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# Stochastic Becker-Döring model: Large population and large time results for phase transition phenomena

Romain Yvinec

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Stochastic Becker-Döring model:  
large population and large time results for phase  
transition phenomena

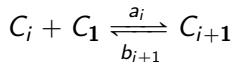
**Romain Yvinec**

BIOS team,  
Physiologie de la Reproduction et des Comportements,  
INRAE Nouzilly, France.

MUSCA team,  
INRIA Saclay-Île-de-France.

## Becker-Döring model

CRN :

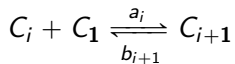
Polymerisation  
with Attachement-  
Detachment of  
single monomer

Systems of ODEs

$$\left\{ \begin{array}{l} \frac{dc_i}{dt} = J_{i-1} - J_i, i \geq 2, \\ J_i = a_i c_1 c_i - b_{i+1} c_{i+1}, i \geq 1, \\ \frac{dc_1}{dt} = -J_1 - \sum_{i=1}^{\infty} J_i, \\ \rho := \sum_{i \geq 1} i c_i(0) = \sum_{i \geq 1} i c_i(t). \end{array} \right.$$

## Becker-Döring model

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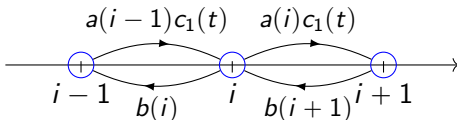
Polymerisation  
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CTMC

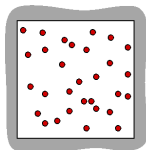
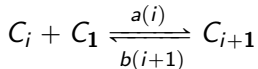
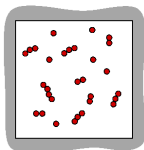
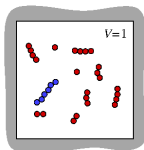
$$\left\{ \begin{array}{ll} \text{Transition} & \text{Intensity} \\ C \rightarrow C + \Delta_i, & a_i C_1 C_i \\ C \rightarrow C - \Delta_i, & b_{i+1} C_{i+1} \end{array} \right.$$

$$\Delta_i = e_{i+1} - e_i - e_1,$$

$$n := \sum_{i=1}^{\infty} i C_i(0) = \sum_{i=1}^{\infty} i C_i(t)$$

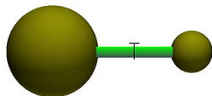
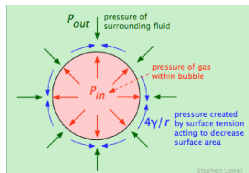
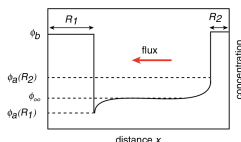


## Becker-Döring model

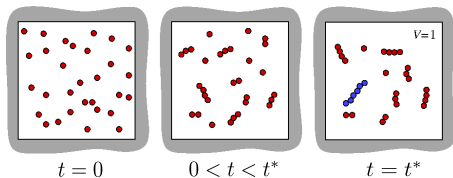
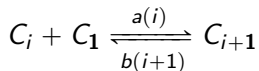
Nucleation and coarsening  
model $t = 0$  $0 < t < t^*$  $t = t^*$ 

Typical (in physics literature) coefficients are :

$$a(i) = i^\alpha, \quad b(i) = a(i) \left( z_s + \frac{q}{i^\gamma} \right), \quad \alpha, \gamma \in (0, 1).$$

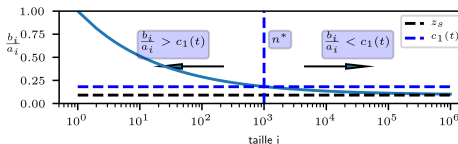
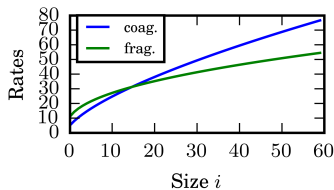


## Becker-Döring model

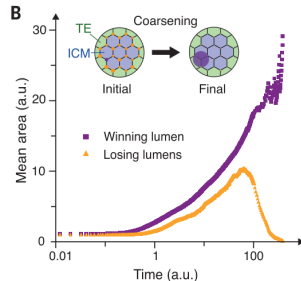
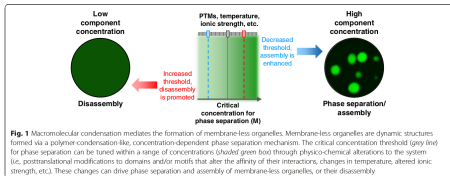
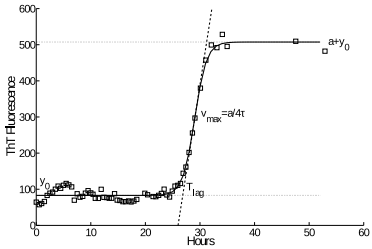
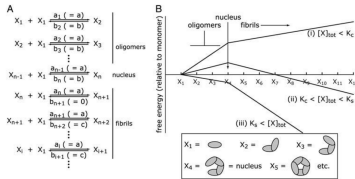
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# Becker-Döring : nucleation, phase transition and coarsening



## General issues

- ▶ Does the nucleation process take place (phase transition) ?
- ▶ How long and how variable is the nucleation period ?
- ▶ How fast the second phase grow after nucleation ?



