Before we start

“Different methodological approaches and terminologies are used in various fields, and the respective communities are often not aware of the work done in neighboring areas since they hardly meet”

taken from the introduction text of this workshop
From Molecule to Man
(or, from DNA to Disease)

Figure 2: Linking molecular and cellular events with physiological function most deal with wide ranges of length scales and timescales. a) Levels of biological organisation from genes to proteins, cells, tissues, organs and finally the whole organism. The range of spatial scales — from $10^{-3}$ m for the whole body — requires a hierarchy of models. Different types of model are appropriate to each level, and relationships must be established between models at one level and the more detailed, but spatially or temporally limited, models at the level below. The organ-level and whole-body-level models shown are the Auckland heart and knee models, respectively. The tissue figure is a re-constructed three-dimensional confocal image of a transversal section of rat myocardium, which is also from the Auckland Engineering Institute, New Zealand. b) The range of temporal scales as shown here is even more daunting and again calls for a hierarchy of models. HGF, human genome project. Modified with permission from Birkhäuser (2003).

Multiscale Computational BioMedicine

Figure 1: Illustration of the relationship between the physiome and other areas of biological organisation. The other area of biological organisation includes the genome (the genes encoded in DNA), transcription (the messages RNA produced by gene expression under particular conditions), metabolism (the metabolites that are present under particular conditions) and proteome (the proteins that are actually produced and where they reside — that is, the translation of the transcriptome together with post-translational modifications and protein trafficking). There is another level of organisation above the physiome, which deals with populations and interactions with the environment. It should be noted that many other processes such as the assimilation of carbohydrates and fats are omitted.

picture taken from:
Peter J. Hunter and Thomas K. Borg, Integration from Proteins to Organs, the Physiome Project, Nature Reviews Molecular Cell Biology, 4, 237-243, 2003

picture taken from:
A.G. Hoekstra and P.M.A. Sloot, Multiscale Biomedical Computing, Briefings in Bioinformatics, in press (January 2010).
Agenda

- Three intertwined parts
  1. In-stent restenosis
  2. Complex Automata and Multiscale Computing
  3. Multiscale model for blood rheology

Coronary Heart Disease statistics

- Coronary heart disease (CHD) remains the most common cause of death in the EU
  - approximately 744,000 deaths each year (European Cardiovascular Disease Stats, 2005).
- Main problem is stenosis of coronary arteries
  - Bad eating habits, too little physical exercise, etc..
- Mainly treated by balloon angioplasty and stenting.
- Restenosis is the maladaptive response of the coronary artery to injury
  - occurs in approximately 5-10% of patients following procedures involving stent deployment.
Structure of Healthy Artery

- Tunica Adventitia
- External Elastic Lamina
- Tunica Media
- Internal Elastic Lamina
- Tunica Intima
- Lumen

Coronary artery disease

Gross appearance  Angiogram
Balloon Angioplasty and Stent implantation

What is Restenosis?

Porcine coronary artery section 28 days post stenting displaying substantial neointima.

Longitudinal section through stented artery showing variation in reaction along vessel length.

Human angiogram depicting restenosis six months post-PCI.
Lots of detailed information available

Detail of single stent post showing vessel wall deformation, smooth muscle cell organisation in the neointima and re-endothelialisation.

Injury vs. Neointima Area

A positive correlation between injury score and intima/media ratio per section is observed at a) 14 days b) 28 days and c) 90 days post-stenting.
Quantification of the Response

In-Stent Restenosis

- Maladaptive response after stenting
  - Uncontrolled formation of ‘scar tissue’
- Main challenges
  - Understand the details of the process
  - Understand why it starts and why it stops
  - Improve treatment
    - e.g. via improved desing of stents
Complex Automata I

- Model a multiscale system as a collection of coupled single scale models.
- Single scale models are cellular automata or agent based models.
- Scale Separation Map

Multi-Scale modeling

- Scale Separation Map
- Nature acts on all the scales
- We set the scales
- And then decompose the multiscale system in single scale sub-systems
- And their mutual coupling
From a Multi-Scale System to many Single-Scale Systems

- Identify the relevant scales
- Design specific models which solve each scale
- Couple the subsystems using a coupling method

The Scale Separation Map

- A powerful methodological way to identify sub-models
- Classify the sub-model interactions as full or partial overlap of scales.
**The Scale Separation Map**

- A powerful methodological way to identify sub-models
- Classify the sub-model interactions as full or partial overlap of scales.
- Specify the relation between the sub models in five interaction regions.

**Region 3.1 Micro ➔ Macro**

- Microscopic (e.g. QM)
- Mesoscopic (e.g. MD)
- Macroscopic (e.g. FE)

Spatial scale vs. Temporal scale
But what about region 3.2?

