Protein polymerization simulation

for amyloid diseases (Prion, Alzheimer’s)

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Outline

- A brief overview:
  - The mathematical context
  - The biological motivation and main goal
  - The reference model
- 3 case studies
  - A growth-nucleation model applied to Huntington’s
  - A growth-fragmentation model applied to Prion
  - A new application of Lifshitz-Slyozov system

The mathematical context

- Coagulation/fragmentation equations in physics

Lifshitz-Slyozov / Bekker-Döring equations

Application to dust formation, gelation, aerosols, etc.

Ball, Carr & Penrose (1986), Niethammer & Pego (2000), etc.

Probabilistic school: Bertoin (2006), Aldous & Pitman (1998), etc.

- (Size-)structured populations in biology

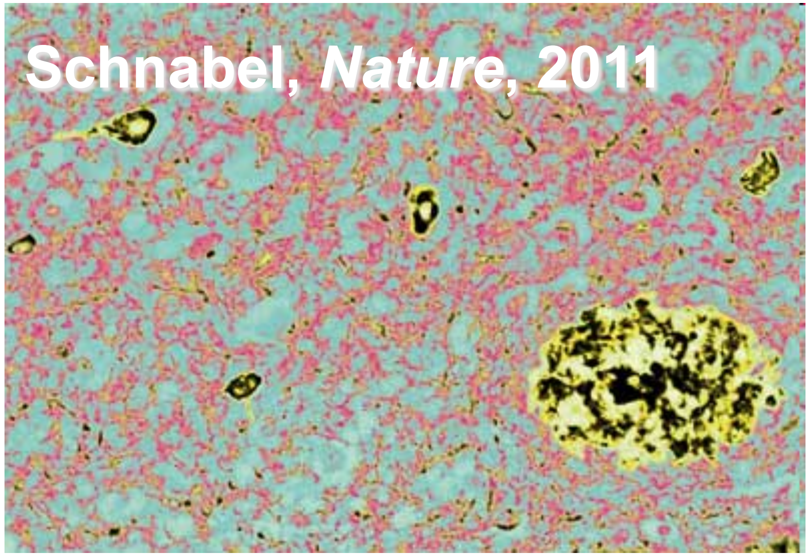
Applications for cancer cells, parasite infection etc.

Metz & Diekmann (1986), Gyllenberg & Thieme (1984)

Perthame & Ryzhik (2004), Escobedo, Laurençot & Mischler (2003) etc.

Common point between:

- Alzheimer's (illustrated)
- Prion (mad cow)
- Huntington's
- and some others (Parkinson's, etc)?



Neurodegenerative diseases characterized by abnormal accumulation of protein aggregates called AMYLOIDS

Healthy state: **mono**meric protein
(PrP Prion, Aβ Alzheimer's, PolyQ Huntington's)

Disease state: **poly**mers

Main challenge:

Key polymerization mechanisms

Address quantitatively major biological questions:

Transient species? Most infectious polymer size?

Application to several proteins

PrPc (Prion), Aβ (Alzheimer’s), PolyQ (Huntington’s)

In constant interaction with biologists

To design and validate model and experiments

The reference PDE model

A reference biologically-derived PDE model

$$\frac{\partial u}{\partial t} + \frac{\partial}{\partial x}\left(\left(\overbrace{V(t)\tau(x)}^{\text{Polym}} \overbrace{- \, d(x)\big)}^{\text{Depolymerization}} \, u \right) =$$

$$- \beta(x)u(t,x) + 2\int_x^{\infty} k(x,y)\beta(y)u(t,y)dy - \overbrace{\mu(x)u(t,x)}^{\text{Degradation}}$$

Fragmentation

Coalescence

$$+ \frac{1}{2}\int_0^{x} c(y,x-y)u(t,y)u(t,x-y)dy - \int_0^{\infty} c(x,y)u(t,x)u(t,y)dy,$$

u(t,x) concentration of polymers of size *x* at time *t*

V(t) concentration of monomers at time *t*

A reference biologically-derived PDE model

original derivation in D, Prigent, Rezaei et al, Plos One, 2012
Previous work: D, Goudon, Lepoutre, 2009,
Laurençot-Mischler, 2005, Collet, Goudon, Poupaud, Vasseur 2004

