Équations de transport-fragmentation et applications aux maladies à prions

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Prion diseases

- Transmissible Spongiform Encephalopathies are infectious, fatal and neurodegenerative diseases
- Examples: madcow disease (BSE), Kreuzfeld Jakob disease, scrapie disease

- The pathogenic agent, known as **prion**, is a protein
- This protein has the ability to aggregate under an abnormal form into polymers

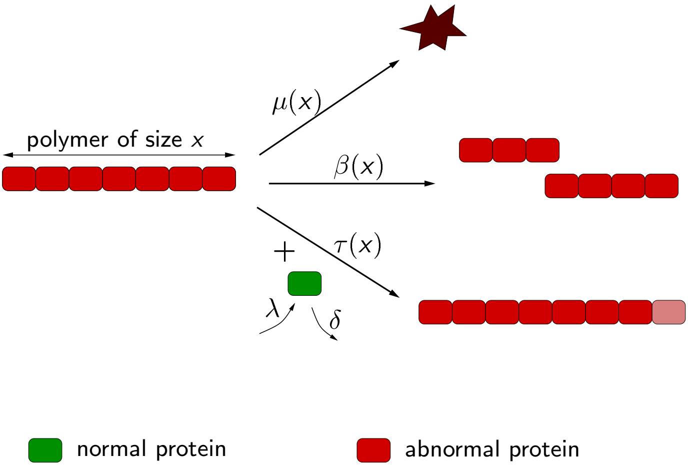

Figure: Prion proliferation

Prion model

$V(t)$: quantity of **monomers** at time t,
$u(t,x)$: quantity of **polymers** of size x at time t.

$$\begin{cases} \dfrac{d}{dt}V(t) = \lambda - \delta V(t) - V(t)\displaystyle\int_0^\infty \tau(x)u(t,x)\,dx, \\ \dfrac{\partial}{\partial t}u(t,x) = -V(t)\dfrac{\partial}{\partial x}\big(\tau(x)u(t,x)\big) - \mu(x)u(t,x) + \mathcal{F}u(t,x), \\ u(t,0)=0, \quad u(0,x)=u_0(x)\geqslant 0, \quad V(0)=V_0\geqslant 0, \quad t\geqslant 0, \quad x>0, \end{cases}$$

where $\quad \mathcal{F}u(x) := 2\displaystyle\int_x^\infty \beta(y)u(y)\,\kappa(x,y)\,dy - \beta(x)u(x).$

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- $\displaystyle\int_0^y x\kappa(x,y)\,dx = \frac{y}{2} \quad \Longrightarrow \quad \int_0^\infty x\,\mathcal{F}u(x)\,dx = 0$ mass conservation

References

- **Masel, Jansen, Nowak** (1999): discrete model for prion proliferation by polymerization
- **Engler, Greer, Prüss, Pujo-Menjouet, Webb, Zacher** (2006): continuous model and long-time behavior in the *"constant"* case $\tau(x) = \tau$, $\beta(x) = \beta x$ and $\kappa(x, y) = \frac{1}{y}$
- **Laurençot, Simonett, Walker** (2006): well-posedness
- **Calvez, Deslys, Laurent, Lenuzza, Mouthon, Oelz, Perthame** (2009): necessity to consider nonconstant coefficients
- **Doumic, Goudon, Lepoutre** (2010): derivation of the continuous model from the discrete model

Outline

The linear growth-fragmentation equation

Steady states of the prion equation

Long-time behavior for prion-type equations

Optimization of an amplification technique

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General Relative Entropy (Michel, Mischler, Perthame 2004):

$$\int_0^\infty \varphi(t,x)v(t,x)H\Big(\frac{u(t,x)}{v(t,x)}\Big)\,dx$$

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$$+ H'\Big(\frac{u(t,x)}{v(t,x)}\Big)\left(\frac{u(t,x)}{v(t,x)} - \frac{u(t,y)}{v(t,y)}\right)\Big]\,dxdy \leqslant 0 \quad \text{for } H \text{ convex}$$

Eigenproblem and convergence

$$\Lambda \mathcal{U}(x) + \partial_x\big(\tau(x)\,\mathcal{U}(x)\big) = \mathcal{F}\,\mathcal{U}(x),$$

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$$\Lambda \mathcal{U}(x) + \partial_x\big(\tau(x)\mathcal{U}(x)\big) = \mathcal{F}\mathcal{U}(x), \qquad \Longrightarrow \qquad \mathcal{U}(x)e^{\Lambda t}$$

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Any solution $u(t,x)$ to the growth-fragmentation equation satisfies

$$u(t,x)e^{-\Lambda t} \xrightarrow[t\to+\infty]{} \rho_0\,\mathcal{U}(x) \qquad \text{with} \qquad \rho_0 = \int_0^\infty u_0(x)\phi(x)\,dx.$$

[Perthame, Ryzhik ; Michel, Mischler, Perthame ; Laurençot, Perthame ; Cáceres, Cañizo, Mischler]

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To avoid formation of infinitely long polymers

- $\displaystyle\lim_{x\to\infty} \frac{x\beta(x)}{\tau(x)} = +\infty.$

Existence and uniqueness

Theorem (Doumic, G.)

