A few mathematical tools for biology and medicine

Thierry GOUDON
COFFEE–Sophia Antipolis

A few words on the scientific landscape

- D. Barbolosi, A. Iliadis, F. Hubert... (Marseille): tumor growth, chemiotherapy, toxicity
- Th. Colin (Bordeaux) team MONC, start-up Nenuphar: image analysis and prediction of tumor growth
- J. Clairambault, M. Doumic, D. Drasdo & B. Perthame, team MAMBA (Paris): chronotherapy, tumor growth
- GDR MaMoVi, T. Lepoutre
- CEMRACS 2018, Biological and medical applications
- French American Innovation Day : Math & Medicine, Houston, March 2018
  with Marc Garbey

Objectives of the mathematical modeling: why could it be useful ?

- To **reproduce** the evolution of tumors
  (with equations and simulations...)
- To **anticipate** the evolution of tumors
- To **anticipate** the action of drugs or therapies
- To **optimize** the action of drugs or therapies

For instance: after resection of a primary tumor, why is a preventative chemiotherapy useful ?
Difficulties for imaging techniques to detect micro-metastases : can we predict *in silico* the growth of residual tumors ?

Basic ODE models

$N(t)$: number of individuals (cells...) in a population, at time t.
Variations due to gain (birth) and loss (death)

$$\frac{\mathrm{d}}{\mathrm{d}t}N(t) = (\lambda - \mu)N(t).$$

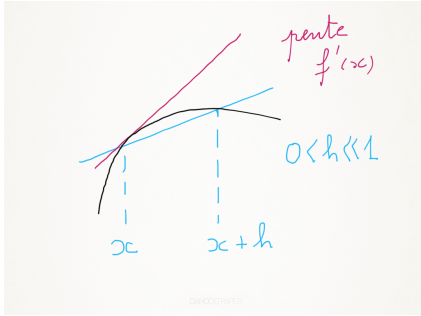
The solution is $N(t) = e^{(\lambda-\mu)t}N_0$:
exponential growth if $\lambda > \mu$, exponential extinction if $\lambda < \mu$
(cf. Malthus, end of XVIIIth century).

The discrete viewpoint

$$\underbrace{X_{n+1}}_{\text{pop. at time } t_{n+1}} = \underbrace{X_n}_{\text{pop. at time } t_n} + \underbrace{(\lambda-\mu)\ h\ X_n}_{\text{Variations due to gain/loss}}$$

h=time interval of observation=$t_{n+1} - t_n$.

Here the rate of variation $\tau_n = \dfrac{X_{n+1} - X_n}{X_n}$ is constant.



We can rewrite $X_n = (1 + (\lambda - \mu)h)^n\ X_0$; with $t = nh$, $h \to 0$... it yields the exponential law.

This is also the approach of **Numerical Schemes** with the "Stability" issue :

the condition $h \leq (\mu - \lambda)^{-1}$ enforces positivity when $\mu > \lambda$.

(Slightly) more complex models

- **Verhulst**: the more important the population, the stronger the loss rate/the lesser the gain rate

$$\frac{\mathrm{d}}{\mathrm{d}t}X(t) = a\left(1-\frac{X(t)}{K}\right)X(t), \qquad X_{n+1} = X_n + ha\left(1-\frac{X_n}{K}\right)X_n.$$

The population grows when $X < K$, decays when $X > K$.

- **Gompertz**: the growth rate itself obeys the exponential law:

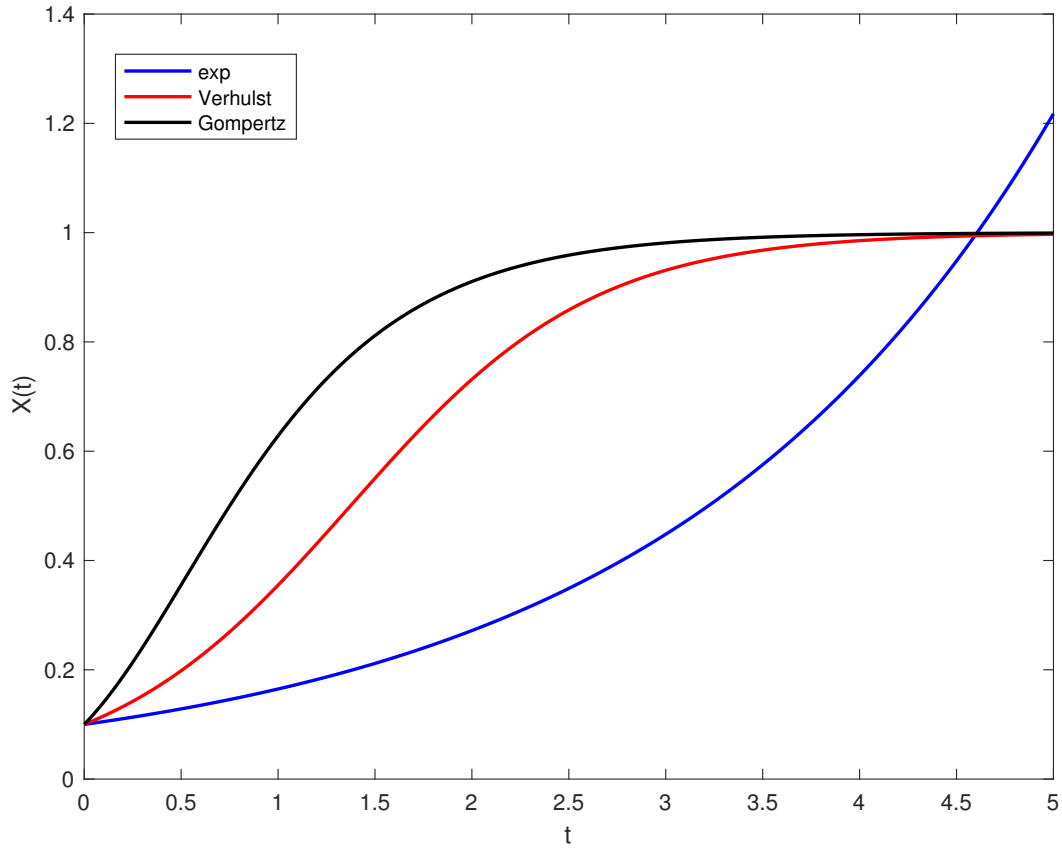
$$\tau(t) = \frac{X'(t)}{X(t)} = \frac{\mathrm{d}}{\mathrm{d}t}\ln\left(\frac{X(t)}{b}\right)$$

satisfies

$$\frac{\mathrm{d}}{\mathrm{d}t}\tau = -a\tau.$$

It yields $\frac{\mathrm{d}}{\mathrm{d}t}X(t) = aX(t)\ln\left(\frac{b}{X(t)}\right)$ or $X_{n+1} = X_n + haX_n\ln(b/X_n)$.

ODE models


exp
Verhulst
Gompertz
X(t)
t
0
0.2
0.4
0.6
0.8
1
1.2
1.4
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5

To incorporate the action of drugs

$$\frac{\mathrm{d}}{\mathrm{d}t}X(t) = \underbrace{X(t)R(X(t))}_{\text{your favorite ODE model}} \qquad \underbrace{-X(t)c(t)}_{\text{acts against the growth}}$$

Take into account **toxicity** (pharmaco-kinetic/dynamic)

- $c(t) = G(t, u)$ with u=given dose.
- Admissible set $K = \{u \text{ s. t. } \underbrace{F(t,u)}_{\text{action on healthy cells}} \leq C\}$.
- Optimize $\underbrace{\min_{u \in K}}_{\text{keeps the patient alive}} \left\{ \min_{0 \leq t \leq T} X_u(t) \right\}$.