Formation Degrad. Depolym Polymerization

$$\frac{dV}{dt} = \lambda - \mu_0 V + \int_0^\infty \big(d(x) - V\tau(x)\big)u(t,x)dx,$$

boundary condition: nucleation

$$\boxed{u(t,x=0) = \frac{k_{\mathrm{on}} V^{i_0}}{k_{\mathrm{off}} + \tau(0)V}}$$

i_0: size of the nucleus

About the reference PDE model

- Present situation: Oversimplifications

  Xue, Radford *et al*, PNAS (2008) - Knowles *et al*, Science (2009)

  Lack of physical justification Silveira *et al*, Nature (2005)

- Our approach:

  keep the original system

  - Nonlinear
  - Nonlocal

  Adapt it to specific biology-driven problems

  - Nucleation
  - Prion model

Case study 1

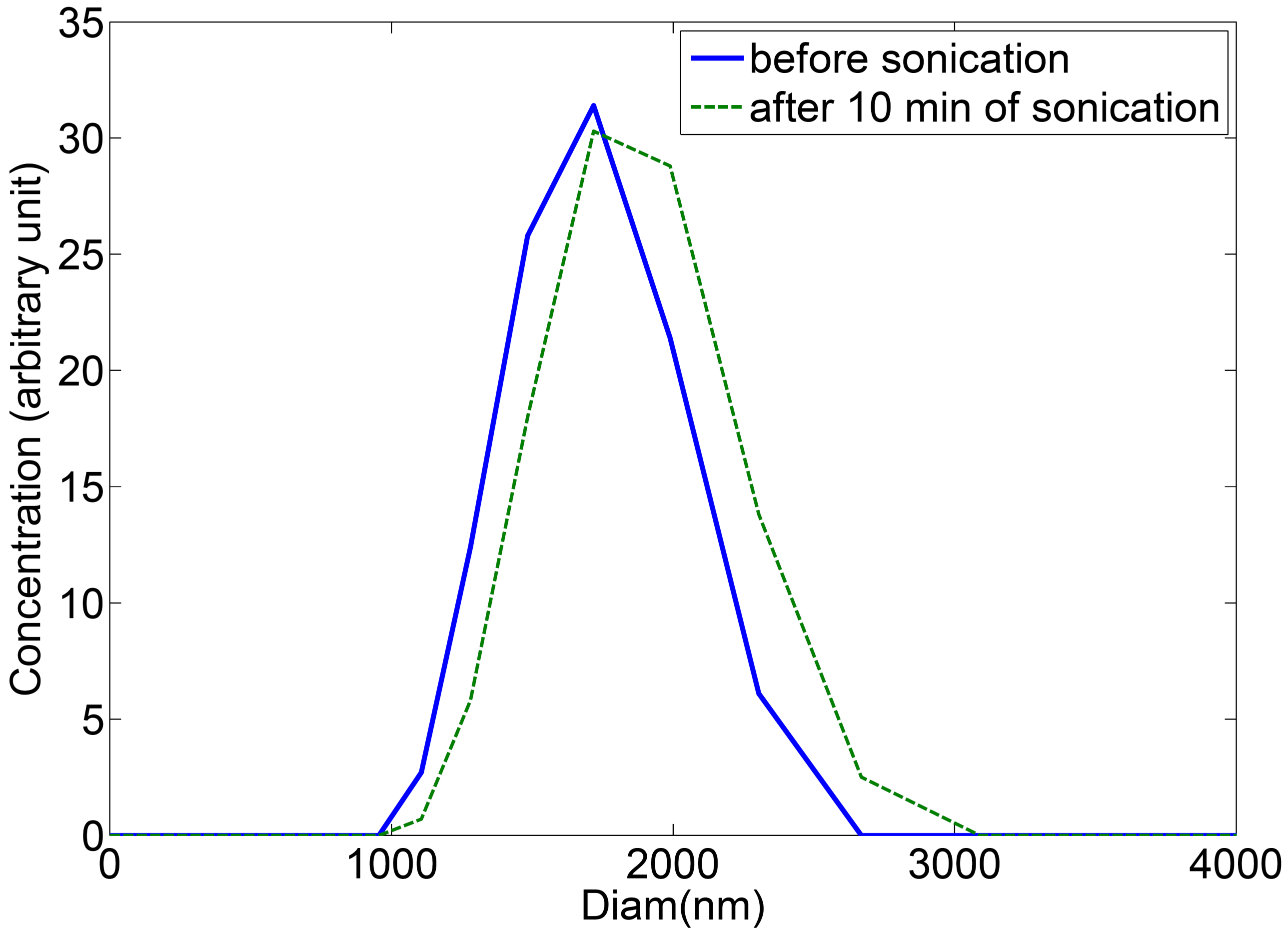
A simple nucleation problem
for PolyQ polymerisation (Huntington’s disease):

an identification question

(D, Prigent, Rezaei et al., Plos One, 2012)

