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Modeling Immunology Mechanisms with Discrete Event Systems

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Abstract. *The immune system is a very complex cognitive system. Based on immunological principles we propose an approach in order to study the mechanisms that govern the immune system's functionality. A two-module algorithm is developed, which launch a specific action against an anomalous situation. The Petri nets tools are assumed in this approach. Also, Markov Decision Processes (MDPs) with a truncated state space to the problem with infinite state space considered. We show that an optimal stationary policy exists and we apply the results of [1] to a dynamic scheduling problem of the immunological response to external stimuli.*

1. Introduction

Immunity depends on continuous movement of cells through blood, tissue and lymph [2]. Lymphoid cells travel to the secondary lymphoid organs of the spleen, lymph nodes and Peyer's patches to encounter antigens acquired from the environment via blood, lymph or across mucous membranes. Where and by which cells antigens are presented to the trafficking cells has a significant influence on the outcome of the immune response with respect to antibody isotype commitment and future homing preference of memory and effectors lymphoid cells (Fig.1).

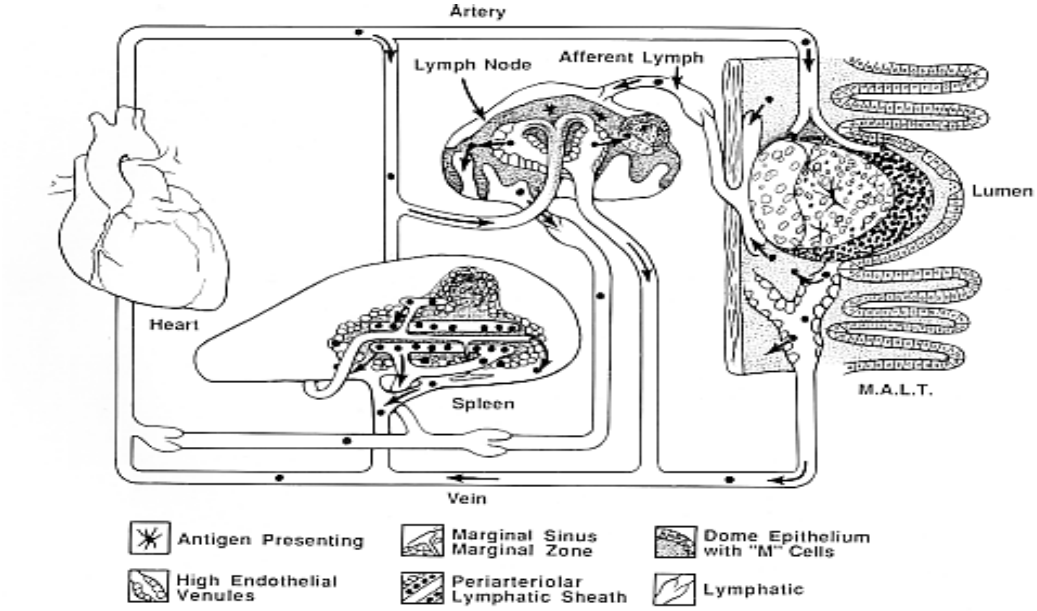

Fig.1 Mammalians immune system components

Lymphocyte traffic patterns, regulated by selective expression of adhesion proteins in peripheral or mucosal lymphatic tissues, permits segregation of immunological memory by causing antigen-primed cells to return to specific anatomic destinations committed to expression of peripheral or mucosal immunity. Among potentially myriad factors, these microenvironments include prevalence of certain cytokines, adhesion to- and co-stimulation by specific cells, and still unknown tissue factors that favor commitment of B cells to specific immunoglobulin types or T cells to peripheral or mucosal immunity.

