Stochastic Protein Assembly Models

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Based on joint works with

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Introduction

Some History: A Disease named "Scrapie"

- An infectious disease of sheep
- Infecting material resistant to
  high temperatures, radiations,
  $\Rightarrow$ not a bacteria, virus, ...no DNA
  (Alper et al. 1967)

- Pattison and Jones (1967), Griffith (1967)

- Prusiner (1982) Identification of
  - Prion protein PrP^{C}
  - Anomalous state of protein PrP^{Sc}
    as the infectious agent of disease

Nobel Prize (1997)

Neuro-Degenerative Diseases

A related disease:
Bovine spongiform encephalopathy (mad cow)

- **Epidemic phenomenon (UK) 1990's**
- **Infectious**
- **Long/Variable incubation period**
  between several months and several years

A (Partially Hypothetical) Description

In neural cells,

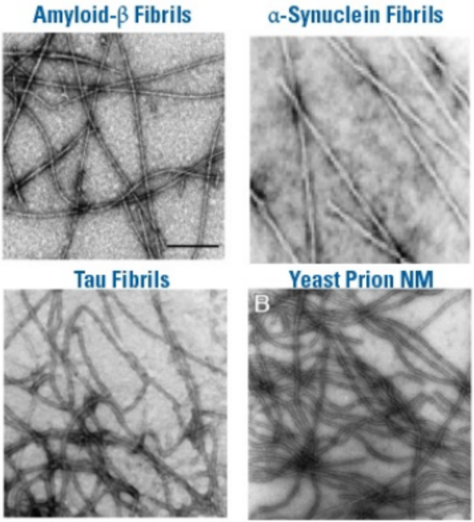
after some time, for some reason

some proteins tend to aggregate

- **long fibrils (polymers)**

$\Rightarrow$ **deterioration of neural cells**

Fibrils



Amyloid-β Fibrils
α-Synuclein Fibrils
Tau Fibrils
Yeast Prion NM
B

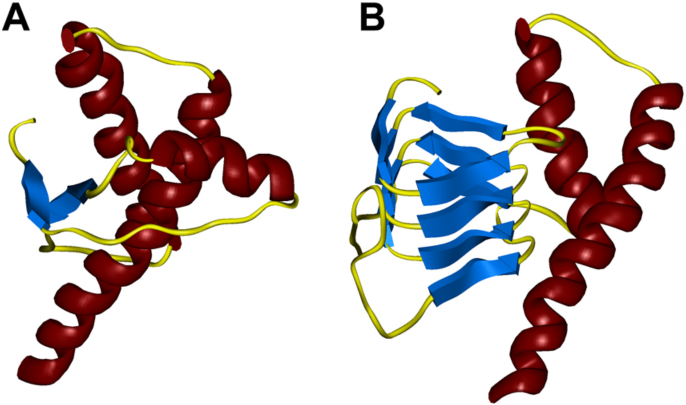
A quite Frequent Scheme

- Creutzfeldt-Jakob Disease
- Huntington Disease
- Alzheimer Disease
- Diabetes type II
- ...

Polymerization: A Universal Phenomenon

- **Cytoskeleton: Polymerization of Actin and Tubulin**
- **Polymerization of Sickle Hemoglobin**
- **. . .**

