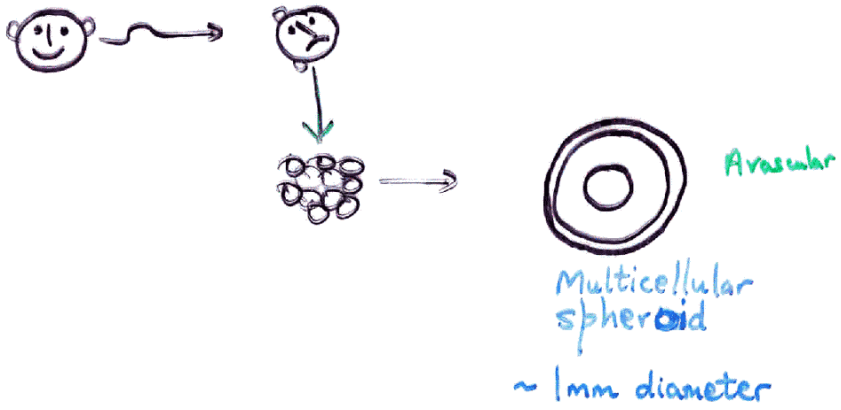
Cancer Modelling – Background

- Diffusion limited aggregation



- Too small to detect – why study it?

  Metastases – Secondaries

- Nutrient required (cf Tissue Engineering)

  Hypoxic core secretes TAF (Tumour Angiogenesis Factor)

- Invasion

  – Tumour produces proteases – digest ECM

- Competition

Normal Environment :

Add H^+

$$\frac{\partial N_1}{\partial t} = D_1 \nabla^2 N_1 + f(N_1, N_2, L)$$

$$\frac{\partial N_2}{\partial t} = \nabla \cdot D_2(N_1) \nabla N_2 + g(N_1, N_2, L)$$

$$\frac{\partial L}{\partial t} = D_3 \nabla^2 L + h(N_2, L)$$

Gatenby & Gawlinski

⇓

GAP

TRUE!!

? ⇒ THERAPY

Therapies

- Kill tumour cells or cut them out
- Anti-angiogenesis drugs — drug delivery
- Treat normals ?

CAN WE BUILD A "WHOLE ORGAN" MODEL FOR CANCER ??

"A journey of a thousand miles starts out with the first few steps."

In fact, this is more at the crawling stage!!

- ~~Effects~~ of environmental heterogeneity
- Cell Cycle
- Future Directions

Cancer Growth

Tissue Level Signalling (Tumour Angiogenesis factors)
Oxygen etc

PDE

Cells

Automaton Elements

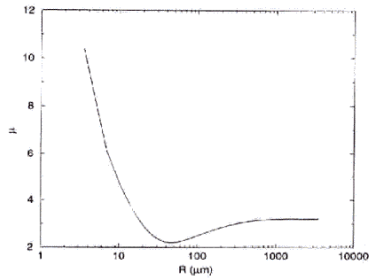
Intracellular : Cell Cycle

molecular elements

ODEs

- Alarcon, Byrne, PKM, J. theor. Biol. to appear
- " " " in prep.

Title Suppressed Due to Excessive Length 9



Fahraeus-Lindquist effect

Fig. 3. Relative blood viscosity $\mu(R)$ as a function of the radius (R) of the vessel. Data from [10] for a proportion of the total volume of blood occupied by red blood cells (hematocrit) of 0.45. (Pries et al, 1994)

Blood rheology

Av. red blood cell diameter in humans ~7-8 μm

$$\mu(R) = \left(\frac{R}{R-R_0}\right)^2\left(1+\left(\frac{R}{R-R_0}\right)^2\left(a_0 + a_1 e^{-\lambda_1 R} - a_2 e^{-\lambda_2 R^{\gamma_2}}\right)\right)$$

Reformulate Minimization principle

$$\Rightarrow \quad \dot{Q} = R^3 \frac{\pi}{2\sqrt{\mu_0}}\sqrt{\frac{\alpha_b}{4\mu - R\mu_R}}$$

$R_0 = 0.55$
$a_0 = 2.2$
$a_1 = 6$
$a_2 = 2.4$
$\lambda_1 = 0.17$
$\lambda_2 = 0.09$
$\gamma_2 = 0.645$

Numerical Soln $\Rightarrow$

$$\dot{Q}_i = C R^{\alpha_i}$$

$$\alpha_i = \begin{cases} 3.00 & \text{if } R_i > R_{cr1} \\ 2.87 & \text{if } R_{cr2} < R_i < R_{cr1} \\ 3.66 & \text{if } R_i < R_{cr2} \end{cases}$$

$R_{cr1} \approx 270\,\mu m$
$R_{cr2} \approx 45\,\mu m$

C_i = etc.

