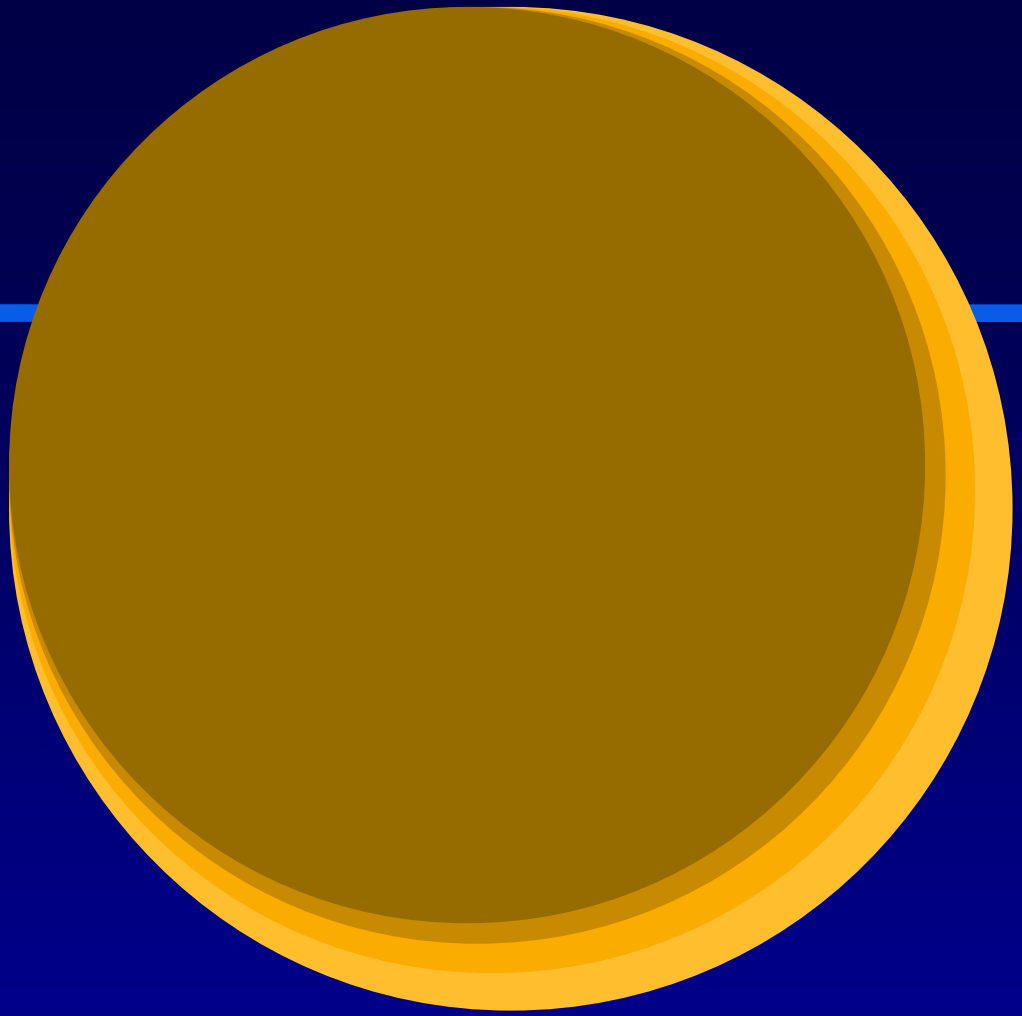

Lecture 2:
An agent-based cell model; application to DCIS

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Motivation

- Want to study ductal carcinoma in situ (DCIS)
  - Impact of adhesive forces and other mechanics
  - Impact of heterogeneity
  - Impact of many processes with varied time scales
  - Impact of many interacting cells, but with some subcellular processes
- Want a predictive model – emergent phenomena
  - If too much assumed *a priori*, then "predictions" just verify your programming
- Want a modular model
- Want to calibrate to patient data (IHC, H&E)
- Model it as a physics problem!
  - Cells are physical objects subject to forces
  - Biology comes in as constitutive relations that tell us:
    - what forces are active
    - what the cells are doing as they're moved around by forces
  - Approach: agent-based model (a.k.a., particle method, individual-based model)

Lecture Outline

- Overall framework
- Cell biomechanics, cell and BM geometry
- Forces acting on the cell
- Phenotypic states as stochastic processes
- Linking with the microenvironment
- Linking with the molecular scale
- Volume-averaged analysis
  - Application: DCIS Ki-67 immunohistochemistry
- Coming next
- References

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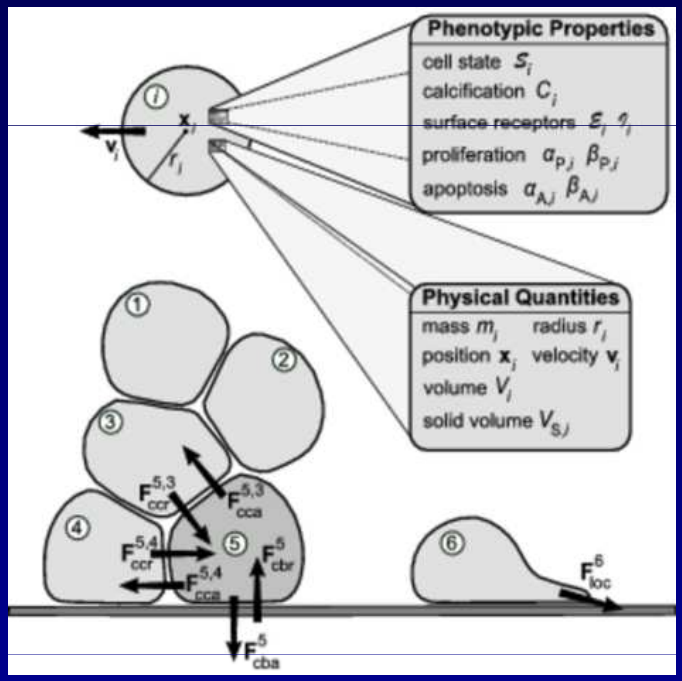
Overall Framework

- Each cell is a physical object
  - Lattice-free position, velocity
- Finite size
  - Nuclear volume, overall volume, solid fraction
- No explicit morphology model
  - Cell-cell interactions designed to partly account for it
- Motion determined by forces
  - Cell-cell adhesion & repulsion
  - Cell-BM adhesion & repulsion
  - Cell-ECM adhesion
  - Fluid drag
  - Net locomotive force



- Each cell endowed with phenotypic state
  - Quiescent (G0), Proliferative (S-G2-M-G1), Motile, Apoptotic, Hypoxic, Necrotic, Calcified Debris
  - Governed by exponentially-distributed random variables – can be matched to IHC
  - Linked to cell's external state, local microenvironment
- Use same model for all cell types – only the parameters vary
  - Similar to Hanahan and Weinberg "Hallmarks of Cancer"

