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

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Becker-Döring model

CRN : Polymerisation with Attachement-Detachement of single monomer

$$C_i + C_1 \underset{b_{i+1}}{\overset{a_i}{\rightleftharpoons}} C_{i+1}$$

Systems of ODEs

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

Becker-Döring model

CRN : Polymerisation with Attachement-Detachement of single monomer

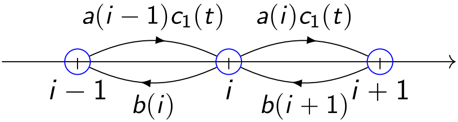
$$C_i + C_{\mathbf{1}} \underset{b_{i+1}}{\overset{a_i}{\rightleftharpoons}} C_{i+\mathbf{1}}$$

CTMC

$$\begin{cases} \quad\quad \text{Transition} & \text{Intensity} \\ C \to C + \Delta_i, & a_i C_1 C_i \\ C \to C - \Delta_i, & b_{i+1} C_{i+1} \end{cases}$$

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

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



Becker-Döring model

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$$C_i + C_1 \underset{b_{i+1}}{\overset{a_i}{\rightleftharpoons}} C_{i+1}$$

Non linear conservation laws

$$\begin{cases} \frac{\partial f}{\partial t} & = & -\frac{\partial (J(x,t) f(t,x))}{\partial x}, \\ J(x,t) & = & a(x) c_1(t) - b(x) . \\ \rho & := & c_1(t) + \int_0^\infty x f(t,x) dx . \end{cases}$$

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

Becker-Döring model

CRN : Polymerisation with Attachement-Detachement of single monomer

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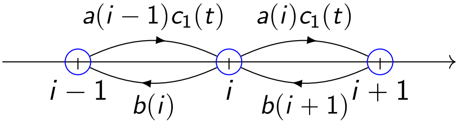
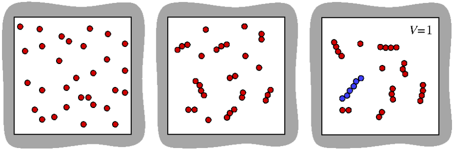


$$\frac{d}{dt}x = a(x)c_1(t) - b(x) = a(x)\left(c_1(t) - \frac{b(x)}{a(x)}\right)$$

Becker-Döring model

Nucleation and coarsening model

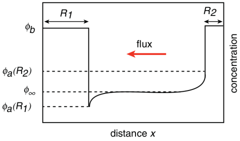
$$C_i + C_1 \underset{b(i+1)}{\overset{a(i)}{\rightleftharpoons}} C_{i+1}$$

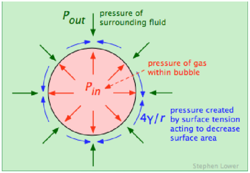


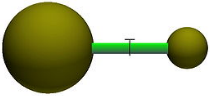
$t = 0$ $\quad$ $0 < t < t^*$ $\quad$ $t = t^*$

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

Nucleation and coarsening model

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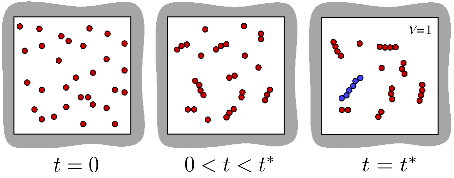

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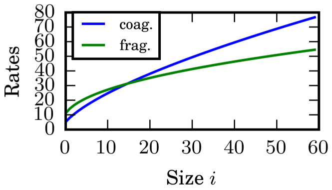
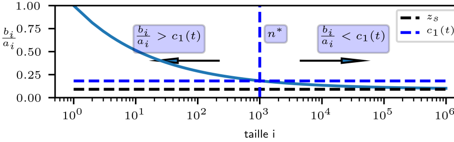
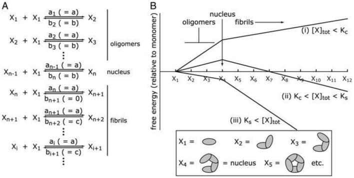
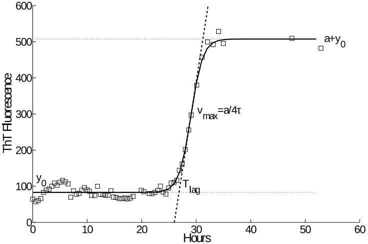




