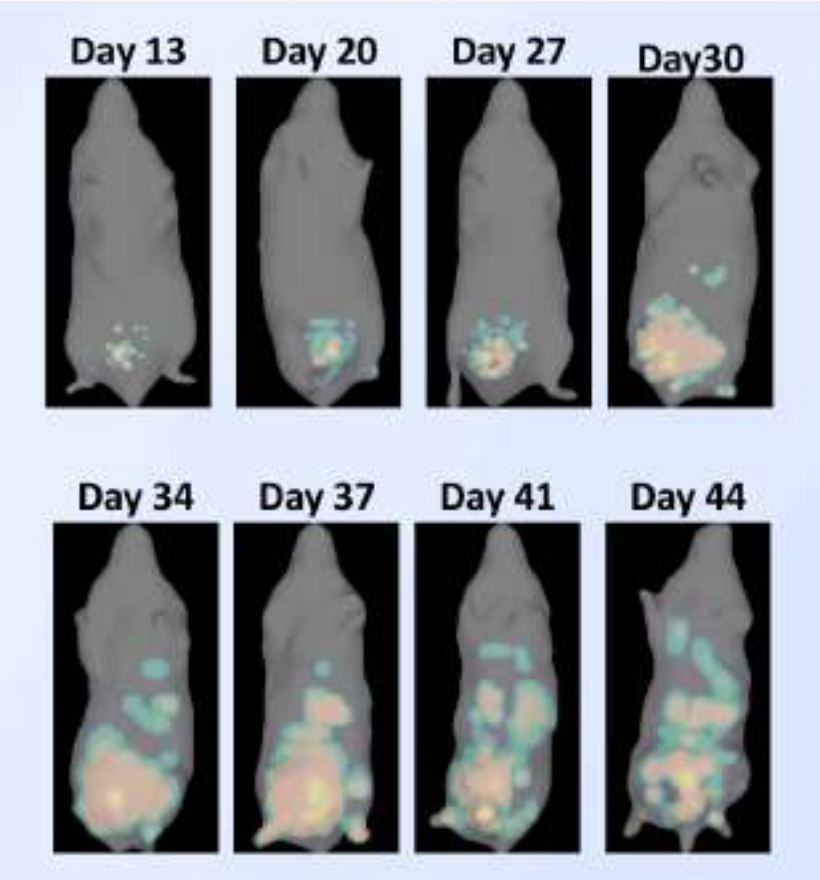
Some mathematical models of tumor growth and metastatic spreading

Florence Hubert

HTE workshop
November, 14th 2018

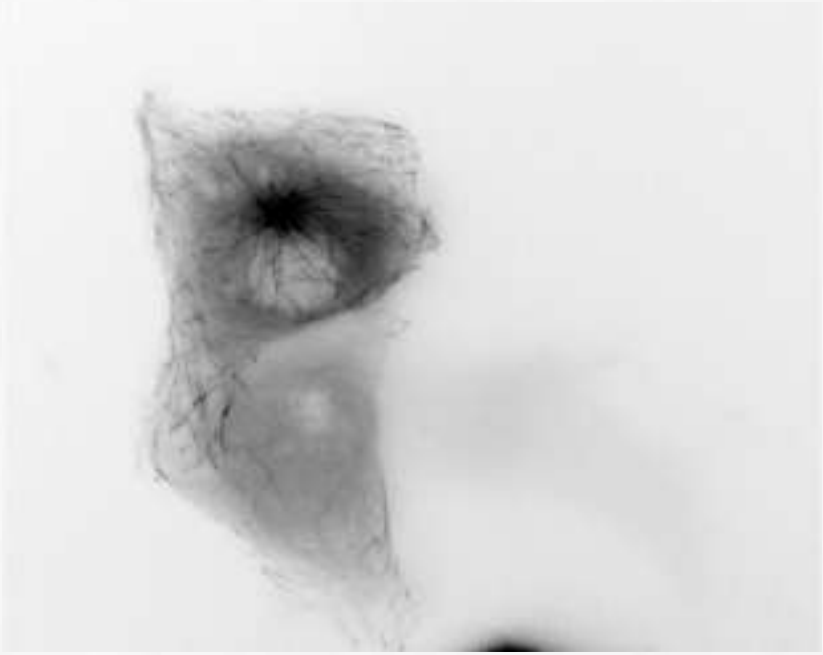
Transport equations in oncology

A large variety of applications



Body scale

Metastatic state of a patient



Intra-cellular scale

Microtubules : an important target in oncology

Outline of the talk

Outline

Von Foerster equation

The most simplest model of cells' growth Assume that a population of cell increase at a constant rate B, then the time evolution of the number of cells $Y(t)$ is given by $Y'(t) = BY(t)$.