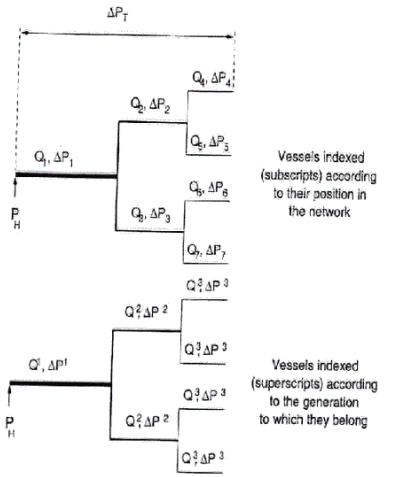


Fig. 5. Schematic representation of the branching structure used in our simulations. See text for details.

Using these results plus

$$\dot{Q}_i = \dot{Q}_j + \dot{Q}_k$$ (flow conservation at each bifn pt)

and

$$\sum_j \Delta P_j = \Delta P_T$$ pressure drop across the whole network

$$\Delta P_j = \frac{8\mu_0 \mu(R_j) L_j}{\pi R_j^4} \dot{Q}_j$$ (Poiseuille flow)

Tumour Growth

First, work out distribution of O_2 (nutrient)

To do so, must consider vasculature:

metabolic response

$$R(t+\Delta t) = R(t) + R\,\Delta t \left(\ln\left(\frac{\tau_w}{\tau(P)}\right) + k_m \ln\left(\frac{\dot{Q}_{met}}{\dot{Q}_H} + 1\right) - k_s \right)$$

response to mechanical stimuli

shrinkage

(Pries et al 1988)

R = radius
$\dot{Q}$ = flow rate
H = haematocrit
τ_w = WSS
P = pressure (transmural)

$$\tau(P) = 100 - 86 \exp(-5000 \ln(\ln P))^{5.4}$$ (rat mesentry)

* Haematocrit: $\mu = \mu(H, R)$ Pries et al, 1994 ($\mu \uparrow$ with H)

* At a bifurcation:

$$H_p = H_1 + H_2$$

$$\frac{H_1}{H_2} = \alpha \frac{V_1}{V_2}, \text{ if } \frac{V_1}{V_2} < T$$ (Fung 1993)

$$H_1 = H_p, \text{ if } \frac{V_1}{V_2} > T$$

Algorithm for structural adaptation

1. ΔP, H_T prescribed

   $\dot{Q} = \frac{\Delta P}{Z}$ $\left(Z = \frac{8\mu(H,R)L}{\pi R^4}\right)$

   ⇒ flow rate

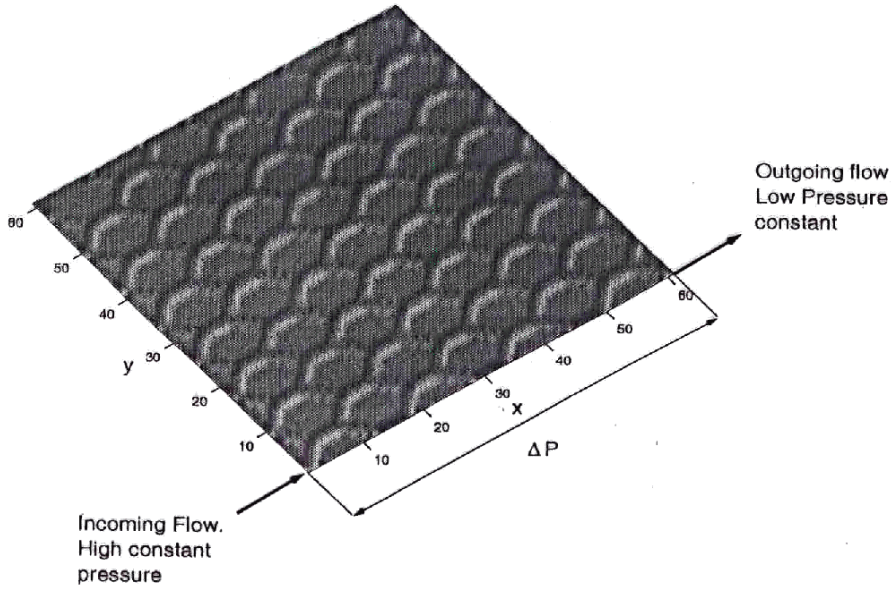
2. Given initial network configuration, compute flow rates through and pressure drops across each vessel using Kirchoff's Law.

