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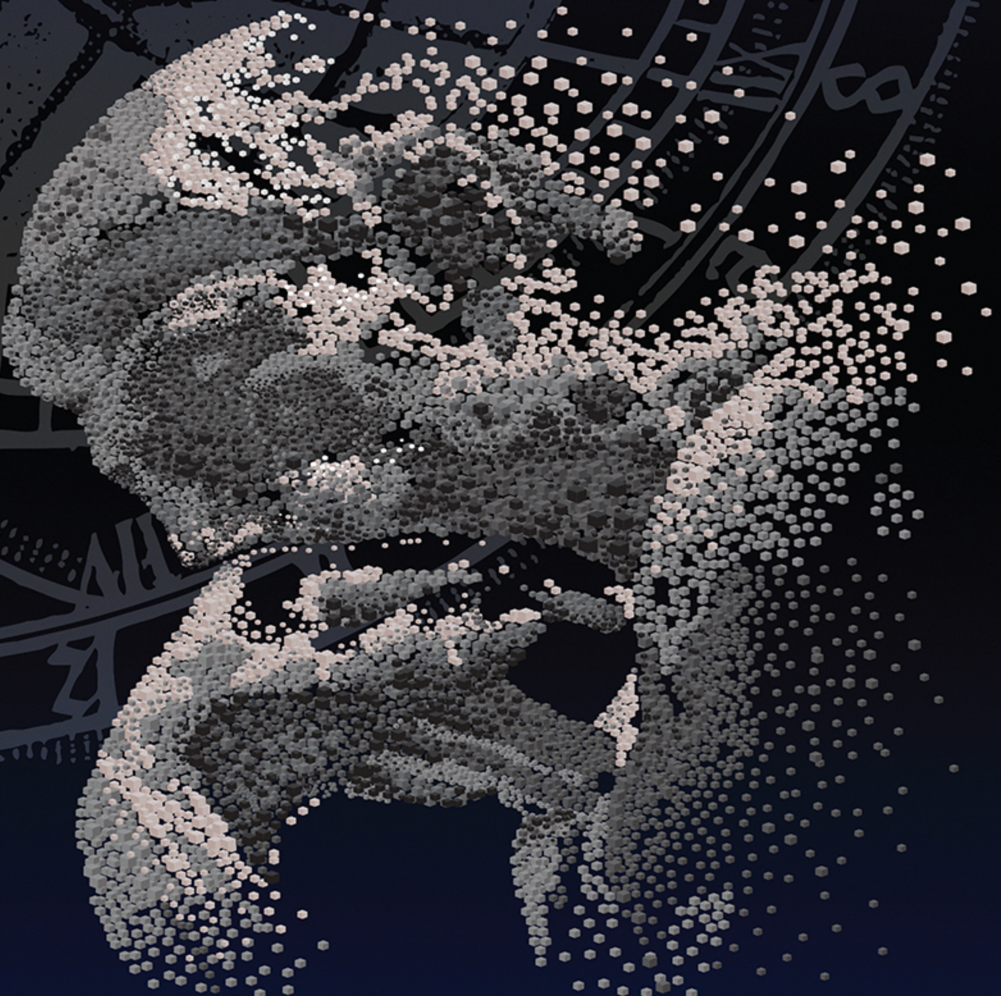
THE EVOLUTION OF SCIENTIFIC KNOWLEDGE

From Certainty to Uncertainty



Edward R. Dougherty

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To Jeffrey M. Trent

Who for twenty years gave me the opportunity
to freely consider fundamental problems of
translational genomics, where complexity
is manifest on an immense scale.

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Preface

This book aims to provide scientists and engineers, and those interested in scientific issues, with a concise account of how the nature of scientific knowledge evolved from antiquity to a seemingly final form in the Twentieth Century that now strongly limits the knowledge that people would like to gain in the Twenty-first Century. Some might think that such issues are only of interest to specialists in epistemology (the theory of knowledge); however, today's major scientific and engineering problems—in biology, medicine, environmental science, etc.—involve enormous complexity, and it is precisely this complexity that runs up against the limits of what is scientifically knowable.

To understand the issue, one must appreciate the radical break with antiquity that occurred with the birth of modern science in the Seventeenth Century, the problems of knowledge and truth engendered by modern science, and the evolution of scientific thinking through the Twentieth Century.

While originally aimed at practicing scientists and engineers, it is my hope that this book can provide a generally educated person with a basic understanding of how our perspective on scientific knowledge has evolved over the centuries to escape pre-Galilean commonsense thinking. Such an appreciation is not only beneficial for one's general education, but is important for non-scientists who must teach young students or make policy decisions in government or business. Physicist and historian Gerald Holton states the dilemma faced by many:

> By having let the intellectuals remain in terrified ignorance of modern science, we have forced them into a position of tragic impotence; they are, as it were, blindfolded in a maze through which they feel they cannot traverse. They are caught between their irrepressible desire to understand the universe and, on the other hand, their clearly recognized inability to make any sense out of modern science. [Holton, 1996]

Perhaps this small book can help some make sense of modern science and the crisis of complexity that will bedevil the Twenty-first Century. Except for the last chapter, mathematics has been avoided, and even in that chapter it has been kept minimal, the only exception being in Section 7.6, which requires some details of the Wiener filter, which are provided. Biological networks are used to illustrate complexity issues, but these are kept mainly at the descriptive level.

Beyond the general issues that have interested me since first encountering them in my genomic research, the immediate motivation behind the book comes from three sources.

First, for several years I have been giving lectures on the "Foundations of Translational Science," which as the name suggests concerns the translation of scientific knowledge into practice. It is a terminology popularly used in medicine. More generally, it refers to modern engineering. The lectures place the problems of computational biomedicine into the framework of classical scientific knowledge and consider the problems of large-scale modeling in medicine. The audience has consisted of Ph.D. students, post-doctoral candidates, and faculty. I have successively added more historical development of scientific epistemology because the audience always asks for more. This book provides it.

Second, in 2011, my colleague Michael Bittner and I published the book *Epistemology of the Cell: A Systems Perspective on Biological Knowledge*, which discusses epistemological problems relating to cellular biology, with emphasis on biomarkers and network models in genomic medicine [Dougherty and Bittner, 2011]. The book has some historical and philosophic background, but, as it has turned out, not a sufficient amount for the large number of contemporary students who have virtually no background in the philosophy of science. The current book rectifies that problem, is focused on science and engineering more generally than cellular biology, includes an extensive discussion of the emerging complexity problems, and puts forward ideas on how one might begin to address these problems in translational science.

Third, in the summer of 2015 I attended a small workshop in Hanover, Germany, entitled *How to Build Trust in Computer Simulations—Towards a General Epistemology of Validation*. The workshop brought together researchers from different fields who were interested in the emerging crisis of scientific knowledge. It was apparent that the issues that I had been grappling with were ubiquitous across science, economics, engineering, and social science. The discussions in Germany stimulated my thinking. This was accentuated because, upon giving a lecture at the University of Munich, I was asked to contribute a chapter to a forthcoming book on epistemology with the idea of speculating on how to deal with model complexity from the perspective of validation and data in the context of translational science [Dougherty, 2016]. Those speculations, which have developed since last summer and have reached a plateau, are discussed in the last chapter of the book, with applications to biomedicine, pattern recognition, and signal processing.

The book is short, a little over one hundred pages. This is intentional because the goal is to succinctly and cohesively hit the necessary points for one to grasp the meaning and structure of scientific thinking, and then engage the current crisis of validation. These are exciting times for a scientist (or anyone) who is interested in fundamental problems of complex systems. Just as physicists in the first half of the Twentieth Century had to squarely confront the unintelligibility of Nature, today's scientist must confront the virtual impossibility of reconciling the desire to model big systems with small data within the context of existing scientific epistemology. The profound question for scientists in the Twenty-first Century: Is it possible to weaken scientific epistemology and broaden the domain of science without destroying it?

Edward R. Dougherty
College Station, Texas
October 2016

Introduction
Challenging Times

Evolution of Galilean–Newtonian Scientific Thinking

Some people are sufficiently fortunate to have their most creative years coincide with great mysteries in human knowledge. One thinks of the magnificent Seventeenth Century. It began with Francis Bacon moving the study of Nature from haphazard experience to designed experiments, and Galileo placing scientific knowledge within the frame of mathematics, not requiring explanation in terms of human physical categories. It ended with Isaac Newton grounding scientific knowledge on mathematical laws applicable to a wide variety of phenomena. The human condition, that is, man's place in the world, changed radically in 1687 with Newton's publication of *Philosophiæ Naturalis Principia Mathematica*.

There was a profound enigma lurking in the thinking of Galileo and Newton. It was genius to declare that knowledge of Nature is constituted within mathematics, not within human categories of understanding; yet, as long as the mathematical laws were consistent with human cognition, the full implication of this thinking lay hidden. The advent of quantum mechanics in the first part of the Twentieth Century brought it to light: a theory may be preposterous from the perspective of human intelligibility but lead to predictions that agree with empirical observation—and therefore be scientifically valid. Man can possess knowledge beyond the limits of his physical understanding. There was excitement in the air. The human condition was changing again, and young scientists dove headlong into the maelstrom.

Today, slightly more than a century since Niels Bohr hypothesized that an electron can jump to a different level without continuously passing through space, and almost a century since Louis de Broglie argued that particles of matter exhibit wave–particle duality, once again science faces an epistemological conundrum, but this time it appears that the resolution does not lie implicitly within Newton's thinking.

Toward the end of the Twentieth Century, the emergence of high-performance computing allowed scientists to construct huge models consisting of thousands of variables and parameters. The complexity of these models prevents them from fulfilling the most basic requirement of science: validation by the successful prediction of future events. System complexity has resulted in data requirements that cannot be met. Model parameters cannot be accurately estimated, thereby resulting in model uncertainty. On the other hand, model simplification means that there can be many models aiming to describe the same complex phenomena, all being inherently partial and hence yielding different predictions. The desire to obtain scientific knowledge of complex systems runs up against the requirements for scientific knowledge. In addition to complexity, there is also an aspiration for systems covering large time scales, so that validating data cannot be obtained. The inability to validate theory via observations constitutes an existential crisis for science.

The first part of this book, comprising Chapters 1 through 5, tells perhaps the greatest saga of the human mind: the evolution of scientific knowledge from explanations of natural phenomena in terms of everyday physical understanding to mathematical models that possess no such understanding and require mathematical formulation of their experimental relation to Nature. The chapters are populated by many of history's greatest scientists and philosophers. Their struggle involves a most perplexing problem: How does mind characterize what mind can know? It is a story that should be known not only to every scientist and engineer, but also to every scholar and educator, for in a world so influenced by science, no discipline can be taken seriously if it does not account for itself in relation to science.

A Radical Shift in the Narrative

A radical shift in the narrative begins with Chapter 6. A chronicle that seemed to be complete runs abruptly into the quandary of complex systems. The issues are essentially mathematical and statistical. Thus, the presentation takes on a more mathematical tone. Many of the specifics are set in the context of biology, which some have proclaimed to be the key science of the Twenty-first Century. In fact, the underlying problems of system complexity and data paucity span the range of scientific investigation, from biology to economics to social science. While our computational ability continues to grow, thereby fueling the demand for modeling complex phenomena, limitations on human conceptualization and data appear to preclude the formation of valid scientific theory in many domains—at least insofar as scientific epistemology has thus far evolved. We are in the midst of a new epistemological crisis. What could be more exhilarating for a scientist, engineer, or philosopher? Yes, we are confused, but confusion is the norm when one is on the frontier–and where else would one want to be?

The last chapter of the book considers the impact of scientific uncertainty on the translation of scientific knowledge into means to alter the course of Nature—that is, the effect of uncertainty in engineering. It proposes a course of action based on integrating existing partial knowledge with limited data to arrive at an optimal operation on some system, where optimality is conditioned on the uncertainty regarding the system. It explains the classical paradigm of optimal operator design based on a scientific model, a class of potential operations, and a quantitative measure of performance, all of which presupposes a system description whose predictions are concordant with observations. It then postulates an alternative optimization paradigm grounded in a Bayesian framework to take advantage of existing partial knowledge pertaining to the physical system of interest. The ultimate scientific problem of model validation is not solved; rather, the thinking here is that of an engineer: find an optimization framework in which pragmatic goals can be achieved. As for a new scientific epistemology in which valid knowledge can be defined, that awaits the bold efforts of fertile minds enriched with the mathematical, scientific, and philosophic education required for such a quest.

Chapter 1

Why Epistemology?

1.1 The Desire to Know

The opening line of Aristotle's *Metaphysics* states, "All men by nature desire to know." But what does it mean to know? While one might wish for a universal answer to this question, none as yet has been forthcoming. As we understand the question, what it means to have knowledge depends on one's standpoint. Moral knowledge is of a different kind than scientific knowledge. Even in science, the domain of scientific knowledge and what is accepted as authentic knowledge, meaning that it is accepted as "true," has changed dramatically over time.

The domain of scientific knowledge for Aristotle was much smaller than it is today. He could not make observations of the atom or of distant galaxies. He could not observe the genes and proteins in a cell, nor could he measure electrical impulses in the brain. His concept of truth was limited by his ability to observe and measure, but it was also limited by the mathematical systems he had available to represent the behavior he viewed. It is naïve to think that our concept of knowledge in today's world of quantum physics and microbiology would be the same as it was for Aristotle in 340 BC, what it was for Newton in 1687, or what it will be in 2500.

Scientific knowledge relates to the manner in which the mind formulates and operates on ideas concerning Nature. These must ultimately be related to our senses that provide the data from which the neural system formulates ideas. My idea of a rock is not outside my mind. Something is out there that results in sensations, that in turn results in the idea of a rock. Such ideas are the raw material of theories that describe the interaction of the ideas—and if a theory is valid it should produce consequences that can be checked against future sensations. The fundamental point is that theoretical operations in the mind correspond to physical operations in Nature that are not directly experienced, but whose activity is reflected in new sensations resulting in new ideas concordant with outcomes the original operations predicted. This very general description of scientific knowledge has been developed over many centuries and is not Aristotle's view.

The first aim of this book is to trace this development up to and including the turbulent effects of quantum mechanics in the Twentieth Century. The second aim, which cannot be accomplished absent an appreciation of the subtle relations between reason, science, and metaphysics, including their historical evolution, is to scrutinize the new and rapidly accelerating crisis of scientific knowledge that has accompanied the desire to model extremely complex systems such as those arising in biology, environmental science, economics, and social science.

1.2 What is Epistemology?

Implicit in these aims is that it is possible to characterize a specific kind of knowledge to be called "scientific." This characterization lies outside of science and must be constructed prior to the organization of experience within scientific categories. Such characterization amounts to having a theory of scientific knowledge. *Epistemology* is defined as the theory of knowledge, so a scientific epistemology is required. What would it entail?

Wilhelm Windelband (1848–1914) defines epistemology in the following way: "The problems, finally, which arise from the questions concerning the range and limit of man's knowing faculty and its relation to the reality to be known form the subject-matter of epistemology or theory of knowledge." [Windelband, 1958] Taking the word "range" to refer to the kind, or nature, of the knowledge under consideration, the nature of scientific knowledge is determined by its manner of representation and its criteria for truth; its limitations are determined by the limits of its form of representation and the degree to which its criteria of truth can be applied; and its relation to reality is determined by the manner in which its representation is connected to physical phenomena and the relation between scientific truth and physical phenomena.

Many researchers appear to believe that epistemological issues are too arcane and irrelevant to their everyday efforts. One just has to get on with gathering data, building models, and justifying the models. But how should one gather data, what kind of models should be constructed, and, most importantly, what constitutes genuine validation? These questions relate to Windelband's definition of epistemology. Absent some understanding of their answers, one might spend years wandering about aimlessly, producing meaningless results, simply because a bona fide theory must conform to the epistemological requirements of science.

José Ortega y Gasset (1883–1944) phrases the matter this way: "Whoever wishes to have ideas must first prepare himself to desire truth and to accept the rules of the game imposed by it. It is no use speaking of ideas when there is no acceptance of a higher authority to regulate them, a series of standards to which it is possible to appeal in a discussion." [Ortega y Gasset, 1994]

The foundations of a discipline are inseparable from the rules of its game, without which there is no discipline, just idle talk. The foundations of science reside in its epistemology, meaning that they lie in the mathematical formulation of knowledge, structured experimentation, and statistical characterization of validity. Rules impose limitations. These may be unpleasant, but they arise from the need to link ideas in the mind to natural phenomena. The mature scientist must overcome the desire for intuitive understanding and certainty, and must live with stringent limitations and radical uncertainty.

Inattention to epistemology results in research that appears scientific but fails to have depth, or even worse, is scientifically unsound. Albert Einstein (1879–1955) writes, “The reciprocal relationship of epistemology and science is of a noteworthy kind. They are dependent upon each other. Epistemology without contact with science becomes an empty scheme. Science without epistemology is—insofar as it is thinkable at all—primitive and muddled.” [Einstein, 1949]

Only through deep reflection on epistemology can one come to grasp what it means to possess scientific knowledge of Nature and therefore be in a position to effectively seek such knowledge. Significant effort must be spent escaping a naïve realism that would attempt to force one’s conceptualizations of Nature to conform to ordinary everyday understanding.

In a letter, Einstein wrote the following:

> I fully agree with you about the significance and educational value of methodology as well as history and philosophy of science. So many people today—and even professional scientists—seem to me like somebody who has seen thousands of trees but has never seen a forest. A knowledge of the historic and philosophical background gives that kind of independence from prejudices of his generation from which most scientists are suffering. This independence created by philosophical insight is—in my opinion—the mark of distinction between a mere artisan or specialist and a real seeker after truth. [Einstein, 1944a]

“Independence from the prejudices of his generation!” Only in this way can one break free of the run-of-the-mill grind that never gets to the heart of the matter.

1.3 Modern Science

Starting in the early part of the Seventeenth Century, a radical new understanding of natural science took shape. On the one hand, Francis Bacon proposed ordered observations in the context of experimental design; on the other, Galileo contended that scientific knowledge must be constituted within mathematics and not be bound by the need to explain matters in ordinary language. Isaac Newton manifested Galileo’s conception with his laws of motion, which he proclaimed free of non-empirical, metaphysical notions such as substance and causality. This was indeed a “new science.” What is gravity? Who knows? All that matters is that science provides mathematical descriptions of behavior. It would no longer be required to satisfy the human desire for explanations in a deeper reality.

Mathematics was not new to science; Archimedes, the greatest scientist of antiquity, was a great mathematician and this was reflected in his scientific thinking. Now, however, instead of supporting a theory whose status as authentic knowledge was rooted in causality, mathematics was the theory. Knowledge was constituted within it, and its validity depended solely on its ability to make predictions confirmed by observation. The birth of modern science was the greatest revolution in human history. It radically changed the human condition because it altered man’s perspective on himself and Nature.

The full extent of the change did not become apparent until the arrival of quantum mechanics in the Twentieth Century. Only then did the unintelligibility of Nature become forcefully apparent with the uncertainty principle and strange notions like wave-particle duality. The theory was mathematically sound and agreed with predictions, but defied human understanding.

Hannah Arendt (1906–1975) frames the dilemma brought about by science in the early Twentieth Century: “To understand physical reality seems to demand not only the renunciation of an anthropocentric or geocentric world view, but also a radical elimination of all anthropomorphic elements and principles, as they arise either from the world given to the five senses or from the categories inherent in the human mind.” [Arendt, 1977a]

It is not just that the senses cannot be trusted; neither can the categories of our understanding, which form the womb in which modern science was conceived. Indeed, Nature is not even thinkable. Arendt writes, “The trouble, in other words, is not that the modern physical universe cannot be visualized, for this is a matter of course under the assumption that Nature does not reveal itself to the human senses; the uneasiness begins when Nature turns out to be inconceivable, that is, unthinkable in terms of pure reasoning as well.” [Arendt, 1977b]

A vast number of scientists have not even taken Newton to heart, let alone come to terms with the strangeness of Nature to which Arendt is referring. Many appear to hope that a light will go on, Nature will become transparent, and simple explanations will emerge. Engaging the subtleties of epistemology will quickly rid one of such a puerile outlook. Indeed, as technology provides more detailed observation, Nature is becoming more unfathomable.

1.4 The Crisis of Complexity

With the advent of the Twenty-first Century, it has become apparent that the epistemology that began with Galileo, took shape with Isaac Newton, and came to fruition in the first half of the Twentieth Century with Niels Bohr, Hans Reichenbach, and others cannot support the desire to model complex systems. Across disciplines, scientists and engineers want to gain knowledge of large-scale systems composed of thousands of variables interacting nonlinearly and stochastically, often over long time periods. This massive complexity makes the standard modes of discovery and validation impossible.

The unverifiable character of many proposed systems is most troubling because the proliferation of such systems compromises the notion of scientific truth and threatens to erode the credibility of science. Consider medicine, which confronts huge complexity in physiological systems. In 2011, Janet Woodcock, Director of the Center for Drug Evaluation and Research at the FDA, estimated that as much as 75% of published biomarker associations are not replicable. She went on to comment, “This poses a huge challenge for industry in biomarker identification and diagnostics development.” [Ray, 2011] This dismal record could only have been produced by a widespread lack of attention to legitimate scientific method. A large number of studies involving immense complexity or dimensionality have been undertaken in which there is no possibility of obtaining scientifically meaningful conclusions.

If, as Aristotle says, all men desire to know, and in the Twenty-first Century the desire is for knowledge of complex systems, then, in Windelband's words, scientists must address "the questions concerning the range and limit of man's knowing faculty," as these pertain to systems involving high dimensionality, complexity, and uncertainty.

Chapter 2
Pre-Galilean Science

2.1 Deep Roots

The roots of science are within the roots of philosophy because until relatively recently science was not distinguished from philosophy; it was considered to be natural philosophy. This lack of separation is reflected throughout Greek science. Proceeding historically from ancient Greece into the Eighteenth Century there is a continuing, although not necessarily progressive, untangling of reason, science, metaphysics, and faith. It is important to recognize the growing demarcation of science, as a subject in its own right, over the centuries if one is going to acquire a deep understanding of the Twentieth Century developments, in particular, the role of uncertainty and the lack of absolute objectivity.

This chapter begins with Aristotle's epistemology and outlines the evolution of reason and science prior to the birth of modern science in the Seventeenth Century. There were outstanding Greek scientists before Aristotle, of which we mention three: (i) Thales (624–546 BC), who first used deduction to prove geometric theorems, studied astronomy independently of astrology, and predicted the eclipse of the sun on May 28, 585 BC; (ii) Empedocles (492–432 BC), who expounded a theory of evolution in which all higher forms develop from lower forms and there are no sharp distinctions between species, with Nature producing monstrosities that perish on account of maladaptation and organisms that propagate by meeting the conditions of survival; and (iii) Democritus (460–370 BC), who proposed an atomic theory of matter governed by necessity via natural causes and who postulated the preservation of matter, it being neither created nor destroyed, with only atomic combinations changing. The roots of science go very deep.

2.2 Aristotle: Causality as the Ground of Knowledge

Aristotle (384–322 BC), a Macedonian, put into place the basic tenets of logic and scientific epistemology that remained dominant for two thousand years. His fundamental aim was to analyze the process and technique of reasoning. What is reason? What is the domain of reason? His major logical treatise, the *Organon*, served as the major logic text for two millennia.

2.2.1 Plato: Allegory of the cave

For Aristotle’s mentor Plato (428–348 BC), the path to true knowledge lies beyond the material world. In *The Republic*, Socrates tells Glaucon the famous allegory of the cave, in which prisoners sit chained with their heads bound straight ahead. Behind them a fire is burning. Between the fire and the prisoners is a raised way with a low wall behind which men move about carrying statues and other structures, held above the wall, so that their shadows appear on the cave wall opposite the fire. These shadows constitute the world observed by the prisoners. We are the prisoners condemned by the human condition to see only the ephemeral shadows of sensibility that are thin reflections of a deeper reality, one that is permanent and, unlike the shadow world, not always passing away.

True knowledge is knowledge of the *forms* that constitute that deeper reality and these can only be reached by reason. Empirical knowledge is shadow knowledge and leaves us in perpetual darkness. Mathematics, which to the ancient Greek mind meant geometry, is unchanging and independent of the senses. As a mathematical entity, a triangle is a form that has permanence and mathematical knowledge of triangles is true knowledge, whereas any physical instance of a triangle is only a crude shadow of a real triangle and knowledge of physical triangles is a vulgar kind of knowledge. Like mathematics, metaphysical knowledge is not transient and concerns the truly real, not shadows. It is not surprising that Plato took so little interest in natural science.

As to a demarcation between science and metaphysics, Windelband writes,

> The general questions which concern the actual taken as a whole are distinguished from those which deal with single provisions of the actual. The former, viz. the highest principles for explaining the universe, and the general view of the universe based on these principles, form the problems of *metaphysics*…. The special provisions of the actual are Nature and History. [Windelband, 1958]

Natural science comes under the province of Nature.

The grand issues that concern explaining the universe as a whole form the problems of metaphysics. Metaphysical explanations go beyond explanations of individual conditions (provisions) within the world to a unity of all individual conditions, not simply as a collection of conditions, but integrated within the context of the whole. Metaphysics does not concern this or that scientific principle but rather the deeper reality governing scientific principles in general. From Plato onward it has been a perpetual struggle to keep science and metaphysics demarcated.

Plato’s placing the physical below the metaphysical has had great impact for over two thousand years. The metaphysician is enlightened; the physical scientist is not. In deprecating the natural sciences in favor of metaphysics, Plato has had the effect of encouraging the infusion of metaphysical speculation into science, a problem still with us today.

2.2.2 Aristotle's epistemology

For Aristotle the basic axiom of logic is the law of contradiction: "X and (not X)" is always false. Logical arguments are based on syllogisms, such as the classical example: All men are mortal; Socrates is a man; therefore, Socrates is mortal. Aristotle put great emphasis on definitions as they pertain to the class of an object and the differences between objects in a class. The defining attribute of a class is called a *universal*; for instance, the class of all triangles is characterized by certain properties that define an abstract triangle, the latter being a universal. Only individual objects exist in the material world. For Plato, a universal exists as a form in a deeper reality, but for Aristotle, a universal is simply a concept, or general idea. This conceptual view is in line with his empirical view that the senses are the only source of knowledge and observation is necessary for science.

While the issue of universals might appear abstruse, one's attitude towards universals is closely related to his view of reality. There tends to be three general positions. In the *realist* view, universals (man, truth,…) are real. "Man" is more than simply the set of individual men. In the *nominalist* view, which is common today, universals are simply names of sets and only the elements are real. In the *conceptualist* view, a universal refers to a general idea in the mind.

Aristotle diverged from Plato by paying serious attention to the physical world, in particular, biology. He made many observations and made serious efforts to record and explain them; however, he lacked the notion of a model-based designed experiment. Although he emphasized observation, Aristotle placed the authenticity of knowledge in metaphysics. In Book III of the *Physics*, Aristotle writes, "Knowledge is the object of our inquiry, and men do not think they know a thing till they have grasped the 'why' of it (which is to grasp its primary cause)." [Aristotle, 335 BC] By insisting on an answer as to why, he points to a deeper reality (cause) beyond the phenomena (shadows). Whereas Plato left the deeper reality to the abstract, mystical world of forms, and therefore had little impact on actual scientific enquiry, Aristotle related the 'why' to the phenomena via causality, thereby having a huge impact on the future development of science. As described by Aristotle, causality has to do with providing categories of explanation. Knowledge is explanation surrounding the question of why and is based on four causes.

The four causes are defined in the *Physics*. A *material cause* is "that out of which a thing comes to be and persists." It is "the bronze of the statue, the silver of the bowl, and the genera of which the bronze and the silver are species." A *formal cause* is "the form or the archetype, i.e. the statement of the essence, and its genera,…and the parts in the definition." An *efficient cause* is "the primary source of the change or coming to rest; e. g. the man who gave advice is a cause, the father is the cause of the child, and generally what makes of what is made and what causes change of what is changed." A *final cause* is "the end, or that for the sake of which a thing is done, e. g. health is the cause of walking about…. The same is true also of all the intermediate steps that are brought about through the action of something else as means toward the end." The same analysis is provided by Aristotle in the *Metaphysics*.

An efficient cause seems most in accord with our ordinary understanding of causality, but what does it mean to be “the primary source of the change or coming to rest?” Perhaps if one thinks of a moving billiard ball hitting another billiard ball at rest, then a casual observer might say in the vernacular that the moving billiard ball is the “cause” of the motion of the previously stationary billiard ball. But this everyday appeal to causality lacks any quantitative description. The latter would involve velocity, impact angle, elasticity, friction, air resistance, etc. Note that we have avoided trying to define “causality” in its current usage, instead allowing the reader to simply recognize the obvious difference or agreement with Aristotle. As we proceed, it will become apparent that defining causality in any meaningful sense is problematic.

The metaphysical nature of Aristotle’s notion of cause is revealed by his use of it to prove the existence of God. He argues that there must be a first cause, uncaused, and that first cause is God. He is the prime mover, after which all movement is imparted.

Our primary concern with the epistemology characterized by Aristotle’s conception of causal knowledge is the orientation towards the science of Nature engendered by it and the resulting impact on the future development of scientific epistemology. Three points are fundamental to Aristotle’s epistemology: (1) to know is to explain; (2) explanation must involve a causal relation; and (3) there is no demarcation between physics and metaphysics. The evolution of scientific epistemology has involved the demolition of these three pillars of Aristotelian epistemology and the removal of their retarding effect on scientific advancement.

2.3 Evolution and the Argument from Design

Empedocles expounded an evolutionary theory, but a more significant and modern articulation of *natural selection* was put forth by Lucretius (99–55 BC) in *De Rerum Natura* (*On the Nature of Things*), one of the greatest treatises of Roman society. He writes,

> Many were the monsters that the earth tried to make.... It was in vain; Nature denied them growth, nor could they find food or join in the way of love.... Many kinds of animals must have perished then unable to forge the chain of procreation...for those to which nature gave no protective qualities lay at the mercy of others, and were soon destroyed. [Lucretius, 56 BC]

As framed by Charles Darwin (obviously without the genetic knowledge available today), organisms possessing different variants of a trait may have environmental advantages, thereby enhancing their survivability relative to other variants and thus facilitating greater reproduction. This natural selection occurs at the phenotypic level but the reproductive advantage (or disadvantage) shows up at the genetic level, the result being that populations evolve. This evolution is broken down into two general categories: (1) *microevolution* refers to changes within a species; and (2) *macroevolution* refers to the emergence of new species.

For this categorization to be meaningful, the definition of a species must be tight and universal, not something vague like a class of organisms possessing many similarities; otherwise, it will be subjective, not inter-subjective, and what for one person is microevolution may be macroevolution for another. Although Lucretius lacked mechanistic understanding of evolution, his analysis in terms of natural selection was sophisticated.

The *argument from design* was also discussed during the Roman period. In fact, it goes back to the Greek Stoics with little change. Cicero (106–43 BC), in *De Natura Deorum* (*On the Nature of the Gods*), writes, "When you see a sundial or a water-clock, you see that it tells the time by design and not by chance. How then can you imagine that the universe as a whole is devoid of purpose and intelligence, when it embraces everything, including these artifacts themselves and their artificers?" [Cicero, 45 BC] This *teleological argument* relates to purpose, or final cause, and not, as is more popular today, an argument based on complexity.

Both Lucretius' theory of evolution and Cicero's argument from design depend on reason operating on observations. The degree to which they are or are not scientific depends on the epistemology of science.

2.4 The Fall and Rise of Reason

Since our interest is primarily in the nature of scientific knowledge, we shall skip to the beginning of the Middle Ages, which we take to be 325 AD, marked by the Council of Nicaea, where the Christian creed was codified under the watchful eye of the emperor Constantine. Much great work was done during the period between Aristotle and the commencement of the Middle Ages, for instance, in geometry and in the studies of Archimedes, but this is not our interest.

We leave it to historians to decipher the factors leading to the abandonment of reason in the Roman world as Rome entered what was perhaps its final great phase under Constantine. Very likely the decline in reason and the move to faith were inextricably interwoven, with the failure of reason to bring material well being and spiritual contentment. For our purposes it is important to mention some markers in the fall and rise of reason.

2.4.1 Believe that you may understand

The fundamental problem was to reconcile reason with faith in the Age of Faith. St. Augustine (354–430) of Hippo and a Doctor of the Church, argued that the intellect is weak and there are many paradoxes that human reason cannot resolve. Therefore, do not try to ground faith upon reason. Augustine advises, "Seek not to understand that you may believe, but believe that you may understand." Put another way, faith precedes understanding. Augustine did not come to this view because his reasoning was weak; rather, his reason was strong but it could not lead him to the certainty of faith. Since faith is primary for Augustine, it must lead the way to understanding. If reason does not agree with faith, then reason must yield.

Regarding the Bible, Augustine applies the same basic argument: “Dispute not by excited argument those things which you do not yet comprehend, or those which in the Scriptures appear…to be incongruous and contradictory; meekly defer the day of your understanding.” [Augustine, in Durant, 1950]. The Bible is not to be taken literally. It cannot be an arbiter of theological disputes. These must be settled by Church councils.

2.4.2 Islamic transition

Although dormant in Europe, reason was far from dead. It had earlier migrated into areas that were to be conquered by Islam and there it was preserved and prospered for some time.

Avicenna (Ibn Sīnā, 980–1037) was a Persian Aristotelian for whom reason is the arbiter of knowledge and knowledge of the natural world is obtained via observation. Like Aristotle, he argued that contingent beings require a first cause; hence, God must exist. He aimed to reconcile Islamic dogma with Aristotelian reason. Regarding the existence of universals, he argued that they exist as real entities in the mind of God, like Plato’s forms, and they exist as concepts in the human mind, in agreement with Aristotle. Regarding religious dogma, parables are needed to ensure the moral order, but for philosophers, reason must ground knowledge. Avicenna influenced medieval European philosophy, including Thomas Aquinas.

It is a common sequence in history for reason as queen to give way to faith when reason proves unable to arrive at truth or to provide answers to the deepest questions men pose: on freedom, on immortality, on God. We have seen this turn with Augustine. His was part of a great millennial metamorphosis into the medieval mind. Following the heights of reason in Plato and Aristotle, it was only a few short years to the skepticism and return to religion of Pyrrho, and more generally of the path trod by the Skeptics and Stoics. An analogous move will play a key role in the Enlightenment during the Eighteenth Century and affect the course of science.

The Enlightenment conflict was foreshadowed in Islam at the end of the Eleventh Century by one of Islam’s greatest philosophers, al-Ghazali (1058–1111). In his critique of reason, he anticipated David Hume by arguing that reason depends on causality and causality is merely temporal regularity. He anticipated Immanuel Kant by contending that reason cannot prove the existence of God or immortality, without which there is no moral order, without which civilization cannot survive. The only option is to return to the orthodoxy of the *Quran* and *Hadith*. Al-Ghazali’s influence was conclusive: reason and science began to wane in Islam. His argument is powerful, not too dissimilar from that of Augustine and Martin Luther. Kant will attempt to preserve both science and faith by limiting “pure reason” to science and basing faith on “practical reason.”

