Continuous models of cell population growth dynamics to optimise anticancer treatments

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Biomat winter school, La Falda, Córdoba, August 2014

Position of the problem: cancer disease and its modelling in the perspective of theoretical treatment optimisation

A general framework to optimise cancer therapeutics: designing mathematical methods along 3 axes

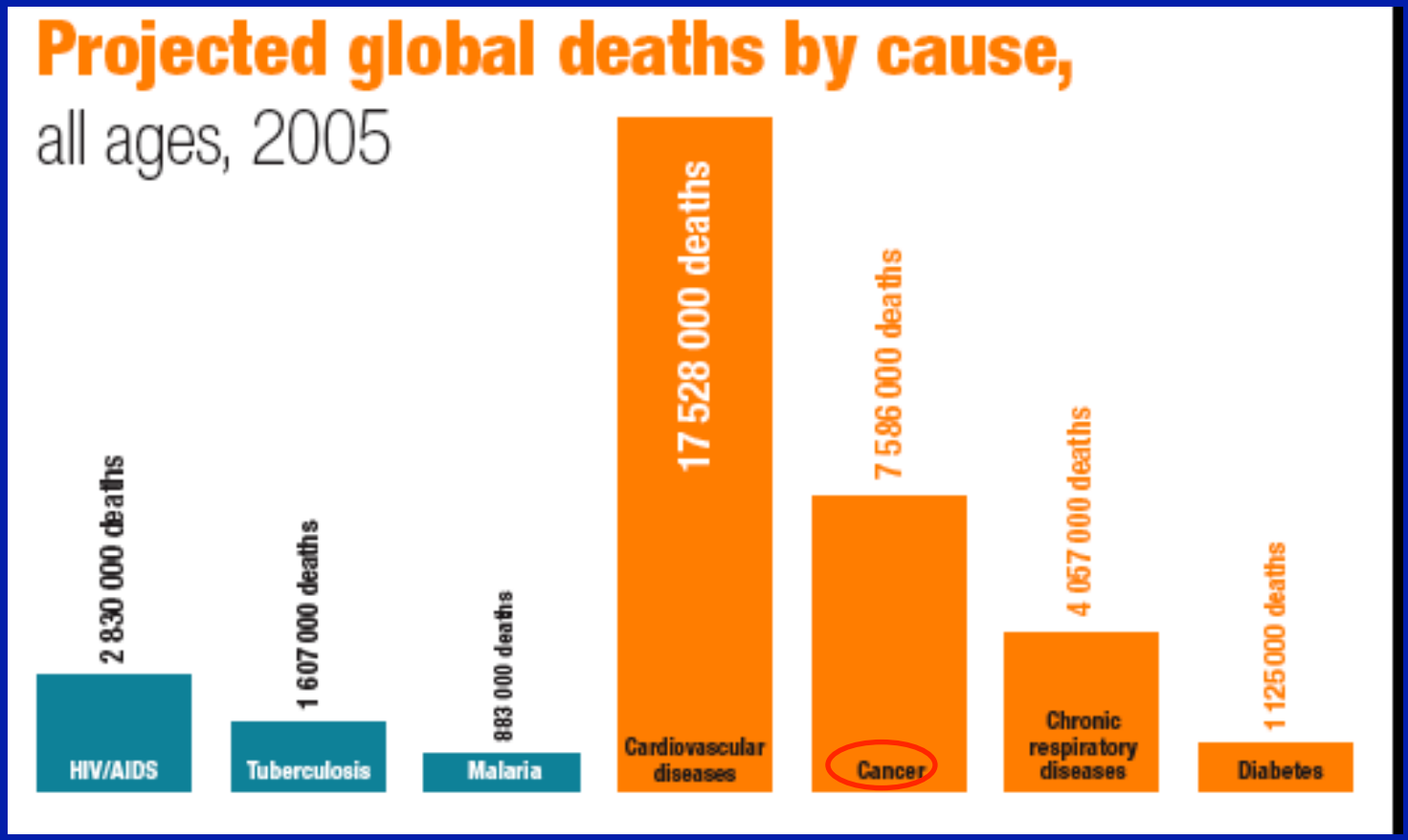
1. Modelling the *behaviour of growing cell populations* on which drugs act (the targeted cell populations): proliferating tumour *and healthy* cell populations, including describing molecular or functional targets for physiological or pharmacological control

2. Modelling the external control system, i.e., fate of drugs in the organism, at the molecular and whole body levels by *molecular pharmacokinetics-pharmacodynamics:* PK-PD (ideally WBPBPKPD = *whole body physiologically based...*) or by *functional representation of drugs in use*: cytotoxic, cytostatic or differentiating agents

3. Optimising the therapeutic control*: dynamically optimised control* of theoretical drug delivery flows, representing time-dependent *objectives and constraints*, using *known or hypothesised differences* between cancer and healthy cell populations

(JC Math Mod Nat Phenom 2009; Pers Med 2011; Springer book chapters 2013, 2014; Lorz et al. 2013, 2014)

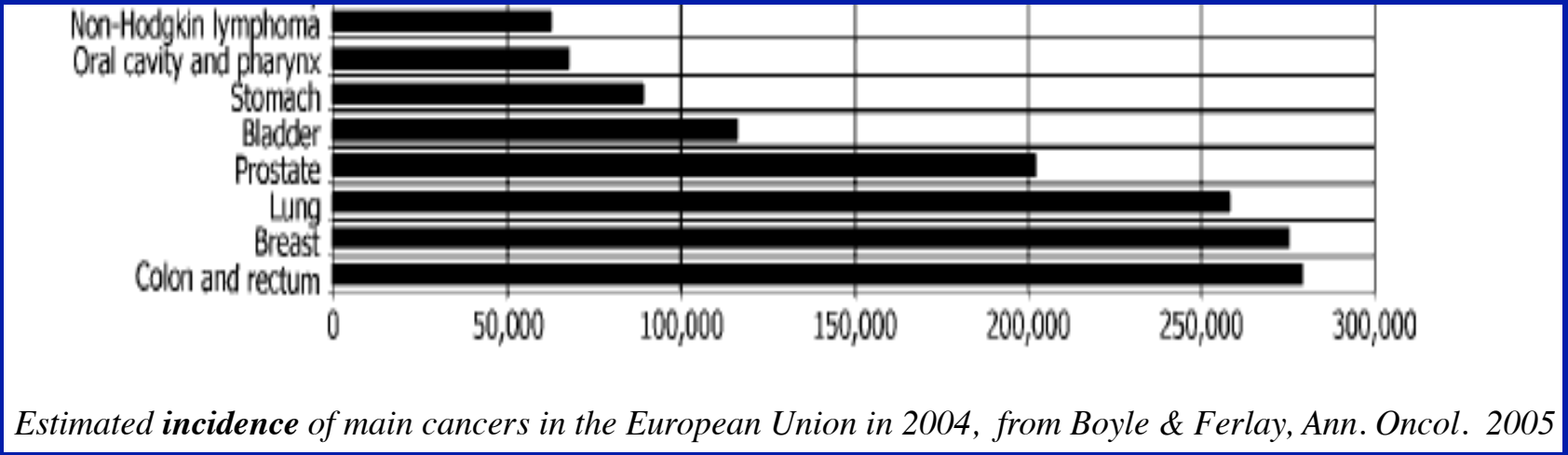
Relative importance of cancer as one of the major killer *chronic* diseases worldwide



WHO source (2005): http://www.who.int/chp/chronic_disease_report/full_report.pdf

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)

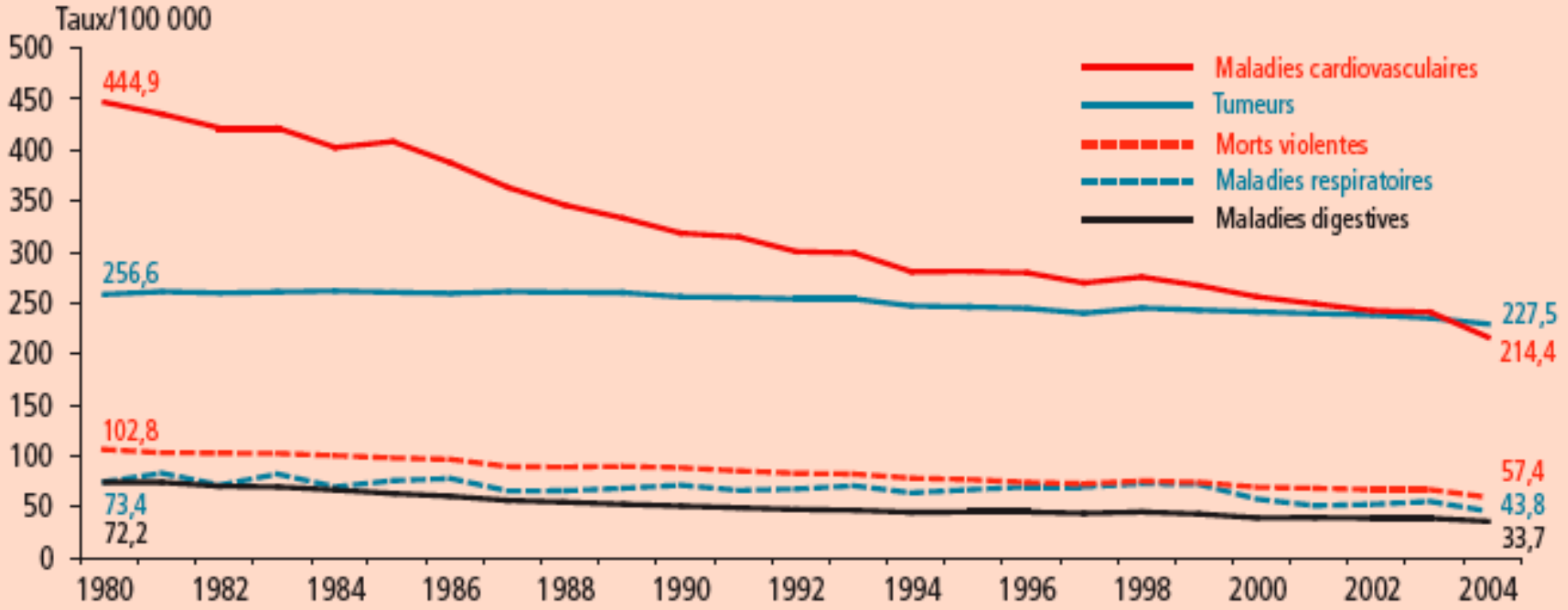


*Estimated **incidence** of main cancers in the European Union in 2004, from Boyle & Ferlay, Ann. Oncol. 2005*

Background: basic facts about cancer

In France, cancer (now 1st) and cardiovascular diseases (2nd) are by far the 2 major killers among *all diseases*

Figure 2 Evolution des taux* de décès par grande catégorie de causes de décès, 1980-2004, France métropolitaine, deux sexes / *Figure 2 Trends in death rates by main category of causes of death, 1980-2004, Metropolitan France, both sexes*



* Taux de décès standardisés pour 100 000.

Bulletin Épidémiologique Hebdomadaire (BEH) de l'INVS, 18/09/2007

(*Bulletin available online*: http://www.invs.sante.fr/beh/2007/35_36/index.htm)

Background: basic facts about cancer

The same trend (Cancer 1st) is also true in the USA

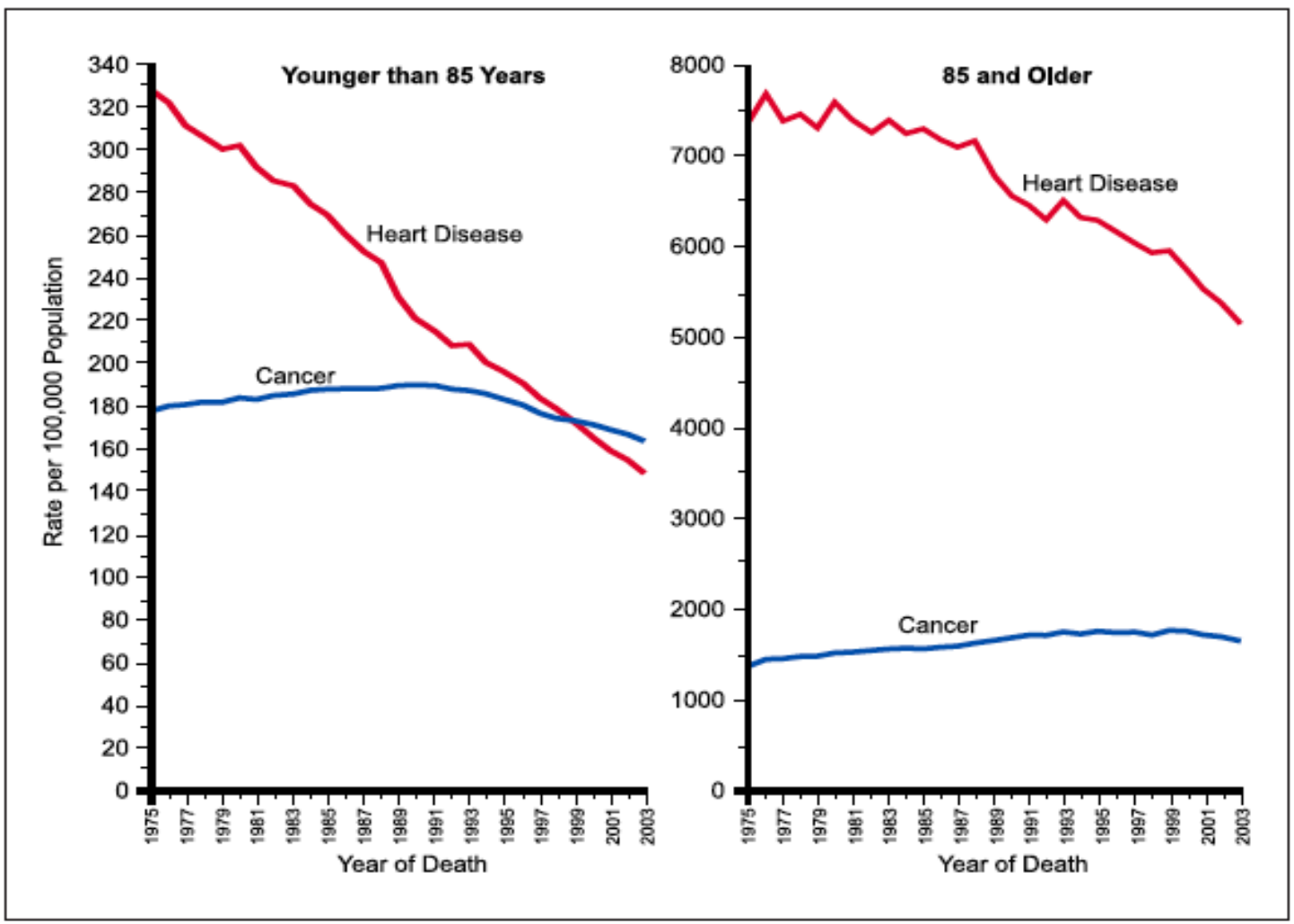


FIGURE 6 Death Rates* From Cancer and Heart Disease for Ages Younger Than 85 and 85 and Older.
*Rates are age-adjusted to the 2000 US standard population.
Source: US Mortality Public Use Data Tapes, 1960 to 2003, National Center for Health Statistics, Centers for Disease Control and Prevention, 2006.

(from Jemal et al., *CA Cancer J Clin 2007)*

Background: basic facts about cancer

Persistence of a very slow decrease in cancer mortality in the US

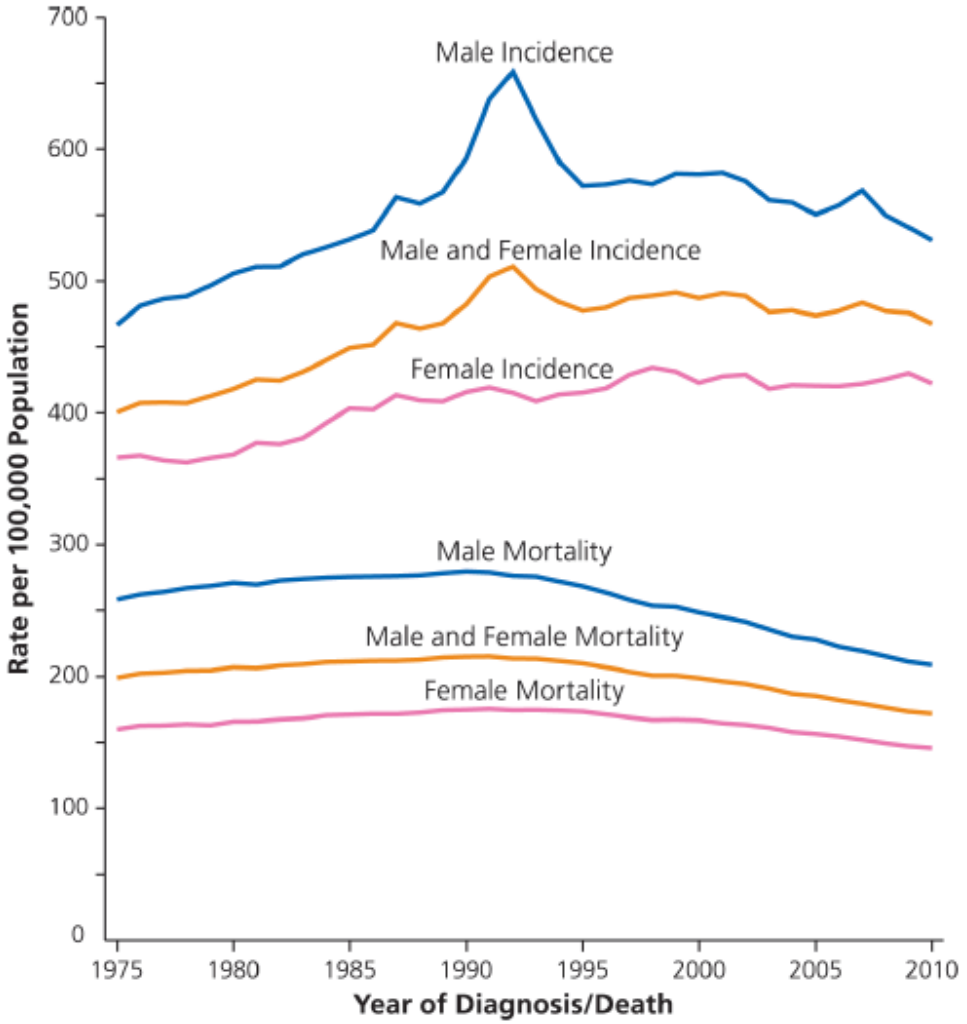


FIGURE 2. Trends in Cancer Incidence and Death Rates by Sex, United States, 1975 to 2010.
Rates are age adjusted to the 2000 US standard population. Incidence rates are adjusted for delays in reporting.

From Siegel et al., Cancer statistics 2014 CA Cancer J Clin 2014

Tissues that may evolve toward malignancy

…are the tissues where cells are committed to fast proliferation
(fast renewing tissues):

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

- liver cells in situations where the liver is called for renewal (e.g., surgery) or, in pathology, hepatocellular carcinoma

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

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

Natural history of cancers: from genes to bedside

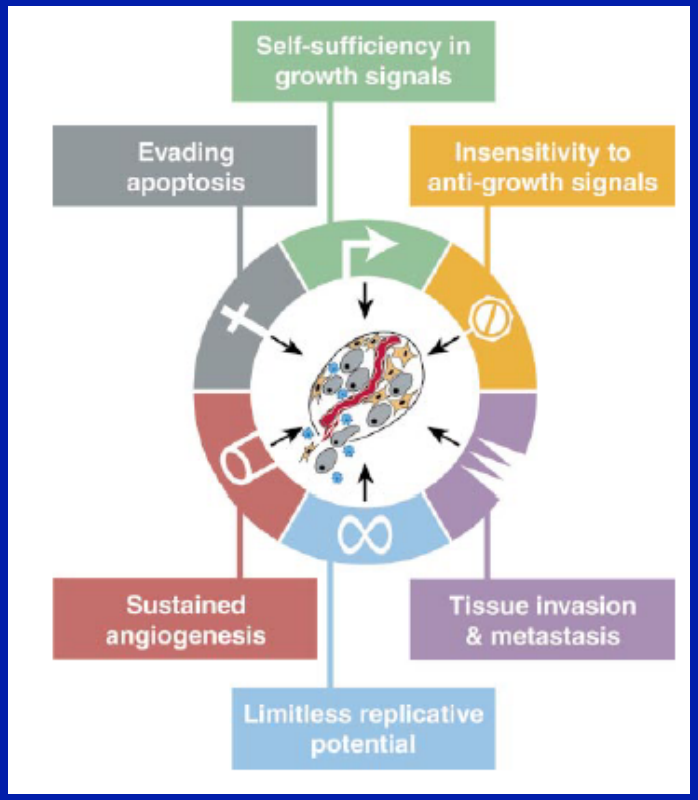
Gene mutations: an evolutionary process which may give rise to abnormal DNA when a cell duplicates its genome, due to defects in tumour suppressor or DNA repair (BER, NER) genes *(Yashiro et al. Canc Res. 2001; Gatenby & Vincent, Canc. Res. 2003)*

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

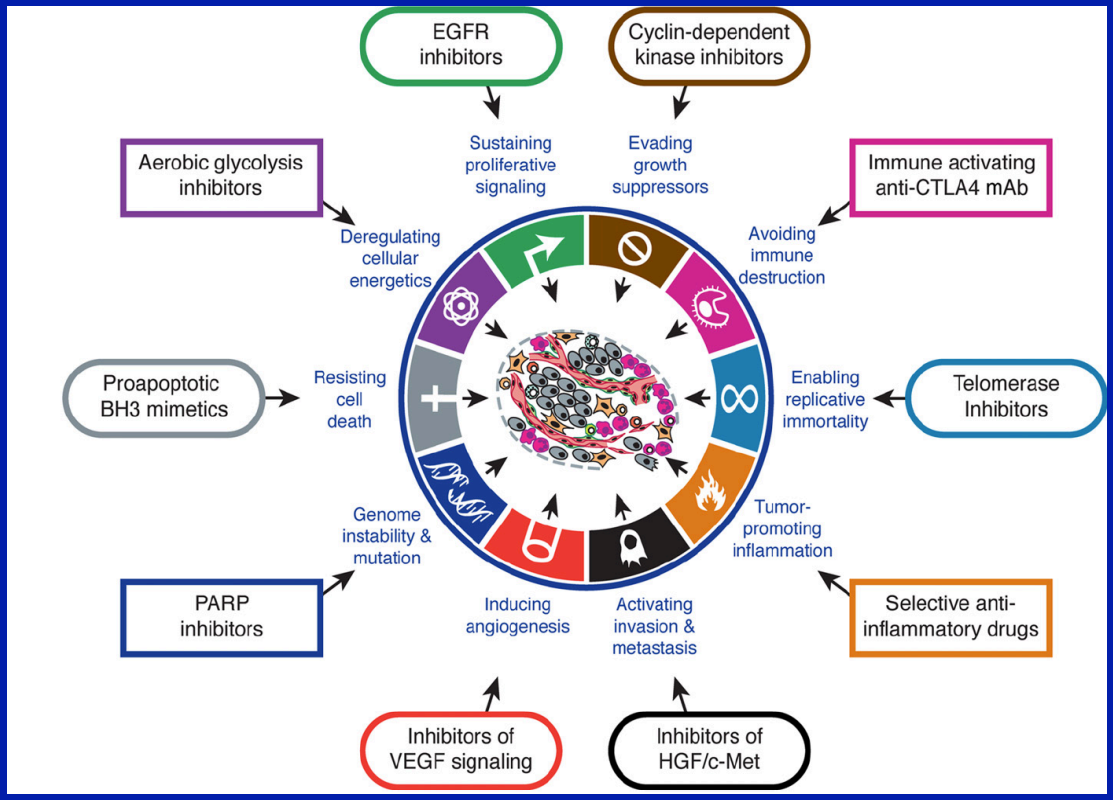
- Control on entry in the cell cycle for quiescent (=non-proliferating) cells
- Control on cell cycle phase transitions and apoptosis for proliferating cells
- Normal inability to use anaerobic glycolysis (selective advantage for cancer cells)
- Contact inhibition by surrounding cells (cell adhesion, cell density pressure)
- Normal inability to stimulate new blood vessels from the vascular neighbourhood
- Normal linking to the extracellular matrix (ECM) fibre network and basal membranes
- Recognition (friend or foe) by the immune system

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

Evading proliferation and growth control mechanisms



(Hanahan & Weinberg, Cell 2000)

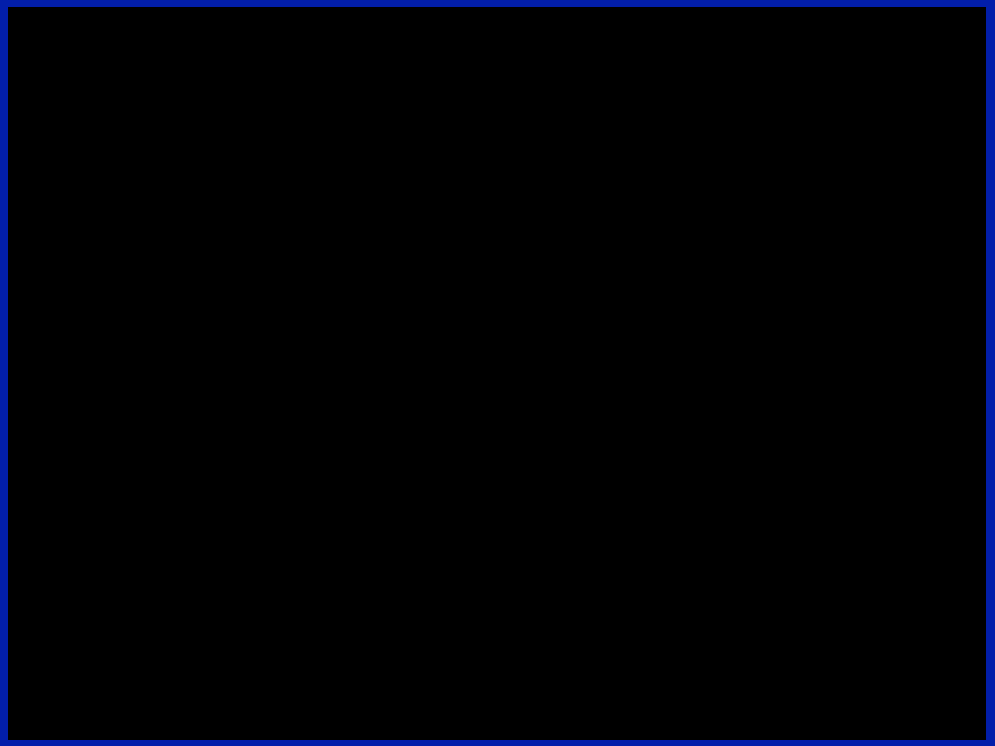


(Hanahan & Weinberg, Cell 2011)

…but just what is cell proliferation?

Background: basic facts about cancer

Cell population growth in proliferating tissues



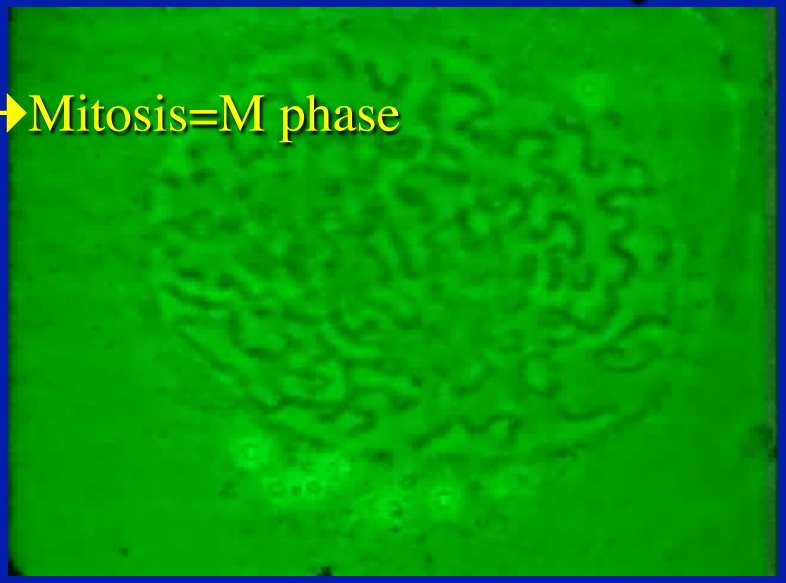
(from Lodish et al., Molecular cell biology, Nov. 2003)

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

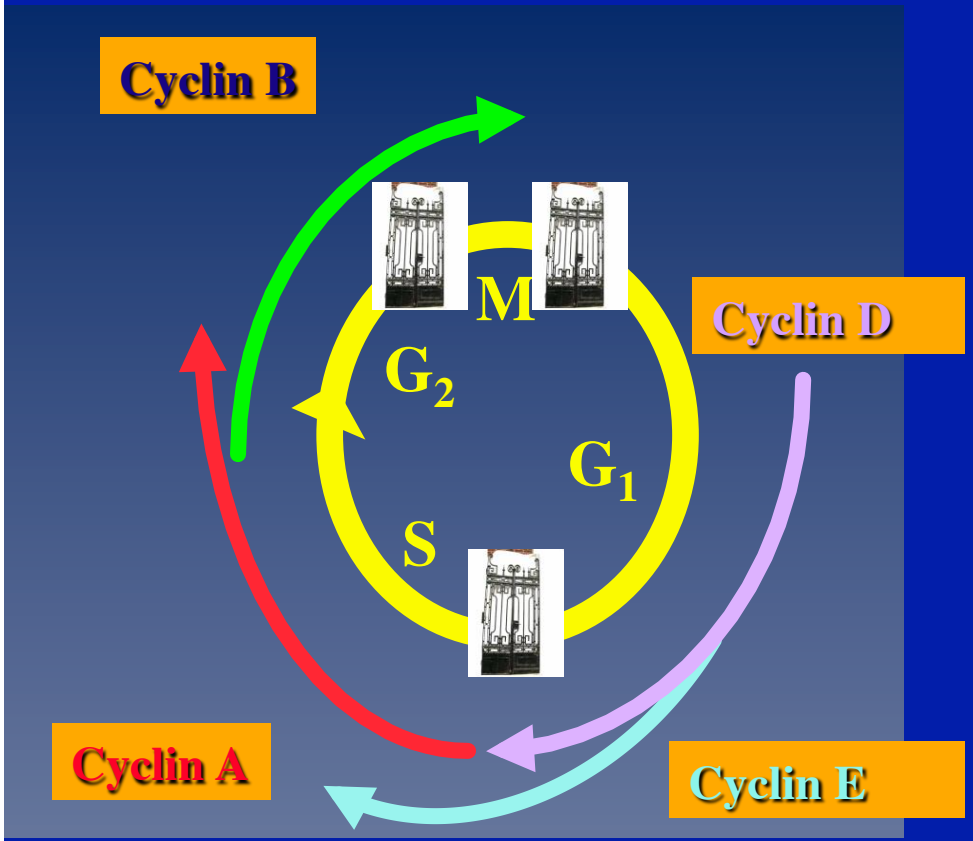
Background: basic facts about cancer

At the origin of proliferation: the cell division cycle

S:=DNA synthesis; G_1,G_2:=Gap1,2; M:=mitosis → Mitosis=M phase



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



Physiological or therapeutic control exerted on:

- transitions between *cell cycle phases* (G_1/S, G_2/M, M/G_1)
- death rates (apoptosis or necrosis) inside cell cycle phases
- velocity of progression of cell populations in cell cycle phases

Background: basic facts about cancer

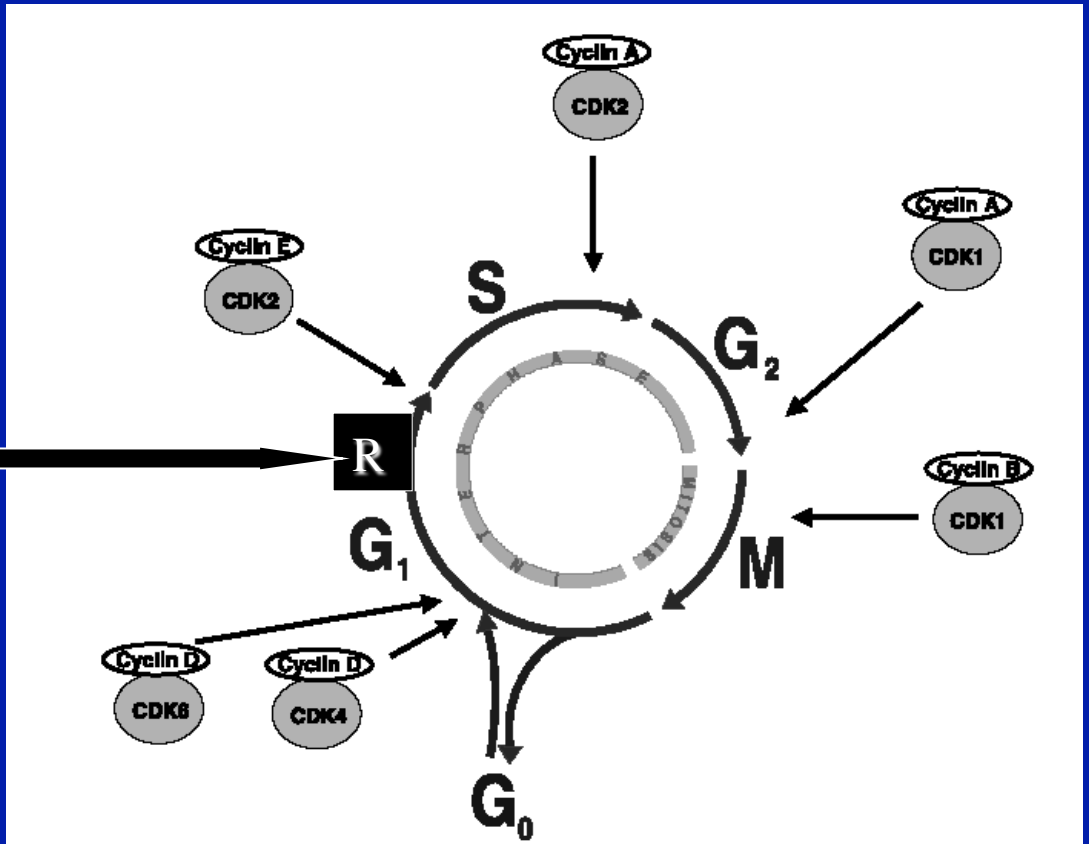
Proliferating and quiescent cells

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

Restriction point (in late G_1 phase)

(Pardee 1974
Zetterberg & Larsson 1985)

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)

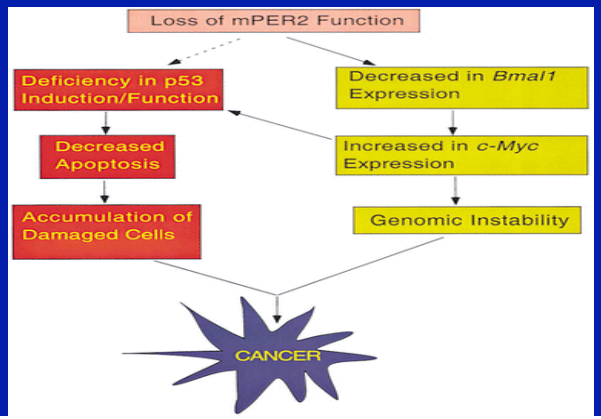
Exchanges between proliferating (G_1SG_2M) and quiescent (G_0) cell compartments are controlled by mitogens and antimitogenic factors in G_1 phase

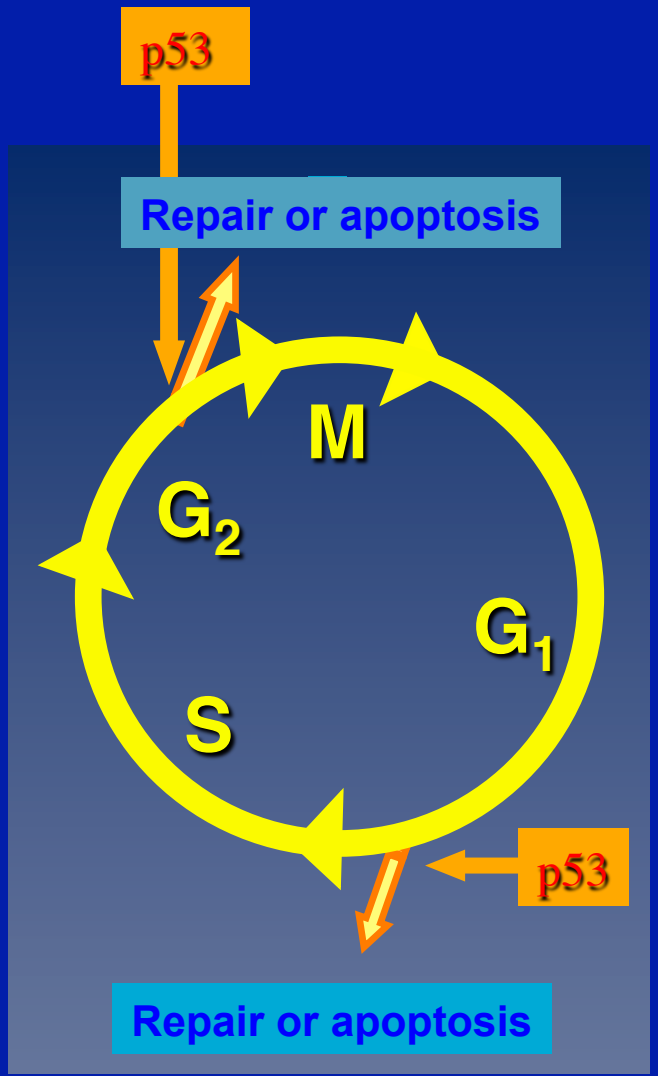
Phase transitions, apoptosis and DNA repair

- 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 expression is known to be down-regulated in about 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



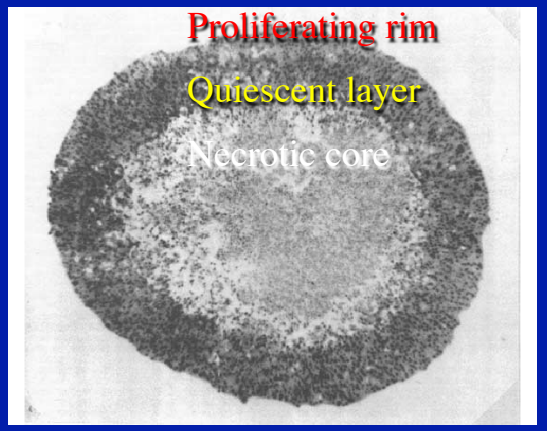


(Fu & Lee, Nature Rev. 2003)

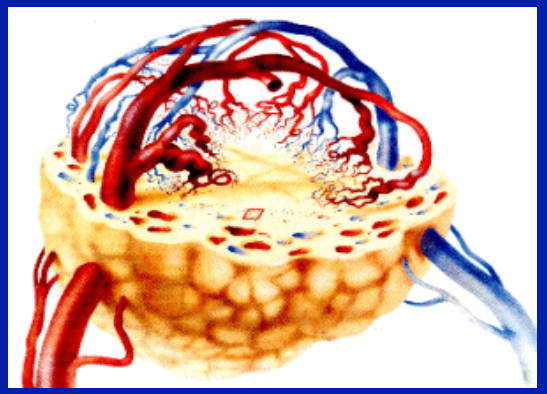
Background: basic facts about cancer

Invasion: local, regional and remote

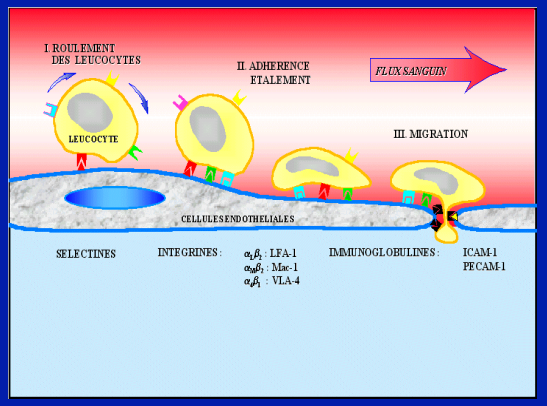
1) Local invasion by tumour cells implies loss of normal cell-cell and cell-ECM (extracellular matrix) contact inhibition of size growth and progression in the cell cycle. ECM (fibronectin) is digested by tumour-secreted matrix degrading enzymes (MDE=PA, MMP) so that tumour cells can move out of it.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



2) 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)



3) 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: (non specific)
Cytokines, macrophage-produced molecules to protect intact cells (e.g. interferon)

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

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

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

Cytotoxic T-Lymphocytes kill specific antigenic cells

(after P. Lollini, 2005)

I. Mathematical models of healthy and cancer tissue growth

Mathematical models of tumour growth and therapy

A great variety of models, depending on what one intends to describe

- 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 loco-regional invasion the main point? Then reaction-diffusion equations (e.g. KPP-Fisher) are widely used, for instance to describe tumour propagation fronts
- Is cell migration to be considered? Then chemotaxis [=chemically induced cell movement] models (e.g. Keller-Segel) have been used

A reference: A. Friedman. 'A hierarchy of cancer models and their mathematical challenges', DCDS-B 2004

Ordinary differential equations

Models of tumour growth 1

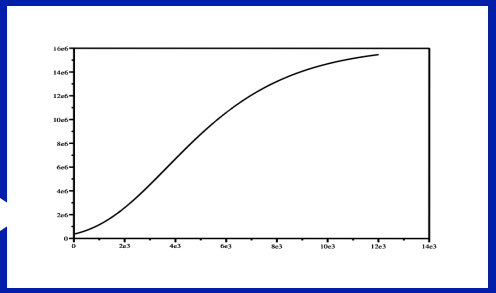
Macroscopic, non-mechanistic models: the simplest ones: exponential, logistic, Gompertz

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

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

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

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



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/space scarcity

[Used to describe therapeutic control by adding a drug action term $-\varphi(d, x)$ *on the RHS*]

Models of tumour growth 2: Gompertz revisited

ODE models a) with 2 cell compartments, proliferating and quiescent,
or b) varying the tumour carrying capacity x_{max} in the original Gompertz model

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

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

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

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

Avowed aim: to justify global Gompertz-like growth

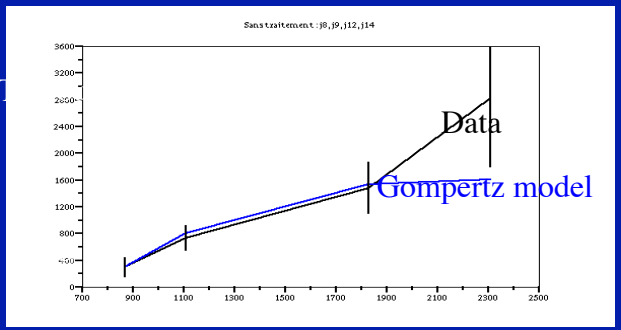
However, a lot of cell colonies and tumours do not follow Gompertz growth

Refinements: Hahnfeldt et al., Canc. Res 1999; Ergun et al., Bull Math Biol 2003

$$\dot{p}_t = -\lambda p_t \ln\left(\frac{p_t}{e_t}\right)$$

$$\dot{e}_t = be_t^{2/3} - de_t^{4/3}$$

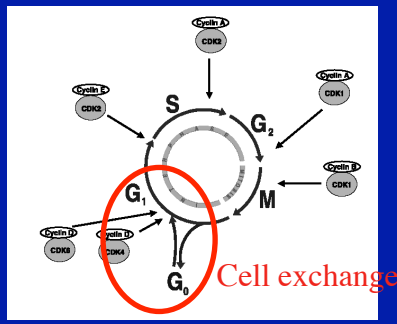
Example of non-Gompertz tumour growth:
(GOS) in a population of mice, laboratory data



Ordinary differential equations

a) ODE models with 2 exchanging cell compartments, proliferating (P) and quiescent (Q)

$$\begin{aligned} \frac{dP}{dt} &= [\beta - \mu_p - r_0(N)]P + r_i(N)Q \\ \frac{dQ}{dt} &= r_0(N)P - [r_i(N) + \mu_q]Q \\ N &= P + Q, \quad P_0 + Q_0 = 1 \end{aligned}$$

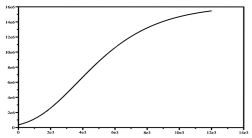


(Gyllenberg & Webb, Growth, Dev. & Aging 1989; Kozusko & Bajzer, Math BioSci 2003)

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



Initial goal: to mimic Gompertz growth

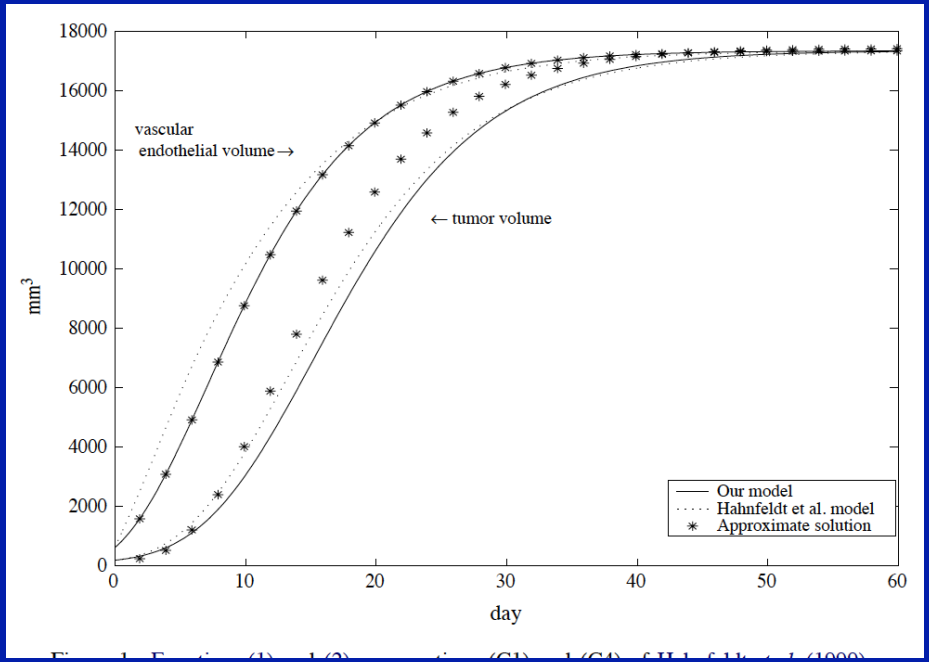
$$\frac{dx}{dt} = kx \ln\left(\frac{x_{max}}{x}\right)$$

b) ODE models with varying carrying capacity

$$\dot{p}_t = -\lambda p_t \ln\left(\frac{p_t}{e_t}\right)$$

$$\dot{e}_t = b e_t^{2/3} - d e_t^{4/3},$$

Hahnfeldt et al., Cancer Res. 1999
Ergün et al., BMB 2003



Used by U. Ledzewicz et al. to optimise combined delivery of cytotoxic and antiangiogenic drugs, acting on p_t and e_t, respectively

Models of tumour growth 3

Physical laws describing macroscopic spatial dynamics of an *avascular* tumour

- 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 occurs 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)

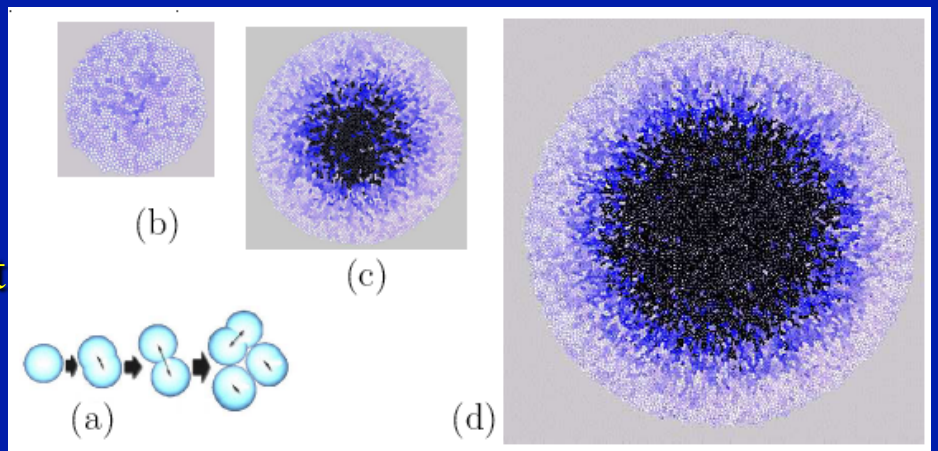


Fig. 1. Typical simulation scenario in the off-lattice model starting from (a) a single cell to (a) three cells and aggregates of (b) $N = 100$, (c) $N = 1000$, and (d) $N = 10000$ cells. (Further

Partial differential equations

Models of tumour growth 3

Mechanical models of macroscopic spatial dynamics involving pressure

Multiphase models with moving boundaries:
proliferating cells, quiescent cells, necrotic cells, surrounding healthy cells…

(see Preziosi et al.)

