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Sepsis: From Pattern to Mechanism and Back

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Abstract

Sepsis is a clinical entity in which complex inflammatory and physiological processes are mobilized, not only across a range of cellular and molecular interactions, but also in clinically relevant physiological signals accessible at the bedside. There is a need for a mechanistic understanding that links the clinical phenomenon of physiologic variability with the underlying patterns of the biology of inflammation, and we assert that this can be facilitated through the use of dynamic mathematical and computational modeling. An iterative approach of laboratory experimentation and mathematical/computational modeling has the potential to integrate cellular biology, physiology, control theory, and systems engineering across biological scales, yielding insights into the control structures that govern mechanisms by which phenomena, detected as biological patterns, are produced. This approach can represent hypotheses in the formal language of mathematics and computation, and link behaviors that cross scales and domains, thereby offering the opportunity to better explain, diagnose, and intervene in the care of the septic patient.

Keywords

sepsis; inflammatory response; SIRS; septic shock; mathematical modeling

I. INTRODUCTION: THE SIGNIFICANCE AND PUZZLE OF SEPSIS

Sepsis is a significant may account for nearly 10% of total U.S. deaths.[1–4] It can be argued that for most infections, death, despite antibiotics, occurs primarily through the final common pathway of sepsis-induced multiple organ dysfunction syndrome (MODS). When viewed thus, sepsis is the tenth leading cause of death overall in the United States.[2,5] Sepsis affects persons of all ages groups,[6] and is the second leading cause of morbidity and mortality for patients admitted to an intensive care unit (ICU).[1,7–10] Sepsis also substantially reduces the quality of life of many of those who survive.[2,11,12] As the population ages, and the increasing preponderance of complex medical comorbidities expected in that population, the impact of sepsis would be expected to increase.[1,2,6,13]

Despite a large body of scientific literature concerning individual mechanisms that are involved in sepsis—ranging from disordered endothelial activation, public [14,15] organ dysfunction due to epithelial cell fail-health concern that ure,[16,17] to dysregulated inflammation and the associated complement and coagulation networks[18,19]—the primary

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challenge in the management of sepsis is the effective integration and characterization of multiple abnormal configurations of all these factors, and the identification of which patients set of disorders. This challenge is manifest not only among individuals (i.e., patient heterogeneity), but also during the course of disease within a single patient (temporal heterogeneity). The heterogeneous nature of the sepsis patient population has made it difficult to parse that population into sufficiently precise, molecularly defined pathophysiologic subgroups. The field has progressed from a recognition of the basic clinical features of sepsis in antiquity[20] through the germ theory (in which pathogens were the sole causes),[21–23] to the development of various sets of fairly rigid diagnostic and evolving guidelines and scoring systems developed in part in response to the inability to curb sepsis solely through therapy aimed at the pathogen.[22,24–26] However, recent advances in the analysis and modeling of high-dimensional, dynamic data (physiologic, genomic, and proteomic) on acutely ill patients (discussed below) suggest that the field is heading toward multidimensional characterization of the state of individual patients, rather than rigid diagnoses.[27–29]

II. PATTERNS OF PHYSIOLOGY AND INFLAMMATION IN SEPSIS

Two, heretofore parallel, approaches have evolved over time in an attempt to address sepsis diagnosis and therapy from a systems perspective, both of which utilize patterns of information. One area of active research involves the analysis of physiological signals retrievable from bedside monitoring devices, dealing with the processing and interpretation of complex physiological signals. Twenty years of research in this area[30] 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 fashion.[31,32] These descriptive methods have been used in an attempt to elucidate more precise and potentially predictive metrics associated with clinical manifestations of sepsis/MODS; the hope is that these metrics will also provide some mechanistic insight into the control systems responsible for their output. For instance, organ dysfunction in sepsis has been viewed as a decoupling of the oscillatory systems manifest in intact organ-to-organ feedback.[33] 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 (Fig. 1).[34–36] Time-domain analysis of heart rate variability (HRV) has subsequently evolved as a potentially noninvasive diagnostic modality for sepsis.[37] Using sophisticated physiological signal-processing techniques, various studies have reported that a decrease in HRV indices may be potentially diagnostic of higher morbidity and mortality in critically ill patients.[35,38–45] In addition to HRV, examination of other physiologic parameters from a complex systems approach has also yielded valuable insights into the physiology of sepsis.[46,47] The rising interest in the diagnostic utility of metrics of HRV in the setting of trauma and sepsis[43,48] was highlighted at the recent Ninth International Conference on Complexity in Acute Illness.[49]

