Cell proliferation, circadian clocks and molecular pharmacokinetics-pharmacodynamics to optimise cancer treatments

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

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Outline of the lectures

- 0. Introduction and general modelling framework
- 1. Modelling the cell cycle in proliferating cell populations
- 2. Circadian rhythm and cell / tissue proliferation
- 3. Molecular pharmacokinetics-pharmacodynamics (PK-PD)
- 4. Optimising anticancer drug delivery: present and future
- 5. More future prospects and challenges

Introduction and general modelling framework

3 short preliminary questions

- What sort of disease is cancer?
- How are anticancer drugs delivered and how do they act?
- How can we improve their efficacy?

Cancer: a *control disease*, defined as uncontrolled 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 healthy and fast renewing tissues (gut, bone marrow…) that is *disrupted in cancer*

Drugs: from delivery (infusion/ingestion) to target
Molecular *PK-PD* modelling in oncology

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

- *Input*: an intravenous [multi-]drug infusion flow
- Drug concentrations in blood *and tissue* compartments (*PK*)
- Control of targets on the cell cycle *in tissues* (cell population *PD*)
- *Output*: a cell population number -or growth rate- in tumour and healthy tissues

Optimising drug delivery: optimisation under constraints

- Optimal control of delivery flow (programmable pumps)
- Objective: minimising tumour cell number
- Constraints: - limiting toxicity to healthy cells
  - avoiding drug resistance in cancer cells

Mathematical modelling to optimise cancer treatments

… hence 3 main research directions:

- Proliferation: cell population dynamics in tissues (PDEs)

- Drugs: molecular pharmacokinetics-pharmacodynamic (ODEs)

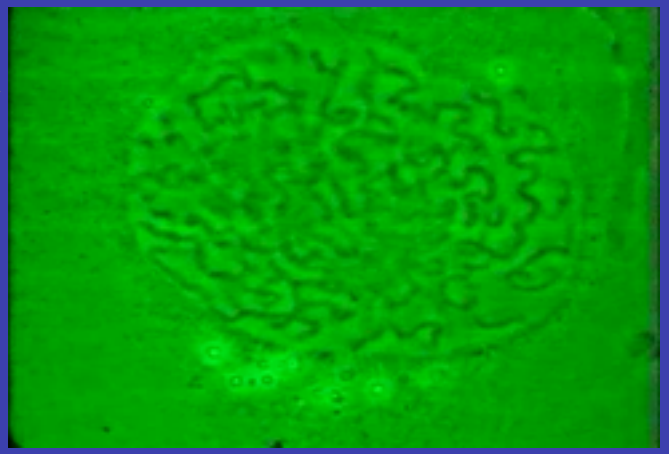
- Therapeutic optimisation: optimal control of drug delivery

(optimal control algorithms)

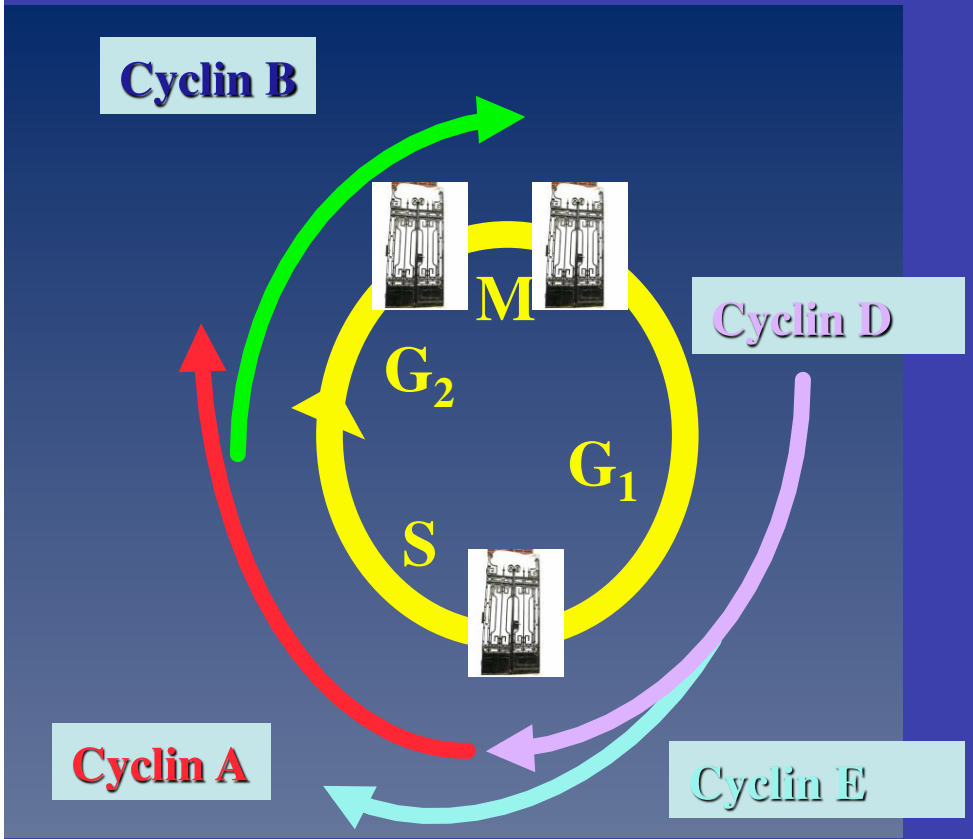
…and future prospects: even more challenges for modelling!

At the origin of proliferation: the cell division cycle

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



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

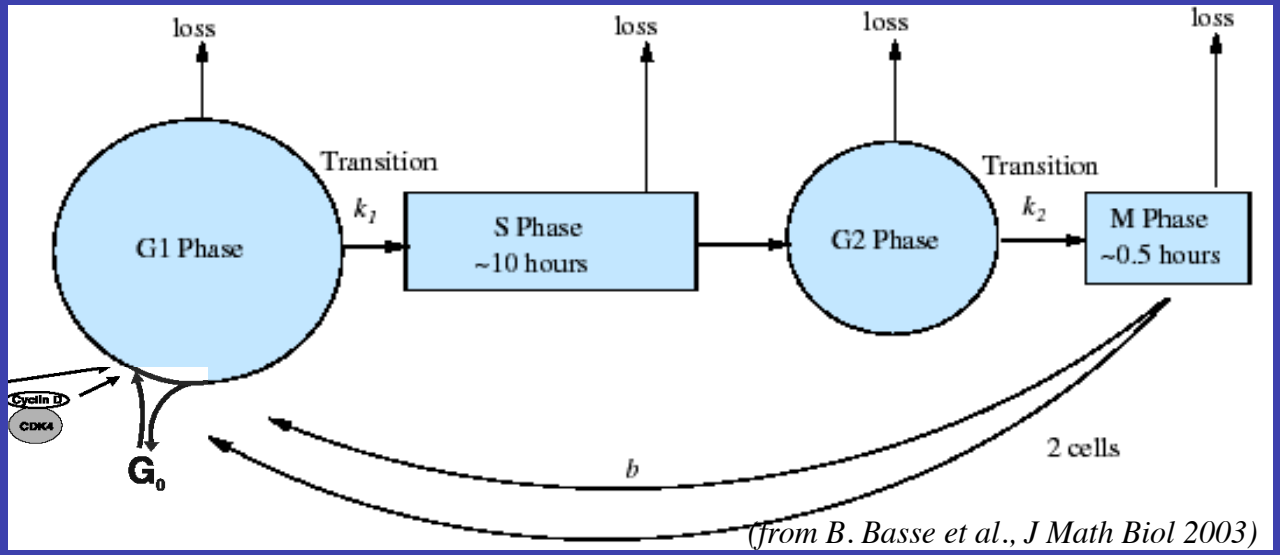


Physiological or therapeutic control exerted on:

- transitions (checkpoints) between phases (G_1/S, G_2/M, M/G_1)
- death rates (apoptosis or necrosis)
- progression speeds inside phases
- exchanges between quiescent (G_0) and proliferative phases (G_1 only)

Modelling the cell division cycle in cell populations

Physiologically structured PDEs



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

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

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

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

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

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

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

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

Death rates d_i: ("loss"), "speeds" v_i and phase transitions $K_{i->i+1}$ 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]

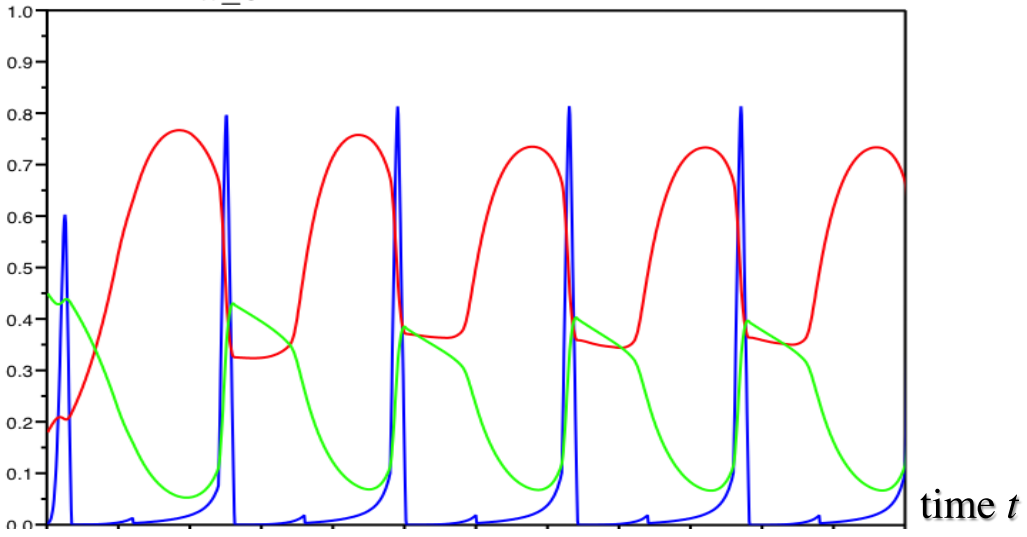
(Firstly presented in: JC, B. Laroche, S. Mischler, B. Perthame, RR INRIA #4892, 2003)

Main result: a growth exponent for the cell population behaviour

Proof of the existence of *a unique growth exponent* λ, the same for all phases i, such that the $\widetilde{N}_i(t,a) = e^{-\lambda t} n_i(t,a)$ are 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 G_2/M transition by 24-h-periodic CDK1-Cyclin B (A. Goldbeter's model)

