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

Romain Yvinec¹, **Samuel Bernard**^{2,3}, **Tom Chou**⁴, **Julien Deschamps**⁵, **Maria R. D'Orsogna**⁶, **Erwan Hingant**⁷ and **Laurent Pujo-Menjouet**^{2,3}

¹BIOS group INRA Tours, France.

²Institut Camille Jordan, Université Lyon 1, Villeurbanne, France.

³INRIA Team Dracula, Inria Center Grenoble Rhône-Alpes, France.

⁴Depts. of Biomathematics and Mathematics, UCLA, Los Angeles, USA.

⁵DIMA, Università degli Studi di Genova, Italy.

⁶Dept. of Mathematics, CSUN, Los Angeles, USA.

⁷Departamento de Matemática, U. Federal de Campina Grande, PB, Brasil.

Amyloid diseases and Becker-Döring model

Numerical results

Coarse-graining

Open problems (for me)

Outline

Amyloid diseases and Becker-Döring model

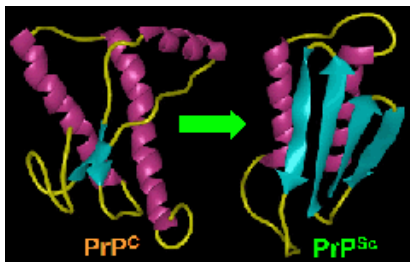
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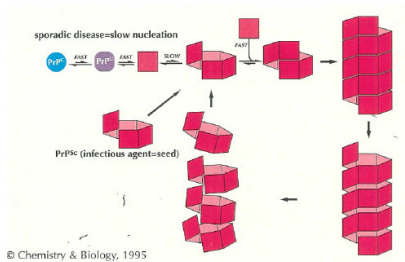
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Protein accumulation in amyloid by nucleation-polymerization

Misfolding



Prusiner model for prion



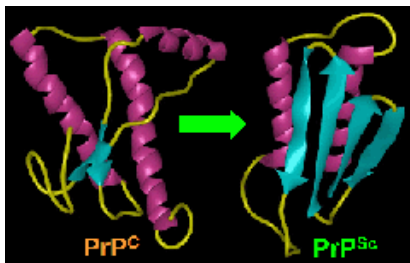
Open access, freely available online [PLOS BIOLOGY](https://doi.org/10.1371/journal.pbio.1000000)

Mechanism of Prion Propagation: Amyloid Growth Occurs by Monomer Addition

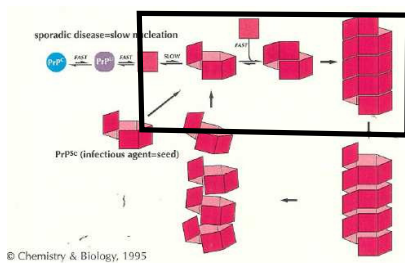
Sean R. Collins, Adam Douglass, Ronald D. Vale, Jonathan S. Weissman*

Protein accumulation in amyloid by nucleation-polymerization

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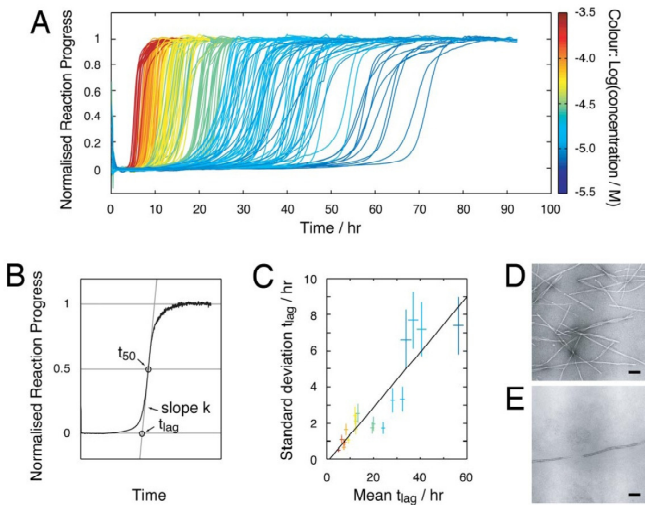


