Analysis of the Protein Aggregation in the Neurodegenerative Diseases

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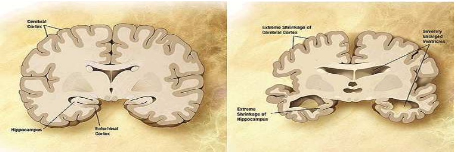
Inrias's Junior Seminar

April, 2014

- What is the **neurodegenerative diseases** ?

↪ **Misfolding** of a monomeric protein, involving its aggregation into polymeric protein fibrils, **amyloïds**, forming a deposit and cavities **within neurons**.



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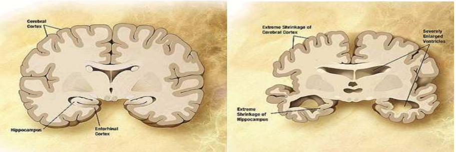
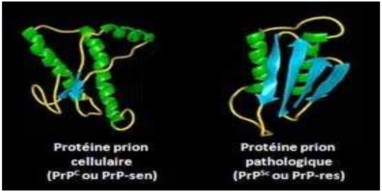


↪ More that 20 neurodegenerative diseases:

- Alzheimer (Aβ),
- Hungtington (Poly Q),
- Parkinson,
- Prion Diseases (PrP),

- What about **prion diseases** ?

$\hookrightarrow$ Induced by **PR**oteinaceous **I**nfectious **O**nly agent, the **prion**(Nobel Prize, 1997, Prusnier). no DNA.



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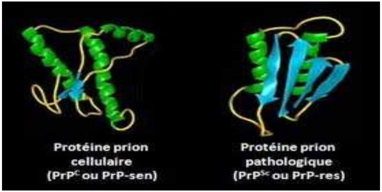

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Humans : Creutzfeldt-Jakob, Kuru, Fatal Familial Insomnia, ...

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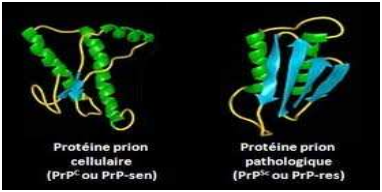

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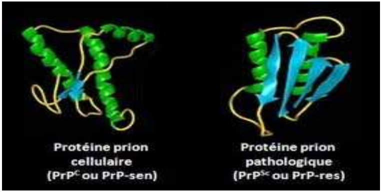

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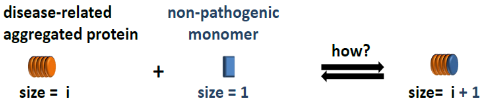
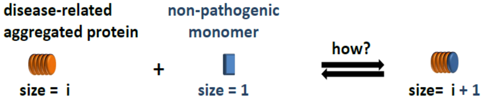
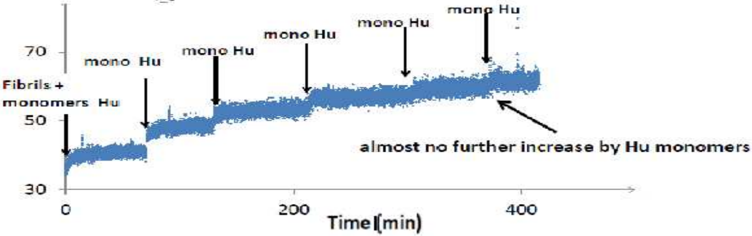
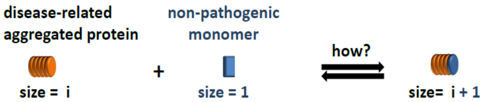
↪ Transmittable.


disease-related
aggregated protein
size = i
+
non-pathogenic
monomer
size = 1
how?
size= i + 1



$$\text{SLS} : M_2^{measured} = \alpha(\sum_{i\geq 1} i^2 c_i) + \beta$$





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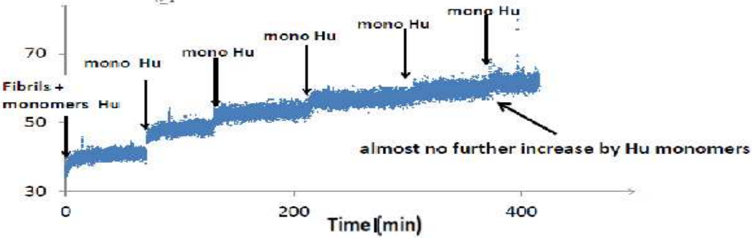

with c_i : the concentration in polymers of size i

α and β experiment parameters.

