CONTINGENCY IN BIOPHYSICAL RESEARCH

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The 2002 meeting in this series*[1] asked whether social scientists should select problems that their most reliable methods can answer or they should address the most important questions, sacrificing reliability. Should they focus on methods or problems? The disrupting consequences of contingency that undermine the ability to find causal relations are common to both directions. Often social scientists look up to "hard" science as a methodology that has satisfactorily handled the uncertainties raised by contingency. The extent to which such science has successfully replaced uncertainty and contingency with reliable relations or laws is best illustrated by physics and its applications. The hope that physical science can help to eliminate contingency suggests that a somewhat detailed examination of the varying roles contingency plays in physical science, particularly in its approach to human issues, might reveal insights that advance the goals of the present volume.

In physical science many laws have been so thoroughly tested that they are generally accepted as true, although it is well known that no generalization is ever proven regardless of the many times it fits the data or predicts the outcome. Newton's laws of motion held for more than two centuries of intense examination until Einstein was able to show that their application was valid only in a limited range of velocities. Notwithstanding their limited validity, and the fact that no induction is ever absolutely true, still we bet our lives and everything we hold dear on the expectation that the laws of classical mechanics will hold in our everyday life when we drive a car or hold a baby.

[1] Add citation to previous series and any publications.

This reliance upon the causal relationships embodied in these laws is what we mean when we allow ourselves to think that causality has been established in physical science and contingency has been banished. However when physical science is applied to the study of organic life, to the biology or social behaviors of individuals or social groups, even the believers in an absolutely true physics will acknowledge that the confidence introduced by reliable laws is eroded. In these applications contingency emerges as a factor that must be considered as being similar but not identical to its role in the social sciences. My argument is that physics is trustworthy within the inorganic world, but when its methods are applied to the biological world, its reliability is circumscribed, although, as we shall see, its strengths can be maintained. The reliability of physical understanding in these applications then depends critically upon methods and assumptions, and thereby varies considerably, ranging from the near certainty of physical laws to the levels of uncertainty that haunt many efforts in the social sciences. In the biophysical world, like George Orwell's pigs, all studies are equally contingent but some are more equal than others: equally contingent because they are all human creations, not absolutes dictated by nature; more equal because some are based more directly than others upon sound physical mechanisms and laws that limit the uncertainty of our interpretations.

To distinguish the different applications of contingency requires a thumbnail sketch of the levels referred to above. The absolute, inescapable level of contingency is that proposed by Richard Rorty, among others, when he says that all understanding of the world is contingent because it is created by humans and expressed in language. Our concepts are not discovered in nature, writ in stone, but are proposed by humans and should be valued only by their usefulness. Although many prominent scientists disagree with this description, I find it valuable and will accept it for purposes of this essay. The next level contains the highly reliable, well-tested laws and methods developed for physical science, which while still contingent, are human creations that only resemble absolute truths in the ways they are useful for understanding and controlling the world. Finally, in the third level, lie all the remaining human efforts to understand the world and to navigate through life, where innumerable factors exist beyond our understanding and control. At this level the contingent nature of human efforts are most evident. It is this third kind of contingency that I assume social scientists are interested in minimizing and for which they sometimes turn to the physical sciences for guidance. In this chapter I illustrate two different ways that physical science can be used to limit contingency in studies of humans, taken from long term research projects my colleagues and I have conducted.

