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Modélisation mathématique de processus d'assemblage (protéïques)

Romain Yvinec

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INRA Nouzilly, France.

Coagulation-fragmentation processes

What do we describe? What is it used for?

Mathematical questions

Outline

Coagulation-fragmentation processes

- Generality

- Chemical kinetics

- Deterministic/Stochastic, well-mixed/spatial

What do we describe? What is it used for?

Mathematical questions

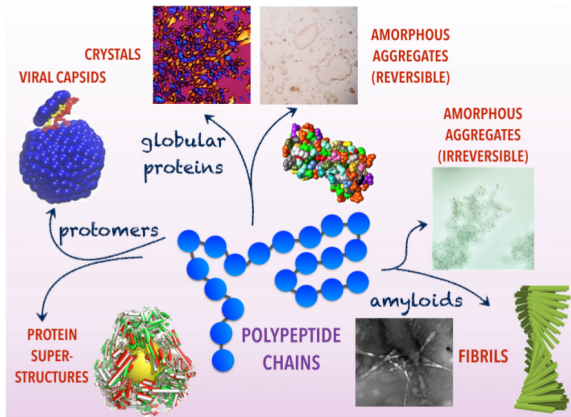
Various ways to describe assembly formation :

- ▶ **Phenomenological approaches** : free energy of a cluster in a given environment by using macroscopic quantities (e.g. surface tension) ;
- ▶ **Chemical kinetic approaches** : represent a dynamic process through (bio-)chemical reactions (or transitions). Typically aims at focusing on time-dependent size distribution.
- ▶ **Microscopic approaches** First-principle models to describe cluster structure. (e.g. computer molecular simulations)

Various ways to describe assembly formation :

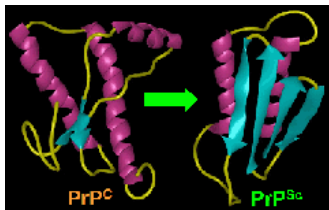
- ▶ **Phenomenological approaches** : free energy of a cluster in a given environment by using macroscopic quantities (e.g. surface tension) ;
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- ▶ **Microscopic approaches** First-principle models to describe cluster structure. (e.g. computer molecular simulations) ;

The detailed structure is not represented...



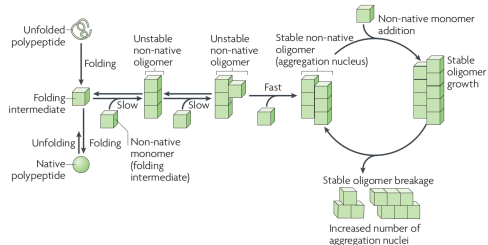
...but the pathway is the key model ingredient

Conformational change



Post-translational Misfolding

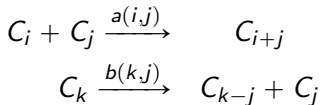
"Prusiner" model



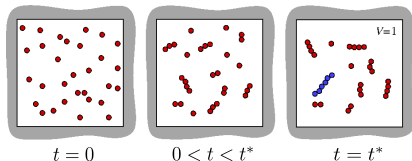
Brundin et al., *Prion-like transmission of protein aggregates in neurodegenerative diseases*, Nat. Rev. Mol. Cell Biol. (2010)

Principles inspired from chemical kinetics : the starting point is an ensemble of (bio-)chemical reactions between assembly of different sizes (*and/or of different types*) :

Chemical kinetics

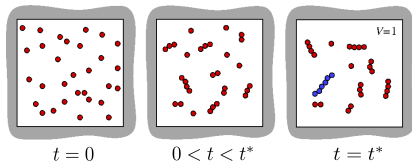
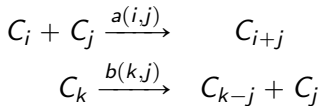


where $C_i = \{\text{assembly of size } i\}$.



Principles inspired from chemical kinetics : the starting point is an ensemble of (bio-)chemical reactions between assembly of different sizes (*and/or of different types*) :

Chemical kinetics



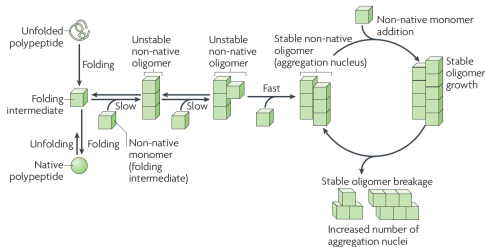
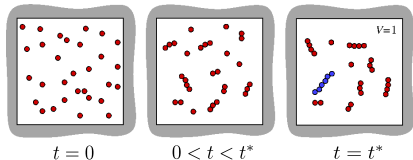
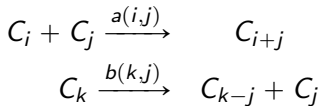
Two major ingredients (*at interdisciplinary interface*)

- ▶ aggregation pathway(s)
- ▶ kinetic rates

I) The aggregation pathway(s)

Which reactions are allowed? How many protein types?

