Linking PK-PD of anticancer drugs with proliferating cell population dynamic models

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http://www-roc.inria.fr/bang/JC/Jean_Clairambault_en.html

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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: proliferating tumour *and healthy* cell populations in homogeneous tissues, including physiological control by molecular circadian clocks

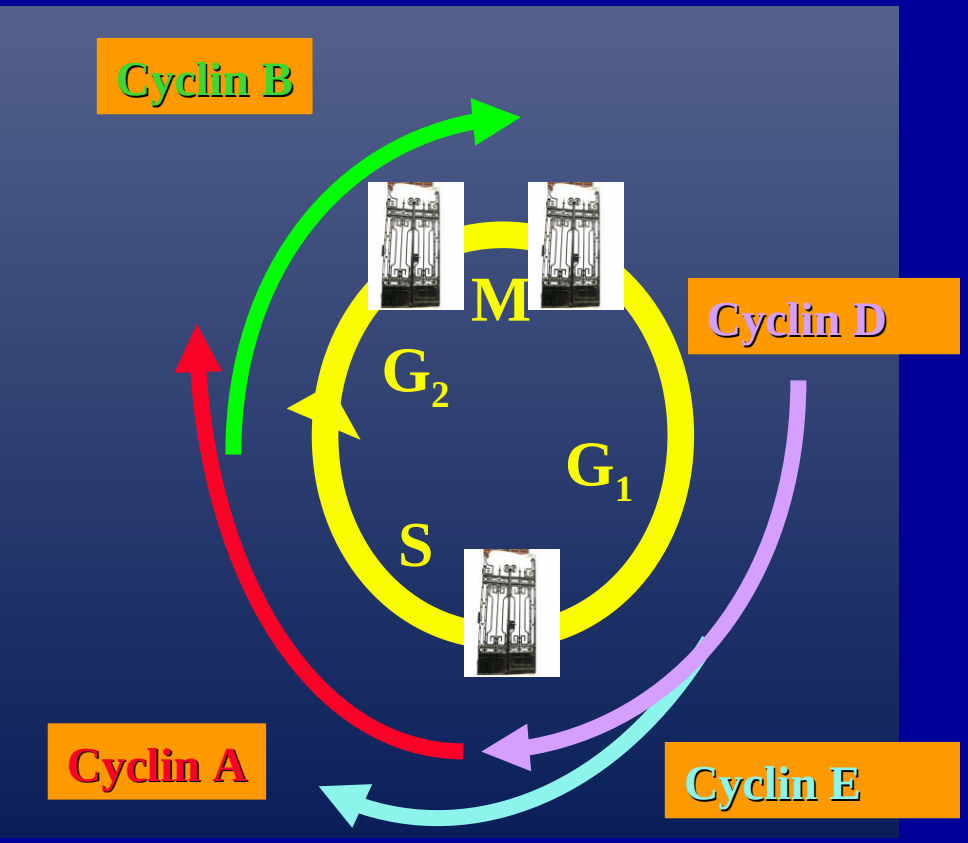
2. Modelling the control system, i.e., fate of drugs in the organism, at the molecular and whole body levels by *molecular pharmacokinetics-pharmacodynamics:* PK-PD (ideally WBPBPKPD = *whole body physiologically based...*)

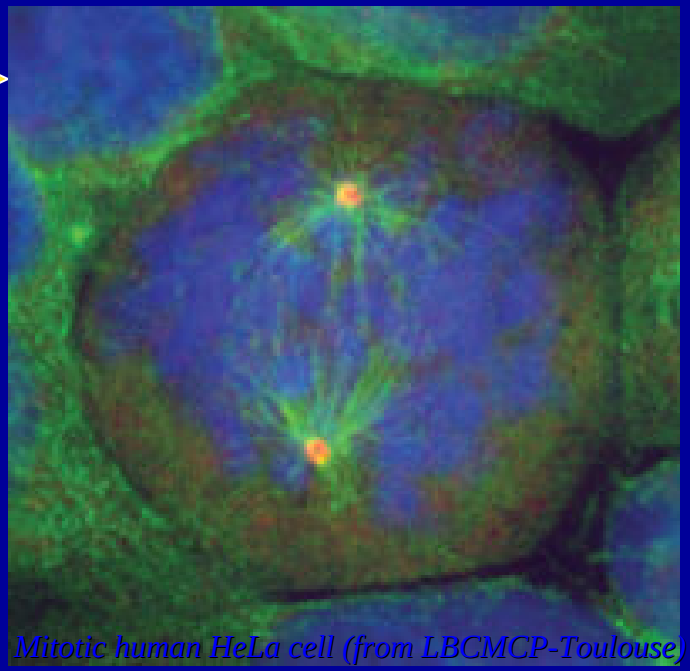
3. Optimising the control: *dynamically* optimised control of drug delivery flows using time-dependent objectives+constraints

(JC Math Mod Nat Phenom 2009; La Recherche 2010; Personalized Medicine 2011)

At the origin of any tissue proliferation: the cell division cycle, a controlled process by which one cell becomes two

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





Mitotic human HeLa cell (from LBCMCP-Toulouse)

Physiological (*circadian clocks*, hormones) / therapeutic (*drugs*) control:

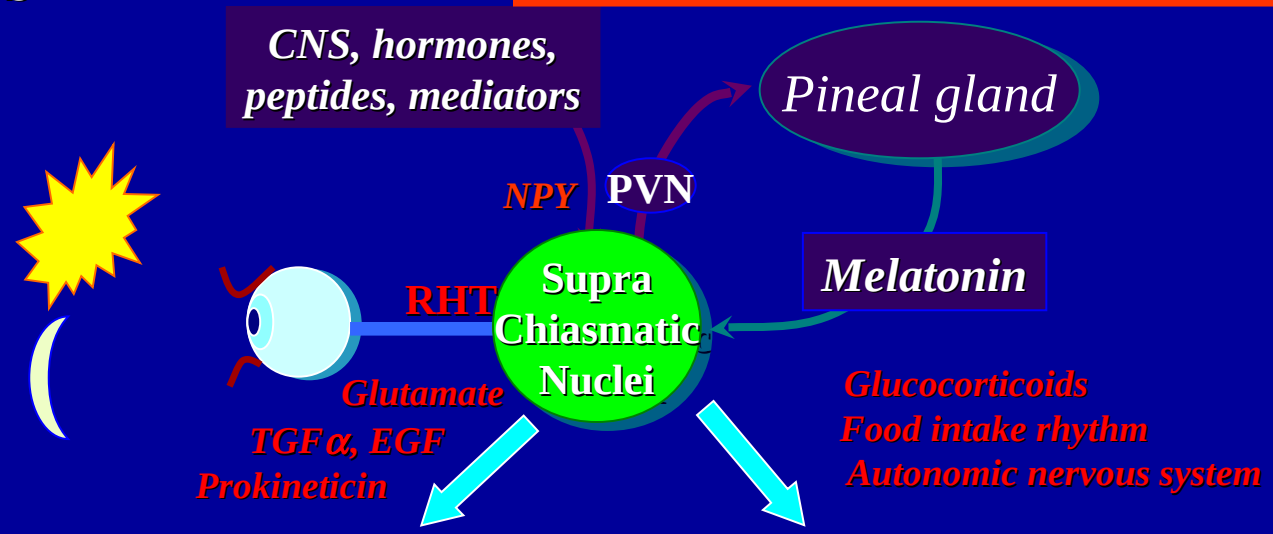
- on transitions between phases (G_1/S, G_2/M, M/G_1)
- on death rates inside phases (apoptosis or necrosis)
- on the inclusion in the cell cycle (G_0 to G_1 recruitment)

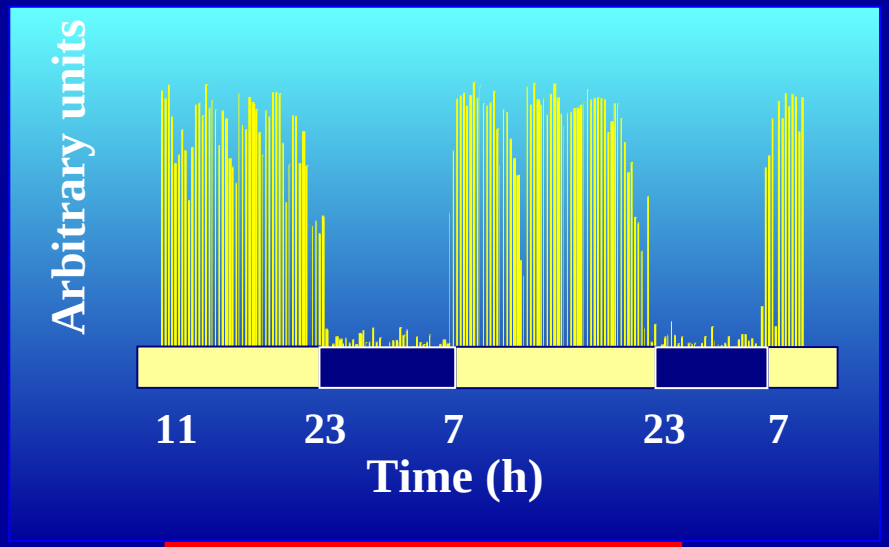
... a control that is disrupted in cancer

Circadian chronobiology (1): the circadian system

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

Central coordination





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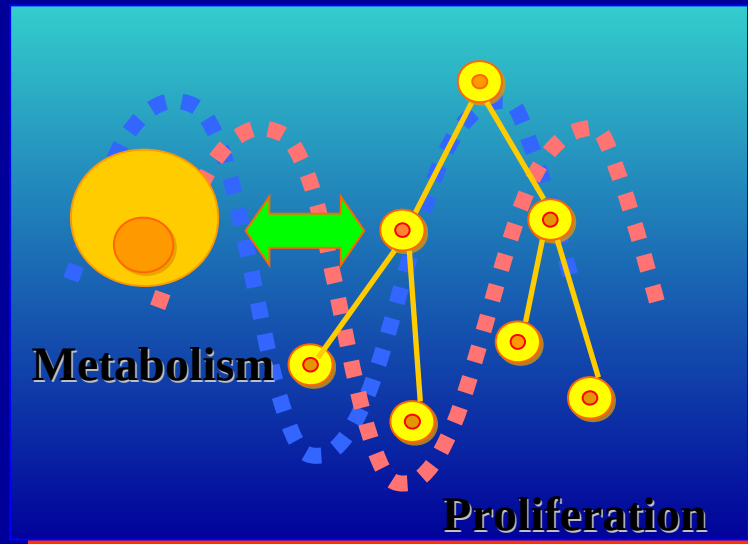


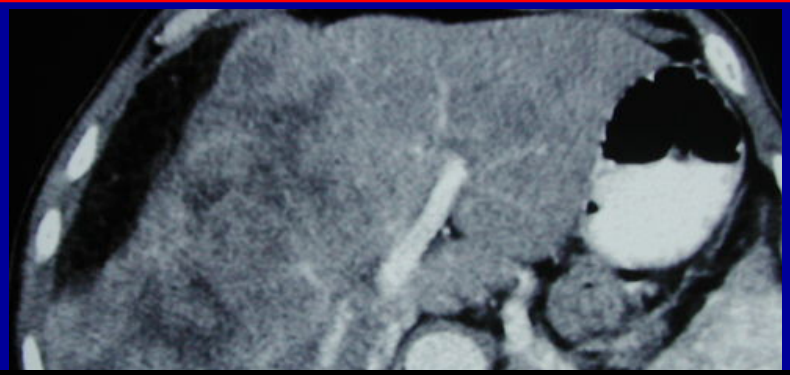
Rest-activity cycle

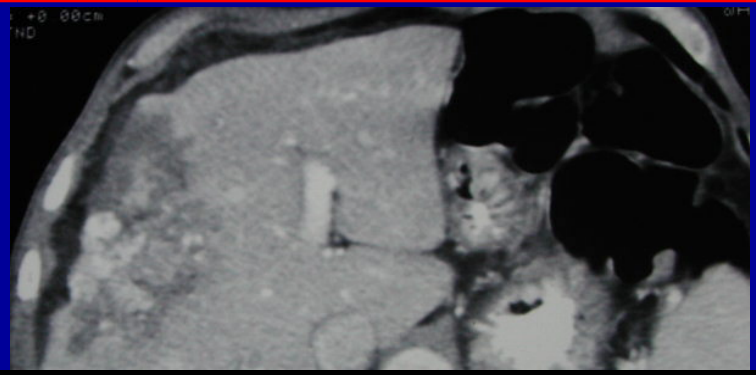
Peripheral oscillators

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

Circadian chronobiology (2): cancer chronotherapy

Metastatic colorectal cancer (Folinic Acid, 5-FU, Oxaliplatin)	Infusion flow		
	Constant	Chrono	
Toxicity			p
Oral mucositis gr 3-4	74%	14%	$<10^{-4}$
Neuropathy gr 2-3	31%	16%	$<10^{-2}$
Responding rate	30%	51%	$<10^{-3}$

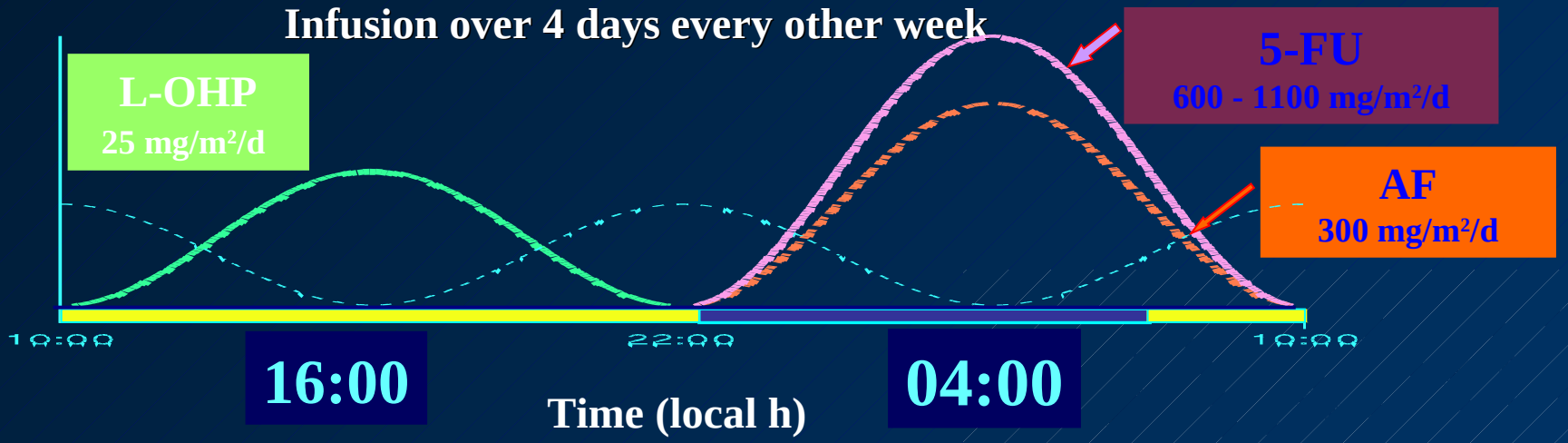




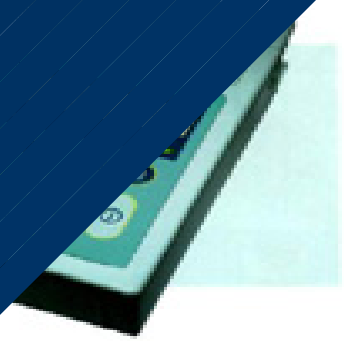
Lévi et al.
JNCI 1994 ;
Lancet 1997 ;
Lancet Onc 2001

How does it work? Proved impact of circadian clocks both on cell drug detoxication enzymes and on cell division cycle determinant proteins

Time-scheduled delivery regimen



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



Can such therapeutic schedules be improved?

Circadian chronobiology (4): Chronotherapy today in the clinic

Multichannel pump for chronotherapy

- Centralised programmation
- Any modulation of delivery rate
- 4 reservoirs (100-2000 mL)
- 2 independent channels
- Rates from 1 to 3000 mL/h

Images from the Chronotherapy Unit, Paul-Brousse Hospital, Villejuif, France

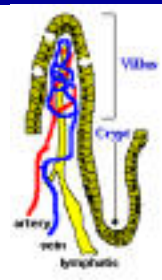
Over 2000 cancer patients registered in clinical Phase I, II or III trials

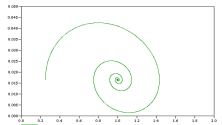
Simple pharmacokinetics-pharmacodynamics (PK-PD) of a cancer drug acting on cell populations: 6 state variables

oxaliplatin infusion flow

Healthy cells (jejunal mucosa)

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



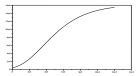


(homeostasis=damped harmonic oscillator)

Tumour cells

(PK)

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



(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:

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

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

then:

$$\min_{F_A(i)\leq 0} G_B(i) = \min_{i \in L^2([t_0,t_f])} \max_{\theta \geq 0} \mathcal{L}(i,\theta)$$

$$\pm\ other\ constraints$$

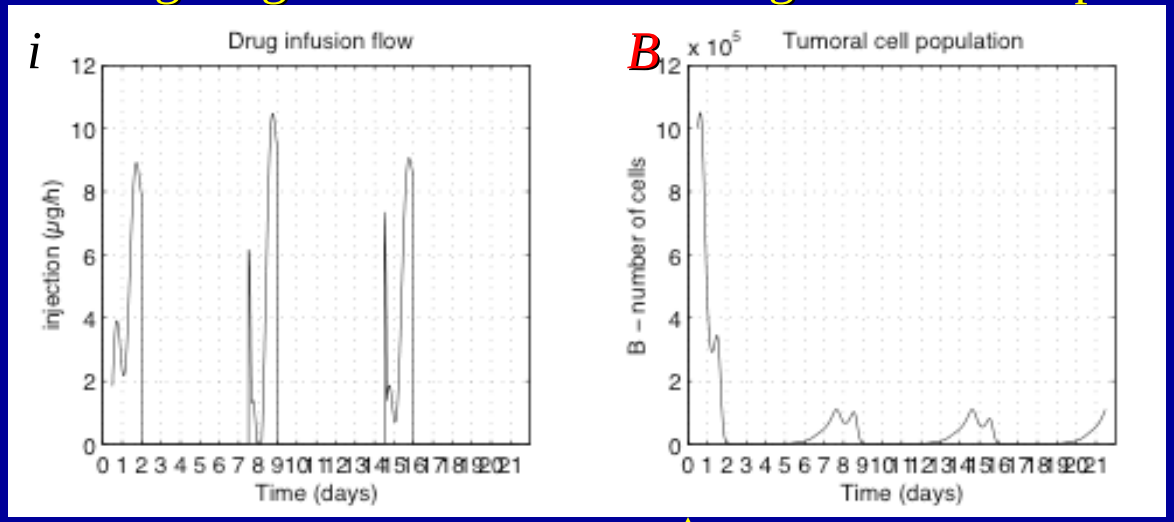
If G_B and F_A were convex, then one should have:

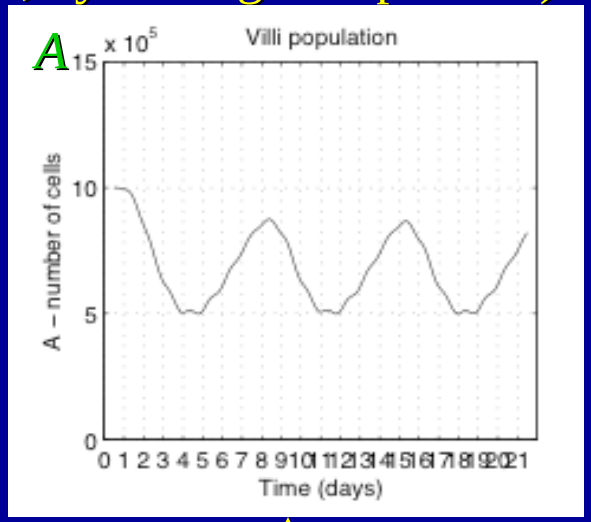
$$\min_i \max_{\theta \geq 0} \mathcal{L}(i,\theta) = \max_{\theta \geq 0} \min_i \mathcal{L}(i,\theta)$$

