Asymptotic Analysis of Protein Polymerisation

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joint work with Marie Doumic, Philippe Robert and Wei-Feng Xue

UPMC, INRIA and University of Kent

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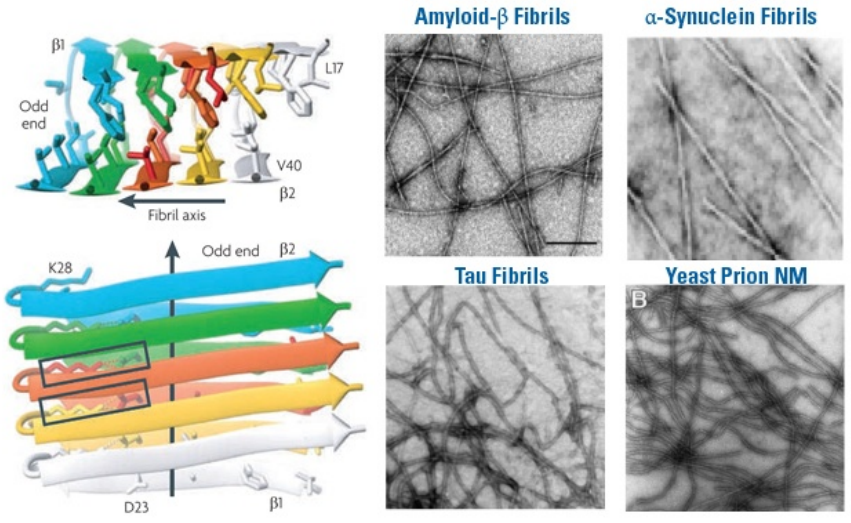
Outline

Amyloid Diseases

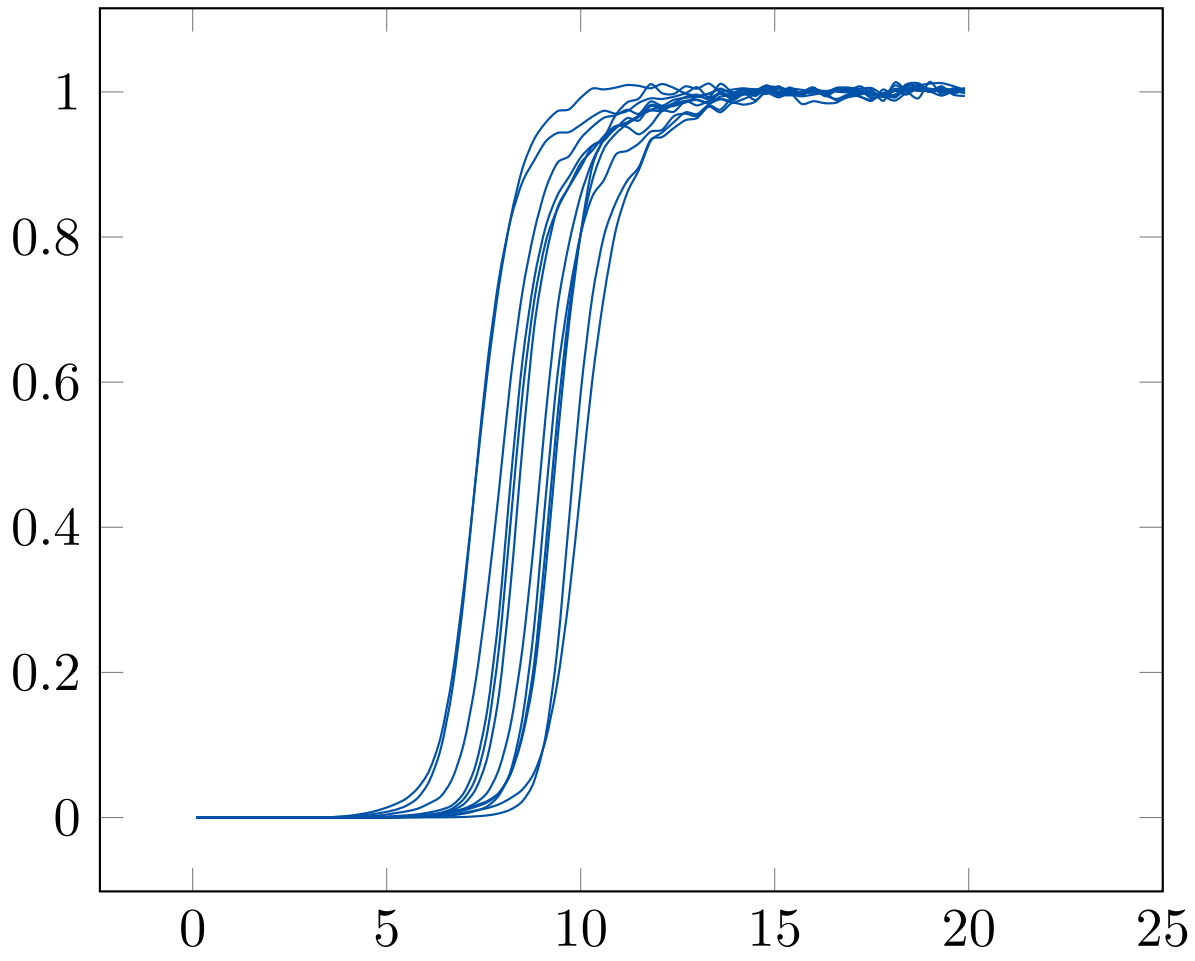


- Polymerisation phenomenon
- Aggregation of misfolded proteins

Experiments

- Slow start, then fast consumption of monomers
- For the same initial concentration of monomers,
  big variability of the take-off (hours)