- Reactional scheme :

- Modelling :

$$\begin{aligned} c_i + c_1 & \xrightarrow{k_i^{on}} c_{i+1}, & i \geq 1, \\ c_i & \xrightarrow[k_i^{dep}]{} c_{i-1} + c_1, & i \geq 2. \end{aligned}$$

- Reactional scheme :

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$$c_i + c_1 \xrightarrow{k_i^{on}} c_{i+1}, \qquad i \geq 1,$$
$$c_i \xrightarrow[k_i^{dep}]{} c_{i-1} + c_1, \qquad i \geq 2.$$

Mass Action Low

$$\begin{cases} \dfrac{dc_i}{dt} = -k_i^{on} c_1 c_i + k_{i-1}^{on} c_1 c_{i-1} - k_i^{dep} c_i + k_{i+1}^{dep} c_{i+1} & i \geq 2, \\ \dfrac{dc_1}{dt} = -\sum_{i=2}^{\infty} \left(k_i^{on} c_1 c_i - k_{i+1}^{dep} c_{i+1} \right) - 2 \left(k_1^{on} c_1^2 - k_2^{dep} c_2 \right). \end{cases}$$

↪ The Becker-Döring system (Becker-Döring, *1935*, Burton, *1977*)

Usually rewritten as:

$$\begin{cases} \dfrac{dc_i}{dt} = J_{i-1}(c) - J_i(c) \qquad i \geq 2, \\ \dfrac{dc_1}{dt} = -\sum_{i=2}^{\infty} J_i(c) - 2J_1(c). \end{cases} \tag{1}$$

Growth rate : $J_i(c) = k_i^{on} c_1 c_i - k_{i+1}^{dep} c_{i+1}$ for $i \geq 1$.

- J. M. Ball and J. Carr and O. Penrose, Commun. Math. Phys., 1986.
- P. E. Jabin and B. Niethammer, J. Diff. Equa., 2003.
- J. A. Canizo and B. Lods,J. Diff. Equa., 2013.

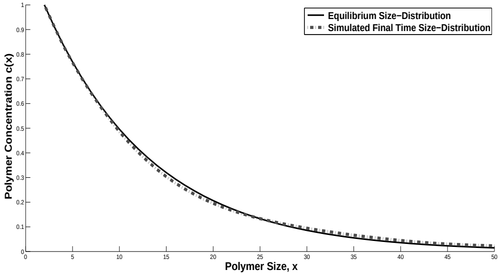
Let's consider :

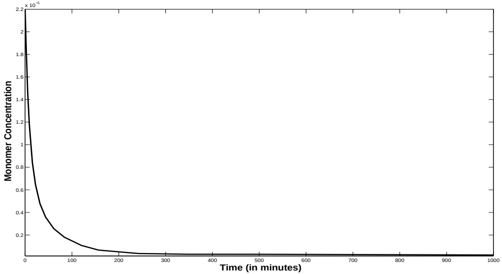
$$k_i^{on} = k^{on} \mathbb{1}_{2 \leq i < \infty} \quad \text{and} \quad k_i^{dep} = k^{dep} \mathbb{1}_{2 < i \leq \infty},$$