Becker-Döring : nucleation, phase transition and coarsening





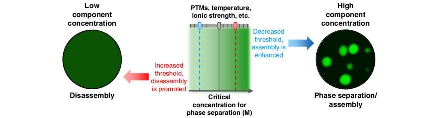
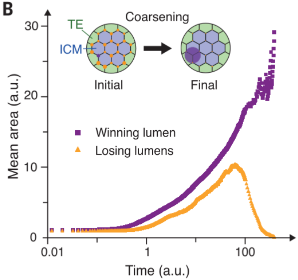
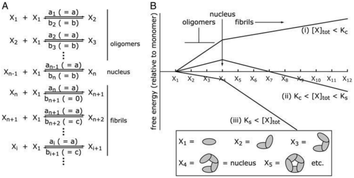
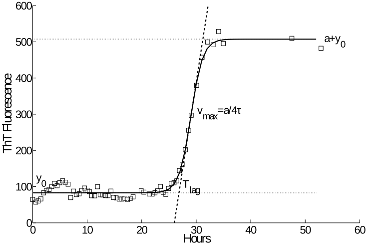


Fig. 1 Macromolecular condensation mediates the formation of membrane-less organelles. Membrane-less organelles are dynamic structures formed via a polymer-condensation-like, concentration-dependent phase separation mechanism. The critical concentration threshold (*grey line*) for phase separation can be tuned within a range of concentrations (*shaded green box*) through physico-chemical alterations to the system (*i.e.,* posttranslational modifications to domains and/or motifs that alter the affinity of their interactions, changes in temperature, altered ionic strength, etc.). These changes can drive phase separation and assembly of membrane-less organelles, or their disassembly



Becker-Döring : nucleation, phase transition and coarsening





Available 2-year post-doc position at MUSCA, INRIA Saclay

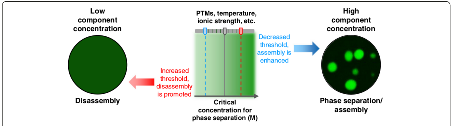
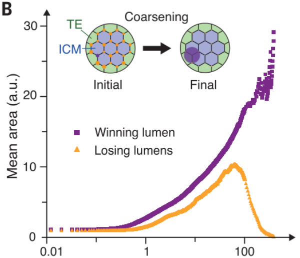


Fig. 1 Macromolecular condensation mediates the formation of membrane-less organelles. Membrane-less organelles are dynamic structures formed via a polymer-condensation-like, concentration-dependent phase separation mechanism. The critical concentration threshold (*grey line*)



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

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

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

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

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

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

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

It is natural to look for a solution of

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

Equilibrium of the BD model

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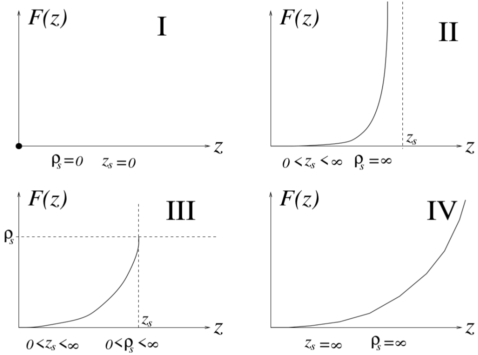

$$Q_i = \frac{a_1 a_2 \cdots a_{i-1}}{b_2 b_3 \cdots b_i}$$

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

Equilibrium of the BD model

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

If the serie $F(z) = \sum_{i \geqslant 1} iQ_i z^i$ 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