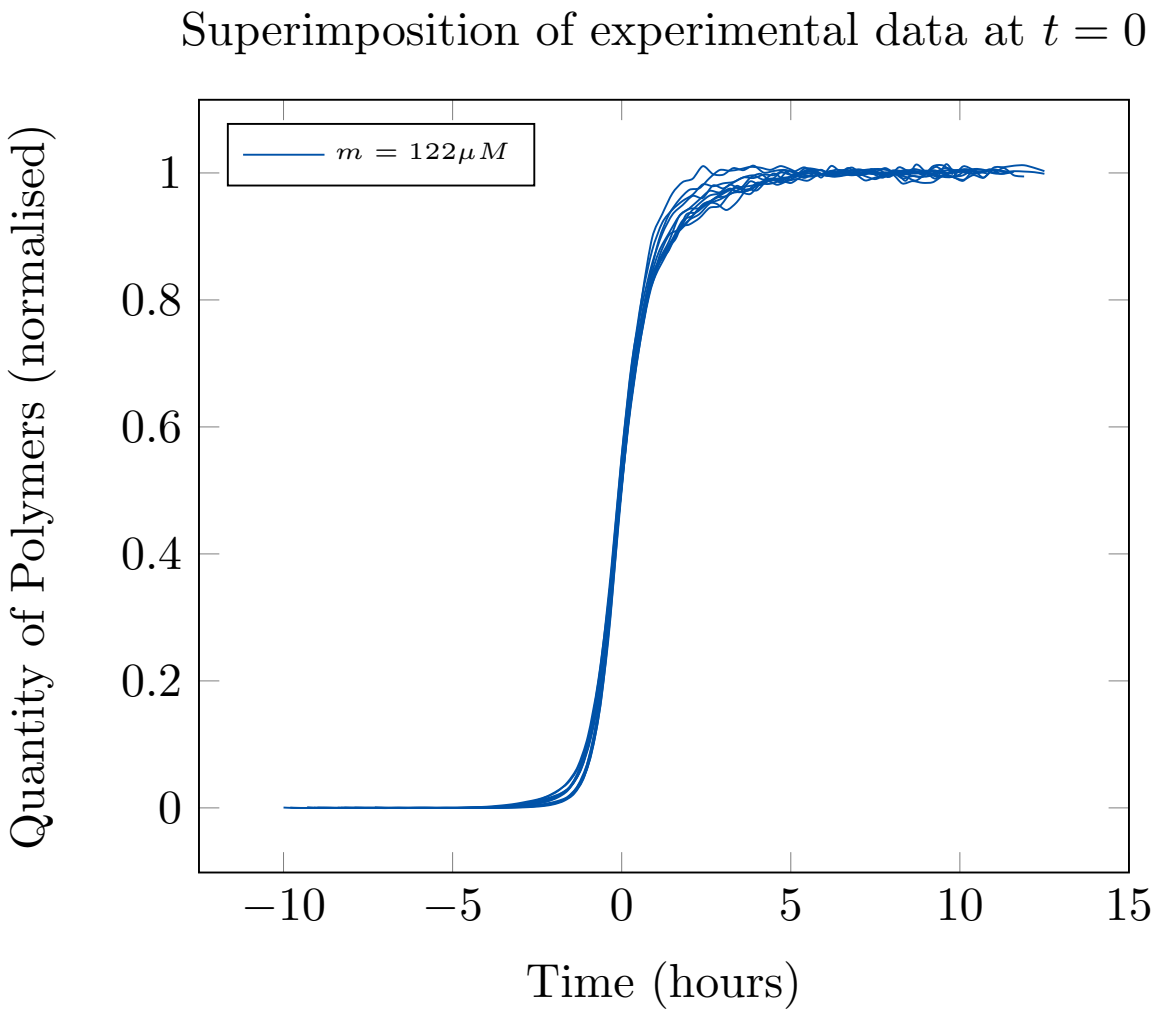
Experimental Curves (Radford et al.)



Goal of the study

- Explain the fluctuations of the take-off of the reaction, also called lag time, by a simple stochastic model

The take-off is the only interesting random variable



Outline

$$\begin{cases} \mathcal{X}_1 + \mathcal{X}_1 \xrightarrow{\alpha(X_1/N)^2} 2\mathcal{X}_2 \\ \mathcal{X}_1 + \mathcal{X}_2 \xrightarrow{\beta X_1.X_2/N^2} 2\mathcal{X}_2 \end{cases}$$

where $\alpha \ll \beta$.

