Mathematical biology
From individual cell behavior
to biological growth and form

Lecture 7:
Multiscale models

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Biological systems have multiscale causation

Denis Noble - The Music of Life (2008)

Genes regulate cell behavior and pattern formation
But patterns also determine gene expression
**In vivo**: task division between endothelial cells

- Tip cells -> leading a sprout
- Stalk cells -> follow the tip cell
- Phalanx cells -> quiescent cells in mature blood vessel

Lateral inhibition determines where tips cells appear:
- Stalk cells laterally inhibit tip cell fate via a Delta-Notch signaling pathway

(Gerhardt et al., J Cell Biol, 2003)
Example: Sprouting angiogenesis

- Original model: only one cell type
Dll4-Notch signaling selects tip cells (yellow)

Sprouts advance much faster than in original model

Palm et al. PLoS ONE, 2017
Example of a multiscale model

*Dictyostelium discoideum*
**Dictyostelium discoideum**

- Amoeba live independently
- When hungry, secrete cAMP pulse
- Also secrete cAMP if they sense cAMP
  - Refractory period after cAMP secretion
- Chemotaxis against cAMP gradients
- Cells form “Excitable medium”
- Aggregation, slug formation, culmination
Phenomena at all scales...

• Molecular level:
  – cAMP sensing, cAMP secretion
  – mechanism of cell motility
  – mechanism of chemotaxis

• Cellular level
  – Cell trajectories; cell velocity
  – Cell-cell adhesion

• Tissue scale:
  – aggregation
  – slug motion

• Can we describe the tissue scale in molecular terms?
cAMP signaling in cell populations

- Full model would have many equations
- So population of $m$ cells: $m \times n$ equations
  - Models become complex:
    - Expensive calculations
    - Practically impossible to understand
  - Can we simplify the single-cell level?
- Bottom line is:
  - if cell senses cAMP, it secretes cAMP
  - Excitable system
    - minimal model: Fitzhugh-Nagumo
Example of an excitable system

- Belousov-Zhabotinsky reaction
  - (see YouTube video: https://www.youtube.com/watch?v=IBa4kgXI4Cg)
Excitable system:
CA example: Green-Hastings

- Three states: $S = \{0, 1, 2\}$
  - $\delta : 0 \rightarrow 1$, if $\geq 1$ neighbor is 1
  - $\delta : 1 \rightarrow 2$
  - $\delta : 2 \rightarrow 0$
Simplified excitable model: Fitzhugh-Nagumo

\[
\frac{\partial c}{\partial t} = D \nabla^2 c - f(c) - r \quad \text{inside amoebae}
\]

\[
\frac{\partial c}{\partial t} = D \nabla^2 c - d_c (c - c_0) \quad \text{outside amoebae}
\]

\[
\frac{\partial r}{\partial t} = \varepsilon(c)(kc - r)
\]

\[f(c) = C_1 c \land \varepsilon(c) = \varepsilon_1 \quad \text{for } c < c_1\]

\[f(c) = -C_2 c + a_t \land \varepsilon(c) = \varepsilon_2 \quad \text{for } c_1 \leq c \leq c_2\]

\[f(c) = C_3 (c - 1) \land \varepsilon(c) = \varepsilon_3 \quad \text{for } c > c_2\]

Null isoclines inside amoebae

Marée et al. JTB 1999
Properties of excitable systems

- Wave annihilation
- Spiral waves
- In continuum systems:
  - curvature effects? Which one moves faster?

Figure from Fast & Kléber, Cardiovascular Research, http://dx.doi.org/10.1016/S0008-6363(96)00216-7
Model simulation
(Savill and Hogeweg 1997, *J. Theor. Biol.* 184, 229)
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Model Simulation

(Savill and Hogeweg 1997, *J. Theor. Biol.* 184, 229)
Slug moves to warm spot

Marée and Hogeweg, *J. Theor. Biol.* 1999
• Slug behavior is *caused* by the underlying genetics, but not necessarily *explained* by it
3D Simulation
(e.g., Marée and Hogeweg 2001, PNAS 98, 3879-3883)
Another example of an excitable system: the heart