3. Compute distribution of haematocrit

4. Update radius of each vessel

5. Compute viscosities (using H and R from ③ and ④ resp.)

6. Repeat until steady state reached



Hexagonal network, similar to avian yolksac (Honda & Yoshizako, 1997)

Liver

Results

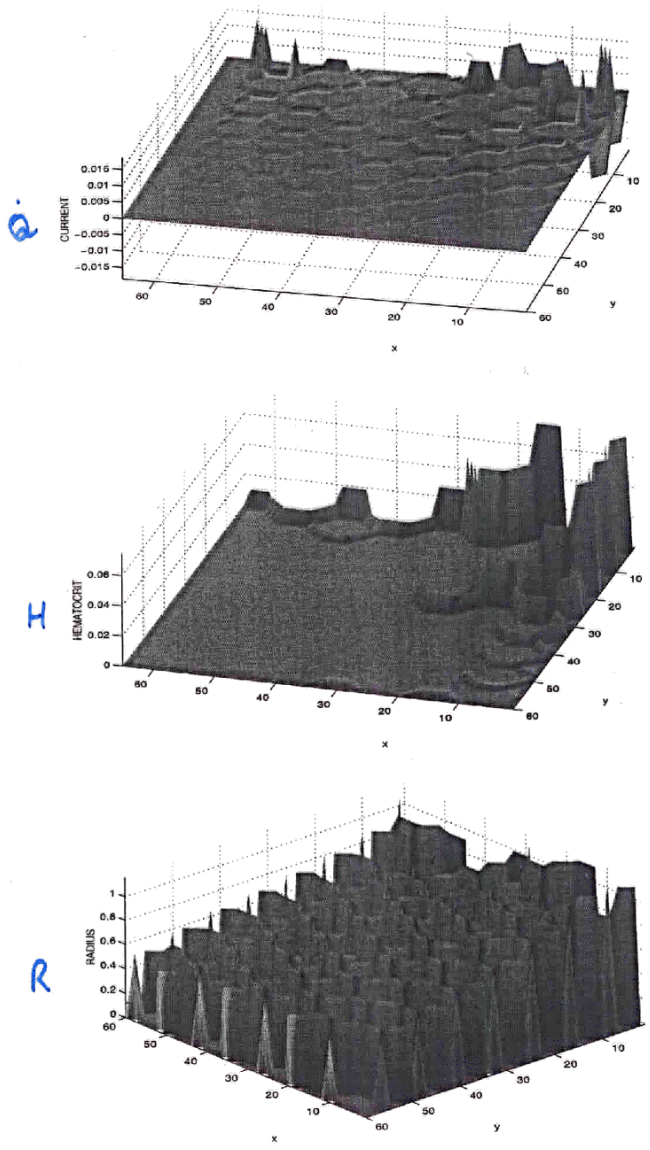


Figure 4:

Parameters

Parameter	Value	Units	Source
k_m	0.83	s^{-1}	Pries et al (1998)
Q_{ref}	40	nl/min	Pries et al (1998)
k_s	1.79	s^{-1}	Pries et al (1998)
α	0.5	none	Fung (1993)
THR	2.5	none	Fung (1993)
D_P	$2.41 \cdot 10^{-5}$	$cm^2 s^{-1}$	Goldman and Popel (2000)
K_N	$1.57 \cdot 10^{-4}$	$mlO_2\, ml^{-1} s^{-1}$	Goldman and Popel (2000)
K_T	$1.57 \cdot 10^{-4}$	$mlO_2 ml^{-1} s^{-1}$	estimated
$\mathcal{P}$	$3.0 \cdot 10^{-4}$	$cm\, s^{-1}$	estimated
N_{T1}	$4.5 \cdot 10^{-4}$	grams	Patel et al (2001)
N_{T2}	$4.5 \cdot 10^{-3}$	grams	
C_{T1}	$1.5 \cdot 10^{-5}$	grams	
C_{T2}	$4.5 \cdot 10^{-5}$	grams	

$\frac{P_G}{\mathcal{P}} = \frac{m_{O_2}}{m_G}$

m = molecular wt
G = glucose (Patel et al 2001)

Automaton Rules

① O_2 distribution determined by BVP

② Cells attempt to divide at each timestep

③ Normal cell: if O_2 < threshold, cell dies

O_2 > threshold, cell attempts to divide

threshold = N_{T_1} if more normal than cancer neighbours

= N_{T_2} " " cancer " normal "

$N_{T_2} > N_{T_1}$

④ Cancer cell: if O_2 > threshold, cell attempts to divide

threshold = C_{T_1} if more cancer than normal neighbours

= C_{T_2} " " normal " cancer "

$C_{T_2} > C_{T_1}$

⑤ Cancer cell: if O_2 < threshold ⇒ cell becomes quiescent

If it remains quiescent for a certain length of time, it dies.