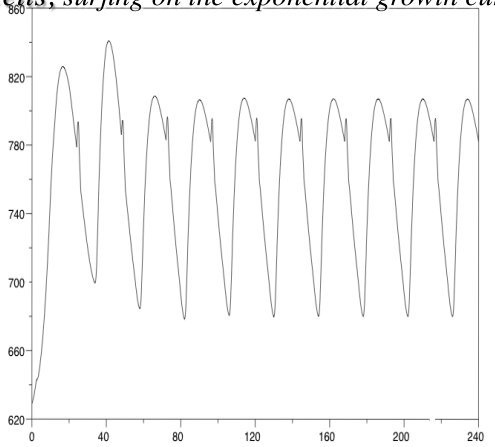
$$\mathcal{N}_i^{tot}(t) = e^{-\lambda t} \int_{\alpha \geq 0} n_i(t,\alpha) d\alpha, \quad i = 1,2$$ (Normalised cell population number)



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

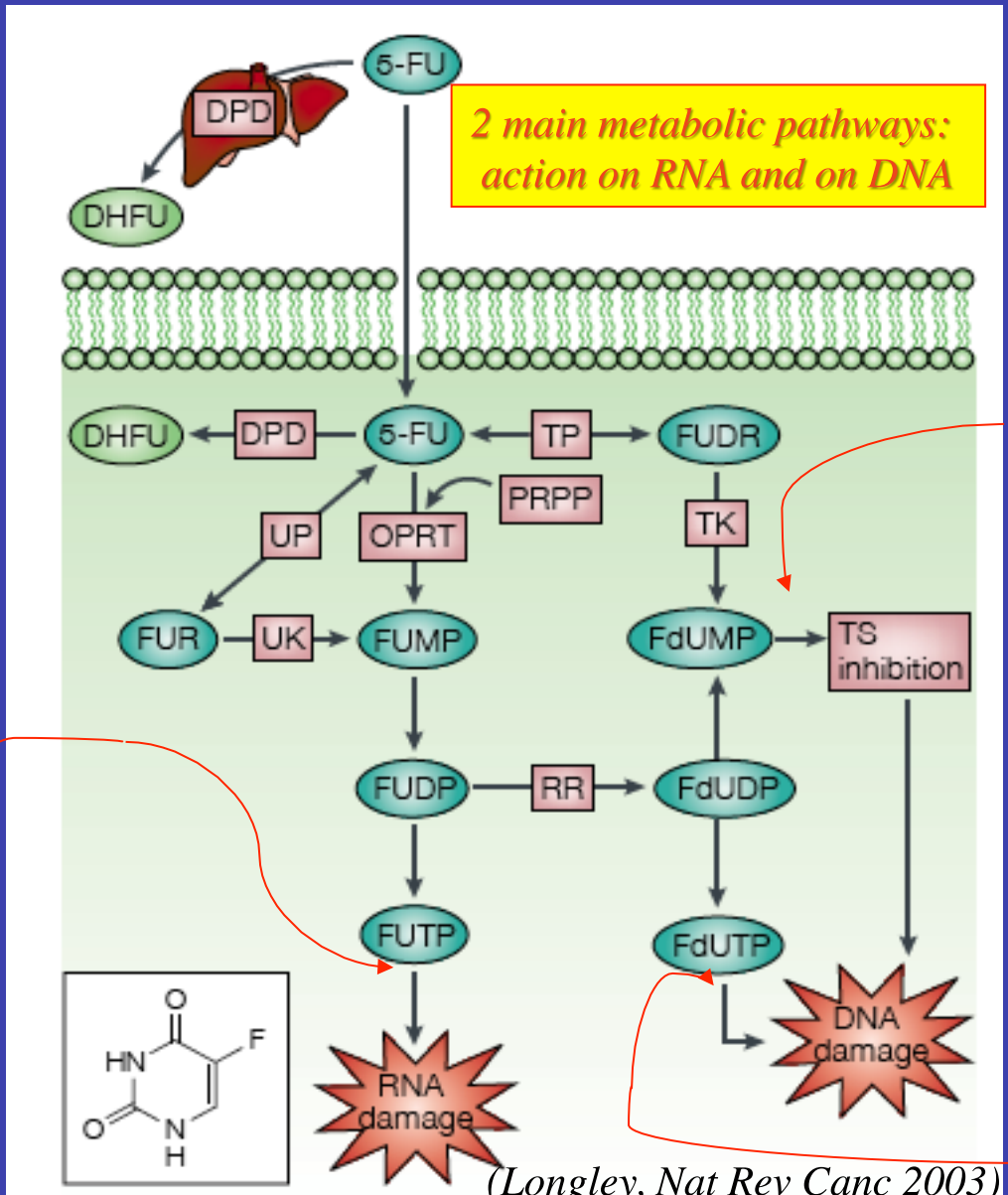
Entrainment of the cell division cycle by CDK1 at the circadian period

All cells, surfing on the exponential growth curve



Example: molecular pharmacodynamics (PD) of 5FU

RNA way



Incorporation of FUTP instead of UTP to RNA

DNA way

Competitive inhibition by FdUMP of dUMP binding to target TS

+

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

Incorporation of FdUTP instead of dTTP to DNA

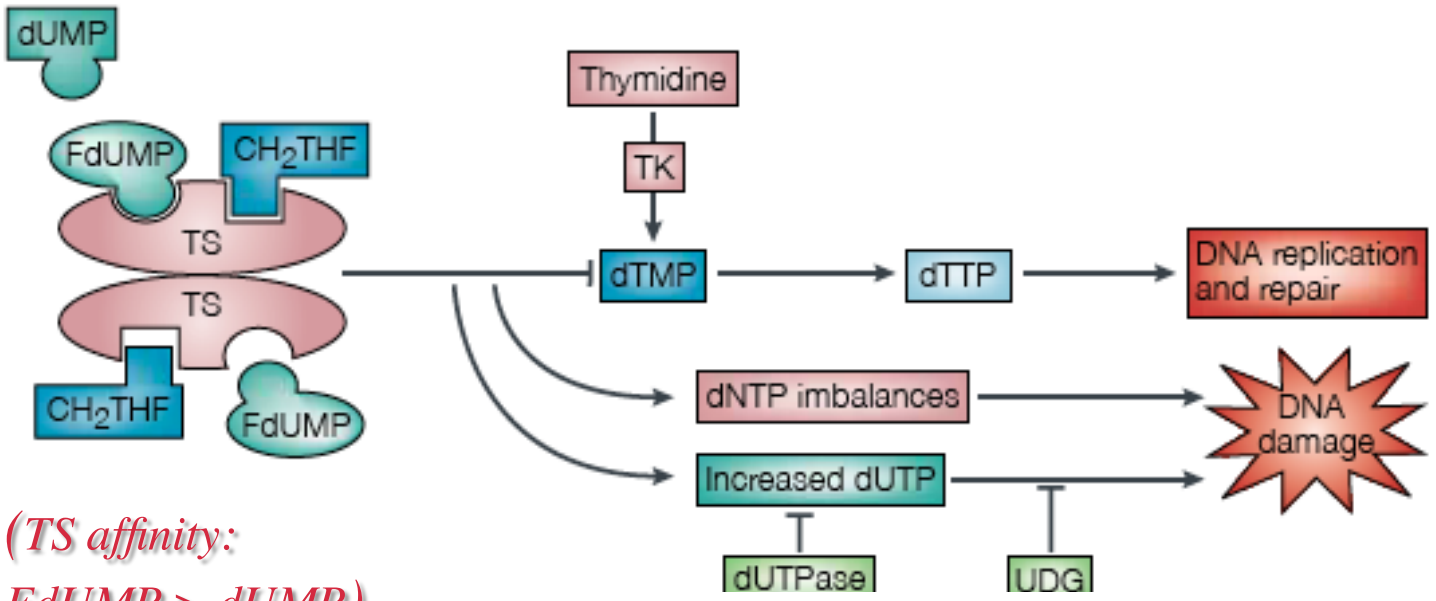
(Longley, Nat Rev Canc 2003)

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

Formyltetrahydrofolate (CHO-THF) = LV

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

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



(TS affinity: FdUMP > dUMP)

(Longley, Nat Rev Canc 2003)

ODEs: PK-PD of 5FU [+ drug resistance] + Leucovorin

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

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

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

Input j = LV infusion flow

Input i = 5-FU infusion flow

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

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

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

A = ABC transporter (active drug efflux)

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

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

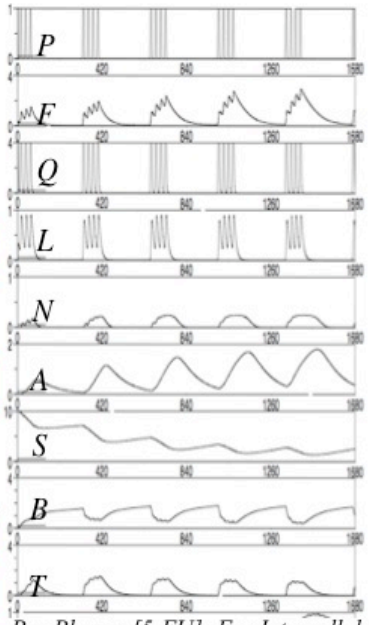
S = Free Thymidylate Synthase (TS)

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

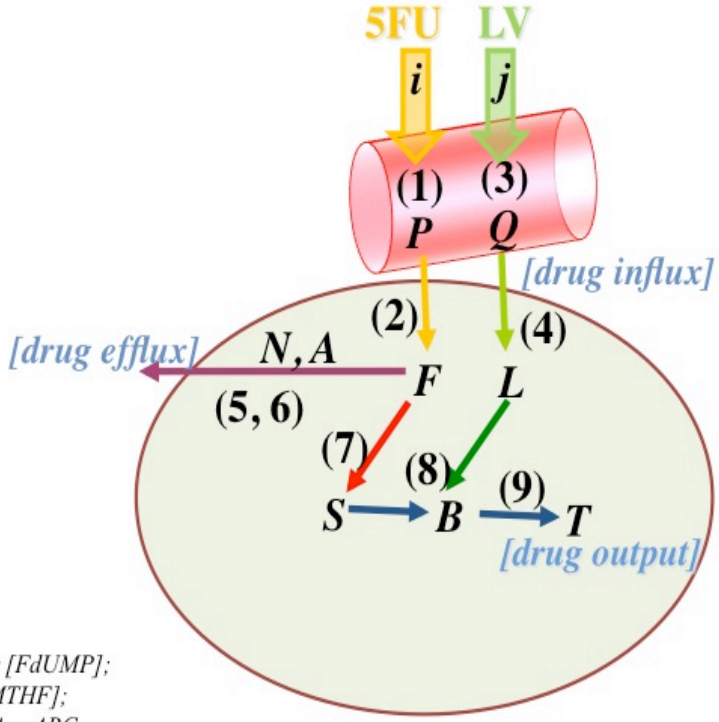
Drug output T = Blocked Thymidylate Synthase (stable ternary FdUMP-MTHF-TS complex)

