Introduction to pharmacokinetics and pharmacodynamics of anticancer drugs

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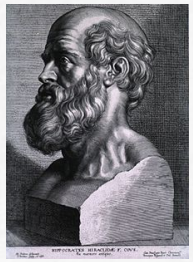
What is a cancer ?

Cancer is a very old disease, already reported by Hippocrate (460-377 b. JC).He compared cancer to a crab, karkinoma in greek.



Definition. Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body.

Characteristics.

- Limitless replicative potential
- Self-sufficiency in growth signals
- Insensitivity in anti-growth signals
- Sustained angiogenesis
- Tissue invasion and metastases
- Dedifferentiation
- Genome instability and mutation
- Deregulation of metabolism
- Deregulation of immune system
- Promoting inflammation

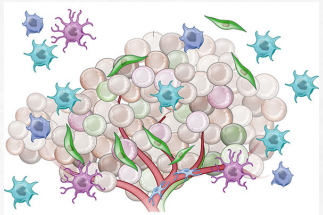
Hanahan, Weinberger 2011

What is a cancer ?

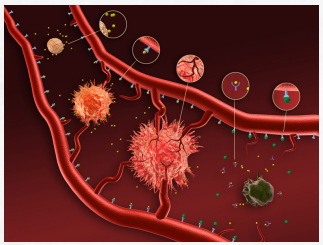
Main steps of the disease

1. **Avascular growth**
   - Cancer cells start dividing
   - Nutrients are transported by blood vessel and diffuse in the tissues

   ⇝ 3-4mm of diameter.

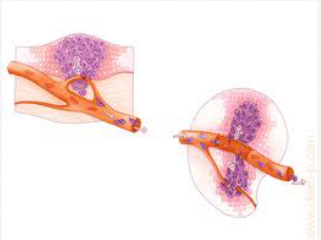


2. **Vascular growth or angiogenesis**
   - Hypoxic cells secrete Endothetial Growth Factors inducing the creation of new vessels.
   - The new vascularization provide the nutrients necessary to the tumor growth.



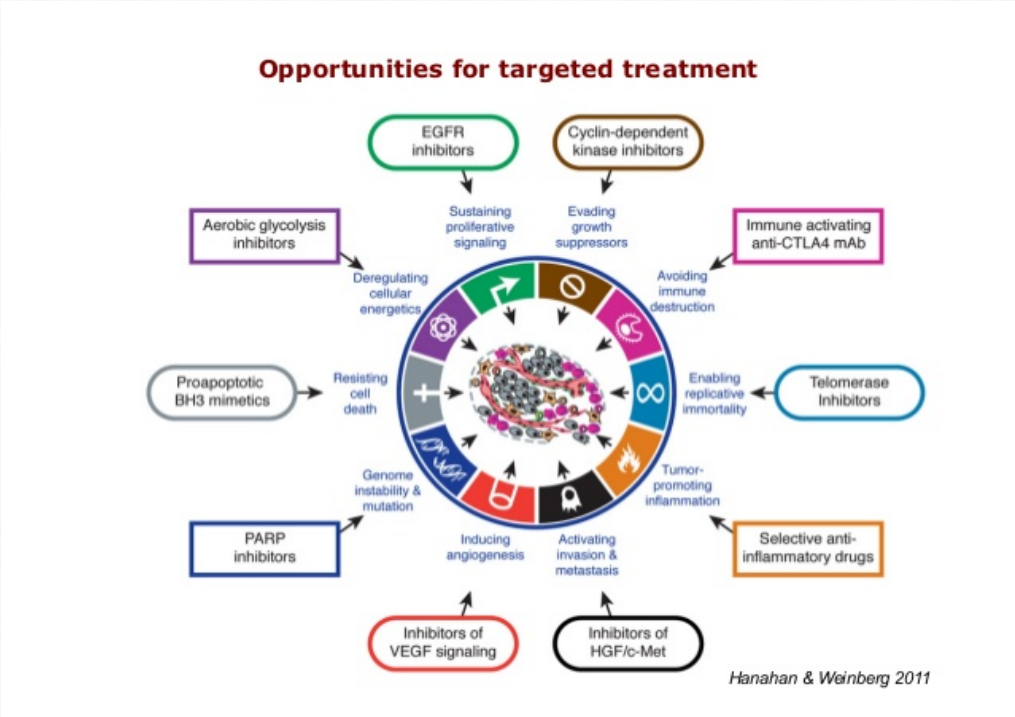
3. **Metastatic invasion**
   - Tumor cells can leave the primary tumor through the blood vessels or the lymphatic network and colonize a distant place.

   ⇝ Development of secondary tumors or **metastases**.



Cancer Treatments

1. Surgery
2. Radiation therapy
3. Anti-cancer drug
   - Chemotherapy
   - Targeted therapy (ex anti angiogenic drugs)
   - Immune therapy
   - Hormone therapy
4. Stem cells transplant



Some medical issues

Is it possible to improve the efficiency of existing treatments ?

- There might exist a metastatic boost after surgery. Can it be anticipated ?
- Chemotherapies induce high toxicities requiring delay between two administrations. Is it possible to reduce this delay ?
- Chemotherapies induce resistance. Is there an administration protocole that could lead to less resistance or postpone it ?
- Chemotherapy are more and more used in combination with anti-angiogenic or immune therapies. Is it possible to optimize the efficiency of such treatment ?
- Treatments efficiency and toxicity is patient dependant. Is it possible to individualize the drug delivery ?
- In radiotherapy, can it be possible to improve the radiated zone ?

Some medical issues

How to evaluate the metastatic state of the patients ?

- Metastases are the major cause of death in cancer. But metastatic state of the patient is often difficult to evaluate, as micro-tumors are hardly detectable from imagery.
- Among patients with a breast cancer detected at early stage that followed an adjuvant chemotherapy, only few of them presented probably a metastatic risk. Elias (2006), Spielmann & al (2006)

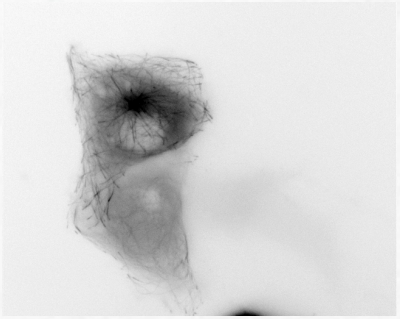
Is it possible to better understand the action of some existing drug ?

- Some chemotherapy agents (MTAs) reveal to have an anti-angiogenic affect at lower dose. Is it possible to understand the mechanism ?
- ....

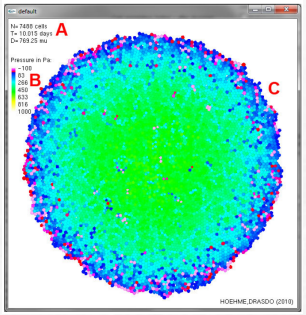
Mathematical issues

1. How build adequate tumor growth models ?
2. How model the efficiency and toxicity of the treatments ?

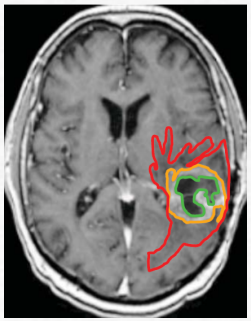
Choose the right scale (Genes-proteins-enzymes-tissus-organs)



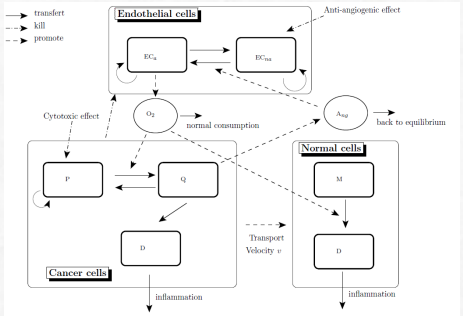
Intra-cellular scale



Microscopic scale



Macroscopique scale



Multi-scale interactions

Mathematical issues

1. How build adequate tumor growth models ?
2. How model the efficiency and toxicity of the treatments ?

Choose the right mathematical tools

- Deterministics models
  - ODE models (population models)
  - PDE models (population structured models, diffusion models, transport models,...)
- Stochastic models

Common issues

- Calibration or estimation of the parameters' s model from the biological data
- Validation of the model in term of reproductability, predictability
- Use the system within an optimization problem (eg. optimize in silico the treatment's protocole)

Outline of the talk

Outline of the talk

The simplest tumor growth models

A tumor can be seen as a population of cancer cells

- Y number of individuals

$$Y'(t) = \underbrace{\text{birth number}}_{N_n} - \underbrace{\text{death number}}_{N_m}$$

1766-1834

Malthus model - end of 18^{th} century

$$Y'(t) = \lambda Y(t) - \mu Y(t) \Rightarrow \frac{Y'}{Y} = \lambda - \mu := a$$

Logistic or Verhultz model (1838)

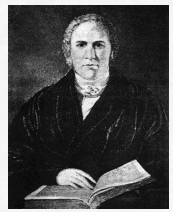
- Populations are able to regulate their natality !

1804-1849

$$\frac{Y'(t)}{Y(t)} = a\left(1 - \frac{Y(t)}{K}\right) \Rightarrow \frac{Y'(t)}{Y(t)} \sim_{t\to\infty} C\, e^{-at}$$

Gompertz model (1825)

- Exponential decay of the growth rate



1779-1865

$$\frac{Y'(t)}{Y(t)} = \mu_0 e^{-at} \Rightarrow \left(\frac{Y'}{Y}\right)' = -a(\ln(Y))' \Rightarrow \frac{Y'(t)}{Y(t)} = a \ln\left(\frac{b}{Y(t)}\right)$$

The simplest tumor growth models

Logistic model (1838)

$$Y'(t) = a\left(1 - \frac{Y(t)}{K}\right)Y(t)$$

Gompertz model (1825)

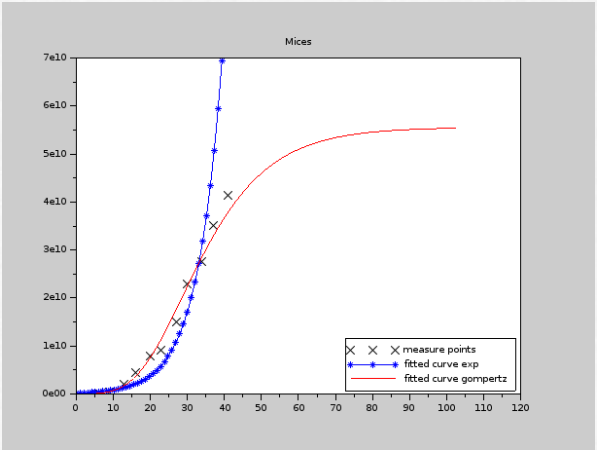
$$Y'(t) = a_g \ln\left(\frac{b}{Y(t)}\right)Y(t)$$

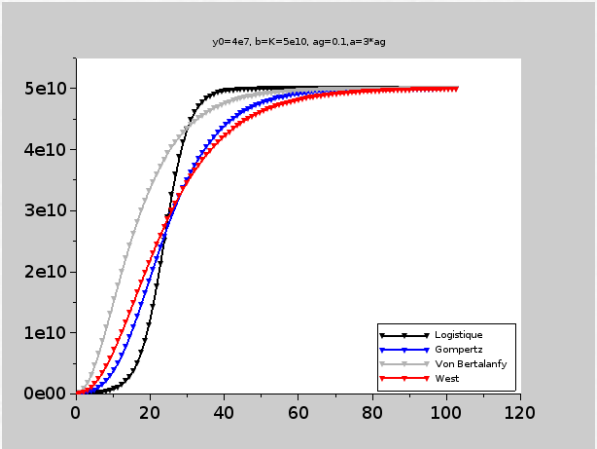
Von Bertalanffy model (1949)

$$Y'(t) = a\left(\left(\frac{Y(t)}{K}\right)^{-\frac{1}{3}} - 1\right)Y(t)$$

West model (1997)

$$Y'(t) = a\left(\left(\frac{Y(t)}{K}\right)^{-\frac{1}{4}} - 1\right)Y(t)$$

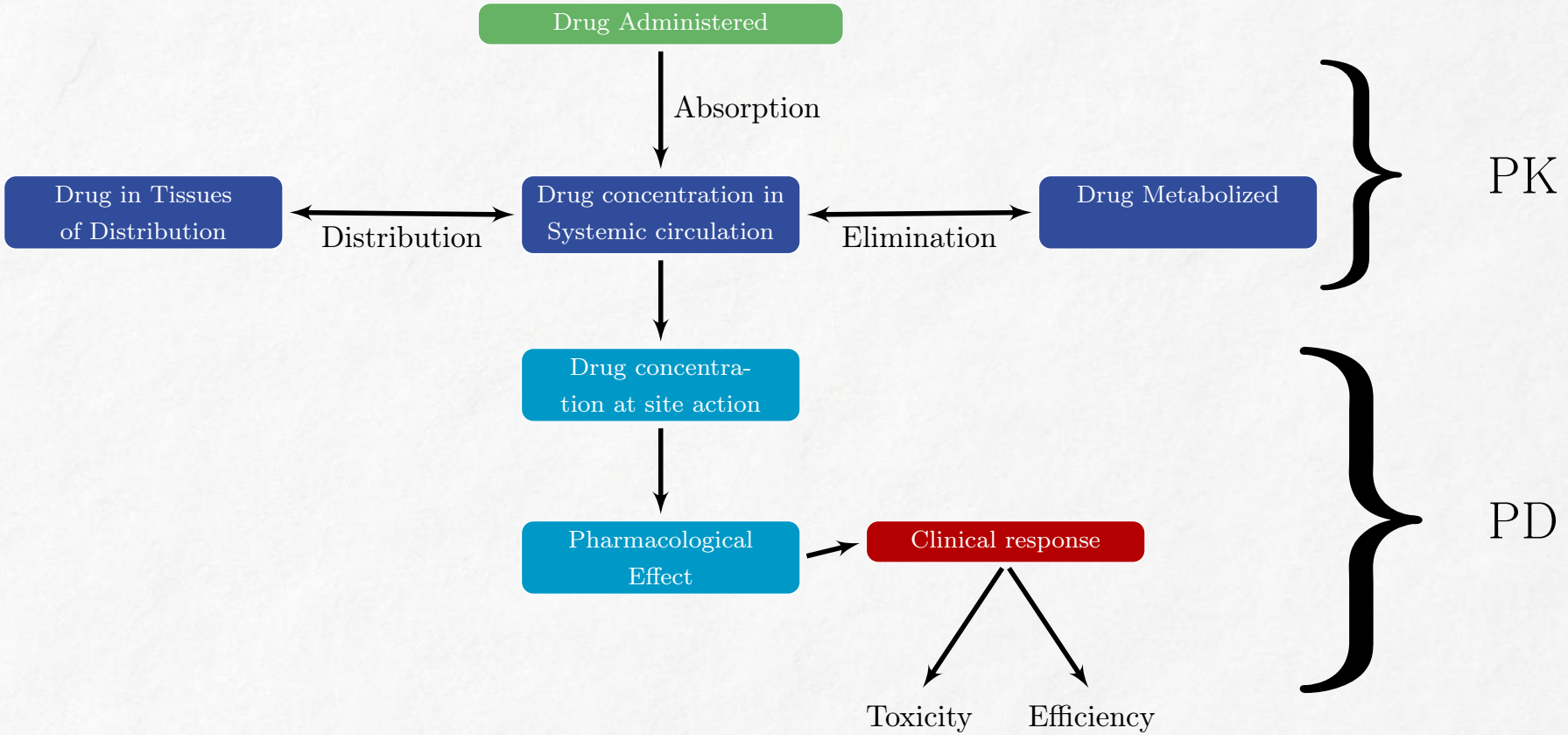




- Sigmoid shape

Outline of the talk

Pharmacokinetics (PK)/Pharmacodynamics (PD) of a drug



1. PK : *How the organism affects the drug*
2. PD : *How the drug affects the organism*

Pharmacokinetics of a drug

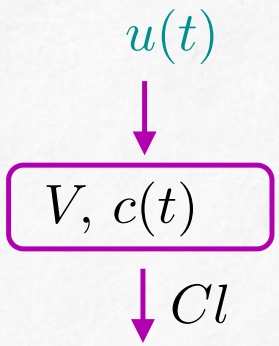
How the organism affects the drug

One compartment model - infusion - one administration

- Example of a cytotoxic : Etoposide oral

Jong et al 1997

  - Small cell lung cancer



$$\frac{dc}{dt} = -\frac{Cl}{V}c + \frac{u(t)}{V},\ c(t_{inj}) = 0$$

- $t \mapsto u(t)$ infusion protocol
- V Specific volume
- Cl Clearance

Pharmacokinetics of a drug

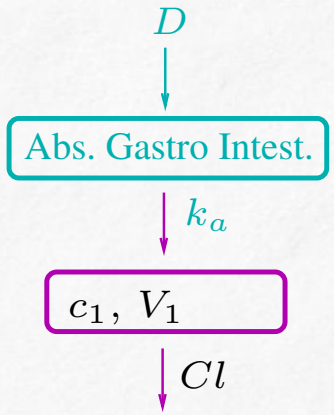
How the organism affects the drug

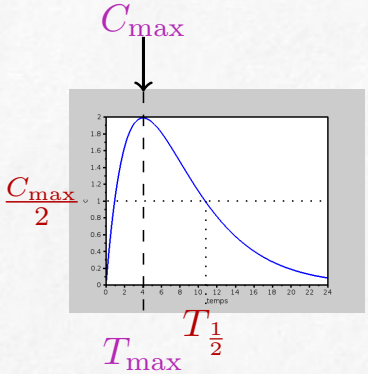
One compartment model - Oral administration - one tablet

- Example of targeted therapy (kinase inibitors) : Imatinib

Widmer et al 2006

- Chronic myelogenous leukemia or Gastro Intestinal Stromal Tumors





$$\frac{dq_a}{dt} = -k_a q_a,\ q_a(t_{abs}) = D$$

$$\frac{dc}{dt} = -\frac{Cl}{V}c + \frac{k_a}{V}q_a,\ c(t_{abs}) = 0$$

- D dose
- k_a Absorption rate
- V Specific volume
- $Cl = \frac{k_{10}}{V}$ Clearance

Pharmacokinetics of a drug

How the organism affects the drug

Informations on Imatinib PK found in the Vidal

La pharmacocinétique de l'imatinib a été évaluée à des doses comprises entre 25 et 1000 mg. Les profils pharmacocinétiques plasmatiques ont été analysés à J1, puis à J7 ou J28, au moment où les concentrations plasmatiques ont atteint un état d'équilibre.

