# 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

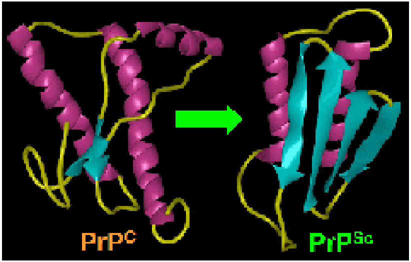
Numerical results

Coarse-graining

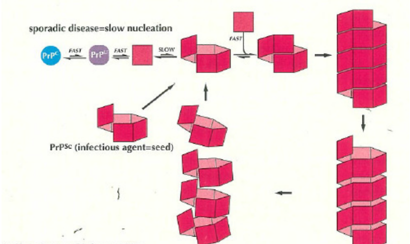
Large deviations

# Protein accumulation in amyloid by nucleation-polymerization

## Misfolding



## Prusiner model for prion



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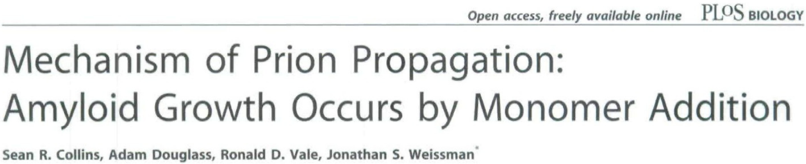

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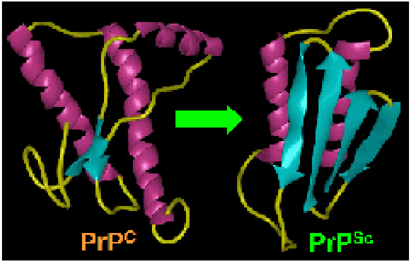
# Mechanism of Prion Propagation: Amyloid Growth Occurs by Monomer Addition

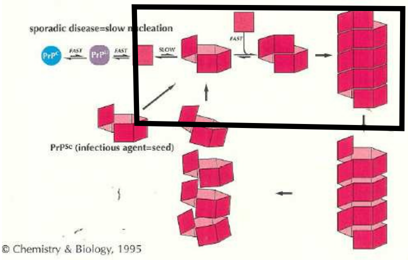
**Sean R. Collins, Adam Douglass, Ronald D. Vale, Jonathan S. Weissman***

# Protein accumulation in amyloid by nucleation-polymerization

## Misfolding



## Prusiner model for prion



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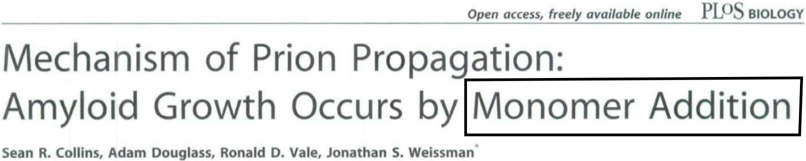

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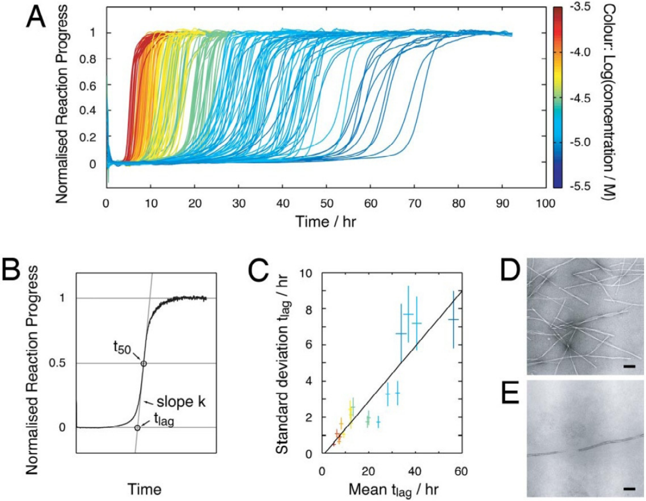
Mechanism of Prion Propagation: Amyloid Growth Occurs by Monomer Addition