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

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)





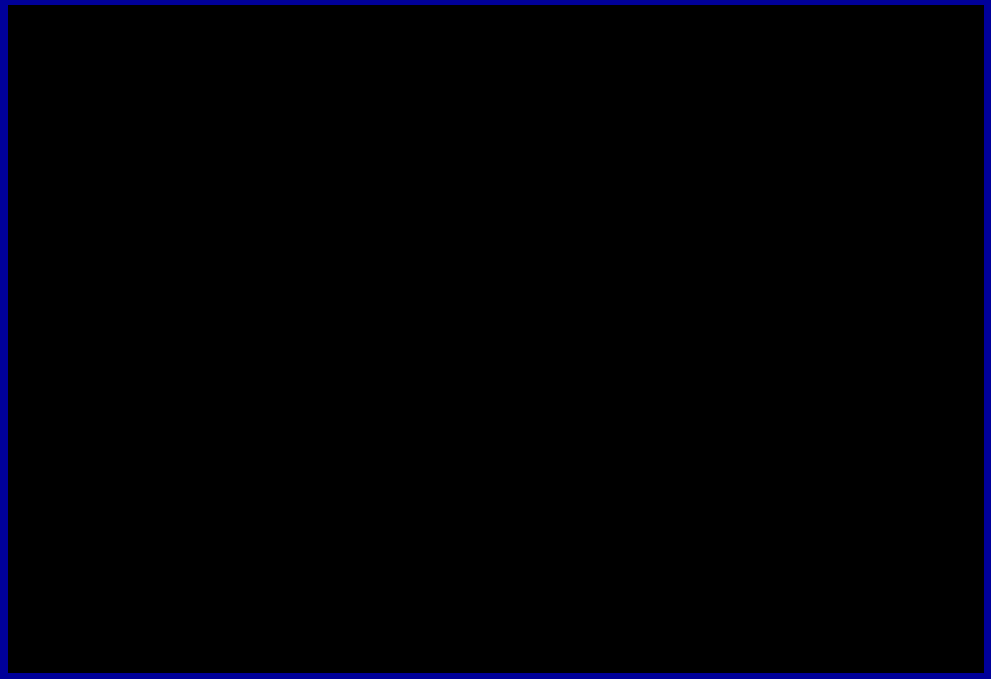
Objective: *minimising the maximum of the tumour cell population*

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 κ_A: here preserving κ_A=50% of enterocytes*)*

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

2. Cell population PDE model of proliferation



(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*

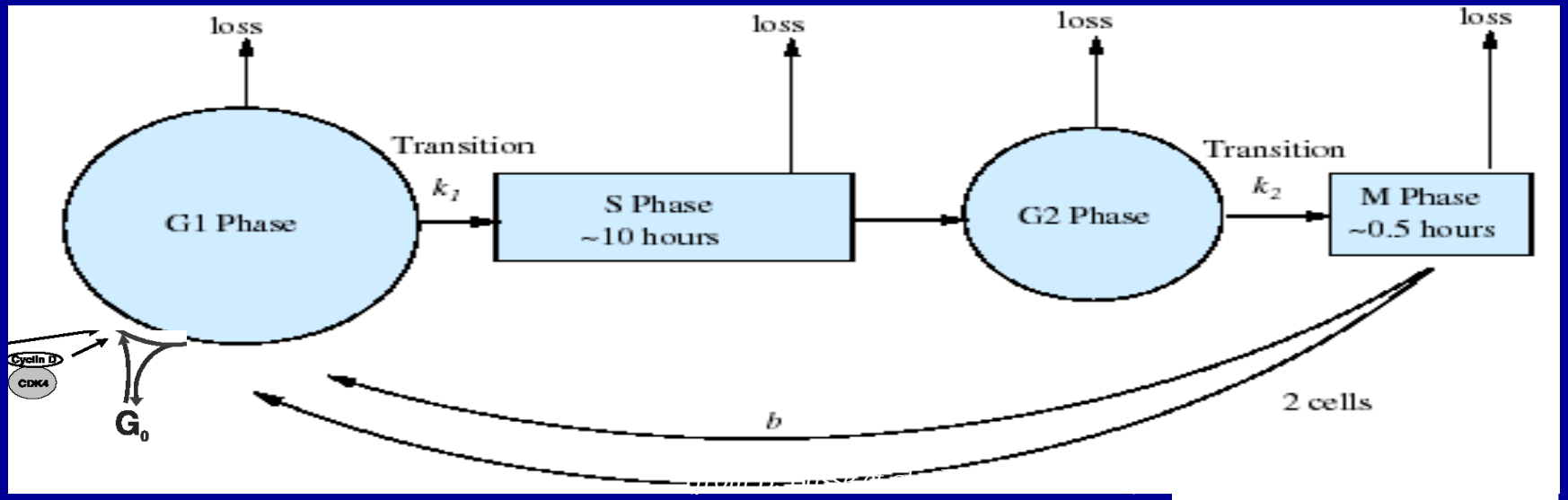
Why model the cell division cycle?

- Need for detailed models of cell proliferation to represent the action of anticancer drugs *in cell populations* with:
  1) Cell cycle phase specificity
  2) Different pharmacological targets on cell cycle control
  3) Action with same targets on tumour cells *and on healthy cells*
     (taking into account *toxic side effects* of anticancer drugs)

- To this aim, even independently of therapeutics, need for models with:
  1) Phase and age-in-phase, possibly cyclin, structure
  2) Transitions between cell division cycle phases (G_1/S, G_2/M)
  3) Exchanges between quiescent and proliferative phases (G_0/G_1)
  4) Targets for control of cell proliferation (physiological / by drugs)

Frame: Age-structured PDE model for the cell division cycle

(here only linear models will be 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 $u(t)$

$u(t)$: 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)

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:

$$\frac{1}{2}=\int_0^{+\infty}f(x)e^{-\lambda x}dx,\ \text{where } f(x)=K(x)e^{-\int_0^x K(y)dy} \text{ is a p.d.f. if } \int_0^{+\infty}K(x)dx=+\infty$$

General case: *I* phases (last = mitosis, or *M* phase)

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

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

with a real number ρ such that for all *i*:

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

(the weights $\varphi_i \geq 0$ being solutions to the dual problem); this can be proved by using
a generalised entropy principle (GRE). *Moreover, if the control (d_i or K_{i_i+1}) is periodic, so are the eigenvectors N_i and weights φ_i, with the same period.*

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

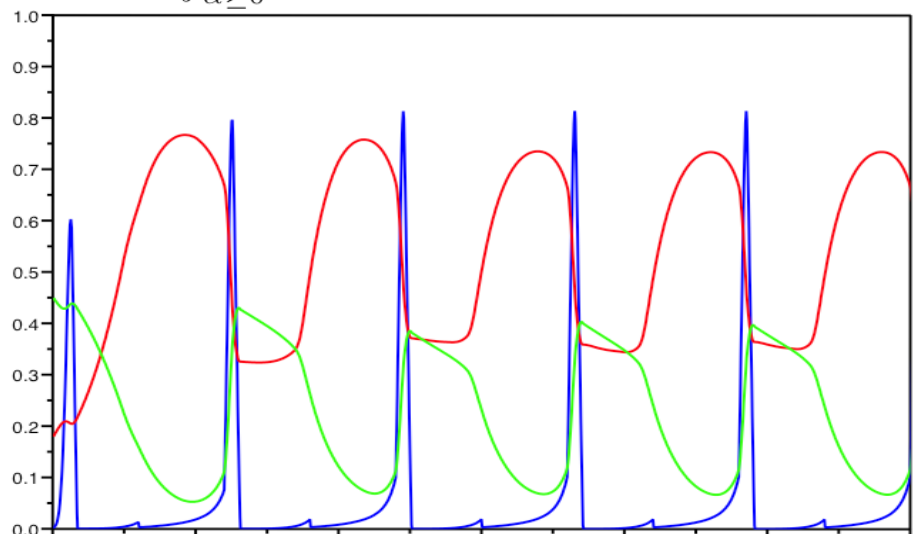
JC, Michel, Perthame C. R. Acad. Sci. Paris Series I (Math.) 2006; Proceedings 2007 of ECMTB Dresden 2005

λ: a growth exponent governing the cell population behaviour

Proof of the existence of a unique growth exponent λ, the same for all phases *i*, such that $\widetilde{N}_i(t,a) = e^{-\lambda t} n_i(t,a)$ 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)

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



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

Entrainment of the cell division cycle by ψ= CDK1 at the circadian period

"Surfing on the exponential growth curve"

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

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:

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

With probability density (experimentally identifiable):

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

A mathematical result:

The growth exponent 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)

This relies on the Proposition: *(Th. Ouillon's report 2010; Billy et al. Math. Comp. Simul. 2012):* For a family (f_i) of pdfs with fixed first moment e_i and varying second moment σ_i, λ increases 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]) :

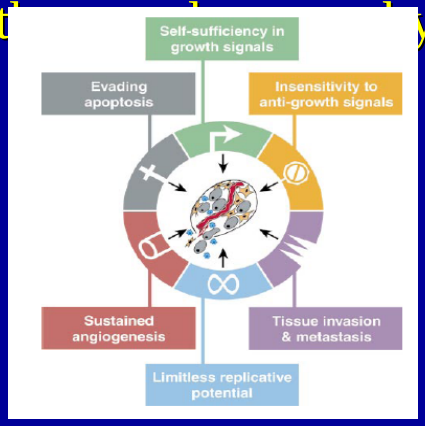
$$\frac{1}{2} = \prod_{i=1}^{I} \int_0^{+\infty} f_i(x) e^{-\lambda x} dx$$

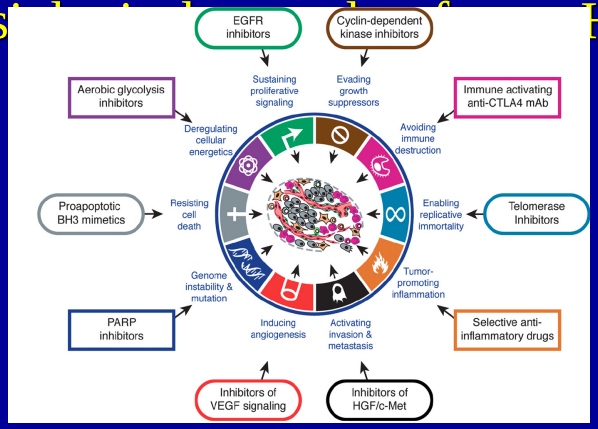
Pour $1 \leq i \leq I$, on pose $e_i = \int_0^{+\infty} x f_i(x)dx$ et $\sigma_i^2 = \int_0^{+\infty} x^2 f_i(x)dx - e_i^2$, et on suppose que les $e_i > 0$ sont constants. Soit $j \in \{1, ..., I\}$. On suppose que les σ_i^2 $(1 \leq i \neq j \leq I)$ sont constants.

Alors λ est croissante avec σ_j^2.

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 t





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

Hanahan & Weinberg, Cell 2000 ⟶ *Hanahan & Weinberg, Cell 2011*

Experimental identification of the basic model parameters with *FUCCI reporters* on a 2-phase model G_1 / S-G_2-M

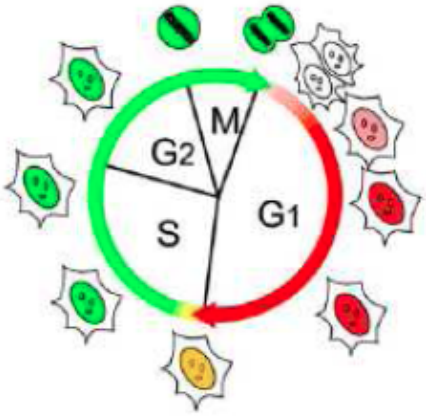
(so far, without circadian control)

Cells:

NIH 3T3 of a common population

(*mouse embryonic fibroblasts*)

without preliminary synchronization

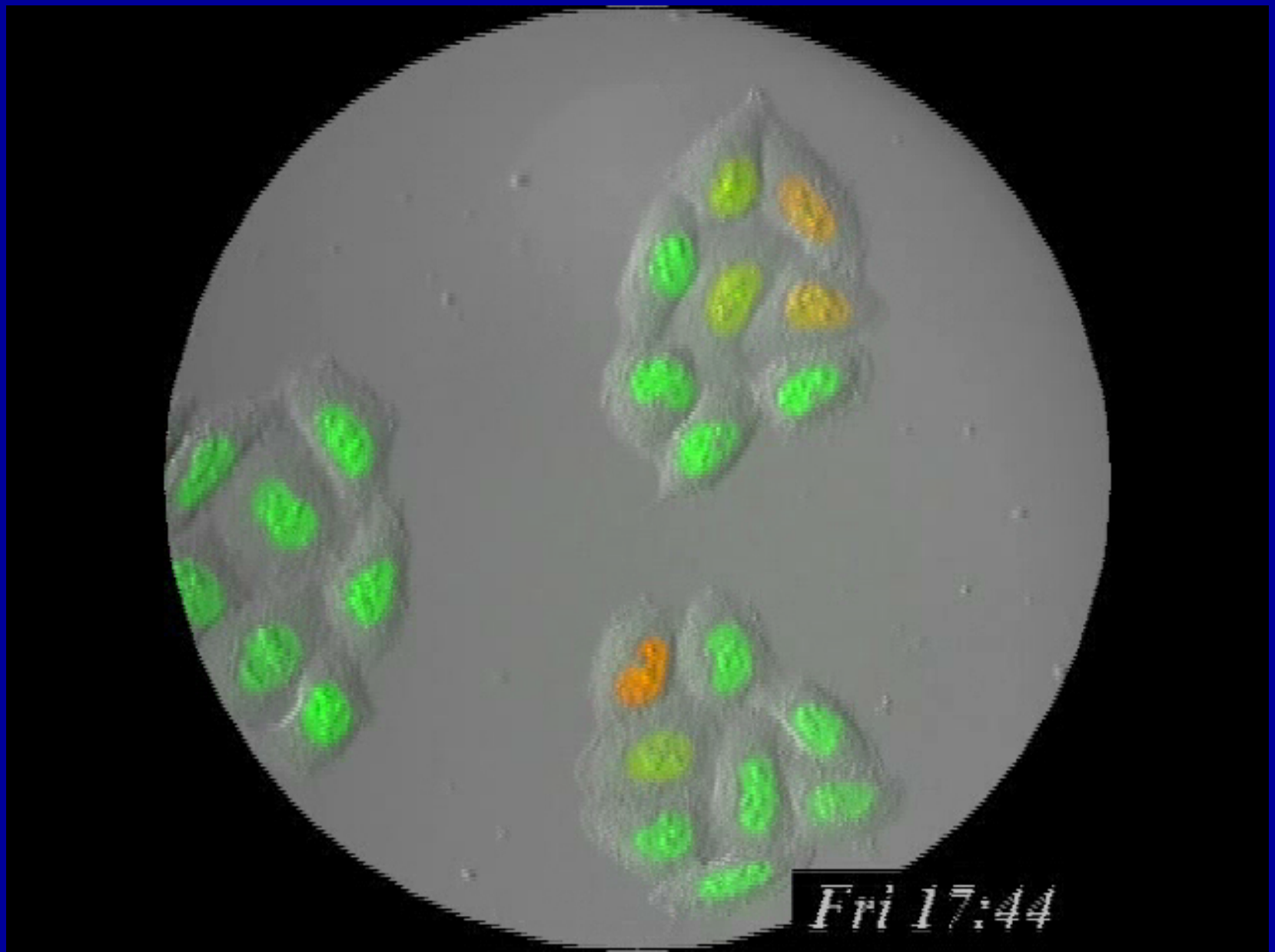


from Sakaue-Sawano et al.
Cell 2008, 132, 487–498

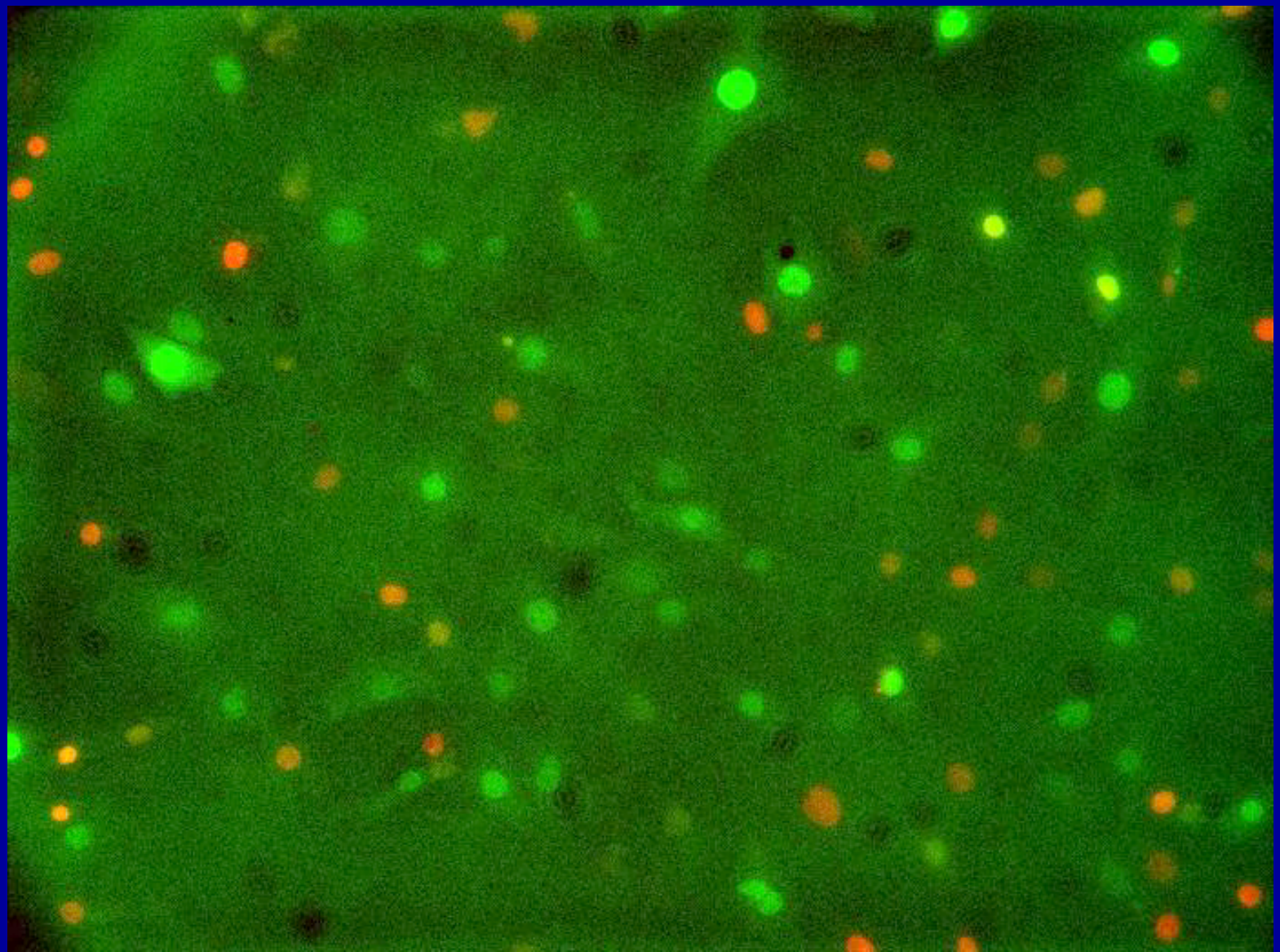
Measures: for each individual cell:
red and green fluorescence time recording