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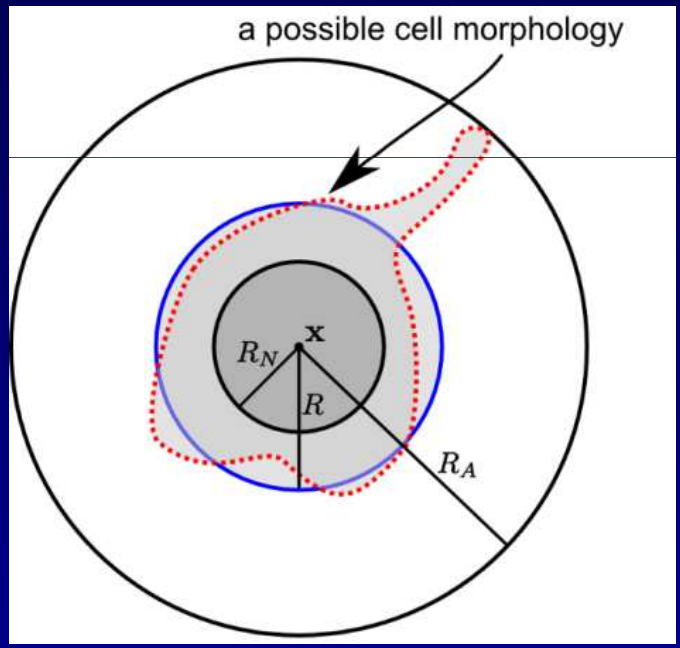
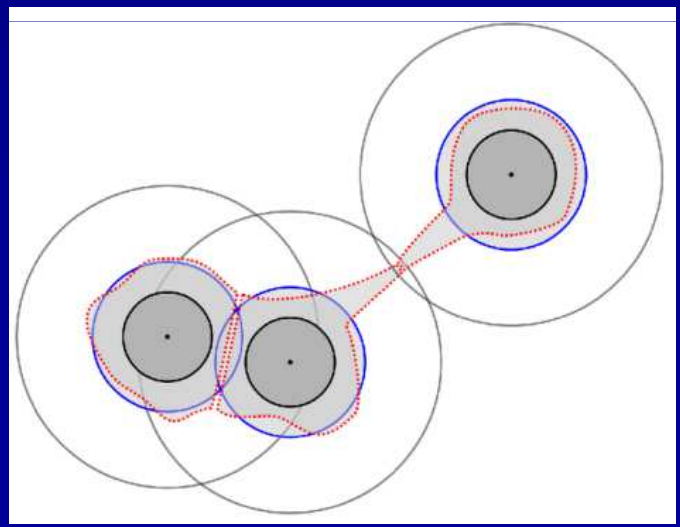
Cell biomechanics, cell and tissue geometry

- Each cell has overall and nuclear volumes V, V_N
  - Regulated by phenotypic "sub-models"
  - Related to equivalent radii (R, R_N) by spherical approximation
- Each cell has maximum interaction distance R_A
  - Approximates cell deformability
  - Accounts for uncertainty in cell position and morphology
- Cell "radii" can overlap
  - Further accounts for deformability and uncertainty



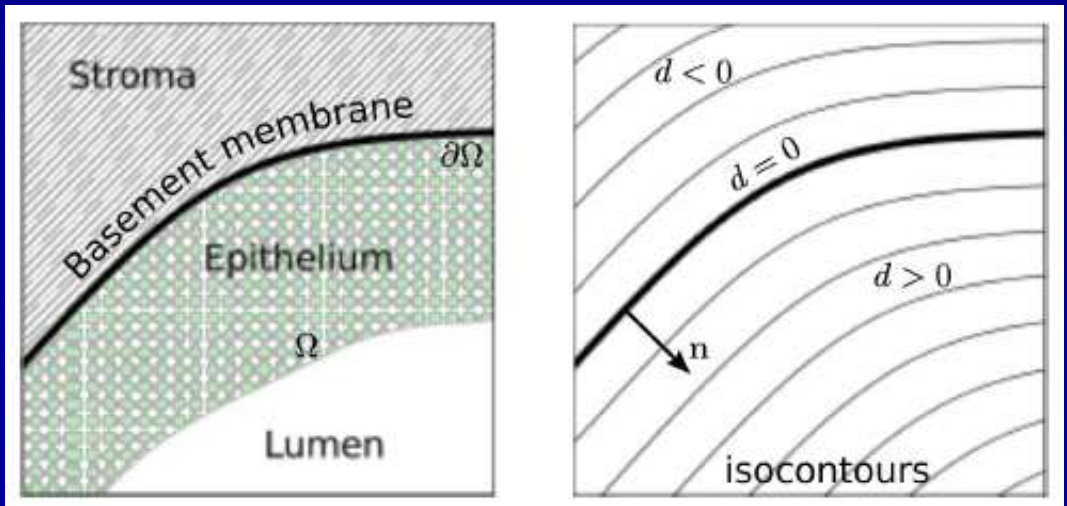


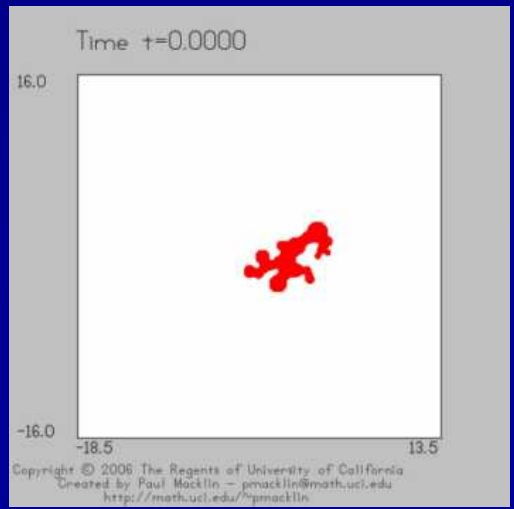
Cell biomechanics, cell and tissue geometry

- Model basement membrane location with signed distance function *d* (level set function):

$$\begin{cases} d(\mathbf{x}) > 0 & \mathbf{x} \in \Omega \\ d(\mathbf{x}) - 0 & \mathbf{x} \in \partial\Omega \\ d(\mathbf{x}) < 0 & \mathbf{x} \notin \overline{\Omega} = \Omega \cup \partial\Omega \\ |\nabla d(\mathbf{x})| = 1. \end{cases}$$

- Encodes geometric information (normal vector, curvature) as derivatives:
  - $\mathbf{n} = \nabla d \,/\, |\nabla d|$ $\qquad \kappa = \nabla \cdot \mathbf{n}$
- Can model very complex shapes
- Method originated in fluid mechanics (Sethian, Osher, Adalsteinsson)
- has also been used to model moving tumour boundary (Macklin et al.)
- Can use level set methods to model BM motion under stresses, similar to work by Ribba et al.





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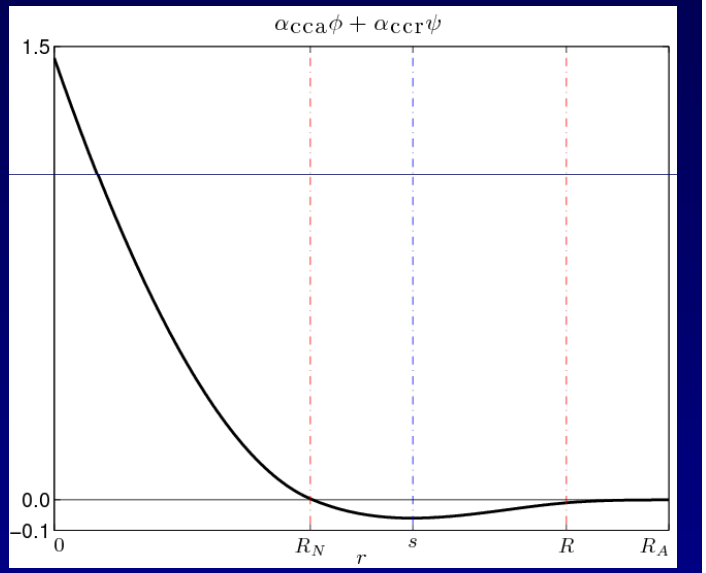
Forces acting on the cell

