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

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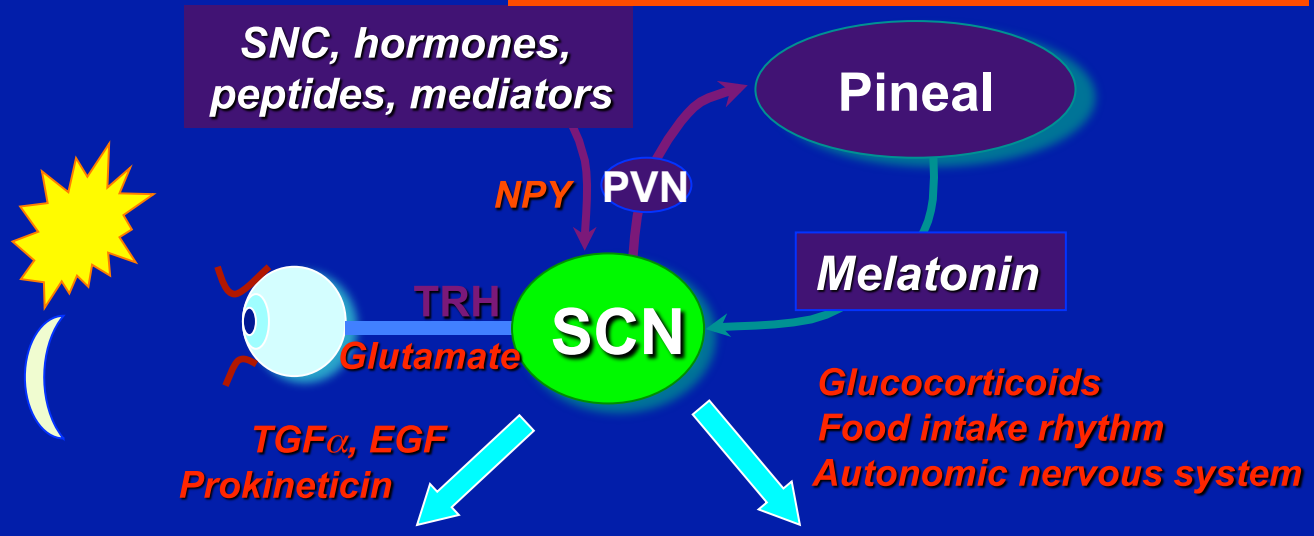
Outline of the lectures

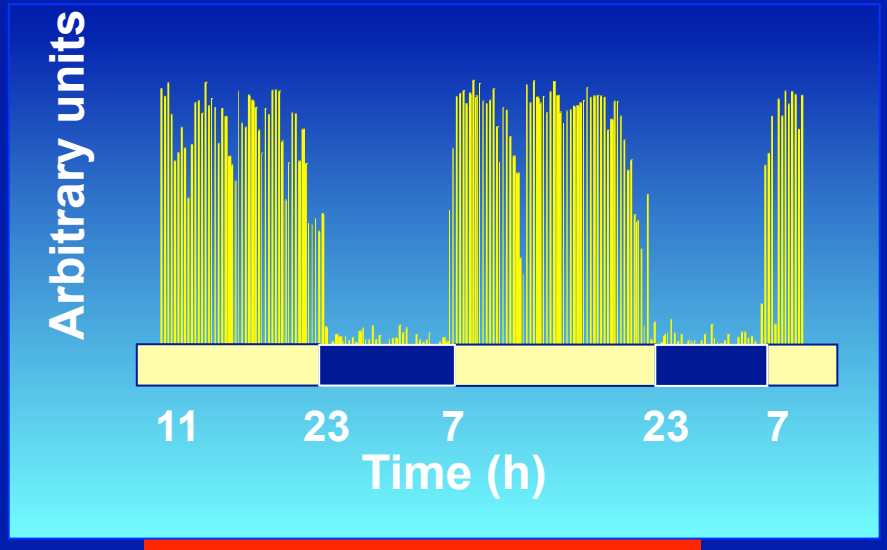
- 0. Introduction and general modelling framework
- 1. Modelling the cell cycle in proliferating cell populations
- 2. Circadian rhythm and cell / tissue proliferation
- 3. Molecular pharmacokinetics-pharmacodynamics (PK-PD)
- 4. Optimising anticancer drug delivery: present and future
- 5. More future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

Optimising anticancer drug delivery: present and future

Chronobiology in a nutshell (1): the circadian system

Central coordination





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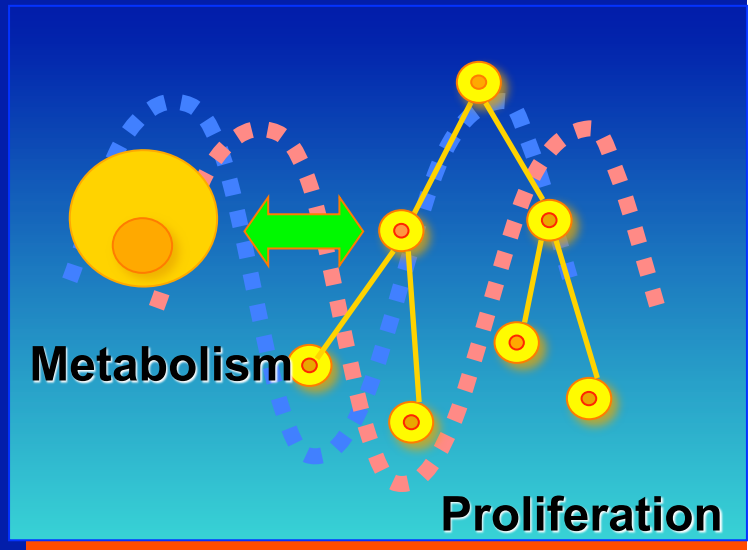


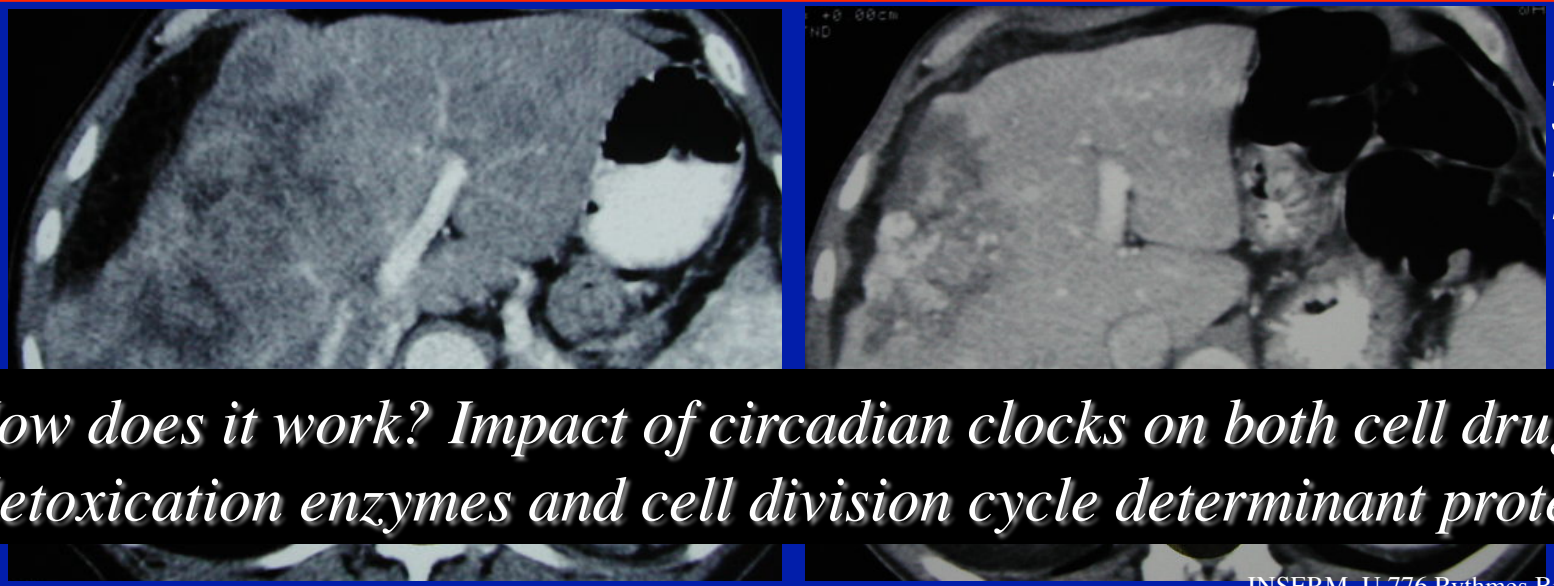
Rest-activity cycle

Peripheral oscillators

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

Chronobiology in a nutshell (2): cancer chronotherapy

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

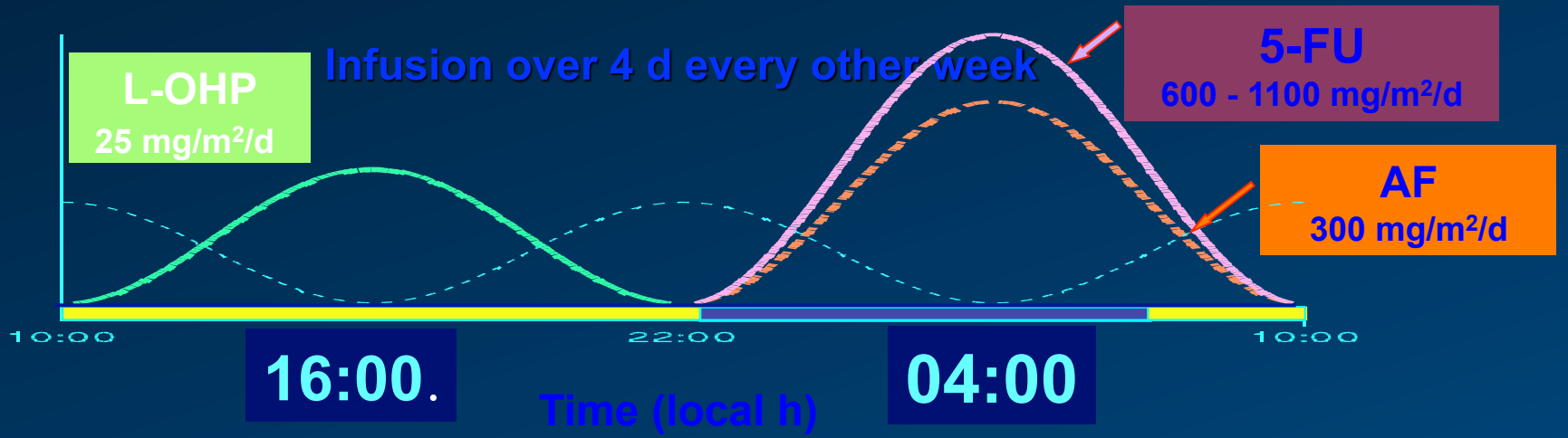


Lévi et al. JNCI 1994 ; Lancet 1997 ; Lancet Onc 2001

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

Chronobiology in a nutshell (3): chronotherapy technology

Time-scheduled delivery regimen



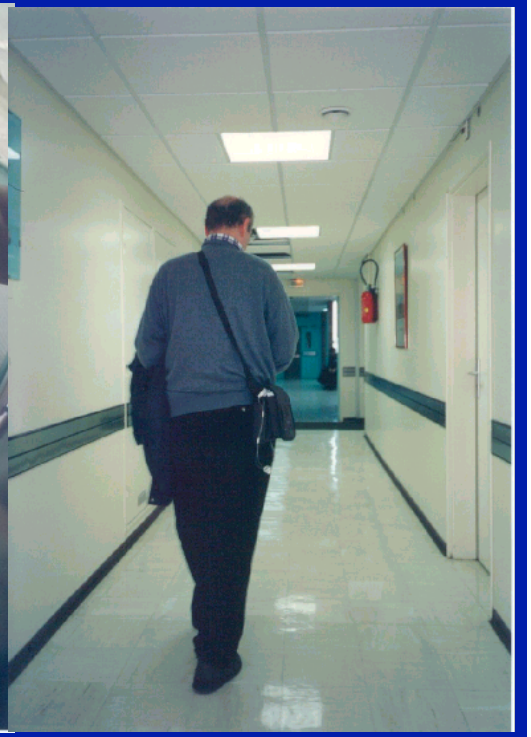
Multichannel programmable ambulatory injector for intravenous drug infusion (pompe Mélodie, Aguettant, Lyon, France)

Can such therapeutic schedules be improved?

