Time scales in a coagulation-fragmentation model, Nucleation Time in Stochastic Becker-Döring Model

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Time scales in a coagulation-fragmentation model

Nucleation Time in Stochastic Becker-Döring Model

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Amyloid diseases and nucleation

Becker-Döring model

Coarse-graining : to include nucleation in continuous model

Stochastic Becker Döring model

Variability in nucleation time
  - Re-scaling reaction rates with M
  - Re-scaling nucleus size with M
  - Back to classical nucleation theory

Outline

Amyloid diseases and nucleation

Becker-Döring model

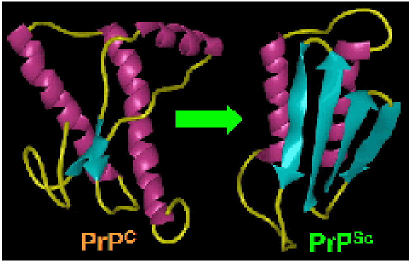
Coarse-graining : to include nucleation in continuous model

Stochastic Becker Döring model

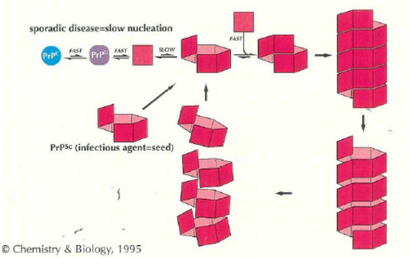
Variability in nucleation time

Protein accumulation in amyloid by nucleation-dependent polymerization

Misfolding



Prusiner model for prion



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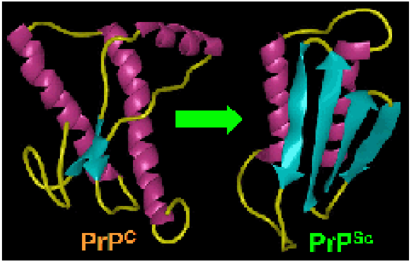
The early aggregation formation requires a series of association steps that are thermodynamically unfavorable (with an dissociation constant $K_d \gg 1$).
These aggregation steps are unfavorable up to a given size (that is not currently known), which is referred to the nucleus size.

Protein accumulation in amyloid by nucleation-dependent polymerization

Misfolding



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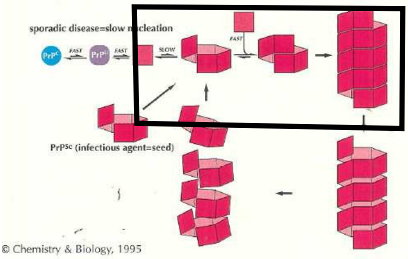

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The early aggregation formation requires a series of association steps that are thermodynamically unfavorable (with an dissociation constant $K_d \gg 1$).
These aggregation steps are unfavorable up to a given size (that is not currently known), which is referred to the nucleus size.

Key questions

We want to study nucleation mechanism for *in-vitro* spontaneous polymerization experiments of *rPrP* (kinetics monitored by fluorescence intensity)

- How to include nucleation in (macroscopic) model of protein polymerization ?
- How to explain large variability in nucleation lag time, despite the large number of proteins ?

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Stochastic Becker Döring model

Variability in nucleation time

Becker-Döring model

Reversible one-step
coagulation-fragmentation

$$C_i + C_1 \underset{q_{i+1}}{\overset{p_i}{\rightleftharpoons}} C_{i+1}\,, \quad i = 2\,,\,,3\,,\cdots$$

- 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

Reversible one-step coagulation-fragmentation

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

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

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

Becker-Döring model

Reversible one-step coagulation-fragmentation

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

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

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

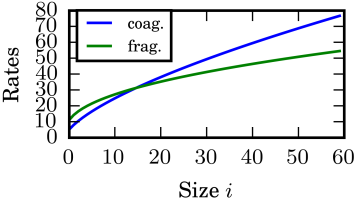
$$C_1(t) + \sum_{i \geqslant 2} iC_i(t) = \text{constant}$$

Becker-Döring model

Reversible one-step coagulation-fragmentation

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

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



- Typical coefficient are derived from physical principles

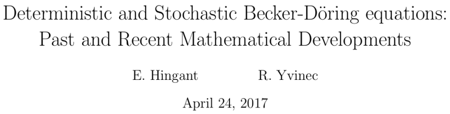
$$p_i = i^{\alpha}\,, \quad q_i = p_i\left(z_s + \frac{q}{i^{\gamma}}\right)\,.$$

Becker-Döring model

Reversible one-step coagulation-fragmentation

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

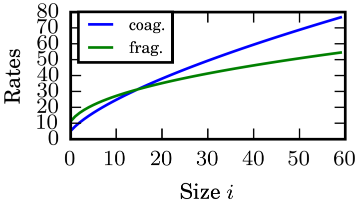
Ball, Carr, Penrose, Comm. Math. Phys 104(4), 1986



Deterministic and Stochastic Becker-Döring equations:
Past and Recent Mathematical Developments

E. Hingant R. Yvinec

April 24, 2017



- Typical coefficient are derived from physical principles

$$p_i = i^{\alpha}\,, \quad q_i = p_i\left(z_s + \frac{q}{i^{\gamma}}\right)\,.$$

Becker-Döring model

Reversible one-step coagulation-fragmentation

Set of kinetic reactions :

$$C_i + C_1 \underset{q_{i+1}}{\overset{p_i}{\rightleftharpoons}} C_{i+1}\,, \quad i \geqslant 1\,.$$

- 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)
- The (observed) nucleation time is given by

$$\inf\{t \geqslant 0 : \sum_{i\geqslant n} iC_i(t) \geqslant \delta m \mid C_i(t=0) = m\delta_{i=1}\}\,.$$

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

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

Deterministic Becker-Döring model

Reversible one-step coagulation-fragmentation

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

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

- Deterministic version : infinite system of ODEs.