# Mathematical issues

- ▶ Well-posedness of the model ("a must be balanced by b")
- ▶ Long-time behavior (Equilibrium, Convergence speed...)
- ▶ Nucleation and Phase transition (metastability...)

## Equilibrium of the BD model

$$\left\{ \begin{array}{l} \frac{dc_i}{dt} = J_{i-1} - J_i, i \geq 2, \\ J_i = a_i c_1 c_i - b_{i+1} c_{i+1}, i \geq 1, \\ \frac{dc_1}{dt} = -J_1 - \sum_{i=1}^{\infty} J_i. \end{array} \right. \quad \begin{array}{l} \text{Ball, Carr, Penrose, Comm.} \\ \text{Math. Phys 104(4), 1986} \end{array}$$

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

$$c_i = Q_i z^i, \quad Q_i = \frac{a_1 a_2 \cdots a_{i-1}}{b_2 b_3 \cdots b_i}, \quad i \geq 1$$

for some  $z$ . Looking at the *mass* at equilibrium,

$$F(z) := \sum_{i \geq 1} i Q_i z^i$$

It is natural to look for a solution of

$$F(z) \stackrel{?}{=} \rho := \sum_{i \geq 1} i c_i(0) = \sum_{i \geq 1} i c_i(t)$$

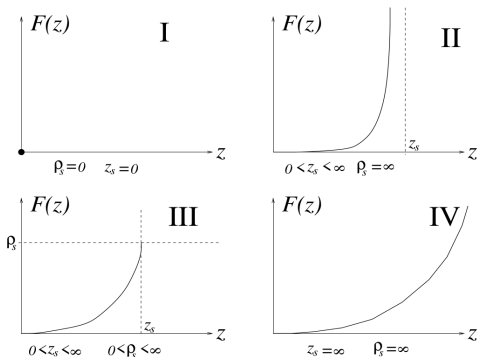
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Ball, Carr, Penrose, Comm.  
Math. Phys 104(4), 1986

$$Q_i = \frac{a_1 a_2 \cdots a_{i-1}}{b_2 b_3 \cdots b_i}$$

$$F(z) = \sum_{i \geq 1} i Q_i z^i \stackrel{?}{=} \rho$$



## Equilibrium of the BD model

$$\left\{ \begin{array}{l} \frac{dc_i}{dt} = J_{i-1} - J_i, i \geq 2, \\ J_i = a_i c_1 c_i - b_{i+1} c_{i+1}, i \geq 1, \\ \frac{dc_1}{dt} = -J_1 - \sum_{i=1}^{\infty} J_i. \end{array} \right. \quad \begin{array}{l} \text{Ball, Carr, Penrose, Comm.} \\ \text{Math. Phys 104(4), 1986} \end{array}$$

If the serie  $F(z) = \sum_{i \geq 1} i Q_i z^i$  has a finite radius of convergence  $z_s$  and if

$$\sup\{F(z), z < z_s\} =: \rho_s < \infty,$$

then there is a critical mass such that there is **no equilibrium** with mass  $\rho > \rho_s$ .

## Equilibrium of the BD model

$$\left\{ \begin{array}{l} \frac{dc_i}{dt} = J_{i-1} - J_i, i \geq 2, \\ J_i = a_i c_1 c_i - b_{i+1} c_{i+1}, i \geq 1, \\ \frac{dc_1}{dt} = -J_1 - \sum_{i=1}^{\infty} J_i. \end{array} \right. \quad \begin{array}{l} \text{Ball, Carr, Penrose, Comm.} \\ \text{Math. Phys 104(4), 1986} \end{array}$$

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

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

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

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

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## Remark

There is a Lyapounov function (or relative entropy), given by

$$H_z(c) = \sum_{i \geq 1} \left\{ c_i \left( \ln \left( \frac{c_i}{Q_i z^i} \right) - 1 \right) + Q_i z^i \right\}.$$

## SBD model

## SDE

$$\left\{ \begin{array}{l} C_1(t) = C_1^{\text{in}} - 2J_1(t) - \sum_{i \geq 2} J_i(t), \\ C_i(t) = C_i^{\text{in}} + J_{i-1}(t) - J_i(t), \\ J_i(t) = Y_i^+ \left( \int_0^t a_i C_1(s) C_i(s) ds \right) \\ \quad - Y_{i+1}^- \left( \int_0^t b_{i+1} C_{i+1}(s) ds \right) \end{array} \right.$$