Recirculation of a precursor pool of uncommitted lymphocytes from the blood into lymph nodes or mucosal lymphatic tissues and then back to the blood again, integrates immuno-surveillance with organ-selective immune functions across the segregated systems. The magnitude of cell traffic reflected by the number of cells returned to the blood in efferent lymph is enormous. Enough lymphocytes recirculate from lymph to blood to replace the total blood lymphocyte pool from 10 to 48 times every 24 hours. Random and segregated traffic patterns are essential for efficient operation of the two separate but overlapping immune systems in mammalian species. The feat of coordinating an anatomically dispersed immune system (comprised of mobile, circulating, individual and extremely diverse cells) depends upon cell movement and a system of membrane recognition and activation signals. A mixture of integrins, selectins and chemokine receptors expressed by lymphocytes and endothelial cells are involved in precipitating selective emigration of lymphoid subsets from the blood in tissues where specific counter-receptors are displayed on luminal surfaces of endothelial cells. These recognition events could occur in skin, mucosae or specific secondary lymphatic tissues such as Peyer's patches or peripheral lymph node. Receptor ligand interactions allow these cells to find their way around the body, where to adhere to endothelium, when to migrate and how to find where they have to act within tissue. The cell diversity and variety of information processing mechanisms make the immune system a very complex system. Understanding the way this organ solves its computational, and how it detects and reacts to novel situations and how it unleashes smooth early secondary responses is a rough job. In this paper we present an approach to immune systems by modeling the characteristics processing mechanisms with discrete event systems (DES) formalisms. Our goal is to introduce a new algorithm in order to analyze the organisms fight with viruses and microbes. The proposed algorithm is inspired in the current understanding of the mammal immune system although, in detail, it does not exactly follow the biological steps. Many of the detailed features of the immune system are dependent on the biological context where it operates and on the type of the cell hardware that it uses. We try to take what is best from the clever evolutionary mechanisms developed by nature, as well as we understand these mechanisms, and to improve theirs analyze, in order to find new models for treating diseases. For example, the interaction between the T-module and B-module takes the reverse order of what is found in nature, with a clone proliferation phase preceding T-phase. Clone proliferation is an expensive operation, but in software, e.g., in modeling process, it is a virtual (not very time consuming) operation. The approach presented in this paper has a wide range of applications to many biological, but also to many technical systems. Moreover, based on the optimal policy for the limiting problem build with Markov decision processes (MDPs), we exemplify an optimal stationary policy [3] on a dynamic scheduling response of the immune systems to the attack of different pathogen agents.

2. Immune system mechanisms

Some of the immune system features are [1], [4], [5]:

- Uniqueness: The immune system of each individual is unique, although they are similar.
- Imperfect detection and mutation: By not requiring a precise identification of every pathogen agent, the immune system becomes flexible and increases its detection range. But, if a pathogen agent is detected, a mutation mechanism refines the identification. Identification of pathogen agents is made by partial matching, and this mechanism allows to a small number of the detectors (10^8 to 10^{12}) to recognize nonself patterns on the order of 10^{16}. This is modeled in DES formalism with a small number of detectors, which are at a later stage modified by the dynamics.
- Learning and memory: The immune system can learn the structure of the pathogen agents, and remember those structures. Future responses are much faster and, when made at an early stage of the infection, no adverse effects are felt by the organism. We underline the importance of this feature for modeling the immune system with Petri nets as an important formalism used in the representation of DES.
- Novelty detection: The immune system can detect and react to pathogen agents that the body has never encountered before. This feature will be modeled with controlled Petri nets, which will determine the appearance of bottlenecks in the net, in order to simulate the censoring mechanism for T-cells that occurs in the thymus.
- Distributed detection: The detectors used by the immune system are highly distributed and not subject to centralized control. This feature can be modeled with free choice Petri nets.

3. Modeling algorithm

Our work is based on the algorithm given in [6]. In this algorithm, the states of the system, both normal condition and anomaly states, are characterized by the values of n variables. The n-dimensional state vector is normalized in such a way that all variables take values in the interval [0,1]. The values of the state vector in normal conditions define the self S of the system. The anomaly states are the nonself of the system. The algorithm adopted by us contains two modules. The T-module discriminates self from nonself. The B-module reacts to all frequently occurring state vector values (self and nonself codes) and reports to the T-module, updating it. T-Module contains a set of detectors which are vectors in nonself space, that is A = $[0,1]^n \setminus S$. Each element $\bar{x}$ of A is able to detect anomalies inside a radius r_x around it. When $\left|\bar{y}-\bar{x}\right| < r_x$, y being the current state of the system, an anomaly of type x is reported. In the Petri net model a bottleneck, caused by the fact that an anomaly of type x is not allowed to fire some transition, permits us to emphasize this.

