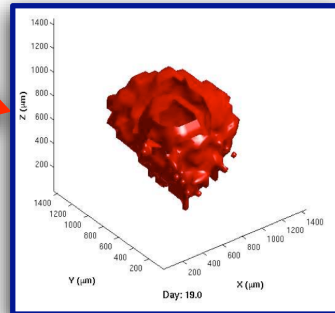
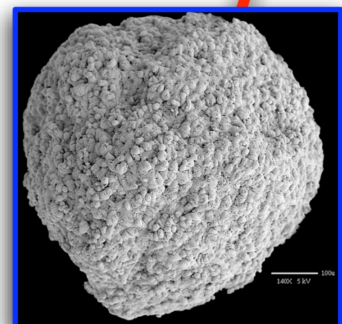
Challenges and Opportunities for *Computational Oncology* in Cellular Automata





complex.upf.es/ ~ricard/spheroid.png

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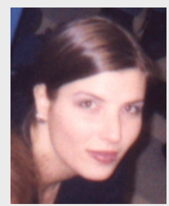
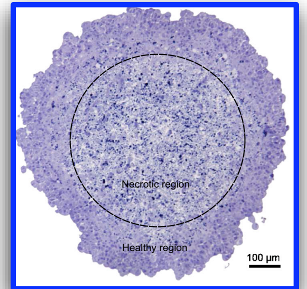
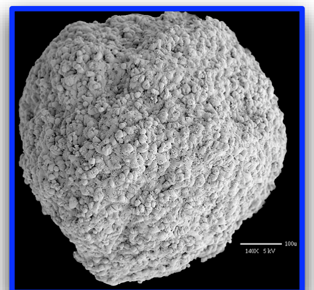


The Challenge
From Spheroids to Models (and back again)



Yu et al., 2007



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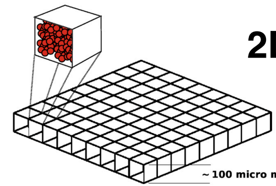
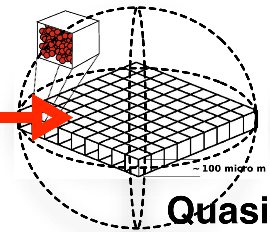
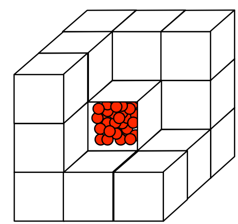


