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# Stochastic coagulation-fragmentation models for the study of protein aggregation phenomena

**Romain Yvinec**<sup>1</sup>, **Samuel Bernard**<sup>2,3</sup>, **Tom Chou**<sup>4</sup>, **Julien Deschamps**<sup>5</sup>, **Maria R. D'Orsogna**<sup>6</sup>, **Erwan Hingant**<sup>7</sup> and **Laurent Pujo-Menjouet**<sup>2,3</sup>

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<sup>5</sup>DIMA, Università degli Studi di Genova, Italy.

<sup>6</sup>Dept. of Mathematics, CSUN, Los Angeles, USA.

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Amyloid diseases and Becker-Döring model

Numerical results

Coarse-graining

Open problems (for me)

# Outline

Amyloid diseases and Becker-Döring model

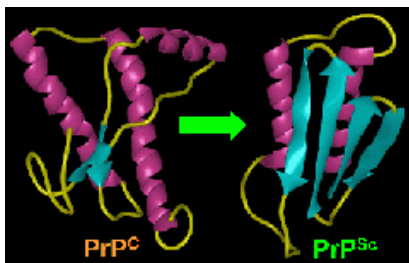
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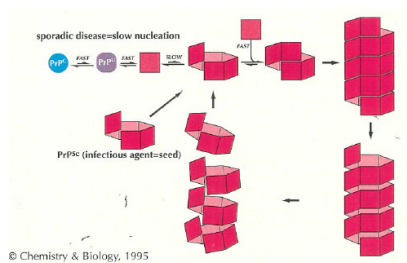
Open problems (for me)

# Protein accumulation in amyloid by nucleation-polymerization

## Misfolding



## Prusiner model for prion

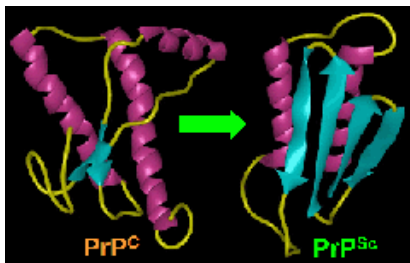


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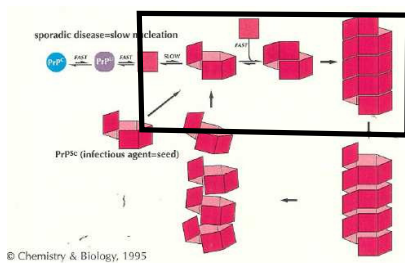
## Mechanism of Prion Propagation: Amyloid Growth Occurs by Monomer Addition

