ON THE ASYMPTOTIC DISTRIBUTION OF NUCLEATION TIMES OF POLYMERIZATION PROCESSES

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ABSTRACT. In this paper, we investigate a stochastic model describing the time evolution of a polymerization process. A polymer is a macro-molecule resulting from the aggregation of several elementary sub-units called monomers. Polymers can grow by addition of monomers or can be split into several polymers. The initial state of the system consists mainly of monomers. We study the time evolution of the mass of polymers, in particular the asymptotic distribution of the first instant when the fraction of monomers used in polymers is above some positive threshold $\delta$. A scaling approach is used by taking the mass $N$ as a scaling parameter. The mathematical model used in this paper includes a nucleation property: if $n_c$ is defined as the size of the nucleus, polymers with a size less than $n_c$ are quickly fragmented into smaller polymers, at a rate proportional to $\Phi(N)$ for some non-decreasing and unbounded function $\Phi$. For polymers of size greater than $n_c$, fragmentation still occurs but at bounded rates. If $T^N$ is the instant of creation of the first polymer whose size is $n_c$, it is shown that, under appropriate conditions, the variable $T^N/\Phi(N)^{n-2N}$ converges in distribution, and that the first instant $L^N_\delta$ when a fraction $\delta$ of monomers is polymerized has the same order of magnitude. An original feature proved for this model is the significant variability of the variable $T^N$. This is a well known phenomenon observed in biological experiments but few mathematical models of the literature have this property. The results are proved via a series of technical estimates for occupation measures of some functionals of the corresponding Markov processes on fast time scales and by using coupling techniques.

1. Introduction

Polymerization is an important phenomenon occurring in many areas, in particular for several biological processes. In a biological context, some species of proteins, also called monomers, may be assembled via chemical reactions into aggregated states called polymers. A polymer is an assembly of proteins linked by some chemical bonds. The size/mass of a polymer is the number of monomers composing it. The random fluctuations generated by the thermal noise within the biological cell are at the origin of the encounters of polymers and monomers which may lead to the growth of existing polymers. These fluctuations may also break some chemical bonds within polymers and thus give polymers

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1. Introduction

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with smaller sizes. From an experimental point of view, the randomness of fluctuations seems to have an important impact on the time evolution of polymerization processes. This is the main motivation of this paper which investigates a stochastic model describing the time evolution of a set of polymers.

Using classical notations for chemical reactions, for \( k \geq 1 \), \( X_k \) represents a polymer of size \( k \), the polymerization process analyzed in this paper can be represented as

\[
\begin{align*}
X_1 + \kappa_k X_k & \xrightarrow{\text{on}} X_{k+1}, \\
X_k & \xrightarrow{\text{off}} X_{a_1} + X_{a_2} + \cdots + X_{a_p}, \quad p \geq 2, a_1 + a_2 + \cdots + a_p = k.
\end{align*}
\]

The quantity \( \kappa_{k_{\text{on}}} \) [resp. \( \kappa_{k_{\text{off}}} \)] is the chemical rate at which a polymer of size \( k \) is bound with a monomer [resp. at which it is broken]. See Appendix 5 for a more detailed description of the biological background. It should be noted that polymers can only grow by the addition of a monomer. This is in fact a common assumption in this domain as long as linear polymers, also called fibrils are considered. The fragmentation mechanism is, a priori, arbitrary.

**The Nucleation Phenomenon.** We introduce the notion of nucleation which is a standard assumption in the corresponding biological literature but, to the best of our knowledge, does not seem to have been considered in the previous stochastic mathematical models of polymerization. See Morris et al. [25], Kashchiev [19]. The assumption is that polymers with small sizes are quite unstable. They are very quickly broken by the random fluctuations of the environment. There is nevertheless a critical size \( n_c \) above which a polymer is more stable. It can be still broken due to random events but at a much smaller rate. The quantity \( n_c \) is called the nucleus size, in this way polymerization can also be seen as a nucleation process as in the literature in physics. These assumptions are generally based on considerations of statistical mechanics expressed in terms of the free energy of assemblies of proteins. See Kashchiev [20]. With a slight abuse of notation we will say that nucleation has occurred when a polymer of size \( n_c \) has been created for the first time.

**The Variability of Polymerization Processes.** When starting with only monomers in experiments, the system stays for some time with a negligible polymerized mass, i.e. with few polymers. The main phenomenon observed is that there is some instant when a sharp phase transition occurs, the polymerized mass goes then from 0 to reach very quickly its final value. This explosive behavior is a constant feature of polymerization processes observed in experiments. Another key property from a biological point of view is that the instant when this event occurs, the lag time, varies significantly from an experiment to another. See Radford [35] and Figure 2 in the appendix. This property is believed to be at the origin of the long delays observed in the development of several neuro-degenerative diseases such as the Bovine Spongiform Encephalopathy (Mad Cow) or Alzheimer’s disease for example. See Appendix 5 for a quick review and references for the biological aspects. The main goal of mathematical analysis in this domain is of providing a simple model exhibiting this phenomenon.