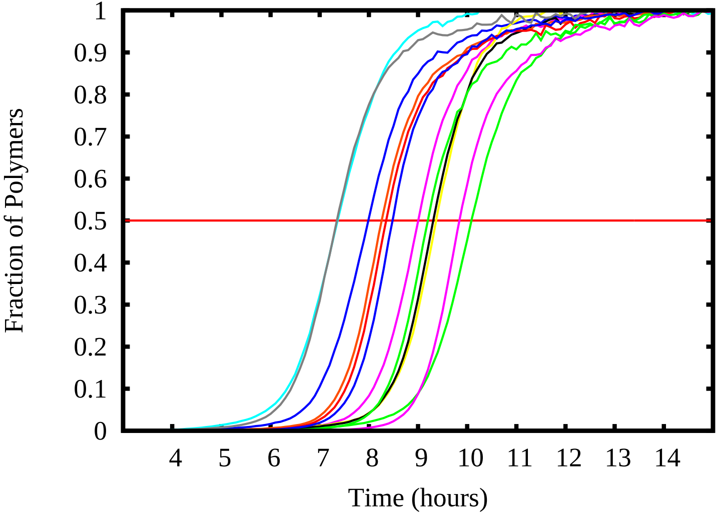
Prion Protein



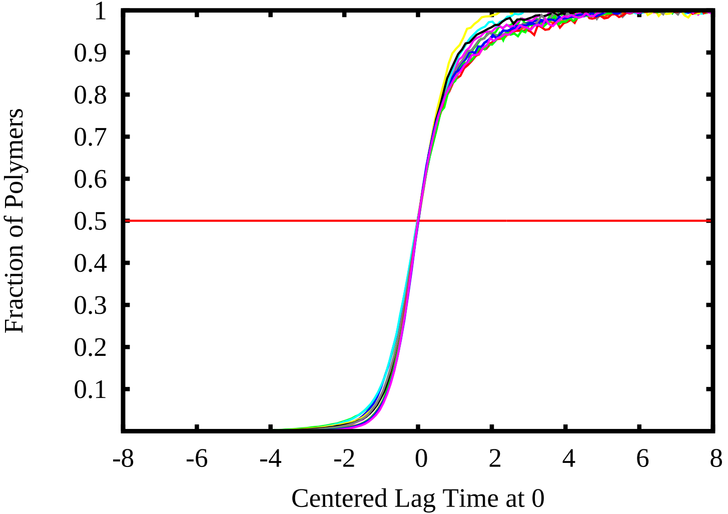
- **A: Normal State, PrP^{C}**
- **B: Misfolded State, PrP^{Sc}**

Experiments

12 Experiments (Xue et al. 2014)



12 Experiments with centered lag time



Goals of Mathematical Models

(try to) Explain

- **Sharp transition of polymerization**
- **High variability of the instant of transition**

Mathematical Literature

HUGE literature in biology, physics

- **Sets of ODEs Oosawa (1960s),**

- **Becker-Döring equations**
  Fragmentation-Coagulation Models.

- **Stochastic Models, Penrose (1986), Ferrone (2006), Hingant et Yvinec (2016)**

History: Pujo-Menjouet HDR (2016)

Mathematical Models (I)

A Simple Mathematical Model

Two Basic Chemical Reactions

- $\mathcal{X}_1$ **monomers (proteins)**
- $\mathcal{X}_2$ **polymers**

$$\mathcal{X}_1 + \mathcal{X}_1 \xrightarrow{\alpha} 2\mathcal{X}_2 \qquad \text{Ignition}$$

$$\mathcal{X}_1 + \mathcal{X}_2 \xrightarrow{\beta} 2\mathcal{X}_2 \qquad \text{Catalytic Reaction}$$

Assumption $\alpha \ll \beta$

Two Basic Chemical Reactions

Simplifications

- **Only two chemical species**

  monomers and polymers

  no dimers trimers, . . .

- **Non-Reversible System** $\mathcal{X}_2 \not\to \mathcal{X}_1$

Some Notations

- N Volume
- $X_1^N(t)$ nb of monomers
- $X_2^N(0)=0$, $X_1^N(0)=M_N \sim mN$
- Lag time, for $\delta \in (0,1)$

$$T^N(\delta) = \inf\left\{t : X_2^N(t) \geq \delta M_N\right\}$$

Stochastic Model: Transition RatesFirst Order

Law of Mass Action: Nb of monomers

$$x \mapsto \begin{cases} x-2 & \text{at rate } \dfrac{\alpha}{N}\dfrac{x(x-1)}{2N} \\ x-1 & \text{“} \quad \dfrac{\beta}{N}\dfrac{x(M_N-x)}{N} \end{cases}$$

Just after time $t=0$, $x = mN - O(1)$

$$x \mapsto \begin{cases} x-2 & \text{at rate } \alpha\dfrac{m^2}{2} \\ x-1 & \text{“} \quad O\left(\dfrac{1}{N}\right) \end{cases}$$

Fluctuations

Polymerization occurs on linear time scale
$t \mapsto Nt$

Proposition. (Central Limit Theorem)
If $X_1^N(0) = mN + o(\sqrt{N})$

$$\lim_{N \to +\infty} \left(\frac{X_1^N(Nt) - Nx_1(t)}{\sqrt{N}} \right) = (U(t))$$

with $\dot{x}_1 = -\alpha x_1^2 - \beta x_1 (m - x_1)$ and $x_1(0) = m$

$$\mathrm{dU(t)} = \sigma(\mathrm{t})\, \mathrm{dW(t)} - h(t) U(t) \mathrm{dt}$$

Fluctuations

$$X_1^N(Nt) = Nx_1(t) + \sqrt{N}U(t),$$

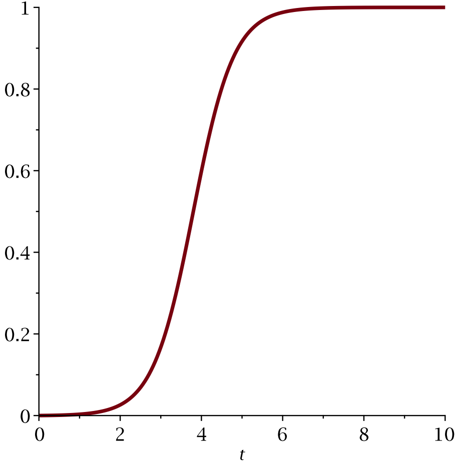
with

$$\mathrm{d}U(t) = \frac{\beta\sqrt{\alpha}\sqrt{e^{\beta mt}+1}}{\alpha e^{\beta mt}+\beta-\alpha}\,\mathrm{d}W(t) - \beta m\frac{e^{\beta mt}+1-\beta/\alpha}{e^{\beta mt}-1+\beta/\alpha}U(t)\mathrm{d}t,$$

