



Review

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Computational modelling of the inflammatory response in trauma, sepsis and wound healing: implications for modelling resilience

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Resilience refers to the ability to recover from illness or adversity. At the cell, tissue, organ and whole-organism levels, the response to perturbations such as infections and injury involves the acute inflammatory response, which in turn is connected to and controlled by changes in physiology across all organ systems. When coordinated properly, inflammation can lead to the clearance of infection and healing of damaged tissues. However, when either overly or insufficiently robust, inflammation can drive further cell stress, tissue damage, organ dysfunction and death through a feed-forward process of inflammation → damage → inflammation. To address this complexity, we have obtained extensive datasets regarding the dynamics of inflammation in cells, animals and patients, and created data-driven and mechanistic computational simulations of inflammation and its recursive effects on tissue, organ and whole-organism (patho)physiology. Through this approach, we have discerned key regulatory mechanisms, recapitulated *in silico* key features of clinical trials for acute inflammation and captured diverse, patient-specific outcomes. These insights may allow for the determination of individual-specific tolerances to illness and adversity, thereby defining the role of inflammation in resilience.

1. Inflammation as a complex system in trauma, sepsis and wound healing

Trauma, sepsis and wounds are acute insults to an organism. These events can be characterized by parameters reflecting magnitude of insult, spatial localization, and perhaps most importantly, multi-dimensional dynamics driven by initial conditions of injury and infection as well as by parameters reflecting individual-specific characteristics such as age, gender and comorbidities. It is now appreciated that it is predominantly inflammation, not the infectious agent or injury, which drives a feed-forward process that can lead to tissue/organ dysfunction and, under certain circumstances, death. However, properly regulated inflammation (i.e. an inflammatory response in which the feed-forward loop of inflammation → damage → inflammation is presumably kept in check through adequate anti-inflammatory responses) is at the same time completely necessary for the healthy resolution of these acute insults. An adequately robust inflammatory response is also a process that underlies muscle growth post-exercise and, perhaps speculatively, resilient responses to other forms of traumatic stress [1–6].

2. Resilience and inflammation

Resilience in settings such as post-traumatic stress disorder (PTSD) has been linked to inflammation. One key feature of resilience is the ability to withstand repeated stress. That is to say, the response to the n th instance of infection, injury or traumatic event should be as close as possible to the response to the first event. Inflammation—and multiple other biological processes such as

neurotransmission—exhibits the phenomenon of preconditioning. Preconditioning refers to the effect that an initial stress exerts on the response to subsequent stress. In the setting of infection or injury, preconditioning refers to an inflammatory response to a secondary challenge that can be the same as, greater than or lesser than the response to the initial challenge [7–10]. This behaviour highlights the nonlinear nature of inflammation, and in a sense is the core confounding feature of inflammation in the clinical setting: it is highly unlikely that any individual presents with an inflammatory response that was never preceded by a prior inflammatory response to a similar or different stress. Nonlinear systems such as the inflammatory response exhibit what might be considered ‘system memory’, in which the state of the system at a given time depends upon the prior dynamics of the system in a non-intuitive fashion that is, nonetheless, amenable to mathematical modelling and, hence, prediction [11].

3. Computational modelling of complex systems

3.1. Features of, and approaches to, complex systems

The complexity and nonlinearity of the acute inflammatory response as described above have largely stymied the development of novel therapies for acute inflammatory conditions such as trauma/haemorrhage and sepsis, and systems biology has been suggested as a means by which to decipher this complexity in order to create new therapies for such complex diseases [4,12].

Complex systems, be they biological, physical or man-made, typically exhibit certain key features. These features include nonlinearity, system properties that cannot be inferred readily from an analysis of component parts (sometimes referred to as emergent behaviour), and, consequently, a strong dependence of the system’s outcomes on the system’s initial conditions [13–15]. The inflammatory response exhibits all of these properties [1,10,16]. Systems biology is an emerging paradigm for tackling such complex biological systems in a holistic fashion [13–15,17]. Computational modelling is the central tool used to study such complex systems. Modelling approaches in systems biology span a broad range of techniques, and can be categorized roughly into correlative or causative methods, with focus on either learning basic principles of system organization and function [13,18,19] or building predictive computational models [18,20]. In the following, some of these modelling approaches and their respective strengths and weaknesses are discussed.