Under the previous assumptions and some technical ones, **there exists a unique solution**

$$(\Lambda, \mathcal{U}, \phi) \in \mathbb{R} \times L^1(\mathbb{R}^+) \times W^{1,\infty}_{loc}(0,\infty)$$

to the eigenvalue problem. Moreover we have: $\Lambda > 0$,

$$x^\alpha \tau \mathcal{U} \in L^p(\mathbb{R}^+), \quad \forall \alpha \geqslant -\bar{\gamma}, \quad \forall p \in [1,\infty],$$

$$x^\alpha \tau \mathcal{U} \in W^{1,1}(\mathbb{R}^+), \quad \forall \alpha \geqslant 0,$$

$$\text{and} \quad \exists k > 0 \quad s.t. \quad \frac{\phi}{1+x^k} \in L^\infty(\mathbb{R}^+).$$

Sketch of the proof

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Details for $\mathcal{U}$:

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More precisely, we define

$$f(x) := \sup_{y \in (0,x)} \{\tau(y)\mathcal{U}(y)\}$$

and we prove that $x^{-\bar{\gamma}} f(x)$ is bounded at $x = 0$.

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&= 2\int_0^{x} \beta\,\mathcal{U}\,dy + 2C\,x^{\bar{\gamma}} \int_x^{\bar{x}} \beta\,\mathcal{U} y^{-\bar{\gamma}} dy + 2C\,x^{\bar{\gamma}} \int_{\bar{x}}^{\infty} \beta\,\mathcal{U} y^{-\bar{\gamma}} dy
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\end{aligned}$$

Choosing $\bar x$ such that $\int_0^{\bar x} \frac{\beta}{\tau} = \rho < \frac{1}{2}$, we obtain

$$(1 - 2\rho)\,x^{-\bar\gamma} f(x) \;\leqslant\; C_1 + C_2 \int_x^{\bar x} \frac{\beta}{\tau}\,y^{-\bar\gamma} f(y)\,dy$$

and we conclude with Grönwall's lemma.

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$$\Longrightarrow \qquad \Lambda(V_\infty) = \mu\,, \qquad u_\infty(x) = \rho_\infty\, \mathcal{U}(V_\infty; x),$$

$$\rho_\infty = \frac{\lambda / V_\infty - \delta}{\int \tau(x) \mathcal{U}(V_\infty; x) dx} > 0 \quad \big(\text{so } V_\infty < \bar{V}\big).$$

Steady states

$$\begin{cases} 0 = \lambda - \delta V - V \displaystyle\int_0^\infty \tau(x) u(x)\, dx, \\ 0 = -V \dfrac{\partial}{\partial x}\big(\tau(x) u(x)\big) - \mu\, u(x) + \mathcal{F} u(x). \end{cases}$$

- disease-free steady state: $\bar{u} \equiv 0, \quad \bar{V} = \dfrac{\lambda}{\delta}$
- disease steady state: $u_\infty \geqslant 0, \quad u_\infty \not\equiv 0 \quad \text{and} \quad V_\infty > 0$

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Powerlaw coefficients

If

$$\tau(x) = \tau x^{\nu} \qquad \text{and} \qquad \beta(x) = \beta x^{\gamma},$$

then the conditions which ensure the existence of eigenelements reduce to

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If additionally $\kappa(x, y) = \frac{1}{y}\kappa_0\left(\frac{x}{y}\right)$, then we can compute explicitly

$$\Lambda(V) = \Lambda(1) V^{\gamma k^{-1}} \qquad \text{and} \qquad \mathcal{U}(V; x) = V^{-k}\,\mathcal{U}(1; V^{-k}x).$$

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So there is a unique possible disease steady state given by

$$V_\infty = \left(\frac{\mu}{\Lambda(1)}\right)^{k\gamma^{-1}}.$$

Existence of multiple disease steady states

Theorem (Calvez, Doumic, G.)

