Polymerization Models for Prion

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BANG day, 22 september 2009

Outline

Biological Model

The pathogenic agent is an abnormal protein present as aggregates :

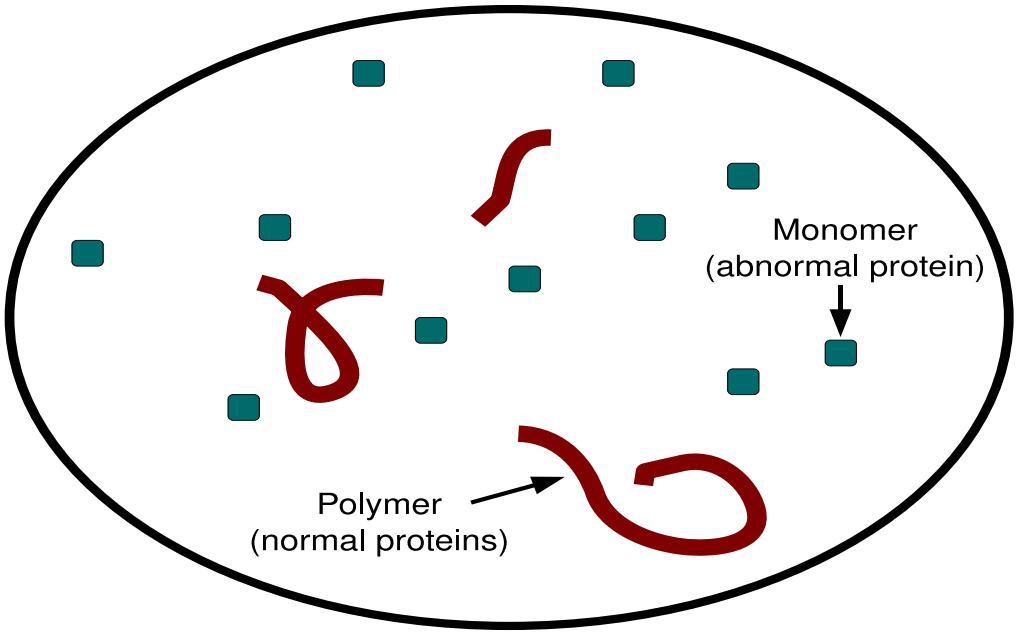

Fig.: Infected cell.

Equations

Model of Greer *et al.* (2006), Calvez *et al.* (2008), Doumic *et al.* (2009) :

$$\begin{cases} \dfrac{dV(t)}{dt} &= \lambda - V(t)\left[\gamma + \displaystyle\int_0^\infty \tau(x)u(x,t)\,dx\right], \\ \dfrac{\partial}{\partial t}u(x,t) &= -V(t)\dfrac{\partial}{\partial x}\big(\tau(x)u(x,t)\big) - [\mu(x)+\beta(x)]u(x,t) \\ &\qquad +2\displaystyle\int_x^\infty \beta(y)\kappa(x,y)\,u(y,t)\,dy, \\ u(0,t) &= 0, \\ u(x,0) &= u_0(x). \end{cases}$$

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

The PMCA (Protein Misfolded Cyclic Amplification) is a protocole which allows to increase *in vitro* the prion quantity of a sample. It consists in the repeated alternation of two phases :

