Aggregation-Fragmentation Models for Protein Polymerization

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Outline

A (very) little bit about the biology of Prion and Alzheimer

Review on existing mathematical models for prion disease
& previous results

Some recent results:

- Link between discrete and continuous modelling
- Eigenvalue problem
- Parameters dependency

Perspectives

What is a common point of

- Prion (Madcow, Kuru, Creutzfeldt-Jakob disease)
- Alzheimer
- Huntington
- … and some others:

Neurodegenerative diseases

characterized by abnormal accumulation of

insoluble fibrous protein aggregates

called AMYLOIDS

Where do these fibrils come from ?

Healthy state: the considered protein **is present**

(APP for Alzheimer, PrP for Prion, HTT for Huntington…)

BUT is monomeric (N.B.: mono=1, poly = several)

Disease : Misfolding of the protein, leading to its polymerization onto long fibrils (monomers attach to one another)

Specificity of Prion disease: transmissible

PRION: PRoteinasceous Infectious Only

(Prusiner 1982, Griffith 1967, Nobel Prize)

Discrete Prion model

Masel, Jansen, Nowak, 1999:

synthesis

Monomer density

degradation

fragmentation

$$\frac{dv}{dt} = \lambda - \gamma v - v \sum_{i=n_0}^{\infty} \tau_i u_i + 2 \sum_{j \geq n_0} \sum_{i < n_0} i k_{i,j} \beta_j u_j ,$$

$$\frac{du_i}{dt} = -\mu_i u_i - \beta_i u_i - v(\tau_i u_i - \tau_{i-1} u_{i-1}) + 2 \sum_{j>i} \beta_j k_{i,j} u_j ,$$

i-polymer density

polymerization

for $i \geq n_0$

Size of a nucleus = minimal size of stable polymers

Remarks on discrete polymerization models

In Biology and Biophysics

- Huge literature
- Simulation tools e.g. softwares “PREDICI”, “POLYRED”

(e.g. see articles by Wulkow *et al.,* Choi *et al.*)

- Main difficulty: large (infinite…) number of parameters

⇒ often drastic simplifying assumptions

In Mathematics

- Family of coagulation-fragmentation models / Becker-Döring

See e.g. work by Aizenman-Back, 79; Ball, Carr, Penrose1990’s; Laurençot 02; Jabin-Niethammer, 03; Fournier-Mischler, 04 ; Dubovski – Stewart ; …

- Specificity of this model: particular role of monomers V

Coupling v / u_i in the “advection” term (replaces coalescence)

Discrete model for prion proliferation:
Nowak et al, 1998 and Masel et al., 1999

$$\frac{dv}{dt} = \lambda - \gamma v - v \sum_{i=n_0}^{\infty} \tau_i u_i + 2 \sum_{j \geq n_0} \sum_{i < n_0} i k_{i,j} \beta_j u_j,$$

$$\frac{du_i}{dt} = -\mu_i u_i - \beta_i u_i - v(\tau_i u_i - \tau_{i-1} u_{i-1}) + 2 \sum_{j > i} \beta_j k_{i,j} u_j,$$

Continuous version: Prüss, Pujo-Menjouet, Webb, Zacher, 2002

$$\frac{\mathrm{d}V}{\mathrm{d}t} = \lambda - \gamma V - V \int_{x_0}^{\infty} \tau(x) u(t,x)\,\mathrm{d}x + 2 \int_{x=x_0}^{\infty} \int_{y=0}^{x_0} y k(y,x) \beta(x) u(t,x)\,\mathrm{d}x\,\mathrm{d}y,$$

$$\frac{\partial u}{\partial t} = -\mu(x) u(t,x) - \beta(x) u(t,x) - V \frac{\partial}{\partial x}(\tau u) + 2 \int_{x}^{\infty} \beta(y) k(x,y) u(t,y)\,\mathrm{d}y.$$

Question: is the continuous framework valid ?

(Investigated in D, Goudon, Lepoutre, Comm. Math. Sc., 2009)

Previous works: Laurençot-Mischler, 2007 (coagulation-fragmentation)
Collet, Goudon, Poupaud, Vasseur, 2002 (Lifshitz-Slyozov)

A- Rescale the equations

$$\bar{t} = \frac{t}{T}, \qquad \bar{v}(\bar{t}) = \frac{v(\bar{t}T)}{\mathcal{V}}, \quad \bar{u}_i(\bar{t}) = \frac{u_i(\bar{t}T)}{\mathcal{U}}, \quad \bar{\beta}_i = \frac{\beta_i}{B}, \quad \bar{\tau}_i = \frac{\tau_i}{\mathcal{T}}$$

$$\bar{\mu}_i = \frac{\mu_i}{d_0}, \quad \bar{\lambda} = \frac{\lambda}{L}, \qquad \bar{\gamma} = \frac{\gamma}{\Gamma}.$$

