Stochastic Model of Prion's Disease: Nucleation-Polymerisation Model Part II

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Modelling each reaction

- Precise reactions step and parameters
- Deterministic rate equations
- Stochastic algorithm

Further...

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- n: is the size of the nucleus.

Nucleation

$$M \underset{c_0}{\overset{1}{\rightleftharpoons}} f_1 \text{ (spontaneous conformation)} \quad (1)$$

$$f_1 + f_1 \underset{\frac{c_f}{d_1}}{\overset{c_f}{\rightleftharpoons}} f_2 \text{ (dimerization)} \quad (2)$$

$$\vdots$$

$$f_{k-1} + f_1 \underset{\frac{c_f}{d_1}}{\overset{c_f}{\rightleftharpoons}} f_k \text{ ((k)-mer formation)} \quad (3)$$

$$\vdots$$

$$f_{n-1} + f_1 \xrightarrow{c_f} u_n \text{ (nucleus formation)} \quad (4)$$

Polymerization

$$
\begin{aligned}
u_i + f_1 &\xrightarrow{k_{pf}} u_{i+1},\ (i \geq n),\ \text{(elongation)} && (5)\\
u_i &\xrightarrow{\frac{k_{pf}}{d_2}} u_{i-1} + f_1,\ (i \geq n),\ \text{(shortening)} && (6)\\
u_i &\xrightarrow{k_b} u_{i-j} + u_j,\ (i \geq n),\ \text{(polymer break)} && (7)\\
\text{and } u_k &\xrightarrow{\infty} k * f_1,\ \text{if k } \leq n-1,\ \text{(oligomer instability)}
\end{aligned}
$$

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- n: nucleus size.

General Behavior: sigmoid

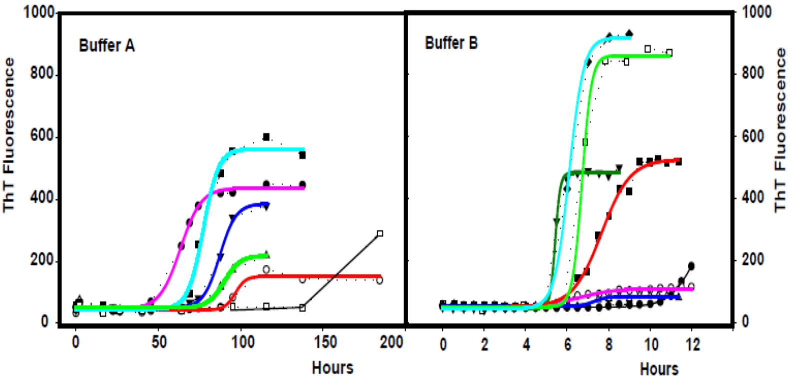
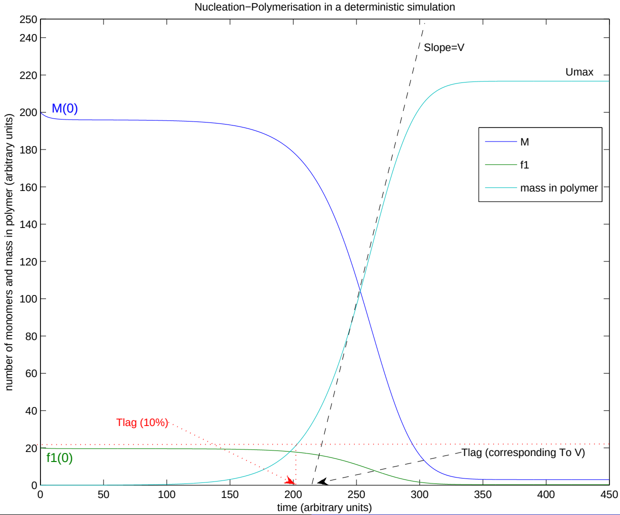
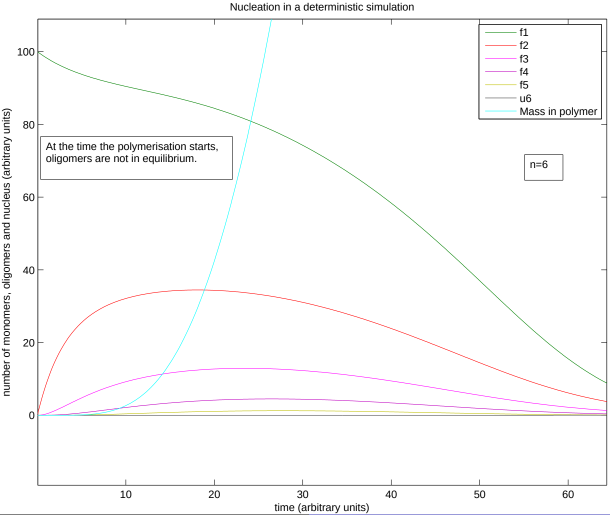


Figure: Several polymerisation experiments

General Behavior: key definitions



General Behavior: nucleation dynamics



Influences of parameters

- c_0: Changes drastically the Lag time and the Growth rate. If c_0 increases, less active monomers will be available, resulting in increasing the time of nucleation and slowing down also the polymerization. It has also by the same way an influence on the final equilibrium.

