A MICROSCOPIC STOCHASTIC MODEL OF THE ADAPTIVE HUMORAL IMMUNE DEVELOPMENT PROCESS

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ABSTRACT. Our in silico model was built to investigate the development process of the adaptive immune system. For simplicity, we concentrated on humoral immunity and its major components: T cells, B cells, antibodies, interleukins, non-immune self cells, and foreign antigens. Our model is a microscopic one, similar to the interacting particle models of statistical physics. Events are considered random and modelled by a continuous time, finite state Markov process, that is, they are controlled by independent exponential clocks. Our main purpose was to compare different theoretical models of the adaptive immune system and self–nonself discrimination: the ones that are described by well-known textbooks, and a novel one developed by our research group. Our theoretical model emphasizes the hypothesis that the immune system of a fetus can primarily learn what self is but unable to prepare itself for the huge, unknown variety of nonself.

The simulation begins after conception, by developing the immune system from scratch and learning the set of self antigens. The simulation ends several months after births when a more-or-less stationary state of the immune system has been established. We investigate how the immune system can recognize and fight against a primary infection. We also investigate that under what conditions can an immune memory be created that results in a more effective immune response to a repeated infection.

The MiStImm simulation software package and the simulation results are available at the address http://kerepesi.web.elte.hu/MiStImm/.

1. INTRODUCTION

Germain et al. [1, Table 1] broadly classifies the computational models in immunology into four groups: individual particle-based stochastic, particle number stochastic, concentration-based spatial non-stochastic, concentration-based non-spatial non-stochastic (see 330 references therein). Our computational model best fits into the second category: particle number stochastic. A great advantage of such a model is that it can easily incorporate the most important types of cells and molecules together with their essential features and events that play important roles in immune reactions. In such a model events – for example interactions of components – occur at random. Also, such a model is typically microscopic in space and limited to a small variety of cells and molecules.

To further simplify things, we chose the humoral immune system as the first modeling objective, since the humoral phase (in particular: blood) may be considered spatially homogeneous; thus a microscopic spatial volume may represent the whole humoral phase well. A major advantage of this approach is that it is not necessary to describe the actual spatial positions and spatial motions in the model.

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Instead, model components randomly choose one of the other components as interaction partners, because any components are close enough to become engaged in an interaction.

One of the major objectives that we aimed at was to compare the more-or-less generally accepted ways of operation of the immune system as described in standard textbooks and a partially new idea of operation that our group had been proposing for some time then [2, 3, 4, 5]. For brevity, the more-or-less generally accepted theoretical models [6, 7] will be called Conventional Role of Self models (CRS models), while our group’s theoretical model will be called the Enhanced Role of Self model (ERS model) from now on. For, our theoretical model emphasizes the hypothesis that the immune system of a fetus can primarily learn what self is but unable to prepare itself for the huge, unknown variety of nonself.

2. The ERS theoretical model

2.1. Arguments that led to a novel immune model.

2.1.1. How does the immune system works? Recently, Thompson [8] painted a picture of the human immune system with broad brush strokes, which represents the consensus view that the immune system is a complex and powerful defense mechanism. We have a somewhat modified picture, Figure 1.

Tauber, in contrast, suggested that “...‘immunity’ may be a semantic trap that has confined our understanding of the immune system to only a narrow segment of defensive, aggressive functions” [9].

Trying to resolve this issue, we suggested a paradigm shift in the immune surveillance theory postulating that the evolutionary pressure driving the creation of the T cell receptor (TCR) repertoire was primarily the homeostatic surveillance of the genome [4]. This is achieved by positively selected T cells, which form a homeostatic coupled system via internal dialogue with tissue cells. An important contribution was the complementarity theorem of Dillon and Root-Bernstein [10, 11], which states that a dynamic steady state is achieved through low affinity complementary TCR-MHC interactions between T cells and host cells [4, 5]. Homeostasis, which includes immunity, is controlled by a so-called coupled system via internal dialogue between tissues and T cells, while molecular complementarity puts strict limits on variations. Therefore, in our view, the primary function of the immune surveillance is homeostatic such that T cells prevent the disappearance of differentiation, the natural tendency of people to turn into tumors. Such shift of emphasis from infections to cancer seems to be consistent with epidemiologic observations [5].

Based on information theoretical principles and the law of parsimony we suggested earlier that recognition of self peptides is sufficient to attack nonself [4, 5]. To this end, we proposed that the positively selected subtly variable T cells constitute an evolutionary link between the invariable innate and the hypervariable B cell systems. In order to discriminate self and nonself, T lymphocytes should primarily recognize the much smaller and always available set of self antigens, rather than the practically unlimited and for the immune system only partially known nonself antigen universe.

Thus far, our theoretical models primarily described the role of T cells. The objective of the present work is to supplement it with the affinity maturation of B lymphocytes in which random events are perhaps the most characteristic.
The immune response

![Image showing the immune response with labels for Pathogens, Infected self cell, B cell, Antibodies, Helper T cell, Cytotoxic T cell, Infected self cell, Innate immune cells, and Memory cells.]

**Figure 1.** How immunity works: Innate immune cells engulf and kill pathogens and release cytokines to enhance the immune response. Cytotoxic T cells kill pathogens and attack infected cells. B cells and helper T cells interact via interleukins and directly to instigate an enhanced immune response. Some hypermutated B cells become plasma cells and make antibodies that target specific antigens. Some B and T cells become memory cells that can quickly fight future infections by the same pathogen.

2.1.2. *The homunculus concept.* For better understanding our B cell model, a short recollection of the homunculus concept and the impetus for the development of our one-signal T cell model will be useful.

To our best knowledge the immunological homunculus concept of autoimmunity theory, which was developed by Irun Cohen [12] [13] [14] [15], is the closest to our current model. It states that the immune system is composed of networks of interacting cells and molecules the aim of which is not to discriminate self from nonself, but continuously respond to self in order to organize inflammation in a way that maintains, heals and regenerates damaged cells and tissues. This is carried out with
a high frequency of lymphocytes that recognize key self-antigens: the immunological homunculus. The immunological homunculus positively selects T cells and B cells responding to key body molecules forming a functional “internal image” of the body. The evolution of the immune system has provided a multilevel system that interconnects the innate and adaptive immune systems to serve at least three central purposes: the defense from microbial pathogens, the capacity for discrimination of self from nonself necessary for the prevention of autoimmune disease, and essential effector roles in wound repair and tissue remodeling. The immune system, therefore, is a cognitive system.