2D

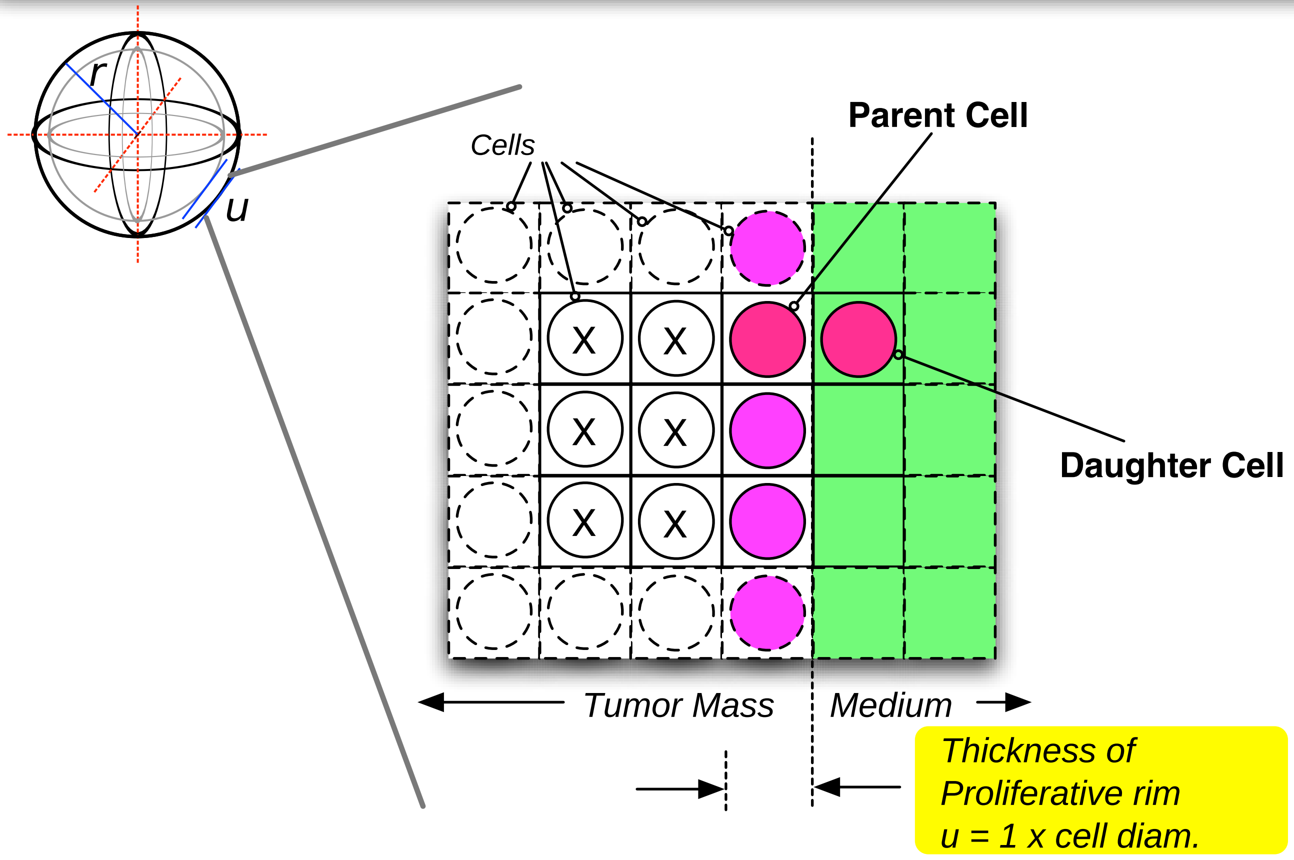


Quasi-3D

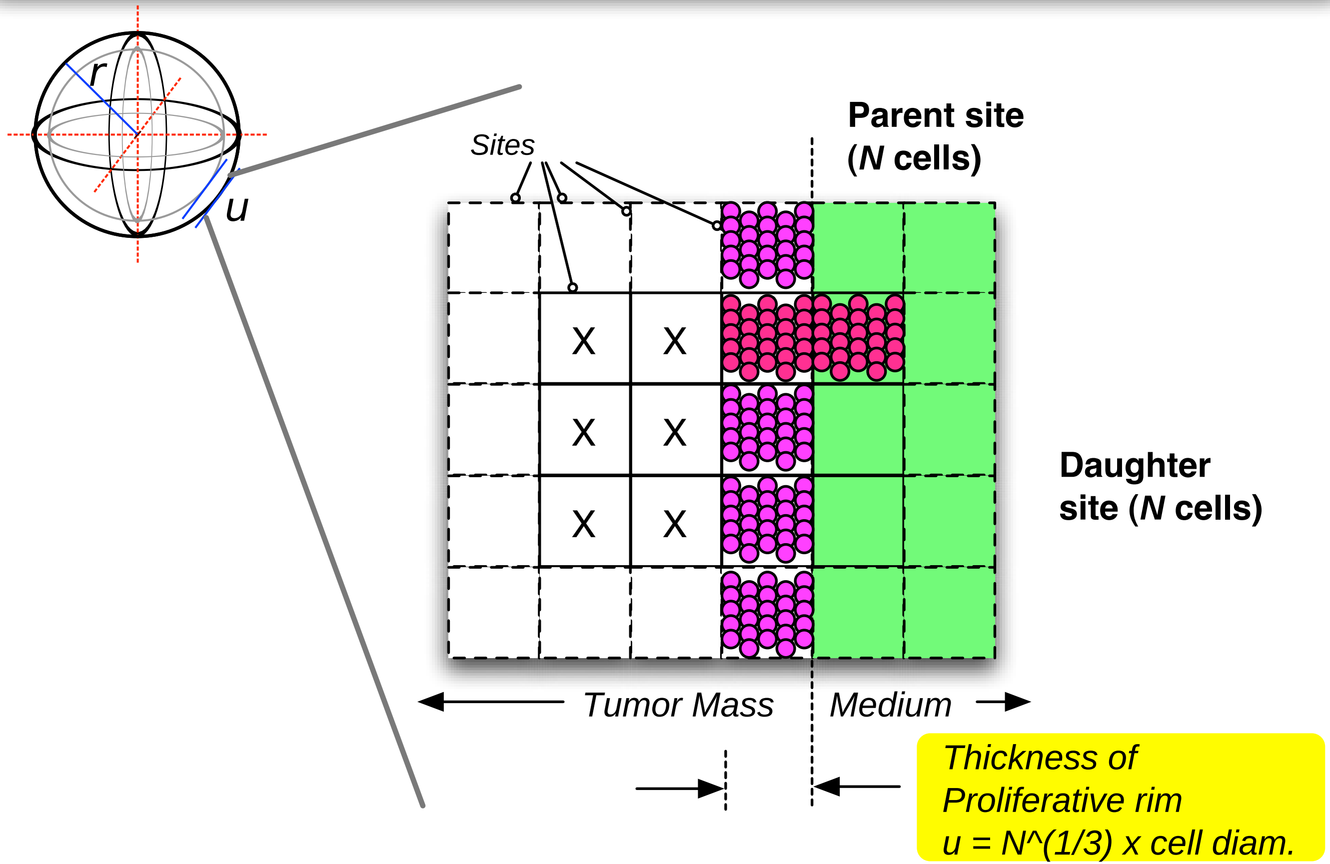


3D

Consequences of the one-to-one assumption



The Many-to-One Assumption



Division
Do CAs Grow as Peripheral Growth Theory (PGT) predicts?

$$\frac{dC(t)}{dt} = kN\epsilon(t)$$

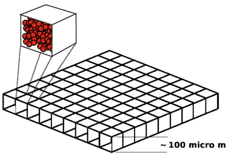
Rate const

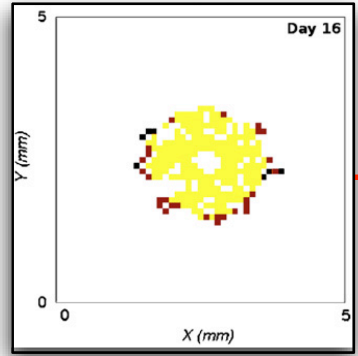
Cells/site

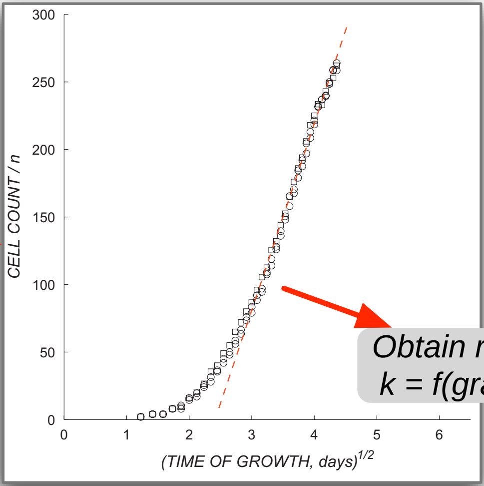
surface sites

$$C(t) = \pi N(kt)^2 + C_0.$$