## CTMC

$$X_n := \left\{ C = (C_i)_{i \geq 1} \in \mathbb{N}^{\mathbb{N}} : \sum_{i=1}^n i C_i = n \right\}.$$

$$\left\{ \begin{array}{l} q(C, R_i^+ C) = a_i C_1 (C_i - \delta_{1,i}), \\ q(C, R_i^- C) = b_i C_i, \end{array} \right.$$

$$R_i^+ C = C - e_1 - e_i + e_{i+1}$$

$$R_i^- C = C + e_1 + e_{i-1} - e_i$$

## Equilibrium of the SBD model

SDE

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Equilibrium, for any  $(a_i), (b_i), n$  :

$$\Pi(C) = B_{n,z} \prod_{i=1}^n \frac{(Q_i z^i)^{C_i}}{C_i!},$$



# Equilibrium of the SBD model

## SDE

$$\begin{cases} C_1(t) &= C_1^{\text{in}} - 2J_1(t) - \sum_{i \geq 2} J_i(t), \\ C_i(t) &= C_i^{\text{in}} + J_{i-1}(t) - J_i(t), \\ J_i(t) &= Y_i^+ \left( \int_0^t a_i C_1(s) C_i(s) ds \right) \\ &\quad - Y_{i+1}^- \left( \int_0^t b_{i+1} C_{i+1}(s) ds \right) \end{cases}$$

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Equilibrium, for any  $(a_i), (b_i), n$  :

$$\Pi(C) = B_{n,z} \prod_{i=1}^n \frac{(Q_i z^i)^{C_i}}{C_i!},$$

Detailed balance property :

$$\Pi(C) q(C, R_i^+ C) = \Pi(R_i^+ C) q(R_i^+ C, C)$$

Rescaled SBD model,  $n \rightarrow \infty$ 

## SDE

$$\begin{cases} c_1(t) &= c_1^{\text{in}} - 2\frac{\rho}{n}J_1(t) - \sum_{i \geq 2} \frac{\rho}{n}J_i(t), \\ c_i(t) &= c_i^{\text{in}} + \frac{\rho}{n}J_{i-1}(t) - \frac{\rho}{n}J_i(t), \\ J_i(t) &= Y_i^+ \left( \int_0^t \frac{n}{\rho} a_i c_1(s) c_i(s) ds \right) \\ &\quad - Y_{i+1}^- \left( \int_0^t \frac{n}{\rho} b_{i+1} c_{i+1}(s) ds \right) \end{cases}$$

## CTMC

$$X_n^\rho := \left\{ c \in \mathbb{R}^{\mathbb{N}} : \frac{n}{\rho} c_i \in \mathbb{N}, \sum_{i=1}^n i c_i = \rho \right\}.$$

$$\begin{cases} q(c, r_i^+ c) &= \frac{n}{\rho} a_i c_1 (c_i - \delta_{1,i}), \\ q(c, r_i^- c) &= \frac{n}{\rho} b_i c_i, \end{cases}$$

$$r_i^+ c = c - \frac{\rho}{n} e_1 - \frac{\rho}{n} e_i + \frac{\rho}{n} e_{i+1}$$

$$r_i^- c = c + \frac{\rho}{n} e_1 + \frac{\rho}{n} e_{i-1} - \frac{\rho}{n} e_i$$

# Rescaled SBD model, $n \rightarrow \infty$

## SDE

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$$\begin{aligned} r_i^+ c &= c - \frac{\rho}{n} e_1 - \frac{\rho}{n} e_i + \frac{\rho}{n} e_{i+1} \\ r_i^- c &= c + \frac{\rho}{n} e_1 + \frac{\rho}{n} e_{i-1} - \frac{\rho}{n} e_i \end{aligned}$$

Large **volume** limit : convergence towards the BD model (for a wide class of "reasonable" coefficients) on finite time intervals

Scaling of the Equilibrium state,  $n \rightarrow \infty$ 

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## Theorem (Hingant, Y. (2019))

If  $\rho \leq \rho_s$ , then for  $c^n \rightarrow c$  (strongly), and  $z = F^{-1}(\rho)$

$$\lim_{n \rightarrow \infty} -\frac{\rho}{n} \ln(\Pi^n(c^n)) = H_z(c)$$

## Scaling of the Equilibrium state, $n \rightarrow \infty$

### SDE

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### Theorem (Hingant, Y. (2019))

If  $\rho > \rho_s$ , then for  $c^n \rightarrow c$  (weak-\*), and  $z_s = F^{-1}(\rho_s)$

$$\lim_{n \rightarrow \infty} -\frac{\rho}{n} \ln(\Pi^n(c^n)) = H_{z_s}(c)$$

## Scaling of the Equilibrium state, $n \rightarrow \infty$

If  $\rho \leq \rho_s$ , then for  $c^n \rightarrow c$  (strongly), and  $z = F^{-1}(\rho)$

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*Method of proof* : Same as Anderson et al. 2015 + continuity property of  $H_z(c)$ .

$$\begin{aligned} -\frac{\rho}{n} \ln \Pi^n(c) &= \sum_{i=1}^n \left\{ -c_i \ln \left( \frac{n}{\rho} Q_i z^i \right) + \frac{\rho}{n} \ln \frac{n}{\rho} c_i! + Q_i z^i \right\} + \frac{\rho}{n} \ln B_n^z \\ &= \sum_{i=1}^n \left\{ c_i \left( \ln \frac{c_i}{Q_i z^i} - 1 \right) + Q_i z^i \right\} + R_n(c) + \frac{\rho}{n} \ln B_n^z \\ &= H_z(c) - \sum_{i=n+1}^{\infty} Q_i z^i + R_n(c) + \frac{\rho}{n} \ln B_n^z \end{aligned}$$

