Structured population models and growth fragmentation models arising in biology

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Motivation I: Metastatic spreading

Metastases: a major cause of death in cancer

- Metastatic state of the patient is often difficult to evaluate, as micro-tumors are hardly detectable from imagery.

Questions

- Can we design a new “in silico” metastatic index?
- Can we infer the metastatic aggressivity from biomarkers?

Mathematic tools

- **McKendrick-Von Foerster equation** for a simple emission
- **Growth-fragmentation equation** for general emission

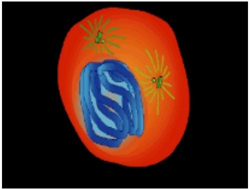
Motivation II: Microtubules

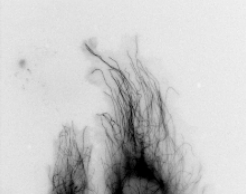
Microtubules: a therapeutic target in oncology

- MTs play a crucial role in **cell division**, in **cell migration**

⇝ MTs are a favorite target of **Microtubule Targeting Agents (MTAs)**, successfully used as **antimitotic** more recently as antiangiogenic agent or antimigratory agent in cancer treatments.

- MTs are **polymers highly dynamic**.





Questions

- Can we model the effect of MTAs on the MT dynamical instabilities?
- Can we better understand the low dose effect of MTAs?

Mathematical tools

- Complex models using **Growth-fragmentation equations**

McKendrick-Von Foerster vs growth-fragmentation eq.

Perthame, Transport equation in biology, 2006

McKendrick-Von Foerster equation

$$\begin{cases} \frac{\partial \rho}{\partial t} + \frac{\partial}{\partial x}(g(x)\rho) = -D(x)\rho(t,x),\ t>0,\ x>0 \\ \rho(t,0) = \int_0^\infty B(y)\,\rho(t,y)\,dy,\ t>0 \\ \rho(0,x) = \rho_0(x),\ x>0 \end{cases}$$

Typically, ρ is the density of a population structured by the age x and g is the growth rate in x, B is the birth rate and D the death rate. In the case where x is the age a, $(g(a)=1)$, the equation is also called the renewal equation.

Growth-fragmentation equation

$$\begin{cases} \frac{\partial \rho}{\partial t} + \frac{\partial}{\partial x}(g(x)\rho) = -B(x)\rho(t,x) + \int_0^\infty B(y)k(x,y)\rho(t,y)\,dy,\ t>0,\ x>0 \\ \rho(t,0) = 0,\ t>0 \\ \rho(0,x) = \rho_0(x),\ x>0 \end{cases}$$

Typically, ρ is the density of a cell population structured by its size x and B is the division rate and $k(x,y)$ is the probability that the division of a cell of size y leads to a cell of size x.

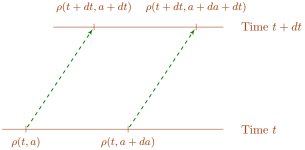
Outline

Outline

Perthame, Transport equation in Biology

Death neglected

$$(*)\begin{cases}\dfrac{\partial\rho}{\partial t}+\dfrac{\partial\rho}{\partial a}=0,\ t>0,\ a>0\\ \rho(t,0)=\int_0^\infty B(y)\,\rho(t,y)\,dy,\ t>0\\ \rho(0,a)=\rho_0(a),\ a>0\end{cases}$$



$$\int_{a+dt}^{a+da+dt}\rho(t+dt,a')\,da'=\int_a^{a+da}\rho(t,a')\,da'$$
$$\Downarrow$$
$$da\,\rho(t+dt,a+dt)\sim da\,\rho(t,a)$$
$$\Downarrow$$
$$da\,dt\ (\partial_t\rho(t,a)+\partial_a\rho(t,a))\sim 0$$

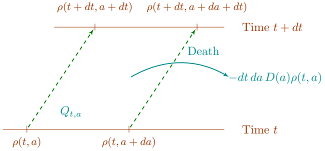
- $\rho(t,a)$ density at time t with an age a
- $B(a)$ is the birth rate

Population structured by age

Perthame, Transport equation in Biology

with a death term

$$(*) \begin{cases} \frac{\partial \rho}{\partial t} + \frac{\partial \rho}{\partial a} = -D(a)\rho(t,a),\ t > 0,\ a > 0 \\ \rho(t,0) = \int_0^\infty B(y)\,\rho(t,y)\,dy,\ t > 0 \\ \rho(0,a) = \rho_0(a),\ a > 0 \end{cases}$$



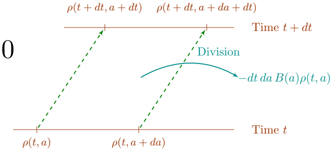
$$\int_{a+dt}^{a+da+dt} \rho(t+dt,a')\,da' = \int_a^{a+da} \rho(t,a')\,da' - \int_{Q_{t,a}} D(a')\rho(s,a')\,da'\,ds$$
$$\Downarrow$$
$$da\,\rho(t+dt,a+dt) \sim da\rho(t,a) - da\,dt\,D(a)\rho(s,a)$$
$$\Downarrow$$
$$da\,dt\,\left(\partial_t\rho(t,a) + \partial_a\rho(t,a)\right) \sim -da\,dt\,D(a)\rho(s,a)$$

- $\rho(t,a)$ density at time t with an age a
- $B(a)$ is the birth rate
- $D(a)$ is the death rate

Mitosis - structuration by age

Population of cells structured by age that divide at a rate B giving 2 cells of age 0.