# Protein accumulation in amyloid by nucleation-polymerization

## Misfolding

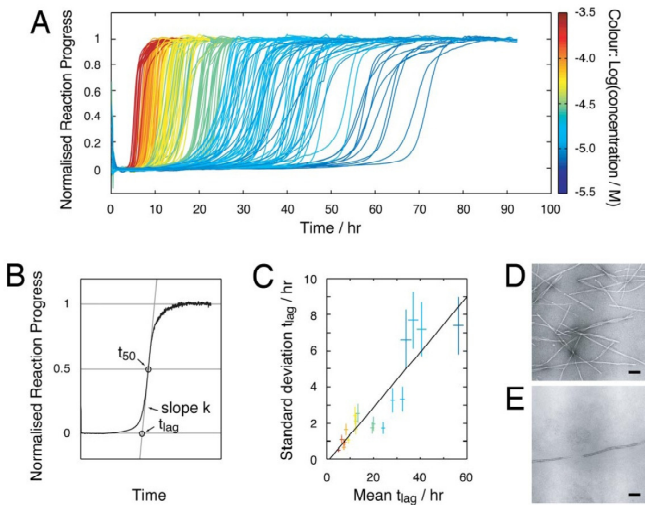


## Prusiner model for prion



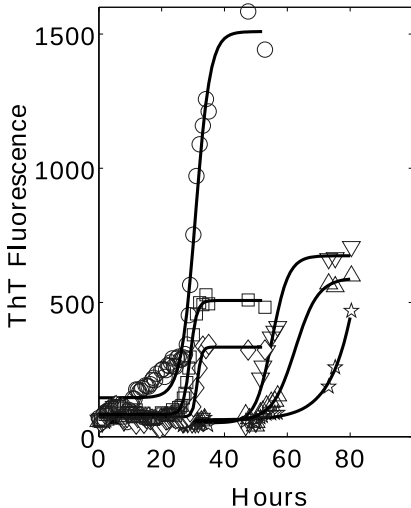
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Mechanism of Prion Propagation:  
Amyloid Growth Occurs by **Monomer Addition**

Times series of *in-vitro* spontaneous polymerization

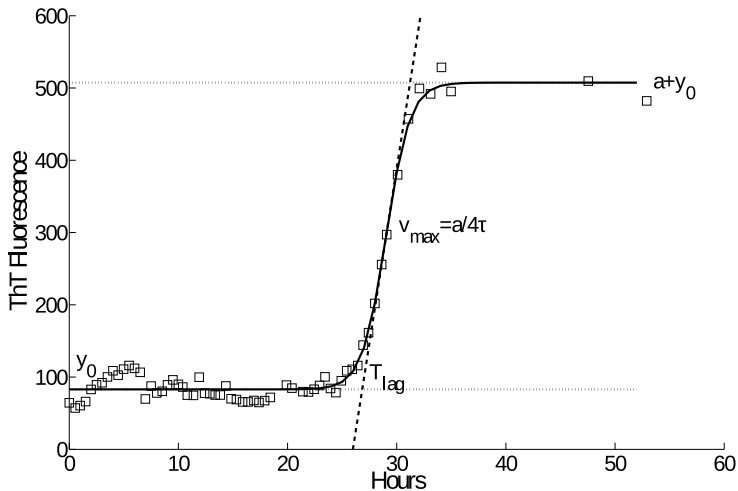
Xue et al. PNAS (2008)

Eugene et al. hal-01205549 (2015)

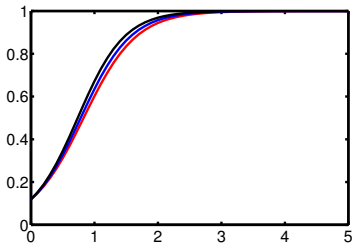
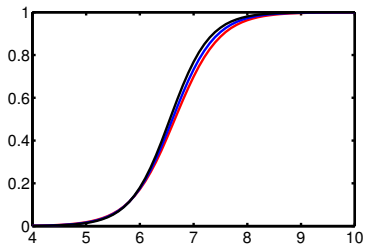
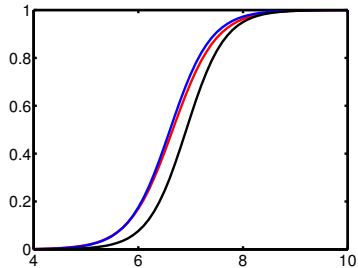
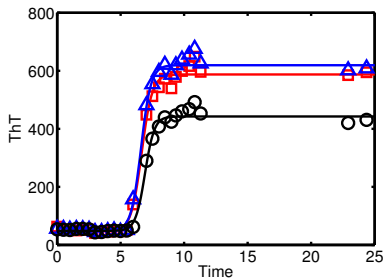
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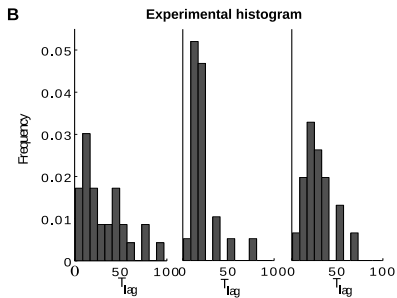
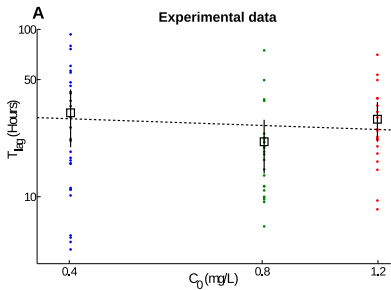
## Quantification of experiment