Prusiner model for prion



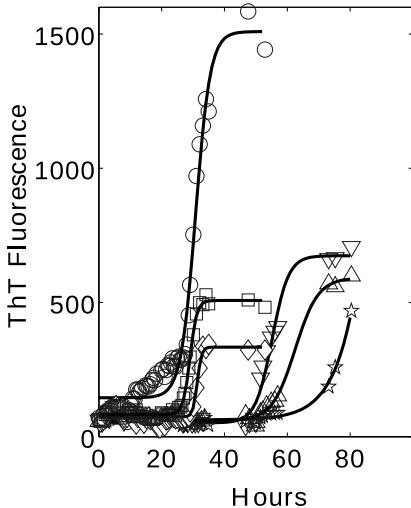
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Mechanism of Prion Propagation:
Amyloid Growth Occurs by **Monomer Addition**

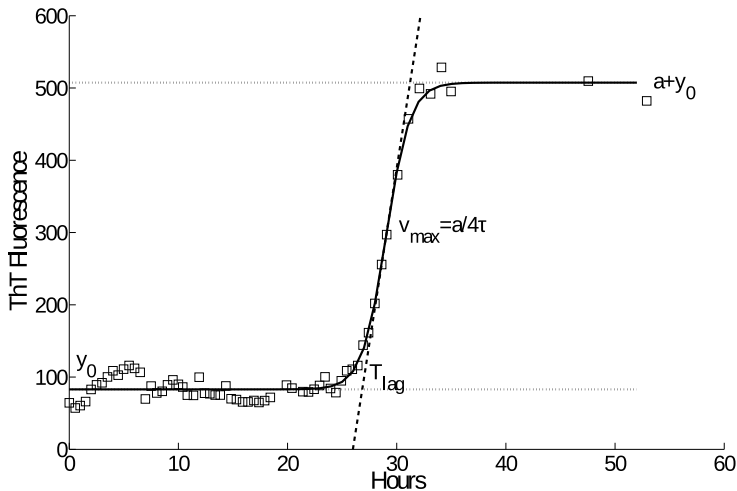
Times series of *in-vitro* spontaneous polymerization

Xue et al. PNAS (2008)

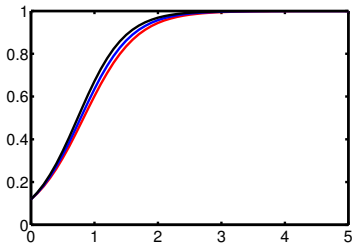
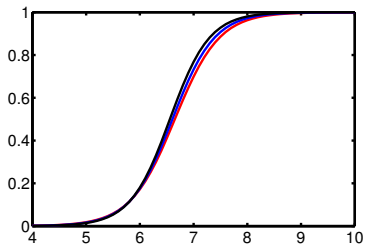
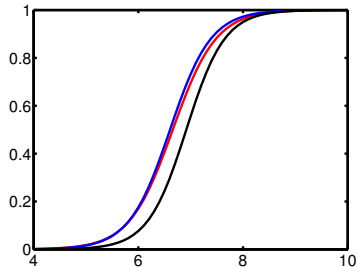
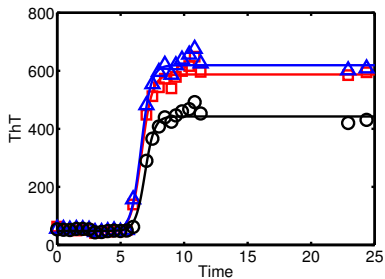
Eugene et al. hal-01205549 (2015)

Times series of *in-vitro* spontaneous polymerization

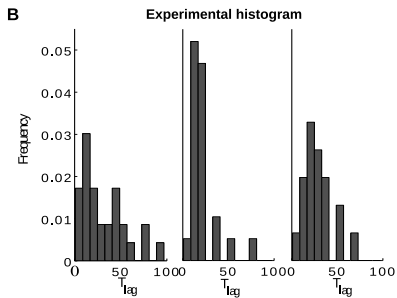
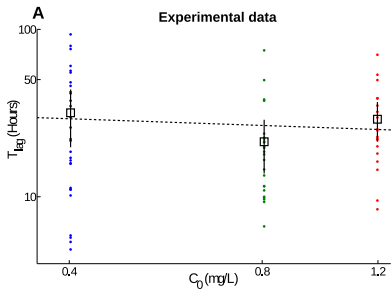
Quantification of experiment



