Published in final edited form as:
*Crit Rev Biomed Eng*. 2012 ; 40(4): 341–351.

# Sepsis: From Pattern to Mechanism and Back

**Gary An**[1,2], **Rami A. Namas**[2,3], and **Yoram Vodovotz**[2,3,*]

[1]Department of Surgery, University of Chicago, Chicago, IL 60637

[2]Center for Inflammation and Regenerative Modeling, McGowan Institute for Regenerative Medicine, University of Pittsburgh, Pittsburgh, PA 15219

[3]Department of Surgery, University of Pittsburgh, Pittsburgh, PA 15213

## 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



*Address all correspondence to: Yoram Vodovotz, Department of Surgery, University of Pittsburgh, W944 Biomedical Sciences Tower, 200 Lothrop St., Pittsburgh, PA 15213: Tel.: 412-647-5609; Fax: 412-383-5946; vodovotzy@upmc.edu.

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.

## Acknowledgments

This work was supported in part by the National Institutes of Health grants R01GM67240, P50GM53789, R33HL089082, R01HL080926, R01AI080799, R01HL76157, R01DC008290, and UO1 DK072146; National Institute on Disability and Rehabilitation Research grant H133E070024; a Shared University Research Award from IBM, Inc.; and grants from the Commonwealth of Pennsylvania, the Pittsburgh Life Sciences Greenhouse, and the Pittsburgh Tissue Engineering Initiative/Department of Defense.

## ABBREVIATIONS

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

## References

1. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001; 29(7):1303–10. [PubMed: 11445675]
2. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med. 2003; 348(16):1546–54. [PubMed: 12700374]
3. Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, Moreno R, Carlet J, Le Gall JR, Payen D. Sepsis in European intensive care units: results of the SOAP study. Crit Care Med. 2006; 34(2):344–53. [PubMed: 16424713]
4. Heron M, Hoyert DL, Murphy SL, Xu J, Kochanek KD, Tejada-Vera B. Deaths: final data for 2006. Natl Vital Stat Rep. 2009; 57(14):1–134. [PubMed: 19788058]
5. Hoyert DL, Arias E, Smith BL, Murphy SL, Kochanek KD. Deaths: final data for 1999. Natl Vital Stat Rep. 2001; 49(8):1–113.
6. Weycker D, Akhras KS, Edelsberg J, Angus DC, Oster G. Long-term mortality and medical care charges in patients with severe sepsis. Crit Care Med. 2003; 31(9):2316–23. [PubMed: 14501962]
7. Wheeler AP, Bernard GR. Treating patients with severe sepsis. N Engl J Med. 1999; 340(3):207–14. [PubMed: 9895401]
8. Angus DC, Wax RS. Epidemiology of sepsis: an update. Crit Care Med. 2001; 29(7 Suppl):S109–16. [PubMed: 11445744]

