Cancer Growth

Tissue Level Signalling (Tumour Angiogenesis Factors)
Oxygen etc

PDE

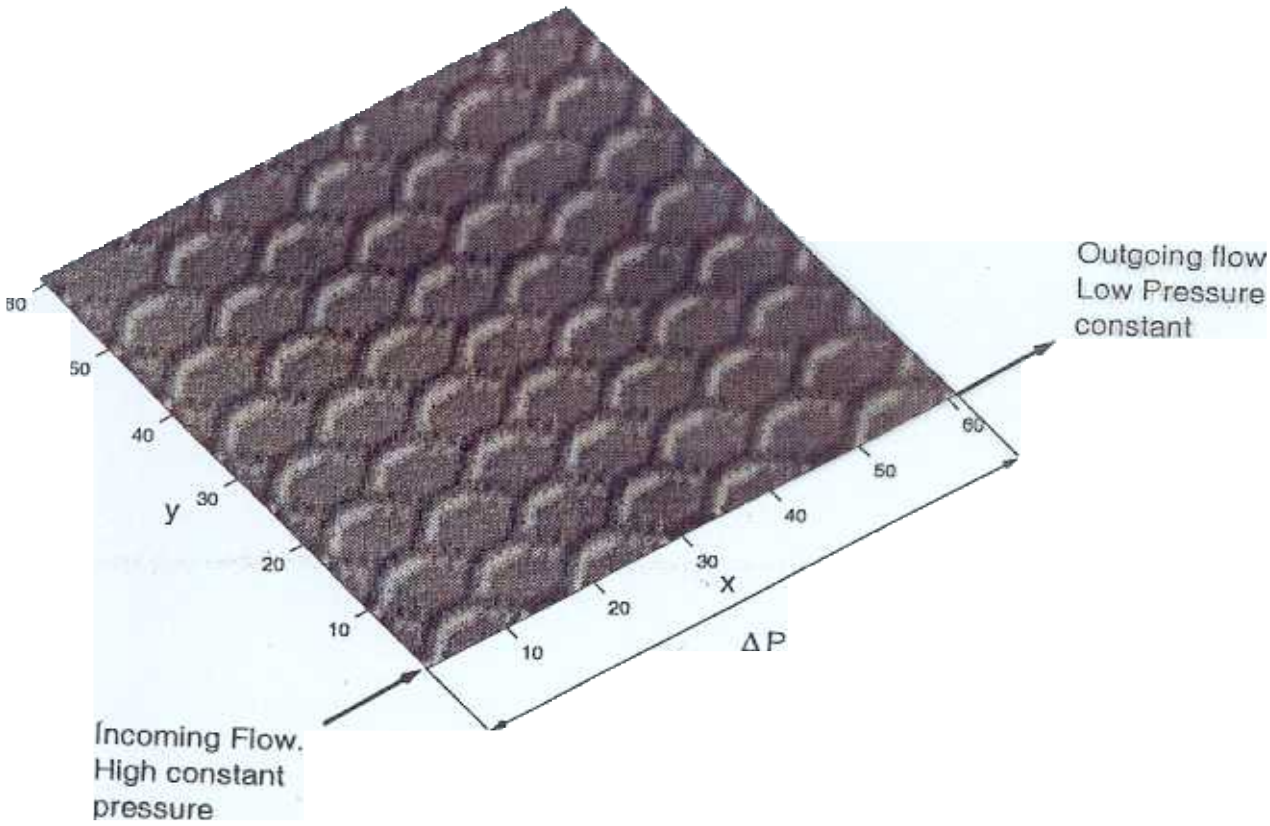
Cells

Automaton Elements

Intracellular Ce Cycle
molecular elements

ODEs

Alarcon Byrne PKM J theor Biol 225, 257-274 2003
~~to appear~~
in prep



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

Liver

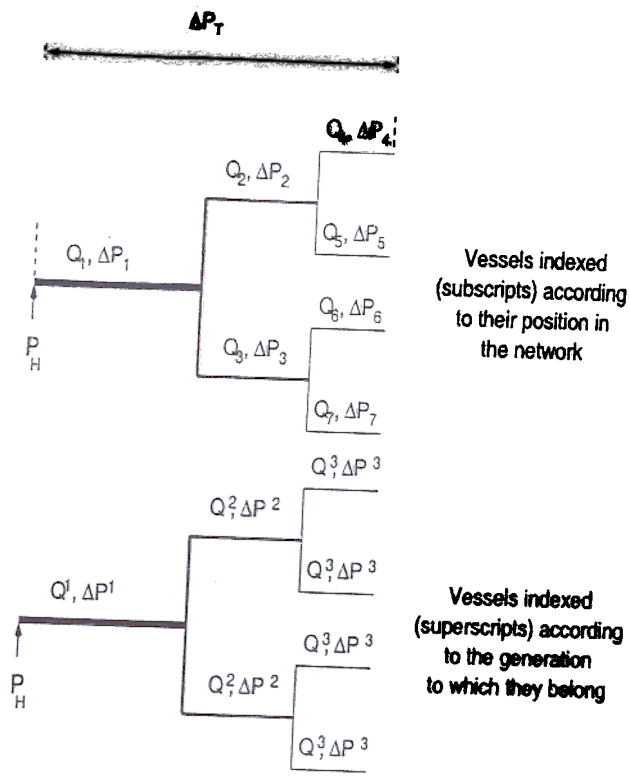


Fig. 5. Schematic representation of the branching structure used in our simulations. See text for details.

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)

Fahraeus-Lindquist effect

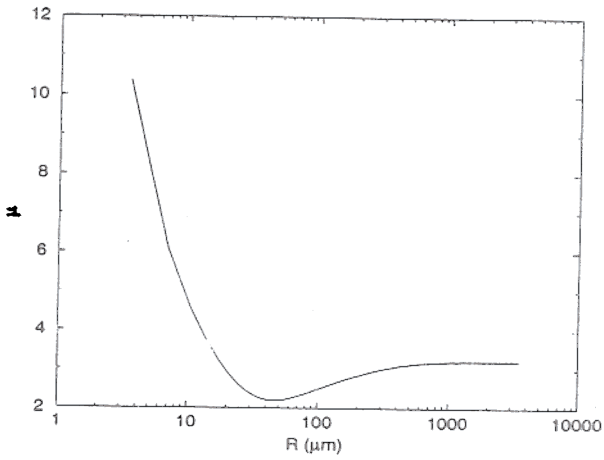


Fig. 3. Relative blood viscosity $\mu(R)$ as a function of the radius (R) of the vessel. Data from [10] for a proportion of the total volume of blood occupied by red blood cells (hematocrit) of 0.45. (Pries et al, 1994)

Blood rheology

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

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

$R_0 = 0.55$

$a_0 = 2.2$

$a_1 = 6$

$a_2 = 2.4$

$\lambda_1 = 0.17$

$\lambda_2 = 0.09$

$\gamma_2 = 0.645$

Reformulate Minimization principle

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

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.