Following a long hiatus of almost a thousand years, reason would return to Europe. A key factor in the process was the attempt of Christianity to regain control of the Holy Land with the Crusades. It was during this period, 1095–1291, that the contact and mixing between a mature Islamic civilization that had preserved the science and philosophy of ancient Greece and an adolescent European civilization that had suffered through the Dark Ages facilitated the movement of knowledge to Europe, including the translation from Arabic into Latin of ancient Greek texts. The Crusades also facilitated the integration of Europe under the Catholic Church, an integration that would break down with the emergence of monarchies.

Averroes (Ibn Rushd, 1126–1198), born in Cordoba, present-day Spain, was a major figure, perhaps the most important, in this movement of knowledge from Islam to Europe. He was an Aristotelian and, contra al-Ghazali, accepted that philosophy may risk atheism, but potentially there can be harmony between religion and philosophy. Indeed, religious dogma as symbol can be harmonized with philosophy by minimizing dogma to reconcile it with reason. Philosophers should be free to think and speak amongst themselves. They do not take the Bible or *Quran* literally but they recognize that the general public needs myths. Taking a view that in several hundred years would be held by many scientists, Averroes believed that natural law rules the world without any interference by God—a position unwelcome by Islam and Christianity. Indeed, Averroes had negligible influence in Islam, which had turned towards orthodoxy following al-Ghazali, but his philosophical thinking swept the educated circles in France and England, where secularism was beginning to contend with orthodox Christianity. It might not be too strong of a statement to say that Averroes brought Aristotle to Europe.

2.4.3 The Thirteenth Century: an age of reason

When Aristotle's *Physics* and *Metaphysics* arrived in Paris during the first decade of the Thirteenth Century, the European mind was roused. All the old conflicts between reason and faith took on new fervor. Out of these disputes arose the great Doctor of the Church, Thomas Aquinas (1225–1274). Contra Averroes, he aimed to make Aristotle consistent with Christianity. Contra Augustine, he elevated the intellect over the heart. Like Aristotle, for Aquinas truth is equivalence, in some sense, of thought with the thing. This view is a form of naïve realism and will be demolished with the coming of modern science.

Yet Aquinas cannot be neatly fit into rigid positions. He agrees with John Locke that there is nothing in the intellect that is not first in the senses, except the intellect itself, which agrees with Kant. Knowledge of Nature is acquired via the senses; metaphysical knowledge, including God, is obtained by analogy; and knowledge of the supernatural world comes only by faith. Taking this as a whole, Aquinas recognizes the roles of faith, reason, and the senses. In his balanced view, reason has its domain but must in some places yield to faith. In the *Summa Theologica*, a treatise that stands as an outstanding testimony to human reason, Aquinas writes, "Man is directed to God as to an end that surpasses the grasp of his reason." [Aquinas, 1485]

Just as al-Ghazali counteracted the reason of Avicenna, John Duns Scotus (1266–1308) followed quickly on the heels of Aquinas to confront reason on behalf of faith. As a forerunner of Kant, Duns Scotus emphasized that reason applied to religion leads to contradictions (Kant's antinomies of pure reason) and, since religion is necessary for morality, dogmas of faith should be accepted as a practical necessity (Kant's practical reason). A battle between faith, the Franciscans (Duns Scotus), and reason, the Dominicans (Aquinas), took place within the Church. Even before Duns Scotus, it appeared that orthodox dogma would prevail. In 1277, three propositions of Aquinas were declared heresies and the Archbishop of Canterbury condemned Thomism.

Aquinas quickly recovered, being canonized as a saint in 1323. The Catholic Church had to some extent legitimized reason and this would have huge effects going further, including for science. Six centuries later in 1921 the Church went so far as to declare Thomism its official philosophy. Much happened during the intervening centuries. In the Sixteenth Century, the Protestant Reformation attacked reason (Martin Luther, "That whore reason."), looking to return to Augustine, and the Catholic Church took an antagonistic view towards both reason and science when they were perceived to threaten the Church—or perhaps more accurately, perceived to threaten powerful interests in the Church. Fall-out from the conflict between reason and faith (or its secular substitute, ideology) always affects science.

Not only was modern philosophy foreshadowed in the Thirteenth Century but so too was modern scientific epistemology. Roger Bacon (1214–1294) asserted the two most fundamental aspects of that epistemology: first, scientific theory takes mathematical form, and second, experiments provide final proof of a theory. It would take many centuries before the meaning and application of these statements would be clarified, but the ground had been seeded with the mental form of theory and the requirement of an empirical connection.

Those living today often possess the distorted view of the days before the Age of Reason as a period containing nothing more than an arid and tedious scholasticism in which theologians argued amongst themselves as to how many angels can dance on a pin head. Certainly there is much truth to this view; however, the Thirteenth Century was itself an age of reason in which great intellectual battles were fought whose outcomes would shape the Western World for centuries, up into the modern period. In the *Age of Faith*, Will Durant writes, "We must see the Thirteenth Century not as the unchallenged field of the great Scholastics, but as a battleground on which, for seventy years, skeptics, materialists, pantheists, and atheists contested with the theologians of the Church for possession of the European mind." [Durant, 1950]

2.4.4 William of Ockham: the razor

The Fourteenth Century produced a remarkably modern mind whose name may be forever linked with the demand for concise theory. In addition to requiring an empirical basis for knowledge, William of Ockham (1287–1347) called for parsimony in reason. The famous *Ockham's razor* states that a plurality (of entities, causes, or factors) is not to be posited without necessity. Aquinas and Duns Scotus had desired parsimony, but they were less rigorous in application. Ockham wanted it applied everywhere, to metaphysics, science, and theology, the latter presenting a particularly thorny domain in which to apply the razor.

Ockham adopts a host of modern positions: philosophical and theological truth are different; nothing can be an object of thought without having been an object of the senses (Locke); universals are abstractions useful for thought, existing only in the mind; reason's conclusions are only meaningful as pertaining to experience; our knowledge is molded by our perception (Kant); and there is no objective truth. And Ockham was a theologian!

Beginning in antiquity we have come to the end of the Middle Ages, having moved at lightning speed, hitting only the highest points; however, in doing so we have touched upon the major issues facing reason and science heading into the modern period by viewing them in terms of their greatest protagonists. This provides a background for the epistemological eruptions to come in the Seventeenth Century and hopefully has given the reader a sense that the big ideas with us today have precursors running back through history.

2.5 Copernicus Moves Man from the Center of the Universe

The geocentric theory of Claudius Ptolemy (90–168), in which the earth is fixed at the center of the universe with the sun and planets revolving around it, had been generally accepted into the Sixteenth Century. The basic orbits are circular but they require complex epicycles within the basic orbit and eccentrics that move the basic orbit off center. The geocentric theory fit the existing data fairly well, did a respectable job at predicting planetary motions for astronomical charts, and had the metaphysically (theologically) pleasing consequence that humanity held a very special place in the universe.

In 1543, Nicolaus Copernicus (1473–1543) in *De Revolutionibus Orbium Coelestium* (*On the Revolution of the Celestial Orbs*) proposed the heliocentric theory. It contained one of the most striking claims in European history: the sun is fixed and the planets, including Earth, move in circular orbits about the sun. Orbital predictions from the heliocentric theory were no better than those from the geocentric theory; however, the heliocentric model was less complex, so that based simply on predictive capacity and parsimony (Ockham's razor) it was superior. Nonetheless, it was not generally accepted; indeed, Tycho Brahe, the greatest astronomer of the time, did not accept it.

The heliocentric theory of Copernicus was not completely novel. The idea went back to Aristarchus of Samos (310–230 BC) and had been followed up in more recent times by Nicole Oresme (1330–1382), Nicholas of Cusa (1401–1464), and Leonardo da Vinci (1452–1519). Nonetheless, it was Copernicus' theory that got attention and ushered in a new conception of the human condition.

How important was it? In *The Story of Civilization*, Will and Ariel Durant state what they consider to be "The basic events in the history of modern Europe." These events are three books: *De Revolutionibus Orbium Coelestium* by Copernicus, *Philosophiae Naturalis Principia Mathematica* by Isaac Newton, and *The Origin of the Species* by Charles Darwin. These books have driven the philosophic, religious, and political evolution of Western Civilization.

Was the theory claimed to be true? Sounding very modern, the preface of *De Revolutionibus* states:

> Many scientists, in view of the already widespread reputation of these new hypotheses, will doubtless be greatly shocked by the theories of this book…. However…the master's hypotheses are not necessarily true; they need not even be probable. It is completely sufficient if they lead to a computation that is in accordance with the astronomical observations.… Let us grant that the following new hypotheses take their place beside the old ones which are not any more probable. Moreover, these are really admirable and easy to grasp, and in addition we shall find here a great treasure of the most learned observations. For the rest let no one expect certainty from astronomy as regards hypotheses. It cannot give this certainty. He who takes everything that is worked out for other purposes, as truth, would leave this science probably more ignorant than when he came to it. [Copernicus, 1543]

Truth is not claimed; only that when used in computations, the new theory predicts the astronomical observations as well as any competing theory.

In fact, the statement was not written by Copernicus but by an assistant, Andreas Osiander, apparently with the aim of keeping Copernicus out of the hands of the Inquisition, and without the permission of the author. Nonetheless, Osiander's preface showed prudence of the kind necessary in science, where final demonstrations are impossible. It is as though a Twentieth Century scientist had stepped back in time to clarify the epistemological ground of the theory.

The Copernican theory suffers on account of the assumption of circular orbits. Johannes Kepler (1571–1630) dropped this assumption and during the period from 1609 to 1619 formulated three laws based on elliptical orbits:

> I. Each planet moves in an elliptical orbit for which one focus is the sun.
> II. Each planet moves faster when nearer the sun and a radius drawn from the sun to the planet covers equal areas in equal times.
> III. The square of the time of revolution of a planet around the sun is proportional to the cube of its mean distance from the sun.

In addition to using elliptical instead of circular orbits to fit the data, Kepler's theory is structurally different than that of Copernicus because it involves formulae for various aspects of planetary motion. The next step would await Isaac Newton: derivation of planetary motion from a general theory of gravitation, that is, from fundamental physical laws.

Chapter 3

The Birth of Modern Science

3.1 The Seventeenth Century

We shall define the Age of Reason to be the period between 1620, publication of the *New Organon* by Francis Bacon, and 1750, publication of *A Discourse on the Moral Effects of the Arts and Sciences* by Jean-Jacques Rousseau. As discussed in the previous chapter, reason was well ensconced in European thought by the end of the Thirteenth Century, but with the publication of the *New Organon*, it took on an empirical flavor, the aim no longer being to reconcile reason with faith, but to use it independently of faith to understand the world. With his rejection of both reason and civilization, Rousseau ushered in the Romantic Period, where sentiment and feeling take preference over reason.

During the Seventeenth Century, which is the focus of the present chapter, Bacon propounded the central role of designed experiments, Galileo advanced the notion that scientific knowledge must take mathematical form, Isaac Newton formulated physics in terms of general mathematical laws, and, both Galileo and Newton put aside the requirement of causal explanation, thereby dropping the Aristotelian epistemology.

3.2 Francis Bacon: Empirical Method

Spurred by growing wealth and commerce, and the cross-pollination of ideas engendered by increasing contact and communication, the Sixteenth Century had witnessed a great increase in scientific investigation, capped by Copernicus' heliocentric theory; nevertheless, Francis Bacon (1561–1626) saw progress being hindered by pointless disputation lacking utility. Laying the blame on Aristotle, he made the first major overt effort to break with *The Philosopher*. In distinction with Aristotle's *Organon*, he wrote the *Novum Organum* (*New Organon*).

In the first aphorism of the *New Organon*, Bacon states emphatically that knowledge is rooted in experience: "Man, being the servant and interpreter of Nature, can do and understand so much and so much only as he has observed in fact or in thought of the course of Nature. Beyond this he neither knows anything nor can do anything." [Bacon, 1620] Empiricism is the ground of knowledge. There will be no sterile speculation.

3.2.1 Idols of the mind

Bacon identifies two key impediments to scientific progress. First, certain prejudices in thinking impede objectivity and, second, efficient knowledge discovery requires a formal method with which to approach and comprehend Nature instead of haphazard observation and undisciplined imagination.

Regarding prejudice, Bacon identifies four “idols of the mind.” *Idols of the tribe* are fallacies common to humanity in general that one holds simply by being human. Our observations are necessarily filtered through our senses and our perceptions are necessarily relative to the structure of our minds. Bacon explicitly recognizes the formative role of the human understanding:

> The Idols of the Tribe have their foundation in human nature itself, and in the tribe or race of men. For it is a false assertion that the sense of man is the measure of things. On the contrary, all perceptions as well of the sense as of the mind are according to the measure of the individual and not according to the measure of the universe. And the human understanding is like a false mirror, which, receiving rays irregularly, distorts and discolors the nature of things by mingling its own nature with it. [Bacon, 1620]

Idols of the cave are personal or parochial prejudices. Arguments can be twisted and turned to fit one’s prejudices and data can be selectively sought:

> The Idols of the Cave are the idols of the individual man. For everyone (besides the errors common to human nature in general) has a cave or den of his own, which refracts and discolors the light of nature, owing either to his own proper and peculiar nature; or to his education and conversation with others; or to the reading of books, and the authority of those whom he esteems and admires; or to the differences of impressions, accordingly as they take place in a mind preoccupied and predisposed or in a mind indifferent and settled. [Bacon, 1620]

Idols of the marketplace are fallacies arising from language, specifically, the use of language to communicate ideas; everyday talk and fanciful story telling distort rigorous scientific investigation:

> The Idols of the Marketplace are the most troublesome of all — idols which have crept into the understanding through the alliances of words and names. For men believe that their reason governs words; but it is also true that words react on the understanding; and this it is that has rendered philosophy and the sciences sophistical and inactive. Now words, being commonly framed and applied according to the capacity of the vulgar, follow those lines of division which are most obvious to the vulgar understanding. [Bacon, 1620]

Idols of the theater involve the uncritical acceptance of dogma and popular theories, in part because they are philosophically delightful or satisfy human desire:

> Idols of the Theater, or of Systems, are many, and there can be and perhaps will be yet many more…. For as on the phenomena of the heavens many hypotheses may be constructed, so likewise (and more also) many various dogmas may be set up and established on the phenomena of philosophy. And in the plays of this philosophical theater you may observe the same thing which is found in the theater of the poets, that stories invented for the stage are more compact and elegant, and more as one would wish them to be, than true stories out of history. [Bacon, 1620]

The deleterious effect of the idols on scientific research leads Bacon to desire a universal method that avoids the temptations of the idols. The method he proposes stems from his understanding of causality, which involves a re-examination of Aristotle's four causes.

3.2.2 Forms as law

Bacon agrees with Aristotle that causality is the ground of knowledge; however, he separates Aristotle's four causes as to whether they apply to physics or metaphysics: material and efficient causes to physics, formal and final causes to metaphysics. Bacon does not demarcate science from metaphysics. While he sees no place for final causes in science, his preference for authentic scientific understanding lies with formal causes. He writes,

> It is a correct position that 'true knowledge is knowledge by causes.' And causes again are not improperly distributed into four kinds: the material, the formal, the efficient, and the final…. The efficient and the material (as they are investigated and received, that is, as remote causes, without reference to the latent process leading to the form) are but slight and superficial, and contribute little, if anything, to true and active science…. For though in nature nothing really exists besides individual bodies, performing pure individual acts according to a fixed law, yet in philosophy this very law, and the investigation, discovery, and explanation of it, is the foundation as well of knowledge as of operation. And it is this law with its clauses that I mean when I speak of *forms*…. Now if a man's knowledge be confined to the efficient and material causes (which are unstable causes, and merely vehicles, or causes which convey the form in certain cases) he may arrive at new discoveries in reference to substances in some degree similar to one another, and selected beforehand; but he does not touch the deeper boundaries of things. But whosoever is acquainted with forms embraces the unity of

> nature in substances the most unlike, and is able therefore to detect and bring to light things never yet done. [Bacon, 1620]

Bacon separates himself from Plato by noting that forms do not give existence and only individual bodies exist in Nature. These bodies act according to a fixed law and "investigation, discovery and explanation of it" is the foundation of knowledge. This law, which by Bacon is called a "form," is not within Nature; rather, it is metaphysical and governs Nature. It is in the domain of metaphysics where "true and active science" resides. Knowing the material out of which something comes to be or the source of change for a body's change of motion is "superficial" in comparison to knowledge of form. Efficient and material causes do not touch "the deeper boundaries of things."

Bacon distinguishes physics and metaphysics, and science intersects both, with the more important aspect of science, that being formal cause, lying within metaphysics. While the language of Bacon might appear muddled, one should not overlook the advance in scientific perspective. Bacon drops final cause and regards efficient and material causes as superficial. Suppose we go a bit further than he and drop all reference to efficient and material causes. Then we are left with only what he calls a formal cause. Let us examine this formal "cause." First, it is not within Nature. Second, it represents "true science." Third, it corresponds to a law governing natural behavior. Fourth, it allows the scientist "to detect and bring to light things never yet done." Thus, if we drop the word "cause," drop the appeal to explanation, and drop the characterization of a natural law as being metaphysical, then it would be seen that Bacon has taken a significant step towards modern science: the business of science is to discover natural law. We are not saying that Bacon dropped Aristotle's efficient and material causes, nor that he disagreed with Aristotle regarding explanation, nor that by law he meant anything beyond simple cause and effect, nor that he put aside metaphysics, but we are saying that one can see in his thinking the beginning of the transformation from Aristotelian to modern science.

3.2.3 Experimental design

Bacon desires a method to ascertain scientific knowledge via experiment, not simply abstract reasoning. He recognizes that more is required than Aristotle's unplanned observations. Given that true knowledge rests upon causality, the form of knowledge and its acquirement should conform to the causal relation. Thus, causality becomes inextricably linked to induction: when we observe that event B follows whenever event A is observed, then a cause-and-effect relation is in some (unspecified) sense "logically" induced between A and B. For Bacon, this relation is a formal cause and goes beyond the list of observations to a deeper knowledge of reality. For Bacon, scientific knowledge is causal knowledge and this knowledge is reached by the "logical" process of induction upon observing one event, the effect, repeatedly following the other, the cause, without exception.

Think of billiard ball A repeatedly sent into billiard ball B. Each time, ball B begins to move when hit by ball A, the latter being the efficient cause. For Bacon, a deeper relation, one possessing true scientific knowledge, is induced in the relation that any moving body *A* hitting a stationary body *B* will always result in the stationary body moving. This more general relation about bodies would constitute a formal cause. It is metaphysical and is induced from repeated observations.

Bacon's attempt to form logical machinery to infer law from data was doomed to fail because it involved metaphysical confusion with science and assumed a very simple physical world that somehow conformed to human logical thinking. Nonetheless, his recognition that haphazard observation will not yield the kind of structured observations that lead to knowledge discovery led Bacon to his greatest contribution, articulation of the experimental method:

> There remains simple experience which, if taken as it comes, is called accident; if sought for, experiment. But this kind of experience is no better than a broom without its band, as the saying is — a mere groping, as of men in the dark, that feel all round them for the chance of finding their way, when they had much better wait for daylight, or light a candle, and then go. But the true method of experience, on the contrary, first lights the candle, and then by means of the candle shows the way; commencing as it does with experience duly ordered and digested, not bungling or erratic, and from it educing axioms, and from established axioms again new experiments. [Bacon, 1620]

Looking back over a century and a half since the *New Organon*, in the *Critique of Pure Reason*, Immanuel Kant commented on the essence and importance of Bacon's call for rational experimental design:

> It is only when experiment is directed by rational principles that it can have any real utility. Reason must approach nature with the view, indeed, of receiving information from it, not, however, in the character of a pupil, who listens to all that his master chooses to tell him, but in that of a judge, who compels the witnesses to reply to those questions which he himself thinks fit to propose. To this single idea must the revolution be ascribed, by which, after *groping in the dark* for so many centuries, natural science was at length conducted into the path of certain progress. [Kant, 1781]

Mind is inextricably embedded in the experimental method. Scientific knowledge is not obtained via abstractions conjured up in thinking isolated from data, nor from the blind collection of data absent a driving mental construct; rather, it is a product of both reason and data, the latter being obtained according to a plan of reason and then digested by reason in its theorizing. Bacon states the matter metaphorically:

> Those who have handled sciences have been either men of experiment or men of dogmas. The men of experiment are like the ant, they only collect and use; the reasoners resemble spiders, who make cobwebs out of their own substance. But the bee takes a middle course: it gathers its material from the flowers of the garden and of the field, but transforms and digests it by a power of its own. [Bacon, 1620]

Kant beautifully summarizes the ants and spiders in the *Critique of Pure Reason*: "Perception without conception is empty; conception without perception is blind." This insight has been validated many thousands of times during the progress of science; nevertheless, there are still many more ants and spiders than there are bees.

3.3 Galileo: The Birth of Modern Science

While Francis Bacon was formulating the experimental method in England, in Italy, besides making contributions to physics and astronomy, Galileo Galilei (1564–1642) was articulating a behavior-oriented mathematical formulation of scientific theory independent of causality. Modern science arrives with Galileo, because he recognizes that science should concern itself solely with quantifiable relations among phenomena. Galileo does not deny causality; rather, he brackets it—sets it aside—and proceeds with the mathematical description of relations between phenomena. In *Dialogues Concerning Two New Sciences*, Galileo puts these words into the mouth of Salviati:

> The present does not seem to me to be an opportune time to enter into the investigation of the cause of the acceleration of natural motion, concerning which various philosophers have produced various opinions, some of them reducing this to approach to the center; others to the presence of successively less parts of the medium [remaining] to be divided; and others to a certain extrusion by the surrounding medium which, in rejoining itself behind the moveable, goes pressing and continually pushing it out. Such fantasies, and others like them, would have to be examined and resolved, with little gain. For the present, it suffices our Author that we understand him to want us to investigate and demonstrate some attributes of a motion so accelerated (whatever be the cause of its acceleration) that the momenta of its speed go increasing, after its departure from rest, in that simple ratio with which the continuation of time increases, which is the same as to say that in equal times, equal additions of speed are made. [Galileo, 1638]

There would be "little gain" in examining the kind of "fantasies" put forth by philosophers to explain acceleration in terms of causality. It is more beneficial to "investigate and demonstrate some attributes of motion." Galileo does not deny causality; rather, he rejects it as a requirement for knowledge, thereby radically breaking with Aristotle.

Galileo is dissatisfied with words, Bacon's idols of the marketplace. These constitute ersatz knowledge, the result being both an illusion of knowledge and an impediment to actual knowledge owing to satisfaction with empty phrases. In *Dialogue Concerning the Two Chief World Systems*, when the Aristotelian Simplicio comments that everyone knows that bodies fall on account of gravity, Salviati responds,

> You are wrong, Simplicio; you should say that everyone knows that it is called 'gravity.' But I am not asking you for the name, but the essence of the thing. Of this you know not a bit more than you know the essence of the mover of the stars in gyration. We don't really understand what principle or what power it is that moves a stone downwards, any more than we understand what moves it upwards after it has left the projector, or what moves the moon round. [Galileo, 1632]

Observation shows that bodies fall, and perhaps something called "causality" is operating here, but to simply say that there is a cause and to name it provides no knowledge. A name tells us nothing about the object being named or if such an object exists. Moreover, understanding the power that moves a stone downwards is not a prerequisite for providing a quantitative relation between the stone and the earth. In general, cogitating on words can lead one away from the phenomena rather than towards a characterization of their attributes.

Galileo contends that the book of Nature is written in mathematics. He writes,

> Philosophy is written in this grand book, the universe, which stands continually open to our gaze. But the book cannot be understood unless one first learns to comprehend the language and read the letters in which it is composed. It is written in the language of mathematics, and its characters are triangles, circles, and other geometric figures without which it is humanly impossible to understand a single word of it; without these, one wanders about in a dark labyrinth. [Galileo, 1623]

In arguing that mathematics is the language of the universe, Galileo mixes metaphysics with science. While science may be written in mathematics, that is, grounded in human epistemology, the extension of human epistemology to the actual nature of Nature lies outside the realm of scientific knowledge and constitutes a metaphysical argument.

3.3.1 Trial of Socrates

There have been two great trials pertaining to science and philosophy: Socrates in 399 BC at the beginning of the greatest period of ancient Greek philosophy and Galileo in 1616 at the dawn of modern science. Tension between science and society exists because political forces are often unhappy with a scientific theory or wish to co-opt scientists to support a pseudo-scientific theory favorable to some ideology. Thus, scientists can find themselves under pressure to keep quiet or bend the epistemological rules. While both political interference with science and acquiescence to such interference certainly deserve disapprobation, it should be recognized that science and philosophy have the potential to threaten the state.

The Peloponnesian War between the Athenian empire and the Spartan led Peloponnesian League lasted from 431 BC to 404 BC and ended with the defeat of Athens. Sparta imposed an Athenian government run by the "Thirty Tyrants." Their rule was brutal with many opponents being killed and they were ousted after ruling for little more than a year. This was the atmosphere in 399 BC when Socrates was brought before an Athenian court on the dual charges of corrupting the youth and impiety. Athens was under dire threat.

In essence, the trial concerned the relationship of philosophy (science) to the state. Where does the freedom to speak cross a line that the state cannot tolerate? It would be facile to argue that there is no line. One cannot expect the freedom to call for the assassination of the king. In effect, Socrates was accused of undermining the viability of the civil society. He was impious because he did not acknowledge the gods of the city. He claimed the right to let his own reason be the arbiter and that he be allowed to promulgate his views. We see again the problem of al-Ghazali: should philosophy be allowed to undermine the moral order, and ultimately the civil order? This is a recurring theme and in 399 BC the problem was exacerbated by the imminent danger faced by Athens.

Plato understands the dilemma. In the *Apology* the case is made for Socrates and in the *Crito* it is made for the state. Socrates is clearly guilty and does not deny it, arguing only that he is following the direction of "the god"—not a god of the city. The profound issue is not whether Socrates is guilty but where the line prohibiting philosophic and scientific enquiry should be drawn, or should there be a line at all? Would not any line stifle free enquiry and ultimately distort human knowledge of Nature? And would it not be inherently fuzzy, thereby inviting abuse by those whose ambitions might be frustrated by such knowledge?

3.3.2 Trial of Galileo

The trial of Galileo is often misunderstood and misrepresented in the popular media. On March 20, 1615, Tommaso Caccini delivered to the Congregation of the Holy Office (the Inquisition) a letter stating that the Copernican heliocentric theory is incompatible with the Bible and informing the Inquisition that Galileo had advocated the theory. Later in the year, Cardinal Robert Bellarmine explained the Church's position at the time:

> To say that on the supposition of the Earth's movement and the Sun's quiescence all the celestial appearances are explained better than by the theory of eccentrics and epicycles is to speak with excellent good sense and to run no risk whatever. Such a manner of speaking is enough for a mathematician. But to want to affirm that the Sun, in very truth, is at the center of the universe and only rotates on its axis without going from east to west, is a very dangerous attitude and one calculated not only to

> arouse all Scholastic philosophers and theologians but also to injure our holy faith by contradicting the Scriptures…. If there were a real proof that the Sun is in the center of the universe,…then we should have to proceed with great circumspection in explaining passages of Scripture which appear to teach the contrary. [Bellarmine, 1955]

Bellarmine is clear: should Galileo take the hypothetical view in Copernicus' preface, then he would be at no "risk whatever;" however, to affirm the theory as true would be "very dangerous." But even should Galileo insist on the truth of the heliocentric theory, if there were "real proof," then the Church might have to change her position. Bellarmine's viewpoint was communicated to Galileo by Piero Dini in a letter stating, in reference to Copernicus, that "with a similar precaution you may at any time deal with these matters."

Galileo decided to play a perilous game with the Inquisition. Still in 1615, he wrote, "I mean to submit myself freely and renounce any errors into which I may fall in this discourse through ignorance of matters pertaining to religion.... But I do not feel obliged to believe that that same God who has endowed us with sense, reason, and intellect has intended us to forgo their use." [Galileo, 1615] He will admit to errors owing to ignorance of religion, but theology must be wrong when it contradicts reason. Like Socrates, he will not submit to the state in matters of religion when his reason disagrees with the state.

The Inquisition responded: "The view that the sun stands motionless at the center of the universe is foolish, philosophically false, and utterly heretical, because [it is] contrary to Holy Scripture. The view that the earth is not the center of the universe and even has a daily rotation is philosophically false, and at least an erroneous belief." [Congregation of the Holy Office, 1616] Whereas the heliocentric theory had been acceptable as philosophy, following Galileo's challenge that compromise was withdrawn.

On February 26, 1616, the Inquisition ordered Galileo "to abstain altogether from teaching or defending the said opinions and even from discussing them." Galileo submitted to the decree and avoided prison. But he never really accepted it and continued to advocate the heliocentric theory, albeit, with less fanfare. Eventually, on June 22, 1633, the Inquisition pronounced Galileo guilty of heresy and disobedience. He spent three days in prison and was released by order of Pope Urban VIII. In December, he was allowed to return to his own villa, still a prisoner and confined to his own property, but free to continue his research and host visitors.

Scientifically, Galileo's position was specious. He was affirming truth when the new science that he was in the process of creating, one absent causality, had yet to establish a theory of knowledge. Moreover, he was supporting Copernicus' theory rather than Kepler's theory, of which he was well aware. The Inquisition's position lacks even a semblance of plausibility. Based on passages in the Bible and the theological desire to have man situated at the center of the universe, it rejected a scientific theory based on empirical observation in favor of another theory that possessed no discernable empirical advantage over the one it was rejecting. As in the Athens of Socrates, the political situation in Europe was not conducive to tolerance. Most of the ordeal between Galileo and the Church took place during the Thirty Years War in Europe, which lasted from 1618 to 1648, during which time great swaths of territory were laid waste and a large portion of the population died from war, famine, and disease.

3.4 Isaac Newton: *Hypotheses Non Fingo*

Owing to our focus on epistemology, we go directly to Isaac Newton (1642–1727), who in 1687 published the greatest scientific work and one of the Durants' three most important events in modern European history, *Philosophiæ Naturalis Principia Mathematica* (*Mathematical Principles of Natural Philosophy*). Newton not only satisfies Galileo's requirement of a strictly mathematical theory; he also formulates the theory of motion in three compact statements from which the quantitative behavior of bodies in motion can be developed via the infinitesimal calculus.

Newton's three laws of motion:

I. Every body continues in its state of rest, or of uniform motion in a straight line, unless it is compelled to change that state by forces impressed upon it.
II. The change of motion is proportional to the motive force impressed, and is made in the direction of the straight line in which that force is impressed.
III. To every action there is always opposed an equal reaction.

Using the laws of motion and the inverse square law, Newton mathematically derived a planetary theory. He grounded his theory in laws that generate an observable theory. The theory is not specific to the planets, as is the strictly descriptive theory of Kepler. The laws are general and apply to planets, billiard balls, and stars.

The epistemology of modern science begins to mature with Newton. The structure is relational, its form is mathematical, and its propositions are ideal, in the sense that relations between phenomena are characterized abstractly with the recognition that in practice they will be affected by other conditions. The theory is connected to the phenomena via its predictive capacity.

Consider gravity. Newton formulates a mathematical law of gravitation that relates distance, mass, and acceleration. The gravitational law is mathematical, relational, idealized insofar as when put into practice it ignores confounding effects such as air resistance, and it can be related to phenomena via experiment. The gravitational law mathematically characterizes a relation in such a way that the relation can be used to make predictions, thereby providing a means for validation and application. The mathematical structure represents a precise, intersubjective, and operational form of knowledge.

The gravitational law contains no reference to some physical process behind the relations and there is no mention of a cause of acceleration. Regarding causality, Bertrand Russell (1872–1970) states,

> In the motions of mutually gravitating bodies, there is nothing that can be called a cause, and nothing that can be called an effect; there is merely a formula. Certain differential equations can be found, which hold at every instant for every particle of the system, and which, given the configuration and velocities at one instant, or the configurations at two instants, render the configuration at any other earlier or later instant theoretically calculable…. But there is nothing that could be properly called 'cause' and nothing that could be properly called 'effect' in such a system. [Russell, 1913]

Like Galileo, Newton does not deny causality; he brackets it and formulates knowledge independent of it. Newton signals his intent near the beginning of the *Principia* when he writes, "For I here design only to give a mathematical notion of these forces, without considering their physical causes and seats." [Newton, 1687] Near the end of the *Principia* he leaves no doubt that he is creating a new scientific epistemology:

> Hitherto I have not been able to discover the cause of those properties of gravity from the phenomena, and I frame no hypothesis; for whatever is not deduced from the phenomena is to be called an hypothesis; and hypotheses, whether metaphysical or physical, whether of occult qualities or mechanical, have no place in experimental philosophy. In this philosophy particular propositions are inferred from the phenomena, and afterward rendered general by deduction. Thus it was the impenetrability, the mobility, and the impulsive forces of bodies, and the laws of motion and of gravitation were discovered. And to us it is enough that gravity does really exist, and acts according to the laws which we have explained, and abundantly serves to account for all the motions of the celestial bodies, and of our sea. [Newton, 1687]

"*Hypotheses non fingo*"—"I frame no hypotheses." In three words, Newton changes man's perspective on himself and the universe, a change more profound than the one brought about by Copernicus because it is a fundamental change in what it means to know.

When speaking of gravity, Newton adds,

> But our purpose is only to trace out the quantity and properties of this force from the phenomena, and to apply what we discover in some simple cases as principles, by which, in a mathematical way, we may estimate the effects thereof in more involved cases: for it would be endless and impossible to bring every particular to direct and immediate

> observation. We said, in a mathematical way, to avoid all questions about the nature or quality of this force. [Newton, 1687]

There are two critical points in this statement. First, Newton is “to avoid all questions about the nature” of gravity. As he said earlier, “it is enough that gravity does really exist.” Something exists, but as Galileo had said, we know nothing of its substance—a basic category of Aristotle that now disappears from science. Second, the mathematical system is not meant to include all factors, but is of sufficient predictive power that it can “estimate” effects in a more general setting. Owing to its predictive nature, the mathematical system can be empirically tested independently of the reasoning leading to it.

Galileo and Newton widen the scope of knowledge to include mathematical systems that relate phenomena, while bracketing “questions about the nature” of the phenomena. The physical substance behind the mathematical relations is bracketed so that physical knowledge is constituted by mathematical knowledge, with the proviso that the mathematical knowledge be explicitly related to observations. Neither Galileo nor Newton explicitly deny causality; nevertheless, they engender a radical epistemological transformation by describing relations among phenomena in terms of mathematical formulas independent of causal or physically intuitive explanations that can lead to “fantasies,” to use Galileo’s terminology.

3.5 Determinism

Newton’s theory is deterministic: given an initial state (set of initial conditions) it will evolve so that a unique state is reached at each point in time. If the universe is causal, then its movement through time would be determined, each event caused by some set of events, these having been in turn caused by preceding events, the causal chain moving endlessly backwards and forwards in time. Newton’s determinism is consistent with causality but does not imply causality. As discussed previously, causality plays no role in Newton’s theory.

