

Giving medical sense to mathematical modelling of cell proliferation and its control

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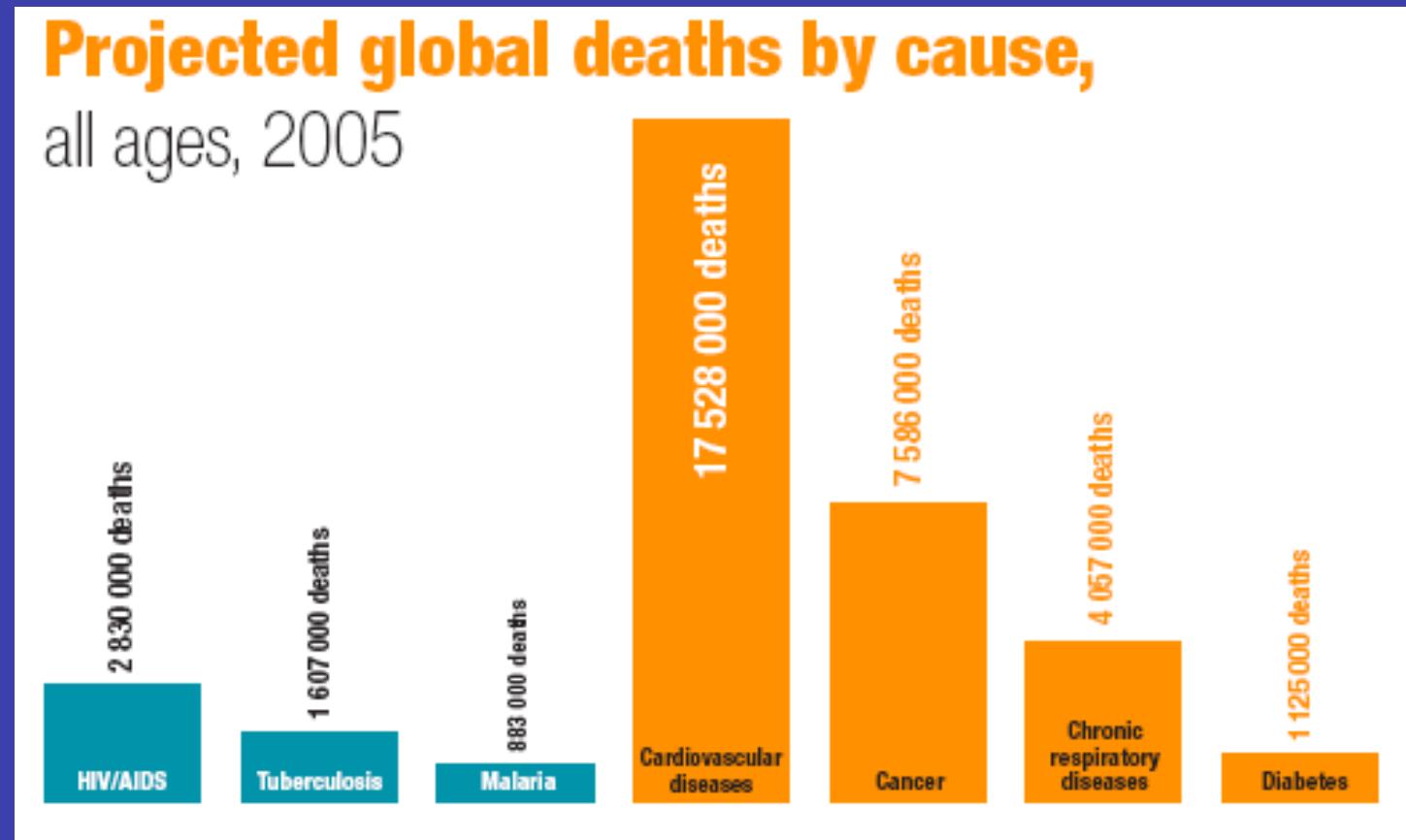
http://www-c.inria.fr/bang/JC/Jean_Clairambault.html

Outline of the talk

- A few public health data on cancer
 - Modelling cell proliferation and its control mechanisms
 - Modelling the circadian system and its disruptions
 - Modelling (circadian) pharmacokinetics-pharmacodynamics (PK-PD) ...at the molecular level
 - Future prospects: toward multitargeted multidrug delivery in a cellular systems biology environment

A few public health data about cancer

The 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

Major killer *non communicable* diseases in Europe

Table 1. Burden of disease and deaths from NCD in the WHO European Region, by cause (2005 estimates)

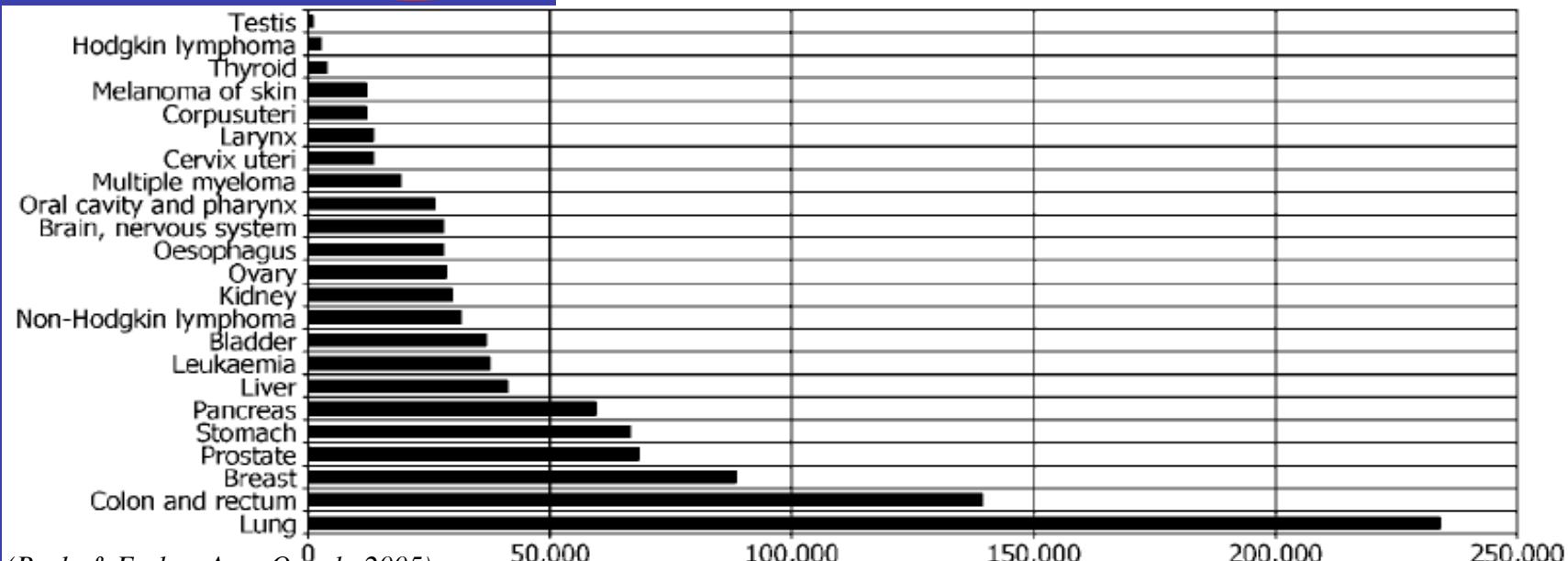
Group of causes (selected leading NCD)	Disease burden (DALYs ^a)(000s)	All causes (%)	Deaths (000s)	All causes (%)
Cardiovascular diseases	34421	23	5067	52
Neuropsychiatric conditions	29370	20	264	3
Cancer (malignant neoplasms)	17025	11	1855	19
Digestive diseases	7117	5	391	4
Respiratory diseases	6835	5	420	4
Sense organ disorders	6339	4	0	0
Musculoskeletal diseases	5745	4	26	0
Diabetes mellitus	2319	2	153	2
Oral conditions	1018	1	0	2
All NCD	115339	77	8210	86
All causes	150322		9564	

^aDALYs: disability-adjusted life years.

WHO source (2006): Fact sheet Euro/03/06

...among which *Cancers*:

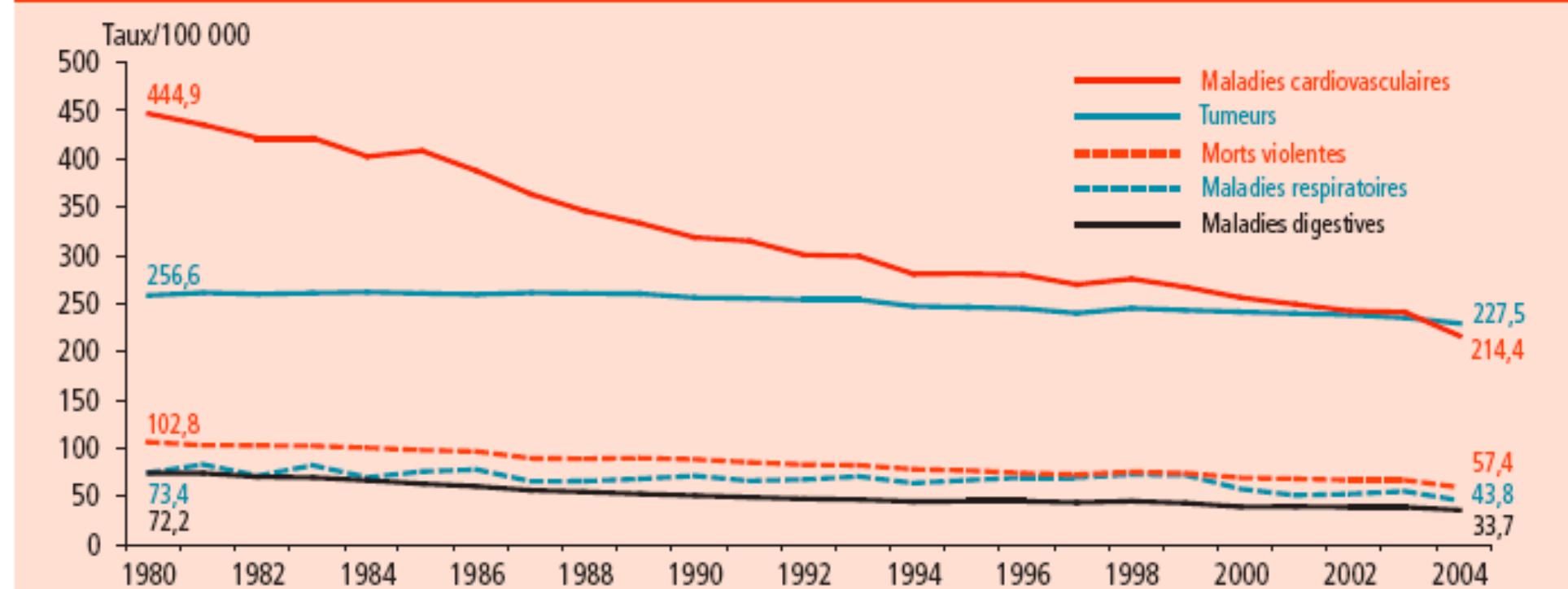
European Union (number of deaths, both sexes)



(Boyle & Ferlay, Ann. Oncol. 2005)

In France, cancer (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)

The same tendency is also true in the USA

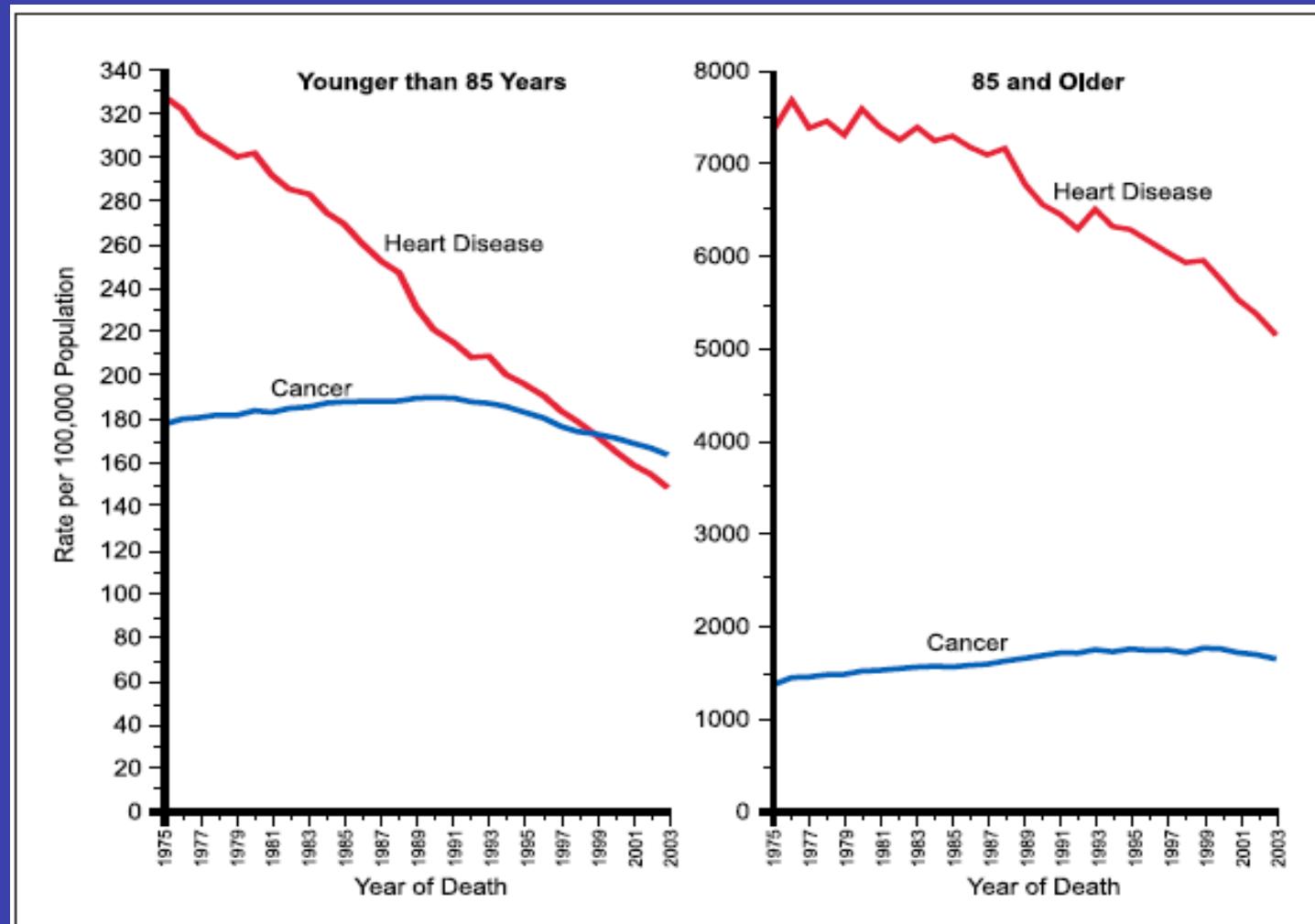


FIGURE 6 Death Rates* From Cancer and Heart Disease for Ages Younger Than 85 and 85 and Older.

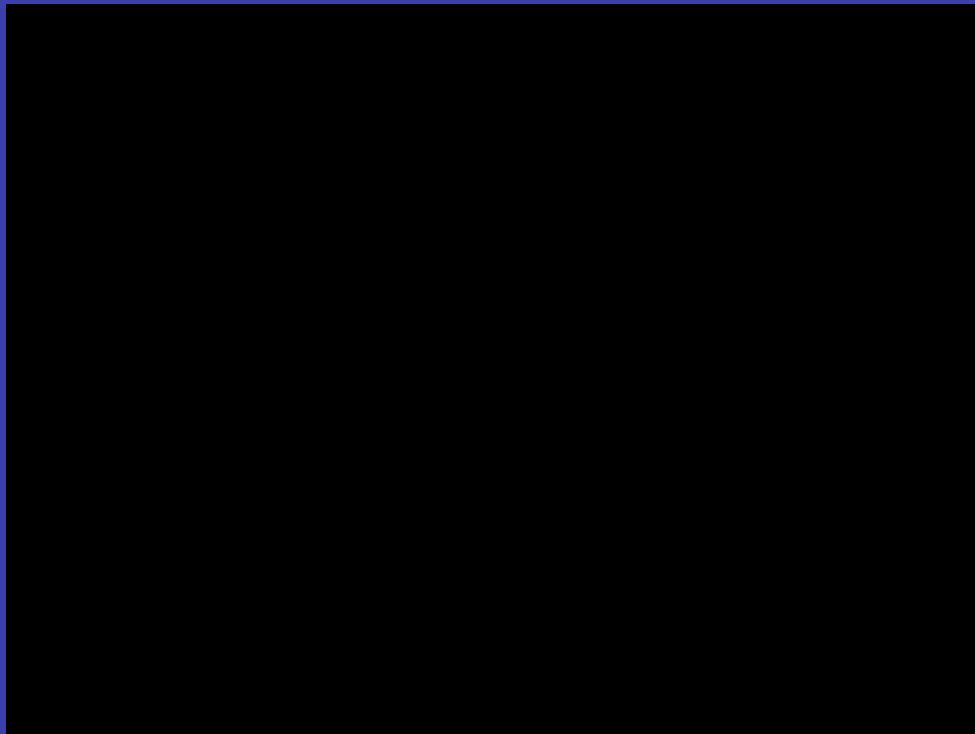
*Rates are age-adjusted to the 2000 US standard population.

