Modélisation probabiliste en biologie cellulaire et moléculaire

Thèse sous la direction de

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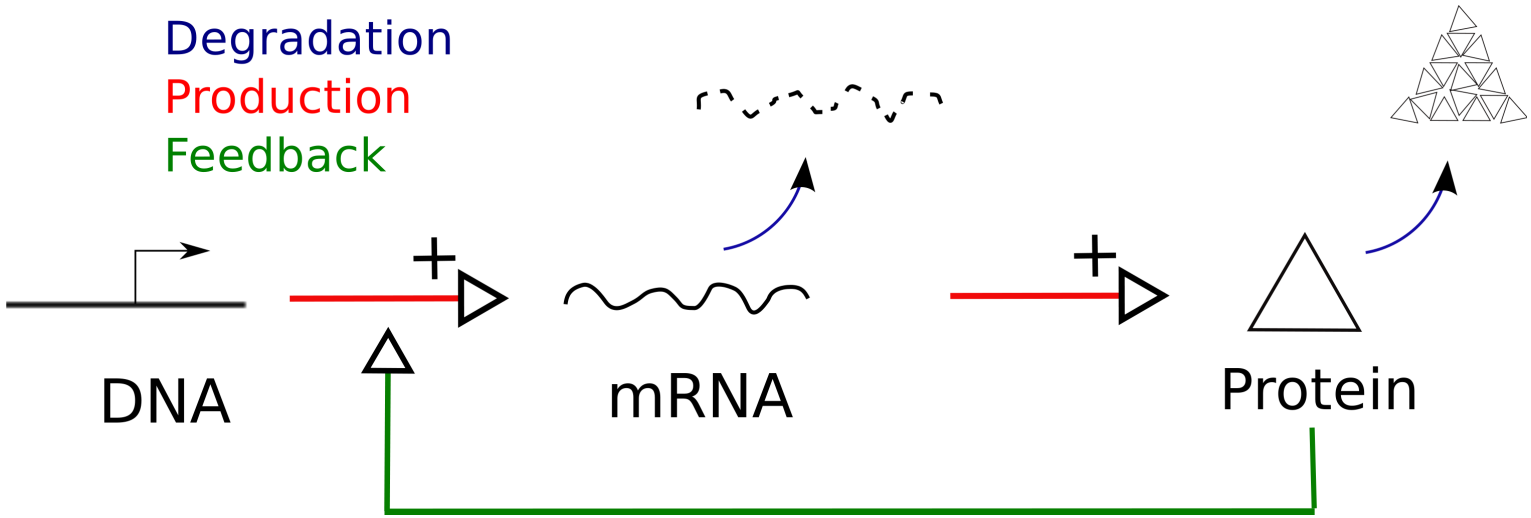
Outline

Outline

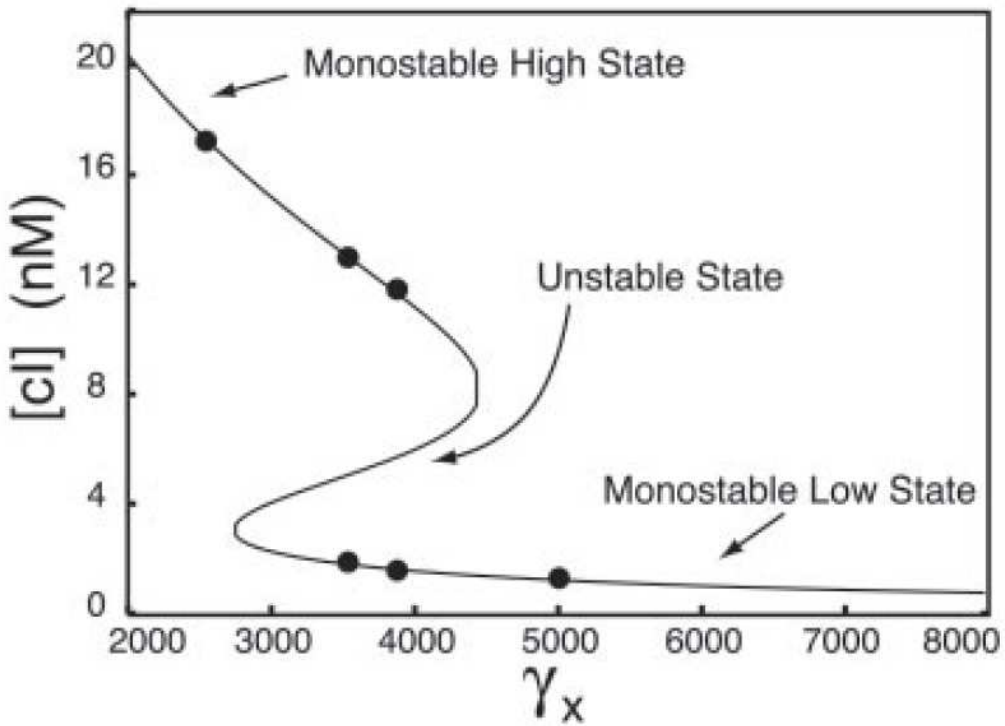
Central Dogma

- Expression of a gene through transcription/translation processes.



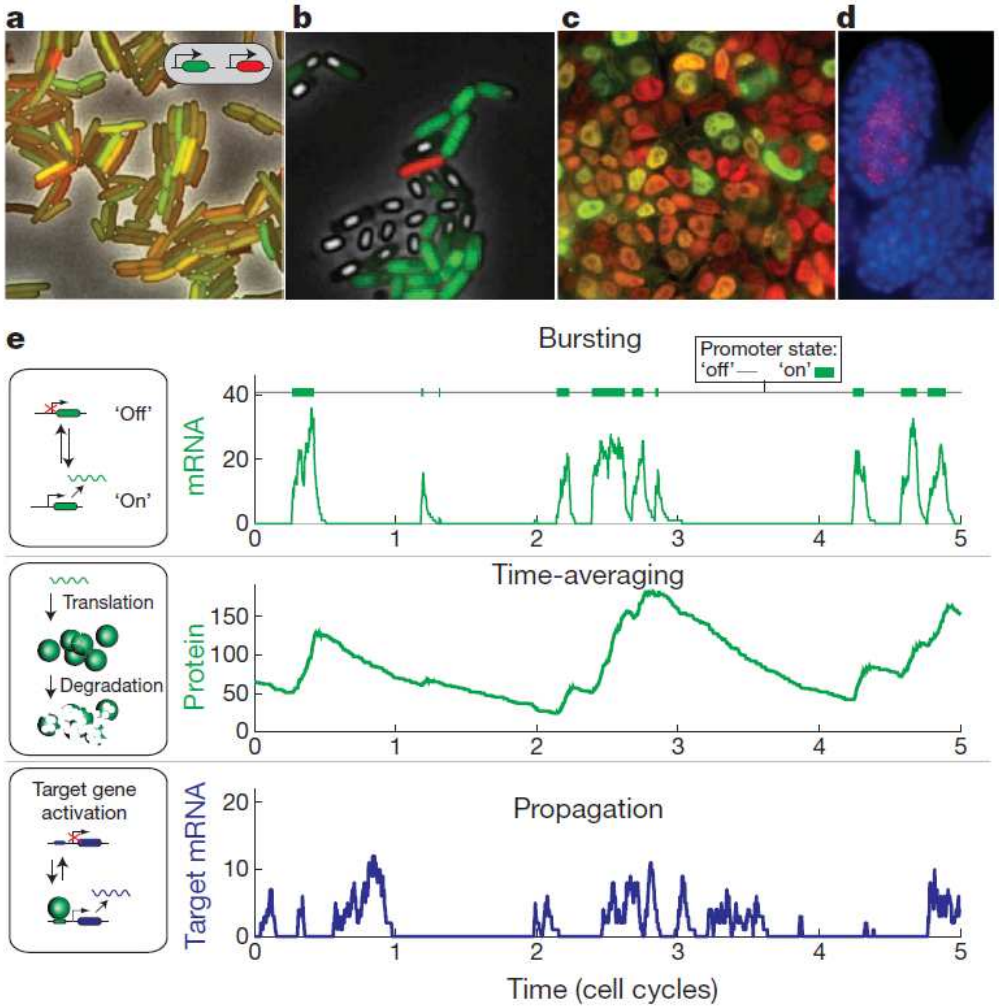
- Non-linear Feedback regulation.

- Bifurcation analysis in Ordinary Differential Equation.
- Application to synthetic biology.



[Goodwin, 1965],[Hasty et al., 2001].

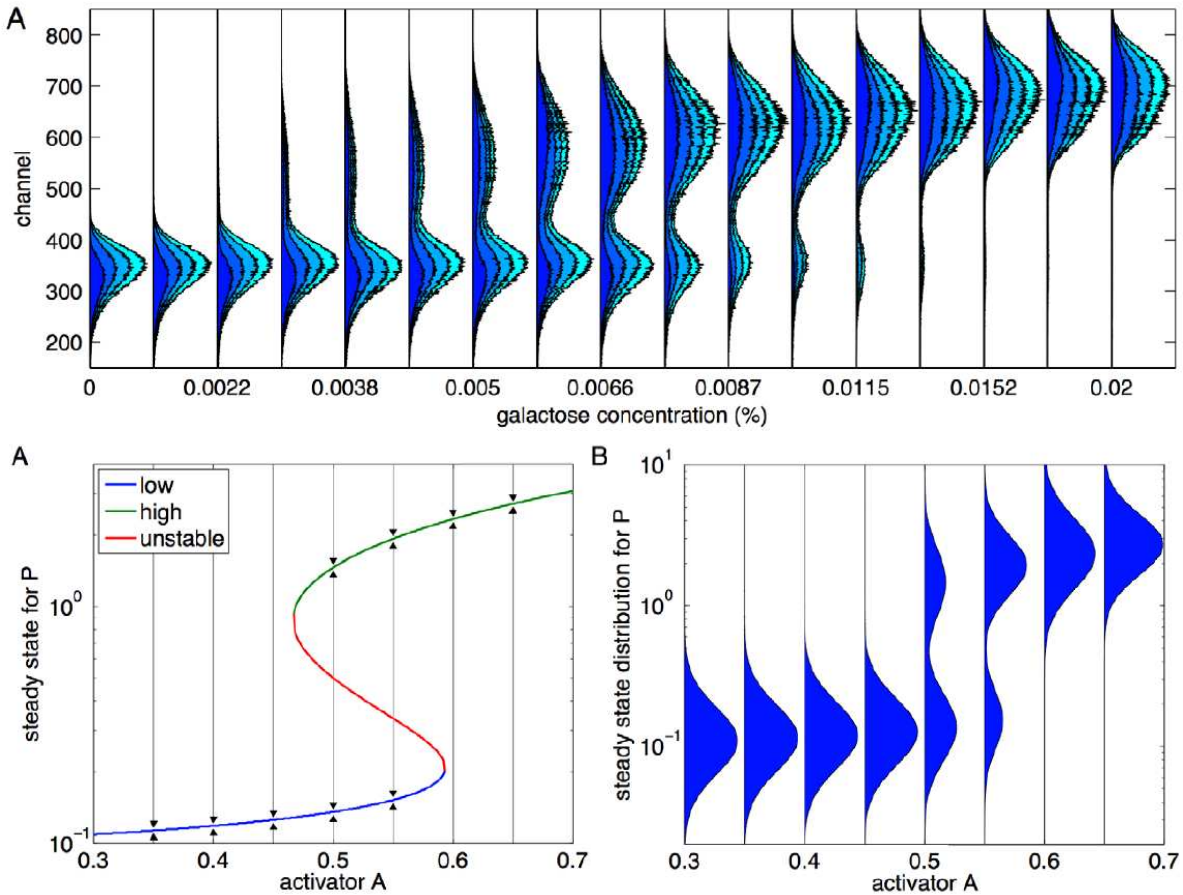
Stochasticity in molecular biology



[Eldar and Elowitz, 2010].

