Optimization of the fragmentation for a prion proliferation model

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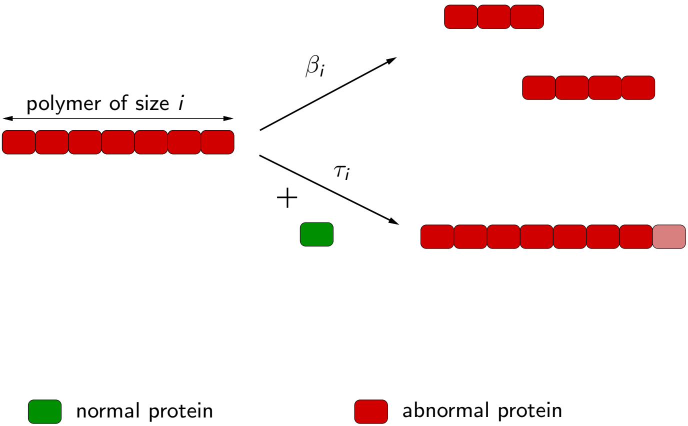
Prion diseases

- 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

Prion proliferation



Discrete growth-fragmentation model [Masel, Jansen, Nowak, 1999]

$u_i(t)$: concentration of polymers of size i $(1 \leqslant i \leqslant n)$ at time t

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

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Matrix formulation: $U(t) := \big(u_1(t)\ u_2(t)\ \dots\ u_n(t)\big)^T$

$$\dot{U}(t) = \big(G + F\big) U(t)$$

Discrete growth-fragmentation model

$$\dot{U}(t) = \big(G + F\big)\,U(t)$$

$$G = \begin{pmatrix} -\tau_1 & & & & \\ \tau_1 & -\tau_2 & & & \\ & \ddots & \ddots & & \\ & & \tau_{n-2} & -\tau_{n-1} & \\ & & & \tau_{n-1} & 0 \end{pmatrix}$$

$$F = \begin{pmatrix} 0 & & & \\ & -\beta_2 & & (2\kappa_{ij}\beta_j)_{i<j} \\ & & \ddots & \\ & \mathbf{0} & & \\ & & & -\beta_n \end{pmatrix}$$

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- Promising tool for diagnosis: the Protein Misfolded Cyclic Amplification (PMCA)

Protein Misfolded Cyclic Amplification

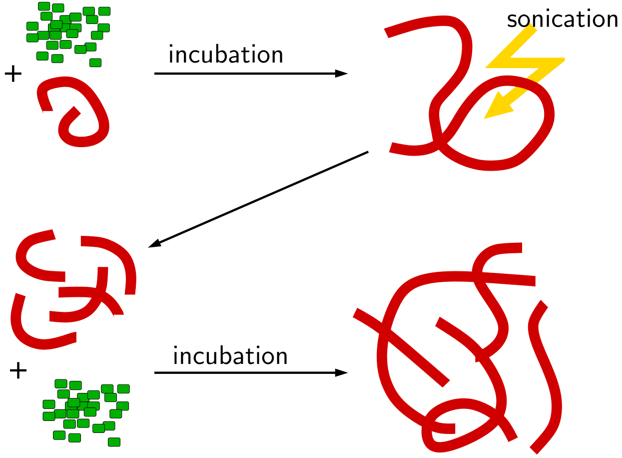

Figure: The PMCA principle.

Modelling the PMCA

$$\dot{U}(t) = \big(F + G\big)\,U(t)$$

Modelling the PMCA

$$\dot{U}(t) = \big(\alpha(t)F + r(\alpha(t))G\big)\,U(t)$$

$\alpha(t)$: sonication parameter

r : represents the influence of the sonication on the polymerization

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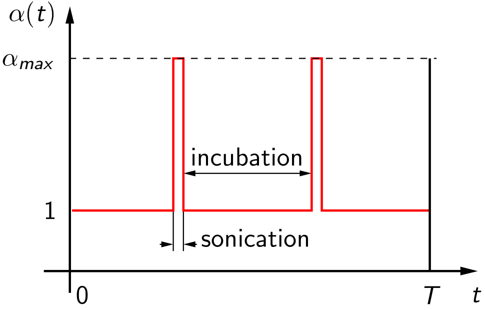

