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MULTISCALE COUPLING OF A LATTICE BOLTZMANN SIMULATION OF BLOOD FLOW TO CELL- AND TISSUE-LEVEL PROCESSES: THE CASE OF IN-STENT RESTENOSIS

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Abstract. *In-stent restenosis, the maladaptive response of a blood vessel to injury caused by the deployment of a stent, is a multiscale system involving a large number of biological and physical processes. We describe a Complex Automata Model for in-stent restenosis, coupling blood flow, drug diffusion, and smooth muscle cell models, all operating on different time scales. The Haemodynamics is handled using a dedicated Lattice Boltzmann simulation. Some details of the coupling of the Lattice Boltzmann simulation to other single scale models are described, together with first simulation results, obtained with a dedicated software environment for Complex Automata simulations.*

1 INTRODUCTION

In-stent restenosis, the maladaptive response of a blood vessel to injury caused by the deployment of a stent, is a multiscale problem involving a large number of processes [1]. We developed a Complex Automata Model for in-stent restenosis [2,3], coupling bulk flow, drug diffusion, and smooth muscle cell model, all operating on different time scales. A 2D version of this model was implemented [2] using MUSCLE (the COAST Multiscale Coupling Library and Environment) [4]. Recently, we added a model for early thrombus formation [5] and realized a 3D version of the simulation. This 3D simulation is executed in a distributed fashion, where the most compute intensive part of the multiscale model is executed on a HPC system while the other single scale models are executed on a dedicated compute server.

In this contribution details of the single scale models are presented, with special attention to the multiscale coupling of the cell- and tissue-level processes (thrombus formation, smooth muscle cell proliferation, drug diffusion) to the lattice Boltzmann flow solver. Moreover, some first results of 3D simulations of in-stent restenosis will be presented. For all details we refer to an upcoming publication [6].

2 COMPLEX AUTOMATA MODELING AND SIMULATION

We proposed Complex Automata (CxA) as a paradigm for multiscale modeling and simulation [3]. CxA theory dictates that a multiscale system can be decomposed into mutually interacting single scale models. The multiscale system, and its formulation as a CxA can be represented graphically on a Scale Separation Map (SSM), where the horizontal and vertical axes represent the temporal and spatial scales. An example of such a SSM (as discussed in detail in section 3) is shown in Figure 1.

An essential step in the modeling process is the inclusion of specific *coupling templates*, designed to mimic the dynamic behavior of the multi-scale process as accurately as possible. In the CxA formulation, a coupling template between two single scale models can be formally expressed as an interaction between the observable of the first, and the execution loop (i.e. initial conditions, collision, boundary condition operators) of the second model.

The conceptual ideas behind the CxA approach (decomposition into single scale models, restriction to a common instruction flow and specification of finite number of coupling templates) have been used to develop the *Multiscale Coupling Library and Environment* (MUSCLE) [4,7], a software environment in which a CxA can be implemented naturally.

Within the coupling library, both the kernels (i.e. the single scale models) and the conduits (i.e. the multiscale coupling) are software agents of the underlying multi agent platform JADE (www.jade.tilab.com). The single scale models do not need to be aware of each other and the information on the coupling and the global setup are held by the framework. This allows the implementation of complex interfaces, where multiscale couplings can be performed by the use of smart conduits. Furthermore, the structure of the coupling library allows complete independence from native codes. These can be replaced with a different source, provided the interface with respect to the framework (i.e. the JAVA-wrapper agent) remains the same. In the particular example of in-stent restenosis, described in section 3, three single scale models have been implemented in different programming languages (FORTRAN90, C++, JAVA), wrapped as JAVA agents, and connected via the MUSCLE framework.

3 MULTISCALE MODEL FOR IN-STENT RESTENOSIS

A *stenosis* is a narrowing of a blood vessel lumen due to the presence of an atherosclerotic plaque. This can be corrected by balloon angioplasty, after which a stent (metal mesh) is deployed to prevent the vessel from collapsing. The injury caused by the stent can lead to a maladaptive biological response of the cellular tissue (mainly due to smooth muscle cell proliferation). The abnormal growth can produce a new stenosis (re-stenosis). Restenosis develops under conditions of pulsatile flow and there exists an interaction between the much studied biological pathways and those of a physical nature

The multiscience and multiscale nature of in-stent restenosis has been discussed in detail previously by Evans et al. [1]. The processes key to the regulation of restenosis were identified, and their temporal and spatial scales determined. Coupling was considered in terms of the interactions between these processes. This allowed us to generate a comprehensive conceptual scale separation map, defining a CxA, containing the sub-models necessary to capture the behavior of the system. The first practical implementation of the CxA reported herein considers a simplified version of the model focusing on Smooth Muscle Cell (SMC) behavior, and its interaction with blood flow and drug eluted from the stent. The simplified SSM is shown in Figure 1.

