# A Hybrid Automata Modell of TCR Triggering Dynamics

Dejan Milutinović, Jorge Carneiro, Michael Athans, Pedro Lima

*Abstract*— **This paper describes a Hybrid Automata approach to the modelling of biological populations composed by a large number of T-Cells. Individual T-Cells are modelled based on a deterministic Hybrid Automata endowed with input events and continuous-valued outputs. The complexity of interaction among the T-Cells and Antigen Presenting Cells is described by a stochastic approach, under which the T-Cells distribution over the state space is modelled. This is based on a Stochastic Hybrid Automaton, which results from inputting a stochastic event sequence to the individual T-Cell model. The dynamics of the state probability density functions is determined and the results applied to the analysis of experimental data.**

*Keywords*— **Hybrid Automata, T-Cell Receptors, Multi Agent Systems.**

## I. Introduction

THE aim of this paper is to shed some light on the prediction of a biological population macro-dynamics based on the micro-dynamics model of individual population members. This paper is motivated by the investigation of biological population dynamics phenomena [1] [2], where biological facts and experimental data were used to investigate the T-Cell receptors (TCR) triggering mechanism. Along these lines an approach in designing experiments based on different hypotheses is presented in [3].

The lessons learned from previous work [3] concern the importance of deriving the macroscopic properties of the phenomena from the properties and interaction among the elementary interaction components. An overview of the most promising methods to reach this goal is provided in [4] [5]. The biological facts used in model design [2] lead us to conclude that biological interaction could have suitable description under a Hybrid Automata framework [6]. This idea is already exploited in [7] where the Hybrid Automata model of single biomolecular network is designed.

In this paper we are using the Hybrid Automata framework to model and analyze the consequence of interactions between the large populations of T-Cells and Antigen Presenting Cells (APCs), where large amounts of biomolecular interactions occur concurrently. The paper starts by the description of the biological phenomenon and of the complexity problem in Section II. The Hybrid Automata framework for modelling T-Cells, under the light of TCR triggering phenomena, is introduced in Section III. The Mathematical definition of the individual T-Cell model (T-Cell Micro Agent model) is presented in Section IV. The complexity of population is modelled by using a Stochastic Hybrid Automata model for the population in Section V. The dynamics of the state probability density function is determined (Section VI) and the results applied to the analysis of experimental data in Section VII.

D. Milutinović and Pedro Lima are with the Institute for Systems and Robotics, Instituto Superior Técnico, Lisbon, Portugal, (e-mail: dejan@isr.ist.utl.pt and pal@isr.ist.utl.pt)

J. Carneiro is with Gulbenkian Institute of Science, Oeiras, Portugal, (e-mail: jcarneir@igc.gulbenkian.pt)

M. Athans is Visiting Research Professor with the Institute for Systems and Robotics, Instituto Superior Técnico, Lisbon,Portugal (e-mail: athans.isr.ist.utl.pt)

## II. Problem Formulation

The interaction between T-Cells and APCs is one of the most important reactions of the immune system. This reaction is called T-Cell Receptor (TCR) triggering and leads to the production of effector cells, which kill antigens. The interaction between T-Cells and APC produces changes in the amount of TCR (TCR dynamics) in a T-cell. The T-Cell should be connected to an APC. However, simultaneously some of the T-Cells will disconnect from APCs, and others will connect again. Figure 1 presents a population of T-Cells surrounded by APCs.

The T-Cell population is definitely a complex system. To follow the complete dynamics of the population, the TCR dynamics and the motion dynamics, which leads to the connection or disconnection of each T-Cell to APCs, should be followed. If we assume a 3D model of motion we need 6 state variables per T-Cell just to describe the position and velocity of a T-Cell. We need also at least one state for TCR dynamics and at least one discrete state variable that contains information on whether the T-Cell is connected or disconnected. In total this means, at least, 8 variables per T-Cell. A population of 1000 T-Cells has a state vector of dimension 8000. Although the simulation of the population would not be impossible with current computational power, the dynamics of the average value and the variance of the TCRs in the population are typically sought by biologists. These moments are particu-

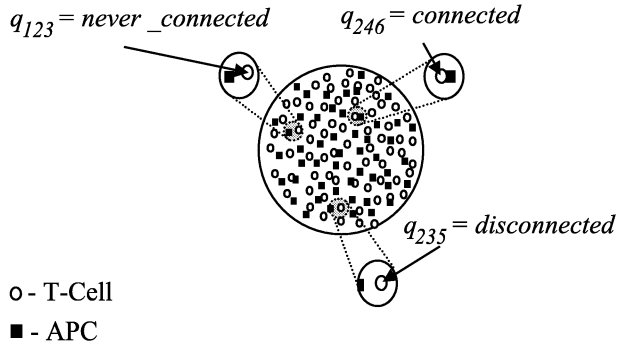


Fig. 1. The T-Cells population surrounded by APCs, $q_i$ is the discrete state of the $i$th T-Cell.

larly important when the population observed data is to be matched to the individual TCR dynamics. These facts motivated a more general approach to the modelling of a multi-agent population, which is described in the sequel.