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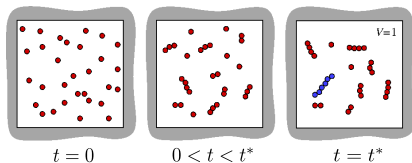
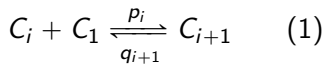


# Statistics of lag time



## Nucleation time in the Stochastic Becker-Döring model

Reversible one-step aggregation

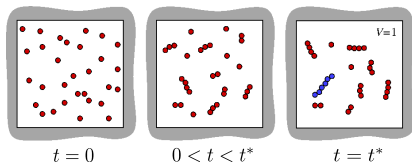
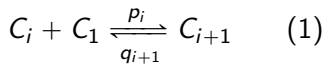


The **nucleation time** is given by the following First Passage Time,

$$T^{N,M} := \inf\{t \geq 0 : C_N(t) = 1 \mid C_i(t=0) = M\delta_{i=1}\}. \quad (2)$$

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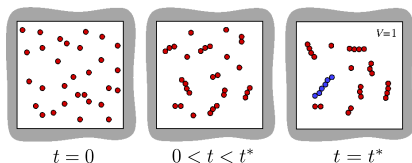
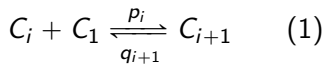
$$T^{N,M} := \inf\{t \geq 0 : C_N(t) = 1 \mid C_i(t=0) = M\delta_{i=1}\}. \quad (2)$$

- ▶ What are the dependencies of the nucleation time with respect to the model parameters?

total mass :  $M$ ;      nucleus size :  $N$   
 aggregation rates :  $p_i, i \geq 1$       fragmentation rates :  $q_i, i \geq 2$

## Nucleation time in the Stochastic Becker-Döring model

## Reversible one-step aggregation



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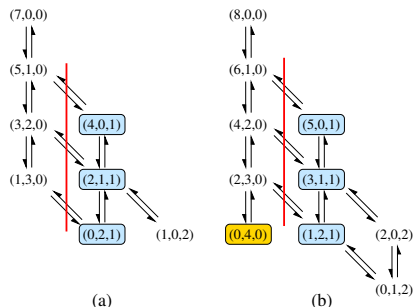
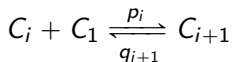
- ▶ What is the nucleation time for very large initial quantity  $M$  and nucleus size  $N$ ?

$$\lim_{M, N \rightarrow \infty} T^{N,M}$$

In data,  $M \approx 10^{10} - 10^{15}$ , Size of (observed) polymers  $\approx 10^3 - 10^6$ ,  
 $N = ?$ .

## Nucleation time in the Stochastic Becker-Döring model

## Reversible one-step aggregation



The **nucleation time** is given by the following First Passage Time,

$$T^{N,M} := \inf\{t \geq 0 : C_N(t) = 1 \mid C_i(t=0) = M\delta_{i=1}\}.$$

# Outline

Amyloid diseases and Becker-Döring model

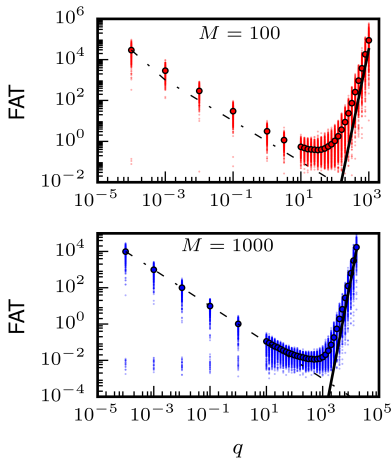
**Numerical results**

Coarse-graining

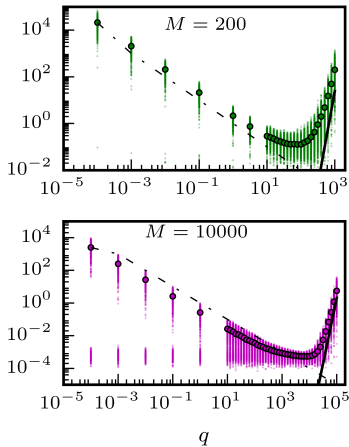
Open problems (for me)



