An overview of the use of hybrid models in biochemical networks

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Special thanks to

The speakers

Konstantinos Koutroumpas

The HYGEIA project

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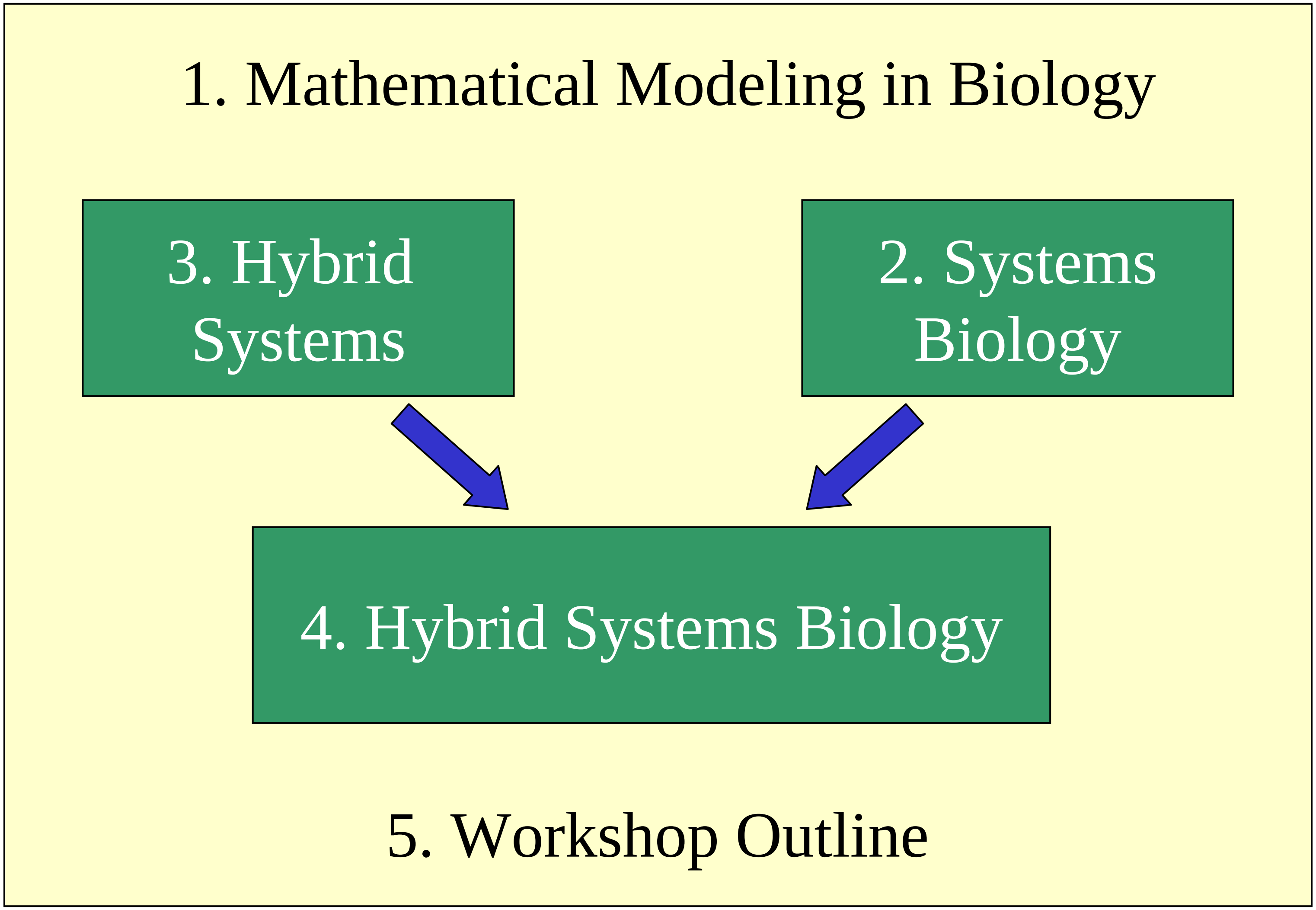
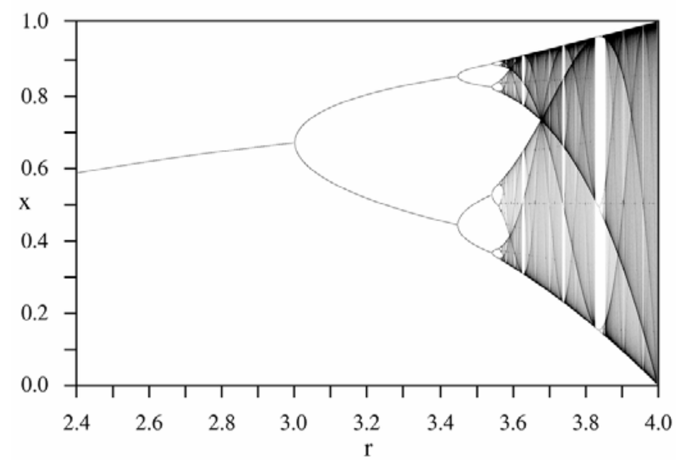
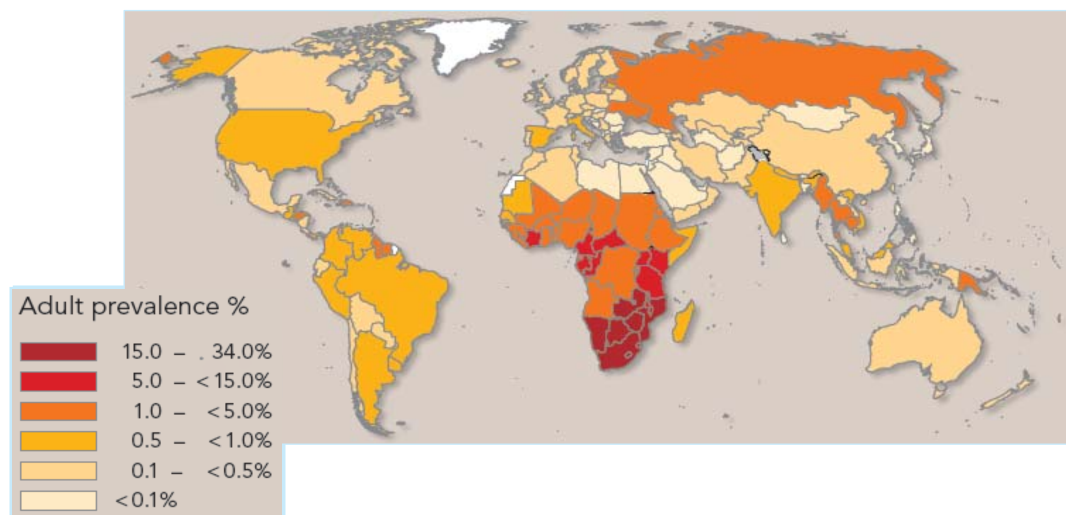
Outline


1. Mathematical Modeling in Biology
3. Hybrid Systems
2. Systems Biology
4. Hybrid Systems Biology
5. Workshop Outline

Mathematical Modeling in Biology

- Long history, many levels
- Population dynamics
  - Single species
  - Predator-prey models
  - Ecosystems
- Epidemiology