Chemical kinetics



II) The kinetic rates

Do they depend on size? or on physical medium?

Chemical kinetics

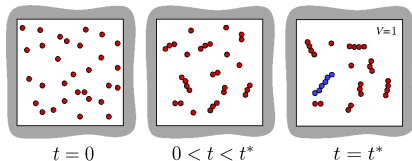
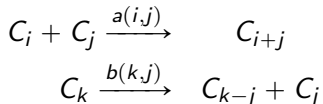


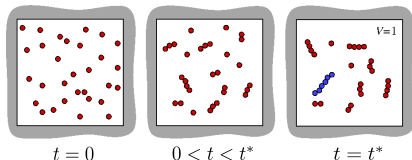
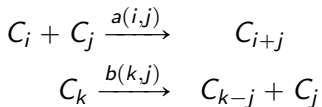
Table 1. Some specific kernels (Smit *et al.* 1994)

$K(x, y)$	Comment
$(x^{1/3} + y^{1/3})(x^{-1/3} + y^{-1/3})$	Brownian motion (continuum regime)
$(x^{1/3} + y^{1/3})^2(x^{-1} + y^{-1})^{1/2}$	Brownian motion (free molecular regime)
$(x^{1/3} + y^{1/3})^3$	Shear (linear velocity profile)
$(x^{1/3} + y^{1/3})^{7/3}$	Shear (nonlinear velocity profile)
$(x^{1/3} + y^{1/3})^2 x^{1/3} - y^{1/3} $	Gravitational settling
$(x^{1/3} + y^{1/3})^2 x^{2/3} - y^{2/3} $	Inertia and gravitational settling
$(x - y)^2(x + y)^{-1}$	Analytic approximation of Berry's kernel
$(x + c)(y + c)$	Condensation and/or branched-chain polymerization

Mathematical modeling to test hypotheses

Often, we have only *some* clues on both ingredients. This approach may **distinguish between several competitive hypotheses**.

Chemical kinetics



Examples of typical questions :

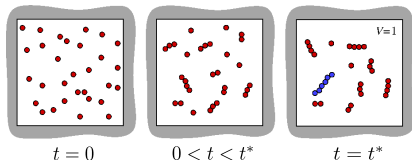
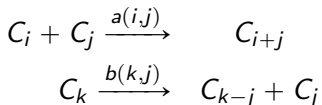
- ▶ Is coagulation occurs only through monomer addition ?
- ▶ Does fragmentation play a role in the acceleration of the dynamics of polymerization ?
- ▶ Is there any conversion mechanisms ?
- ▶ How many different structures coexist ?

Going from reactions to equations and evolution laws

- ▶ Time derivative of position = velocity !

$$\frac{dx}{dt} = v(t, x)$$

Chemical kinetics

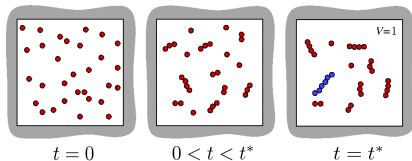
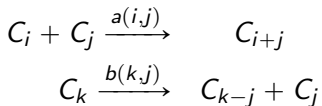


Going from reactions to equations and evolution laws

- ▶ Time derivative of position = velocity!

$$\frac{dx}{dt} = v(t, x)$$

Chemical kinetics



Well-mixed deterministic mass-action law

- ▶ Coagulation velocity : $V_{i,j}^+(t, C) = a(i, j) C_i(t) C_j(t)$
- ▶ Fragmentation velocity : $V_k^-(t, C) = \left(\sum_j b(k, j) \right) C_k(t)$

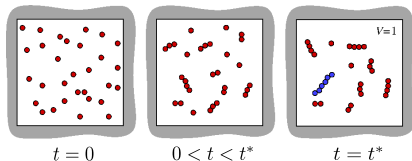
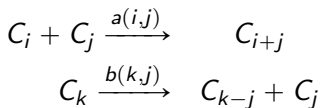
We obtain *ordinary differential equations* by "adding" each **velocity** with its **stoichiometry**