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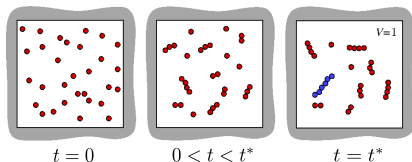
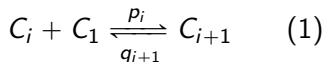


Statistics of lag time



Nucleation time in the Stochastic Becker-Döring model

Reversible one-step aggregation

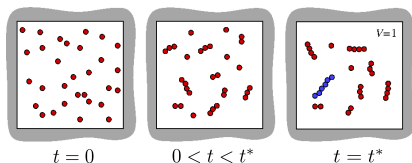
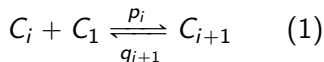


The **nucleation time** is given by the following First Passage Time,

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

Nucleation time in the Stochastic Becker-Döring model

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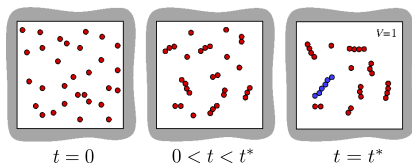
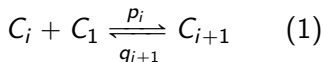
$$T^{N,M} := \inf\{t \geq 0 : C_N(t) = 1 \mid C_i(t=0) = M\delta_{i=1}\}. \quad (2)$$

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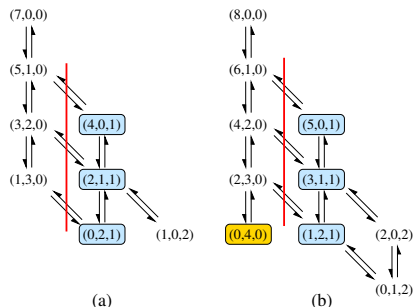
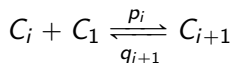
- ▶ What is the nucleation time for very large initial quantity M and nucleus size N ?

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

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

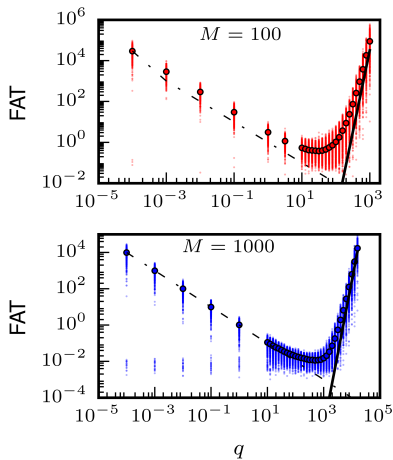
Amyloid diseases and Becker-Döring model

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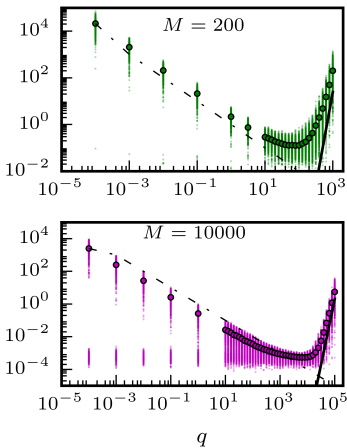
Coarse-graining

Open problems (for me)

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



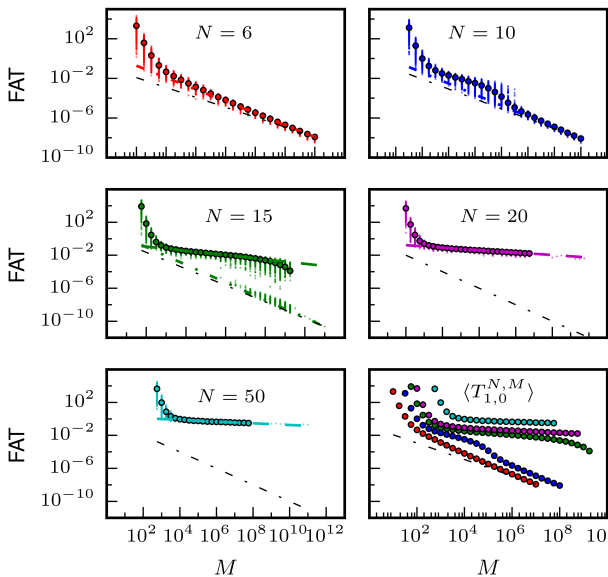
- ▶ Bimodal for 'small' fragmentation rate