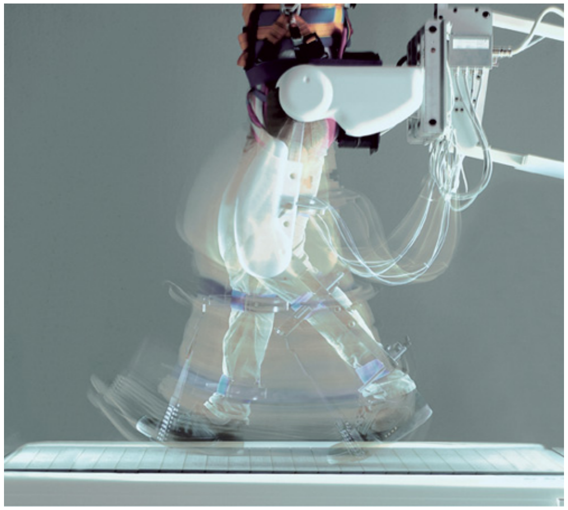




Mathematical Modeling in Biology

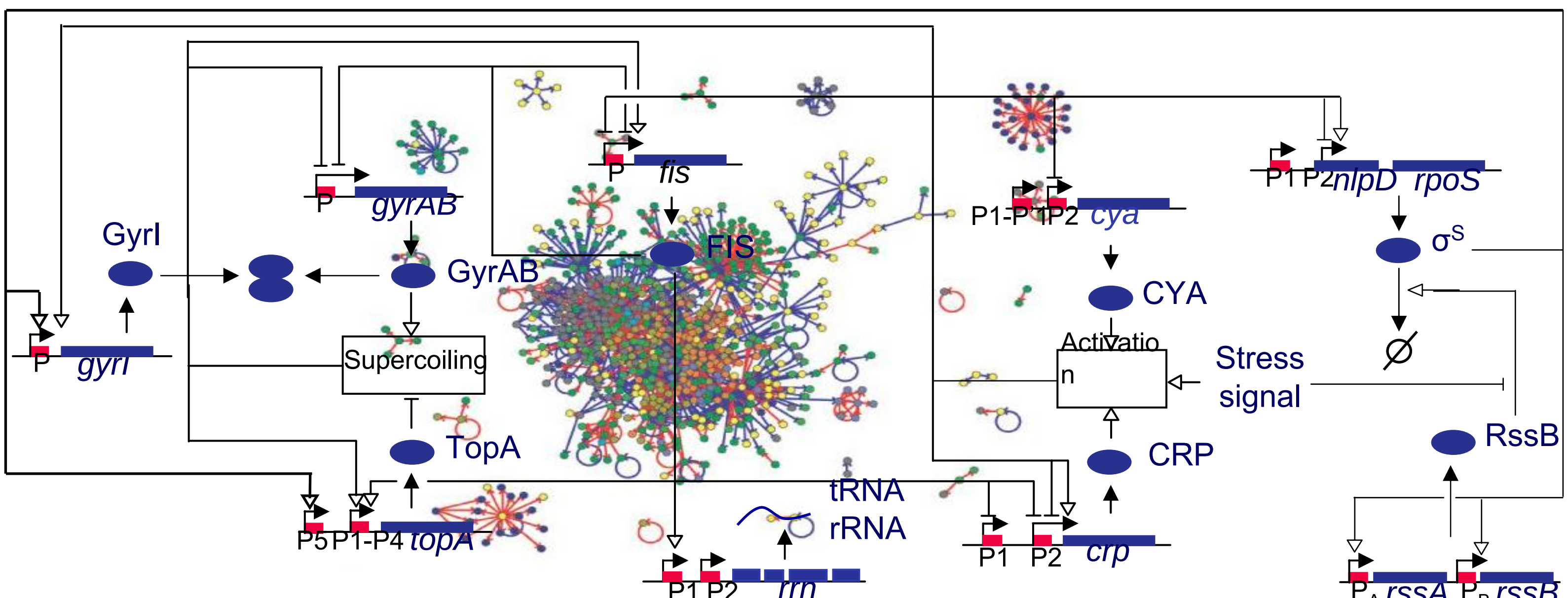
- Organisms of parts thereof

  - Neurophysiology
  - Aneasthesia
  - Exercise and rehabilitation



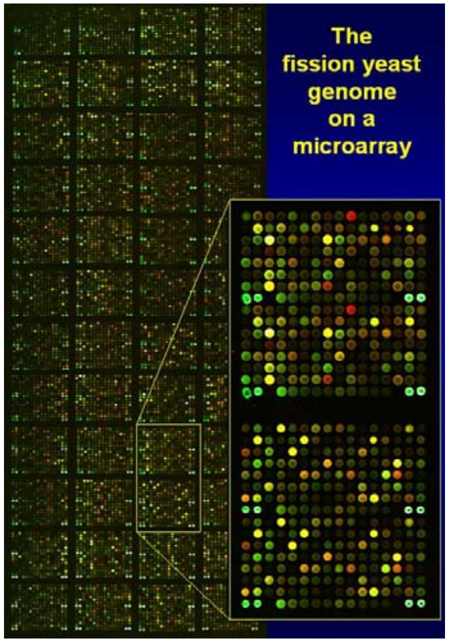
Mathematical Modeling in Biology

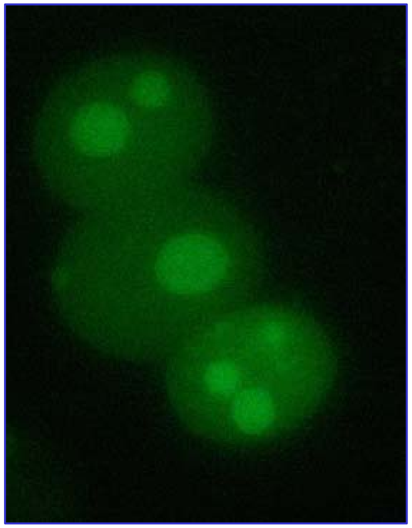
- Molecular level
  - Genes and protein coding
  - Protein-protein interactions
  - Signaling within the cell
  - Signaling between cells

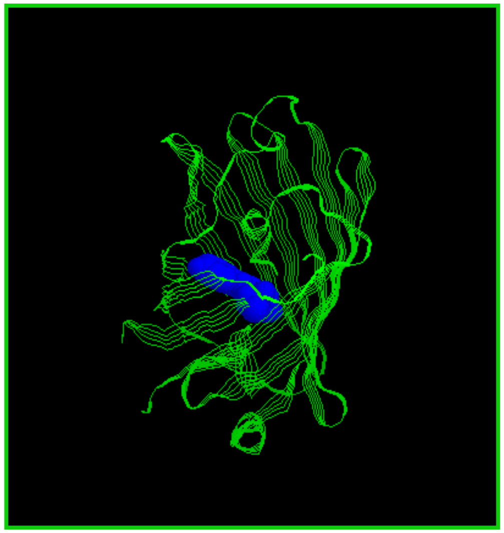


Systems biology

- Here refers to mathematical modeling of biological processes at the molecular level
- Genes proteins and their interactions
- Field driven by abundance of data
  - Micoarray
  - Imaging and microscopy
  - Reporter systems, micorarrays, bioinformatics, robotics