Simplified models with only intra-tumour cell pressure p and cell velocity $\underline{v}$:

$$\nabla \cdot \underline{v} = s_0 H(p_0 - p)$$
$$\underline{v} = -\mu \nabla p,$$

(from H. Byrne & D. Drasdo JMB 2009)

where $H(p_0 - p)$ denotes the Heaviside step function

Simplified models involving pressure p and nutrient concentration c *(ρ=cell density)*:

$$\begin{cases} \partial_t \varrho - \operatorname{div}(\varrho \nabla p) = \varrho\, \Phi(p, c), \\ \partial_t c - \Delta c = -\varrho\, \Psi(p, c), \\ c(x,t) \to c_B > 0 \qquad \text{as} \quad |x| \to \infty \end{cases}$$

(from Perthame-Quiroz-Vazquez Arch Rat Mech Anal 2014)

$$\partial_p \Phi < 0, \qquad \partial_c \Phi \geq 0, \qquad \Phi(p_M, c_B) = 0,$$
$$\partial_p \Psi \leq 0, \qquad \partial_c \Psi \geq 0, \qquad \Psi(p, 0) = 0.$$

Partial differential equations

Models of tumour growth 4

Macroscopic reaction-diffusion evolution equations (travelling wave fronts)

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

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

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

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

(Gatenby & Gawlinski, Canc. Res. 1996)

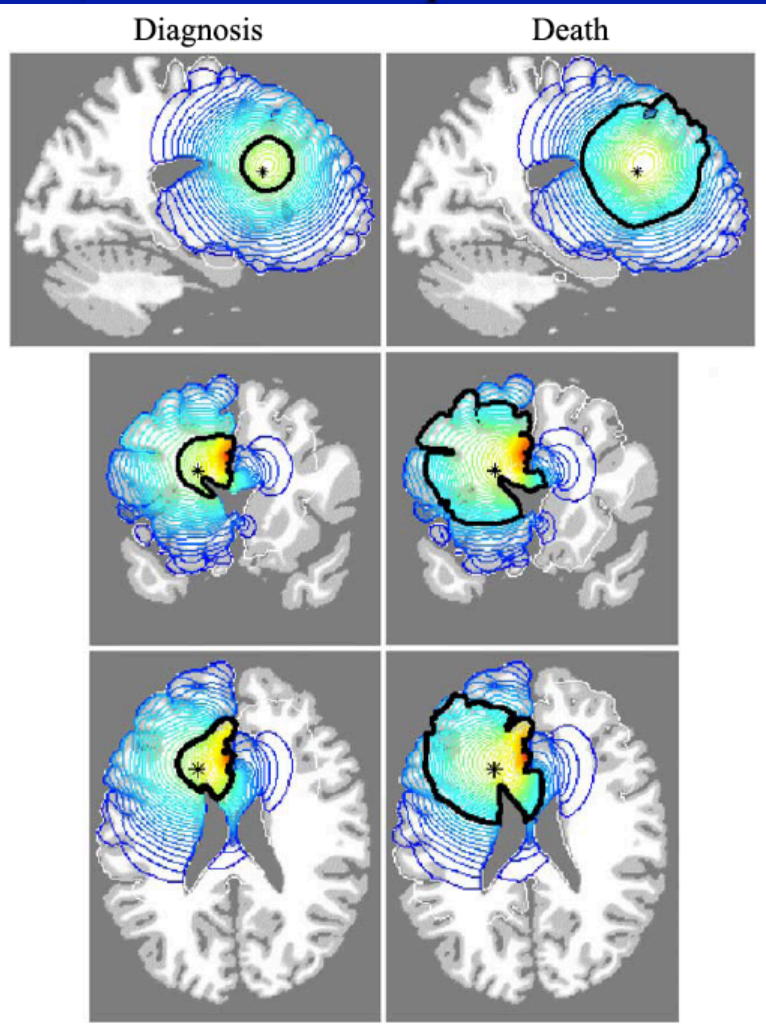
Prediction: interstitial cell gap between tumour propagation and healthy tissue recession fronts

PDE models of tumour growth: invasion

Macroscopic reaction-diffusion equations to represent invasion front

1-dimensional 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, x spatial variable (1-d, 2-d or 3-d) and c: density of tumour cells, used to represent brain tumour radial propagation from a centre. If $D(x) = D$, then v= 2.sqrt(ρD) is the front propagation speed

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

Partial differential equations

PDE models of tumour growth: invasion as competition

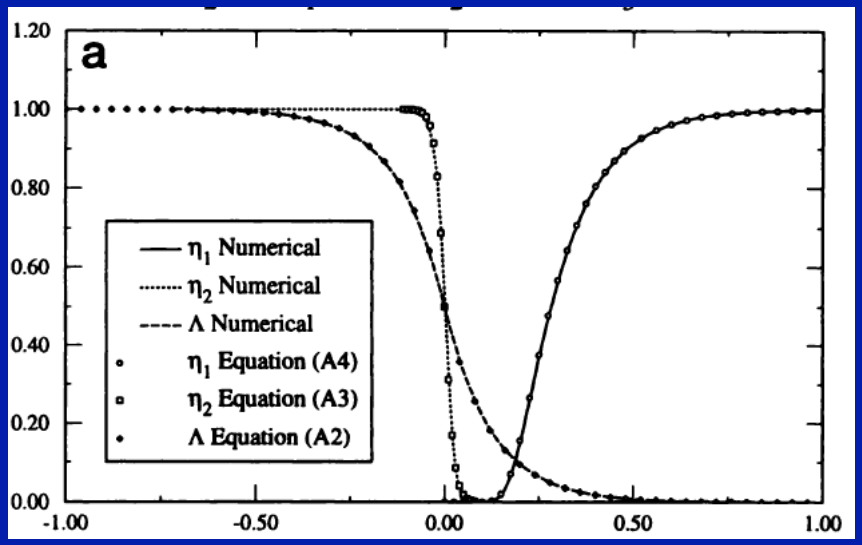
Macroscopic reaction-diffusion equations to represent invasion / recession fronts

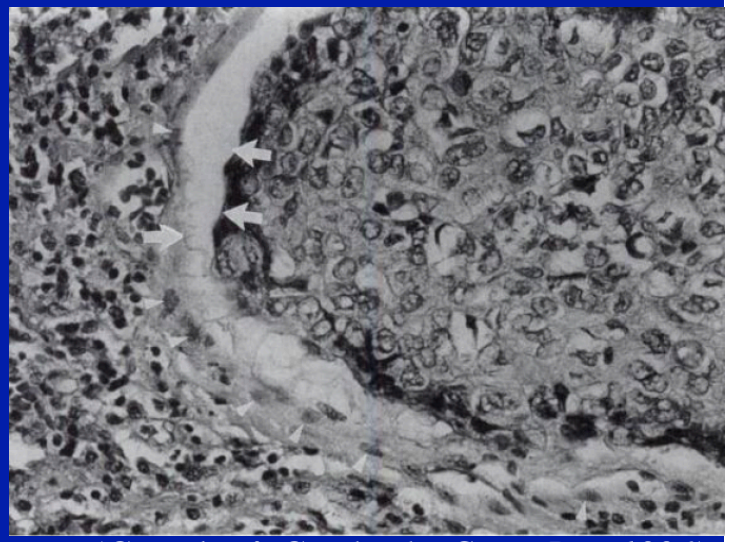
2 or more variables: ex.: healthy cells N_1, tumour cells N_2, excess H^+ ions L

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

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

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





(Gatenby & Gawlinski, Canc. Res. 1996)

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

PDE models for moving tumour cells in the ECM

Chemotaxis: chemo-attractant induced cell movements

Keller-Segel model

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

p = density of cells
w = density of chemoattractant

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

(Keller & Segel, J Theoret Biol 1971)

Anderson-Chaplain model for local invasion by tumour cells in the ECM

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

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

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

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

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)

Integro-differential models

Models of tumour growth 5

Models of Lotka-Volterra type, phenotype-structured, with built-in growth limitation

$$\frac{\partial}{\partial t}n(x,t) = \overbrace{\frac{\theta}{1+\alpha c_2(t)}\left(\int r(y)M(y,x)n(y,t)dy - r(x)n(x,t)\right)}^{\text{mutations and renewal}} + \underbrace{\left(\frac{r(x)}{1+\alpha c_2(t)} - d(x)I(t)\right)n(x,t)}_{\text{growth with cytostatic therapies and death}} - \underbrace{c_1(t)\mu(x)n(x,t).}_{\text{effect of cytotoxic therapies}}$$

(mentioned in Billy & Clairambault, DCDS-B 2013); see also Delitala & Lorenzi's papers

or:

$$\partial_t n(t,x,y) = \left[\frac{r(x,y)}{1+\mu_2(x,y)c_2(t)} - d(x,y)I(t) - \mu_1(x,y)c_1(t)\right]n(t,x,y)$$

(mentioned in Billy & Clairambault, DCDS-B 2013); see also Delitala & Lorenzi's papers

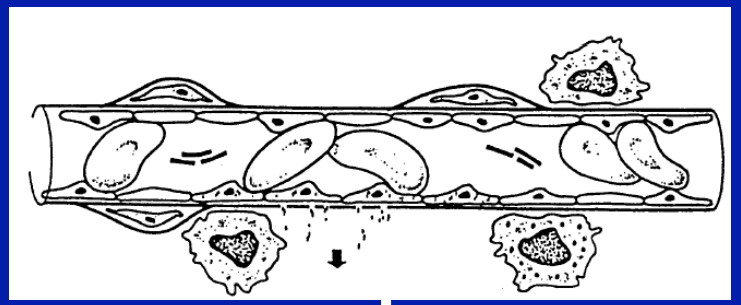
where $I(t) = \int_0^1 \int_0^1 n(x,y,t)\,dx\,dy$ is the total cell population or, more generally, a *[total]* cell population-dependent environment variable = growth limitation

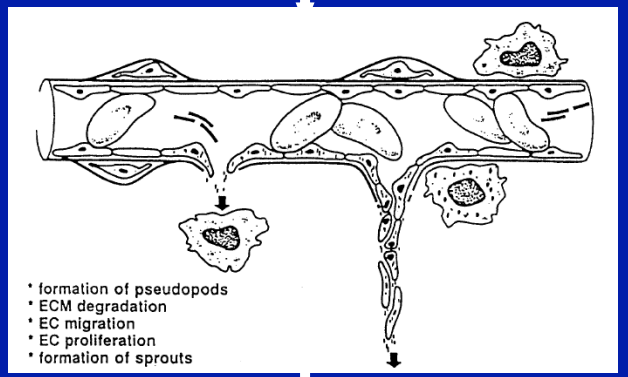
Partial differential equations

Models for angiogenesis

VEGF-induced endothelial cell movements towards tumour

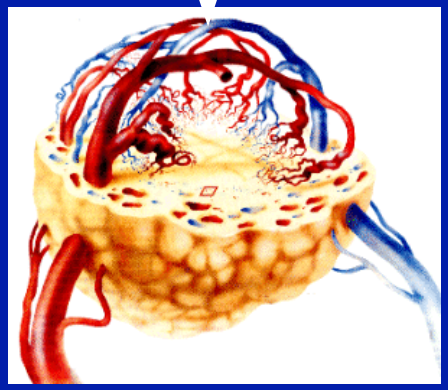
- Biochemical enzyme kinetics
- Chemical transport (capillary and ECM)
- “Reinforced random walks”
- Cell movements in the ECM





Models by Anderson and Chaplain, Levine and Sleeman

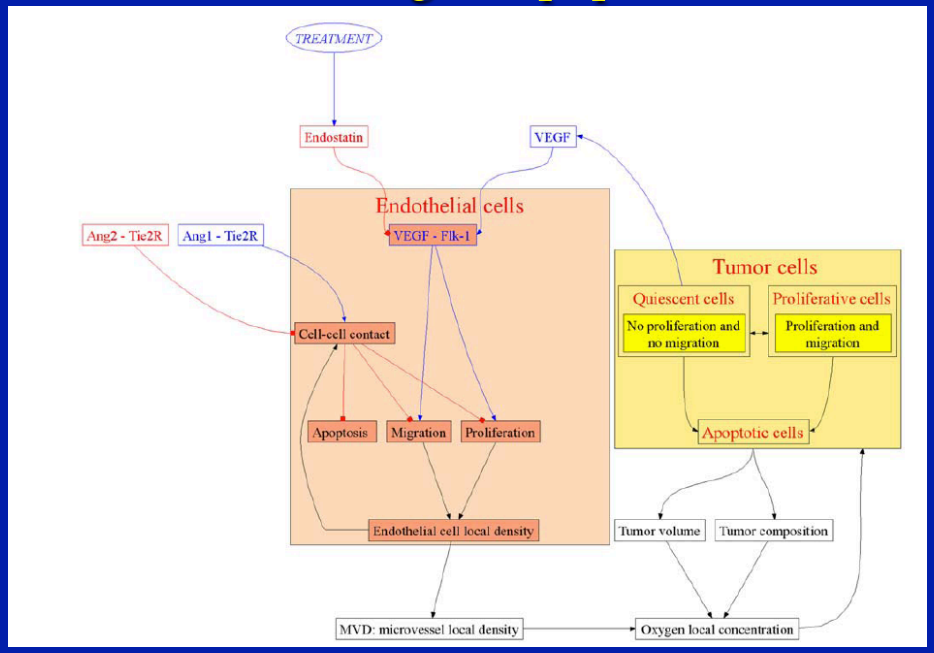
(Levine & Sleeman,Chap. 6 in Cancer modelling and simulation, L. Preziosi Ed, Chapman & Hall 2003)



Partial differential equations

A multiscale angiogenesis model

Interacting cell populations



Proliferating cancer cell population

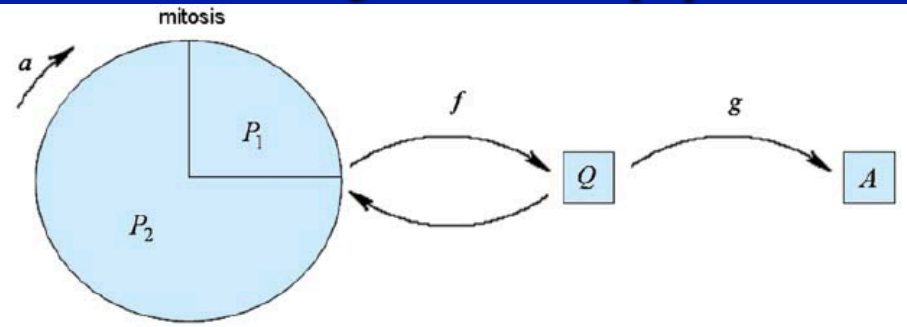


Fig. 4. Schematic representation of our age-structured cell cycle regulation model. We took into account two proliferative phases P_1 and P_2, one quiescent phase Q, and one apoptotic phase A. At the end of the P_1 phase, environmental conditions are checked; this checking is modeled through functions f and g. In a context of overpopulation or hypoxia, proliferative cells become quiescent (through function f). If the hypoxic stress is too high, cells can become apoptotic (through function g). If the environmental conditions become more favorable, quiescent cells can revert to the proliferative phase. We suppose that mitosis occurs at the end of the P_2 phase, leading to the generation of new cells.

Coupling by oxygen concentration, acting on actual commitment of cells into the division cycle (passing the restriction point)

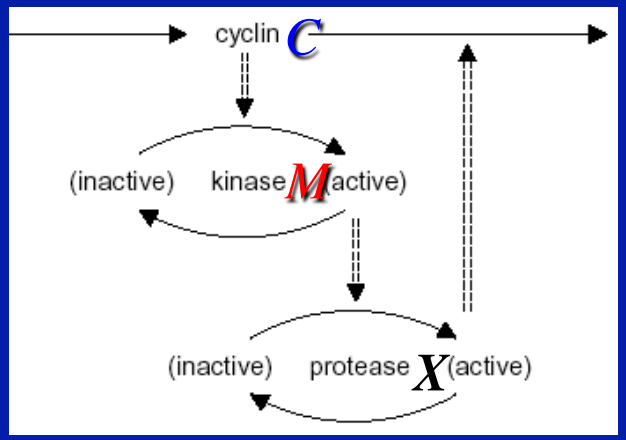
Aim: assessment of an antiangiogenic treatment by endostatin

F. Billy et al., J. Theor. Biol. 2009

Modelling the cell cycle 1 (single-cell models)

Ordinary differential equations to describe progression in the cell cycle

A. Golbeter's minimal model for the « mitotic oscillator »



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

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

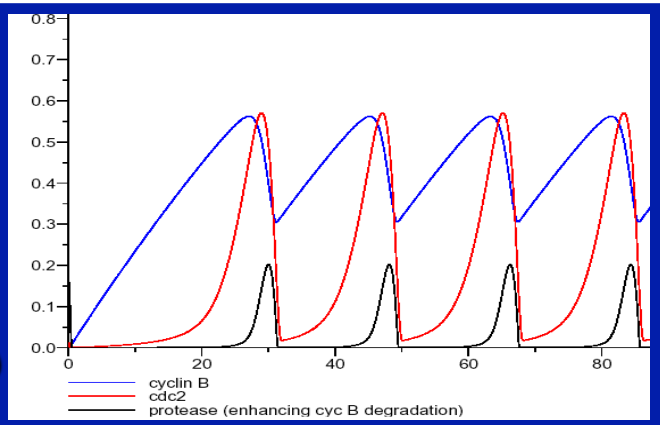
$$\frac{dX}{dt} = v_3 M \frac{(1 - X)}{K_3 + (1 - X)} - V_4 \frac{X}{K_4 + X}.$$

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

Switch-like dynamics of kinase cdk1, M

Adapted to describe G_2/M phase transition, which is controlled by Cyclin B

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



Ordinary differential equations

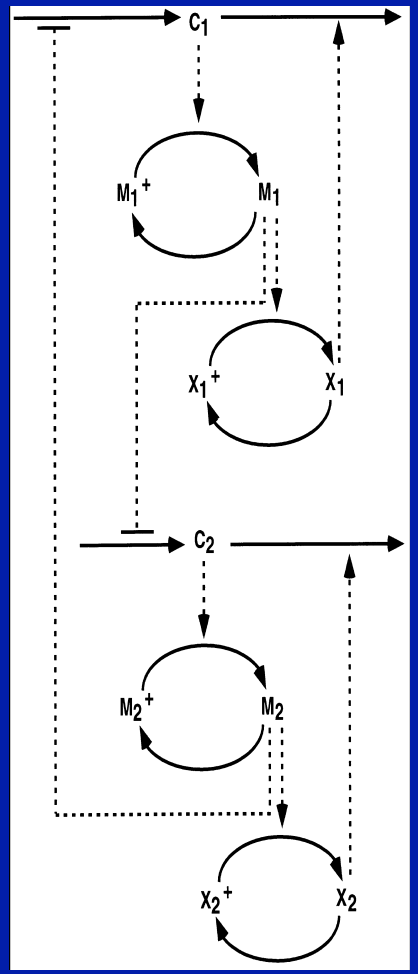
Including more phase transitions in the cell cycle model?

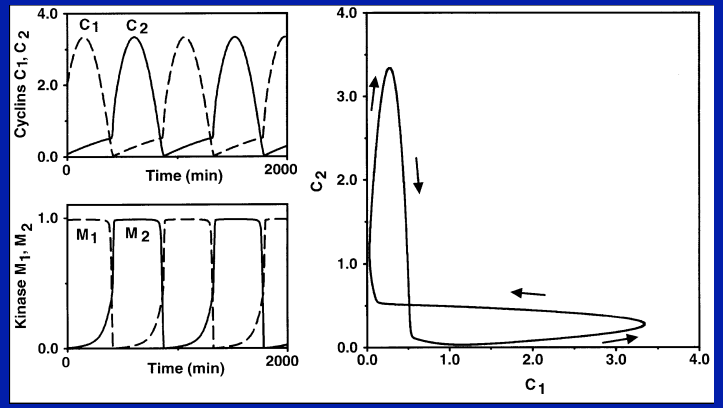
Hint: an existing model for G_1/S and G_2/M synchronisation

(recalling the minimum mitotic oscillator *(C, M, X)* by A. Goldbeter, 1996, here duplicated to take into account synchronisation between G_1/S and G_2/M transitions)

i=1: G_1/S

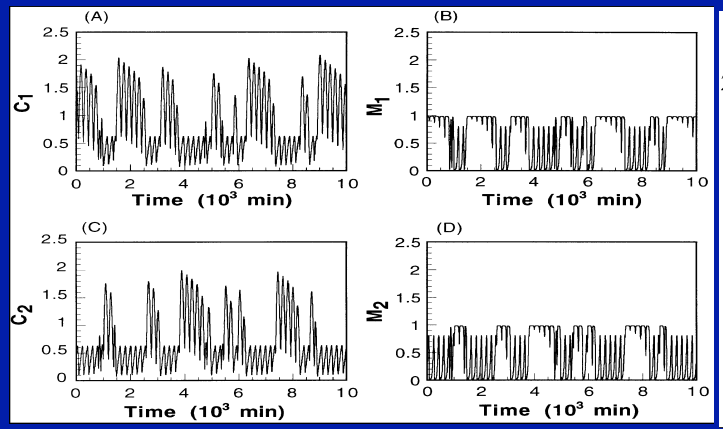
i=2: G_2/M

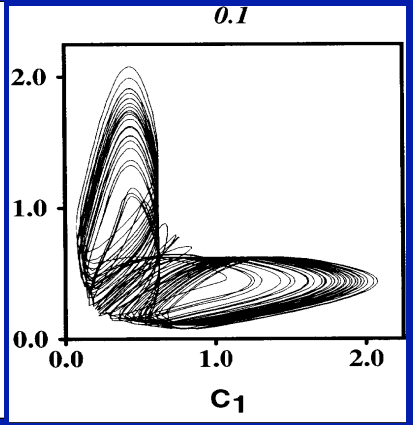




C_i=Cyclin
M_i=CDK
X_i=Protease

Changing the coupling strength may lead to:

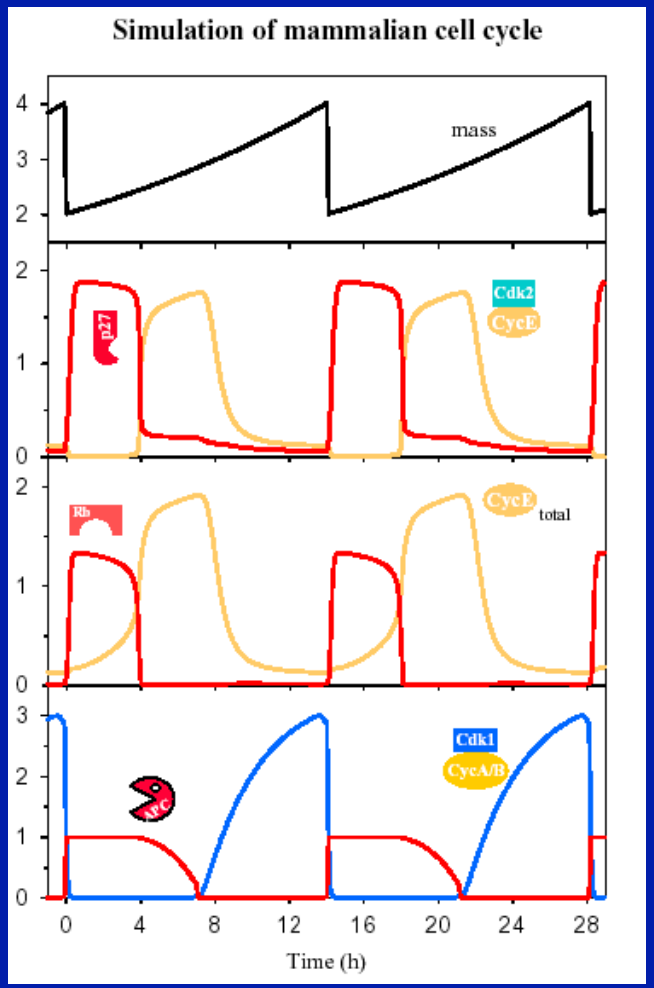




Romond, Gonze, Rustici, Goldbeter, Ann NYAS, 1999

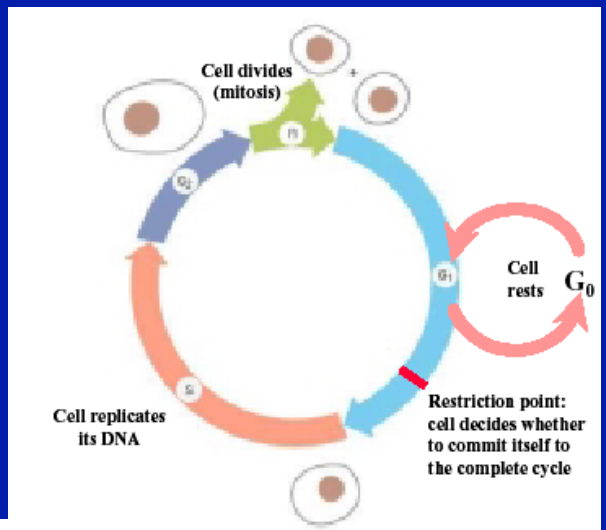
Modelling the cell cycle 2 (single-cell models)

Detailed ODE models to describe progression in the cell cycle



Phase transitions:
-G_1/S
-G_2/M
-Metaphase/anaphase

…due to steep variations of Cyc-cdk concentrations (bifurcation parameter=cell mass)



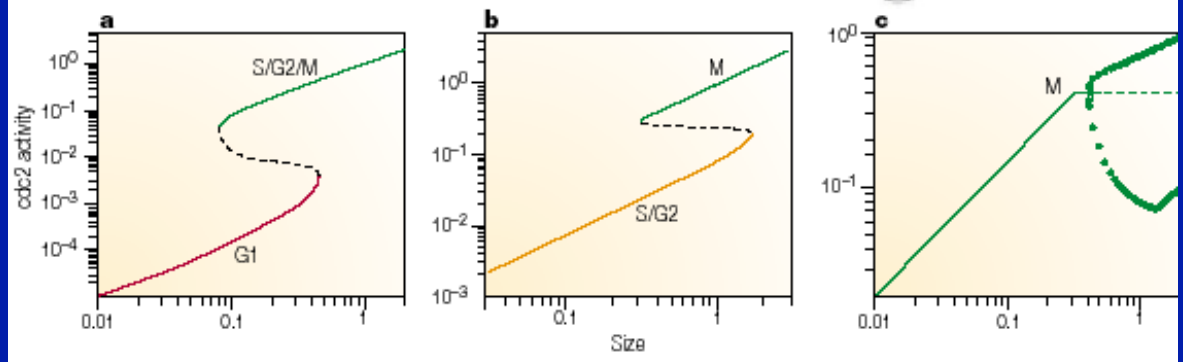


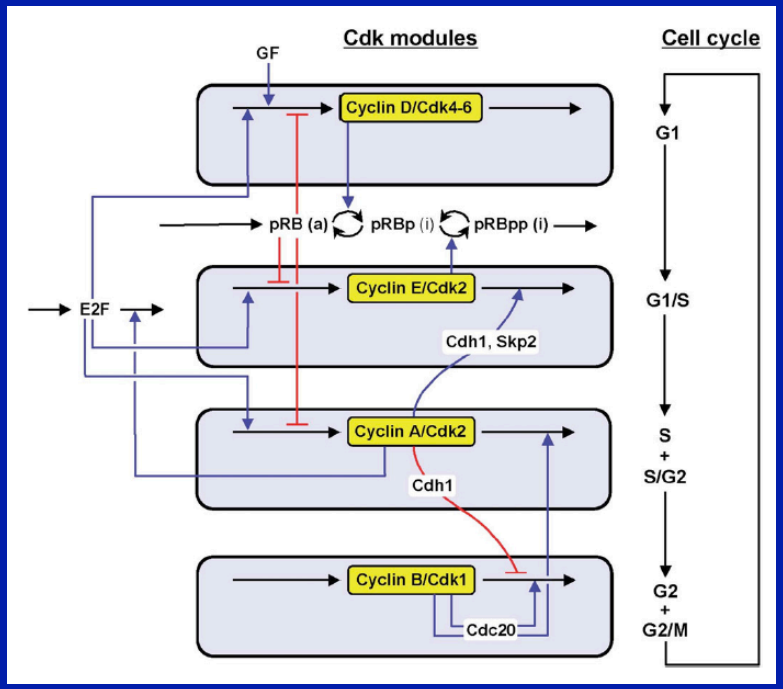
Figure 5 | **Bifurcation diagrams for the three control modules of the cell cycle.** The activity of cdc2–cdc13 dimers (an indicator of the state of the control system) is plotted against 'size' (the number of ribosomes per nucleus, an indicator of cell growth and division). All variables are expressed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

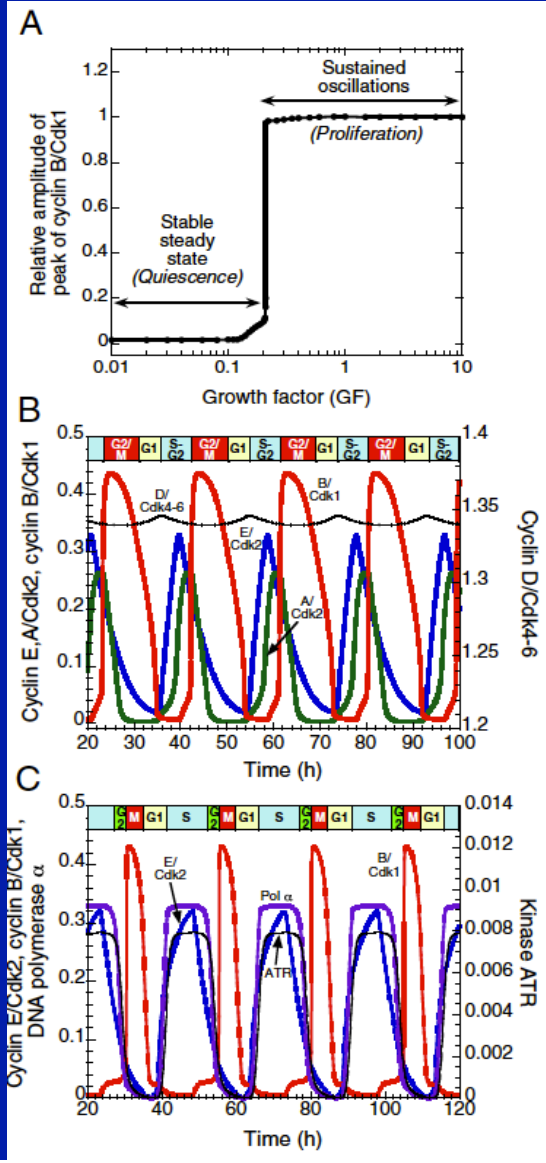
(Novak, Bioinformatics 1999)

(Tyson, Chen, Novak, Nature Reviews 2001)

Modelling the cell cycle 2: single cell (continued)

Even more detailed ODE models to describe progression in the cell cycle





39 variables. Growth factor, rather than cell mass (as in Tyson, Chen & Novak) is the driving parameter for bifurcations

A simplified model has been proposed, with 5 variables

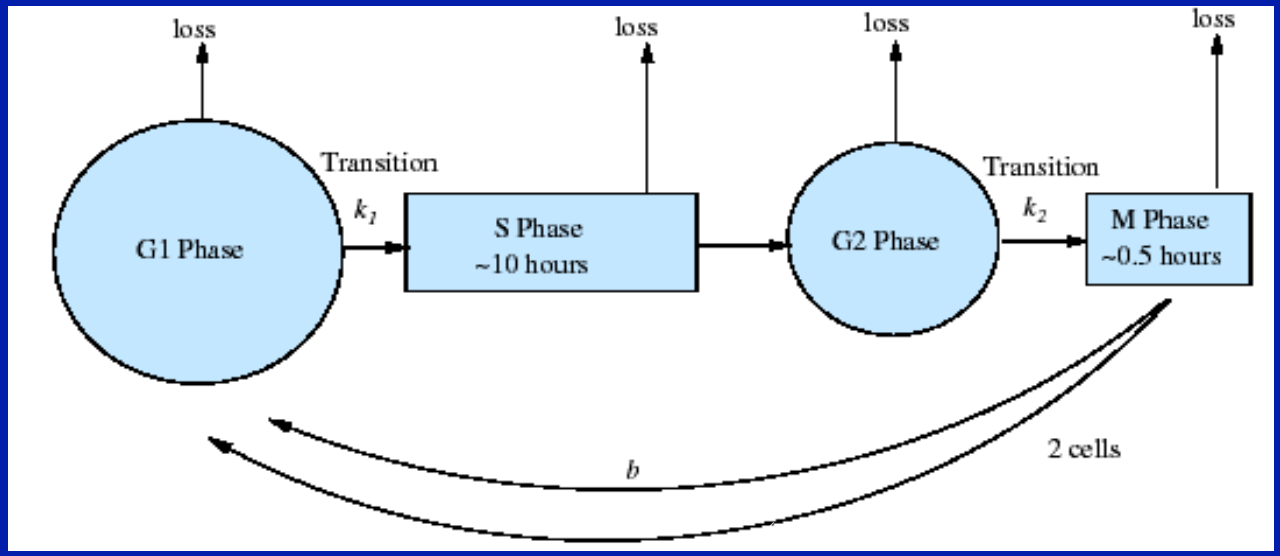
C. Gérard & A. Goldbeter, PNAS 2009; Interface Focus 2011

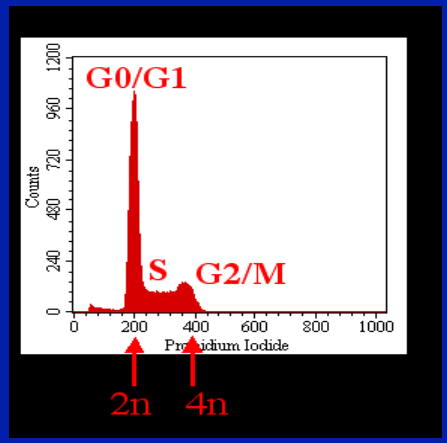
C. Gérard, D. Gonze & A. Goldbeter, FEBS Journal 2012

Partial differential equations

Modelling the cell cycle 3

PDE models for age-structured cycling cell populations





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 2 for $i=1$)

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

General case (N phases): by the Krein-Rutman theorem (infinite-dimensional form of the Perron-Frobenius theorem), there exists a nonnegative first eigenvalue λ and, if $\widetilde{N}_i(t,a) = e^{-\lambda t} n_i(t,a)$, N_i, bounded solutions to the problem *(here $v_i(a)=1$)* :

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

with a real number ρ such that the asymptotics of $\widetilde{N}_i(t,a) = e^{-\lambda t} n_i(t,a)$ follow:

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

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

Ph. Michel, S. Mischler, B. Perthame, C. R. Acad. Sci. Paris Ser. I (Math.) 2004; J Math Pures Appl 2005
Ph. Michel, B. Perthame, C. R. Acad. Sci. Paris Ser. I (Math.) 2006; Proc. ECMTB Dresden 2005, Birkhäuser 2007

JC.