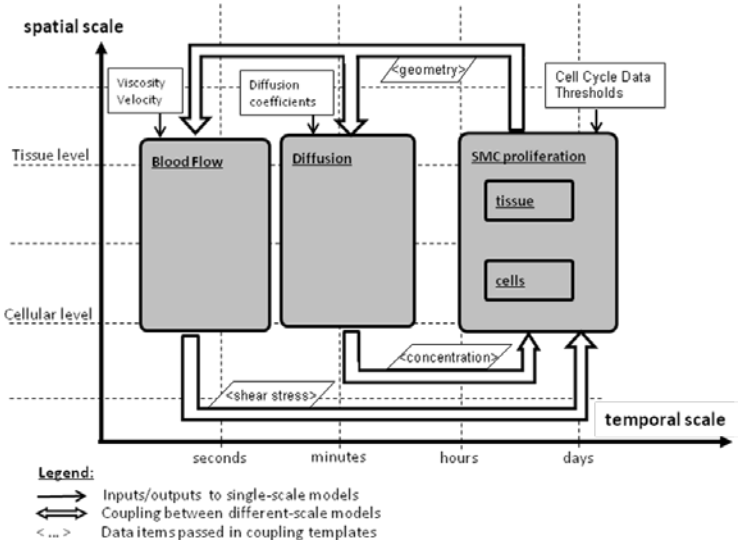

Figure 1: The simplified SSM, depicting the three single scale models and their mutual coupling.

Following deployment of the stent, which is modelled as a separate process to provide an initial condition (see [2,6]), SMCs start to proliferate. The rate of smooth muscle cell proliferation is dependent on the blood flow (specifically wall shear stress (WSS) and oscillatory stress index (OSI)), the number of neighbouring smooth muscle cells, and in the case of a drug eluting stent, the local concentration of drug. The blood flow, in turn, depends on the luminal geometry (and thus changes with the proliferation of SMCs), and the concentration of drug depends on the SMC/tissue domain (and therefore also on SMC proliferation). The SMC proliferation is the slowest process, dictated by the cell cycle, whereas flow is a fast process, dictated by the length of one cardiac cycle. Due to the specific value of the diffusion coefficients and the typical spatial dimensions of the arterial tissue, the temporal scale of the diffusion process resides between that of flow and SMC scales.

4 SINGLE SCALE MODELS AND COUPLING TEMPLATES

In this section, the CxA model of in-stent restenosis is presented in brief, details can be found in [2,6]. We first describe the kernels of the CxA, i.e. the algorithms used to simulate the single scale models (Bulk Flow, SMC Behavior and Drug Diffusion). The native codes of these have been constructed independently from the multiscale application. Then, we show how these elements are connected via smart conduits using a CxA dedicated coupling library.

Blood flow is modeled as a Newtonian incompressible fluid, employing the Lattice Boltzmann Method [8-11]. The observable related to the Bulk Flow single scale model is the wall shear stress on the vessel boundary (WSS), which is needed as input for the SMC model, after being properly mapped from the Cartesian lattice on the individual cells.

The dynamics of the smooth muscle cells are simulated using an Agent Based Model. Each single cell is represented by agent, which is identified by a set of state-variables: position, radius, biological state, drug concentration and structural stress. Each SMC agent evolves in time according its own current state and to the states of neighboring cells. Each time step involves a physical solver, simulating the structural dynamics of cells, and a biological solver, which simulates the cell cycle, according to a biological rule set. From the structural point of view, cells are represented by their centers, and a potential function, which determines non-linear repulsive and attractive inter-cell forces. In addition, boundary forces, viscous friction, radial elastic forces (modeling the primary fiber direction of SMCs in a physiologically relevant environment) and motility forces (modeling cell migration) are taken into account. The cell cycle model consists of a discrete set of states, a quiescent state G0, a growth state G1 and a mitotic state S/G2/M. Progression through the cell cycle takes place at a fixed rate, culminating in mitosis (cell division; a mother cell divides into two new daughter cells). Cells may enter or leave an inactive phase of the cell cycle (G0) depending on certain rules based on contact inhibition, structural stress, and local drug concentration. Additionally, for SMCs in contact with the fluid, rules are based on thresholds of wall shear stress (WSS) and oscillatory shear index (OSI) received from the Bulk Flow also apply.