Going from reactions to equations and evolution laws

- ▶ Time derivative of position = velocity!

$$\frac{dx}{dt} = v(t, x)$$

Chemical kinetics

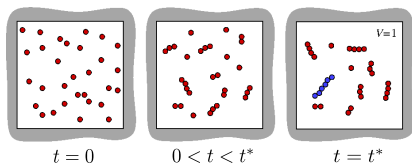
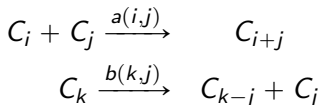


Well-mixed stochastic mass-action law ($\delta t \ll 1$)

- ▶ Coag. "probability": $V_{i,j}^+(t, C) = a(i, j) C_i(t) C_j(t) \cdot \delta t$
- ▶ Frag. "probability": $V_k^-(t, C) = \left(\sum_j b(k, j) \right) C_k(t) \cdot \delta t$
- ▶ "No move probability": $1 - \sum_{i,j} V_{i,j}^+ - \sum_k V_k^-$

We obtain *stochastic equations* by "adding" each **velocity** with its **stoichiometry**

Chemical kinetics



Different formalism :

- ▶ Deterministic vs Stochastic (concentration/number)
- ▶ Well-mixed vs Spatial (homogeneous / heterogeneous, motion)
- ▶ Discrete vs Continuous size ($i \in \mathbb{N}$ or $x \in \mathbb{R}^+$)

The common point of those formalism is to model **size repartition** of assemblies along **time**

Outline

Coagulation-fragmentation processes

What do we describe? What is it used for?

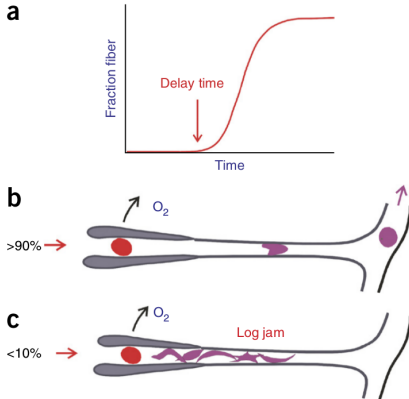
- Sickle Hemoglobin

- Protein aggregation linked to neurodegenerative diseases

- Spatial modeling and sub-cellular compartment

Mathematical questions

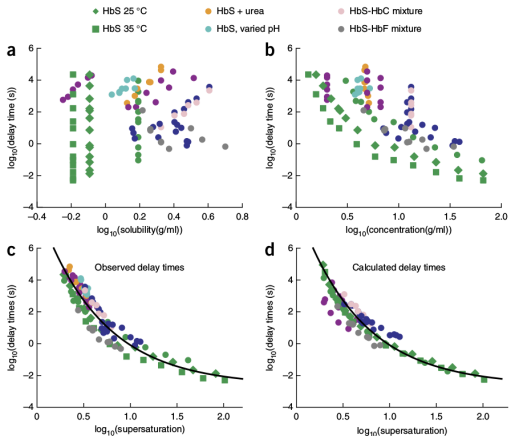
Modeling the kinetics of Hemoglobin fiber



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

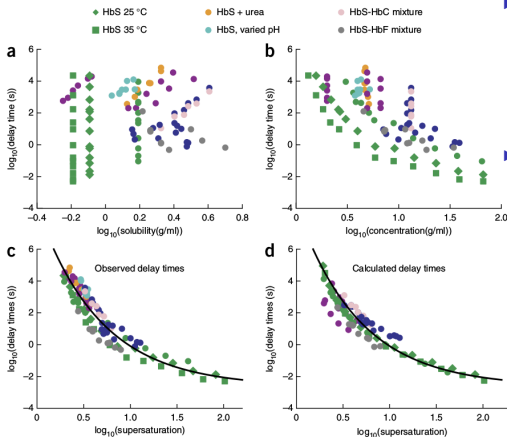


Delay (nucleation, lag) time



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

Delay (nucleation, lag) time



- ▶ Qualitative and quantitative explanation of lag time before fiber formation (*in-vitro*)

- ▶ Double-nucleation model

$$P = \sum_{i \geq i_0} C_i,$$

$$Z = \sum_{i \geq i_0} i C_i :$$

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

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



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



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

Protein aggregation diseases : Working hypothesis

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*.

Proof of principles

NATURE, VOL. 215, SEPTEMBER 2, 1967

Nature of the Scrapie Agent

There is evidence to suggest that the infectious disease scrapie is caused by an agent which does not depend on a nucleic acid for its ability to replicate. In the first of the two following articles it is suggested that scrapie can best be considered to arise from a replicable change in the structural pattern of a commonly occurring unit membrane. In the second article it is suggested that the agent is a protein and three possible mechanisms for its self-replication are proposed.