- $X_1(t)$: number of monomers at time t
- $X_2(t)$: number of polymers at time t

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- $X_1(t)$: number of monomers at time t
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- M monomers at $t = 0$: $X_1(t) + X_2(t) = M$
- large volume N
- the initial concentration of monomers $M/N \sim m$ remains constant

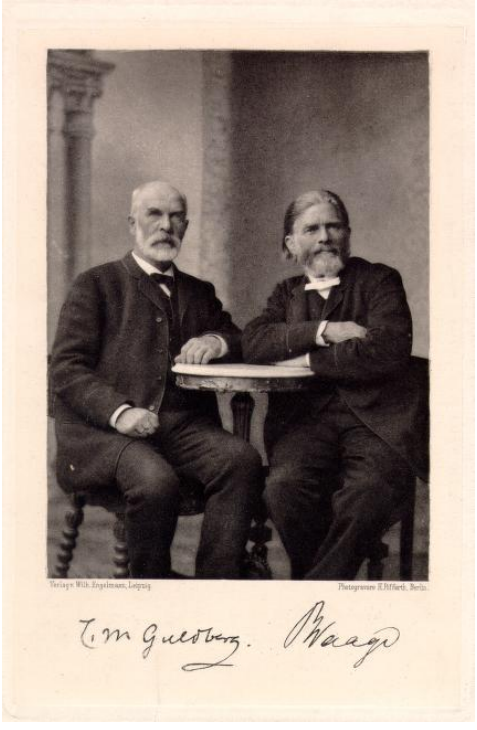
A Classical Approach in Chemistry: Law of Mass Action

$$A + B \underset{k^-}{\overset{k^+}{\rightleftharpoons}} C$$

is translated by

$$\frac{d[A]}{dt} = -k^+[A][B] + k^-[C],$$

for large volumes.



(Guldberg & Waage, 1867)

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Associated Markov Process

$$\begin{cases} \mathcal{X}_1 + \mathcal{X}_1 & \xrightarrow{\alpha(X_1/N)^2} 2\mathcal{X}_2 \\ \mathcal{X}_1 + \mathcal{X}_2 & \xrightarrow{\beta X_1.X_2/N^2} 2\mathcal{X}_2 \end{cases}$$

- Transition rates of the Markov Process $(X_1(t), X_2(t))$:

$$\begin{cases} (x_1, x_2) & \longrightarrow (x_1, x_2) + (-2, 2) \text{ at rate } \alpha(x_1/N)^2 \\ (x_1, x_2) & \longrightarrow (x_1, x_2) + (-1, 1) \text{ at rate } \beta x_1.x_2/N^2 \end{cases}$$

Time Scale of Polymerisation

Normal Time Scale

There is no polymerisation yet:

$$\frac{X_2(t)}{N} \underset{N\to\infty}{\longrightarrow} 0$$

$\Longrightarrow$ The polymerisation is a **slow** process. It happens on a **linear** time scale!

Proposition

$$\frac{X_1(Nt)}{N} \underset{N\to\infty}{\sim} x_1(t) + \frac{1}{\sqrt{N}} U(t)$$

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where:

- x_1 is solution of the Mass Action Law:

$$\dot{x_1} = -\alpha x_1^2 - \beta x_1 (m - x_1)$$

- U is a diffusion:

$$dU_t = \frac{\beta\sqrt{\alpha}\sqrt{e^{\beta m t}+1}}{\alpha e^{\beta m t} + \beta - \alpha} dW_t + \beta m \left[\frac{\beta - \alpha - \alpha e^{\beta m t}}{\beta - \alpha + \alpha e^{\beta m t}}\right] U_t dt$$