Absorption : La biodisponibilité absolue moyenne de l'imatinib est de 98 %. Il existe une forte variabilité interpatient de l'ASC de l'imatinib plasmatique après une prise orale. Lorsqu'il est pris au cours d'un repas riche en lipides, le taux d'absorption de l'imatinib est peu réduit (diminution de 11 % de la Cmax et prolongation de 1,5 h de Tmax), avec une légère diminution de l'ASC (7.4 %) comparée à une prise à jeun. L'effet d'une chirurgie gastro-intestinale antérieure sur l'absorption du produit n'a pas été étudiée.

Distribution : A des concentrations d'imatinib cliniquement significatives, la fraction liée aux protéines plasmatiques est approximativement de 95 %, sur la base des études in vitro ; il s'agit principalement d'une liaison à l'albumine et aux alphaglycoprotéines acides et, dans une faible mesure, aux lipoprotéines.

Pharmacokinetics of a drug

How the organism affects the drug

Informations on Imatinib PK found in the Vidal

Elimination : Après administration d'une dose orale d'imatinib marqué au ^{14}C, environ 81 % de la dose est éliminée au bout de 7 jours (68 % dans les fèces et 13 % dans les urines). La forme inchangée représente 25 % de la dose (5 % dans les urines, 20 % dans les fèces), le reste étant composé de métabolites.

Pharmacocinétique plasmatique : Après administration par voie orale chez le volontaire sain, la demi-vie, d'environ 18 h, est compatible avec une prise quotidienne unique. L'augmentation de l'ASC moyenne de l'imatinib est linéaire et proportionnelle à la dose administrée à des doses orales allant de 25 à 1000 mg. Lors d'administrations répétées en prise quotidienne unique, la cinétique de l'imatinib n'est pas modifiée, mais son accumulation, à l'état d'équilibre, est augmentée d'un facteur de 1,5 à 2,5.

Pharmacokinetics of a drug

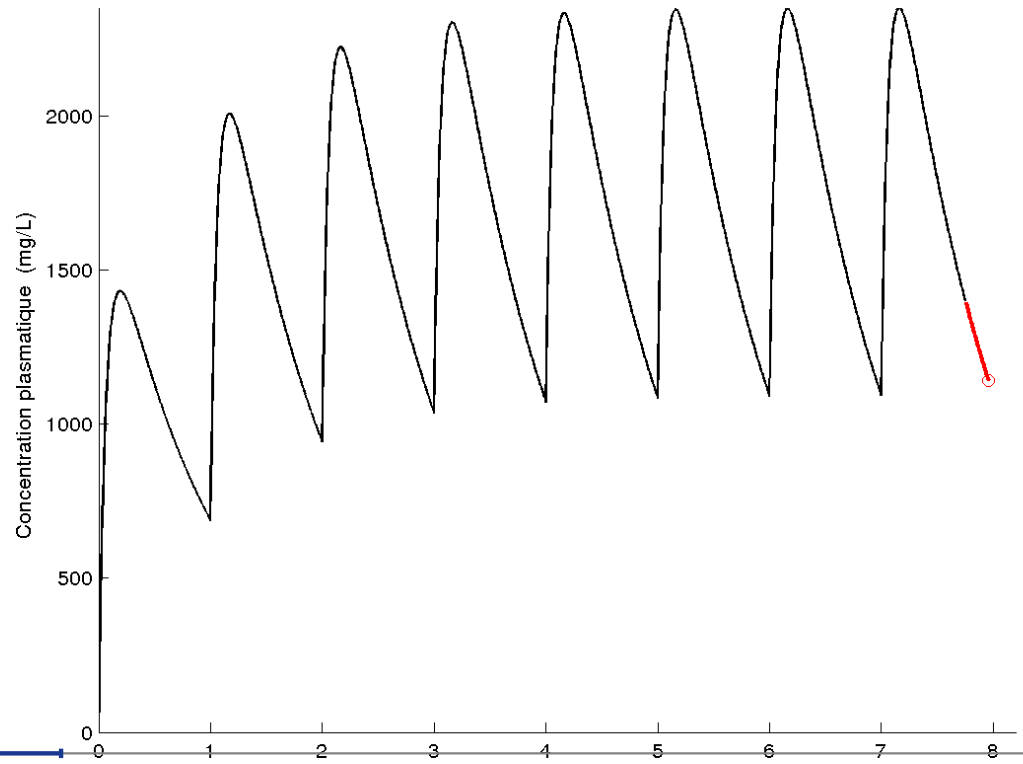
How the organism affects the drug

One compartment model - Oral administration - one week of treatment

- Example of targeted therapy (kinase inibitors) : Imatinib

Widmer et al 2006

  - Chronic myelogenous leukemia or Gastro Intestinal Stromal Tumors

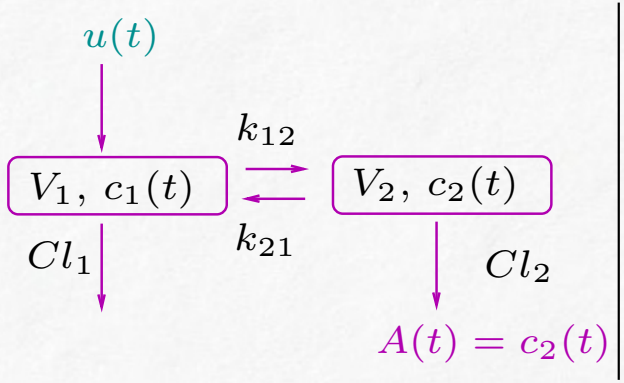


Pharmacokinetics of a drug

How the organism affects the drug

Two compartments model - injection

- Example of anti-angiogenic drug : Bevacizumab Bruno et al 1996
  - Lung cancer, kidney cancer, glioblastoma,...



$$\frac{dc_1}{dt} = -\left(\frac{Cl_1}{V_1} + k_{12}\right) c_1 + k_{21}\frac{V_2}{V_1} c_2(t) + \frac{U(t)}{V_1}$$

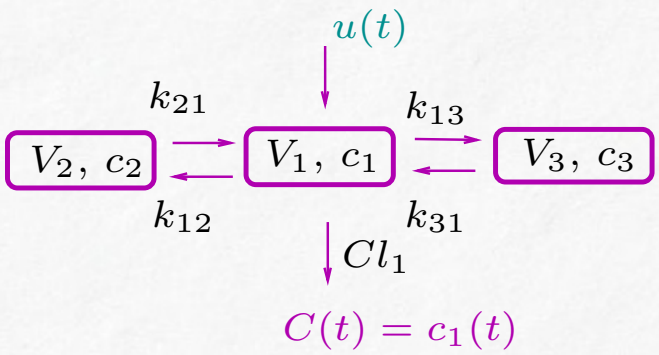
$$\frac{dc_2}{dt} = k_{12}\frac{V_1}{V_2} c_1 - \left(\frac{Cl_2}{V_2} + k_{21}\right) c_2$$

Pharmacokinetics of a drug

How the organism affects the drug

Three compartment model - injection

- Example of a chemotherapy agent : Doxetacel Meille et al 2008
  - Breast cancer

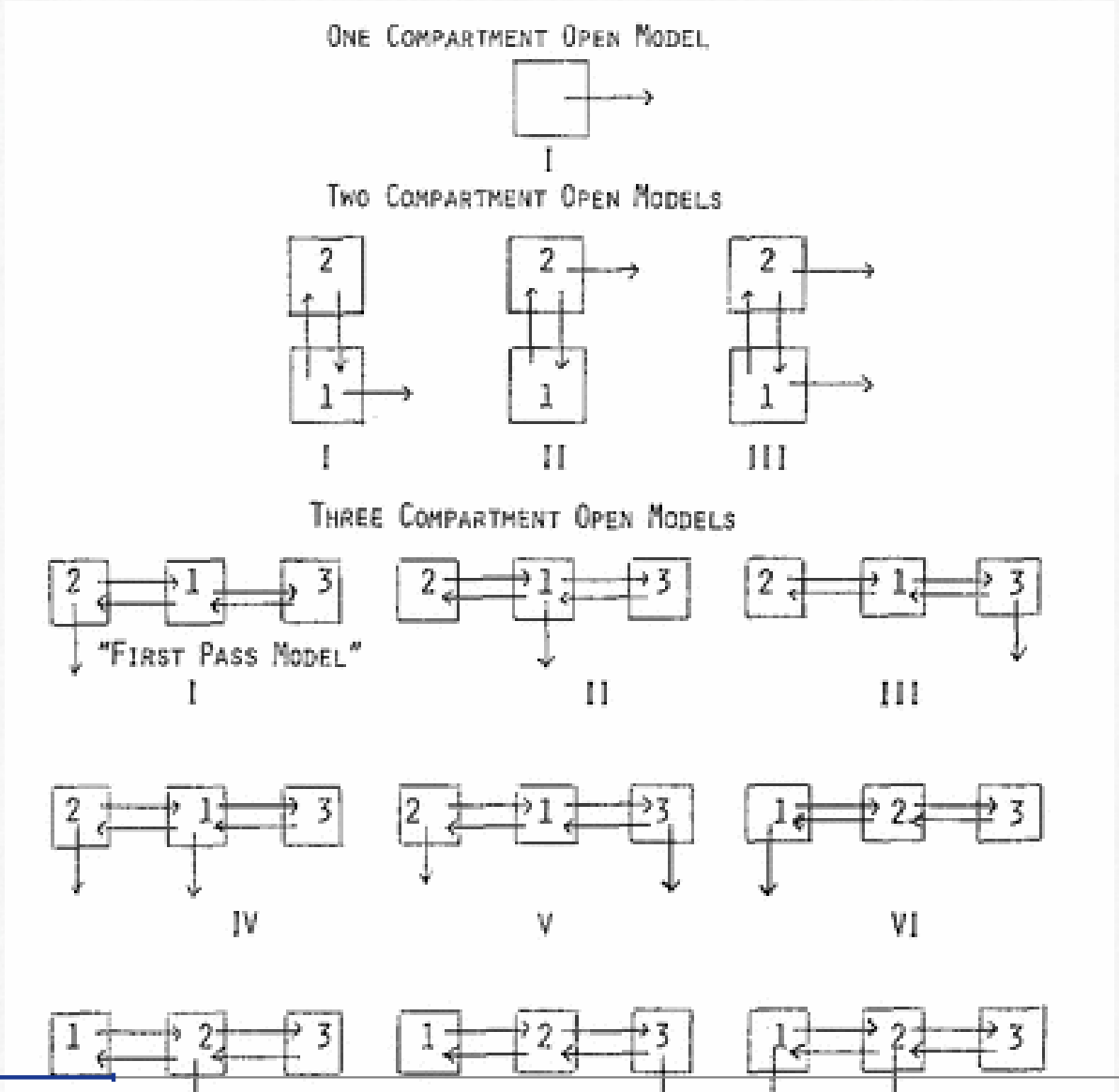


$$
\begin{aligned}
\frac{dc_1}{dt} &= -\left(\frac{Cl_1}{V_1} + k_{12} + k_{13}\right) c_1 + k_{21}\frac{V_2}{V_1} c_2(t) \\
&\quad + k_{31}\frac{V_3}{V_1} c_3(t) + \frac{U(t)}{V_1} \\
\frac{dc_2}{dt} &= k_{12}\frac{V_1}{V_2} c_1 - \left(\frac{Cl_2}{V_2} + k_{21}\right) c_2 \\
\frac{dc_3}{dt} &= k_{13}\frac{V_1}{V_3} c_1 - \left(\frac{Cl_3}{V_3} + k_{31}\right) c_3
\end{aligned}
$$

Pharmacokinetics of a drug

How the organism affects the drug

Compartment models

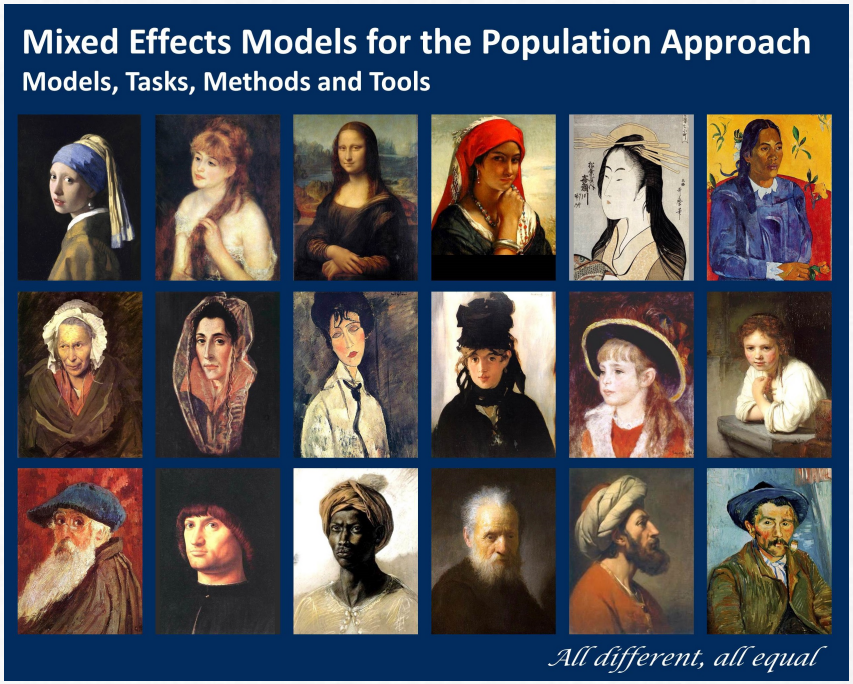


Pharmacokinetics of a drug

How the organism affects the drug

How to choose the best model ?