Dimensionless parameters appear in the equation:

$$a = \frac{LT}{\mathcal{V}}, \quad b = BT, \qquad c = \Gamma T, \qquad s = \frac{\mathcal{U}}{\mathcal{V}}, \qquad \nu = T\mathcal{T}\mathcal{V} \qquad d = d_0 T$$

$$\frac{\mathrm{d}v}{\mathrm{d}t} = a\lambda - c\gamma v - \nu s v \sum \tau_i u_i + 2bs \sum_{j \geq n_0} \sum_{i < n_0} i k_{i,j} \beta_j u_j,$$

$$\frac{\mathrm{d}u_i}{\mathrm{d}t} = -d\mu_i u_i - b\beta_i u_i - \nu v(\tau_i u_i - \tau_{i-1} u_{i-1}) + 2b \sum\nolimits_{j>i} \beta_j k_{i,j} u_j, \qquad \text{for } i \geq n_0.$$

Mass conservation:

$$v + s \sum_{i=n_0}^{\infty} i u_i = \rho$$

B- Define a small parameter

$$\frac{\mathrm{d}v}{\mathrm{d}t} = a\lambda - c\gamma v - \nu s v \sum \tau_i u_i + 2bs \sum_{j \ge n_0} \sum_{i < n_0} i k_{i,j} \beta_j u_j,$$

$$\frac{\mathrm{d}u_i}{\mathrm{d}t} = -d\mu_i u_i - b\beta_i u_i - \nu v(\tau_i u_i - \tau_{i-1} u_{i-1}) + 2b \sum_{j>i} \beta_j k_{i,j} u_j, \qquad \text{for } i \ge n_0.$$

And mass conservation: $v + s \sum_{i=n_0}^{\infty} i u_i = \rho$

$\Rightarrow$ $s = \dfrac{\mathcal{U}}{\mathcal{V}} = \varepsilon^2$

Biological interpretation: if $v \approx \sum i u_i$ and i_M typical size of a polymer

$\mathcal{V} \approx \sum i u_i \approx i_M^2 \mathcal{U}$. $\Rightarrow$ $\varepsilon = \dfrac{1}{i_M}, \qquad i_M \gg 1.$

C- Assumptions on the coefficients

$$\frac{\mathrm{d}v}{\mathrm{d}t} = a\lambda - c\gamma v - \nu s v \sum \tau_i u_i + 2bs \sum_{j\geq n_0} \sum_{i<n_0} i k_{i,j} \beta_j u_j,$$

$$\frac{\mathrm{d}u_i}{\mathrm{d}t} = -d\mu_i u_i - b\beta_i u_i - \nu v(\tau_i u_i - \tau_{i-1} u_{i-1}) + 2b \sum_{j>i} \beta_j k_{i,j} u_j, \qquad \text{for } i \geq n_0.$$

Under the following assumption

There exists $K > 0$, $\alpha \geq 0$, $m \geq 0$ *and* $0 \leq \theta \leq 1$ *such that*
$0 \leq \beta_i \leq K i^\alpha \qquad 0 \leq \mu_i \leq K i^m, \qquad 0 \leq \tau_i \leq K i^\theta.$

We set $a = 1, \quad b = \varepsilon^\alpha, \quad c = 1, \quad d = \varepsilon^m, \quad \nu = \varepsilon^{\theta-1}$

$$\frac{\mathrm{d}v}{\mathrm{d}t} = \lambda - \gamma v - \varepsilon^{\theta+1} v \sum \tau_i u_i + 2\varepsilon^{2+\alpha} \sum_{i\geq n_0} \sum_{j<n_0} j k_{j,i} \beta_i u_i,$$

$$\frac{\mathrm{d}u_i}{\mathrm{d}t} = -\varepsilon^m \mu_i u_i - \varepsilon^\alpha \beta_i u_i - \varepsilon^{\theta-1} v(\tau_i u_i - \tau_{i-1} u_{i-1}) + 2\varepsilon^\alpha \sum_{j>i} \beta_j k_{i,j} u_j, \qquad \text{for } i \geq n_0$$

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Assumption on n_0 : $\lim_{\varepsilon \to 0} \varepsilon n_0(\varepsilon) = x_0 \geq 0$

Biological interpretation: $x_0=0$ *iff* $n_0 << i_M$

Lemma. Under the previous assumptions + some compactness, we can define continuous functions μ, τ, β, k and extract a subsequence ε_n such that

$$\mu^{\varepsilon_n}, \tau^{\varepsilon_n}, \beta^{\varepsilon_n}, k^{\varepsilon_n} \longrightarrow \mu, \tau, \beta, k$$