**Central Limit vs Rare Events Theorems.** An analysis of the fluctuations has been achieved in the literature in terms of a central limit theorem (CLT) around this sigmoid function with \( N \), the total mass, as a scaling parameter. See Szavits et al. [33], Eugène et al. [11], see also Doumic et al. [9]. These references generally consider only two species of macro-molecules, monomers and polymerized monomers. Unfortunately, when compared with experimental data, these mathematical models fail in general to explain the order of magnitude of the variability observed in the experiments. The main reason, as it is natural in a classical CLT setting, is that the variance is of the lag time of the order of \( \sqrt{N} \), and therefore much smaller than its average value, of the order of \( N \). This is not
what is observed in the experiments. See Figure 2 in the appendix for example. For small volumes, estimations obtained in this way can nevertheless be reasonably accurate, see Eugène et al. [11].

The variability can thus be hardly explained only by a central limit theorem. The main result of this paper states that the fluctuations are, more likely, due to the occurrence of a set of rare events. This has been suggested in the biological literature, see Section 4 b) and c) of Hofrichter [13] for example, see also Yvinec et al. [37].

But, to the best of our knowledge, it has never been established rigorously with a convenient mathematical model.

### A Scaling Assumption For the Stochastic Model.

In the chemical reactions (1) the existence of a nucleus size is generally represented as follows: for a polymer of size $k<n_c$, the chemical rate of fragmentation is much larger than the chemical rate of association to another monomer, i.e. $k^\text{off} \gg k^\text{on}$. Otherwise, it is of the same order of magnitude or much smaller.

A natural Markovian description involves a multi-dimensional state space, the state descriptor is given by a vector $u=(u_k)$ where, for $k \geq 1$, $u_k$ is the number of polymers of size $k$. The growth of polymers of size $k$ is described by the interaction of the $k$th coordinate and of the first coordinate, $u_k$ and $u_1$. The fragmentation of a polymer is a more intricate transition since a polymer can be fragmented into a subset of polymers of smaller sizes. In our Markovian model, this is translated in the following way, recall that $N$ is the total mass of the system, in state $u=(u_k)$,

(I) Growth. A monomer is added to a given polymer of size $k$ at rate $\lambda_k u_1 N$, for some positive constant $\lambda_k$. Three coordinates of the state change at this occasion: $u_1 \rightarrow u_1 - 1$, $u_k \rightarrow u_k - 1$ and $u_{k+1} \rightarrow u_{k+1} + 1$. See for example Anderson and Kurtz [3] for a general presentation of mathematical models of chemical reactions in a stochastic context.

(II) Fragmentation. The fragmentation of a given polymer of size $k$ occurs at rate $\mu_k N$, with

$$\mu_k \equiv \left\{ \begin{array}{ll} \Phi(N) \mu_k & \text{if } k<n_c, \\
\mu_{n_c} & \text{if } k \geq n_c, \end{array} \right.$$  

for some positive constants $\mu_k$, $1 \leq k \leq n_c$. The way the polymer is fragmented is described by a fragmentation measure. See Section 2.

See Figure 1. Small polymers disappear at rate proportional to $\Phi(N)$, where $\Phi$ is some non-decreasing function converging to infinity. In our approach $N$, the scaling parameter, can be also thought as a volume. With this interpretation, the quantity $u_1/N$ used in the rate of growth above is the concentration of “free” monomers, i.e. polymers of size 1. See van Kampen [17] or Yvinec et al. [36]. The function $\Phi$ can be taken as $\Phi(x)=x^\gamma$, with $\gamma \in (0,1]$.

### The Main Results.

Assuming that $N$ is the mass of the system and that the initial state does not contain any polymer of size greater or equal to $n_c$ and consists mainly of monomers, if $T_N$, the first nucleation time, is the first instant when a polymer of size $n_c$ is created, we prove that, under appropriate conditions, the convergence in distribution holds

$$\lim_{N \to +\infty} \frac{N}{\Phi(N)^{n_c-2}} T_N = F_\pi,$$

where $F_\pi$ is an exponential random variable with parameter $\pi$, a constant depending on the constants $\lambda_k$, $\mu_k$, $k<n_c$, the polymerization and fragmentation rates of polymers of sizes less than $n_c-1$. See Relation (32) for an explicit expression. In particular, the variable
$T^N$ has a significant variability, its variance being of the same order of magnitude in $N$ as its average value. The variable $L^N_\delta$, the lag time, is defined as the first instant when a fraction $\delta$ of monomers is polymerized into polymers of size greater than $n_c$. We show that, in the limit and under appropriate conditions, $L^N_\delta$ has the same order of magnitude in $N$ as $T^N$. See Theorem 2.

The mathematical analysis is decomposed into two steps.

