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# From data patterns to mechanistic models in acute critical illness ☆

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ABSTRACT

The complexity of the physiologic and inflammatory response in acute critical illness has stymied the accurate diagnosis and development of therapies. The Society for Complex Acute Illness was formed a decade ago with the goal of leveraging multiple complex systems approaches to address this unmet need. Two main paths of development have characterized the society's approach: (i) data pattern analysis, either defining the diagnostic/prognostic utility of complexity metrics of physiologic signals or multivariate analyses of molecular and genetic data and (ii) mechanistic mathematical and computational modeling, all being performed with an explicit translational goal. Here, we summarize the progress to date on each of these approaches, along with pitfalls inherent in the use of each approach alone. We suggest that the next decade holds the potential to merge these approaches, connecting patient diagnosis to treatment via mechanism-based dynamical system modeling and feedback control and allowing extrapolation from physiologic signals to biomarkers to novel drug candidates. As a predicate example, we focus on the role of data-driven and mechanistic models in neuroscience and the impact that merging these modeling approaches can have on general anesthesia.



## 1. Equal but separate: The state of complexity in acute critical illness

Acute critical illness can be defined as the constellation of acute inflammatory and pathophysiologic consequences that occur subsequent to sepsis, trauma/hemorrhage, and other acute events such as pancreatitis that can be differentiated from acute critical illnesses that do not require critical care (such as acute psychiatric illness). Sepsis alone is responsible for more than 215 000 deaths in the United States per year and an annual health care cost of more than $16 billion [1], whereas trauma/hemorrhage is the most common cause of death for young people in the United States, costing more than $400 billion annually [2-4].

There is currently not a single drug approved by the US Food and Drug Administration specifically for the treatment of acute critical illness. The one drug that had previously been approved for sepsis, recombinant human–activated protein C, was found on a Food and Drug Administration–mandated repeat phase III clinical trial to offer no benefit over standard of care; this drug was subsequently removed from the market [5,6]. We suggest that inflammation and associated cellular, tissue, and organ dysfunction form an interconnected complex biological system whose very architecture is both robust and fragile [7-9]; identifying the critical control points in such systems is extremely challenging. In addition, animal models that have formed the primary preclinical experimental platforms have often failed to replicate the full spectrum of human responses to infection or injury [10-12]. Together, these factors are likely to blame for the failure of the current reductionist paradigm for discovery of novel therapeutics for these diseases [13].

The integrated nature of inflammatory and physiologic derangements that characterize acute critical illness has largely defied a synthetic understanding of this disease, and this complexity, which we define as emergent behaviors and outcomes that cannot be predicted based on an understanding of the component organs, tissues, cells, and molecules in isolation, has hampered diagnosis and treatment. Over the period of more than two decades, multiple

*Abbreviations:* DAMP, damage-associated molecular pattern molecule; FDA, Food and Drug Administration; HRV, heart rate variability; MODS, Multiple Organ Dysfunction Syndrome; SCAI, Society for Complex Acute Illness; SIRS, Systemic Inflammatory Response Syndrome.

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investigators have attempted to decipher this complexity through the adoption of computational tools that colloquially fall under the rubric of "complex systems analyses," which, however, are in fact, quite different in their underlying theory and methodology [14,15]. Generally speaking, these methods can be grouped broadly into distinct but complementary investigatory approaches. Namely, signal processing algorithms that can discern the degree of complexity of physiologic waveforms (e.g., heart rate variability [HRV]), data-driven analysis of patterns at the molecular level (e.g., bioinformatics applied to changes in messenger RNA, protein, or various metabolites), and mechanistic mathematical and computational modeling of the biological processes thought to drive acute critical illness.

The Society for Complex Acute Illness ([SCAI], originally called the Society for Complexity in Acute Illness), was established in 2004 to provide an organizational structure and a forum to facilitate the integration of these complex systems methods into the field of acute critical illness. Two recent annual international conferences on complex acute critical illness—the 11th annual meeting in Ottawa, Canada and the 12th annual meeting in Budapest, Hungary—highlighted the international scope, clinical achievements, and scientific advances made in furthering complex systems analysis in acute critical illness (see the Journal of Critical Care, volume 28, issues 1 and 6, respectively). These conferences also demonstrated the robustness, durability, and maturity of this field. Society for Complex Acute Illness members have conclusively demonstrated that metrics such as HRV can alert caregivers to impending clinical complications of acutely ill patients; have highlighted examples of informatics-based analyses of networks and principal drivers of outcomes in cells, animals, and patients; and have demonstrated the potential utility of mechanistic modeling for simulating clinical trials and predicting the inflammatory trajectories of individuals.

