Institute of Natural Sciences, SJTU

Winter School on "Mathematical Models of Tumour and Disease"

From single-cell molecular to cell-populational phenotypically structured models to optimise cancer therapeutics

II. Controlling the cell division cycle using chronotherapeutics of anticancer drugs

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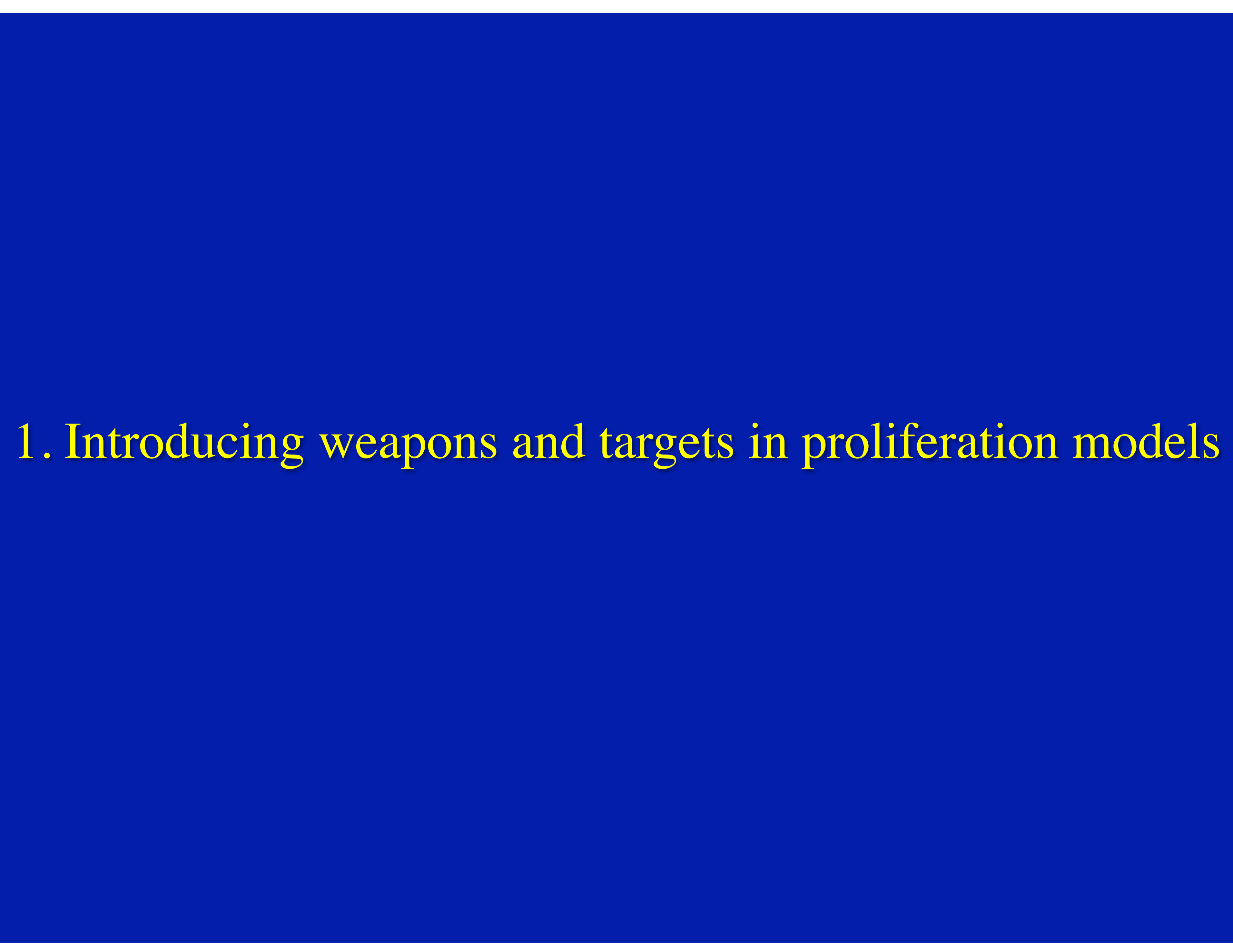
A general framework to optimise cancer therapeutics: designing mathematical methods along 3 axes

- Modelling the behaviour of growing cell populations on which anticancer drugs act (the targeted cell populations): proliferating tumour and healthy cell populations, including representing functional (not necessarily molecular) targets for pharmacological control
- (When PK-PD models are available) Modelling the external control system, i.e., fate of drugs in the organism, at the level of functional targets (proliferation, death, differentiation) in cell populations by functional, rather than molecular, pharmacokinetics-pharmacodynamics (PK-PD)
- Optimising therapeutic controls: dynamically optimised control of theoretical drug delivery flows representing time-dependent objectives and constraints, making use of known or hypothesised differences between cancer and healthy cell populations


1. Introducing weapons and targets in proliferation models

Cancer therapeutics summed up

- Surgery: highly localised
- Radiotherapy: localised, kills all renewing cells… including tumour cells
- Chemotherapy: - usually general, adapted to diffuse and metastatic cancers; *acts on all renewing cells* at the subcellular level (degrading DNA, blocking phase transitions, inducing apoptosis), at the cell and tissue level (antiangiogenic drugs), or at the whole organism level
  - but: new molecules = monoclonal antibodies (xxx-mab) directed toward tumours or tumour-favoring antigenic sites
- Immunotherapy: - injection of cytokines (*interferon, interleukins*) = boosters
  - use of engineered macrophages or lymphocytes directed toward specific targets: future?

Some pitfalls of cancer therapeutics

- Surgery: - (partly) blindfold
  - not feasible when tumour is adherent to vital blood vessels (liver)

  To overcome these drawbacks: - radio-guided surgery, possibly using DTI
  - previous use of radio- or chemotherapy

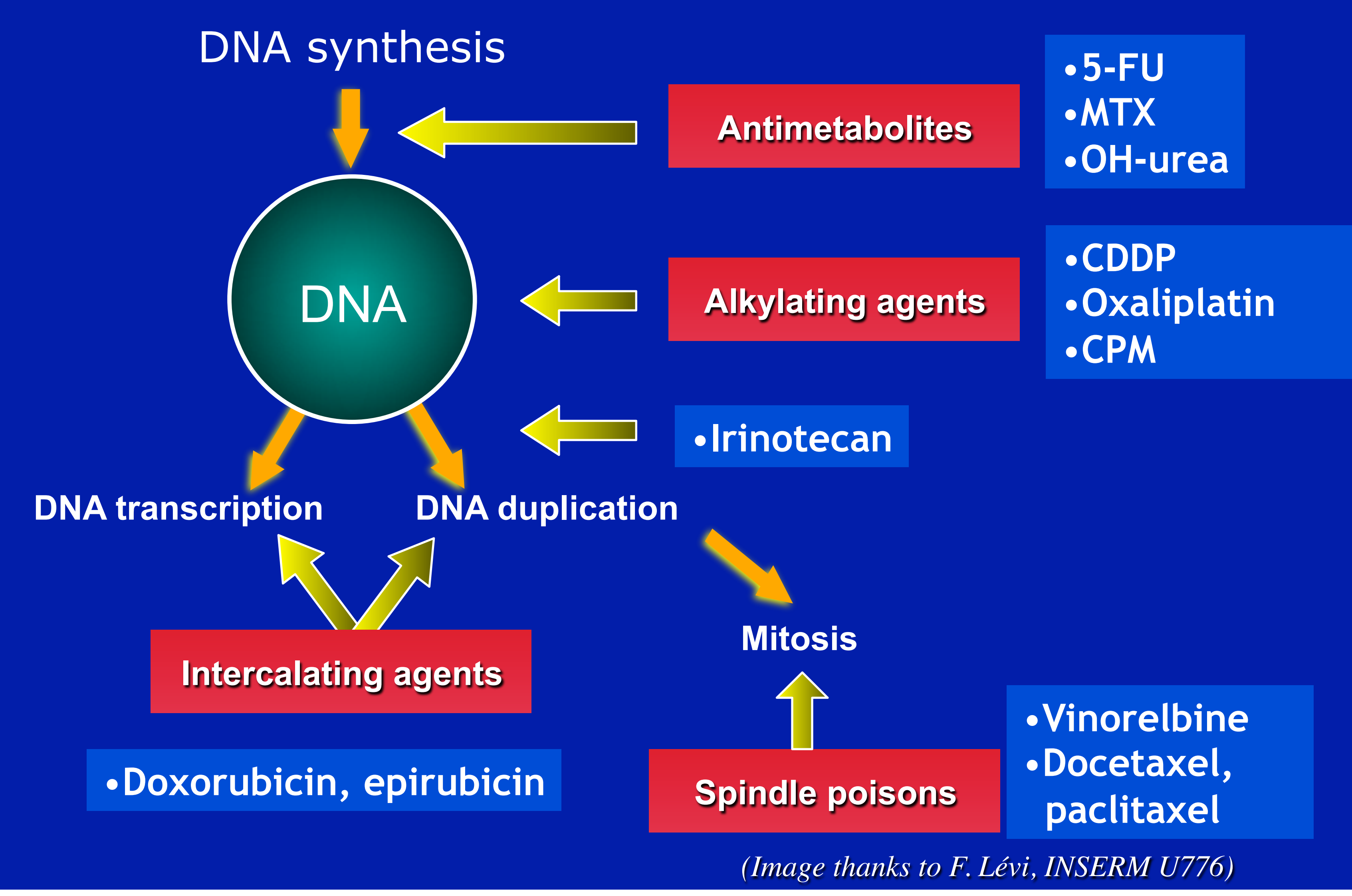
- Radiotherapy: not enough localised or not enough energetic
  Recently proposed: hadrontherapy = particle beam therapy (protons, neutrons and helium, carbon, oxygen and neon ions instead of photons): better localisation, possibility to deliver higher doses without unwanted damage

- Chemotherapy: - toxic to all fast renewing tissues (including healthy ones: gut and other digestive epithelia, skin, bone-marrow)
  - induces development of drug resistance by selecting resistant clones among cancer cells

  Proposed: optimisation of treatment to reduce toxicity and drug resistance

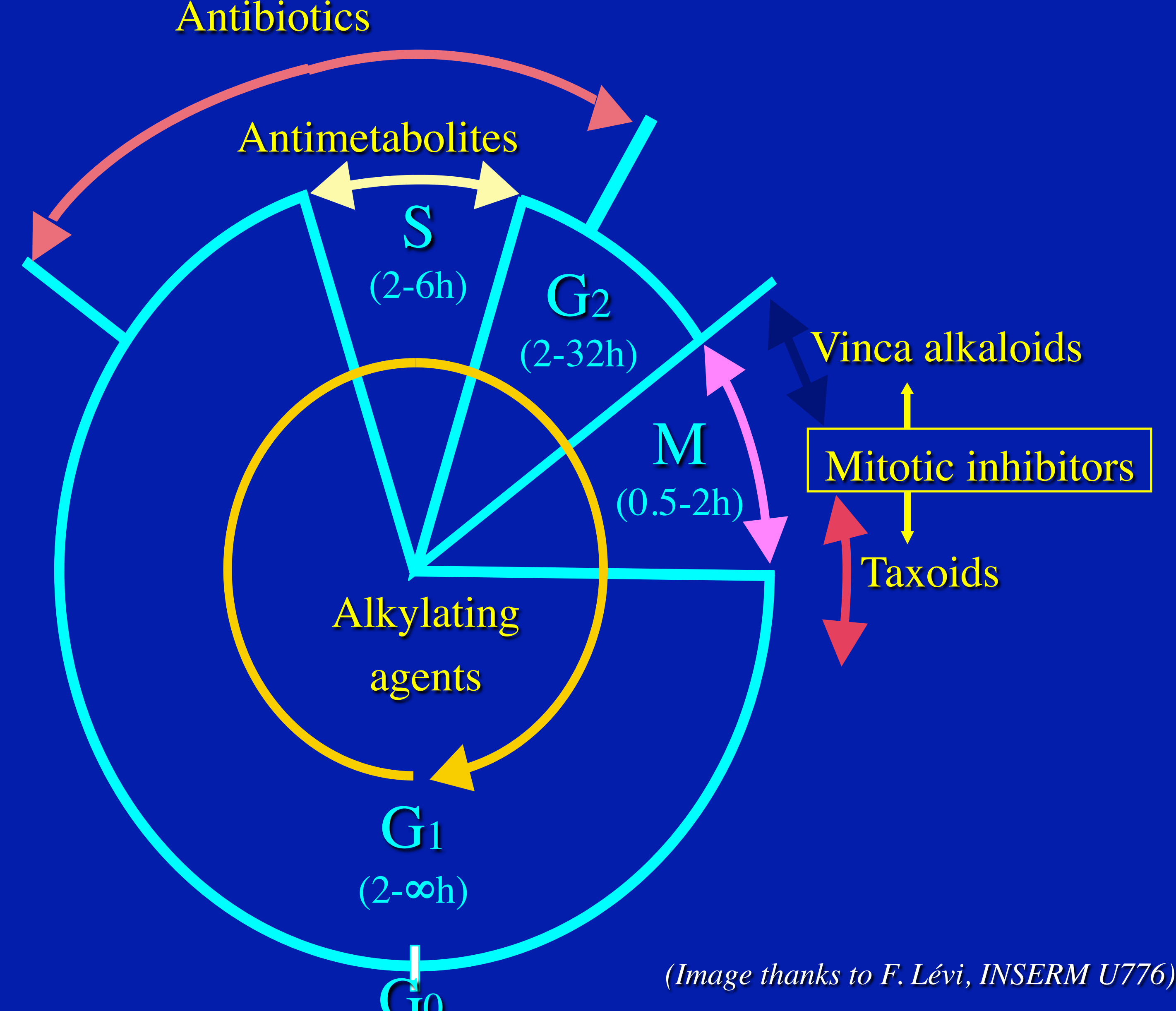
…..New molecules: xxx-mab, e.g. EGFR inhibitors (cytostatic drugs)
- monoclonal antibodies are mouse antibodies!-> HAMA

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



(Image thanks to F. Lévi, INSERM U776)

Cell cycle phases as targets for chemotherapy agents



(Image thanks to F. Lévi, INSERM U776)

Different viewpoints to represent tumour therapies

1. At the molecular level:

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

2. At the cell and molecular level:

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

3. At the cell population level:

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

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

Examples: macroscopic models of the action of drugs

1. ODE with functional representation of pharmacodynamics for bone marrow toxicity

$$\frac{dPBM}{dt} = [1 - f(D)] \cdot r(N) \cdot PBM - k_1 \cdot PBM,$$

$$\frac{dNBM_1}{dt} = k_1 \cdot PBM - k_2 \cdot NBM_1,$$

$$\frac{dNBM_2}{dt} = k_2 \cdot NBM_1 - k_3 \cdot NBM_2,$$

$$\frac{dN}{dt} = k_3 \cdot NBM_2 - k_{el} \cdot N,$$

$$r(N) = r_{max} - (r_{max} - r_{min}) \cdot \frac{N}{K_m + N}, \quad \text{PD model}$$

$$f(D) = \frac{D^m}{K_D^m + D^m},$$

PBM, NBM_i = bone marrow cells, *N* = circulating neutrophils, *D* = drug concentration

(JC Panetta, Math BioSci 2003)

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

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

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

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

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

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

Pharmacokinetic-pharmacodynamic (PK-PD) modelling

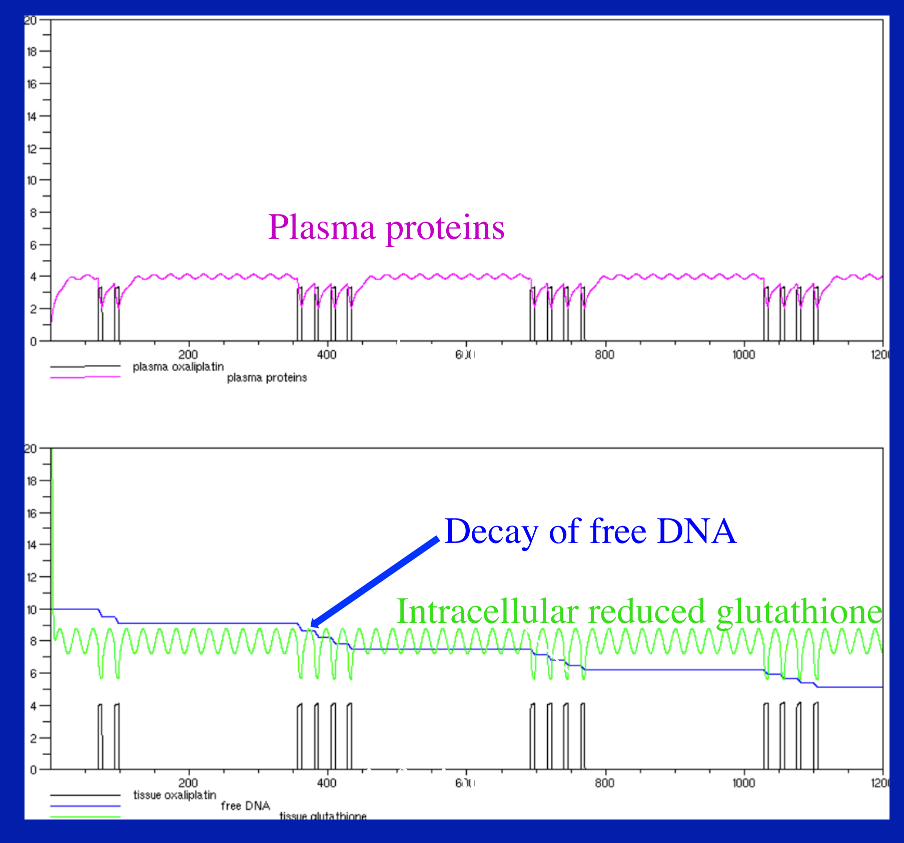
"Pharmacokinetics is what the organism does to the drug,
Pharmacodynamics is what the drug does to the organism"

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

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

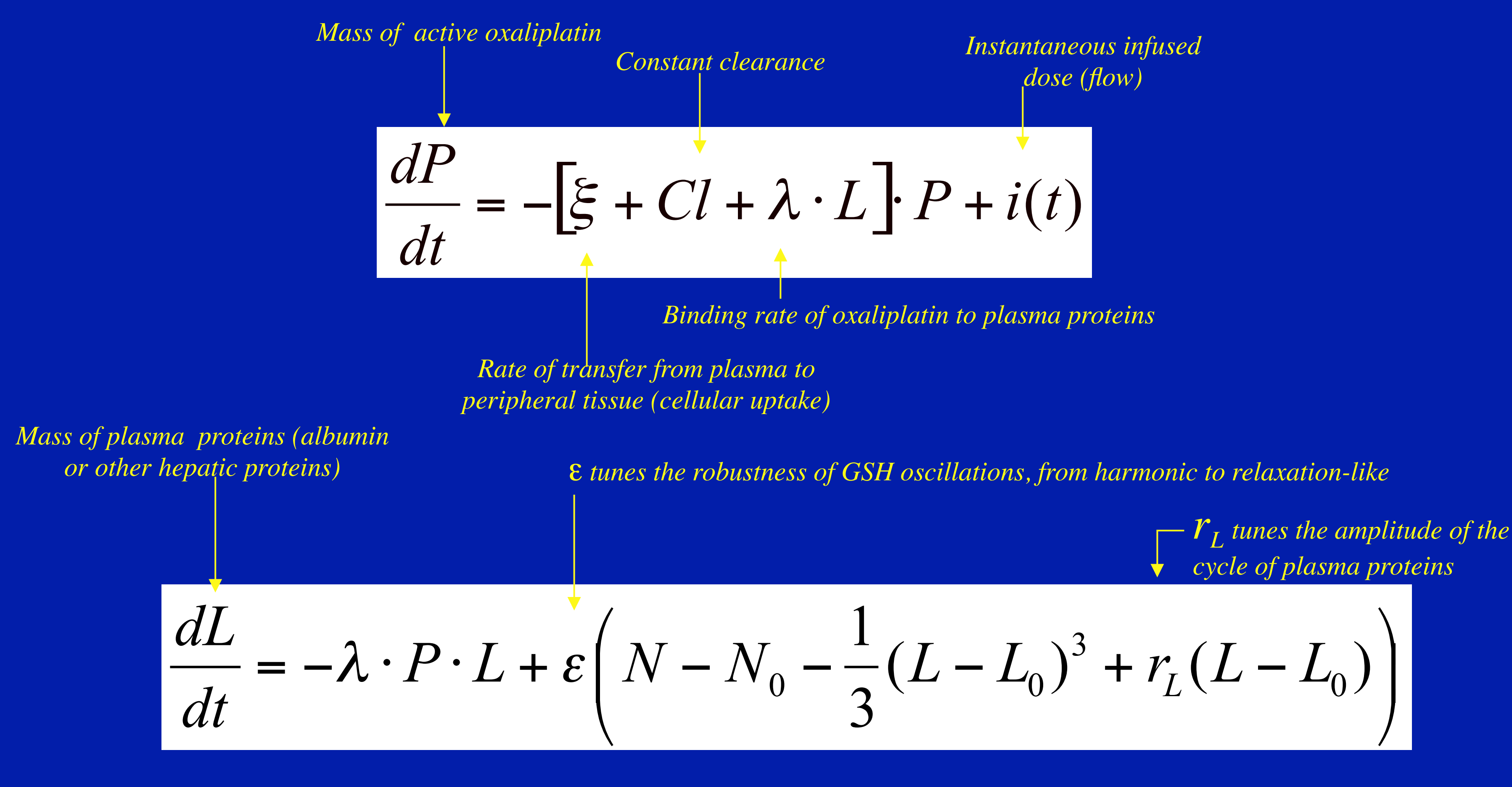
$$
\begin{cases}
\dfrac{dR}{dt} = -[\xi + cl + \lambda K]R + i(t) \\
\dfrac{dK}{dt} = -\lambda RK + \mu_K (K_0 - K) \\
\dfrac{dC}{dt} = -V_{GST} \dfrac{CG^2}{K_{GST}^2 + G^2} - k_{DNA} CF + \xi R \\
\dfrac{dF}{dt} = -k_{DNA} CF + \mu_F (Fo - F) \\
\dfrac{dG}{dt} = -V_{GST} \dfrac{CG^2}{K_{GST}^2 + G^2}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