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)

*Modelling cell proliferation
and its control mechanisms*

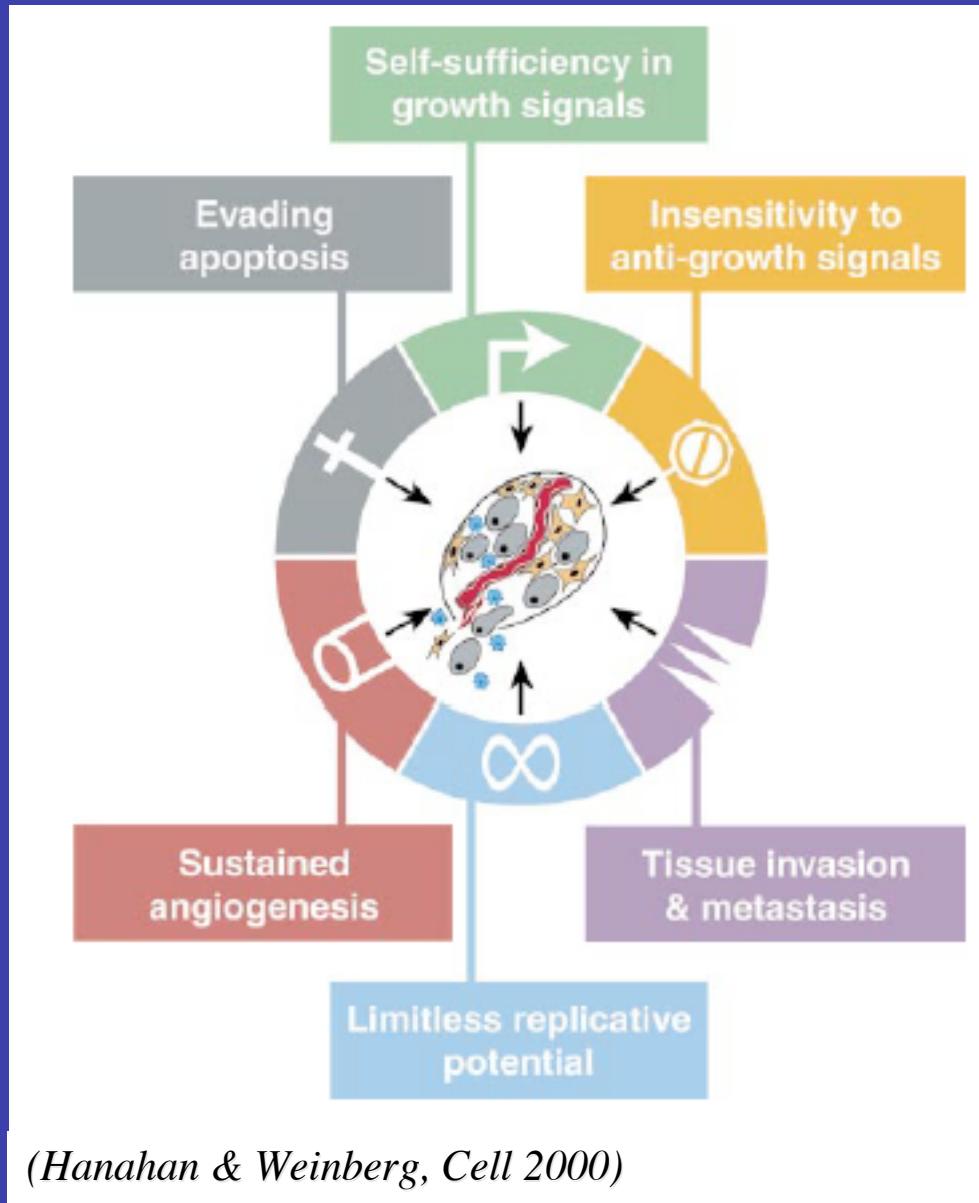
Cell population growth in proliferating tissues



(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 fast renewing tissues (gut, skin, bone marrow...) that is *disrupted in cancer*

Cancer: a cell proliferation control disease

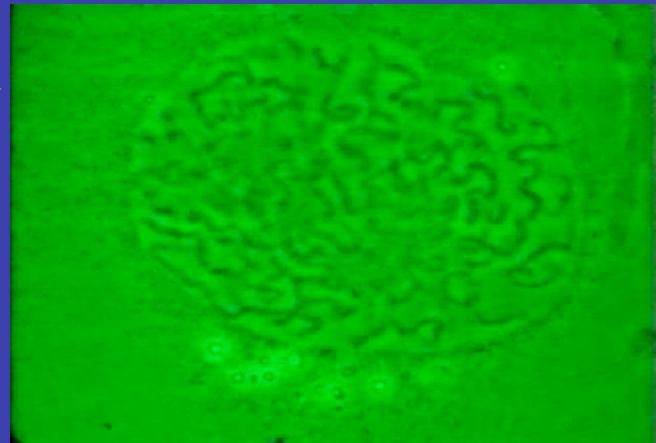
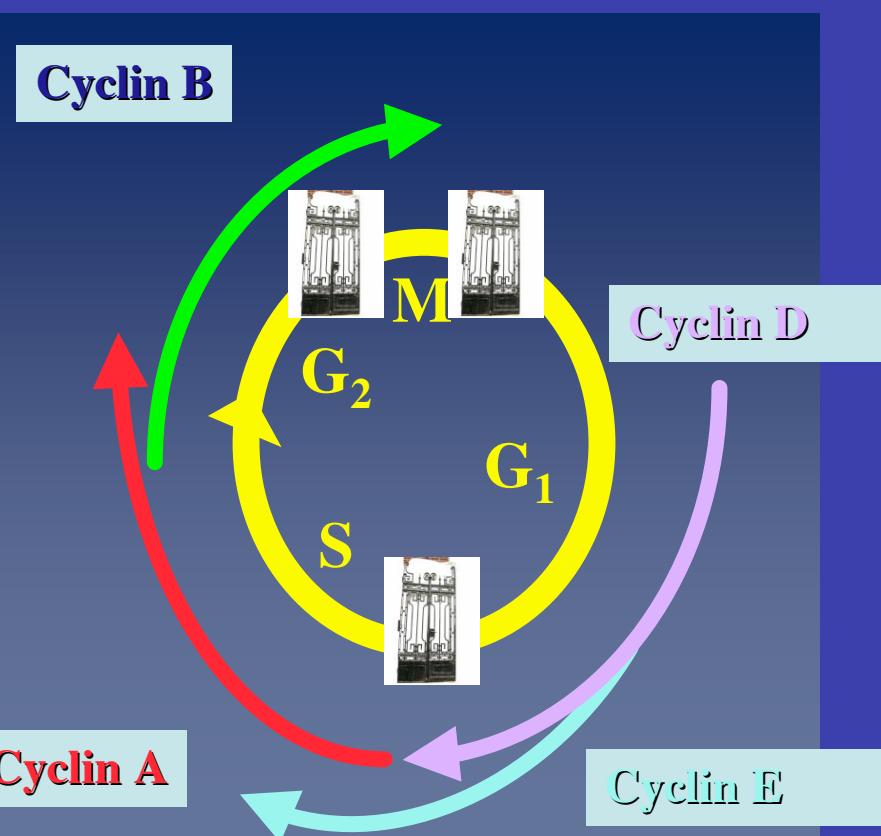


Gene mutations: an evolutionary process which may give rise to abnormal DNA when a cell duplicates its genome due to defects in tumour suppressor or DNA mismatch repair genes (*Yashiro, M et al. Canc Res. 2001; Gatenby, RA, Vincent, TL. Canc. Res. 2003*)

...but just what is cell proliferation?

At the origin of proliferation: the cell division cycle

S:=DNA synthesis; G₁,G₂:=Gap1,2; M:=mitosis ►



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

Physiological or therapeutic control exerted on:

- transitions (checkpoints) between phases (G₁/S, G₂/M, M/G₁)
- death rates (apoptosis or necrosis) inside phases
- exchanges between quiescent (G₀) and proliferative phases (G₁ only)

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

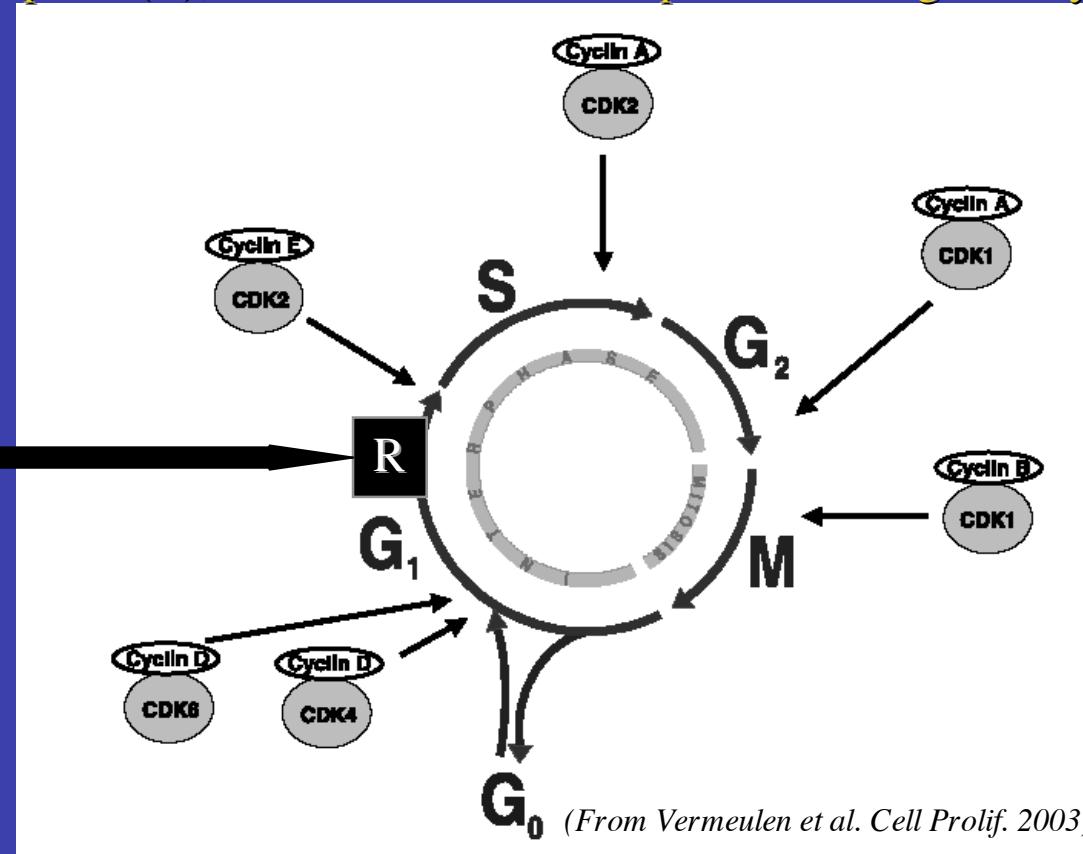
Before the restriction point (R), cells can transit from G_1 to G_0 and vice versa

After the restriction point (R), cells are committed to process through the cycle until division

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

Restriction point
(late G_1 phase)

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

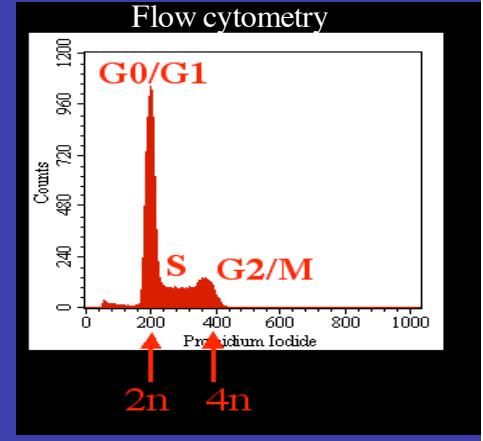
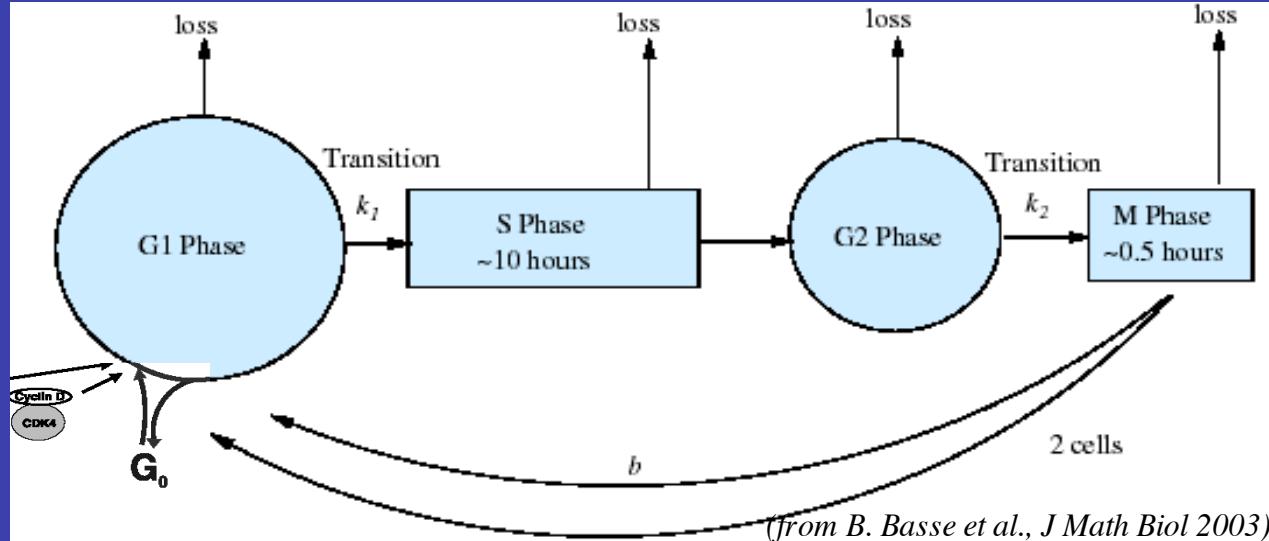


Most cells do not proliferate physiologically, even in fast renewing tissues

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

Modelling the cell division cycle in cell populations

Age-structured PDE models



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

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

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

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

n_i :=cell population density in phase i ;
 v_i :=progression speed;
 d_i :=death rate;
 $K_{i-1 \rightarrow i}$:=transition rate
 (with a factor 2 for $i=1$)
 $d_t, K_{i \rightarrow i+1}$ constant or periodic w. r. to time t
 $(1 \leq i \leq I, I+1=1)$

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

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

(Firstly presented in: JC, B. Laroche, S. Mischler, B. Perthame, RR INRIA #4892, 2003)

The simplest case: 1-phase model with division

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

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

where $K(t, a) = K_0 \psi(t) \mathbb{1}_{[a^*, +\infty[}(a)$
 and $\psi(t) = \mathbb{1}_{[0, \tau[}(t)$, 1-periodic

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

Then it can be shown that the eigenvalue problem: $n(t, a) = e^{\lambda t} N(t, a)$

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

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

has a unique positive 1-periodic eigenvector N , with a positive eigenvalue λ and an explicit formula can be found for λ when $K_0 \rightarrow +\infty$ (T. Lepoutre's PhD work)

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 $\tilde{N}_i(t, a) = e^{-\lambda t} n_i(t, a)$, N_i , bounded solutions to the problem (here $v_i(a)=1$):

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

with functions $\rho_i(a)$ such that the asymptotics of $\tilde{N}_i(t, a) = e^{-\lambda t} n_i(t, a)$ follow:

$$\int_{\alpha \geq 0} |\tilde{N}_i(t, \alpha) - \rho_i(\alpha) N_i(t, \alpha)| \varphi_i(t, \alpha) d\alpha \rightarrow 0 \quad \text{as } t \rightarrow \infty$$

the 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 $K_{i \rightarrow i+1}$) is constant, or if it is periodic, so are the N_i , with the same period in the periodic case.

[Hence, for the same N_i to be solutions, the higher the d_i , the lower the λ]

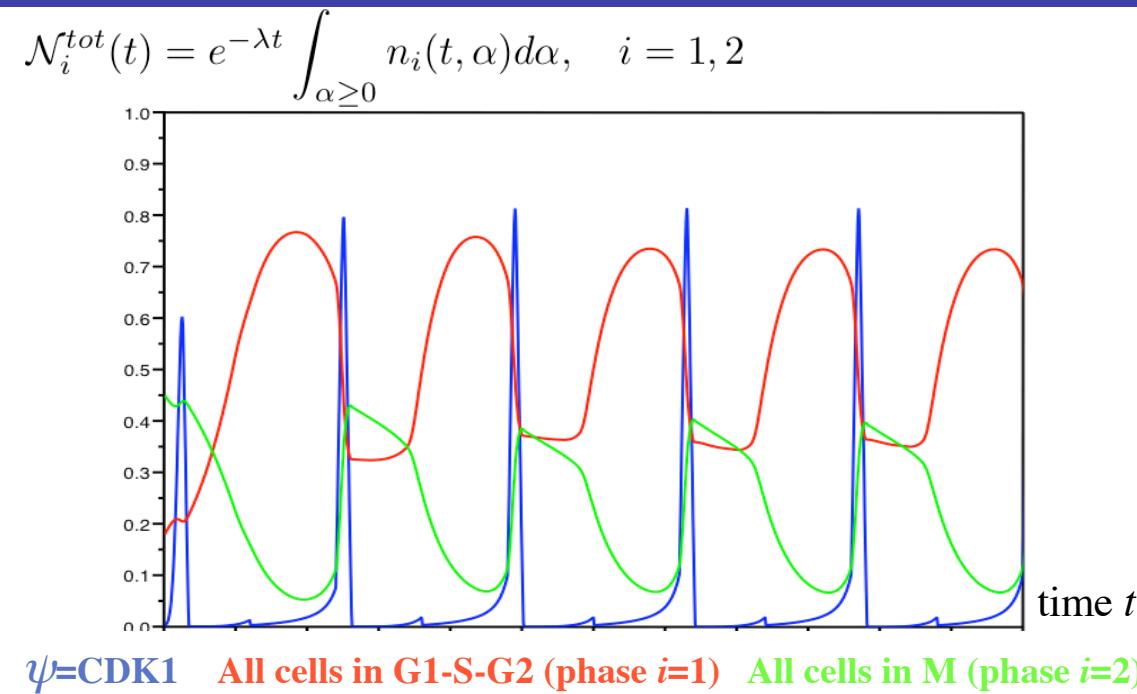
Ph. Michel, S. Mischler, B. Perthame, C. R. Acad. Sci. Paris Ser. I (Math.) 2004; J Math Pures Appl 2005

JC, Ph. Michel, B. Perthame, C. R. Acad. Sci. Paris Ser. I (Math.) 2006; Proc. ECMTB Dresden 2005, Birkhäuser 2007

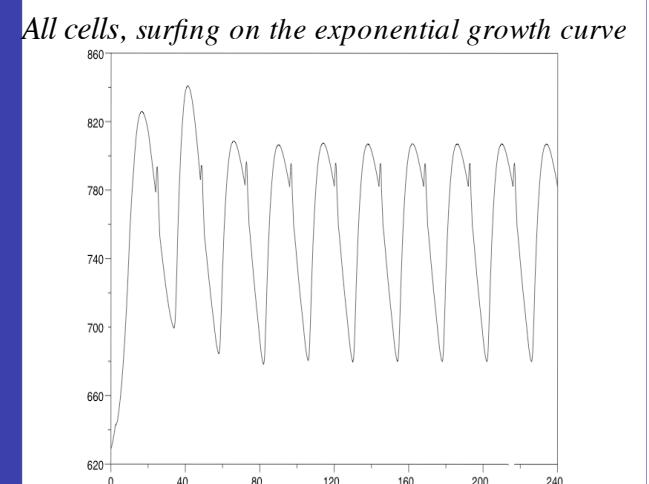
To sum up: a growth exponent for the cell population

Proof of the existence of a unique growth exponent λ , the same for all phases i , such that the $\tilde{N}_i(t, a) = e^{-\lambda t} n_i(t, a)$ are asymptotically (i.e., for large times) bounded, and asymptotically periodic if the control is periodic

Surfing on the exponential growth curve, example (periodic control case): 2 phases, control on G₂/M transition by 24-h-periodic CDK1-Cyclin B (A. Goldbeter's model)

