In Silico Modeling: Methods and Applications toTrauma and Sepsis

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Abstract

Objective—To familiarize clinicians with advances in computational disease modeling applied to trauma and sepsis.

Data Sources—PubMed search and review of relevant medical literature.

Summary—Definitions, key methods, and applications of computational modeling to trauma and sepsis are reviewed.

Conclusions—Computational modeling of inflammation and organ dysfunction at the cellular, organ, whole-organism, and population levels has suggested a positive feedback cycle of inflammation → damage → inflammation that manifests via organ-specific inflammatory switching networks. This structure may manifest as multi-compartment "tipping points" that drive multiple organ dysfunction. This process may be amenable to rational inflammation reprogramming.

Keywords

Inflammation; mathematical model; trauma; sepsis

INTRODUCTION

Critical illness comprises a constellation of pathophysiological derangements that ensues in the setting of trauma, hemorrhagic shock, and sepsis. Trauma, often accompanied by hemorrhage, is among the leading causes of morbidity and mortality worldwide, often leading to inflammation-related late complications that include sepsis and multiple organ dysfunction syndrome (MODS) (1–3). Sepsis alone is responsible for more than 215,000 deaths in the United States per year and an annual healthcare cost of over $16 billion (4),

while trauma/hemorrhage is the most common cause of death for young people in the U.S., costing over $400 billion annually (5–7).

It is now beyond doubt that the acute immuno-inflammatory response, with its manifold manifestations at the molecular, cellular, tissue, organ, and whole-organism levels, drives outcomes in critical illness. Though properly regulated inflammation allows for timely recognition and effective reaction to injury or infection, both trauma and sepsis are manifestations of disordered and mis-compartmentalized inflammation that in turn impairs physiological functions. This paradox of a robust, evolutionarily conserved network of inflammation whose very structure may lead to disease(8–10) has resulted in a lack of therapeutic options other than supportive care (11, 12). Indeed, the current lack of therapeutic options may result from the failure to fully understand this structure, and thus certain modes of supportive care (e.g. ventilation) may propagate inflammation and organ damage as compared to others (13).

Over a decade ago, there was recognition of the complex interplay between inflammation and physiology in critical illness and of the need to apply complex systems approaches such as computational modeling to unravel this complexity (14, 15). In the context of this review, we use the term "*in silico* modeling" to refer to the constellation of computational approaches utilized in an attempt to define and, in a sense, defeat the complexity of critical illness (Figure 1; Table 1). The advent of "omics" methodologies, with the theoretical capability of interrogating the complete responses of cells and tissues, spurred the application of these methodologies to critical illness (16–23); the resultant formation of the Inflammation and the Host Response to Injury "glue" consortium (http://www.gluegrant.org/) led to seminal contributions to the understanding of the myriad pathways induced by injury and infection in humans(24, 25). More recently, Translational Systems Biology has been suggested asa rational, systems engineering-oriented, computationally-based frameworkfor integrating data derived from basic biology experiments as well as pre-clinical studies and clinical studies(26–29). This recognition of the need to apply such complex systems approaches critical illness led to the formation of the Society for Complexity in Acute illness (SCAI; www.scai-med.org) in 2003, has been a featured topic of discussion in meetings of various other scientific societies, and has been recognized by funding agencies as an important means by which to grapple with the multidimensional problem of critical illness. The tremendous progress and remaining challenges of computational modeling in critical illnessare reviewed in this article.

CONCEPTS, APPROACHES, AND FRAMEWORKS FOR COMPUTATIONAL MODELING IN CRITICAL ILLNESS

There is a fairly long history of quantitative modelingapproaches to critical illness, as summarized in Figure 1 and detailed below. Initial studies were based on statistical, data-driven methods that have been employed to better define the patient state and predict clinical outcomes (e.g. the APACHEscore and numerous other scoring systems utilized in sepsis and trauma (30)); these approaches are summarized in Table 1, which is an expansion of the excellent summary given in (31). These methods are based on associations among variables, and include time-tested logistic regression techniques as well as more recent tools that enable graphical views of network interconnectivity (31). Such methods were used predominantly in an attempt to develop better prognostic and diagnostic scoring systems for critically ill patients, and incorporated both clinical data and levels of circulating inflammation biomarkers in recognition of the interrelated nature of inflammation and (patho)physiology (32–34). More recently, the advent of multiple high-content ("omic") technologies has resulted in a deluge of data in all fields of biology(35), including critical illness(24, 25, 36–42). In addition, there has been an explosion in the use of multiple