⑥ Cells are sinks of O_2

⑦ If O_2 level is such that a cell may divide, sample neighbourhood for space. If more than one available space, go to the one with largest O_2 (Patel et al 2001)

If no space, die (Kansal et al, 2000)

O_2 distribution

$D_p \nabla^2 P - k(\underline{x}) P = 0$ (adiabatic approx.)

$P = O_2$ conc.

$k(\underline{x}) = \begin{cases} k_N & \text{for normal cell} \\ k_C & \text{for cancer cell} \\ 0 & \text{o.w.} \end{cases}$

B.C. $-D_p \underline{n}_w \cdot \nabla P = \mathcal{P}(P_b - P)$

$\underline{n}_w$ = normal to vessel wall

P_b = O_2 level in blood

$\mathcal{P}$ = permeability

$\underline{n}_\partial \cdot \nabla P = 0$ (at edge of domain, no flux)

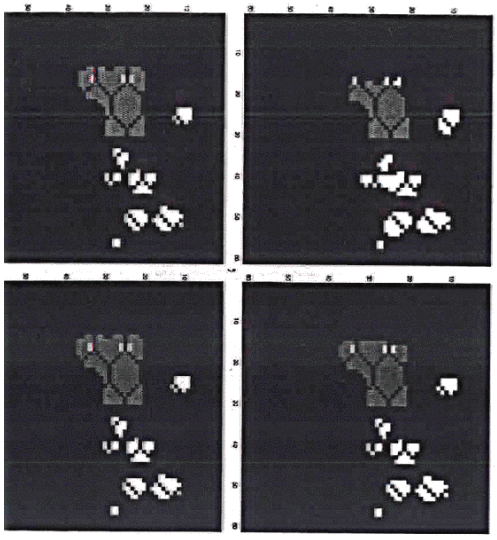
Cell Dynamics

$N \times N$ automaton elements.

State vector has 3 components:

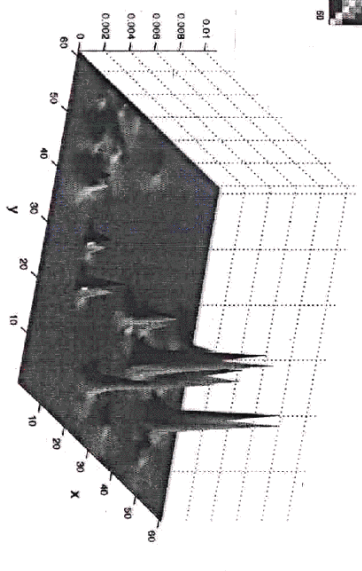
- Occupation: normal cell / cancer cell / vessel / empty
- Cell status: proliferative / quiescent
- Local O_2 conc.

We assume, for simplicity, vessel structure does not evolve.