Deterministic Becker-Döring model

Reversible one-step coagulation-fragmentation

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

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

- Deterministic version : infinite system of ODEs.
- Well-posedness theory for sublinear coefficients in

$$\mathcal{X} = \left\{ (c_i)_{i \geqslant 1} \in \mathbb{R}_+^{\mathbb{N}} \ : \sum_{i \geqslant 1} i c_i < \infty \right\}$$

Deterministic Becker-Döring model

Reversible one-step coagulation-fragmentation

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

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- Deterministic version : infinite system of ODEs.
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$$\mathcal{X} = \left\{ (c_i)_{i \geqslant 1} \in \mathbb{R}_+^{\mathbb{N}} \, : \sum_{i \geqslant 1} i c_i < \infty \right\}$$

- Preserves mass for all times

$$\sum_{i=1}^{\infty} i c_i(t) = \sum_{i=1}^{\infty} i c_i(0) =: m \,.$$

Equilibrium of the BD model

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

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

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

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

z is given by the mass at equilibrium,

$$m(z) := \sum_{i \geqslant 1} i Q_i z^i$$

Is there a solution of

$$m(z) \overset{?}{=} m(= \sum_{i \geqslant 1} i c_i(t))$$

Equilibrium of the BD model

Ball, Carr, Penrose, Comm. Math. Phys 104(4), 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 the serie $m(z) = \sum_{i \geqslant 1} i Q_i z^i$ has a finite radius of convergence z_s and if

$$\sup\{m(z) \,, z < z_s\} =: m_s < \infty \,,$$

then there is a critical mass such that there is **no equilibrium** with mass $m > m_s$.

Deterministic BD model and Classical Nucleation Theory

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

Ball, Carr, Penrose, Comm. Math. Phys 104(4), 1986
Slemrod, Nonlinearity 2(3), 1989
Cañizo, Lods, J. Diff. Eqs. 255(5), 2013

If $m \leqslant m_s$, then (with strong convergence)

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

If $m > m_s$, then (with weak convergence)

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

Remark

There is a Lyapounov function, given by

$$H(c) = \sum_{i\geq 1} c_i \left(\ln\left(\frac{c_i}{Q_i}\right) - 1 \right) \,.$$

Deterministic BD model and Classical Nucleation Theory

Penrose, Comm. Math. Phys 124, 1989

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

There exist "almost steady-states", for which $J_i \equiv J^*(m) \neq 0$. As $m \searrow m_s$, if such steady-states are used as initial condition, then the solution

- (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

Moreover $J^*(m)$ is exponentially small

- **The new phase is being formed extremely slowly, after a long metastable period**.

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

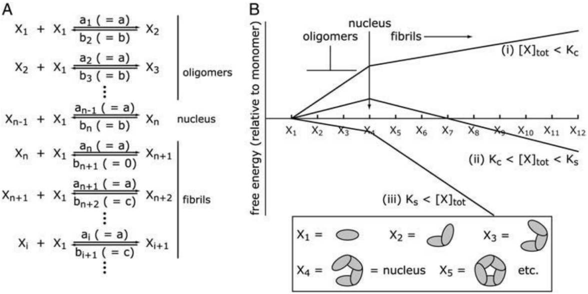
$$c_1 \,, \quad \sum_{i \geqslant 2} c_i \,, \quad \sum_{i \geqslant 2} i c_i \,.$$

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
$$c_1 \,, \quad \sum_{i\geqslant 2} c_i \,, \quad \sum_{i\geqslant 2} i c_i \,.$$
- Based on scaling arguments, one can show that for $q_i = 0$ (irreversible nucleation),
$$\inf\{t \geqslant 0 : c_n(t) \geqslant \delta m \mid c_i(t=0) = m\delta_{i=1}\} \simeq \frac{1}{m} \,.$$
while for "$q_i \to \infty$" (pre-equilibrium nucleation),
$$\inf\{t \geqslant 0 : c_n(t) \geqslant \delta m \mid c_i(t=0) = m\delta_{i=1}\} \simeq \frac{1}{m^n} \,.$$

Use of BD-like model in protein polymerization models

Irreversible nucleation step, "Heaviside" rates



Powers & Powers, Biophys. J. 91, 2006

For $b \gg c$: pre-equilibrium hypothesis.

Use of BD-like model in protein polymerization models

pre-equilibrium nucleation step, constant rates

$$\begin{cases} \dfrac{dc_1}{dt} &= -(pc_1 - q)y, . \\ \dfrac{dy}{dt} &= Kc_1^n(+Q(m - c_1(t))), \\ \dfrac{dz}{dt} &= (pc_1 - q)y, . \end{cases}$$

Ferrone et al., Bophys. J. 32, 1980

$y = \sum_{i \geqslant n} c_i$
$z = \sum_{i \geqslant n} ic_i$
$p(i) = p$, $q(i) = q$
Q = secondary nucleation mechanism (fragmentation, heterogeneous nucleation...)