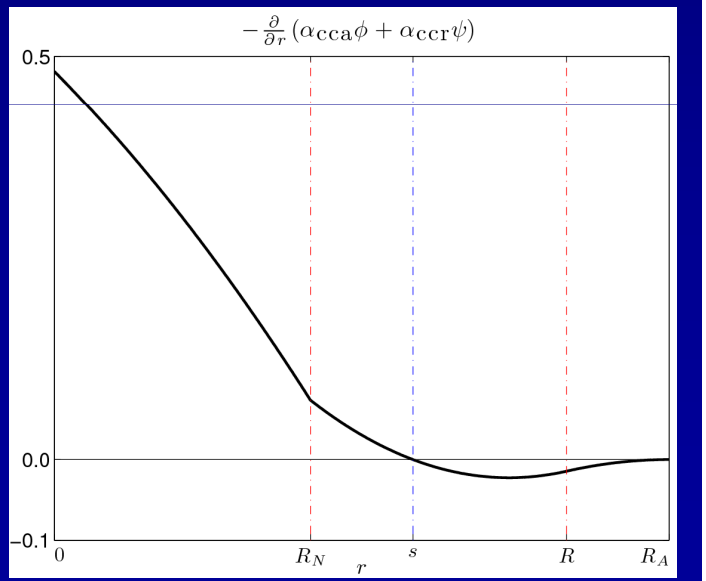
- Cell's motion is given by the sum of the forces acting upon it
  - Homophilic and heterophilic cell-cell adhesion ($\mathbf{F}_{cca}$)
  - Cell-cell repulsion ($\mathbf{F}_{ccr}$)
  - Cell-BM adhesion and repulsion ($\mathbf{F}_{cba}$ and $\mathbf{F}_{cbr}$)
  - Cell-ECM adhesion ($\mathbf{F}_{cma}$)
  - Fluid drag ($\mathbf{F}_{drag}$)
  - Net locomotive force ($\mathbf{F}_{loc}$)
- Sum these to get motion by Newton's 2nd law:

$$m_i \dot{\mathbf{v}}_i = \sum_{\substack{j=1 \\ j \neq i}}^{N(t)} \left(\mathbf{F}^{ij}_{\mathrm{cca}} + \mathbf{F}^{ij}_{\mathrm{ccr}} + \mathbf{F}^{ij}_{\mathrm{dda}} \right) + \mathbf{F}^{i}_{\mathrm{cma}} + \mathbf{F}^{i}_{\mathrm{cba}} + \mathbf{F}^{i}_{\mathrm{cbr}} + \mathbf{F}^{i}_{\mathrm{loc}} + \mathbf{F}^{i}_{\mathrm{drag}}$$

Forces acting on the cell

- Model adhesive and repulsive forces using potential functions
  - See earlier models by Drasdo, Höhme, Galle, Ramis-Conde, …
- Cells move down the potential gradient (minimise energy)
- Separate potentials for each force
- Compact support
  - finite interaction distances
  - Helpful for computations
- Repulsive properties separately defined in cytoplasm and nucleus
- Can be applied to cells with varying size and mechanical properties





Adhesive Potential

$$\nabla\varphi(\mathbf{r}; R_A, n) = \begin{cases} \left(1 - \frac{|\mathbf{r}|}{R_A}\right)^{n+1} \frac{\mathbf{r}}{|\mathbf{r}|}, & 0 \le |\mathbf{r}| \le R_A \\ \mathbf{0} & \text{else,} \end{cases}$$

Repulsive Potential

$$\nabla\psi(\mathbf{r}; R_N, R, M, m) = \begin{cases} \left(c\,\frac{|\mathbf{r}|}{R_N} + M\right) \frac{\mathbf{r}}{|\mathbf{r}|} & 0 \le |\mathbf{r} \le R_N \\ -\left(1 - \frac{|\mathbf{r}|}{R}\right)^{m+1} \frac{\mathbf{r}}{|\mathbf{r}|} & R_N \le |\mathbf{r}| \le R \\ \mathbf{0} & \text{else,} \end{cases}$$

where

$$c = \left(\left(1 - \frac{R_N}{R}\right)^{m+1} - M\right).$$

Forces acting on the cell

- Homophilic cell-cell adhesion
  - Proportional to E-cadherin on cell and neighbours

$$\mathbf{F}^{ij}_{\mathrm{cca}} = -\alpha_{\mathrm{cca}} \mathcal{E}_i \mathcal{E}_j \nabla\varphi\left(\mathbf{x}_j - \mathbf{x}_i; R^i_N + R^j_N, R^i_{\mathrm{cca}} + R^j_{\mathrm{cca}}\right)$$

- Heterophilic cell-cell adhesion
  - Proportional to adhesion molecules and ligands on both cell and neighbours

$$\mathbf{F}^{ij}_{\mathrm{cca}} = -\alpha_{\mathrm{cca}} \left(\mathcal{I}_{A,i}\mathcal{I}_{B,j} + \mathcal{I}_{B,i}\mathcal{I}_{A,j}\right) \nabla\varphi\left(\mathbf{x}_j - \mathbf{x}_i; R^i_N + R^j_N, R^i_{\mathrm{cca}} + R^j_{\mathrm{cca}}\right)$$

- Cell-cell repulsion

$$\mathbf{F}^{ij}_{\mathrm{ccr}} = -\alpha_{\mathrm{ccr}} \nabla\psi\left(\mathbf{x}_j - \mathbf{x}_i; R^i_N + R^j_N, R_i + R_j, M\right)$$

Forces acting on the cell

- Cell-BM adhesion

$$\mathbf{F}^{i}_{\mathrm{cba}} = -\alpha_{\mathrm{cba}} \mathcal{I}_{B,i} B \nabla \varphi \left(d(\mathbf{x}_i)\mathbf{n}\left(\mathbf{x}_i\right) ; R^{i}_{N}, R^{i}_{\mathrm{cba}} \right)$$

- Cell-BM repulsion

$$\mathbf{F}^{i}_{\mathrm{cbr}} = -\alpha_{\mathrm{cbr}} B \nabla \psi \left(d(\mathbf{x}_i)\mathbf{n}\left(\mathbf{x}_i\right) ; R^{i}_{N}, R_i, M \right)$$

- Cell-ECM adhesion and fluid drag

$$\mathbf{F}_{\mathrm{cma}} = -\alpha_{\mathrm{cma}} \mathcal{I}_{E,i} E \mathbf{v}_i$$

$$\mathbf{F}_{\mathrm{drag}} = -\nu \mathbf{v}_i$$

- Net locomotive force
  - Depends upon model complexity
  - Can range to full actin polymerisation dynamics (e.g., Lauffenburger motility models) to chemotaxis as constitutive relation (e.g., McDougall, Chaplain, Anderson angiogenesis work)

Forces acting on the cell

- Inertialess assumption
  - Forces equilibrate quickly
  - can solve for "terminal" velocity

$$\mathbf{v}_i = \frac{1}{\nu + \alpha_{\text{cma}} \mathcal{I}_{E,i} E} \left(\sum_{\substack{j=1 \\ j \neq i}}^{N(t)} \left(\mathbf{F}^{ij}_{\text{cca}} + \mathbf{F}^{ij}_{\text{dda}} + \mathbf{F}^{ij}_{\text{ccr}} \right) + \mathbf{F}^{i}_{\text{cba}} + \mathbf{F}^{i}_{\text{cbr}} + \mathbf{F}^{i}_{\text{loc}} \right)$$

