

# Stochastic model of nucleation

## Becker-Döring Model

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Motivation

Becker-Döring model

Stochastic Becker Döring model

# Outline

Motivation

Becker-Döring model

Stochastic Becker Döring model

# Key questions

- ▶ What is a nucleus? How large should it be?
- ▶ How is lag phase related to nucleation?
- ▶ What is the time scale of nucleation formation? What is the variability of this step?
- ▶ How to include (stochastic) unfavorable aggregation steps in a coagulation-fragmentation model?

# Outline

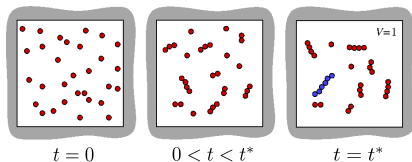
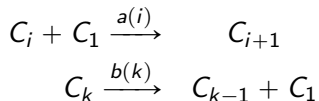
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# Becker-Döring model

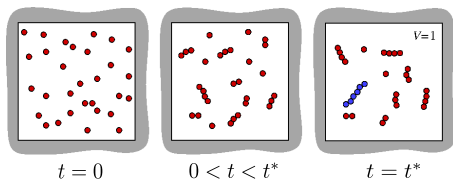
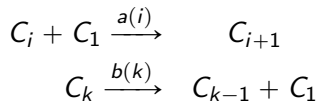
Reversible one-step  
coagulation-fragmentation



- ▶ First used in the work *Kinetic treatment of nucleation in supersaturated vapors* by physicists Becker and Döring (1935).
- ▶ Traditionally used as an infinite set of Ordinary Differential Equations. More recently used as a finite state-space Markov Chain.

# Becker-Döring model

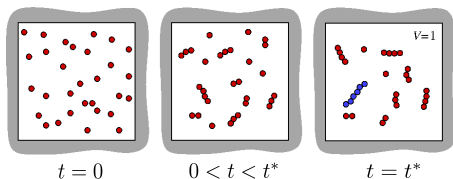
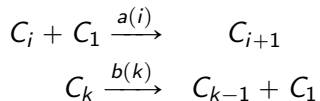
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- Purely kinetic model (law of mass-action) : no space, no polymer structure (but size-dependent kinetic rates).

# Becker-Döring model

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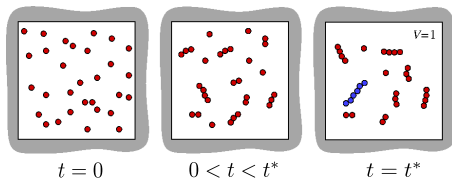
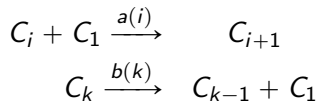
- ▶ Purely kinetic model (law of mass-action) : no space, no polymer structure (but size-dependent kinetic rates).
- ▶ Indirect interaction between polymer  $C_i$ ,  $i \geq 2$  via the available number of monomers  $C_1$ .

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



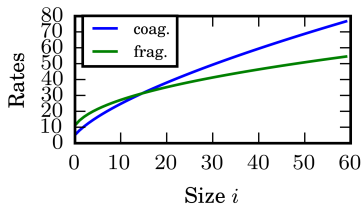
# Becker-Döring model

Reversible one-step  
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- ▶ Typical (in physics literature) coefficients are :

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



# What is a nucleus? What is its size?

Schematically, there is two different conceptual ways to think of a nucleus :

- ▶ 1) As a fixed cluster size, (mainly) depending on structural properties
- ▶ 2) As a varying cluster size, depending on thermodynamic quantities (and concentration of monomers).