Scaling of the Equilibrium state,  $n \rightarrow \infty$ 

If  $\rho \leq \rho_s$ , then for  $c^n \rightarrow c$  (strongly), and  $z = F^{-1}(\rho)$

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If  $\rho > \rho_s$ , then for  $c^n \rightarrow c$  (weak-\*), and  $z_s = F^{-1}(\rho_s)$

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### Remark

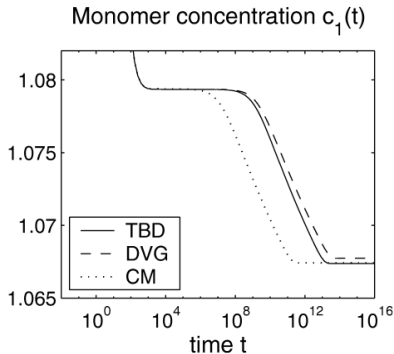
For  $\rho > \rho_s$ , we believe that a single giant cluster emerges, of size  $\approx n(1 - \rho_s/\rho)$  (see work on limiting shapes of random combinatorial structures)

## Metastability BD

$$\begin{cases} \frac{dc_i}{dt} = J_{i-1} - J_i, i \geq 2, \\ J_i = a_i c_1 c_i - b_{i+1} c_{i+1}, i \geq 1, \\ \frac{dc_1}{dt} = -J_1 - \sum_{i=1}^{\infty} J_i. \end{cases}$$

- For an  $z > z_s$ , there exists admissible configuration  $f = f_i(z)$  such that  $J_i \equiv J \neq 0$  and  $f_1(z) = z$ . We start with  $c^{\text{in}} = f$  and consider  $z \searrow z_s$ :

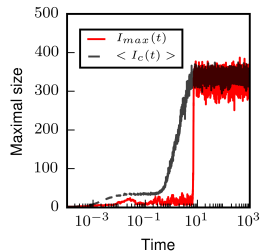
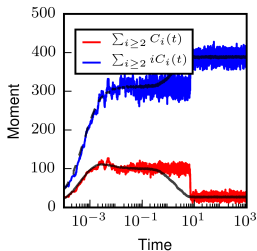
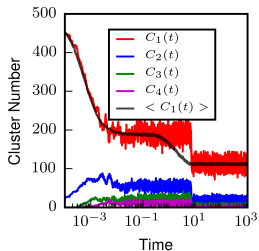
- For algebraically large time  $t$ ,  $c(t) - f$  is exponentially small
- $\lim_{t \rightarrow \infty} c(t) - f(t)$  is not exponentially small
- $\sum_{i > n^*} c_i(t) \leq \sum_{i > n^*} c_i(0) + J^* t$  with  $J^*$  exponentially small,





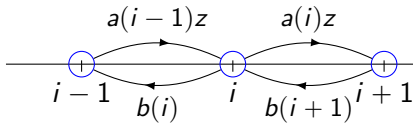
## Metastability for the SBD ?

Numerical simulation "shows" metastability with sharp transition between "metastable state" and stationary state



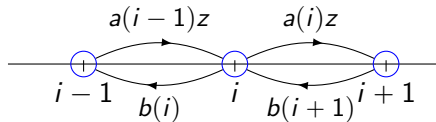
Metastability SBD for  $c_1(t) \equiv z$ 

Taking the monomer number as a **constant** allows to view the SBD process as a superposition of (independent) Birth-Death process on  $\mathbb{N}^*$ .



Metastability SBD for  $c_1(t) \equiv z$ 

Taking the monomer number as a **constant** allows to view the SBD process as a superposition of (independent) Birth-Death process on  $\mathbb{N}^*$ .

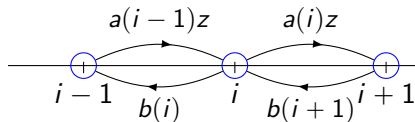


- For  $z < z_s$  : sub-critical, absorption at 1 is almost sure.
- For  $z > z_s$  : super-critical, absorption at 1 is NOT almost sure.

# Metastability SBD for $c_1(t) \equiv z$

**nucleation** : we look for the first time a cluster of size greater than  $n$  appears :

$$\tau_n := \inf \{ t \geq 0, \sum_{i \geq n} C_i(t) > 0 \}$$



Metastability SBD for  $c_1(t) \equiv z$ 

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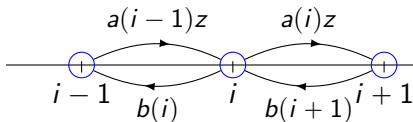
$$\tau_n := \inf\{t \geq 0, \sum_{i \geq n} C_i(t) > 0\}$$