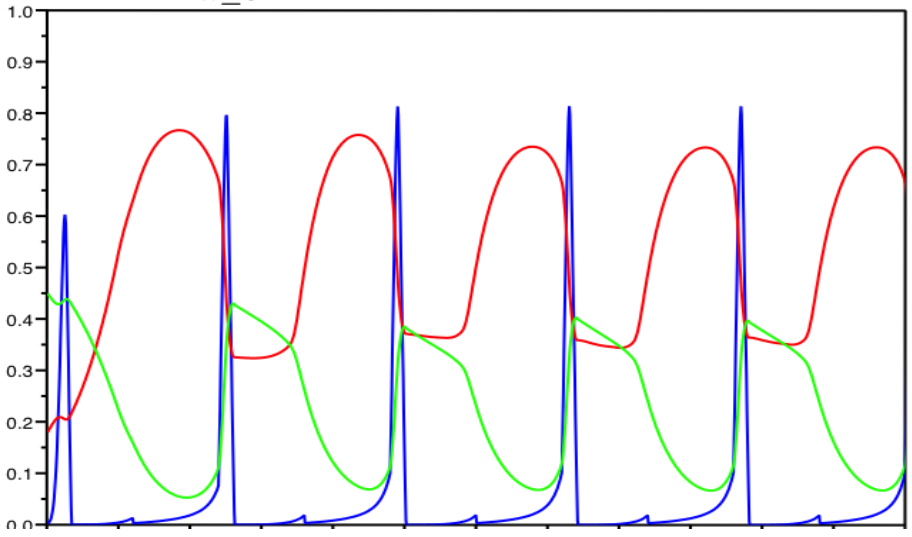
Partial differential equations

λ: a growth exponent governing the cell population behaviour

In summary: proof of the existence of a unique growth exponent λ, the same for all phases i, such that the $\widetilde{N}_i(t,a) = e^{-\lambda t} n_i(t,a)$ are bounded, and asymptotically periodic if the control is periodic

Example of control (periodic control case): 2 phases, control on G_2/M transition by 24-h-periodic CDK1-Cyclin B (from A. Goldbeter's minimal mitotic oscillator model)

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



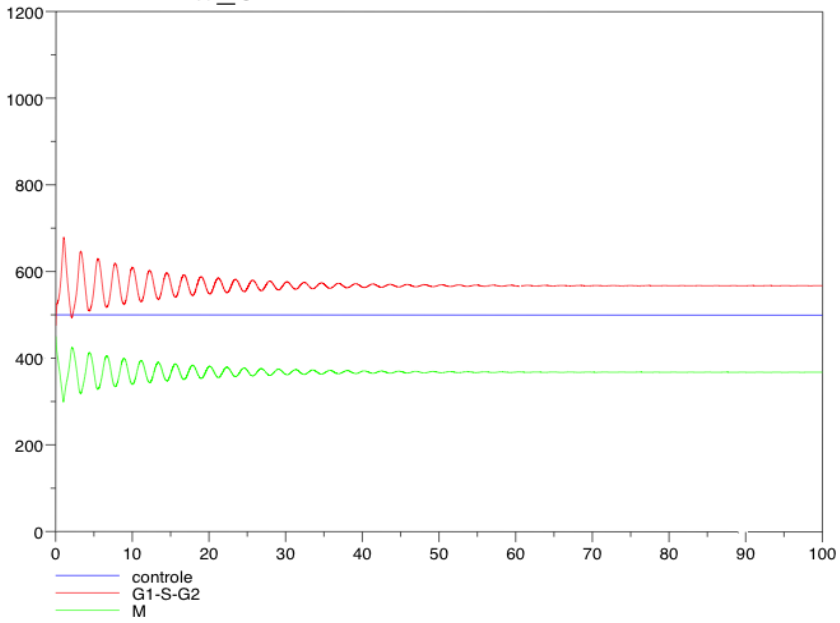
ψ=CDK1 All cells in G1-S-G2 (phase i=1) All cells in M (phase i=2)

"Surfing on the exponential growth curve"

(= the same as adding an artificial death term +λ to the d_i)

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

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

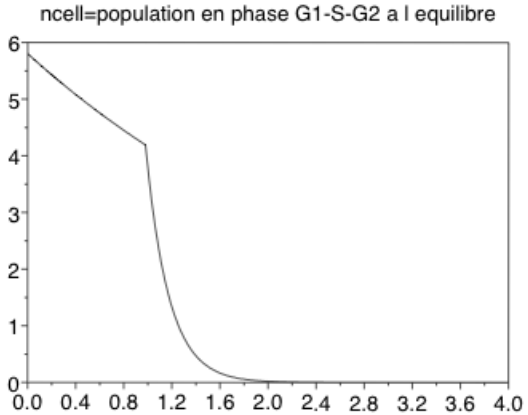


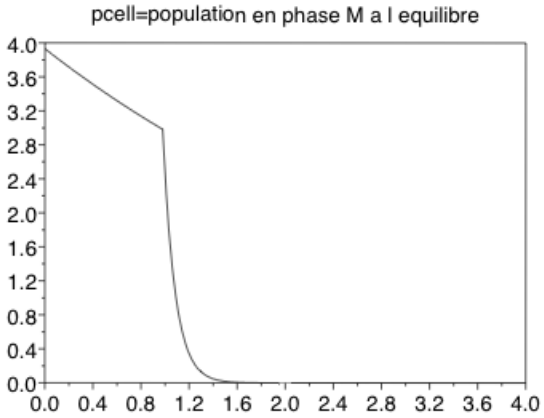
The total population of cells

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

inside each phase follows asymptotically an exponential behaviour

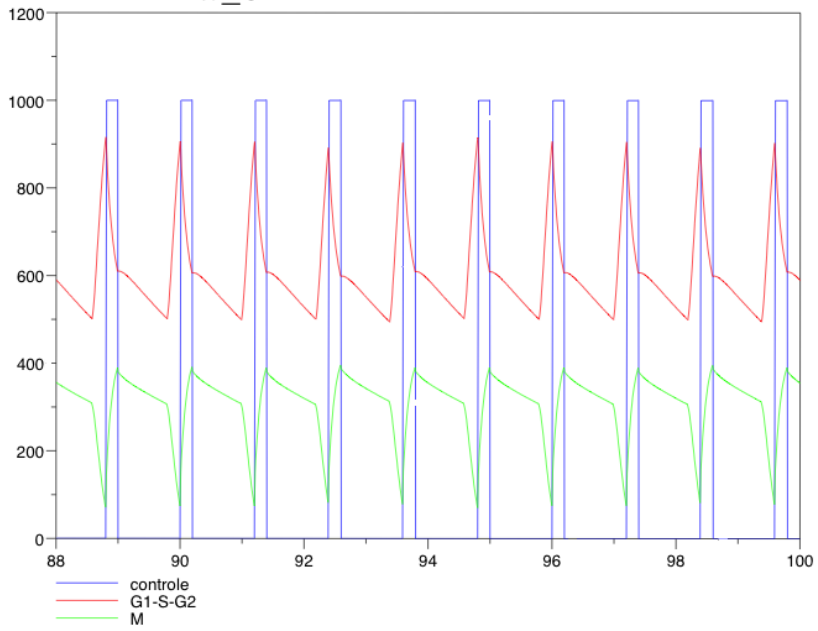
Stationary state distribution of cells inside phases according to age *a*: *no control, hence exponential decay*





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

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

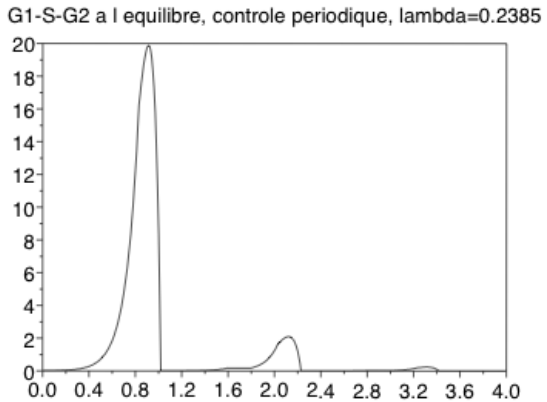


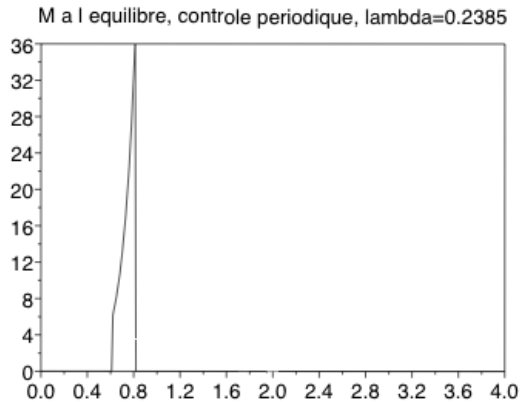
The total population of cells

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

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, hence sharp rise and decay*





Partial differential equations

The simplest case: 1-phase model with division

$$\frac{\partial}{\partial t}n(t,a)+\frac{\partial}{\partial a}[n(t,a)]+[d(t)+K(t,a)]\,n(t,a)=0$$

$$n(t,a=0)=2\int_{\alpha\geq 0}K(t,\alpha)\,n(t,\alpha)\,d\alpha$$

$$\text{where } K(t,a)=K_0\psi(t)\mathbb{1}_{[a^*,+\infty[}(a)$$

$$\text{and } \psi(t)=\mathbb{1}_{[0,\tau[}(t),\ 1\text{-periodic}$$

(Here, $v(a)=1$, a^* is the cell cycle duration, and $\tau(<1)$ is the time during which the 1-*periodic control* ψ is actually exerted on cell division)

Then it can be shown that the eigenvalue problem:

$$n(t,a)=e^{\lambda t}N(t,a)$$

$$\int_{\alpha\geq 0}N(t,a)da=1$$

$$\frac{\partial}{\partial t}N(t,a)+\frac{\partial}{\partial a}[N(t,a)]+[\lambda+d(t)+K(t,a)]\,N(t,a)=0$$

$$N(t,a=0)=2\int_{\alpha\geq 0}K(t,\alpha)\,N(t,\alpha)\,d\alpha$$

has a unique positive 1-*periodic* eigenvector N, with a positive eigenvalue λ, solution, if $d(t)=d$, $K(t,a)=K(a)$ of Lotka's (=Euler's) equation: $\frac{1}{2}=\int_0^{+\infty}f(x)e^{-\lambda x}dx$, where $f(x)=K(x)e^{-\int_0^x K(y)dy}$ is a p.d.f. if $\int_0^{+\infty}K(x)dx=+\infty$

Partial differential equations

Experimental measurements to identify transition kernels K_{i_i+1}

(and simultaneously experimental evaluation of the first eigenvalue λ)

In the simplest model with d=0 (one phase with division) and assuming K=$K(x)$ (instead of indicator functions $\mathbb{1}_{[a^*,+\infty[}$, experimentally more realistic transitions):

$$\begin{cases} \frac{\partial}{\partial t}n(t,x) + \frac{\partial}{\partial x}n(t,x) + K(x)n(t,x) = 0, \\ n(t,0) = 2\int_0^\infty K(x)n(t,x)dx. \end{cases}$$

Whence (by integration along characteristic lines):

$$n(t+x,x) = n(t,0)e^{-\int_0^x K(y)dy}$$

Interpreted as: if τ is the age in phase at division, or transition:

$$P(\tau > x) = e^{-\int_0^x K(y)dy} \text{ with } \int_0^\infty K(x)dx = +\infty$$

With probability density (experimentally identifiable):

$$f(x) = K(x)e^{-\int_0^x K(y)dy} \text{ i.e., } K(x) = \frac{f(x)}{\int_x^\infty f(y)dy}$$

Experimental parameter identification for this cell cycle model with 2 phases G1 / S-G2-M using *FUCCI reporters*

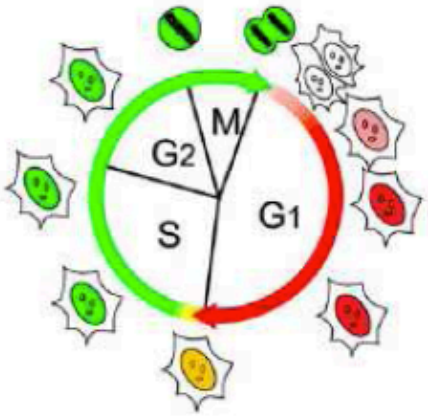
FUCCI=Fluorescent Ubiquitination-based Cell Cycle Indicator

Cells:

NIH 3T3 of a common population
(*mouse embryonic fibroblasts*)
without preliminary synchronization

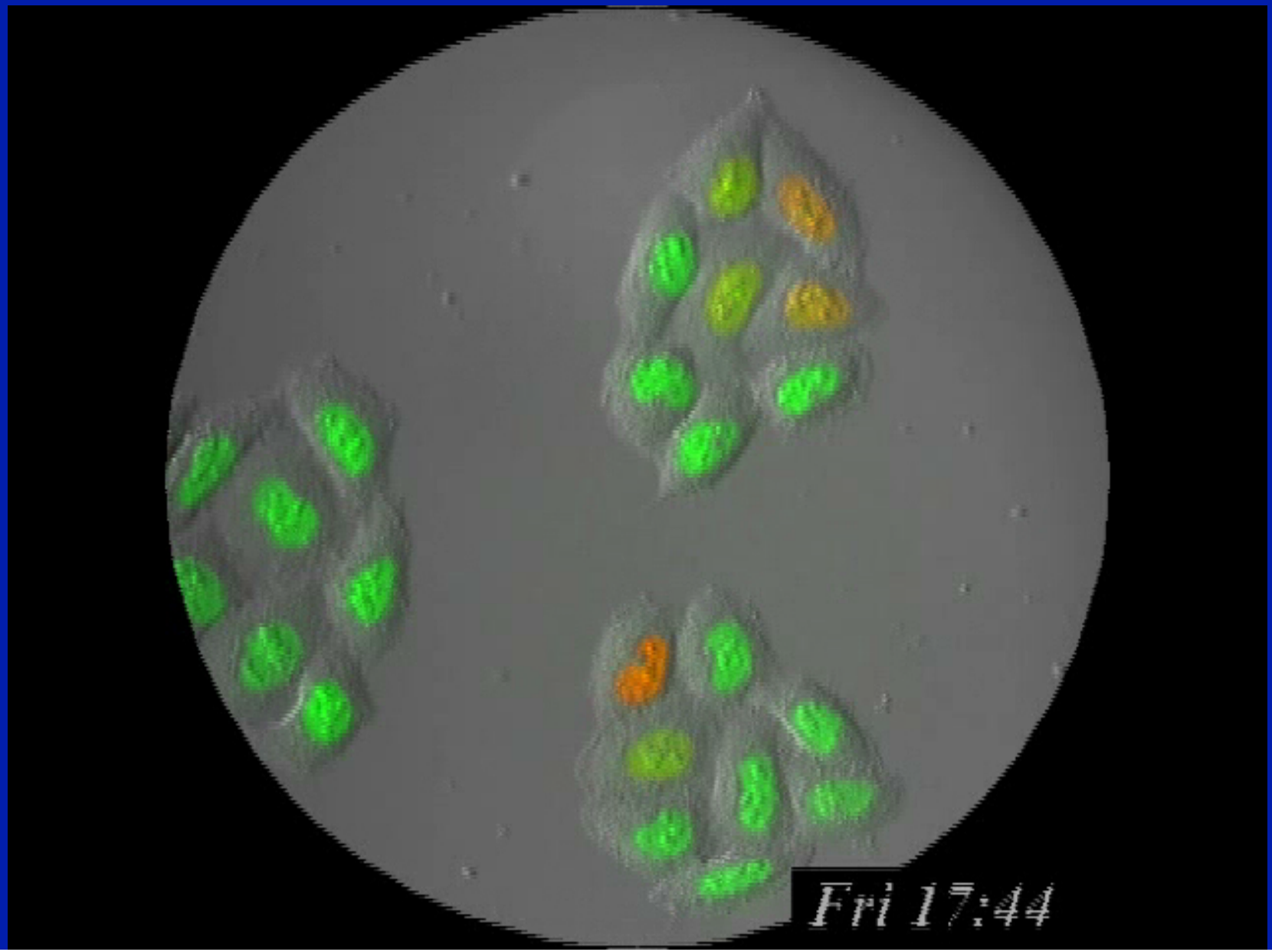
Measures: for each individual cell:
red and green fluorescence time recording

- ⇝ every 15 min
- ⇝ approx. 150 measures for each cell

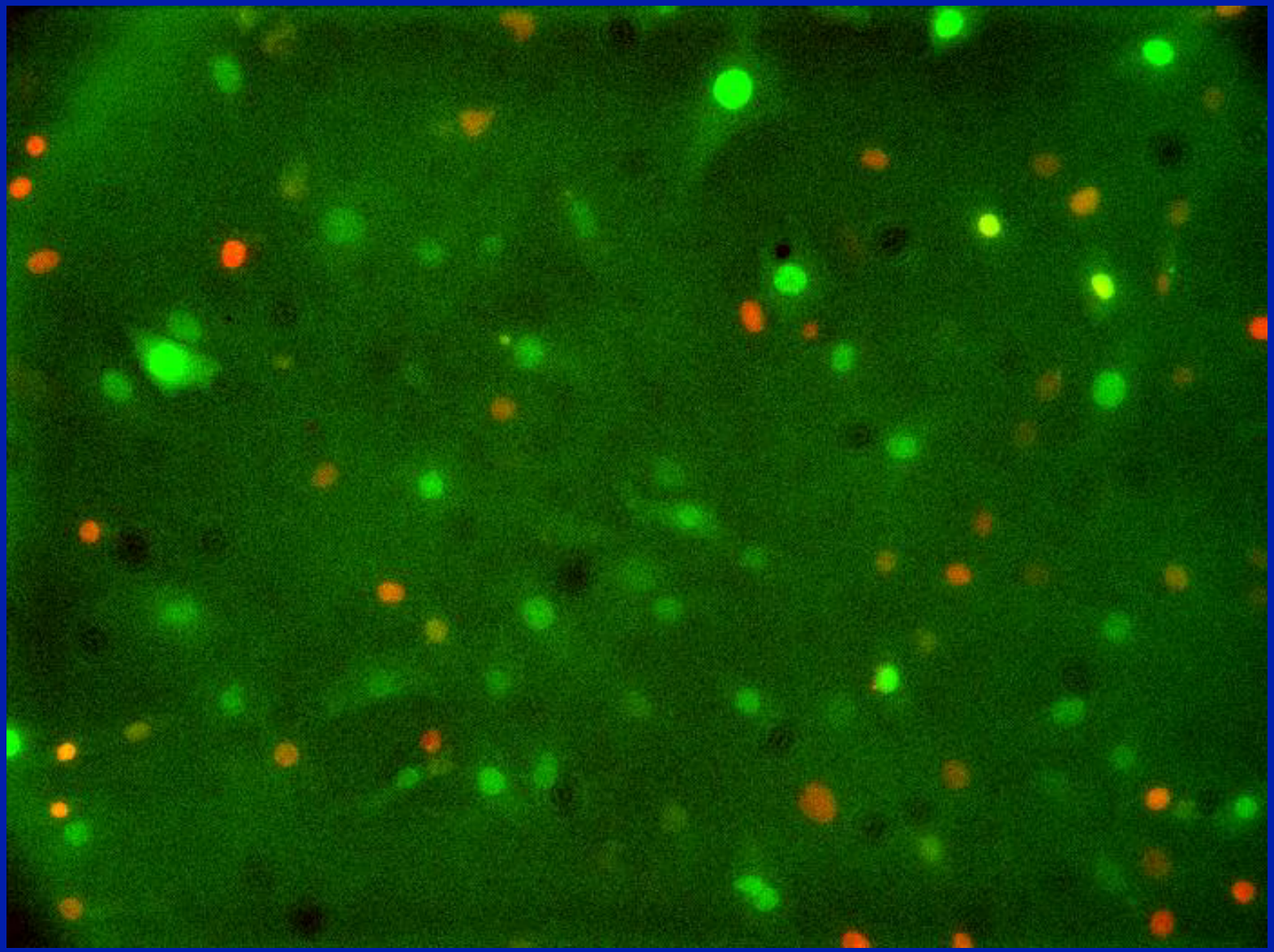


from Sakaue-Sawano et al.
Cell 2008, 132, 487–498

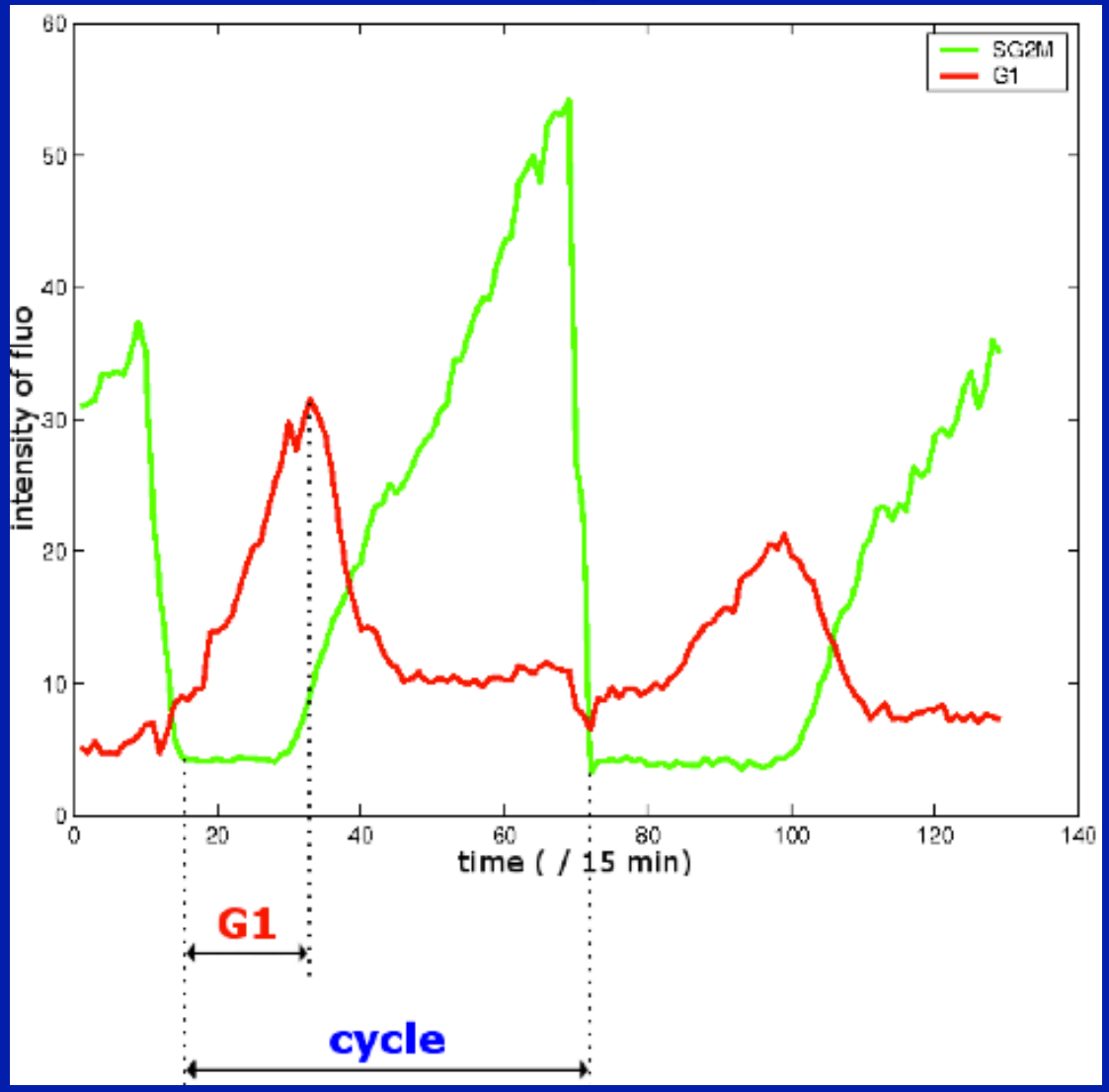
FUCCI: a movie (Sakaue-Sawano 2008), HeLa cells



Another FUCCI movie (C. Feillet, IBDC Nice), NIH3T3 cells



FUCCI reporters + individual cell tracking (non trivial…):
Measuring time intervals: G_1 and total division cycle durations

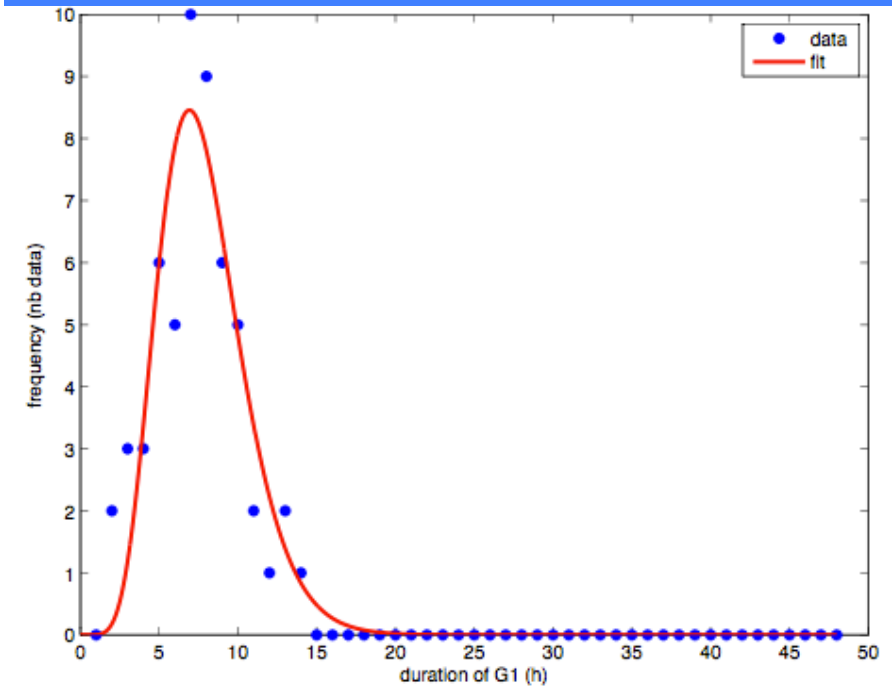


Data from Bert van der Horst's lab, Erasmus University, Rotterdam, processed by Frédérique Billy at INRIA

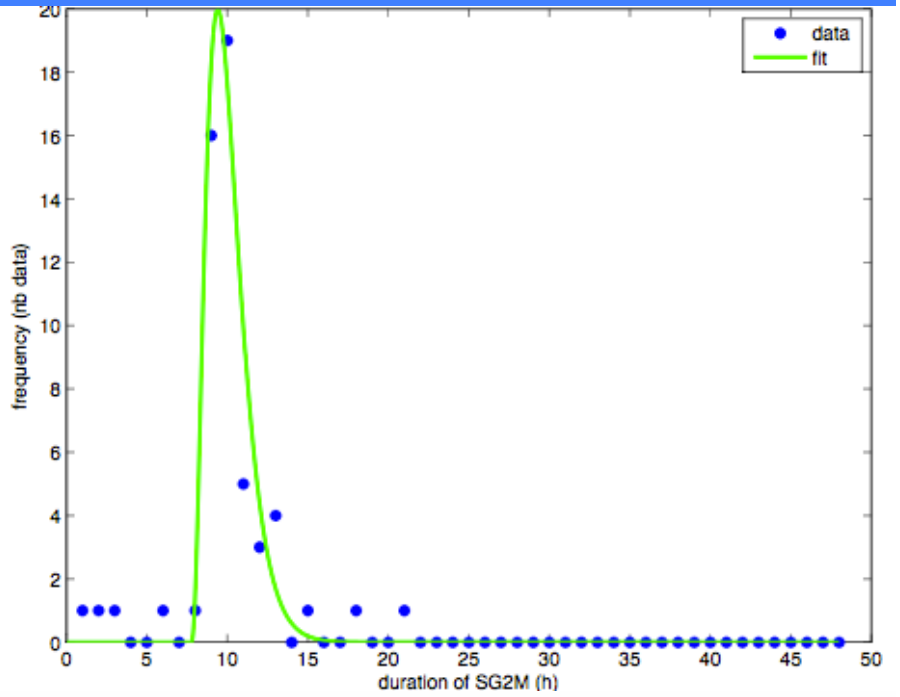
Phase durations (hence transitions, using $K(x) = \frac{f(x)}{\int_x^\infty f(y)dy}$) in age x
Pdfs *f(x)* fitted from data on 50 NIH 3T3 proliferating cells

(mouse embryonic fibroblasts)

Density of duration of G1 phase



Density of duration of SG2M



FUCCI data in NIH3T3 cells, that are healthy mouse fibroblasts tracked in liquid medium

Fitting probability density functions to data and computing λ:
Gamma p.d.f.s were best fits and yielded simple computations

$$f_i(x) = \frac{1}{\Gamma(\alpha_i)}(x-\gamma_i)^{\alpha_i-1}\beta_i^{\alpha_i}e^{-\beta_i(x-\gamma_i)}\mathbb{1}_{[\gamma_i;+\infty[}(x) \qquad i=1,2, \quad \text{where}$$

$$\alpha_1 = 8.28,\ \beta_1 = 1.052h^{-1},\ \gamma_1 = 0h,\ \alpha_2 = 3.42,\ \beta_2 = 1.47h^{-1},\ \gamma_2 = 7.75h$$

2-phase Lotka's equation simply reads:

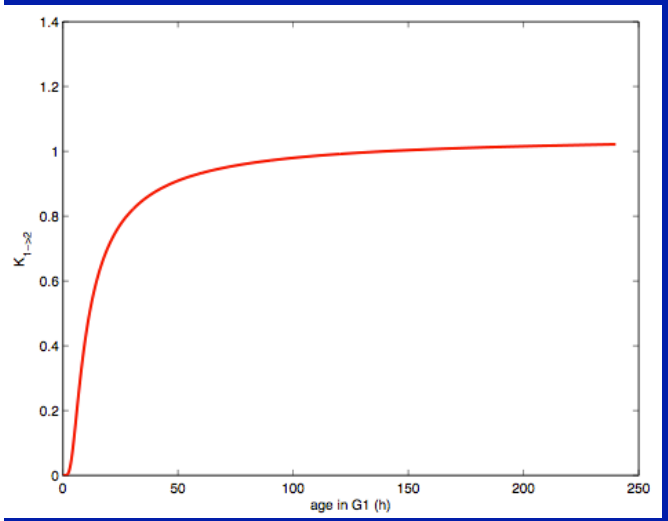
$$\left(1+\frac{\lambda}{\beta_1}\right)^{\alpha_1}\left(1+\frac{\lambda}{\beta_2}\right)^{\alpha_2}e^{\lambda(\gamma_1+\gamma_2)} = 2$$

... which yields here $\lambda = 0.039\ h^{-1}$

(and yields mean doubling time T_d=17.77 h, and mean cell cycle time T_c =17.95 h)

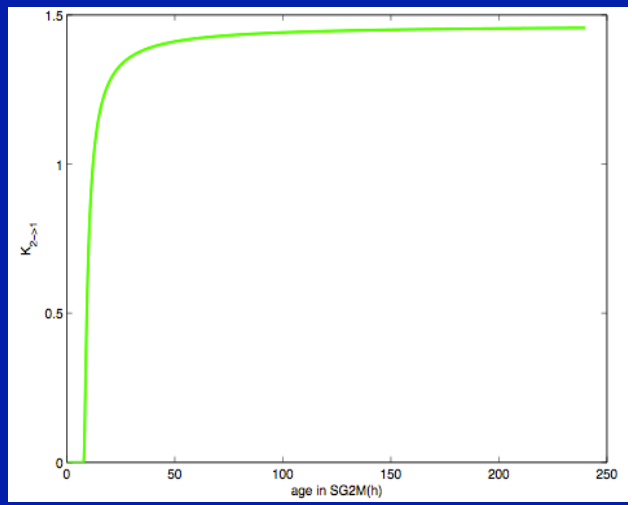
(Billy et al., Math. Comp. Simul. 2014)

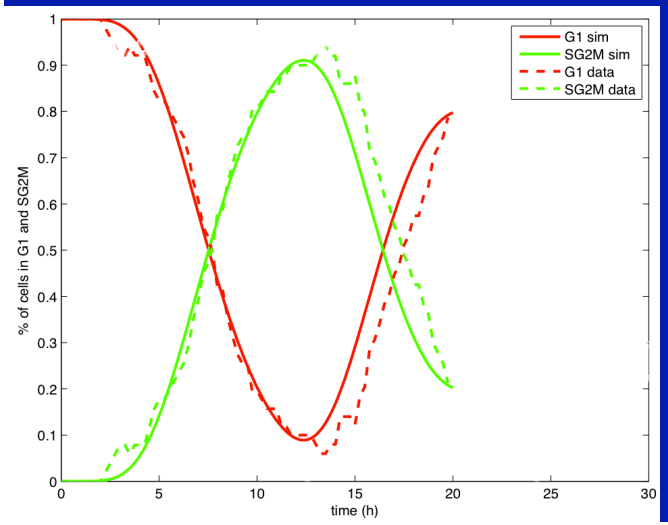
Phase transitions w.r.t. age x: Transition rates $K(x)$ from pdfs $f(x)$ on NIH 3T3 healthy cells and resulting population evolution without control on transitions

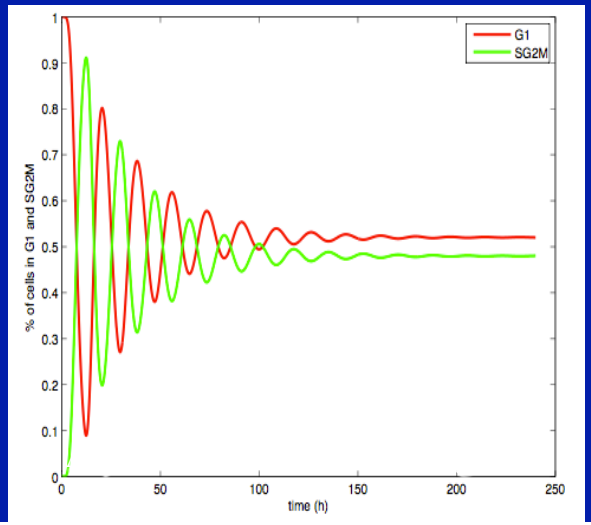


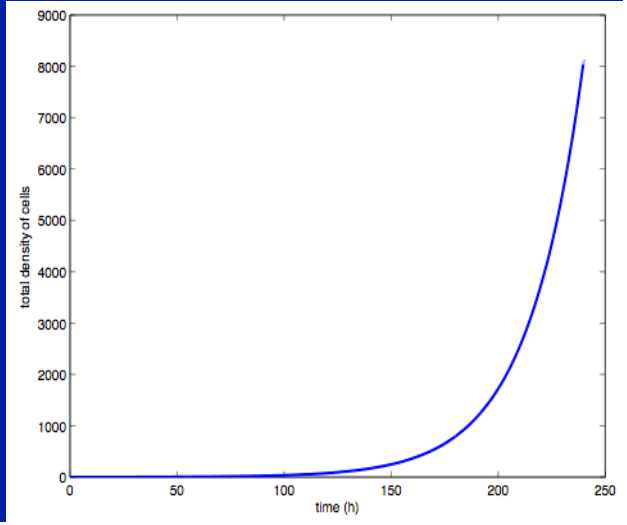
Recalling that in the model
f = p.d.f. of phase duration time
and K = phase transition kernel:

$$K_{i\to i+1}(x) = \frac{f_i(x)}{1 - \int_0^x f_i(\xi)d\xi}$$









More single cell data to build population data from IBDC (F. Delaunay, C. Feillet) in Nice

- 117+150 single NIH3T3 cell data stained by FUCCI, plus a RevErb-α track
- 117 in 10% Fœtal Calf Serum (FCS) and 150 in 15% FCS (150 out of many; only the ones with a robust RevErb-α circadian clock were kept)
- Results: evaluation of phase transition rates in a 2-phase model of the cell cycle in the two concentration media
- Increasing FCS from 10 to 15% reduces standard deviation of both phase durations, suggesting increased synchrony between cell cycle phases
- Good agreement of the model behaviour with the data, evidencing higher velocity v in cell cycle progression with 15% FCS
- v: 15% FCS cell population grows approximately 10% faster than the 10% FCS

More on FUCCI to identify cell cycle phase durations: Effects of growth factors on NIH3T3 cell populations

117 cells
in 10% FBS

150 cells
in 15% FBS

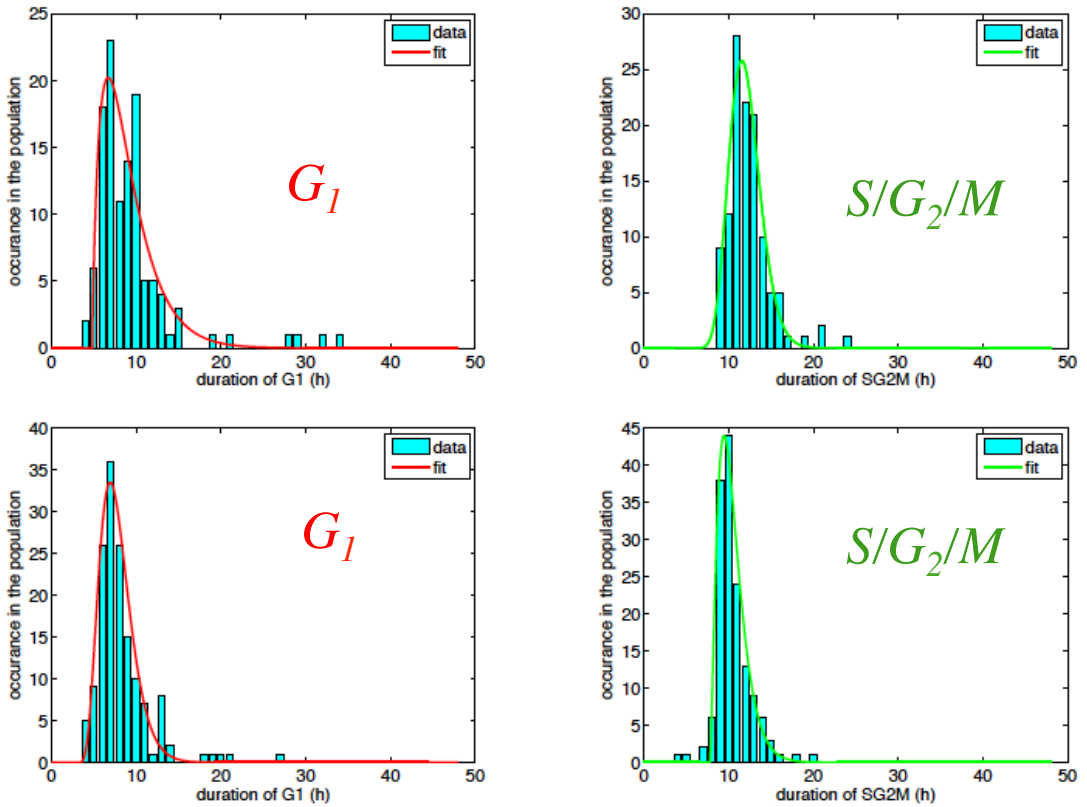


FIGURE 3. Gamma laws (solid line) (multiplied by a coefficient equal to the total number of data) that fit experimental data (bars) for the distribution of the duration of phases G_1 (left) and $S/G_2/M$ (right), for the two experimental conditions i.e., 10% FBS (top) and 15% FBS (bottom).

F. Billy et al. Math BioSci Eng 2013

Descriptive statistics: influence of growth factors on m and sd

	10% FBS		15% FBS	
	mean (h)	sd (h)	mean (h)	sd (h)
G_1	9.3	4.9	8.2	3.3
$S/G_2/M$	12.1	2.5	10.4	2.1
cycle	21.4	5.5	18.6	4.1

TABLE 1. Mean and standard deviation (sd) (in hours) of the duration of the phases G_1 and $S/G_2/M$ and of the cell cycle for two experimental conditions (culture medium composed of 10% of FBS or of 15% of FBS).

Coefficient of variation (sd/m)

G_1: 0.53 / 0.40

$S/G_2/M$: 0.21 / 0.20

	10% FBS		15% FBS	
	G_1 $(i=1)$	$S/G_2/M$ $(i=2)$	G_1 $(i=1)$	$S/G_2/M$ $(i=2)$
α_i	1.80	16.96	5.68	2.71
β_i	0.43h^{-1}	2.22h^{-1}	1.23h^{-1}	1.01h^{-1}
γ_i	4.83h	4.37h	3.13h	7.77h

TABLE 2. Parameters used to fit experimental data of the distribution of the durations of phases G_1 and $S/G_2/M$ in the population by Gamma laws, for the two experimental FBS supplementation of the medium (10% FBS and 15% FBS).

$$m = \frac{\alpha}{\beta} + \gamma \qquad sd = \frac{\sqrt{\alpha}}{\beta}$$

	10% FBS		15% FBS	
	m (h)	sd (h)	m (h)	sd (h)
G_1	9.0	3.1	7.7	1.9
$S/G_2/M$	12.0	1.9	10.5	1.6

TABLE 3. Mean (m) and standard deviation (sd) (in hours) of the Gamma distributed duration of the phases G_1 and $S/G_2/M$ for two experimental conditions (culture medium composed of 10% of FBS or of 15% of FBS), according to the parameters mentioned in Table 2.

Coefficient of variation (sd/m)

G_1: 0.34 / 0.25

$S/G_2/M$: 0.16 / 0.15

F. Billy et al. Math BioSci Eng 2013

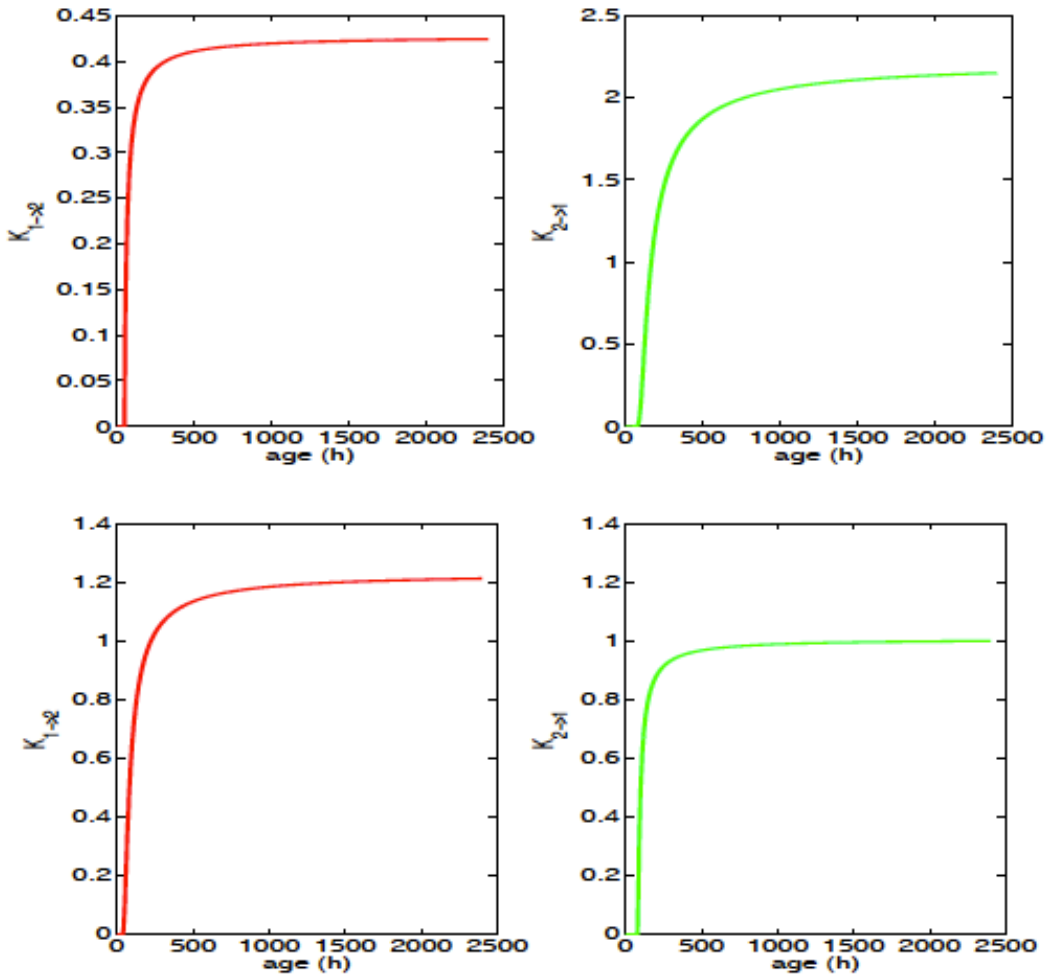


FIGURE 4. Transition rates from G_1 to $S/G_2/M$ (left) and from $S/G_2/M$ to G_1 (right) for the two experimental conditions, i.e. 10% FBS (top) and 15% FBS (bottom). These rates are functions of age of cells in the phases only.

(F. Billy et al., Math Biosci. Eng. 2013)

Taking into account different progression velocities in the cycle

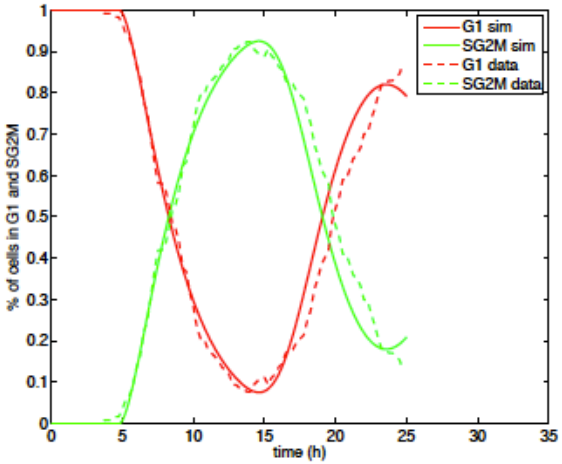
- The complete model, with speed of progression v (in age x w.r.t. time t):

$$\begin{cases} \dfrac{\partial}{\partial t} n_i(t,x) + \dfrac{\partial}{\partial x}\left(v_i(x)\, n_i(t,x)\right) + \left(d_i(t,x) + K_{i\to i+1}(t,x)\right) n_i(t,x) = 0 \\ n_i(t,x=0) = \displaystyle\int_{\xi\geq 0} K_{i-1\to i}(t,\xi)\, n_{i-1}(t,\xi)\, d\xi \quad 2 \leq i \leq I \ , \\ n_1(t,x=0) = 2\displaystyle\int_{\xi\geq 0} K_{I\to 1}(t,\xi)\, n_I(t,\xi)\, d\xi \ . \end{cases}$$

- ... or, choosing a constant speed v independent of age x:

$$\begin{cases} \dfrac{\partial}{\partial t} n_i(t,x) + v\, \dfrac{\partial}{\partial x} n_i(t,x) + \ K_{i\to i+1,10\%}(x)\ \ n_i(t,x) = 0 \qquad i = 1,2 \\ n_2(t,x=0) = \displaystyle\int_{\xi\geq 0} K_{1\to 2,10\%}(\xi)\, n_1(t,\xi)\, d\xi \ , \\ n_1(t,x=0) = 2\displaystyle\int_{\xi\geq 0} K_{2\to 1,10\%}(\xi)\, n_2(t,\xi)\, d\xi \ , \end{cases}$$

Results: better fit with evaluation of varying speed v



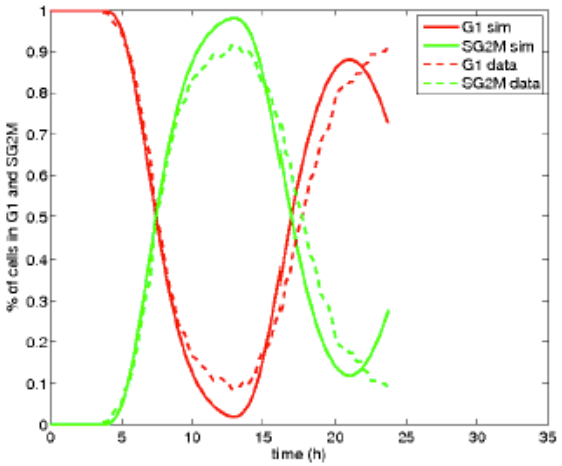


FIGURE 5. Time evolution of the percentages of cells in G_1 (red or deep grey) and $S/G_2/M$ (green or light grey) phases from biological data (dashed line) and from numerical simulations (solid line), in the case of 10% FBS (top) and 15% FBS (bottom). Our model results in a good approximation of the biological data.

Setting free the parameter v = speed of progression in the cell cycle for 15% FCS cells (with basis v=1 in the 10% FCS cell population) yielded v=1.095 in the 15% FCS cell population and better fit of model to experimental data (with T_d=15.4 h instead of 18.1 h in 15% FCS compared with T_d=20.8 h in 10% FCS)

v=1.095 in 15% FCS

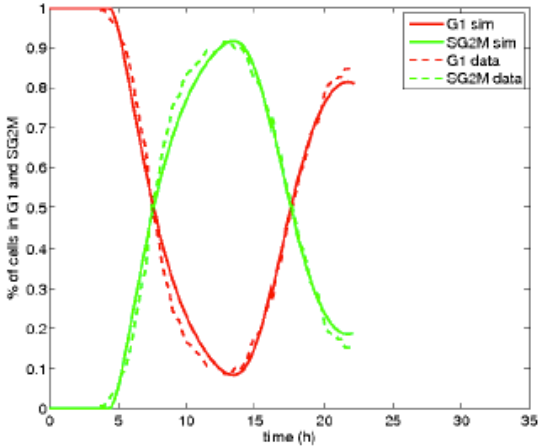
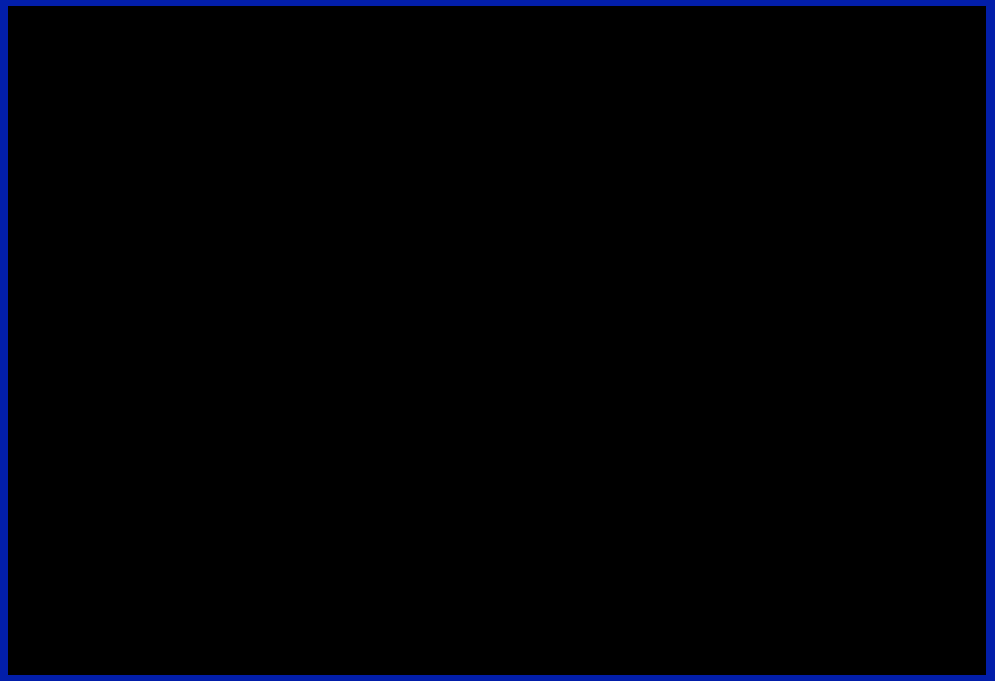


FIGURE 7. Time evolution of the percentages of cells in G_1 (red or deep grey) and $S/G_2/M$ (green or light grey) phases from biological data in the case of 15% FBS (dashed line) and from numerical simulations (solid line) resulting from Equations (13) for $v = 1.095$. Our model results in a good approximation of the biological data.