For $L = 0$ or $L = +\infty$, if

$$\beta(x) \underset{x \to L}{\sim} \beta x^{\gamma} \qquad \text{and} \qquad \tau(x) \underset{x \to L}{\sim} \tau x^{\nu},$$

then

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then

$$\lim_{V \to L} \Lambda(V) = \lim_{x \to L} \beta(x).$$

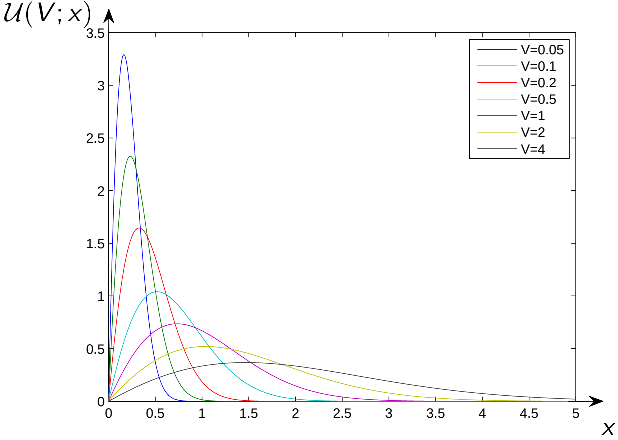
Consequence: if

$$\lim_{x \to 0} \beta(x) = \lim_{x \to \infty} \beta(x) = 0$$

then, for μ small enough, there exist at least two values of V such that

$$\Lambda(V) = \mu.$$

Idea of the proof



$$\Lambda(V) = \int_0^\infty \beta(x)\,\mathcal{U}(V;x)\,dx$$

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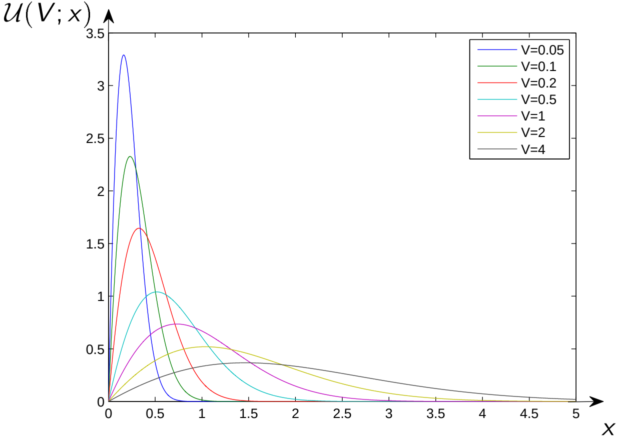

$$\Lambda(V) = \int_0^\infty \beta(V^k x)\, V^k\, \mathcal{U}(V; V^k x)\, dx$$

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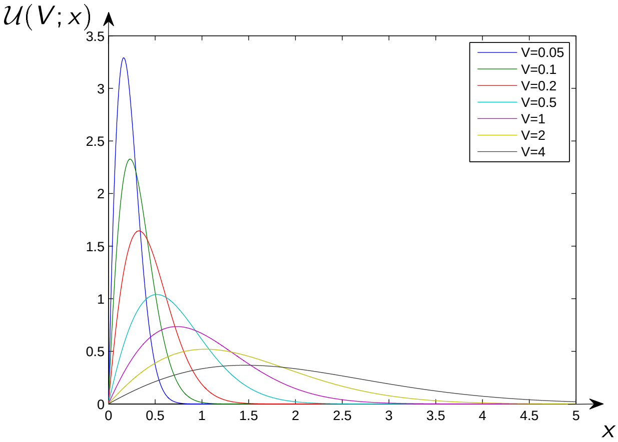
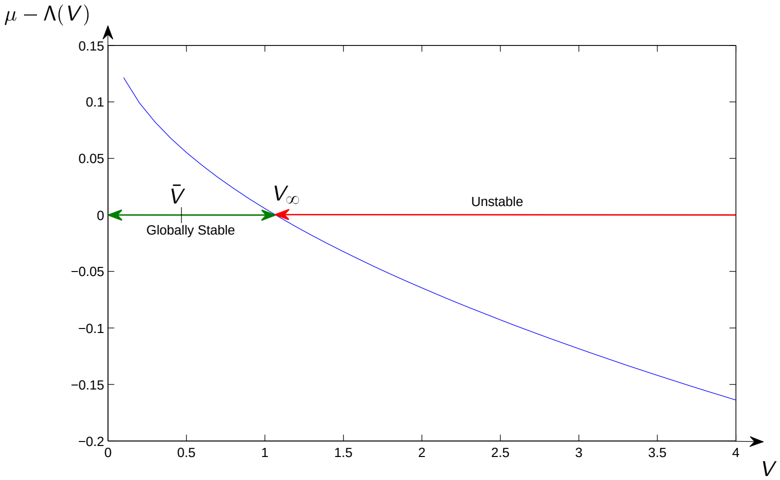


$$V^{-k\gamma}\Lambda(V) = \int_0^\infty V^{-k\gamma}\beta(V^k x)\, V^k\, \mathcal{U}(V; V^k x)\, dx$$

Constant case: $\tau(x) = \tau,\ \beta(x) = \beta x,\ \kappa(x, y) = \frac{1}{y}$