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

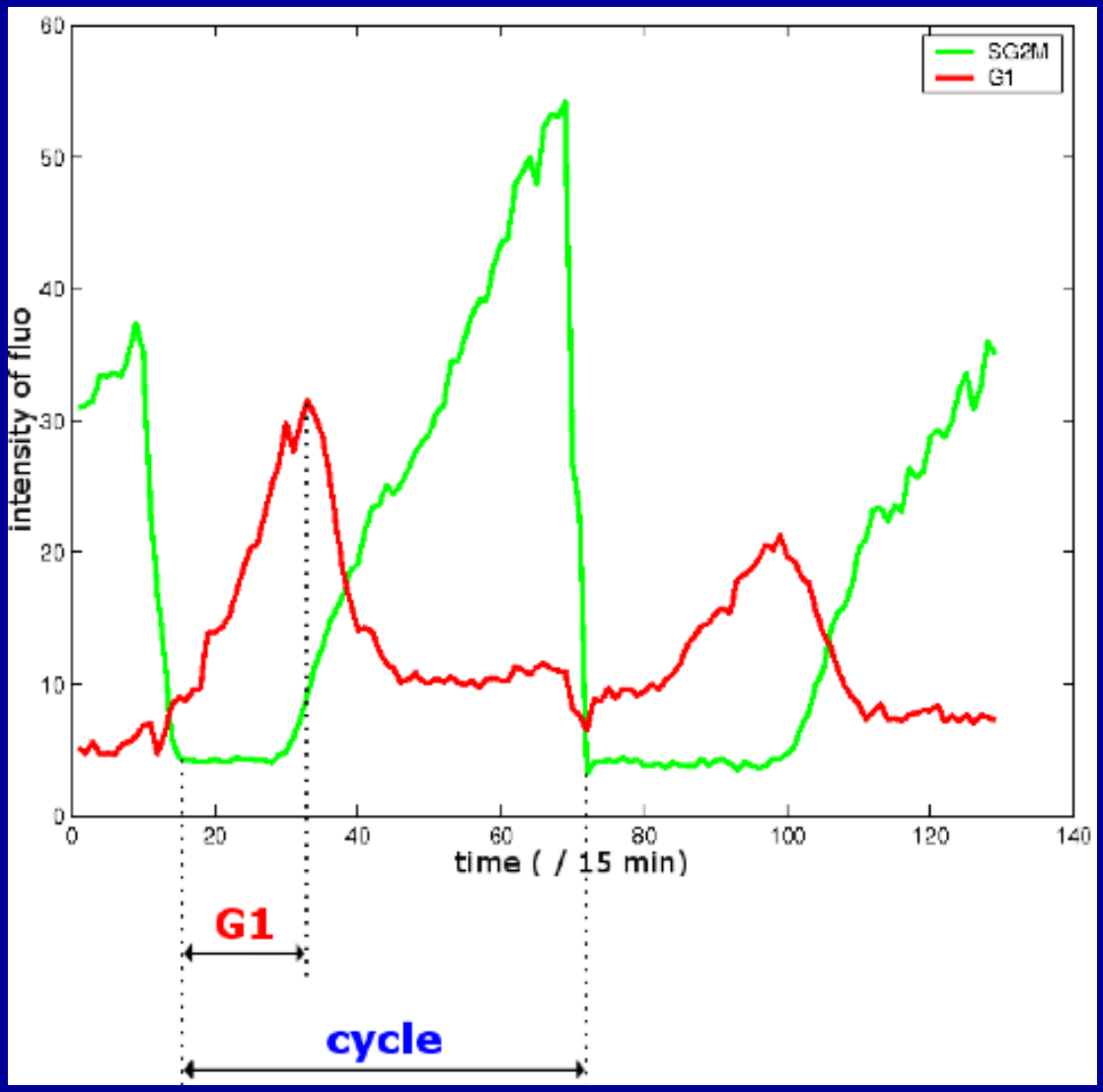
FUCCI: a movie (Sakaue-Sawano, 2008) on HeLa cells



Another FUCCI movie on NIH3T3 cells (C. Feillet, F. Delaunay, IBDC Nice, 2012)



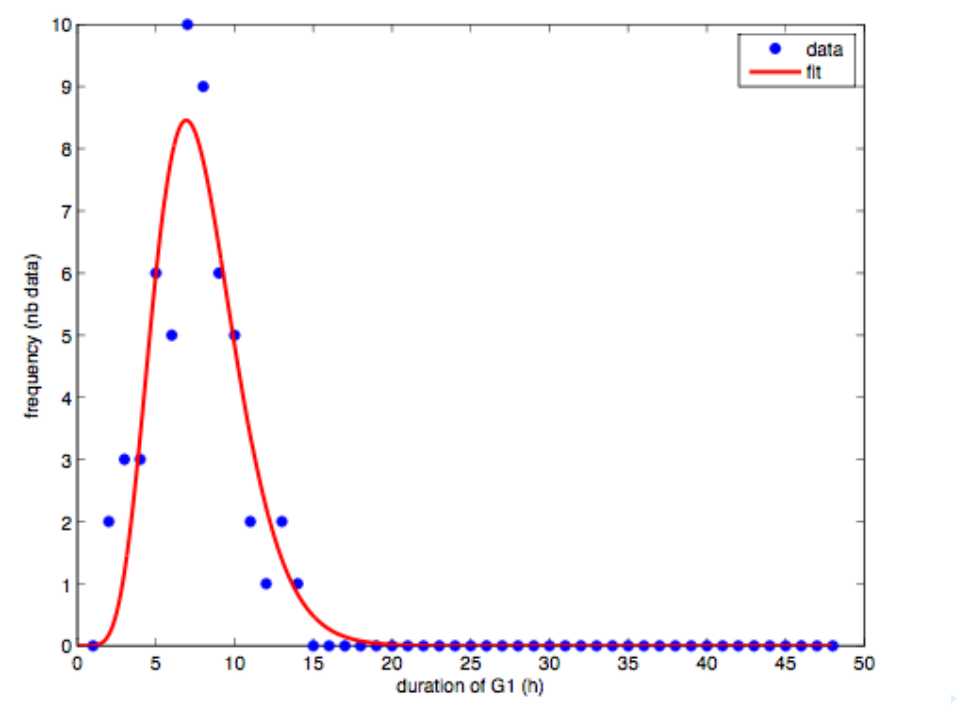
FUCCI reporters + individual cell tracking (non trivial...):
Measuring time intervals: G_1 and total division cycle durations



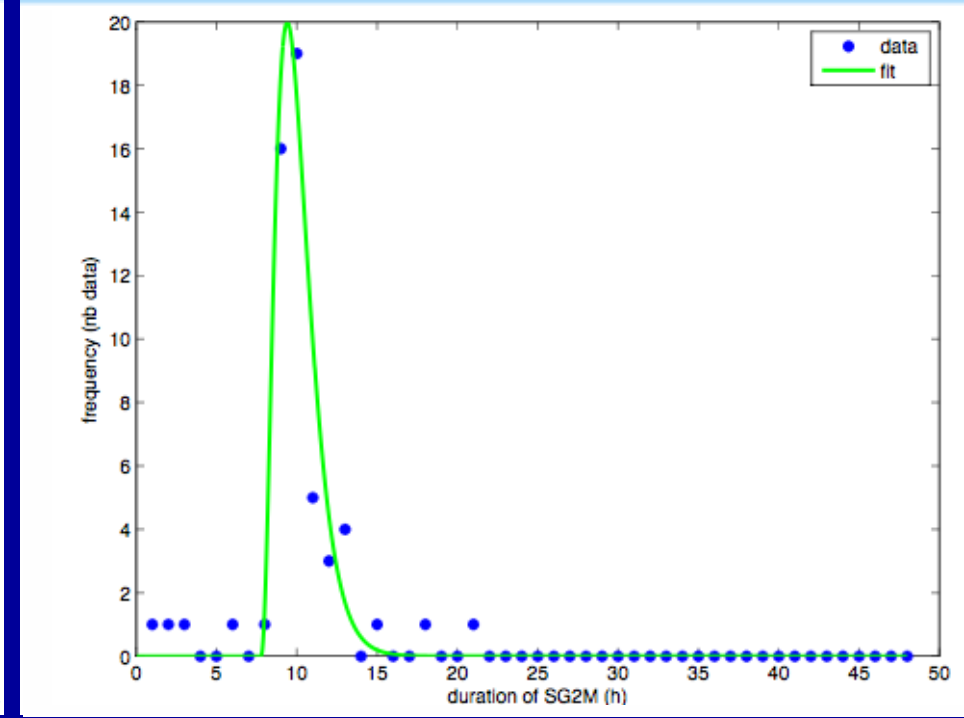
Data from Bert van der Horst's lab, Erasmus University, Rotterdam, processed by Frédérique Billy at INRIA

Phase transitions w.r.t. age x
Pdfs $f(x)$ fitted from data on 50 NIH 3T3 proliferating cells

Density of transition from G1 to SG2M



Density of transition from SG2M to G1



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

Computing the growth exponent, fitting data to p.d.f.s:

Gamma p.d.f.s were best fits and yielded simple computations:

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

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

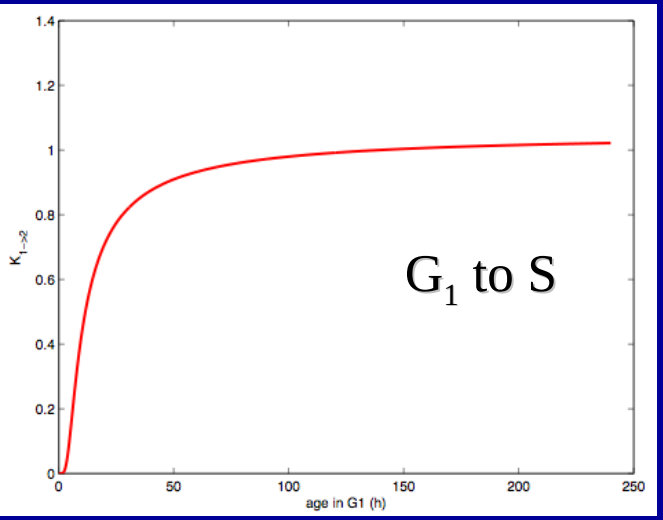
2-phase Lotka's equation simply reads:

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

... which yields here λ = 0.039 h^{-1}

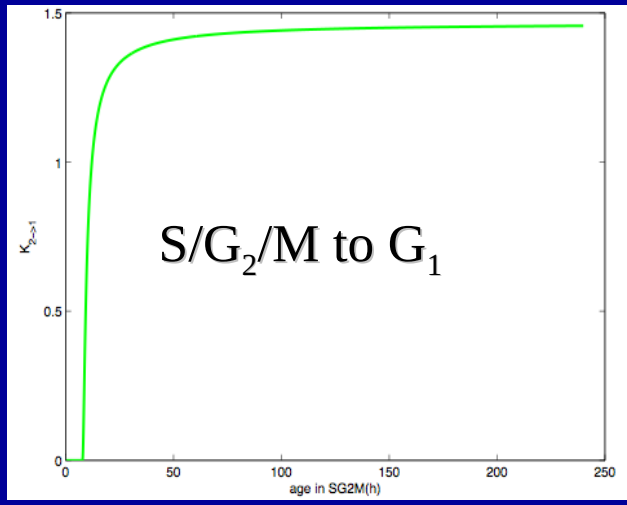
(and yields mean doubling time T_d =17.77 h, with mean cell cycle time T_c =17.95 h)

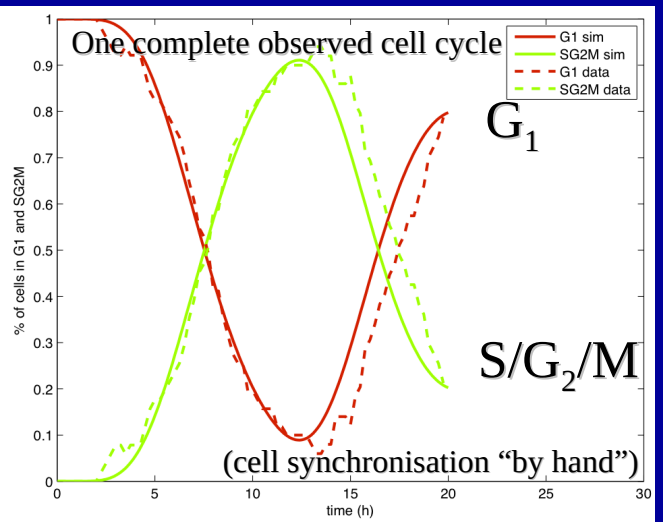
Phase transitions w.r.t. age x
Transition rates $K(x)$ from pdfs $f(x)$ on NIH 3T3 healthy cells and resulting population evolution

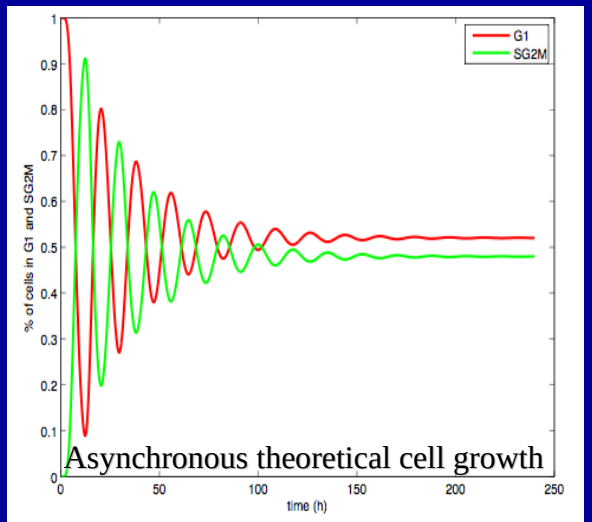


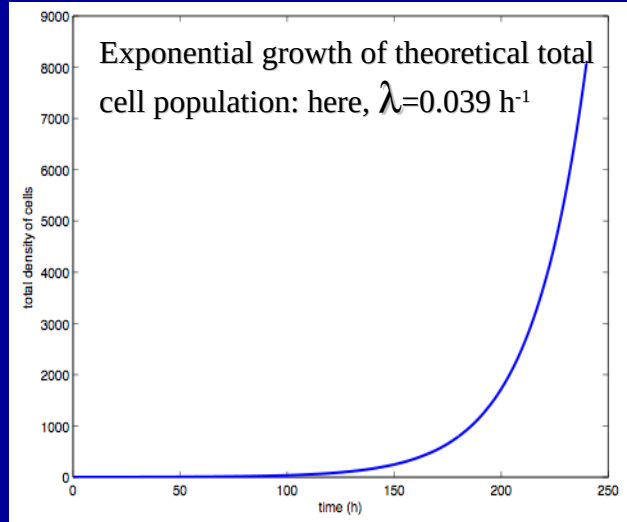
Recalling that in the model
f = p.d.f. of phase duration time
and K = phase transition kernel:

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



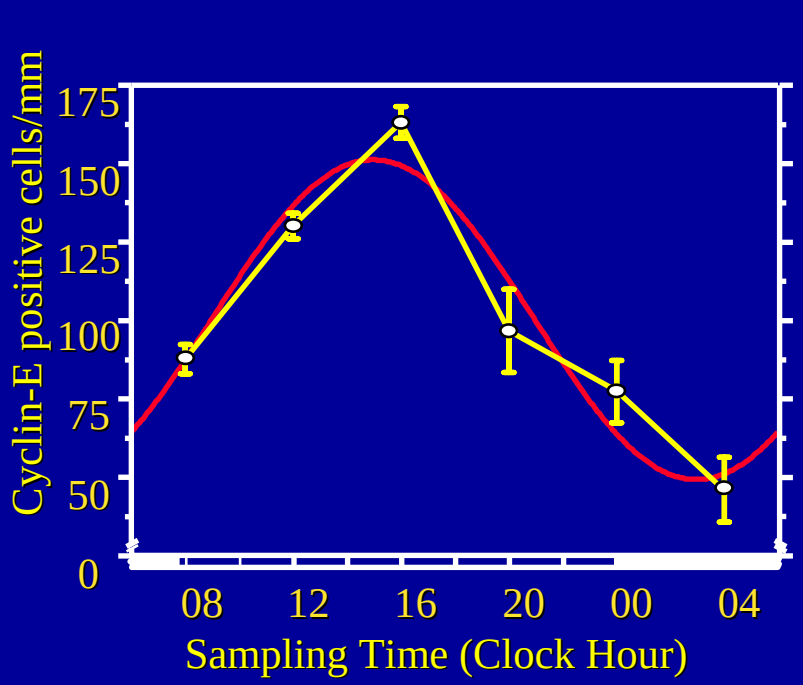


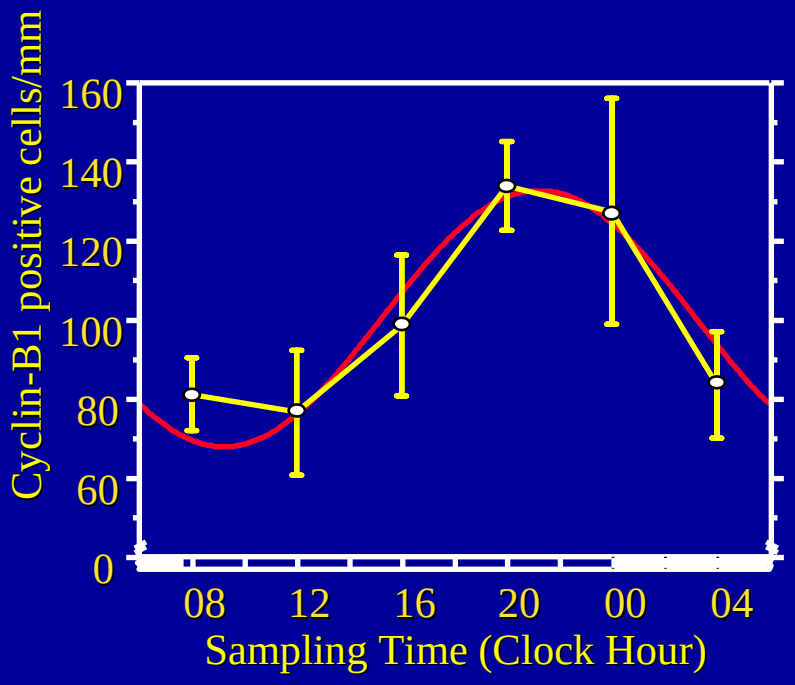




Human physiology: circadian rhythms in the Human cell division cycle

Example of circadian rhythm in normal (=homeostatic) Human oral mucosa for Cyclin E (control of G_1/S transition) and Cyclin B (control of G_2/M transition)