## III. Introduction to Mathematical Definitions

In this section we will introduce the Hybrid Automata framework into the problem of TCR triggering phenomenon modelling. Each T-Cell, regarding the connection to an APC, could be in one of the three discrete states: *1-never connected*, *2-connected* and *3-disconnected*. Before the T-Cell - APC connection, the amount of TCRs presented on the T-Cell surface is constant. The consequence of connection between the T-Cell and APC is a decrease in the amount of TCRs. The dynamics of decrease and dynamics after the T-Cell - APC disconnection are unknown.

If the amount of the TCRs is designated by $x$ then, without any restriction, we can say that for each discrete state $i$ the TCR dynamics are given by

$$\dot{x}(t) = f((x,i),t) \tag{1}$$

With the assumption that TCR dynamics depends only on $x$ we have

$$f((x,1),t) = 0;\ f((x,2),t) = f_2(x);\ f((x,3),t) = f_3(x) \tag{2}$$

The overall T-Cell dynamics regarding to the TCR triggering mechanism can be described by discrete states, transitions between discrete states and continuous dynamics of TCRs in each discrete state. This kind of dynamical systems are called Hybrid Automata. The proposed Hybrid Automaton model which describes T-Cell dynamics, designated as T-Cell Micro Agent is depicted in Fig. 2. The prefix "Micro" is used because this model describes the population behavior at the micro level, i.e., at the level of the individual behavior.

## IV. Micro Agent Individual Model

A Micro Agent is a single-input multi-output hybrid system. The input to a Micro Agent is a continuous time discrete event sequence. The output of a Micro Agent is a continuous time real vector. The output of a Micro Agent is a function of the hybrid system state. This hybrid system state is a function of the discrete event time sequence at the system input.

*Definition 1* [6]. A hybrid automata H is a collection H=(Q,X,Init, f, Inv, E, G, R) where:

- $Q$ is a finite set of discrete states (1)
- $X$ is $R^n$ the continuous state space (2)
- $Init \subseteq Q \times X$ is the set of initial states (3)
- $f : Q \times X \to TX$ assigns to each $q \in Q$ a vector field $f(x,q)$ (4)
- $Inv : Q \to 2^X$ assigns to each $q \in Q$ an invariant set (5)
- $E \subseteq Q \times Q$ is a collection of discrete transitions (6)
- $G : E \to 2^X$ assigns to $e \in E$ a guard set, representing the collection of the discrete transitions allowed by the state vector (7)
- $R : X \times E \to 2^X$ assigns to $e \in E$ and $x \in X$ a reset map, describing jumps in the continuous state space due to event $e$. (8)

*Definition 2.* A Micro Agent $\mu A$ is a single-input multi-output hybrid automaton. It is a collection $\mu A = (H, U, \tau, Y)$ where:

- $H$ is a Hybrid automaton (9)
  $H = (Q, X, Init, f, Inv, E, G, R)$ satisfying properties:
  - $Inv : X, \forall Q$ (10)
  - $R(e,x),\ \forall(e \in E \wedge x \in X)$ (11)
- $U$ is a finite set of input discrete events including the *nil* event $\varepsilon$ (12)
- $\tau : U \times Q \to E$, assigns to the discrete event $u \in U$ and discrete state $q \in Q$ the transition $e = (q, q') \in E$, (13)
  where $\tau(\varepsilon, q) = (q, q)$
- $X$ is $R^n$, the state space of the continuous piece of $H$ (14)
- $Y$ is $R^m$, is the output state, a $\mu A$ output $y \in Y$ is a function of the continuous state $x$, $y = g(x)$ (15)

*Remark1.* The Micro Agent state, called micro state, is a pair $(x,q) \in X \times Q$. This couple consists of continuous $x \in X$ and discrete state $q \in Q$ parts.

Properties (10) and (11) in Definition 2 mean that, for hybrid system H, discrete and continuous dynamics could evolve in a free manner. However, jumps in the continuous state space part are not allowed. It should also be underlined that a Micro Agent is a *deterministic* system.