It was just such causal reasoning that led Aristotle to conclude that there must be a first cause, uncaused, that being God. In *The Leviathan*, Thomas Hobbes (1588–1679) states the implication of causality as it pertains to man’s freedom:

> Because every act of man’s will, and every desire and inclination, proceedeth from some cause, and that from another cause, in a continual chain (whose first link is in the hand of God the first of all causes), they proceed from necessity. So that to him that could see the connection of those causes, the *necessity* of all men’s voluntary actions would appear manifest. [Hobbes, 1651]

The world is a machine governed by law, and so is man, whose desires and actions proceed from necessity. As a consequence, free will is an illusion. Since free will is required for man to be a moral being, he has no moral nature.

Pierre-Simon Laplace (1749–1827), who is among the founders of probability theory and a great physicist, recognizes the uncertainty in making predictions but attributes this uncertainty to ignorance. While he sees the practical need for a probabilistic approach to Nature, he holds on to causality as existing in Nature. In the following famous passage from *A Philosophical Essay on Probabilities* he formulates a complete determinism:

> We ought then to regard the present state of the universe as the effect of its anterior state and the cause of the one which is to follow. Given for one instant an intelligence which could comprehend all the forces by which nature is animated and the respective situation of the beings who compose it—an intelligence sufficiently vast to submit this data to analysis—it would embrace in the same formula the movements of the greatest bodies of the universe and those of the lightest atom; for it, nothing would be uncertain and the future, as the past, would be present in its eyes. [Laplace, 1814]

By conditioning deterministic knowledge on a "sufficiently vast" intelligence, Laplace does not claim that human beings can achieve a completely deterministic theory of Nature; nevertheless, he postulates determinism in Nature based on causality in Nature. This causality is not merely temporal contiguity. His words, "the present state of the universe as the effect of its anterior state and the cause of the one which is to follow," clearly suggest that there is more to cause and effect than anterior to posterior.

Laplace's statement makes it clear that determinism is a metaphysical, not a scientific concept: it concerns a grand issue explaining the universe as a whole. It does not concern this or that scientific principle but a deeper reality governing scientific principles in general. Laplace speaks of an intelligence that can grasp the movements of all bodies, but does not claim that the intelligence exists. Laplace prefaces his determinism with causality but this need not have been the case. He could have hypothesized a vast intelligence that knew all the laws of physics and could at one instant make all the necessary measurements, and that Nature is completely described by these laws.

3.6 Dissenting Voices

Newton's *Principia* leaves us with a science that is both rational and empirical. Reason supplies the laws but they are arrived at and validated empirically. If one rejects either reason or the senses as being too unreliable to serve as a source of knowledge, then science must be rejected. In the allegory of the cave, Plato rejects the empirical as a source of certain knowledge and argues that only reason can provide certain knowledge. This section considers two French philosophers of the first half of the Seventeenth Century, one who distrusts the senses and turns to rationalism, and another who distrusts reason and embraces faith.

3.6.1 René Descartes: *Cogito ergo sum*

René Descartes (1596–1650), French philosopher and mathematician, employed the principle of methodological doubt in his *Meditations on First Philosophy* to arrive at certainty by wiping the slate clean of his prior beliefs, which rest on uncertain grounds, and by thinking of some underlying certainty upon which to ground his beliefs. Such an undertaking would seem to be in accord with Bacon's criticism of the idols of the mind; however, whereas Bacon looks to observation, Descartes rejects observation: "Everything which I have thus far accepted as entirely true and assured has been acquired from the senses or by means of the senses. But I have learned by experience that these senses sometimes mislead me, and it is prudent never to trust wholly those things which have once deceived me." [Descartes, 1641].

Descartes postulates a situation in which he doubts all and only accepts that which cannot be doubted. He does this by distrusting his senses, because these sometimes mislead him and he distrusts all things that have ever deceived him. But he trusts his reason. Whereas Bacon adopts an empiricism filtered by reason, Descartes turns to a strict rationalism.

He assumes the existence of an evil spirit who is using all of his guile and power to deceive him, so that it is possible that all his senses have been put there to trick him. He will assume himself to possess neither hands, nor eyes, nor flesh, nor blood, nor senses, but will assume that he has been tricked into believing that he has all of these. Even in the face of this powerful, tricky, and perpetual deceiver, Descartes concludes,

> There can be no slightest doubt that I exist, since he deceives me; and let him deceive me as much as he will, he can never make me be nothing as long as I think that I am something. Thus, after having thought well on this matter, and after examining all things with care, I must finally conclude and maintain that this proposition: *I am, I exist*, is necessarily true every time that I pronounce it or conceive it in my mind. [Descartes, 1641]

This is the famous "*Cogito ergo sum*" ("I think, therefore I am."). In doubting there is thinking, there must be a thinker doing the doubting. As stated long before by Augustine, "Who doubts that he lives and thinks?… For if he doubts, he lives."

Descartes concludes that he is a thinking being. He writes, "Thought is an attribute that belongs to me; it alone is inseparable from my nature." He goes on to claim that it is inherent in a thinking being that he understands, conceives, affirms, denies, wills, rejects, imagines, and perceives. He argues that these are parts of thinking and it is "obvious that it is I who doubt, understand, and desire."

In the *Meditations*, certainty is not rooted in any kind of concrete existence, be it spiritual or corporeal; instead, it is rooted in the isolated thinking ego. Existence must be demonstrated by a rational proof from within the isolated ego, without recourse to the world in which actual existence takes place.

To prove the existence of God, Descartes invokes a form of the *ontological argument*. The thinker has a clear and distinct idea of God that includes perfection, and existence is a necessary attribute for divine perfection. Descartes conceives of a perfect, existing being. Were that being not to exist, then his mental conception would be in error, and this cannot be since he has a clear and distinct understanding of divine perfection. He writes,

> That which we clearly and distinctly understand to belong to the true and immutable nature of anything, its essence or form, can be truly affirmed of that thing. But after we have with sufficient accuracy investigated the nature of God, we clearly and distinctly understand that to exist belongs to His true and immutable nature. Therefore we can with truth affirm of God that He exists. [Descartes, 1963]

Descartes goes on to argue that, since God has now been proven to exist and He is perfect, God cannot be a deceiver because Descartes' idea of Him includes that He is perfect and Descartes' idea of perfection includes the attribute that a perfect being cannot be a deceiver. Hence, Descartes is not being deceived into believing something exists that does not exist when he has ideas of corporeal objects. Descartes can now re-visit his doubting of ideas originating in his senses.

For Descartes, God's existence depends on his having an idea of Him. Other truths can be reached by his having clear and distinct conceptions. He writes,

> Whenever I restrict my volition within the bounds of my knowledge, whenever my volition makes no judgment except upon matters clearly and distinctly reported to it by the understanding, it cannot happen that I err. For every clear and distinct conception is without doubt something real and positive, and thus cannot derive its origin from nothingness, but must have God for its author — God, I say, Who, being supremely perfect, cannot be the cause of any error — and consequently we must conclude that such a conception or such a judgment is true. [Descartes, 1641]

Ultimately, the ground of truth lies in the thinking being's clarity of thought. Any judgment of Descartes based on a clear and distinct idea cannot be in error.

What if I have a clear and distinct conception that statement *X* is true and Descartes has a clear and distinct conception that *X* is false? Unless Descartes is going to argue that only his clear and distinct conceptions are true, both *X* and not-*X* must be true. As for the ontological argument, which long preceded its use by Descartes, suppose I clearly and distinctly understand that immortality belongs to the true and immutable nature of a cat. *Ipso facto*, cats are immortal.

Descartes' rationalism is anti-scientific because scientific knowledge is rooted in the phenomena and must be tied to it, not do Descartes' clear and distinct ideas. In Bacon's metaphor, Descartes is a spider making cobwebs according to is own fancy. Furthermore, whereas science aims to be inter-subjective, so that concepts can be shared and agreement reached as to why a proposition is acceptable or not acceptable, even though there might not be agreement on whether to accept or not accept, Descartes engages in a radical subjectivism. No one but Descartes can judge the clearness and distinctness of his conceptions.

One might be tempted to dismiss the *Meditations* as an absurd amusement, but this would ignore the enormous impact of Descartes on Western thinking; indeed, during the first two decades of the Twenty-first Century, the view that truth is a private matter based solely on one's internal thoughts has become widespread. Such thinking is anathema to science. A major motivation in the development of scientific epistemology has been to eliminate spider-cobweb thinking.

3.6.2 Blaise Pascal: the eternal silence

Francis Bacon envisioned unending progress as scientific knowledge would allow man to control Nature and extract the benefits. His maxim: "Nature, to be commanded, must be obeyed." Man shall obey Nature to learn her secrets but once they are known he will command her. A utopia will ensue in which scientists provide all the benefits to mankind. Blaise Pascal (1623–1662) had doubts. Looking into the night sky at the dawn of modernity, he remarked, "The eternal silence of those infinite spaces frightens me." Philosopher William Barrett comments that Western civilization is split in two by Pascal's thought: before there was Nature, a gift of God in which man was at home; after, man is homeless and alienated within the cosmos.

Pascal is one of the most subtle thinkers the world has known. His *Pensées*, although a collection of notes and fragments, reveals a mind that cuts everywhere to the quick. He was a scientist and great mathematician. He built the first mechanical calculator and, along with Pierre Fermat, founded the calculus of probabilities. He was among the greatest writers of French prose. Lastly, but not least, he was a defender of faith in the Age of Reason.

Rather than like Descartes extolling the ability of reason to provide certain knowledge or Bacon hoping that a new form of logical reasoning along the lines of the inductive methods presented in the *New Organon* would reveal the causality driving the physical world, Pascal saw reason to be weak and very limited. Sounding like Immanuel Kant almost 150 years later, he argues that reason cannot ground morality, reason cannot grasp the real nature of the world, and reason cannot comprehend God, prove His existence, or prove immortality. Portending the Romantic Period, Pascal exclaims, "The heart has its reasons, which reason does not know."

Pascal puts the deepest question of man before us:

> When I consider the short duration of my life, swallowed up in the eternity before and after, the little space which I fill, and even can see, engulfed in the infinite immensity of spaces of which I am ignorant and which know me not, I am frightened and I am astonished at being here

> rather than there; for there is no reason why here rather than there, why now rather than then. Who has put me here? By whose order and direction have this place and this time been allotted to me? The eternal silence of those infinite spaces frightens me. [Pascal, 1986]

Pascal is not speaking here of rational analysis, propositions, and logical proofs. Perhaps he wrote these lines in the hours after midnight, after having lain in the grass on his back gazing up at the stars on a moonless night. Billions of stars, light years away, appear at every angle above him. He imagines the mass of all these stars measured against his own mass, which at once becomes nothing. He imagines the light years and age of the universe measured against his own time on earth, which is infinitesimal in comparison. Nothing! All of his mathematical and scientific learning, and he knows nothing.

His advice: “Know then, proud man, what a paradox you are to yourself. Humble yourself, weak reason; be silent, foolish nature; learn that man infinitely transcends man, and learn from your Master your true condition, of which you are ignorant. Hear God.” [Pascal, 1670]

So, in the Seventeenth Century, in which science emerges as a colossus to transform man’s thinking and his place in the world, two of the greatest minds of the century demur, one on behalf of reason over observation and the other on behalf of faith over reason. These are two very different messages. Descartes’s extreme rationalism is destructive of science, whereas Pascal is simply warning of the limitations of science

In the *Critique of Pure Reason*, Immanuel Kant sounds a similar warning:

> [Reason] begins with principles, which cannot be dispensed with in the field of experience, and the truth and sufficiency of which are, at the same time, insured by experience. With these principles it rises, in obedience to the laws of its own nature, to ever higher and more remote conditions. But it quickly discovers that, in this way, its labors must remain ever incomplete, because new questions never cease to present themselves; and thus it finds itself compelled to have recourse to principles which transcend the region of experience, while they are regarded by common sense without distrust. It thus falls into confusion and contradictions. [Kant, 1781]

One may wish that science could uncover “the highest principles for explaining the universe,” but it cannot.

Chapter 4
Reflections on the New Science

4.1 Critique of Knowledge

As monumental as it was with respect to man's view of the solar system, his perception of his place in the universe, and his relation to God, the Copernican theory did not structurally differ from Ptolemy's theory. Thus, the Sixteenth Century ended with no significant change in the structure of scientific knowledge or its causal basis, which had been in place for approximately 2000 years. On the other hand, beginning with Kepler's laws, Bacon's experimental method, and Galileo's mathematical epistemology, the Seventeenth Century produced a radical break with the past, its greatest achievement being Newtonian science based on general relational laws that applied to phenomena without requiring reference to strictly physical categories.

Looking back on the Seventeenth Century, Alfred North Whitehead (1861–1947), one the greatest philosophers of the Twentieth Century, commented,

> A brief, and sufficiently accurate, description of the intellectual life of the European races during the succeeding two centuries and a quarter up to our own times is that they have been living upon the accumulated capital of ideas provided for them by the genius of the seventeenth century. The men of this epoch…bequeathed formed systems of thought touching every aspect of human life. [Whitehead, 1990]

It should not be surprising that philosophers in the Eighteenth Century turned their attention to gaining an appreciation of what this "new science" meant, in particular, the relationship of Nature to both man and science, which involves the relationship of science to man—his body, his mind, and his God. The result was a profound critique of knowledge that saw the Eighteenth Century begin with science virtually unchallenged and end with science in a virtual war with feeling.

4.2 John Locke: The Mind as White Paper

John Locke (1632–1704) lived almost his entire life in the Seventeenth Century and published *An Essay Concerning Human Understanding* in 1689. We include him in this chapter for two reasons: first, he published the *Essay* near the end of the Seventeenth Century and after Newton's *Principia* and, second, he is the first of three major empiricists whom we will discuss, Locke followed by George Berkeley and David Hume.

What is empiricism? Typically, it is defined as the theory that all knowledge is derived from sense experience. This definition requires defining knowledge and explaining what it means to be derived. Knowledge can be of many kinds. Here we are working our way towards a modern definition of scientific knowledge. Even more abstruse is what it means to derive knowledge from sense experience. This must somehow characterize the manner in which sensation is processed to arrive at knowledge.

Empiricism may also be defined as the theory that all concepts come from sense experience. This is a bit more general since concepts do not have to represent knowledge. Concepts are called *a posteriori* if they can be applied only on the basis of experience and *a priori* if they can be applied independently of experience. The problem is that these terms are also problematic. Consider the concept triangle. Its definition and properties are all in the mind and so one might argue that the concept triangle is *a priori*; however, an empiricist may claim that the concept triangle has arisen from the experience of physical objects that are essentially triangular so that it is *a posteriori*. We leave these conundrums to philosophers and proceed with a general understanding that an empiricist takes the view that all knowledge is derived from sense experience. This certainly rules out God and immortality.

Regarding his empiricism, in *An Essay Concerning Human Understanding*, Locke writes,

> Let us then suppose the mind to be, as we say, white paper, void of all characters, without any ideas. How comes it to be furnished?... To this I answer, in one word, from experience. In that all our knowledge is founded; and from that it ultimately derives itself. Our observation employed either, about external sensible objects, or about the internal operations of our minds perceived and reflected on by ourselves, is that which supplies our understandings with all the materials of thinking. [Locke, 1689]

To all the subtleties mentioned previously, we can add what is meant by the mind being a "white paper." If the mind is totally void, then how is experience processed? What does the writing on the paper?

Locke breaks the properties we observe into two categories. *Primary qualities* are "utterly inseparable from the body" and are objective. These include solidity, extension, number, and motion. They exist in a substratum ("matter").

Secondary qualities “are nothing in the objects themselves but powers to produce various sensations in us by their primary qualities” and are subjective. These include color, sound, taste, and odor. The separation into primary and secondary properties is an old distinction, essentially adopted by Aquinas, Descartes, Galileo, and Hobbes.

The salient point is that we experience sensations and actually know nothing of the underlying substratum, so that the Aristotelian notion of substance is meaningless. How do we know that matter even exists? Using an empiricist epistemology based strictly on sensation, Locke is driven towards *idealism*, meaning that mind is more fundamental than material and that material objects, insofar as human understanding is concerned, are at least in part products of the mind. If this sounds strange, then think of what Newton has already done: “I frame no hypotheses.” He has abandoned the physical substratum in favor of equations relating quantitative observations.

If all knowledge is derived from sensation, then so too must knowledge of the mind. Thus, if Locke is to carry his reasoning to the bitter end, then just as the existence of matter is brought into question, so too must the existence of the mind itself. The following statement from the *Essay* is a bit convoluted but its prescience of the devastating analysis of David Hume yet to come makes reading it well worth the effort:

> It is evident that, having no other idea or notion of matter, but something wherein those many sensible qualities which affect our senses do subsist; by supposing a substance wherein thinking, knowing, doubting, and a power of moving, etc., do subsist, we have as clear a notion of the substance of spirit, as we have of body; the one being supposed to be (without knowing what it is) the substratum to those simple ideas we have from without; and the other supposed (with a like ignorance of what it is) to be the substratum to those operations we experiment in ourselves within. It is plain then, that the idea of corporeal substance in matter is as remote from our conceptions and apprehensions, as that of spiritual substance, or spirit. [Locke, 1689]

In sum, why should an empiricist sensation-based epistemology leave us with any more certainty regarding the existence of mind than regarding the existence of matter?

4.2.1 Innate principles of thought

Gottfried Wilhelm Leibniz (1645–1716) is one of history’s greatest geniuses. Not only was he a leading philosopher of his time, independently of Newton he discovered the infinitesimal calculus. In fact, the notation employed today is basically that proposed by Leibniz. Contrary to Locke, and anticipating the view of Kant, Leibniz took the position that mind is not a passive receptacle of experience but rather, via its structure, it transforms the data of sensation: “Nothing is in the mind that has not been in the senses, except the mind itself.”

For Leibniz, mind supplies categories of thought and understanding, such as substance, identity, and cause. There are innate principles of thought that develop through experience. Leibniz includes the principle of contradiction and the principle of sufficient reason—"Nothing happens without a reason why it should be so rather than otherwise." For Leibniz, these principles are inherent in the structure of the mind, but only take active form as a person recognizes their operation in his experience. These principles correspond to Kant's notion of *a priori* categories which drive the mind's understanding of Nature. The point is that mind is not completely a clean slate (*tabula rasa*), but that it has an intrinsic operational structure.

4.3 George Berkeley: *Esse Est Percipi*

If all knowledge is derived from the senses, then, comments George Berkeley (1685–1753), there is no reality outside what we have perceived. The primary qualities are as subjective as the secondary qualities. What then is left of matter? Berkeley states, "It is the mind that frames all that variety of bodies which compose the visible world, any one whereof does not exist longer than it is perceived." [Berkeley, 1710] Thus, to be is to be perceived (*esse est percipi*). But what happens if there is no one perceiving? Does the tree crashing in the forest make a sound if there is no one to hear it? But there is a constant perceiver: God. Hence, the external world is not denied, only its materiality. Given Berkeley's arguments, should God not exist, then what?

Like Locke, Berkeley goes on to bring into question the existence of mind. In his *Three Dialogues* (1713), Hylas states,

> You admit nevertheless that there is spiritual substance, although you have no idea of it, while you deny there can be such a thing as material substance, because you have no notion or idea of it…. It seems to me that according to your own way of thinking, and in consequence of your own principles, it should follow that you are only a system of floating ideas, without any substance to support them. Words are not to be used without a meaning. And as there is no more meaning in spiritual substance than in material substance, the one is to be exploded as well as the other. [Berkeley, 1713]

At this point Berkeley demurs and in the *Dialogues* Phylonous rejoins Cartesian-like that he is aware of his own consciousness. Thus, mind is saved, but only momentarily, since Hume will reject the rejoinder.

Are we to take any of this seriously? Yes, if we are concerned about scientific knowledge. In the Twentieth Century, implications of the subtleties introduced by the Seventeenth Century empirical grounding of science, which necessarily include issues regarding human sensation and the existence of objects external to perception, will become clear. In the Introduction to the 1957 Dover Edition of Erwin Schrödinger's *Science Theory and Man*, James Murphy writes,

> The trend of theoretical physics today, in its search for a definite epistemological standpoint, is somewhat in the nature of a pilgrimage to the Cathedral of Cloyne.… The key to much of what Schrödinger writes in the following chapters, about the difficulties of the epistemological problem in quantum mechanics as a whole and especially in wave mechanics, will be found in Berkeley. [Murphy, 1957]

4.4 David Hume: Reason Is Humbled

When Galileo and Newton bracket causality, they not only posit non-causal knowledge, they also permit themselves the luxury of not addressing the meaning of causality. In particular, if we focus on Bacon's perspective, then there is a temporal aspect to causality in that the cause occurs prior to the event and this temporality plays a key role in Bacon's proposed inductive method. David Hume (1711–1776) raises a crucial epistemological question: Are a cause and its effect merely related via temporal priority, with the cause prior to the effect, or is there more than temporal contiguity? To wit, is there something that touches "the deeper boundaries of things," as Bacon would have it? Is there a necessary connection between the cause and the effect? Hume argues that in using the phrase "cause and effect," we mean the latter.

4.4.1 The ghost in the Galilean brackets

In *An Enquiry Concerning Human Understanding* (1751), Hume writes,

> When one particular species of events has always, in all instances, been conjoined with another, we make no longer any scruple of foretelling one upon the appearance of the other, and of employing that reasoning, which alone can assure us of any matter of fact or existence. We then call one object, Cause; and the other, Effect. We suppose that there is some connexion between them; some power in the one, by which it infallibly produces the other, and operates with the greatest certainty and strongest necessity. [Hume, 1751]

Do repeated conjoined observations warrant the supposition of a necessary connection? Is there a ground in reason or an empirical ground for judging there to be a necessary connection? Hume states emphatically that there is no such ground. Belief in causality rests not on reason, but on habit. In one of the key epistemological passages, he writes,

> But there is nothing in a number of instances, different from every single instance, which is supposed to be exactly similar; except only, that after a repetition of similar instances, the mind is carried by habit, upon the appearance of one event, to expect its usual attendant, and to believe that it will exist. This connexion, therefore, which we *feel* in the mind, this customary transition of the imagination from one object to its usual

> attendant, is the sentiment or impression from which we form the idea of power or necessary connexion. Nothing farther is in the case. Contemplate the subject on all sides; you will never find any other origin of that idea. This is the sole difference between one instance, from which we can never receive the idea of connexion, and a number of similar instances, by which it is suggested. The first time a man saw the communication of motion by impulse, as by the shock of two billiard balls, he could not pronounce that the one event was *connected*: but only that it was *conjoined* with the other. After he has observed several instances of this nature, he then pronounces them to be *connected.* What alteration has happened to give rise to this new idea of *connexion?* Nothing but that he now *feels* these events to be *connected* in his imagination, and can readily foretell the existence of one from the appearance of the other. When we say, therefore, that one object is connected with another, we mean only that they have acquired a connexion in our thought. [Hume, 1751]

In *A Treatise of Human Nature* (1738), Hume states,

> [The] supposition that the future resembles the past is not founded on arguments of any kind, but is derived entirely from habit, by which we are determined to expect for the future the same train of objects to which we have been accustomed.… All our reasonings concerning causes and effects are derived from nothing but custom and belief is more properly an act of the sensitive than of the cogitative part of our nature. [Hume, 1738]

The sticking point is necessity. In the *Treatise*, Hume writes, “From the mere repetition of any past impression, even to infinity, there never will arise any new original idea, such as that of a necessary connexion; and the number of impressions has in this case no more effect than if we confined ourselves to one only.” [Hume, 1738] Repetition may lead to increased expectation, but not necessity—and certainly not to some deeper relationship. Induction does not depend upon causality; in fact, it is the opposite. Belief in causality is itself an unwarranted leap from repeated observations.

The implications of this conclusion are immense. If, as Aristotle and Bacon believed, scientific knowledge is knowledge of causes, and if causality rests on habit and custom, then the ground of scientific knowledge is brought into question. If, as Hume argues, the concept of a necessary connection between phenomena is subjective, then does not this entail the subjectivity of scientific knowledge?

Hume does not miss this point. Regarding his conclusion that the connection between cause and effect is arrived at by habit and exists only in human thought, in the *Enquiry*, he writes,

> For surely, if there be any relation among objects which it imports to us to know perfectly, it is that of cause and effect. On this are founded all our reasonings concerning matter of fact or existence. By means of it alone we attain any assurance concerning objects which are removed from the present testimony of our memory and senses. The only immediate utility of all sciences, is to teach us, how to control and regulate future events by their causes. Our thoughts and enquiries are, therefore, every moment, employed about this relation: Yet so imperfect are the ideas which we form concerning it, that it is impossible to give any just definition of cause, except what is drawn from something extraneous and foreign to it. Similar objects are always conjoined with similar. Of this we have experience. [Hume, 1751]

In these few words, Hume unsettles the foundations of scientific knowledge. If all reasoning concerning matter of fact or existence is founded on causality and the utility of all sciences is to control nature through the regulation of events via their causes, and if causality is simply a product of habit, then scientific understanding rests on habit, or custom, not on objective physical relations.

All reasoning concerning matter of fact is not founded on causality, and Hume should have been aware of this. While he may have shown there to be nothing of consequence inside the brackets that Galileo and Newton put aside, his skeptical assault does nothing to undercut the mathematical-experimental structure of modern science as conceived by its founders. Their scientific theories do not rest upon causality. Nevertheless, in showing that the brackets contain a ghost—at least insofar as causality represents some intrinsic physical reality—Hume deals a severe blow to the human desire for certainty.

Einstein writes, “Man has an intense desire for assured knowledge. That is why Hume's clear message seems crushing: the sensory raw material, the only source of our knowledge, through habit may lead us to belief and expectation but not to the knowledge and still less to the understanding of lawful relations.” [Einstein, 1944b]

4.4.2 Modernity arrives

Hume forever buried the Aristotelian concept of science, and he fundamentally went beyond Galileo and Newton, who recognized that his mathematical theories of science are idealized and can only “estimate” actual behavior. When Hume wrote, “the mind is carried by habit, upon the appearance of one event, to expect its usual attendant,” he made the monumental shift from causality to expectation, thereby recognizing that scientific statements are inherently probabilistic; indeed, in the *Enquiry*, the section dealing with the fundamental issues surrounding causality is entitled, “Of the Probability of Causes.”

Modernity fully arrives with Hume (and not just in science). He does not bracket causality as a scientific category; he dismisses it as a scientific category altogether by showing that it has no grounding in reason or in Nature, at least insofar as is empirically discernable. Necessary connections are subjective impressions, not objective relations. Observations lead to expectation, a probabilistic category, not to certainty. Scientific certitude is a fiction, a product of a leap of thought.

Two centuries after Hume's *Treatise*, Erwin Schrödinger wrote, "It can never be decided experimentally whether causality in Nature is 'true' or 'untrue.' The relation of cause and effect, as Hume pointed out long ago, is not something that we find in Nature but is rather a characteristic of the way in which we regard Nature." [Schrödinger, 1957]

Having eliminated causality and weakened scientific knowledge, Hume was not done. Whereas Locke and Berkeley had toyed with the eradication of mind but did not pursue it, Hume was not so hesitant. In the *Treatise* he wrote,

> That which we call a mind is nothing but a heap or collection of different perceptions, united together by different relations, and supposed, though falsely, to be endowed with a perfect simplicity and identity…. The mind is a kind of theatre, where several perceptions successively make their appearance; pass, repass, glide away, and mingle in an infinite variety of postures and situations. There is properly no *simplicity* in it at one time, nor *identity* in different [times], whatever natural propension we may have to imagine that simplicity and identity. The comparison of the theatre must not mislead us. They are the successive perceptions only that constitute the mind. [Hume, 1738]

There is no connecting mind. Experience is a succession of atomistic sense impressions disconnected from each other. The mind is nothing but a bundle of perceptions. Berkeley had eliminated matter; Hume dispenses with mind.

Why did the Age of Reason not lead to clarity and certainty? For Hume the answer was obvious if only we be brutally honest: "Reason is and ought only to be the slave of the passions." The landscape was clear for the Romantic Period, which only awaited the arrival of Jean-Jacques Rousseau, a few years hence.

If reason is a slave to the passions, how can it support religion and morality? Hume does not temporize. Sounding a bit like Augustine, in the *Treatise* he writes, "Belief is more properly an act of the sensitive than of the cognitive part of our natures." Since morality is also thrown back on the passions, like faith, it too is subjective. Hume writes, "We tend to give the name of virtue to any quality in others that gives us pleasure by making for our advantage, and to give the name of vice to any human quality that gives us pain." [Hume, 1738]

Causality, reason, scientific certainty, metaphysics, faith, and morality—all are slain by Hume's dialectical scalpel. Surely such carnage would generate a titanic reaction. And it did—Immanuel Kant.

4.5 Immanuel Kant: Critique of Reason

In his *Prolegomena to Any Future Metaphysics* (1783), Immanuel Kant (1724–1804) tells us whose thinking interrupted his ordered life as a philosopher and astronomer in Königsberg and galvanized him into action: "I freely admit that the remembrance of *David Hume* was the very thing that many years ago first interrupted my dogmatic slumber and gave a completely different direction to my researches in the field of speculative philosophy." [Kant, 1783] Now awoken, he would counter Hume's skepticism on all fronts and in doing so become the greatest philosopher of modernity. In the process he would write three celebrated critiques: the *Critique of Pure Reason* (1781), the *Critique of Practical Reason* (1788), and the *Critique of Judgment* (1790). Our main interest is with the first critique because of its strong focus on scientific epistemology; however, we will consider the second critique to understand Kant's notion of practical reason and his grounding of morality outside of experience. The *Prolegomena* is to a large extent a shortened and somewhat easier to read version of the first critique.

This section is difficult to read because Kant is difficult and because it will bring many readers into areas of thinking far outside where they have heretofore ventured. For motivation, we begin with a quote by Arthur Schopenhauer (1788–1860) from his classic work, *The World as Will and Representation*:

> Kant's teaching produces a fundamental change in every mind that has grasped it. This change is so great that it may be regarded as an intellectual rebirth. It alone is capable of really removing the inborn realism which arises from the original disposition of the intellect.... The mind undergoes a fundamental undeceiving, and thereafter looks at things in another light.... On the other hand, the man who has not mastered the Kantian philosophy, whatever else he may have studied, is, so to speak, in a state of innocence; in other words, he has remained in the grasp of that natural and childlike realism in which we are all born. [Schopenhauer, 1818]

As brought home by quantum mechanics in the first half of the Twentieth Century, natural realism is a powerful impediment to the progress of science.

4.5.1 Categories of the understanding

The linchpin of Hume's analysis is his elimination of causality. Kant would have to re-establish causality in a way that would not be susceptible to Hume's arguments. Recall that for an empiricist all knowledge is *a posteriori*, meaning that it is derived from sense experience. Kant concurs with this empiricist view up to a point. He accepts that knowledge begins with sensations (stimulations of the senses) but insists that these are at once transformed by the mind to form perceptions (mental objects) that are conceptually organized by the mind's *categories of the understanding*, which are part of its structure (recall Leibniz). The categories are *a priori* because they are intrinsic to the structure of the mind and therefore exist prior to experience.

In this way, Kant defines pure reason: "The faculty of knowledge from *a priori* principles may be called pure reason, and the general investigation of its possibility and bounds the critique of pure reason." [Kant, 1790] Pure reason concerns *a priori* knowledge, and the examination of the possibility and limits of pure reason constitute its critique. *Pure theoretical (speculative) reason*, the subject of the first critique, employs the categories of the understanding, and its application is limited to experience.

Kant agrees with Hume that the principle of causality is not a product of reason. In the *Prolegomena*, he writes, "[Hume] justly maintains that we cannot comprehend by reason the possibility of causality, that is, of the reference of the existence of one thing to the existence of another, which is necessitated by the former." [Kant, 1783] However, whereas for Hume habit underlies causality, for Kant, causality is a category of the understanding. It is a form imposed on phenomena by the nature of the human mind. The mind imposes forms on the data of sensation, and scientific knowledge is limited by these forms. The way things appear, such as being spatially coordinated and connected by causality, are due to subjective *a priori* conditions for knowledge. One cannot know things apart from the manner in which they conform to these *a priori* mental forms.

Of the categories of the understanding, including causality, in the *Critique of Pure Reason*, Kant writes,

> Conceptions of objects in general must lie as *a priori* conditions at the foundation of all empirical cognition; and consequently, the objective validity of the categories, as *a priori* conceptions, will rest upon this, that experience (as far as regards the form of thought) is possible only by their means. For in that case they apply necessarily and *a priori* to objects of experience, because only through them can an object of experience be thought. [Kant, 1781]

The last line is the crux: only through the categories can an object of experience be thought.

The mind, in its very structure, imposes causality on our experiences as a prior condition for thinking about the experiences. In the *Prolegomena*, Kant writes, "We ourselves introduce that order and regularity in the appearance which we entitle 'Nature.' We could never find them in appearances had we not ourselves, by the nature of our own mind, originally set them there." [Kant, 1783]

Kant's argument imposes causality upon the phenomena we experience but not on the *things-in-themselves* that underlie the phenomena, the *noumena*, as he calls them, or what we might refer to as reality. We cannot experience the things-in-themselves because they lie outside our sense experience. Kant asserts the existence of things-in-themselves, which for a strict empiricist like Hume cannot be asserted. Kant does not ascribe causality to the things-in-themselves, only to the phenomena. The mind imposes causality on the phenomena as a condition of thinking about them, but the categories of the understanding apply only to phenomena, not to noumena (reality beyond experience). For Aristotle causality is in Nature; Kant moves it to the mind.

Reasoning in terms of the categories can yield certain conclusions because they cannot be contradicted by experience since they are prior to experience;

however, pure theoretical reason is limited by the categories and the categories are applicable only to the phenomena. Proofs of the existence of God are out—a conclusion regarding a first cause would have to apply the category of causality outside the phenomena and therefore would be fallacious, but proofs about God's nonexistence are also out. Hume's attack on causality is circumvented because science is not about the noumena; it is about the phenomena, and there causality is imposed by the understanding. Metaphysics is possible because its subject matter consists of the categories themselves. Mind can study mind, insofar as the categories are concerned.

Among Kant's categories, causality is a category of relation, between cause and effect. Surely the mind relates events. But if there is contiguity between a prior event *A* and a posterior event *B*, then why insist that the mind imposes the category of causality as the relation between them? If causality is more than mere temporal contiguity, then the category seems to say that the mind imposes the belief that there is some occult connection, precisely the notion that Newton brackets and Hume rejects as having no logical or empirical foundation. Hume has already seen that the functional category of understanding is expectation. Observation of event *A* leads one to expect event *B*. Hume sees correctly that expectation is a probabilistic concept. There is simply no empirical or logical reason to raise the idea of causality. If experience shows that event *A* tends to precede event *B*, or even if in our experience event *A* has always preceded event *B*, then why go beyond saying that upon observation of event *A* we expect to observe event *B*? Hume recognizes that there is no empirical or logical reason for introducing a category beyond expectation. What he fails to see, and what would await the Twentieth Century, is the manner in which expectation would be incorporated into a rigorous mathematical theory of probability and how scientific knowledge would be constituted in a probabilistic framework.