Stability results: Engler, Prüss, Pujo-Menjouet, Webb, Zacher 2006

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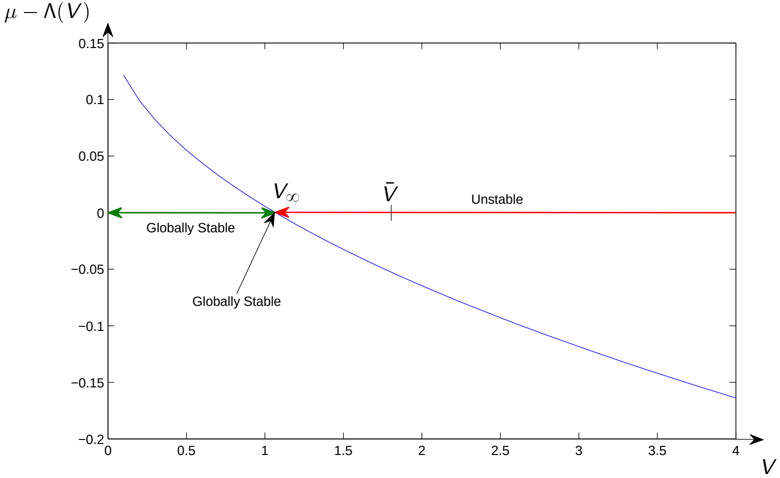

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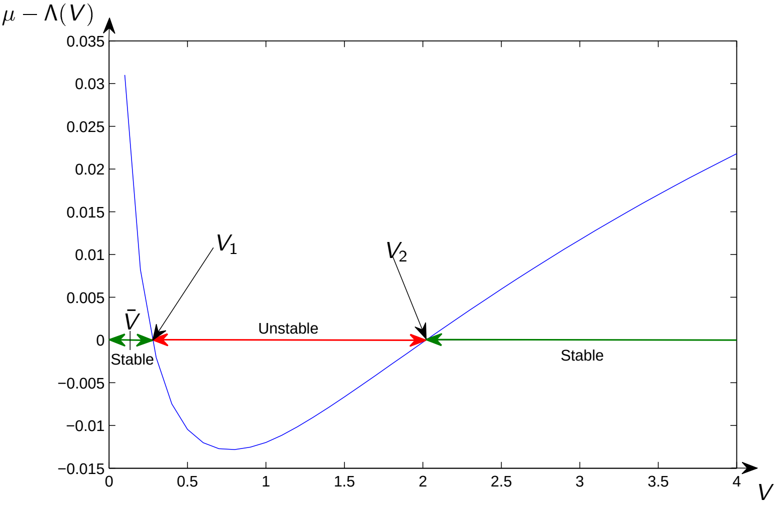

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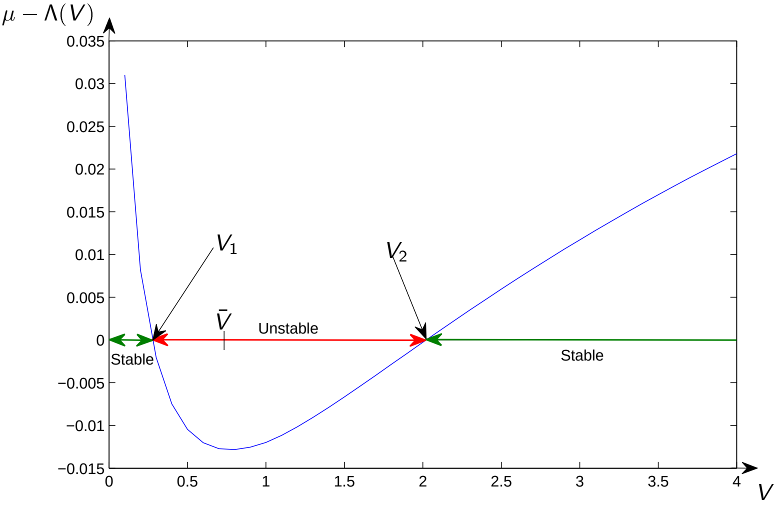

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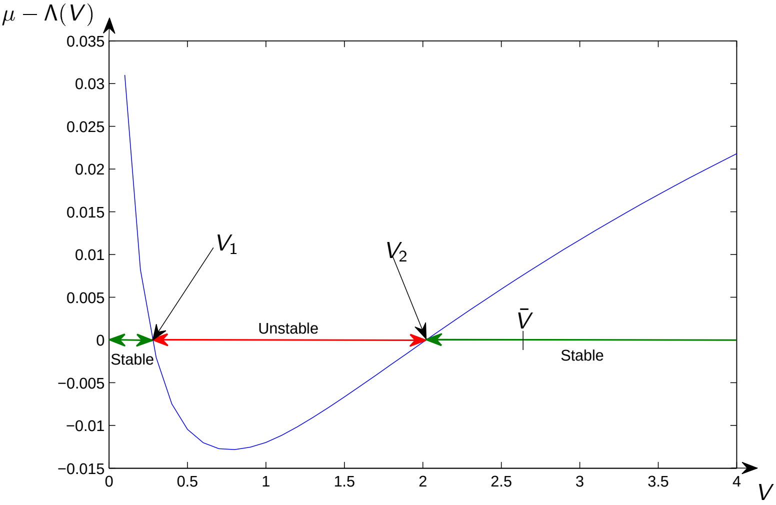

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Outline

A prion-type equation with particular solutions

Consider the nonlinear growth-fragmentation equation

$$\frac{\partial}{\partial t}u(t,x) = -f\left(\int x^p u\right)\frac{\partial}{\partial x}\big(xu(t,x)\big) - g\left(\int x^q u\right)u(t,x) + \mathcal{F}u(t,x) \qquad (1)$$

with $\beta(x) = \beta x^\gamma$ and $\kappa(x,y) = \frac{1}{y}\kappa_0\big(\frac{x}{y}\big)$.