Input *i =oxaliplatin infusion*



(JC, O. Fercoq, submitted, 2016 and preprint https://hal.archives-ouvertes.fr/hal-01321536)

Molecular PK of Oxaliplatin in plasma compartment



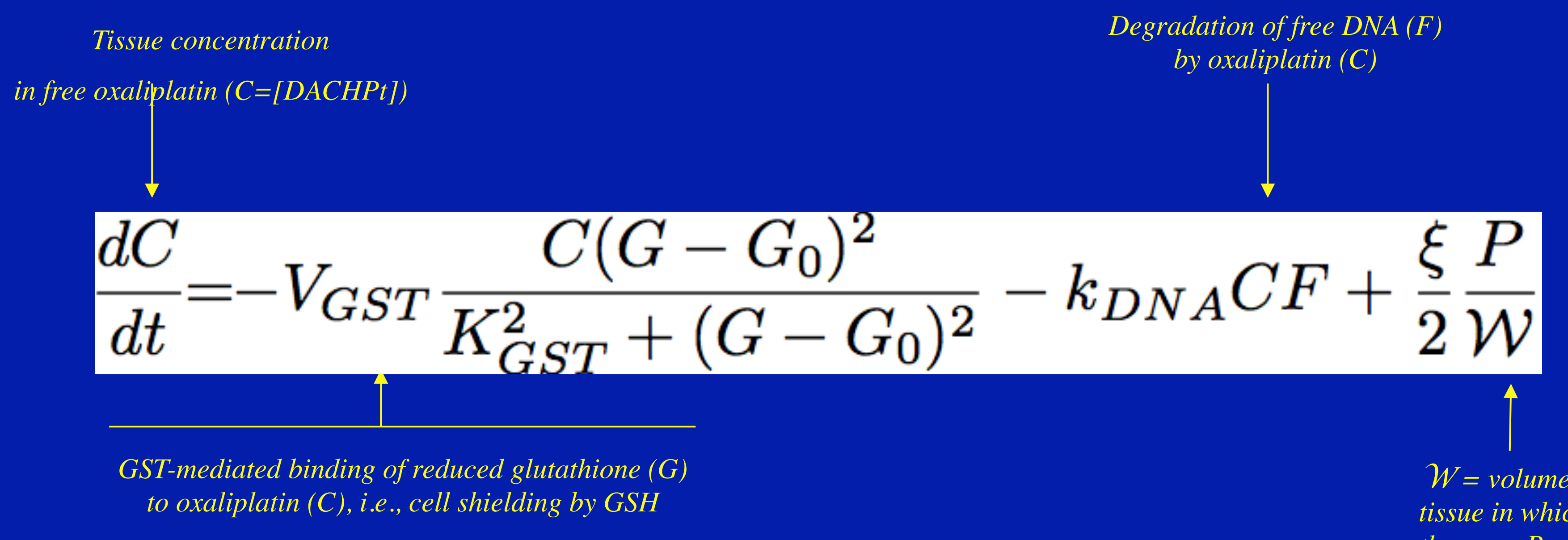
Hepatic synthesis activity of plasma proteins

ω_L *tunes the period of the cycle of plasma proteins*

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

Plasma protein synthesis shows circadian rhythm

Molecular PK of Oxaliplatin: tissue concentration



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

Molecular PD of Oxaliplatin activity in tissue

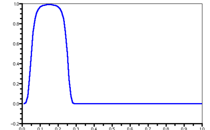
Mass of free DNA

Action of oxaliplatin on free DNA (F)

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

DNA repair function

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



Mass of reduced glutathione in target cell compartment

Oxaliplatin cell concentration

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

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

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

Activity of γ-Glu-cysteinyl ligase (GCS)

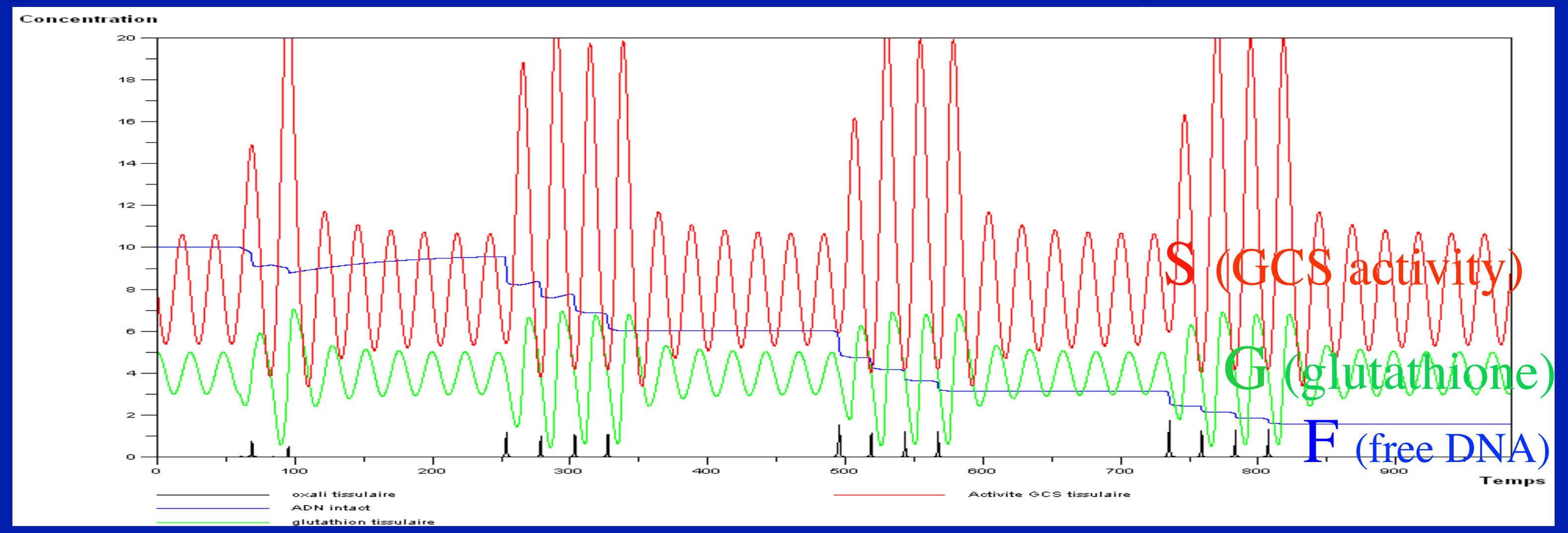
ω_G tunes the period of the cycle of GSH synthesis by GCS

Glutathione synthesis (→detoxification) in cells shows circadian rhythm

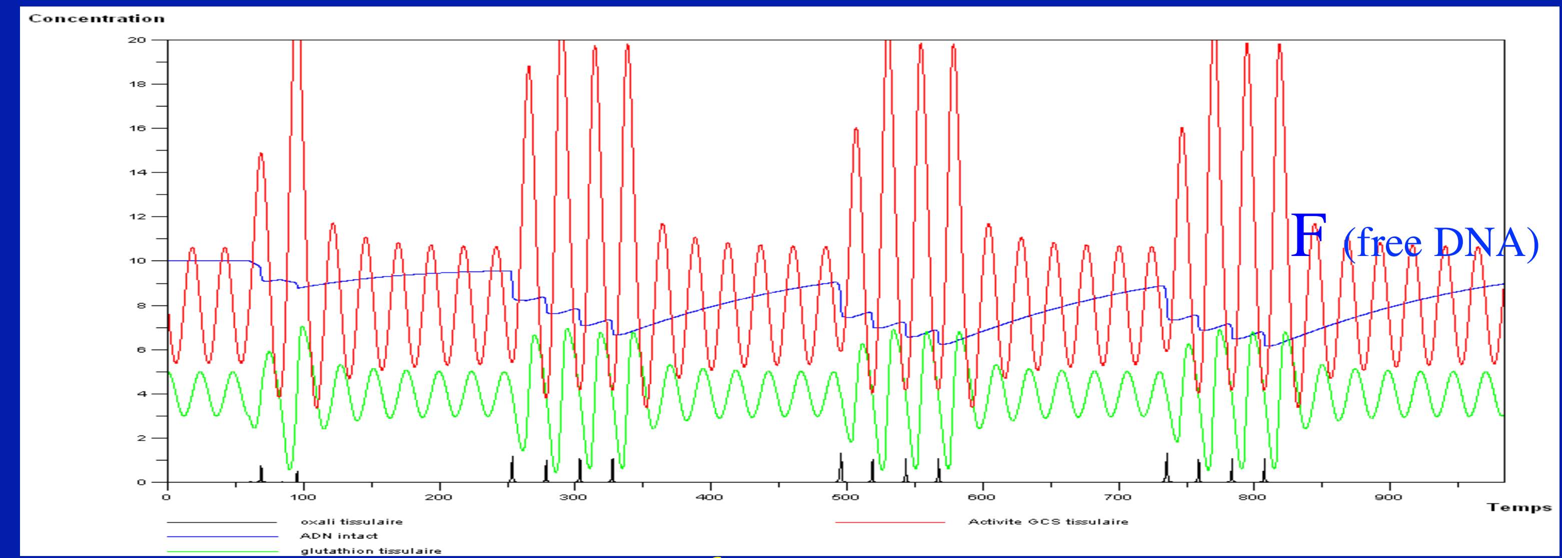
$$\frac{dN}{dt} = -\frac{\omega_L^2}{\varepsilon}(L - L_0)$$

$1 - F/F_0$ = DNA damage

PD of Oxaliplatin on DNA and genetic polymorphism of repair function in tumour cells: drug resistance or not

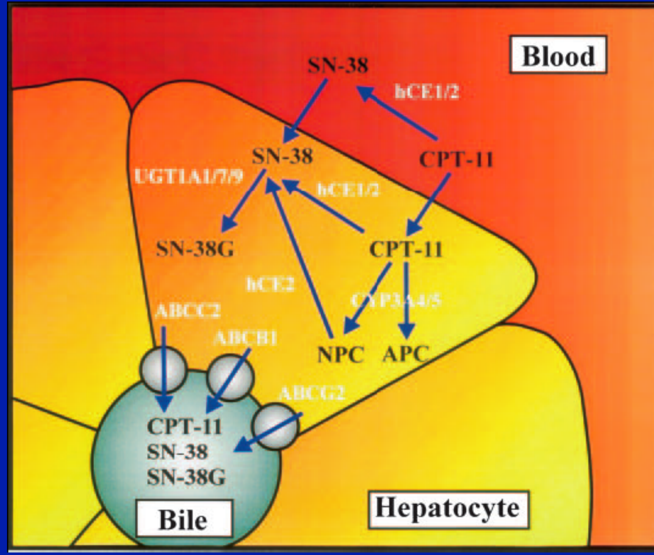


…the same with stronger DNA repair function, ERCC2=XPD-determined:



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

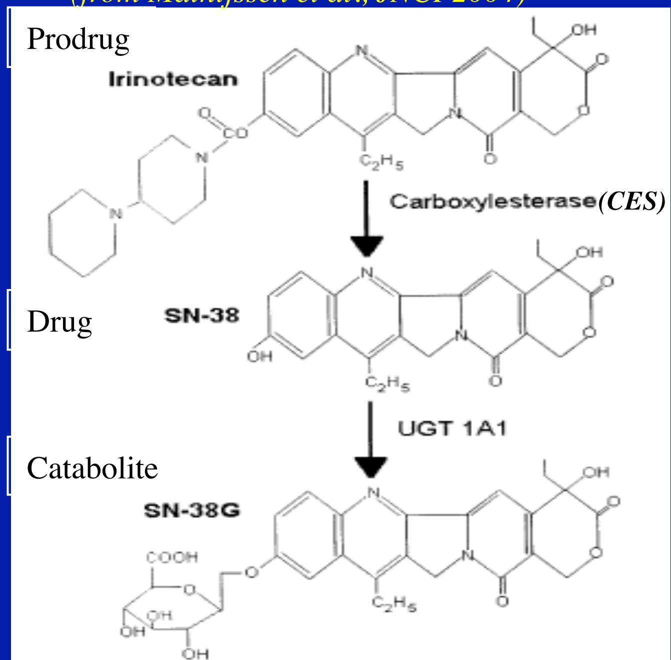
2nd example: cytotoxic drug *Irinotecan* (CPT11)



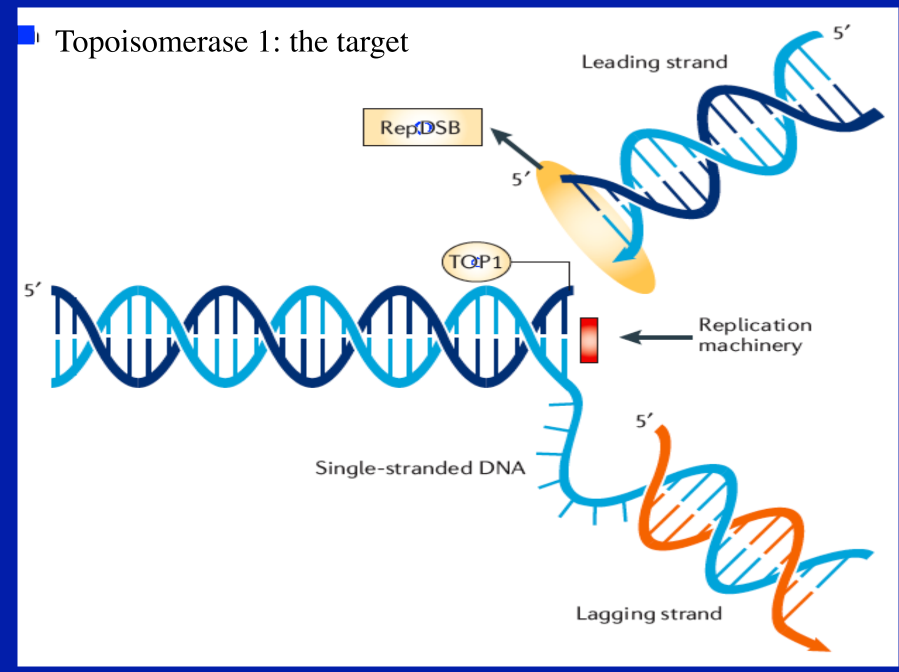
(from Mathijssen et al., JNCI 2004)

Intracellular PK-PD model of CPT11 activity:

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



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



(from Pommier, Nature Rev Cancer 2006)

Intracellular PK-PD of *Irinotecan* (CPT11)

PK

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

PD

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

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

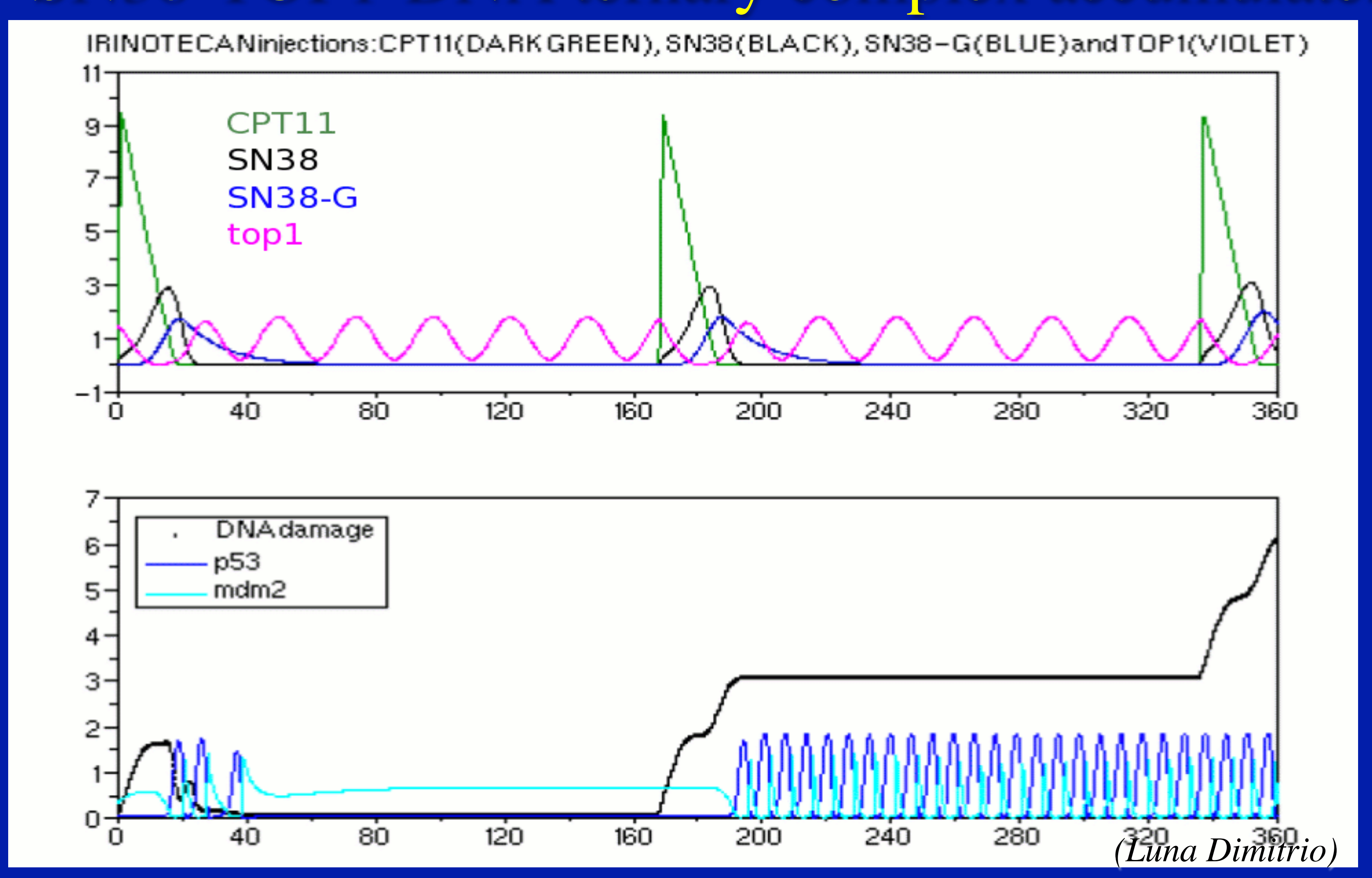
(Luna Dimitrio's Master thesis 2007; A. Ballesta's PhD work 2012)

A. Ciliberto's model of p53-Mdm2 oscillations

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

(Ciliberto, Novak, Tyson, Cell Cycle 2005)