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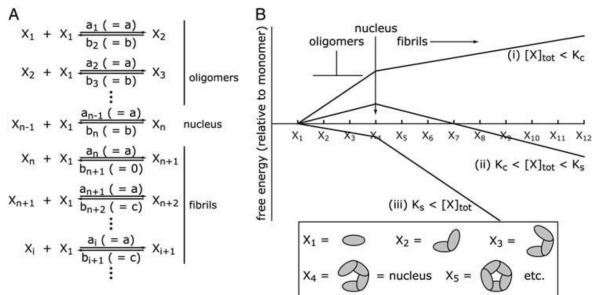
Within BD model, both definition are compatible. The size of a cluster evolves "roughly" as

$$\frac{d}{dt} \langle i \rangle = a(i)c_1(t) - b(i) = a(i) \left( c_1(t) - \frac{b(i)}{a(i)} \right)$$

# Use of BD-like model in protein nucleated-polymerization models

Irreversible nucleation step, "piecewise constant" rates

*Powers & Powers, Biophys. J. 91, 2006*



# How is lag phase related to nucleation ?

The lag phase of spontaneous polymerization experiment is usually decomposed in two phases

- ▶ 1) A nucleation phase (  $t$  or  $t^N$  )
- ▶ 2) (if it exists) an auto-catalytic phase (  $e^t$  )

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The nucleation phase is much slower, and is believed to more subject to *inherent stochastic* fluctuations

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However, we often measure a mixture of both (tenth time of polymerization curves)

# Concentration-dependence in BD model

- ▶ Based on scaling arguments, one can show that for  $b_i \equiv 0$  (irreversible nucleation),

$$\inf\{t \geq 0 : c_n(t) \geq \delta m \mid c_i(t=0) = m\delta_{i=1}\} \simeq \frac{1}{m}.$$

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

$$\inf\{t \geq 0 : c_n(t) \geq \delta m \mid c_i(t=0) = m\delta_{i=1}\} \simeq \frac{1}{m^n}.$$



# Use of BD-like model in protein nucleated-polymerization models

pre-equilibrium nucleation step, constant rates

$$\left\{ \begin{array}{l} \frac{dc_1}{dt} = -(ac_1 - b)y, \\ \frac{dy}{dt} = Kc_1^n (+Q(m - c_1(t))), \\ \frac{dz}{dt} = (ac_1 - b)y, \end{array} \right.$$

*Ferrone et al., Biophys. J.*  
32, 1980

$$y = \sum_{i \geq n} c_i$$

$$z = \sum_{i \geq n} i c_i$$

$$a(i) = a, b(i) = b$$

$Q$  = secondary nucleation mechanism (fragmentation, heterogeneous nucleation...)

# Outline

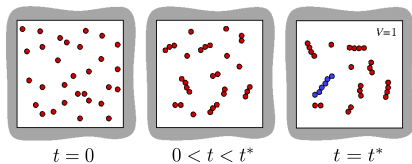
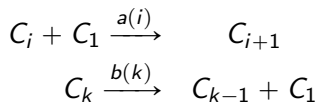
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# Stochastic Becker-Döring model

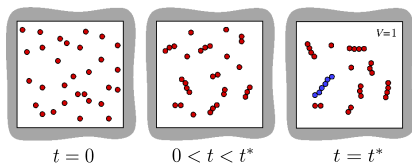
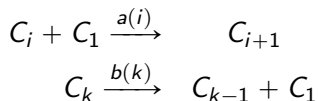
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- Reactions now happen with stochasticity.

# Stochastic Becker-Döring model

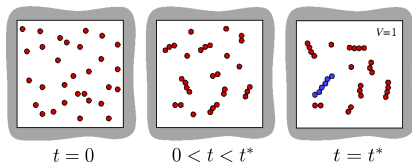
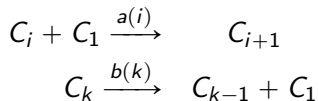
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- ▶ Reactions now happen with stochasticity.
- ▶ *Yet with a large number of particles, one may expect the stochasticity to averaged out.* Under which condition(s) the nucleation phase is "stochastic"?