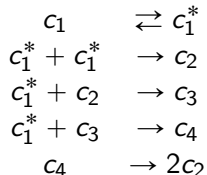
1041



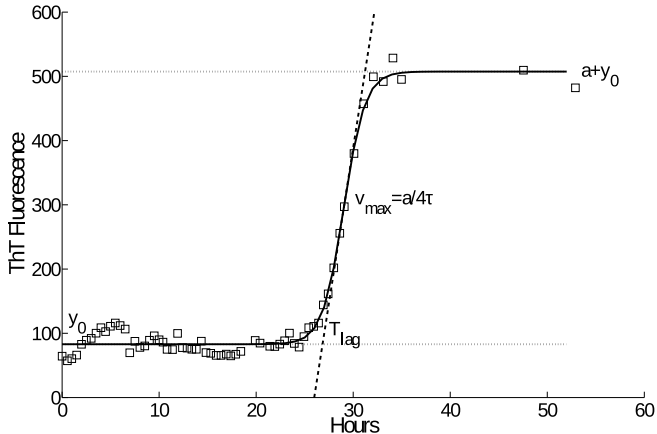
Griffith *Nature of the Scrapie Agent*
Nature (1967)

- ▶ Hypotheses for self-replication of an (unknown) infectious agent

- ▶ Auto-catalytic model :



Does a Mathematical model reproduce the data?



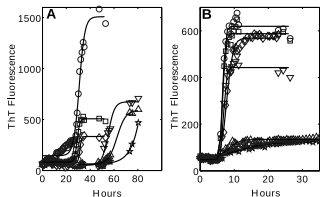
How does that help to understand the mechanistic phenomenon of the aggregation process?

Model and data

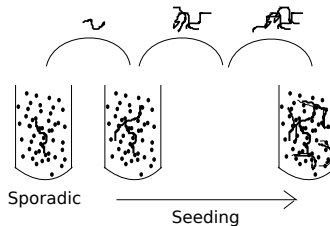
The mathematical model needs to be adapted to each experimental protocol and measurement

- ▶ Total mass or moment measurements (Fluorescence reporter (ThT))
- ▶ Individual size measurements (Flow cytometry (FACS), Side-scattered light (SSC))
- ▶ Population size measurements (Electron microscopy)
- ▶ Binding/Unbinding kinetic measurement (Biacore)
- ▶ ...

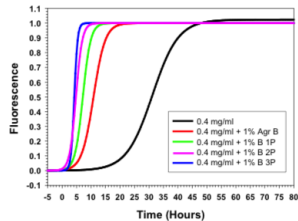
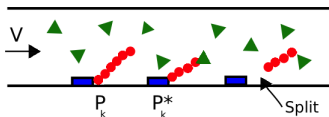
Spontaneous polymerization



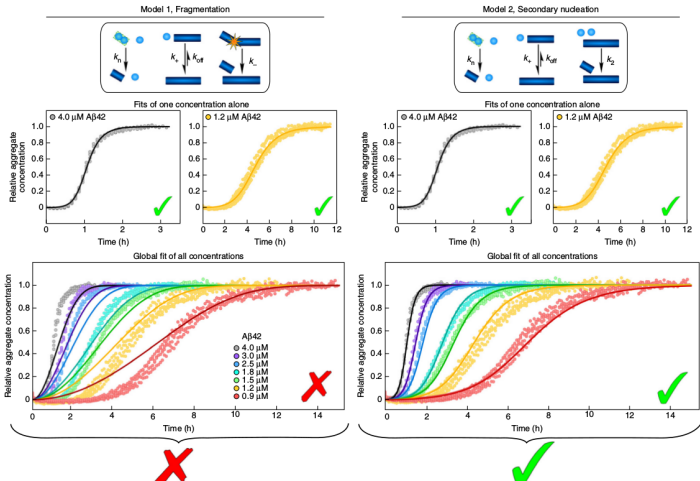
Seeding experiment



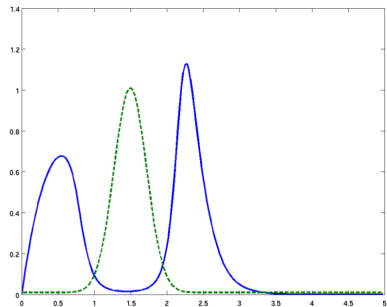
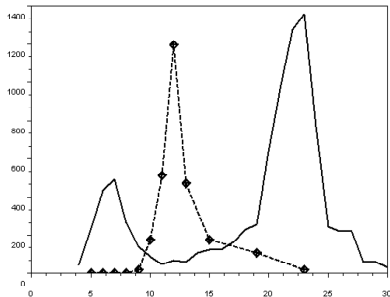
Biacore



