Role of Feedback in Some Models for Tumour Growth

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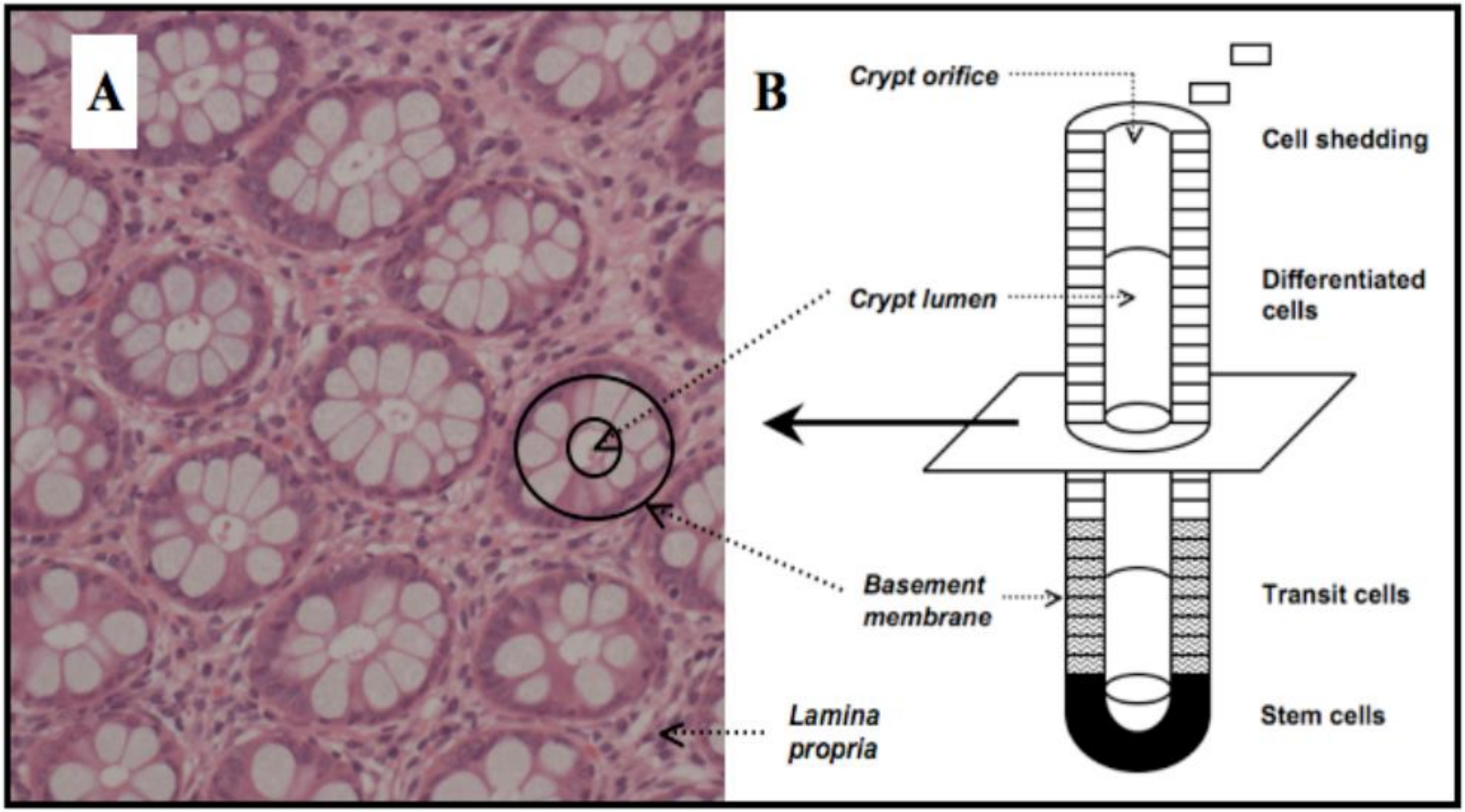
Outline

- A very simple ODE model for cell population dynamics in intestinal crypts
- An individual-based model for the above
- A multiscale model for vascularised tumour growth

Colorectal Cancer

- Second leading cause of cancer deaths in the US


A
B
Crypt orifice
Cell shedding
Differentiated cells
Crypt lumen
Basement membrane
Transit cells
Lamina propria
Stem cells

Cell population dynamics in the colonic crypt

- Johnston, Edwards, Bodmer, PKM, Chapman, PNAS, 104, 4008-4013 (2007)

- Crypt can be considered as 3-compartments:
  Stem cells,
  Semi-Differentiated (transit-amplifying) Cells,
  Fully Differentiated Cells

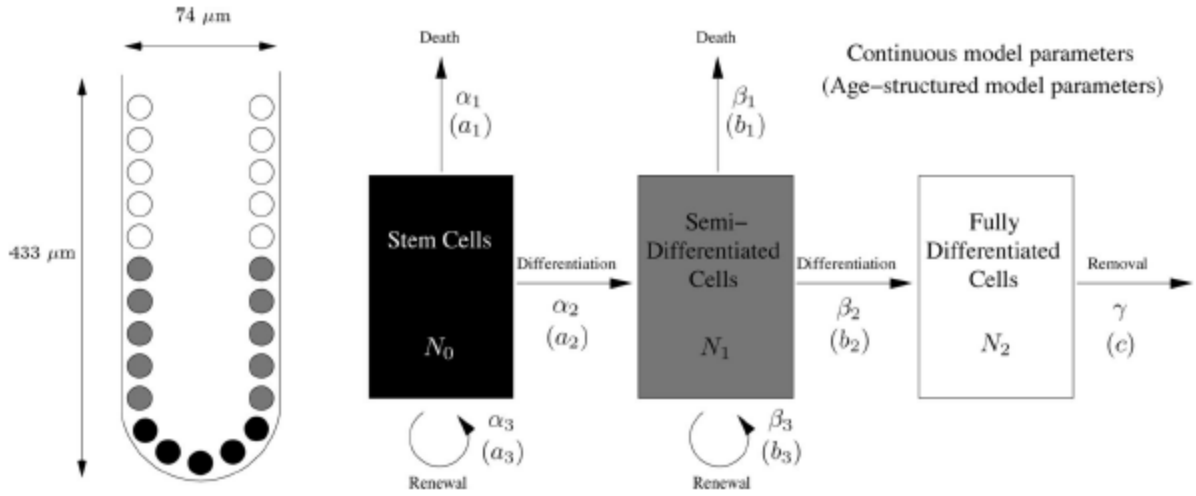


Fig. 1. Schematic representation of a colonic crypt. (*Left*) A schematic diagram of a crypt, with stem, semidifferentiated (transit-amplifying), and fully differentiated cell populations. The dimensions given are for a human colonic crypt according to Halm and Halm (23). (*Right*) A diagram showing the compartmental structure used in the model by Tomlinson and Bodmer (22). The stem cells differentiate into semidifferentiated cells, which in turn differentiate into fully differentiated cells. Each cell population can die, and the stem cells and semidifferentiated cells can renew. The parameters for the age-structured model are the proportions of the populations a_i, b_i, and c that are leaving the compartments, and the parameters for the continuous model are rates of conversion α_i, β_i, and γ.