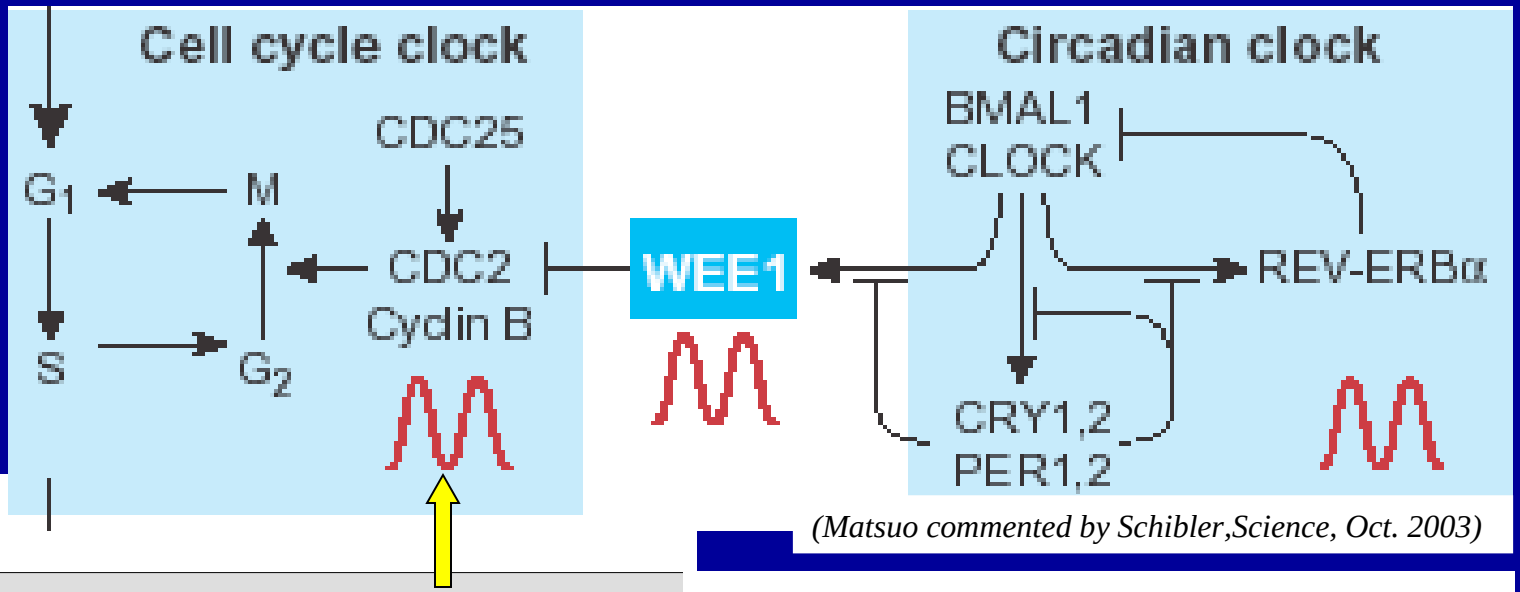




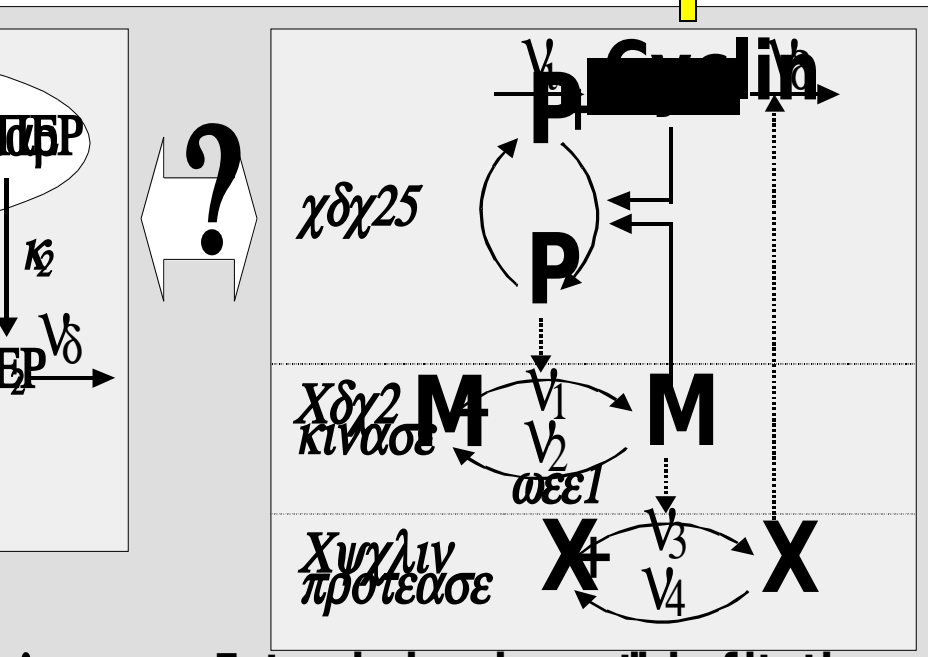
Nuclear staining for Cyclin-E and Cyclin-B1. Percentages of mean ± S.E.M. in oral mucosa samples from 6 male volunteers. Cosinor fitting, $p < 0.001$ and $p = 0.016$, respectively.

(from Bjarnason et al. Am J Pathol 1999)

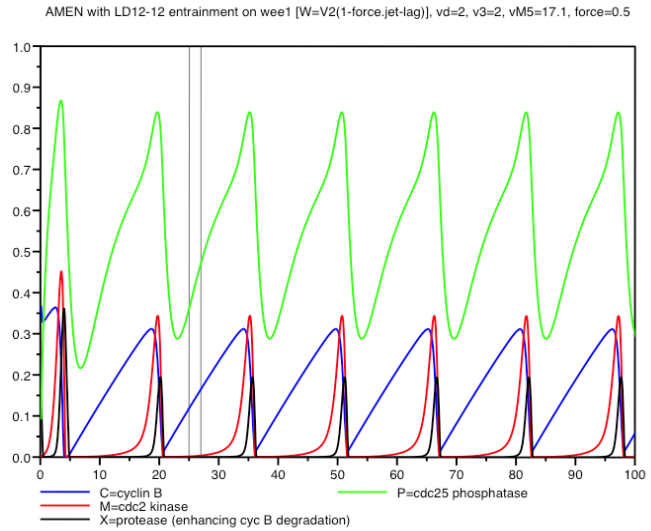
A connection between cell cycle and circadian clocks: Cdk1 opens G2/M gate; Wee1 inhibits Cdk1; Per2 inhibits Wee



(Matsuo commented by Schibler,Science, Oct. 2003)

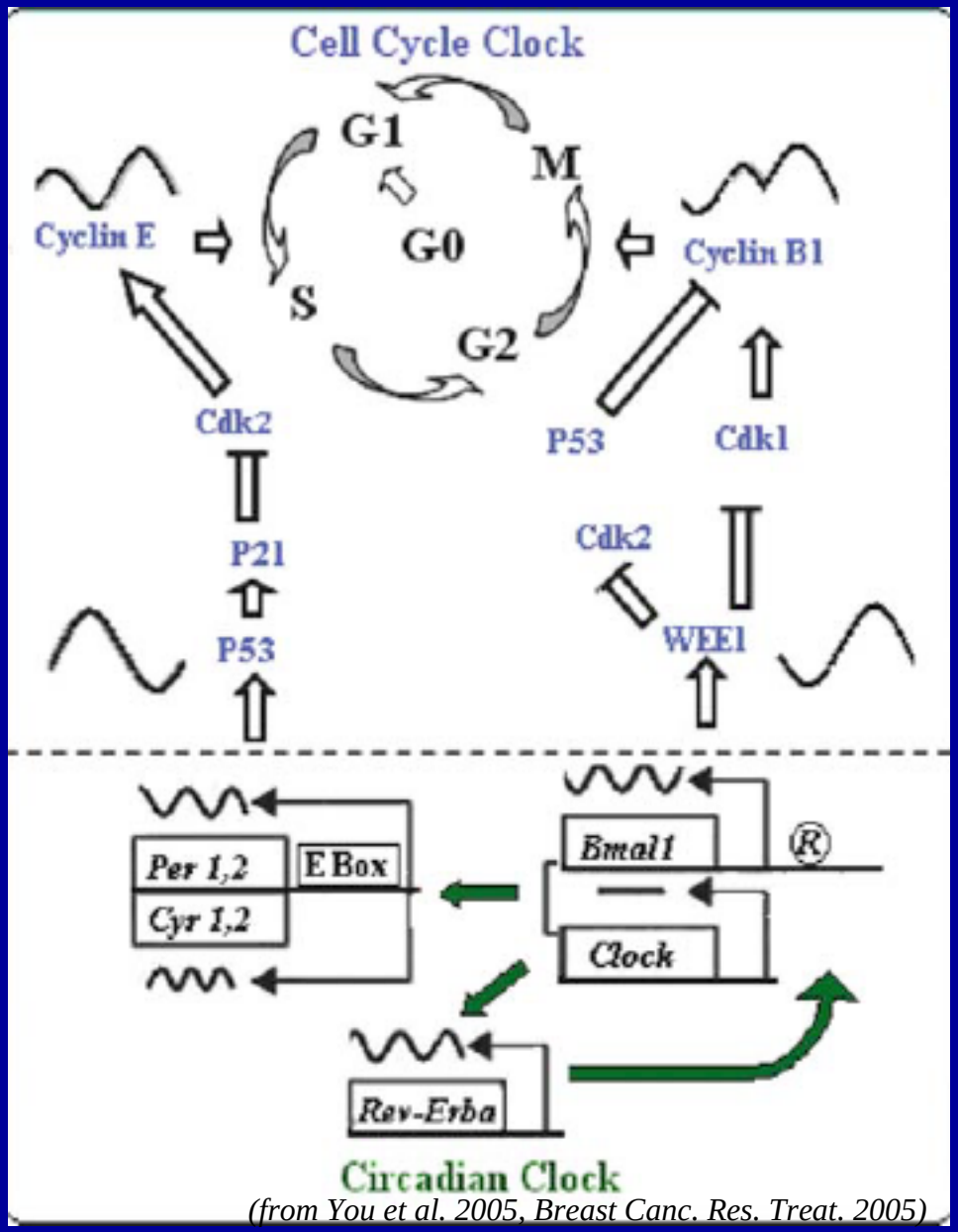


Extended cascade model of mitotic osc



Mitotic oscillator model by Albert Goldbeter, 1997, here with circadian entrainment by a square wave standing for Wee1

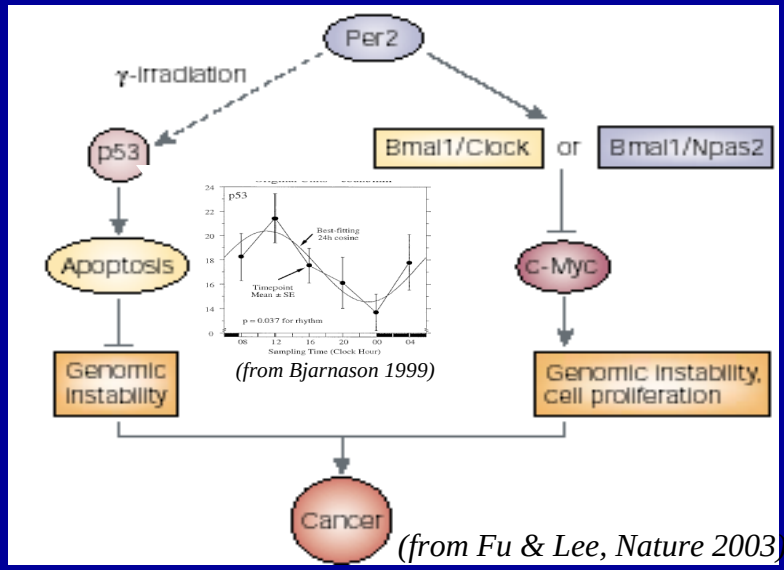
More connections between the cell cycle and circadian clocks



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

1) The circadian clock gene Bmal1 might be a synchroniser in each cell between G_1/S and G_2/M transitions *(Wee1 and p21 act in antiphase)*

2) Protein p53, the major sensor of DNA damage ("guardian of the genome") , is expressed according to a 24 h rhythm (not altered in Bmal1$^{-/-}$ mice)

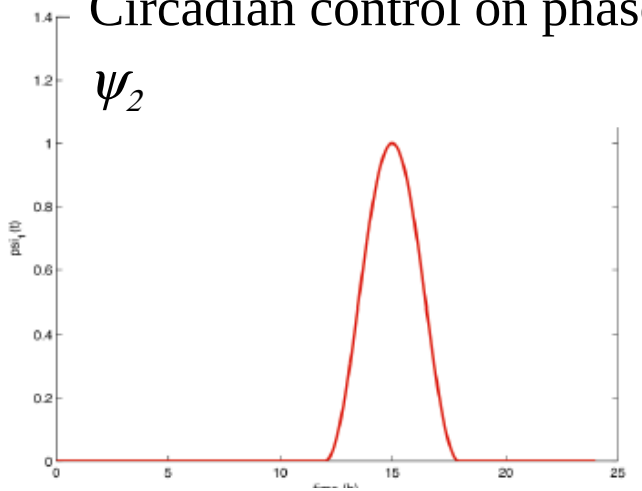


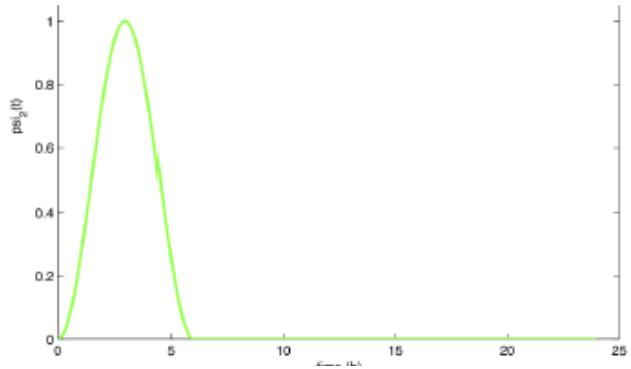
(from Bjarnason 1999)

(from Fu & Lee, Nature 2003)

Adding circadian control on transitions

Circadian control on phase transitions: two cosines for ψ_1 and ψ_2

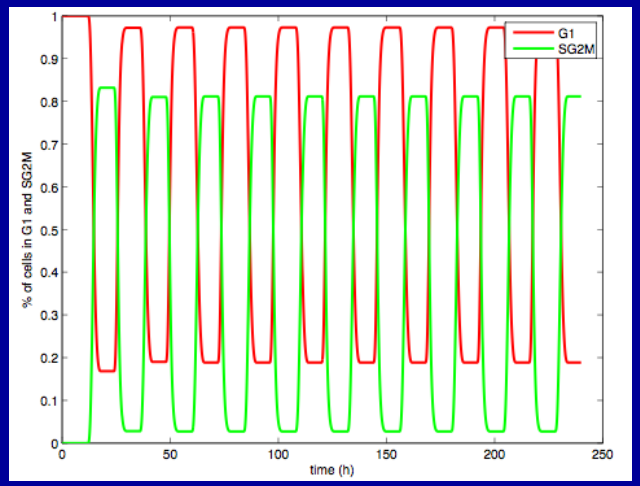




$$\psi_1(t) = \cos^2(2\pi(t-3)/12)\mathbb{1}_{[12;18]}(t)+\varepsilon, \quad \psi_2(t) = \cos^2(2\pi(t-3)/12)\mathbb{1}_{[0;6]}(t)+\varepsilon$$

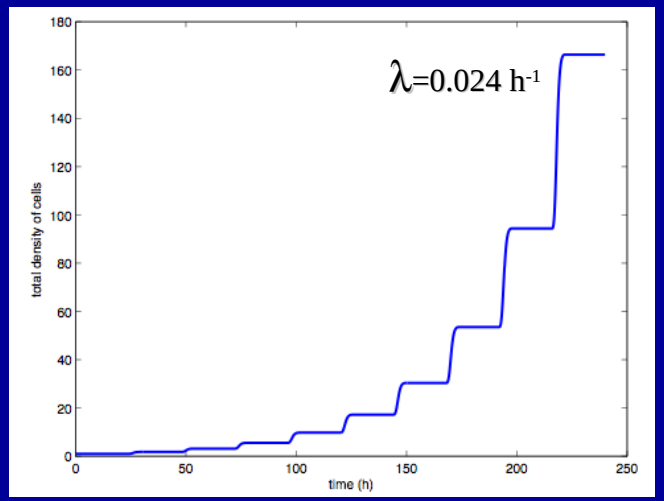
(a 12 h-delay between the two cosines was determined as the one that maximised the λ)

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



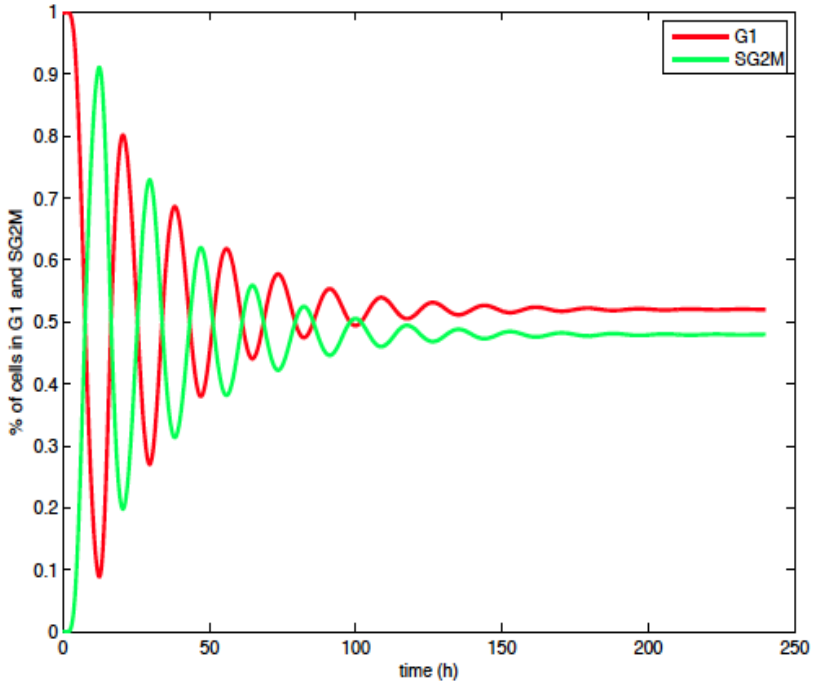
Here we put
$K(x,t) = \kappa(x).\psi(t)$
with κ = FUCCI-identified
and ψ = a cosine