Tumour Growth

First work out distribution of O_2 (nutrient)

To do so must consider vasculature

metabolic response

$$R(t+\Delta t) = R(t) + R\Delta t\left(\ln\left(\frac{\tau_w}{\tau(P)}\right) + k_m \ln\left(\frac{Q_{ref}}{Q+1}\right) + k_s\right)$$

response to mechanical stimuli

shrinkage

(Pries et al 1988)

R radius

Q flow rate

haematocrit

WSS

P pressure (transmural)

$\tau(P) = 86\exp(5000\ln(\ln P))^5$ (rat mesentry)

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

* At a bifurcation

$H_p = H_1 + H_2$

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

$H_2 = H_p$ if $\frac{V_1}{V_2} > T$

Algorithm for structural adaptation

① ΔP H_T prescribed

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

$\Rightarrow$ flow rate

② Given initial network configuration compute flow rates through and pressure drops across each vessel using Kirchoffs Law

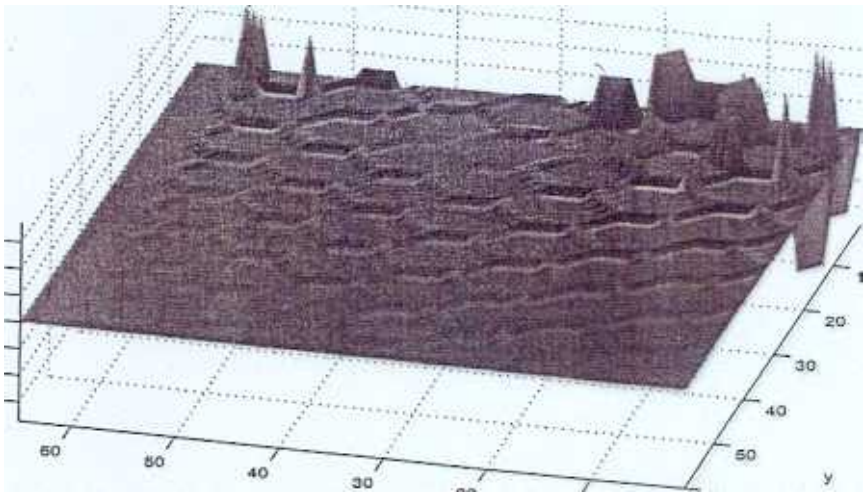
③ Compute distribution of haematocrit

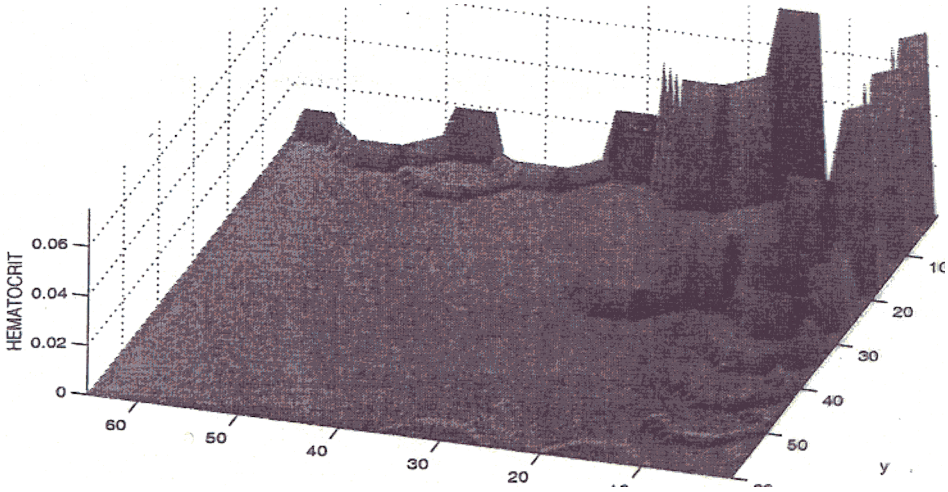
④ Update radius of each vesse

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

⑥ Repeat until steady state reached

Results





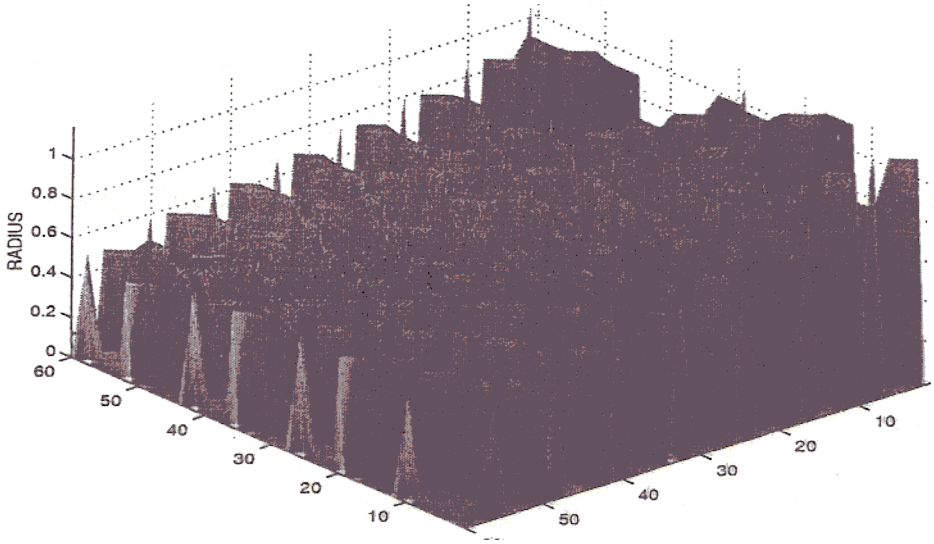


Figure 4:

Automaton Rules

① O_2 distribution determined by BVP

② [illegible]

③ Normal cell if O_2 < threshold cell dies

> 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 neighbour

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

are sinks of O_2

(7) If O_2 level is such that a cell can divide sample neighbourhood for space

If more than one available space go to the one with largest $(\cdot)_2$ Patel et al 200

If no space die (Kansal et al 2000)

O_2 distribution

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

P O_2 conc

$k(\underline{x})$ k_N for normal cell
k_c for cancer cel
0 o w.

