Event based modeling & Multilevel modeling in CA
LAST TIME:

Network models: Gene regulation
themes
Multiple attractors, domain of attraction,
divergent trajectories
(double) knockouts and “buffering”
Multiple models for predefined behaviour (cf struct stab):
no reversed engineering; not simplest one ’best’ (evolved)
how “special” is observed behaviour: assessment by “smart” randomization

TODAY:

• Event based models
data intensive modeling of specific systems
• Multilevel modeling: predefined multiple levels.
counterintuitive behavior
debugging experimental inferences
debugging models
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):

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

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

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

else \[ N = N - 1; \]
Population vs Individual doubling time
population grows faster than average individual
(Hashimoto et al PNAS 2016)
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 yeast cell
- diffusion constant ribosomes, tRNA’s
- $\rightarrow$ > 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 postion, free - bind tRNA)
# Yeast data on cell content

## Table 1. Summary of Model Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value or Range of Values</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_i$</td>
<td>number of ribosomes</td>
<td>$2 \times 10^5$</td>
<td>(Warner, 1999; von der Haar, 2008)</td>
</tr>
<tr>
<td>$A_i$</td>
<td>number of mRNAs</td>
<td>$6 \times 10^4$</td>
<td>(Zenklusen et al., 2008)</td>
</tr>
<tr>
<td>$T_i$</td>
<td>number of tRNAs</td>
<td>$3.3 \times 10^6$</td>
<td>(Waldron and Lacroute, 1975)</td>
</tr>
<tr>
<td>$T_{ij}$</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>$\sim 12,000$–$190,000$</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>$\sim 3.5 \times 10^{-6}$–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 \textit{initializable}, $f_i$ - i.e., those mRNAs with first 10 codons unbound.

Number of \textit{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: $\rho^t = \sum_{i=1}^{n} \frac{R^f_i A_i p_i}{\tau R_N}$

Total elongation rate: $\epsilon^t = \sum_{j=1}^{61} \frac{R^b(j) T_{\phi(j)}^f w_j s}{\tau_t N_t}$

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 $\phi(j)$, $T_{\phi(j)}^f$

end
Table S2. Markov States and Transition Rates, Related to Figure 1

<table>
<thead>
<tr>
<th>Initiation</th>
<th>Gene #</th>
<th>mRNA #</th>
<th>Initiation rate</th>
<th>Event probability</th>
<th>∆State</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td></td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td></td>
<td>( \frac{R^f p_1}{\tau_i N_i} )</td>
<td>( \frac{R^f p_1}{\tau_i N_i (p^f + \epsilon^f)} )</td>
<td>( R^f \rightarrow R^f - 1 )</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td></td>
<td>( \frac{R^f p_1}{\tau_i N_i} )</td>
<td>( \frac{R^f p_1}{\tau_i N_i (p^f + \epsilon^f)} )</td>
<td>( R^f \rightarrow R^f - 1 )</td>
</tr>
<tr>
<td>1</td>
<td>A_1</td>
<td></td>
<td>( \frac{R^f p_1}{\tau_i N_i} )</td>
<td>( \frac{R^f p_1}{\tau_i N_i (p^f + \epsilon^f)} )</td>
<td>( R^f \rightarrow R^f - 1 )</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td></td>
<td>( \frac{R^f p_2}{\tau_i N_i} )</td>
<td>( \frac{R^f p_2}{\tau_i N_i (p^f + \epsilon^f)} )</td>
<td>( R^f \rightarrow R^f - 1 )</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td></td>
<td>( \frac{R^f p_2}{\tau_i N_i} )</td>
<td>( \frac{R^f p_2}{\tau_i N_i (p^f + \epsilon^f)} )</td>
<td>( R^f \rightarrow R^f - 1 )</td>
</tr>
<tr>
<td>n</td>
<td>A_n</td>
<td></td>
<td>( \frac{R^f p_n}{\tau_i N_i} )</td>
<td>( \frac{R^f p_n}{\tau_i N_i (p^f + \epsilon^f)} )</td>
<td>( R^f \rightarrow R^f - 1 )</td>
</tr>
</tbody>
</table>

Total initiation rate:
\[ \rho^i = \sum_{i=1}^n R^f (i) p_i \frac{1}{\tau_i N_i} \]

<table>
<thead>
<tr>
<th>Elongation</th>
<th>Gene #</th>
<th>mRNA #</th>
<th>Codon position</th>
<th>Ribosome bound</th>
<th>Elongation rate</th>
<th>Event probability</th>
<th>∆State</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>N</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>3</td>
<td>N</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>L_1</td>
<td>N</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>1</td>
<td>Y</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>( \frac{T^f \phi(i,2) w_{i,2,y}}{\tau_i N_i} )</td>
<td>Ribosome bound at codon 2 ( \rightarrow ) N</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>11</td>
<td>Y</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>L_1</td>
<td>Y</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>A_2</td>
<td>L_2</td>
<td></td>
<td></td>
<td>( \frac{T^f \phi(i,11) w_{i,11,y}}{\tau_i N_i} )</td>
<td>Ribosome bound at codon 11 ( \rightarrow ) N</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>A_n</td>
<td>L_n</td>
<td></td>
<td></td>
<td>( \frac{T^f \phi(i,2) w_{i,2,y}}{\tau_i N_i} )</td>
<td>Ribosome bound at codon 12 ( \rightarrow ) Y</td>
<td></td>
</tr>
</tbody>
</table>

Total elongation rate:
\[ \epsilon^i = \sum_{i=1}^n R^f (j) \frac{T^f \phi(i,j) w_j}{\tau_i N_i} \]
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
Under amino-acid starvation down regulating ribosomes can increase protein production because translation becomes elongation limited reducing Ribosomes increases free TRNA'
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