1. The evolution of the process until a polymer of size $n_c$ is created. With our scaling assumptions, this is a rare event as mentioned above, from this point of view the convergence (2) is natural in probability theory. For stochastic processes converging quickly to equilibrium, rare events are, generally, reached after an exponentially distributed amount of time with a large average. See Keilson [21] and Aldous [1] for example. Nevertheless, getting an explicit expression for the asymptotic exponential random variable and establishing the corresponding technical estimates turn out to be a quite challenging problem. See Section 3 and Appendix.

2. With an initial state with only one polymer of size $n_c$, if this polymer grows sufficiently quickly, its fragmentation will give several stable polymers that will also consume monomers and therefore may generate other stable polymers. It turns out that this is a very fast way to create stable polymers. It is shown in fact that, with this initial state, the number of stable polymers can be stochastically lower-bounded by a supercritical branching process, in particular with positive probability it is growing exponentially fast or it dies out. This is the explosion phase of the polymerization process.

Our model has thus the two main characteristics observed in the experiments in biology: a take-off phase with a large variability, the corresponding exponential distribution, and a steep growth, the super-critical branching process.

Remarks

(i) Relation (2) is proved under quite general assumptions on the way a polymer of size $k \geq 2$ is fragmented. In the stochastic model it is represented by a probability distribution $\nu_k$ on the space of all possible decompositions of the integer $k$. See Section 2. The limiting distribution of Relation (2) does not depend in fact on $\nu_k$ but only on fragmentation and growth rates. The intuitive, non-rigorous, reason is the following: the first polymer of size $n_c$ is built from successive additions of monomers and the key step is in fact the one to have the “last” monomer added to a polymer of size $n_c - 1$. If it is fragmented before then, very quickly, it is reduced to a set of $n_c - 1$ monomers. Of course this is a rough description. The precise result is established in Section 3.

(ii) When $\Phi(N) = N^\gamma$, as our results show, this phenomenon occurs when the nucleus size satisfies the relation $n_c > 2 + 1/\gamma$. For the current mathematical literature, the nucleus size used is (implicitly sometimes) 2, which may explain that this phenomenon has not been yet established rigorously.

(iii) The results are obtained via a series of (quite) technical estimates for occupations measures of the corresponding Markov process on the fast time scale $t \mapsto \Psi(N)_t \overset{\text{def}}{=} \Phi(N)^{n_c - 2}/N \cdot t$. Stochastic calculus with Poisson processes, coupling arguments and branching processes are the main ingredients of the proofs. It should be noted that one of the main difficulties while using stochastic calculus is of controlling the fluctuations of the associated martingales, on the a priori very fast time scale ($\Phi(N)_t$). This is where a coupling with a strongly ergodic process plays a major role. See the proof of Proposition 5.

Literature. There is a past and recent interest in growth-fragmentation models which are generalizations of the polymerization process described by Relation (1). In the context
of coagulation and fragmentation models, the Smoluchowski model is a classical mathematical model. See Aldous [2] for a general survey. For these models, the growth can occur also by coagulation and not only by addition of a single particle/monomer at a time. Additionally, the rates of occurrence of the growth or fragmentation events can be state dependent. These processes are also used to study some population processes. The studies focus mainly on the existence of such processes, on their scaling properties (like self-similarity) or their branching process representation. A special and important case for polymerization processes is the Becker-Döring model for which the chemical reactions are given by

\[ X_1 + X_k \overset{\kappa_{k+1}}{\underset{\kappa_k}{\rightleftharpoons}} X_{k+1}, \quad k \geq 1. \]

In particular the fragmentation mechanism is, in some way, degenerated since at most one monomer can be detached at a time from a polymer. In a deterministic setting, there is an associated system of ODEs called the Becker-Döring Dynamical System \((c_k(t))\) solution of the system of differential equations

\[
\begin{cases}
\frac{dc_1}{dt}(t) = -2J_1(c(t)) - \sum_{k \geq 2} J_k(c(t)), \\
\frac{dc_k}{dt}(t) = J_{k-1}(c(t)) - J_k(c(t)), \quad k > 1,
\end{cases}
\]

with \(J_k(c) = \kappa_{on} c_1 c_k - \kappa_{off} c_{k+1}^2\) if \(c = (c_k) \in \mathbb{R}^N_+\) and with a convenient initial condition. This is a first order description of the process, the term \(c_k(t)\) should be thought of the concentration of polymers of size \(k \geq 1\). See Becker and Döring [6] for the original paper. The conditions of existence and uniqueness of solutions have been extensively investigated. See Ball et al. [5] for example.

In the literature of mathematical models of this biological phenomenon it has been extensively used, see the various classes of ODEs in Table 2 of Morris et al. [25]. With convenient parameters estimations, these ODEs can describe first order characteristics such as the mean concentration of polymers with a given size. See Prigent et al. [28] for example. Due to their deterministic formulation, they cannot really be used to investigate the fluctuations of the polymerization process.

