# Computational modeling of atherosclerotic plaque progression through an efficient 3D agent-based modeling approach


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***Abstract*— Since atherosclerosis has been declared as the leading cause of mortality worldwide, the imminent need for the design and development of straightforward computational modeling workflows to improve the existing cardiovascular disease risk stratification models is more important than ever. Agent-based modelling (ABM) is a promising computational approach which can be utilized for decision making in various domains from the healthcare sector to industrial applications. In the present study, we propose a straightforward approach for atheromatic plaque progression in the coronary and peripheral arteries using specialized mathematical models and computational simulations which will enable the accurate prediction of the cardiovascular disease evolution. The model incorporates the realistic 3D geometry of the artery and is the first ABM implemented in C#. According to our results, the 3D ABM was able to simulate the Trans Endothelial Migration of Lymphocytes, Monocytes and Neutrophils, the artery wall cells, endothelium cells and plaque cells reducing the time step for each cycle from 40 seconds to 0.04 seconds per cycle.**



***Keywords*— *agent-based modeling, computational simulations, atherosclerosis, plaque progression.***


## I. Introduction

Coronary heart disease (CHD) has been characterized as the main cause of mortality worldwide with more than 60% of the global burden in developing countries [1]. Atherosclerosis is the most prevalent manifestation of CHD. As a matter of fact, computational models are crucial in order to facilitate the improvement of preventive care, as well as, to enable the design of new computational approaches for atherosclerosis plaque progression.

Agent-based modelling (ABM) is an example of such a computational approach which can be utilized for decision making in the healthcare sector. More specifically, ABM is a computational modelling approach which can capture the evolution of complex dynamical systems [2].This approach is useful not only for understanding complex biological systems, but also for facilitating *in silico* experiments in a cost- and time-efficient manner.

Several advanced models have been presented in the literature [1-6]. Most of these studies, however, have used idealized 2D geometries of the artery although only a few of them have utilized realistic patient geometries [7, 8]. Through the different imaging modalities, such as, MR angiography, Intravascular ultrasound (IVUS), Optical coherence tomography (OCT), and Computerized tomography (CT), realistic 3D models of human vessel geometries can be acquired. Images can then be used for patient-specific 3D reconstruction of the vessel's lumen and outer wall, and application of computational fluid dynamics (CFD) simulations. ABMs will be combined with the existing plaque growth models and the underlying interactions between continuum mechanics and finite elements towards the proper simulation of the atherosclerotic plaque growth. None of these studies, however, have focused on the development of a 3D ABM but rather on the simulation of 2D ABMs for multiple planes. In addition, the existing ABMs for plaque growth [2, 4] have been implemented, employing conventional software tools like Matlab and Net3Dlogo


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which are computationally demanding for the simulation of millions of agents over time.

To address these needs, a straightforward computational method is proposed to simulate atherosclerotic plaque progression using a coronary lesion from a patient using agent-based models (ABMs). The regular cylinder-shape artery was replaced with the reconstruction of a real segment of the human carotid/coronary artery. This was enabled by the 3D reconstruction of real carotid/coronary artery, where 3D .stl (standard triangle language) files were translated into coordinates in the 3D space. These coordinates were then used to calculate the exact dimension of the 3D grid. The 3D ABM design and development process took place in C# through Unity to leverage the complexity of the simulation process. The resulting ABM was able to simulate the Trans Endothelial Migration of Lymphocytes, Monocytes and Neutrophils, as well as, the artery wall cells, endothelium and plaque cells. The transformation from lists of agents and space analysis to agent dictionaries shortened the time step for each cycle from 40 seconds to 0.04 seconds per cycle. This can enable the log-term simulation of the 3D ABM with significantly reduced computational cost.

## II. Materials And Methods

### A. Data acquisition protocol

OCT imaging data (in DICOM format) were acquired by one patient who provided written informed consent at the University Hospital of Ioannina (UOI). The clinical study protocol conformed to the Declaration of Helsinki and was approved by the institutional ethics committee.