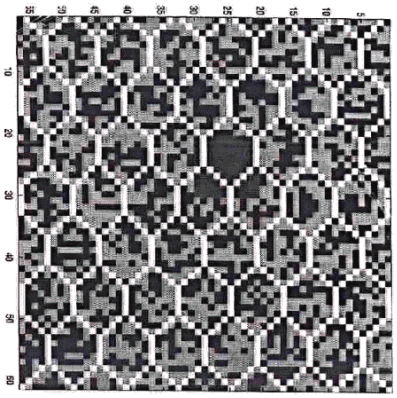


Invasion dynamics

- normal
- empty or blood vessels
- grey - cancer



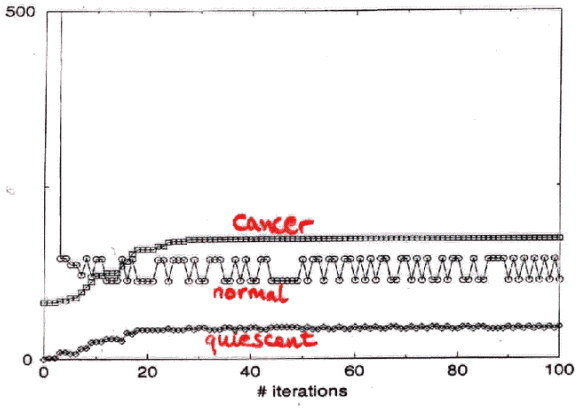
O_2 distribution



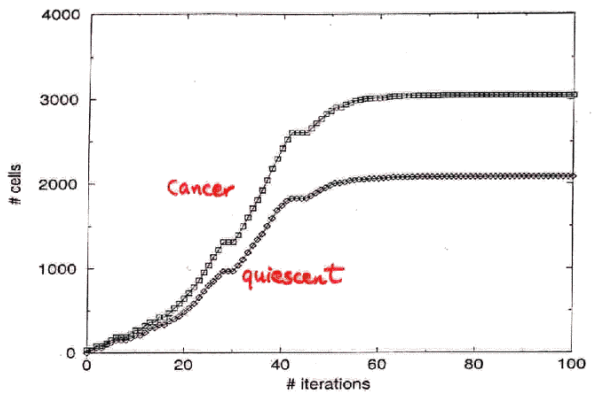
Invasion Dynamics

Heterogeneous

- empty
- dark grey - cancer
- light grey - normal
- Blood vessels



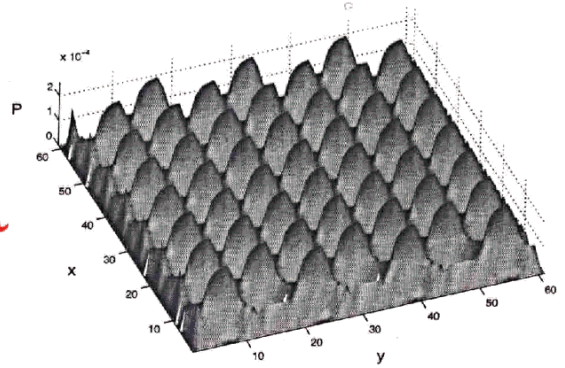
Heterogeneous

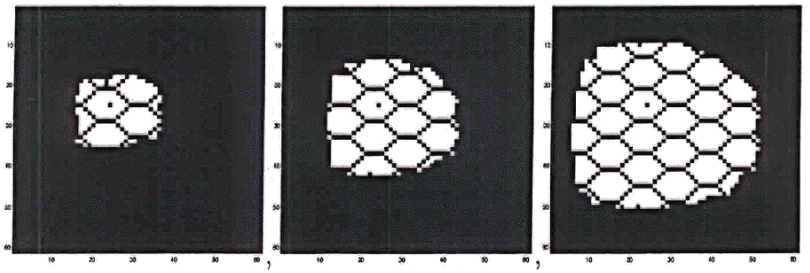


Corresponding homogen. case

normals ↓ 0

O_2 distribution





Growth dynamics

CONCLUSIONS

* Environmental heterogeneity restricts dramatically the ability of malignant colonies to invade healthy tissue

GAPS Really exciting opportunities

- Growth of vessels — vasculature design (angiogenesis)
- Immature versus mature vessels
- Cell cycle
- Competition
- Couple vessel dynamics with cell dynamics & cell needs
- Growth factors
- p53 – normals undergo p53-mediated apoptosis under hypoxia (tumour suppressor gene) mutants become quiescent
- Geometry

Cell-Cycle Dynamics

- Why?

- nutrient demand
- hypoxia-induced quiescence
- drugs work only on cells in a certain part of their cell cycle.

- Cell Cycle: G_1 S G_2 M

cyclin-dependent kinases (CDK) } 2 families of proteins
cyclins

In G_1, CDK activity is low because its cyclin partners are missing

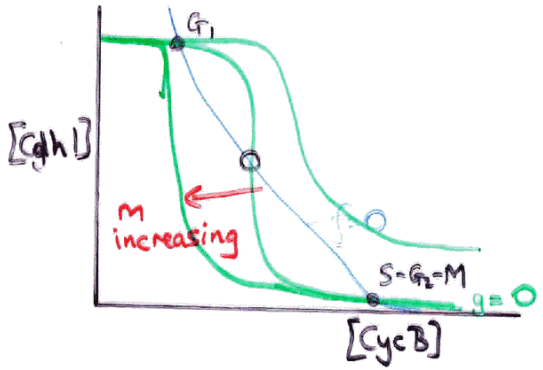
At Finish Cdh1 (and Cdc20) concs are high → degrade cyclins.