2.2. Main features of the ERS theoretical model.

2.2.1. A single T cell cannot discriminate self and nonself, only a wide T cell repertoire can. One of the most important points in our argument is that a single T cell alone is unable to distinguish between self and non-self, only a wide T cell repertoire can.

Shapes of self and nonself entities are intricately interwoven sets; in the language of the shape space model (see below), the subsets of points representing self and non-self are complexly interlaced and cannot be separated by a nice smooth mathematical curve. Therefore the complexity of the antigen universe exceeds the capacity of an individual T cell. The “knowledge” of each specific T cell is reflected by the shape of its TCR. An individual T cell therefore is able to recognize only a complementary or near complementary MHC-peptide molecule. This way, any given T cell clone is responsible for a tiny set of nearly complementarily shaped self-MHC-peptide complexes. In the present paper T cells with nearly complementary TCR to self-MHC-peptide complexes are designated as regulatory T cells.

In particular, the complete repertoire of regulatory T cells (see in particular Fig. 3 below), is able to reflect the whole set of self antigens. The repertoire of regulatory T cells is first created in the thymus of the fetus by negative and positive selection and it constitutes the basis for self-nonself discrimination. Any self-MHC-peptide complex that is able to attach to one of the regulatory T cell repertoire with intermediate affinity can be classified as self; any other MHC-peptide complexes - that has weak affinity to each regulatory T cell or strong affinity to one of the T cells – can be classified as nonself. Thus the regulatory T cell repertoire – like the conductor of an orchestra – controls other elements of the adaptive immune system. This does not exclude the possibility that regulatory T cells – like players of an orchestra – may take part in immune reactions similarly to other T cells as well. See further details in [5]. After birth, development of infection specific T cell and B cell clones are under regulatory T cell control, see below.

2.2.2. Different T cell – B cell interactions in the serum. As in our current in silico model T cell – B cell interactions in the humoral phase is a basic phenomenon, here we describe three different types of it.

In a healthy individual during intrauterine life, randomly produced moderately self-reactive B cell clones are confronted with an overwhelming quantity of self antigens. Those B cells (and APCs) that attach with intermediate affinity to any of these self antigens will present self peptides in their surface MHCII molecules to regulatory Th cells. This ensures B cell and regulatory Th cell survival, respectively, but it is insufficient to trigger extensive clonally based B cell expansion required for specific immunity or autoimmunity. It will be called weak interaction and division.
from now on. Thus positively selected regulatory Th cells are critical parts of the homeostatic control in our model, so that regulatory Th cell clones exist for practically all kinds of self-MHCII – self-peptide complexes presented by any of the APC’s. After birth, this process maintains an immune image of self which can control self-nonself discrimination.

During an infection a new antigen (e.g. bacterium) appears in the serum. Some APC’s, in particular B cells, with appropriate affinity for the new antigens, present foreign peptides on their surface MHCII proteins. Since in our model foreign peptides transiently inhibit the complementary TCR-MHC interactions in general, such perturbation creates steric hindrance that “obstructs” the docking of positively selected regulatory Th cells to their cognate ligands. Disruption of such contact between B cells and regulatory Th cells for a critical period of time by a foreign peptide results in an emergency. In order to reestablish contact, foreign peptide presenting B cells will secrete chemotactic alarm signals (“smoking gun”) attracting Th cells to this region. This initiates a non-specific, polyclonal activation in local Th lymphocytes via the CD28 receptor alone [16] such that a limited beneficial local cytokine storm is generated in local Th cells triggering B cells to clonal expansion, hypermutation, and eventually they develop into specific antibody producing plasma cells. This will be called intermediate interaction and division from now on. The resulting inner state of the affected Th and B cells will be called “activated” state.

The default mode of our model is that a random peptide decreases complementarity between a naïve TCR and the MHC. However, following the initial polyclonal activation phase, there is always a possibility that rare T cell and B cell clones with higher affinity may well recognize foreign antigens, particularly when a significant fraction of host cells is infected and viral load is high (for example in hepatitis, see in [17]). Such higher affinity interactions would then drive clonal (e.g. HCV specific) T cell proliferation, activation, lysis of infected cells, as described by the conventional two-signal models. Having cleared the infection, specific T cells could eventually become an expanded memory type T cell clone, while B cells could differentiate into antibody producing plasma cells. It is thought that acquisition of memory T-cell function is an irreversible differentiation event. Unlike regulatory T cells, such population does not require self-peptide–MHC complexes for maintenance. Nevertheless, sustaining the functional phenotype of T memory cells requires active signaling via CD27 [18]. Specific T and B cell activation, proliferation and lysis of infected cells, therefore, obey the rules of the conventional two-signal model. Clearly, this process may require several days in general. It will be called strong interaction and division in the sequel. The resulting inner state of the affected Th and B cells will be called “strongly activated” state.

3. Description of the MiStImm in silico model

3.1. Basics. We call our in silico model Microscopic Stochastic Immune model or briefly MiStImm model. It is a further developed version of our 1994-98 B cell model [19]. According to the broad classification by Germain et al. [1 Table 1] our model is a particle number stochastic computational model. Our software is a C program, though it was written in the spirit of the agent-based models.
Theoretically, the interactions of the components and other events are described by a continuous time, finite state Markov process. A Markov process is a memoryless stochastic process: if we specify the present state of the system, then we may forget about its history when we want to investigate its behavior in the future.

Our model has finitely many components: helper T cells (regulatory Th cells and potentially infection/mutation specific Th cells), B cells, antibodies, interleukins, non-immune self cells, and foreign antigens. Presently, other than helper type T cells or other antigen presenting cells besides B cells are not represented in our computer model. Each component has a number of characteristics (parameters) and certain attached random events or processes of events that may occur at random. This means that to each potential event there belongs an independent random exponential clock. That is, the model is simulated by independent exponential random variables. The expected waiting time \( \tau \) of each clock may depend on the present state of the whole system. The main step of the algorithm in the computer model is that the event whose clock rings first occurs. For example, the corresponding component interacts with a randomly chosen partner. The occurrence of such an event may cause several changes in the model, like births, deaths, and updates of parameters. Also, in general, expected waiting times of several clocks have to be updated. Then the Markov process – that is, each existing clock – starts again with the new settings.