Drug eluting stents represent an effective way of inhibiting neointima formation after stent-deployment. This process is captured in the present model through implementation of the Drug Diffusion (DD) kernel. Drug is eluted from the stent and diffuses into the cellular tissue. Thus the spatial domain for the DD kernel is coincident with that of the SMC. Stent struts act as a source whilst boundaries between flow and cells are considered sinks (this assumes that drug eluted into the lumen is continuously flushed away by the faster blood flow). Biological tissues are heterogeneous in nature so we assume that this process can be described using a generic anisotropic diffusion law.

In order to combine the single scale kernels described above using MUSCLE [4,7], we need to define a communication graph, the Connection Scheme (CS), which specifies in detail the communication topology of the CxA, defining which pairs of kernels communicate. The Connection Scheme for the CxA model of in-stent restenosis is shown in Figure 2. In addition to BF, DD and SMC kernels, the current CxA setup includes a kernel which generates the initial conditions (IC) by simulating stent deployment into the cellular tissue.

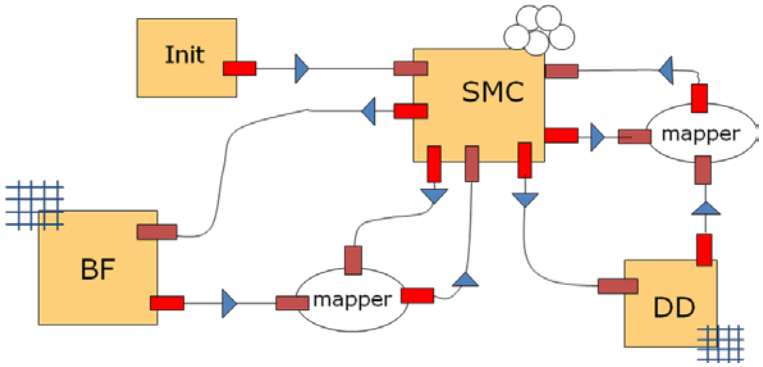

Figure 2: The Connection Scheme, showing the single scale models (Bulk Flow, SMC, Drug Diffusion), the Init agent (used to generate the initial structural stress condition in the tissue), the mapper agents and the conduits. Single scale models are mesh-based (BF, DD) or Agent-based (SMC).

Multiscale coupling is implemented using special agents called smart conduits. Often, these perform filtering operations, converting output data from one single scale model to appropriate input for another. This is the case for geometrical couplings (through changes in the domains), when new SMC configurations (continuum based) are transformed into lattice based computational domains for BF and DD.

The SMC to BF conduit converts the array of positions and radii of cell agents, into a computational mesh for the flow solver which is decomposed into fluid and solid nodes. Similarly, the SMC to DD conduit converts the array of positions and radii of the cells, into a computational mesh for the drug diffusion solver, marking the nodes as tissue, source, or sink.

In some instances, the interaction between kernels is slightly more complex, and multiple inputs are required to compute one output. In these cases we introduce *mapper* agents which are required whenever an input to the SMC model is generated. The values of fluid shear stress at the boundary affect the biological evolution of the cells. Given the output of the bulk flow solver, and the current cell configuration, a mapper agent computes the shear stress on each cell. Depending on the discretization used for the flow solver, different approaches are used. If the flow grid is coarser than the spatial scale of the SMC model (the radius of the cells), an algorithm must be used in order to determine which cells are in contact with the flow, then the shear stress is extrapolated from the closest boundary fluid nodes for each cell position. On the other hand, if the flow discretization is sufficiently fine more fluid boundary nodes interact with a single cell and the shear stress on the cell surface can be calculated by averaging the values of the closest nodes.

The drug concentration calculated in the DD has to be mapped to the SMC agents. Given the current drug concentrations and the SMC configuration, the mapper agent approximates the concentration on each cell. As for the shear stress approximation, the algorithm used depends on the grid size of the DD model. If the grid is fine enough (with many lattice nodes per SMC), the concentration on a cell can be integrated. If a coarse DD grid is used, the concentration for each cell is extrapolated using data from the closest nodes.

5 SELECTED RESULTS

As a benchmark geometry for the 2D CxA model, we consider a vessel, of length 1.5 mm and width 1.24 mm, where two square struts of side length 90 μm have been deployed. The vessel wall has a thickness of 120 μm. Smooth muscle cells are generated with an average radius of 15 μm and densely packed inside the wall.

