Cancer growth and therapy and the use of mathematical models

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http://www-rocq.inria.fr/bang/JC/Jean_Clairambault.html

Abstract:

I shall present some important principles governing the development of cancer at the cell, tissue and whole organism levels, and how each of them is the result of the disruption of physiological mechanisms which control cell proliferation and migration.

Current medical cytotoxic therapies, their pitfalls and proposed ways to overcome them will be reviewed, taking these mechanisms into account.

Then I will show a variety of mathematical models which have been used to describe cancer growth and its control by pharmacological means, and examples of anti-cancer therapeutic optimisation procedures based on such models.

Plan of the talk

Natural history of cancers: a multiscale vision

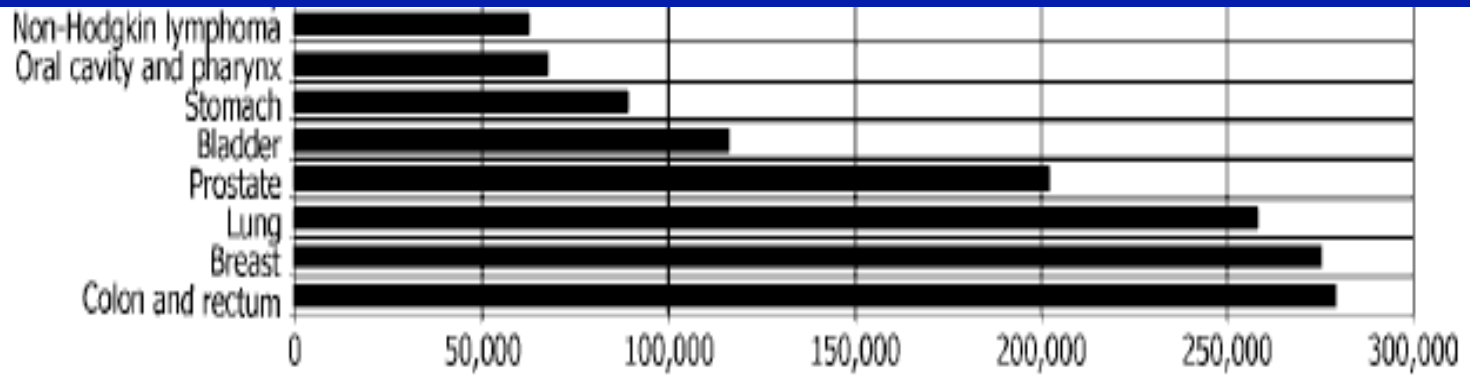
Cancer therapeutics: current regimens and pitfalls

Various models of cancer growth and therapy

Using mathematical models to optimise therapy

Cancer, a major public health problem in Europe

2 major killers in Western Europe:
Cardio-vascular diseases: 35% of deaths by disease, and Cancer: 25%
(precise data according to zones and countries: http://www.euro.who.int)



*Estimated **incidence** of main cancers in the EU in 2004, extracted from Boyle & Ferlay, Ann. Oncol. 2005*

Tissues that may evolve toward malignancy

…are the tissues where cells are committed to proliferate:

-epithelial cells+++, i.e., cells belonging to those tissues which cover the free surfaces of the body (namely *epithelia*): gut (colorectal cancer), lung, glandular coverings (breast, prostate),…

-cells belonging to the different blood lineages, produced in the bone marrow: liquid tumours, alias malignant haemopathies

-others (rare: sarcomas, neuroblastomas, dysembryomas…)

Natural history of cancers: from genes to bedside

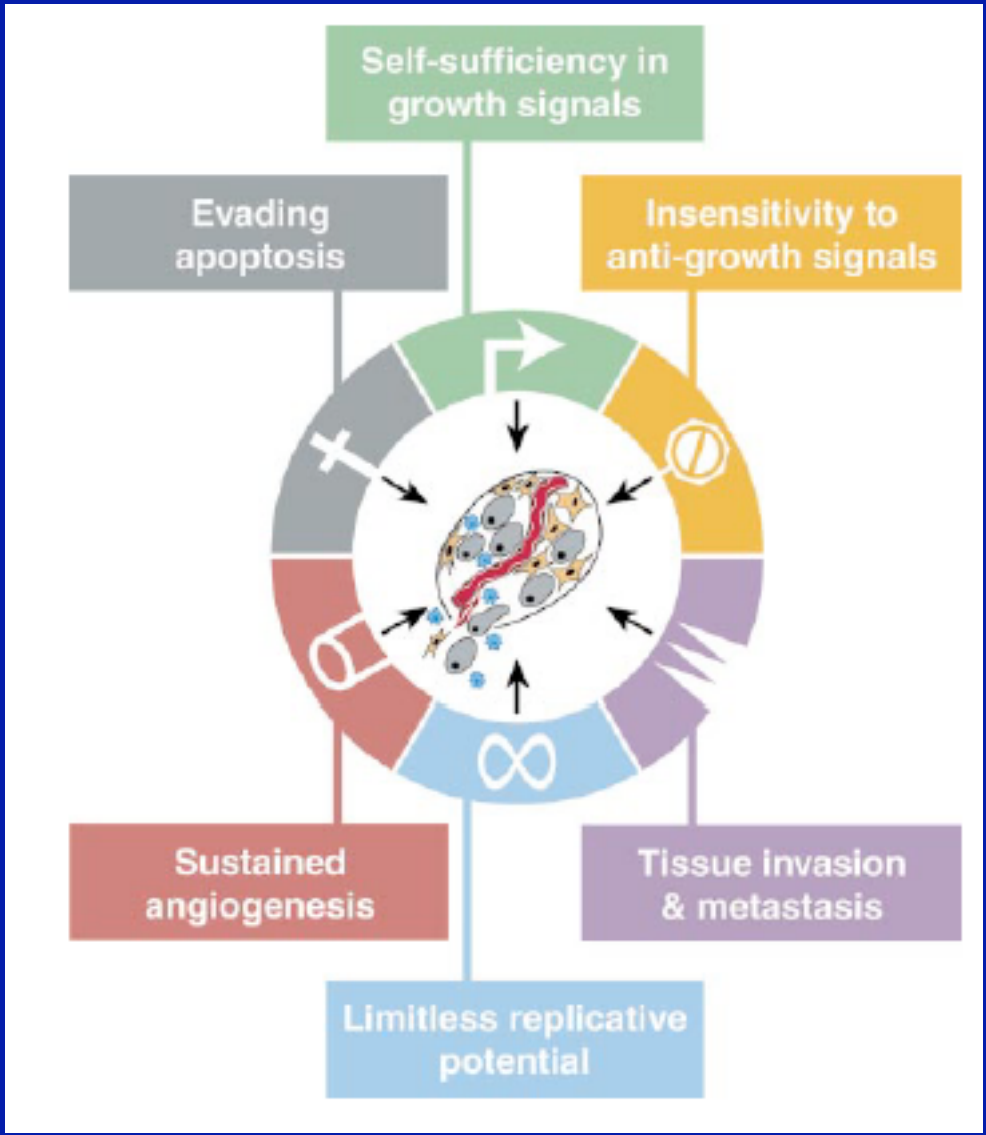
Gene mutations: an evolutionary process which may give rise to abnormal DNA when a cell duplicates its genome due to defects in tumour suppressor or DNA mismatch repair genes *(Yashiro, M et al. Canc Res. 2001; Gatenby, RA, Vincent, TL. Canc. Res. 2003)*

Resulting *genomic instability* allows malignant cells to escape proliferation and growth control at different levels: subcellular, cell, tissue and whole organism:

- Enhancing entry in the cell proliferation cycle for quiescent (=non-proliferating) cells
- Skipping phase transitions and apotosis [=controlled cell death] for cycling cells
- Using anaerobic glycolysis (selective advantage for cancer cells)
- Suppressing contact inhibition by surrounding cells (chemicals, density pressure)
- Escaping or dissolving links to the extracellular matrix (ECM) and basal membranes
- Stimulating sprouting of new blood vessels from the neighbouring vessels (angiogenesis)
- Modifying recognition (friend or foe) by the immune system

Cancer invasion is the macroscopic result of these breaches in control mechanisms

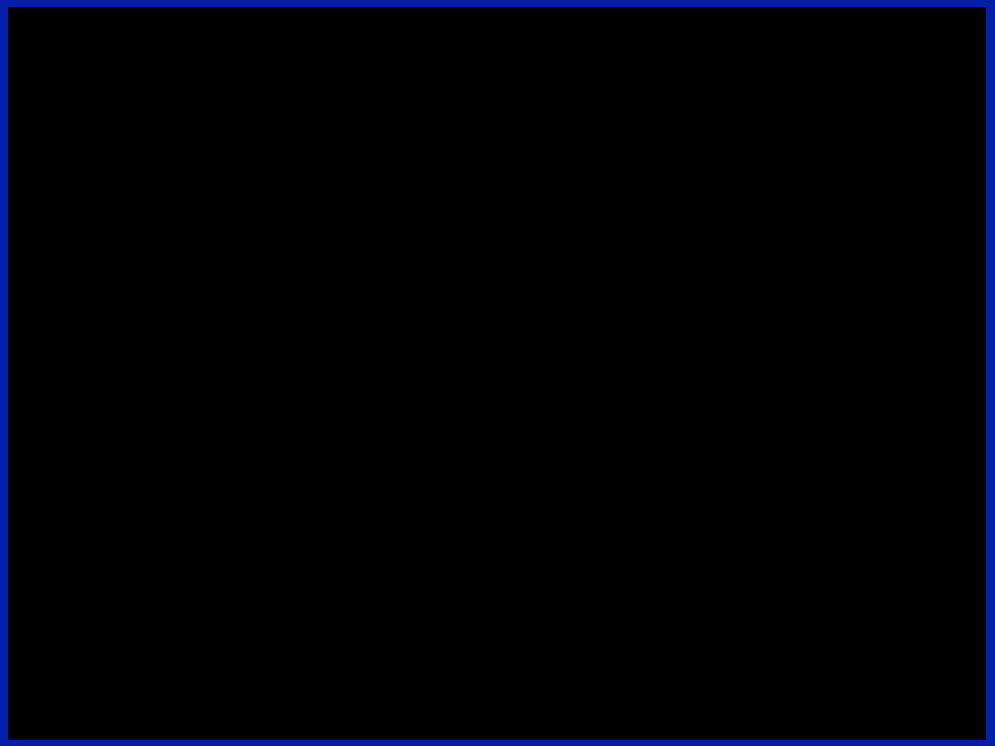
Evading proliferation and growth control mechanisms



(After Hanahan & Weinberg, Cell 2000)

…but just what is cell proliferation?