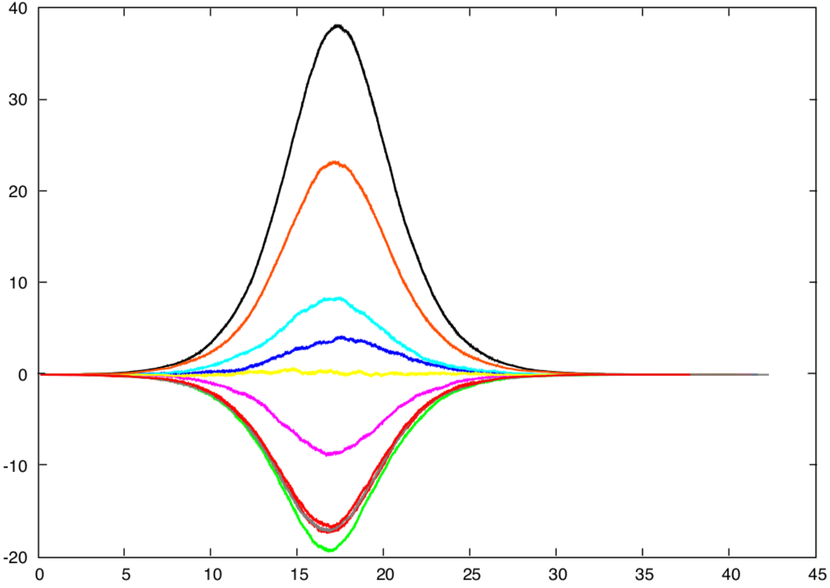
$(W(t))$ **standard Brownian motion.**

First Order

α=0.001 β=2 and m=1



Fluctuations



Fluctuations of Lag Time

If t_δ with $x_1(t_\delta)=\delta$ $\dot{x}_1=-\alpha x_1^2-\beta x_1(m-x_1)$

Fluctuations

$$\lim_{N\to+\infty}\frac{T^N(\delta)-Nt_\delta}{\sqrt{N}}=\frac{U(t_\delta)}{m[\alpha(1-\delta)^2+\beta\delta(1-\delta)]}$$

when $\alpha \ll \beta$

$$\mathrm{Var}\left(T^N(1/2)\right)\sim\frac{3}{2m^2M_N\alpha\beta}$$

Simple Model with a Conformation Step

Extended Model with Conformation

- $\mathcal{X}_0$ monomers
- $\mathcal{X}_1$ misfolded monomers
- $\mathcal{X}_2$ polymers

Only misfolded monomers polymerize

$$\mathcal{X}_0 \underset{\gamma^*}{\overset{\gamma}{\rightleftarrows}} \mathcal{X}_1 \qquad \begin{cases} \mathcal{X}_1 + \mathcal{X}_1 \xrightarrow{\alpha} 2\mathcal{X}_2 \\ \mathcal{X}_1 + \mathcal{X}_2 \xrightarrow{\beta} 2\mathcal{X}_2 \end{cases}$$

with $\gamma \ll \gamma^*$

Extended Model with Conformation

- $(X_0^N(t))$ nb of monomers
- $(X_1^N(t))$ nb of misfolded monomers
- $(X_2^N(t))$ nb of polymers

Conservation of mass

$$X_0^N(t) + X_1^N(t) + X_2^N(t) = M_N$$

Two Processes

Folding/Misfolding Process

$(X_0^N(t), X_1^N(t)) = x = (x_0, x_1) \in \mathbb{N}^2$

$$x \mapsto \begin{cases} x+(1,-1) \text{ at rate } \gamma^* x_1 \\ x+(-1,1) \qquad\qquad \gamma\, x_0 \end{cases}$$

An Ehrenfest Urn Process

if $(x_0, x_1) \sim (y_0, y_1) N$

Transition Rates of the order of N

Two Processes

Polymerization Process

$(X_1^N(t), X_2^N(t)) = (x_1, x_2) \in \mathbb{N}^2$

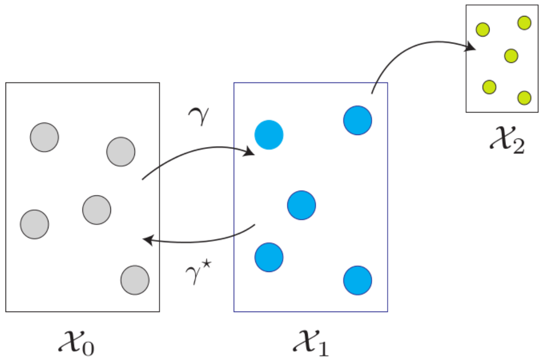
$$x \mapsto \begin{cases} x+(-2,2) \text{ at rate } \dfrac{\alpha}{N} \dfrac{x_1(x_1-1)}{2N} \\ x+(-1,1) \qquad \dfrac{\beta}{N} x_1 \dfrac{x_2}{N} \end{cases}$$

