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COMMENTARY

Systems Biology: The Case for a Systems Science Approach to Diabetes

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Abstract

The unprecedented accumulation of biological data in recent decades has underscored the need to organize and integrate the massive collection of information. In addition, there is rising agreement among biologists that a complete understanding of a single cell will not lead directly to a complete understanding of a system of cells. The success of a systems science approach in engineering and physics may be of great value in the evolution of biological science. This article reviews some examples that suggest the importance of a systems biology approach and, in addition, advance one specific systems science principle, the conservation of uncertainty, which may give insight into the emergent behavior of numerous biological and physiological phenomena.

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Introduction

For molecular and cell biology, the past decade has witnessed an accelerated and unprecedented accumulation of data. The symbolic culmination of this effort was the completion of human genome sequencing. The challenges in analyzing and integrating these results are ongoing and have inspired whole new fields of biological computation, genomics, and informatics. For medical science, the need has always been to understand and exploit the relationship between molecular mechanisms and system (whole body) physiology. The gap between our knowledge at the cell level and our understanding of the macrophysiology underscores the need for *mesophysiology*. Mesophysiology is the processes or mechanisms that connect the various components of the microsystem and then integrate them so that the emergent behavior represents the "system." This in fact defines a type of systems biology. Unfortunately, the term systems biology has taken on multiple definitions. The one definition that is consistent with what I describe is that described by Leroy Hood, founder for the Institute of Systems Biology in Washington: "We call these properties and functions that arise from the interacting parts in a system 'emergent properties.' The concept of emergent properties is central to the study of systems. Any function performed by a system that is not the result of a single part in the system, but rather is the result of interacting parts in the system, is an emergent property."[1] The concept remains an abstraction, but is clarified most efficiently by concrete examples. This article outlines at least one such system biology principle that may have direct relevance and application to clinical practice.

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Clinicians have always been faced with navigating the "system biology" of their patients. A large experience has accumulated that guides the practicing physician in manipulating the physiology so that the healthy state is restored and maintained. These practices are often based on a phenomenological understanding of the physiology and not on fundamental scientific principles of the type seen in physics. This is not a commentary on the practitioner but on the state of biology and its historical scientific development. Until recently, many, if not most, biological scientists held that a complete understanding of a single isolated cell would be sufficient to explain an entire organism.[2] This idea has been eroded by numerous examples. An excellent illustration is provided by Fitzpatrick and Leong,[3] who demonstrated the difference in secretory function of single isolated parathyroid cells compared with the secretion of individual cells residing in a connected group. The average parathyroid hormone secretion of a single cell within a group is significantly higher than the isolated cell and was shown to be a function of its connections to neighboring cells. Thus, a demonstration of the emergent properties is only visible in the presence of group physiology. This is also clearly the case when the events of cell differentiation in developmental biology are observed. The formation of organs in *Caenorhabditis elegans* (a well-studied worm used as a biological model) is a well-documented example of the patterns that occur repeatedly while a system is intact. In the setting of *C. elegans* vulvar development, individual cells are replaceable parts.[4] The cells take on different roles depending on their spatial positioning. The anchor cell, which is the central cell whose function helps determine the fate of its neighbors, can be replaced by its neighbor and the roles reversed, thus showing that there is a systemic pattern or rule that is preserved rather than an individual cell governing the fate of the rest.

A key philosophical/scientific question for a systems approach is the following. If there is an incomplete understanding of the details of the components of the system, is it still possible to form legitimate macrophysiological or systems biology principles? Clearly, it will take some time, if ever, to decipher all the molecular and cell biological rules that govern the complete function of a cell. Is it then folly to consider forming a systems biology approach given that we do not have all the detailed facts?

A good heuristic for evaluating this question is to look at other scientific disciplines that have faced these questions and examine the ideas and techniques that have worked there. A notable success in physics is the field of thermodynamics.[5] The laws of thermodynamics are a fundamental part of how we understand Nature. They in fact are accurate descriptions of ensembles of countless "invisible" components that, interacting under prescribed conditions, behave in predictable patterns. It would be futile, for example, to model the trajectory of individual molecules and their interaction with billions of other molecules. So here in fact is an example of a systems solution that does not need specific details of the components. Another example is the theory of elasticity, where the governing formula does not in fact need the detailed quantum mechanical description of each individual atom to accurately describe or predict the system properties that emerge. As physicians and biological scientists, we could ask ourselves whether there are systems approaches in other fields that could be applied to medical science and specifically to the understanding of endocrine physiology and diabetes.