Then:

$$\begin{cases} \tilde{c}_i = P_1 \left(1 - \dfrac{\tilde{c}_1}{c_1^s}\right) \left(\dfrac{\tilde{c}_1}{c_1^s}\right)^{i-2} & \text{when } 2 \leq i \leq \infty, \\ \tilde{c}_1(\rho) = \dfrac{1}{2} (\rho - P_1 + c_1^s) - \sqrt{(\rho - P_1 - c_1^s)^2 + 4 c_1^s P_1}, & \end{cases}$$

$$c_1^s = \frac{k^{dep}}{k^{on}}, P_1 = \sum_2^\infty c_i(t=0).$$





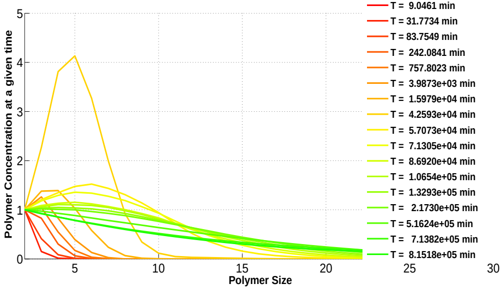
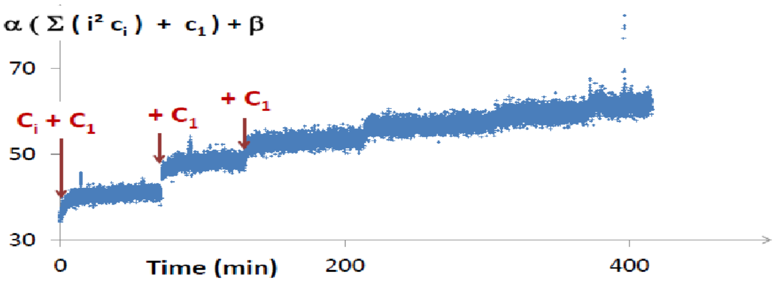
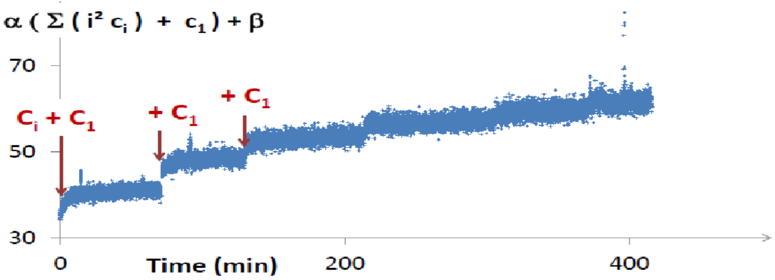


Figure: $\rho = c_1(t=0) = 2.2.10^{-5}\mu M$, $k^{dep}/k^{on} = 2.10^{-5}\mu M$, $\tilde{c}_1 = 1.5.10^{-7}\mu M$

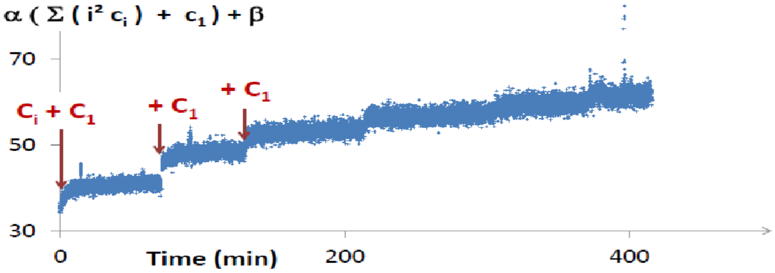


$\alpha (\Sigma (i^2 c_i) + c_1) + \beta$
70
50
30
$C_i + C_1$
$+ C_1$
$+ C_1$
0
Time (min)
200
400



which variation is written :