Use of BD-like model in protein polymerization models

pre-equilibrium nucleation,
polymerization-fragmentation, "oligomers at 0"

Knowles et al., Science 326, 2009

Approximate analytical solution.

$$\begin{cases} \dfrac{dc_1}{dt} &= -pc_1 \sum\limits_{i\geqslant n} c_i + 2q \sum\limits_{i=1}^{n-1} \sum\limits_{j\geqslant i+1} ic_j - nKc_1^n \,. \\ \dfrac{dc_i}{dt} &= pc_1(c_{i-1}-c_i) - q(i-1)c_i + 2q \sum\limits_{j\geqslant i+1} c_j + Kc_1^n \delta_{i,n} \,, \, i \geqslant n \,, \end{cases}$$

$$\begin{cases} \dfrac{dc_1}{dt} &= -pc_1 y + n(n-1)qy - nKc_1^n \,. \\ \dfrac{dy}{dt} &= qz - (2n-1)qy + Kc_1^n \,, \quad y = \sum\limits_{i\geqslant n} c_i \,, \\ \dfrac{dz}{dt} &= pc_1 y - n(n-1)qy + nKc_1^n \,, \quad z = \sum\limits_{i\geqslant n} ic_i \,. \end{cases}$$

Use of BD-like model in protein polymerization models

Continuous approximation, nucleation as a boundary condition

Helal et al., J. Math. Biol., 2013

$f(t,x)$=number of polymer size x
$N(c_1) = \alpha c_1^n$

$$\left\{ \begin{array}{rcl} \dfrac{\partial f(x,t)}{\partial t} + c_1(t)\dfrac{\partial p(x) f(x,t)}{\partial x} & = & [\cdots]\,. \\ c_1(t) p(x_0) f(x_0,t) & = & N(c_1(t))\,, \\ \dfrac{dc_1}{dt} & = & \lambda - \gamma c_1 - nN(c_1) - c_1 \displaystyle\int_{x_0}^{\infty} p(x) f(x,t) \end{array} \right.$$

Use of BD-like model in protein polymerization models

Prigent et al., Plos One, 7, 2012
Banks et al., J. Math. Biol., 74, 2017

Continuous approximation, nucleation as a boundary condition

$$\left\{ \begin{array}{rcl} \dfrac{\partial f(x,t)}{\partial t} + \dfrac{\partial (p(x)c_1(t) - q(x))f(x,t)}{\partial x} & = & [\cdots] \, . \\ p(x_0)f(x_0,t) & = & p(x_0)\dfrac{p_N c_1(t)^n}{q_N + p(x_0)c_1(t)} \, , \end{array} \right.$$

Outline

Amyloid diseases and nucleation

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Stochastic Becker Döring model

Variability in nucleation time

Large Size, Excess of monomer

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

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

Scaling idea : **excess of monomer**, time scale $= 1/\varepsilon$

$$c_1^\varepsilon(t) := \varepsilon^2 c_1(t/\varepsilon) , \quad c_i^\varepsilon(t) := c_i(t/\varepsilon)$$

Compensated aggregation / fragmentation

$$p_i^\varepsilon := \frac{p_i}{\varepsilon^2} , \quad q_i^\varepsilon := q_i , \quad J_i^\varepsilon = p_i^\varepsilon c_1^\varepsilon c_i^\varepsilon - q_{i+1}^\varepsilon c_{i+1}^\varepsilon$$

and **slow first step** :

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

Large Size, Excess of monomer

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

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

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

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

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

Large Size, Excess of monomer

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

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

Weak form : for any test function (φ_i),

$$\frac{d}{dt}\sum_{i\geqslant 2} c_i^\varepsilon \varphi_i = \frac{1}{\varepsilon} J_2^\varepsilon \varphi_2 + \sum_{i\geqslant 3} J_i^\varepsilon \left[\frac{\varphi_{i+1} - \varphi_i}{\varepsilon}\right].$$

Large Size, Excess of monomer

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

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

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

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

where $\Delta_\varepsilon\varphi(x) = \frac{\varphi(x+\varepsilon)-\varphi(x)}{\varepsilon}$ and $J^\varepsilon(t,x) = .p^\varepsilon(x)c_1^\varepsilon(t)f^\varepsilon(t,x) - q^\varepsilon(x+\varepsilon)f^\varepsilon(t,x+\varepsilon)$

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

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

We suppose :

- *Control and convergence of rate functions*
- *Control and convergence of initial condition*
- $p(x) \sim \overline{p}x^{r_p}$, $q(x) \sim \overline{q}x^{r_q}$ *near* $x = 0$, *and* $r_q \geqslant r_p$.
- $c_1(0) > \rho := \lim_{x\to 0} q(x)/p(x)$

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

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

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

we have $f^\varepsilon \to f$ *(in* $\mathcal{C}\left([0,T]; w-*-\mathcal{M}([0,\infty))\right)$*) solution of*

$$\frac{d}{dt}\int_0^{+\infty} f(t,x)\varphi(x)\,dx = N(t)\varphi(0)$$

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

for all $\varphi \in C_0[0,\infty)$*, which is the weak form of*

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

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

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

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

$$\begin{cases} 0 &= \left[J_{i-1}(c_1) - J_i(c_1)\right]\,, \quad i \geqslant 2\,, \\ c_1(t) &= c_1\,. \\ J_i(c_1) &= \overline{p} i^{r_p} c_1 - \overline{q}(i+1)^{r_q}\mathbf{1}_{r_p=r_q}\,. \end{cases}$$

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.