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

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



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

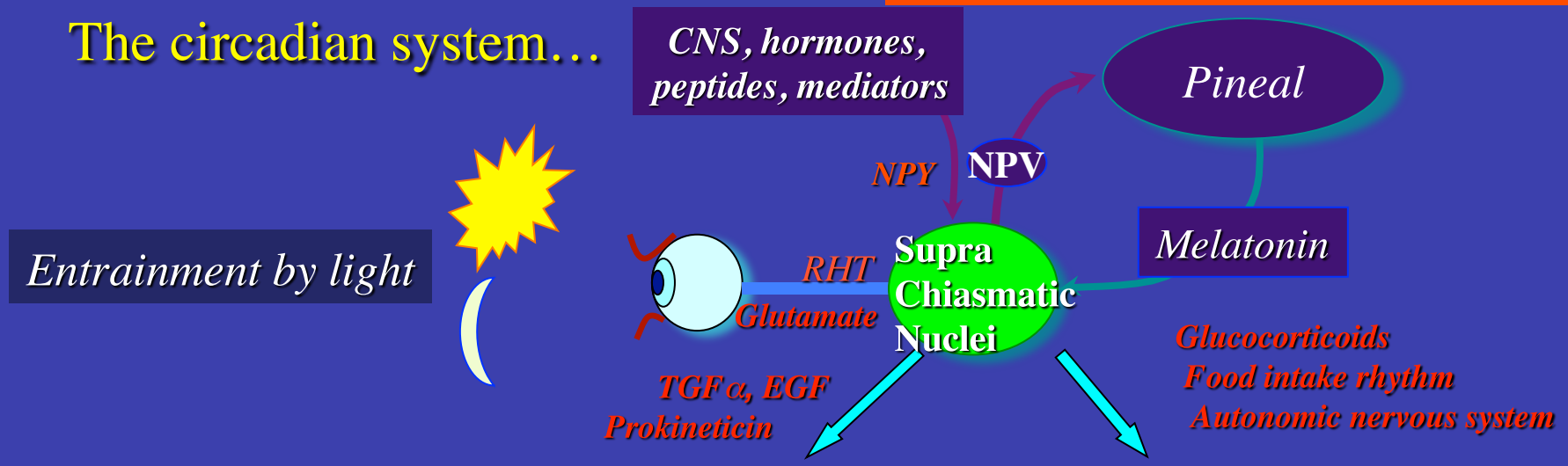


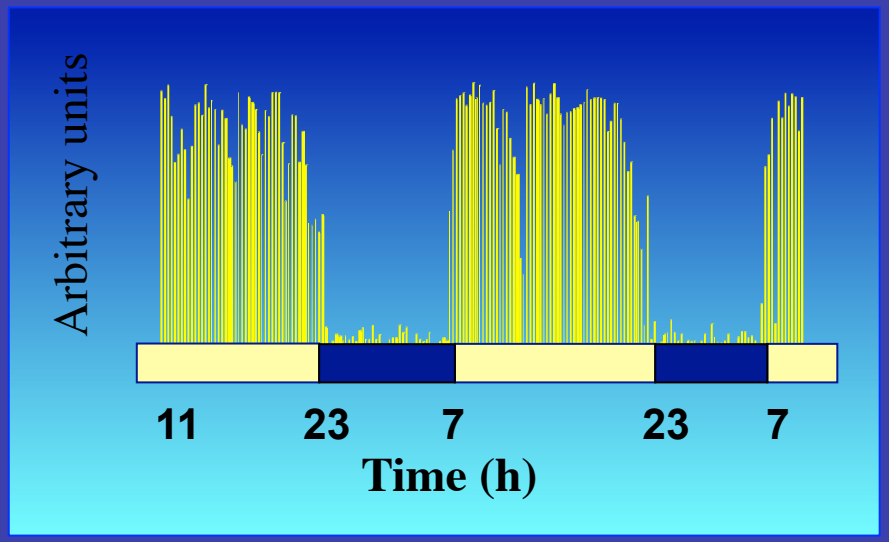
F. Lévi, A. Okyar, S. Dulong, JC, Annu Rev Pharm Toxicol 2010

Circadian clocks

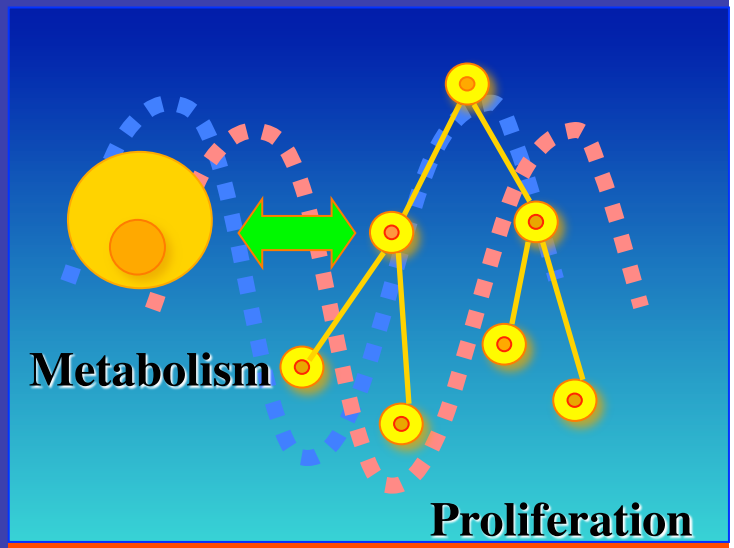
Central coordination

The circadian system…





Rest-activity cycle: open window on SCN central clock



Peripheral oscillators

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

…is an orchestra of cell clocks with one neuronal conductor in the SCN and molecular circadian clocks in all nucleated cells

SCN=suprachiasmatic nuclei (in the hypothalamus)

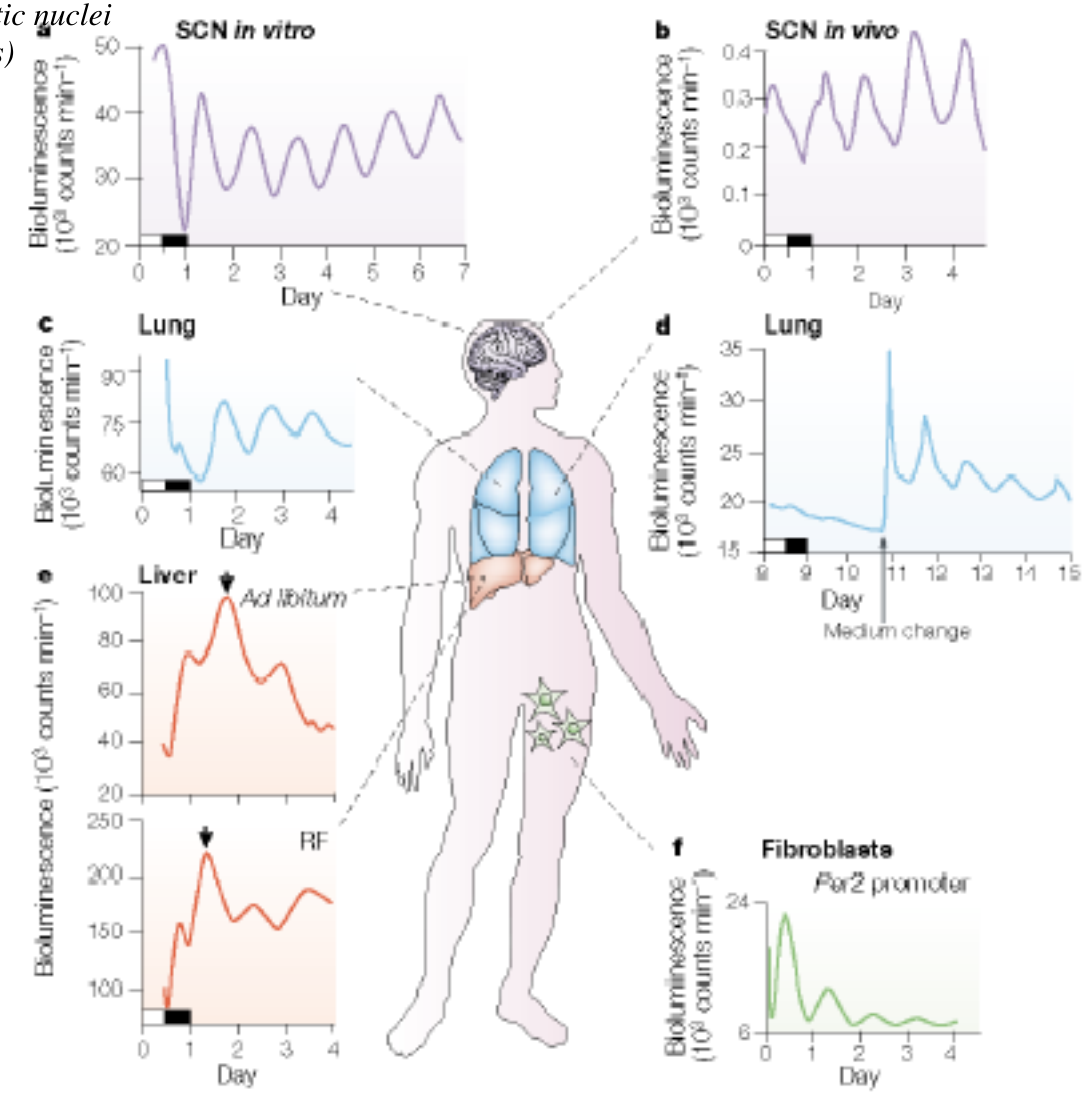
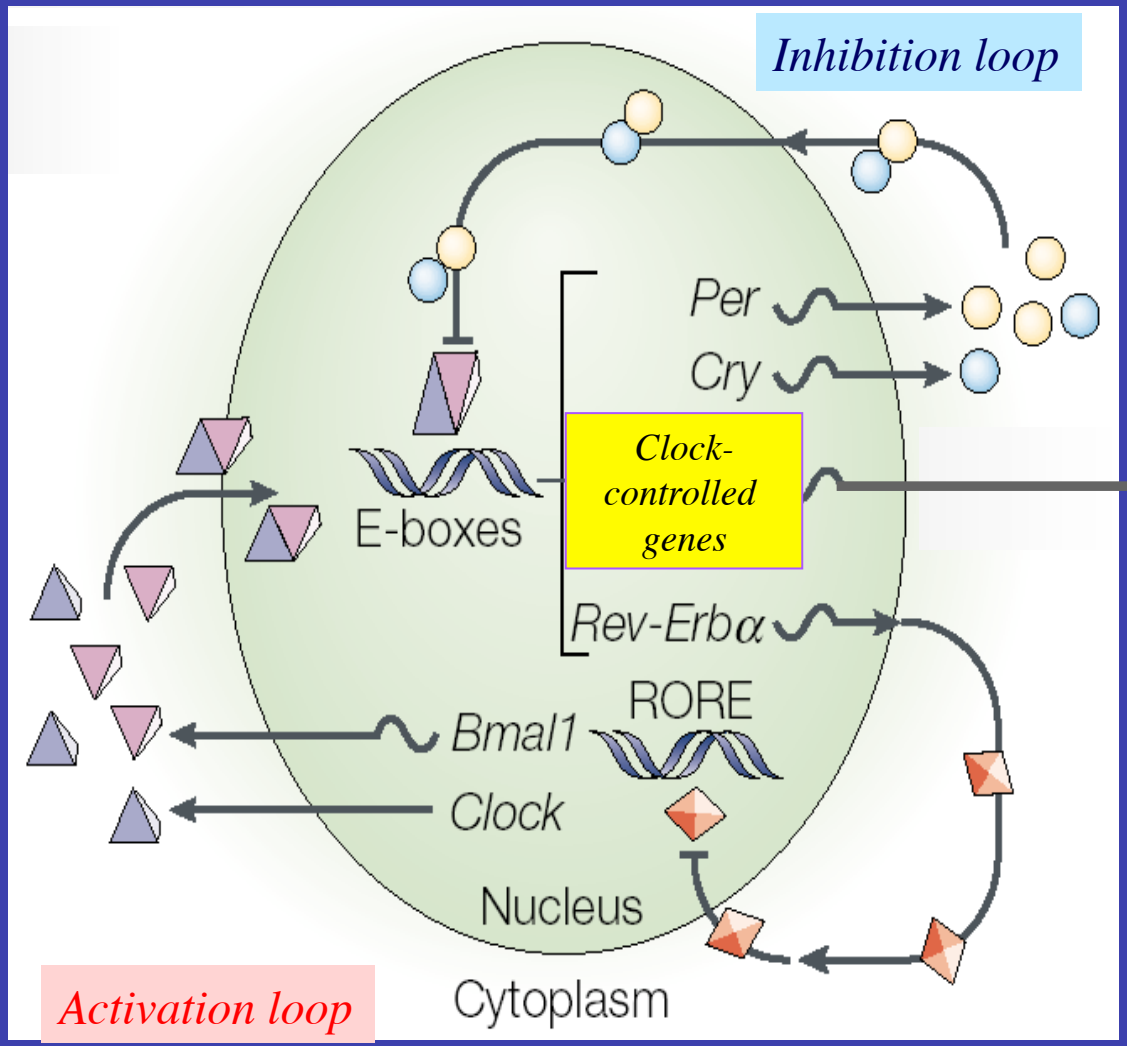


