ADAPTIVE HYBRID MODEL OF THE IMMUNE SYSTEM RESPONSE IN SEPSIS

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Abstract: There is an increasing interest in modelling biochemical pathway as dynamic systems. The main challenge is the necessity to drastically decrease the huge number of parameters involved in the biological process, thus operating a selection, which renders analytical dynamic models tractable. This paper comments a three order non-linear differential model of a sepsis shock and proposes a MATLAB-Simulink simulation model which captures both the free evolution and the treatment of the infection. Additionally, the opportunities offered by using hybrid modeling are underlined and two applications based on models that include resetting hybrid systems are presented.

Keywords: sepsis, complex system, cellular pathways, hybrid modeling, adaptive simulation model

1. INTRODUCTION

Biological systems are complex systems built from a dynamic web of interconnected feedback loops marked by interdependence, and redundancy. Illness represents a systemic functional alteration in the human organism. Multiple organ dysfunction syndrome (MODS) represents the ultimate multi-system illness, really representing a common end stage pathway of inflammation, infection, dysfunctional host response and organ failure in critically ill patients, and frequently leading to death. Because in MODS host-related factors were shown to be associated with patient outcome, the focus shifted to the study of host response in trauma, shock and sepsis. Usually, *sepsis* represent the *systemic inflammatory response syndrome* (SIRS) associated with infection. The most critical aggravation of sepsis is the septic shock. In intensive care units (ICUs) the septic shock is an event which only rarely occurs, but which indicates a very critical condition of the patient. Up to now, there is neither a successful clinical therapy to deal with this problem nor are there reliable early warning criteria to avoid such a situation. The diagnosis of septic shock is still made too late, because at present there are no adequate tools to predict the progression of sepsis to septic shock. The criteria for sepsis are both non-specific and potentially restrictive [1].

Our main goal is the statement of diagnosis and treatment on the rational ground of septic data. By the data analysis we aim to elaborate a model of the dynamic response of the immune system, in order to provide the necessary prerequisites for a more successful conduct of innovative therapeutic approaches and for improved diagnosis and treatment of septic shock.

The discovery of multiple proinflammatory mediators including endotoxin, tumor necrosis factor (TNF)-α and interleukin (IL)-1β or (IL)-6 brought about new theories regarding the patho-physiology of MODS and in particular in Sepsis. The immune system is a highly complex and integrated system which has evolved to provide the organism with substantial defenses against pathogenic organisms. In order to perform this function, the immune system has evolved strategies that allow successful elimination of a wide variety of pathogens, including viruses, bacteria and parasites. At its turn, the immune response to pathogens is a complex, highly regulated system involving numerous interactions between different cell types. The cells of the immune system communicate with each other by direct cell-cell contact and deliver signals to each other directly, through cell surface molecules, or indirectly, via secreted proteins, known as cytokines. Experimental advances in immunology over the last two decades have been immense and many of the important questions surrounding the issues of pathogen recognition, immune cell development, immune

regulation and effector mechanisms are well on the way to being answered [2]. What seems to be an important result is that the immune response evolves rapidly in time and its interactions are all highly regulated, that means that the only real way to study the whole integrated system is through the use of mathematical modeling. Mathematical models can be used to analyze experimental results and provide predictions and suggestions for follow-up experiments, or they can attempt to synthesize existing knowledge and provide a theoretical framework for the interpretation of existing paradigms.

2. SEPSIS MODELING APPROACHES

The evolution in every biological phenomenon, including Sepsis, can be considered as a result of information transfer in a complex cellular/molecular communication system. Although molecular biology is mainly focused on identification of genes and functions of their products, which are components of the system, the major challenge in analyzing sepsis is to understand at the system level the biological system within a consistent framework of knowledge built up from the molecular level to the functional system level – not only gene networks, but also protein networks, signaling networks, metabolic networks and specific systems such as the immune system. At a very abstract level, a cell can be divided into two general sub-networks, a regulatory network [3] and a metabolic network [4]. The metabolic network is mainly occupied with substance transformation to provide metabolites and cellular structures. The regulatory network's main task is information processing for the adjustment of enzyme concentrations to the requirements of variable internal and external conditions.