Chronnobiology in a nutshell (4): Chronotherapy today in the clinic

Multichannel pump for chronotherapy

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



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

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

Francis Lévi, INSERM U 776 Rythmes Biologiques et Cancers

Theoretical optimisation of Oxaliplatin drug delivery with model parameter identification in mice

Aims of this study

- Taking into account (observation facts) that for a given cytotoxic drug, better anti-tumour efficacy and lesser toxicity are obtained when delivered at a well-determined time of the circadian cycle, we want to:

- Provide clinicians with a practical tool allowing to improve the efficacy of an anti-tumoral treatment while minimizing its toxicity on healthy tissues by optimizing the infusion flow.

- Such a tool should be based on pharmacokinetic-pharmacodynamic modelling mimicking the observed chronosensitivity of the tumour and healthy tissue to the drug, and on optimal control of the infusion flow.

Application chosen for a feasibility study

- Oxaliplatin (one of the few active drugs on human colorectal cancer) is also active on Glasgow osteosarcoma in $B6D2F_1$ mice.
- The treatment of this murine tumour by oxaliplatin has been extensively studied in our laboratory at Hôpital Paul-Brousse, Villejuif (INSERM EPI 0354), according to various time-scheduled dose regimens.
- Its clinical toxicity consists in peripheral sensory neuropathy, diarrhoea and vomiting, and haematological suppression; in mice, leukopenia, jejunal mucosa necrosis (and premature death) have been reported.
- Jejunal villi enterocyte population was chosen as toxicity target in mice.

Physiological hypotheses, literature data

- Oxaliplatin after IV or IP injection diffuses (as free Pt) according to order 1 kinetics firstly in the plasma, then to the healthy tissue and to the tumour.
- The drug activity may be represented by an efficacy function (Hill function) inhibiting cell population growth in each compartment (healthy and tumoral).
- Without treatment, the tumour grows according to a Gompertz law: firstly exponential growth,then convergence towards a plateau.
- In the tumour compartment there may exist cells developing drug resistance.
- Without treatment, the elimination of mature cells from jejunal villli into the bowel lumen is exactly compensated at any moment by the influx of young cells from the crypts.
- In the jejunal mucosa, only crypt cells are directly sensitive to the drug, whereas villi cells are only secondarily affected by it.

Measurements that are available at the laboratory

- Published laboratory data reporting diffusion parameters for oxaliplatin and optimal (=yielding smallest tumour weight at 14 or 21 days) injection time.

- Measure of tumour weight as a function of time (days) of $B6D2F_1$ mice bearing Glasgow osteosarcoma, without treatment.

- Measure of tumour weight as a function of time (days) of $B6D2F_1$ mice bearing Glasgow osteosarcoma treated by 4 injections (bolus, 2 distinct doses) of oxaliplatin delayed by 24 hours, and at different injection times.

The model: 1/ Pt concentration

- $dP/dt = -\lambda P + i(t)/V$ (P = free Pt plasma concentration)
- $dC/dt = -\mu C + P$ (C = total Pt concentration in healthy tissue)
- $dD/dt = -\nu D + P$ (D = total Pt concentration in tumour)

- Therapeutic control: t -->i(t) = intravenous drug infusion flow (µg/h) at time t

- V = distribution volume (mL); λ,μ,ν: diffusion parameters calculated after the half-life (ln 2 / half-life), known or estimated, of the drug in each compartment

The model : 2/ drug efficacy and toxicity functions

- Toxicity function in healthy tissue:

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

gS = Hill coefficient; C_{50} = half-saturation concentration; $\mathcal{T}$ (24 h) = period of drug sensitivity variations; ϕ_S = maximum toxicity phase (h); F= half-maximum toxicity

- Efficacy function in tumour:

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

gT = Hill coefficient; D_{50} = half-saturation concentration; $\mathcal{T}$ (24 h) = period of drug sensitivity variations; ϕ_T = maximum efficacy phase (h); H= half-maximum efficacy

The model: 3/ enterocyte population

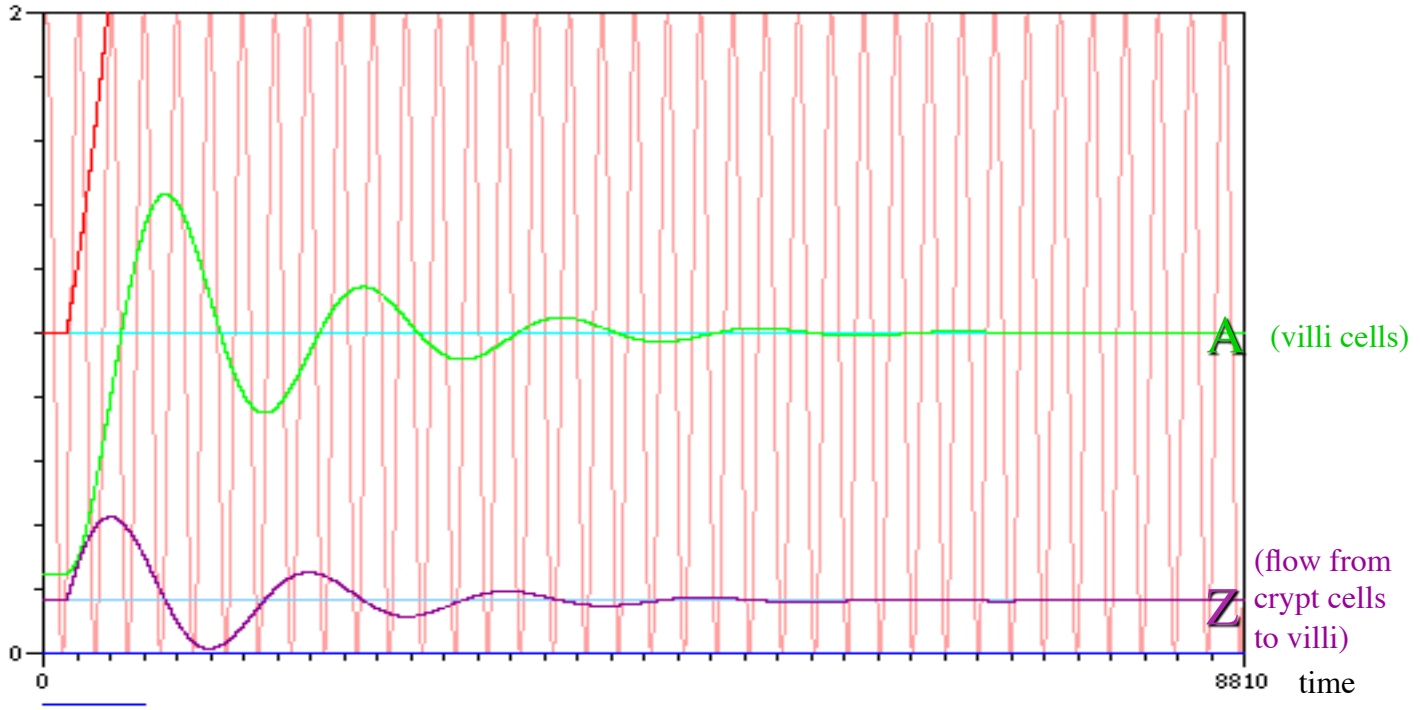
- $dA/dt = Z - Z_{eq}$ (A = number of cells borne by jejunal villi)
- $dZ/dt = -[\alpha + f(C,t)] Z - \beta A + \gamma$ (Z = number of cells per time unit (h) migrating from crypts towards villi; Z_{eq} =Z at steady state)

- γ: a positive constant; α: a positive constant standing for a natural inhibition rate (autoregulation); β: a positive constant standing for a mitosis inhibiting factor (a so-called 'chalone') coming from neighbouring villi to crypts

- This linear system may be seen as the linearisation of an unknown nonlinear system around its stable equilibrium point $[A_e=\beta^{-1}. (-\alpha Z_e + \gamma) , Z_e]$ without treatment, assuming hyperbolicity of this equilibrium, which ensures the validity of the linear approximation, since stability of this equilibrium is granted: in case of a sudden perturbation, return to steady state with damped oscillations, cf. Wright & Alison.

Model oscillations of the enterocyte population

(without treatment, response to radiotoxic or cytotoxic brief insult)



Model oscillations of enterocyte population

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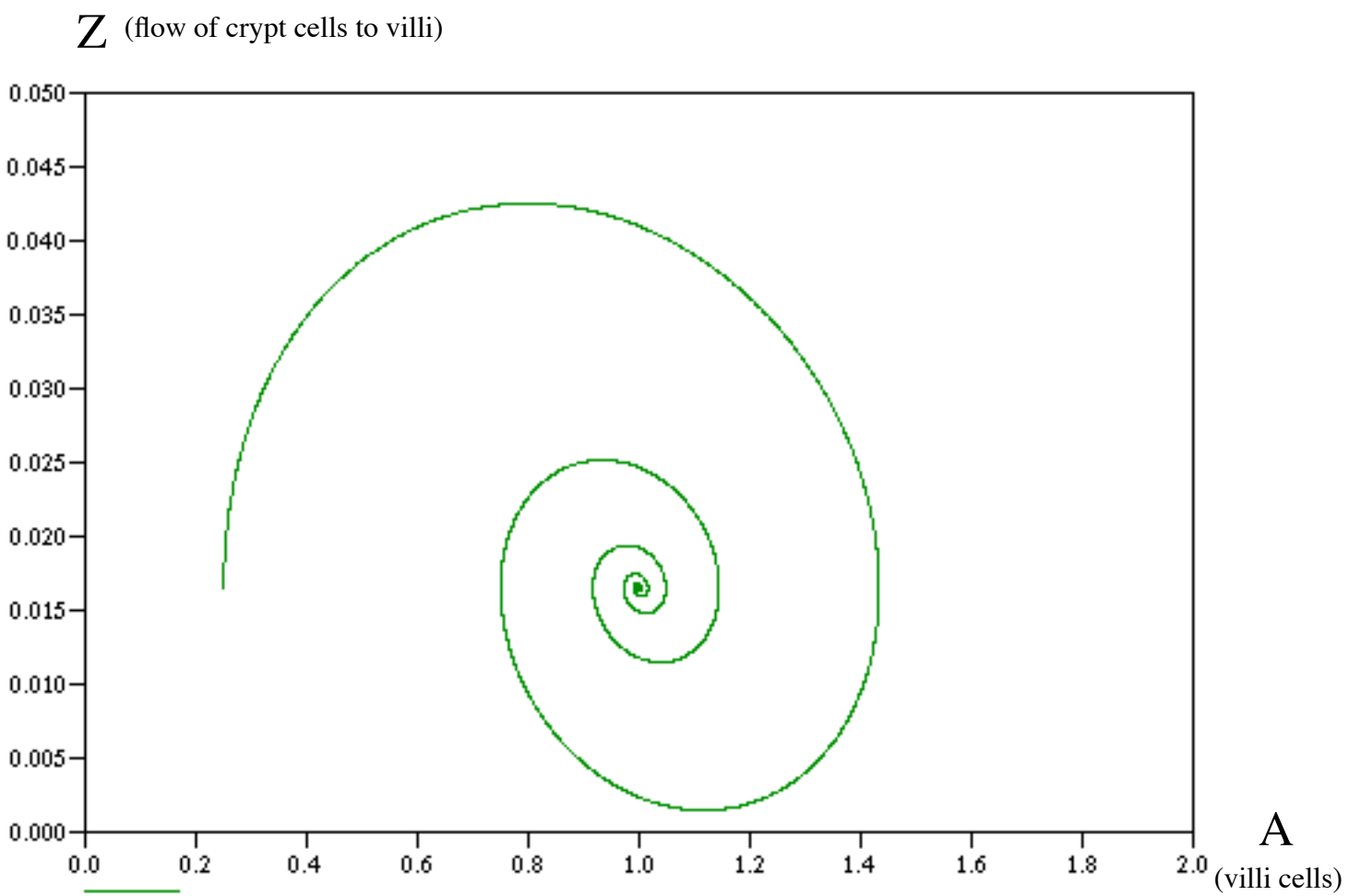