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

Remark

We may consider that $\lim_{i \to \infty} b_i / a_i = z_s$

Equilibrium of the BD model

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

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

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

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

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

Equilibrium of the BD model

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

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Remark

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

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

SBD model

SDE

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

CTMC

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

$$
\begin{cases}
q(C, R_i^+ C) & = & a_i C_1 (C_i - \delta_{1,i})\,, \\
q(C, R_i^- C) & = & b_i C_i\,,
\end{cases}
$$

$$
\begin{array}{rcl}
R_i^+ C & = & C - e_1 - e_i + e_{i+1} \\
R_i^- C & = & C + e_1 + e_{i-1} - e_i
\end{array}
$$

Equilibrium of the SBD model

SDE

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

CTMC

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

$$\begin{cases} q(C, R_i^+ C) &= a_i C_1 (C_i - \delta_{1,i})\,, \\ q(C, R_i^- C) &= b_i C_i\,, \end{cases}$$

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

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

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

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

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$$\begin{aligned} R_i^+ C &= C - e_1 - e_i + e_{i+1} \\ R_i^- C &= C + e_1 + e_{i-1} - e_i \end{aligned}$$

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, $n \to \infty$

SDE

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

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, $n \to \infty$

SDE

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

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

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

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

Rescaled SBD model, $n \to \infty$

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 $\|\sum_{j\geqslant i} c_j^n - \sum_{j\geqslant i} c_j\|$ (pathwise convergence)

Equilibrium of the rescaled SBD model, $n \to \infty$

SDE

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

CTMC

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

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

Theorem (Hingant, Y. (2019))

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

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

Equilibrium of the rescaled SBD model, $n \to \infty$

SDE

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

CTMC

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

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

Theorem (Hingant, Y. (2019))

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

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

Equilibrium of the rescaled SBD model, $n \to \infty$

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

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

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

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

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

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

Equilibrium of the rescaled SBD model, $n \to \infty$

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

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

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

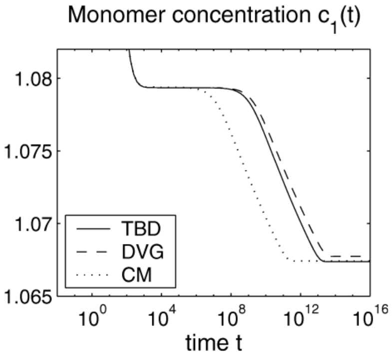
$$\lim_{n\to\infty} -\frac{\rho}{n} \ln(\Pi^n(c^n)) = H_{z_s}(c)$$

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

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



• 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 $z \searrow z_s$:

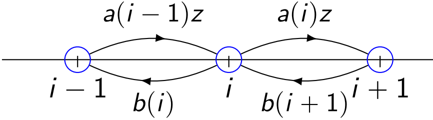
(*i*) For algebraically large time t, $c(t) - f$ is exponentially small

(*ii*) $\lim_{t\to\infty} c(t) - f(t)$ is not exponentially small

(*iii*) $\sum_{i>n^*} c_i(t) \leqslant \sum_{i>n^*} c_i(0) + J^* t$ with J^* exponentially small,

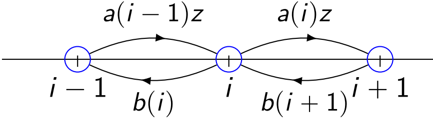
Metastability SBD for $c_1(t) \equiv z$

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 $c_1(t) \equiv z$

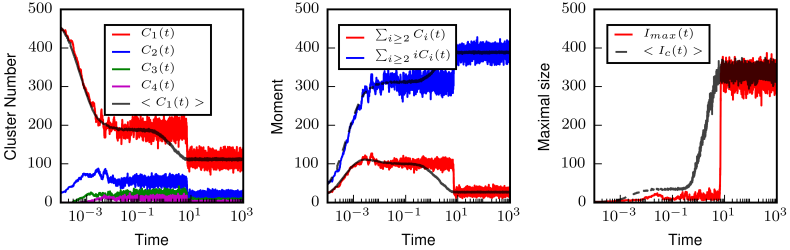
Taking the monomer number as a **constant** allows to view the SBD process as a superposition of (independent) Birth-Death process on $\mathbb{N}^*$.



