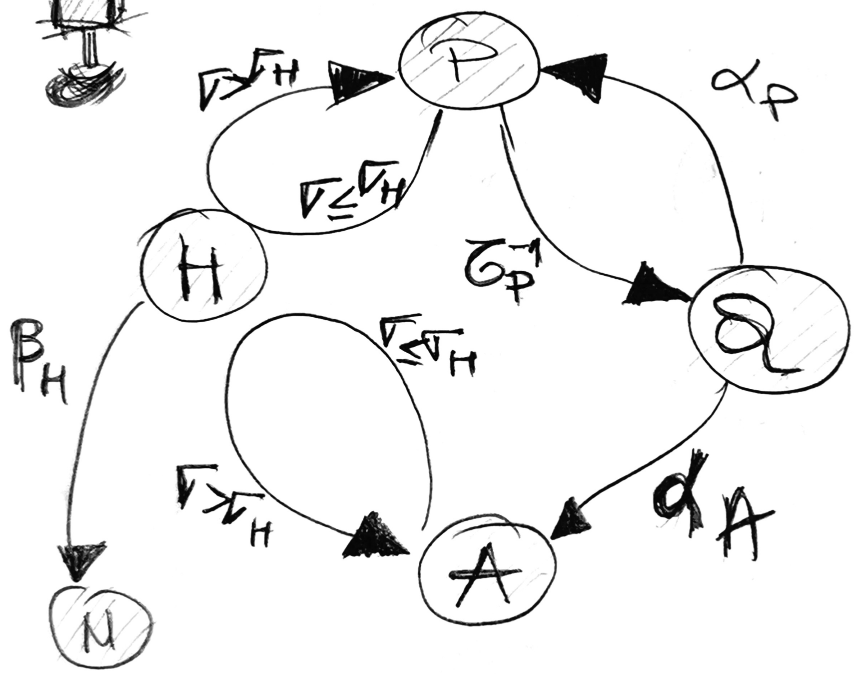
Ductal Carcinoma in Situ (DCIS)

J. Theol. Biol.

- Macklin et al. 2012
- Edgerton et al. 2011

Phenotypic transition network (general)



Q - quiescent cells

P - proliferative cells

A - apoptotic cells

H - hypoxic cells

N - necrotic cells

- Transitions are stochastic events with exp distributed random vars generated by a nonhomogeneous Poisson process.

$$\langle \nu \rangle = \nu_H \frac{L}{\langle T \rangle} \left[\sqrt{\Lambda_b} \tanh\left(\frac{\langle R \rangle - \langle T \rangle}{\frac{L}{\sqrt{\Lambda_b}}} \right) \cosh\left(\frac{\langle T \rangle}{L} - 1 \right) + \sinh \frac{\langle T \rangle}{L} \right]$$

$\langle T \rangle$ - rim thickness $\nu(\langle T \rangle) = \nu_H$

$$\Lambda_b = \frac{\lambda_b}{\lambda} = \frac{O_2 \text{ decay rate}}{O_2 \text{ uptake rate of tumor}} = \frac{0.01\lambda}{\lambda}$$

R - cell radius

L - oxygen diffusion length scale

1

$$\langle \alpha_p \rangle = \frac{\left(\frac{1}{\tau_p} (PI + PI^2) - \frac{1}{\tau_A} AI \cdot PI \right)}{(1 - AI - PI)}$$

τ_P - cell cycle time (18h literature)

τ_A = apoptosis time (8.64 literature).

$$\alpha_A = \frac{\left(\frac{1}{\tau_A} (AI - AI^2) + \frac{1}{\tau_p} AI \cdot PI \right)}{(1 - AI - PI)}$$

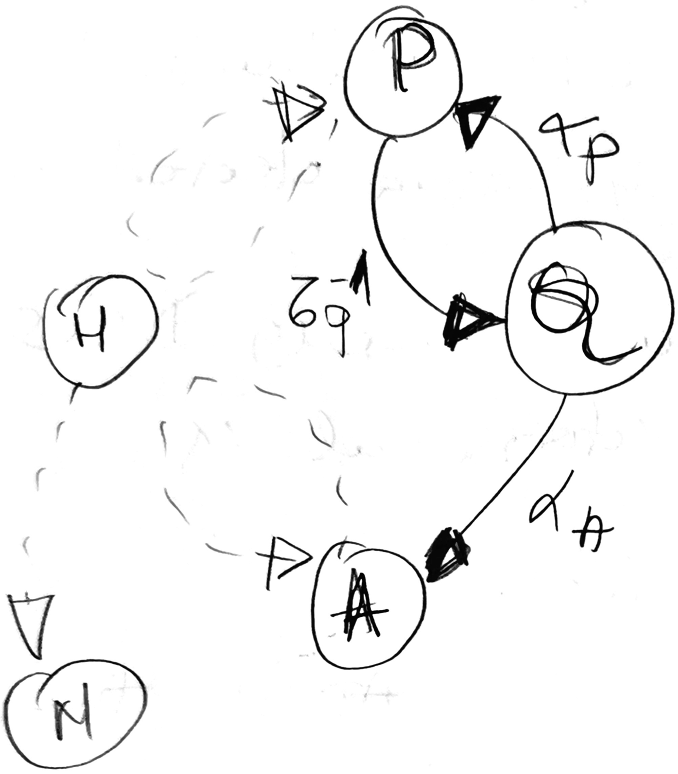
Prolif/Apopt. indices:

$PI = \frac{P}{N}$ $AI = \frac{A}{N}$ $N = A + P + Q$ number of cells

And

$$\left\{ \begin{array}{ll} \frac{dP}{dt} = \langle \alpha_p \rangle Q - \frac{1}{\tau_p} P & \text{Proliferation} \\ \frac{dA}{dt} = \alpha_A Q - \frac{1}{\tau_A} A & \text{Apoptosis} \\ \frac{dQ}{dt} = 2 \frac{1}{\tau_p} P - \left(\langle \alpha_p \rangle + \alpha_A \right) Q & \text{quiescence} \end{array} \right.$$

+



Phenotypic Transition Network particularized in DCIS (P, Q, A) only

Review in Feitelson et al. 2015 Elsevier, Seminars Cancer Biology

Mechanisms of proliferation

Phenotypic params α_P, α_A, τ_P

Volumes (V_C, V_N, V)

Radii (R_N, R) L-oxygen diffusion length

$\tau_P = 18h$

$L = 100\mu m$

$\lambda = 0.1$, $L = \sqrt{\frac{D}{\lambda}}$

$\lambda_b = 0.01\lambda$

$\sigma_H = 0.2$

PI — obtained from staining images for Ki-67 (protein marker)
(inserted above: "measured" over "obtained"; "nuclear" over "marker")

AI — measured by staining cleaved Caspase3

Data/ timeseries 100019 DCIS from Edgerton et al 11

Population dynamics

given τ_P, τ_A, AI, PI timeseries

compute α_P and α_A

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

$$\alpha_A = \left(\frac{\frac{1}{\tau_A}\left(AI - AI^2\right) + \frac{1}{\tau_P} AI\, PI}{1 - AI - PI} \right)$$

Governing Equations

$$\frac{dP}{dt} = (\alpha_P) \cdot Q - \frac{1}{\tau_P} \cdot P$$

(Supplem Macklin et al 2012)

$$\frac{dA}{dt} = \alpha_A \cdot Q - \frac{1}{\tau_A} \cdot A$$

$$\frac{dQ}{dt} = 2 \frac{1}{\tau_P} \cdot P - ((\alpha_P) + \alpha_A) Q$$

$$N = P + A + Q$$

DCIS

$$\frac{dN}{dt} = \left(\frac{1}{\tau_P} P - \frac{1}{\tau_A} A \right) \cancel{N}$$

$$PI = \frac{P}{N} \quad \& \quad AI = \frac{A}{N}$$

$$\frac{dPI}{dt} = (\alpha_P)(1 - AI - PI) - \frac{1}{\tau_P}(PI + PI^2) + \frac{1}{\tau_A} AI \cdot PI$$

$$\frac{dAI}{dt} = \alpha_A (1 - AI - PI) - \frac{1}{\tau_A}(AI - AI^2) - \frac{1}{\tau_P} AI \cdot PI$$

Learning Patient specific pathology of DCIS

Patient timeseries

Core points: * identify predictors of tumor growth used in practice to improve accuracy of surgery / intervention

* capture the peculiarities of biological data by extracting / learning the underlying functional dependency of phenotypical transitions of cancer cells

* learn the volume / size of breast affected by tumor in-situ (ducts) as an approximation of a function based on the ratio of tumor cell proliferation-to-apoptosis indices which can be measured from immunohistochemical & morphometric analysis of histopathology with no need for multiple measurements

* 17 cases histology
mammography

* model used to estimate size of tumor for surgery

- Tumor growth is a multifactorial dynamic phenomenon which evolves over time
- clinicians need to make diagnosis & decisions on treatments from a small number or one-time measurements of a few tumor properties (radiology or histology)
- using biophysical math. models or learnt models to make better predictions based on individual patients' tumors
- such a model can capture slow, long term behaviors from fast transients and learn the underlying functional relation from a limited number of measurements & ~~readily~~ can be readily incorporated in clinical practice
- learning model predicting tumor volume of DCIS for surgical planning

- Unmet need for more accurate pre-surgical determination of newly diagnosed breast cancer
  - DCIS prevalent precursor of invasive breast cancer
- Handling DCIS:
  - breast conserving surgery (fails to remove entire tumor in 38-72% cases)
  - without adjuvant radiation & hormonal therapy recurrence up to 25%
  - with adjuvant 10% recurrence
- has been hypothesized & postulated with clinical data that:

in DCIS final volumes can be directly & quantitatively linked to the breast density (ducts in breast tissue) and the relative rates of proliferation and apoptosis of the tumor

- future work to augment mammography (imaging) with ML models knowing patient peculiarities from histopathology

- Tumor cells phenotypic states
  P, A, Q, (N, H)

all phenotypic parameters $(\alpha_P, \alpha_A, \tau_P)$

Volumes (V, V_C, V_N)

radii (R_N, R)

from Macklin 11

$\tau_P = 18h$

$\tau_A = 8.6\,h$

$L = 100\mu m$

$\lambda = 0.1 \cdot min^{-1}$ $\left(L = \sqrt{\frac{D}{\lambda}} \right)$

$\lambda_b = 0.01\lambda$

$\sigma_H = 0.2$

$R = 9.953\mu m$

$R_N = 5.295\mu m$

$\sigma_B = 0.263717$

$\langle \sigma \rangle = 0.22106$

$\alpha_P^{-1} = 115.25 min$

$\langle \alpha_P \rangle = 0.0137 h^{-1}$

$\alpha_A = 0.001271\, h^{-1}$

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

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