(F. Billy et al., Math Biosci. Eng. 2013)

A possible application to the investigation of synchronisation between cell cycle phases



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

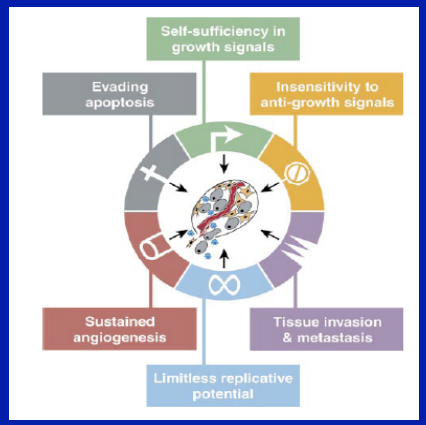
One cell divides in two: a physiologically controlled process at cell and tissue levels in all healthy and fast renewing tissues (gut, bone marrow) that is *disrupted in cancer:*

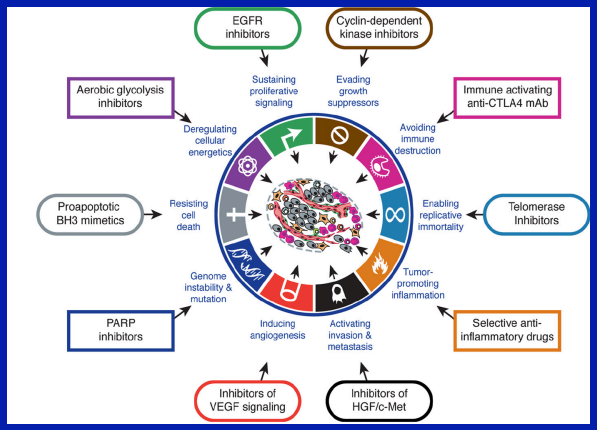
Is cell cycle phase synchronisation a mark of health in tissues?

A working hypothesis that could explain differences in responses to drug treatments between healthy and cancer tissues

Healthy tissues, i.e., cell populations, would be well synchronised w. r. to proliferation rhythms and w. r. to circadian clocks, whereas…

...tumour cell populations would be desynchronised w. r. to both, and such proliferation desynchronisation would be a consequence of an escape by tumour cells from central circadian clock control messages, just as they evade most physiological controls, cf. e.g., Hanahan & Weinberg:





Question:
is cell cycle phase desynchronisation another hallmark of cancer ***in cell populations****?*

A mathematical result: λ increases with desynchronisation

where desynchronisation is defined as a measure of phase overlapping at transition

Proliferation, as measured by the Malthus growth exponent, or first eigenvalue, increases with overlapping between cell cycle phases

i.e., the less synchronised phases are, the faster is proliferation

(NB: so far, this has not been extended to the periodic control case, i.e., phase transitions have been assumed to be uncontrolled)

i.e.,for a given family (f_i) of p.d.f.s with second moment σ_i, λ is increasing with each σ_i

Proposition 1. *Soit f_i, $1 \leq i \leq I$, une famille de fonctions de densité sur $\mathbb{R}_+$. Les taux de transition associés $K_{i\to i+1}$ sont ainsi donnés par (voir (2)) :*

$$K_{i\to i+1}(x) = \frac{f_i(x)}{\int_x^{+\infty} f_i(x')dx'} = \frac{f_i(x)}{1 - \int_0^x f_i(x')dx'}$$

En supposant $d_i = 0$ $(1 \leq i \leq I)$, la première valeur propre du système (1) $\lambda > 0$ est donnée par (voir [1]) :

$$\frac{1}{2} = \prod_{i=1}^{I} \int_0^{+\infty} f_i(x) e^{-\lambda x} dx$$

Pour $1 \leq i \leq I$, on pose $e_i = \int_0^{+\infty} x f_i(x)dx$ et $\sigma_i^2 = \int_0^{+\infty} x^2 f_i(x)dx - e_i^2$, et on suppose que les $e_i > 0$ sont constants. Soit $j \in \{1, ..., I\}$. On suppose que les σ_i^2 $(1 \leq i \neq j \leq I)$ sont constants.

Alors λ est croissante avec σ_j^2.

(also shown in Billy et al., Math. Comp. Simul., 2014)

Simple age-structured PDE models representing exchanges between proliferation and quiescence

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

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

$$\text{with :}$$

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

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

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

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

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

Delay differential equations

Delay differential models with two cell compartments, proliferating (P)/quiescent (Q): *Haematopoiesis models*

(obtained from the previous model with additional hypotheses and integration in x 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 division 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)

Oscillatory behaviour is observed in *periodic Chronic Myelogenous Leukaemia* (*CML*) where oscillations with limited amplitude are compatible with survival, whereas explosion (blast crisis, alias acutisation) leads to *AML* and death

(Mackey and Bélair in Montréal; Adimy, Bernard, Crauste, Pujo-Menjouet, Volpert in Lyon)

From Adimy, Crauste, ElAbdllaoui J Biol Syst 2008 (see also: Özbay, Bonnet, Benjelloun, JC MMNP 2012)

Modelling haematopoiesis for *Acute Myeloblastic Leukaemia* (AML)

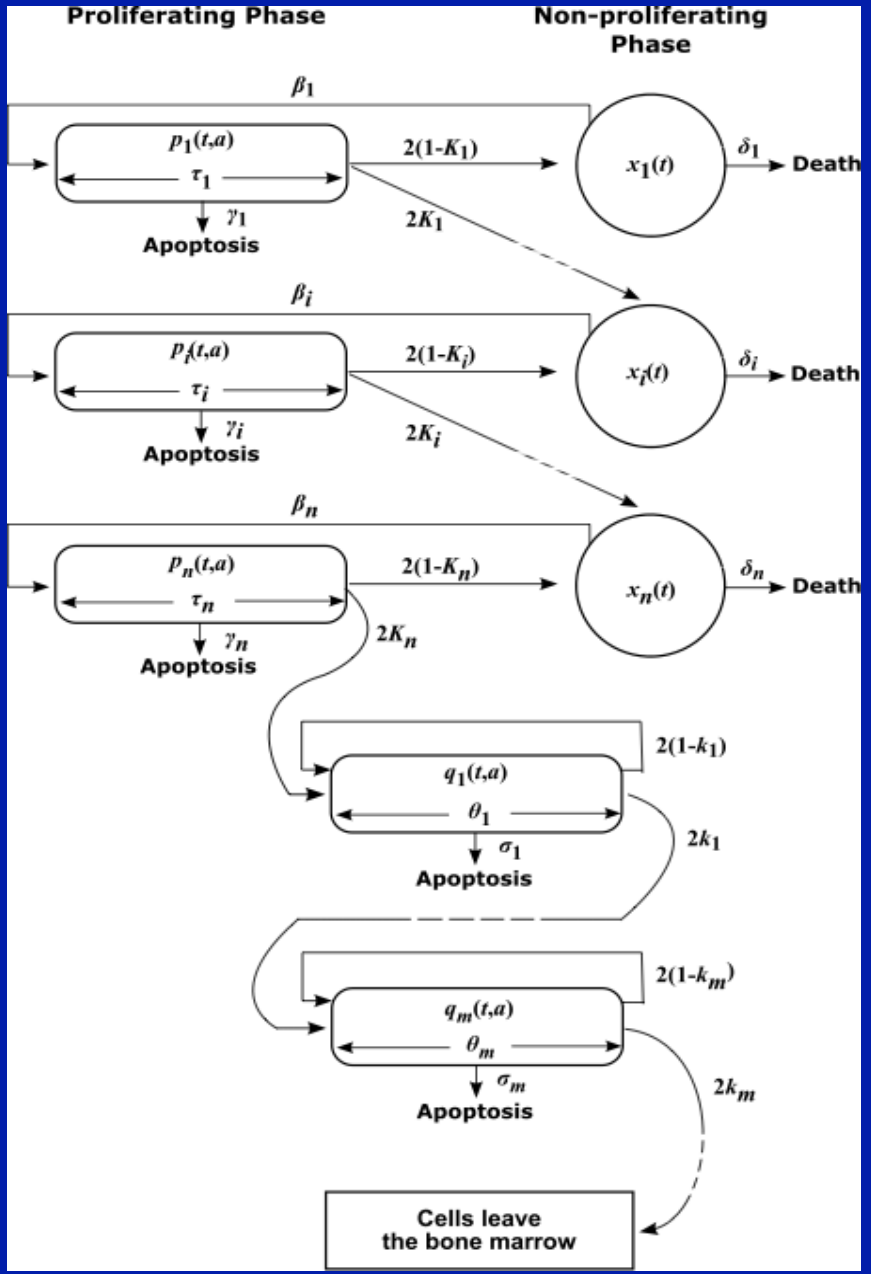
…aiming at *non-cell-killing therapeutics* by inducing *re-differentiation of cells using molecules (e.g. ATRA) enhancing differentiation rates represented by K_i terms*

$$\begin{aligned}
&\frac{\partial r_i}{\partial t} + \frac{\partial r_i}{\partial a} = -(\delta_i + \beta_i)\, r_i, && a > 0,\ t > 0,\\
&\frac{\partial p_i}{\partial t} + \frac{\partial p_i}{\partial a} = -(\gamma_i + g_i(a))\, p_i, && 0 < a < \tau_i,\ t > 0
\end{aligned}$$

where r_i and p_i represent resting and proliferating cells, respectively, with reintroduction term $\beta_i = \beta_i(x_i)$ positive decaying to zero, with population argument: $x_i(t) := \int_0^{+\infty} r_i(t,a)da$

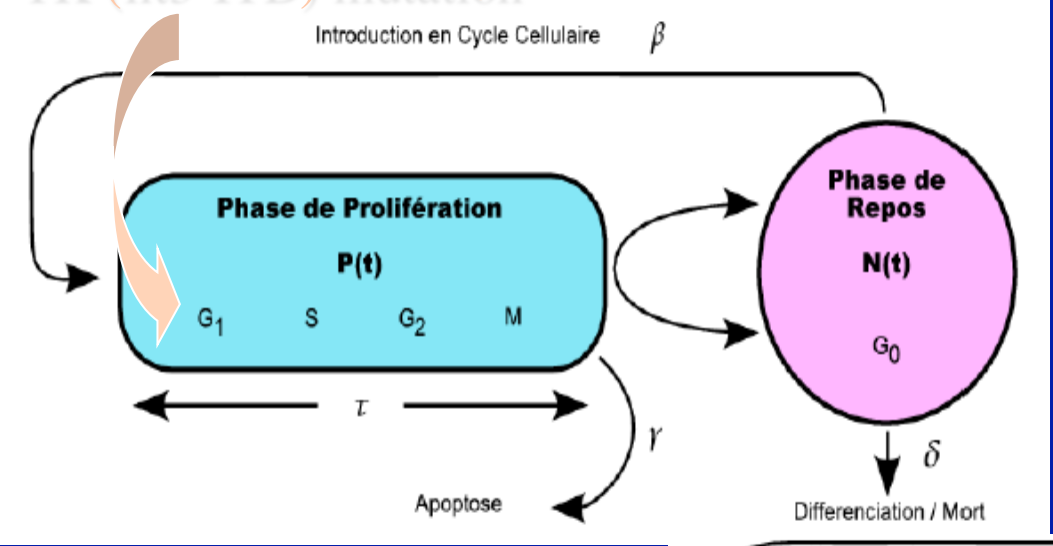
and boundary conditions:

$$\begin{cases}
r_1(t,0) = 2(1-K_1)\displaystyle\int_0^{\tau_1} g_1(a)p_1(t,a)da,\\
r_i(t,0) = 2(1-K_i)\displaystyle\int_0^{\tau_i} g_i(a)p_i(t,a)da\\
\qquad\qquad +2K_{i-1}\displaystyle\int_0^{\tau_{i-1}} g_{i-1}(a)p_{i-1}(t,a)da, \qquad i \geq 2,\\
p_i(t,0) = \displaystyle\int_0^{+\infty} \beta_i(x_i(t))r_i(t,a)da = \beta_i(x_i(t))x_i(t), \quad i \in I_n,\\
\lim\limits_{a\to+\infty} r_i(t,a) = 0.
\end{cases}$$



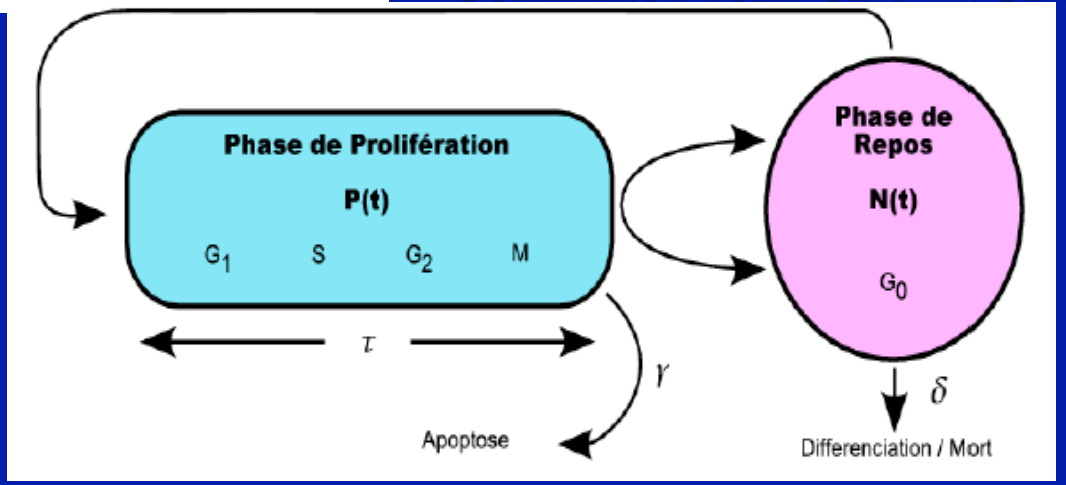
Modelling leukaemic haematopoiesis (Mackey/Adimy) : proliferation advantage?

TK (flt3-ITD) mutation



'Stem-like' cells CD34+/CD38-

Committed cells CD34+/CD38+



Blood/ bone marrow sampling in AML patients
Cell sorting (magnetic beads)

FACS for cell cycle phases
Self-renewal: critical penomenon
Measuring apoptosis and cell division in each population should lead to model identification

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 recruitments G from q to p differ)

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

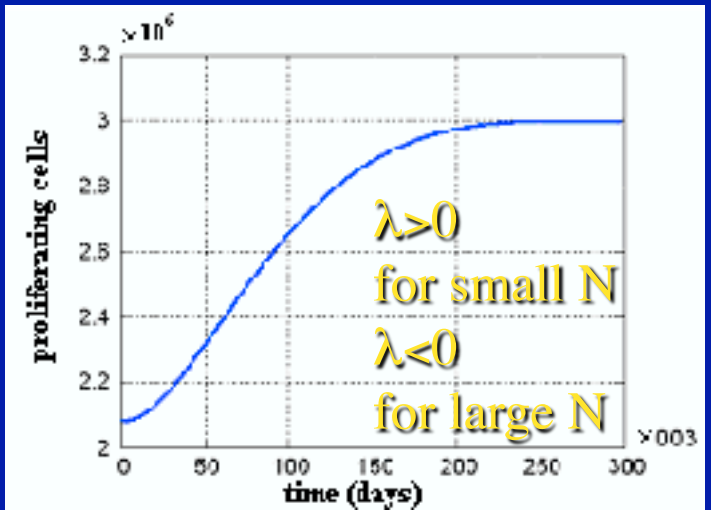
N=p+q: total number of cells
L: leak term from *p* to *q*
F: mitosis

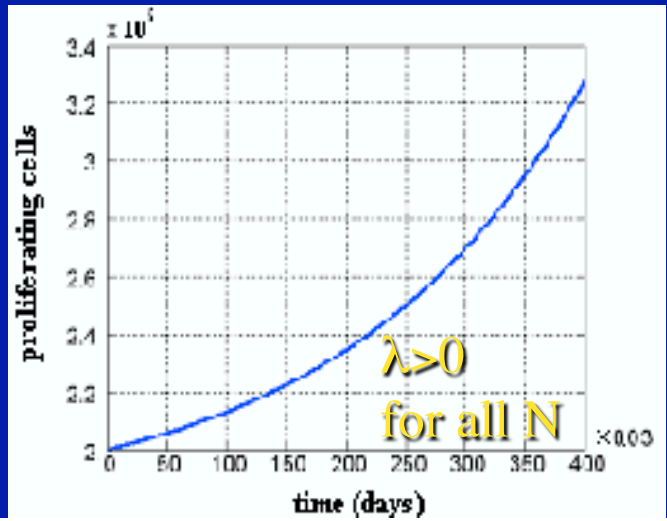
$$G(N) = \frac{\alpha_1\theta^n}{\theta^n + N^n}$$

Healthy tissue recruitment *G*: homeostasis

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

Tumour recruitment *G*: *(α_2>0)* exponential growth





F. Bekkal Brikci, JC, B. Ribba, B. Perthame J Math Biol 2008; Math Comp Mod 2008; M. Doumic-Jauffret, MMNP 2007

To conclude this first part, quoting Aristotle:

ἔοικε δ΄ ὅ τε λόγος τοῖς φαινομένοις μαρτυρεῖν, καὶ τὰ φαινόμενα τῷ λόγῳ

i.e., "It is appropriate to the model to testify for the phenomena, and to the phenomena for the model"

(in Aristotle's *Περί Ουρανού [Sky], from which I freely translate λόγος by model)*

II. Introducing weapons and targets in proliferation models

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
  - 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?

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
  - previous use of radio- or chemotherapy

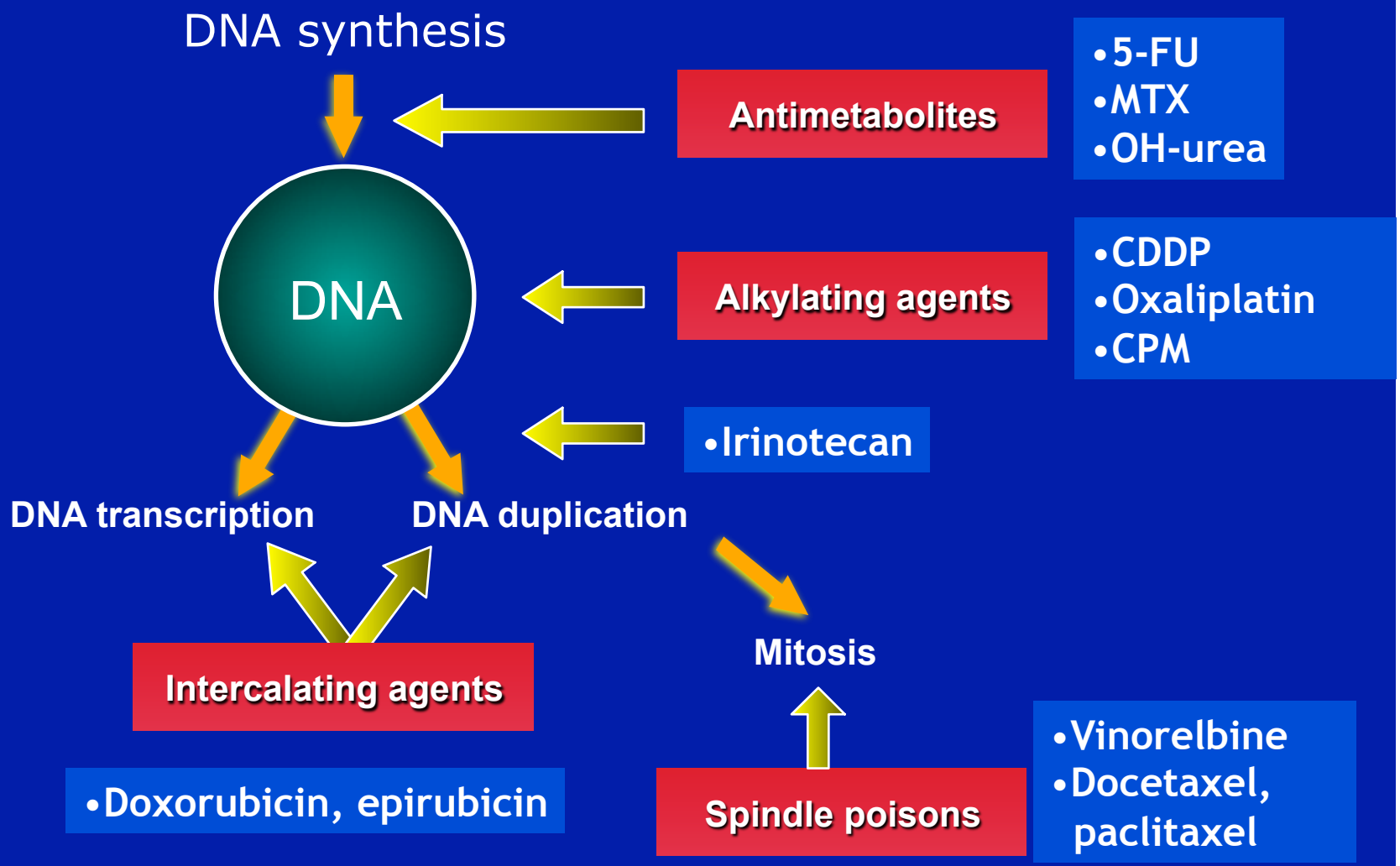
- Radiotherapy: not enough localised or not enough energetic
  Recently proposed: hadrontherapy = particle beam therapy (protons, neutrons and helium, carbon, oxygen and neon ions instead of photons): better localisation, possibility to deliver higher doses without unwanted damage

- 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

  Proposed: optimisation of treatment to reduce toxicity and drug resistance

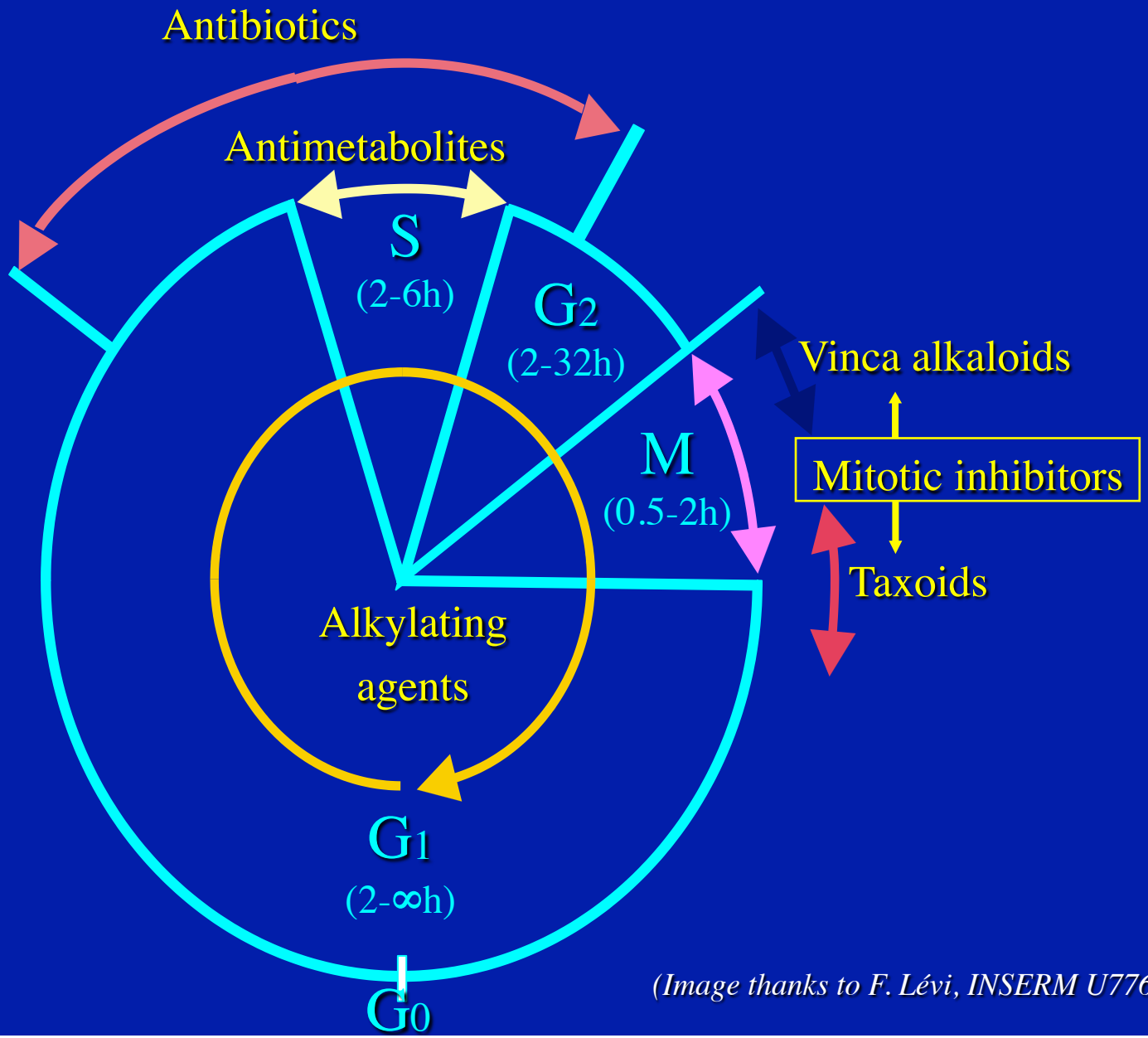
…..New molecules: xxx-mab, e.g. EGFR inhibitors (cytostatic drugs)
- monoclonal antibodies are mouse antibodies!-> HAMA

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



(Image thanks to F. Lévi, INSERM U776)

Cell cycle phases as targets for chemotherapy agents



(Image thanks to F. Lévi, INSERM U776)

Different viewpoints to represent tumour therapies

1. At the molecular level:
Hitting specific molecular targets in cancer cells by "targeted therapies"
Presently the most popular point of view among cancer biologists
Achievements: imatinib in chronic myelogenous leukaemia (CML),
ATRA+anthracylins in acute promyelocytic leukaemia (APL)
Problems: (often very) relative specificity; toxicity to healthy tissues;
not taking into account emergence of drug resistance

2. At the cell and molecular level:
Taking into account *all intracellular molecular pathways* involved in proliferation,
cell death and [de-]differentiation: a *biocomputer scientist's point of view*
Problems: scores of reaction networks, hundreds of parameters to estimate,
not taking into account emergence of drug resistance

3. At the cell population level:
Defining functional targets for drugs in qualitative population dynamics models
with added external control: PDEs or IDEs (integro-differential equations).
Advantages: the right level to take into account population level effects
(in particular emergence of drug resistance) and to design optimisation strategies
Problems: attributing specific functional effects to given drugs

"Functional"=by designing targets related to those fates that are considered as relevant for cell and tissue behaviour in cancer: proliferation, cell death, [de-]differentiation

Examples: macroscopic models of the action of drugs

1. ODE with functional representation of pharmacodynamics for 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)

2. PDEs describing action of a drug (*d*) on proliferating (*p*) and quiescent (*q*) cells

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

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

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

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

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

Pharmacokinetic-pharmacodynamic (PK-PD) modelling

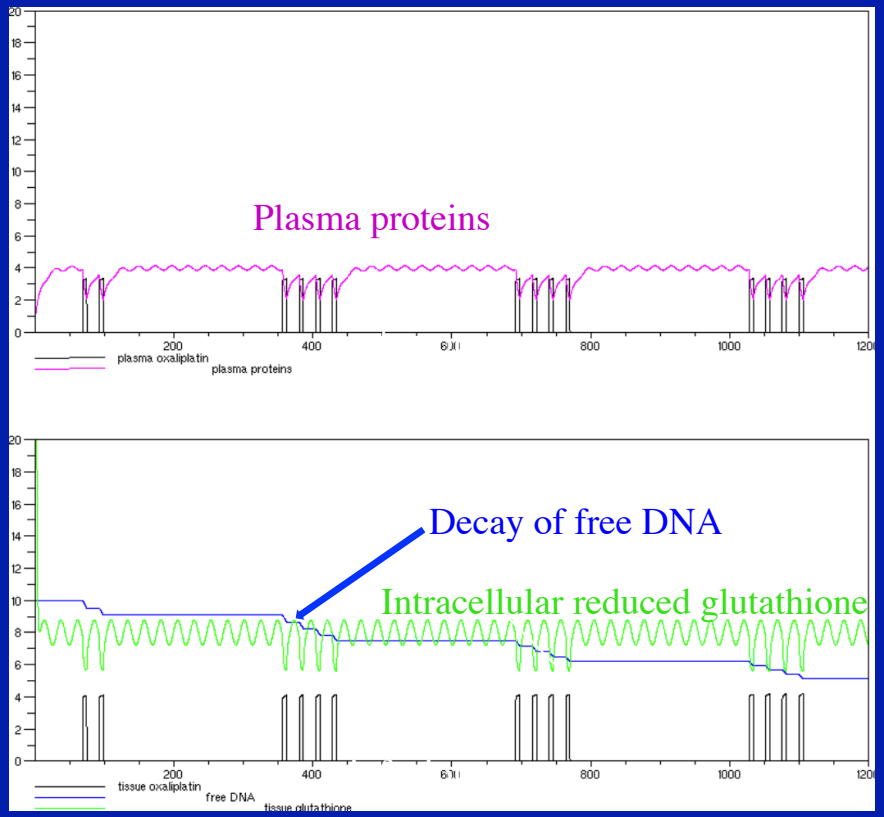
"Pharmacokinetics is what the organism does to the drug,
Pharmacodynamics is what the drug does to the organism"

3 detailed examples of molecular PK-PD modelling: Oxaliplatin, Irinotecan, 5-Fluorouracil

1st example: Modelling PK-PD of cytotoxic drug Oxaliplatin (cytotoxic action exerted on DNA in all phases except M phase)

$$
\begin{cases}
\dfrac{dR}{dt} = -[\xi + cl + \lambda K]R + i(t) \\
\dfrac{dK}{dt} = -\lambda RK + \mu_K(K_0 - K) \\
\dfrac{dC}{dt} = -V_{GST}\dfrac{CG^2}{K_{GST}^2 + G^2} - k_{DNA}CF + \xi R \\
\dfrac{dF}{dt} = -k_{DNA}CF + \mu_F(Fo - F) \\
\dfrac{dG}{dt} = -V_{GST}\dfrac{CG^2}{K_{GST}^2 + G^2} + \mu_G(G_0 - G)
\end{cases}
$$

Input i = *oxaliplatin infusion*



(JC, O. Fercoq, submitted as Springer book chapter, 2014)

Molecular PK of Oxaliplatin in plasma compartment

Mass of active oxaliplatin

Constant clearance

Instantaneous infused dose (flow)

$$\frac{dP}{dt} = -\left[\xi + Cl + \lambda \cdot L\right] \cdot P + i(t)$$

Binding rate of oxaliplatin to plasma proteins

Rate of transfer from plasma to peripheral tissue (cellular uptake)

Mass of plasma proteins (albumin or other hepatic proteins)

ε tunes the robustness of GSH oscillations, from harmonic to relaxation-like

r_L tunes the amplitude of the cycle of plasma proteins

$$\frac{dL}{dt} = -\lambda \cdot P \cdot L + \varepsilon\left(N - N_0 - \frac{1}{3}(L - L_0)^3 + r_L(L - L_0)\right)$$

Hepatic synthesis activity of plasma proteins

ω_L tunes the period of the cycle of plasma proteins

$$\frac{dN}{dt} = -\frac{\omega_L^2}{\varepsilon}(L - L_0)$$

Plasma protein synthesis shows circadian rhythm

Molecular PK of Oxaliplatin: tissue concentration

Tissue concentration in free oxaliplatin (C=[DACHPt])

Degradation of free DNA (F) by oxaliplatin (C)

$$\frac{dC}{dt} = -V_{GST}\frac{C(G-G_0)^2}{K_{GST}^2 + (G-G_0)^2} - k_{DNA}CF + \frac{\xi}{2}\frac{P}{\mathcal{W}}$$

GST-mediated binding of reduced glutathione (G) to oxaliplatin (C), i.e., cell shielding by GSH

$\mathcal{W}$ = volume of tissue in which the mass P of free oxaliplatin is infused

"Competition" between free DNA [=F] and reduced glutathione GSH [=G] to bind oxaliplatin [=C] in proliferating cells

Molecular PD of Oxaliplatin activity in tissue

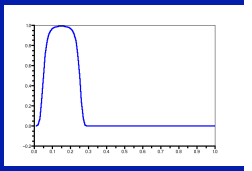
Mass of free DNA

Action of oxaliplatin on free DNA (F)

$$\frac{dF}{dt} = -k_{DNA}\mathcal{W}CF + k_R F\frac{F_0 - F}{F_0} repair\left(g_R, \theta_1, \theta_2, \frac{F_0 - F}{F_0}\right)$$

DNA repair function

($\theta_1 < \theta_2$: activation and inactivation thresholds; g_R: stiffness)



Mass of reduced glutathione in target cell compartment

Oxaliplatin cell concentration

δ tunes the robustness of GSH oscillations, from harmonic to relaxation-like

$$\frac{dG}{dt} = -V_{GST}\frac{\mathcal{W}C(G - G_0)^2}{K_{GST}^2 + (G - G_0)^2} + \delta\left(S - S_0 - \frac{1}{3}(G - G_0)^3 + r_G(G - G_0)\right)$$

ρ_G tunes the amplitude of the cycle of GSH synthesis by GCS = γ-Glu-cysteinyl ligase

Activity of γ-Glu-cysteinyl ligase (GCS)

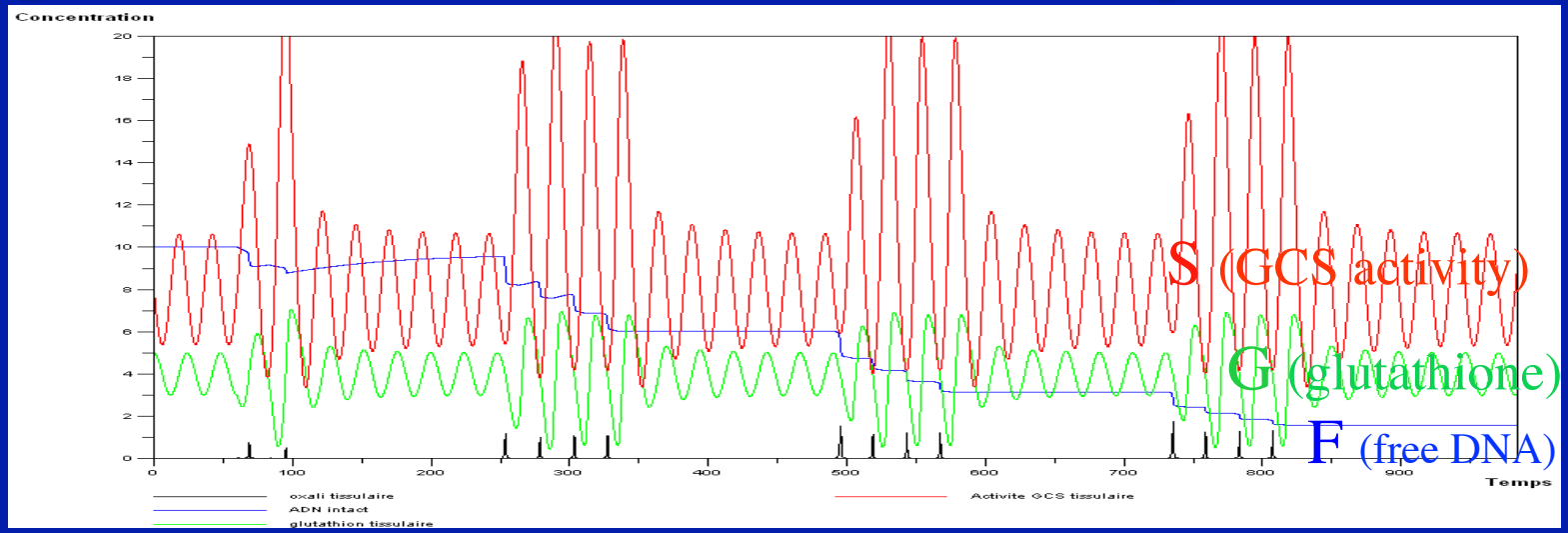
ω_G tunes the period of the cycle of GSH synthesis by GCS

Glutathione synthesis (→detoxification) in cells shows circadian rhythm

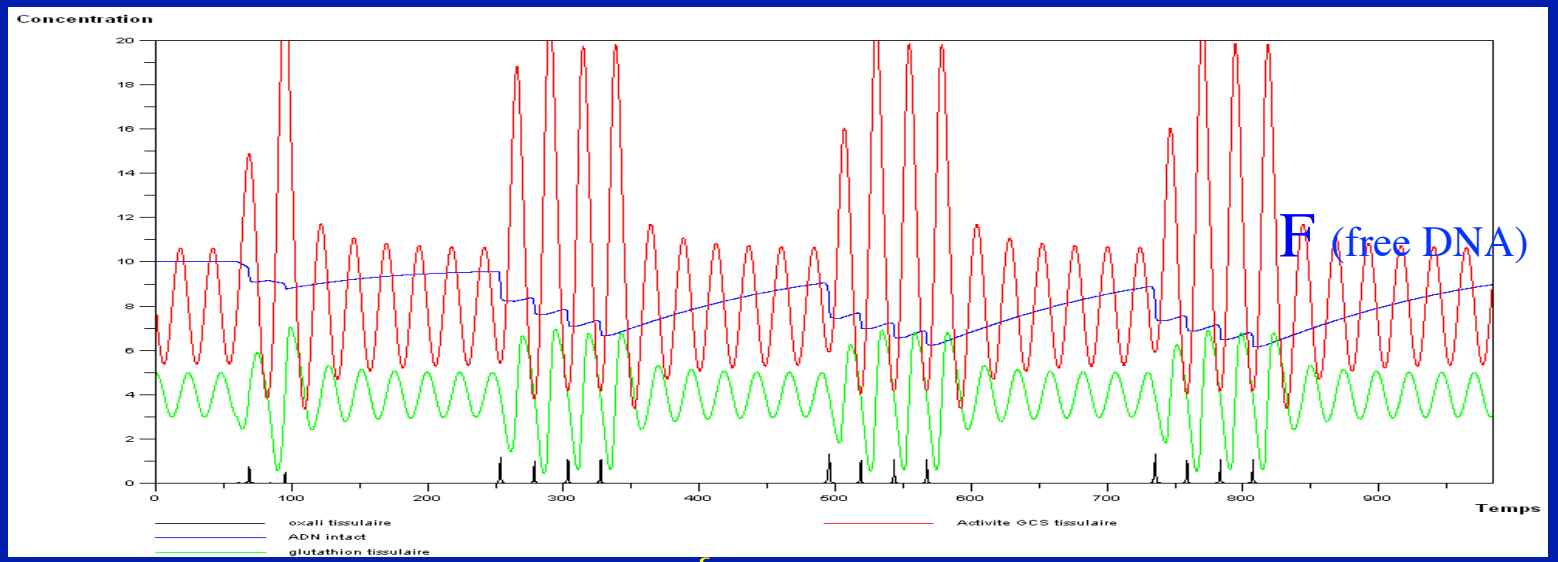
$$\frac{dN}{dt} = -\frac{\omega_L^2}{\varepsilon}(L - L_0)$$

$1-F/F_0$ = DNA damage

PD of Oxaliplatin on DNA and genetic polymorphism of repair function in tumour cells: drug resistance

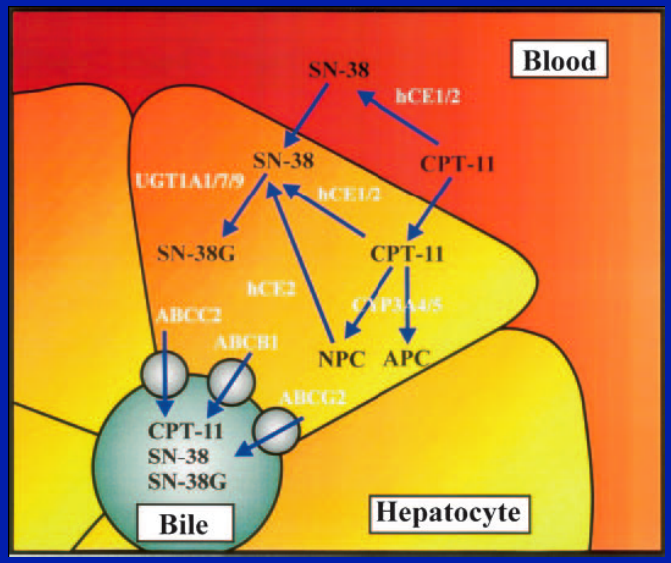


…the same with stronger DNA repair function, ERCC2=XPD-determined:



(Diminished V_{GST} binding to GSH / cellular uptake ξ, changed infusion peak time, lead to comparable results)

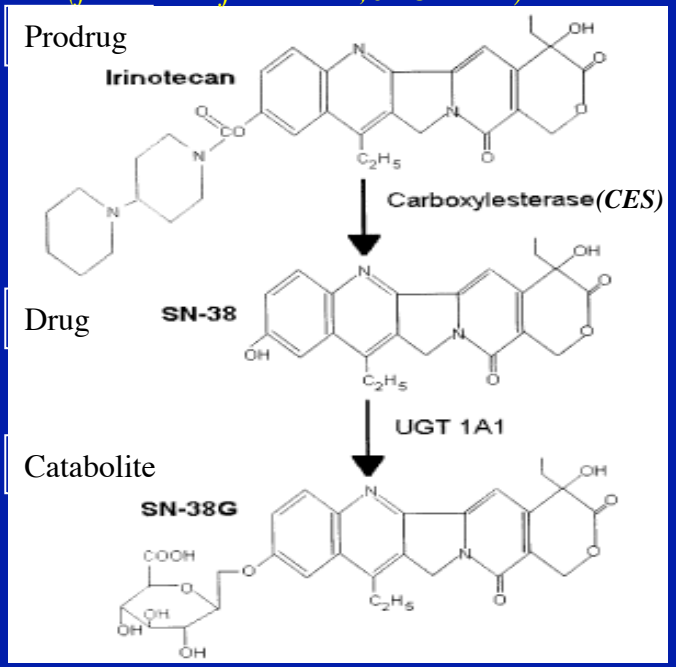
2nd example: cytotoxic drug *Irinotecan* (CPT11)



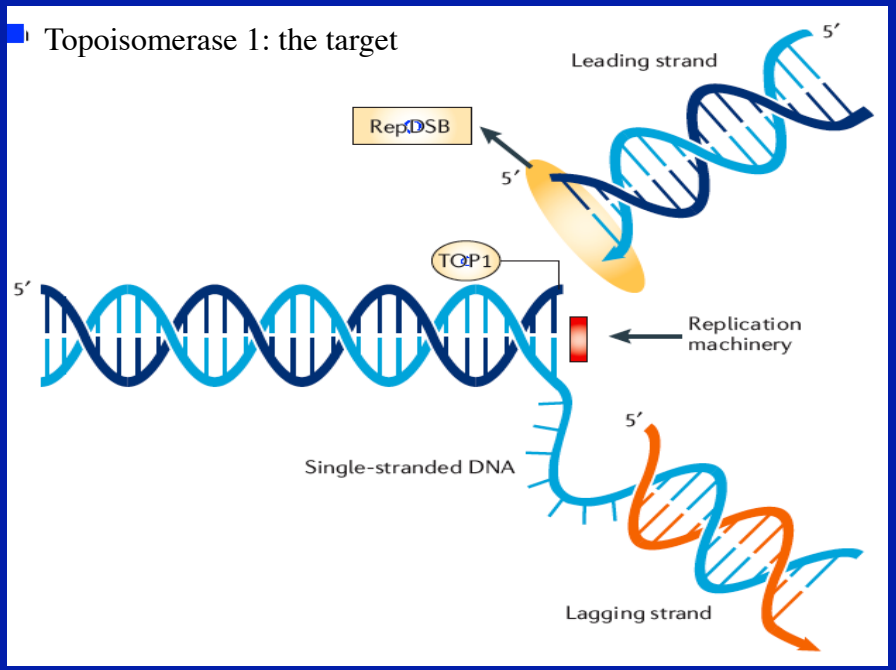
(from Mathijssen et al., JNCI 2004)