A previous model

- Tomlinson and Bodmer, PNAS, 92, 11130-11134 (1995) – proposed cell cycle synchrony and no feedback
- D'Onofrio, Tomlinson, JTB, 244, 367-374 (2006) – feedback, but still cell synchrony
- Both ignore the compounding effect of TA cells cycling faster than stem cells

Continuous Model

- Interested on time scales greater than the cell cycle time – continuous cell division

$$\frac{dN_0}{dt} = (\alpha_3 - \alpha_1 - \alpha_2)N_0\,,$$

$$\frac{dN_1}{dt} = (\beta_3 - \beta_1 - \beta_2)N_1 + \alpha_2 N_0,$$

$$\frac{dN_2}{dt} = \beta_2 N_1 - \gamma N_2\,.$$

Steady States

- For both these models, non-trivial steady states (corresponding to homeostatis) only occur if the parameters take specific values --- STRUCTURALLY UNSTABLE

Need Feedback

- Wodarz 2007 (mutations) – feedback in stem cell compartment
- Boman et al 2001 – no feedback in stem cells so they tend to zero
- Komarova – series on papers on mutations

Model 1 – Linear Feedback

- Assume that when the population of stem or TA cells increase, the per capita rate at which they differentiate increases in proportion

$$\frac{dN_0}{dt} = (\alpha_3 - \alpha_1)N_0 - N_0(\alpha_2 + k_0 N_0),$$

$$\frac{dN_1}{dt} = (\beta_3 - \beta_1)N_1 - N_1(\beta_2 + k_1 N_1) + N_0(\alpha_2 + k_0 N_0),$$

$$\frac{dN_2}{dt} = -\gamma N_2 + N_1(\beta_2 + k_1 N_1).$$

Steady States

- Stem cells exhibit logistic growth – nice bounded stable steady state solution
- For a very large region in parameter space this model predicts homeostatis
- Only a genetic hit which removes the feedback in the model will lead to unbounded growth

Model 2 – Saturating Feedback

- Assume maximum per-capita rate of differentiation

$$\frac{dN_0}{dt} = (\alpha_3 - \alpha_1 - \alpha_2)N_0 - \frac{k_0 N_0^2}{1 + m_0 N_0},$$

$$\frac{dN_1}{dt} = (\beta_3 - \beta_1 - \beta_2)N_1 - \frac{k_1 N_1^2}{1 + m_1 N_1}$$

$$+ \alpha_2 N_0 + \frac{k_0 N_0^2}{1 + m_0 N_0},$$

$$\frac{dN_2}{dt} = -\gamma N_2 + \beta_2 N_1 + \frac{k_1 N_1^2}{1 + m_1 N_1}.$$

Steady States

- Nice homeostatic steady state as long as net linear growth rate of stem cells lies in a certain region in parameter space. If a mutation moves us out of this region then the population grows unbounded, even in the presence of feedback

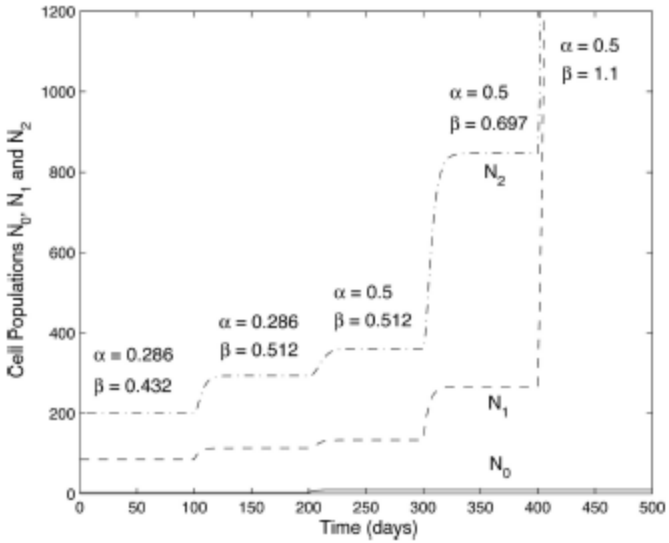
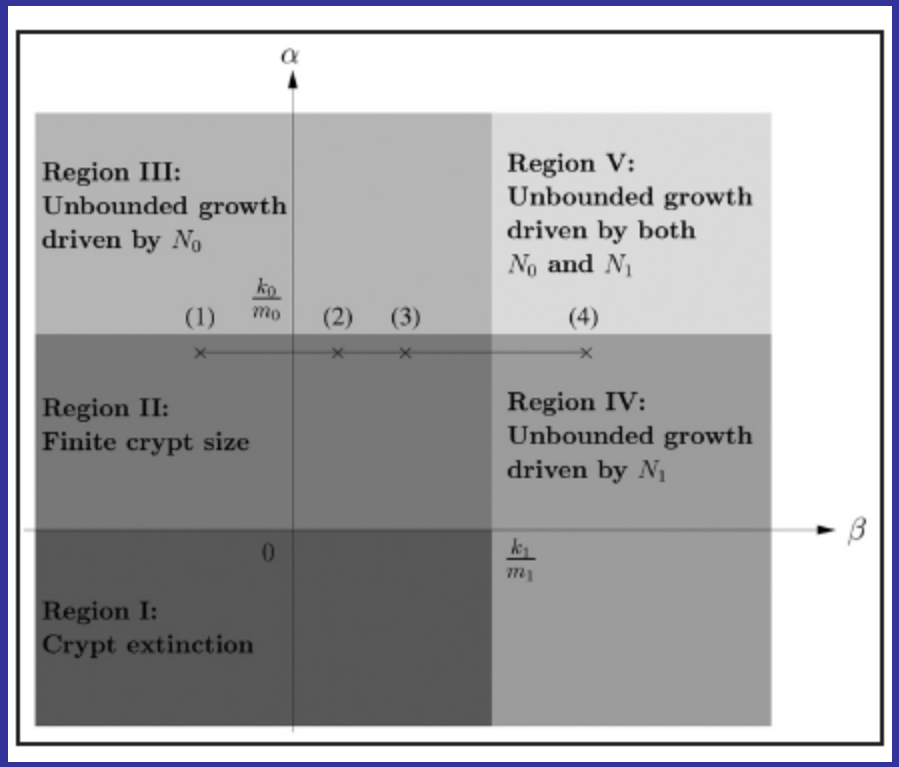


Fig. 2. An illustrative sequence of mutations (occurring every 100 days) in the saturating feedback model (feedback model 2). The initial parameters are taken to be $\alpha = 0.286$, $\alpha_2 = 0.3$, $\beta = 0.432$, $\beta_2 = 0.3$, $\gamma = 0.323$, $k_0 = 0.1$, $m_0 = 0.1$, $k_1 = 0.01$, and $m_1 = 0.01$. The mutations cause, successively, $\beta = 0.512$, $\alpha = 0.5$, $\beta = 0.697$, $\beta = 1.1$. For $\beta = 1.1$ there is no steady state and unbounded growth occurs.