1. **Incubation** during which the polymerization is promoted
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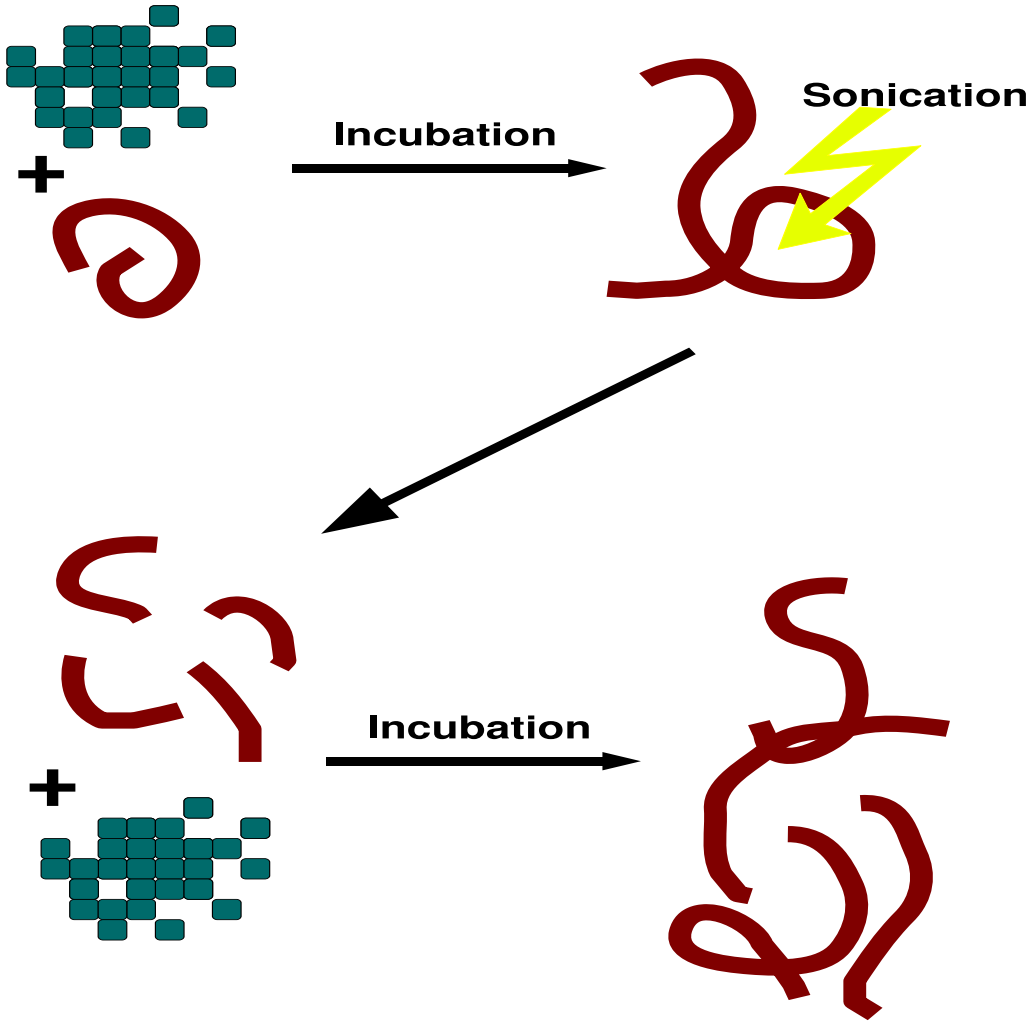

Fig.: PMCA principle.

We model the sonication multiplying the fragmentation $\beta(x)$ by a parameter $\alpha(t)$:

$$\frac{\partial}{\partial t}u(x,t) = -\frac{\partial}{\partial x}\big(\tau(x)u(x,t)\big) - \beta(x)u(x,t) + 2\int_x^\infty \beta(y)\kappa(x,y)\,u(y,t)\,dy,$$