However, despite the demonstrated validity and usefulness of these types of physiological signal analyses, these methods remain primarily phenomenological and diagnostic in nature —in essence, connecting biological pattern with clinical outcome through the use of statistical methods.[50] The clinical management of sepsis/MODS is significantly hampered in both diagnostics and therapeutics; therefore, any cohesive attempt to deal with the challenge of sepsis needs to connect phenomenology with mechanism in order to attack both needs simultaneously. There have been some attempts to establish anatomic correlates to the control systems involved in organ-to-organ oscillatory coupling: HRV data have been used indirectly to detect variability attributed to sympathetic and parasympathetic branches of the autonomic nervous system as well as other physiological processes that affect heart rate, including respiration, blood pressure, and temperature.[37] However, in order to design and

develop therapeutics in a rationally directed manner, a precise dynamic characterization of the cellular and molecular mechanisms responsible for generating the sepsis phenotype is required.

Toward this end, the other parallel track of complex systems analysis in the study of sepsis invovles dynamic mathematical and computational modeling at the cellular and molecular level. It is well appreciated that inflammation is both a communication mechanism for, and the primary driver of, the cascading organ dysfunction characteristic of sepsis and MODS[51] (Fig. 1). Inflammation in trauma/hemorrhage and sepsis manifests in patterns evident at the genomic,[50–53] proteomic,[28,56,57] and metabolomic[28,58] levels. The complexity of dynamic patterns in inflammation is potentially daunting, and multiple groups have approached characterizing this critical generative process through pattern-oriented analyses.[59–66] Such analyses may suggest principal drivers of inflammation and MODS, and may define the interconnected networks of mediators and signaling responses that underlie the pathobiology of critical illness.

III. A TRANSLATIONAL SYSTEMS BIOLOGY APPROACH TO CRITICAL ILLNESS

Despite these advanced pattern-oriented methods, the knowledge necessary to both decipher the complexity of acute inflammation and MODS may require going beyond patterns toward mechanism, using the tools of mathematical modeling.[29,67–75] The pathogenesis of sepsis is dynamic and involves tissue-level cellular activation resulting in the release of inflammatory mediators such as cytokines; the activation of neutrophils, monocytes, and microvascular endothelial cells; triggered involvement of neuroendocrine mechanisms; and activation of the complement, coagulation, and fibrinolytic systems[76,77](Fig. 1). The innate immune/acute inflammatory response recognizes the presence of invading pathogens, acts toward initial containment, recruits additional cells to eliminate the pathogens, and, concurrently, involves feedback mechanisms that serve to limit and restrict the proinflammatory component such that homeostatic dynamic equilibrium can be reestablished.[78] These factors function in a series of interlinked and overlapping networks that function at multiple scales, suggesting that “inflammation is communication.”[79] As in any situation that involves communication, the content, tone, and context are of critical importance. For instance, an appropriately robust inflammatory response is necessary to survive trauma/hemorrhage, both in the very short and long terms,[66,80] a finding that contradicts the driving dogma of trauma/sepsis from the 1980s and 1990s.[81,82]