The individual T-Cell Micro Agent is presented in Fig. 2. The continuous dynamics over the discrete states are given by (2). The Function which defines the output in this case is $g(x) = x$. It means that the value of the output $y$ is the amount of the TCRs, which is also the state variable $x$.

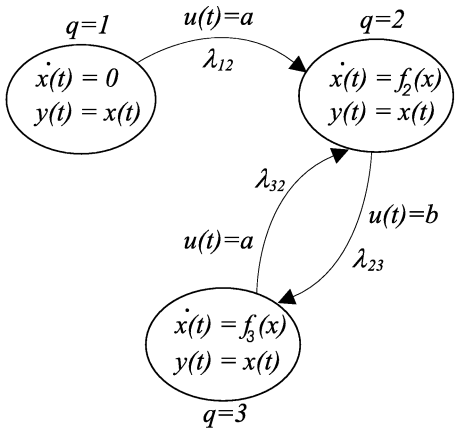


Fig. 2. The graphical description of the T-Cell Micro Agent model (definition includes discrete states and input events) and the T-Cells population Stochastic Micro Agent model (definition includes discrete states, input events and event rates) under the light of the TCR triggering phenomenon. Discrete states: 1-*never connected*, 2-*connected*, 3-*disconnected*. Continuous state: $x$- TCRs amount. Input events $u$: *a-connection*, *b-disconnection*. Event rates: $\lambda_{ij}$-event rate that creates transition from $i$th to $j$th discrete state. Output: $y$- TCRs amount

## V. Stochastic Micro Agent

The Micro Agent model is deterministic since it is based on a deterministic Hybrid System. Here, a Stochastic Micro Agent model will be introduced.

*Definition 3* [8]. (Micro Agent Stochastic Execution) A stochastic process $(x(t), q(t)) \in X \times Q$ is called a *Micro Agent Stochastic Execution* iff a Micro Agent stochastic input event sequence $e(\tau_n)$, $n \in N$, $\tau_0 = 0 \leq \tau_1 \leq \tau_2 \leq \dots$ generates transitions such that in each interval $[\tau_n, \tau_{n+1})$, $n \in N$, $q(t) \equiv q(\tau_n)$.*Remark 1.* The $x(t)$ of a Stochastic Execution is a continuous time function since the transition changes only the discrete state of a Micro Agent.

*Definition 4.* (Micro Agent Continuous Time Markov Process Execution) A Micro Agent Stochastic Execution $(x(t), q(t)) \in X \times Q$ is called a Micro Agent Continuous Time Markov Process Execution iff the input stochastic event sequence $e(\tau_n)$, $n \in N$, $\tau_0 = 0 \leq \tau_1 \leq \tau_2 \leq \dots$ generates transitions whose conditional probability satisfies: $P[q(\tau_{k+1}) = q_{k+1} | q(\tau_k) = q_k, q(\tau_{k-1}) = q_{k-1}, \dots q(\tau_0) = q_0] = P[q(\tau_{k+1}) = q_{k+1} | q(\tau_k) = q_k$. *Remark 1.*The $q(t)$ of a Micro Agents Continuous Markov Process Execution is a Continuous Time Markov chain.

*Definition 5.* (Stochastic Micro Agent, $S\mu A$) A Stochastic Micro Agent is a pair $S\mu A = (\mu A, e(t))$, where $\mu A$ is a Micro Agent and $e(t)$ is a Micro Agent stochastic input event sequence such that the stochastic process $(x(t), q(t)) \in X \times Q$ is a Micro Agent Stochastic Execution.

*Definition 6.* Continuous Time Markov Process Micro Agent, $CTMP\mu A$. A Stochastic Micro Agent is called a Continuous Time Markov Process Micro Agent iff $(x(t), q(t)) \in X \times Q$ is a Micro Agent Continuous Time Markov Process Execution.

Previous definitions were aimed at making clear that a Stochastic Micro Agent is a Stochastic Hybrid Automaton based on a Micro Agent, which is a deterministic system. In the sequel, a Stochastic Micro Agent will be used as a model of Micro Agents populations.

The T-Cell population $CTMP\mu A$ derived from T-Cell Micro Agent is presented in Fig. 2. The graphical presentation of this stochastic model is composed from Micro Agent presentation and event transition rates.

## VI. Mathematical Analysis

The connection between the individual micro dynamics and the population macro dynamics is strongly related to statistical physics [9] where behavior and properties of mechanical bodies, made up of a very large number of separate particles, are studied. In this framework the connection between the micro and macro dynamics is established through the probability density function (pdf) of system particles over a state space.