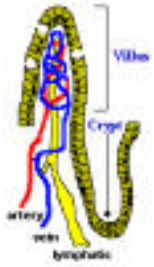
The model: 4/ tumour cell population

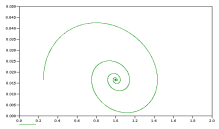
- $dB/dt = -a.B.\ln(B/B_{max}) - g(D) . B . (1+B^q)/2$ (B = number of tumour cells)
- a= Gompertz exponent; B_{max} asymptotic (=maximal) value of B
- If $G = dB/Bdt_{|t=t_0}$,initial growth exponent at chosen initial observation time t_0 , then $B_{max} = B(t_0) . e^{G/a}$, and without treatment, $dB/dt=G.e^{-a(t-t_0)}.B$
- $B.(1-B^q)/2$ = population of drug resistant cells (according to Goldie-Coldman), where q is -2 times the probability for a tumour cell to become resistant

The complete initial system (IS): 6 state variables

Healthy cells (jejunal mucosa)

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

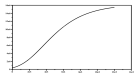




(PK)

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 »)

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

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

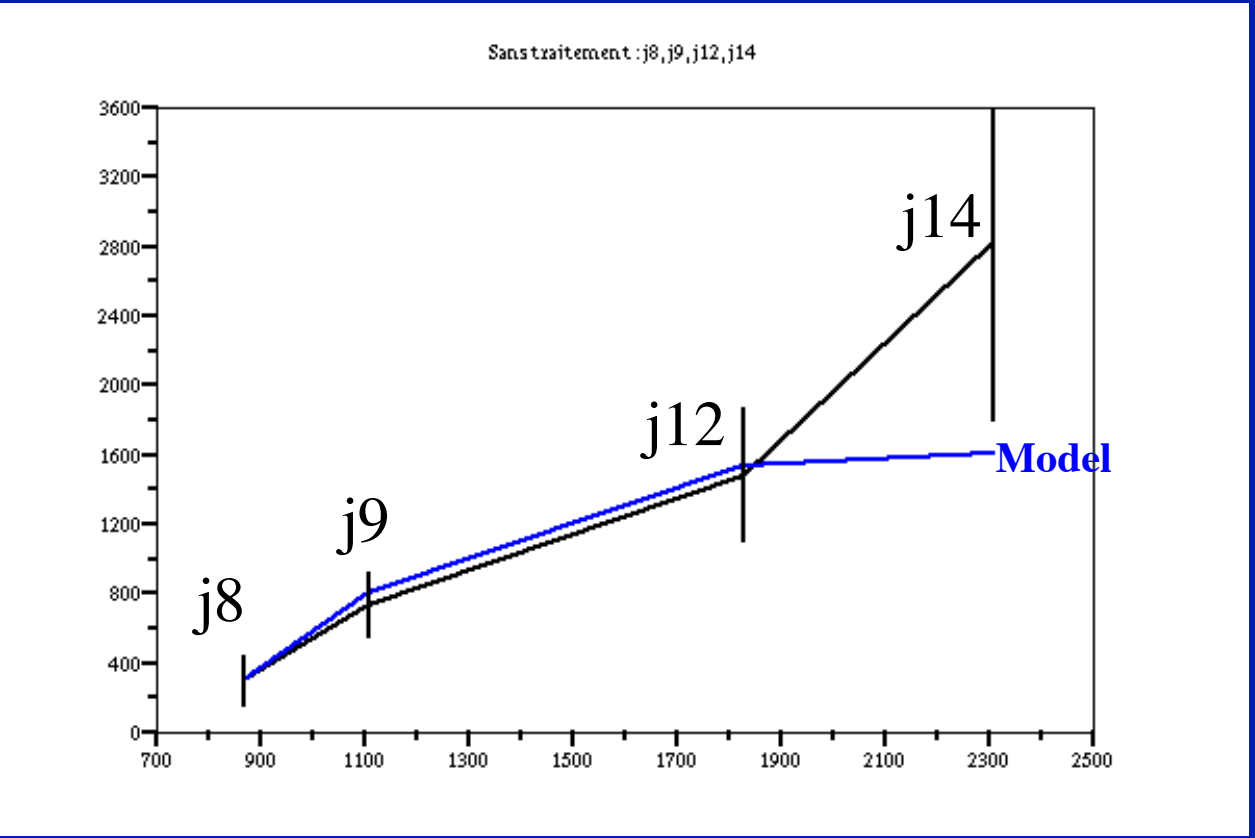
Aim: balancing IV delivered drug anti-tumour efficacy by healthy tissue toxicity

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

Model parameter identification

- The daily dose of injected drug was fixed as 60 µg of free Pt (corresponding to 4 mg/kg/d of oxaliplatin for a 30 g mouse, a common value at the laboratory).
- Diffusion parameters ($\mathcal{V}$, λ, μ, ν) : laboratory data
- Optimal injection phase ϕ_{opt} (whence ϕ_S et ϕ_T) : laboratory data
- Laboratory observation: maximal anti-tumour efficacy phase ϕ_T and minimal healthy tissue toxicity phase 12 + ϕ_S coincide.
- gS and gT have been arbitrararily fixed as 1, C_{50} and D_{50} at a high value (10) so as to bring the efficacy/toxicity functions in a linear zone.
- Equilibrium point $[A_e=\beta^{-1}.(-\alpha Z_e + \gamma) , Z_e]$, period (6 d) and dampening factor (1/3) for oscillations of the enterocyte population chosen after Potten et al., whence α, β, γ
- F, H, G and a have been determined after laboratory curves, q fixed as 0 or -0.002.

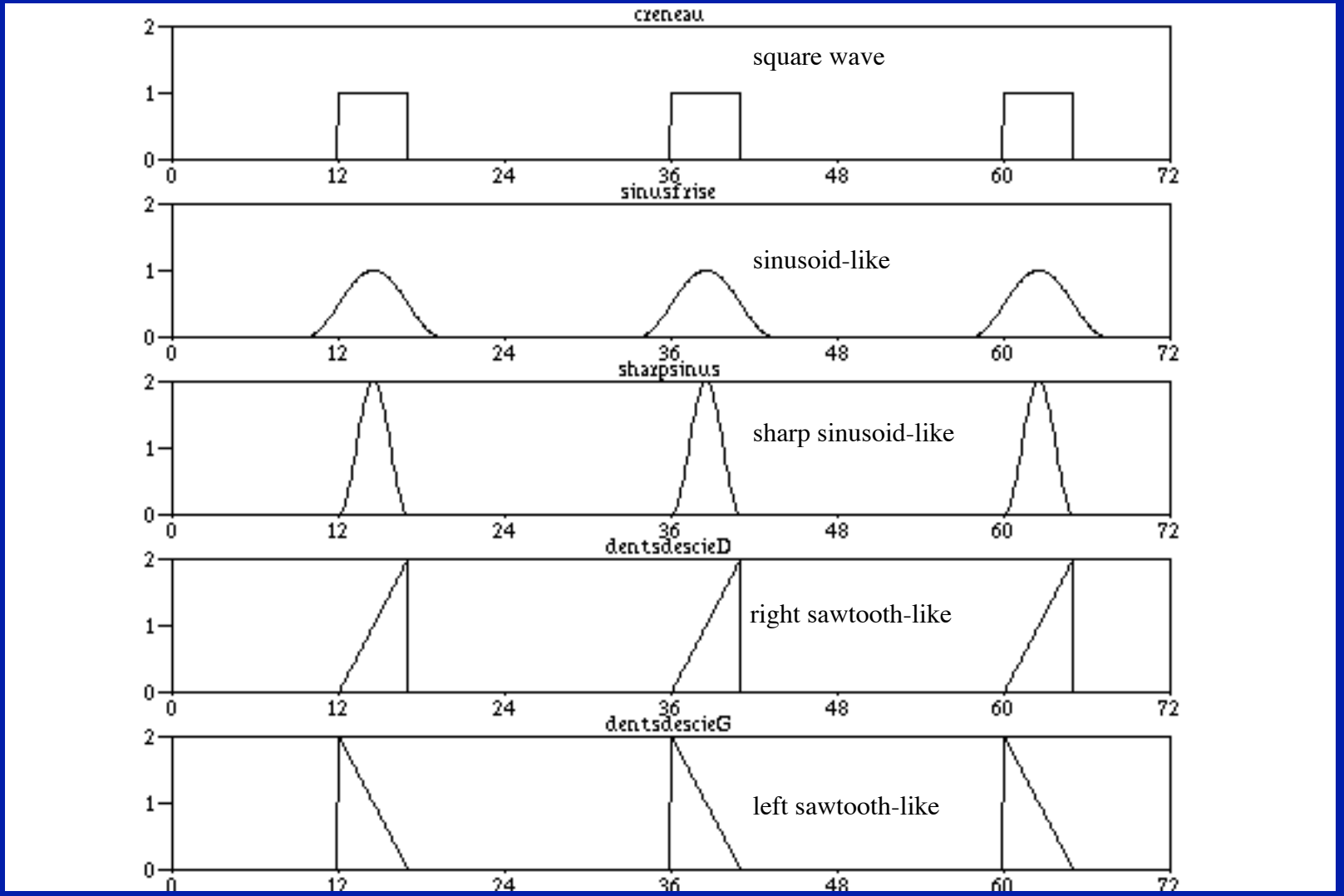
Example of parameter identification for the tumour growth model: fitting the model to mice data, tumour burden in untreated mice



