[Non]-deterministic dynamics in cells: From multistability to stochastic switching

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Cells as machines

• We know a lot about the processes that take place in cells
  • Gene expression (transcription, translation)
  • Sensing, signaling, control of gene expression

• Processes can be described as "reactions"

\[ A + B + E \xrightarrow{R(a,b,e,\ldots)} C + D + E \]

  • Molecular species consumed (A,B) produced (C,D), or neither (E)

• Changes are modeled by differential equations

\[ \frac{dc}{dt} = -\frac{da}{dt} = R(a,b,e,\ldots) \]

• Issues: uncertainty, parameter variability, stochasticity
Phenotypes and Steady states

- Genetically identical cells can exhibit different phenotypes
  - Cell differentiation in multicellular organisms
  - Examples in the bacterial world: alternative phenotypes, possibly with a role in survival, adaptation,..

- Due to the different sets of genes that are “on”

- Multiple phenotypes correspond to different equilibria of the dynamical system encoded in the DNA.

- Is phenotype multiplicity always the same as multistability?

- Model predictions may change when including stochastic and spatial effects
Lac system

Network of 5 substances
Example of positive feedback in a genetic network discovered in the 50’s
This model due to Yildirim and Mackey, based on MM and Hill reaction rates; time delays omitted
Lac system

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\frac{dM}{dt} = \alpha_M \frac{1 + K_1 T^2}{K + K_1 T^2} + \Gamma_0 - (\gamma_M + \mu)M
\]

\[
\frac{dB}{dt} = \alpha_B M - (\gamma_B + \mu)B
\]

\[
\frac{dT}{dt} = \alpha_L P \frac{T_e}{K_{T_e} + T_e} - \beta_L P \frac{T}{K_L + T} - (\gamma_T + \mu)T
\]

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Bistability provides for switching:
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Bistability provides for switching:
Abstractions

- A **two-state automaton** captures the switching behavior
  - The states can be further characterized, individually
  - More often than not, many details are not important as far as the rest of the system is concerned
Lac system, stochastic model
The ODE description is not satisfactory:
- once a stable state is attained, the system (cell) should stay there indefinitely
- experimental results show spontaneous transitions and coexistence of two states

(Ozbudak, Thattai, Lim, Shraiman, van Oudenaarden, Nature 2004)
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Discrepancy due to small molecule count:
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More efficient ‘mixed’ simulations:
- can perform aggregate simulations
- equilibrium distributions
- compute transition rates
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A stochastic abstraction

- For intermediate values of $T_e$ there is a quantifiable stochastic switching rate
- Stochastic transitions occur in addition to the deterministic switching triggered by extreme values of $T_e$
Lac system

System well described by an abstraction:
- two-state Markov chain model
- transition rates depend on external TMG
- can be computed from the full model

Macrosopic behavior well fitted by this model
- the *timescale of individual transitions* is smaller than the *characteristic time of transition initiation*

Remaining issue:
Model parameters are typically fitted to macroscopic measurements
- need to reconcile microscopic and macroscopic model predictions
- possible new insight into *in vitro* vs. *in vivo* parameters
Lac system

- A classic gene switch
- Simple deterministic dynamics
  - bistability through positive feedback
- Spontaneous transitions due to stochastic effects
  - fluctuations, finite molecule numbers
- Phenomenologically, the two modes coexist
  - the same colony has populations of cells in either state
- Relative population sizes influenced by the characteristic times of the transitions
Competence in B. subtilis (based on a paper from the Elowitz lab)

- A two-prong response to nutritional stress
  - Most cells commit to sporulation
  - A small minority (<4%) become competent for DNA uptake
- ComK acts as a "master" transcription factor
Competence in B. subtilis

1. *comK* is self-promoting, and is expressed at a basal rate
2. ComK is degraded by MecA
3. ComS competes with MecA, inhibiting ComK degradation
4. *comS* is induced by stress, and is susceptible to noise
5. Overexpression of ComK suppresses *comS*

[Suel et al., Nature, 2006]
Bistability and slow return

- Two genes with mutual influence:
  - A fluctuation induces Gene 1 (comK)
  - Gene 2 (comS) is inhibited; drops below the threshold for Gene 1
  - Gene 1 returns to its low state, and Gene 2 slowly increases
Competence in B. subtilis

- A fluctuation in ComS blocks the degradation of ComK
- Increased ComK induces comK and the module "flips" into the high mode
- Eventually, the high level of ComK suppresses comS
- Lack of ComS leads to increased degradation of ComK
- comK "flips" back into the low mode

ComS (red) and ComK (green) activities during a competence event

[From Suel et al., Nature, 2006]
The competence example

• Two phenotypes, with identifiable roles in the survival of the species

• Entry into competence is triggered stochastically, similarly to "spontaneous induction" in the *lac* system.

• However, exit from competence is deterministic; it is guaranteed by the dynamics of the network.

• Even though a bistability motif is present (self-promotion of *comK*), the system is **not** bistable.
A different abstraction

- Only one steady state and a transient
  - Stochastic transition in one direction
  - Deterministic trajectory on the way back
- Similar long-term population distributions
Bacterial persistence

Discovered in the 1940’s during the first large scale administration of antibiotics

- Small fraction survive therapy at a higher rate than the rest of the colony
- Persistence opens the door to the emergence of resistant strains
- Persisters are genetically identical to the rest
- They give rise to a colony identical to the old one
Bacterial persistence

- Persisters are non-growing cells
  - Some are generated during stationary phase
  - There is spontaneous persister generation
- Persistence is an alternative phenotype
  - “Hedging strategy”
- Mechanism not well understood
- Likely an example of spontaneous entry and slow, deterministic return to growth

[From Balaban et al., Science, 2004]
Spatial effects in cell signaling

- Cells must coordinate in multicellular organisms
  - This is achieved through signaling; signals are special substances
  - Specialized receptors on the cell membrane, some inside the cell

- Receptor tyrosine kinase (RTK) receptors have to dimerize in order to signal
  - These are membrane receptors; they can move more or less freely on the membrane
  - Dimerization is more likely if the receptors are located in high density patches, rather than being uniformly distributed
  - Such patches have been observed; the mechanism behind their formation is unclear

- Spatial self-organization contributes to the dynamics of signal initiation
Membrane receptors

• Large molecules which straddle the cell membrane
• Ligand binding and dimerization are required for signal initiation
Spatial Monte-Carlo simulation

- Sometimes the only approach to signal initiation
- Molecules are simulated individually
- The system evolves as a Markov chain with spatial and chemical transitions
Summary

• Cellular processes can usually be described by ODE-based rate laws
• Two apparently conflicting challenges
  • The complexity of the networks requires simplifications (abstractions)
  • The ODE approach is itself an idealization of a richer underlying phenomenology of stochastic effects and spatial structure
• There are good mathematical methods for abstraction, and good algorithms for simulation
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