computational techniques that could be classified as "complex systems" approaches, including signal processing techniques, multivariate dynamic clustering, and machine-learningand network discovery algorithms based on physiologic measurements as well as inflammation biomarkers (22, 43–47). Importantly, these systems biology and computational biology studies verified the importance of known biological pathways in critical illness and injury, as well as suggesting potentially novel pathways for further study (22, 36, 48–50).

The increasing use of these techniques has led to a growing recognition that more data leads to more possible explanations for those data; that there are multiple technical, practical, and economic challenges to implementing these purely data-driven systems biology approaches as diagnostic strategies; and thatinvestigators' intuition is not up to the task of unraveling causal mechanisms from highly-dimensional, data-based associations (3, 13, 51). In contrast to data-driven modeling, mechanistic computational simulations depict biological interactions (e.g. among cells, their products, and the outcomes that result under a given set of conditions). Such computational models simulations may be used as "knowledge stores" that may be queried as to the emergent behavior of the sum total of known or hypothesized reductionist biological interactions (52–56); to suggest novel interactions not yet described by experimental data(57); and to address controversies based on diverseexperimental/clinical conditions or other experimental differences among groups studying any given complex biological system(58). Unlike data-driven models, dynamic mechanistic models offer the possibility of prediction outside of the time range or other specific conditions of the data on which they were trained(3, 13, 29, 51). The primary methods of dynamic mechanistic modeling used to datein acute inflammation and other phenomena related to critical illnessare agent-based modeling(57, 59–62) and equation-based modeling(63–71), though rules-based modeling has also been used for some studies of inflammatory and immune intracellular signaling (26, 72–76). These modeling frameworks have their respective strengths and weaknesses(26, 27, 77, 78), but have all proven valuable in the critical care arena(8, 9, 77, 79–82).

However, as useful as mechanistic computational modeling has been in integrating known interactions gleaned from the literature, this approach is inherently biased given the tremendous volume of information that could, in theory, be incorporated into models and that is deemed irrelevant or unnecessary for the degree of abstraction chosen by the modeler. Bias is also introduced based on the level of interest devoted to a particular pathway by the scientific community and thus ignores potentially important pathways that are less studied or yet to be discovered. In response to this concern,there has been an attempt to couple the less-biased data-driven approach with mechanistic mathematical modeling, in studies focused on the acute inflammatory response(3, 9, 13, 28, 29, 51, 83, 84). In these studies, mechanistic computational simulations were created based on biology abstracted from "omics" data (85–90) or inferred from data-driven analysis of principal drivers (91). This type of combined data-driven and mechanistic modeling allows for a further, intermediate validation step with regards to hypotheses inferred from the original data. Furthermore, these studiesreflect the maturity of computational modeling in acute illness. Importantly, this combined data-driven and mechanistic approach is likely to be the area of study with the most growth in coming years due to the inherent appeal of unifying – and gaining testable mechanistic insights from – the growing repository of "omics" data.

This progression from multivariate regression models through various quasi-mechanistic associate methods to dynamic mechanistic modeling (and the integration across methods) is depicted in Figure 1. Below, we discuss the insights gleaned from computational modeling in acute illness, and suggest challenges and opportunities for future work.

KEY INSIGHTS FOR CRITICAL ILLNESS FROM COMPUTATIONAL MODELING

Early studies utilizing complex systems approaches in critical illness suggested the concept of "coupled oscillators" that become uncoupled as inflammation becomes dysregulated and organ dysfunction progresses (14). More recent *in silico* modeling work has posed specific hypotheses with regard to the mechanisms by which inflammation is coupled nonlinearly to physiological (dys)function, namely due to multiple feedback loopsthat manifest at the cellular, tissue/organ, and whole-organism levels(3, 13, 27, 51, 60–65, 67–70, 84–86, 91–93). Positive feedback loops allow rapid ramping up of a response to biological stress, while the negative feedback works to suppress inflammation and restore homeostasis once the threat (infection, damaged tissue, etc.) has been eliminated.