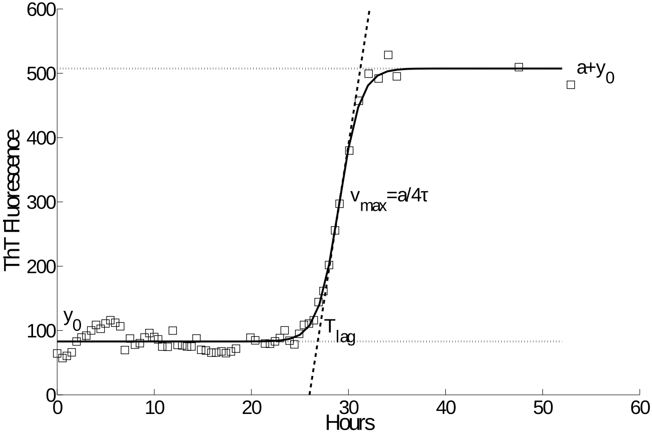
Sean R. Collins, Adam Douglass, Ronald D. Vale, Jonathan S. Weissman*

# Times series of *in-vitro* spontaneous polymerization



Xue et al. PNAS (2008)
Eugene el al. hal-01205549 (2015)

# Quantification of experiment



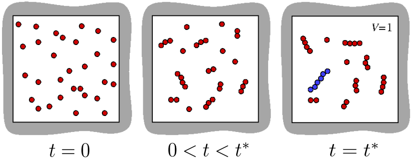
ThT fluorescence ≈ Number of polymerized protein

[Courtesy of J.P. Liautard]

# Becker-Döring model

## Reversible one-step agregation

$$C_i + C_1 \underset{q_{i+1}}{\overset{p_i}{\rightleftharpoons}} C_{i+1} \qquad (1)$$



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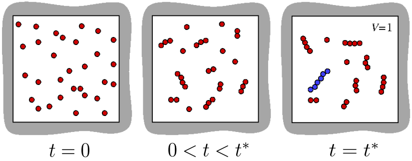
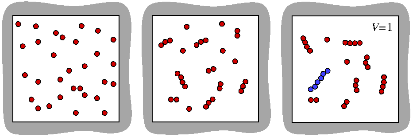


- Purely dynamic model (law of mass-action) : no space, no polymer structure.

# Becker-Döring model

## Reversible one-step agregation

$$C_i + C_1 \xrightleftharpoons[q_{i+1}]{p_i} C_{i+1} \qquad (1)$$



$t = 0$ $\quad 0 < t < t^*$ $\quad t = t^*$

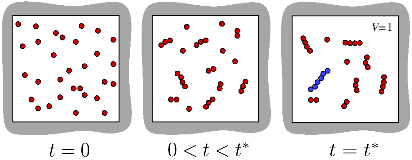
- Indirect interaction between polymer $C_i$, $i \geqslant 2$ via the available number of monomers $C_1$.

$$C_1(t) + \sum_{i \geqslant 2} iC_i(t) = \text{constant} := M \qquad (2)$$

# Becker-Döring model

## Reversible one-step agregation

$$C_i + C_1 \underset{q_{i+1}}{\overset{p_i}{\rightleftharpoons}} C_{i+1} \qquad (1)$$

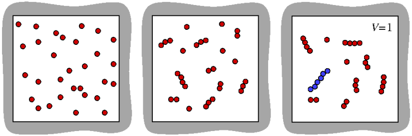


- In spontaneous polymerization experiment,
  - Initial condition given by $C_i(t = 0) = 0 \ \forall i \geqslant 2$.
  - Measured variable : $\sum_{i \geqslant N} iC_i$ ($N$ is an unknown parameter)

# Becker-Döring model

## Reversible one-step agregation

$$C_i + C_1 \underset{q_{i+1}}{\overset{p_i}{\rightleftharpoons}} C_{i+1} \qquad (1)$$



$t = 0$ $0 < t < t^*$ $t = t^*$

- The (observed) nucleation time is given by

$$\inf\{t \geqslant 0 : \sum_{i \geqslant N} iC_i(t) \geqslant \rho M \mid C_i(t=0) = M\delta_{i=1}\}\,.$$

