



Dynamics of the prion proliferation

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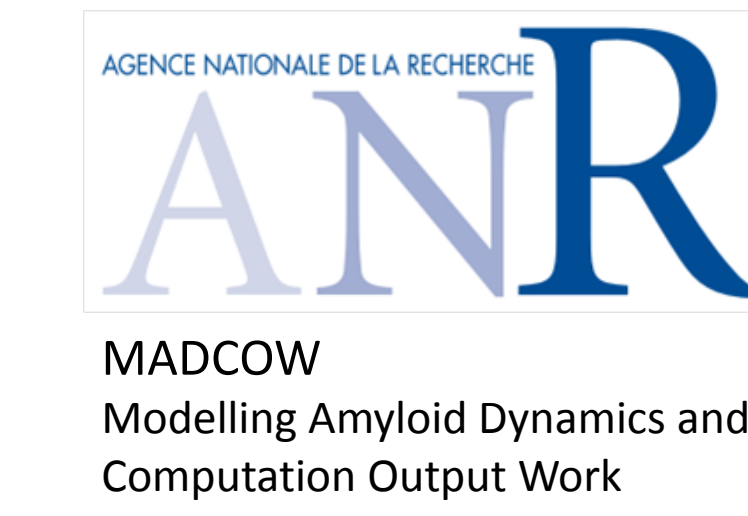
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Dynamics of the prion proliferation



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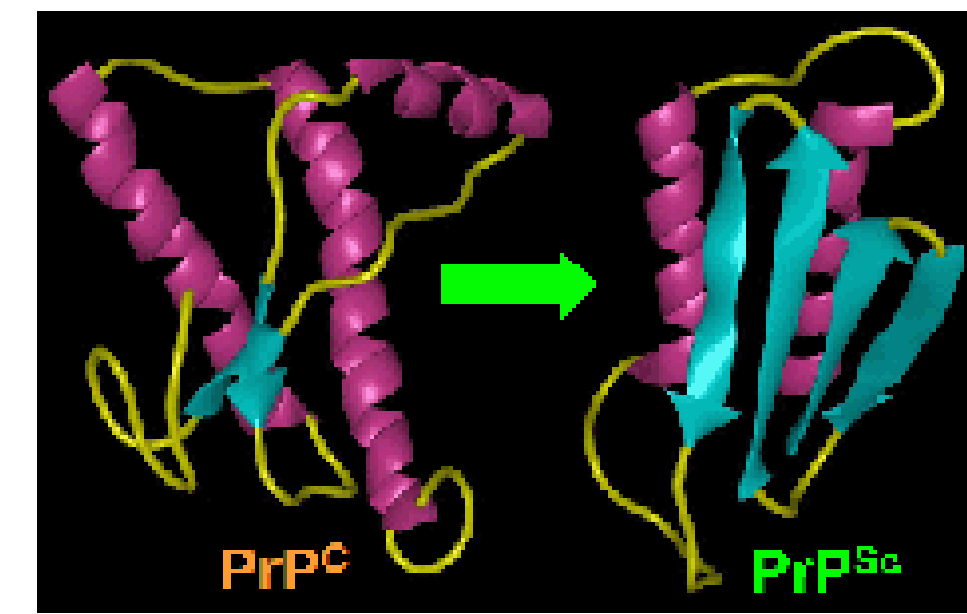
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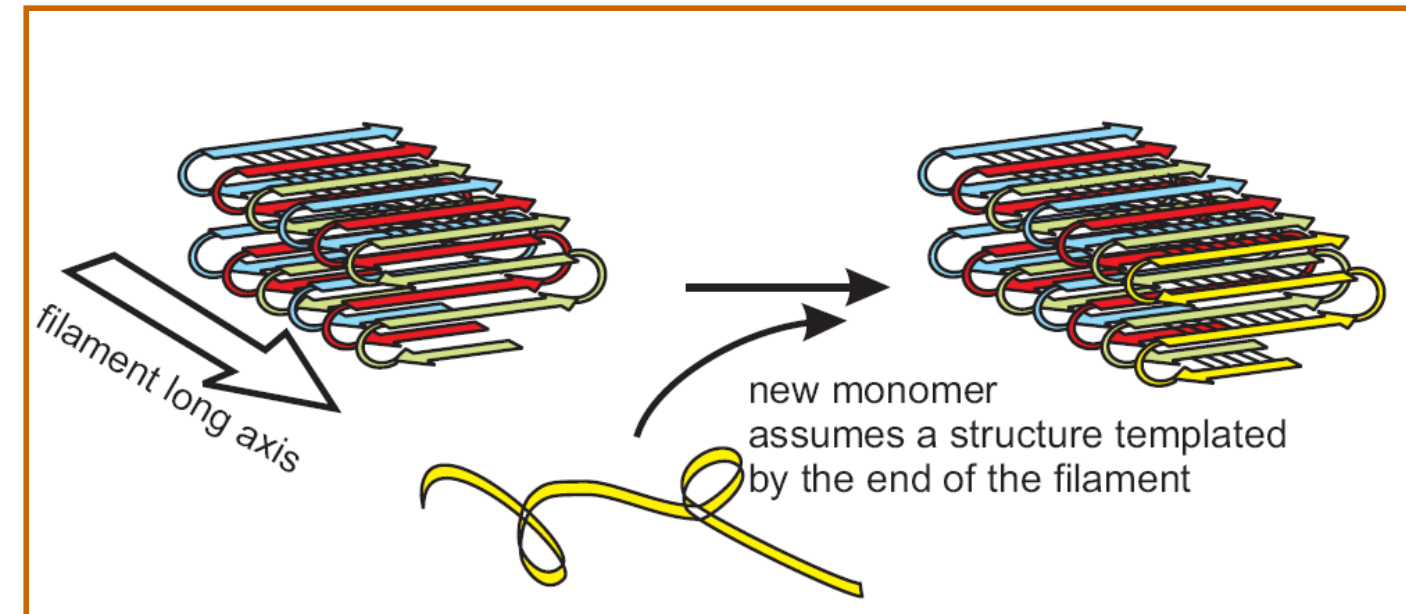
TSE (Transmissible Spongiform Encephalopathies) and prion hypothesis