Despite this encouraging progress or perhaps because of it, there has been a certain solidification of work in these distinct complex systems arenas. Although such specialization and focus are inevitable outcomes of the scientific endeavor, the simple recognition of this phase of scientific development should trigger compensatory strategies to integrate and unify what is certainly a common target of investigation. Therefore, we suggest that the time nigh to begin to unify and synthesize these distinct complex systems approaches to acute critical illness. In fact, we assert that the different aforementioned approaches represent complementary viewpoints of the same system, each with its distinct benefits but individually incapable of providing the global view necessary to engineer effective control/therapeutic strategies to positively affect human health.

In short, the various aspects of complex systems analysis can be categorized as follows:

(i) Analyses of molecular and physiologic patterns: multidimensional analysis of molecular/genetic data provide high-resolution component characterization of system phenotypes, that is, identification of the various molecular and genetic configurations that are associated with different types and phases of disease. Sophisticated analysis of physiologic signals, such as heart rate, provides high-level physiologic phenotype characterization of clinically relevant output behaviors of the integrated biological system, that is, organ behavior and state. These pattern-oriented data are analyzed and interpreted using data-driven (statistically based) computational models.

(ii) Mechanistic modeling (at both the molecular and physiologic control levels): dynamic linking between phenotypic states, that is, how does one state (be it characterized as a physiologic signal or a molecular/genetic configuration) transition to another? This step is critical to the development of putative clinically applicable control/therapeutic strategies to enhance human health.

In this article, we outline the progress in each distinct field and highlight the pitfalls inherent in maintaining the status quo. We then describe a vision for linking data-driven and mechanistic models to drive innovations in acute critical illness diagnosis and care. We cite a predicate example from the field of neuroscience, in which data-driven network models of the brain may be leveraged, via the intermediacy of mechanistic mathematical and computational modeling, to yield novel insights into general anesthesia.

## 2. Data patterns: From molecules to physiology to models

The responses to severe infection and trauma/hemorrhage involve a generalized activation and systemic expression of the host's inflammatory pathways—the so-called systemic inflammatory response syndrome (SIRS). In parallel to, and at least in part driven by SIRS, a profound physiologic dysfunction accompanies acute critical illness. At the genomic level, it is now clear that most cell types and a plethora of biological pathways are induced in acutely ill patients [16]. This dysfunction can be observed in the failure of organs to carry out proper functions, and this progressive failure of the lungs, kidneys, liver, and heart is known as the multiple organ dysfunction syndrome (MODS). Systemic inflammatory response syndrome and MODS evolve rapidly in sepsis and trauma. Treatment of existing MODS beyond supportive therapy is quite difficult, so there has been a search for therapeutic modalities that could be deployed as early as possible.

The search for early diagnostics as well as efficacious and safe therapeutic options has been stymied by the complexity of the underlying, dynamically coupled inflammatory and pathophysiologic sequelae of acute critical illness. Furthermore, a notion has emerged that reductionist approaches to such a complex system may be inadequate to this task. Over the past decade, systems and computational biology have emerged as an alternative to reductionist, molecule-, pathway-, and physiologic end point–centric conceptual frameworks. Two, heretofore parallel, approaches have evolved over time in an attempt to address the diagnosis and therapy of acute critical illness from a systems perspective, both of which use patterns of information.

One area of active research involves the analysis of physiologic signals retrievable from bedside monitoring devices, dealing with the processing and interpretation of complex physiologic signals. Twenty years of research in this area have led to the identification of metrics representing loss of complexity of physiologic variability in heart rate and breathing patterns; these metrics are finally being used for the diagnosis of sepsis in a limited capacity [17-20]. These descriptive methods have been used in an attempt to elucidate more precise and potentially predictive metrics associated with clinical manifestations of sepsis/MODS, with the hope that these metrics will also provide some mechanistic insight into the control systems responsible for their output.