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with $\beta(x) = \beta x^\gamma$ and $\kappa(x,y) = \frac{1}{y}\kappa_0\big(\frac{x}{y}\big)$.

If (W, Q) is a solution to the ODE system,

$$\begin{cases} \dot{W} &= \gamma W\big(f(W^{p/\gamma}Q) - W\big), \\ \dot{Q} &= Q\left(W - g(W^{q/\gamma}Q)\right), \end{cases}$$

then $\quad (t,x) \mapsto Q(t)\,\mathcal{U}(W(t);x) \quad$ is a solution to equation (1).

Long-time behavior

$$\frac{\partial}{\partial t}u(t,x) = -f\left(\int x^p u\right)\frac{\partial}{\partial x}\big(xu(t,x)\big) - \mu\, u(t,x) + \mathcal{F}u(t,x)$$

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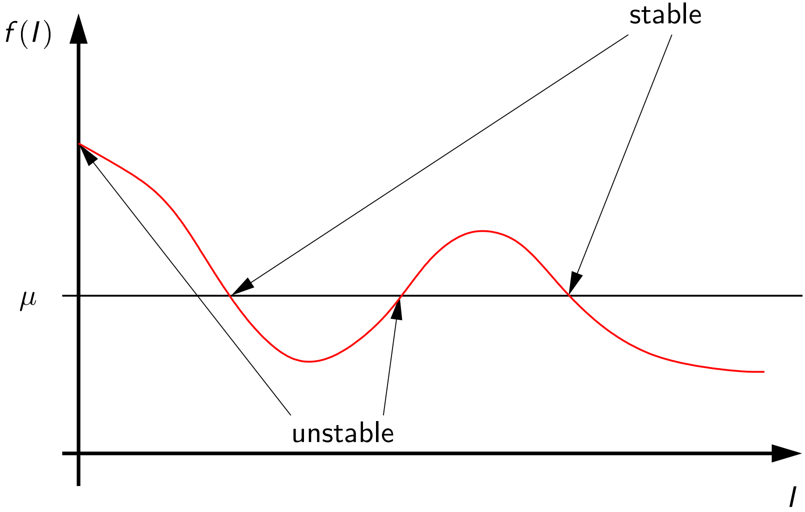
Theorem (G.)

- If $\limsup_{I\to+\infty} f(I) < \mu$, then any solution converges to a steady state.
- The trivial steady state is:
  - stable if $f(0) < \mu$,
  - unstable if $f(0) > \mu$.
- A positive steady state u_∞ is:
  - stable if $f'\left(\int x^p u_\infty(x)\,dx\right) < 0$,
  - unstable if $f'\left(\int x^p u_\infty(x)\,dx\right) > 0$.

Steady states and stability



Long-time behavior

$$\frac{\partial}{\partial t}u(t,x) = -f\left(\int x^p u\right)\frac{\partial}{\partial x}\big(xu(t,x)\big) - g\left(\int x^q u\right)u(t,x) + \mathcal{F}u(t,x)$$

Can we prove the same kind of behavior for general functions g?

Long-time behavior

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Can we prove the same kind of behavior for general functions g?

→ No

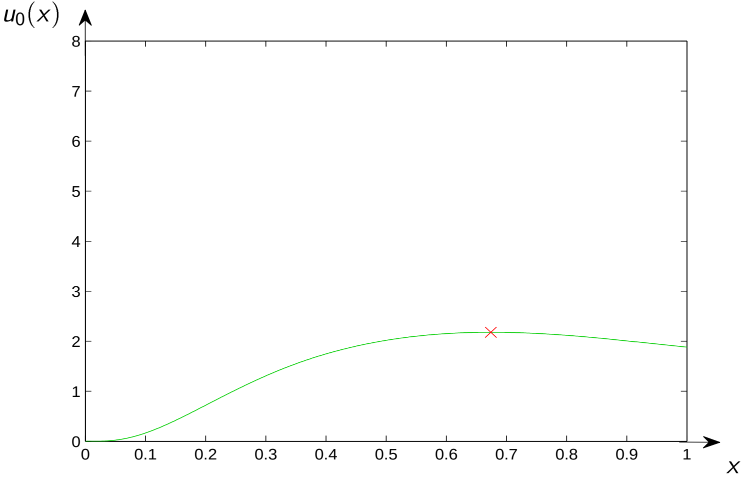
Theorem (G.)