Cell population growth in proliferating tissues

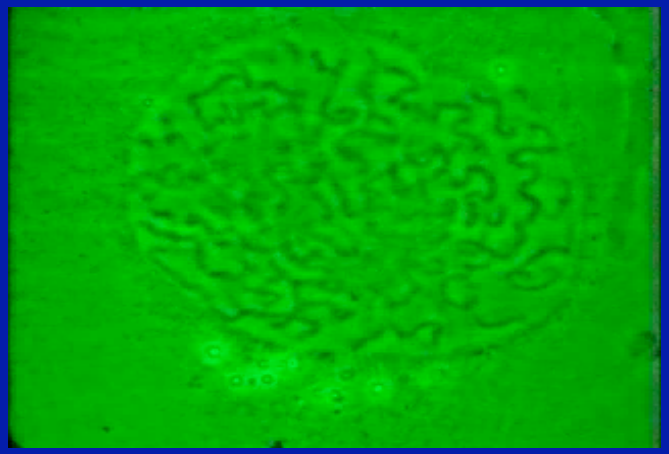


(after Lodish et al., Molecular cell biology, Nov. 2003)

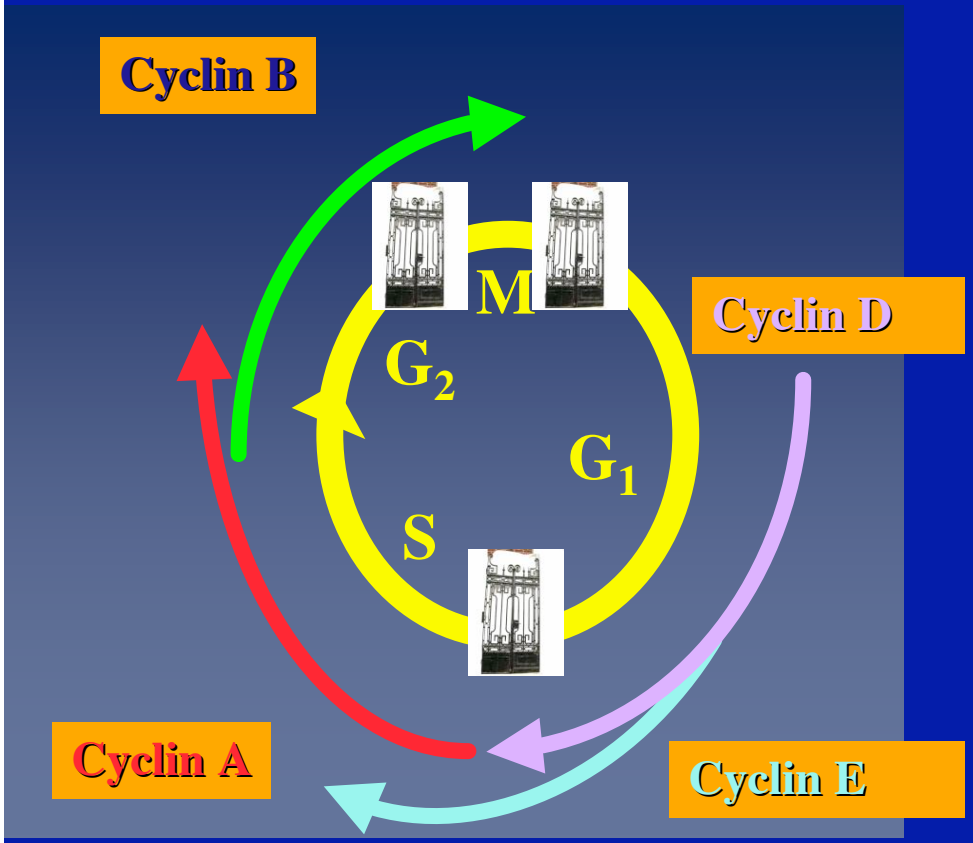
One cell divides in two: a controlled process at cell and tissue levels

At the origin of proliferation: the cell division cycle

S:=DNA synthesis; G_1,G_2:=Gap1,2; M:=mitosis↦



(after Lodish et al., Molecular cell biology, 2003)



(Image thanks to F. Lévi)

Physiological or therapeutic control exerted on:

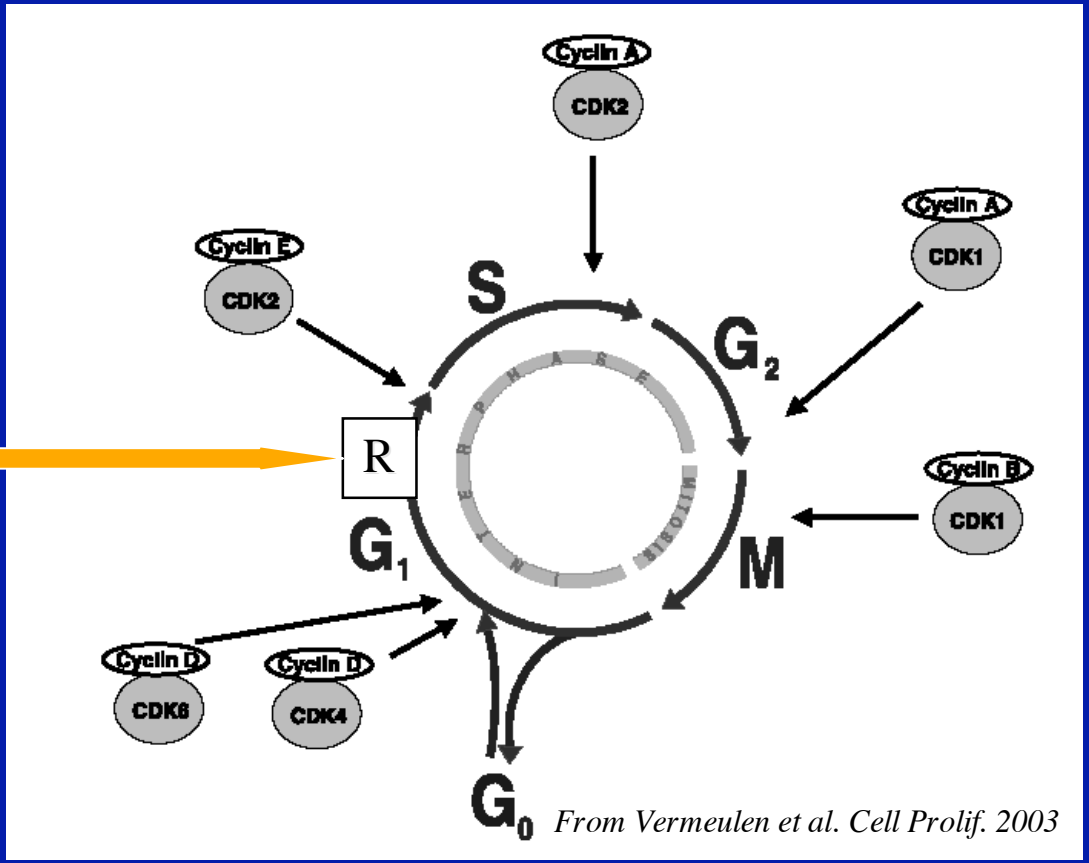
- transitions between phases (G_1/S, G_2/M, M/G_1)
- death rates (apoptosis or necrosis) inside phases

Proliferating (G_1/S/G_2/M) and quiescent (G_0) cells

after R:
mitogen-independent
progression through G_1 to S
(no way back to G_0)

Restriction point
(late G_1 phase)

before R:
mitogen-dependent
progression through G_1
(possible regression to G_0)



From Vermeulen et al. Cell Prolif. 2003

Most cells do not proliferate physiologically, even in fast renewing tissues (e.g. gut)

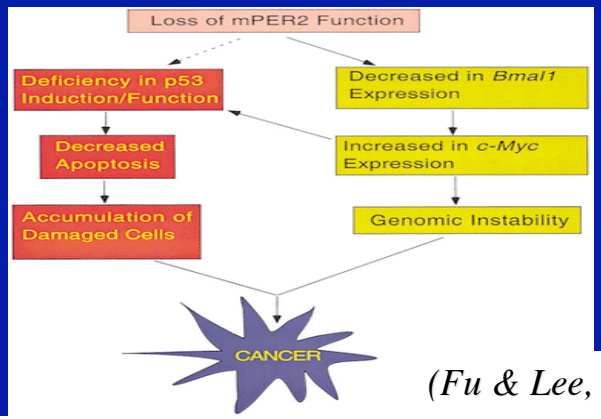
Exchanges between proliferating (G_1/S/G_2/M) and quiescent (G_0) cell compartments are controlled by mitogens and antimitogenic factors in G_1 phase

Phase transitions, apoptosis and DNA mismatch repair

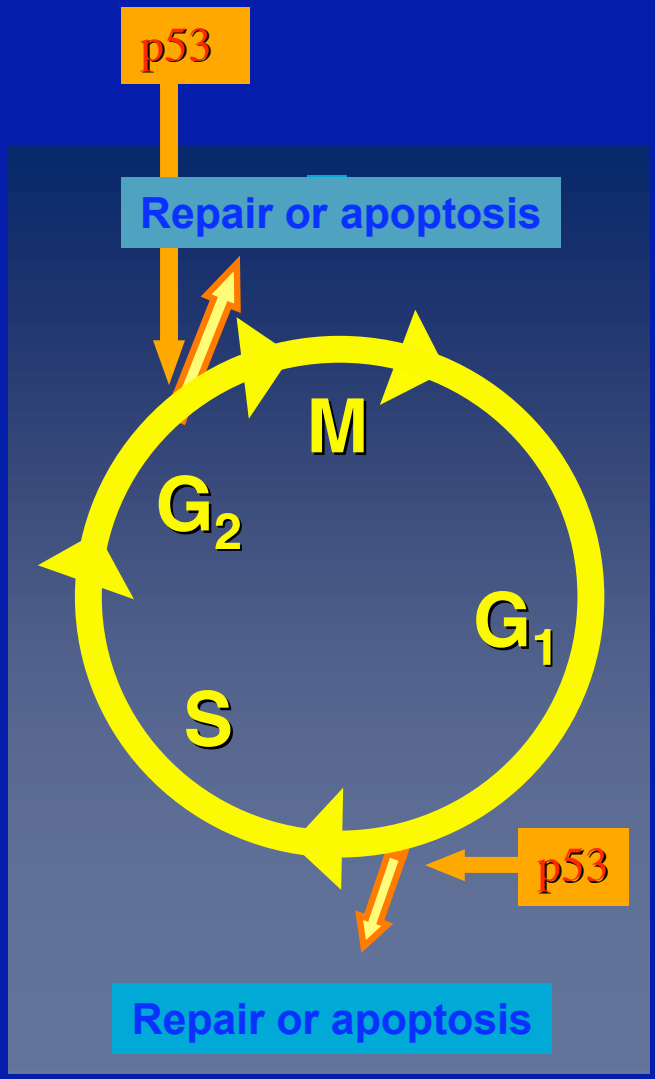
-Sensor proteins, e.g. p53, detect defects in DNA, arrest the cycle at G_1/S and G_2/M phase transitions to repair damaged fragments, or lead the whole cell toward controlled death = apoptosis

-p53 is known to be mutated (resulting in inefficient control) in 50% of cancers

-Physiological inputs, such as circadian gene PER2, control p53 expression; circadian clock disruptions (*shiftwork*) may result in low p53-induced genomic instability and higher incidence of cancer