For example, MODS has been viewed as a decoupling of the oscillatory systems manifest in intact organ-to-organ feedback [21]. Both experimental and clinical studies have suggested that one measure of this disrupted oscillatory coupling is reduced variability (or increased regularity) in various physiologic signals, chief among them being heart rate [22-24]. Time-domain analysis of HRV has subsequently evolved as a potentially noninvasive diagnostic modality for sepsis [23,25-33]. In addition to HRV, examination of other physiologic parameters using a complex systems approach has also yielded valuable insights into the physiology of sepsis [34,35]. There have been some attempts to establish anatomical correlates to the control systems involved in organ-to-organ oscillatory coupling. In particular, HRV data have been used indirectly to detect variability attributed to sympathetic and parasympathetic branches of the autonomic nervous system as well as other physiologic processes that affect heart rate, including respiration, blood pressure, and temperature [25].

However, despite the demonstrated validity and usefulness of these types of biological patterns and physiologic signal analyses, these methods remain primarily phenomenologic in nature, in essence connecting physiologic patterns with clinical outcome through the use of statistical methods [36]. As in HRV, inflammation in acute critical illness manifests in patterns evident at the genomic [37-40], proteomic [41-44], and metabolomic [43-45] levels. The growing number of these studies has resulted in a "data deluge [46]." Researchers are being overwhelmed by data in large part because the methods of choice for analysis of these data are invariably based on statistical associations [47-54]. Such analyses may suggest principal drivers of inflammation and MODS [54,55] and may define the interconnected networks of mediators and signaling responses that underlie the pathobiology of acute critical illness [56,57]. However, to gain mechanistic insights necessary for the rational design and development of therapeutics and potentially also for the next generation of diagnostic applications, a precise dynamic characterization of the cellular and molecular mechanisms responsible for generating the acute critical illness phenotype is required [58-61].

A second area of active research involves data-based or data-driven modeling approaches that do not rely on *a priori* knowledge of the internal state of the system but rather on input-output data measured directly on the system [62-64]. Frequently used data-driven approaches applied to biological system analysis include input-output transfer function models [65-68], autoregressive time series analysis [69,70], nonlinear time series, and Voltera integral series analysis methods (such as principal component analysis [54,55,71,72]), and network-centric models [54]. For monitoring of biological systems, these data-driven approaches have several advantages. Because these data-driven modeling methods are based on data and not on *a priori* knowledge reflecting the complexity of the system, they only describe the dominant (dynamic) modes as present in the data, which results in compact model structures that can be easily implemented in process hardware [73]. These can include, for example, intelligent machines such as computer hardware and signal processors as well as computer software algorithm execution. Furthermore, several time-efficient, recursive parameter estimation methods allow these data-driven approaches to be applied in real-time and model parameter values to be updated frequently, which allows for quantification of time-varying nonlinear dynamic features of biological systems [74,75].

Models based on data-driven techniques such as principal component analysis can suggest independent drivers of complex biological phenomena [54,55,71,72], and there are examples in the literature of using principal component analysis to derive key modules of mechanistic mathematical models [72], which we discuss in greater detail below. Network-based models can suggest how multiple, ostensibly related variables interact with each other across individuals, across time, or both [54,56,57,76]. Finally, in applications, where sensors and/or measuring techniques are available for capturing data on individuals, these data-driven modeling approaches allow modeling and monitoring dynamic changes (in real time) on an individual basis, in essence comprising a novel class of biomarkers [77].

However, there are also important limitations to be taken into account when applying these data-driven modeling approaches. These approaches, by definition, rely on available data and as such are dependent on the quality of the sampled data [78]. More specifically, measurement problems can occur on different levels. In particular, the selection of the relevant system variables to be measured can, in certain applications, be nontrivial. In several applications, the system cannot be sampled at high sampling rates resulting in aliasing or loss of dynamic information [79]. For proper parameter estimation and model structure selection, it is important that the measured data contain sufficient dynamic information, which under field or clinical conditions is not always the case. In many applications, system data measurements are collected in real time, and the system cannot be perturbed dynamically [70]. In certain cases, sampling too quickly can influence the biological response of the system [79]. Because of sensor constraints, measurement artifacts can influence the quality of the model parameter estimation significantly [62]. Furthermore, because data measurements are often corrupted by noise, appropriate preprocessing techniques and/or parameter estimation is needed for reliable model estimation [64].