- Couple physics with biology
- Blood flow in artery
  - $O(\text{mm})$ length scale
  - $O(\text{second})$ time scale
- Cell proliferation
  - $O(0.01 \text{ mm})$ length scale
  - $O(\text{day})$ time scale

SSM for ISR

- Large number of relevant processes, from the sub-cellular level up to the tissue level where identified, as well as their coupling.
- Details of (biological) single scale models were formulated.
- Some (but by far not all) couplings were modelled in detail.

Complex Automata II

• Submodel execution loop and coupling templates
• Taxonomy of multiscale models
• Formalism

Relation between computational domains

The computational domain is split into a coarse and a fine sub domain

Multi Domain

Single Domain

(scale overlap)

(micro-macro separation)
Classification of systems

- single-Domain (sM) or multi-Domain (mD)
- Relation on the Scale Separation Map

<table>
<thead>
<tr>
<th>Space Separation</th>
<th>Single Domain</th>
<th>Multi Domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coupling through collision operator.</td>
<td>Snow transport, diffusion/advective, ...</td>
<td>Smaller domains need to be coalesced to form the next domain.</td>
</tr>
<tr>
<td>Algae-Water ecological model, ...</td>
<td>Wave propagation in two media, ...</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time Separation</th>
<th>Single Domain</th>
<th>Multi Domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coupling through boundary condition.</td>
<td>Fluid structure, grid refinement, ...</td>
<td>Forest-Savannah-Fire interactions</td>
</tr>
<tr>
<td>Hierarchical Coupling</td>
<td>Coupling through collision operator and initialization.</td>
<td>Suspension Fluid, ...</td>
</tr>
<tr>
<td>“Physics-Biology Coupling”</td>
<td>Coupling through boundary conditions and initialization.</td>
<td>Oscillating blood flow and endothelial cells, ...</td>
</tr>
</tbody>
</table>

Complex Automata: Ingredients

- scale separation map
- submodel execution loop
- collision + propagation

```
Model
D := Dinit
f := finit
t := 0
While Not EC
  t := t + Dt
  D := U(D)
  f := B(f)
  f := C(f)
  f := P(f)
  O(f)
End
```

- initial condition
- domain update
- boundary cond.
- collision
- propagation
- observation
Complex Automata: Ingredients

- scale separation map
- submodel execution loop
- collision + propagation
- coupling templates
- connection scheme (graph)

Examples

- reaction-diffusion

CA-reaction (fast)  CA-diffusion (slow)

coupling through IC and collision operator
Examples

- reaction-diffusion
  - CA-reaction (fast)
  - CA-diffusion (slow)

- flow - sedimentation
  - flow model
  - sedimentation
  - coupling through collision operator and BC

Flow

1. Initialize: $D := D_{init}$
2. Initialize: $f := f_{init}$
3. Update: $t := t + Dt$
4. While Not EC
   1. Update: $D := U(D)$
   2. Update: $f := B(f)$
   3. Update: $f := C(f)$
   4. Update: $f := P(f)$
   5. Output: $O_i(f)$
5. End
6. Output: $O_{of}(f)$

Sediment

1. Initialize: $D := D_{init}$
2. Initialize: $f := f_{init}$
3. Update: $t := t + Dt$
4. While Not EC
   1. Update: $D := U(D)$
   2. Update: $f := B(f)$
   3. Update: $f := C(f)$
   4. Update: $f := P(f)$
   5. Output: $O_i(f)$
5. End
6. Output: $O_{of}(f)$

Examples

- reaction-diffusion
  - CA-reaction (fast)
  - CA-diffusion (slow)

- flow - sedimentation
  - flow model
  - sedimentation
  - coupling through collision operator and BC

Fine

1. Initialize: $D := D_{init}$
2. Initialize: $f := f_{init}$
3. Update: $t := t + Dt$
4. While Not EC
   1. Update: $D := U(D)$
   2. Update: $f := B(f)$
   3. Update: $f := C(f)$
   4. Update: $f := P(f)$
   5. Output: $O_i(f)$
5. End
6. Output: $O_{of}(f)$

Coarse

1. Initialize: $D := D_{init}$
2. Initialize: $f := f_{init}$
3. Update: $t := t + Dt$
4. While Not EC
   1. Update: $D := U(D)$
   2. Update: $f := B(f)$
   3. Update: $f := C(f)$
   4. Update: $f := P(f)$
   5. Output: $O_i(f)$
5. End
6. Output: $O_{of}(f)$

grid-coupling coarse grid
fine grid
Example: multiscale model for blood rheology

- **Configuration**
  - Space Scale Separation, Time Scale Separation,
  - Single-Domain.