Bolus

$$\frac{\mathrm{d}}{\mathrm{d}t}X(t) = X(t)\big[R(X(t)) - c(t)\big]$$

Question: How can we find $t \mapsto c(t)$ that minimizes $X(T)$ with T=a certain degradation time... under a **constraint** on the dose

$$\int_0^T c(s)\,\mathrm{d}s \leq C_M.$$

- **Bang-bang strategy**: to give C_M at time T Go1
- In fact $c_\epsilon(t) = \dfrac{C_M}{\epsilon}\mathbf{1}_{T-\epsilon \leq t \leq T}$, with $0 < \epsilon \ll 1$.
- As $\epsilon \to 0$: $\dfrac{\mathrm{d}}{\mathrm{d}t}\bar{X}(t) = \bar{X}(t)R(\bar{X}(t))$ and $X(T^+) = X(T^-)e^{-C_M}$.

A multi-dimensional model: Leslie's system, population structured by age

x_j=# of individuals with age $j \in \{1, ..., N\}$
$f_j > 0$ fertility rate, $t_{j+1,j}$ transition rate $j \to j+1$.

$$L = \begin{pmatrix} f_1 & f_2 & \cdots & f_n \\ t_{2,1} & 0 & \cdots & 0 \\ 0 & t_{3,2} & \ddots & \vdots \\ 0 & \cdots & 0 & t_{n,n-1} & 0 \end{pmatrix}$$

The model says: Le

$$X^{(k+1)} = LX^{(k)}$$

with $X^{(k)} = (x_1^{(k)}, ..., x_n^{(k)})$

Leslie's system ctn'd

$\lambda \in \mathbb{C}$ is an **eigenvalue** iff there exists $x \neq 0$ such that $Lx = \lambda x$.

Here L has a very specific property: L^n has strictly positive entries (**primitive matrix**).

Perron-Frobenius theorem: $\mu = \max\{|\lambda|,\ \lambda \text{ eigenvalue of } L\}$ is an eigenvalue, it can be associated to a vector $\bar{X}$ with non negative components.
It governs the asymptotic behavior

$$X^{(k)} \underset{k\to\infty}{\sim} \mu^k\ C(X^{(0)})\ \bar{X}.$$

Similar conclusion for the differential system $\dfrac{\mathrm{d}}{\mathrm{d}t}X = (L - I)X$: blow up of the population if $\mu > 1$, extinction of $\mu < 1$.

What did we learn ?

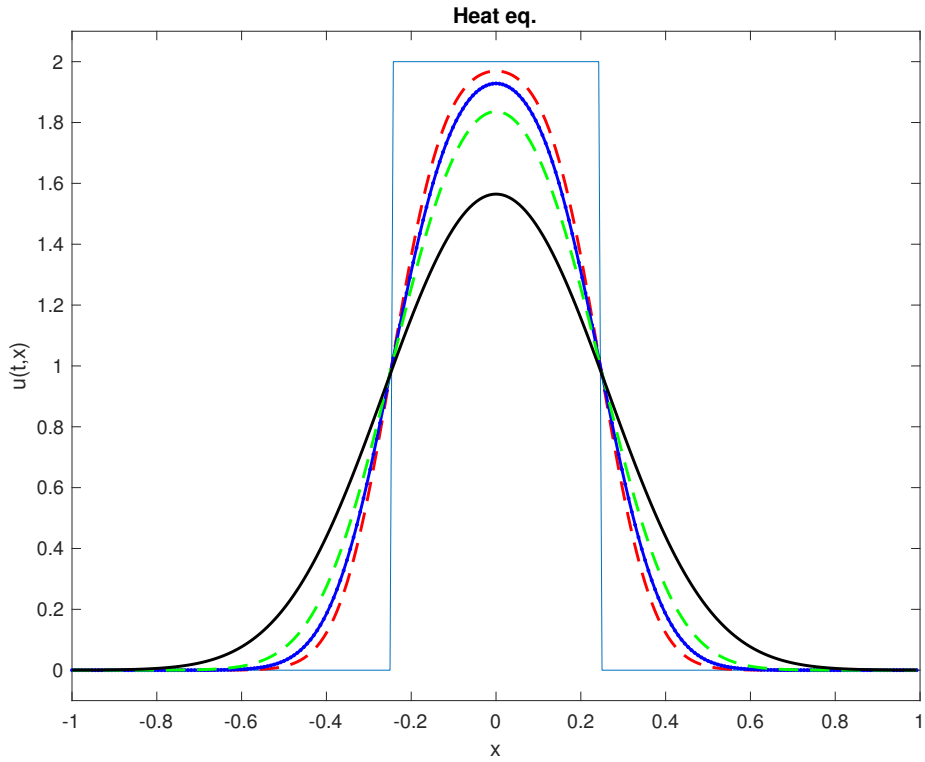
Large time asymptotics often corresponds to **observable** behaviors.