D- Asymptotic result (based on moment estimates)

Theorem (D, Goudon, Lepoutre). If moreover

$$\varepsilon \sum_{i=n_0(\varepsilon)}^{\infty} u_i^{0,\varepsilon} \leq M_0 < +\infty,$$

$$\varepsilon^{2+\sigma} \sum_{i=n_0(\varepsilon)}^{\infty} i^{1+\sigma} u_i^{0,\varepsilon} \leq M_{1+\sigma} < +\infty, \qquad 1+\sigma > \max(1, \alpha, 1+m, 1+\theta).$$

We can extract a subsequence ε_n such that

$$u^{\varepsilon_n} \rightharpoonup U, \ \ in\ \mathcal{C}([0,T]; \mathcal{M}^1([0,\infty)) - \mathrm{weak} - \star)),$$
$$v^{\varepsilon_n} \rightharpoonup V \qquad uniformly\ on\ [0,T].$$

weak solution of :

$$\frac{\mathrm{d}V}{\mathrm{d}t} = \lambda - \gamma V - V \int_{x_0}^{\infty} \tau(x) U(t,x)\,\mathrm{d}x + 2 \int_{x=x_0}^{\infty} \int_{y=0}^{x_0} y k(y,x) \beta(x) U(t,x)\,\mathrm{d}x\,\mathrm{d}y,$$

$$\frac{\partial U}{\partial t} = -\mu(x) U(t,x) - \beta(x) U(t,x) - V \frac{\partial}{\partial x}(\tau U) + 2 \int_x^{\infty} \beta(y) k(x,y) U(t,y)\,\mathrm{d}y.$$

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$$v^{\varepsilon_n} \rightharpoonup V \qquad uniformly\; on\; [0,T].$$

weak solution of :

$$V(t) + \int_{x_0}^{\infty} xU(t,x)\,\mathrm{d}x \quad = \quad V_0 + \int_{x_0}^{\infty} xU_0(x)\,\mathrm{d}x + \lambda t - \int_0^t \gamma V(s)\,\mathrm{d}s - \int_0^t \int_{x_0}^{\infty} x\mu(x)U(s,x)\,\mathrm{d}x\,\mathrm{d}s.$$

$$\frac{\partial U}{\partial t} = -\mu(x)U(t,x) - \beta(x)U(t,x) - V\frac{\partial}{\partial x}(\tau U) + 2\int_x^{\infty} \beta(y)k(x,y)U(t,y)\,\mathrm{d}y.$$

E- What to choose for a boundary condition ?

Discrete model: no boundary condition.

Continuous model: needs one to be well-posed

-> obtained rigorously if

By setting (in a weak sense): if

$$k(x,y) = l(x,y) + \delta(x = x_0^+)\psi^+(y) + \delta(x = x_0^-)\psi^-(y),$$

$$x_0 V \tau(x_0) U(t, x_0) = 2x_0 \int_{x_0}^{\infty} \psi^+(x)\beta(x)U(t,x)\,\mathrm{d}x.$$

-> obtained only formally otherwise

Some comments

- Several different possible continuous equations as limits of the discrete one, according to assumptions on the coefficients:

e.g. fragmentation term $$2\varepsilon^{\alpha}\sum_{j>i}\beta_j k_{i,j} u_j,$$

Can give depolymerization, a boundary condition or a fragmentation kernel

⇒ Necessity to obtain orders of magnitude

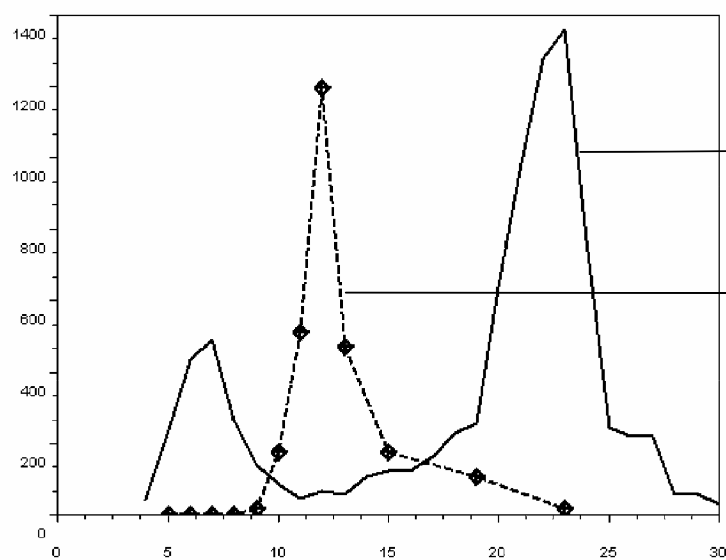
- Coalescence has been neglected but may be added