Much more accurate measurements

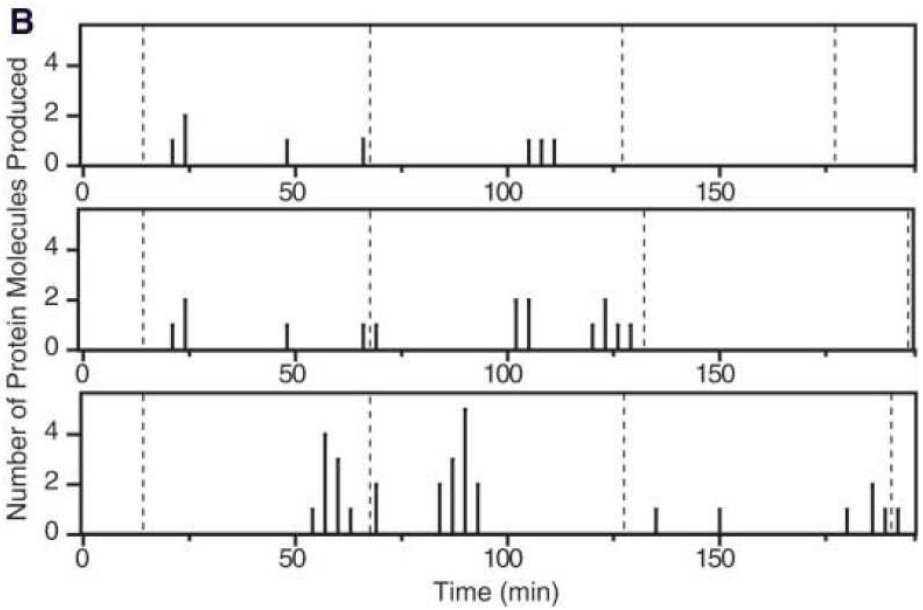
- Bifurcation can be studied on probability distributions.

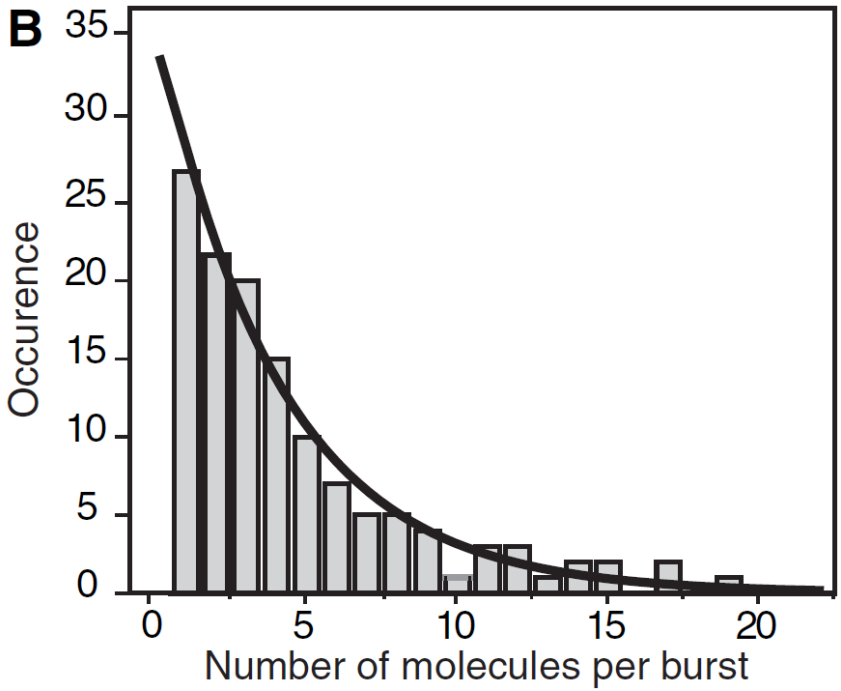


[Song et al., 2010].

Much more accurate measurements

- Trajectories can be analyzed on single cells.

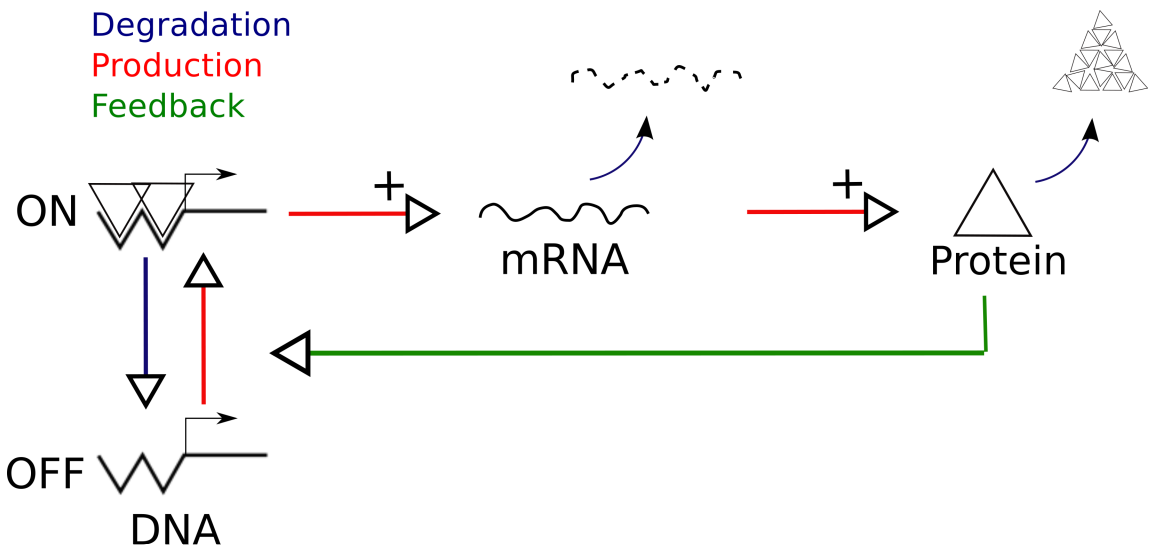




[Yu et al., 2006].

New Central dogma

- Take into account gene state switching. Interpretation as stochastic processes.



[Berg, 1978],
[Peccoud and Ycart, 1995],
[Kepler and Elston, 2001],
[Paulsson, 2005],
[Lipniacki et al., 2006],
[Paszek, 2007],

[Shahrezaei and Swain, 2008].

The bursting phenomena

Question 1) **When does the stochastic model predict burst phenomenon ?**

Question 2) **What can we say in such cases ?**

Outline

We consider the following 2d stochastic kinetic chemical reaction model (X='mRNA', Y='Protein')

$$
\begin{aligned}
\emptyset &\xrightarrow{\lambda_1(X,Y)} X, && \text{Production of } X \text{ at rate } \lambda_1(X,Y)\\
X &\xrightarrow{N\gamma_1(X,Y)} \emptyset, && \text{Destruction of } X \text{ at rate } N\gamma_1(X,Y)\\
\emptyset &\xrightarrow{N\lambda_2(X,Y)} Y, && \text{Production of } Y \text{ at rate } N\lambda_2(X,Y)\\
Y &\xrightarrow{\gamma_2(X,Y)} \emptyset, && \text{Destruction of } Y \text{ at rate } \gamma_2(X,Y)
\end{aligned}
$$

with $\gamma_1(0,Y) = \gamma_2(X,0) = 0$ to ensure non-negativity.

$$
\begin{aligned}
\mathbb{B}_N f(x,y) =& \lambda_1(x,y)\Big[f(x+1,y) - f(x,y)\Big]\\
&+ N\gamma_1(x,y)\Big[f(x-1,y) - f(x,y)\Big]\\
&+ N\lambda_2(x,y)\Big[f(x,y+1) - f(x,y)\Big]\\
&+ \gamma_2(x,y)\Big[f(x,y-1) - f(x,y)\Big].
\end{aligned}
$$

Theorem (R.Y.)

If

- The degradation function on X satisfies

$$\inf_{x\geq 1, y\geq 0} \gamma_1(x,y) = \underline{\gamma} > 0.$$

- The production rate of Y satisfies $\lambda_2(0,y) = 0$, for all $y \geq 0$.
- λ_1 and λ_2 are linearly bounded by $x+y$, and either λ_1 or λ_2 is bounded.

Then, for all $T > 0$, $(X^N(t), Y^N(t))_{t\geq 0}$ converges in $L^1(0,T)$ to $(0, Y(t))$, whose generator is given by

$$\begin{cases} \mathbb{B}_\infty \varphi(y) &= \lambda_1(0,y)\Big(\int_0^\infty P_t(\gamma_1(1,\cdot)\varphi(\cdot))(y)dt - \varphi(y)\Big) \\ &\qquad + \gamma_2(0,y)\Big[\varphi(y-1)-\varphi(y)\Big], \\ P_t g(y) &= \mathbb{E}\Big[g(Z(t,y)e^{-\int_0^t \gamma_1(1,Z(s,y))ds}\Big], \\ Ag(z) &= \lambda_2(1,z)\big(g(z+1)-g(z)\big). \end{cases}$$

Sketch of the proof

- We first show tightness and convergence of X based on

$$N\underline{\gamma}\mathbb{E}\Big[\int_0^t \mathbf{1}_{\{X^N(s)\geq 1\}} ds\Big] \leq \mathbb{E}\big[X^N(0)\big] + \mathbb{E}\Big[\int_0^t \lambda_1(X^N(s), Y^N(s)) ds\Big].$$

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- We identify the limiting martingale problem

$$\lambda_2(x,y)\Big[f(x,y+1)-f(x,y)\Big] + \gamma_1(x,y)\Big[f(x-1,y)-f(x,y)\Big] = 0.$$

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- We identify the limiting martingale problem

$$A^x g(y) = \lambda_2(x,y)\Big[g(y+1) - g(y)\Big],$$

for any $x \geq 1$. and we introduce the semigroup P_t^x

$$P_t^x g(y) = \mathbb{E}\big[g(Z_t^{x,y}) e^{-\int_0^t \gamma_1(x, Z_s^{x,y}) ds}\big].$$

Now for any bounded function g, define $f(0,y) = g(y)$ and

$$f(x,y) = \int_0^\infty P_t^x(\gamma_1(x,.) f(x-1,.))(y) dt.$$

Then

$$\lambda_2(x,y)\Big[f(x,y+1) - f(x,y)\Big] + \gamma_1(x,y)\Big[f(x-1,y) - f(x,y)\Big] = 0.$$

- A similar proof for a (continuous state) PDMP model, of generator

$$\mathbb{B}f(x,y) = -N\gamma_1(x,y)\frac{\partial f}{\partial x} + (N\lambda_2(x,y) - \gamma_2(x,y))\frac{\partial f}{\partial y} + \lambda_1(x,y)\int_0^\infty (f(x+z,y) - f(x,y))h(z)dz.$$

- These proofs are based on a simple idea ([Debussche et al., 2011],[Kang and Kurtz, 2011]).
- Other proof : reduction on the Fokker-Planck equation.
- Different scalings lead to different models.