- Related to Darcy's law for continuum models (Cristini et. al 2003 …):
  - $\mathbf{u} = -\mu \nabla P$
  - P is mechanical pressure generated by proliferating cells
  - Gradient pushes cells through porous medium (ECM)
  - μ is the mobility: ability of tissue to respond to ∇P
    - Cells overcome cell-cell, cell-ECM adhesion and move
    - Tissue deformsi
    - **V** is the net balance of repulsion + proliferation vs. adhesion
- Matches func. form of μ from Frieboes et al. (2007), Macklin et al. (2009):

$$\mu = \frac{1}{\alpha + \beta E + \frac{1}{\varepsilon} S}$$

  - *S* is a structure variable (1 in rigid barriers, 0 elsewhere)

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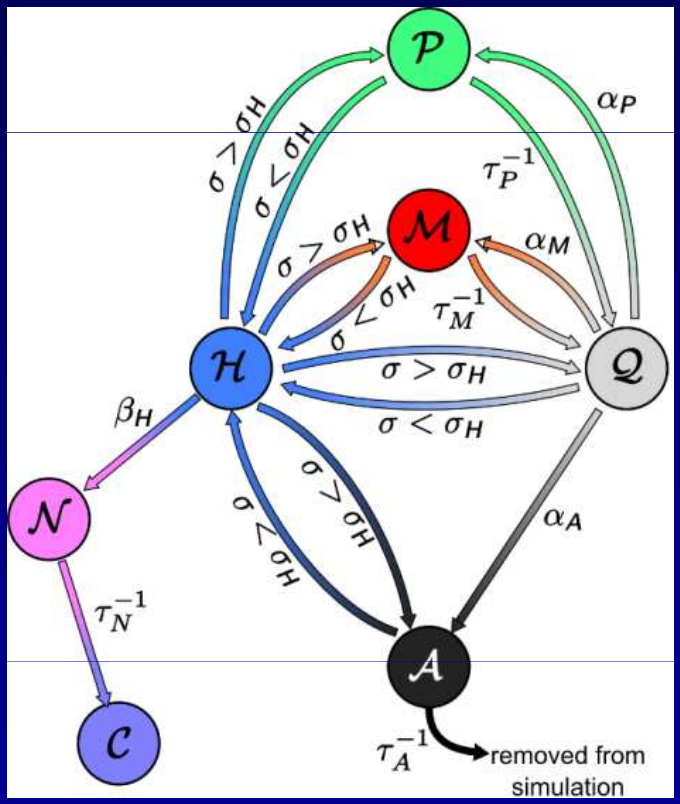
Phenotypic states as stochastic processes

- Each cell has phenotypic state S(t)
- Each state has finite (and nonzero) duration, with activity governed by a sub-model
- Transition probabilities among states governed by exponential random variables
  - Tied to internal state and microenvironment through the rate parameter
  - Originate from nonhomogeneous Poisson processes
  - Generalise constant-probability-per-constant-time models in widespread use today
  - Can be rigorously varied with variable time step size (e.g., for numerical stability conditions)



Phenotypic states as stochastic processes: Proliferation

- Probability of Q → P transition in (t,t+Δt]:
  - Rate α_P depends upon internal state ● and microenvironment ○

$$\begin{aligned}\Pr\left(\mathcal{S}(t+\Delta t)=\mathcal{P}|\mathcal{S}(t)=\mathcal{Q}\right) &= 1-\exp\left(-\int_t^{t+\Delta t}\alpha_P(\mathcal{S},\bullet,\circ)(s)\,ds\right)\\ &\approx 1-\exp\left(-\alpha_P(\mathcal{S},\bullet,\circ)(t)\Delta t\right),\end{aligned}$$

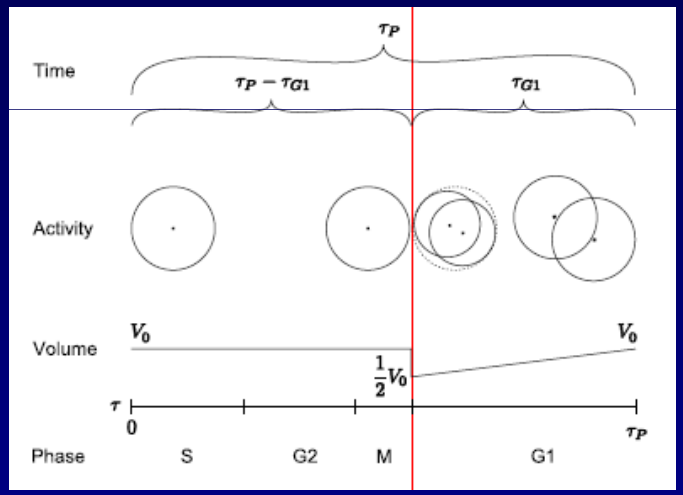
- Model extra biology with α_P as constitutive relations
  - Dependence upon oxygen due to observed radial variation in Ki-67 IHC

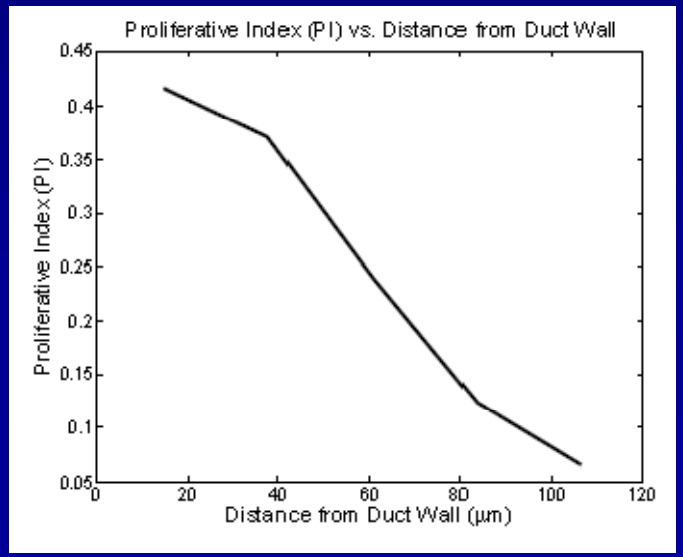
$$\alpha_P = \alpha_P(\mathcal{S},\sigma,\bullet,\circ)(t) = \begin{cases}\overline{\alpha}_P(\bullet,\circ)\frac{\sigma-\sigma_H}{1-\sigma_H} & \text{if } \mathcal{S}(t)=\mathcal{Q}\\ 0 & \text{else,}\end{cases}$$

- Model volume change after mitosis and during subsequent G1 growth

$$V(\tau) = \begin{cases}V_0 & 0\le\tau\le\tau_P-\tau_{G1}\\ \frac{1}{2}V_0\left(1+\frac{\tau_{G1}+(\tau-\tau_P)}{\tau_{G1}}\right) & \tau_P-\tau_{G1}\le\tau\le\tau_P,\end{cases}$$

- Fixed cycle length τ_P, G1 length τ_{G1}, but could be made to vary with additional submodels