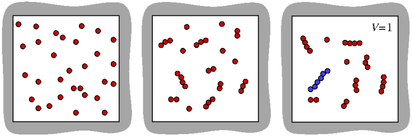
Another quantity of interest is the following **First Passage Time**,

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

# Becker-Döring model

## Reversible one-step agregation

$$C_i + C_1 \xrightleftharpoons[q_{i+1}]{p_i} C_{i+1}$$



$t = 0$ $0 < t < t^*$ $t = t^*$

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

total mass : $M$ ; nucleus size : $N$

aggregation rates : $p_i$ , $i \geqslant 1$ fragmentation rates : $q_i$ , $i \geqslant 2$

- 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

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

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

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

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

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

# Deterministic BD model and Classical Nucleation Theory

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

$$\begin{cases} \dfrac{dc_i}{dt} &= J_{i-1} - J_i \,, i \geqslant 2 \,, \\ J_i &= p_i c_1 c_i - q_{i+1} c_{i+1} \,, i \geqslant 1 \,, \\ \dfrac{dc_1}{dt} &= -J_1 - \sum_{i=1}^{\infty} J_i \,. \end{cases}$$

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

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

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

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

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
- $\lim_{t\to\infty} c_i(t) - c_i(0)$ 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

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

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

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

while for "$q_i \to \infty$" (pre-equilibrium nucleation),

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

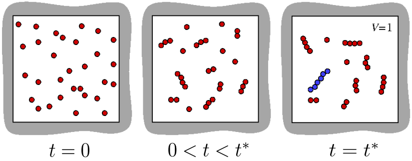
# Stochastic Becker-Döring model

## Reversible one-step agregation

$$C_i + C_1 \underset{q_{i+1}}{\overset{p_i}{\rightleftharpoons}} C_{i+1}$$

We define a continuous time Markov Chain on

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



Transitions are given by

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

# Stochastic Becker-Döring model

## Reversible one-step agregation

$$C_i + C_1 \underset{q_{i+1}}{\overset{p_i}{\rightleftharpoons}} C_{i+1}$$

We define a continuous time Markov Chain on

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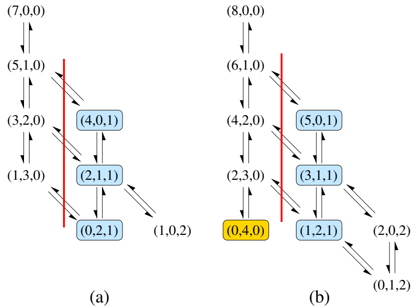


We are interested in

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

# Outline

Amyloid diseases and Becker-Döring model

Numerical results

Coarse-graining

Large deviations

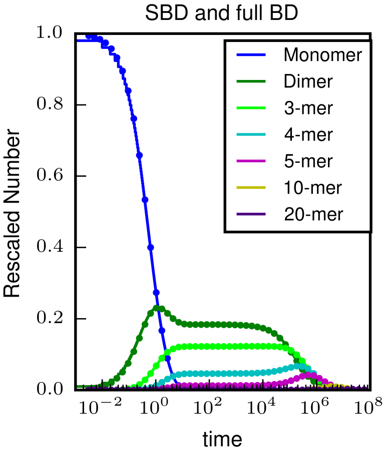
- Law of large numbers as $M \to \infty$ [Jeon. CMP (1998)]
- Any macroscopic quantity like.