3.1.1. Some related computational models. One of the first experiments with a detailed agent-based model (IMMSIM) of immune system was the work of Celada and Seiden \[20, 21, 22\]. Their goal was to capture the dynamics of the immune system and to perform experiments in silico. In \[23\], they studied the thymus, the regulation of positive and negative selection, and the dynamics of the production of the TCR repertoire in the thymus.

A closely related agent-based model, the C-ImmSim package has been developed and investigated by Rapin et al. An excellent recent description of their work can be found in \[24\]. Their model represents pathogens, as well as lymphocytes receptors, by means of their amino acid sequences and makes use of bioinformatics methods for T and B cell epitope prediction. This is a key step for their simulation of the immune response, because it determines immunogenicity. The related book \[25\] can be used as a practical guide to implement a computational model with which one can study a specific disease.

The Basic Immune Simulator (BIS) \[26\] is also an agent-based computing model to study the interactions between innate and adaptive immunity. The BIS was created using the Recursive Porus Agent Simulation Toolkit (RepastJ) library, an open-source software library that is available online.

Finally, Kalita et al. \[27\] have developed SIMISYS, which is also a cellular automata model of the human immune system. It uses tens of thousands of cells and innate and adaptive components of the immune system. In particular, the model contains macrophages, dendritic cells, neutrophils, natural killer cells, B cells, T helper cells, complement proteins, and pathogenic bacteria.

3.1.2. Peptide lattice. Our computer model takes a microscopic volume of the humoral phase and also a microscopically small part of the shape space universe. To explain what we mean by shape space, assume that the shape of a T cell receptor
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Figure 2. Two simplified complementary shapes characterized by the points \((x_P, y_P)\) and \((x_P, -y_P)\), respectively

(TCR) can be represented by a point in a large set of a Euclidean space. Theoretical considerations compared with experimental data led to the conclusion \[28\] that the dimension of this shape space, i.e. the number of parameters essential in describing a binding, is not too large, probably around five.

The microscopically small part of the shape space that we consider in our model is a small discrete \(N \times N\) planar grid in the shape space (e.g. \(N = 1000\)). The \(x \in \{0, 1, \ldots, N\}\) coordinate of a shape point may represent a “horizontal” coordinate of the main part of the binding profile of a TCR or an MHC+peptide complex, while the \(y \in \{-N/2, \ldots, N/2\}\) coordinate may represent the “vertical” coordinate of the main part of the binding profile. A positive coordinate represents “convexity”, while a negative coordinate represents “concavity”. Figure 2 shows our underlying idea for the shape of a peptide characterized by a single point \((x_P, y_P)\). Needless to say that our model of shapes is a much simplified one, but is still suitable to represent essential binding properties of antigens. We call the above finite square grid the peptide lattice in the sequel.

3.1.3. Antigen lattice. Shape of a B cell receptor (BCR) or shape of an antigen is similarly represented by a point of an antigen lattice in the model. Here again the \(x \in \{0, 1, \ldots, N\}\) coordinate of a shape point may represent a “horizontal” coordinate of the main part of the binding profile of the BCR or antigen, while the \(y \in \{-N/2, \ldots, N/2\}\) coordinate may represent the “vertical” coordinate of the main part of the binding profile; a positive coordinate representing “convexity”, while a negative coordinate representing “concavity”, see Fig. 1.

For simplicity, to each antigen \((x_A, y_A)\) in the antigen lattice we assign exactly one peptide \((x_P, y_P)\) in the peptide lattice. To make identification of an antigen and its corresponding peptide easier, we will use the convention that \(x_A = x_P\) and \(y_A = y_P\).

3.1.4. Complementarity. Complementarity plays a basic role in binding. The perfect fit between a TCR and an MHC+peptide complex means in the model that the shape \((x_T, y_T)\) of the TCR and the shape \((x_P, y_P)\) of the MHC+peptide satisfy the equalities \(x_T = x_P\) and \(y_T = -y_P\), see Fig. 1. In the model we introduce a metric or distance \(d\) to measure the degree of similarity of two shapes \(z_1 := (x_1, y_1)\)
Figure 3. Simplified graphical representation of the difference between the ERS and the CRS model

and \( z_2 := (x_2, y_2) \):

\[
d(z_1, z_2) := \max\{|x_2 - x_1|, |y_2 - y_1|\}.
\]

A TCR \( z_T := (x_T, y_T) \) and an MHC+peptide \( z_P := (x_P, y_P) \) is nearly complementary in our model if the distance of \( z_T \) and \( z_P := (x_P, -y_P) \) is small enough. Similar is the representation of the complementarity between BCRs and antigens in the model.

Only complementary or nearly complementary shaped ligands and receptors can bind. The dots in Figure 3 represent TCRs that are exactly complementary to some self MHC+self-peptide complex. The areas shaded in darker green are called the characteristic rings of self-peptides. They represent the set of shapes that are allocated to possible regulatory T cells after negative and positive selection in the ERS model, see 3.3.7 below. The areas denoted by lighter green correspond to possible shapes of classical, potentially infection (or mutation) specific T cells, while white areas are representing self-reactive T cells that are prohibited for T cells in the two respective models. Observe that in the ERS model, moderately self-reactive T cells are present after negative and positive selection. In fact, they constitute the most important class of T cells that decide self–nonself discrimination. On the other hand, such moderately self-reactive T cells are negatively selected out in CRS models.

We mention that with the above metric, “circles” are in fact squares in our shape space model.