Control theory used for systems analysis and design contains an extremely useful conservation principle known by several names, one of which is Bode's integral formula or the "conservation of uncertainty."[6] This concept has found its way into biological science through the work of leading control theorist John Doyle and others. Csete and Doyle[7] examined this principle in the setting of glycolysis and refer to it as the "conservation of fragility." Different names address the application, but what is an invariant is that there is a mathematical expression that precisely describes this principle and predicts certain outcomes with the same validity as other physical principles, which is something that is needed desperately in the field of medical science. Having successfully evaded defining it, I will now describe the concept (without the math) and then give some potential examples as to how it may have a role in diabetes, metabolism, and other biological systems.

The level of complexity in engineering design today is approaching that of biological systems. Control engineers have to contend with designing features and functions that must be robust with respect to many potential conditions. The conservation of uncertainty, simply stated, is the notion that a whole system has a quantity of uncertainty that is always present and constant, but may be shifted around or distributed among the component parts but can never be done away with. The flip side is that there is a conservation of the robustness as well. In an engineered system such as the Boeing 777 commercial jet, where there are 150,000 connected parts, the design principle is aimed at maintaining "certainty" or stability in certain critical features, such as making

sure the wings or engines are secure by bolting them redundantly. The conservation principle thus implies that while the certainty is increased in some components, such as the wings, uncertainty is increased automatically in others. The design strategy would therefore be to cause the uncertainty to be distributed in components whose function is less critical for the safety of the passengers, such as toilet covers or reading light switches. The intuition here becomes more apparent in simple systems, for example, a water pipe where the first half is strengthened with extra materials that can withstand greater pressures and thus increase certainty or stability there and automatically increase uncertainty in the second half of the pipe. Therefore, as the water pressure increases, the likelihood of a fracture and collapse is largely in the second half.

When we cross over to clinical management of patients we are likely affecting the system in similar, albeit more complex, ways. Imagine a patient who has the common cluster of high cholesterol counts, hypertension, resistant diabetes, and poor glycemic control in addition to atrial fibrillation. We could impose a typical regimen of pharmacological therapies so that the certainty of a certain physiological and biochemical response is increased. This can be done by restricting the cholesterol from rising above a certain level, maintaining the diastolic blood pressure under 90 mm Hg, attempting to restrict the glucose levels from rising beyond a prescribed level, treating with digoxin to restrict the pulse rate, and elongating the pro time to a certain range "therapeutic" domain. All these measures impose increased physiological certainty, but from a systems understanding, we are clearly distributing uncertainties to unknown components and physiological functions. Although anecdotal, I am certain that many physicians have witnessed patients who are difficult to control when they try to corral multiple physiological functions. The resistance to controlling may be the body's way of informing us about deeper systems properties, such as adaptation and robustness, which are being studied intensely at the cellular level today.[8] There are many anecdotal reports of patients having had unexpected catastrophic events shortly after becoming well controlled. Seasoned clinicians know intuitively not to force the "system." The practice of medicine already embraces some of these concepts informally, but a formal systems understanding at this level would be a wonderful tool that could be applied to therapy and may unveil physiological connections that appear to be disparate and strange.

A systems approach to diabetes seems uniquely appropriate. Diabetes has all of the features of a control feedback system where many of the key parameters are measurable and capable of being manipulated. The artificial pancreas, where a reservoir of insulin and a man-made sensor in a closed loop already exist, although certainly not perfected, is a good test case. Here we have the opportunity to employ systems theory and create a new system biology approach that may be physiologically more accurate than what we are able to do currently. The debate concerning "tight" glycemic control will naturally extend into the domain of continuous glucose monitoring and continuous insulin infusion. Our collective understanding of glycemic health comes from data sets that are fundamentally different in nature: epidemiological, molecular, transgenic models and clinical trials. These data are usually static in nature, meaning that they are snapshots in time; interpreting them becomes much like trying to understand the rules of football by studying a few photographs from distinct isolated moments in the game. Once continuous monitoring becomes more prevalent we will have a better chance at getting the rules because we will be in essence watching the whole movie. Important features of insulin and glucose metabolism, such as oscillations, overshoots, and undershoots, will become more transparent. For example, there have already been strong suggestions in the diabetes literature that pulsatile insulin release is fundamental to better glycemic control.[9] With the current standard diabetes management, these questions cannot be addressed. Although there is a current dogma of what is correct therapy today, I believe that there is room for a deeper, more integrated view on therapy when we are in a position to study a continuous physiology. Consequently, questions concerning glycemic control will be addressed more advantageously in the framework of a systems approach. This was certainly the case in control engineering.

We have yet to define or discover the correct system physiology, but by surveying the ideas and concepts from other systems disciplines and forming collaborative interdisciplinary teams, we may be able to draw important lessons for implementing this program.

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