Exemples

- For $r_p < r_q$, we get $N(c_1) = \alpha c_1^2$, and

$$\lim_{x\to 0^+} x^{r_p} f(t,x) = \frac{\alpha}{\overline{p}} c_1(t)\,.$$

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- For $r_p = r_q$, we get $N(c_1) = \frac{\alpha}{\overline{p}} c_1(\overline{p}c_1 - \overline{q})$, and
$$\lim_{x\to 0^+} x^{r_p} f(t,x) = \frac{\alpha}{\overline{p}} c_1(t)\,.$$

Exemples

- For $r_p < r_q$, we get $N(c_1) = \alpha c_1^2$, and
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- For $r_p = r_q$, we get $N(c_1) = \frac{\alpha}{\overline{p}} c_1(\overline{p}c_1 - \overline{q})$, and
$$\lim_{x\to 0^+} x^{r_p} f(t,x) = \frac{\alpha}{\overline{p}} c_1(t)\,.$$
- For faster fragmentation rate q_2^ε, we may get $N(c_1) = \alpha c_1^2 \frac{\overline{p}c_1}{\overline{p}c_1 + q_2}$ and
$$\lim_{x\to 0^+} x^{r_p} f(t,x) = \alpha c_1(t) \frac{c_1(t)}{\overline{p}c_1(t) + q_2}\,,$$
or $N(c_1) = 0$, and
$$\lim_{x\to 0^+} x^{r_p} f(t,x) = 0\,.$$

Outline

Amyloid diseases and nucleation

Becker-Döring model

Coarse-graining : to include nucleation in continuous model

Stochastic Becker Döring model

Variability in nucleation time

Stochastic Becker Döring model

Reversible one-step coag.-frag.

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

$$\left\{ \begin{array}{rcl} C_i(t) & = & C_i^{\text{in}} + J_{i-1}(t) - J_i(t)\,, \quad i \geqslant \\ J_i(t) & = & Y_i^+\Big(\int_0^t p_i C_1(s) C_i(s) ds \Big) \\ & & - Y_{i+1}^-\Big(\int_0^t q_{i+1} C_{i+1}(s) ds \Big) \\ C_1(t) & = & C_1^{\text{in}} - 2J_1(t) - \sum_{i \geqslant 2} J_i(t)\,, \end{array} \right.$$

- Stochastic version : Finite-state space Markov Chain, in

$$X_M := \left\{ C = (C_i)_{i \geqslant 1} \in \mathbb{N}^{\mathbb{N}} \, : \, \sum_{i=1}^{\infty} i C_i = M \right\} .$$

Stochastic Becker Döring model

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

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$$X_M := \left\{ C = (C_i)_{i \geqslant 1} \in \mathbb{N}^{\mathbb{N}} \; : \; \sum_{i=1}^{\infty} i C_i = M \right\} .$$

- Preserves mass for all times

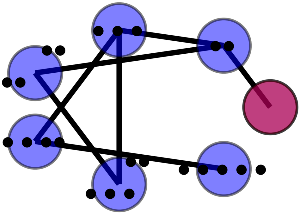
$$\sum_{i=1}^{\infty} i C_i(t) = \sum_{i=1}^{\infty} i C_i(0) =: M\,.$$

Stochastic Becker-Döring model

Reversible one-step coag.-frag.

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

Graph (M=5) at iter. 0



Transitions are given by

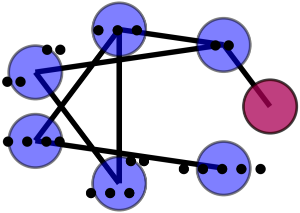
$$\mathcal{P}\left\{ \begin{array}{l} C_1(t+dt) = C_1(t) - 2 \\ C_2(t+dt) = C_2(t) + 1 \end{array} \right\} = p_1 C_1(t)(C_1(t)-1)dt + o(dt)$$

Stochastic Becker-Döring model

Reversible one-step coag.-frag.

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

Graph (M=5) at iter. 0



Transitions are given by

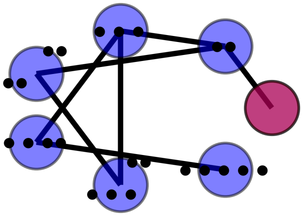
$$\mathcal{P}\left\{\begin{array}{rcl} C_1(t+dt) &=& C_1(t)-1 \\ C_i(t+dt) &=& C_i(t)-1 \\ C_{i+1}(t+dt) &=& C_{i+1}(t)+1 \end{array}\right\} = p_i C_1(t) C_i(t) dt + o(dt)$$

Stochastic Becker-Döring model

Reversible one-step coag.-frag.

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

Graph (M=5) at iter. 0



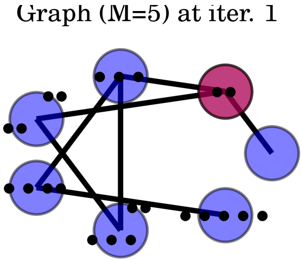
Transitions are given by

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

Stochastic Becker-Döring model

Reversible one-step coag.-frag.

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



Time interval between transition

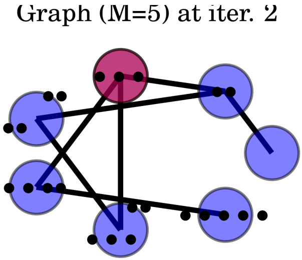
$$T_{i+1} - T_i \sim \mathcal{E}\left(p_1 C_1 (C_1 - 1) + \sum_{i \geqslant 2} p_i C_1 C_i + q_i C_i\right)$$

A given transition is selected at random according to its weight.