Ehrenfest Urn is "losing" balls

if $(x_1, x_2) \sim (y_1, y_2)N$

Transition Rates $O(1)$

A Leaking Ehrenfest Urn



Two Processes

- **Polymerization** $t \mapsto X_2^N(t)$ **Slow Process**
- **Ehrenfest with** $M_N - X_2^N(t)$ **balls**

  Fast Process

An Analytic Picture

The associated operator $\mathcal{G}_N$ is

$$\mathcal{G}_N(f)(x) = \gamma(M_N - x_1 - x_2)\nabla_{1,0}(f)(x) + \gamma^* x_1 \nabla_{-1,0}(f)(x) + \frac{\alpha}{N}\frac{x_1(x_1-1)}{2N}\nabla_{-2,2}(f)(x) + \frac{\beta}{N}x_1\frac{x_2}{N}\nabla_{-1,1}(f)(x),$$

$x = (x_1, x_2)$, with $\nabla_a(f)(x) = (f(x+a) - f(x))$

Stochastic Averaging/Homogenization: Literature

Singular Perturbation Theory

Probability

- **From Khasminskii (1968)**
  to Freidlin, Wentzell (1979)
- **Papanicolaou, Stroock, Varadhan (1977)**
- **Kurtz (1992) jump processes**

Stochastic Averaging Principle

A Rough Picture

If $X_0^N(t)+X_1^N(Nt)\sim b(t)N$

- If Local Equilibrium of Ehrenfest
  $\gamma^* X_1^N \sim \gamma X_0^N$

$$\frac{1}{N}\left(X_0^N(Nt), X_1^N(Nt)\right)\sim b(t)\,(1-r, r)\,,$$

$$r=\frac{\gamma}{\gamma+\gamma^*}$$

- Tech. Pb.
  Size of State Space of Fast Process $\nearrow +\infty$

Occupation Measures

$$\langle \mu_N, g\rangle = \int_0^{+\infty} g\left(\frac{X_0^N(Nu)}{N}, \frac{X_1^N(Nu)}{N}, u\right) \mathrm{du}$$

μ_N random measure on $[0,m]^2 \times \mathbb{R}_+$

- (μ_N) is tight If μ_∞ is a limit

$$\langle \mu_\infty, g\rangle = \int g(x,y,u)\pi_u(\mathrm{dx},\mathrm{dy})\mathrm{du}$$

π_u random Radon measure on $[0,m]^2$

Proof: Some technicalities to get convenient measurability properties...

Occupation Measures

$$\langle \mu_\infty, g \rangle = \int g(x, y, u)\pi_u(\mathrm{dx}, \mathrm{dy})\mathrm{du}$$

Support of $\pi_u \subset \{(\gamma x, \gamma^* x), x \geq 0\}$**?**

Support of $(\pi_{\mathbf{u}})$

Stochastic Calculus: if f is $\mathcal{C}^1 \Rightarrow$

$$\lim_{N\to+\infty}\int_0^T\int\left(\gamma^*\frac{X_1^N(Nu)}{N}-\gamma\frac{X_0^N(Nu)}{N}\right)\left(\frac{\partial}{\partial x}-\frac{\partial}{\partial y}\right)f\left(\frac{X_0^N(Nu)}{N},\frac{X_0^N(Nu)}{N}\right)\mathrm{du}=0$$

$$\int_0^T\int\left(\gamma^*\frac{X_1^N(Nu)}{N}-\gamma\frac{X_0^N(Nu)}{N}\right)\left(\frac{\partial}{\partial x}-\frac{\partial}{\partial y}\right)f\left(\frac{X_0^N(Nu)}{N},\frac{X_0^N(Nu)}{N}\right)\mathrm{du}$$

$$=\int_0^T\int(\gamma^* y-\gamma x)\left(\frac{\partial f}{\partial x}-\frac{\partial f}{\partial y}\right)(x,y)\mu_N(\mathrm{dx},\mathrm{dy},\mathrm{du})$$

Convergence

The variables

$$\left(\mu_N, \left(\overline{X}_2^N(t)\right)\right) = \left(\mu_N, \left(\frac{X_2^N(Nt)}{N}\right)\right)$$

are tight.

