Dynamics of the prion proliferation

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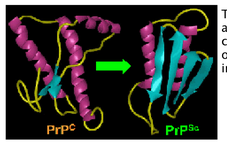
MADCOW
Modelling Amyloid Dynamics and Computation Output Work

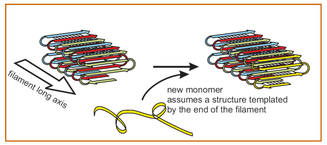
TSE (Transmissible Spongiform Encephalopathies) and prion hypothesis

Prion protein is responsible for some of the transmissible spongiform encephalopathies diseases. These long-time incubation neurodegenerative dieases are infectious and always fatal. They are due to amyloid formation in the brain. S. Prusiner established infectiousity of the protein and the existence of two different conformational states. He received the Nobel Price in 1997.

Prion PrP^c is a protein naturally produced in a conventional configuration.



This mechanism self-propagates a conformational change from conventional to misfolded form of the protein. The latter is the infectious agent

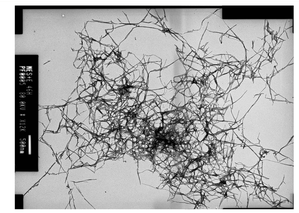


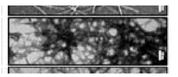
The unconventional proteins PrP^{Sc} create polymers that aggregate in amyloids.

The appearance of the disease can have two causes :
· A sporadic (spontaneous) apparition of a misfolded protein.
· A contamination by the infectious agent PrP^{Sc} , a seed or an amyloïd.

Well-known diseases :
· **Bovine spongiform encephalopathy**
· Scrapie in sheep
· **Creutzfeldt-Jakob** disease
· Kuru

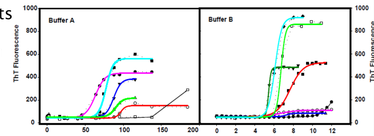
OUR GOAL: some experiments suggest the existence of different PrP^{Sc} strains. We would like to understand the replication mechanism and the sporadic appearance of amyloid to identify these strains. Our goal is to specify the parameters involved in the prion polymerization and determine prion strain according to these parameters.



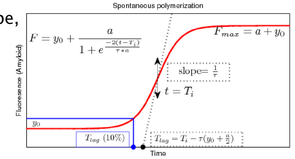


Spontaneous polymerization experiment

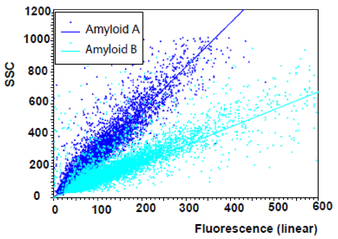
Spontaneous polymerization starts with an initially population of recombinant PrP^c Prion protein with continuous shaking.



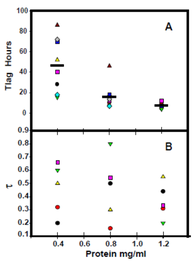
All experiments display a sigmoid shape, with three main characteristics:
T_{lag}, τ, and F_{max}

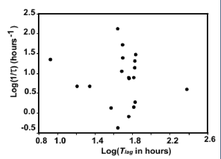


Spontaneous polymerization can lead to very different amyloid structures:



While the T_{lag} variability is greatly reduced with increased initial concentration, growth rate variability is maintained.



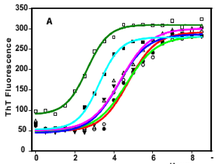


The growth rate and the T_{lag} are uncorrelated.

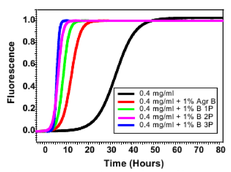
Seeding experiment

These experiments starts with pre-formed seeds.

While increasing the seeds, the T_{lag} is maintained.

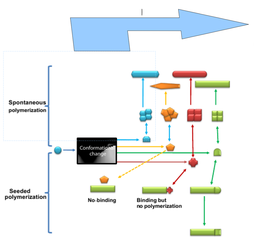


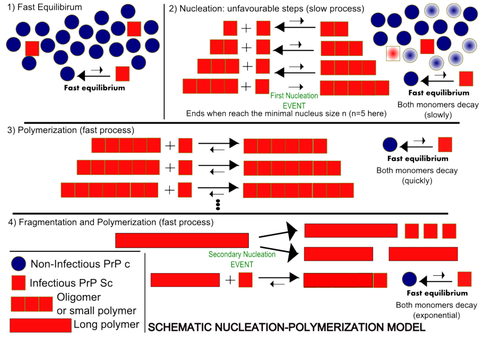
While performing successive seeds, the structure is preserved



In vitro Prion amyloids formation present a primarily conformational change step ans a nucleation-dependent polymerization.