We can try to exhibit **structure properties** (here L is a primitive matrix) that govern this behavior.

We have efficient **numerical procedures** to compute directly the leading eigenpair, and thus to have direct access to the asymptotic state.

Towards PDE models: diffusion

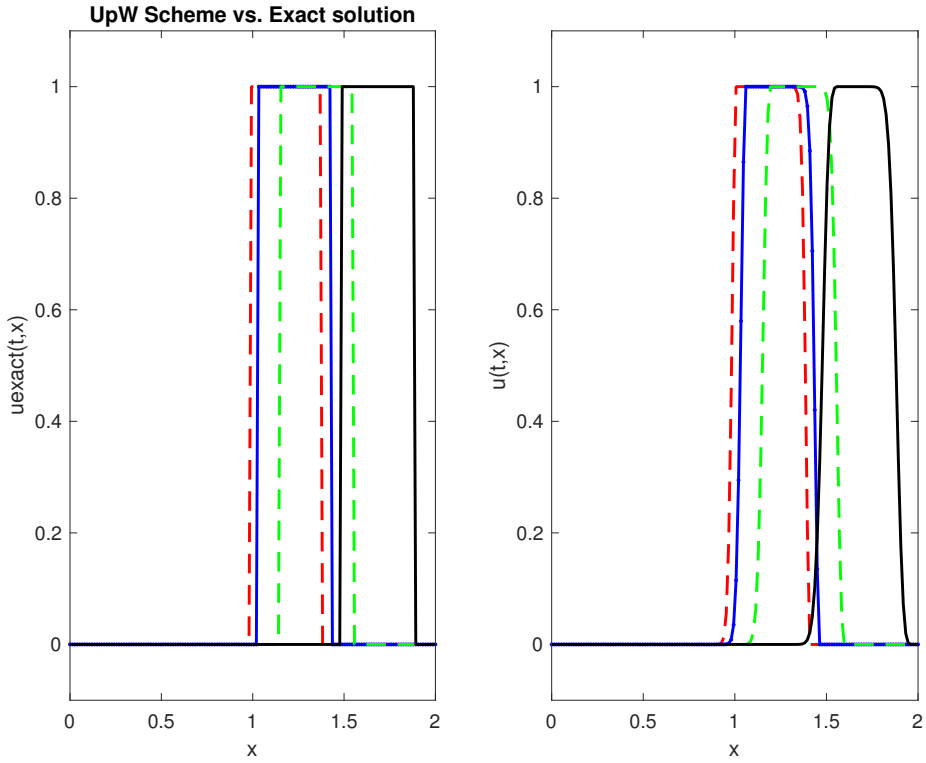
Diffusion $\partial_t u = \partial^2_{xx} u$



- the solution is spread
- the solution becomes instantaneously smooth

Towards PDE models: transport

Diffusion $\partial_t u + \partial_x(cu) = 0$ (here $c > 0$ constant)



- the solution is... transported (finite speed)
- the solution keeps its regularity (singularities)

Note: numerical schemes solve instead $\partial_t u + \partial_x(cu) = \epsilon \partial^2_{xx} u$,
$0 < \epsilon \ll 1$,

K. Iwata, K. Kawasaki, N. Shigesada's model for tumor growth

A Dynamical Model for the Growth and Size Distribution of Multiple Metastatic Tumor,
Journal of Theoretical Biology, 2000.