Intracellular PK-PD model of CPT11 activity:

- [CPT11], [SN38], [SN38G], [ABCG2], [TOP1], [DNA], [p53], [Mdm2]
- Input=CPT11 intracellular concentration
- Output=DNA damage *(Double Strand Breaks)*
- Constant activities of enzymes CES and UGT1A1
- A. Ciliberto's model for p53-Mdm2 dynamics



(from Klein et al., Clin Pharmacol Therap 2002)



(from Pommier, Nature Rev Cancer 2006)

Intracellular PK-PD of *Irinotecan* (CPT11)

PK

$$
\begin{cases}
\dfrac{d[CPT11]}{dt} = In(t) - k_1 \dfrac{[CES][CPT11]}{K_{m1} + [CPT11]} - k_{t1} \dfrac{[ABCG2][CPT11]}{K_{t1} + [CPT11]} \\
\dfrac{d[SN38]}{dt} = k_1 \dfrac{[CES][CPT11]}{K_{m1} + [CPT11]} - k_{t2} \dfrac{[ABCG2][SN38]}{K_{t2} + [SN38]} - k_2 \dfrac{[UGT1A1][SN38]^n}{K_{m2}^n + [SN38]^n} \\
\qquad -k_{compl}[SN38][TOP1][ADN_{libre}] + k_{compl_1}[CC] \\
\dfrac{d[SN38G]}{dt} = k_1 \dfrac{[UGT1A1][SN38]^n}{K_{m1}^n + [SN38]^n} - k_{d1}[SN38G] \\
\dfrac{d[ABCG2]}{dt} = k_{t2}[ABCG2] \left(\dfrac{[SN38]}{K_{t2} + [SN38]} + k_{t1} \dfrac{[CPT11]}{K_{t1} + [CPT11]} \right) + -k_{d2}[ABCG2]
\end{cases}
$$

PD

$$
\begin{cases}
\dfrac{d[TOP1]}{dt} = k_{top1} \left(1 + \varepsilon \cos \left(\dfrac{2\pi(t - \varphi)}{24} \right) \right) - k_{compl}[SN38][TOP1][ADN_{libre}] + k_{compl_1}[CC] - k_{dtop1}[TOP1] \\
\dfrac{d[DNA_{libre}]}{dt} = -k_{compl}[SN38][TOP1][ADN_{libre}] + k_{compl_1}[CC] + repairDNA([p53_{tot}], [CC_{irr}]) \\
\dfrac{d[CC]}{dt} = k_{compl}[SN38][TOP1][ADN_{libre}] - k_{compl_1}[CC] - k_{irr}[CC] \\
\dfrac{d[CC_{irr}]}{dt} = k_{irr}[CC] - repairDNA([p53_{tot}], [CC_{irr}])
\end{cases}
$$

$$
repairDNA([p53_{tot}], [CC_{irr}]) = -k_{dDNA}[p53_{tot}] \frac{[CC_{irr}]}{J_{DNA} + [CC_{irr}]}
$$

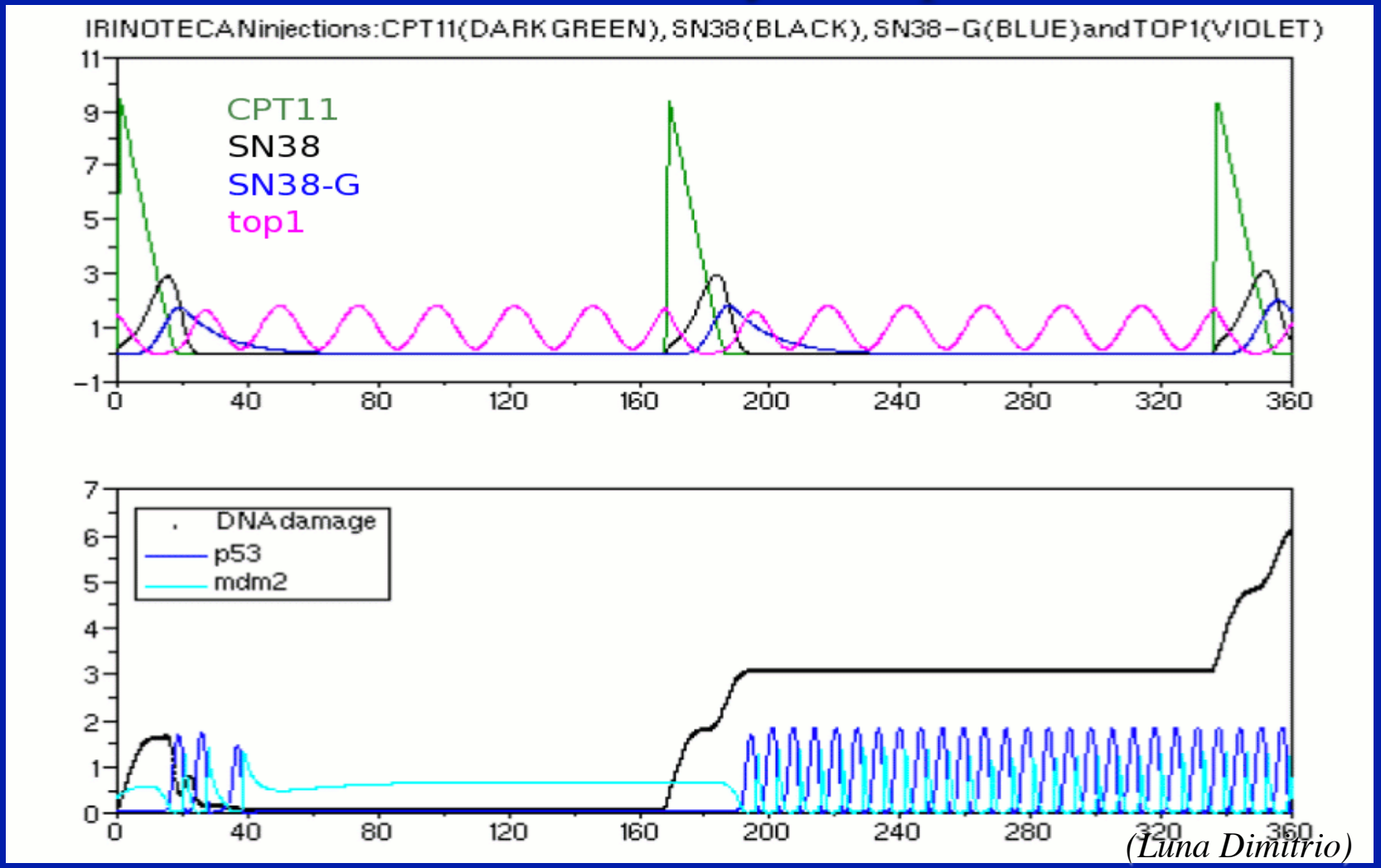
(Luna Dimitrio's Master thesis 2007; A. Ballesta's PhD work 2012)

A. Ciliberto's model of p53-Mdm2 oscillations

$$
\begin{cases}
\dfrac{d[p53_{tot}]}{dt} &= k_{s53} - k_{d53'}[p53_{tot}] - k_{d53}[p53UU] \\
\dfrac{d[p53U]}{dt} &= k_f[Mdm2_{nuc}][p53] + k_r[p53UU] - [p53U](k_r + k_f[Mdm2_{nuc}]) + -k_{d53'}[p53U] \\
\dfrac{d[p53UU]}{dt} &= k_f[Mdm2_{nuc}][p53U] - [p53UU]k_r - [p53UU](k_{d53'} + k_{d53}) \\
\dfrac{d[Mdm2_{nuc}]}{dt} &= V_{ratio}(k_i[Mdm2P_{cyt}] - k_0[Mdm2_{nuc}]) - k_{bif}[Mdm2_{nuc}] \\
\dfrac{d[Mdm2_{cyt}]}{dt} &= k_{s2'} + \dfrac{k_{s2}[p53_{tot}]^3}{J_s^3 + [p53_{tot}]^3} - k_{d2'}[Mdm2_{cyt}] + k_{deph}[MMdm2P_{cyt}] - \dfrac{k_{ph}}{J_{ph} + [p53_{tot}]}[Mdm2_{cyt}] \\
\dfrac{[Mdm2P_{cyt}]}{dt} &= \dfrac{k_{ph}}{J_{ph} + [p53_{tot}]}[Mdm2_{cyt}] - k_{deph}[Mdm2P_{cyt}] - k_i[MMdm2P_{cyt}] + k_0[Mdm2_{nuc}] - k_{d2'}[MMdm2P_{cyt}]
\end{cases}
$$

(Ciliberto, Novak, Tyson, Cell Cycle 2005)

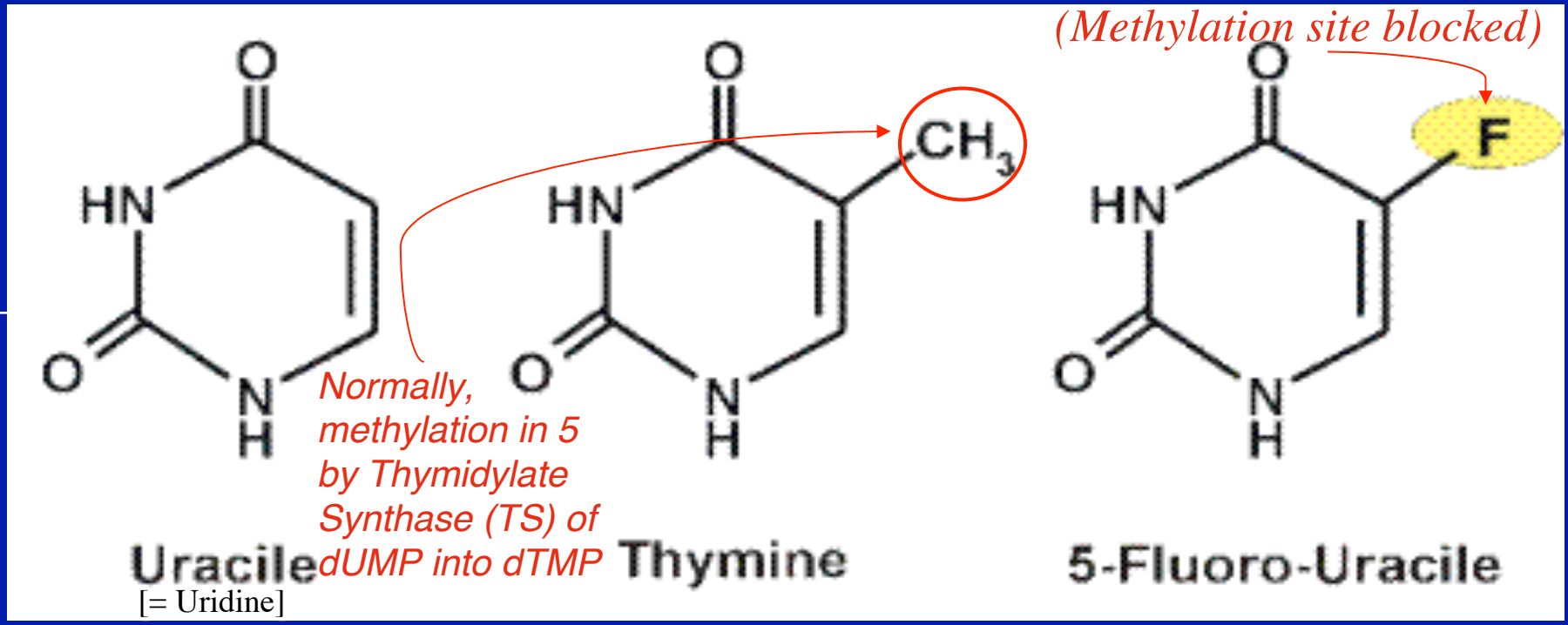
PD of *Irinotecan*: p53-Mdm2 oscillations can repair DNA damage provided that not too much SN38-TOP1-DNA ternary complex accumulates



(Intracellular PK-PD of irinotecan and A. Ciliberto's model of p53-MDM2 oscillations)

3rd example: PK-PD of cytotoxic drug 5-Fluorouracil

5-FU: 50 years on the service of colorectal cancer treatment



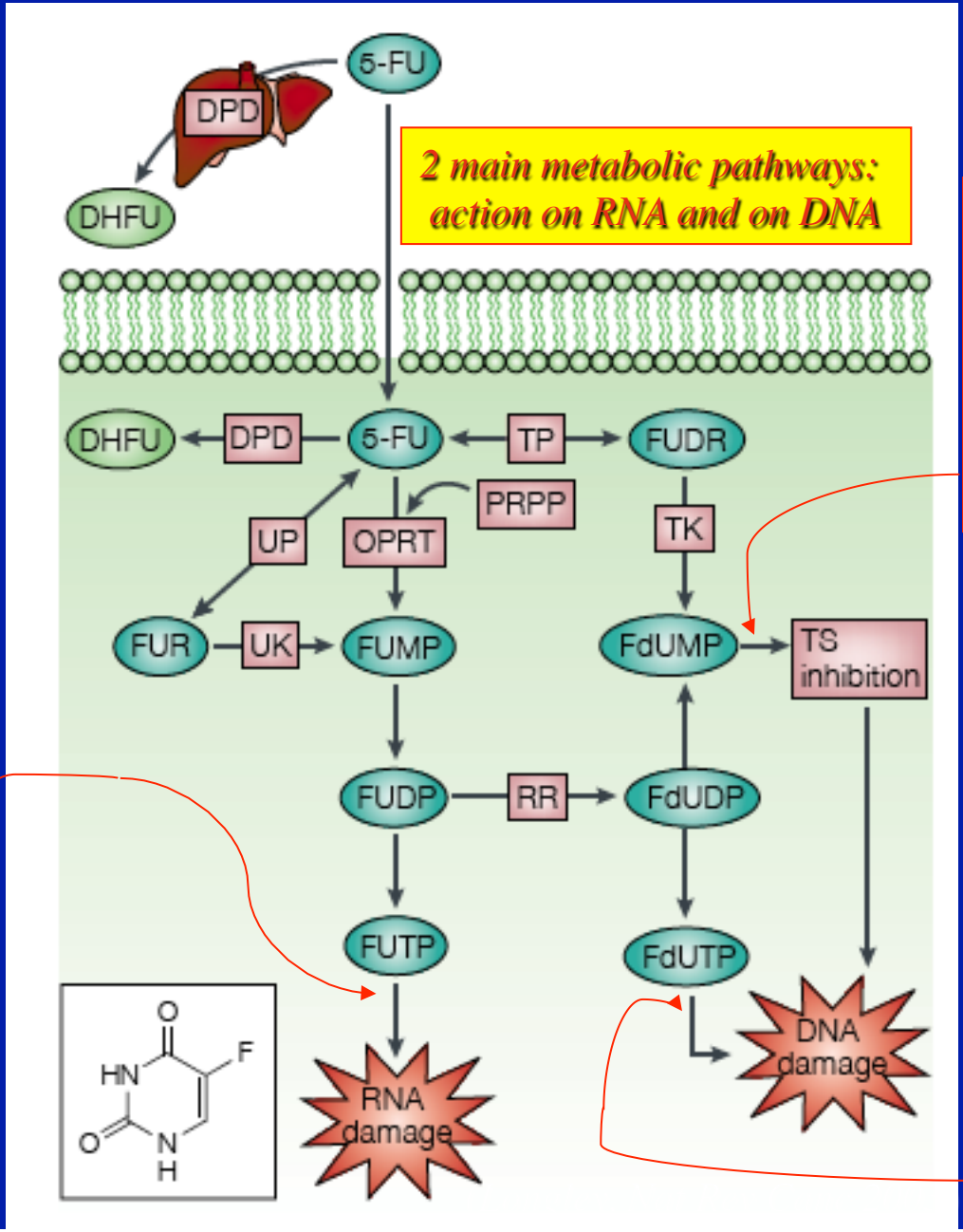
(NB : Uracil is found only in DNA)

(5-FU will be later transformed into FdUMP instead of normal dUMP)

PK-PD of 5-FU

RNA pathway

DNA pathway



Competitive inhibition by FdUMP of dUMP binding to target TS

+

[Stabilisation by CH_2-THF of binary complex FdUMP-TS]

Incorporation of FUTP instead of UTP to RNA

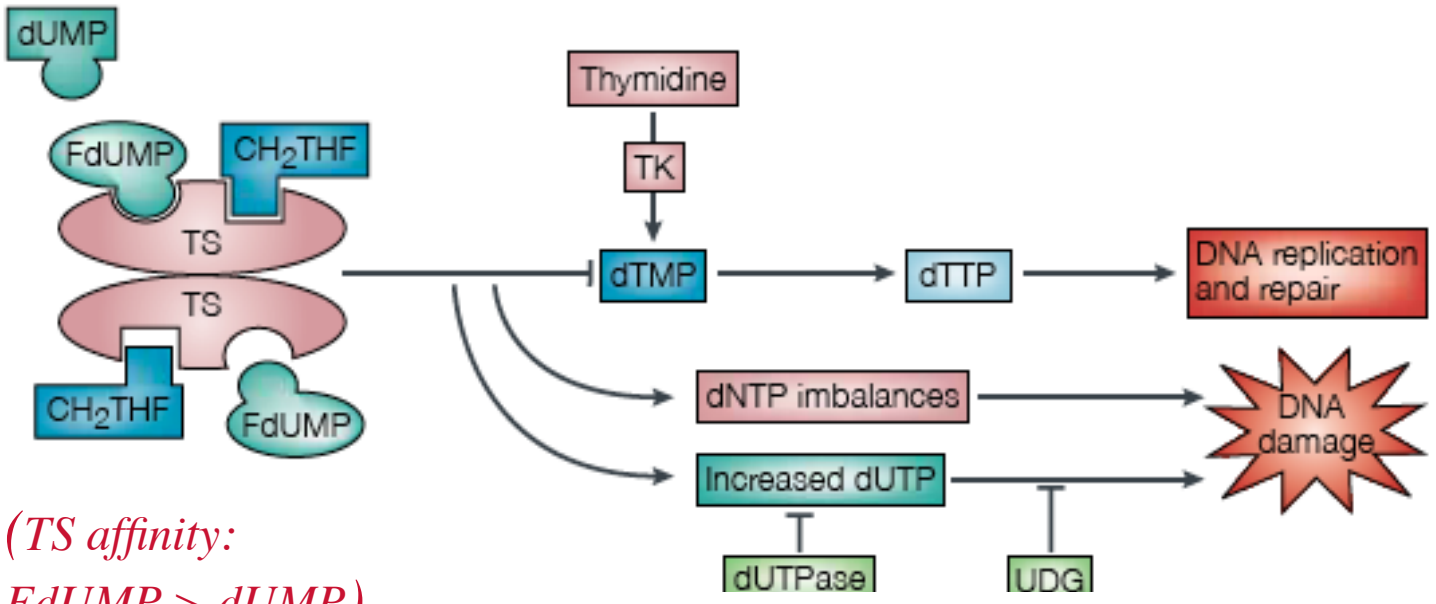
Incorporation of FdUTP instead of dTTP to DNA

Inhibition of Thymidylate Synthase (TS) by 5-FU and Leucovorin

Formyltetrahydrofolate (CHO-THF) = LV
a.k.a. Folinic acid, a.k.a. Leucovorin

Precursor of CH_2-THF, coenzyme of TS, that forms with it and FdUMP a stable ternary complex, blocking the normal reaction

$$5,10\text{-}CH_2\text{-}THF + dUMP + FADH_2 \overset{TS}{\rightleftharpoons} dTMP + THF + FAD$$



(TS affinity: FdUMP > dUMP)

(Longley, Nat Rev Canc 2003)

Plasma and cell pharmacokinetics (PK) of 5-FU

- Poor binding to plasma proteins
- Degradation +++ (80%) by liver DPD
- Cell uptake using a saturable transporter
- Rapid diffusion in fast renewing tissues
- 5-FU = prodrug; main active anabolite = Fd-UMP
- Fd-UMP: active efflux by ABC transporter ABCC11 = MRP8

(Oguri, Mol Canc Therap 2007)

5-FU catabolism: DPD (dihydropyrimidine dehydrogenase)

- 5-FU $\xrightarrow{\text{DPD}}$ 5-FU H_2, hydrolysable [$\rightarrow$ FβAlanin]
- DPD: hepatic +++
- DPD: limiting enzyme of 5FU catabolism
- Michaelian kinetics
- Circadian rhythm of activity
- Genetic polymorphism +++ (very variable toxicity)

Modelling PK-PD of 5-FU [with drug resistance] + Leucovorin (action exerted on thymidylate synthase only in the S-G_2 phase)

$$(1)\quad \frac{dP}{dt} = -k_0 P - \frac{aP}{b+P} - l_{DPD}\frac{P}{m_{DPD}+P} + \frac{i(t)}{V}$$

$$(2)\quad \frac{dF}{dt} = \frac{a}{\xi}\frac{P}{b+P} - \frac{AF}{c+F} - k_1 FS + k_{-1}B$$

$$(3)\quad \frac{dQ}{dt} = -k_2 Q + \frac{j(t)}{V}$$

$$(4)\quad \frac{dL}{dt} = \frac{k_2}{\xi}Q - k_3 L - k_4 BL$$

$$(5)\quad \frac{dN}{dt} = \frac{\kappa F^n}{\lambda^n + F^n} - \mu N$$

$$(6)\quad \frac{dA}{dt} = \mu N - \nu A$$

$$(7)\quad \frac{dS}{dt} = -k_1 FS + k_{-1}B + \theta_{TS}(S_0 - S)$$

$$(8)\quad \frac{dB}{dt} = k_1 FS - k_{-1}B - k_4 BL$$

$$(9)\quad \frac{dT}{dt} = k_4 BL - v_T T$$

Input j = LV infusion flow

Input i = 5-FU infusion flow

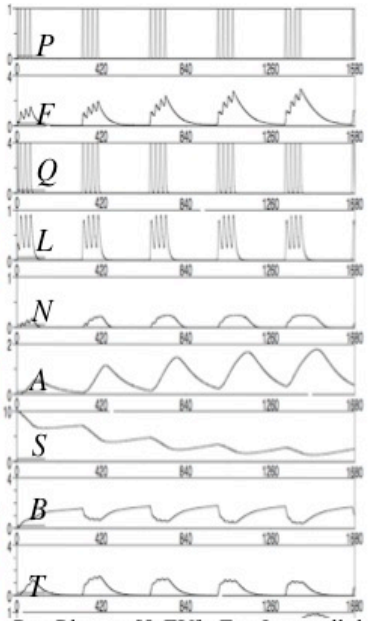
A = ABC transporter (active drug efflux)

S = Free Thymidylate Synthase (TS)

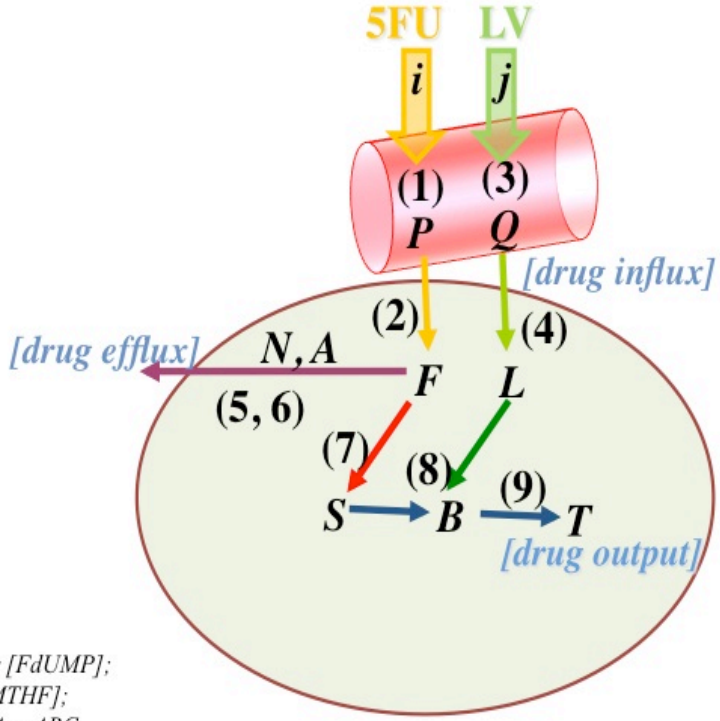
Drug output T = Blocked Thymidylate Synthase (stable ternary FdUMP-MTHF-TS complex)

where $l_{DPD} = l_{DPD\_BASE}\left\{1 + \varepsilon\cos\frac{2\pi(t-\varphi_{DPD})}{24}\right\}$

and $S_0 = S_{0\_BASE}\left\{1 + \delta\cos\frac{2\pi(t-\varphi_{TS})}{24}\right\}$



P = Plasma [5-FU]; F = Intracellular [FdUMP];
Q = Plasma [LV]; L = Intracellular [MTHF];
N = 5-FU-triggered Nuclear Factor; A = ABC Transporter activity, NuclearFactor-induced;
S = Free [TS] (not FdUMP-bound);
B = [FdUMP-TS] reversible binary complex;
T = [FdUMP-TS-MTHF] stable ternary complex



(F. Lévi, A. Okyar, S. Dulong, JC, Annu Rev Pharm Toxicol 2010)

5-FU (+ drug-induced drug resistance) + Leucovorin

P = Plasma [5FU]

F = Intracellular [FdUMP]

Q = Plasma [LV]

L = 'Intracellular [LV]'=[CH_2THF]

N = [nrf2] efflux Nuclear Factor

A = ABC Transporter activity

S = Free [TS] (not FdUMP-bound)

B = [FdUMP-TS] binary complex

T = [FdUMP-TS-LV] irreversible ternary complex (TS blockade)

$$\frac{dP}{dt} = -k_0 P - \frac{aP}{b+P} - l_{DPD}\frac{P}{m_{DPD}+P} + \frac{i(t)}{V}$$

$$\frac{dF}{dt} = \frac{a}{\xi}\frac{P}{b+P} - \frac{AF}{c+F} - k_1 FS + k_{-1}B$$

$$\frac{dQ}{dt} = -k_2 Q + \frac{j(t)}{V}$$

$$\frac{dL}{dt} = \frac{k_2}{\xi}Q - k_3 L - k_4 BL$$

$$\frac{dN}{dt} = \frac{\kappa F^n}{\lambda^n + F^n} - \mu N$$

$$\frac{dA}{dt} = \mu N - \nu A$$

$$\frac{dS}{dt} = -k_1 FS + k_{-1}B + \theta_{TS}(S_0 - S)$$

$$\frac{dB}{dt} = k_1 FS - k_{-1}B - k_4 BL$$

$$\frac{dT}{dt} = k_4 BL - v_T T$$

Input = LV infusion flow

Input = 5FU infusion flow

Output = blocked Thymidylate Synthase

where $l_{DPD} = l_{DPD\_BASE}\left\{1 + \varepsilon \cos\frac{2\pi(t-\varphi_{DPD})}{24}\right\}$ and $S_0 = S_{0\_BASE}\left\{1 + \delta \cos\frac{2\pi(t-\varphi_{TS})}{24}\right\}$

5-FU and LV, plasma and intracellular PK: uptake, degrading enzymes, active efflux

FdUMP extracellular efflux (by ABC Transporter ABCC11)

5-FU cell uptake

5-FU DPD detoxication in liver

$i(t)$ = 5-FU infusion flow

$$\frac{dP}{dt} = -k_0 P - \frac{aP}{b+P} - l_{DPD}\frac{P}{m_{DPD}+P} + \frac{i(t)}{V}$$

$$\frac{dF}{dt} = \frac{a}{\xi}\frac{P}{b+P} - \frac{AF}{c+F} - k_1 FS + k_{-1}B$$

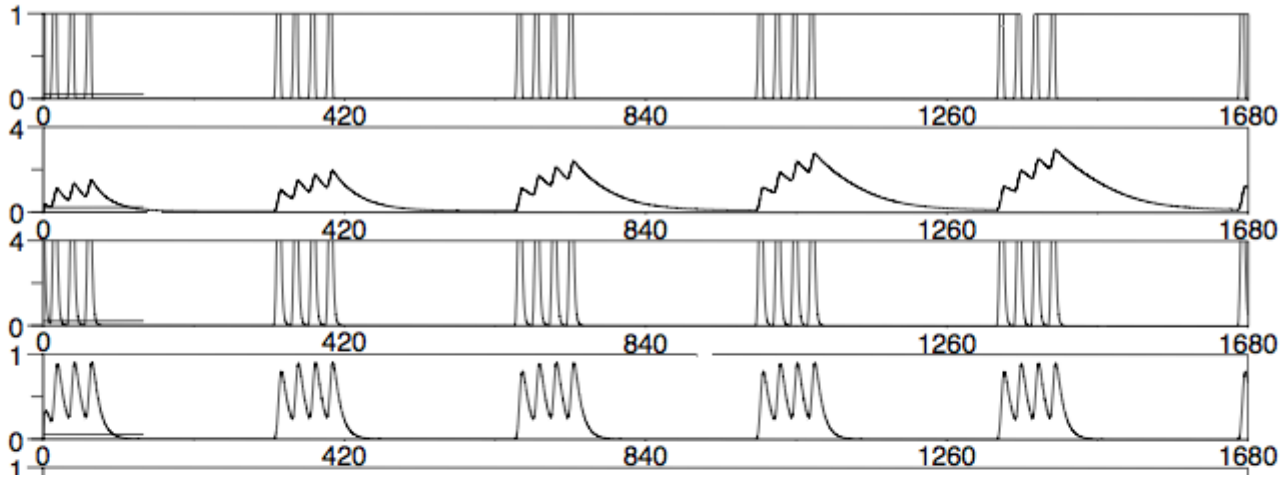
$j(t)$ = LV infusion flow

$$\frac{dQ}{dt} = -k_2 Q + \frac{j(t)}{V}$$

$$\frac{dL}{dt} = \frac{k_2}{\xi}Q - k_3 L - k_4 BL$$

Binding of FdUMP to TS to form a *reversible* binary complex B

Binding of LV to FdUMP-TS = B to form a *stable* ternary complex



Resistance? Induction of ABC Transporter activity by FdUMP-triggered synthesis of nuclear factor *nrf2*

$$\frac{dF}{dt} = \frac{a}{\xi}\frac{P}{b+P} - \frac{AF}{c+F} - k_1 F S + k_{-1} B$$

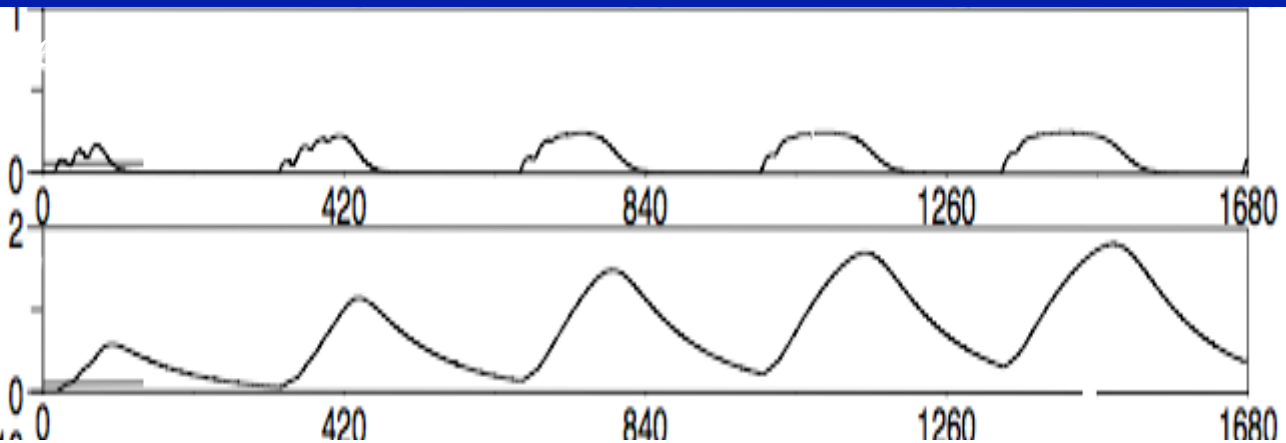
$$\frac{dN}{dt} = \frac{\kappa F^n}{\lambda^n + F^n} - \mu N$$

$$\frac{dA}{dt} = \mu N - \nu A$$

FdUMP

Nuclear factor *(e.g., nrf2)*

ABC Transporter activity (ABCC11=MRP8)

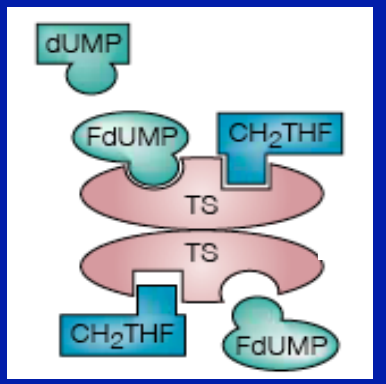


Targeting Thimidylate Synthase (*TS*) by FdUMP: Formation of binary and ternary *TS*-complexes

$$\frac{dS}{dt} = -k_1 FS + k_{-1} B + \theta_{TS}(S_0 - S)$$

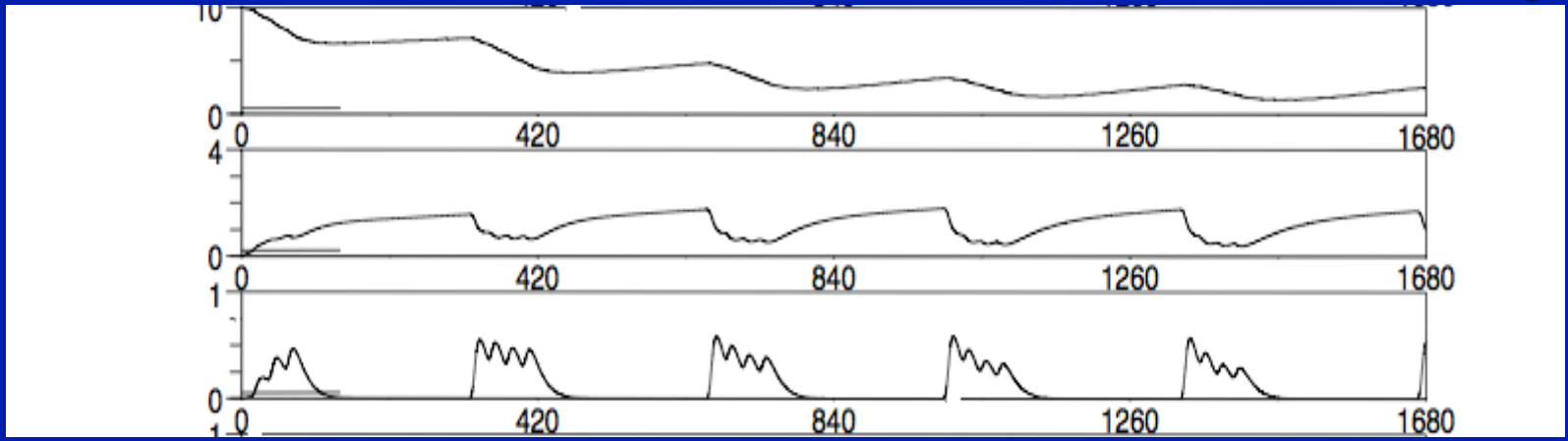
$$\frac{dB}{dt} = k_1 FS - k_{-1} B - k_4 BL$$

$$\frac{dT}{dt} = k_4 BL - v_T T$$



$F + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} F\text{-}S = B$ *(FdUMP-TS 2-complex)*

$B + L \xrightarrow{k_4} B\text{-}L = T$ *(FdUMP-TS-LV 3-complex)*



TS blockade results in subsequent DNA damage

Simulation: 5 sequences of 2-week therapy courses

4 days of 5-FU+LV infusion,12 hours a day, every other week

P = Plasma [5FU]

F = Intracellular [FdUMP]

Q = Plasma [LV]

L = Intracellular [LV]

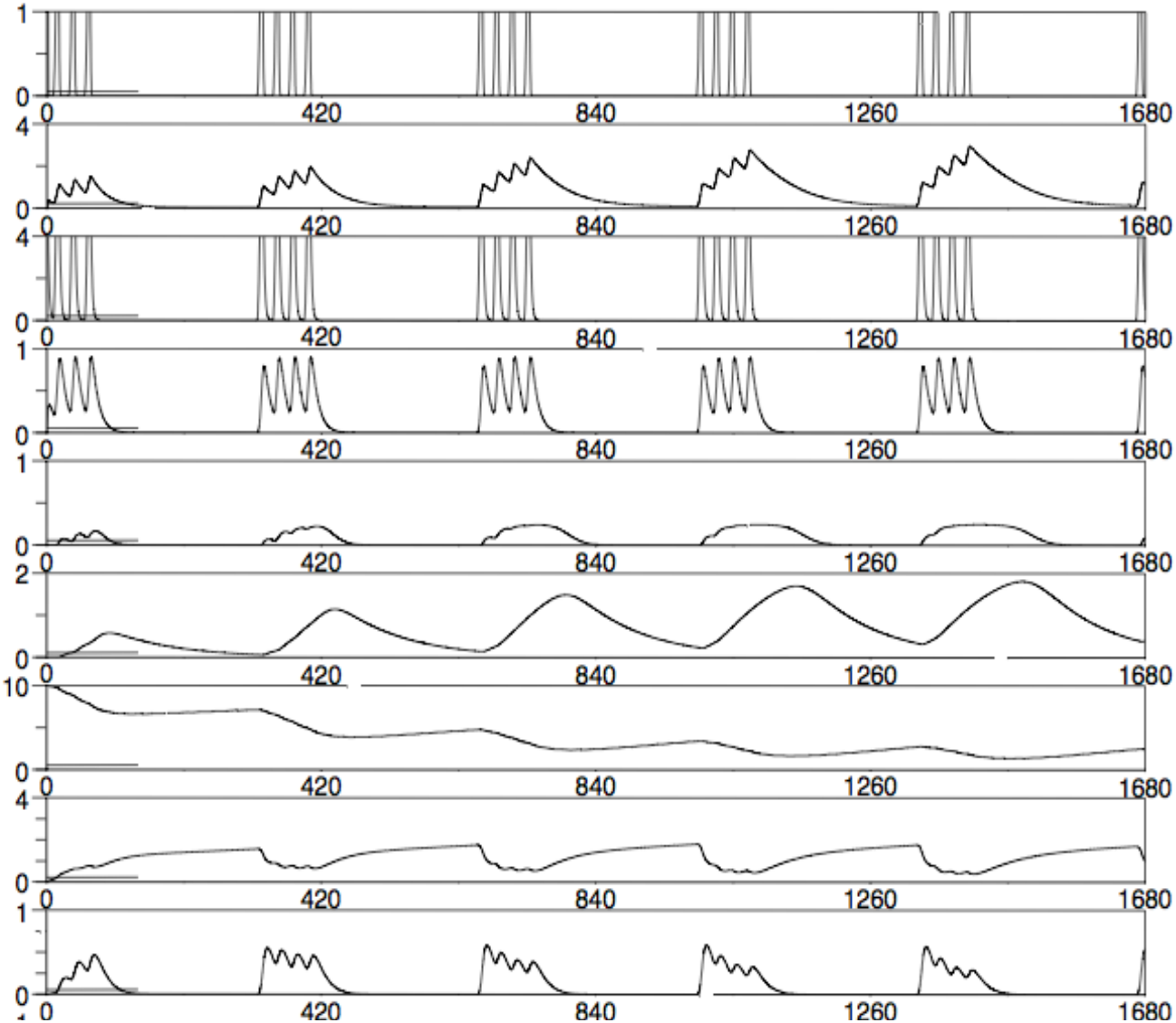
N = [nrf2] 5FU-triggered Nuclear Factor

A = ABC Transporter activity, nrf2-inducted

S = Free [TS] (not FdUMP-bound)

B = [FdUMP-TS] reversible binary complex

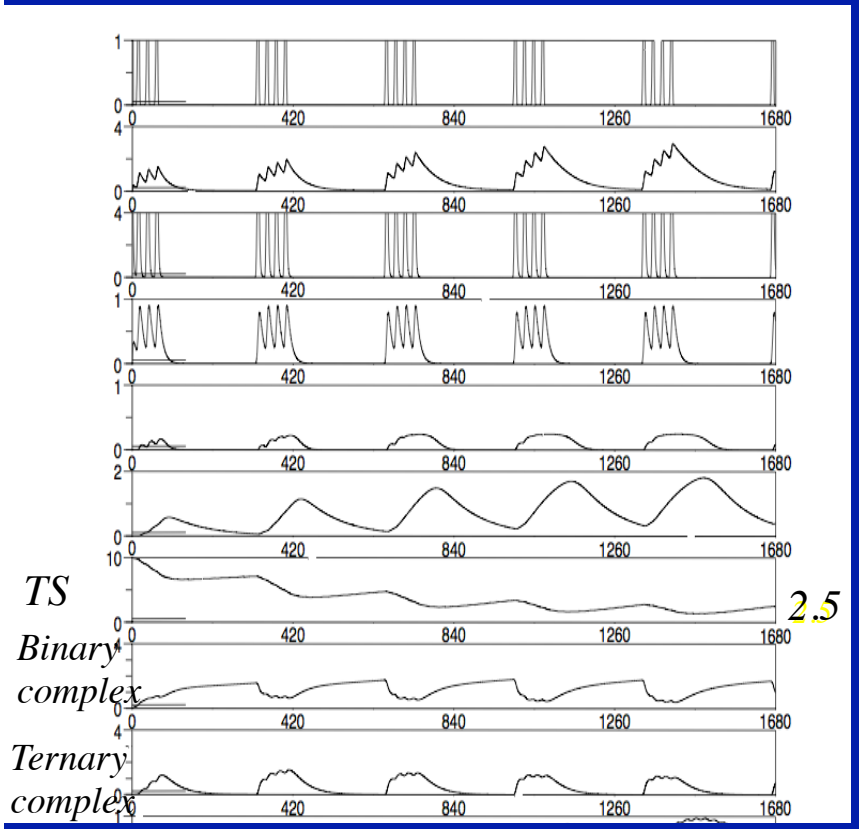
T = [FdUMP-TS-LV] stable ternary complex



Some features of the model:

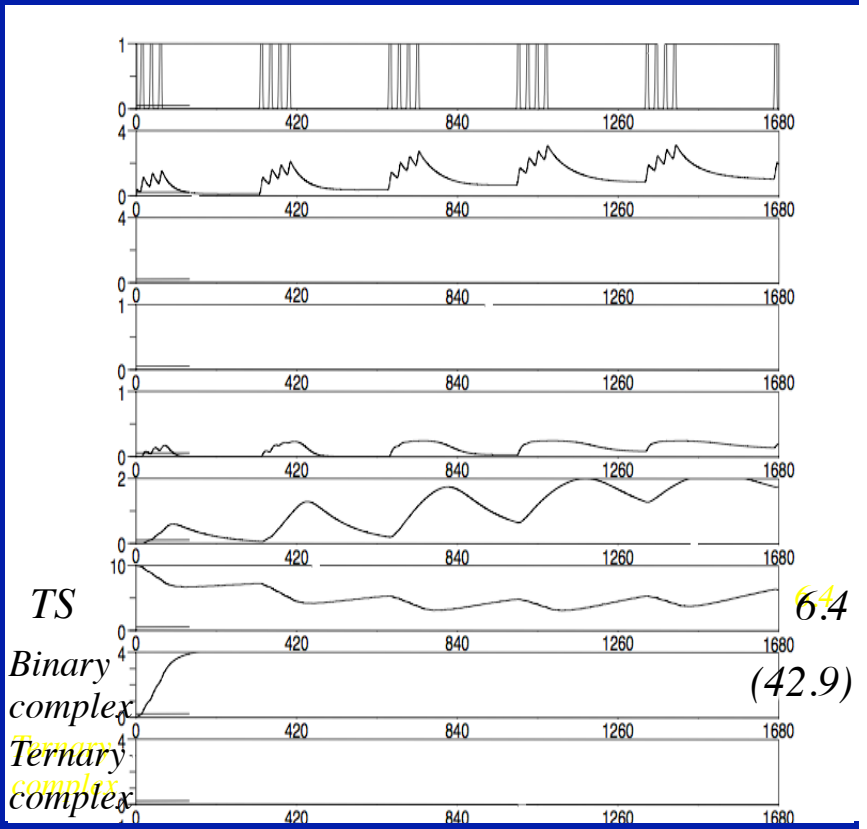
a) 5-FU with/without LV in resistant cancer cells (=MRP8+ cells)