$$d(t) = 2k(N/\rho)^{1/3}t + d_0$$







Obtain rate coeff.
k = f(gradient,N)

Piotrowska & Angus, J. Th. Biol. (2009)

Division
Do *Real Spheroids* Grow as PGT predicts?

$$\frac{dC(t)}{dt} = kN\epsilon(t)$$

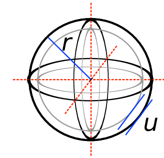
Rate const

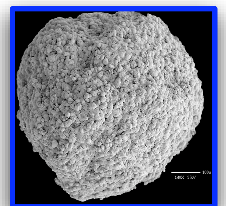
Cells/site

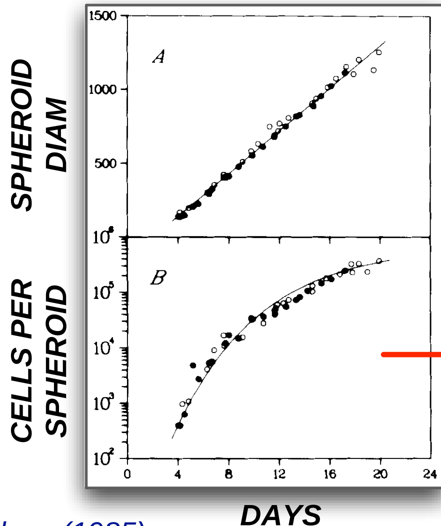
surface sites

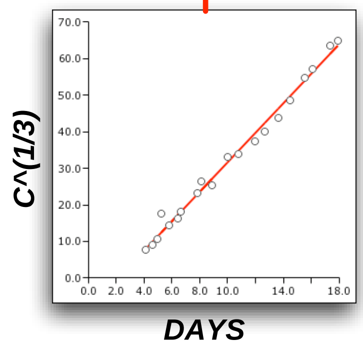
$$C(t) = [(\frac{4}{3}\pi N)^{\frac{1}{3}} kt + C^{\frac{1}{3}}(0)]^3$$