We have run the simulation for an equivalent of 72 days (1700 time steps with a time step of 1h for the SMC model) for both a bare metal stent and a drug eluting stent. Our preliminary results demonstrate neointimal growth (proliferation of smooth muscle cells) in response to stent-induced injury. If we compare the output from immediately after stent deployment with that of 28 days later (Figure 3) it is apparent that the developing neointima causes a reduction in lumen diameter and an increase in wall shear stress. Because the SMC rule set dictates that SMC agent proliferation is inhibited by high shear, once the neointimal growth causes shear stress to increase past a threshold, an equilibrium is reached and no more proliferation occurs. This fits nicely with biological theory which asserts that a vessel remodels in response to changes in haemodynamic forces, until those forces are normalized [12].

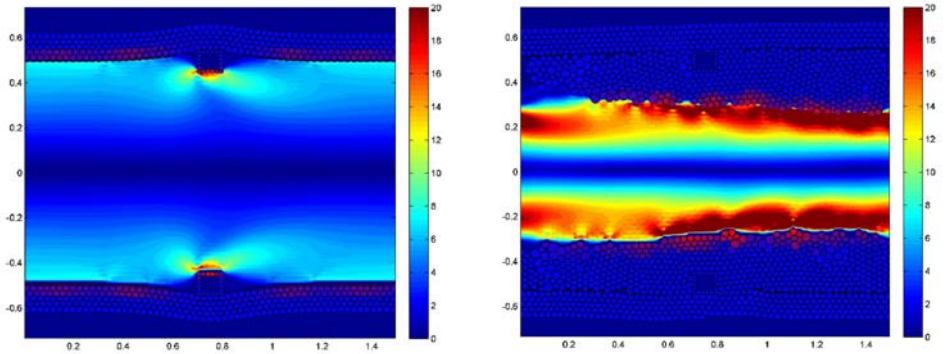

Figure 3: Left: Initial condition for the CxA model, including cell configuration, equilibrated after stent deployment, and the blood flow. Fluid shear stress is color coded (red high, blue low). Right: The same domain at 28 days post-stent deployment (672 iterations of the simulation). A neointima of SMC agents has developed in the lumen. Colour bars refer to the wall shear stress within the lumen in Pascals.

The proliferative response is reduced in the presence of drug; at the simulation endpoint (72 days), average neointimal thickness at the strut site in the absence of drug was 0.206 ± 0.005 mm versus 0.192 ± 0.001 mm in the presence of drug.

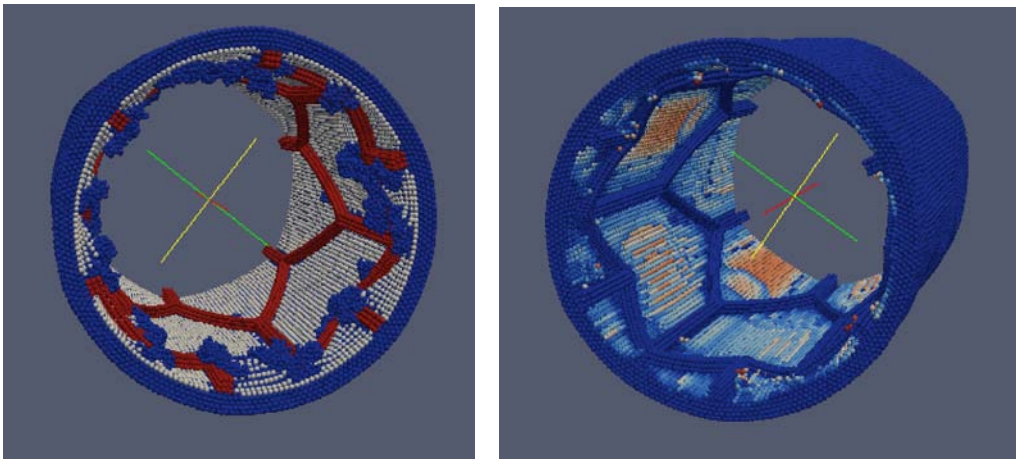

Figure 4: Left: The 3D SMC model. A simplified representation of the BiodivYsio stent (red) is deployed into the vessel wall which is composed of several layers of smooth muscle cell agents (blue) lined with a single layer of IEL agents (white). Right: Visual output from 3D simulations showing SMC and IEL agents coloured according to Wall Shear Stress. Neointima is observed forming around the stent struts.

The two dimensional CxA provides us with a tool for testing simple hypotheses regarding the relationship between stent geometry, the cellular response to injury and the influence of haemodynamic forces. In order to evaluate realistic stent designs, however, it is necessary to run three dimensional simulations. MUSCLE was used to

couple three dimensional versions of the bulk flow, SMC and drug diffusion kernels, and additionally, a thrombus kernel. Again, MUSCLE was employed to pass information between kernels using conduits and a modified generic mapper agent (in instances when multiple inputs were required to calculate one output). A simplified geometry of the BiodivYsio stent was deployed into a three dimensional representation of the vessel wall, causing laceration of the internal elastic lamina, thus permitting underlying SMC agent proliferation. Figure 4 depicts preliminary output from the 3D CxA in which neointimal formation is clearly visible in areas adjacent to stent struts. The wall shear stress distribution can be visualized at the vessel surface.