### B. 3D reconstruction of the coronary artery and plaque tissue components

As far as the initial step of the 3D reconstruction method is concerned, the automated registration of the angiographic views was applied with respect to the R-peak OCT frames. Then, a pre-processing procedure took place for the annotation of lumen borders. Next the automatic extraction of the 2D centerline was accomplished by the angiographic views and then it was used to generate the 3D centerline path. Afterwards the detection of the atherosclerotic plaque and characterization were performed. The segmented R-peak OCT frames were placed in a perpendicular plane within the 3D centerline path. The absolute orientation of the 3D model was accomplished by taking the annotated branches of the OCT frames to create the final 3D arterial model (Fig. 1).

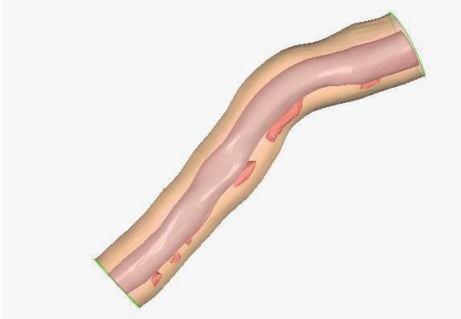

**Figure 1**. An illustration of the 3D reconstructed artery.

### C. Agent based modeling

#### 1) Proposed workflow

The proposed workflow (Fig.2) consists of three computational stages, namely: (i) the agent's allocation stage, (ii) the engine execution stage, and (iii) the ABM results stage. The agent's allocation stage involves the definition of different algorithmic parameters, such as, the number of agents, the type of agents (e.g., monocytes, leukocytes, TNF-α) and the time-interval for simulation (e.g., 2 months). The simulation of the mathematical equations for agent modeling is then conducted in the engine execution stage until the tolerance criteria are met. In case the simulation criteria do not converge, the overall process is repeated until convergence or is terminated after a pre-defined number of rounds. The engine's output is the 3D ABM with all the agents which can be visualized either through a horizontal or a vertical plane, as well as, in a 3D format. In any case, the ABM is displayed to the user through the user-interface.

#### 2) ABM simulation workflows

The proposed methodology will be based on the findings from studies [2, 4], as well as, in the previous knowledge available in the laboratory from several research projects (SMARTool [4], TAXINOMISIS [7], INSILC [8]) in order to develop a multiscale framework which simulates atherosclerotic plaque growth progression.

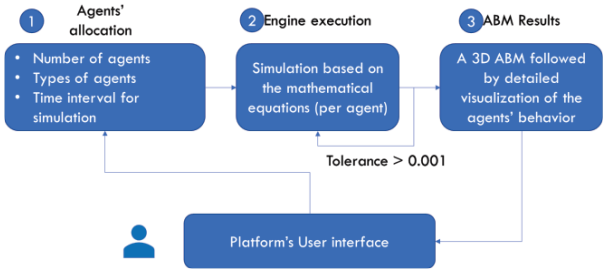


**Figure 2.** The proposed workflow for the ABM construction method.

The 2D ABM was fed with an initial WSS profile, which can potentially trigger a pathologic vascular remodeling[9]. WSS values were obtained from the 3D CFD (computational fluid dynamics) simulation, and a level of endothelial dysfunction $D^i$ was computed as in:

$$D(WSS^{\mathrm{i}}) = D^i = \begin{cases} 1 - \frac{WSS^{\mathrm{i}}}{WSS^{\,0}}, if\ WSS^{\mathrm{i}} < WSS^{\,0} \\ 0, \qquad otherwise \end{cases}, \tag{1}$$

where $WSS^i$ refers to the wall shear stress at the $i$-th location and $WSS^{\,0}$ refers to the normal value. Every problematic endothelial location $i$, $D^i \neq 0$, activates several alterations that diffuse within the intima, starting from a peak of intensity $D^i$ having a diffusion constant $\varphi$:

$$A^{i,l}(D^i, f) = A^{i,l} = D^i\, exp\left(-\frac{1}{2}\left(\frac{f}{4\varphi t}\right)^2\right), \tag{2}$$

where $A^{i,l}(D^i, f)$ quantifies the extent of the modification that originates from the $i$-th endothelial location and is captured at the $l$-th site, at a distance $f$ from the $i$-th location. The individual levels of modification across the endothelial sites per location $l$, are then combined to yield the overall extent of inflammation of the $l$-th location, say $I^l$:

$$I^l = \sum_{j=1}^{N_L} A^{j,l}, \tag{3}$$

where $N_L$ is the initial number of sites of the lumen wall and the resulting $I^l$ affect the agent dynamics.