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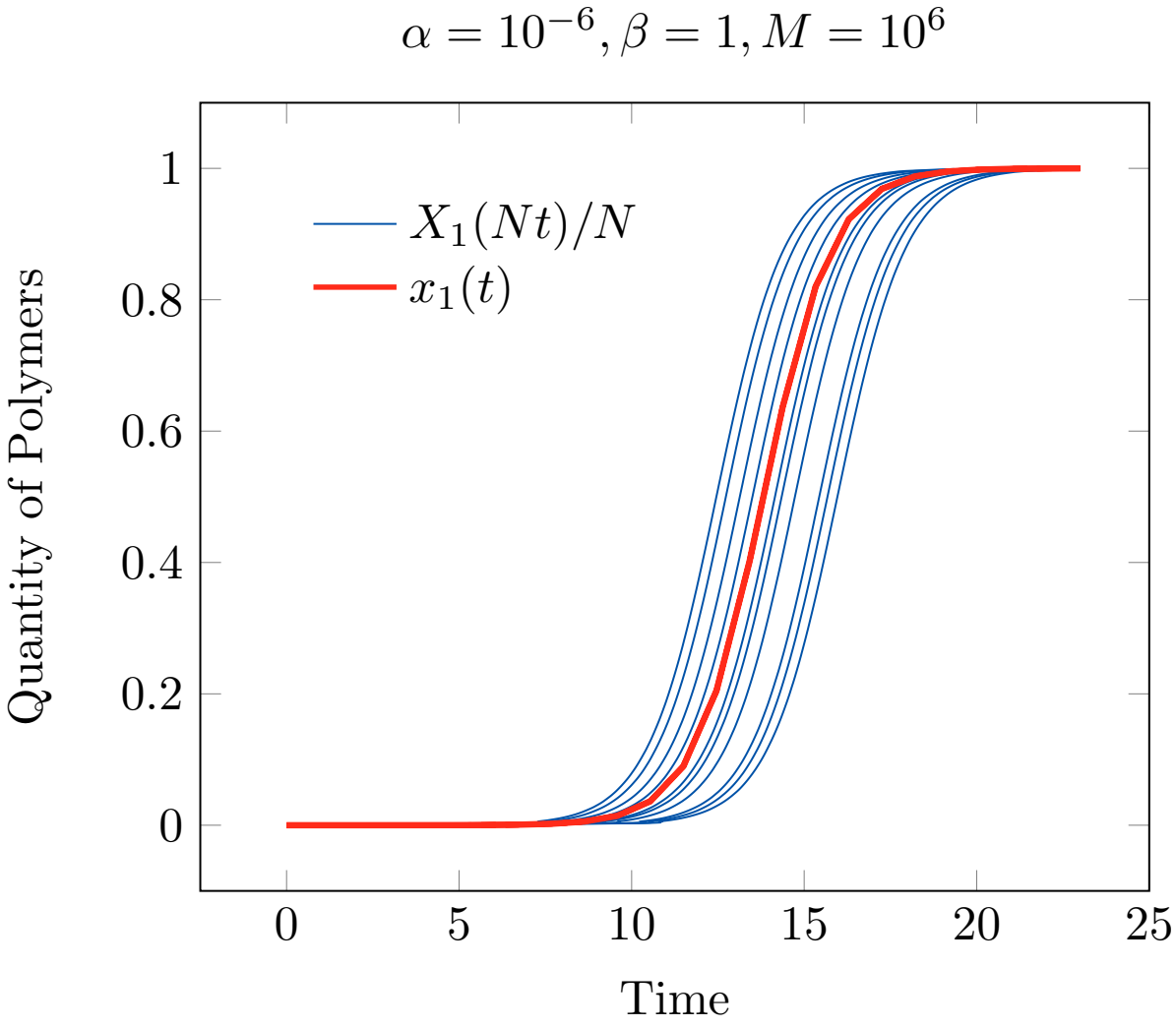
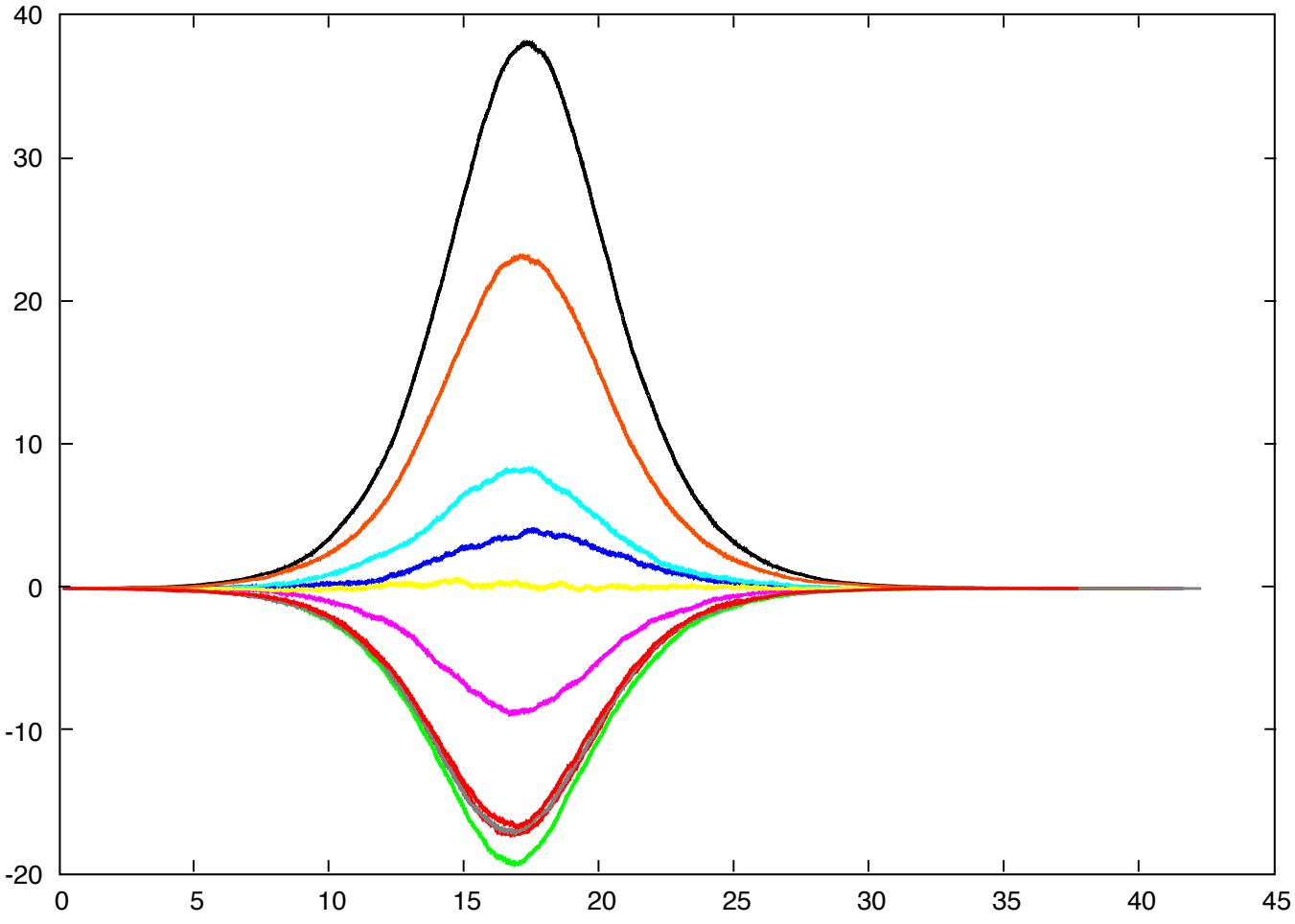
Proof : Standard Stochastic Calculus Methods

