COMPLEX SYSTEMS ANALYSIS: A TOOL FOR SHOCK RESEARCH

Timothy G. Buchman,* J. Perren Cobb,* Alan S. Lapedes,‡ and Thomas B. Kepler†

*Washington University School of Medicine, St. Louis, Missouri; †Santa Fe Institute, Santa Fe, New Mexico; and ‡Los Alamos National Laboratory, Los Alamos, New Mexico

ABSTRACT—For the past century, students of shock have focused research efforts to illuminate specific mechanisms that cause, or fail as a consequence of, circulatory collapse. Although clinical strategies aimed at supporting or restoring individual organ systems have proven effective, many patients succumb to more generalized multiple organ system failure. We suggest that general biological systems failure cannot be interpreted through reliance on reductionist science. We propose that complex systems analysis is an essential tool for shock research and we evaluate its application to genomic technologies.

KEYWORDS—Shock, MODS, complex systems, reductionism

Shock continues to challenge patients, their physicians, and a community of investigators. The symptoms and clinical signs of shock have been known for centuries. Modern physiological descriptions of the shock state are built upon Walter B. Cannon’s interpretation of Bernard’s precepts (2). That interpretation invoked a new concept, homeostasis, which suggested that each organ is regulated by one or more mechanisms that serve to restore function to a healthy set-point. Such mechanisms (for example, the balanced actions of insulin and glucagon upon plasma glucose) have been identified, studied, experimentally perturbed, and clinically managed.

Left untreated, shock culminates in death. The clinical imperative to reverse the cause while stabilizing the performance of physiological systems has remained unchanged for decades. General shock therapies are now established, including (but not limited to) fluid resuscitation and the administration of oxygen. Specific therapies address underlying causes such as the drainage of abscesses and the administration of antibiotics. Pharmacology and technology are employed to independently support such enervated organs as the heart, lungs, kidneys, and gut.

In 1973, Tilney described a cohort of desperately ill patients who had undergone surgery to repair abdominal aortic aneurysm only to experience failure of multiple organ systems (3). Baue (4) and Eiseman (5) recognized that the syndrome of multiple organ failure followed shock. Multiple organ failure patients had been appropriately treated for their shock state, but nevertheless failed to promptly improve. Once multiple organs had failed, nearly all patients died, despite aggressive support.

The search for a “cause” of shock-induced multiple organ failure was spurred by the observation of Fry and colleagues (6) that infection appeared to be a common predecessor of that organ failure. The development of potent antimicrobials, as well as CT scans, promised detection and eradication of the precipitating infections. However, despite eradication of infection, multiple organ failure persisted and killed patients.

By 1985, students of shock-induced multiple organ dysfunction championed three complementary “causes” of multiple organ dysfunction (7). First, they suggested that the microvascular thrombosis that accompanied late multiple organ dysfunction might disrupt delivery of oxygen to vital tissues (8). Administration of heparin to patients with organ failure did not affect survival; whether engineered anticoagulants will prove effective remains to be determined. Second, they suggested that the gut constituted a reservoir of bacteria causing chronic infection. Gut decontamination has had, at best, only limited success and acceptance as a strategy to prevent multiple organ failure or alter its outcome (9). Third, they suggested that biological mediators—molecules produced in response to diverse stimuli—caused widespread inflammation that resulted in multiple organ failure. Pharmacologic neutralization of candidate mediators have generally failed to improve outcome and, in some cases, appear to worsen that outcome (10).

The notion of a “cause” of multiple organ failure evolved, at least in part, from the idea that disease states are generally attributable to a specific physiologic defect causing derangement and ultimately, the failure of homeostasis. The notion of a “cause” was reinforced by investigational strategies that focused on individual genes, transcripts, proteins, molecules, and/or pathways. Comparing either (outbred) ill patients with healthy counterparts, and later, laboratory models using (inbred) ill animals with healthy counterparts, many derangements were identified, modeled, and corrected in animals with impressively favorable results, only to have no (or worse, adverse) effect in the ill human.

During the past 5 years, technologies emerged to evaluate entire complements of macromolecules—RNA and protein—in parallel. Application of these technologies (including RNA differential display, microarrays, multidimensional protein electrophoresis, and atomic force mass spectroscopy) to specimens obtained both from patients in shock sepsis and multiple...
organ failure and from appropriate control patients demonstrate widespread changes in content and relative concentrations of specific macromolecules (messenger RNAs) (11).

These two observations—the unexpected failure of therapies directed towards single candidate mediators and the unanticipated finding of widespread shock-induced changes in gene expression even within single cell types—together challenge the idea that the undesirable outcome of resuscitated shock (namely, multiple organ dysfunction) is due to malfunction of a specific regulator, pathway, or molecule. We consider an alternative view of stability, instability, and adaptive responses refracted through the prism of complex systems science.

