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Computational approach of the homeostatic turnover of memory B cells.

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Abstract
In this paper, a discrete mathematical model inspired by control mechanisms is used to explore the factors potentially responsible for maximum immunization capacity in mammals. The results have been discussed in light of recent work, and refer to the adoption of parameter values chosen among data gathered from the literature. The model used in this study took into consideration that the immune system is a network of molecules and cells that can recognize itself.

Key words: B cells, mathematical model, homeostatic turnover,immune memory

I. INTRODUCTION

At the endof the last decade Tarlinton et al. (2008) published a review paper suggesting that the homeostasis of immune memory (control mechanism) can only occur if new cell populations arise over others, i.e., to reach the dynamic equilibrium, some memory cells need to disappear for others to arise, because the immune system has a maximum capacity of stochastic memorization (Abbas et al., 2011; Booer and Oprea, 2001;Bueno and Pacheco-Silva,1999; Dimitrijevic et al., 2004; Etchegoin, 2005; Hendrikxa et al., 2009; Kamradt and Avrion, 2001; Lanzavecchia and Sallusto, 2009;Lima and Carneiro-Sampaio, 1999; Matzinger, 1995; Obukhanych and Nussenzweig, 2006; Peterand Roitt, 2000; Tarlinton et al., 2008; Tizard, 1995; Utzny and Burroughs, 2001; Yao et al., 2006.

Starting from an Ag (antigen)-independent approach, Choo et al. (2010) also reported the same finding; however, these authors have no taking into account the antigen role to suggest that the memory cell memory is stochastic rather than deterministic.In this work is considered a previous network model (Castro, 2012) that takes into account that the mammalian immune system is a chain of molecules and cells that can interact (to learn) with outside elements and, also, recognize itself (Farmer et al., 1986; Hofmeyr, 2000; Jerne, 1974; Klein, 1990; Lederberg, 1988; Perelson and Weisbuch, 1997; Roitt et al., 1998) Starting from an Ag-dependent approach, B cells and antibody populations are treated as a clone pools because their receptors are represented by the same shapes.Thesepatterns are represented by string of bits, σ, and the temporal evolution of the populations is described by the $N(\sigma, t)$ concentration. The model also considers a source term that simulates the role played by the bone marrow, where new bit-strings are presented. The death or depletion of clones occurs by means of a general suppression mechanism represented by a Verhulst-like factor (Ausloos and Dirickx 2006), which is widely used in simulations of biological systems, because it limits the maximum population that can survive in a particular environment.

2. SIMULATION MODEL

The Ag-dependent approach used here considers that the molecular receptors of B cells are represented by bit-strings with 2^B diversity, where B is the number of bits in the strings. The epitopes (Farmer et al., 1986; Jerne, 1974; Mitra-Kaushik et al., 2001; Nayak et al., 2001; Perelson et al., 1978) portions of an antigen that can be connected by the B cell receptor (BCR) , are also represented by bit-strings, even as the antibodies, which receptors (paratopes) (Farmer et al., 1986; Jerne;1974; Mitra-Kaushik et al., 2001; Nayak et al., 2001; Perelson et al., 1978) are represented by the same bit-string pattern as the B cell that produced them. Thus, the entities of the adaptive immune system, such as B cells (clones), antibodies, and antigens, are located at the vertices of hypercubes of size B. In the Fig. 1 is shown an example of cubic spatial arrangement.

The dynamic equation that describes the behavior of the clonal population is shown below:

$$Bcell(\sigma,t+1) = (1 - Bcell(\sigma,t))\left\{m + (1-d)Bcell(\sigma,t) + b\frac{Bcell(\sigma,t)}{POP(t)}\zeta_{ah}(\bar{\sigma},t)\right\}, \quad (1)$$

with complementary shapes included in the term $\zeta_{ah}(\bar{\sigma},t)$,

$$\zeta_{ah}(\bar{\sigma},t) = (1-a)[Bcell(\bar{\sigma},t) + Ag(\bar{\sigma},t) + Ab(\bar{\sigma},t)] + a\sum_{i=1}^{B}[Bcell(\bar{\sigma}_i,t) + Ag(\bar{\sigma}_i,t) + Ab(\bar{\sigma}_i,t)].$$

Here the *POP(t)* term represents the sum of the components that belong to an adaptive subset of the immune system. Such elements are expressed as bit-stringconcentrations.

Therefore, the sum of the adaptive component is given by equation:

$$POP(t) = \sum_{\sigma}[Bcell(\sigma,t) + Ag(\sigma,t) + Ab(\sigma,t)]. \quad (2)$$

The temporal evolution of the 2^B antigen population, starting from an initial condition, $Ag_{initial}$, can be defined by equation below:

$$Ag(\sigma,t+1) = Ag(\sigma,t) - k\frac{Ag(\sigma,t)}{POP(t)}\left\{(1-a)[Bcell(\bar{\sigma},t) + Ab(\bar{\sigma},t)] + a\sum_{i=1}^{B}[Bcell(\bar{\sigma}_i,t) + Ab(\bar{\sigma}_i,t)]\right\}. \quad (3)$$

The antibody population also can be described by a group of 2^B variables interacting with the antigen populations of equations (1) and (3), as following:

$$Ab(\sigma,t+1) = Ab(\sigma,t) + b_A\frac{Bcell(\sigma,t)}{POP(t)}[(1-a)Ag(\bar{\sigma},t) + a\sum_{i=1}^{B}Ag(\bar{\sigma}_i,t)] - k\frac{Ab(\sigma,t)}{POP(t)}\zeta_{ah}(\bar{\sigma},t). \quad (4)$$

whereb_A is the antibody proliferation parameter; and *k* is the parameter related to the antibodies and antigens that will be removed.

In this iterative modeling, the antibody proliferation is boosted by the mutual recognition between $Ab(\sigma,t) \Leftrightarrow Ag(\bar{\sigma},t)$, and this same antibody population is regulated by the following interaction:

In all cases, $\frac{Ag(\sigma,t)}{POP(t)}$and $\frac{Ab(\sigma,t)}{POP(t)}$factors also help to regulate the antigen and antibody populations, while the $\frac{Bcell(\sigma,t)}{POP(t)}$term is the corresponding factor of clonal regulation involved in the homeostasis (negative feedback) of immunological memory.