Case 1: Huntington's disease (PolyQ)

No fragmentation & No coalescence - experimental proof:



A simple nucleation model

- No coalescence nor fragmentation (experimental proof)
- Here a still simplified version for clarity
- Nucleation – what is the value of i_0?

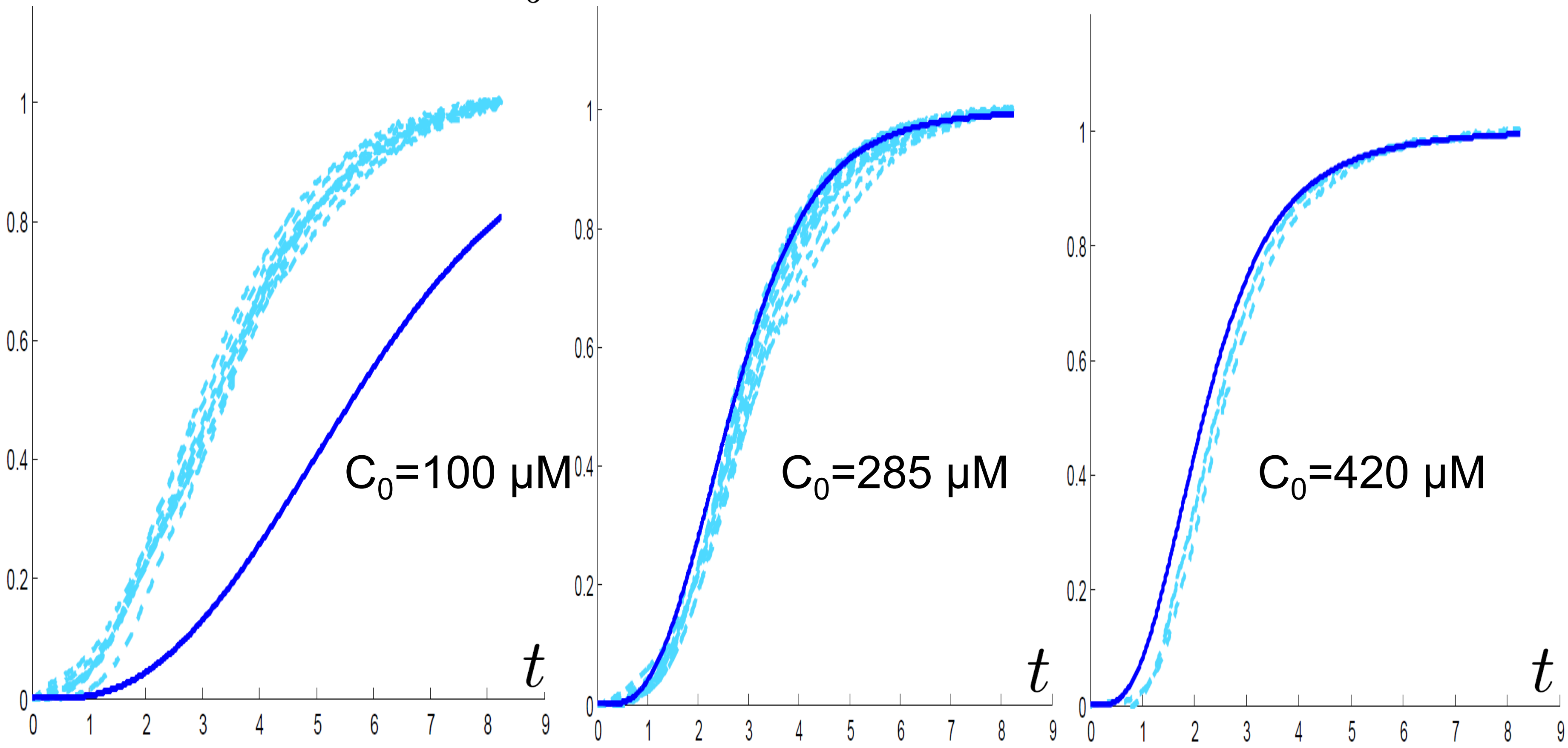
$$\frac{\partial u(t,x)}{\partial t} + V \frac{\partial}{\partial x}\big(\tau(x) u(t,x)\big) = 0,$$

$$\frac{dV}{dt} = -V \int_0^\infty \tau(x)\, u(t,x) dx, \qquad u(t, x=0) = \frac{k_{\text{on}} V^{i_0}}{k_{\text{off}} + \tau(0) V},$$