BC $-D_p \underline{n}_w \nabla P \quad \mathcal{P}(P_b \; P)$

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

P_b O_2 level in blood

$\mathcal{P}$ permeability

$\underline{n} \quad \nabla P = 0$ (at edge of domain no flux)

Cell Dynamics

N×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

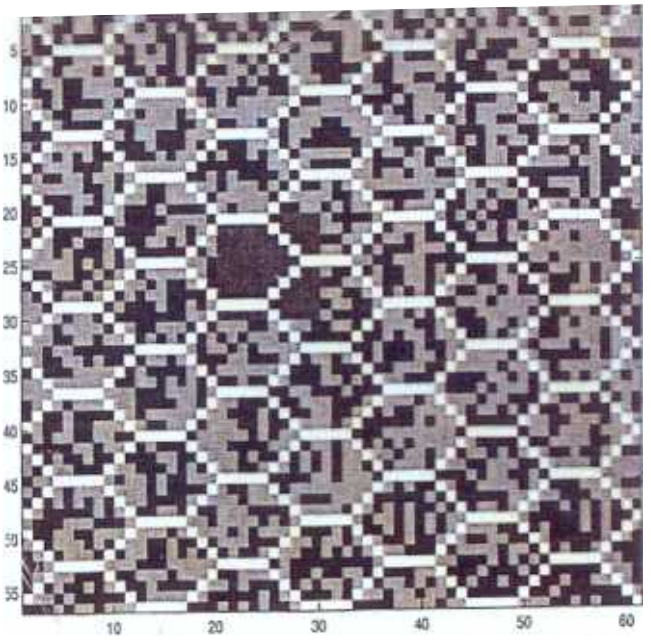
Parameters

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	$1.57 \cdot 10^{-4}$	$ml O_2\, ml^{-1} s^{-1}$	Goldman and Popel (2000)
K_T	$1.57 \cdot 10^{-4}$	$ml O_2 ml^{-1} s^{-1}$	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	

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

m = molecular wt

G = glucose (Patel et al 2001)

