Spatiotemporal Modeling and Simulation

01 - Introduction

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Overview of spatio-temporal modeling and simulation in biology

1. Modeling in Biology: where and why?
2. Diffusion in a complex-shaped cell organelle
3. Other examples
4. Summary
Modeling in Biology

Where and Why?
Computer science will be for 2020 biology what mathematics is for today’s physics.

Microsoft Report “2020 Science”
Life

- Highly organized
- Regulated
- Complex shapes
- Non-equilibrium
- Nonlinear
- Coupled
Life in space AND time

Molecules
Organelles
Cells
Organs
Organisms
Ecosystems

Wolters et al., IJBEM 7:203, 2005
Genotype / Phenotype

1. Modeling in Biology
What is the connection?

In order to understand how genotype and phenotype are connected, we also have to consider:

- Spatial organization and compartmentalization
- Temporal plasticity and dynamics
- Environmental influences
- Physics of interactions
- Regulatory mechanisms
Computational Biology

- Physics as the basis of function of biological systems
- Understanding of function with minimal assumptions
- Data analysis and modeling using computers
Why Computers?

- Amount of data / Reproducibility: Manual evaluation too slow or too unreliable
- Complexity: System behavior not apparent from description
- Time/length scales: Too big/small, slow/fast for experimental measurement
- Ethics: No living beings involved
- Controllability: Variables controllable
- Observability: Variables measurable

1. Modeling in Biology
Interdisciplinary work

Biology
- experiment
- interpretation
- knowledge

Computer Science
- raw data
- processed data
- modelling and simulation
- analysis
- interpretation

1. Modeling in Biology
2. Example

Diffusion in a complex-shaped cell organelle
The Endoplasmic Reticulum (ER)

**Synthesis plant** for proteins and lipids in eucaryotic cells.

Enclosed by a **contiguous** membrane.

2. Diffusion in the ER
FRAP: Fluorescence Recovery After Photobleaching

- Protein fluorescently tagged
- **Region Of Interest (ROI)** bleached with laser
- recovery of fluorescence monitored over time

**FRAP**: Fluorescence Recovery After Photobleaching

**Diffusion**

**Graph**: FRAP over time

- pre-bleach
- t=0 min
- t=2 min

Helenius group
Identification of diffusion constants from fluorescence recovery curves.
Why this is not easy

- Bleached region is larger than ER structures
- **Separation of scales:** Observation summed (or averaged) over bleached region
- 2D projection (or slice) of a 3D object

Have to be corrected, but are not controllable in the experiment ... ➔ **Modeling and simulation!**
2. Diffusion in the ER

FRAP experiment

Experimental FRAP curve

Micrograph sections of the same organelle

3D reconstruction

Simulation

Simulated FRAP curve

Fit in time

Time unit $t_s$

Molecular diffusion constant

$D = \frac{D_{sim}}{t_s}$
Reconstruction of the real ER geometry

Parallel sections from confocal imaging of fluorescently stained ER.

Movie: Helenius group, D-BIOL, ETHZ
3D reconstruction

Reconstruction error determined by:

- Threshold
- Resolution of the microscope

Find optimal threshold in the computer

Figure 5.47: Plot of errors for smallMU, \( \mu = 2 \)

Table 5.14: Error listing

<table>
<thead>
<tr>
<th>Threshold</th>
<th>Hits</th>
<th>Missed</th>
<th>Excess</th>
<th>Total Error</th>
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<tr>
<td>90</td>
<td>0.3782</td>
<td>0.9699</td>
<td>0.0301</td>
<td>0.3482</td>
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<tr>
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<td>0.9218</td>
<td>0.0782</td>
<td>0.2465</td>
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<tr>
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<td>0.7922</td>
<td>0.2078</td>
<td>0.0922</td>
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<tr>
<td>140</td>
<td>0.4547</td>
<td>0.5820</td>
<td>0.4180</td>
<td>0.0367</td>
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<tr>
<td>160</td>
<td>0.6405</td>
<td>0.3719</td>
<td>0.6281</td>
<td>0.0124</td>
</tr>
</tbody>
</table>

Figure 5.48: Three reconstructions with thresholds: 90, 110, 120
2. Diffusion in the ER
Computer simulation

1. Mathematical description of the process
2. Discretization of the model
3. Programming in the computer
4. Simulation
5. Validation of the correctness of the results
6. Evaluation and interpretation of the results
1. Mathematical description

\[ \langle u(x, t) \rangle = \frac{1}{|\text{ROI}|} \int_{\text{ROI}} u(y, t) \, d^3y \]

Physical process: transport by diffusion

\[ \frac{\partial u(x, t)}{\partial t} = \nabla \cdot (D(x, t) \nabla u(x, t)) \]

Dynamics of the observed (measurement) quantity

\[ \partial_t \langle u(x, t) \rangle = \nabla \cdot (D_{\text{app}} \nabla \langle u(x, t) \rangle) \]

\[ D_{\text{app}} = \left[ D + \frac{1}{|\text{ROI}|} \int_{\partial\text{ROI}} b(x, t)^\top \cdot n \, dA \right] \]
2. Discretization

Fill geometry with interacting particles.

Interaction such that the mathematical model is solved.

Particle methods
Diffusion in space
Formulation of the diffusion operator on particles

For (anisotropic) diffusion:

\[
\frac{du_p}{dt} = \sum_{q \neq p} \sigma_\epsilon(x_p, x_q, D, t)(u_q - u_p)V_q
\]


Extension to any differential operator:

\[
L^\beta_h f(x_p) \approx \frac{1}{\epsilon |\beta|} \sum_q V_q (f(x_q) \pm f(x_p)) \eta_\epsilon^\beta (x_p - x_q)
\]

2. Diffusion in the ER

5. Validation of results

Comparison with control experiments.

Simulation and experiment in the same ER

6. Interpretation of results

FRAP simulations in the lumen of different ER

All simulation use the same diffusion constant

Influence (artifact) of geometry: 250%

3. Other examples

Examples from outside MOSAIC
3. Other examples

Kaandorp et al., Amsterdam

Coral growth using reaction-diffusion model
Simulations of blood flow in sclerotic arteries and bypasses.
3. Other examples

Marc Thiriet, INRIA

Cerebral aneurisms
Calcium activation waves in a muscle fiber
3. Other examples

**Bioengineering, U. Auckland**

Growth of coronary vessels in the human heart
Summary
A symbiosis

- Computer modeling and simulation enables larger amounts of data and model complexities
- Observation and control of processes that are not observable/controllable in the experiment
- New algorithms and programming techniques are inspired or required
- Direct links to many areas in core CS
- New knowledge on both sides

Common goal: understand systems