3.1.5. A logistic function. In biology it is typical that when the size of a certain cell population gets larger the per capita birth rate in the population decreases. Thus the size of a population first increases fast, later it slows down, and in many cases at the end it gets relatively stable, depending on model parameters. So to control the birth rate or other quantities we use a class of logistic functions, previously applied by many other authors (see e.g. [29, 30]). In general, the next function is
Figure 4. Two examples of a logistic function

a useful tool to smoothly and flexibly bound a quantity:

\[
g_{\theta,\eta}(x) := \frac{\theta^n}{\theta^n + x^n} = \left(1 + \left(\frac{x}{\theta}\right)^\eta\right)^{-1} \quad (x \geq 0; \theta > 0, \eta > 0).
\]

This formula describes a decreasing function which is equal to 1 for \( x = 0 \), \( 1/2 \) for the threshold value \( \theta \), and goes to 0 as \( x \to \infty \), see Figure 4. Its parameters \( \theta \) and \( \eta \) are set from case to case.

3.2. Self cells. At time zero, there is a number (say, 3) of different types of non-immune self cells (briefly: self cells), each with a given initial population size (e.g. 150). A certain type of self cells is represented by its position \((x_S, y_S)\) in the antigen lattice and its peptide \((x_P, y_P)\) in the peptide lattice. Specifically, there is a population of bone marrow cells, handled separately from other self cells, with a given initial population size.

Each type of self cells comes with a birth process with a given initial rate (that is, with a given initial average waiting time \( \tau_{s0} \) between divisions). If the size of the population of a specific self cell at a certain time \( t \) is \( s = s(t) \), then the conditional expected waiting between two divisions in this population is

\[
\tau_s = \frac{\tau_{s0}}{s g_{\theta,\eta}(s)} = \frac{\tau_{s0}}{s} \left(1 + \left(\frac{s}{\theta}\right)^\eta\right).
\]

Formula (3.2) indicates that when the number \( s \) of a type of self cells becomes significantly larger than its threshold value \( \theta \) its division rate gets close to zero.

The case of bone marrow cells is special because it comes not only with a birth rate, but, with given rates, bone marrow cells also produce naïve B cells and Th cells. Naïve B and Th cells have randomly determined BCR and TCR shapes that are uniformly distributed on the antigen and peptide lattices, respectively.

3.3. Th cells. While different types of non-immune self cells and foreign antigens are treated as populations, B and Th cells are handled individually in the model. Naïve Th cells are born in the bone marrow. The birth of a Th cell initiates its own (natural) death event and a Th cell action process.

3.3.1. Th cell recognition region. Each Th cell has a recognition region in the peptide lattice. If a TCR is described by the point \((x_T, y_T)\), then the corresponding recognition region is a square with center \((x_T, -y_T)\) and radius \( r_T \). The radius of the TCR is a constant, there is no hypermutation or affinity maturation for Th cells. The recognition region describes the potential shapes of antigens with which a TCR can bind: the smaller the distance between a peptide \((x_P, y_P)\) located on an
MHCII and the center \((x_T, -y_T)\) of the recognition region of the TCR, the better the fit.

3.3.2. Thymus. To each naïve Th cell there is assigned a random event that places it into the thymus. Here the Th cell goes under a negative and a positive selection process. Negative selection kills Th cells that are closer to one of the self-peptides than a minimum radius \(r_{\min}\); negative selection occurs with a given large probability, typically \(p_N = 0.99\).

Positive selection kills Th cells that are farther from each self peptide than a maximum radius \(r_{\max}\); positive selection occurs with a given, relatively smaller probability, typically \(p_P = 0.9\). This way, some of the randomly generated Th cells that cannot bind self-peptides may still survive and they can become infection or mutation specific Th cells later.

The degree of maturity of a naïve Th cell is 0. If a TCR is in the characteristic ring around the reflected image of some self-peptide (see Fig.2), that is, \(r_{\min} < d(z_P, z_T) < r_{\max}\), where \(z_T := (x_T, -y_T)\) is the center of the recognition region of the Th cell and \(z_P := (x_P, y_P)\) represents the shape of a self-peptide, then it is called a regulatory Th cell and its degree of maturity is set to 2. In our model a regulatory Th cell has double role. On one hand, it takes part in the controlling role of the regulatory T cell repertoire, but it can also act as a Th cell.

Other Th cells that have survived the negative and positive selections, but are outside of the characteristic ring of each self-peptide, are called potential infection or mutation specific Th cells, and their degree of maturity is set to 1.

3.3.3. Th cell actions. For each Th cell, there is a sequence of actions, with exponential random waiting times between two actions. At each action the Th cell is to randomly choose one of the potential target MHCII+peptide complexes in its recognition region. The closer an MHCII+peptide complex to the center of the recognition region, the bigger its chance of being selected.

3.3.4. Th cell activation control process. It is a sequence of frequently occurring random events whose purpose is to check and possibly change the state of activation of a Th cell. A Th cell can be in a state of activated or non-activated. This process checks if this Th cell has received interleukin of type 1 in a critical period of time before this check. If the result of this check is “yes”, then the Th cell is set to “activated” (stress=1); otherwise it is set to “non-activated” (stress=0).

An “activated” Th cell starts an interleukin of type 2 sending process. This process is a signal of its activated state for “activated” B cells in its environment. We use the symbolic names “interleukin of type 1 or 2” in this paper, without specifying the exact type of these interleukins.

An “activated” Th cell begins cell division of intermediate kind. Division of the intermediate kind is different from the weak or strong kind, see below.

3.3.5. Self-nonself discrimination. When a regulatory Th cell (degree of maturity is 2) binds with intermediate affinity an MHCII+peptide complex which has state “non-activated” (see below), then with high confidence it means that the peptide is a self-peptide. This contact initiates a division of weak kind for both this regulatory Th cell and the attached B cell. This weak division helps to stabilize this interaction among three partners: self-cells, B cells that can react to self, and regulatory Th cells that can attach to this self-peptide with intermediate affinity. It is also
important that B cells that can process self antigens cannot start a intermediate or strong division process. This is an important inhibitory effect of regulatory Th cells. For, such B cells that react to self are in a state of “non-activated” permanently with large probability.

When a Th cell that has already went through the thymus, but it is not a regulatory Th cell (thus its degree of maturity is 1), obtains interleukin of type 1 then it may begin a non-specific division of intermediate kind and may start to secrete interleukin of type 2 to start division of intermediate kind of activated B cells.