α
Region III:
Unbounded growth
driven by N_0
Region V:
Unbounded growth
driven by both
N_0 and N_1
$\frac{k_0}{m_0}$
(1)
(2)
(3)
(4)
Region II:
Finite crypt size
Region IV:
Unbounded growth
driven by N_1
β
0
$\frac{k_1}{m_1}$
Region I:
Crypt extinction

Ratio of N_1 to N_2 is given by

$$1 : \frac{\beta_2}{\beta + \gamma}$$

- Therefore the proportion of cancer-driving cells may vary greatly from tumour to tumour (Johnston, Edwards,Chapman, PKM, Bodmer, JTB online 2010)

- Nature Reports Stem Cells:

- Cancer stem cells, becoming common, M. Baker, 3/12/08

- Lander, Nie and Wan: olfactory endothelium

Some bad things ☹

- Continuum approximation – individual-based model approach in IB
- Handling of mutations – properly including mutant population

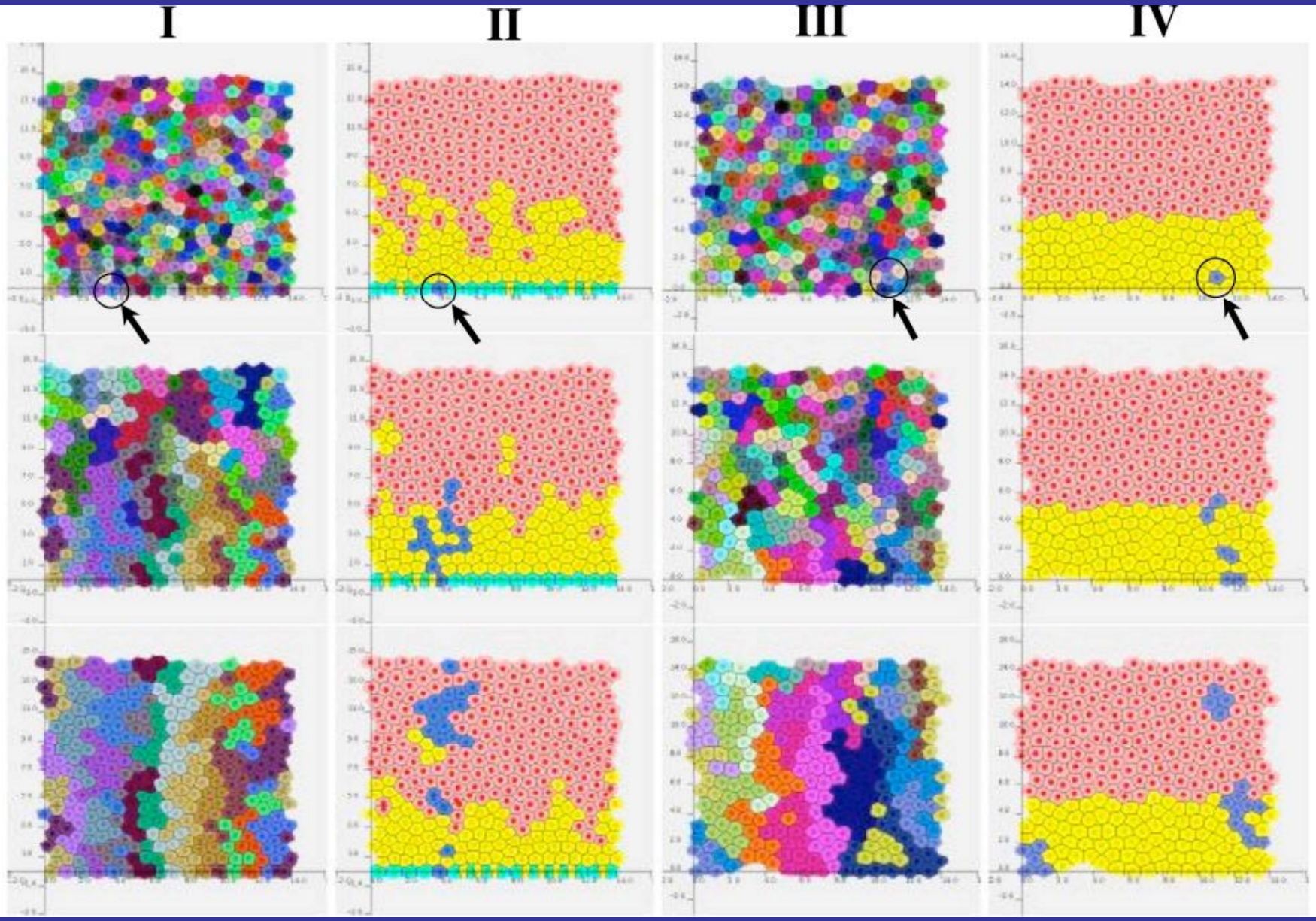
Conclusions

- Developed a robust model for cell populations in the crypt
- Shown that the key parameters are the net per-capita growth rates of the stem cells and TA cells. So, the failure of programmed cell death or differentiation could lead to tumour growth, as well as increased proliferation rate
- Saturating feedback could explain the existence of benign tumours before carcinogenesis takes over – early mutations could keep parameters below their critical values, later stage mutations could push them above their critical values.
- Evidence suggests that nearly all colorectal cancers go through benign stages, but not all develop into carcinomas

