

An AnyLogic Agent Based Model for the Lymph Node Lymphocytes First Humoral Immune Response

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Abstract. The simulation of the first humoral immune response, that refers to the process of producing antibodies in response to a first exposure to an antigen, is extremely complex due to the high mechanisms and interactions known between its major implicated components; however we are attempting in this paper to present a computational model for this process that is initiated and fully controlled by the Lymph Nodes organs, for the ultimate aim to enrich the current existing immune system models. The model studies in particular the Lymph node lymphocytes primary humoral immune response against both T-Dependent and T-Independent antigens. It's developed under the AnyLogic simulation tool and it's a Multi-Agent system based model in which the behavior of the constitute agents are modeled using the Statecharts formalism. Using AnyLogic as implementation platform agents wherein Statecharts can be programmed very conveniently; offers a great advantages among the other platforms especially final models can be modified, extended and handled in an elegant way. The results issued from our AnyLogic simulation respect several immunology experimentations (B-Cell activation, proliferation, differentiation and antibody generation).

Keywords: Simulation, AnyLogic, Multi-Agent system, Statecharts, First humoral immune response, Lymph Node.

1. Introduction

The first humoral immune response refers ^{1,2} to the production of antibodies and the accessory processes that accompany it in response to a first exposure to an antigen. Its process ^{2,3} begins once an encountered antigen is recognized leading to the activation of unstimulated naïve B lymphocytes that enter so on in the clonal expansion phase where large clones of identical cells are produced; the proliferating cells will then differentiate into either antibody-producing plasma cells, or memory cells.

The humoral immunity might be stimulated either ^{3,4} by T-Independent antigens that can instantly mount an humoral immune response without the help of T-Helper Cells, or by T-Dependent ones that must implicate T-Helper cells in order to mount an humoral immune response. The humoral immunity processes are fully orchestrated by special immune organs called Lymph Nodes (LNs). These last, which act as filters that are sampling lymphatic fluid for foreign organisms ⁵, are secondary lymphoid organs that provide an environment to facilitate the meeting and the interaction between the antigens and the various immune cells implicated in this process.

The researches ⁶ that have been issued during the last years to simulate the immune system as a whole system or as a part of it such as LNs varies from mathematical simulation models ^{7,8} to Cellular Automata (CA) ^{9,10} to Multi-Agent based models (ABM) ^{11,12} and finally to the Reactive Animation (RA) models ^{5,13,14}. The RA models, which aim to couple between state-of-the-art reactivity and state-of-the-art animation ^{13,15}, are based on two combined techniques: the Statecharts formalism ¹⁶ to model the system' behavior and the front-end animation tool to visualize the animation simulation with enabling natural-looking. The most well-known immunology works based on this technique is the David Harel's works: modeling the maturation of T-cells in the thymus ¹⁵ and the development of the lymph node ⁵. This last studies the dynamic development of the LN with a focus on the behavior of a subset of immune cells that enter a single, 2-dimentionel LN with immunogenic antigens.

2. Modeling

We have focused here on modeling the first humoral immune response initiated in the LN as an encountered antigen (either a T-Independent or a T-Dependent one) is recognized. Our model is an ABM^{17,18,19,20} that is defined as a computational model aiming to offer a manner on how to build complex systems composed of autonomous interacting computing elements called agents.

The behavior of our constitute agents are modeled via the Statecharts formalism which is considered as graphical state-transition formalism²¹ based on exchanging messages or events between the system and its environment; Statecharts are essentially Finite State Machines extended into a modular, highly structured, and economical description language^{21,22,23}.

The model is developed under the AnyLogic²⁴ simulation tool which is a Java based multi-approach simulation modeling tool based on advanced technologies such as UML, hybrid systems theory, and best numerical methods. The AnyLogic simulation tool provides great features such: reducing development cost and time, developing more models with one tool and improving the visual Impact of models.

Our AnyLogic simulation takes into account the three correlated modeling activities suggested in¹⁸: “*the behavior module*”, concerns modeling the agent behaviors; “*the environment module*”, defines the virtual place wherein the agents evolve and interact; and finally, “*the scheduling module*” which is related to the definition of how the two above modules are coupled and managed with taking into account the time factor.