Convergence

$(\mu_\infty, (x_2(t))$ a limit of $(\mu_N, (\overline{X}_2^N(t)))$

$$\left(\int_0^t g(x,y)\mu_\infty(\mathrm{dx},\mathrm{dy})\,\mathrm{du}\right) \stackrel{\text{dist.}}{=} \left(\int_0^t g\left((m - x_2(u))(1-r, r)\right)\,\mathrm{du}\right)$$

with $r = \gamma/(\gamma^* + \gamma)$

Proof: $X_0^N + X_1^N = M_N - X_2^N$

First Order Convergence

$$\lim_{N\to+\infty}\left(\frac{X_2^N(Nt)}{N}\right) = (x_2(t))$$

$(x_2(t))$ solution of

$$\dot{x} = -\alpha r^2 x^2 - \beta r x(m-x), \quad r = \frac{\gamma}{\gamma^* + \gamma}$$

Same as Simple Model $\alpha \mapsto \alpha r^2$ and $\beta \mapsto \beta r$

Second Order Convergence

$$\lim_{N\to+\infty}\left(\frac{X_2^N(Nt)-Nx_2(t)}{\sqrt{N}}\right)=(U(t))$$

$$\mathrm{dU(t)}=\sqrt{\sigma(\mathrm{t})}\mathrm{dB(t)}+\mathrm{h(t)U(t)\,dt},$$

$$\begin{cases}\sigma(t)=2\alpha r^2(m-x_2(t))^2+\beta r(m-x_2(t))x_2(t)\\ h(t)=r(\beta-2\alpha r)(m-x_2(t))-\beta r x_2(t).\end{cases}$$

Second Order Convergence: Proof

First Order

$$\lim_{N\to+\infty}\int_0^t\int_{\mathbb{R}_+^2}(\gamma^* y-\gamma x)\left(\frac{\partial f}{\partial x}-\frac{\partial f}{\partial y}\right)(x,y)\mu_N(\mathrm{dx},\mathrm{dy},\mathrm{du})=0$$

Extension for Second Order

$$\lim_{N\to+\infty}\sqrt{N}\int_0^t\int_{\mathbb{R}_+^2}(\gamma^* y-\gamma x)\left(\frac{\partial f}{\partial x}-\frac{\partial f}{\partial y}\right)(x,y)\mu_N(\mathrm{dx},\mathrm{dy},\mathrm{du})=0$$

Fluctuations of Lag Time

when $\alpha \ll \beta$

$$\mathrm{Var}\left(T^N(1/2)\right) \sim \frac{3}{2r^3 m^2 M_N \alpha\beta}$$

with $r = \gamma/(\gamma^* + \gamma)$

Experiments

Estimation of Parameters with Data

m	α	β
12.3	$6.18 \cdot 10^{-7}$	$5.07 \cdot 10^{4}$
14.6	$2.81 \cdot 10^{-6}$	$4.54 \cdot 10^{4}$
16.7	$1.59 \cdot 10^{-4}$	$3.75 \cdot 10^{4}$
17.0	$1.88 \cdot 10^{-3}$	$3.70 \cdot 10^{4}$
29.5	$1.40 \cdot 10^{-5}$	$3.34 \cdot 10^{4}$
30.2	$2.89 \cdot 10^{-2}$	$2.96 \cdot 10^{4}$
30.5	$9.57 \cdot 10^{-8}$	$4.16 \cdot 10^{4}$
43.7	$7.99 \cdot 10^{-3}$	$2.35 \cdot 10^{4}$
48.5	$1.68 \cdot 10^{-2}$	$2.01 \cdot 10^{4}$
61.0	$2.61 \cdot 10^{-2}$	$2.04 \cdot 10^{4}$
61.0	$2.22 \cdot 10^{-5}$	$2.56 \cdot 10^{4}$
84.1	$4.53 \cdot 10^{-4}$	$2.24 \cdot 10^{4}$
102.2	$1.52 \cdot 10^{-3}$	$1.88 \cdot 10^{4}$
122	$1.33 \cdot 10^{-4}$	$1.75 \cdot 10^{4}$
123.5	$2.13 \cdot 10^{-4}$	$1.79 \cdot 10^{4}$
142.1	$2.58 \cdot 10^{-4}$	$1.74 \cdot 10^{4}$
243.5	$1.75 \cdot 10^{-3}$	$1.09 \cdot 10^{4}$