Outline

We look at the stochastic process

$$dx = -\gamma(x)dt + dN(\lambda(x), h(x,\cdot)),$$

whose generator is

$$Af = -\gamma(x)f'(x) + \lambda(x)\Big(\int_0^\infty f(x+y)h(x,y)dy - f(x)\Big),$$

and evolution equation on densities

$$\frac{\partial u(t,x)}{\partial t} = \frac{\partial \gamma(x)u(t,x)}{\partial x} - \lambda(x)u(t,x) + \int_0^x u(t,y)\lambda(y)h(y,x-y)dy,$$

and with $\int_0^\infty h(x,y)dy = 1$, for all x.

Probabilistic techniques

If jumps are independent of positions, *i.e.* $h(x,y) = h(y)$, we have :

Proposition

Suppose $x \mapsto \lambda(x)$ *is continuous on* $(0,\infty)$, $\lambda(0) > 0$, $\gamma(x) = \gamma x$, $\mathbb{E}\left[h\right] < \infty$, *and*

$$\lim_{x\to\infty} \frac{\lambda(x)\mathbb{E}\left[h\right]}{\gamma x} < 1,$$

then there exist $\beta < 1$, $B < \infty$ *and* π *(invariant measure) such that*

$$\|P(t,x,\cdot) - \pi\|_V \leq BV(x)\beta^t, \quad x \in E, \quad t > 0,$$

where $\|\mu\|_f = \sup_{|g|\leq f} \mid \mu(g) \mid$ *and* $V(x) = x + 1$.

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- $Ax = -\gamma x + \lambda(x)\Big(\int_0^\infty (x+y)h(y)dy - x\Big) = -(1 - \frac{\lambda(x)\mathbb{E}\left[h\right]}{\gamma x})\gamma x$

Semigroup techniques

$$\underbrace{\frac{\partial u(t,x)}{\partial t}}_{\frac{du}{dt}} = \underbrace{\frac{\partial \gamma(x)u(t,x)}{\partial x} - \lambda(x)u(t,x)}_{Au=(A_0-\lambda)u} + \underbrace{\int_0^x u(t,y)\lambda(y)h(y,x-y)dy}_{Bu=J(\lambda u)}$$

$$(A, D(A)) \Rightarrow S(t)u(x) = P_0(t)u(x)e^{-\int_0^t \lambda(\phi_r x)dr}$$

Let $C = A + B$. Denote the resolvent $R_s^S u = \int_0^\infty e^{-st} S(t)udt$.

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Let $C = A + B$. Denote the resolvent $R_s^S u = \int_0^\infty e^{-st} S(t)udt$.

Theorem ([Tyran-Kamińska, 2009])
There is a minimal substochastic semigroup P generated by an extension of $(C, D(A))$, and which resolvent is given by

$$R_s^P u = \lim_{n\to\infty} R_s^S \sum_{k=0}^{n} (J(\lambda R_s^S))^k u,$$

and if $K = \lim_{\sigma\to 0} J(\lambda R_\sigma^S)$ has a unique invariant density, then so does for P (and P is stochastic).

- Under good conditions, K is the transition operator for the discrete Markov chain "post-jump", and has for kernel

$$\begin{cases} k(x,y) &= \displaystyle\int_0^x \mathbf{1}_{\{(0,y)\}}(z) h(z,y-z) \frac{\lambda(z)}{\gamma(z)} e^{Q(x)-Q(z)} dz, \\ Q(x) &= \displaystyle\int_x^{\overline{x}} \frac{\lambda(z)}{\gamma(z)} dz. \end{cases}$$

- Modulo integrability conditions, invariant density v^* for K and invariant density u^* for P are related through

$$\begin{cases} \gamma(x)u^*(x) = \displaystyle\int_0^x \overline{H}(z,x-z)\lambda(z)u^*(z)dz, \ \overline{H}(z,x) = \int_x^\infty h(z,y)dy, \\ v^*(x) = \displaystyle\int_0^x h(z,x-z)\lambda(z)u^*(z)dz, \\ u^*(x) = \displaystyle\frac{1}{\gamma(x)} \int_x^\infty e^{Q(y)-Q(x)} v^*(y)dy, \\ v^*(x) = \displaystyle\int_0^x h(z,x-z)\frac{\lambda(z)}{\gamma(z)} e^{-Q(z)} \int_z^\infty v^*(y) e^{Q(y)} dydz. \end{cases}$$

Condition for ergodicity in the exponential case

If jumps are independent of positions, *i.e.* $h(x,y) = h(y)$ and exponentially distributed, of mean b, *i.e.* $h(y) = \frac{1}{b}e^{-y/b}$, then

Theorem (M. Tyran-Kamińska, M. Mackey, R.Y.)

Under technical assumptions (for integrability), and if

$$\lim_{x\to\infty} \frac{\lambda(x)}{\gamma(x)} < \frac{1}{b},$$

$$Q(0) := \int_0^{\overline{x}} \frac{\lambda(z)}{\gamma(z)} dz = \infty,$$

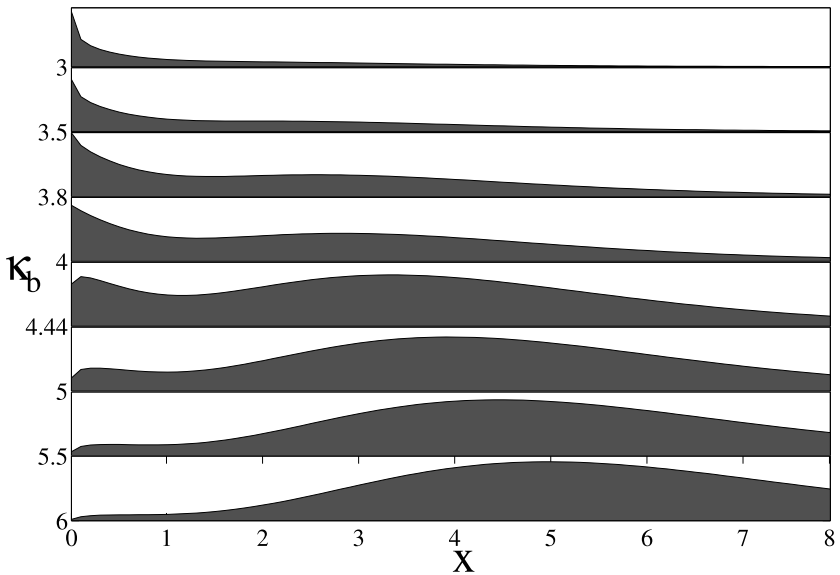
then P is ergodic with unique invariant density

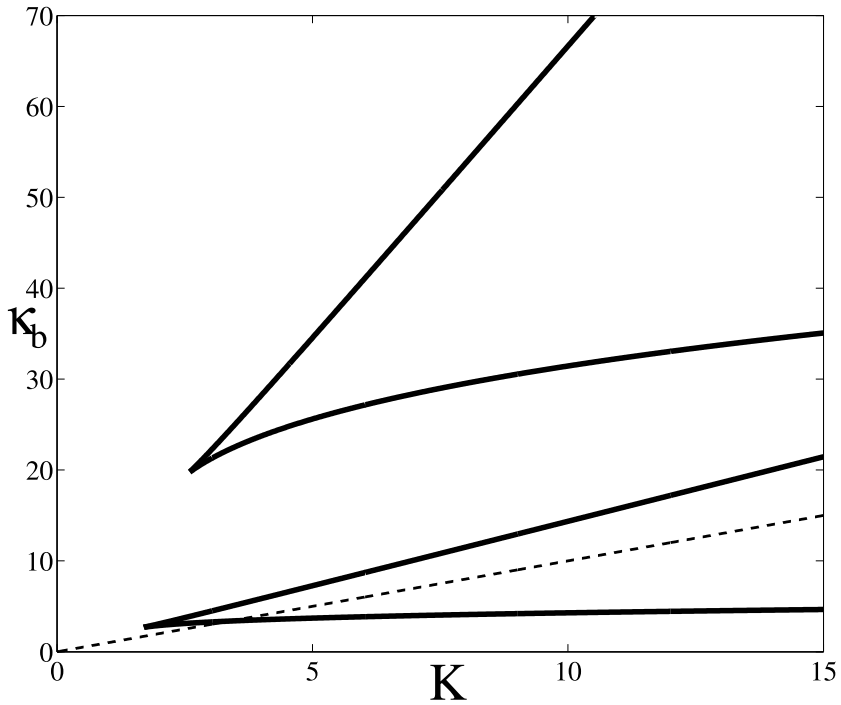
$$u^*(x) = \frac{1}{c\gamma(x)} e^{-x/b - Q(x)}.$$

Bifurcation

This analytical approach allows us to deduce that the number of modes of the stationary state is linked to the solution of

$$\lambda(x) = \frac{\gamma(x)}{b} + \gamma'(x).$$





Further results (not developed here)

- This can be used to find $\lambda(x)$ and b from observations of (u^*, γ).
- The convergence rate can be estimated from coupling techniques.

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- The convergence rate can be estimated from coupling techniques.

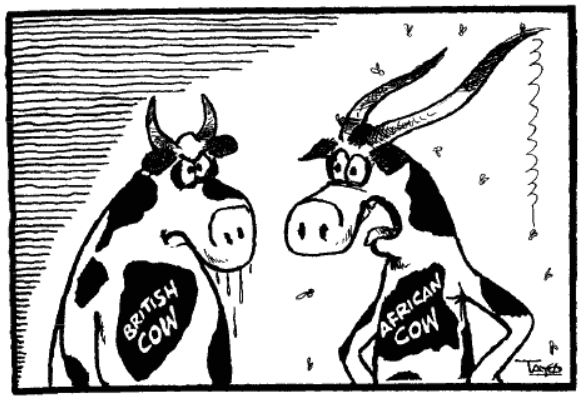
Perspectives

- Other jump size kernel h.
- Waiting time properties.
- Switch and bursting model.
- Include cell division and study population dynamics.
- Characterize oscillations in two-dimensional model.

Outline

Prion Diseases

- Creutzfeldt-Jakob : First human prion disease described (1929).
- Mad cow disease, Scrapie.
- Kuru (New Guinea)



We may be skinny, but at least we're not MAD !