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

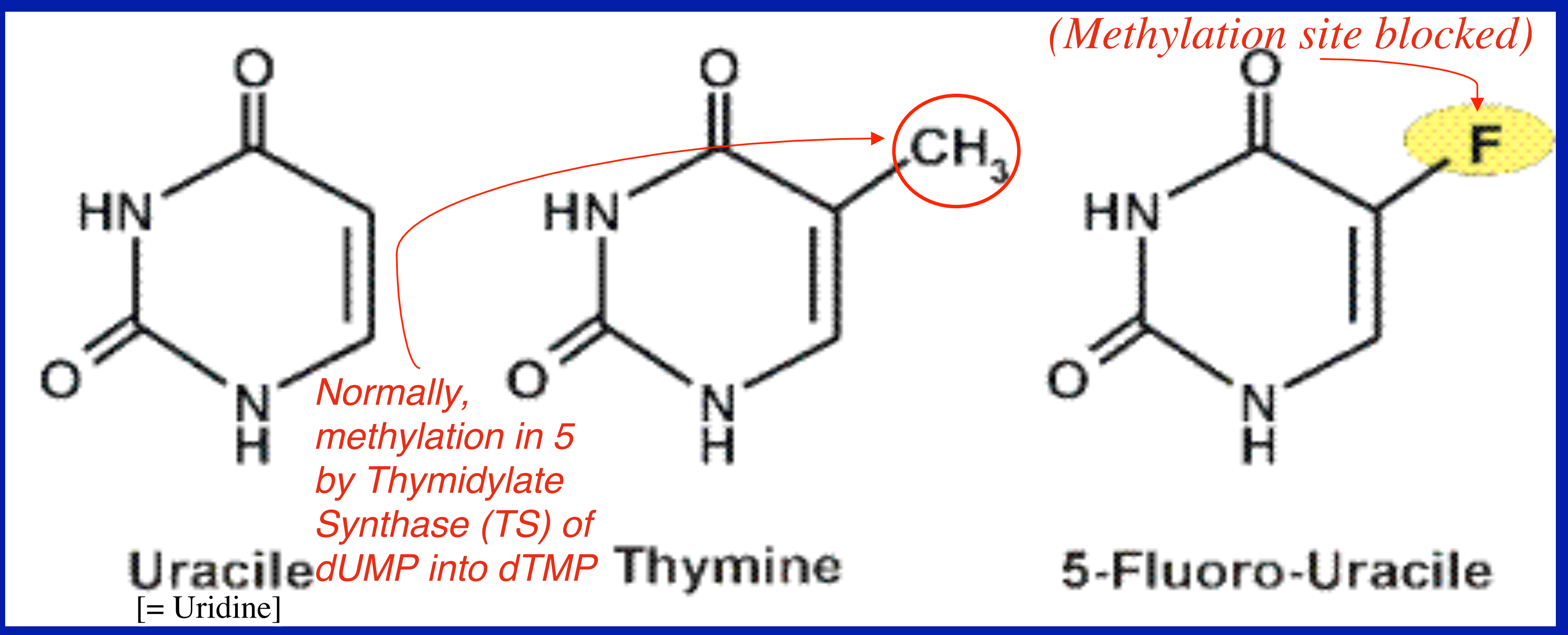


(Luna Dimitrio)

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

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

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



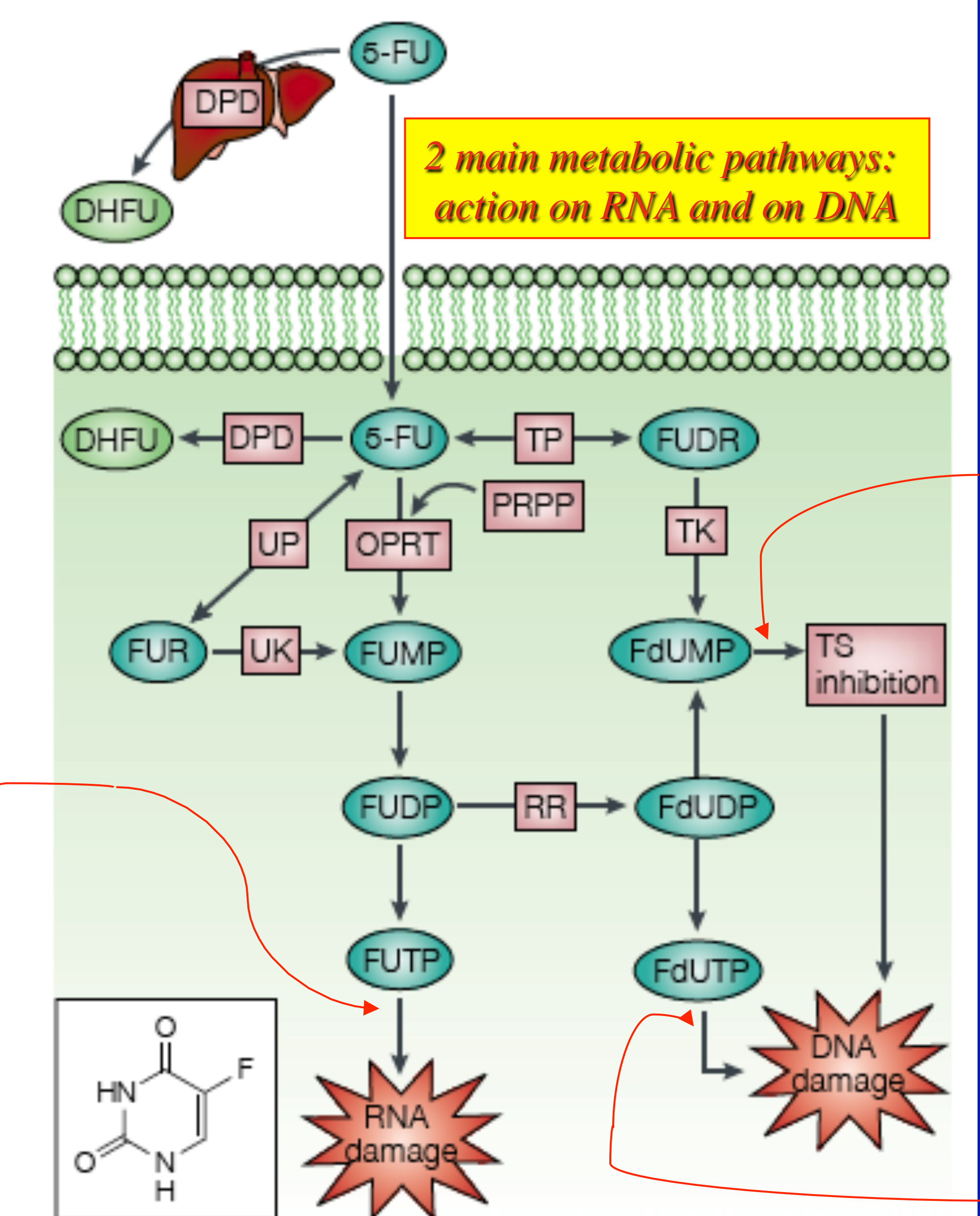
(NB : Uracil is found only in DNA)

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

PK-PD of 5-FU

RNA pathway

DNA pathway



Competitive inhibition by FdUMP of dUMP binding to target TS

+

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

Incorporation of FUTP instead of UTP to RNA

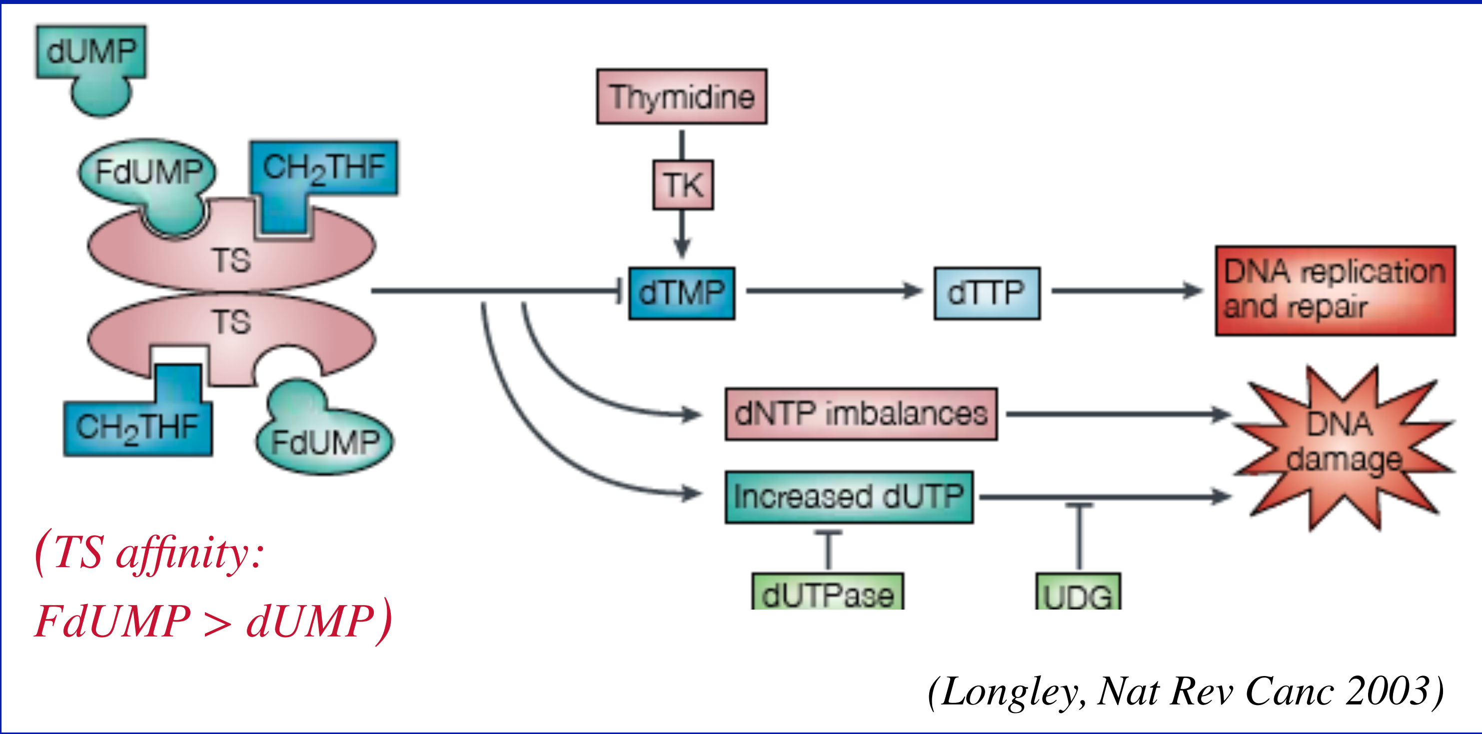
Incorporation of FdUTP instead of dTTP to DNA

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

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

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

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



(TS affinity: FdUMP > dUMP)

(Longley, Nat Rev Canc 2003)

Plasma and cell pharmacokinetics (PK) of 5-FU

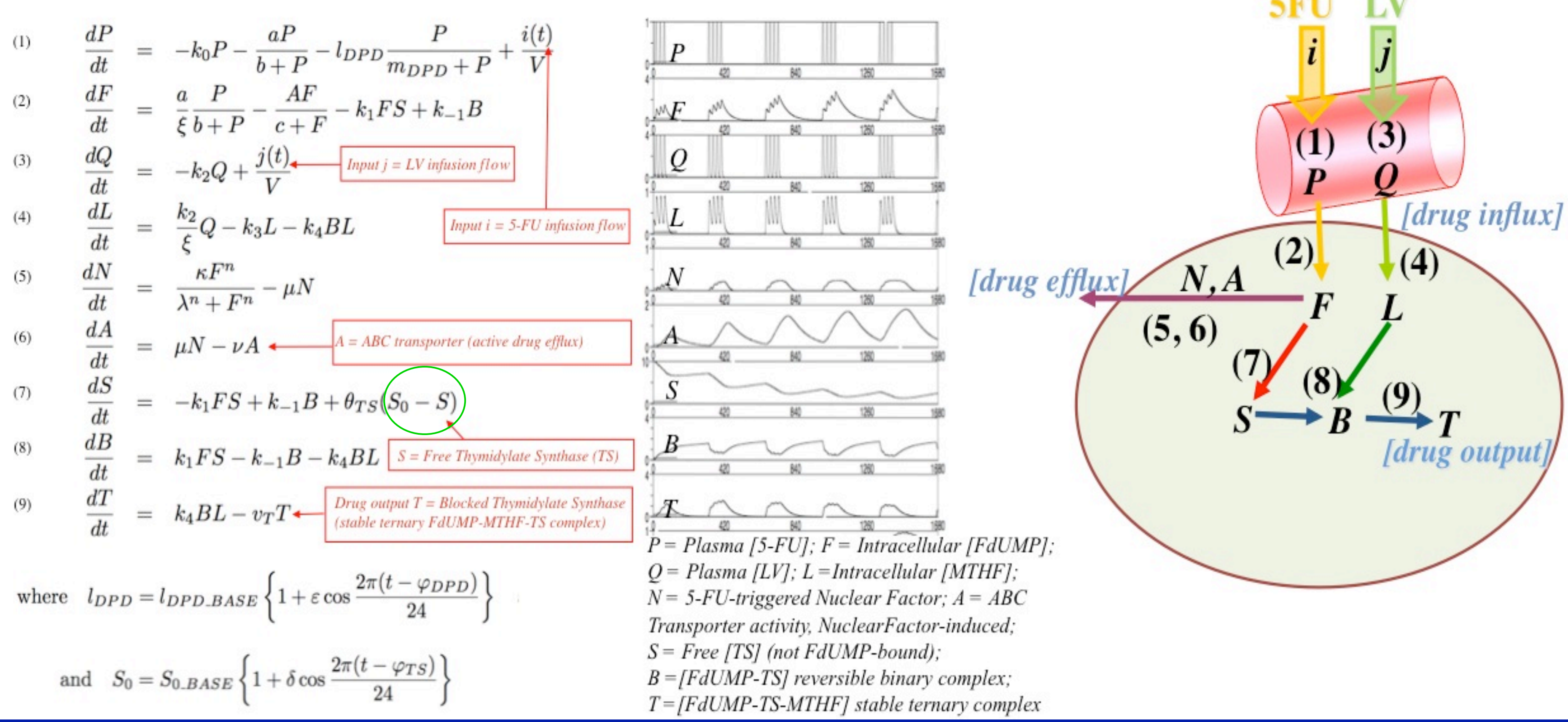
- Poor binding to plasma proteins
- Degradation +++ (80%) by liver DPD
- Cell uptake using a saturable transporter
- Rapid diffusion in fast renewing tissues
- 5-FU = prodrug; main active anabolite = Fd-UMP
- Fd-UMP: active efflux by ABC transporter ABCC11 = MRP8

(Oguri, Mol Canc Therap 2007)

5-FU catabolism: DPD
(dihydropyrimidine dehydrogenase)

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

P = Plasma [5FU]

F = Intracellular [FdUMP]

Q = Plasma [LV]

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

N = [nrf2] efflux Nuclear Factor

A = ABC Transporter activity

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

B = [FdUMP-TS] binary complex

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

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

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

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

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

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

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

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

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

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

Input = LV infusion flow

Input = 5FU infusion flow

Output = blocked Thymidylate Synthase

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

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

FdUMP extracellular efflux (by ABC Transporter ABCC11)

5-FU cell uptake

5-FU DPD detoxication in liver

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

$j(t)$ = LV infusion flow

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

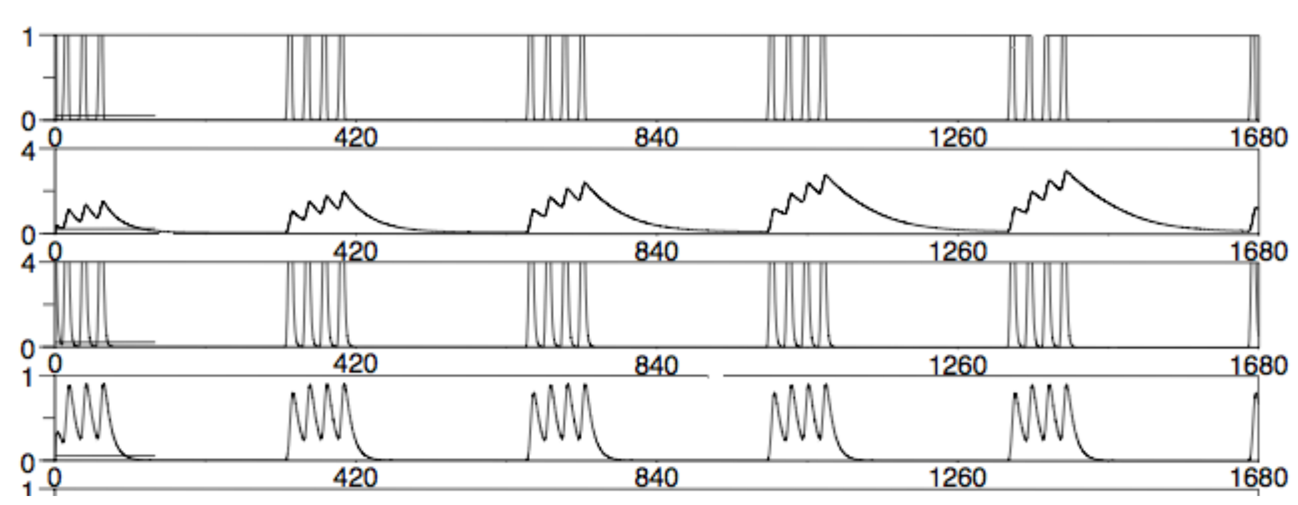
$$\frac{dF}{dt} = \frac{a}{\xi}\frac{P}{b+P} - \frac{AF}{c+F} - k_1 FS + k_{-1}B$$

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

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

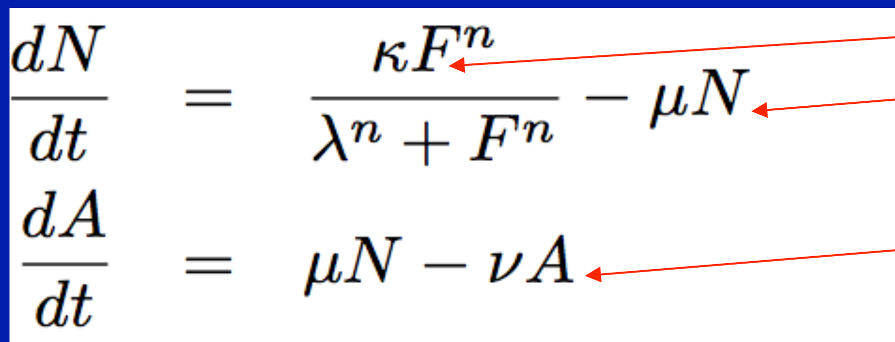
Binding of FdUMP to TS to form a *reversible* binary complex B

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



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

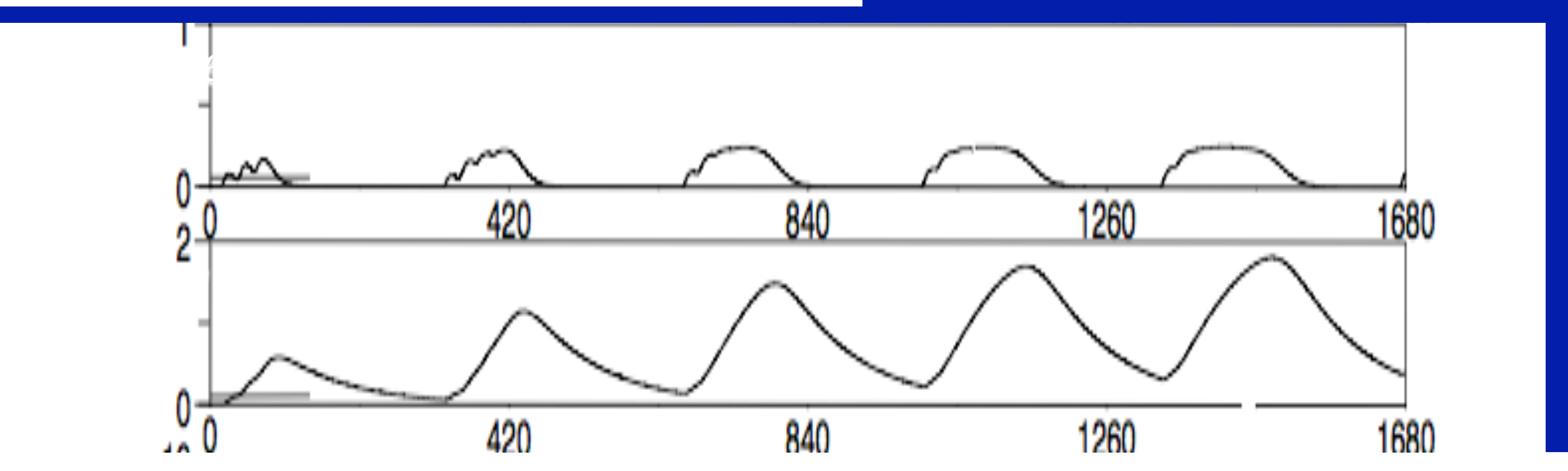
$$\frac{dF}{dt} = \frac{a}{\xi}\frac{P}{b+P} - \frac{AF}{c+F} - k_1 FS + k_{-1}B$$