Stochastic Becker-Döring model

Reversible one-step coag.-frag.

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



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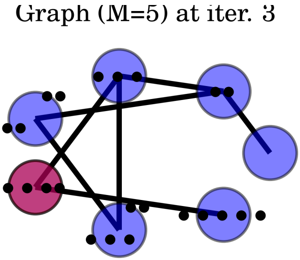

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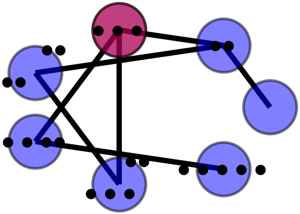
Stochastic Becker-Döring model

Reversible one-step coag.-frag.

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

Graph (M=5) at iter. 4



Time interval between transition

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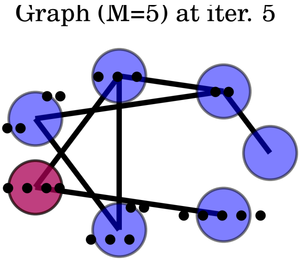
Stochastic Becker-Döring model

Reversible one-step coag.-frag.

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



Time interval between transition

$$T_{i+1} - T_i \sim \mathcal{E}\left(p_1 C_1 (C_1 - 1) + \sum_{i \geqslant 2} p_i C_1 C_i + q_i C_i\right)$$

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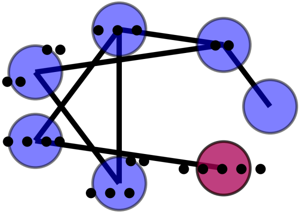
Stochastic Becker-Döring model

Reversible one-step coag.-frag.

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

Graph (M=5) at iter. 6



Time interval between transition

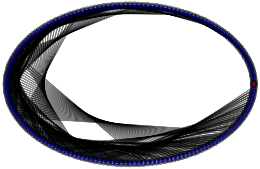
$$T_{i+1} - T_i \sim \mathcal{E}\left(p_1 C_1 (C_1 - 1) + \sum_{i \geqslant 2} p_i C_1 C_i + q_i C_i\right)$$

A given transition is selected at random according to its weight.

Stochastic Becker-Döring model

Reversible one-step coag.-frag.

Graph (M=15) at iter. 0



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

$$X_M := \left\{ C \in \mathbb{N}^{\mathbb{N}} \; : \; \sum_{i=1}^{\infty} iC_i = M \right\}$$

Drawback : exponential increase of the size of the state-space !

$$M \mid X_M \mid = \sum_{i=1}^{M} \sigma(i) \mid X_{M-i} \mid , \quad \mid X_M \mid \propto \frac{1}{4M\sqrt{3}} \exp\left(\pi\sqrt{\frac{2M}{3}}\right) ,$$

where $\sigma(i)$ is the sum of the divisors of i

Stochastic Becker-Döring model

Reversible one-step coag.-frag.

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

Due to detailed-balance, the asymptotic prob. distribution is

$$\Pi(C) = B_M \prod_{i=1}^{M} \frac{(Q_i)^{C_i}}{C_i!}\,, \quad Q_i = \frac{p_1 p_2 \cdots p_{i-1}}{q_2 q_3 \cdots q_i}\,.$$

Stochastic Becker-Döring model

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The expected number of clusters of size i is

$$\mathbf{E}_\Pi C_i = Q_i B_M / B_{M-i}\,, \quad \text{and } M B_M^{-1} = \sum_{i=1}^{M} i Q_i B_{M-i}^{-1}\,.$$

Stochastic Becker-Döring model

Reversible one-step coag.-frag.

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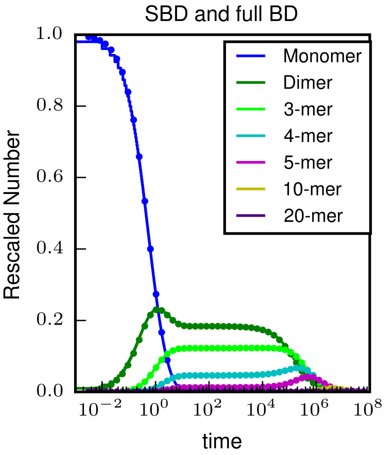
Moreover, analogy with supercritical case in BD holds :

$$\left(\lim_{i\to\infty} \frac{p_i}{q_{i+1}} = z_s > 0\right) \Rightarrow \left(\lim_{M\to\infty} \mathbf{E}_\Pi C_i = Q_i z_s^i\right)$$

- With the large volume scaling : $c_i^{\varepsilon} = \varepsilon C_i$, and $p_i = \varepsilon \overline{p}_i$, $q_i = \overline{q}_i$: Law of large numbers as $M \to \infty$ [Jeon, CMP (1998)]
- Any macroscopic quantity like

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

converges *(in standard scaling)* to a finite deterministic value as $M \to \infty$.



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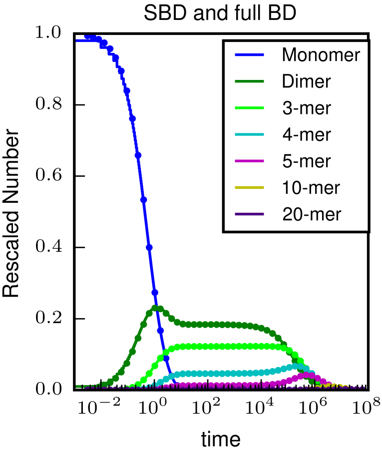
converges *(in standard scaling)* to a finite deterministic value as $M \to \infty$.