There exists a quasi-stationary distribution,

$$\mathbf{P}_{\Pi_n^{\text{qsd}}} \{\mathbf{C}(t) \in \cdot \mid \tau_n > t\} = \Pi_n^{\text{qsd}} \quad \text{and} \quad \mathbf{P}_{\Pi_n^{\text{qsd}}} \{\tau_n > t\} = \exp(-J_n(z)t)$$

where  $\Pi_n^{\text{qsd}}$  is given by, for some (explicit)  $J_n(z), f_n(z)$

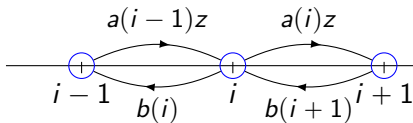
$$\Pi_n^{\text{qsd}}(\mathbf{C}) = \prod_{i=2}^n \frac{(f_i^n)^{C_i}}{C_i!} e^{-f_i^n},$$



Metastability SBD for  $c_1(t) \equiv z$ 

**nucleation** : we look for the first time a cluster of size greater than  $n$  appears :

$$\tau_n := \inf\{t \geq 0, \sum_{i \geq n} C_i(t) > 0\}$$



## Theorem (Hingant, Y. 2021)

(for a class of initial condition  $\Pi^{\text{in}}$ ), for any  $\varepsilon$ , and  $z$  close enough to  $z_s$ , there exists  $K_*, \gamma_{n^*}, J_{n^*} > 0$  such that

$$\|\mathbb{P}_{\Pi^{\text{in}}}(C(t) \in \cdot \mid \tau_{n^*} > t) - \Pi_{n^*}^{\text{qsd}}\| \leq K_* e^{(J_{n^*} - \gamma_{n^*})t},$$

where  $\mathbb{P}_{\Pi^{\text{in}}}(\tau_n > t) \geq (1 - \varepsilon)e^{-J_{n^*}t}$ ,

- ▶  $K_*, 1/\gamma_{n^*}$  are at most algebraically large
- ▶  $J_{n^*}$  is exponentially small

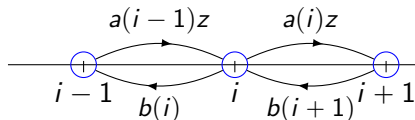
Metastability SBD for  $c_1(t) \equiv z$ 

**nucleation** : we look for the first time a cluster of size greater than  $n$  appears :

$$\tau_n := \inf\{t \geq 0, \sum_{i \geq n} C_i(t) > 0\}$$

Method of proof :

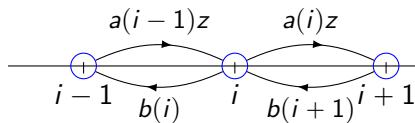
- (i) Coupling arguments exploiting independence of particles
- (ii) Known probability of absorption for birth-death process



# Metastability SBD for $c_1(t) \equiv z$

**nucleation** : we look for the first time a cluster of size greater than  $n$  appears :

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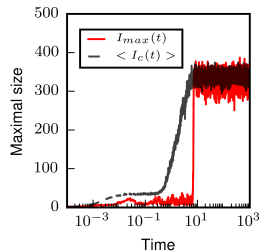
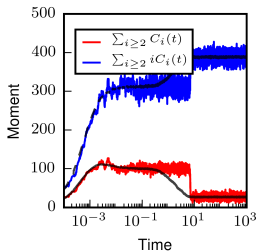
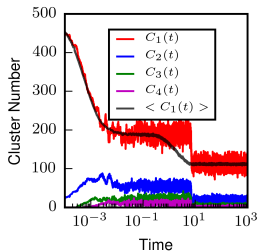
## Remark

Whether similar results holds true for the original SBD is an open question.



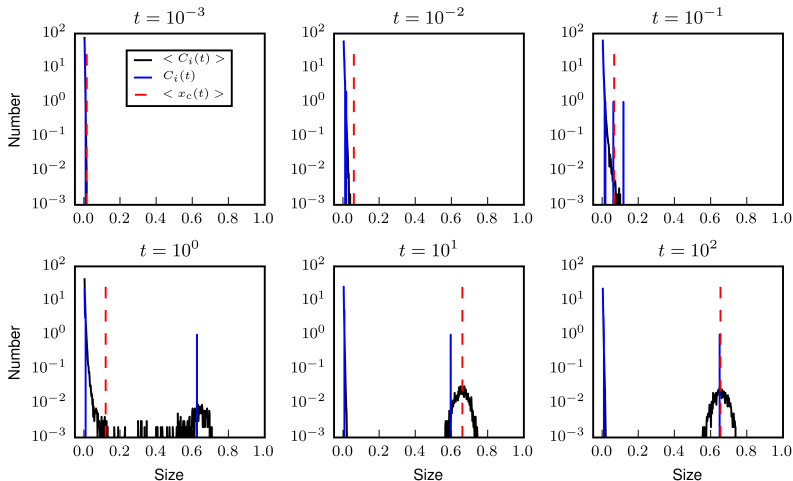
# Metastability SBD

One sample path simulation of the "nonlinear" SBD, with  $a_i = i^{2/3}$ ,  
 $b_i = a_i(z_s + q/i^{1/3})$ ,  $n = 500$ ,  $\rho = 1 > \rho_s = 0.1056$