It is important to note that organs obtained from sepsis patients postmortem do not exhibit histological damage;[83] however, these organs are nonetheless dysfunctional through various functional defects identified at the cellular/molecular level in both epithelial[84] and endothelial cells.[14,15] This dysfunction may evolve from and help maintain disordered positive feedback loops, in which inflammation induced by pathogen-derived signals leads to the release from epithelial and endothelial cells of molecular messengers of tissue damage, namely, damage-associated molecular pattern (DAMP) molecules. These alarm/danger signals recruit and stimulate inflammatory cells to produce more inflammatory mediators, leading to a further release of DAMPs, resulting in a self-maintaining inflammatory cycle, even after the pathogen has been cleared. The body is equipped to suppress inflammation and promote the healing of cells, tissues, and organs both through the production of anti-inflammatory mediators as well as through an inherent suppression of proinflammatory signaling (referred to as tolerance or desensitization). In sepsis, these anti-inflammatory influences are either insufficient to suppress self-maintaining inflammation, or are overproduced and lead to an immunosuppressed state.[78,85–87] Given the complexity of these feedback relationships, it not surprising that, despite promising results at the basic

science and preclinical level, large-scale trials of therapies targeted at inhibiting specific inflammatory mediators have generally failed to improve survival.[88]

Inflammatory pathways and the organ-level physiology to which they are coupled exhibit nonlinear behavior, significantly limiting the intuitive extrapolation of mechanistic knowledge derived from basic science to clinically relevant effects at the level of the whole patient.[89–93] Reductionism, the primary approach in biomedical research, has been successful when applied to systems whose behavior can be reduced to a "linear" (i.e., single direct relationship) representation such that the results of various independent experiments can be aggregated additively to obtain and predict the behavior of the system as a whole.[89] However, systems that have multiple positive and negative feedback loops, and therefore display nonlinear behavior such as the acute inflammatory response, require more sophisticated mathematical representation for their characterization. It is now recognized that such an approach is necessary to understand complex biologic processes.[89,91,94–98]

Systems biology provides some methods and approaches that move in the appropriate direction.[95,99] *In silico* (i.e., computer-based) research consisting of the use of dynamic mathematical and computational models has been suggested as a necessary step in untangling complex biological processes such as the acute inflammatory response by both the NIH in its Roadmap Initiative[100] and the FDA in its "Critical Path" document.[99] Dynamic mathematical and computational models characterize the evolution of variables (corresponding to observable properties in the real world) over time, and thus account for the temporal dimension in the description of a biological phenomenon/system. Therefore, the purpose of such computational models is predictive description—to provide entailment and insight into the future state of the system given knowledge of the current state of the system. This property suggests that dynamic mathematical and computational models can be considered testable hypotheses. When such a model predicts measurable behavior that matches the corresponding metrics experimentally observed in the system under study, one can reasonably infer that the model has captured potentially useful interrelations.[89] Conversely, when model and experiment disagree, the assumptions/hypotheses represented in the model must be reassessed (it should be noted that this process is not limited to mathematical models).

Transparency in model construction is critical, insomuch that the assumptions underlying a particular model must be able to be examined in detail so that the iterative process of model refinement (essentially a proxy for the scientific method) can be executed.[101,102] Furthermore, the formal process of creating and executing *in silico* models can provide useful frameworks for integrating hypotheses and dealing with the uncertainties associated with the calibration of experimental data, given behavioral nonlinearities, high-dimensional parameter spaces, and sparse sample points.[103]

Mechanistic *in silico* models of acute inflammation have been applied successfully to sepsis, trauma, and wound healing, leading to the concept of translational systems biology of inflammation.[29,67,70–75,104,105] In terms of theory, simple models of acute inflammation have suggested that morbidity and mortality in sepsis may arise from diverse insult- and patient-specific circumstances, [106] and have given basic insight into properties of molecular control structures and sufficient levels of representation.[107,108] Dynamic mathematical and computational models have been used to characterize inflammatory signal-transduction cascades, and these studies may help drive mechanism-based drug discovery.[109–111] Other computational models were used to yield insights into the acute inflammatory response in diverse shock states,[112–117] as well as the responses to anthrax,[118] necrotizing enterocolitis,[119] and toxic-shock syndrome.[120] *In silico* modeling has helped define and predict the acute inflammatory responses seen in both experimental animals[112,115,121–123]

and humans.[124] Initial translational successes of dynamic mathematical and computational models involved the ability to reproduce (and suggest improvements to) clinical trials in sepsis,[98,125] and these successes have been extended to the design of prospective clinical trials.[67,71,72,74,75] An *in silico* clinical trial environment, consisting of a multiscale, equation-based mechanistic simulation that encompasses dynamic interactions among multiple tissues, immune cells, and inflammatory mediators, has been augmented with a "virtual clinician" in order to better reproduce the clinical environment of critical care.[61,71,72,74,75]