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

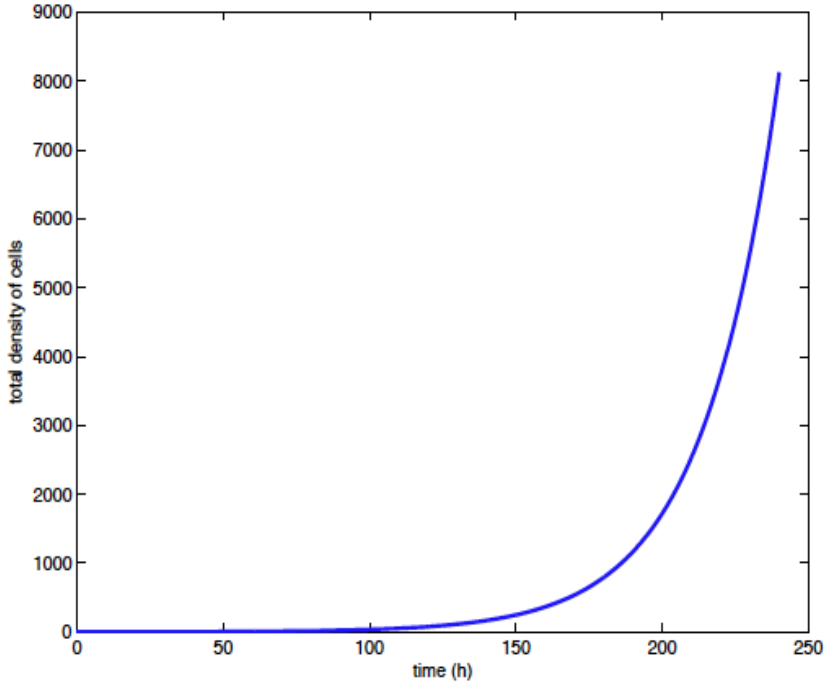


without time control

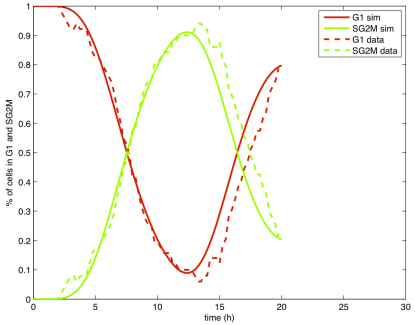
Phases: asynchronous cell growth



Global: sheer exponential cell growth



[Agreement between model and data on the first division] →

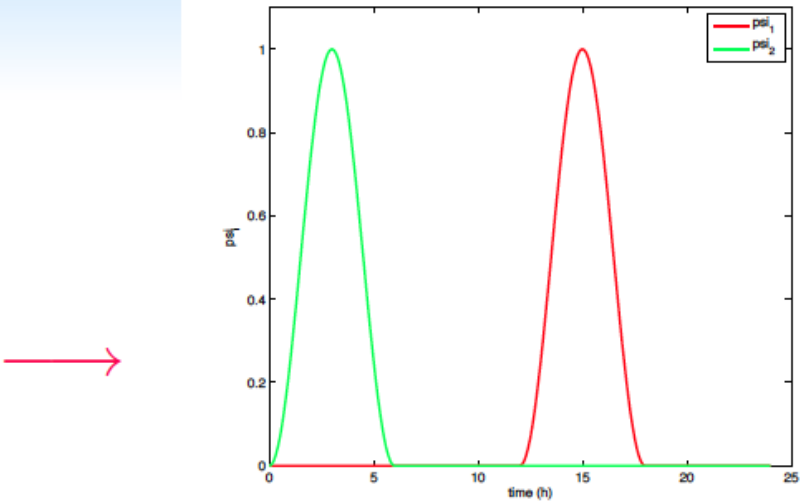


$\lambda = 0.039 h^{-1}$ $T_d = 18h$

F. Billy

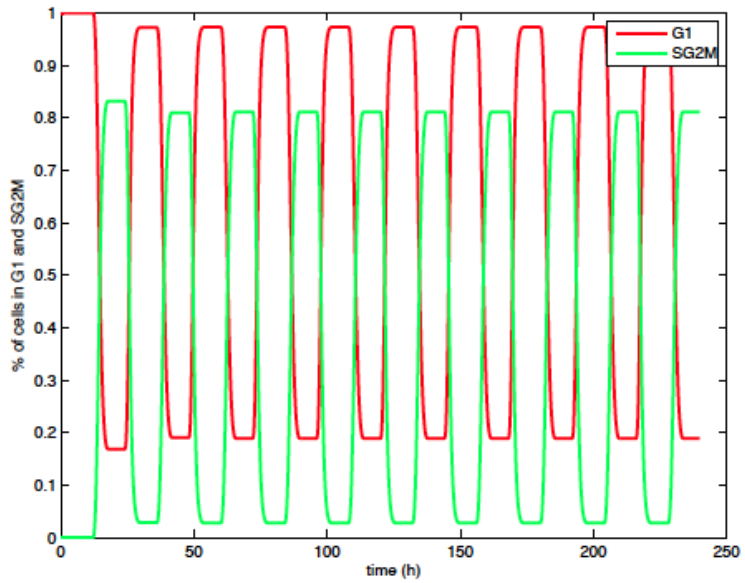
With time control (1)

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

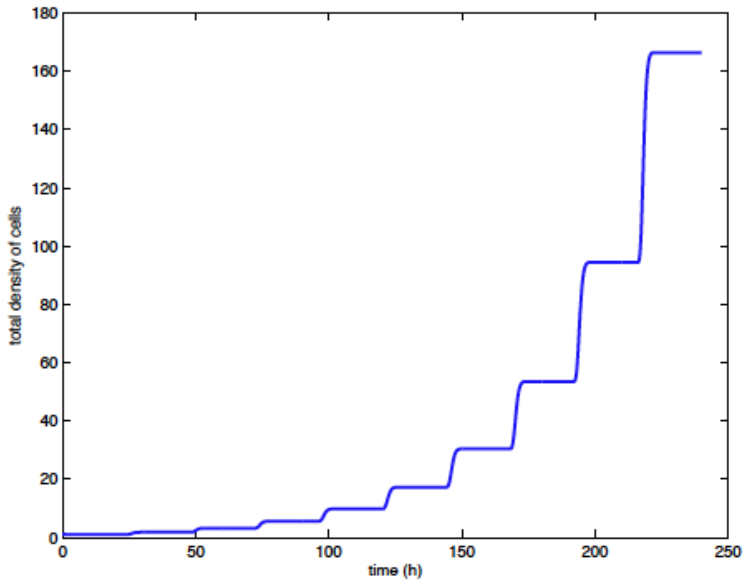


(1) healthy cell population (=sharp gating by circadian clock)

Steep synchronisation within the cell cycle



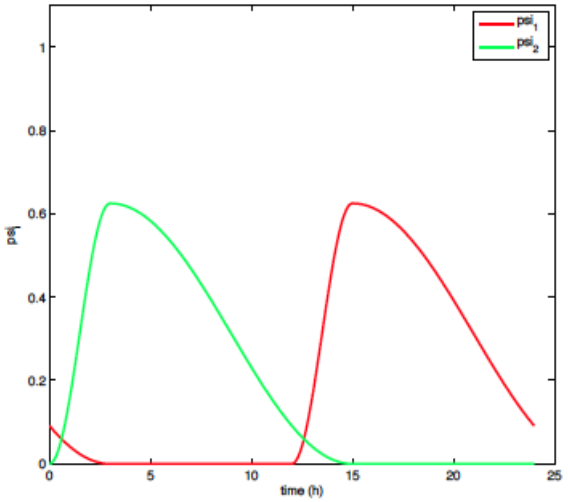
Stepwise cell population growth



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

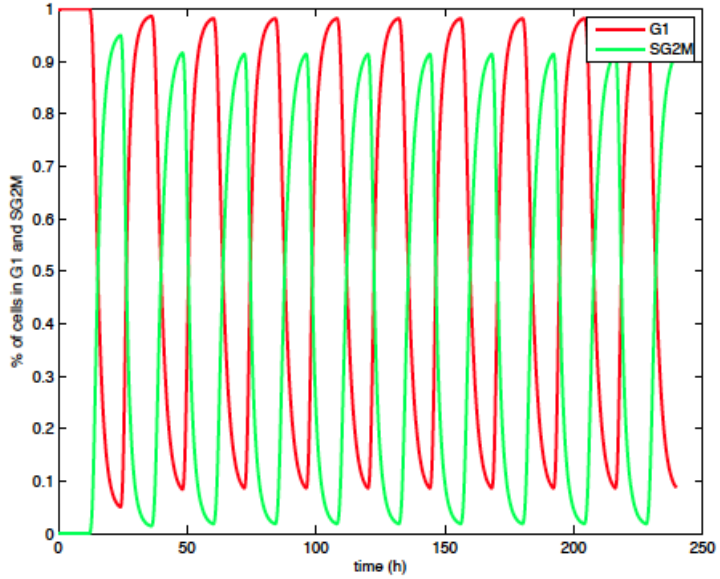
With time control (2)

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

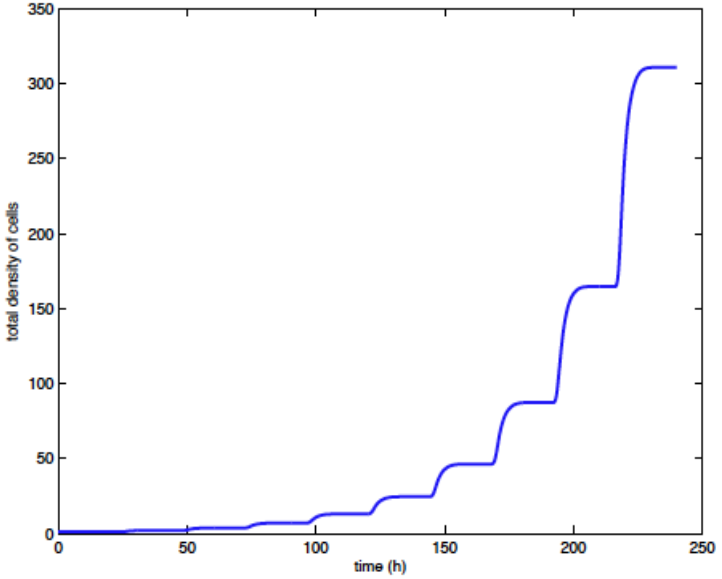


(2) cancer cell population (=lazy gating by circadian clock)

Soft synchronisation within the cell cycle

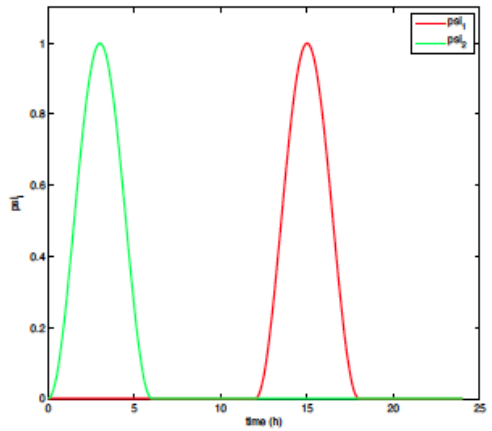


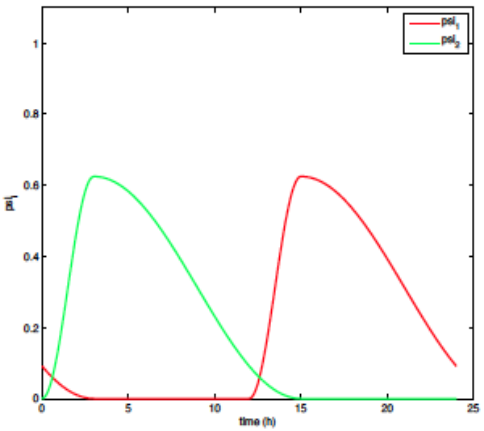
Stepwise cell population growth

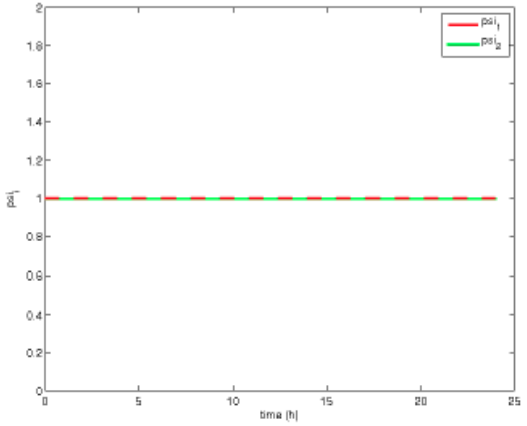


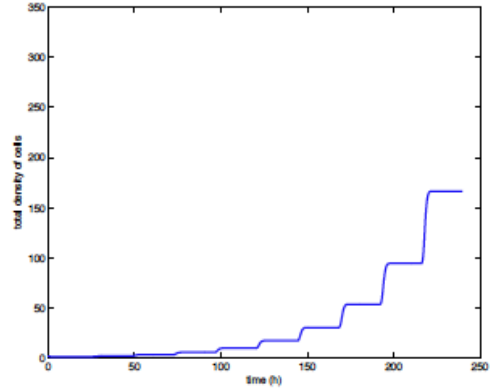
$\lambda = 0.026 h^{-1}$ $T_d = 26.3h$

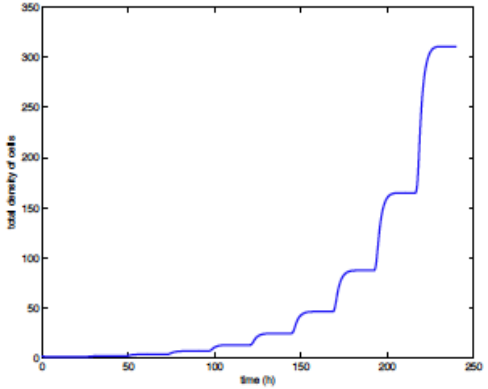
Summary

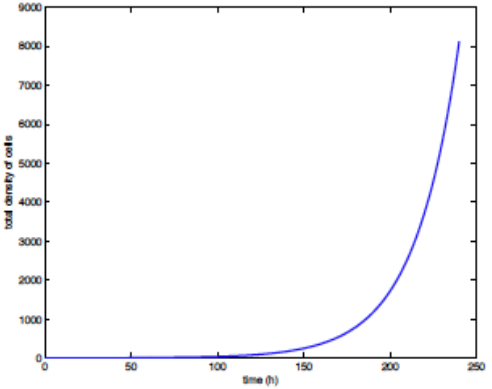












$\lambda = 0.024 h^{-1}$
$T_d = 29.4h$

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

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

Circadian + pharmacological control on transitions

K(x,t) = κ(x).ψ(t).[1-g(t)]: κ FUCCI-identified, ψ clock, g optimal drug effect

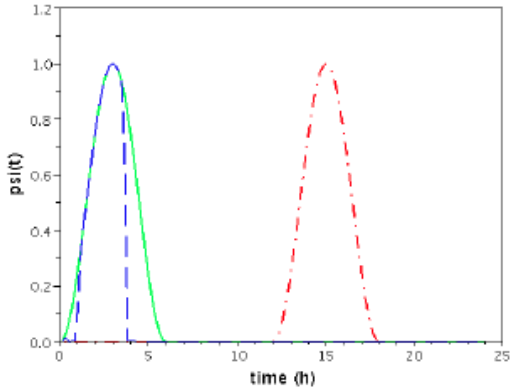


Figure 9: Modelled circadian control for transition G_1 to $S/G_2/M$ (dashdotted line) and transition $S/G_2/M$ to G_1. The natural control for $S/G_2/M$ to G_1 transition is in solid line, the drug induced control is in dashed line.

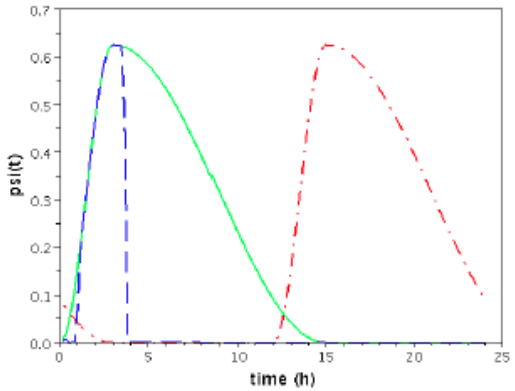


Figure 10: Modelled answer of cancerous cells to circadian control for transition G_1 to $S/G_2/M$ (dash-dotted line) and transition $S/G_2/M$ to G_1. The answer to natural control for $S/G_2/M$ to G_1 transition is in solid line, the drug-induced control is in dashed line.

green and red: ψ

blue: $[1-g].\psi$
(g blocks ψ)

Theoretical chronotherapeutic optimisation of a 1st eigenvalue (cancer growth) under the constraint of preserving another 1st eigenvalue (healthy tissue growth)

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

- 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 λ_2-Λ (with penalty)
- Arrow-Hurwitz (or Uzawa) algorithm to track saddle points of the Lagrangian
- …thus obtaining only suboptimality (necessary to obtain critical points) conditions

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

Circadian control, no drug infusion

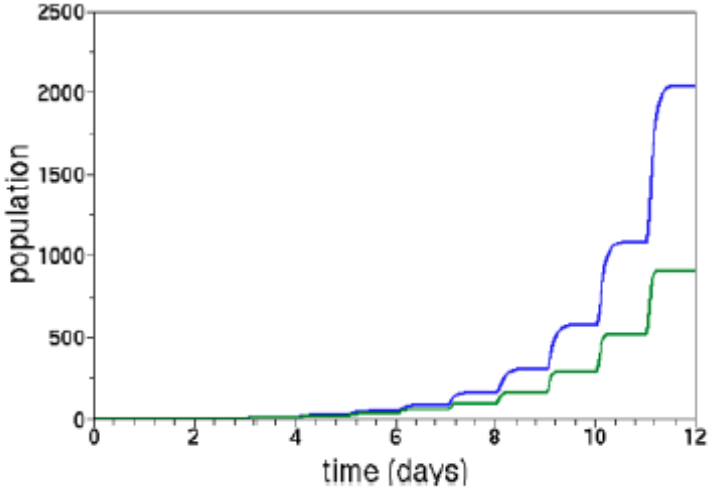


Figure 11: Evolution of the population of cancer (blue, beneath) and healthy (green, above) cells without drug infusion during 12 days. We can see that the populations have different exponential growth rates ($\lambda_{cancer} = 0.026$ and $\lambda_{healthy} = 0.024$). In the beginning, there were as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

Circadian control, added drug infusion

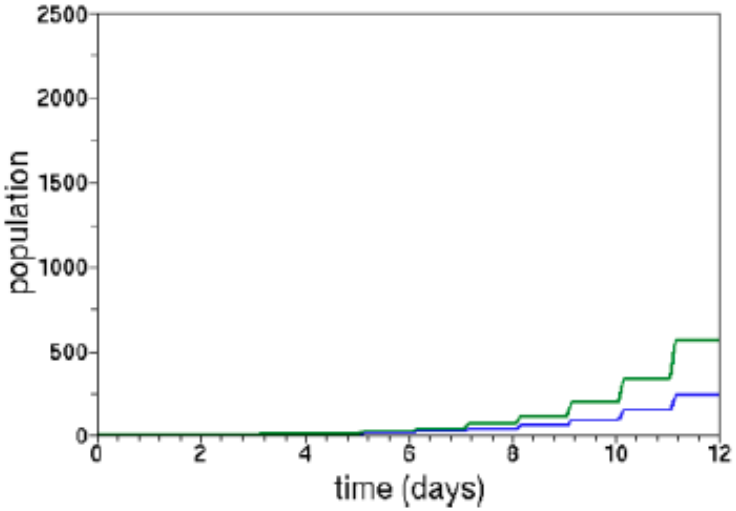


Figure 12: Evolution of the population of cancer (blue, beneath) and healthy (green, above) cells with the drug infusion, starting at time 0, given by the algorithm. Healthy cells keep multiplying ($\lambda_{healthy} = 0.022$) while the cancer cell population is weakened ($\lambda_{cancer} = 0.019$).

(F. Billy et al. 2011, submitted)

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

Infusion scheme *g(t)*

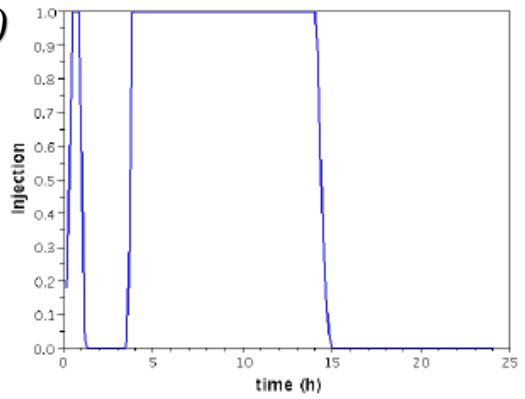


Figure 11: Locally optimal drug injection strategy found by the optimisation algorithm.