In vitro PolyQ spontaneous polymerization

Comparison **experiments** & **simulations** (with A. Ballesta, post-doc)

$$\text{Polymerised mass:} \quad \int xu(t,x)dx$$

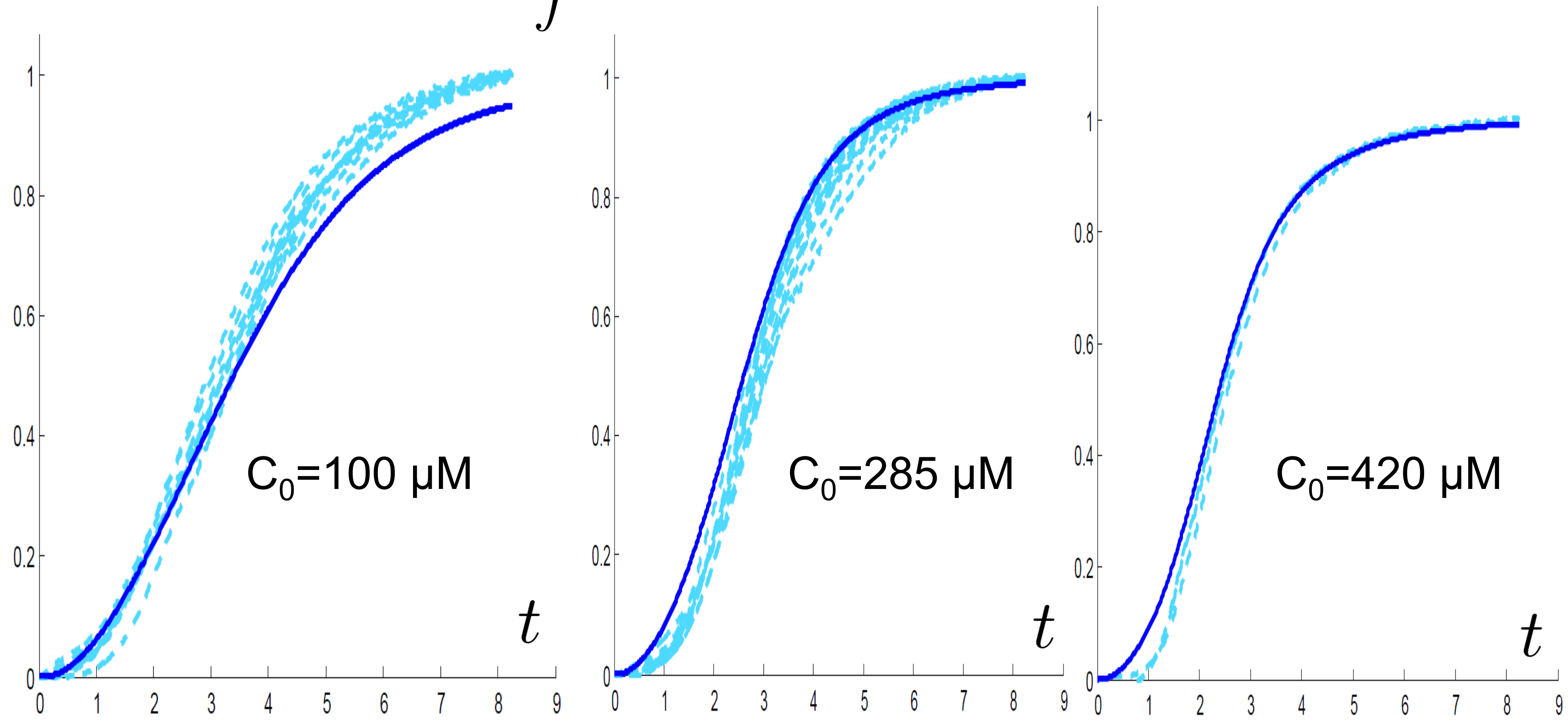


Nucleus size i_0=3 – global error: 40% - not satisfactory

In vitro PolyQ spontaneous polymerization

Comparison **experiments** & **simulations** (with A. Ballesta, post-doc)