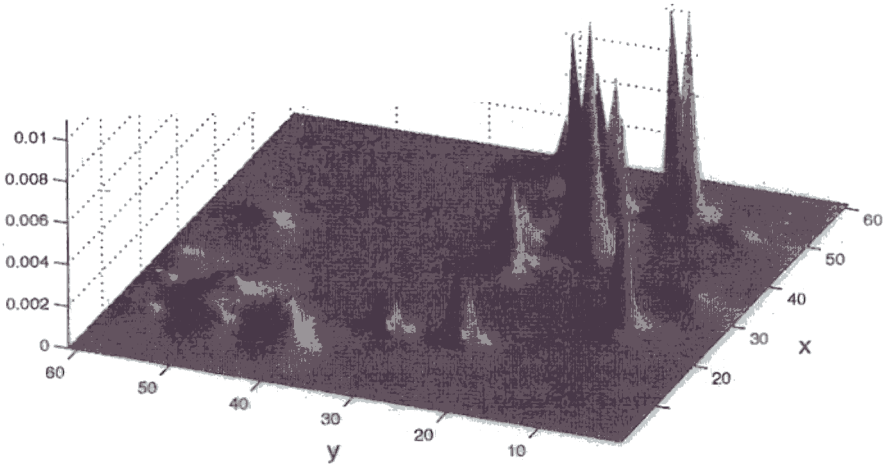


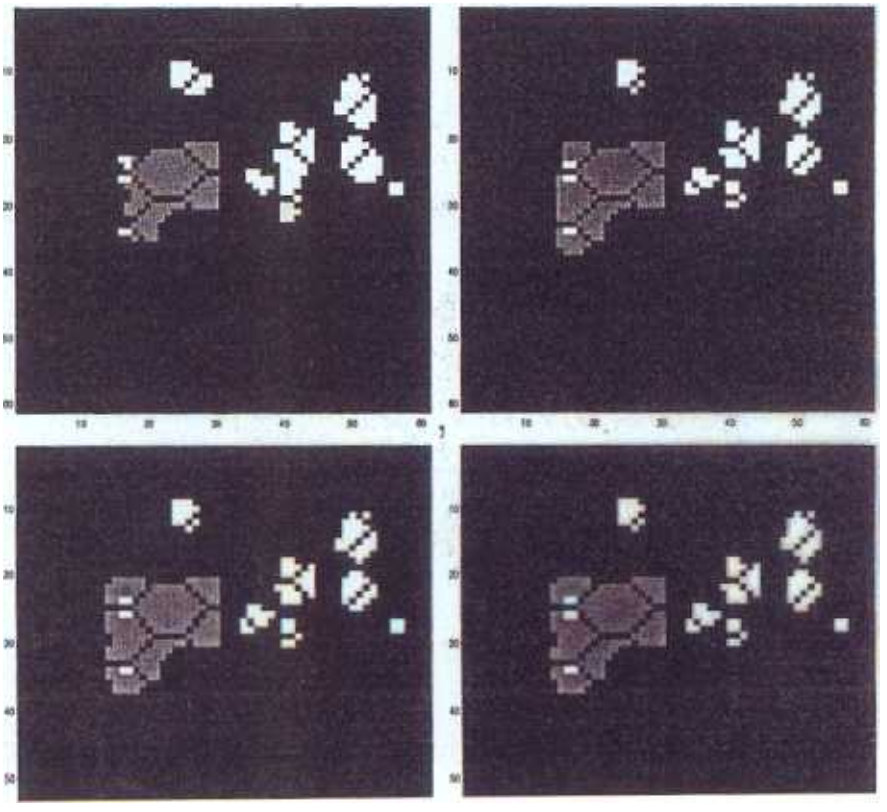
Invasion Dynamics

Heterogeneou

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

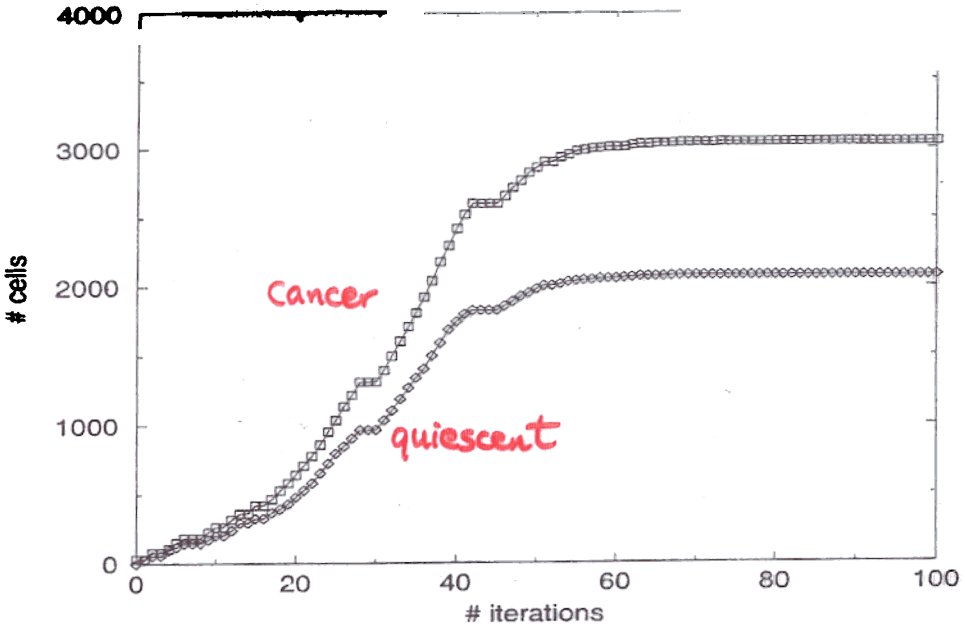
O_2 distribution





Invasion dynamics

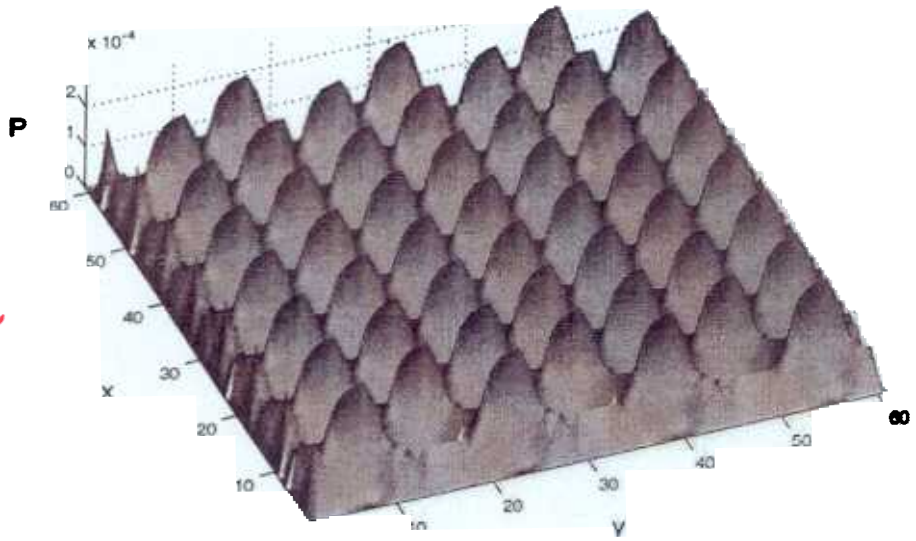
- □ normal
- ■ empty or blood vessa
- grey - cancer

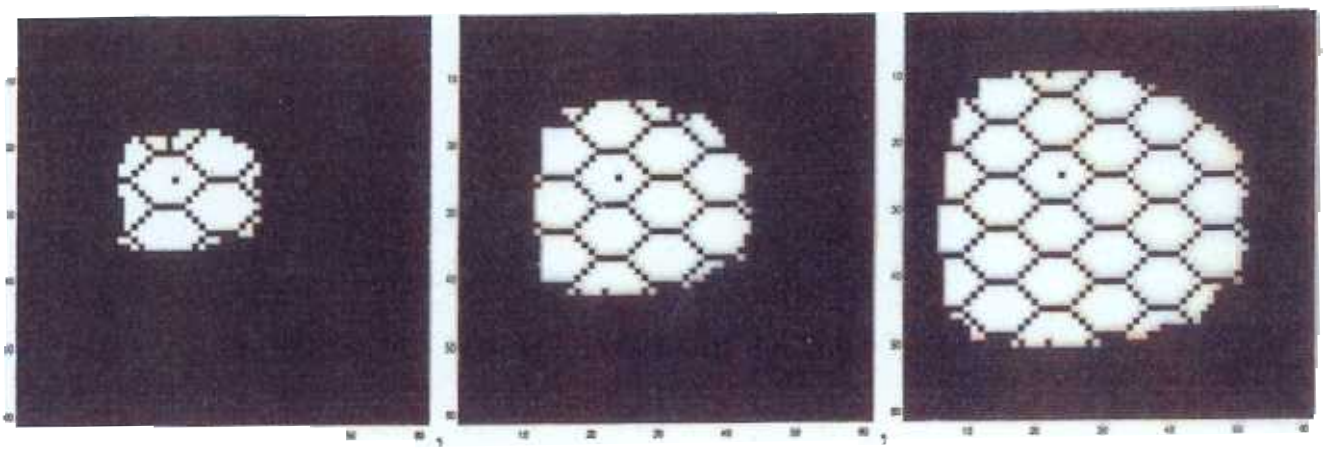


Corresponding homogen case

normals ↓ 0

O_2 distribution



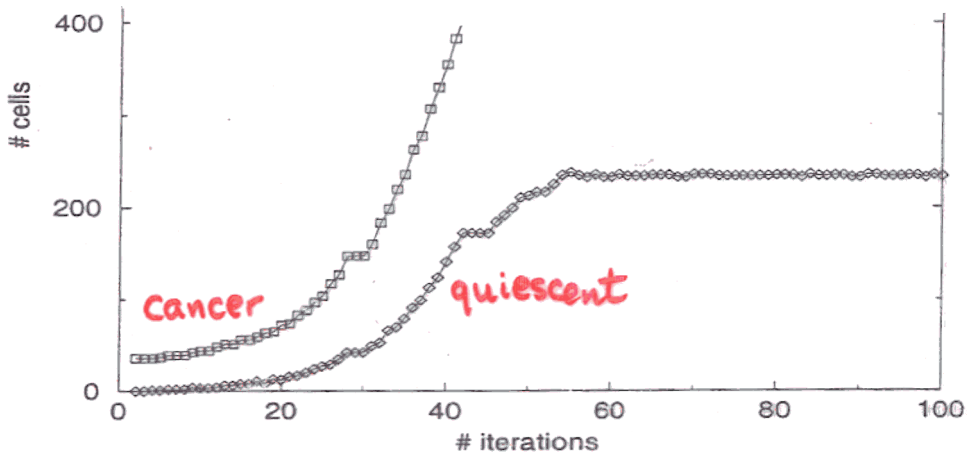


Growth dynamics

[redacted]