9. Sands KE, Bates DW, Lanken PN, Graman PS, Hibberd PL, Kahn KL, Parsonnet J, Panzer R, Orav EJ, Snydman DR, Black E, Schwartz JS, Moore R, Johnson BL Jr, Platt BL. Epidemiology of sepsis syndrome in 8 academic medical centers. JAMA. 1997; 278(3):234–40. [PubMed: 9218672]
10. Parrillo JE, Parker MM, Natanson C, Suffredini AF, Danner RL, Cunnion RE, Ognibene FP. Septic shock in humans. Advances in the understanding of pathogenesis, cardiovascular dysfunction, and therapy. Ann Intern Med. 1990; 113(3):227–42. [PubMed: 2197912]
11. Heyland DK, Hopman W, Coo H, Tranmer J, McColl MA. Long-term health-related quality of life in survivors of sepsis. Short Form 36: a valid and reliable measure of health-related quality of life. Crit Care Med. 2000; 28(11):3599–605. [PubMed: 11098960]
12. Perl TM, Dvorak L, Hwang T, Wenzel RP. Long-term survival and function after suspected gram-negative sepsis. JAMA. 1995; 274(4):338–45. [PubMed: 7609265]
13. Increase in National Hospital Discharge Survey rates for septicemia—United States, 1979–1987. MMWR Morb Mortal Wkly Rep. 1990; 19;39(2):31–4.
14. Aird WC. The role of the endothelium in severe sepsis and multiple organ dysfunction syndrome. Blood. 2003; 101(10):3765–77. [PubMed: 12543869]
15. Ait-Oufella H, Maury E, Lehoux S, Guidet B, Offenstadt G. The endothelium: physiological functions and role in microcirculatory failure during severe sepsis. Intensive Care Med. 2010; 36(8):1286–98. [PubMed: 20443110]
16. Protti A, Singer M. Bench-to-bedside review: potential strategies to protect or reverse mitochondrial dysfunction in sepsis-induced organ failure. Crit Care. 2006; 10(5):228–34. [PubMed: 16953900]
17. Balestra GM, Legrand M, Ince C. Microcirculation and mitochondria in sepsis: getting out of breath. Curr Opin Anaesthesiol. 2009; 22(2):184–90. [PubMed: 19307893]
18. Rittirsch D, Flierl MA, Ward PA. Harmful molecular mechanisms in sepsis. Nat Rev Immunol. 2008; 8(10):776–87. [PubMed: 18802444]
19. Levi M, van der Poll T. Inflammation and coagulation. Crit Care Med. 2010; 38(2 Suppl):S26–S34. [PubMed: 20083910]
20. Geroulanos S, Douka ET. Historical perspective of the word “sepsis”. Intensive Care Med. 2006; 32(12):2077. [PubMed: 17131165]
21. Ewald PW. Evolution of virulence. Infect Dis Clin North Am. 2004; 18(1):1–15. [PubMed: 15081500]
22. Vincent JL. Clinical sepsis and septic shock—definition, diagnosis and management principles. Langenbecks Arch Surg. 2008; 393(6):817–24. [PubMed: 18584205]
23. Schottmueller H. Wesen und Behandlung der Sepsis. Inn Med. 2009; 31:257–80. (1914).
24. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med. 1992; 20(6):864–74. [PubMed: 1597042]
25. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med. 2003; 31(4):1250–6. [PubMed: 12682500]
26. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992; 101(6):1644–55. [PubMed: 1303622]
27. Ventetuolo CE, Levy MM. Biomarkers: diagnosis and risk assessment in sepsis. Clin Chest Med. 2008; 29(4):591–603. vii. [PubMed: 18954695]
28. Claus RA, Otto GP, Deigner HP, Bauer M. Approaching clinical reality: markers for monitoring systemic inflammation and sepsis. Curr Mol Med. 2010; 10(2):227–35. [PubMed: 20196725]
29. Namas R, Zamora R, Namas R, An G, Doyle J, Dick TE, Jacono FJ, Androulakis IP, Chang S, Billiar TR, Kellum JA, Angus DC, Vodovotz Y. Sepsis: Something old, something new, and a systems view. J Crit Care. 2012 Jun; 27(3):314.e1–11. [PubMed: 21798705]
30. www.physionet.org 2012.