In biophysical chemistry we study the place that biochemical reactions occupy in the overall functions of the complex organisms with an eye toward a better understanding of life. These studies are considered physical science because their explanations are acceptable only to the extent they can be expressed in terms of the laws of physics. We study biochemical pathways *in vivo* in bacteria, animals and humans with highly technical methods and machines that have been developed in the past thirty years. The research designs and the interpretation of the results depend upon the century old physics of quantum mechanics, spectroscopy and thermodynamics. Historically thermodynamics has supported many important applications of physical laws to biological questions, and its well established laws have provided valuable guidance for studying and interpreting normal and abnormal human physiology. Before considering different examples I would again emphasize that reliance upon physical laws, with their quite dependable causal interpretations, is itself a starting point dedicated to minimizing contingency. Relying upon the methodology of thermodynamics in biophysical research limits the biological questions that can be addressed but improves the reliability of the answers. The use of thermodynamics depends upon the ability to make quantitative measurements of work, energy, and rates of well delineated chemical systems. Very few biological systems and even fewer experimental methodologies can provide such information, so that choosing subjects because of their suitability for this kind of study places our research in the methodological camp. The strengths of physics that have guided our method-driven studies can minimize contingency; they do not eliminate it, but they can localize it and limit its consequences. This criterion for choosing subjects differs from the majority of biophysical or biochemical studies in which the problems are selected by their worldly significance and the standard methodological rigor of physical science is sacrificed.[2]

To illustrate how physical science encounters contingency in the complexity of humans as subjects of investigation, or as investigators of the subject, in this chapter we present two cases illustrating how biophysical research proceeds until it runs head long into unyielding contingencies.

The first example, a study of diabetes, illustrates the management of contingency in a well-defined biomedical question. In Non Insulin Dependent Diabetes (NIDD), the pancreas secretes insulin but the body does not use it effectively to remove glucose from the blood. NIDD has a genetic component, as evidenced by high correlation to family

[2] A well publicized example of the approach we have not taken is offered by genomics in which the DNA sequence is confidently predicted to explain important biological functions e.g. inheritable traits, behavior and disease. However answers to these questions are still unavailable since they await resolution of the thorny methodology required by genetic determinism.

history and by its high concordance in identical twins. Certain life style contributions play important roles since a controlled diet and active exercise can contribute to delaying or ultimately avoiding the high blood glucose and its harmful consequences. Absent these preventative lifestyle changes-and sometimes in spite of them- the disease follows as fairly predictive course. In early life the pancreas over produces insulin which compensates for its ineffectiveness, so that blood glucose concentrations are maintained in the normal range. However in later life the overproduction may cease, creating high concentrations of blood glucose that subsequently damage muscle, eyes, or other organs with devastating consequences for the quality and duration of life. Based upon these properties and the definition of the disease developed over the centuries by medical science, and armed by earlier biochemical studies, my colleagues and I studied this disease in humans by the use of thermodynamic methods we had developed to follow metabolic fluxes by Nuclear Magnetic Resonance Spectroscopy. Similar to the more familiar Magnetic Resonance Imaging (MRI) that follows water non-invasively in the body; Nuclear Magnetic Resonance Spectroscopy (MRS) can measure the flow of biochemicals such as glucose non-invasively in humans. MRS has enabled us to locate the particular chemical step in diabetic patients, and their off-spring, responsible for the slower clearance of glucose under insulin stimulation. Further, we showed how the well known protocols of diet and exercise can restore normal glucose storage rates by normalizing this particular step.

It was at this point, however, that we were forced to confront the limitations of biophysical science with its powerful tools for explaining causality. In some patients genetically predisposed to the disease, the pancreas continues to overproduce insulin even later in life, and the glucose levels remain at tolerable levels, so the patient stays healthy. We do not know why some fare better than others. Despite the odds, some sedentary obese subjects remain healthy while some vigorous lean, subjects fall ill. In both groups factors beyond our ken, arising from the individual's contingent history, have an effect on their fate. We face two distinct limitations on our ability to help patients. The first uncertainty comes from failing to understand the mechanism of pancreatic failure. Fortunately we can reasonably expect that this complex and seemingly contingent event will soon be understood by additional research. But the second factor that determines who gets the disease, is life style: some subjects simply cannot stick to a healthy regimen of diet and exercise, a fact that reflects the contingencies of the human mind, and such mechanisms are presently not explainable by spectroscopy.