If cell division rate depends on age's cell

- $\rho(t,a)$ density of tumor cells at time t of age a, $Y(t) = \int_0^{+\infty} \rho(t,a)\,da$.
- $B(a)$ 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 $t+dt$.
- A tumor cell of size a can divide into two cells of age 0.

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

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

McKendrick-vonFoerster equation

Extensions of Von Foerster equation

To take into 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 $t+dt$.

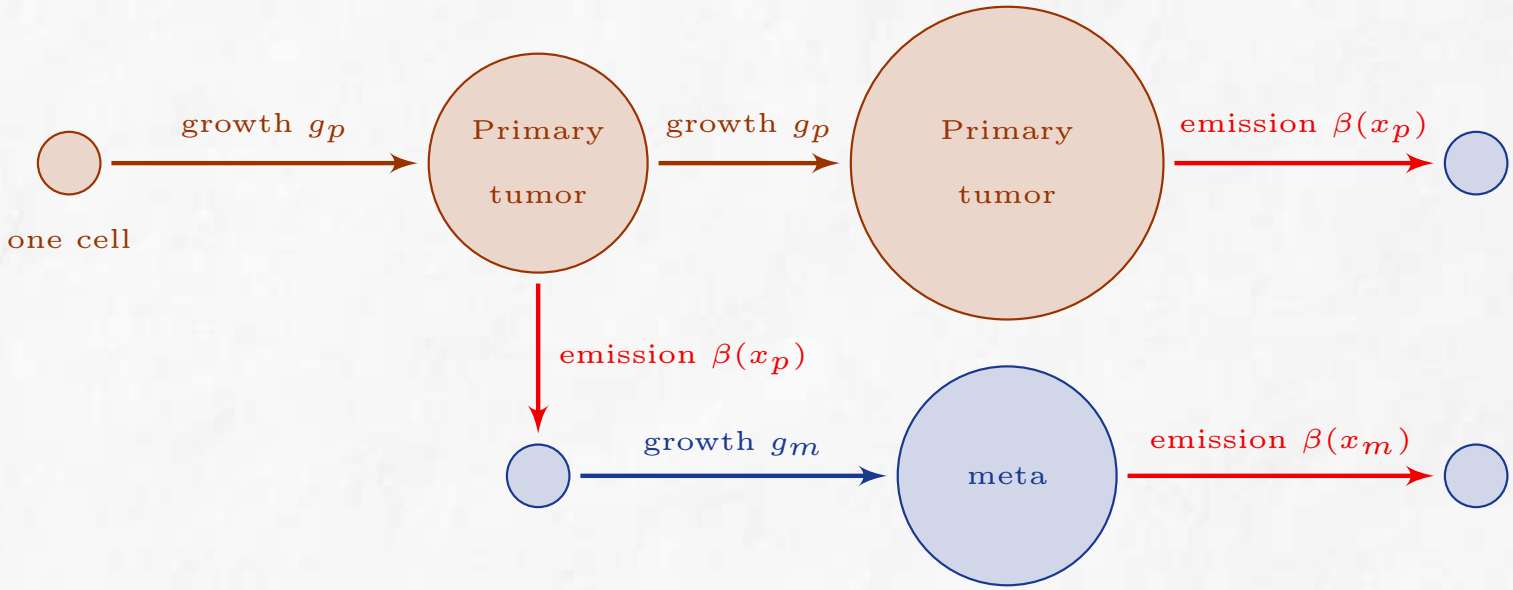
$\rightsquigarrow$ Extensions to account the immune system (Atsou, Goudon 2018).

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

where $I(t)$ describes the impact of the immune system.

Outline

Structure of the metastatic spreading model



- The primary tumor with a feature x_p grows at speed $g_p(x_p)$
- The primary tumor emits at any time metastases at a rate $\beta(x_p)$
- Each metastase with a feature x_m grows at speed $g_m(x_m)$
- Each metastase emits at any time metastases at a rate $\beta(x_m)$

The simplest tumor growth models

1766-1834

A tumor can be seen as a population of cancer cells

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 in competition for resources !