Kant's basic position is that mind imposes categories on the way in which Nature is humanly understood. He agrees with Hume that causality cannot be grounded in Nature, but argues that it is more than habit because, in conjunction with other categories of the understanding, it is imposed upon experience. One need not agree with Kant that the categories lie in the domain of metaphysics, in the sense that they "determine the whole range of the pure reason, in its limits as well as in its content, completely according to universal principles." Yet, the point remains that human experience does not arrive qua experience; rather, as human experience it arrives via the senses and the mind. The mind imposes connectivity upon events. For Hume, there is no mind to organize successive perceptions into a coherent whole because the perceptions, themselves, "constitute the mind." Kant puts mind, as an organizing and connecting entity, prior to experience.

As for causality, although it is not a scientific category, humans do tend to apply it to events in their ordinary understanding. While Kant disagrees with Newton when he imposes a subjective form of causality on scientific thinking to replace the objective form discredited by Hume, at minimum, his insistence on causality being intrinsic to human understanding possesses considerable merit.

In arguing that the application of causality lies at the level of the phenomena, Kant is making a second, fundamental point: whatever ultimately lies behind the phenomena is outside the domain of science. A strict empiricist like Hume dogmatically asserts that one cannot speak of anything lying behind the phenomena. Kant argues otherwise and, in doing so, is more in line with Newton, who believes that gravity exists, although he can say nothing about it except what is revealed by the mathematical formulae expressing phenomenal relations. Insofar as science is concerned, Galileo, Newton, and Kant bracket physical substance, but among the three, Kant does not bracket causality. He places it in a different place—in the mind, but not as Hume would have it, as habit, but as a prior condition for experience.

The differing views of Hume and Kant on causality lead to two fundamentally different perspectives on the structure of scientific propositions. For Hume, science is intrinsically probabilistic, so that scientific statements are framed in terms of probabilities; for Kant, causality leads to determinism. Given the accuracy of predictions resulting from Newtonian mechanics, whose equations are deterministic, it is easy to see that, even if one were to disagree with Kantian epistemology, he might still reject Hume's probabilistic interpretation and remain a determinist, agreeing with Laplace that observed variation is due to measurement error or ignorance of deeper laws, which when discovered would eliminate uncertainties.

4.5.2 The transformation of human reason

We started out this section with a quote from Arthur Schopenhauer to the effect that Kant ended the human period of naïve realism. Let us say that Kant, reflecting on the scientific events from Bacon and Galileo through Newton and on into the Eighteenth Century recognized the massive role of mind in the new science. He was not primarily about building an idealistic epistemology in which objects are a product of the mind; rather, his idealism resulted from his assessment of his empiricist predecessors, especially Hume.

In *The Illusion of Technique*, William Barrett writes,

> Kant…has more than a century of the new science to reflect upon, and he is the first philosopher to understand what has happened. The whole of his *Critique of Pure Reason* is not primarily an attempt to set up a system of idealistic philosophy; it is the effort, stubborn and profound, to grasp the meaning of the new science and its consequences for human understanding generally…. What has happened is nothing less than the transformation of human reason itself. [Barrett, 1979]

Barrett argues that the key to the scientific revolution is that the scientist no longer tries to conform his understanding to haphazard data; rather, his reason becomes "legislative of experience," to the extent that concepts are no longer expected to be realized in Nature but instead are to dictate how the facts are to be measured. Kant, he claims, is the first person to recognize the significance of this change. Barrett writes,

> What does Galileo do? He does not turn to the 'irreducible and stubborn' facts; rather, he sets up a concept [inertia] that can never be realized in actual fact…. Rationalism does not surrender here to the brute facts. Rather, it sets itself over the facts in their haphazard sequence; it takes the audacious step of positing conditions contrary to fact, and it proceeds to measure the facts in the light of these contrafactual conditions. Reason becomes 'legislative of experience'—this was the decisive point that Kant's genius perceived as the real revolution of the new science. [Barrett, 1979]

Recall Kant's words: "Reason must approach nature…in the character…of a judge, who compels the witnesses to reply to those questions which he himself thinks fit to propose."

4.5.3 The moral philosopher

Kant's second goal is to rescue the moral law from Hume's skepticism, which had left morality as nothing more than subjective desire. Our interest being science, for most philosophers their moral philosophy would be irrelevant, but with Kant this would leave a very wrong impression of this thinking, especially because his moral theory depends on the limitations he has imposed upon the domain of application for theoretical reason. In the preface to the second edition of the *Critique of Pure Reason*, Kant writes, "I have found it necessary to deny knowledge [of things-in-themselves] in order to make room for faith." In addition, Kant's role in the transformation of the Age of Reason to the Romantic Period would be completely missed, a transformation that continues to have major impact today, including a significant detrimental influence on science.

To recover the moral order requires that Kant establish human freedom in the moral sphere conditioned on causality being a category of the understanding, which has as a consequence a deterministic understanding of phenomena. His solution is a duality. As phenomena, human actions are viewed in the light of cause and effect, so that the necessary condition for moral action, freedom, does not exist; however, causality and its consequent elimination of moral action only apply to the phenomenal world because that is the world experienced through the categories of the understanding. Causality does not apply to the noumenal world, and freedom resides therein.

Essentially, Kant wants to show that the moral law is *a priori*, that it is universal and does not depend upon experience. Whereas pure theoretical reason applies to phenomena, *pure practical reason* applies to action, which in all cases (at least for Kant) has a moral dimension. As Kant had flipped causality from being a part of Nature to being a condition of experiencing Nature, he now flips morality as emanating from God to emanating from the nature of man. In the *Critique of Practical Reason*, he famously writes,

> Two things fill the mind with ever new and increasing admiration and awe, the oftener and the more steadily we reflect on them: the starry heavens above and the moral law within. I have not to search for them and conjecture them as though they were veiled in darkness or were in the transcendent region beyond my horizon; I see them before me and connect them directly with the consciousness of my existence. [Kant, 1788]

The moral law is immediate, not a matter of reflection. Kant feels it as directly part of his existence.

The moral law does not derive from experience: it is *a priori*. It is not a collection of prudent rules to facilitate social cohesion. It is universal and, like the categories, inherent in our being. It is absolute and unconditional, that is, categorical. Kant has the problem of providing a *categorical imperative* to serve as the fundamental law of the practical reason. He gives two forms of his categorical imperative: (1) “Act so that the maxim of thy will can always hold good as a principle of universal legislation;” and (2) “So act as to treat humanity, whether in thine own person or in that of any other, in every case as an end, never only as a means.”

The categorical imperative is supposed to provide a way of rationally judging maxims. For instance, under the categorical imperative, if I hold the maxim that it is acceptable to lie, then I must be able to will lying as a universal principle. This means that I accept being lied to. As a second example, if I hold the maxim that it is acceptable to kill those who are inconvenient, then I must be able to will such killing as a universal principle, even if I am the one who is judged inconvenient by those holding the power to do so.

While the two formulations of the categorical imperative might at first sound appealing, they are fraught with difficulties. For instance, if my child is about to be killed and I have a gun, should I shoot the assailant? Kant seems to saying that if I shoot, then I am acting so as to make shooting another human being a principle of universal legislation; however, if I do not shoot, then I am acting so as to make not defending my child a principle of universal legislation. Surely such a simplistic seemingly rational imperative cannot serve as a fundamental law of the moral order.

Given the existence of the moral law, Kant argues that, since freedom, immortality, and God cannot be theoretically established or rejected based on the theoretical reason, and since our belief in them provides vital practical support to the moral law, he will postulate their existence, believe in them, and act according to this belief.

Being more specific, having arrived at the moral law from feeling, Kant proceeds to arrive at God via the will:

> Admitting that the pure moral law inexorably binds every man as a command (not as a rule of prudence), the righteous man may say: ‘I will that there be a God, that my existence in this world be also an existence

> outside the chain of physical causes, and in a pure world of the understanding, and lastly, that my duration be endless; I firmly abide by this, and will not let this faith be taken from me; for in this instance alone my interest, because I must not relax anything of it, inevitably determines my judgment.' [Kant, 1788]

In the first critique Kant moves science from the study of Nature to the study of the product of man's categories of the understanding applied to Nature; then, in the second critique, he moves religion from being grounded in scripture or reason to being grounded in feeling and will.

To get a better sense of Kant's thinking in the *Critique of Practical Reason*, consider the following comment on the argument from design:

> I see before me order and design in Nature, and need not resort to speculation to assure myself of their reality, but to explain them I have to presuppose a Deity as their cause; and then since the inference from an effect to a definite cause is always uncertain and doubtful, especially to a cause so precise and so perfectly defined as we have to conceive in God, hence the highest degree of certainty to which this presupposition can be brought is that it is the most rational opinion for us men. [Kant, 1788]

Kant cannot apply pure theoretical reason to assure himself of the reality of order and design, so they are not part of science. To explain them he would need to infer God as a cause but he cannot because causality only applies to the phenomena. Thus, the "most rational opinion" is to suppose the existence of a deity behind the order and design.

In the second critique Kant takes the very practical position that one cannot live within the domain of pure theoretical reason. Human beings possess feelings and desires, and these must be considered by a philosopher if he is to take his subject, man, as a whole. With respect to the movement from the *Critique of Pure Reason* to the *Critique of Practical Reason*, the Spanish philosopher Miguel de Unamuno says, "He [Kant] reconstructs in the latter what he destroyed in the former…. Kant reconstructed with the heart that which with the head he had overthrown." [Unamuno, 1954]

Partly because he embraces both theoretical and practical reason, and partly because he wishes to save both science and faith from Hume's criticism, Kant's thinking is rife with paradox. What else could be expected from one whose purview is so vast? Barrett calls Kant "the pivot." There is philosophy anterior to Kant and philosophy posterior to Kant. Barrett has a figure entitled, "A Map of the Modern World." It shows two arrows leading into Kant, one from empiricism and another from rationalism. It shows four arrows emanating from Kant: idealism, pragmatism, existentialism, and positivism. Each of these and their variants begins with an aspect of Kant but under the desire for consistency narrows its scope and resorts to marginal thinking. On the other hand, Kant takes the whole man as his subject matter—a much more difficult endeavor.

4.6 Jean-Jacques Rousseau: No to Science

Kant’s appeal to the heart has roots in the thinking of Jean-Jacques Rousseau (1712–1778), whose picture hung on the wall of Kant’s study. Rousseau comes chronologically before Kant but since Hume awoke Kant from his dogmatic slumber and the *Critique of Pure Reason* was a response to Hume regarding reason and science, we wanted to discuss them in sequence. Rousseau is a major intellectual figure of the Eighteenth Century. He almost single handedly brought an end to the Age of Reason and that is why we have dated its end with the publication of his first discourse. Rousseau shunned the salons of Paris where wealthy aristocratic intellectuals held sway. He was not from their class and the air of the salons was not conducive to his sensitivity.

Prior to Rousseau’s emergence, reason had ruled the French Enlightenment. Voltaire was the great champion of reason and a bitter foe of the Catholic Church, although he remained religious and in old age attended Mass regularly. The first volume of the great *Encyclopédie*, edited by Denis Diderot and Jean le Rond d’Alembert, which was to be a paean to The Age of Reason, was published in 1751, but Rousseau’s *Discourse on the Arts and Sciences* had already appeared in 1750 and his *Discourse on the Origin and Basis of Inequality Among Mankind* would appear in 1754. An age of sensibility had already begun.

Rousseau saw civilization as the bane of mankind and saw primitive man as free from civilization’s discontents and a natural repository of pity, an emotion that he claimed had waned when men began to parcel out property and ceased to take sexual partners as one would pick apples from a tree. He opposed reason on behalf of feeling and openly rejected logic and the need for facts.

In the *Discourse on Inequality*, Rousseau wastes no time in rejecting science: “Let us begin therefore, by laying aside facts, for they do not affect the question…. You shall hear your history such as I think I have read it, not in books composed by those like you, for they are liars, but in the book of Nature which never lies.” [Rousseau, 1754] Rousseau’s anthropology of primitive man will not be affected by facts, nor will it be related to Nature via observation. Absent data, he will read the book of Nature. Rousseau’s arguments cannot be invalidated with data because these are not relevant. Like Descartes, Rousseau exemplifies Bacon’s spiders spinning their webs—with the exception that Descartes has the excuse that he was meditating a half century before Newton’s *Principia*, whereas Rousseau was meditating more than a half century after.

Further on in the *Discourse on Inequality*, Rousseau tells us that although his explanations are conjectural, because his conclusions are certain, any set of conjectures acceptable to him would lead to the same conclusions:

> I must own that, as the events I am about to describe might have happened many different ways, my choice of these I shall assign can be grounded on nothing but mere conjecture; but besides these conjectures becoming reasons, when they are not only the most probable that can be drawn from the nature of things, but the only means we can have of

> discovering truth, the consequences I mean to deduce from mine will not be merely conjectural, since, on the principles I have just established, it is impossible to form any other system, that would not supply me with the same results, and from which I might not draw the same conclusions. [Rousseau, 1754]

Rousseau's "conclusions" regarding anthropological phenomena are true *a priori*!

Having eliminated observation in the *Discourse on Inequality*, in his immensely influential work, *The Social Contract* (1762), Rousseau goes on to reject logic when he states the fundamental problem to be solved by *The Social Contract*: "The problem is to find a form of association which will defend and protect with the whole common force the person and goods of each associate, and in which each, while uniting himself with all, may still obey himself alone, and remain as free as before." [Rousseau, 1762] Consider the logic. Statement *X* is that a person will always be as free as before, meaning in the state of Nature where he is free to do anything he desires. Statement not-*X* is that he will not always have such freedom, in particular, when the state says that he cannot do something he desires. Rousseau proposes to provide an instance where the statement "*X* and not-*X*" is true, thereby denying the law of contradiction.

To get around it, Rousseau creates a fiction called the *general will*, which is more than the sum of the individual wills of the body politic. He spuriously solves the problem by defining freedom to be conformity with the general will. He appears to believe that redefining a term as its negation can escape a contradiction. It reminds one of George Orwell's "Freedom is Slavery." Lest his thinking not be clear, Rousseau explains, "Whoever refuses to obey the general will shall be compelled to do so by the whole body. This means nothing less than that he will be forced to be free." [Rousseau, 1762]

The general will is a prominent example of an idol of the marketplace, the kind that Bacon describes as "names of things which do not exist (for as there are things left unnamed through lack of observation, so likewise are there names which result from fantastic suppositions and to which nothing in reality corresponds)." These include "Fortune, the Prime Mover, Planetary Orbits, Element of Fire, and like fictions which owe their origin to false and idle theories." Had Bacon lived long enough he could have added the general will to his list.

While scientists tend to have negligible interest in Rousseau, his opposition to science, his elevation of sentiment over reason, and his political philosophy are ubiquitous. Whereas Descartes' legacy is a tendency to subordinate the empirical to the rational, Rousseau's thinking is manifested in a rejection of both the empirical and the rational in favor of desire and will. Those who believe that modernity and science are concomitant, and that science is unassailable, need to reflect on Rousseau's continuing influence.

At this point, when discussing perhaps the greatest modern foe of science, it might be enlightening to reflect on the following words of Ortega y Gasset:

> Experimental science is one of the most unlikely products of history. Seers, priests, warriors and shepherds have abounded in all times and places. But this fauna of experimental man apparently requires for its production a combination of circumstances more exceptional than those that engender the unicorn. Such a bare, sober fact should make us reflect on the supervolatile, evaporative character of scientific inspiration." [Ortega y Gasset, 1994]

This thought should arouse our vigilance as the Twenty-first Century human longing for knowledge of complex systems and the benefits that would accrue from such knowledge pushes against the limitations of scientific epistemology.

4.6.1 Kant and Rousseau

How deep was the impact of Rousseau on Kant? Clearly there was negligible impact on the *Critique of Pure Reason*, but what about Kant's moral theory in the *Critique of Practical Reason*? Political philosopher Stephen Smith thinks that Rousseau's influence on Kant was considerable. He states, "Kant's entire moral philosophy is a kind of deepened and radicalized Rousseauianism where what Rousseau called the general will is transmuted into what Kant calls the rational will and the categorical imperative." [Smith, 2008]

One can certainly debate the relationship between the categorical imperative and the general will; nevertheless, Kant makes it clear that for him the moral law arises from feeling and belief in the existence of God is a product of will. Recall his words on willing God. Then consider the closing words of Rousseau in a letter to Voltaire (1756):

> I have suffered too much in this life not to look forward to another. All these metaphysical subtleties may embitter my pains, but none can cause me to doubt a time of immortality for the soul and a beneficent providence. I sense it, I believe it, I wish it, I hope for it, I will uphold it until my last gasp—and of all the cases I will have supported, it will be the only where my own interest will not be forgotten. [Rousseau, 1756]

The similarity is striking.

Now consider Kant's own thoughts on Rousseau: "There was a time when I thought that this [knowledge] alone could constitute the honor of mankind, and I despised the people, who know nothing. Rousseau brought me to rights. This blind prejudice vanished. I learned to honor human beings." [Kant, 1997] Whereas Hume awoke Kant from his dogmatic slumber on metaphysics, it seems that Rousseau awoke him from his indifference to human dignity.

If Rousseau awakened the heart of Kant, then this is to the good, but with respect to reason the salient point is that Rousseau appears to have widened Kant's thinking beyond logic and the categories of the understanding. Kant, having to his satisfaction demonstrated that pure theoretical reason is limited to phenomena and that it frames human experience relative to those phenomena, had severely limited its domain of application. Proofs of God's existence and His nonexistence were out, as well as any possible theoretical grounding for the moral law. So Kant, emulating Rousseau, based the moral law and God on his inner feelings.

Yet there is a huge difference between Kant and Rousseau. Rousseau makes no critique of reason; rather, he simply makes a shambles of it. Kant absorbs what has come before and proceeds to analyze the transformation in reason and perception that was underway thanks to the scientific revolution of Bacon, Galileo, and Newton. Mathematical and scientific developments would make many of his particulars wrong, especially developments in the Twentieth Century, but in recognizing the role of the understanding in framing experience, he found a nugget. Rousseau on the other hand seems ignorant of the scientific revolution that had preceded him and would change man's perspectives on Nature and himself. Perhaps Hume, who personally knew Rousseau, stated it best when he said of Rousseau, "He has not, indeed, much knowledge. He has only felt, during the whole course of his life."

4.7 Mill: Metaphysics through the Back Door

John Stuart Mill (1806–1873) wished to empirically ground science in induction, which, following Bacon, means that he had to resuscitate causality. In *A System of Logic, Ratiocinative and Inductive* (1843) he wrote, "At the root of the whole theory of induction is the notion of physical cause. To certain phenomena, certain phenomena always do, and, as we believe, always will, succeed. The invariable antecedent is termed the 'cause,' the invariable consequent, the 'effect.'" [Mill, 1843] Mill proceeded to the following definition: "The Law of Causation, the recognition of which is the main pillar of inductive science, is but the familiar truth that invariability of succession is found by observation to obtain between every fact in nature and some other fact which has preceded it." [Mill, 1843]

There are four salient points to Mill's view: (1) no necessary connection is implied by causality; (2) the effect must be the "invariably and unconditionally consequent" of the cause; (3) causality makes no reference to what is behind the phenomena; and (4) causality is "coextensive with human experience." In one sense, Mill escapes Hume's criticism by abandoning any notion of necessary connection and making induction purely sequential, but he misses Hume's critical scientific point regarding the impossibility of arriving at the unconditional invariability of succession by any finite number of observations.

Mill recognizes that causality cannot be as simple as a single event being the sole cause of an effect. Regarding the complexity of causation, he states, "But the real cause is the whole of the antecedents, the whole of the contingencies of every description, which being realized, the consequent invariably follows. Yet even invariable sequence is not synonymous with causation. The sequence, besides being invariable, must be unconditional." [Mill, 1843] Clearly, "the whole of the antecedents, the whole of the contingencies of every description" has no bounds and may very well be the entire universe, which would reduce the entire notion of cause and effect to a statement about universal determinism. This would be a restatement of Laplacian determinism absent any individual causal relations within the universe. It is therefore not surprising that Mill adopts a Laplace-like position, except that unlike Laplace, who appeals to a "sufficiently vast" intelligence, Mill remains within the realm of human experience. He writes,

> The state of the whole universe at any instant, we believe to be the consequence of its state at the previous instant; insomuch that one who knew all the agents which exist as the present moment, their locations in space, and all of their properties, in other words, the laws of their agency, could predict the whole subsequent history of the universe, at least unless some new volition of a power capable of controlling the universe should supervene. [Mill, 1843]

If causality depends on knowing all the antecedents composing a cause, then surely it is not coextensive with human experience. On the other hand, expectation is very much coextensive with human experience.

Mill follows Bacon in recognizing that haphazard observation is insufficient for the discovery of causal relations. He writes,

> We must either find an instance in nature suited to our purposes, or by an artificial arrangement of circumstances make one. When we make an artificial arrangement, we are said to experiment; and experimentation has great advantages over observation in that it often enables us to obtain innumerable combinations of circumstances which are not to be found in nature. [Mill, 1843]

But instead of the Newtonian recognition that experimental constraint leads to relations that "estimate" relations among naturally occurring phenomena, Mill wants to use experiment to obtain "innumerable combinations of circumstances," a goal that on its face is impossible.

In trying to circumvent Hume's attack on causality on strictly empiricist grounds, Mill returns to a pre-Galilean world in the sense that, although necessary connection is abandoned, causality remains a requirement for knowledge. Hume's analysis regarding uncertainty and the impossibility of concluding a necessary connection, one that is unconditional and invariable, is impenetrable because the certainty of formal logic does not apply to human interaction with Nature. Expectation, not causality, is coextensive with human experience. Mill's problem is that he wants to bring metaphysics in through the back door. Aristotle was correct in placing the four forms of causality in the *Metaphysics*, but not correct in placing them in the *Physics*. Mill's hope of grounding causality in invariable and unconditional empirical sequences had already been doomed by Hume. Kant had recognized this but Mill did not.

4.8 Bertrand Russell: Causality, a Relic of a Bygone Age

In his 1913 essay, *On the Notion of Cause*, Bertrand Russell (1872−1970) stresses the impossibility of giving precise meaning to several different attempts to define "cause." For the sake of argument, he settles on the previously cited definition of Mill as perhaps the best attempt at a viable definition of causality. He shows that this attempt fails owing to the impossibility of supplying it with a suitable notion of event and the "insuperable difficulties," which Russell carefully articulates, of trying to define the timing between a cause and an effect.

Russell recognizes that Mill's reasoning regarding induction and causality are based on the appearance of uniformities in Nature and addresses the issue:

> It must, of course, be admitted that many fairly dependable regularities of sequence occur in daily life. It is these regularities that have suggested the supposed law of causality; where they are found to fail, it is thought that a better formulation could have been found which would have never failed. I am far from denying that there may be such sequences which in fact never do fail. It may be that there will never be an exception to the rule that when a stone of more than a certain mass, moving with more than a certain velocity, comes in contact with a pane of glass of less than a certain thickness, the glass breaks…. What I deny is that science assumes the existence of invariable uniformities of sequence of this kind, or that it aims at discovering them. All such uniformities, as we saw, depend upon a certain vagueness in the definition of the 'events.' That bodies fall is a vague qualitative statement; science wishes to know how fast they fall. This depends upon the shape of the bodies and the density of the air. It is true that there is more nearly uniformity when they fall in a vacuum; so far as Galileo could observe, the uniformity is then complete. But later it appeared that even there the latitude made a difference, and the altitude. Theoretically, the position of the sun and moon must make a difference. In short, every advance in a science takes us farther away from the crude uniformities which are first observed, into greater differentiation of antecedent and consequent, and into a continually wider circle of antecedents recognized as relevant. The principle 'same cause, same effect,' which philosophers imagine to be vital to science, is therefore utterly otiose. As soon as the antecedents have been given sufficiently fully to enable the consequent to be calculated with some exactitude, the antecedents have become so complicated that it is very unlikely they will ever recur. Hence, if this were the principle involved, science would remain utterly sterile. [Russell, 1913]

Russell makes it clear that the Laplace-Mill effort to frame causality in terms of "the state of the whole universe at any instant" is vacuous.

Russell neatly sums up his view of causality: "The law of causality, I believe, like much that passes muster among philosophers, is a relic of a bygone age, surviving, like the monarchy, only because it is erroneously supposed to do no harm." [Russell, 1913]

To the extent that science must be grounded on certainty, or on unconditional and invariable sequences, Hume's analysis is devastating. In the *Rise of Scientific Philosophy*, Hans Reichenbach (1891–1953) writes, "Empiricism broke down under Hume's criticism of induction, because it had not freed itself from a fundamental rationalist postulate, the postulate that all knowledge must be demonstrable as true. For this conception the inductive method is unjustifiable, since there is no proof that it will lead to true conclusions." [Reichenbach, 1971] Science does not depend on unconditional sequences, does not base its formulations on a notion of "logical" induction, and does not have a notion of certainty. This does not mean that science is ungrounded, only that its theoretical home is in probability theory and statistical inference, not in deterministic logic and induction.

4.9 James Clerk Maxwell: Hoping for an Intelligible Theory

The electromagnetic field theory, which is responsible for much of today's technology, is based on equations proposed by James Clerk Maxwell (1831–1879). Its applications depend on the behavior of detectors as predicted by the theory. As to the nature of the physical processes behind the equations, Maxwell does not know. In his theorizing he finds himself on the horns of a dilemma. He is unhappy with a purely mathematical theory because he desires a physical understanding of the phenomena and yet he fears physical hypotheses because these can filter the facts according to preconceptions.

In his 1861 paper *On Faraday's Lines of Force*, Maxwell writes,

> The first process therefore in the effectual study of the science, must be one of simplification and reduction of the results of previous investigation to a form in which the mind can grasp them. The results of this simplification may take the form of a purely mathematical formula or of a physical hypothesis. In the first case we entirely lose sight of the phenomena to be explained and though we may trace out the consequences of given laws, we can never obtain more extended views of the connexions of the subject. If, on the other hand, we adopt a physical hypothesis, we see the phenomena only through a medium, and are liable to that blindness to facts and rashness in assumption which a partial explanation encourages. We must therefore discover some method of investigation which allows the mind at every step to lay hold of a clear physical conception, without being committed to any theory founded on the physical science from which that conception is borrowed, so that it is neither drawn aside from the subject in pursuit of analytical subtleties, nor carried beyond the truth by a favorite hypothesis. [Maxwell, 1855]

In fearing that a mathematical approach "may lose sight of the phenomena to be explained," Maxwell still has one foot in the Aristotelian epistemology; in his concern that adopting a "physical hypothesis" that may lead to "blindness to facts and rashness," he reminds us of Newton's *Hypotheses non fingo*. Hypothetical assumptions based on human understanding cannot be trusted. They can lead to distorted interpretations of the observations to fit a "favorite hypothesis." Maxwell instead desires a "physical conception" to guide his thinking while at the same time not being committed to the science behind the conception—an analogy to guide his thinking but not bias it towards a preconceived notion. The question one might ask is why analogical thinking would be free from distortion, except perhaps that one knows it to be analogical and is therefore less likely to overly rely upon it.

Following an explanation of how analogies with physically based models are often useful for arriving at satisfactory theories, even when a model may relate to a different physical setting than the one being considered, Maxwell comments that he will analogize lines of force as "fine tubes of variable section carrying an incompressible fluid." After discussing the aim and methodology of the fluid analogy, he writes,

> I propose, then, first to describe a method by which the motion of such a fluid can be clearly conceived; secondly to trace the consequences of assuming certain conditions of motion, and to point out the application of the method to some of the less complicated phenomena of electricity, magnetism, and galvanism; and lastly to shew how by an extension of these methods, and the introduction of another idea due to Faraday, the laws of the attractions and inductive actions of magnets and currents may be clearly conceived, without making any assumptions as to the physical nature of electricity, or adding anything to that which has been already proved by experiment. By referring everything to the purely geometrical idea of the motion of an imaginary fluid, I hope to attain generality and precision, and to avoid the dangers arising from a premature theory professing to explain the cause of the phenomena. If the results of mere speculation which I have collected are found to be of any use to experimental philosophers, in arranging and interpreting their results, they will have served their purpose, and a mature theory, in which physical facts will be physically explained, will be formed by those who by interrogating Nature herself can obtain the only true solution of the questions which the mathematical theory suggests. [Maxwell, 1855]

Maxwell proceeds "without making any assumptions as to the physical nature of electricity." In this way he avoids being constrained by "a premature theory professing to explain the cause of the phenomena," that is, by a misleading application of the categories of the understanding. Nevertheless, he remains hesitant, adding that the mathematical theory is only suggestive of the "true solution." He hopes for an intelligible "mature theory, in which physical facts will be physically explained."

Maxwell is not alone in this dissatisfaction. Historian Morris Kline writes,

> Despite the Herculean efforts to determine physically what an electric field and a magnetic field are, scientists are unsuccessful…. We do not have any physical account of the knowledge of the electromagnetic waves as waves. Only when we introduce conductors such as radio antennae in electromagnetic fields do we obtain any evidence that those fields exist. Yet we send radio waves bearing complex messages thousands of miles. Just what substance travels through space we do not know. [Kline, 1985]

As Newton brackets causality and the physical nature of gravity in favor of mathematical relations, Maxwell brackets the physical waves behind the field theory. The upshot of all this bracketing is that the subject of physics (as science) is embedded within mathematics. Science does not try to force Nature into the straight jacket of human intelligibility. Thus, it is free to develop mathematical systems that allow us to build devices that respond according to the equations and thereby produce pragmatic effects in the physical world. The full meaning of putting aside the categories of the understanding in favor of mathematics will become clear in the Twentieth Century.

Chapter 5

A Mathematical–Observational Duality

5.1 The End of Intelligibility

When discussing the enormity of the transformation wrought by Galileo and Newton, Kline states, “What science has done, then, is to sacrifice physical intelligibility for the sake of mathematical description and mathematical prediction.” [Kline, 1985] Sacrificing physical intelligibility does not involve an abandonment of knowledge; on the contrary, it involves the recognition that everyday human categories concerning Nature—those that arise from ordinary interaction with the physical world, such as pushing and pulling—are, at best, only suitable for describing simple phenomenal relations. Kline writes,

> The insurgent seventeenth century found a qualitative world whose study was aided by mathematical abstractions. It bequeathed a mathematical, quantitative world that subsumed under its mathematical laws the concreteness of the physical world. In Newton’s time and for two hundred years afterwards, physicists spoke of the action of gravity as ‘action at a distance,’ a meaningless phrase that was accepted as a substitute for explaining the physical mechanism, much as we speak of spirits or ghosts to explain unseen phenomena. [Kline, 1985]

Kline’s point is twofold. First, the transformation to a mathematical world was accomplished before the end of the Seventeenth Century. Second, for two hundred years afterwards many scientists refused to accept this transformation—and many today still do not.

5.2 Quantum Mechanics

The development of quantum mechanics during the first third of the Twentieth Century compelled scientists to confront the epistemological issues lurking within Newton’s *Hypotheses non fingo*, as it applies to causality/determinism and to the structure and validation of scientific theories. This section describes some basic aspects of quantum theory that foster a deeper understanding of what it means for knowledge to be framed as a mathematical-observational duality and then discusses epistemological implications.

5.2.1 The Bohr atom

Up until shortly after the beginning of the Nineteenth Century, Newton's corpuscular theory of light, which claimed that light consisted of tiny particles, was widely accepted. Then, around 1803, Thomas Young performed his famous double-slit experiment in which light from a point source emanated in the direction of a barrier with two holes (called "slits"), passed through the slits, and was captured on a flat detector (Fig. 5.1). The light arriving on the detector was distributed in a manner consistent with wave interference from the light passing through the two slits, not as one would expect if particles were passing through the slits. Although not accepted at first, Young's wave theory became predominant in the Nineteenth Century.

In 1900, based on his study of blackbody radiation, Max Planck proposed that light and other electromagnetic waves are emitted in discrete packets (*quanta*) of energy that can only take on certain discrete values. These values are multiples of a constant h, now called *Planck's constant*. Energy radiated from a blackbody must be a multiple of hf, f being the frequency of the radiation.

In 1905, in the paper that earned him the Nobel Prize in 1921, Einstein went further by not just claiming emission in discrete packets, but that light is composed of discrete packets. He did this by considering the *photoelectric effect*, discovered in 1887 by Heinrich Hertz, which refers to the ejection of electrons by metals when exposed to light. Behavior that he observed regarding the ejected electrons appeared inconsistent with the view that light is a wave phenomenon.

Regardless of brightness, only light above a certain frequency prompts electrons to emit. As the frequency increases, the maximum kinetic energy of the ejected electrons increases proportionally with the frequency of the light, but does not vary with the intensity of the light, which would accord with wave theory. Moreover, the electrons are emitted almost simultaneously with the arrival of the light. Einstein explained the behavior of the emissions by assuming light to be made of individual particles, later called *photons*. Each photon possesses a quantum of energy $E = hf$. Hence, argued Einstein, it is not simply the emission of energy that is quantized, but that energy itself is quantized.

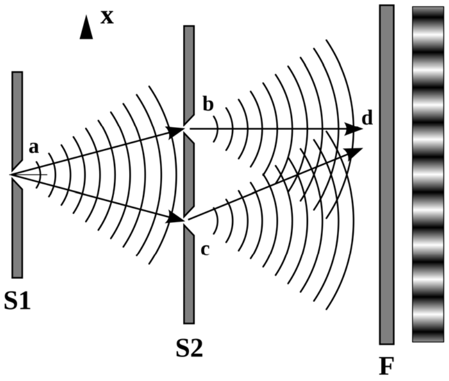


Figure 5.1 Young's double-slit experiment [*Fermilab Today*, 2008].

A second discrete phenomenon, discovered in the Nineteenth Century, concerned atomic emission spectra. When solids, liquids, and dense gases are heated to high temperatures, for instance, as occurs when electricity is passed through a light filament, light possessing a continuous spectrum is emitted. However, when energy is supplied to gas atoms under low pressure, the atoms emit light consisting of only discrete frequencies and these form a discrete atomic emission spectrum (Fig. 5.2).

In 1897, J. J. Thomson proposed a model of the atom in which tiny negatively charged electrons float in a “pudding” of positive change. In 1911, Ernest Rutherford shot high-velocity alpha particles (helium nuclei) into gold foil and captured the locations of the alpha particles on a fluorescent screen after they had passed through the gold foil. Most of the alpha particles passed through with very little deflection, as might be expected given the Thompson model; however, some deviated substantially and a small number bounced back. Rutherford hypothesized that the atom had a small dense positively charged nucleus at its center with negatively charged electrons orbiting around it. Although this planetary model was consistent with the charges and the behavior of the alpha particles in his experiment, it had problems. In particular, an electron circling a nucleus should be continually sapped of its energy and thus rapidly spiral into the nucleus. Moreover, the model could not explain discrete atomic emission lines.