Prion Diseases

Epidemiology

- All prion diseases are transmissible, *i.e.* infectious.
- Some prion diseases are sporadic, they appear spontaneously, without cause.
- Some prion diseases are genetic.

Symptoms

- Affect the structure of the brain ;
- Convulsion, Dementia, Loss of balance ;
- Always fatal.

Outline

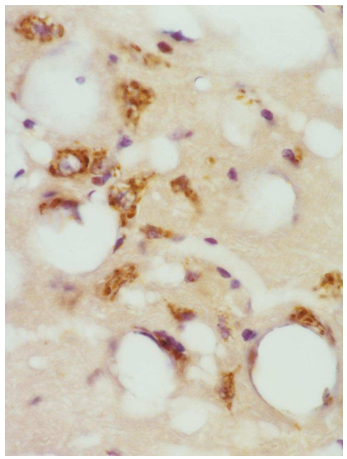
What is prion ?

A protein

- A protein called PRION is the cause of this disease
- It is neither a bacteria, nor an viroid like agent !
- Stanley Prusiner was awarded Nobel price in Physiology and Medicine in 1997 for his discovery.

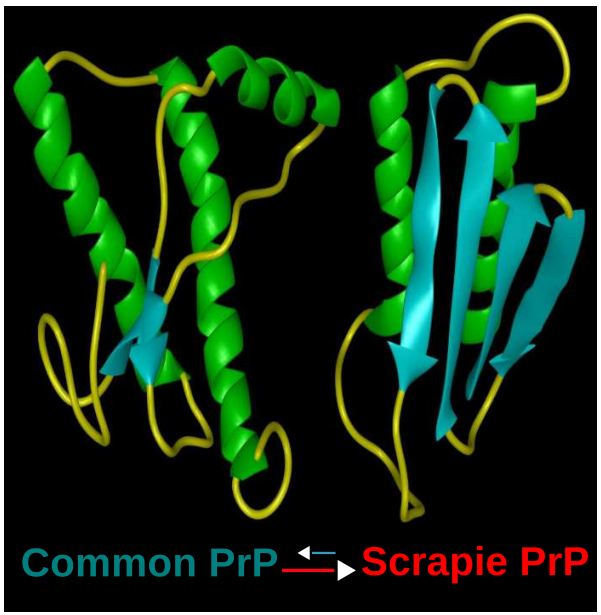
Histopathology

- Accumulation of a protein in the amyloid form.
- Spongiosis.



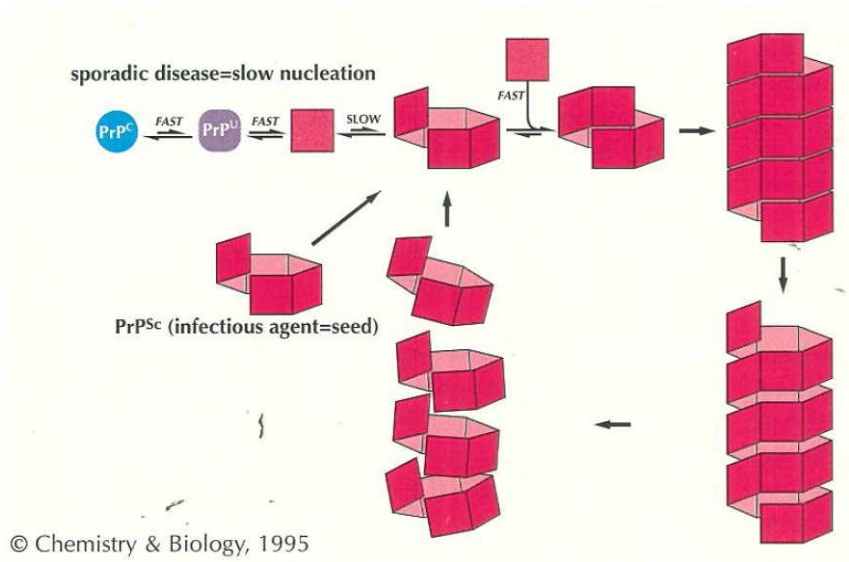
Nucleation-Polymerization

Conformation change



Normal $\Leftrightarrow$ Misfolded

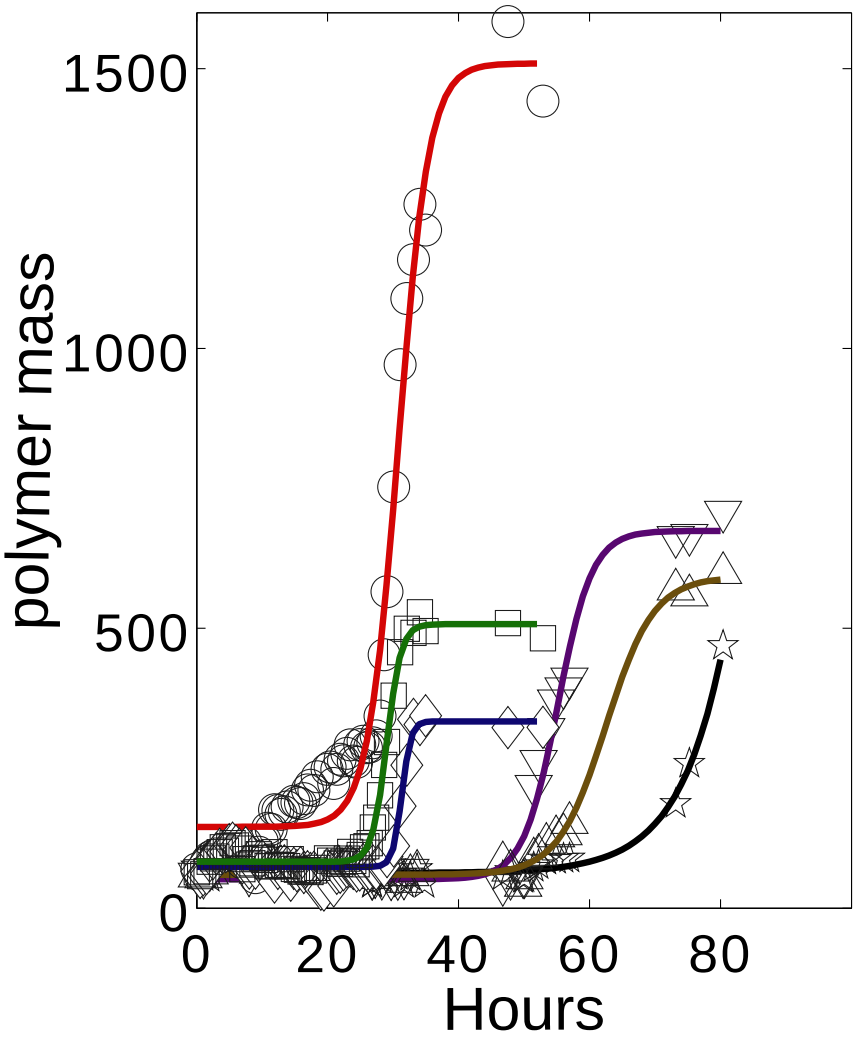
Lansbury's model



[Lansbury and Caughey, 1995].

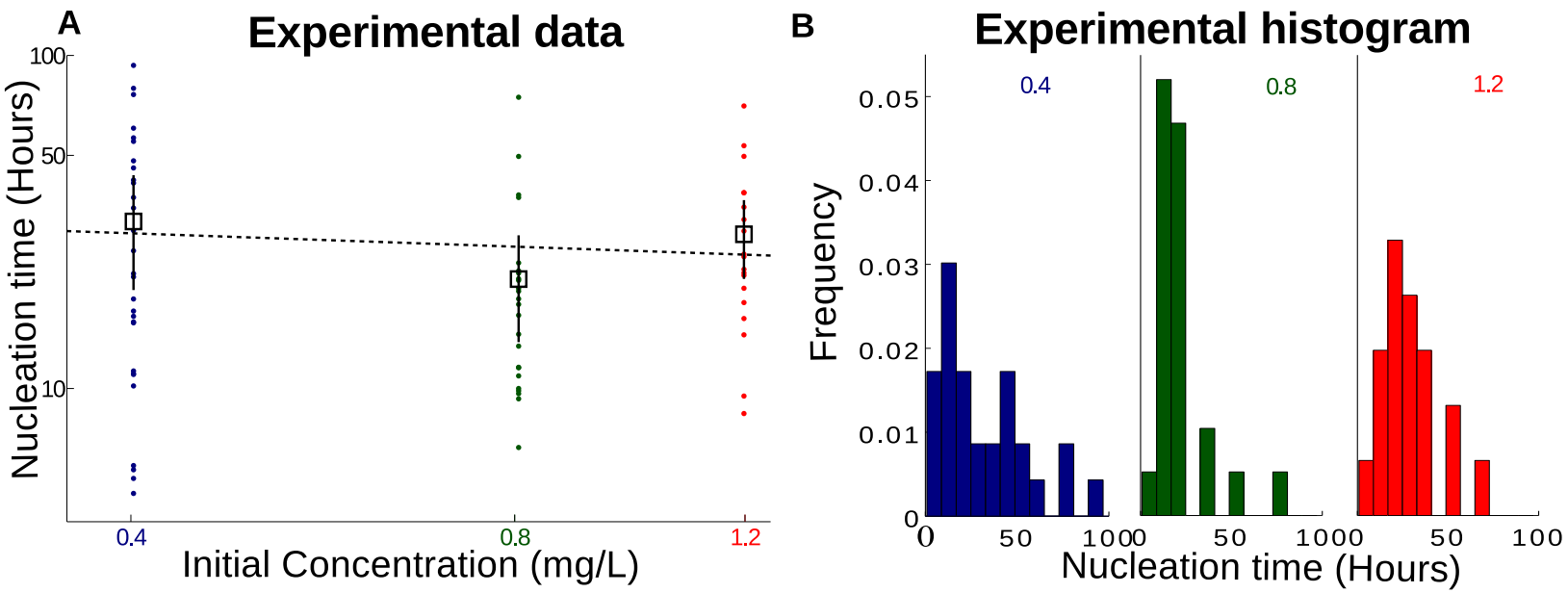
Outline

- *In vitro* spontaneous polymerization experiments.
- Time series of polymer mass.



Statistics of nucleation time

- Relation between the nucleation time and the initial concentration in log plots.



- Full distribution of the nucleation time.

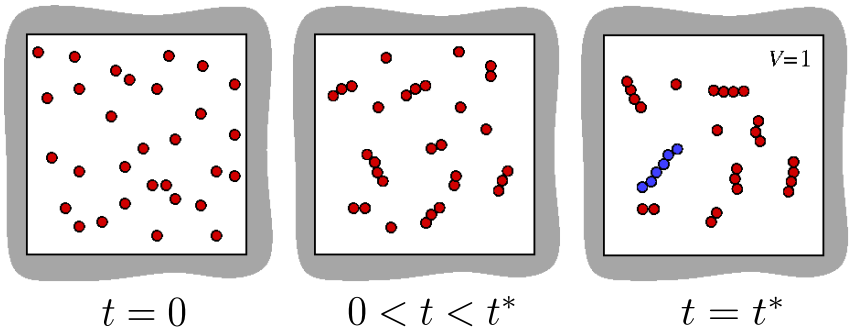
Questions

- Can a probabilistic model reproduce the observed variability ?
- Can it help to identify parameters ?
- Can a model include different strain structures ?