- Population of tumors **structured by their size** x
  $\int_a^b \rho(t,x)\,\mathrm{d}x = \#$ of cells with size in $[a,b]$ at time t.
- The growth rate depends on the size according to governed by Gompertz' law $g(x)$
- Each tumor produces new (small) cells with a rate $\beta(x)$.
- McKendrick–Von Foerster type equation:

$$\begin{cases} \partial_t \rho + \partial_x(g(x)\rho) = 0, \quad \text{for } t \geq 0 \text{ and } 1 < x < b, \\ \rho(0,x) = \delta_{x=1}, \\ g(1)\rho(t,1) = \displaystyle\int_1^b \beta(x)\rho(t,x)\,\mathrm{d}x + \beta(x_p(t)). \end{cases}$$

$$g(x) = ax \ln\left(\frac{b}{x}\right),\ \beta(x) = mx^\alpha,\ \text{(typiquement } \alpha = 2/3)$$

Inria

we have a formula for the solution...

By using Laplace's transform

$$\rho(t,x) = \frac{a}{mb^{\alpha} \ln b} \frac{1}{x} \sum_{k=1}^{\infty} e^{\lambda_k t} \left(1 - \frac{\ln x}{\ln b}\right)^{\lambda_k/a - 1} \frac{1}{c(\lambda_k)},$$

where the λ_k's are the roots of

$$\frac{a}{m}\lambda_k = F(1, \frac{\lambda_k}{a} + 1; \alpha \ln b) = \sum_{n=0}^{\infty} \frac{1}{(\frac{\lambda_k}{a} + 1) \ldots (\frac{\lambda_k}{a} + n)} (\alpha \ln b)^n,$$

and

$$c(\lambda_k) = \sum_{n=0}^{\infty} \frac{(-\alpha \ln b)^n}{n!(\frac{\lambda_k}{a} + n)^2}.$$

Eigenvalue problem

$$\begin{cases} \dfrac{\partial}{\partial x}(g(x)N(x)) + \lambda N(x) = 0, \\ g(1)N(1) = \displaystyle\int_1^b \beta(y)N(y)dy, \\ -g(x)\dfrac{\partial}{\partial x}\Phi(x) + \lambda\Phi(x) = \Phi(1)\beta(x), \\ \lambda > 0, \quad N(x) \geq 0, \quad \Phi(x) \geq 0, \quad \displaystyle\int_1^b N\Phi = 1, \quad \int_1^b N = 1. \end{cases}$$

There exists a unique triple (N, λ_0, Φ) solution of this problem, with $N(x) > 0$, $\Phi(x) > 0$

An infinite-dimensional version of the Perron-Frabenius theorem...

Consequences

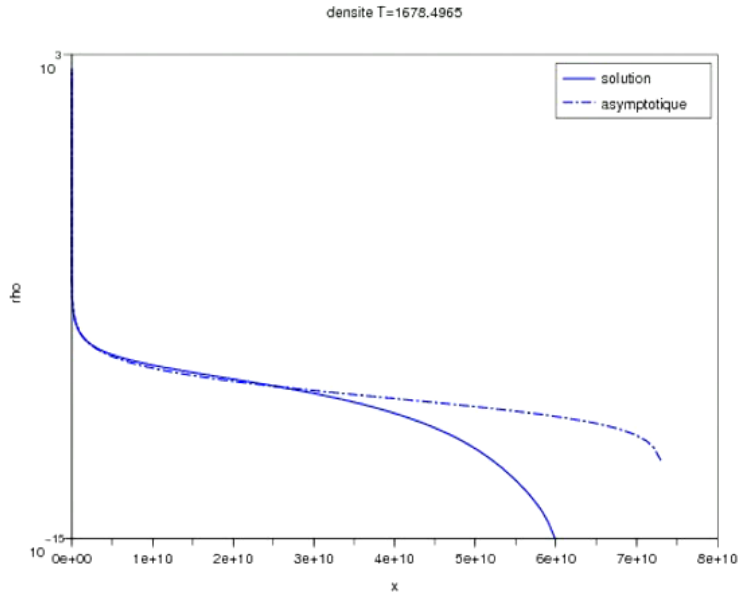
1. A conservation law:

$$\int_1^b \Phi(x)\rho(x,t)e^{-\lambda_0 t}dx = \int_1^b \Phi(x)\rho_0(x)dx$$

2. Estimates in L^∞ : if $cN(x) \leq \rho_0(x) \leq CN(x)$ then $cN(x) \leq \rho(t,x)e^{-\lambda t} \leq CN(x)$
3. and in $L^p(\Phi(x)N(x)dx)$.
4. The asymptotic behavior is driven by the leading eigenpair

$$\rho(t,x) \underset{t\to\infty}{\sim} C\ e^{\lambda t}N(x).$$

Simulation (A. Devys' Phd thesis)