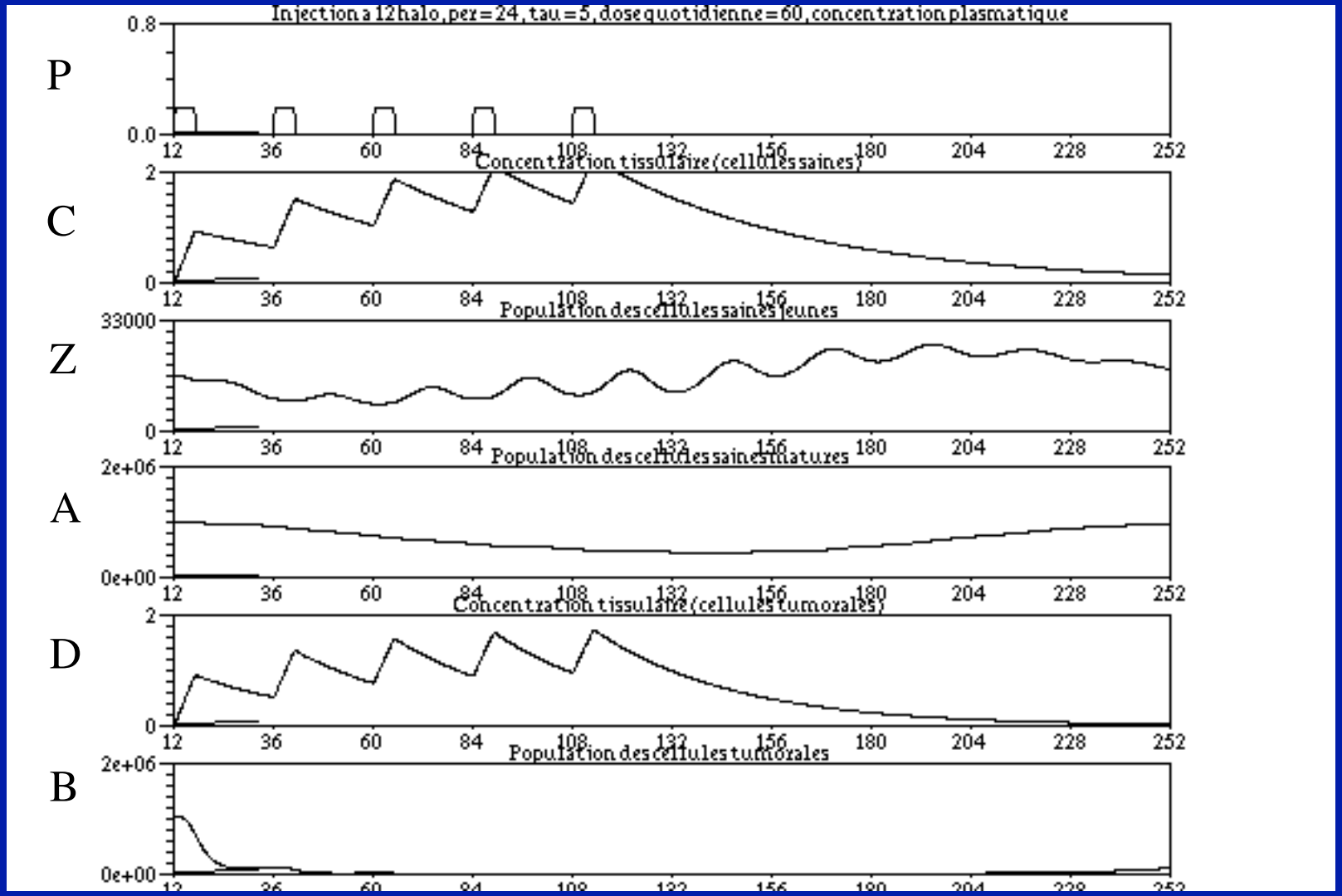
Computer simulation with SCILAB or MATLAB

- SCILAB / MATLAB programming
- Time unit: hour, counted from 0 halo (hours after light onset) at day 1;
  integration step = 0.1 hour
- Integration of the ordinary differential equations system beginning with treatment, with interruption at each discontinuity step (for square wave or sawtooth-like control laws); used solvers: Adams or implicit (BDF) scheme.

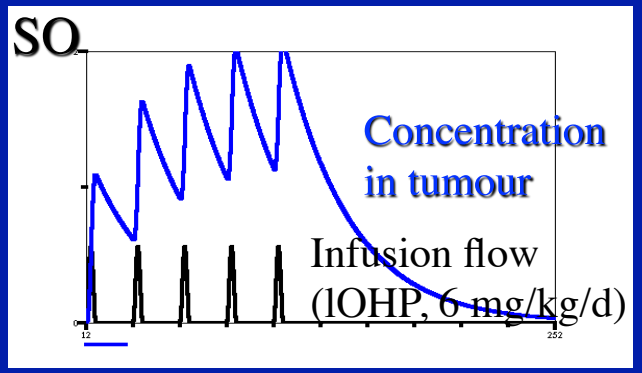
First attempt: periodic drug flow control according to clinical habits (5d treatment +16 d recovery)

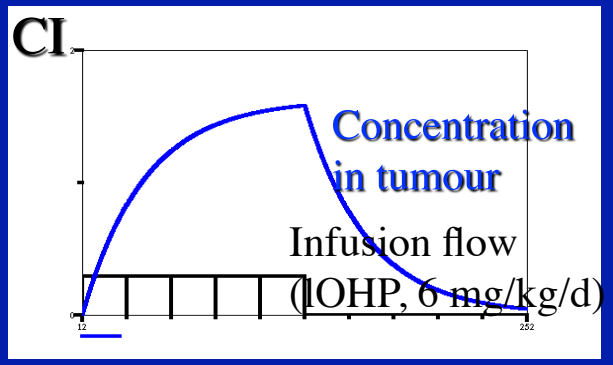


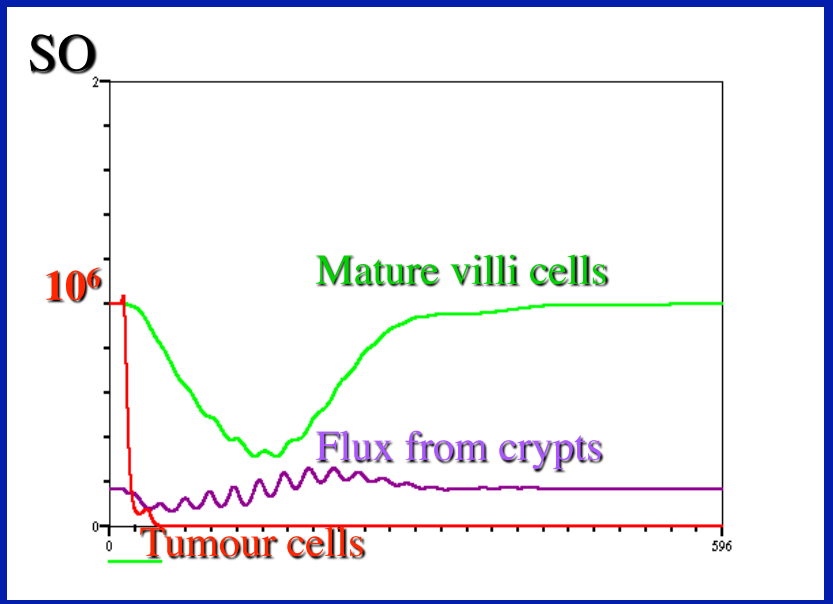
SCILAB: visualisation of variables (square wave)

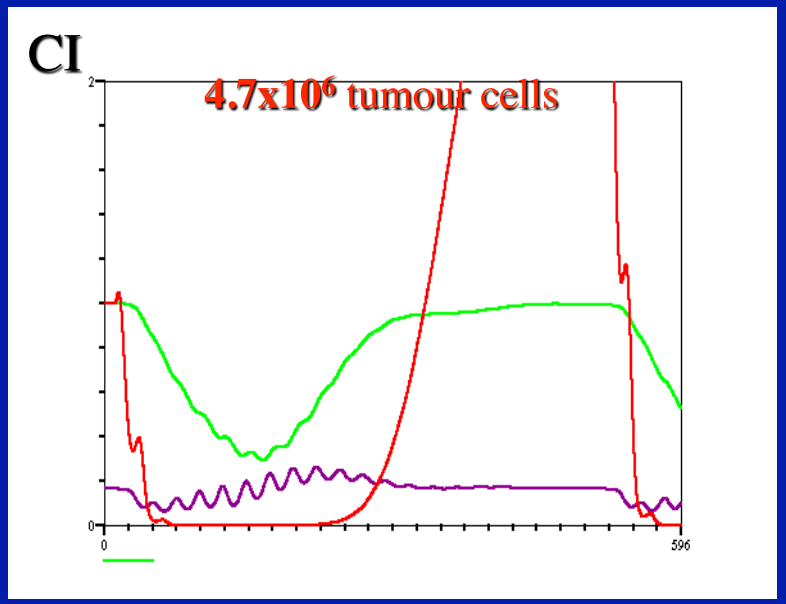


Comparison: periodic time-scheduled regimen (sinus-like optimal control law, SO) vs constant infusion (CI) over 5 days, followed by 16 days of recovery