31. Gang Y, Malik M. Heart rate variability in critical care medicine. Curr Opin Crit Care. 2002; 8(5): 371–5. [PubMed: 12357103]
32. Moorman JR, Lake DE, Griffin MP. Heart rate characteristics monitoring for neonatal sepsis. IEEE Trans Biomed Eng. 2006; 53(1):126–32. [PubMed: 16402612]
33. Godin PJ, Buchman TG. Uncoupling of biological oscillators: a complementary hypothesis concerning the pathogenesis of multiple organ dysfunction syndrome. Crit Care Med. 1996; 24(7): 1107–16. [PubMed: 8674321]
34. Annane D, Trabold F, Sharshar T, Jarrin I, Blanc AS, Raphael JC, Gajdos P. Inappropriate sympathetic activation at onset of septic shock: a spectral analysis approach. Am J Respir Crit Care Med. 1999; 160(2):458–65. [PubMed: 10430714]
35. Korach M, Sharshar T, Jarrin I, Fouillot JP, Raphael JC, Gajdos P, Annane D. Cardiac variability in critically ill adults: influence of sepsis. Crit Care Med. 2001; 29(7):1380–5. [PubMed: 11445691]
36. Piepoli M, Garrard CS, Kontoyannis DA, Bernardi L. Autonomic control of the heart and peripheral vessels in human septic shock. Intensive Care Med. 1995; 21(2):112–9. [PubMed: 7775691]
37. Fairchild KD, Saucerman JJ, Raynor LL, Sivak JA, Xiao Y, Lake DE, Moorman JR. Endotoxin depresses heart rate variability in mice: cytokine and steroid effects. Am J Physiol Regul Integr Comp Physiol. 2009; 297(4):R1019–27. [PubMed: 19657103]
38. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur Heart J. 1996; 17(3):354–81. [PubMed: 8737210]
39. Kleiger RE, Stein PK, Bigger JT Jr. Heart rate variability: measurement and clinical utility. Ann Noninvasive Electrocardiol. 2005; 10(1):88–101. [PubMed: 15649244]
40. Pomeranz B, Macaulay RJ, Caudill MA, Kutz I, Adam D, Gordon D, Kilborn KM, Barger AC, Shannon DC, Cohen RJ, Benson H. Assessment of autonomic function in humans by heart rate spectral analysis. Am J Physiol. 1985; 248(1 Pt 2):H151–3. [PubMed: 3970172]
41. Godin PJ, Fleisher LA, Eidsath A, Vandivier RW, Preas HL, Banks SM, Buchman TG, Suffredini AF. Experimental human endotoxemia increases cardiac regularity: results from a prospective, randomized, crossover trial. Crit Care Med. 1996; 24(7):1117–24. [PubMed: 8674322]
42. Barnaby D, Ferrick K, Kaplan DT, Shah S, Bijur P, Gallagher EJ. Heart rate variability in emergency department patients with sepsis. Acad Emerg Med. 2002; 9(7):661–70. [PubMed: 12093705]
43. Chen WL, Kuo CD. Characteristics of heart rate variability can predict impending septic shock in emergency department patients with sepsis. Acad Emerg Med. 2007; 14(5):392–7. [PubMed: 17389245]
44. Pontet J, Contreras P, Curbelo A, Medina J, Noveri S, Bentancourt S, Migliaro ER. Heart rate variability as early marker of multiple organ dysfunction syndrome in septic patients. J Crit Care. 2003; 18(3):156–63. [PubMed: 14595568]
45. Ahmad S, Ramsay T, Huebsch L, Flanagan S, McDiarmid S, Batkin I, McIntyre L, Sundaresan SR, Maziak DE, Shamji FM, Hebert P, Fergusson D, Tinmouth A, Seely AJ. Continuous multi-parameter heart rate variability analysis heralds onset of sepsis in adults. PLoS ONE. 2009; 4(8):e6642. [PubMed: 19680545]
46. Magder S. Bench-to-bedside review: ventilatory abnormalities in sepsis. Crit Care. 2009; 13(1): 202–13. [PubMed: 19216724]
47. Preas HL, Jubran A, Vandivier RW, Reda D, Godin PJ, Banks SM, Tobin MJ, Suffredini AF. Effect of endotoxin on ventilation and breath variability: role of cyclooxygenase pathway. Am J Respir Crit Care Med. 2001; 164(4):620–6. [PubMed: 11520726]
48. Cancio LC, Batchinsky AI, Salinas J, Kuusela T, Convertino VA, Wade CE, Holcomb JB. Heart-rate complexity for prediction of prehospital lifesaving interventions in trauma patients. J Trauma. 2008; 65(4):813–9. [PubMed: 18849796]
49. www.iccai.org/sci_info_2010.php.
50. An G. Phenomenological issues related to the measurement, mechanisms and manipulation of complex biological systems. Crit Care Med. 2006; 34(1):245–6. [PubMed: 16374188]