One of the key drawbacks of purely data-driven modeling techniques for monitoring of biological processes is their input-output nature, which does not provide any knowledge of the internal state of the process. In most physical systems, the output of the system also depends on the system's initial state. In addition, an input-output system description cannot deal with physical system interconnections [80]. Hence, these methods do not provide any direct mechanistic information about the system; rather, they are based on association among data variables in some fashion or another [63,81]. This concern may not present a problem when these models are used for predicting future system behavior when a large amount of data is available regarding the behavior of the system. However, for monitoring the status of a system, it becomes more difficult when the quantified model features cannot be interpreted in a biologically/physiologically meaningful way [82]. As such, data-driven models alone should not be used to determine means for controlling biological systems because the lack of biological knowledge in these models can potentially result in control actions that harm the system [83].

Finally, it should be noted that the black-box, input-output nature of data-driven models for biological systems can form an important obstacle when introducing these models into practical applications because the users (e.g., health care providers) of model-based decision software are often convinced to use the model when they understand the biological/physiologic principles that form the basis of the models [82]. However, despite these limitations, the results of data-driven modeling provide a necessary link toward mechanistic modeling by adding inference of potential causal relationships onto the molecular configurations identified in high-throughput data.

## 3. Applications of mechanistic models to acute critical illness

The ultimate translational goal of biomedical research is to be able to affect control on the biosystem to positively affect human health, and this requires the construction of mechanistic knowledge-based models. Dynamical systems modeling predicated on mechanistic models, wherein an internal state model is used to describe the system dynamics using biological and physiologic laws and system interconnections, is of fundamental importance in the description of physical dynamical systems. Toward this end, comprehensive complex systems analysis in the study of sepsis involves mathematical and computational dynamical modeling at the cellular and molecular level. In the setting of acute critical illness, we suggest that the development of novel treatment strategies for acute critical illness must be driven by mechanistic computational modeling [84] because inevitably, data must be integrated to predict higher-order system properties in a clinically relevant manner.

There are predicate examples of the utility of mechanistic models in science. The physical sciences over the last century have made significant progress, in large part, due to scientific investigation that relied heavily on mathematical models of physicochemical processes [64]. Translating that success to the biological arena, however, presents a different level of challenge. Biological reality is very complex, involving multiple feedback loops, nonlinear interactions, system uncertainty, and dependence on system initial conditions as well situation-specific rates of reactions that often necessitate large-scale stochastic modeling. The literature contains many reports of simplified (reduced-order) mechanistic models, including those focused on aspects of acute inflammation, which have yielded useful insights into the mechanisms and pathophysiology of acute critical illness [85-88]. However, such models are at best only capable of

general, high-level predictions, which are not sufficiently specific so as to be testable in individual patients or in *in vitro*/*in vivo* experiments.

Alternatively, modeling biological systems in a realistic fashion often necessitates complex, large-scale models describing the underlying system dynamics [89]. An important advantage of such mechanistic models is that they represent the state-of-the-art knowledge of the considered system [7,90-3] and are particularly useful in the general scientific process of connecting biophysical findings to psychophysical phenomena, generating new hypotheses and developing new assertions [94], and improving reliability of drug development and drug dosing [13]. However, in terms of direct translational utility in terms of clinical decision making (monitoring and/or controlling of systems), these models are either too unwieldy [95,96] or contain too much uncertainty [94].

Nevertheless, mechanistic modeling has made key contributions to the study of acute critical illness. For example, mechanistic models have helped suggest the central role of damage-associated molecular pattern molecules in acute critical illness, specifically in establishing and perpetuating the positive feedback loop of inflammation-damage-inflammation [8,9,58,77,84,93,97]. Mechanistic modeling has also helped decipher inflammatory preconditioning, namely, the different inflammatory responses that ensue when multiple stimuli are given in succession [88,98-103]. Other applications of mechanistic modeling involve the understanding of multifactorial therapies for critical illness, suggesting specific ways by which they reprogram and recompartmentalize the inflammatory response [55,104]. Key translational applications such as in silico clinical trials based on mechanistic models of inflammation and damage/dysfunction were pioneered in the arena of critical illness [105,106]. These models have grown in sophistication and are beginning to show the potential for predicting the inflammatory responses of individual human subjects [107,108] and large, outbred animals [13,72,109].