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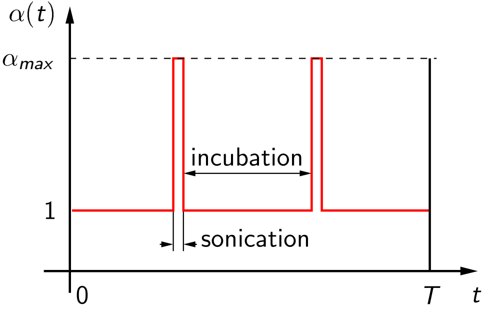

Problem: maximize the quantity $\sum_{1}^{n} i\, u_i(T)$ for a given final time T.

First approach: optimization for α constant

We consider a constant control $\alpha(t) \equiv \alpha$ and we want to maximize the Perron eigenvalue $\Lambda(\alpha)$ of the matrix $\alpha F + r(\alpha) G$. Indeed we know that, for a given control α,

$$U(t) \sim V \, e^{\Lambda(\alpha) t}$$

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Theorem (Calvez, G.)

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

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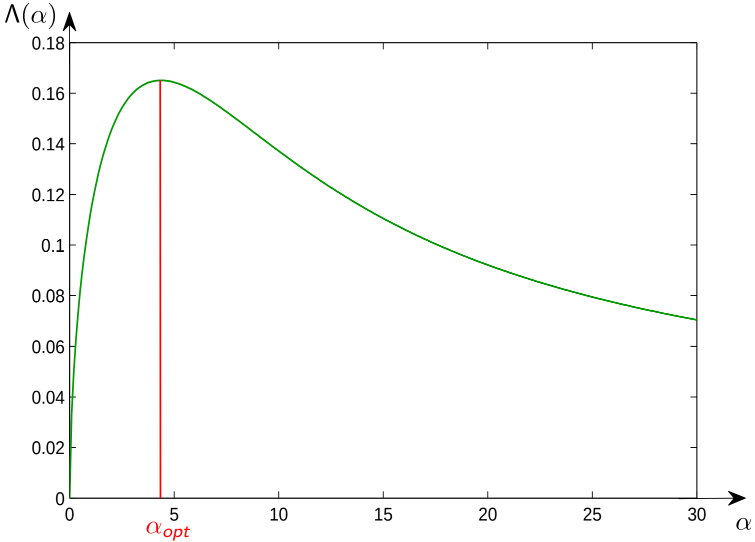
Continuous model: **Calvez, Doumic, G.**, Self-similarity in a general aggregation-fragmentation problem ; application to fitness analysis, *JMPA*, to appear.

Optimal eigenvalue



Periodic control

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

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

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<u>Proof:</u> $\Lambda_\omega(\epsilon) := \Lambda_F[\alpha_{opt} + \epsilon \cos(\omega t)]$,

$$\forall\, \omega, \;\; \frac{d}{d\epsilon}\Lambda_\omega(0) = 0$$

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Proof: $\Lambda_\omega(\epsilon) := \Lambda_F[\alpha_{opt} + \epsilon \cos(\omega t)]$,

$$\lim_{\omega \to +\infty} \frac{d^2}{d\epsilon^2} \Lambda_\omega(0) = \frac{1}{2} \frac{r''(\alpha_{opt})}{r(\alpha_{opt}) - \alpha_{opt} r'(\alpha_{opt})} \Lambda(\alpha_{opt})$$

Graphic interpretation

For r convex,

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

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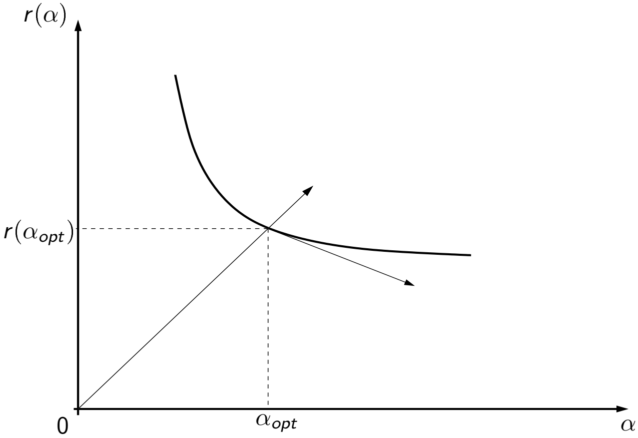

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Problem: find a control $\alpha(t)$ which maximizes, for a given time T, the payoff

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Define the control set

$$\Omega := \big\{(\alpha, r(\alpha)),\ \alpha \in [\alpha_{min}, \alpha_{max}]\big\}.$$

If r is affine, then Ω is convex and there exists an optimal control (cf. [Lee, Markus]).