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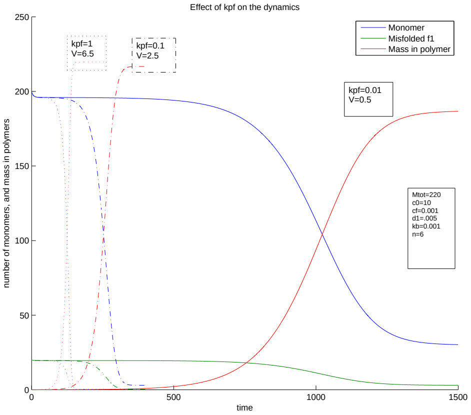
- c_f: Only changes the Lag time.
- d_1: Influences the nucleation time. Can also limit the polymerisation if the oligomers don't disappears quickly enough (ie if $d1$ high, which is unlikely to be).

Influences of parameters

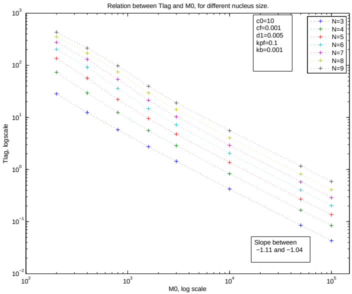
- k_{pf} and k_b: Influence both polymerization and nucleation in the same way. Change also the final equilibrium.



Influences of parameters

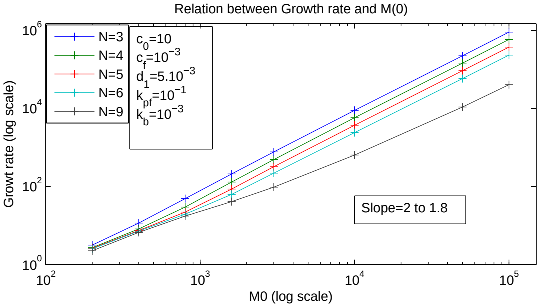
- $M(0)$ and n: $M(0)$ reduces the lag time, while n increases it. Up to a constant, Tlag follows the same relation with $M(0)$, whatever the nucleus size is. In agreement with experimental date. We have

$$log(Tlag) \simeq -1.07 * log(M(0)) \quad (8)$$



Influences of parameters

- $M(0)$ and n: $M(0)$ speeds up the polymerization, while n slightly decreases it. This contradicts experiments.



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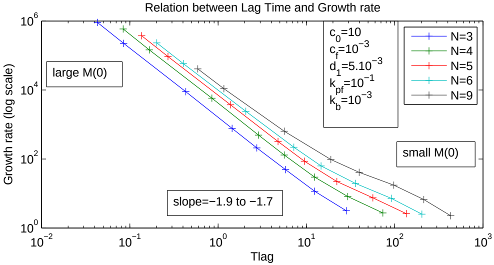
- $M_{tot} * k_{pf} \gg k_b$ guarantee an initially growing polymer.
- $Tlag$ versus V: For large $M(0)$, they are clearly inversely correlated. This contradicts experiments.

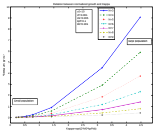


Some key factor: general scaling laws

- $\kappa = \sqrt{2 * M_{tot} * k_{pf} * k_b}$: In Knowles et al. (2009), using the nucleated equilibrium hypothesis, and a analytical approximation of the solution, the authors show a relation between the normalized growth $(V/M(0))$ and κ, and between T_{lag} and κ