- Population studies using parameter estimation with non-linear mixed effect models (SAEM, see eg Monolix software)



Marc Lavielle, Chapman et al 2014

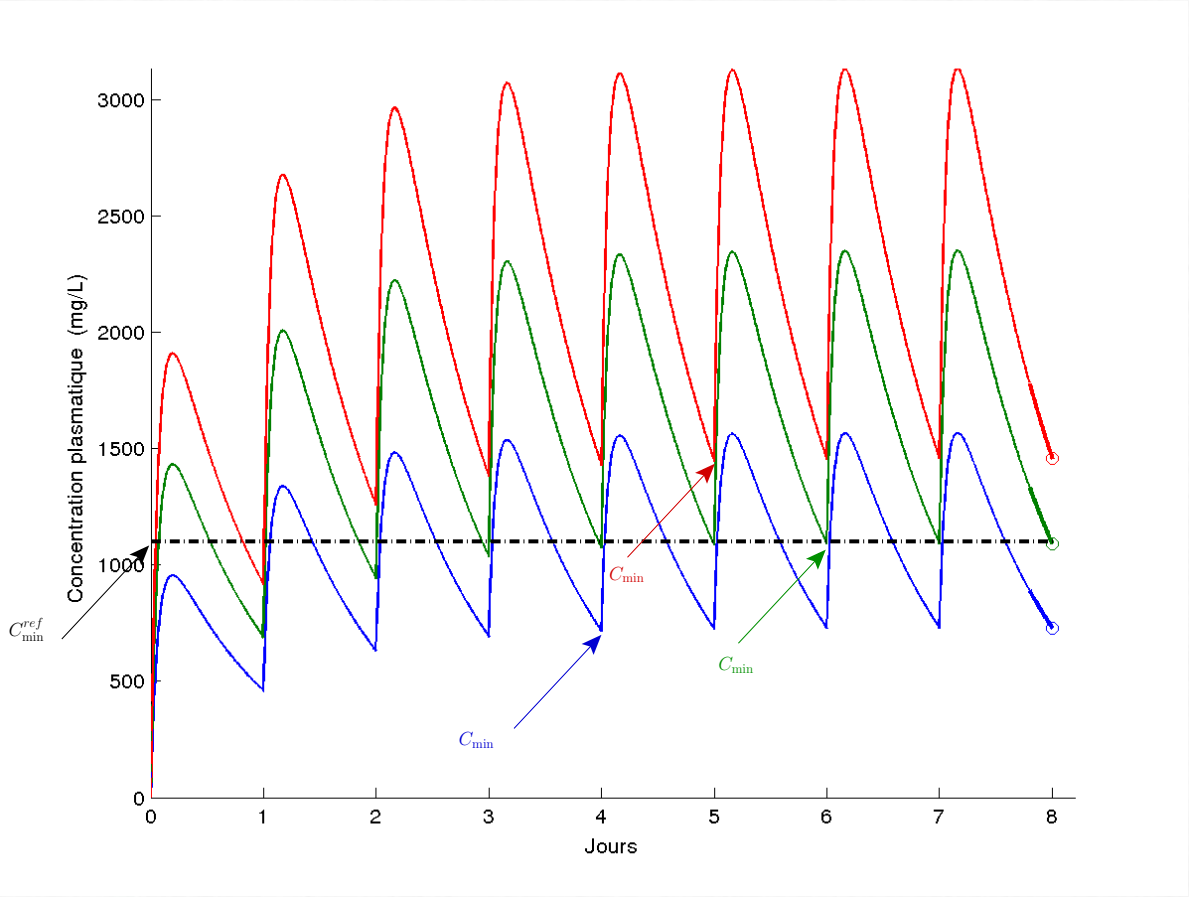
Pharmacodynamics of the drug

How drug affects the organism

A non quantitative approach : the minimal concentration

Demetri et al, 2009

- Imatinib - Gastro Intestinal Stromal Tumors



Efficiency is deeply patient dependant !

Pharmacodynamics of the drug

How drug affects the organism

A non quantitative approach : the minimal concentration

Demetri et al, 2009

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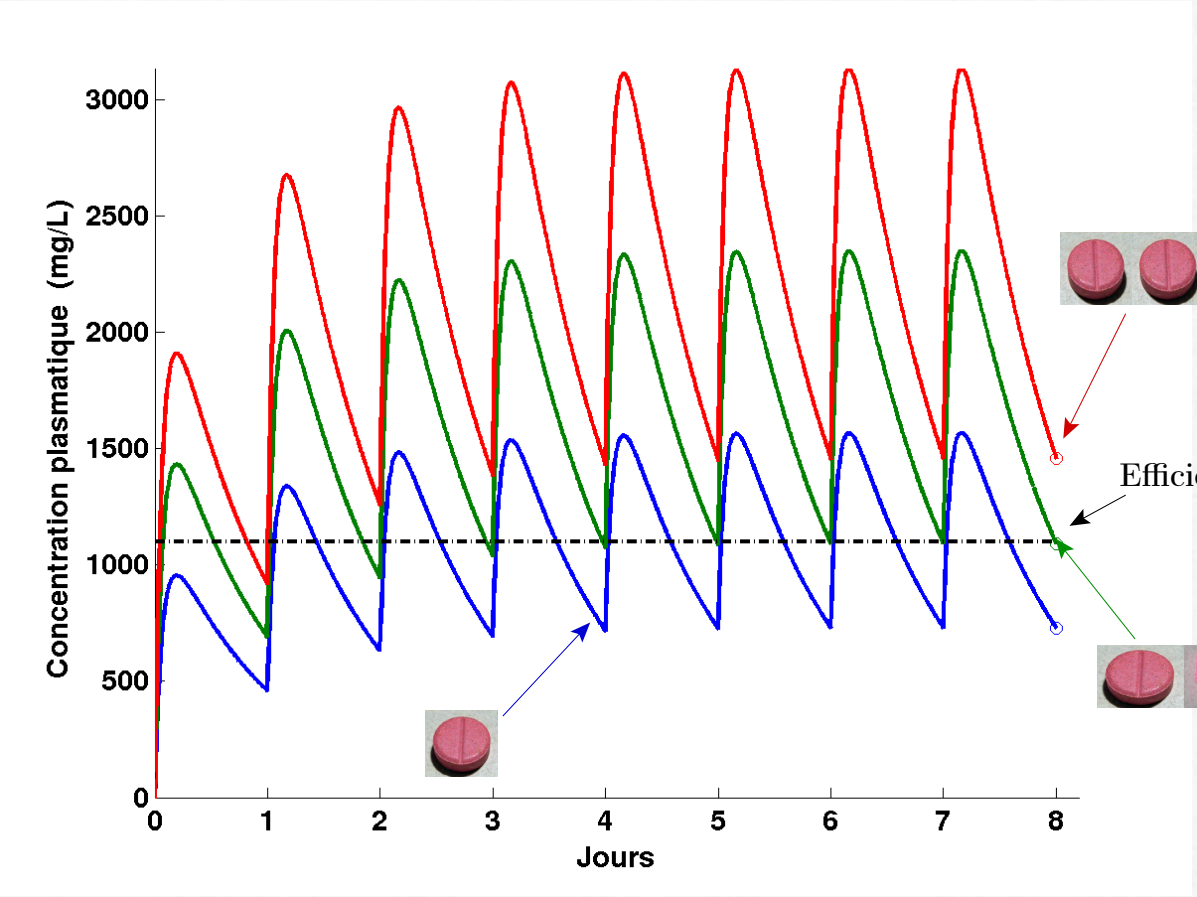


The dose 600mg is classical administrated, it corresponds to the minimal dose ensured the efficiency of the drug for a "mean"

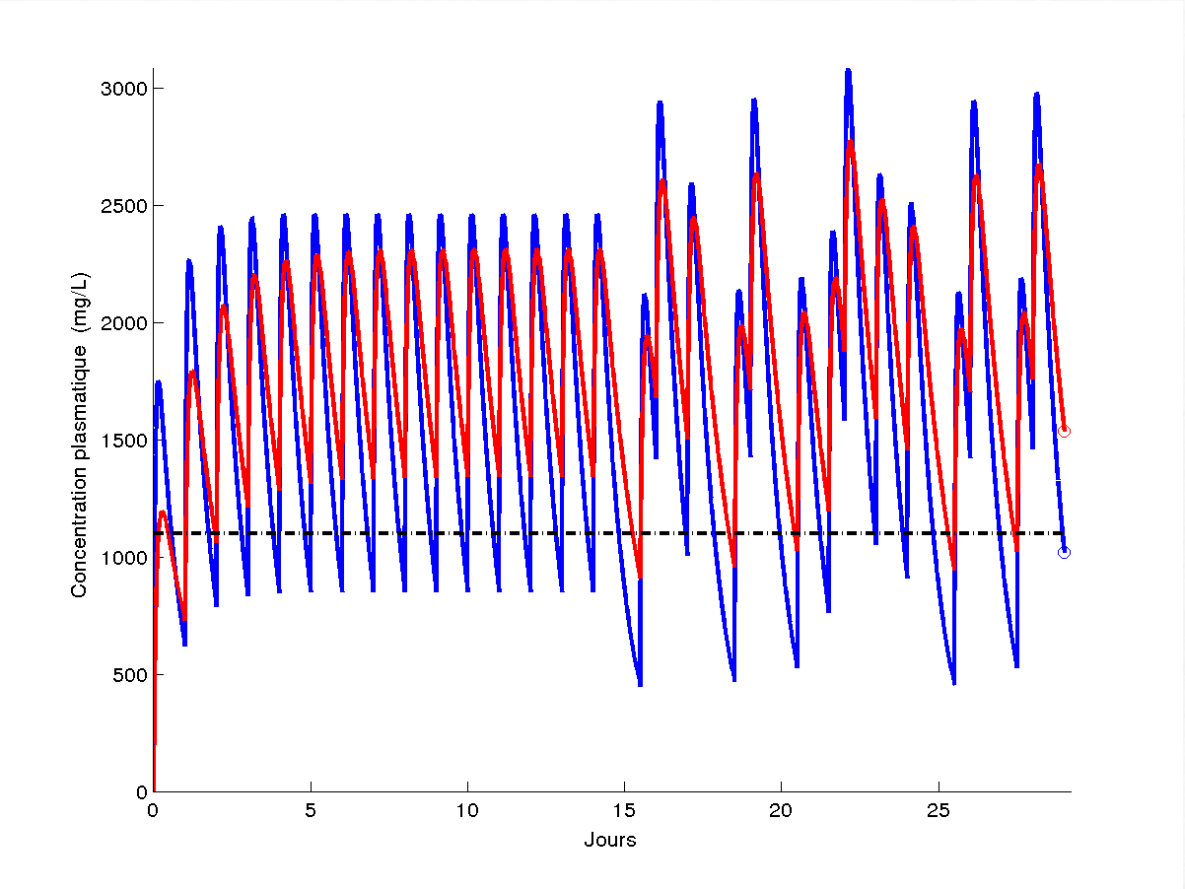
Pharmacodynamics of the drug

How drug affects the organism

A non quantitative approach : the minimal concentration

Honoré,Hubert, 2016

- Imatinib - Gastro Intestinal Stromal Tumors



The efficiency is deeply related to the regularity of the uptake !

Pharmacodynamics of a cytotoxic drug

How drug affects the organism

A quantitative approach. First models

Action proportional to

- The drug concentration in the plasma.
  Example for a cytotoxic drug :

$$Y'(t) = Y(t)\ln\left(\frac{b}{Y(t)}\right) - C(t)Y(t)$$

- The concentration above a threshold C_{thres}

$$Y'(t) = Y(t)\ln\left(\frac{b}{Y(t)}\right) - (C(t) - C_{thres})^{+}Y(t)$$

Pharmacodynamics of a cytotoxic drug

How drug affects the organism

A quantitative approach. Interface model Meille et al 2008 Drug efficiency is linked to its exposition c_e

$$\frac{dc_e}{dt} = -Ac_e e^{-Bc_e} + (C(t) - C_{thres})^+$$

- Case $A = 0$. c_e corresponds to $\int_0^t (C(s) - C_{thres})^+ \, ds$: AUC
- General case. Model saturation effects in the effect compartment.

$$Y'(t) = Y(t)\ln\left(\frac{b}{Y(t)}\right) - c_e(t)Y(t)$$

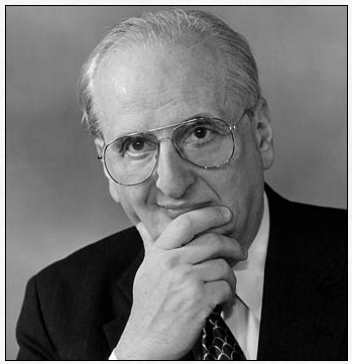
Pharmadynamics of an anti-angiogenic drug

Extension of the Gompertz model

Hahnfeldt, Folkman & al model

- The tumor size Y follows a Gompertz law.
- The maximal size θ of the tumor changes with its vascularization = the carrying capacity .

$$\begin{aligned} \frac{dY}{dt} &= aY \ln\left(\frac{\theta}{Y}\right) \\ \frac{d\theta}{dt} &= \underbrace{cY}_{\text{(VEGF)}} \quad \underbrace{-d\theta Y^{\frac{2}{3}}}_{\text{Vasculature inhibition}} \end{aligned}$$



M. J. Folkmann (1933-2008)

Pharmadynamics of an anti-angiogenic drug

Extension of the Gompertz model

Hahnfeldt, Folkman & al model

Effect of a combined anti-angiogenic therapy

$$\begin{aligned} \frac{dx}{dt} &= ax \ln\left(\frac{\theta}{x}\right) \\ \frac{d\theta}{dt} &= \mathcal{R}_2(c_{angio}(t))x - d\theta x^{\frac{2}{3}} - \gamma\theta\mathcal{R}(c_{angio}(t)) \end{aligned}$$

- Antiangiogenic drugs acts on the carrying capacity :
  - Reduction
  - Possible stimulation at the beginning reflecting the normalization of its vascularization.

Ebos & al. Cancer cell (2009)

Pharmadynamics of an anti-angiogenic drug

Extension of the Gompertz model

Hahnfeldt, Folkman & al model

Effect of a combined anti-angiogenic/chemotherapy

$$\begin{aligned} \frac{dx}{dt} &= ax \ln\left(\frac{\theta}{x}\right) - \mathcal{F}(x)\mathcal{R}_1(c_{chemo}(t)) \\ \frac{d\theta}{dt} &= \mathcal{R}_2(c_{angio}(t))x - d\theta x^{\frac{2}{3}} - \gamma\theta\mathcal{R}(c_{angio}(t)) \end{aligned}$$

- Chemotherapy acts on the tumor size.
- Antiangiogenic drugs acts on the carrying capacity.
  - Reduction.
  - Possible stimulation at the beginning reflecting the normalization of its vascularization.

Ebos & al. Cancer cell (2009)

Pharmadynamics of an anti-angiogenic drug

Extension of the Gompertz model

Hahnfeldt, Folkman & al model

Benzekry, Chapuisat, Ciccolini, Erlinger, H. (2011) Feature :

- Chemotherapy is distributed through vessels.
- Antiangiogenic drugs on one hand destroy vessels, on the other hand normalize vasculature.

$\Rightarrow$ Take into account stable (functional, mature,...) endothelial cells and unstable (non functional, new...) ones !

Biological assumptions :

- Only stable ECs are able to distribute nutrients, drugs.... with a rate depending on their quality.
- Only unstable ECs are perturbed by stimulation or inhibitor growth factors.
- The quality of vasculature depends on the proportion of stable ECs amount the global amount of ECs.