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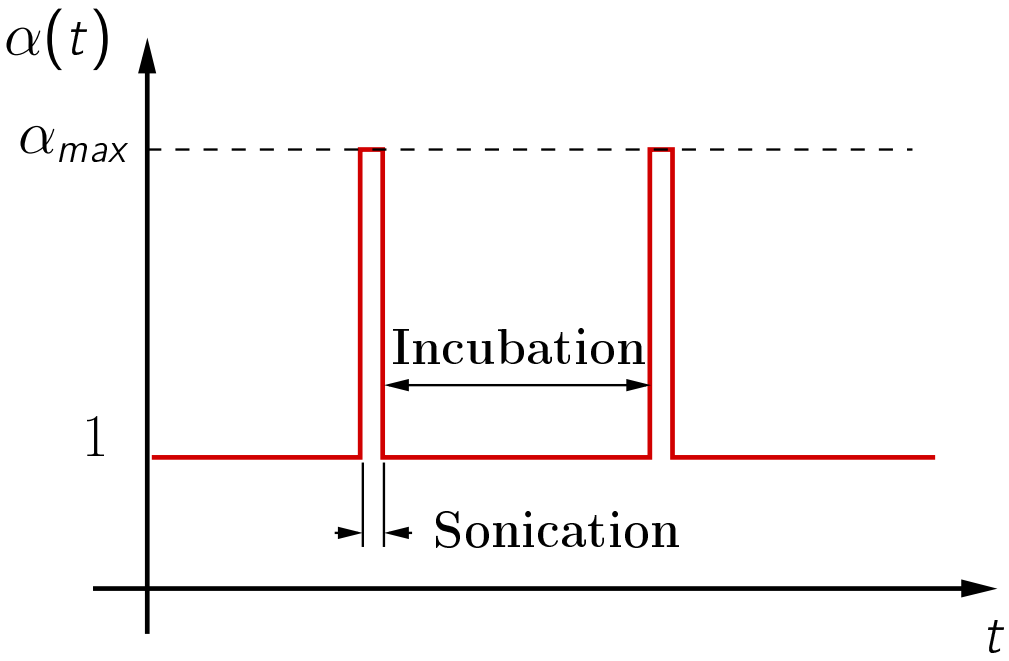

α constant (with V. Calvez and M. Doumic)

For a constant sonication $\alpha(t) \equiv \alpha$, there exists a principal eigenvalue λ_α for the equation :

Existence of Eigenelements for a General Aggregation-Fragmentation Model, M. Doumic et P. G., to appear in M3AS.

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Theorem : Existence of α_{opt} (V. Calvez, M. Doumic, P. G.)

If the polymerization rate τ satisfies

- $\tau(0) = 0$ and τ is convex in a neighborhood of 0,
- $\tau(x) = o(x)$ when x tends to $+\infty$,

Then there exists a α_{opt} such that $\lambda_\alpha \leq \lambda_{\alpha_{opt}}$ for all $\alpha > 0$.