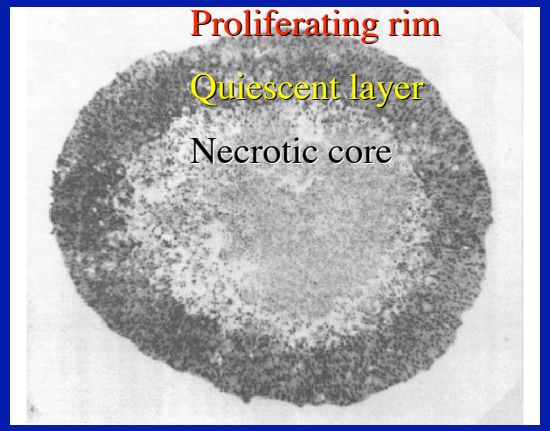
(Fu & Lee, Nature Rev. 2003)



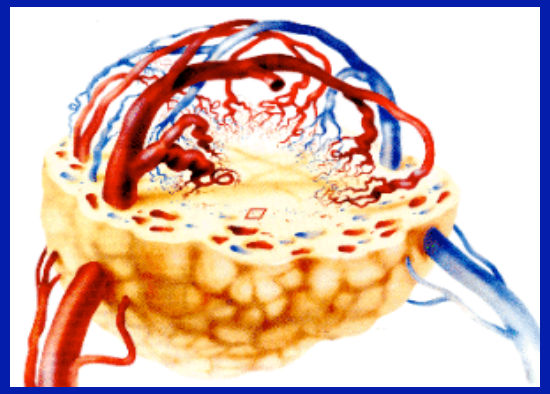
(Image thanks to F. Lévi)

Invasion, local and remote

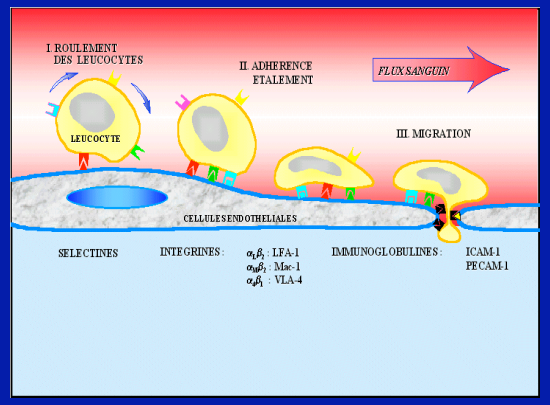
Local invasion by tumour cells implies loss of normal cell-cell and cell-ECM (extracellular matrix) contact inhibition of size growth and progression in the cell cycle. ECM (fibronectin) is digested by tumour-secreted matrix degrading enzymes (MDE=PA, MMP) so that tumour cells can move out of it. Until 10^6 cells (1 mm d) is the tumour in the *avascular stage*.



To overcome the limitations of the avascular stage, local tumour growth is enhanced by tumour-secreted endothelial growth factors which call for blood vessel sprouts to bring nutrients and oxygen to the insatiable tumour cells (*angiogenesis*, vasculogenesis)



Moving cancer cells can achieve intravasation, i.e., *migration* in blood and lymph vessels (by diapedesis), and extravasation, i.e. evasion from vessels, through vascular walls, to form new colonies in distant tissues. These colonies are called metastases.



(Images thanks to A. Anderson, M. Chaplain, J. Sherratt, and Cl. Verdier)

Interactions with the immune system

Tumours are antigenic, i.e., recognisable as foes by the immune system:

Innate immunity: *Cytokines*, macrophage-produced molecules to protect intact cells

(non specific) (e.g. interferon)

NK Lymphocytes = cells which sense foe antigens, migrate (receptors->modifications of cytoskeleton) into blood and tissues to kill antigenic cells

Adaptive immunity: *B Lymphocytes* produce specific antibodies (immunoglobulins)

(immune memory)

Helper T-Lymphocytes produce cytokines (e.g. interleukins) which boost the immune response

Cytotoxic T-Lymphocytes kill specific antigenic cells

Cancer therapeutics summed up

- Surgery: highly localised
- Radiotherapy: localised, kills all renewing cells… including tumour cells
- Chemotherapy: -usually general, adapted to diffuse and metastatic cancers

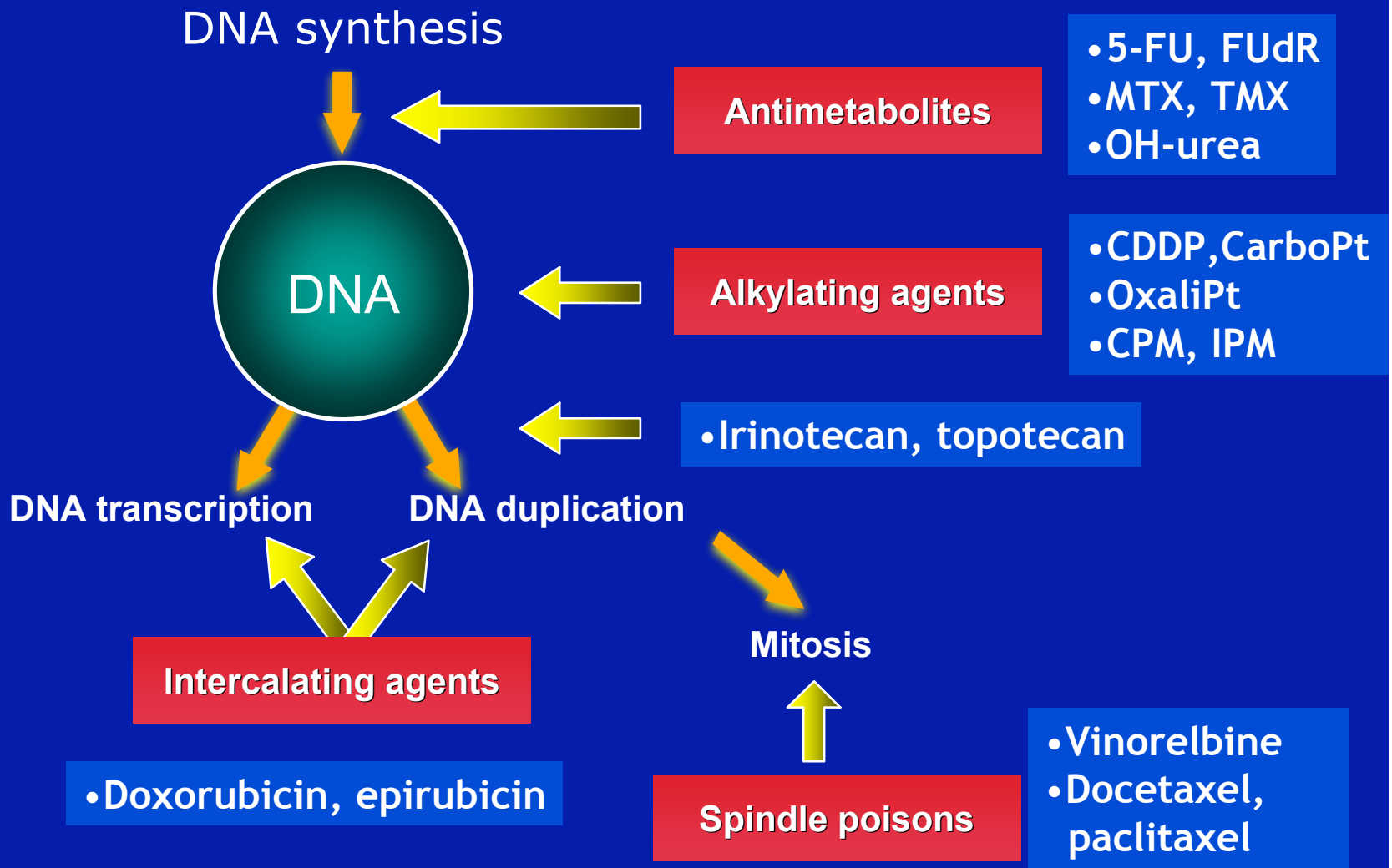
  acts on all renewing cells at the subcellular level (degrading DNA, blocking phase transitions, inducing apoptosis), at the cell and tissue level (antiangiogenic drugs), or at the whole organism level (adjuvants)

  -but: new molecules= monoclonal antibodies (xxx-mab) directed toward tumours or tumour-favoring antigenic sites
- Immunotherapy: -injection of cytokines (*interferon, interleukins*) = boosters

  -use of engineered macrophages or lymphocytes directed toward specific targets: future?

Examples of drugs and their targets at the subcellular level: chemotherapy for liver, pancreatic or biliary cancers

(F. Lévi, INSERMU 776, Villejuif)



Some pitfalls of cancer therapeutics

- Surgery: -(partly) blindfold
  -not feasible when tumour is adherent to vital blood vessels (liver)

  To overcome these drawbacks: -radio-guided surgery, possibly using DTI
  -preliminary use of radio- or chemotherapy

- Radiotherapy: not enough localised or not enough energetic
  Recently proposed: hadrontherapy = particle beam therapy (protons, neutrons and helium, carbon, oxygen and neon ions instead of photons): better localisation, possibility to deliver higher doses without damage

- Chemotherapy: -toxic to all fast renewing tissues (including healthy ones: gut and other digestive epithelia, skin, bone-marrow)
  -induces development of drug resistance by selecting resistant clones among cancer cells and by creating mutations in genes of drug processing enzymes

  Proposed: optimisation of treatment to reduce toxicity and drug resistance

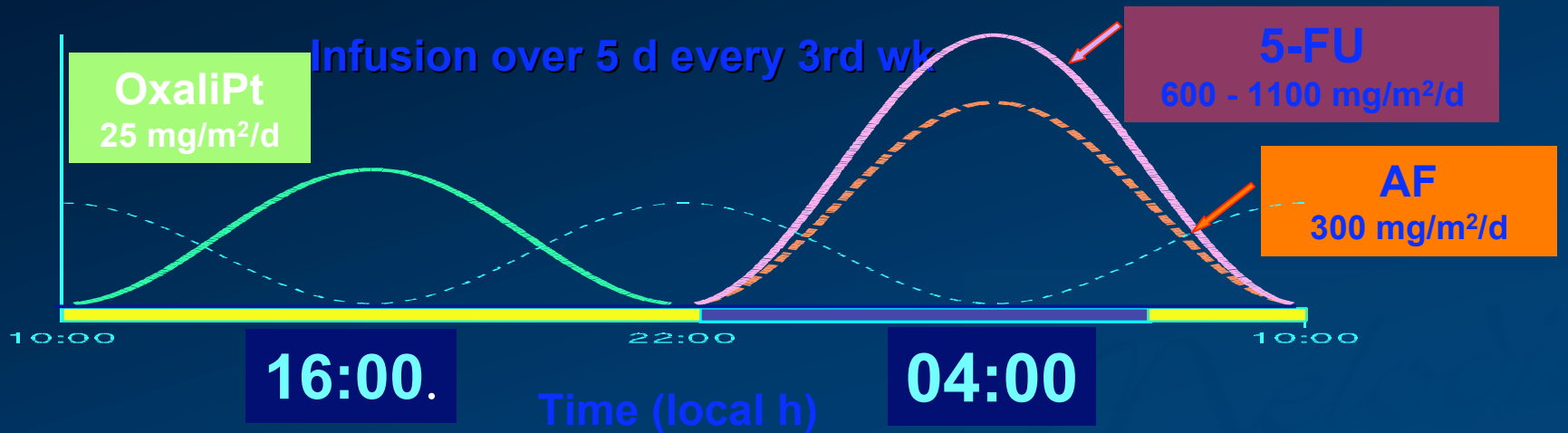
Immunotherapy: -monoclonal antibodies are mouse antibodies!-> HAMA
(Human AntiMouse Antibodies)

Current chronotherapy for metastatic colorectal cancer

(enhances efficacy and reduces unwanted toxicity on healthy tissues)

(F. Lévi, INSERM U 776, Villejuif)

Time-scheduled delivery regimen



Multichannel programmable ambulatory injector for intravenous drug infusion (pompe Mélodie, Aguettant, Lyon, France)

Can such therapeutic schemes be improved?