Difficulties:

- the growth rate g vanishes at $x = b$,
- $b \gg 1$,
- the source at $x = 1$ is "large".

For $t \geq 2000$ jours $\simeq 5.5$ years the asymptotic profile is a fair approximation of the solution.

Comparison with Tubbiana's experimental data and incoroporation of the action of treatments by the research group in Marseille

AABG model for tumor growth

Interacting populations, **structuration in size and space**

- size-structured tumor concentration $(t, z) \mapsto T(t, z)$. The mass of the tumor changes due to

  natural growth + **cell division**.

- a bath of passive cells that become either immune $((t, x) \mapsto E(t, x))$ or "collaborative" $((t, x) \mapsto B(t, x))$.

The model involves **two** distinct length scales; it assumes "scale separation: $z \ll x$".

It also means that we neglect some fine scale phenomena...

AABG model: evolution of tumor cells

$$\partial_t T + \underbrace{\partial_z (VT)}_{\text{“transport”=growth}} = \underbrace{Q(T) - m(E,T)}_{\text{cell division - destruction by immune cells}}$$

$$Q(T)(t,z) = 4K(2z)T(2z) - K(z)T(z) \quad \text{(binary division)}$$

The operator Q increases the **number of tumoral cells** $\mu_0(t) = \int_0^\infty f(t,z)\,\mathrm{d}z$, but does not change the **total mass** of the tumor $\mu_1(t) = \int_0^\infty z f(t,z)\,\mathrm{d}z$.

If $m(E,T) = 0$, we get

$$\frac{\mathrm{d}}{\mathrm{d}t}\mu_0(t) = \int_0^\infty K(z)T(t,z)\,\mathrm{d}z \geq 0,$$

$$\frac{\mathrm{d}}{\mathrm{d}t}\mu_1(t) = V\mu_0(t) \geq 0.$$

Inria

AABG model: motion of the immune cells

- a natural space diffusion,
- a natural death,
- a convection guiding the cells towards the tumor,
- conversion rates from the background passive cells, which are activated by the presence of the tumor.

We are thus led to the following PDE

$$\partial_t E - d\Delta_x E - \nabla_x \cdot (E \nabla_x \Phi_{\mathrm{f}}) = -\gamma_{\mathrm{f}} E + p_{\mathrm{f}} \mu_0 S,$$

$$\partial_t B - d\Delta_x B - \nabla_x \cdot (B \nabla_x \Phi_{\mathrm{coll}}) = -\gamma_{\mathrm{coll}} B + p_{\mathrm{coll}} \mu_0 S,$$

coupled with a "chemotactic-like" effect

$$\Delta_x \Phi_{\mathrm{f}} = \mu_0 \sigma_{\mathrm{f}}, \qquad \Delta \Phi_{\mathrm{coll}} = \mu_0 \sigma_{\mathrm{coll}}.$$

AABG model: interaction terms

- Coupling term $m(E, T)$: immune response modeled by Michaelis-Menten kinetics

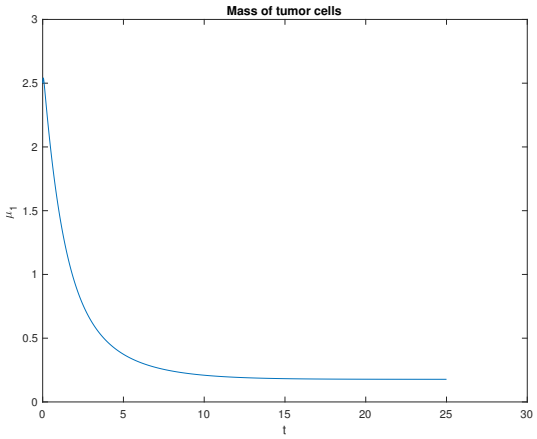
$$m(E, T)(t) = \int_\Omega a(y)E(t, y)\,\mathrm{d}y \times \frac{T}{\alpha + T}.$$