IV. SEPSIS: FROM PATTERN TO MECHANISM VIA TRANSLATIONAL SYSTEMS BIOLOGY

Despite all of the aforementioned research into, and emerging translational applications of, complex systems methods, there has been little success in mechanistically connecting inflammation and physiologic variability. Our long-term goal is a systems understanding of sepsis that will allow us to unify the pattern-based, diagnostically relevant use of physiological waveforms with the increasingly detailed, mechanistic understanding of acute inflammation in order to improve therapy for sepsis. At present, however, patterns of physiologic signals and inflammatory mediators are, at best, statistically associated with changes in organ function and overall health status.[126] We suggest that these processes need to be viewed from a dynamic, mechanistic standpoint, and that the missing ingredient in many current research endeavors is the ability to connect multidimensional data with underlying biological and physiologic mechanisms. In short, we are not satisfied with associations and correlations between patterns of signals and disease state; we seek to understand the generative processes by which those signals arise. We suggest that translational systems biology is the path to representing this critical connectivity, an approach that involves mechanistic mathematical modeling with a clinically translational focus.[67,71–75] We view both inflammation and physiologic variability from a "Goldilocks" perspective, i.e., too little or too much of either is a hallmark of disease, and our engineering focus[104] has led us to suggest that we need to understand the control architecture involved in balancing inflammation and physiologic demands. We hypothesize that breakdowns in the control architecture and connectivity lead to the myriad derangements associated with sepsis, and that these failure modes can be described and quantified in order to separate critical signals from "red herring" signals that arise from the inherent system architecture (Fig. 1). We suggest that future sepsis research would be greatly enhanced by developing approaches to bridge the gap between cellular-molecular mechanism and clinically relevant physiological phenomenon, hopefully leading to a solid mechanistic foundation to diagnostically relevant changes in physiologic waveforms and patterns of inflammatory mediators.

V. CONCLUSIONS AND FUTURE PROSPECTS

There can be little doubt about the potential future societal impact of sepsis.[1,2,6,13] As with virtually all aspects of sepsis, the difficulties clinicians face in the future are due, ironically, at least to some degree to the prior successes of the very same clinical community: the consequences of their successes are that people are now older and generally sicker when they reach the ICU. The advances in mechanistic understanding associated with the pathophysiology of sepsis are also impressive, but these advances, too, have often only served to complicate matters: we now recognize that "sepsis" is not one clinical entity, but rather a broad and heterogeneous spectrum of acute systemic inflammation. Any rational approach to the challenge of sepsis and related disorders requires the ability to parse out the clinical population into more mechanistically defined subgroups; it is only then that

effective interventions might be designed and implemented with a nonrandom chance of success (in contrast to the past 25 years of attempts at therapeutic intervention in sepsis).

Many research communities have recognized the importance of mathematical and computational integration of knowledge in order to advance their science. Drawing on the experience in physics,[127] ecology,[128] material science,[129] geochemistry,[130] and many other scientific fields, we do not suggest that mathematical modeling is a substitute for experiments performed in the real world. However, computational modeling of critical illness and intervention is a means of leveraging the expertise in knowledge integration and engineering present across scientific disciplines. Specifically related to critical illness and sepsis, computational modeling serves at least two purposes. First, any model that predicts behaviors closely corresponding to experiment and/or clinical observation reassures us that the model has, in fact, captured the relevant components and their interactions.[131] Second, and perhaps most important, discordance between the model's behavior and anticipated or actual outcomes illuminates those areas where further experiments should focus.[131] Ultimately, translational systems biology should continue to inspire both hope[131] and skepticism[132] on the path to mechanism from biological and physiological patterns.