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

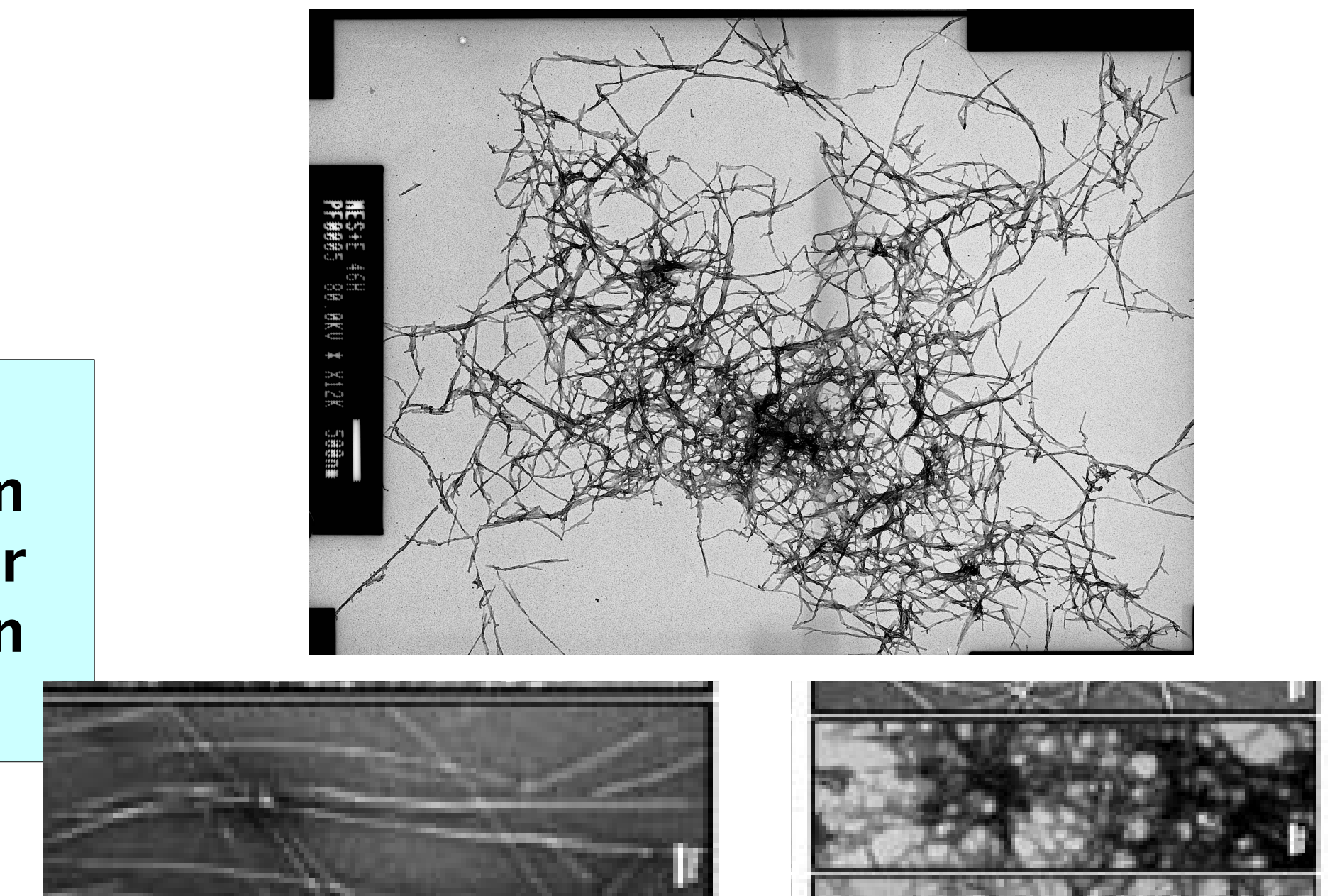


The appearance of the disease can have two causes :
· A sporadic (spontaneous) apparition of a misfolded protein.
· A contamination by the infectious agent PrP^{Sc} , a seed or an amyloid.

Well-known diseases :

- Bovine spongiform encephalopathy
- Scrapie in sheep
- Creutzfeldt-Jakob disease
- Kuru