FdUMP

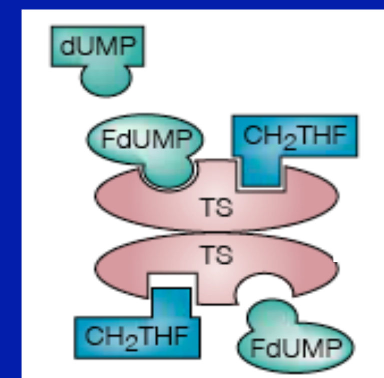
Nuclear factor *(e.g., nrf2)*

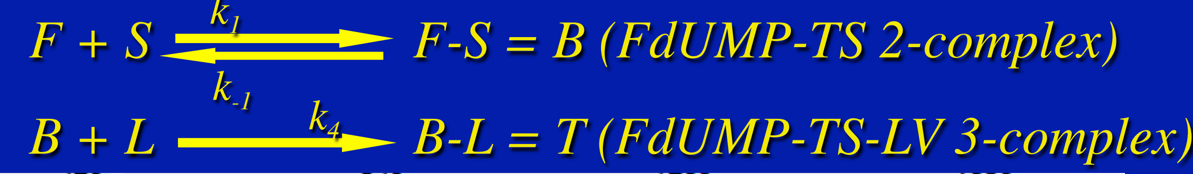
ABC Transporter activity (ABCC11=MRP8)

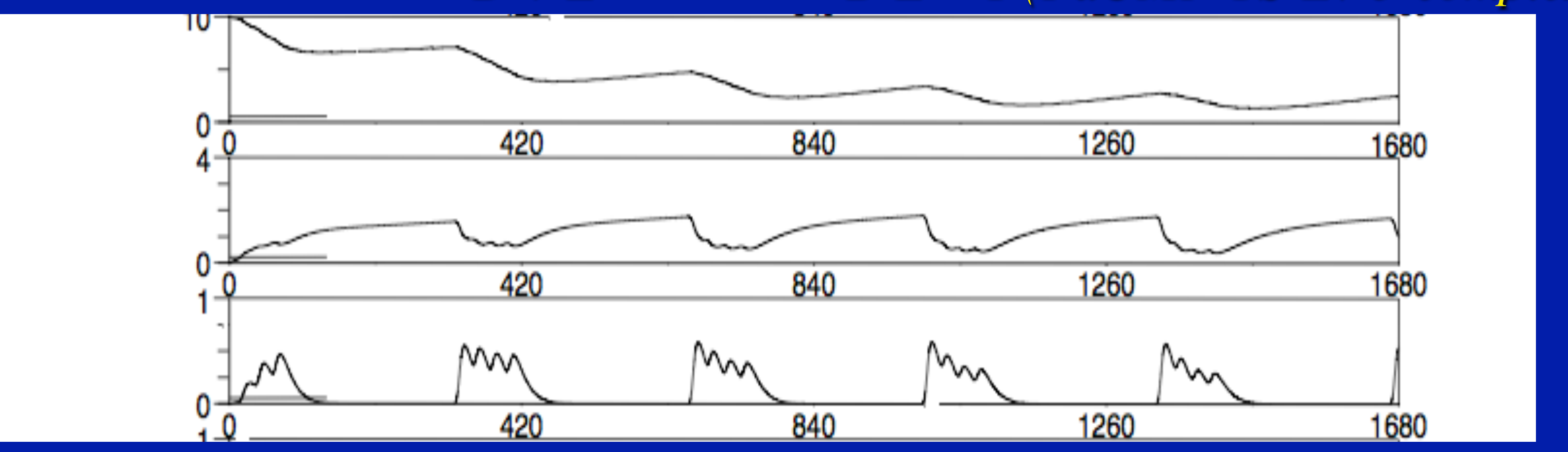


Targeting Thimidylate Synthase (*TS*) by FdUMP: Formation of binary and ternary *TS*-complexes

$$\frac{dS}{dt} = -k_1 FS + k_{-1}B + \theta_{TS}(S_0 - S)$$
$$\frac{dB}{dt} = k_1 FS - k_{-1}B - k_4 BL$$
$$\frac{dT}{dt} = k_4 BL - v_T T$$







TS blockade results in subsequent DNA damage

Simulation: 5 sequences of 2-week therapy courses

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

P = Plasma [5FU]

F = Intracellular [FdUMP]

Q = Plasma [LV]

L = Intracellular [LV]

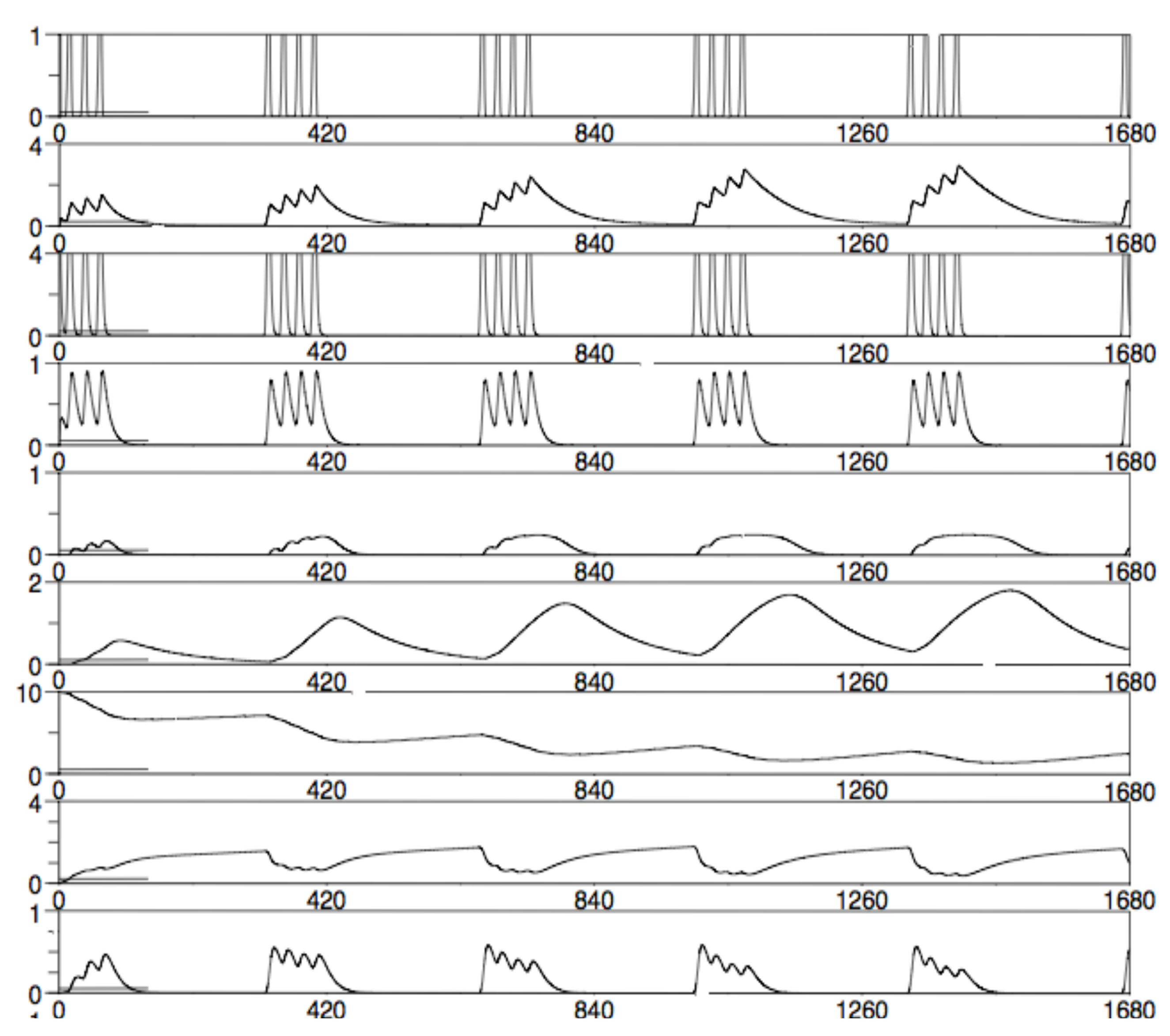
N = [nrf2] 5FU-triggered Nuclear Factor

A = ABC Transporter activity, nrf2-inducted

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

B = [FdUMP-TS] reversible binary complex

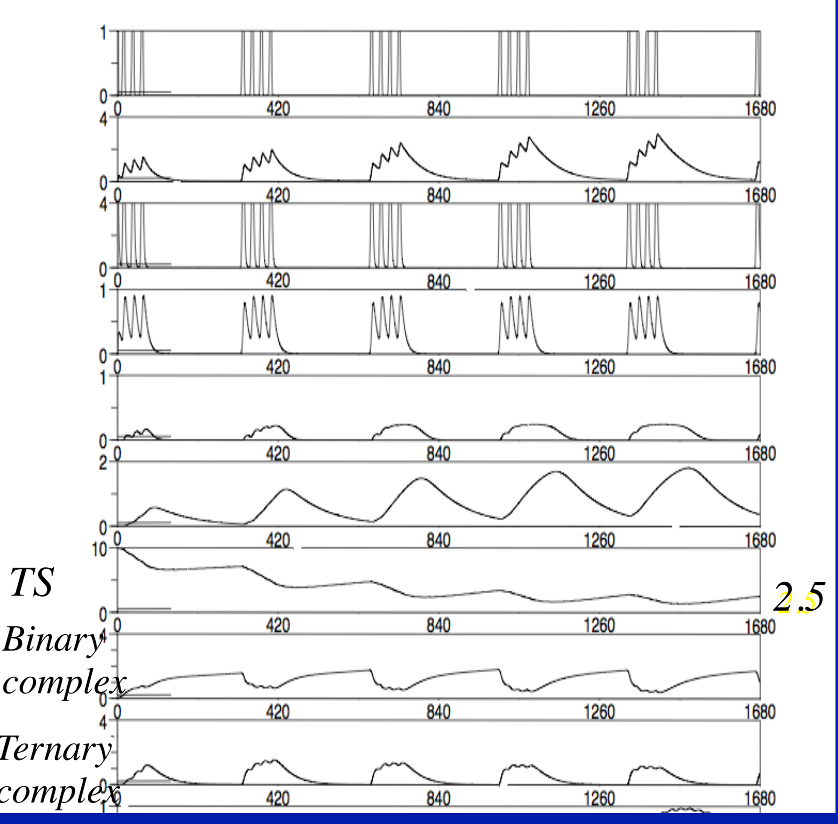
T = [FdUMP-TS-LV] stable ternary complex



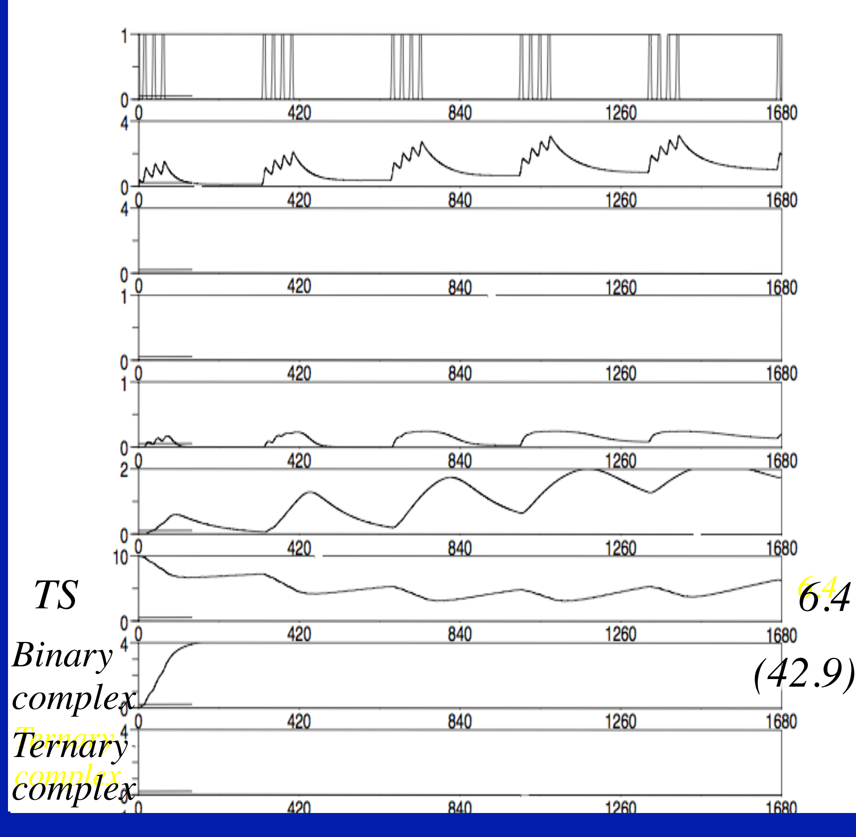
Some features of the model:

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

With Leucovorin added in treatment



Without Leucovorin added

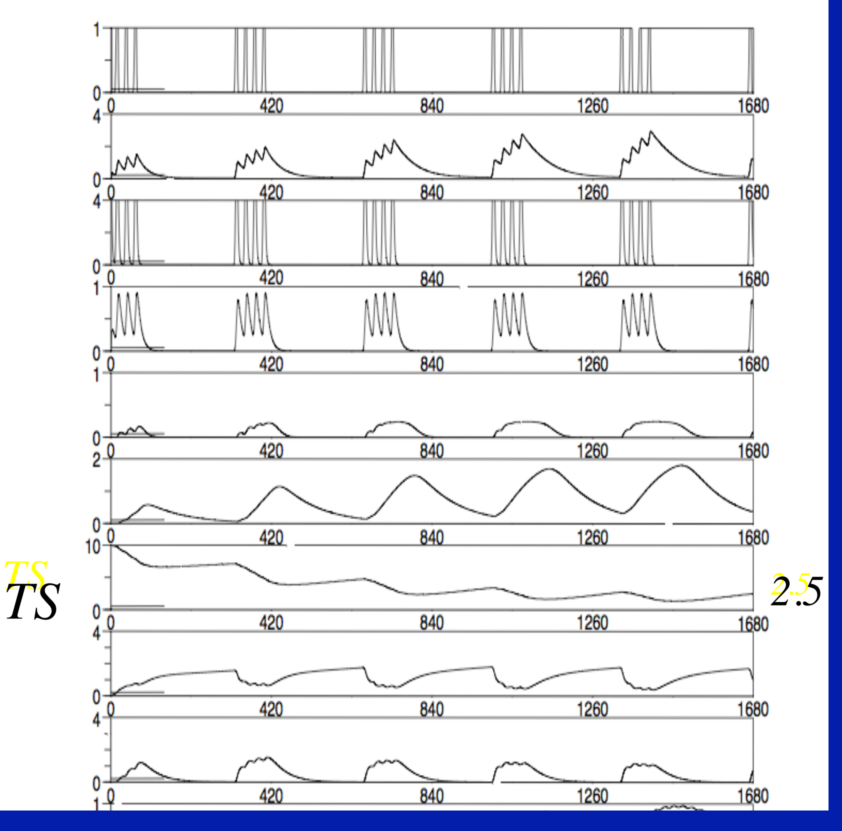


Cancer cells die

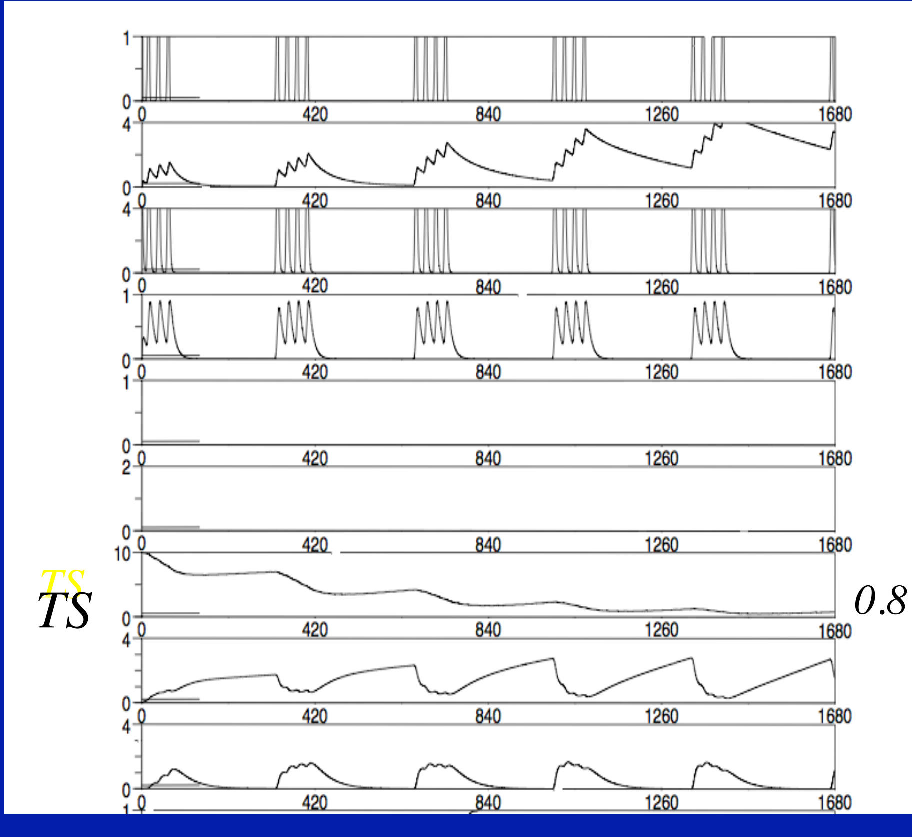
Cancer cells survive

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

Resistant cancer cells (=MRP8+)



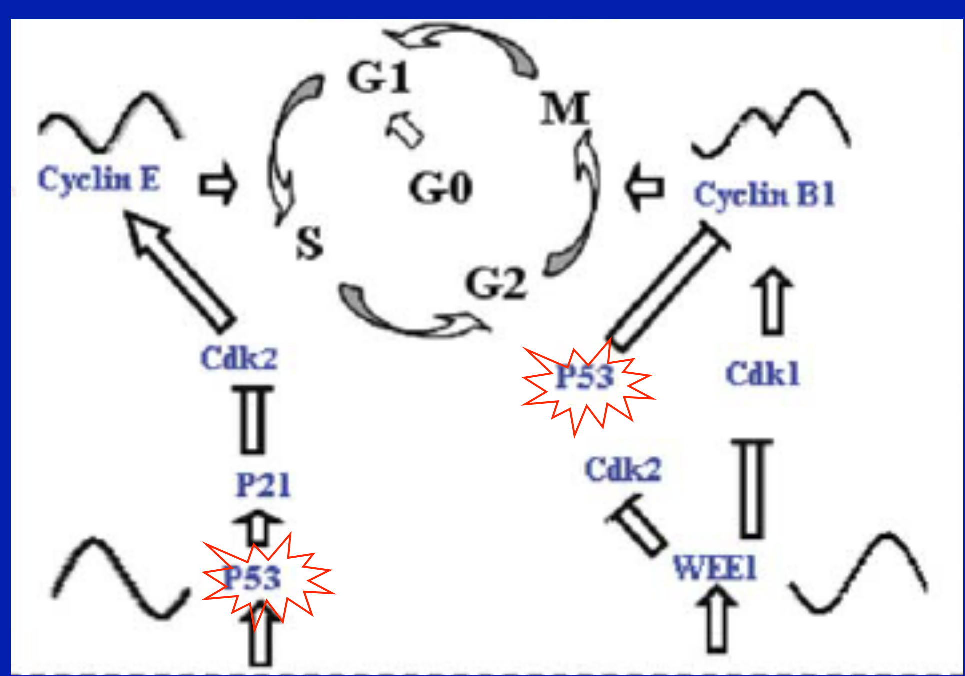
Healthy or sensitive cells (=MRP8-)



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

(actively effluxed from cells by ABC Transporter MRP8)

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



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

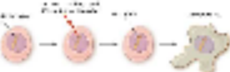
Connecting DNA damage with cell cycle arrest at G1/S and G2/M checkpoints through inhibition by p53 of the activity of Cdks / cyclins at G1/S and G2/M

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

What is p53?