To correct some of the defects in the Rutherford model, in 1913, Niels Bohr hypothesized that electrons orbit the nucleus of an atom at discrete distances, the actual distances depending on the element (Fig. 5.3) Electrons closer to the nucleus have lower energy than those further away. An electron must occupy definite energy levels, known as *quantum states*. It can jump to a different level without passing through intermediate levels, a so-called *quantum jump*. If light with the right energy encounters an atom, then the light will be absorbed, the atom’s electrons will be excited, and they will rise to higher energy states. In the other direction, when an electron jumps from a higher energy orbit to a lower one, it emits a photon whose energy equals the difference between the energy levels of the orbits. The discrete jumps fit neatly with the discrete spectral lines.

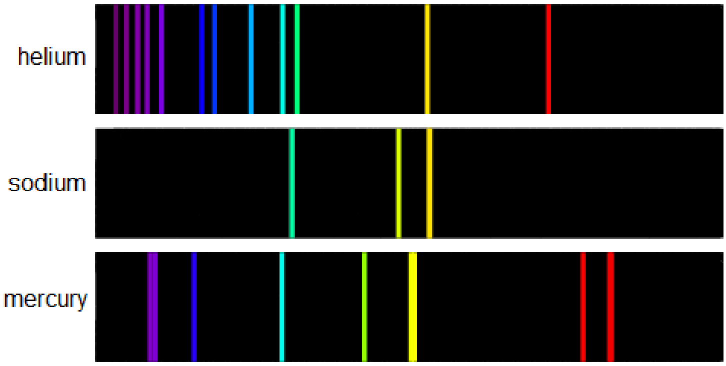


Figure 5.2 Atomic emission spectra.

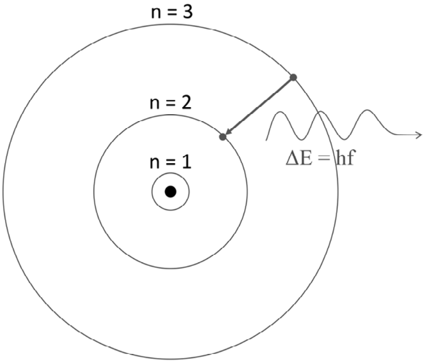


Figure 5.3 Bohr atomic model [Wikipedia, 2007].

5.2.2 Wave–particle duality

While the Bohr model predicts empirical observations better than the Rutherford model, quantum jumps are not in accord with our ordinary experience of continuity: an electron never occupies space between its original level and the one to which it jumps. Furthermore, is light a particle or a wave? Our ordinary experience seems to say that it must be one or the other, but not both. But suddenly it appears that light behaves as both a particle and a wave, depending on the experiment. Thus, physicists are confronted with a wave–particle duality, a notion that defies our ordinary categories of the understanding.

In 1924, Louis de Broglie argued that wave–particle duality is characteristic of both radiation and all particles of matter, not just light. Whereas Planck and Einstein had demonstrated that what was thought to be waves act like particles, de Broglie asserted that what was thought to be particles act like waves. In the case of electrons, a wave-like character implies that interference can only be avoided by occupying orbits at certain distances from the nucleus, in accordance with the Bohr atomic model. De Broglie's wave–particle duality theory was later supported when wave-like interference patterns were observed when electrons were passed through a double-slit experiment.

We consider the double-slit experiment more closely. It is possible to generate light of such low intensity that the experimenter can keep track of individual photons and record hits on the detector as they build up. It turns out that each individual photon falls randomly on the detector; however, after a large number of photons have arrived, a wave pattern emerges. What then is the path of an individual photon? Which slit does it go through, or does it go through both? Are these questions even meaningful? All that is known is that probabilities can be assigned to regions in which a photon might hit, these being consistent with the wave pattern. Various experiments have been performed and sundry observations have been made. What seems to be safe to say is that, from the perspective of ordinary understanding, strange phenomena have been observed.

To illustrate wave–particle behavior associated with a double-slit experiment, we consider an experiment performed by a group led by Akira Tonomura. Single electrons are emitted one by one from the source in an electron microscope. They pass through a device called an "electron biprism," which consists of two parallel plates with a fine filament at the center (each side of which corresponds to a slit) and they are individually observed as particles on a detector. Parts (a) through (e) of Fig. 5.4 show increasing numbers of electrons on the detector: 11, 200, 6000, 40,000, and 140,000. With a small number of electrons, the pattern appears completely random; however, as the number of electrons increases the interference pattern becomes increasingly visible, even though the electrons are emitted individually. Are the electrons waves or particles?

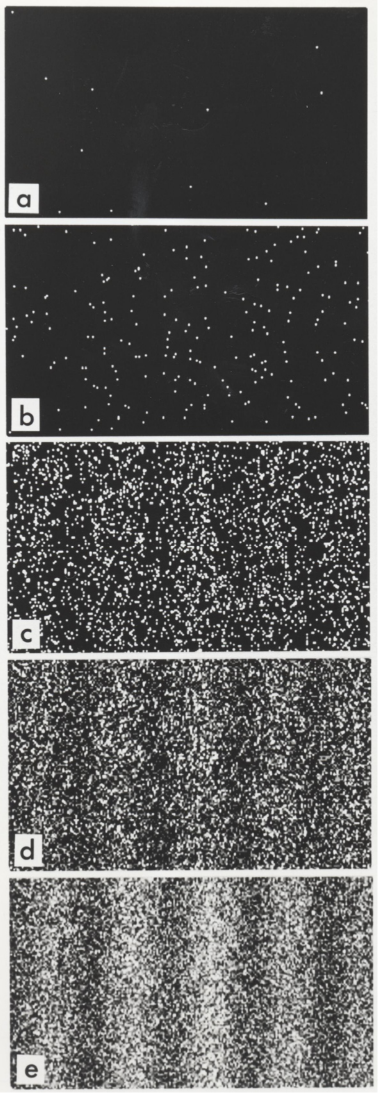


Figure 5.4 Electron waves in the double-slit experiment [Wikipedia, 2012].

Regarding the wave–particle behavior observed in double-slit experiments, in his *Lectures on Physics*, Richard Feynman writes,

> In this chapter we shall tackle immediately the basic element of the mysterious behavior in its most strange form. We choose to examine a phenomenon which is impossible, *absolutely* impossible, to explain in any classical way, and which has in it the heart of quantum mechanics. In reality, it contains the *only* mystery. We cannot make the mystery go away by "explaining" how it works. We will just *tell* you how it works. In telling you how it works we will have told you about the basic peculiarities of all quantum mechanics. [Feynman, 1964]

Once an individual electron hits the detector, its position is known exactly, but before then its position can only be described probabilistically. The behavior of an electron is governed by Schrödinger's wave equation (for the mathematical form of which we refer the interested reader to the abundant literature). Max Born showed that the square of the wave function is a probability density governing particle position. In principle, Schrödinger's equation applies to all non-relativistic matter; however, only for small systems are the wavelengths observable and significant. Schrödinger solved for the exact solutions of the wave equation for the hydrogen atom. The results match the known energy levels of the atom. Figure 5.5 shows probability density plots for the hydrogen atom orbitals. The plots are two-dimensional slices; the actual densities are three-dimensional. Given that an electron is in an orbital, the probability of finding the electron in any region of the orbital is the probability of that region.

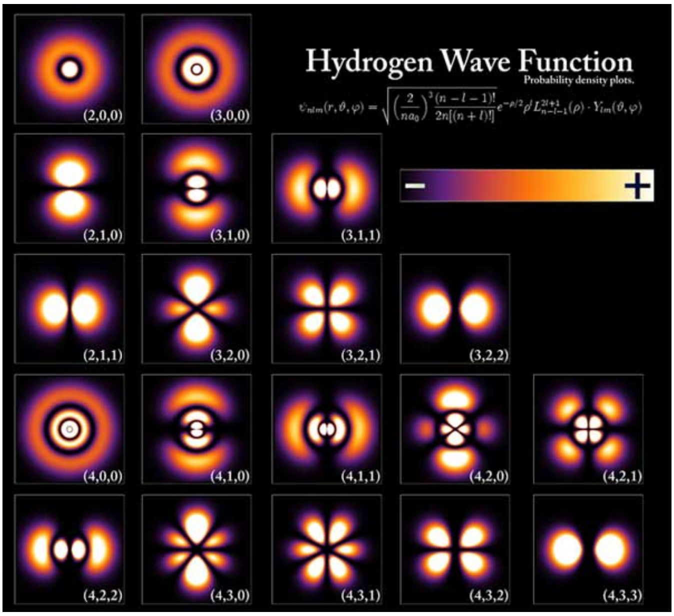


Figure 5.5 Hydrogen atom orbitals [Sevencolors.org, 2009].

5.2.3 The uncertainty principle

In 1927, Werner Heisenberg stated the famous uncertainty principle with which his name is often associated:

> At the instant of time when the position is determined, that is, at the instant when the photon is scattered by the electron, the electron undergoes a discontinuous change in momentum. This change is the greater the smaller the wavelength of the light employed, i.e., the more exact the determination of the position. At the instant at which the position of the electron is known, its momentum therefore can be known only up to magnitudes which correspond to that discontinuous change; thus, the more precisely the position is determined, the less precisely the momentum is known, and conversely. [Heisenberg, 2006]

Heisenberg originally conceived the idea by considering the measurement of a particle's position and velocity using an optical microscope. Light hits the particle and is reflected. When the light photons hit a sub-atomic particle, it moves. The position is accurately measured but the velocity of the particle is affected. Hence, the position is obtained but knowledge pertaining to the velocity is lost. Based upon this thinking, Heisenberg proposed that the certainty with which we know the location of a particle is inversely related to the certainty with which we know its momentum.

The uncertainty principle is often written as $\Delta x \Delta p \geq h/4\pi$, where Δx and Δp denote the uncertainties in position and momentum, respectively, and h is Planck's constant. More precisely, it takes the form $\sigma_x \sigma_p \geq h/4\pi$, where σ_x and σ_p denote the standard deviations of the position and momentum, respectively. Whereas Heisenberg originally thought of the uncertainty principle as due to the measurement process, it arises as a consequence of the quantum wave nature of the electron. Consequently, it is a fundamental physical property, not a statement concerning measurement technology.

According to the uncertainty principle, a particle does not possess specific position and velocity; instead, these are known probabilistically and there is an intrinsic limitation of the accuracy with which the system composed of the position and momentum can be known. Physical laws can only provide probabilistic descriptions up to the limit allowed by the uncertainty principle. Epistemologically, this differs radically from the basic deterministic principle of classical physics in which the state of a system can be precisely determined and, once this is determined, future states can be predicted precisely by the laws.

5.3 Epistemological Reflections on Quantum Theory

Quantum theory is inconsistent with many commonplace assumptions: continuity, causality, determinism, a particle having a unique position, and the distinction between particles and waves. Thus, it is not surprising that the theory provoked much debate as to its meaning, its status as a physical theory, and its implications for epistemology.

5.3.1 The Copenhagen interpretation

Prior to the measurement of its position on the detector, an electron has no definite position, at least insofar as physics is concerned, there being only a probability distribution characterizing the likelihood of its position, but once detected, it has a definite position. How is this to be interpreted? The view taken by Bohr and Heisenberg is that once a particle is measured, the probability of its being detected elsewhere becomes zero. Prior to detection, the particle's position is inherently random. The randomness disappears upon interaction with a measuring device. Bohr believed that there is no precise way to define the exact point at which this so-called *wave function collapse* occurs. Hence, there is no deep quantum reality, no actual world of electrons and photons. Quantum mechanics provides a formalism that we can use to predict and manipulate events. There is no knowledge beyond that. However, once the measurements are made, these behave in the classical manner and should be describable in classical language. On account of Bohr’s laboratory being in Copenhagen, this perspective is known as the *Copenhagen interpretation*.

From the human perspective, the theory views Nature as intrinsically random and somehow interdependent with human observation. One thinks of Berkeley (*esse est percipi*). When observed, an electron has a position; when not being observed it does not. And, according to the uncertainty principle, if it is observed with perfect precision, then its momentum, which means its velocity, is totally unknown.

Einstein was uncomfortable with this interpretation. There can be no proof that there are not hidden variables whose discovery would eliminate randomness. Perhaps quantum theory is incomplete. This would agree with Laplace’s view that the randomness we observe is always due to ignorance. The argument cannot be decided beforehand, that is, before the actual discovery of the variables, so that they are no longer hidden. Beyond that, Einstein believed that science has to be deterministic because he believed reality is deterministic. Referring to the Seventeenth Century philosopher Baruch Spinoza, Einstein wrote, “He was utterly convinced of the causal dependence of all phenomena, at a time when the success accompanying efforts to achieve a knowledge of the causal relationship of natural phenomena was still quite modest.” [Einstein, 1982] Thus, Einstein is taking a metaphysical position in agreement with Spinoza.

Although there are other interpretations of quantum theory, it appears that the Copenhagen interpretation is held by the majority of physicists. This is consistent with Newton’s *Hypotheses non fingo*, although one would be rash to conclude that Newton would agree with the extension of his dictum to the Copenhagen interpretation. In any event, it is a minimalist view and consistent with maintaining a demarcation between science and metaphysics.

5.3.2 Knowledge depends on the questions asked

As one might expect from the originator of the uncertainty principle, Heisenberg puts great emphasis on the interaction between the scientist and Nature. He writes, “Natural science does not simply describe and explain Nature; it is part of the interplay between nature and ourselves.” The key to that interplay is the manner in which we probe Nature. In Heisenberg’s words, “What we observe is not Nature itself, but Nature exposed to our method of questioning.” Think of the uncertainty principle. Does the question concern the position or the momentum? Heisenberg says that we must choose where to put our focus: “We decide, by our selection of the type of observation employed, which aspects of nature are to be determined and which are to be blurred.” [Heisenberg, 1977a]

Since the knowledge gained depends on the questions asked, the mathematical system, which constitutes the frame of thinking, is in some sense determinative of the kind of knowledge to be gained because the questions must lead to answers that can be formulated in the language of the system. Thus, depending on the mathematical system chosen, the same phenomena may be modeled (thought about) in different ways. Heisenberg considers this idea to be the most important concept arising from quantum theory:

> The most important new result of nuclear physics was the recognition of the possibility of applying quite different types of natural laws, without contradiction, to one and the same physical event. This is due to the fact that within a system of laws which are based on certain fundamental ideas only certain quite definite ways of asking questions make sense, and thus, that such a system is separated from others which allow different questions to be put. [Heisenberg, 1977b]

Questions presuppose answers and scientific answers are quantitative. They involve measurement. The uncertainty principle raises the following question: Does a property that cannot be measured exist? According to Percy Bridgman,

> On careful examination the physicist finds that, in the sense in which he uses language, no meaning at all can be attached to a physical concept which cannot ultimately be described in terms of some sort of measurement. A body has position only in so far as its position can be measured; if a position cannot in principle be measured, the concept of position applied to the body is meaningless, or in other words, a position of the body does not exist. Hence if both the position and velocity of the electron cannot in principle be measured, the electron cannot have the same position and velocity; position and velocity as expressions of properties which an electron can simultaneously have are meaningless. To carry the paradox one step further, by choosing whether I shall measure the position or the velocity of the electron, I thereby determine whether the electron has position or velocity. The physical properties of

> the electron are not inherent in it, but involve also the choice of the observer. [Bridgman, 1950]

It has long been known that science is inextricably tied to technology because the capacity to measure depends directly on the instrumentation available, but quantum theory goes beyond that by saying that certain measurements are intrinsically impossible and therefore the impossibility of measurement cannot be overcome by improved technology.

5.3.3 Nature is absurd

Given that scientific knowledge depends on the questions asked, which are in turn limited by the mathematical apparatus and the measurement process, what then is the relation between scientific knowledge and Nature? On this most fundamental point, Bohr takes a Kantian position: "It is wrong to think that the task of physics is to find out how Nature is. Physics concerns what we say about Nature."

For Bacon, the essence of a phenomenon pertains to its metaphysical form, which constitutes a deeper reality than the empirical observation and would have to be where meaning resides. Bohr dismisses any hope for meaning:

> A subsequent measurement to a certain degree deprives the information given by a previous experiment of its significance for predicting the future course of the phenomena. Obviously, these facts not only set a limit to the *extent* of the information obtainable by measurements, but they also set a limit to the *meaning* we may attribute to such information. We meet here in a new light the old truth that in our description of Nature the purpose is not to disclose the real essence of the phenomena (i.e., the quantum character of their ultimate constitution) but only to track down, as far as possible, relations between the manifold aspects of our experience. [Bohr, 2012]

Indeed, it is an "old truth"—in Galileo, Newton, and Kant.

For Kant there is a deeper reality, the noumena, but this is not accessible to the categories of the understanding, which apply to phenomena. Here Bohr parts with Kant because Bohr's description of Nature is not limited to the categories of the understanding; indeed, it is precisely the ordinary human understandings about Nature that quantum mechanics rejects.

What we can say about Nature depends on what we can observe and what mathematical tools can be brought to bear. As Newton's desire to quantitatively express mechanical concepts led him to develop the calculus, the probabilistic nature of quantum events in space and time helped spur the rapid development of the theory of random processes in the 1930s and 1940s. The formulation of quantum theory in terms of operators depends on the theory of Hilbert spaces, which illustrates the dependency of science on the language of mathematics. There is the famous example of Einstein approaching David Hilbert for help in formulating the general theory of relativity and Hilbert suggesting Riemannian geometry as an appropriate language.

Did quantum theory fundamentally advance the epistemology of the Seventeenth Century, which, as stated by Kline, “bequeathed a mathematical, quantitative world that subsumed under its mathematical laws the concreteness of the physical world?” Perhaps not theoretically! But practically it did. One could no longer depend on the language of ordinary experience, such as “wave” and “particle,” to formulate laws. One could no longer depend on using everyday models such as billiard balls banging into each other to explain the theory. Galileo had dismissed explanation as science in principle. Quantum mechanics left no doubt that Nature cannot be described in mental pictures.

In the *Mysterious Universe*, James Jeans writes,

> The final truth about phenomena resides in the mathematical description of it; so long as there is no imperfection in this, our knowledge is complete. We go beyond the mathematical formula at our own risk; we may find a [nonmathematical] model or picture that helps us to understand it, but we have no right to expect this, and our failure to find such a model or picture need not indicate that either our reasoning or our knowledge is at fault. [Jeans, 1930]

Non-mathematical reasoning may be useful for the scientist in exploratory thinking, but scientific knowledge is constituted in a mathematical model. One might use a metaphor of observers holding lights on approaching trains to make an intuitive point concerning relativity, but the scientific theory lies properly within the equations. Any attempt to force a non-mathematical understanding creates the risk of having a diminished (or erroneous) scientific theory because it substitutes readily understandable and often convincing descriptions in place of strict scientific knowledge, which must take a mathematical form.

With all of this mathematics, where is the concreteness of the physical world? Indeed, is there something concrete? If we cannot express it, then is there an “it” to express? Jeans writes,

> A mathematical formula can never tell us what a thing is, but only how it behaves; it can only specify an object through its properties. And these are unlikely to coincide *in toto* with the properties of any single macroscopic object of our everyday life…. We need no longer discuss whether light consists of particles or waves; we know all there is to be known about it if we have found a mathematical formula which accurately describes its behavior, and we can think of it as either particles or waves according to our mood and the convenience of the moment. [Jeans, 1930]

There is behavior apprehended as measurements. These are abstracted as variables in a mathematical system and comprise the elements related by the mathematics. That is it. Concreteness is a will-o'-the-wisp. Not only is there an unbridgeable chasm between the phenomenal and noumenal worlds, there is also a huge gulf between human understanding and the phenomena.

Schrödinger states the matter metaphorically:

> As our mental eye penetrates into smaller and smaller distances and shorter and shorter times, we find nature behaving so entirely differently from what we observe in visible and palpable bodies of our surrounding that no model shaped after our large-scale experiences can ever be 'true'. A completely satisfactory model of this type is not only practically inaccessible, but not even thinkable. Or, to be precise, we can, of course, think it, but however we think it, it is wrong; not perhaps quite as meaningless as a 'triangular circle', but much more so than a 'winged lion'. [Schrödinger, 2004]

Where does this leave us in our relationship with Nature? Beginning a lecture series on quantum electrodynamics to an audience of non-specialists, Richard Feynman is unequivocal:

> What I am going to tell you about is what we teach our physics students in the third or fourth year of graduate school—and you think I'm going to explain it to you so you can understand it? No, you're not going to be able to understand it…. You see, my physics students don't understand it either. That is because I don't understand it. Nobody does.... It is whether or not the theory gives predictions that agree with experiment. It is not a question of whether a theory is philosophically delightful, or easy to understand, or perfectly reasonable from the point of view of common sense. The theory of quantum electrodynamics describes Nature as absurd from the point of view of common sense. And it agrees fully with experiment. So I hope you can accept Nature as she is—absurd. [Feynman, 1985]

Nature qua Nature is not absurd. Nature qua the human categories of the understanding is absurd. Would it not be presumptuous to suppose otherwise? A mathematical theory is intelligible because it is a product of the human intellect; Nature is not a product of the human intellect.

5.4 The Structure of Scientific Knowledge

Feynman's statement posits two definitive assumptions underlying scientific knowledge: (1) understanding in the form of intelligibility is neither necessary nor sufficient for scientific knowledge, and (2) the sole criterion for the validity ("truth") of a scientific theory is concordance between predictions derived from the theory and corresponding observations.

Everything begins with an experiment designed to answer questions in the mind of the scientist. The product of an experiment is a set of measurements that form the data of sensibility, the empirical (as opposed to a rational) basis for knowledge. In themselves, measurements do not constitute scientific knowledge. They must be integrated into a conceptual system. Scientific knowledge is constituted via synthesis of the observed measurements. These are related to variables and relations among the variables. Modern science is based on the integration of two fundamental principles: (1) the design of experiments under constrained circumstances to extract specifically desired information; and (2) the mathematical formulation of knowledge. The two principles arise from the two sides of the scientific problem, the source of knowledge and the representation of knowledge in the knower.

Scientific knowledge necessarily takes the form of mathematics for four reasons:

1. Scientific knowledge is based on quantitative measurements, be they logical or numeric.
2. Scientific knowledge concerns relations, and mathematics provides the formal structure for relations.
3. The validity of a scientific theory depends on predictions, and this requires a quantitative structure from which to generate predictions and a theory of probability in which the goodness of predictions can be quantified.
4. Mathematics provides a formal language in which both the constituting theory and the experimental protocols for prediction are inter-subjective, once the underlying mathematical representation of the theory is agreed upon.

Regarding the last requirement, Karl Popper (1902–1994) writes, “The objectivity of scientific statements lies in the fact that they can be inter-subjectively tested.” [Popper, 1959] Inter-subjectivity demands that scientific knowledge not depend on reason, except within the strict rules of mathematics and logic; otherwise, philosophical theories like Marxism could legitimately claim to be science. This would be “cult science,” open only to those who claim to understand empty phrases such as “dialectical materialism.”

There is much more to a model than the defining relations, that is, the general principles of the model. A great power of the scientific epistemology lies in the deducibility of logically necessary relations from the defining relations—the *hypothetico-deductive method*. This deduction can reveal critical relations not at once apparent in the defining relations. A full mathematical model consists of the defining relations and all relations logically deduced from these. The knowledge constituted by the derived relations is implicit in the defining structure but only becomes apparent when derived explicitly.

A mathematical model alone does not constitute a scientific theory; the model must be related to phenomena, that is, the formal mathematical system must be related to the empirical ground of science. Validation of a system requires that it be tied to observations by rules that relate not necessarily to its defining relations but to conclusions logically deduced from the defining relations. There must be a formal protocol for testing the theory by checking measurable consequences of the theory. Bridgman observed that the relational rules involve the description of physical operations and called them *operational definitions*.

The operational definitions are an intrinsic part of a scientific theory, for without them there would be no connection between the mathematics and observation, between the conceptual system and the experiments. The conceptual system must have consequences that can be checked via their relation to sensory observations. There must be a defined procedure for relating the consequences of the equations to quantifiable observations, such as the compression of a spring or the distribution of electrons on a detector.

A scientific theory consists of two parts:

1. A mathematical model composed of symbols (variables and relations between the variables).
2. A set of operational definitions that relate the symbols in the model and measurements of corresponding physical events.

In addition, two requirements must be met to have a validated scientific theory:

3. There must be validating data, that is, a set of future quantitative predictions derived from the theory and corresponding measurements.
4. A statistical analysis that supports acceptance of the theory, that is, supports the concordance of the predictions with the physical measurements—including the mathematical theory justifying application of the statistical methods.

The fourth requirement means that one cannot apply a statistical technique unless there is solid theory demonstrating the validity and specificity of the conclusions drawn relating the predictions and measurements, and there is theoretical justification for applying the statistical technique under the current conditions. For instance, if the statistical theory requires that the data come from a normal distribution, then there must be evidence that an assumption of normality, while not necessarily guaranteed, is at most only weakly violated. One might apply a hypothesis test and show that the data do not support rejection of the normality assumption.

5.5 Scientific "Truth"

For Plato, true knowledge involves certainty and resides in the deeper reality of the forms, not in the shadow world of empirical observations, where uncertainty prevails. While dismissing the deeper reality as a fiction, Hume agrees that knowledge gained via the senses is inherently uncertain. This does not leave us with a categorical absence of knowledge, nor does it render the notion of truth meaningless. On the contrary, taking expectation as the ground of scientific knowledge leads to the basis of scientific truth. Predictive relations characterize model validity and are necessary for scientific knowledge. Truth is determined by concordance of the predictive relations with future observations corresponding to the predictions. Scientific truth relates to the predictive capacity of a scientific theory. Scientific knowledge is about the future. Past observations may lead to discovery of a theory but the theory must predict the future.

Reichenbach writes,

> If the abstract relations are general truths, they hold not only for the observations made, but also for observations not yet made; they include not only an account of past experiences, but also predictions of future experiences. That is the addition which reason makes to knowledge. Observation informs us about the past and the present, reason foretells the future. [Reichenbach, 1971]

Foretelling the future is the crux. A model may fit existing data, but the model must incorporate mathematical machinery that makes it predictive across time to be scientifically valid.

Prediction is not certitude. Instead of causality, science involves conditional distributions that describe the probability of a *target* random variable Y given the values of a set of *predictor* random variables, $X_1, X_2, \ldots, X_m$. The target measures some process, and it has a probability distribution quantifying its behavior. The predictor variables possess the quality of causes in that their outcomes condition the behavior of the target, in analogy to causes determining an effect, but they do so in a probabilistic manner. Specifically, the original probability distribution of the target Y is altered depending on the outcomes of the predictors $X_1, X_2, \ldots, X_m$. In particular, given values of the predictor random variables, the best prediction (relative to mean-square error) of Y is its conditional expectation, meaning its expectation conditioned on the values of $X_1, X_2, \ldots, X_m$.

Causality is replaced by conditioning. Statements concerning conditional prediction can be validated via experimentation. The meaning of a statement can be defined within the framework of probability theory, and its relation to measurable phenomena can be mathematically characterized within the theory of statistics. If the predictor variables are antecedent to the variable to be predicted, then we have forward prediction. The terms “cause” and “effect” never appear.

The general epistemological perspective does not specify how it is to be applied in particular settings. According to Einstein,

> In order that thinking might not degenerate into ‘metaphysics,’ or into empty talk, it is only necessary that enough propositions of the conceptual system be firmly enough connected with sensory experiences and that the conceptual system, in view of its task of ordering and surveying sense experience, should show as much unity and parsimony as possible. Beyond that, however, the system is (as regards logic) a free play with symbols according to (logically) arbitrarily given rules of the game. [Einstein, 1944b]

The model (conceptual system) is a creation of the imagination, in accordance with the rules of the game. The manner of this creation is not part of the scientific theory. The classical manner is that the scientist combines an appreciation of the problem with reflections upon relevant phenomena and, based on mathematical knowledge, creates a model. As Einstein states, this creation is free except that it must conform to the rules of the mathematical game.

Epistemologically more problematic is that Einstein's prescription does not lead to a unique, absolute truth because validation is a process and the "truth" of the theory is relative to that process. Indeed, what is meant by "enough propositions" being "firmly enough connected with sensory experiences?" How many propositions? How firmly? The model must be connected to observations but the specification of this connection in a given circumstance is left open. This specification constitutes an epistemological requirement that must be addressed in mathematical statements. Absent such a specification, a purported scientific theory is meaningless. Different people may set different requirements, so that one may accept the theory as valid and the other may not.

A scientific theory is incomplete without a formal specification of achievable measurements that can be compared to predictions derived from the conceptual theory and the manner in which the measurements are to be compared to the conceptual system, in particular, validity criteria and the mathematical properties of those criteria as applied in different circumstances. The validity of a theory is relative to this specification, but what is not at issue is the necessity of a set of relations tying the conceptual system to operational measurements. A scientific theory is inter-subjective, but the epistemological criteria underlying a particular validation are open to debate. Once the validation requirements are specified, the mathematical model (conceptual system) is valid relative to the validation criteria and to the degree that the requirements are satisfied, that is, to the degree that predictions demanded by the validation protocol and resulting from the mathematical model agree with experimental observations.

Reichenbach states, "Scientific philosophy has constructed a *functional* conception of knowledge, which regards knowledge as an instrument of prediction and for which sense observation is the only admissible criterion of nonempty truth." [Reichenbach, 1971]

Scientific knowledge is worldly knowledge in the sense that it points into the future by making predictions about events that have yet to take place. Scientific knowledge is contingent, always awaiting the possibility of its invalidation. Its truth or falsity lies in the verity of its predictions and, since these predictions depend upon the outcomes of experiments, ultimately the validity of scientific knowledge is relative to the methodology of verification.

This is a long way from Plato's cave, in which the prisoners see only shadows but reason can reach deeper to the true forms casting the shadows. These exist in some timeless place where there is no idea of process. It is also a long way from Aristotle's three pillars: causality, explanation, and metaphysics. For Aristotle, reason could explain the observations by placing them within some rational structure intrinsic to the whole of reality. For both Plato and Aristotle, truth is metaphysical, it being a property of an idea that, while it might be only partially revealed in observations, is intrinsic to the idea. For science, the truth of an idea depends on the process of validating its truth. Since many processes might be used, there are many truths. Change the process and the truth may change.

Some might try to argue that a truth relative to its process of verification is no more solid than Rousseau's mental fantasies. This would be a grossly fallacious analogy. Rousseau specifically states that facts do not matter, whereas a scientific theory must show concordance with facts. What is open in science is the manner in which concordance is to be manifested. One might argue that this leaves open the possibility of positing operational requirements that are so loose that any theory could be validated. This argument is facetious because it presupposes scientific nihilism, a position rejected by serious scientists and demonstrated by their willingness to put aside the idols of the mind to discover mathematical conceptualizations of natural processes consistent with observations across time.

5.6 A New Role for Reason

Aristotle provides four causes as the basis for explanation of the physical world. Irrespective of the continuing appeal to causality, explanation remains ubiquitous and is perhaps the greatest impediment to meaningful scientific enquiry. Explanation makes the world intelligible by characterizing it via categories grasped by the intellect, thereby satisfying the emotional desire to give order to the physical world and comprehend the "why" of that order. Nature seemingly becomes accessible to the human intellect. The result is reason working *a posteriori* on observations or perhaps in the absence of observations (think of Rousseau) to construct a mental picture of the world. This would be a picture in terms of human physical concepts such as particles, gravity, force, etc. It would be a picture of Nature filtered through the idols of the tribe, seen in the reflection of "a false mirror, which, receiving rays irregularly, distorts and discolors the nature of things by mingling its own nature with it."

Science has not abandoned reason; rather, the role of reason has changed. Scientific knowledge is constituted in a most pure form of reason, mathematics, but the truth of that knowledge is not ascertained directly by reason, nor is that knowledge required to conform to ordinary categories of intelligibility. In one sense, reason loses its lofty position because it cannot remain independent in its judgments; these must be tied to phenomena in well-defined ways. To put the matter more forcefully, reason is no longer trusted.

The Enlightenment, in the person of its two greatest philosophers, Hume and Kant, turns reason upon itself and exposes its limitations, at least in its pure form. When Maxwell speaks of discovering a method that allows the mind not to be "carried beyond the truth by a favorite hypothesis," he is warning of the danger of unchecked reason, a warning given more forcefully by Hume, who, in the *Treatise*, asserts, "Reason is, and ought only to be the slave of the passions, and can never pretend to any other office than to serve and obey them." [Hume, 1738] Whereas Maxwell is concerned about tilting one's reason in the direction of a favorite hypothesis owing to "that blindness to facts and rashness in assumption which a partial explanation encourages," Hume, with his usual flair for directness, states that reason is a servant of desire and therefore cannot be trusted as an arbiter of its own deliberations. One should not only be wary of blindness to the facts affecting explanations but also recognize that explanations may be constructed in such a way as to "serve and obey" the passions (again think of Rousseau). Consider two scientific protagonists who firmly believe in the products of their individual reason. We need not dig into the intricacies of their cobwebs. We need only test their claims, which can be done because they must each provide operational definitions in conjunction with their models.

Perhaps modernity has to some extent deprived reason of its lofty perch; however, it has also made reason more powerful in other ways. First, it has made an extraordinary move away from the immediate perceptions that were previously the basis for understanding the natural order. This entails a huge leap in creativity. Einstein writes, "Experience, of course, remains the sole criterion for the serviceability of mathematical constructions for physics, but the truly creative principle resides in mathematics." [Einstein, 1933] The veracity of a scientific model lies in experience, but its conception arises from the imagination, an imagination freed from the fetters of Euclidean geometry, linear time, certainty, causality, and other constraints of the past. Second, when confronting Nature, reason no longer is confined to groping through aimlessly collected data; instead, it views Nature though an experimental filter based upon its own needs. Third, science has abandoned the rational explanation of Nature, and reason no longer is stuck looking backwards in an attempt to explain the past; rather, its role is to foretell the future. Recall Reichenbach: "Observation informs us about the past and the present, reason foretells the future." To be able to predict the future puts great power into the hands of mankind because it facilitates the predictable transformation of Nature resulting from human action in the world. Science provides a "functional conception of knowledge."

5.7 Deterministic or Stochastic Models?

An advantage of a deterministic theory is that, assuming sufficient knowledge, there is no uncertainty in the evolution of the state of the system. In practice, measurements are not perfectly precise, so there is always uncertainty as to the value of any variable. This uncertainty does not undermine a deterministic epistemology; rather, it pertains to the actualization of the epistemology in the measurement process. One might anticipate increasingly precise measurements, to the point that measurement error would be negligible. This assumption vanishes with quantum theory, where, in principle, there is a hard limit.

According to the uncertainty principle, at any moment in time, the product of the uncertainties in position and momentum of a particle must exceed $h/4\pi$. The position and momentum can be measured separately without a limit on accuracy, but not jointly. According to the Copenhagen interpretation, the uncertainty principle is intrinsic to human interaction with Nature, so that stochastic modeling in quantum mechanics is necessary. However, suppose Einstein is vindicated and hidden variables are found, so that a deterministic theory is sufficient relative to all known phenomena, or that the level of randomness is reduced. The new theory would be contingent, as are all scientific theories, awaiting new observations that might render it inadequate.

The fundamental point is that causality and determinism are metaphysical concepts. Recall Schrödinger's comment that causality is just "a characteristic of the way in which we regard Nature." For a scientific theory, the choice of a stochastic or deterministic model is pragmatic: Which gives better predictions?