$$\frac{d}{dt}[CycB] = f([CycB],[Cdh1])$$

$$\frac{d}{dt}[Cdh1] = g([CycB],[Cdh1],m)$$

Tyson & Novak

m = mass of cell



$$\frac{dm}{dt} = k\left(1-\frac{m}{m_*}\right)m$$

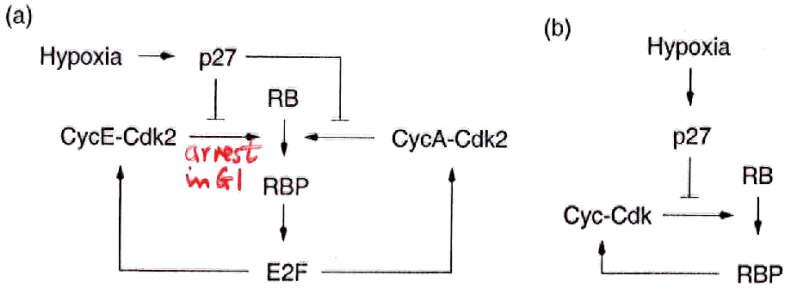


Figure 1: Schematic representation of the mechanism for hypoxia-induced cell-cycle arrest. (a) The original mechanism proposed by Gardner et al (2001). (b) Our simplified version for modelling purposes. RBP stands for the phosphorylated form of the RB protein.

E2F - transcription factor

Take Tyson & Novak model:

incorporate inhibition by a $-kz$ term

↑ p27 conc.

$$\frac{dz}{dt} = k_1\left(1 - \frac{m}{m_x}\right) - k_2 \frac{P}{B+P} z$$

oxygen

Normals

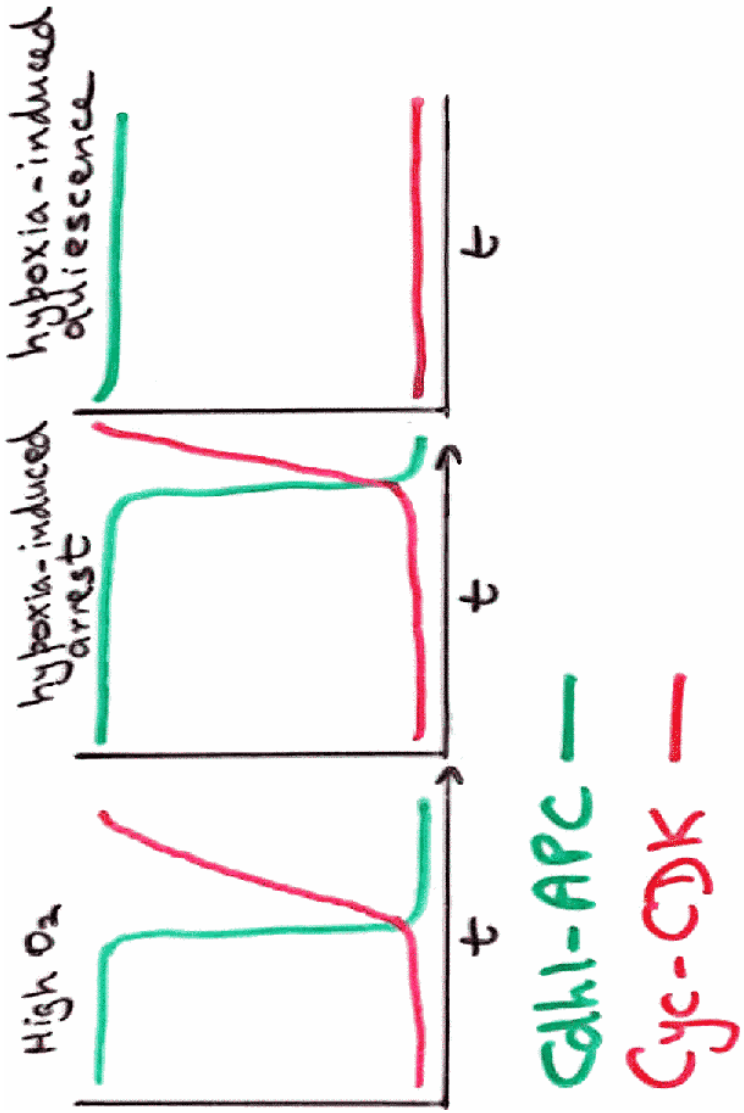
growth regulation [as m↑ z↓]

hypoxia

$$\frac{dz}{dt} = k_1 - \frac{k_2 P}{B+P} z$$

Cancer Cells

Hypothesis – growth regulation is lost



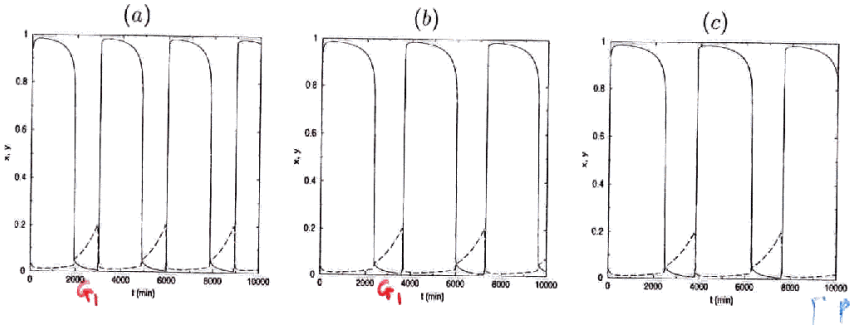


Figure 2: Numerical solutions of the system Eqs. (5)-(6) for different values of the oxygen tension P: (a) $P = 1$, (b) $P = 0.025$, (c) $P = 0.02$. Solid lines correspond to x and dashed lines to y. The parameter values used in this simulations are shown in Table 1.