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

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



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

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

Outline

Amyloid diseases and nucleation

Becker-Döring model

Coarse-graining : to include nucleation in continuous model

Stochastic Becker Döring model

Variability in nucleation time
- Re-scaling reaction rates with M
- Re-scaling nucleus size with M
- Back to classical nucleation theory

How to explain large variability in $M \to \infty$?

Roughly speaking, due to the law of large number (+CLT), in order to obtain a positive variance in a continuous settings, one needs to avoid that the nucleation occurs in finite time in the limit $M \to \infty$.

- We seek situations (model, scaling) where the nucleation is a *rare event*, that do not occurs in the deterministic limit $M \to \infty$.

Coarse-Grained model

$$C_1, Y, Z \mapsto \begin{cases} C_1 - n, Y+1, Z+n & \text{at rate} \quad \alpha(C_1)\,, \\ C_1 - 1, Y, Z+1 & \text{at rate} \quad pC_1 Y\,, \\ C_1, Y+1, Z & \text{at rate} \quad qZ\,. \end{cases}$$

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

Szavits-Nossan et al., PRL 113, 2014

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

$$\begin{cases} \dfrac{dc_1}{dt} = -pc_1 y \; (-n\alpha(c_1))\,. \\ \dfrac{dy}{dt} = qz \; (+\alpha(c_1))\,, \quad y = \displaystyle\sum_{i\geqslant n} c_i\,, \\ \dfrac{dz}{dt} = pc_1 y \; +(n\alpha(c_1))\,, \quad z = \displaystyle\sum_{i\geqslant n} ic_i\,. \end{cases}$$

Coarse-Grained model

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

Then, for $\nu > 1$, and $\varepsilon \to 0$, 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)

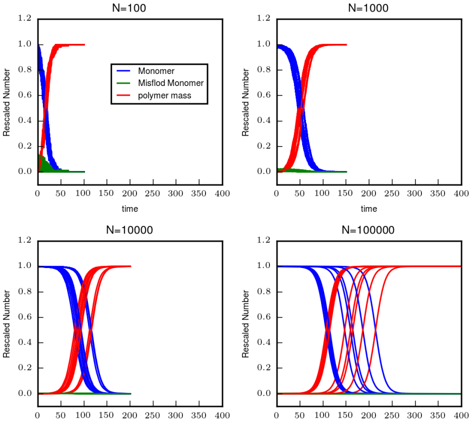
$Z = \sum_{i \geqslant 2} iC_i$

$$\begin{cases} \dfrac{dc_1}{dt} & = & -pc_1 z \ (-2\alpha c_1^2)\,. \\ \dfrac{dz}{dt} & = & pc_1 z \ (+2\alpha c_1^2)\,, \quad z = \sum\limits_{i \geqslant n} ic_i\,. \end{cases}$$

Coarse-Grained model

$$
\begin{cases}
C_1 \underset{\gamma_*/\varepsilon^{\nu}}{\overset{\gamma}{\rightleftharpoons}} C_1^* \,, \\
C_1^* + C_1^* \xrightarrow{\varepsilon\alpha} 2Z \,, \\
C_1 + Z \xrightarrow{\varepsilon p} 2Z \,.
\end{cases}
$$

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 observ "translated trajectory" as $\varepsilon \to 0$

Unfavorable aggregation in SBD

Y. et al., JCP, 144, 2016

Reversible one-step coag.-frag.

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

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

$$< T > \approx_{\varepsilon \to 0} \frac{1}{\varepsilon^{N-2}} \frac{\prod_{k=2}^{N-1} q_k}{\prod_{k=1}^{N-1} p_k \prod_{k=0}^{N-1} (M-k)} .$$

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

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

Unfavorable aggregation in SBD

Y. et al., JCP, 144, 2016

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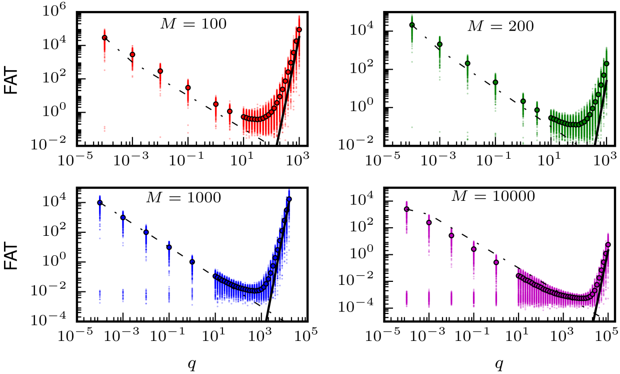

Unfavorable aggregation in SBD

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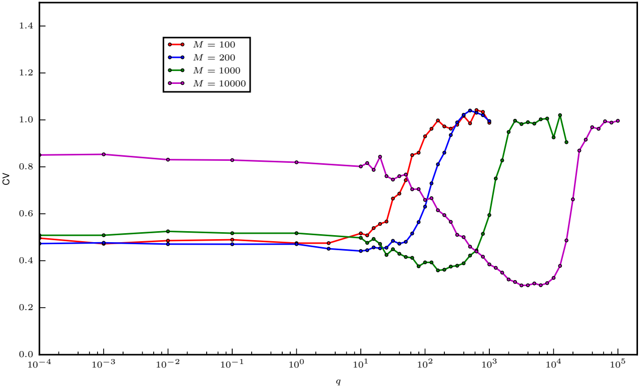


Large nucleus scaling

Reversible one-step coag.-frag.

