An Autonomous Multi-Agent Simulation Model for Acute Inflammatory Response

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ABSTRACT

This research proposes an agent-based simulation model combined with the strength of systemic dynamic mathematical model, providing a new modeling and simulation approach of the pathogenesis of AIR. AIR is the initial stage of a typical sepsis episode, often leading to severe sepsis or septic shocks. The process of AIR has been in the focal point affecting more than 750,000 patients annually in the United State alone. Based on the agent-based model presented herein, clinicians can predict the sepsis pathogenesis for patients using the prognostic indicators from the simulation results, planning the proper therapeutic interventions accordingly. Impressively, the modeling approach presented creates a friendly user-interface allowing physicians to visualize and capture the potential AIR progression patterns. Based on the computational studies, the simulated behavior of the agent-based model conforms to the mechanisms described by the system dynamics mathematical models established in previous research.

Keywords: Acute Inflammatory Mediator, Agent-Based Model System, Dynamics Model, Multi-Agent Simulation Model, Simulation Model

INTRODUCTION

The function of the human immune system is to respond to intruding pathogens or damage tissues (e.g., trauma) and to prevent them from spreading to the entire body by producing warning chemical signals, activating relevant immune cells in the blood circulation system near the infected area, and then killing the intruded pathogens or microbial organisms. The process to protect the human body from further infection by harmful stimuli is commonly referred as the immune responses or acute inflammatory responses. However, an uncontrolled series of Acute Immune Responses (AIR) may lead to possible sepsis, severe sepsis or sepsis shocks since the immune cells and their released cytokines eliminate pathogens and microbial organisms but which also kill neighboring healthy cells. Recent census found that more than 750,000 severe sepsis or sepsis shock cases developed from sepsis in the US (Angus,
2001) with mortality rates between 20% and 80% (Zeni, 1997). In the United States alone, almost $17 billion is spent each year, treating patients with sepsis (Angus, 2001). Therefore, it is necessary to find an effective methodology that can help physicians predict the outcomes of an AIR, prevent possible severe sepsis or septic shocks, and control the involved risks for patients, which is the focus of this research.

This article presents a new modeling approach to predict the evolution of the Acute Inflammatory Response (AIR) which is the initial stage of sepsis pathogenesis. This predictive agent-based model (ABM) uses the system dynamics model developed by Reynolds et al. (2006) as a benchmark.

The organization of this paper is as follows: first we present the basic biological process of AIR, using a system dynamics model developed in previous research. Next, the agent-based model embedded with an existing system dynamics model is presented while its implementation detail is discussed. Outcomes of the agent based simulation are demonstrated and a sensitivity analysis is presented. Finally, conclusions and potential applications of the proposed model are discussed.

BIOLOGICAL MECHANISM OF ACUTE INFLAMMATORY RESPONSE

Process Description

The Acute Inflammatory Response, which can be the initial stage of sepsis, usually occurs when the human immune system detects intruding pathogens or existing tissue damages and sends out a signal (e.g., Interleukin-8 (IL-8) and C5a, the process is referred to as the chemotaxis) to the resting phagocyte cells such as the neutrophils initially and followed by the monocytes (two typical immune cells in the human body) in the blood vessel near the infected tissue. The resting phagocyte cells are activated and start to migrate towards the pathogens or damaged tissue whose recognizable protein on the surface is similar to those of the immune cells. Once the activated phagocyte cells reach the infection site, they start to engulf and consume the pathogens. Meanwhile, these activated phagocyte cells release pro-inflammatory cytokines such as Tumor Necrosis Factor (TNF), Interleukins (IL-1), IL-6, IL-8 and High Mortality Group Box-1 (HMGB-1) that activate more phagocyte cells and recruit them to the infection site. All those activated phagocyte cells not only eliminate the pathogens but also secrete substances which contribute to killing healthy cells and induce more inflammation in the initial progression of sepsis. Almost at the same time, several types of anti-inflammatory mediators such as IL-6, IL-10, soluble TNF receptors (sTNFRs) and IL-1 receptor antagonist (IL-1ra) are also released by the activated phagocyte cells in this stage. These anti-inflammatory mediators inhibit the production of pro-inflammatory mediators and therefore inhibit recruiting more phagocyte cells (Gogos, 2000).

System Dynamics Modeling of AIR

Undoubtedly, the complex mechanism of the AIR allows various possibilities of sepsis progression which may lead to a healthy response or a septic shock. Thus, based on insights into the biological mechanism of AIR a three equation system dynamics model was developed by Kumar et al. (2004). In the three equations model, pathogen level, early pro-inflammatory mediator, and late pro-inflammatory mediators were defined respectively. Moreover, those three essential indicators in AIR were measured by three individual equations. However, considering many other important indicators involved in AIR, a more complete system dynamics model based on five equations was developed by Reynolds et al. (2006). This model is shown next:

\[
\frac{dP}{dt} = K_{pp}P \left(1 - \frac{P}{P_{\infty}}\right) - \frac{K_{mr}S_{m}P}{l_{m} + K_{mr}P} - K_{m}f\left(N^{*}\right)P
\]

(1)

\[
\frac{dN_{R}}{dt} = S_{n} - R1N_{R} - l_{n}N_{R}
\]

(2)
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