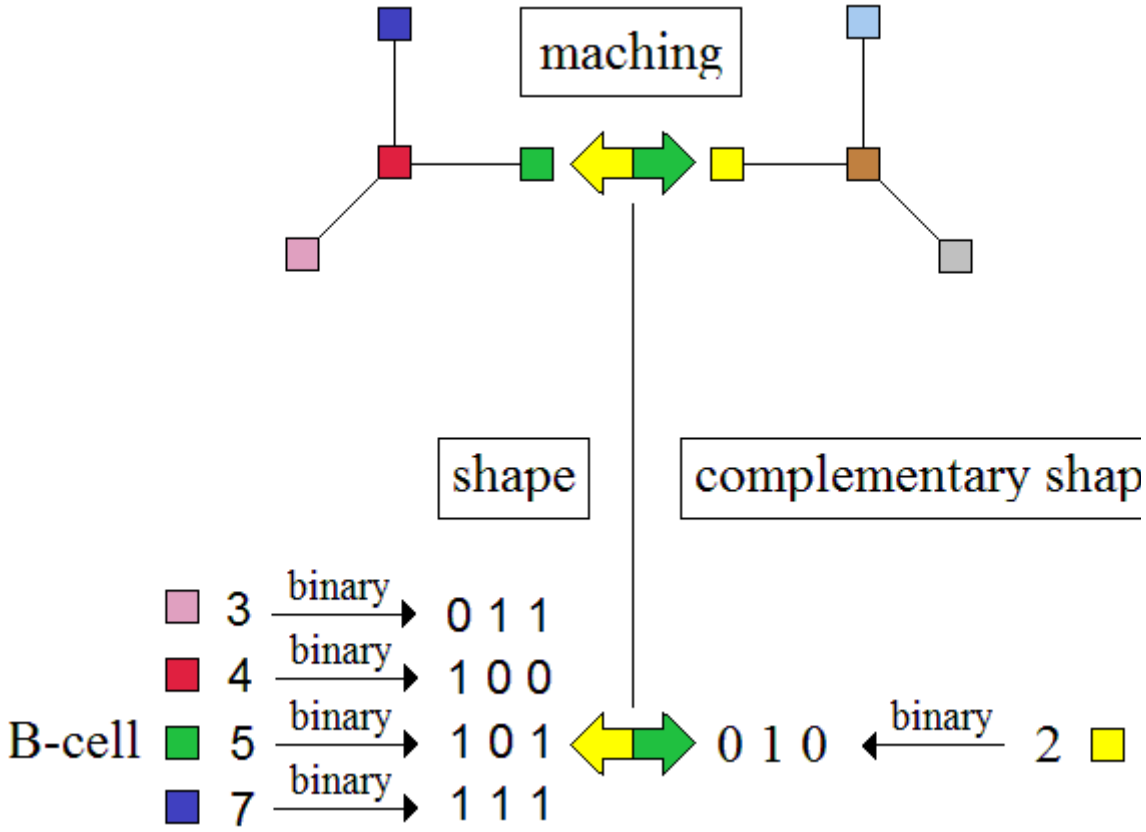


Figure 1 – For a 3-D configuration, the following algorithm describes how to obtain the first neighbors and the complementary shape of the B cell population identified by the integer $\sigma = 4$. For *B*=3, there is a repertoire containing 2^B = 8 integer numbers arranged in the vertices of the cube. These integer numbers represent the 8 different B cell populations. Each integer, *M*, must be restrained in the interval $0 \leq M \leq 2^B - 1$. From this condition, the smallest value of *M* is equal to 0 and the largest value is equal to 7. Consequently, the shape space, *S*,is equal to {0,1,2,3,4,5,6,7}. To represent the interaction of the lock-and-key type, every cell population, in a cubic configuration, needs to be represented by 8 bit-strings. Namely, for $\sigma = 4$, $\sum_{i=2}^{0} 2^i \, a_i = 2^2 a_2 + 2^1 a_1 + 2^0 a_0 = 4$, where, $a_2 = 1, a_1 = 0$ and $a_0 = 0$. Thus, in this case, the decimal base corresponds to (1 0 0), in binary base. For the other 7 vertices, $\sigma = 0 = (000)$, $\sigma = 1 = (001)$, $\sigma = 2 = (010)$, $\sigma = 3 = (011)$, $\sigma = 4 = (100)$, …, $\sigma = 7 = (111)$. Thereby, for a lock-and-key reaction to occur, there must be another shape $\bar{\sigma}$ that is complementary to $\sigma = 4$, i.e., $\bar{\sigma} = M - \sigma$ [16,21]. Then, $M = 2^B - 1 = 7$ and $\sigma = 4 \rightarrow \bar{\sigma} = M - \sigma = 7 - 4 = 3$, or (0 1 1), in binary base. This complementary shape is, in principle, an antigen population, however, based on Immune Network Theory, B cells also recognize antibodies and other complementary lymphocytes (Farmer et al., 1986; Heyman, 2000; Jerne ,1974; Mitra-Kaushik et al., 2001; Nayak et al., 2001; Perelson et al., 1978). Lastly, a search for the first neighbors of the complementary shape $\bar{\sigma} = 3$ is done, starting from $\sigma_i = (2^i - 1X0R\sigma)$ $\sigma_i = (2^i - 1X0R\sigma)$(De Boer et al., 2001; Lagreca et al., 2001). So, for *B* = 3 (i = 1,2,3), one obtains $\sigma_1 = (2^1 - 1X0R3) = 2\ (0\ 1\ 0)$, $\sigma_2 = (2^2 - 1X0R3) = 0\ (0\ 0\ 0)$, $\sigma_3 = (2^3 - 1X0R3) = 4\ (1\ 0\ 0)$. Accordingly, in this example, a B cell population identified by $\sigma = 4$ or (1 0 0) would have recognized an antigen population that is perfectly complementary that is identified by $\bar{\sigma} = 3$ (0 1 1). The antigen populations identified as the first neighbors for $\bar{\sigma} = 3$ are 0, 2 and 4, and can also be recognized by the $\sigma = 4$, depending on the value of the connectivity parameter (a) that appears in equations (1)-(4).

II. RESULTS

In this section, it is presented the dynamics used in the *in silico* experiments. To simulate the behavior of the immune system, it was developed a computational application in the Fortran programming language. The source codes were compiled with GFortran (GNU Fortran Compiler) on a Linux Operating System platform.

3.1 MODEL PARAMETERS

The following table shows the parameters used in simulations.

Table 1- Parameters used in the proposed model.

Symbol	Function	Value used in the model	Information obtained from the literature
d[1]	Apoptosis	0.99	De Boeret al.(2001): 0.95 Buenoand Pacheco-Silva(1999):0.95Lima and Carneiro-Sampaio(2007): d>0.95 $d > 0.95$
m[2]	Source term	10^{-7}	Monvel and Martin (1995): $m \approx 0.0$
b[3]	Clonal proliferation	2.0	De Boer et al. (2001): 2.5-3.0 Utznyand Burroughs (2001): 2.0 von Laer et al. (2008): 1.2
k[4]	Removal of antibodies and antigens	0.1	von Laer et al. (2008): 0.01-0.1
a[5]	Connectivity	0.01	Perelson et al. (1978): 0.01
B[6]	Bit-string length	12	Lagreca et al. (2001): 12

[1]Here, d represents the fraction of cells that is subjected to natural death (apoptosis); thus $s + d = 1$, where $s = 1 - d$ is the fraction of cells that avoids apoptosis. In the literature, the apoptosis of lymphocytes is typically assumed to occur in percentages not less than 95% (De Booer et al., 2001; Lima and Carneiro-Sampaio (2007). For the simulations developed in this study, the natural death parameter was fixed at 0.99 (99%). To give an idea of the effect of varying this parameter, the performances of the model for two different apoptotic events and for the first inoculation antigen were compared.