Figure 3 | ***Per::luciferase* transgenes reveal a diversity of tissue-based circadian oscillators.**

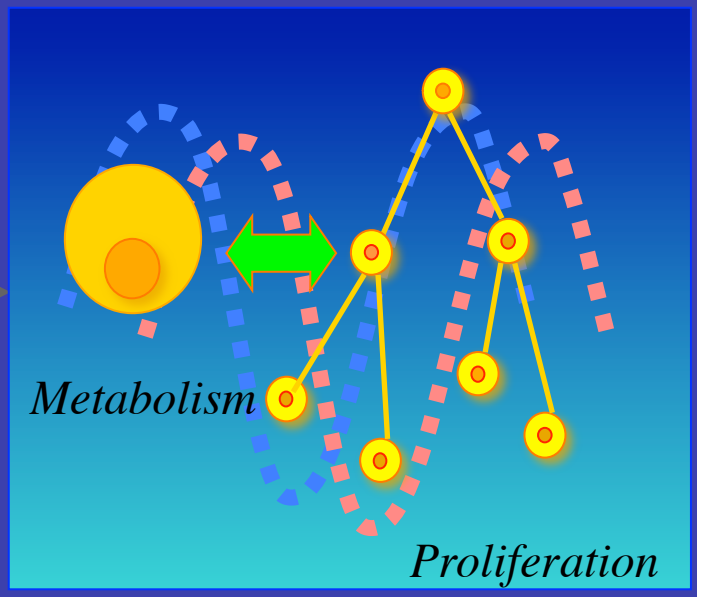
(Hastings, Nature Rev. Neurosci. 2003)

In each nucleated cell: a molecular circadian clock



(after Hastings, Nature Rev. Neurosci. 2003)

Cellular rhythms

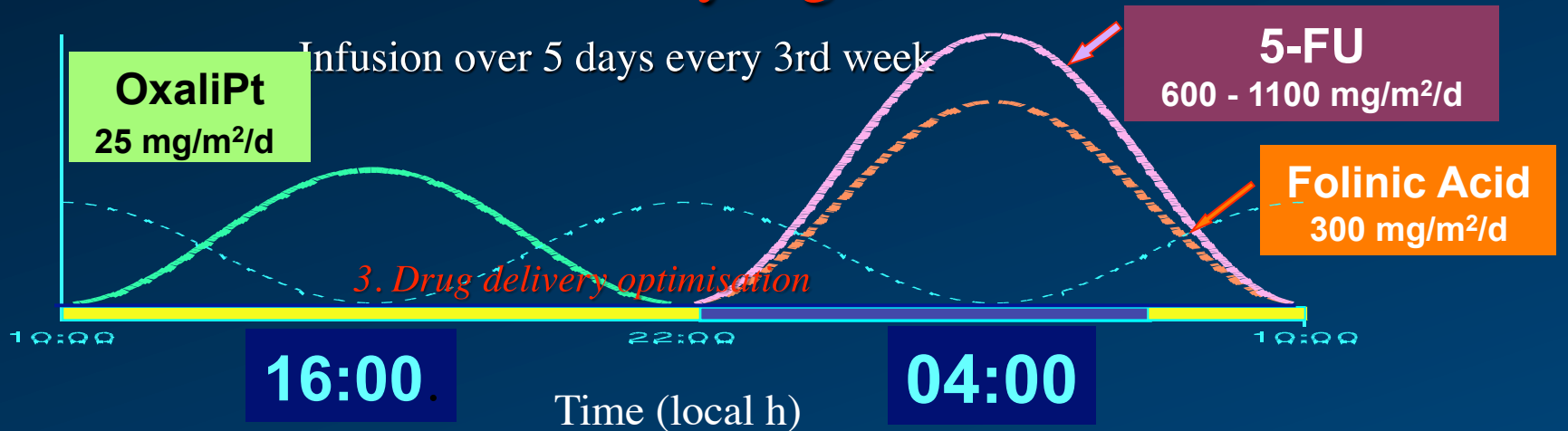


24 h-rhythmic transcription:
10% of genome, among which:
10% : cell cycle
2% : growth factors

Circadian rhythms and cancer chronotherapeutics

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

Time-scheduled delivery regimen for metastatic CRC

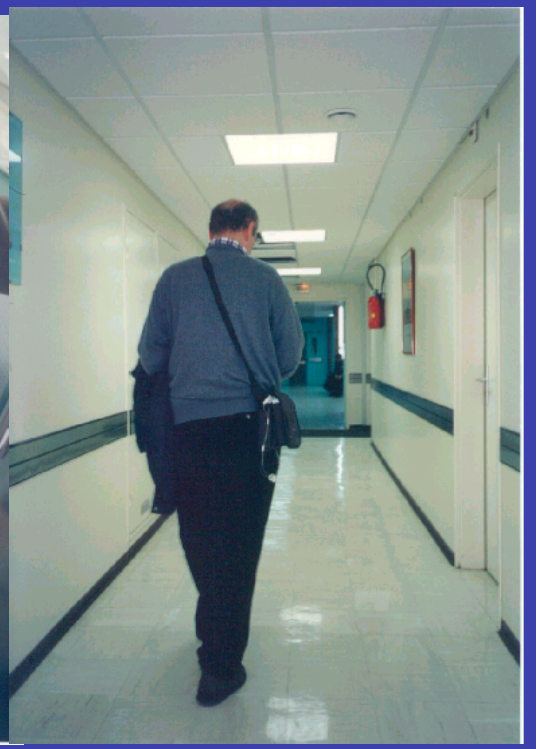


Multichannel programmable ambulatory injector for intravenous drug infusion (pompe Mélodie, Aguettant, Lyon, France)

Can such therapeutic schedules be improved?

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

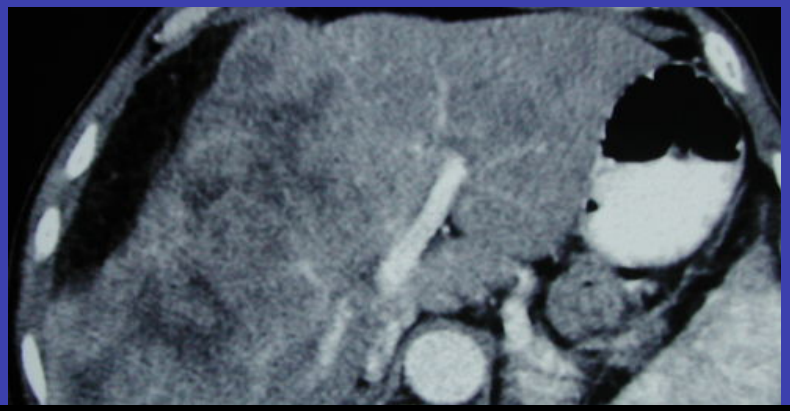


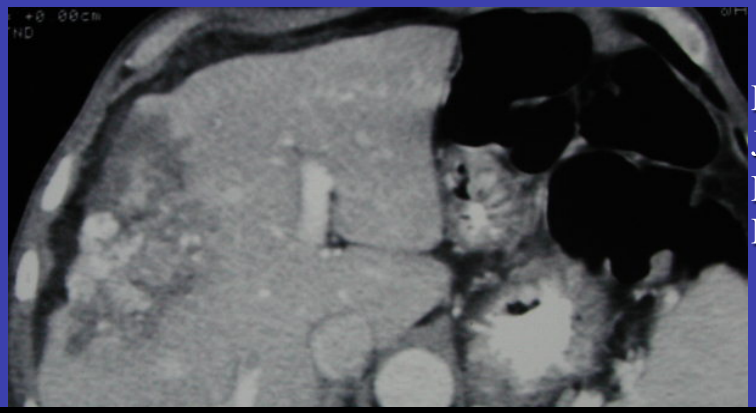
Images from the Chronotherapy Unit, Paul-Brousse Hospital, Villejuif, France

