



## Nucleation time in stochastic Becker-Doring model

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# Nucleation Time in Stochastic Becker-Döring Model

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## Amyloid diseases and Becker-Döring model

Numerical results

Coarse-graining

Large deviations

# Outline

Amyloid diseases and Becker-Döring model

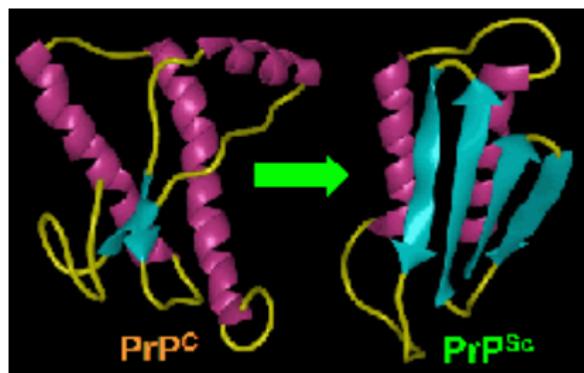
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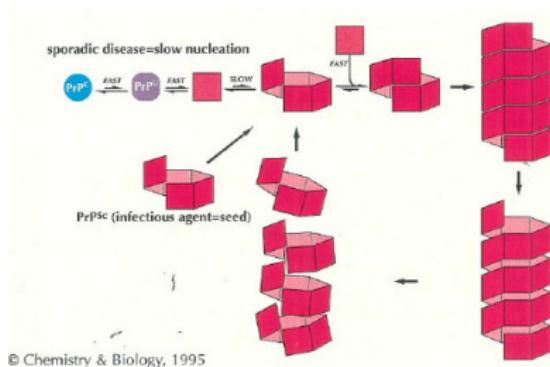
Large deviations

# Protein accumulation in amyloid by nucleation-polymerization

## Misfolding



## Prusiner model for prion

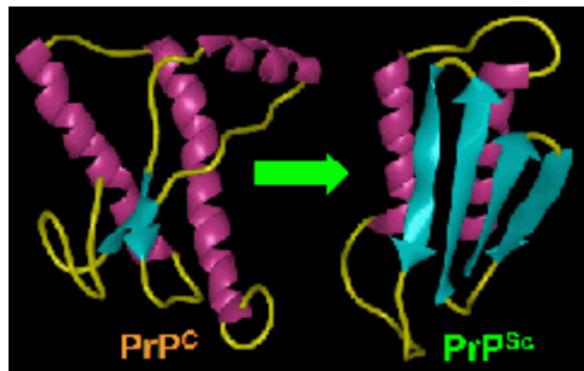


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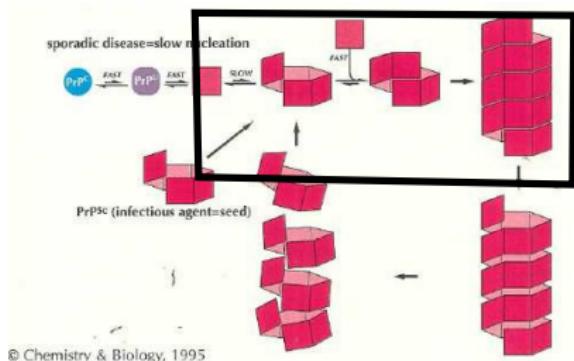
Mechanism of Prion Propagation:  
Amyloid Growth Occurs by Monomer Addition

# Protein accumulation in amyloid by nucleation-polymerization

## Misfolding



## Prusiner model for prion

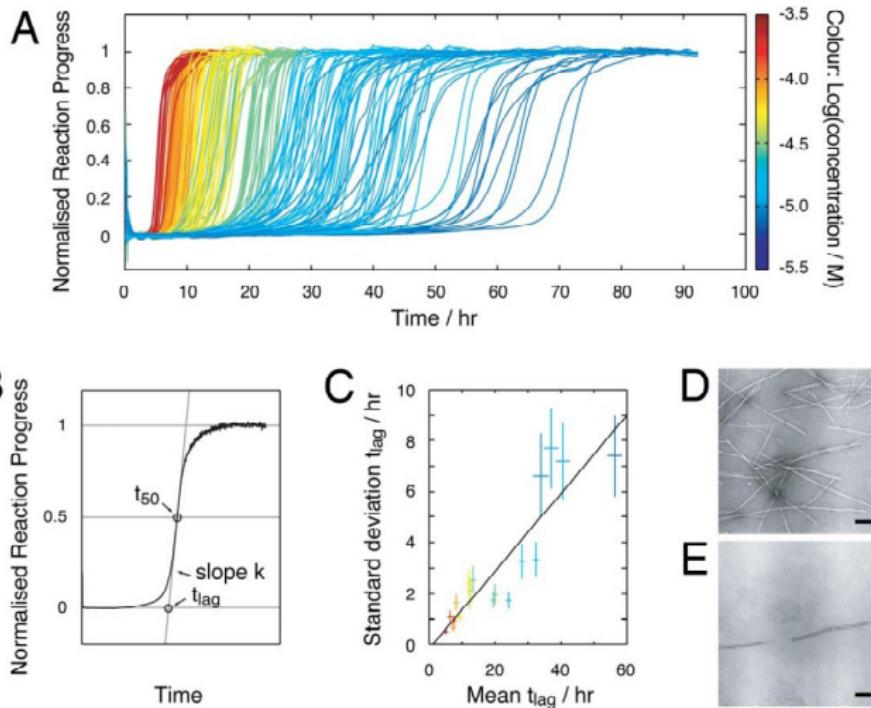


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Mechanism of Prion Propagation:  
Amyloid Growth Occurs by Monomer Addition