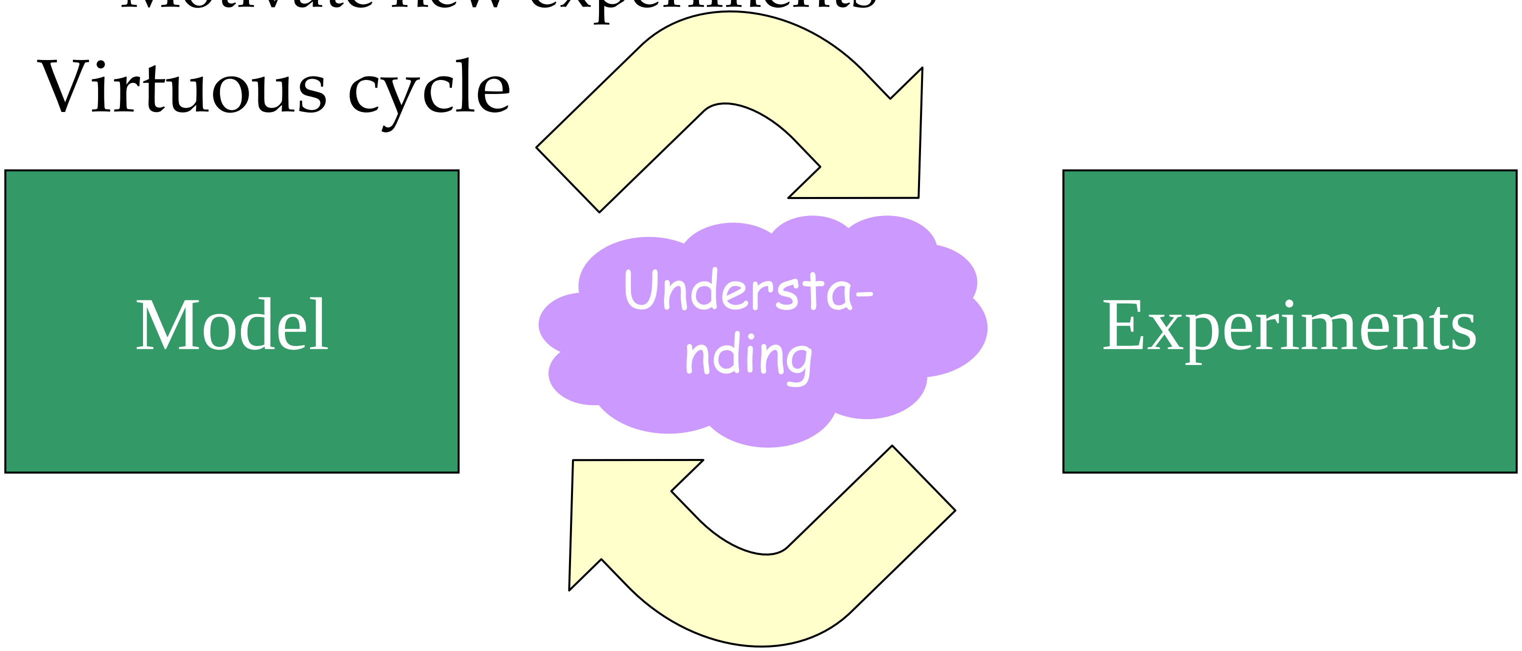






Systems biology

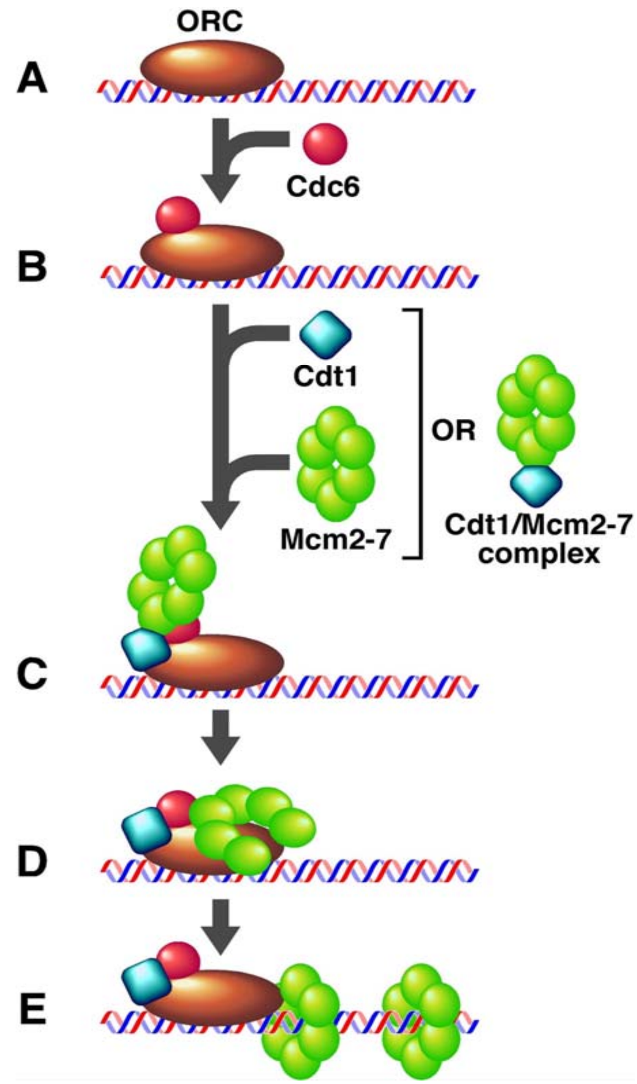
- Models based on biologists intuition
- Used to "correlate" large data sets
- Model predictions
  - Highlight "gaps" in understanding
  - Motivate new experiments
- Virtuous cycle



Example: DNA replication

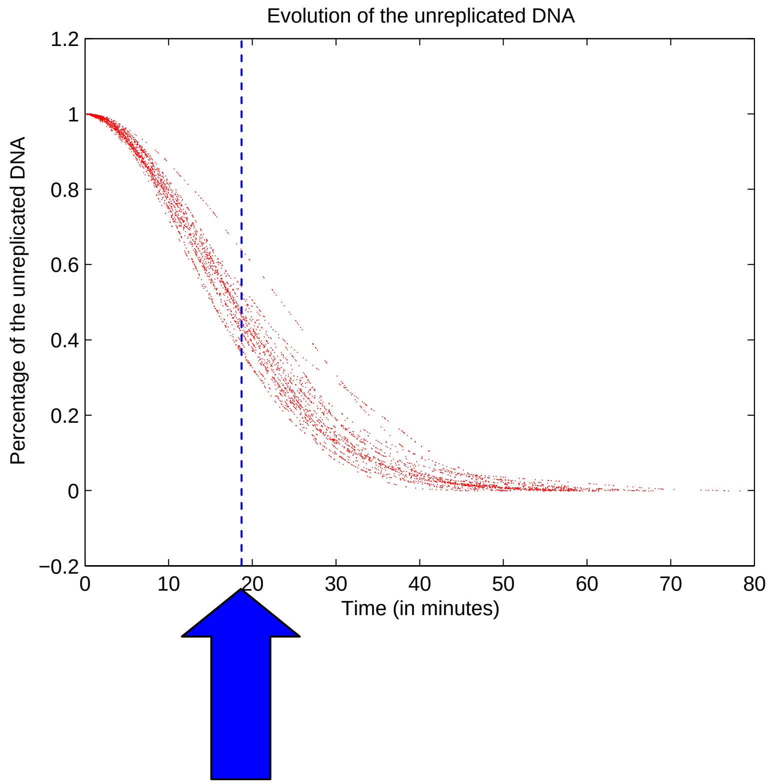
- Microarray data:
  - Positions along genome
  - Efficiencies