[2]The source term *m* simulates the stochastic behavior of the bone marrow in the production of new lymphocytes (Lagreca et al., 2001; Monvel and Martin, 1995). In the model described in this work, if the pseudo-random number generator returns a value less than or equal to 0.1, the source term takes the value $m = 10^{-7}$, because *m* is experimentally small compared with the levels of lymphocytes produced in the immune response (Monvel and Martin, 1995;Von Laer et al., 2008; Walker et al., 1998). If the generator returns values greater than $p = 0.1$, the source term takes the value $m = 0.0$ (Lagreca et al., 2001).

[3]Both the pioneering work and the recent work in the literature on theoretical immunology present results on the dynamics of the immune system and the search for attractors of the fixed point type to determine *in machine* clonal homeostasis (equilibrium) in the virgin state (antigen without inoculation) and in the excited state (when an antigen is recognized by some clonal population) (Antia et al., 2000; Etchegoin, 2005; Monvel and Martin, 1995). The condition $Ag = Ab = 0$ is satisfied when the virgin state of the immune system is considered, i.e., without the presentation of antigens, no antibodies are produced. Also, considering that the system only allows high-affinity connections (connections between perfectly complementary shapes), the connectivity factor $a = 0$.
In the virgin state, the sum total of the immune populations is restricted to B lymphocytes:

$$POP(t) = \sum_{\sigma} [Bcell(\sigma,t) + Ag(\sigma,t) + Ab(\sigma,t)] = \sum_{\sigma} Bcell(\sigma,t)$$

Hence, equation 5 reduces to the following:

$$Bcell(\sigma,t+1) = (1 - Bcell(\sigma,t))\left\{m + (1-d)Bcell(\sigma,t) + b\frac{Bcell(\sigma,t)}{\sum_{\sigma} Bcell(\sigma,t)} Bcell(\bar{\sigma},t)\right\}$$

As in the dynamic simulation used in this work, the virgin state occurs in the interval of 0 to 1000 time steps, and only a pseudo-random number is generated (σ^*). Then,

$$\sum_{\sigma} Bcell(\sigma,t) = Bcell(\sigma,t) = Bcell(\sigma^*,t) = Bcell(t) = Bcell_t \text{ and } Bcell_t = Bcell(\bar{\sigma},t)$$

because, according to Immune Network Theory, for each lymphocyte population, there is another complementary population (Jerne, 1974; Mitra-Kaushik et al., 2001; Nakai and Mitra-Kaushik, 2001). A more detailed explanation can be found in the results section.

Because the bone marrow term in the absence of infection (virgin state of the immune system) is much smaller than the clonal proliferation parameter ($m << b$) (Von Laer et al., 2008; Walker et al., 1998), one obtains:

$$Bcell_{t+1} = [(1-d)Bcell_t + bBcell_t](1 - Bcell_t),$$

$$\text{or} Bcell_{t+1} = [1 - d + b]\, Bcell_t(1 - Bcell_t)$$

Defining $r \equiv 1 - d + b$, the equality results in the following: $Bcell_{t+1} = rBcell_t(1 - Bcell_t)$, a logistic map-type equation). Moreover, for the system under study to evolve to a fixed point, the condition $1 < 1 - d + b < 3$must be satisfied.

Consequently, taking into account an apoptosis parameter equal to$d = 0.99$, the clonal proliferation parameter *b* must be located within the following range: $1 < 1 + b - 0.99 < 3 \Rightarrow 0.99 < b < 2.99$. In the simulations presented in this paper, the clonal proliferation parameter *b* was set to 2.0.

[4]The parameter for the removal of antigens and antibodies, *k*, was set to 0.1 to ensure that the populations of antigens and antibodies decay to zero before the antigen is presented. This procedure, which is adopted for a new antigen, is applied only after the previous antigen has been completely removed (Lagreca et al., 2001; Yao et al., 2006).

In the model presented in this work, the initial antigenic dose ($Ag_{initial}$) was set to study the influence of parameter, b_A, on the immune memory in some simulations. In other simulations, this parameter was set to study the consequences to the memory of varying the antigen dosage. To clarify, the limit value of $b_A = 0.0$corresponds to the model previously proposed by Lagreca et al., (2001). and the limit value of $Ag_{initial} = Ag = 0.0$corresponds to the virgin state of the immune system.

[5]The connectivity parameter used was 0.01, so that 99% of the populations are coupled to their perfect complement, and only 1% of the populations are coupled to the first neighbors of their complement. The quality of the immune response is directly related to the degree of affinity among the elements of the adaptive system (Perelson et al., 1978).

[6]Considering the available hypercube immune populations represented by the model, the length of the bit-string *B* were set at 12. This value corresponds to 2^{12} = 4,096 different antigens.

The role performed by the clonal regulation factor, in addition to helping with the B cell response regulation, is fundamental to the regulation of the memorization ability and clonal homeostasis (Antia et al., 1998; Monvel and Martin, 1995; Vani et al., 2008) The importance of the effect of the clonal regulation factor over immune system memory evolution is shown in Fig. 2. Three distinct situations are possible:

1 - Antibody populations are included in the model (which corresponds to the model

proposed in this work);

2 - Antibody populations are not included in the model (which corresponds to the Lagreca et al. 2001 model);

3 - Memory expansion is not limited by the clonal regulation factor (which corresponds to the results obtained by Etchegoin (2005).

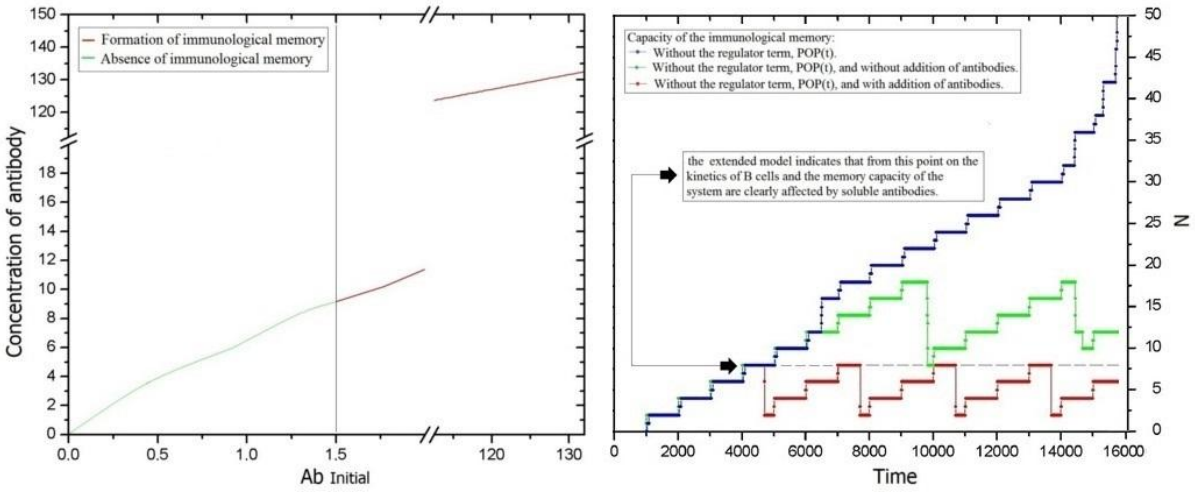


Figure 2 – Capacity of immune system memory in three distinct situations.