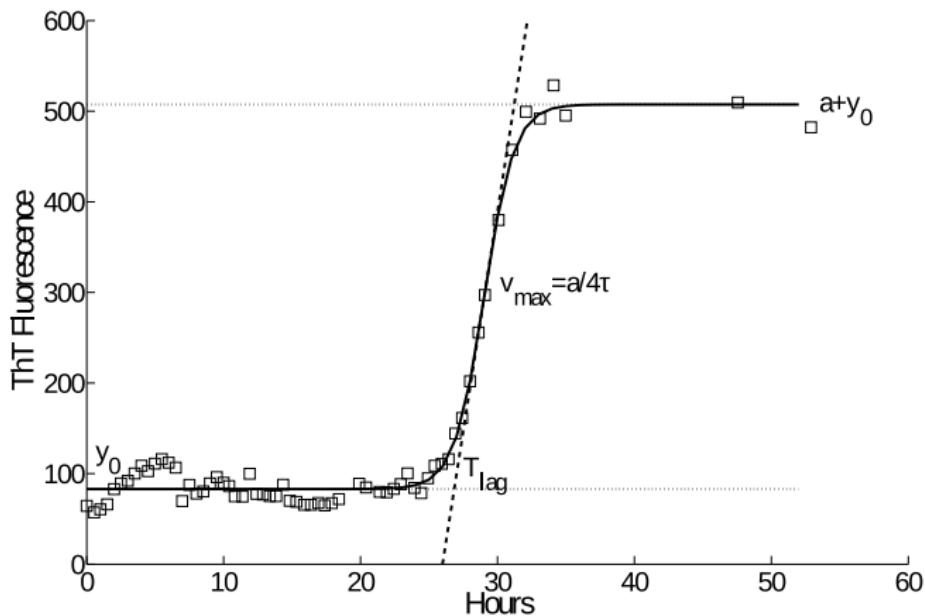
# Times series of *in-vitro* spontaneous polymerization



Xue et al. PNAS (2008)

Eugene et al. hal-01205549 (2015)

# Quantification of experiment

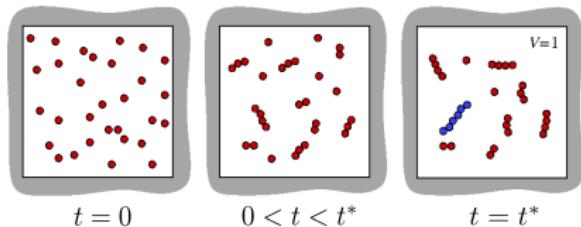
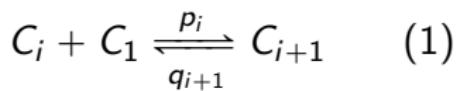


ThT fluorescence  $\approx$  Number of polymerized protein

[Courtesy of J.P. Liautard]

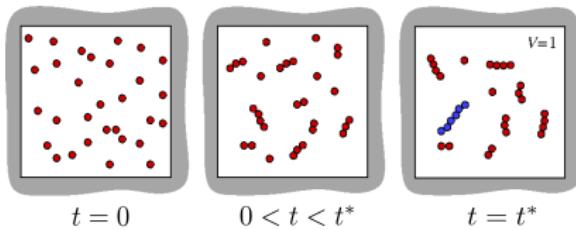
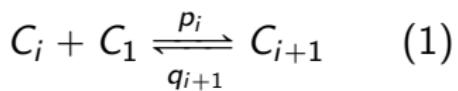
# Becker-Döring model

Reversible one-step aggregation



# Becker-Döring model

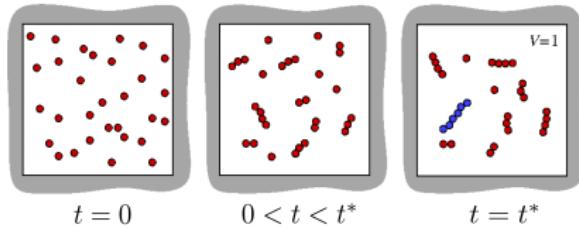
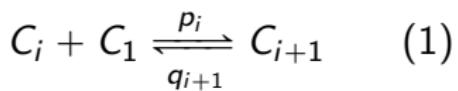
Reversible one-step aggregation



- ▶ Purely dynamic model (law of mass-action) : no space, no polymer structure.

# Becker-Döring model

Reversible one-step aggregation

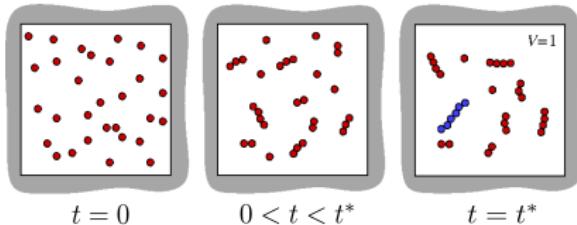
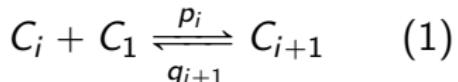


- Indirect interaction between polymer  $C_i$ ,  $i \geq 2$  via the available number of monomers  $C_1$ .

$$C_1(t) + \sum_{i \geq 2} i C_i(t) = \text{constant} := M \quad (2)$$

# Becker-Döring model

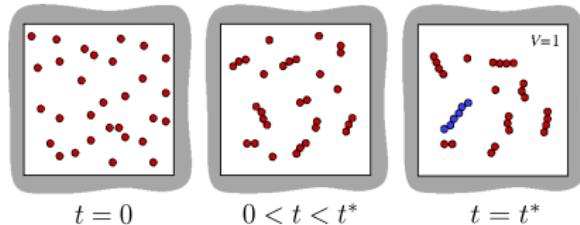
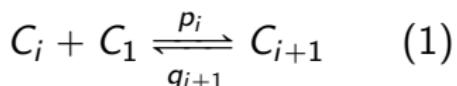
## Reversible one-step aggregation



- ▶ In spontaneous polymerization experiment,
  - ▶ Initial condition given by  $C_i(t = 0) = 0 \forall i \geq 2$ .
  - ▶ Measured variable :  $\sum_{i \geq N} iC_i$  ( $N$  is an unknown parameter)

# Becker-Döring model

Reversible one-step aggregation



- The (observed) nucleation time is given by

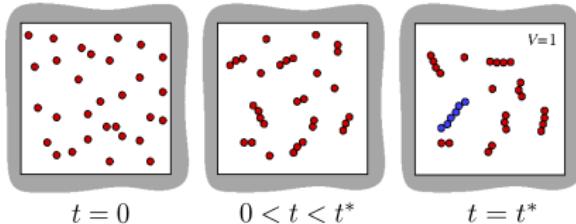
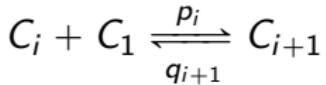
$$\inf\left\{t \geq 0 : \sum_{i \geq N} i C_i(t) \geq \rho M \mid C_i(t=0) = M \delta_{i=1}\right\}.$$

Another quantity of interest is the following **First Passage Time**,

$$\inf\left\{t \geq 0 : C_N(t) \geq \rho \mid C_i(t=0) = M \delta_{i=1}\right\}.$$

# Becker-Döring model

## Reversible one-step aggregation



- ▶ 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 :     $q_i, i \geq 2$

- ▶ What is the nucleation time for very large initial quantity  $M$  and nucleus size  $N$  ?
- ▶ In experiment,  $M \approx 10^{10} - 10^{15}$ ,  
 Size of (observed) polymers  $\approx 10^3 - 10^6$ ,  $N = ?$ .