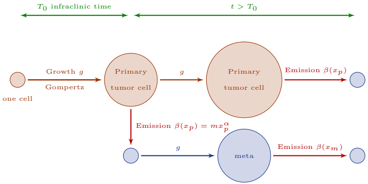
$$(**)\begin{cases} \frac{\partial \rho}{\partial t} + \frac{\partial \rho}{\partial a} = -B(a)\rho(t,a),\ t>0,\ a>0 \\ \rho(t,0) = 2\int_0^\infty B(y)\,\rho(t,y)\,dy,\ t>0 \\ \rho(0,a) = \rho_0(a),\ a>0 \end{cases}$$

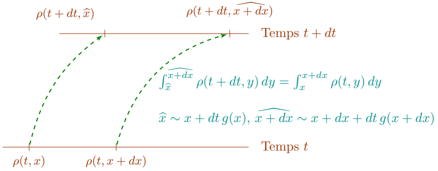


- $\rho(t,a)$ density at time t with an age a
- $B(a)$ is the division rate

The original model of metastases

Iwata & al (2000)





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

A transport equation for the growth of metastases

$$\partial_t \rho(t,x) + \partial_x (g(x)\rho(t,x)) = 0,\ t > 0,\ x > 1$$

A boundary condition for the emission

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

Growth law

$$x_p' = g(x_p) \text{ with } g(x) = ax \ln\left(\frac{b}{x}\right) \rightsquigarrow \text{ Gompertz law}$$

Mitosis - structuration by size

$$\begin{cases} \partial_t \rho + \partial_x (g(x)\rho) = -B(x)\rho(t,x) + \int_x^{+\infty} B(y)k(x,y)\rho(t,y)\,dy, \\ \rho(t,0) = 0,\ \rho(0,x) = \rho_0(x) \end{cases}$$

Properties of the kernel

- No fragmentation to a bigger size: $k(x,y) = 0$ if $x > y$
- Conservation of the total size: $\int_0^y xk(x,y)\,dx = y$
- For division into a fixed number p of pieces: $\int_0^y k(x,y)\,dx = p$

Classical examples

- Division into 2 cells of equal size - equal mitosis

$$\begin{cases} \partial_t \rho + \partial_x (g(x)\rho) = -B(x)\rho(t,x) + 4B(2x)\rho(t,2x),\ x > 0,\ t > 0, \\ \rho(t,0) = 0,\ \rho(0,x) = \rho_0(x) \end{cases}$$

with $k(x,y) = 2\delta_{x=\frac{y}{2}}$, so that $\int_0^y k(x,y)\,dy = 2$.

- Division into 2 cells with different sizes

$$\begin{cases} \partial_t \rho + \partial_x (g(x)\rho) = -B(x)\rho(t,x) + 2\int_x^{+\infty} B(y)\kappa(x,y)\rho(t,y)\,dy, \\ \rho(t,0) = 0,\ \rho(0,x) = \rho_0(x) \end{cases}$$

here $k(x,y) = 2\kappa(x,y)$

Mitosis - structuration by size

$$\begin{cases} \partial_t \rho + \partial_x (g(x)\rho) = -B(x)\rho(t,x) + \int_x^{+\infty} B(y)k(x,y)\rho(t,y)\,dy, \\ \rho(t,0) = 0,\ \rho(0,x) = \rho_0(x) \end{cases}$$

Properties of the kernel

- No fragmentation to a bigger size: $k(x,y) = 0$ if $x > y$
- Conservation of the total size: $\int_0^y xk(x,y)\,dx = y$
- For division into a fixed number p of pieces: $\int_0^y k(x,y)\,dx = p$

Classical examples

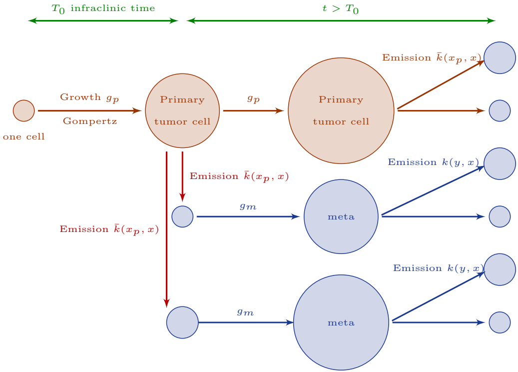
- Renewal equation: $k(x,y) = \frac{1}{2}(\delta(x=0) + \delta(x=y))$
- Autosimilar case: $k(x,y) = \frac{1}{y}\kappa_0\left(\frac{x}{y}\right)$ with $\int_0^1 s\kappa_0(s)\,ds = 1$.

  $\rightsquigarrow$ general mitosis: $\kappa_0 = \delta_r + \delta_{1-r}$, $r \in [0, \frac{1}{2}]$

  $\rightsquigarrow$ homogeneous fragmentation: $\kappa_0(s) = (1+\alpha)\left(s^\alpha + s^{1-\alpha}\right)$, $\alpha > -1$

General emission of metastases

Each tumor (primary or secondary) can emit several tumors of different size !



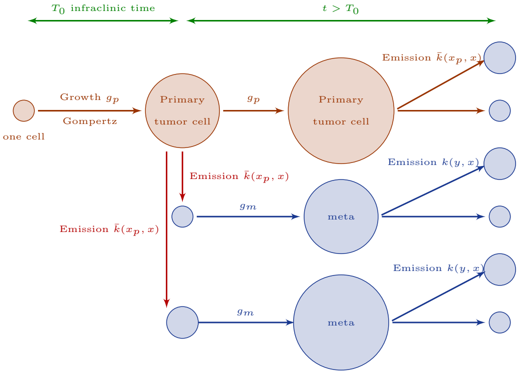
Caracterisation of the emission

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

$\rightsquigarrow$ a growth-fragmentation equation with source term

General emission of metastases

Each tumor (primary or secondary) can emit several tumors of different size !



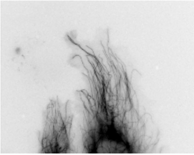
$$\frac{\partial}{\partial t}\rho(t,x) + \frac{\partial}{\partial x}[g_m(x)\rho(t,x)] = \bar{k}(x, x_p(t)) - \beta(x)\rho(t,x) + \int_x^{+\infty}\beta(y)k(x,y)\rho(t,y)\,dy$$

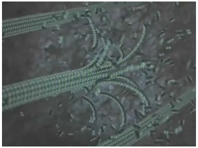
Few results on this equation and still open questions on this equation!