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

Results of 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%	$<10^{-3}$





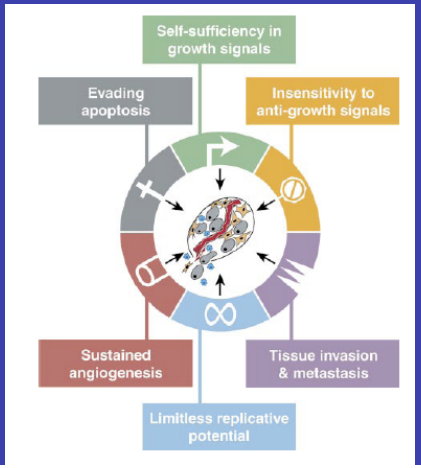
Lévi et al.
JNCI 1994 ;
Lancet 1997 ;
Lancet Oncol 2001

How does it work? Impact of circadian clocks on 1) cell drug detoxication enzymes and 2) cell division cycle determinant proteins (cyclins/CDKs)

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 peripheral cells from central circadian clock control messages, just as tumour cells evade most physiological controls, cf. Hanahan & Weinberg:



Optimal control of anticancer chronopharmacotherapy

1) *Objective function* to be minimised: cell population growth rate or cell population density in tumour tissues

2) *Control function*: instantaneous [dynamic] intravenous infusion = [multi-]drug delivery flow via external programmable pumps

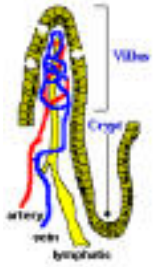
3) *Constraints* to be satisfied:
- maintaining healthy cell population over a tolerability threshold
- taking into account circadian phases of drug processing systems (model prerequisite)
- *maintaining normal tissue synchronisation control by circadian clocks*
- limiting resistances in tumour cells (*e.g. controlling induction of nrf2)*
- others: maximal daily dose, maximal delivery flow,…

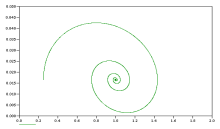
4) *With adaptation* of drug delivery flow to *patient-specific parameters* (clock phases, enzyme genetic polymorphism, target protein levels): *towards personalised medicine*

PK-PD simplified model for cancer chronotherapy (here with only toxicity constraints; target=death rate)

Healthy cells (jejunal mucosa)

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

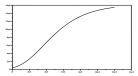




(PK)

Tumour cells

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



(homeostasis=damped harmonic oscillator)

(tumour growth=Gompertz model)

(« chrono-PD »)

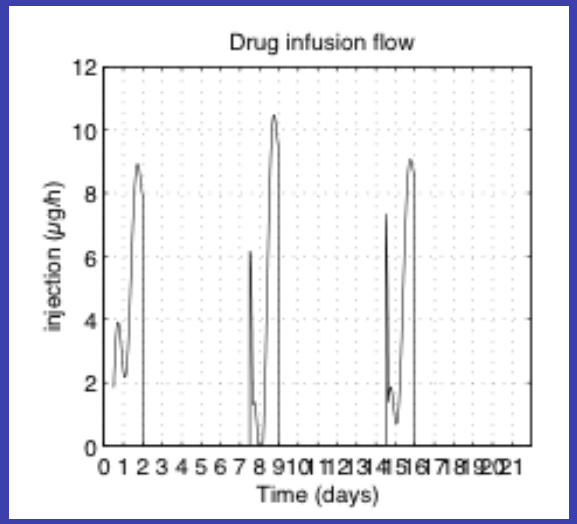
$f(C,t)=F.C^{\gamma}/(C_{50}{}^{\gamma}+C^{\gamma}).\{1+\cos 2\pi(t-\varphi_S)/T\}$

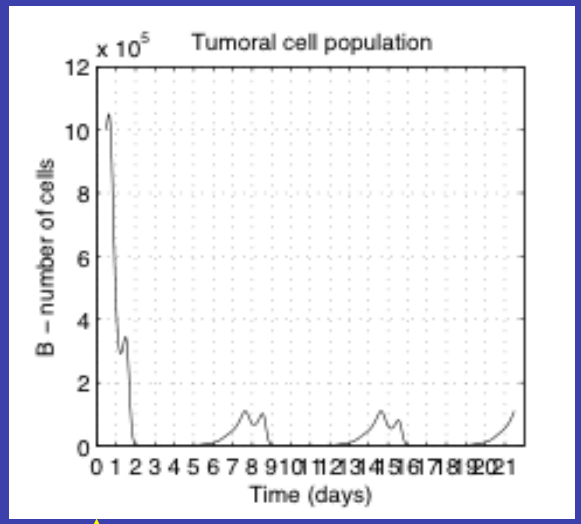
$g(D,t)=H.D^{\gamma}/(D_{50}{}^{\gamma}+D^{\gamma}).\{1+\cos 2\pi(t-\varphi_T)/T\}$

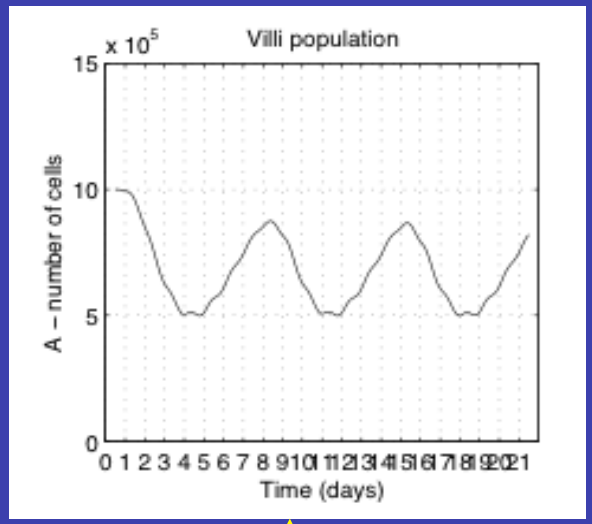
Aim: balancing IV delivered drug anti-tumour efficacy by healthy tissue toxicity

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

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 tunable parameter τ_A: here preserving τ_A=50% of enterocytes*)*

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

Individualised treatments in oncology

Genetic polymorphism: between-subject variability

for pharmacological model parameters

- According to subjects, different expression and activity levels of drug processing enzymes and proteins (uptake, degradation, active efflux, e.g. GSTπ, DPYD, UGT1A1, P-gp,…) and drug targets (e.g. Thymidylate Synthase, Topoisomerase I)

- The same is true of DNA mismatch repair enzyme gene expression (e.g., ERCC1, ERCC2)

- More generally, pharmacotherapeutics should be guided more by molecular alterations of the DNA than by location of tumours: genotyping patients with respect to anticancer drug processing may become the rule in oncology in the future *(see e.g. G. Milano & J. Robert in Oncologie 2005)*

- …Which leads, using actively searched-for biomarkers, to *populational PK-PD*

Other frontiers in cancer therapeutics

1. Immunotherapy:

Not only using cytokines and actual anticancer vaccines, but also examining delivery of cytotoxics from the point of view of their action on the immune system

(Review by L. Zitvogel in Nature Rev. Immunol. 2008)

2. The various facets of (innate/acquired/(ir)reversible) drug resistance:

- Repair enzymes, mutated p53: cell cycle models with by-pass of DNA damage control
- ABC transporters, cellular drug metabolism: molecular PK-PD ODEs (or PDEs)
- Microenvironment, interactions with stromal cells: competition/cooperativity models
- Mutations of the targets: evolutionary game theory, evolutionary dynamics models

3. Developing non-cell-killing therapeutic means:

- Associations of cytotoxics and redifferentiating agents (e.g. retinoic acid in AML3)
- Modifying local metabolic parameters? (pH) to foster proliferation of healthy cells

Collaborators

INRIA Bang project-team: *Annabelle Ballesta, Fadia Bekkal Brikci, Luna Dimitrio, Marie Doumic, Herbert Gayrard, Thomas Lepoutre, Benoît Perthame, Emilio Solis*

Other INRIA project-teams: Maxplus (*Stéphane Gaubert*), Contraintes (*François Fages*), Disco (*Catherine Bonnet*), Dracula (*Mostafa Adimy, Vitaly Volpert*)

INSERM U 776 "Biological Rhythms and Cancers" (*F. Lévi*, Paul-Brousse hospital, Villejuif): Solid tumours of Mice and Men, chronotherapeutics of colorectal cancer

UMRs UPMC- INSERM U 872 Team 18 "Resistance and survival of tumour cells" (*J.-P. Marie*, Cordeliers Research Centre and Saint-Antoine Hospital, Paris): Leukaemias

Université Paris-Nord (*Claude Basdevant)*: Optimal control theory and algorithms

past ARC INRIA ModLMC: http://www.math.u-bordeaux1.fr/~adimy/modlmc/
past FP6 STREP Tempo: http://www.chrono-tempo.org/
past FP6 NoE BioSim: http://biosim.fysik.dtu.dk:8080/biosim/index.jsp
past FP6 MCRTN M3CSTGT: http://calvino.polito.it/~mcrtn/
present FP7 ERASysBio C5Sys:http://www.erasysbio.net/index.php?index=272
present ANR Bimod