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

$f^\varepsilon(t,x) = \sum_{i\geqslant 2} C_i^\varepsilon(t)\mathbf{1}_{[(i-1/2)\varepsilon,(i+1/2)\varepsilon)}(x)$ converges towards solution of

$$\frac{\partial f}{\partial t} + \frac{\partial(J(x,t)f(t,x))}{\partial x} = 0\,,$$

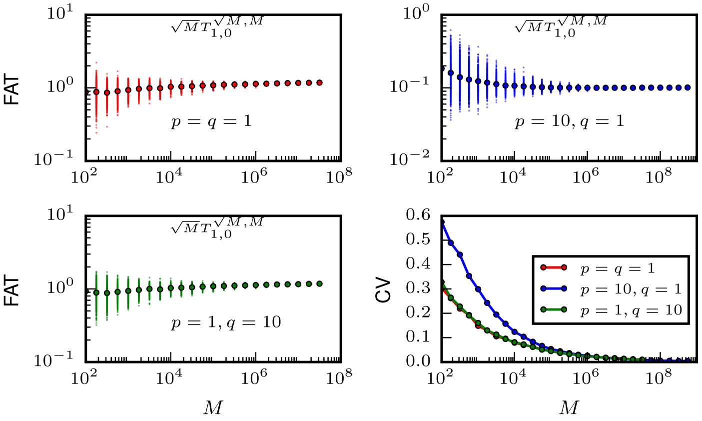
(+boundary condition, if needed) and

$$J(x,t) = p(x)c_1(t) - q(x)\,.$$

- How can we obtain large assembly time in this scaling ?

Large nucleus scaling

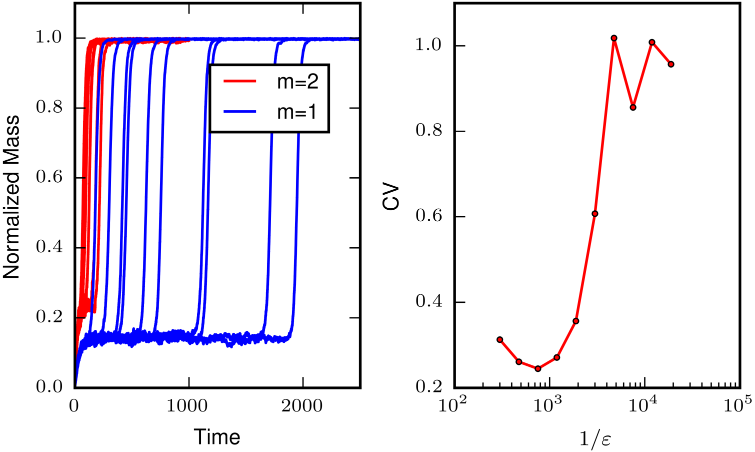
- First case ($p(0)m > q(0)$) : Convergence towards a deterministic value.



- case A
- case B

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

- Second case $(p(0)M < q(0))$: Exponentially large time and 'translated' trajectory. ($p(x) = x$, $q(x) = 0.1$.)



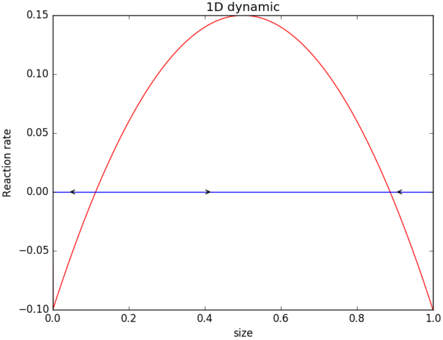
Quantifying the rare event in a toy model

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

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

which converges (with time rescaling) to

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



$$(m = 1,\ p(x) = x,\ q(x) = 0.1)$$

Quantifying the rare event in a toy model

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

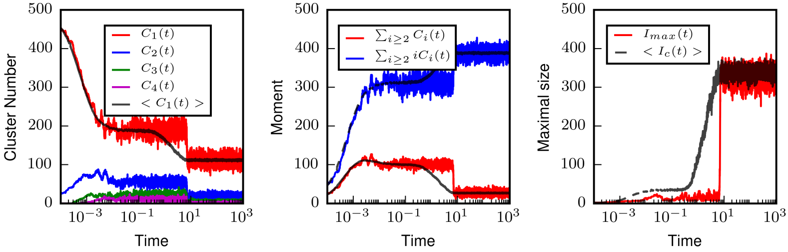
- To leading order the stationary prob. density is

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

- MFPT is explicit and is exponentially large in ε
- The “rate” is exponentially small

Stochastic view of Classical Nucleation Theory

In the classical scaling from SBD to BD, with gelation coefficients $\left(\sup\left(\sum iQ_iz^i\right) = \rho_s < \infty\right)$, 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