- 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 for the SBD ?

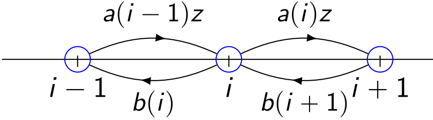
Numerical simulation "shows" metastability with sharp transition between "metastable state" and stationary state



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

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

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



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

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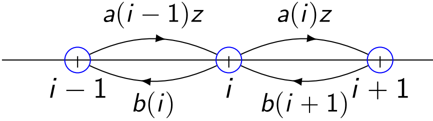


$$\tau_n := \inf\{t \geqslant 0, \sum_{i \geqslant n} C_i(t) > 0\}$$

There exists a quasi-stationary distribution,

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

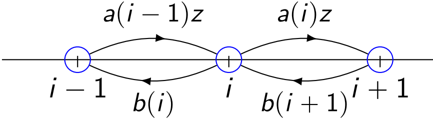
where Π_n^{qsd} is given by, for some (explicit) $J_n(z)$, $f_n(z)$

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

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

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

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



Theorem (Hingant, Y. 2021)

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

$$\|\mathbb{P}_{\Pi^{\rm in}}\left(C(t) \in \cdot \mid \tau_{n*} > t\right) - \Pi^{\rm qsd}_{n*}\| \leqslant K_* e^{(J_{n*} - \gamma_n)t},$$

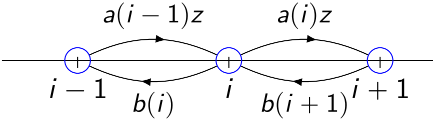
$$\mathbb{P}_{\Pi^{\rm in}}\left(\tau_n > t\right) \geqslant (1-\varepsilon)e^{-J_{n*}t},$$

where

- $K_*, 1/\gamma_{n*}$ *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 :



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

Method of proof :

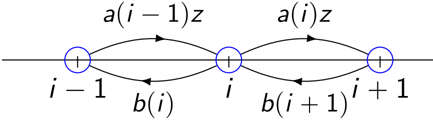
(i) Coupling arguments exploiting independence of particles

(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 :

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



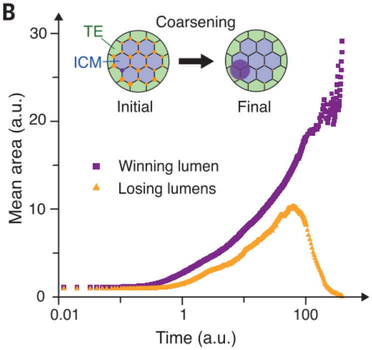
Remark

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

Coarsening dynamics

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 ?



Nucleation + Coarsening dynamics

We start from a rescaled model

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

$$\xrightleftharpoons[\frac{1}{\varepsilon} b_2^\varepsilon C_2^\varepsilon]{\frac{1}{\varepsilon} a_1^\varepsilon C_1^\varepsilon C_1^\varepsilon} C_2^\varepsilon$$

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

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

Nucleation + Coarsening dynamics

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*

$$\frac{d}{dt}\int_0^{+\infty} f(t,x)\varphi(x)\,dx = \mathbf{1}_{c_1(t)>\lim_{x\to 0}\frac{b(x)}{a(x)}} N(t)\varphi(0) + \int_0^{+\infty}\left[a(x)c_1(t) - b(x)\right]\varphi'(x)f(t,x)\,dx\,,$$

