Long time behavior for some continuous polymerization models

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Neurodegenerative diseases

Neurodegenerative diseases are quite a concern for our society. **No effective treatment for them –not even to slow down their progression– is currently known.**

Many such neurodegenerative diseases (e.g. Alzheimer's, Prion) belong to the group of amyloid diseases, being characterized by an abnormal accumulation of protein aggregates.

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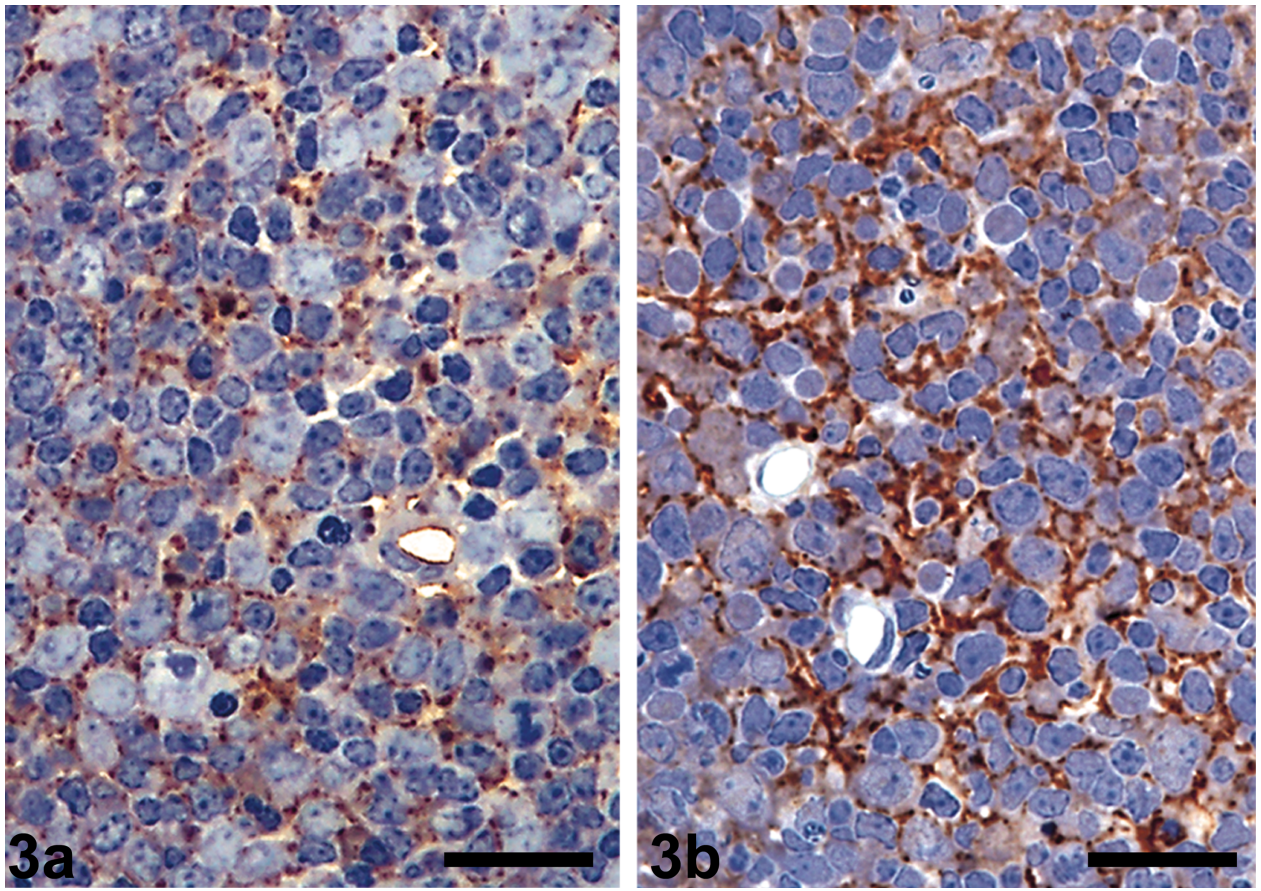
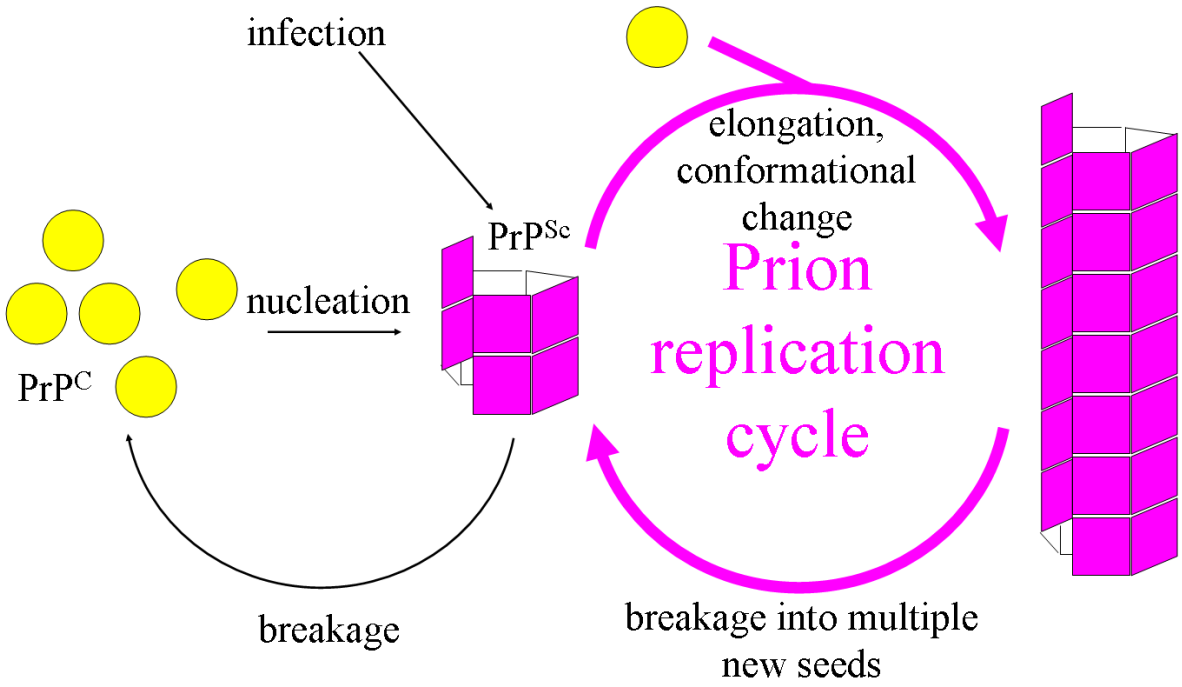
An example of neurodegenerative diseases: Prion Disease (Scrapie) in sheep