Simulations: $X_1(Nt)/N$ and $x_1(t)$



Simulations: $U_N(t) = (X_1(Nt) - Nx_1(t))/\sqrt{N}$



Definition of the lag time

$$T_\delta^N = \inf\{t > 0, X_2(t) \geq \delta M\}$$

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Corollary

As N tends to infinity :

$$\frac{T_\delta^N}{N} = t_\delta + \frac{1}{\sqrt{N}} \frac{U(t_\delta)}{-\dot{x_1}(t_\delta)} + o\left(\frac{1}{\sqrt{N}}\right)$$

where $t_\delta = x_2^{-1}(\delta m)$, with $x_2(t) = \lim_{N\to\infty} X_2(Nt)/N$.

Variance of the Lag Time

Proposition

When N tends to ∞:

$$\mathrm{Var}\left(\frac{T_\delta^N}{N}\right) \sim \frac{3}{2M\alpha\beta m^2}$$

where:

- M is the initial number of monomers, $M \sim mN$
- m is the initial concentration of monomers

Numerical Estimation of Parameters:

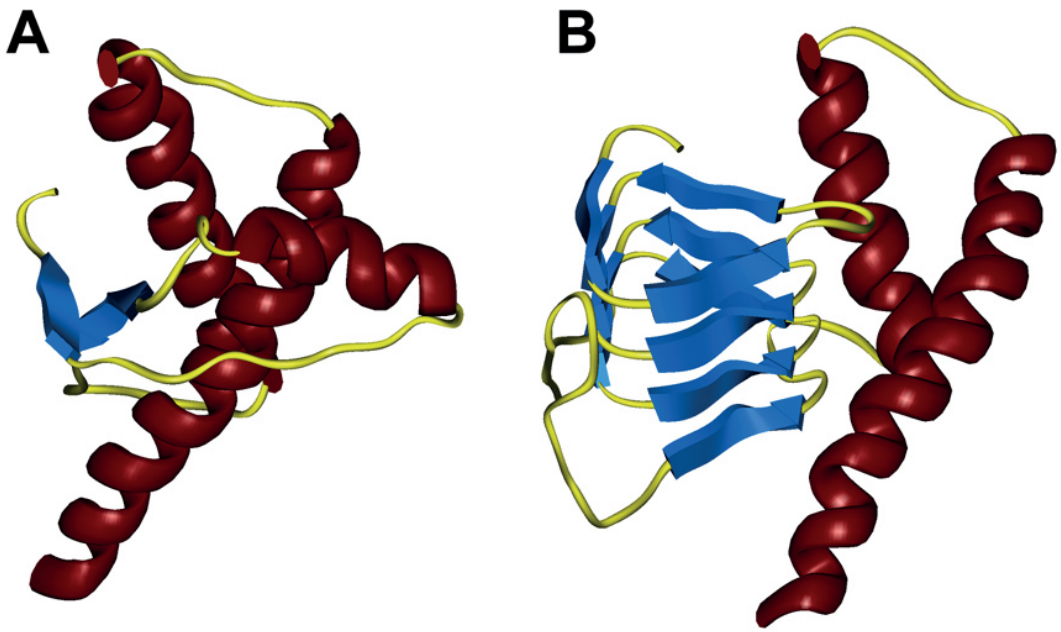
$$m = 122\,\mu M$$
$$M = 10^{15}$$
$$\alpha = 1.33 \times 10^{-10} h^{-1}.\mu M^{-1}$$
$$\beta = 1.75 \times 10^{-2} h^{-1}.\mu M^{-1}$$

No variance for experimental volumes

$$M = 10^{6} \implies \text{Var} = 1 \text{ hour}$$
$$\text{But: } M = 10^{15} \implies \text{Var} = 10^{-4} \text{ hour}$$