The list of rules that were used for the ABM simulation were based on the work of Hayenga [2]. An indicative set of the rules that were implemented including the following: (i) dependence of neutrophil adhesion on TNF-α, IL-1, WSS, (ii) monocyte adhesion on TNF-α, IL-1, WSS, (iii) lymphocyte adhesion on TNF-α, IL-1, WSS, (iv) LDL infiltration through wall, (v) LDL oxidation (OxLDL) rate, (vi) Monocyte to macrophage type ratio, (vii) Foam cell formation, (viii) Removal of IL1β by IL-10 and IL1β by IL-10, (ix) lifespan of leukocytes in wall, and (ix) production of IL-1, TNF-α, IL-10, among others.

*3) Implementation details for the ABM model*

Agent Based Model can be separated into two main parts: (a) agent placement, and (b) agent control.

*a) Agent placement*

Agent placement is performed in a space defined by the size of the carotid vessel which is being modeled with a fixed step in each axis, defined by the user. Agent type is defined by the collision detection (Unity mesh collision libraries) at each point of space. This provides us the precise placement and definition of endothelial, lumen, plaque, and wall agents. All agents which are being dynamically placed, such as TNF-α, IL-1, IL-10, Lymphocyte, Monocyte, Neutrophil, M1, M2, Foam cells and LDL are defined by the calculated parameters[2, 10-12], including: leukocyte, lymphocyte, neutrophil, LDL, monocyte concentration in blood, diffusion coefficient of cytokines and LDL, healthy WSS (Pa), stiffness of artery wall (kPa), diameter of foam cell (μm), monocytes (μm), and lymphocytes (μm), among others.

*b) Agent control*

Agent control is performed with a fixed time step which is one hour. All agent data (position, role, interaction, lifespan, and dependencies) is stored, accessed, and modified in dictionaries, where the dictionary key is a unique Agent identification code. With provided conditions and rules, the simulation of ABM is being performed for the time defined by the user. Simulation time is divided by the number of checkpoints and on each checkpoint ABM results are exported.

### *D. Computational Complexity*

The computational complexity of this platform is correlated to the number of agents. The simulation puts the most load on RAM while the processor is relatively unloaded since the needed calculations for each agent are simple. Switching from lists of agents and space analysis to agent dictionaries has shortened the time step for each cycle from 40 seconds to 0.04 seconds per cycle. Every simulation has been performed on personal computer configuration without hardware, software, and driver optimization for simulation purposes.

## III. Results

The provided preliminary results are obtained using the equations and parameters (Table I) [2, 13].

Table I. List of Concentration Values for the ABM parameters.

| ***Parameters*** | ***Concentration*** |
|---|---|
| "Leukocyte" | "$7x10^9$/liter" |
| "Neutrophil" | "62% of leukocytes" |
| "Monocyte" | "5.3% of leukocytes" |
| "Lymphocyte" | "30% of leukocytes" |
| "LDL" | "Normal: 950±970 ng/μl,Unhealthy:1900±2000 ng/μl" |
| "Diffusion coefficient of cytokines" | "$3x10^{11}$ $m^2/s$" |
| "Diffusion coefficient of LDL" | "$2.5x10^{11}$ $m^2/s$" |
| "Healthy WSS (Pa) " | "1.4" |
| "Stiffness of artery wall (kPa) " | "Normal:3; Unhealthy: > 3" |
| "Diameter of neutrophils & lymphocytes (μm) " | "12" |
| "Diameter of monocytes (μm) " | "24" |
| "Diameter of foam cell (μm) " | "25" |

A preliminary result of our model is presented in Fig. 3. The model includes different types of agents, such as, Trans Endothelial Migration (TEM) of Lymphocytes (in purple), Monocytes (in dark Red), Neutrophils (in cyan), Artery wall cells (in light red), endothelium cells (in light yellow) and plaque cells (in gray). These Leukocytes are instantiated in the endothelium cells, and they are being moved by TEM to environments with higher levels of TNF-alpha, IL-1, and IL-10. Each Leukocyte is moving towards the center of the nearest Plaque cluster. This has been implemented as a traveling salesman problem with directional vectors to the nearest plaque center, where all travel costs are equal, and the only restriction is that movement outside of the artery wall is prohibited.