Pharmadynamics of an anti-angiogenic drug

Extension of the Gompertz model

Hahnfeldt, Folkman & al model

Benzekry, Chapuisat, Ciccolini, Erlinger, H. (2011)

Recent preclinical study Benzekri et al. 2017

Variables

$Y(t)$: tumor size

$s(t)$: density of stable ECs

$u(t)$: density of unstable ECs

$q(t)$: quality of the vasculature

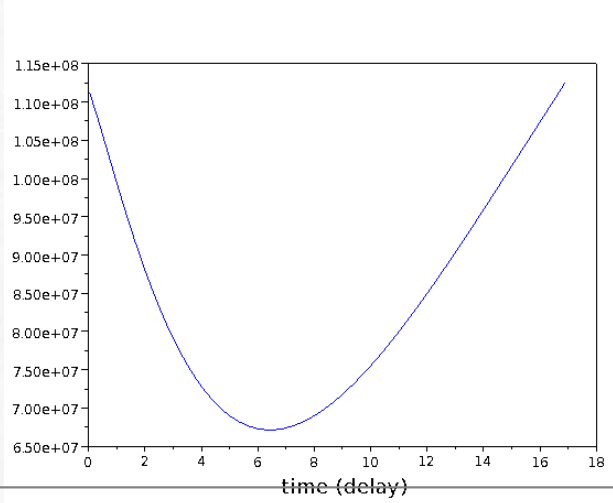
Equations :

$$\frac{dY}{dt} = \lambda Y \log\left(\frac{s}{Y}\right) \underbrace{-kY c_{chemo}(t) q s}_{\text{Chemo effect}}$$

$$\frac{ds}{dt} = \chi u - \tau s$$

$$\frac{du}{dt} = -\chi u + \gamma Y - \delta Y^{\frac{2}{3}} u \underbrace{-\eta u c_{angio}(t)}_{\text{AA effect}}$$

Optimal delay between the two drugs : One week

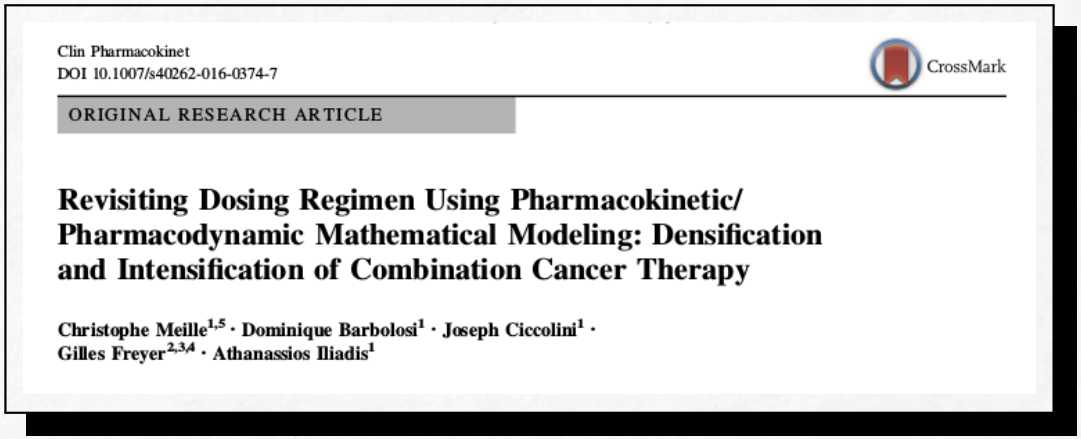


Outline of the talk

Clinical trial of phase I/II (2005-2009) : MODEL I

Le groupe de chercheurs

- Hôpitaux Lyon Sud (Group of Pr Freyer)
- Mathematicians and pharmacokinetician of Marseille (D. Barbolosi and A. Iliadis)



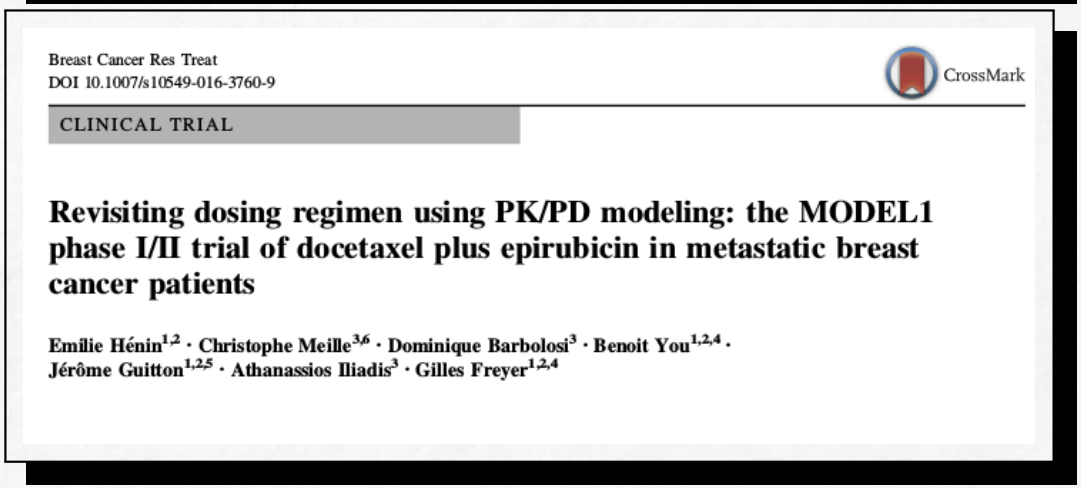
Clin Pharmacokinet
DOI 10.1007/s40262-016-0374-7

CrossMark

ORIGINAL RESEARCH ARTICLE

Revisiting Dosing Regimen Using Pharmacokinetic/ Pharmacodynamic Mathematical Modeling: Densification and Intensification of Combination Cancer Therapy

Christophe Meille[1,5] · Dominique Barbolosi[1] · Joseph Ciccolini[1] · Gilles Freyer[2,3,4] · Athanassios Iliadis[1]



Breast Cancer Res Treat
DOI 10.1007/s10549-016-3760-9

CrossMark

CLINICAL TRIAL

Revisiting dosing regimen using PK/PD modeling: the MODEL1 phase I/II trial of docetaxel plus epirubicin in metastatic breast cancer patients

Emilie Hénin[1,2] · Christophe Meille[3,6] · Dominique Barbolosi[3] · Benoit You[1,2,4] · Jérôme Guitton[1,2,5] · Athanassios Iliadis[3] · Gilles Freyer[1,2,4]

Clinical trial of phase I/II (2005-2009) : MODEL I

CRO2 Marseille/ Hôpitaux Lyon Sud

Densification of a chemotherapy driven by a mathematical model with a control of hematological toxicity.

Clinical description

- 20 patients with a metastatic breast cancer (HER2-, hormon resistant),
- Classical protocol in the 2000's : 6 cycles of chemo for each patients, cocktail of two chemotherapeutic agents DTX + EPI with 21-days cycle
- Question : is it possible to administrate such a cocktail on 15-days cycles, while controling toxicities ?

The chemotherapeutical drugs

- Kill indifferently all proliferating cells.
- Cause severe toxicities (hematologic, ...)
- Necessity to space treatments, to let patient recover their immunity 21-days cycles

Clinical trial of phase I/II (2005-2009) : MODEL I

CRO2 Marseille/ Hôpitaux Lyon Sud

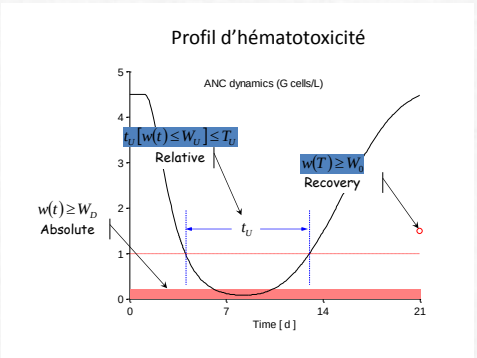
Mathematical description

- Tumor growth model
  - Gompertz model adapted to take into account the treatment. Let $\text{eff}_{trait}(t,u)$ be death rate due to drugs evaluated through PK-PD model.

$$x'_u = a x_u \ln\left(\frac{b}{x_u}\right) - x_u \,\text{eff}_{trait}(t,u)$$

- Toxicities constraints $\rightsquigarrow$ hematological constraints.
  - W_D WBC should not fall down below a concentration W_D
  - W_U The patient should not stay too long aplasia.
  - W_a WBC should recover a concentration W_a before a new cycle.

$\Rightarrow$ **Results :** Modeling the hematoxicity model leads to $t \mapsto W(t;u)$, contraints becomes $F(t,u) \leq W$ where $t \mapsto u(t) \in \mathbb{R}^n$ stands for doses of the drugs.



Clinical trial of phase I/II (2005-2009) : MODEL I

Mathematical description

- Tumor growth

$$x'_u = a x_u \ln\left(\frac{b}{x_u}\right) - x_u \, \mathrm{eff}_{treat}(t,u)$$

with $\mathrm{eff}_{treat}(t,u)$ obtained through an ODE system

- Toxicity constraints. $t \mapsto W(t)$ solves an ODE system involving $\mathrm{tox}_{treat}(t,u)$. So that toxicities can be reduced into

$$K = \{u / F(t,u) \leq C\}$$

with $F(t,u)$ obtained through an ODE system.

- Optimisation of the protocol

$$\min_{u \in K} \min_{t \in [0,T]} x_u(t)$$

Find an "admissible" protocol leading to the best tumoral recession.

Clinical trial of phase I/II (2005-2009) : MODEL I

CRO2 Marseille/ Hôpitaux Lyon Sud

Mathematical results

- Existence of an optimal protocol requiring an injection of G-CSF.

Methodology

- Protocol of the first cycle based on average parameters.
- Assay of ANC et wafer on 3 blood specimen during the first cycle.
- Estimation of individual PK/PD parameters thanks to Bayesian methods.
- Optimisation of the protocol for the following cycles.

Conclusion

- Densification possible.
- Optimized protocols require injection of hematopoietic factors G-csf. Necessity to reverse the order of administration of the two drugs.
-
- Response rate lightly lower than in previous study (31.5% vs 49-88 %) .
- But Weeker progression (6% vs 5-18 %) and a better survival median (54.6 vs 19.5-34 month) .

Outline of the talk

Low grade glioma

ENS Lyon group/ CHU Lyon

Prolonged action of TMZ

Published OnlineFirst on July 3, 2012; DOI:10.1158/1078-0432.CCR-12-0084

Clinical Cancer Research

Cancer Therapy: Clinical

A Tumor Growth Inhibition Model for Low-Grade Glioma Treated with Chemotherapy or Radiotherapy

Benjamin Ribba[1], Gentian Kaloshi[6], Mathieu Peyre[2], Damien Ricard[7], Vincent Calvez[1], Michel Tod[3,4], Branka Čajavec-Bernard[1], Ahmed Idbaih[6], Dimitri Psimaras[6], Linda Dainese[8], Johan Pallud[9], Stéphanie Cartalat-Carel[2], Jean-Yves Delattre[6], Jérôme Honnorat[2,4,5], Emmanuel Grenier[1], and François Ducray[2,4,5]

Citation: CPT Pharmacometrics Syst. Pharmacol. (2015) 4, 728–737; doi:10.1002/psp4.54

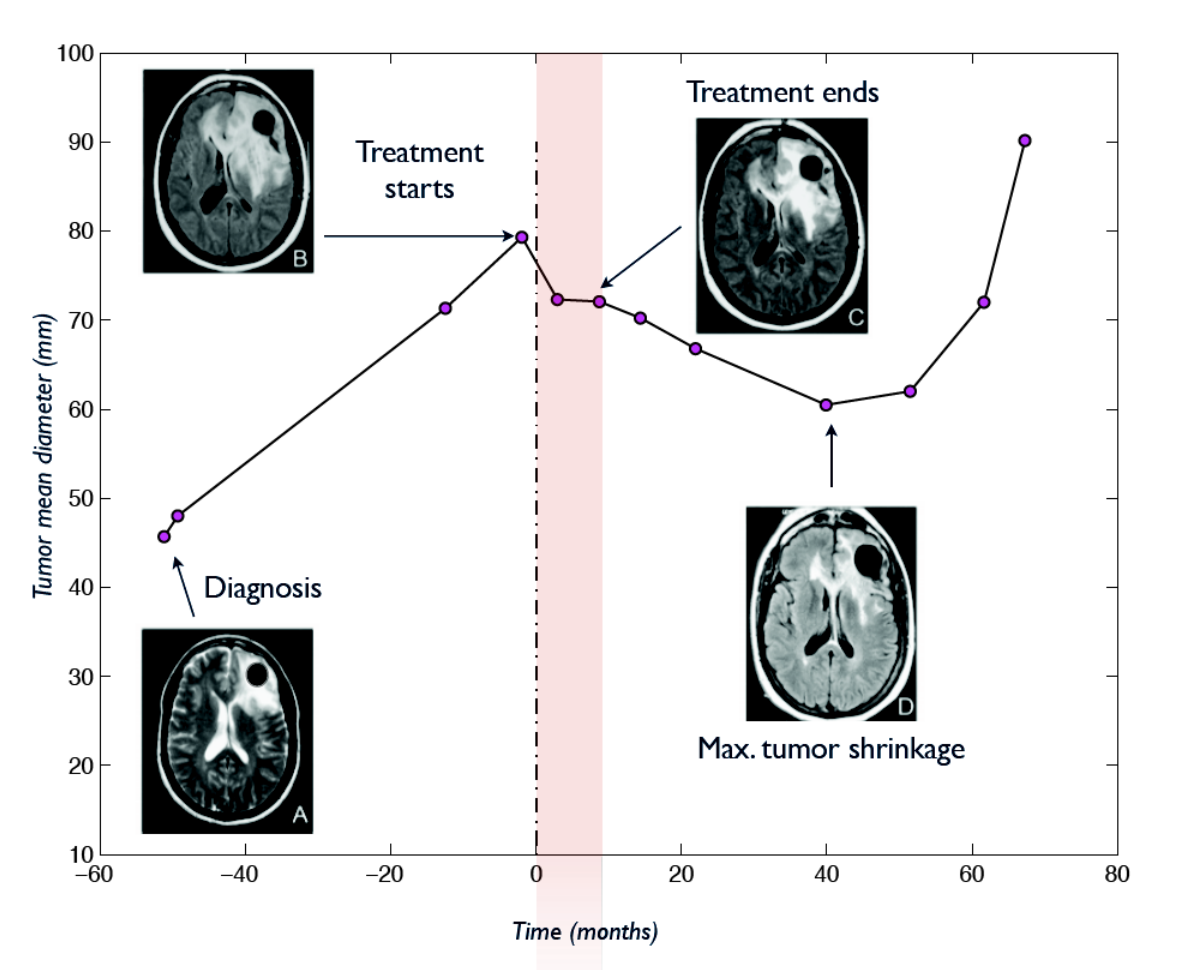
ORIGINAL ARTICLE

Prediction of Response to Temozolomide in Low-Grade Glioma Patients Based on Tumor Size Dynamics and Genetic Characteristics

P Mazzocco[1], C Barthélémy[2], G Kaloshi[3], M Lavielle[2], D Ricard[4], A Idbaih[3], D Psimaras[3], M-A Renard[3], A Alentorn[3], J Honnorat[5], J-Y Delattre[3], F Ducray[5] and B Ribba[1]*

Low grade glioma

Observations

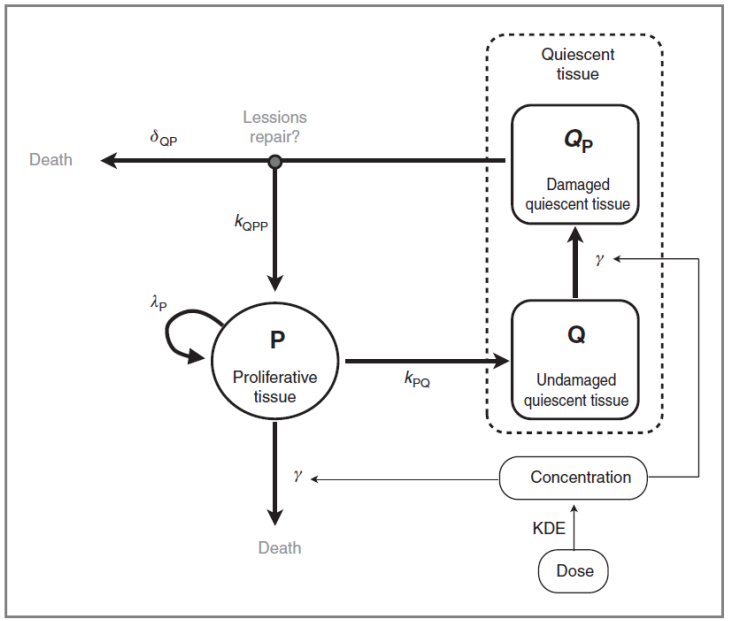


Low grade glioma

ENS Lyon group/ CHU Lyon

Model

$$
\begin{aligned}
\frac{d}{dt}C &= -KDEC \\
\frac{d}{dt}P &= \lambda_P P\left(1-\frac{P+Q+Q_p}{K}\right) \\
&\quad +k_{Q_pP}Q_p - k_{PQ}P \\
&\quad -\gamma e^{-rest}KDECP \\
\frac{d}{dt}Q &= k_{PQ}P - \gamma KDECQ \\
\frac{d}{dt}Q_p &= -k_{Q_pP}Q_p - \delta_{Q_p} + \gamma KDECQ
\end{aligned}
$$



Results

- Predition of the amplitude and the duration of the response to TMZ.
- A tool to optimize the drug scheduling leading optimise to the best response.