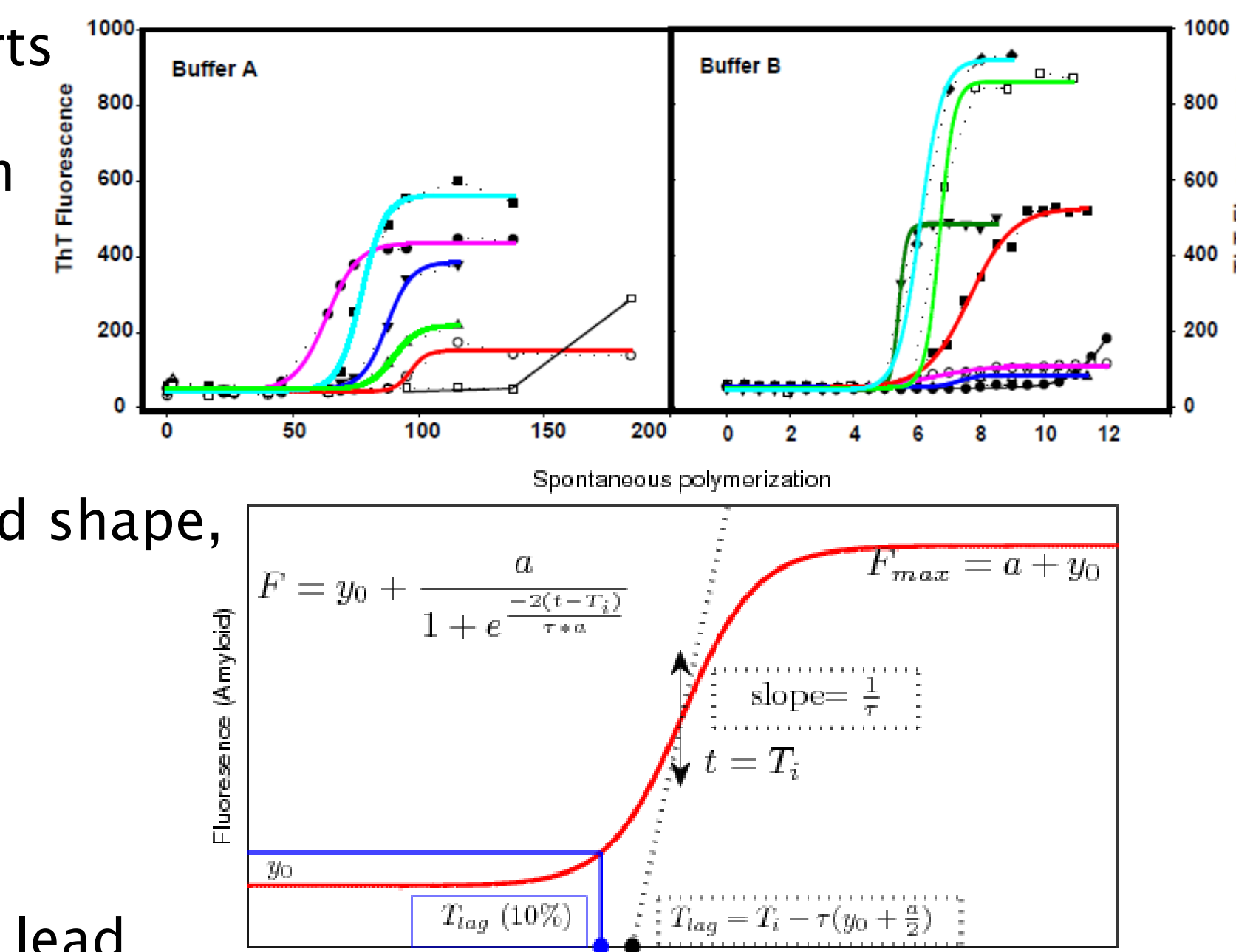
OUR GOAL: some experiments suggest the existence of different PrP^{Sc} strains. We would like to understand the replication mechanism and the sporadic appearance of amyloid to identify these strains. Our goal is to specify the parameters involved in the prion polymerization and determine prion strain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



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

Spontaneous polymerization experiment

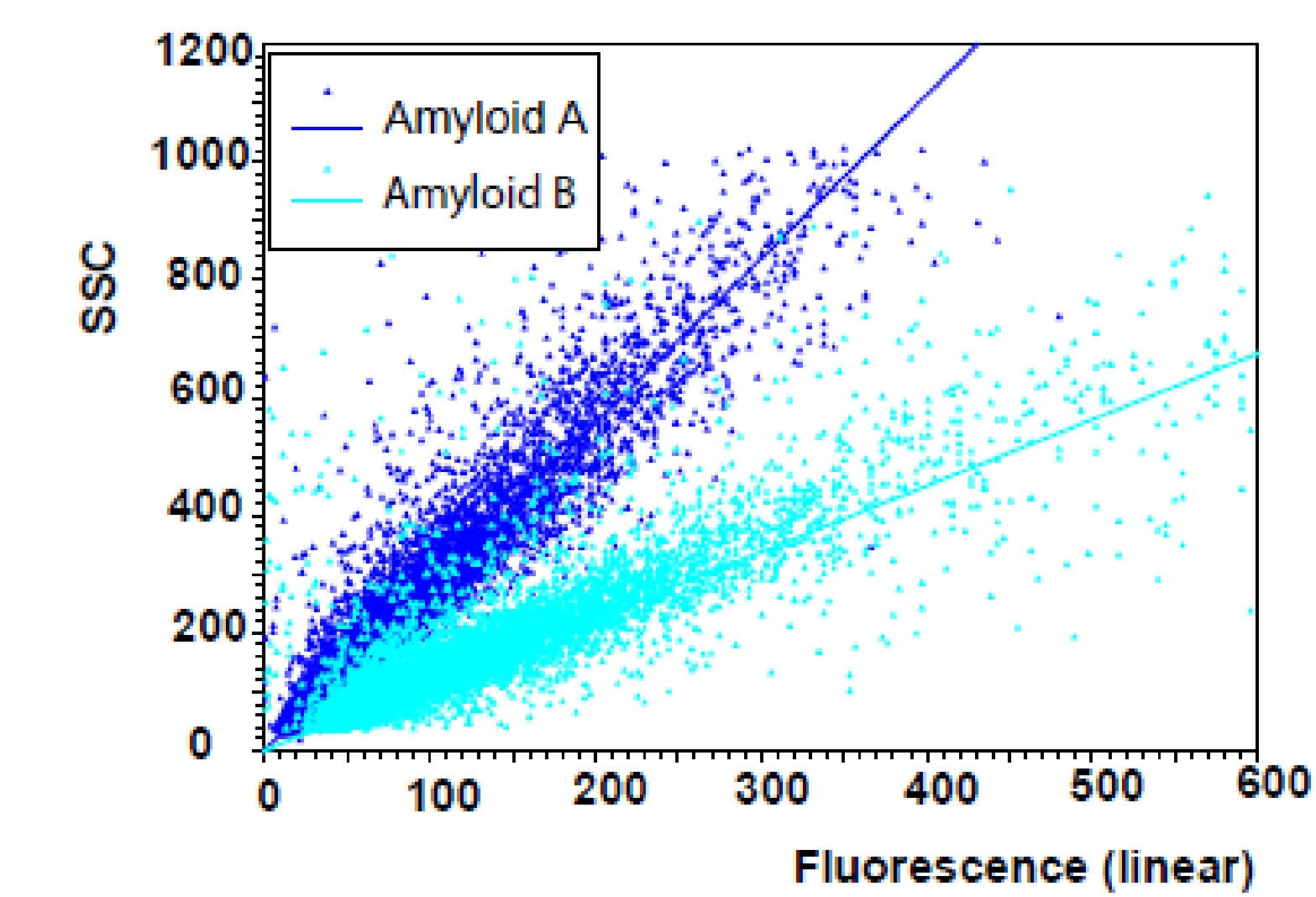
Spontaneous polymerization starts with an initially population of recombinant PrP^c Prion protein with continuous shaking.