One of the first used in model molecular interactions were the stochastic methods. In the stochastic modeling approach, rate equations are replaced by individual reaction probabilities and the output has a physically realistic stochastic nature. But in the cell, various components interact in diverse manners. All cellular subsystems are highly nonlinear, and subsystem couplings are often nonlinear as well. There is no universal algorithm that can efficiently simulate all subsystems at once, so simulators must allow multiple computation algorithms to coexist in a single model. What has not been taken into account yet is the *humoral* network of *intercellular* communication, which links *intracellular* signaling networks of different cells and cell types. Cells communicate in various ways. In this work, we concentrate on humoral communication through cytokine messengers in the human body in general and in a sepsis state especially. The related substances act as first messengers and thus are released from specific cells to regulate functions in distant target cells by binding as ligands to specific receptors. One can consider that there are two kinds of communication mechanisms for SEPSIS modeling, both based on signal transduction in biological networks. The first mechanism can be represented by signaling intracellular networks, the other by signaling intercellular networks.

Signal transduction networks allow cells to perceive changes in the extracellular environment in order to produce an appropriate response. A cellular process network mediates the transmission of extracellular signals to their intracellular targets. The external signals are transmitted to the interior of the cells through receptors activating diverse signaling pathways. Computational models in signal transduction pathways have been made using different types of information processing present at cellular level, such as sequential, parallel, distributed, concurrent and emergent. In this sense, several computational approaches have been proposed to model the cellular signaling pathways, such as artificial neural networks [5], Boolean networks [6], Petri nets [7], rule-based systems [8], cellular automata [9], and multi-agent systems [10].

From the above mentioned methods, in this paper we focus on those based on Differential Equations System (DES) model. We will mention two kinds of DES:

Ordinary Differential Equations (ODE). The general form of an DES model can be written as $\frac{dx}{dt} = f_i(x), i = 1,2,...,n$, where x_i, $1 \le i \le n$ are states of molecular species. In a molecular network model, an ODE equation is built for each molecule x quantitatively describing its relationship with all relevant molecules and solving all equations simultaneously. There have been several platforms for ODE based modeling. Among them are Gepasi [11] and Virtual Cell [12]. However, though metabolic reactions can be simulated by these tools, signaling activities may not be well supported. Furthermore, signaling networks are non static and undergo evolution [13]. Thus, modeling of the context dependent cellular processes merits a more elaborated approach, like hybrid modeling, which is our proposal for improvements of model credibility.

Stochastic Differential Equations(SDE). SDE has been adopted to study physical system with random elements, including population dynamics, stock market fluctuations and protein interaction. SDEs cannot be solved analytically, and simulations are necessary. It involves the following steps: 1) to compute various sample paths and determine the stability and convergence of each trajectory and 2) to compute the approximation to the probability distribution of the solution and determine various statistical measures such as mean and variance.

The general form of SDE is

$\frac{dx}{dt} = a(x,t) + b(x,t)n(t)$ where x_i, $1 \le i \le n$ are states of molecular species, $a(x,t)$ and $b(x,t)$ represents changes of x in time t and $n(t)$ represents the noise term that is dependant on time t.

3. DES BASED MODEL FOR THE CELLULAR INTERACTIVITY IN SEPSIS

A solution based on *Differential Equations System (DES)* has been practically used in many quantitative models. The molecular or cellular network is modeled as a collection of (usually nonlinear) differential equations, where reaction rates and compound concentrations are the variables. These are solved then numerically for each time step. Stoichometric coefficients, starting concentrations and rate constants for all interactions are needed. Due to the complexity of the biological phenomenon, biochemical pathways of molecules can be modeled by many differential equations, with a huge number of parameters. In this regard, complex biological processes are modelled by differential equations systems with up to 7000 equations and 20000 associated parameters [14]. Starting from model with 16 differential equations and 117 parameters [15], Brause uses a reduced order approximation model, with three variables. So pushing the limits we have a 3-rd order non-linear approximating dynamical model of septic shock, which was implemented as a MATLAB-Simulink simulation model of several Sepsis treatment scenarios.