Study of the continuous model

Constant coefficient case (reduces to 3 coupled ODE) studied by Engl, Prüss, Pujo-Menjouet, Webb, Zacher

Motivation for studying the general case:

- Silveira et al: 2-peak size distributions of polymers
- Biophysical considerations (Radford et al, PNAS 09)



Size of particles

Density of polymers

"infectious efficiency":

≈ Polymerization rate

Continuous model – Well-Posedness

A key feature : Mass balance equation:

$$\varrho(t) = V(t) + \int_{x_0}^{\infty} xU(t,x)\,\mathrm{d}x = \varrho(0) + \lambda t - \int_0^t \gamma V(s)\,\mathrm{d}s - \int_0^t \int_{x_0}^{\infty} x\mu(x)U(t,x)\,\mathrm{d}x.$$

(Simonnett, Walker, JMAP, 2006
& Laurençot, Walker, J. Evol. Equ. 2007): proved

For positive polymerization rate

- Existence and uniqueness of classical solutions for regular initial condition and bounded coefficients

- Existence of weak solutions for L^1 initial condition

- Stability of the disease-free steady state when it is unique

Continuous model – Asymptotic behaviour

(Calvez, Lenuzza, Mouthon, Perthame *et al*, BMB 08 & JBD 08)

For a polymerization rate possibly vanishing toward zero:

- Stability or unstability of the zero steady state under 2 conditions:
  - Solution for the eigenvalue problem
  - The eigenvalue decreases with $V(t)$

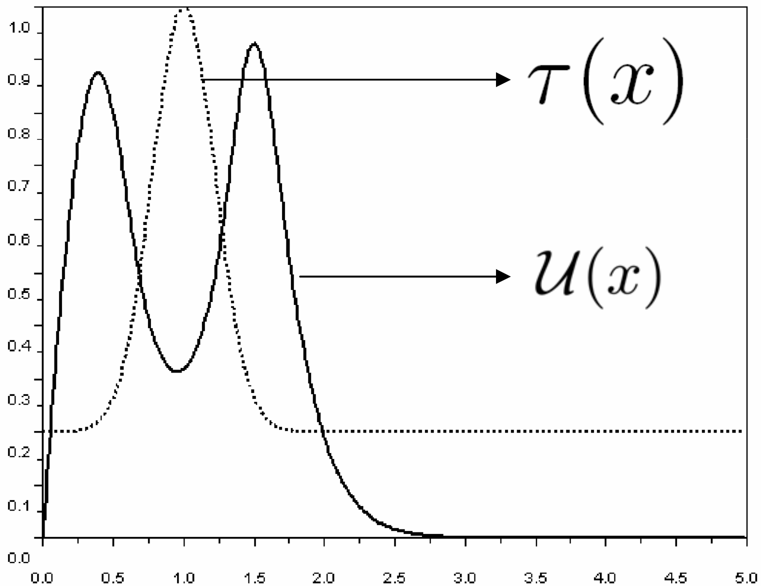
  Tool: General Relative Entropy (see Perthame, Michel, Mischler, etc)

- Boundedness of the solution

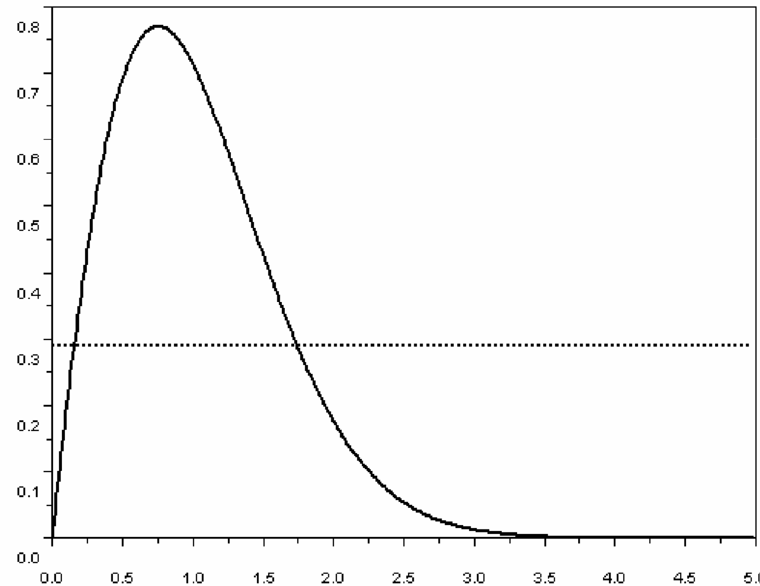
- Necessary assumptions on τ to obtain an eigenvector with two peaks

Shape of the eigenvector

(figures from Calvez, Lenuzza et al, 2008)



Variable polymerization rate



Constant coefficient case

Question: what conditions to ensure existence and uniqueness of a solution to the eigenvalue problem ?

