Grid-based Atherosclerosis Simulations

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***Abstract*—Atherosclerosis, a pathology affecting arterial blood vessels, is one of most common disease of the developed countries. We present studies on the increased atherosclerosis risk using an agent based model of atherogenesis that has been previously validated using clinical data. It is well known that the major risk in atherosclerosis is the persistent high level of low density lipoprotein (LDL) concentration. However, it is not known if short period of high LDL concentration can cause irreversible damage and if reduction of the LDL concentration (either by life style or drug) can drastically or partially reduce the already acquired risk. We used the Sicilian Grid infrastructure to simulate three different clinical situations in a large set of virtual patients (200 per clinical scenario). In the first one the patients lifestyle maintains the concentration of LDL in a no risk range. This is the control case simulation. In the second and in the third simulations, the lifestyle of the virtual patients raises the LDL concentration to a risk level. Differences in the foam cells formation can be interpreted as permanent or non-permanent risk effects. Finally we consider virtual patients whose life style raises many times the level of LDL concentration just above the normal but this is quickly reduced using appropriate treatment. Those preliminary results obviously need to be clinically investigated. The Grid power allowed us to retrieve results of the simulation in a short time.**

***Index Terms*—Agent based model, atherosclerosis, Grid, HPC.**

I. Introduction

ATHEROSCLEROSIS, a disease affecting arterial blood vessels, is one of most common disease of the developed countries. It is, in large part, due to the deposition of low density lipoproteins (LDLs), i.e., plasma proteins carrying cholesterol and triglycerides, that determine the formation of multiple plaques within the arteries [1], [2]. The origin of atherosclerosis is still not fully understood. However there are risk factors which increase the probability of developing atherosclerosis in humans. Some of these risk factors are beyond a person's control (smoking, obesity), others seem to have genetic origin (familial hypercholesterolemia, diabetes, hypertension) [3]. Common denominator in all the form of atherosclerosis is the elevated level of LDL, which is subject to oxidation becoming ox-LDL, that promotes an inflammatory response and immune activation in the artery walls [4]. The formation of atherosclerotic plaques in the artery reduces both the internal diameter of vessels and the blood flux leading to a number of serious pathologies [5]. Early studies demonstrated that ox-LDL can induce activation of monocytes/macrophages, endothelial cells and T cells. Ox-LDLs engulfed by macrophages form the so called foam cells [6]. These cells represent the nucleus of the plaques formation. Ox-LDL promotes also immune activation of B cells inducing the production of specific anti ox-LDL antibody (OLAB).

Atherosclerosis and their anatomical consequences cause severe problems. Stenosis (narrowing) and aneurysm of the artery are chronic, slowly progressing and cumulative effects indicating the progression of atherosclerotic disease. In both case the result is an insufficient blood supply to the organ fed by the artery. Most commonly, soft plaque suddenly ruptures, causes the formation of a thrombus that will rapidly slow or stop blood flow, leading to death of the tissues fed by the artery. This catastrophic event is called infarction and is not predictable. The most common event is thrombosis of the coronary artery causing infarction (a heart at-

tack): However, since atherosclerosis is a body wide process, similar events also occur in the arteries of the brain (stroke attack), intestines, kidneys, etc. Those atherosclerosis associated events often cause of dead or serious invalidate diseases and require preventive treatments. Vaccine research for atherosclerosis is a hot pharmaceutical topic.

Recently we proposed a model based on the Agent Based Model (ABM) paradigm [7] which reproduces clinical and laboratory parameters associated to atherogenesis. The model and its computer implementation (SimAthero simulator) considers all the relevant variables that play an important role in atherogenesis and its induced immune response, i.e., LDL, ox-LDL, OLAB, chitotriosidase and the foam cells generated in the artery wall.

In this paper we will analyze three different situations over a time scale of two years. The standard normal patients where no foam cells are formed; patients having high level of LDL but who delay to apply appropriate treatments and finally patients who may have many events of high level of LDL but takes immediately appropriate treatments.