Outline

Reversible aggregation model

$$C_i + C_1 \underset{q}{\overset{p}{\rightleftharpoons}} C_{i+1}$$



where

$$C_i = \sharp\{\text{molecules of size i}\}.$$

The nucleation time is given by a waiting time problem,

$$T_{lag} = \inf\{t \geq 0 : C_N(t) = 1\},$$

with initial condition $C_1(0) = M$, $C_i(0) = 0$, $i \geq 2$.
N is the nucleus size.

Constant monomer formulation

If we suppose

$$C_1(t) \equiv M$$

We can solve exactly the probability distributions (Poisson) and we deduce

$$S(t) := \mathbb{P}\big\{C_N(s) = 0, s \leq t\big\} = \mathbb{P}\big\{C_N(t) = 0\big\} = e^{-c_N(t)},$$

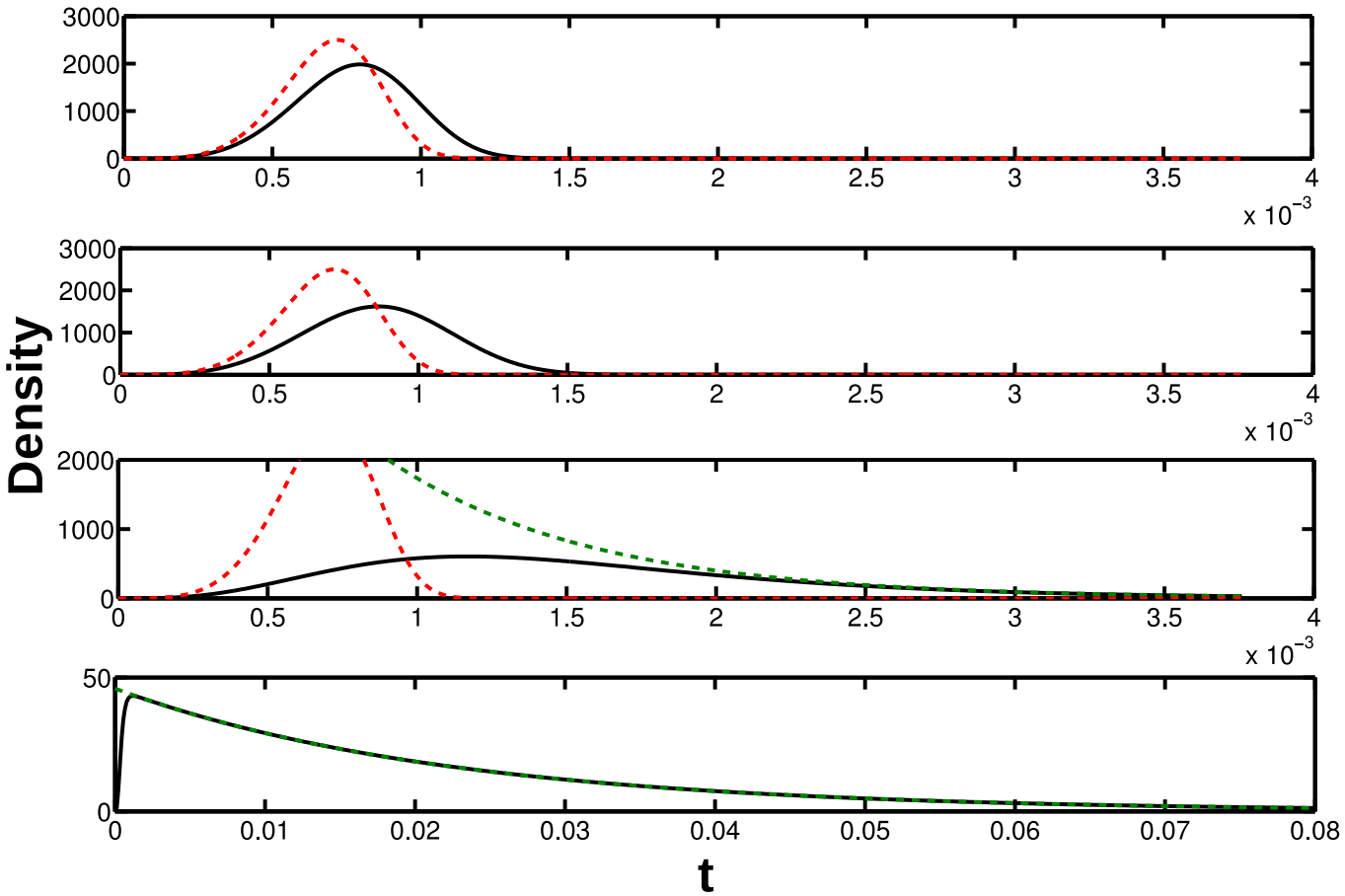
where $(c_i)_{i=2..N}$ are solution of the linear deterministic system (c_n is absorbing) :

$$\begin{cases} \dot{c}_2 &= pM(\frac{1}{2}M - c_2) - q(c_2 - c_3), \\ \dot{c}_i &= pM(c_{i-1} - c_i) - q(c_i - c_{i+1}), \quad 3 \leq i \leq N-2, \\ \dot{c}_{N-1} &= pM(c_{N-2} - c_{N-1}) - qc_{N-1}, \\ \dot{c}_N &= pMc_{N-1}. \end{cases}$$

Nucleation time distribution ($C_1(t) \equiv M$)

$M \to \infty$: Weibull $\frac{M^N}{2(N-2)!} t^{N-2} \exp(-\frac{M^N}{2(N-1)!} t^{N-1})$

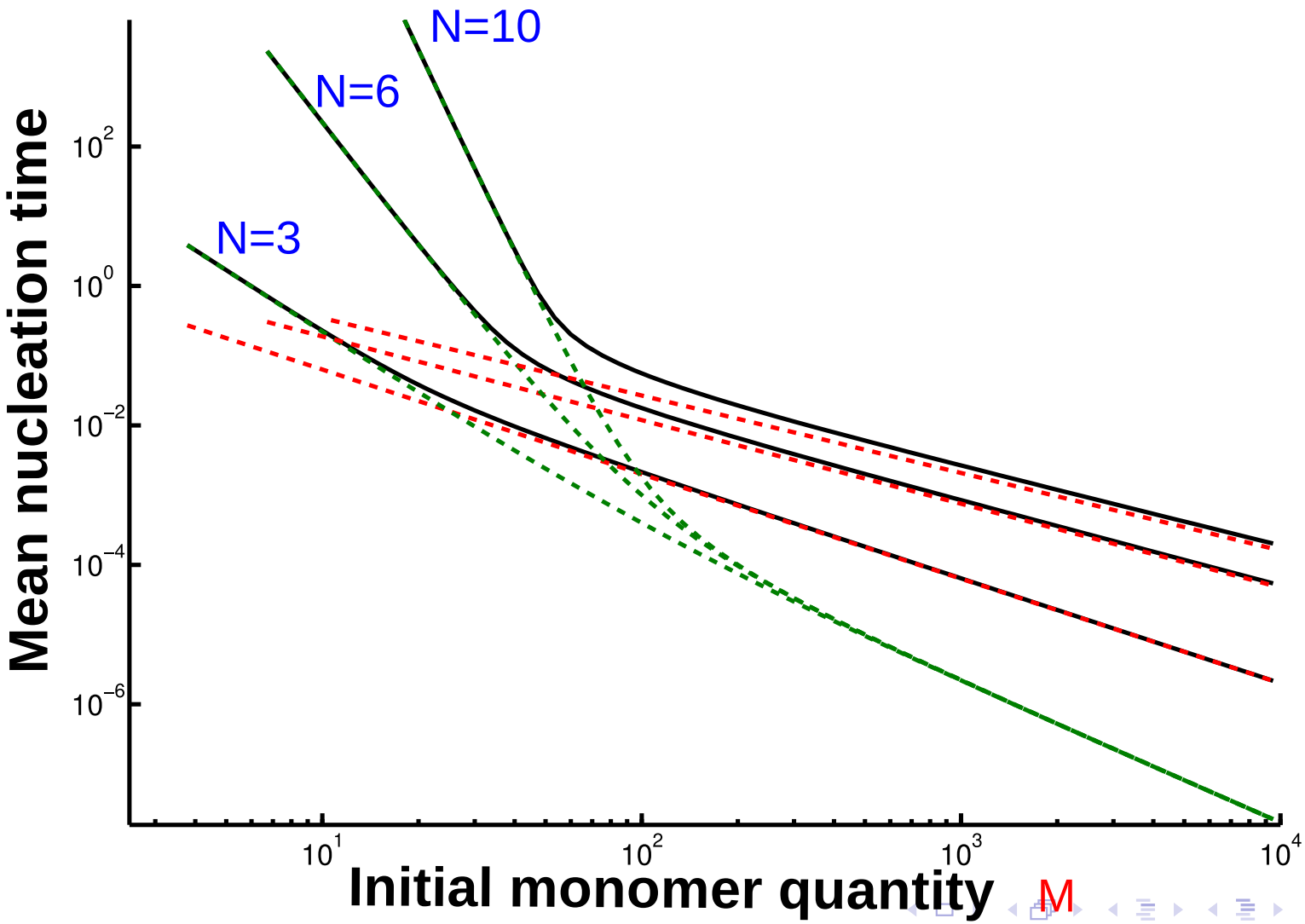
$q \to \infty$: exponential $\frac{M^N}{2q^{N-2}} \exp(-\frac{M^N}{2q^{N-2}} t)$



$N = 6$,
$M = 1000$,

$$q = \begin{cases} 10^2, \\ 10^3, \\ 4.10^3, \\ 10^4. \end{cases}$$

Mean nucleation time versus initial monomer quantity in log scale ($C_1(t) \equiv M$)