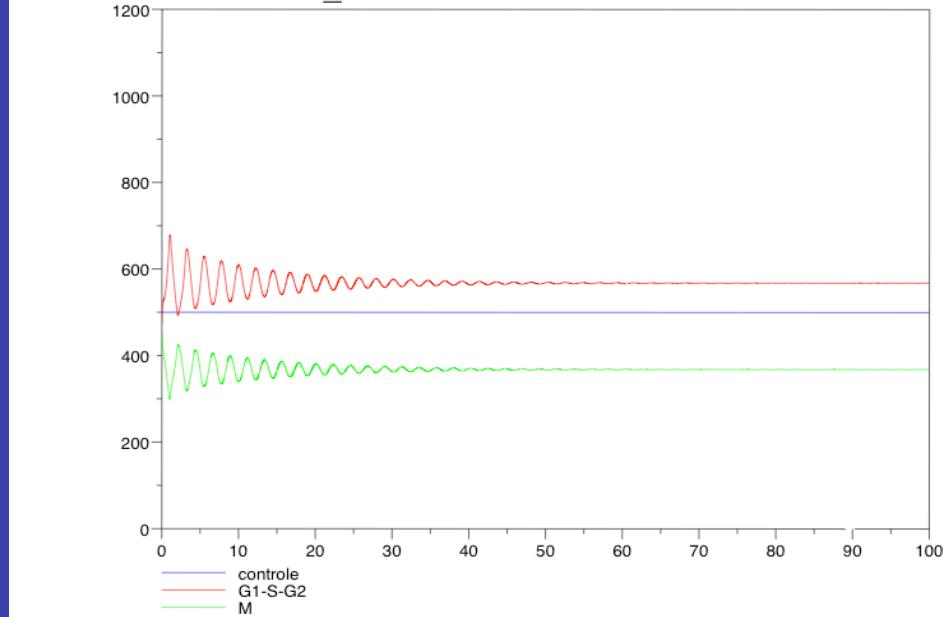


Entrainment of the cell division cycle by CDK1 at the circadian period



Details (1): 2 phases, no control on G₂/M transition

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

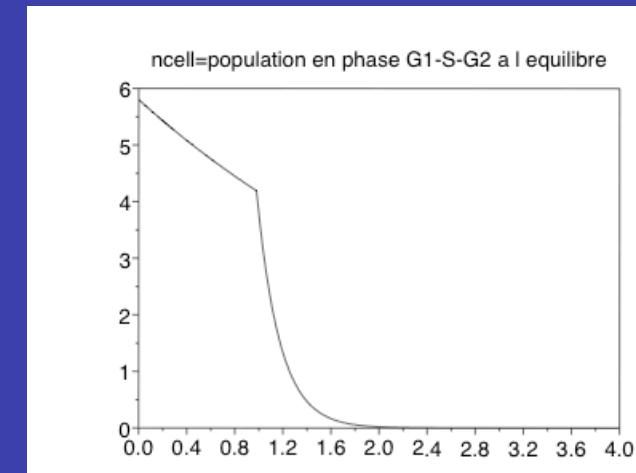


The total population of cells

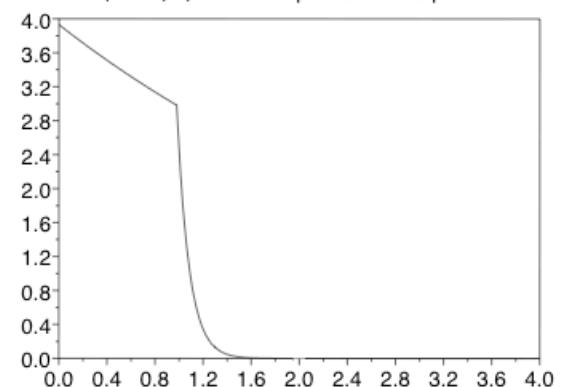
$$\int_{\alpha > 0} n_i(t, \alpha) d\alpha, \quad i = 1, 2$$

inside each phase follows asymptotically an exponential behaviour

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

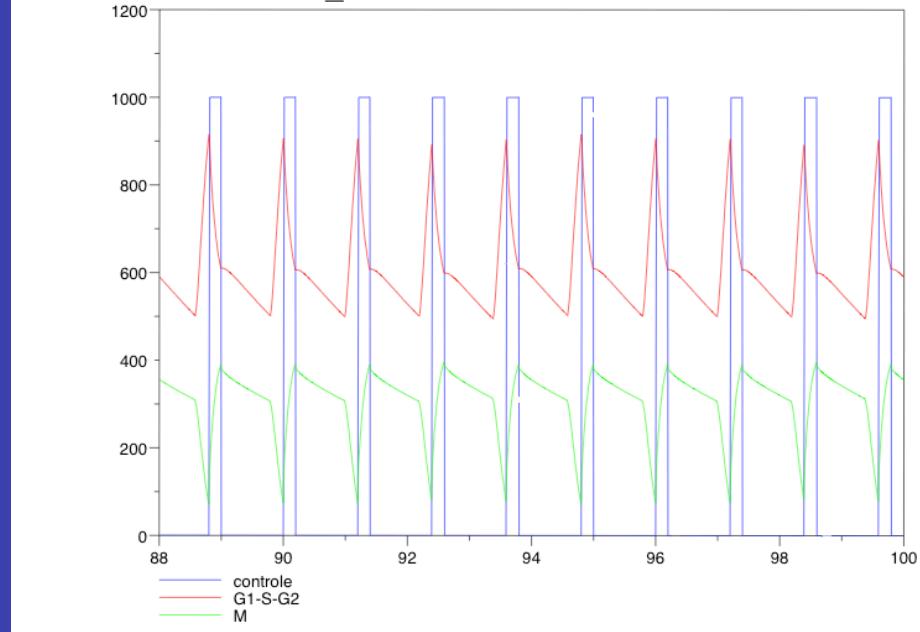


pcell=population en phase M a l equilibre



Details (2): 2 phases, periodic control ψ on G₂/M transition

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

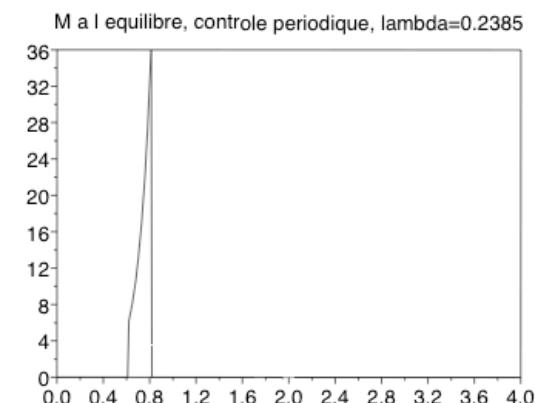
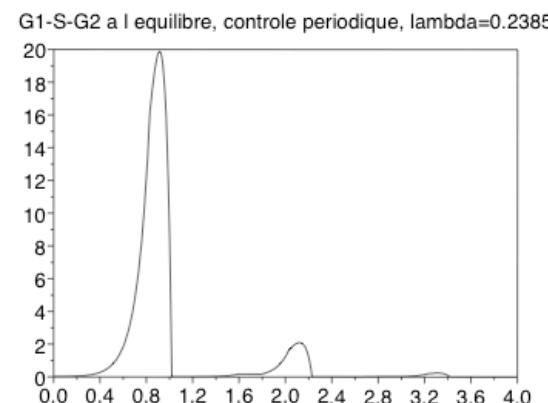


The total population of cells

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

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

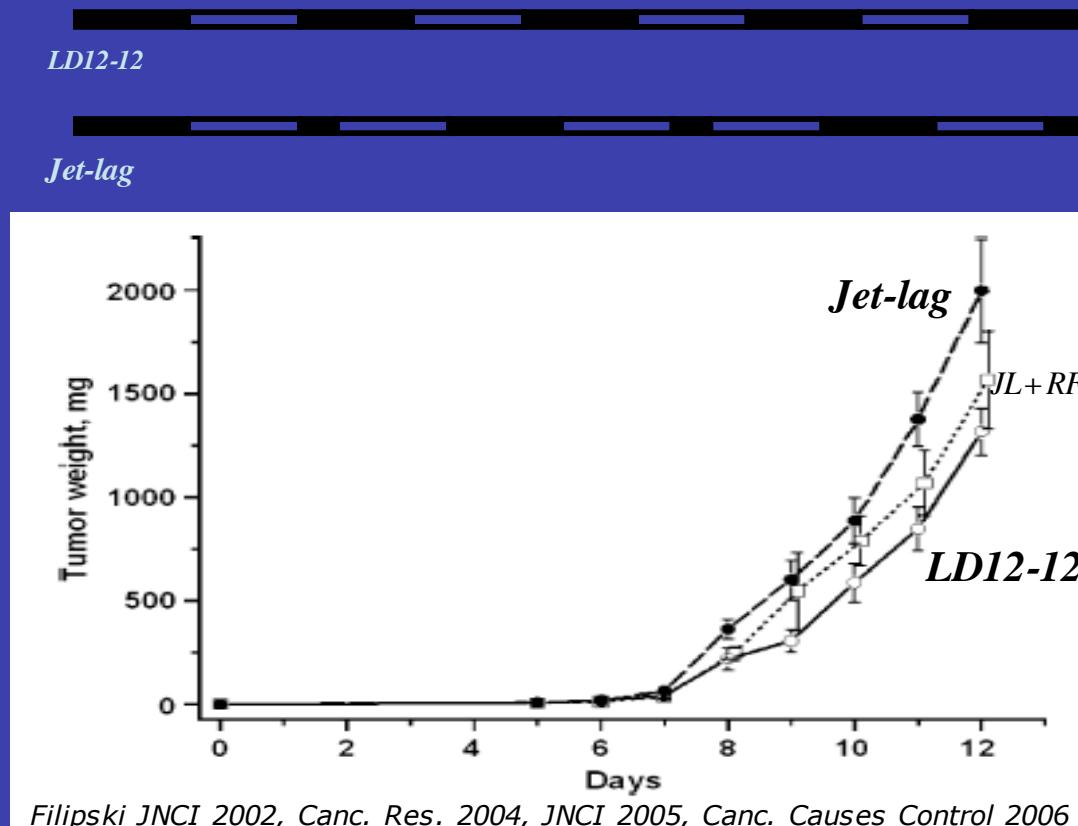
Stationary state distribution of cells inside phases according to age a : *sharp periodic control ->sharp rise and decay*



Circadian rhythms, cancer growth and cancer chronotherapeutics

1) A question from animal physiopathology: tumour growth and circadian clock disruption

Observation: a circadian rhythm perturbation by chronic jet-lag-like light entrainment (phase advance) enhances GOS tumour proliferation in B6D2F₁ mice



Filipski JNCI 2002, Canc. Res. 2004, JNCI 2005, Canc. Causes Control 2006

Here, clearly:
 $\lambda(\text{Jet-lag}) > \lambda(\text{LD 12-12})$
if λ is a growth exponent

How can this be accounted for in a mathematical model of tumour growth?
Major public health stake! (does shift work enhance the incidence of cancer in Man?)

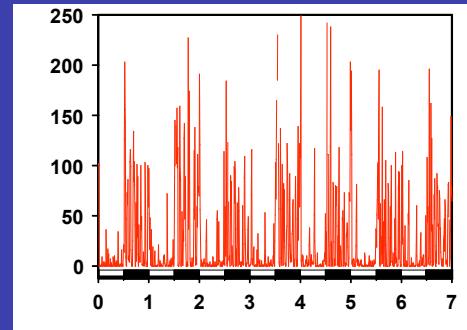
(The answer is yes, cf. e.g. Davis, S., Cancer Causes Control 2006)

Circadian rhythm disruption by SCN perturbations in mice

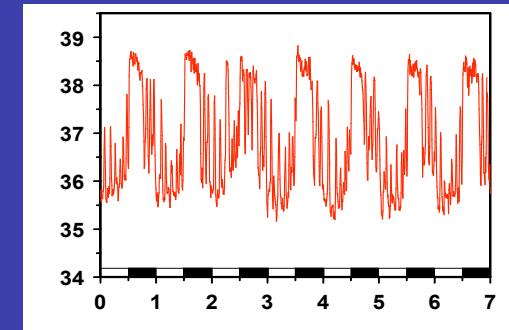
Rest-activity



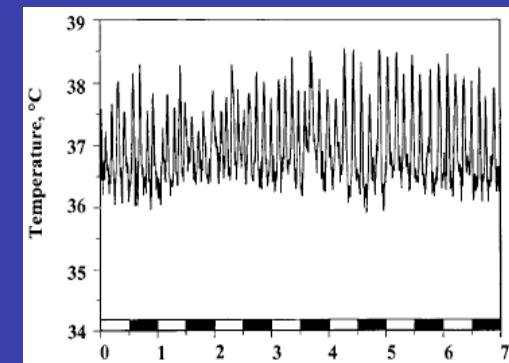
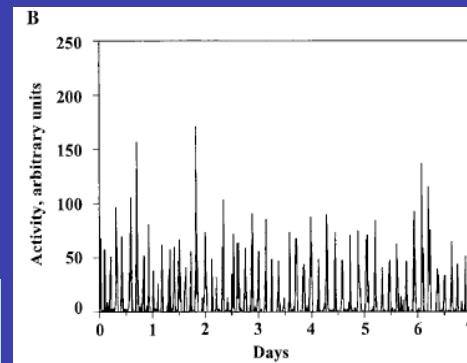
Intact SCN



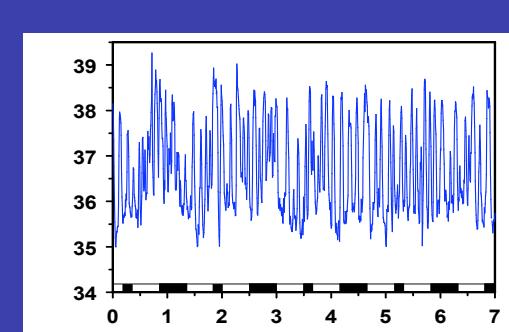
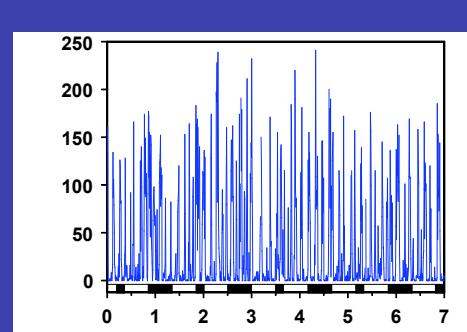
Body temperature



Electrocoagulation



Intact+Jet-lag



Filipski JNCI 2002, Canc. Res. 2004, JNCI 2005, Canc. Causes Control 2006

2) Pathology: insights from molecular biology in mice

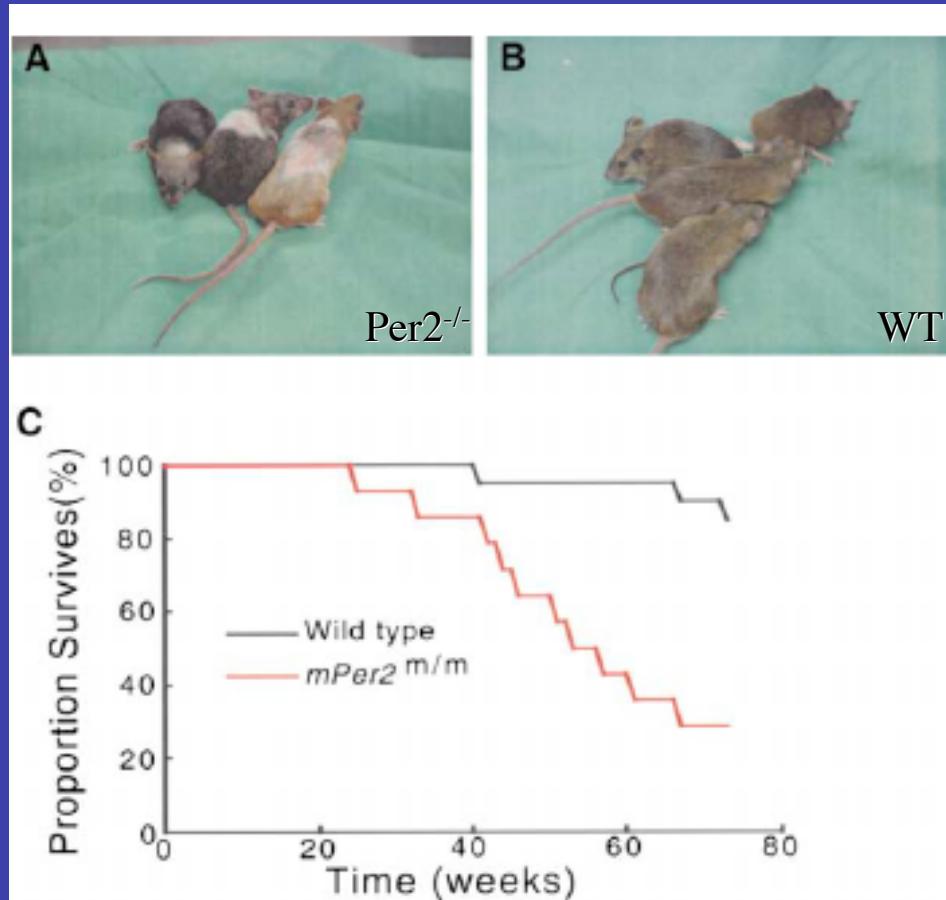


Figure 2. *mPer2^{m/m}* Mice Show Increased Sensitivity to γ Radiation
(A) All the irradiated *mPer2^{m/m}* mice show hair graying at 22 weeks after irradiation. Some of them also show hair loss on the back.
(B) Wild-type mice at 22 weeks after irradiation.
(C) Survival curve for wild-type and *mPer2^{m/m}* mice after irradiation.