Fig. 2 illustrates the situation in which growth capacity increases indefinitely, which is when the clonal regulation factor is suppressed in the modeling phase. This shows that clonal regulation can be fundamental to the immune system reaching clonal homeostasis.

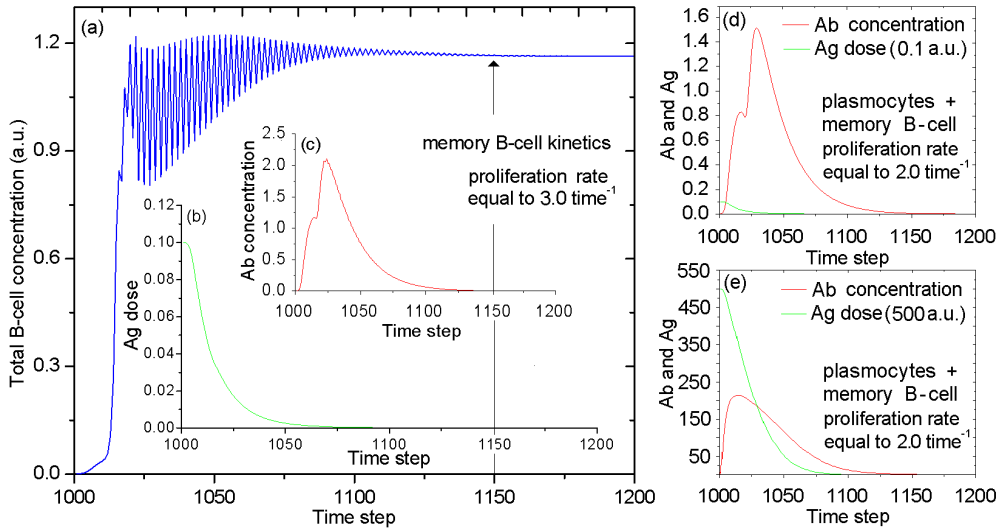


Figure 3 – Evolution of populations of antigens, B lymphocytes, antigens and antibodies with respect to natural death parameter d = 0.99. The virgin state of the system is the range of 0 to 1000. In (a), (b) and (c) the kinetics are shown for a B cell proliferation rate equal to 3.0, the parameter = 100 and initial antigen dosing $Ag_{initial} = 0.1$ In (d) and (e), the proliferation rate is 2.0 and antigen doses are 0.1 and 500, respectively. In (a), from the time step equal to 1150 (after the expansion of B cells) memory cells begin to appear showing that the dynamic behavior of proposed model captures the concept built in the last years what memory B cells are functionally distinct B cell compartment (Hofmeyr, 2000; Roitt et al., 1998).

The evolution curves of antibodies (humoral response) to the antigen doses are presented Figural 4. These results show that for the range of values between0.001 to 0.05, occurs a delay for the humoral response if the initial antigen dosage is small.

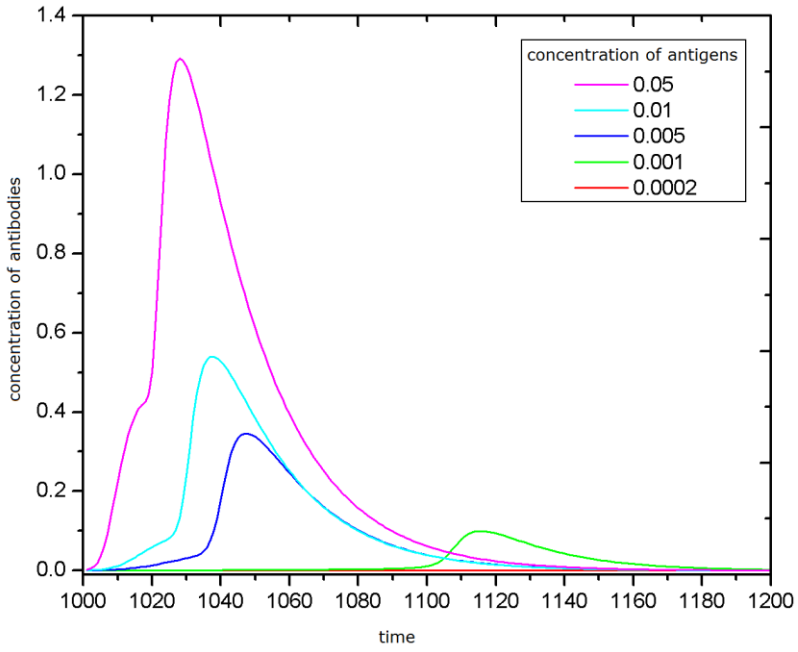
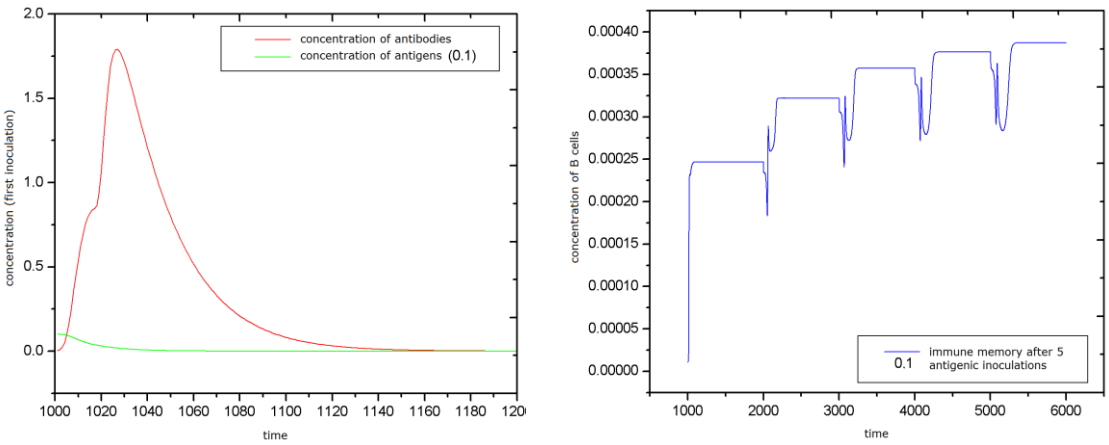
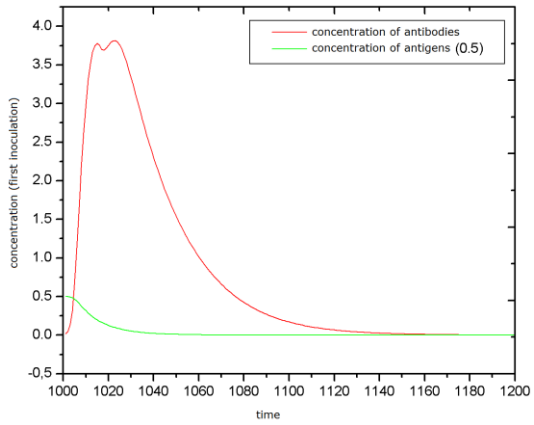
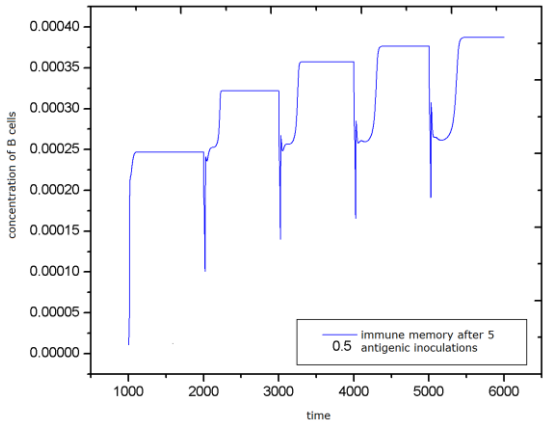