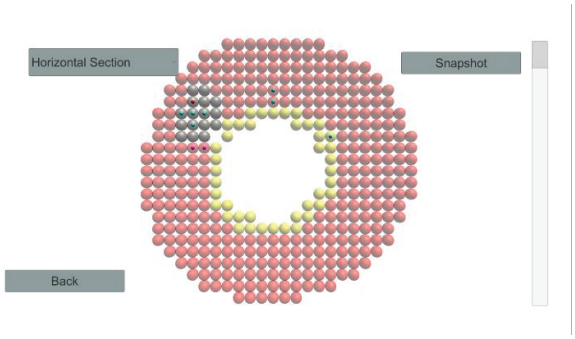


**Figure 3**. Preliminary results of our model. The Trans Endothelial Migration of Lymphocytes (Purple), Monocytes (Dark Red) and Neutrophils (Cyan), there are also Artery wall cells (light red), endothelium cells (light yellow) and plaque cells (gray) are shown with appropriate color coding.

## IV. Conclusions

In the present work, a straightforward 3D ABM model is proposed for atheromatic plaque growth progression in the coronary and peripheral arteries using mathematical models and computational simulations which will enable the accurate prediction of the cardiovascular disease evolution. One main advantage of this new approach is the use of 3D realistic reconstructed artery aiming to provide a personalized simulation of the atherosclerosis plaque progression.

The 3D model was developed in C# under Unity which is flexible and overcomes the computational burden that is introduced by ABM simulation through existing software

packages like Matlab and Net3Dlogo. The proposed 3D ABM is based on a discretized 3D environment which was implemented as a grid. The grid is composed of single spherical blocks, called patches, of size 100x100x100μm (this can be also adjusted by the provided user interface). Each patch can be populated by different agents (e.g., leukocytes, neutrophils, macrophages, Foam Cells, Endothelial cells, LDL, OxLDL, IL-1, TNF, and IL-10). Although smaller patch sizes would increase the resolution, possibly allowing better capture of the dynamics of plaque progression, the computational performance would be drastically reduced.

To make all these feasible, the proposed ABM utilizes every type of agent following specific rulesets. These rulesets, which drive agent behaviors, are derived from the published literature[2]. Each mathematical equation was individually modeled in C# avoiding any computational restrictions, such as, the overlap of agents during simulation or the automated adjustment of neighboring agents' position which was triggered by the simultaneous adjustment of specific agents.

Current practice has provided us that the conventional methods for simple simulations are not enough to perform this task. After analyzing all possibilities for further development and improvement of this platform, our plan is to:

(i) Improve the computational performance by using the equipment dedicated for the mentioned simulations.

(ii) Optimize algorithms, which will be done by performing vectorization and parallelization of current processes.

(iii) Use tools which will significantly improve the performance and reduce the execution (CUDA drivers, Server execution, Distributed programming etc.).

(iv) Validate the biological properties and mechanisms of the proposed 3D ABM (e.g., LDL) with the corresponding values from the literature. To this end, the size of the agents will be properly adjusted to yield standard biological properties over time (e.g., stable LDL values).

## V. Conclusion

The present work focuses on the development of a straightforward workflow towards the effective simulation of atherosclerotic plaque progression across real patient lesions. The 3D agent-based model (ABM) takes into consideration the biological properties and mechanisms of atherosclerotic plaque progression based on the extracted 3D baseline geometry. Although a preliminary version of a fully functionable C# implementation is ready and able to support the simulation of the Trans Endothelial Migration of Lymphocytes, Monocytes and Neutrophils, the artery wall cells, endothelium cells and plaque cells, additional simulations will be conducted on more patients to assess the generalizability of the proposed procedure. Furthermore, the fact that the proposed implementation can reduce the time step for each cycle from 40 seconds to 0.04 seconds per cycle enables the 3D ABM simulation to be significantly reduced in time.

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