**COMPLEX SYSTEMS SCIENCE**

A “system” is a collection of parts or elements that form a functional whole and have some sort of dynamic behavior. Neither a piece of string nor a metal ball merits description as a system. Tying the string and the ball together to form a pendulum creates a system—one that happens to have highly predictable dynamics described by Newton’s laws of motion. The adjective “complex” refers to those systems composed of several interacting elements whose collective behavior is not readily predicted from the behaviors of the elements or from the laws governing the interactions among those elements, but rather emerges as a property of the system as a whole at a coarser level of resolution. Unlike merely “complicated” systems that can be dissected into component parts that obey rules of superposition and proportionality, a complex system has a sort of irreducibility: taking it apart destroys dependencies that contribute to its characteristic behavior. An internal combustion engine may be a complicated system, but it is not complex. It behaves in a predictable manner: power is developed in proportion to the number of cylinders receiving a fuel/air mixture, timing of the spark, the amount of fuel and air fed to those cylinders, and the displacement of those cylinders.

A beaker containing supercooled water seems “simple.” If the beaker is tapped to introduce just the right amount of energy, the liquid will suddenly freeze. Just how much energy is required defies prediction (one-half the amount of supercooled water does not necessarily respond to one-half the amount of energy), and repeating a seemingly identical tap on a seemingly identical beaker of supercooled water may—or may not—leave the water liquid. In this respect, a beaker of supercooled water is profitably treated as a complex system.

At first glance, biological systems may appear more like the internal combustion engine, albeit with more parts and subsystems. However, engineered objects emerge from detailed plans that specify interrelationships among components, careful manufacture, and precise assembly. Unexpected performance is generally traceable to design flaws, manufacturing flaws, assembly errors, or use failure (i.e., wear-and-tear). Such systems are manifestly predictable from the behavior of their component parts.

Biological function is not the product of human engineering, life is not assembled according to a blueprint, and unexpected performance may not be so readily explained. Cell duplication, differentiation, and aggregation into tissues and into organs is programmed such that the passage of time and the accumulation of cell mass is sufficient to signal progressive and sequential changes in organization and function. Put differently, since the DNA of every somatic cell is nearly identical, the function of each cell depends on other cells and on the sequence in which it was created. There is no pre-existing matrix into which cells are inserted as they are manufactured: cells organize themselves into tissues, tissues into organs, and so on. Self-organization is a characteristic of complex systems in general, and formal biological systems in particular (12).

Such self-organization does not preclude the programmatic creation and maintenance of specific feedback mechanisms that maintain relationships. But self-organizing systems are often stable, persist without self-destructing, show resilience to modest external perturbation, and recover from some larger perturbations without discernible feedback mechanisms (13). This aggregate “robustness” appears to be a property of many self-organizing complex systems such as the stock market. Like the stock market, human physiology has frequent “corrections.” Like the stock market, human physiology can “crash” and require external support. Like the stock market, there is no obvious way to predict what supports, order of supports, or intensity of supports will promote recovery. Simply “undoing” what appears to have precipitated the crash is necessary, but almost never sufficient to prompt that recovery.

**THE CELL: AN IRREDUCIBLE COMPLEX SYSTEM**

A cell is the smallest independent unit of life. Differentiated cells have characteristic appearances and behaviors, and for most cells, there appear to be a relatively limited repertoire of behaviors or states of the cell. But do cells behave as complex systems? Yes, because they frequently exhibit decidedly non-linear responses to external stimuli. For example, cells have relatively few responses to environmental stress. They mount an acute phase response to inflammatory stimuli such as exposure to endotoxin and to tumor necrosis factor. They mount a heat shock response in response to hyperthermia or to chemical stimuli such as sodium arsenite. Each response includes distinct changes in gene expression observable at the level of transcription and translation. However, sequential application of the stimuli to certain cell types (e.g., endothelial cells) results in further alterations that depend on the sequence in which the stimuli are applied. Prior heat shock renders the cell refractory to an inflammatory stimulus, whereas induction of the acute phase response sensitizes the cell to a subsequent heat shock such that apoptosis (programmed cell death) is executed (14). The two stresses do not commute, and the commutative results of sequential stresses are not predictable from the response to the individual stresses. We have termed these behaviors the “heat shock paradox” (15). Such unpredictable behaviors (state-dependent responses to perturbations) are characteristic of complex systems.

What, then, can complex systems analysis offer to the student of shock with respect to the biology of the cell?

First, complex systems analysis provides tools to manage massively parallel sets of data. For example, microarray technology gives simultaneous quantitative estimates of changes in
concentration of thousands of specific messenger RNA species. The changes are not independent of one another, rather they depend upon an underlying regulatory network. The changes can be used to classify the states of cells, providing the power to discriminate among morphologically identical cells. This approach has been used to discriminate among seemingly similar hematologic malignancies and melanomas (16, 17). At present, shock researchers rely on expression of at most a few candidate genes to classify cell states. The analytic tools of complex systems science can make that classification rigorous.