Microtubule dynamical instabilities

MT in the cell

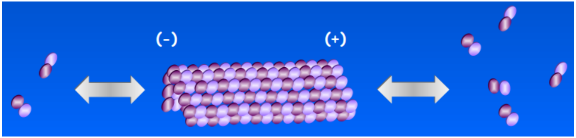
- MTs are part of the cytosqueleton.
- MTs are caracterized by their instabilities.





Protein structure

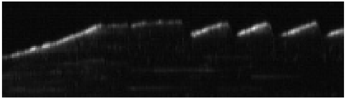
- Each MT is a long (up to 50μm) hollow cylinder of 25nm diameter built from about 13 protofilaments.
- Each protofilament is composed by an assembly of $\alpha|\beta$ tubulin dimers.
- The assembly is polarized with different dynamics at the + end (highly dynamic) or - end (fixed in cells).
- Dimers can be in two energy states :
  - GTP : Guanosine **tri**phosphate - active form
  - GDP : Guanosine **di**phosphate - inactive form



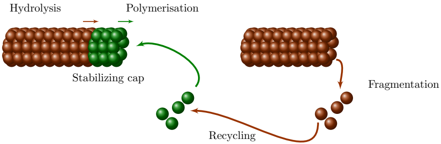
Dynamics of one MT at its + end

Dimers of tubulin

- Dimers can be in two energy states :
  - GTP : Guanosine **tri**phosphate - active form
  - GDP : Guanosine **di**phosphate - inactive form
- Dimers can be polymerized or not. In fine,
  - GTP polymerized in MTs
  - GDP polymerized in MTs
  - Free GTP
  - Free GDP
- Biological observations:
  - Existence of a GTP-stabilizing cap
  - Disparition of the cap at the catastrophe



- Four reactions



MTs dynamical instabilities

A structured population approach as in Hinow et al. (2009)

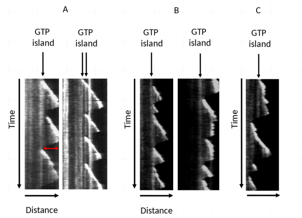
1. $u(t, z, x)$ density of MT in polymerisation
   - t time, x length, z length of the cap.
2. $v(t, x)$ density of the population of MT in depolymerisation
   - t time, x length.
3. $p = p(t)$ Free GTP tubulin
   - t time.
4. $q = q(t)$ Free GDP tubulin
   - t time.

$\rightsquigarrow$ Two transport equations (for both polymerisation and depolymerisation) coupled to two ODEs.

$\rightsquigarrow$ Several extensions

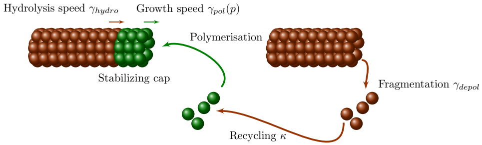
Barlukova PHD

New issue for the depolymerisation: $\rightsquigarrow$ fragmentation process



MTs dynamical instabilities

FH, M. Tournus, D. White, JTB (2017)



Equation for u

$$\partial_t u + \gamma_{pol}(p(t))\partial_x u + (\gamma_{pol}(p(t)) - \gamma_{hydro})\partial_z u = 0$$

Equation for v

$$\partial_t v = -R(t)u(t,0,x) + \gamma_{depol}\left(-\int_0^x k(x,\tilde{x})v(t,x)\,d\tilde{x} + \int_x^\infty k(\tilde{x},x)v(t,\tilde{x})\,d\tilde{x}\right)$$

Equation for p

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

Equation for q

$$\frac{d}{dt}q = \gamma_{depol}\int_0^\infty\int_0^x (x-\tilde{x})k(x,\tilde{x})v(t,x)\,d\tilde{x}\,dx - \kappa q$$

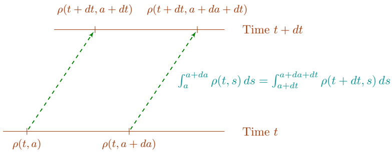
Outline

A population structured by age

Perthame, Transport equation in Biology

Death rate neglected

$$(*)\begin{cases}\frac{\partial\rho}{\partial t}+\frac{\partial\rho}{\partial a}=0,\ t>0,\ a>0\\ \rho(t,0)=\int_0^\infty B(y)\,\rho(t,y)\,dy,\ t>0\\ \rho(0,a)=\rho_0(a),\ a>0\end{cases}$$



- $\rho(t,a)$ density at time t with an age a
- $B(a)$ is the birth rate

Theorem

Assume that $B\in L^\infty(\mathbb{R}^+)$ with $B\geq 0$ and $1<\int_0^\infty B(y)\,dy$, then (*) admits a unique solution $\rho\in\mathcal{C}(\mathbb{R}^+;L^1(\mathbb{R}^+,\phi(x)dx))$ and if $|\rho_0(x)|\leq C_0N(x)$ then

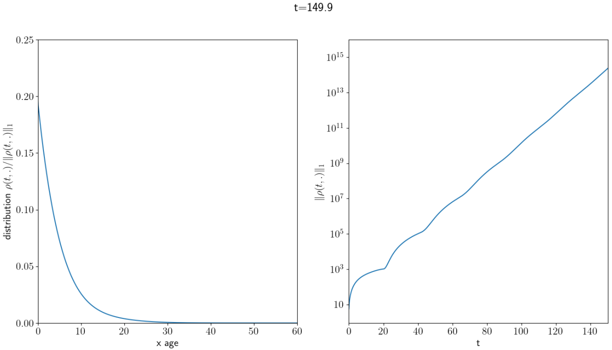
$$\int_0^\infty |e^{-\lambda_0 t}\rho(t,x)-\bar{\rho}_0N(x)|\phi(x)dx \underset{t\to\infty}{\longrightarrow} 0$$

where (λ_0,N,ϕ) are the eigenelements associated to the problem.