## 4. Conceptualizing data with mechanism: An example from neuroscience and general anesthesia

The foregoing sections have delineated the benefits and challenges inherent in purely data-driven and mechanistic modeling in the setting of acute critical illness. Thus, neither method is ideal, although it may be argued that both approaches offer complementary value to a purely reductionist approach. In multiple fields of biomedical science, there is a growing recognition of the need to link purely data-driven models with mechanistic models to retain the advantages while minimizing the disadvantages of these 2 modeling approaches [110,111]. As mentioned above, there have been rare examples of this type of synthesis in acute critical illness. One such example [72] involved using principal component analysis to define the key inflammatory mediators involved is the lung and blood responses to Gram-negative bacterial endotoxin in swine and then using that information to construct a 2-compartment, mechanistic dynamical model of inflammation and pathophysiology in these animals.

However, such examples are the exception rather than the rule. There is a great deal of "activation energy" required to drive this type of synthesis, and a key barrier that must be overcome is the cost versus benefit of investing this effort. Thus, we discuss general anesthesia as a useful example of how complex dynamical mechanistic models can interact with data-driven modeling of a complex physiologic system to provide an integrating conceptual framework of value to the critical care community.

Although general anesthesia has been used in the clinical practice of medicine for more than 150 years, the mechanism of action for inducing general anesthesia is still not fully understood [112] and is still under considerable investigation [113-117]. With advances in biochemistry, molecular biology, and neurochemistry, there has been impressive progress in the understanding of the molecular properties of anesthetic agents. However, despite these advances, we still do not understand how anesthetic agents affect the properties of neurons that translate into the induction of general anesthesia at the macroscopic level. In fact, to date, no single unifying receptor mediating general anesthesia has been identified. We suggest that the most likely explanation for the mechanisms of action of anesthetics lies in the network properties of the brain, where the fundamental unit in the brain is the excitable neuron. These network properties are being discovered largely through data-driven modeling [118,119].

In fact, it has been known for a long time that general anesthesia has profound effects on the spectrum of oscillations in the electroencephalograph [120,121]. In both animal and human studies, it has been observed that with increased doses of anesthetic agents, the transition from consciousness to unconsciousness or from responsiveness to nonresponsiveness in individual subjects is very sharp, almost an all-or-none transition [122], confirming the clinical observations of generations of clinicians. There is also extensive experimental verification that collections of neurons may function as oscillators [123-125] and that synchronization of oscillators may play a key role in the transmission of information within the central nervous system.

More recently, the authors in [117] have suggested that thalamocortical circuits function as neural pacemakers and that alterations in the thalamic oscillations are associated with the induction of general anesthesia. Furthermore, it is well known that anesthetic drugs frequently induce epileptiform activity as part of the sharp progression to the state of unconsciousness [126]; epileptiform activity implies synchronization of oscillators. This leads to the possibility that synchronization of these oscillators is involved in the transition to the anesthetic state, in a manner similar to the aforementioned concept of oscillators in organ-organ coupling [21].

One fascinating possibility in understanding how the molecular properties of anesthetic agents lead to the behavior of the intact organism exhibiting nearly discontinuous transitions from consciousness to unconsciousness as the concentration of anesthetic drugs increases, is to develop mechanistic models that capture phase transitions of the neural network that resemble a thermodynamic phase change [127]. By merging the two universalisms of thermodynamics and dynamical systems theory—both of which are aspects of mechanistic modeling—with neuroscience, the authors in [128-130] provide insights to the theoretical foundation for understanding the network properties of the brain by rigorously addressing large-scale interconnected biological neuronal network models that govern the neuroelectronic behavior of biological excitatory and inhibitory neuronal networks. As in thermodynamics, neuroscience is a theory of large-scale systems, wherein graph theory [131]—a form of data-driven modeling—can be used in capturing the connectivity properties of system interconnections, with neurons represented by nodes, synapses represented by edges or arcs, and synaptic efficacy captured by edge weighting.