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

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

Nucleation + Coarsening dynamics

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

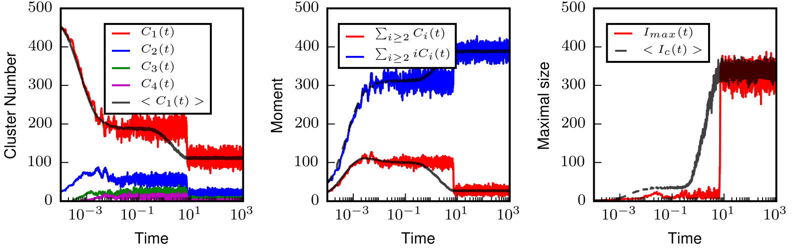
$N(t)$ is an explicit function of $c_1(t)$, and is given by a quasi steady-state approximation of $c_2^\varepsilon = f^\varepsilon(t, 2\varepsilon)$, given by the solution of

$$\begin{cases} 0 &= [J_{i-1}(c_1) - J_i(c_1)] \,, \quad i \geqslant 2 \,, \\ c_1(t) &= c_1 \,. \\ J_i(c_1) &= \overline{a}_i c_1 - \overline{b}_{(i+1)} \,. \end{cases}$$

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

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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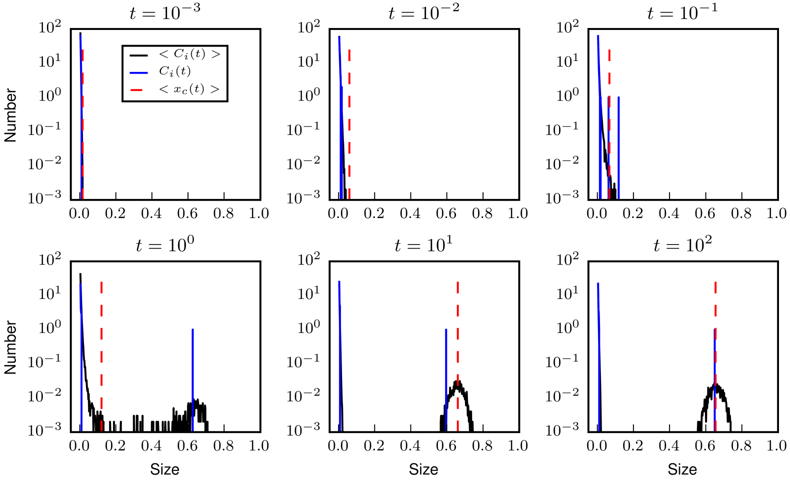
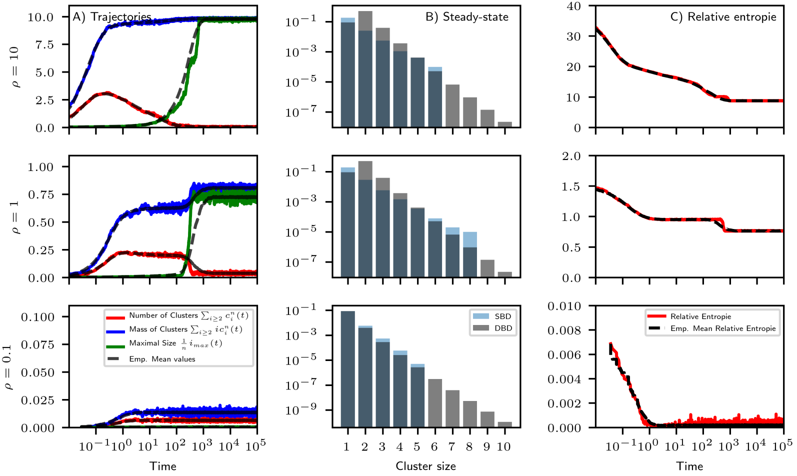


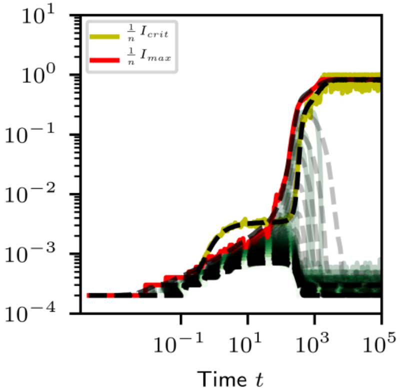
Metastability SBD

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



Coarsening dynamics : the "three eras" hypothesis

- Appearance of large clusters.
- Coarsening dynamics that leads to a single cluster, in a competition-like process.
- Steady-state convergence of small cluster-size.