Mathematical models of tumour growth and therapy:

(a great variety of models)

- In vivo (tumours) or in vitro (cultured cell colonies) growth? In vivo (diffusion in living organisms) or in vitro (constant concentrations) growth control by drugs?
- Scale of description for the phenomenon of interest: subcellular, cell, tissue or whole organism level? … may depend upon therapeutic description level
- Is space a relevant variable? [Not necessarily!] Must the cell cycle be represented?
- Are there surrounding tissue spatial limitations? Limitations by nutrient supply or other metabolic factors?
- Is cell invasion the main point to be described? Then reaction-diffusion equations (KPP-Fisher) are widely used, for instance to represent tumour propagation fronts
- Is cell migration to be considered? Then chemotaxis [=chemically induced cell movement] models (e.g. Keller-Segel) may be used

Models of tumour growth 1

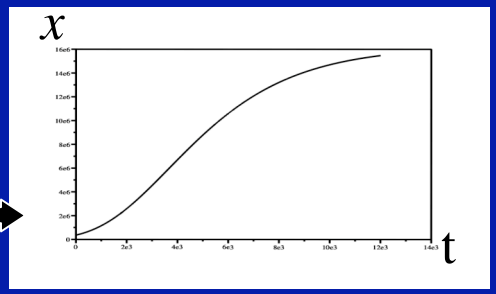
Macroscopic, non-mechanistic models: the simplest ones:
exponential, logistic, Gompertz

$$\frac{dx}{dt} = kx \quad (exponential)$$

$$\frac{dx}{dt} = kx(1-x) \quad (logistic)$$

$$\frac{dx}{dt} = kx \ln\left(\frac{x_{max}}{x}\right) \quad (Gompertz)$$

x= tumour weight
or volume, proportional
to the number of cells



Exponential model: relevant for the early stages of tumour growth only

[Logistic and] Gompertz model: represent growth limitations (S-shaped curves with plateau=maximal growth), due to mechanical pressure or nutrient scarcity

[May be used to describe therapeutic control by adding a drug action term $-\varphi(d,x)$]

Models of tumour growth 2: proliferation / quiescence

a) ODE models with 2 cell compartments, proliferating and quiescent (Gompertz growth revisited)

$$\frac{dP}{dt} = [\beta - \mu_p - r_0(N)]P + r_i(N)Q \quad (1)$$

$$\frac{dQ}{dt} = r_0(N)P - [r_i(N) + \mu_q]Q \quad (2)$$

$$N = P + Q, \quad P_0 + Q_0 = 1$$

(Gyllenberg & Webb, Growth, Dev. & Aging 1989; Kozusko & Bajzer, Math BioSci 2003)

where, for instance:

$$r_0(N) = \frac{\alpha N^\gamma}{K^\gamma + N^\gamma}, \quad r_i(N) = \frac{\beta L^\delta}{L^\delta + N^\delta}$$

r_0 representing here the rate of inactivation of proliferating cells, and r_i the rate of recruitment from quiescence to proliferation

Avowed aim: to justify global Gompertz growth

However, a lot of cell colonies and tumours do not follow Gompertz growth

Models of tumour growth 2: proliferation / quiescence

b) Age[x]-structured PDE models with 2 cell compartments, proliferating and quiescent

$$\frac{\partial}{\partial t}p(t,x) + \frac{\partial}{\partial x}p(t,x) + [K(x) + \gamma(t)]p(t,x) = 0$$

$$\frac{\partial}{\partial t}q(t,x) + \frac{\partial}{\partial x}q(t,x) + [\beta(t) + \delta(t)]q(t,x) = 0$$

$$\text{with :}$$

$$p(0,x) = p^0(x),$$

$$q(0,x) = q^0(x),$$

$$p(t,0) = \beta(t)\int_0^\infty q(t,\xi)d\xi,$$

$$q(t,0) = 2\int_0^\infty K(\xi)p(t,\xi)d\xi$$

p=density of proliferating cells; q=density of quiescent cells;
K=term describing cells leaving proliferation to quiescence, due to mitosis;
β=term describing "reintroduction" (or recruitment) from quiescence to proliferation

Models of tumour growth 2: proliferation / quiescence

c) D(*for Delay*)DE models with 2 cell compartments, proliferating (P) / quiescent (Q)

(can be obtained from the previous model with additional hypotheses and integration along characteristics)

$$\frac{dP}{dt} + \gamma P - \beta(Q(t))Q(t) + \beta(Q(t-\tau))e^{-\gamma\tau}Q(t-\tau) = 0$$

$$\frac{dQ}{dt} + [\beta(Q(t)) + \delta]Q - 2\beta(Q(t-\tau))e^{-\gamma\tau}Q(t-\tau) = 0$$

$$\text{where } \beta(Q) = \frac{\beta_0\theta^n}{\theta^n + Q^n}$$

(delay τ =cell cycle time)

(from Mackey, Blood 1978)

Properties of this model: depending on the parameters, one can have positive stability, extinction, explosion, or sustained oscillations of both populations

(Hayes stability criteria, see Hayes, J London Math Soc 1950)

Such behaviour can be observed in *periodic Myeloid Chronic Leukemia* where oscillations with limited amplitude are compatible with survival, whereas explosion (blastic transformation, or acutisation) leads to death

(studied by Mackey, Adimy, Bélair, Bernard, Crauste, Pujo-Menjouet…)

Models of tumour growth 2: proliferation / quiescence

d) An age[a]-and-cyclin[x]-structured PDE model with proliferating and quiescent cells

(exchanges between *(p)* and *(q)*, healthy and tumour tissue cases: G_0 to G_1 recruitment differs)

$$\begin{cases} \dfrac{\partial}{\partial t}p(t,a,x) + \dfrac{\partial}{\partial a}\left(\Gamma_0 p(t,a,x)\right) + \dfrac{\partial}{\partial x}\left(\Gamma_1(a,x)\,p(t,a,x)\right) = \\ -\left(L(a,x) + F(a,x) + d_1\right)p(t,a,x) + G(N(t))\,q(t,a,x), \\ \dfrac{\partial}{\partial t}q(t,a,x) = L(a,x)\,p(t,a,x) - \left(G(N(t)) + d_2\right)q(t,a,x). \end{cases}$$

N: total number of cells

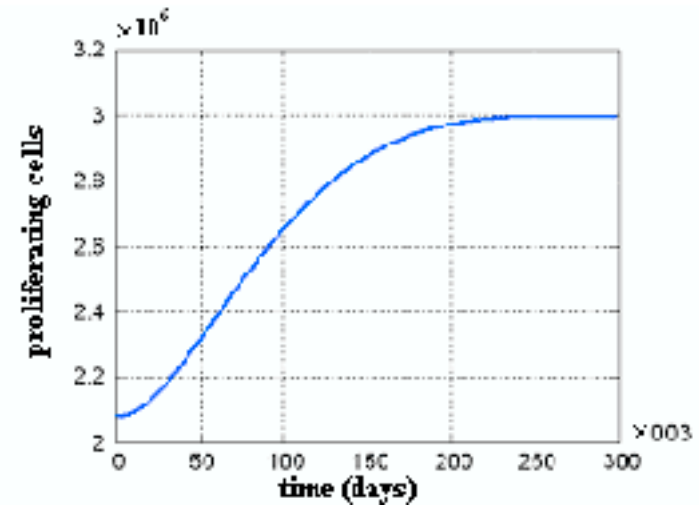
(Here, no circadian control is represented)

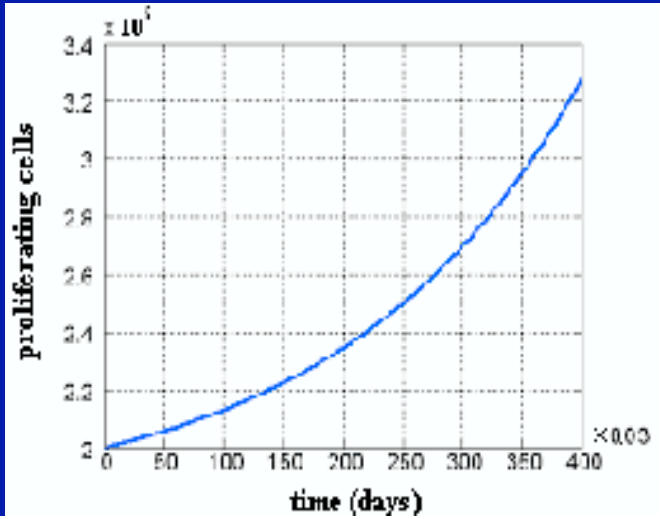
$$G(N) = \frac{\alpha_1\theta^n}{\theta^n + N^n}$$

Healthy tissue recruitment: homeostasis

$$G(N) = \frac{\alpha_1\theta^n + \alpha_2 N^n}{\theta^n + N^n}$$

Tumour recruitment: exponential growth





Bekkal Brikci, Clairambault, Ribba, Perthame submitted 2007; RR INRIA #5941

Models of tumour growth 3

Physical laws describing macroscopic spatial dynamics of *avascular* tumours

-Fractal-based phenomenological description of growth of cell colonies and tumours, relying on observations and measures: roughness parameters for the 2D or 3D tumour

Findings: -all proliferation seems to occur at the outer rim
-cell diffusion *along* (not from) the tumour border or surface
-*linear growth of the tumour radius* after a critical time (before: exponential)

(A. Bru et al. Phys Rev Lett 1998, Biophys J 2003)

-Individual-based models:
-cell division and motion described by stochastic algorithm then continuous limit
-permanent regime = KPP-Fisher-like (also linear growth of the tumour radius)

(D. Drasdo, Math Comp Modelling 2003; Phys Biol 2005)