One of the earliest insights to come from computational modeling was the crucial role of "late" mediators in sepsis (now known as Damage-associated Molecular Pattern [DAMP] molecules), intracellular components whose release into the extracellular environment signals stress, damage, or dysfunction (63), in the establishing and perpetuating the positive feedback loop of inflammation $\rightarrow$ damage $\rightarrow$ inflammation (9, 10, 13, 27, 51, 84, 94, 95). *In silico* modeling studies support the notion that this dysfunction occurs via a positive feedback loop in which inflammation induced by pathogen-derived molecular pattern (PAMP) molecules leads to the secondary release of DAMP molecules. In turn, DAMP's stimulate nearby inflammatory cells to produce more of the classical inflammatory mediators, leading to further release of DAMP's and therefore to self-maintaining inflammation even after the pathogen has been cleared. The recognition that PAMP's and DAMP's signal via common pathways (e.g. the Toll-like receptors) (96, 97)has helped validate this concept at the molecular level.

The concept of inflammatory preconditioningis another key area in which *in silico* modeling has yielded key insights. Inflammatory preconditioning refers to the spectrum of possible responses to stimulation with two or more pro-inflammatory stimuli in succession, namely responses that are equal to, greater than, or lesser than each stimulus in isolation. For example, repeated treatment with bacterial lipopolysaccharide can lead to desensitization or enhancement of subsequent pro-inflammatory responses that manifest at the cellular, tissue/organ, and whole-organism levels(98, 99). *In silico* modeling studies using various platforms have suggested that the aforementioned positive and negative feedback loops of the inflammatory response can explain the various phenotypes characteristic of inflammatory preconditioningboth *in vitro* and *in vivo*(62, 68, 74, 85, 100–102).

PERSPECTIVES AND CHALLENGES

In silico modeling has yielded both basic insights and translational applicationsin critical illness (3, 9, 13, 27, 29, 51, 82, 84, 92). Indeed, key translational applications such as *in silico* clinical trials were pioneered in the arena of critical illness (61, 64). One of these studies suggested mechanistic reasons for the failure of neutralizing anti-TNF-α antibodies in sepsis, due to cohort-specific beneficial and detrimental effects that ultimately resulted in the lack of net benefit for this drug (64). Recent studies showing the potential to predict the individual inflammatory and pathophysiologic outcomes of human subjects (103) and large, outbred animals(91) subjected to acute inflammatory stress suggest the possibility of predicting the outcomes of – and possibly tailoring therapy for – individual patients(29, 82). Recently, we constructed a hybrid equation- and agent-based model that simulates blood flow along with skin injury, inflammation, and ulcer formation(104), since pressure ulcers are a complication that con occur in critically ill patients (105). The relationship between pressure and the course of ulcer formation, as well as several other important characteristic

patterns of pressure ulcer formation, was demonstrated in this model. The equation-based portion of this model was calibrated to data related to blood flow following experimental pressure responses in non-injured human subjects or to data from people with spinal cord injury (SCI). This hybrid model predicted a higher propensity to form ulcers in response to pressure in people with SCI vs. non-injured control subjects (both as cohorts and individual patients), and thus may serve as novel diagnostic platform for post-SCI ulcer formation(104). Other emerging applications of computational modeling to understand multi-factorial therapies for critical illness that reprogram the inflammatory response, such as hemoadsorption (106, 107) also point to an exciting and valuable application of *in silico* methods.