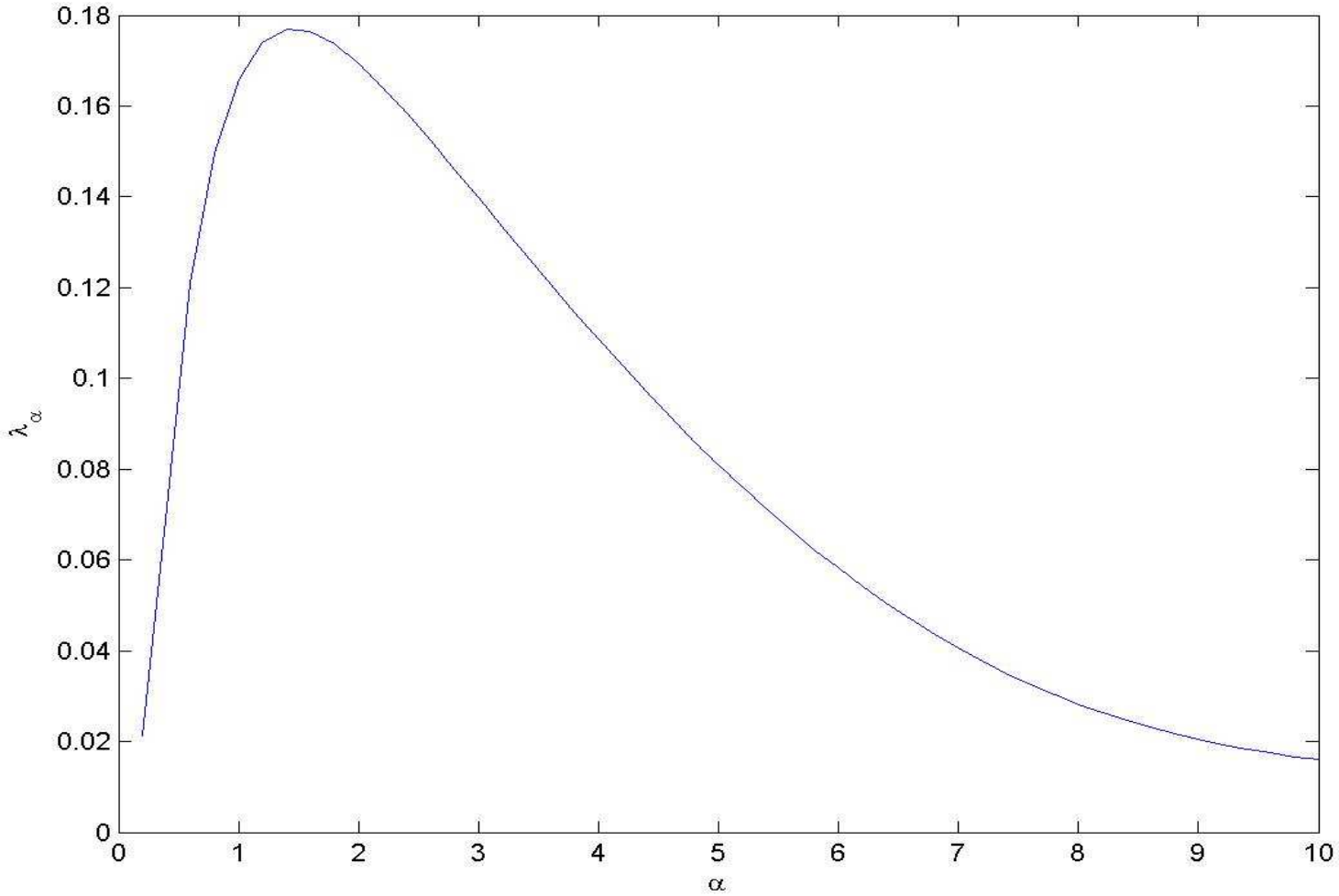

Fig.: Existence of an optimal α.

Any α (with V. Calvez)

For a given outlook T, we search a control $\alpha : [0, T] \longrightarrow [1, \alpha_{max}]$ which maximizes the mass obtained at the final time T. For this we come back to a discrete in size model :

$$\begin{cases} \dfrac{du_i}{dt} = -\tau_i(u_i - u_{i-1}) - \alpha(t)\beta_i u_i + 2\displaystyle\sum_{j=i+1}^{n} \alpha(t)\beta_j \kappa_{i,j} u_j \ , \\ u_i(0) = u_i^0 \ , \end{cases}$$

for all $1 \leq i \leq n$. Then we search to optimize $\displaystyle\sum_{i=1}^{n} i u_i(T)$.