Standard Deviation

m	Exp.	Pred.
12.3	7.95	$5.34 \cdot 10^{-2}$
14.6	2.98	$2.05 \cdot 10^{-2}$
16.7	2.68	$2.45 \cdot 10^{-3}$
17.0	1.52	$6.98 \cdot 10^{-4}$
29.5	2.13	$3.7 \cdot 10^{-3}$
30.2	2.57	$8.40 \cdot 10^{-5}$
30.5	1.53	$3.84 \cdot 10^{-2}$
43.7	2.10	$1.03 \cdot 10^{-4}$
48.5	1.56	$6.55 \cdot 10^{-5}$
61.0	1.03	$3.71 \cdot 10^{-5}$
61.0	2.55	$1.14 \cdot 10^{-3}$
84.1	1.59	$1.66 \cdot 10^{-4}$
102.2	0.62	$7.39 \cdot 10^{-5}$
122	0.90	$1.98 \cdot 10^{-4}$
123.5	0.90	$1.52 \cdot 10^{-4}$
142.1	1.11	$1.13 \cdot 10^{-4}$
243.5	0.60	$2.46 \cdot 10^{-5}$

Discussion

Fluctuations underestimated

With respect to concentration values

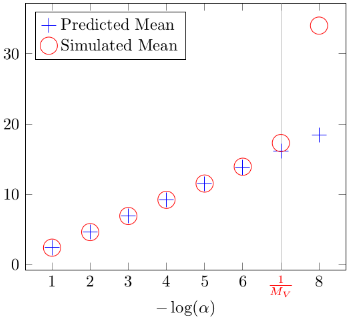
- Estimation of catalytic parameter β robust
- Ignition parameter α varies between 10^{-3} and 10^{-8}

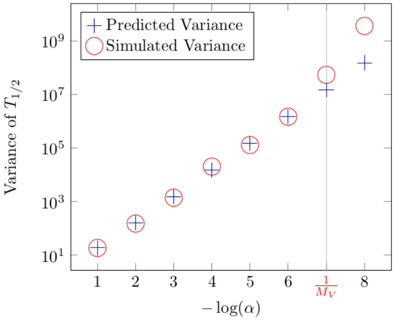
Discussion

An Additional Problem

- Experiments: $M_N \sim 10^{15}$ and $N \sim 10^{15}$
  if $\alpha \sim 10^{-8}$ then $\alpha \sim N^{-\eta}$ with $\eta = 0.53$
- CV results do not really apply

Comparison for $M_N \sim 10^7$





Conclusions

Simple Model

- Order of magnitudes of fluctuations
  correct for "small" volumes N
- Does not work for "normal" volumes

Central Limit Picture

$$T_N(\delta) = \mathbb{E}(T_N(\delta)) + G\sqrt{\mathbb{E}(T_N(\delta))}$$

does not allow really "large" fluctuations

A Second Mathematical Model

Polymers of Multiple Sizes

- $\mathcal{X}_i$: Polymers of size $i \geq 1$
- two types of chemical reactions

$$\mathcal{X}_1 + \mathcal{X}_i \xrightarrow{k_i^+} \mathcal{X}_{i+1}$$

$$\mathcal{X}_i \xrightarrow{k_i^-} \sum_{j=1}^{i-1} a_k^i \mathcal{X}_k$$

A Special Case: Becker-Döring (1935)

$$\mathcal{X}_1 + \mathcal{X}_i \xrightarrow{k_i^+} \mathcal{X}_{i+1}$$

$$\mathcal{X}_i \xrightarrow{k_i^-} \mathcal{X}_{i-1} + \mathcal{X}_1$$

A Dynamical System Description

Becker-Döring Equations (1935)

A infinite set of ODEs: $(c_i(t))$ solution of

$$\dot{c}_i(t) = J_{i-1}(t) - J_i(t)$$

with $J_i(t) = \lambda_{i+1} c_1(t) c_i(t) - \beta_{i+1} c_{i+1}(t)$ and

$$c_1(t) + 2c_2(t) + \cdots + ic_i(t) + \cdots = 1.$$

A Convergence Result

stochastic context:

$X_i^N(t)$, nb of polymers of size i at t

If $X_1^N(0)=M_N\sim mN$ and $X_1^N(0)=0$

$$\lim_{N\to+\infty}\left(\frac{X_i^N(t)}{N}\right)=(c_i(t))$$

$(c_i(t))$ Becker-Döring ODEs's (Jeon 1998).

Second Order fluctuations (Sun, 2017)

Becker-Döring as a Model

Similar Behavior as our simple model

- An asymptotic dynamical system

  infinite dimensional state space

- "Small" fluctuations associated with a CLT

As before, a lack of "variability"

Source of Variability/Randomness

Brownian Fluctuations do not seem to explain the observed variability.

randomness due to
the occurrence of a set of rare events ?

Poisson processes
to describe the asymptotic behavior ?

Biological Literature

Two phenomena

- **Nucleation Phenomenon:** $\exists n_c \geq 2$
  a polymer of size i is
  - **very unstable if $i < n_c$**
  - **(quite) stable if $i \geq n_c$**

  n_c nucleus size

- **Fragmentation speeds up polymerization**

  A polymer of "large" size may break into two stable polymers

A Stochastic Model: Growth

$X_i^N(t)$: nb of polymers of size i at t.