  ~900 origins of replication
- Manual analysis impossible
- Develop stochastic model
- Monte-Carlo simulation
- Model predictions unrealistic



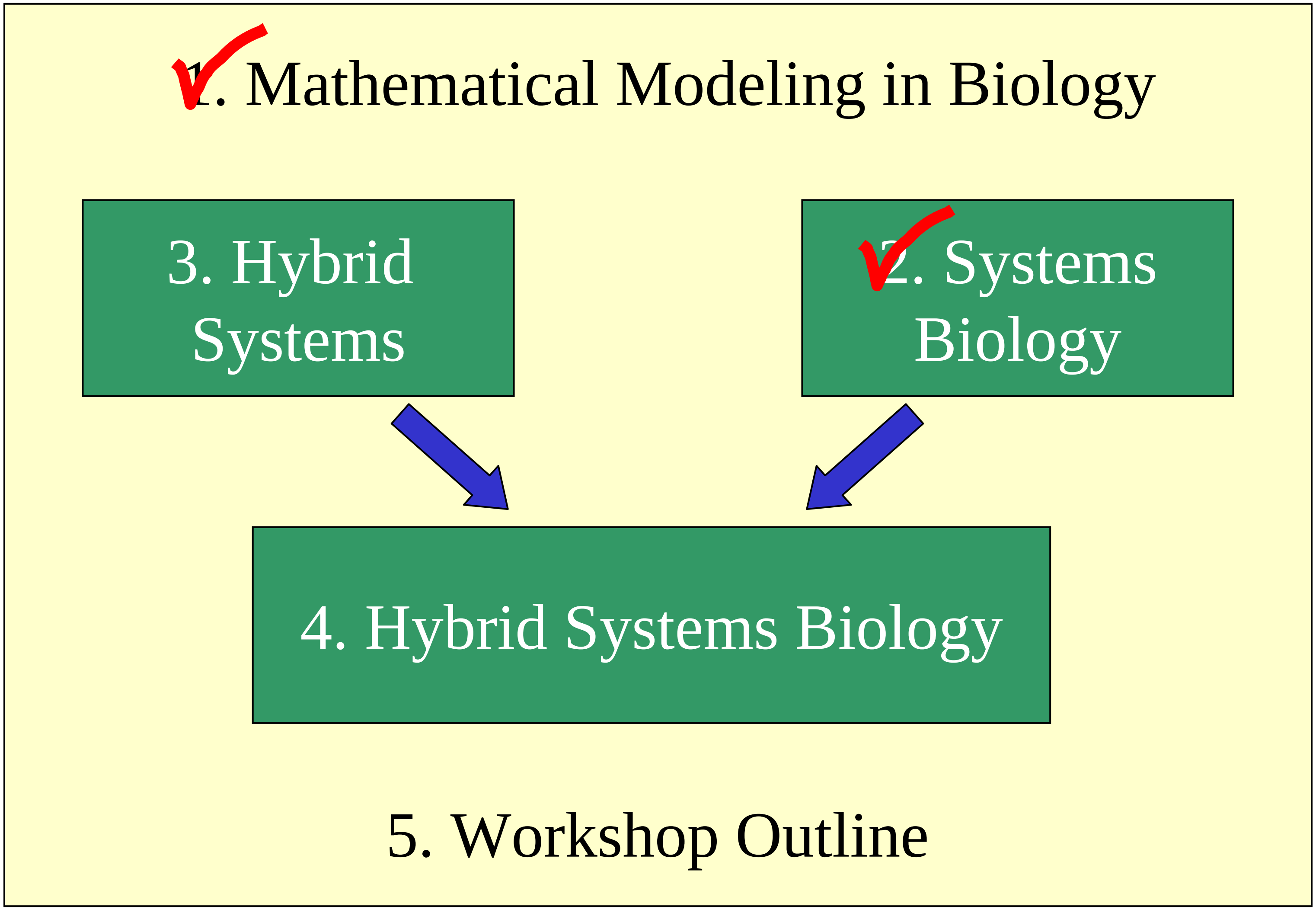
Example: DNA replication

- Predicted duration of DNA replication too long
- Many possible explanations
- Tested on the model
- Only two seem plausible
- New data will allow us to test one (hopefully!)
- Targeted experiments designed to test the other



Expected outcome

Outline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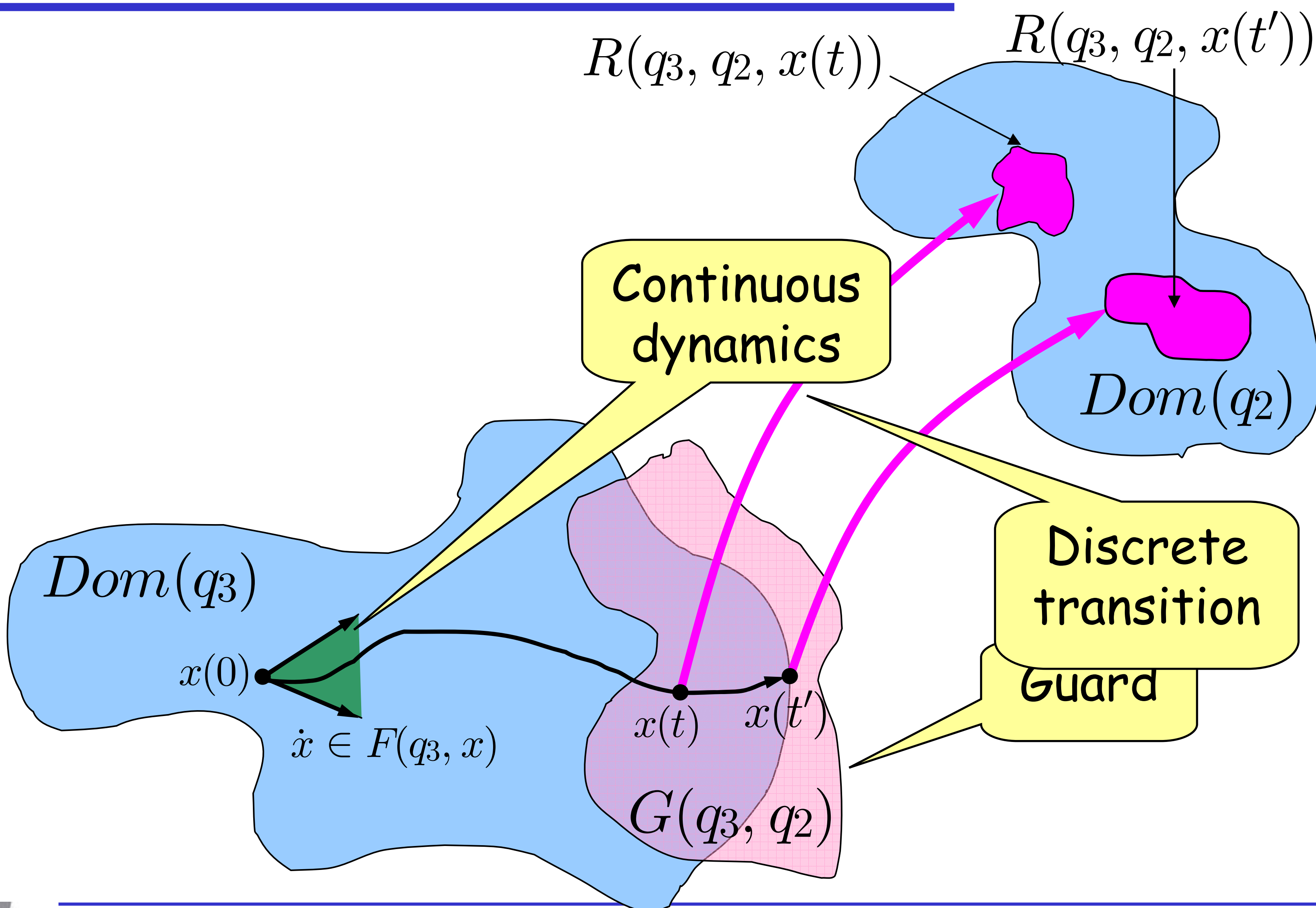
Hybrid systems