A population structured by age

Death rate neglected $\rightsquigarrow \rho(t,.) \sim e^{\lambda_0 t}\bar{\rho}_0 N(.)$

$$\frac{\partial \rho}{\partial t} + \frac{\partial \rho}{\partial a} = 0,\ \rho(t,0) = \int_0^\infty B(y)\,\rho(t,y)\,dy,\ \rho(0,a) = \rho_0(a)$$



A population structured by age

$$\frac{\partial \rho}{\partial t} + \frac{\partial \rho}{\partial a} = 0,\ \rho(t,0) = \int_0^\infty B(y)\,\rho(t,y)\,dy,\ \rho(0,a) = \rho_0(a)$$

Existence thanks to a fixed point

- Along the characteristic lines: $X(s;t,a) = a + s - t$

$$s \mapsto X(s;t,a) \text{ is constant.}$$

- Case $a > t$

$$\rho(t,a) = \rho_0(a-t)$$

- Case $a \leq t$

$$\rho(t,a) = \rho(t-a,0) = \int_0^\infty B(y)\,\rho(t,y)\,dy$$

Finally, if ρ is a solution, ρ is a fixed point of

$$F(\rho)(t,a) = \begin{cases} \rho_0(a-t) \text{ if } a > t \\ \int_0^\infty B(y)\,\rho(t,y)\,dy \text{ else} \end{cases}$$

with F a contraction in $\mathcal{C}([0,T[, L^1(\phi(x)\,dx))$ for T small enough.

A population structured by age

Death rate neglected $\rightsquigarrow \rho(t,.) \sim e^{\lambda_0 t}\bar{\rho}_0 N(.)$

$$\frac{\partial \rho}{\partial t} + \frac{\partial \rho}{\partial a} = 0,\ \rho(t,0) = \int_0^\infty B(y)\,\rho(t,y)\,dy,\ \rho(0,a) = \rho_0(a)$$

Eigenvalue problem

▸ Sketch of proof

- Eigenvalue problem:

$$\lambda_0 N(a) + N'(a) = 0,\ N(0) = \int_0^\infty B(a)N(a)\,da \qquad (*)$$

- Adjoint problem

$$-\lambda_0\phi(a) + \phi'(a) = \phi(0)B(a) \qquad (**)$$

$\rightsquigarrow$ If B is a positive continuous function $\exists!(N,\phi,\lambda)$ taking positive values solution to $(*) - (**)$ such that

$$\int_0^\infty N(a)\,da = \int_0^\infty \phi(a)N(a)\,da = 1$$

A population structured by age

Death rate neglected $\rightsquigarrow \rho(t,.) \sim e^{\lambda_0 t}\bar{\rho}_0 N(.)$

$$\frac{\partial \rho}{\partial t} + \frac{\partial \rho}{\partial a} = 0,\ \rho(t,0) = \int_0^\infty B(y)\,\rho(t,y)\,dy,\ \rho(0,a) = \rho_0(a)$$

Eigenelements

$$\begin{cases} \lambda_0 N(a) + N'(a) = 0,\ N(0) = \int_0^\infty B(a)N(a)\,da & (*) \\ -\lambda_0 \phi(a) + \phi'(a) = \phi(0)B(a) \qquad (**) \end{cases}$$

Method of generalized entropy

- Conservation properties

$$\int_0^\infty \phi(a)e^{-\lambda_0 t}\rho(t,a)\,da = \int_0^\infty \phi(a)\rho^0(a)\,da := \bar{\rho}^0$$

- Let $m(t,a) = e^{-\lambda_0 t}\frac{\rho(t,a)}{N(a)}$, then for all convex function $\mathcal{H}$

$$\frac{d}{dt}\int_0^\infty \phi(a)N(a)\mathcal{H}\left(m(t,a)\right)\,da := \Delta \leq 0$$

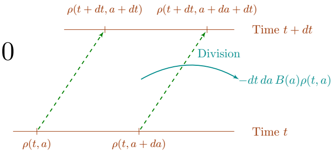
  and applied it for $\mathcal{H}(m) = |m - \bar{\rho}_0|$.
- If $\exists \mu_0 > 0$ such that $\forall a \in \mathbb{R}^+$, $\frac{\phi(0)B(a)}{\phi(a)} \geq \mu_0$ then

$$\Delta \leq -\mu_0 \int_0^\infty \phi N \mathcal{H}(m)$$

Mitosis - structuration by age

Population of cells structured by age that divide at a rate B giving 2 cells of age 0.

$$(**)\begin{cases}\frac{\partial\rho}{\partial t}+\frac{\partial\rho}{\partial a}=-B(a)\rho(t,a),\ t>0,\ a>0\\ \rho(t,0)=2\int_0^\infty B(y)\,\rho(t,y)\,dy,\ t>0\\ \rho(0,a)=\rho_0(a),\ a>0\end{cases}$$



- $\rho(t,a)$ density at time t with an age a
- $B(a)$ is the division rate

Similar results in that case

$$\int_0^\infty |e^{-\lambda_0 t}\rho(t,a)-\bar{\rho}_0 N(a)|\phi(a)da \underset{t\to\infty}{\longrightarrow} 0$$

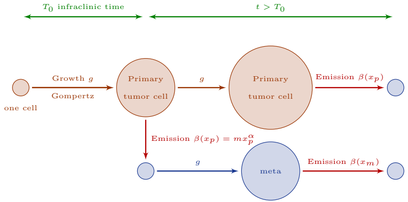
where (λ_0,N,ϕ) are the eigenelements, $\bar{\rho}^0=\int_0^\infty \phi(a)\rho^0(a)\,da$, and under assumptions on B, for instance

$$\int_0^\infty B(y)\,dy=\infty,\ 2B(a)\geq\mu_0\frac{\phi(a)}{\phi(0)}$$

Metastase model

The original model of metastases

Iwata & al (2000)