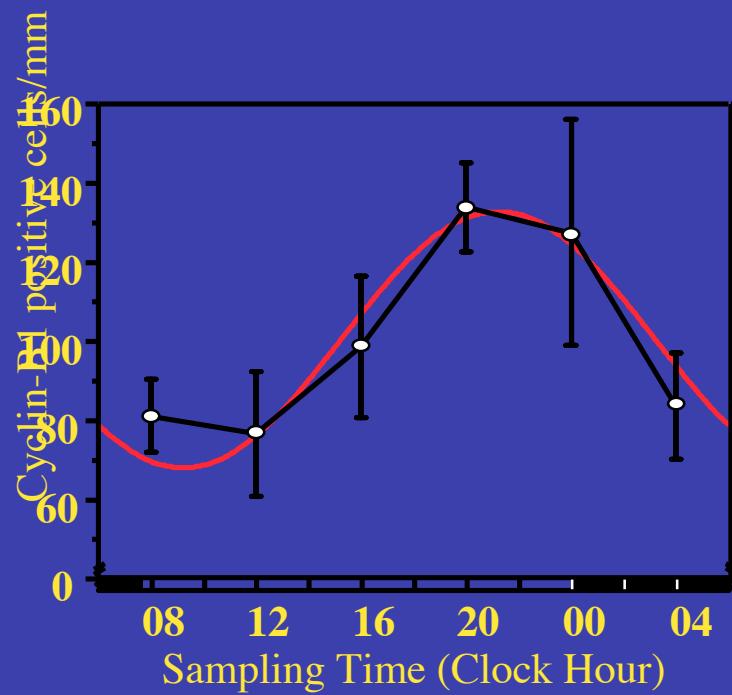
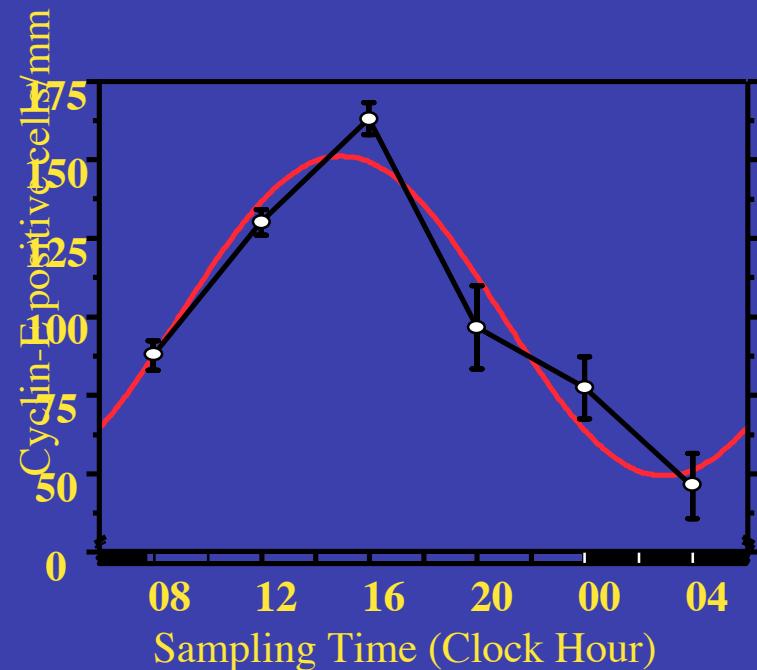
NB: Per2 is a gene of the circadian clock that has been found in all nucleated cells

Per2^{-/-} mice are more prone to develop (various sorts of) cancer following γ -irradiation than wild type mice

Hypothesis: loss of control of cell proliferation by circadian clock genes confers a selective advantage to cancer cells by comparison with healthy cells

3) Physiology: examples of circadian rhythms in the Human cell division cycle

Example of circadian rhythm in normal (=homeostatic) Human oral mucosa for Cyclin E (control of G₁/S transition) and Cyclin B (control of G₂/M transition)

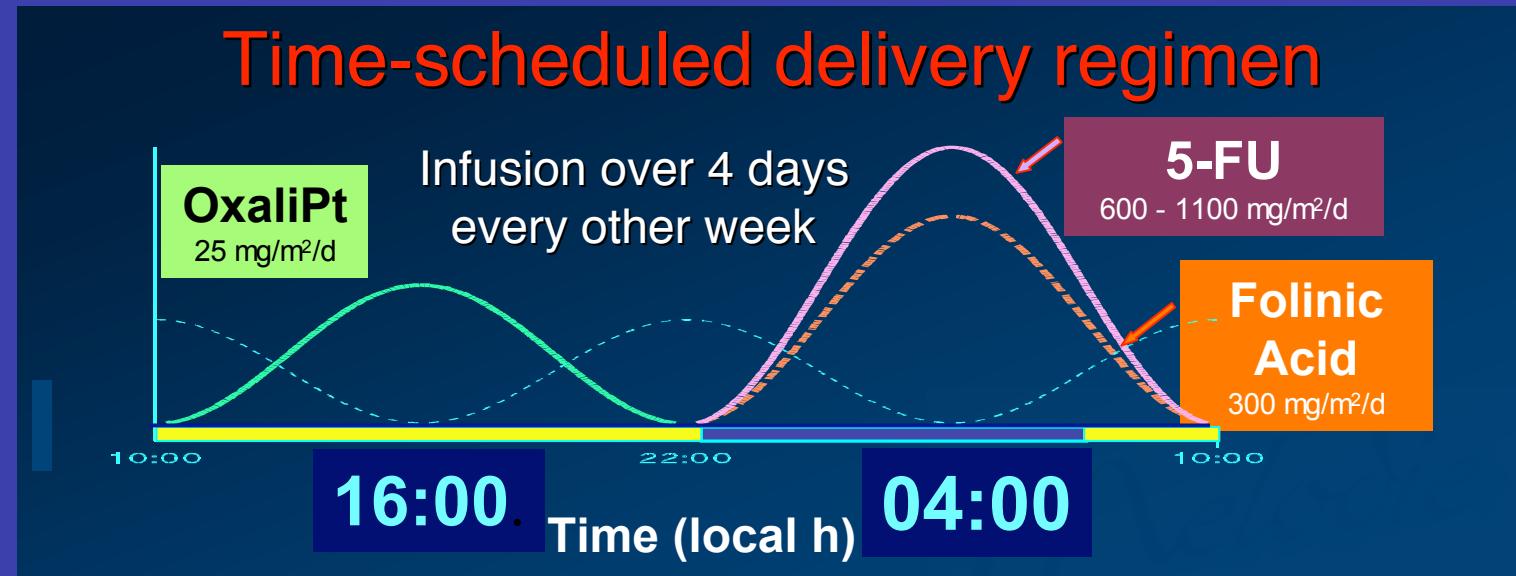


Nuclear staining for Cyclin-E and Cyclin-B1. Percentages of mean \pm S.E.M. in oral mucosa samples from 6 male volunteers. Cosinor fitting, $p < 0.001$ and $p = 0.016$, respectively.

(from Bjarnason et al. Am J Pathol 1999)

4) Circadian rhythms and cancer chronotherapeutics

(Results from Francis Lévi's INSERM team U 776, Villejuif, France)



Improvements in response to treatment and survival of patients with *colorectal cancer* have been obtained by chronotherapy (=drug delivery according to 24 h-rhythmic time schedules)

Patients with disrupted circadian rhythms (plasma cortisol, central temperature, rest-activity alternations) are less responsive to treatment and of poorer prognosis

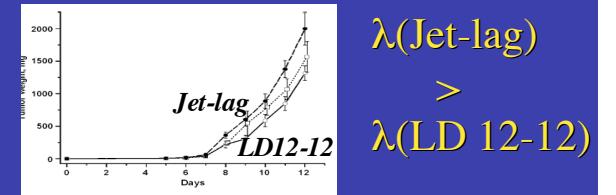


Circadian rhythm disruption in Man

[= loss of synchronisation between circadian molecular clocks?]

- Circadian desynchronisation (loss of rhythms of temperature, cortisol, rest-activity) is a factor of poor prognosis in response to anticancer chemotherapy (*Mormont & Lévi, Cancer 2003*)
- Desynchronising effects of *cytokines* and anticancer drugs on circadian clock: *fatigue* is a constant symptom in patients with cancer (*Rich et al., Clin Canc Res 2005*)
- ...effects that are analogous to those of chronic « jet-lag » (photic entrainment phase advance or delay) on circadian rhythms, known to enhance tumour growth
(*Hansen, Epidemiol 2001; Schernhammer, JNCI 2003; Davis, JNCI 2001, Canc Causes Control 2006*)
- ...hence questions: 1) is the molecular circadian clock the main synchronising factor between phase transitions? And 2) do tumours enhance their development by disrupting the SCN clock?
- [...and hence resynchronisation therapies (by melatonin, cortisol) in oncology??]

Circadian rhythm and tumour growth: How can we define and compare the λ s?



Instead of the initial system with periodic coefficients:

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

Define the stationary system with constant coefficients:

$$\left\{ \begin{array}{l} \frac{\partial}{\partial x} \bar{N}_i(x) + [\langle d_i(x) \rangle_a + \lambda_{stat} + \langle K_{i \rightarrow i+1}(x) \rangle_a] \bar{N}_i(x) = 0, \\ \bar{N}_i(x=0) = \int_{\xi \geq 0} \langle K_{i-1 \rightarrow i}(\xi) \rangle_a \bar{N}_{i-1}(\xi) d\xi, \quad 2 \leq i \leq I \\ \bar{N}_1(x=0) = 2 \int_{\xi \geq 0} \langle K_{I \rightarrow 1}(\xi) \rangle_a \bar{N}_I(\xi) d\xi, \quad \text{with } \sum_{i=1}^I \int_{x \geq 0} \bar{N}_i(x) dx = 1 \end{array} \right. \rightarrow \lambda_{stat}$$

$$\langle K_{i \rightarrow i+1}(x) \rangle_a := \frac{1}{T} \int_0^T K_{i \rightarrow i+1}(t, x) dt, \quad \langle d_i(t, x) \rangle_a := \frac{1}{T} \int_0^T d_i(t, x) dt$$

Comparing λ_{per} and λ_{stat} : control on apoptosis

(comparison of periodic versus constant [=no] control with same mean)

Theorem (B. Perthame, 2005):

If the control is exerted on the sole loss (apoptosis) terms d_i , then $\lambda_{per} \geq \lambda_{stat}$

i.e., $\lambda(\text{periodic control}) \geq \lambda(\text{constant control})$

if the control is on the d_i only

... which is exactly the contrary of what was expected, at least if one assumes that

$\lambda_{per} \approx \lambda(LD12-12)$ and $\lambda_{stat} \approx \lambda(jet-lag)$!

Comparing λ_{per} and λ_{stat} : control on transitions only (comparison of periodic versus constant [=no] control with same mean)

Numerical results for the periodic control of the cell cycle on phase transitions

$$(K_{i \rightarrow i+1}(t, a) = \psi_i(t) \cdot \mathbf{1}_{\{a \geq a_i\}}(a))$$

Two phases, control ψ on phase transition 1->2 only:

both situations may be observed, i.e., $\lambda_{stat} <$ or $>$ λ_{per}

depending on the duration ratio between the two phases and on the control:

ψ_1 : G2/M gate open 4 h / closed 20 h

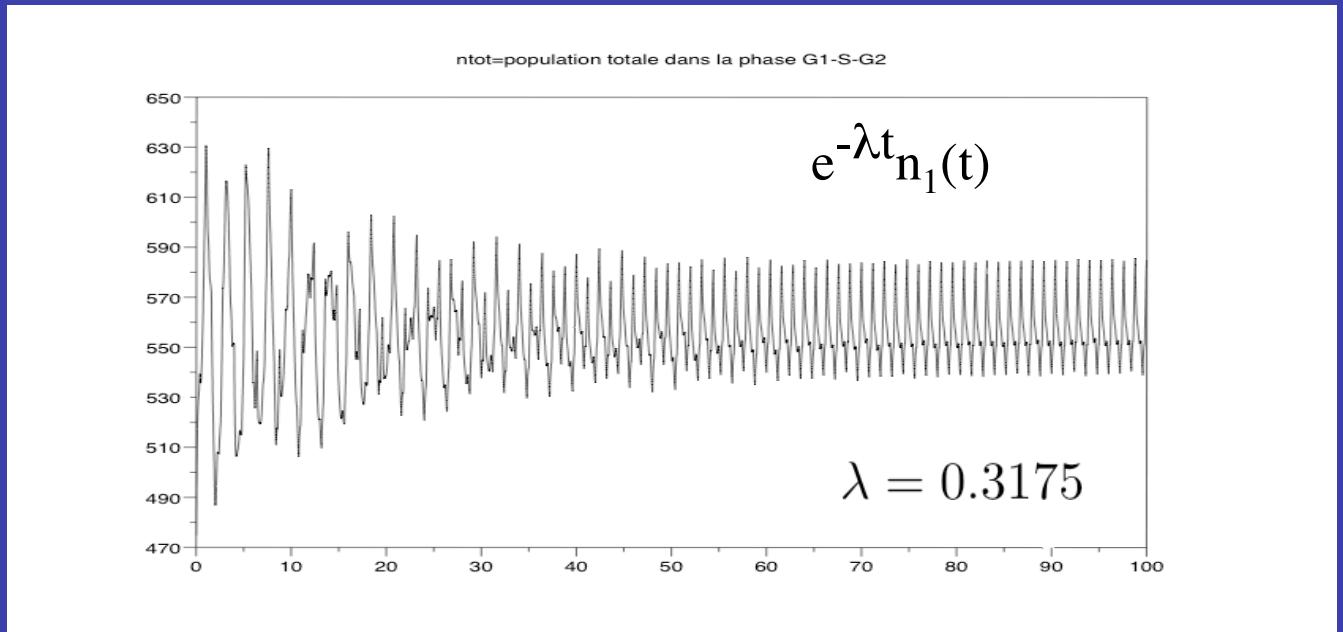
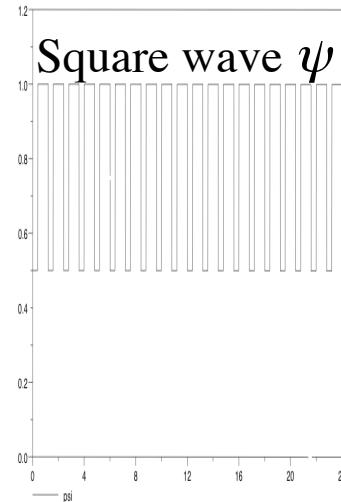
(G1-S-G2/M)	(periodic)	(constant)
time ratio, ψ_1	λ_{per}	λ_{stat}
1	0.2385	0.2350
2	0.2260	0.2923
3	0.2395	0.3189
4	0.2722	0.3331
5	0.3065	0.3427
6	0.3305	0.3479
7	0.3472	0.3517
8	0.3622	0.3546
10	0.3808	0.3588
20	0.4125	0.3675

ψ_2 : G2/M gate open 12 h / closed 12 h

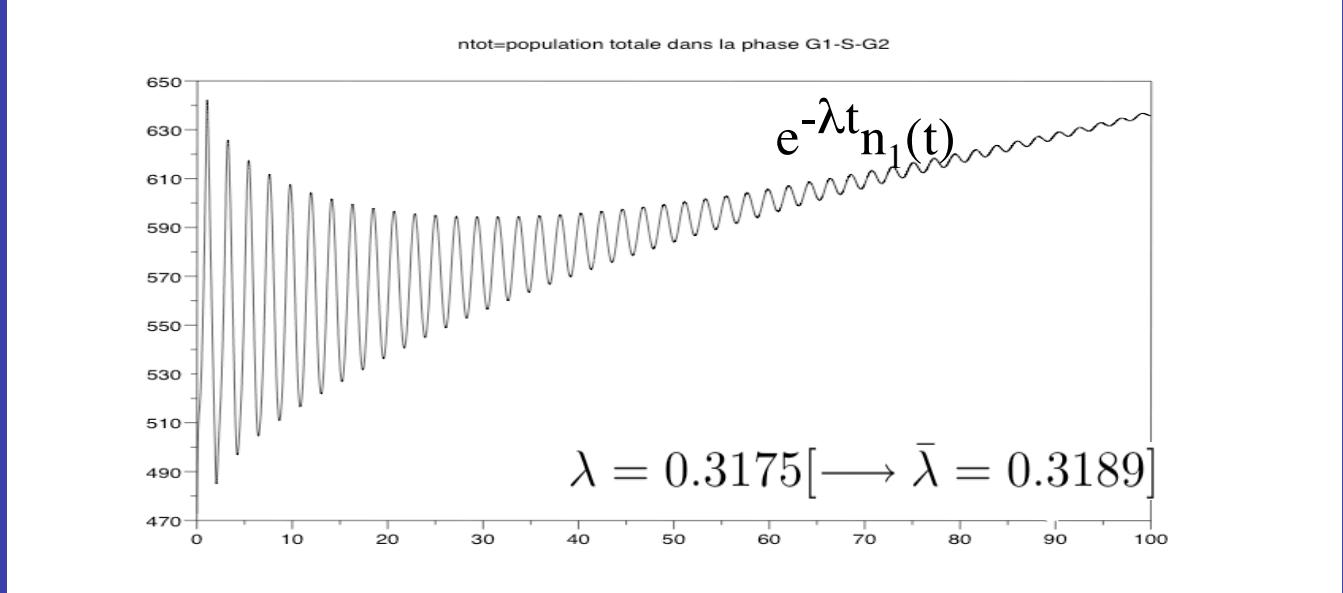
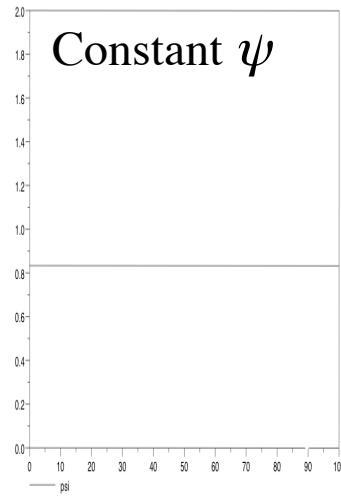
(G1-S-G2/M)	(periodic)	(constant)
time ratio, ψ_2	λ_{per}	λ_{stat}
1	0.2623	0.2821
2	0.3265	0.3448
3
4
5
6
7	0.4500	0.4529
8	0.4588	0.4575
10	0.4713	0.4641
20	0.5006	0.4818

Example: $\psi=1(16h)+.5(8h)$ sq. wave vs. constant (=no) control

Two phases



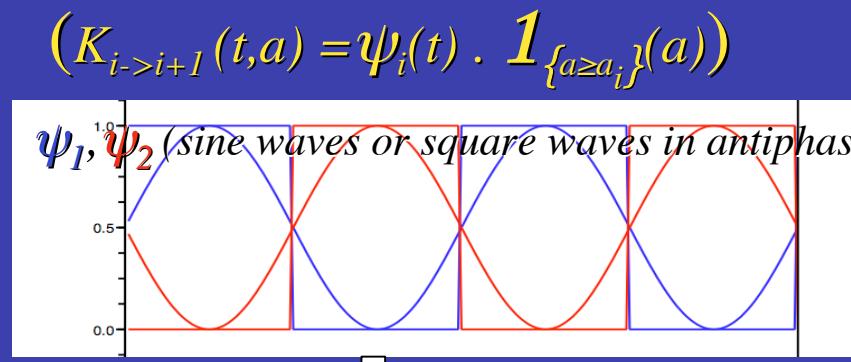
Two phases



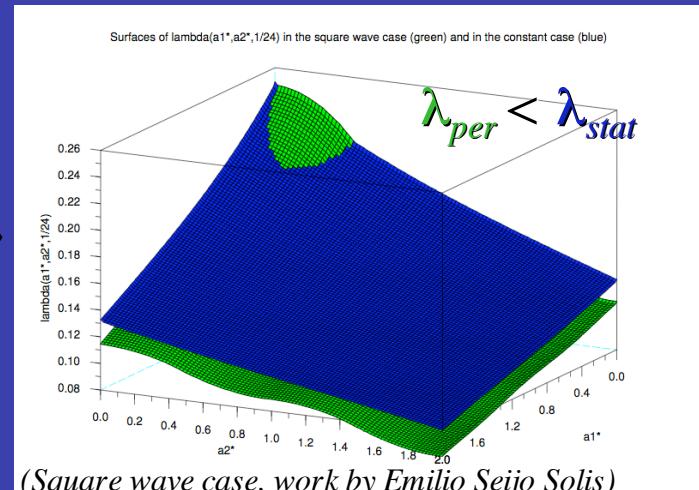
(Here: 2 cell cycle phases of equal duration, control exerted on G₂/M transition)