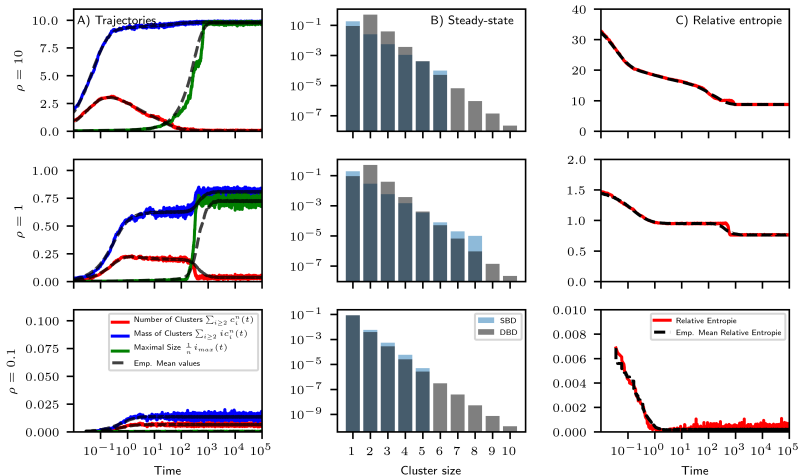
# Metastability SBD

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# Metastability SBD

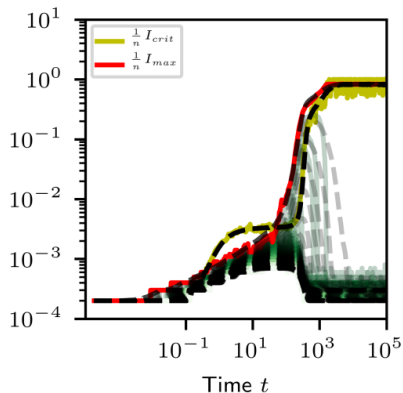
One sample path simulation of the "nonlinear" SBD, with  $a_i = i^{2/3}$ ,  $b_i = a_i(z_s + q/i^{1/3})$ ,  $n = 10000$ ,  $\rho_s = 0.1056$



## Open questions

For large super-saturated density  $\rho > \rho_s$ , many super-critical clusters form in a small time.

- ▶ How many super-critical clusters are they and how fast do they grow?
- ▶ How long does it takes for a single large cluster to take over the other ones?
- ▶ Are there situations where many large clusters persist?



Thank you for your attention !

## Becker-Döring model



Julien  
Deschamps



Erwan  
Hingant



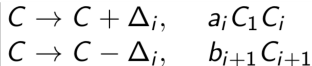
Juan  
Calvo

### Determinist

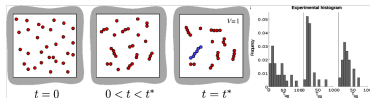
$$\frac{d}{dt} c_i = J_{i-1} - J_i, \quad i \geq 2,$$

$$J_i = a_i c_1 c_i - b_{i+1} c_{i+1}$$

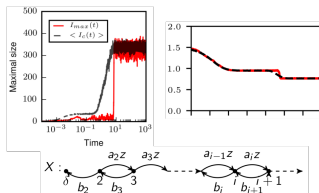
### Stochastic



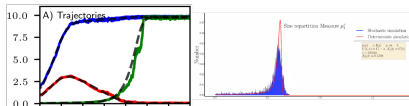
### Nucleation time



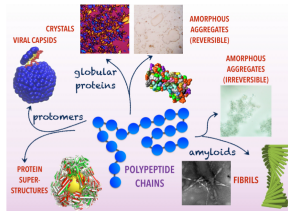
### Equilibrium / Metastability



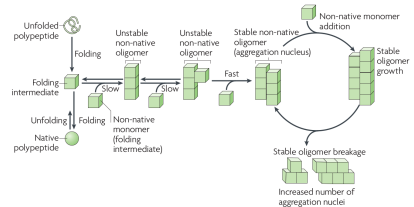
### limit theorem SBD/BD/LS



# Protein aggregation diseases : Working hypothesis



McManus et al., *The Physics of Protein Self-Assembly*,  
Curr. Opin. Colloid Interface Sci (2016)

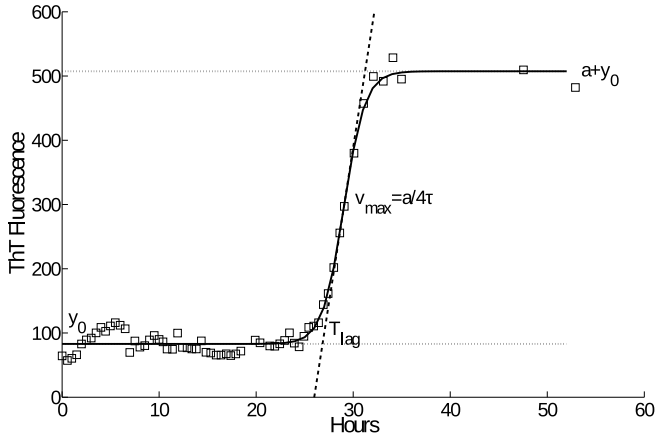


Brundin et al., *Prion-like transmission of protein aggregates in neurodegenerative diseases*, Nat. Rev. Mol. Cell Biol. (2010)