More results

- See also works of Víctor M Pérez-García group at Universidad de Castilla-La Mancha, SPAIN

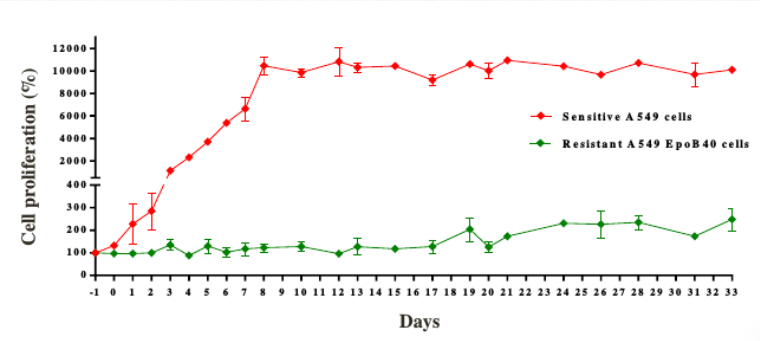
Outline of the talk

Drug resistance

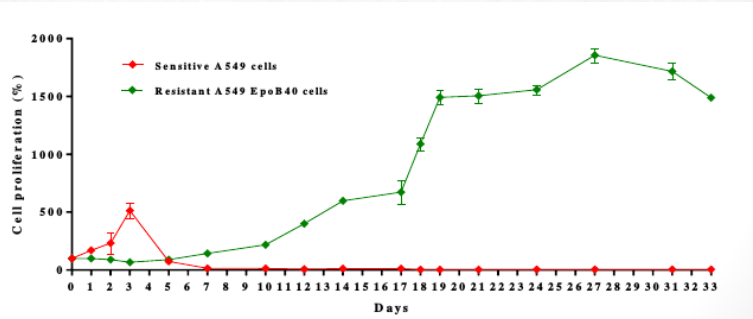
Carré,Carrère,Chapuisat

Tumor heterogeneity

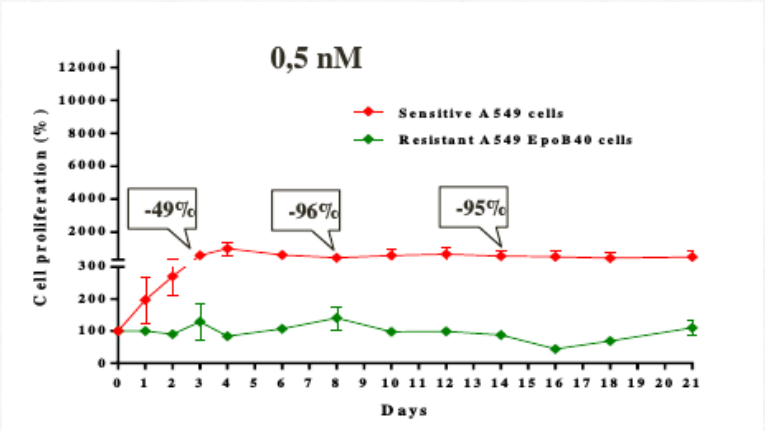
- Only part of the cells are sensible to the drug.
- Sensible cells may control the resistant cells.



Without Treatment



MTD 5nM



Metronomic

Is it possible to control the tumor thank to a "good protocol" ?

Drug resistance

Carré,Carrère,Chapuisat

Tumor heterogeneity

- Only part of the cells are sensible to the drug.
- Sensible cells may control the resistant cells.

$$
\begin{aligned}
S'(t) &= \rho S(t)\left(1-\frac{S(t)+mR(t)}{K}\right)\underbrace{-\alpha C(t)S(t)}_{\text{Drug effect}}\\
R'(t) &= \rho R(t)\left(1-\frac{S(t)+mR(t)}{K}\right)\quad\underbrace{-\beta R(t)S(t)}_{\text{Control by sensible cells}}
\end{aligned}
$$

$\rightsquigarrow$ Optimize protocoles studied by C. Carrère.

Outline of the talk

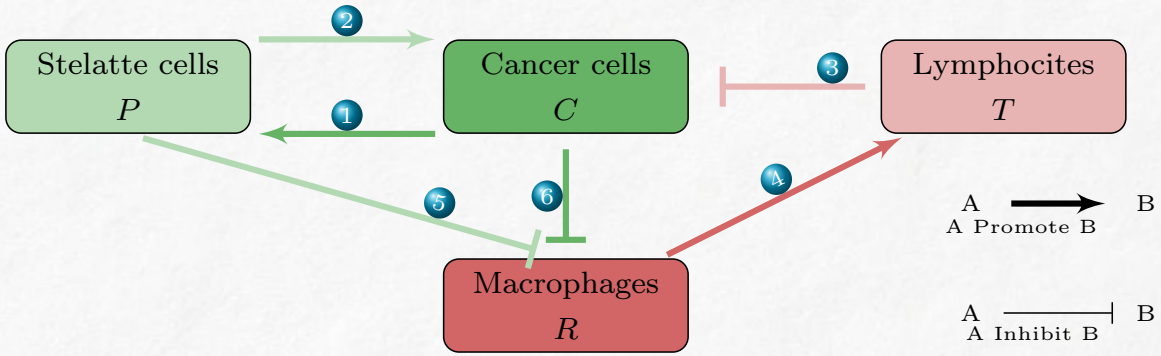
Interaction with the immune system

Example in the case of the pancreatic cancer

Published in final edited form as:
J Theor Biol. 2014 June 21; 351: 74–82. doi:10.1016/j.jtbi.2014.02.028.

A mathematical model for pancreatic cancer growth and treatments

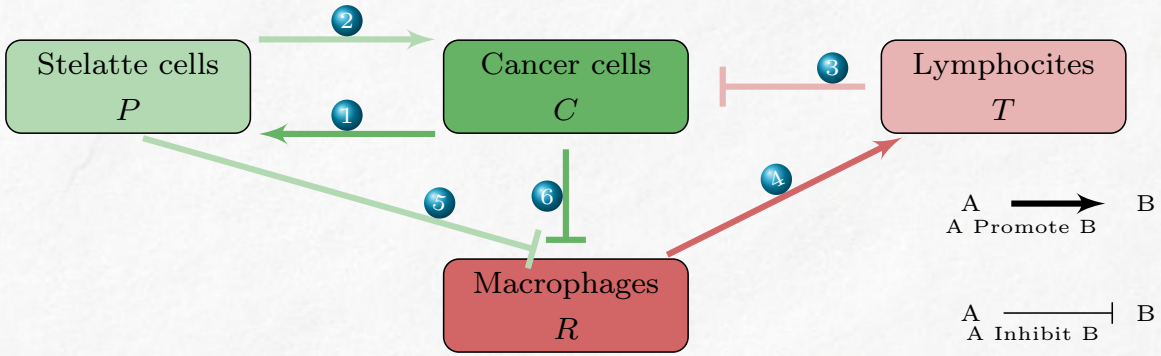
Yoram Louzoun[a], **Chuan Xue**[b], **Gregory B. Lesinski**[c], and **Avner Friedman**[b]



- C PCC Pancreatic Cancer Cells
- P PSC Pancreatic Stellate Cells
- R Fraction of pro-inflammatory macrophage amoung the macrophage
- T CD8+ Tcells (immune cells cytotoxic)

Interaction with the immune system

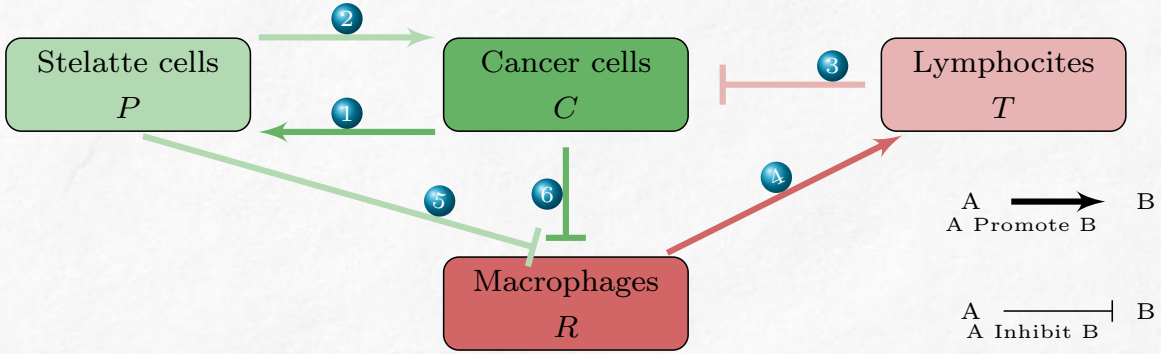
Example in the case of the pancreatic cancer



1. PCC promote growth and activity of PSC through the secretion of TGF_β
2. PSC promote PCC growth and metastase
3. TCells are cytotoxic
4. R is the fraction of pro-inflammatory macrophage so promote Tcells
5. PSC and PCC inhibites pro-inflammatory macrophages recruitment

Interaction with the immune system

Example in the case of the pancreatic cancer



The dynamical system

$$\frac{dC}{dt} = \underbrace{(k_c + \mu_c P)}_{2} C^{\frac{3}{4}} \left(1 - \left(\frac{C}{C_0}\right)^{\frac{1}{4}}\right) - \underbrace{\frac{\lambda_c}{K_c + (1-R)}}_{3} CT$$

$$\frac{dP}{dt} = \underbrace{\left(k_p + \frac{\mu_p C}{K_p + C}\right)}_{1} P\left(1 - \frac{P}{P_0}\right) - \lambda_p P$$

$$\frac{dR}{dt} = k_r - \underbrace{(\lambda_r + \gamma_p P + \gamma_c C)}_{5,6} R$$

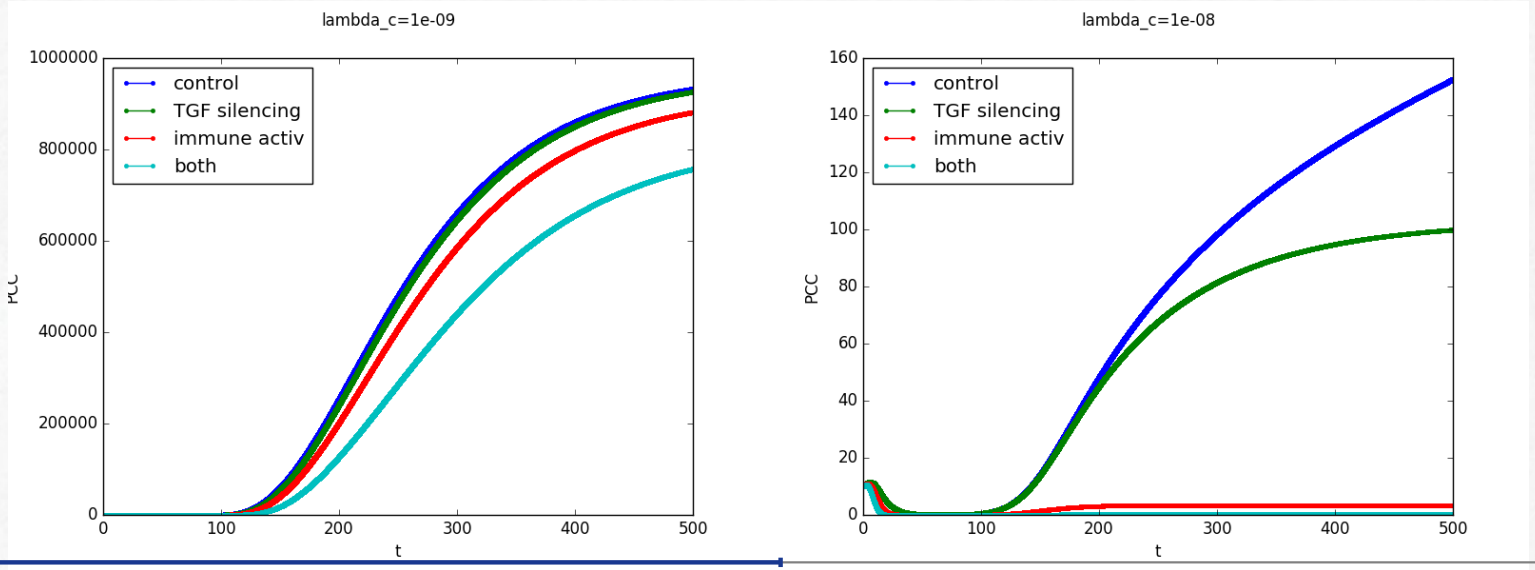
$$\frac{dT}{dt} = \underbrace{\frac{k_t R}{K_t + (1-R)}}_{4} - \lambda_t T$$

Interaction with the immune system

Action of a drug treatment

$$
\begin{aligned}
\frac{dC}{dt} &= (k_c + \mu_c P) C^{\frac{3}{4}} \left(1 - \left(\frac{C}{C_0}\right)^{\frac{1}{4}}\right) - \frac{\lambda_c}{K_c + (1-R)} CT \\
\frac{dP}{dt} &= \left(k_p + \frac{\mu_p C}{K_p + C}\right) P \left(1 - \frac{P}{P_0}\right) - \lambda_p P \\
\frac{dR}{dt} &= k_r - (\lambda_r + \gamma_p P + \gamma_c C) R \\
\frac{dT}{dt} &= \frac{k_t R}{K_t + (1-R)} - \lambda_t T
\end{aligned}
$$

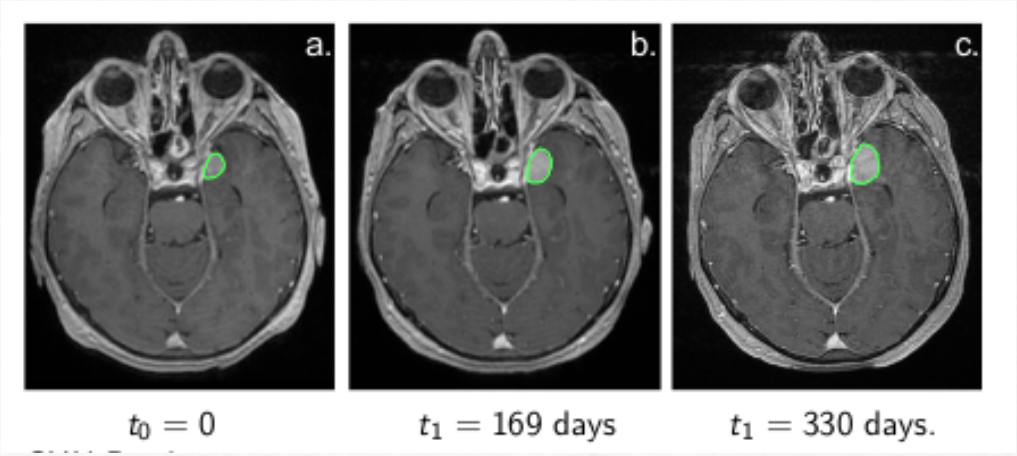
- TGF_β silencing : $\gamma_c, \gamma_p, \mu_p$ reduced of 10%
- Immune activation - EGFR silencing : k_t multiply by a factor 2



Outline of the talk

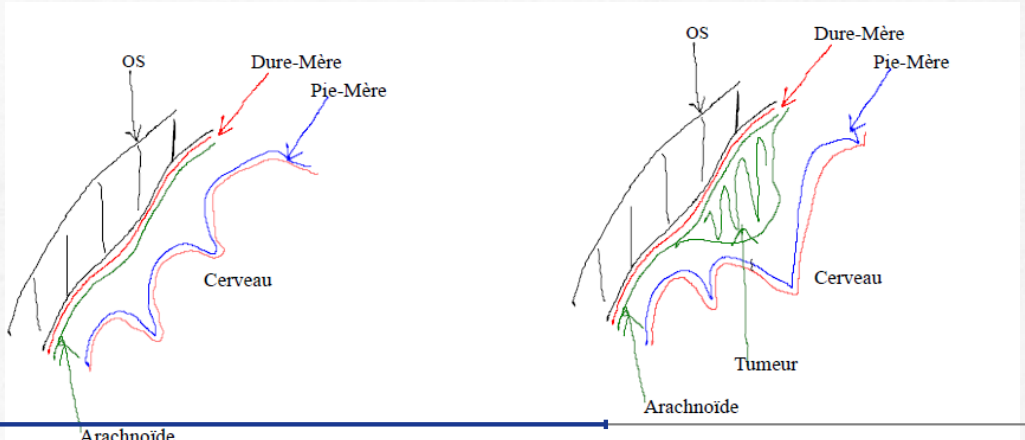
Meningioma

Issues How to model an predict the tumour growth in such a complex geometry ?