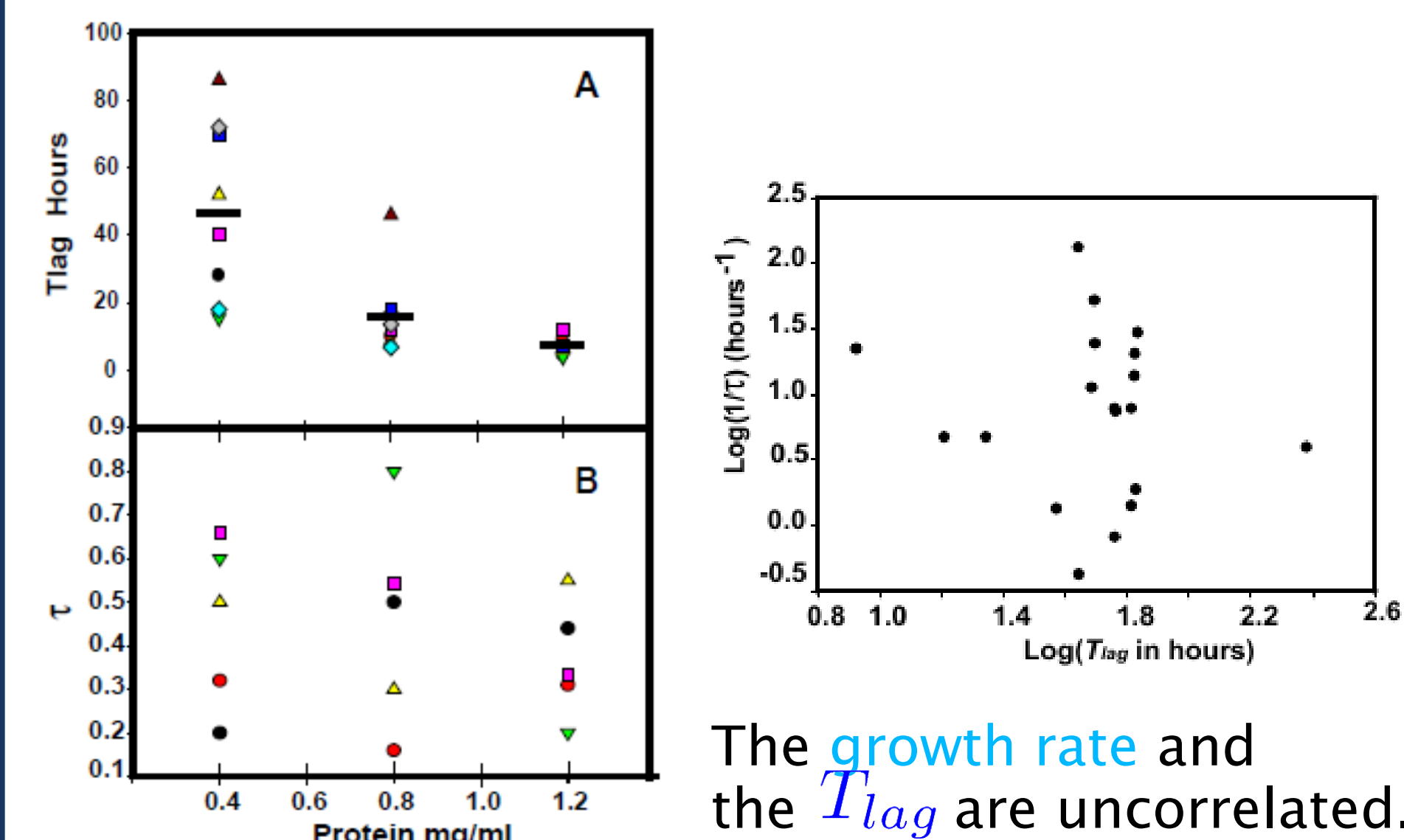
All experiments display a sigmoid shape, with three main characteristics:

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.



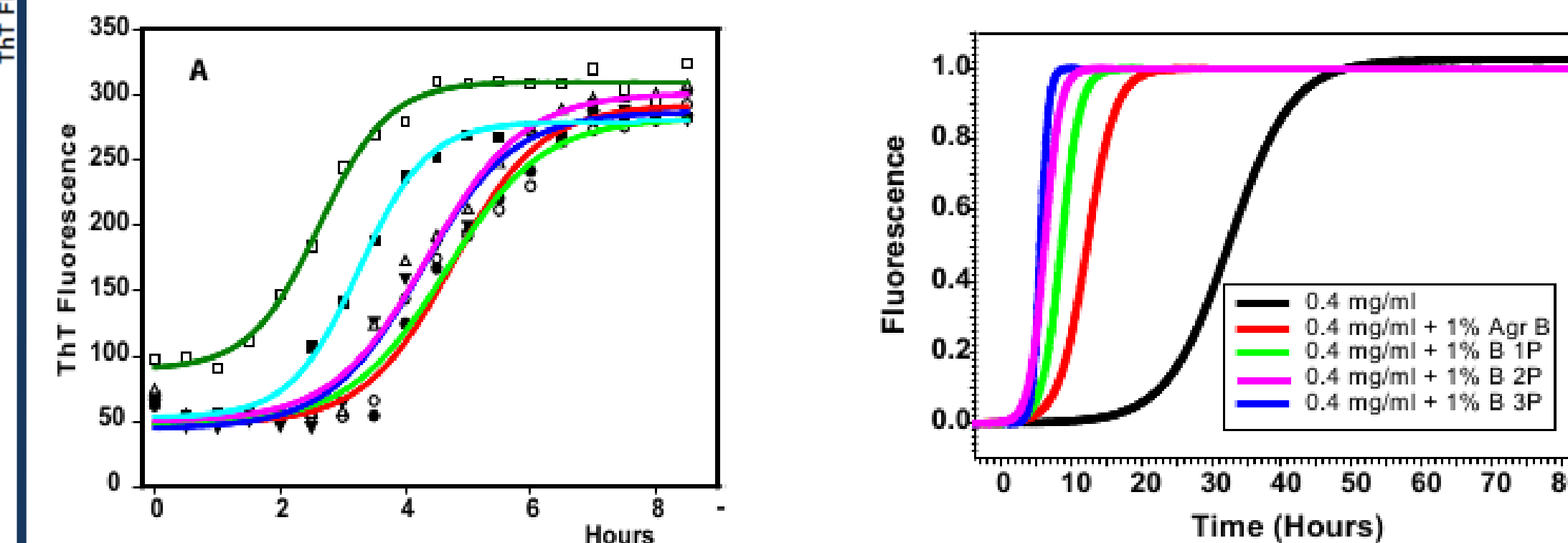
The growth rate and the T_{lag} are uncorrelated.