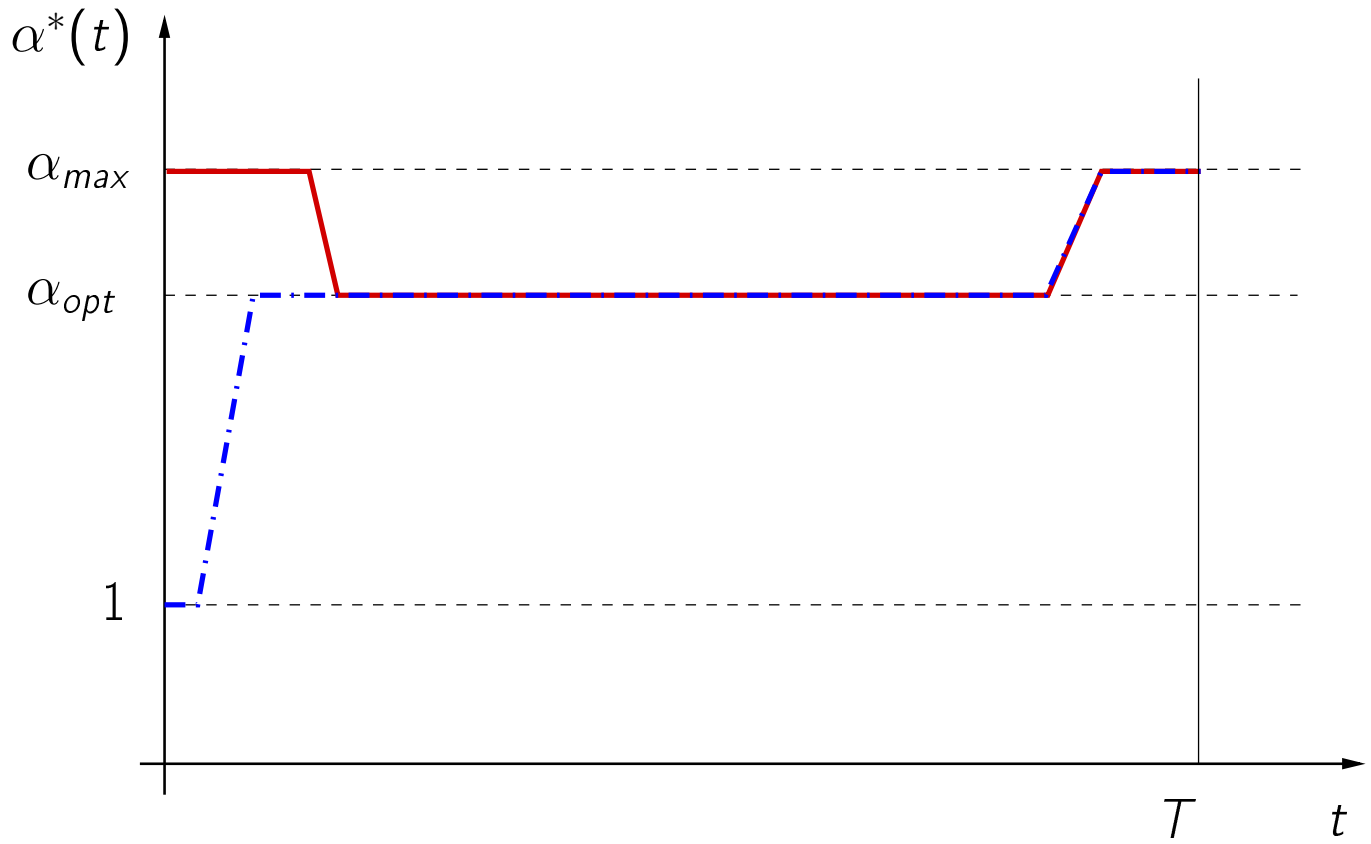

Fig.: Profils of $\alpha^*(t)$ when $1 < \alpha_{opt} < \alpha_{max}$.

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- polymerization
- depolymerization
- coagulation
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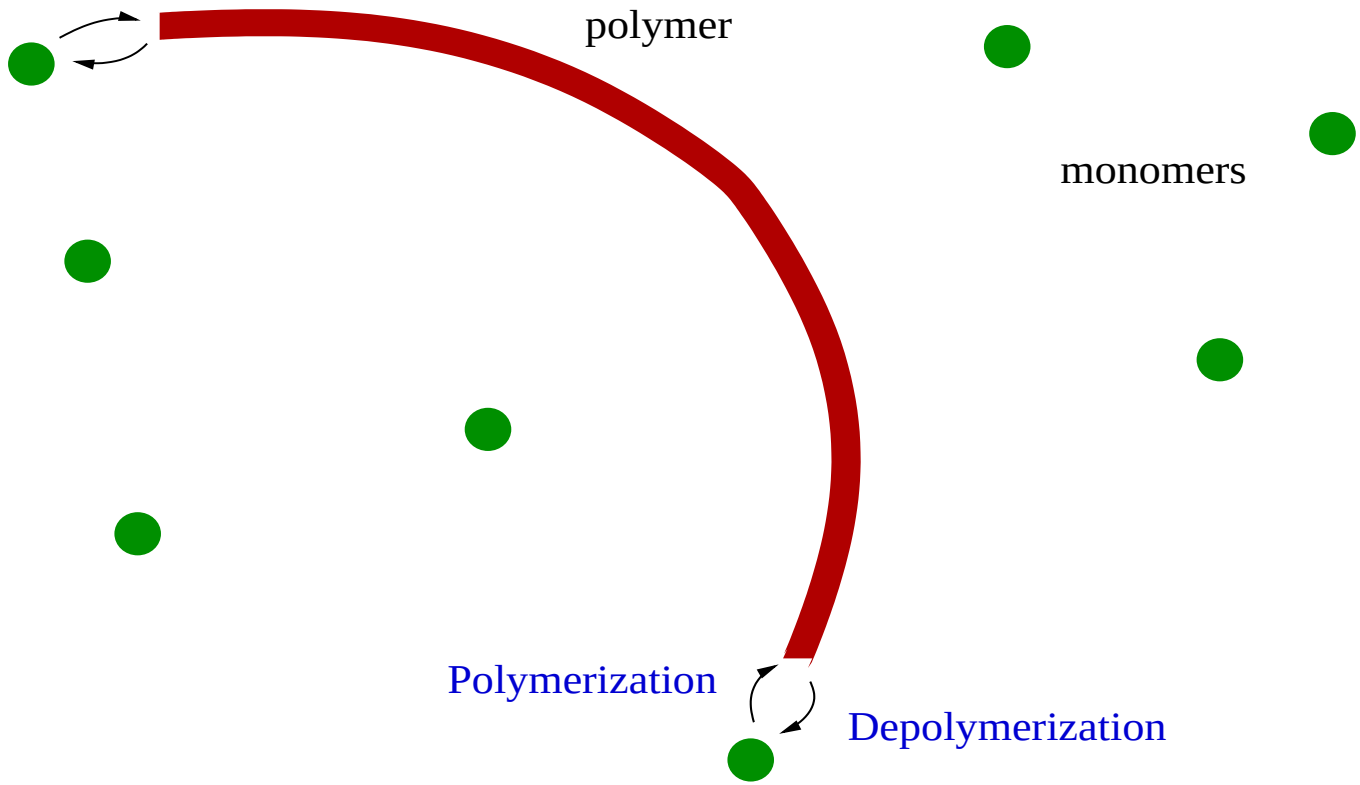

