

## Toward multi-organs simulations of immune-pathogen interactions

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### Abstract

*Computer simulations play an increasingly important role in bio-medical research by allowing cheap verification of conjectures and exploration of ideas.*

*The IMMUNOGRID project, among other things, has contributed to the development of computer models for the simulation of different human pathologies by adopting the agent-based modeling paradigm.*

*In pursuing the main goal of the project, that is to construct a virtual immune system, we have unwrapped challenges and opportunities.*

*In this article we discuss one of them, that is, how to envisage a multi-scale, multi-organ three dimensional simulator of the immune response that can be a useful tool in medical bioinformatics with the special requirement of being user friendly to non specialists.*

### 1. Introduction

Mathematical biology has a long tradition dating back to the Lotka-Volterra system of equations describing the predator-prey relationship. The wide spread availability of extremely powerful computers has allowed to solve virtually any kind of system of equations, being them “simple” ordinary or complex partial differential equations.

More recently, the Agent-Based paradigm has evolved from the ground breaking novelty called Cellular Automata [22, 23]. This paradigm of simulation turned out to be well suited to represent biological systems where discreteness of the constituent parts is the main determinant of the driving overall dynamics [14, 15, 21]. Agent-Based models (ABM), in fact, are very useful in understanding systems with a high degree of inhomogeneity as is the case of the

immune system [10].

Armed with these simple knowledge we, within the IMMUNOGRID project [5], have developed a set of simulation tools to study both the disease progression and the effects of therapies for the Acquired Immune Deficiency Syndrome, the infections by the Epstein-Barr or the influenza virus, the arteriosclerosis and for the simulation of cancer immunoprevention. Almost all of them are agent-based models where agents represent the most important actors of the immune/pathogen interaction at the cellular level.

Whereas the first goal of the project was to scale up simulations to the size of organs and possibly (*small*) organisms level, another goal was to incorporate molecular details to allow patient specific therapeutic effects. The latter revealed to be the most challenging for a number of reasons whose details we will not mention here. Suffice to say the molecular level process of outmost interest in immunology is that of the antigen-peptide recognition by immune competent cells, and that no unanimously accepted techniques for this purpose exist. Here bioinformatics comes into play whence binding prediction tools engineered with machine learning techniques are utilized [16, 17, 18]. Unfortunately, although a great deal of progresses in this field has been done in the last years [20], the technology is not yet quantitatively reliable to the point to allow the development of a large multi-scale simulation tool of cell-cell interaction and antigen recognition that could, eventually, support clinical investigation or drug design. As a consequence of this fact, the IMMUNOGRID portal [5, 19] has been constructed on top of the cell level models and of the binding prediction tools, without an explicit linkage between the two.

Going back to the first aim of the IMMUNOGRID project, that is to construct an immune system simulator at the natural scale of, say, a mice, it is fair to say that this task has guided us toward a set of ideas and the development of

proofs of concepts more than a concrete and “final” simulation tool.

These ideas are partially covered in this article. In particular we will describe how to link high-resolution in-vivo medical imaging like Nuclear Magnetic Resonance (NMR) with computer simulation, a task that is already on the edge in certain areas of research like for example in the field of modeling of cardiovascular diseases (euHeart project [2]) or in the determination of neuroanatomical connectivity at mesoscopic scale [9], and that are likely to be faced by a greater number of researcher in the not-so-far future.

It is worth to mention that this particular aspect has been recently recalled in the First International Workshop on Virtual Tissues (v-Tissues 2009) in North Carolina, last April [3] that has gathered researchers involved in simulating case studies on different target organs like heart, liver, and kidney.

## 2. The tissue representation and the modeling choice

Whereas the simulation of relatively homogenous organs like the heart has already reached a mature stage [2], the simulation of the immune response at a system level is far from being reached. The reason certainly lies in the enormous complexity of the immune system as a whole and at its high level of inhomogeneity at any level of description, being it molecular, cellular, organ or organismal [19]. Since lymphocytes play the central role in the immune response, the mostly adopted level of description of the immune response has been, historically, the cellular level. The majority of immune models concentrate on the adoptive immune response in terms of population dynamics models. The modeling choice is therefore somehow dictated: either ordinary differential equations that do not represent spatiality, or partial differential equations that specifically take into account the space dimension. Spatially extended models have shown to generate a more faithful approximation of the reality of the immune system [15]. It seems then clear that, for example, a major understanding of the overall immune dynamics during infections or cancer development can be achieved including the spatiality among the main ingredients of the model. Partial differential equations however represent averaged quantities while, as introduced above, inhomogeneities are intrinsically important in this case.