Properties. Slow and relatively homogeneous growth

Difficulty. The 3D geometry plays an important role



Meningioma

Group INRIA MONC / CHU Bordeaux

A PDE model with 4 equations

- Tumor growth $P(t,x)$

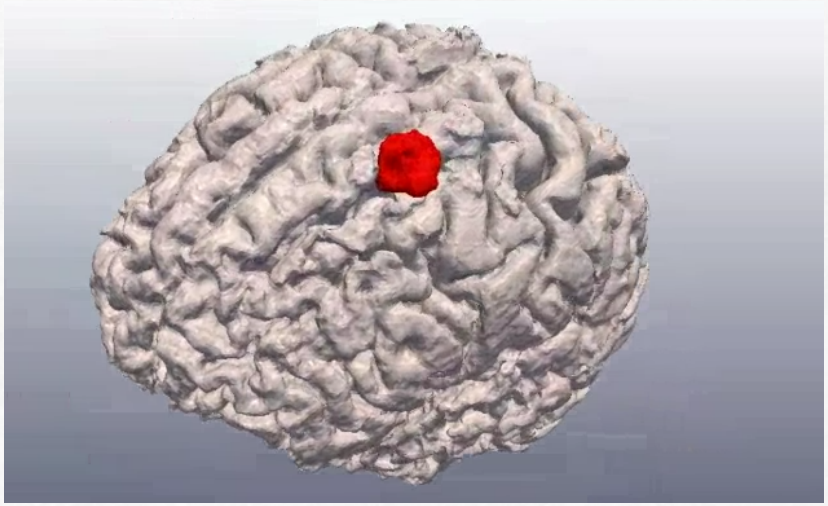
$$\partial_t P + \mathrm{div}(vP) = MP$$

- Host system $S(t,x)$

$$\partial_t S + \mathrm{div}(vS) = 0$$

- Vascularization $M(t,x)$

$$\partial_t M = -\alpha M$$



https ://www.youtube.com/watch ?v=l6XvWZXQNlg

- Velocity induced by the growth $v(t,x)$

$S+P=1 \Rightarrow \mathrm{div}(v) = MP$ with $v = \nabla\pi$ and $\nabla\pi \cdot n = 0$ on arachnoid matter

Approach already used in

- Ribba et al JTB 2006

Outline of the talk

Radiotherapy driven by imagery

Many works !

Swanson Lab, Group INRIA Asclepios Sophia Antipolis

Magnetic Resonance in Medicine 54:616–624 (2005)

Simulation of Anisotropic Growth of Low-Grade Gliomas Using Diffusion Tensor Imaging

Saâd Jbabdi,[1] Emmanuel Mandonnet,[2*] Hugues Duffau,[1,2] Laurent Capelle,[1,2] Kristin Rae Swanson,[3] Mélanie Pélégrini-Issac,[1] Rémy Guillevin,[4] and Habib Benali[1,5]

Physics in Medicine and Biology

PAPER

Radiotherapy planning for glioblastoma based on a tumor growth model: improving target volume delineation

Jan Unkelbach[1], Bjoern H Menze[2,3], Ender Konukoglu[4], Florian Dittmann[1], Matthieu Le[1,2], Nicholas Ayache[2] and Helen A Shih[1]

Published 20 January 2014 • 2014 Institute of Physics and Engineering in Medicine
Physics in Medicine and Biology, Volume 59, Number 3

Physics in Medicine and Biology

PAPER

Radiotherapy planning for glioblastoma based on a tumor growth model: implications for spatial dose redistribution

Jan Unkelbach[1], Bjoern H Menze[2,3], Ender Konukoglu[4], Florian Dittmann[1], Nicholas Ayache[2] and Helen A Shih[1]

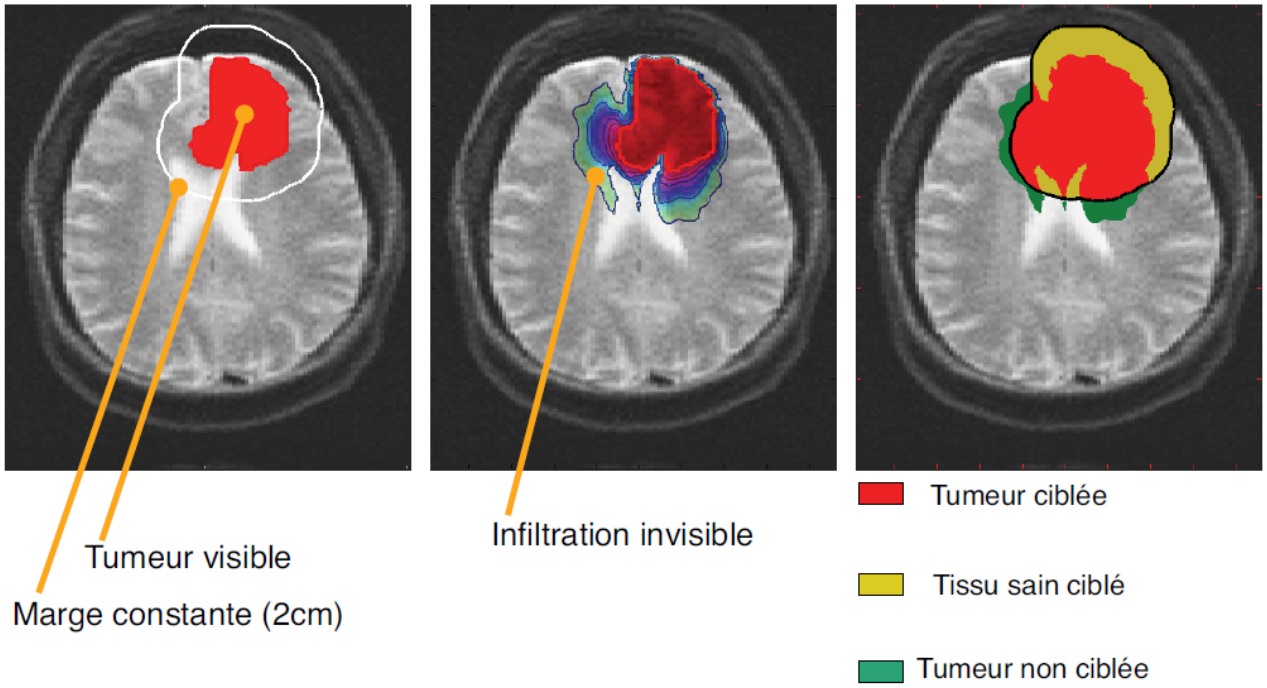
Published 20 January 2014 • 2014 Institute of Physics and Engineering in Medicine
Physics in Medicine and Biology, Volume 59, Number 3

Radiotherapy driven by imagery

One issue :

- Irradiated zone not always covers the infiltrated zone

$\Rightarrow$ How to optimize the radiated zone ?



Radiotherapy driven by imagery

Swanson group

Tumor model

- The Fisher Kolmogorov equation :

Spatio-temporal evolution of the density of tumor cells

$$\partial_t u = \underbrace{\operatorname{div}(D\nabla u)}_{\text{Anisotropic diffusion}} \underbrace{+\rho u(1-u)}_{\text{Logistic growth}}$$

Parameters

- Anisotropic diffusion $D(x)$ in the white matter, but isotropic in the grey matter.
- Growth rate ρ.

Radiotherapy driven by imagery

Towards personnalized therapy

Original studies

Swanson group

- Anisotropy in the white matter D_0 (obtained with a diffusion MRI)
- Infiltration index : d/ρ (obtained with one MRI T2 flair + MRI T1 Gd)
- Propagation speed : $2\sqrt{d\rho}$ (obtained with two acquisitions of MRI T1 Gd)

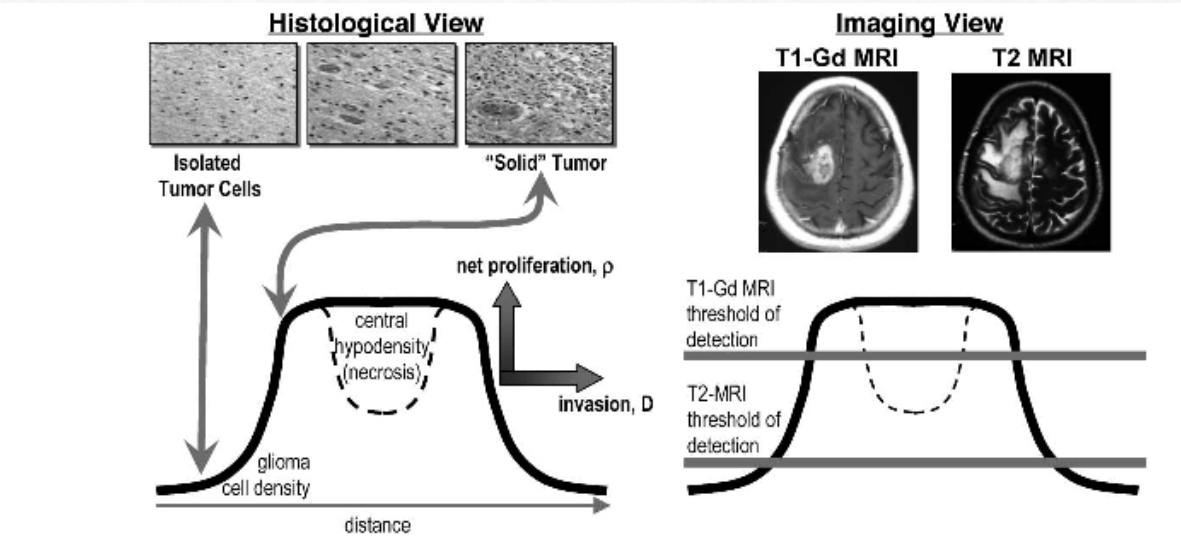


FIGURE 5. Schematic view of a typical glioblastoma as seen microscopically and by MRI in T1-Gd and T2 images.

Swanson et al , 2007

Radiotherapy driven by imagery

Towards personnalized therapy

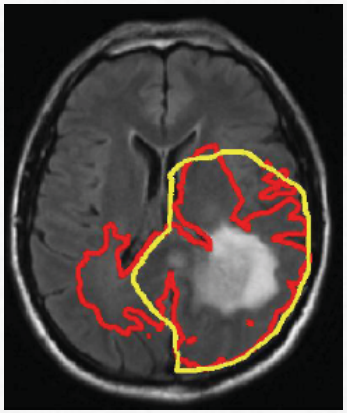
A more complex strategy

Group INRIA Asclepios Sophia Antipolis/Centre Lacassagne/MGH Boston

- Radiotherapy optimization

  $\rightsquigarrow$ Estimation for each voxels of the dose d_i minimizing the number of survival cells for a total dose imposed.

$$\min_{d \text{ dose}} \sum_{i \text{voxels}} \underbrace{u_i}_{\text{tumor model}} \underbrace{exp\left(-d_i\left(\alpha + \frac{\beta}{\alpha N_f} d_i\right)\right)}_{\text{Radiotherapy effect}} \text{ with } \frac{1}{N_T}\sum_i d_i \leq D_{\max}$$



Outline of the talk

First example : A population balance equation for mitosis

Perthame, 2007

To take into account that cell division may depend on their age
A tumor cell of size a can divide into two cells of age 0.

$$\partial_t \rho + \partial_a \rho = -B(a)\rho(t,a),\ x > 0,\ t > 0$$

$$\rho(t,0) = 2\int_0^\infty B(a)\rho(t,a)\,da,\ \rho(0,x) = \rho_0(x)$$

- $\rho(t,a)$ density of tumor cells at time t of age a.
- $B(a)$ division rate
- $-B(a)\rho(t,a)da\,dt$ number of cell of age between a and $a+da$ that divide between time t and $t+dt$.

McKendrick-vonFoerster equation or renewal equation

First example : A population balance equation for mitosis

Perthame, 2007

To take intot account that cell division may depend on their size
A tumor cell of size x can divide into two cells of equal size $x/2$.

$$\partial_t \rho + \partial_x (g(x)\rho) = -B(x)\rho(t,x) + 4B(2x)\rho(t,2x),\ x > 0,\ t > 0$$

$$\rho(t,0) = 0,\ \rho(0,x) = \rho_0(x)$$

- $\rho(t,x)$ density of tumor cells at time t of size x.
- $B(x)$ division rate
- $-B(x)\rho(t,x)dx\,dt$ number of cell of size between x and $x+dx$ that divide between time t and $t+dt$.
- $2B(2x)\rho(t,2x)d(2x)\,dt$ number of cell of size between $2x$ and $2(x+dx)$ that divide between time t and $t+dt$.

$\rightsquigarrow$ Extensions to bacteria proliferation (Doumic, Gabriel, Martin 2018).

$\rightsquigarrow$ Extensions to account the immune system (Atsou, Goudon 2018).

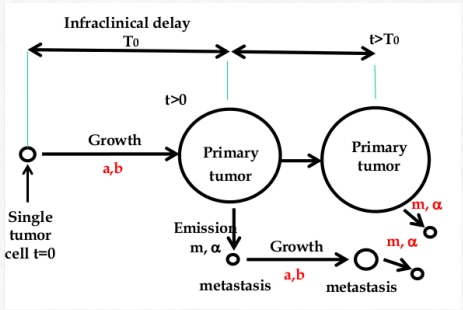
Second example : metastase spreading

The original model of metastases

Iwata & al (2000) Verga, PhD Marseille (2010) Devys,PhD Lille (2011)

A tumor growth = ODE system : gompertz's law

$$x'(t) = g_{a,b}(x) := ax \ln\left(\frac{b}{x}\right)$$



Metastases = renewal equation

$\rho(t,x)$ density of metastases at time t of size x.

$$\partial_t \rho + \partial_x \left(g_{a,b}(x)\rho\right) = 0,\ t > 0,\ x \geq 1$$

Emission of metastases = a boundary layer : $\beta(x) = mx^{\alpha}$

$$g_{a,b}(1)\rho(t,1) = \underbrace{\beta(x_p(t))}_{\text{Emission by the primary tumor}} + \underbrace{\int_1^b \beta(x)\rho(t,x)\,dx}_{\text{emission by the metastases}} \quad t > 0$$

$\rightsquigarrow$ McKendrick-vonFoerster equation

Second example : metastase spreading

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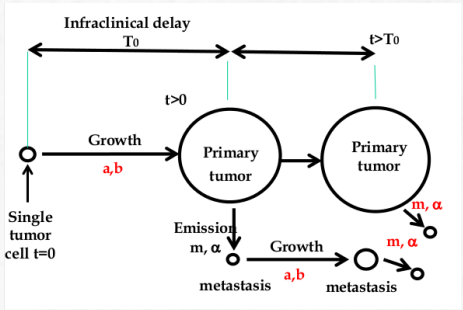

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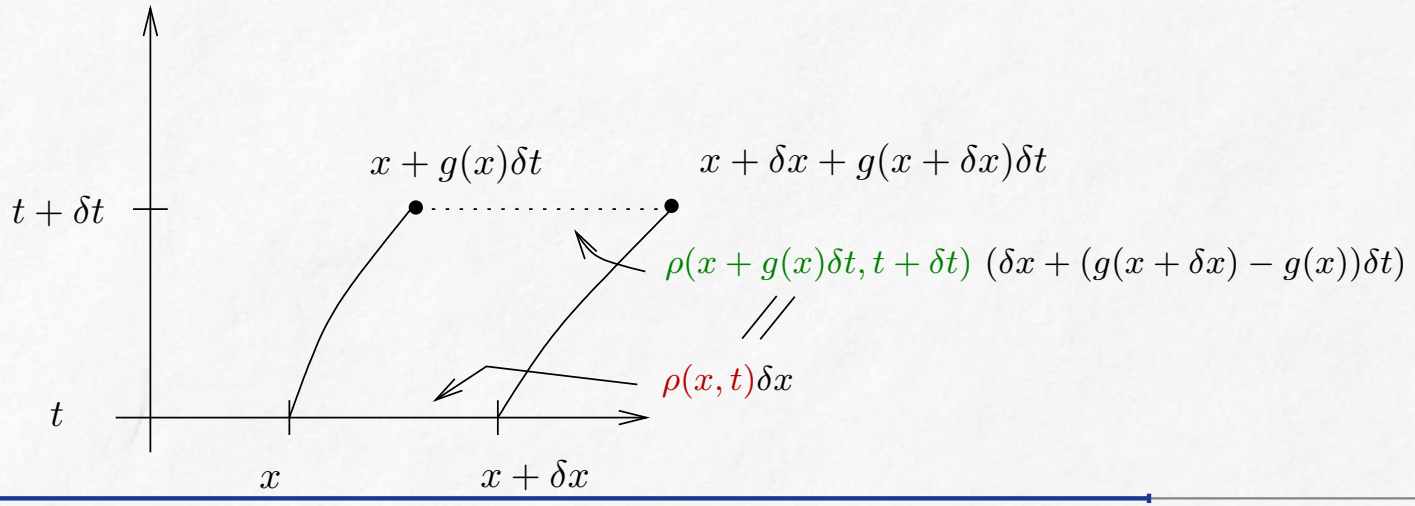