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

A transport equation for the growth of metastases

$$\partial_t \rho(x,t) + \partial_x (g(x)\rho(x,t)) = 0, \; t > 0, \; x > 1$$

A boundary condition for the emission

$$g(1)\rho(t,1) = \underbrace{\beta(x_p(t))}_{\text{Emission by the primary tumor: } \rho_{in}(t)} + \underbrace{\int_1^b \beta(x)\rho(t,x)\,dx}_{\text{Emission by the metastases}}, \; t > 0$$

Growth law

$$x_p' = g(x_p) \text{ with } g(x) = ax \ln\left(\frac{b}{x}\right) \rightsquigarrow \text{ Gompertz law}$$

Metastases model

$$\begin{cases} \partial_t \rho(x,t) + \partial_x(g(x)\rho(x,t)) = 0,\ t > 0,\ x > 1 \\ g(1)\rho(t,1) = \rho_{in}(t) + \int_1^b \beta(x)\rho(t,x)\,dx \end{cases}$$

Existence and uniqueness

Barbolosi, Benabdallah, FH, Verga 2008

- If $\rho_0 \in L^1(1,b)$, there exists a unique weak solution $\rho \in \mathcal{C}([0,\infty[; L^1(1,b))$.
- Existence of strong solution for more regular ρ_0 and compatibility condition between ρ_0 and $\beta(x_p(0))$.

Asymptotic behaviour

Barbolosi, Benabdallah, FH, Verga 2008

- There exists (λ_0, N, ϕ) and $\gamma > 0$ such that

$$\left\| e^{-\lambda_0 t}\rho(t) \quad - \bar{\rho}_0 N \right\|_{L^1_\phi(1,b)} \leq e^{-\gamma t} \|\rho_0\|_{L^1_\phi(1,b)} + \int_0^t e^{-\lambda_0 \tau} |\rho_{in}(\tau)|\, d\tau.$$

Metastases model

$$\begin{cases} \partial_t \rho(x,t) + \partial_x(g(x)\rho(x,t)) = 0,\ t>0,\ x>1 \\ g(1)\rho(t,1) = \rho_{in}(t) + \int_1^b \beta(x)\rho(t,x)\,dx \end{cases}$$

Inverse problem

Hartung, 2015

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

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

Theorem

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

Metastases model

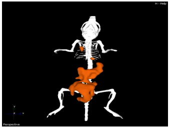
$$\begin{cases} \partial_t \rho(x,t) + \partial_x (g(x)\rho(x,t)) = 0,\ t>0,\ x>1 \\ g(1)\rho(t,1) = \rho_{in}(t) + \int_1^b \beta(x)\rho(t,x)\,dx \end{cases}$$

Confrontation to the data

Hartung & al, 2014

- Extension on the model

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



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

Gompertz model (1825)	$g(x) = ax \ln\left(\frac{b}{x}\right)$
Hybrid Gompertz (HG)	$g(x) = \min\left(a_{invitro}, ax\ln\left(\frac{b}{x}\right)\right)$
Logistic model (1838)	$g(x) = ax\left(1 - \frac{x}{b}\right)$
Von Bertalanffy (1949)	$g(x) = ax\left(\left(\frac{x}{b}\right)^{-\frac{1}{3}} - 1\right)$
West& al (1997)	$g(x) = ax\left(\left(\frac{x}{b}\right)^{-\frac{1}{4}} - 1\right)$
Hybrid West (HW)	$g(x) = \min\left(a_{invitro}, ax\left(\left(\frac{x}{b}\right)^{-\frac{1}{4}} - 1\right)\right)$

- Use SAEM algorithm

.

- Good estimates for
  - HG
  - HW

Growth fragmention equation

$$\begin{cases} \frac{\partial \rho}{\partial t} + \frac{\partial}{\partial x}(g(x)\rho) = -B(x)\rho(t,x) + \int_0^\infty B(y)k(x,y)\rho(t,y)\,dy,\ t>0,\ x>0 \\ \rho(t,0) = 0,\ t>0 \\ \rho(0,x) = \rho_0(x),\ x>0 \end{cases}$$

- ρ is the density of a population structured by a variable (trait) x at time t
- g is the growth rate
- B is the total division/fragmentation rate
- $k(x,y)$ is the fragmentation kernel: rate at which individuals of trait x are obtained from an individual of trait y.

Growth fragmentation equation

$$\begin{cases} \partial_t \rho + \partial_x (g(x)\rho) = -B(x)\rho(t,x) + \int_x^{+\infty} B(y)k(x,y)\rho(t,y)\,dy, \\ \rho(t,0) = 0,\ \rho(0,x) = \rho_0(x) \end{cases}$$

Some references

- Perthame, 2007: Study for $g = 1$ of the eigenvalue problem via the Krein-Rutman problem. Hints for the proof of convergence.
- Doumic-Gabriel, 2013: existence of a solution to the eigenvalue problem (direct and dual) given with many details for the case $\int \kappa(x,y)dy = 2$ and for B and g general.
- Gabriel & al, 2021: Asymptotic behaviour $\rho(t,x) \sim e^{\lambda t} N(x)$ for quite general assumption on k and B using a probabilistic approach namely **Harry's theorem**.