Seeding experiment

These experiments start with pre-formed seeds.

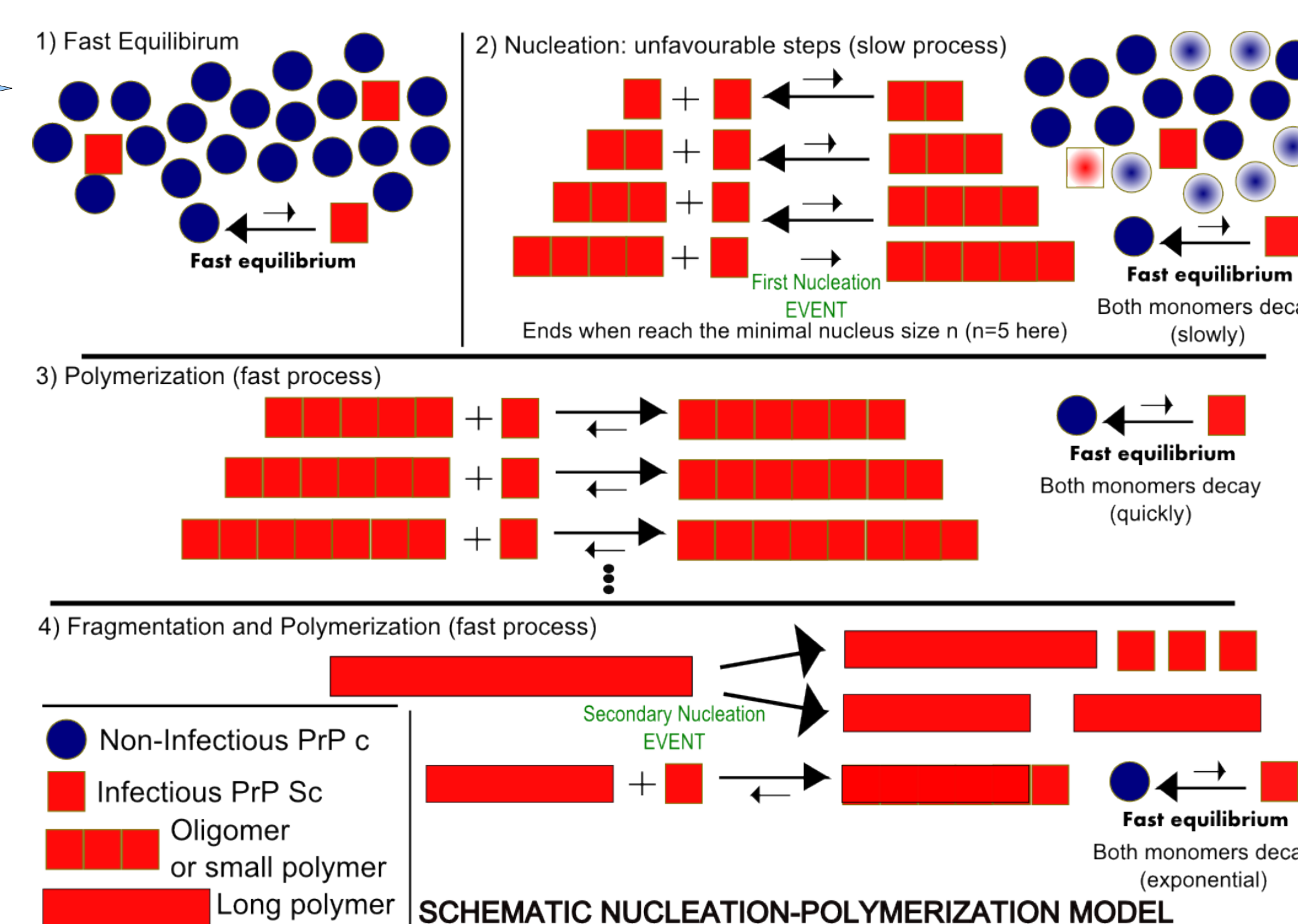
While increasing the seeds, the T_{lag} is maintained.