Healthy vs infected limph nodes



(Picture authorship: Gillian McGovern, Martin Jeffrey, Plos One)

Prion replication and fibril formation



(Picture authorship: Joanna Masel, wikipedia)

Fibril formation in neurodegenerative diseases

The intrinsic mechanisms of these chain reactions are currently not very well known.

The processes may involve an infinite number of species -polymer sizes- and reactions (e.g. nucleation, (de)polimerization, fragmentation, etc).

We want to understand what are the main reaction mechanisms and which are secondary. Currently this cannot be achieved solely on an experimental basis.

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Polymerization + fragmentation

Let $V(t)$ be the quantity of monomers. We use the variable $x \geq 0$ to represent polymer size, being $u(t,x)$ the density of polymers of size x:

$$\begin{cases} \dfrac{dV}{dt} = -V \displaystyle\int_0^\infty g(x)u(t,x)\,dx \\ \dfrac{\partial u}{\partial t} + V\dfrac{\partial}{\partial x}(g(x)u) = -B(x)u + 2\displaystyle\int_x^\infty B(y)k(y,x)u(t,y)\,dy. \end{cases}$$

(Prüss, Pujo–Menjouet, Webb, Zacher, Disc. Cont. Dyn. Syst. B 2006)

(Calvez, Lenuzza, Doumic, Deslys, Mouthon, Perthame, J. Biol. Dynamics 2010)

Conservation of mass (in vitro)

- $x \mapsto u(x)$ gives the size distribution, thus

$$\rho(t) := \int_0^\infty u(t,x)\,dx$$

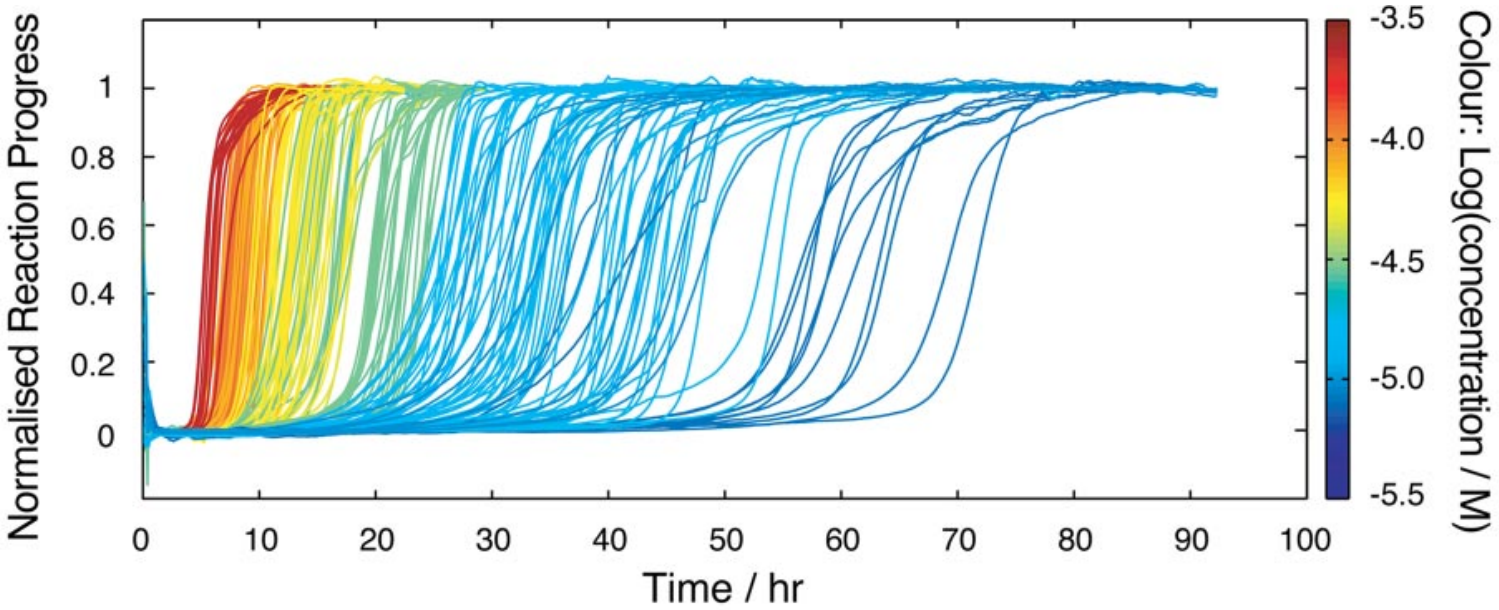
  yields the number of polymers,
- $x \mapsto x\,u(x)$ is the polymerized mass distribution, and hence