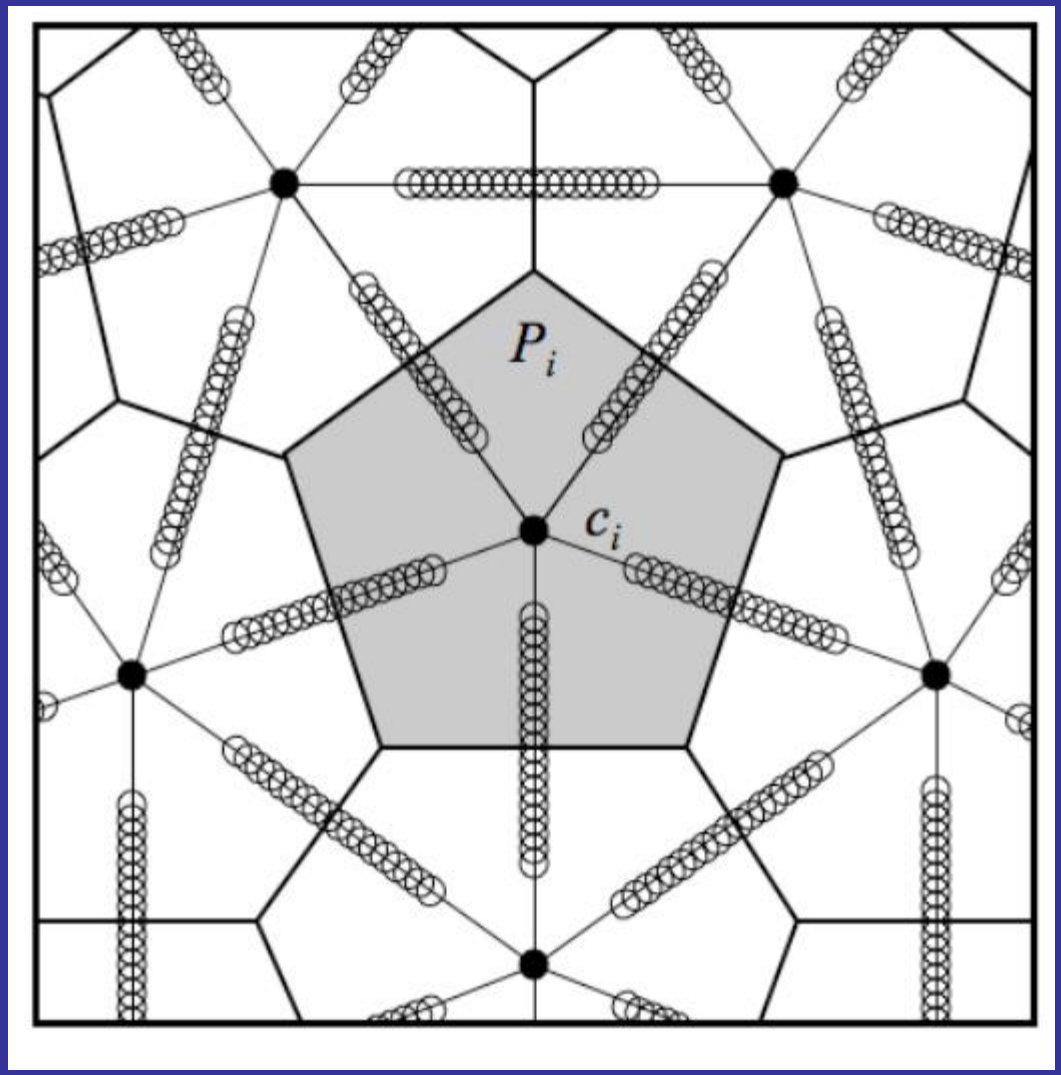
An integrative computational model for intestinal tissue renewal

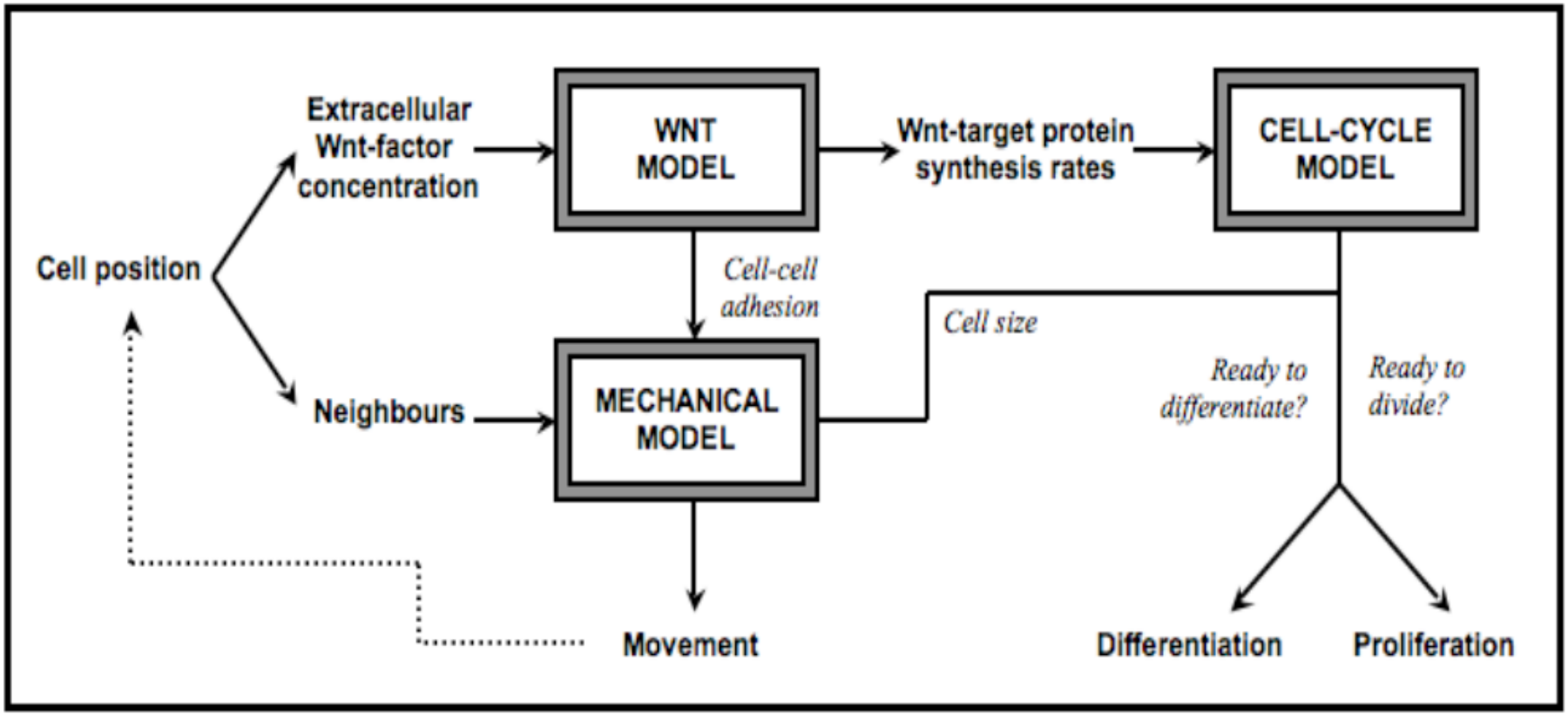
- Van Leeuwen, Mirams, Walter, Fletcher, Murray, Osbourne, Varma, Young, Cooper, Pitt-Francis, Momtahan, Pathmanathan, Whiteley, Chapman, Gavaghan, Jensen, King, PKM, Waters, Byrne (Cell Proliferation, 2009)