- ▶ Non-monotonous w.r.t reaction rate



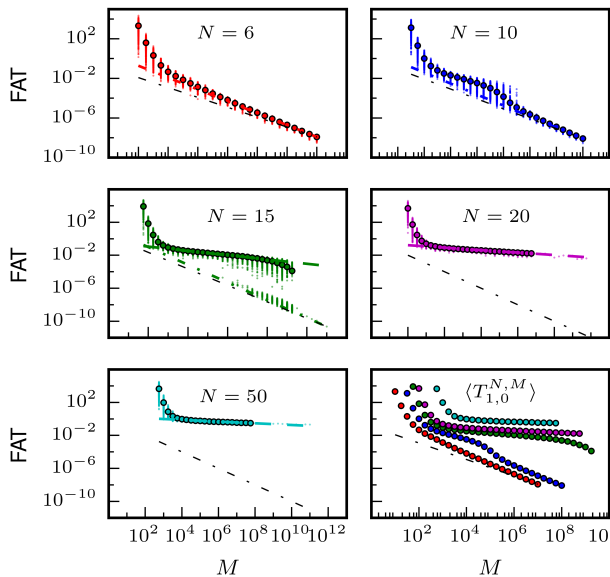
- ▶ Bimodal for 'small' fragmentation rate



$N=10$ ,  $p_1 = 0.5$ ,  $p_k = 1$  and  $q_k \equiv q$  for  $k \geq 2$ .

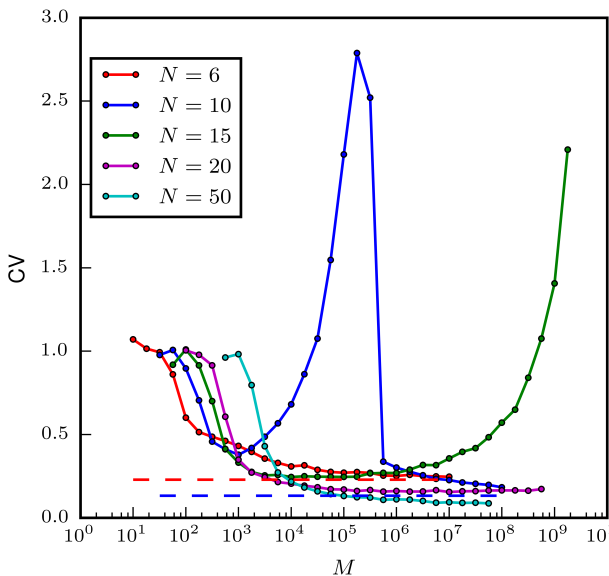
- 'Weak' dependency w.r.t. total monomer number  $M$

$p_1 = 0.5$ ,  $p_k = 1$   
and  $q_k \equiv 100$  for  $k \geq 2$ .

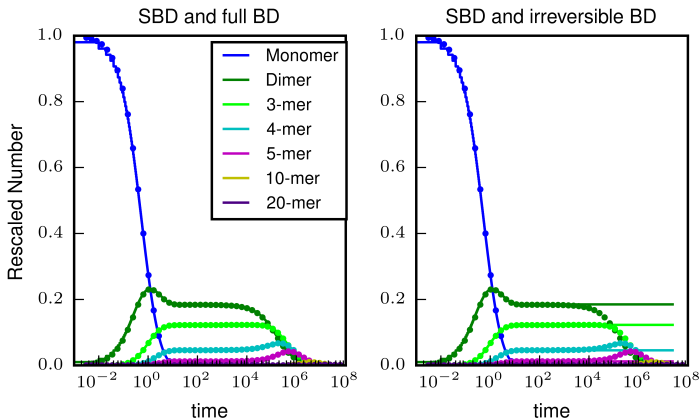


- ▶ Normalized variance non-monotonous.
- ▶ Normalized variance non zero pour  $M \rightarrow \infty$ .