The T-module is initialized by choosing points in A at random with corresponding radius r_x, until a reasonable coverage of the space A is achieved with d detectors. Fig.2.a illustrates this: the small circles are the self patterns. To each point in the self corresponds a code (a set of vector coordinates) and an affinity neighborhood of normal operating conditions inside a radius r_x. This approach corresponds to an initial marking in the Petri net model. The anomaly detectors are shown in the figure as large circles. When a measurement $\bar{y}$ of the system arrives at the T-module, the algorithm verifies whether this code has affinity with one of the detectors or with the self. The affinity of this vector with those defining the self and the other is measured by the Euclidean distance, and correspondingly in the Petri net model is measured with the predicates, assigned to certain transitions, which can or can not validate the firing of the respective transitions. If the detection algorithm falls in the self domain, no detector is activated.

If affinity is found with one of the detectors $\bar{x}$', an anomaly of type $\bar{x}$' is registered. This means, that in the Petri net model we'll create new predicates for certain transitions, in order to continue the simulation and to ensure the Petri net vivacity. The B-module generates vector codes corresponding to the most frequently occurring states of the system and sends these codes as alert codes to the T-module. By itself or in interaction with the B-module, the T-module is an adaptive system. As an illustration in Fig. 2.a., and in Fig.2.b, is considered a typical situation: suppose that a nonself code (the star symbol in Fig.2.a) is detected. Then, first, the detector changes its code to increase the affinity to this type of anomaly, and secondly, the algorithm creates a new detector (supposing that the old one has not enough affinity with the external code) with a resolution defined by the smallest distance to the other detector boundaries as shown in Fig.2.b. In the above way, the T-module modifies the initial set of detectors produced by the censoring mechanism. This means that it change the number, modify the space distribution and change the resolution, creating a specific anomaly detection system. Regarding the Petri net model we may say that we are dealing with an adoptive Petri net (AdPN).

B-module improve the A space coverage of the T-module and, it has a total population of n_t vectors given by relation (1).

$$n_t = n_l + n_{lc} \tag{1}$$

Where, n_l represents the initial population of vectors $\overline{x_l}$

n_{lc} represents the population of clone vectors $\overline{x_{lc}}$.

The number of clone vectors changes as the system evolves. In [6] it is allowed that the number of clone vectors is limited to a fraction β of the initial population:

$$n_{lc} = \beta \cdot n_l \tag{2}$$

The dynamical evolution of the vector population involves mutation and stimulation features that are described next. Mutation takes place every time an external code $\bar{y}$ arrives to the B-module. The mutation process begins by selecting, from the total population, a sample of vectors $\overline{x_m}$. The mutation process

operates only in this part of the population and in those codes that are close to the external signal $\bar{y}$. The mutation process depends on the affinity between the vectors $\overline{x_m}$ in the sample and the external code $\bar{y}$.