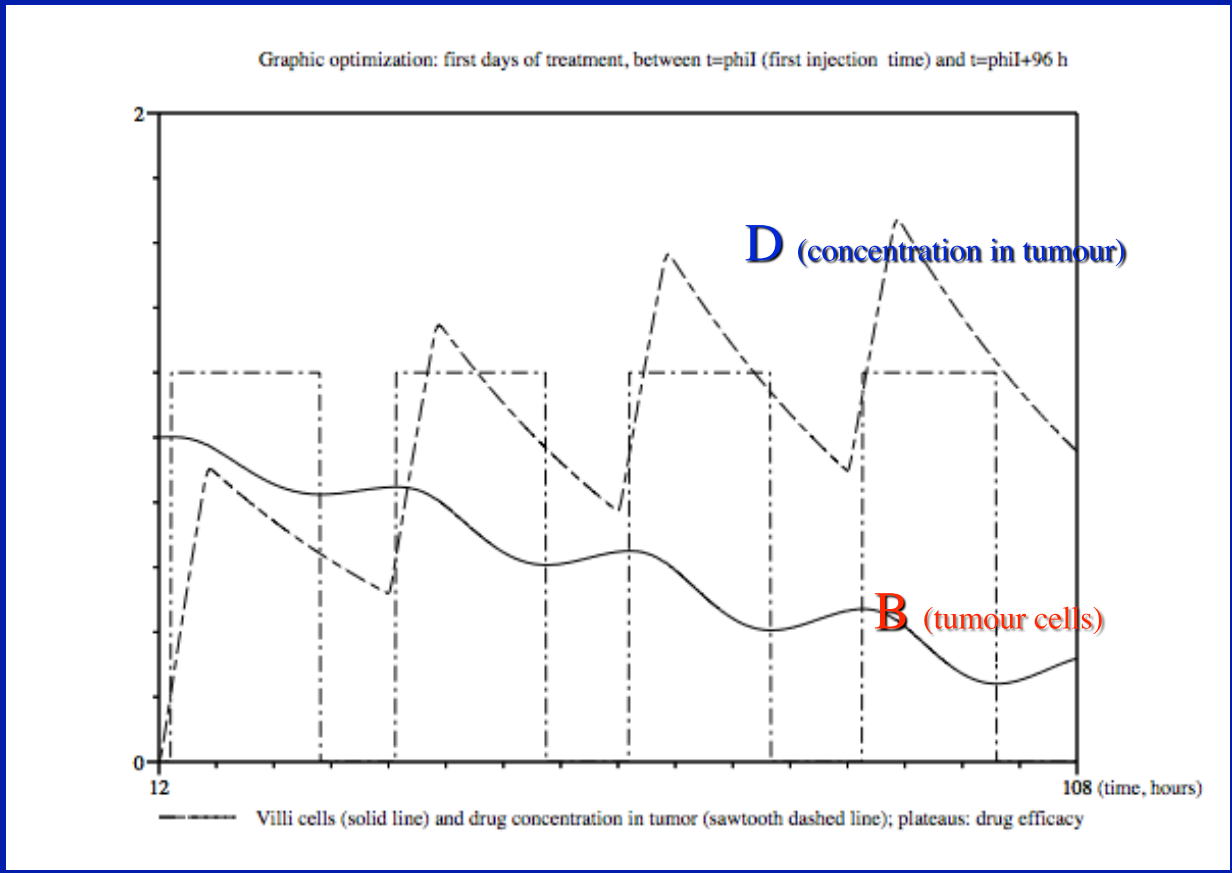




Eradication on day 5

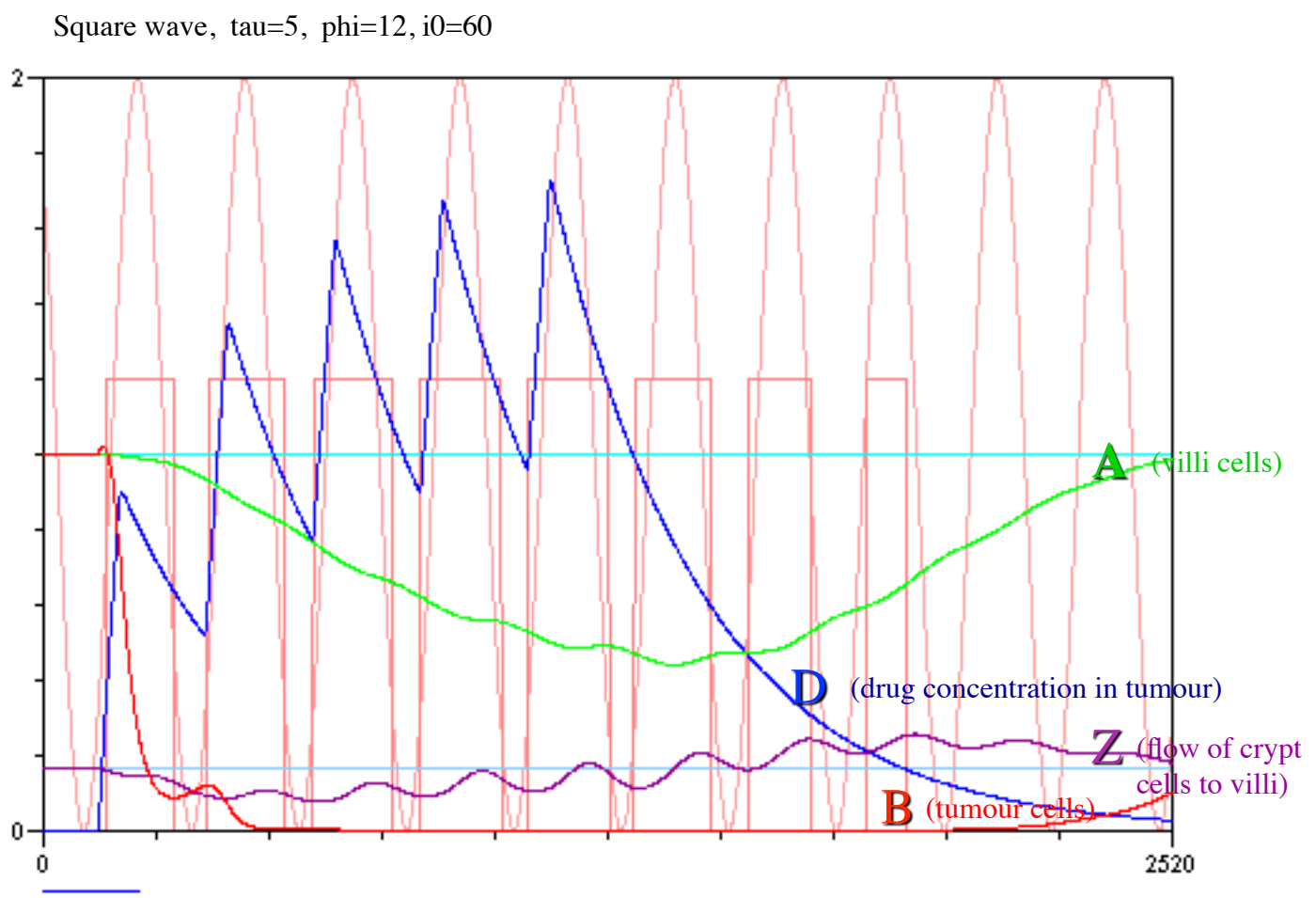
Cancer cell persistence and tumour regrowth

Graphical optimisation: superimposing infusion peaks on maximal chronoefficacy epochs



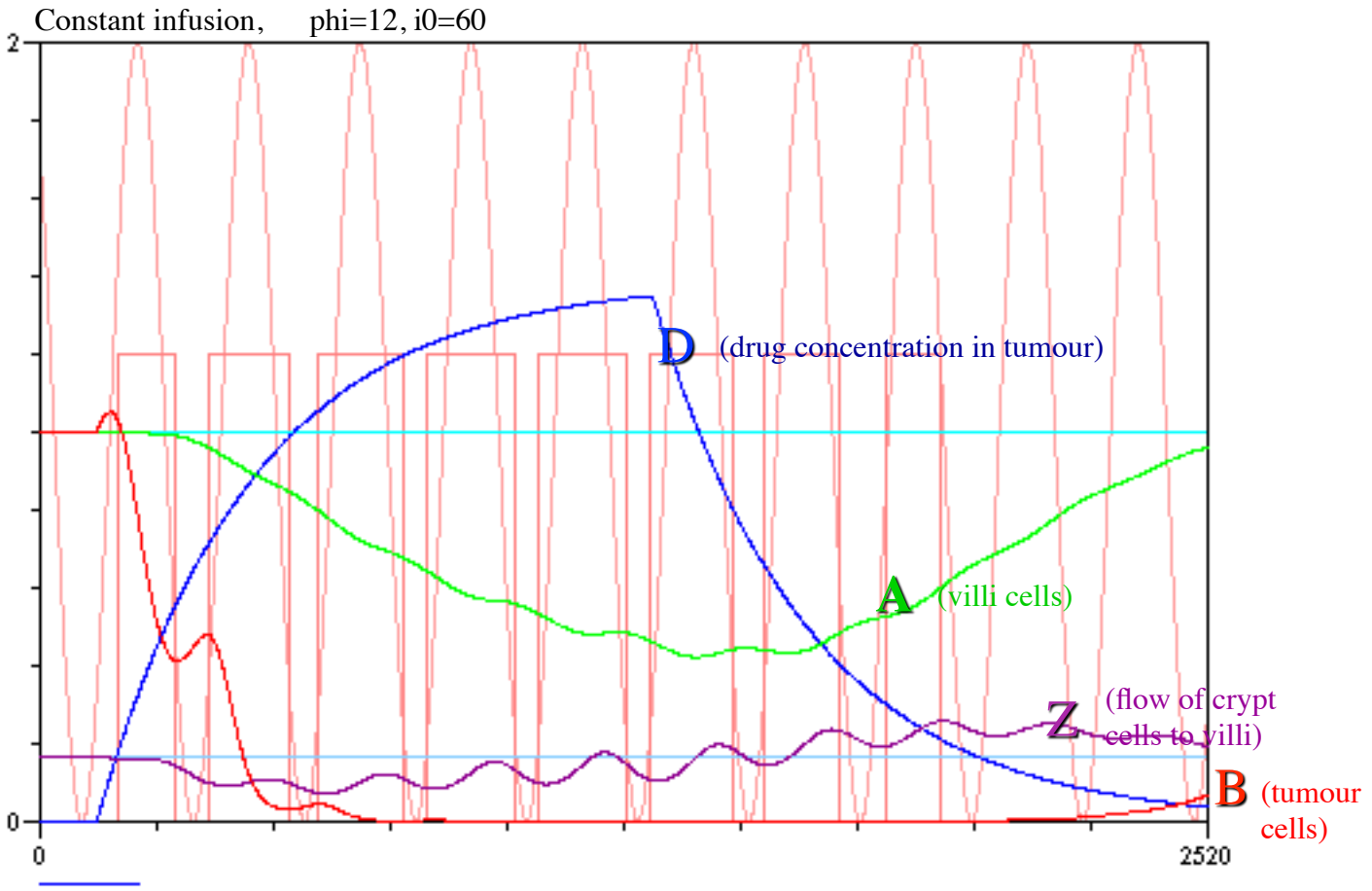
Detail of a 5-day regimen

(optimal square wave time schedule)



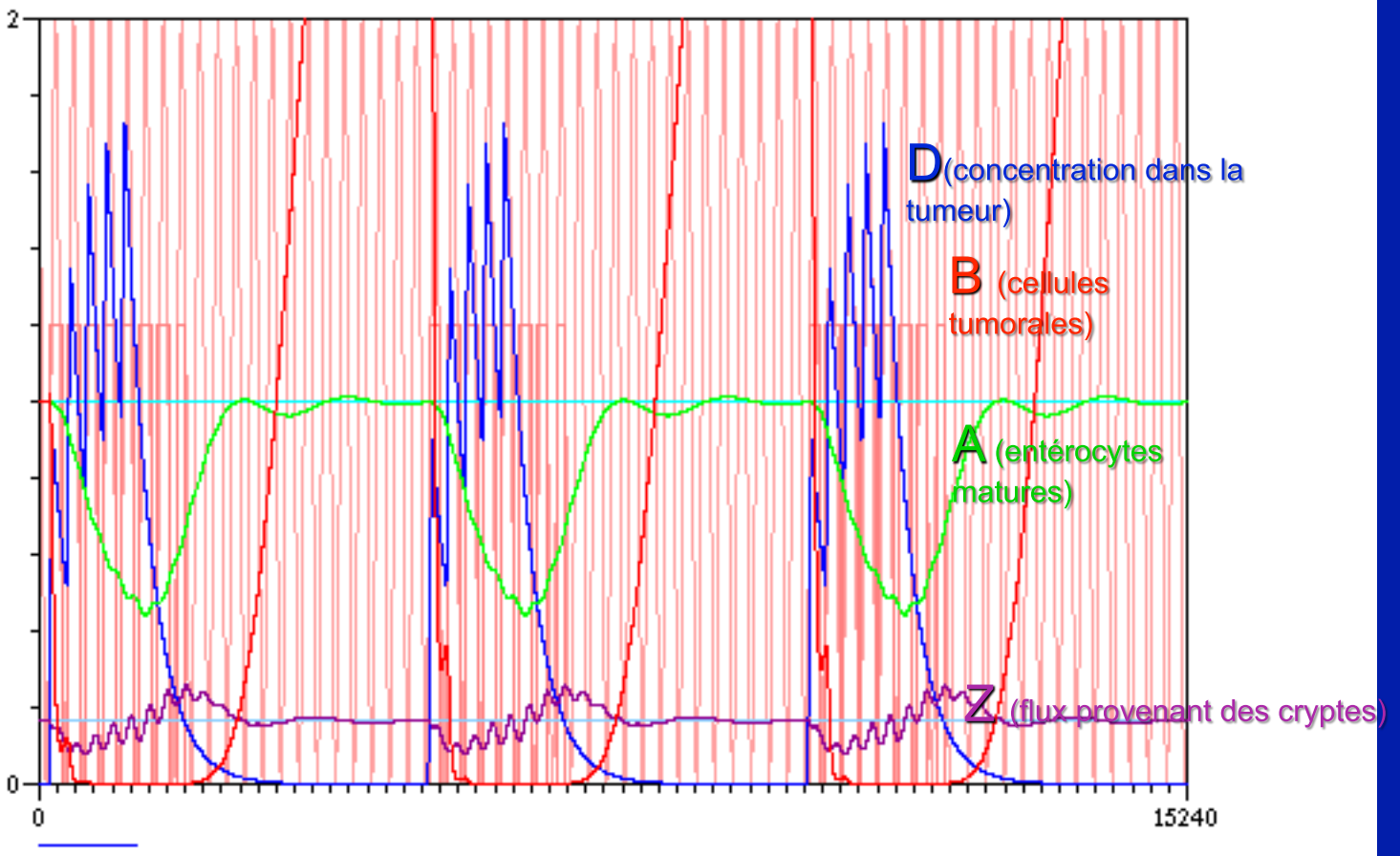
Detail of a 5-day regimen

(comparison with constant infusion schedule)