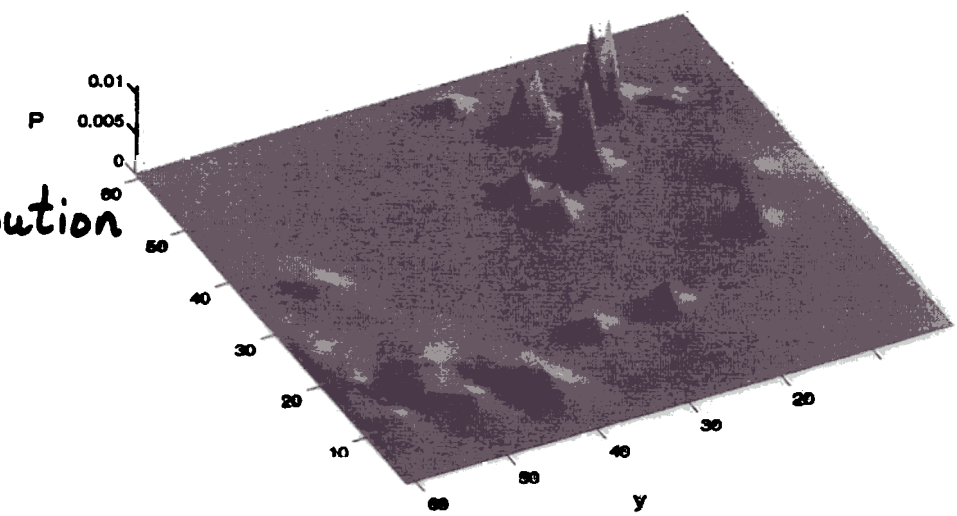
Results

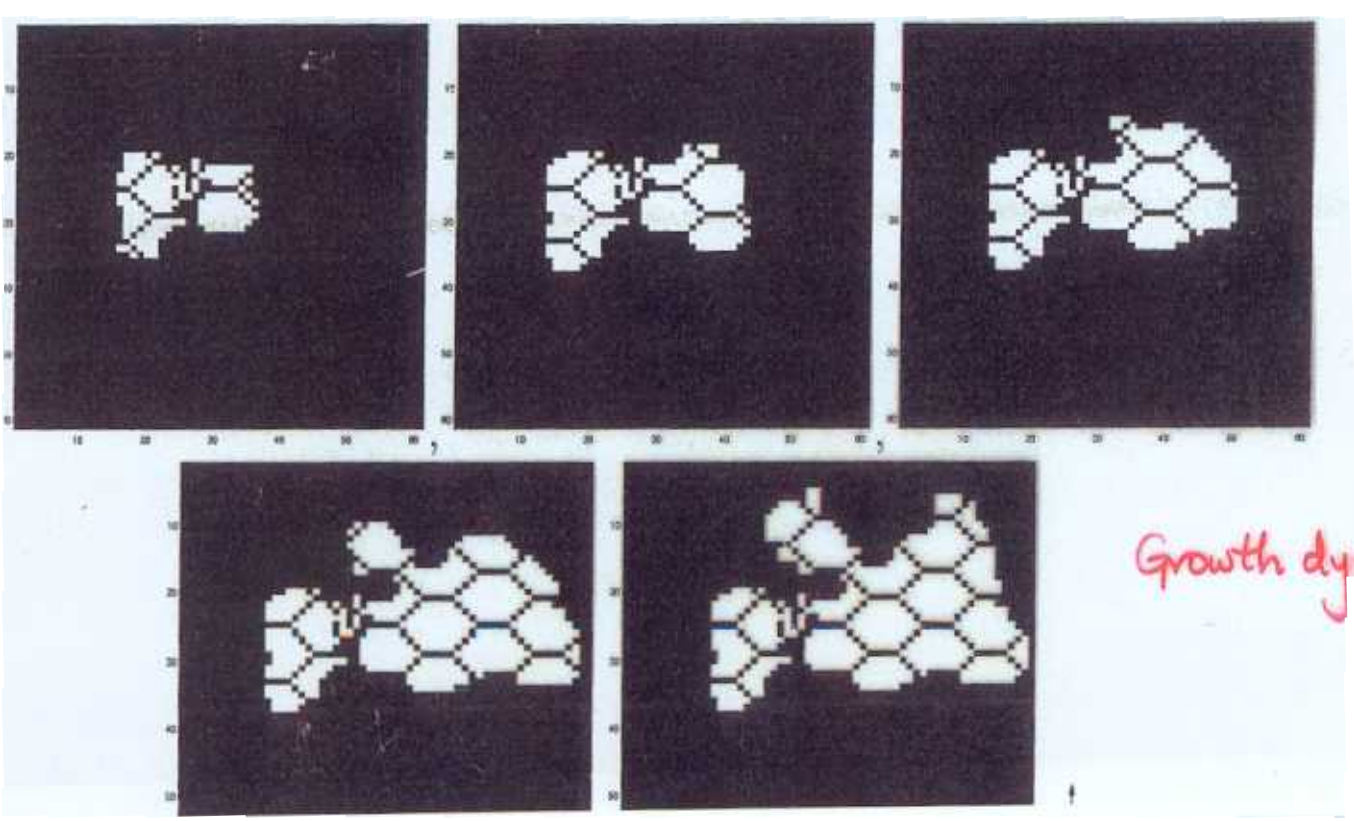
Heterogeneous Case



normals ↓ 0

O_2 distribution





Growth dynamics

N .ON

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

Cell-Cycle Dynamics

- Why?