Growth fragmentation equation

$$\begin{cases} \partial_t \rho + \partial_x (g(x)\rho) = -B(x)\rho(t,x) + \int_x^{+\infty} B(y)k(x,y)\rho(t,y)\,dy, \\ \rho(t,0) = 0,\ \rho(0,x) = \rho_0(x) \end{cases}$$

Results from Gabriel & al, 2021

Assumptions (H_*)

- Assumptions on the kernel.
  - Autosimilar kernel such that $\kappa_0(s) \geq \underline{c} > 0$ and $\int_0^1 \kappa_0 < \infty$.
  - $\kappa_0 = 2\delta_{\frac{1}{2}}$ (can be relax)
- Asumption on the growth term :
  - $\int_0^1 \frac{1}{g} < \infty$
  - Asumption on H defined by $H(z) = \int_0^z \frac{1}{g} < \infty$ eg $H < \infty$ on $\mathbb{R}^+$, H invertible, H^{-1} does not grow too fast
- Asumptions on the relation between B and g
  - $\int_0^1 \frac{B}{g} < \infty$, $\lim_0 \frac{xB(x)}{g(x)} = 0$, $\lim_{+\infty} \frac{xB(x)}{g(x)} = +\infty$

Growth fragmentation equation

$$\begin{cases} \partial_t \rho + \partial_x (g(x)\rho) = -B(x)\rho(t,x) + \int_x^{+\infty} B(y)k(x,y)\rho(t,y)\,dy, \\ \rho(t,0) = 0,\ \rho(0,x) = \rho_0(x) \end{cases}$$

Results from Gabriel & al, 2021

Theorem

1. *Under asumptions* (H_*), *the eigenvalue problem*

$$\begin{cases} -(gN)' - BN + \int_x^{\infty} B(y)k(x,y)N(y)\,dy = \lambda_0 N,\ (gN)(0) = 0,\ \int N = 1 \\ -g\phi' - B\phi + \int_x^{\infty} B(y)k(x,y)\phi(y)\,dy = \lambda_0 \phi,\ \int N\phi = 1 \end{cases}$$

admits a unique solution (λ_0, N, ϕ).

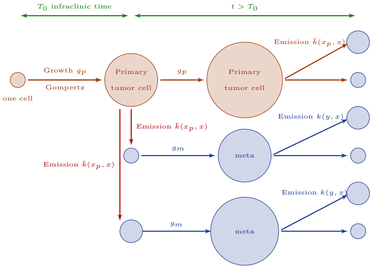
2. *If* $\|\rho_0\|_V < \infty$,

$$\left\| e^{-\lambda_0 t}\rho(t,.) - \bar{\rho}_0 N \right\|_V \le C e^{-\gamma t} \|\rho_0 - \bar{\rho}_0 N\|_V,\ \forall t \ge 0$$

where V is a weight depending on the data.

General emission of metastases

Each tumor (primary or secondary) can emit several tumors of different size !



Caracterisation of the emission

- $\beta(x)$ emision rate
- $k(y, x)$ probability for a tumor of size x to emmit a metastase of size y, typically

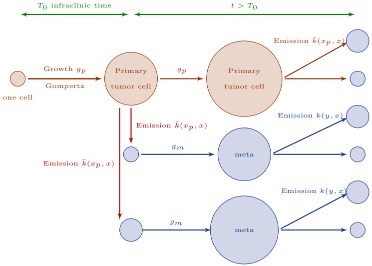
$$k(y, x) = k_0(y) + k_0(x - y)$$

with $Supp(k_0) \subset]x_0, x_1[$ and $\int_{x_0}^{x_1} k_0(y)\, dy = 1$.

$\rightsquigarrow$ a growth-fragmentation equation with source term

General emission of metastases

Each tumor (primary or secondary) can emit several tumors of different size !



$$\frac{\partial}{\partial t}\rho(t,x) + \frac{\partial}{\partial x}[g_m(x)\rho(t,x)] = \bar{k}(x, x_p(t)) - \beta(x)\rho(t,x) + \int_x^{+\infty}\beta(y)k(x,y)\rho(t,y)\,dy$$

Few results on this equation and still open questions on this equation !

MTs dynamical instabilities

Coupled fragmentation equations with ODE small

1. $u(t,z,x)$ density of MT in polymerisation
2. $v(t,x)$ density of the population of MT in depolymerisation
3. $p = p(t)$ Free GTP tubulin
4. $q = q(t)$ Free GDP tubulin

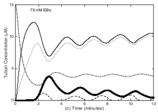
At Macroscopic level

1. $M_u : t \mapsto \int_0^\infty \int_0^x xu(t,z,x)\,dzdx$ Total amount of MT in polymerisation
2. $M_v : t \mapsto \int_0^\infty xv(t,x)\,dx$ Total amount of MT in depolymerisation

$\rightsquigarrow$ Conservation of the tubulin

$$M_u(t) + M_v(t) + p(t) + q(t) = Cte$$

Asymptotic behaviour at the macroscopic level



$\rightsquigarrow$ Damped oscillations at the macroscopic level !

Simplified models to understand the asymptotics

- The population of polymer represented by w : $\rightsquigarrow w(t,x)$
  - The model reduces to evolution of w, p, q
- Model should nevertheless reflects
  - The role of the balance between hydrolysis and growth rate.
    - $\gamma_{pol}(p(t)) < \gamma_{hydro} \quad \Rightarrow$ period of catastrophe
    - $\gamma_{pol}(p(t)) > \gamma_{hydro} \quad \Rightarrow$ period of rescue

  We introduce a threshold $\rightsquigarrow p_h$ such that $\gamma_{pol}(p_h) = \gamma_{hydro}$
    - $p < p_h \quad \Rightarrow$ period of catastrophe
    - $p > p_h \quad \Rightarrow$ period of rescue

Simplified models to understand the asymptotics

Equation for w

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

Equation for p

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

Equation for q

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

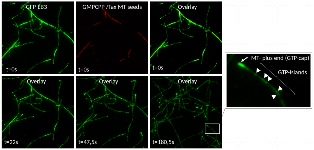
Simplified models to understand the asymptotics

