Event based modeling & Multilevel modeling in CA
modeling formalisms (last)

LAST TIME:

Network models: Gene regulation - (Neural networks) themes
Multiple models for predefined behaviour (cf robustness):
no reversed engineering; not simplest one 'best'
realized network 'typical'? (randomizations)
parameter-sweep (connectivity) vs causes.

TODAY:

● Event based models
data intensive modeling of specific systems
● Multilevel modeling: predefined multiple levels.
counterintuitive behavior
debugging experimental inferences
debugging models
Overview single level (Autonomous) Dynamical Systems
timing regimes

<table>
<thead>
<tr>
<th>continuous var.</th>
<th>continuous time</th>
<th>discrete time</th>
</tr>
</thead>
<tbody>
<tr>
<td>continuous var.</td>
<td>ODE</td>
<td>MAPS</td>
</tr>
<tr>
<td>discrete var./nominal entities</td>
<td>EVENT</td>
<td>FSM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(n)-FSMs: CAs, B-nets</td>
</tr>
</tbody>
</table>
**EVENT based models: continuous time, discrete events**

**Gillespie algorithm**

1: *seen als stochastic ODE*

Example: logistic stochastic population growth

\[
\frac{dN}{dt} = aN - bN^2 + \text{noise}
\]

**EVENT based**

all events (birth + death):

\[
e_0 = (a_1 + a_2)N - b_1 N^2 + b_2 N^2
\]

\[
\tau = \frac{1}{e_0 \ln(1/\text{rand1})}; \quad T = T + \tau
\]

\[
N = N + 1 \text{ if } (a_1 N - b_1 N^2) < \text{rand2} \ast e_0
\]

else \(N = N - 1;\)
EVENT based models: continuous time, discrete events
Gillespie algorithm

seen as multi-entity - multistate decomposition

Example

Rate-Limiting Steps in Yeast Protein Translation
Premal Shah et al Cell 2013
Data, states, events

**DATA**
- fasta file of yeast mRNA + number of mol/cell
- yeast tRNA's (41) + number in cell + wobble
- number of ribosomes
- initiation prob of all mRNA types
- size of ribosome/tRNA's yeastcell
- diffusion constant ribosomes, tRNA's
- —— > characteristic times

**STATES**
- number of free ribosomes/tRNA's(of every type)
- Position of each bound ribosomes/tRNA's on each individual mRNA

**EVENTS**
- Initiation (binding of ribosome at free 5'end of mRNA)
- Elongation (change position, free - bind tRNA)
## Yeast data on cell content

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value or Range of Values</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R^t$</td>
<td>number of ribosomes</td>
<td>$2 \times 10^5$</td>
<td>(Warner, 1999; von der Haar, 2008)</td>
</tr>
<tr>
<td>$A^t$</td>
<td>number of mRNAs</td>
<td>$6 \times 10^4$</td>
<td>(Zenklusen et al., 2008)</td>
</tr>
<tr>
<td>$T^t$</td>
<td>number of tRNAs</td>
<td>$3.3 \times 10^6$</td>
<td>(Waldron and Lacroute, 1975)</td>
</tr>
<tr>
<td>$T_n$</td>
<td>number of types of tRNAs</td>
<td>41</td>
<td>(Chan and Lowe, 2009)</td>
</tr>
<tr>
<td>$T_{ij}$</td>
<td>number of tRNAs of type $j$</td>
<td>$\sim 12,000\text{−}190,000$</td>
<td>(Chan and Lowe, 2009)</td>
</tr>
<tr>
<td>$A_i$</td>
<td>number of mRNAs of type $i$</td>
<td>1−1,254</td>
<td>(Ingolia et al., 2009)</td>
</tr>
<tr>
<td>$p_i$</td>
<td>gene-specific initiation probability</td>
<td>$\sim 3.5 \times 10^{-6}\text{−}0.115$</td>
<td>(Experimental Procedures)</td>
</tr>
<tr>
<td>$n$</td>
<td>number of genes</td>
<td>3,795</td>
<td>(Ingolia et al., 2009)</td>
</tr>
<tr>
<td>$D_r$</td>
<td>diffusion coefficient of ribosomes</td>
<td>$3 \times 10^{-13}$ m$^2$/s</td>
<td>(Politz et al., 2003)</td>
</tr>
<tr>
<td>$D_t$</td>
<td>diffusion coefficient of tRNAs</td>
<td>$8.42 \times 10^{-11}$ m$^2$/s</td>
<td>(Werner, 2011)</td>
</tr>
<tr>
<td>$C_r$</td>
<td>size of ribosome footprint in codons</td>
<td>10</td>
<td>(Ingolia et al., 2009)</td>
</tr>
<tr>
<td>s</td>
<td>tRNA competition coefficient</td>
<td>$7.78 \times 10^{-4}$</td>
<td>(Experimental Procedures)</td>
</tr>
<tr>
<td>V</td>
<td>volume of the cell</td>
<td>$4.2 \times 10^{-17}$ m$^3$</td>
<td>(Siwiak and Zielenkiewicz, 2010)</td>
</tr>
</tbody>
</table>
Algorithm (pseudocode)

while time < t (total simulation time) do
  Calculate
  Fraction of mRNAs of gene i that are initiable, $f_i$ - i.e., those mRNAs with first 10 codons unbound.
  Number of elongatable ribosomes waiting at codon $j$, $R^b(j)$ - ribosomes with next 10 codons unbound.
  Rates of all possible events (see Table S2)
    Total initiation rate: $\rho^t = \sum_{i=1}^{n} \frac{R^f_i A_i p_i}{\tau_r N_r}$
    Total elongation rate: $\epsilon^t = \sum_{j=1}^{61} \frac{R^b(j) T^f_{\phi(j)} w_j s}{\tau_l N_l}$
  Probability of each possible event (see Table S2)
  Randomly select an event based on its probability of occurrence (see Table S2)
  Update the changes in the state of the cell (see $\Delta State$ in Table S2)
  Increment time by $\frac{1}{\rho^t + \epsilon^t}$
  Update the number of free ribosomes, $R^f$
  Update the number of free tRNAs of type $\phi(j)$, $T^f_{\phi(j)}$
end
Is protein production initiation or elongation limited in exponential growing yeast populations?