Outline

Misfolding of Proteins



A: Normal Prion Protein
B: Diseased Prion Protein

https://www.ucsf.edu/news/2001/08/4709/ucsf-study-finds-two-old-drugs-may-help-fight-prion-diseases

Adding a Conformation Step

$$\begin{cases} \mathcal{X}_0 \underset{\gamma^* X_1}{\overset{\gamma X_0}{\rightleftharpoons}} \mathcal{X}_1 \\ \mathcal{X}_1 + \mathcal{X}_1 \xrightarrow{\alpha (X_1/N)^2} 2\mathcal{X}_2 \\ \mathcal{X}_1 + \mathcal{X}_2 \xrightarrow{\beta X_1/N . X_2/N} 2\mathcal{X}_2 \end{cases}$$

- $X_0^N(t)$: number of introduced monomers at time t
- $X_1^N(t)$: number of misfolded monomers at time t
- $X_2^N(t)$: number of polymers at time t

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- $X_1^N(t)$: number of misfolded monomers at time t
- $X_2^N(t)$: number of polymers at time t
- M_N introduced monomers: $X_0^N(t) + X_1^N(t) + X_2^N(t) = M_N$
- $M_N/N \sim m$ remains constant

Associated Markov Process

- Transition rates of the Markov Process $(X_0(t), X_1(t), X_2(t))$:

$$\begin{cases} (x_0, x_1, x_2) \longrightarrow (x_0, x_1, x_2) + (-1, 1, 0) \text{ at rate } \gamma x_0 \\ (x_0, x_1, x_2) \longrightarrow (x_0, x_1, x_2) + (1, -1, 0) \text{ at rate } \gamma^* x_1 \end{cases}$$

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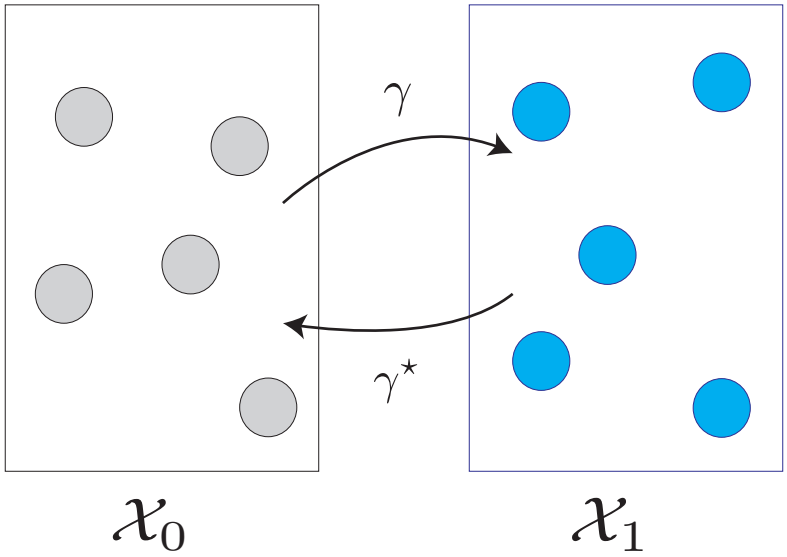
Adding a Conformation Step

$$\begin{cases} & \mathcal{X}_0 \quad \underset{\gamma^* X_1}{\overset{\gamma X_0}{\rightleftharpoons}} \quad \mathcal{X}_1 \\ \mathcal{X}_1 + \mathcal{X}_1 & \xrightarrow{\alpha (X_1/N)^2} 2\mathcal{X}_2 \\ \mathcal{X}_1 + \mathcal{X}_2 & \xrightarrow{\beta X_1/N . X_2/N} 2\mathcal{X}_2 \end{cases}$$

Coexistence of two processes:

- Misfolding (Ehrenfest Urn)
- Polymerisation (Escape of the urn)

$$\mathcal{X}_0 \underset{\gamma^* X_1}{\overset{\gamma X_0}{\rightleftharpoons}} \mathcal{X}_1$$



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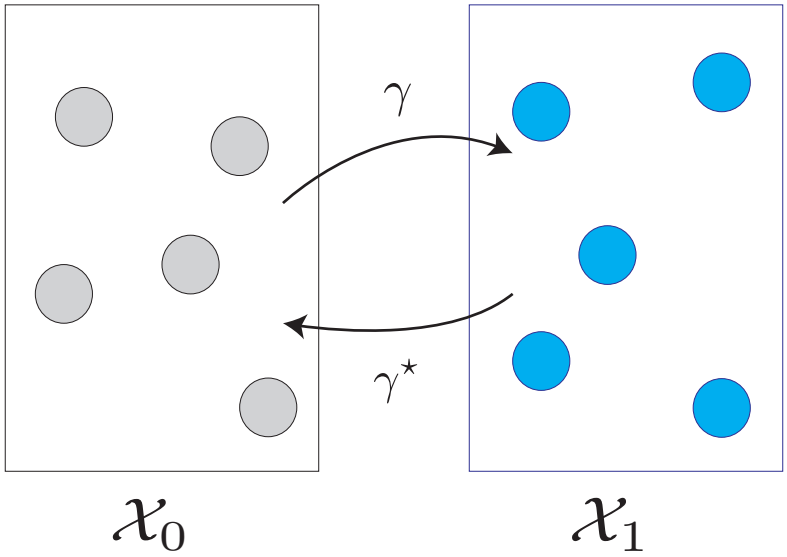