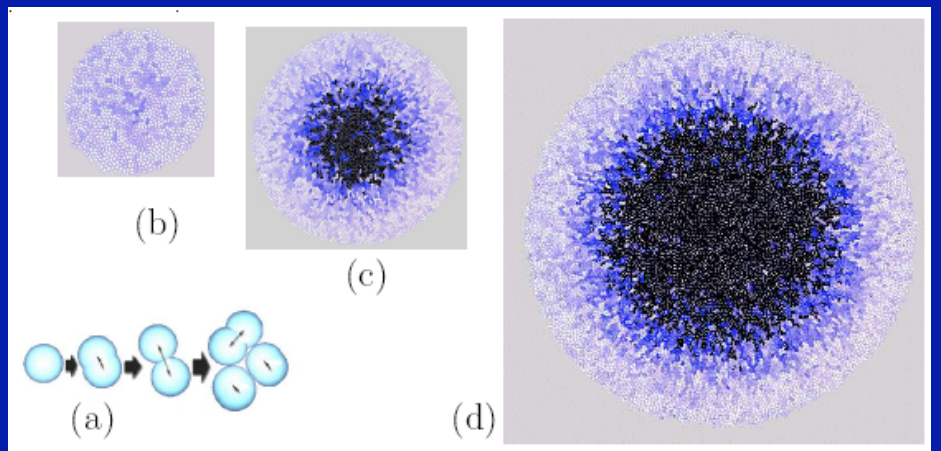


Fig. 1. Typical simulation scenario in the off-lattice model starting from (a) a single cell to (a) three cells and aggregates of (b) $N = 100$, (c) $N = 1000$, and (d) $N = 10000$ cells. (Further

Models of tumour growth 4

Macroscopic reaction-diffusion evolution equations for cancer invasion

1 variable c = density of tumour cells): KPP-Fisher equation

$$\frac{\partial c}{\partial t} = \nabla.(D(x)\nabla c) + \rho c(1-c)$$

$D(x)$ = diffusion (motility) in brain tissue, ρ (reaction)=growth of tumour cells

1D x and c instead of $c(1\text{-}c)$: used to represent brain tumour radial propagation

(K. Swanson & J. Murray, Cell Prolif 2000; Br J Cancer 2002; J Neurol Sci 2003)

2 or more variables: ex.: healthy cells N_1, tumour cells N_2, excess H^+ ions L

$$\frac{\partial N_1}{\partial t} = r_1 N_1\left(1-\frac{N_1}{K_1}-\alpha_{12}\frac{N_2}{K_2}\right)-d_1 L N_1 \quad (1)$$

$$\frac{\partial N_2}{\partial t} = r_2 N_2\left(1-\frac{N_2}{K_2}-\alpha_{21}\frac{N_1}{K_1}\right)+\nabla.\left(D_2\left(1-\frac{N_1}{K_1}\right)\nabla N_2\right) \quad (2)$$

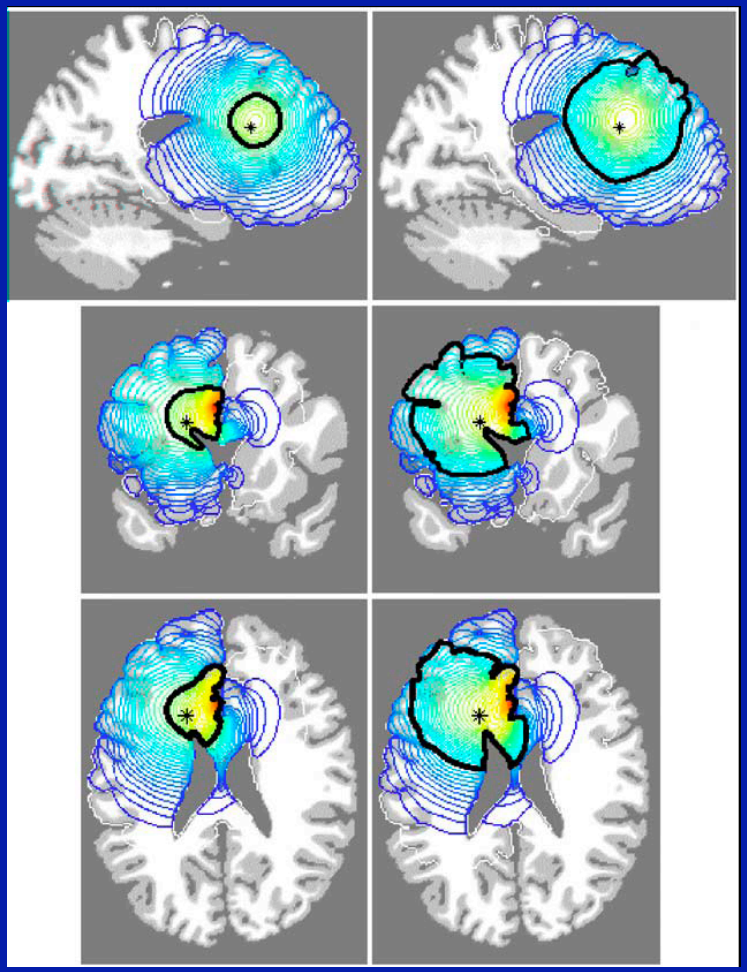
$$\frac{\partial L}{\partial t} = r_3 N_2 - d_3 L + D_3\nabla^2 L \quad (3)$$

(R. Gatenby & E. Gawlinski, Canc Res 1996)

Prediction: interstitial cell gap between tumour propagation and healthy tissue recession fronts

Illustrations

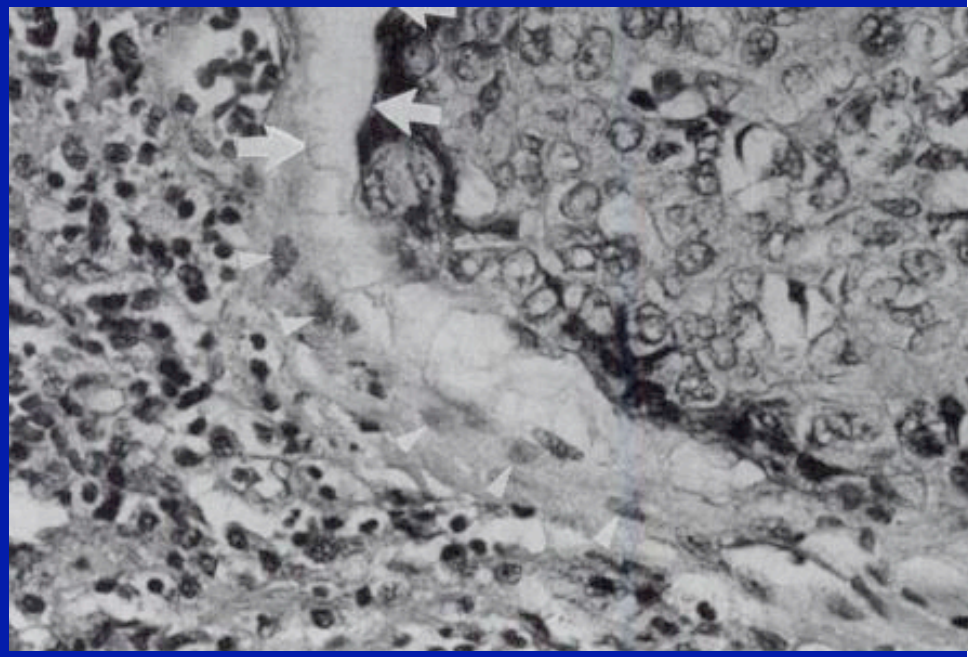
1D (radial), 1 population=cancer cells



Virtual brain tumour: spatial progression between diagnosis (left) and death (right)

(From Swanson et al. J Neurol Sci 2003)

3D, 3 populations (N_1, N_2, L=[H^+])



Predicted and observed interstitial acellular gap between tumour (right) and normal cells

(From Gatenby & Gawlinski, Canc Res 1996)

Models for moving tumour cells

Chemotaxis: chemo-attractant induced cell movements

Keller-Segel model

$$\frac{\partial p}{\partial t} = \Delta p - \mathrm{div}\left(p\chi(w)\nabla w\right),$$
$$0 = \Delta w + (p - 1).$$

p = density of cells
w = density of chemical

(Originally designed for movements of bacteria, with w=[cAMP])

(Keller & Segel, J Theoret Biol 1971, see also more recent works, in particular by B. Perthame)

Anderson-Chaplain model for local invasion by tumour cells

$$\frac{\partial n}{\partial t} = \overbrace{D_n\nabla^2 n}^{random\ motility} - \overbrace{\chi\nabla.(n\nabla f)}^{haptotaxis} \quad (1)$$

$$\frac{\partial f}{\partial t} = -\overbrace{\delta m f}^{degradation} \quad (2)$$

$$\frac{\partial m}{\partial t} = \overbrace{D_m\nabla^2 m}^{diffusion} + \overbrace{\mu n}^{production} - \overbrace{\theta u m}^{neutralisation} - \overbrace{\lambda m}^{decay} \quad (3)$$

$$\frac{\partial u}{\partial t} = \overbrace{D_u\nabla^2 u}^{diffusion} + \overbrace{F(m,f)}^{production} - \overbrace{\theta u m}^{neutralisation} - \overbrace{\varepsilon u}^{decay} \quad (4)$$

n = density of cells

f = ECM density

m = MDE (tumour metalloproteases)

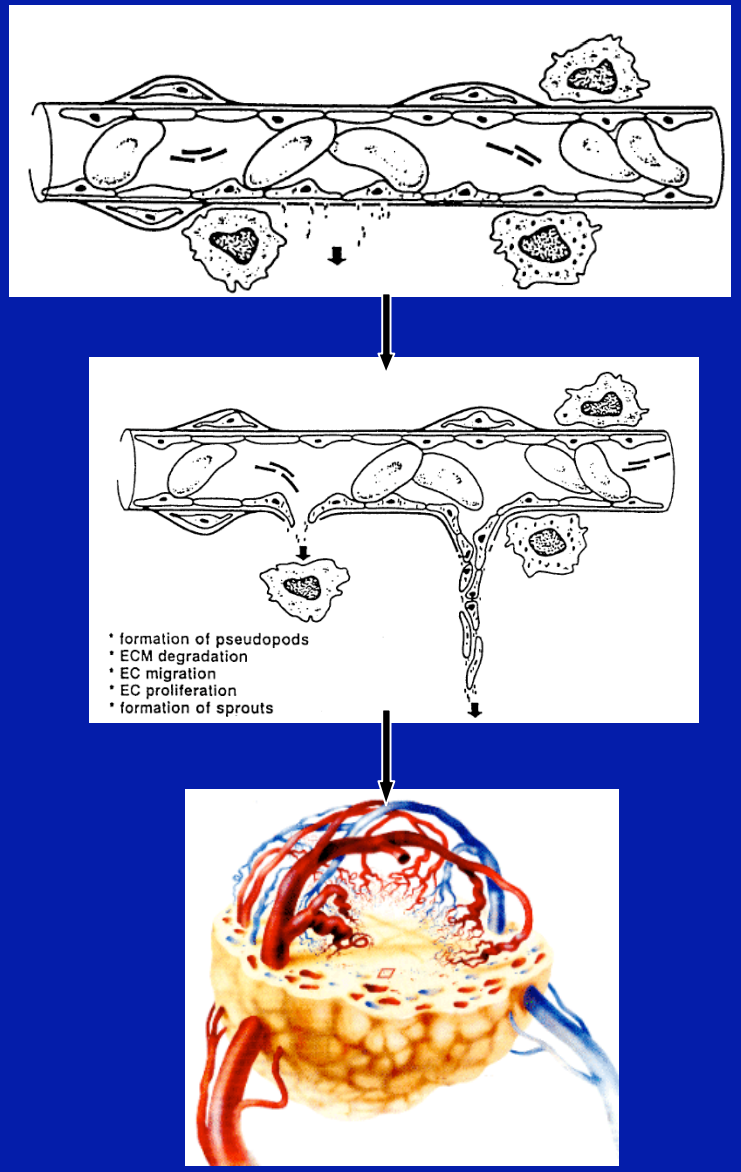
u = MDE inhibitor

(Anderson & Chaplain, Chap 10 in Cancer modelling and simulation, L. Preziosi Ed, Chapman & Hall 2003)