$$\int_0^\infty x\,u(x)\,dx$$

  amounts for the polymerized mass,
- The total mass of the system is a conserved quantity,

$$M := V(t) + \int_0^\infty x\,u(t,x)\,dx.$$

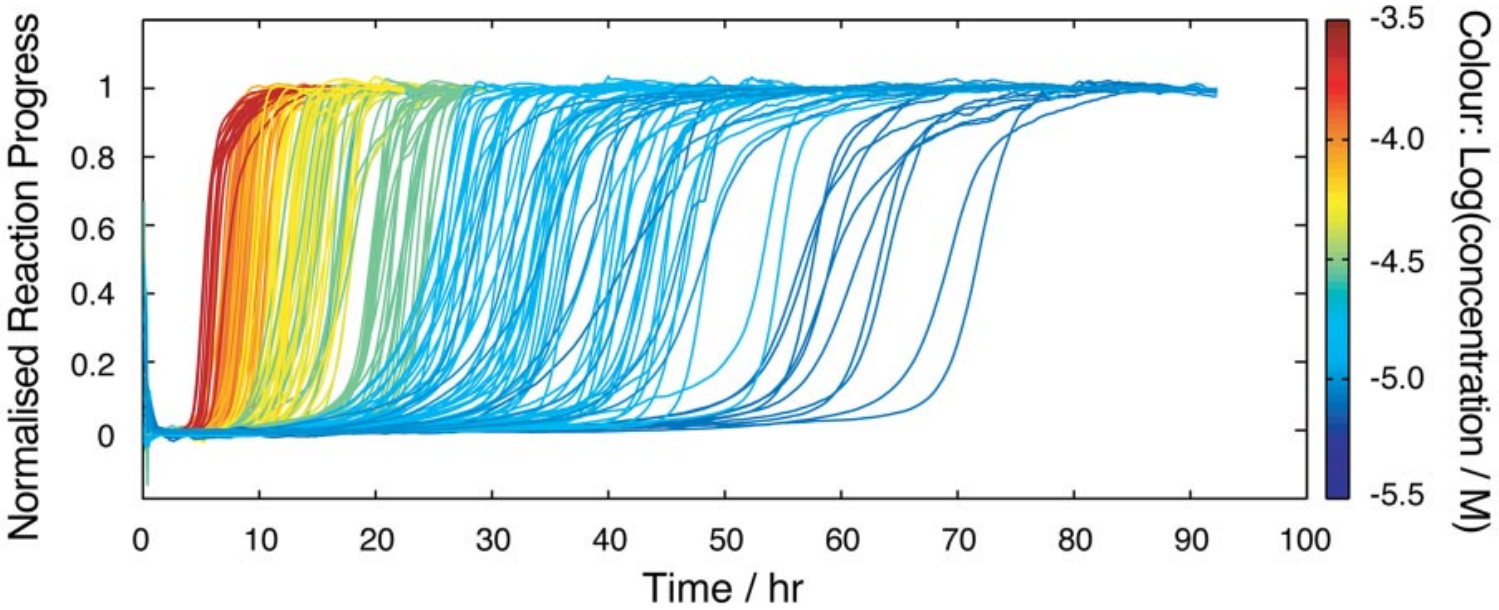
Experimental measurements



(Xue, Homans, Radford, PNAS 2008)

- For a given protein concentration, a significant variant in the lag time is observed. (previous talks)
- The steepness of the transitions indicates the presence of "secondary processes" accelerating the reaction.

Experimental measurements



(Xue, Homans, Radford, PNAS 2008)

- Analyze continuous models combining some basic ingredients: To what extent do we get similar dynamics?
- Here we will combine: Polimerization, nucleation, fragmentation and/or depolimerization.

A slight diversion: Lifshitz–Slyozov's model

Kinetics of precipitation from supersaturated solid solutions: Cluster grow/diminish solely by the attachment/detachment of monomers.