3.2. Data-driven models

Statistical-based (also known as data-driven) modelling approaches, with which most biologists and clinicians are generally familiar, include regression techniques that build models predictive within the conditions of the data on which the models were trained [21]. Although these methods cannot provide detailed mechanistic insights, they can be used to understand abstract features of the response, such as the presence of nonlinearities or the identification of factor interactions that affect the response. The main drawback of this class of models is the fact that they often are devoid of mechanistic insights, and their linearity in the parameters can over-fit to the data on which they were trained. Associative methods such as hierarchical clustering may be used to

highlight the natural variability, as well as any overlap, across experimental or clinical conditions.

Other, less well-known, data-driven modelling tools have been used in the systems biology realm, including hierarchical clustering and principal component analysis (PCA) [19]. PCA reduces a high-dimensional dataset into a few principal components that account for much of the observed variance in the data. When applied to time-series data, PCA may identify the subsets of the variables under study (genes/proteins, etc.) that are most strongly representative of the response [19]. In the setting of inflammation, PCA has been used to gain insights into the mechanisms by which proposed therapeutic modalities may function [22]. Similarly, PCA may aid the development of diagnostics by analysing the cytokine milieu in the blood resulting from inflammatory spillover [23]. Recently, in the setting of human blunt trauma, we used PCA to suggest patient-specific, early drivers of system inflammation in the form of ‘inflammation barcodes’, followed by hierarchical clustering of PCA-transformed data to define patient subgroups. PCA/hierarchical clustering segregated the patients into groups that differed significantly in their composite measure of organ dysfunction within the first 24 h post-injury and independently of the specific set of inflammatory mediators analysed. Importantly, these patients were otherwise highly similar, and could not be segregated into subgroups based on the raw inflammation biomarker data [24].

Like most biological processes, inflammation proceeds as a series of interacting cascades of signalling events that are often reflected in the production and secretion of inflammatory mediators that likely form well-coordinated networks [25–33]. In order to better discern organizational aspects of interacting networks of inflammatory mediators, such as coregulation or autoinduction, a variety of methods have been developed. Hierarchical clustering and Bayesian methods use high-throughput genomic or proteomic data of several time-points and/or conditions to correlate gene expression patterns with function and infer regulatory networks of correlated genes [34–37]. Focusing on the dynamics of inflammation, we used a simple network analysis method used over discrete intervals of data to analyse the commonality and differences between experimental surgical cannulation trauma + haemorrhage in mice versus the sham procedure (surgical cannulation only) [25].

Among network methods, dynamic Bayesian networks (DBNs) are particularly suited for inferring directed (causative) networks of interactions based on the probabilistic measure of how well the network can explain observed data. DBNs provide a good platform for incorporating biological knowledge alongside data in order to increase our knowledge of connectivity in biological processes, and may be supplemented by additional experimental evidence and expert knowledge to hypothesize mechanistic models. We are currently incorporating DBN inference analysis into our studies of the dynamics of inflammation in cells, experimental animals and humans [38]. We recently demonstrated the potential clinical utility of DBN in the setting of paediatric acute liver failure (PALF). In that study, DBN of serum inflammatory mediators segregated spontaneous survivors from non-survivors when the raw mediator trajectories could not. Interestingly, this retrospective analysis showed that PALF patients selected for liver transplant had similar DBN to spontaneous survivors [39].

An intriguing possibility, therefore, is that circulating inflammation biomarkers or other molecules in the blood of patients with PTSD or related disorders may be amenable

to analysis using methods such as PCA and DBN. In essence, this is a form of 'precision medicine'. Precision medicine is an emerging concept for diagnosis and treatment based on quantitative segregation of patients rather than a reliance on historical diagnostic and staging criteria [40]. In this vein, as discussed above, we suggest that data-driven patient segregation could differentiate subgroups of PTSD patients based on markers of resilience in cohorts that could not be segregated based on clinical or standard laboratory parameters.