The plan of the paper is the following. In §II we briefly describe the model of the Immune control of atherogenesis; in §III we describe our simulated patients and show the simulator results. We briefly draw conclusions and future extension of this work in §IV.

II. **Description of the model**

a) ***The biological scenario.:*** Exogenous and endogenous factors induce in humans a very small, first oxidative process of blood circulating native LDLs (minimally modified LDLs or mm-LDLs). In endothelium mm-LDLs are extensively oxidized from intracellular oxidative products and then recognized by the macrophage scavenger receptor. High level and persistent in time LDLs lead to macrophages engulfment and their transformation in foam cells. Contrary, low level of LDLs and their oxidized fraction, lead to the internalization of the oxidized low density lipoproteins and subsequent presentation by major histocompatibility complex class II at the macrophages surface. Recognition of ox-LDL by macrophages and naive B cells, leads, by T helper lymphocytes cooperation, to the activation of humoral response and production of OLAB. When the OLAB/ox-LDL immune complexes are generated in the vascular wall, the macrophages catch them by the Fc receptor or via phagocytosis and destroy ox-LDL in the lysosome system. During this process, the activated macrophage releases chitotriosidase enzyme, that is then used as a marker of macrophage activation.

b) ***The Model.:*** To describe the above scenario one needs to include all the crucial entities (cells, molecules, adjuvants, cytokines, interactions) that biologists and medical doctors recognize as relevant in the game. The model described in [7] contains entities and interactions which both biologist and MD considered relevant to describe the process.

Atherosclerosis is a very complex phenomenon which involves many components some of them not fully understood. In the present version of the simulator we considered only in the immune system processes that control the atherogenesis. These processes may occur in immune system organs like lymph nodes or locally in the artery endothelium. To describe the Immune processes we considered both cellular and molecular entities.

Cellular entities can take up a state from a certain set of suitable states and their dynamics is realized by means of state-changes. A state change takes place when a cell interacts with another cell or with a molecule or both of them. We considered the relevant lymphocytes that play a role in the atherogenesis-immune system response, B lymphocytes and helper T lymphocytes. Monocytes are represented as well and we take care of macrophages. Specific entities involved in atherogenesis are present in the model: low density lipoproteins, oxidized low density lipoproteins, foam cells, auto antibodies anti oxidized low density lipoproteins and chitotriosidase enzyme. Cytotoxic T lymphocytes

are not taken into consideration because they are not involved in the immune response (only humoral response is present during atherogenesis).

Molecular entities The model distinguishes between simple small molecules like interleukins or signaling molecules in general and more complex molecules like immunoglobulins and antigens, for which we need to represent the specificity. We only represent interleukin 2 that is necessary for the development of T cell immunologic memory, one of the unique characteristics of the immune system, which depends upon the expansion of the number and function of antigen-selected T cell clones. For what is related to the immunoglobulins, we represent only type IgG. This just because at the actual state we don't need to represent other classes of Ig and because IgG is the most versatile immunoglobulin since it is capable of carrying out all of the functions of immunoglobulins molecules. Moreover IgG is the major immunoglobulin in serum (75% of serum Ig is IgG) and IgG is the major Ig in extra vascular spaces.

The actual model does not consider multicompartments processes and mimics all processes in a virtual region in which all interactions take place. Our physical space is therefore represented by a 2D domain bounded by two opposite rigid walls and left and right periodic boundaries. This biological knowledge is represented using an ABM technique. This allows to describe, in a defined space, the immune system entities with their different biological states and the interactions between different entities. The system evolution in space and in time is generated from the interactions and diffusion of the different entities. Compared to the complexity of the real biological system our model is still very naive and it can be extended in many aspects. However, the model is sufficiently complete to describe the major aspects of the atherogenesis-immune system response phenomenon.

The computer implementation of the model (SimAthero hereafter) has two main classes of parameters: the first one refers to values known from standard immunology literature [8], [9] [10], [11]; the second one collects all the parameters with unknown values which we arbitrarily set to plausible values after performing a series of tests (*tuning phase*).