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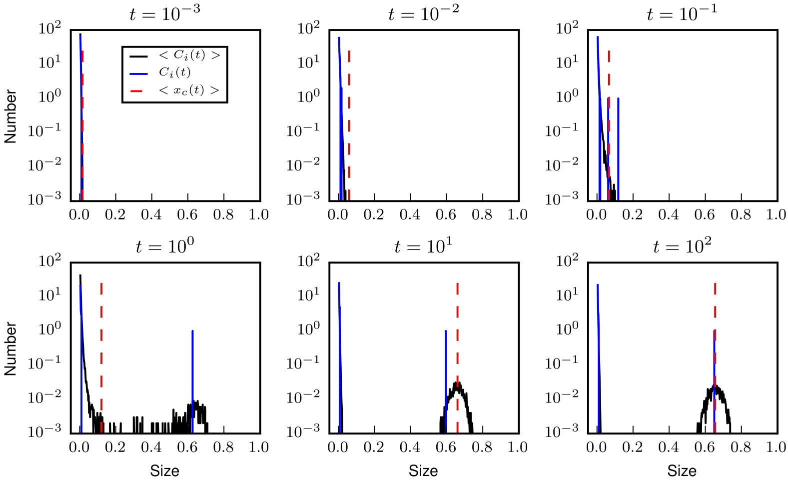
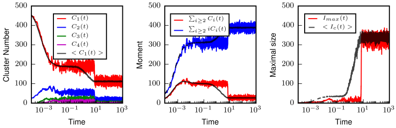
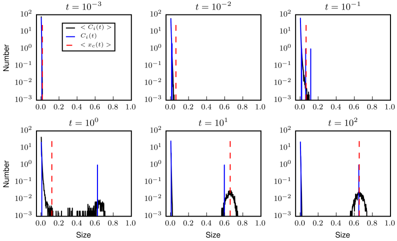


The transition phase is abrupt, occurs at a **random time** and corresponds to the rapid formation of a **single** large cluster

Open Questions on Metastability in the (S)BD model



Schweitzler et al., Physica A, 150, 1988



- Which initial conditions go through the metastable state ? *Completely open*
- How long (and variable) is the metastable period ? *[Partial numerical answers in Y. et al, JCP 137 (2012), Y. et al, JCP 144 (2016)]*
- How does the largest cluster size I_{max} behave as $M \to \infty$? *[Partial answers in the literature : Niethammer, Penrose, Wattis, etc...*

Summary

- A framework to include nucleation in continuous-size model
- A stochastic version of a classical model of nucleation
- Several scaling possibilities to obtain positive variance in the limit $M \to \infty$.
    - Rate scaling
    - Size scaling
    - Large time behavior (metastability)

Thanks for your attention !

n cluster models

Can we perform LDP calculations with n clusters ?

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which converges (with time rescaling) to

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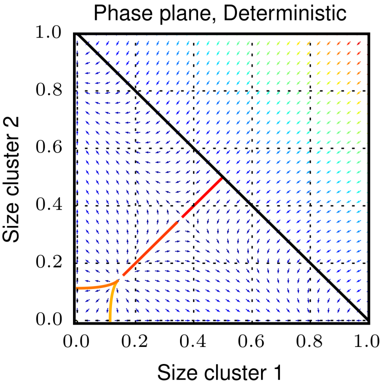

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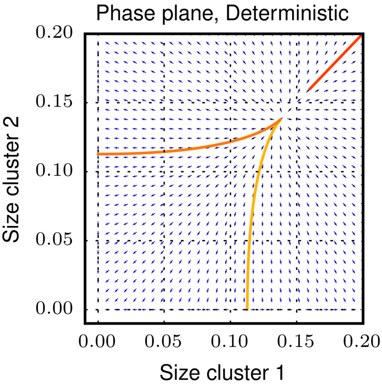

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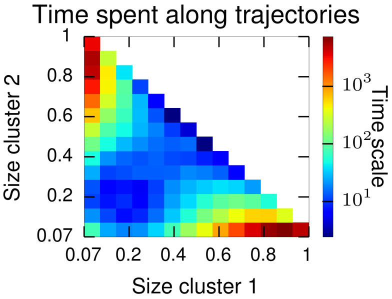

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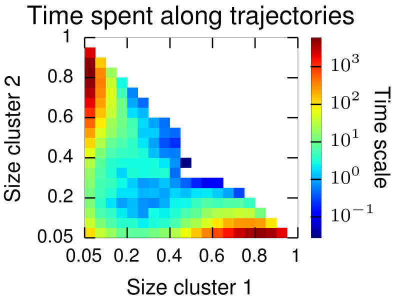

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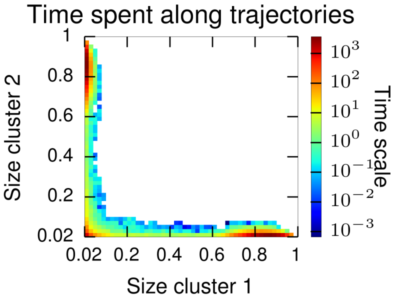

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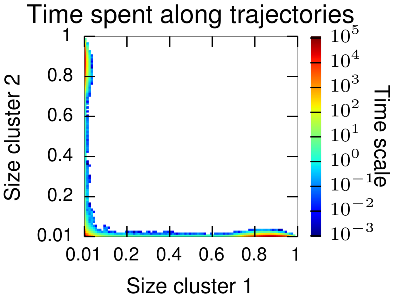

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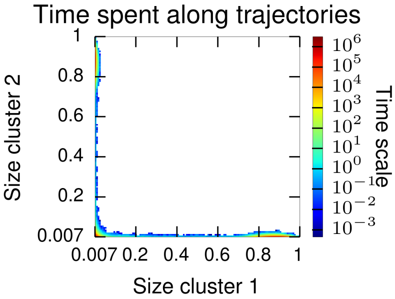

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