# Deterministic BD model and Classical Nucleation Theory

$$\left\{ \begin{array}{lcl} \frac{dc_i}{dt} & = & J_{i-1} - J_i, i \geq 2, \\ J_i & = & p_i c_1 c_i - q_{i+1} c_{i+1}, i \geq 1, \\ \frac{dc_1}{dt} & = & -J_1 - \sum_{i=1}^{\infty} J_i. \end{array} \right.$$

Equilibrium is given by  $J_i \equiv J = 0$ , which implies

$$c_i = Q_i c_1^i, \quad Q_i = \frac{p_1 p_2 \cdots p_{i-1}}{q_2 q_3 \cdots q_i}$$

The mass at equilibrium is given by

$$\rho(c_1) = \sum_{i \geq 1} i Q_i c_1^i$$

If this series has a finite radius of convergence,  $z_s$ , then there is a critical mass

$$\rho_s = \sum_{i \geq 1} i Q_i z_s^i$$

# Deterministic BD model and Classical Nucleation Theory

$$\left\{ \begin{array}{lcl} \frac{dc_i}{dt} & = & J_{i-1} - J_i, i \geq 2, \\ J_i & = & p_i c_1 c_i - q_{i+1} c_{i+1}, i \geq 1, \\ \frac{dc_1}{dt} & = & -J_1 - \sum_{i=1}^{\infty} J_i. \end{array} \right.$$

[Ball, Carr, Penrose,  
CMP (1986)]

If  $M \leq \rho_s$ , then (with strong convergence)

$$\lim_{t \rightarrow \infty} c_i(t) = Q_i z^i, \quad \rho(z) = M$$

If  $M > \rho_s$ , then (with weak convergence)

$$\lim_{t \rightarrow \infty} c_i(t) = Q_i z_s^i, \quad M - \rho(z_s) = \text{"loss of mass"}$$

As  $M \searrow \rho_s$ , there is a solution for which  $J_i \approx J^*$  is exponentially small, and

- ▶ (for finite  $t$ )  $c_i(t) - c_i(0)$  is exponentially small
- ▶  $\lim_{t \rightarrow \infty} c_i(t) - c_i(0)$  is not exponentially small

# Deterministic BD model – Some remarks

- For constant or linear kinetic rates  $p_i, q_i$ , one can reduce the system to 1 or 2 ODEs on

$$\sum_{i \geq 1} c_i, \quad \sum_{i \geq 1} i c_i.$$

- Based on scaling arguments, one can show that for  $q_i = 0$  (irreversible nucleation),

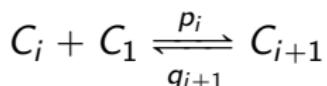
$$\inf\{t \geq 0 : c_N(t) \geq \rho M \mid c_i(t=0) = M\delta_{i=1}\} \simeq \frac{1}{M}.$$

while for “ $q_i \rightarrow \infty$ ” (pre-equilibrium nucleation),

$$\inf\{t \geq 0 : c_N(t) \geq \rho M \mid c_i(t=0) = M\delta_{i=1}\} \simeq \frac{1}{M^N}.$$

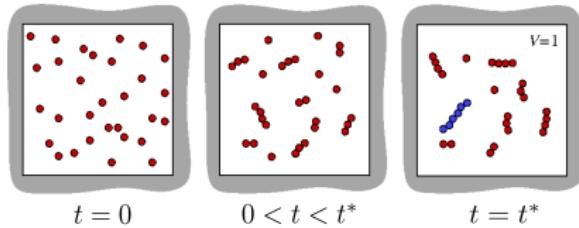
# Stochastic Becker-Döring model

Reversible one-step aggregation



We define a continuous time  
Markov Chain on

$$\{(C_i)_i \geq 1 : C_i \in \mathbb{N}, \sum_{i \geq 1} i C_i = M\}$$

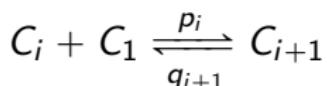


Transitions are given by

$$\mathcal{P} \left\{ \begin{array}{l} C_1(t+dt) = C_1(t) - 1 \\ C_i(t+dt) = C_i(t) - 1 \\ C_{i+1}(t+dt) = C_{i+1}(t) + 1 \end{array} \right\} = p_i C_1(t) C_i(t) dt + o(dt)$$

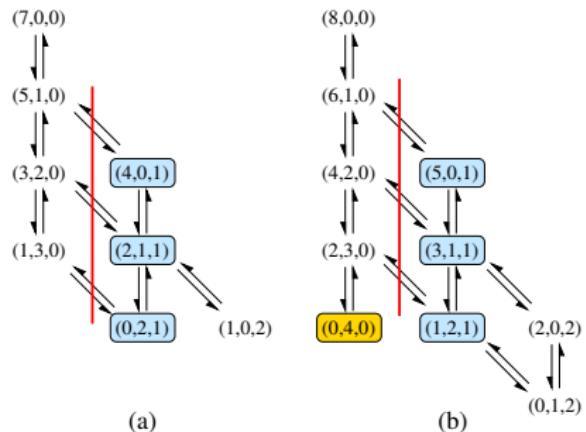
# Stochastic Becker-Döring model

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We define a continuous time  
Markov Chain on

$$\{(C_i)_i \geq 1 : C_i \in \mathbb{N}, \sum_{i \geq 1} i C_i = M\}$$



We are interested in

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

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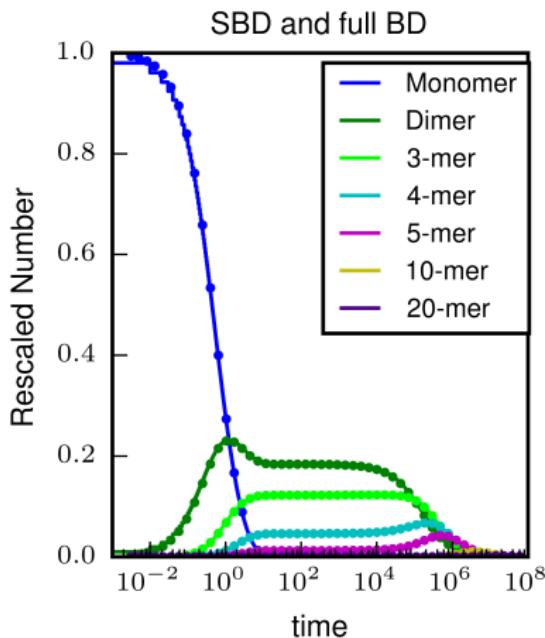
- ▶ Law of large numbers as  $M \rightarrow \infty$  [Jeon. CMP (1998)]
- ▶ Any macroscopic quantity like.

$$\inf\{t \geq 0 : \sum_{i \geq N} i C_i(t) \geq \rho M \\ | C_i(t=0) = M \delta_{i=1}\}.$$

converges (if reachable) to a finite deterministic value as  $M \rightarrow \infty$ .