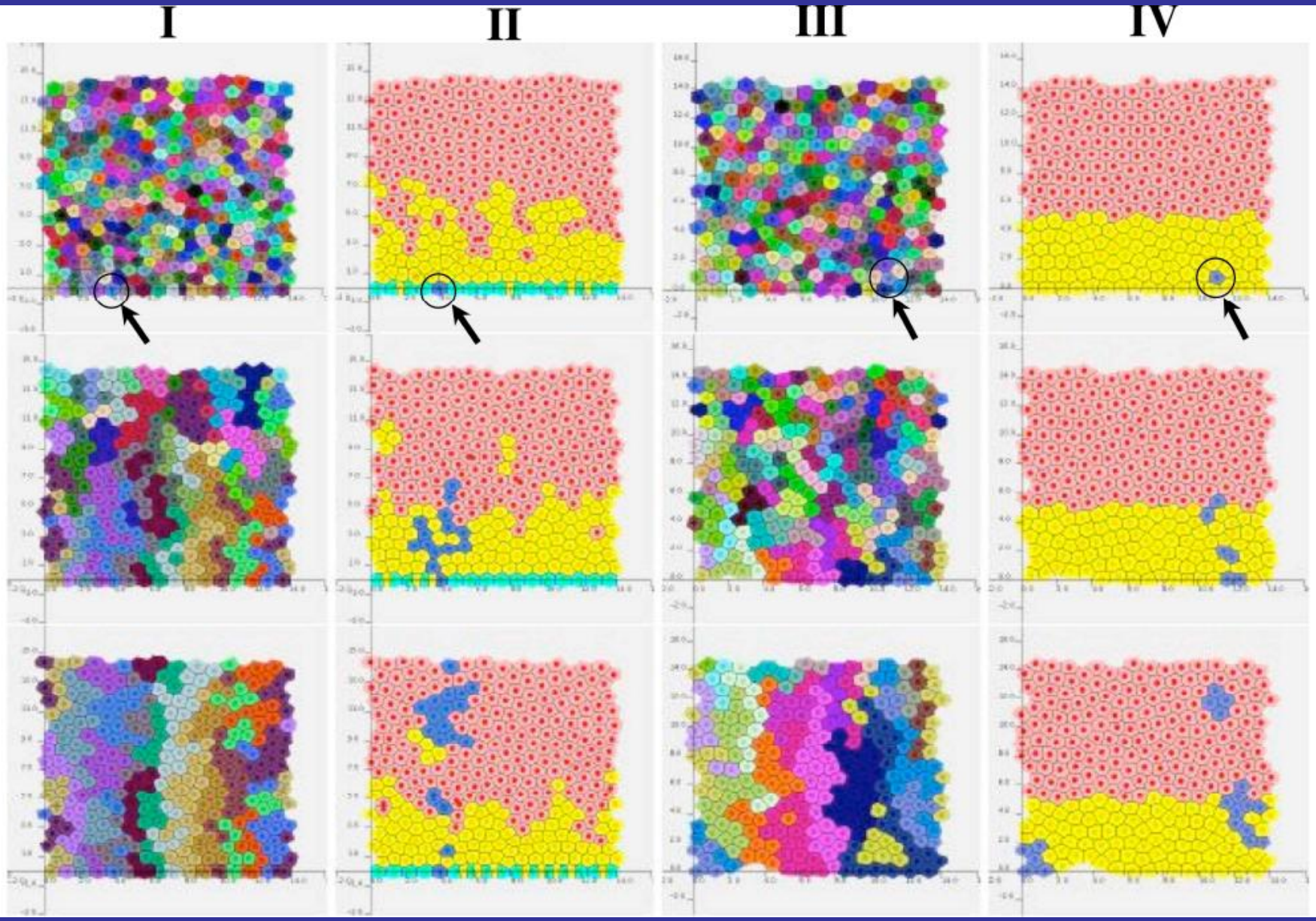
- Chaste – Cancer, Heart And Soft Tissue Environment
- Modular


I
II
III
IV

- Follow Meinke et al and use a cell-centred approach – basically consider cells as point masses connected by springs and use Delauny triangularisation and Voronoi tesselation to determine nearest neighbours and for visualisation.

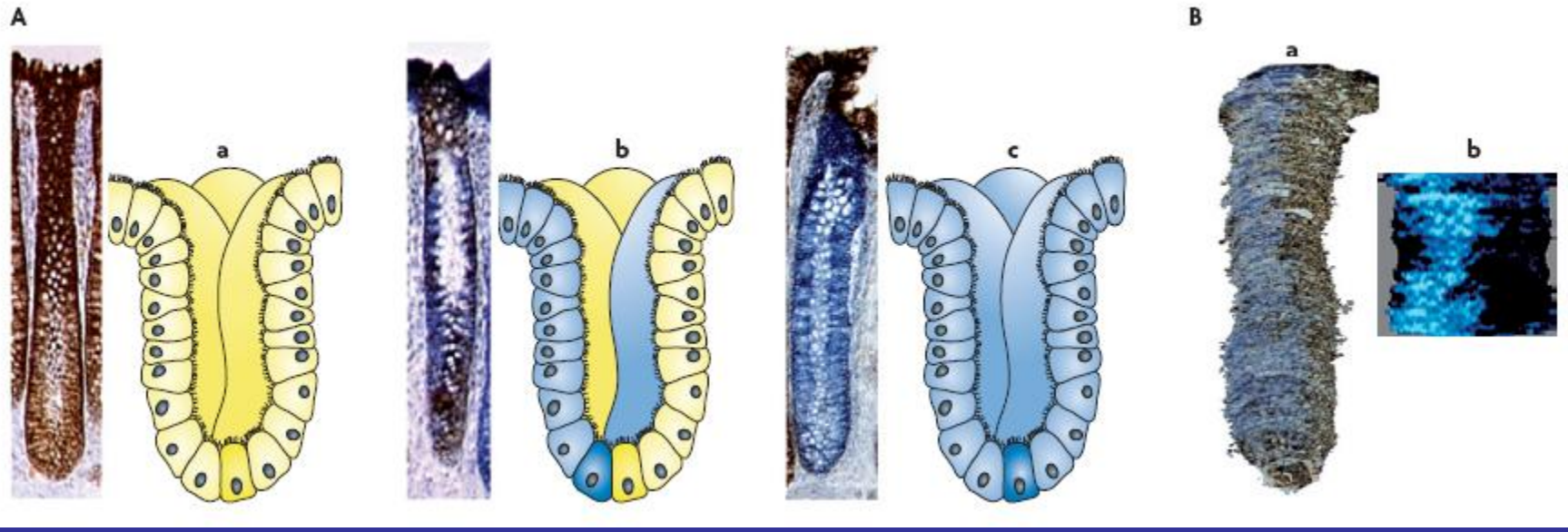

P_i
c_i


Extracellular
Wnt-factor
concentration
WNT
MODEL
Wnt-target protein
synthesis rates
CELL-CYCLE
MODEL
Cell position
Cell-cell
adhesion
Cell size
Neighbours
MECHANICAL
MODEL
Ready to
differentiate?
Ready to
divide?
Movement
Differentiation
Proliferation


I
II
III
IV

Colonic crypt organization and tumorigenesis

Adam Humphries and Nicholas A. Wright



PHYSICAL REVIEW E 80, 031912 (2009)

From a discrete to a continuum model of cell dynamics in one dimension

Philip J. Murray,[1] Carina M. Edwards,[2] Marcus J. Tindall,[3] and Philip K. Maini[1,4]

$$\frac{\partial q}{\partial \tau} = \frac{\partial}{\partial r}\left(\frac{k}{\eta q^2}\frac{\partial q}{\partial r}\right), \qquad (1)$$

where k is the spring constant, η is the cell viscosity, τ is time, and r is the spatial coordinate. We define the nonlinear diffusion coefficient $D(q)=k/\eta q^2$.