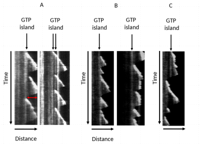
The fragmentation terms

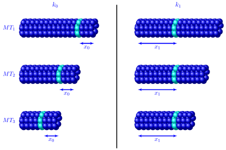
$$-\gamma_{depol}\int_0^x k(\tilde{x},x)w(t,x)\,d\tilde{x} + \gamma_{depol}\int_x^{\infty} k(x,\tilde{x})w(t,\tilde{x})\,d\tilde{x}$$

with $k(\tilde{x},x)$ the probability for a MT of size x to reach the size $\tilde{x} < x$

Two types of kernel identified from the experiments







- $k_0(y,x) = G(y-x)$: depolymerisation length is almost fixed
- $k_1(y,x) = G(x)$: size of the MTs after a depolymerisation is almost fixed

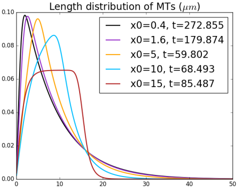
here $G(z) = \frac{1}{\sigma\sqrt{2\pi}} \exp \frac{-(z-x_0)^2}{2\sigma^2}, \quad x_0 > 0,\ \sigma > 0$

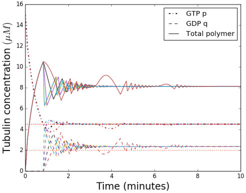
Properties

$\rightsquigarrow$ Reduction to ODE system is impossible

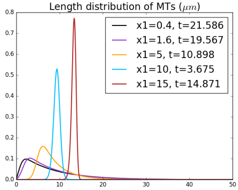
Simplified models to understand the asymptotics

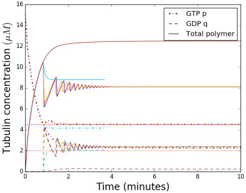
Asymptotics for the kernel k_0





Asymptotics for the kernel k_1





$\rightsquigarrow$ Rapid convergence at the macroscopic level, slow convergence of the distribution profil

Simplified models to understand the asymptotics

The most simplified model

Equation for w

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

Equation for p

$$\frac{d}{dt}p = -\gamma_{pol}(p(t))\int_0^\infty \int_0^x w(t,z,x)\,dzdx - \bar{\mathcal{N}}(p(t))$$
$$+\beta(p(t))\int_0^\infty \int_0^x (x-\tilde{x})k(x,\tilde{x})w(t,x)\,d\tilde{x}\,dx$$

- **Wellpossness of the system** with conservation properties

$$\int_0^\infty xw(t,x)\,dx + p(t) = \int_0^\infty xw(0,x)\,dx + p(0) := M_1^0$$

- **Numerical observations** $p(t) \to p^\infty$, $w(t,.) \to W$ for large time FH, Tournus, White, 2017
- **Existence and uniqueness of the asymptotic profile** (W, p^∞)
- **Convergence** Work in progress with M. Potomkin, S. D. Ryan, M. Tournus

Conclusion

Transport equations with eventually fragmentation terms are a powerfull tool to model biological issues.

Thank you for your attention !

Return

Direct problem.

$$\lambda_0 N(a) + N'(a) = 0,\ N(0) = \int_0^\infty B(a)N(a)\,da \qquad (*)$$

We have $N(a) = N(0)e^{-\lambda_0 a}$ with

$$N(0) = \int_0^\infty B(a)N(a)\,da = N(0)\int_0^\infty B(a)e^{-\lambda_0 a}\,da$$

$\rightsquigarrow$ Existence of N $\Leftrightarrow$ Existence of λ_0 such that $F(\lambda_0) = 1$ where

$$F(\lambda) = \int_0^\infty B(a)e^{-\lambda a}\,da.$$

If $B \in L^\infty$ with $1 < \int_0^\infty B$, F is a decreasing function and

$$\lim_{\lambda\to 0} F(\lambda) = \int_0^\infty B > 1 \text{ and } \lim_{\lambda\to\infty} F(\lambda) = 0$$

Therefore, there exists a unique (λ_0, N) solution of $(*)$ such that $\int_0^\infty N(a)\,da = 1$: $N(a) = \lambda_0 e^{-\lambda_0 a}$. The parameter λ_0 is called the **the Malthus parameter**.

A population structured by age

Return

Direct problem.

$$\lambda_0 N(a) + N'(a) = 0, \; N(0) = \int_0^\infty B(a)N(a)\,da \qquad (*)$$

Adjoint problem

$$-\lambda_0 \phi(a) + \phi'(a) = \phi(0)B(a) \qquad (**)$$

To find the adjoint problem, multiply $(*)$ by ϕ and integrate

$$0 = \int_0^\infty (\lambda_0 N + N')\phi\,da = \int_0^\infty N(\lambda_0\phi - \phi')\,da - \phi(0)N(0) = \int_0^\infty N(a)(\lambda_0\phi(a) - \phi'(a) - B(a)\phi(0))\,da$$

The solution of $(**)$ is given by

$$\phi(a) = \phi(0)\left(e^{\lambda_0 a} + \int_0^a e^{\lambda_0(a-a')}B(a')\,da'\right) \text{ with } \phi(0) \text{ such that } \int_0^\infty N\phi = 1.$$

A population structured by age

Return

- Conservation properties

$$\Psi(t) = \int_0^\infty \phi(a) e^{-\lambda_0 t} \rho(t,a)\, da = \int_0^\infty \phi(a) \rho^0(a)\, da := \bar{\rho}^0$$

Indeed,

$$\begin{aligned}
\frac{d}{dt}\Psi(t) &= \int_0^\infty \phi e^{-\lambda_0 t}(-\lambda_0 \rho + \partial_t \rho)\, da = \int_0^\infty \phi e^{-\lambda_0 t}(-\lambda_0 \rho - \partial_a \rho)\, da \\
&= e^{-\lambda_0 t}\left(\int_0^\infty \rho(-\lambda_0 \psi + \phi')\, da - \rho(t,0)\phi(0)\right) \\
&= e^{-\lambda_0 t}\phi(0)\left(\int_0^\infty \rho B - \rho(t,0)\right) = 0
\end{aligned}$$