- Size of the Urn $:= B_N = X_0^N(t) + X_1^N(t)$

Equilibrium of a Ehrenfest Urn of fixed size

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Proposition

If $B_N \underset{N\to\infty}{\sim} bN$, then **at equilibrium**, when N tends to ∞:

$$\frac{X_0^N}{N} \sim \frac{\gamma^*}{\gamma+\gamma^*}b \qquad \text{and} \qquad \frac{X_1^N}{N} \sim \frac{\gamma}{\gamma+\gamma^*}b$$

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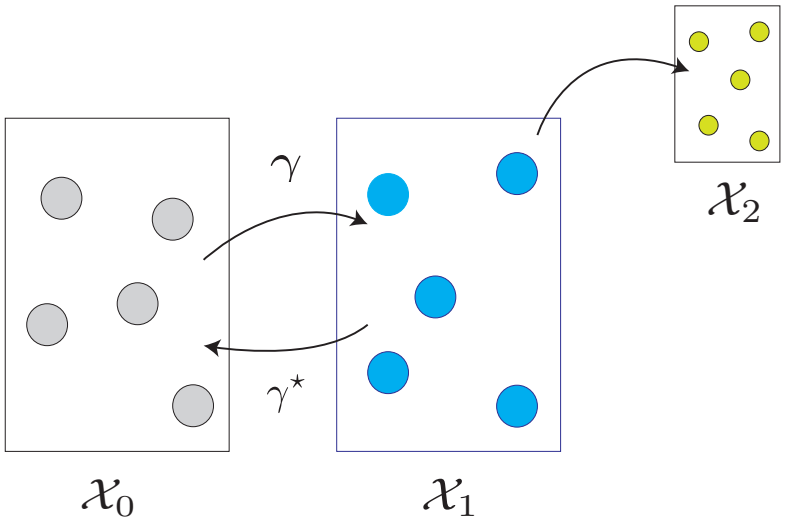
In particular:

$$\gamma\frac{X_0^N}{N} \sim \gamma^*\frac{X_1^N}{N}$$

Polymerisation: Escape from the Urn



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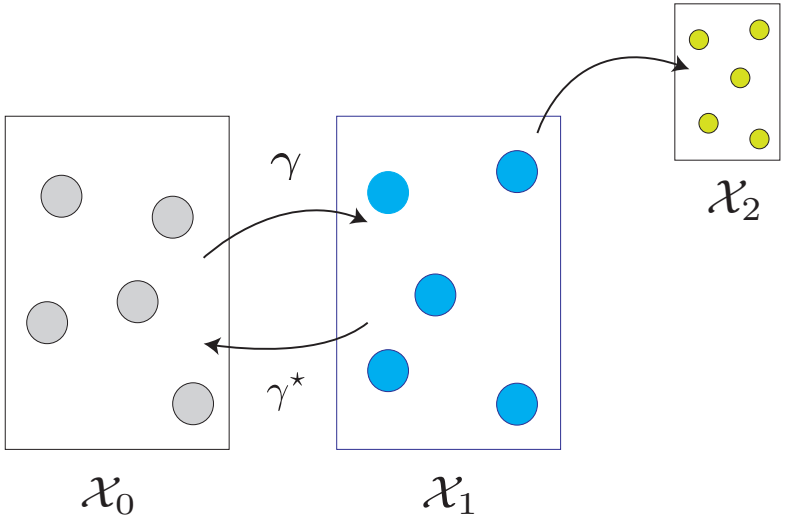

- Size of the Urn: $B_N(t) = M_N - X_2^N(t)$
- $X_2^N(t)$ is the escape of the urn, i.e the polymerised mass

Coexistence of the two processes

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Stochastic dynamic

- Operator for the misfolding process (Ehrenfest urn of size b):

$$\Omega[b](f)(x_0, x_1) = \gamma x_0[f(x_1+1/N)-f(x_1)]$$
$$+\gamma^* x_1[f(x_1 - 1/N) - f(x_1)]$$

- Operator for the polymerisation process:

$$\Delta^-(f)(x_1) = f(x_1 - 2/N) - f(x_1)$$

Stochastic Dynamic of the Polymerised Mass

$$\mathrm{d}X_2(t) = 2 \sum_{i=1}^{X_1^N(X_1^N-1)(s-)/2} \mathcal{N}^i_{\alpha/N^2}(\mathrm{d}t) + \sum_{i=1}^{X_1^N(s-)X_2^N(s-)} \mathcal{N}^i_{\beta/N^2}(\mathrm{d}t)$$