$$\frac{V}{M_{tot}} = C^{te}_{M(0),n} * \kappa \qquad (9)$$

$$T_{lag} = \frac{log(C^{te}_{M(0),n})}{\kappa} \qquad (10)$$



experimental variability

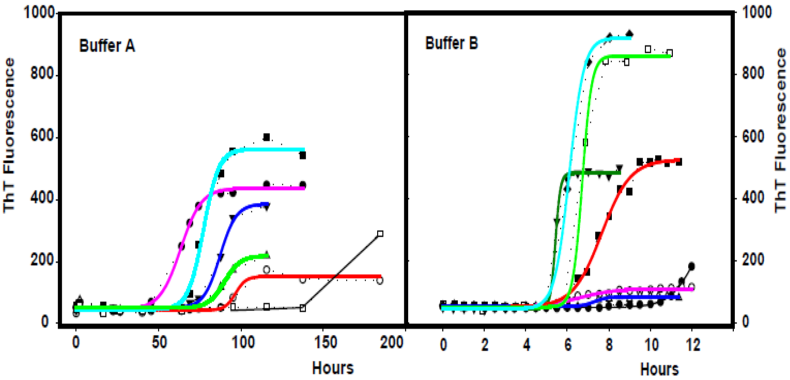


Figure: Several polymerisation experiments

Variability in Lag Time and Growth rate (Controversial)

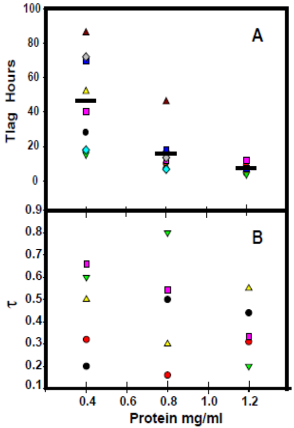


Figure: Relation between $M(0)$ and $Tlag$ and V

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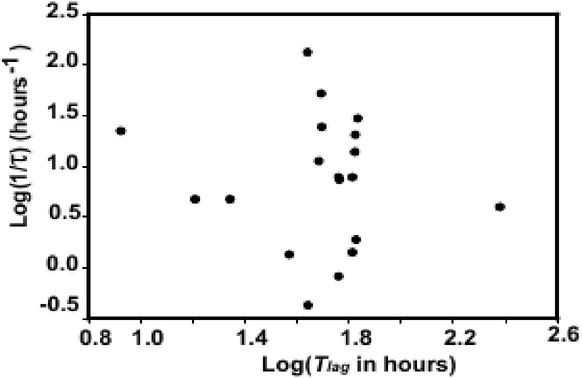
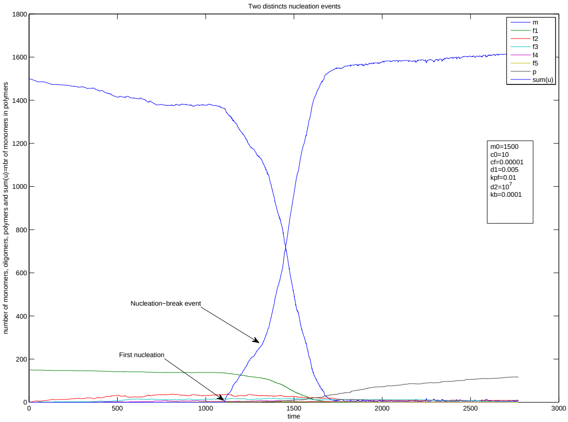


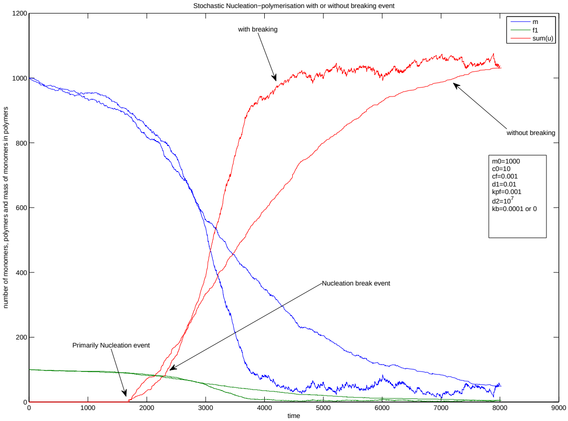
Figure: Relation between *Tlag* and *V*

Stochastic algorithm - global dynamic



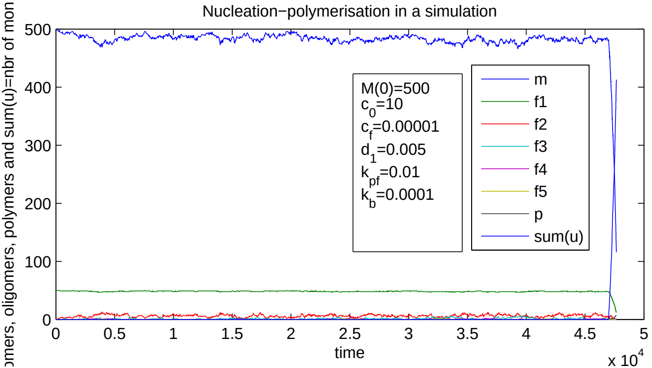
Break events or Secondary nucleation pathway