2.1 Modeling the time

As we are modeling a biological system for which time is an important factor (for example a typical lymphocyte circulation cycle takes 12–24 hours⁵; normal proliferation takes 8–12 hours⁵; etc.); we have attempted to calculate the corresponding time values between its different processes; for that we have used the AnyLogic simulated time unit (TU) which is fixed to (0.001) and which in our model corresponds to 1 second so an hour is evaluated to (0.36 UT).

2.2 Modeling the LN environment

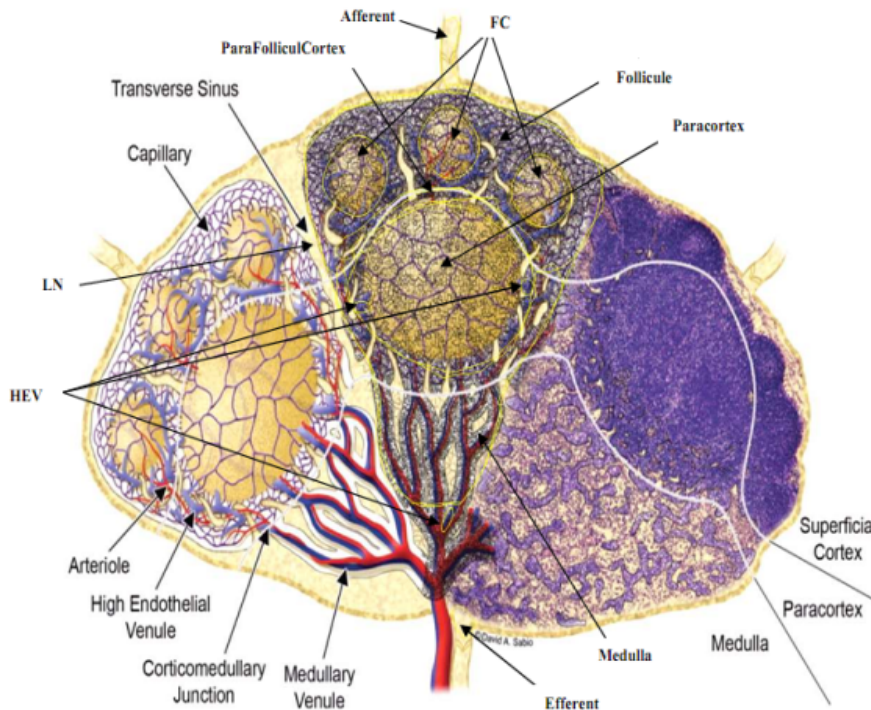


Figure 1. The AnyLogic simulation LN zones²⁵.

To let the simulation realistic, it's suitable to use a real image of a LN²⁵ which can show its different constitute regions. To model these regions we have used as it's shown in [Figure 1] a set of closed curves, each represents a special LN area. The center LN is chosen to be the environment where all the interacted agents are distributed, the movement of these agents between the LN areas is specified by a set of functions

that control the movement from one zone to another, for example the function `moveToGC` (`AgentContinuous2D` cell) moves a given cell from its current location to one of the GCs illustrated in the Figure. The path followed to reach the target location is specified automatically by the AnyLogic move API.

2.3 Modeling the immune cells agents

The different developed agents that are captured to model our system include:

1. The Lymphocyte Agent: represents B-Cells, B-Memory Cells and T-Helper Cells.
2. The Plasma Agent,
3. The Antibody Agent,
4. And the Antigen Agent.

The behavior of each modeled agent is specified via the AnyLogic integrated Statecharts formalism. Each behavior is divided into two main Statecharts: one to model the life cycle of the agent, the other is for modeling its location cycle.

2.3.1 Representative example of our Anylogic ABM: the lymphocyte agent

The lymphocyte agent models different cells including B-Cells, Memory B-Cells, and T-Helper Cells. For each of the B-Cells and Memory B-Cells, two kinds of cells are taken into account: ones are matured to recognize T-Dependent antigens, the others are matured to recognize T-Independent antigens; the T-Helper Cells are implicated only in the humoral immune response to T-Dependent antigens.