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

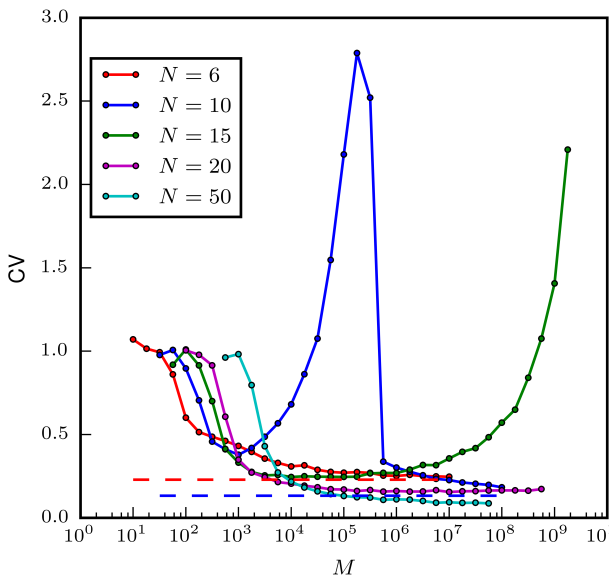
- 'Weak' dependency w.r.t. total monomer number M

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

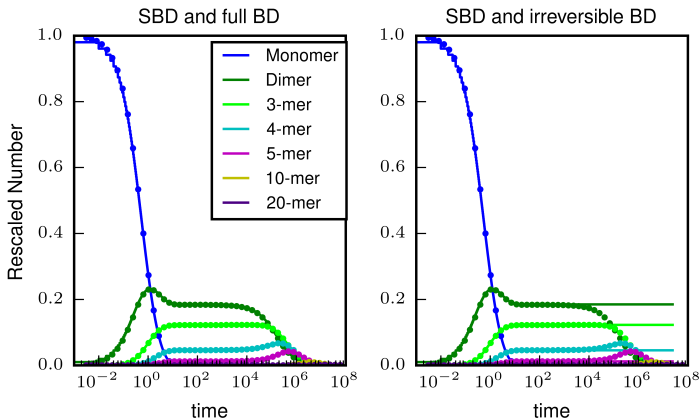


- ▶ Normalized variance non-monotonous.
- ▶ Normalized variance non zero pour $M \rightarrow \infty$.

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



- ▶ 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

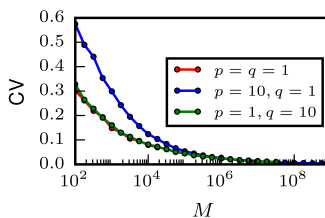
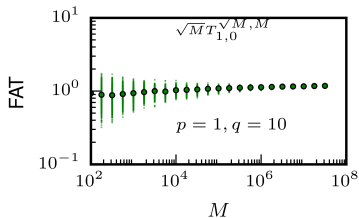
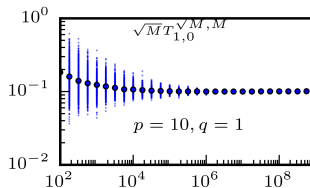
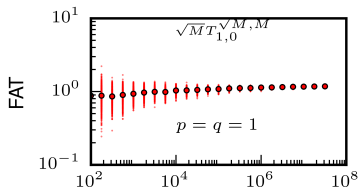
Numerical results

Coarse-graining

Open problems (for me)