Modelling the cell division cycle in proliferating cell populations

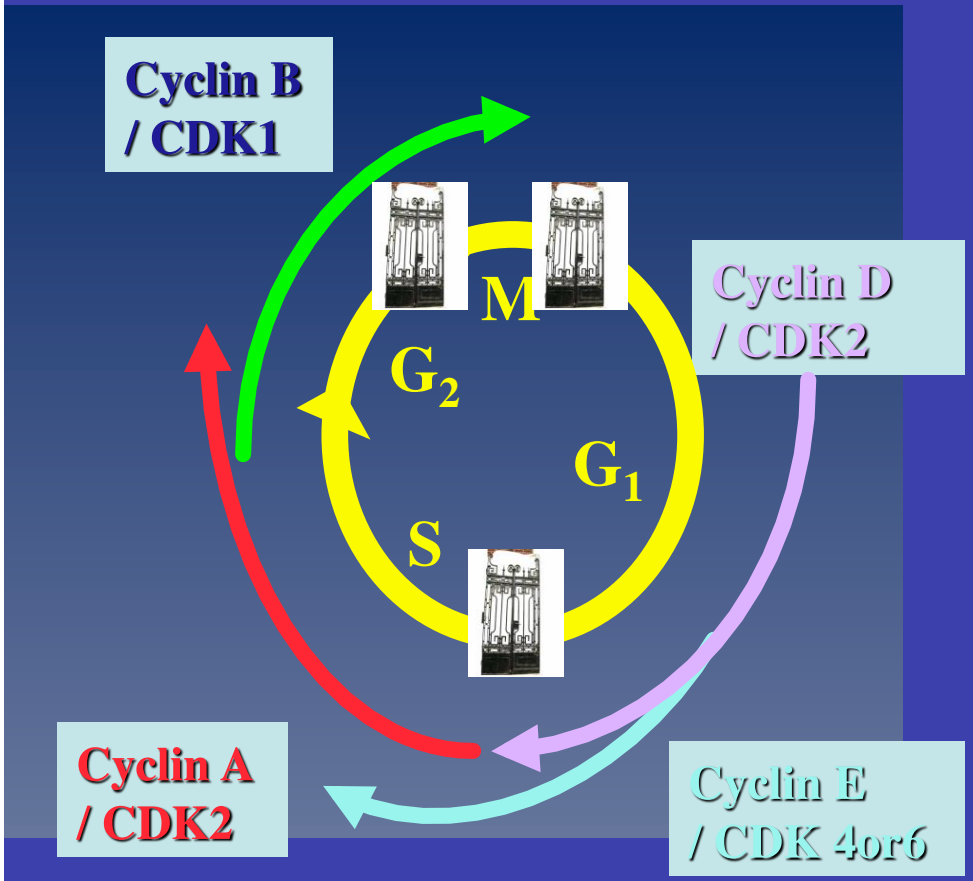
Why model the cell division cycle?

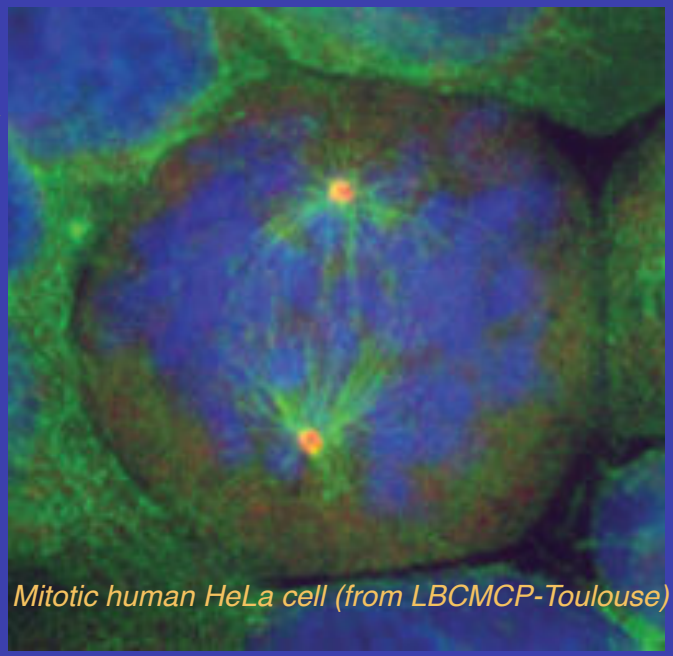
- Need for detailed models of cell proliferation to represent the action of anticancer drugs *in cell populations* with:
  1) Cell cycle phase specificity
  2) Different pharmacological targets on cell cycle control
  3) Action with same targets on tumour cells *and on healthy cells*
     (toxic side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

- Hence, 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)

At the origin of proliferation: the cell division cycle in proliferating cell populations

S:=DNA synthesis; G_1,G_2:=Gap1,2; M:=mitosis
(one cell divides in two)

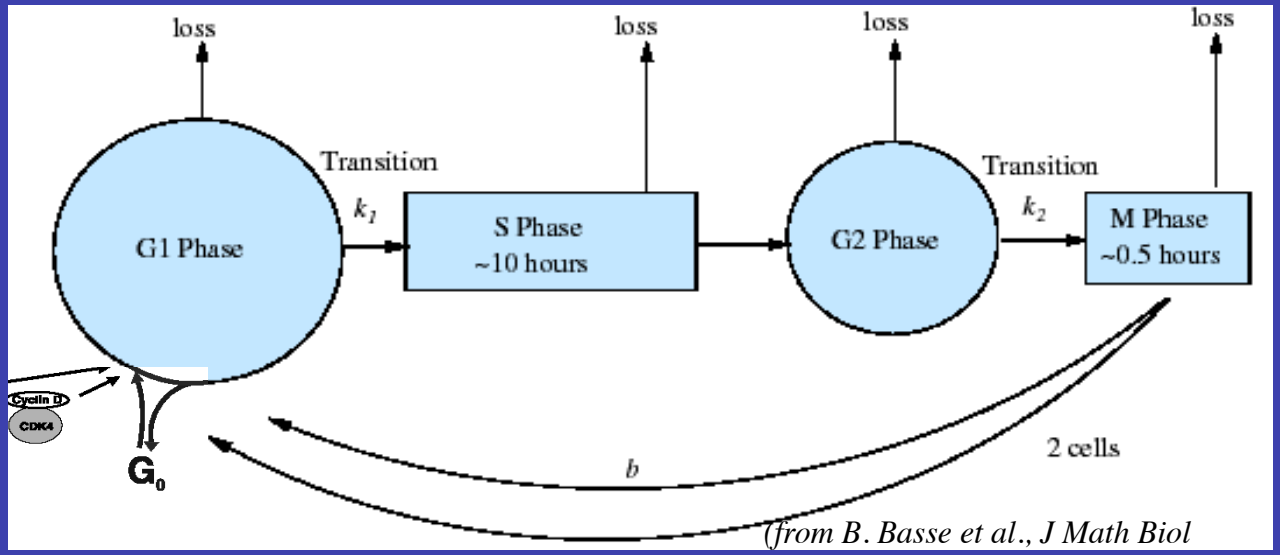



Mitotic human HeLa cell (from LBCMCP-Toulouse)

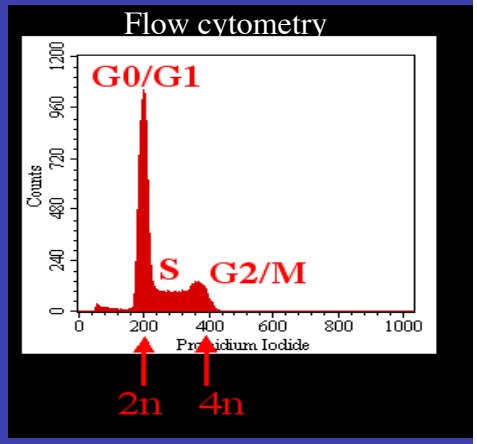
Physiological and therapeutic control exerted on:

- transitions (checkpoints) between phases (G_1/S, G_2/M, M/G_1)
- death rates (apoptosis or necrosis) and progression speeds inside phases
- exchanges between quiescent (G_0) and proliferative phases (G_1 only)

Age-structured PDE models



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



In each phase *i*, a Von Foerster-McKendrick-like 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;
v_i:=progression speed;
d_i:=death rate;

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

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

Death rates d_i: ("loss"), "speeds" v_i and phase transitions $K_{i->i+1}$ are model targets for physiological (e.g., circadian) or therapeutic (drug) control $\psi(t)$
[$\psi(t)$: e.g., clock-controlled CDK1 or intracellular output of drug infusion flow]

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

The simplest case: 1-phase model with division

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

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

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

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

(Here, $v(a)=1$, a^* is the cell cycle duration, and $\tau(<1)$ is the time during which the 1-*periodic control* ψ ισ 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 $K_0 \longrightarrow +\infty$ *(T. Lepoutre)*

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

(Note that exchanges between G_0 and G_1 are not considered in this linear model, i.e., all cells are assumed to proliferate)

Then, provided that reasonable assumptions on death and transition rates are satisfied:

$$K_{i\to i+1}(t,a) \geq 0,\ d_i(t,x) \geq 0 \qquad \text{bounded}, \tag{1}$$

and, setting: $\min_{0\leq t\leq T} K_{i\to i+1}(t,a) := k_{i\to i+1}(a)$,

$\max_{0\leq t\leq T}[d_i + K_{i\to i+1}] := \mu_i(a)$, $M_i(a) = \int_0^a \mu_i(\alpha)d\alpha$,

$$\prod_{i=1}^{I} \int_{\alpha\geq 0} k_{i\to i+1}(\alpha)e^{-M_i(\alpha)}d\alpha > 1/2 \tag{2}$$

(thus ensuring positive growth), one can establish that:

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 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 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

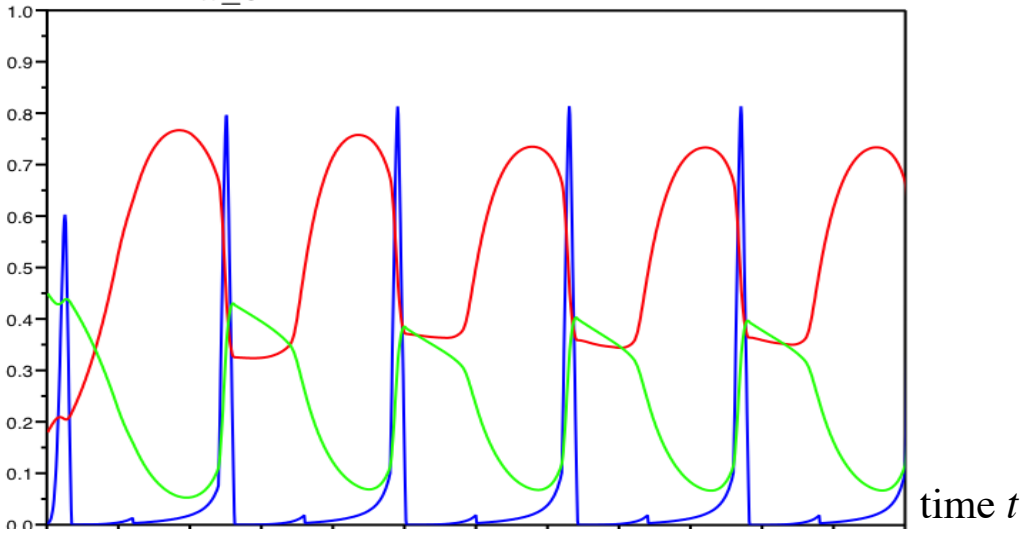
JC, Michel, Perthame C. R. Acad. Sci. Paris Series I (Math.) 2006; Proceedings ECMTB Dresden 2005