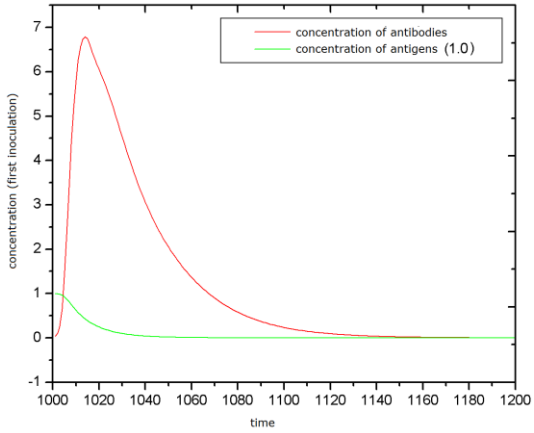
Figure 4 – Developmentsof the humoral responseto low antigenicdosages. The curvesrepresentthe antibody responsetothe firstantigeninoculation.

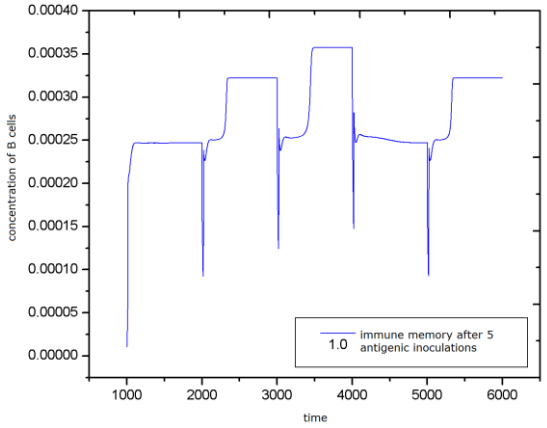
The humoralantigenicchangesindoses from0.1to 100 are presented in Fig. 5. Thisset offiguresshownon the left,the behaviorof populationsof antibodies andantigens for thefirst inoculation. On the rightare shown theevolutionof memory,consideringsimulationsuntil the fifthinoculation.

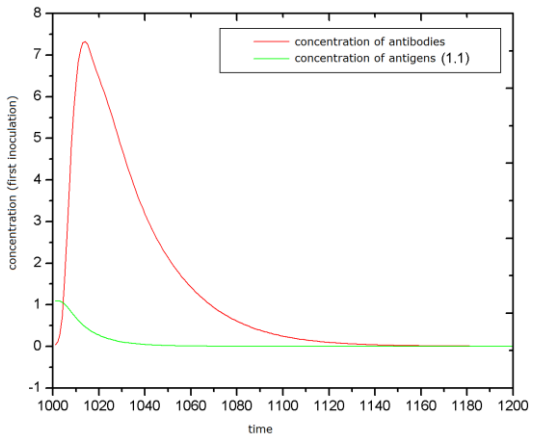


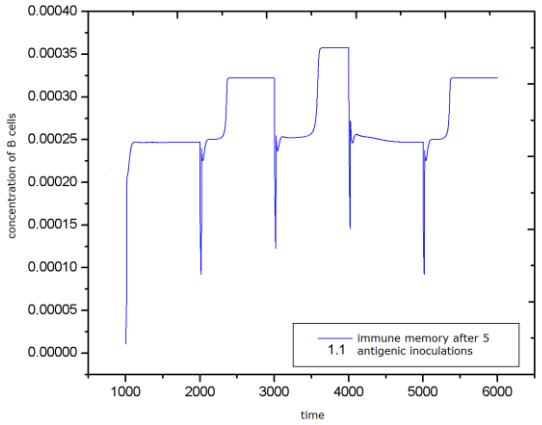

concentration of antibodies
concentration of antigens (0.5)
concentration (first inoculation)
time

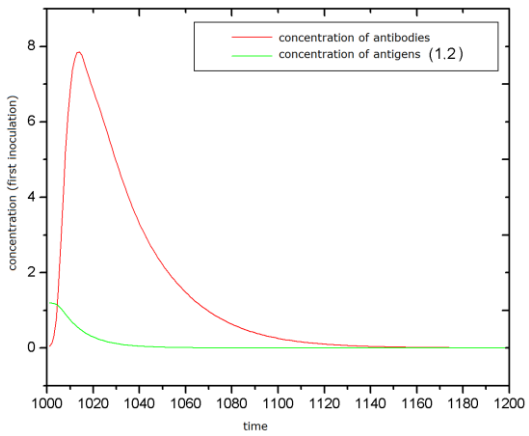

concentration of B cells
immune memory after 5
0.5 antigenic inoculations
time

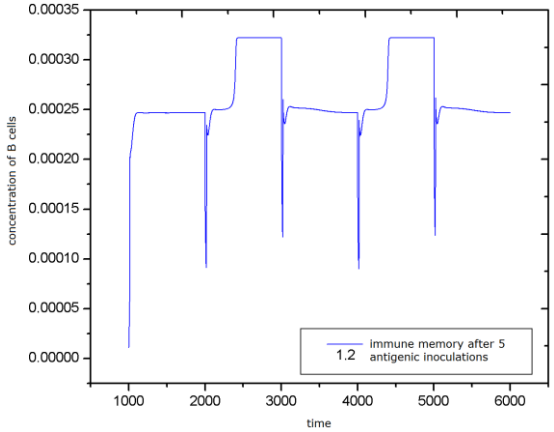

concentration of antibodies
concentration of antigens (1.0)
concentration (first inoculation)
time