$p_1 = 0.5$ ,  $p_k = 1$   
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 $k \geq 2$ .



- ▶ For  $M \rightarrow \infty$  : deterministic trajectory.
- ▶ Metastable behavior : 'pure-aggregation'.
- ▶ Medium-large polymer formed only after a longer time



$p_k = 1$  and  $q_k \equiv 1$  for  $k \geq 2$ ,  $M = 10^5$  (we plot  $M^{-1}C_k(tM^{-1})$ ).  
Detailed Analysis : cf [Wattis, J. Phys. A : Math., 35 (2002)]

# Outline

Amyloid diseases and Becker-Döring model

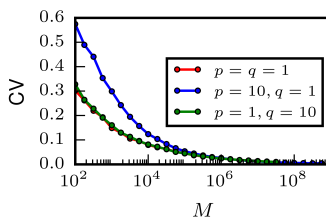
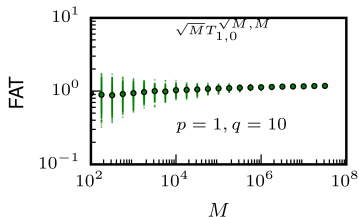
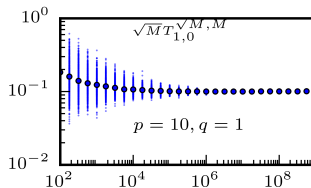
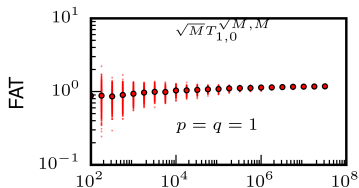
Numerical results

**Coarse-graining**

Open problems (for me)

# Large nucleus $N \sim \sqrt{M}$

- ▶ First case ( $p(0)m > q(0)$ ) : Convergence towards a deterministic value.

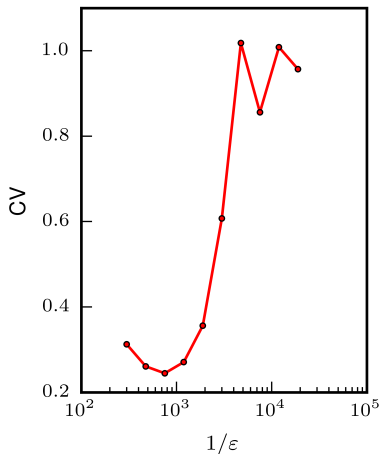
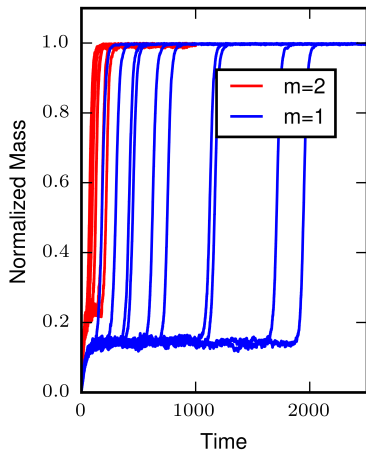


▶ case A

▶ case B

# Large nucleus $N \sim \sqrt{M}$

- ▶ Second case ( $p(0)M < q(0)$ ) : Exponentially large time and 'translated' trajectory.