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 the $\widetilde{N}_i(t,a) = e^{-\lambda t} n_i(t,a)$ are bounded, and asymptotically periodic if the control is periodic

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

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



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

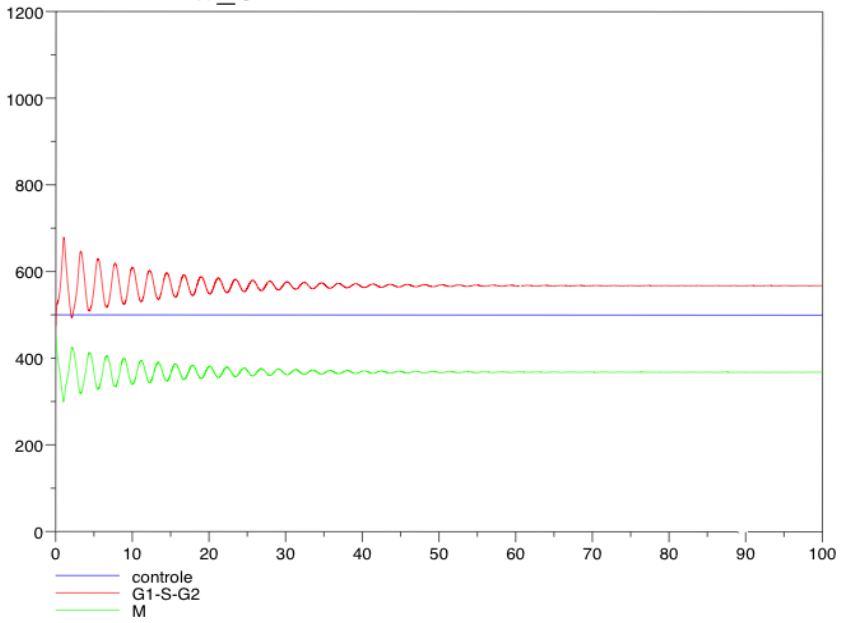
Entrainment of the cell division cycle by **ψ=** *CDK1 at the circadian period*

"Surfing on the exponential growth curve"

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

Details (1): 2-phase model, no control on transition

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

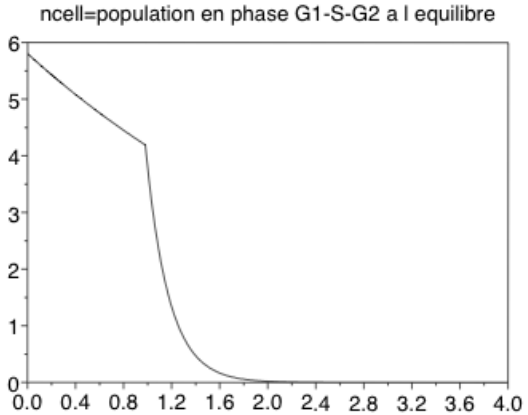


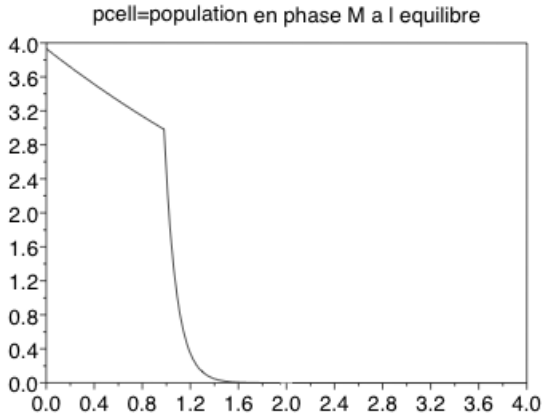
The total population of cells

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

inside each phase follows asymptotically an exponential behaviour

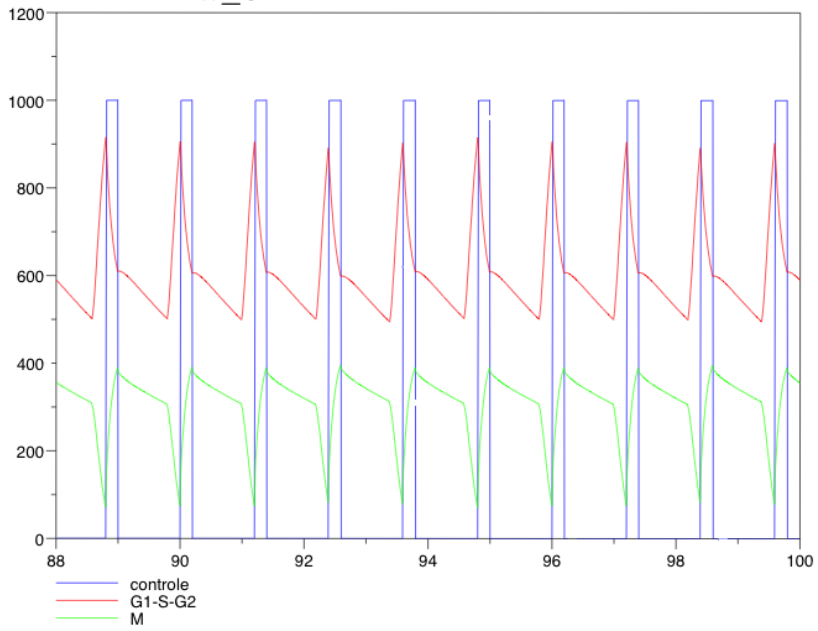
Stationary (=asymptotic) state distribution of cells inside phases according to age *a: no control -> exponential decay*





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

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

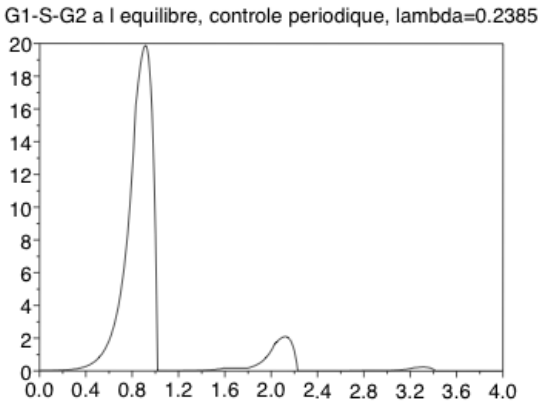


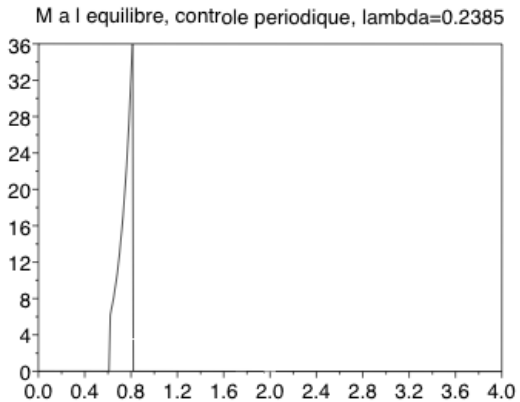
The total population of cells

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

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

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





Desynchronisation of cells within populations w. r. to cell cycle timing = phase overlapping at transition:

Possible experimental measurements to identify transition kernel *K*

Starting from the simplest model with *d*=0 (one phase with division):

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

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

Interpreted as: if τ is the age at division, or transition: (remark by Th. Lepoutre)

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

where the probability density is:

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

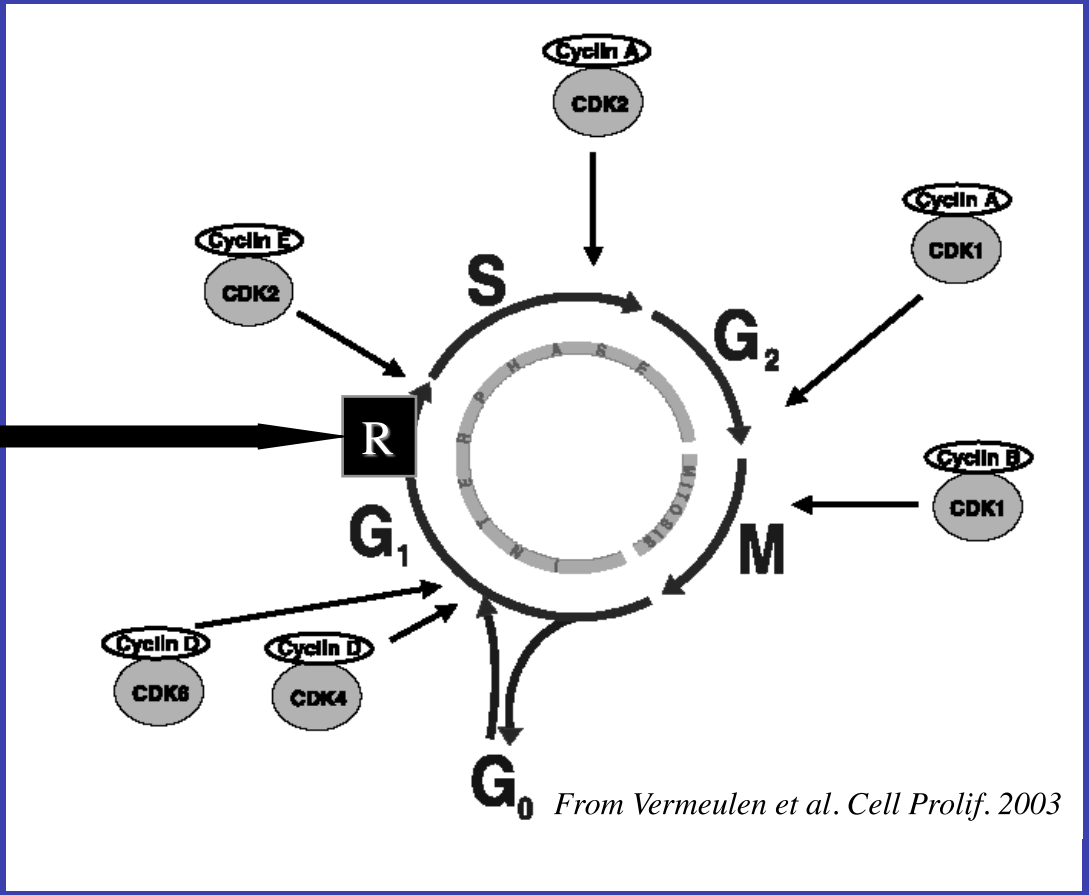
Modelling cell proliferation *and quiescence*