....
Event based models (2)

Individual based models (IBM, IOM, agent based models)

*simple rules* $\rightarrow$ *complex behavior*

**Simplest form:**

Individual simple (in)finite state machine
“schedules” its own next “event” in continuous time
Interacts with (potentially complex) environment
and other individuals like it

LOCAL information determines behavior

Variable structure: not invariant set of interaction partners
(in contrast to CA, Boolean nets)

distributed (shared) environmental “memory”
$\rightarrow$ flexible behaviour from rigid rules / automatic adaptation

**The best model of the world is the world**
internal model of the world as ” for information shortage

*contexts*
Ethology; Ecology, Evolution, (also transcription) swarm intelligence
*’intelligence without reasoning’ (Brooks)*
simple rules to complex behavior

cf “Simon (1969)

“an ant seen as a behavioral system is quite simple - the apparent complexity of its behavior is due to the complexity of the environment in which it finds itself”

“a human seen as a behavioral system is quite simple - the apparent complexity of his behavior is due to the complexity of the environment in which it finds himself”
Social structure as side-effect of foraging

Question: social structure of chimpanzees
Why all males groups in Chimpanzees?
Why single females?
Why do males travel further?

Modeling strategy: Make model WITHOUT behavior we are interested in
(but include some basic structure of system under consideration)
and OBSERVE

individuals: (CHIMPS)
- go to nearest fruit tree and eat until satisfied or fruit exhausted - rest
- males: search for receptive females - females eat protein food not eaten by males

environment: GOMBE-like

→ Social structure of Chimpanzees

opportunity vs optimality based explanation

Hogeweg & Hesper 1990; te Boekhorst H. 1994
MCHIMP
if DARK then SLEEP
elseif there is a CHIMP at \( 15 < \text{DIST} < 100 \) (ANGLE < 120) then
  if TUMESCENT FCHIMP then FOLLOW
  else GO TO the CHIMP most in front and
  if there is FRUIT at DIST < 10 then EAT
  else REST (.RAND .02 .03)
elseif there is a FRUIT at \( 5 < \text{DIST} < 100 \) then
  GO TO FRUIT most in front and EAT
else FORWARD (RAND 25 40)
  if just eaten then REST (.3 * amount eaten)
  else REST (RAND .02 .03)

FRUIT
number 1200 (variable \( \rightarrow \) ca 250 ) (600 1800)
size 1 - 35 chimphours (2-70, 1-23)
renewel 5 - 10 days

FCHIMP
if DARK then SLEEP
elseif there is a FRUIT at \( 5 < \text{DIST} < 100 \) then
  GO TO FRUIT most in front and EAT
elseif there is a PROT at \( 5 < \text{DIST} < 100 \) ANGLE<120 then
  GO TO FRUIT most in front and EAT
else FORWARD (RAND 25 40)
  if just eaten then REST (.3 * amount eaten)
  else REST (RAND .02 .03)

PROT
number 250 fixed (125 275)
size .03 * FRUIT
renewel when eaten
Fig. 5. Distance travelled by CHIMP's in the standard environment. Average values of individual CHIMP's are shown data from MALEs are in the dark shaded area.
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 bond $J_{ij}$ 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:
  \[ P_{i \rightarrow j} = 1 \text{ if } \Delta H < -\beta; \quad P_{i \rightarrow j} = e^{-(\Delta H + \beta)/M} \text{ if } \Delta H \geq -\beta \]
<table>
<thead>
<tr>
<th>Description</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial configuration</td>
<td></td>
</tr>
<tr>
<td>Cell Sorting</td>
<td></td>
</tr>
<tr>
<td>$J_{\text{white,white}} = J_{\text{grey,gray}} &lt; J_{\text{white,gray}}$</td>
<td></td>
</tr>
<tr>
<td>Cell Mixing</td>
<td></td>
</tr>
<tr>
<td>$J_{\text{white,white}} = J_{\text{grey,gray}} &gt; J_{\text{white,gray}}$</td>
<td></td>
</tr>
<tr>
<td>Engulfment</td>
<td></td>
</tr>
<tr>
<td>$J_{\text{white,gray}} &lt; J_{\text{white,medium}}$</td>
<td>$J_{\text{grey,medium}} &lt; J_{\text{white,medium}}$</td>
</tr>
<tr>
<td>No cell cell adhesion</td>
<td></td>
</tr>
<tr>
<td>$J_{\text{cell,cell}} &gt; 2J_{\text{cell,medium}}$</td>
<td></td>
</tr>
</tbody>
</table>

Table 2.2: A list of cell sorting behaviours in the Glazier and Graner model
• cell sorting by differential adhesion

• Individual cells 'wiggle' through cell mass

• 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 artifacts*

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

(3D)

(2D)

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

<table>
<thead>
<tr>
<th>space / time / var.</th>
<th>formalism</th>
</tr>
</thead>
<tbody>
<tr>
<td>ccc (ddc)</td>
<td>partial differential equations (PDE) reaction diffusion systems</td>
</tr>
<tr>
<td>ddc</td>
<td>map lattices</td>
</tr>
<tr>
<td>ddd</td>
<td>CA</td>
</tr>
<tr>
<td>ccd</td>
<td>individual oriented models off lattice particle systems / event-based</td>
</tr>
<tr>
<td>dcc</td>
<td>meta-population models</td>
</tr>
<tr>
<td>c/dc (d+c)</td>
<td>hybrid models</td>
</tr>
</tbody>
</table>

note: translations