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

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



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

The Model

NUCLEUS

$$
\begin{cases}
\frac{\partial[p53]}{\partial t} = d_p\Delta[p53] \overbrace{-k_1[mdm2]\frac{[p53]}{K_1+[p53]} + k_{-1}\frac{[p53_U]}{K_{-1}+[p53_U]}}^{\text{Ubiquitination-Deub.}} \\
\quad -k_3A\frac{[p53]}{K_{ATM}+[p53]} \\
\frac{\partial[p53_U]}{\partial t} = d_{p'}\Delta[p53_U] + k_1[mdm2]\frac{[p53]}{K_1+[p53]} - k_{-1}\frac{[p53_U]}{K_{-1}+[p53_U]} \\
\frac{\partial[p53_p]}{\partial t} = d_{p''}\Delta[p53_p]^{(n)} + \overbrace{k_3A^{(n)}\frac{[p53]}{K_{ATM}+[p53]}}^{\text{Phosphorylation}} - k_{Sp}\frac{([p53_p])^4}{([p53_p]^{(n)})^4+K_{Sp}} \\
\frac{\partial[mdm2]}{\partial t} = d_m\Delta[mdm2] - \delta_m[mdm2] \\
\frac{\partial[mdm2_{RNA}]}{\partial t} = k_{Sm} + \overbrace{k_{Sp}\frac{([p53_p])^4}{([p53_p])^4+K_{Sp}}}^{\text{p53-dependent-trascription}} + d_{mRNA}\Delta[mdm2_{RNA}] \\
\quad -\delta_{mRNA}[mdm2_{RNA}]
\end{cases}
$$

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

The Model

CYTOPLASM

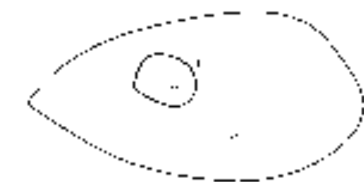
$$
\begin{cases}
\frac{\partial[p53]}{\partial t} = k_{Sp53}\chi_R + d_p\Delta[p53] - k_1[mdm2]\frac{[p53]}{K_1+[p53]} + k_{-1}\frac{[p53_U]}{K_{-1}+[p53_U]} \\
\quad -k_3A\frac{[p53]}{K_{ATM}+[p53]} \\
\frac{\partial[p53]_U}{\partial t} = d_{p'}\Delta[p53]_U + k_1[mdm2]\frac{[p53]}{K_1+[p53]} - k_{-1}\frac{[p53_U]}{K_{-1}+[p53_U]} \\
\quad \overbrace{-\delta_{pu}[p53_U]}^{\text{degradation}} \\
\frac{\partial[p53_p]}{\partial t} = d_{p''}\Delta[p53_p] + k_3A\frac{[p53]}{K_{ATM}+[p53]} \\
\frac{\partial[mdm2]}{\partial t} = d_m\Delta[mdm2] + \overbrace{[mdm2_{RNA}]\chi_R}^{\text{translation}} - \delta_m[mdm2] \\
\frac{\partial[mdm2_{RNA}]}{\partial t} = d_{mRNA}\Delta[mdm2_{RNA}] - [mdm2]_{RNA}\chi_R \\
\quad -\delta_{mRNA}[mdm2_{RNA}]
\end{cases}
$$

The Model

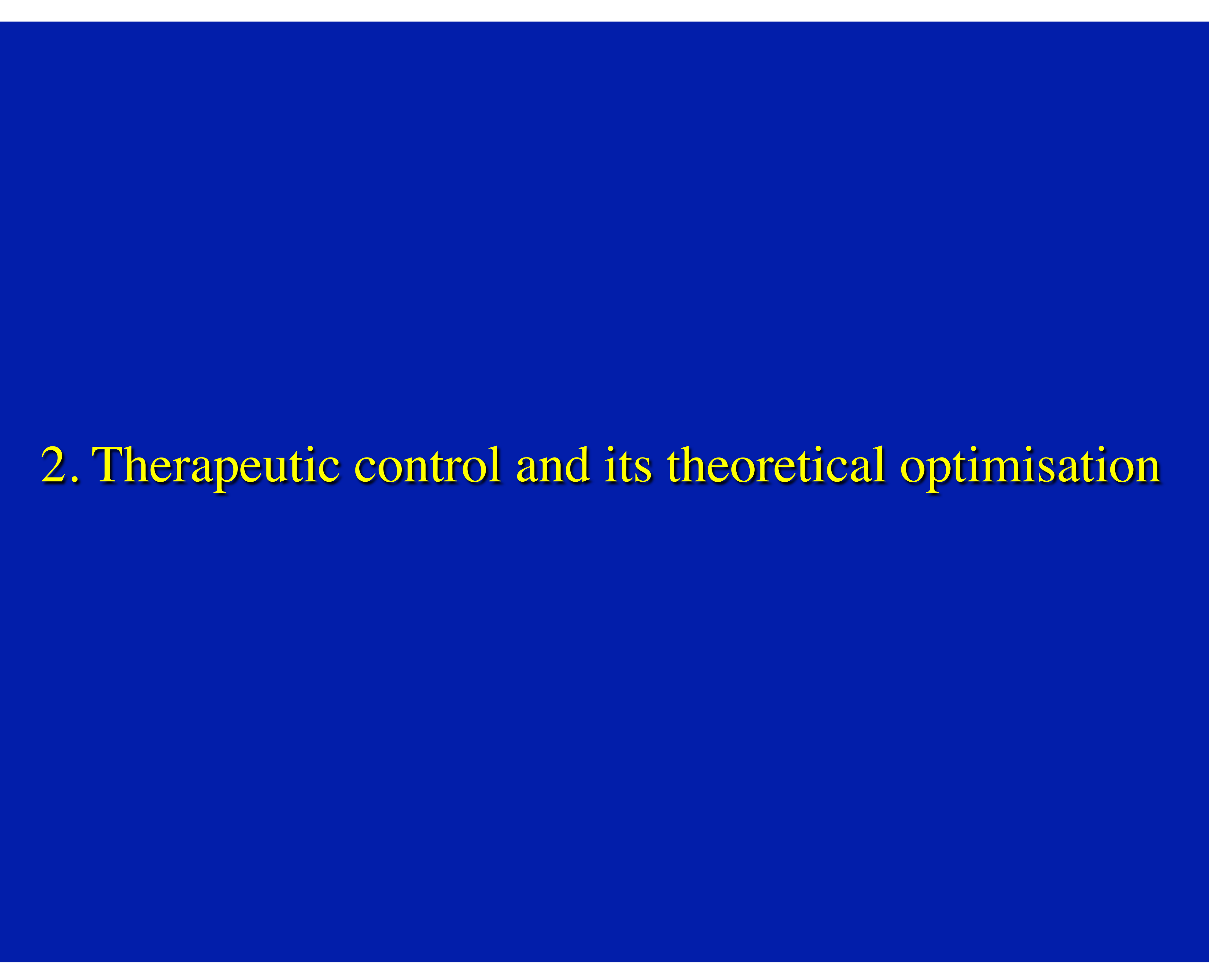
and the following boundary condition:

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

on the common boundary Γ.



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


2. Therapeutic control and its theoretical optimisation

Optimising cancer therapy by drugs

- Pulsed chemotherapies aiming at synchronising drug injections with cell cycle events to enhance the effect of drugs on tumours: e.g. optimal control of IL21 injection times and doses $\Sigma\, u_i\, \delta\,(t-t_i)$ using variational methods *(Z. Agur,IMBM, Israel)*

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

- Chronotherapy = continuous infusion time regimens taking advantage of optimal circadian anti-tumour efficacy and healthy tissue tolerability for each particular drug: *has been in use for the last 15 years, with achievements for colorectal cancer treatment* in human *males (M.-C. Mormont & F. Lévi, Cancer 2003)*

- Optimising combined delivery of cytotoxic and antiangiogenic drugs *(U. Ledzewicz et al. MBE 2011, H. Schättler and U. Ledzewicz's Springer books 2013, 2015)*

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

(M. Kimmel & A. Swierniak, Springer LN Math 1872, 2006; Lorz et al. 2013, 2015; Pouchol et al., underway)

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

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

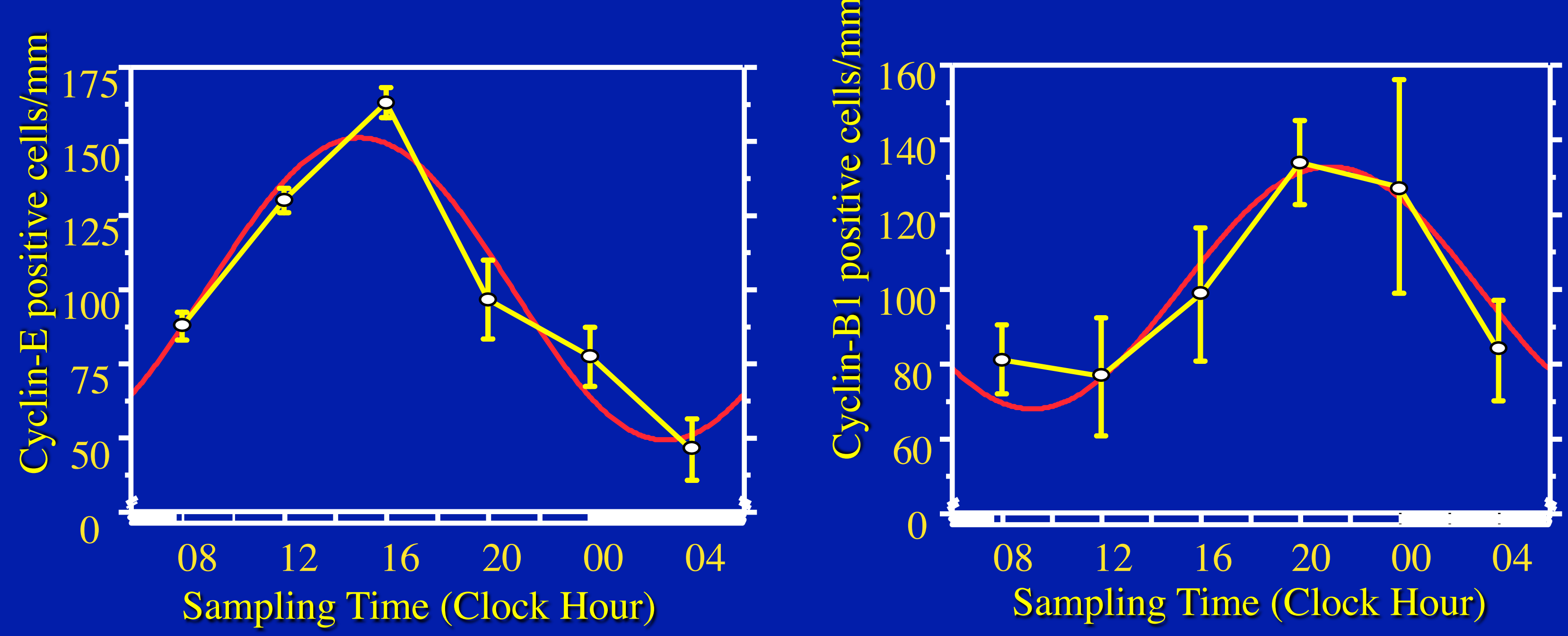
- *Drug resistance issues*. Controlling emergence of drug-induced drug-resistant cell subpopulations in tumour tissues leads to using phenotypic trait-structured models of proliferation: physiologically structured evolutionary integro-differential equations

Hereafter, we aim to minimise unwanted toxic side effects on healthy cells

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

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

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



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

(from Bjarnason et al. Am J Pathol 1999)

Circadian chronobiology: the circadian system

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

Central coordination

CNS, hormones, peptides, mediators

Pineal gland

NPY

PVN

RHT

Supra Chiasmatic Nuclei

Melatonin

Glutamate

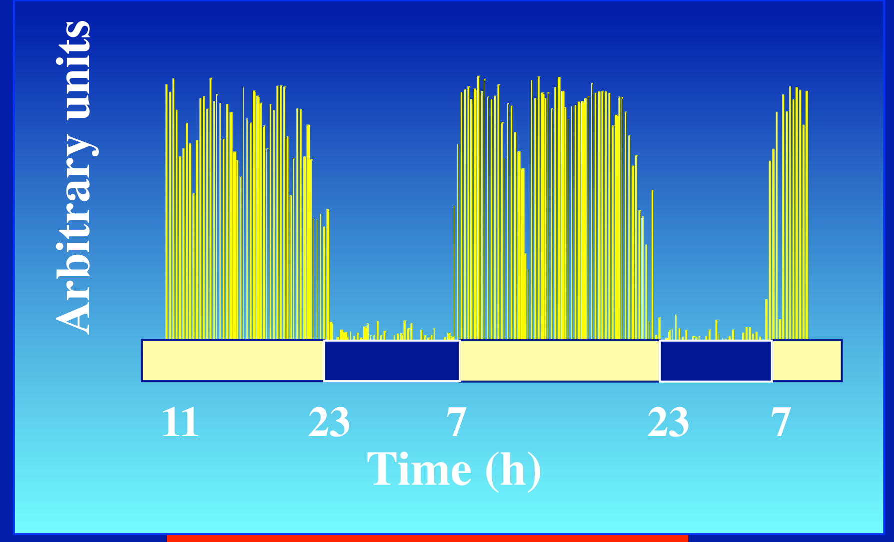
TGF α, EGF

Prokineticin

Glucocorticoids

Food intake rhythm

Autonomic nervous system



Rest-activity cycle

?

Metabolism

Proliferation

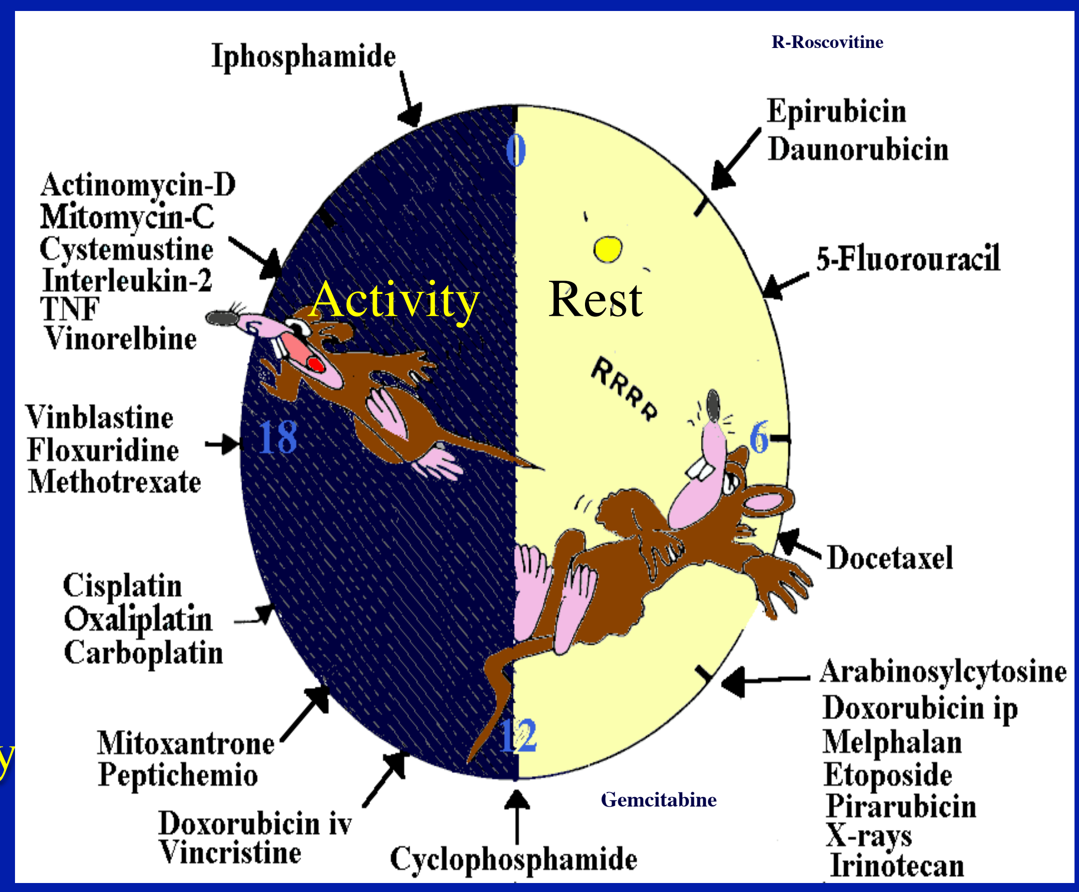
Peripheral oscillators

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

Chronotherapeutic principles, according to F. Lévi

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

Experimental settings for laboratory rodents



(M.-C. Mormont & F. Lévi, Cancer 2003

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

oxaliplatin infusion flow

Healthy cells (jejunal mucosa)

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

(homeostasis=damped harmonic oscillator)

(PK)

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 »)

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

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

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

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

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

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

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

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

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

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

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

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

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

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:

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

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

then:

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

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

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

…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
$i \to A(t,i)$ and $i \to B(t,i)$ are continuous by integration of the initial system:

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

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

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

Investigating the minima of the objective function: a differentiable problem

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

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

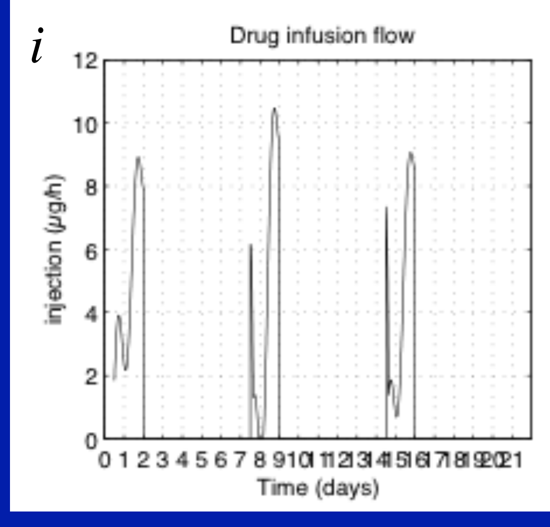
In the same way, t_B , defined by $G_B(i) = \max_t B(i,t) = B(i,t_B(i))$, is, provided that $\partial^2 B(t_B(i),i) / \partial t^2 < 0$, a differentiable function of i

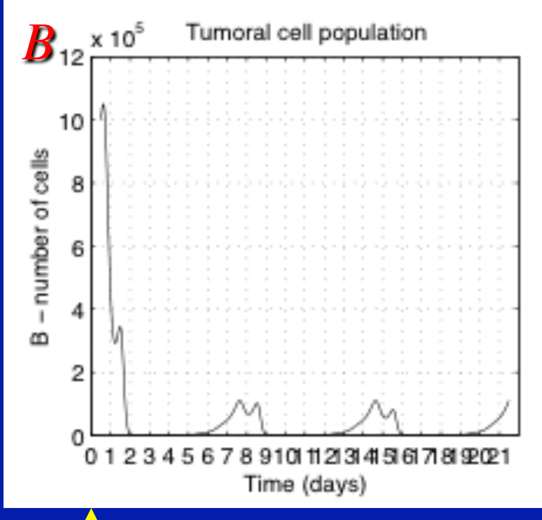
Hence, the infusion flow optimatisation problem is liable to differentiable optimisation techniques, and though the problem is not convex, so that searching for saddle points of the Lagrangian will only yield sufficient conditions,

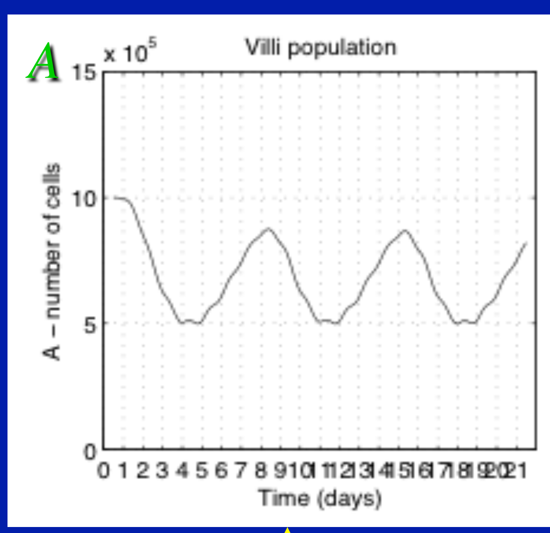
We nevertheless can define a heuristics to obtain minima of the objective function G_B submitted to the constraint $F_A \leq 0$, based on a Uzawa-like algorithm with a nonlinear conjugate gradient