The biologic experimental^{3,4} illustrates that B-Cells enter permanently into the LN via HEVs and migrate to its zone area (Follicles) where they may meet and recognize antigens; belongs to the presented antigen type, the humoral immune response process will differ as follow:

If the antigen is a T-Independent one the B-Cell becomes an activated cell and migrates to the Follicle Center (FC) where it begins what the immunologist called clonal expansion phase. At this moment a large number of B-Cell clones are generated; some of them become a plasma cells, others become a memory B-Cells and the others are died. Whereas if the type of the presented antigen is a T-Dependent : the stimulated B-Cell will be completely activated when it migrates to the Paracortex zone and waits for an activated T-Helper Cell which activates the B-Cell after a set of biochemical interactions between them. The activated B-Cell will then take the same process of clonal expansion followed by a matured B-Cell activated by a T-Independent antigen.

All the lymphocyte cells which either recognize or do not recognize antigen live the LN via efferent zone than restart the recirculation process. They are death after an expiration of their life duration.

In our AnyLogic model we have developed a Lymphocyte class which extends the `AnyLogicAgentContinuous2D` subclass. The Lymphocyte properties, methods and Statecharts behavior are illustrated in [Figure 2].

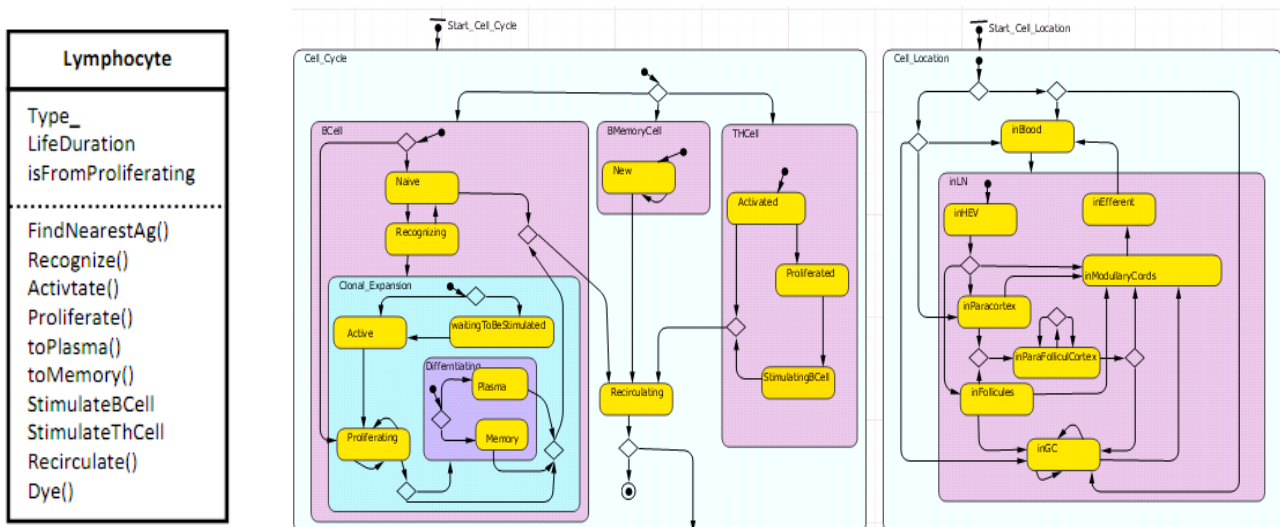


Figure 2. The Lymphocyte agent: properties, methods and Statecharts behavior.