With Leucovorin added in treatment



Cancer cells die

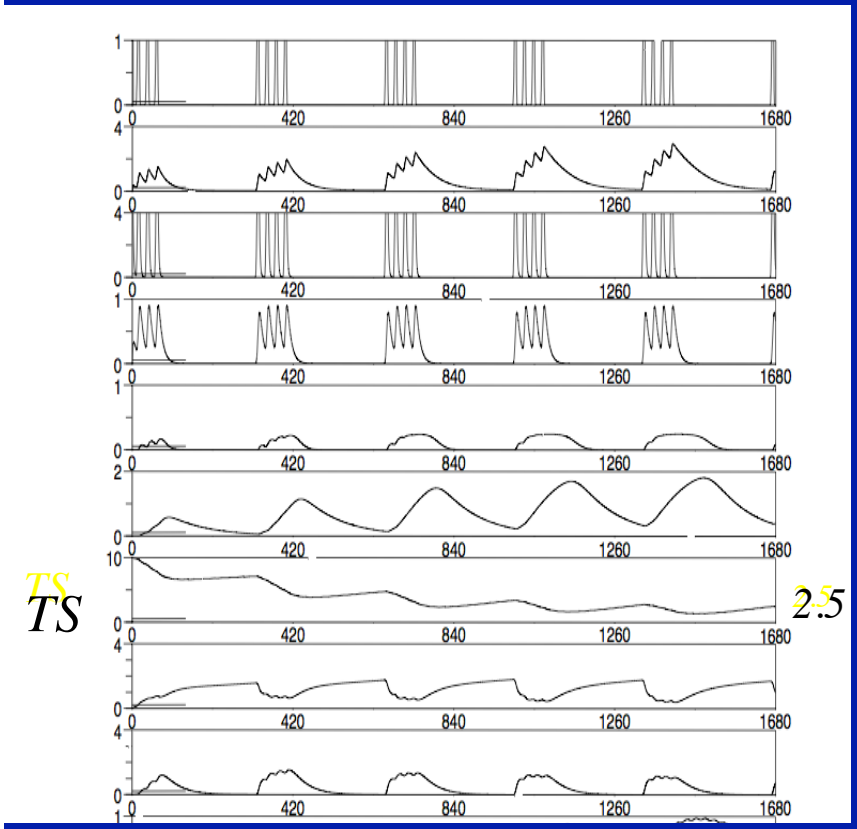
Without Leucovorin added



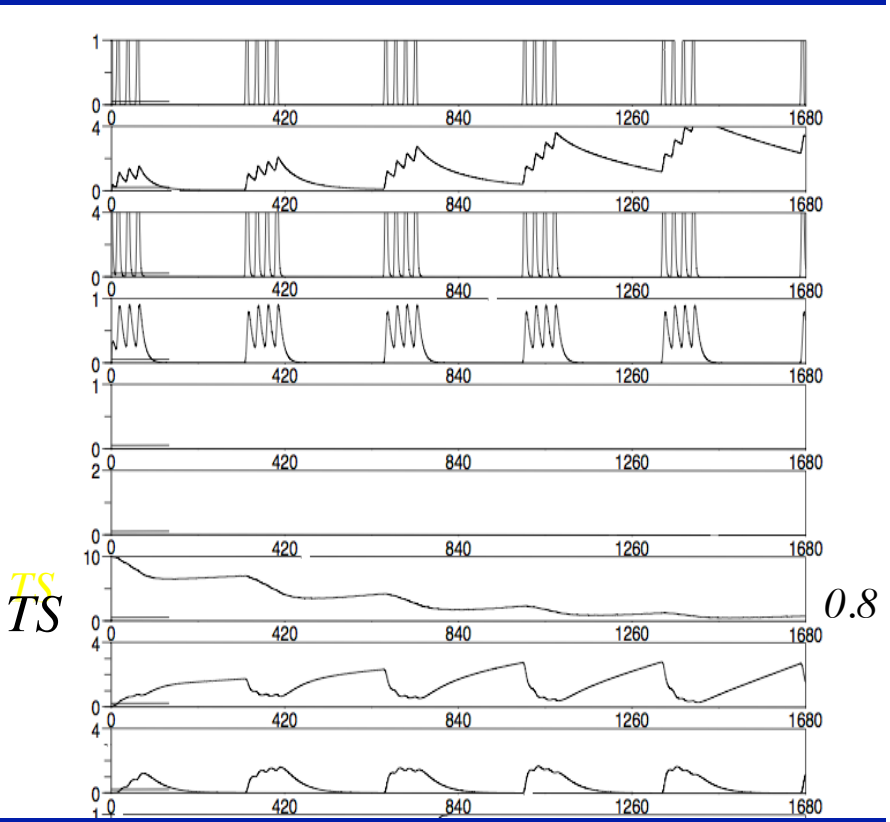
Cancer cells survive

b) 5-FU+LV with/without MRP8 (cancer vs. healthy cells)

Resistant cancer cells (=MRP8+)



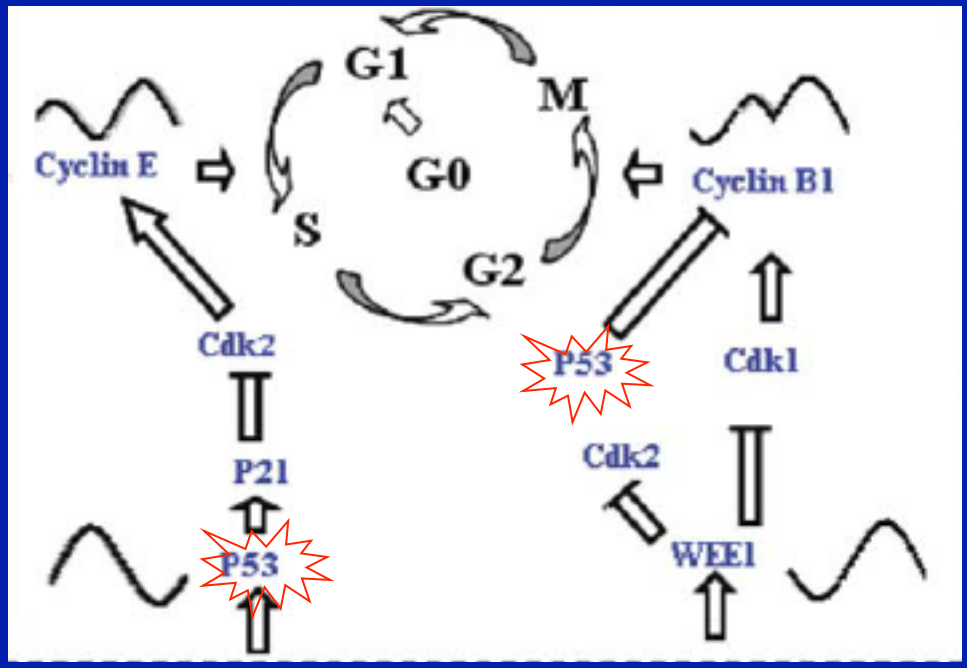
Healthy or sensitive cells (=MRP8-)



Cancer cells resist more than healthy cells, due to lesser exposure to FdUMP

(actively effluxed from cells by ABC Transporter MRP8)

The sentinel protein p53 senses DNA damage due to cytotoxic drugs, induces cell cycle arrest and launches DNA repair or (in case of failure) apoptosis



(from You et al., Breast Canc Res Treat 2005)

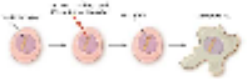
Connecting DNA damage with cell cycle arrest at G1/S and G2/M checkpoints by inhibition of phase transition functions ψ_i and by induction of cell death

Modelling p53 cell dynamics *(L. Dimitrio's, then J. Elias's theses)*

What is p53?

In 1979 a protein of molecular mass of 53 kDa was isolated. It was named p53.

At first biologists believed that p53 was an oncogene, i.e. an **abnormal gene** that predisposes cells to develop into cancers.



10 years after they discovered that p53 is a **tumor suppressor** and so it acts to fix the cell or to trigger apoptosis.

The Model

NUCLEUS

$$
\begin{cases}
\frac{\partial [p53]}{\partial t} = d_p \Delta [p53] \overbrace{- k_1 [mdm2] \frac{[p53]}{K_1 + [p53]} + k_{-1} \frac{[p53_U]}{K_{-1} + [p53_U]}}^{\text{Ubiquitination-Deub.}} - k_3 A \frac{[p53]}{K_{ATM} + [p53]} \\
\frac{\partial [p53_U]}{\partial t} = d_{p'} \Delta [p53_U] + k_1 [mdm2] \frac{[p53]}{K_1 + [p53]} - k_{-1} \frac{[p53_U]}{K_{-1} + [p53_U]} \\
\frac{\partial [p53_p]}{\partial t} = d_{p''} \Delta [p53_p]^{(n)} + \overbrace{k_3 A^{(n)} \frac{[p53]}{K_{ATM} + [p53]}}^{\text{Phosphorylation}} - k_{Sp} \frac{([p53_p])^4}{([p53_p]^{(n)})^4 + K_{Sp}} \\
\frac{\partial [mdm2]}{\partial t} = d_m \Delta [mdm2] - \delta_m [mdm2] \\
\frac{\partial [mdm2_{RNA}]}{\partial t} = k_{Sm} + \overbrace{k_{Sp} \frac{([p53_p])^4}{([p53_p])^4 + K_{Sp}}}^{\text{p53-dependent-trascription}} + d_{mRNA} \Delta [mdm2_{RNA}] - \delta_{mRNA} [mdm2_{RNA}]
\end{cases}
$$

Single-cell intracellular reaction-diffusion oscillatory dynamics of p53 and Mdm2

The Model

CYTOPLASM

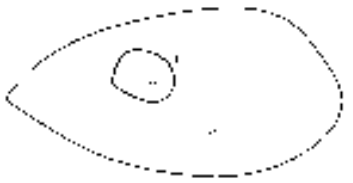
$$
\begin{cases}
\frac{\partial [p53]}{\partial t} = k_{Sp53} \chi_R + d_p \Delta [p53] - k_1 [mdm2] \frac{[p53]}{K_1 + [p53]} + k_{-1} \frac{[p53_U]}{K_{-1} + [p53_U]} - k_3 A \frac{[p53]}{K_{ATM} + [p53]} \\
\frac{\partial [p53]_U}{\partial t} = d_{p'} \Delta [p53]_U + k_1 [mdm2] \frac{[p53]}{K_1 + [p53]} - k_{-1} \frac{[p53_U]}{K_{-1} + [p53_U]} \\
\qquad \overbrace{- \delta_{pu} [p53_U]}^{\text{degradation}} \\
\frac{\partial [p53_p]}{\partial t} = d_{p''} \Delta [p53_p] + k_3 A \frac{[p53]}{K_{ATM} + [p53]} \\
\frac{\partial [mdm2]}{\partial t} = d_m \Delta [mdm2] + \overbrace{[mdm2_{RNA}] \chi_R}^{\text{translation}} - \delta_m [mdm2] \\
\frac{\partial [mdm2_{RNA}]}{\partial t} = d_{mRNA} \Delta [mdm2_{RNA}] - [mdm2]_{RNA} \chi_R - \delta_{mRNA} [mdm2_{RNA}]
\end{cases}
$$

The Model

and the following boundary condition:

$$
\begin{cases}
d_p \left(\frac{\partial [p53]^{(n)}}{\partial n} \right) = p_{p53} [p53]^{(c)} = -d_p \left(\frac{\partial [p53]^{(c)}}{\partial n} \right) \\
d_{p'} \left(\frac{\partial [p53_U]^{(n)}}{\partial n} \right) = -p_u [p53]_U^{(n)} = -d_{p'} \left(\frac{\partial [p53_U]^{(c)}}{\partial n} \right) \\
d_{p''} \left(\frac{\partial [p53_p]^{(n)}}{\partial n} \right) = p_{pp} ([p53]_p^{(c)} - [p53]_p^{(n)}) = -d_{p''} \left(\frac{\partial [p53_p]^{(c)}}{\partial n} \right) \\
d_m \left(\frac{\partial [mdm2]^{(n)}}{\partial n} \right) = p_{mdm2} ([mdm2]^{(c)} - [mdm2]^{(n)}) = -d_m \left(\frac{\partial [mdm2]^{(c)}}{\partial n} \right) \\
d_{mRNA} \left(\frac{\partial [mdm2_{RNA}]^{(n)}}{\partial n} \right) = -p_{mRNA} [mdm2_{RNA}]^{(n)} = -d_{mRNA} \left(\frac{\partial [mdm2_{RNA}]^{(c)}}{\partial n} \right)
\end{cases}
$$

on the common boundary Γ.



Dimitrio et al. JTB 2012; further work by Elias et al. BBA Prot 2014, Phys Biol 2014, CSBJ 2014

III. Therapeutic control and its theoretical optimisation

Optimising cancer therapy by drugs

- 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)*

- Optimising [combined delivery of cytotoxic drugs and] immunotherapy
  (L. de Pillis & A. Radunskaya Cancer Res 2005, JTB 2006, Frontiers Oncol 2013)

- 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 achievements for colorectal cancer treatment* in human *males* *(M.-C. Mormont & F. Lévi, Cancer 2003)*

- Optimising combined delivery of cytotoxic and antiangiogenic drugs
  (U. Ledzewicz et al. MBE 2011)

- Overcoming drug resistance +++: optimal control strategies to overcome the development of drug resistant cell populations, using different drugs

(M. Kimmel & A. Swierniak, Springer LN Math 1872, 2006; Lorz et al. 2013, 2014; Trélat et al., underway)

Choosing the constraint to be represented may determine the model of proliferation used to optimise drug delivery, aiming at avoiding the two main pitfalls of pharmacotherapy:

- *Toxicity issues*. Controlling toxic side effects to preserve healthy cell populations leads to representing proliferating cell populations by ordinary differential equations, or by age-structured models: physiologically structured partial differential equations

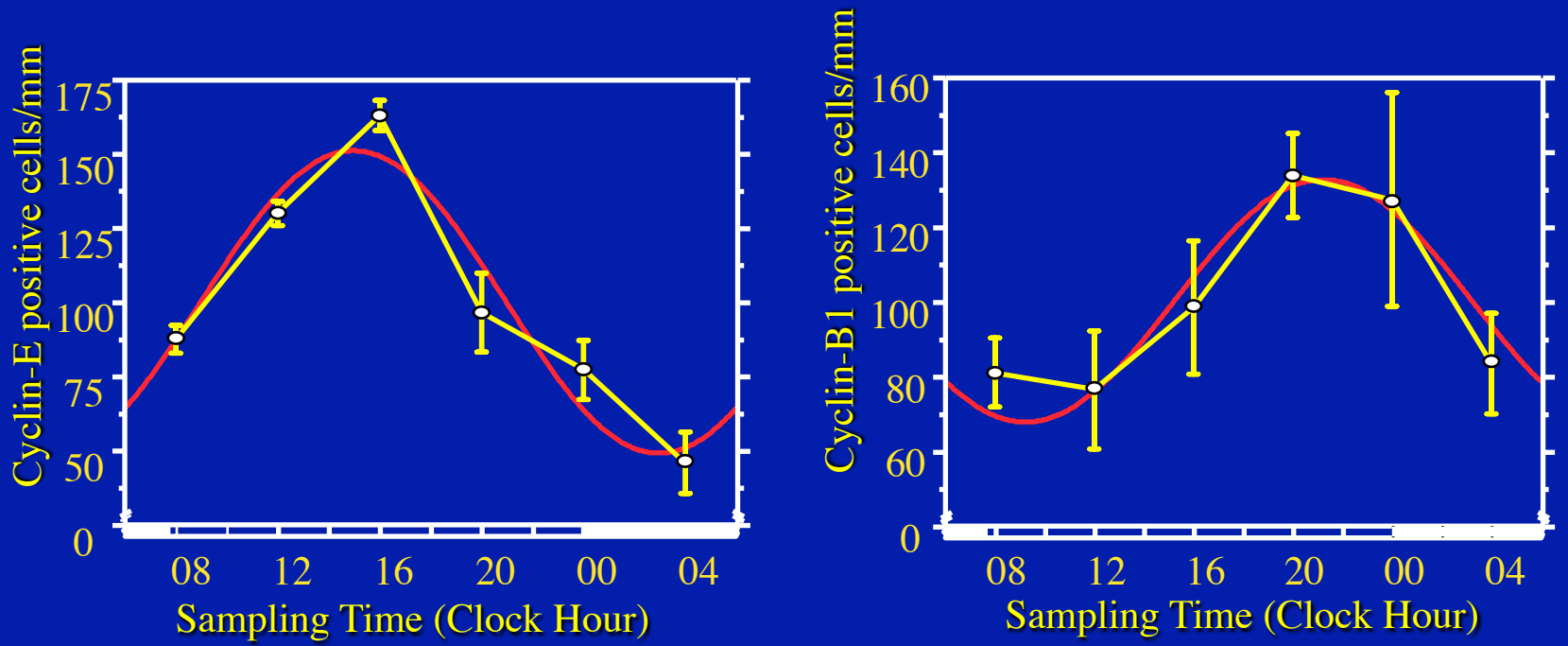
- *Drug resistance issues*. Controlling emergence of drug-induced drug-resistant cell subpopulations in tumour tissues leads to using phenotypic trait-structured models of proliferation: physiologically structured evolutionary integro-differential equations

1. Minimising unwanted toxic side effects on healthy cells

Search for a difference between healthy and cancer cell populations: possible role of circadian rhythms?

Mammalian physiology at the macroscopic level: control by circadian rhythms of the cell division cycle at checkpoints

Example of circadian rhythm in normal Human oral mucosa: tissue concentrations in Cyclin E (control of G_1/S transition) and Cyclin B (control of G_2/M transition)



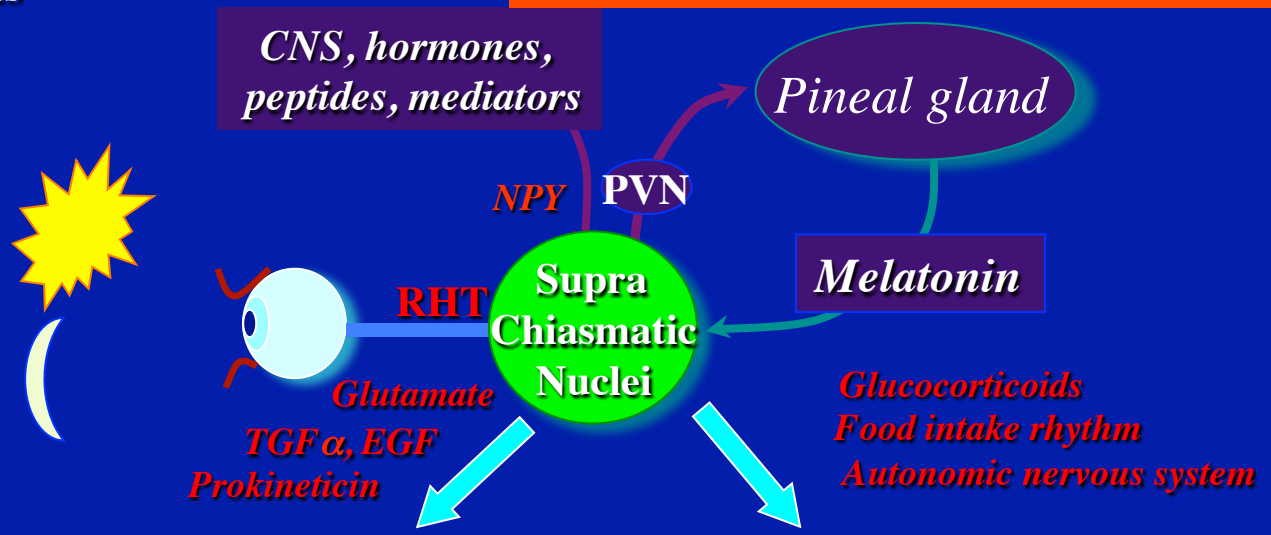
Nuclear staining for Cyclin-E and Cyclin-B1. Percentages of mean ± S.E.M. in oral mucosa samples from 6 male volunteers. Cosinor fitting, $p < 0.001$ and $p = 0.016$, respectively.

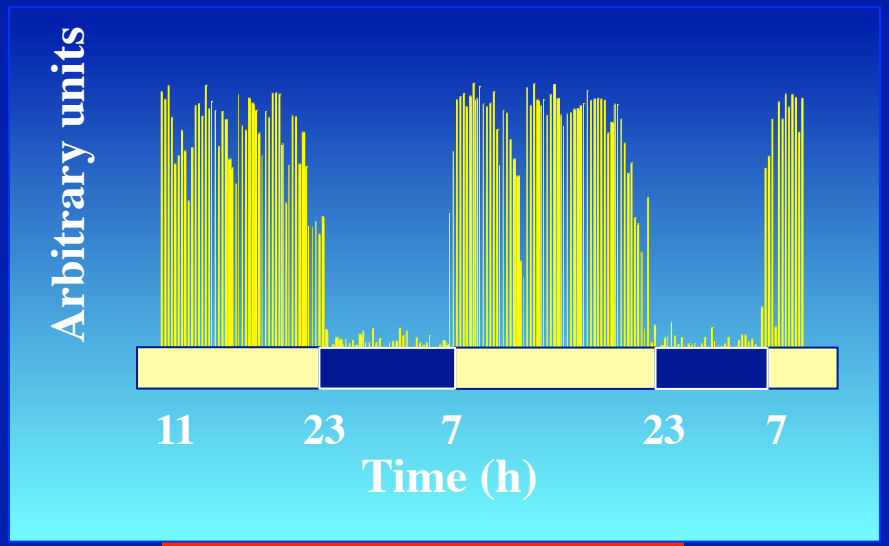
(from Bjarnason et al. Am J Pathol 1999)

Circadian chronobiology: the circadian system

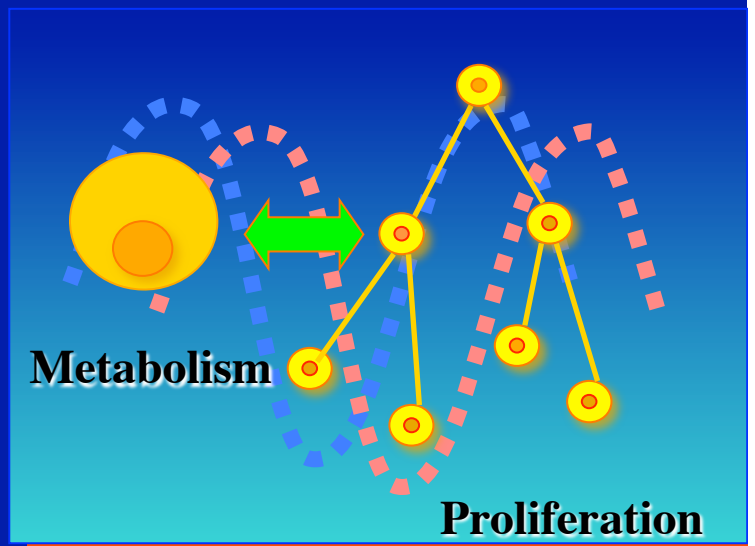
A system of molecular clocks that gives a 24 h rhythm to all cells in our organism

Central coordination





?



Rest-activity cycle

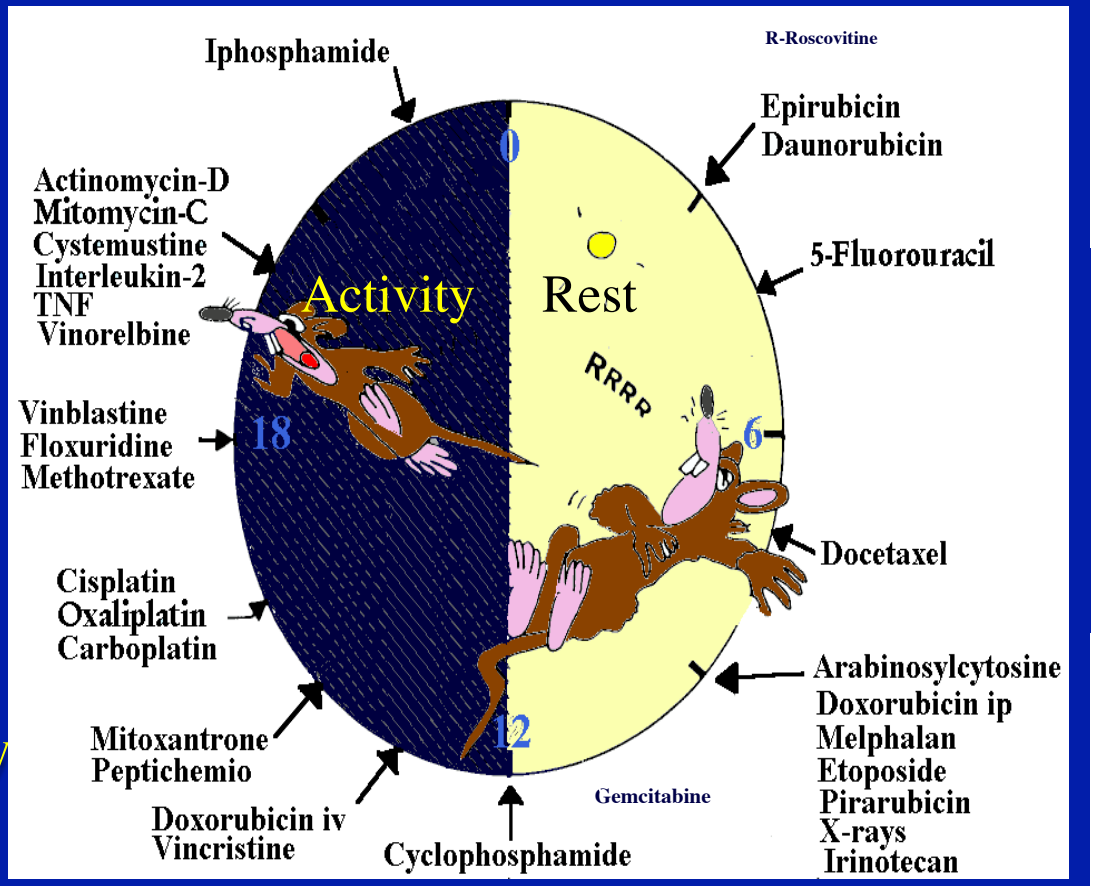
Peripheral oscillators

Lévi, Lancet Oncol 2001 ; Mormont & Lévi, Cancer 2003

Chronotherapeutic principles, according to F. Lévi

- Tolerance for anticancer drugs: variation > 50% as a function of circadian timing
- Determinants: rhythms in metabolism, proliferation, apoptosis, repair
- Antitumour activity: best near the time of best tolerance
- Combination of cytotoxic drugs most effective following the delivery near its time of best tolerance

Experimental settings for laboratory rodents



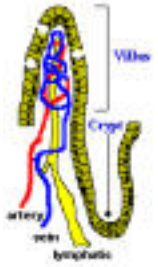
(M.-C. Mormont & F. Lévi, Cancer 2003

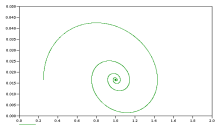
Simple pharmacokinetics-pharmacodynamics (PK-PD) of a cancer drug acting on cell populations: 6 state variables

oxaliplatin infusion flow

Healthy cells (jejunal mucosa)

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

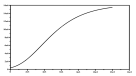




(PK)

Tumour cells

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



(homeostasis=damped harmonic oscillator)

(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

Main work hypothesis: $\varphi_T=\varphi_S+12$

(JC, Pathol-Biol 2003; Adv Drug Deliv Rev 2007)

Optimal control, step 1: deriving a constraint function from the enterocyte population model

$$\frac{dP}{dt} = -\lambda P + \frac{i(t)}{\mathcal{V}} \quad (1)$$

$$\frac{dC}{dt} = -\mu C + P \quad (2)$$

$$\frac{dZ}{dt} = -\{\alpha + f(C,t)\}Z - \beta A + \gamma \quad (3)$$

$$\frac{dA}{dt} = Z - Z_e \quad (4)$$

Minimal toxicity constraint, for $0<\tau_A<1$ (e.g. τ_A =60%):

$$\min_{t\in[t_0,t_f]} A(t,i) \geq \tau_A A_e,\ i \in L^2([t_0,t_f])\ ,\ \text{or}:$$
$$F_A(i) = \tau_A - \min_{t\in[t_0,t_f]} A(t,i)/A_e \leq 0$$

Other possible constraints: $\max_{t\in[t_0,t_f]} i(t) \leq i_{max}\ ,\ \int_{t_0}^{t_f} i(t) \leq AUC_{max}$

Optimal control, step 2: deriving an objective function from the tumoral cell population model

$$\frac{dP}{dt} = -\lambda P + \frac{i(t)}{\mathcal{V}} \quad (1)$$

$$\frac{dD}{dt} = -\nu D + P \quad (2)$$

$$\frac{dB}{dt} = a \ln \frac{B_{max}}{B} - g(D,t)B \quad (3)$$

Objective function 1: *Eradication strategy*: minimize $G_B(i)$, where;

$$B = B(t,i) \ , i \in L^2([t_0, t_f])$$

$$G_B(i) = \min_{t \in [t_0, t_f]} B(t,i)$$

or else:

Objective function 2: *Stabilisation strategy*: minimize $G_B(i)$, where;

$$G_B(i) = \max_{t \in [t_0, t_f]} B(t,i)$$ or $$G_B(i) = B(t_f, i)$$

Optimal control problem (eradication): defining a Lagrangian:

$$\mathcal{L}(i,\theta) = G_B(i) + \theta F_A(i)\,, \text{ where}$$

$$0 \le i \le i_{max}\,,\ i \in L^2([t0, t_f]),\ \int_{t_0}^{t_f} i(t) \le AUC_{max}\,, \text{ and } \theta \ge 0$$

then:

$$\min_{F_A(i)\le 0} G_B(i) = \min_{i \in L^2([t_0,t_f])} \max_{\theta \ge 0} \mathcal{L}(i,\theta) \pm other\ constraints$$

If G_B and F_A were convex, then one should have:

$$\min_i \max_{\theta>0} \mathcal{L}(i,\theta) = \max_{\theta>0} \min_i \mathcal{L}(i,\theta)$$

…and the minimum would be obtained at a saddle-point of the Lagrangian, reachable by an Uzawa-like algorithm

Investigating the minima of the objective function: a continuous problem

…but G_B and F_A need not be convex functions of infusion flow i!!

Yet it may be proved using a compacity argument that
the minimum of G_B under the constraint $F_A \leq 0$ actually exists:

F_A and G_B are weakly continuous functions of *i*, from $L^2([t_0,t_f])$ to $H^2([t_0,t_f])$ since *i->A(t,i)* and *i->B(t,i)* are continuous by integration of the initial system:

$$P(t) = P(t_0)e^{-\lambda t} + \int_{t_0}^{t} \frac{i(\tau)}{\mathcal{V}} \Phi(\tau) e^{-\lambda(t-\tau)} d\tau$$

hence also are C,D,A,B as functions of *i*

and the constraint set $\{i, 0 \leq i \leq i_{max}, F_A(i) \leq 0\}$ is weakly compact in $L^2([t_0,t_f])$

Investigating the minima of the objective function: a differentiable problem

Moreover, A and B are C^2 as functions of time t (by integration of the initial system)

The minimum of A being attained at $t_A(i)$, i.e., $F_A(i) = \tau_A\text{-}A(t_A, i)/A_{eq,}$ it can be proved, assuming that $\partial^2 A(t_A(i),i) / \partial t^2 > 0$ and using the implicit function theorem, that t_A is a differentiable function of i

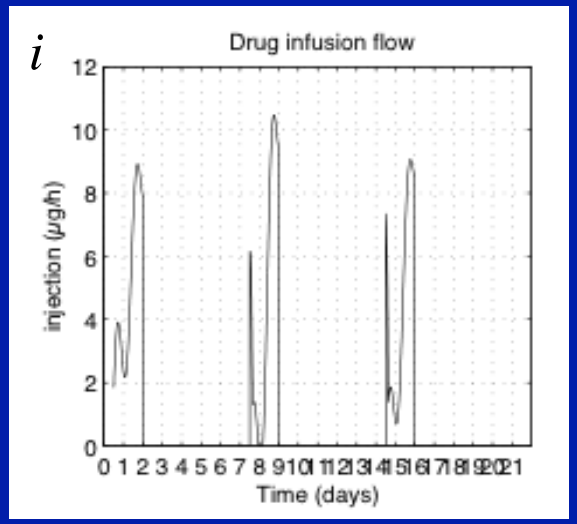
In the same way, t_B , defined by $G_B(i)=\max_t B(i,t)=B(i,t_B(i))$, is, provided that $\partial^2 B(t_B(i),i) / \partial t^2 < 0$, a differentiable function of i

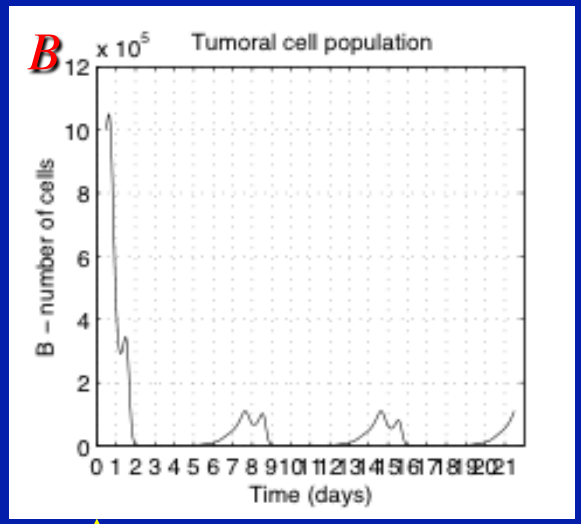
Hence, the infusion flow optimatisation problem is liable to differentiable optimisation techniques, and though the problem is not convex, so that searching for saddle points of the Lagrangian will only yield sufficient conditions,

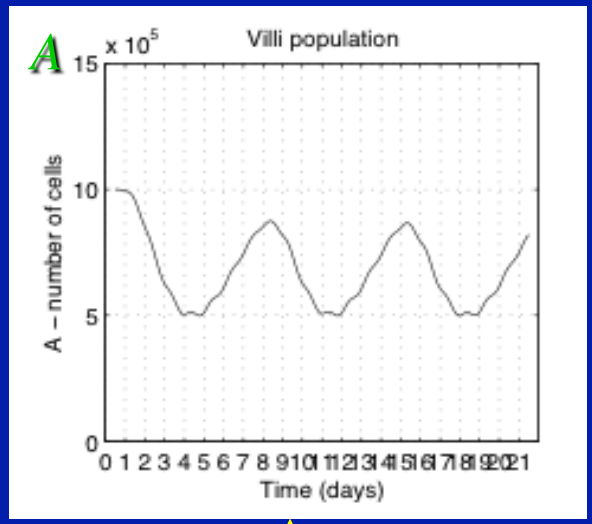
We nevertheless can define a heuristics to obtain minima of the objective function G_B submitted to the constraint $F_A \leq 0$, based on a Uzawa-like algorithm with a nonlinear conjugate gradient

Optimal control: results of the tumour stabilisation strategy using this simple one-drug PK-PD model

(and investigating more than Uzawa's algorithm fixed points, by storing best profiles)







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

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

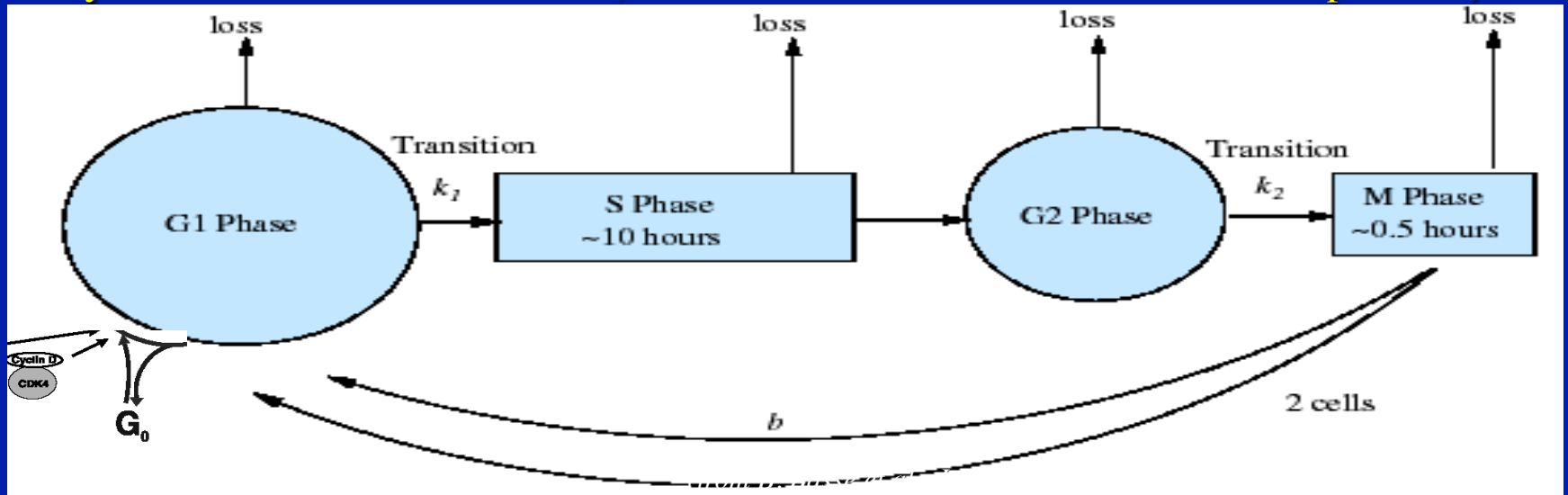
Solution : optimal infusion flow i(t) adaptable to the patient's state of health

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

(C. Basdevant, JC, F. Lévi, M2AN 2005; JC Adv Drug Deliv Rev 2007)

Physiologically and pharmacologically controlled model: age-structured PDE model for the cell division cycle

(here only linear models are considered, but nonlinear models with feedback are possible)



In each phase i, a McKendrick linear model:

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

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

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

n_i:=cell population density in phase i ; d_i:=death rate; v_i :=progression speed;

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

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

Death rates d_i: ("loss"), "speeds" v_i and phase transitions $K_{i->i+1}$ are model targets for physiological (e.g., circadian) or therapeutic (drug) control $\psi(t)$

[$\psi(t)$: e.g., clock-controlled CDK1 or intracellular output of drug infusion flow]

(Presented in: JC, B. Laroche, S. Mischler, B. Perthame, RR INRIA #4892, 2003; recently: JC, S. Gaubert, T. Lepoutre MMNP, MCM 2009, 2011)

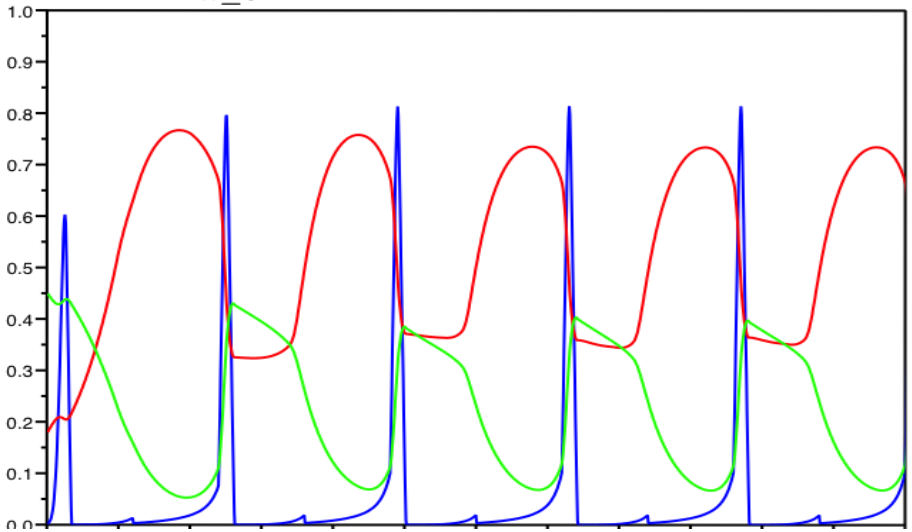
Main output of this age-structured PDE model

λ: a first eigenvalue governing the cell population behaviour

In summary: proof of the existence of a unique growth exponent λ, the same for all phases i, such that the $\widetilde{N}_i(t,a) = e^{-\lambda t} n_i(t,a)$ are bounded, and asymptotically periodic if the control is periodic

Example of control (periodic control case): 2 phases, control on G_2/M transition by 24-h-periodic CDK1-Cyclin B (from A. Goldbeter's minimal mitotic oscillator model)

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



ψ=CDK1 **All cells in G1-S-G2 (phase *i*=1)** **All cells in M (phase *i*=2)**

"Surfing on the exponential growth curve"

(= the same as adding an artificial death term +λ to the d_i)

Circadian rhythms and physiological control of the cell cycle:

Known connections between the cell cycle and circadian clocks

At the molecular level (*Bmal1* and *Per2* are constituents of the circadian clock):

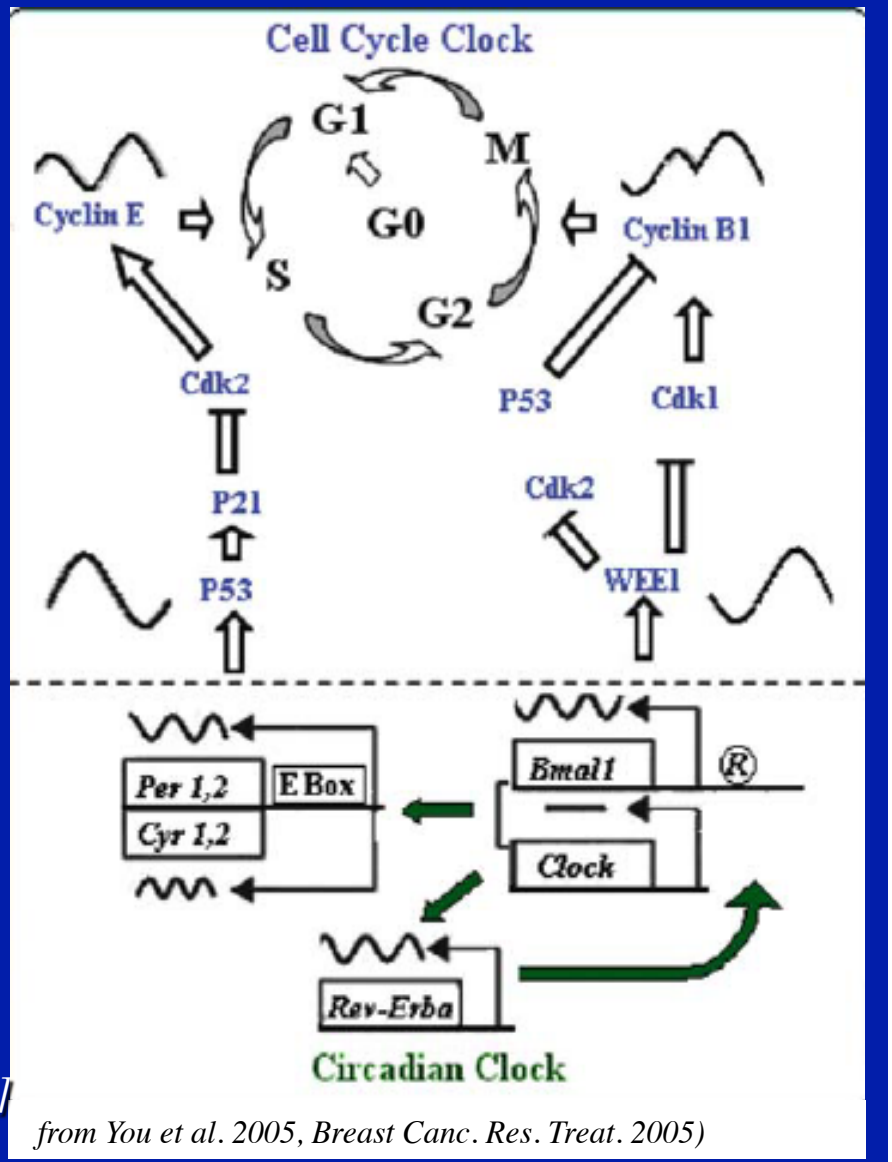
Bmal1 controls Wee1 and Cyclin B-Cdk1

Per2 controls p21 and Cyclin E- Cdk2

Wee1 and p21 act in antiphase

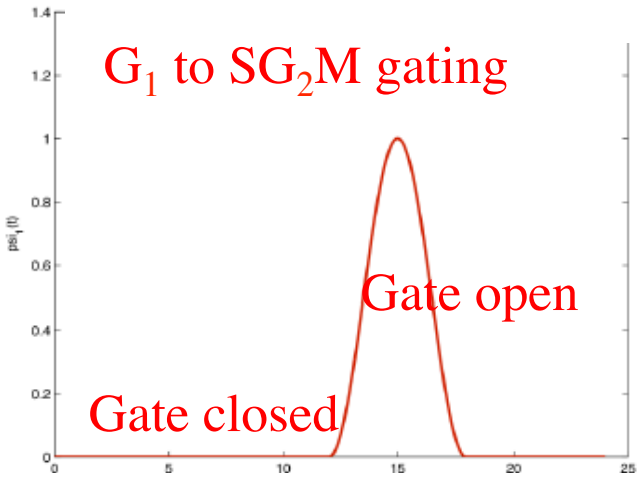
The circadian clock (*Bmal1*, *Per2*) might thus be a synchroniser in control of cell populations between G_1/S and G_2/M transitions