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

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

Impact of a chemotherapy

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

Vascular tumor growth models

An 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)

Vascular tumor growth models

An 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)

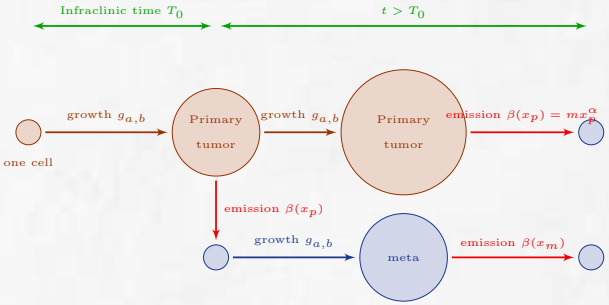
Model of metastatic spreading

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

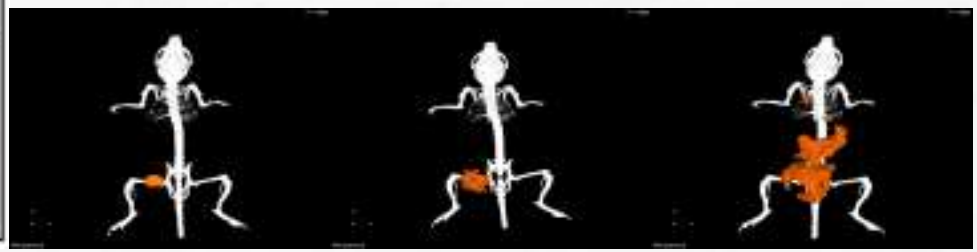
Validation of the metastatic spreading model

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).

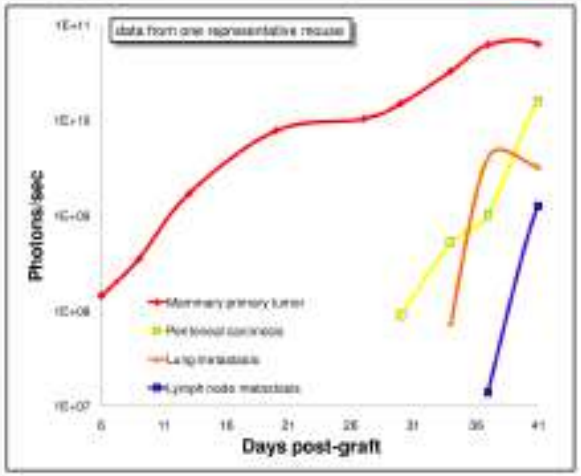


Validation of the metastatic spreading model

J. Ciccolini, S. Mollard (CRO2)

Comparison with the model

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



Strategy to identify a, b, x_0, m, α

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

Validation of the metastatic spreading model

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)	$g(x) = ax\left(x^{-\frac{1}{4}} - d\right)$

Validation of the metastatic spreading model

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 metastase model.
- The estimated growth rate a_m in metastases differs from a_p.

Metastatic spreading and anti-cancer drugs

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

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

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

Metastatic spreading and anticancer drugs

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 $X=(x,\theta)$.

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

Obtention of an optimal delay between the administration of the 2 drugs

Benzekry et al. 2017

Metastatic spreading - to go further

Extend the model to more general emission

$$\begin{aligned}
\frac{\partial}{\partial t}\rho(t,x) \quad + \quad & \frac{\partial}{\partial x}[g_m(x)\rho(t,x)] = k(x,x_p(t)) \\
& +2\int_x^{+\infty} k(x,y)\rho(t,y)\,dy - \rho(t,x)\int_0^x k(y,x)\,dy \\
\rho(t,0) \quad = \quad & 0,\ \rho(0,x) = 0, \\
x_p'(t) \quad = \quad & g_p(x_p(t))
\end{aligned}$$

- Calibration thanks to CTC informations, thanks to heterogeneity indicators on the primary tumor.

Schlicke, 2018. Hubert, Rat, Tournus 2018

Extend the model to take into account tumor heterogeneity

- Resistance to chemotherapy
- Immune system

Outline

Dynamic instabilities of Microtubules (MT)

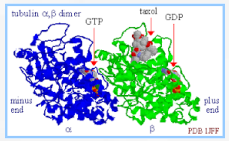
MT : a therapeutic target in oncology

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

- MTs are a 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**.