Models for angiogenesis

VEGF-induced endothelial cell movements towards tumour

-Biochemical enzyme kinetics
-Chemical transport (capillary and ECM)
-«Reinforced random walks»
-Cell movements in the ECM



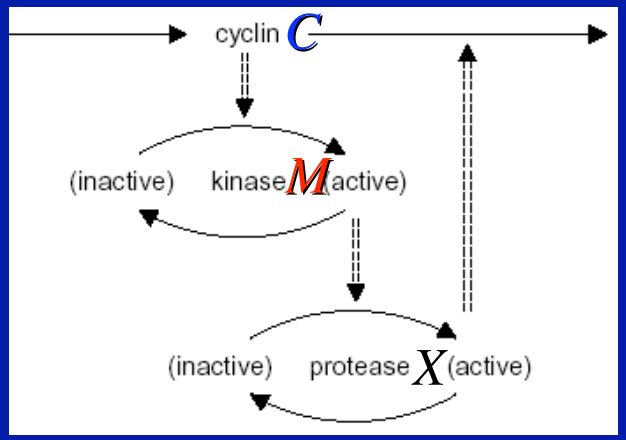
Models by Anderson and Chaplain, Levine and Sleeman

(Levine & Sleeman,Chap. 6 in «Cancer modelling and simulation», L. Preziosi Ed, Chapman & Hall 2003)

Modelling the cell cycle 1

ODE to describe progression in the cell cycle at the single-cell level

A. Golbeter's minimal model for the « mitotic oscillator » (G_2/M transition)



$$\frac{dC}{dt} = v_i - k_d C - v_d X \frac{C}{K_d + C}$$

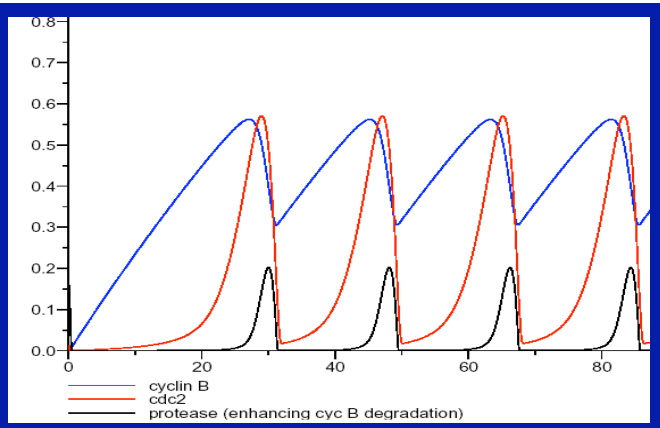
$$\frac{dM}{dt} = v_1 \frac{C}{K_c + C} \frac{(1 - M)}{K_1 + (1 - M)} - V_2 \frac{M}{K_2 + M},$$

$$\frac{dX}{dt} = v_3 M \frac{(1 - X)}{K_3 + (1 - X)} - V_4 \frac{X}{K_4 + X}.$$

C = cyclin B, M = Cyclin-linked cyclin dependent kinase, X = degrading protease

Switch-like dynamics of dimer Cyclin B-cdk1

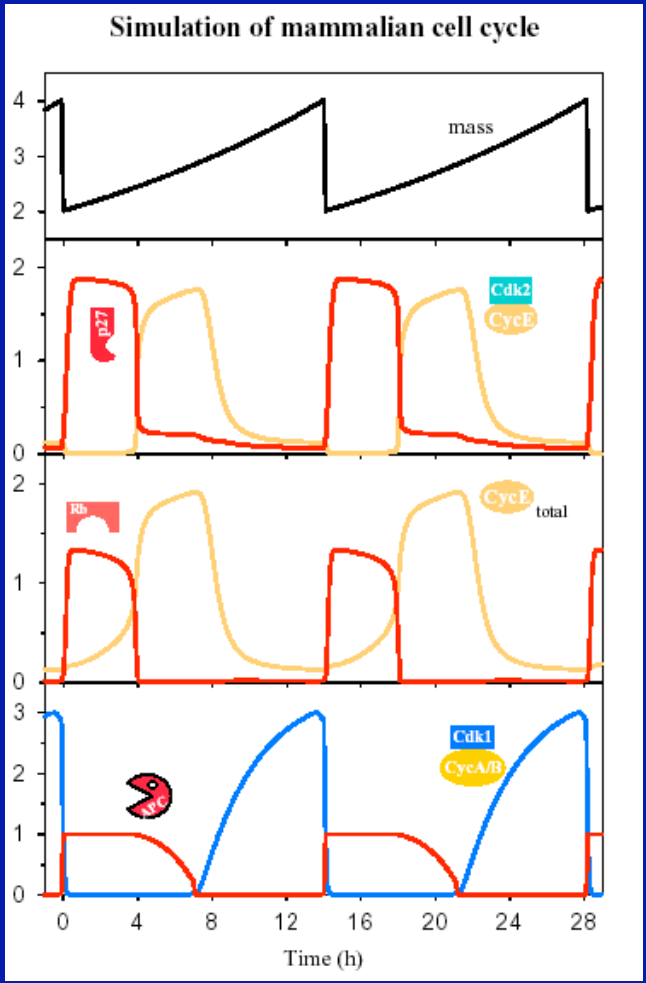
Adapted to describe G_2/M phase transition



(A. Goldebeter Biochemical oscillations and cellular rhythms, CUP 1996)

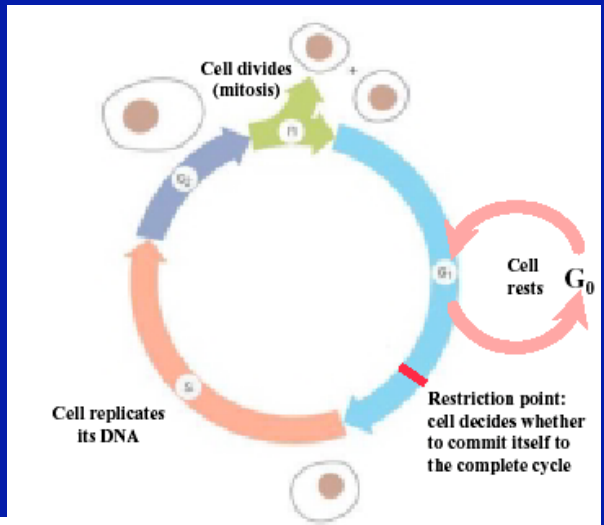
Modelling the cell cycle 2

ODE models to describe progression in the cell cycle at tthe single-cell level



Focus on phase transitions:
-G_1/S
-G_2/M
-Metaphase/anaphase

…due to steep variations of Cyc-cdk concentrations



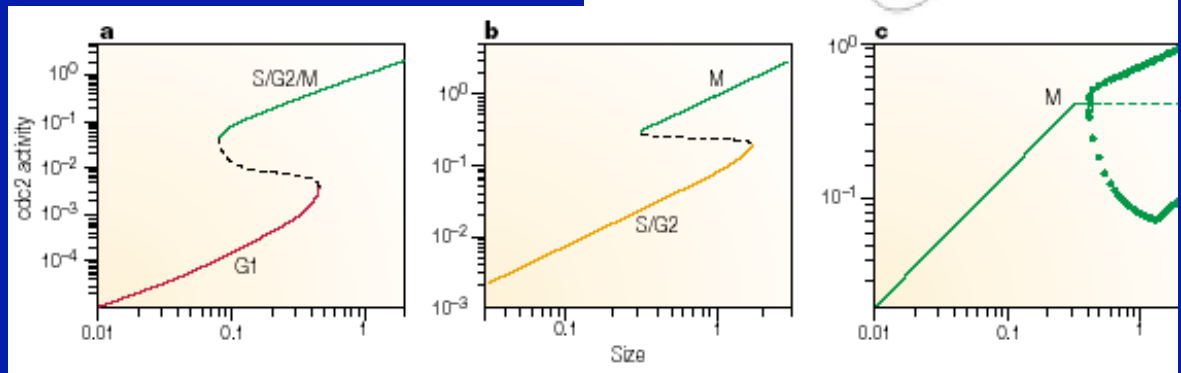


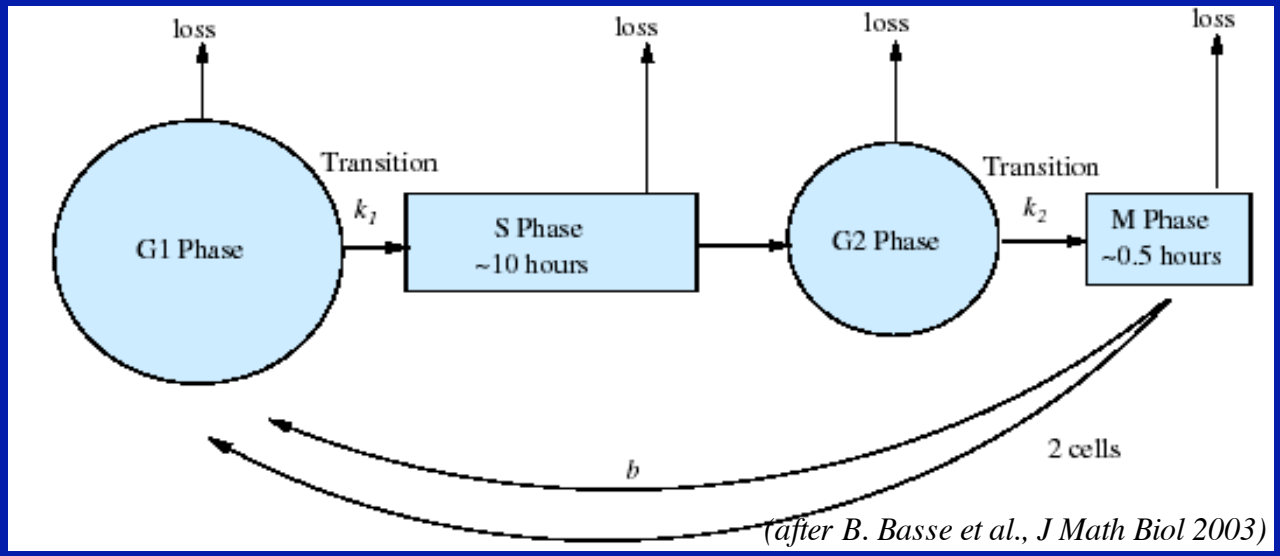
Figure 5 | **Bifurcation diagrams for the three control modules of the cell cycle.** The activity of cdc2–cdc13 dimers (an indicator of the state of the control system) is plotted against 'size' (the number of ribosomes per nucleus, an indicator of cell growth and division). All variables are expressed in arbitrary units. For each value of size, we compute the steady-state activity