- **Macroscopic model**
  - Lattice Boltzmann fluid model.
  - Lattice Boltzmann advection diffusion model

- **Microscopic model**
  - Fully resolved Lattice Boltzmann suspension model.
  - Complete micro model on each (or many) macro model lattice points.
  - Micro model computes local viscosity and shear induced diffusion.
    - Used in collision operator of macro model.
  - The macro model provides the micro-models with boundary conditions
    - shear rate, particle density/distribution

---

HMM for suspensions

**Macro-scale**
- LBM fluid with local viscosity $\nu$
- Advection/Diffusion of local particle density $\phi$

**Micro-scale**
- fully resolved LBM suspension sheared by Lees-Edwards BC's to obtain
  - stress $\rightarrow$ viscosity
  - particle flux $\rightarrow$ diffusivity tensor
**HMM Suspension – Stress Computation**

total stress $\tau = \sigma_f + \sigma_s + \tau_f + \tau_s$ along surfaces $S$:

- **fluid phase:**
  - $\tau_f = (\Pi_f - C_f)$ (visc. stress)
  - $\sigma_f = (C_f)$ (conv. stress)

- **solid phase:**
  - $\sigma_s = (C_s)$
  - $\tau_s = (F_{pp}^x/A_p) + (F_{pp}^y/A_p)$

forces on surface $A_p$:

- $F_{pp} = \frac{m_d \Delta p}{M_p \Delta t}$ (particle collision)

  
  $F_{fp} = -F_f + m_d a$

  
  $+m_d a \times r_d + m_d \omega^2 r_d e_y$

  (fluid-particle interaction)

- apparent viscosity:
  
  $\eta_{app} = \frac{\tau_f}{\dot{\gamma}}$

---

**CXA Formalism**

- mathematical description: $A(\Delta x, \Delta t, X, T, F, \Phi, u)$
CXA Formalism

- mathematical description: $A(\Delta x, \Delta t, X, T, F, \Phi, u)$
- update rule: $f^{n+1} = \Phi(u)f^n$ \hspace{1em} $\Phi : F \rightarrow F$

- scale splitting:

  $f'^{n+1} = \Phi_1(u_1)f^n_1$

  $f'^{n+1} = \Phi_2(u_2)f^n_2$
CXA Formalism

- mathematical description: \( A(\Delta x, \Delta t, X, T, F, \Phi, u) \)

update rule: \( f^{n+1} = \Phi(u)^n \quad \Phi : F \rightarrow F \)

- scale splitting:
  \( F_1 \times F_2 \rightarrow \)
  \( f_1^{n+1} = \Phi_1(u_1)f_1^n \)
  \( f_2^{n+1} = \Phi_2(u_2)f_2^n \)

- coupling: \( \Phi_1(u_1) = P \circ C(u_1) \circ B(u_1) \quad u_1 = u_1(f_2) \)

- multiscale technique:
  - time splitting
  - coarsening
  - amplification
  \( \Phi \rightarrow (\Phi_1, \Phi_2) \)
**Time Splitting**

- Assume we have a sD problem with the following SEL

\[ P_{\Delta t} C_{\Delta t} = P_{\Delta t} C_{\Delta t}^{(1)} C_{\Delta t}^{(2)} \]

- Then if \( C^{(1)} \) acts on a longer time than \( C^{(2)} \) we may want to approximate

\[ [P_{\Delta t} C_{\Delta t}]^M = P_{M_{\Delta t}} C_{M_{\Delta t}}^{(1)} [C_{\Delta t}^{(2)}]^M \]

---

**Coarse graining**

- This strategy consists in expressing a sD problem as

\[ [P_{\Delta x} C_{\Delta x}]^n = \Gamma^{-1} [P_{2\Delta x} C_{2\Delta x}]^{n/2} \Gamma \]

- Where \( \Gamma \) is a projection operator
**Amplification**

- Here we consider a process acting at low intensity but for a long time, in a time periodic environment (e.g. growth processes in a pulsatile flow). We have two coupled processes which are iterated $n >> 1$ time

\[
[P^{(1)}C^{(1)}]^n \text{ and } [P^{(2)}C^{(2)}(k)]^n
\]

- Where $k$ expresses the intensity of process $C^{(2)}$. If the period of process $C^{(2)}$ is $m << n$, we can approximate the above evolution as

\[
[P^{(1)}C^{(1)}]^m \text{ and } [P^{(2)}C^{(2)}(k')]^m
\]

- with $k' = (n/m)k$, for a linear process.