Concerning the Micro Agent population we assume that:
- *The interaction between individuals is modelled as a Micro Agent* (16)
- *The complexity of the interactions among individuals in the population produces the Micro Agent Stochastic Execution of a Micro Agent in the population.* (17)

The previous assumptions bring us directly to similar problems in statistical physics and the following conclusion: *The individual Micro Agent dynamics and the dynamics of the Micro Agents population measurements are connected through the probability density function of a Stochastic Micro Agent state which represents the population state.*

Different kinds of Stochastic Micro Agents could be considered. In sequel we will interested in $CTMP\mu A$s. The following theorem concerns the probability density function of a $CTMC\mu A$ over the state space.

*Theorem 1.* For a $CTMP\mu A$ with $N$ discrete states and discrete state probability satisfying

$$\dot{P}(t) = L^T P(t) \tag{18}$$

where $P(t) = [P_1(t) P_2(t) \dots P_N(t)]^T$, $P_i$ is the probability of discrete state $i$, $L = [\lambda_{ij}]^T_{N \times N}$, is transition rate matrix and $\lambda_{ij}$ is a transition rate from discrete state $i$ to discrete state $j$, the vector of state probability density functions $\rho(x,t) = [\rho((x,1),t), \rho((x,2),t), \dots, \rho((x,N),t)]^T$ where $\rho((x,i),t)$ is the pdf of state $(x,i)$ at time $t$, satisfies the following equation:

$$\frac{\partial \rho(x,t)}{\partial t} = L^T \rho(x,t) - \begin{bmatrix} \nabla(f(x,1)\rho((x,1),t)) \\ \nabla(f(x,2)\rho((x,2),t)) \\ \vdots \\ \nabla(f(x,N)\rho((x,N),t)) \end{bmatrix} \tag{19}$$

where $f(x,i)$ is the vector field value at state $(x,i)$.

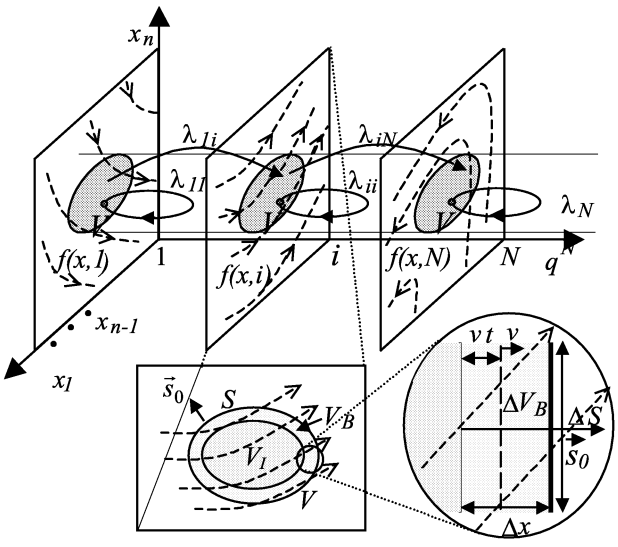


Fig. 3. Possible trajectories in the Micro Agent state space: $x_i$-state of continuous space, $q$-state of discrete space, $f(x,i)$- vector field for $q = i$, $V$-trajectory volume, $V_I$-volume of trajectories not crossing the surface $S$ in the time interval $[t, t + \Delta t)$, $V_B$ - volume of trajectories crossing surface $S$ in the time interval $[t, t+\Delta t)$, $\Delta V_B$ - element of the volume $V_B$, $\Delta S$-element of the surface $S$, $v$-projection of the vector field $f(x,i)$ onto the surface vector $\vec{s}_0$, $\Delta x$-length $v\Delta t$.

*Proof.* The state space $X \times Q$ of the Stochastic Micro Agent is presented in Fig. 2. Transition between the discrete states is a Continuous Time Markov Chain

stochastic process and $x(t)$ is a continuous time function i.e. $x(t^-) = x(t^+) = x(t)$. The probability $p_{V,i}$ that Micro Agent state $(x,q) \in \{(x,q)|x \in V, q = i\}$ is given by

$$p_{V,i} = \int_V \rho((x,i),t)dV \tag{20}$$

where $\rho(x,i)$ is the probability density function of the state $(x,i)$ and arbitrary chosen volume $V$ in $X$. The time derivative of $p_{V,i}$ is:

$$\dot{p}_{V,i}(t) = \int_V \frac{\partial \rho((x,i),t)}{\partial t} dV \tag{21}$$