Optimal control

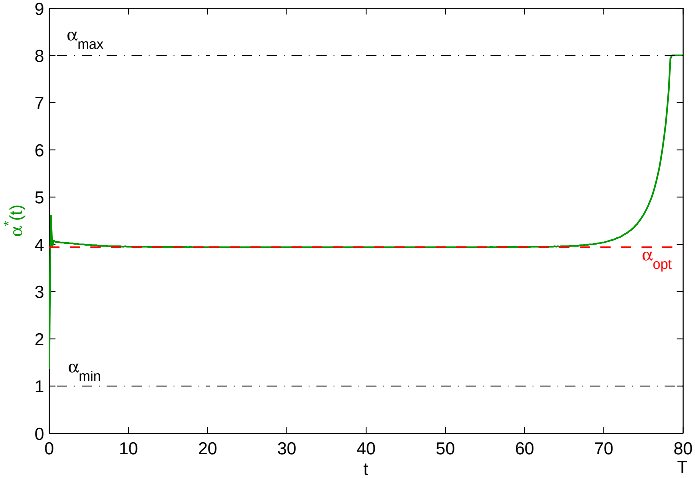

Figure: Optimal control for affine r.

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

Optimal control

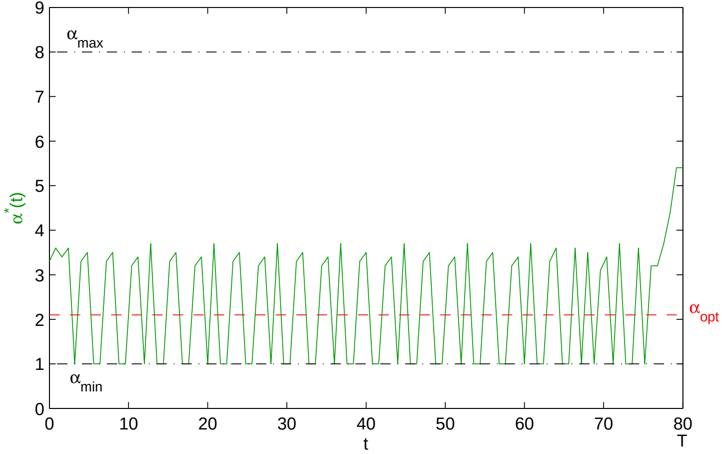

Figure: Optimal control for r decreasing convex, with $\Delta t = 0.8$.

Optimal control

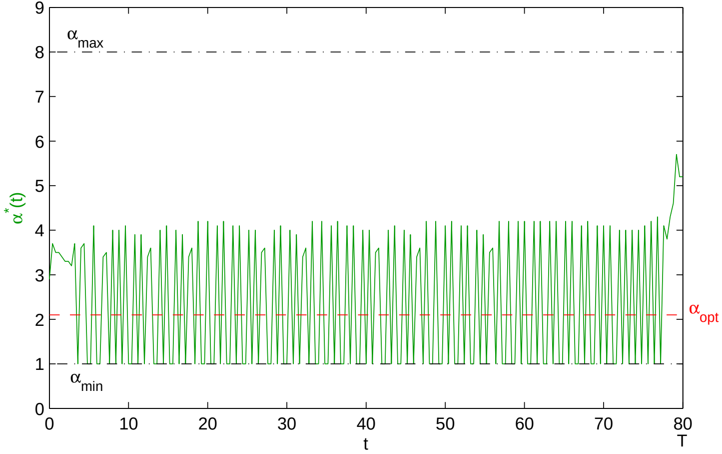

Figure: Optimal control for r decreasing convex, with $\Delta t = 0.4$.