A. The Differential Equations System of the model

As basis was used Brause's reduced order approximation model, with three variables:

- *P* representing the *pathogen influence*, $P \in [0,1]$,
- *M* representing the immune response, namely the *macrophage action*, $M \in [0,1]$, and
- *D* representing *the percent of damaged noble cell tissue*, which is destroyed in the fight between *P* and *M*, $D \in [0,1]$.

The dynamic equations are:

$$\dot{P} = \alpha_1 P(1-P) - \alpha_2 MP,\ \alpha_i > 0,\ i = \overline{1,2} \qquad (1)$$

$$\dot{M} = -\beta_1 M + M(1-M)(\beta_2 P + \beta_3 D),\ \beta_i > 0\ i = \overline{1,3} \qquad (2)$$

$$\dot{D} = -\chi_1 D + \chi_2 h((M-\theta)/\chi_3),\ \chi_i > 0,\ i = \overline{1,3} \qquad (3)$$

where $\theta = 0.5$ is a threshold value. A typical parameter regime takes the maximal values specified in Table 3 and

$$h(x) = \frac{1}{1+\exp(-x)} \qquad (4)$$

The maximal parameter values are as follows:

α_1=0.1; α_2=1.0; β_1=1.0; β_2=10.0; β_3=1.0; β_1=1.0; γ_1=0.1;γ_2=0.04; γ_3=0.25; (5)

The dynamical model described by equation (1)-(3) reflects some basic qualitative features of the sepsis phenomenon and assume that the rate of cells damage increases also with a sigmoid function (4) of macrophages action, limited by a threshold θ. The introduction of *h(x)* represents the main improvement in the Brause model.

B. Results of Sepsis dynamics simulation

Consider firstly the case of the free evolution of sepsis shock, given by equations (1)-(3). The simulation is performed in MATLAB, using the ODE45 integration routine based on the Runge-Kutta procedure (Fig.1) with the constant parameter values given in (5). The Simulink model schemes were elaborated by Ecaterina Oltean [16].

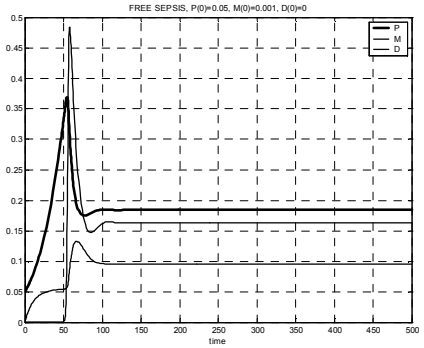


Fig. 1. MATLAB simulation results for (1)-(3) DES

An important change in the initial model was to introduce a parameter that signifies the initialization of a treatment (medication procedure). That is the main difference between Brause approach and ours, Sepsis treatment can be modelled by introducing an exogenous signal into the right hand term of (1):

$$T(t) = \begin{cases} l, when: t = kp, \forall k \in N \\ 0, else \end{cases} \qquad (6)$$

where *l* is the level of medication and *p* is the period of administration.

Now let consider first the case of an *asymptotically constant treatment*. A straightforward way to model this case is by introducing, as control signal, the negative output of a first order element with a step input. The parameters values are the same as in (5) with initial conditions specified in Fig.1. The step height is chosen 0.18, which reflects an approximation of the stationary value of the pathogen action. The simulation results are depicted in Fig.2, column of the left.

The second case considered is an *asymptotically constant treatment with delay*. This models the situation in which the treatment is decided after the pathogen action reaches a maximum. The considered delay is 70 time units. The pathogen influence, macrophage action and damaged tissue percent are depicted in Fig. 2, column in the middle.