Target eigenvalues:
Cancer (blue)
Healthy (green)

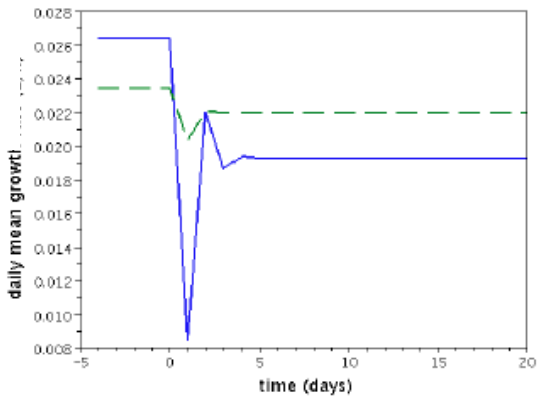


Figure 12: Daily mean growth rates for cancerous (solid line) and healthy cells (dashed line) when starting drug injections at time 0. After a 10 day transitional phase, the biological system stabilises towards the expected asymptotic growth rate

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)

What remains to be done to complete the design of this model:

- Identify actual doubling times and compare them with calculated $T_d = \ln 2 / \lambda$
- Replace cosines by identified circadian gating functions
- Identify transition p.d.f.s in a broad variety of cell populations, healthy and cancer
- Assess actual (de)synchronisation in cancer vs. healthy proliferating cell populations
- Relate it with the variance of cell cycle phase duration p.d.f.s (i.e., transition kernels)
- Extend from cell cultures in liquid media to solid tissues (using nonlinear modelling)

Plasma and cell pharmacokinetics (PK) of 5-fluorouracil (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)

5FU and LV: plasma and intracellular PK

FdUMP extracellular efflux (by ABC Transporter ABCC11)

5FU cell uptake

5FU DPD detoxication in liver

i(t) = 5FU infusion flow

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

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

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

j(t) = LV infusion flow

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

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

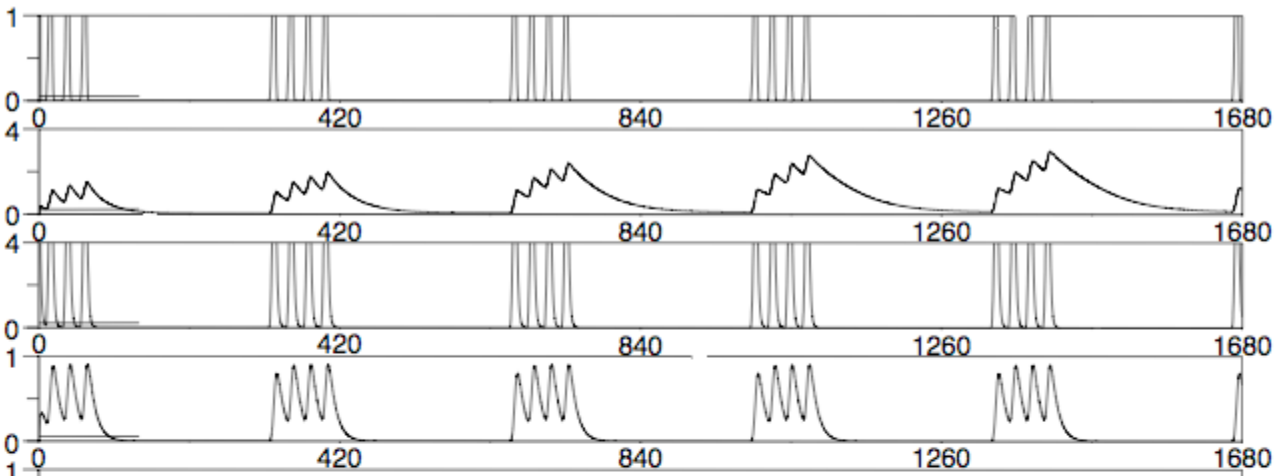
Binding of LV to FdUMP-TS = B to form a *stable* ternary complex

P=5FU (plasma)

F=FdUMP (cell)

Q=LV (plasma)

L=LV (cell)



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

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

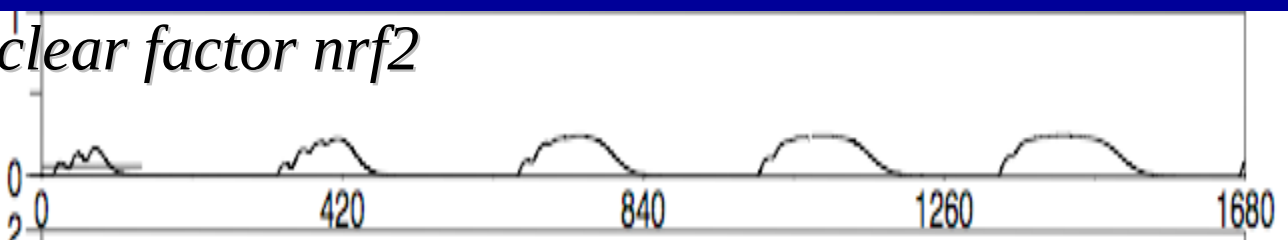
$$\frac{dN}{dt} = \frac{\kappa F^n}{\lambda^n + F^n} - \mu N$$

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

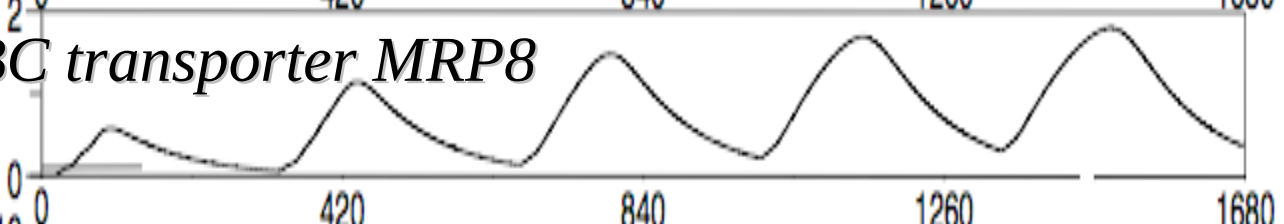
Nuclear factor *(e.g., nrf2)*

ABC Transporter (ABCC11=MRP8)

N=nuclear factor nrf2



A=ABC transporter MRP8

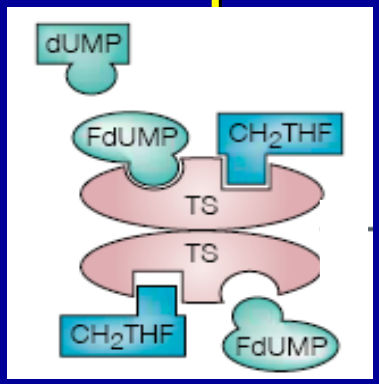


Targeting Thimidylate Synthase (*TS*) by FdUMP: Formation of binary and ternary *TS*-complexes

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

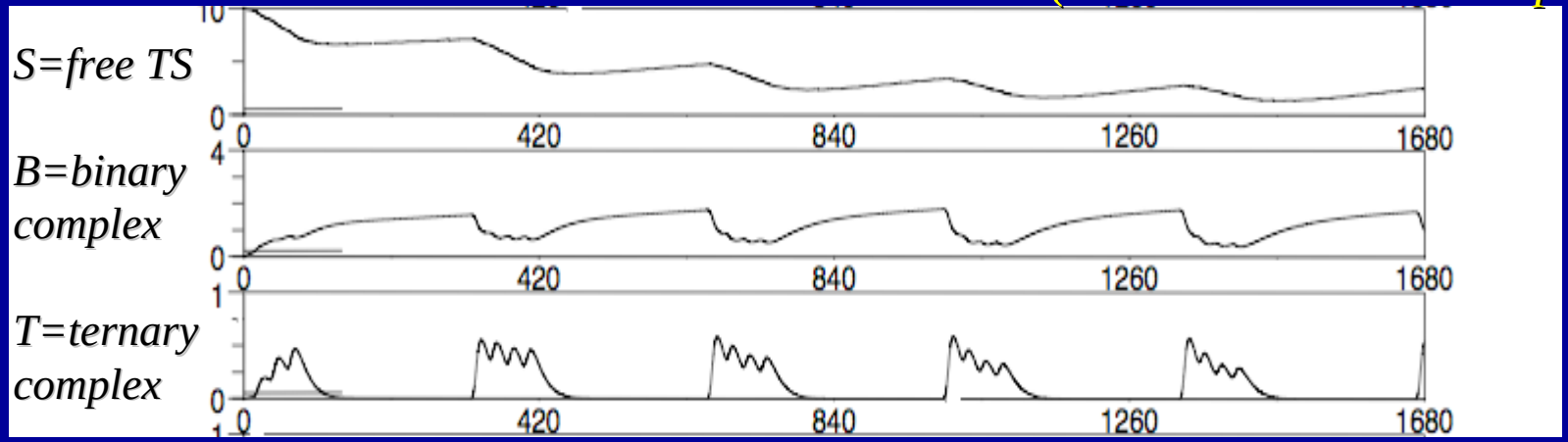
$$\frac{dB}{dt} = k_1 FS - k_{-1} B - k_4 BL$$

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



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

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



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

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

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

(3) $$\frac{dQ}{dt} = -k_2 Q + \frac{j(t)}{V}$$ ← *Input j = LV infusion flow*

(4) $$\frac{dL}{dt} = \frac{k_2}{\xi}Q - k_3 L - k_4 BL$$ ← *Input i = 5-FU infusion flow*

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

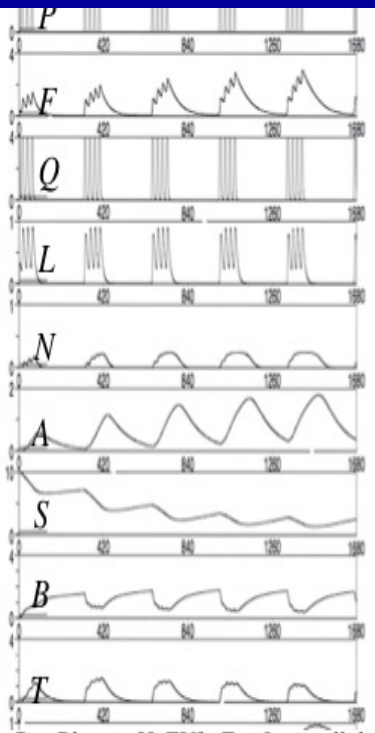
(6) $$\frac{dA}{dt} = \mu N - \nu A$$ ← *A = ABC transporter (active drug efflux)*

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

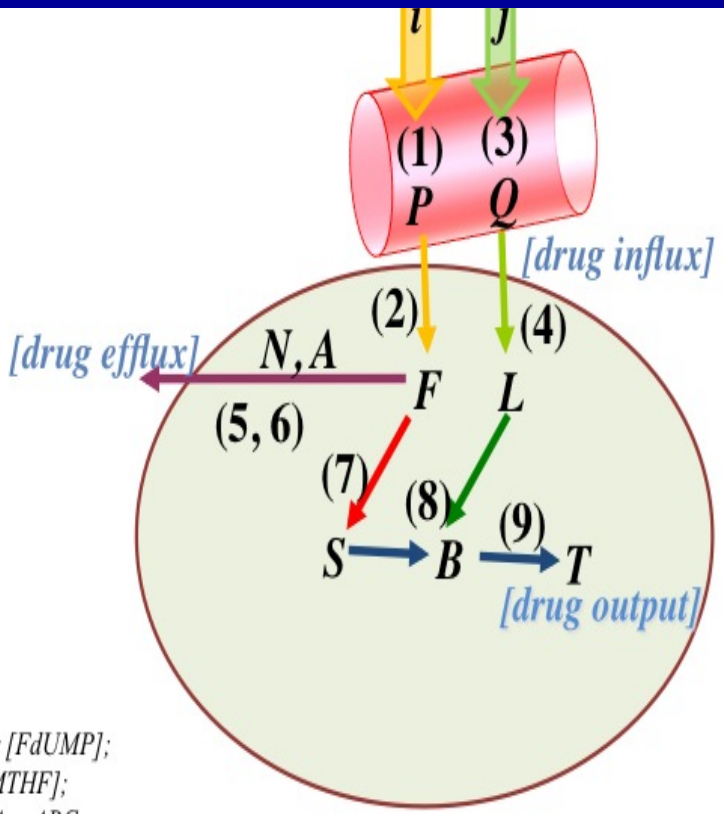
(8) $$\frac{dB}{dt} = k_1 FS - k_{-1}B - k_4 BL$$ ← *S = Free Thymidylate Synthase (TS)*

(9) $$\frac{dT}{dt} = k_4 BL - v_T T$$ ← *Drug output T = Blocked Thymidylate Synthase (stable ternary FdUMP-MTHF-TS complex)*

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



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;

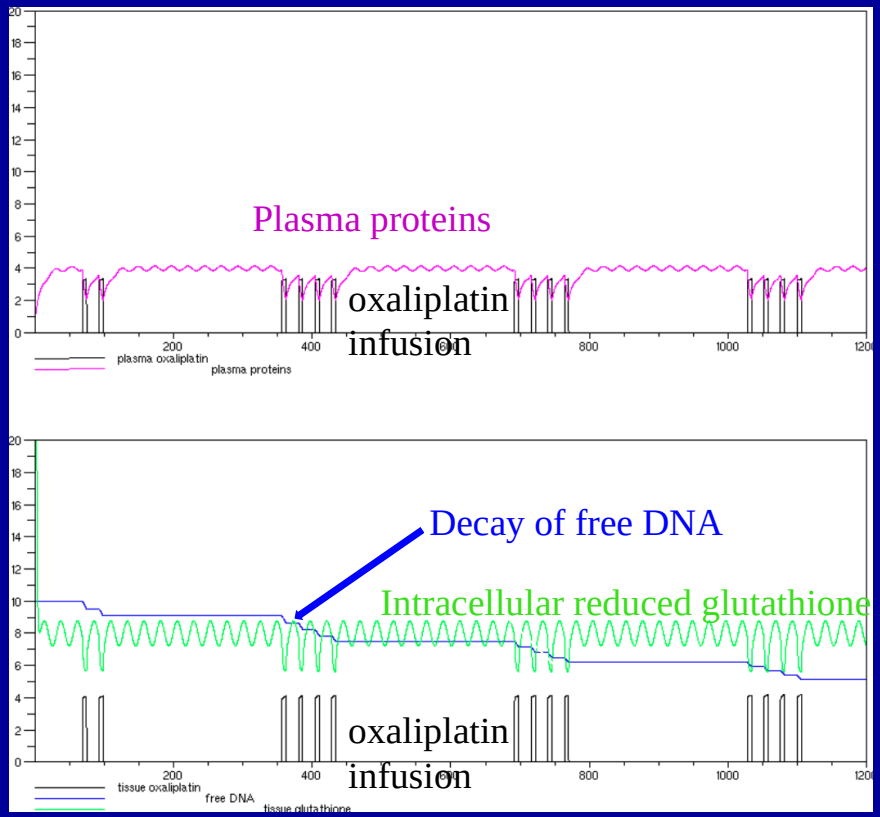


(F. Lévi, A. Okyar, S. Dulong, JC, Annu Rev Pharm Toxicol 2010)

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

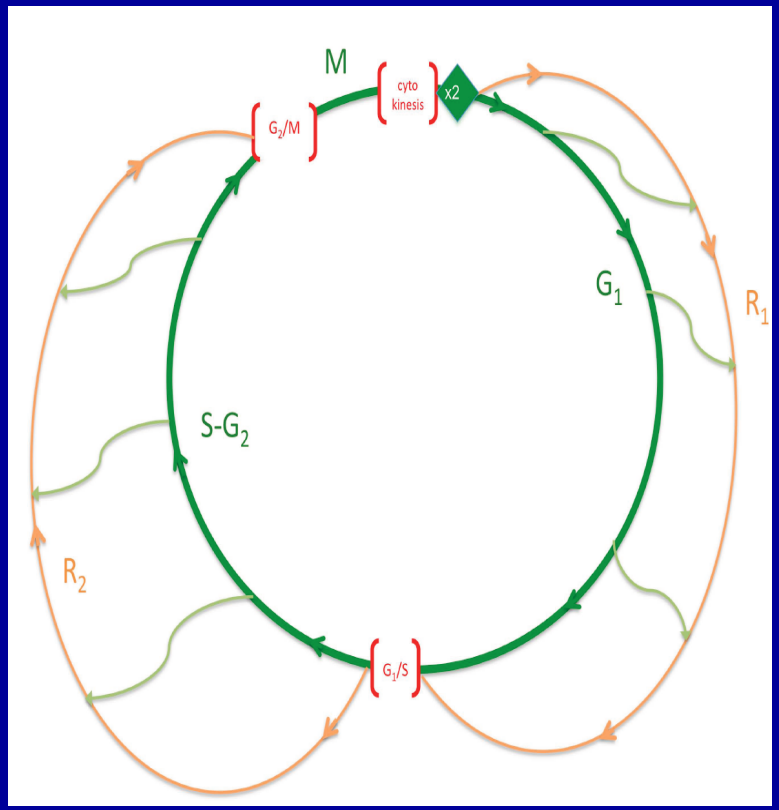
$$\begin{cases} \dfrac{dR}{dt} = -[\xi + cl + \lambda K]R + i(t) \\ \dfrac{dK}{dt} = -\lambda RK + \mu_K(K_0 - K) \\ \dfrac{dC}{dt} = -V_{GST}\dfrac{CG^2}{K_{GST}^2 + G^2} - k_{DNA}CF + \xi R \\ \dfrac{dF}{dt} = -k_{DNA}CF + \mu_F(Fo - F) \\ \dfrac{dG}{dt} = -V_{GST}\dfrac{CG^2}{K_{GST}^2 + G^2} + \mu_G(G_0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

Input i = *oxaliplatin infusion*



(JC, O. Fercoq, submitted as Springer book chapter, 2013)

Connecting molecular PK-PD with cell population dynamics: Introduction of PK-PD effects on death rates with repair



$$
\begin{cases}
\bullet\ \dfrac{\partial}{\partial t}n_1(t,x)+\dfrac{\partial}{\partial x}n_1(t,x)+\{K_1(t,x)+L_1(t)+d_1\}\,n_1(t,x)-\varepsilon_1 r_1(t,x)=0\ , \\
\dfrac{\partial}{\partial t}r_1(t,x)+\{d_{\kappa\tau 1}+\varepsilon_1\}r_1(t,x)-L_1(t)n_1(t,x)=0\ , \\
n_1(t,x=0)=2n_3(x_M,t)\ ,n_1(0,x)=v_1(x)\ ,r_1(0,x)=\rho_1(x)\ , \\
\text{with } L_1(t)=C_1\dfrac{F_0-F(t)}{F_0} \text{ and } K_1(t,x)=\kappa_1(x)\psi_1(t,x)\ , \\
\bullet\ \dfrac{\partial}{\partial t}n_2(t,x)+\dfrac{\partial}{\partial x}n_2(t,x)+\{K_2(t,x)+L_2(t)+d_2\}\,n_2(t,x)-\varepsilon_2 r_2(t,x)=0\ , \\
\dfrac{\partial}{\partial t}r_2(t,x)+\{d_{\kappa\tau 2}+\varepsilon_2\}r_2(t,x)-L_2(t)n_2(t,x)=0\ , \\
n_2(t,x=0)=\displaystyle\int_{\xi\geq 0}K_1(t,\xi)n_1(\xi,t)\,d\xi\ ,n_2(0,x)=v_2(x)\ ,r_2(0,x)=\rho_2(x)\ , \\
\text{with } L_2(t)=C_2\dfrac{F_0-F(t)}{F_0}+C_2'\dfrac{S_0-S(t)}{S_0} \text{ and } K_2(t,x)=\kappa_2(x)\psi_2(t)\ , \\
\bullet\ \dfrac{\partial}{\partial t}n_3(t,x)+\dfrac{\partial}{\partial x}n_3(t,x)+M.\mathbb{1}_{[x_M,+\infty[}(x)\,n_3(t,x)=0\ , \\
n_3(t,x=0)=\displaystyle\int_{\xi\geq 0}K_2(t,\xi)n_2(t,\xi)\,d\xi\ ,\ ,n_3(0,x)=v_3(x)\ .
\end{cases}
$$

