Multiscale Modelling and Simulation of restenosis

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COMPLEX AUTOMATA MODELLING

Many complex systems encompass a wide range of spatial and temporal scales, and are difficult to describe using a homogeneous model.

A **Complex Automaton (CxA)** for a multiscale problem is defined by

- a collection of **single scale models** based on Cellular Automata, lattice Boltzmann models, Agent Based models.
- a **Scale Separation Map** (SSM), where the subprocesses occupy well-defined regions in the plan of temporal-spatial scales (fig.1)
- **coupling templates**: defining the way the subprocesses interact.

The **COAST** project (Complex Automata Simulation Technique) aims at developing a general formalism for the CxA approach and a simulation framework for multiscale modelling.

In-stent Restenosis

A *stenosis* is a narrowing in a blood vessel. A possible treatment consists of deploying a metal mesh (*stent*) against the wall of the artery. A maladaptive response of the artery to the injury can trigger an abnormal tissue growth, causing eventually a restenosis (figure 2).

It is a multi-scale multi-science system, covering a range of phenomena from *biology*, *physics*, *chemistry* and *medicine*, and crossing many orders of magnitude in temporal and spatial scales.

In-stent restenosis has been selected as the primary demonstrator application for complex automata modelling.

A simplified description of the system in terms of relevant scales is drawn in fig. 1.

A model for Smooth Muscle Cell growth (slowest time scale) is coupled to the more rapid blood flow. A diffusion model acting on an intermediate time scale can be used to take into account drug release from an eluting stent.

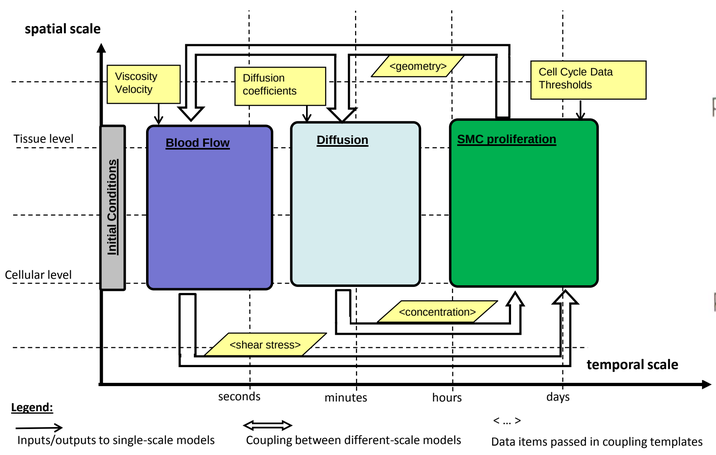

Figure 1: Simplified Scale Separation Map for in-stent restenosis, presenting the relevant subprocesses, their ranges of spatial and temporal scales, and the mutual coupling.

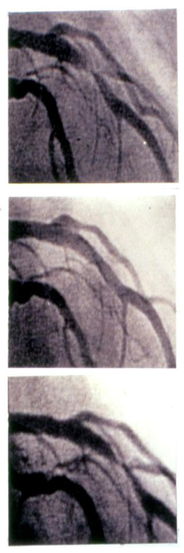

Figure 2: Typical course of restenosis. Before and after stenting, until restenosis appears.

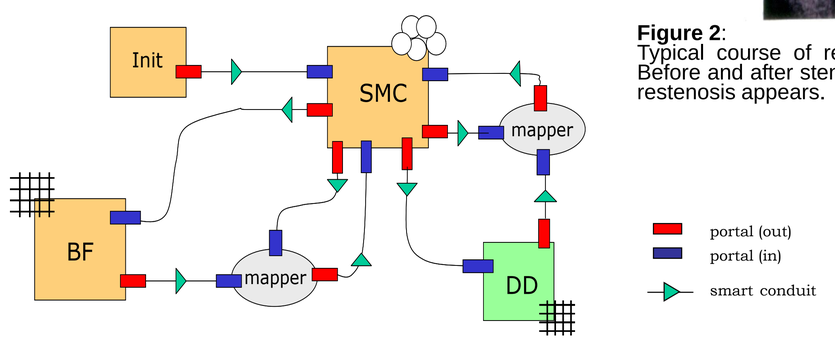

Figure 3: Connection Scheme for the CxA model of ISR, including Bulk Flow (**BF**), **SMC**, Drug Diffusion (**DD**), initial condition generation (**Init**), and two mappers, dealing with coordinates conversion (lattice to cells). Single scale models are connected to framework with portals, and communicate via smart conduits.