more ribosomes at 5´ end BUT due to >> initiation prob. on short genes

initiation limited

debugging of wrong inference from exp. data
Optimizing codon usage of transgenes only useful at very high dosage due to freeing of ribosomes.
Under aminoacid starvation down regulating ribosomes can increase protein production because translation becomes elongation limited reducing Ribosomes increases free TRNA’s
conclusions event based modeling of stochastic reaction kinetics

Data intensive modeling

Quantitative conclusions

Upscaling to “whole cell modeling” feasible

But note simplifications:

space but no spatial structure

fixed number of molecules

fixed conditions

....
modeling biotic systems as multilevel systems

Previously:

**EMERGENT MESOSCALE ENTITIES:**
- discovery and description
- modeling these entities
- variable number of 'entities,
- mean field approximation

Now:

**PREDEFINED MULTIPLE LEVEL**

- e.g. predefined cells as mesoscale
- multiple timescales of information transfer
- multiple scales of interaction

example of cell movement
How to represent a cell?

cell basic unit in single celled and multi-cellular organisms

- **cell as a dimensionless point**: PDE
- **cell as occupation of a patch of space**: CA
  
  NB particle conservation!
- **cell as a “homunculus”**: IBM
- **cell as a ball being moved by external forces** (finite element models)
- Cells are deformable highly viscous objects,
  
  behaviour determined by internal state (gen expression)
  
  and external interactions operating in subcellular scale

How to model? Multilevel model formalism (CPM)
A 'biotic' cell consists of many lattice sites in same 'state' (= cell identity)

Cells have a type $\tau$, volume $v$ (and...)

Between cells: free energy bod $J_{ij}$ where $i$ and $j$ are the types of the cells

**dynamics**: Free energy minimization with volume conservation:

$$H = \sum \frac{J_{ij}}{2} + \sum J_{im} + \lambda (v - V)^2$$

Copy state of neighbouring cell with probability:

$$P_{i \rightarrow j} = 1 \text{ iff } \Delta H < -\beta \ ; \ P_{i \rightarrow j} = e^{-(\Delta H + \beta)/M} \text{ iff } \Delta H \geq -\beta$$
<table>
<thead>
<tr>
<th>Configuration</th>
<th>Diagram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial configuration</td>
<td><img src="image" alt="Diagram" /></td>
</tr>
<tr>
<td>Cell Sorting</td>
<td>$J_{white,white} = J_{grey,grey} &lt; J_{white,grey}$</td>
</tr>
<tr>
<td>Cell Mixing</td>
<td>$J_{white,white} = J_{grey,grey} &gt; J_{white,grey}$</td>
</tr>
<tr>
<td>Engulfment</td>
<td>$J_{white,gray} &lt; J_{white,medium}$</td>
</tr>
<tr>
<td>No cell cell adhesion</td>
<td>$J_{cell,cell} &gt; 2J_{cell,medium}$</td>
</tr>
</tbody>
</table>

Table 2.2: A list of cell sorting behaviours in the Glazier and Graner model.
from cells to tissues (and beyond)

- cell sorting by differential adhesion
- Individual cells 'wiggle' through cellmass

- Individual cells can 'move against the flow'
  e.g. by being larger; being in the minority, adhesion

Käfer, Hogeweg & Marée 2006
change direction without changing cell or environmental properties

---

chenotaxis
Cell movement in Lymphnode:
stop and go (Beltman et al 2007)

in vitro (Miller et al)

in silico (Beltman et al)
Cell movement in empty Lymphnode
Beltman et al 2007

Cell track of individual lone cell

Cell track of 5 cells in an environment with many cells
Chemotaxis in lymphnodes?
beware of modeling artefacts

Weak chemotaxis hard to detect by cell tracking. Augment by modeling: what would the effect of chemotaxis be?

2 recent models: opposite conclusions

Riggs et al JTB 2008:”A comparison of random vs. chemotaxis-driven contacts of T cells with dendritic cells during repertoire scanning”.

Our [CA modeling results] suggest that, within a LN T-zone, a random search strategy is optimal for a rare cognate T cell to find its DC match and maximize production of activated T cells “

Vroomans et al 2012: “Chemotactic Migration of T Cells towards Dendritic Cells Promotes the Detection of Rare Antigens”

Our [CPM] simulations show that chemoattraction of T cells enhances the DC scanning efficiency, leading to an increased probability that rare antigen-specific T cells find DCs carrying cognate antigen.

Models incorporate very similar biological assumptions
Difference in modeling formalism
CA model of Riggs et al

CPM model of Vroomans et al

RANDOM CHEMOTAXIS

Vroomans: sensitive T cells (blue), insensitive T cells (yellow), DCs (red), reticular
network (green)