Nonlinear models: introducing exchanges between proliferating (G_1/S/G_2/M) and quiescent (G_0) cells

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

Restriction point
(late G_1 phase)

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



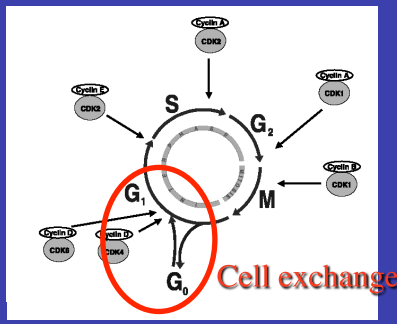
From Vermeulen et al. Cell Prolif. 2003

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

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

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

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

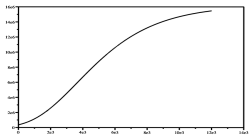


(Gyllenberg & Webb, Growth, Dev. & Aging 1989; Kozusko & Bajzer, Math BioSci 2003)

where, for instance:

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

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



Initial goal: to justify Gompertz growth (a popular model among radiologists)

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

Simple PDE models, age-structured with exchanges between proliferation and quiescence

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

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

with :

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

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

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

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

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

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

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

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

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

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

(delay τ = cell division cycle time)

(from Mackey, Blood 1978)

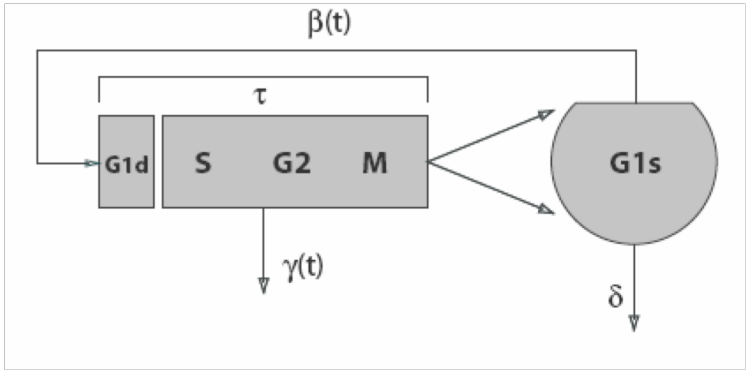
Properties of this model: depending on the parameters, one can have positive stability, extinction, explosion, or sustained oscillations of both populations

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

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

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

CINÉTIQUE DU CYCLE CELLULAIRE



$$\frac{dN}{dt} = -[\delta + \beta(N)]N + 2e^{-\gamma\tau}\beta(N_\tau)N_\tau \quad (\text{where} \quad N_\tau(t) = N(t-\tau))$$

Michael Mackey a calculé les 4 paramètres du cycle cellulaire pour les cellules souches hématopoïétiques saines *Mackey, 2000, Cell Prolif.*

- δ = 0.01–0.02/d
- β = 0.02–0.05/d
- γ = 0.07–0.23/d
- τ = 1.4-4.3d

De plus entre 3 et 8 fois plus de précurseurs que de cellules matures sont produits, le surplus meurt par apoptose

Modelling haematopoiesis for *Acute Myelogenous Leukaemia* (AML)

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

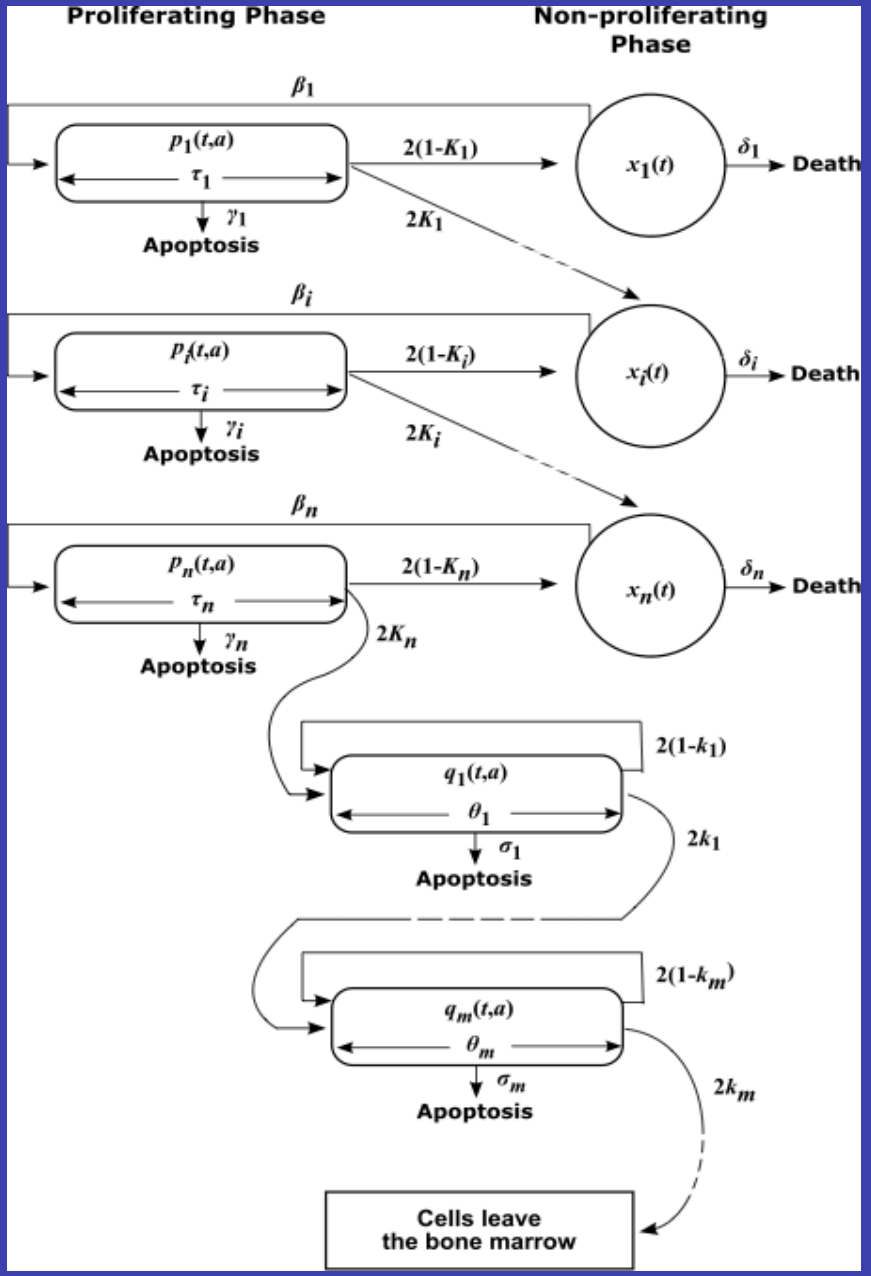
$$\frac{\partial r_i}{\partial t} + \frac{\partial r_i}{\partial a} = -(\delta_i + \beta_i)\, r_i, \qquad a > 0,\ t > 0,$$

$$\frac{\partial p_i}{\partial t} + \frac{\partial p_i}{\partial a} = -(\gamma_i + g_i(a))\, p_i, \qquad 0 < a < \tau_i,\ t > 0$$

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

and boundary conditions:

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



(see *Adimy et al. JBS 2008* for more details)

A model of tissue growth with proliferation/quiescence

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

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

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

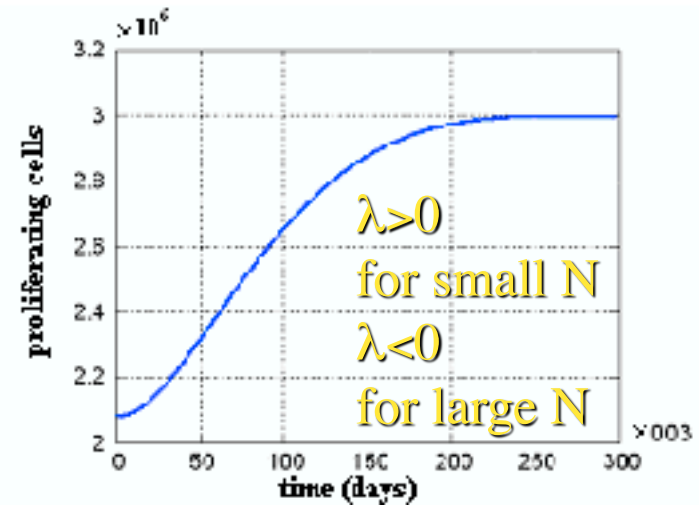
p: proliferating cells

q: quiescent cells

N: all cells (p+q)

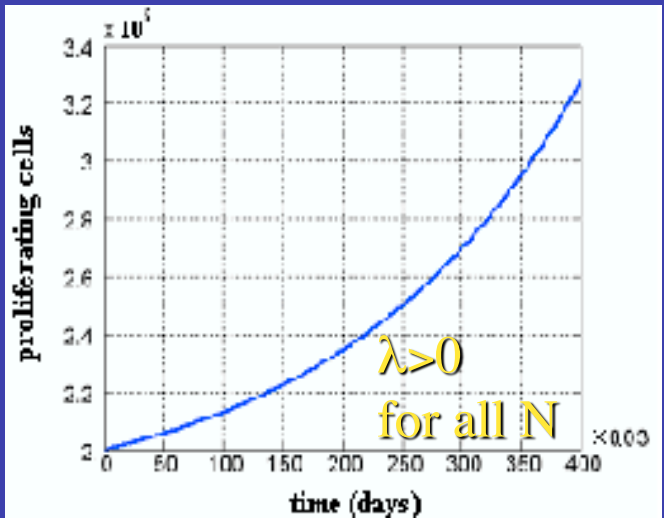
$$G(N) = \frac{\alpha_1\theta^n}{\theta^n + N^n}$$

Healthy tissue recruitment: homeostasis



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

Tumour recruitment: exponential (*possibly polynomial*) growth



F. Bekkal Brikci, JC, B. Ribba, B. Perthame JMB 2008; MCM 2008

M. Doumic-Jauffret, MMNP 2008

Next step: integrating the two models (Von Foerster-McKendrick-like linear and nonlinear proliferation/quiescence) in a complete cell cycle model with phases G_0-G_1-S-G_2-M

Keeping the same control targets, adding control by growth factors, hence on cyclin D, on the recruitment function G from G_0 to G_1 and on progression speed in G_1

…Work in progress…