MODEL





HYPOTHESIS

→**Conformational change (fast equilibrium)**

→**Heterogeneous nucleus formation**

→**Specific strain or amyloid**

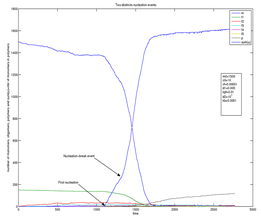
→**Specific polymerization, by binding to amyloid seed**

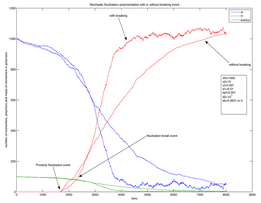
→**Fragmentation**

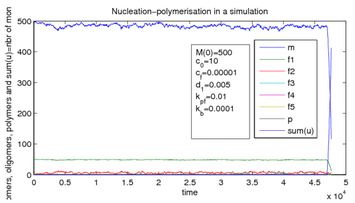
$$
\begin{aligned}
M &\underset{c_0}{\overset{1}{\rightleftharpoons}} f_1 \\
f_1 + f_1 &\underset{d_1}{\overset{c_f}{\rightleftharpoons}} f_2 \\
&\vdots \\
f_{k-1} + f_1 &\underset{d_1}{\overset{c_f}{\rightleftharpoons}} f_k \\
&\vdots \\
f_{n-1} + f_1 &\xrightarrow{c_f} u_n \\
u_i + f_1 &\xrightarrow{k_{bf}} u_{i+1},\ (i \geq n) \\
u_i &\xrightarrow[d_2]{k_{bf}} u_{i-1} + f_1,\ (i \geq n) \\
u_i &\xrightarrow{k_b} u_{i-j} + u_j,\ (i \geq n) \\
\text{and } u_k &\xrightarrow{\infty} k * f_1,\ \text{if k} \leq (n-1)
\end{aligned}
$$

Stochastic Nucleation-Polymerisation Model

Simulation was performed using a **Gillespie algorithm**.
The model exhibits sigmoid shape, and the polymerisation process is dependent of **discrete nucleation event**.

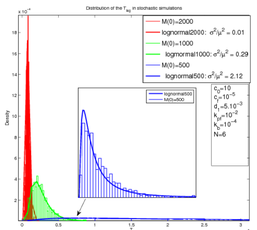


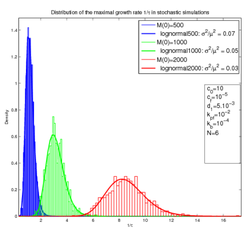




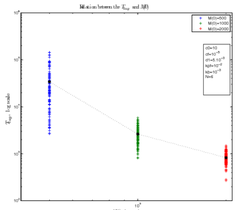
Breaking events are responsible for the sigmoid shape.
One can have **many fluctuations** before reaching the formation of the first seed.

T_{lag} is much more dependent of the initial amount of protein than the growth rate.
Both quantities are following a **log-normal distribution**

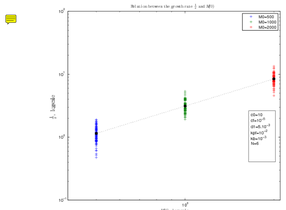




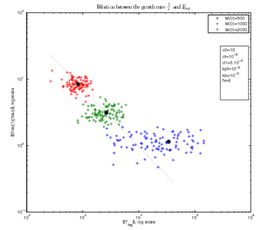
The evolution of T_{lag} while increased initial population is in good agreement with data.

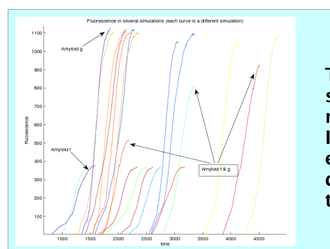


But the growth rate is also dependent of the initial population. This contradicts data, although the variability put into perspective this dependency



Both quantities are somewhat correlated, although here again variability could explain the experimental observations.





CONCLUSION:

This preliminary work shows that a stochastic nucleation-polymerization model can explain the observed variability. In a stochastic description, discrete events are responsible for the overall dynamic. Variability can also be an artifact to some observable experimental laws.

GOING FURTHER:

- **Analytical study will be performed to gain more insight into the effects of stochasticity on the dynamics.**
- **General scaling laws such as the value of Lag Time (exit time problem) and the growth rate are expected.**
- **Given this information and improving the algorithm could lead to precise date fitting.**
- **Interactions between different structures (strain) can then be of importance.**