$$d(t) = 2k(N/\rho)^{\frac{1}{3}} t + d(0)$$





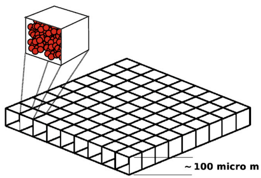




Obtain rate coeff.
k = f(gradient,N)

EMT6/Ro Cells:
Freyer & Sutherland, J. Cell Phys. (1985)

Nutrient Transport
Discrete Diffusion Transport in CAs



'Numerical' diffusion coefficient

$$x_i^{t+1} = \frac{\alpha}{f}\left(\sum_{j\in\mathcal{O}^i} x_j^t + \frac{1}{\sqrt{2}}\sum_{j\in\mathcal{D}^i} x_j^t - f x_i^t\right) + x_i^t,$$

Normalising term

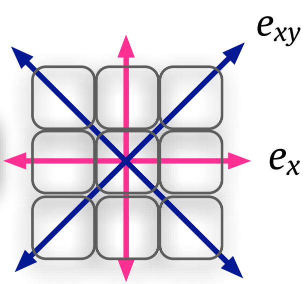
$$f = 4 + 2\sqrt{2}$$

Orthogonal components

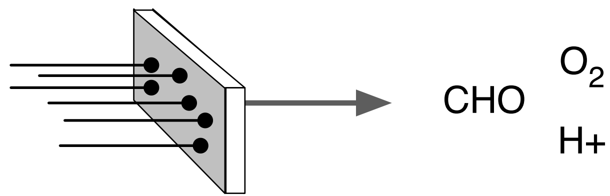
Diagonal components

Topology/Qualitative Considerations

$$\frac{e_{xy}}{e_x} = \theta = \frac{\sqrt{2}(1+\lambda)}{2\lambda+1}$$



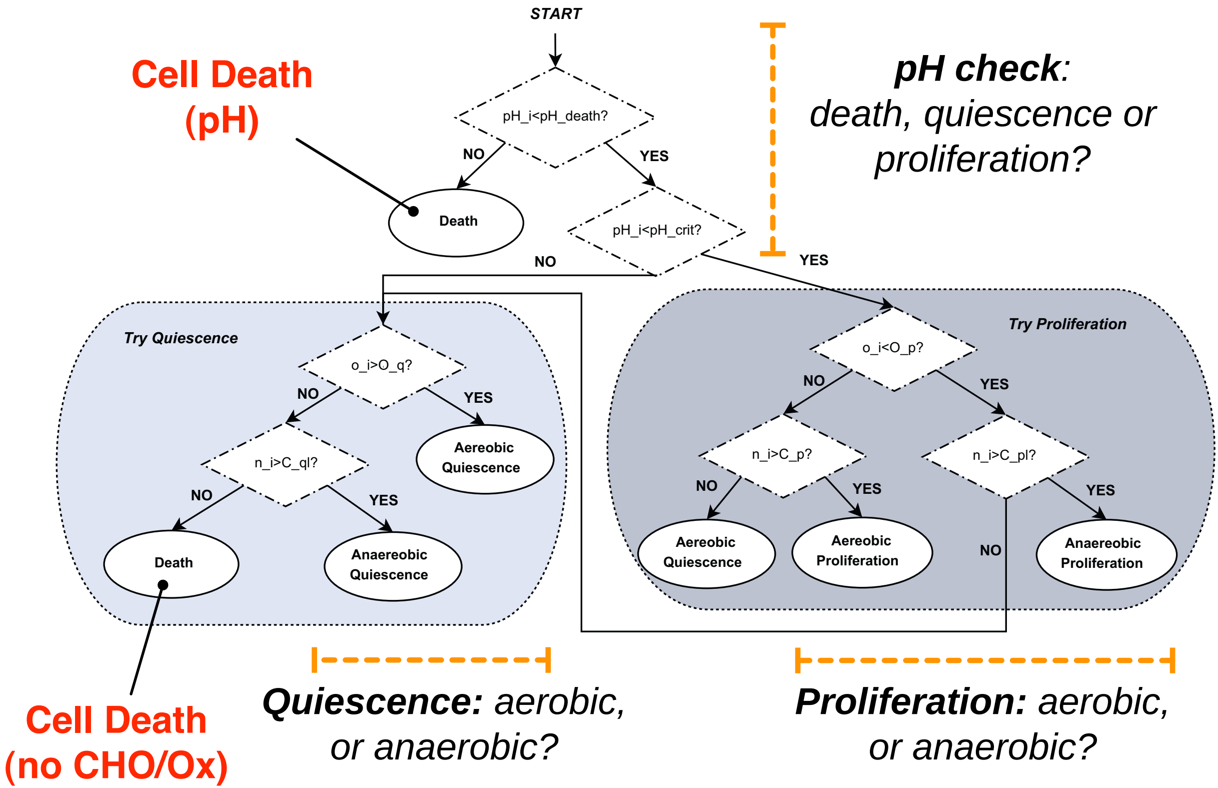
Scaling/Quantitative Considerations



$cm^2\ s^{-1}$ → $\mu m^2\ s^{-1}$?

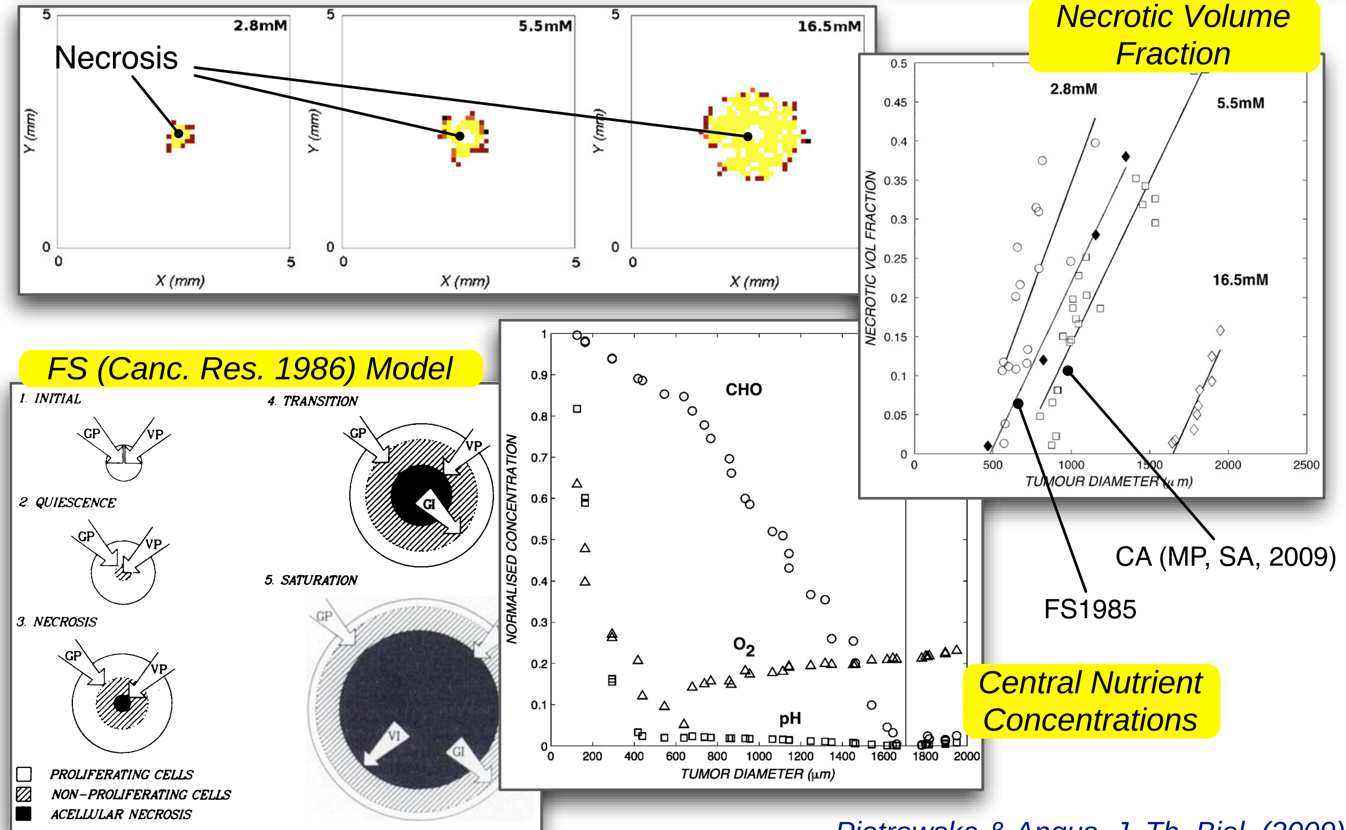
Drasdo, D., 2005. Coarse graining in simulated cell populations. Adv. Comput. Syst. 8, 319–363.