Finally, the third case considered in the simulation experiment is the one of a "cheap" treatment, represented by a *delayed pulse control signal*. This could capture the situation in which the doses are administrated at regular time intervals, and the dose might be too little to cover the entire time interval to the next dose administration. The only modification introduced in the Simulink model is the replacement of the step input with a pulse generator with a period of 10 time units. The corresponding simulated evolutions of the pathogen action, macrophage action and damaged tissue are presented in Fig. 2, column of the right.

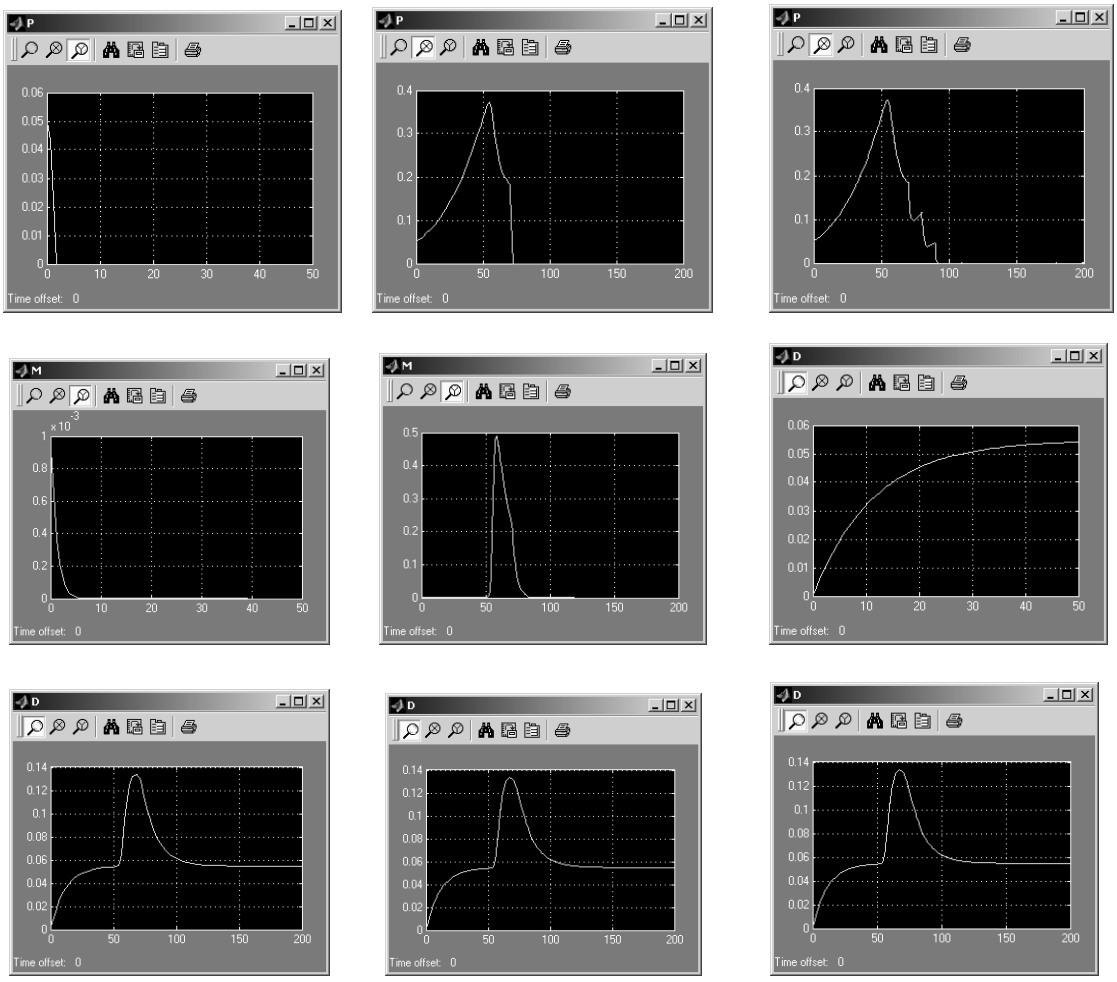


Fig.2. Simulated evolution of the pathogen action (P), macrophage action (M) and damaged tissue (D)

One can observe that the approximating sepsis dynamics (1)-(3) is a well-suited model also for a more general "war game" approach, in which a protection agent (the macrophage action *M*) fights against an *invader* (the pathogen action *P*), but produces also collateral victims (the cell damage *D*) in its actions.