Fig.: Polymerization-depolymerization

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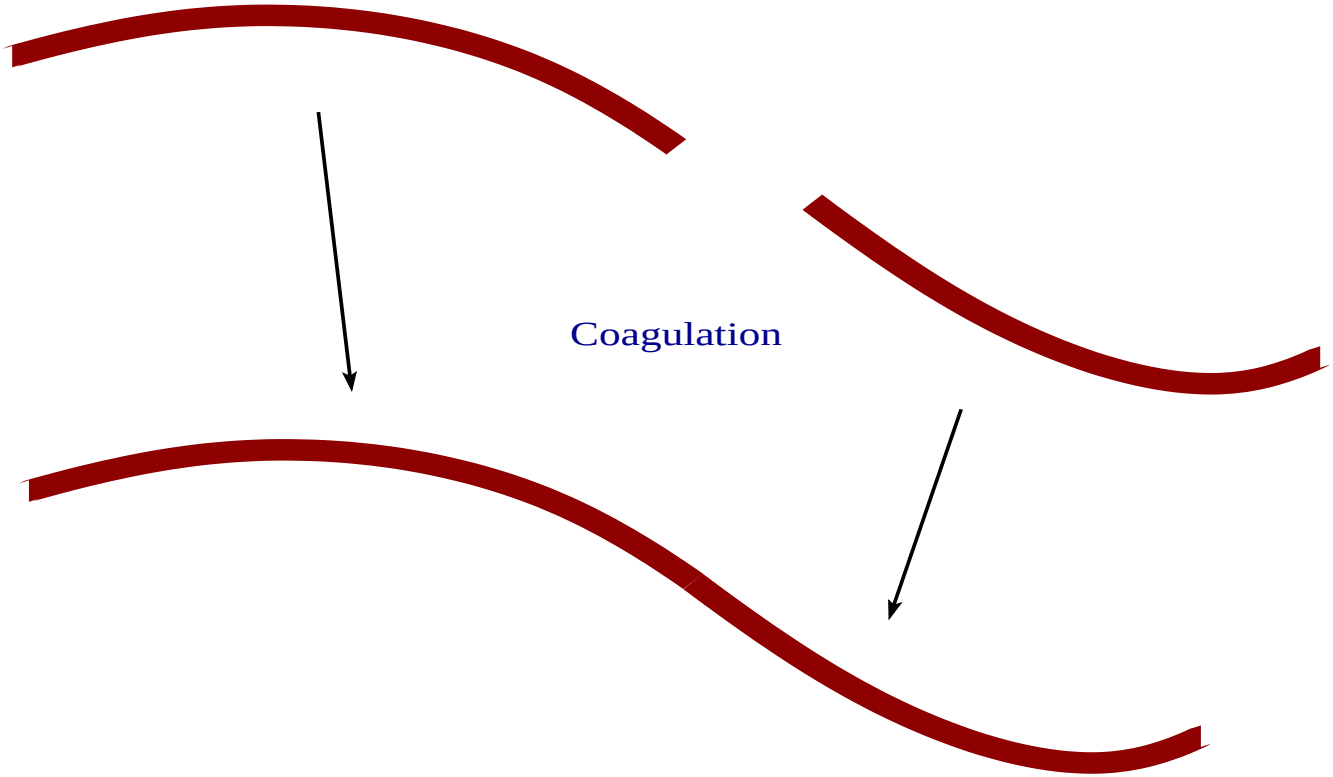