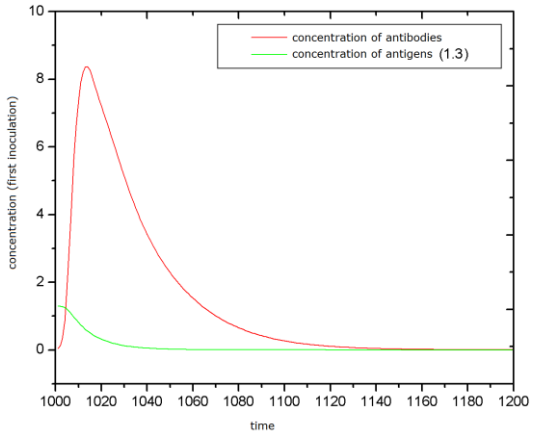

concentration of B cells
immune memory after 5
1.0 antigenic inoculations
time

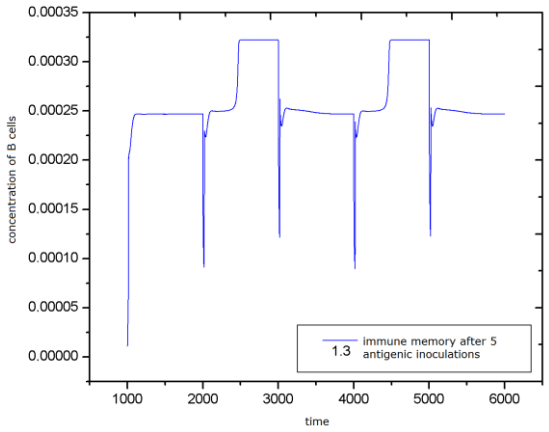

concentration of antibodies
concentration of antigens (1.1)
concentration (first inoculation)
time

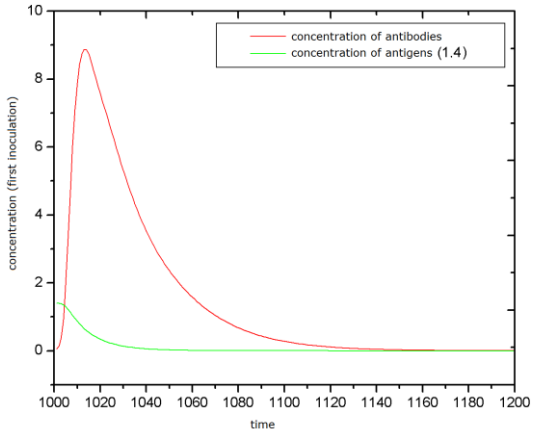

concentration of B cells
immune memory after 5
1.1 antigenic inoculations
time

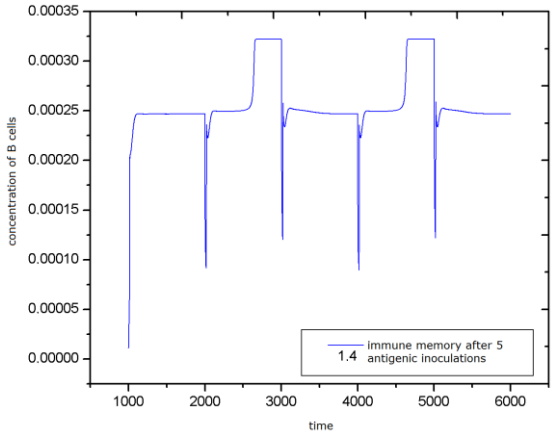

concentration of antibodies
concentration of antigens (1.2)
concentration (first inoculation)
time

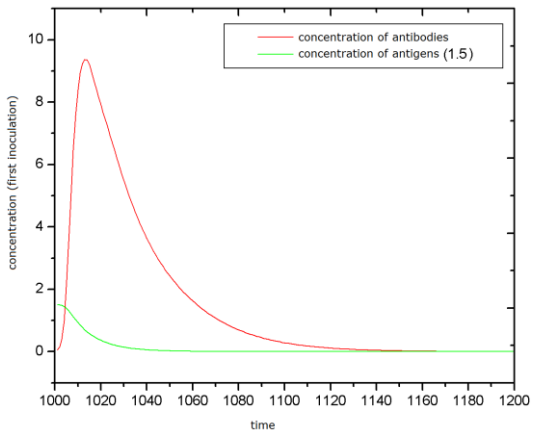

concentration of B cells
immune memory after 5
1.2 antigenic inoculations
time

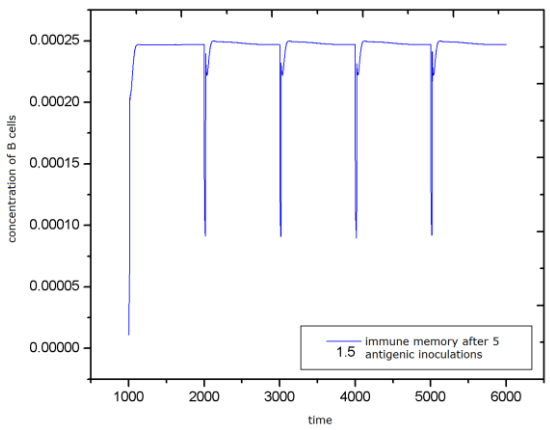

concentration of antibodies
concentration of antigens (1.3)
concentration (first inoculation)
time

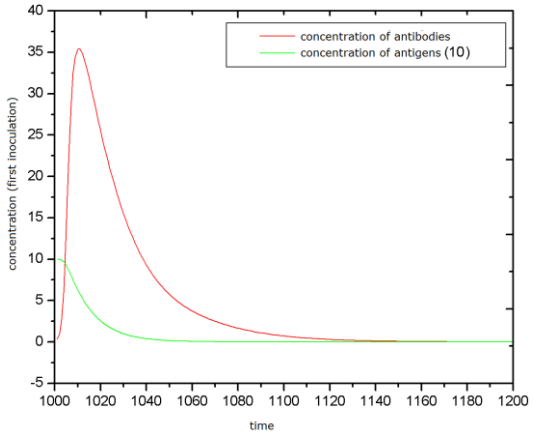

concentration of B cells
immune memory after 5
1.3 antigenic inoculations
time

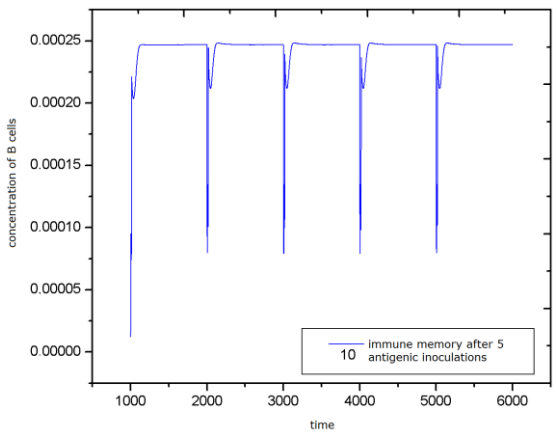

concentration of antibodies
concentration of antigens (1.4)
concentration (first inoculation)
time


concentration of B cells
immune memory after 5
1.4 antigenic inoculations
time


concentration of antibodies
concentration of antigens (1.5)
concentration (first inoculation)
time


concentration of B cells
immune memory after 5
1.5 antigenic inoculations
time


concentration of antibodies
concentration of antigens (10)
concentration (first inoculation)
time