- ▶ This may not be true for microscopic quantity, for instance.

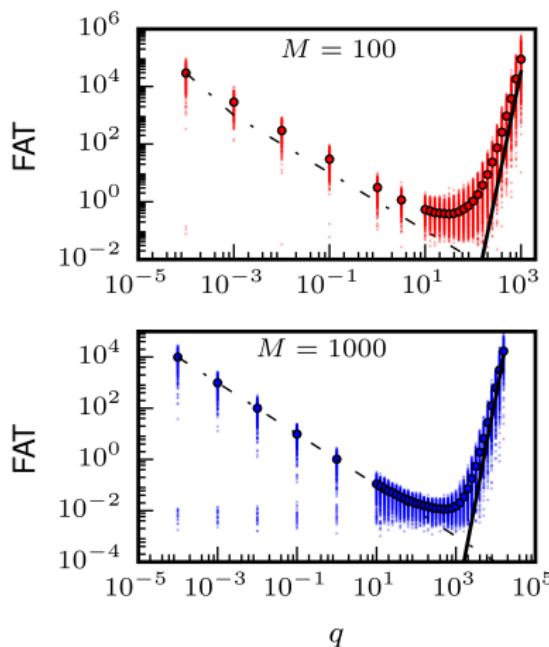
$$\inf\{t \geq 0 : C_N(t) \geq 1 \\ | C_i(t=0) = M \delta_{i=1}\}.$$



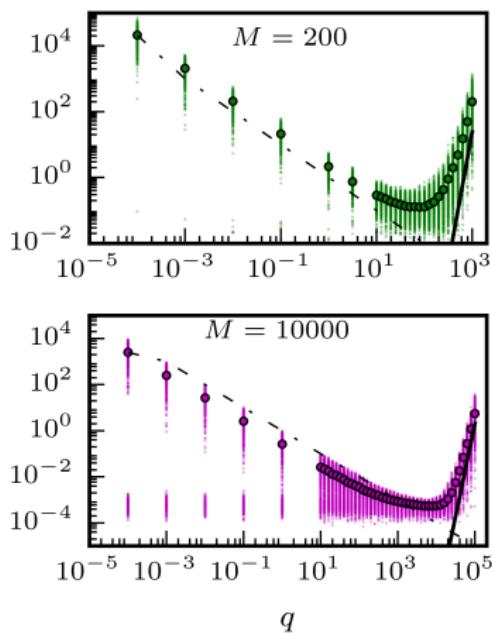
[Y., D'Orsogna, Chou JCP (2012)]

[Y., Bernard, Hingant, Pujo-Menjouet JCP (2016)]

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



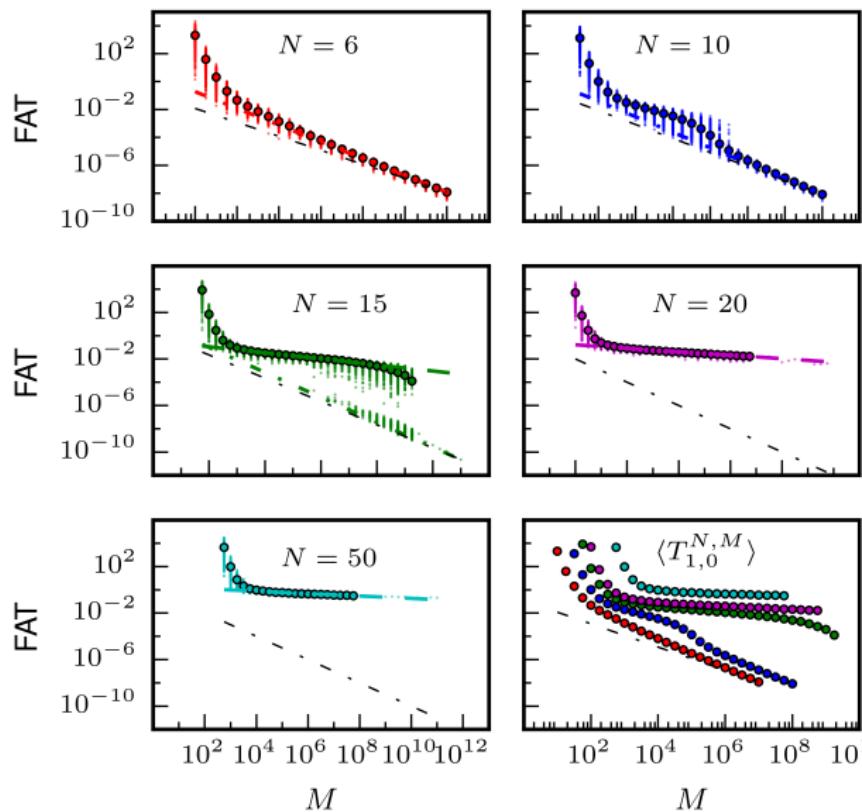
- ▶ Bimodal for 'small' fragmentation rate