3 phase-model: numerical results with phase-opposed periodic control functions ψ_1 and ψ_2 transitions G₁/S and G₂/M

Numerical simulations have shown that if transition control functions ψ_1 on G₁/S and ψ_2 on G₂/M are of the same period 24 h and are out of phase (e.g. 0 between 0 and 12 h, and 1 between 12 and 24 h for ψ_1 , with the opposite for ψ_2), then the resulting λ_{per} is always lower than the corresponding value λ_{stat} for $\psi_1 = \psi_2 = 0.5$, whatever the durations a_1, a_2 of the first 2 phases (the third one, M, being fixed as 1 h in a total of 24 h for the whole cell cycle, with no control on M/G₁, i.e., $\psi_3 = 1$).



$$\begin{aligned} & \forall a_1 > 0, \forall a_2 > 0, \\ & \text{if } a_1 + a_2 + 1/24 = 1 \\ & \text{then } \lambda_{per} < \lambda_{stat} \end{aligned}$$

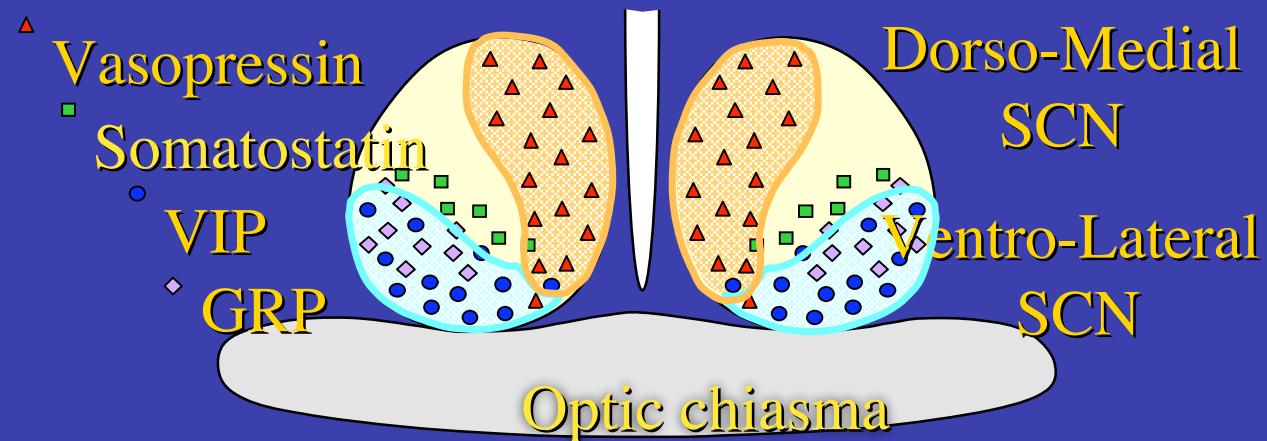


(Square wave case, work by Emilio Seijo Solis)

...more consistent with observations, assuming
 $\lambda(LD\ 12-12) = \lambda_{per} < \lambda_{stat} = \lambda(jet-lag)$
(jet-lag=desynchronisation between clocks?)

Modelling circadian clock inputs:

The central circadian pacemaker:
the suprachiasmatic (SCN) nuclei



(after Inouye & Shibata 1994)

20 000 coupled neurons, in particular electrically (coupling blocked by TTX),
each one of them oscillating according to a period ranging between 20 et 28 h

With entrainment by light (through the retinohypothalamic tract) for VL neurons

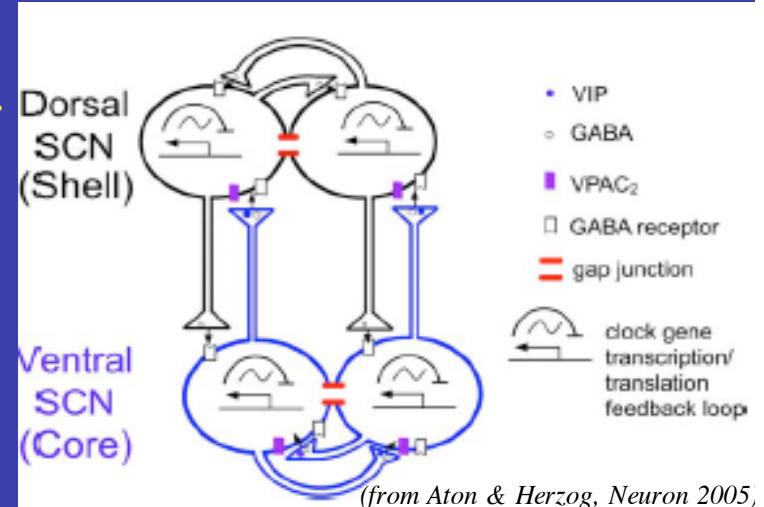
Modelling the SCN as a network of coupled oscillators: diffusive (electric?) coupling between neurons

$$\begin{aligned}\frac{dmRNA(i)}{dt} &= V_s \frac{K^n}{K^n + Z(i)^n} - V_m(i) \frac{mRNA(i)}{K_m + mRNA(i)} \\ \frac{dPER(i)}{dt} &= k_s mRNA(i) - V_d \frac{PER(i)}{K_d + PER(i)} - k_1 PER(i) + k_2 Z(i) + K_e \sum_{j \neq i} [PER(j) - PER(i)] \\ \frac{dZ(i)}{dt} &= k_1 PER(i) - k_2 Z(i)\end{aligned}$$

(after Leloup, Gonze, Goldbeter, *J Biol Rhythms* 1999)

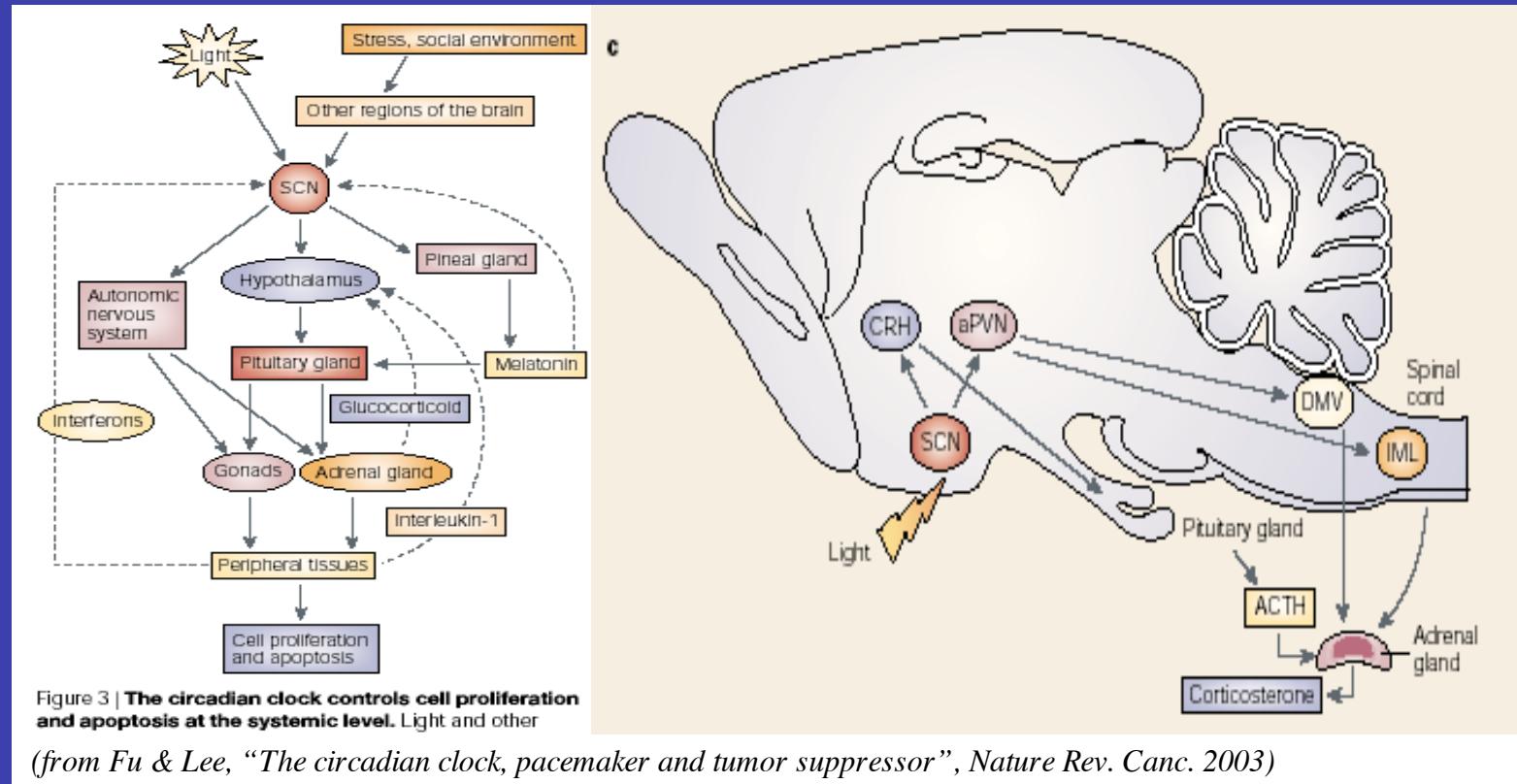
V_s : $V_s = 1.6 (1+L \cos(2\pi t/24))$ target of entrainment by light L ; K : target of transcriptional inhibition (e.g. by cytokines); $V_m(i)$: the carrier of variability of the oscillatory period in this model

3 variables for the i^{th} neuron that communicates with all other ($j \neq i$) neurons of the SCN through cytosolic PER protein, with coupling constant K_e : electric? gap junctions? VIP / VPAC₂ signalling?



Pathways from the SCN toward peripheral tissues

(messages suppressed by TTX blockade of interneuronal coupling in the SCN)



Neural messages (ANS), humoral messages (MLT, ACTH) toward periphery
(and secretions: TGF α , prokineticin 2, giving rise to the rest-activity rhythm)

Representation of messages from the SCN to the periphery

$$\begin{aligned}\frac{dU}{dt} &= k_3 \overline{PER(NSC)} - k_4 U \\ \frac{dV}{dt} &= k_4 U - k_5 V \\ \frac{dW}{dt} &= \frac{aV}{b + V} - cW\end{aligned}$$

U = intercentral messenger

V = hormonal messenger (e.g. ACTH)

W = tissue messenger (e.g., cortisol)

Individual peripheral circadian oscillators:
same model as in the SCN, *without intercellular coupling of clocks*
but with entrainment by a common messenger from the SCN

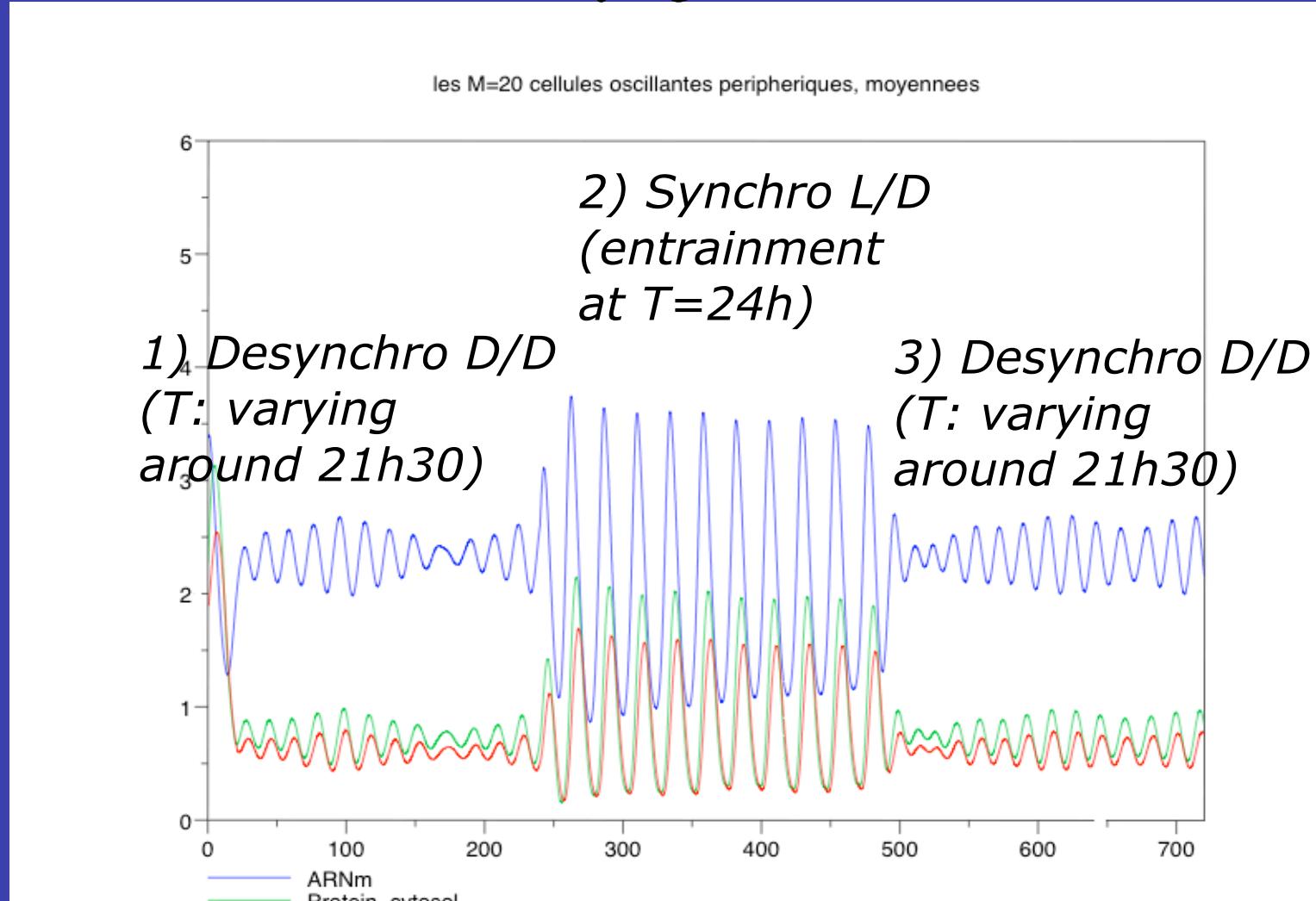
$$\frac{dARN_m}{dt} = V_s \frac{K^n}{K^n + Z^n} - V_m \frac{ARN_m}{K_m + ARN_m}$$

$Z \longrightarrow Z + r W$

(W = messager tissulaire)

...determining an average circadian oscillator in each peripheral organ
or tissue, as peripheral clock *PER* averaged over individual clocks

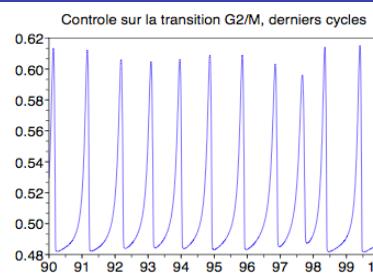
Example of disrupted clock model: averaged *peripheral* oscillator
 1) without *central* entrainment by light; 2) with; 3) without



Resulting Per to control Wee1, that inhibits CDK1 = ψ , in proliferating cells

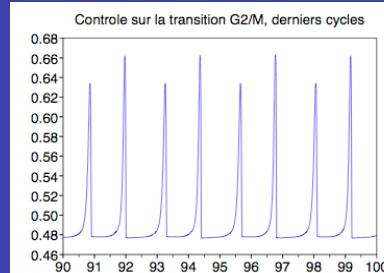
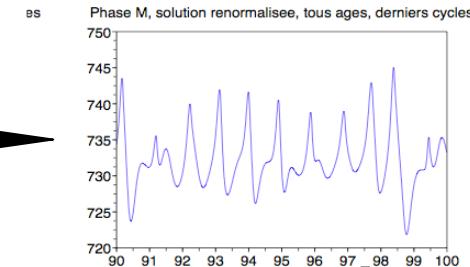
Clock perturbations and cell population proliferation

(*Wee1* here identified as averaged *Per* in a circadian clock model)



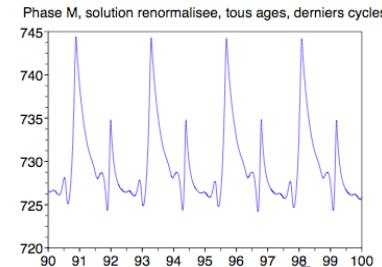
Desynchronised Wee1
(no entrainment by light):
Control $cdk1 = \psi$
with perturbed clock

Resulting
irregular cell
population
dynamics
in M phase



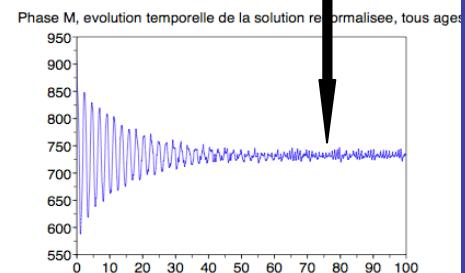
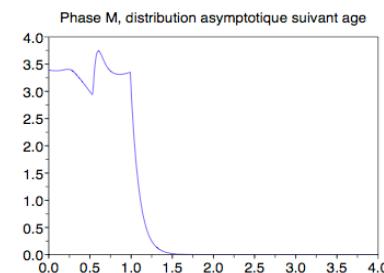
Synchronised Wee1
(entrainment by light):
Control $cdk1 = \psi$
with unperturbed clock

Resulting
regular cell
population
dynamics
in M phase



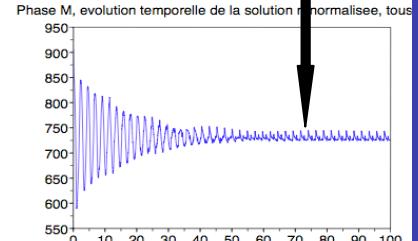
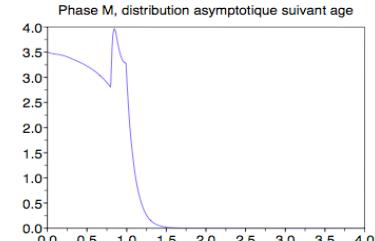
Wee1=Per is desynchronised
at the central (NSC) level

Resulting $\lambda=0.0466$



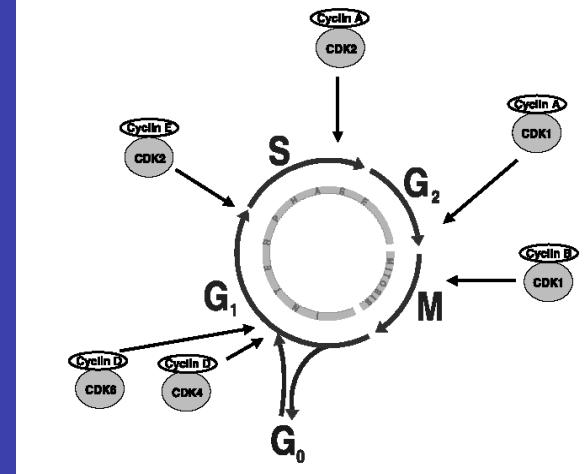
Wee1=Per is synchronised
at the central (NSC) level

Resulting $\lambda=0.0452$



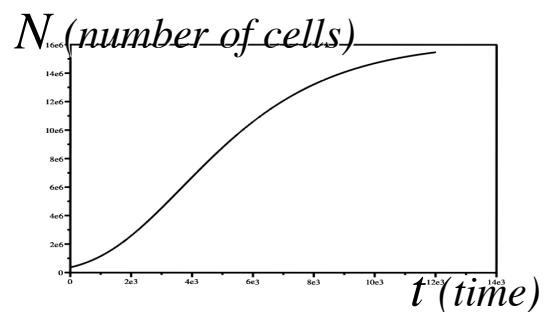
Underlying physiopathological questions:

- What is the benefit of a periodic control on the cell cycle to limit cell proliferation?
- Is the circadian disruption effect on tumour growth due to a direct effect on tumour cells or to differences between competing cell populations? (e.g. insensitive tumour vs. sensitive neighbouring stroma or immune cells)
- How is a periodic (circadian) control Ψ best -synchronously?- exerted on the phase transitions (by influencing molecules known to be physiological controls)?
- What is a “good control” Ψ on the cell cycle and what is a “disrupted control” (representing pathology for uncontrolled cancer cell proliferation)?
- Can the physiological control Ψ be seen as a solution to an eigenvalue optimisation problem (under what constraints??) and if so, how should therapeutic (pharmacological) means be designed to restore it?