A general eigenvalue problem

(D. Gabriel, M3AS, 2010)

The polymerization rate possibly vanishes toward zero

$$\begin{cases} \frac{\partial}{\partial x}(\tau(x)\mathcal{U}(x)) + (\beta(x)+\Lambda)\mathcal{U}(x) = 2\int_x^\infty \beta(y)\kappa(x,y)\mathcal{U}(y)dy, & x \geqslant 0, \\ \tau\mathcal{U}(x=0) = 0, \qquad \mathcal{U}(x) \geq 0, \qquad \int_0^\infty \mathcal{U}(x)dx = 1, & \\ -\tau(x)\frac{\partial}{\partial x}(\phi(x)) + (\beta(x)+\Lambda)\phi(x) = 2\beta(x)\int_0^x \kappa(y,x)\phi(y)dy, & x \geqslant 0, \\ \phi(x) \geq 0, \qquad \int_0^\infty \phi(x)\mathcal{U}(x)dx = 1. & \end{cases}$$

Rejoin general problems of cell division (see Michel, M3AS, 2006 and Perthame, 2007), and general aggregation/fragmentation models.

Many other possible applications

Study of the eigenvalue problem

Theorem (D., Gabriel). Under some technical assumptions, there exists a u$(\Lambda, \mathcal{U}, \phi)$ution to the previous eigenvalu$\Lambda > 0$lem, and

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

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

$$\exists k > 0 \ s.t. \ \frac{\phi}{1 + x^k} \in L^\infty(\mathbb{R}^+) \qquad \tau \frac{\partial}{\partial x} \phi \in L^\infty_{loc}(\mathbb{R}^+)$$

Application. by General Relative Entropy principle

(work by Michel, Mischler, Perthame, Ryzhik,…)

define $\langle u_0, \phi \rangle = \int u_0(y) \phi(y) dy$

then

$$\int_0^\infty \left| u(y,t) e^{-\Lambda t} - \langle u_0, \phi \rangle \mathcal{U}(y) \right| \phi(y) \, dy \underset{t \to \infty}{\longrightarrow} 0$$

Assumptions for well-posedness of the eigenvalue problem

Some necessary assumptions for the previous theorem

- For the kernel k: $\int \kappa(x,y)dx = 1,$ $\quad \int x\kappa(x,y)dx = \frac{y}{2}$

$$\int \frac{x^2}{y^2}\kappa(x,y)dx \leq c < 1/2$$

- To avoid shattering:

$$\exists C > 0, \gamma \geq 0 \quad s.t. \qquad \int_0^x \kappa(z,y)\,dz \leq \min\Big(1, C\Big(\frac{x}{y}\Big)^\gamma\Big) \qquad \text{and} \qquad \frac{x^\gamma}{\tau(x)} \in L_0^1$$

- Fragmentation and polymerization rates:

$$\tau,\ \beta \in L^1_{loc}(\mathbb{R}^+) \cap \ \{f \geq 0 \ : \ \exists \mu, \nu \geq 0,\ \limsup_{x\to\infty} x^{-\mu} f(x) < \infty \text{ and } \liminf_{x\to\infty} x^\nu f(x) > 0\}$$

$$\frac{\beta}{\tau} \in L_0^1 \qquad\qquad \lim_{x\to+\infty} \frac{x\beta(x)}{\tau(x)} = +\infty$$

Well-posedness for the Eigenvalue problem – sketch of the proof

- Truncated & regularized problem
  -> existence and uniqueness (Krein-Rutman)

- A priori estimates

(by integration of the equation against proper weights,…)

-> weak compactness in L^1 (Dunford Pettis) & convergence of the regularized problem

Eigenvalue problem – Fitness dependency on the coefficients

(Calvez, D., Gabriel, in progress)

Question:

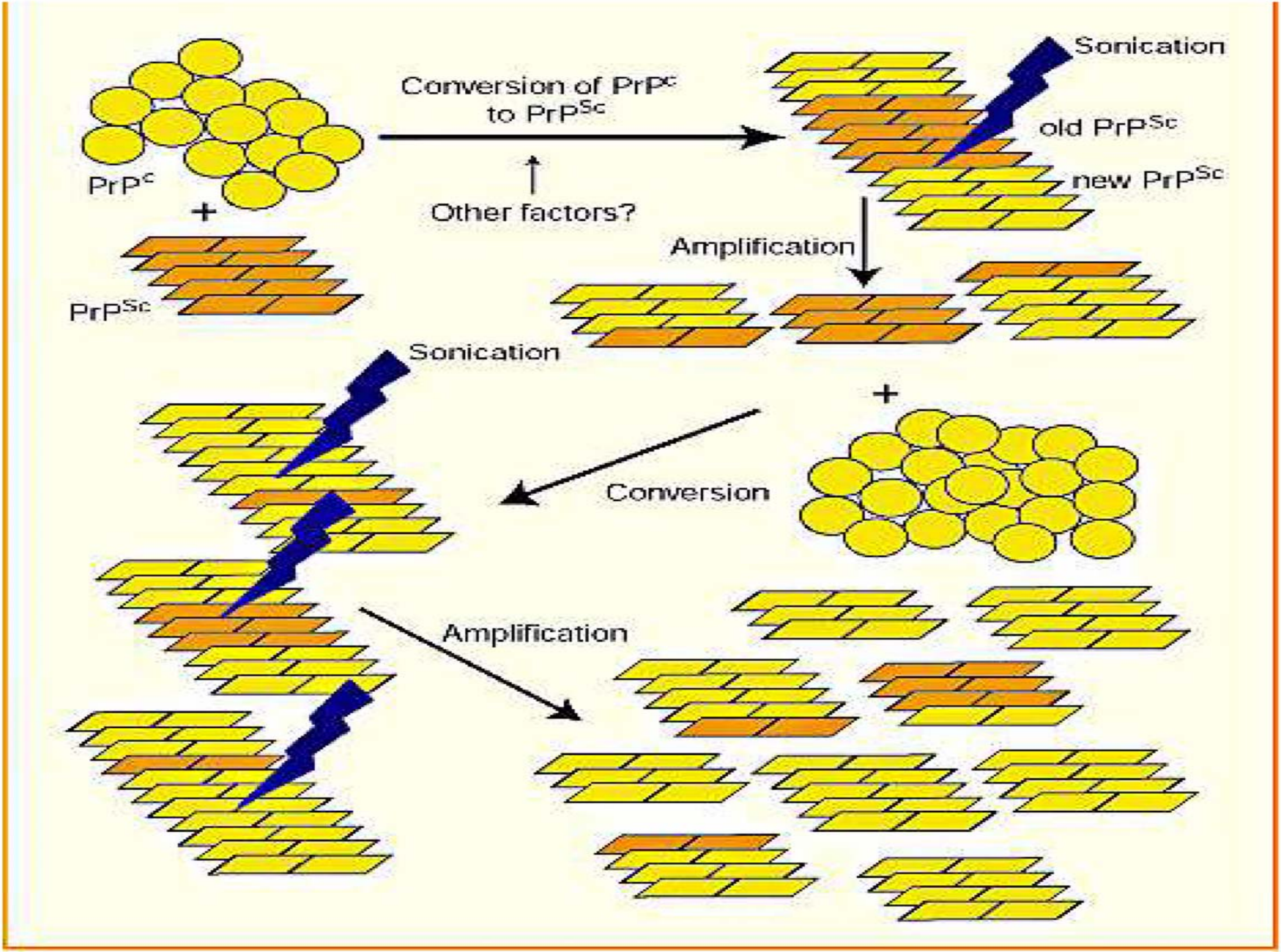
how does the eigenvalue depend on the parameters ?

Application:

- Asymptotic behaviour (see above: monotonous dependency on *V* is required
- Better understanding of paradoxical biological behaviour

(e.g. : what happens if fragmentation increases ? See Knowles et al, Science 09)

- Improve “PMCA” protocole



Sonication
Conversion of PrP^c to PrP^Sc
old PrP^Sc
new PrP^Sc
PrP^c
+
Other factors?
Amplification
PrP^Sc
Sonication
+
Conversion
Amplification

$$\frac{\mathrm{d}V}{\mathrm{d}t} = \lambda - \gamma V - V\int_{x_0}^{\infty} \tau(x)u(t,x)\,\mathrm{d}x + 2\int_{x=x_0}^{\infty}\int_{y=0}^{x_0} yk(y,x)\beta(x)u(t,x)\,\mathrm{d}x\,\mathrm{d}y,$$

$$\frac{\partial u}{\partial t} = -\mu(x)u(t,x) - \beta(x)u(t,x) - V\frac{\partial}{\partial x}(\tau u) + 2\int_{x}^{\infty} \beta(y)k(x,y)u(t,y)\,\mathrm{d}y.$$

Sonication phase: increase of β

Incubation phase: natural coefficients

Some questions:

- Is there an optimal finite λ when β increases ?
- How to choose an optimal strategy for incubation/sonication times in order to increase the polymer density as fast as possible ?