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

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

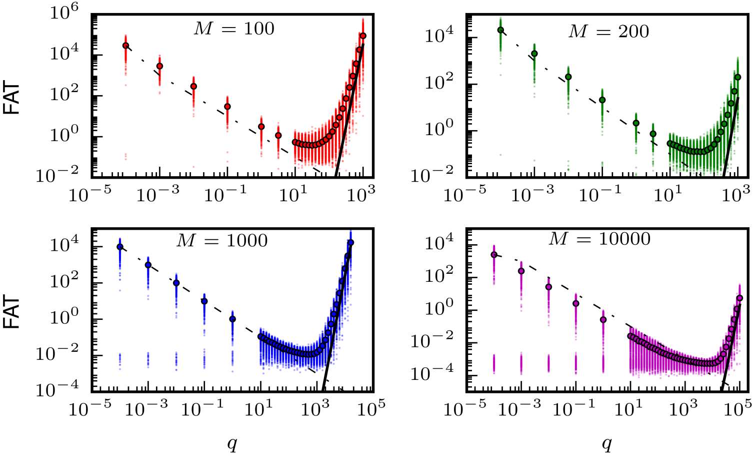
- This may not be true for microscopic quantity, for instance.

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



[Y., D'Orsogna, Chou JCP (2012)]
[Y., Bernard, Hingant, Pujo-Menjouet JCP (2016)]

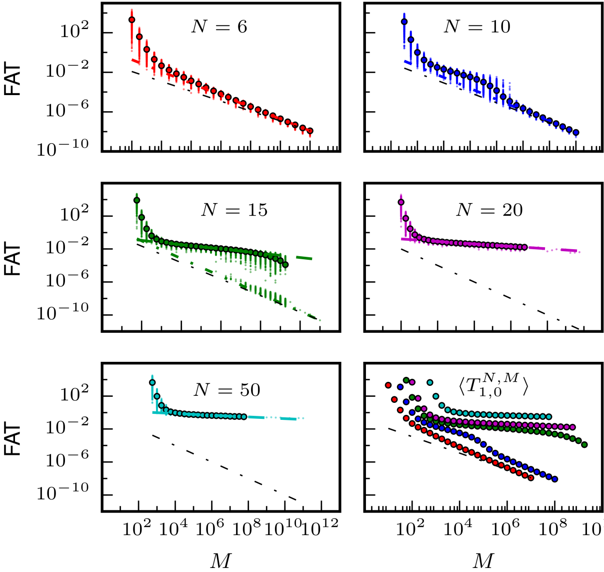
- Non-monotonous w.r.t reaction rate
- Bimodal for 'small' fragmentation rate



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

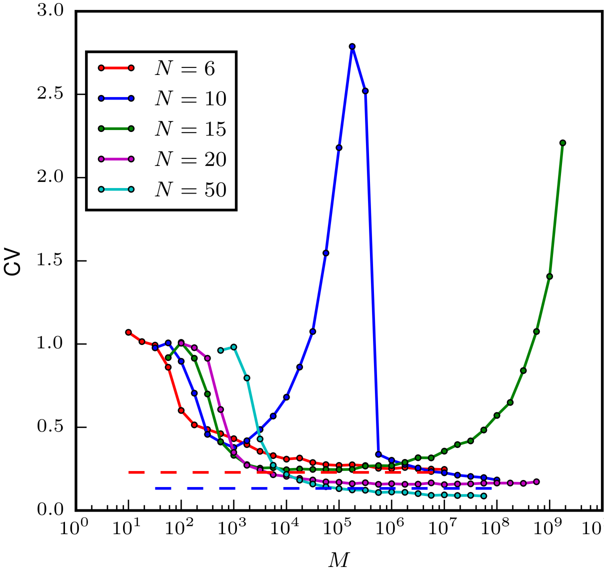
- 'Weak' dependency w.r.t. total monomer number $M$

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



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

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



# Outline

- Amyloid diseases and Becker-Döring model
- Numerical results
- Coarse-graining
- Large deviations

# When $N \to \infty$?

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

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

With $f^\varepsilon(t,x) = \sum_{i\geqslant 2} c_i^\varepsilon(t)\mathbf{1}_{[(i-1/2)\varepsilon,(i+1/2)\varepsilon)}(x)$,
Scaling idea : **excess of monomer**

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

Compensated aggregation / fragmentation

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

and **slow first step** :

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

# When $N \to \infty$?

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

$$\left\{\begin{array}{rcl} \dfrac{dc_i^\varepsilon}{dt} & = & \dfrac{1}{\varepsilon}\left[J_{i-1}^\varepsilon - J_i^\varepsilon\right], \quad i \geqslant 2, \\ m^\varepsilon & = & c_1^\varepsilon(t) + \varepsilon^2 \displaystyle\sum_{i \geqslant 2} i c_i^\varepsilon(t). \end{array}\right.$$