(JC, O. Fercoq, submitted as Springer book chapter, 2013)

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

Solution to the chronotherapeutic combined drug delivery optimisation problem

Here, only cytotoxic drugs acting on death rates

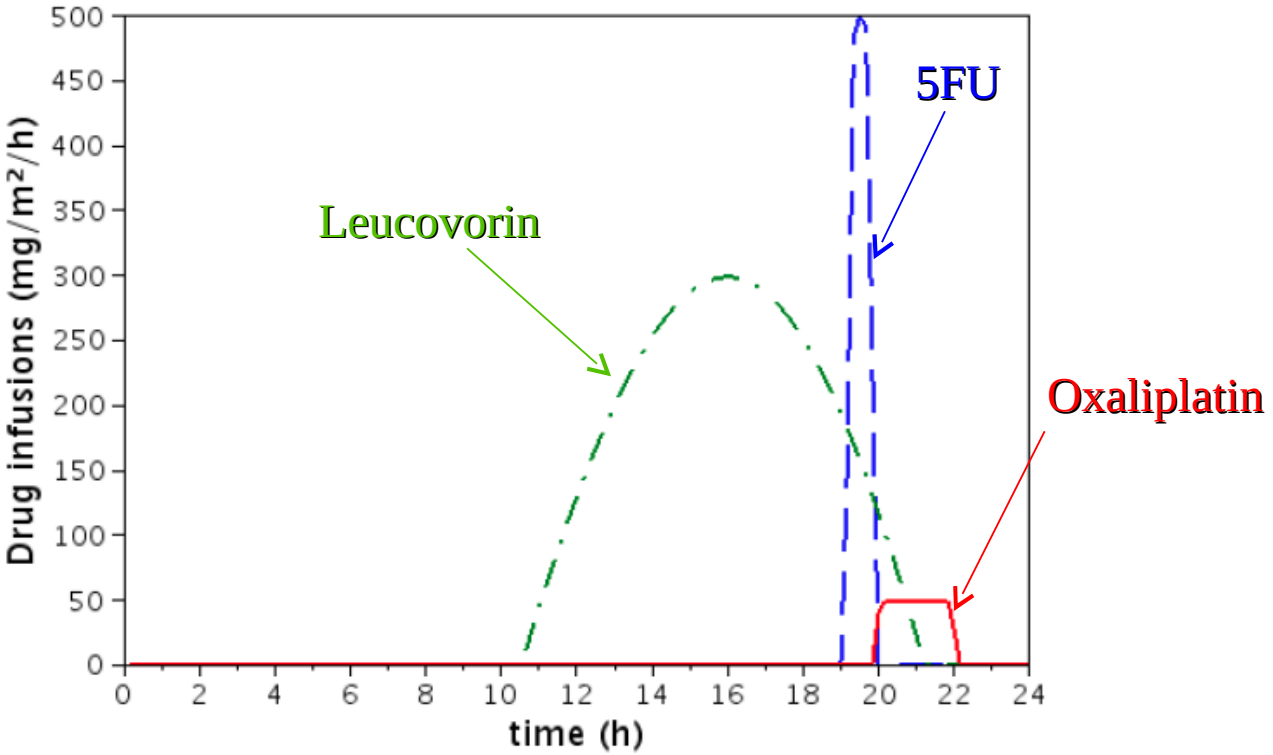


Fig. 6 Locally optimal infusion strategy with a combination of leucovorin (dash-dotted line), 5-FU (dotted line) and oxaliplatin (solid line). These infusions are repeated every day in order to minimise the growth rate of the cancer cell population while maintaining the growth rate of the healthy cell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

(JC, O. Fercoq, submitted as Springer book chapter, 2013)

Effects of this optimised periodic drug delivery regimen on growth rates

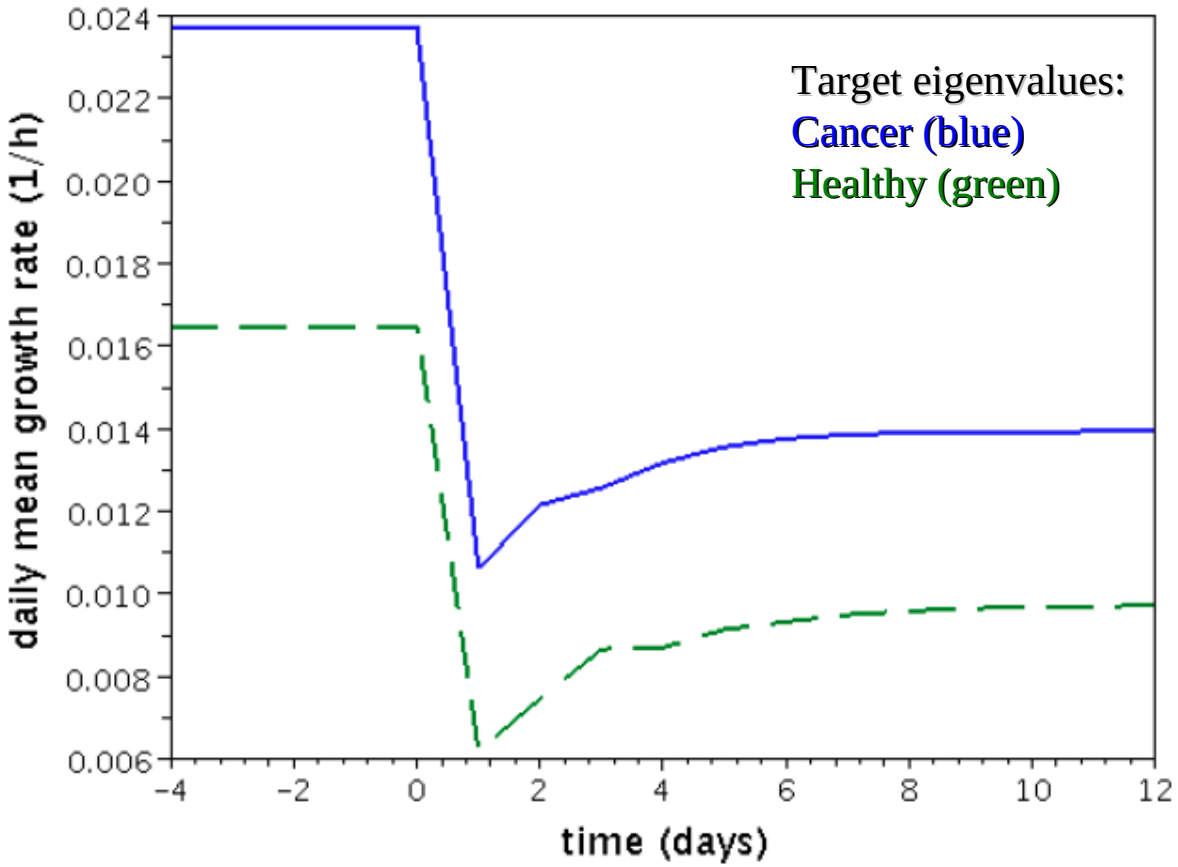


Fig. 11 Daily mean growth rates for cancer (solid line) and healthy cells (dashed line) when starting drug infusions at time 0. After a 10-day transitional phase, the biological system stabilises towards the expected asymptotic growth rate.

(JC, O. Fercoq, submitted as Springer book chapter, 2013)

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

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

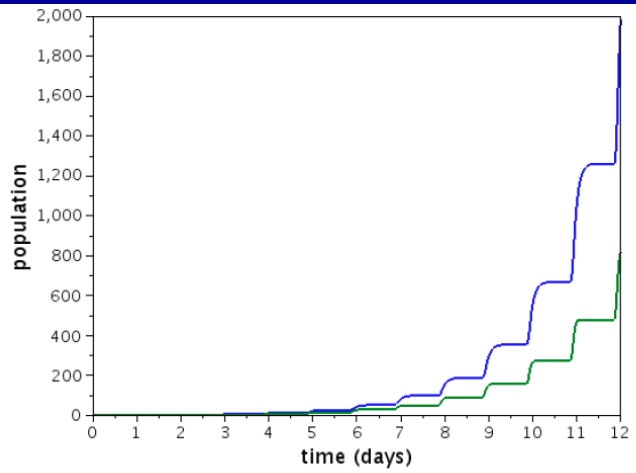


Fig. 7 Evolution of the population of cancer (blue, above) and healthy (green, beneath) cells without drug infusion during 12 days. We can see that the populations have different exponential growth rates ($\lambda_{cancer} = 0.0265$ and $\lambda_{healthy} = 0.0234$). Cancer cells proliferate faster than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

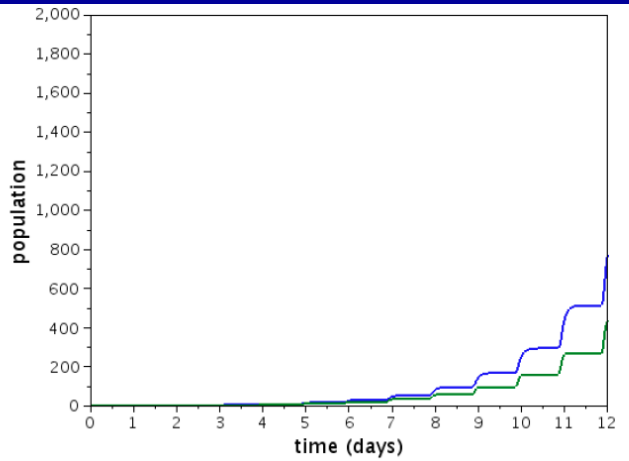
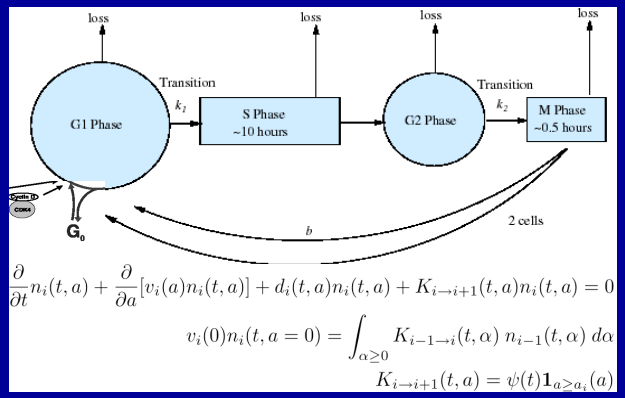


Fig. 8 Evolution of the population of cancer (blue, above) and healthy (green, beneath) cells with the drug infusion, starting at time 0, given by the algorithm. Healthy cells keep multiplying ($\lambda_{healthy} = 0.021$) while the cancer cell population is weakened ($\lambda_{cancer} = 0.0229$).

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, submitted as Springer book chapter, 2013)

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



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

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

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

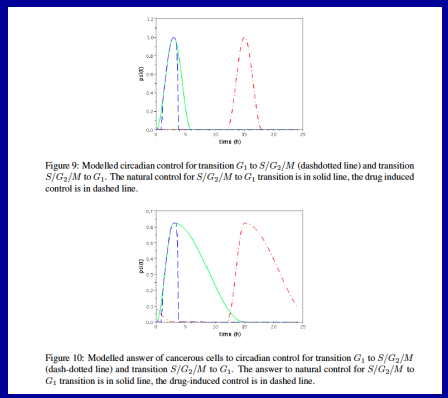


Figure 9: Modelled circadian control for transition G_1 to $S/G_2/M$ (dashdotted line) and transition $S/G_2/M$ to G_1. The natural control for $S/G_2/M$ to G_1 transition is in solid line, the drug induced control is in dashed line.

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 (experimentally measurable)**

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

New mitosis term

(not done thus far, waitinng for PK-PD of cytostatics...)

Tackling another 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 perspective.*

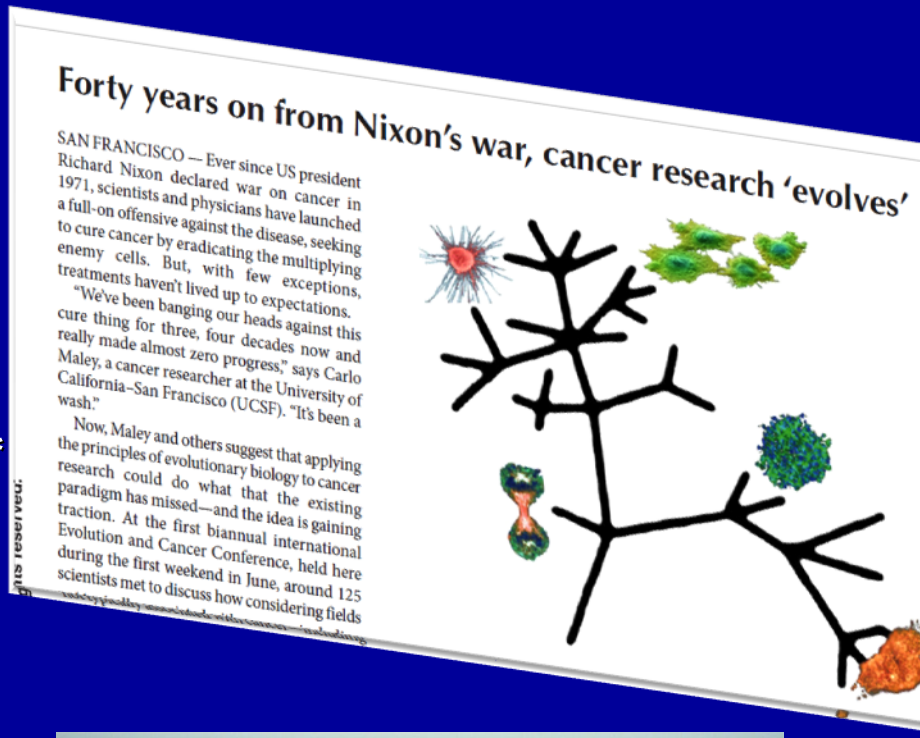
Assumption: Cancer cell populations, under the pressure of a drug-enriched environment, may develop (costly) mutations yielding resistant cell clones, less fit in a drug-free environment, but better survivors in a hostile environment.

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, next one 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

A first model with 'resistance phenotype expression' structure

x ($0 \leq x < +\infty$): a resistance phenotype level (e.g., activity of an ABC transporter)

The growth dynamics of healthy and tumor cells with a chemotherapy is given by the system

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

$$\frac{\partial}{\partial t} n_C(x,t) = \Big[(1-\theta_C)\, r(x) - d(x) - c(t)\mu_C(x) \Big] n_C(x,t) + \theta_C \int r(y) M_{\sigma_C}(y,x) n_C(y,t) dy, \tag{2}$$

and the total population is defined as

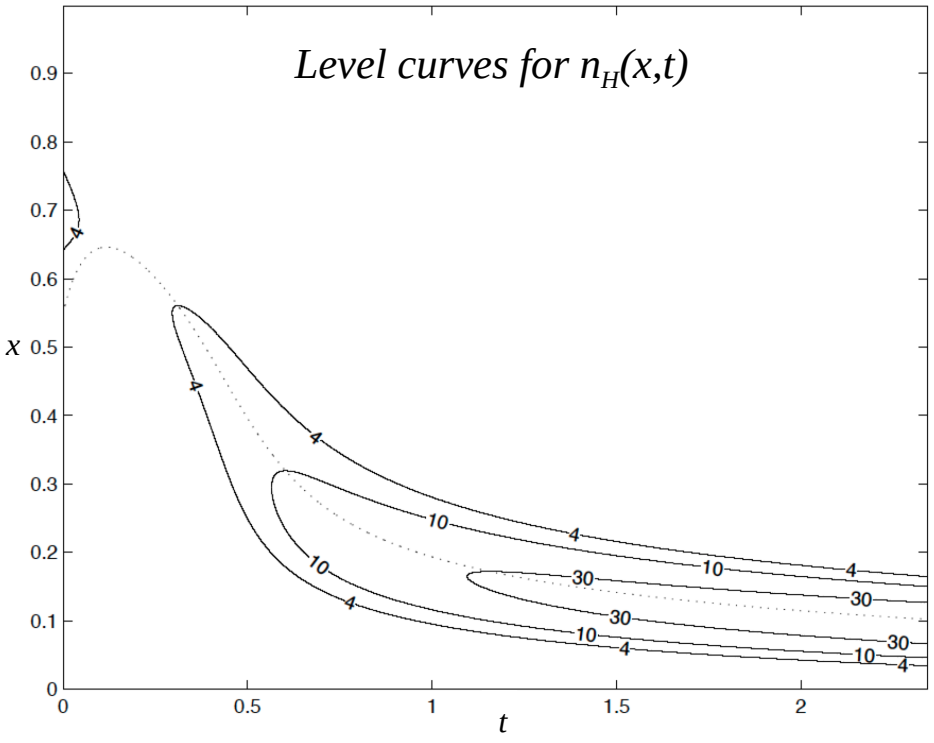
$$\rho(t) = \rho_H(t) + \rho_C(t), \qquad \rho_H(t) = \int_{x=0}^{\infty} n_H(x,t)dx, \quad \rho_C(t) = \int_{x=0}^{\infty} n_C(x,t)dx. \tag{3}$$

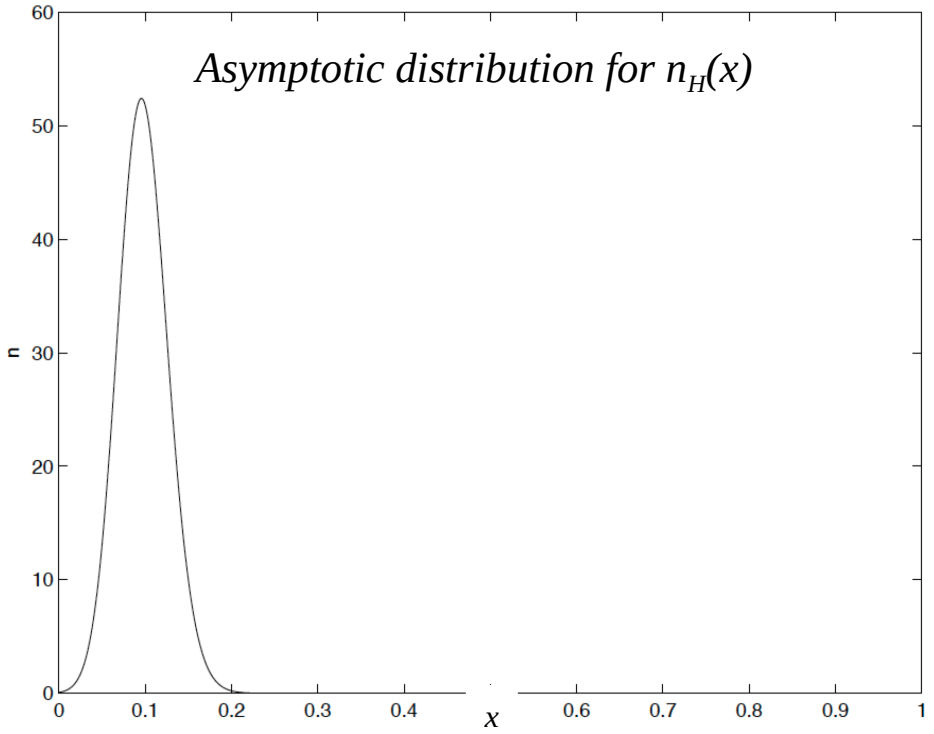
(A model that is still not able to yield gene polymorphism in cancer cells)

A. Lorz et al. M2AN 2013, preprint http://hal.archives-ouvertes.fr/hal-00714274

Probability distribution functions in cell populations for the resistant phenotype under the pressure of a drug