A population structured by age

Return

- Let $m(t,a) = e^{-\lambda_0 t}\frac{\rho(t,a)}{N(a)}$, then for all convex function $\mathcal{H}$

$$\frac{d}{dt}\int_0^\infty \phi(a)N(a)\mathcal{H}\left(m(t,a)\right)\,da := \Delta \leq 0$$

Indeed,

$$\partial_t m + \partial_a m = e^{-\lambda_0 t}\frac{(-\lambda_0\rho + \partial_t\rho + \partial_a\rho)N - N'\rho}{N^2} = e^{-\lambda_0 t}\frac{(-\lambda_0 N - N')\rho}{N^2} = 0$$

with

$$m(t,0) = \int_0^\infty m(t,a)d\mu(a),\ d\mu(a) = \frac{B(a)N(a)}{N(0)}$$

$$\frac{d}{da}\phi N = -\phi(0)B(a)N(a)$$

Thus, for $\bar{m}(t,a) = \phi(a)N(a)\mathcal{H}(m(t,a))$, we have

$$\partial_t\bar{m}(t,a) + \partial_a\bar{m}(t,a) = -\chi(a)\bar{m}(t,a) \text{ with } \chi(a) = 2\phi(0)\frac{B(a)}{\phi(a)}$$

and thus

$$\begin{aligned}
\frac{d}{dt}\int_0^\infty \bar{m}(t,a)\,da &= \bar{m}(t,0) - \int_0^\infty \chi(a)\bar{m}(t,a)\,da \\
&= \phi(0)N(0)\mathcal{H}(m(t,0)) - \int_0^\infty 2\phi(0)B(a)N(a)\mathcal{H}(m(t,a))\,da \\
&= \phi(0)N(0)\left(\mathcal{H}\left(\int_0^\infty m(t,a)d\mu(a)\right) - \int_0^\infty \mathcal{H}(m(t,a)d\mu(a)\right) \leq 0
\end{aligned}$$

A population structured by age

Return

- If $\exists \mu_0 > 0$ such that $\forall a \in \mathbb{R}^+$, $\frac{\phi(0)B(a)}{\phi(a)} \geq \mu_0$ for a $\mathcal{H}(m) = |m - \bar{\rho}_0|$ we have $\Delta \leq -\mu_0 \mathcal{H}(m)$.

Mitosis - structured by age

Return

$$\lambda_0 N(a) + N'(a) = -B(a)N(a), \; N(0) = 2\int_0^\infty B(a)N(a)\,da \qquad (*)$$

We have $N(a) = N(0)e^{-\int_0^a (\lambda_0 + B(s))\,ds}$ with

$$N(0) = 2\int_0^\infty B(a)N(a)\,da = 2N(0)\int_0^\infty B(a)e^{-\lambda_0 a}\,da$$

$\rightsquigarrow$ Existence of N $\Leftrightarrow$ Existence of λ_0 such that $F(\lambda_0) = 1$ where

$$F(\lambda) = 2\int_0^\infty B(a)e^{-\int_0^a (\lambda + B(a))}\,da.$$

If $B \in L^\infty$ with $\int_0^\infty B = +\infty$, F is a decreasing function and

$$\lim_{\lambda \to 0} F(\lambda) = 2 \text{ and } \lim_{\lambda \to \infty} F(\lambda) = 0$$

Therefore, there exists a unique (λ_0, N) solution of $(*)$ such that $\int_0^\infty N(a)\,da = 1$.
The parameter λ_0 is called the **the Malthus parameter**.

Mitosis - structured by age

Return

$$\lambda_0 N(a) + N'(a) = -B(a)N(a),\ N(0) = 2\int_0^\infty B(a)N(a)\,da \qquad (*)$$

Adjoint problem

$$\lambda_0\phi(a) - \phi'(a) + B(a)\phi(a) = 2\phi(0)B(a) \qquad (**)$$

To find the adjoint problem, multiply $(*)$ by ϕ and integrate

$$0 = \int_0^\infty (\lambda_0 N + N' + BN)\phi\, da = \int_0^\infty N(\lambda_0\phi - \phi' + B)\, da - \phi(0)N(0) = \int_0^\infty N(a)(\lambda_0\phi - \phi' + B - 2B\phi(0))\, da$$

The solution of $(**)$ is given by

$$\phi(a) = 2\phi(0)\int_a^\infty B(a')e^{-\int_a^{a'}(\lambda + B(s))\,ds}\, da' \text{ with } \phi(0) \text{ such that } \int_0^\infty N\phi = 1.$$

Properties of the fragmentation kernels

Return

$$k(x,y) = B(x)\kappa(x,y) \text{ with } \int \kappa(x,y)\,dy = 1,\ \kappa(x,y) = 0 \text{ if } y > x$$

The kernel $k_0(x,y) = G(x-y)(x>y)$ with $\int_0^\infty G < +\infty$

$$B(x) = \int_0^x G(x-y)\,dy = \int_0^x G(y)\,dy,\ \int_x^\infty B(y)(\kappa(y,x)\,dy = \int_x^\infty G(y-x)\,dy = \int_0^\infty G(z)\,dz < \infty$$

The kernel $k_1(x,y) = G(y)(x>y)$ with $\int_0^\infty G < +\infty$

$$B(x) = \int_0^x G(y)\,dy,\ \int_x^\infty B(y)\kappa(y,x)\,dy = \int_x^\infty G(y)\,dy < \infty$$

In both cases, G is a non negative function with

$$B(x) \le B_M \text{ if } \int_0^\infty G(y)\,dy < +\infty$$

B is an increasing function such that $B(0) = 0$,

$$\exists x_- > 0 \text{ such that } B(x) \ge B_m > 0\,\forall x > x_- \text{ if } \int_0^\infty G(y)\,dy \ne 0$$