There exist situations with increasing functions f and g where periodic solutions appear. More precisely there exist solutions of the form

$$u(t,x) = Q(t)\,\mathcal{U}(W(t);x)$$

with Q and W periodic functions.

Periodic oscillations



A generalized prion equation

$$\begin{cases} \dfrac{d}{dt}V(t) = \lambda - \delta V(t) - V(t)\, f\left(\int x^p u\right) \int_0^\infty xu(t,x)\, dx\,, \\ \dfrac{\partial}{\partial t}u(t,x) = -V(t)\, f\left(\int x^p u\right) \dfrac{\partial}{\partial x}\big(xu(t,x)\big) - \mu\, u(t,x) + \mathcal{F}u(t,x), \end{cases}$$

introduced by *Greer, van den Driessche, Wang and Webb* (2007).

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Theorem (G.)

There exist functions f and parameters λ, δ, μ, γ and p for which this equation admits periodic solutions.

Outline

Protein Misfolded Cyclic Amplification

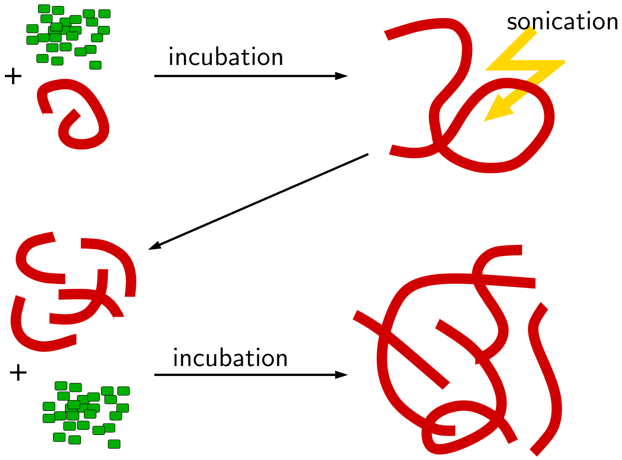

Figure: The PMCA principle.

Modeling

We model the sonication by multiplying the fragmentation $\mathcal{F}$ by a parameter $\alpha(t)$:

$$\frac{\partial}{\partial t}u(x,t) = -\frac{\partial}{\partial x}\big(\tau(x)u(x,t)\big) + \alpha(t)\mathcal{F}u(x,t)$$

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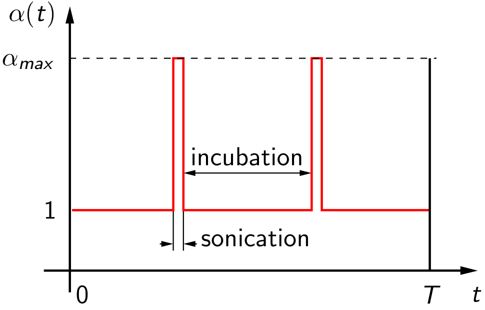

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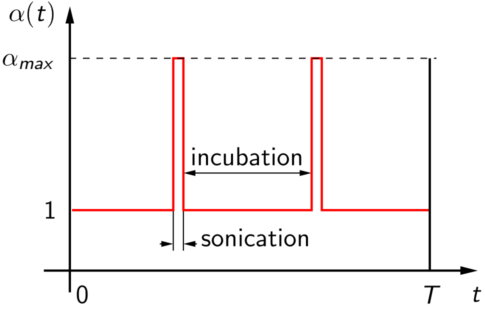

Problem: maximize the quantity $\int_0^\infty x\, u(T,x)\, dx$ for a given time T.

First approach: optimization for α constant

We consider a steady control $\alpha(t) \equiv \alpha$ and we want to maximize the eigenvalue $\Lambda(\alpha)$.

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Theorem (Calvez, Doumic, G.)

For $L = 0$ or $L = +\infty$, if β and τ are equivalent to powerlaws at $x = \frac{1}{L}$ then

$$\lim_{\alpha \to L} \Lambda(\alpha) = \lim_{x \to \frac{1}{L}} \frac{\tau(x)}{x}.$$

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Consequence: if

$$\lim_{x \to 0} \frac{\tau(x)}{x} = \lim_{x \to \infty} \frac{\tau(x)}{x} = 0$$

then

$$\exists\, \alpha_{opt} > 0\,, \qquad \forall\, \alpha > 0\,, \qquad \Lambda(\alpha) \leqslant \Lambda(\alpha_{opt})\,.$$