1. No resistance (healthy cells, or sensitive tumour cells)

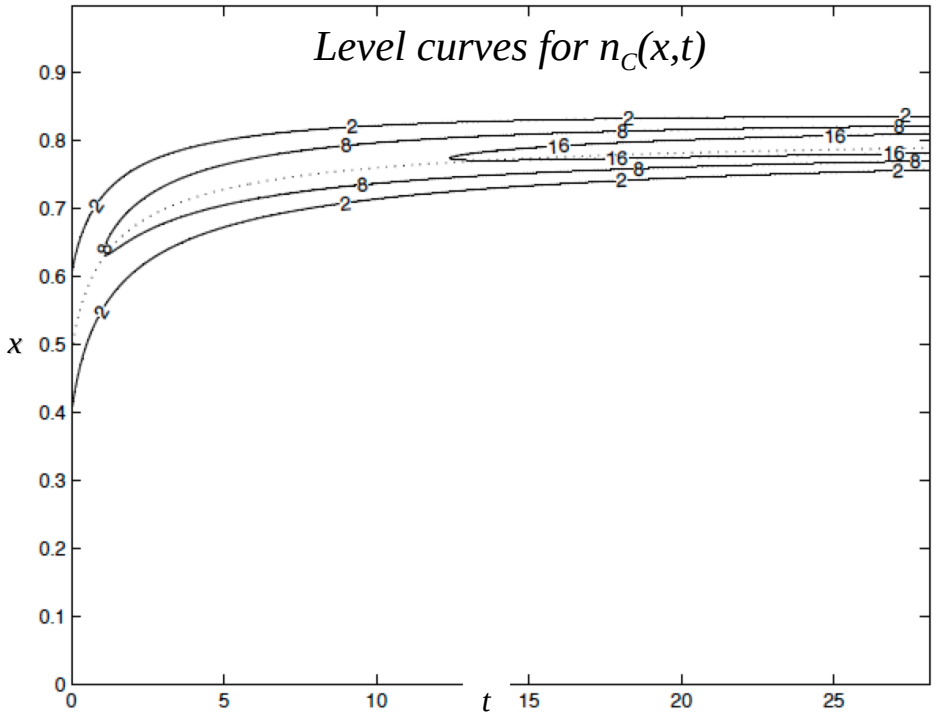


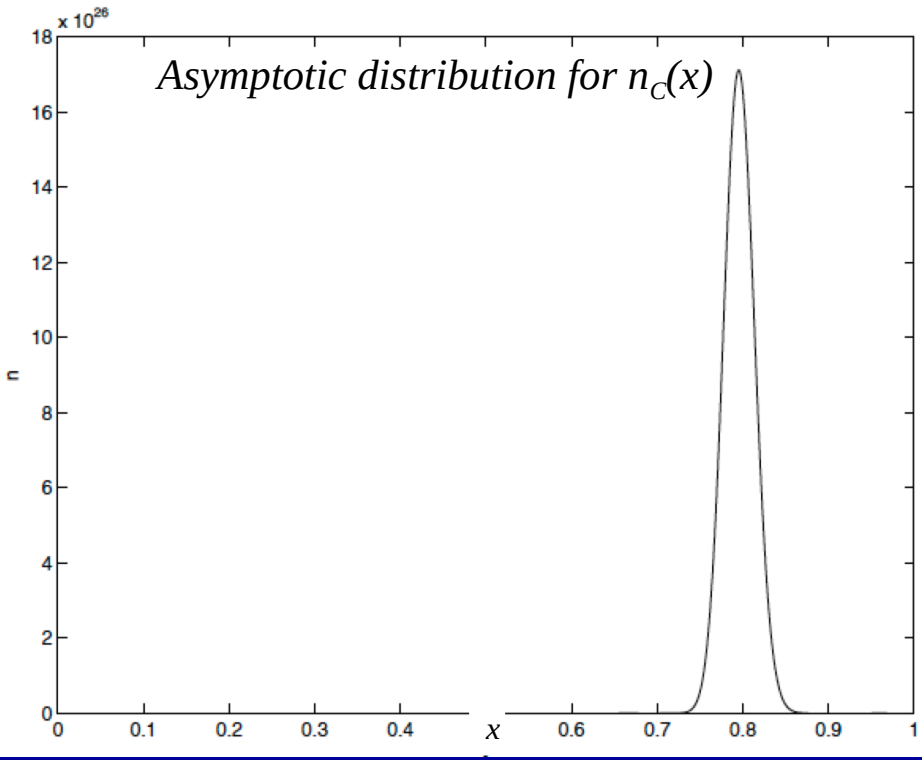


A. Lorz et al. M2AN 2013, preprint http://hal.archives-ouvertes.fr/hal-00714274

Probability distribution functions in cell populations for the resistant phenotype under the pressure of a drug

2. Resistance (in a drug-resistant tumour cell clone)





A. Lorz et al. M2AN 2013, preprint http://hal.archives-ouvertes.fr/hal-00714274

2nd point of view : two different drugs, cytotoxic and cytostatic, two resistance traits x and y,'no mutations, exchanges with the environment instead'

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

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

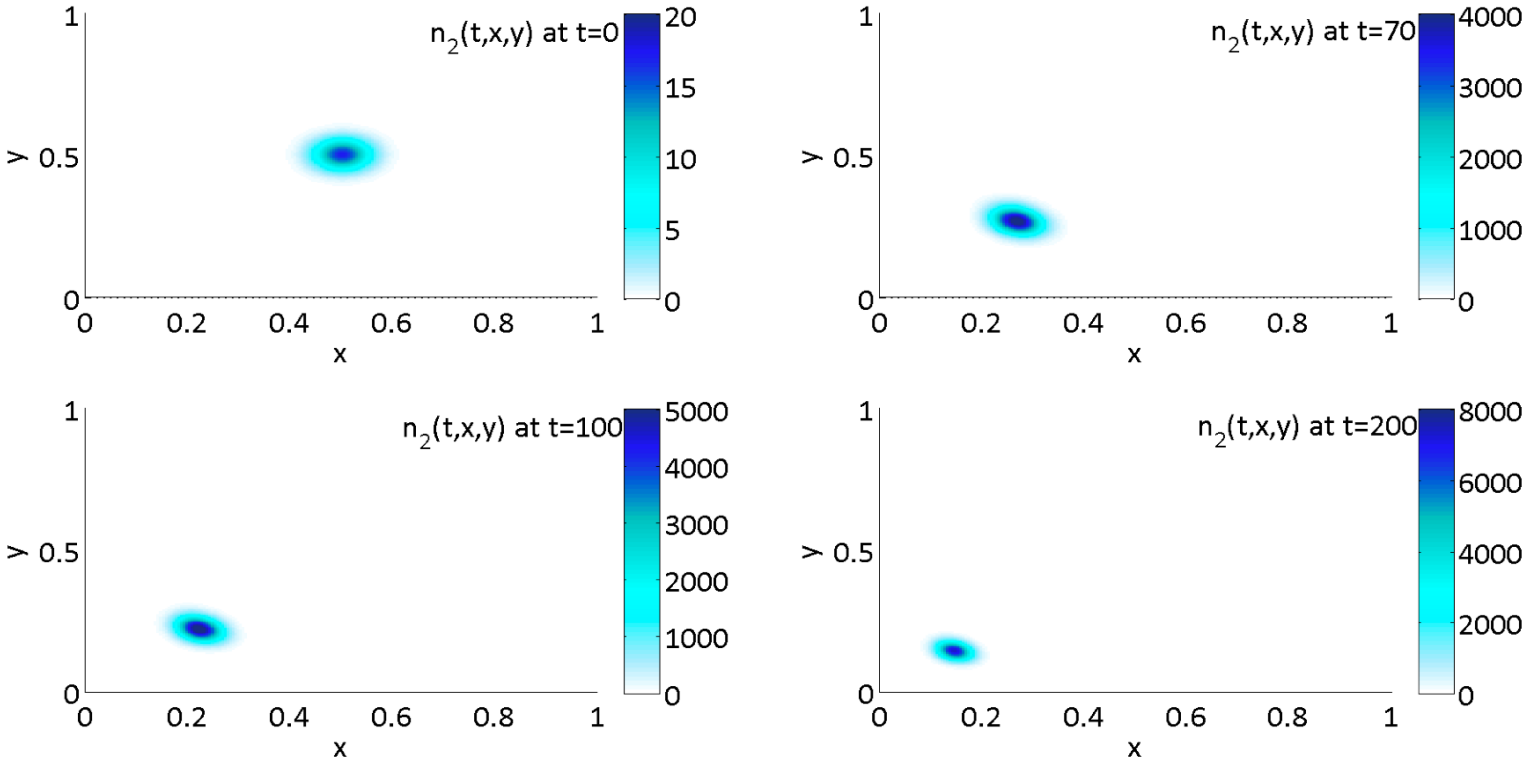
$$
r_C(x,y;c_P) := 4\left[1 + 2\frac{(1-\alpha_C c_P)}{1+(x^2+y^2)} + (1-x)^2y^2 + (1-y)^2x^2 - c_P(1-x)^4y^4\right],
$$

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

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 $\alpha_C = 2$.

Monomorphism in the healthy cell population

No mutations: non-resistant ('healthy') cells: starting from a common medium phenotype (cytotoxic res.=.5, cytostatic res.= .5), evolution towards the non-resistant (0,0) phenotype

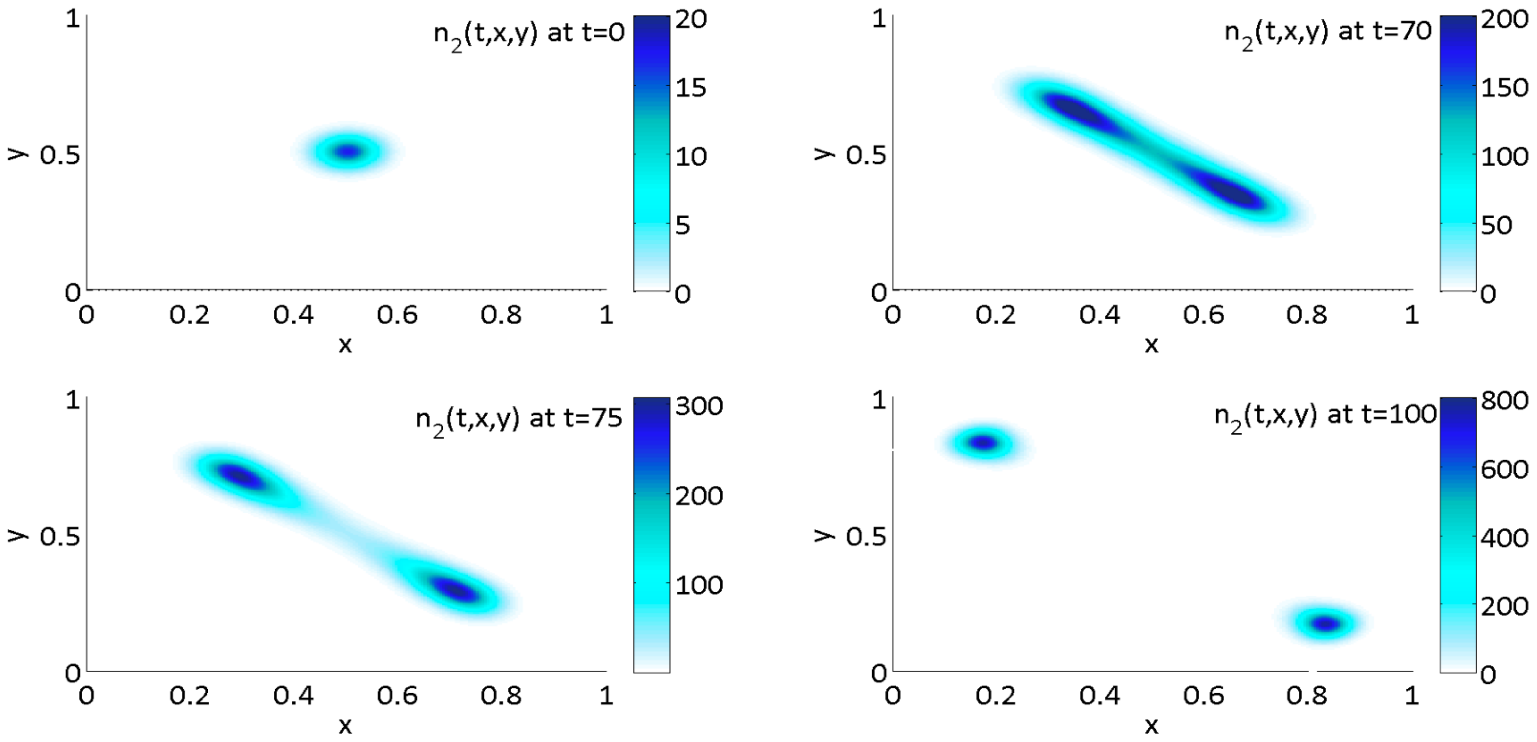


Model, simulations and figures by Tommaso Lorenzi

Dimorphism in the cancer cell population

No mutations: Resistant ('cancer') cells: starting from the same common medium phenotype

(5, 5): evolution towards 2 different resistant phenotypes: (1,0) and (0,1)



Model, simulations and figures by Tommaso Lorenzi

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

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

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

(Alexander Lorz and Tommaso Lorenzi)

Cancer cells

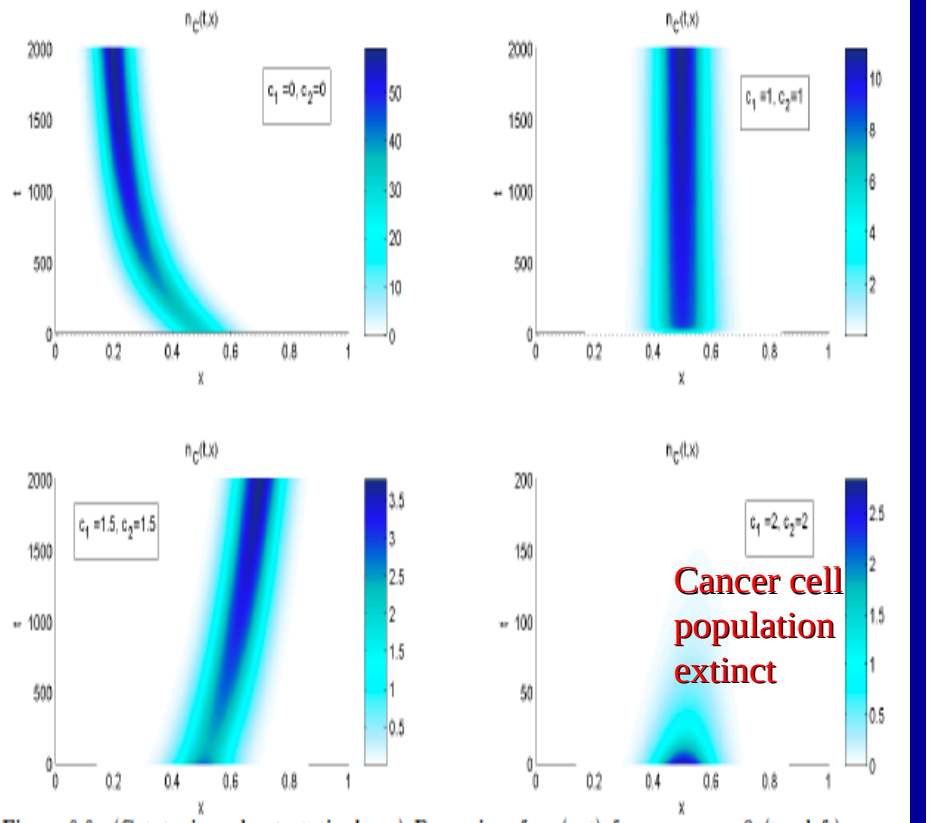


Figure 6.6: (Cytotoxic and cytostatic drugs) Dynamics of $n_C(x,t)$ for $c_1 = c_2 = 0$ (top-left), $c_1 = c_2 = 1$ (top-right), $c_1 = c_2 = 1.5$ (bottom-left) and $c_1 = c_2 = 2$ (bottom-right). As long as parameters c_1 and c_2 increase, the maximum value of $n_C(t = 2000, x)$ becomes smaller so that,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

Healthy cells

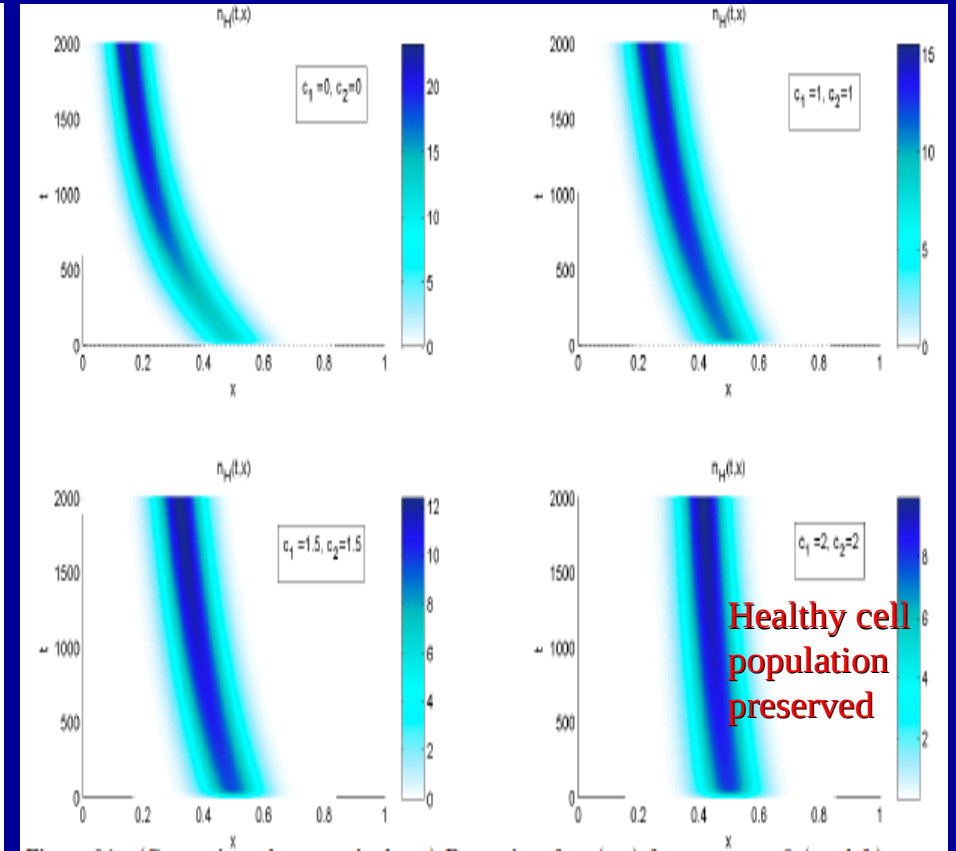


Figure 6.7: (Cytotoxic and cytostatic drugs) Dynamics of $n_H(x,t)$ for $c_1 = c_2 = 0$ (top-left), $c_1 = c_2 = 1$ (top-right), $c_1 = c_2 = 1.5$ (bottom-left) and $c_1 = c_2 = 2$ (bottom-right). As long as parameters c_1 and c_2 increase, the maximum value of $n_H(t = 2000, x)$ becomes smaller but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

A. Lorz et al. M2AN 2013, preprint http://hal.archives-ouvertes.fr/hal-00714274

Collaborators

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INSERM U 776 “Biological Rhythms and Cancers” (*Francis Lévi*, Villejuif):
Solid tumours, of Mice and Men (particularly colorectal cancer)

Université Paris-Nord (*Claude Basdevant*): optimisation algorithms

EU Network ERASysBio+ C5Sys *Circadian and cell cycle clock systems in cancer*
http://www.erasysbio.net/index.php?index=272
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