Optimal control

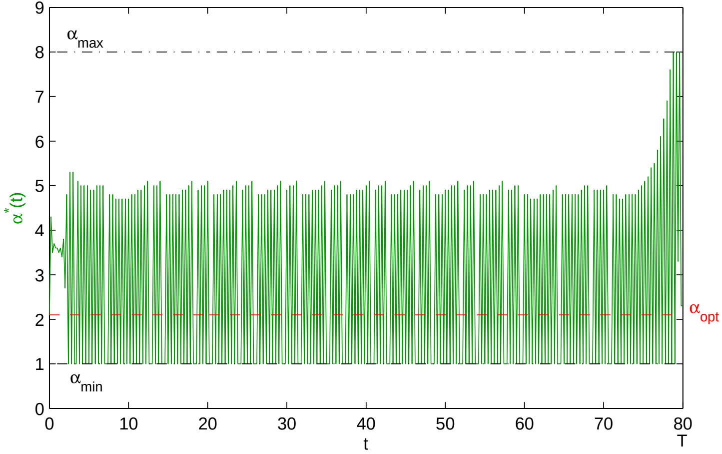

Figure: Optimal control for r decreasing convex, with $\Delta t = 0.2$.

Optimal control

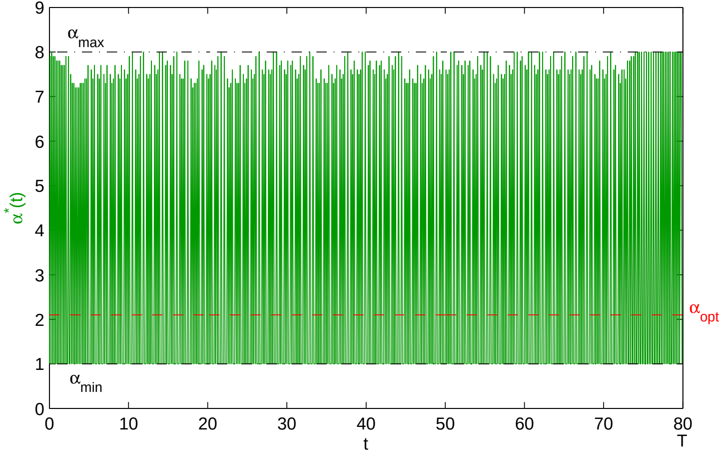

Figure: Optimal control for r decreasing convex, with $\Delta t = 0.1$.

Relaxed control

The optimal control problem also writes

$$\dot{U}(t) = \big(\alpha_1(t)F + \alpha_2(t)G\big)U(t)$$

with $\big(\alpha_1, \alpha_2\big) \in \Omega = \{(\alpha_1, \alpha_2),\ \alpha_2 = r(\alpha_1),\ \alpha_1 \in [\alpha_{min}, \alpha_{max}]\}$.

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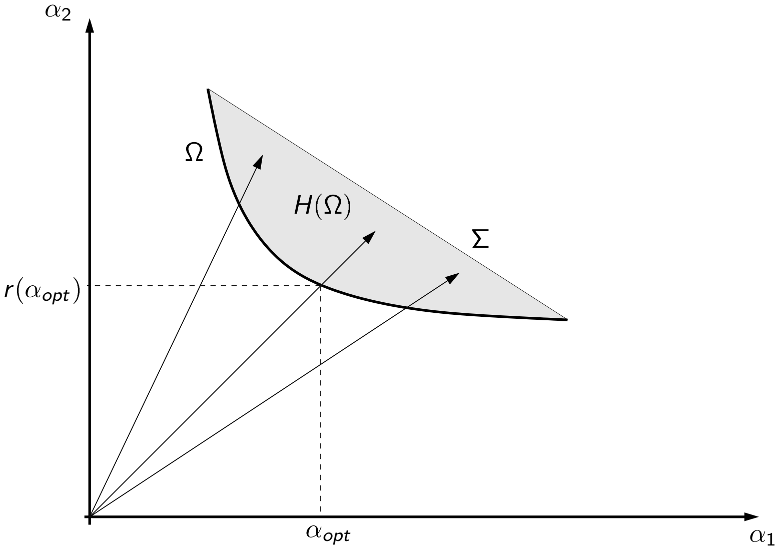
→ **New problem:** maximize the eigenvalue $\Lambda(\alpha_1, \alpha_2)$ on $H(\Omega)$.