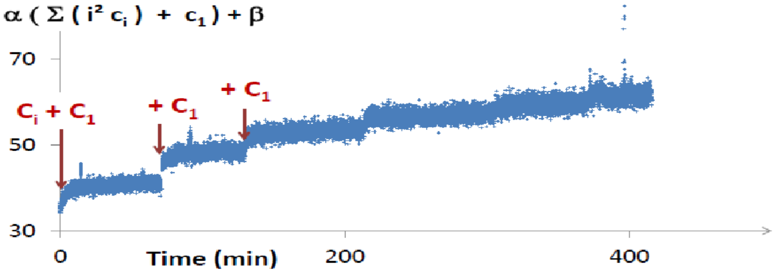
$$\frac{d M_2^{measured}}{dt} = \frac{d}{dt} \sum_{i \geq 2} i^2 c_i + \frac{d c_1}{dt},$$



which variation is written :

$$\frac{d\mathrm{M}_2^{measured}}{dt} = \frac{d}{dt}\sum_{i\geq 2} i^2 \mathrm{c}_i + \frac{d\mathrm{c}_1}{dt},$$

$$\Rightarrow \frac{d\mathrm{M}_2^{measured}}{dt} = 2\mathrm{k}^{\mathrm{on}}\mathrm{c}_1\mathrm{M} - 2\mathrm{k}^{\mathrm{dep}}\left(\mathrm{M} - \mathrm{P}\right). \qquad (2)$$



which variation is written :

$$\frac{dM_2^{measured}}{dt} = \frac{d}{dt}\sum_{i\geq 2} i^2 c_i + \frac{dc_1}{dt},$$

$$\Rightarrow \frac{dM_2^{measured}}{dt} = 2k^{on}c_1 M - 2k^{dep}(M - P). \qquad (2)$$

$P := \sum_{i\geq 2} c_i(t)$ and $M := \sum_{i\geq 2} ic_i(t)$

- System Summation:

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$$\frac{dP}{dt} = 0,$$

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$$\left.\begin{aligned} \frac{dP}{dt} &= 0, \\ \frac{dM}{dt} &= k^{on}c_1P - k^{dep}P, \\ \frac{dc_1}{dt} &= -k^{on}c_1P + k^{dep}P, \end{aligned}\right\}$$

$$\Rightarrow \left\{ \begin{aligned} & P = P^{in} \\ & M(t) = M^{in} - k^{on}\left(c_1^{in} - c_1^{eq}\right) e^{-k^{on}P^{in}t} P^{in} + \left(c_1^{in} - c_1^{eq}\right) \\ & c_1(t) = \left(c_1^{in} - c_1^{eq}\right) e^{-k^{on}P^{in}t} + c_1^{eq} \end{aligned}\right.$$

$$\Rightarrow \mathrm{M}_2^{measured} = \mathrm{M}_2^{in} - \frac{2}{\mathrm{P}^{in}}(\mathrm{M}^{in} + \mathrm{c}_1^{in} - \mathrm{c}_1^{eq})(\mathrm{c}_1^{in} - \mathrm{c}_1^{eq})(e^{-\mathrm{k}^{\mathrm{on}}\mathrm{P}^{in}t} - 1) + \frac{(\mathrm{c}_1^{eq} - \mathrm{c}_1^{in})^2}{\mathrm{P}^{in}}(e^{-2\mathrm{k}^{\mathrm{on}}\mathrm{P}^{in}t} - 1) + 2\mathrm{k}^{\mathrm{dep}}\mathrm{P}^{in}t,$$

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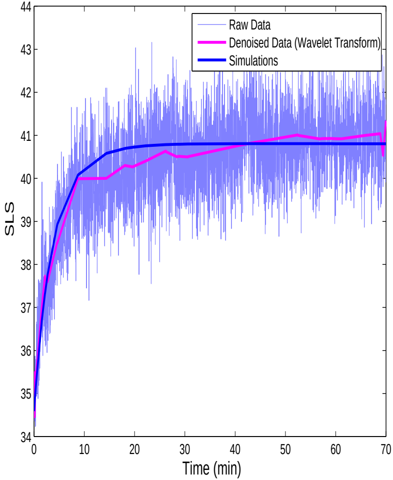
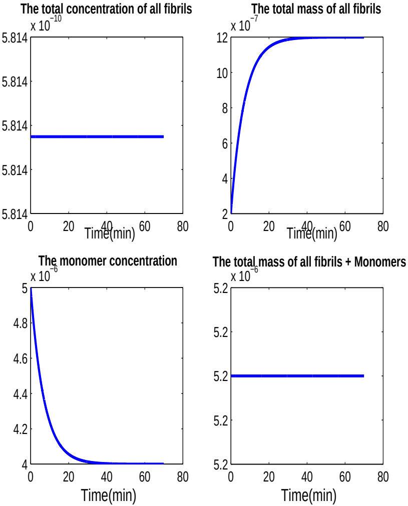
$\Rightarrow$ By the least squared method :