Modelling exchanges between proliferative and quiescent cell compartments:

Introducing a *nonlinear feedback control* to allow for healthy tissue homeostasis



Main goal: to define a common developmental frame (in particular for the effect of cytotoxic drugs) for healthy as much as for cancer tissue growth

ODE models with 2 cell compartments, proliferating and quiescent

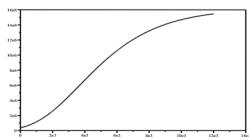
$$\begin{aligned}\frac{dP}{dt} &= [\beta - \mu_p - r_0(N)]P + r_i(N)Q \\ \frac{dQ}{dt} &= r_0(N)P - [r_i(N) + \mu_q]Q \\ N &= P + Q, \quad P_0 + Q_0 = 1\end{aligned}$$

(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 justify Gompertz growth
(a popular model among radiologists)

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

Age[x]-structured PDE models with proliferation and quiescence

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

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

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 models with 2 cell compartments, proliferating (P) / quiescent (Q)

(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)

Such behaviour can be 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

(studied by Mackey, Adimy, Bélair, Bernard, Crauste, Pujo-Menjouet, and ARC INRIA ModLMC)

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)

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

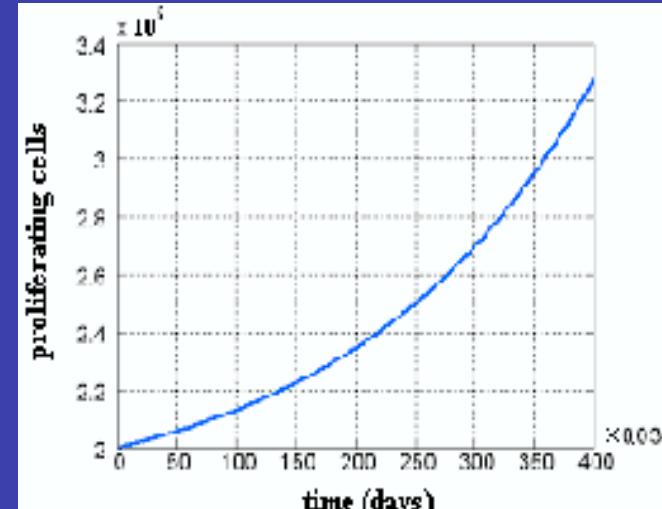
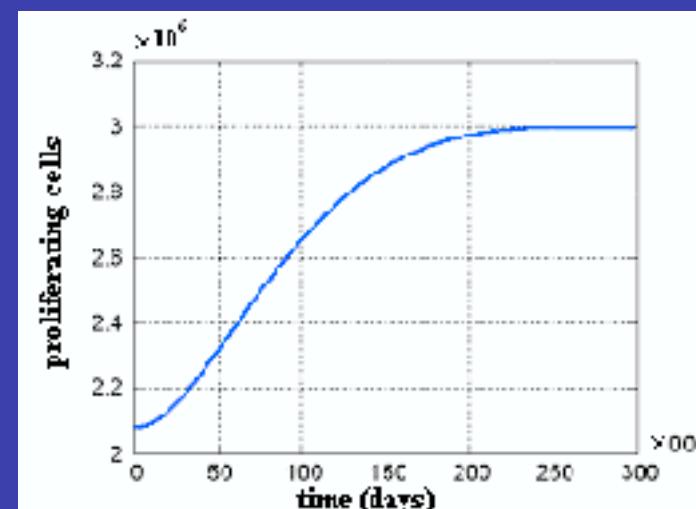
$N=p+q$:
total number
of cells
 L : leak term
from p to q
 F : mitosis
term

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

Healthy tissue
recruitment G :
homeostasis

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

Tumour recruitment G :
($\alpha_2 > 0$) exponential growth



*F. Bekkal Brikci,
JC, B. Ribba,
B. Perthame, RR
INRIA 5941 2006
J Math Biol 2008
(accepted);
M. Doumic-
Jauffret, MMNP
2008 (accepted)*

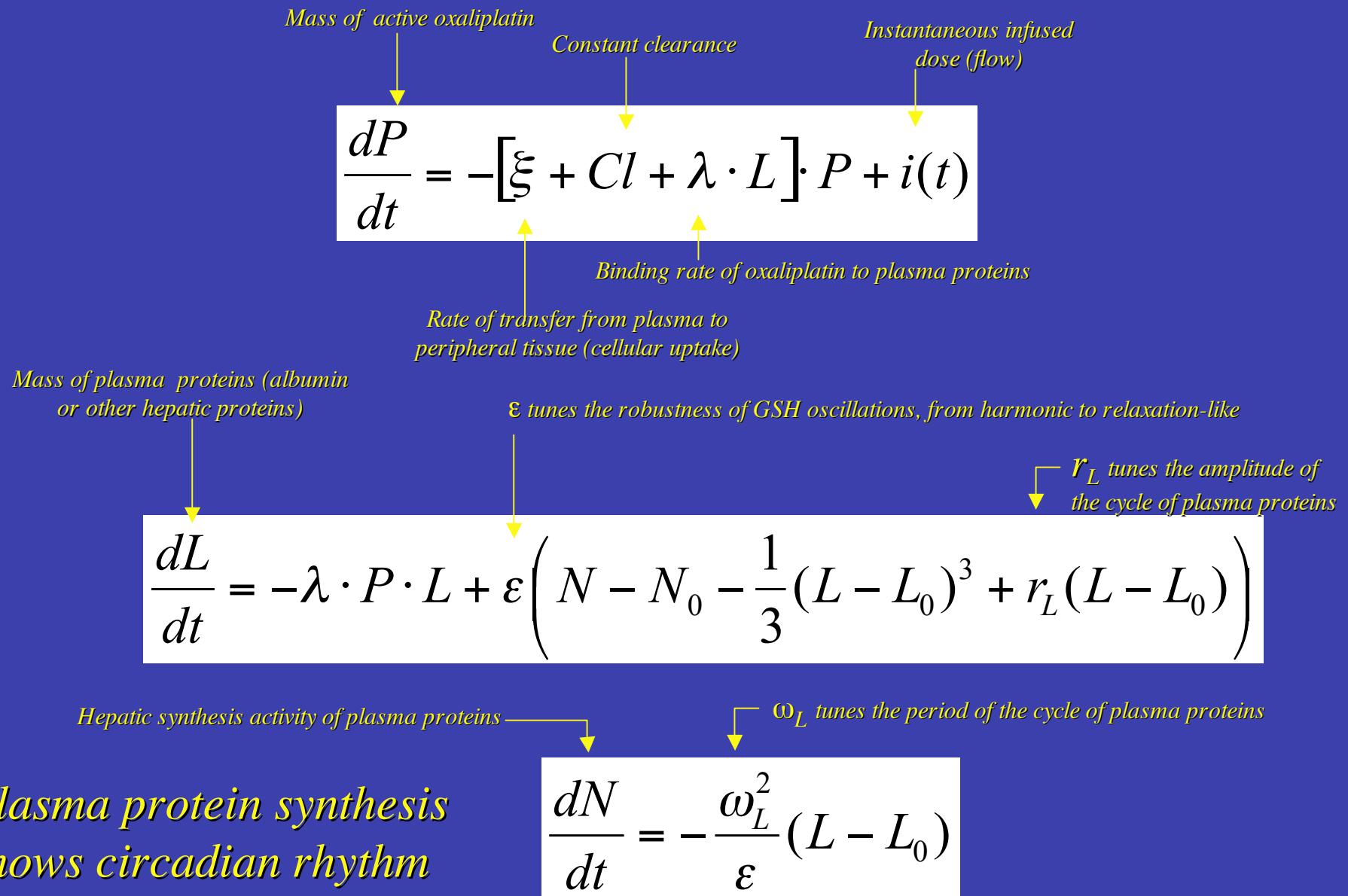
Action of classical cytotoxic drugs: Pharmacokinetic-pharmacodynamic (PK-PD) modelling

“Pharmacokinetics is what the organism does to the drug,
Pharmacodynamics is what the drug does to the organism”

Therapeutic optimisation

1st example: cytotoxic drug Oxaliplatin

Molecular PK of Oxaliplatin in plasma compartment



Molecular PK of Oxaliplatin: tissue concentration

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

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

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

*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

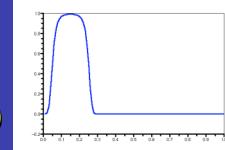
Action of oxaliplatin on free DNA (F)

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

Mass of reduced glutathione in target cell compartment

Oxaliplatin cell concentration

DNA Mismatch Repair (MMR) function
 $(\theta_1 < \theta_2)$: activation and inactivation thresholds; g_R : stiffness



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

*Glutathione synthesis
 (→detoxification) in cells shows circadian rhythm*

Activity of γ -Glu-cysteinyl ligase (GCS)

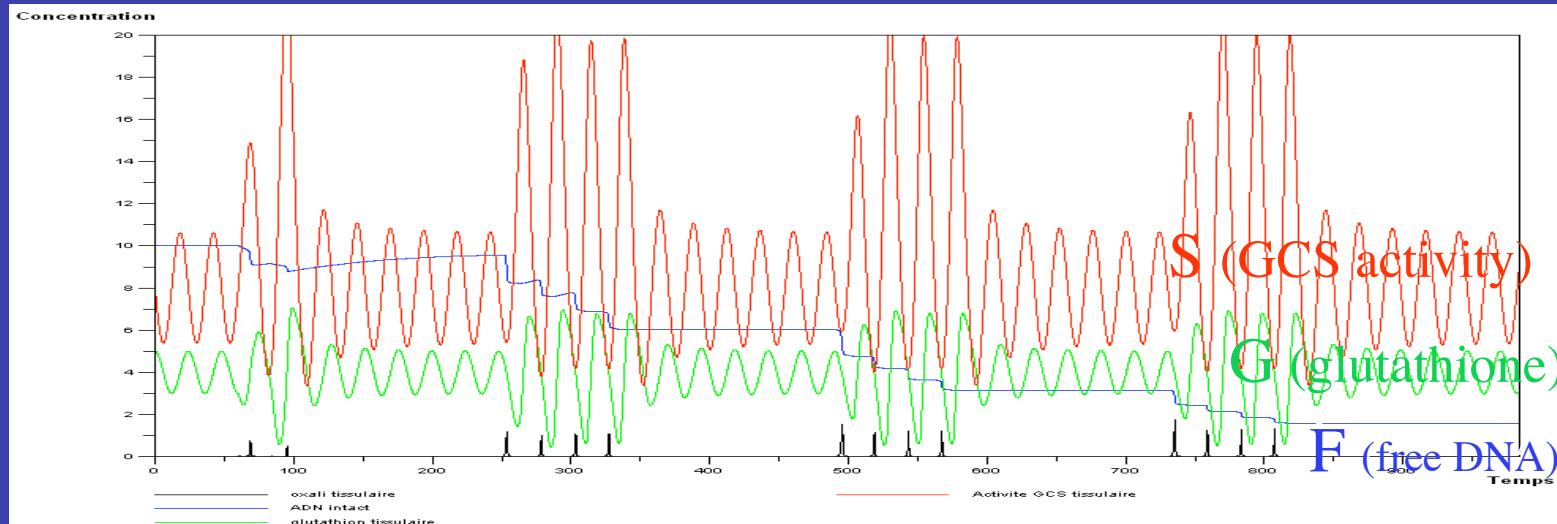
r_G tunes the amplitude of the cycle of GSH synthesis by GCS = γ -Glu-cysteinyl ligase

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

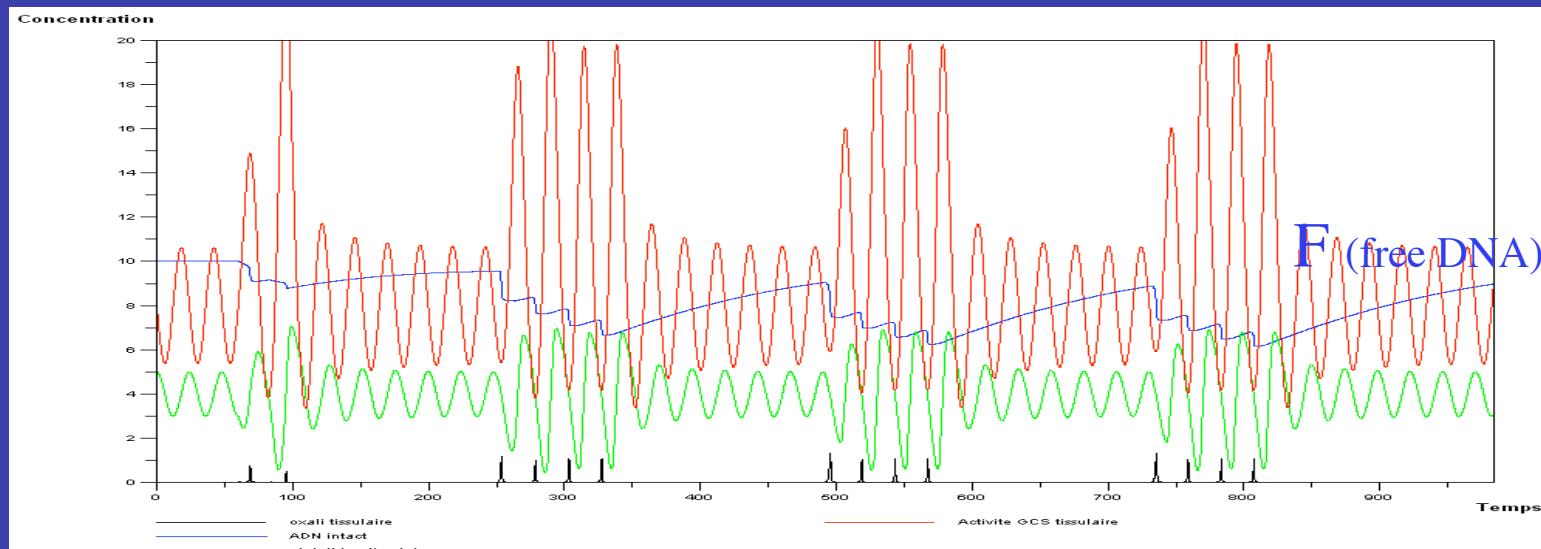
$$\frac{dS}{dt} = -\frac{\omega_G^2}{\delta} (G - G_0)$$

$1 - F/F_0 = \text{DNA damage}$

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

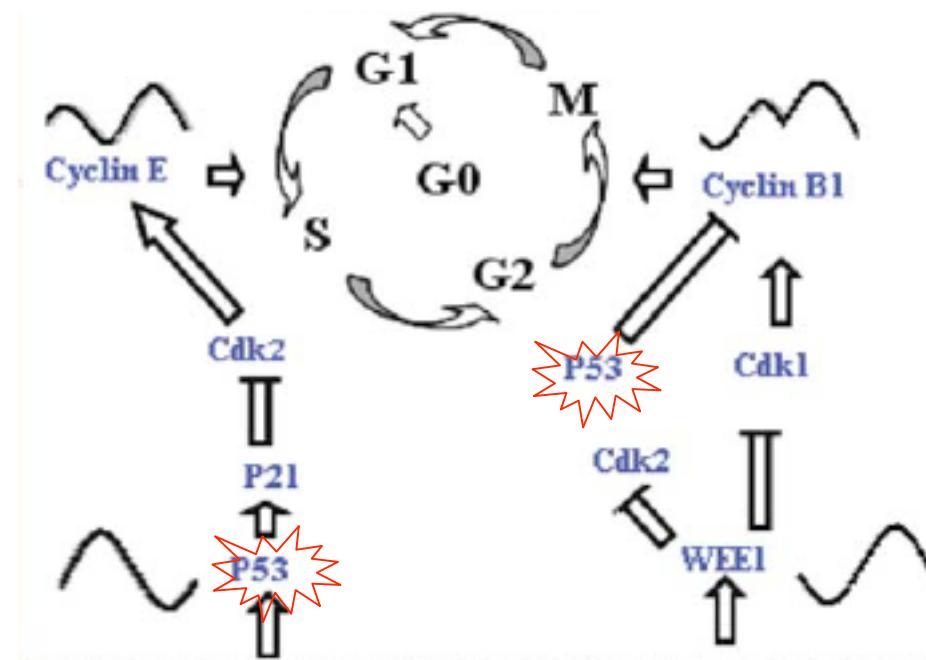


...the same with stronger MMR function (ERCC2=XPD-determined):