In the simulation, the height of the step control input representing the treatment was chosen empirically, in two steps. Firstly, by inspecting the final (stationary) values of the free sepsis evolution in Fig.1(a), the point

$x0 = [P(0), M(0), D(0)] = [0.2, 0.15, 0.1]$ is

chosen as starting point for *the numerical search of a stationary point* of system (1)-(3). The obtained stationary point is x_0 = [0.183, 0.157, 0.092]. Consequently, the height of the step control input for the pathogen action *P* is chosen as 0.18. The same value holds also for the height of the pulse. Simulations show that treatment is possible in case of an asymptotically constant input with the height value similar to the stationary value of the free pathogen action, and also if this treatment is delayed or administrated at regular time intervals.

4. A PROPOSAL FOR HYBRID MODELING

Hybrid modeling can have multiple meanings. First of all, a model containing metabolic and signaling networks is a hybrid model. Actually these two networks are not independent of each other. In such model, very often, different description methods should be employed to disclose different aspects or parts of a biological system, because, when ODEs are used to describe deterministic events, the basic assumption on continuity and determinism in ODE methods hamper the true representation of noise and stochastic events in cellular environment [17]. The second approach on hybrid modeling derived from the expertise of control systems and computer science specialists. From their point of view, hybrid systems are characterized by continuous evolution of process variables, governed by differential equations or difference equations, and discrete transitions. Hybrid phenomena include switching between different dynamics due to changes in a model's operating conditions or a control action, as well as state resets at discrete instants of time. Such transitions can be triggered by state events, time events or memory.

The analysis of stability of hybrid systems has lead to several important results in the last few years. For systems with state resets, usually referred to as impulsive systems, a common Lyapunov function was used to analyze both continuous-time dynamics and the discrete-time dynamics of the resetting law [18], [19]. In the line of these works, we propose to improve the model of patient evolution in Sepsis under treatment, discussed in section 3, by using as model a resetting hybrid system (RHS), also known as impulsive system. RHS is defined as a system combining continuous state variables, governed by differential equations for which some or all of its states are being reset at discrete time instances via a resetting law, i.e., a difference equation. The discrete states are the indexes of these resets.

A hybrid resetting system is defined by the equations

$$\begin{aligned} &\dot{x}(t) = f(x,t),t \neq t_j \\ &x(t)^+ = h(x,t),t = t_j \\ &j(t)^+ = g(x,t),t,j(t)) \end{aligned} \qquad (7)$$

Here, $t \in \mathbf{R}_+$ and $x \in \mathbf{R}^n$ is the continuous state and the discrete state $j \in \mathbf{N}_+$ is a piecewise constant signal, which is the resetting index. The discrete state can be triggered by a state event, a time event or discrete state history, i.e., memory.

A resetting system is associated with differential dynamics:

$$\begin{aligned} &\frac{d}{dt}\delta x(t) = J_c(x,t)\delta x(t), t \neq t_j \qquad (8) \\ &\delta x(t)^+ = J_d(x,t)\delta x(t), t = t_j, j = 1,2,... \end{aligned}$$

where $J_c(x,t) = \partial f(x,t)/\partial x$ is the Jacobian of the vector field f; $J_d(x,t) = \partial h(x,t)/\partial x$ is the Jacobian of the vector field h and t_j is the j^{th} resetting time.