In a stochastic context, Jeon [16] shows for the Smoluchowski model, that with Poisson processes governing the dynamics of the transitions of binary coagulation and fragmentation, then, under appropriate conditions, a convergence result holds for the coordinates properly scaled and the limit is the solution of a set of deterministic ODE’s. For this model the corresponding functional central limit theorem has been proved in Sun [31]. See Szavits et al. [33], Eugène et al. [11] and Doumic et al. [9] for related stochastic models. The Becker-Döring model itself cannot be a convenient model to describe the variability of polymerization processes. The fragmentation mechanism of the model, the removal of monomers one by one from a polymer cannot give an appropriate explosive behavior as observed in practice. On this matter, Condition A-3 of Assumption A∗ of our model below is key to get this property.

Outline of the Paper. Section 2 introduces the stochastic model used to investigate the polymerization process, together with the notations and definitions used throughout this paper. In Section 3 limiting results are proved for the first instant when there is a stable polymer, see Theorem 1 and Proposition 5. Section 4 considers the dynamic of the polymerization for the polymers whose sizes are above the level of nucleation \(n_c\). The main results for the asymptotic behavior of the distribution of the lag time are then proved, see Theorem 2. The appendix gives a quick overview of some biological aspects of these processes.
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2. Stochastic Model

In this section we introduce the stochastic model describing the polymerization processes with a nucleation phenomenon. For this model, polymers of small sizes are unstable and quickly break into polymers with smaller sizes.

The state of the model is represented by a vector \( \mathbf{u} = (u_i) \), where \( u_i \) is the number of polymers of size \( i \). For \( p \geq 1 \) we define

\[
S_p \overset{\text{def}}{=} \left\{ (u_i) \in \mathbb{N}^p : u_1 + 2u_2 + \cdots + \ell u_{\ell} + \cdots = p \right\},
\]

the state space of the process is thus given by \( S_N \). Since for \( u \in S_p \), all components with index strictly greater than \( p \) are null, we will occasionally use the slight abuse of notation \( u = (u_1, \ldots, u_p) \) in this situation. We denote by

\[
S_\infty = \bigcup_{k \geq 0} S_k,
\]

the set of states with finite mass. For \( p \in \mathbb{N} \), \( e_p \) will denote the \( p \)th unit vector of \( S_\infty \).

One starts from an initial state with total mass \( N \) and consisting mainly in monomers. It will be also interpreted as a volume parameter. When the system is in state \( u = (u_k) \in S_N \) then, for \( k \geq 1 \), the quantity \( u_k/N \) is defined as the concentration of polymers of size \( k \). In the following, \( N \) is used as a scaling parameter.

In a deterministic context the law of mass action gives the Michaelis Menten’s kinetics equations for the concentration of the various polymers. See Chapter 6 of Murray [26].

Growth of Polymers. The growth of polymers occurs only through successive additions of monomers. The rate at which a given polymer of size \( k \), \( k < n_c \), is aggregated with a polymer of size 1 is taken as proportional to the concentration \( u_1/N \) of these polymers. See Anderson and Kurtz [3]. Hence the total rate of production of polymers of size \( k+1 \) via this kind of reaction is given by

\[
\lambda_k u_k \frac{u_1}{N},
\]

for some constant \( \lambda_k > 0 \).
Fragmentation. This is where the nucleation phenomenon is introduced in the stochastic model. It is assumed that \( n_c \in \mathbb{N} \) such that \( n_c > 2 \). For \( k \geq 2 \), the fragmentation rate of a polymer of size \( k \) is given by

\[
\mu_k^N = \begin{cases} 
\Phi(N) \mu_k & \text{if } k < n_c, \\
\mu_{n_c} & \text{if } k \geq n_c,
\end{cases}
\]

where \( x \mapsto \Phi(x) \) is a positive non-decreasing function on \( \mathbb{R}_+ \) converging to infinity at infinity and \( \mu_k, 2 \leq k \leq n_c \), are positive real numbers. In the following polymers whose size is greater than \( n_c \) will be qualified as stable to indicate that their fragmentation rate is not large. Stable polymers are fragmented at a constant rate \( \mu_{n_c} \).

In the literature for chemical reactions of polymerization processes, the ratio of growth rate and fragmentation rate, \( \frac{k_{\text{off}}}{k_{\text{on}}} \), in our previous notations, is assumed to be large for \( k < n_c \) and small otherwise. See Kashchiev [19]. In our case the scaling parameter \( \Phi(N) \) stresses the difference of the dynamical behavior of polymers with size less than \( n_c \).