Phenotypic states as stochastic processes: Apoptosis

- Probability of $\mathcal{Q} \rightarrow \mathcal{A}$ transition in (t,t+Δt]:
  - Rate α_A depends upon internal state ● and microenvironment ○

$$\Pr\left(\mathcal{S}(t+\Delta t)=\mathcal{A}|\mathcal{S}(t)=\mathcal{Q}\right) = 1 - \exp\left(-\int_t^{t+\Delta t} \alpha_A(s)\,ds\right)$$
$$\approx 1 - \exp\left(-\alpha_A(t)\Delta t\right),$$

where

$$\alpha_A(t) = \alpha_A(\mathcal{S},\bullet,\circ)(t) = \begin{cases} \overline{\alpha}_A(\bullet,\circ) & \text{if } \mathcal{S}(t)=\mathcal{Q} \\ 0 & \text{else,} \end{cases}$$

  - Cell removed from simulation after fixed time τ_A
    - Models phagocytosis by neighbours
    - Cell's volume now available to other cells
    - Similar to pressure / stress relief in continuum models

Phenotypic states as stochastic processes: Hypoxia, Necrosis, Calcification

- Deterministic shift to hypoxic state $\mathcal{H}$ if $\sigma < \sigma_H$:
- Probability of $\mathcal{H} \rightarrow \mathcal{N}$ increases with time spent in H:

$$\begin{aligned}\Pr\left(\mathcal{S}(t+\Delta t)=\mathcal{N}|\mathcal{S}(t)=\mathcal{H}\right) &= 1-\ \exp\left(-\int_t^{t+\Delta t}\beta_H(\sigma)(s)\,ds\right)\ ds \\ &\approx 1-\ \exp\left(-\beta_H\left(\sigma\right)(t)\Delta t\right).\end{aligned}$$

- If normoxia restored, resumes previous state
- Currently no HIF signalling – see Gatenby, Smallbone, Silva …
- Necrotic cells lose their adhesion receptors (exponential decay)
- Necrotic cells swell and lyse:

$$V(\tau)=\begin{cases} V_0\left(1+f_{\mathrm{NS}}\frac{\tau}{\tau_{NL}}\right) & \text{if } 0\le\tau<\tau_{NL} \\ V_S & \text{if } \tau_{NL}<\tau, \end{cases}$$

- Remaining solid component calcifies:

$$C(t)=\tau/\tau_C$$

- Model debis-debris adhesion as homophilic (in the microcalcification)

Phenotypic states as stochastic processes: Mathematical Context

- Probability of changing from state $\mathcal{Q}$ to state $\mathcal{X}$ with rate parameter α is approximately linear (when α is constant) for very short times:

$$\begin{aligned}\Pr\left(\mathcal{S}(t+\Delta t)=\mathcal{X}|\mathcal{S}(t)=\mathcal{Q}\right) &= 1-\ \exp\left(-\int_t^{t+\Delta t}\alpha(s)\,ds\right)\\ &\approx 1-e^{-\alpha(t)\,\Delta t}\\ &= \alpha(t)\Delta t+\mathcal{O}\left(\Delta t^2\right).\end{aligned}$$

- This linearisation is common, particularly in cellular automata:
  - constant probability for a fixed time step size
- So, the exponential transition probability is a natural generalisation
- Stochastic process: A series of random variables indexed by time *t:* N_t
- Counting process:

(1) $N_0 \geq 0$. (The initial number of events N_0 is at least zero.)
(2) $N_t \in \mathbb{Z}$ for all $t \geq 0$. (The cumulative number of events N_t is an integer.)
(3) If $s < t$, then $N_t - N_s \geq 0$. (N_t is nondecreasing.)

- Poisson process:
- α is the *intensity function*

(1) $X_0 = 0$. (The initial count is 0.)
(2) If $(s, s+\Delta s]$ and $(t, t+\Delta t]$ are non-overlapping, then $X_{s+\Delta s} - X_s$ and $X_{t+\Delta t} - X_t$ are independent random variables. (What happens in the interval $(t, t+\Delta t]$ is independent of what happened in $(s, s+\Delta s]$.)
(3) For any $0 \leq s < t$, the distribution of $X_t - X_s$ only depends upon the length of $(s, t]$ (stationary increments), and in particular, if $n \in \mathbb{N}$,

$$\Pr\left(X_t - X_s = n\right) = \frac{e^{-\alpha(t-s)}\left(\alpha(t-s)\right)^n}{n!}. \qquad (3)$$

Phenotypic states as stochastic processes: Mathematical Context

- Probability of (≥) one event in (t,t+Δt] is exponential:
  - X_t is poisson process, number of events of some type at time t
  - A_n is time of n^{th} event (arrival time)
  - T_n is the time between the A_n and A_{n-1} events (interarrival time)

$$\begin{aligned}\Pr\left(X_{t-\Delta t} - X_t \geq 1\right) &= \Pr\left(A_n \in (t, t+\Delta t] | A_n > t\right) \\ &= \Pr\left(T_n \leq \Delta t\right) = 1 - e^{-\alpha \Delta t}.\end{aligned}$$

- If the $\alpha = \alpha(t)$, lose stationary intervals, get nonhomogeneous Poisson process
- So, our model (and by generalisation, all models with probabilistic phenotypic transitions) stems from nohomogeneous Poisson processes
- Useful tool for further understanding. Apply stochastic processes theory, queueing theory, Markov chains, etc.
- Example:
  - P_t is number of $\mathcal{Q} \rightarrow \mathcal{P}$ transitions by time t. (for a cell, its ancestors, and progeny)
  - A_t is the number of $\mathcal{Q} \rightarrow \mathcal{A}$ transitions by time t (for a cell, its ancestors, and progeny)
  - $N_t = A_t + P_t$ ← A Poisson process with intensity function $\alpha_A + \alpha_P$
  - Time to next event is exponential with rate $\alpha_A + \alpha_P$
  - Time to next event is minimum to next proliferation, apoptosis times
  - Probability next event is proliferation: $\alpha_P / (\alpha_A + \alpha_P)$
    - Cell decisions as a "race" between competing processes

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Linking with the microenvironment

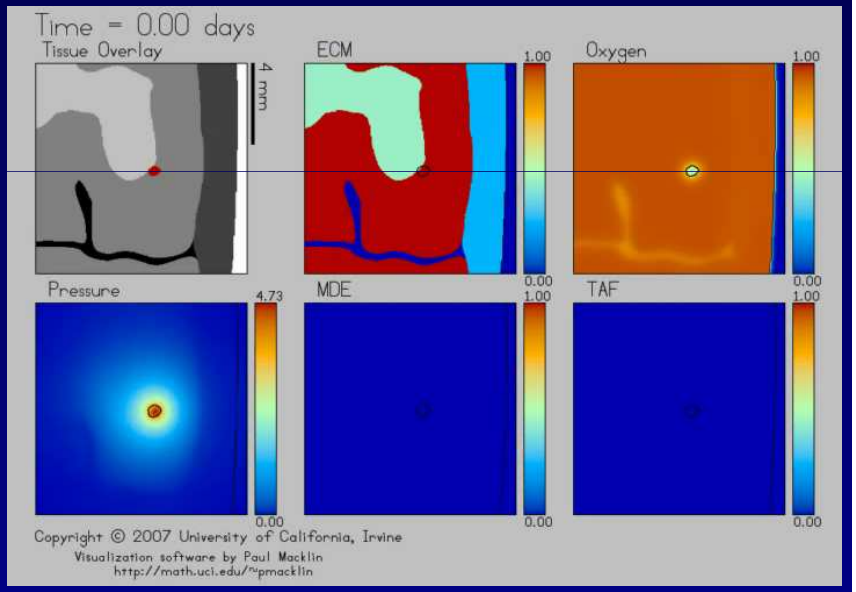
- Oxygen transport
  - Uptake rate varies on the cell scale