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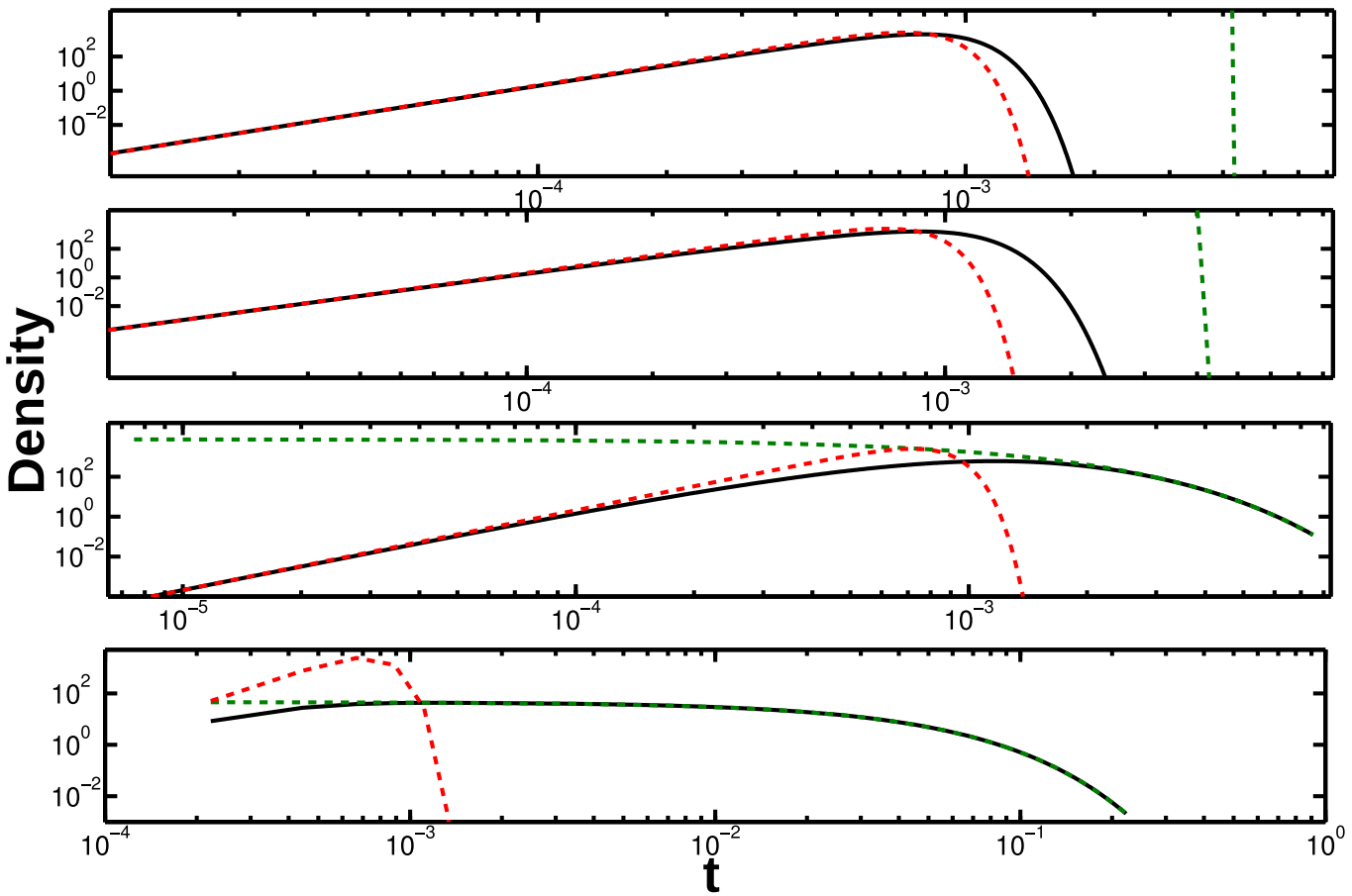

$N = 6$,
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Mass conservative formulation

We now suppose

$$\sum_{i=1}^{N} iC_i(t) \equiv M.$$

Kolmogorov backward equations $\Rightarrow$ Linear system on

$$S(t, \{C^0\}) = \mathbb{P}\{C_N(t) = 0 \mid C_i(0) = C_i^0\}$$

Problem : Dimension of the system

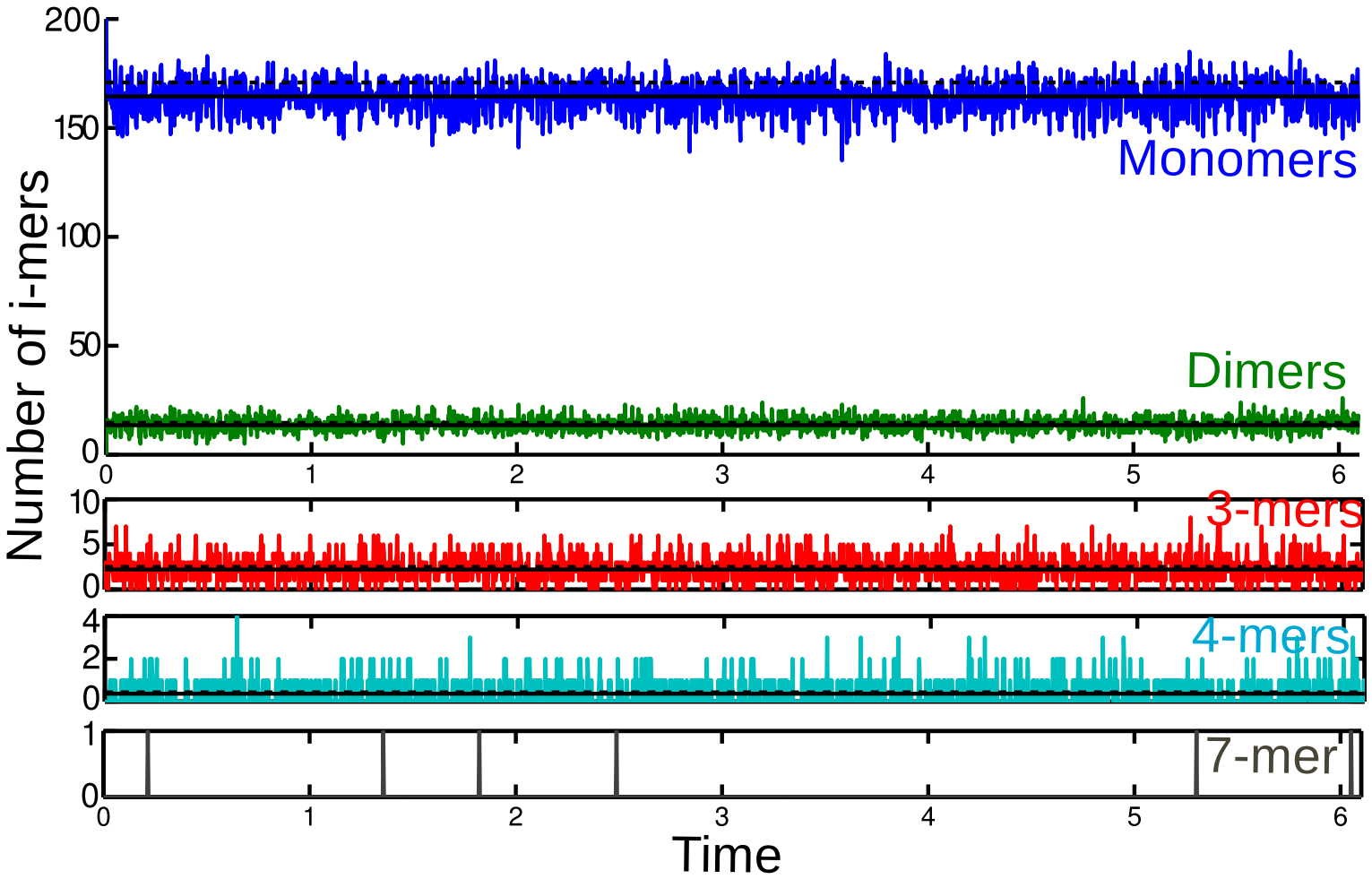
$$\sharp\{\text{configuration } \{C^0\}, \sum_{i=1}^{N} iC_i^0 = M, C_N^0 = 0\} \approx \frac{M^N}{N!}$$

In general, we look for approximate solution for extreme parameter values : $q \gg M$ and $q \ll M$. We use

- known deterministic solution ;
- time scale separation ;
- scaling laws ;
- phase space dimension reduction ;
- linear model ;
- numerical simulation.

Trajectories in the unfavorable case $q \gg M$

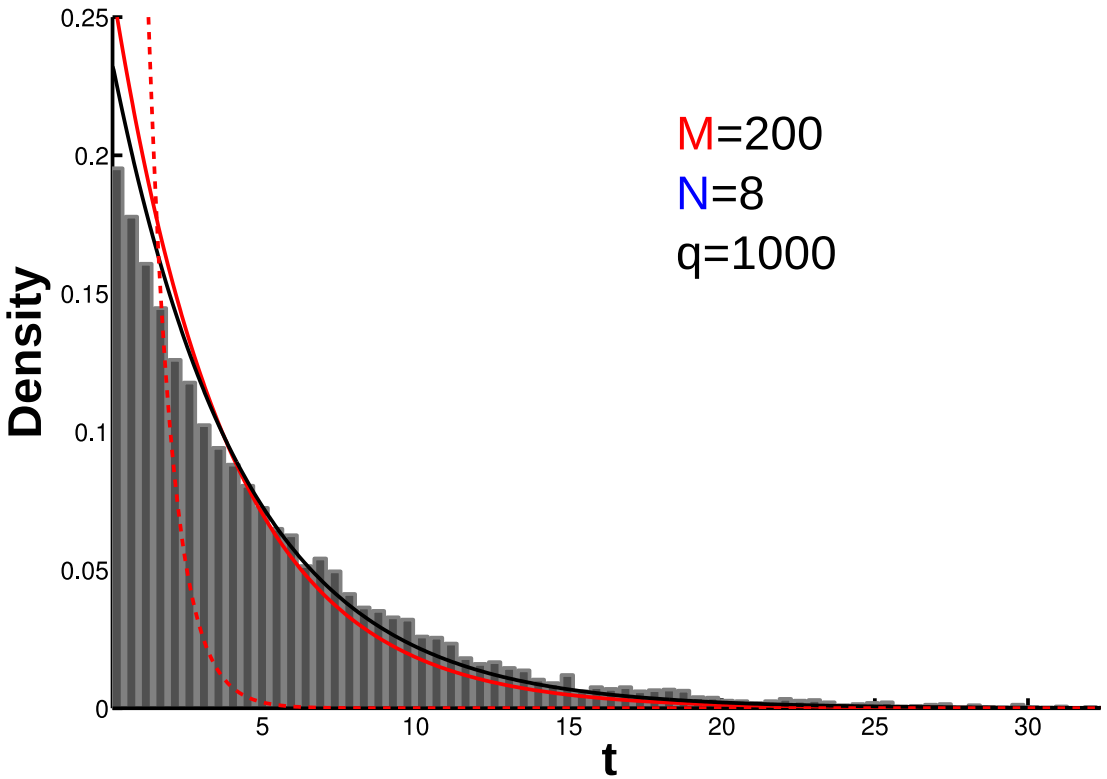
Pre-equilibrium hypothesis (ex : $M = 200, N = 8, q = 1000$).