If a Th cell has already went through the thymus, but it is not a regulatory Th cell (thus its degree of maturity is 1), the target is an activated B cell, and the distance of attachment satisfies \( d(z_P, \overline{z_T}) < \frac{r_{\text{min}}^2}{2} \), then with high confidence it means that the peptide is foreign or mutated self. Here \( \overline{z_T} = (x_T, -y_T) \) is the center of the recognition region of the Th cell, \( z_P := (x_P, y_P) \) is the point representing the peptide, and \( r_{\text{min}} \) is the inner radius of the characteristic ring around the reflected image of self-peptides. Remember that because of the negative selection, such short distance between a self-peptide and the center of recognition region is extremely unlikely. Then both this B cell and Th cell are very likely useful tools to fight against an infection. As a result, this interaction may initiate a division of strong kind both in the affected B and Th cells, plus stimulates the secretion of interleukin of type 1 (in the B cell) and type 2 (in the Th cell). Strong division of a B cell implies its hypermutation with given probability as well. This is a direct help of the Th cell for the affected B cell.

### 3.3.6. Th cell divisions

The probability of division of a Th cell may depend on several factors. It may get bigger when the distance \( d \) between the MHCH+peptide complex and the TCR is smaller (i.e., the complementarity is better). It gets smaller when the number \( n_0 \) of all TCR's is large (i.e., the concentration of Th cells is already large). It gets smaller when the number \( n_1 \) of TCR's in a neighborhood of the Th cell is large (i.e., the local concentration of Th cells is already large). The formula for the probability of division is given by somewhat different formulas for the three different kinds of division: weak, intermediate, and strong; namely, not each of these depends on all the three factors.

The probability of a division of weak kind of a Th cell is given by

\[
(3.3) \quad p_{T,w} = k_w g_{\theta_{w0}, \eta_{w0}}(n_0) g_{\theta_{w1}, \eta_{w1}}(n_1).
\]

The purpose of division of weak kind is to establish a stable contact between self antigens, B cells reacting to self with a weak affinity, and Th cells reacting to self peptides with an intermediate, standard affinity.

The probability of a division of intermediate kind of a Th cell is given by

\[
(3.4) \quad p_{T,m} = k_m g_{\theta_{m0}, \eta_{m0}}(n_0) g_{\theta_{m1}, \eta_{m1}}(n_1).
\]

The purpose of division of intermediate kind is to create a fast, non-specific immune reaction to a new, typically quickly growing number of nonself antigens. The growing amount of Th cell help (interleukin of type 2) can help the division of intermediate kind of B cells that are able to bind the new nonself antigens in the humoral phase.

The probability of a division of strong kind of a Th cell is given by

\[
(3.5) \quad p_{T,s} = k_s g_{\theta_{s0}, \eta_{s0}}(d) g_{\theta_{s0}, \eta_{s0}}(n_0) g_{\theta_{s1}, \eta_{s1}}(n_1).
\]
The purpose of division of strong kind of Th cells is to initiate a strong immune reaction when infection or mutation specific Th cells appear and can bind infection or mutation specific B cells. Important requirements to such a division that the binding distance satisfy $d < \frac{r_{\text{min}}}{2}$ and the attached MHCII be “activated”. These requirements can guarantee with large probability that this strong reaction is not arising against self. Then this Th cell becomes “strongly activated” (stress=2). This condition is independent of interleukins of type 1.

3.3.7. Regulatory Th cells. As we saw above, the regulatory Th cell repertoire plays a most important role in our model. This role is similar to the one they have in the computational model [31]. Starting in the fetus, and throughout the entire life span, they give a faithful mirror-image of the self-peptide repertoire.

- They regularly visit B cells having only self-peptides on their MHCII and inhibit their strong division, but support their weak division.
- They are players in normal Th cell roles, like helping non-specific intermediate type and specific strong type division of B cells. They can also secrete interleukins of type 2.

3.4. Interleukins. We use the symbolic names “interleukin of type 1 or 2” in this paper, without specifying the exact type of these interleukins, similarly to Figure 3 of [32].

Interleukins of type 1 are emitted by activated B lymphocytes. This process initiates an action process and also a death process of these interleukins. Each interleukin of type 1 molecule randomly chooses a Th cell. This is a signal for the Th cell to start intermediate type division and to secrete interleukin of type 2.

Interleukins of type 2 are emitted by Th lymphocytes. This process initiates an action process and also a death process of these interleukins. Each interleukin of type 2 molecule randomly chooses a B cell. This is a signal (an indirect help) for a activated B cell to start cell division of intermediate kind.

3.5. B cells. Naïve B cells are born in the bone marrow. The birth of a B cell initiates its own (natural) death event, B cell action process, and B cell activation control process, each with separate rate. Each B cell carries a number (say, 3) of MHCII molecules.

3.5.1. B cell recognition region. Each B cell has a recognition region in the antigen lattice. If a BCR is described by the point $(x_B, y_B)$, then the corresponding recognition region is a square with center $(x_B, -y_B)$ and radius $r_B$. The radius of the BCR of a naïve B cell is a given constant, while B cells that are born in the periphery after hypermutation may have smaller radii. The BCR $z'_B = (x'_B, y'_B)$ of a hypermutated B cell offspring is determined at random, uniformly on a square around the mother BCR. Thus there is only a chance that its affinity to a given antigen $z_A = (x_A, y_A)$ is higher, that is, the distance $d(z_A, z'_B)$ is smaller than that of its mother cell. The radius $r'_B$ of a hypermutated offspring will be smaller than that of its mother cell depending on the above distance: $r'_B = cr_B + r_0$. Typical values are $c = 0.9$ and $r_0 = 5$. This effect may increase the affinity of some “lucky” offspring to the given antigen.

In sum, the recognition region describes the potential shapes of antigens with which a BCR can bind: the smaller the distance between an antigen $z_A = (x_A, y_A)$
and the center \( \overrightarrow{z_B} = (x_B, -y_B) \) of the recognition region, the better the fit between the antigen and the BCR.