In this setting, a quite general fragmentation process is considered. A polymer of size \( k \) splits at rate \( \mu_k^N \) according to a fragmentation distribution \( \nu_k \) on the state space \( S_k \). More precisely, a polymer of size \( k \) is broken into \( Y^k \) polymers with size \( i \), \( 1 \leq i \leq k-1 \) where \( Y^k = (Y^k_1, \ldots, Y^k_{k-1}) \) are random variables such that

\[
\mathbb{E} \left( f(Y^k_1, \ldots, Y^k_{k-1}) \right) = \int_{S_k} f(y_1, \ldots, y_{k-1}) \nu_k(dy).
\]

For \( p < k \), we denote by \( I_p(y) \) the \( p \)th coordinate of \( y \in S_k \) and

\[
\langle \nu_k, I_p \rangle \overset{\text{def.}}{=} \int_{S_k} I_p(y) \nu_k(dy) = \int_{S_k} y_p \nu_k(dy)
\]

is the average number of polymers of size \( p \) for \( \nu_k \), in particular

\[
\sum_{p=1}^{k-1} p \langle \nu_k, I_p \rangle = k.
\]

Remark on the Nucleus Size. If the nucleus size is 2, in state \( u \in S_N \) stable polymers are created at rate \( \lambda_1 u^2 / N \). Hence, initially, stable polymers are created directly from monomers at a rate \( \lambda_1 N \): a significant fraction of monomers is polymerized right away. When \( n_c \geq 3 \), it will be seen that, under some conditions, stable polymers are essentially produced as follows: a stable polymer grows for some time and then is fragmented into multiple polymers and, with positive probability, the size of several of them may be larger than \( n_c \). A stable polymer can create stable polymers with positive probability. It turns out that this production scheme is much faster than the creation of stable polymers by the successive addition of monomers to polymers with size less than \( n_c-1 \). For this reason the case \( n_c = 2 \) stands out. It is in fact used in most of the mathematical models of polymerization, implicitly sometimes. In our view, this is the reason why it cannot be really used to explain the large variability observed in the experiments.

Examples of Fragmentation Measures. Fragmentation can be seen to a decomposition of integers. An important literature is in fact devoted to this topic: from the point of view of combinatorics as well as for statistical aspects. See, for example, Fristed [12], Pitman [27] or Ercolani et al. [10]. We now give some classical examples.

Recall that, for \( k \geq 2 \), a polymer of size \( k \) is split according to the distribution \( \nu_k(.) \).
(1) UF: Uniform Binary Fragmentation, for $0 < \ell < k$, 
\[
\nu^\text{UF}_k(\ell + e_{\ell-k}) = \begin{cases} 
\frac{2}{k-1}, & k \text{ odd}, \\
\frac{2}{k}, & \ell \neq k/2 \text{ even}, \\
\frac{1}{k-1}, & \ell = k/2 \text{ even},
\end{cases}
\]
where $e_\ell$ is the $\ell$th unit vector of $\mathbb{N}^n$, $e_\ell$ is representing a single polymer of size $\ell$.

(2) BF: Binomial Fragmentation, $p \in (0, 1)$, if $k$ is odd and $0 < \ell < k$,
\[
\nu^\text{BF}_k(\ell + e_{k-\ell}) = \frac{2}{1-p^\ell -(1-p)^k} \left(\frac{k}{\ell}\right) p^{\ell/2} (1-p)^{k-\ell}.
\]
If $k$ is even, the case $\ell = k/2$ has to be singled out as before.

(3) MF: Multiple Fragmentations.
For $m \geq 2$ and $p=(p_i) \in (0, 1)^m$ with $p_1 + p_2 + \cdots + p_m = 1$, a polymer of size $k \geq m$ is fragmented into $m$ polymers with sizes $k_1+1, k_2+1, \ldots, k_m+1$ according to a multinomial distribution, if $\ell = e_{k_1+1} + e_{k_2+1} + \cdots + e_{k_m+1} \in S_k$.
\[
\nu^\text{MF}_{k,m}(\ell) = \sum_{(n_1, \ldots, n_m) \in \mathbb{N}^m} \frac{(k-m)!}{n_1! n_2! \cdots n_m!} \prod_{i=1}^m p_i^{n_i}.
\]
if $k < m$, one set $\nu^\text{MF}_{k,m}(\ell) = 1$ for $\ell = k e_1$.

The family of probability distributions to describe fragmentation have various definitions depending on the context investigated. For continuous fragmentation, i.e. when the state space is $\mathbb{R}_+$ instead of $\mathbb{N}$, the corresponding quantity is the dislocation measure. In the self-similar case, the fragmentation process is described by a measure associated with the outcome of the breaking of a particle of size 1. There are generalizations in this continuous setting with fragmentation kernels $K(x, dy)$ depending on the initial size $x$ to decompose. See Bertoin \[7\] for example. For fragmentation of integers, as it is our case, Mohamed and Robert \[24\] describes the fragmentation also via a single measure, the splitting measure for the analysis of first order quantities. See \[24\] for an overview of this literature in this framework.

We introduce the following conditions under which our main results are established.