Protein structure

- Each MT is a long (up to 50μm) hollow cylinder of 25nm diameter built from about 13 protofilaments.
- Each protofilament is an assembly of $\alpha|\beta$ tubulin dimers.
- The assembly is polarized with different dynamics at the $_{+/-}$ end.
- Dimers can be in two energy states : GTP /GDP



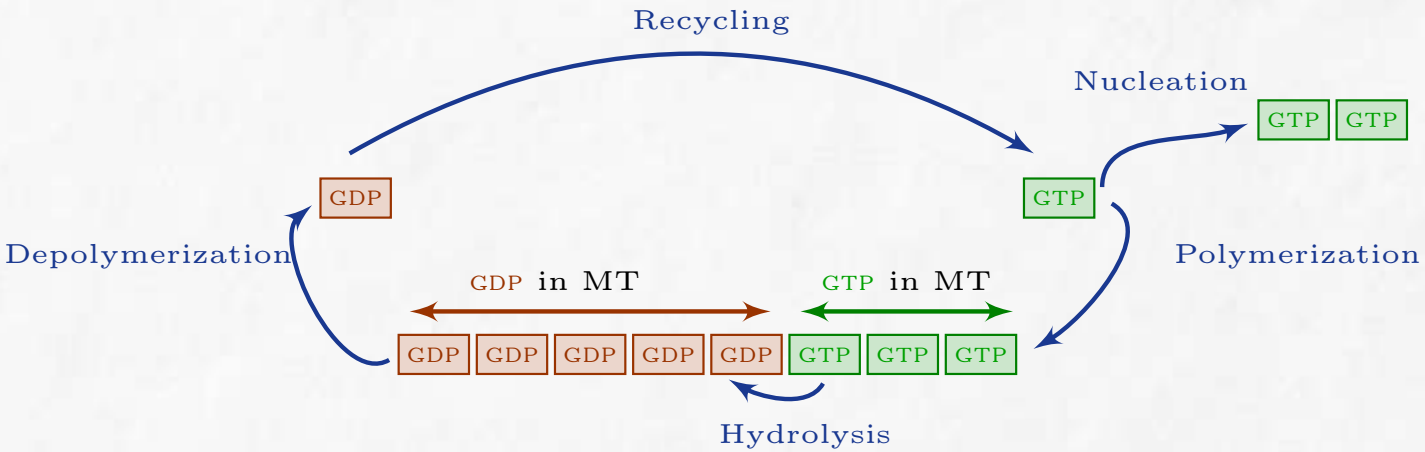
A model of MT dynamic instabilities

work with S. Honoré, M. Tournus, D. White, Bull Math Biol 2018

Different state of the dimers

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

Main reactions



$\rightsquigarrow$ Alternance between growing events and shrinking events.

A model of MT dynamic instabilities

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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 shrinking events

Structure of the model

- $(t, x) \mapsto u(t, x)$ density of MT at time t of size x
- $t \mapsto p(t)$ time evolution of free GTP
- $t \mapsto q(t)$ time evolution of free GDP

We introduce a threshold $\rightsquigarrow p_h$

- $p < p_h \quad \Rightarrow$ period of shrinking

A model of MT dynamic instabilities

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Equation for u

$$\partial_t u + \gamma_{pol}(p(t))\partial_x u = \psi(x)\mathcal{N}(p(t))$$
$$+(p(t) < p_h)\beta \left(- \int_0^x k(x,\tilde{x})u(t,x)\, d\tilde{x} + \int_x^\infty k(\tilde{x},x)u(t,\tilde{x})\, d\tilde{x} \right)$$

Equation for p

$$\frac{d}{dt}p = -\gamma_{pol}(p(t)) \int_0^\infty \int_0^x u(t,z,x)\, dzdx + \kappa q - \mu p^2$$

Equation for q

$$\frac{d}{dt}q = (p(t) < p_h)\beta \int_0^\infty \int_0^x (x-\tilde{x})k(x,\tilde{x})u(t,x)\, d\tilde{x}\, dx - \kappa q$$