3. Results

In this section we describe firstly the behavior of the simulator, and then show the type of results it generates. During a typical run of the simulator, the user defines the initial number of the different implicated agents then he can switch to the root simulation that shows the initial allotment of the entire implicated agents. The running simulation illustrates firstly the random distribution of the concerned defined agents; each cell agent is located in its specified LN zone. Then the simulation begins showing the movement of each agent from its current location to its target zone with regards to the movement rules defined in its Statecharts location behavior. The user can interact whenever he wants with the simulation interface by a set of available controls: for example he can inject T-Independent antigens; if any specified B-Cell that is matured to recognize this antigen type has encountered the antigen, the humoral immune response will instantly begin processing as we have explained in the previous section. In our model the details behind the antigen recognition phase isn't taken into account due to the extreme chemical interconnection signals known in this case between an antigen and a B-Cell; in consequence we have only develop an event that periodically calculate the distance between the current B-Cell and all the antigens injected in the LN. If the calculated distance is less or equal to two (2), the concerned B-Cell is then becoming in the active state of the Clonal_Expansion composite state that invokes an immediate migration of the concerned B-Cell to one of the FCs and starts proliferating with a specific modified proliferate rate initially has the value $\rho = (24/6.24) * \ln(2)^{-26}$. The proliferation process, which itself involves the creation of an additional instance of the same object, is stopped when the number of the total proliferate B-cells exceeds the allowed total proliferated number which in our model assigned the value $T_{prolif} = (2^{\rho} - 1) * 100$. The proliferated cells will then either dye with a probability of 1%⁵ or differentiate either to Plasma Cells or Memory Cells; the probability of this differentiating phase is defined by the user (the initial used probabilities are⁵: $P_{plasma} = 66\%$ to become a plasma cell and $P_{mem} = 33\%$ to become a memory cell). After that the generating cells migrate to the Modullary Cords zone where each plasma cell has a user defined probability initiated to 25% to begin secreting a huge number of antibodies (Ab); it's around 2000 Abs are secreted every second for a few days⁵; in our model the total number of secreted antibodies is fixed to $T_{Ab} = (T_{prolif} * P_{plasma})/2$ per plasma cell due to the limitations of the resources (memory and processor frequency) of the computer we have used for the simulation.

The snapshots illustrated from [Figure 3] to [Figure 7] mention a situation such this in which a complete first immune response is simulated: beginning from the injection of a set of T-Independent antigens [Figure 3] to a proliferation phase shown in [Figure 4] to a differentiation phase mentioned in [Figure 5] and [Figure 6] and finally to a secreting antibodies phase viewed in [Figure 7].

During the simulation the user can also modify the parameters that control the proliferation rate, differentiation rate and antibody secreting rate. Our model offers also statistical presentations to the user showing him in every time the occupation of the total number of each Cell per LN zone; the graphs viewed in the left side of the shown snapshots illustrate the occupation of: the both types of B-Cells, Memory Cells, Plasma Cells, Th-Cells and Antibodies for each of: the GCs zone, the Paracortex zone, the Modullary cords zone, the HEVs zone and the Efferent zone.

The user has moreover a possibility to know the current state of any agent via the tools offer by the AnyLogic toolbar. For instance the snapshot mentioned in [Figure 8] highlights the current state of the first generated B-Cell matured to recognize a T-Independent antigen; the figure shows that the concerned Lymphocyte is actually on parallel composite states: the Cell_cycle one and the Cell_Location one. Inside the Cell_Cycle composite state the Lymphocyte is in its BCell composite state wherein the current active state is the Naïve state; whereas inside the Cell_Location composite state the figure shows that the specified Lymphocyte is actually in the inLN composite state and inside it the current active state is the inFollicles state.

4. Discussion

The study described in this issue demonstrates how we can use an Agent-Based approach for which every agent behavior is controlled completely by the Statecharts formalism to simulate a part of the first LN humoral

immune response against antigens. The use of the Statecharts technique proves that it's a suitable and powerful visual modeling technique to be applied in biologic systems as they are considered as reactive systems.

The work presented here aims to profit from the work done in ⁵; in which the Statecharts technique has been used as a state-of-the-art reactivity to model the development of a LN; in our work we have remodeled completely the LN using the AnyLogic simulation tool with regards to the immunological experimentations. Although we haven't modeled all the experimental details that are issued from the immunology researches due to its immense complexity, however our simulation results those are compared at run time with a real LN image are close to the reality.

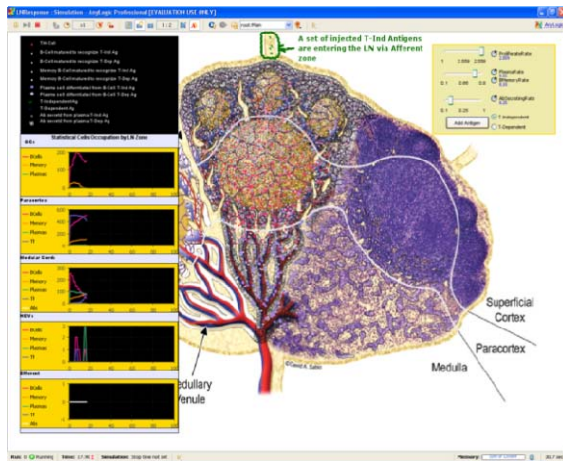


Figure 3. A number of injected T-Independent antigens (green color) are entering the LN via afferent area.