Polymerised mass: $\int xu(t,x)dx$



Nucleus size **i0=1** – global error: 10%: **relevant**

Open problems

- Sensitivity analysis (H.T. Banks)

  Inverse problem: observability - methodology (D. Chapelle, P. Moireau)

- Stochastic model for intrinsic variability (P. Robert)

- Test and validate our predictions on new experimental data

Case study 2

The growth-fragmentation equation
and the nonlinear Prion model:

mathematical analysis

(Calvez, D, Gabriel, JMPA, 2012)

The Prion model

First studied by Greer, Pujo-Menjouet, Prüss, Webb et al. (2004-2006)

$$\frac{\partial u(t,x)}{\partial t} + \frac{\partial}{\partial x}\Big(\overbrace{V(t)\tau(x)}^{\text{growth}}\, u(t,x)\Big) = -\beta(x)u(t,x) + \overbrace{2\int_x^\infty k(x,y)\beta(y)u(t,y)dy}^{\text{Fragmentation}},$$

$$\frac{dV}{dt} = \lambda - \mu_0 V - V\int_0^\infty \tau(x)u(t,x)dx, \qquad u(t,x=0)=0.$$

The growth-fragmentation / cell division equation:

- **A rich model**

Diekmann, Gyllenberg & Thieme (1984) – Escobedo, Mischler (2004) – etc.

- **Recent inverse problem solution**

Doumic, Perthame, Zubelli *et al.* (2009 to 2012)

A counter-intuitive behaviour

Theorem. [Calvez, D, Gabriel, J. Math. Pures Appl. (2012)]

The Malthus coefficient (first eigenvalue) does not necessarily depend in a monotonous way on *V.*

To be more specific, under technical assumptions, it behaves like the fragmentation rate β behaves:

- *around ∞ if V tends to ∞*
- *or around 0 if V tends to 0*

(+ eigenvector profile obtained by self-similarity)

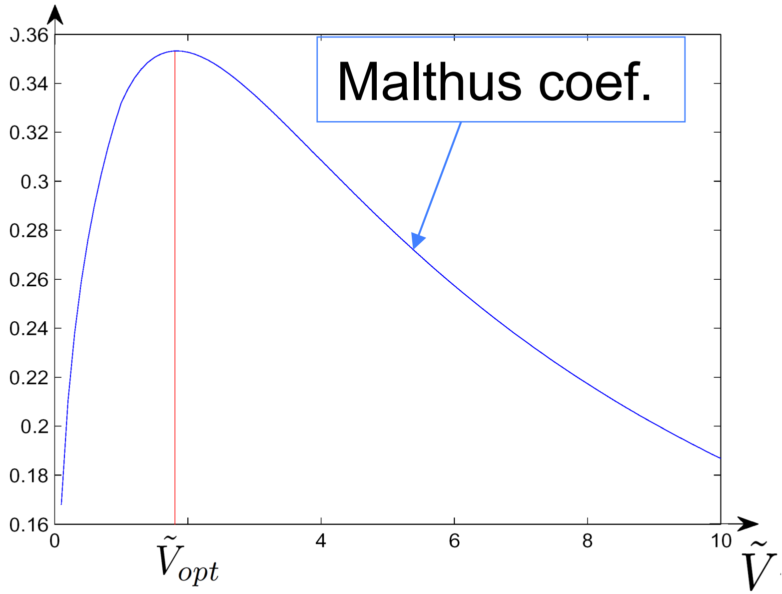


Illustration: example with

β vanishing at *0* and ∞

Open problems linked to the growth-frag. eq.