While performing successive seeds, the structure is preserved



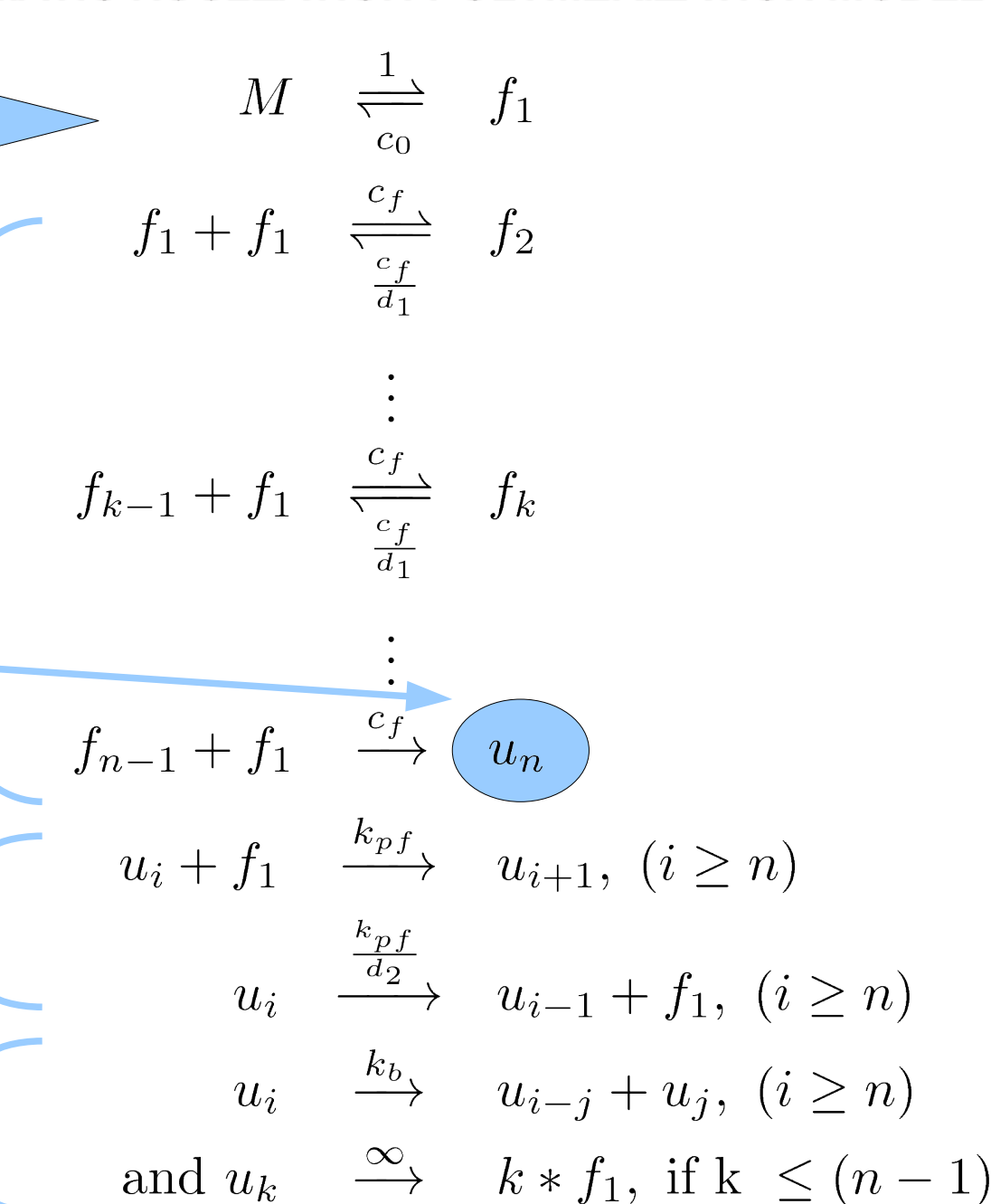
In vitro Prion amyloids formation present a primarily conformational change step and a nucleation-dependent polymerization.