nutrient demand

hypoxia-induced quiescence

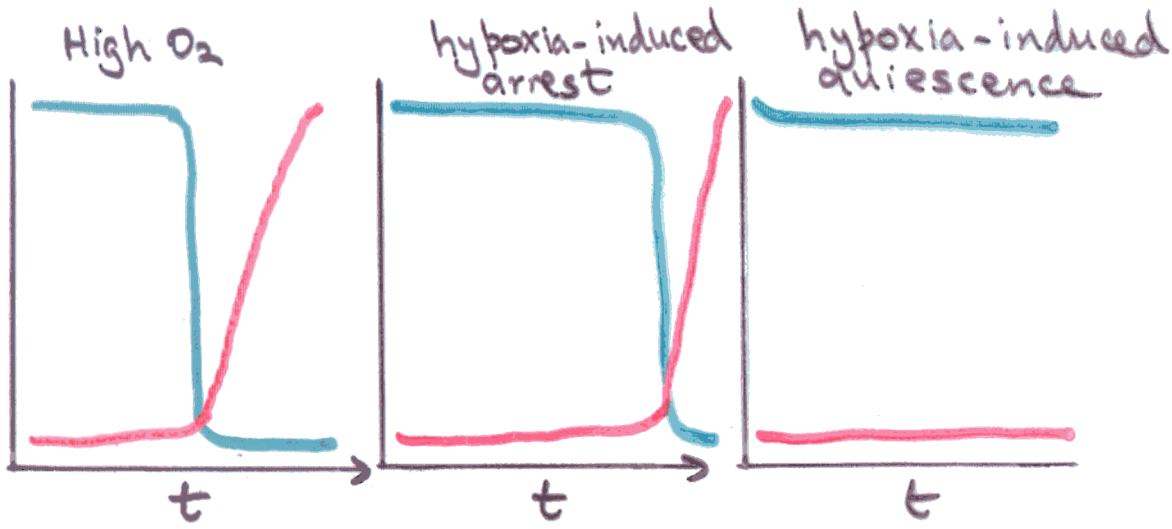
drugs work only on cells in a certain part of their cell cycle.

Cell Cycle G_1 S G_2

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

In G_1, CDK activity slow because its cyclin partners are missing

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



Cdh1-APC —

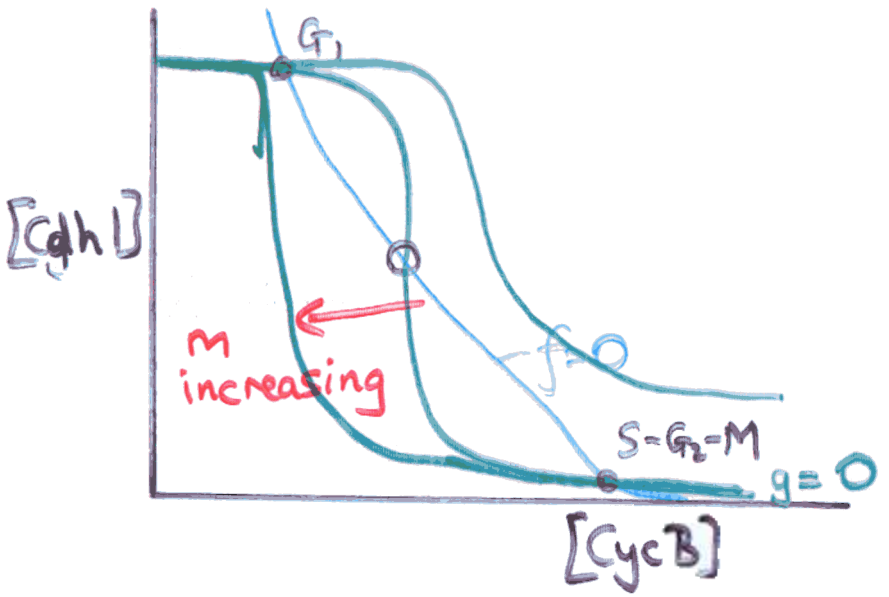
Cyc-CDK —

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

Tyson & Novak

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

mass of cell



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

This is a model for the G S transition – NOT the cell cycle.

Response to hypoxia (ow O_2)

Expts on mouse embryo fibroblasts

Normal cells $\xrightarrow{\text{hypoxia}}$ G arest

Does not occur with p27 nu mutants

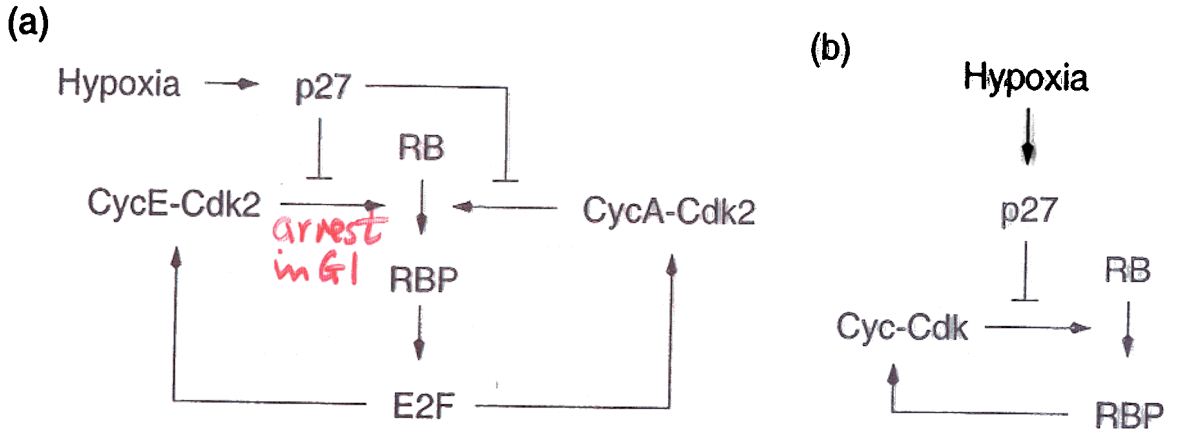


Figure 1: Schematic representation of the mechanism for hypoxia-induced cell-cycle arrest. (a) The original mechanism proposed by Gardner et al (2001). (b) Our simplified version for modelling purposes. RBP stands for the phosphorylated form of the RB protein.

E2F - transcription factor

Take Tyson & Novak model:

incorporate inhibition by a $-kz$ term

p27 conc. in Cdh1

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

Normals

growth regulation [as $m\uparrow$ $z\downarrow$]