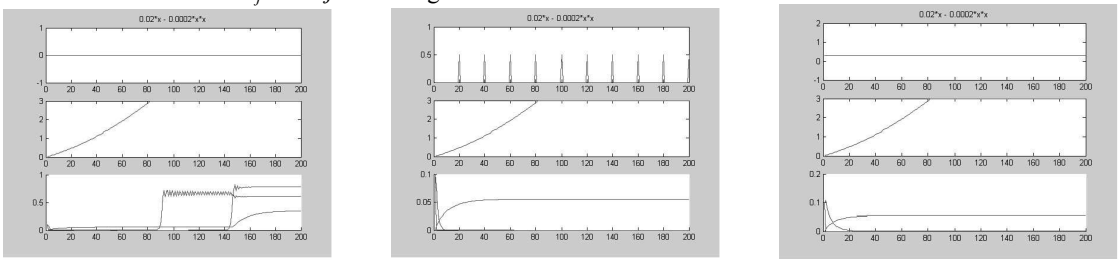
For resetting systems, where for every specific resetting sequence $\{(t_j,h(t_j))\}$ we can represent the system (7) by a single differential equation representing a *particular system*

$$\dot{x}(t) = f_r^*(x,t),t) \qquad (9)$$

Note that (9) is an impulsive differential equation, i.e., f_r^* contains Dirac impulses, which is another method to represent resetting systems. Again when the differential dynamics (8) is exponentially stable for all sequences $\{(t_j,h(t_j))\}$ then the system is contracting [20]. Then, all solutions of each particular system (9) converge exponentially to a single *particular trajectory*. Consequently a hybrid resetting system of type (7) is said to be contracting if and only if the associated differential dynamics of (8) is uniformly exponentially stable.

5. ADAPTING A HYBRID MODEL FOR BETTER SEPSIS SIMULATION

The hybrid solution was used to model the response of a patient affected by Sepsis, when a treatment is introduced (see equ. 6). The hybrid approach allows to differentiate between two kind of systems – without or with antibiotics. In the first situation one can consider that the treatment appears as a sequence of Dirac impulses, in the second, due to the persistent effect of antibiotics, the signal representing the treatment can be considered as continuous. Three cases of simulation for the situation when the pathogen attack is weak are presented in fig. 3.: a) absence of medication; b) medication with pulses of period p=20; c) contiuous medication with intensity level n = 0.3.



a) b) c)

Fig. 3. Simulations of the response to medication

The pictures in fig.3. suggest the following remarks:

a) In the absence of medication the affection trends to chronic disease

b) Because the effects of the pathogen attacks are practically cancelled after medication, one can consider the treatment as correct.

c) The introduction of antibiotics was not necessary

6. CONCLUSIONS AND FUTURE WORK

In this work we focused on Sepsis, one of the most complicated processes due to the diversity of involved cellular pathways. The most challenging task was to simulate collaborative interactions among molecules that produce and transfer signals. Signaling pathways, the most difficult to model due to a heterogeneous mix of activities involved, can be seen as a kind of molecular body language. It is the main argument to use this way in modeling Sepsis phenomena. In the deterministic case of a DES with no random influences, the parameters can even be directly computed: *m* samples give us *m* equations for *m* parameters that are easily computable by the well-known Gaussian elimination method. The discriminative variables are selected from the set of all variables which were sufficiently often measured. Quite variables like the concentrations of specific

cytokines and the inflammation state (hyper/hypoinflammation) of the patients were not available to our analysis, one could agree that the used equations give a good description of the first step in endotoxin tolerance and consequently offer a satisfactory prediction of the immune system response and on the efficiency of a treatment. One can observe when the system returns to the "initial condition" or in another stabile state. This seems compatible with the intuition of the role of the innate immune system as a protector again attacks. However, because our predictive variables are very general and are influenced by a myriad of biochemical processes we do not attend a better performance by specific molecules.

An improvement can be made be using hybrid modeling, that contribute to better understanding of cell behavior at different level of interest namely the molecular level, process level and disease level. An improved simulation was obtained by exploiting exponential convergence of hybrid nonautonomous resetting systems. In the proposed model the description of the transition of resetting hybrid systems is reduced to a simple compositional operation. This yields stability conditions generalizing and relaxing several existing results.

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