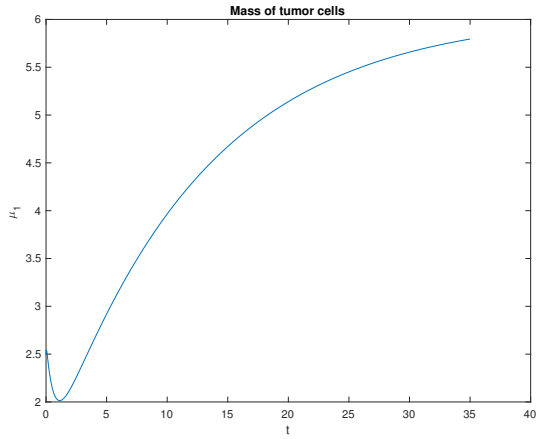
- The collaborative cells promote cell divisions: multiply the division operator by

$$1 + \int_\Omega b(y)\frac{B(t, y)}{1 + B(t, y)}\,\mathrm{d}y.$$

Qualitative features

Numerically, we observe “extinction” or “explosion” depending on the parameters.

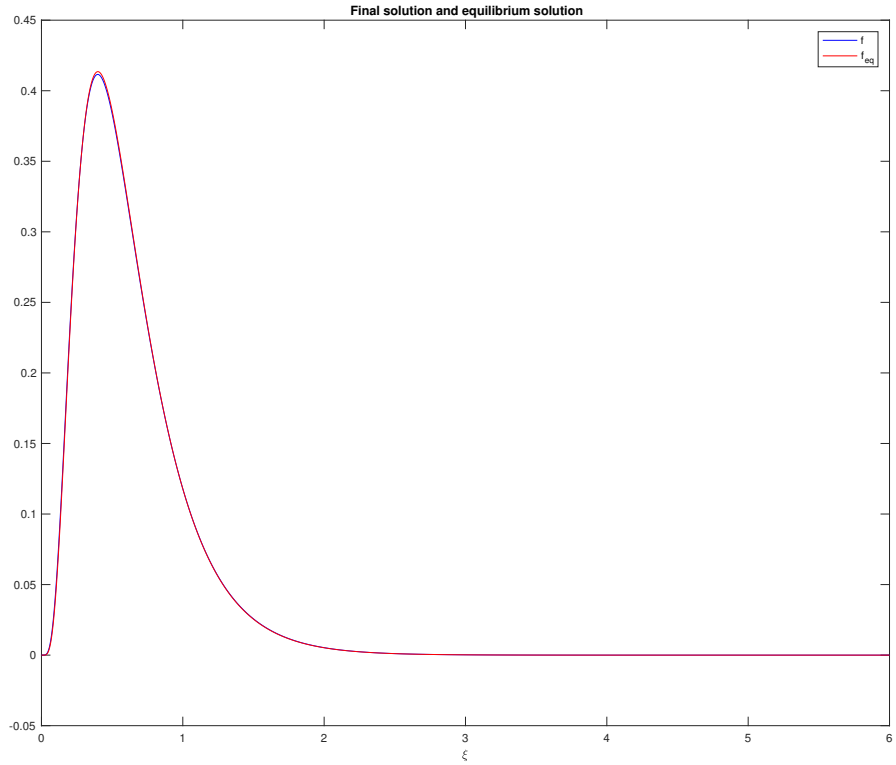




An important difficulty (in any application in biology): how should be fixed the parameters of the model ?

Qualitative features: residual distribution

In fact, one may reach a stable state with residual tumors... again characterized by means of an eigenvalue problem.



Possible mechanism...