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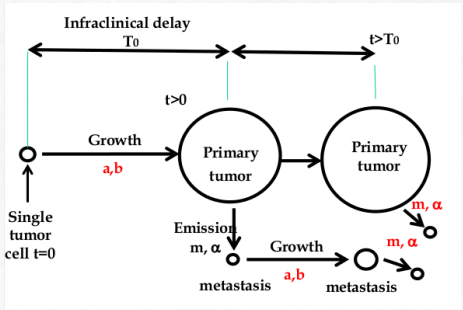


Metastases = renewal equation

$\rho(t,x)$ density of metastases at time t of size x.

$$\partial_t \rho + \partial_x \left(g_{a,b}(x)\rho\right) = 0,\ t > 0,\ x \geq 1$$

thus

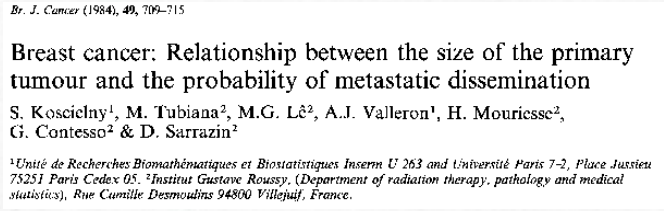
$$\rho(t+\delta t, x + g(x)\delta t)(\delta x + (g(x+\delta x) - g(x))\delta t) = \rho(t,x)\delta x$$

and then

$$(\rho(t,x) + \delta t(g(x)\partial_x \rho(x,t) + \partial_t \rho(x,t)) + o(\delta x, \delta t))(\delta x + \delta t \delta x g'(x) + o(\delta x)) = \rho(t,x)\delta x$$

Second example : metastase spreading

Calibration of Iwata & al. model

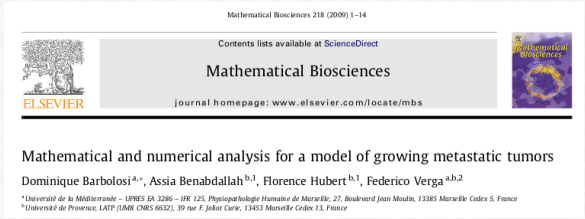


Br. J. Cancer (1984), **49**, 709–715

Breast cancer: Relationship between the size of the primary tumour and the probability of metastatic dissemination

S. Koscielny[1], M. Tubiana[2], M.G. Lê[2], A.J. Valleron[1], H. Mouriesse[2], G. Contesso[2] & D. Sarrazin[2]

[1]*Unité de Recherches Biomathématiques et Biostatistiques Inserm U 263 and Université Paris 7-2, Place Jussieu 75251 Paris Cedex 05.* [2]*Institut Gustave Roussy, (Department of radiation therapy, pathology and medical statistics), Rue Camille Desmoulins 94800 Villejuif, France.*



Mathematical Biosciences 218 (2009) 1–14

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journal homepage: www.elsevier.com/locate/mbs

Mathematical and numerical analysis for a model of growing metastatic tumors

Dominique Barbolosi[a,*], Assia Benabdallah[b,1], Florence Hubert[b,1], Federico Verga[a,b,2]

[a]*Université de la Méditerranée – UPRES EA 3286 – IFR 125, Physiopathologie Humaine de Marseille, 27, Boulevard Jean Moulin, 13385 Marseille Cedex 5, France*

[b]*Université de Provence, LATP (UMR CNRS 6632), 39 rue F. Joliot Curie, 13453 Marseille Cedex 13, France*

Koscienly & al (1984)

Verga PhD (2010)

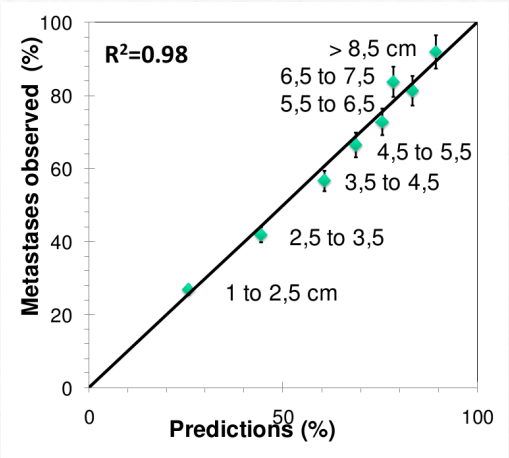
Tubbiana's study

- 2648 patients treated for breast cancer at Institut Gustave Roussy, Paris between 1954 and 1972.
- Proportion of patients that present metastases at detection.

In silico study

- 800 virtual patients. Parameters a, b fixed. Parameters m and α following a log-normal distribution.

Results



Second example : metastase spreading

Identifiability of the parameters

$$\partial_t \rho + \partial_x (g_{a,b}(x)\rho) = 0,\ g(1)\rho(t,1) = \beta_{m,\alpha}(x_p) + \int_1^b \beta_{m,\alpha}(x)\rho(t,x)\,dx$$

a real patient.  A set of parameter $a, b, m, \alpha, x_0, \cdots$

Parameters of the primary tumor spreading

- Parameters (a, b, x_0) can be identify from 3 observations from the primary tumor.

Parameters of the metastases spreading : link to Volterra equation

Hartung (2013)

- Observables $F_f(t) = \int_1^b f(x)\rho(t,x)\,dt$ are solution of a Volterra equation

$$F_f(t) = [f(x_p) * \beta(x_p)](t) + [F_f * \beta(x_p)](t)$$

$\rightsquigarrow$ if $F_f \in \mathcal{C}^1, F_f(0) = 0$ and $F_f + f(x_p) \in \mathcal{C}^1, F_f + f(x_p)(0) \neq 0$, β can be identified from $F_f(t)$ and x_p.

Second example : metastase spreading

Preclinical validation

J. Ciccolini, S. Mollard (CRO2)

Animal experiments

- **Animals :** 16 Female NOD Scid mice (8 weeks old)

  ⇝ very immunodefficient.
- **Graft :** orthoptic xenograft (Mammary glands).

  ⇝ human tumor Luciferase transvected cells
- **Cells** (human) MDA-MB-231-LUC (Caliper)

  ⇝ cells that emits photons in presence of Luciferin.
- **Injection at d=0** 150 000 cells/50μL Matrigel
- **Follow up** by bioluminescence twice a week.

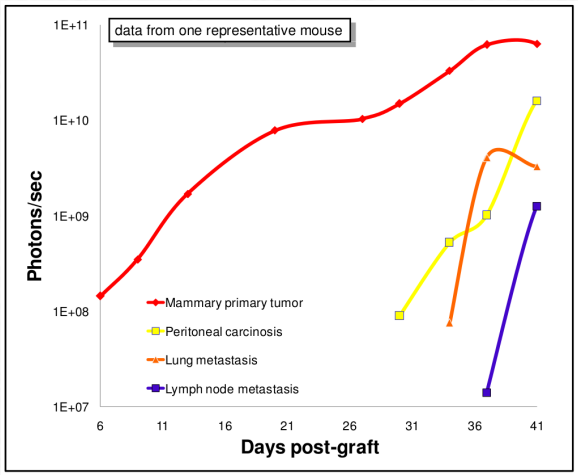
  ⇝ 3D reconstruction of the main tumor and the metastases (IVIS Sectrum. Living Image 4.2).

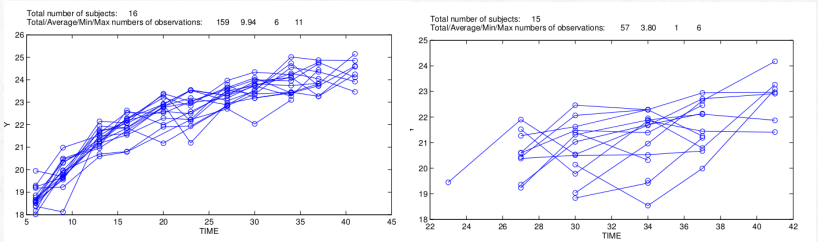
Second example : metastase spreading

J. Ciccolini, S. Mollard (CRO2)

Comparison with the model

- 16 mice with few data per mouse. Total amount of observations : 166.

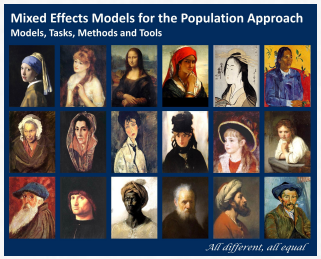




Primary Tumor Metastases

Strategy to identify a, b, x_0, m, α

- Use of Stochastic algorithm of Expectation-Maximization proposed Monolix tools (SAEM algorithm).



Second example : metastase spreading

Extension of the Iwata & al. model

$$\begin{cases} \frac{\partial}{\partial t}\rho(t,x) + \frac{\partial}{\partial x}[g_m(x)\rho(t,x)] = 0, \ x \in [1,b), \ t \geq 0 \\ g_m(1)\rho(t,1) = \int_1^b \beta(x)\rho(t,x)dx \ + \ \beta(x_p(t)) \\ \rho(0,x) = 0, \end{cases}$$

with

$$x_p' = g_p(x_p)$$

where g_p and g_m are one of the classical growth speed :

Gompertz model (1825)	$g(x) = ax \ln\left(\frac{b}{x}\right)$
Logistic model (1838)	$g(x) = ax\left(1 - \frac{x}{K}\right)$
Von Bertalanffy (1949)	$g(x) = ax\left(x^{-\frac{1}{3}} - c\right)$
West& al (1997)	$g(x) = ax\left(x^{-\frac{1}{4}} - d\right)$

Second example : metastase spreading

Conclusions

- The logical model is rejected by statistical tests.
- Overestimation the value of x_0 due to a poor estimate of the initial growth speed.

⟹ An hybrid model is necessary !

- Gomp-exp model $g_p(x) = \min\left(a_{invitro}, ax \ln\left(\frac{b}{x}\right)\right)$
- West-exp model $g_p(x) = \min\left(a_{invitro}, ax\left(\left(\frac{x}{b}\right)^{-\frac{1}{4}} - 1\right)\right)$

- The parameter $a_{invitro}$ is evaluated *in vitro* !
- The new estimated sizes x_0 correspond to a 40-50% loss of cells after the graft that sounds reasonnable.
- In peritoneum, for most the mice, we observed two secondary tumoral mass. We proved that their growth can not be explain by the classical ODE models. That enforced the utility of such a metastases model.
- The estimated growth rate a_m in metastases differs from a_p.

Second example : metastase spreading

Metastases and chemotherapy

Verga PhD 2010

A tumor growth = ODE system : gompertz's law extended

$$x'(t) = G(t,x) := ax \ln\left(\frac{b}{x}\right) - xC_{chemo}(t)$$

where C_{chemo} resumes the PK/PD of the chemotherapeutic agent.

Metastases = a new transport equation

$\rho(t,x)$ density of metastases at time t of size x.

$$\partial_t \rho + \partial_x \left(G(t,x)\rho\right)\ t > 0,\ x \geq 1$$

Emission of metastases seen as a boundary layer : Birth law

$$G(1,t)\rho(t,1) = \underbrace{mx_p(t)^\alpha}_{\text{Emission by the primary tumor}} + \underbrace{\int_1^b mx^\alpha \rho(t,x)\,dx}_{\text{emission by the metastases}} \quad t > 0$$

$\rightsquigarrow$ Individualization of protocoles, taking into account metastases

Second example : metastase spreading

Combined anti-angiogenesis/chemotherapy I Hahnfeldt & al (1999), Benzekry & al (2012)

Tumor growth : Hahnfeldt & al model

$$\begin{aligned}\frac{dx}{dt} &= ax\ln\left(\frac{\theta}{x}\right) - \mathcal{F}(x)\mathcal{R}_1(c_{chemo}(t)) \\ \frac{d\theta}{dt} &= \mathcal{R}_2(c_{angio}(t))x - d\theta x^{\frac{2}{3}} - \gamma\theta\mathcal{R}(c_{angio}(t))\end{aligned}$$

- Chemotherapy acts on the tumor size.
- Antiangiogenic drugs acts on the carrying capacity.
  - Reduction of the growth velocity.
  - Possible stimulation at the beginning reflecting the normalization of the tumor.

Ebos & al. Cancer cell (2009)

Metastases growth = A transport equation

$\rho(t, x, \theta)$ density of metastases at time t with a feature $X = (x, \theta)$.

$$\partial_t \rho + \operatorname{div}\left(G(t, X)\rho\right), \ t > 0, \ X \in \Omega$$

...

Second example : metastase spreading

Extension to general emission

$$
\begin{aligned}
\frac{\partial}{\partial t}\rho(t,x) \quad + \quad & \frac{\partial}{\partial x}[g_m(x)\rho(t,x)] = k(x,x_p(t)) \\
& + \int_x^{+\infty} k(x,y)\rho(t,y)\,dy - \rho(t,x)\int_0^x k(y,x)\,dy \\
\rho(t,1) \quad = \quad & 0 \\
\rho(0,x) \quad = \quad & 0, \\
x_p'(t) \quad = \quad & g_p(x_p(t))
\end{aligned}
$$

- $k(x,y)$ probability for a tumor of size x to emmit a metastase of size y.

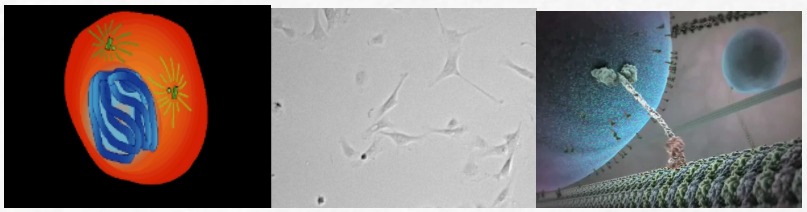
Schlicke, 2018. Hubert, Tournus 2018

Outline of the talk

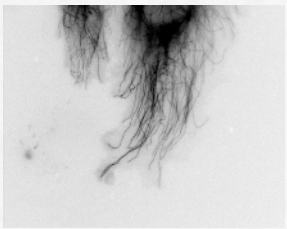
Microtubules targeting agent

A therapeutic target in oncology

- MTs play a crucial role in
  - **cell division**
  - **cell migration**
  - **intracellular transport**



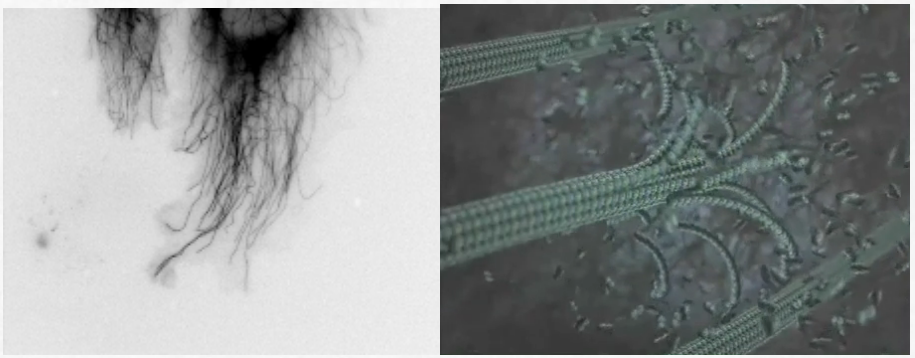
- MTs are a favorite target of **Microtubule Targeting Agents (MTAs)**
- **MTAs** (taxanes, vinca alkaloids) are successfully used as **antimitotic and antiangiogenic agent** in cancer treatments but also in neurodegenerative diseases.
- MTs are **highly dynamic**.
  - The dynamics is complex
  - The dynamics is mandatory to cell division and cell migration.