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ABBREVIATIONS

DAMP	damage-associated molecular pattern
ICU	intensive care unit
MODS	multiple organ dysfunction syndrome

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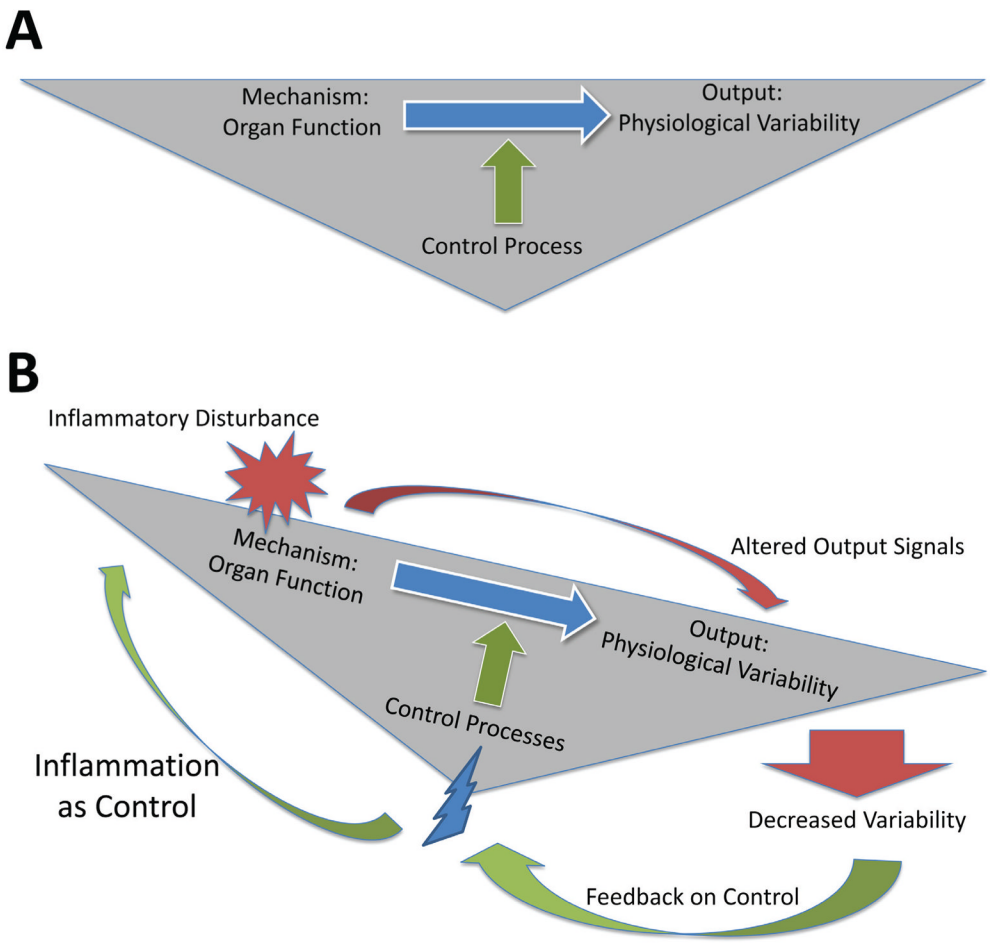

FIGURE 1.

The effects of inflammation on organ function and accompanying physiologic variability occur via a neuroendocrine control architecture. (A) In the healthy state, normal organ function manifests in physiologic variability due to the actions of a neuroendocrine control architecture. (B) Inflammation affects healthy physiologic variability, and defined changes in physiologic variability are sensed via the neuroendocrine control architecture (that in turn is itself affected by inflammation). This control system in turn induces further inflammation in an attempt to restore healthy variability, but is most likely degraded in the face of persistent inflammation, creating a positive feedback loop of inflammation → dysfunction → inflammation.