# Stochastic Becker-Döring model

Reversible one-step  
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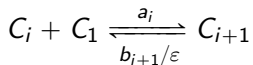
- ▶ Reactions now happen with stochasticity.
- ▶ *Yet with a large number of particles, one may expect the stochasticity to averaged out.* Under which condition(s) the nucleation phase is "stochastic"?

The nucleation phase is "stochastic" for **unfavorable** aggregation

# Unfavorable aggregation : 1) scaled reaction rates

Reversible one-step coag.-frag.

*Y. et al., JCP, 144, 2016*



Using pre-equilibrium hypothesis, in the unfavorable aggregation limit, the leading order of the first assembly time of a cluster of size  $N$  is

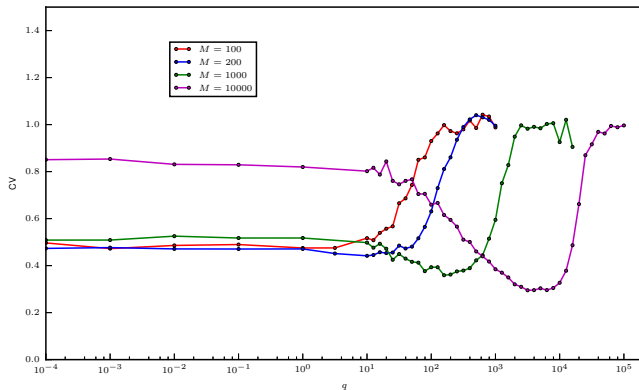
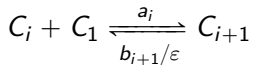
$$\langle T \rangle \approx_{\varepsilon \rightarrow 0} \frac{1}{\varepsilon^{N-2}} \frac{\prod_{k=2}^{N-1} b_k}{\prod_{k=1}^{N-1} a_k \prod_{k=0}^{N-1} (M-k)}.$$

Also, in the asymptotic  $\varepsilon \rightarrow 0$  the first assembly time  $T$  is an exponential distribution.

# Unfavorable aggregation : 1) scaled reaction rates

Reversible one-step coag.-frag.

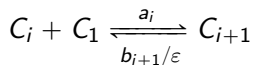
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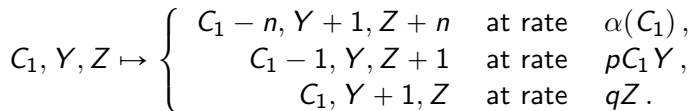
*Y. et al., JCP, 144, 2016*



- ▶ This behavior can be used to couple a first part, very unfavorable, to a second part, favorable or irreversible



# Unfavorable aggregation : 1) scaled reaction rates



Then, for "small  $\alpha$ ", and large volume, the lag time is composed of the convolution of an Exponential variable of rate  $\alpha$  and a deterministic time given by the ODE

*Szavits-Nossan et al., PRL 113, 2014*

$$Y = \sum_{i \geq 2} C_i, \quad Z = \sum_{i \geq 2} iC_i$$

$$\begin{cases} \frac{dc_1}{dt} = -pc_1y (-n\alpha(c_1)), \\ \frac{dy}{dt} = qz (+\alpha(c_1)), & y = \sum_{i \geq n} c_i, \\ \frac{dz}{dt} = pc_1y +(n\alpha(c_1)), & z = \sum_{i \geq n} ic_i. \end{cases}$$

# Unfavorable aggregation : 1) scaled reaction rates

$$C_1, Z \mapsto \begin{cases} C_1 - 2, Z + 2 & \text{at rate } \varepsilon^\nu \alpha (\varepsilon C_1)^2, \\ C_1 - 1, Z + 1 & \text{at rate } p(C_1 \varepsilon)(Z \varepsilon). \end{cases}$$