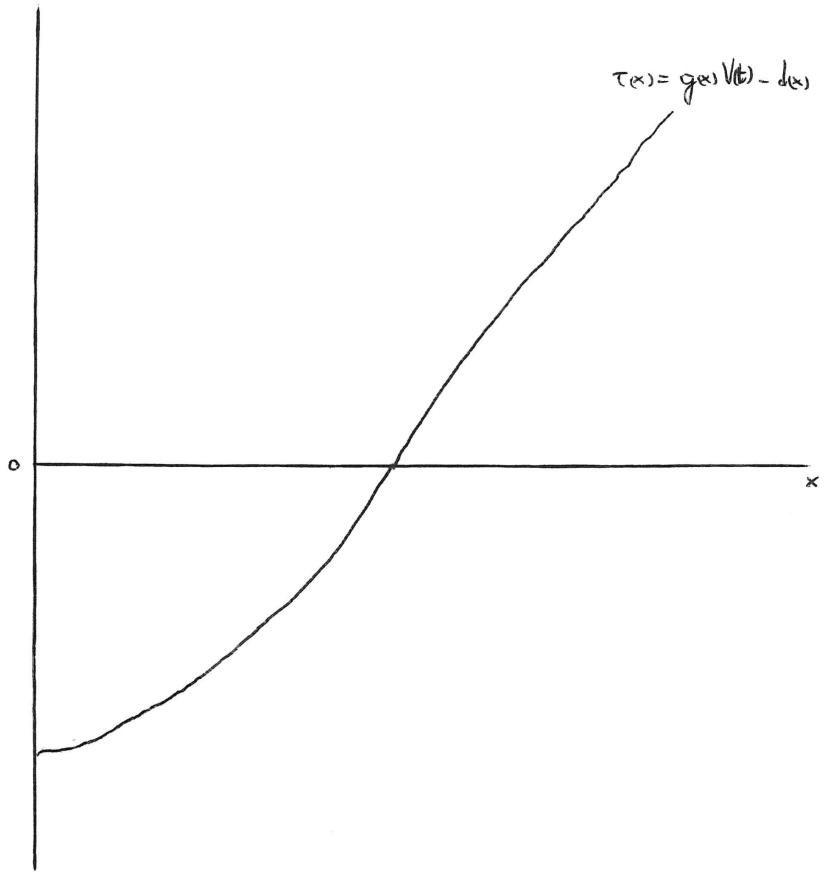
$$\begin{cases} \dfrac{dV}{dt} = -V\displaystyle\int_0^\infty g(x)u(t,x)\,dx + \int_0^\infty d(x)u(t,x)\,dx \\ \\ \qquad\qquad \dfrac{\partial u}{\partial t} + \dfrac{\partial}{\partial x}((g(x)V - d(x))u) = 0. \end{cases}$$

Usual physical setting: $g(x) = x^{1/3},\ d(x) = 1$. No need for a boundary condition.

(Niethammer, Pego, Velazquez, Goudon, Tine, Lagoutière, Collet, Vasseur, Poupaud, Laurençot, Mischler...)

Ostwald ripening

Large clusters tend to become larger and larger at the extent of small ones



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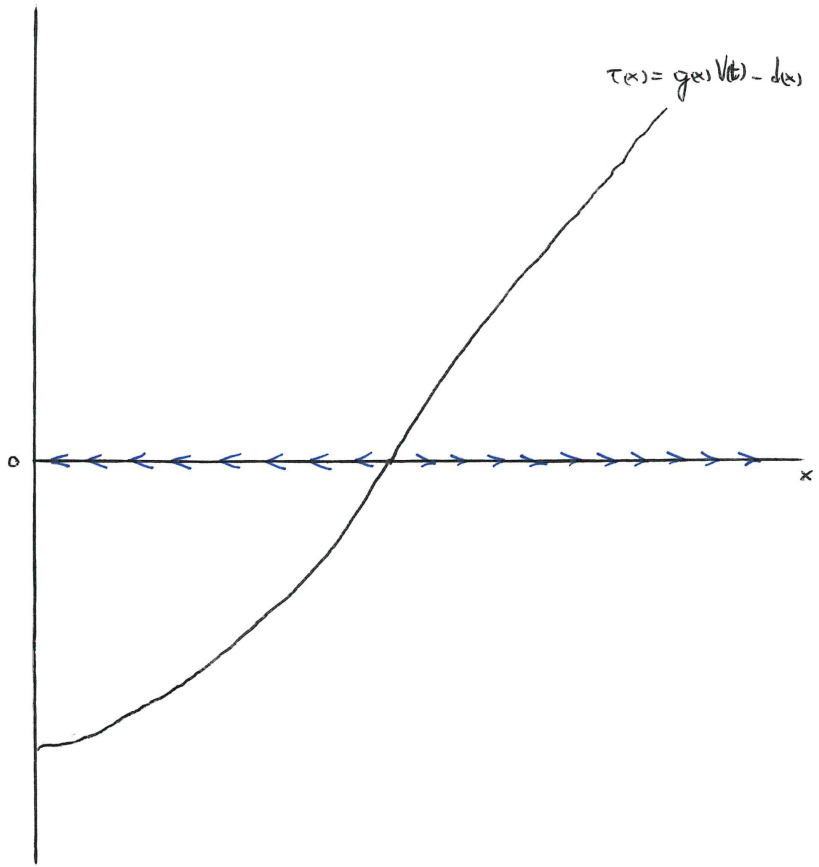