Despite this progress, many challenges remain for this rapidly-evolving field. At the most practical level, *in silico* modelers must prove the translational benefit of this technology through prospective clinical studies and ultimately through the development of computationally-based diagnostics or therapeutics for critical illness. At the grandest scale, the key challenge revolves around the inherently multi-scale, multi-system nature of critical illness. As has likely occurred in many other complex biological systems (108), inflammation may have evolved to be robust in response to a broad range of perturbations at multiple biological scales of organization, but at a cost of fragility in key control nodes. We speculate that the aforementioned positive and negative feedback loops manifest dynamically as cellular, tissue/organ, and whole-organism "tipping points" that drive MODS (13, 51). *In silico* modeling could therefore rise to the challenge of integrating inflammatory, neuro-endocrine, and physiologic processes in order to unravel the multi-dimensional, multi-compartment, and highly dynamic landscape of critical illness.

Acknowledgments

ABBREVIATIONS

DAMP	damage-associated molecular pattern molecule
IL	interleukin
IP-10	interferon-gamma inducible protein of 10 kDa
MIG	monokine inducible by gamma interferon
PAMP	pathogen-associated molecular pattern molecule
SCI	spinal cord injury
TNF-α	tumor necrosis factor-α

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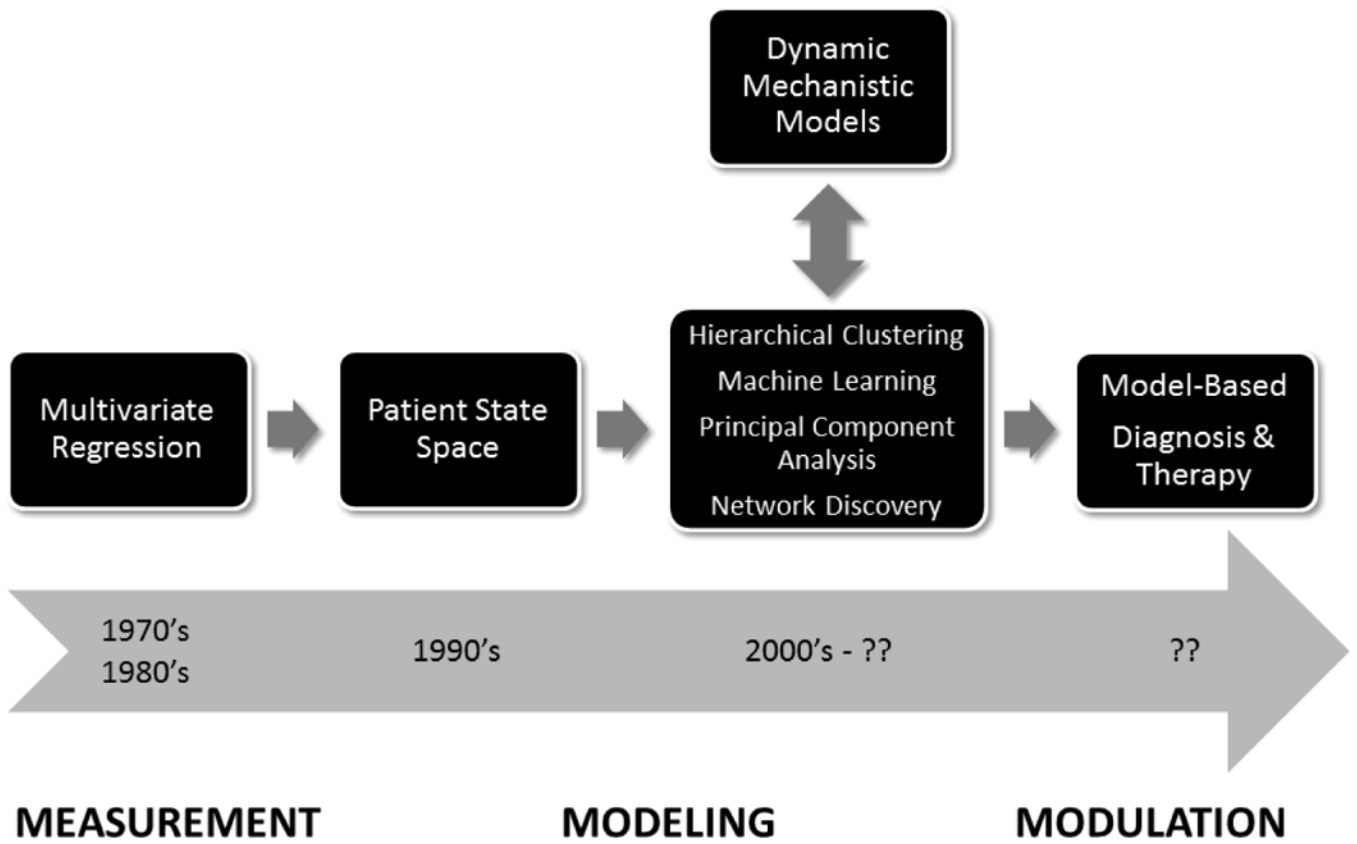
Figure 1. The progression from measurement to modeling to modulation in sepsis and trauma
Quantitative (*in silico*) methods have progressed from purely association-based statistical methods to dynamic mechanistic modeling capable of predicting the responses of patient cohorts and individuals as well as suggesting novel therapies. Data-driven and mechanistic modeling methods are now being integrated. Future possibilities include the design of novel diagnostics and therapies based on *in silico* modeling.