- Nonlinear behaviour, spectral gap
- Asymptotics when no steady profile
- Inverse Problem for general fragmentation kernels

  (PhD of T. Bourgeron, in progress)

- Adapt to different growth pathways Rezaei et al, PNAS (2008)
- Include the nucleation step & coagulation

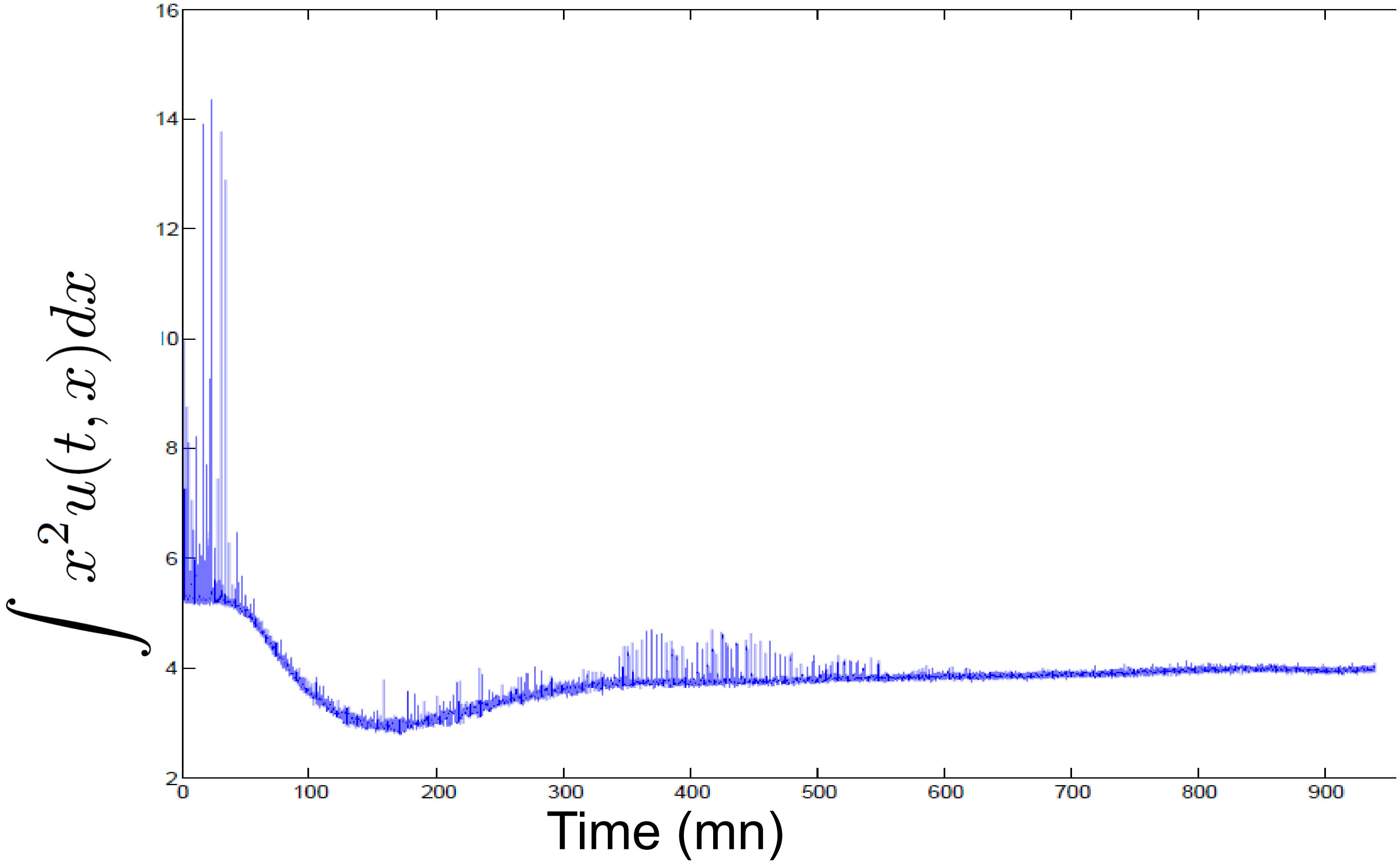
Case study 3 (still in progress)

A data-driven problem and
a new application for Lifshitz-Slyozov system:

Prion fibrils depolymerization

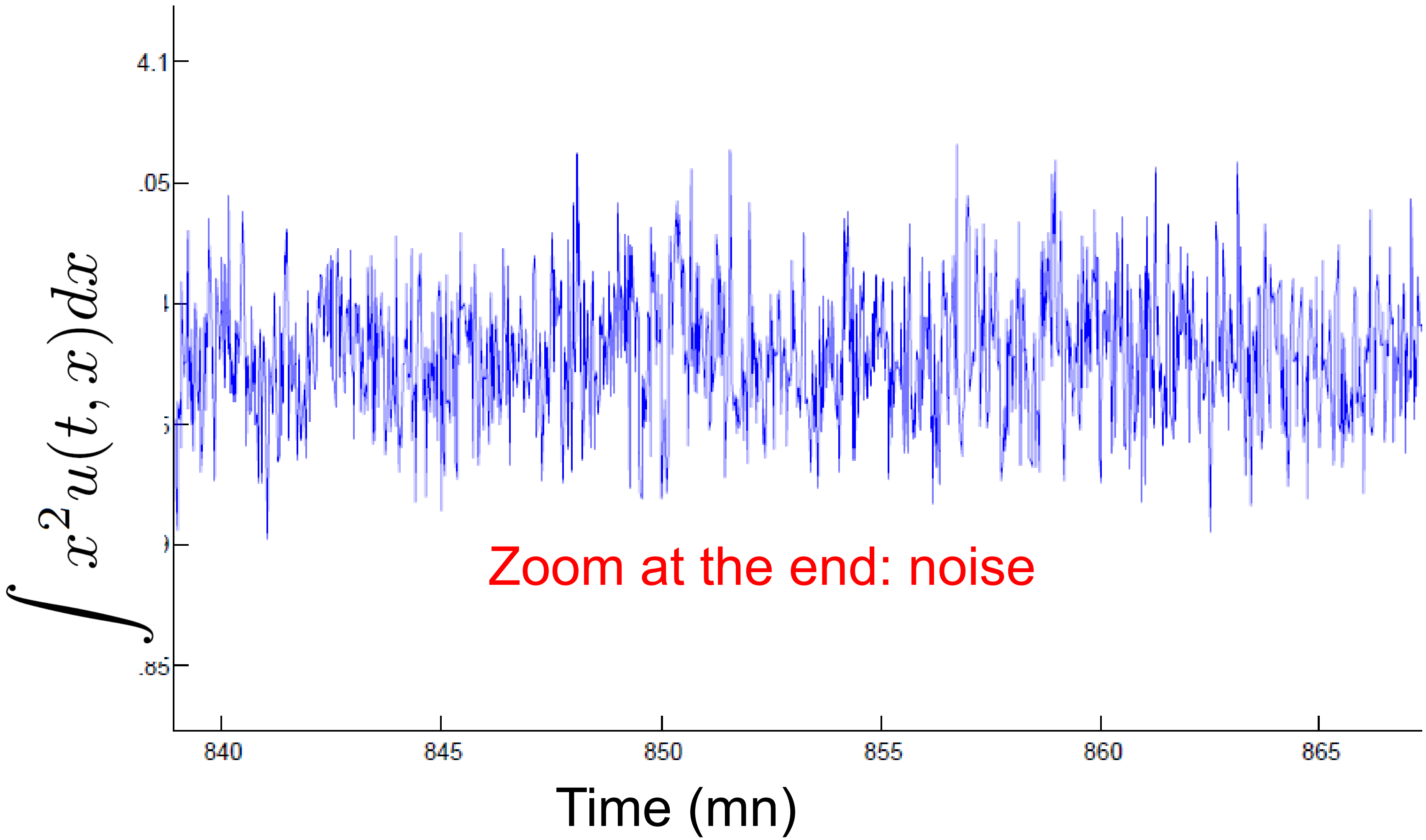
(PhD. Of H.W. Haffaf,
in collaboration with P. Moireau, S. Prigent, H. Rezaei)