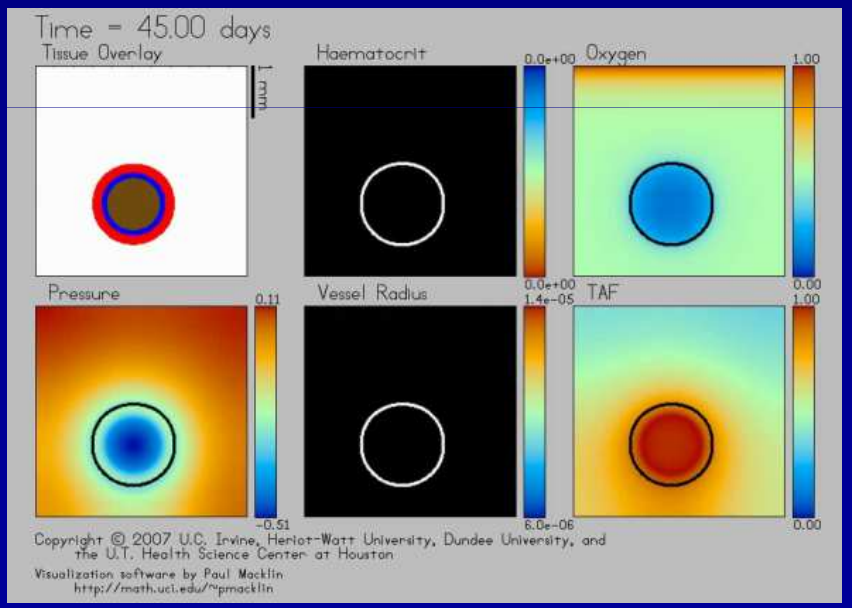
$$\frac{\partial \sigma}{\partial t} = \nabla \cdot (D \nabla \sigma) - \lambda \sigma,$$

- MMP secretion, ECM-MMP dynamics
  - Secretion rate varies on cell scale

$$\frac{\partial E}{\partial t} = \lambda^{E}_{\text{production}}(\mathbf{x}) - \lambda^{E}_{\text{degradation}} EM$$
$$\frac{\partial M}{\partial t} = \nabla \cdot (D_M \nabla M) + \lambda^{M}_{\text{production}}(\mathbf{x}) - \lambda^{M}_{\text{decay}} M,$$

- Solve these on the tissue scale, get the rate constants by upscaling
- These feed back to affect cell phenotype and mechanics





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Linking with the molecular scale

- Each cell gets a set of genes **G**, proteins **P**, samples microenvironmental stimuli **S**, and a signalling network:

$$\dot{\mathbf{P}} = \mathbf{f}(\mathbf{G}, \mathbf{P}, \mathbf{S})$$

- Make the phenotypic transition rates depend upon this network.
- Example: E-cadherin/β-catenin signalling:
  - P1: unligated E-cadherin
  - P2: ligated E-cadherin
  - P3: free β-catenin
  - P4: sequestered β-catenin

$$\dot{P}_1 = \overbrace{c_1}^{\text{synthesis}} \quad \overbrace{c_2 S_1 P_1}^{\text{homophilic binding}} + \overbrace{c_3 P_2}^{\text{dissociation}} \quad \overbrace{c_4 P_1}^{\text{proteolysis}} \tag{6.32}$$

$$\dot{P}_2 = c_2 S_1 P_1 - c_3 P_2 - \overbrace{c_5 P_2}^{\text{proteolysis}} - \overbrace{d_2 P_2 P_3}^{\beta\text{-catenin binding}} + \overbrace{d_3 P_4}^{\beta\text{-catenin dissociation}} \tag{6.33}$$

$$\dot{P}_3 = \overbrace{d_1}^{\text{synthesis}} - d_2 P_2 P_3 + d_3 P_4 - \overbrace{d_4 P_3}^{\text{proteolysis}} \tag{6.34}$$

$$\dot{P}_4 = d_2 P_2 P_3 - d_3 P_4 - \overbrace{d_5 P_4}^{\text{proteolysis}} \tag{6.35}$$

  - Free β-catenin can reach nucleus, transcribe other proteins, promote cycle progression

$$\alpha_P = \overline{\alpha}_P f_P(P_3) \frac{\sigma - \sigma_H}{1 - \sigma_H}$$

    - f_P is increasing, with $f_P(0) \geq 0$, $f_P(1) \leq 1$.
- See great work by Diesboeck et al. (for EGFR)
- Ramis-Conde, Chaplain and others (E-cadherin/β-catenin)

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Volume-averaged analysis

- Fix any volume Ω in a normoxic region.
- Consider the state space {Q, A, P}
- Let $Q(t)$, $A(t)$, $P(t)$ be total number of cells in Ω in each state at time t
- Let $N = Q + A + P$ be the total number of cells in Ω
- Use the Q →P probability and cell cycle length to get an equation for P:

$$\begin{aligned} P(t+\Delta t) &= P(t) + \Pr\left(\mathcal{S}(t+\Delta t) = \mathcal{P} | \mathcal{S}(t) = \mathcal{Q}\right) Q(t) - \frac{1}{\tau_P} P(t)\Delta t \\ &\approx P(t) + \left(1 - e^{-\langle \alpha_P \rangle \Delta t}\right) Q(t) - \frac{1}{\tau_P} P(t)\Delta t, \end{aligned}$$

- Take the limit as Δt → 0:

$$\dot{P} = \langle \alpha_P \rangle Q - \frac{1}{\tau_P} P.$$

- Similarly:

$$\begin{aligned} \dot{A} &= \alpha_A Q - \frac{1}{\tau_A} A \\ \dot{Q} &= 2\frac{1}{\tau_P} P - \left(\langle \alpha_P \rangle + \alpha_A\right) Q. \end{aligned}$$

$$\dot{N} = \frac{1}{\tau_P} P - \frac{1}{\tau_A} A.$$

Volume-averaged analysis

- Want to match to immunohistochemistry:
  - Proliferative index: PI = P/N (by Ki-67 staining)
  - Apoptotic index: AI = A/N (by cleaved Caspase-3 staining)

- Divide equations by *N*, be careful with quotient rule:
  - $PI' = P' / N - PI\, N' / N = P' / N - PI\,(PI/\tau_P - AI/\tau_A)$
  - $AI' = A' / N - AI\, N' / N = A' / N - AI\,(PI/\tau_P - AI/\tau_A)$

- and get a nonlinear system for AI and PI:

$$\dot{\mathrm{PI}} = \langle \alpha_P \rangle (1 - \mathrm{AI} - \mathrm{PI}) - \frac{1}{\tau_P}\left(\mathrm{PI} + \mathrm{PI}^2\right) + \frac{1}{\tau_A}\mathrm{AI}\cdot\mathrm{PI}$$

$$\dot{\mathrm{AI}} = \alpha_A (1 - \mathrm{AI} - \mathrm{PI}) - \frac{1}{\tau_A}\left(\mathrm{AI} - \mathrm{AI}^2\right) - \frac{1}{\tau_P}\mathrm{AI}\cdot\mathrm{PI}.$$

- Very simple argument on magnitude of τ_A and τ_P says this reaches steady state on the order of 10 to 100 days
- If AI and PI are known, and if the cell cycle and apoptosis times are known, can solve for the transition rates! (Hint hint. Next lecture)