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

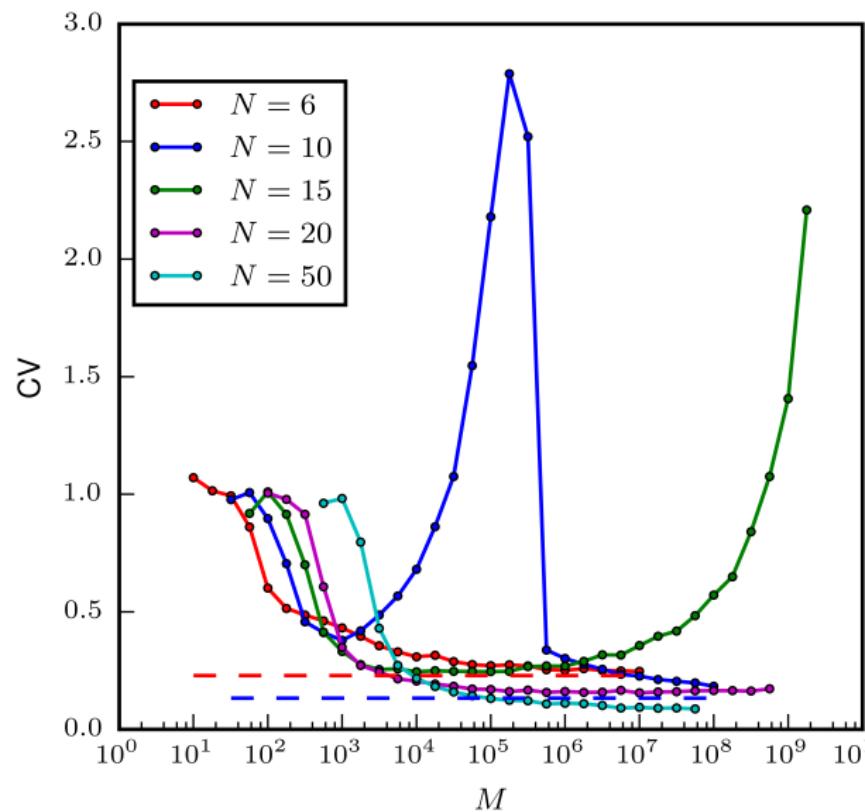
- ▶ 'Weak' dependency w.r.t. total monomer number  $M$

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



- Normalized standard deviation non-monotonous.
- Normalized standard deviation non zero pour  $M \rightarrow \infty$ .

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



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# When $N \rightarrow \infty$ ?

We start from a rescaled model ( $\varepsilon = 1/N$ ,  $\varepsilon^2 = 1/M$ )

$$\begin{cases} \frac{dc_i^\varepsilon}{dt} &= \frac{1}{\varepsilon} [J_{i-1}^\varepsilon - J_i^\varepsilon] , \quad i \geq 2 , \\ m^\varepsilon &= c_1^\varepsilon(t) + \varepsilon^2 \sum_{i \geq 2} i c_i^\varepsilon(t) . \end{cases}$$

With  $f^\varepsilon(t, x) = \sum_{i \geq 2} c_i^\varepsilon(t) \mathbf{1}_{[(i-1/2)\varepsilon, (i+1/2)\varepsilon)}(x)$ ,

Scaling idea : **excess of monomer**

$$c_1^\varepsilon(t) = \varepsilon^2 c_1(t) ,$$

Compensated aggregation / fragmentation

$$p^\varepsilon(x) = \sum_{i \geq 2} (p_i/\varepsilon^2) \mathbf{1}_{[\varepsilon i, \varepsilon(i+1)[} \quad q^\varepsilon(x) = \sum_{i \geq 3} q_i \mathbf{1}_{[\varepsilon i, \varepsilon(i+1)[}$$

and **slow first step** :

$$p_1^\varepsilon = \frac{p_1}{\varepsilon^4} ,$$

# When $N \rightarrow \infty$ ?

We start from a rescaled model ( $\varepsilon = 1/N$ ,  $\varepsilon^2 = 1/M$ )

$$\begin{cases} \frac{dc_i^\varepsilon}{dt} &= \frac{1}{\varepsilon} [J_{i-1}^\varepsilon - J_i^\varepsilon], \quad i \geq 2, \\ m^\varepsilon &= c_1^\varepsilon(t) + \varepsilon^2 \sum_{i \geq 2} i c_i^\varepsilon(t). \end{cases}$$

With  $f^\varepsilon(t, x) = \sum_{i \geq 2} c_i^\varepsilon(t) \mathbf{1}_{[(i-1/2)\varepsilon, (i+1/2)\varepsilon)}(x)$ ,

From the polymer point of view, we have accelerated fluxes, all of the same order :

$$\overbrace{\frac{\frac{1}{\varepsilon} p_1^\varepsilon C_1^\varepsilon C_1^\varepsilon}{\frac{1}{\varepsilon} q_2^\varepsilon C_2^\varepsilon}}{} C_2^\varepsilon$$

$$C_{i-1}^\varepsilon \xrightarrow[\frac{1}{\varepsilon} q^\varepsilon(\varepsilon i) C_i^\varepsilon]{\frac{1}{\varepsilon} p^\varepsilon(\varepsilon(i-1)) C_1^\varepsilon C_{i-1}^\varepsilon} C_i^\varepsilon \xrightarrow[\frac{1}{\varepsilon} q^\varepsilon(\varepsilon(i+1)) C_{i+1}^\varepsilon]{\frac{1}{\varepsilon} p^\varepsilon(\varepsilon i) C_1^\varepsilon C_i^\varepsilon} C_{i+1}^\varepsilon,$$

# When $N \rightarrow \infty$ ?

We start from a rescaled model ( $\varepsilon = 1/N$ ,  $\varepsilon^2 = 1/M$ )

$$\begin{cases} \frac{dc_i^\varepsilon}{dt} &= \frac{1}{\varepsilon} [J_{i-1}^\varepsilon - J_i^\varepsilon], \quad i \geq 2, \\ m^\varepsilon &= c_1^\varepsilon(t) + \varepsilon^2 \sum_{i \geq 2} i c_i^\varepsilon(t). \end{cases}$$

With  $f^\varepsilon(t, x) = \sum_{i \geq 2} c_i^\varepsilon(t) \mathbf{1}_{[(i-1/2)\varepsilon, (i+1/2)\varepsilon)}(x)$ ,

$$\begin{cases} \frac{d}{dt} \int_0^{+\infty} f^\varepsilon(t, x) \varphi(x) dx = [p_1^\varepsilon c_1^\varepsilon(t)^2 - q_2^\varepsilon c_2^\varepsilon(t)] \left( \frac{1}{\varepsilon} \int_{3/2\varepsilon}^{5/2\varepsilon} \varphi(x) dx \right) \\ \quad + \int_0^{+\infty} [p^\varepsilon(x) c_1^\varepsilon(t) f^\varepsilon(t, x) \Delta_\varepsilon \varphi(x) - q^\varepsilon(x) f^\varepsilon(t, x) \Delta_{-\varepsilon} \varphi(x)] dx, \\ m^\varepsilon = c_1^\varepsilon(t) + \int_0^{+\infty} x f^\varepsilon(t, x) dx. \end{cases}$$

where  $\Delta_\varepsilon \varphi(x) = \frac{\varphi(x+\varepsilon) - \varphi(x-\varepsilon)}{2\varepsilon}$ .