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$$\frac{X_2(Nt)}{N} = \alpha \int_0^t \left(\frac{X_1(Ns)}{N}\right)^2 \mathrm{d}s + \beta \int_0^t \frac{X_1(Ns).X_2(Ns)}{N^2}\,\mathrm{d}s + \mathcal{M}_t^N$$

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- $(X_2^N(Nt)/N)_N$ is tight $\implies \exists (N_k), X_2^{N_k}(N_k t)/N_k \to x_2(t)$

Slow VS fast process

Stochastic Dynamic of the Ehrenfest Urn

$$
\begin{aligned}
f\left(\frac{X_1^N(Nt)}{N}\right) - f\left(\frac{X_1^N(0)}{N}\right) - \mathcal{M}_1(Nt) \\
&= N^2 \int_0^t \Omega\left[m - \frac{X_2^N(Nu)}{N}\right](f)\left(\frac{X_1^N(Nu)}{N}\right) du \\
&+ \alpha N \int_0^t \Delta^-(f)\left(\frac{X_1^N(Nu)}{N}\right)\left(\frac{X_1^N(Nu)}{N}\right)^2 du \\
&+ \beta N()
\end{aligned}
$$

Let μ_N be the following random Radon measure on $\mathbb{R}^3_+$:

$$\langle \mu_N, g \rangle = \int_{\mathbb{R}_+} g\left(\frac{X_0^N(Nu)}{N}, \frac{X_1^N(Nu)}{N}, u \right) \mathrm{d}u$$

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Proposition 1

Then μ_N is tight and any limiting point μ_∞ satisfies:

$$\langle \mu_\infty, g \rangle = \int_{\mathbb{R}_+} \int_{[0,m]^2} g(x, y, u) \pi_u(\mathrm{d}x, \mathrm{d}y) \, \mathrm{d}u$$

where for each $u \geq 0$, π_u is a random Radon measure on $\mathbb{R}_+^2$.

Proposition 2

If μ_∞ is a limiting point of μ_N with the previous representation, then:

$$\int_0^t \int_{\mathbb{R}_+^2} (\gamma^* y - \gamma x) \left(\frac{\partial}{\partial x} f(x,y) - \frac{\partial}{\partial y} f(x,y) \right) \pi_u(\mathrm{d}x, \mathrm{d}y)\, \mathrm{d}u = 0$$

In particular,

$$\int_0^t \int_{\mathbb{R}_+^2} (\gamma^* y - \gamma x)^2 \pi_u(\mathrm{d}x, \mathrm{d}y)\, \mathrm{d}u = 0$$

Proposition: Local Equilibrium

The measure π_u is concentrated on the $\{(x, \gamma/\gamma^* x) : 0 \leq x \leq m\}$:

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$$\pi_u = \delta_{\left(\frac{\gamma^*}{\gamma+\gamma^*}(m-x_2(u)), \frac{\gamma}{\gamma+\gamma^*}(m-x_2(u)\right)}$$

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Intuition

Where:

$$\text{“}x_0(t) = \lim_{N\to\infty} \frac{X_0^N(Nt)}{N}\text{”}$$
$$= \frac{\gamma^*}{\gamma+\gamma^*}(m - x_2(t))$$

$\Longrightarrow$ $x_0(t)$ is the limit of the concentration of monomers of type $\mathcal{X}_0$ in an Ehrenfest Urn of size $M - X_2^N(t) \sim N(m - x_2(t))$.

$$\begin{aligned}
\frac{X_2(N_k t)}{N_k} &= \alpha \int_0^t \left(\frac{X_1(N_k s)}{N_k} \right)^2 \mathrm{d}s + \beta \int_0^t \frac{X_1(N_k s).X_2(N_k s)}{N_k^2} \, \mathrm{d}s \\
&= \alpha \int_0^t \int_{[0,m]^2} y^2 \mu_{N_k}(\mathrm{d}x, \mathrm{d}y, \mathrm{d}u) + \beta \int_0^t \int_{[0,m]^2} \ldots \\
&\underset{k \to \infty}{\longrightarrow} \alpha \int_0^t \int_{[0,m]^2} + \ldots \\
&= \left(\frac{\gamma}{\gamma + \gamma^*} \right)^2 \int_0^t (m - x_2(u))^2 \, \mathrm{d}u + \ldots
\end{aligned}$$

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(Recall the simple model: $\dot{x_2} = \alpha (m - x_2)^2 + \beta (m - x_2) x_2$)

- Same diffusion as the simple model where α becomes αr^2, and β, βr

- Same variance formula:

$$\mathrm{Var}\left(\frac{T_\delta^N}{N}\right) \sim \frac{3}{2M\alpha r^2 \beta r m^2}$$

Outline

Perspectives

- numerical estimation of the parameters
- adding a scaling in the reaction rates

Second Approach

$$\begin{cases} \mathcal{X}_1 + \mathcal{X}_1 \xrightarrow{\alpha/N^{\nu}.(X_1/N)^2} 2\mathcal{X}_2 \\ \mathcal{X}_1 + \mathcal{X}_2 \xrightarrow{\beta X_1.X_2/N^2} 2\mathcal{X}_2 \end{cases}$$

Merci