Using Fig. 2. the time derivative of $p_{V,i}$ could be written as:

$$\dot{p}_{V,i}(t) = \lim_{\Delta \to 0} \frac{1}{\Delta t} \left[ \Delta p_{V_I} + \sum_{S,\Delta S \to 0} \Delta p_{\Delta S \Delta x} \right] \tag{22}$$

where $\Delta p_{V_I}$ and $\Delta p_{\Delta S \Delta x}$ are probability changes in the volumes $V_I$ and $\Delta V_B = \Delta S \Delta x$, respectively, and $V_B = \sum_{S,\Delta S \to 0} \Delta S \Delta x$. Due to the continuity of $x(t)$

$$\lim_{\Delta t \to 0} \frac{1}{\Delta t} \Delta p_{V_I} = \sum_{k=1}^{N} \lambda_{ki} \int_{V_I} \rho(x,i) dV \tag{23}$$

since, in the time interval $[t, t+\Delta t)$, $x(t)$ does not leave volume $V_I$ and probability in $V_I$ changes due to the Markov Chain transitions. During the same interval, the increase of probability in the volume $\Delta V_B = \Delta S \Delta x$ is

$$\Delta p_{\Delta S \Delta x}(t) = \tag{24}$$
$$-\Delta S \left[ \int_t^{t+\Delta t} v\rho((x,i),\tau) + \dot{\rho}((x,i),\tau)(\Delta x - v\tau) d\tau \right]$$

where $x \in \Delta V_B$. Taking into account the Markov Chain transitions in the volume $\Delta V_B$ and equation (23) we have

$$\lim_{\Delta t \to 0} \frac{\Delta p_{\Delta S \Delta x}(t)}{\Delta t} = -\Delta S v \rho((x,i),\tau) + \Delta x \sum_{k=1}^{N} \lambda_{ki} \rho((x,k),t) \tag{25}$$

Substituting (23) and (25) in (22) gives

$$\dot{p}_{V,i}(t) = \sum_{k}^{N} \lambda_{ki} \int_{V_I} \rho(x,i) dV + \tag{26}$$

$$+ \sum_{\Delta S, \Delta S \to 0} \left[ -\Delta S v \rho((x,i),t) + \Delta S \Delta x \sum_{k=1}^{N} \lambda_{ki} \rho((x,k),t) \right]$$

i.e.

$$\dot{p}_{V,i}(t) = \sum_{k=1}^{N} \lambda_{ki} \int_V \rho(x,i) dV - \oint_S f(x,i) \rho((x,i),t) dS \tag{27}$$

With the use of Gauss' theorem we have:

$$\dot{p}_{V,i}(t) = \int_V \left[ \sum_{k=1}^{N} \lambda_{ki} \rho(x,i) - \nabla(f(x,i)\rho((x,i),t)) \right] dV \tag{28}$$

Taking the small volume limit of the equations (21) and (28) we have

$$\frac{\partial \rho((x,i),t)}{\partial t} = \sum_{k=1}^{N} \lambda_{ki} \rho(x,i) - \nabla(f(x,i)\rho((x,i),t)) \tag{29}$$

Using $\rho(x,t) = [\rho((x,1),t), \rho((x,1),t), \ldots, \rho((x,N),t)]^T$ the equation system (29) becomes

$$\frac{\partial \rho(x,t)}{\partial t} = L^T \rho(x,t) = \begin{bmatrix} \nabla(f(x,1)\rho((x,1),t)) \\ \nabla(f(x,2)\rho((x,2),t)) \\ \vdots \\ \nabla(f(x,N)\rho((x,N),t)) \end{bmatrix} \tag{30}$$

Q.E.D

Equation (19) is an extension of the Liouville's equation [9] and fundamentally it is a conservation law for the pdf over the state space. This hyperbolic partial differential equation is in the form of a Convection-Diffusion equation [10], which is used for description of incompressible fluids. The solution of this equation is the pdf of $CTMP\mu A$ state as a function of time. A numerical method for solving this equation is discussed in [10].

## VII. Model Test Based on Experimental Data

The study of the TCR triggering motivated the Micro Agent model development. In Section IV we proposed the T-Cell Micro Agent model (Fig.2.) based on a biological facts. In this section the theoretically predicted TCR distribution will be matched to experimental data.

The basis for this analysis is the experimental data [1]. The experiment shows that after a time long enough the TCRs distribution stays unchanged [1]. This constant distribution will be designated in the sequel by *steady state* distribution. According to the stochastic approach, if the TCRs distribution is normalized in such a way that integral of the distribution is equal to 1, the normalized TCRs distribution should be equal to the T-Cell $CTMP\mu A$ pdf of the output (Definition VI).