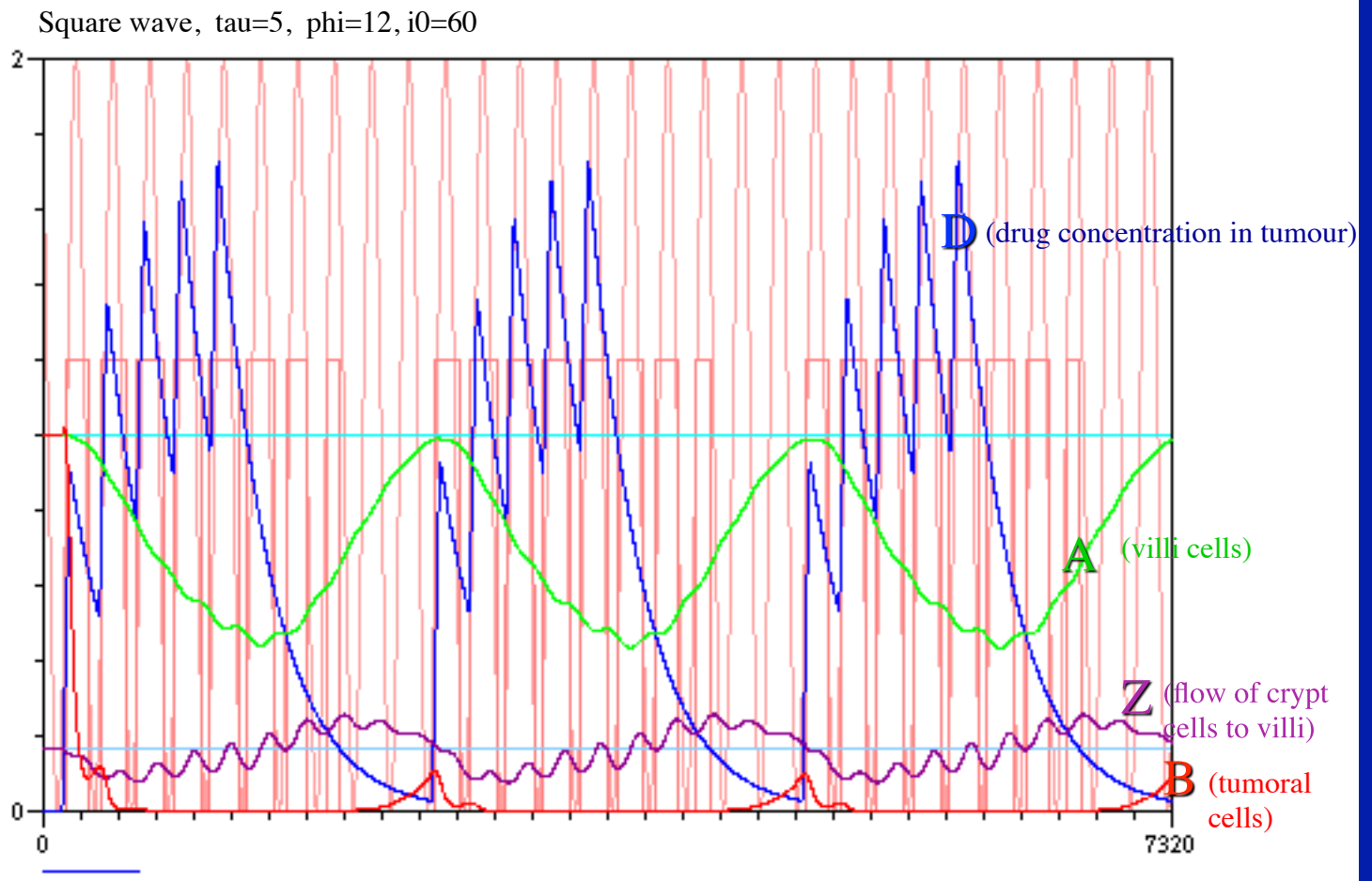
Typical periodic infusion course: 5d+16d of recovery+5d

(square wave time schedule)



A more aggressive regimen: 5d+5d (recovery)+5d

(optimal square wave time schedule)



Summary of results for this "poorman's optimisation scheme"

1/ Optimal time schedule > constant infusion > worst possible time schedule
(4 residual tumoral cells out of 10^6 initially < 17 out of 10^6 < 52 out of 10^6)

2/ ' Aggressive curative regimen ', allowing a wide toxicity limit, here a decrease down to 40 % of initial villi population:

Best result (3 residual tumoral cells) for the same daily dose (60 µg/d free Pt) obtained with a sharp sinusoid-like law for 5 hours , beginning at 12 *halo*

3/ ' Reduced toxicity regimen ', prohibiting the decrease of the villi population below a given threshold, here 60 % of initial villi population:

Best result (516 residual tumoral cells out of 10^6 initially) obtained with a right sawtooth-like law for 1 hour beginning at 14 *halo*,
allowing the infusion of a maximum dose of 45 µg/d.

Main drawback : high drug concentrations over a short period.

Advantage: better anti-tumoral results than constant infusion which, for the same tolerability limit, imposes not to deliver above 34 µg/d (2626 residual tumoral cells out of 10^6 initially).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

or else:

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

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

Optimal control problem (eradication): defining a lagrangian:

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

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

then:

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

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

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

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

Investigating the minima of the objective function: a continuous problem

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

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

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

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

hence also are
C(t),D(t),A(t),B(t)

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

Investigating the minima of the objective function: a differentiable problem

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

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

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

A heuristics for finding minima of the objective function

Hence, the infusion flow optimatisation problem is liable to differentiable optimisation techniques,

and though the problem is not convex, so that searching for saddle points of the lagrangian will only yield sufficient conditions,

we nevertheless define a heuristics to obtain minima of the objective function G_B submitted to the constraint $F_A \leq 0$, based on a Uzawa-like algorithm based on a nonlinear conjugate gradient, which will need defining 2 adjoint systems:

1/ Adjoint system (AS1) for calculating the gradient of F_A

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

Then, if $t_A(i)$, time at which the minimum of F_A is attained, is defined by $F_A(i) = \tau_A - A(t_A, i) / A_e$, it can be proved, provided that $\partial^2 A(t_A(i),i) / \partial t^2 > 0$ and using the implicit function theorem, that t_A is a differentiable function of i

Then the gradient of F_A with respect to i is $\partial F_A(i) / \partial i = U_P \cdot \mathbf{1}_{[t_0,\eta]} / V$, where $[t_0, \eta] = \text{Supp}(i)$ (=injection interval) and U_P is the first component of the Lagrange multiplier (U_P, U_C, U_Z, U_A), solution of the adjoint system:

$$\begin{aligned}
\frac{dU_P}{dt} &= \lambda U_P - U_C \\
\frac{dU_C}{dt} &= \mu U_C - \frac{\partial f}{\partial C}(C,t) Z.U_Z \\
\frac{dU_Z}{dt} &= \{\alpha + f(C,t)\} U_Z - U_A \\
\frac{dU_A}{dt} &= \beta U_Z
\end{aligned}$$

with initial conditions:
$U_P(\eta) = U_C(\eta) = U_Z(\eta) = 0$
and $U_A(\eta) = -1/A_e$
and vanishing conditions at t_0

2/ Adjoint system (AS2) for calculating the gradient of G_B (designing an objective function for the eradication strategy)

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

If $t_B(i)$, time at which the minimum of G_B is attained, is defined by $G_B(i) = B(t_B, i)$, it can be proved, provided that $\partial^2 B(t_B(i), i) / \partial t^2 > 0$, by using the implicit function theorem, that t_B is a differentiable function of i

And the gradient of G_B with respect to i is $\partial G_B(i) / \partial i = V_P \, .\mathbf{1}_{[t_0,\eta]} / \mathcal{V}$, where $[t_0, \eta] = \text{Supp}\,(i)$ (=injection interval), and V_P is the first component of the Lagrange multiplier (V_P, V_D, V_B), solution of the adjoint system:

$$\begin{aligned}
\frac{dV_P}{dt} &= \lambda V_P - V_D \\
\frac{dV_D}{dt} &= \nu V_D - \frac{\partial g}{\partial D}(D,t).B.V_B \\
\frac{dV_B}{dt} &= \left(a \ln \frac{B}{B_{max}} + a - g(D,t) \right) .V_B
\end{aligned}$$

with initial conditions: $V_P(\eta) = V_D(\eta) = 0$ and $V_B(\eta) = 1$ at the upper bound η of the injection interval, and vanishing conditions at t_0

2'/ An adjoint system for calculating the gradient of G_B (designing an objective function for the stabilisation strategy)

If we choose: $G_B(i) = B(t_f)$ the problem is theoretically simpler, since we are not interested in local or global minima of B, but only in its maximum at the end of the cbservation interval $[t_0, t_f]$; the differentiability of G_B with respect to *i* is also valid; the same adjoint system with initial conditions in t_f: $V_P(t_f)= V_D(t_f)=0$ and $V_B(t_f)= 1$ will also yield the required gradient by $\partial G_B(i) / \partial i = V_P \,.\, \mathbf{1}_{[t_0,t_f]} / \mathcal{V}$

But in fact, because observation periods run over several chemotherapy cycles, and it is not granted that $t_A=t_f$, we chose to use:

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

plainly replacing a minimum in the eradication strategy by a maximum; the use of the implicit function theorem is also valid, even with $t_A=t_f$, provided that $\partial^2 B / \partial t^2(t_f) \neq 0$

And the same algorithm holds as in the eradication strategy

Computation summed up: a Uzawa-like descent algorithm

1. Start from initial infusion profile and Lagrange multiplier i_0 and θ_0 (cst. and 1)

2. Given the infusion profile i_k, integrate the initial dynamical system (IS) with 6 state variables, between t_0 and t_f, yielding population profiles $A(i_k)$ and $B(i_k)$