- Dynamical systems that involve interaction of discrete & continuous dynamics
- Systems with phased operation
  - Bouncing balls, walking robots
  - Systems controlled by valves, pumps, computers
  - Embedded systems
- Focus of interest for over a decade

Dynamical evolution

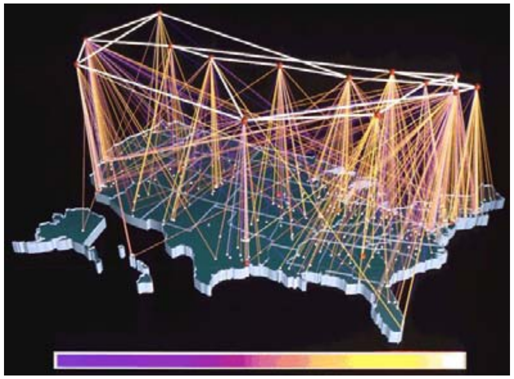


Uncertainty

- Dynamical systems often deterministic: One solution for each initial condition
- Hybrid systems allow uncertainty in
  - Initial condition
  - Flow direction
  - Discrete & continuous state destinations
  - Choice between flowing and jumping
- "Traditionally" uncertainty worst case
- This may be too coarse for biological systems
- Stochastic hybrid systems: Probabilities

Hybrid Systems

- Methods and computational tools
  - Modeling & simulation
  - Identification & observers
  - Analysis & verification
  - Controller design
- Numerous successful applications
  - Automotive & avionics
  - Industrial processes
  - Transportation
  - Telecom & power networks
  - Biochemical systems



Why hybrid systems biology?

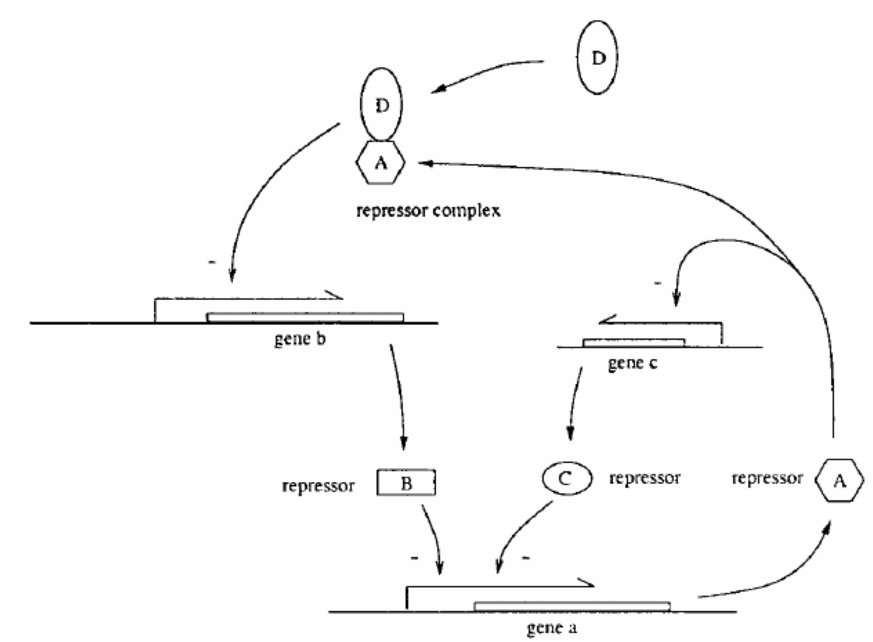
Different modeling methods at molecular level

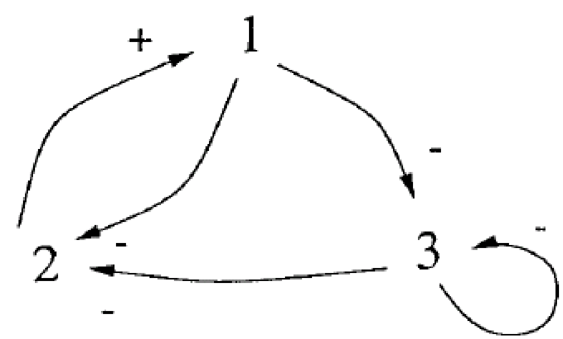
- Discrete: Finite states and their interactions
- Continuous: ODE, PDE
- Stochastic: Master equation, Markov chain
- Hybrid

H. de Jong, "Modeling and simulation of genetic regulatory systems: A literature review", *Journal of Computational Biology*, 9(1):67-103, 2002

Discrete models

Example: Directed and undirected graphs





Other examples: Bayesian & Boolean networks

Discrete models

- Advantages:
  - Easy to develop: Directly map biological intuition
  - Easy to analyze: Graph operations
  - Analysis can lead to interesting conclusions
    - Cycles suggest feedback relations
    - Sub-graphs suggest functional modules
    - Graph comparisons suggest evolutionary conserved mechanisms
- Disadvantages:
  - Somewhat coarse
  - No temporal variation or spatial information
- Alternative: Add continuous dynamics

Continuous models: ODE

- Model evolution of concentrations of RNA, proteins, etc.
- Chemical reactions, interdependencies lead to nonlinear differential equations
- Nonlinearities often due to sigmoidal activation functions

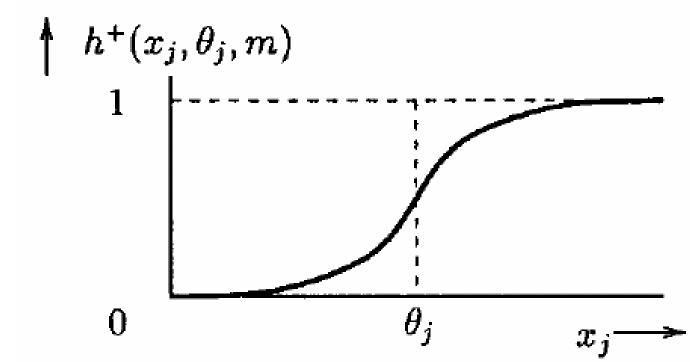
CyclinB/Cdk dimers

$$\frac{\mathrm{d}[\mathrm{CycB}]}{\mathrm{d}t} = k_1 - (k_2' + k_2'' [\mathrm{Cdh1}])[\mathrm{CycB}]$$

$$\frac{\mathrm{d}[\mathrm{Cdh1}]}{\mathrm{d}t} = \frac{(k_3' + k_3'' A)(1 - [\mathrm{Cdh1}])}{J_3 + 1 - [\mathrm{Cdh1}]} - \frac{k_4 m [\mathrm{CycB}][\mathrm{Cdh1}]}{J_4 + [\mathrm{Cdh1}]}.$$