## The aggregation dynamic is linked to the disease 'onset'

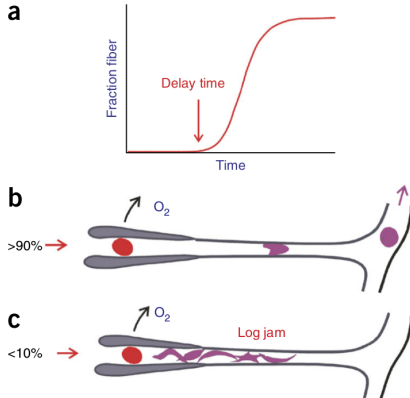
Hence studying quantitatively the properties of the aggregation dynamic is relevant to understand some mechanisms of the Proteopathies. This can be done by reproducing the aggregation process *in vitro*.

# Does a Mathematical model reproduce the data ?



How does that help to understand the mechanistic phenomenon of the aggregation process ?

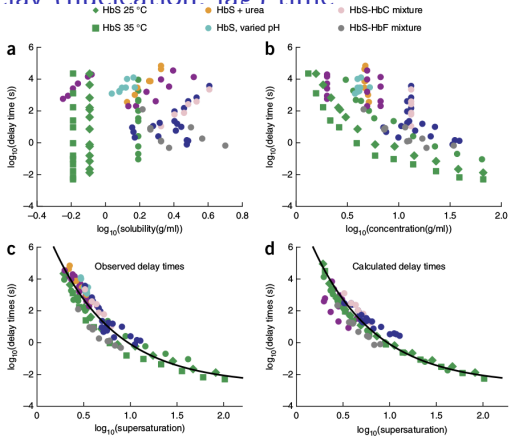
# Modeling the kinetics of Hemoglobin fiber



- ▶ Gene mutation linked to Hemoglobin
- ▶ The Kinetics of sickle-hemoglobin aggregation is connected to disease pathogenesis.

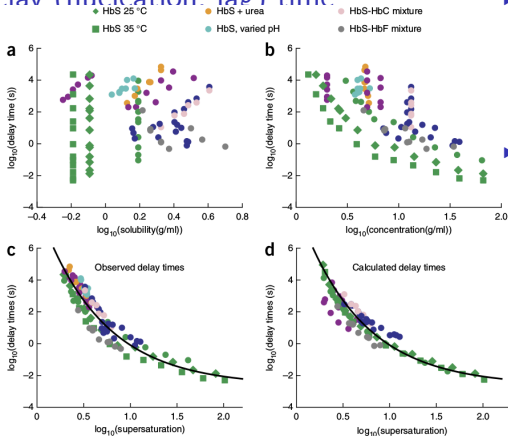




Delay (nucleation,  $\lambda\sigma$ ) time

Cellmer et al. *Universality of supersaturation in protein-fiber formation*  
Nat. Struct. Mol. Biol. (2016)

## Delay (nucleation, lag) time



Cellmer et al. *Universality of supersaturation in protein-fiber formation*  
Nat. Struct. Mol. Biol. (2016)

- ▶ Qualitative and quantitative explanation of lag time before fiber formation (*in-vitro*)

- ▶ Double-nucleation model ( $P = \sum_{i \geq i_0} C_i$ ,  $Z = \sum_{i \geq i_0} i C_i$ ):

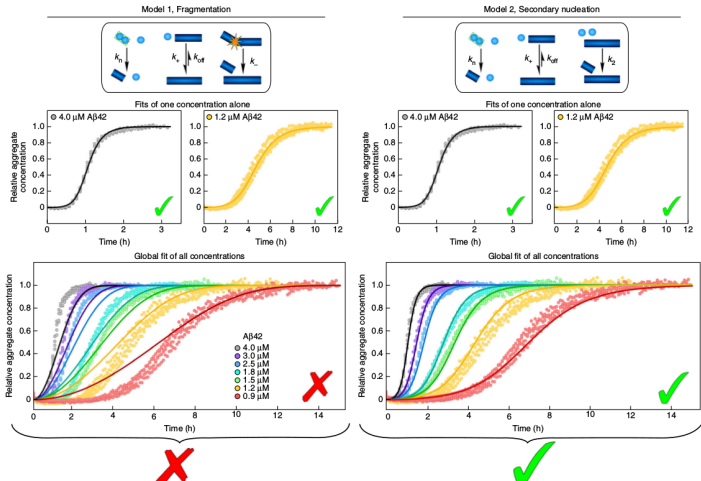
$$\frac{dZ}{dt} = \left( \overbrace{k^+ c_1}^{\text{polym.}} - \overbrace{k^-}^{\text{depolym.}} \right) P$$

$$\frac{dP}{dt} = \underbrace{k_{i_0} c_1^{i_0}}_{1^{\text{st}} \text{ nucl.}} + \underbrace{k_{j_0} c_1^{j_0}}_{2^{\text{nd}} \text{ nucl.}} Z$$