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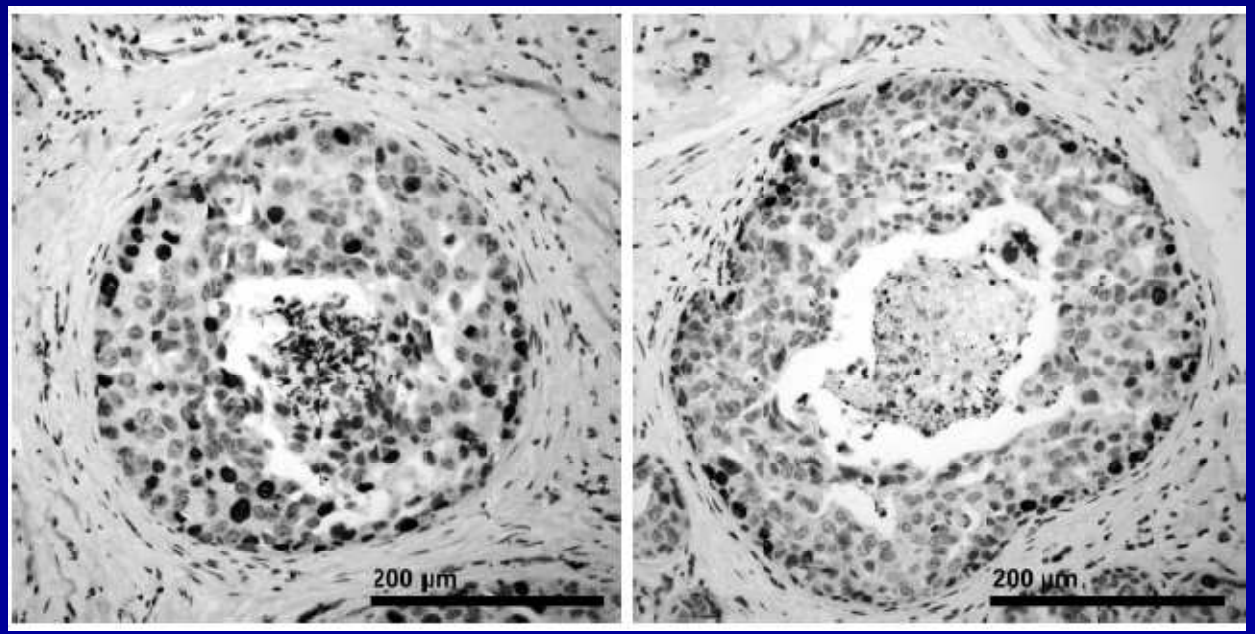
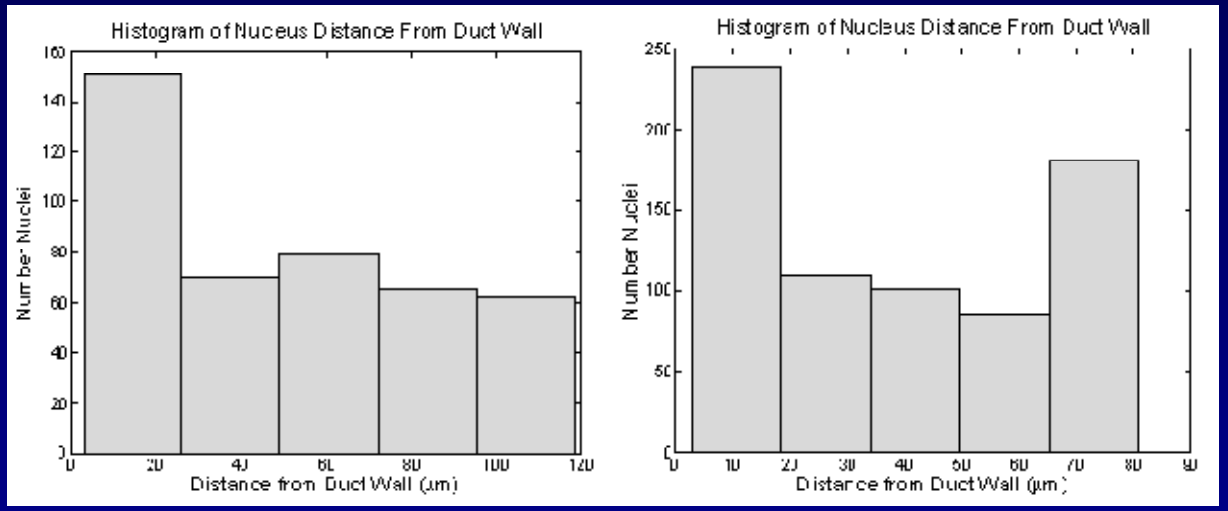
Application: DCIS Ki-67 Immunohistochemistry

- If you solve the ODE system to steady state for fixed parameters, can get AI and PI as a function of any input parameter for α_P
- We applied this to understand PI vs O_2 in DCIS
- Ki-67 IHC:
  - Ki-67 is a nuclear protein present through most of the cell cycle
  - Immunohistochemistry:
    - Immuno = uses antibody to protein X to attach stain to target protein
    - Histochemistry = chemistry of tissues
  - Very standard immunostain in pathology and experimental biology
  - In these images, Ki-67 positive nuclei are dark → indicates non-Go viable cell

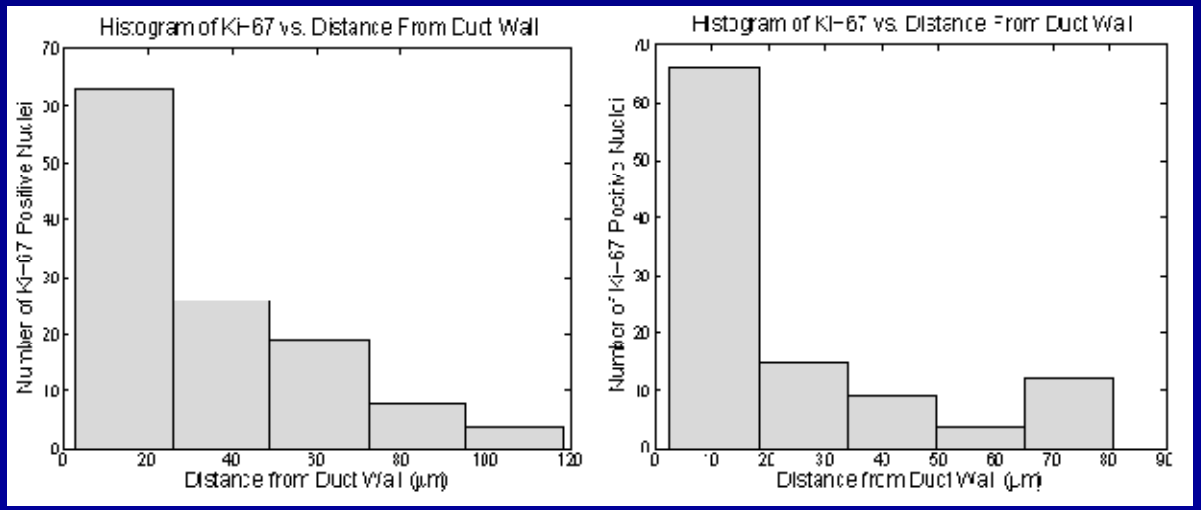


Application: DCIS Ki-67 Immunohistochemistry

- Step 1: Get a histogram of total nucleus count vs. distance for breast duct wall in viable rim

