Mathematical Biology: The virtual cell

Lecture series for master
Bioinformatics, Mathematics or LST

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The virtual cell

‘Virtual Cell’: commonly used to mean a computational approach to simulate (part of) the functioning of a living cell

It requires:

- Mathematical modeling of relevant biological processes
  -- to enable computations;
  -- what type of modeling is appropriate depends on the processes…

- A suitable computational environment
  -- to make the computations

Various ‘virtual cell’ initiatives exist

-- check e.g. ‘VCell’: www.vcell.org
-- Tyson Lab – mpf.biol.vt.edu
-- Virtual Cell environment of the (US) National Resource for Cell Analysis and Modeling (NRCAM)
**The virtual cell**

**Why ‘Virtual Cell’?**  *Why simulate a living cell?*

- Enable theoretic interpretation of experimental data
- Validate or falsify biophysical / biochemical hypotheses concerning the functioning of cellular processes
- As part of ‘Reverse Engineering’ of cellular system:
  - what subsystems can be identified?
  - what is their role?
  - how are these (and the whole) controled?

**In (far?) future:**
- Predict outcome of modifications / external challenges

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**So ‘Virtual Cell’ requires**
- Mathematical modeling
- A computational environment

What may be neglected easily is, that it also requires:
- **Modeling skills**
  - what to do when... what to do not... why...
  - what are reasonable assumptions / approximations / etc.
- **Mathematical skills**
  - to master manipulation and modification of models
  - to interpret computational results
  - assess validity of results, comparison with experiment, etc.
Objectives of this course

- Provide basic knowledge of biology, biophysics and biochemistry to enable collaboration in the field
- Provide understanding of mathematical modeling of biochemical processes with differential equations
- Acquaintance with tools to analyse these models and skills to interpret computational results
- Be able to read the current research literature on this topic
- Start to appreciate the complexity of Life
  e.g. through issues that arise when applying methods to:
  - Mammalian or plant cells, instead of bacteria
  - Higher organisms, instead of unicellular ones

Literature

Christopher P. Fall, Eric S. Marland, John M. Wagner, John J. Tyson:

**Computational Cell Biology.**


- Lecture notes and slides
  - Some material will become available on pub.math.leidenuniv.nl/~hillesc/

- Auxiliary research and review papers
  - Download from electronic library, using ULCN login name and password
**Book coverage**

**Part I: Introductory Course**
- Ch 1. Dynamic Phenomena in Cells
- Ch 2. Voltage gated Ionic Currents
- Ch 3. Transporters and Pumps
- Ch 4. Fast and Slow Time Scales
- Ch 5. Whole Cell Models
- Ch 6. Intercellular Communication

**Part II: Advanced Material**

**Appendices**
- A. Qualitative Analyses of Differential Equations
- B. Solving and Analyzing Dynamical Systems Using XPPAUT
- C. Numerical Algorithms

+ additional literature

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**What to expect?**
-- outline of lecture series --

- **A short introduction to (cell) biology**
  - To appreciate the complexity and simplification of biological questions

- **Discussion of relevant biochemistry/-physics**
  - For understanding building blocks of models

- **Mathematical modeling**
  - Why/when take particular mathematical approach?
  - Pitfalls…

- **Mathematical analysis and/or simulation:**
  - Tools, interpretation of results

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What to expect?
-- biological and mathematical focus --

**Modeling electrical activity of cells**
- Neurons, pancreatic beta cells *(insulin/hormone secretion)*

**Effective membrane transport**
- Biophysics / thermodynamics
- How to compute/approximate rate expressions?

**Mathematical modeling:**
- Non-spatial compartment models
- Mainly deterministic: systems of ODEs
- Touch upon stochastic viewpoint sometimes…

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Positioning:

*Mathematical Biology*
Positioning:

Quantitative Biology
Mathematical Biology
Biomathematics
Computational Biology
Systems Biology
Bioinformatics

Biological introduction

The ‘Tree of Life’
(Charles Darwin, 1837);

Concept needs replacement
though -- cross breeding
Biological introduction

- The ‘Tree of Life’
- Some cell biology
  (‘the cell’ does not exist…)
- A feel for complexity in higher organisms
- Fundamentals on biological networks:
  metabolic, signaling and regulatory networks

Bron: Introduction to the Archaea (http://www.ucmp.berkeley.edu/archaea/archaea.html)
A history of life (and the solar system)

(time measured in years before this day…)

-4.57 bio  Formation of the Sun
-3.5 bio  First life forms on Earth
-3  Cambrian explosion of life
-2  Formation of the Earth
-1  First bacteria
-0.5 bio  First multicellular organism
1  First fungi
1.5 bio  First plants
0.5 bio  First dinosaurs
-0.2 mio  Homo sapiens
-230 mio  Extinction of dinosaurs
-65 mio  End of life supportability

(NOW)

(1 bio = 1 billion = 10^9; 1 mio = 1 million = 10^6)

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Biological introduction
-- diversity in cells --

Prokaryotic cell
- Capsule
- Ribosomes
- Cytoplasm
- DNA
- Cell wall
- Flagellum
- Plasma membrane
- Pili

Eukaryotic cells
- Mitochondrion
- Golgi Complex
- Endoplasmic reticulum
- Golgi Complex
- Ribosome
- Nucleus
- Microtubules
- Microtubules
- Plasma membrane
- Membrane

(no organelles, length ~ 1 µm)

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There is no ‘generic cell’…

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There is no ‘generic cell’.

Prokaryotic cell
(no organelles, length ~ 1 µm)

Eukaryotic cells
(organelles, diameter ~ 10 µm and much larger in plants)

Single cell of 3-8 cm!