**Scale Splitting Error**

\[
f^{n+1} = \Phi(u)f^n
\]

\[
\Phi \quad \Pi = (\Pi_1, \Pi_2) \quad (f_1, f_2) \in F_1 \times F_2
\]

\[
f_1^{n+1} = \Phi_1(u_1)f_1^n
\]

\[
f_2^{n+1} = \Phi_2(u_2)f_2^n
\]

\[
\Phi_1, \Phi_2 \quad F_1 \times F_2
\]
**Scale Splitting Error**

\[
\begin{align*}
 f^{n+1} &= \Phi(u) f^n \\
 f_1^{n+1} &= \Phi_1(u_1) f_1^n \\
 f_2^{n+1} &= \Phi_2(u_2) f_2^n \\
 f &\in F \\
 \Pi &\left( \Pi_1, \Pi_2 \right) \\
 O(f) &\left( f_1, f_2 \right) \in F_1 \times F_2 \\
 \Phi_1, \Phi_2 &\downarrow \\
 F &\xrightarrow{O_{\text{obs}}} \Omega \\
 \end{align*}
\]

observable (project on quantities of interest)

- formal scale splitting error
- difference between observed results (in opportune norm)
- case by case, use the properties of problem and algorithms

We have detailed results, but not discussed here, see e.g. A. Caiazzo, J.-L. Falcone, B. Chopard, and A.G. Hoekstra, Asymptotic analysis of Complex Automata models for reaction-diffusion systems, Applied Numerical Mathematics 59, 2023-2034, 2009.

---

**Again, Scale Separation Map for ISR**

[Diagram of scale separation map with spatial and temporal scales, showing various processes at different levels: Blood Flow, Diffusion, SMC proliferation, Cell Cycle, etc., with inputs/outputs and coupling between different scales.]
Simplified model

- 2D
- three single scale models
  - bulk flow (lumen)
  - smooth muscle cells (tissue)
  - drug diffusion (tissue)
- initial conditions
- scale map
- connection scheme
- details of single scale models and coupling templates

Initial condition

- geometry:
  - 2D vessel: 1.5mm x 1mm
  - square struts, 90mm
  - tunica: 120mm
- initial conditions:
  - deployment + SMC relaxation
CxA for ISR: Connection Scheme

Single Scale Models: bulk flow

- Lattice Boltzmann Method
  \[ \Delta t = 10^{-5} \text{s}, \Delta x = 0.01\text{mm} \]
- receive: geometry updates
- send: shear stress at boundary
**Single Scale Models: SMC growth**

- Agent Based Model
- structural solver + biological rule-set

\[ \Delta t = 1 \text{h}, \ \Delta x = 6 \mu m \]

- receive: shear stresses, drug concentration
- send: cell positions and radii

---

**Agent Based Model**

Three agent classes are currently implemented in the agent based model:

- Smooth Muscle Cell agents (blue; scale = structural stress)
- Internal Elastic Lamina agents (red)
- Obstacle agents (strut; black)
Single Scale Models: drug diffusion

- Finite Difference
- SOR to determine steady state
  \[ T = 1h, \Delta x = 0.01 \text{mm} \]
- receive: geometry information
- send: drug concentrations

Mappers

BF2SMC
- receive cell positions
- receive flow stresses
- map onto SMC stresses
**Mappers**

- **Init**
- **SMC**
- **mapper**
- **BF**
- **DD**

**DD2SMC**
- receive cell positions
- receive drug concentrations
- map onto SMC conc

**ISR simulation in MUSCLE**

- 3 single scale processes
  - written in Fortan, C++, Java
- 2 mappers
  - Written in Java
- 20 Conduits
  - Written in Java
- Total of 25 agents
- Executed on a compute server with 8 Intel Xeon woodcrest cores, each 2.8 GHz
preliminary results

\[ \text{time} = 2 \text{ days} \]
preliminary results

\[\text{time} = 4 \text{ days}\]

preliminary results

\[\text{time} = 6 \text{ days}\]
preliminary results

\[ \text{time} = 8 \text{ days} \]

preliminary results

\[ \text{time} = 10 \text{ days} \]
preliminary results

time = 12 days

preliminary results

time = 14 days
preliminary results

time = 16 days

- More detailed results being produced
  - ISR as function of injury score
  - Comparison with histological sections
Not Discussed

- Multiscale Computing
  - Multiscale Simulation Library & Environment (MUSCLE)
- Full blown coupled 3D models
- Distributed Multiscale Supercomputing
  - Running large scale multiscale simulations on (distributed) supercomputers

How to bridge community boundaries?

Journal of Computational Science  Workshop Simulating Multiphysics Multiscale Systems
Associated with the yearly ICCS conference

Thank you!

And thanks to all the members of the COAST consortium

www.complex-automata.org

Some references

Multiscale Biomedical modeling
2. A.G. Hoekstra and P.M.A. Sloot, Multiscale Biomedical Computing, Briefings in Bioinformatics, in press (January 2010).

In-Stent Restenosis

Complex Automata