oxygen

hypoxia

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

Cancer Cells

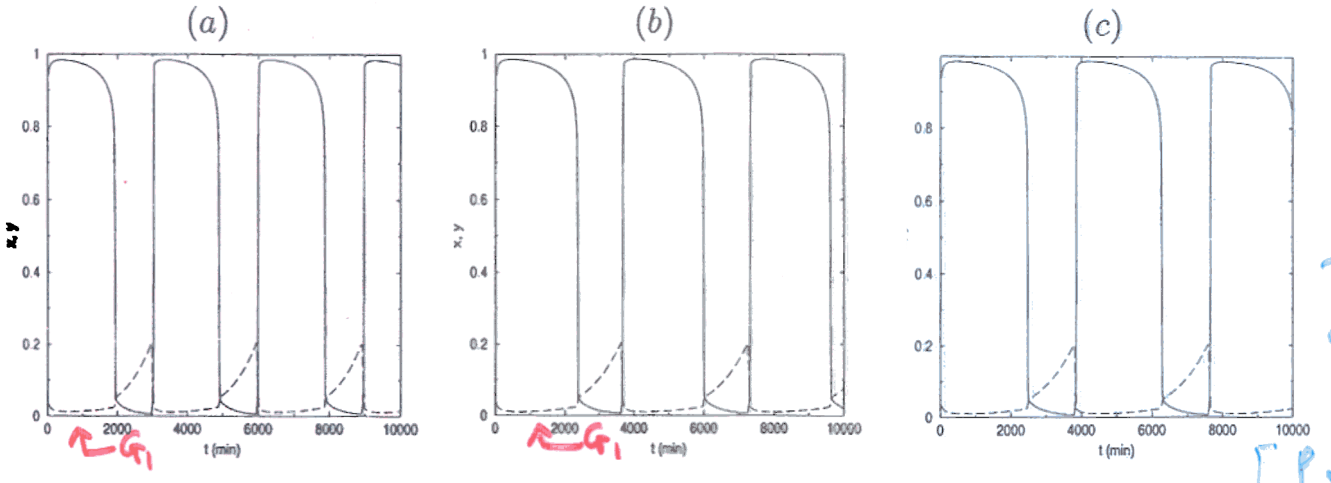
Hypothesis – growth regulation is lost

Growth regulation of p27?

↑ Growth factors ⟹ p27 ↓

Normals ✓
Cancer ✗

If growth is arrested, p27 is upregulated



Normal Cells

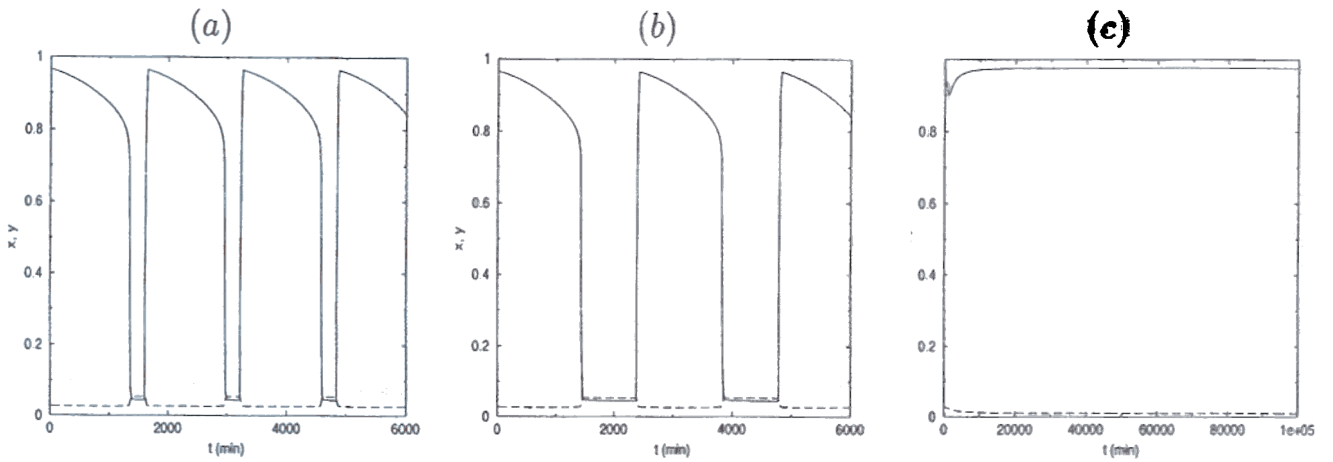
P↓ G_1↑

agrees wi exp't

[P↓ 1/40

G_1↑ 1/4]

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.

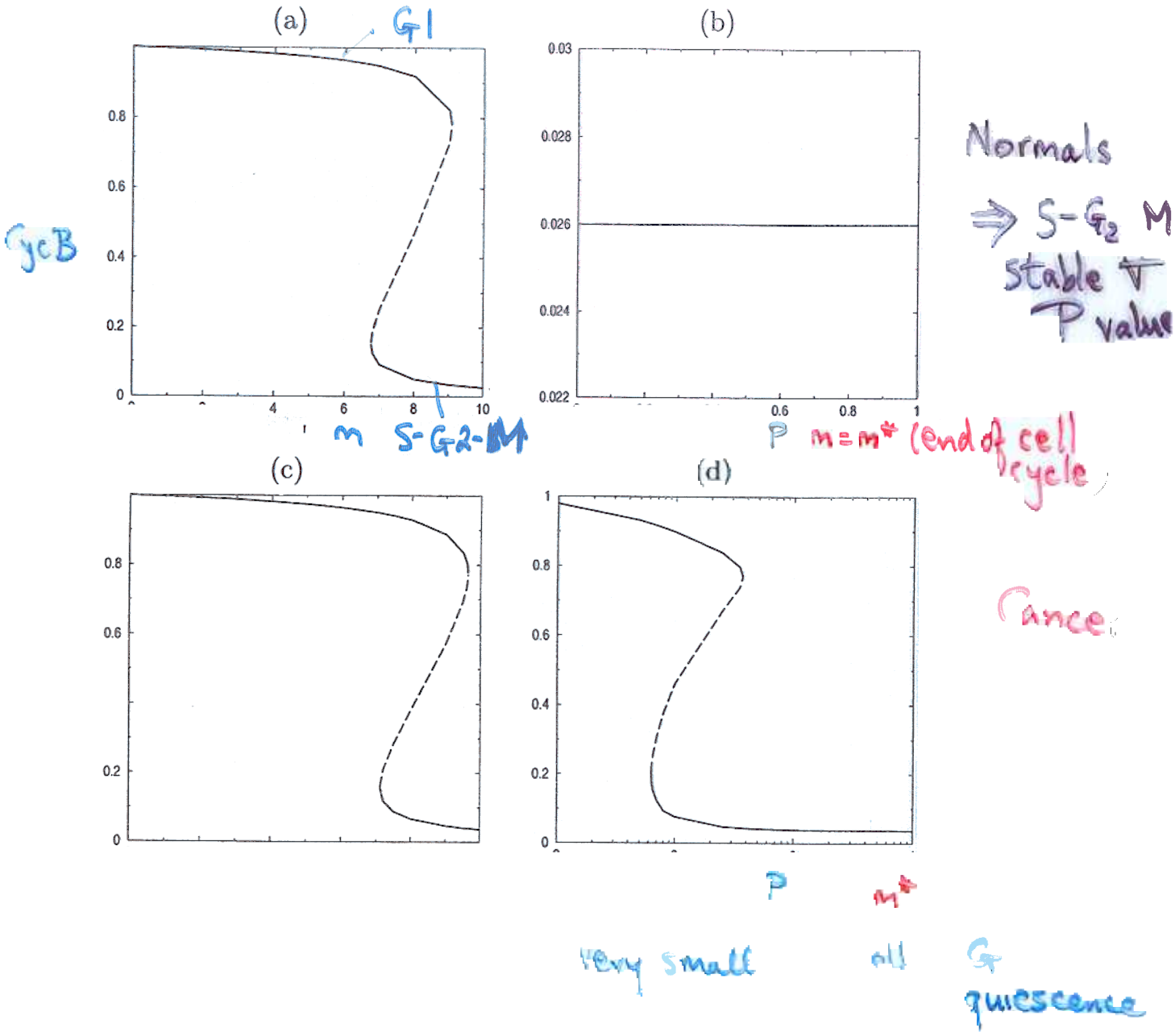


Cancer Cells

P↓ [illegible]

quiescen

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.