Our research on diabetes has built upon the cumulative advances in medicine, chemistry and physics over the centuries. Diabetes has long been recognized, and the anomalously high blood glucose has been identified as a pathology whose resolution would be beneficial. Reliable advances in understanding and control of the questions identified in this disease have been made by our modern Magnetic Resonance methods. This progress has assuaged the need for questioning the methods of science. Some uncertainties such as pancreatic failure remain as challenges, practical contingencies that further study will probably explain. Disagreements about how to proceed abound, but presumably many such questions can be resolved by experiment and theory. The study of diabetes illustrates the successful results of a scientific research program– there is a well-identified question, and we are learning more about how to answer it. This is precisely the sort of technical problem our methods are best suited to explain. However the limitations that arise from a patient's inability to follow treatment reflect an individual's mind, which, in the context of diabetes, is a contingency. Contingency, I propose, is an uncontrolled complex phenomenon that affects a study, which, if it could be understood, appears to require an effort in a different direction that the original study.

Achieving such scientific progress also seems a laudable goal for political science. During times of normal science, Thomas Kuhn claimed, puzzles are solved which are the strengths of science. To reach the felicitous advances in understanding diabetes celebrated above, advances in many subfields had to be brought to bear upon this disease. Genetics and population analysis had to be developed sufficiently so as to identify the inheritable component of NIDD. Likewise, comprehensive biochemistry and highly technical magnetic resonance methods had to be developed to enable us to undertake the in vivo studies. These advances were made during a period of "normal" science during which biophysical research managed to reduce, but not completely eliminate, the prevailing contingency. These findings are now being exploited to develop drugs and other treatments that would increase our control of the disease by going around the non-treatable contingent resistances to medical advice. Scientific advances sometimes follow military strategies and fortified, resistant positions are overcome not by direct attack but by circumvention. The NIDD research is an example of the second level of investigations, described above, in which studies are based upon defined physical parameters like the mass of glycogen and the rates of its formation and are explained by physical laws like the conservation of mass e.g. the mass of glucose stays constant as it flows into glycogen. These results show how reliance upon physical research allows progress to be made by avoiding a confrontation with inexplicable contingencies.

My second example of recent biophysical research is found in studies of Brain/Mind – a field roiling in the throes of changing scientific directions, a field in which novel methods and vast accumulations of data have encouraged scientists to ask previously unanswerable questions about the material nature of mental activity. However, I hope to make clear that when scientists plan to study mental activity they leave behind the hard won strengths of physics and chemistry that have no definition of mental activity. To study mental activities or Mind, scientists have been describing it as the function of brain. Although this starting point has a long history the present scientific usage owes much to the computer scientist David Marr who, in 1972, declared we must know the brain's function before studying how it serves that goal, and who thereupon claimed that the brain's function was to handle intelligence, or to compute (3, Marr, 1972). This assumption, although understandably appealing to a computer scientist, has been transformed into other fields so that, for example, psychologists study the computer-like brain by Cognitive Psychology. In fact, once one is allowed to assume a function for brain there are no real limits; any experimenter can assume almost anything about brain function and test the assumption by highly technical scientific measurements. And as we shall see this is the present state of the field.

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The structure of this procedure resembles Descartes' early formulation of scientific method when he proposed that to understand the whole it should be broken into parts. The parts then were to be studied and the understanding so gained would reflect back upon the original whole. For Descartes the starting point, the whole, was chosen so that in his opinion it was indubitable. This was the importance of his claims for the statement "I think therefore I am." The remaining years of the 17th century, culminating in Newton's studies, created modern physical science by relinquishing the absolute certainty accorded by Descartes to starting assumption and instead starting with hypotheses that were to be evaluated by experimentation. I propose that a large fraction of Brain/Mind studies are making Cartesian like assumptions about brain functions which are then supported rather than tested by experiments. In such a tumultuous stage of research, scientists can find practical insight and support in the views of such modern philosophers as Richard Rorty who emphasizes the contingent nature or all assumptions about the world. We do not find scientific laws, says Rorty, we create them – we do not find scientific problems, we formulate them. Assumptions are completely contingent, depending upon who, what, when and where of their formulation and are to be judged not by any absolute standards but merely by their usefulness. Scientific problems are man-made constructs as we seek to master "nature" or our environment. This philosophy emphasizes that scientific discovery depends upon contingent happenings similar to all creative acts. Likewise, "science" is a human activity not a set of abstract laws and understanding waiting to be revealed. Where science differs from other creative acts is that well established methods of experimentation and reasoning have provided support for the usefulness of the hypothesis, as in our example of thermodynamics. Apples always fall from trees and never rise to them.