Cdh1/APC complexes

[Tyson & Novak, 1999]



Continuous models: ODE

- Advantages
  - Direct link to biochemical understanding
  - Standard nonlinear systems tools applicable (e.g. bifurcation analysis)
- Disadvantages
  - Model quickly becomes very complex

Continuous models: ODE

$$\frac{d[\mathrm{CycB}]}{dt} = k_1 - (k_2' + k_2''\,[\mathrm{Cdh1}])\,[\mathrm{CycB}]$$

$$\frac{d[\mathrm{Cdh1}]}{dt} = \frac{(k_3' + k_3'' A)(1 - [\mathrm{Cdh1}])}{J_3 + 1 - [\mathrm{Cdh1}]} - \frac{k_4 m [\mathrm{CycB}][\mathrm{Cdh1}]}{J_4 + [\mathrm{Cdh1}]}.$$

[Tyson & Novak, 1999]

$$\frac{d\,\mathrm{Sic1}}{dt} = k_5 - k_6'\,\mathrm{Sic1} - k_p\mathrm{Sic1} + k_{pp}\,\mathrm{Cdc14}\cdot\mathrm{Sic1P} - k_j\mathrm{Clb}\cdot\mathrm{Sic1} + k_{jr}\,\mathrm{Tri} + k_{2c}\,\mathrm{Tri}$$

$$\frac{d\,\mathrm{Sic1P}}{dt} = k_p\,\mathrm{Sic1} - k_{pp}\,\mathrm{Cdc14}\cdot\mathrm{Sic1P} - (k_6' + k_6'')\mathrm{Sic1P} - k_j\mathrm{Clb}\cdot\mathrm{Sic1P} + k_{jr}\,\mathrm{TriP} + k_{2c}\,\mathrm{TriP}$$

$$\frac{d\,\mathrm{Tri}}{dt} = k_j\mathrm{Clb}\cdot\mathrm{Sic1} - k_{jr}\,\mathrm{Tri} - k_{2c}\,\mathrm{Tri} - k_6'\,\mathrm{Tri} - k_p\,\mathrm{Tri} + k_{pp}\,\mathrm{Cdc14}\cdot\mathrm{TriP}$$

$$\frac{d\,\mathrm{TriP}}{dt} = k_p\,\mathrm{Tri} - k_{pp}\,\mathrm{Cdc14}\cdot\mathrm{TriP} + k_j\mathrm{Clb}\cdot\mathrm{Sic1P} - k_{jr}\,\mathrm{TriP} - k_{2c}\,\mathrm{TriP} - (k_6' + k_6'')\mathrm{TriP}$$

$$\frac{d\,\mathrm{C1b}}{dt} = k_1\,\mathrm{mass} - k_j\mathrm{Clb}\cdot\mathrm{Sic1} + k_{jr}\,\mathrm{Tri} - k_j\mathrm{Clb}\cdot\mathrm{Sic1P} + k_{jr}\,\mathrm{TriP} - \mathrm{k}_2\,\mathrm{Clb} + k_6'\,\mathrm{Tri} + (k_6' + k_6'')\mathrm{TriP}$$

$$\frac{d\,\mathrm{Hct1}}{dt} = \frac{k_{hctr}(1 - \mathrm{Hct1})}{J_{hctr} + 1 - \mathrm{Hct1}} - \frac{k_{hct}\,\mathrm{Hct1}}{J_{hct} + \mathrm{Hct1}}$$

$$\frac{d\,\mathrm{Cdc20}}{dt} = k_{as}\,\mathrm{Clb} - k_{aa}\,\mathrm{Cdc20} + k_{ai}\,\mathrm{Cdc20}_A - k_{ad}\,\mathrm{Cdc20}$$

$$\frac{d\,\mathrm{Cdc20}_A}{dt} = k_{aa}\mathrm{Cdc20} - k_{ai}\,\mathrm{Cdc20}_A - k_{ad}\,\mathrm{Cdc20}_A$$

$$\frac{d\,\mathrm{INH}}{dt} = k_3 - k_i\,\mathrm{INH\ Cdc14} + k_{ir}\,\mathrm{IC} - k_4\,\mathrm{Cdc20}_A\,\mathrm{INH}$$

$$\frac{d\,\mathrm{IC}}{dt} = k_i\,\mathrm{INH\ Cdc14} - k_{ir}\,\mathrm{IC} - k_4\,\mathrm{Cdc20}_A\,\mathrm{IC}$$

$$\frac{d\,\mathrm{mass}}{dt} = \mu\,\mathrm{mass}$$

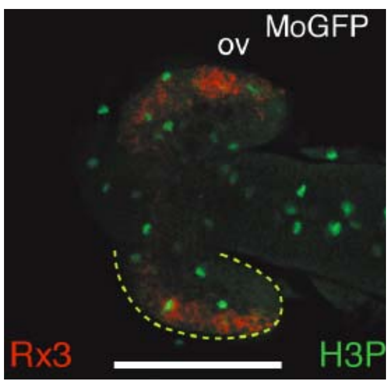
[Tyson & Novak 2001]

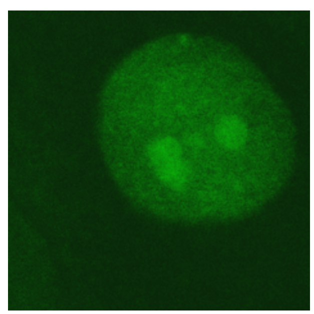
Continuous models: ODE

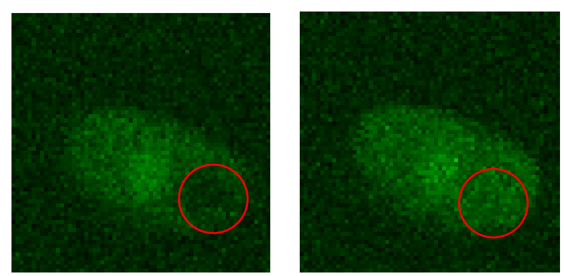
- Advantages
  - Direct link to biochemical understanding
  - Standard nonlinear systems tools applicable (e.g. bifurcation analysis)
- Disadvantages
  - Model quickly becomes very complex
  - Sensitivity w.r.t. parameter values
  - Concentration approximation often inaccurate
  - Deterministic
  - No spatial component
- Alternative: Abstract nonlinearities by switches

Continuous models: PDE

- Model evolution of concentrations
- But with a spatial component
- Reaction diffusion equations
- Can be model variations of concentrations
  - Between cells
  - Between different compartments in a cell
  - Between different areas in a nucleus

