Rule-Based Modeling of Sepsis

Justin S. Hogg[1], James R. Faeder[2], Robert S. Parker[3] and Gilles Clermont[4]

***Short Abstract* — Rule-based modeling is applied to sepsis and inflammation. A compartmental model of sepsis is constructed and simulated using the BioNetGen platform. The model is populated by pathogen, macrophage, neutrophils, endothelial cells and signaling molecules. Simulations replicate observations reported in experimental literature and yield mechanistic hypotheses.**

***Keywords* — Rule-Based Modeling, BioNetGen, Sepsis, Inflammation, Innate Immunity.**

I. Introduction

SEPSIS is a serious medical condition characterized by systemic inflammation and the presence of an infection. While inflammation is an essential component of innate immunity, a systemic inflammatory response may lead to multiple organ dysfunction and death. The incidence and mortality of sepsis remain high, despite a long search for drugs and therapies [1].

Inflammation involves multiple cell types, organs, and soluble mediators. Previous studies dissected this complexity using differential equations [2,3] and agent-based approaches [4]. While these methods have been applied successfully, each has limitations. Differential equation simulations are fast, but complex systems may require hundreds of equations that are typically hand-written. Stochastic agent-based models naturally handle complexity, but require repeated simulation and statistical analysis. The technical language of these platforms may be a barrier outside the modeling community.

II. Rule-Based Modeling

Rule based modeling (RBM) was developed to describe complexity in cell signaling pathways. An RBM consists of structured objects and rules that describe how object components interact. Rules are written in a formal language derived from chemical reaction equations and emphasize the underlying biological interactions. Rules may be automatically expanded into a full reaction network, eliminating the need to write large reaction sets by hand. RBMs separate model specification from simulation, allowing for ODE, Gillespie or agent simulations [5].

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[1]Carnegie Mellon – University of Pittsburgh Ph.D. Program in Computational Biology, Pittsburgh, PA. E-mail: jsh32@pitt.edu

[2]Dept. of Chemical and Petroleum Engineering, University of Pittsburgh, Pittsburgh, PA. E-mail: rparker@pitt.edu

[3]Dept. of Computational Biology, University of Pittsburgh, Pittsburgh, PA. E-mail: faeder@pitt.edu

[4]Critical Care Medicine, School of Medicine, University of Pittsburgh, Pittsburgh, PA. E-mail: clermontg@ccm.upmc.edu

III. A Rule-Based Model of Sepsis

A model of sepsis was constructed using the rule-based modeling platform BioNetGen [6]. The model includes three compartments (infection site, blood, other tissues) and is populated by pathogen, macrophage, neutrophils and endothelial cells. Macrophage detect pathogen and secrete the signaling molecule Interleukin-1, which activates local endothelial cells [7]. Endothelial cells bind circulating neutrophils, which migrate into tissue and then capture and digest pathogen. Recruited neutrophils secrete the anti-inflammatory molecule Interleukin-1 receptor antagonist [8]. Soluble mediators leak between compartments and are eliminated in the blood.

Cells and signaling molecules are treated as structured objects in the RBM framework. Cell components correspond to macroscopic state values (e.g. *activated* or *resting*), membrane receptors, or cell-cell interaction sites. Compartments, migration and transport were implemented in a new compartmental extension to BioNetGen [9].

IV. Results

ODE simulations of the rule-based model replicated two experimental results reported in the literature. Increasing pathogen dose from sub lethal to lethal levels resulted in suboptimal neutrophil recruitment to the infection site while recruitment to healthy tissues increased [10]. Next, simulations of blood purification demonstrate improved infection clearance and reduced neutrophil accumulation in healthy tissue. This result provides a mechanistic hypothesis for hemoadsorption, a blood purification therapy that improves short-term survival in a rat model of sepsis [11].

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