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

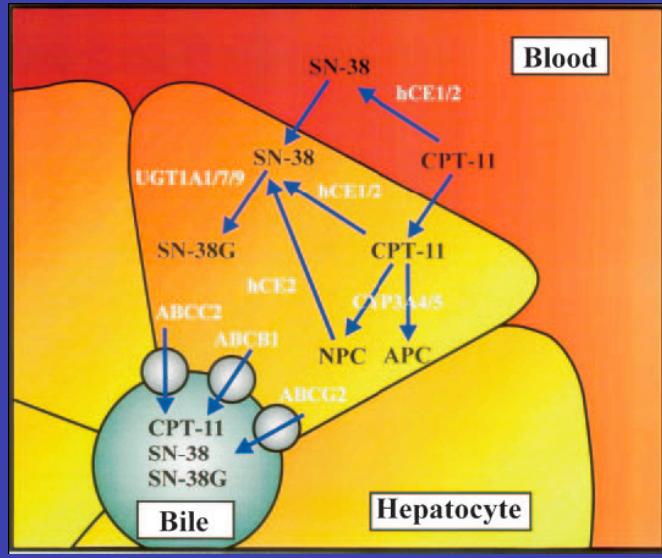
The sentinel protein p53 senses DNA damage due to cytotoxic drugs, induces cell cycle arrest and launches either DNA mismatch repair or apoptosis



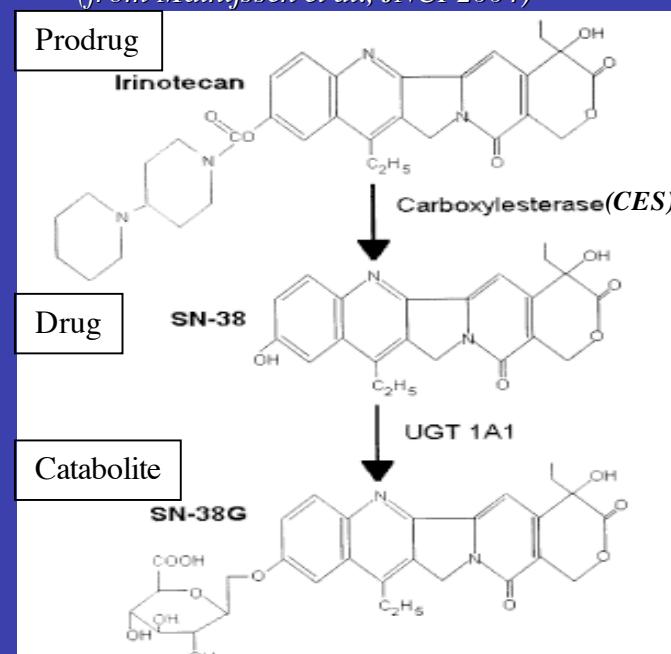
(from You et al., Breast Canc Res Treat 2005)

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

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



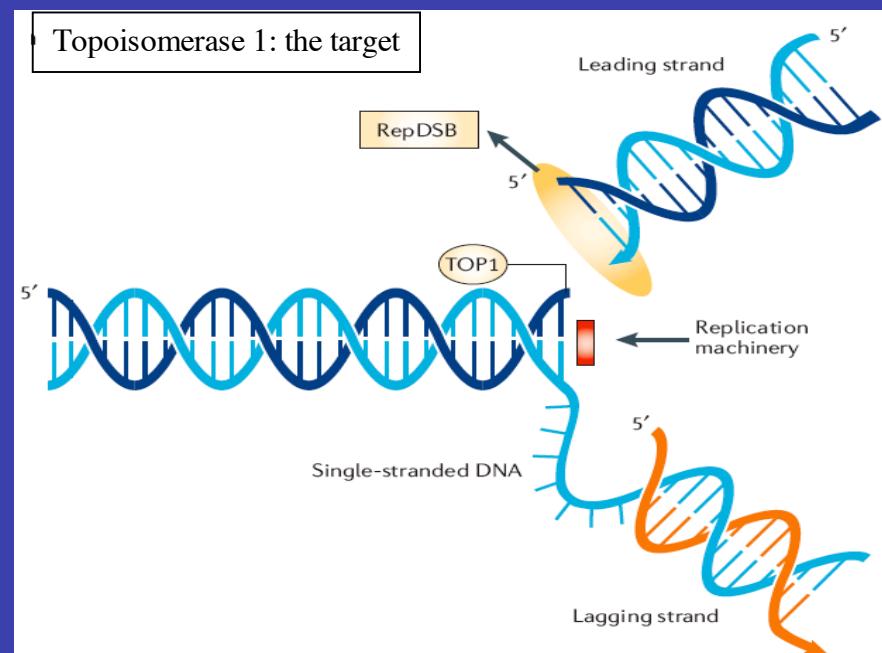
(from Mathijssen et al., JNCI 2004)



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

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 Pommier, Nature Rev Cancer 2006)

Intracellular PK-PD of *Irinotecan* (CPT11)

PK

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

PD

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

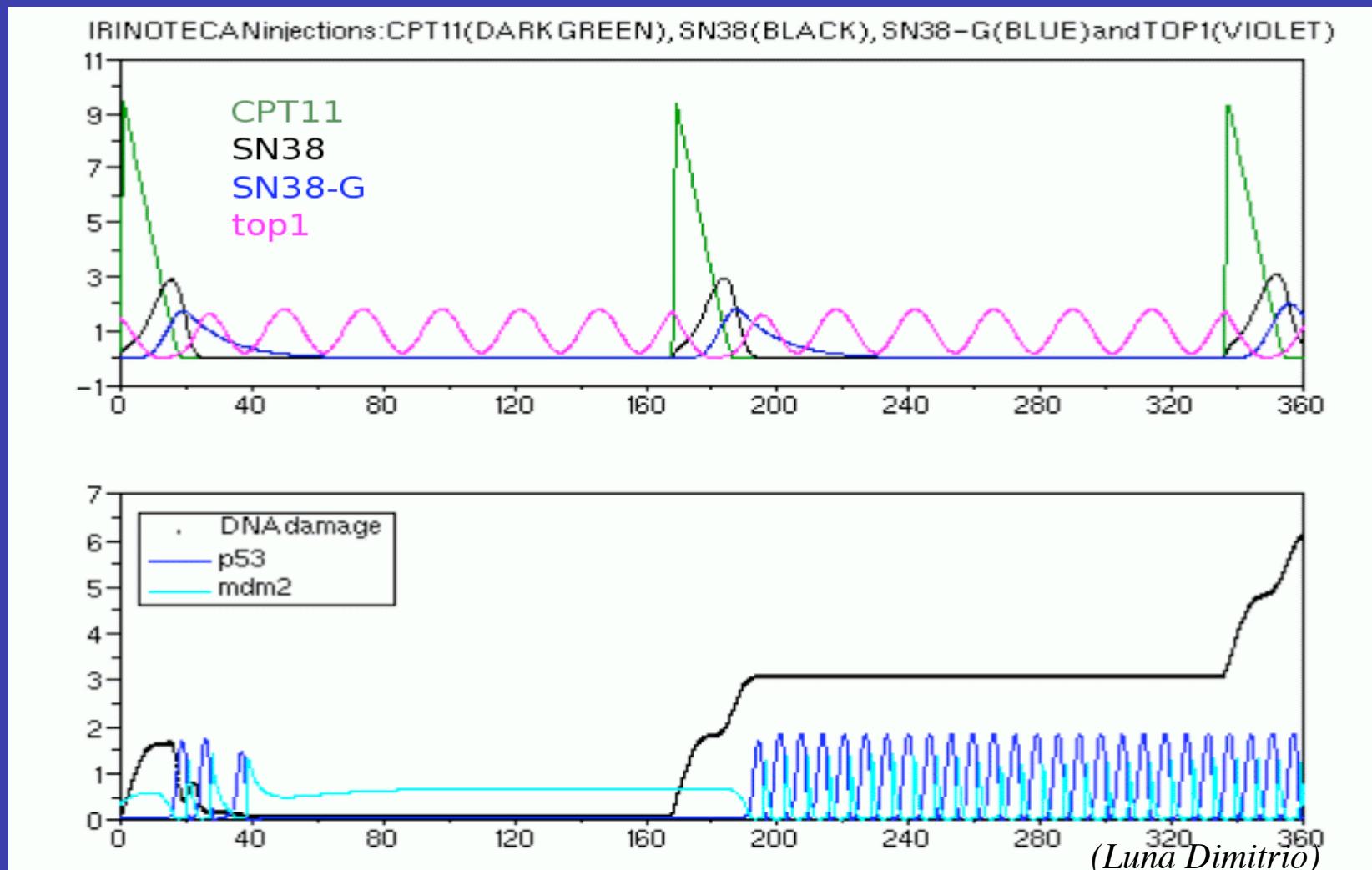
$$repairDNA([p53_{tot}], [CC_{irr}]) = -k_{dDNA}[p53_{tot}] \frac{[CC_{irr}]}{J_{DNA} + [CC_{irr}]} \quad (Luna Dimitrio's Master thesis 2007; A. Ballesta's present PhD work)$$

A. Ciliberto's model of p53-Mdm2 oscillations

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

(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)

Ultimate goal: to optimise cancer therapeutics

Use (and restore) the circadian clock to synchronise drug delivery with cell cycle timing, a rationale for cancer chronotherapeutics

Use synergies between drugs with different metabolic mechanisms to enhance their therapeutic effects

Enzymatic systems of drug detoxification and active drug efflux transporters in the hepatic filter or in peripheral tissues, and their circadian and genetic polymorphism variations, are sources of parameters to be adapted for *patient-tailored therapeutics*

Representing *acquired resistances* to anticancer drugs should also involve model of cell populations by *PDEs structured in a genetic trait* with branching behaviour

Ultimately: optimal control methods of drug infusion flow delivery...but the objective may be to control a growth exponent λ rather than population numbers

PK-PD simplified model for cancer chronotherapy

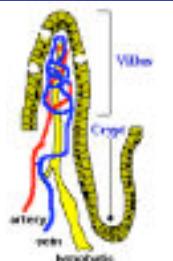
Healthy cells (jejunal mucosa)

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

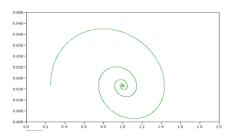
$$\frac{dC}{dt} = -\mu C + P$$

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

$$\frac{dA}{dt} = Z - Z_{eq}$$



(PK)



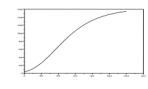
(homeostasis=damped harmonic oscillator)

Tumour cells

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

$$\frac{dD}{dt} = -\nu D + \xi_D P$$

$$\frac{dB}{dt} = \left[a \ln \frac{B_{max}}{B} - g(D, t) \right] B$$



(tumour growth=Gompertz model)

(« chrono-PD »)

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

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

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

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

Optimal control, step 1: deriving an objective function from the tumour cell population model

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

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

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

(Φ characteristic function of the allowed infusion periods)

Eradication strategy: minimise $G_B(i)$, where:

$$G_B(i) = \min_{t \in [t_1, t_f]} B(t, i)$$

or else:

Stabilisation strategy: minimise $G_B(i)$, where:

$$G_B(i) = \max_{t \in [t_1, t_f]} B(t, i)$$

($t_1 < t_f$ being some fixed observation time after t_0 , beginning of infusion interval)

Optimal control, step 2: deriving a constraint function from the enterocyte population model

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

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

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

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

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

$$F_A(i) = \tau_A - \min_{t \in [t_0, t_f]} A(t, i)/A_e \leq 0$$

± other possible constraints:

$$\max_{t \in [t_0, t_f]} i(t) \leq i_{max}, \quad \int_{t_0}^{t_f} i(t) dt \leq AUC_{max}$$

Optimal control problem: defining a lagrangian:

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

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

then:

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

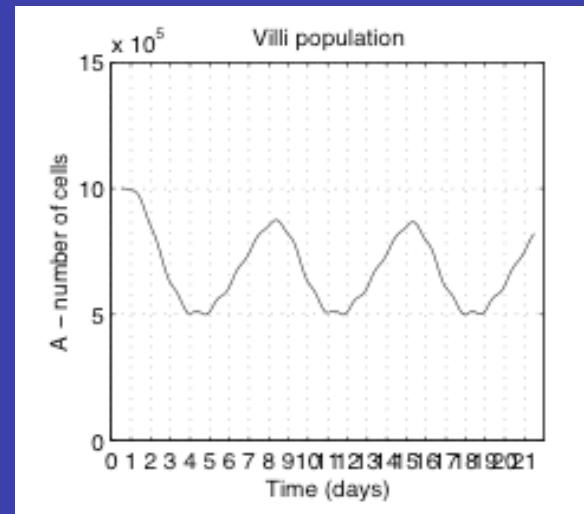
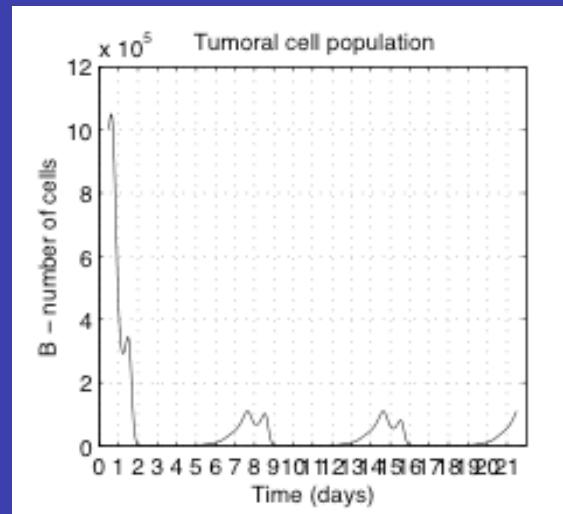
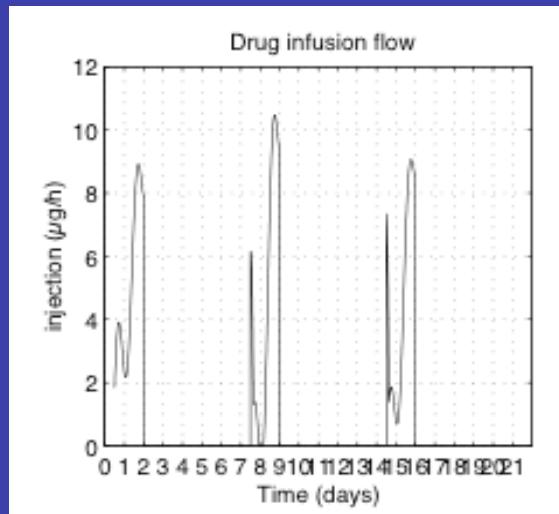
± other constraints

If G_B and F_A were convex, then a necessary and sufficient condition would be:

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

...i.e. the minimum would be obtained at a saddle point of the lagrangian, reachable by a Uzawa-like algorithm

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



Objective: minimising the maximum
of the tumour cell population

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

Result : optimal infusion flow $i(t)$ adaptable to the patient's state of health
(according to a parameter τ_A : here preserving at least $\tau_A=50\%$ of enterocytes)

(C. Basdevant, JC, F. Lévi, M2AN 2005)

Toward whole body physiologically based PK-PD (“WBPBPKPD”) modelling and model validation

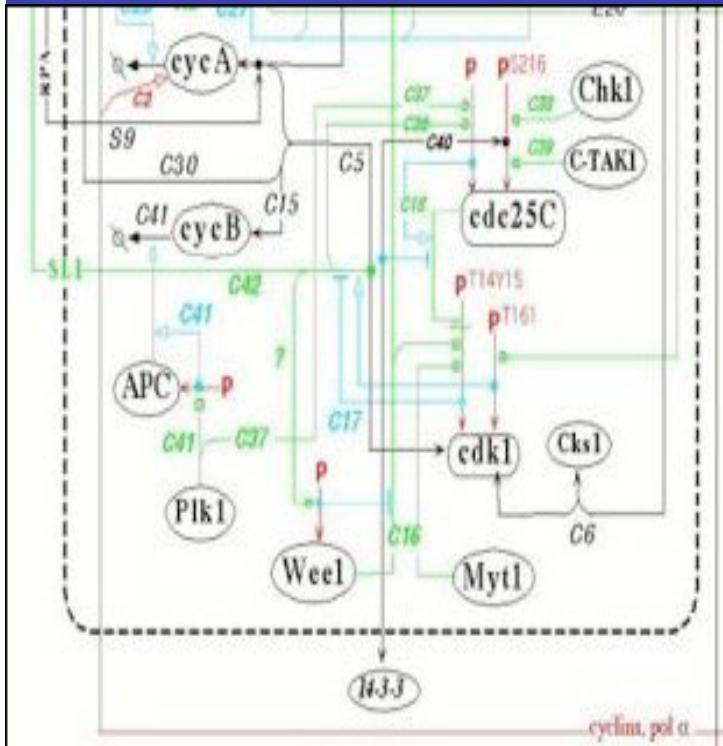
Controlling cell proliferation for medicine *in the clinic* is a multiscale problem, since drugs act at the single cell and cell population levels, but their clinical effects are measured at a single patient (=whole organism) and patient population levels

1. Drug detoxification enzymes, active efflux, etc.: molecular PK-PD ODEs, with validation by biochemistry data collection and in vitro experiments
2. Drug effects on cells and cell populations: averaged molecular effects on cell proliferation PDE models, with validation by measures of growth in cell cultures
3. Drug effects at the organism level: *WBPBPKPD* modelling: compartmental ODEs, with validation by tissue measurements: animal experiments, clinical trials
4. Interindividual variations (genetic polymorphism): discriminant and cluster analyses on populations of patients (populational PK-PD to individualise therapies)
5. Optimisation of treatments: optimisation methods, with validation by clinical trials

Future prospects:
Optimising multitargeted multidrug delivery in a
cellular systems biology environment

Necessity of a systems biology environment: *Biocham* (<http://constraintes.inria.fr/BIOCHAM/>)

Ex.: transcription of Kohn's map



- $_ = [E2F13-DP12-gE2] \Rightarrow cycA$.
- ...
- $cycB = [APC \sim \{p1\}] \Rightarrow _$.
- $cdk1 \sim \{p1, p2, p3\} + cycA \Rightarrow cdk1 \sim \{p1, p2, p3\}-cycA$.
- $cdk1 \sim \{p1, p2, p3\} + cycB \Rightarrow cdk1 \sim \{p1, p2, p3\}-cycB$.
- ...
- $cdk1 \sim \{p1, p3\}-cycA = [Wee1] \Rightarrow cdk1 \sim \{p1, p2, p3\}-cycA$.
- $cdk1 \sim \{p1, p3\}-cycB = [Wee1] \Rightarrow cdk1 \sim \{p1, p2, p3\}-cycB$.
- $cdk1 \sim \{p2, p3\}-cycA = [Myt1] \Rightarrow cdk1 \sim \{p1, p2, p3\}-cycA$.
- $cdk1 \sim \{p2, p3\}-cycB = [Myt1] \Rightarrow cdk1 \sim \{p1, p2, p3\}-cycB$.
- ...
- $cdk1 \sim \{p1, p2, p3\} = [cdc25C \sim \{p1, p2\}] \Rightarrow cdk1 \sim \{p1, p3\}$.
- $cdk1 \sim \{p1, p2, p3\}-cycA = [cdc25C \sim \{p1, p2\}] \Rightarrow cdk1 \sim \{p1, p3\}-cycA$.
- $cdk1 \sim \{p1, p2, p3\}-cycB = [cdc25C \sim \{p1, p2\}] \Rightarrow cdk1 \sim \{p1, p3\}-cycB$.