3.3. Mechanistic models

Mechanistic computational models are based on causative interactions, and can be constructed using ordinary differential equations (ODEs), rules-based models or agent-based models (ABMs; along with other methods that include hybrid methods). Mechanistic models have the advantage of potentially being predictive outside the range of conditions/time-points on which they were calibrated, and thus can unveil system properties not immediately obvious from the interactions that are encoded in the model (so-called emergent phenomena).

Much of the mechanistic modelling work in systems biology has understandably been in simpler, well-studied model organisms, but even among studies focused on pre-clinical science, there has been an overall lack of translation to the clinical arena. *Translational systems biology* is a framework with a focus on translational insights for novel diagnostic or therapeutic purposes and predictive mathematical models that inform *in silico* clinical trials [1,41,42]. Initially formulated to deal with the clinical challenge of integrating acute inflammation and organ dysfunction in critical illness, this work expanded to include healing of acute and chronic wounds and infections in various diseases, and rational dynamic modulation of inflammation. Under the umbrella of translational systems biology of inflammation, we and others have created mechanistic computational models of acute inflammation in sepsis [43–47], endotoxemia [48–62] and trauma/haemorrhage [48,50,63,64]. In large part, these models (both ODE and ABM) are based on the typical progression of the inflammatory pathway described in the preceding section. Some of these models are purely theoretical [43–47,49], whereas others are based on data either at the protein [48,50,63,64] or mRNA [52,53,58–60] level. Similar mechanistic models have focused on related diseases such as necrotizing enterocolitis [65–68]. From a translational perspective, mechanistic modelling of inflammation has led to the generation of model-based *in silico* clinical trials [43,45,47,69], modelling the tissue inflammatory responses of individual patients [70,71], as well as the inflammatory and organ dysfunction profiles of large, outbred animals [57].

As a showcase for the capabilities of this type of modelling, we constructed a multi-compartment ODE model of the whole-organism response to blunt trauma, consisting of 'tissue' (in which physical injury could take place), 'lungs' (which can experience dysfunction) and 'blood' (representing the circulation as well as a surrogate for the rest of the body), along with inflammatory cells and mechanisms that drive whole-organism 'damage'. Individual-specific variants of this model were generated from clinical data on 33 blunt trauma survivors. A cohort of 10 000 virtual trauma patients was generated from the 33 patients' individual inflammatory and physiological trajectories. Each virtual patient was then subjected to three insults of trauma: low/intermediate

Injury Severity Score (ISS) (5–20), intermediate/high ISS (20–35) and severe ISS (35–50). The *in silico* distributions of model variables equated with length of stay in the intensive care unit, degree of multiple organ dysfunction and interleukin (IL)-6 area under the curve were in concordance with those observed in a separate validation cohort of 147 blunt trauma patients. In the virtual patients, IL-6 was the main driver of outcome in patients with moderate or severe ISS, and *in silico* elevation of IL-6 was predicted to convert survivors to non-survivors. Non-intuitively, however, simulated outcomes in the *in silico* cohort as a whole were independent of propensity to produce IL-6, a finding verified in a subcohort of blunt trauma patients whose clinical outcomes and plasma IL-6 levels were independent of high versus low IL-6 single nucleotide polymorphisms [72].