- One single nucleation event then elongation and break events can explain the sigmoid form



Stochasticity in the oligomer

- One can have many (small) fluctuations in the oligomer species, before reaching nucleation



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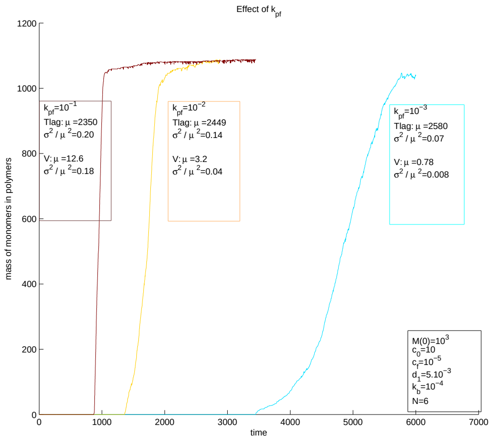
- d_1: Has no evident effect on variability.

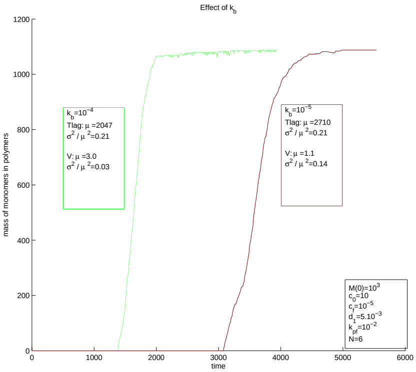
Influences of parameters - stochastic algorithm

- k_{pf}: Large k_{pf} will increase the variability of the growth rate.



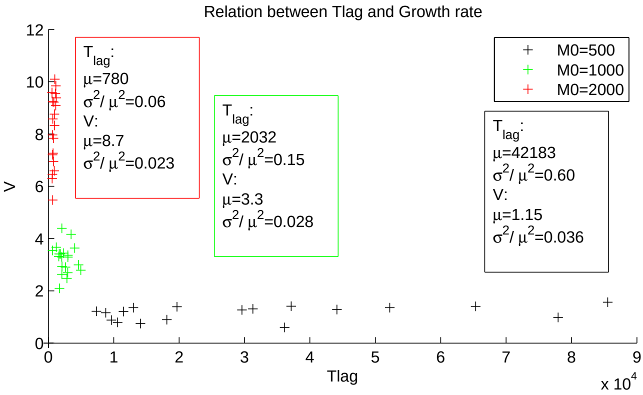
Influences of parameters - stochastic algorithm

- k_b: Influences on the respective numbers of nucleation events/ break events. Small k_b appears to give higher variability on the growth rate.



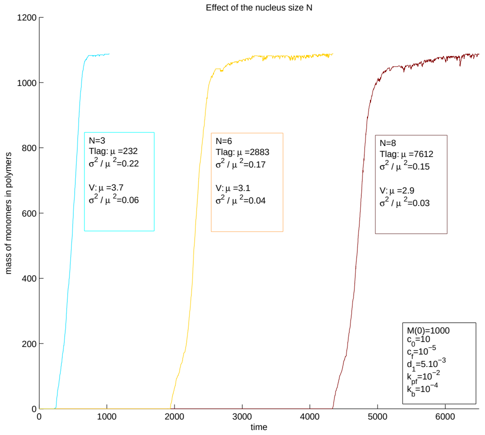
Influences of parameters - stochastic algorithm

- $M(0)$: Small $M(0)$ will increase variability in both Lag time and polymerization speed.



Influences of parameters - stochastic algorithm

- *n*: Small nucleus increases the variability.



algorithm results

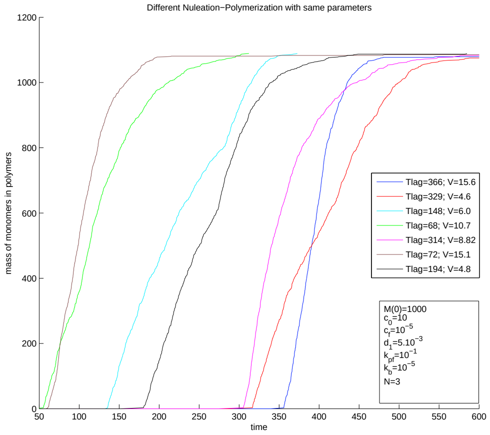


Figure: reproducing the variability in polymerization

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- Introduction of structure variability.