51. Hodgin KE, Moss M. The epidemiology of sepsis. Curr Pharm Des. 2008; 14(19):1833–9. [PubMed: 18691094]
52. Chung TP, Laramie JM, Province M, Cobb JP. Functional genomics of critical illness and injury. Crit Care Med. 2002; 30(1 Suppl):S51–7.
53. Cobb JP, O'Keefe GE. Injury research in the genomic era. Lancet. 2004; 363(9426):2076–83. [PubMed: 15207961]
54. Wurfel MM. Microarray-based analysis of ventilator-induced lung injury. Proc Am Thorac Soc. 2007; 4(1):77–84. [PubMed: 17202295]
55. Winkelman C. Inflammation and genomics in the critical care unit. Crit Care Nurs Clin North Am. 2008; 20(2):213–21. vi. [PubMed: 18424350]
56. Nguyen A, Yaffe MB. Proteomics and systems biology approaches to signal transduction in sepsis. Crit Care Med. 2003; 31(1 Suppl):S1–6. [PubMed: 12544970]
57. Bauer M, Reinhart K. Molecular diagnostics of sepsis--where are we today? Int J Med Microbiol. 2010; 300(6):411–3. [PubMed: 20510650]
58. Serkova NJ, Standiford TJ, Stringer KA. The Emerging Field of Quantitative Blood Metabolomics for Biomarker Discovery in Critical Illnesses. Am J Respir Crit Care Med. 2011 Sep 15; 184(6): 647–55. [PubMed: 21680948]
59. Calvano SE, Xiao W, Richards DR, Felciano RM, Baker HV, Cho RJ, Chen RO, Brownstein BH, Cobb JP, Tschoeke SK, Miller-Graziano C, Moldawer LL, Mindrinos MN, Davis RW, Tompkins RG, Lowry SF. Large Scale Collab Res Program. A network-based analysis of systemic inflammation in humans. Nature. 2005; 437:1032–7. [PubMed: 16136080]
60. Liu T, Qian WJ, Gritsenko MA, Xiao W, Moldawer LL, Kaushal A, Monroe ME, Varnum SM, Moore RJ, Purvine SO, Maier RV, Davis RW, Tompkins RG, Camp DG, Smith RD. High dynamic range characterization of the trauma patient plasma proteome. Mol Cell Proteomics. 2006; 5(10):1899–913. [PubMed: 16684767]
61. McDunn JE, Husain KD, Polpitiya AD, Burykin A, Ruan J, Li Q, Schierding W, Lin N, Dixon D, Zhang W, Coopersmith CM, Dunne WM, Colonna M, Ghosh BK, Cobb JP. Plasticity of the systemic inflammatory response to acute infection during critical illness: development of the riboleukogram. PLoS ONE. 2008; 3(2):e1564. [PubMed: 18270561]
62. Warren HS, Elson CM, Hayden DL, Schoenfeld DA, Cobb JP, Maier RV, Moldawer LL, Moore EE, Harbrecht BG, Pelak K, Cuschieri J, Herndon DN, Jeschke MG, Finnerty CC, Brownstein BH, Hennessy L, Mason PH, Tompkins RG. A genomic score prognostic of outcome in trauma patients. Mol Med. 2009; 15(7–8):220–7. [PubMed: 19593405]
63. Cobb JP, Moore EE, Hayden DL, Minei JP, Cuschieri J, Yang J, Li Q, Lin N, Brownstein BH, Hennessy L, Mason PH, Schierding WS, Dixon DJ, Tompkins RG, Warren HS, Schoenfeld DA, Maier RV. Validation of the riboleukogram to detect ventilator-associated pneumonia after severe injury. Ann Surg. 2009; 250(4):531–9. [PubMed: 19730236]
64. Qian WJ, Petritis BO, Kaushal A, Finnerty CC, Jeschke MG, Monroe ME, Moore RJ, Schepmoes AA, Xiao W, Moldawer LL, Davis RW, Tompkins RG, Herndon DN, Camp DG, Smith RD. Plasma proteome response to severe burn injury revealed by 18O-labeled "universal" reference-based quantitative proteomics. J Proteome Res. 2010; 9(9):4779–89. [PubMed: 20698492]
65. Zhou B, Xu W, Herndon D, Tompkins R, Davis R, Xiao W, Wong WH, Toner M, Warren HS, Schoenfeld DA, Rahme L, McDonald-Smith GP, Hayden D, Mason P, Fagan S, Yu YM, Cobb JP, Remick DG, Mannick JA, Lederer JA, Gamelli RL, Silver GM, West MA, Shapiro MB, Smith R, Camp DG, Qian W, Storey J, Mindrinos M, Tibshirani R, Lowry S, Calvano S, Chaudry I, West MA, Cohen M, Moore EE, Johnson J, Moldawer LL, Baker HV, Efron PA, Balis UG, Billiar TR, Ochoa JB, Sperry JL, Miller-Graziano CL, De AK, Bankey PE, Finnerty CC, Jeschke MG, Minei JP, Arnoldo BD, Hunt JL, Horton J, Cobb JP, Brownstein B, Freeman B, Maier RV, Nathens AB, Cuschieri J, Gibran N, Klein M, O'keefe G. Analysis of factorial time-course microarrays with application to a clinical study of burn injury. Proc Natl Acad Sci U S A. 2010; 107(22):9923–8. [PubMed: 20479259]
66. Mi Q, Constantine G, Ziraldo C, Solovyev A, Torres A, Namas R, Bentley T, Billiar TR, Zamora R, Puyana JC, Vodovotz Y. A dynamic view of trauma/hemorrhage-induced inflammation in mice: Principal drivers and networks. PLoS ONE. 2011; 6:e19424. [PubMed: 21573002]