Table 1

Comparison of modeling methods and applications to sepsis and trauma

Key primary and review papers are provided to guide the reader.

Modeling method	Description	Examples of Applications to sepsis/trauma	Key References
Data-driven Modeling	A compendium of methods that are primarily based on associations among data variables. These methods can be applied to either static or dynamic data	Prediction of likelihood to worsen or improve clinical state	Reviews: (31, 109, 110)
Multivariate regression	Methods for exploring the relationships of each of multiple variables to a given outcome	Associating inflammatory mediator levels with clinical outcomes	Primary papers: (50, 111, 112)
Hierarchical clustering	A technique for grouping multivariate data based on similarity in vectors of values.	Highlighting the natural variability, as well as any overlap, in gene transcripts, inflammatory mediators, or physiologic/biochemical clinical data	Primary papers:(22, 24, 50)
Principal Component Analysis	A non-parametric statistical method of reducing a multidimensional dataset to a few principal components. These are the components that account for the most variability in the dataset. The underlying hypothesis is that a variable that changes during a specific process is important to that process.	Suggesting principal inflammatory drivers or biomarkers of sepsis or trauma, either to guide further study directly or to suggest which variables should be included in a mechanistic model.	Primary papers: (50, 91, 113)
Network Discovery Methods	Methods that can suggest relationships among variables as well as key features of connectivity in a multivariate dataset.	Suggesting biomarkers and possible interactions among mediators in sepsis or trauma.	Primary papers: (22, 24, 50)
Mechanistic Modeling	A compendium of methods that are primarily based on mechanistic abstractions that simulate key intracellular, cell/cell, tissue/organ, organ system, or whole-organism level, or that can tie across levels of organization (multiscale modeling)	Gaining mechanistic knowledge about sepsis/trauma; simulating clinical trials; prediction of likelihood to worsen or improve clinical state	Reviews: (9, 26, 27, 92, 114, 115)
Equation-based models	A compendium of methods based on ordinary or partial differential equations that typically describe the change over time of variables. These models are typically deterministic but can be stochastic, and are are based on the average behavior of components in a well-mixed system.	Qualitatively and quantitatively predictive models of inflammation (at the cellular, tissue/organ, and whole-organism levels) in sepsis and trauma, including in silico clinical trials and individual-specific models.	Primary papers:(63–65, 91, 100, 116)
Agent-based models	Cellular automa models in which individual agents interact with each other and with their environment in a given space by following rules that are applied in a probabilistic manner. These models are therefore generally stochastic.	Qualitatively and quantitatively predictive models of inflammation (at the cellular, tissue/organ, and whole-organism levels) in sepsis and trauma, including in silico clinical trials and individual-specific models.	Primary papers:(60–62)
Rule-basedmodels	Similar to agent-based models, rules-based models are typically used to model detailed biochemical intreactions among molecules. These models are typically stochastic.	Models of inflammatory signal transduction pathways.	Primary papers:(74, 75, 117)