**Assumptions A:**

**A-1** Lower Bound for Polymerization and Fragmentation Rates.
\[
\lambda^\text{def} = \inf_{k \geq 1} \lambda_k > 0 \quad \text{and} \quad \inf_{k \leq n_c} \mu_k > 0.
\]

**A-2** Scaling function $\Phi$ for Fragmentation. It is assumed that
\[
\Psi(N) \overset{\text{def}}{=} \frac{1}{N} \Phi(N)^{n_c-2} \quad \text{is such that} \quad \lim_{N \to +\infty} \frac{\Psi(N)}{\log N} = +\infty,
\]
and, for any $\eta \geq 0$, $(N/\Phi(N))^{\eta}$ is a converging sequence with a limit in $\mathbb{R}_+ \cup \{+\infty\}$.
We define
\[
k_c \overset{\text{def}}{=} \sup \left\{ k \in \mathbb{N}_+ : \lim_{N \to +\infty} \frac{N}{\Phi(N)^{k-1}} = +\infty \right\},
\]
not that, by the assumption on $\Psi$, $k_c \leq n_c - 2$.

**A-3** Fragmentation of Polymers. There exists $C_0 > 0$ and $K$ such that, for $k \geq K$,
\[
\nu_k \left( y = (y_i) \in S_k : \sum_{i < n_c} y_i \leq C_0 \right) = 1,
\]
and

\[ \liminf_{k \to +\infty} \nu_k \left( y = (y_i) \in \mathcal{S}_k: \sum_{i \geq n_c} y_i \geq 2 \right) > 0. \]

A-4) **Monotonicity Property:** If \( k \leq k' \), then, for all \( a \in \mathbb{N} \) and \( \ell \geq 1 \), the relation

\[ \nu_k \left( y \in \mathcal{S}_k; \sum_{i=1}^{+\infty} \mathbb{1}_{(y_i \geq \ell)} \geq a \right) \leq \nu_{k'} \left( y \in \mathcal{S}_{k'}; \sum_{i=1}^{+\infty} \mathbb{1}_{(y_i \geq \ell)} \geq a \right) \]

holds.

The condition on the convergence of \( (N/\Phi(N)^\eta) \), \( \eta > 0 \), is for technical convenience, mainly in the proof of Proposition 2.

Assumption A-3 states that, with probability 1, the fragmentation of a large polymer can give at most \( C_0 \) unstable polymers, i.e. whose size is less than \( n_c \). Under this condition, a large polymer cannot be broken into monomers only. Consequently, the fragmentation of a polymer of size greater than \( n_c C_0 \) produces at least a polymer of size greater than \( n_c \). Furthermore, with a positive probability, two stable polymers are produced from the fragmentation of such a large polymer. Note that the fragmentation process of the Becker-Döring model (3) does not satisfy this condition. Recall, as mentioned in the introduction, that this mathematical model fails to exhibit an explosive growth behavior. The monotonicity property A-4 gives that the sizes of fragments are stochastically increasing with respect to the size of the fragmented polymer.

**Proposition 1.** The fragmentation measures UB, UF and MB satisfy Assumption A*.

**Proof.** The proof is done for the multinomial fragmentation, the proof for the symmetrical fragmentation is similar. The fragmentation as the distribution of \( k-m \) balls into \( m \) urns so that the probability the \( i \)th urn is chosen is \( p_i \), if \( A_i^k \) the number of balls in this urn, then \( \nu_k \) is simply the empirical distribution of these variables. A simple coupling can be constructed so that \( A_i^k \leq A_i^{k+1} \) holds for all \( i \in \{1, \ldots, m\} \). This gives right away the monotonicity property. The law of large numbers gives the convergence in distribution

\[ \lim_{k \to +\infty} \frac{1}{k} (A_1^k, \ldots, A_m^k) = (p_1, \ldots, p_m). \]

Condition A-3 holds since \( p_i \) is positive for all \( i \). \( \square \)

**The Infinitesimal Generator of the Stochastic Evolution.** We define by \( U_k^N(t) \) the number of polymers of size \( k \geq 1 \) at time \( t \geq 0 \). Clearly, the process \( (U_k^N(t))_{t \geq 0} \) has the Markov property on the countable state space \( \mathcal{S}_N \). The generator \( \Omega_N \) of this process is given by, for \( u \in \mathcal{S}_N \),

\[ \Omega_N(f)(u) = \sum_{k=1}^{+\infty} \lambda_k u_k \frac{u_1}{N} [f(u+e_{k+1}-e_k-e_1) - f(u)] \]

\[ + \sum_{k=2}^{+\infty} \mu_k^N u_k \int_{\mathcal{S}_k} [f(u+y-e_k) - f(u)] \nu_k(dy) \]

where, for \( i \geq 1 \), \( e_i \) is the \( i \)th unit vector of \( \mathbb{N}^i \) and \( f \) is a function on \( \mathcal{S}_N \) with finite support.