Nucleation + Coarsening dynamics

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

(*i*) $J(x,t) = a x^r c_1(t) - bx$, $r < 1$: $f \to \delta_0$ (nucleation keeps creating "infinitesimal" clusters, no coarsening)

(*ii*) $J(x,t) = (a c_1(t) - b) x^r$, $r < 1$: $f \to f_\infty$, $c_1(t) \to \frac{b}{a}$ many large clusters persist, no coarsening)

- case (*i*)
- case (*ii*)

Becker-Döring model

Reversible one-step coagulation-fragmentation

$$C_i + C_1 \xrightarrow{a_i} C_{i+1}$$
$$C_i \xrightarrow{b_i} C_{i-1} + C_1$$

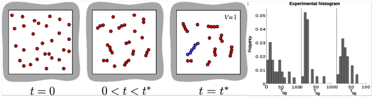
Determinist

$$\frac{d}{dt} c_i = J_{i-1} - J_i \,, i \geq 2 \,,$$
$$J_i = a_i c_1 c_i - b_{i+1} c_{i+1}$$

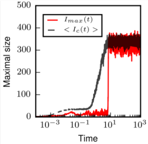
Stochastic

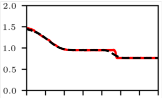
$$C \to C + \Delta_i, \qquad a_i C_1 C_i$$
$$C \to C - \Delta_i, \qquad b_{i+1} C_{i+1}$$

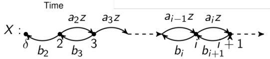
Nucleation time



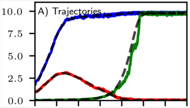
Equilibrium / Metastability

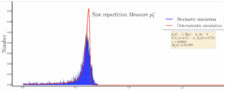






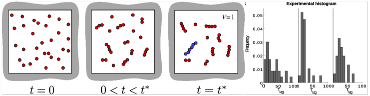
limit theorem SBD/BD/LS



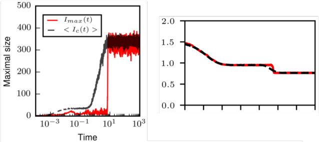


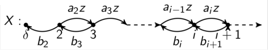
Becker-Döring model

Nucleation time



Equilibrium / Metastability





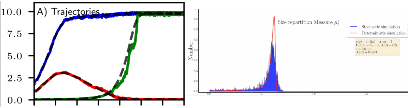
Determinist

$$\frac{d}{dt} c_i = J_{i-1} - J_i \,, i \geq 2 \,,$$
$$J_i = a_i c_1 c_i - b_{i+1} c_{i+1}$$

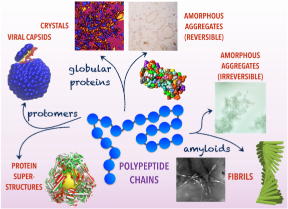
Stochastic

$$C \to C + \Delta_i, \qquad a_i C_1 C_i$$
$$C \to C - \Delta_i, \qquad b_{i+1} C_{i+1}$$