6 CONCLUSIONS

We have shown how Complex Automata methodology can be applied in a challenging multiscale model of in-stent restenosis, and how a Lattice Boltzmann model for blood flow can seamlessly be coupled with other single scale kernels using the MUSCLE library

Although the models is at a relatively early stage, certain emergent behaviors are already apparent. For example, proliferation begins in response to injury, peaking at approximately 20 days following deployment in the absence of drug (data not shown). We are currently in the process of running additional simulation series, to validate the CxA against a biological data-set obtained from in vivo and in vitro experimentation using stented porcine arteries. In particular, we aim to characterize restenosis behavior as a function of injury index [13] and to investigate the positive correlation between injury and restenosis.

This first realization of the coupled CxA is an important milestone on the journey towards a full multiscale model of in-stent restenosis. Future developments will require development of the single scale kernels. Implementation of more complex rule sets will allow intercellular signaling pathways and the effects of deep injury to be modeled.

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REFERENCES

[1] D.J.W. Evans, P.V. Lawford, J. Gunn, D. Walker, D.R. Hose, R.H. Smallwood, B. Chopard, M. Krafczyk, J. Bernsdorf, and A. Hoekstra, The application of multiscale modelling to the process of development and prevention of stenosis in a stented coronary artery. *Phil.Trans. R. Soc. A* **366**, 3343-3360, (2008).

[2] A. Caiazzo, D. Evans, J.-L. Falcone, J. Hegewald, E. Lorenz, B. Stahl, D. Wang, J. Bernsdorf, B. Chopard, J. Gunn, R. Hose, M. Krafczyk, P. Lawford, R. Smallwood, D. Walker, and A.G. Hoekstra, Towards a Complex Automata Multiscale Model of In-stent Restenosis in *Lecture Notes in Computer Science*, eds G. Allen, J. Nabrzyski, E. Seidel, G.D.v. Albada, J.J. Dongarra, and P.M.A. Sloot)

[3] A.G. Hoekstra, E. Lorenz, J.-L. Falcone, and B. Chopard, Towards a Complex Automata Framework for Multi-scale Modeling. *International Journal for Multiscale Computational Engineering* **5**, 491-502, (2007).

[4] J. Hegewald, M. Krafczyk, J. Tölke, A. Hoekstra, and B. Chopard. in *Computational Science – ICCS 2008* 227-233 (2008).

[5] E. Lorenzand A. Hoekstra. *to be published*, (2009).

[6] A. Caiazzo, D. Evans, J.-L. Falcone, J. Hegewald, E. Lorenz, B. Stahl, D. Wang, J. Bernsdorf, B. Chopard, J. Gunn, R. Hose, M. Krafczyk, P. Lawford, R. Smallwood, D. Walker, and A. Hoekstra, A Complex Automata approach for In-stent Restenosis: two-dimensional multiscale modeling and simulations. *Journal of Computational Science*, (2010 (submitted)).

[7] *The Multiscale Coupling Library and Environment (MUSCLE). Sources and Documentation available at http://muscle.berlios.de.*

[8] S. Succi. The Lattice Boltzmann Equation for Fluid Dynamics and Beyond. Clarendon Press, (2001).

[9] A.G. Hoekstra, Image-based computational hemodyanamics with the Lattice Boltzmann Method in *Computational Fluid and Solid Mechanics 2005*, ed K.J. Bathe)

[10] L. Axner, A. Hoekstra, A. Jeays, P. Lawford, R. Hose, and P. Sloot, Simulations of time harmonic blood flow in the Mesenteric artery: comparing finite element and lattice Boltzmann methods. *BioMedical Engineering OnLine* **8**, 23, (2009).

[11] A.M.M. Artoli, A.G. Hoekstra, and P.M.A. Sloot, Mesoscopic simulations of systolic flow in the Human abdominal aorta. *Journal of Biomechanics* **39**, 873--884, (2006).

[12] Y.S. Li, J.H. Haga, and S.Chien, Molecular basis of the effects of shear stress on vascular endothelial cells. *J. Biomech.* **38**, 1949-1971, (2005).

[13] J. Gunn, N. Arnold, K.H. Chan, L. Shepherd, D.G. Cumberland, and D.C. Crossman, Coronary artery stretch versus deep injury in the development of in-stent neointima. *Heart* **88**, 401-405, (2002).