concentration of B cells
immune memory after 5
10 antigenic inoculations
time

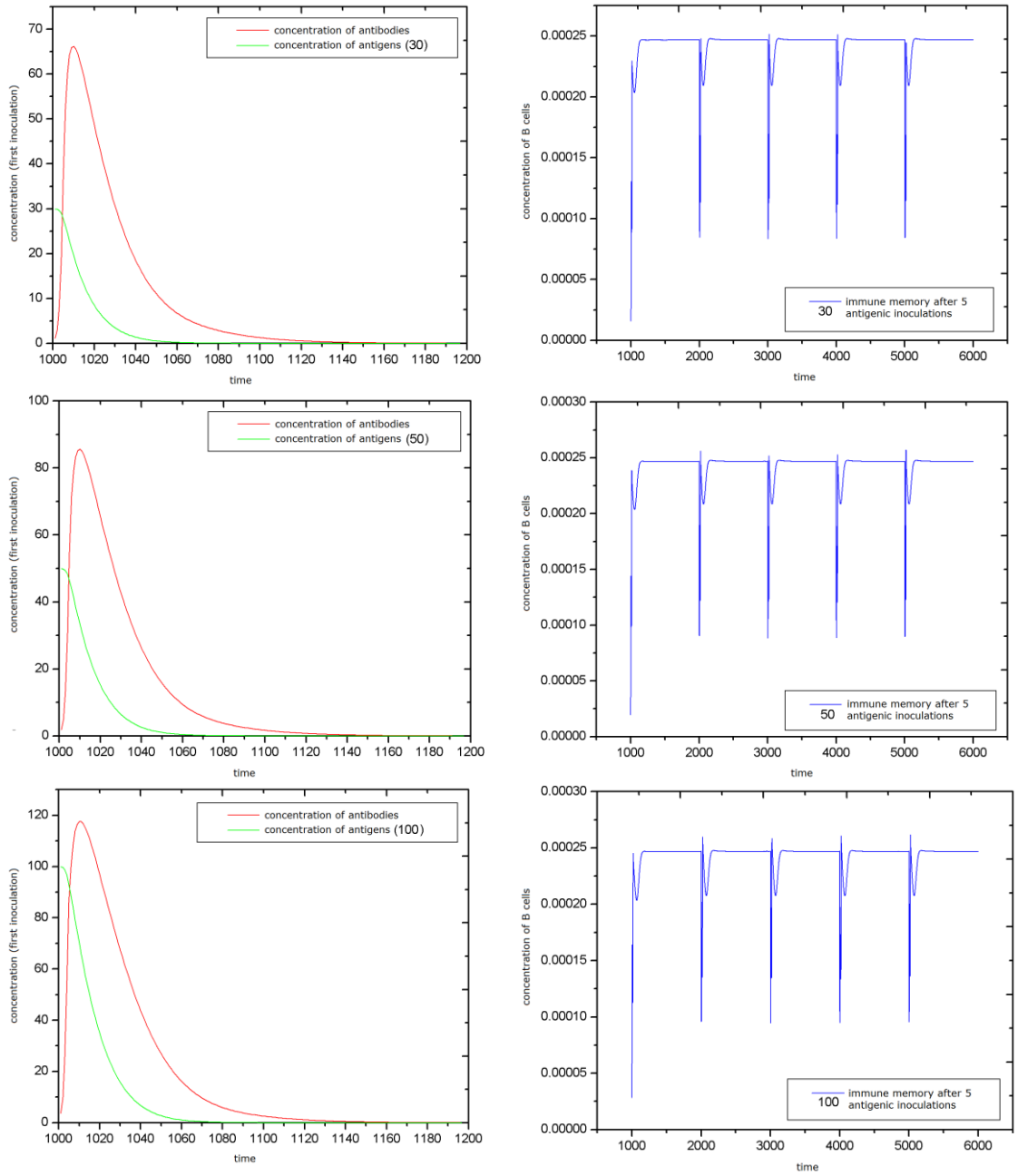


Figure 5 – Set offiguresshowingthe behaviorof populations ofantibodiesand thestorage capacityof the systemaccording to theantigenicdosages.This set ofresultsshows that, until theinitial doseequalto1.0, therememorizationof5inoculatedantigens. From thisinitial dose, the ability to store information abouttheantigenbegins todecrease totheinability to1.5.The results alsoshow that evenreachingtheinability to remember, the system also featuresa state ofimmune competence, as the antibody levelsremainabove theantigeniclevels.

A comparison ofantibody productionand immune competence(or efficiency of the response)from theantigenicdetermination ispresentedin Fig. 6.Results showthat the relationship betweenantibody titerandantigeninitial dosedecreases asthe initial dose ofantigenincreases.

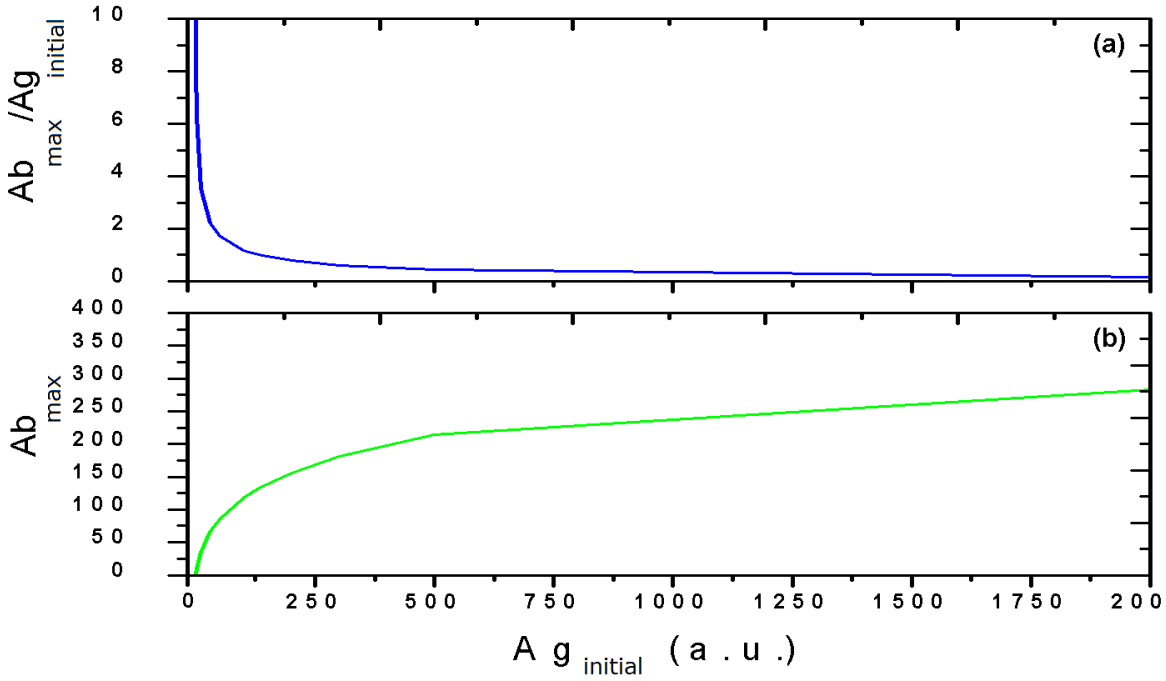


Figure 6 – Relation betweenantibody titersandantigendoses (a) and levels ofantibodies againstantigenicdosages between0and 2000.