M. Alber, N. Chen, P. M. Lushnikov, and S. A. Newman, Phys. Rev. Lett. **99**, 168102 (2007).

The effects of different individual cell-based approaches

- (to appear in Phil Trans R Soc A)

A hybrid approach to multiscale modelling of cancer

J. M. Osborne[1,6*], A. Walter[2*], S. K. Kershaw[1], G. R. Mirams[3], A. G. Fletcher[4,6], P. Pathmanathan[1], D. Gavaghan[1,6], O. E. Jensen[5], P. K. Maini[4,6], H. M. Byrne[5]

Cancer Growth

Tissue Level Signalling: (Tumour Angiogenesis Factors)
Oxygen etc

Partial Differential Equations

Cells:

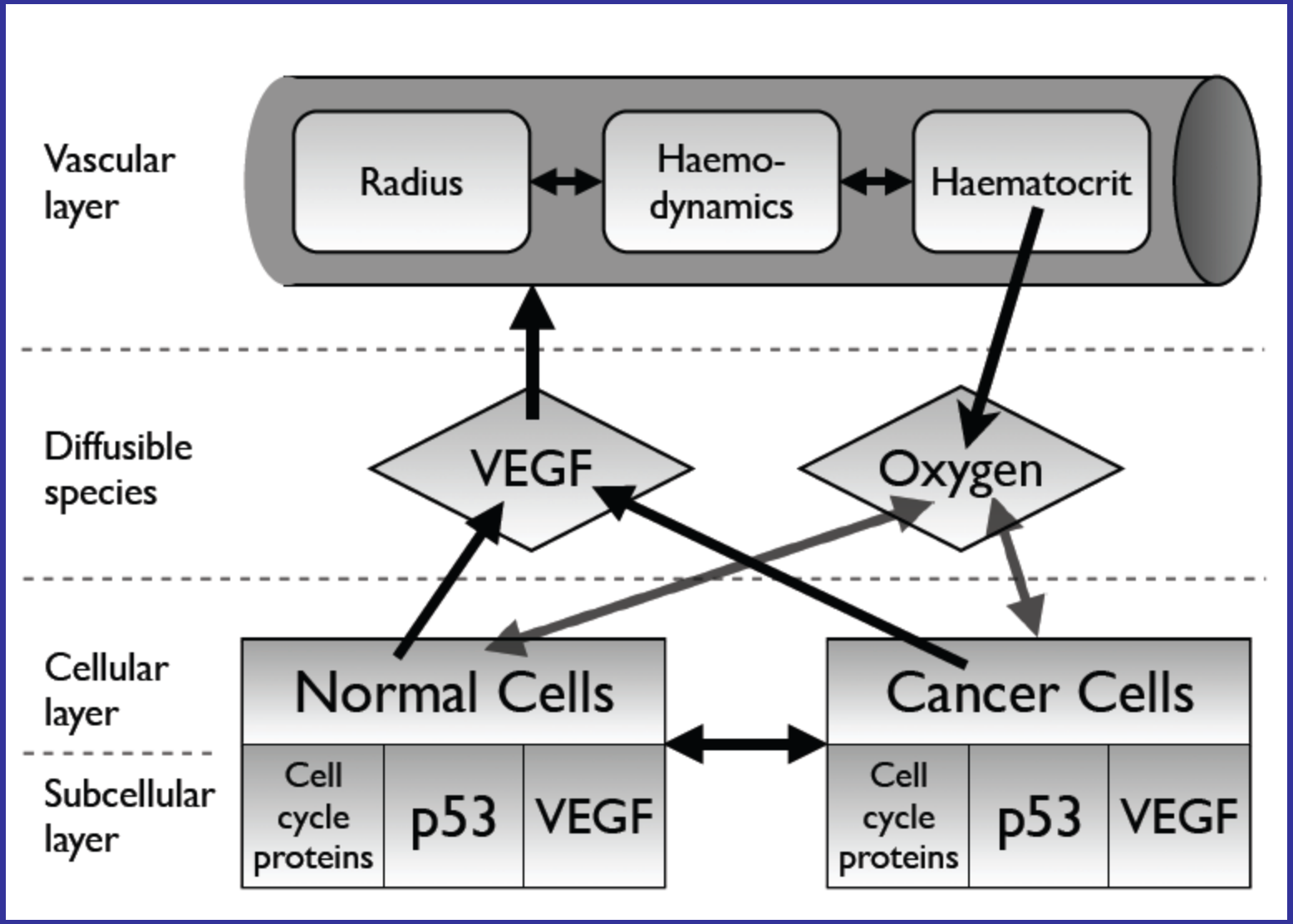
Automaton Elements

Intracellular: Cell cycle,
Molecular elements

Ordinary differential equations

- Tomas Alarcon
- Markus Owen
- Helen Byrne

- James Murphy
- Russel Bettridge


Vascular layer
Radius
Haemo-dynamics
Haematocrit
Diffusible species
VEGF
Oxygen
Cellular layer
Normal Cells
Cancer Cells
Subcellular layer
Cell cycle proteins
p53
VEGF
Cell cycle proteins
p53
VEGF

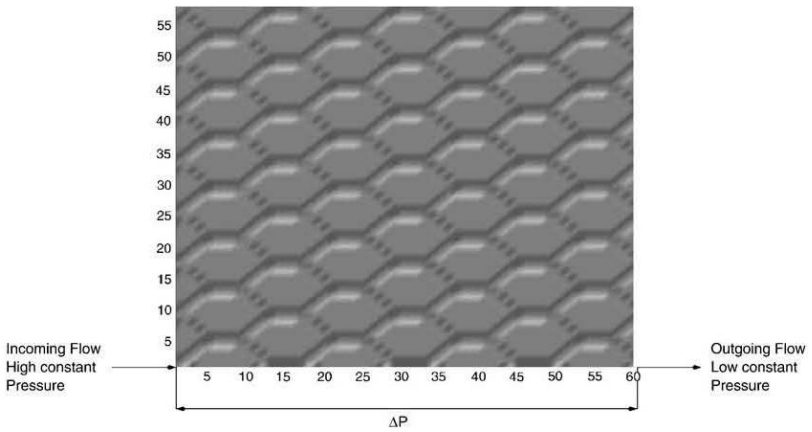


Fig. 2. Initial conditions for the adaptation algorithm: all vessels have the same radius (10 μm) and length (80 μm). In the blood flow simulations, we have imposed no-flux conditions for all the vessels on the boundary of the domain except at the ends marked in the figure as "incoming flow" and "outlet flow", where a given value of the current has been prescribed (see Alarcón et al., 2003a for further details). In all the figures hereafter, the numbers on the axis refer to the position in the cellular automaton lattice which is a subset of $\mathbb{Z}^2$. One unit in this lattice corresponds to 20 μm in real tissue.