67. Vodovotz Y, Csete M, Bartels J, Chang S, An G. Translational systems biology of inflammation. PLoS Comput Biol. 2008; 4:1–6.
68. Foteinou PT, Yang E, Androulakis IP. Networks, biology and systems engineering: a case study in inflammation. Comput Chem Eng. 2009; 33(12):2028–41. [PubMed: 20161495]
69. Foteinou PT, Calvano SE, Lowry SF, Androulakis IP. Translational potential of systems-based models of inflammation. Clin Transl Sci. 2009; 2(1):85–9. [PubMed: 20443873]
70. Vodovotz Y, Constantine G, Rubin J, Csete M, Voit EO, An G. Mechanistic simulations of inflammation: Current state and future prospects. Math Biosci. 2009; 217:1–10. [PubMed: 18835282]
71. Vodovotz, Y.; An, G.; Yan, Q., editors. Systems biology in drug discovery and development: methods and protocols. Totowa, NJ: Springer Science & Business Media; 2009. p. 181-201.
72. Vodovotz Y, Constantine G, Faeder J, Mi Q, Rubin J, Sarkar J, Squires R, Okonkwo DO, Gerlach J, Zamora R, Luckhart S, Ermentrout B, An G. Translational systems approaches to the biology of inflammation and healing. Immunopharmacol Immunotoxicol. 2010; 32:181–95. [PubMed: 20170421]
73. Vodovotz Y. Translational systems biology of inflammation and healing. Wound Repair Regen. 2010; 18(1):3–7. [PubMed: 20082674]
74. Mi Q, Li NYK, Ziraldo C, Ghuma A, Mikheev M, Squires R, Okonkwo DO, Verdolini Abbott K, Constantine G, An G, Vodovotz Y. Translational systems biology of inflammation: Potential applications to personalized medicine. Personalized Med. 2010; 7:549–59.
75. An G, Bartels J, Vodovotz Y. In silico augmentation of the drug development pipeline: Examples from the study of acute inflammation. Drug Dev Res. 2010; 72:1–14.
76. Vincent JL, Abraham E. The last 100 years of sepsis. Am J Respir Crit Care Med. 2006; 173(3): 256–63. [PubMed: 16239619]
77. Cinel I, Opal SM. Molecular biology of inflammation and sepsis: a primer. Crit Care Med. 2009; 37(1):291–304. [PubMed: 19050640]
78. Vodovotz Y, Chow CC, Bartels J, Lagoa C, Prince JM, Levy RM, Kumar R, Day J, Rubin J, Constantine G, Billiar TR, Fink MP, Clermont G. In silico models of acute inflammation in animals. Shock. 2006; 26(3):235–44. [PubMed: 16912648]
79. Mi Q, Li NYK, Ziraldo C, Ghuma A, Mikheev M, Squires R, Okonkwo DO, Verdolini Abbott K, Constantine G, An G, Vodovotz Y. Translational systems biology of inflammation: Potential applications to personalized medicine. Personalized Med. 2010; 7:549–59.
80. Namas R, Ghuma A, Torres A, Polanco P, Gomez H, Barclay D, Gordon L, Zenker S, Kim HK, Hermus L, Zamora R, Rosengart MR, Clermont G, Peitzman A, Billiar TR, Ochoa J, Pinsky MR, Puyana JC, Vodovotz Y. An adequately robust early TNF-α response is a hallmark of survival following trauma/hemorrhage. PLoS ONE. 2009; 4(12):e8406. [PubMed: 20027315]
81. Rose S, Marzi I. Mediators in polytrauma--pathophysiological significance and clinical relevance. Langenbecks Arch Surg. 1998; 383(3–4):199–208. [PubMed: 9776443]
82. Smith RM, Giannoudis PV. Trauma and the immune response. J R Soc Med. 1998; 91(8):417–20. [PubMed: 9816356]
83. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. N Engl J Med. 2003; 348(2): 138–50. [PubMed: 12519925]
84. Fink MP, Delude RL. Epithelial barrier dysfunction: a unifying theme to explain the pathogenesis of multiple organ dysfunction at the cellular level. Crit Care Clin. 2005; 21(2):177–96. [PubMed: 15781156]
85. Marshall JC. Inflammation, coagulopathy, and the pathogenesis of multiple organ dysfunction syndrome. Crit Care Med. 2001; 29(7 Suppl):S99–106. [PubMed: 11445742]
86. Jarrar D, Chaudry IH, Wang P. Organ dysfunction following hemorrhage and sepsis: mechanisms and therapeutic approaches (Review). Int J Mol Med. 1999; 4(6):575–83. [PubMed: 10567665]
87. Crouser E, Exline M, Knoell D, Wewers MD. Sepsis: links between pathogen sensing and organ damage. Curr Pharm Des. 2008; 14(19):1840–52. [PubMed: 18691095]
88. Bone RC. Why sepsis trials fail. JAMA. 1996; 276(7):565–6. [PubMed: 8709407]