The results inFig. 6show thatthe proposedmodel presentedin this workthe behaviorof immune deficient orimmune toleranceas theantigenicdosewas increased. Empirical resultsalso show that theacquired tolerancearisesin vivowhen highantigendoseare inoculated.

CONCLUDING REMARKS

Nonlinear approaches have been used to model several complex biological systems, such as immunological equilibrium and cell-mediated immunity in mammals. In this work, simulations are performed using a Verhulst-like model that considers the time evolution of the adaptive immune repertoire (B cells, antigens and antibodies) in order to study the regulation of memory reservoir. The regulation mechanisms (homeostasis) are still not sufficiently understood, but, recently, the literature has reported experimental works using Ag-independent approaches to quantitatively analyze memory cell turnover. Such studies have shown that immune equilibrium behaves stochastically, rather than deterministically. However, this paper started from an Ag-dependent approach to model a non-random kinetics for the cell turnover. The numerical outcome presented in this work suggests that a more extensive empirical protocol for investigating the homeostasis should be considered.

The results show typical behavior for a population of antibodies that specifically recognize a first antigen. Experimental results in the literature show that in a first immune response there is a predominance of IgM class, and second, there is a predominance of IgG antibodies class. In the simulations considered in this work, the evolution of antibodies showed a typical behavior for the IgM class, as in all simulations a particular antigen was inoculated only once, with no re -exposure to the same antigen system.

The evolutions of populations of antibody were also compared to the antigenic evolution in Fig. 5. The antigenic populations showed a decrease after increasing the production of antibodies, and decayed to zero before the populations of antibodies. This result is interesting because it shows that the proposed model is able to reproduce the behavior of immune competence.

The model used in this study also took into consideration that the immune system is a network of molecules and cells that are recognized even in the absence of antigens. Antibodies are generated by random arrangements and may be treated as foreign bodies by the body. The same can happen for clones surface receptors (BCRs) that can react with each other and also with the antibodies.

The cells that recognize antigens and clonal derivatives, select a set of complementary clone (anti- idiotype) that can react with the idiotypes of other cells. Thus, the clonal expansion of additional cells can also occur when cells of these two types interact through type connector lock and key.

In the results presented in this paper, such

behavior was observed when the antigen was inoculated into the system and two populations were excited : the population of cells that recognize the antigen and its complement.

The number of clonal populations remaining after a simulation for 16000 time steps was presented in Fig. 5. . These simulations represent a sequence of inoculation with 5 different antigens, and the results showed that for all simulations, the system had lower levels of memorizing the higher the values of the parameter proliferation of antibodies.

Considering that the system was not re - exposed to the same antigen stimulation and, therefore, developments accounted for the predominance of IgM antibodies, it is inferred that the results indicate a role regulatory mainly of IgM antibodies on immune memory.

Currently, there is extensive literature on the regulatory role of antibodies (immunoglobulins) on the immune response, but they rarely about a possible extension of this regulatory role on immune memory. Dimitrijevic et al.(2004), published a paper theorizing about a possible role of IgM and other idiotypes in the regulation of immune memory .More recently, Obukhanych and Nussenzweig (2006) published empirical results demonstrate that IgG antibodies in addition to their effector functions, also act as a suppressor of B cell memory mechanism in order to maintain the humoral immune homeostasis system.

The work Obukhanych and Nussenzweig, (2006) served as a reference for Lanzavecchia and Sallusto (2009) write a review in Current Opinion in Immunology renowned on the state of the art in terms of immunological memory in humans.Returning to the model proposed here, the results obtained by dynamic modeling suggests that antibodies of the IgM class, in addition to IgG , can also play a regulatory role on the memory. These results align with the biological hypothesis by Dimitrijevic et al.(2004) and also with the experimental results at Obukhanych and Nussenzweig (2006). Because the evolution of populations of antibodies obtained through the proposed model represent titers of IgM, IgG coupled with the predominance of IgM . Thus generally, the model indicated that immunological memory was generally populations affected by soluble antibodies.

Tarlinton et al. (2008), published a review paper suggesting that the homeostasis of immune memory can only occur if new populations of memory arise over others , ie , that a balance occurs between populations , some need to disappear so that other may arise , since the immune system has a maximum storage capacity .The results presented in Figs. 5 and 6 indicated , in part, an alignment work Tarlinton et al.(2008)Because some people have "forgotten " for others to be stored , thereby respecting one storage capacity . However, Tarlinton et al. (2008) suggested that the mechanism to achieve homeostasis is random , contrary to some earlier work of Matzinger (1995) and Nayak et al (2001). which indicates that the durability of memory depends on the antigenic species.

In this sense, the model is aligned with the work of Matzinger (1995) and Nayak et al (2001), and also shows an alignment of the work Tarlinton et al. (2008) specifically regarding the storage capacity, but results are not aligned with a hypothesis of randomness of the durability of immune memory.The model also reproduces the expected for a state of ignorance clonal results, as shown in Fig. 5. These results show that for the range of values between 0.001 and 0.05 were larger and larger gaps and increasingly lower levels to the lower humoral response was the initial antigen dosage.

Another important result obtained by the model is the memory capacity clonal be influenced by critical values of the antigenic dosages. Within the space of parameters used in the simulations, the model presented a limit of memory for water antigenic dose equal 1.5, as shown in the set of Figs 5 and 6. This result is particularly interesting and should be investigated in-depth, it suggests that above a particular antigen produces no dosing system memory even still in the state of immune competence.

The model also allowed studying the behavior of populations of antibodies against the high antigenic doses. The set of Figs 5 shows that the level of antibodies increases with the initial antigen dosage. Regarding the levels of antibodies, the behavior obtained by the model aligns with the recently published in 2009 by Hendrikx et al results. Where the authors showed experimentally that vaccines administered with high antigen concentrations induce high levels of antibodies.

However, the results obtained in this study using the proposed model indicated that the immune competence system decreased as the dose increased antigenic reproducing a state of immunodeficiency or tolerance of the system, according to experimental results found in the literature.

Importantly, the results obtained and discussed in the light of some previous (including experimental) studies , refer to the adoption of some parameter values chosen from data gathered from the literature. Obviously , a more robust study across the parameter space needs to be done in order to expand the possibilities, mainly on the influence of antibodies and antigen dose on immune memory. In this context, it opens up space for a more comprehensive study protocol for the behavior of the term bone marrow, since the term is not well discussed in the original work Lagreca et al. However, the choice of small to represent bone marrow production, although small

amounts occurred in only 10% of the times that the experiment presented here was performed. Thus , the lack of maintenance guidelines recommended by protocol Lagreca et al. Other computational experiments can be performed by changing the probability of production from the parameter *m.*

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