Vascular Adaptation

- Series of papers by Secomb and Pries modelling vessels in the rat mesentry – they conclude:

R(t) = radius at time t:

$$R(t+dt) = R(t) + R\ dt\ S$$

S = M + Me – s + C

M = mechanical stimulus (wall shear stress)

Me = metabolic demand

s = shrinkage

C= conducted stimuli: short-range (chemical release under hypoxic stress?)

long-range (mediated through membrane potential?)

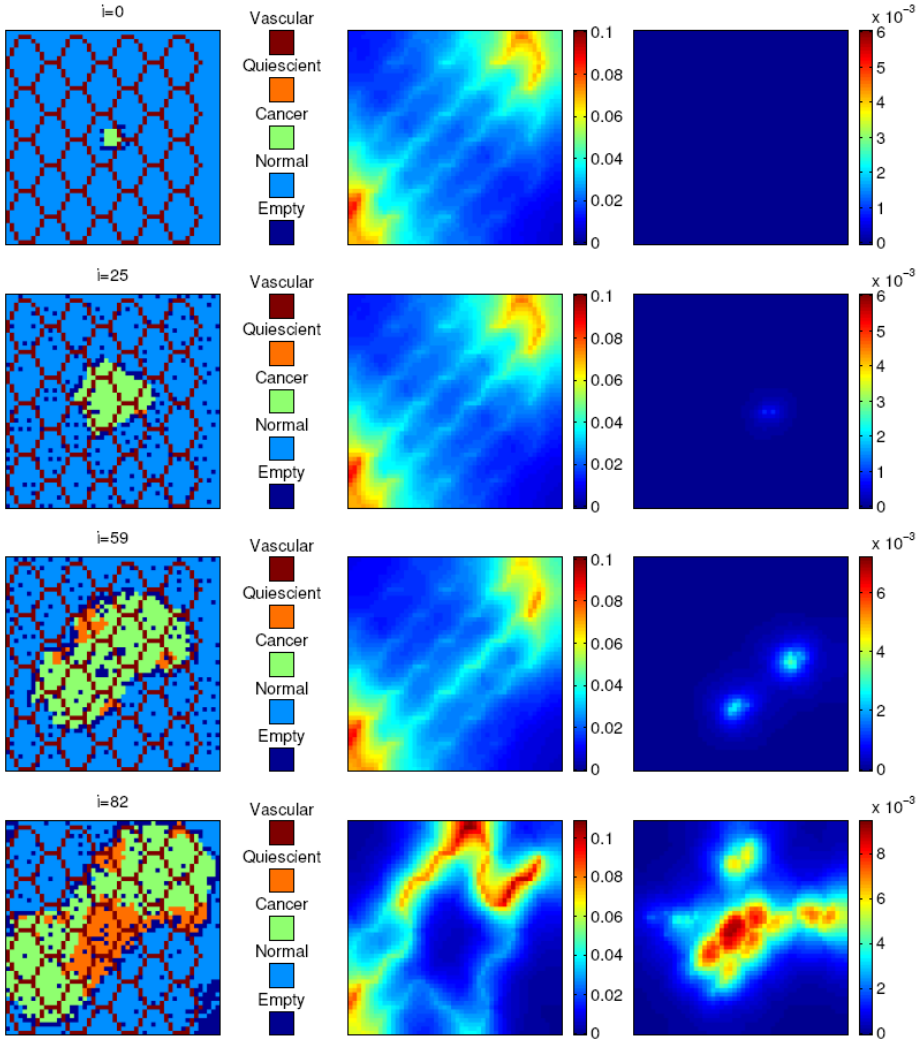


Fig. 4. Four snapshots showing simulations with vascular adaptation coupled to VEGF released by hypoxic cells. Time increases from top to bottom. The left column corresponds to the evolution of the colonies of normal and cancer cells, the central column to the distribution of oxygen and the right column to VEGF distribution.

- By varying the strengths of the different adaptation mechanisms we can hypothesise how defects in vasculature lead to different types of tumours: Conclude that losing the long range stimuli looks a reasonable assumption

- Tim Secomb has shown this more convincingly recently (PLoS Comp Biol 2009)

Potential uses of the model

- Chemotherapy
- Impact of cell crowding and active movement
- Vessel normalisation