89. Vodovotz Y, Clermont G, Chow C, An G. Mathematical models of the acute inflammatory response. Curr Opin Crit Care. 2004; 10(5):383–90. [PubMed: 15385756]
90. Neugebauer EA, Willy C, Sauerland S. Complexity and non-linearity in shock research: reductionism or synthesis? Shock. 2001; 16(4):252–8. [PubMed: 11580105]
91. Tjardes T, Neugebauer E. Sepsis research in the next millennium: concentrate on the software rather than the hardware. Shock. 2002; 17(1):1–8. [PubMed: 11795662]
92. Buchman TG, Cobb JP, Lapedes AS, Kepler TB. Complex systems analysis: a tool for shock research. Shock. 2001; 16(4):248–51. [PubMed: 11580104]
93. Seely AJ, Christou NV. Multiple organ dysfunction syndrome: exploring the paradigm of complex nonlinear systems. Crit Care Med. 2000; 28(7):2193–200. [PubMed: 10921540]
94. An G. Agent-based computer simulation and sirs: building a bridge between basic science and clinical trials. Shock. 2001; 16(4):266–73. [PubMed: 11580108]
95. Kitano H. Systems biology: a brief overview. Science. 2002; 295(5560):1662–4. [PubMed: 11872829]
96. Vodovotz Y, Csete M, Bartels J, Chang S, An G. Translational systems biology of inflammation. PLoS Comput Biol. 2008; 4(4):e1000014. [PubMed: 18437239]
97. Cohen MJ, Grossman AD, Morabito D, Knudson MM, Butte AJ, Manley GT. Identification of complex metabolic states in critically injured patients using bioinformatic cluster analysis. Crit Care. 2010; 14(1):R10–20. [PubMed: 20122274]
98. An G. In-silico experiments of existing and hypothetical cytokine-directed clinical trials using agent based modeling. Crit Care Med. 2004; 32:2050–60. [PubMed: 15483414]
99. Vodovotz Y. Deciphering the complexity of acute inflammation using mathematical models. Immunol Res. 2006; 36(1–3):237–45. [PubMed: 17337784]
100. http://commonfund.nih.gov/aboutroadmap.aspx
101. An G. Translational systems biology using an agent-based approach for dynamic knowledge representation: An evolutionary paradigm for biomedical research. Wound Rep Reg. 2010; 18:8–12.
102. An G. Closing the scientific loop: Bridging correlation and causality in the petaflop age. Sci Transl Med. 2010; 2:41ps34.
103. Vodovotz Y, Clermont G, Hunt CA, Lefering R, Bartels J, Seydel R, Hotchkiss J, Ta'asan S, Neugebauer E, An G. Evidence-based modeling of critical illness: an initial consensus from the Society for Complexity in Acute Illness. J Crit Care. 2007; 22(1):77–84. [PubMed: 17371750]
104. An G, Faeder J, Vodovotz Y. Translational systems biology: Introduction of an engineering approach to the pathophysiology of the burn patient. J Burn Care Res. 2008; 29:277–85. [PubMed: 18354282]
105. An G, Mi Q, Dutta-Moscato J, Solovyev A, Vodovotz Y. Agent-based models in translational systems biology. WIRES. 2009; 1:159–71.
106. Kumar R, Clermont G, Vodovotz Y, Chow CC. The dynamics of acute inflammation. J Theoretical Biol. 2004; 230:145–55.
107. An G, Faeder JR. Detailed qualitative dynamic knowledge representation using a BioNetGen model of TLR-4 signaling and preconditioning. Math Biosci. 2009; 217:53–63. [PubMed: 18835283]
108. An G. A model of TLR4 signaling and tolerance using a qualitative, particle event-based method: Introduction of Spatially Configured Stochastic Reaction Chambers (SCSRC). Math Biosci. 2009; 217:43–52. [PubMed: 18950646]
109. Gibbs JB. Mechanism-based target identification and drug discovery in cancer research. Science. 2000; 287(5460):1969–73. [PubMed: 10720316]
110. Faeder JR, Hlavacek WS, Reischl I, Blinov ML, Metzger H, Redondo A, Wofsy C, Goldstein B. Investigation of early events in Fc epsilon RI-mediated signaling using a detailed mathematical model. J Immunol. 2003; 170(7):3769–81. [PubMed: 12646643]
111. Rivière B, Epshteyn Y, Swigon D, Vodovotz Y. A simple mathematical model of signaling resulting from the binding of lipopolysaccharide with toll-like receptor 4 demonstrates inherent preconditioning behavior. Math Biosci. 2009; 217:19–26. [PubMed: 18950647]