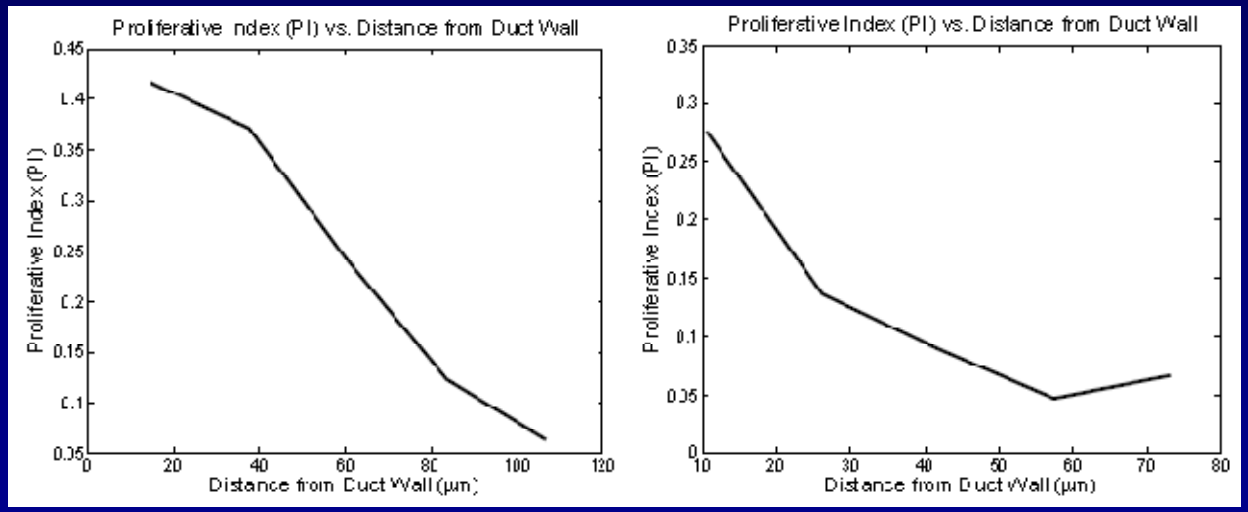


- Step 2: Get a histogram of total Ki-67 positive nucleus count vs. distance for *same bins*



Application: DCIS Ki-67 Immunohistochemistry

- Step 3: Divide these to get PI vs. distance from duct wall

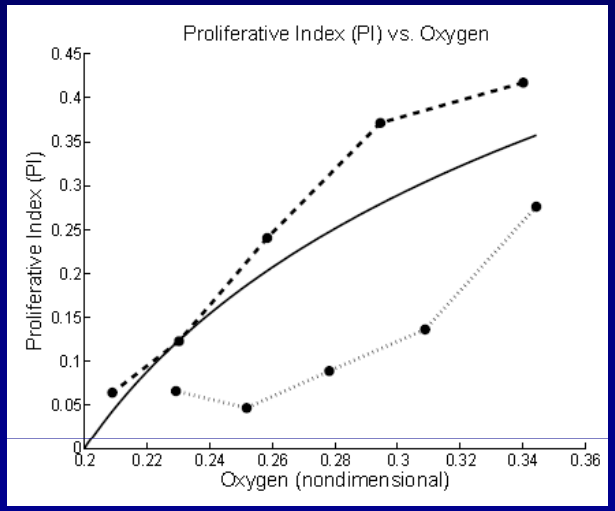


- Step 4: Estimate oxygen profile in duct

$$\sigma(r) = \frac{\sigma_H}{I_0\left(\frac{R_{\text{duct}}-T}{L}\right)} I_0\left(\frac{r}{L}\right)$$

Application: DCIS Ki-67 Immunohistochemistry

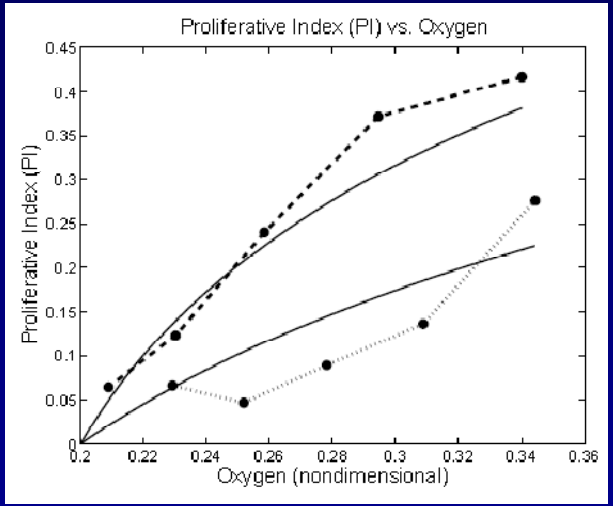
- Step 5: Solve the nonlinear system to steady state for various values of σ to get predicted PI-vs-σ curve
- Step 6: Compare results
  - Qualitative match → general constitutive relation and model are good
  - No quantitative match → some biology unaccounted for



- Step 7: New hypotheses, try again
  - Redo the PI-vs-σ on a duct-by-duct basis (use individual duct data)
    - Left duct: $\alpha_A \approx 0.00162405\ \mathrm{h}^{-1}$, $\overline{\alpha_P}(\mathcal{S}, \bullet) \approx 0.270331\ \mathrm{h}^{-1}$
    - Right duct: $\alpha_A \approx 0.00129067\ \mathrm{h}^{-1}$, $\overline{\alpha_P}(\mathcal{S}, \bullet) \approx 0.109562\ \mathrm{h}^{-1}$
  - Should be able to match curves quantitatively

Application: DCIS Ki-67 Immunohistochemistry

- Step 8: Compare again
  - Much better quantitative match



- Step 9: More analysis, new hypotheses
  - Both ducts had similar estimated oxygenation
  - Must be signalling heterogeneity
  - Notice densities are different → E-cadherin/β-catenin?
    - Higher proliferation where less of cell's surface area is in cell contact.
  - New functional form?

$$\alpha_P(\mathcal{S}, \sigma, \bullet, \circ) = \overline{\alpha}_P(\bullet, \circ)\left(1 - \mathcal{E}\langle\mathcal{E}\rangle\frac{\rho}{\rho_{\max}}\right)\left(\frac{\sigma - \sigma_H}{1 - \sigma_H}\right)$$

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Coming Next:

- **Lecture 1:**
  - **Cancer biology for modellers**
- **Lecture 2:**
  - **An agent-based cell model; application to DCIS**
- **Lecture 3:**
  - **Parameter estimation, patient-specific calibration**
- **Lecture 4:**
  - **Numerical method, simulation results**

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Some References

- The agent model presented here is published in:
  - P. Macklin et al. Agent-based modeling of ductal carcinoma in situ: Application to patient-specific breast cancer modeling. In: T. Pham (ed). *Computational Biology: Issues and Applications in Oncology*. Springer, New York, NY USA, 2009. Chapter 4, pages 77-112. ISBN 978-1-4419-0810-0.
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- References on other agent modelling can be found in the papers above, as well as the recent review:
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- The level set / continuum work can be found in:

- P. Macklin, S.R. McDougall, A.R.A. Anderson, M. Chaplain, J. Lowengrub, and V. Cristini, Nonlinear simulation of the effects of tumor growth on neovascular remodeling, *Bull. Math. Biol.*, 2007. (search google – published).
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