### 3.5.2. B cell action process

For each B cell, there is a sequence of actions, with independent exponential waiting times between two actions. At each action the B cell is to randomly choose one of the potential target antigens in its recognition region. A target can be another B cell, an antibody, a non-immune self cell, or a foreign antigen. The closer an antigen \( z_A = (x_A, y_A) \) to the center \( \overrightarrow{z_B} = (x_B, -y_B) \) of the recognition region, the bigger its chance of being selected as the next target. The chosen target can be killed only if the above distance is smaller than the recognition radius \( r_B \) of the B cell, that is, \( d(z_A, \overrightarrow{z_B}) < r_B \). The smaller this distance, the larger the probability that the antigen will really be destroyed. Since smaller distance represents stronger affinity in the model, it means longer attachment between an antigen and the BCR. So this condition is equivalent to the fact that a target can be killed if it is bound to the BCR for a long enough time.

When the chosen target is destroyed, its peptide is placed on one of the MHCII’s of the B cell. The MHCII selected is primarily an empty one; when all of the MHCII’s are already loaded, then one of them is chosen at random to replace the old peptide by the new one.

### 3.5.3. B cell negative selection filter in the bone marrow

To each naïve (immature) B cell there is assigned a random event that places it into a negative selection filter in the bone marrow. Negative selection kills B cells that are closer to one of the self-antigens than a minimum radius \( r_{minb} \); negative selection occurs with a given large probability, typically \( p_{Nb} = 0.99 \).

The degree of maturity of a naïve B cell is 0. A B cell that has survived the negative selection is called a mature B cell, and their degree of maturity is set to 1. Only B cells with degree of maturity \( \geq 1 \) can function as normal B cells.

### 3.5.4. B cell activation control process

It is a sequence of frequently occurring events whose purpose is to check and possibly change the state of activation of a B cell. The main parameter is the critical time \( t_{crit} \). Each of the MHCII carried by a B cell can be in a state of “activated” or “non-activated”. An empty MHCII is not “activated” by definition.

- A given non-empty MHCII is set to “non-activated” when the time elapsed since the last event effecting this MHCII is less than \( t_{crit} \). Such an event can be a regulatory Th cell attaching to this MHCII, or placing a new peptide on this MHCII.
- A given MHCII is set to “activated” when the time elapsed since the last event effecting this MHCII is greater than or equal to \( t_{crit} \). Similarly, a B cell can also be in a state of “activated” or “non-activated”.

- When its each MHCII is in the state of “non-activated”, the B cell itself is set to state of “non-activated”.
- When at least one of its MHCII is “activated”, then the B cell is set to “activated”.

An “activated” B cell starts an interleukin of type 1 sending process. This process is a signal of its activated state for Th cells in its environment. An “activated” B cell may start a cell division of intermediate kind if it obtains help from non-specific Th cells. Help may come as interleukin of type 2 produced.
by Th cells, that has arrived in a critical period of time before this check. (This kind of cell division cannot occur with plasma cells or memory cells.) Division of the intermediate kind is different from the weak or strong kind. Here the activation (stress) level is 1.

In the case of cell division of the strong kind, which occurs by the help of infection or mutation specific Th cells, the activation (stress) level is 2.

3.5.5. B cell division and maturity. Each B cell has a degree of maturity. A naïve, immature B cell has degree 0, while B cells that have survived a negative selection filter in the bone marrow are mature B cells, having degree of maturity 1 first. Mature B cells may encounter antigens at the periphery. A B cell division can be the result of an encounter with an antigen which is escorted by a direct or indirect (via interleukin) help from a Th cell, see below. At each division of a B cell, one of the two offspring inherits all characteristics of the mother cell (let us call it the first offspring for explicitness), while the other offspring (let us call it the second offspring) may undergo hypermutation with given probability. The first offspring inherits the mother’s MHCII-peptide complexes, while the second offspring starts with empty MHCII’s. The second offspring after the first division has a degree of maturity 2. The result of a hypermutation is a B cell with randomly shaped BCR. The possible shapes are uniformly distributed on a square of the antigen lattice, with given radius around the mother BCR.

A second division may lead to two different outcomes with given probabilities: the second offspring can be either a memory cell (degree=3) or a plasma cell (degree=4). A memory cell has the same characteristics as a normal B cell except that its average lifespan is significantly longer (e.g. 10 days instead of the standard 3 days). A plasma cell constantly – at random time instants – produces antibodies of the type of its own BCR.

Possibility of division of a B cell arises after contacting an antigen or obtaining Th help in the form of interleukin of type 2. The probability of division of a B cell depends on several factors. It gets bigger when the distance \(d\) between the antigen and the BCR is smaller (i.e., the complementarity is better), or when the radius \(r\) of the recognition region of the BCR is smaller (i.e., the affinity of the B cell is bigger). It gets smaller when the number \(n_0\) of other BCRs in a rectangle around the BCR is small (i.e., the concentration of B cells is already large). Finally, one or two factors can depend on the concentration difference \(c\) between the number of targets in the recognition region of the B cell and the number of targets in the reflected image of the recognition region. If the concentration difference is too small, the B cell may get insensitive. If the concentration difference is too large, the B cell may get anergic.

The specific formulas for the probability of division in the respective cases of weak, intermediate, and strong B cell divisions are as follows. The probability of a division of weak kind of a B cell is given by

\[
p_{B,w} = k_w g_{\text{min}} + \theta_{d,\eta_d}(d) \left(1 - g_{\text{min}} - \theta_{d,\eta_d}(d)\right) g_{\theta_{\eta},\eta}(r) g_{\theta_{n},\eta}(n_0) \left(1 - g_{\theta_{n},\eta}(c)\right).
\]

The purpose of division of weak kind is to establish a stable contact between self antigens, B cells reacting to self with a weak affinity, and Th cells reacting to self peptides with a intermediate, standard affinity. The first, constant factor \(k_w\) is typically 1. The purpose of the second and third factors depending on \(d\) is to help
those B cells that are at a standard distance from their targets, in the present case, self antigens. The last factor, depending on $c$ intends to guarantee that a large number of antigens, typical for self antigens, be in the recognition region of the weakly dividing B cells. The first parameter $n_m$ here is the actual number of bone marrow cells, which is a common measure of the size of non-immune self cell populations.