With $f^\varepsilon(t,x) = \sum_{i \geqslant 2} c_i^\varepsilon(t) \mathbf{1}_{[(i-1/2)\varepsilon,(i+1/2)\varepsilon)}(x)$,
From the polymer point of view, we have accelerated fluxes, all of the same order :

$$\xrightleftharpoons[\frac{1}{\varepsilon} q_2^\varepsilon C_2^\varepsilon]{\frac{1}{\varepsilon} p_1^\varepsilon C_1^\varepsilon C_1^\varepsilon} C_2^\varepsilon$$

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

# When $N \to \infty$?

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

$$\left\{\begin{array}{rcl} \dfrac{dc_i^\varepsilon}{dt} & = & \dfrac{1}{\varepsilon}\left[J_{i-1}^\varepsilon - J_i^\varepsilon\right] , \quad i \geqslant 2 , \\ m^\varepsilon & = & c_1^\varepsilon(t) + \varepsilon^2 \displaystyle\sum_{i\geqslant 2} i c_i^\varepsilon(t) . \end{array}\right.$$

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

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

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

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

$$+\int_0^{+\infty}\left[p^\varepsilon(x)c_1^\varepsilon(t)f^\varepsilon(t,x)\Delta_\varepsilon\varphi(x) - q^\varepsilon(x)f^\varepsilon(t,x)\Delta_{-\varepsilon}\varphi(x)\right]\,dx\,,$$

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

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

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

*and* $c_1(t) + \int xf(t,x) = m$*, for all* $\varphi \in C_c(0,\infty)$*.*
*This is the weak form of*

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

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

$$+\int_0^{+\infty}\left[p^\varepsilon(x)c_1^\varepsilon(t)f^\varepsilon(t,x)\Delta_\varepsilon\varphi(x) - q^\varepsilon(x)f^\varepsilon(t,x)\Delta_{-\varepsilon}\varphi(x)\right]dx\,,$$

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

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

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

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

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

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

$$+\int_0^{+\infty}\left[p^\varepsilon(x)c_1^\varepsilon(t)f^\varepsilon(t,x)\Delta_\varepsilon\varphi(x) - q^\varepsilon(x)f^\varepsilon(t,x)\Delta_{-\varepsilon}\varphi(x)\right]dx\,,$$

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

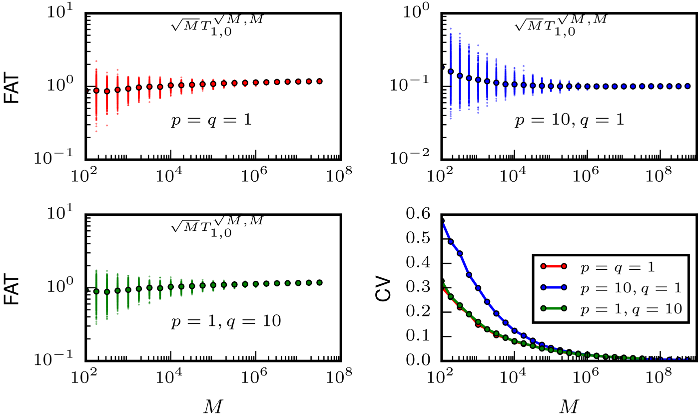
*$N(t)$ is an explicit function of $c_1(t)$, and is given by a quasi steady-state approximation of $c_2^\varepsilon = f^\varepsilon(t,2\varepsilon)$, given by the solution of*

$$\left\{\begin{array}{rcl} 0 & = & \left[J_{i-1}(c_1) - J_i(c_1)\right]\,, \quad i \geqslant 2\,, \\ c_1(t) & = & c_1\,. \end{array}\right.$$