In the unsettled Brain/Mind field when assumptions that are made from many different perspectives about mental activities stimulate research, the degree of contingency is very high. No longer does the scientist start with the very well tested, but still intrinsically contingent, hypotheses of physical science, but rather with a view of mental activity from some different perspective such as psychology or computer science

Biophysical research in this field is met by a fundamental contingency at the onset, not after substantial progress towards understanding a goal. In studying the pathological state of NIDD, the goal was well defined – to understand in chemical terms the origins and mechanisms of glucose disposal in this diseased state. We were seeking there to correct one of the most readily observed and agreed upon pathologies. But how can we study the origins and mechanisms of Mind when the chemical nature of Mind is an unsettled assumption, where the definition of Mind is itself the question?

Because of the human complexities involved in Mind/Brain studies, where forces such as intent, will or the passions are not at home in physical science, the starting assumptions and the goals in brain studies vary greatly. There is little commonality even in sub-fields of biophysics where varied standards make it difficult to identify a biophysical formulation of Brain/Mind beyond the common assumption that something like Mind is created by some activity of Brain.

A most active contemporary methodology, responsible for much of the optimistic expectations of understanding Mind is Functional Magnetic Resonance Imaging (FMRI). When I first did FMRI experiments of the brain my wish, as a naïve biophysicist was to find a collaborator who knew how the Mind worked, who could describe the functions of brain which these novel experiments could localize and identify as the brain correlates of Mind. This wish flowed from the Cartesian philosophy that is the foundation of physical science – identify the whole and break it into parts that can be studied. Previous studies of other organs had built comfortably on the knowledge that kidneys, liver and muscle had specific chemical functions and the research had revealed how these functions were fulfilled by molecular mechanisms. This conventional methodology, so successful in physical science has been replaced in the usual formulation and interpretation of Brain/Mind experiments by psychology. Qualities that are assumed in functional imaging experiments to constitute Mind are now almost universally derived from a particular top-down form of psychology. A psychology that has broadly accepted a Computational Theory of Mind (CTM). In this theory, concepts such as memory, attention or awareness are assumed to exist as representations that are operated on by a computer-like brain. Computational Theories of Mind identify such components of Mind and embody them in a task, which subjects are requested to perform while their brain responses are imaged. For comparison, the brain is imaged with the subject in a "control state" where memory, the brain component being studied, is presumably not being exercised. Subtracting one image from another, increments are found in several regions, and investigators claim that these incremental activities identify and localize the activity, in this case, of memory. These localized responses have generated excitement based on their claims that, in contrast to all previous brain studies, brain activity relating inputs and outputs is actually measured, and is now finally and objectively identified. The brain, it is claimed, is merely a logical, computer-like machine in which specific stimuli will be supported by identifiable regional activity.

However the results of these efforts do not support the model of a rational brain operating by fixed computer-like rules to evaluate qualities of Mind as defined in Cognitive Psychology. Although many interesting correlations have been found, particularly in sensory responses, confounding factors that are inconsistent with a computer Theory of Mind are clearly at work. In such model of brain a representation of a particular mental activity, i.e. memory, when performed by a logical, computer-like brain would activate a specific brain region, and that region, being the source of memory, would not be activated by any other mental activity. From the very first experiments on cognitive concepts it was seen that this is not what happens. No matter how tightly the mental representation is defined, no matter how it is broken down into possible components, non-reproducible, different brain regions are activated by the same concept when embodied in different tasks. In other words, the context in which the proposed mental activity is embedded, as well as the modality of its presentation e.g. visual, aural or sensory are just some of the factors that differ from the expectations of a logical, computer-like brain. In the early days of CTM, before fMRI, these departures from the predictions of this model were designated "parallel processing". More recently they are called "context", and responses are acknowledged to be "context dependent". These factors are not small perturbations of otherwise perfectly rational brain activity; they are very significant in magnitude. Considerable efforts have been made to patch up the model so as to retain the mantle of rationality. But careful philosophical analysis, such as that conducted by Jerry Fodor, showed that once the rational model requires consideration of context, it has failed and cannot be fixed (4, Fodor, 2000). Any attempt to explain "context" requires recourse to empiricism, and empirical inputs explaining contextual contributions undermine the claim that a system is purely rational.