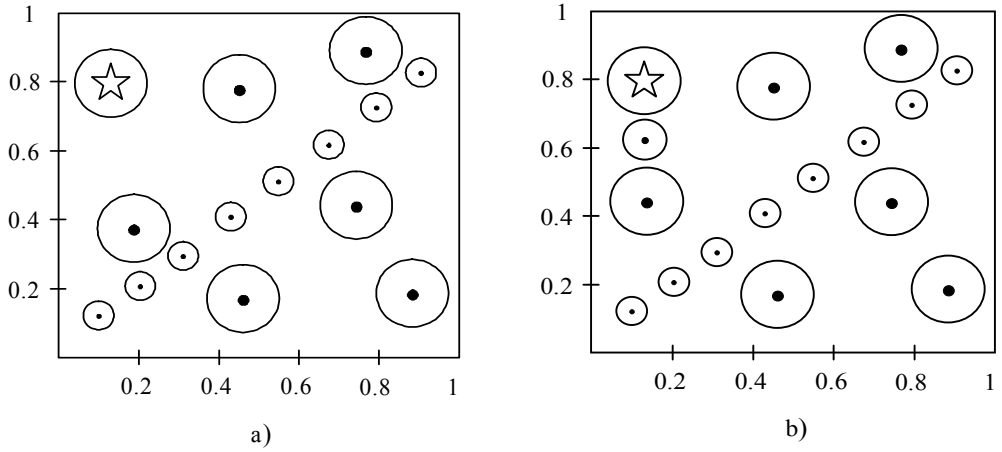

Fig.2. T-module structure. a) Self patterns (small circles) and anomaly detectors. b) Creation of a new detector and shift to a new detector to increase affinity with an anomaly.

If the code $\bar{y}$ and the vector $\overline{x_m}$ are far away, as in zone A of Fig.3, no affinity is considered to exist and the code $\overline{x_m}$ is not changed. Also, in zone B there is no modification.

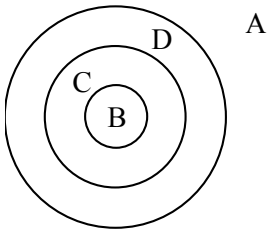

Fig.3. Zones A-D for the mutation process

For codes $\overline{x_c}$ in zone C, the mutation process occurs in a deterministic way. The external code $\bar{y}$ is assumed to have mass one and the vectors in zone C mass m_l. The new code in population corresponds to the center of mass given in relation (3).

$$\overline{x_c}(t+1) = \frac{m_l \cdot \overline{x_c}(t) + \bar{y}}{1 + m_l} \tag{3}$$

For zone D, the mutation assumes a random process. The new position of the population vector $\overline{x_D}$ is given by a random distribution for each point of the line defined by the old position of the vector and the position of the external code

$$\overline{x_D}(t+1) = \overline{x_D}(t) + \eta\left(\bar{y} - \overline{x_D}(t)\right) \tag{4}$$

When the external code appears repeatedly in the same region, the mutation process leads to a population cluster in that region. As we mentioned in Section 2 the cluster of population in some regions is modeled with controlled Petri nets, which will determine the appearance of bottlenecks in the net.
Stimulation is a necessary process in the case when new external codes arrive in the B-module and the mutation process destroys the initial uniformity of the vector population. In this situation, if a strange

external code appears, its detection may be missed. To ensure that this case is avoided, a stimulation or cloning mechanism has been included in the algorithm to create new vectors in the region where the external code appears. The cloning mechanism is activated when the rate of external codes arriving in a region exceeds a specified threshold. In the Petri net model, this process is modeled adding to the net new location, e.g., building a more complex net. In order to simplify the Petri net model, a pruning algorithm given in [7] is applied. This simplification of the Petri net has a real support, because in the immune systems there is a death mechanism for the clone vectors.