Hypotheses testing through global fitting of experiment

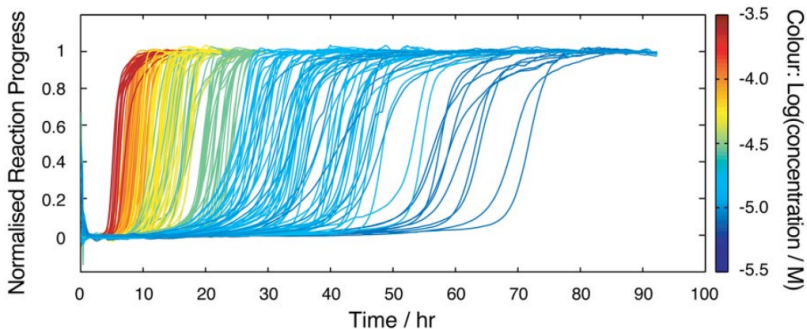


Size distribution modeling



Calvez et al. *Size distribution dependence of prion aggregates infectivity* Math. Biosc. (2009)

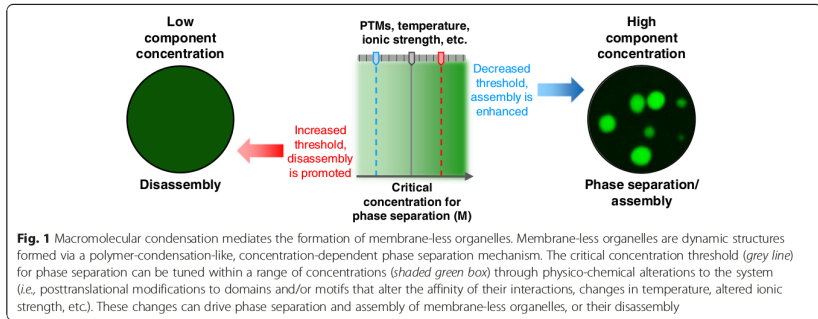
Stochasticity at different concentration

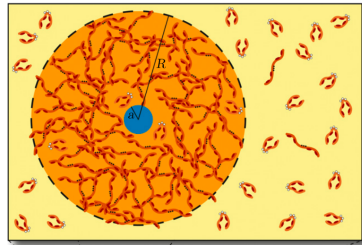
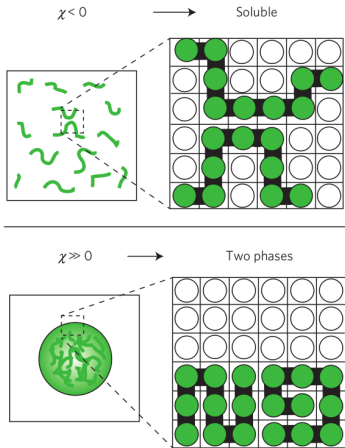


Xue et al. *Systematic analysis of nucleation-dependent polymerization reveals new insights into the mechanism of amyloid self-assembly.* PNAS (2008)

Dynamic & spatial processes

Several ingredients can be added : physical space, compartmentalization (multi-cellular structure)...





Reaction-diffusion PDE



Zwicker et al., *Centrosomes are autocatalytic droplets of pericentriolar material organized by centrioles*, PNAS (2014)



Brangwynne et al., *Polymer physics of intracellular phase transitions*, Nature Physics (2015)

Outline

Coagulation-fragmentation processes

What do we describe? What is it used for?

Mathematical questions

Mathematical issues

- ▶ Well-posedness of the model
- ▶ Long-time behavior (Equilibrium, Convergence speed, self-similarity...)
- ▶ Stochasticity in nucleation and Phase transition (loss of mass, metastability...)
- ▶ Inverse Problem (Data Fitting, identifiability, hypothesis testing...)

All those questions are non-trivial for many models, but are useful for applications !

Key messages

- ▶ Coagulation-fragmentation models : time-dependent assembly sizes
- ▶ Interdisciplinary ingredients : reaction pathways and kinetic rates
- ▶ Hypotheses testing of (nonlinear) biological phenomena.

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Thanks for your attention !