112. Chow CC, Clermont G, Kumar R, Lagoa C, Tawadrous Z, Gallo D, Betten B, Bartels J, Constantine G, Fink MP, Billiar TR, Vodovotz Y. The acute inflammatory response in diverse shock states. Shock. 2005; 24:74–84. [PubMed: 15988324]

113. Reynolds A, Rubin J, Clermont G, Day J, Vodovotz Y, Ermentrout GB. A reduced mathematical model of the acute inflammatory response: I. Derivation of model and analysis of anti-inflammation. J Theor Biol. 2006; 242:220–36. [PubMed: 16584750]

114. Day J, Rubin J, Vodovotz Y, Chow CC, Reynolds A, Clermont G. A reduced mathematical model of the acute inflammatory response: II. Capturing scenarios of repeated endotoxin administration. J Theor Biol. 2006; 242:237–56. [PubMed: 16616206]

115. Torres A, Bentley T, Bartels J, Sarkar J, Barclay D, Namas R, Constantine G, Zamora R, Puyana JC, Vodovotz Y. Mathematical modeling of post-hemorrhage inflammation in mice: Studies using a novel, computer-controlled, closed-loop hemorrhage apparatus. Shock. 2009; 32:172–8. [PubMed: 19008782]

116. Foteinou PT, Calvano SE, Lowry SF, Androulakis IP. Modeling endotoxin-induced systemic inflammation using an indirect response approach. Math Biosci. 2009; 217:27–42. [PubMed: 18840451]

117. Foteinou PT, Calvano SE, Lowry SF, Androulakis IP. In silico simulation of corticosteroids effect on an NFkB-dependent physicochemical model of systemic inflammation. PLoS ONE. 2009; 4(3):e4706. [PubMed: 19274080]

118. Kumar R, Chow CC, Bartels J, Clermont G, Vodovotz Y. A mathematical simulation of the inflammatory response to anthrax infection. Shock. 2008; 29:104–11. [PubMed: 18157069]

119. Arciero J, Rubin J, Upperman J, Vodovotz Y, Ermentrout GB. Using a mathematical model to analyze the role of probiotics and inflammation in necrotizing enterocolitis. PLoS ONE. 2010; 5:e10066. [PubMed: 20419099]

120. Chau TA, McCully ML, Brintnell W, An G, Kasper KJ, Vines ED, Kubes P, Haeryfar SM, McCormick JK, Cairns E, Heinrichs DE, Madrenas J. Toll-like receptor 2 ligands on the staphylococcal cell wall downregulate superantigen-induced T cell activation and prevent toxic shock syndrome. Nat Med. 2009; 15(6):641–8. [PubMed: 19465927]

121. Prince JM, Levy RM, Bartels J, Baratt A, Kane JM III, Lagoa C, Rubin J, Day J, Wei J, Fink MP, Goyert SM, Clermont G, Billiar TR, Vodovotz Y. *In silico* and *in vivo* approach to elucidate the inflammatory complexity of CD14-deficient mice. Mol Med. 2006; 12:88–96. [PubMed: 16953560]

122. Lagoa CE, Bartels J, Baratt A, Tseng G, Clermont G, Fink MP, Billiar TR, Vodovotz Y. The role of initial trauma in the host's response to injury and hemorrhage: Insights from a comparison of mathematical simulations and hepatic transcriptomic analysis. Shock. 2006; 26:592–600. [PubMed: 17117135]

123. Daun S, Rubin J, Vodovotz Y, Roy A, Parker R, Clermont G. An ensemble of models of the acute inflammatory response to bacterial lipopolysaccharide in rats: results from parameter space reduction. J Theor Biol. 2008; 253:843–53. [PubMed: 18550083]

124. Foteinou PT, Calvano SE, Lowry SF, Androulakis IP. Multiscale model for the assessment of autonomic dysfunction in human endotoxemia. Physiol Genomics. 2010; 42(1):5–19. [PubMed: 20233835]

125. Clermont G, Bartels J, Kumar R, Constantine G, Vodovotz Y, Chow C. In silico design of clinical trials: a method coming of age. Crit Care Med. 2004; 32(10):2061–70. [PubMed: 15483415]

126. Tateishi Y, Oda S, Nakamura M, Watanabe K, Kuwaki T, Moriguchi T, Hirasawa H. Depressed heart rate variability is associated with high IL-6 blood level and decline in the blood pressure in septic patients. Shock. 2007; 28(5):549–53. [PubMed: 18075483]

127. Fokas, AS.; Halliwell, J.; Kibble, T.; Zegarlinski, B., editors. Highlights of Mathematical Physics. Providence, RI: American Mathematical Society; 2002.