Attempts to control context are also limited by the very uncertainties of the concepts. For example, considering "simplicity" as a concept, Fodor notes it has entirely different meanings depending what is being simplified. To simplify some texts, for example, would require more explanation, in others less, so that the activities directed by "simplicity" can be opposites in different contexts. Similarly "memory" and other such concepts float with their context. The attempt to identify absolute concepts of mental activity, entirely independent of their contingent context, fails because theories of a rational mind are undermined by the contingent nature of the presumed activities of Mind. Assuming there are pure concepts, as Cognitive Psychology does, always fails because as is said in the title of Fodor's small book "the mind doesn't work that way". Most imaging scientists cling to the validity of this view of Mind by interpreting their rich imaging data sets so as to support their assumptions. The alternative, of using the data to refine assumptions about the nature of mental activites, while formally more in accord with scientific methods, has not been much followed.

In addition to the contingencies implicit in specifying mental concepts, the response of an individual to a task depends upon the individual's intrinsically contingent history dominated by chance events that can be traced back at least as far as the particular antecedent sperm and egg. A specified task does not mean the same to different individuals. Responses are affected by subjectivity, and individual subjective responses differ. The result of these uncontrolled responses to the task further negate the model of a rational Mind whose relations to Brain are presumed to be uniquely determined in the imaging experiment. The attempts of CTM to ignore or eliminate contingency from scientific studies of the brain, while to many representing progress, in my opinion, leads science down dead ends.

But if we regard all understanding of the larger subjects like Mind to be not an absolute description, found in nature, but a contingent description discovered and proposed by humans, how can we begin to explain Mind in terms of Brain activity? How could we bootstrap ourselves into an understanding of higher order functions? How can we take advantage of the validity of physical science to study properties that we cannot identify?

The answer is near at hand if we examine what biological scientists actually do. They are, in fact, quite opportunistic using whatever tools or methods are available. They adopt neither a top-down approach starting from a fixed view of Mind nor a bottom-up view in which molecular features would be studied regardless of their possible relevance to brain function. Robert Brandon analyzed scientific methodology by rejecting the either - or alternatives of reductionism and holism (5, Brandon, 1996). Brandon claimed that biology follows neither approach. Nor, he argues, should it. Instead, he says, biologists are indifferent to this distinction and move freely in both directions. Their goal is to find a causal mechanism and such an understanding can only be achieved, he suggests, by considering parts and whole together. The piston can only be understood as part of an engine.

In this way, physical scientists can study mechanisms of cerebral neuronal activity, the work of the brain. The distinction between method and importance becomes, for the physical scientist, a straw man. Out of this integration of approaches, searching for mechanisms relating Mind and Brain, a clearer understanding of function can emerge. The reliable physical understanding produced by thermodynamic research of brain energy and work provides a basis for redefining Mind in terms of physically defined causalities. Concepts of Mind derived from psychology or everyday experiences, which incorporate the large common assumptions about Mind, may or may not provide a suitable basis for biophysical studies. In my opinion, attributes of Mind based securely upon physical results have a better chance of allowing a reformulation of Mind that would facilitate future study. The advantage of a reliable basis, or methodology, is that it can support such a conceptual structure, in contrast to less certain direct studies of the larger questions of Mind, which are dispersing uncertainty, rather than containing it.