(Novak, Bioinformatics 1999)

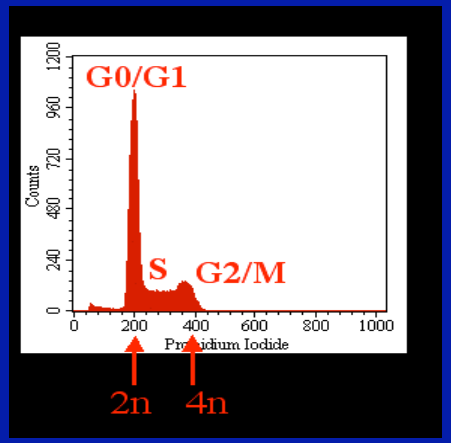
(Tyson, Chen, Novak, Nature Reviews 2001)

Modelling the cell cycle 3

PDE models for age-structured cycling cell populations



(after B. Basse et al., J Math Biol 2003)



Flow cytometry may help quantify proliferating cell population repartition according to cell cycle phases

In each phase *i*, a Von Foerster-McKendrick-like equation:

$$\frac{\partial}{\partial t} n_i(t,a) + \frac{\partial}{\partial a}[v_i(a) n_i(t,a)] + d_i(t,a) n_i(t,a) + K_{i\to i+1}(t,a) n_i(t,a) = 0$$

$$v_i(0) n_i(t, a=0) = \int_{\alpha \geq 0} K_{i-1\to i}(t,\alpha)\, n_{i-1}(t,\alpha)\, d\alpha$$

$$K_{i\to i+1}(t,a) = \psi(t) \mathbf{1}_{a \geq a_i}(a)$$

n_i:=cell population density in phase i

d_i:=death rate

$K_{i->i+1}$:=transition rate (with a factor 2for $i=1$)

d_i, $K_{i->i+1}$ constant or periodic w. r. to time t ($1 \leq i \leq I$, $I+1=1$)

Death rates d_i and phase transitions $K_{i->i+1}$ are targets for physiological (e.g. circadian) and therapeutic (drugs) control

According to the Krein-Rutman theorem (infinite-dimensional form of the Perron-Frobenius theorem), there exists a nonnegative first eigenvalue λ such that, if $\widetilde{N}_i(t,a) = e^{-\lambda t} n_i(t,a)$ then there exist bounded solutions N_i to the problem:

$$\begin{cases} \frac{\partial}{\partial t} N_i(t,a) + \frac{\partial}{\partial a} N_i(t,a) + [d_i(t,a) + \lambda + K_{i\to i+1}(t,a)] N_i(t,a) = 0, \\ N_i(t,a=0) = \int_{\alpha\geq 0} K_{i-1\to i}(t,\alpha)\, N_{i-1}(t,\alpha)\, d\alpha, \quad 2 \leq i \leq I \\ N_1(t,a=0) = 2\int_{\alpha\geq 0} K_{I\to 1}(t,\alpha)\, N_I(t,\alpha)\, d\alpha, \quad \text{with} \sum_{i=1}^{I} \int_{\alpha\geq 0} N_i(t,a) da = 1 \end{cases}$$

with functions $\rho_i(a)$ such that

$$\int_{\alpha\geq 0} \left| \widetilde{N}_i(t,\alpha) - \rho_i(\alpha)\, N_i(t,\alpha) \right| \varphi_i(t,\alpha) d\alpha \to 0 \qquad \text{as } t \to \infty$$

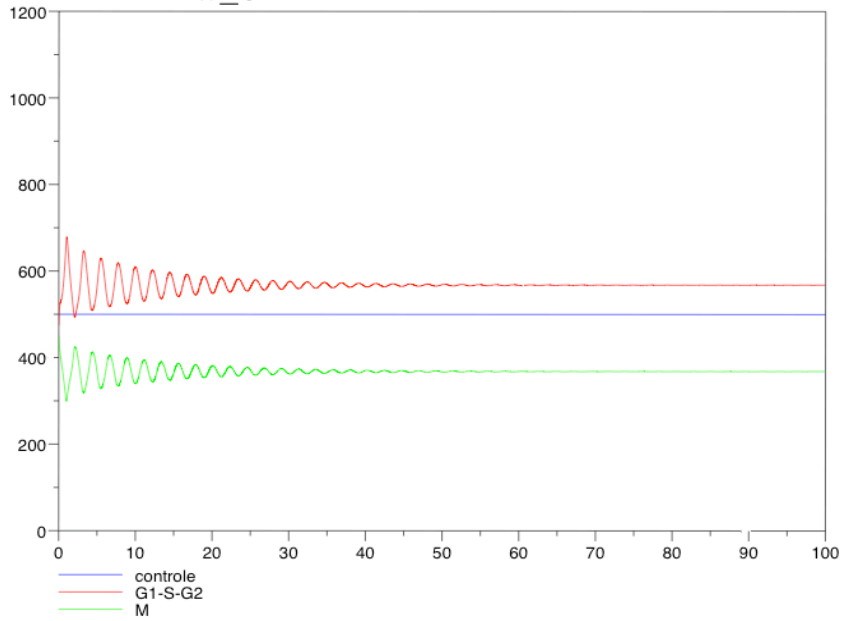
φ_i being solutions to the dual problem; this can be proved using a generalised entropy principle. Moreover, if the control (d_i or $\kappa_{i->i+1}$) is constant, or if it is periodic, so are the N_i, with the same period in the periodic case.

(Clairambault, Laroche, Mischler, Perthame, RR INRIA n° 4892, 2003,
Michel, Mischler, Perthame, CRAS 2004, J Math Pures Appl 2005,
Clairambault, Michel, Perthame, CRAS 2006, Proc. ECMTB Dresden 2005)

Hence exponentially growing cell populations: describing early tumour stages

Details (1): 2 phases, no control on G_2/M transition

$$\mathcal{N}_i^{tot}(t) = e^{-\lambda t} \int_{\alpha \geq 0} n_i(t,\alpha) d\alpha, \quad i = 1,2$$

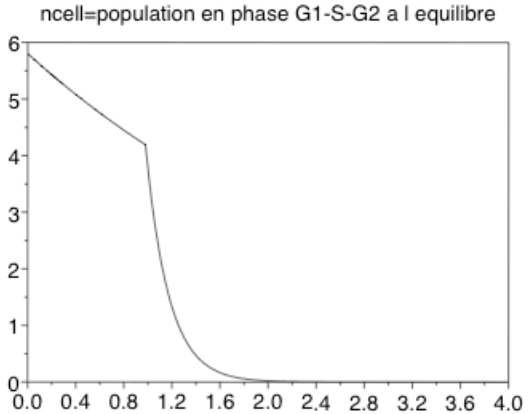


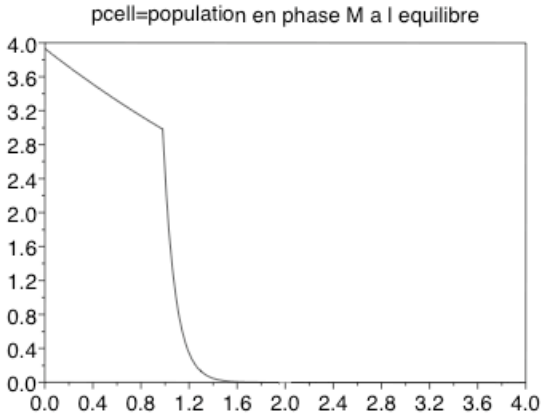
The total population of cells

$$\int_{\alpha>0} n_i(t,\alpha) d\alpha, \quad i = 1,2$$

inside each phase follows asymptotically an exponential behaviour

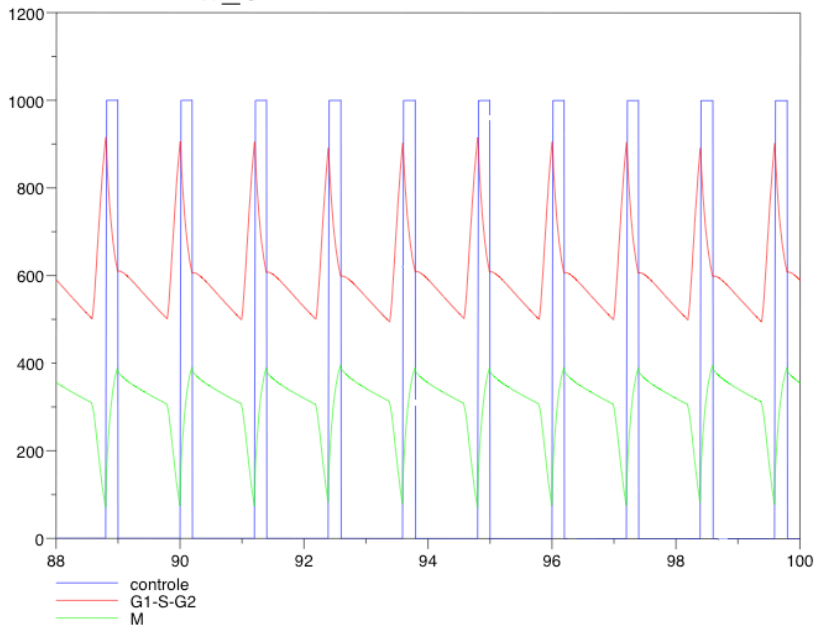
Stationary state distribution of cells inside phases according to age *a:*
no control -> exponential decay





Details (2): 2 phases, periodic control ψ on G_2/M transition

$$\mathcal{N}_i^{tot}(t) = e^{-\lambda t} \int_{\alpha \geq 0} n_i(t,\alpha) d\alpha, \quad i = 1,2$$

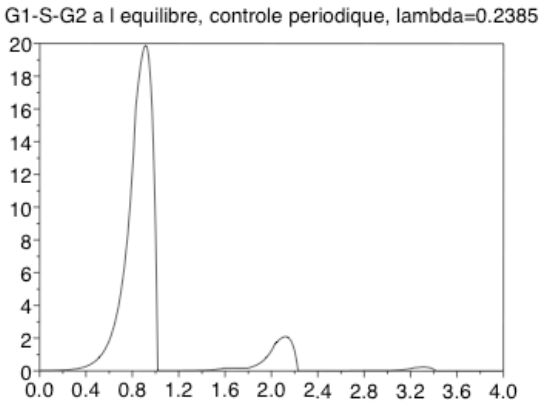


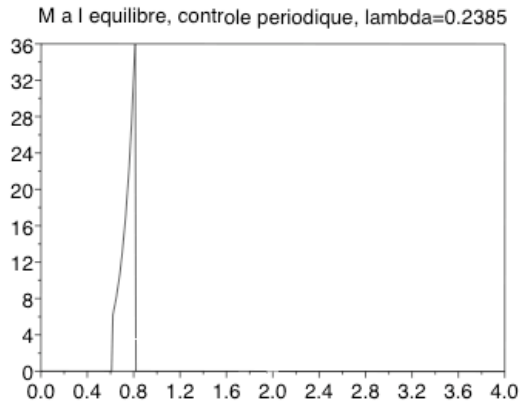
The total population of cells

$$\int_{\alpha > 0} n_i(t,\alpha) d\alpha, \quad i = 1,2$$

inside each phase follows asymptotically an exponential behaviour *tuned by a periodic function*