128. Kot, M. Elements of Mathematical Ecology. Cambridge, UK: Cambridge University Press; 2001.

129. Baskes MI. The status role of modeling and simulation in materials science and engineering. Curr Opin Solid State Mater Sci. 1999; 4(3):273–7.

130. van der Lee J, De Windt L. Present state and future directions of modeling of geochemistry in hydrogeological systems. J Contam Hydrol. 2001; 47(2–4):265–82. [PubMed: 11288582]

131. Buchman TG. In vivo, in vitro, in silico. Crit Care Med. 2004; 32(10):2159–60. [PubMed: 15483435]

132. Marshall JC. Through a glass darkly: the brave new world of in silico modeling. Crit Care Med. 2004; 32(10):2157–9. [PubMed: 15483434]

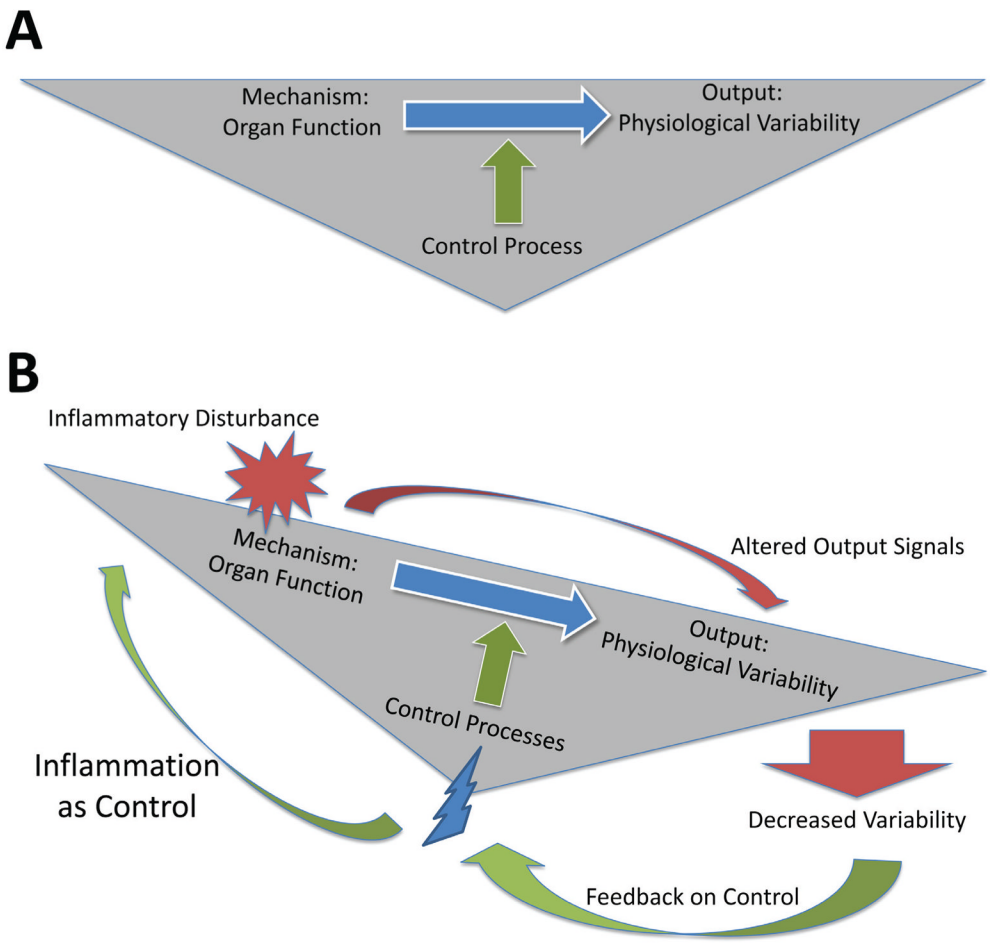


**FIGURE 1.**

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.