Constraints are typically imposed on science by observational limitations. Since a model can only be verified to the extent that its symbols can be tied to observations, the ability to design and perform suitable experiments, including the availability of technology to make the desired measurements, is mandatory. Limitations on experimentation can result in limitations on the complexity or details of a theory. To be validated, a theory cannot exceed the experimentalist's ability to conceive and perform appropriate experiments. With the uncertainty theory, modern physics appears to have brought us beyond the situation where limitations on observation result only from insufficient experimental apparatus to a point where limitations are unsurpassable in principle.

Schrödinger states,

> It really is the ultimate purpose of all schemes and models to serve as scaffolding for any observations that are at all conceivable.... There does not seem to be much sense in inquiring about the real existence of something, if one is convinced that the effect through which the thing would manifest itself, in case it existed, is certainly not observable. [Schrödinger, 1957]

Absent observable effects due to an object, the object is not a suitable subject for scientific inquiry.

We need not go to the uncertainty theory to appreciate Schrödinger's point. The inability to experience absolute simultaneity and other such absolutes plays a key role in Einstein's approach to relativity theory. He writes,

> A further characterization of the theory of relativity is an epistemological point of view. In physics no concept is necessary or justifiable on an *a priori* basis. A concept acquires a right to existence solely through its obvious and unequivocal place in a chain of events relating to physical experiences. That is why the theory of relativity rejects concepts of absolute simultaneity, absolute speed, absolute acceleration, etc.; they can have no unequivocal link with experiences. Similarly, the notions of 'plane,' and 'straight line,' and the like, which form the basis of Euclidean geometry, had to be discarded. Every physical concept must

> be defined in such a way that it can be used to determine in principle whether or not it fits the concrete case. [Einstein, 1993]

A second constraint on scientific theory imposed by observational limitations concerns the kind of mathematical models to be employed. If there is inherent uncertainty in the measurements relating to a model, then a deterministic model is limited in its ability to produce accurate predictions because phenomenal predictions tied to the model via its operational definitions will be affected by the uncertainty and therefore validation is problematic. Consequently, probabilistic models, taking uncertainty into account, are preferable. Whereas imprecise measurements always affect model validation, the uncertainty principle makes this problem intrinsic. This does not imply that deterministic models are no longer useful. In the classical setting, when measurement error is very small, it can be ignored. This is also true in the macroscopic world when it comes to quantum uncertainty because Planck's constant is very small and the uncertainty can be practically ignored.

Deterministic models may be suitable for simple physical systems not subject to consequential changes outside those internal to the system; however, they are rarely, if ever, satisfactory for modeling complex interactive physical systems subject to external variables outside the system, which are ubiquitous in biology. If a dynamical process is repeatedly observed and measurements made on some set of variables over time, one cannot expect the measurements to remain the same across the different trials because, even if one could somehow replicate the initial state of the variables for each trial, unless the process is completely isolated so that the variables being measured are affected by no others but themselves, its evolution will depend upon variables outside the set.

Like determinism interpreted as a world view, randomness is a metaphysical category that can neither be proved nor disproved by empirical observations. The assumption of a stochastic model is a scientific decision, not a metaphysical perspective. Andrey Kolmogorov, discoverer of the measure-theoretic approach to probability theory, writes, "The possibility of using, in the treatment of a real process, schemes of well-determined or of only stochastically definite processes stands in no relation to the question whether the real process is itself determined or random." [Kolmogorov, 1931] The "real process" is not a subject of scientific knowledge.

Chapter 6

Complex Systems: A New Epistemological Crisis

6.1 The Twenty-first Century: Starved for Data

The preceding chapter discussed the manner in which the modern scientific epistemology originating with Galileo reached a deep understanding in the first half of the Twentieth Century; however, the book on epistemology is far from closed. The epistemological challenges confronting the Twenty-first Century are the most severe since the dawning of the Seventeenth Century. They arise from a desire to model complex systems that exceed human conceptualization ability. As a consequence, people attempt to use highly flexible mathematical structures with large numbers of parameters that can be adjusted to fit the data, the result often being models that fit the data well but lack structural representation of the phenomena and thus are not predictive outside the range of the data. The situation is exacerbated by uncertainty regarding model parameters on account of insufficient data relative to model complexity, which in fact means uncertainty regarding the models themselves. More importantly from the standpoint of epistemology, the amount of available data is often miniscule in comparison to the amount needed for validation. The desire for knowledge has far outstripped experimental/observational capability. We are starved for data.

With all the talk these days of "Big Data," one must remember that bigness is relative to need. While the current amount of data may be big relative to small systems, it is paltry compared to the data required for large complex systems, especially if it is not collected with a sharp eye to the intended use, which often it is not. We need only recall the warnings of Bacon and Kant about groping in the dark. With complex systems, experimental design is even more imperative. Still, with or without experimental design, in many cases it is virtually impossible to obtain the data required for model validation.

6.2 Gene Regulatory Networks

The Twenty-first Century is sometimes viewed as the century of biology; yet in biology complexity reaches heights undreamed of until very recently. A human body consists of trillions of cells containing about 100,000 different types of proteins and 30,000 genes interconnected in a myriad of signaling pathways, and let us not forget that each gene consists of a region of DNA, and the genome is subject to an immense number of single nucleotide polymorphisms, which are variations in a single nucleotide. We will discuss complexity in the context of modeling gene regulation in a single cell, which, although it represents only a small portion of the full system, presents unworkable levels of complexity even when only a relatively small number of genes are involved.

The regulatory system in a cell is mainly based in its genetic structure. The basic paradigm has two parts. *Transcription* refers to the process by which the genetic information in a gene is copied into messenger RNA (mRNA). When this process is occurring the gene is said to be *expressing* (or activated). Expression is governed by signaling proteins attaching themselves (binding) to the gene's *promoter region*. In essence, each gene is controlled by the states of a set of genes, so that its activation or non-activation depends on a combination of the expression levels in its regulating genes. *Translation*, which occurs subsequent to transcription, refers to the production of protein based on the code carried by the mRNA. The resulting protein can either be involved in maintaining the cell structure or function as a signal (*transcription factor*) to instigate or prohibit further gene expression by binding to the promoter region of a gene and forming a complex with other transcription factors to regulate the gene. This process goes on continuously across the genome to produce signaling pathways that regulate gene activity dynamically. Other factors affect gene activity, but we will focus solely on this basic transcriptional system.

A *gene regulatory network* (GRN) is a mathematical model comprised of a set of entities called "genes" and a regulatory structure that governs their behavior over time. GRNs can be finely detailed, as with differential-equation models, or coarse-grained, with discrete expression levels transitioning over discrete time. There is no expectation that coarse models closely represent actual molecular structure; rather, their purpose is to model interaction at the gene level in order to serve as a framework for studying regulation and provide rough models that can be used to develop strategies for controlling aberrant cell behavior, such as finding optimal drug treatments. While it might appear that gene-level modeling mistakenly ignores the molecular interaction constituting genetic activity, as well as the myriad of other molecular activity in a cell, it needs to be recognized that, while biological function requires chemistry, biology is not chemistry. Although there is no clear dividing line, biology concerns the operation of the cell at the level of genes, proteins, and other macromolecules involved in the life functions of the cell, not the physiochemical infrastructure of these macromolecules.

6.2.1 Deterministic Boolean networks

In the late 1960s, Stuart Kauffman introduced a discrete model known as a *Boolean network* [Kauffman, 1993]. Each gene can have logical values 1 or 0, corresponding to expressing or not expressing, respectively, and regulation is specified by logical operations among genes. Thus, the functional relationships between genes can be specified by a truth table. While the Boolean model is very coarse, it does model the thinking of cancer biologists, who speak of a gene being on or off under different conditions. Moreover, although the original formulation is two-valued, 0 or 1, the concept applies to any number of discrete gene values.

Formally, a Boolean network is defined by k binary variables, $x_1, x_2, \ldots, x_k$, where the value x_i of gene g_i at time $t + 1$ is determined by the values of some regulator genes at time t via a Boolean function f_i operating on the regulator genes. A typical function would be of the form $x_3 = f_3(x_2, x_4) = x_2 \wedge x_4$, where $\wedge$ means "and." This means that gene g_3 is on (expressing) at time $t + 1$ if and only if genes g_2 and g_4 are on (expressing) at time t. There are k such Boolean functions, one for each gene, and together they determine the deterministic dynamic evolution of the system over time. If there are four genes, then a typical dynamic trajectory over three time points would look like 0101 → 1100 → 1101. Given an initial state, a Boolean network will eventually reach a set of states, called an *attractor cycle*, through which it will cycle endlessly. Each initial state corresponds to a unique attractor cycle and the set of initial states leading to a specific attractor cycle is known as the *basin of attraction* of the attractor cycle.

We consider a small network involving the tumor suppressor gene p53. In mammalian genomes p53 is a transcription factor for hundreds of downstream genes that modulate cell cycle progression, repair damaged DNA, and induce senescence and apoptosis (cell self-destruction). Figure 6.1 shows some major pathways involving p53 that are activated in the presence of DNA double strand breaks. Adapted from [Batchelor, et al., 2009], it is not meant to be inclusive. An arrow indicates an activation signal, and a blunt end indicates suppression. Note that p53 activates Mdm2 and activated Mdm2 has a suppressing effect on p53. Even in this small network one can see the complicating effect of feedback.

Given this kind of pathway diagram, which is inherently logical, one would like to find Boolean networks whose state transitions generate the pathways [Layek et al., 2011]. The problem is ill-posed because there may be numerous networks that realize the pathways and there may be logical inconsistencies among the pathways since they have been found under various conditions in different studies. These kinds of issues are common with complex systems.

We consider two Boolean networks having states [ATM, p53, Wip1, Mdm2] generated for the pathways in Fig. 6.1. An external input signal, denoted dna_dsb, takes on the value 1 or 0, depending on whether there is or is not DNA damage. This leads to two 4-gene Boolean networks determined by the following logical rules [Imani and Braga-Neto, 2016]:

$$\mathrm{ATM}_{\mathrm{next}} = \overline{\mathrm{Wip1}} \wedge \mathrm{dna\_dsb}$$

$$\mathrm{p53}_{\mathrm{next}} = \overline{\mathrm{Mdm2}} \wedge \mathrm{ATM} \wedge \overline{\mathrm{Wip1}}$$

$$\mathrm{Wip1}_{\mathrm{next}} = \mathrm{p53}$$

$$\mathrm{Mdm2}_{\mathrm{next}} = (\overline{\mathrm{ATM}} \wedge (\mathrm{p53} \vee \mathrm{Wip1})) \vee (\mathrm{p53} \wedge \mathrm{Wip1})$$

The symbols $\wedge$, $\vee$, and ‾ represent logical "and", "or", and "not", respectively.

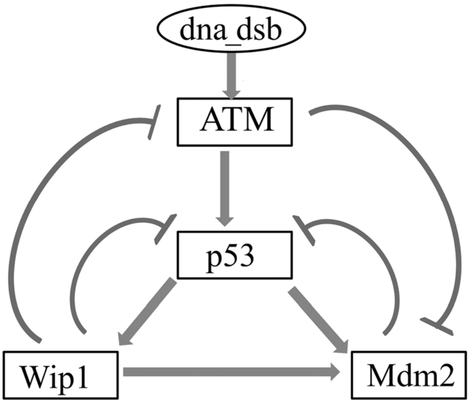


Figure 6.1 p53 pathways (adapted from [Imani and Braga-Neto, 2016]).

The state transition diagrams for these networks are shown in Fig. 6.2: (a) dna_dsb = 0; (b) dna_dsb = 1. Absent damage, from any initial state the network evolves into the single attractor state 0000; with damage, the network evolves into a 5-state attractor cycle in which p53 (state number 2) oscillates between expressing and not expressing. If one were to observe the network without knowing the damage status, then network behavior would appear stochastic, for instance, 0001 → 0000 when dna_dsb = 0 and 0001 → 1000 when dna_dsb = 1.

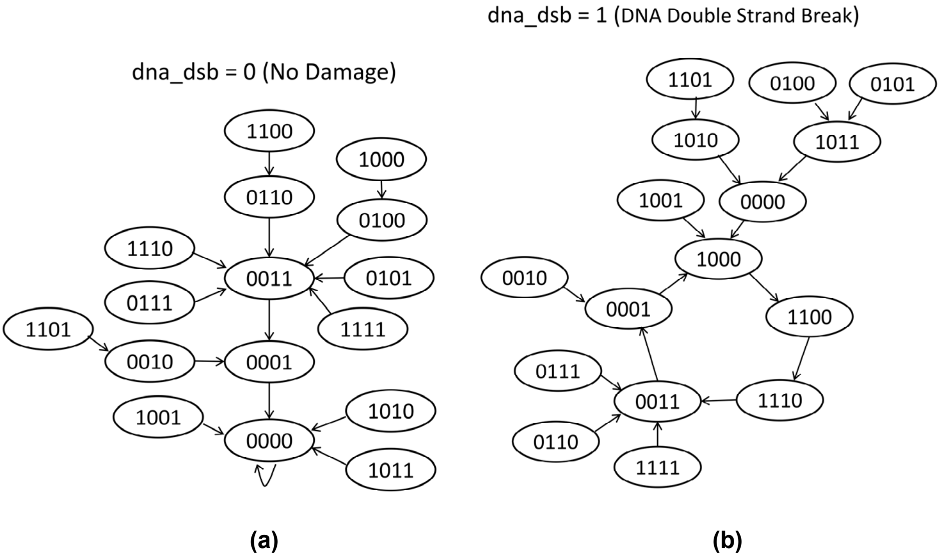


Figure 6.2 State transition diagrams for p53 networks: (a) no damage—single attractor state; (b) damage—five-state attractor cycle.

6.2.2 Probabilistic Boolean networks

From the perspective of each of the two p53 networks, the damage signal is a *latent variable* exterior to the network. Given the value of the latent variable, the network is deterministic; however, latency means that the damage signal is not part of the network and is not observed. Hence, when observed the network is stochastic. One might argue that the problem would be solved by including dna_dab in the network. That would just push the latency further out because dna_dab is being influenced by other unobserved physical events. The central point is that the model system cannot be isolated from interaction with its environment, so, recalling Russell, even if the universe is deterministic, one would have to include all events not totally disconnected from the network, a practical impossibility.

One can incorporate both p53 Boolean networks into a single network by viewing each individual Boolean network as a *context* (constituent) of a network whose regulatory structure is defined at a given time point by setting the damage signal to either 0 or 1. The new network maintains that regulatory structure until it randomly switches to the other Boolean regulation, say dna_dsb = 0 to dna_dsb = 1, with some *switching probability*. The resulting network is called a *probabilistic Boolean network* (PBN) [Shmulevich and Dougherty, 2010]. The PBN inherits the attractor structures of the constituent Boolean networks, the difference being that context switching can result in the network jumping out of an attractor cycle into a different basin of attraction and then transitioning into a different attractor cycle. While the p53 PBN has two contexts, the general definition of a PBN allows any number of context Boolean networks. It also does not require binary-valued genes.

To illustrate network (and biological pathway) switching, suppose there is no damage and the network has settled into the attractor state 0000, as shown in Fig. 6.2(a). Since the role of the p53 network is to respond to DNA damage and since there is no damage, this dormant state is what one might expect. Suppose DNA damage is detected. Then dna_dsb flips to 1, the Boolean network of Fig. 6.2(b) becomes operative, and the state changes from 0000 to 1000 in the next time step, so that almost immediately the 5-state cyclic attractor is entered and p53 oscillates between 0 and 1 on each cycle.

The PBN model incorporates randomness in a structured manner. Should this uncertainty be considered intrinsic, as in the case of quantum mechanics? One could certainly argue that there are hidden variables and that, if we could observe all of them, then the uncertainty would be eliminated. The debate is academic because the physical system is too complex and consists of tens of thousands of variables—genes, proteins, and other macromolecules within a single cell plus all elements pertaining to extra-cellular signaling. Forming a sufficiently extensive model to eliminate latency is impossible. There are two choices: use a deterministic model if the latency is very small, or include the latency-induced stochasticity in the model, as with PBNs.

Further randomness can be introduced to a Boolean network via perturbations. Specifically, for each gene there is some small *perturbation* *probability* that it will randomly switch values. This is practical because there is random variation in the amount of mRNA and protein produced. Perturbations allow a network to jump out of an attractor cycle and, as with context switching, eventually transition to a new attractor. A probabilistic Boolean network is usually assumed to have perturbation randomness in addition to context-switching randomness.

6.3 Validation of Complex Systems

In the classical deterministic scenario, a model consists of a few variables and physical constants. The relational structure of the model is conceptualized by the scientist via intuition gained from thinking about the physical world. Intuition means that the scientist has some mental construct regarding the interactions beyond positing a skeletal mathematical system he believes is sufficiently rich to capture the interactions and then depending upon data to infer the relational structure and estimate a large number of parameters. Classically, there are few parameters to estimate and they are estimated from a handful of experiments. Owing to the deterministic character of the model, it can be tested with a few numerical predictions whose disagreement with future observations is due to either experimental error or model failure, with the former being mitigated by careful experimentation. The theory is contingently accepted if predictions are deemed to be concordant with observations.

As model complexity grows to tens, then hundreds, and then thousands of variables and parameters, the classical procedures become increasingly difficult to carry out. The problem is exacerbated by stochasticity because prediction then includes testing the accuracy of probability distributions in the model. Systems with thousands of variables are virtually unvalidatable.

6.3.1 Validation of deterministic models

For a deterministic model, initial conditions can be set and, in principle, the state at some future time determined exactly, although in practice there will be some experimental variability. If the initial conditions of a test experiment are aligned with those of the model and the experiment run to some future time, then agreement between the final model and experimental states can be checked. Large-scale deterministic systems have high-dimensional state vectors, so that test experiments are more demanding; nevertheless, the ultimate comparison is still between model and experimental state vectors. It is prudent to run tests using a variety of initial conditions so that a large portion of the state space is tested.

Consider validating a Boolean network with k genes. Initializing the state vector at $\mathbf{x}_0$, one determines the state vectors $\mathbf{x}_1, \mathbf{x}_2, \ldots, \mathbf{x}_b$ at times $t = 1, 2, \ldots, b$ via the regulatory logic, initializes the experimental set-up at $\mathbf{z}_0$, runs the experiment taking measurements at each step to compute $\mathbf{z}_1, \mathbf{z}_2, \ldots, \mathbf{z}_b$, and checks for agreement between $\mathbf{x}_1, \mathbf{x}_2, \ldots, \mathbf{x}_b$ and $\mathbf{z}_1, \mathbf{z}_2, \ldots, \mathbf{z}_b$, or perhaps just at some subset of time points.

To see why it is prudent to consider various initial conditions, suppose the Boolean network has two attractor cycles A_1 and A_2, with corresponding basins B_1 and B_2. If the initial state lies in basin B_1, then after some number of steps the network will arrive in attractor cycle A_1. If A_1 and A_2 correspond to modeling two different phenotypes, since the regulatory pathways in the different phenotypes are different, the model might be a good fit for one phenotype but not the other, and this would never be tested by a single initial condition in basin B_1. One would at least need to test initial conditions in the two basins. Beyond that, a single initial condition in a basin will lead to a specific state trajectory, so that disagreements on other pathways might not show up. Thus, prudence dictates testing a number of initial conditions. As network complexity increases, so does the number of tests.

As an example, suppose there is a mutation and the p53 network of Fig. 6.2(b) is altered so that state 0000 becomes an attractor; that is, the network stays in 0000 when there is DNA damage. This can happen with a single alteration in the regulatory logic: when the network is in state 0000, instead of $\text{ATM}_{\text{next}} = 1$, $\text{ATM}_{\text{next}} = 0$. This is a serious mutation because p53 remains off when there is DNA damage so that the downstream effects that it should actuate are not actuated. Regarding validation, the mutated network has two attractors, the singleton 0000 and the original 5-state attractor cycle. If one proceeds to validate the network starting from initial state 1101, then the experiment should end with state 0000. Is this sufficient validation? All that has been tested is the path 1101 → 1010 → 0000. What about initialization at 0101 or, more importantly, at 0111 or 1111, where the cyclic attractor would be tested? It is clear that testing must involve more than a single initial state.

6.3.2 Validation of stochastic models

With a stochastic model, the situation is more challenging. Given an initial state, the final state will not be determined exactly; rather, there will a probability distribution of possible final states. Hence, comparison must be between the state distribution, which is generally multivariate, and a state histogram generated by many experimental runs, the number of required runs growing exponentially with the number of variables. Distributional statistical tests are required. For instance, with hypothesis testing one decides between two hypotheses—the distributions match or they do not match. A decision to accept the theory depends on the acceptance threshold. The theory and test are inter-subjective, but the decision to accept or reject depends on subjective considerations, as with a hypothesis test, where the acceptance region depends on a chosen level of significance. The overall procedure can be onerous (or impossible) depending on the number of experimental runs required, especially with complex systems, where distributions are high-dimensional. Validation of a wave pattern in the double-slit experiment constitutes a low-dimensional example of the method: compare the electron distribution on the detector with the pattern predicted by the wave model.

To illustrate the problem, consider the p53 network in Fig. 6.2(b). State 0000 is important because, if there is no damage, then the ground state is 0000, but now there is damage. At once the cyclic attractor is entered, so that oscillation of p53 takes place. Now suppose ATM is unstable and is subject to perturbation with some probability. While cycling through the attractor states, suppose at state 0011 ATM flips to 1 so that the network is in state 1011. It will then transition through 0000 into the attractor cycle. After several cycles suppose the network arrives at state 1100 and ATM flips to 0 so that the network is in state 0100. Then it will transition through 1011 and 0000 to again be in the attractor cycle. The point is that starting at the initial state 0000 the network will not reach a determined state after a given amount of time; instead, there will be probabilities of being in many, or all, states. To check the model this probability distribution must be tested against living cells, which is extremely difficult even for modest sized networks. This is for one initial state among 16 possible initial states. For a Boolean network with k genes there are 2^k possible initial states.

6.4 Model Uncertainty

Parameter estimation is a basic aspect of model construction and historically it has been assumed that data are sufficient to estimate the parameters, for instance, correlations that are part of the model; however, when the number of parameters is too large for the amount of data, accurate parameter estimation becomes impossible. The result is model uncertainty.

Insufficient data for accurate estimation is an old problem in statistics. For a simple illustration, consider a one-dimensional variable governed by a normal distribution with known standard deviation and unknown mean μ. The standard method of estimating μ is to take a random sample of points $x_1, x_2, \ldots, x_n$ and form the *sample mean* $(x_1 + x_2 + \ldots + x_n)/n$. The sample mean provides a good estimate of the mean if the sample size n is sufficiently large. The precision of the estimate can be quantified in terms of the sample size. If the sample size is small, then rather than a point estimate it may be preferable to provide an interval estimate of the form $[a, b]$, so that there is no specific estimate of the mean. In effect, this means that one is assuming that the "true" model is among the infinite number of possible models compatible with the interval estimate.

For a situation in which model complexity plays a role, consider the p53 network for no damage and suppose that the regulatory function for ATM is unknown. The truth table defining the regulatory structure for the network has 64 $= 4\times2^4$ rows because there are 2^4 possible input states for each of the four genes: 0000, 0001,…, 1111. This means that there are 64 parameters taking values 0 or 1. If there is no existing knowledge concerning the regulation of ATM, then there are 16 unknown parameters: $f_1(0000), f_1(0001), \ldots, f_1(1111)$. Since each of these can have two possible values, 0 or 1, there are 2^{16} possible networks, one for each combination. Owing to uncertainty, instead of one network there is an *uncertainty class* of 65,536 possible networks. Each is represented by a parameter vector θ_k of length 16, so that the uncertainty class takes the form $\Theta = \{\theta_1, \theta_2, \ldots, \theta_{65,536}\}$. This is for a single unknown regulatory function in a single 4-gene binary network!

If there is prior knowledge that can be applied, then the uncertainty class can be reduced. For example, suppose it is known that $\text{ATM}_{\text{next}} = 0$ if $\text{Wip1} = 1$. This knowledge would result from a scenario in which the presence of the Wip1 transcription factor on the promoter region of ATM blocks the binding of activating proteins. In this case, there are only 8 unknown parameters, $f_1(0000)$, $f_1(0001),\ldots, f_1(0111)$, and 2^8 networks in the uncertainty class. This kind of huge complexity reduction puts a premium on prior (existing) knowledge in model construction. The effect of prior knowledge will be seen in the next chapter when we discuss model-based operator design.

6.5 Data Mining

The classical approach to model design is to construct a mathematical structure satisfying the scientist's conceptualization of phenomenal behavior and then estimate model parameters. As models become more complex, in addition to increasing numbers of parameters to estimate, conceptualizing interacting phenomena becomes more taxing. Thus, it has become popular to posit a very general mathematical structure and then, instead of using some statistically best estimate such as maximum likelihood to estimate individual parameters, the parameters are manipulated as a group until the model fits the data to some desired degree. Data-fitting algorithms can be ingenious and may take advantage of high-performance computing to employ models with thousands of parameters.

6.5.1 Overfitting

At first glance, this approach, known as *data mining*, may seem attractive and appear to circumvent the need for conceptualization; however, fitting the data without a satisfactory conceptualization of the interactions (law) underlying the behavior of the phenomena can easily lead to a model that *overfits* the data. The model fits the data but does not model the relevant physical processes, the result being that it poorly predicts future observations and may not even successfully predict existing data not used in model construction. Indeed, the mathematical structure (neural network, graph, etc.) may not be of a suitable form to model the physical processes but is sufficiently flexible on account of its complexity and high dimensionality that it can be fit to the data. To add to the predicament, even if the fitted structure should happen to provide a good model for the underlying processes, there often is no method for precisely estimating its accuracy. Hence, if it is accurate, there is no way to know so.

Climate scientists Tibaldi and Knutti articulate the problem as manifested in their discipline:

> Most models agree reasonably well with observations of the present-day mean climate and simulate a realistic warming over the Twentieth Century (of course, the specific performance depends on each model/metric combination), yet their predictions diverge substantially for

> the Twenty-First century, even when forced with the same boundary conditions. [Tibaldi and Knutti, 2007]

Recall Reichenbach: "Observation informs us about the past and the present, reason foretells the future." Perhaps some reason has been used in constructing climate models, but not enough. Faced with the complexity of climate systems, is it reasonable to believe that there can ever be enough reason?

To illustrate overfitting, consider the problem of finding a *regression* function $y = g(x)$ that best estimates the value of Y given a value of X, where X and Y possess a joint distribution. We denote the random value of Y given a fixed value $X = x$ by $Y|x$. The best estimate in the mean-square sense is the one that minimizes the average value of $|Y|x - \gamma_x|^2$ among all possible estimates γ_x. This average value is known as the expected value and is denoted by E, so the aim is to minimize $E[|Y|x - \gamma_x|^2]$. The minimum mean-square estimate is the mean of $Y|x$, which is denoted by $\mu_{Y|x}$.

In the case of a bivariate normal distribution, if the means of X and Y are μ_X and μ_Y, respectively, their standard deviations are σ_X and σ_Y, respectively, and the correlation coefficient is ρ, then the regression function is given by

$$\mu_{Y|x} = \mu_Y + \rho\frac{\sigma_Y}{\sigma_X}(x - \mu_X), \tag{6.1}$$

which is a straight line with slope $\rho\sigma_Y/\sigma_X$.

A basic problem in statistics is to estimate the regression function from points randomly drawn from the joint distribution. Since for normal distributions the regression function is a straight line, given a joint normal distribution the estimated regression function is taken to be a straight line also. This *sample regression line* constructed from the data is the line $y = a + bx$ that minimizes the error sum of squares

$$\text{SSE} = |y_1 - (a + bx_1)|^2 + |y_2 - (a + bx_2)|^2 + \ldots + |y_n - (a + bx_n)|^2, \tag{6.2}$$

where the sample points are $(x_1, y_1), (x_2, y_2),\ldots, (x_n, y_n)$. As the number of data points grows, the sample regression line becomes closer to the true regression line (in a probabilistic sense).

Suppose one does not know that the joint distribution is normal. Then the true regression line can take almost any form. Should the regression line be highly nonlinear, then assuming a straight line, in particular, using the best-fit regression line for a normal distribution would constrain the estimation to one that is far from accurate regardless of the number of data points. To avoid this kind of constraint, instead of assuming a linear regression, one can assume a polynomial regression. But what order polynomial should be chosen? Should it be high order to better fit the data? Such a choice may provide excellent data fitting on account of complexity and the large number of parameters to be adjusted, but this may result in overfitting if the assumed regression model is overly complex relative to the true regression equation.

Figure 6.3 provides an example involving a joint normal distribution with means $\mu_X = \mu_Y = 3$, standard deviations $\sigma_X = \sigma_Y = 1$, and correlation coefficient $\rho = 0.5$. Each part of the figure shows ten randomly generated data points, the true regression line, and a sample regression line found via the error sum of squares for the assumed form of the line: linear, cubic, fifth-order polynomial, seventh-order polynomial, ninth-order polynomial, and eleventh-order polynomial. As the order of the polynomial grows, the sample regression line fits the data better but gets further away from the true regression line. This is classic overfitting.

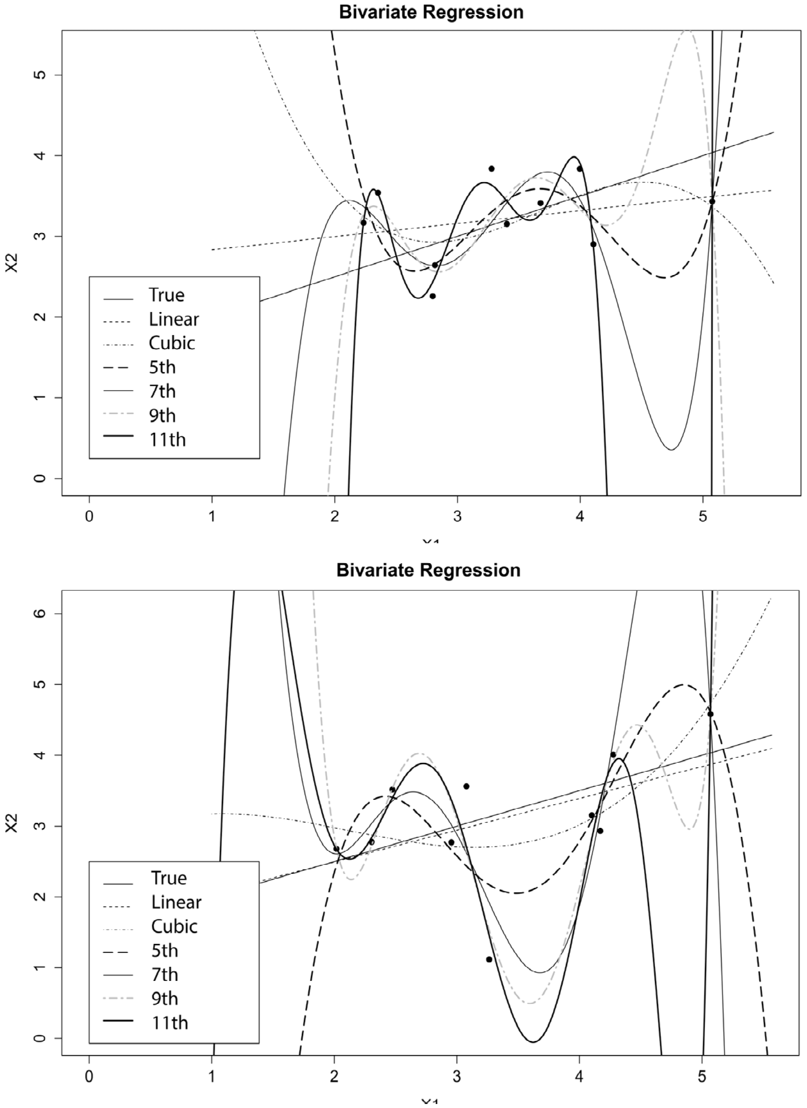


Figure 6.3 Polynomial regression lines of increasing degree fit to two different sets of 10 randomly generated points from a bivariate normal distribution.

If fitting the data is the sole aim, then having enough computing power to fit a complex model, say, one with tens of thousands of parameters in an equally vast dimensional space, is typically the sole issue; however, scientifically, fitting the data is not a sensible aim. A hundred points are lost in thousand-dimensional space and are easily overfit. Think of modeling the approximately 30,000 genes in the human genome. The bigness of data depends on its relation to model dimension, not simply the number of gigabytes.

The complexity dilemma—choosing low model complexity and not capturing behavioral complexity versus choosing high model complexity and overfitting the data—is caused by ignorance. One is trying to model phenomena without sufficient knowledge to do so.

Maxwell addresses the issue squarely:

> As students of physics we observe phenomena under varied circumstances and endeavor to deduce the laws of their relations. Every natural phenomenon is, to our minds, the result of an infinitely complex system of conditions. What we set ourselves to do is to unravel these conditions, and by viewing the phenomenon in a way which is in itself partial and imperfect, to piece out its features one by one, beginning with that which strikes us first, and thus gradually learning how to look at the whole phenomenon so as to obtain a continually greater degree of clearness and distinctness. In this process, the feature which presents itself most forcibly to the untrained inquirer may not be that which is considered most fundamental by the experienced man of science; for the success of any physical investigation depends on the judicious selection of what is to be observed as of primary importance, combined with a voluntary abstraction of the mind from those features which, however attractive they appear, we are not yet sufficiently advanced in science to investigate with profit. [Maxwell, 2003]

In Maxwell's phraseology, an "untrained inquirer" throwing together a huge number of features in the hope that some data-mining algorithm in conjunction with massive computational machinery will discover a nugget is "not yet sufficiently advanced in science." Or, as stated by William Barrett, "The absence of an intelligent idea in the grasp of a problem cannot be redeemed by the elaborateness of the machinery one subsequently employs." [Barrett, 1979]

6.5.2 Asymptotic theory

The complexity dilemma arises from insufficient knowledge to make sufficient assumptions to render principled model design feasible. Modeling assumptions carry risk in the sense that the phenomena may not satisfy them; in fact, they will almost certainly not satisfy them. Nevertheless, absent assumptions there can be no propositions. Omitting distributional assumptions might seem desirable so as not to limit the scope of the theory; however, as seen with regression, the absence of distributional assumptions easily leads to meaningless results.

Can we appeal to asymptotic (sample size $\rightarrow \infty$) statistical theory to guarantee model accuracy? Theorems concerning the convergence to zero of the difference between a parameter estimate and the parameter as sample size goes to infinity go back to Jacob Bernoulli (1655–1705). At best, asymptotic results may say something about estimation accuracy for large samples but they say virtually nothing about small samples—and small samples are the problem for complex systems. Even if data are abundant, unless there are distributional assumptions, an asymptotic theorem usually does not specify how large the sample must be and assumptions have to be imposed to obtain propositions concerning required sample size.