This study raises the possibility of, at some point, modelling key aspects of resilience and generating *in silico* clinical trials aimed at testing interventions. Despite the potential for mechanistic computational modelling as a tool for integrating and predicting the behaviour of complex systems, this methodology does have several drawbacks relative to data-driven modelling. First, it must be emphasized that mechanistic models are nearly always abstractions of what is known about a complex system, because one goal of mechanistic modelling is to discern emergent phenomena or system properties not encoded explicitly in the model. In the setting of resilience, much new knowledge must be gained for such an approach to become feasible, though it should be noted that initial models could be much less than complete and yet lead to valuable suggestions regarding therapy. Another, related disadvantage of mechanistic models versus data-driven models is that the modeller—or, perhaps more accurately, the interdisciplinary team that is trying to create such a mechanistic model [73]—must determine which of the myriad mechanisms to include, the level/scale (e.g. molecular/tissue–organ/whole organism/population) for the model, and the modelling framework (e.g. ODE versus ABM). As knowledge and data evolve, mechanistic models can grow in concert and thus yield ever more quantitative predictions. This is a worthwhile endeavour because, ultimately, the concept of ever-deeper and wider data gathering to feed purely data-driven models is simply not feasible. In contrast, mechanistic models have the potential to streamline and focus the data gathering effort. Indeed, data-driven models are often much better than mechanistic models at predicting phenomena that occur within the range of conditions (e.g. time frame) of the dataset on which they were trained, whereas mechanistic models generally are better than data-driven models at predicting phenomena that occur outside the range of the training dataset. Thus, the most productive approach may be one that integrates data-driven and mechanistic models, as discussed below.

3.4. Integrating data-driven and mechanistic models

Although there is overlap between data-driven and mechanistic modelling, most efforts at elucidating biological mechanisms from high-dimensional data have traditionally focused on particular points along this spectrum of computational approaches. We suggest that gleaning translationally relevant insights into the inflammatory response and its interconnected (patho)physiology will require integration of methods from across this spectrum [25,46–50,63,64,74], in order to progress from data

to models to actionable knowledge and prediction (ideally in an *in vivo* or clinical context) [6,75].

4. Towards modelling of inflammation in defining resilience

If we define resilience at the purely physical level, we are concerned with the ability to withstand either a single major challenge (e.g. a major battlefield trauma that results in extensive physical injuries) or repeated instances of more minor injuries (e.g. multiple instances of concussion) and retain a high degree of biological/physiological function. A more nuanced view of resilience would incorporate additional dimensions such as psychosocial responses to such stresses, and in this context resilience might be viewed as avoiding PTSD following major or repeated stress. We view the individual response to stress as lying on a continuum that spans these two extremes, and we acknowledge the role of inflammation in mediating—and likely connecting—these two extremes. Thus, we might hypothesize that measuring, modelling and modulating inflammation could improve an individual's resilience. This proposed approach would synergize with calls in the literature to synthesize processes from the cell to the society in dealing with resilience [76].

How might this be carried out? We would suggest the following approach. Data would be gathered that would reflect both individual variability in, and the dynamics of, responses to stress associated with either favourable or negative resilience outcome measures. This process would initially involve gathering multivariate data that reflect multiple facets of inflammation and, importantly, relevant physiological responses. Data-driven modelling would be used initially to define the control structures of the inflammatory response, leading to the

generation of reduced mechanistic models, which in turn would be initially validated in cohorts reflecting multiple outcome groups. This process would be initiated with a reduced set of parameters, and expanded iteratively to include additional inflammatory and physiological parameters. This process could be expanded to include such variables as the microbiota [77] as well as factors from the external environment that are known to modulate the inflammatory response.

5. Conclusions and perspectives

Acute inflammation is in essence a form of multi-scale cell–cell, tissue–tissue and organ–organ communication. When confined to the immediate environment of the initiating stimulus, and when induced only to a level commensurate with the initiating stimulus, inflammation is generally beneficial and self-resolving. However, overly robust inflammation can become self-sustaining and hence harmful. We suggest that an appropriate inflammatory response in the face of stress, injury or infection is a necessary part of resilience. Moreover, we hypothesize that a resilient response to stress is reflected in the ability to mount repeated, appropriate and self-resolving inflammatory responses in the face of repeated challenges. A corollary to this hypothesis, then, is that self-maintaining or inadequate inflammation reflects maladaptation and lack of resilience.

We have gained many insights into the inflammatory response through combined experimental/clinical and computational studies. We suggest that these lessons could be leveraged to gain insights into the mechanisms underlying resilience. We further suggest that this combined approach could be used to define specific biomarkers of resilience in individuals, and possibly also to define resilience as a surrogate endpoint in clinical trials using *in silico* approaches.

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