# Outline

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# Quantifying the large deviation in the SBD model

A much simpler version of this model consider that a **single** aggregate may be formed at a time :

$$k \xrightleftharpoons[q_{k+1}]{p_k(m-k\varepsilon)} k+1,$$

which converges (with time rescaling) to

$$\frac{dx}{dt} = p(x)(m-x) - q(x)$$

FPT are given by

$$\mathbb{E}[T_{1,0}^N] = \sum_{i=1}^{N-1} \sum_{j=1}^i \frac{\prod_{k=j+1}^i q_k}{\prod_{k=j}^i p_k(m-\varepsilon k)}.$$

which converges (with time rescaling) to

$$\int_0^1 \int_0^y \cdot \exp \left[ \varepsilon^{-1} \int_z^y \ln \left( \frac{q(x)}{p(x)(m-x)} \right) dx \right].$$

# Quantifying the large deviation in the SBD model

Can we perform similar calculations with  $n$  clusters?

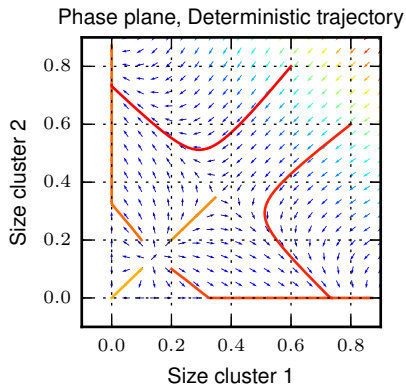
$$(k_0, k_1) \xrightleftharpoons[q_{k_0+1}]{p_{k_0}(m-(k_0+k_1)\varepsilon)} (k_0 + 1, k_1),$$

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$$\frac{dx}{dt} = p(x)(m - x - y) - q(x)$$

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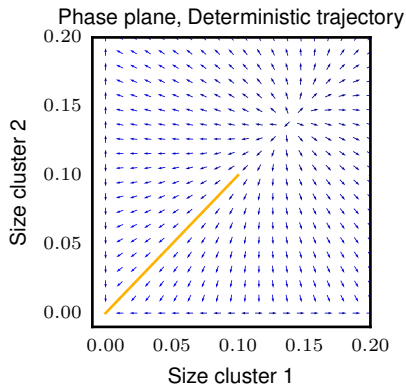
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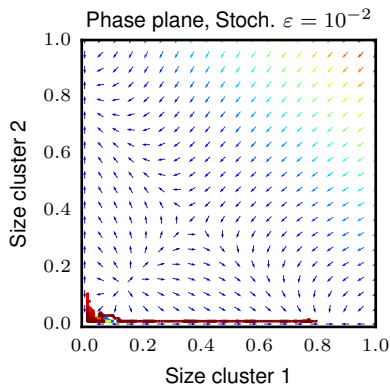
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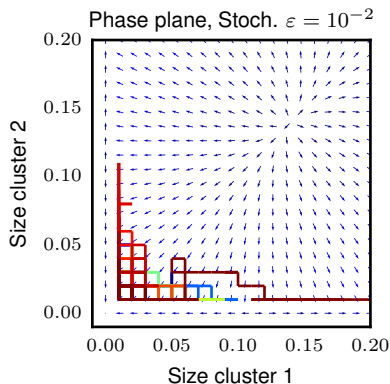
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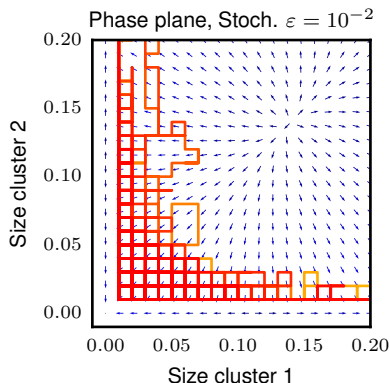
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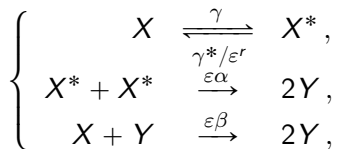
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- ▶ **Extension to spatial models (diffusion) ?**
- ▶ **Data fitting with  $10^{10} - 10^{15}$  proteins ?**

## Toy model with time-scale separation



with initial condition

$$Z^\varepsilon(0) = ([x_0/\varepsilon], 0, 0).$$