5. Given (i_k, θ_k) search for $t_A(i_k)$ and $t_B(i_k)$ and compute $G_B(i_k)$, $F_A(i_k)$, $\pounds(i_k, \theta_k)$

6. Integrate the adjoint systems (AS1) from t_A down to t_0 and (AS2) from t_B down to t_0 to obtain the gradient of $\pounds(., \theta_k) = G_B(.) + \theta_k F_A(.)$

7. Define a descent direction by $d_k = \partial \pounds(i,\theta_k)/\partial i$ or by a linear combination of $\partial \pounds(i,\theta_k)/\partial i$ and previous descent directions $d_{k-1}, d_{k-2}, \ldots$

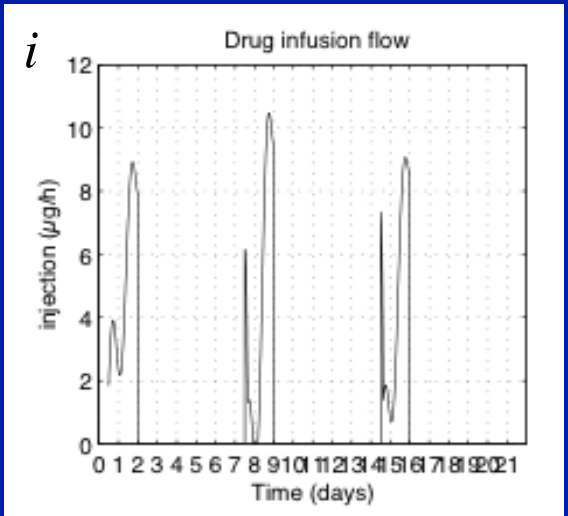
8. Determine i_{k+1} by minimizing $\pounds(i_k + s d_k, \theta_k)$ w. r. to s (i.e. along direction d_k)

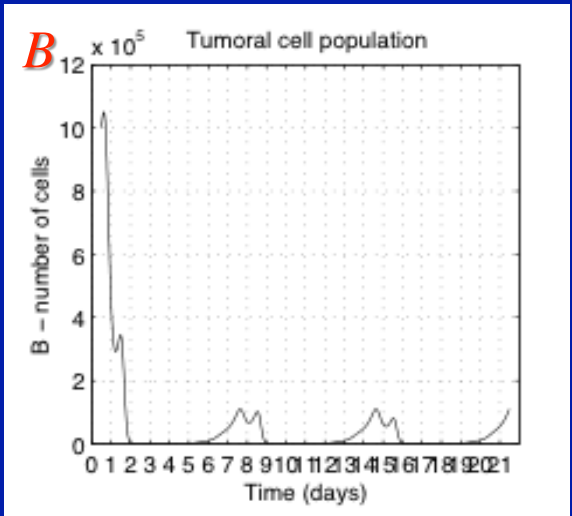
9. Compute $\theta_{k+1} = \max(\theta_k + \rho F_A(i_k), 0)$, for a given $\rho > 0$

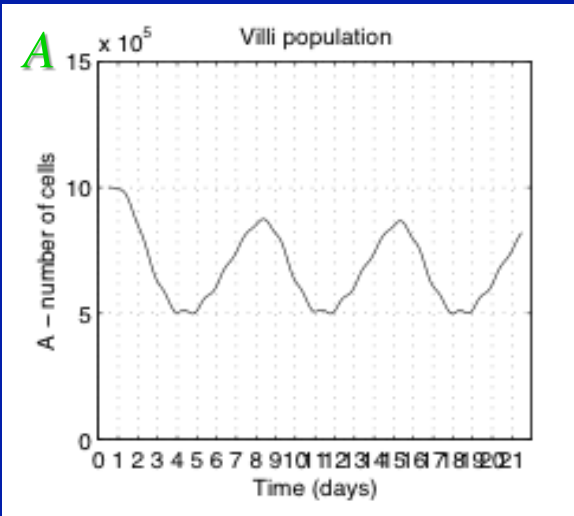
10. Until convergence, i.e. with stopping condition $|F_A(i_k)| < \varepsilon$ (constraint saturation)

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

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







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

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

Solution : optimal infusion flow i(t) adaptable to the patient's state of health (according to a tunable parameter τ_A*:* here preserving τ_A=50% of enterocytes*)*

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

Detailed results: eradication strategy

τ_A=50 %

HQ1013 –canceQwe – ituz=2

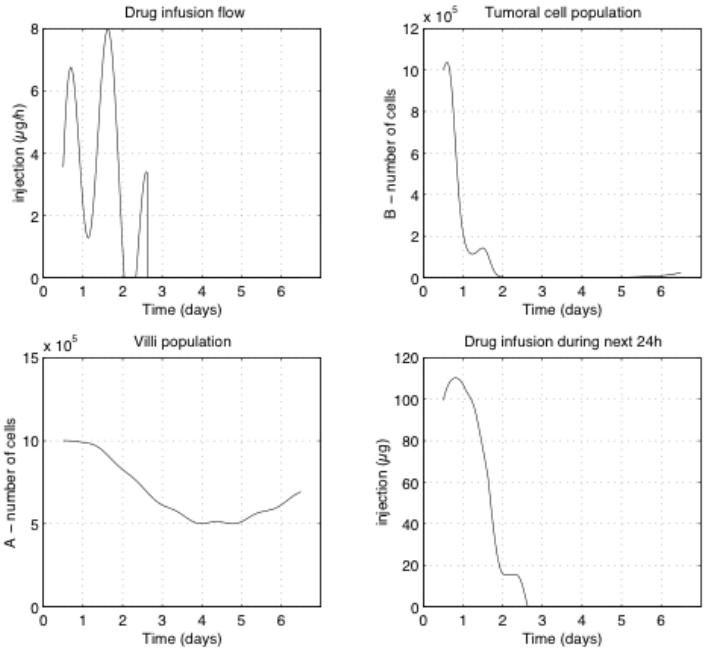
io=0.417 µg/h dt=0.1 h Tio=To+1 j
lbd=6, mu=0.015, nu=0.03
To=12 h, Tf=To+6 j, toA=50%
B(0)=1000000 cells, cTi=4
ca0=6000, ca=6250
eps=9e–06, epsa=0.001
ci=300 µg, imax=10 µg/h
Ti=To+2 j+3.25 h =To+2.1354 j
Tia=To+0 h

itrt=54

<i>=3.63 µg/h, Sum i=185.7 µg
Max i=7.977 µg/h

MinA=50.03 %Aeq, tMinA=4.783 j
Bmin=159 cells, tBmin=3.142 j

Bmax=1.04e+06 cells
tBmax=To+0.0917 j
B(Tf)=24121.4919 cells



τ_A=60 %

HQ1012 -canceQwe - ituz=3

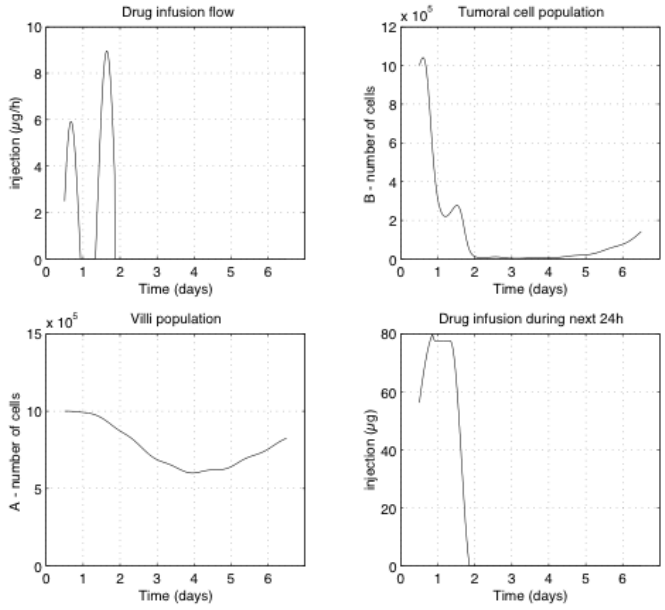
io=0.417 µg/h dt=0.1 h Tio=To+1 j
lbd=6, mu=0.015, nu=0.03
To=12 h, Tf=To+6 j, toA=60%
B(0)=1000000 cells, cTi=4
ca0=60000, ca=82500
eps=9e-06, epsa=0.001
ci=300 µg, imax=10 µg/h
Ti=To+1 j+8.73 h =To+1.3639 j
Tia=To+0 h

itrt=64

<i>=3.692 µg/h, Sum i=120.2 µg
Max i=8.96 µg/h

MinA=60 %Aeq, tMinA=3.958 j
Bmin=2.91e+03 cells, tBmin=3.117 j

Bmax=1.04e+06 cells
tBmax=To+0.1 j
B(Tf)=142058.7998 cells



Detailed results: eradication strategy, optimisation w.r. to *i and* η

If, as defined earlier, $[t_0, \eta]$ = Supp (i) (=injection interval), we also may optimize w. r. to (i, η) in $L^2([t_0, t_f]) \times [t_0, t_f]$. Then, for the eradication problem:

τ_A	$\eta - t_0$ (days)	min B(t)
40 %	1.37	3.65
50 %	2.13	159
60 %	1.36	2910

Summing up: for a chemotherapy course of 7 days, the best results are obtained with a short infusion interval (1.5 to 2 days) at the beginning of the course, followed by recovery during the remaining time of the week, i.e. a « German scheme » for oxaliplatin chronotherapy rather than the usual « French schemes » of 5 d + 16 d (recovery time) or 4 d + 10 d (recovery time)

Detailed results: stabilisation strategy

With τ_A = 50 %:

ChimioS0j

CS00 – dt=0.1 h
lbd=6, mu=0.015, nu=0.03
To=12 h, Tf=To+21 j
B(0)=1000000 cells
Gaussian noise – zero mean
standard deviation=0 µg/h