The simulator takes care of the main interactions that happens during an immune response against atherogenesis.

Physical proximity is modeled through the concept of lattice-site. All interactions among cells and molecules take place within a lattice-site in a single time step, so that there is no correlation between entities residing on different sites at a fixed time. The simulation space is represented as a $L \times L$ hexagonal (or triangular) lattice (six neighbors), with periodic boundary conditions to the left and right side, while the top and bottom are represented by rigid walls. All entities are allowed to move with uniform probability between neighboring lattices in the Grid with equal diffusion coefficient. In the present release of the simulator chemotaxis is not implemented.

LDLs values can be fixed in order to simulate different patients both in normolipidic condition and in hypercholesterolemic condition. The same applies to ox-LDLs. However human habits change with time and personal life style. A normolipidic patient can change its attitude becoming an hypercholesterolemic one and vice versa. For this reason we allow the simulator to accept varying life style conditions and preventive actions to decrease risk factors.

III. **Results**

The model described include the possibility of mimicking biological diversity between patients. The general behavior of a class of virtual patients arise from the results of a suitable set of patients, i.e., the mean values of many runs of the simulator of different patients under the same conditions. The class of virtual patients described by the model were tuned against *human* data data collected by [12], [13] where different conditions, normal and hypercholesterolemic diabetic patients were analyzed.

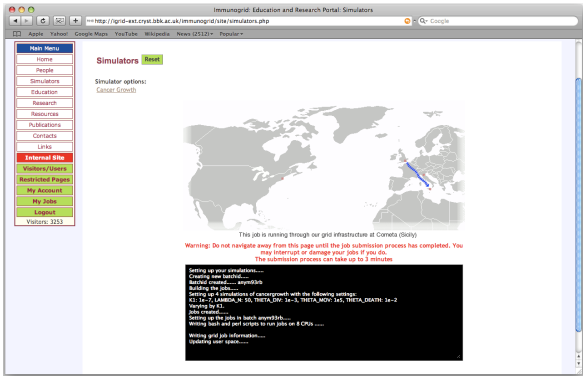

Fig. 1. The submission process of Grid jobs to COMETA infrastructure using ImmunoGrid web portal

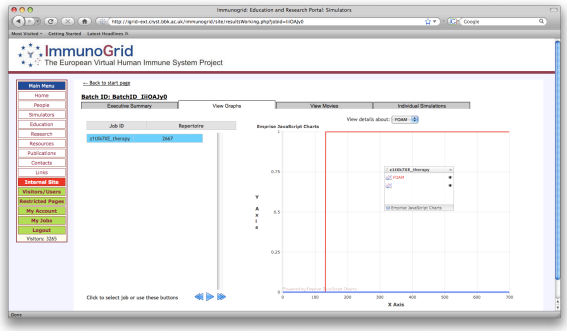

Fig. 2. Simulation results of a virtual patient with level of LDL considered normal. The follow-up period is two years. The figure shows that foam cells formation is absent in this patient.

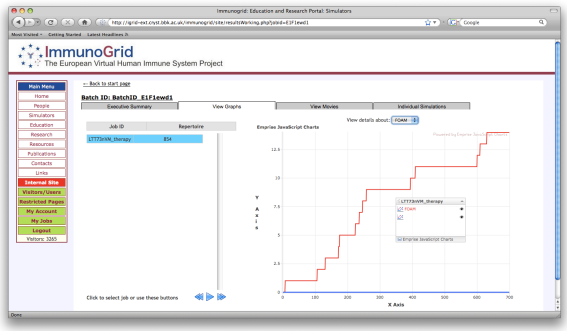

Fig. 3. Simulation results of a virtual patient with level of LDL considered at high risk. The follow-up period is two years. The figure shows that foam cells formation is present, leading to an atherogenesis process.