The growth mechanism involves the scaled term \( u_k/N \), the concentration of monomers. This is not the case for the rates of fragmentation which do not depend on the concentration, in the state \( u = (u_i) \in \mathcal{S}_N \), one of the polymers of size \( k \) is fragmented at rate \( \mu_k^N u_k \).
Stochastic Differential Equations. Throughout the paper, we use the following notations for Poisson processes. For $\xi > 0$, $\xi(t)$ is a Poisson point process on $\mathbb{R}$ with rate $\xi$. For $k \geq 2$, $\xi^k(t)$ is a marked Poisson point process on $\mathbb{R} \times S_k$ with intensity measure $\xi dt \otimes \nu_k(dy)$ and $(\xi^k(t),\ell)$ is an i.i.d. sequence of such processes. Such a process can be represented as follows. If $\xi(t)$ is a Poisson process on $\mathbb{R}$ with rate $\xi$, then $\xi(t)$ has the same distribution as the point process on $\mathbb{R} \times S_k$ given by

$$\sum_{n \geq 1} \delta_{(t_n^k,y_n^k)},$$

where $\delta_{(a,b)}$ is the Dirac mass at $(a,b)$. See Kingman [22] for an introduction on marked Poisson point processes. All Poisson processes used are assumed to be independent.

In this context, the Markov process $(U^N(t))$ can also be seen as the stochastic process solution of the system of stochastic differential equations

$$dU^N_k(t) = \begin{cases} U^N_k(t^-) - \sum_{m=k+1}^{\infty} \sum_{\ell=1}^{U^N_m(t^-)} \int_{S_m} \nu_k(y_m^\mu)(dt,dy) \\ \quad - \sum_{\ell=1}^{U^N_k(t^-)} \nu_k^d(dy_k^\mu(t^-,S_k)) - \sum_{\ell=1}^{U^N_k(t^-)} NU_{k/N}(dt), & k \geq 2. \end{cases}$$

The evolution of $(U^N_k(t))$, the process of the number of monomers, is defined via the conservation of mass condition.

$$\sum_{k \geq 1} kU^N_k(t) = \sum_{k \geq 1} kU^N_k(0) = N.$$

Condition for the Initial State

For any $k \geq n_c$, $U^N_k(0) = 0$. For any $\varepsilon > 0$ and $2 \leq k \leq k_c$, the relations

$$\lim_{N \to +\infty} \frac{1}{N} U^N_k(0) = 1,$$

hold for the convergence in distribution. The function $\Psi$ is defined by Relation (7) and $k_c$ by Relation (8).

The motivation for this condition is that

- The limit result, Proposition [5] for the first instant when a stable polymer is created, holds for all these initial states.
- Condition (I) is in fact satisfied as long as few stable polymers have been created.

This property will play an important role in Section 3.

The initial state $(U^N(0)) = (N,0,\ldots,0\ldots)$ with only monomers, which is the classical initial condition used in the literature, satisfies this property. The process $(U^N(t))$ is càdlàg, i.e. right continuous with left limits at every point of $\mathbb{R}_+$, and $dU^N_k(t)$ is $U^N_k(t) - U^N_k(t^-)$, where $f(t^-)$ denotes the left limit of a function $f$ at $t$.

Nucleation Times. We can now introduce the lag time of the polymerization process, for $\delta \in (0,1)$,

$$L^N_\delta = \inf \left\{ t \geq 0 : \sum_{k=n_c}^{+\infty} kU^N_k(t) \geq \delta N \right\}.$$
NUCLEATION OF POLYMERIZATION PROCESSES

This is the main quantity of interest in the paper, the first instant when there is a fraction $\delta$ of the mass (in terms of monomers) used in stable polymers, i.e. whose sizes are greater than $n_c$. The first nucleation time is defined as

$$T^N = \inf\{t \geq 0 : U^N_{n_c}(t) = 1\},$$

it is the first instant when a stable polymer is created.

3. The First Instant of Nucleation

The purpose of this section is of proving a convergence theorem for the first time when a polymer of size $n_c$ is created when the initial mass $N$ converges to infinity. This hitting time is of the order $\Psi(N)$ defined by Relation (7). The proof is quite technical, we outline the general strategy to establish Proposition 5 which is the main convergence result.

1. An auxiliary $n_c$-dimensional Markov process $(X^N(t))$ describing particles evolving state 1 and state $n_c-1$ is introduced. It corresponds to the original process but truncated at the $(n_c-1)$th coordinate and with a different dynamic at node $n_c$. For this process, the node $n_c$ is a cementary state for the particles.

2. This process is analyzed on a fast time scale $t \rightarrow \Psi(N)t$, Proposition 3 shows that the order of magnitude of coordinates with index greater or equal to 2 are negligible with respect to $N$. A further result, Lemma 1 states that, still on this time scale, “most” of particles are in state 1, in particular “few” particles are at node $n_c$.