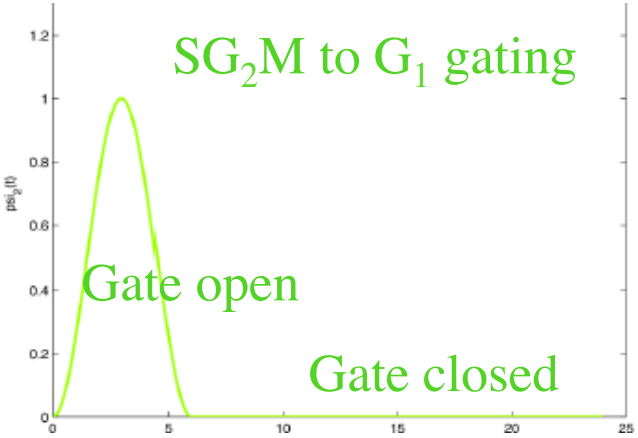
So, what if we add circadian clock control??
i.e., what if we put $K(t,x) = \kappa(x).\psi(t)$
with κ = FUCCI-identified and ψ = a cosine?
[cosine: in the absence of a better identified clock thus far!]



from You et al. 2005, Breast Canc. Res. Treat. 2005)

Adding theoretical circadian control on phase transitions

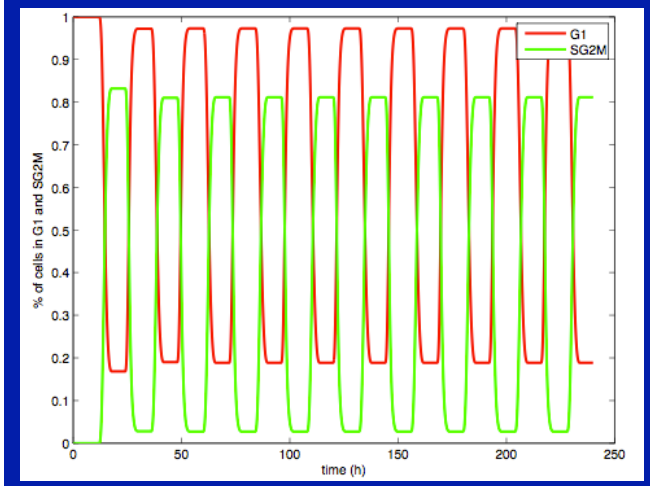




$$\psi_1(t) = \cos^2(2\pi(t-15)/12)\mathbb{1}_{[12;18]}(t)+\varepsilon, \quad \psi_2(t) = \cos^2(2\pi(t-3)/12)\mathbb{1}_{[0;6]}(t)+\varepsilon$$

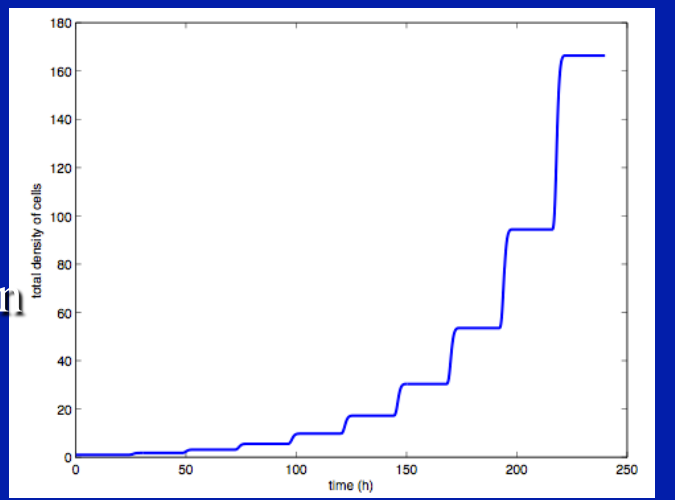
(a 12 h delay between the two cosines was determined as the one that maximised the λ)

Resulting evolution of the clock-controlled cell population: λ=0.024 h^{-1} (<0.0039 h^{-1})



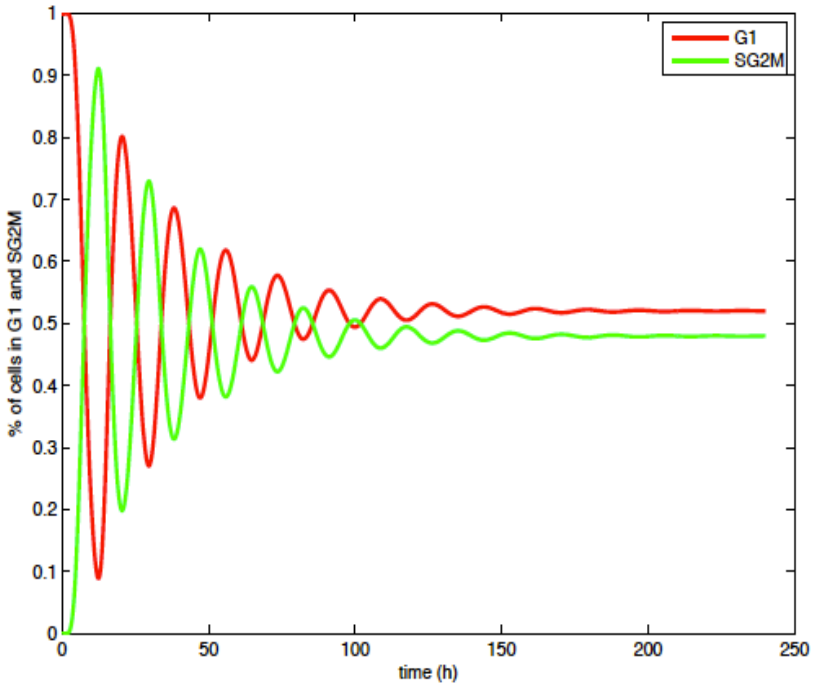
Here we put
$K(t,x) = \kappa(x).\psi(t)$
with κ = FUCCI-identified
and ψ = cosine-like function

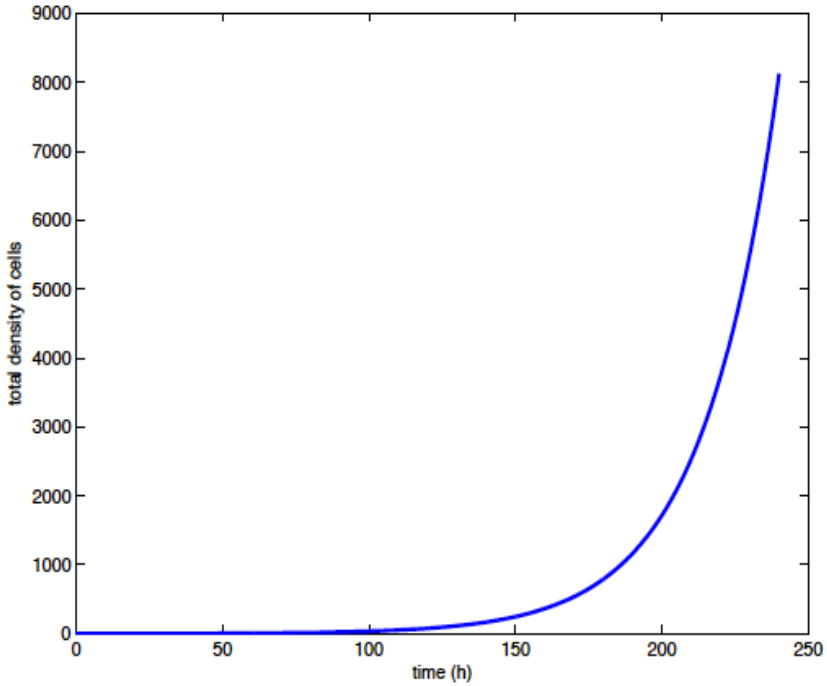
[cosine: in the absence of a better identified clock thus far]

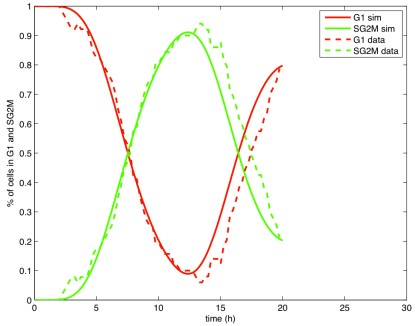


Without time control

Phases: asynchronous cell growth



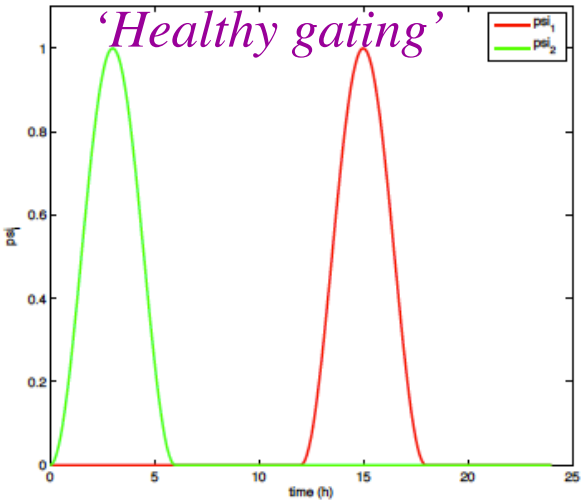




$\lambda = 0.039h^{-1}$ $T_d = 18h$

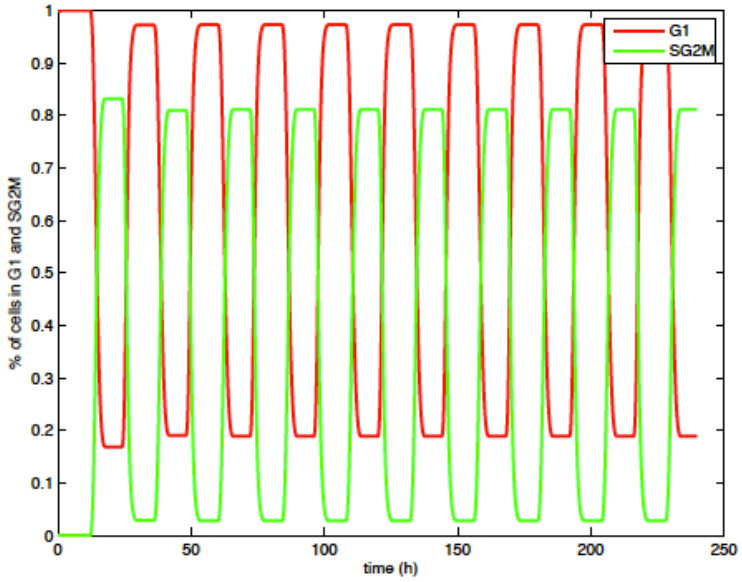
With time control (1)

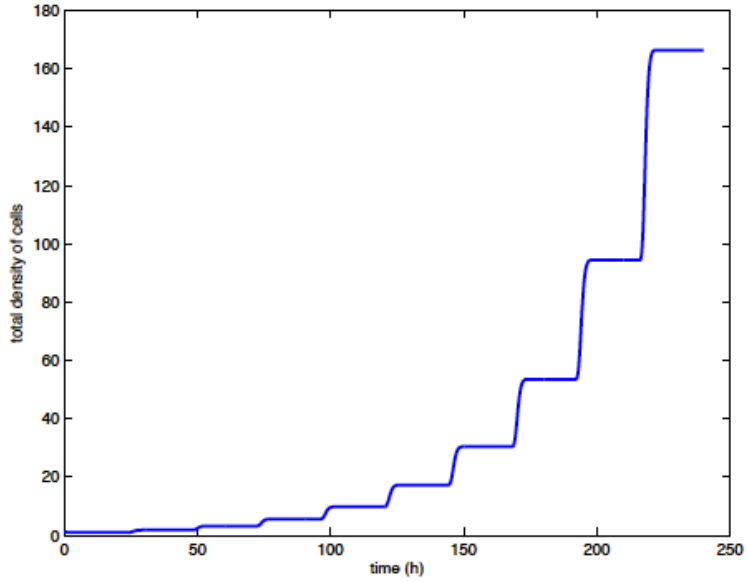
$$K_{i\to i+1}(a,t) = \underbrace{\kappa_{i\to i+1}(a)}_{\text{from exp. data}} \times \underbrace{\psi_i(t)}_{\text{circ. clock}}$$



*(1) **Healthy** cell population (=**sharp** gating by circadian clock)*

Steep synchronisation within the cell cycle

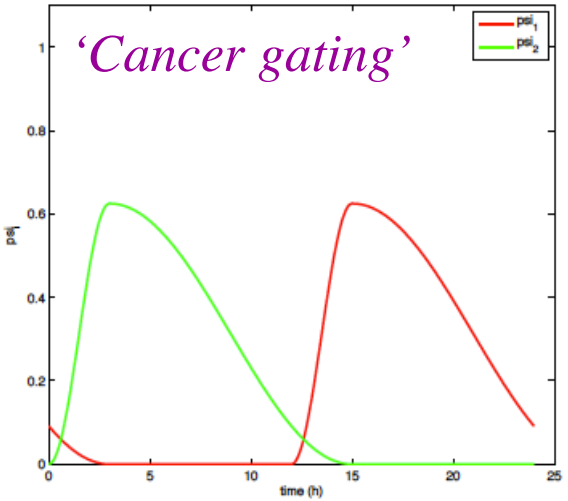




$\lambda = 0.024h^{-1}$ $T_d = 29.4h$

With time control (2)

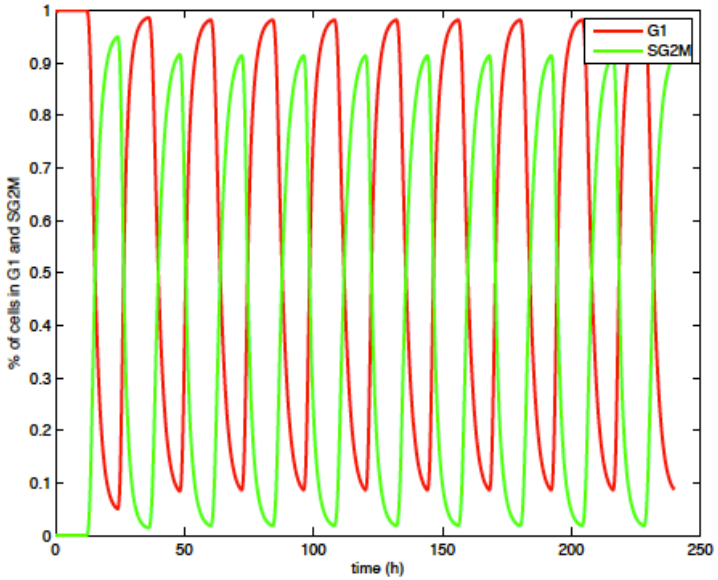
$$K_{i\to i+1}(a,t) = \underbrace{\kappa_{i\to i+1}(a)}_{\text{from exp. data}} \times \underbrace{\psi_i(t)}_{\text{circ. clock}}$$

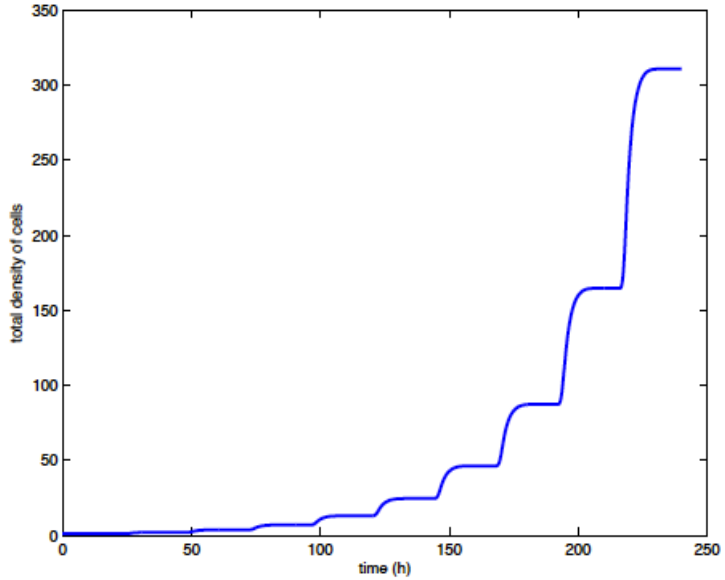


Main work hypothesis (difference from healthy cells)

*(2) **cancer** cell population (=**lazy** gating by circadian clock)*

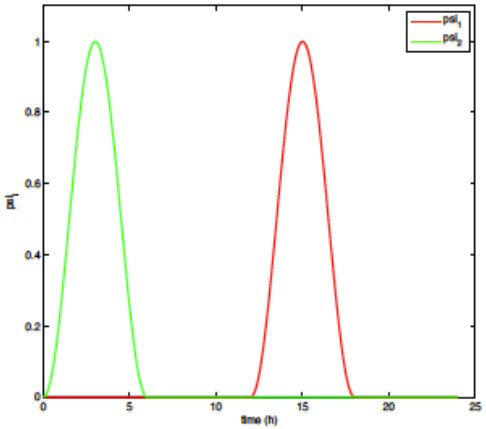
Loose synchronisation within the cell cycle





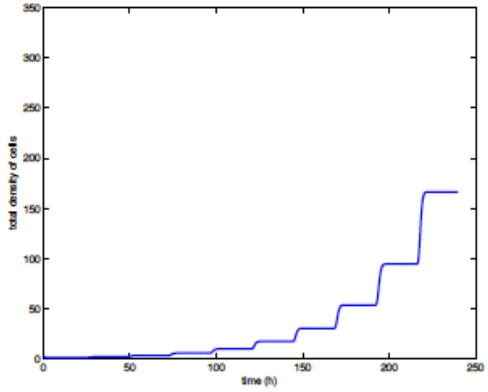
$\lambda = 0.026h^{-1}$ $T_d = 26.3h$

Summary



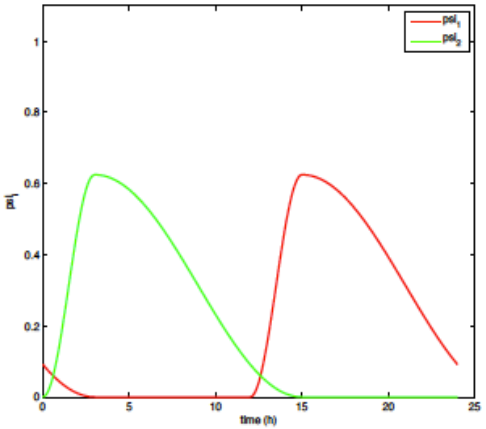
Healthy control case ψ

$\Downarrow$



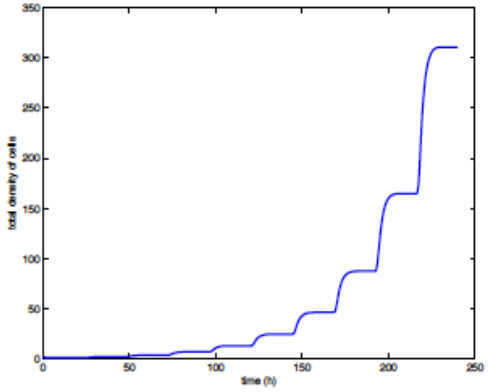
$\lambda = 0.024h^{-1}$

$T_d = 29.4h$



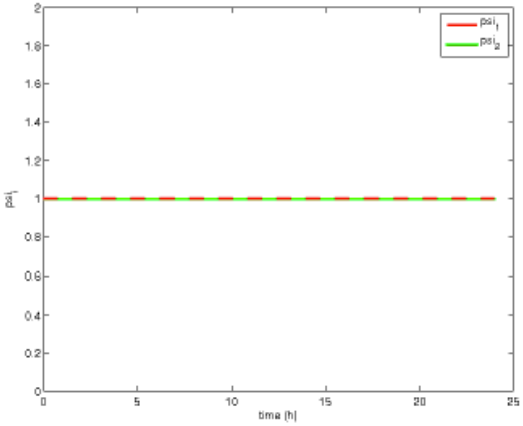
Cancer control case ψ

$\Downarrow$



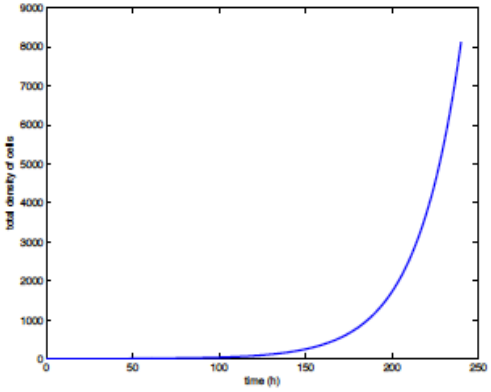
$\lambda = 0.026h^{-1}$

$T_d = 26.3h$



No control

$\Downarrow$



$\lambda = 0.039h^{-1}$

$T_d = 18h$

Theoretical chronotherapeutic optimisation of a first eigenvalue (for cancer growth) under the constraint of preserving another first eigenvalue (healthy tissue growth)

i.e., what if now we add a drug control, setting $K(t,x) = \kappa(x).\psi(t).[1-g(t)]$?

- McKendrick's model of cell population proliferation
- Control of proliferation by blocking K_{i_i+1} using theoretic periodic drug delivery:

$K(t,x)=[1-g(t)].\psi(t).\kappa(x)$ *where:* $g(t)$ *is a periodic external control (chronotherapy)*

$\psi(t)$ *is a circadian clock control on the cell cycle*

$\kappa(x)$ *is an [only] age-dependent transition rate*

- Objective function to be minimised: λ_1, 1st eigenvalue of cancer cell population
- Constraint function to be preserved: λ_2 $[\geq\Lambda]$, 1st eigenvalue of healthy cell population
- Design of an augmented Lagrangian by combining λ_1 and $\lambda_2-\Lambda$ (with penalty)
- Arrow-Hurwitz (or Uzawa) algorithm to track saddle points of the Lagrangian
- …thus obtaining only suboptimality (necessary to obtain critical points) conditions

Results: circadian + 24h-periodic drug control on transitions

$K(x,t) = \kappa(x).\psi(t).g(t)$: κ FUCCI-identified, ψ clock, g optimal drug effect on S-phase

***healthy* case:**
sharp ψ gating

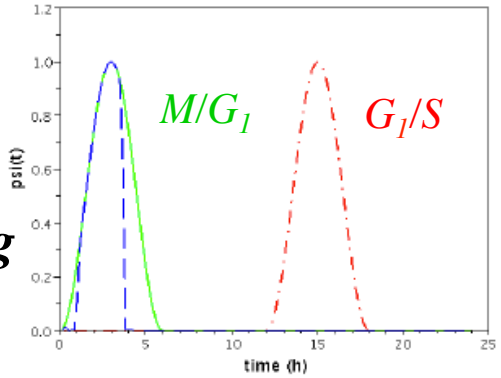


Figure 9: Modelled circadian control for transition G_1 to $S/G_2/M$ (dashdotted line) and transition $S/G_2/M$ to G_1. The natural control for $S/G_2/M$ to G_1 transition is in solid line, the drug induced control is in dashed line.

***cancer* case:**
lazy ψ gating

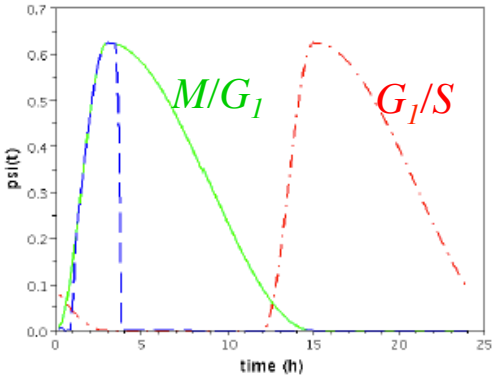


Figure 10: Modelled answer of cancerous cells to circadian control for transition G_1 to $S/G_2/M$ (dash-dotted line) and transition $S/G_2/M$ to G_1. The answer to natural control for $S/G_2/M$ to G_1 transition is in solid line, the drug-induced control is in dashed line.

green and red gating: ψ (circadian clock control without drug)

blue: $g.\psi$ (drug + circadian control) g here numerical solution to the optimisation problem

F. Billy et al. Math Comp Simul 2012, Math Biosc Eng 2012, DCDS-B 2012, Springer book chapter 2013

Evolution of the two populations: cancer (blue), healthy (green)

Circadian control, no drug infusion

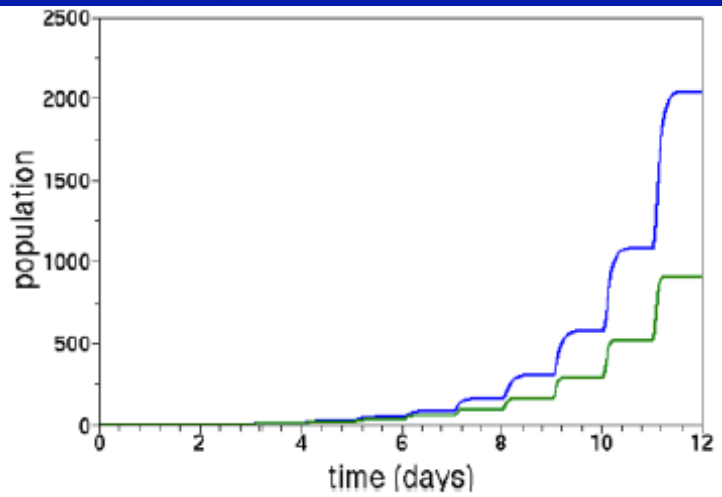


Figure 11: Evolution of the population of cancer (blue, beneath) and healthy (green, above) cells without drug infusion during 12 days. We can see that the populations have different exponential growth rates ($\lambda_{cancer} = 0.026$ and $\lambda_{healthy} = 0.024$). In the beginning, there were as many cancer cells as healthy cells, in the end they represent a much larger part of the total population.

Circadian control, added drug infusion

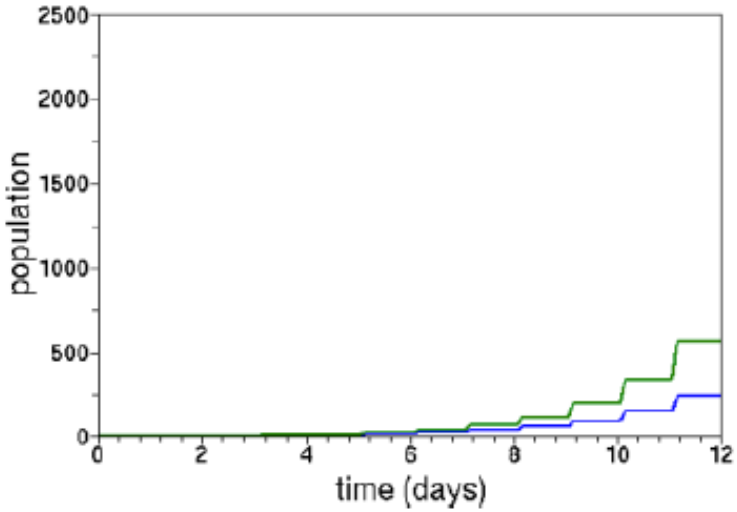


Figure 12: Evolution of the population of cancer (blue, beneath) and healthy (green, above) cells with the drug infusion, starting at time 0, given by the algorithm. Healthy cells keep multiplying ($\lambda_{healthy} = 0.022$) while the cancer cell population is weakened ($\lambda_{cancer} = 0.019$).

(F. Billy et al. 2013, 2014)

Numerical solution to the optimal infusion problem (Uzawa) and effect on eigenvalues, healthy and cancer

Infusion scheme *g(t)*

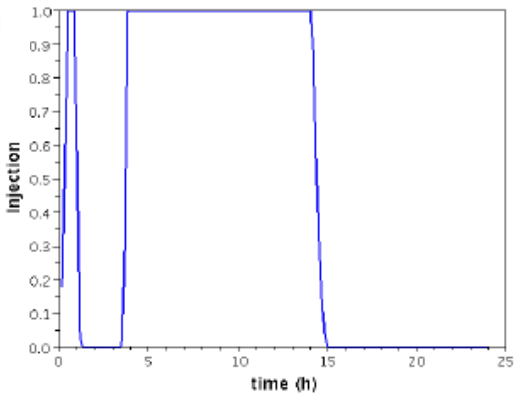


Figure 11: Locally optimal drug injection strategy found by the optimisation algorithm.

Target eigenvalues:
Cancer (blue)
Healthy (green)

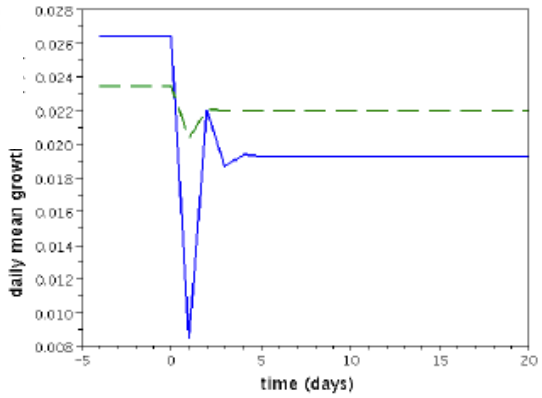


Figure 12: Daily mean growth rates for cancerous (solid line) and healthy cells (dashed line) when starting drug injections at time 0. After a 10 day transitional phase, the biological system stabilises towards the expected asymptotic growth rate

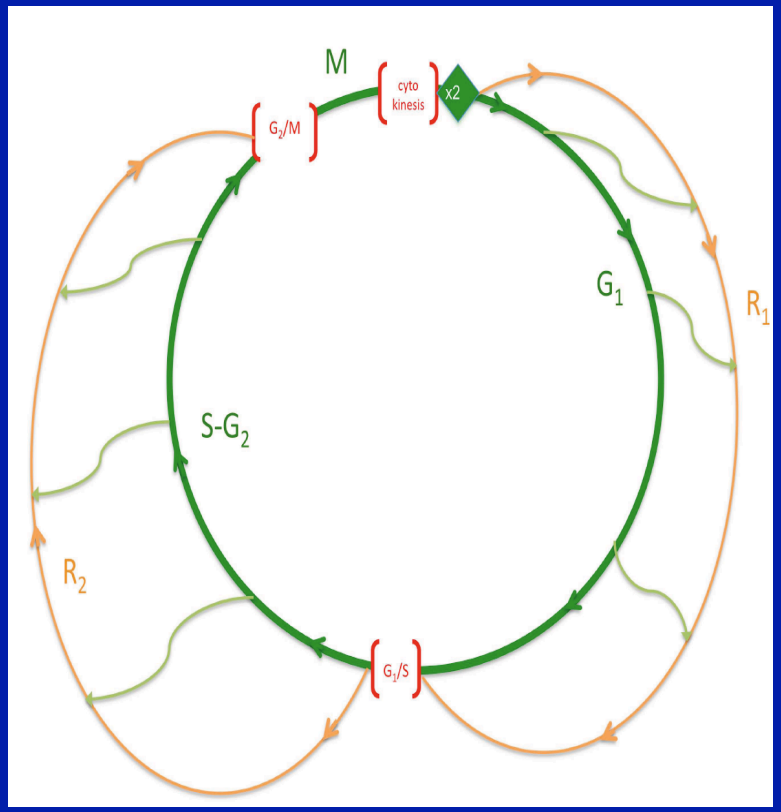
In favour of this approach:

- characterises long-term trends with one number,
- easily accessible target for control
- fits to physiologically structured growth models

Its drawbacks:

- deals with asymptotics, not with transients
- assumes a linear model for proliferation
- assumes periodic control by drugs (but the period can be infinitely long)

Introducing pharmacological effects on death rates with repair (rather than on phase transitions): extension of the model



$$
\begin{cases}
\bullet\ \dfrac{\partial}{\partial t}n_1(t,x)+\dfrac{\partial}{\partial x}n_1(t,x)+\{K_1(t,x)+L_1(t)+d_1\}\,n_1(t,x)-\varepsilon_1 r_1(t,x)=0\ ,\\
\dfrac{\partial}{\partial t}r_1(t,x)+\{d_{\kappa\tau 1}+\varepsilon_1\}r_1(t,x)-L_1(t)n_1(t,x)=0\ ,\\
n_1(t,x=0)=2n_3(x_M,t)\ ,n_1(0,x)=\nu_1(x)\ ,r_1(0,x)=\rho_1(x)\ ,\\
\text{with } L_1(t)=C_1\dfrac{F_0-F(t)}{F_0} \text{ and } K_1(t,x)=\kappa_1(x)\psi_1(t,x)\ ,\\
\bullet\ \dfrac{\partial}{\partial t}n_2(t,x)+\dfrac{\partial}{\partial x}n_2(t,x)+\{K_2(t,x)+L_2(t)+d_2\}\,n_2(t,x)-\varepsilon_2 r_2(t,x)=0\ ,\\
\dfrac{\partial}{\partial t}r_2(t,x)+\{d_{\kappa\tau 2}+\varepsilon_2\}r_2(t,x)-L_2(t)n_2(t,x)=0\ ,\\
n_2(t,x=0)=\displaystyle\int_{\xi\geq 0}K_1(t,\xi)n_1(\xi,t)\,d\xi\ ,n_2(0,x)=\nu_2(x)\ ,r_2(0,x)=\rho_2(x)\ ,\\
\text{with } L_2(t)=C_2\dfrac{F_0-F(t)}{F_0}+C_2'\dfrac{S_0-S(t)}{S_0} \text{ and } K_2(t,x)=\kappa_2(x)\psi_2(t)\ ,\\
\bullet\ \dfrac{\partial}{\partial t}n_3(t,x)+\dfrac{\partial}{\partial x}n_3(t,x)+M.\mathbb{1}_{[x_M,+\infty[}(x)\,n_3(t,x)=0\ ,\\
n_3(t,x=0)=\displaystyle\int_{\xi\geq 0}K_2(t,\xi)n_2(t,\xi)\,d\xi\ ,\ ,n_3(0,x)=\nu_3(x)\ .
\end{cases}
$$

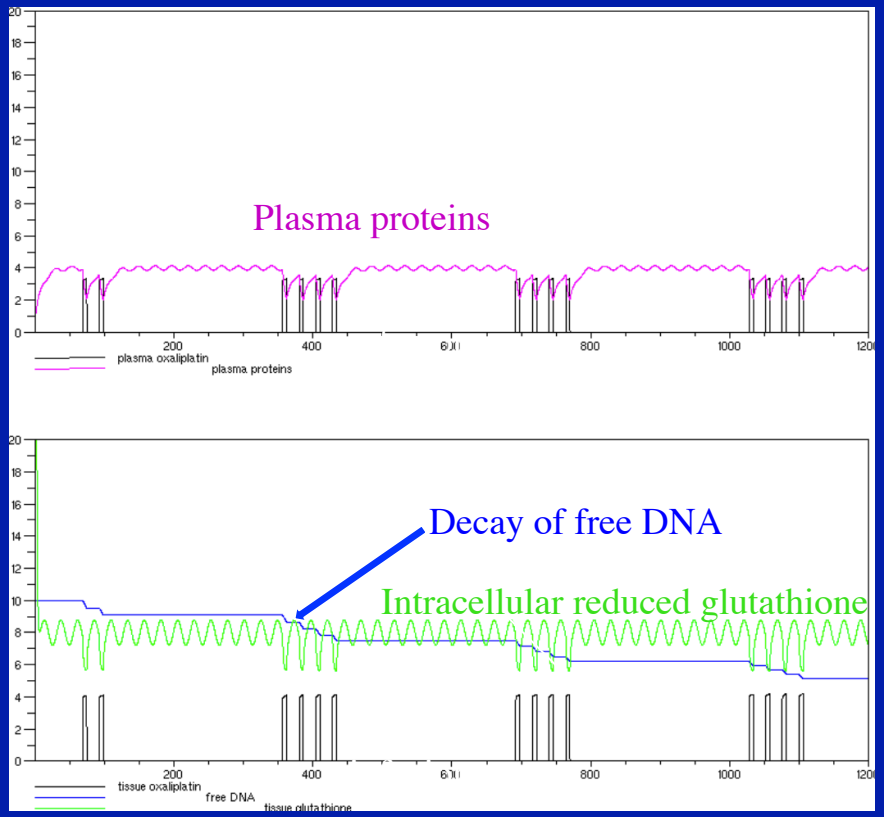
(JC, O. Fercoq, book chapter to appear, 2014)

\+ PK-PD added models: cytotoxic (*death rates*) effects

Pharmacokinetics-pharmacodynamics (PK-PD) of oxaliplatin (cytotoxic action exerted on DNA in all phases except M phase)

$$
\begin{cases}
\dfrac{dR}{dt} = -[\xi + cl + \lambda K]R + i(t) \\
\dfrac{dK}{dt} = -\lambda RK + \mu_K(K_0 - K) \\
\dfrac{dC}{dt} = -V_{GST}\dfrac{CG^2}{K_{GST}^2 + G^2} - k_{DNA}CF + \xi R \\
\dfrac{dF}{dt} = -k_{DNA}CF + \mu_F(Fo - F) \\
\dfrac{dG}{dt} = -V_{GST}\dfrac{CG^2}{K_{GST}^2 + G^2} + \mu_G(G_0 - G)
\end{cases}
$$

Input i = *oxaliplatin infusion*



(JC, O. Fercoq, Springer book chapter to appear, 2014)

PK-PD of 5FU [with drug resistance] + Leucovorin (action exerted on thymidylate synthase only in the S-G_2 phase)

$$(1)\quad \frac{dP}{dt} = -k_0 P - \frac{aP}{b+P} - l_{DPD}\frac{P}{m_{DPD}+P} + \frac{i(t)}{V}$$

$$(2)\quad \frac{dF}{dt} = \frac{a}{\xi}\frac{P}{b+P} - \frac{AF}{c+F} - k_1 FS + k_{-1}B$$

$$(3)\quad \frac{dQ}{dt} = -k_2 Q + \frac{j(t)}{V}$$

$$(4)\quad \frac{dL}{dt} = \frac{k_2}{\xi}Q - k_3 L - k_4 BL$$

$$(5)\quad \frac{dN}{dt} = \frac{\kappa F^n}{\lambda^n + F^n} - \mu N$$

$$(6)\quad \frac{dA}{dt} = \mu N - \nu A$$

$$(7)\quad \frac{dS}{dt} = -k_1 FS + k_{-1}B + \theta_{TS}(S_0 - S)$$

$$(8)\quad \frac{dB}{dt} = k_1 FS - k_{-1}B - k_4 BL$$

$$(9)\quad \frac{dT}{dt} = k_4 BL - v_T T$$

Input j = LV infusion flow

Input i = 5-FU infusion flow

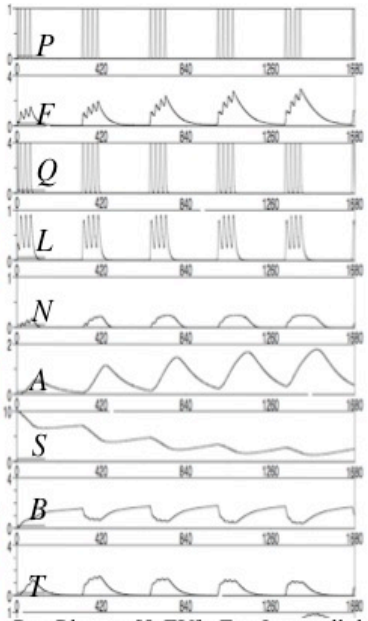
A = ABC transporter (active drug efflux)

S = Free Thymidylate Synthase (TS)

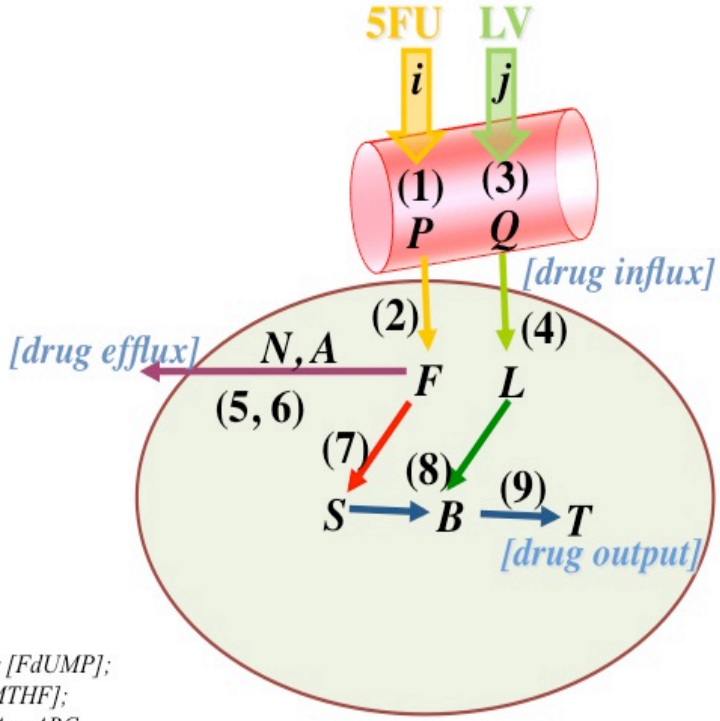
Drug output T = Blocked Thymidylate Synthase (stable ternary FdUMP-MTHF-TS complex)

where $l_{DPD} = l_{DPD\_BASE}\left\{1 + \varepsilon \cos\frac{2\pi(t-\varphi_{DPD})}{24}\right\}$

and $S_0 = S_{0\_BASE}\left\{1 + \delta \cos\frac{2\pi(t-\varphi_{TS})}{24}\right\}$



P = Plasma [5-FU]; F = Intracellular [FdUMP];
Q = Plasma [LV]; L = Intracellular [MTHF];
N = 5-FU-triggered Nuclear Factor; A = ABC Transporter activity, NuclearFactor-induced;
S = Free [TS] (not FdUMP-bound);
B = [FdUMP-TS] reversible binary complex;
T = [FdUMP-TS-MTHF] stable ternary complex



(F. Lévi, A. Okyar, S. Dulong, JC, Annu Rev Pharm Toxicol 2010)

Solution to the chronotherapeutic combined drug delivery optimisation problem

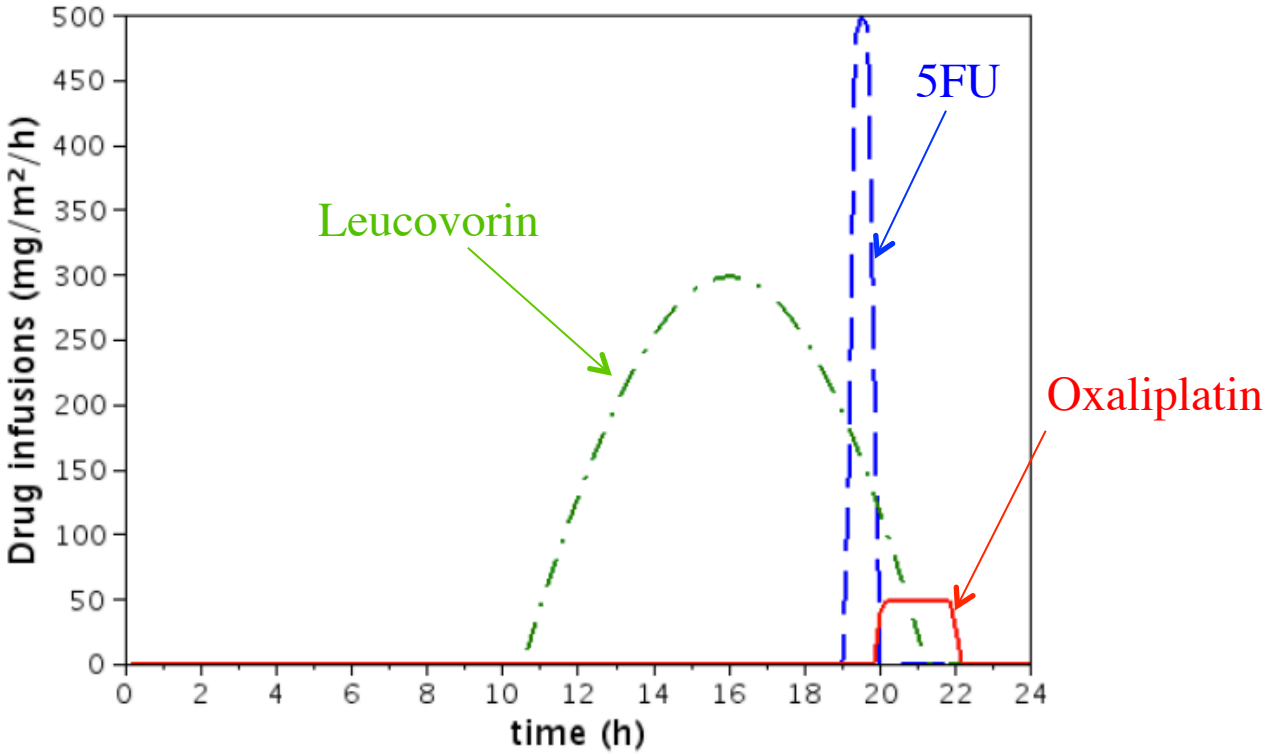


Fig. 6 Locally optimal infusion strategy with a combination of leucovorin (dash-dotted line), 5-FU (dotted line) and oxaliplatin (solid line). These infusions are repeated every day in order to minimise the growth rate of the cancer cell population while maintaining the growth rate of the healthy cell population above the toxicity threshold of 0.021.