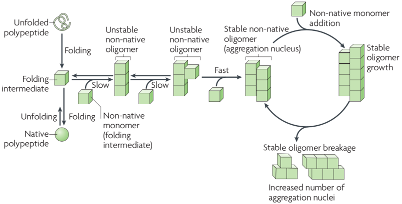
limit theorem SBD/BD/LS



Protein aggregation diseases : Working hypothesis



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

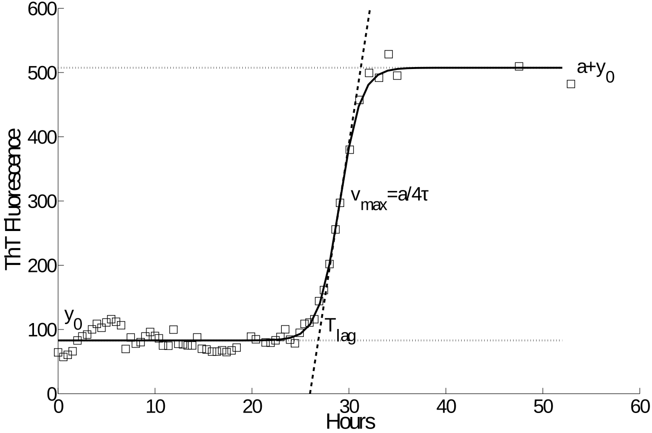


Brundin et al., *Prion-like transmission of protein aggregates in neurodegenerative diseases*, Nat. Rev. Mol. Cell Biol. (2010)

The aggregation dynamic is linked to the disease 'onset'

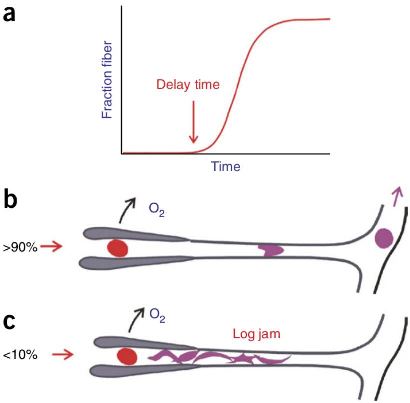
Hence studying quantitatively the properties of the aggregation dynamic is relevant to understand some mechanisms of the Proteopathies. This can be done by reproducing the aggregation process *in vitro*.

Does a Mathematical model reproduce the data ?



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

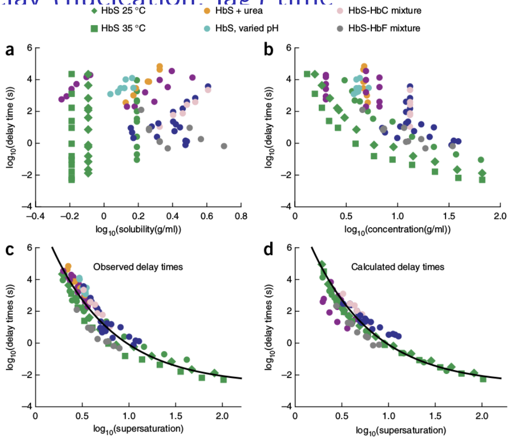
Modeling the kinetics of Hemoglobin fiber



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

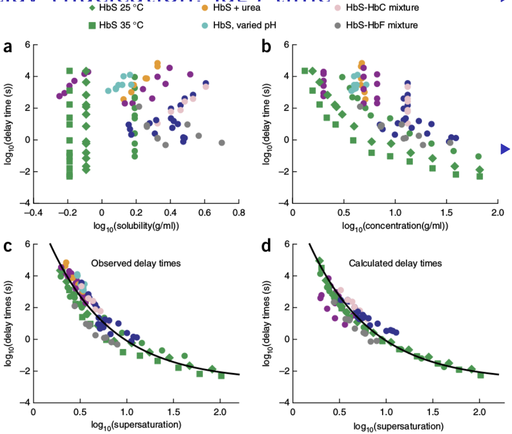
Cellmer et al. *Universality of supersaturation in protein-fiber formation* Nat. Struct. Mol. Biol. (2016)