- Growth: $\mathcal{X}_1 + \mathcal{X}_i \rightarrow \mathcal{X}_{i+1}$
  If $x = (x_i)$,

$$\begin{cases} x_i \rightarrow x_i - 1 \\ x_1 \rightarrow x_1 - 1 \\ x_{i+1} \rightarrow x_{i+1} + 1 \end{cases} \quad \text{at rate } \lambda_i x_1 \frac{x_i}{N}$$

A Stochastic Model: Nucleation

μ_i^N : fragmentation rate of a polymer of size i

Reaction $x_i \to x_i - 1$ occurs at rate $\delta_i^N x_i$ with

$$\delta_i^N = \begin{cases} \Phi(N)\mu_i & \text{if } i < n_c, \\ \mu_i & \text{if } i \geq n_c, \end{cases}$$

with $(\Phi(N)) \nearrow +\infty$.

Example $\Phi(N) = N^{1/3}$

A Stochastic Model: Fragmentation

How a polymer of size i is fragmented

$\Rightarrow$ n_k **polymers of size** $k \in \{1, \ldots, i-1\}$

$$\sum_{k=1}^{i-1} k n_k = i.$$

with probability $\nu_i(n_1, \ldots, n_{i-1})$

ν_i : **dislocation measure**

A Stochastic Model

Assumptions on dislocation measures $(\nu_i, i \geq 2)$

- $\exists C_0 > 0$ and K such that, for $i \geq K$,

$$\nu_i \left(y=(y_k) : \sum_{i<n_c} y_i \leq C_0 \right) = 1,$$

- $$\liminf_{i \to +\infty} \nu_i \left(y=(y_k) : \sum_{k \geq n_c} y_k \geq 2 \right) > 0.$$

A Continuous Stochastic Model for polymers with multiple sizes

Lifshitz-Slyozov model

Set of sizes replaced by $\mathbb{R}_+$

Dynamic: PDE formulation

Calvo, Doumic, Perthame, (2018)
Hingant et Yvinec (2016)

A Stochastic Model: Initial state

- $X_1^N(0) = N$
- $X_i^N(0) = 0$ for $i \geq 2$

Lag Time, for $\delta \in (0, 1)$,

$$T_N(\delta) = \inf \left\{ t \geq 0 : \sum_{k \geq n_c} X_k^N(t) \geq \delta M_N \right\}$$

How polymerization occurs in two steps

A rough picture

1. **Nucleation phase:**
   A polymer of size n_c is created.

2. **Growth: With positive probability a polymer of size n_c generates a large nb, $\sim \delta N$, $\delta > 0$, of stable polymers.**

How polymerization occurs in two steps

Orders of magnitude

of the duration of the steps

1. Nucleation:

$$\Psi(N) \stackrel{\text{def.}}{=} \frac{1}{N}\Phi(N)^{n_c-2}$$

2. Successful Growth: $O(\log N)$.

Growth: A Branching Process

Starting with a polymer of size n_c with positive proba:

- **its size grows to $n_c + K_0$**
- **A polymer of size $n_c + K_0$ gives birth to at least two polymers of size $\geq n_c$**

  $\Rightarrow L^N_{n_c}(t)$ nb of polymers of size $\geq n_c$ lower-bounded by super-critical branching process

  $\Rightarrow L^N_{n_c}(t)$ grows at least exp. fast with positive proba

Nucleation Time

Theorem.

If $T^N = \inf\{t>0 : X_{n_c}^N(t) = 1\}$ then

$$\lim_{N\to+\infty} \frac{N}{\Phi(N)^{n_c-2}} T^N = E_\rho,$$

where $E_{\overline{\rho}}$ is an exp. r.v. with mean $1/\rho$

$$\rho \stackrel{\text{def.}}{=} \lambda_1 \prod_{k=2}^{n_c-1} \frac{\lambda_k}{\mu_k},$$

Does not depend on dislocation measures (ν_i) !