$$\begin{aligned} \frac{d}{dt} \int_0^{+\infty} f^\varepsilon(t, x) \varphi(x) dx &= [p_1^\varepsilon c_1^\varepsilon(t)^2 - q_2 c_2^\varepsilon(t)] \left( \frac{1}{\varepsilon} \int_{3/2\varepsilon}^{5/2\varepsilon} \varphi(x) dx \right) \\ &+ \int_0^{+\infty} [p^\varepsilon(x) c_1^\varepsilon(t) f^\varepsilon(t, x) \Delta_\varepsilon \varphi(x) - q^\varepsilon(x) f^\varepsilon(t, x) \Delta_{-\varepsilon} \varphi(x)] dx, \end{aligned}$$

Theorem (Deschamps, Hingant, Y. (2016))

we have  $f^\varepsilon \rightarrow f$  (weakly in  $\mathcal{X} = \{\nu \in \mathcal{M}_b([0, \infty) : \int x\nu(dx) < \infty\})$ )  
solution of

$$\frac{d}{dt} \int_0^{+\infty} f(t, x) \varphi(x) dx = \int_0^{+\infty} [p(x) c_1(t) - q(x)] \varphi'(x) f(t, x) dx,$$

and  $c_1(t) + \int x f(t, x) = m$ , for all  $\varphi \in C_c(0, \infty)$ .

This is the weak form of

$$\frac{\partial f}{\partial t} + \frac{\partial (J(x, t) f(t, x))}{\partial x} = 0, \quad J(x, t) = p(x) c_1(t) - q(x).$$

$$\begin{aligned} \frac{d}{dt} \int_0^{+\infty} f^\varepsilon(t, x) \varphi(x) dx &= [p_1^\varepsilon c_1^\varepsilon(t)^2 - q_2 c_2^\varepsilon(t)] \left( \frac{1}{\varepsilon} \int_{3/2\varepsilon}^{5/2\varepsilon} \varphi(x) dx \right) \\ &+ \int_0^{+\infty} [p^\varepsilon(x) c_1^\varepsilon(t) f^\varepsilon(t, x) \Delta_\varepsilon \varphi(x) - q^\varepsilon(x) f^\varepsilon(t, x) \Delta_{-\varepsilon} \varphi(x)] dx, \end{aligned}$$

Theorem (Deschamps, Hingant, Y. (2016))

When  $c_1(0) > \lim_{x \rightarrow 0} \frac{q(x)}{p(x)}$ ,

$$\begin{aligned} \frac{d}{dt} \int_0^{+\infty} f(t, x) \varphi(x) dx &= N(t) \varphi(0) \\ &+ \int_0^{+\infty} [p(x) c_1(t) - q(x)] \varphi'(x) f(t, x) dx, \end{aligned}$$

for all  $\varphi \in C_b(0, \infty)$ , which gives the boundary condition

$$\lim_{x \rightarrow 0} J(x, t) f(t, x) = N(t).$$

$$\begin{aligned} \frac{d}{dt} \int_0^{+\infty} f^\varepsilon(t, x) \varphi(x) dx &= [p_1^\varepsilon c_1^\varepsilon(t)^2 - q_2 c_2^\varepsilon(t)] \left( \frac{1}{\varepsilon} \int_{3/2\varepsilon}^{5/2\varepsilon} \varphi(x) dx \right) \\ &+ \int_0^{+\infty} [p^\varepsilon(x) c_1^\varepsilon(t) f^\varepsilon(t, x) \Delta_\varepsilon \varphi(x) - q^\varepsilon(x) f^\varepsilon(t, x) \Delta_{-\varepsilon} \varphi(x)] dx, \end{aligned}$$

Theorem (Deschamps, Hingant, Y. (2016))

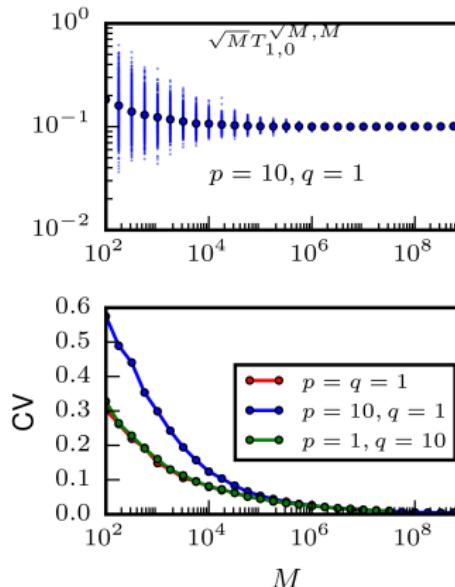
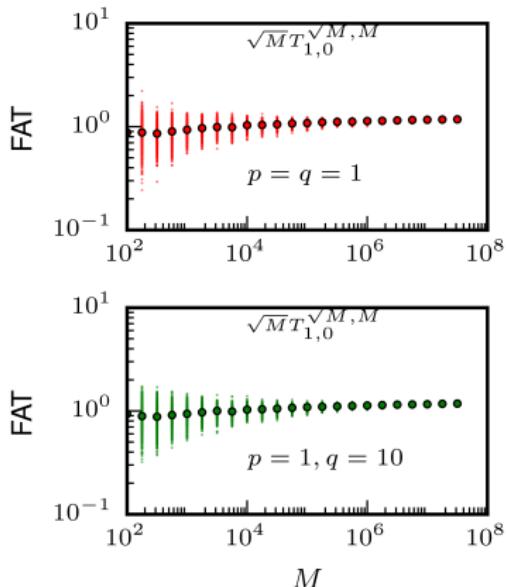
$N(t)$  is an explicit function of  $c_1(t)$ , and is given by a quasi steady-state approximation of  $c_2^\varepsilon = f^\varepsilon(t, 2\varepsilon)$ , given by the solution of

$$\begin{cases} 0 &= [J_{i-1}(c_1) - J_i(c_1)] , \quad i \geq 2 , \\ c_1(t) &= c_1 . \end{cases}$$

When  $c_1 > \lim_{x \rightarrow 0} \frac{q(x)}{p(x)}$ , the solution of  $J_i \equiv J \neq 0$  is linked to the loss of mass in the classical BD theory.