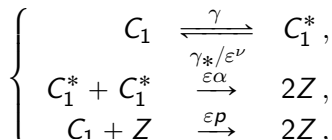
Then, for  $\nu > 1$ , and  $\varepsilon \rightarrow 0$ , the lag time converges "essentially" to an exponential distribution (in the time scale  $\varepsilon^\nu t$ )

*Doumic et al., SIAM J. App. Math., 76(6) (2016)*

$$Z = \sum_{i \geq 2} i C_i$$

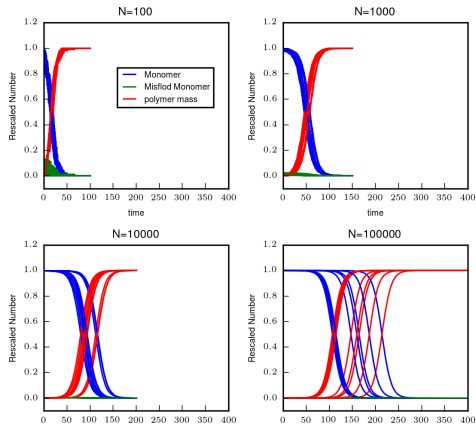
$$\begin{cases} \frac{dc_1}{dt} = -p c_1 z (-2\alpha c_1^2). \\ \frac{dz}{dt} = p c_1 z (+2\alpha c_1^2), \quad z = \sum_{i \geq n} i c_i. \end{cases}$$

# Unfavorable aggregation : 1) scaled reaction rates



Adapted from *Eugène et al., JCP, 144(17), 2016*

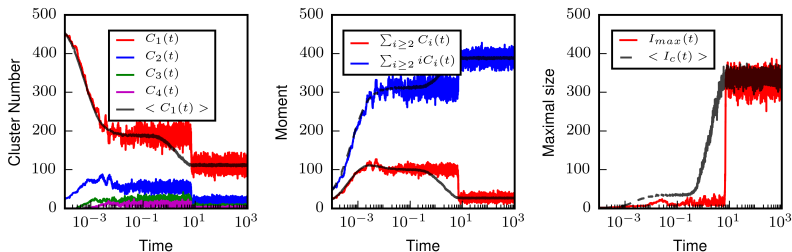
and Doumic et al., *SIAM J. App. Math., 76(6) 2016*



Then, for the rescaled process  $\varepsilon(C_1(t), C_1^*(t), Z(t))$  we observe "translated trajectory" as  $\varepsilon \rightarrow 0$

## Unfavorable aggregation : 2) Large nucleus size

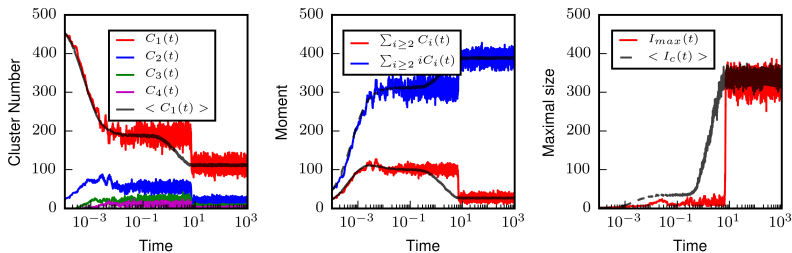
The classical nucleation theory considers small excess of monomers (supersaturated solution) which corresponds to very large nucleus size. In the stochastic setting, there is a phase transition in **finite random time**



The transition phase is abrupt and corresponds to the rapid formation of a **single** large cluster

# Unfavorable aggregation : 2) Large nucleus size

The classical nucleation theory considers small excess of monomers (supersaturated solution) which corresponds to very large nucleus size. In the stochastic setting, there is a phase transition in **finite random time**



The scaling limit of this random time for large number / (vanishingly small) supersaturated density is an open problem.

# Summary

- ▶ Different definitions of nucleus consistent in BD model
- ▶ Concentration-dependence of nucleation (and lag) phase
- ▶ Variability in nucleation phase

Thanks for your attention !