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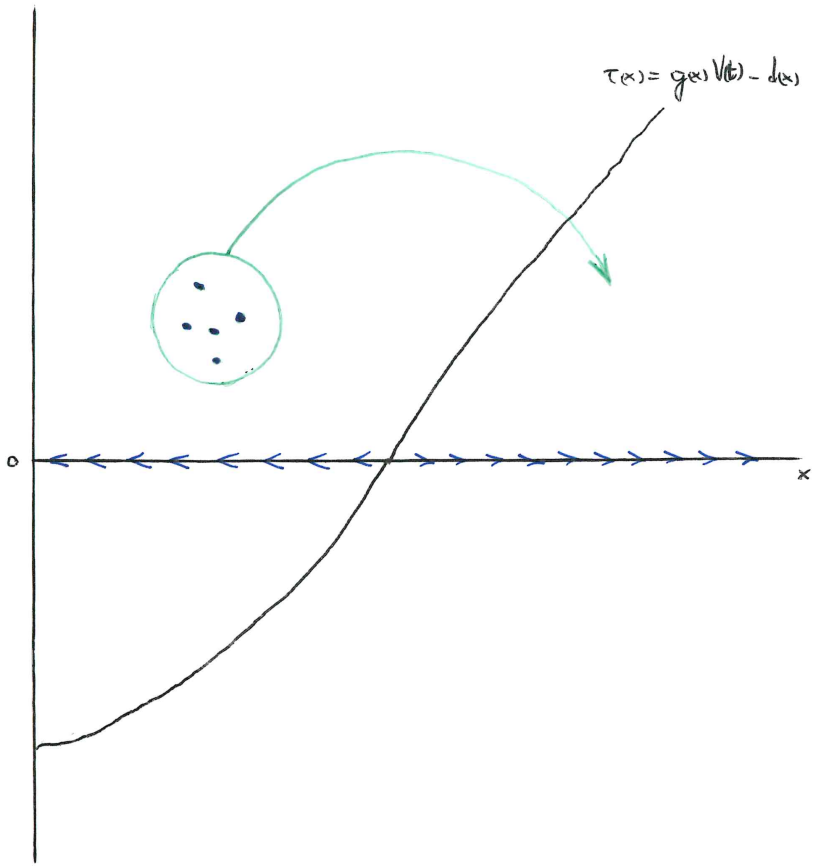

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Lifshitz–Slyozov revisited

When describing fibrils we expect to have $g(x) = 1$ and $d(x)$ to be increasing. This requires a boundary condition at zero size.

No nucleation case (J.C., M. Doumic, B. Perthame)

Let $0 < \alpha \leq d' \leq \beta$ and $g(x) = 1$. Assume that $V(0) > d(0)$. Consider a solution (u, V) of Lifshitz–Slyozov equations together with the following boundary condition:

$$(V(t) - d(0))u(t,0)\chi_{V(t)-d(0)>0} = 0.$$

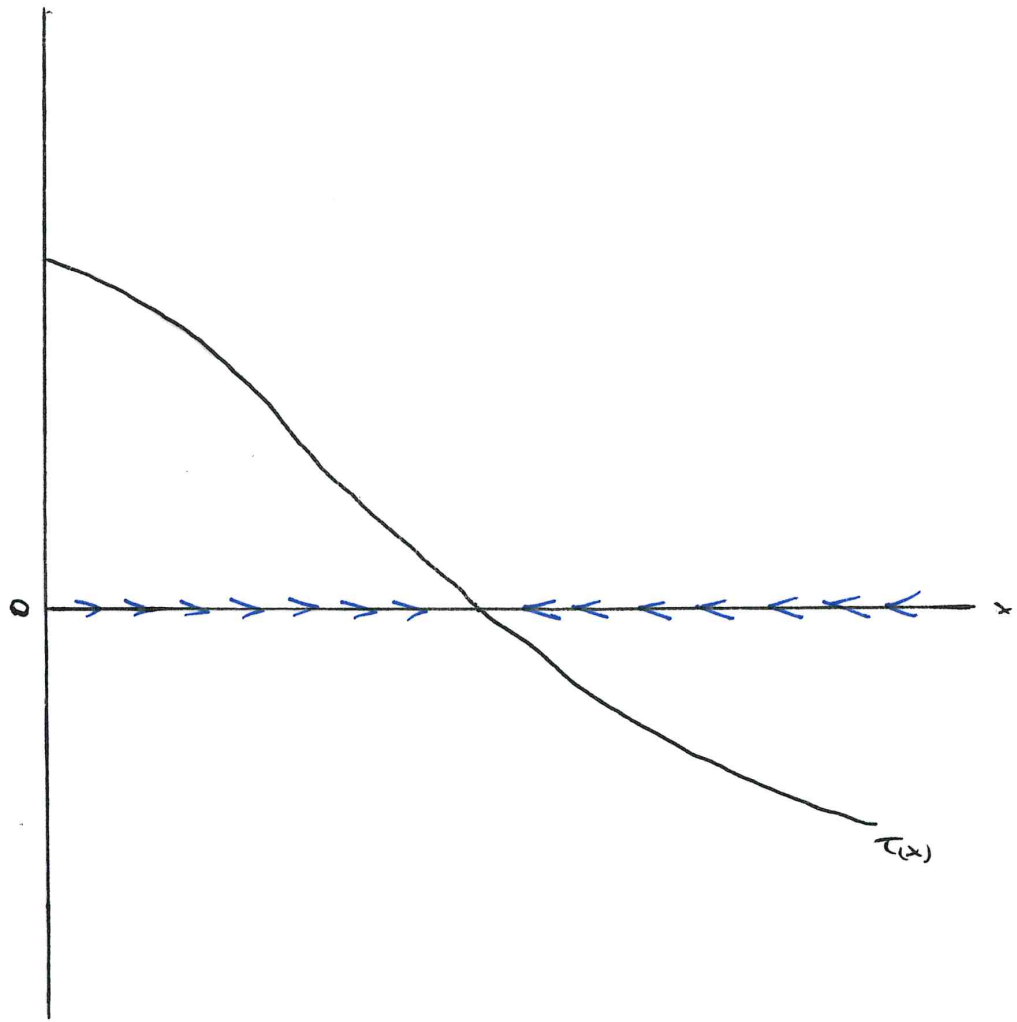
Then, there holds that

$$\lim_{t\to\infty} V(t) = d(\bar{x}) \quad \text{and} \quad \lim_{t\to\infty} u(t,x) = \rho_0\delta(x - \bar{x})$$

weakly as measures, being $\bar{x}$ the unique solution of

$$M = \rho_0\bar{x} + d(\bar{x}).$$

Lifshitz–Slyozov revisited (no nucleation)



Lifshitz–Slyozov revisited II

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$$(V(t) - d(0))u(t,0)\chi_{V(t)-d(0)>0} = aV(t)^{i_0}\chi_{V(t)-d(0)>0}.$$

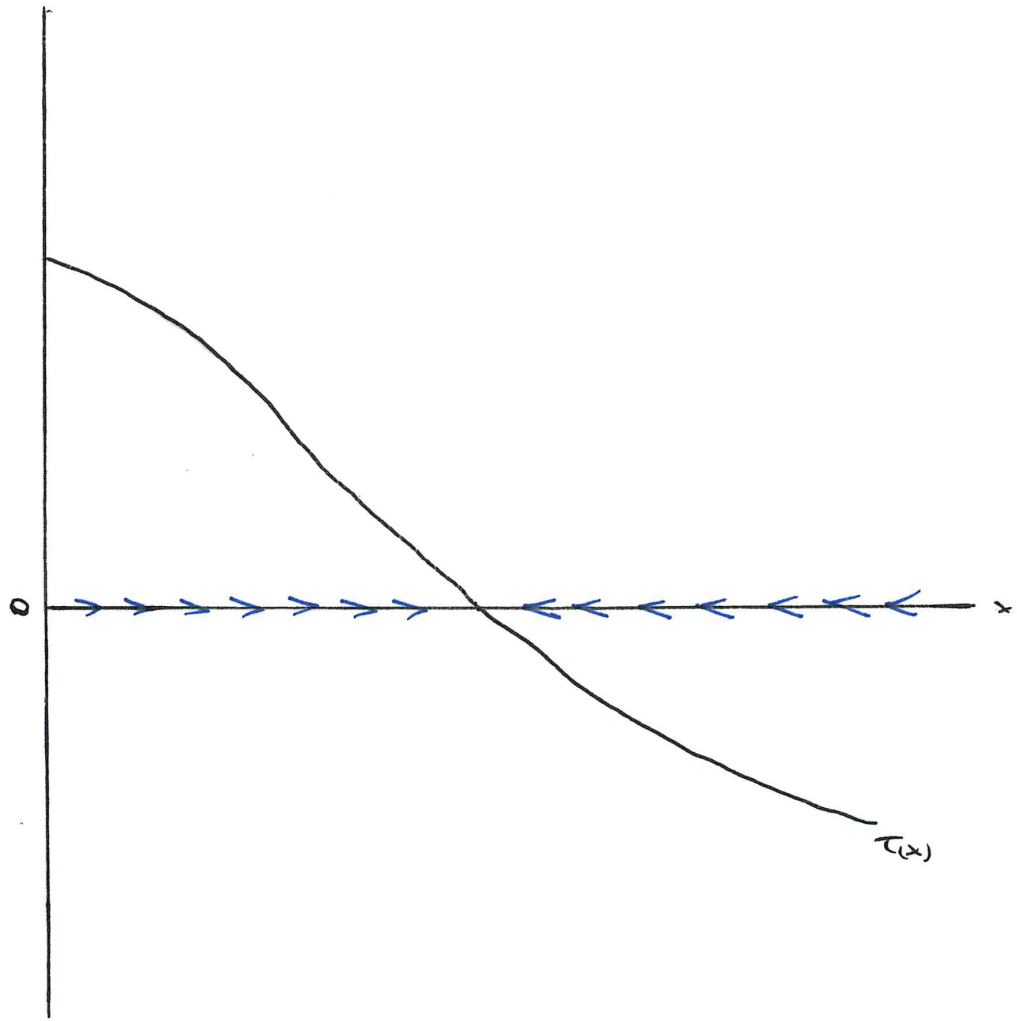
Then, there holds that

$$\lim_{t\to\infty} V(t) = d(0), \quad \lim_{t\to\infty} \rho(t) = +\infty$$

and (**fibril instability**)