Global existence and uniqueness of a solution to the system

A model of MT dynamic instabilities

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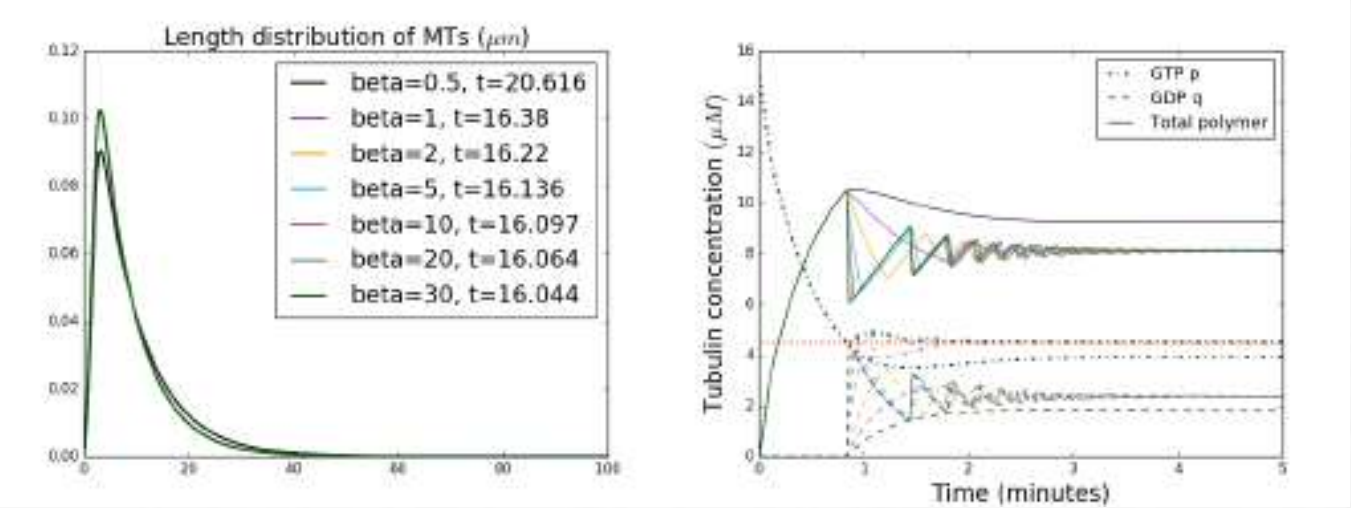
Towards a MTA effect - case $k(x, \tilde{x}) = \frac{1}{\sigma\sqrt{2\pi}} \exp \frac{-(\tilde{x}-x_1)^2}{2\sigma^2}$



Asymptotics for $\beta \in [0.5, 30]$, $x_1 = 1.6$

A model of MT dynamic instabilities

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Analysis of oscillations in the case $k(x,\tilde{x}) = \delta_{\tilde{x}=x_1}$

The macroscopic behaviour of the system reduces to an ODE system

$$\begin{aligned} U'(t) &= \mu H(p(t), p_N) p(t)^2 I_\xi, \\ p'(t) &= -\gamma(p(t))U(t) + \kappa q(t) - \mu H(p(t), p_N) p(t)^2, \\ q'(t) &= -\kappa q(t) + \beta(1 - H(p(t), p_h))\,(M_0 + p_0 + q_0 - p(t) - q(t) - x_1 U(t)), \\ & U(0) = U_0, \quad p(0) = p_0, \quad q(0) = q_0 \geq 0. \end{aligned}$$

with

- $U(t) = \int_0^\infty u(x,t)dx$, $M(t) = \int_0^\infty x u(x,t)dx$.
- $H(p,z)$ approx of the Heaviside function
- $p_c \ll p_h \ll p_N$

Equilibrium

Without loss of generality, we can assume that $\mu = 0 \Rightarrow U(t) = U_0$

Let $M_0, p_0, q_0, x_1 \geq 0$ and $U_0 > 0$, the system admits a unique equilibrium (p^*, q^*) which is stable with oscillations for a range of p^* that can be explicited

Models of MTAs

A more complex model to understand

- a vincristin effect

  Phd work of A. Barlukova

- the synergy of MTAs and EB proteins — Post-doct work of D. White
- the impact of MTAs on migration (anti-angiogenic effect at low doses) — Phd thesis of R. Tesson

Advertissement

February 3-March 6, 2020 in CIRM Marseille.

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Thank you for your attention !