Sasha Panfilov - Ghent University
Multiscale models of tumor progression

- What makes cancer cells metastatic?
- Clonal evolution of tumor cells (Nowell, 1976)
- Cancer cells compete for glucose, oxygen, space
- What happens in harsh microenvironment?
  - Stronger selections pressure?
  - Relapses after cancer treatment?
- Model by Anderson et al., 2006
  - Tumor cell properties (adhesion, growth rate) affect tumor morphology
Tumor evolution
Anderson et al. Cell 2006

\[ P_0 = 1 - 4D_N - 4\chi \left( f_{i+1,j} + f_{i-1,j} - 4f_{i,j} + f_{i,j+1} + f_{i,j-1} \right) \]
\[ P_1 = D_N - \chi \left[ f_{i+1,j} - f_{i-1,j} \right] \]
\[ P_2 = D_N + \chi \left[ f_{i+1,j} - f_{i-1,j} \right] \]
\[ P_3 = D_N - \chi \left[ f_{i,j+1} - f_{i,j-1} \right] \]
\[ P_4 = D_N + \chi \left[ f_{i,j+1} - f_{i,j-1} \right] \]

Unbiased motility
Motility to higher concentrations of ECM (haptotaxis)
Tumor evolution
Anderson et al. Cell 2006

- Tumor cells move randomly
- Tumor cells move up ECM gradients
- Cells produce matrix-degrading enzymes (MDE)
  - E.g. MMPs
- Tumor cells consume oxygen
- Vasculature delivers oxygen: proportional to ECM
Tumor evolution

Anderson et al. Cell 2006 - Equations

\[
\frac{\partial c}{\partial t} - \alpha c = \nabla D \nabla c + \frac{c}{2A^2} - \frac{c}{\beta f}
\]

rate of change of oxygen

diffusion of oxygen
decay of oxygen
oxygen consumption by tumour cell
production of oxygen by MM

\[
\frac{\partial \theta}{\partial t} = \frac{\partial}{\partial t} \left( f \theta \frac{\partial m}{\partial \theta} \right) + \frac{\partial}{\partial \theta} \left( \frac{\partial m}{\partial \theta} \frac{\partial m}{\partial \theta} \right) - \frac{\partial m}{\partial \theta} - \lambda m
\]

rate of change of Matrix Macromolecule (MM)
degradation of MM by MDE
diffusion of MDE by tumour cell
decay of MDE
production of MDE by tumour cell
MMPs
Tumor evolution
Anderson et al. Cell 2006

- Cell-based model:
  - possible to give each cell different properties
- Evolve cellular properties
  - Exp. I: “Vogelgram” accumulation of mutations

- Fearon and Vogelstein, 1990
• Phenotype I:
  - Proliferative, adhesive, consumes little oxygen, produces few MMPs

• Phenotype IV:
  - Slow proliferation, not adhesive, consumes lots of oxygen, produces lots of MMPs
Homogenous ECM

Anderson et al. Cell 2006
Homogenous ECM
"Bumpy" ECM

Anderson et al. Cell 2006
“Grainy” ECM
Progressive mutation

- Selection for aggressive phenotype IV (blue)
- “Harsh” environment (bumpy or grainy ECM)
  - Fingering boundary
- In reality:
  - Tumors are genetically heterogeneous
- Alternative test for “random” mutation scheme;
  - Cells “jump” between any of 100 parameter sets
  - No “progressive” evolution possible
100 phenotypes

- Any combination of traits possible

Selection rounds of oxygen limitation and oxygen excess
Selection for aggressive phenotypes

- Selected clones:
  - no cell-cell adhesion
  - low oxygen consumption
  - high proliferation
  - high haptotaxis

- Stronger selection in “harsh” environments
Model predictions

- Tumor microenvironment guides tumor shape
  - Homogeneous ECM: smooth tumor boundary
  - Grainy or bumpy ECM: fingering tumor boundary
- Harsh environment, e.g. hypoxia:
  - Selection for more aggressive phenotypes
- Consequences for treatments?
  - Do harsh treatments induce aggressive treatments?
    - Relapse after therapies
  - Some authors suggest to treat cancer as “chronic disease”: non-resistant cells outcompete resistant ones
    - E.g. Gatenby and others
Multiscale models of angiogenesis:
Mechanisms of tip cell overtaking