Optimal Perron eigenvalue on $H(\Omega)$



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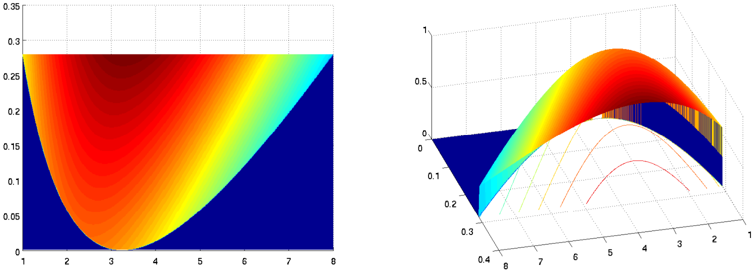

Figure: The function $\Lambda(\alpha_1, \alpha_2)$ plotted on the convex hull $H(\Omega)$.

Optimal relaxed control

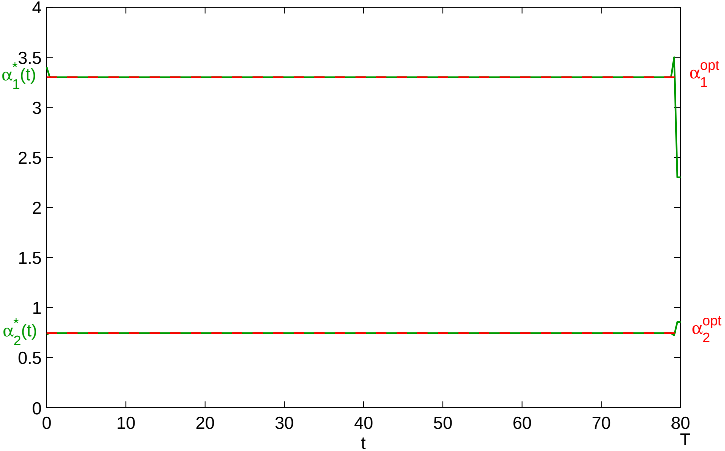

Figure: Optimal relaxed control for r decreasing convex.

Bang-bang approximation

The response $U(t)$ to a relaxed control $(\alpha_1, \alpha_2) \in H(\Omega)$ can be uniformly approximated by a sequence of responses $U^k(t)$ to classical controls $(\alpha^k, r(\alpha^k))$.

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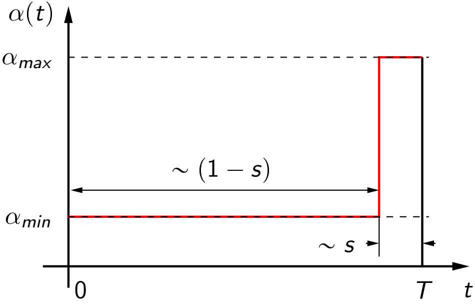

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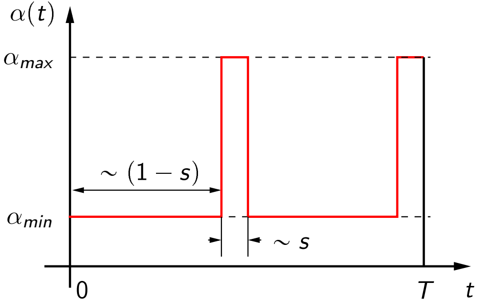

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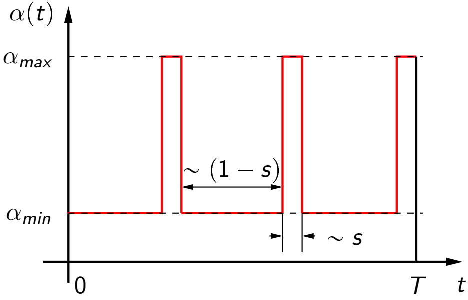

$k = 3$