Journal of Theoretical Biology 358 (2014) 132–148

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Global sensitivity analysis of a mathematical model of acute inflammation identifies nonlinear dependence of cumulative tissue damage on host interleukin-6 responses

Shibin Mathew [a,*], John Bartels [c], Ipsita Banerjee [a,b,f], Yoram Vodovotz [c,d,e,**]

[a] Department of Chemical and Petroleum Engineering, University of Pittsburgh, Pittsburgh, PA 15261, USA
[b] Department of Bioengineering, University of Pittsburgh, Pittsburgh, PA 15219, USA
[c] Immunetrics, Inc., Pittsburgh, PA 15203, USA
[d] Department of Surgery, University of Pittsburgh, Pittsburgh, PA 15213, USA
[e] Center for Inflammation and Regenerative Modeling, McGowan Institute for Regenerative Medicine, University of Pittsburgh, Pittsburgh, PA 15219, USA
[f] McGowan Institute for Regenerative Medicine, University of Pittsburgh, Pittsburgh, PA 15219, USA

HIGHLIGHTS

- The parametric space of an acute inflammation model was analyzed using global sensitivity analysis (GSA).
- GSA suggested the importance of IL-6 and NO in affecting inflammatory damage.
- Increasing IL-6 leads to transition from low to high sustained damage.
- At high IL-6, NO produced by macrophages can still repress overall damage.

ARTICLE INFO

Article history:
Received 26 January 2014
Received in revised form
22 May 2014
Accepted 23 May 2014
Available online 5 June 2014

Keywords:
Inflammation dynamics
Meta-modeling
Endotoxin
Cytokines
Nitric oxide

ABSTRACT

The precise inflammatory role of the cytokine interleukin (IL)-6 and its utility as a biomarker or therapeutic target have been the source of much debate, presumably due to the complex pro- and anti-inflammatory effects of this cytokine. We previously developed a nonlinear ordinary differential equation (ODE) model to explain the dynamics of endotoxin (lipopolysaccharide; LPS)-induced acute inflammation and associated whole-animal damage/dysfunction (a proxy for the health of the organism), along with the inflammatory mediators tumor necrosis factor (TNF)-α, IL-6, IL-10, and nitric oxide (NO). The model was partially calibrated using data from endotoxemic C57Bl/6 mice. Herein, we investigated the sensitivity of the area under the damage curve (AUC_D) to the 51 rate parameters of the ODE model for different levels of simulated LPS challenges using a global sensitivity approach called Random Sampling High Dimensional Model Representation (RS-HDMR). We explored sufficient parametric Monte Carlo samples to generate the variance-based Sobol' global sensitivity indices, and found that inflammatory damage was highly sensitive to the parameters affecting the activity of IL-6 during the different stages of acute inflammation. The AUC_{IL6} showed a bimodal distribution, with the lower peak representing healthy response and the higher peak representing sustained inflammation. Damage was minimal at low AUC_{IL6}, giving rise to a healthy response. In contrast, intermediate levels of AUC_{IL6} resulted in high damage, and this was due to the insufficiency of damage recovery driven by anti-inflammatory responses from IL-10 and the activation of positive feedback sustained by IL-6. At high AUC_{IL6}, damage recovery was interestingly restored in some population of simulated animals due to the NO-mediated anti-inflammatory responses. These observations suggest that the host's health status

Abbreviations: AUC_D, area under the damage curve; AUC_{IL6}, area under the interleukin-6 curve; DAMPS, damage associated molecular pattern molecules; eNOS, endothelial NO synthase; GSA, global sensitivity analysis; HS, hemorrhagic shock; iNOS, inducible NO synthase; IO, input–output; IL, interleukin; LPS, gram-negative bacterial lipopolysaccharide (endotoxin); MODS, multiple organ dysfunction syndrome; NO, nitric oxide; ODE, ordinary differential equation; RS-HDMR, random sampling high dimensional model representation; SA, sensitivity analysis; TNF-α, tumor necrosis factor alpha

* Corresponding author. Tel.: +1 412 251 2383; fax: +1 412 624 9639.
** Corresponding author at: Department of Surgery, University of Pittsburgh, W944 Starzl Biomedical Sciences Tower, 200 Lothrop St., Pittsburgh, PA 15213, USA. Tel.: +1 412 647 5609; fax: +1 412 383 5946.
E-mail addresses: shm82@pitt.edu (S. Mathew), vodovotzy@upmc.edu (Y. Vodovotz).

http://dx.doi.org/10.1016/j.jtbi.2014.05.036

during acute inflammation depends in a nonlinear fashion on the magnitude of the inflammatory stimulus, on the host's propensity to produce IL-6, and on NO-mediated downstream responses.

1. Introduction

1.1. Modeling acute inflammation

Acute inflammation is the initial response of the body to various biological stresses, including bacterial infection and tissue injury. Inflammation is a multi-scale process manifesting at the molecular, cellular, tissue, organ, and whole-organism levels. The action of immune cells and secreted molecules combat the offending insult and also trigger a repair process to allow the body to return to pre-insult homeostasis. Properly regulated inflammation allows for timely recognition and effective reaction to injury or infection, but diseases such as sepsis involve disordered inflammation that in turn impairs physiological functions (An et al., 2012; Vodovotz and Billiar, 2013).