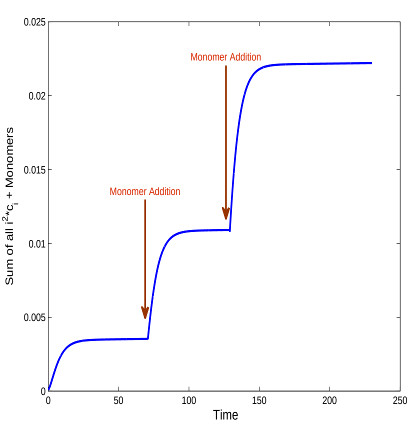
$$J\left(\mathrm{k}^{\mathrm{on}}, \mathrm{k}^{\mathrm{dep}}, \alpha, \beta\right) = \sum_{i=1}^{n} \left| \left(\alpha \mathrm{M}_2^{measured}\left(t_i; \mathrm{k}^{\mathrm{on}}, \mathrm{k}^{\mathrm{dep}}\right) + \beta\right) - SLS(t_i) \right|^2$$

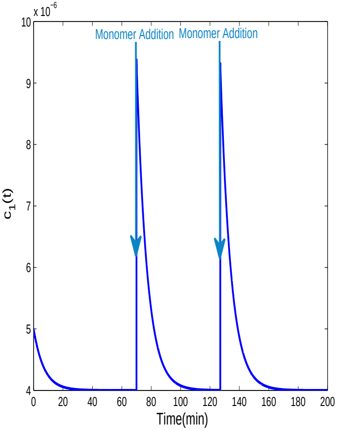




$\Rightarrow \mathrm{k}^{\mathrm{on}} = 2.7.10^8 mol.L^{-1}.min^{-1}$ and $\mathrm{k}^{\mathrm{dep}} = 950 min^{-1}$

- Further monomer addition :





High monomer consumption $\rightarrow$ High increase of i $\rightarrow$ High gaps in $\sum i^2 c_i$.

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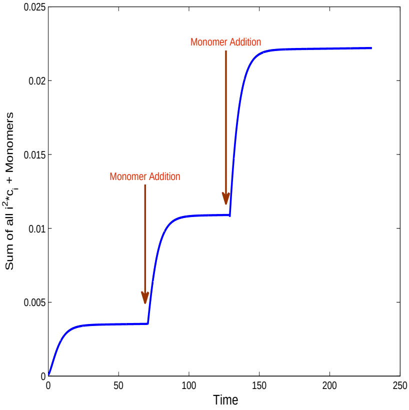
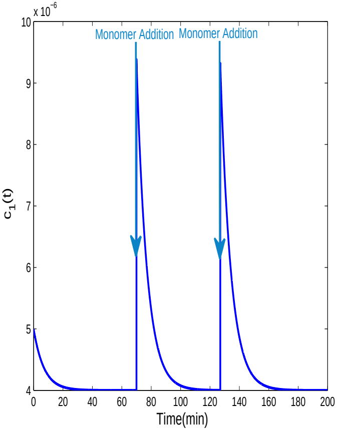
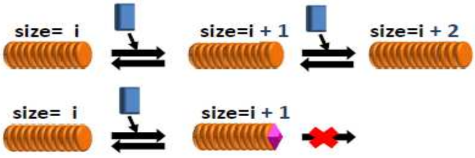




High monomer consumption $\rightarrow$ High increase of i $\rightarrow$ High gaps in $\sum i^2 c_i$.
The polymerization is not slowing down.