Fig.: Coagulation of two polymers

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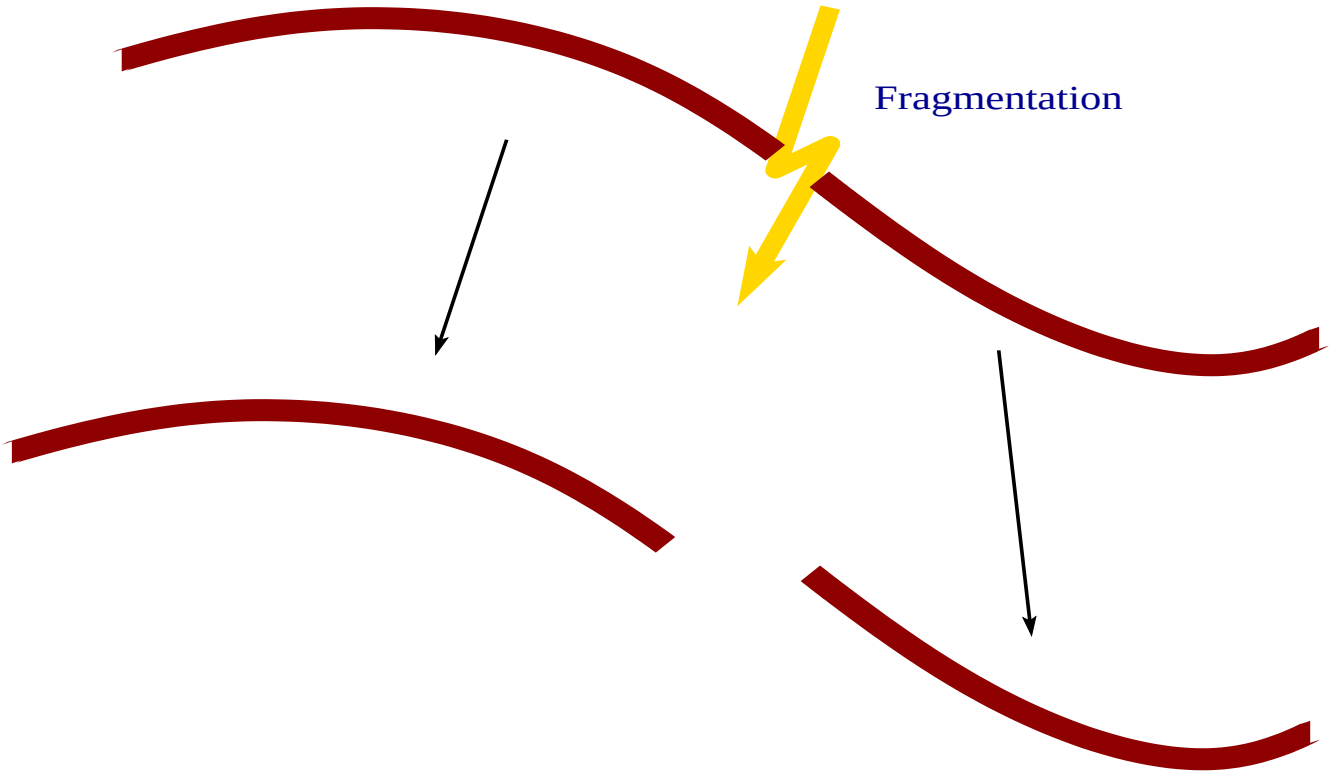