In this section we analyze the behavior of the same patients in three broad class of clinical conditions to show how SimAthero could be used in order to analyze and predict the effects of various LDL levels in blood. The normal patient simulation is used as control experiment for the other simulations. The differences among these four clinical conditions depend on the LDL level and the time interval which occurs between the time in which concentration of LDL rise above normal level and the time in which the patient take appropriate treatments (lifestyle o drug) to reduce it to normal level.

Jobs were launched using the SimAthero simulator on the COMETA Grid. The submission process was done through the web interface of the ImmunoGrid project (http://www.immunogrid.eu). Figure 1 shows the submission process.

A patient with a LDL level of roughly 950-970 ng/μl of blood is considered normal in clinical practice and he has with very low risk of atheroslerotique plaque. The results of SimAthero for a virtual normal patient (Figure 2) show that he will not support the formation of foam cells and, as a consequence, the beginning of atherogenesis process is absent.

We then simulated a scenario in which a patient, due to several reasons (diet, life style, oxidative agents and so on, so forth) leads its LDL level at 1300 ng/μl, taking it up to 1700 ng/mul. Looking at figure 3 one can observe about 12 foam cells per μl at the end of in silico follow up. This leads to a small atherogenesis process due to the high level of LDL.

Lastly (figure 4), we analyzed a virtual patient that initially takes its LDL level to small peaks, causing no damage. After that, he takes its LDL level to a hypercholesterolemic behavior, generating a small damage, as shown. This shows that small LDL alteration are completely taken under control by the normal behavior of the organism, but high LDL peaks lead to foam cells formation and then to the beginning of the atherogenesis process.

IV. **Conclusions**

Atherosclerosis is a pathology where the immune control plays a relevant role. In this article, we presented studies on the increased atherosclerosis risk using an ABM model of

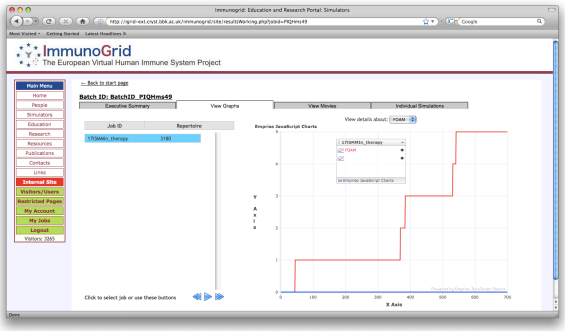

Fig. 4. Simulation results of a virtual patient with level of LDL considered quasi-normal at the beginning and then at high risk. The follow-up period is two years. The figure shows that foam cells formation is negligible in the first time, but becomes important soon after.

atherogenesis and its induced immune system response in humans. Very few mathematical models [14], [15] and (to our best knowledge) no computational models of atherogenesis have been developed to date.

It is well known that the major risk in atherosclerosis is persistent high level of LDL concentration. However it is not known if short period of high LDL concentration can cause irreversible damage and if reduction of the LDL concentration (either by lfe style or drug) can drastically or partially reduce the already acquired risk.

Using an ABM cellular model describing the initial phase of plaque formation (atherogenesis) we are able to simulate the effect of life style which increases the risk of atherosclerosis.

The Cometa Grid infrastructure allowed us to launch hundreds of jobs and obtain results in a reasonable time.

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Francesco Pappalardo earned his master and PhD. degree from University of Catania, in 2000 and 2004 respectively. Actually he is holding a postdoctoral fellow and he is temporarily assigned to the professorship of Mathematics at the University of Catania. From 2001 to 2004 he did research in computer operating system security. In 2008 he was visiting scholar at Dana-Farber Cancer Institute in Boston (USA) while in 2006 he visited the Molecular Immunogenetics Labs, IMGT in Montpellier (France). His major research areas are on modeling human and mouse immune system responses involved in several pathologies, including viral infections, tumors, and atherosclerosis. This effort leaded and actually leads to both a better understanding of the immune system, and to the application of these modeling approaches to vaccine research. Up to now, Francesco Pappalardo published more than 40 reviewed research papers. He serves the scientific community as editorial board member, reviewer and program committee member for major journals and conferences in the area of computer science and computational biology.

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