4. Scheduling the models of immune systems

The algorithm described in Section 3 does not specify the way of action of the immune system when several extern pathogens occur simultaneously. In order to respond to these pathogens, the immune system needs an action rule similar to the rule of attending to several clients in a queue. The associated Petri net model will be a colored Petri net, where the known pathogens are scheduled in a color code ordered by priorities. The unknown pathogens will be isolated until the known pathogens will be treated by the system. This means that the unknown pathogens will have invalidated entering transitions, because the corresponding predicates are not yet allocated to these transitions.
According to the huge dimensions of Petri net models we try to find out if this scheduling problem has a limit. The answer to this problem is based on the convergence of Markov decision processes (MDPs) with a truncated state space to the problem with infinite state space. In [1] it is shown that an optimal stationary policy exists for this problem, such that the number of randomizations it uses is less or equal to the number of constrains plus one. The following example focuses on this approach.
We suppose that different pathogens compete for access to an immune system, which we assume that is a shared resource. At the beginning of each time slot priority is given to one of the pathogens according to a pre-specified decision rule, and the service is made in one unit of time (we may consider here the incubation time, which is different for each type of disease). If the service (i.e., the action of the immune system) is successful, the pathogen disappears from the system; otherwise it remains in the queue.
The problem is to find a scheduling policy that minimizes a linear combination of the average delays of some types of traffic subject to constrains on average delays of other types. At time t, M_t^i pathogens arrive to queue i, 1 ≤ i ≤ N. Arrival vectors $M_t = \left(M_t^1,...,M_t^N\right)$ are independent and form a renewal sequence, with finite means λ_i. During a time slot (t, t+1) a pathogen from any class i, 1 ≤ i ≤ N, may be treated, according to some policy, which is a pre-specified dynamic priority assignment. If treated, with probability μ_i it completes its service and leaves the system; otherwise it remains in its queue.
A generic element of the state is given by $x = \left(x^1, x^2,..., x^N\right)$ and it represents an N dimensional vector of different queues' size. Assume that $\sum_{i=1}^{N} \frac{\lambda_i}{\mu_i} < 1$. Consider the linear cost function $c(x,a) = \sum_{i=1}^{N} c_i \cdot x_i$ and $d^k(x,a) = \sum_{i=1}^{N} d_i^k \cdot x_i$, for 1 ≤ k ≤ K, where c_i and d_i^k are non-negative constants. Thus the costs $C(x,u)$ and $D^k(x,u)$ are related to linear combinations of expected average length of the different queues. The constrained control problem is: find u ∈ U that minimizes $C(x,u)$ s.t. $D^k(x,u) \le V_k$, k = 1, …, K, where V_k are given constants. Consider the expected average costs. By Little's law this quantities are proportional to the respective waiting times in the different queues. Let $G = \{g_j\}$ be the set of all strict priority rules. A strict priority rule is a policy for which each type of pathogen is served only if there are no pathogens with higher priority in the system, and if it is the first in his queue.
Optimal policies for constrained control problem are obtained by time multiplexing between the different g_j. Define an L dimensional vector parameter $\alpha = (\alpha_1, \alpha_2,..., \alpha_L)$, where α is a probability measure, and $L = |G|$. Define a "cycle" as the time between two consecutive instants that the system is empty (e.g. the immune system is not busy with external pathogens). During any cycle, a g_j is used. A policy α^* is

defined as a policy that chooses different policies g_j s.t. the relative average number of cycles during which g_j was used is equal to α_j, where $t \to \infty$. It is shown in [7] that

$$C_1\left(x, \alpha^*\right) = \sum_{j=1}^{L} \alpha_j \cdot C_1\left(x, g_j\right) \tag{5}$$

For a given d > 0, consider the following linear programming problem: Find $\alpha \in R^L$ that minimize $\sum_{j=1}^{L} \alpha_j \cdot C_1\left(x, g_j\right)$, subject to $\sum_{j=1}^{L} \alpha_j \cdot D_1^k\left(x, g_j\right) \le V_k - d$, where k = 1, …, K, and $\sum_{j=1}^{L} \alpha_j = 1, \alpha \ge 0$.

In [7] it is shown that $\alpha^*(0)$ is an optimal policy for such a constrained control problem. For the Petri net model of the immune system, this means that the initial marking defines the vivacity of the net.

5. Conclusions

In time, nature's evolutionary processes created an efficient weapon to fight with all kinds of hostile environments. To model these natural mechanisms seems to be a sensible approach. In this paper we proposed a possible tool for this approach: Petri nets. However, some of the features of the biological processes are domain specific and depend on the cell hardware that is used. Therefore, to understand and to model these processes is a hard task.

The immune system, with its cell diversity and variety of information processing mechanisms, is a very complex system. The high complexity of the immune system implicates very large Petri nets models. In order to minimize the dimensions of models, we introduce the notion of adaptive Petri nets. Therefore we have shown that there is a limit in the schedule problem of different pathogens, which compete to access a limited service capacity of the immune system. For this we considered the Markov Decision Processes with a truncated state space to the problem with infinite space. Future work will refine the above presented approach by considering differential adaptive Petri nets for modeling the mechanism which govern the immune system; this is motivated by the necessity to model certain nonspecific mechanisms like cell apoptosis, s.a., which was not discussed here.

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