Let assume that the transition rates of proposed T-Cell Micro Agent model $\lambda_{12}, \lambda_{23}, \lambda_{32}$ are constant and:

$$f((x,1),t) = 0;\ f((x,2),t) = f_2(x);\ f((x,3),t) = f_3(x) \tag{31}$$

due to the reasons already explained in Section III. The equation which describes the evolution of the pdf over the $CTMP\mu A$ state space (Theorem 1) is given by:

$$\frac{\partial \rho_1}{\partial t} = -\lambda_{12}\rho_1 - \nabla(f_1\rho_1) \tag{32}$$

$$\frac{\partial \rho_2}{\partial t} = \lambda_{12}\rho_1 - \lambda_{23}\rho_2 + \lambda_{32}\rho_3 - \nabla(f_2\rho_2) \tag{33}$$

$$\frac{\partial \rho_3}{\partial t} = \lambda_{23}\rho_2 - \lambda_{32}\rho_3 - \nabla(f_3\rho_3) \tag{34}$$

where $\rho_i = \rho((x,i),t)$. Since the output $y = x$, the pdf of the $CTMP\mu A$ output $\eta(x,t)$ is given by

$$\eta(x,t) = \rho_1 + \rho_2 + \rho_3 \tag{35}$$

Taking the limit, $t \to \infty$, the steady state of (32)-(34) is:

$$\begin{aligned} 0 &= -\lambda_{12}\rho_1^s - \nabla(f_1\rho_1^s) && (36)\\ 0 &= \lambda_{12}\rho_1^s - \lambda_{23}\rho_2^s + \lambda_{32}\rho_3^s - \nabla(f_2\rho_2^s) && (37)\\ 0 &= \lambda_{23}\rho_2^s - \lambda_{32}\rho_3^s - \nabla(f_3\rho_3^s) && (38) \end{aligned}$$

where $\rho_i^s = \rho_i^s(x)$. Since $f_1 = 0$ we can conclude that $\rho_1^s(x) = 0$ and transform the system of equations (36)- (37) to the equivalent one:

$$\begin{aligned} 0 &= -\lambda_{23}\rho_2^s + \lambda_{32}\rho_3^s - \nabla(f_2\rho_2^s) && (39)\\ 0 &= \nabla(f_2\rho_2^s + f_3\rho_3^s) \Leftrightarrow f_2\rho_2^s + f_3\rho_3^s = const && (40) \end{aligned}$$

Since the functions $\rho_i^s$ are pdf*s* then $\rho_i^s(x) \geq 0$, $\forall x \in R$. The number of TCRs can not be negative, thus exists a point $x^0 \in R$ where $\rho_2^s(x^0) = \rho_3^s(x^0) = 0$, and the system of equations (39)-(40) becomes:

$$\begin{aligned} 0 &= -\lambda_{23}\rho_2^s + \lambda_{32}\rho_3^s - \nabla(f_2\rho_2^s) && (41)\\ 0 &= f_2\rho_2^s + f_3\rho_3^s && (42) \end{aligned}$$

After substituting $\rho_3^s(x) = \eta^s(x) - \rho_2^s(x)$, the solution for the steady state of equations (32)-(35) is equivalent to the solution of the following differential equation:

$$\frac{d\eta^s}{dx} = -\left[\left(\frac{f_3 - f_2}{f_3 f_2}\right)^{-1}\frac{d}{dx}\left[\frac{f_3 f_2}{f_3 - f_2}\right] + \frac{\lambda_{23}}{f_2} + \frac{\lambda_{32}}{f_3}\right]\eta^s \tag{43}$$

The solution of this equation is:

$$\eta^s(x) = c\left(\frac{1}{f_3(x)} - \frac{1}{f_2(x)}\right)e^{-\int\left(\frac{\lambda_{23}}{f_2(x)} + \frac{\lambda_{32}}{f_3(x)}\right)dx} \tag{44}$$

where $c$ has a value such that $\int_\infty^\infty \eta^s(x)dx = 1$. The equation (44) is the steady state pdf of the T-Cell $CTMP\mu A$ and defines the shape of the TCRs distribution. This result is very important because it shows that TCRs distribution contains information about TCR triggering dynamics.