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

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

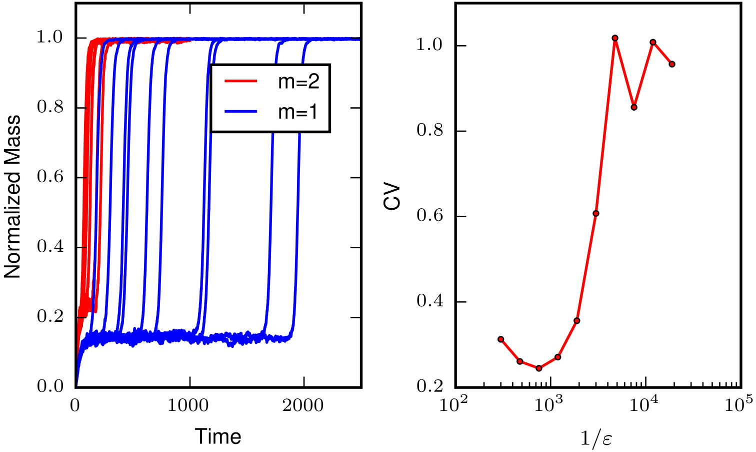
- First case $(p(0)m > q(0))$ : Convergence towards a deterministic value.



- case A
- case B

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

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



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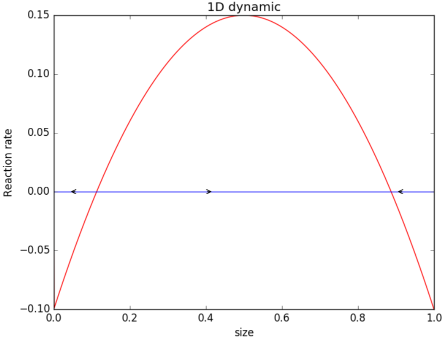
# Quantifying the large deviation in toy model

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

$$k \underset{q_{k+1}}{\overset{p_k(m-k\varepsilon)}{\rightleftharpoons}} k+1\,,$$

which converges (with time rescaling) to

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



# 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 :

$$k \underset{q_{k+1}}{\overset{p_k(m-k\varepsilon)}{\rightleftharpoons}} k+1\,,$$

which converges (with time rescaling) to

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

- To leading order the stationary prob. density is

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

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

# Quantifying the large deviation in toy model

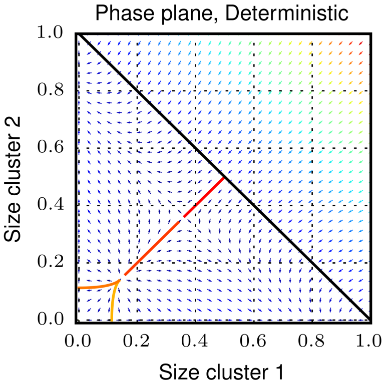
**Can we perform similar calculations with $n$ clusters ?**

$$(k_0, k_1) \underset{q_{k_0+1}}{\overset{p_{k_0}(m-(k_0+k_1)\varepsilon)}{\rightleftharpoons}} (k_0+1, k_1)\,,$$

$$(k_0, k_1) \underset{q_{k_1+1}}{\overset{p_{k_1}(m-(k_0+k_1)\varepsilon)}{\rightleftharpoons}} (k_0, k_1+1)\,,$$

which converges (with time rescaling) to

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



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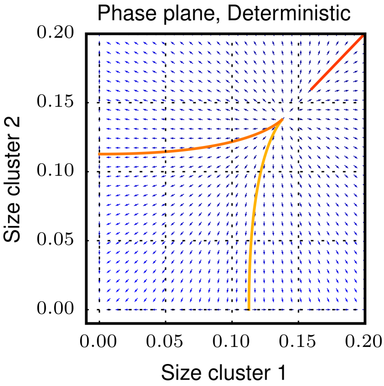
$$\begin{aligned} \frac{dx}{dt} &= p(x)(m-x-y)-q(x) \\ \frac{dy}{dt} &= p(y)(m-x-y)-q(y) \end{aligned}$$