MODEL



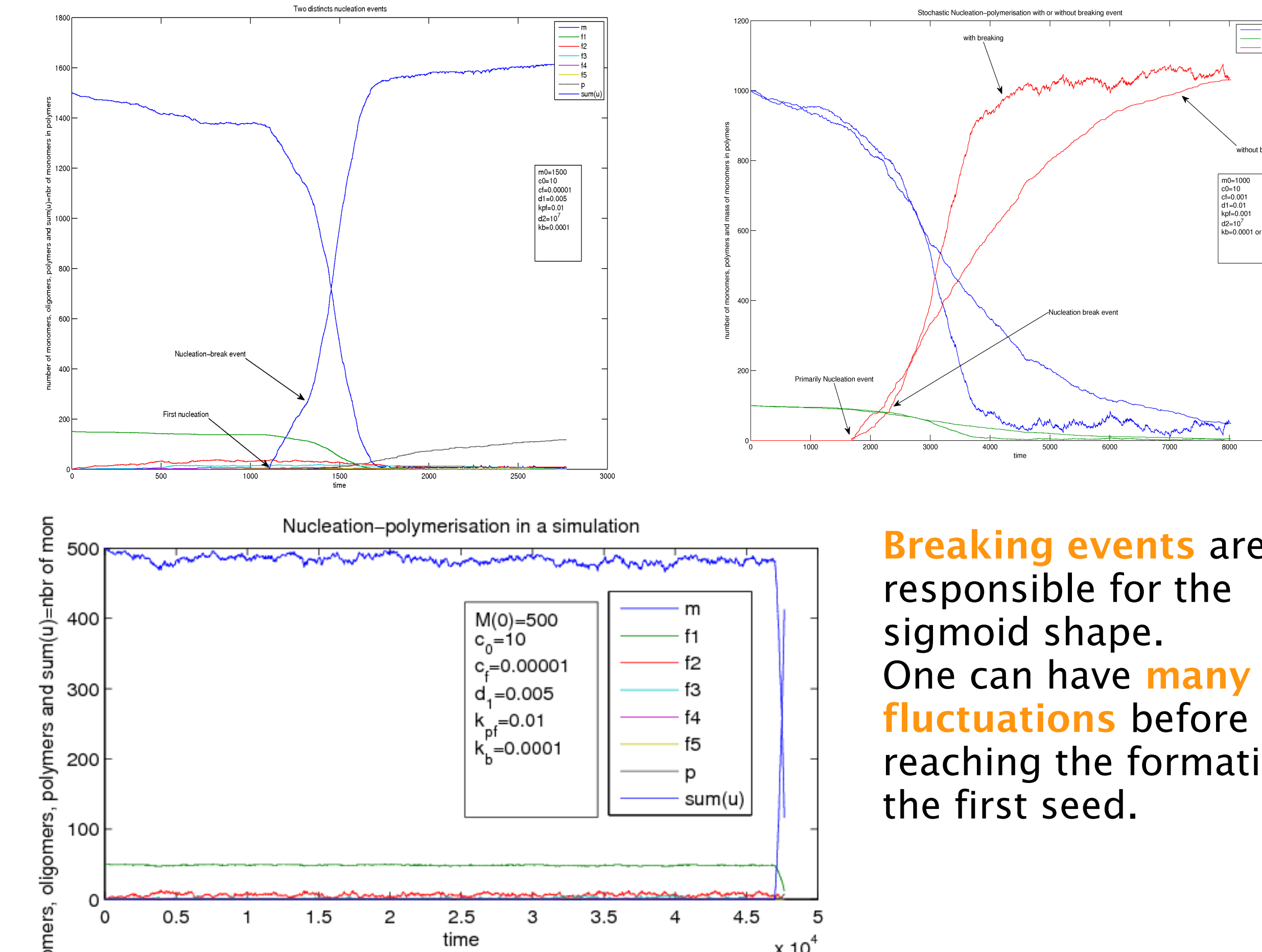
HYPOTHESIS

- Conformational change (fast equilibrium)
- Heterogeneous nucleus formation
- Specific strain or amyloid
- Specific polymerization, by binding to amyloid seed
- Fragmentation