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

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

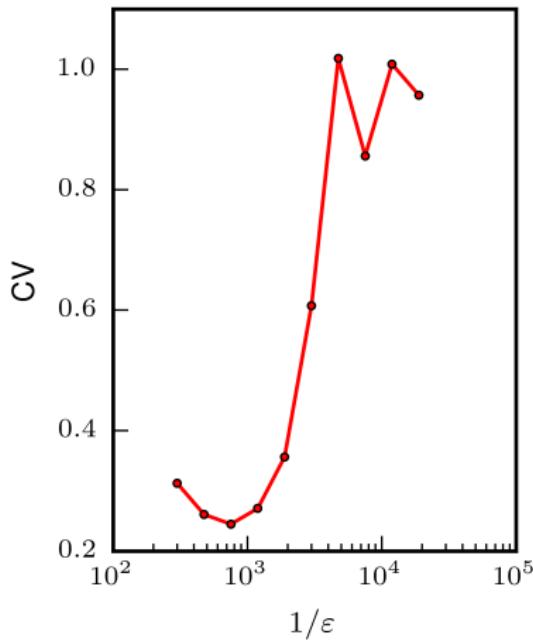
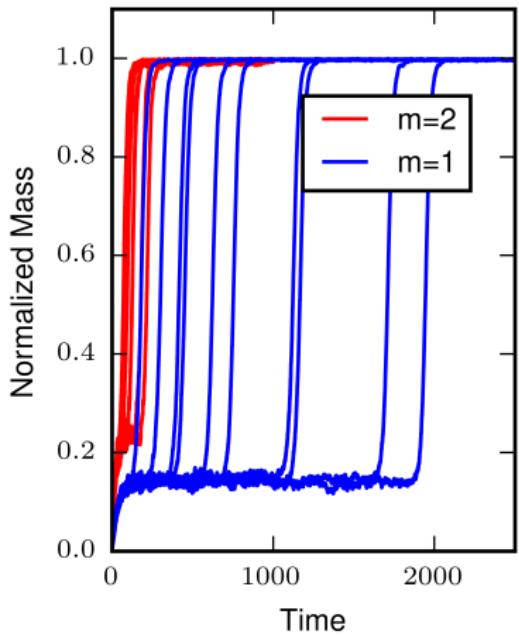


▶ case A

▶ case B

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

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



# Outline

Amyloid diseases and Becker-Döring model

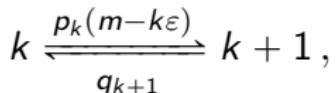
Numerical results

Coarse-graining

Large deviations

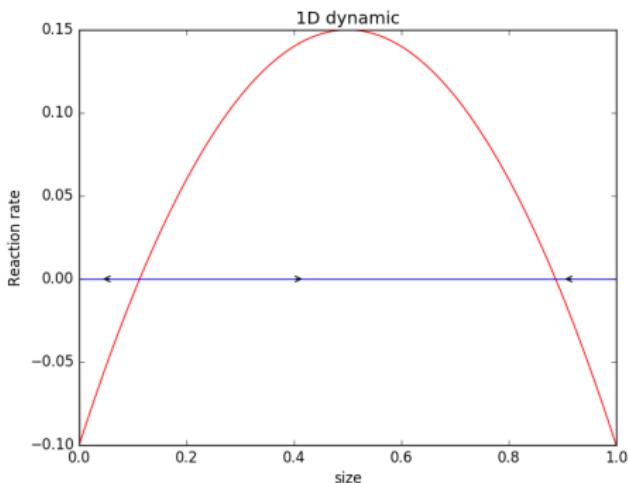
# Quantifying the large deviation in toy model

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



which converges (with time rescaling) to

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



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

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

which converges (with time rescaling) to

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- ▶ To leading order the stationary prob. density is

$$u^*(x) = C \frac{e^{-\frac{1}{\varepsilon} \int_x^\infty \log\left(\frac{q(y)}{p(y)(m-y)}\right) dy}}{\sqrt{p(x)(m-x)q(x)}}.$$

- ▶ MFPT is explicit and is exponentially large in  $\varepsilon$
- ▶ The “rate” is exponentially small

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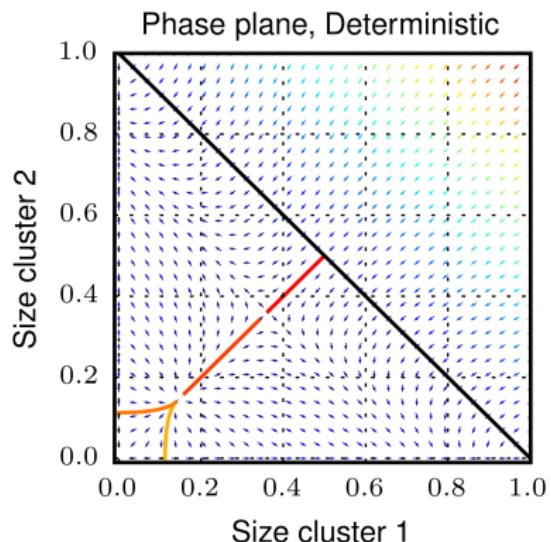
**Can we perform similar calculations with  $n$  clusters ?**

$$(k_0, k_1) \xrightarrow{\frac{p_{k_0}(m-(k_0+k_1)\varepsilon)}{q_{k_0+1}}} (k_0 + 1, k_1),$$