In Figure 4a, experimental data [1] of initial $\eta_(x,0)$ and steady state $\eta_{exp}^s(x)$ distribution of TCRs over the T-Cell population are *approximated by log-normal* distributions:

$$\begin{aligned} \eta(x,0) &= \frac{1}{2\sigma_0 x\sqrt{(\pi)}}e^{-\frac{(M_0 - ln(x))^2}{2\sigma_0^2}} && (45)\\ \eta_{exp}^s(x) &= \frac{1}{2\sigma_\infty x\sqrt{(\pi)}}e^{-\frac{(M_\infty - ln(x))^2}{2\sigma_\infty^2}} && (46) \end{aligned}$$

where $M_0 = log_{10}(100)$, $\sigma_0 = 0.19$ and $M_\infty = log_{10}(50)$, $\sigma_\infty = 0.27$. In order to match steady state distribution (44) to equation (46) we will make the first derivatives in the exponent equal:

$$\frac{\lambda_{23}}{f_2(x)} + \frac{\lambda_{32}}{f_3(x)} = \frac{d}{dx}\frac{(ln(x) - M_\infty)^2}{2\sigma_\infty^2} \tag{47}$$

After differentiation in (47) we have:

$$\frac{\lambda_{23}}{f_2(x)} + \frac{\lambda_{32}}{f_3(x)} = -\frac{M_\infty}{\sigma_\infty^2}\frac{1}{x} + \frac{1}{\sigma_\infty^2}\frac{ln(x)}{x} \tag{48}$$

The solution of the equation (48) includes $1/x$ and $ln(x)$ functions and is not unique. The solution should take into account that $f_2$ describes the decrease of the TCRs, so we should have $f_2(x) < 0, \forall x > 0$. For the same reason $f_3 > 0, \forall x > 0$, since it describes an increase of TCRs. Following the idea that increase and decrease dynamics follows different dynamical shape one possible solution is

$$\begin{aligned} f_2(x) &= -k_2 x && (49)\\ f_3(x) &= k_3\frac{x}{ln(x)} && (50) \end{aligned}$$

where

$$k_2 = \frac{\sigma_\infty^2\lambda_{23}}{M_\infty}, k_3 = \sigma_\infty^2\lambda_{32} \tag{51}$$

The previous relations show that the micro dynamics parameters $k_2$ and $k_3$ functionally depend on the *connection* and *disconnection rates*, $\lambda_{32}$ and $\lambda_{23}$, respectively. If the rate of disconnection is bigger, then the decreasing rate of TCR, $k_2$ should be bigger, i.e., TCR triggering interaction should be more efficient. Similar conclusions can be made about parameter $k_3$. This functional dependence has been recently reported and some optimal value hypothesis is suggested [11].

Besides the steady state values, the experimental data [1] contains also the time record of the average value of TCRs during the experiment (Fig. 5.). Taking into account biological fact that decrease dynamics rate of the TCRs is much bigger than increase dynamics rate we assumed

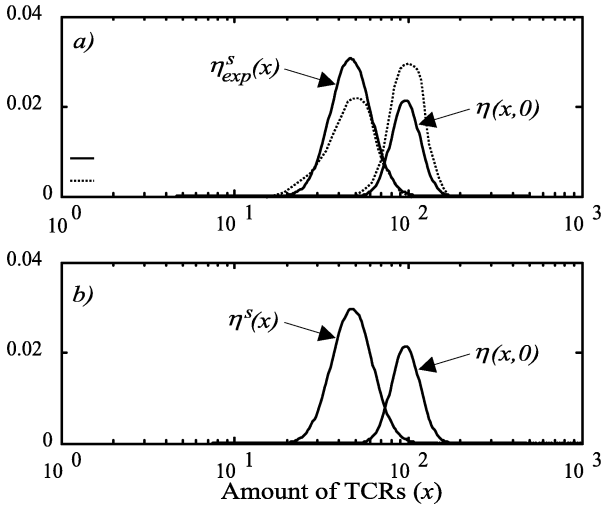


Fig. 4. Normalized TCRs distributions: *a)* Experimental data: *dotted* - non-normalized smoothed experimental data for initial(right) and steady state(left) distribution, $\eta(x,0)$ - log-normal approximation of initial distribution($N_{log}(log_{10}(100), 0.19)$), $\eta_{exp}^s(x)$ - log-normal approximation of steady state distribution ($N_{log}(log_{10}(50), 0.27)$). *b)* The model predicted steady state distribution $\eta^s(x)$.

$k_2 \simeq 100k_3$. To predict the TCR distribution the following parameters are chosen:

$$\lambda_{12} = \lambda_{32} = 7, \lambda_{23} = 7000, M_\infty = log_{10}(50), \sigma_\infty = 0.27 \quad (52)$$

Predicted steady state TCRs distribution $\eta^s(x)$ and average value $\overline{\eta}^s(t)$ are presented in Fig. 4b and Fig. 5., respectively.