Eigenvalue problem – Fitness dependency on the coefficients

(Calvez, D., Gabriel, in progress)

Fragmentation dependence:

$$\begin{cases} \lambda_\alpha \mathcal{U}_\alpha = -\partial_x(\tau(x)\mathcal{U}_\alpha(x)) - \alpha\beta(x)\mathcal{U}_\alpha(x) + 2\alpha \displaystyle\int_x^\infty \beta(y)\kappa(x,y)\mathcal{U}_\alpha(y)\,dy, \qquad x \geqslant 0, \\ \tau\mathcal{U}_\alpha(x=0) = 0, \qquad \mathcal{U}_\alpha(x) > 0 \text{ for } x > 0, \qquad \int_0^\infty \mathcal{U}(x)dx = 1. \end{cases}$$

Proposition. i) If $\lim\limits_{x\to\infty} \dfrac{\tau(x)}{x} = 0,$ then $\lim\limits_{\alpha\to 0} \lambda_\alpha = 0.$

Eigenvalue problem – Fitness dependency on the coefficients

(Calvez, D., Gabriel, in progress)

Fragmentation dependence:

$$\begin{cases} \lambda_\alpha \mathcal{U}_\alpha = -\partial_x(\tau(x)\mathcal{U}_\alpha(x)) - \alpha\beta(x)\mathcal{U}_\alpha(x) + 2\alpha\int_x^\infty \beta(y)\kappa(x,y)\mathcal{U}_\alpha(y)\,dy, & x \geqslant 0, \\ \tau\mathcal{U}_\alpha(x=0) = 0, \qquad \mathcal{U}_\alpha(x) > 0 \ \text{ for } x > 0, \qquad \int_0^\infty \mathcal{U}(x)dx = 1. \end{cases}$$

Proposition. ii) If $\tau(x) \underset{x\to 0}{\sim} \tau x^\nu$ then

$$\textit{If } \nu < 1, \ \textit{then} \ \lim_{\alpha\to\infty} \lambda_\alpha = +\infty,$$
$$\textit{if } \nu = 1, \ \textit{then} \ \lim_{\alpha\to\infty} \lambda_\alpha = \tau \ (= \tau'(0)),$$
$$\textit{if } \nu > 1, \ \textit{then} \ \lim_{\alpha\to\infty} \lambda_\alpha = 0.$$

Eigenvalue problem – Fitness dependency on the coefficients

Idea: use a self-similar transformation: if $\beta(x) \underset{x\to 0}{\sim} \beta x^\gamma$
(in the spirit of Escobedo, Mischler, Rodriguez Ricard, 04)

Define $\tau_\alpha(x) := \alpha^{k\nu}\tau(\frac{x}{\alpha^k}), \quad \beta_\alpha := \alpha^{k\gamma}\beta(\frac{x}{\alpha^k}). \quad \mathcal{U}_\alpha(x) = \alpha^k v_\alpha(\alpha^k x)$

For $k = \frac{1}{1+\gamma-\nu}$ one has

$$\delta_\alpha v_\alpha(x) = -\frac{\partial}{\partial x}\Big(\tau_\alpha(x) v_\alpha(x)\Big) - \beta_\alpha(x) v_\alpha(x) + 2\int_x^\infty \beta_\alpha(y)\kappa_\alpha(x,y) v_\alpha(y)\,dy,$$

And $\delta_\alpha = \alpha^{\frac{\nu-1}{1+\gamma-\nu}}\lambda_\alpha$

Proving $\delta_\alpha \underset{\alpha\to\infty}{\longrightarrow} l < +\infty$ gives the result.

Eigenvalue problem – Fitness dependency on the coefficients

(Calvez, D., Gabriel, in progress)

Polymerization dependence: similarly

$$\lambda_\alpha \mathcal{U}_\alpha = -\alpha \partial_x (\tau(x) \mathcal{U}_\alpha(x)) - \beta(x)\mathcal{U}_\alpha(x) + 2\int_x^\infty \beta(y)\kappa(x,y)\mathcal{U}_\alpha(y)\,dy.$$

Proposition. *If* $\lim_{x\to 0} \beta(x) = 0$ *then* $\lim_{\alpha \to 0} \lambda_\alpha = 0$

If $\beta(x) \underset{x\to\infty}{\sim} \beta_\infty x^\gamma$ *and* $\tau(x) \underset{x\to\infty}{\sim} \tau_\infty x^\nu$, *then*

$$\gamma < 0 \implies \lambda_\alpha \underset{\alpha\to\infty}{\longrightarrow} 0.$$

Perspectives

- Many open questions concerning the eigenvalue problem / asymptotic behaviour

- Optimization of the PMCA protocole

(Calvez, Gabriel)