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

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

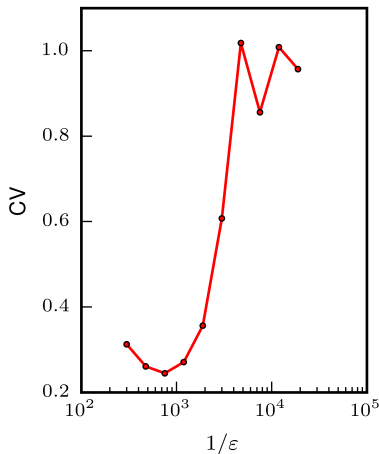
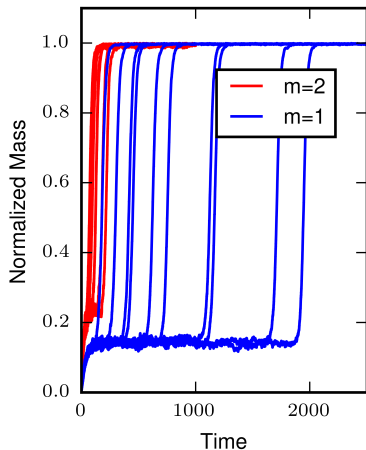


▶ case A

▶ 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?

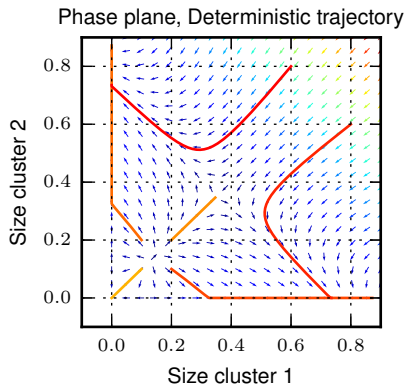
$$(k_0, k_1) \xrightleftharpoons[q_{k_0+1}]{p_{k_0}(m-(k_0+k_1)\varepsilon)} (k_0 + 1, k_1),$$

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

which converges (with time rescaling) to

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

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



Quantifying the large deviation in the SBD model

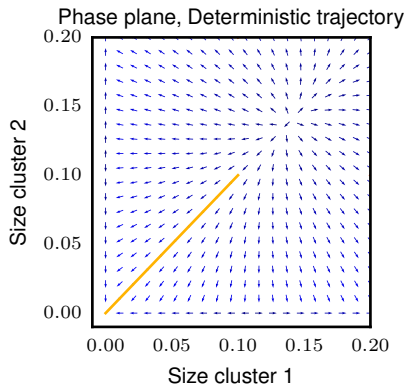
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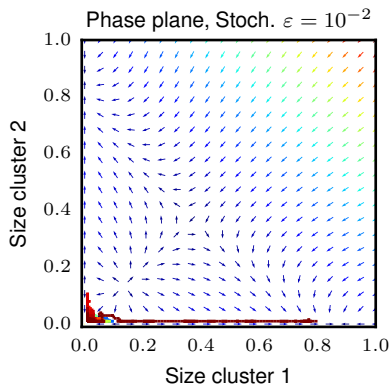
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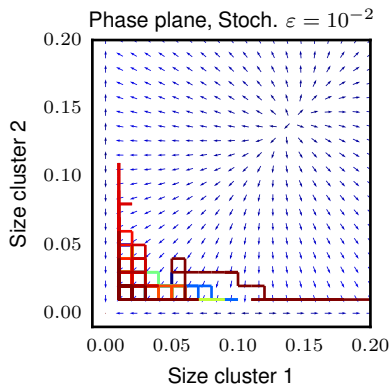
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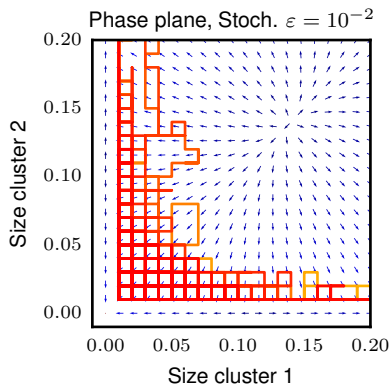
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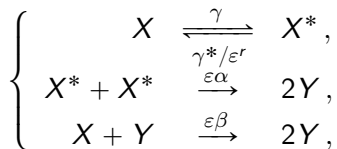
$$\frac{dx}{dt} = p(x)(m - x - y) - q(x)$$

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



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

Toy model with time-scale separation



with initial condition

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