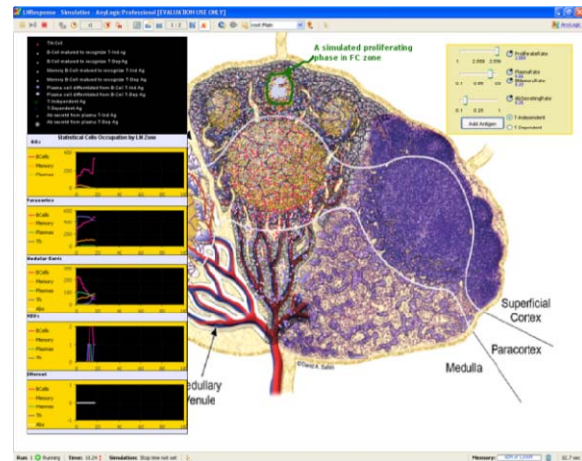


Figure 4. A simulation of an humoral immune proliferation phase.

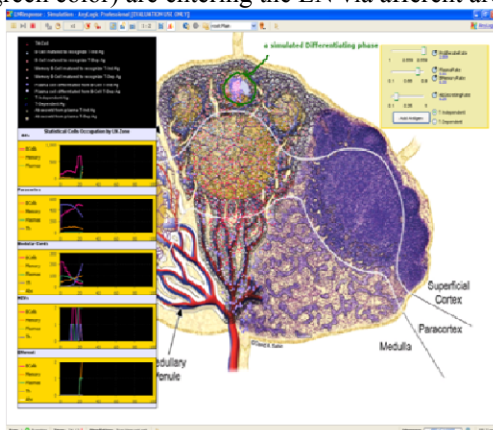


Figure 5. A simulation of an humoral immune differentiation phase (processed in a FC Zone).

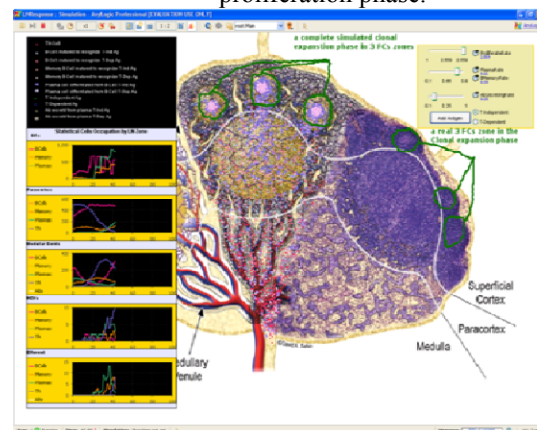


Figure 6. A simulation of a complete humoral immune clonal expansion phase (processed in a 3 FCs zones).

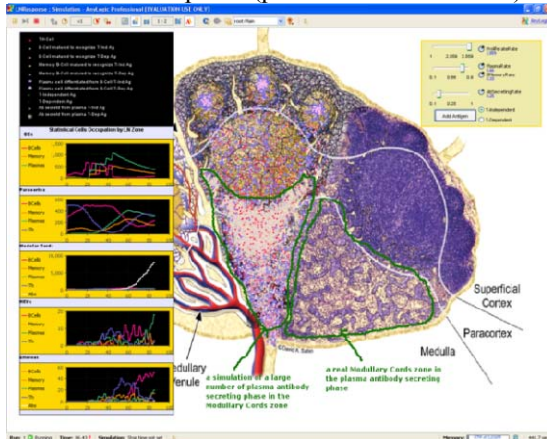


Figure 7. A simulation of an humoral immune plasma secreting antibodies phase (processed in a Medullary Cords zone).