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

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







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

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

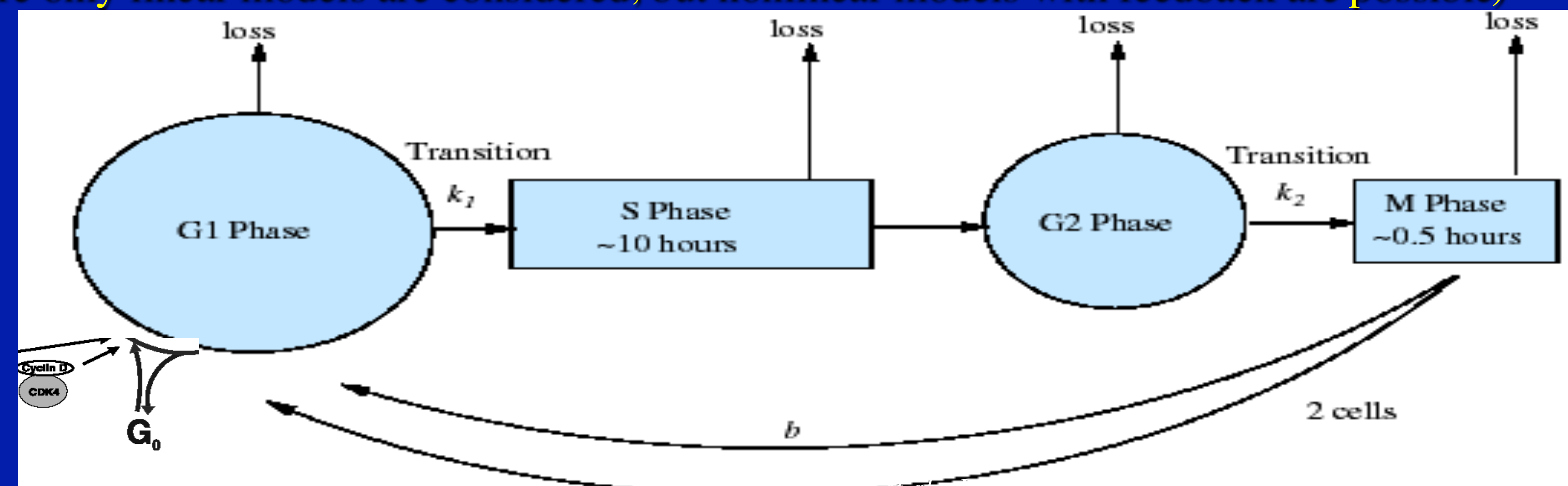
Solution : optimal infusion flow i(t) adaptable to the patient's state of health

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

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

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

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



In each phase i, a McKendrick linear model:

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

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

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

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

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

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

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

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

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

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

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

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

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

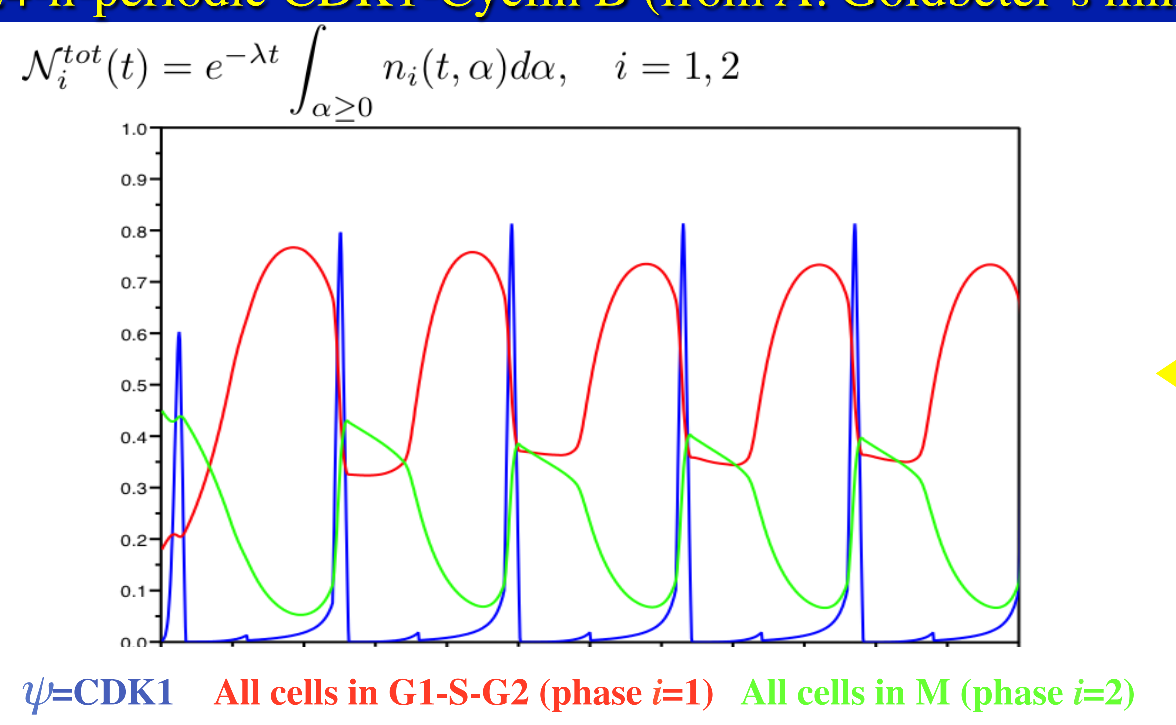
Ph. Michel, S. Mischler, B. Perthame, C. R. Acad. Sci. Paris Ser. I (Math.) 2004; J Math Pures Appl 2005
JC, Ph. Michel, B. Perthame, C. R. Acad. Sci. Paris Ser. I (Math.) 2006; Proc. ECMTB Dresden 2005, Birkhäuser 2007

Main output of this age-structured PDE model

λ: a first eigenvalue governing the cell population behaviour

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

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



"Surfing on the exponential growth curve"

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

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

(and simultaneously experimental evaluation of the first eigenvalue λ)

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

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

Whence (by integration along characteristic lines):

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

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

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

With probability density (experimentally identifiable):

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

Circadian rhythms and physiological control of the cell cycle:

Known connections between the cell cycle and circadian clocks

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

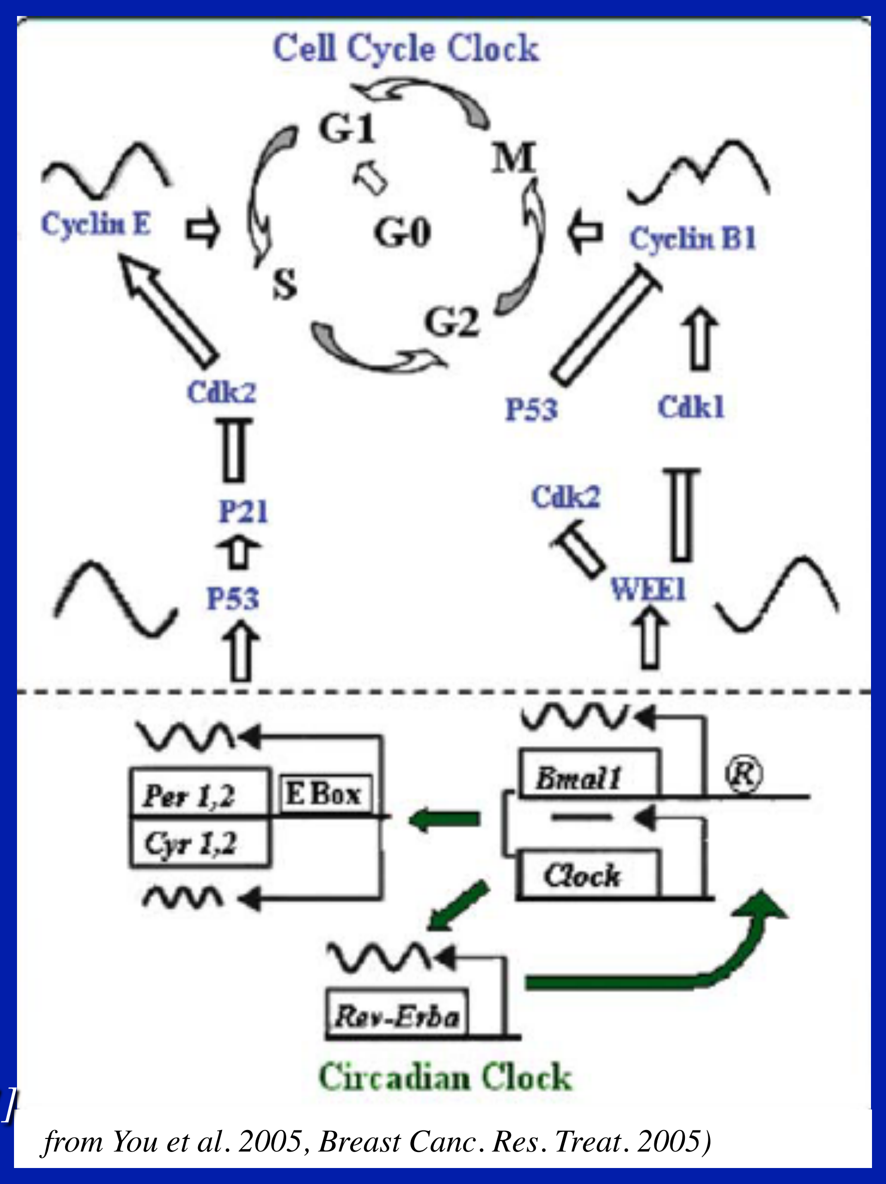
Bmal1 controls Wee1 and Cyclin B-Cdk1

Per2 controls p21 and Cyclin E- Cdk2

Wee1 and p21 act in antiphase

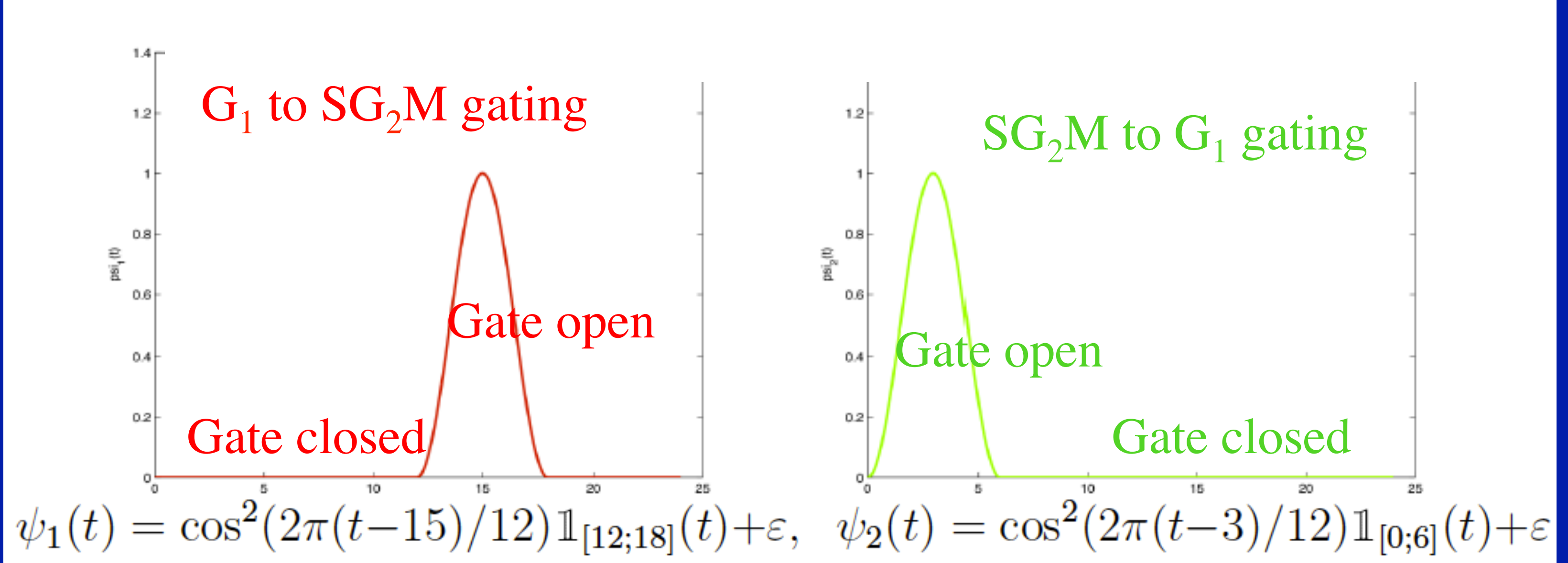
The circadian clock (*Bmal1*, *Per2*) might thus be a synchroniser in control of cell populations between G_1/S and G_2/M transitions

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



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

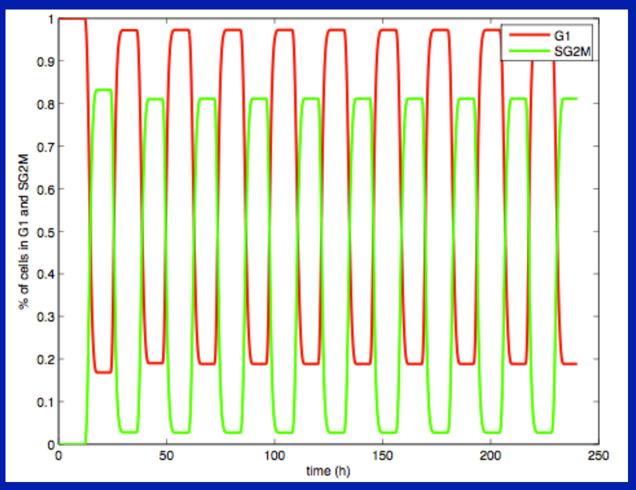
Adding theoretical circadian control on phase transitions



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

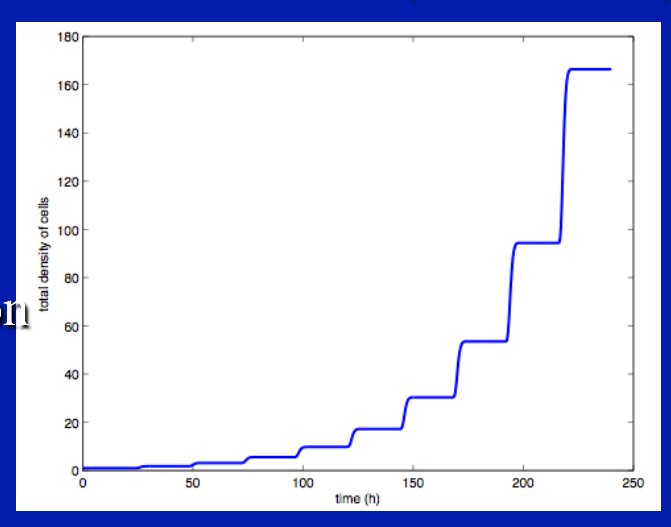
(a 12 h delay between the two cosines was determined as the one that maximised the λ)

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



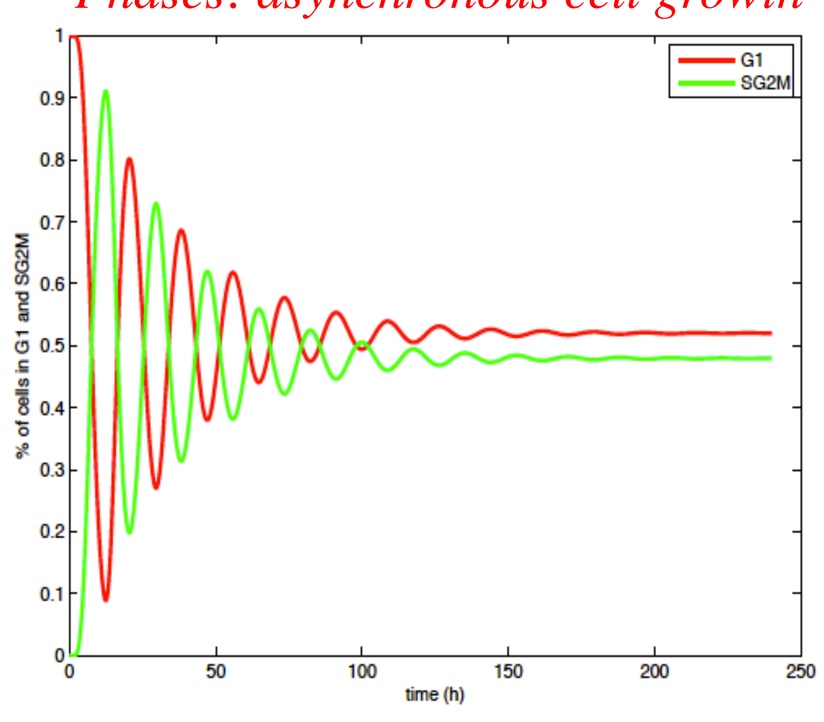
Here we put
K(t,x) = κ(x).ψ(t)
with *κ* = FUCCI-identified
and *ψ* = cosine-like function

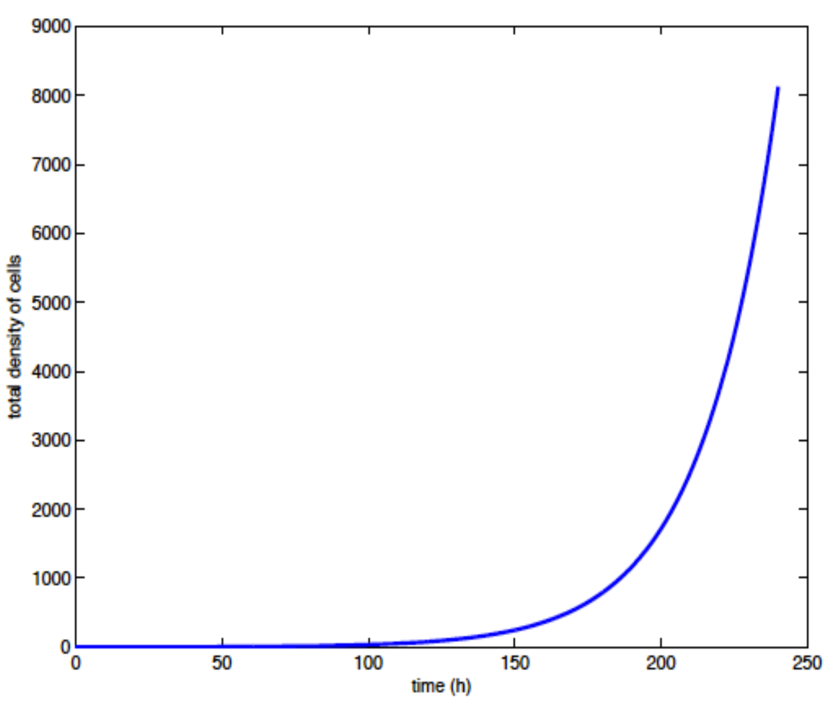
[cosine: in the absence of a better identified clock thus far]

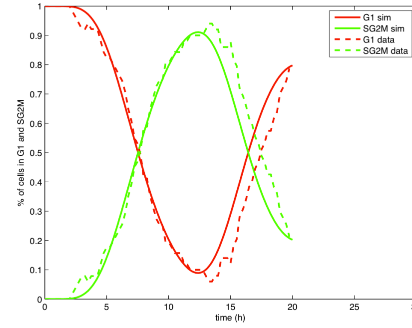


Without time control

Phases: asynchronous cell growth





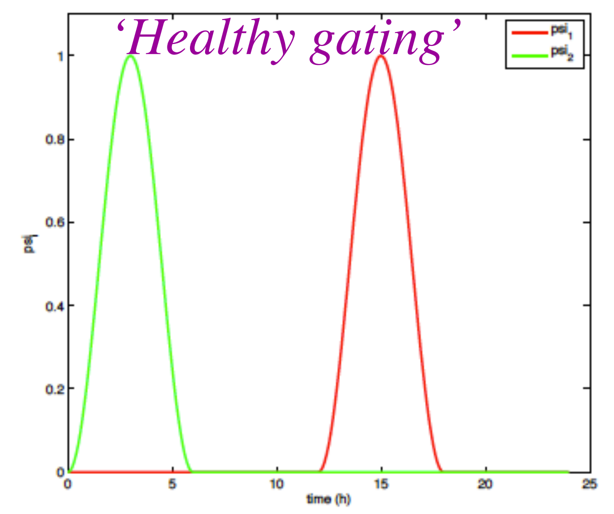


$$\lambda = 0.039 h^{-1} \qquad T_d = 18 h$$

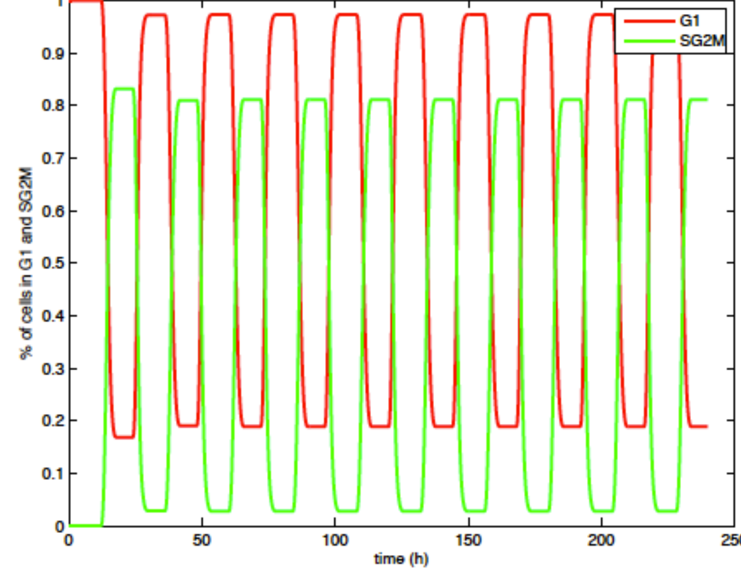
With time control (1)