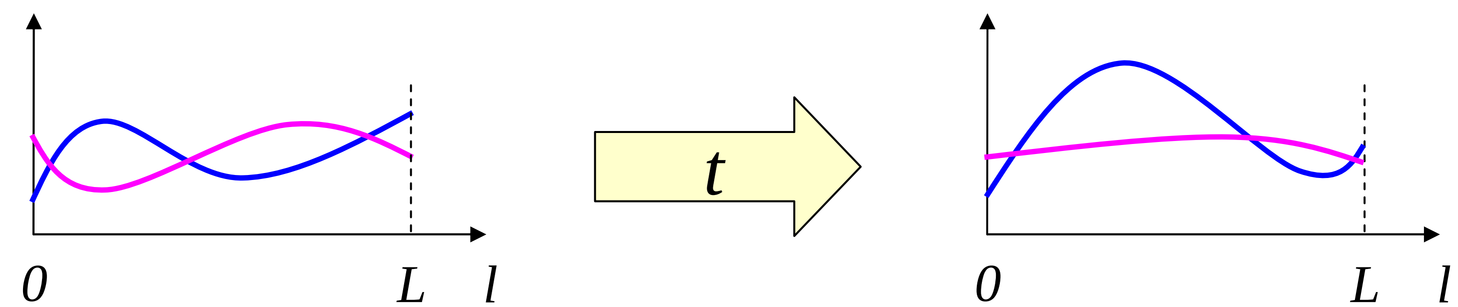






Continuous models: PDE

- Concentrations of chemicals, $x_i(t,l)$, $i=1, 2, \ldots, n$
- In parameterized by 1 dimension (l) + time (t)



$$\frac{\partial x_i}{\partial t} = f_i(x) + d_i \frac{\partial^2 x_i}{\partial l^2}$$

Reaction term (as for ODE)

Diffusion term (spatial component)

Continuous models: PDE

- n coupled PDE + boundary conditions
- Normally in 3 dimensions + time
- Disadvantages
  - Very difficult to solve
    - By hand for few chemicals, low dimension
    - Numerically?
  - Sensitivity w.r.t. parameter values
  - Concentration approximation often inaccurate
  - Deterministic
- Advantages
  - Fairly faithful representation of reality
  - Simplification often possible (eg. radial symmetry)

Stochastic master equations

- Treat every molecule separately
- State, *X*, number of molecules of chemicals
- Joint probability distribution *p(X,t)*
- Evolves according to *m* reactions

$$\frac{\partial}{\partial t}p(X,t) = \sum_{j=1}^{m}[b_j - a_j p(X,t)]$$

Effect of reaction j

Stochastic master equations

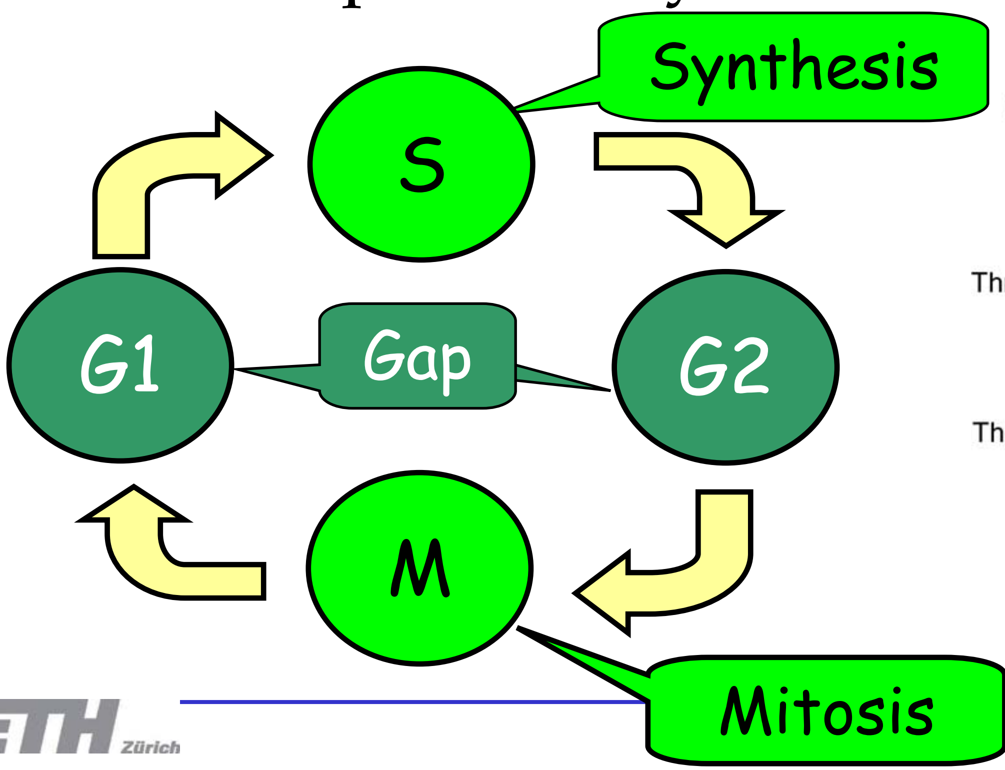
- Advantages
  - Very faithful representation of reality
  - Can deal with few copies of molecules
  - Can be blended with/simplified to ODE models
  - Spatial component can be added
- Disadvantages
  - Very difficult to solve in general
  - Often resort to simplifications
  - Stochastic simulation

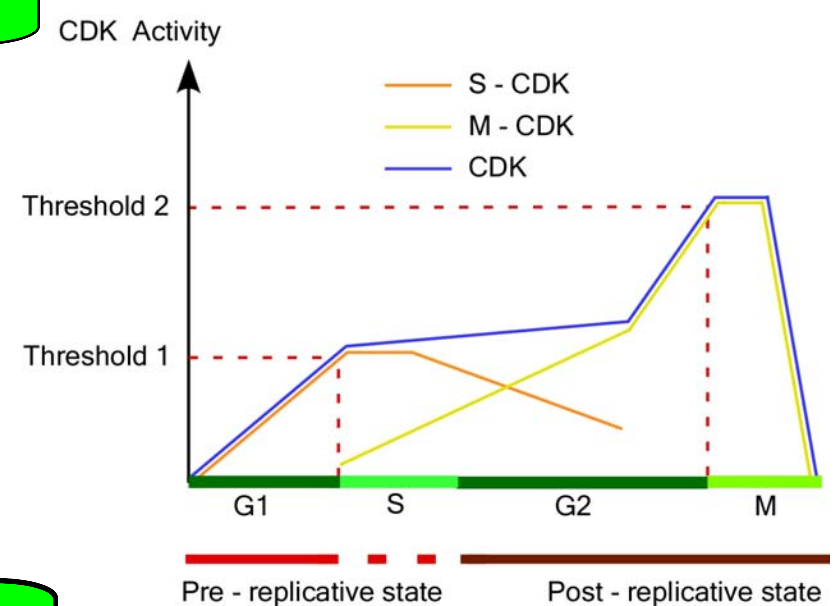
Stochastic simulation [Gillespie]

- Monte-Carlo type simulation
- State: Number of molecules of each chemical
- Algorithm
  1. Determine when next reaction will be (stochastic)
  2. Determine which reaction this will be (stochastic)
  3. Update system state according to reaction
  4. Repeat
- Complexity, efficient implementation
- Widely used in practice
- Spatial variation possible (e.g. step 1)

Why hybrid systems biology?