Stationary state distribution of cells inside phases according to age *a*: *sharp periodic control ->sharp rise and decay*





Macroscopic models of the action of drugs, examples

ODE with representation of pharmacodynamics for unwanted bone marrow toxicity

$$\frac{\mathrm{dPBM}}{\mathrm{d}t} = [1 - f(D)] \cdot r(N) \cdot \mathrm{PBM} - k_1 \cdot \mathrm{PBM},$$
$$\frac{\mathrm{dNBM}_1}{\mathrm{d}t} = k_1 \cdot \mathrm{PBM} - k_2 \cdot \mathrm{NBM}_1,$$
$$\frac{\mathrm{dNBM}_2}{\mathrm{d}t} = k_2 \cdot \mathrm{NBM}_1 - k_3 \cdot \mathrm{NBM}_2,$$

$$\frac{\mathrm{d}N}{\mathrm{d}t} = k_3 \cdot \mathrm{NBM}_2 - k_{\mathrm{el}} \cdot N,$$
$$r(N) = r_{\max} - (r_{\max} - r_{\min}) \cdot \frac{N}{K_m + N}, \quad \text{PD model}$$
$$f(D) = \frac{D^m}{K_D^m + D^m},$$

PBM, NBM_i = bone marrow cells, N = circulating neutrophils, D = drug concentration

(JC Panetta, Math BioSci 2003)

PDE (R-D) describing action of a drug (*d*) on proliferating (*p*) and quiescent (*q*) cells

$$\frac{\partial d}{\partial t} + \nabla \cdot (\mathbf{u}d) = \nabla \cdot (D(r)\nabla d) + \Gamma(r)(d_B(t) - d) - \lambda d,$$

$$\frac{\partial p}{\partial t} + \nabla \cdot (\mathbf{u}p) = D_p \Delta p + F_p(p) - C_p(d, p),$$

$$\frac{\partial q}{\partial t} + \nabla \cdot (\mathbf{u}q) = D_q \Delta q + F_q(q) - C_q(d, q).$$

(T. Jackson & H. Byrne, Math BioSci 2000)

p (resp. *q*) cells:
high (resp. low)
susceptibility to drug *d*

Optimisation of cancer therapy by cytotoxic drugs

- Optimal control strategies to overcome the development of drug resistant cell populations, using different drugs *(M. Kimmel & A. Swierniak, preprint Ohio State Univ 2003)*

- Pulsed chemotherapies aiming at synchronising drug injections with cell cycle events to enhance the effect of drugs on tumours: e.g. optimal control of IL21 injection times and doses $\Sigma\, u_i\, \delta(t\text{-}t_i)$ using variational methods *(Z. Agur, IMBM, Israel)*

- Chronotherapy = continuous infusion time regimens taking advantage of optimal circadian anti-tumour efficacy and healthy tissue tolerability for each particular drug: *has been in use for the last 15 years, with particular achievements for colorectal cancer* *(F. Lévi, INSERM U776, e.g. Mormont & Lévi, Cancer 2003)*

PK-PD (pharmacokinetics-pharmacodynamics) macroscopic modelling for cancer chronotherapy

Healthy cells (jejunal mucosa)

$$\begin{aligned}
\frac{dP}{dt} &= -\lambda P + \frac{i(t)}{V}\Phi(t) \\
\frac{dC}{dt} &= -\mu C + P \\
\frac{dZ}{dt} &= -\{\alpha + f(C,t)\}Z - \beta A + \gamma \\
\frac{dA}{dt} &= Z - Z_{eq}
\end{aligned}$$

(homeostasis=damped harmonic oscillator)

(PK)

Tumour cells

$$\begin{aligned}
\frac{dP}{dt} &= -\lambda P + \frac{i(t)}{V}\Phi(t) \\
\frac{dD}{dt} &= -\nu D + P \\
\frac{dB}{dt} &= \left[a \ln \frac{B_{max}}{B} - g(D,t)\right] B
\end{aligned}$$

(tumour growth=Gompertz model)

(« chrono-PD »)

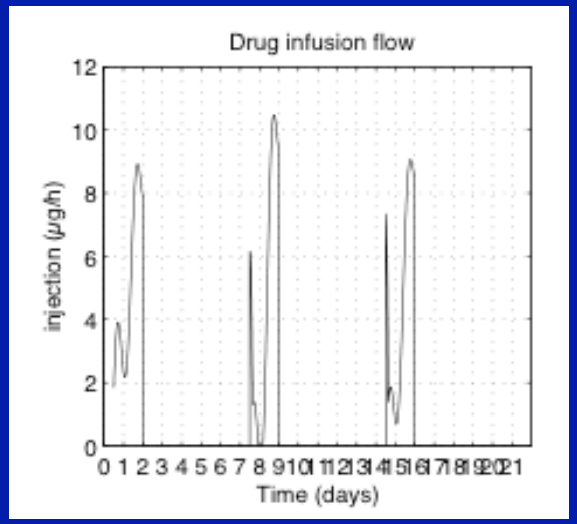
$f(C,t)=F.C^{\gamma}/(C_{50}{}^{\gamma}+C^{\gamma}).\{1+\cos 2\pi(t-\varphi_S)/T\}$

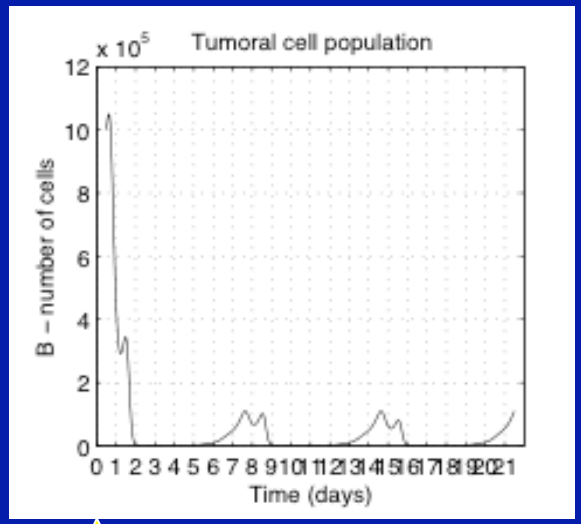
$g(D,t)=H.D^{\gamma}/(D_{50}{}^{\gamma}+D^{\gamma}).\{1+\cos 2\pi(t-\varphi_T)/T\}$

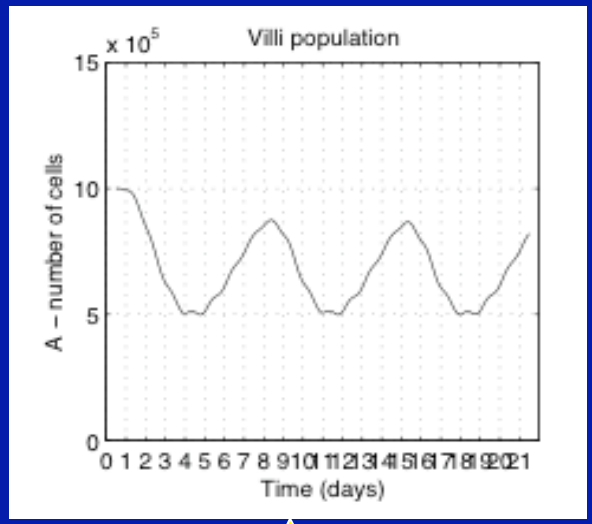
Aim: balancing IV delivered drug anti-tumour efficacy by healthy tissue toxicity

(Clairambault, Pathol-Biol 2003; ADDR 2007, in press)

Optimal control: results of a tumour stabilisation strategy using this simple PK-PD model







Objective: *minimising the maximum of the tumour cell population*

Constraint : *preserving the jejunal mucosa according to the patient's state of health* (τ_A)

Result : optimal infusion flow adaptable to the patient's state of health

(according to a parameter τ_A: here preserving at least τ_A=50% of enterocytes*)*

(Basdevant, Clairambault, Lévi, INRIA internal research report RR #5407; 2004; published M2AN 2005)

Toward multiscale PK-PD control of tumour and healthy tissue growth to optimise therapy

- Tissue proliferation relies on the cell cycle for healthy and tumour cells and cytotoxic drugs act at the subcellular level
- Their mechanisms of diffusion in the organism and action in cells (PK-PD) should be represented as much as possible to take into account cell cycle timing in therapeutic optimisation
- Control by physiological inputs (circadian system, hormones) at the whole organism level should also be taken into account in optimisation procedures
- Integration of biomolecular mechanisms of tissue growth to macroscopic scale should be guided by specificity of tumoral pathologies and drugs used

Other challenges for cancer therapeutic optimisation

Overcoming drug resistances

-Developing strategies to minimise the occurrences of gene mutations (e.g. fewer doses of more different drugs to diminish dose-dependent mutation pressure)

-Reversing drug insensitivity by adding other drugs (e.g. *imatinib* reverses resistance to SN-38 by drug efflux mediated by ABCG2 protein: modelling ABCG2 inhibition?)

Blocking the recruitment from quiescence to proliferation

e.g. by anti-EGFRs or other tyrosine kinase inhibitors: in association with cytotoxics

Fighting neoangiogenesis in association with cytotoxics

e.g. by antagonists of VEGFRs (*bevacizumab*) associated with 5-FU

Fighting invasion by cancer cells which use digesting enzymes

(MMP Inhibitors?)

Stimulating the immune system (Vaccination?)

Coming next: a 4-day school in March 2008

Models of cancer and its therapeutic control: From molecules to the organism.

CEA-EDF-INRIA Winter school in Rocquencourt (close to Versailles, France).
Targeted dates: March 11-14, 2008. Scientific organisers: J. Clairambault and D. Drasdo.

Tentative programme of lectures (all given in English):

1. The cell division cycle and its control: individual cells and proliferating cell populations.
2. Tissue proliferation and invasion: from individual-based to continuum models.
3. Molecular networks: a systems biology approach to robustness and implications for cancer.
4. Therapeutic optimisation problems in oncology: side effects, resistance, synergies.

Proposed 2-hour lectures (3 lectures each of the 4 days of the school):

1. ODE models for the cell cycle / PDE (age or DNA content-structured) models for the cell cycle / Delay Differential Equations for proliferating cell populations.
2. Tissue proliferation and invasion phenomena / From individual-based to continuous models / Probabilistic and deterministic models of tumour growth.
3. Molecular networks, fragility and robustness in cancer / Gene evolutionary dynamics of cancer / Gene evolutionary continuous models (adaptive evolution).
4. Therapeutic optimisation: minimising toxicity by using anticancer drug synergies with chronotherapy (and optimal control) / Therapeutic optimisation: overcoming drug resistances by using drug synergies. / Targeting stem cells.

+ Complementary technical half-an-hour lectures: (1 each day): focus on: Flow cytometry / Cell and tissue image processing / DNA microarray analysis / Cancer databank design.