Nucleation time distribution in the unfavorable case $q \gg M$: exponential law

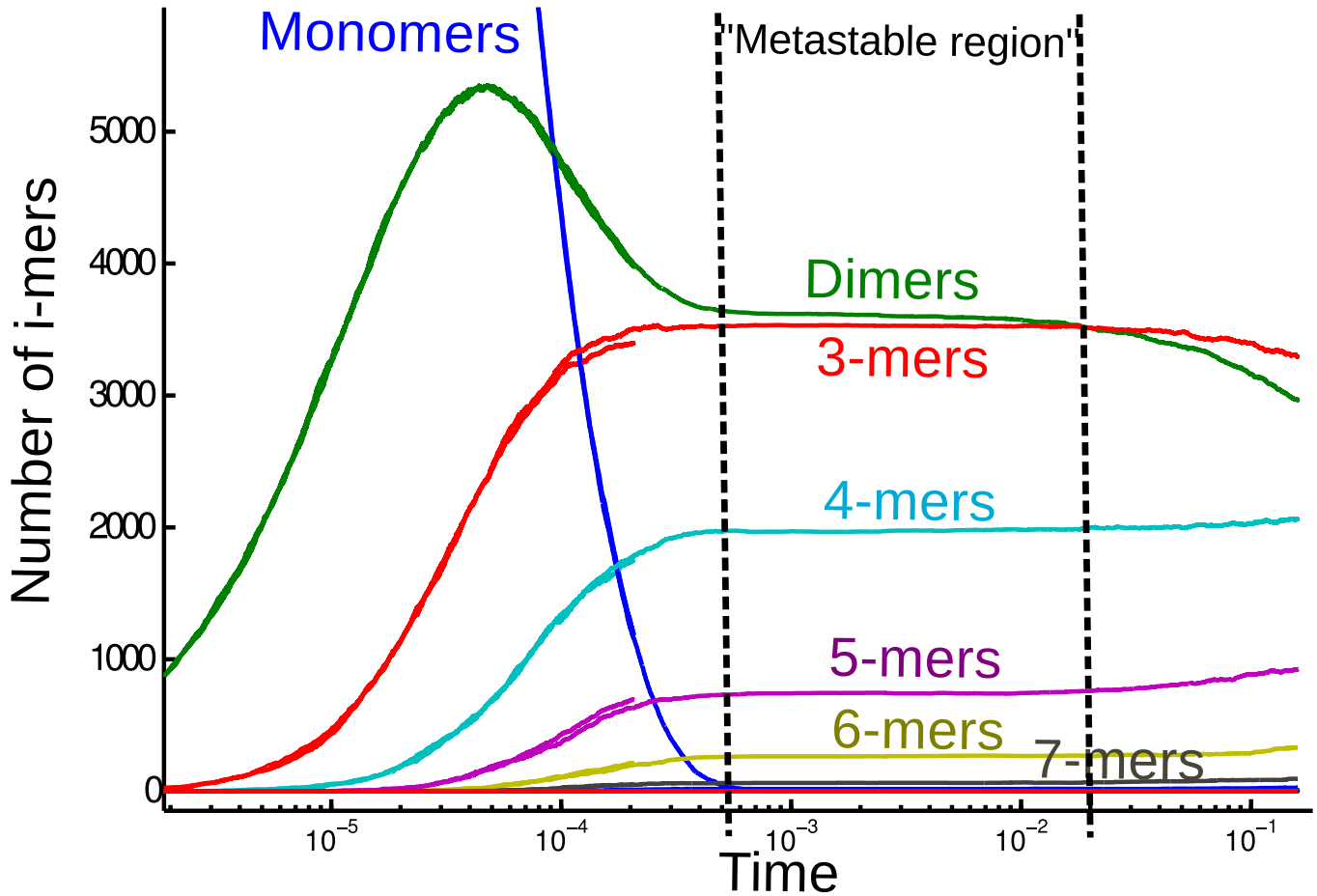
$T_{lag} \sim$ exponential law, of parameter

$$< C_1 C_{N-1} >_{t\to\infty} (M) \approx c_1(t \to \infty) c_{N-1}(t \to \infty) \approx \frac{M^N}{2q^{N-2}}$$



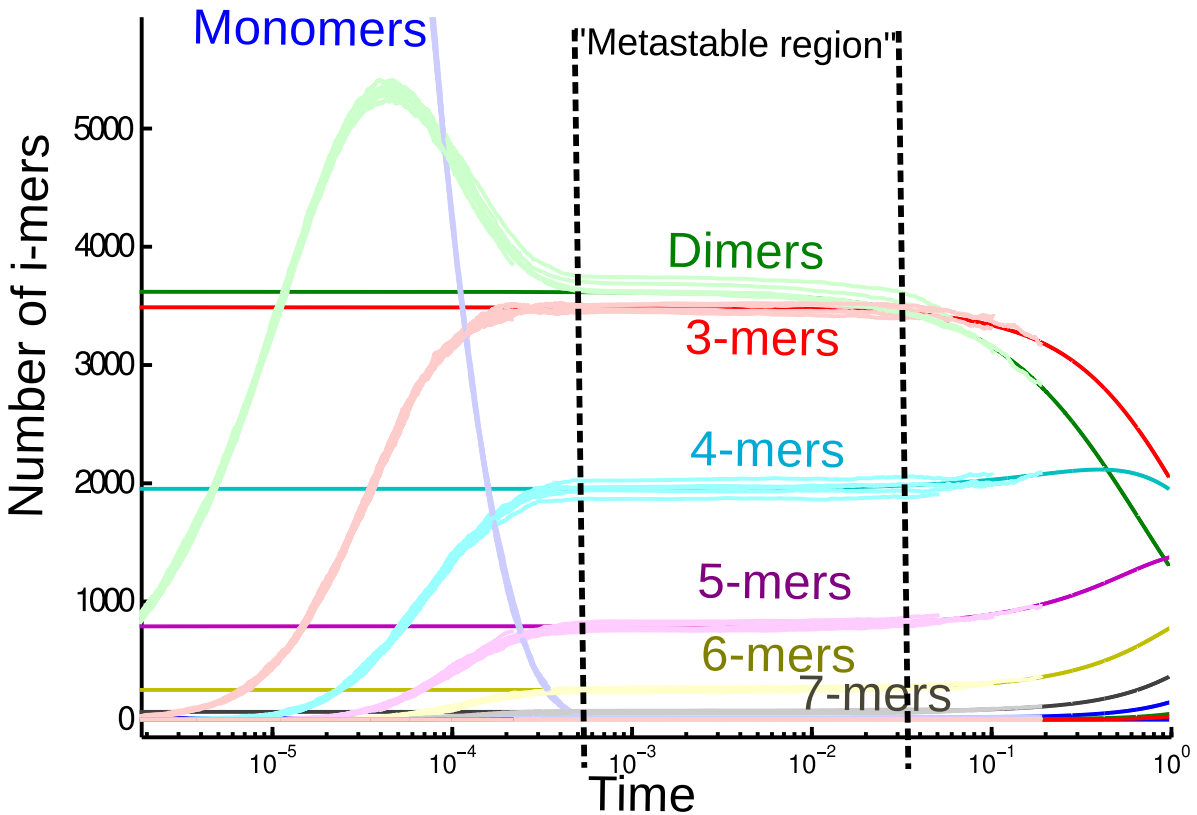
Trajectories in the favorable case $M >> q$ and N large

"Metastable" trajectory (ex : $M = 30000, N = 10, q = 1$).



Trajectories in the favorable case $M >> q$ and N large

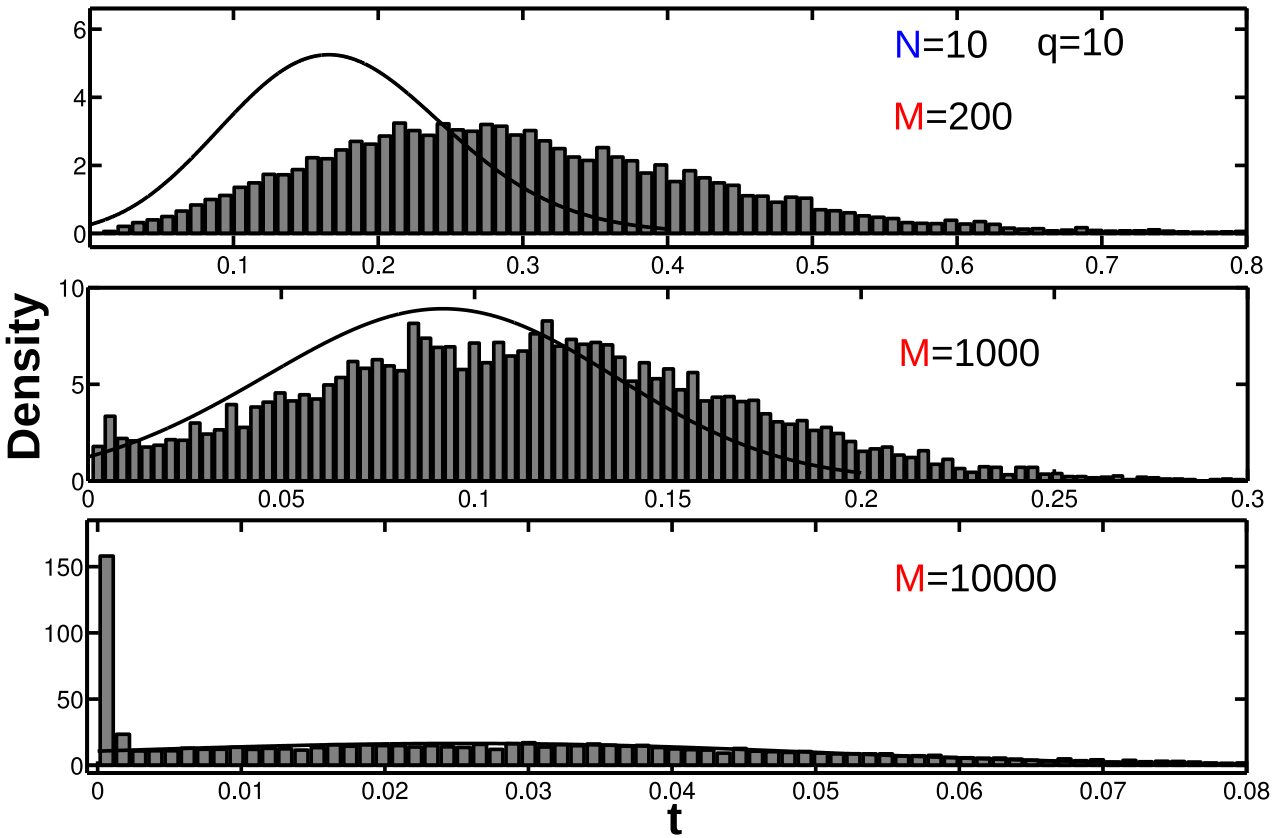
"Metastable" trajectory. Known phenomenon for the deterministic model ([Penrose, 1989],[Wattis, 2006])



1. irreversible aggregation (up to c_i^*)
2. slow "diffusion" with constant monomer $C_1(t) \equiv c_1^*$
3. convergence to equilibrium