Actually, there is a third modeling choice, those of cellular automata. Cellular automata are fully discrete dynamical systems that are very well suited for studying complex systems composed by a large number of interacting components. Recently people refer to cellular automata with the name of agent-based models although, strictly speaking, the two paradigms are different. To be more precise, the agent-based includes cellular automata as a specific case

[11]. Agent-based models come in hand since they allow to individually represent entities at any level of details to perform four dimensional simulation of immune/pathogen interaction. There is another aspect for which ABMs as modeling paradigm could be preferred to partial differential equations, the possibility to represent the space in a very complex/detailed way and to assign each entity a set of rules that take this other feature into account in shaping their behavior. Thus to represent the tissue.

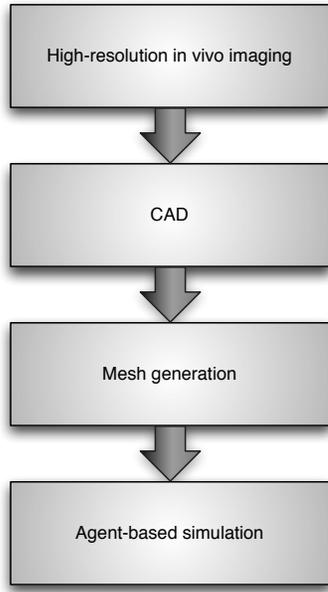
## 3. Multi-node simulation workflow

Representing the tissue at the core of a computational model of the immune system means to attach to each *voxel* (a voxel is a portion of volume in a three dimensional image) of our three dimensional discretization of the volume under study, a set of labels describing physical/biological properties like density, temperature, physical resistance, viscosity, etc. , to be used by the agents' rules to decide how they have to behave in this or that situation. For example, a leukocyte that is close to the endothelial wall of a post-capillary venule that extravasates to reach the site of tissue injury or infection during the innate immune response. Or, another example, lymphocyte extravasation through high endothelial venules of Peyer's patches (or lymph nodes in general) in homing and inflammation [7, 8]. In those cases, the rule coding for the extravasation would take into account tissue-specific information to determine, say, the probability (or the rate) of extravasation, the time to extravasate, a possible change of conformation or state, a check for the occupancy of the volume that would also determine the probability to extravasate, and so on.

Along this line, it is not difficult to see how this modeling process is very similar to that used in automobile industry simulation of fluid dynamics, to study for example the aerodynamical properties of a certain car.

In our case, taking for granted that a huge level of approximation is needed, much more than in the fluid dynamics field where the physical laws are known, the workflow would start from image acquisition and ending with an agent-based simulation of the cellular dynamics in the complex spatial mesh representation calculated as intermediate step. The applications of a simulation architecture that includes tissue-specific information are countless. Still, the overall computing architecture and information workflow roughly be the same.

The overall architecture of a simulator of one or more virtual tissue/organ can be schematized as in Figure 1. Let's go a bit deeper in the details of this process. The first stage of image acquisition translates in fine grain NMR of the organ under study. NMR technology has reached a very good level and high-definition imaging are already at hand. The second stage of volume determination by image segmen-



**Figure 1. In order to label each single voxel we need first to construct the three dimensional image from two-dimensional high-resolution images like NMR. The second step is to delimit the area of interest. The third is to discretize the volume in voxels and to label the volumes in a suitable way to represent simulation relevant information. The final stage is to perform a detailed three dimensional spatial extended simulation of the immune dynamics at the chosen level of description.**

tation can be performed with various free or commercial software as for example the free open source software 3D Slicer [1] or the free software IA-FEMesh [4] just to mention some. The successive phase consists in constructing a volumetric (i.e., three dimensional) mesh of the organ. Also in this case, the two softwares mentioned above can be used. Moreover, for this purpose there are already a number of available softwares since the field of engineering has already pushed a lot in this direction in the past and our aim is not different from that of engineers who want to perform their simulation to compute, for example, the structural properties of a bridge or of a car-racing (Formula 1) team who wants to study the aerodynamics effect of a front wing.

The above mentioned phases are more or less already solved problems and do not provide any particular challenge from the research point of view. In contrast, the last phase

of this workflow is more interesting for us since the simulation of biological processes is at the core of current system biology/medicine research. Think for example at the utility of calculating the pharmacodynamics/pharmacokinetics property of a compound.

### 3.1. An example

As an example of the architecture described above we now describe a work in progress whose focus is at the construction of a multi-organ simulator of the Multiple Sclerosis (MS). This example highlights the need for a computational architecture that allows the concurrent execution of simulation codes specialized for different tissues/organs. At this stage, the example lacks a definition of “quasi”-real meshes derived from high resolution imaging. Nevertheless the code is capable to read any kind of mesh as input file. At the same time, more specific instructions can be added to simulate tissue-specific characteristics.

After a brief introduction of the MS we describe the modeling architecture used to simulate the role of the immune response in this pathology.