Normal Cells
P↓ G1↑
agrees with expt
[P↓ 1/40 G1↑ 1/4]

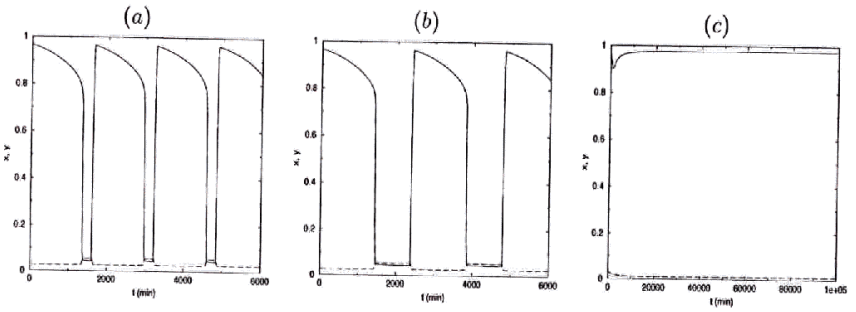
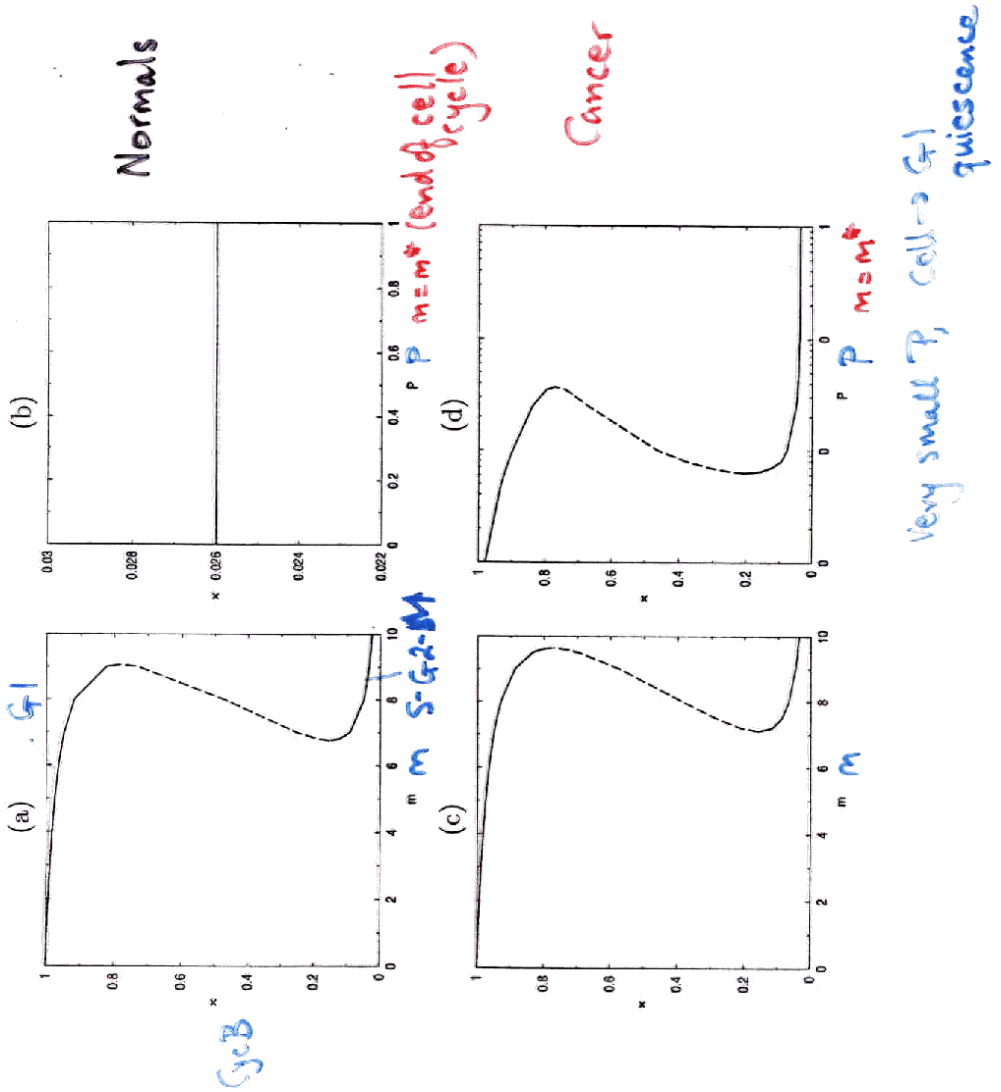