In current clinical practice, potent drugs are administered, which profoundly influence levels of consciousness and vital respiratory (ventilation and oxygenation) and cardiovascular (heart rate, blood pressure, and cardiac output) functions. These variation patterns of the physiologic parameters (i.e., ventilation, oxygenation, heart rate, blood pressure, and cardiac output) and their alteration with levels of consciousness can potentially provide scale-invariant fractal temporal structures to characterize the degree of consciousness in sedated patients. In particular, the degree of consciousness reflects the adaptability of the central nervous system and is proportional to the maximum work output under a fully conscious state divided by the work output of a given anesthetized state [132]. The fractal nature (i.e., complexity) of conscious variability enables the central nervous system, as a large-scale interconnected neuronal network, to maximize entropy production and optimally dissipate energy gradients. A fully conscious healthy patient would exhibit rich fractal patterns in space (e.g., fractal vasculature) and time (e.g., cardiopulmonary

variability) that optimize the ability for oxygenation and ventilation. Within the context of aging and acute illness, variation of physiologic parameters and their relationship to system complexity, fractal variability, and system thermodynamics have been explored in [21,132-136].

Merging system thermodynamics with neuroscience can provide the theoretical foundation for understanding the mechanisms of action of general anesthesia using the network properties of the brain. Developing a mechanistic, dynamical systems framework for neuroscience [128-130] and merging it with system thermodynamics [137-139] by embedding thermodynamic state notions (i.e., entropy, energy, free energy, chemical potential, etc) in theory would allow us to directly address the otherwise mathematically complex and computationally prohibitive large-scale neural population models that have been developed in the literature. In particular, a thermodynamically consistent neuroscience model would emulate the clinically observed self-organizing, spatiotemporally fractal structures that dissipate energy optimally and optimize entropy production in thalamocortical circuits of fully conscious patients. This thermodynamically consistent neuroscience framework can provide the necessary tools involving semistability [130], synaptic drive equipartitioning (i.e., synchronization across time scales) [130], energy dispersal, and entropy production for connecting biophysical findings to psychophysical phenomena for general anesthesia.

In particular, we hypothesize that as the model dynamics describing the cortical neural network transition to an anesthetic state, the system will involve a reduction in system complexity—defined as a reduction in the degree of irregularity across time scales—exhibiting semistability and synchronization of neural oscillators (i.e., thermodynamic energy equipartitioning) [129,140]. In addition, connections among thermodynamics, neuroscience, and the arrow of time [137-139] can be explored by developing an understanding of how the arrow of time is built into the very fabric of our conscious brain. Connections between thermodynamics and neuroscience are not limited to the study of consciousness in general anesthesia; they can also be seen in biochemical systems, ecosystems, gene regulation, and cell replication as well as numerous medical conditions (eg, seizures, epilepsy, schizophrenia, hallucinations, etc), which are obviously of great clinical importance but have been lacking rigorous theoretical frameworks.

## 5. Conclusions and future prospects

The unmet need for new treatments and diagnostic modalities for acute critical illness is, in a word, acute. Although decades of work have led to many novel insights from the molecular to the physiologic level, the net result has been disappointing. We suggest that this is not because the effort has not been worthwhile or because promising candidate approaches were not pursued. Rather, it is our contention that what has not taken place is the process of synthesis of these insights into a larger whole. Computational modeling is a promising avenue for such synthesis; however, the current approach is based purely on statistical tools by which to associate multiple variables to outcomes. Mechanistic mathematical modeling based on dynamic measurements can circumvent many of the pitfalls of data pattern analysis, but what is needed is a synthesis of these 2 approaches.

In this article, we have attempted to present this perspective, with an example from the arena of anesthesia with which we hope members of the critical care community will be acquainted. Researchers in the neurosciences are attempting to synthesize data-driven concepts of neural circuits with mechanistic models of brain function and general anesthesia, although this effort is still ongoing. The anticipated payoff is the development of anesthetic models that can significantly advance our understanding of pharmacologic agents and anesthetics as well as advance the state-of-the-art of drug delivery for general anesthesia. We suggest the need for similar efforts in the setting of acute critical illness. The payoff for this community would be personalized (or precision) medicine using known drugs but driven by quantitative data via predictive, mechanistic models. Ultimately, such models could be used to design completely new drugs or feedback control devices (or combinations thereof) that would modulate inflammation and physiology to reduce morbidity and mortality from acute critical illness. Although this vision is also a ways off, early steps in this direction are promising and merit further effort. We hope that members of the SCAI will lead the way in this endeavor and take the advantage of the undeniable opportunities offered by bringing together these two complexity-inspired approaches.

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