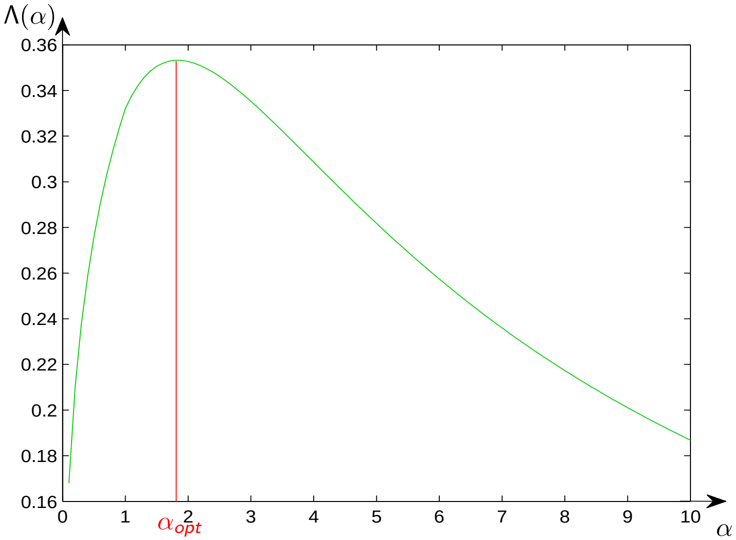

Figure: Existence of an optimal α.

Discrete model

$$\frac{d}{dt}u_i(t) = -r(\alpha(t))\big(\tau_i u_i(t) - \tau_{i-1}u_{i-1}(t)\big) - \alpha(t)\beta_i u_i(t) + 2\,\alpha(t)\sum_{j=i+1}^{n}\beta_j\kappa_{i,j}u_j(t), \qquad 1 \leqslant i \leqslant n,$$

where r represents the influence of the sonication on the polymerization.

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where r represents the influence of the sonication on the polymerization.

For the steady controls, we have

Theorem (Calvez, G.)

If r is nonincreasing and $\tau_2 > 2\,\tau_1$, then $\exists\,\alpha_{opt} > 0$ such that

$$\forall\,\alpha > 0\,, \qquad \Lambda(\alpha) \leqslant \Lambda(\alpha_{opt})\,.$$

Periodic control

For $\alpha(t)$ a periodic control, the Floquet theory allows to define, for the discrete model, a principal eigenvalue

$$\Lambda_F[\alpha].$$

Theorem (Calvez, G.)

If there exists an optimal value α_{opt} for the Perron eigenvalue and if

$$\frac{r''(\alpha_{opt})}{r(\alpha_{opt}) - \alpha_{opt} r'(\alpha_{opt})} > 0,$$

then there exist periodic controls $\alpha(t)$ such that $\Lambda_F[\alpha] > \Lambda(\alpha_{opt})$.

Optimal control

Problem: find a control $\alpha(t)$ which maximizes, for a given time T, the payoff

$$\sum_{i=1}^{n} i\, u_i(T).$$

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Lemma (G.) If r is affine, then there exists an optimal control.

Optimal control

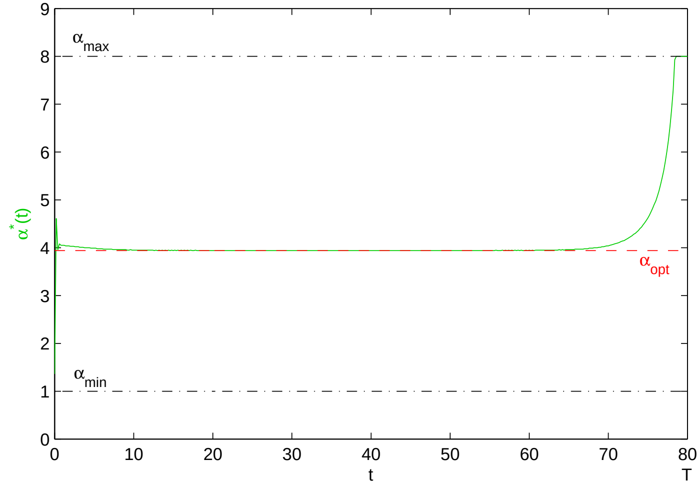

Figure: Optimal control for affine r.

Optimal control

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Lemma (G.) If r is affine, then there exists an optimal control.

Question: If r is not affine, is there an optimal control?

Optimal control

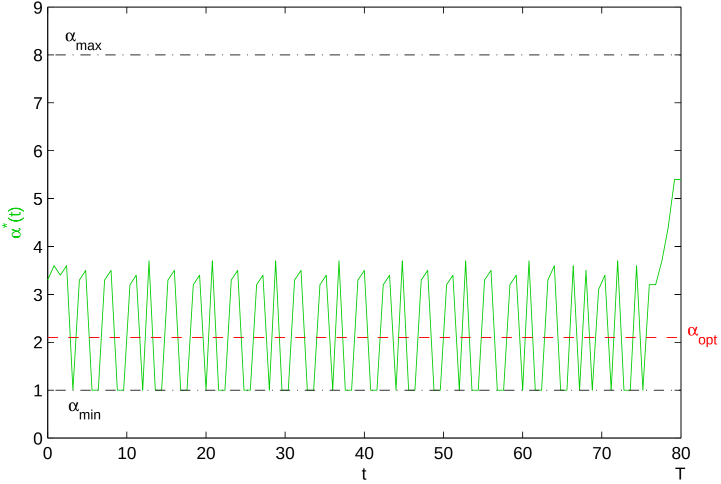

Figure: Optimal control for r decreasing convex, with $\Delta t = 0.8$.