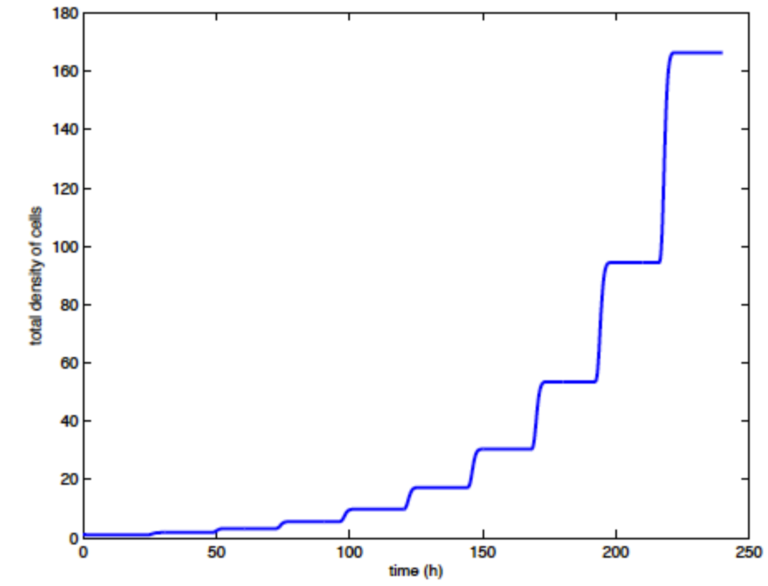
$$K_{i\to i+1}(a,t) = \underbrace{\kappa_{i\to i+1}(a)}_{\text{from exp. data}} \times \underbrace{\psi_i(t)}_{\text{circ. clock}} \longrightarrow$$

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



Steep synchronisation within the cell cycle



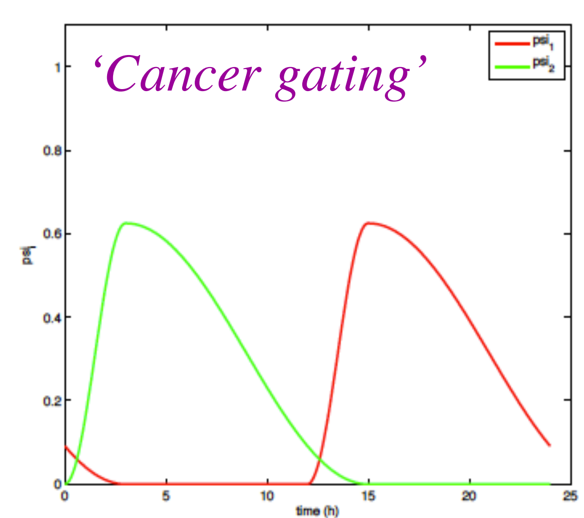


$\lambda = 0.024h^{-1}$ $T_d = 29.4h$

With time control (2)

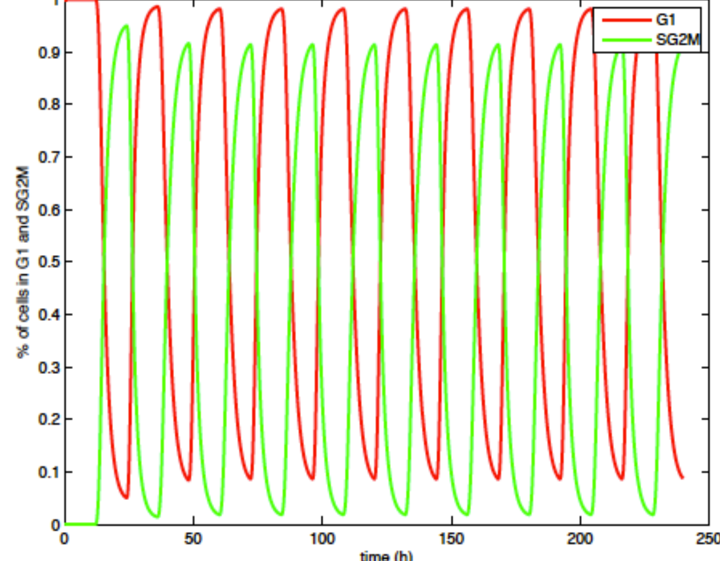
$$K_{i\to i+1}(a,t) = \underbrace{\kappa_{i\to i+1}(a)}_{\text{from exp. data}} \times \underbrace{\psi_i(t)}_{\text{circ. clock}}$$

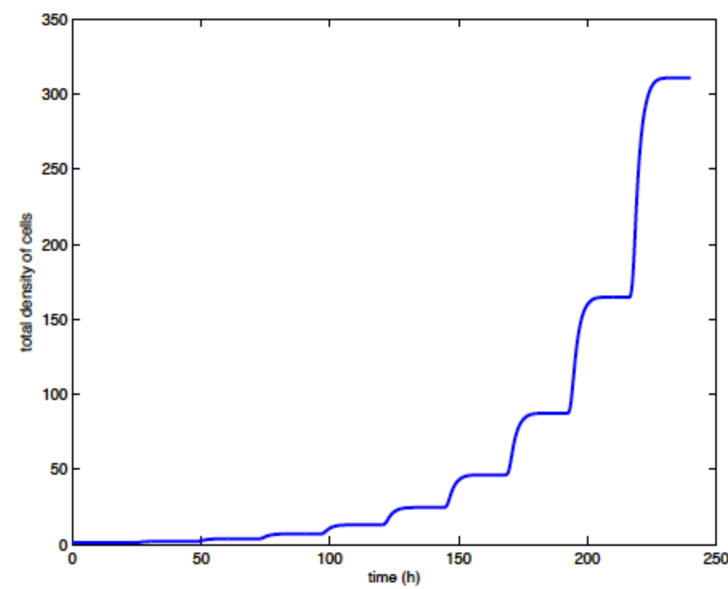
***(2) cancer** cell population (=**lazy** gating by circadian clock)*



Main work hypothesis (difference from healthy cells)

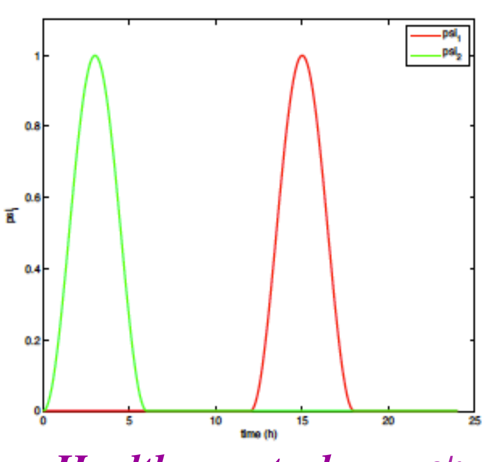
Loose synchronisation within the cell cycle

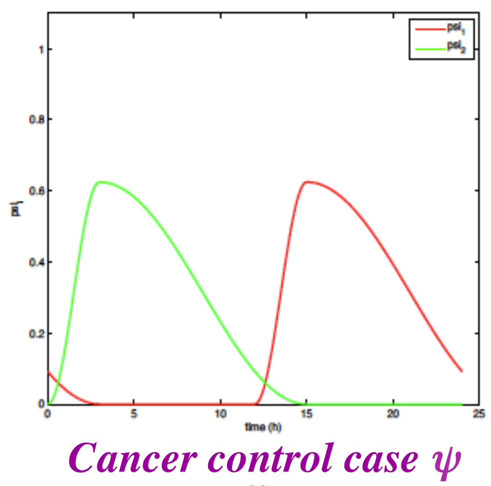


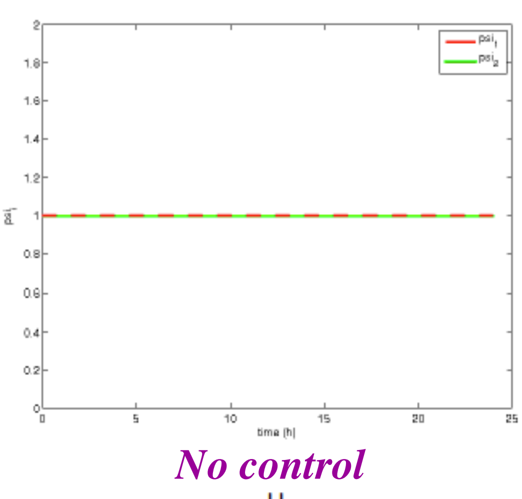


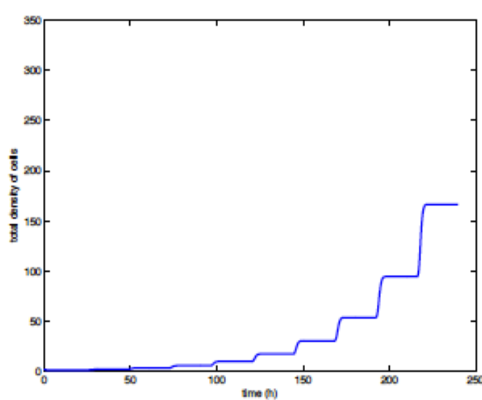
$\lambda = 0.026h^{-1}$ $T_d = 26.3h$

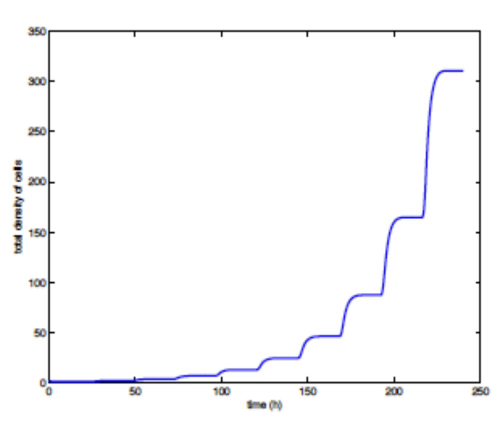
Summary

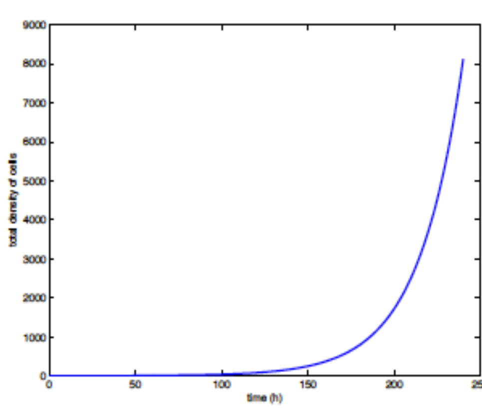












$\lambda = 0.024h^{-1}$

$T_d = 29.4h$

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

$T_d = 26.3h$

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

$T_d = 18h$

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

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

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

$K(t,x)=[1-g(t)].\psi(t).\kappa(x)$ *where:* $g(t)$ *is a periodic external control (chronotherapy)*
$\psi(t)$ *is a circadian clock control on the cell cycle*
$\kappa(x)$ *is an [only] age-dependent transition rate*

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

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

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

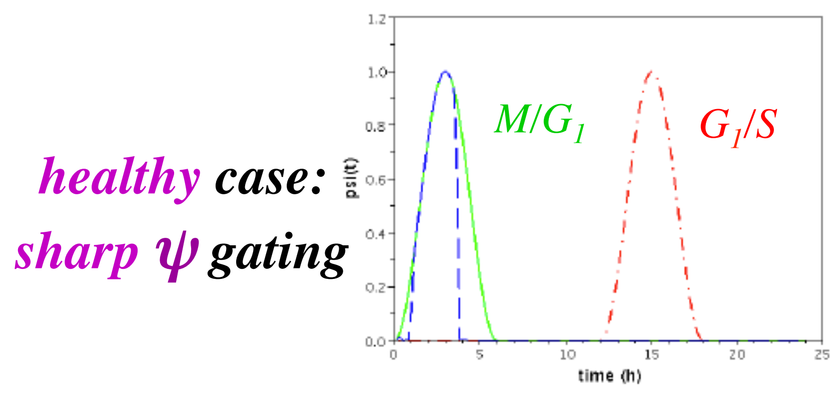


Figure 9: Modelled circadian control for transition G_1 to $S/G_2/M$ (dashdotted line) and transition $S/G_2/M$ to G_1. The natural control for $S/G_2/M$ to G_1 transition is in solid line, the drug induced control is in dashed line.

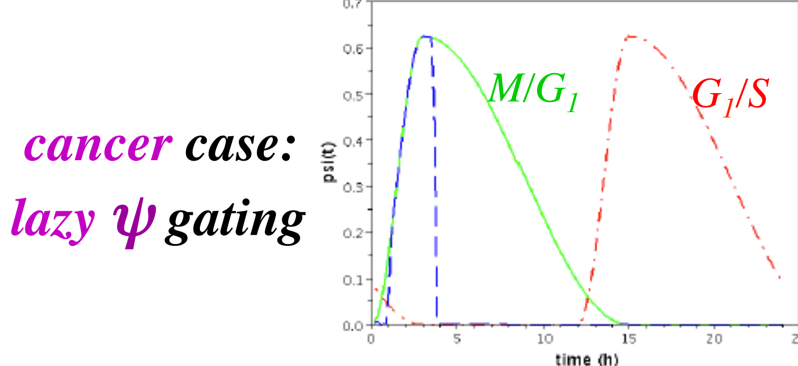


Figure 10: Modelled answer of cancerous cells to circadian control for transition G_1 to $S/G_2/M$ (dash-dotted line) and transition $S/G_2/M$ to G_1. The answer to natural control for $S/G_2/M$ to G_1 transition is in solid line, the drug-induced control is in dashed line.

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

blue: $[1-g].\psi$
(drug + circadian control)
g here numerical solution to the optimisation problem

F. Billy et al. Math Comp Simul 2012, Math Biosci Eng 2012, DCDS-B 2012, JC Springer book chapters 2013, 2014

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

Circadian control,
no drug infusion

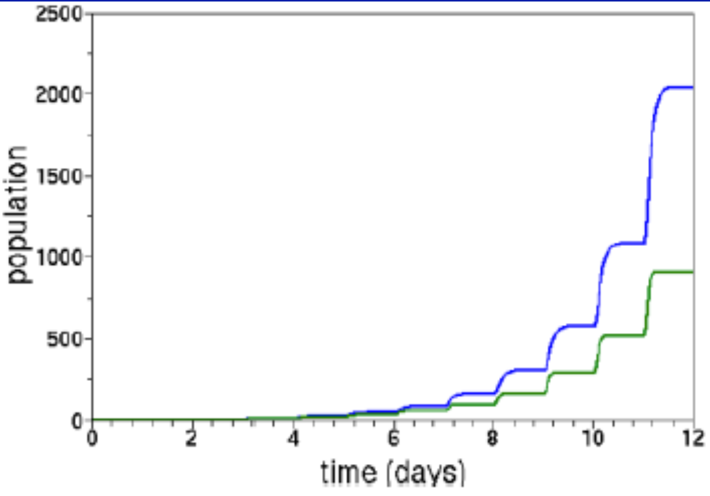


Figure 11: Evolution of the population of cancer (blue, beneath) and healthy (green, above) cells without drug infusion during 12 days. We can see that the populations have different exponential growth rates ($\lambda_{cancer} = 0.026$ and $\lambda_{healthy} = 0.024$). In the beginning, there were as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

Circadian control,
added drug infusion

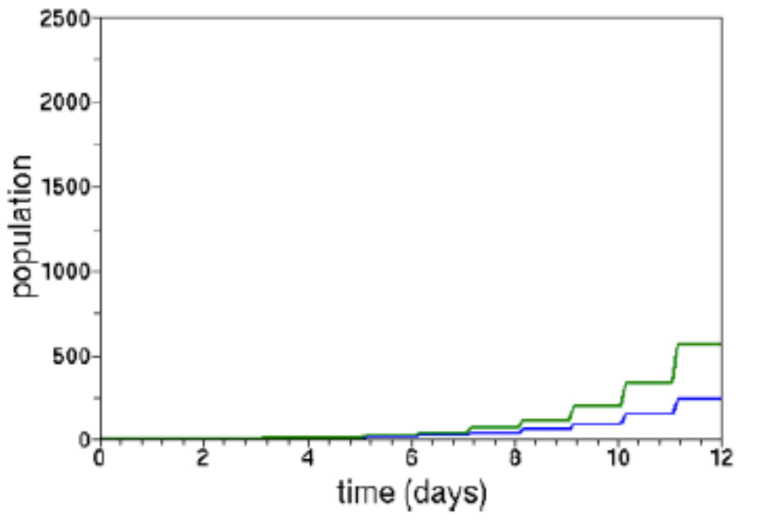


Figure 12: Evolution of the population of cancer (blue, beneath) and healthy (green, above) cells with the drug infusion, starting at time 0, given by the algorithm. Healthy cells keep multiplying ($\lambda_{healthy} = 0.022$) while the cancer cell population is weakened ($\lambda_{cancer} = 0.019$).

(F. Billy et al. 2013, 2014)

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

Infusion scheme $g(t)$

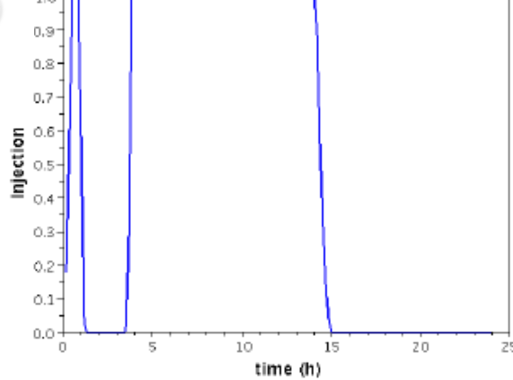


Figure 11: Locally optimal drug injection strategy found by the optimisation algorithm.