Relevance For Political Science

The diabetes study allows us to make the point that a “hard science” such as biophysical chemistry constantly navigates in seas of contingency. The molecular findings in the diabetes studies have moved forward until they reached the contingencies of human mind, and can still advance, around those uncertainties when necessary. The descriptions of how biophysical science struggles for explanations while reckoning with the coexistence of contingency and scientific mechanisms might provide political scientists, engaged in a similar struggle, with examples of the benefits of a reliable methodology,

At first glance the method in political science that Ian Shapiro calls scientific realism closely resembles the scientific methodology we used in the diabetes research. However his definition (6, Shapiro, 2005) of scientific realism “I take the core commitment of scientific realism to consist in the twofold conviction that the world consists of causal mechanisms that exist independently of our study-or even awareness-of them, and that the methods of science hold the best possibility of grasping their true character” soon raises some differences in our understanding of the scientific method. In contrast to his emphasis upon finding truth by the scientific method I have emphasized the contingent nature of scientific hypotheses and explanations. Following Rorty, I have proposed that scientific hypotheses are contingent not because we have not yet found the true hypothesis but they are inescapably contingent, they can never become absolutely

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true. In my view there is a real world out there, and it has been very valuable to understand causal mechanisms that have given us control of that natural world but those mechanisms are our contingent creation-they do not exist ”independently of our study”. There is no “true reality.” There is only our more or less useful understanding. To illustrate the contingency of hypotheses, even when they seem well supported empirically, I will bring the diabetes research up to date. Given the inheritable nature of the reduced activity in the glucose transporter in diabetics and their descendents, the results seemed to support our conclusion, or hypothesis, that the glucose transporter pathway was the site of the responsible mutation. However more recent results are showing that that reduced activity is a consequence of other metabolic differences so that newer hypotheses identifying the mutation site are no longer implicating the glucose transporter. At first Shapiro’s commitment of political science to scientific realism resembles my advocacy of the scientific method as described in the diabetes study. However when he states that scientists” see their enterprise as superior to religion, superstition, tradition and other pretenders to authority “*in accounting for reality* “ (7, Ibid, pg. 9) we part ways. Science has proven to be more useful than these other methods in providing us with understanding and control of large sections of the world. However in my view the strength of the scientific method is based upon the uncertainty and flexibility of its findings – upon its contingent results that seem to have no place in scientific realism. Perhaps it is this advocacy of absolutes even in his preferred method of scientific realism that brings Shapiro to deplore the dependence upon method in political science. His major criticism of method has been of those such as Rational Choice Theory that premise an understanding of complex human activities. Rational Choice Theory assumes how the mind works and goes on to explain political and economic behavior by the application of that assumption. In its unquestioned assumptions of a simplistic model of human mental activity, and by its forcing of data to confirm its assumptions, at the neglect of understanding, it shares the logical structure and empirical failings of the contemporary theories of mind like Computer Theory of Mind that I have criticized in Mind/Brain studies.7 (A coalescence of economic and psychological computer theories is flourishing as the new field of Neuroeconomics summarized in “Decisions,Uncertainty and the Brain:The Sience of Neuroeconomics” MIT Press 2003 by Paul W. Glimcher. Glimcher elaborates upon his solution of Brain/Mind in which simple reflex-like behavior is acknowledge to be a useless over-simplification but where the seemingly chaotic complex cognitive mechanisms can be defined very scientifically by “using tools developed for economic analysis” Instead of being asked to choose between method and important questions for research guidance it might be simpler, and create more congenial bedfellows, to propose that the choice should be between answers that are absolute or contingent. In that case I would come down strongly in favor of the contingent answers that are found by scientific methods.

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In the study of complex human activities like mind, or of similar concepts in the social sciences, the contingent nature of assumptions that guide study should be acknowledged from the start. However, unfortunately many scientists in functional imaging are dedicated to accumulating large data banks so that their “information” can someday, somehow answer questions about the human brain. Their assumption is that there are questions, such as what is the nature of Mind that their data can answer. I suggest that if we stay away from rigid preconceptions about the nature of questions and answers, and instead search for mechanisms, that are at the same time both useful and contingent, then the methods we need for improved understanding are presently available.

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1. Add citation to previous series and any publications

2. Is this is a citation or footnote?

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