165 proteins and genes, 500 variables, 800 rules (F. Fages, S. Soliman, CONTRAINTES)

Ex. of CML: multiple roles of BCR-ABL in proliferation

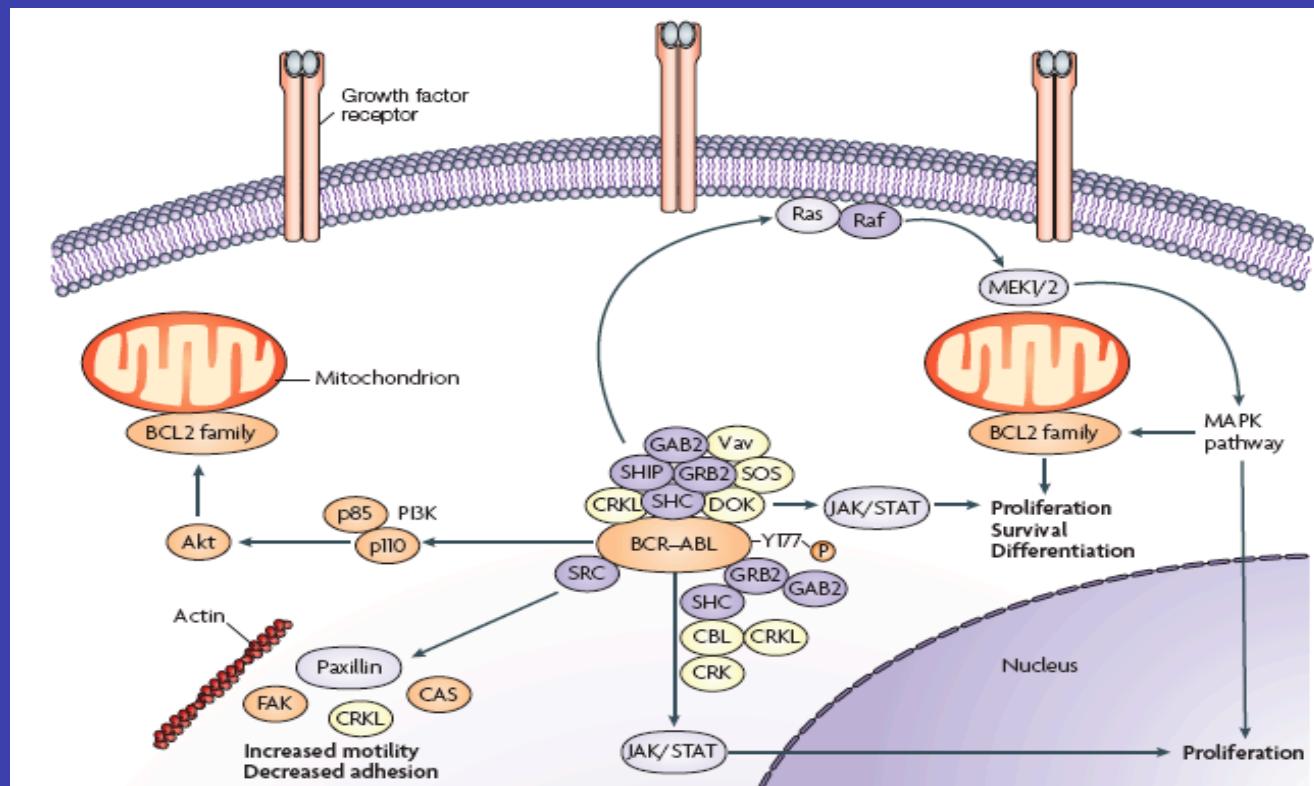


Figure 1 | BCR-ABL signalling in chronic myeloid leukaemia. With the aid of several mediator proteins, BCR-ABL associates with Ras and stimulates its activation. The adaptor protein, growth factor receptor-bound protein 2 (GRB2), interacts with BCR-ABL through the proximal SRC homology 2 (SH2)-binding site that develops when the tyrosine 177 (Y177) residue of BCR-ABL is autophosphorylated. GRB2, when bound to BCR-ABL, interacts with the son of sevenless (SOS) protein. The resulting BCR-ABL-GRB2-SOS protein complex activates Ras. The adaptor proteins CRKL (CRK-like) and SHC (SH2-containing protein) can also mediate the BCR-ABL activation of Ras. Ras and the mitogen activated protein kinase (MAPK) pathway are coupled by Raf (a serine/threonine kinase). Raf catalyses the phosphorylation of the mitogen-activated and extracellular-signal regulated kinase kinases 1 and 2 (MEK1 and MEK2); this results in their activation. Through the stimulation of the Ras-Raf pathway, BCR-ABL increases growth factor-independent cell growth. BCR-ABL also associates with and activates the phosphatidylinositol-3 kinase (PI3K) pathway, suppressing programmed cell death and increasing cell survival. BCR-ABL is associated with components of the focal adhesion (that is, actin, paxillin and focal adhesion kinase, or FAK); the activation of CRKL-FAK-PYK2 leads to a decrease in cell adhesion. BCR-ABL also associates with the Janus kinase and signal transducer and activator of transcription (JAK-STAT) pathway. Finally, BCR-ABL activates pathways that lead to atypical responses to chemotactic factors, which leads to an increase in cell migration. BCR-ABL also associates with survival proteins that interact with the mitochondrial-based BCL2 family. CAS, p130 CRK-associated substrate; GAB2, GRB2-associated binding protein 2; SHIP, SH2-containing inositol-5-phosphatase.

(from Weisberg Nature Rev Cancer 2007)

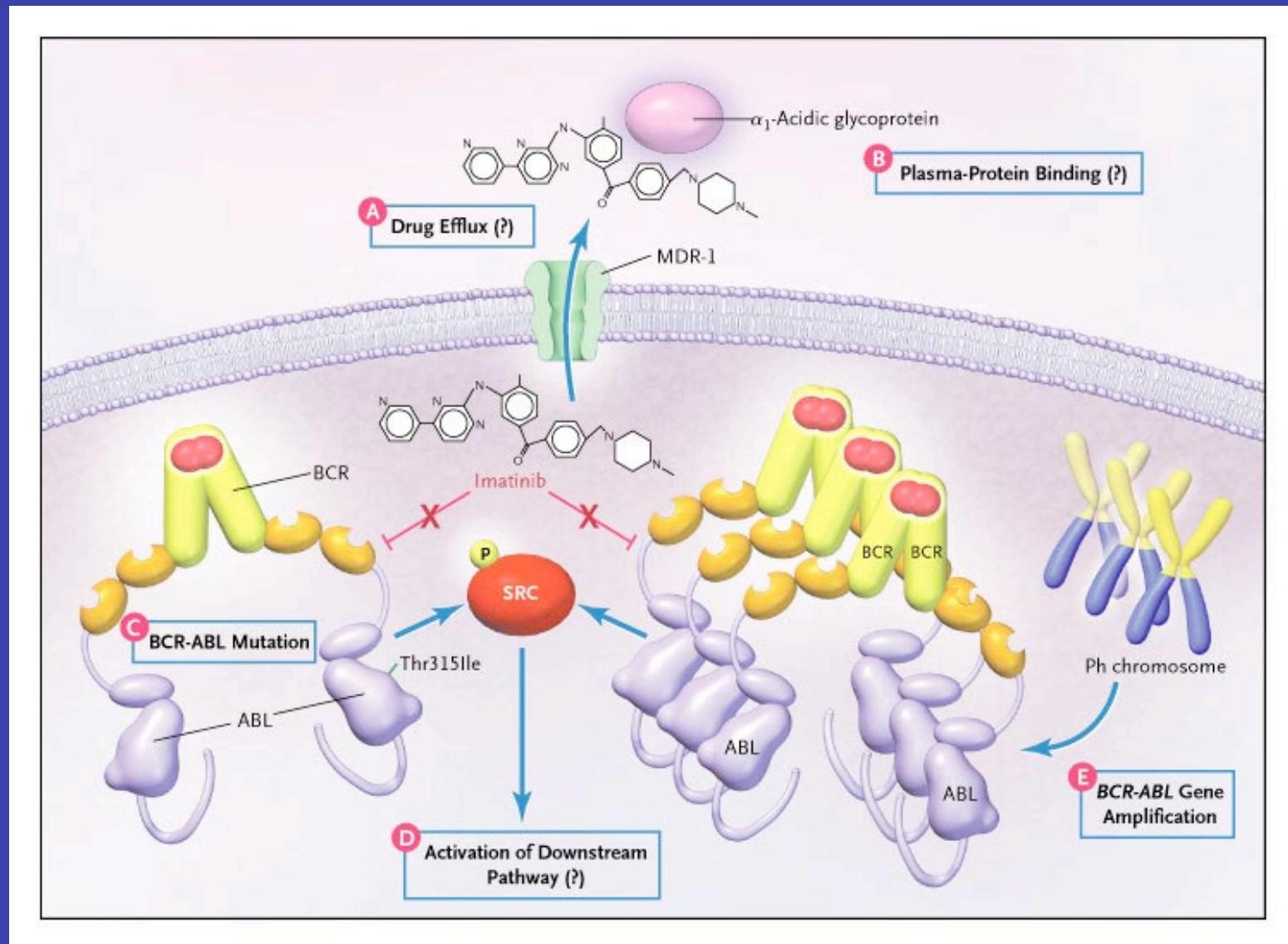
Main drugs used in CML, the Tyrosine Kinase Inhibitors: Multiple targets, great efficacy, ...but acquired resistances

Imatinib (targets=*ABL*, *PDGFR*, *KIT*): now 1st line treatment of CML
New TK Inhibitors in Clinical Trials for CML, with their targets:

Inhibitor	Company	Targets	Route of administration	Developmental status
Nilotinib (AMN 107)	Novartis	ABL, PDGFR, KIT, EPHB4	Oral	Phase II
Dasatinib (BMS-354825)	Bristol-Myers Squibb	ABL, PDGFR, KIT, FGR, FYN, HCK, LCK, LYN, SRC, YES, EPHB4	Oral	Approved
Bosutinib (SKI-606)	Wyeth	ABL, FGR, LYN, SRC	Oral	Phase II
INNO-406 (NS-187)	Innovive	ABL, LYN, PDGFR, KIT	Oral	Phase I
AZD0530	AstraZeneca	Src family kinases	Oral	Phase II (solid tumours)
MK-0457 (VX-680)	Merck	Aurora kinases, FLT3, JAK2, ABL (including T315I)	Intravenous	Phase II
PHA-739358	Nerviano	Aurora A, B and C	Oral	Phase II

(from Weisberg, *Nature Rev Cancer* 2007)

Mechanisms of resistance to TK Inhibitor therapy in CML (the main one being BCR-ABL mutation: >60% of relapses)



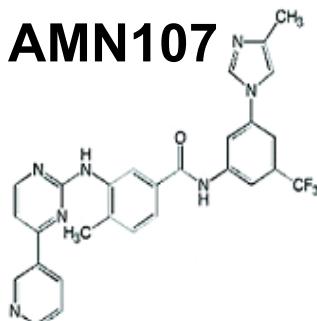
(from Krause N Engl J Med 2005)

In vitro activity of BCR-ABL inhibitors against Imatinib-resistant Abl kinase domain mutants

AMN107 and BMS-354825 are more effective than STI 571 in inhibiting proliferation of Ba/F3 cells expressing wild type Bcr-Abl or Bcr-Abl mutants

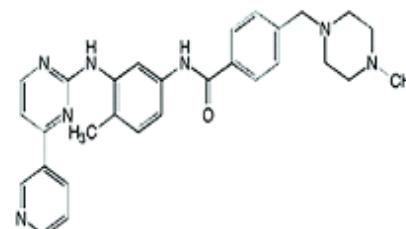
Nilotinib

AMN107



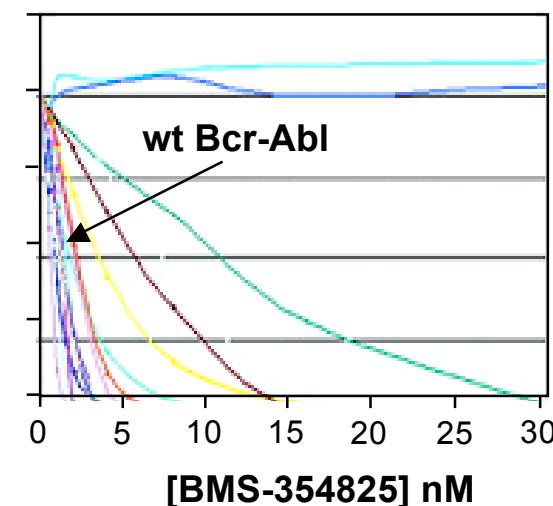
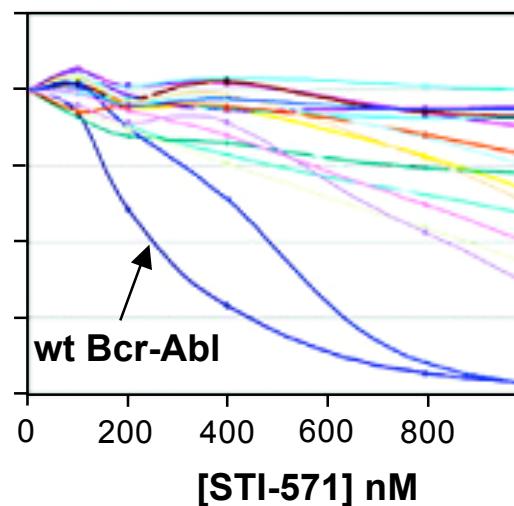
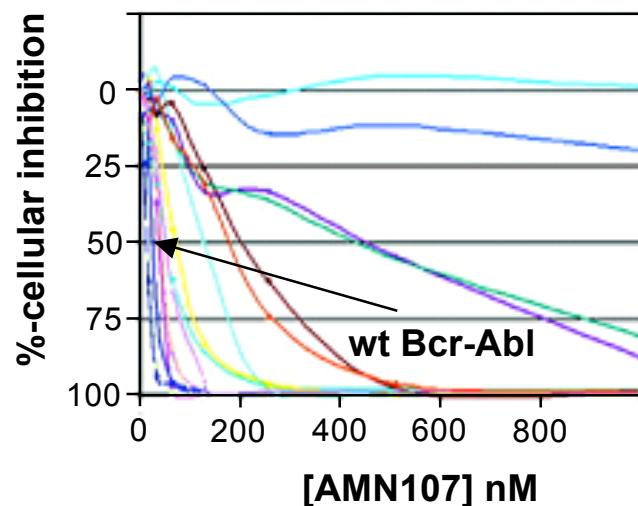
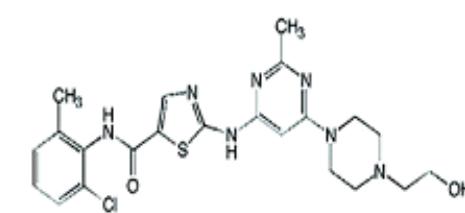
Imatinib

STI 571



Dasatinib

BMS-354825



(from O'Hare Cancer Res 2005)

Given that TK Inhibitors show little toxicity side effects on healthy tissues:

The main therapeutic issue with TKI is less to limit toxicity than to *prevent resistances due to mutations*, in combined drug therapies by diminishing mutagenic pressure on tyrosine kinases, otherwise induced by high levels of specific drugs

Representing *acquired resistances* to anticancer drugs should thus lead to model the evolution of cell populations by *PDEs structured in a genetic trait* with branching

Therapeutic constraints could then consist in imposing intracellular levels of drugs to *remain below a given mutagenic threshold* for each drug involved in polytherapies

...But such models remain to be designed and their therapeutic control optimised

Collaborations

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

In progress: Hôtel-Dieu and INSERM U 872, team 18 (Jean-Pierre Marie, Paris):
Malignant haemopathies (AML, CLL, resistances to cytostatic drugs)

Networks:

ARC INRIA ModLMC: <http://www.math.u-bordeaux1.fr/~adimy/modlmc/>
FP6 STREP Tempo: <http://www.chrono-tempo.org/>
FP6 NoE BioSim: <http://biosim.fysik.dtu.dk:8080/biosim/index.jsp>
FP6 MCRTN M3CSTGT: <http://calvino.polito.it/~mcrtn/>

Coming next: a 4-day school on cancer modelling in March 2008 in Rocquencourt
(<http://www.inria.fr/actualites/colloques/cea-edf-inria/2008/models-cancer/info.fr.html>)

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

CEA-EDF-INRIA Winter school in Rocquencourt (close to Versailles, France).

Targeted dates: March 11-14, 2008. Scientific organisers: J. Clairambault and D. Drasdo.

Tentative programme of lectures (all given in English):

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

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

- 1. ODE models for the cell cycle / PDE (age or DNA content-structured) models for the cell cycle / Delay Differential Equations for proliferating cell populations.*
 - 2. Tissue proliferation and invasion phenomena / From individual-based to continuous models / Probabilistic and deterministic models of tumour growth.*
 - 3. Molecular networks, fragility and robustness in cancer / Gene evolutionary dynamics of cancer / Gene evolutionary continuous models (adaptive evolution).*
 - 4. Therapeutic optimisation: minimising toxicity by using anticancer drug synergies with chronotherapy (and optimal control) / Therapeutic optimisation: overcoming drug resistances by using drug synergies. / Targeting stem cells.*
- + Complementary technical half-an-hour lectures: (1 each day): focus on: Flow cytometry / Cell and tissue image processing / DNA microarray analysis / Cancer databank design.*

..and a 2-day workshop
on haematopoiesis and its disorders,
joint meeting of ModLMC with the
Société Française d'Hématologie
(for the first day)
in the following week in Paris:

WORKSHOP
« Haematopoiesis and its Disorders.
Modelling, Experimental and Clinical Approaches »
March 20-21, 2008, in Paris

Committee

Guy (INRIA Futurs Bordeaux), Jean Clairambault (INRIA Rocquencourt), Fabien Crauste (CNRS Université Lyon 1), Jean-Pierre Marie (Hôtel Dieu Paris)

Thursday, March 20th 2008

Maison de la Chimie (SFH Congress)

9h	Mackey Michael C. (McGill University, Montreal) <i>A 30-year retrospective on continuous mathematical models for haematopoiesis, with confrontation to data</i>
10h	Pujo-Menjouet Laurent (University Lyon 1) <i>Multi-Agent System Approach for Hematopoiesis Modelling</i>
10h30	Coffee break
11h	Pacheco Jorge (Lisbon University) <i>Estimating the number of haematopoietic stem cells and maturation compartments in mammalian species</i>
12h	Lunch
14h	Plenary Conference of the SFH Congress
15h	Coffee break
15h30	Kitano Hiroaki (Tokyo) <i>Robustness and fragility in biological networks, implications for cancer therapy</i>
16h30	Génieys Stéphane (University Lyon 1) <i>Evolutionary branching processes and cellular differentiation</i>
17h	Clairambault Jean (INRIA Rocquencourt) <i>Optimising cancer chronotherapy under the constraint of preserving healthy tissues from unwanted toxicity</i>
17h30	Discussions
18h	