(JC, O. Fercoq, Springer book chapter to appear, 2014)

Effects of this optimised periodic drug delivery regimen on growth rates

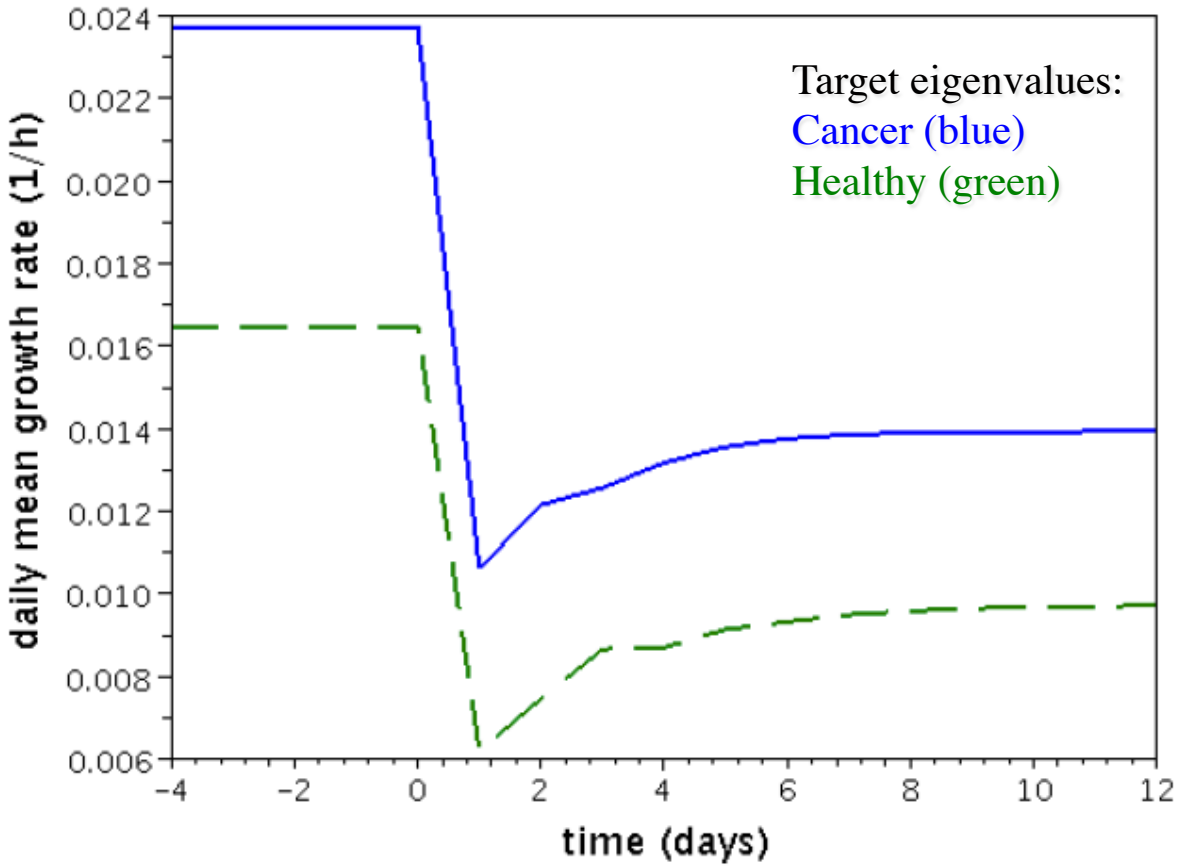


Fig. 11 Daily mean growth rates for cancer (solid line) and healthy cells (dashed line) when starting drug infusions at time 0. After a 10-day transitional phase, the biological system stabilises towards the expected asymptotic growth rate.

(JC, O. Fercoq, Springer book chapter to appear, 2014)

Evolution of the two cell populations, without, then with cytotoxic drugs

(Here, drugs acting on death rates and not on transition rates)

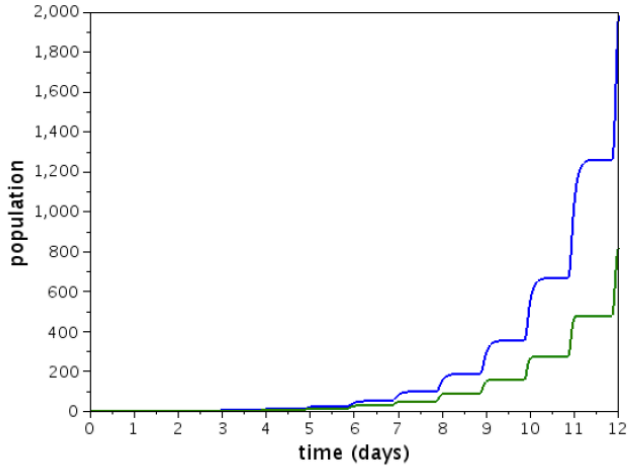


Fig. 7 Evolution of the population of cancer (blue, above) and healthy (green, beneath) cells without drug infusion during 12 days. We can see that the populations have different exponential growth rates ($\lambda_{cancer} = 0.0265$ and $\lambda_{healthy} = 0.0234$). Cancer cells proliferate faster than healthy cells.

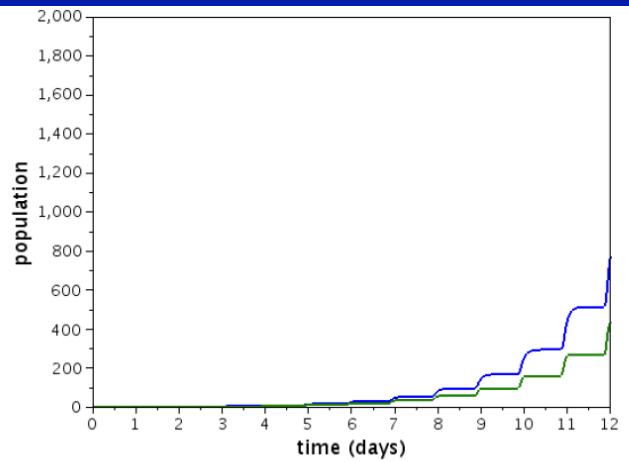


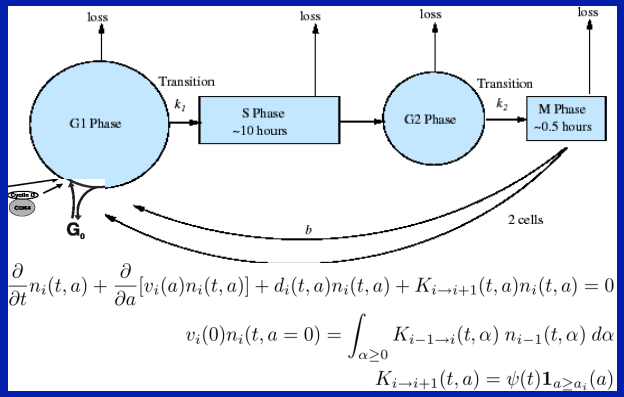
Fig. 8 Evolution of the population of cancer (blue, above) and healthy (green, beneath) cells with the drug infusion, starting at time 0, given by the algorithm. Healthy cells keep multiplying ($\lambda_{healthy} = 0.021$) while the cancer cell population is weakened ($\lambda_{cancer} = 0.0229$).

A result not as good as in the previous case, when drugs were applied on transition rates... hence the suggestion of a cytotoxic+cytostatic treatment (e.g., 5FU+oxaliplatin+cetuximab): a story to be continued

(JC, O. Fercoq, Springer book chapter to appear, 2014)

Optional (not done, to be added)

+Modelling effects of cytostatics (CDKIs, TKIs, ...) acting on cell cycle phase transition rates [and boundary conditions]



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

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

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

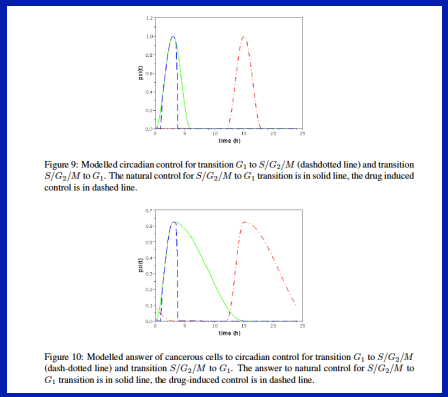


Figure 9: Modelled circadian control for transition G_1 to $S/G_2/M$ (dashdotted line) and transition $S/G_2/M$ to G_1. The natural control for $S/G_2/M$ to G_1 transition is in solid line, the drug induced control is in dashed line.

Figure 10: Modelled answer of cancerous cells to circadian control for transition G_1 to $S/G_2/M$ (dash-dotted line) and transition $S/G_2/M$ to G_1. The answer to natural control for $S/G_2/M$ to G_1 transition is in solid line, the drug-induced control is in dashed line.

Control on inputs from G_0 phase may be represented by a multiplicative factor in the first (G_1) boundary condition (which is the same as modifying the first transition rate); for instance, following Pierre Gabriel and Glenn Webb (JTB 2012):

$$\begin{cases}\dfrac{\partial}{\partial t}n_1(t,x)+\dfrac{\partial}{\partial x}n_1(t,x)+(1-f)K_{1\to 2}(t,x)n_1(t,x)+\{fK_{1\to 2}(t,x)+d_1(x)\}n_1(t,x)=0\ ,\\ n_2(t,x=0)=(1-f)\displaystyle\int_{\xi\geq 0}K_{1\to 2}(t,\xi)\,n_1(t,\xi)\,d\xi\ ,\\ n_2(0,x)=n_{2,0}(x),\end{cases}\tag{5}$$

with the adjunction of a quiescent phase G_0 represented by

$$\begin{cases}\dfrac{d}{dt}Q(t)=f\displaystyle\int_{\xi\geq 0}K_{1\to 2}(t,\xi)\,n_1(t,\xi)\,d\xi-\nu Q(t)\ ,\\ Q(0)=Q_0\ ,\end{cases}\tag{6}$$

which is thus fed only by cells escaping from G_1 instead of processing into S phase.

f: target of cytostatic drug, sending cells to quiescence (measurable)

New 'death' term (=death + escape towards G_0)

New mitosis term

[Therapeutic control and its theoretical optimisation]

2. Overcoming resistance in cancer cell populations

Cancer as an evolutionary problem

"Nothing in biology makes sense except in the light of evolution"

Theodosius Dobzhansky, 1973

Tackling this other main issue in cancer pharmacotherapeutics: Emergence of drug resistance in cancer cell populations

(another model of cell population dynamics, with thus far no PK-PD)

Instead of controlling drug resistance at the individual cell level (ABC transporters), representing the possible emergence of resistant cell clones due to mutations occurring at mitoses in a *cell Darwinism evolutionary perspective*.

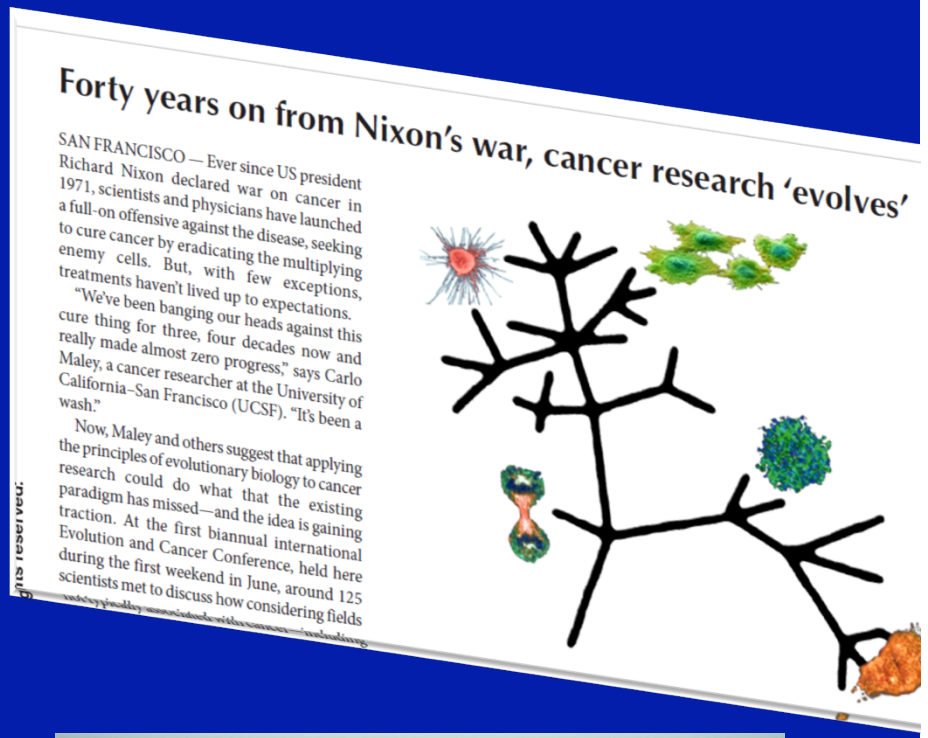
Assumption: Cancer cell populations, under the pressure of a drug-enriched environment, may develop (costly) mutations evolving into resistant cell clones, less fit in a drug-free environment, but better survivors in a hostile environment.

A therapeutic objective, under these circumstances, may be not to eradicate all cancer cells (in fact only all drug-sensitive cells), but instead to let some of them live so as to limit the growth of an emergent resistant cell clone ('adaptive therapy').

A soaring theme on the international scene: ***Evolution and cancer***

Carlo Maley

Robert Gatenby, MD*



Forty years on from Nixon's war, cancer research 'evolves'

SAN FRANCISCO — Ever since US president Richard Nixon declared war on cancer in 1971, scientists and physicians have launched a full-on offensive against the disease, seeking to cure cancer by eradicating the multiplying enemy cells. But, with few exceptions, treatments haven't lived up to expectations.

"We've been banging our heads against this cure thing for three, four decades now and really made almost zero progress," says Carlo Maley, a cancer researcher at the University of California–San Francisco (UCSF). "It's been a wash."

Now, Maley and others suggest that applying the principles of evolutionary biology to cancer research could do what that the existing paradigm has missed—and the idea is gaining traction. At the first biannual international Evolution and Cancer Conference, held here during the first weekend in June, around 125 scientists met to discuss how considering fields

First international
Evolution and cancer conference
SF, June 3-5, 2011, second in 2013

** RG advocates 'adaptive therapy', cf. Gatenby Nature 2009, Gatenby et al. Cancer Research 2009*

Gatenby's new paradigm: rational management of cancer burden by 'adaptive therapy'

OPINION NATURE|Vol 459|28 May 2009

ESSAY

A change of strategy in the war on cancer

Patients and politicians anxiously await and increasingly demand a 'cure' for cancer. But trying to control the disease may prove a better plan than striving to cure it, says **Robert A. Gatenby**.

See also review on evolution and cancer by Aktipis et al. PLoS One, Nov. 2011

Evolution of cell populations toward resistance under anticancer drug pressure: ecological-like integro-differential models

- Exposure to anticancer drugs is an environmental factor to which cell populations adapt or not, according to their evolution abilities

- Due to genomic instabilities (mutated p53, error-prone DNA polymerases), resulting in higher genomic variability at division, cancer cell populations have better capacities than healthy cell populations to adapt to a changing environment

- Such variability is multiple and cannot be reduced to only pointwise mutations

- Inspired by ecological models, one can represent it by a continuous trait x governing an evolving phenotype expressed as resistance to a drug, or to multiple drugs

First point of view: 'small mutations only', one cytotoxic drug c(t), evolutionary trait x

a) Healthy cells

$$\frac{\partial}{\partial t} n_H(x,t) = \Big[\overbrace{\frac{1-\theta_H}{\big(1+\rho(t)\big)^{\beta}} r(x)}^{\text{growth with homeostasis}} - \overbrace{d(x)}^{\text{natural apoptosis}} - \overbrace{c(t)\mu_H(x)}^{\text{effect of drug}} \Big] n_H(x,t)$$
$$+ \frac{\theta_H}{\big(1+\rho(t)\big)^{\beta}} \underbrace{\int r(y) M_{\sigma_H}(y,x) n_H(y,t)\,dy,}_{\text{birth with mutation}}$$

la population totale est définie comme

$$\rho(t) = \rho_H(t) + \rho_C(t), \qquad \rho_H(t) = \int_{x=0}^{\infty} n_H(x,t)\,dx, \quad \rho_C(t) = \int_{x=0}^{\infty} n_C(x,t)\,dx.$$

- $\beta > 0$ to impose healthy tissue homeostasis,
- $c(t)$ denotes the dose of chemotherapy. Here we assume it has only an effect on increasing apoptosis,

A. Lorz et al. M2AN 2013

Mathematical models: integro-differential equations

First point of view: 'small mutations only', one cytotoxic drug c(t), evolutionary trait x
b) Cancer cells

Point of view 'mutations only'

- $x =$ expression of a single resistance phenotype
- $n_H(x,t)$, $n_C(x,t)$ density of cell populations de cellules (healthy or tumour)

$$\frac{\partial}{\partial t} n_C(x,t) = \Big[(1-\theta_C)\, r(x) - d(x) - c(t)\mu_C(x)\Big] n_C(x,t) + \theta_C \int r(y) M_{\sigma_C}(y,x) n_C(y,t)\, dy,$$

- $r(x) =$ basic reproduction rate and $d(x) =$ basic death rate. They depend on the gene expression level x; in order to incorporate a cost to produce the resistance gene, we assume

$$r(0) > d(0) > 0, \qquad r'(\cdot) < 0, \qquad r(+\infty) = 0, \qquad d'(\cdot) > 0,$$

- $0 \leq \theta_{H,C} < 1$ denotes the proportion of divisions with mutations, we can assume it to be higher for cancer cells
- $\mu_{H,C}(x)$ represents the phenotypical dependent response to the drug; drugs are designed to target cancer cells more than healthy cells.

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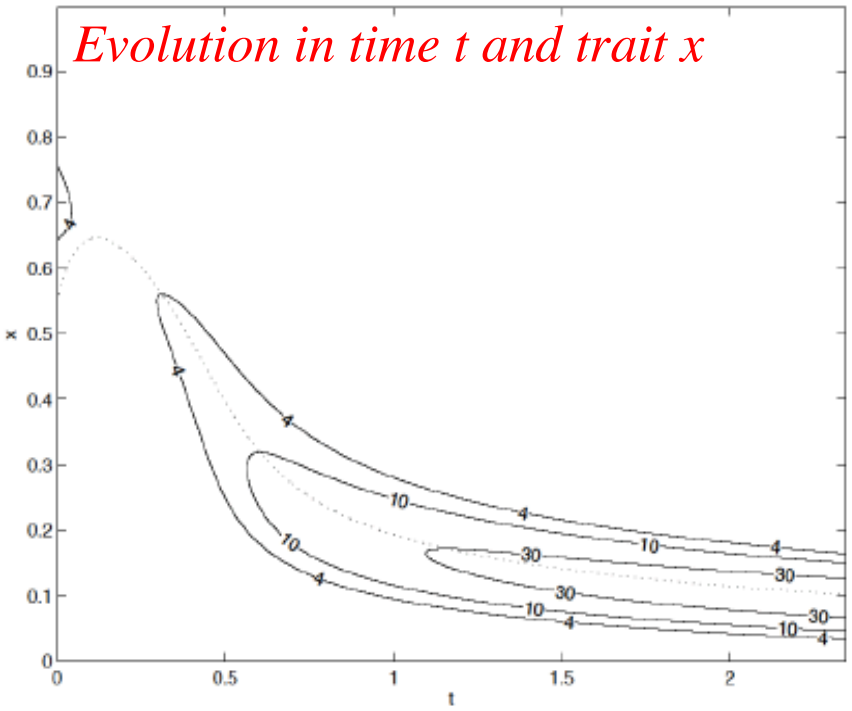
Small mutations only: monomorphism= evolution towards a single phenotype

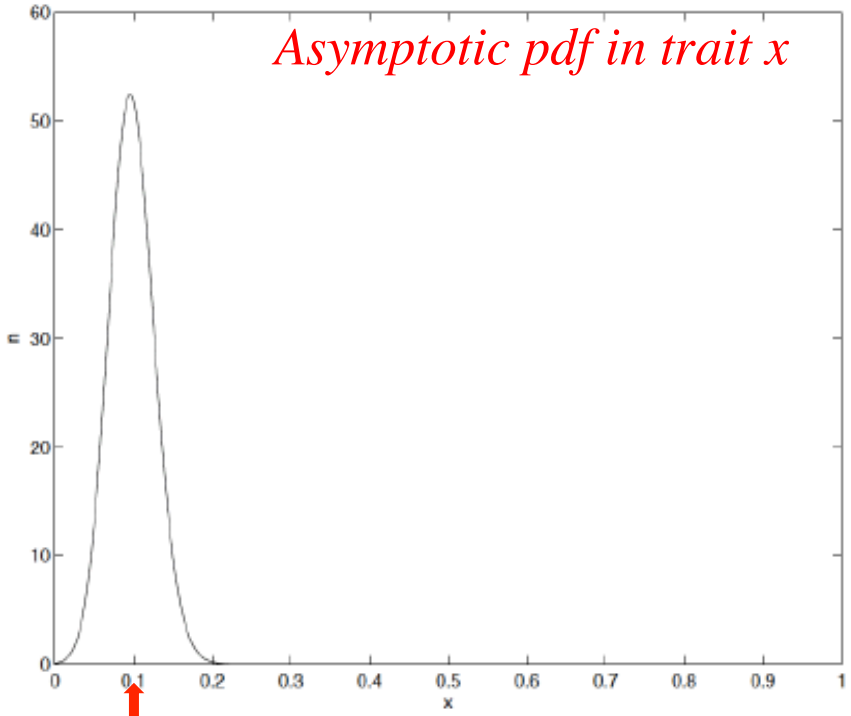
On such models, one observes, starting from a middle phenotype :
1) Healthy case : evolution towards a sensitive phenotype

(illustrations with θ_H=0, i.e., no mutations and $\mu_H(x)$=0, i.e., no drug-induced resistance)

Evolution in time t and trait x



Asymptotic pdf in trait x



x_H, *fittest trait*

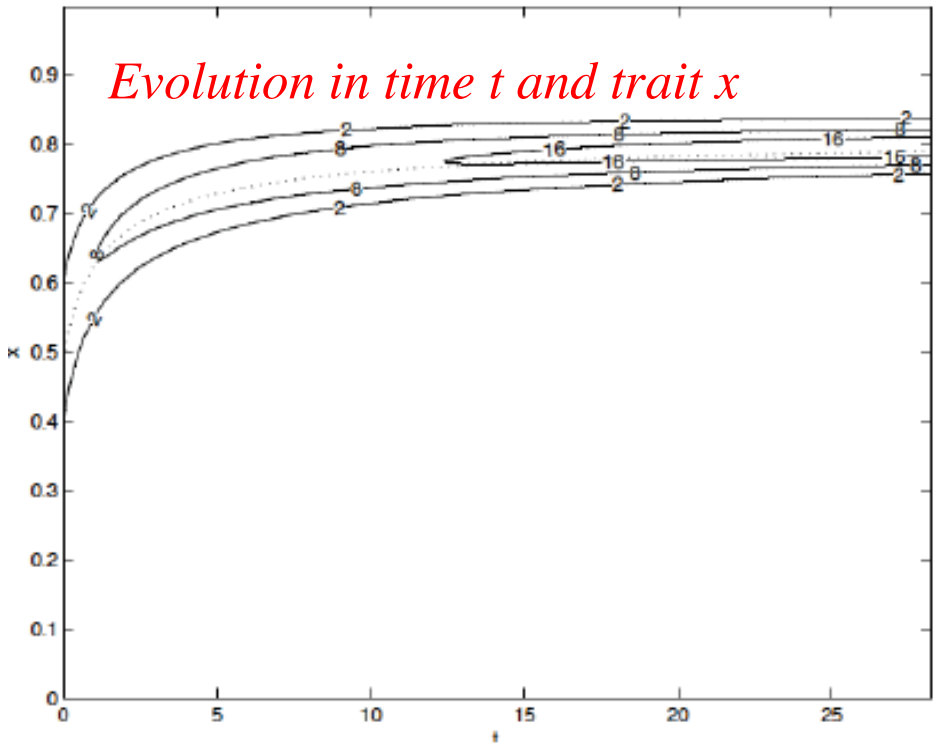
***Theorem**: evolution towards monomorphism (proved in A. Lorz et al., M2AN 2013)*

Small mutations only: monomorphism= evolution towards a single phenotype

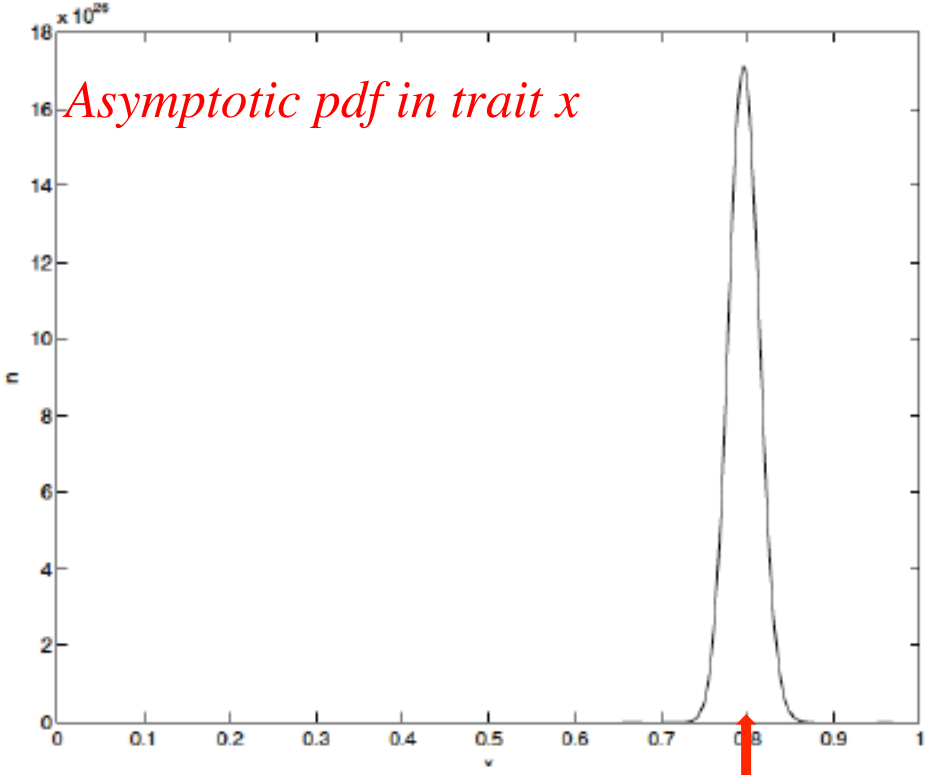
2) The cancer case : evolution towards a resistant phenotype

(illustrations with θ_C=0, i.e., no mutations and $\mu_C'(x)<0$, i.e., drug-induced resistance)

Evolution in time t and trait x



Asymptotic pdf in trait x



x_C, *fittest trait*

***Theorem**: evolution towards monomorphism (proved in A. Lorz et al., M2AN 2013)*

Second point of view : 'no mutations, exchanges with the environment', cytotoxic and cytostatic drugs, 2d resistance trait (x [cytotoxic],y [cytostatic])

$$
\begin{cases}
\frac{\partial}{\partial t} n_H(t,x,y) = \overbrace{\left[r_H(x,y;c_P) - d_H(x,y) I_H(t)\right] n_H(t,x,y)}^{\text{growth with cytostatic therapies and death}} - \overbrace{h_H(x,y;c_K) n_H(t,x,y)}^{\text{effect of cytotoxic therapies}} \\
\frac{\partial}{\partial t} n_C(t,x,y) = \overbrace{\left[r_C(x,y;c_P) - d_C(x,y) I_C(t)\right] n_C(t,x,y)}^{\text{growth with cytostatic therapies and death}} - \overbrace{h_C(x,y;c_K) n_C(t,x,y)}^{\text{effect of cytotoxic therapies}} \\
\frac{d}{dt} I_H(t) + \overbrace{\tau I_H(t)}^{\text{environment evolution}} = \overbrace{\tau \left[a_{HC}\rho_C(t) + a_{HH}\rho_H(t)\right]}^{\text{effect of cells on the environment}} \\
\frac{d}{dt} I_C(t) + \overbrace{\tau I_C(t)}^{\text{environment evolution}} = \overbrace{\tau \left[a_{CC}\rho_C(t) + a_{CH}\rho_H(t)\right]}^{\text{effect of cells on the environment}}
\end{cases}
$$

where:

$$
\rho_H(t) = \int_0^1 \int_0^1 n_H(t,x,y)\,dx\,dy, \qquad \rho_C(t) = \int_0^1 \int_0^1 n_C(t,x,y)\,dx\,dy.
$$

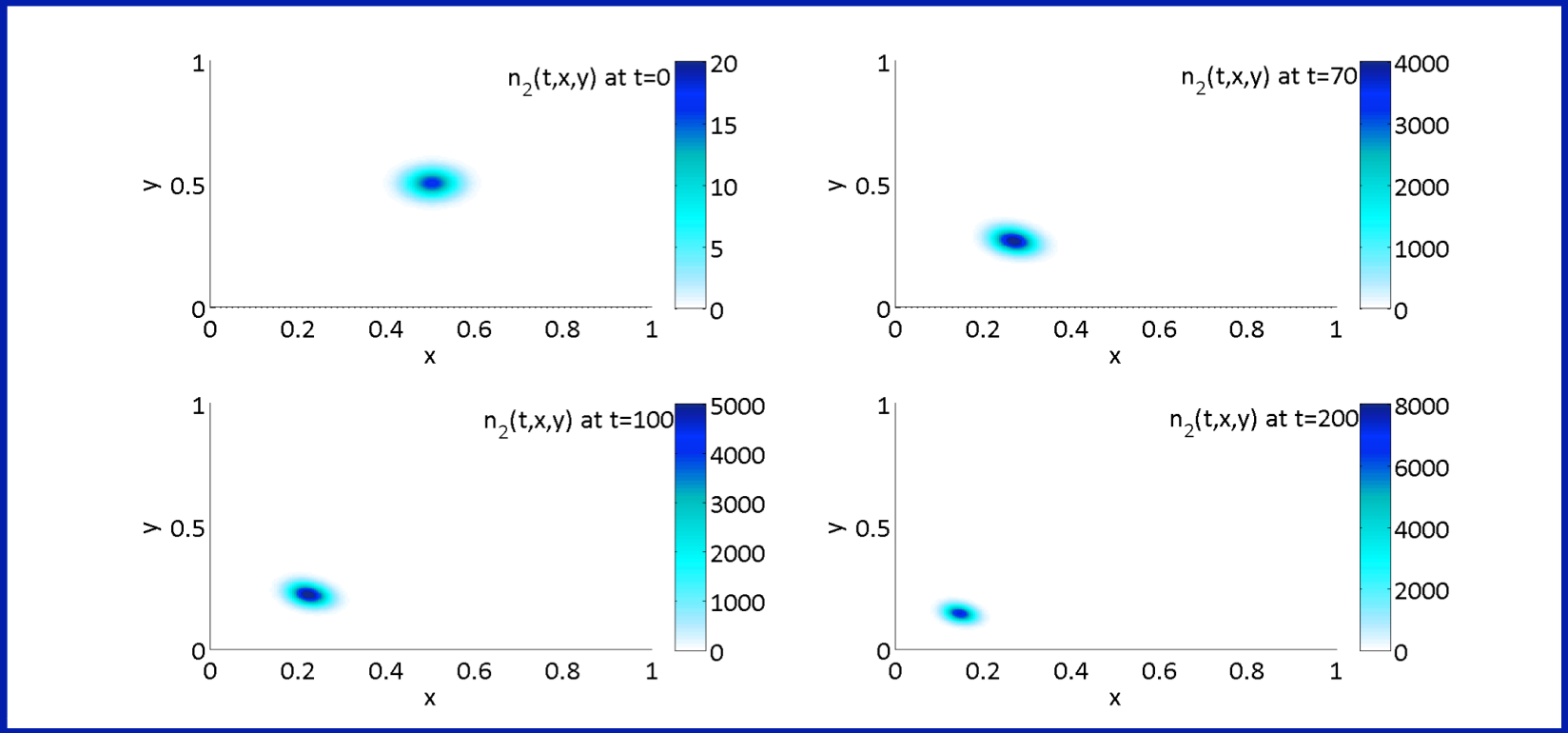
With particular reference to $n_C(t,x,y)$, simulations have been developed assuming the following definitions to hold

$$
r_C(x,y;c_P) := 4\left[1 + 2\frac{(1-\alpha_C c_P)}{1+(x^2+y^2)} + (1-x)^2y^2 + (1-y)^2x^2 - c_P(1-x)^4y^4\right],
$$

$$
d_C(x,y) := \frac{1}{2} \ \forall (x,y), \qquad h_C(x,y;c_K) := c_K(1-y)^4x^4,
$$

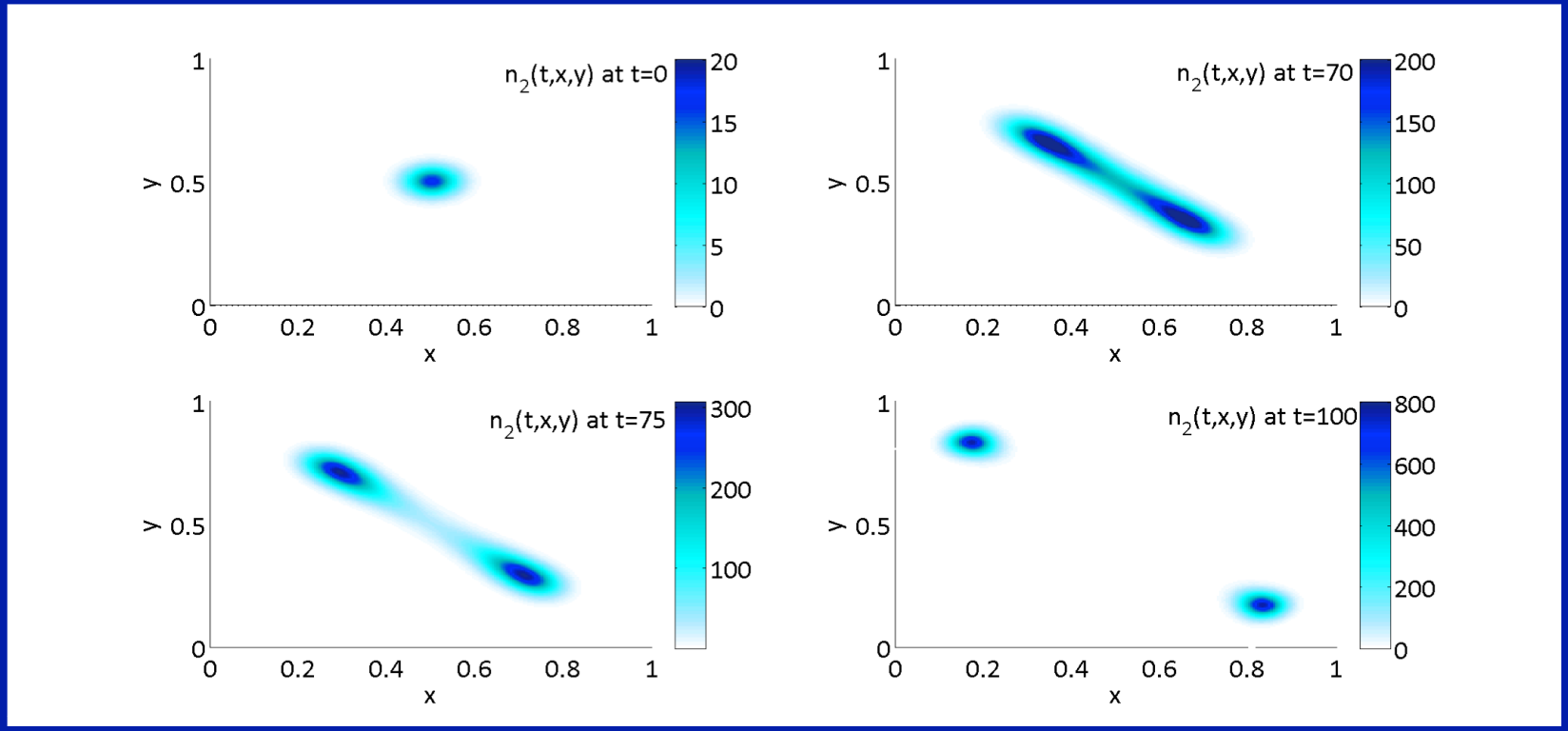
under distinct scenarios defined by different values of parameters c_K, c_P and α_C. In particular, we considered $c_K = c_P = 0$ and $\alpha_C = 1$ or $c_K = 2$, $c_P = \frac{1}{2}$ and $\alpha_C = 2$.

No mutations: sensitive ('healthy') cells. Starting from a common medium phenotype (cytotoxic res.=.5, cytostatic res.= .5), evolution towards the non-resistant (0,0) phenotype: Monomorphism of asymptotic cell populations



Model, simulations and figures by Tommaso Lorenzi (work underway)

No mutations: resistant ('cancer') cells. Starting from the same common medium phenotype (.5,.5), evolution towards 2 resistant phenotypes, (1,0) and (0,1): Dimorphism (which is in fact a 'double monomorphism' of asymptotic cell populations)



Model, simulations and figures by Tommaso Lorenzi (work underway)

Mutations again, cytotoxic and cytostatic drugs, with a 1d drug resistance trait x for both drugs

$$\frac{\partial}{\partial t} n_H(x,t) = R_H(I_H(t), c_1(t), c_2(t), x) n_H(x,t) + \frac{\theta_H}{1+\alpha_H c_2(t)} \int r_H(y) M(y,x) n_H(t,y) dy$$

$$\frac{\partial}{\partial t} n_C(x,t) = R_C(I_C(t), c_1(t), c_2(t), x) n_C(x,t) + \frac{\theta_C}{1+\alpha_C c_2(t)} \int r_C(y) M(y,x) n_C(t,y) dy,$$

with

$$R_H(I_H(t), c_1(t), c_2(t), x) := \frac{r_H(x)(1-\theta_M)}{1+\alpha_H c_2(t)} - d_H(x) I_H(t) - \mu_H(x) c_1(t),$$

$$R_C(I_C(t), c_1(t), c_2(t), x) := \frac{r_C(x)(1-\theta_M)}{1+\alpha_C c_2(t)} - d_C(x) I_C(t) - \mu_C(x) c_1(t).$$

(A. Lorz et al., M2AN 2013)

'Pedestrian's optimisation: distinct drug effects on the two cell populations

Cancer cells

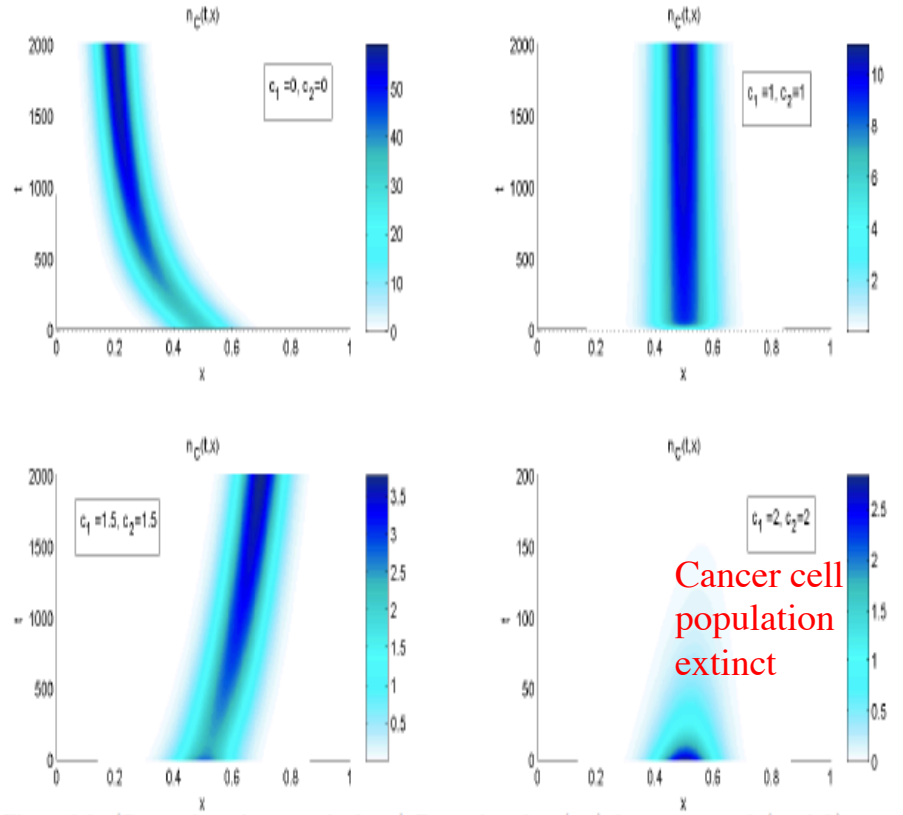


Figure 6.6: (Cytotoxic and cytostatic drugs) Dynamics of $n_C(x,t)$ for $c_1 = c_2 = 0$ (top-left), $c_1 = c_2 = 1$ (top-right), $c_1 = c_2 = 1.5$ (bottom-left) and $c_1 = c_2 = 2$ (bottom-right). As long as parameters c_1 and c_2 increase, the maximum value of $n_C(t = 2000, x)$ becomes smaller so that, under the choice $c_1 = c_2 = 2$, function $n_C(x,t)$ tends to zero across time.

Healthy cells

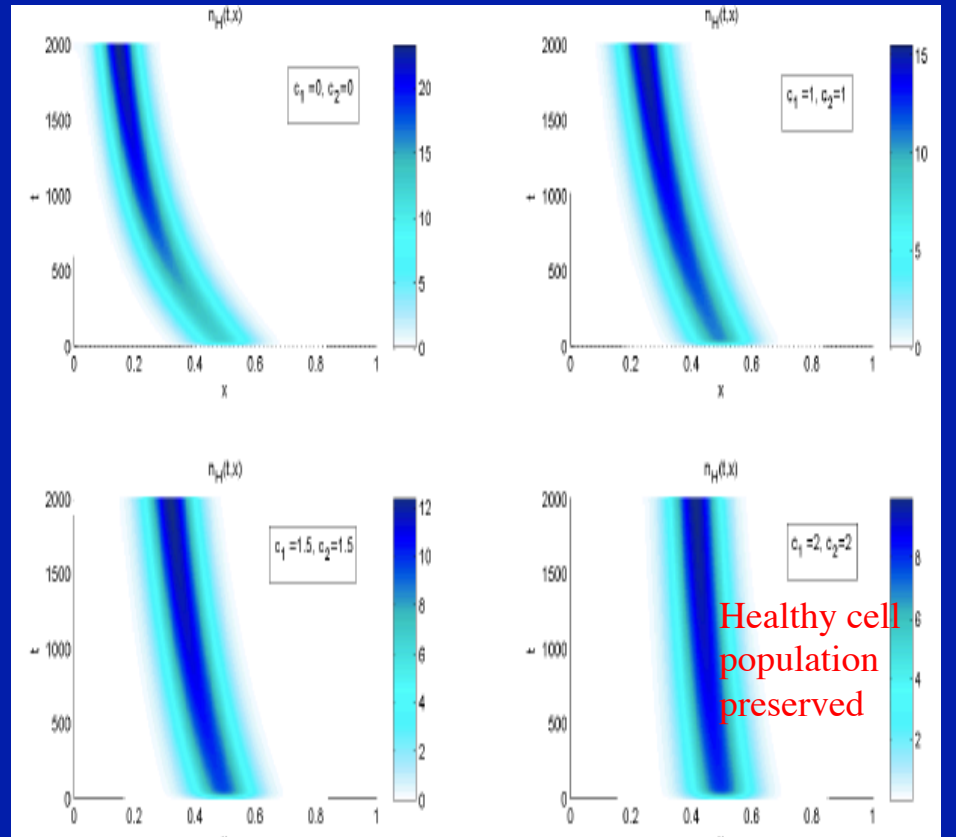


Figure 6.7: (Cytotoxic and cytostatic drugs) Dynamics of $n_H(x,t)$ for $c_1 = c_2 = 0$ (top-left), $c_1 = c_2 = 1$ (top-right), $c_1 = c_2 = 1.5$ (bottom-left) and $c_1 = c_2 = 2$ (bottom-right). As long as parameters c_1 and c_2 increase, the maximum value of $n_H(t = 2000, x)$ becomes smaller but about one half of the healthy cells is still alive at the end of computations.

[illustrations with $\theta_H=\theta_C=0.1$, $\mu_H'(x)<0$, $\mu_C'(x)<0$, $\mu_C(x)=2.\mu_H(x)$]

A. Lorz et al. M2AN 2013

And, time permitting, more recent developments about drug resistance in cancer…