Optimal control

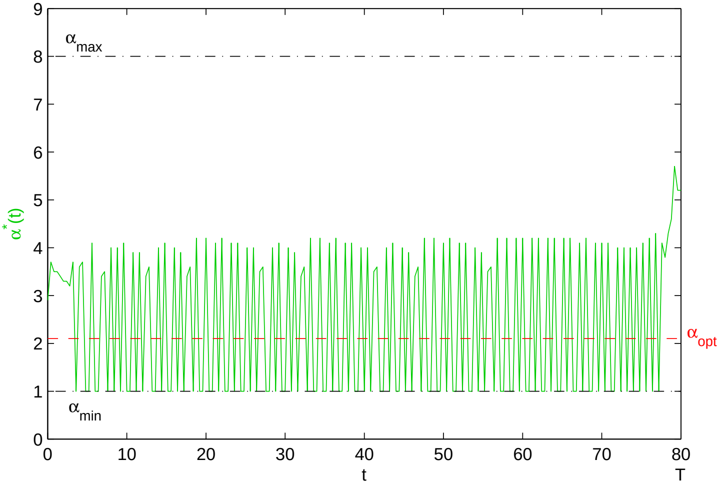

Figure: Optimal control for r decreasing convex, with $\Delta t = 0.4$.

Optimal control

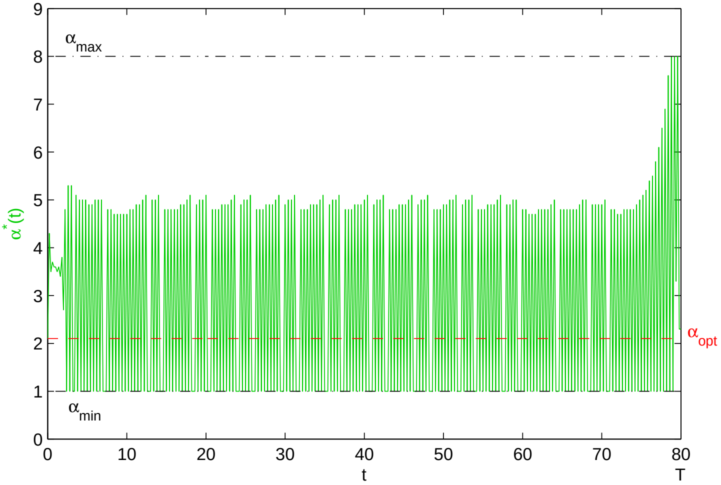

Figure: Optimal control for r decreasing convex, with $\Delta t = 0.2$.

Optimal control

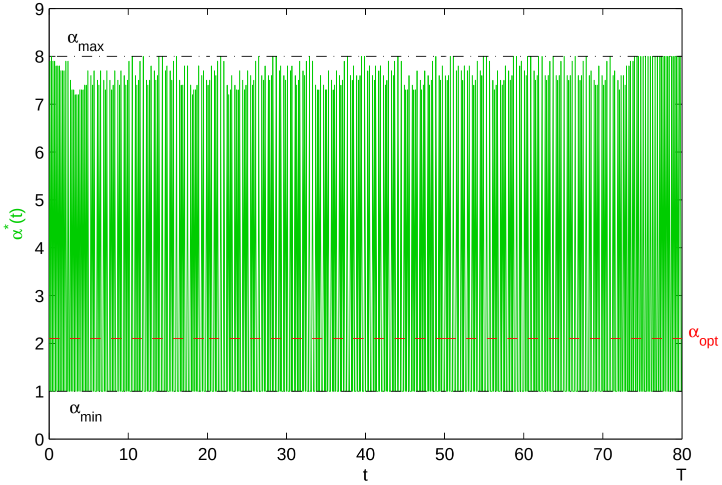

Figure: Optimal control for r decreasing convex, with $\Delta t = 0.1$.

Perspectives

Long-time asymptotics

- Generalize the assumptions which ensure the exponential decay in the linear case (in progress, with J. A. Cañizo and D. Balagué)
- What happens when the assumptions which ensure the existence of eigenelements are not satisfied? (with T. Lepoutre)
- Obtain stability results for the disease steady states of the prion equation with general coefficients
- Introduce a coagulation operator and a space variable (post-doc)

Optimization

- Prove that the optimal control is α_{opt} when r is affine (with V. Calvez)
- Investigate the Floquet problem for the continuous model

Age-structured models

- The renewal equation to model and investigate a cancer treatment (with G. F. Webb)