Fig.: Fragmentation of a polymer

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Equations

with F. Charles, M. Doumic, N. Lenuzza, H. Rezaeï

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\qquad\qquad - c(x,t)\displaystyle\int_0^x k_{frag}(y,x)\,dy + 2\int_x^\infty k_{frag}(x,y)\,c(y,t)\,dy \\
\qquad\qquad\qquad + \dfrac{1}{2}\displaystyle\int_0^x c(y,t)c(x-y,t)k_{coag}(y,x-y)\,dy \\
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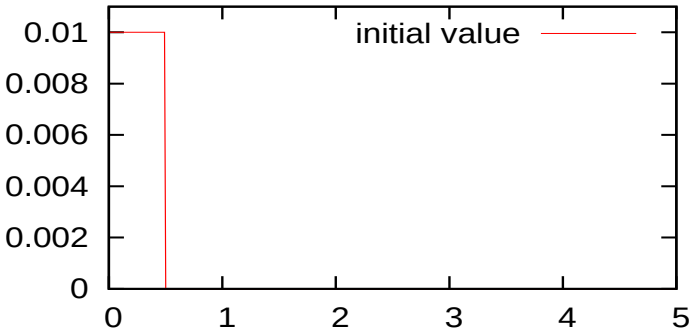
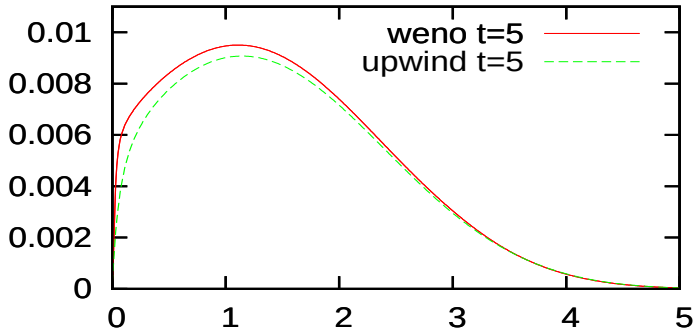
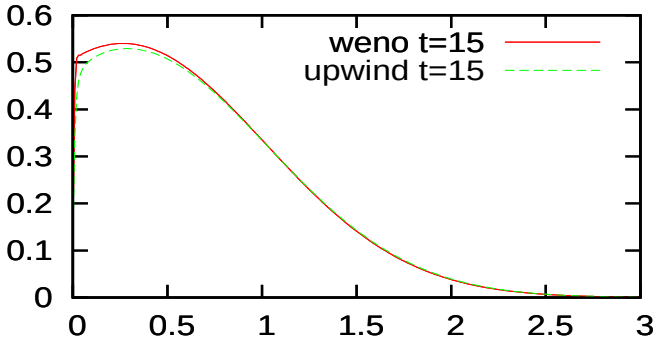
- RK3 for the time evolution

Simulations (comparison WENO/Upwind) with L.M. Tine







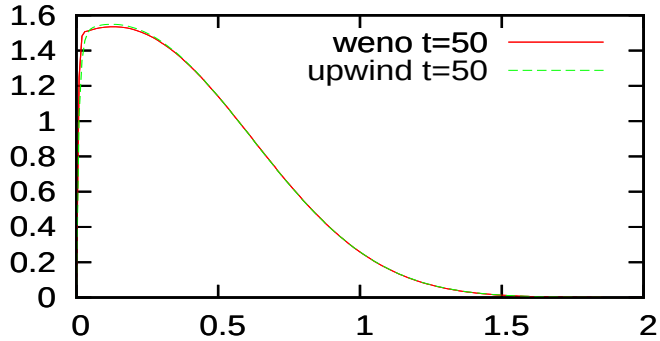


Fig.: Evolution of the size repartition