(a)
G1
0.8
0.6
0.4
0.2
0
4
6
8
10
CycB
m
S-G2-M
(b)
0.03
0.028
0.026
0.024
0.022
0.6
0.8
1
P
m=m* (end of cell cycle)
Normals
⇒ S-G2 M
stable ∀ P value
(c)
0.8
0.6
0.2
0
(d)
1
0.8
0.6
0.4
0.2
0
P
m*
Cancer
very small
all
G
quiescence

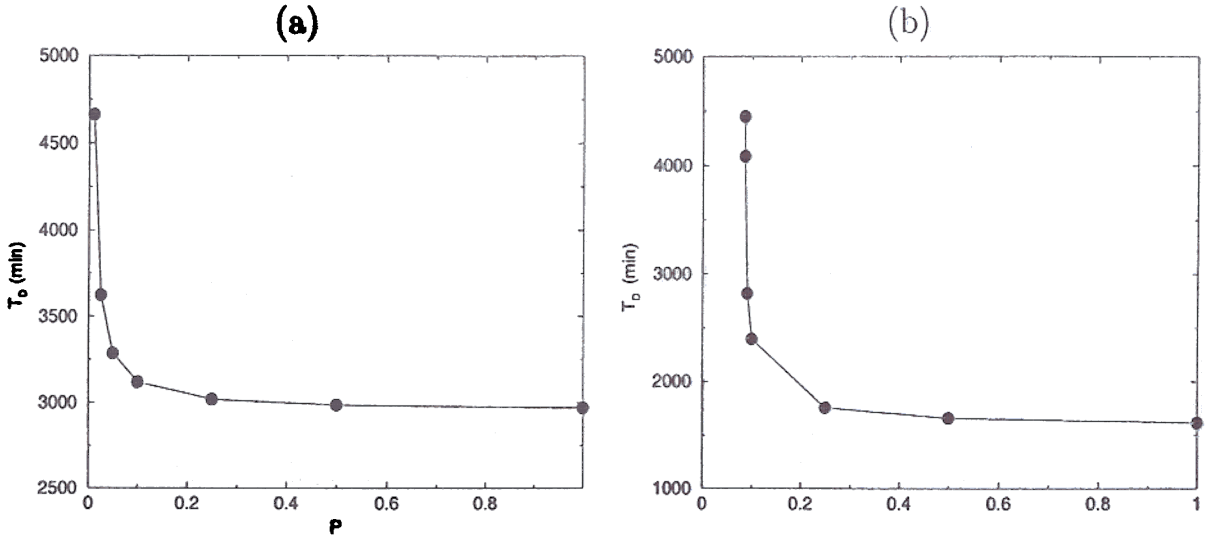
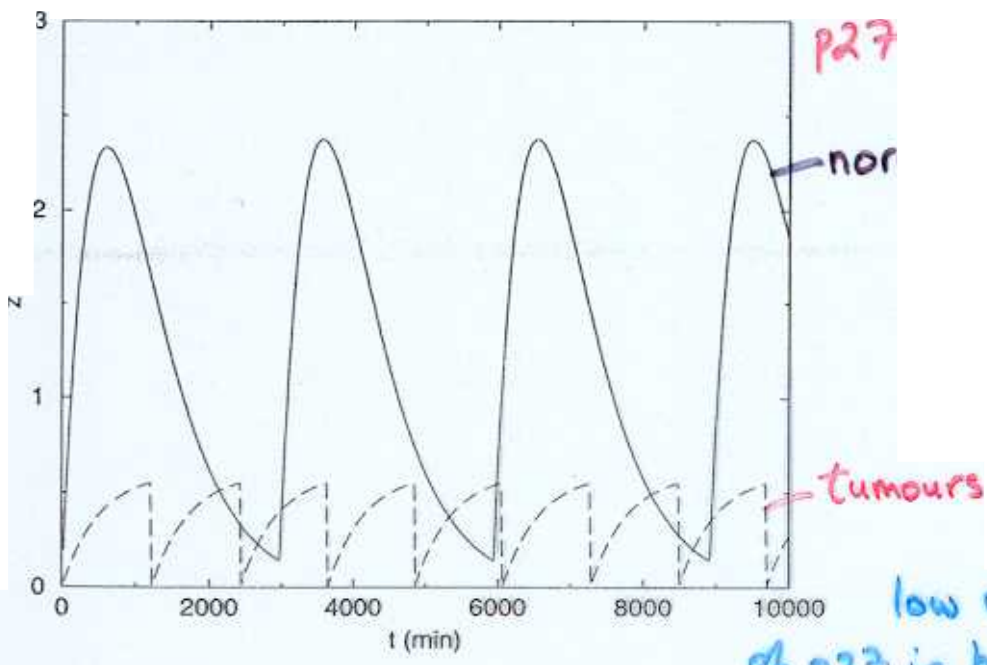


Figure 4: Division time as a function of the oxygen tension, P. (a): normal cells, (b): cancer cells. Note the vertical asymptote in (b) at $P \simeq 0.085$, which is the critical value of the oxygen tension for the transition to quiescence in cancer cells. The parameter values used in this simulations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

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 Hodgkins lymphoma

(Ben Kibba, Evia Agur Tomas Alarcon FKM)
K Marron

Structural adaptation — Vessels surrounded by NHL ⇒ leaky & unstable

Nutrient diffusion

drug pharmacokinetics in plasma $\frac{\partial c}{\partial t}$ kc

pharmacodynamics kills proliferating cells

tissue dynamics adiabatic approx

AIM Explore different protocols of treatment (presently a 2 day cycle is employed

CONCLUSION

- heterogeneities have a profound effect on tumour dynamics

  effects of p27 possible mechanism

- efficency of drug treatments

Future Directions