In 1925, Ronald Fisher commented on the limitations of asymptotic theory:

> Little experience is sufficient to show that the traditional machinery of statistical processes is wholly unsuited to the needs of practical research. Not only does it take a canon to shoot a sparrow, but it misses the sparrow! The elaborate mechanism built on the theory of infinitely large samples is not accurate enough for simple laboratory data. Only by systematically tackling small sample problems on their merits does it seem possible to apply accurate tests to practical data. [Fisher, 1925]

Twenty years later, Harald Cramér strongly supported Fisher's position:

> It is clear that a knowledge of the *exact* form of a sampling distribution would be of a far greater value than the knowledge of a number of moment characteristics or a limiting expression for large values of n. Especially when we are dealing with *small samples*, as is often the case in the applications, the asymptotic expressions are sometimes grossly inadequate, and a knowledge of the exact form of the distribution would then be highly desirable. [Cramér, 1945]

Fisher and Cramér, two giants of statistics, make it very clear that real-world problems are often small-sample problems and, for these, asymptotic theory will not do—and they never witnessed today's complexity. Small-sample theory is necessary for statistics to play a major role in acquiring scientific knowledge. For the most part, data mining, which is void of small-sample theory, is high-performance pre-Baconian groping in the dark.

6.6 Limitations of Science

While post-Galilean science has from the outset been restricted to mathematical representation and the ability to perform confirming experiments, the strong limitations of science, as a form of knowledge, implied by these restrictions has become clearer with the desire to apply scientific method to complex stochastic systems. The stumbling block is that the predominant problems in the Twenty-first Century are very different from Einstein's $E = hf$, which only requires estimating Planck's constant. Even modest-sized models in biology contain large numbers of parameters, dwarfing the complexity of the p53 network considered herein. Model uncertainty together with stochasticity precludes the possibility of full-model validation. Partial validation via prediction of some characteristics (features or properties) of the model may be feasible; however, even accepting Einstein's stipulation that "it is only necessary that enough propositions of the conceptual system be firmly enough connected with sensory experiences," this proviso must be applied to such a degree that validation can, at best, be only fragmentary.

Beyond the impediment of mathematical and computational complexity, limitations on measurement accuracy and the inability to perform the large number of experiments required to validate large stochastic systems limit the degree of validation, and therefore the knowledge carried by a model.

A salient example of experimental limitation on scientific knowledge occurs in climate science, where model validation can involve various characteristics, such as mean global temperature and the amount of atmospheric CO_2. While these may be weak compared to full-model validation, application-wise they are important. Because the system is stochastic, prediction involves distributions and data must be obtained for constructing empirical distributions. Is this possible? If a prediction involves the earth and takes place over a long time period, then it may be hard to draw a sufficient number of points. For a time period of ten years, even without random initialization and using successive ten-year periods, it would take a millennium to generate a decent histogram. Reducing validation to model characteristics does not help; the impediment is that sufficient observation of the system is impossible.

Tibaldi and Knutti state the problem:

> The predictive skill of a model is usually measured by comparing the predicted outcome with the observed one. Note that any forecast produced in the form of a confidence interval, or as a probability distribution, cannot be verified or disproved by a single observation or realization since there is always a non-zero probability for a single realization to be within or outside the forecast range just by chance. Skill and reliability are assessed by repeatedly comparing many independent realizations of the true system with the model predictions through some metric that quantifies agreement between model forecasts and observations (e.g. rank histograms). For projections of future climate change over decades and longer, there is no verification period, and in a strict sense there will never be any, even if we wait for a century. The reason is that the emission scenario assumed as a boundary condition is very likely not followed in detail, so the observations from the single climate realizations will never be fully compatible with the boundary conditions and scenario assumptions made by the models. And even if the scenario were to be followed, waiting decades for a single verification dataset is clearly not an effective verification strategy. This

> might sound obvious, but it is important to note that climate projections, decades or longer in the future by definition, cannot be validated directly through observed changes. Our confidence in climate models must therefore come from other sources. [Tibaldi and Knutti, 2007]

Tibaldi and Knutti confront the epistemological crisis of the Twenty-first Century: the desire for valid scientific knowledge and the inability to get it on account complexity or experimental limitations. They state that "climate projections, decades or longer in the future by definition, cannot be validated directly through observed changes." Combine this with Schrödinger's statement that "there does not seem to be much sense in inquiring about the real existence of something, if one is convinced that the effect through which the thing would manifest itself, in case it existed, is certainly not observable." One might argue that climate projections are not theoretically impossible, only pragmatically impossible. But does this matter in practice? Tibaldi and Knutti say that confidence must come from "other sources," but this does not produce a validated scientific theory. There is no scientific truth.

Confronting the limits of verifiability in evolutionary theory, Kauffman calls for a new scientific epistemology:

> What we think of as natural law may not suffice to explain Nature. We now know for example, that evolution includes Darwinian pre-adaptations—unused features of organisms that may become useful in a different environment and thus emerge as novel functionalities, such as our middle ear bones, which arose from the jaw bones of an early fish. Could we pre-state all the possible Darwinian pre-adaptations even for humans, let alone predict them? It would seem unlikely. And if not, the evolution of the biosphere, the economy and civilization are beyond natural law. If this view holds, then we will undergo a major transformation of science. [Kauffman, 2007]

Kauffman is expressing a desire for knowledge that lies outside the bounds of science but he wants it to be scientific in character. This can only be achieved if the requirements for scientific knowledge are weakened.

Regarding the inability to make predictions, in his essay, "Breaking the Galilean Spell," Kauffman writes,

> This incapacity to foresee has profound implications. In the physicist Murray Gell-Mann's definition, a 'natural law' is a compact description beforehand of the regularities of a process. But if we cannot even pre-state the possibilities, then no compact descriptions of these processes beforehand can exist. These phenomena, then, appear to be partially beyond natural law itself. This means something astonishing and powerfully liberating. We live in a universe, biosphere, and human

> culture that are not only emergent but radically creative. We live in a world whose unfoldings we often cannot prevision, prestate, or predict—a world of explosive creativity on all sides. This is a central part of the new scientific worldview. [Kauffman, 2008]

Standing in opposition to Kauffman's new scientific worldview is physicist Lee Smolin, who, in reference to string theory, writes,

> A theory has failed to make any predictions by which it can be tested, and some of its proponents, rather than admitting that, are seeking leave to change the rules so that their theory will not need to pass the usual tests we impose on scientific ideas. It seems rational to deny this request and insist that we should not change the rules of science just to save a theory that has failed to fulfill the expectations we originally had for it. [Smolin, 2006]

The conflict between the desire for knowledge concerning complex systems and the impossibility of testing a model by observing future behavior lies at the center of the epistemological crisis of the Twenty-first Century. There appear to be four basic options for science:

1. Dispense with modeling complex systems that cannot be validated.
2. Model complex systems and pretend they are validated.
3. Model complex systems, admit that the models are not validated, utilize them pragmatically where possible, and be extremely prudent when interpreting them.
4. Strive to develop a new and perhaps weaker scientific epistemology.

Option three carries the risk of eviscerating science as a result of laziness; however, option one leaves major problems in medicine, engineering, economics, etc. that have substantial impact on the human condition outside of systematic investigation. Option three is certainly better than option two, which appears to be widespread. Recall Woodcock's estimate that as much as 75% of published biomarker associations are not replicable—and although these may be high dimensional, their complexity is low compared to other systems being investigated. Pretending that theories are scientifically valid when they are not inevitably leads to poor policy decisions by political leaders who must put their faith in science, while at the same time rendering the scientific literature suspect. Pursuing option three may motivate a serious effort in regard to option four, which could lead to a multi-level epistemology that would support meaningful scientific theories at different levels of validation.

If the requirements of science are to be weakened, this needs to be done with great care, deep philosophic reflection, and in a manner that maintains a rigorous formal relationship between theory and phenomena. Given the substantial obstacles confronting the pursuit of scientific knowledge in complex systems, a satisfactory resolution could easily be a century or more away, if at all. Human beings are limited in their capacity for knowledge. It took three centuries from the birth of modern science until quantum theory to fully clarify the epistemological revolution of Galileo, during which time the greatest minds took up the challenge. Perhaps we have reached our limit and the rules of the game cannot be relaxed without collapsing the entire enterprise into a Tower of Babel. Whatever the case, the issue is too important to ignore and let science aimlessly become “primitive and muddled.”

Chapter 7

Translational Science under Uncertainty

7.1 Translational Science

Modern engineering begins with a scientific model but in addition to the model there is an objective, such as making a decision based on observations, filtering a signal to reduce noise or accentuate particular frequencies, or intervening in a natural system to force its behavior in a more beneficial direction. The situation changes from modeling behavior to affecting behavior. In medicine, engineering is popularly called *translational science*, which accurately describes modern engineering. A scientific model, whose purpose is to provide a conceptualization of some portion of the physical world, is transformed into a model characterizing human action in the physical world. Scientific knowledge is translated into practical knowledge by expanding a scientific system to include inputs that can be adjusted to affect the behavior of the system and outputs that monitor the effect of the external inputs and feed back information on how to adjust the inputs [Dougherty, 2009a]. For example, in biomedical science models are created with the intention of using them for diagnosis, prognosis, and therapy.

If one is going to transform a physical process, then the conceptualization of that physical transformation takes the form of a mathematical operator on some mathematical system, which itself is a scientific model for the state of Nature absent the transformation. It may be that one cannot obtain a model that can be validated via prediction—that is, a model that has scientific validity—but one may nevertheless find a model that can be used to determine a beneficial operator. The product of pure science is a validated model, whereas the product of translational science is an operator that transforms some aspect of Nature in a quantifiably useful manner. When modeling a cell, the endpoint for pure science is a representation of the dynamical interaction between its macromolecules; for translational science the endpoint might be determination of a drug that will block a signal activating unwanted cellular proliferation. For translation, the scientific model is an intermediate construct used to facilitate control of Nature; its descriptive power is of concern only to the degree that it affects the operator designed from it. For translational science, the epistemological requirements for accepting the model as scientifically valid are replaced by requirements regarding the performance of the operator derived from it. The epistemology of pure science is replaced by the epistemology of practical science [Dougherty, 2016].

The aim of the present chapter is to discuss the basic aspects of translational science in the classical framework of a fully known model and then to examine the situation where the model is uncertain. It is in the presence of uncertainty that the epistemology of translational science confronts operator design in the context of Twenty-first Century complexity. Optimal operator design under uncertainty will be considered in three settings: therapeutic intervention in gene regulatory networks, pattern classification, and signal filtering. Each of these requires some mathematics, but only in the case of signal filtering is some special knowledge required, and we have tried to keep that to a minimum so that the basic ideas are accessible to most readers.

7.2 Anatomy of Translational Science

There are two basic operator problems concerning systems. One is *analysis*: given a system, characterize the properties of the transformed system resulting from the operator in terms of the properties of the original system. Often it is not mathematically feasible to characterize completely the transformed system, or only certain properties of the original system may be known, so that the best one can do is to characterize related properties of the transformed system. This is fine so long as one can characterize those properties of interest to the application. As an example, for a linear operator on a stochastic process, it is usually sufficient to characterize the output covariance function in terms of the input covariance function.

The second basic operator problem is *synthesis*: given a system, design an operator to transform the system in some desirable manner. Synthesis represents the critical act for intervention and forms the basis of modern engineering (translational science). One could grope in the dark, trying one operation after another and observing the result; however, since groping is not grounded in scientific knowledge, we do not consider it to be translational science. In the context of translational science, synthesis begins with the relevant scientific knowledge constituted in a mathematical theory that is used to arrive at an optimal (close to optimal) operator for accomplishing a desired transformation under the constraints imposed by the circumstances. A criterion, called a *cost function* (*objective function*) is defined to judge the goodness of the response—the lower the cost, the better the operator. The objective is to find an optimal way of manipulating the system, which means minimizing the cost function.

Translational-scientific synthesis originated with optimal time series filtering in the classic work of Andrey Kolmogorov [Kolmogorov, 1941] and Norbert Wiener [Wiener, 1949]—although published in 1949, an unpublished version of Wiener's work appeared in 1942. In the Wiener–Kolmogorov theory, the scientific model consists of two random signals, one being the true signal and the other being an observed "noisy" variant of the true signal. The translational aim is to linearly operate on the observed signal so as to transform it to be more like the true signal. Being that a linear operator is formed by a weighted average, the synthesis problem is to find an optimal weighting function for the linear operator and the goodness criterion is the mean-square difference between the true and filtered signals (for a detailed account of the translational nature of the Wiener–Kolmogorov theory, see [Dougherty, 2009b]).

For translational science, synthesis generally involves four steps:

1. Construct the mathematical model.
2. Define a class of operators.
3. Define the optimization problem via a cost function.
4. Solve the optimization problem.

One might prefer a valid scientific model when synthesizing an operator because design would then be based on a system that accurately reflects Nature and thus would portend a better performing operator; however, there is no requirement that the model provides a predictive representation of Nature when application is the goal. With translation, one approaches Nature with the aim of achieving a practical benefit, which is contextual, relative to the cost function and the conditions of application. A translational perspective may be the only viable option when only a targeted objective can reduce the scale of the problem to one that is experimentally, mathematically, and computationally tractable. The predictive capacity of the scientific model is not primary because it is merely a tool and the relevant knowledge applies to the objective, not to the tool. The objective is an optimally performing operator, where performance is measured by the cost function.

In practice, optimality will not be achieved because a physical realization of the mathematical operator must be constructed. Moreover, since there is no assumption of validity regarding the scientific model, one cannot expect that a translationally optimal operator will perform optimally relative to a validated model, although it might. Thus, while the theoretical objective is an optimal mathematical operator, the practical objective is a close-to-optimal physical operator. The actual performance can be evaluated by applying the designed physical operator and estimating the cost function from the data. This is often less burdensome than model validation; nevertheless, there may still be insufficient data for obtaining a good estimate, depending on the complexity of the cost function and the difficulty of testing.

7.2.1 Structural intervention in gene regulatory networks

When every gene in a Boolean network (or PBN) has a positive perturbation probability, then for any state $\mathbf{x}$ the probability that the network is in state $\mathbf{x}$ in the long run (in the limit) is independent of the initial state. This limiting probability is called a *steady-state probability* and the collection of all such probabilities is called the *steady-state distribution*. Not every network possesses a steady-state distribution. For instance, consider a 3-gene deterministic Boolean network with two basins: 100 → 010 → 001 → 000 and 110 → 011 → 101 → 111. Then the long-run probability of 000 is 1 if the network is initialized at 100 and is 0 if it is initialized at 110. There is no steady-state distribution.

Assuming the existence of a steady-state distribution, structural intervention in a gene regulatory network involves a one-time change of the regulatory structure to reduce the steady-state probabilities of undesirable (pathological) states [Qian and Dougherty, 2008]. This means minimizing the sum of the steady-state probabilities corresponding to the undesirable states. Following [Yoon et al., 2013], to illustrate structural intervention we consider a mammalian cell cycle Boolean network with perturbation ($p = 0.01$) based on a regulatory model proposed by [Faure et al., 2006]. Intervention is based on the fact that in molecular biology there are techniques for “pathway blockage.” We employ a structural intervention that models small interfering RNA (siRNA) interference in regulatory relationships: an intervention blocks the regulation between two genes in the network.

The cell cycle involves a sequence of events resulting in the duplication and division of the cell. It occurs in response to growth factors and under normal conditions it is a tightly controlled process. The model contains 10 genes: CycD, Rb, p27, E2F, CycE, CycA, Cdc20, Cdh1, UbcH10, and CycB, with genes numbered in this order. The cell cycle in mammals is controlled via extra-cellular stimuli. Positive stimuli activate Cyclin D (CycD) in the cell, thereby leading to cell division. CycD inactivates the Rb protein, which is a tumor suppressor. When gene p27 and either CycE or CycA are active, the cell cycle stops, because Rb can be expressed even in the presence of cyclins. States in which the cell cycle continues even in the absence of stimuli are associated with cancerous phenotypes. For this reason, states with down-regulated CycD, Rb, and p27 ($x_1 = x_2 = x_3 = 0$) are undesirable.

The regulatory model, shown in Fig. 7.1, has blunt arrows representing suppressive regulations and normal arrows representing activating regulations. Genes are assumed to be regulated according to the majority vote rule. At each time point, a gene takes the value 1 if the majority of its regulator genes are activating and the value 0 if the majority of the regulator genes are suppressive; otherwise, it remains unchanged. A structural intervention removes an arrow from the regulatory graph because it blocks a regulation between two genes. By the optimization methods of [Qian and Dougherty, 2008] it is determined that the structural intervention that maximally lowers undesirable steady-state probability blocks the regulatory action from gene CycE to p27 and reduces total undesirable steady-state probability from 0.3405 to 0.2670. The steady-state distributions for the original network and the treated network are shown in Fig. 7.2.

The translational character of structural intervention is reflected in how the four aspects of synthesis are manifested:

1. Model the cell cycle by a Boolean network with perturbation.
2. An intervention operator blocks a single regulation between two genes.
3. The cost is the total steady-state probability of the undesirable states.
4. An optimal action is found via the method of [Qian and Dougherty, 2008].

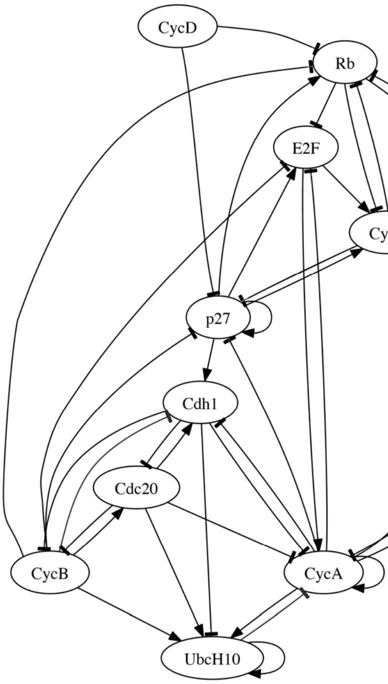
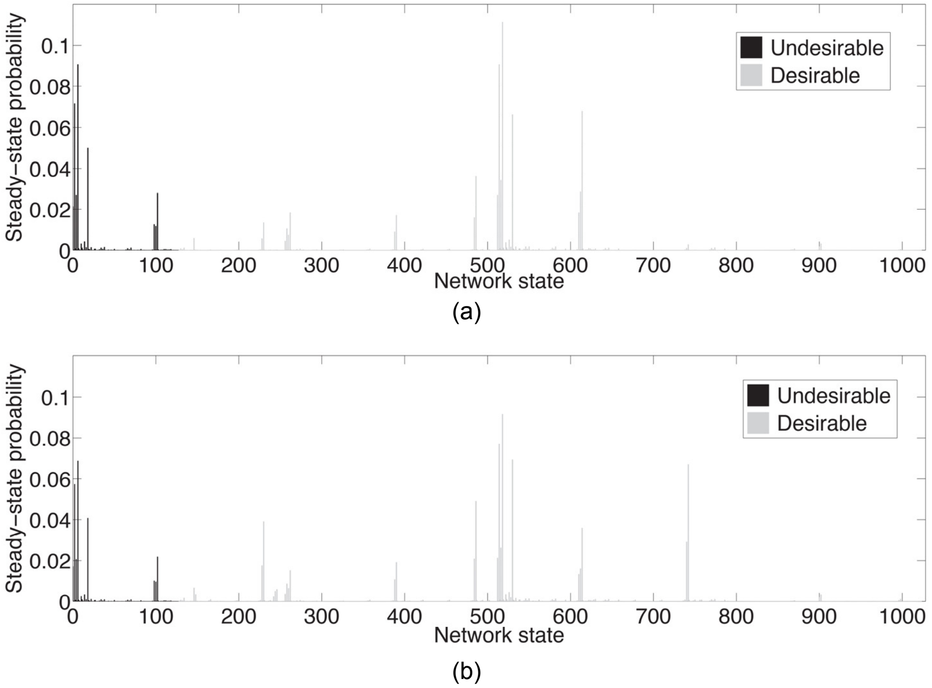


Figure 7.1 Mammalian cell cycle network (adapted from [Yoon et al., 2013]).



(a)

(b)

Figure 7.2 Steady-state distribution for mammalian cell cycle network (states listed numerically): (a) original and (b) after optimal structural intervention. (Part (a) adapted from [Yoon et al., 2013]).

In practice, basing the optimization on a cost function alone may not be satisfactory and constraints on the optimization may need to be imposed. In the case of gene regulation optimization can be phenotypically constrained, meaning that when altering steady-state probabilities one may wish to constrain where the probability is moved [Qian and Dougherty, 2012]. For instance, while lowering steady-state probability for undesirable states, one may wish to keep it from being moved to states known to be associated with carcinogenesis or to states that do not typically occur in healthy cells. In general, the optimization problem should be set up with input from cancer biologists.

7.3 Operator Design in the Presence of Model Uncertainty

To formulate optimization when there is model uncertainty, consider a stochastic model $\mathcal{M}$ with uncertainty class Θ. For example, $\mathcal{M}$ might be a gene regulatory network with some unknown regulations, so that Θ consists of all possible parameter vectors corresponding to the unknown regulations. Let C be a cost function and Ψ be a class of operators on the model whose performances are measured by the cost function. This means that for each operator $\psi \in \Psi$ there is a cost $C_\theta(\psi)$ of applying ψ on model $\theta \in \Theta$. For example, suppose Ψ consists of 5 drugs, meaning that each operator acts by applying a drug. Suppose the goal of the drug treatment is to reduce the expression of a particular gene g associated with metastasis in breast cancer and that the gene regulatory network being used is uncertain, so that there is an uncertainty class Θ of models. The cost function might be the average gene expression for g over some time interval after the drug has had time to take effect. Then $C_\theta(\psi)$ is the average gene expression over the time interval when drug ψ is applied to model θ. Since the full network model is unknown, there being uncertain parameters, one would like to choose a drug whose performance works well over the uncertainty class.

An *intrinsically Bayesian robust* (IBR) operator on $\mathcal{M}$ is an operator $\psi_{\mathrm{IBR}} \in \Psi$ such that the expected (average) value over Θ of the cost $C_\theta(\psi)$ is minimized by ψ_{IBR}, the expected value being with respect to a *prior probability distribution* $\pi(\theta)$ over Θ [Dalton and Dougherty, 2014]. An IBR operator is robust in the sense that on average it performs well over the whole uncertainty class. Since each parameter vector $\theta \in \Theta$ corresponds to a model, a probability distribution on the space of possible models quantifies our belief that some models are more likely to be the actual full model than are others. Such a distribution reflects prior knowledge. If there is no prior knowledge beyond the uncertainty class itself, then the prior distribution is taken to be *uniform*, meaning that all models are assumed to be equally likely.

Denoting the expected value over Θ by E_Θ, an IBR operator minimizes the expected value of the cost:

$$E_\Theta[C_\theta(\psi_{\mathrm{IBR}})] = \min\{E_\Theta[C_\theta(\psi)],\ \psi \in \Psi\}. \tag{7.1}$$

If the uncertainty class is finite, say, $\Theta = \{\theta_1, \theta_2, \ldots, \theta_m\}$, then the expected cost over the uncertainty class is a weighted average, the costs being weighted by the prior distribution:

$$E_\Theta[C_\theta(\psi)] = C_{\theta_1}(\psi)\pi(\theta_1) + C_{\theta_2}(\psi)\pi(\theta_2) + \ldots + C_{\theta_m}(\psi)\pi(\theta_m). \tag{7.2}$$

If Θ is infinite, then the expected value over Θ is given by the integral of the cost over Θ with respect to the prior distribution:

$$E_\Theta[C_\theta(\psi)] = \int_\Theta C_\theta(\psi)\pi(\theta)d\theta. \tag{7.3}$$

The basic idea is straightforward: find an operator that minimizes the average cost when applied to all models in the uncertainty class. Based on existing knowledge, which is captured in the known parameters and the prior probability distribution over the uncertainty class, an IBR operator provides the best robust performance across the uncertainty class. When one possesses no knowledge concerning the likelihoods of the models in the uncertainty class and the prior distribution is *uniform* over Θ, then $\pi(\theta_1) = \pi(\theta_2) = \ldots = \pi(\theta_m) = 1/m$ in Eq. (7.2).

7.3.1 IBR structural intervention in gene regulatory networks

We return to the mammalian cell cycle network but now consider intrinsically Bayesian robust structural intervention. Uncertainty occurs because there are D pairs of genes for which the existence of a regulatory relationship is known but the type of relationship, activating or suppressing, is unknown. Consequently, the network uncertainty class Θ consists of 2^D possible networks, where each $\theta \in \Theta$ corresponds to a specific assignment of regulation types to the D uncertain edges. The uncertainty class is governed by a uniform prior distribution, meaning that we have no knowledge concerning model likelihood and all uncertain parameters have prior probability $1/2^D$. As previously assumed, a structural intervention blocks the regulatory action between a pair of genes in the network. Once gain, the cost function is the total undesirable steady-state probability. Based on the given mammalian cell cycle network, simulations have been run in [Yoon et al., 2013] that incrementally increase the number of edges with unknown regulation from $D = 1$ to $D = 10$. In each case, 50 uncertain networks are created by randomly selecting uncertain edges while keeping the regulatory information for the remaining edges.

Grouping the models with 1 to 5 uncertain edges, 54.0% of the time the IBR structural intervention is the actual optimal intervention, which blocks the regulation from CycE to p27. As seen in Section 7.2.1, when applied to the full model, this reduces total undesirable steady-state probability to 0.2639. The second most selected IBR intervention blocks the regulation from CycE to Rb. It is chosen 41.6% of the time and reduces total undesirable steady-state probability to 0.2643. Four other interventions are chosen a total of 4.4% of the time.

Since the optimization provides the intervention that works best on average over the uncertainty class, it may choose an intervention that performs poorly on the full network. In this simulation, blocking regulation between CycB and p27 is selected 2.0% of the time and only reduces undesirable steady-state probability to 0.3244. When the simulation is run with 6 to 10 uncertain edges, blocking CycE to p27 or blocking CycE to Rb accounts for 88.8% of the IBR interventions, as opposed to 95.6% of the IBR interventions for 1 to 5 uncertain edges. This change reflects the greater uncertainty.

7.4 Pattern Classification

Pattern classification is used in every applied discipline because it is the mathematical formulation of decision making and every discipline requires decisions. In cancer medicine, classification can be between different kinds of cancer, stages of tumor development, or prognoses. This section considers optimal binary classification when the model is known and when it is uncertain.

7.4.1 Optimal classification for a known feature-label distribution

The basic idea for classification is that *features* are calculated on objects from two different populations, and based on a vector of features a classifier decides which population an object belongs to. For instance, gene expressions are measured for k genes, and based on the measurements it is decided which drug should be administered. A feature vector belongs to one of two classes, labeled 0 and 1. The model is stochastic and consists of feature-label pairs $(\mathbf{X}, Y)$, where $\mathbf{X} = (X_1, X_2, \ldots, X_k)$ and $Y = 0$ or $Y = 1$. A *classifier* ψ is a decision function on the set of feature vectors: $\psi(\mathbf{X}) = 0$ or $\psi(\mathbf{X}) = 1$. It partitions the feature space into two regions, R_0 and R_1.

For classification, the scientific model consists of two distributions, called *class-conditional distributions*: $f(\mathbf{x}|0)$ and $f(\mathbf{x}|1)$ are the probability distributions governing the behavior of feature vectors in class 0 and class 1, respectively. The model also requires the probability c_0 that a randomly selected object comes from class 0, which automatically gives the probability c_1 that it comes from class 1 since $c_1 + c_0 = 1$. Taken together, $f(\mathbf{x}|0)$, $f(\mathbf{x}|1)$, and c_0 provide the *feature-label distribution* $f(\mathbf{x}, y)$ governing the feature-label vectors. For simplicity, we assume that $c_0 = c_1 = ½$, so that the classes are equally likely.

The *error* of any classifier ψ is the probability of erroneous classification, $\varepsilon[\psi] = P(\psi(\mathbf{X}) \neq Y)$, which can be found from the feature-label distribution. Letting Ψ denote the set of all classifiers on the model, an optimal classifier is called a *Bayes classifier* and is denoted by ψ_{Bay}. It has minimum error among all classifiers in Ψ and need not be unique. Given $c_0 = c_1 = ½$, a Bayes classifier is defined by a simple rule: for a given feature vector $\mathbf{x}$,

$$\psi_{\text{Bay}}(\mathbf{x}) = \begin{cases} 1, \text{if } f(\mathbf{x}\,|\,1) \geq f(\mathbf{x}\,|\,0) \\ 0, \text{if } f(\mathbf{x}\,|\,1) < f(\mathbf{x}\,|\,0) \end{cases}. \tag{7.4}$$

This is equivalent to $\psi_{\text{Bay}}(\mathbf{x}) = 1$ if and only if $f(\mathbf{x}, 1) \geq f(\mathbf{x}, 0)$, which intuitively means that ($\mathbf{x}$, 1) is more likely than ($\mathbf{x}$, 0). The error of a Bayes classifier is known as the *Bayes error*. It is denoted by ε_{Bay} and is the minimum among the errors of all classifiers on the feature-label distribution. While there may be many Bayes classifiers for a feature-label distribution, the Bayes error is unique.

Consider a single measurement X of a system that has a normal distribution with mean 0 and standard deviation σ when the system is in the unperturbed state, but when the system is perturbed in a particular way the normal distribution shifts so that its mean becomes $\theta > 0$, while maintaining the same standard deviation. We desire a classifier to predict the state of the system (unperturbed or perturbed) based on the measurement X. Assuming equal likelihood for the two states, Fig. 7.3 shows that a Bayes classifier is defined by

$$\psi_{\text{Bay}}(x) = \begin{cases} 1, \text{if } x \geq \theta/2 \\ 0, \text{if } x < \theta/2 \end{cases}, \tag{7.5}$$

and the error is the area of the shaded region.

For a more visual example, consider the two normal two-dimensional class-conditional distributions in Fig. 7.4. They have different mean vectors in the plane and have the same covariance matrix (which determines the shape of the surfaces). A Bayes classifier is defined by the straight line that separates the plane into regions R_0 and R_1. If $\mathbf{x} \in R_0$, then $\psi_{\text{Bay}}(\mathbf{x}) = 0$; if $\mathbf{x} \in R_1$, then $\psi_{\text{Bay}}(\mathbf{x}) = 1$. If the covariance matrices were not equal, then the class-conditional distributions would not have the same shape and the decision boundary would be quadratic instead of linear.

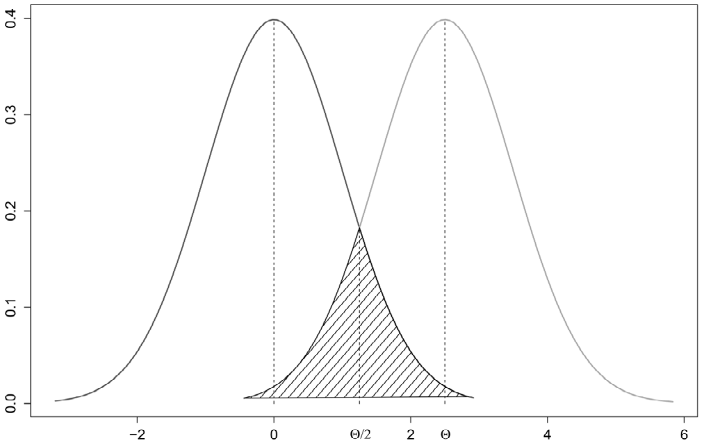


Figure 7.3 Bayes classifier for one-dimensional normal class-conditional distributions.

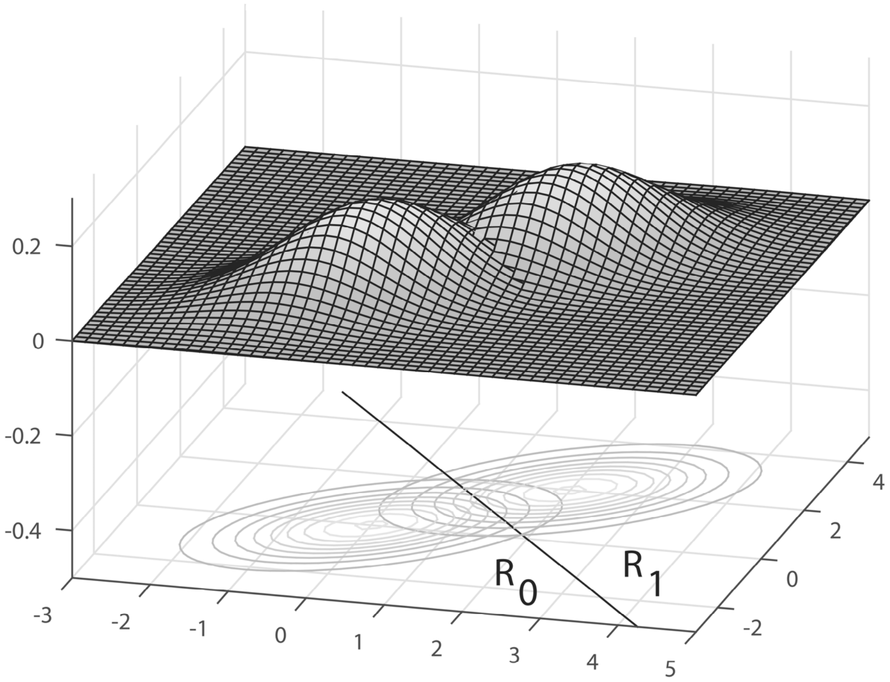


Figure 7.4 Bayes classifier for two-dimensional normal class-conditional distributions.

Considering features and labels as physical measurements, the feature-label distribution represents knowledge of the variables X_1, X_2,…, X_k, Y. The Bayes error is intrinsic to the model and quantifies the separability of the classes relative to the features. We desire features that separate well the class-conditional distributions. Given a feature-label distribution, one can in principle find a Bayes classifier and the Bayes error; however, for important models, only in rare cases have these been analytically derived from the feature-label distribution, but they can be approximated by numerical methods.

Corresponding to the four generic steps for optimal operator synthesis are the following four steps for classification:

1. Construct the feature-label distribution.
2. The operators consist of classifiers on the feature-label distribution.
3. The cost is classifier error.
4. An optimal operator is given by a Bayes classifier.

7.4.2 Intrinsically Bayesian robust classification

Model uncertainty arises when full knowledge of the feature-label distribution is lacking. Knowledge must come from existing scientific knowledge regarding the features and labels or be estimated from data. Since accurate estimation of distributions requires a huge amount of data, the amount increasing rapidly with dimension and distributional complexity, full knowledge of the feature-label distribution is rare. With model uncertainty, there is an uncertainty class Θ of parameter vectors corresponding to feature-label distributions. In this setting, an intrinsically Bayesian robust classifier is defined by minimizing the expected error across the uncertainty class. Letting $\varepsilon_\theta[\psi]$ denote the error of classifier ψ on model θ and recalling Eq. (7.1), an IBR classifier satisfies

$$E_\Theta[\varepsilon_\theta[\psi_{\mathrm{IBR}}]] = \min\{E_\Theta[\varepsilon_\theta[\psi]], \psi \in \Psi\} = \min\left\{\int_\Theta \varepsilon_\theta[\psi]\pi(\theta)d\theta, \psi \in \Psi\right\}, \quad (7.6)$$

where $\pi(\theta)$ is the prior distribution over Θ and where the integral has the same dimensionality as the parameter vectors in Θ.