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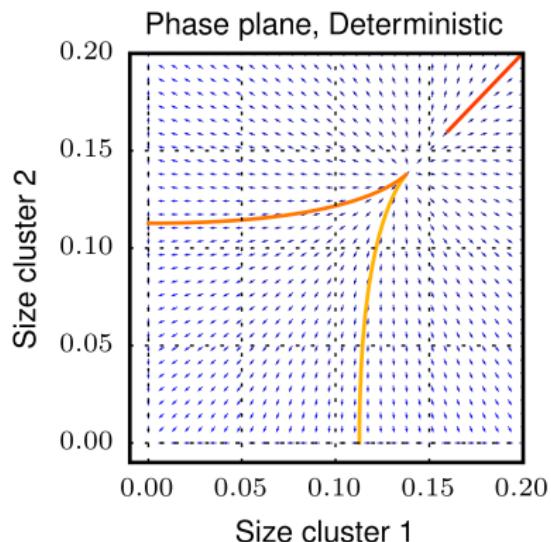
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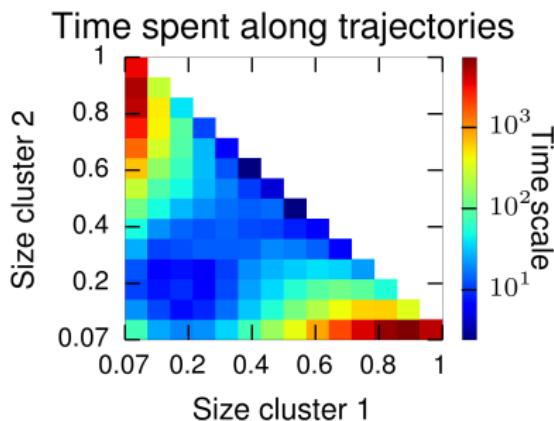
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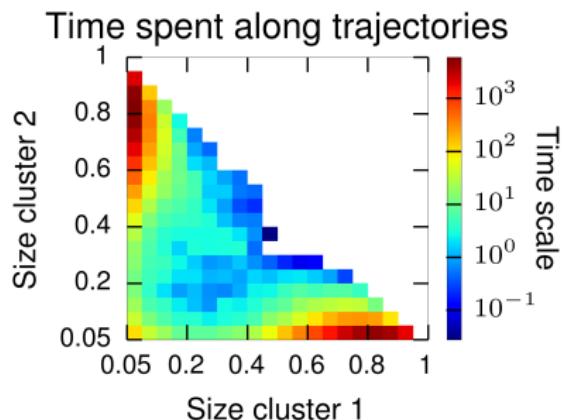
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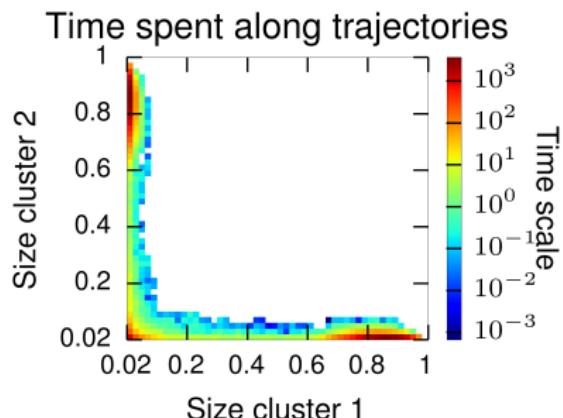
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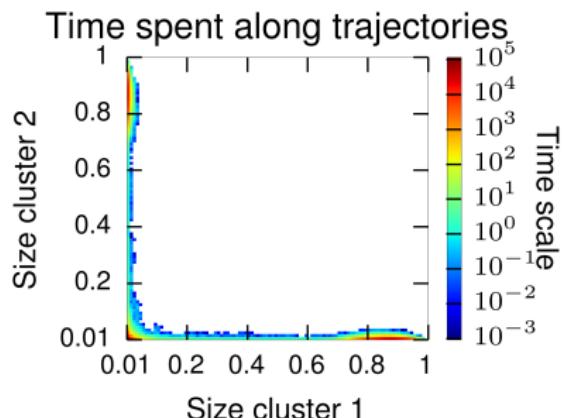
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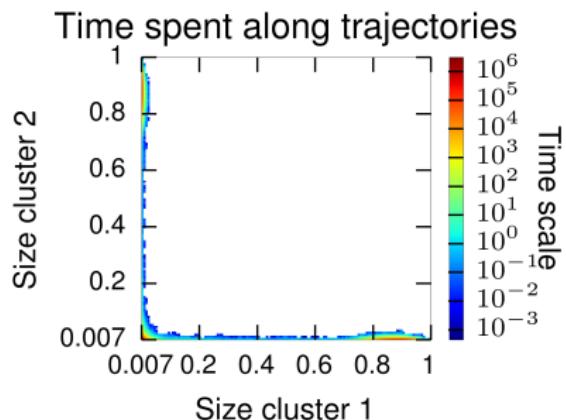
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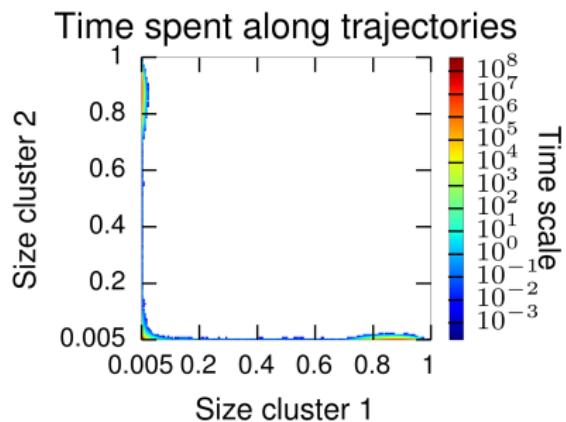
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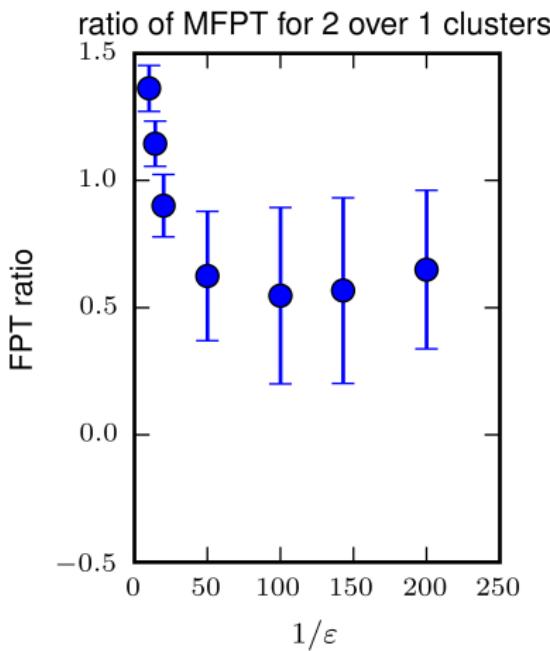
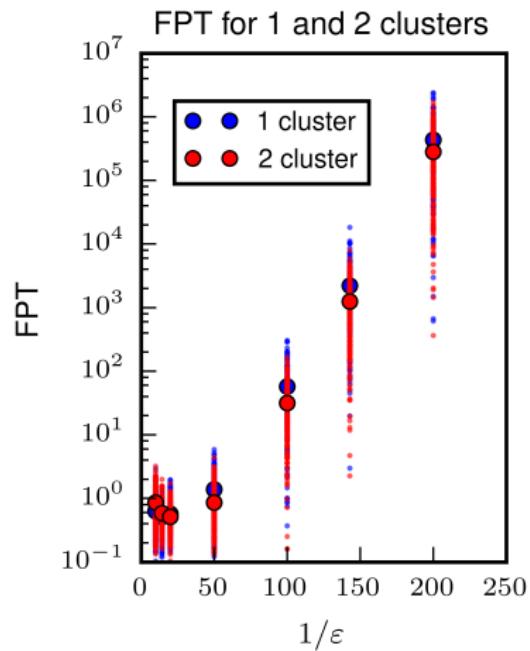
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Next :

- ▶ **Proving Large Deviation Principle for the full (S)BD**
- ▶ **Quantifying the MFPT**
- ▶ **Data fitting in spontaneous polymerization experiment**

Thanks for your attention !