A ‘typical’ bacterial cell

An animal cell
Diversity in cells

Eukaryotic cells are highly compartmentalised; in particular they have a nucleus.

A ‘typical’ bacterial cell

An animal cell  A plant cell

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Cellular membranes

Compartments are created by cellular membranes
- Consist of phospholipid bilayer with various embedded proteins
- Is a viscous, fluid-like structure!

Figure 1S-1. Molecular Biology of the Cell, 4th Edition

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Cellular membranes

‘Head’: hydrophilic

‘Tails’: hydrophobic

Membrane lipid(s) (Borislav Mitev)

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Cellular membranes

water

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Diversity in cells (2) -- different membrane structures --

Gram-positive and Gram-negative bacteria

Examples:
- Bacillus anthracis
- Bacillus subtilis
- Listeria ...
- Escherichia coli
- Salmonella ...
- Legionella ...

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Unicellular and higher organisms
-- beyond comparison… --

B. subtilis

C. elegans: 959/1031 cells

Human skin only: \(10^{11}\)
Human total: \(10^{14}\)

Caenorhabditis elegans

Dictyostelium discoideum

Arabidopsis thaliana

Homo sapiens

Remote tribal village

Metropolis

Interaction with the environment

environment

Observation

Behaviour
Interaction with the environment

Environment

Environmental Observation

Internal Observation

Behaviour

Memory

‘Decision making’

Behaviour, e.g.:

- Cellular movement
  -- individual
  -- collective,
  with intercellular communication

- Organisation of internal processes, e.g.
  -- Developmental ‘programme’:
    vegetative, sporulation,
    programmed cell death (apoptosis)
  -- Metabolism

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Intracellular dynamics

Three fundamental chemical reaction networks:

- **Metabolic networks** – *metabolism*
- **Signaling networks** – *signal reception & transduction*
- **Regulatory networks** – *gene transcription & translation*

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**Metabolism:**

The set of chemical reactions that occur in living organisms in order to sustain life.

- Nutrients
- Structural components
  - proteins (e.g. enzymes)
  - membranes
  - RNA / DNA
  - organelles
  - ...
  - sugars
  - cellulose
  - proteins
  - fats
  - …
Metabolism:
The set of chemical reactions that occur in living organisms in order to sustain life.

- Catabolism: Breaking down of large compounds into smaller intermediaries.
- Anabolism: Synthesis of larger molecules from smaller ones.

Metabolites must cross membranes.

- Almost all metabolic reactions are catalysed by enzymes.
  E.g.: First steps in glycolysis:
  - Glucose → G6P → F6P
  - Hexokinase and phosphoglucone isomerase

- Some reactions effectively do not occur in their absence.

- Metabolites must cross membranes:
  - Passive transport:
    1. Simple diffusion
    2. Carrier mediated
    3. Selective channels or pores
  - Active transport:
    a. Transporters / ion pumps
Intracellular dynamics
-- Signaling --

- Observation and part of decision making realised by the **signaling network**
- Environmental observation e.g. through **receptor proteins**

An activated receptor catalyses further chemical reactions, 'integrating' other internal observations.
Observation and part of decision making realised by the **signaling network**

Environmental observation e.g. through **receptor proteins**

- An activated receptor catalyses further chemical reactions, ‘integrating’ other internal observations
- Often in interaction with regulation of gene expression

**Signaling network -- *E. coli* chemotaxis motor control --**

- Chemotactic agent (aspartate)
- Receptor (Tar)
- ATP
- ADP
- W
- R
- m
- A
- p
- B
- Y
- Z
- Control of direction of rotation
- Intra-cellular diffusion
- Cytoplasm
- Flaggellum
- Outer membrane
- Plasmamembrane
- Molecular motor

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‘Implements decision-making’ on the basis of a perceived environment as realised by the signaling network(s).

- Acts over the cell’s DNA
  - Single molecule interaction
  - Stochastic (= random) effects may play a role or may need to be controlled / reduced

- Involves:
  - Transcription
  - Translation

Gene transcription

(Basics… for prokaryotes – eukaryotic transcription much more involved)

1. Bound transcription factor
2. RNA strand (mRNA)
3. RNA polymerase
mRNA translation

Regulatory networks -- sporulation control in B. subtilis --
Regulatory networks
-- sporulation control in B. subtilis --

Part of signaling network

Regulatory feedback

Some aspects to remain aware of
The crowded cell

Molecular crowding in the synapse of a neuron

(http://mgl.scripps.edu/people/goodsell/)

Further reading:

- Many different molecules can function independently under extremely crowded conditions
- (Oppositely) charged polar groups on the molecular surfaces (self-)organise the packing
- Small mutations in genes coding for proteins may result in unwanted aggregation…

Free diffusion??

Sickle cell anaemia

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Dynamics

Living systems may look static at macroscopic time scale, but they are dynamic at smaller time scales…

- Turnover of cellular metabolites: ~ minute

Average life span of human cells (days):
- White blood cell: 1.0 – 3.0
- Liver: 10 – 20
- Skin (epidermis): 14 – 34
- Red blood cell: 120
- Nervous system: No (hardly any) regeneration

(Flindt (2004), Amazing numbers in Biology)

- The complete cytoskeleton has been recycled several times when cell has moved one cell length…

Different notions of ‘model’

- **(Biological) ‘Model system’**
  A specific organism that is used in experiments, e.g.
  - E. coli
  - B. subtilis
  - Dictyostelium discoideum
  - Caenorhabditis elegans
  - Arabidopsis thaliana
  - … etc. …
  i.e. a mechanistic view of how the system could work

- **A ‘cartoon’**

- **‘Mathematical model’**
  - a system of equations,
  - of various types (as we will see…)