Delay (nucleation, lag) time



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

Delay (nucleation, lag) time



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

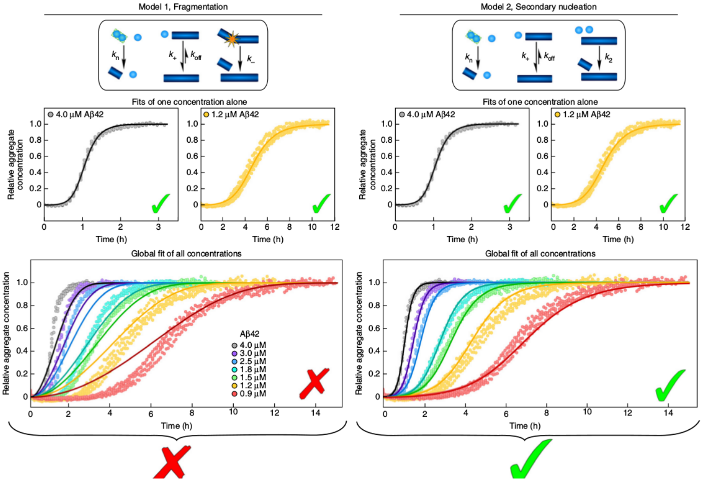
- Qualitative and quantitative explanation of lag time before fiber formation *(in-vitro)*
- Double-nucleation model ($P = \sum_{i \geqslant i_0} C_i$, $Z = \sum_{i \geqslant i_0} iC_i$) :

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

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

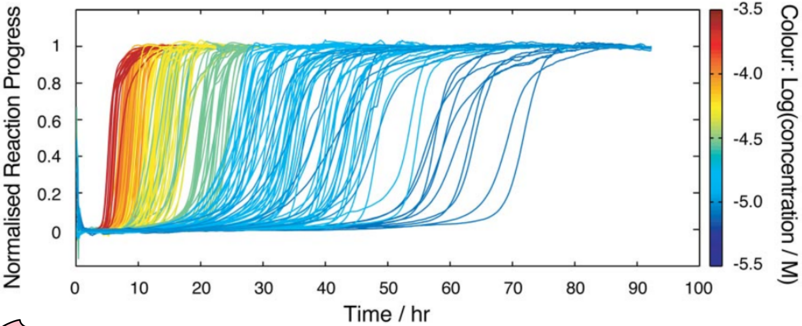
Bishop et Ferrone *Kinetics of nucleation-controlled polymerization* Biophys. J. (1984)

Hypotheses testing through global fitting of experiment



Meisl et al. *Molecular mechanisms of protein aggregation from global fitting of kinetic models* Nature Protocols (2016)

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

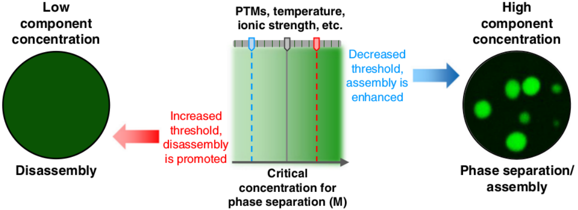
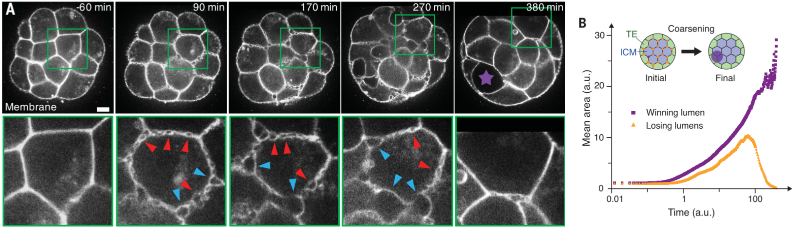


Fig. 1 Macromolecular condensation mediates the formation of membrane-less organelles. Membrane-less organelles are dynamic structures formed via a polymer-condensation-like, concentration-dependent phase separation mechanism. The critical concentration threshold (*grey line*) for phase separation can be tuned within a range of concentrations (*shaded green box*) through physico-chemical alterations to the system (*i.e.,* posttranslational modifications to domains and/or motifs that alter the affinity of their interactions, changes in temperature, altered ionic strength, etc.). These changes can drive phase separation and assembly of membrane-less organelles, or their disassembly

Mitrea 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)