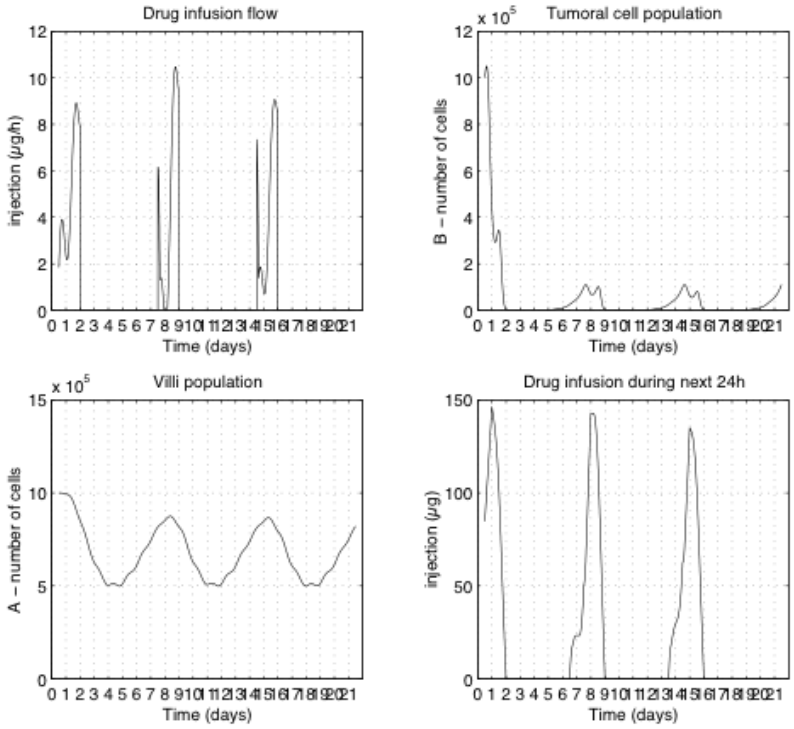
Ti=To+15 j+12 h =To+15.5 j

Sum i=515.4 µg
Max i=10.47 µg/h

MinA=49.9 %Aeq, tMinA=11.8 j
Bmin=144.8 cells, tBmin=10.14 j

Bmax=109876 , tBmax=14.63 j

B(Tf)=109691.5206 cells

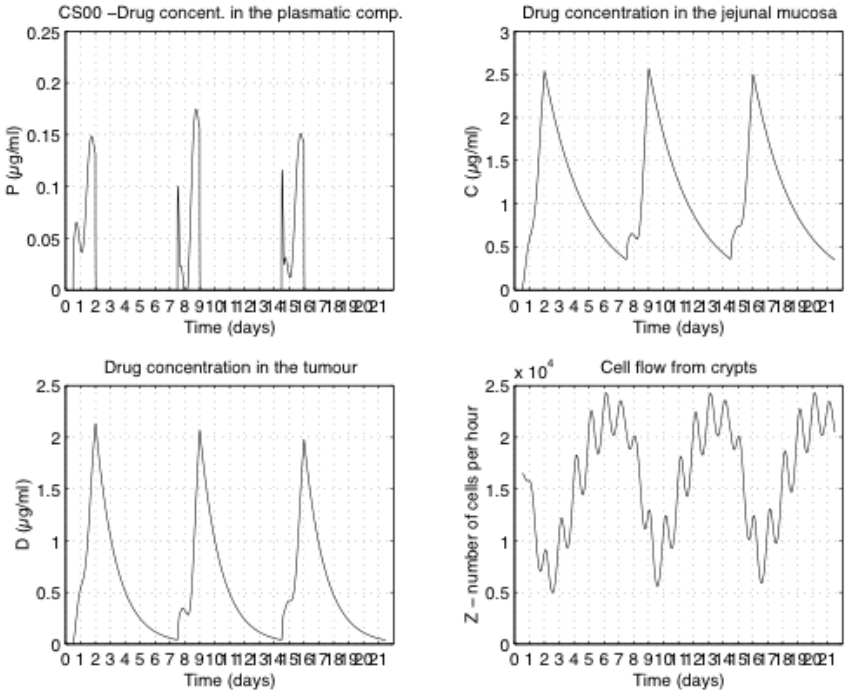


Varying τ_A:

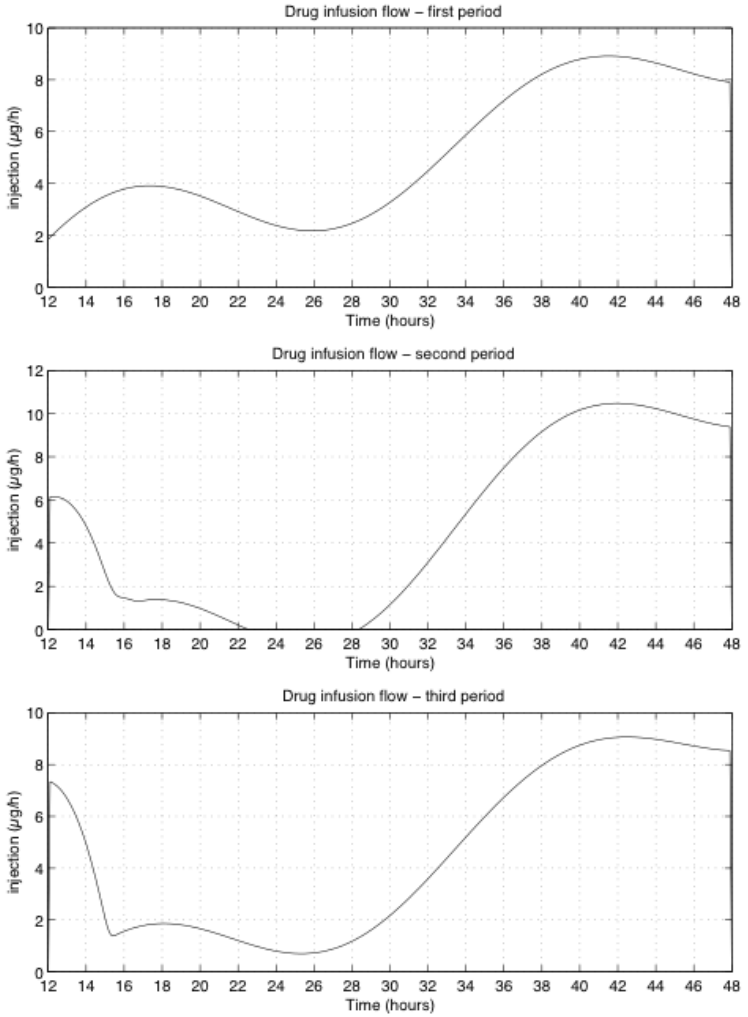
Numerical results for 1.5 days infusion + 5.5 days recovery:

τ_A	max B(t)	min B(t)
40 %	28 000	6
50 %	102 000	147
60 %	305 000	2700

Detailed results: stabilisation strategy with $\tau_A = 50\ \%$, zoom:



P, C, D, Z behaviours



Drug infusion flow: 3 periods

Other optimisation techniques have been used

1) Augmented Lagrangian (AL)

2) SQPAL (Sequential Quadratic Programming AL, *author: Jean-Charles Gilbert, INRIA*)

…yielding similar results, but SQPAL is much faster

In conclusion to this optimal control study

- Optimal control of the chemotherapy infusion flow is possible using a simple quasilinear model taking into account both efficacy and toxicity

- It should be performed using: 1/ chronobiology constraints regarding antitumour efficacy and clinical toxicity
  2/ a peak infusion flow during the very first days of the chemotherapy course
  3/ a rather short chemotherapy course as much as possible, i.e. as long as the patient's health allows it

- The choice of the strategy (eradication or stabilisation) for the objective function, and of the constraints representing various forms of toxicity is essential and may depend on the particuliar drug and on the patient

- As much as possible, one should choose dynamic constraints (i.e. depending on time at each instant) rather than global constraints of the type $AUC \leq AUC_{max}$

Other recent theoretical approaches to cancer chronotherapy

- Albert Goldbeter and Attila Altinok, with Francis Lévi:
  Cellular automata model of the cell cycle, 5FU (S-phase specific), synchronised (healthy) vs. desynchronised (cancer) cells
  Altinok A., Lévi F., Goldbeter A, Adv Drug Deliv Rev. 2007; Eur J Pharm Sci. 2009

- Samuel Bernard, with Francis Lévi:
  Delay differential model of the cell cycle, 5FU, differences in S-phase timing and in cycle duration between healthy and cancer cells
  Bernard S,, Čajavec Bernard B,, Lévi F,, Herzel H, PLOS Comp. Biol. 2010

More future prospects and challenges

More challenges and future prospects:

Individualised treatments in oncology

Genetic polymorphism: between-subject variability

for pharmacological model parameters

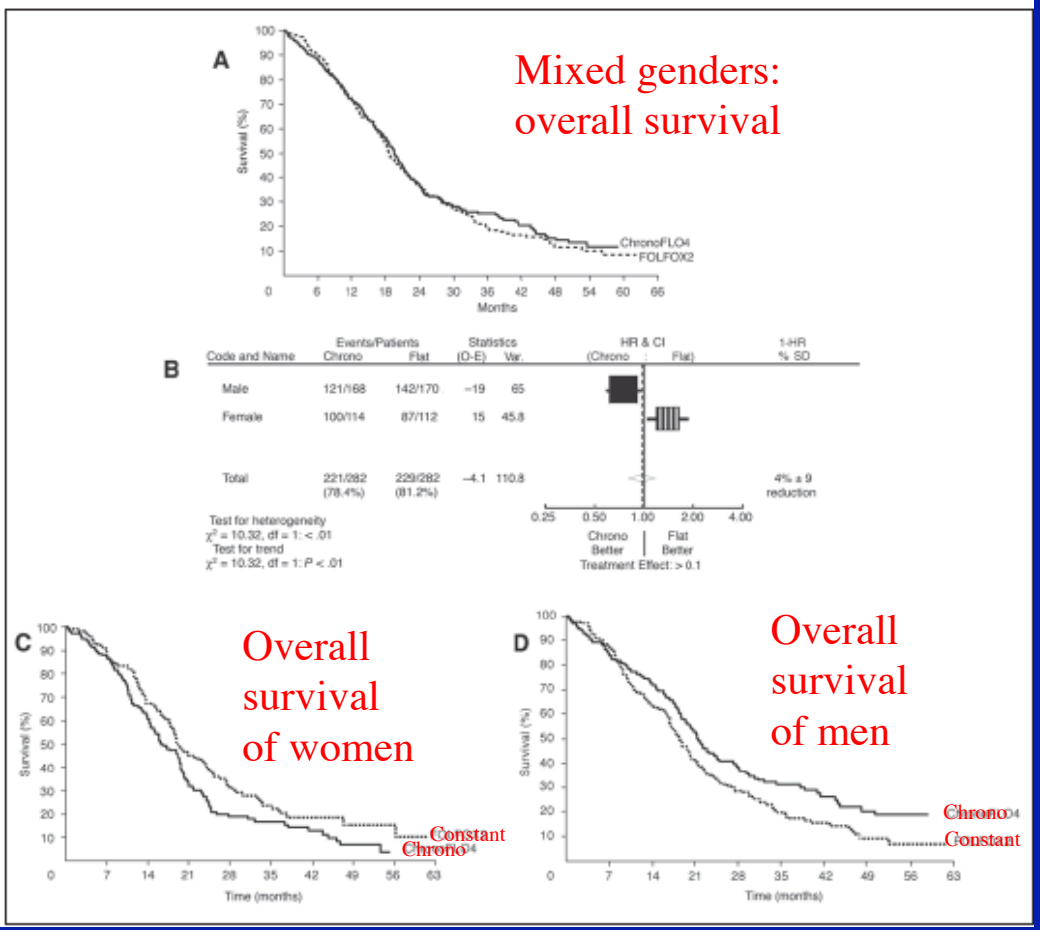
- According to subjects, there exist different expression and activity levels of drug processing enzymes and proteins (uptake, degradation, active efflux, e.g. GSTπ, DPYD, UGT1A1, P-gp,…) and drug targets (e.g. Thymidylate Synthase, Topoisomerase I)

- 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 (G. Milano & J. Robert in Oncologie 2005) with *individualised medicine*

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

A particular aspect of individualised medicine: Gender issues



It has been shown by large population studies in patients with CRC treated by 5FU+Oxaliplatin classical chronotherapy vs. constant infusion:
- that chronotherapy is beneficial in male patients
- that chronotherapy is detrimental in female patients

(Giacchetti et al. J Clin Oncol 2006)

Possible explanation: differences in toxicity (levels and peak times of enzyme activities?) between genders, hardly taken into account so far
Recommendation: find different optimised schedules for women

More challenges and future prospects (continued): 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? (e.g. pH) to foster proliferation of healthy cells rather than cancer cells

4. Associating drugs with other mechanisms: antiangiogenics, MMPIs, …

(Often disappointing due to unpredicted toxicity issues)