Jakobsson et al. 2010
The two groups have different views

- Jakobsson et al.: “Notch regulates shuffling of tip cells”
- Arima et al.: “Cell mixing”
Is overtaking a side-effect of sprouting?
Identify cells at sprout tips

Make a graph out of the vascular network

Find the leader cell of the sprout

Boas and Merks BMC Syst. Biol. 2015
Spontaneous tip cell overtaking

Contact-inhibition model:
Approx. 1 overtake per 7 h

Cell elongation model:
Approx. 1 overtake per 24 h

Boas and Merks BMC Syst. Biol. 2015
Computational pipeline

A. Question 1: Can tip cell overtaking occur spontaneously as a side effect of sprouting?

Boas and Merks BMC Syst. Biol. 2015
Quantify and compare with experimental data

Boas and Merks BMC Syst. Biol. 2015
Model refinement: tip and stalk cell differentiation

VEGFR2 + VEGF

Figure 1. Ultrasensitivity due to mutual inactivation of Notch and DSL. (A) Plot of free DSL (red) and free Notch (blue) as a function of DSL production rate, $\beta_D$. A sharp switch (high logarithmic derivative) between sender and receiver states occurs when $\beta_D = \beta_N$. (B) Schematic illustration of sending and receiving states, showing that while very little signaling occurs when two neighboring cells are both senders (top) or both receivers (middle), strongly biased signaling can occur for the case of neighboring sender and receiver cells (bottom).

doi:10.1371/journal.pcbi.1002069.g001
Introduce subcellular DLL4-Notch network

DLL4-Notch may act to stabilize tip cell at sprout front

Boas and Merks BMC Syst. Biol. 2015
Model helps reinterpret published data

- WT cells win over Vegfr2+/- cells in competition for tip cell position (Jakobsson et al.) - why?
- In model: make phenotype depend on Dll4-level
  - lower cell-cell adhesion
  - or: lower chemoattractant sensitivity
- Simulation assumes that Vegfr2+/- cells do not differ from WT phenotypically
- Still: simulated Vegfr2+/- cells do not make it to the tip
- Reason: lower Dll4 activation in Vegfr2+/- cells, they cannot differentiate into tip cells

Data: Jakobsson et al. 2010
Boas and Merks BMC Syst. Biol. 2015
Cancer stem cells
Sottoriva et al. Cancer Res. 2010

- Hybrid cellular automata (cells on a grid)
- Oxygen:
  - constant around tumor, tumor cells consume it
    \[ \frac{\partial c}{\partial t} = D_c \nabla^2 c - \kappa n \]
  - Cells become quiescent at low hypoxia and die at strong hypoxia
- Cells divide close to perimeter
  - Shift surrounding cells aside
  - \( P_s \): cancer stem cell (CSC), \( 1-P_s \): differentiated cell (DCC)
  - DCC divides up to 5 times
Exp. 1 $P_s=1$: only stem cells
Sottoriva et al. Cancer Res. 2010
Exp. 2 $P_s = 0.03$: few stem cells
Sottriva et al. Cancer Res. 2010
Fingering morphology with few CSCs
Sottoriva et al. Cancer Res. 2010
Tumor cell invasion
Sottoriva et al. Cancer Res. 2010
Clonal selection
Sottoriva et al. Cancer Res. 2010

- Mutate to random phenotype
  - proliferation rate, diffusion, adhesion, oxygen consumption
- More heterogenous tumors in CSC models
- Genetic drift (no direct competition between clones)
Clonal selection, all CSCs
Clonal selection, few CSCs
Consequences for therapy
Sottoriva et al. Cancer Res. 2010

- Killing only DCCs may lead to aggressive and diverse relapse, unless CSCs killed as well
Conclusions

- Space matters for tumor growth!
  - Tumors grow at edges: no exponential growth

- Cell-based models suggest causes of invasion / fingering growth
  - Clonal selection in “harsh” micro-environments (Anderson et al.)
  - Cancer Stem Cells (Sottoriva et al.)

- Further reading: e.g. Gatenby
  - See reader