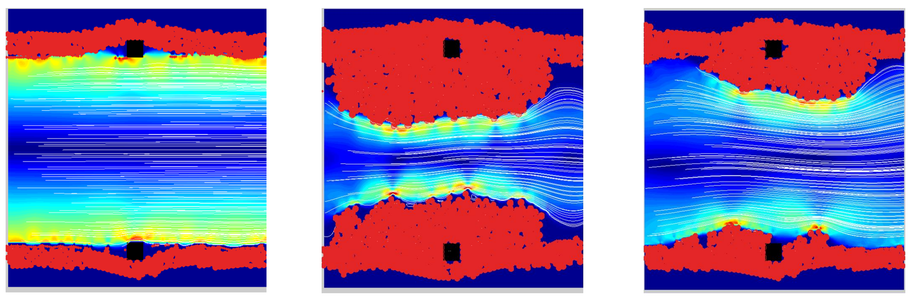

Figure 4: Results of ISR simulations: struts (black), SMC (red), blood flow (streamlines and colour coding according to shear stress (red high, blue low)).
Left: Equilibrated initial condition after stent deployment; Middle: Simulated ISR with bare metal stent after 400 time steps (~ 18 days); Right: with a drug eluting stent after 400 time steps.

SMOOTH MUSCLE CELL HYPERPLASIA

SMCs are simulated via an Agent Based Model, where each agent represents a cell, reacting to mechanical and biological inputs

Migration: mechanical interactions

- attractive force depending on adhesion
- repulsive force depending on overlap
- frictional force with the surrounding tissue

Proliferation: Cell Cycle

The cells have a three-stage cycle:

- **G0**: quiescent state
- **G1**: first growth stage
- **G2**: final stage leading eventually to proliferation (*mitosis*)

Checkpoints are introduced in the cycle, regulated by a set of biological rules, depending on the presence of neighbouring cells, **fluid wall shear stresses**, **drug concentration**.

Coupling templates: Bulk flow to SMC

Averaged fluid wall stresses are integrated along the tissue boundary. Taking the grid points in the fluid domain close to each cell Agent, we compute;

- Oscillatory Stress Index (OSI),
- Maximum Wall Shear Stress.

Drug Diffusion to SMC

In the steady state, drug concentrations for each SMC agent are computed, integrating the concentration field over the area of each cell.

SMC to Bulk Flow, SMC to Drug Diffusion

After cell migration and proliferation, new cell positions and radii are sent to the coupling framework and transformed into a new voxelized geometry, depending on the space discretization of BF and DD.

BLOOD FLOW (BF)

Blood flow is governed by incompressible Navier-Stokes equations, and simulated numerically using a **lattice Boltzmann method**

- flow simulation is run until a stationary (periodic) state (fig. 1)
- results for averaged wall stresses (pressure and stress) are passed to the SMC model.
- when tissue growth modifies the vessel geometry, a new flow simulation is carried out.

MUSCLE: A COMPLEX AUTOMATA FRAMEWORK

Within COAST, we have developed a software environment where CxA can be naturally implemented.

The MUltiscale Simulation Coupling Library and Environment (MUSCLE)

- based on ***JADE***: Java **platfo**rm for multi agent based simulation (MABS)
- CA-like single scale models are wrapped into agent
- agents communicate via *smart conduits*, a kind of “pipes” where data can be modified to match a specific output format
- these conduits have filter mechanisms, allowing configuration of common conduit functionality (interpolation, scaling, etc.)
- compatible with different software, programming languages and hardware
- distributed communication
- open source

With MUSCLE, a CxA-simulation is driven by a **Connection Scheme** graph (fig.3) whose vertices are the *kernels* (single scale codes + Java portals connecting it to the framework) and *smart conduits* defining the edges.

DRUG DIFFUSION (DD)

Drug eluting stents represent an effective way of inhibiting neointima formation after stent deployment. We have modelled this process with a generic anisotropic diffusion equation, solved numerically by a Cellular Automata – Finite Difference method.

The computational domain is decomposed in *tissue* (portion of space occupied by SMC), *source* (the stent strut) and *sink* (the lumen).

We assume that DD has a timescale smaller than the SMC. After each SMC iteration a new steady state concentration field is computed as input to the SMC model.

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