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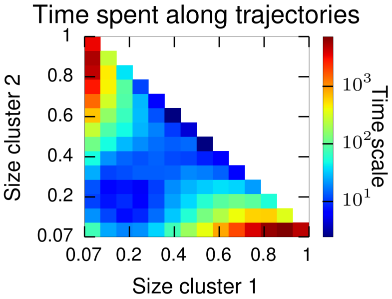

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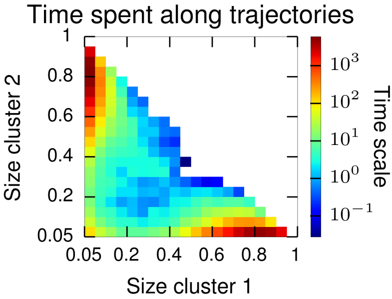

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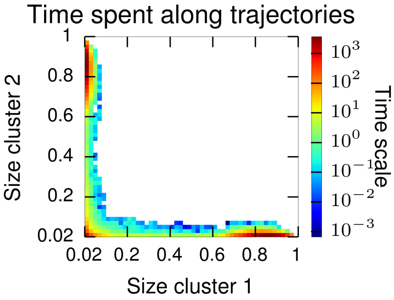

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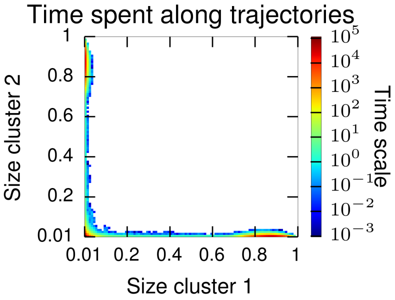

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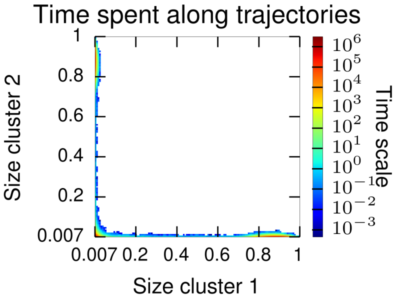

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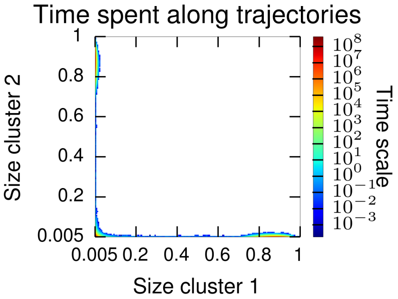

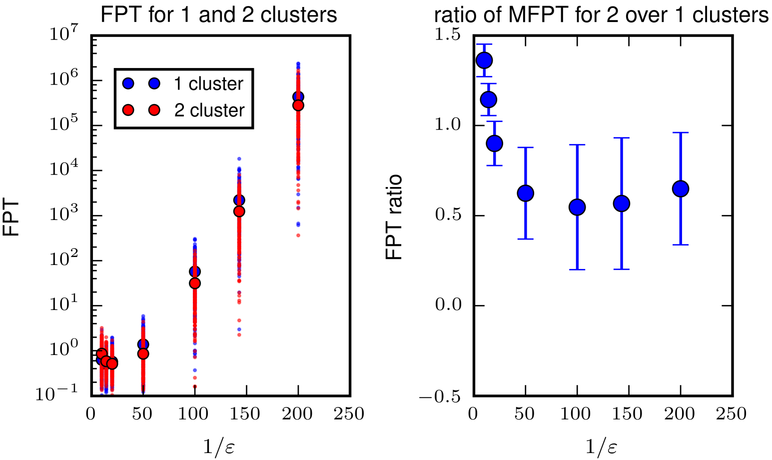
FPT for 1 and 2 clusters
FPT
$10^{-1}$
$10^{0}$
$10^{1}$
$10^{2}$
$10^{3}$
$10^{4}$
$10^{5}$
$10^{6}$
$10^{7}$
● ● 1 cluster
● ● 2 cluster
0
50
100
150
200
250
$1/\varepsilon$
ratio of MFPT for 2 over 1 clusters
FPT ratio
$-0.5$
0.0
0.5
1.0
1.5
0
50
100
150
200
250
$1/\varepsilon$

Next :

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

Thanks for your attention !