A “**deficient**” fibril would be created by the polymerization of a “**classical**“ fibril with a polymerization rate k^{on_m}.



So that :

$$M_2^{measured} = \alpha \left(\sum_{i=1}^{\infty} i^2 c_i + \sum_{i=1}^{\infty} i_m^2 c_i^m \right) + \beta.$$

↪ The reactions scheme :

$$\begin{aligned}
\mathsf{C}_i + \mathsf{C}_1 &\xrightarrow{\mathsf{k}_i^{\mathsf{on}}} \mathsf{C}_{i+1}, \\
\mathsf{C}_i &\xrightarrow[\mathsf{k}_i^{\mathsf{dep}}]{} \mathsf{C}_{i-1} + \mathsf{C}_1, \\
\mathsf{C}_i + \mathsf{C}_1 &\xrightarrow{\mathsf{k}_i^{\mathsf{on_m}}} \mathsf{C}_{i+1}^{\mathsf{m}} \not\rightarrow, \\
\mathsf{C}_i^{\mathsf{m}} &\xrightarrow[\mathsf{k}_i^{\mathsf{dep_m}}]{} \mathsf{C}_{i-1} + \mathsf{C}_1,
\end{aligned}$$

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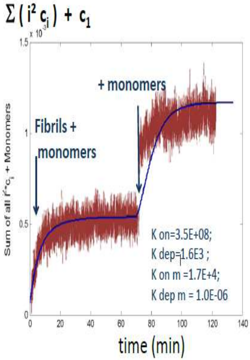
c_i^{m} &\xrightarrow[k_i^{dep_m}]{} c_{i-1} + c_1,
\end{aligned}
$$

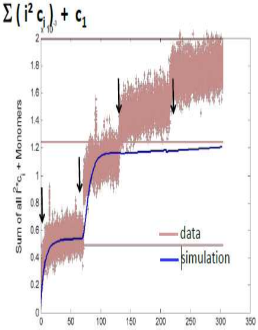
Mass Action Low

$$
\left\{
\begin{aligned}
\frac{dc_i}{dt} &= -k_i^{on} c_1 c_i + k_{i-1}^{on} c_1 c_{i-1} - k_i^{on_m} c_1 c_i - k_i^{dep} c_i \\
&\qquad + k_{i+1}^{dep} c_{i+1} + k_{i+1}^{dep_m} c_{i+1}^{m}, \quad i \geq 2 \\
\frac{dc_i^{m}}{dt} &= k_{i-1}^{on_m} c_1 c_{i-1} - k_i^{dep_m} c_i^{m}, \quad i \geq 3 \\
\frac{dc_1}{dt} &= -\sum_{i=2}^{\infty} k_i^{on} c_1 c_i - \sum_{i=2}^{\infty} k_i^{on_m} c_1 c_i + \sum_{i=2}^{\infty} k_i^{dep} c_i + \sum_{i=3}^{\infty} k_i^{dep_m} c_i^{m} \\
&\qquad -2\left(k_1^{on} c_1^2 - k_2^{dep} c_2\right)
\end{aligned}
\right.
$$

Fitting the 2nd plateau.



Fitting till the 4th plateau.



On contrast to the basic model,
the defective fibril model => a correct 2nd plateau height

But slopes of the 2nd and next additions : not satisfactory.

- The discrete model is able to fit the first steps of the experiments, converging to a size-distribution that fits the size-distribution of fibrils experimentally formed.
- Giving an idea about the order of the kinetics parameters.

- Further work :

  - Trying a successive inactivation pathway.
  - Varying the kinetics parameters (Continuous model).
  - Use the new data with more known parameters ($\alpha, \beta, \mathsf{c}^{\mathsf{in}}$).
  - Scheme considering a two-ends polymerization.