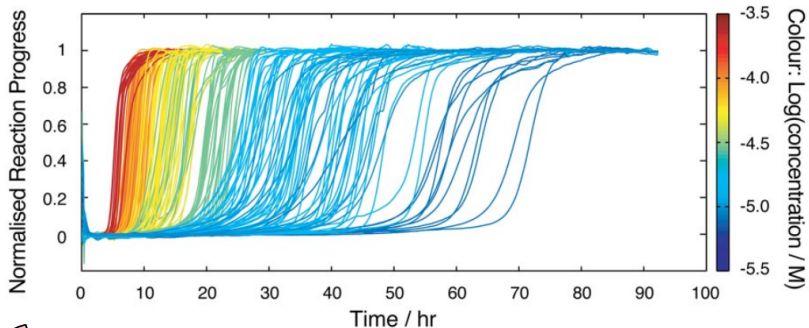


Bishop et Ferrone *Kinetics of nucleation-controlled polymerization*  
Biophys. J. (1984)

## Hypotheses testing through global fitting of experiment



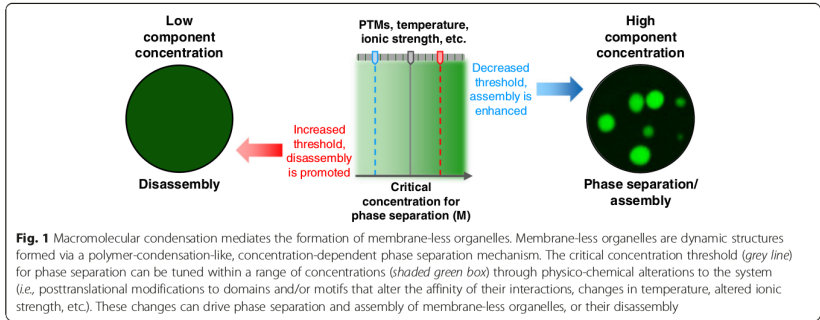
# Stochasticity at different concentration



Xue et al. *Systematic analysis of nucleation-dependent polymerization reveals new insights into the mechanism of amyloid self-assembly*. PNAS (2008)

# Intra-cellular compartmentalization

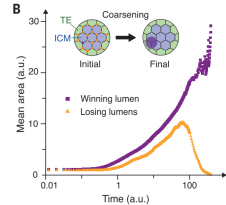
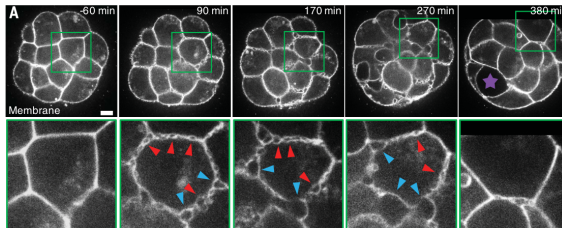
## Reaction-Diffusion PDE



Mitreu et Kriwacki, *Phase separation in biology; functional organization of a higher order*, Cell Commun Signal. (2016)

# Lumen formation

## Coarsening on a graph structure



Dumortier et al., *Hydraulic fracturing and active coarsening position the lumen of the mouse blastocyst*, Science (2019)

# Rescaled SBD model, $n \rightarrow \infty$

## SDE

$$\begin{cases} c_1(t) &= c_1^{\text{in}} - 2\frac{\rho}{n}J_1(t) - \sum_{i \geq 2} \frac{\rho}{n}J_i(t), \\ c_i(t) &= c_i^{\text{in}} + \frac{\rho}{n}J_{i-1}(t) - \frac{\rho}{n}J_i(t), \\ J_i(t) &= Y_i^+ \left( \int_0^t \frac{n}{\rho} a_i c_1(s) c_i(s) ds \right) \\ &\quad - Y_{i+1}^- \left( \int_0^t \frac{n}{\rho} b_{i+1} c_{i+1}(s) ds \right) \end{cases}$$

## CTMC

$$X_n^\rho := \left\{ c \in \mathbb{R}^{\mathbb{N}} : \frac{n}{\rho} c_i \in \mathbb{N}, \sum_{i=1}^n i c_i = \rho \right\}.$$

$$\begin{cases} q(c, r_i^+ c) &= \frac{n}{\rho} a_i c_1 (c_i - \delta_{1,i}), \\ q(c, r_i^- c) &= \frac{n}{\rho} b_i c_i, \end{cases}$$

$$r_i^+ c = c - \frac{\rho}{n} e_1 - \frac{\rho}{n} e_i + \frac{\rho}{n} e_{i+1}$$

$$r_i^- c = c + \frac{\rho}{n} e_1 + \frac{\rho}{n} e_{i-1} - \frac{\rho}{n} e_i$$

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Large **volume** limit : convergence towards the BD model (for a wide class of "reasonable" coefficients) on finite time intervals



## Rescaled SBD model, $n \rightarrow \infty$

Large **volume** limit : convergence towards the BD model (for a wide class of "reasonable" coefficients) on finite time intervals

*3 Methods of proof :*

- (1) Tightness and identification of the limit (convergence in law)
- (2) Contraction of  $\|c^n - c\|$  (pathwise convergence)
- (3) Contraction of  $\|\sum_{j \geq i} c_j^n - \sum_{j \geq i} c_j\|$  (pathwise convergence)