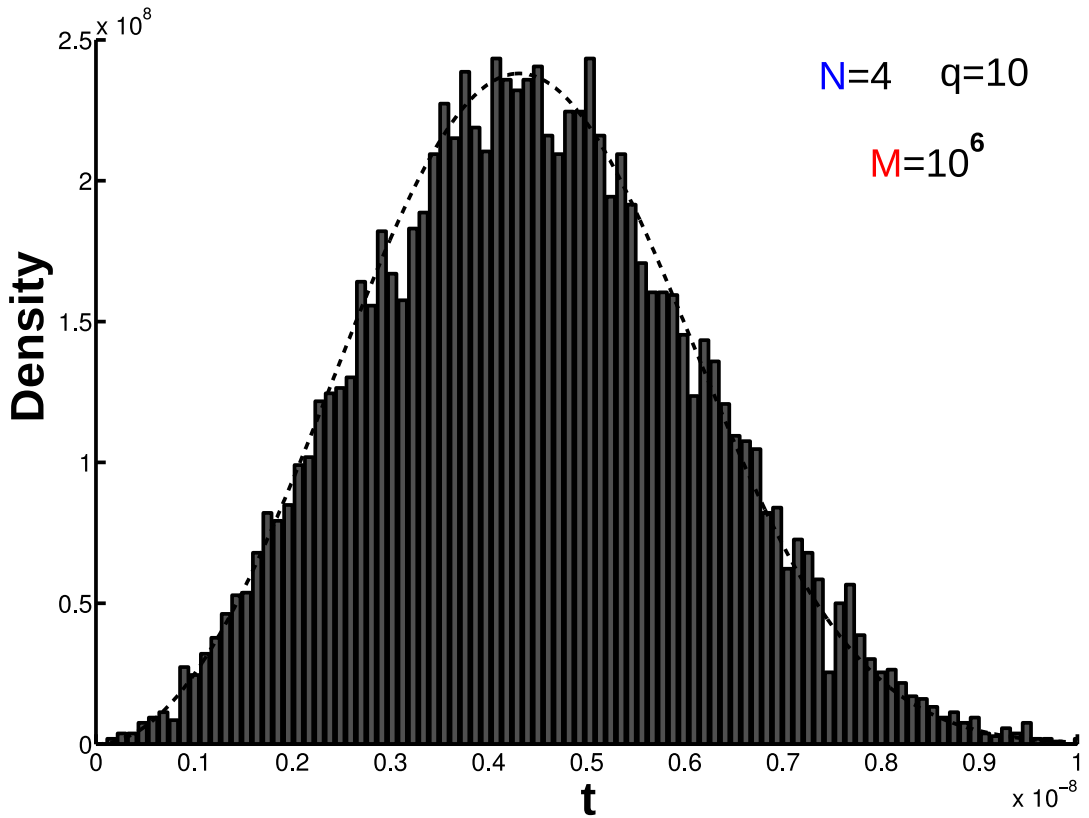
Nucleation time distribution in the favorable case $M >> q$ and N large, $c_N^* < 1$: bimodal distribution

$c_N^* < 1$: Linear model with $C_1 \equiv c_1^*$, $C_i(0) = c_i^*$ (solid line).

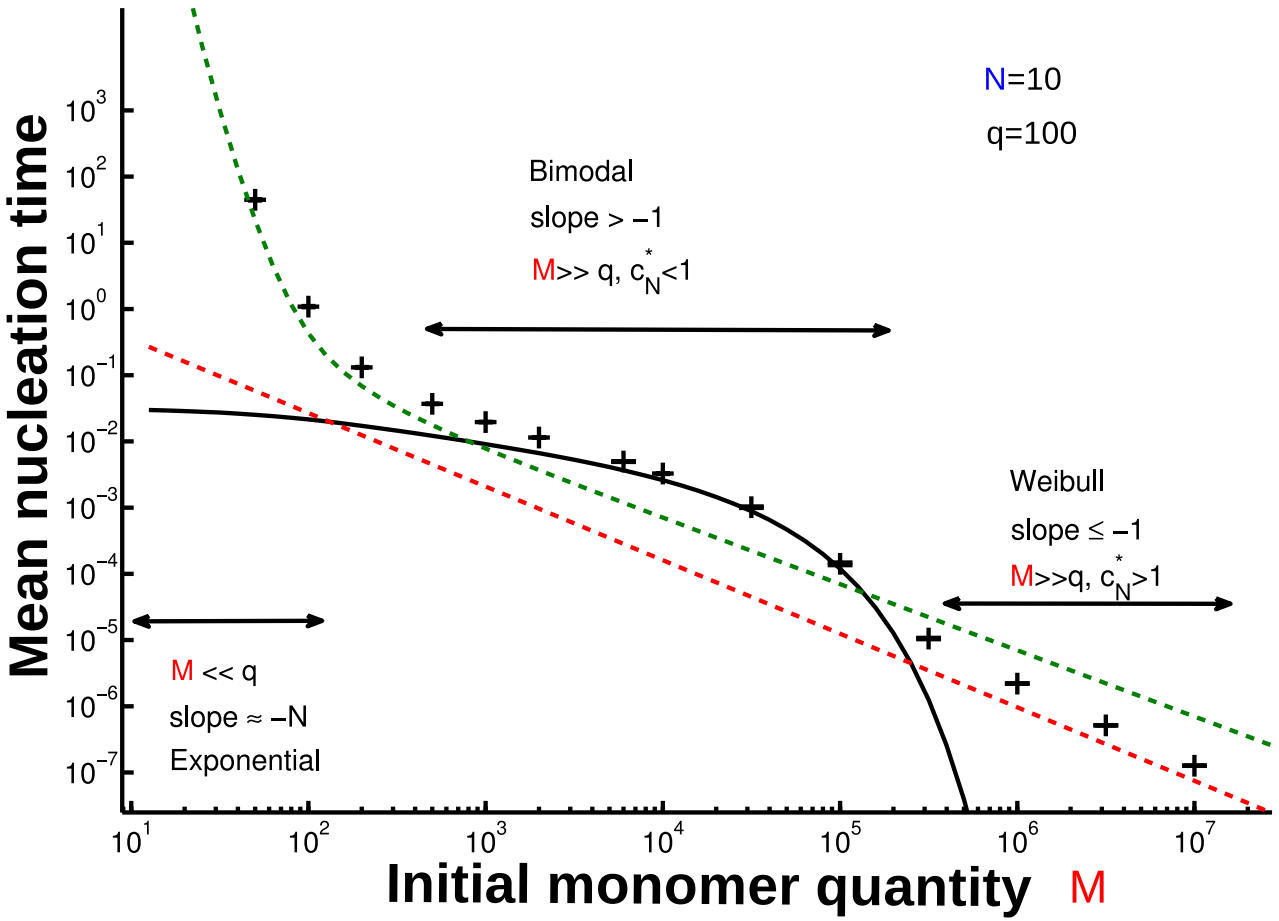


Nucleation time distribution in the favorable case $M >> q$ and N small, $c_N^* > 1$: Weibull law

$c_N^* > 1$: Linear model with $C_1 \equiv M$, Weibull law (dashed line).

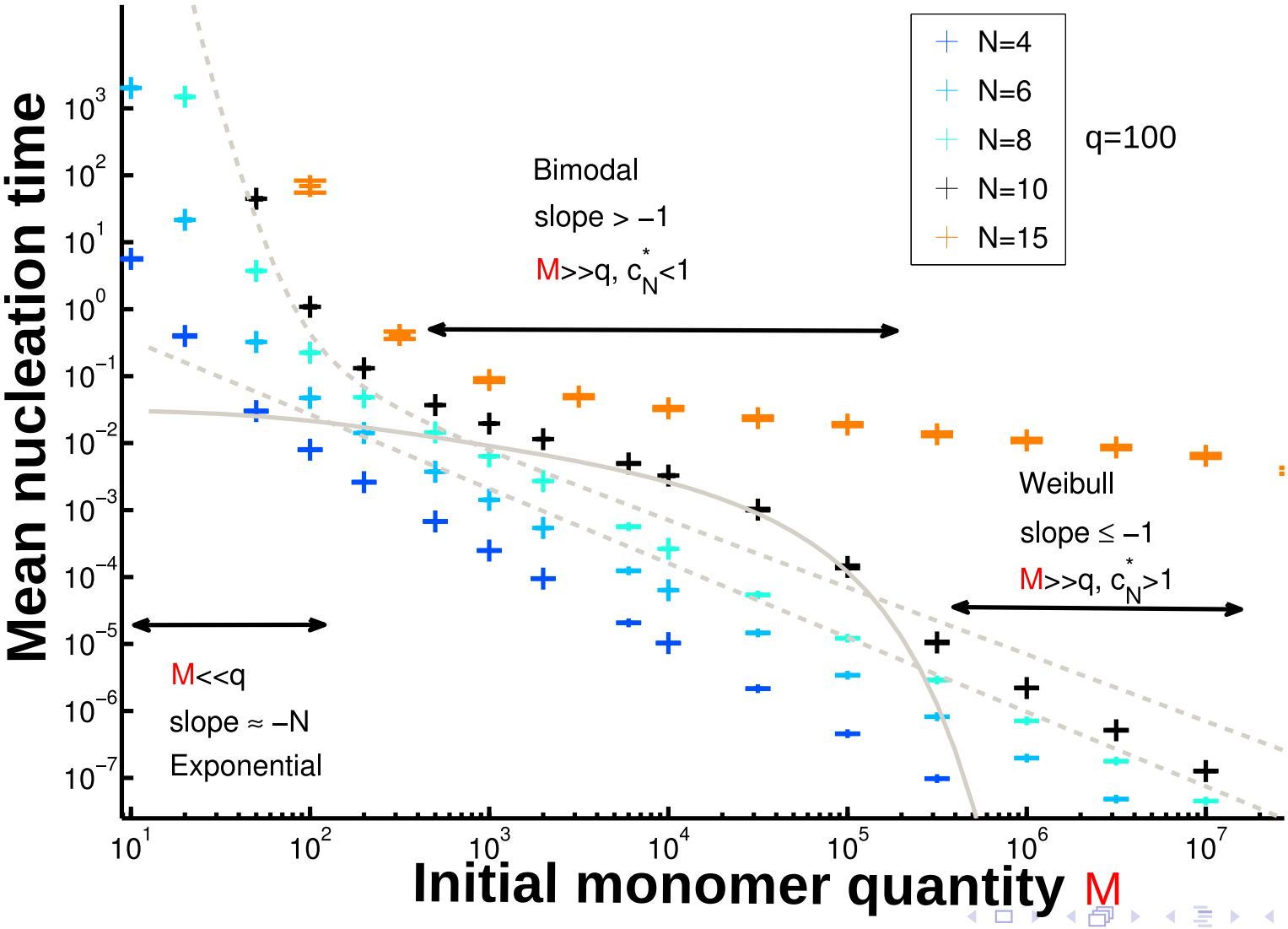


Mean nucleation time versus initial monomer quantity in log scale : 2 or 3 phases according nucleus size N



1. exponential
2. Linear model (starting from c_i^*)
3. Weibull

Mean nucleation time versus initial monomer quantity in log scale : 2 or 3 phases according nucleus size N



Conclusion/Perspectives

- Different behavior of the nucleation time
- Parameter Identifiability depending on parameter region

Conclusion/Perspectives

- Different behavior of the nucleation time
- Parameter Identifiability depending on parameter region

Perspectives

- Different nucleation regime $\Rightarrow$ Different polymerization regime
- Possibility to take into account different polymer structures
- Study the nucleation time for size-dependent rates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