MS belongs to the class of autoimmune diseases. It affects the central nervous system (CNS) in which CD4+ T lymphocytes of the Th1 and/or Th17 subset react against self myelin antigens. The immune system reaction results in the activation of macrophages around nerves in the brain and spinal cord, destruction of the myelin, abnormalities in nerve conduction, and neurological deficits. MS is the most common neurological disease of young adults [6]. The pathologic effect is represented by a general inflammation in the central nervous system white matter with secondary demyelination. The clinical characteristics of MS are weakness, paralysis, and ocular symptoms with exacerbations and remissions.

There are several biological models that are available for the multiple sclerosis. For example, experimental autoimmune encephalomyelitis in mice, rats, guinea pigs, and non-human primates. The latter is one of the best characterized experimental models of an organ-specific autoimmune disease mediated mainly by T lymphocytes.

In the following we will briefly describe the multi-organ model of the immune reaction to myelin leading to the permanent neurological damage. The architecture of our model consists in two organs, one representing a lymph-node, and a second representing a portion of the central nervous system. At this stage the lymph node description is not detailed as the one in [8] but is limited to the principal processes of antigen presentation without an explicit representation of spatial effects like precise localization of exit areas or chemotaxis.

The model is meant to represent immune cell movements from and to the effector organ (the portion of the CNS)

through the lymph node whereby myelin self peptides are presented to T cytotoxic cells for activation of the immune response. This process goes in stages: first the myelin self peptides are collected by antigen presenting cells in the CNS; then they are transported to lymph nodes; there, they are presented to Th cells that recognize them and get active. Activated Th cells bind to the epithelial walls of the brain by releasing cytokines (mediator cells) such as interferon gamma, interleukin-2 and lymphotoxin. These regulate the production of complementary adhesion molecules to the cohesion molecules on the walls of the brain, causing Th cells to bind to them. Within the CNS, the cytokines released by the Th cells act on microglia, transforming them into antigen-presenting cells capable of displaying myelin fragments. Cytotoxic T cells, activated to attack the myelin-mimicking antigen, bind to the myelin microglia and destroy them. Interleukins cause the inflammation of the blood-brain barrier, thinning it so that Th cells, B lymphocytes and macrophages can enter. Macrophages complete the process by stripping the myelin sheath directly off the nerves. In turn, they release necrosis factor alpha, which is believed to damage oligodendrocytes (i.e., the cells that produce myelin) making the damage irreparable.

From the computational point of view this architecture has been implemented to run on shared memory multi-processor computers. Message Passing Interface (MPI) has been used for interprocess communication. At the current stage, the simulation procedure for each single organ is executed on one or more processors and can, in principle be run on a different grid node. This architecture is highly scalable because interprocess communication needs to account for those cells or molecules that migrate from one organ to another. Since migration implies a long latency in real bodies due to traveling of cells in lymphatic channels, there is no real hazard for the processors to waste time sitting up for informations from another processor (i.e., organ).

The grid has been used to perform thousands of similar executions, needed, in certain cases, to perform statistics, rather than splitting different organs to different grids.

The computational Grid set up from the ImmunoGrid consortium was devised to maximize the range and number of resources that can be added into it, from local desktop workstations to national/international grid services [13]. The AHE (the Application Hosting Environment) and DESHL (DEISA Services for the Heterogeneous management Layer) were used together, to provide access to the maximum range of resources. Finally the ImmunoGrid framework [5] also allows the simulation tools to be accessed via a Web Service that provides an Application Programming Interface (API) to enable users integrating a remotely-hosted service. For ImmunoGrid, instances of our simulators can be wrapped as Web Services, deployed on a local machine, and accessed via the Grid framework men-

tioned above. In case studies, access was restricted to local resources in London (UK), Bologna (Italy) and Boston (US) that were made available by members of the ImmunoGrid Consortium. Details of these resources are given in [13].

## 4. Conclusions

The spatial description of human organs in computational models will be more and more of importance to study the effects of propagation of signals in pathogenesis and in therapeutic regimens. Quoting I. Cohen “a good model has to talk to us in a language we understand” [12] we want to make the point that a great deal of knowledge can emerge when going from actual spatial limited (or free) mathematical models of the immune system, to four dimensional simulations that take into account a detailed description of the tissues.

In this article we have described a possible architecture for complex simulation whose workflow starts with image acquisition by commonly available scans (e.g., NMR) and terminates with a spatially extended detailed agent-based simulation of the cell movement and interaction in pathological conditions.

We have also briefly outlined a work in progress that utilizes such workflow and that strives for the study of the still unknown processes leading to the Multiple Sclerosis.