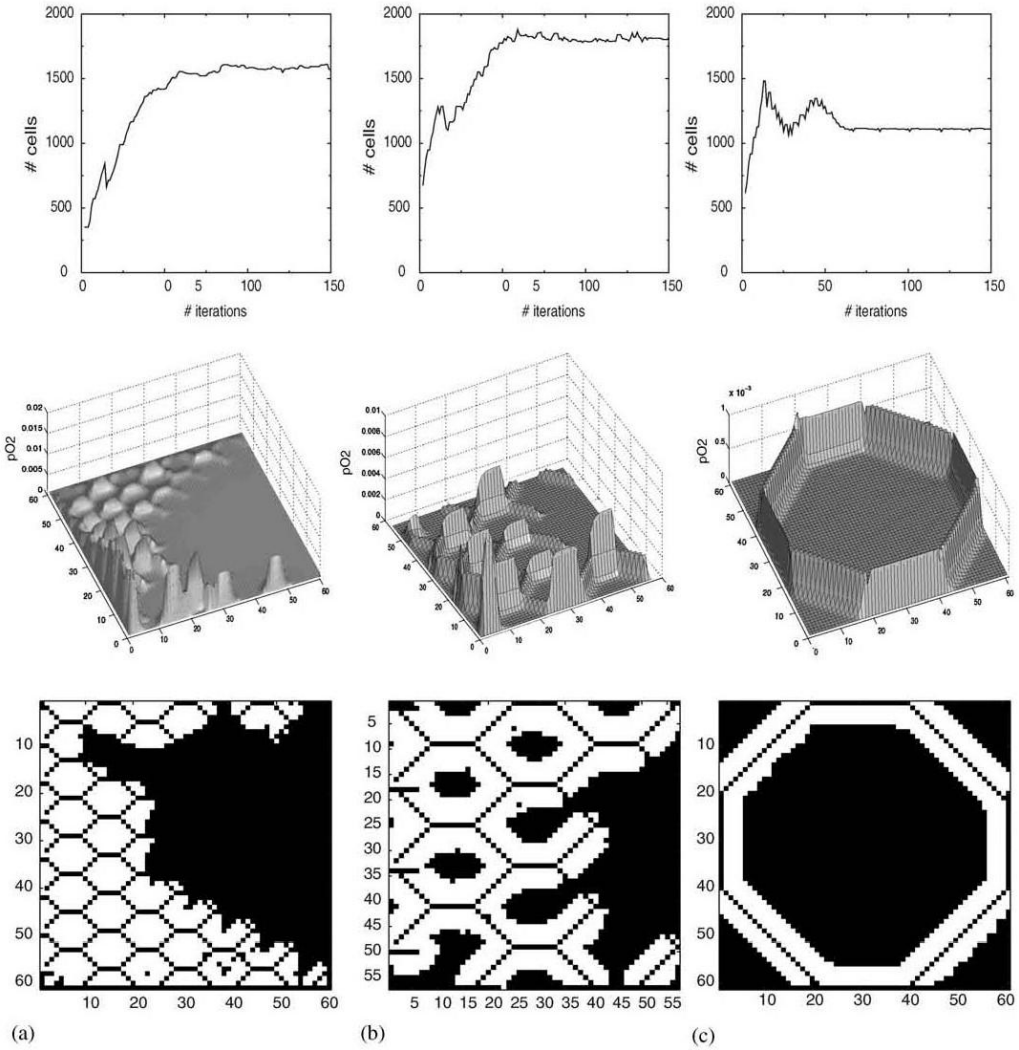
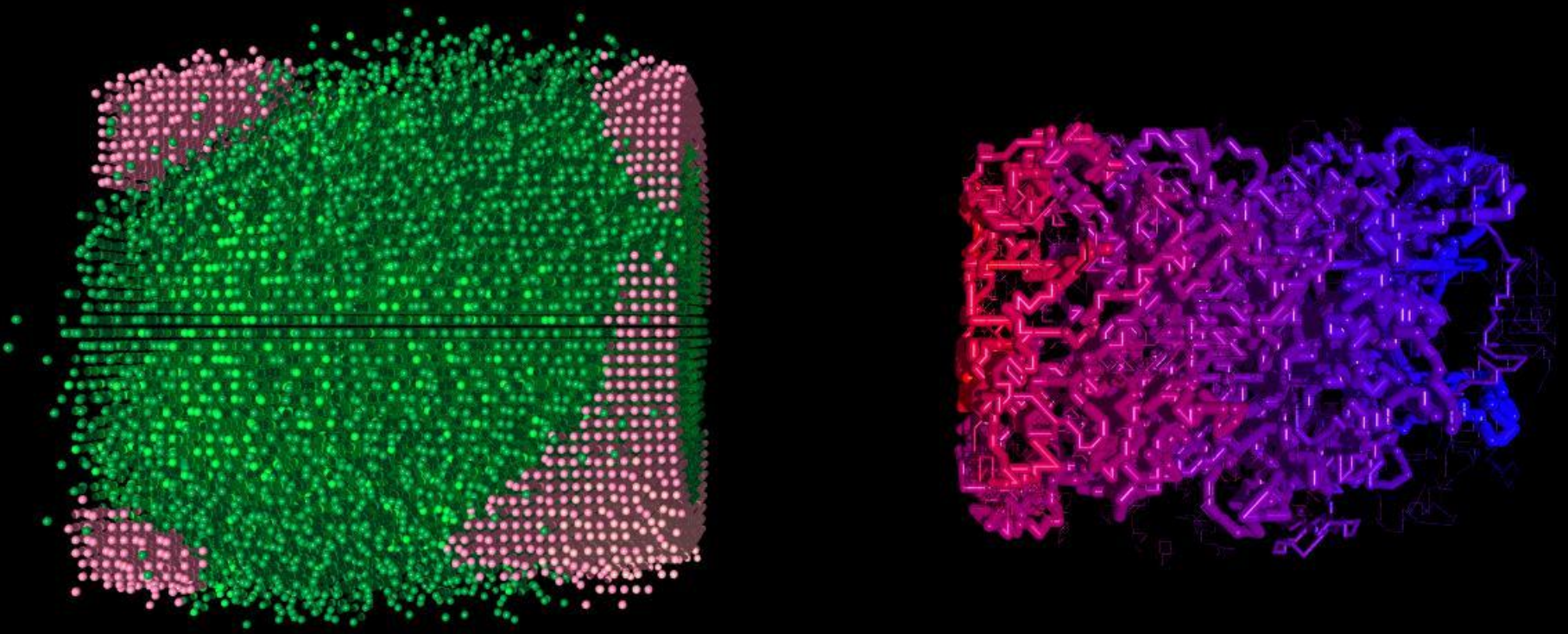


Fig. 10. Simulation for systems whose vascular networks have different sparsity, i.e. we have varied the *vascular density*, defined as the number of vessels per surface unit. In column (a) we have plotted the results for a system with vascular density = 114 vessels/mm^2, column (b) corresponds to vascular density = 24 vessels/mm^2, and column (c) corresponds to vascular density = 4 vessels/mm^2. The results plotted in the first row corresponds to the evolution of the size of cancer colony in time (where each iteration corresponds to 15 h, which is an estimation of the duplication time of our cancer cells), the second row, to the stationary distribution of oxygen (pO_2 in dimensionless units), and the third row, to the stationary cell distribution. In the middle set of figures, the vertical axis is the oxygen concentration. In the bottom panel of each column white spaces are occupied by cancer cells, whereas black spaces are either empty or occupied by vessels.

Angiogenesis

- Recently, we have added in angiogenesis (Owen, Alarcon, PKM and Byrne, J.Math. Biol, 09)



- Movie – both2_mov

So what?

- Mark Lloyd (Moffitt) is now doing experiments on cancer angiogenesis in mice to allow us to derive data for model testing.

Conclusions and Criticisms

- Simple multiscale model – gain some insight into why combination therapies might work
- Heterogeneities in environment play a key role
- No matrix included! – Anderson has shown adhesivity could be important
- Cellular automaton model – what about using Potts model, cell centred, cell vertex models? – DOES IT MAKE A DIFFERENCE (Murray et al, 2009; Byrne et al, 2010)
- There are many other models and I have not referred to any of them! (Jiang, Bauer, Chaplain, Anderson, Lowengrub, Drasdo, Meyer-Hermann, Rieger, Cristini, Enderling, Meinke, Loeffler, TO NAME BUT A FEW)

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