Figure 3: Numerical solutions of the system Eqs. Eqs (4)-(6) and (9)-(10) for different values of the oxygen tension P: (a) $P = 1$, (b) $P = 0.1$, (c) $P = 0.01$. Solid lines correspond to x and dashed lines to y. The parameter values used in this simulations are shown in Table 1.

Cancer Cells
P↓ ⇒ quiescence



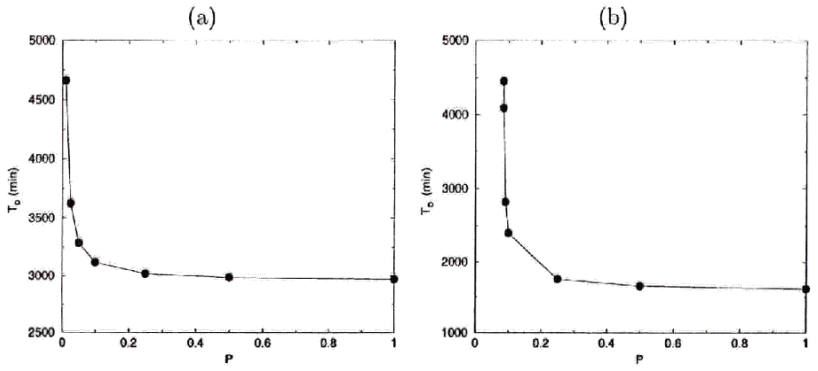
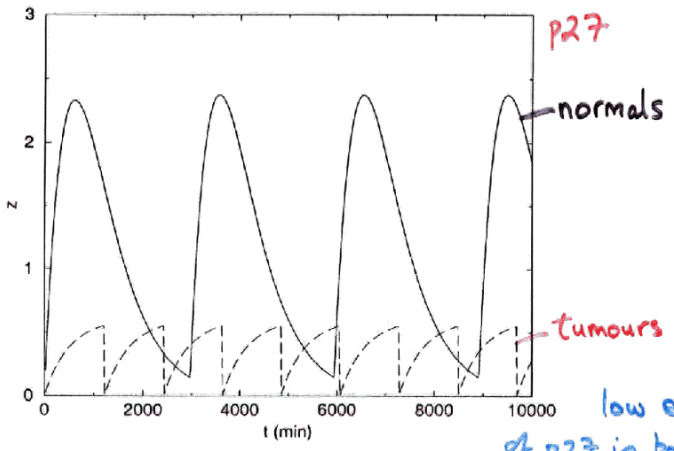


Figure 4: Division time as a function of the oxygen tension, P. (a): normal cells, (b): cancer cells. Note the vertical asymptote in (b) at $P \simeq 0.085$, which is the critical value of the oxygen tension for the transition to quiescence in cancer cells. The parameter values used in this simulations are shown in Table 1.

concentration of p27 increases as k_5/k_5' increases. Also, the division time is an increasing function of k_5/k_5'. However in this case we do not observe any divergence in T_D, which confirms that quiescence cannot be induced in this model.



low expression of p27 is poor prognostic factor (Kirla et al, 2003)

Figure 5: Comparison between the concentration of p27 protein predicted by our two different models. Solid line corresponds to normal cells whereas dashed line corresponds to cancer cells. The parameter values used in this simulations are shown in Table 1. See text for details.

Possible Application

Doxorubicin treatment of non-Hodgkin's lymphoma (Ben Ribba, Evia Agur, Tomas Alarcon, PKM, K. Mayer)

- Structural adaptation – Vessels surrounded by NHL ⇒ leaky/unstable

- Nutrient diffusion

- drug pharmacokinetics in plasma $\frac{dC}{dt} = -kC$

pharmacodynamics [kills proliferating cells]

tissue dynamics (adiabatic approx)

AIM – Explore different protocols of treatment (presently a 21-day cycle is employed)

Conclusion

- heterogeneities have a profound effect on tumour dynamics
- effects of p27 - possible mechanism
- efficency of drug treatments

Future Directions