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## References

- [1] 3D slicer. <http://www.slicer.org/>.
- [2] euHeart project. <http://www.euheart.eu/>.
- [3] First international workshop on virtual tissues (v-tissues 2009). [http://www.epa.gov/NCCT/virtual\\_tissues/index.html](http://www.epa.gov/NCCT/virtual_tissues/index.html).
- [4] Ia-femesh. <http://www.ccad.uiowa.edu/mimx/IA-FEMesh/>.
- [5] ImmunoGrid project. [www.immunogrid.org](http://www.immunogrid.org).
- [6] A. K. Abbas, A. H. Lichtman, and S. Pillai. *Cellular and molecular immunology*. Saunders Elsevier, 2007.
- [7] G. Azzali, M.-L. Arcari, and G. F. Caldara. The ‘mode’ of lymphocyte extravasation through heV of peyer’s patches and its role in normal homing and inflammation. *Microvascular Research*, 75(2):227–37, 2008.
- [8] V. Baldazzi, P. Paci, M. Bernaschi, and F. Castiglione. Modeling lymphocytes homing and encounters in lymph nodes. *BMC Bioinformatics*, 2009. Submitted.

- [9] J. Bohland, C. Wu, H. Barbas, H. Bokil, M. Bota, H. Breiter, H. Cline, J. Doyle, P. Freed, R. Greenspan, S. Haber, M. Hawrylycz, D. Herrera, C. Hilgetag, Z. Huang, A. Jones, E. Jones, H. Karten, D. Kleinfeld, R. Kötter, H. Lester, J. Lin, B. Mensh, S. Mikula, J. Panksepp, J. Price, J. Safdieh, C. Saper, N. Schiff, J. Schmahmann, B. Stillman, K. Svoboda, L. Swanson, A. Toga, D. V. Essen, J. Watson, P. Mitra, and O. Sporns. A proposal for a coordinated effort for the determination of brainwide neuroanatomical connectivity in model organisms at a mesoscopic scale. *PLoS Comp Biol*, 5(3):e1000334(1–9), 2009.
- [10] E. Bonabeau. Agent-based modeling: Methods and techniques for simulating human systems. *PNAS*, 99(3):7280–7, 2002.
- [11] F. Castiglione. Agent based modeling. *Scholarpedia*, page 3735, 2006.
- [12] I. Cohen. Modeling immune behavior for experimentalists. *Immunological Reviews*, 216(1):232–36, 2007.
- [13] M. D. Halling-Brown, D. S. Moss, and A. J. Shepherd. Towards a lightweight generic computational grid framework for biological research. *BMC Bioinformatics*, 9:407, 2008. doi:10.1186/1471-2105-9-407.
- [14] Y. Louzoun. The evolution of mathematical immunology. *Immunological Reviews*, 216(1):9–14, 2007.
- [15] Y. Louzoun, S. Solomon, H. Atlan, and I. Cohen. Modeling complexity in biology. *Physica A*, 297(1-2):242–52, 2001.
- [16] O. Lund, M. Nielsen, C. Lundegaard, C. Kesmir, and S. Brunak. *Immunological Bioinformatics*. MIT Press, Cambridge, Massachusetts, 2005.
- [17] C. Lundegaard, O. Lund, C. Kesmir, S. Brunak, and M. Nielsen. Modeling the adaptive immune system: predictions and simulations. *Bioinformatics*, 23(24):3265–75, 2007.
- [18] M. Nielsen, C. Lundegaard, S. Brunak, and O. Lund. Modelling the human immune system by combining bioinformatics and systems biology approaches. *Journal of Biological Physics*, 32(3-4):335–53, 2006.
- [19] F. Pappalardo, M. D. Halling-Brown, N. Rapin, P. Zhang, D. Alemanni, A. Emerson, P. Paci, P. Duroux, M. Pennisi, A. Palladini, O. Miotto, D. Churchill, E. Rossi, A. J. Shepherd, D. S. Moss, F. Castiglione, M. Bernaschi, M.-P. Lefranc, S. Brunak, S. Motta, P.-L. Lollini, K. E. Basford, and V. Brusic. Immunogrid, an integrative environment for large-scale simulation of the immune system for vaccine discovery, design, and optimization. *Briefing in Bioinformatics*, 10(3):330–40, 2009.
- [20] N. Rapin, O. Lund, M. Bernaschi, and F. Castiglione. Computational immunology meets bioinformatics. *BMC Bioinformatics*, 2009. Submitted.
- [21] N. Shnerb, Y. Louzoun, E. Bettelheim, and S. Solomon. The importance of being discrete: life always wins on the surface. *PNAS*, 97(19):10322–4, 2000.
- [22] S. Wolfram. *Theory and Application of Cellular Automata*. World Scientific, Singapore, 1986.
- [23] S. Wolfram. *Cellular Automata and Complexity*. Addison-Wesley, Reading, 1994.