Microtubule targetting agent

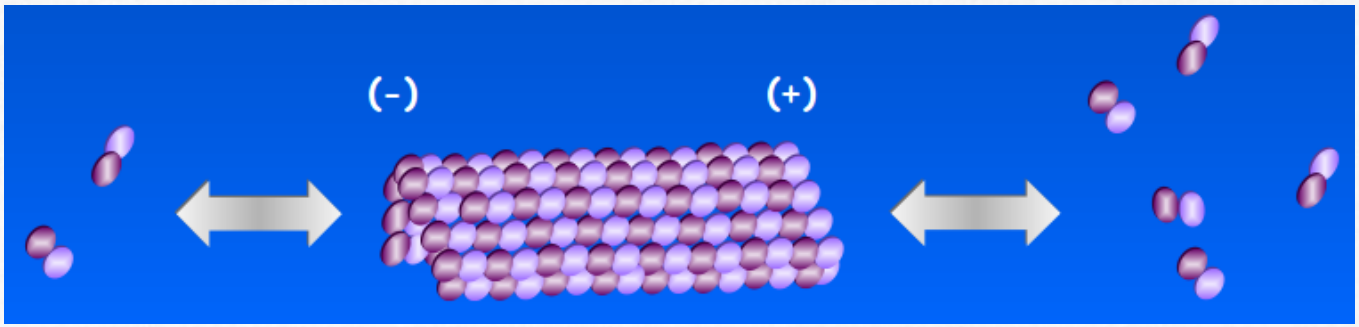
MT in the cell

- MTs are part of the cytosqueleton.
- MTs are caracterized by their instabilities.

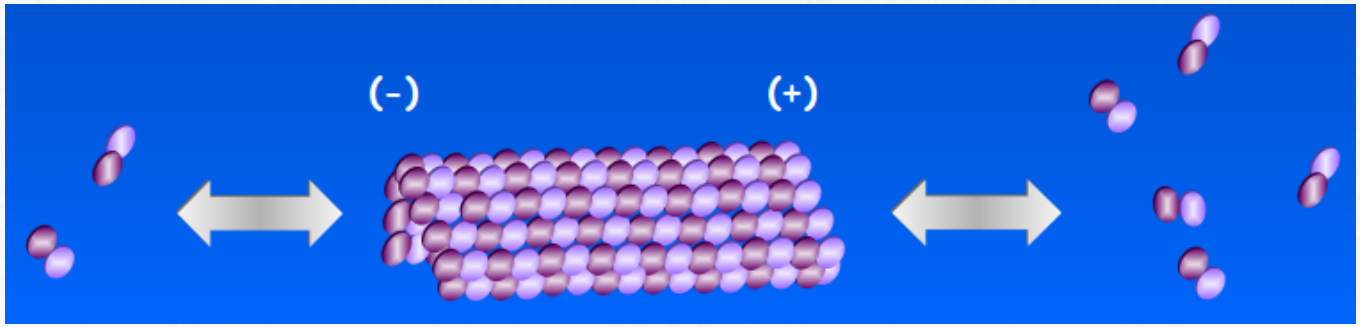


Protein structure

- Each MT is a long (up to 50μm) hollow cylinder of 25nm diameter built from about 13 protofilaments.
- Each protofilament is composed by an assembly of $\alpha|\beta$ tubulin dimers.
- The assembly is polarized with different dynamics at the + end or - end.



Microtubule targetting agent

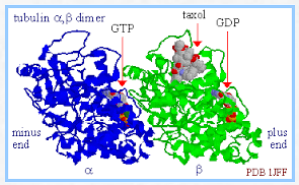


MT structure

- Each MT is a long (up to 50μm) hollow cylinder of 25nm diameter built from about 13 protofilaments.
- Each protofilament is composed by an assembly of $\alpha|\beta$ tubulin dimers.
- The assembly is polarized with different dynamics at the + end or - end.
  - + End (tubulin β) : highly dynamic
  - − End (tubulin α) : link to centrosome in cells

Energetic structure of the dimers

- Dimers can be in two energy states :
  - GTP : Guanosine **tri**phosphate - active form
  - GDP : Guanosine **di**phosphate - inactive form



Microtubule targeting agent

Different state of the dimers

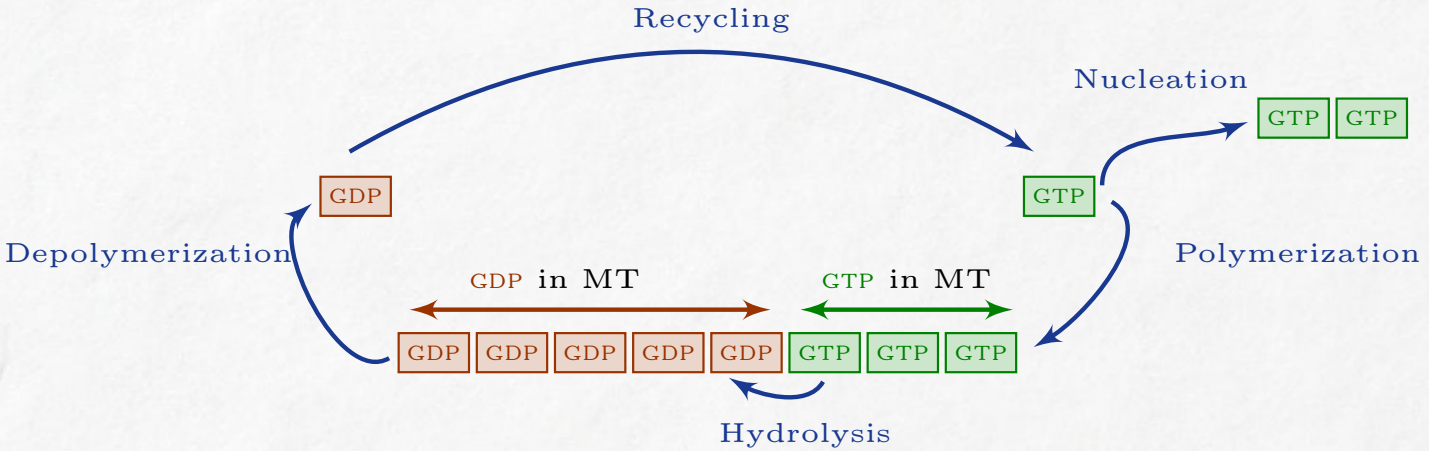
	Polymerized	Non polymerized
Active form	GTP polymerized in MTs	Free GTP
Inactive form	GDP polymerized in MTs	Free GDP

Stabilizing GTP -cap

Thanks to EB-GFP fluorescent proteins that bind to GTP-tubulin, are observed

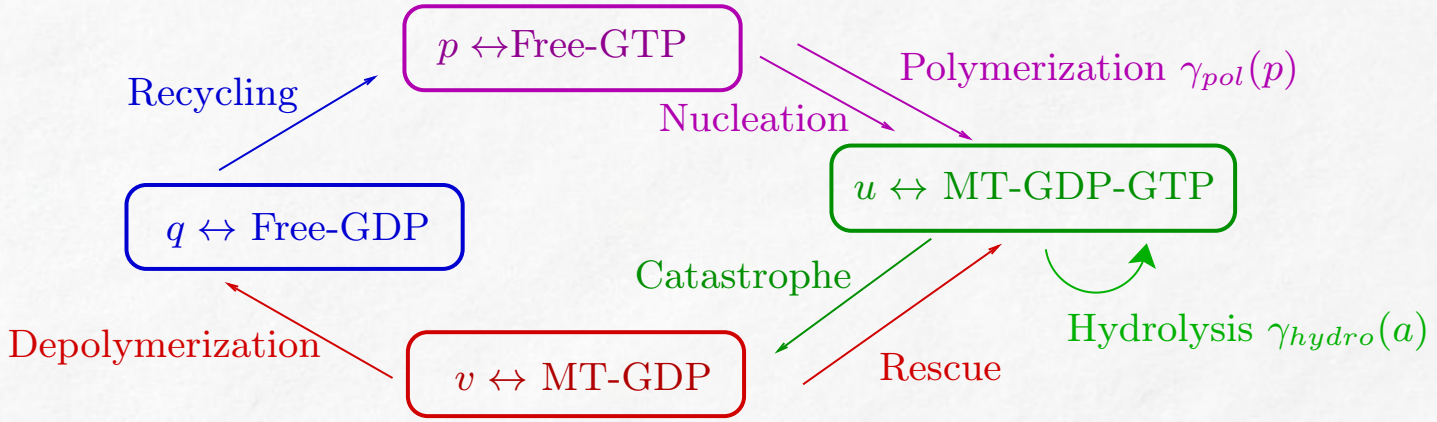
- A GTP-stabilizing cap
- The disparition of the cap at the catastrophe

Main reactions



Microtubule targeting agent

A. Barlukova PhD 2016



MTs in polymerization

1. $u(t, a, z, x)$ density of MT in polymerization
   - t time, a age, x length, z length of the cap.
2. $v(t, a, x)$ density of the population of MT in depolymerization
   - t time, a age, x length.
3. $p = p(t)$ Free GTP tubulin
   $\rightsquigarrow$ t time.
4. $q = q(t)$ Free GDP tubulin
   $\rightsquigarrow$ t time.

Microtubule targeting agent

A. Barlukova PhD 2016

Balance equation for MT in Polymerization u

$$\partial_t u + (\underbrace{\gamma_{pol}(p(t))}_{\text{Polymerization}} - \underbrace{\gamma_{hydro}(a)}_{\text{Hydrolysis}})\partial_z u + \underbrace{\gamma_{pol}(p(t))}_{\text{Polymerization}} \partial_x u + \partial_a u = 0$$

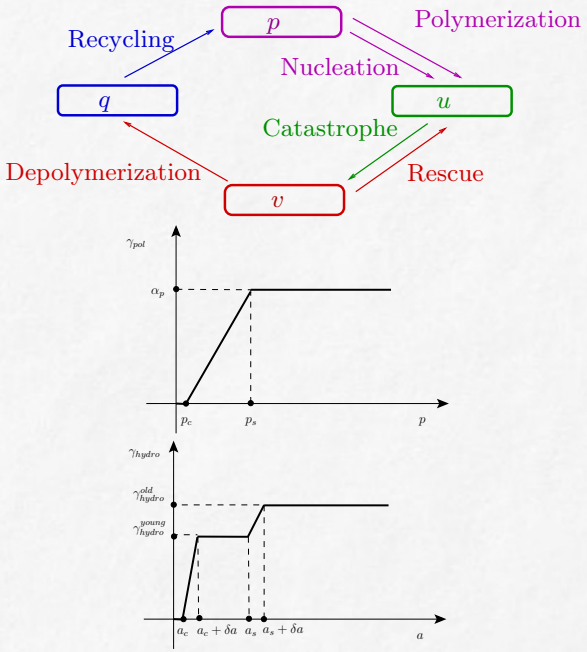
Boundary conditions for u

- **Nucleation**,

$$u(t, a, x, x) = \psi(x)\Psi(a)\mathcal{N}(p(t)).$$

- **Rescue event**, if
  $\gamma_{pol}(p(t)) - \gamma_{hydro}(a) > 0$

$$v \quad \Rightarrow \quad u$$



Microtubule targeting agent

A. Barlukova PhD 2016

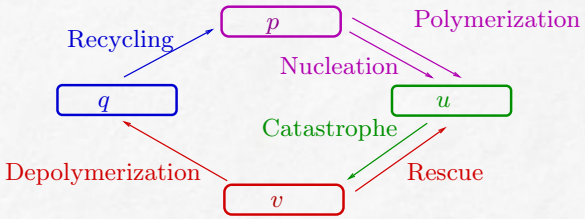
Equation for MT in depolymerization v

$$\partial_t v \underbrace{-\gamma_{depol}\partial_x v}_{\text{Depolymerization}} + \partial_a u = I_{u\to v} - I_{v\to u}$$

where

$I_{v\to u}$: Rescue event

$I_{u\to v}$: Catastrophe event



Microtubule targeting agent

A. Barlukova PhD 2016

Equation for free GTP p

$$\frac{d}{dt}p = \underbrace{-\gamma_{pol}(p(t)) \int_0^\infty \int_0^x \int_0^\infty u(t,a,z,x)\, da dz dx}_{\text{Polymerization}} + \underbrace{\kappa q}_{\text{Recycling}} \underbrace{-\mu \mathcal{N}(p)}_{\text{Nucleation}}$$

Equation for free GDP q

$$\frac{d}{dt}q = \underbrace{\gamma_{depol} \int_0^\infty \int_0^\infty v(t,a,x)\, da\, dx}_{\text{Depolymerization}} \underbrace{-\kappa q}_{\text{Recycling}}$$

Microtubule targeting agent

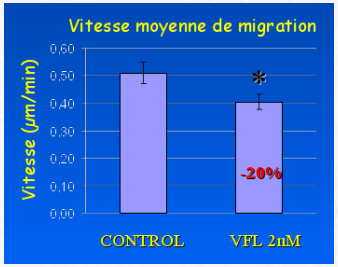
Output of the model concerning MTA

- Small delay in the hydrolysis may explain the comportment at low doses !

MTAs and migration

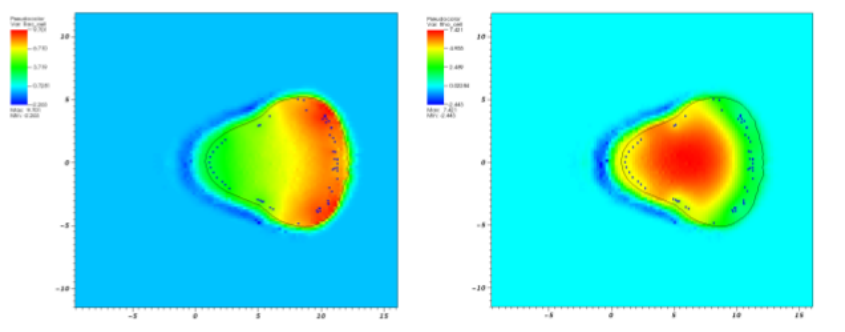
- MTAs reduce endothelial migration even at non-cytotoxic concentration.

$\Rightarrow$ Antiangiogenic effect at low dose.



Pourroy & al 2006

For more informations on MT and migration - see R.Tesson



Conclusions

Winter 2020. Residential month on mathematical issues in biology

Coordinators : F.Hamel, F. Hubert, E. Pardoux, P. Pudlo (I2M)

- **Week 1 : February 3-7** Winter School *PDE and probability for biology*
  - **OC.** G. Chapuisat, B. Cloez C. Henderson, P. Pudlo, G. Raoul
- **Week 2 : February 10-14** Workshop on *Mathematical issues of evolutionary biology*
  - **OC.** N. Champagnat, J. Coville, R. Gomulkiewicz, F. Hamel, L. Roques
- **Week 3 : February 17-21** Workshop on *Mathematical modeling and statistical analysis of infectious disease outbreaks*
  - **OC.** T. Britton, E. Pardoux
- **Week 4 : February 24-28** Workshop on *Mathematical issues of complex systems in biology and medecine*
  - **OC.** M. Cristofol, J.- M Freyermuth, C. Gomez, F. Hubert, S. Ryan, M. Tournus
- **Week 5 : March 2-6** Winter school on *Networks and molecular biology*
  - **OC.** A. Baudot, B. Mossé, E. Remy, L. Tichit, M. Vignes

Website : https ://mathsbiomonth.sciencesconf.org

Conclusions

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4

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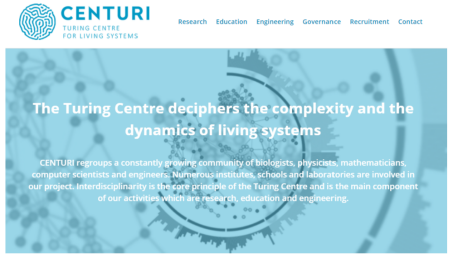

http://centuri-livingsystems.org

Calls

Postdoc

- **Interdisciplinary** projects
- **20 recruitments** between 2017 and 2025
- 1 call **every year**

6

CENTURI Graduate School

PhD programme

- **> 80 Fellowships** (between 2017 and 2025)
- Students involved in **interdisciplinary research projects**
- PhD students mentored by **2 supervisors** coming from a wet and a dry lab
- **Dedicated trainings** (image analysis, statistics, paper writing, etc.)

10

Conclusions

Thank you for your attention !