Target eigenvalues:
Cancer (blue)
Healthy (green)

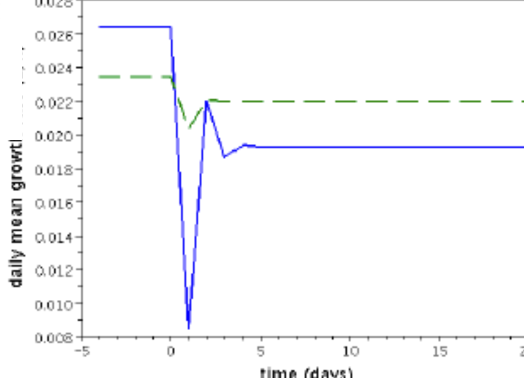


Figure 12: Daily mean growth rates for cancerous (solid line) and healthy cells (dashed line) when starting drug injections at time 0. After a 10 day transitional phase, the biological system stabilises towards the expected asymptotic growth rate

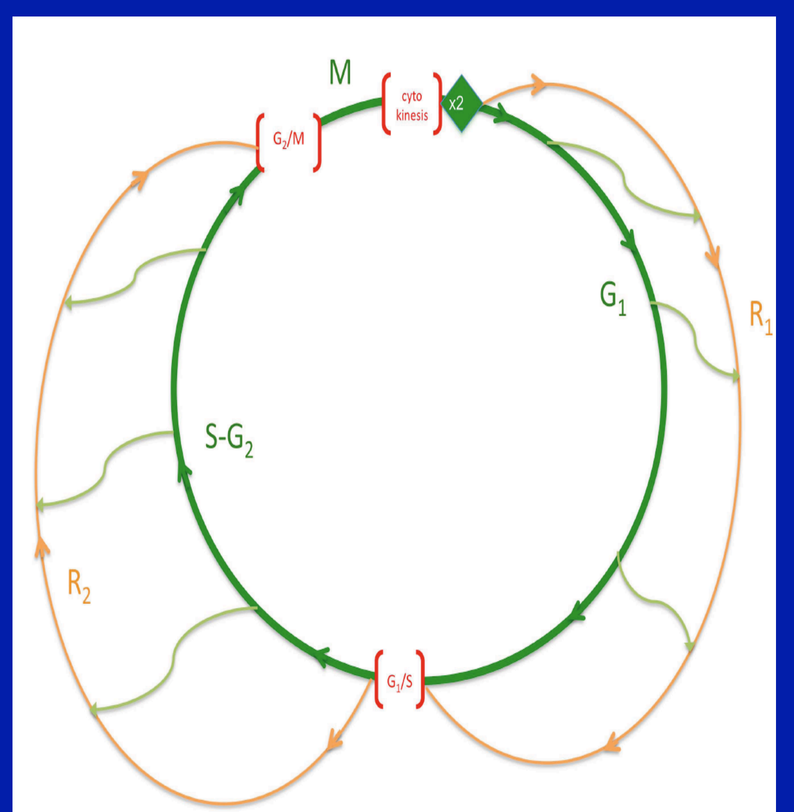
In favour of this approach:

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

Its drawbacks:

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

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



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

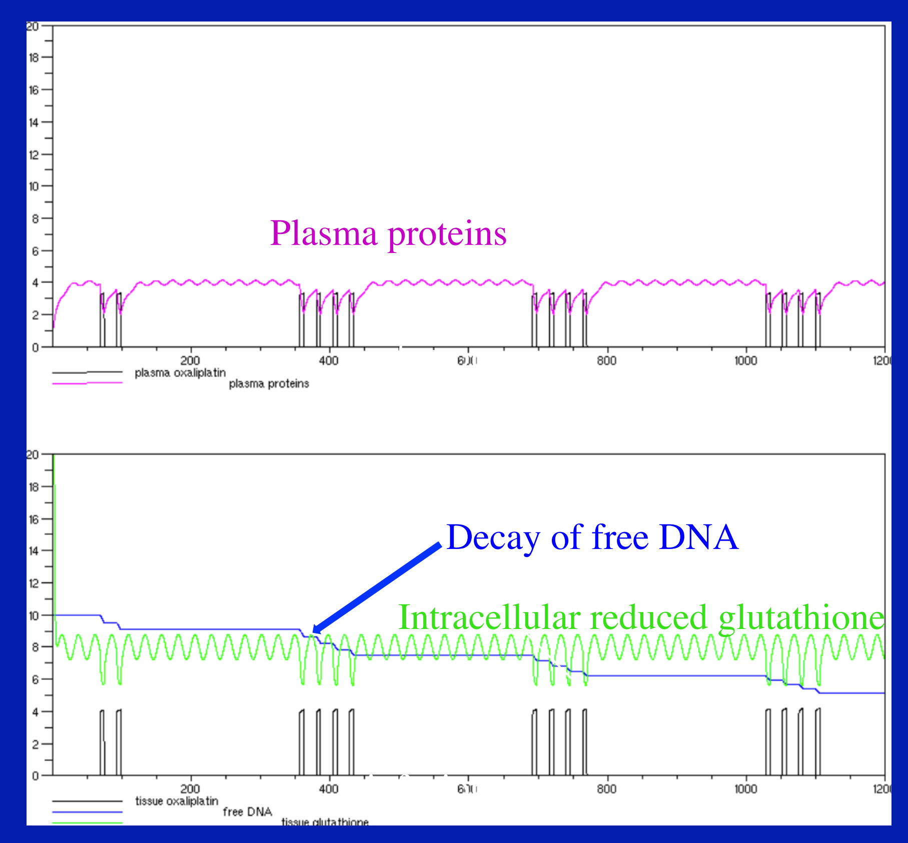
(JC, O. Fercoq, MMNP 2017 and preprint https://hal.archives-ouvertes.fr/hal-01321536)

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

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

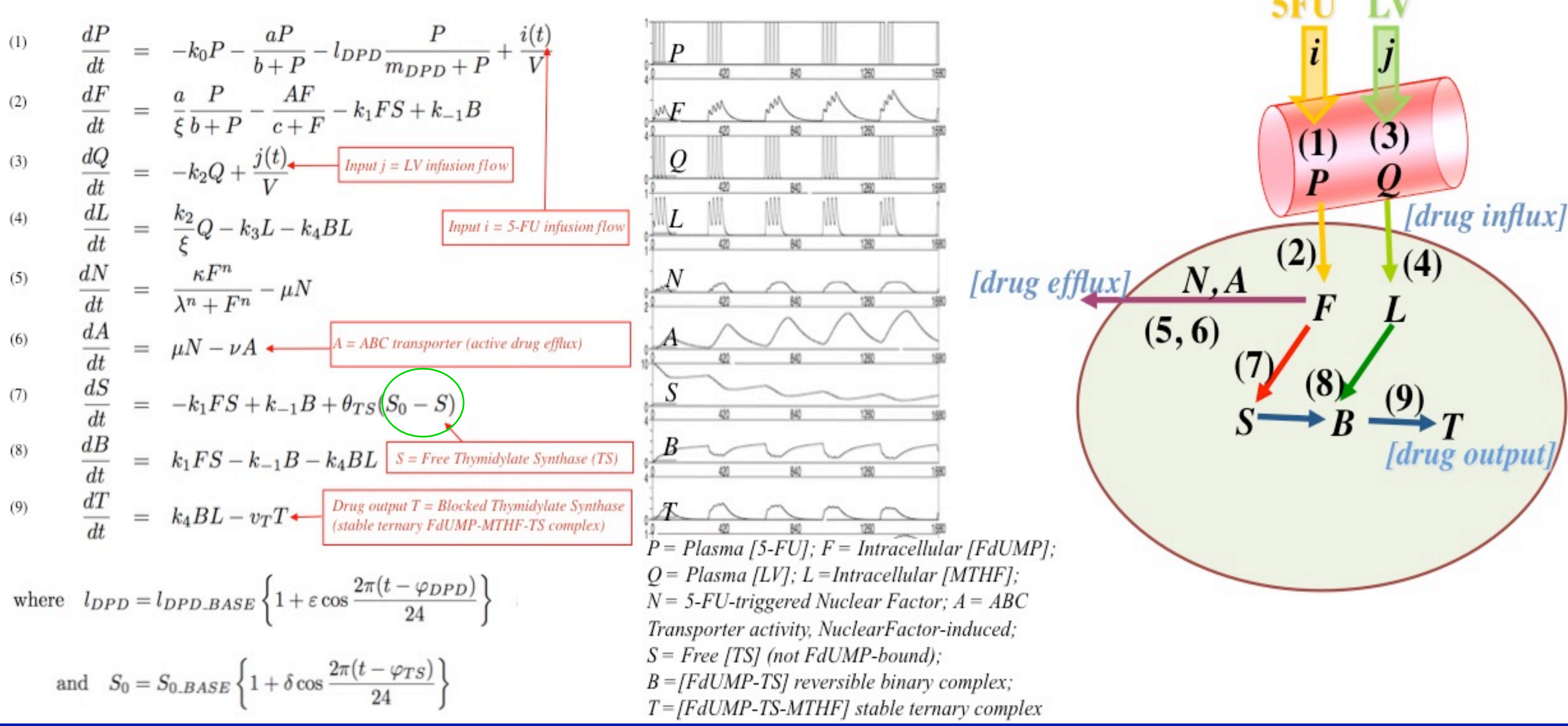
$$
\begin{cases}
\dfrac{dR}{dt} = -[\xi + cl + \lambda K]R + i(t) \\[2ex]
\dfrac{dK}{dt} = -\lambda RK + \mu_K (K_0 - K) \\[2ex]
\dfrac{dC}{dt} = -V_{GST}\dfrac{CG^2}{K_{GST}^2 + G^2} - k_{DNA}CF + \xi R \\[2ex]
\dfrac{dF}{dt} = -k_{DNA}CF + \mu_F (Fo - F) \\[2ex]
\dfrac{dG}{dt} = -V_{GST}\dfrac{CG^2}{K_{GST}^2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

Input *i =oxaliplatin infusion*



(JC, O. Fercoq, MMNP 2017 and preprint https://hal.archives-ouvertes.fr/hal-01321536)

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



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

Solution to the chronotherapeutic combined drug delivery optimisation problem

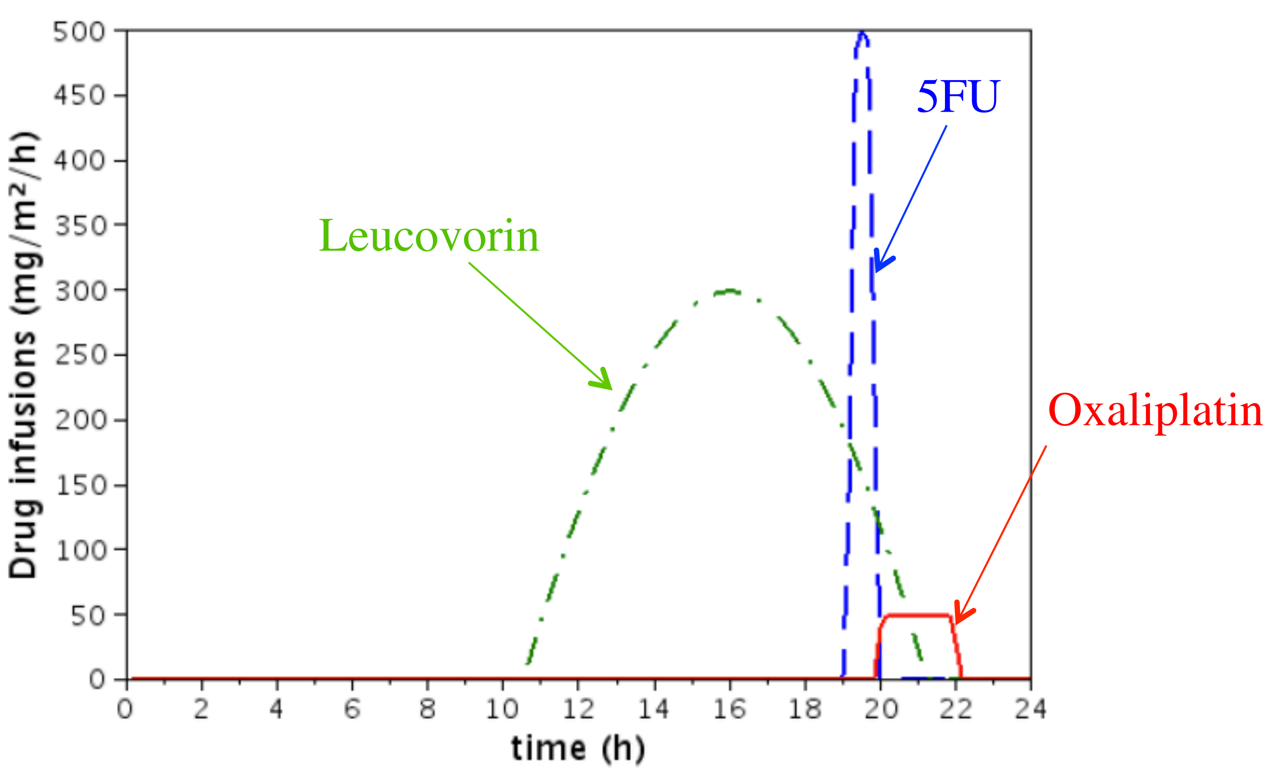


Fig. 6 Locally optimal infusion strategy with a combination of leucovorin (dash-dotted line), 5-FU (dotted line) and oxaliplatin (solid line). These infusions are repeated every day in order to minimise the growth rate of the cancer cell population while maintaining the growth rate of the healthy cell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

(JC, O. Fercoq, MMNP 2017 and preprint https://hal.archives-ouvertes.fr/hal-01321536)

Effects of this optimised periodic drug delivery regimen on growth rates

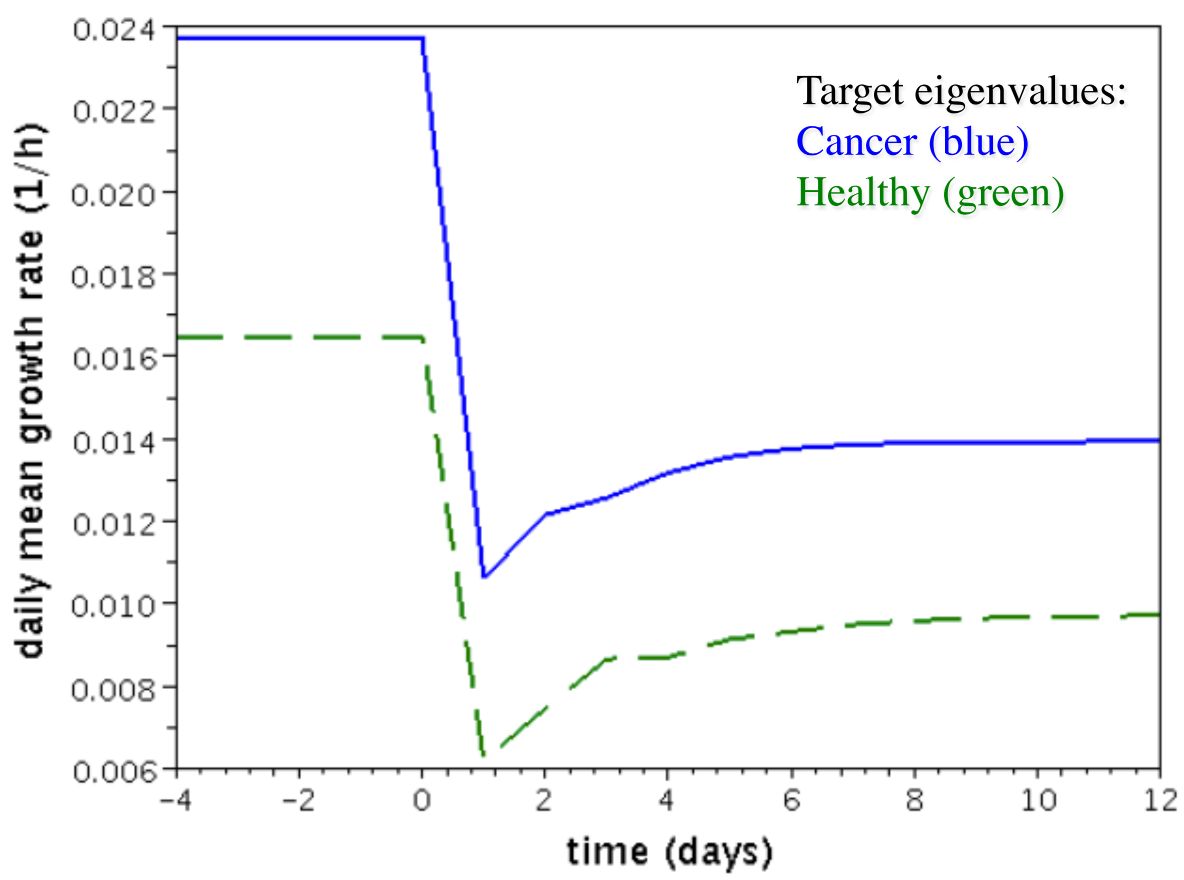


Fig. 11 Daily mean growth rates for cancer (solid line) and healthy cells (dashed line) when starting drug infusions at time 0. After a 10-day transitional phase, the biological system stabilises towards the expected asymptotic growth rate.

(JC, O. Fercoq, MMNP 2017 and preprint https://hal.archives-ouvertes.fr/hal-01321536)

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

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

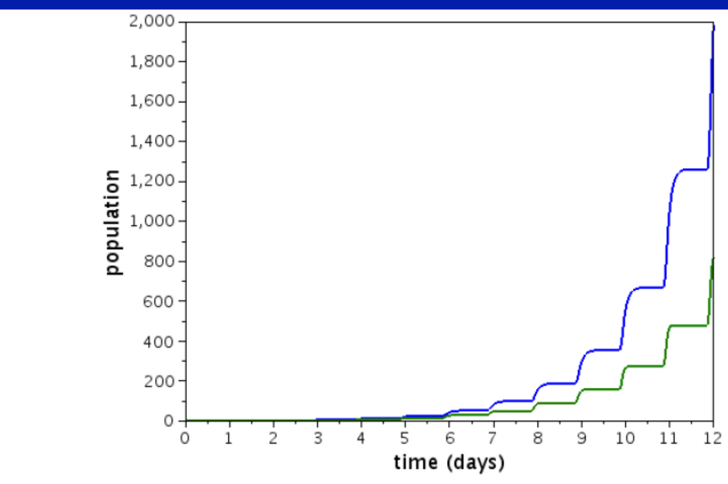


Fig. 7 Evolution of the population of cancer (blue, above) and healthy (green, beneath) cells without drug infusion during 12 days. We can see that the populations have different exponential growth rates ($\lambda_{cancer} = 0.0265$ and $\lambda_{healthy} = 0.0234$). Cancer cells proliferate faster than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

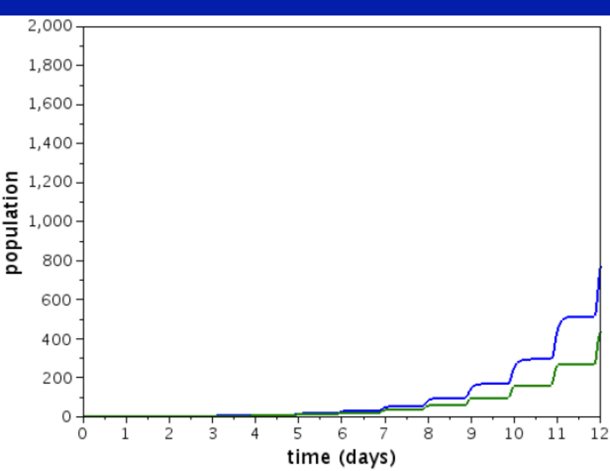


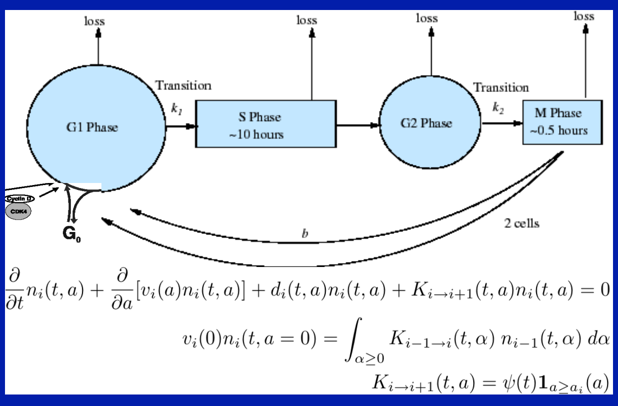
Fig. 8 Evolution of the population of cancer (blue, above) and healthy (green, beneath) cells with the drug infusion, starting at time 0, given by the algorithm. Healthy cells keep multiplying ($\lambda_{healthy} = 0.021$) while the cancer cell population is weakened ($\lambda_{cancer} = 0.0229$).

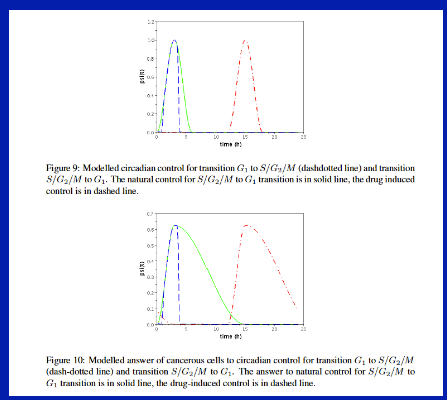
A result not as good as in the previous case, when drugs were applied on transition rates... hence the suggestion of a cytotoxic+cytostatic treatment (e.g., 5FU+oxaliplatin+cetuximab): a story to be continued

(JC, O. Fercoq, MMNP 2017 and preprint https://hal.archives-ouvertes.fr/hal-01321536)

Optional (not done, to be added)

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





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

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

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

New mitosis term

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

with the adjunction of a quiescent phase G_0 represented by

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

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

Next: tackling the question of
drug resistance in cancer cell populations