Metabolism
Metabolism in a CHO, O2, H+ world



Piotrowska & Angus, J. Th. Biol. (2009)

Necrosis
Using CAs to Probe Theory



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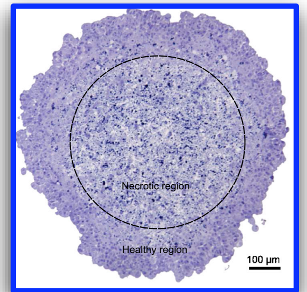
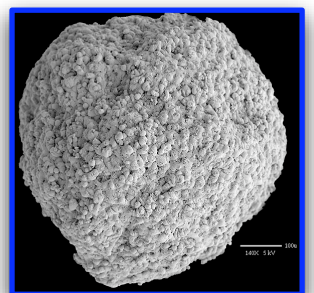


Yu et al., 2007



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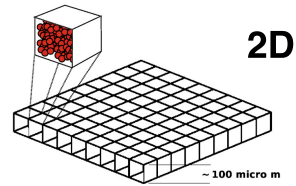
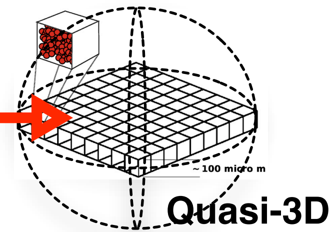
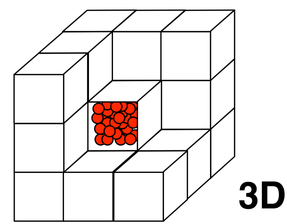
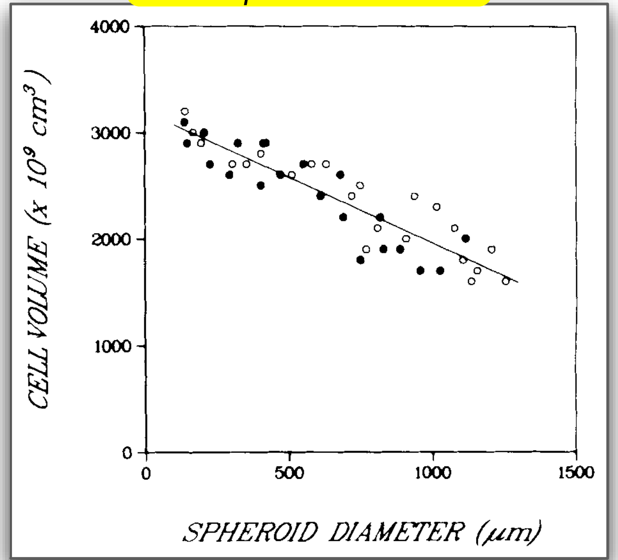






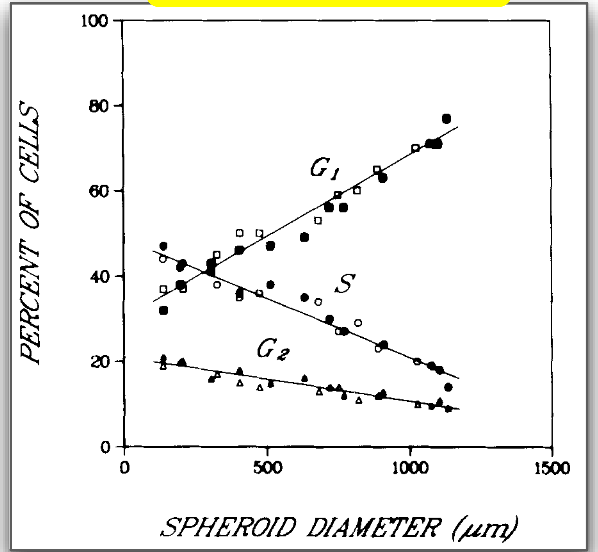
Looking Ahead
Still on the 'wish-list'

Cell Volume Reduces with Spheroid Size ...