The probability of a division of intermediate kind of a B cell is given by

$$p_{B,m} = k_m g_\theta,\eta_4(d) g_\theta,\eta_r(r) g_\theta,n_0(n_0) g_\theta,c_2,c(c) (1 - g_\theta,c_1,c(c)).$$

The purpose of division of intermediate kind is to create a fast, non-specific immune reaction to a new, typically quickly growing number of nonself antigens. The growing amount of B cells that are able to bind the new nonself antigens in the humoral phase even when there exist no infection or mutation specific B or Th cells can give an early start to an effective immune reaction. Activated B cells can release interleukin of type 1 to initiate a non-specific Th help as well. The value of the constant multiplier $k_m$ is typically 100.

The probability of a division of strong kind of a B cell is given by

$$p_{B,s} = k_s g_\theta,\eta_4(d) g_\theta,\eta_r(r) g_\theta,n_0(n_0) g_\theta,c_2,c(c) (1 - g_\theta,c_1,c(c)).$$

The purpose of division of strong kind of B cells is to initiate a strong immune reaction when infection or mutation specific Th cells appear and can bind infection or mutation specific B cells. Important requirements to such a division that an “activated” Th cell binds an “activated” MHCII of this B cell and the binding distance between the reflected image of the TCR and the peptide is smaller than $r_{min}^2$. These requirements can guarantee with large probability that this strong reaction is not arising against self. The value of the constant $k_s$ is typically 200.

3.5.6. B cell affinity maturation and network memory. Like in natural selection, there exists neither intelligence control which would direct genetic mutations toward better fit, nor memory that would save cells from genetically searching a proved wrong “direction”. The major effect which has physiological consequences on a B cell is the strength of antigen binding. This is like finding the source of heat in a dark room, using a single thermometer, with no direct sensing of direction and with no memory. The technique the present model applies is a microscopic analog of evolution: hypermutation and selection, with survival of the fittest. Namely, the program uses a stochastic search for best fit (or a stochastic learning process):

- An offspring may be randomly hypermutated, so a random variation is created in the affinity to the given antigen.
- The stronger a B cell can bind an given antigen, the more offspring it can produce.
- When the concentration of the given antigen is decreasing, a competition arises among B cells for the antigen, and those having higher affinity would win in this selection process.

An affinity maturation model has to handle the danger of autoimmunity. Even if naïve Th cells which can strongly bind self peptides are deleted as a result of negative selection in the thymus, and also naïve B cells which can strongly bind self antigens are deleted as a result of negative selection in the bone marrow, still there is the danger that autoimmune B cell clones may be produced as a result
of hypermutation. In the presented model there is a double defense against this danger.

- The absence of T cell help in the case of B cells that react strongly to non-immune self antigens inhibits their division. This is an essential difference between self and nonself in the model.
- Since nonself antigens which can start somatic hypermutation typically appear after birth, when the number of self cells is already very large, one can argue that at that time randomly produced self-reactive B cell clones are confronted with an overwhelming quantity of self antigens. As a result, these B cell clones would become anergic [33]. In the model this is simulated in the B cell division process: divisions of a B cell, see (3.7) and (3.8), become less frequent when the number of objects in its recognition region becomes overwhelmingly large. The reproduction process of B cells is fastest when the concentration of the complementary antigens is neither too small, nor too large. This is common for both self or nonself antigens in the model, so when nonself overgrows an upper threshold, the model immune system remains practically defenseless against it as well.

As a result of the double defense described above, there will be “holes” in the adaptive immune system, both in the T cell and B cell populations, around the mirror image of non-immune self cells [34, 35]. The negative selection in the model is especially important during early ontogenesis when the smaller population of host cells is vulnerable to self-reactive immune cells. As the individual reaches adult size, the large number of host cells plus the absence of T cell help can alone inhibit reproduction and affinity maturation of immune cells. Then negative selection in the model (like in reality in the thymus) becomes less essential.

It is reasonable to expect that after a somatic hypermutation - affinity maturation process the resulted specific B cell clones may survive for a certain period of time as a local memory. In the model, expansion of certain B cell clones (e.g. as a result of an infection by a foreign antigen), under favorable conditions, stimulates the reproduction of secondary B cells which are complementary to the expanded primary B cell clones and whose receptors are, therefore, similar to the infecting antigens. (Of course, similarity here means a mimicry of a binding partner and not similarity at the molecular level.) Thus a mirroring process (“ping-pong”) and a local network memory may develop and last for a longer time, even in the absence of the stimulating antigen. While this memory lasts, repeated infection of the same pathogen is eliminated more efficiently. This network model of immune memory essentially conforms to Jerne’s immune network concept. Beside other factors, like longer living memory cells or antigen preserving follicular dendritic cells, this could be a possible explanation of immune memory.

3.6. Antibodies. A plasma cell is a special kind of B cells, a result of a B cell maturity process, cf. 3.5.5. A plasma cell has neither a B cell action process (cf. 3.5.2), nor a B cell activation control process (cf. 3.5.4). On the other hand, it has an antibody birth and an antibody death process. An antibody has the same shape in the antigen lattice as the BCR of its mother plasma cell.

Antibodies have similar action processes as B cells, but, naturally, when destroying a target, peptide of the target does not appear on an MHCII. The complement sub-system of the immune system is currently not represented in the model, so it is
supposed that attached antibodies lead to the destruction of the targeted antigen with certain probabilities.

3.7. **Foreign antigens.** After birth, different nonself antigens may enter the body, perhaps several times (e.g. repeated infections with the same disease). A foreign antigen is represented by its position \((x_F, y_F)\) in the antigen lattice and its peptide \((x_{FP}, y_{FP})\) in the peptide lattice. A foreign cell comes with an initial population size and a birth process with a given initial rate (that is, with a given initial average waiting time \(\tau_{f0}\) between divisions). If the size of the population of a specific nonself cell at a certain time \(t\) is \(f = f(t)\), then the conditional expected waiting time between two divisions in this population is

\[
\tau_f = \frac{\tau_{f0}}{g_{\theta,\eta}(f)} = \frac{\tau_{f0}}{f} \left(1 + \left(\frac{f}{\theta}\right)^\eta\right).
\]

4. Simulation results

4.1. **Initial parameters.** In this chapter we assign specific parameters to the MiStImm in silico model discussed above and we describe the results obtained by the corresponding computer simulations. Due to computational limitations, simplifications in the parameter settings were necessary. Nevertheless, we tried to make the model so that it can reflect the processes that play an essential role in the self–nonself discrimination of the adaptive immune system.