Second, complex systems science provides tools for planning experiments to yield the most information when a traditional full factorial experimental design is not possible or not affordable. Since the goal of most students of shock is to solve the “inverse problem” (namely, to make inferences about regulatory mechanisms from what is being regulated), application of complex systems science has at least the potential to inform investigators about the point in the continuum of potential experiments at which the most information might be gained from the data.

Third, complex systems science provides a framework for development of mathematical models that can illuminate regulatory architectures that yield counterintuitive responses. An example of a counterintuitive response is the repeated failure of antimediator therapy applied to septic humans following inflammatory mediator and several antiinflammatory mediators. Interruption of a specific signal connecting cells in one species causes a different result in another species despite the homologies among cell types and mediators. A typical model is illustrated in Figure 1. The cells have been labeled T and H to signify the tail and head of the arrow, respectively. Cell T produces a mediator that affects the function of cell H. A more detailed view of the situation might be as illustrated in Figure 2, where cells T and H are not only connected directly, but also indirectly, via cells 1,2, . . . M. The complex systems question, then, is what is the consequence of severing the direct connection between T and H?

The surprising, if counterintuitive, answer is that it depends strongly on the coupling through the 1,2, . . . M cells. Within a specific range of coupling strengths through the 1,2, . . . M cells (particularly when the actions of the indirect connections through the 1,2, . . . M cells runs counter to the effect of the direct H to T connection) breaking the direct (“mediator”) connection between T and H actually strengthens the correlation between T and H (18). For the shock investigator this means that even subtle differences in the network that indirectly links T and H can change the consequence of severing a direct T → H connection. This finding does not mean that experimental animals should be discarded as a vehicle for testing hypotheses or therapies, but rather that the observations discordant between mice and men provide clues to the importance and scope of indirect connections linking the popular targets of shock therapy.

Finally, complex systems analysis provides tools that are applicable to coarse-grained (i.e., organs), as well as fine-grained (i.e., cells), systems. Although each organ within the network of organ systems has a unique type of (time-dependent) signal (the beat of the heart, the pulsatile secretion of hormones, the respiratory cycle, and so on), the tools of complex systems are sufficiently flexible to afford an analysis of the interactions among organs via analysis of those time-dependent signals. For example, evidence is accumulating that loss of variability in the heart rate (“decomplexification”) is associated not only with progressive diverse illnesses (ranging from brain injury to organ rejection to sepsis), but also with changes in the way the vital organs exchange information: the heart appears to “decouple” from other organ systems (19). Moreover, the normal state of health is not a stable “coupling,” but rather an ongoing change in couplings among vital organs (20).

**IMPEDEMENTS TO PROGRESS**

One impediment to the application of complex systems tools to shock research appears to be the failure of theorists, experimentalists, and analysts to self-organize. Theorists and analysts need to understand the biomedical and experimental systems and appreciate the problems in their own terms to guide their modeling. Experimentalists need to provide access to reliable data in a uniform format (perhaps through a central repository), remain open to the novel integrative perspectives that modeling provides, and learn to work with theorists and analysts to maximize the information extracted from their data. What stands in the way?

There appear to be two hurdles. The first and simpler hurdle is language. Experimentalists work with cells and tissues, theorists work with dynamical equations, and analysts work with statistical models. The second and arguably the more challenging hurdle relates to each camp’s approach to science. While biomedicine is very much hypothesis driven, in complex systems research, often “the hypothesis is there is no hypoth-
esis” (21)—system dynamic regulation is not accomplished via simple, isolable mechanisms; the value of a theoretical model largely lies in its ability to facilitate exploration. This activity is critically important for developing intuitions and ideas, through it can be mistakenly criticized as unfocused and unproductive by experimentalists and their peer-reviewers.

What is needed to advance the application of complex system tools to the challenge of shock and related problems of sepsis and organ dysfunction? Seely and Christou (22) have recently reviewed and summarized recent achievements. As a next step we suggest that theorists, experimentalists, and analysts should jointly address a problem of common interest, employing novel modeling and computational techniques. The need to study a widely available, reproducible, and perturbable system cannot be overemphasized. Since the inflammatory response is at least partially reflected in circulating white blood cells, and since those cells can be isolated and sorted into relatively pure populations, and since the cells can be repeatedly sampled over time, they are attractive as initial objects for study. The problem of mixed responses owing to genetic variation in outbred man can be at least partially overcome in parallel studies of genetically identical mice. Experiments perturbing the cells must be performed using common protocols, described in simple and unambiguous language, and the data deposited into an accessible repository using non-proprietary formats. In order to catalyze such progress, funding agencies (and their peer reviewers) must set aside prejudices concerning formats. In order to catalyze such progress, funding agencies (and their peer reviewers) must set aside prejudices concerning models, hypotheses, and the need to draw a dichotomous conclusion from every experiment. Individual scientists must set aside ideas about the ownership of ideas, data, and models. Given the current state of shock research, the question is not whether we investigators can afford to take such bold steps; rather, it is whether our patients can afford not to have us take them.

REFERENCES