$$\lim_{t\to\infty} x\, u(t,x) = (M - d(0))\delta(x) \quad \text{weakly as measures.}$$

Lifshitz–Slyozov revisited II (with nucleation)



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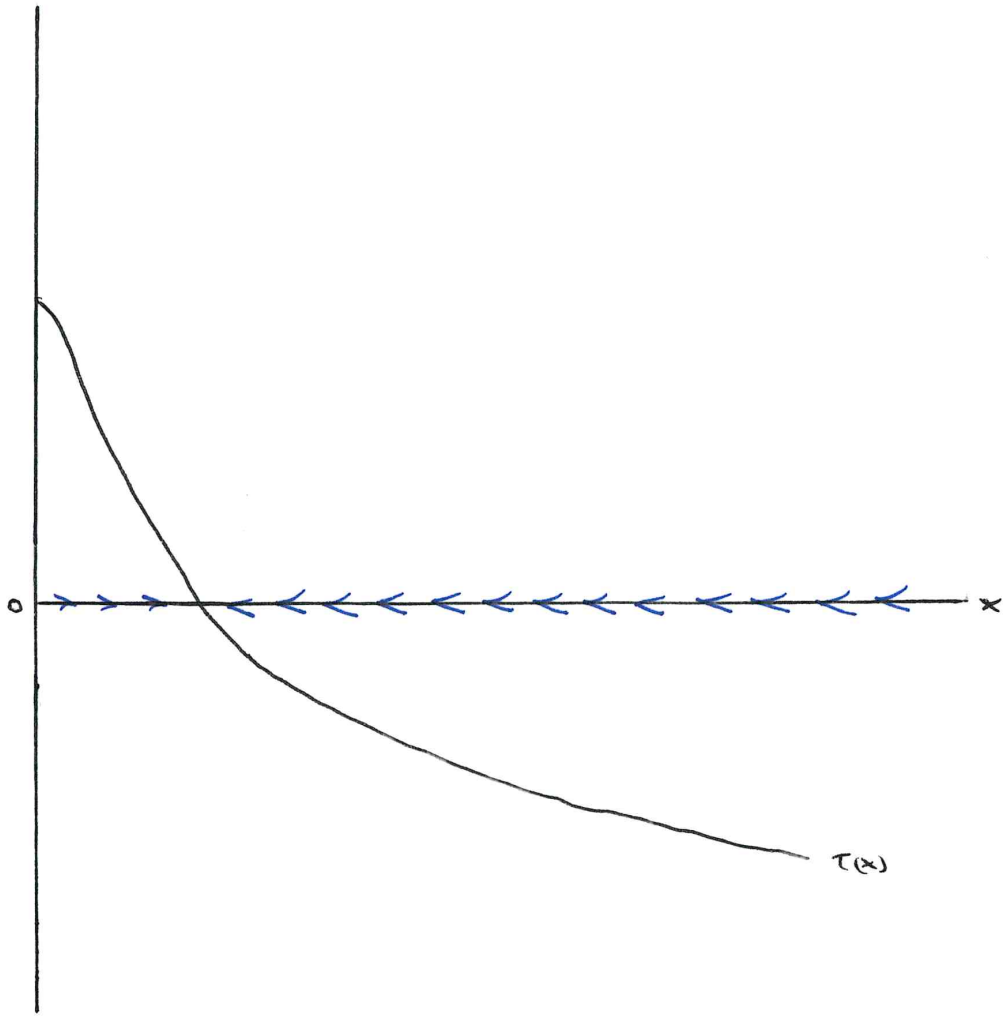


Adding fragmentation

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

$$\frac{\partial u}{\partial t} + \frac{\partial}{\partial x}((g(x)V - d(x))u) - B(x)u = 2\int_x^\infty B(y)k(y,x)u(t,y)\,dy,$$

Lifshitz–Slyozov+fragmentation (J.C., M. Doumic, B. Perthame)

Let $0 < \alpha \le d' \le \beta$ and $g(x) = 1$. Assume that $V(0) > d(0)$. Consider a solution (u, V) of Lifshitz–Slyozov equations with fragmentation, with or without nucleation. Then, as before,

$$\lim_{t\to\infty} V(t) = d(0), \quad \lim_{t\to\infty} \rho(t) = +\infty$$

and (**fibril instability**)

$$\lim_{t\to\infty} x\,u(t,x) = (M - d(0))\delta(x) \quad \text{weakly as measures.}$$

Adding fragmentation II

If we consider Lifshitz–Slyozov plus fragmentation with decreasing depolymerization then nucleation stops after a while.