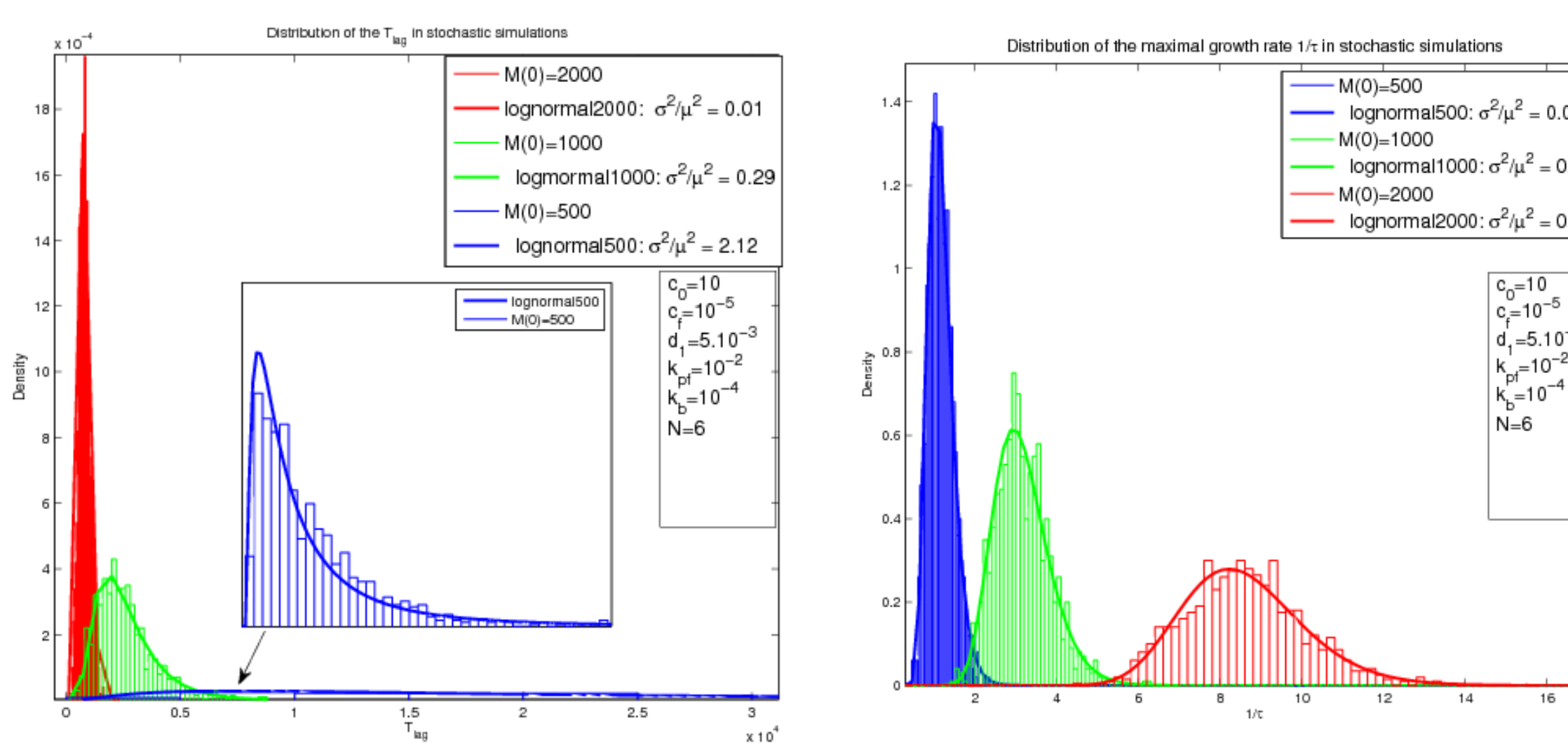


Stochastic Nucleation-Polymerisation Model

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

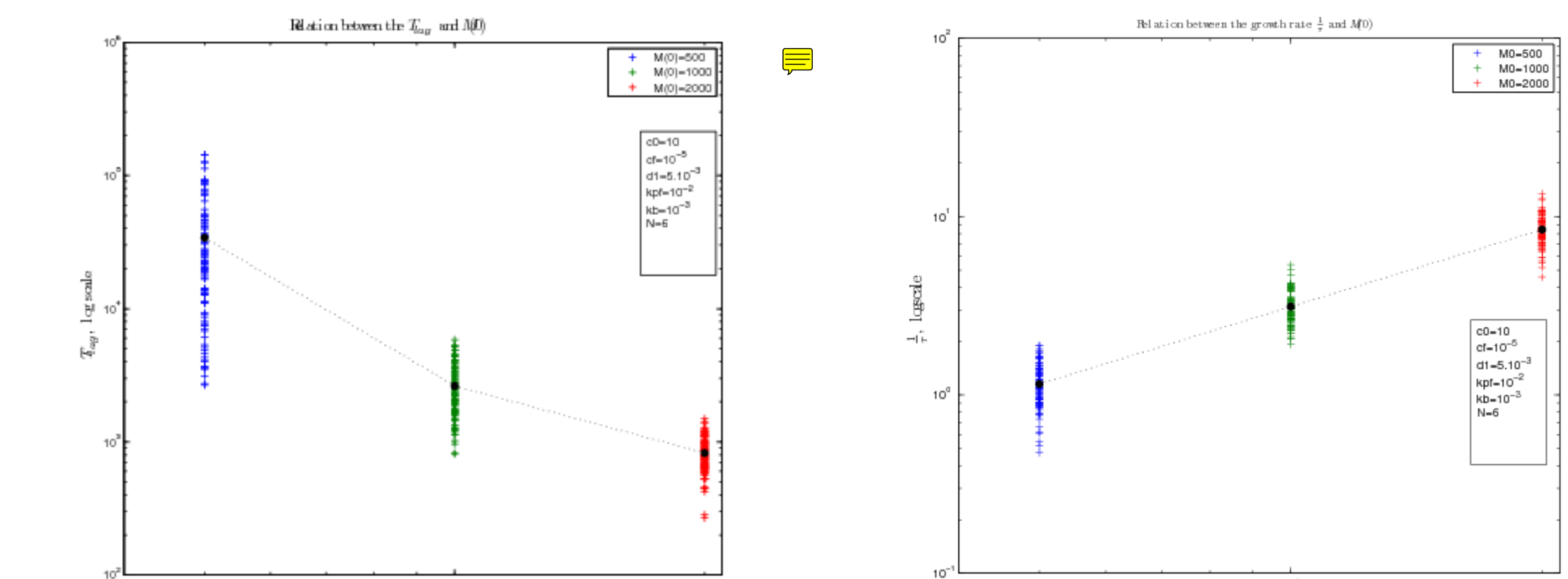


T_{lag} is much more dependent of the initial amount of protein than the growth rate. Both quantities are following a log-normal distribution

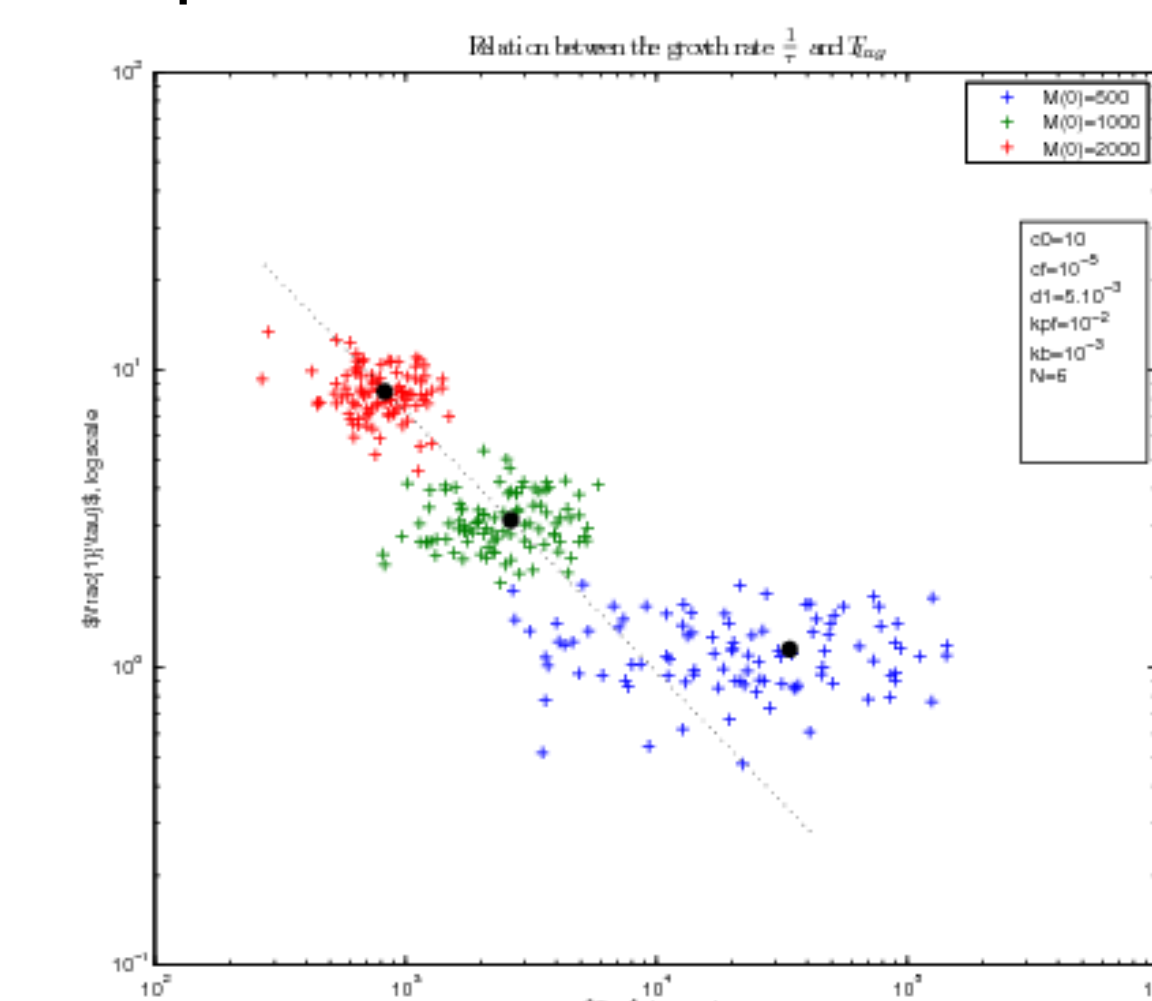


The evolution of T_{lag} while increased initial population is in good agreement with data.

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 data fitting.
- Interactions between different structures (strain) can then be of importance.