experiments by Human Rezaei and Joan Torrent



Third case: a data-driven problem
Prion fibrils depolymerization

experiments by Human Rezaei and Joan Torrent



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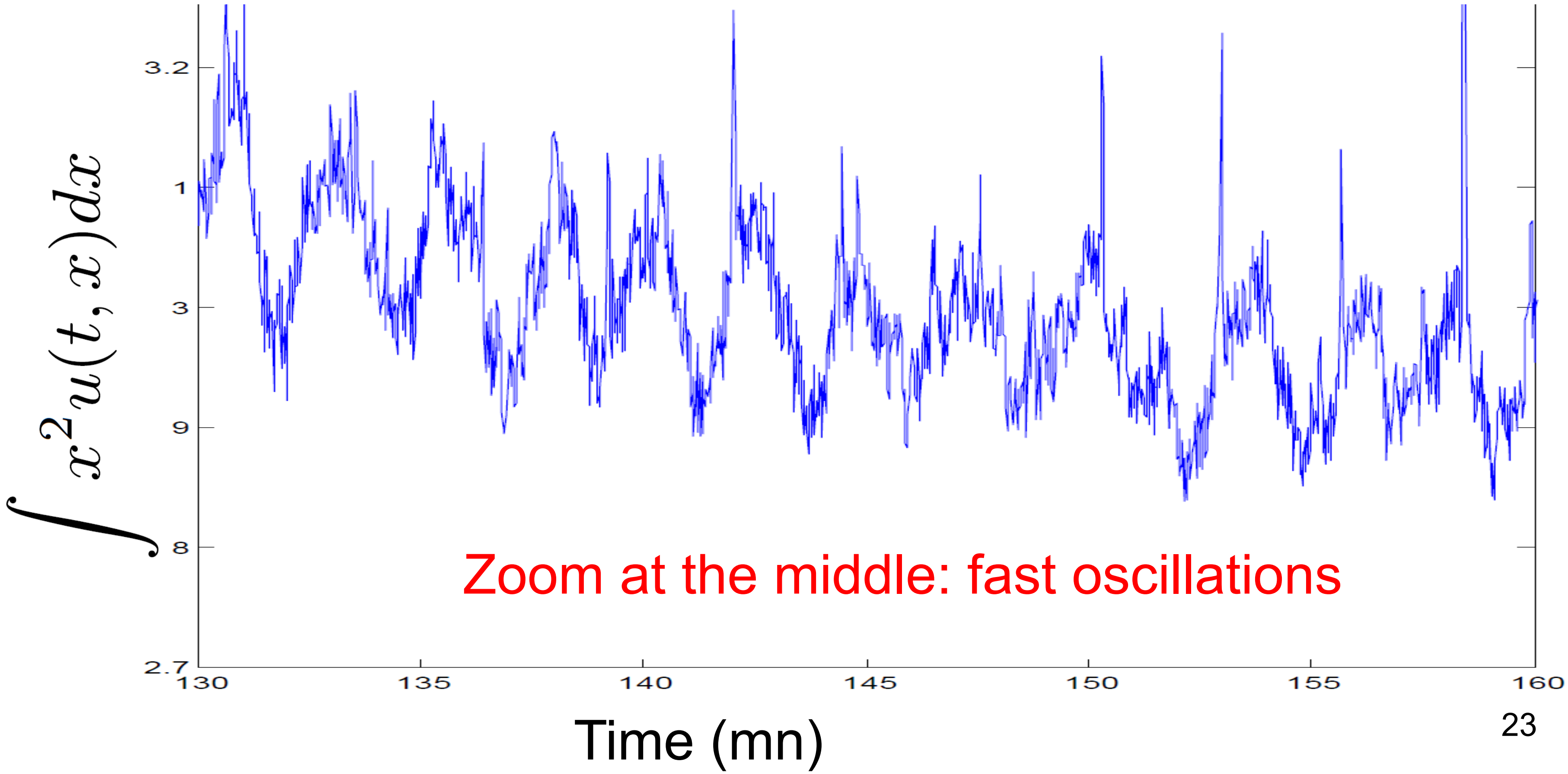

Simplest Model: the *Lifshitz-Slyozov* system

(*Becker-Döring* : discrete in size)

$$\frac{\partial u}{\partial t} + \frac{\partial}{\partial x}\Big(\big(V(t)\tau(x) - d(x)\big) u \Big) = 0,$$

$$\frac{dV}{dt} = \int_0^\infty \big(d(x) - V\tau(x)\big) u(t,x) dx,$$

A seminal model – Lifshitz & Slyozov (1961) - **revisited**

new problems:

- inverse Problem solution (with P. Moireau) ?
- How to modify it to understand the oscillations ?
- Dirac mass solutions and trend to equilibrium ?

In a nutshell

❑ In Mathematics

- A new light on seminal models : many applications
- Inverse problem for fragmentation/coalescence
- A bridge between statistical and deterministic modelling of coalescence/fragmentation models

❑ In Biology and in Society

- Bring mathematical and numerical research to biologists: analysis will motivate new experiments
- Find the key mechanisms of polymerization
- Identify targets for **therapeutics**

To be continued…

i the ERC starting grant

MERCI JEAN-PIERRE !

AD

Simulation of the Kineti oblem

for the Protein PolymERization in A iseases

(Prion, Alzheimer's)