We can see that T-Cell $CTMP\mu$A predicts steady state TCRs distribution (Fig. 4b) which, for the given parameters, could not be distinguished from the log-normal distribution $\eta^s_{exp}(x)$ which approximates the *non-normalized* experimental steady state distribution (Fig.4a, *dotted*), and differs slightly from the later. The predicted average values fit well the experimental average values as well. From the previous we can conclude that proposed T-Cell Micro Agent model produces meaningful results.

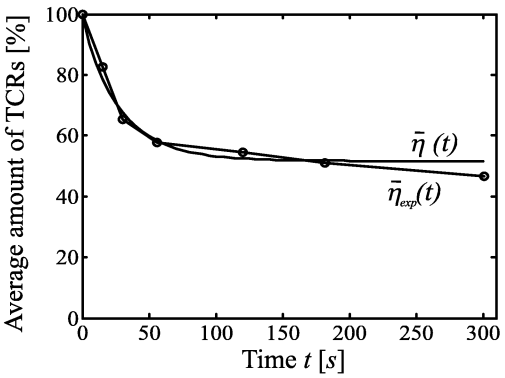


Fig. 5. Average amount of TCRs (relative to the initial TCRs amount): $\overline{\eta}_{exp}(t)$-experimentally obtained values (o), $\overline{\eta}^(t)$-the model predicted average values

## VIII. Conclusions

In this paper the T-Cell Receptors triggering mechanism is studied. Each T-Cell is described by deterministic Micro Agent model, which is defined in the Hybrid Automata framework. Under a stochastic assumption about the Micro Agent input event sequence the Stochastic Micro Agent model of T-Cell population is introduced. The relation between the deterministic model Continuous Markov Chain stochastic event sequence and the pdf of the Stochastic Micro Agent state is derived. Using this analytical relation the proposed T-Cell Micro Agent model is tested against the experimental data, and close agreement was found.

Potential future work along this research line includes a test of the proposed model using experimentally obtained statistics of stochastic event sequence. The initial and steady state distribution could be more carefully studied using better approximations or including hypothesis about the TCRs dynamics in the absence of APCs. The theory presented here could be used to have more insight in other biological phenomena and planing biological experiments. We have also been using it to model and stochastically control large populations of robots [12].

## Acknowledgments

This work was supported by grant SHFR/2960/2000 from the Portuguese Fundação para a Ciência e a Tecnologia.

## References

[1] Valitutti, S., Muller, S., Cell, M., Padovan, E., Lanzavechia, A., *Serial triggering of many T cell receptors by a few peptide-MHC complexes* Nature, 1995 375:148-151

[2] Sousa, J., Carneiro J., *A mathematical analysis of TCR serial triggering and down-regulation*, Eur.J.Immuno, 2000, 30:3219-3227

[3] Milutinović, D., Athans, M., Lima, P., Carneiro, J., *Application of Nonlinear Estimation Theory in T-Cell Receptor Triggering Model Identification*, ISR/IST Lisbon, Portugal, 2002, Tecnical Report RT-401-02, RT-701-02

[4] Perelson, A. A., *Immunology for Physicists*, Reviews of Modern Physics, October 1997, Vol. 69, No. 4, 1219-1267.

[5] Kitano, H., *Computational Systems Biology*, accepted for publication in Nature, Nov. 2002.

[6] Schaft A., Schumacher H., *An Introduction to Hybrid Dynamical Systems*, Lecture Notes in Control and Information Sciences 251, Springer 2000.

[7] Rajeev, A., Belta C., Ivancic, F., Kumar, V., Mintz, M., Pappas, G., Rubin, H., Schug, J., *Hybrid Modeling and Simulation of Biomolecular Networks*, HSCC 2001, LNCS 2034, Springer-Verlag 2001.

[8] Jianghai, H., Lygeros, J., Sastry, S., *Towards a Theory of Stochastic Hybrid Systems*, HSCC 2000, LNCS 1790, 160-173, Springer-Verlag 2000.

[9] Landau, L.D., Lifshitz, E.M., *Statistical Physics*, Pergamon Press, 1959

[10] Zienkiewitz, O.C, Taylor, R.L., *The Finite Elemet Method*, Vol.3., Fluid Dynamics, Butterworth- Heinemann, 2000.

[11] Chakraborty, A., *Lighting up TCR takes advantage of serial triggering*, Nature Immunology, 2002, Vol 3, No.10:895-896

[12] Milutinović D., Lima, P., Athans, M., *Biologically Inspired Stochastic Hybrid Control of Multi-Robot Systems*, submitted to the 11th International Conference on Advanced Robotics ICAR 2003, June 30 - July 3, 2003 University of Coimbra, Portugal