Nucleation Time

for $3 \leq n_0 \leq k < n_c$ the sequence of instants

$$\left\{ t : \sum_{j \geq k} X_j(t-) = 0, X_k(t) = 1 \right\}$$

is asymptotically a Poisson process with parameter

$$\rho \frac{N}{\Phi(N)^{k-2}}$$

Nucleation Time

$$T^N \sim \frac{\Phi(N)^{n_c-2}}{N} E_\rho,$$

T^N exp. with mean $\Phi(N)^{n_c-2}/(N\rho)$

A Large Variability

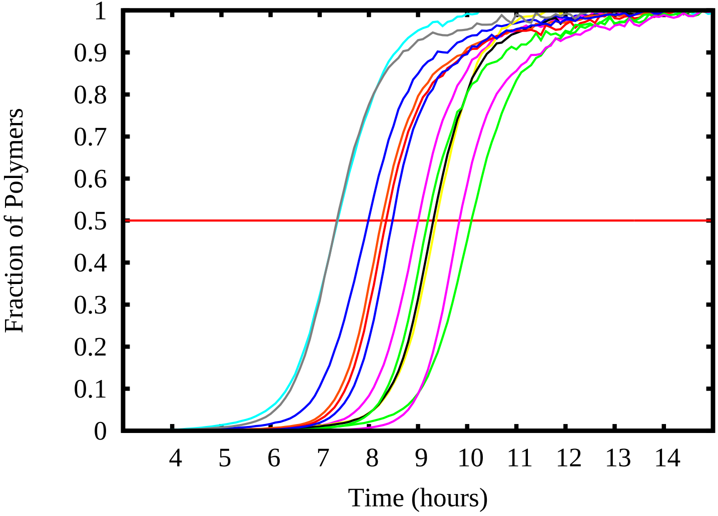
$$\boxed{\sqrt{\mathrm{Var}(T_N(\delta))} \sim \mathbb{E}(T_N(\delta))}$$

Conclusion

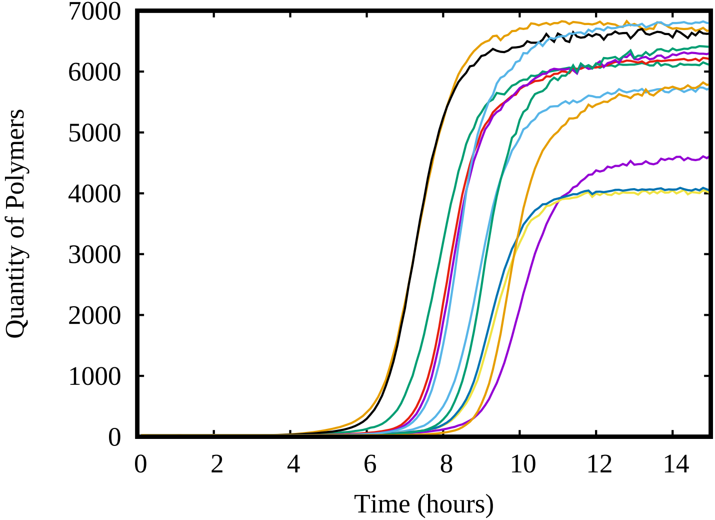
Future work

- Back to data: how to estimate n_c, Φ, ρ ?
- Levels of Polymerization

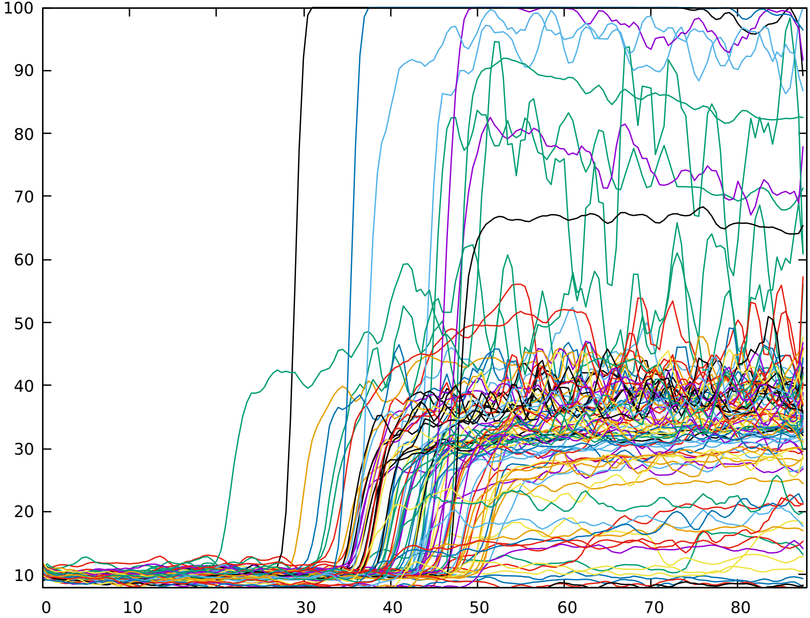
12 Experiments (Xue et al. 2014)



Experiments without renormalization



Experiments (Rezaei et al. INRA)



Conclusion: Future work

- **Levels of Polymerization: Variable level**
- **Equilibrium of Polymerization**
- **Multiple Species of Polymers**

References

- S. Eugène, W. Xue, P. Robert, and M. Doumic,
  "Insights into the variability of nucleated amyloid polymerization by a minimalistic model of stochastic protein assembly,"
  Journal of Chemical Physics, 2016

- M. Doumic, S. Eugène, and P. Robert,
  Asymptotics of Stochastic Protein Assembly Models,
  SIAM Journal on Applied Mathematics, 2016.

- P. Robert and W. Sun,
  "On the Asymptotic Distribution of Nucleation Times of Polymerization Processes",
  Preprint, 2018.

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