The simulation program can be initialized by about one hundred input parameters, most of which are used to set various immune system models, first of all the above mentioned ERS and CRS models. Once one has selected a model, there are parameters with which one can make individual specific settings and start various event processes (for example different foreign cell injections). Furthermore, we have the opportunity to set different random numbers to run different realizations with the same parameter settings, thereby observing the role of randomness.

The following parameter settings were chosen so that they comply with the ERS model and if nothing else said we keep these settings. Firstly, we wanted to show that a simulation driven by the ERS model can comply with the basic requirements that are expected from an immune system model. Secondly, we used simulation results of the ERS and CRS models to compare the two. We hope that our ideas and our in silico model may encourage investigations about the disputed problems by in vitro and in vivo experiments as well. We would especially like to see experiments clarifying questions about the self–nonself discrimination.

4.2. **Development and homeostasis of the immune system.** The simulation starts from a few days after conception and goes until the 5000th time instant, the unit of time being a tenth of a day (2 hours and 24 minutes). Initially there are only three types of non-immune self cell populations in the model, each with 150 cells, and no other components. Each of these populations is accompanied by a cell division process which results a continuous growing of the number of cells in the population, with decreasing rate in time, as one might expect (Figure 5).

Coordinates of different antigens of the three different self cells are respectively \((550, 300)\), \((700, -200)\), \((850, 150)\) in the \(\{0, 1000\} \times \{-500, 500\}\) antigen lattice. Coordinates of peptides belonging to these self cells are chosen the same values in the \(\{0, 1000\} \times \{-500, 500\}\) peptide lattice.
Bone marrow cells, and the B and T cells generated by them, first appear at the 100th time instant. The number of these cells also grow continuously with a decreasing rate. TCR rings around the mirror images of self peptides (letters ‘s’) – that are characteristic features of the ERS model – begin to develop about the 1500th time instant and more or less stabilize by the 2800th time instant (Figure 6). There are random fluctuations of these rings: Sometimes the local and global T cell populations overgrowth the upper limits and this reduces the probability of T cell division. Another reason is that there is a fluctuation in the peptide presentation of B cells.

In sum, one can observe that the qualitative behavior of the development and homeostasis in the immune system are not significantly affected by random factors.

4.3. Normal immune response. In this subsection we show that MiStImm can model normal immune response. Firstly, immune system with normal parameters do not attack self cells strongly, only to a very limited extent. Some B cells must continuously present self peptides to ensure that T cell characteristic rings around self peptides are persistently maintained. Because of anergy, this type of immune response is weak and always settles down quickly before it becomes pathological.

Secondly, a normal immune response should have the ability to destroy the majority of pathogens – some of them quickly, others perhaps slowly, while in some cases it may fail. In our model, death of an individual occurs when the pathogen population grows up irreversibly so that its size reaches 4000 items. Diversity of foreign intruders are represented by different locations of their receptors and different speeds of growth. In the current settings we work with one kind of antigen. Table 1 shows the frequency of winning against pathogen destroyed by a healthy immune system – considering three different growth rate and three different initial sizes. Figure 7 shows a typical B cell response to an infection over the antigen lattice; the position of nonself population is denoted by a letter ‘n’.

The third important feature of a normal immune response is immune memory. Thanks to memory cells, a second immune response against the same infection will be more effective than at the primary infection. We have tested this phenomena with 100 simulations, adding the same pathogen at 3000th and 3150th time instant. There was 81 cases when immune system won against both infections and these times the average time interval of the wins were 88.91 and 53.28 (the first and the second occasions, respectively). The p-value of the two samples was less then 0.0001. Figures 8 and 9 show an example for an infection that was repeated once.
Experiments with our microscopic computational model showed that it cannot fight effectively against more than a couple simultaneous infections. Similar is the case with the development of immune memory. This observation fits experimental results [36].

4.4. **Autoimmunity.** Lack of negative selection of B cells results autoimmunity (Figure 10).

4.5. **ERS model vs CRS model.** One can switch the ERS model to a CRS model by modifying three parameters. Simulation results with a CRS model was very similar to simulation results obtained with the ERS model above, except the establishment of characteristic T cell rings around self antigens. One can say that CRS models also satisfy the basic requirements that are expected from an immune system model.

However, the two model are different in one important aspect. We compared the efficiencies of the immune reactions in the two models. Our results showed that in the ERS model the adaptive immune reaction started faster and was able to destroy infections with critically large initial sizes more often than a CRS model (Table 1).
Table 1. Normal immune response against of the ERS model vs the CRS model simulated by MiStImm 500-500 times at various type of infections. Foreigns: the initial number of foreign cells at the time instant 3000. Avg. div t.: the expectation of the waiting time between two divisions of the foreign cells. Wins ERS: number of wins of the immune system against the foreign cells using the ERS model settings. Wins CRS: number of wins of the immune system against the foreign cells using the CRS model settings.

| Foreigns | Avg. div. t. | Wins ERS | Wins CRS |
|----------|-------------|----------|----------|
| 300      | 50          | 448      | 310      |
| 350      | 40          | 75       | 66       |
| 350      | 50          | 307      | 225      |
| 350      | 70          | 487      | 400      |
| 400      | 50          | 134      | 135      |

5. Conclusion

First we described arguments that led us to the ERS theoretical model that emphasizes the role of self in creating, maintaining and controlling immune responses.
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Figure 8. Normal immune response against a repeated infection

Figure 9. Division of weak/intermediate/strong kind of T and B cells in the simulation showed in Figure 8

to self and nonself. Then we discussed the MiStImm in silico model that was made to investigate some important characteristics of immune development, starting from conception and ending some time after birth. Finally, results of some computer experiments were discussed. An important part of the latter was the comparison of the CRS and ERS theoretical models. In sum, we think that it is likely that evolution preferred adaptive immune systems whose basic mechanism is closer to the ERS model than to a CRS model, because ERS gives better results to overcome a critical primary infection.

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Figure 10. Lack of negative selection of B cells results autoimmunity

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