Freyer & Sutherland, J. Cell. Phys. (1986)

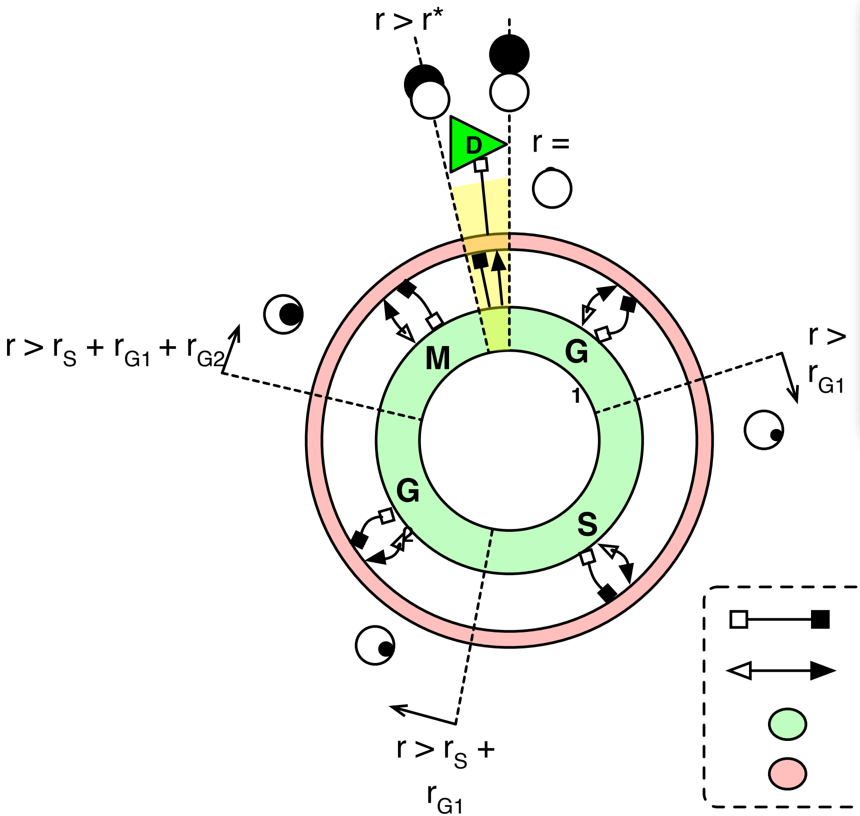
Can we match Mitotic State Data?

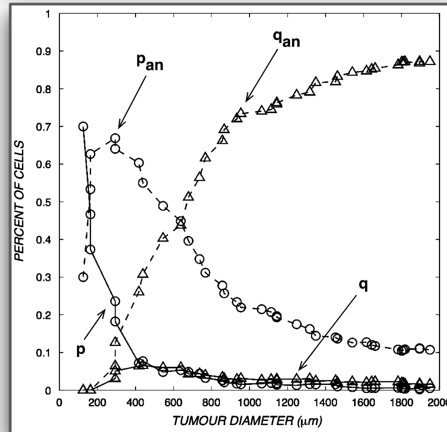


Freyer & Sutherland, J. Cell. Phys. (1986)

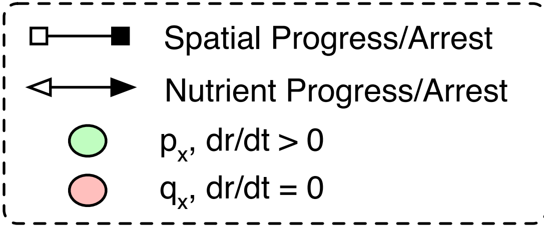
Updating Metabolism

Incorporating the mitotic development cycle





Piotrowska & Angus, J. Th. Biol. (2009)



Summing Up
CAs: Opportunities & (ongoing) Challenges

Opportunities

1// CAs are not the perfect model, but are a reasonable choice for tumour dynamics;

2// The dynamics of CAs are a good representation of real Spheroid dynamics (in vivo?)

3// CAs allow investigation of non-experimentally accessible data;

4// CAs show good promise for investigation of theory (qualitative & quantitative)

Challenges

1// Contingent metabolism needs to be handled carefully (where do you stop?)

2// Mapping from continuous to numerical diffusion not straight-forward (scaled?)

3// Migration & metastasis?;

4// Cell volume considerations?