Simplified problem

$$\partial_t T + V\partial_z T = Q(T) - T\int_\Omega a(x)E(t,x)\,\mathrm{d}x, \qquad T(t,0) = 0,$$

$$Q(T)(z) = 4\ell T(2z) - \ell T(z),$$

$$\partial_t E - d\Delta_x E - \nabla_x \cdot (E\nabla_x \Phi_\mathrm{f}) = -\gamma_\mathrm{f} E + p_\mathrm{f}\mu_0 S,$$

$$\Delta_x \Phi_\mathrm{f} = \mu_0 \sigma_\mathrm{f}.$$

It yields[1]

$$\frac{\mathrm{d}}{\mathrm{d}t}\mu_0 = \mu_0\left(\ell - \int_\Omega a(x)E(t,x)\,\mathrm{d}x\right),$$

and

$$\frac{\mathrm{d}}{\mathrm{d}t}\mu_1 = V\mu_0 - \mu_1\int_\Omega a(x)E(t,x)\,\mathrm{d}x.$$

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[1] $\mu_0(t) = \int T(t,z)\,\mathrm{d}z$ and $\mu_1(t) = \int z\ T(t,z)\,\mathrm{d}z$

Possible mechanism...: stationary solutions

With $\partial_t \to 0$, we get the constraints

$$\ell = \int_\Omega a(x) E(t,x)\,\mathrm{d}x, \qquad V\mu_0 = \mu_1 \ell$$

and the stationary equations

$$V\partial_z T = Q(T) - \ell\ T = 0 \quad \textbf{eigenvalue pb. !}$$

$$-d\Delta_x E - \mu_0 \nabla_x \cdot (E \nabla_x \Phi_0) = -\gamma_{\mathrm{f}} E + p_{\mathrm{f}} \mu_0 S,$$

$$\Delta_x \Phi_0 = \sigma_{\mathrm{f}}.$$

It defines μ_0 as a function of ℓ...

Workplan

- Are the numerically observed behaviors **qualitatively** relevant... or do we miss some important features ?
- Can we understand **theoretically** these behaviors: parameters thresholds, large time asymptotics... ? What are the hidden structure properties of the PDE system ? Can we relate them to biological interpretation ?
- Analyse and improve the **numerical tool** (multi-D, parameter investigation, stability issues...).
- **Identify the parameters**: some are known/observable from experiments, reduce as far as possible the blind parameters. What are the relevant units ? What should be produced by numerics ? Compare to experimental data.
- Incorporate actions of drugs and therapy...

Bolus

Bk1

- First $X(t) \leq \bar{X}(t)$, for $0 \leq t < T$:
  Set $U = \ln(X)$, $G(U) = R(X) = R(e^U)$, so that

$$(U-\bar{U})'(t) = G(U(t))-G(\bar{U}(t))-c(t) \leq \int_{\bar{U}(t)}^{U(t)} G'(\sigma)\,\mathrm{d}\sigma \leq C|U-\bar{U}|(t).$$

  It implies $([U-\bar{U}]_+^2)'(t) \leq 2C[U-\bar{U}]_+^2$.
- Second since $R' \leq 0$, and thus $G' \leq 0$, we have

$$(U-\bar{U})'(t) \geq -c(t)$$

  which yields $U(T) - \bar{U}(T^-) \geq 0 - \int_0^T c(s)\,\mathrm{d}s \geq -C_M$; thus

$$U(T)-\bar{U}(T^+) = U(T)-\bar{U}(T^-)+\bar{U}(T^-)-\bar{U}(T^+) \geq -C_M+C_M = 0.$$

Leslie model

Bk2

$$X_1^{(k+1)} = f_1 X_1^{(k)} + f_2 X_2^{(k)} + \ldots + f_n X_n^{(k)},$$

$$X_2^{(k+1)} = t_{2,1}\ X_1^{(k)},$$

$$X_3^{(k+1)} = t_{3,2}\ X_2^{(k)},$$

$$\vdots$$

$$X_n^{(k+1)} = t_{n,n-1}\ X_{n-1}^{(k)}$$