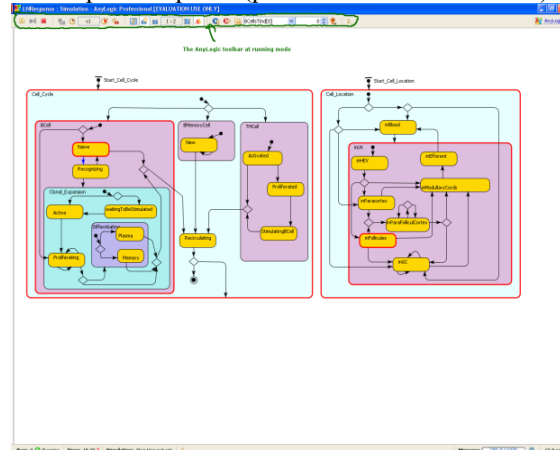


Figure 8. The current highlighted active state for the first T-Independent B-Cell at run time.

The results issued during the execution of our AnyLogic simulation model shows that the process of mounting a LN humoral immune response against both T-Dependent and T-Independent antigens is much faster than the biologic experiments; all the phenomenon emerged from the application of the behavior rules defined in the Statecharts of each implicated cell are compared with the real images issued from the immunology experimentations. The obtained results demonstrate also that we were able to transform a part of this static experimental data into dynamical behavior including: cell migration from LN zone to another, cell proliferation, cell differentiation into memory or plasma cells and generation of antibodies; a statistical analysis of the dynamic occupancy of the different LN zones is also given to the final users in order to illustrate statistics about the total numbers of cells that are actually residing in each LN zone.

As a deep analyze of our LN AnyLogic model which has much been simplified due to the immense complexity of some immune mechanisms, and with regards to the LN model established in ⁵; our model haven't detailed the cell interactions signals that can be viewed during an immune response. For example: the antigen-BCells interaction signals, the antigen-ThCell interaction signals and BCell-ThCell ones aren't carried out in our model. The model also doesn't take into account the orthogonal states feature used in the work of ⁵ for the reason that the AnyLogic simulation tool doesn't support in its current release this powerful Statecharts features; nevertheless we have simulated this feature on profiting from the ability of the AnyLogic simulation tool to create multi-statecharts for the same agent. These multi-statecharts can be executed on parallel manner with the same execution fashion of orthogonal states.

A positive view point of our model is that it deals with two kinds of antigens: T-Dependent and T-Independent, it's also developed with one simulation tool that can combine different modeling approaches at once, and which integrates also a 2D and 3D render engine that can animate the simulation in two or three dimensions. Contrary to the model of ⁵ which dials only with the T-Dependent antigens and it's developed using two different tools: the IBM Rhapsody developer tool to model the cells behavior and the Adobe Flash tool as a render engine to animate the cells behavior.

5. Conclusion & Future Works

In the AnyLogic model proposed in this paper we have focused on modeling the first humoral immune response initiated in the LN as an encountered antigen is recognized. The model dials with two kinds of antigens: the T-Independent antigens and the T-Dependent ones.

Although the simulation of such an immune response is very highly complex due to the high complexity of the mechanism behind it; we believe that we have succeeded to build a simplified AnyLogic model for the studied system with taking into account a part of the immunology experimentations. Our results obtained during the execution simulation of the modeled system shows that the model respects several immunology experimentations (B-Cell activation, proliferation, differentiation and antibody generation) even that some behaviors such as cell signal interactions, activation of Th-cells, etc., aren't carried on for which a perspective future work can be initiated to extend the model. The model also can be extended to tack into account the secondary humoral immune response initiated when the same antigen caused mounting a previous first humoral immune response has been recognized; in this case Memory B-Cells play the major factors in mounting such humoral immune response.

We hope also that other AnyLogic immune researches works can be initiated to involve the other immune organs such Spleen, Bone Marrow and Thymus for the aim to model the entire immune response by gathering piece to piece the models of each immune organ. This also can initiate a collaboration work between computing laboratories as a computing simulation research side with hospital immunology laboratories as biology research side.

Finally it would be a great pleasure for us that our AnyLogic model is the first attempt in our laboratory even in the entire world to initiate a simulation of a first LN humoral immune response against antigens using the AnyLogic simulation tool; as consequence we hope that we have enriched the existing immune models that have taken place and we have opened a research windows for the future extension of our work.

6. References

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