We return to the classification problem of Fig. 7.3 with the supposition that θ is unknown but is known to lie in the interval $[0, b]$. Then the uncertainty class $\Theta = [0, b]$ corresponds to an infinite number of feature-label distributions. Absent other knowledge of θ, it is assumed to be uniformly distributed over $[0, b]$, meaning that it is described by the prior distribution $\pi(\theta) = 1/b$ if $\theta \in [0, b]$ and $\pi(\theta) = 0$ if $\theta \notin [0, b]$. For each value of $\theta \in [0, b]$, a Bayes classifier is defined by Eq. (7.5) and its error is found as in Fig. 7.3. Then, according to Eq. (7.6), an IBR classifier satisfies

$$E_\Theta[\varepsilon_\theta[\psi_{\mathrm{IBR}}]] = \min\left\{\frac{1}{b}\int_0^b \varepsilon_\theta[\psi]d\theta, \psi \in \Psi\right\}, \quad (7.7)$$

where the integral is one-dimensional.

The minimization of Eq. (7.6) is analogous to the minimization for determining a structural intervention in a gene regulatory network except that, whereas for structural intervention as defined for the mammalian cell cycle network one can compute a finite number of operator costs (undesirable steady-state probabilities) and take the least, for IBR classification there is an infinite number of operators (classifiers) to consider. As expressed in Eq. (7.6), and exemplified in Eq. (7.7), one is left with the problem of finding a minimizing classifier when the collection of classifiers is infinite. A formula is needed that produces an IBR classifier.

This problem is solved in [Dalton and Dougherty, 2013] under very general conditions. The method uses *effective class-conditional distributions* for the uncertainty class. These are defined by the expected values of the individual class-conditional distributions over the uncertainty class. Formally, let $f(\mathbf{x}|0; \theta)$ and $f(\mathbf{x}|1; \theta)$ denote the class-conditional distributions for $\theta \in \Theta$. Then the effective class-conditional distributions are defined by the expected values (averages) of these over the uncertainty class:

$$f(\mathbf{x}|0;\Theta) = E_\Theta[f(\mathbf{x}|0;\theta)] = \int_\Theta f(\mathbf{x}\,|\,0;\theta)\pi(\theta)\,d\theta\,, \tag{7.8}$$

$$f(\mathbf{x}|1;\Theta) = E_\Theta[f(\mathbf{x}|1;\theta)] = \int_\Theta f(\mathbf{x}\,|\,1;\theta)\pi(\theta)\,d\theta\,. \tag{7.9}$$

Continuing to assume that $c_0 = c_1 = ½$, an IBR classifier is found in exactly the same manner as a Bayes classifier, except that the effective class-conditional distributions are used:

$$\psi_{\text{IBR}}(\mathbf{x}) = \begin{cases} 1, \text{if } f(\mathbf{x}\,|\,1;\Theta) \geq f(\mathbf{x}\,|\,0;\Theta) \\ 0, \text{if } f(\mathbf{x}\,|\,1;\Theta) < f(\mathbf{x}\,|\,0;\Theta) \end{cases}. \tag{7.10}$$

7.5 Posterior Distribution

In addition to a prior distribution coming from existing knowledge, suppose one has a data sample S independently sampled from the full model. Then a *posterior distribution* is defined by $\pi^*(\theta) = \pi(\theta|S)$, which is the prior distribution conditioned on the sample. The posterior distribution is derived using standard statistical techniques, although, depending on the prior distribution, it may not be mathematically feasible to obtain an exact expression for $\pi^*(\theta)$ and numerical methods may be used to approximate it. Once the posterior distribution has been found, the IBR theory can be used with $\pi^*(\theta)$ in place of $\pi(\theta)$, the resulting operator being known as an *optimal Bayesian operator*. As illustrated in Fig. 7.5, under appropriate conditions, as the sample grows, the posterior distribution becomes more tightly centered about the parameter vector for the full model.

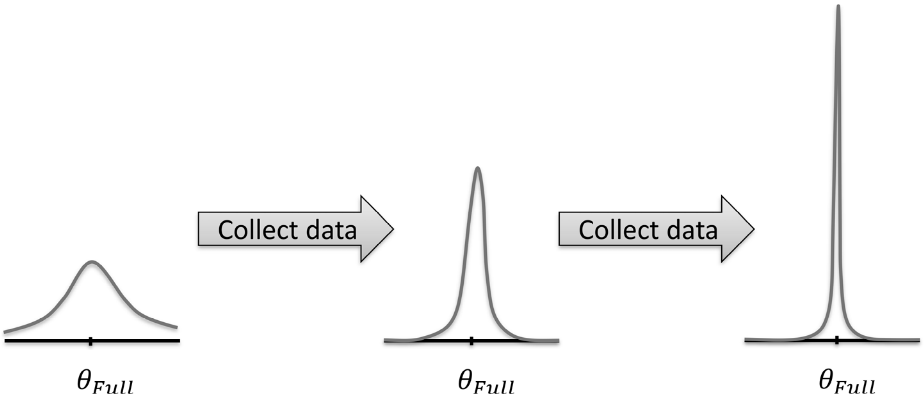


Figure 7.5 Tightening of the posterior distribution with increasing data.

7.5.1 Optimal Bayesian classification

For classification, the sample data consist of feature-label pairs and these are used to find the posterior distribution [Dalton and Dougherty, 2011]. Effective class-conditional distributions are defined by Eqs. (7.8) and (7.9) with $\pi^*(\theta)$ in place of $\pi(\theta)$, and an *optimal Bayesian classifier* (OBC) is defined by Eq. (7.10) [Dalton and Dougherty, 2013]. An OBC has minimum expected error relative to the posterior distribution $\pi^*(\theta)$, which contains all of our knowledge, prior knowledge as interpreted via the prior distribution and experimental data.

Owing to the growing concentration of the posterior distribution around the full model, as illustrated in Fig. 7.5, as the sample size grows ever larger, the OBC typically converges to a Bayes classifier for the full model (Fig. 7.6). While this is an attractive property and is common for optimal Bayesian operators defined via posterior distributions, its practical significance is limited because the basic problem is lack of data.

Figure 7.7 illustrates OBC behavior. There is an uncertainty class of feature-label distributions, each possessing normal class-conditional distributions with equal covariance matrices. The dotted lines are level curves for the normal class-conditional distributions corresponding to the average means and covariance matrices relative to a given posterior distribution. The dashed straight line is the decision boundary for the Bayes classifier corresponding to average mean and covariance parameters. The solid line is the boundary for the OBC. Note that every feature-label distribution in the uncertainty class and the average feature-label distribution have linear (straight line) Bayes classifiers; however, the OBC has a more complex decision boundary. This results from the fact that all class-conditional distributions in the uncertainty class are normal but the effective class-conditional distributions are not normal.

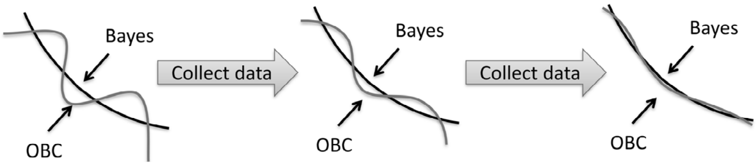


Figure 7.6 Convergence of the OBC to the Bayes classifier.

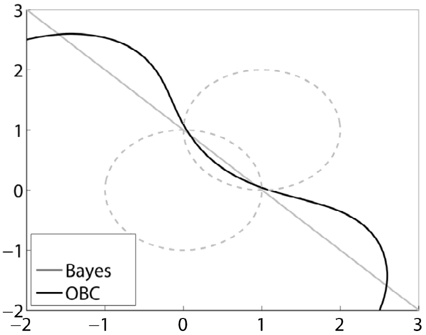


Figure 7.7 Comparison of OBC and Bayes classifier for an average model.

7.5.2 Distribution-free classification

In pattern recognition it is common to assume no prior knowledge concerning the feature-label distribution, so that classifier design is *distribution-free*. Hence, the subject has grown around the notion of a *classification rule*, which is some procedure applied to the sample data to construct a classifier, such as a support vector machine, neural network, or a host of other procedures. The particularities of classification rules are not of interest here. For our purposes, one need only recognize that a classification rule uses sample data to construct a classifier, and individual performance depends on the unknown feature-label distribution and sample size. The rules are heuristic, in the sense that their formulation is based on some guiding principle rather than optimization.

Once a classifier is designed, the salient issue is its error. The problem is that, given a sample, we cannot find the error of the resulting classifier because the feature-label distribution is not known. The problem then is to find an estimate of the error. In general, this can be approached in two ways.

If there is an abundance of sample data, then the data can be split into two disjoint sets: a *training set* used to design the classifier and *test set* used to estimate the error of the classifier. Once the classifier is designed, the test error is the proportion of errors it makes on the test set. This error is called the *hold-out error* owing to the fact that the test set has been held out from the training procedure. How good is the hold-out estimate? The obvious answer would be to quantify goodness by $|\hat{\varepsilon} - \varepsilon|$, where ε and $\hat{\varepsilon}$ are the true and estimated errors, respectively; however, this is impossible because the true error is unknown. Instead, we consider how well the estimation procedure works on average. This performance measure is given by the root-mean-square (RMS) error, which is the square root of the expected value of $|\hat{\varepsilon} - \varepsilon|^2$, namely, RMS = $E[|\hat{\varepsilon} - \varepsilon|^2]^{1/2}$, which is the square root of the mean-square error (MSE) and where the expectation (average) is taken with respect to the sampling procedure.

As it stands, the RMS cannot be found because it requires knowledge of the feature-label distribution. Nevertheless, it is known that, irrespective of the feature-label distribution, RMS $\leq 1/(2m^{1/2})$, where m is the size of the test set [Devroye, et al., 1996]. This is a good result since it is distribution-free and for a test sample of the modest size $m = 100$, RMS ≤ 0.05. It does not depend on dimension (number of features) or classifier complexity. Even though the accuracy of the specific estimate is not known, there is a precise bound on estimation performance. While the RMS bound for classification error estimation is encouraging, one should keep in mind that a classifier is a very simple model, just a binary function.

Because classifier error quantifies the predictive capacity of a classifier, error-estimation accuracy is the salient epistemological issue for classification. Hence, the bound on the hold-out estimate is a fundamental epistemological measure.

Hold-out error estimation requires a sufficiently large sample so that there are enough data to design the classifier (a problem we will not consider) and enough independent data for error estimation. Based on the RMS bound, 100 test points provides reasonably good error estimation. If sample data are limited, say, to a sample size of 100, then hold-out error estimation cannot be employed and the error must be estimated using the training data. Numerous methods have been proposed for training-data-based error estimation, each possessing different properties [Braga-Neto and Dougherty, 2015]. The simplest method is known as *resubstitution*, where the error estimate is the proportion of errors made by the designed classifier on the training data. Resubstitution is usually optimistically biased (often strongly) and therefore rarely used. Error-estimation methods in which the training data are re-sampled for design and testing within the training data include cross-validation and bootstrap. These tend to perform poorly on small samples owing to large variance and lack of regression with the true error. There are very few known distribution-free RMS bounds for training-data error estimation. For the few cases in which distribution-free RMS bounds are known, they are very weak and a large sample is required to obtain an acceptable bound, which renders the bound useless because training-data error estimation methods are being used precisely because the sample is too small to split into training and test data. In sum, the salient epistemological issue for small-sample classification is that quantifiable distribution-free error estimation is virtually impossible.

If one has distributional knowledge in the form of an uncertainty class and a prior distribution, then a posterior distribution can be derived using the sample data, in which case the error of a designed classifier can be estimated as the expected error over the posterior distribution. The resulting estimate is known as the *Bayesian error estimate* (BEE) [Dalton and Dougherty, 2011]. This can be done because the true error of the classifier can be evaluated for each model in the uncertainty class, after which these errors are averaged with respect to the posterior distribution. It can be proven that the resulting error estimate is optimal relative to the expected (average) RMS over the uncertainty class. It may not be best for all models in the uncertainty class, but it is best on average, which means it is best relative to all of our knowledge, prior distribution plus sample data.

In sum, given a prior distribution on the uncertainty class and sample data, the OBC is the optimal classifier and the BEE is the optimal error estimate. Absent prior knowledge, small-sample classification is essentially pointless owing to the impossibility of obtaining an error estimate whose accuracy can be quantified.

7.6 Translational Science under Model Uncertainty

When the uncertainty class is finite, an intrinsically Bayesian robust operator can be found by computing a finite number of costs, as in Eq. (7.2); however, for infinite uncertainty classes, some other approach must be found. In the case of classification, for each model in the uncertainty class the individual class-conditional distributions are considered as characteristics of the full model that define an optimal operator (Bayes classifier) for that model. The methodology of [Dalton and Dougherty, 2013] is to construct *effective characteristics* and then prove that an IBR operator, which in this case is an IBR classifier, can be constructed in the same way as an individual optimal operator (Bayes classifier) by replacing the individual model characteristics with effective characteristics.

Thus, with model uncertainty we have the following IBR synthesis protocol, which will be illustrated in subsequent subsections:

1. Construct the mathematical model.
2. Define a class of operators.
3. Define the basic optimization problem via a cost function.
4. Solve the basic optimization problem via characteristics of the model.
5. Identify the uncertainty class.
6. Construct a prior distribution.
7. State the IBR optimization problem.
8. Construct the appropriate effective characteristics.
9. Prove that the IBR optimization problem is solved by replacing the model characteristics by the effective characteristics.

7.6.1 Wiener filter

Wiener filtering involves two random signal processes, an unobserved true signal and an observed signal, with the aim being to apply a linear filter on the observed signal to estimate the true signal. For details, see Section 4.7.2 in [Dougherty, 1999]. Here, for those with some background in filtering, we provide highlights without supporting theory to illustrate how the various steps for translational synthesis apply. The true signal and observation processes, $Y(t)$ and $X(t)$, respectively, are jointly wide-sense stationary (WSS) and possess zero means. The autocorrelation function for the observation process is denoted by $r_X(\tau)$ and the cross-correlation function between the signal and observation processes is denoted by $r_{YX}(\tau)$.

A linear filter with weighting function $\hat{g}$ takes the form

$$\hat{Y}(s) = \int_T \hat{g}(s-t)X(t)\,dt\,, \tag{7.11}$$

where the integral is over an observation window T. The objective is to obtain an estimate of the true signal that minimizes the mean-square error (MSE) at a given point s, which is defined as

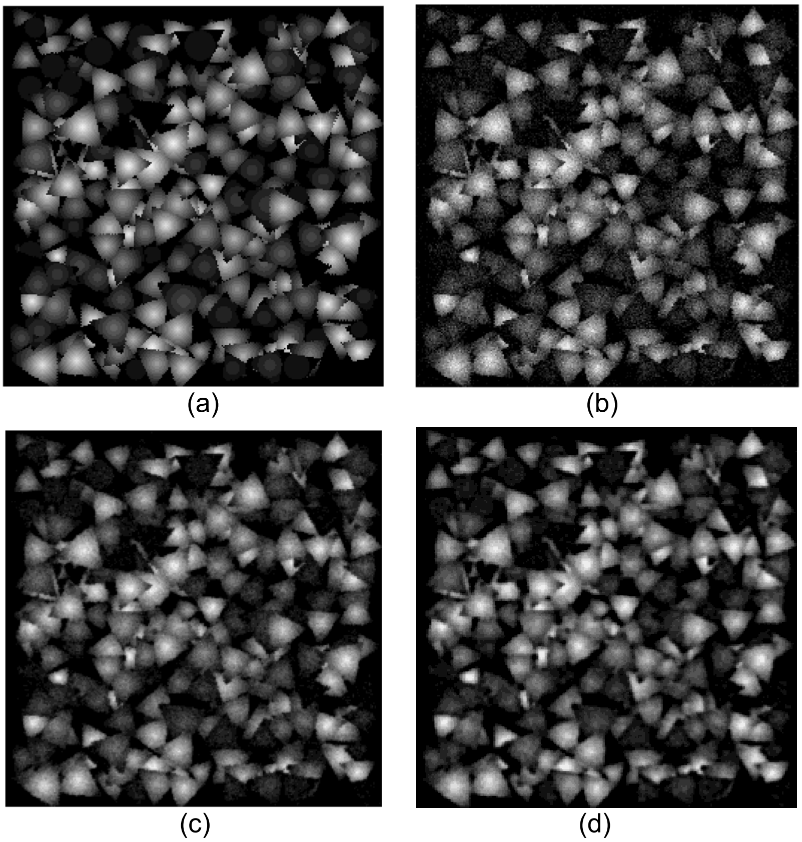
$$\text{MSE}\langle \hat{Y}(s)\rangle = E[|\hat{Y}(s)-Y(s)|^2]\,. \tag{7.12}$$

For any WSS random process, the *power spectral density* of the process is the Fourier transform of the autocorrelation function. For the observation process, it is given by $S_X(\omega) = \mathcal{F}[r_X](\omega)$, where $\mathcal{F}$ denotes the Fourier transform. The *cross power spectral density* is $S_{YX}(\omega) = \mathcal{F}[r_{YX}](\omega)$, the Fourier transform of the cross-correlation function between the signal and observation processes. $S_X(\omega)$ and $S_{YX}(\omega)$ are characteristics of the model, and under rather general conditions it is well-known that the Fourier transform of the optimal weighting function is

$$\hat{G}(\omega) = \frac{S_{YX}(\omega)}{S_X(\omega)}. \tag{7.13}$$

The optimal weighting function, which defines the *Wiener filter*, is obtained by taking the inverse Fourier transform. This is the major classical result of signal filter theory. It applies to images by performing all operations in two dimensions.

Figure 7.8 illustrates Wiener filtering with a digital image process consisting of random grains. Parts (a), (b), and (c) of the figure show an image generated by the process, that image degraded by both blurring and random point noise, and the noisy image filtered by the Wiener filter for the random process, respectively. The filtering problem is made more difficult when there is both blurring and point noise because for blurring alone the image can be "sharpened" and for point noise alone it can be "smoothed." Mixed blurring and point noise is tricky because sharpening makes point noise worse and smoothing makes blurring worse. Without a mathematical approach to the problem it would be virtually impossible to find a close-to-optimal weighting function.



(a) (b)

(c) (d)

Figure 7.8 Wiener filtering of blurred and noisy image: (a) original image, (b) degraded image, (c) optimally filtered image, (d) IBR filtered image (adapted from [Dalton and Dougherty, 2014]).

Notice the basic four steps of translational synthesis in the present context:

1. The model consists of two jointly WSS random processes.
2. The operator class consists of linear filters over an observation window.
3. Optimization: minimize the MSE as defined in Eq. (7.12).
4. The optimization problem is solved by the Fourier transform of the weighting function in terms of the power spectra $S_X(\omega)$ and $S_{YX}(\omega)$.

7.6.2 IBR Wiener filter

Model uncertainty arises in Wiener filtering when either the autocorrelation or cross-correlation function is unknown. For $\theta \in \Theta$, the signal and observation processes are $Y_\theta(s)$ and $X_\theta(t)$, respectively, and the autocorrelation and cross-correlation functions are $r_{\theta,X}(\tau)$ and $r_{\theta,YX}(\tau)$, respectively. The *effective power spectra* are the Fourier transforms of the expected autocorrelation function, $S_{\Theta,X}(\omega) = \mathcal{F}[E_\Theta[r_{\theta,X}]](\omega)$, and the expected cross-correlation function, $S_{\Theta,YX}(\omega) = \mathcal{F}[E_\Theta[r_{\theta,YX}]](\omega)$. While it is easy to write these down abstractly, the difficulty of evaluating them depends on how the observation process is modeled because they can involve complicated integrals.

With model uncertainty, the optimal linear filter has to minimize the expected mean-square error over the uncertainty class, $E_\Theta[\mathrm{MSE}\langle \hat{Y}_\theta(s) \rangle]$. Under rather general conditions the Fourier transform of the weighting function for the IBR Wiener filter is given by

$$\hat{G}_\Theta(\omega) = \frac{S_{\Theta,YX}(\omega)}{S_{\Theta,X}(\omega)} \tag{7.14}$$

[Dalton and Dougherty, 2014]. The form of the filter is the same as when the model is known, except that the characteristics $S_X(\omega)$ and $S_{YX}(\omega)$ are replaced by the effective characteristics $S_{\Theta,X}(\omega)$and $S_{\Theta,YX}(\omega)$.

For the Wiener filter, the second part of the IBR synthesis protocol takes the following form:

5. The uncertainty class is defined in terms of the uncertain parameters in the autocorrelation and cross-correlation functions.
6. A prior distribution is constructed for these parameters.
7. IBR optimization: minimize the expected MSE.
8. The effective characteristics are the effective power spectra.
9. Prove that the IBR optimization problem is solved by replacing the model characteristics by the effective characteristics.

The fundamental part of the protocol is the last step: find conditions under which the solution to the IBR optimization is solved by replacing the characteristics in the ordinary solution with effective characteristics—and prove it.

A suboptimal Bayesian approach to filtering under model uncertainty was first taken in the case of nonlinear filtering of digital binary images [Grigoryan and Dougherty, 1999] and then for linear filtering of random signals as considered here [Grigoryan and Dougherty, 2001]. These solutions were suboptimal because they restricted filter selection to a filter that is optimal for at least one model in the uncertainty class. An intrinsically Bayesian robust linear filter, where there is no such constraint, was solved more recently. Interestingly, full optimization via the IBR paradigm is mathematically less complex than the suboptimal solution—once conditions are found so that ordinary characteristics can be replaced by effective characteristics. As is often the case in mathematics, framing a problem "correctly" makes the solution transparent.

7.6.3 A more general synthesis protocol

There is a long history of robust Wiener filtering under model uncertainty. The problem was first treated in the form of *minimax* optimization, where the aim was to find a filter having best worst-case performance: if possible, find a linear filter that has the minimum maximum MSE over all models in the uncertainty class [Kuznetsov, 1976; Kassam and Lim, 1977; Poor, 1980]. Minimax robustness is conservative. The drawback is that it can be overly conservative, especially if the uncertainty class is large. From a probabilistic perspective, a minimax robust filter can be overly influenced by outlier models because it does not take into account a prior (or posterior) distribution on the uncertainty class. To place minimax robust filtering into a translational synthesis framework, step 6 of the IBR synthesis protocol is omitted and the optimization of step 7 becomes minimization of the maximum MSE instead of the expected MSE.

Considering translational synthesis from a general perspective, a cost function is introduced based on minimization of the original full-model cost function relative to the uncertainty. In this view, IBR optimization has cost function $C_\Theta(\psi) = E_\Theta[C_\theta(\psi)]$ and minimax robust optimization has cost function $C_\Theta(\psi) = \max_\Theta\{C_\theta(\psi)\}$. From a completely general perspective, steps 6 through 9 of the IBR synthesis protocol reduce to

6′. Choose a cost function on the uncertainty class.
7′. Optimization: minimize the cost function over the uncertainty class.
8′. Find conditions under which the optimization problem can be solved.

The IBR synthesis protocol is a special case of this general synthesis protocol. As stated, the IBR protocol assumes that IBR optimization will take the form of effective characteristics. While this has been the case thus far, it may turn out that for some synthesis problems an IBR operator will not be defined in terms of effective characteristics. Then IBR synthesis will fall into the more general paradigm with cost function $C_\Theta(\psi) = E_\Theta[C_\theta(\psi)]$.

7.7 Objective Cost of Uncertainty

The IBR principle is to find an operator (classifier, filter, structural intervention, etc.) that, based on a cost function, is optimal over an uncertainty class relative to a prior (or posterior) distribution reflecting the state of our knowledge regarding the underlying physical processes. While an IBR operator is optimal over the uncertainty class Θ, it is likely to be suboptimal relative to the full model. This loss of performance is the cost of uncertainty.

To quantify this cost, for $\theta \in \Theta$, let C_θ be the cost function applied on model θ and let ψ_θ be an optimal operator for θ. Then $C_\theta(\psi_\theta) \leq C_\theta(\psi)$ for any operator ψ. Let ψ_{IBR} be an IBR operator for Θ. Owing to the optimality of the IBR operator over the uncertainty class, $E_\Theta[C_\theta(\psi_{\mathrm{IBR}})] \leq E_\Theta[C_\theta(\psi)]$ for any operator ψ. An IBR operator is optimal over Θ; however, there is a cost to this choice relative to applying the optimal operator for θ on θ because $C_\theta(\psi_\theta) \leq C_\theta(\psi_{\mathrm{IBR}})$ for all $\theta \in \Theta$.

For any $\theta \in \Theta$, the *objective cost of uncertainty* (OCU) relative to θ is the cost differential between an IBR operator and an optimal operator for θ applied on θ:

$$\mathrm{OCU}(\theta) = C_\theta(\psi_{\mathrm{IBR}}) - C_\theta(\psi_\theta). \tag{7.15}$$

The cost of uncertainty relative to the full model is $\mathrm{OCU}(\theta_{\mathrm{full}})$, where θ_{full} is the value of θ for the full model; however, since the full model is unknown, this quantity cannot be calculated. Thus, as the basic quantification of uncertainty we use the *mean objective cost of uncertainty* (MOCU):

$$\mathrm{MOCU}(\Theta) = E_\Theta[\mathrm{OCU}(\theta)] = E_\Theta[C_\theta(\psi_{\mathrm{IBR}}) - C_\theta(\psi_\theta)] \tag{7.16}$$

[Yoon, et al., 2013]. If there is no uncertainty, then the uncertainty class contains only one model and $\mathrm{MOCU}(\Theta) = 0$; however, the converse is not true.

From a scientific perspective, one might prefer to use the entropy of the prior (or posterior) distribution because it measures uncertainty with respect to the model; however, entropy does not focus on the translational objective. There may be large entropy but with most (or all) of the uncertainty irrelevant to the objective. For instance, in controlling a network there may be much uncertainty in the overall network but a high degree of certainty regarding the mechanisms involved in the control. In this case, the entropy might be large but the MOCU be small, which is what matters from a translational perspective. Because the MOCU is intrinsic to the translational system, given our knowledge and objective (cost function), it quantifies the uncertainty in our knowledge with respect to our objective and therefore is an epistemological parameter.

Knowledge can be increased by generating data to produce a new posterior distribution. If there is a collection of possible experiments that can supply information relating to the unknown parameters, which experiment should be performed first? (Here we ignore time and cost but these can be factored in if desired.) Since the MOCU quantifies the average lack of optimality owing to uncertainty, a reasonable course of action is to choose an experiment from the space of possible experiments that yields the minimum expected MOCU given the experiment [Dehghannasiri, et al., 2015]. This requires, for each possible experiment, computing the MOCU for every possible outcome of the experiment, averaging these MOCU values, and then taking the minimum of these averages over all possible experiments. The result is *optimal experimental design* relative to the objective uncertainty. This can be done in an iterative fashion, at each stage choosing an optimal experiment, running the experiment, updating to a new posterior distribution, re-computing the MOCUs, determining an optimal experiment, and so on.

Figure 7.9 illustrates the benefit of optimal experimental design in the context of IBR structural intervention (Section 7.3.1). Five parameters in a mammalian cell cycle network are randomly selected to be unknown; two sequences of five experiments are simulated, one in which the experiments are randomly chosen and another in which they are chosen via an optimized iteration; at each step of each sequence the total undesirable steady-state probability is computed for the IBR structural intervention; this procedure is repeated a number of times; and the average undesirable probabilities are computed and plotted on the vertical axis. The advantage of optimal experimental design is clear: on average, the objective knowledge gained from the first two optimally chosen experiments is equivalent to that gained via four randomly chosen experiments.

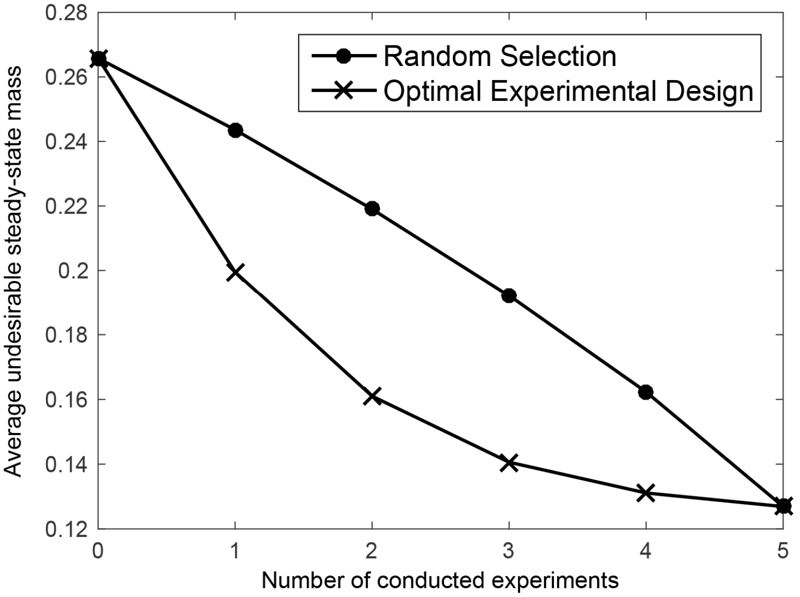


Figure 7.9 Random versus optimal experimental design (adapted from [Dehghannasiri et al., 2015]).

7.8 Small-Data Epistemology

The current crisis in scientific epistemology results from a severe lack of data in relation to the complexity of the systems that people wish to model. Although “Big Data” is the buzzword, the profound problem for science and engineering is small data. There is insufficient data for validation and insufficient data for estimating model parameters. In the present chapter we have taken the view that insufficient data for estimation can be framed in terms of uncertainty classes with prior knowledge represented via a prior distribution over the uncertainty class and translational operator design optimized relative to the posterior distribution.

What kind of knowledge is this prior knowledge? Consider a numerical (not a vector) model parameter θ and suppose, based on an accepted scientific theory, it is deduced that $a \leq \theta \leq b$. For instance in a multi-dimensional normal model, θ might represent the correlation between two features and in the physical system from which the features are constructed it may be that $0 \leq \theta \leq 0.5$. Absent more knowledge concerning θ, we have taken the view that a uniform distribution over the interval $[a, b]$ is a suitable form of prior knowledge. θ is what it is, and that we do not know. True, we know that it is between a and b, but it is not uniformly distributed over $[a, b]$. Saying that θ possesses a uniform prior distribution over $[a, b]$ is not a statement pertaining to the actual value of θ.

Essentially, a prior distribution is a pragmatic construct based on belief as to where a parameter is located. It is clearly advantageous to have scientific knowledge that constrains the parameter and thereby constrains its prior distribution. Since a prior is a construct, not validated scientific knowledge, the more it is constrained by scientific knowledge and the more experience one has with the physical system, the more confident one can be that the prior distribution is concentrated around the full model. If one has confidence, then a tight prior is preferable because tighter priors require less data for good performance; however, there is risk because a prior distribution whose mass is concentrated away from the true parameter will perform worse than one that is uniform. These issues have long been discussed in the Bayesian literature.

In 1946, Harold Jeffreys proposed a uniform prior, referred to as *Jeffrey’s prior* [Jeffreys, 1946]. Objective-based methods were subsequently proposed, a few early ones being [Kashyap, 1971], [Bernardo, 1979], and [Rissanen, 1983]. The principle of maximum entropy can be seen as providing a method of constructing least-informative priors [Jaynes, 1957, 1968]. These methods are general and do not target any domain-specific type of prior information. More targeted approaches can be constructed that integrate scientific knowledge specific to the problem at hand. For instance, in relation to the pathway knowledge we have utilized in the p53 and mammalian cell cycle networks, one can construct a prior distribution quantifying and integrating prior knowledge in the form of signaling pathways [Esfahani and Dougherty, 2014]. In 1968, E. T. Jaynes remarked, “Bayesian methods, for all their advantages, will not be entirely satisfactory until we face the problem of finding the prior probability squarely.” [Jaynes, 1968] The problem remains.

Yet we must remember that for translational science the prior distribution is a construct to facilitate operator design. Given a cost function, an IBR operator is optimal on average relative to the prior (or posterior) distribution but our real interest is an operator that is optimal relative to θ_{full}, the value of θ for the full model. Only rarely will an IBR operator be optimal for θ_{full}. Can an IBR operator somehow be "validated" on the model corresponding to θ_{full}? Strictly speaking, the question makes no sense if it means to show that an IBR operator is optimal for θ_{full}; indeed, we expect it not to be optimal for θ_{full}, which we do not know. An IBR operator has no direct connection to the full model. It is only related via the prior (or posterior) distribution.

Intrinsically Bayesian robust operators cannot cure the small-data epistemological problem for the complex systems that modern engineering wishes to study and control. What they can do is place operator design under uncertainty in a rigorous optimization framework grounded in an infrastructure utilizing prior knowledge and data, while providing uncertainty quantification relative to a translational objective at the level of the underlying processes. The deep problem is that there appears to be no way to objectively transform existing knowledge into a prior distribution. Although there are ways to construct a mathematically rigorous transformation, these ultimately involve subjective considerations.

Within the bounds set by existing scientific knowledge, the formalization of uncertainty, which is the prior distribution, must be constructed via subjectively imposed criteria. This is similar to the basic epistemology of prediction, since in the latter, even though the model and experimental protocol are inter-subjective, the decision whether to accept or reject a theory depends on subjective criteria; nevertheless, with model uncertainty the situation is more unsettling because it is not even clear that the notion of predictive validation can be tied to observations. If, however, we take the perspective that when application is primary and doing nothing is, in fact, a decision, then at least if one follows a formal translational science optimization protocol the overall procedure will be inter-subjective even though there may be disagreement regarding the criteria imposed for construction of the prior distribution. Subsequent to that construction, the prior distribution and cost function jointly form a hypothesis from which an optimal operator can be deduced.

All men are mortal.
Socrates is a man.
Therefore, Socrates is mortal.

But are all men mortal?

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THE EVOLUTION OF SCIENTIFIC KNOWLEDGE

From Certainty to Uncertainty

Edward R. Dougherty

This book aims to provide scientists and engineers, and those interested in scientific issues, with a concise account of how the nature of scientific knowledge evolved from antiquity to a seemingly final form in the Twentieth Century that now strongly limits the knowledge that people would like to gain in the Twenty-first Century. Some might think that such issues are only of interest to specialists in epistemology (the theory of knowledge); however, today's major scientific and engineering problems—in biology, medicine, environmental science, etc.—involve enormous complexity, and it is precisely this complexity that runs up against the limits of what is scientifically knowable. To understand the issue, one must appreciate the radical break with antiquity that occurred with the birth of modern science in the Seventeenth Century, the problems of knowledge and truth engendered by modern science, and the evolution of scientific thinking through the Twentieth Century.

The book concludes by considering the impact of scientific uncertainty on the translation of scientific knowledge into means to alter the course of Nature—that is, the effect of uncertainty in engineering. It proposes a course of action based on integrating existing partial knowledge with limited data to arrive at an optimal operation on some system, where optimality is conditioned on the uncertainty regarding the system. As for a new scientific epistemology in which valid knowledge can be defined, that awaits the bold efforts of fertile minds enriched with the mathematical, scientific, and philosophic education required for such a quest.

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