- Generalize the original model, and justify its use by asymptotic analysis and experiences

(in strong interaction with H. Rezaei)

- Apply inverse problem techniques to recover the equation parameters from INRA experiments

(F. Charles, in strong interaction with J. Zubelli)

To be continued…

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TOPPAZ

Theory and Observation of Protein polymerization

in Prion and Alzheimer diseases

Discrete-continuous

Compactness assumptions on the coefficients:

$$\begin{cases} \text{There exists } K > 0 \text{ such that} \\ \left|\beta_{i+1} - \beta_i\right| \leq K i^{\alpha-1} \\ \left|\mu_{i+1} - \mu_i\right| \leq K i^{m-1}, \\ \left|\tau_{i+1} - \tau_i\right| \leq K i^{\theta-1}, \end{cases}$$

$$\begin{cases} \text{There exists } K > 0 \text{ such that for any } i, j \\ \left|\sum_{p=0}^{i-1}\sum_{r=0}^{p-1} k_{r,j+1} - \sum_{p=0}^{i-1}\sum_{r=0}^{p-1} k_{r,j}\right| \leq K. \end{cases}$$

Lemma 1 *Let* $(z_i)_{i\in\mathbb{N}}$ *be a sequence of nonnegative real numbers verifying*

$$0 \leq z_i \leq K i^{\kappa}, \qquad \left|z_{i+1} - z_i\right| \leq K i^{\kappa-1}$$

for some $K > 0$ *and* $\kappa \geq 0$*. For* $x \geq 0$*, we set* $z^{\varepsilon}(x) = \sum_i \varepsilon^{\kappa} z_i \chi_{[\varepsilon i, \varepsilon(i+1))}(x)$*. Then there exist a subsequence* $\varepsilon_n \to 0$*, and a continuous function* $z : x \in [0,\infty) \mapsto z(x)$ *such that* z^{ε_n} *converges to* z *uniformly on* $[r,R]$ *for any* $0 < r < R < \infty$*. If* $\kappa > 0$*, the convergence holds on* $[0,R]$ *for any* $0 < R < \infty$ *and we have* $z(0) = 0$*.*

Lemma 2 *Let the coefficients* $k_{i,j}$ *satisfy Assumptions (5),(6) and (23). Then there exist a subsequence* $(\varepsilon_n)_{n\in\mathbb{N}}$ *and* $k : y \in [0,\infty) \mapsto k(\cdot,y) \in \mathcal{M}^1_+([0,\infty))$ *which belongs to* $\mathcal{C}([0,\infty); \mathcal{M}^1_+([0,\infty)) - \mathrm{weak} - \star)$ *satisfying also (5) and (6) (in their continuous version) and such that* k^{ε_n} *converges to* k *in the following sense: for every compactly supported smooth function* $\varphi \in \mathcal{C}^\infty_c([x_0,\infty))$*, denoting*

$$\phi^{\varepsilon_n}(y) = \int_{n_0(\varepsilon_n)\varepsilon_n}^{y} k^{\varepsilon_n}(x,y)\varphi(x)\,\mathrm{d}x, \qquad \phi(y) = \int_{x_0}^{y} k(x,y)\varphi(x)\,\mathrm{d}x, \tag{24}$$

we have $\phi^{\varepsilon_n} \to \phi$ *uniformly locally in* $[x_0,+\infty)$*.*

Moments estimate

Lemma 3 *Let the assumptions of Theorem 2 be fulfilled. Then for any $T > 0$, there exists a constant $C < \infty$ which only depends on $M_0, M_{1+\sigma}, K$ and T, such that for any $\varepsilon > 0$:*

$$\sup_{t\in[0,T]} \int_0^\infty (1 + x + x^{1+\sigma}) u^\varepsilon(t,x)\,\mathrm{d}x \le C, \qquad 0 \le v^\varepsilon(t) \le C$$

Cantor diagonal process, we can extract a subsequence u^{ε_n} and $U \in \mathcal{C}([0,T]; \mathcal{M}^1([0,\infty)) - \text{weak} - \star)$, such that the following convergence

$$\int_0^\infty u^{\varepsilon_n}(t,x)\varphi(x)\,\mathrm{d}x \to \int_0^\infty U(t,x)\varphi(x)\,\mathrm{d}x,$$

as $\varepsilon_n \to 0$, holds uniformly on $[0,T]$, for any $\varphi \in \mathcal{C}_0([0,\infty))$. As $u^\varepsilon(t,x) = 0$ for $x \le \varepsilon n_0(\varepsilon)$, we check that $U(t,.)$ has its support in $[x_0, \infty[$. It remains to prove that (U,V) satisfies (13) (14).