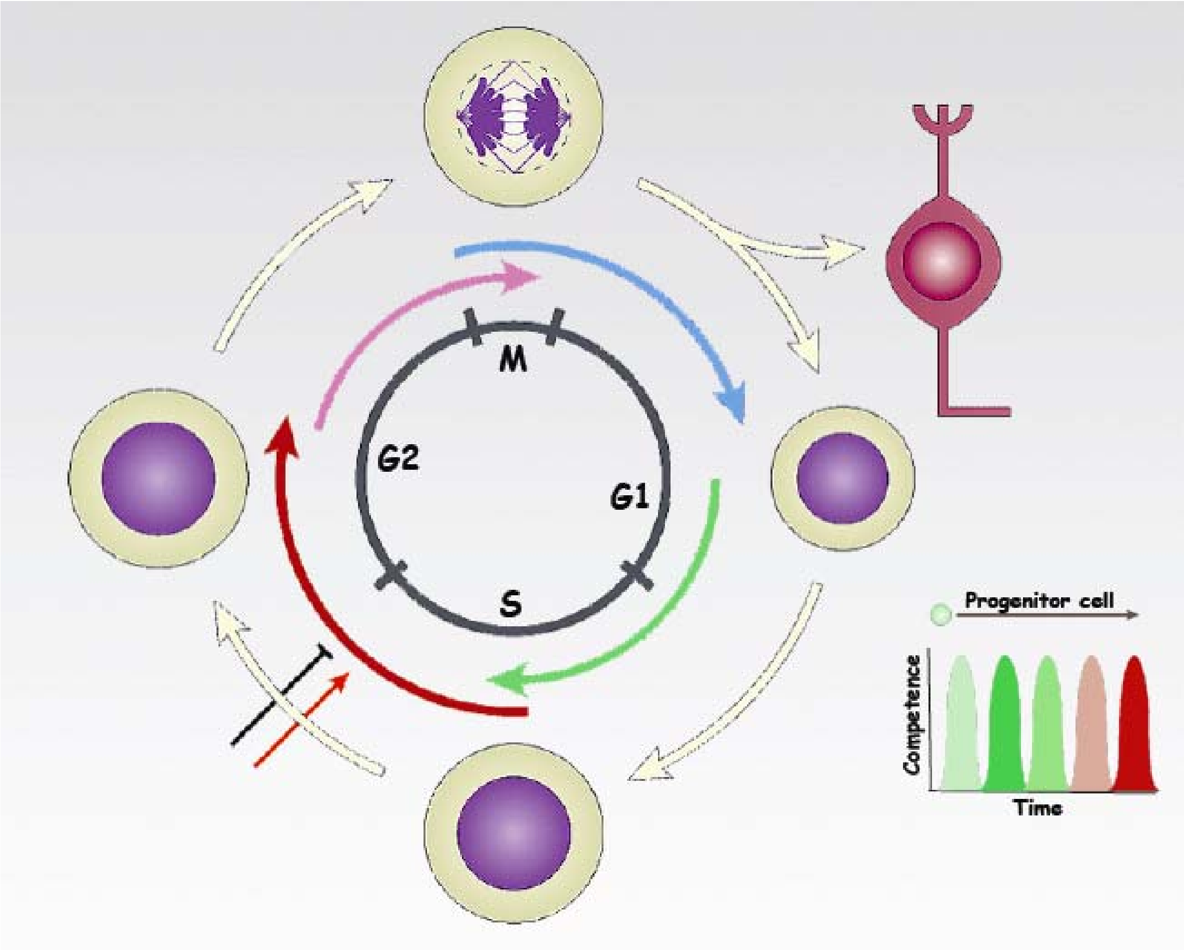
- Model exist to deal with discrete, continuous and stochastic aspects of the problem
- Often the interaction makes the difference
- Example: Cell cycle





Why hybrid systems biology?

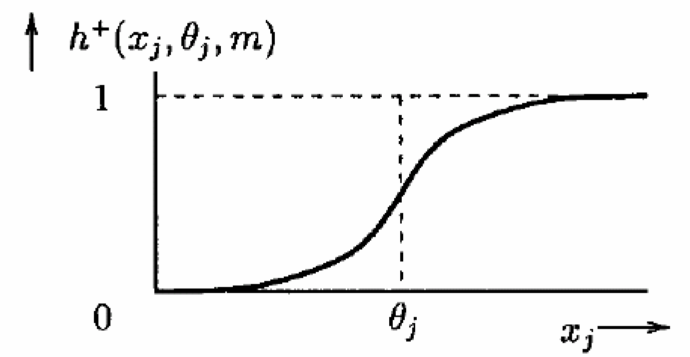
- Example: Cell differentiation

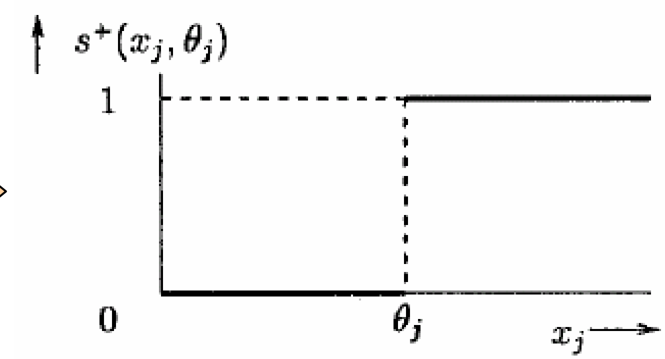


Courtesy:
J. Wittbrodt

Why hybrid systems biology?

- Time scale hierarchies
- Abstract nonlinearities by switches





$$\dot{x}_i = k_i h(x_j, \theta_j, m) - l_i x_i \quad \Rightarrow \quad \dot{x}_i = \begin{cases} k_i - l_i x_i & \text{if } x_j \geq \theta_j \\ - l_i x_i & \text{else} \end{cases}$$

Nonlinear ⇒ Piecewise affine

Why hybrid systems biology?

- PWA systems
  - Special type of hybrid systems
  - Not general nonlinear systems
  - Provide enough structure to allow some analysis
- Biological networks → special class of PWA
  - Dynamics decoupled
  - Switching boundaries aligned with the axes
- Special care is needed
  - Dynamics discontinuous
  - Sliding modes, pseudo equilibria

Stochastic hybrid systems

- In some cases stochastic terms central
- Examples:
  - Master equation, stochastic simulation
  - Cell cycle
  - Cell differentiation
- Stochastic hybrid models
  - Discrete states
  - Continuous states
  - Probabilistic representation of uncertainty

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Workshop overview

~~8:45 - 9.30 **John Lygeros**: An overview of hybrid models for biochemical systems~~

9:45 - 10.30 **Zoe Lygerou**: An introduction to information flows within the cell

11:00 - 11:45 **Zoe Lygerou**: Tools and approaches in modern biological science

12:00 - 12:45 **Hidde de Jong**: Qualitative analysis and verification of piecewise affine models of genetic regulatory networks

14:30 - 15.15 **Delphine Ropers**: Development and experimental validation of piecewise affine models of carbon starvation response in Escherichia coli

15:30 - 16:15 **Giancarlo Ferrari-Trecate**: Identification of deterministic piecewise affine models of genetic regulatory networks

16:45 - 17:30 **John Lygeros**: Stochastic hybrid models of DNA replication