The complex, non-linear nature of inflammation has made it difficult to directly translate results from animal studies to clinical trials (Neugebauer et al., 2001; Vodovotz and Billiar, 2013; Vodovotz et al., 2008). Several computational representations of the acute inflammatory response developed in the recent years have provided tools for gaining insights into and making testable predictions of this complex biological process (Parker and Clermont, 2010; Vodovotz and An, 2009; Vodovotz and Billiar, 2013; Vodovotz et al., 2004, 2008, 2009). Various frameworks have been used successfully to represent inflammation computationally; for example, equation-based models such as difference and differential equations (Scheff et al., 2013; Vodovotz and Billiar, 2013; Vodovotz et al., 2004, 2009), data-driven models (An et al., 2012; Croft et al., 2012; Vodovotz and Billiar, 2013; Vodovotz et al., 2009), and agent-based models (An et al., 2012; Vodovotz and An, 2009; Vodovotz and Billiar, 2013). Differential equation-based representations can adequately address the complex, non-linear, dynamic interactions characterizing a well-mixed system, especially when such models are based on data obtained in bio-fluids such as serum or plasma (An et al., 2012; Scheff et al., 2012).

1.2. Analysis of large-scale ODE models for inflammation

1.2.1. Current models of acute inflammation

In our earlier models of acute inflammation, we studied the role of a small number of key mediators using techniques such as bifurcation analysis (Kumar et al., 2004; Reynolds et al., 2006). With further advances in experimental models of inflammation, species-specific parameters were determined to explain differences in the dynamics of inflammation with changes in the sources of inflammation as well as the primary drivers of inflammation (Daun et al., 2008b; Nieman et al., 2012; Vodovotz et al., 2006). This led to large-scale ODE models containing a large number of distinct mediators as well as local and systemic compartments (Chow et al., 2005; Nieman et al., 2012; Torres et al., 2009). These models have been successful in explaining the dynamics of various mediators as well as the identification of processes responsible for various clinical outcomes of inflammation (Nieman et al., 2012; Vodovotz and Billiar, 2013; Vodovotz et al., 2008).

1.2.2. Analyzing ODE behavior using sensitivity analysis

Inflammation can either resolve or become self-sustaining, depending on a complex interaction between the original insult and host factors (Medzhitov, 2008; Nathan, 2002). Analysis and extraction of key mechanisms that drive inflammation into different clinically relevant regimes, however, has been difficult for high-dimensional ODE models. The challenges arise from two sources, namely the uncertainty of the model parameters and the computational burden of exploring the influence of a large number of parameters and their correlations. To overcome these challenges, large-scale ODE models have to employ supplementary tools like sensitivity and uncertainty analysis, model identifiability analysis and parameter set reduction in the modeling loop (Chu and Hahn, 2012; Jayaraman and Hahn, 2009; Kiparissides et al., 2011; Vodovotz et al., 2009).

Sensitivity analysis (SA) is an increasingly important step in this process and is often the first step in learning the nature of different parameters in the model (Marino et al., 2008; Sahle et al., 2008; Saltelli et al., 2008). SA can also guide other processes like parameter estimation in the modeling loop by providing importance measures to the model parameters (Kiparissides et al., 2009). In general, SA can be carried out by two approaches: local and global. Local methods study the influence of single parameter in isolation and the other parameters are kept constant at their nominal values. Global methods study the influence of a parameter by varying it in a defined direction and also simultaneously varying the other parameters in a random fashion in the entire parameter space (Saltelli et al., 2008). While local methods are valid near the nominal region of the parameter space, global methods are independent of the nominal values and also provide a complete mapping of the input–output (IO) behavior of the model (Sobol′, 2001). Given the nature of large-scale inflammation models, it is necessary to apply global sensitivity analysis (GSA) tools to identify and validate key mechanisms predicted by the models. These methods also hold the potential to help in the classification of mechanisms that can lead to clinically distinct outcomes such as resolution vs. self-maintenance of inflammation.

The traditional methods of GSA are variance decomposition schemes and they employ computationally expensive exploration of the parameter space using different sample generation techniques (Sobol′, 2001). Sobol' and FAST algorithms are two popular techniques for variance-based GSA (Saltelli et al., 1999). The advantages of these algorithms are, however, challenged by the large number of Monte Carlo (MC) samples ($\geq 10^5$) necessary for complete identification of the IO space of the model (Sobol′, 1998). This aspect renders the use of a detailed parametric analysis of the large-scale ODE expensive, and thereby restricts the modeler to fairly simple local analysis.

The computational cost for evaluating GSA can be reduced in two ways: reducing the time required for evaluating the model at a single point in the parameter space, and reducing the number of samples required for GSA. A common method is model order reduction, which employs various approximations to “reduce” the original complex ODE model to a reduced set of ODEs containing only key model species (Hahn and Edgar, 2002; Okino and Mavrovouniotis, 1998; Schilders et al., 2008). These approximations may employ lumping of the species, removal of non-sensitive species, or quasi steady state assumptions of the fast time-scale reactions (Okino and Mavrovouniotis, 1998). An alternate strategy is the meta-modeling approach, which “replaces” the entire complex ODE model with a set of approximation functions that capture accurate model dynamics over a prescribed parameter space (Barton, 1992, 1998). The essential difference between the