Lifshitz–Slyozov+fragmentation (J.C., M. Doumic, B. Perthame)

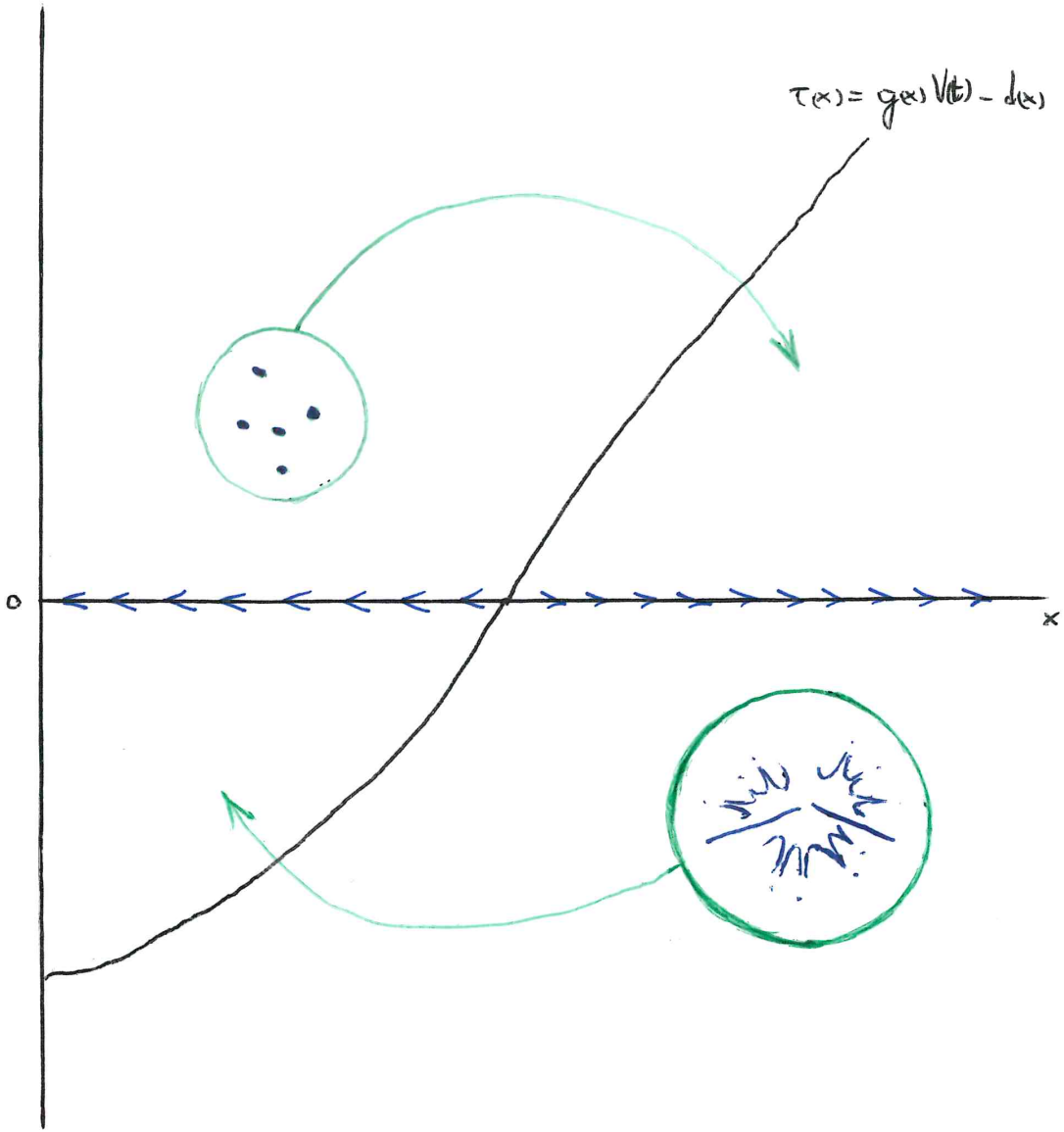
Let $d(x)$ be decreasing and $g(x) = 1$. Assume that $V(0) > d(0)$. Then, under balance assumptions for B, k and d there exists a unique steady state solution $(U, \bar{V})$ of Lifshitz–Slyozov+fragmentation,

$$\bar{V} \int_0^\infty g(x)U(t,x)\,dx = \int_0^\infty d(x)U(t,x)\,dx.$$

$$\frac{\partial}{\partial x}((g(x)\bar{V} - d(x))U) - B(x)U(x) = 2\int_x^\infty B(y)k(y,x)U(y)\,dy,$$

Depolimerization may stabilize the system.

Adding fragmentation II



To sum up

- We have consider different theoretical designs for fibril formation reaction pathways in the framework of continuous polimerization models.
- Our models considered combinations of the following: Polimerization, nucleation, fragmentation and/or depolimerization.
- The only combination so far that led to useful dynamics was polimerization+ *decreasing* depolimerization +fragmentation.

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