3. Proposition 3 and Proposition 4 investigate the asymptotic behavior of occupation times of the Markov process $(X^N(t))$ of the form

$$\int_0^{\Psi(N)t} f(X^N(s)) \, ds,$$

where $f(\cdot)$ is a specific family of polynomial functions on $\mathbb{R}^{n_c}$. The key convergence result of Proposition 4 can be interpreted as a kind of flow balance equation between the nodes 1,.., $n_c-1$ on the fast time scale $t \rightarrow \Psi(N)t$. It gives, with an additional convenient martingale argument, the convergence in distribution of the sequence of instants when particles arrive at node $n_c$ to a Poisson process, this is Theorem 1. The main result of this section, Proposition 5, is then a simple consequence of this theorem. The proof of Proposition 4 is quite involved, it uses Proposition 3 and several estimates. The proof of Proposition 3 has been put in the appendix to make the section more readable.

We define the Markov process $(X^N(t)) \overset{\text{def}}{=} (X^N_k(t))$, the solution of the system of stochastic differential equations

$$dX^N_k(t) = \sum_{\ell=1}^{X^N_k(t)-1} \mathcal{N}_{\lambda_{k-1/N,\ell}}(dt) + \sum_{m=k+1}^{n_c-1} \sum_{\ell=1}^{X^N_m(t)-1} y_n \mathbb{N}_{\mu_m,\Phi(N),\ell}(dt,dy)$$

$$- \sum_{\ell=1}^{X^N_{n_c-1}(t-)} \mathcal{N}_{\lambda_{n_c-1/N,\ell}}(dt,S_k) - \sum_{\ell=1}^{X^N_{n_c}(t-)} \mathcal{N}_{\lambda_{n_c/N,\ell}}(dt), \quad 2 \leq k \leq n_c-1,$$

and

$$dX^N_{n_c}(t) = \sum_{\ell=1}^{X^N_{n_c-1}(t-)} \mathcal{N}_{\lambda_{n_c-1/N,\ell}}(dt),$$

with initial condition $(X^N(0))$ satisfies Condition 4.
As before, the mass conservation condition,
\[ \sum_{k=1}^{n} kX_k^N(t) = \sum_{k=1}^{n} kX_k^N(0) = N, \]
on any finite time interval defines the evolution of the first coordinate \((X_1^N(t))\). By comparing SDE’s \([12]\) and \([16]\), we remark that the process \((X_1^N(t))\) is closely related to the polymerization process. The main difference is that the \(n_c\)th coordinate is a cemetery state. With a slight abuse, for convenience, for \(1 \leq k \leq n_c\) and \(t \geq 0\), we will refer to \(X_k^N(t)\) as the number of polymers of size \(k\) at time \(t\). This process is used to investigate the first phase of the polymerization process, until the first nucleus is created. Another auxiliary process will be introduced in section 4 to investigate the second phase during which polymers of size greater than \(n_c\) have a total mass of the order of \(N\).

Remark.
A related model (in a quite different context) with a Becker-Döring flavor is analyzed in Sun et al. \([32]\) with a different perspective since the goal is of analyzing the asymptotic behavior of a transient multi-dimensional Markov process. Outside the fragmentation approach, several estimates on fast time scales have nevertheless to be derived. The strategy to derive the limiting behavior of the distribution of the sequence \((X_1^N(\Psi(N)t))\), where \(\Psi\) is defined by Relation \([7]\) is explained briefly. One will first prove, via quite technical estimates, that, on the fast time scale \(t \rightarrow \Psi(N)t\), the values of the coordinates with index between 2 and \(n_c - 1\) are essentially negligible with respect to \(N\). See Proposition 2. The second key result is the asymptotic balance equations \([27]\) of Proposition 4 giving estimations of occupation measures associated to the coordinates of the process on the time scale \(t \rightarrow \Psi(N)t\). Theorem 1 is the main result of this section which establishes the convergence in distribution of the sequence \((X_{n_c}^N(\Psi(N)t))\) to an homogeneous Poisson process. A limit result for the asymptotic behavior of the first nucleation time \(T^N\) defined by Relation \([15]\) is derived from this theorem.

The integration of Equations \([16]\) gives the following representation, for \(1 < k < n_c\),
\[ X_k^N(t) = X_k^N(0) + \frac{\lambda_{k-1}}{N} \int_0^t X_1^N(s)X_{k-1}^N(s) \, ds + \sum_{\ell=k+1}^{n_c-1} \mu_\ell \Phi(N) \left\langle \nu_\ell, I_k \right\rangle \int_0^t X_\ell^N(s) \, ds 
- \mu_k \Phi(N) \int_0^t X_k^N(s) \, ds - \frac{\lambda_k}{N} \int_0^t X_1^N(s)X_k^N(s) \, ds + M_k^N(t), \]
where \((M_k^N(t))\) is a martingale, obtained by the compensation of the Poisson processes of the dynamics. Stochastic calculus, see Section 5.2 of the Appendix for example, gives that its previsible increasing process is
\[ \left\langle M_k^N \right\rangle(t) = \frac{\lambda_{k-1}}{N} \int_0^t X_1^N(s)X_{k-1}^N(s) \, ds + \sum_{\ell=k+1}^{n_c-1} \mu_\ell \Phi(N) \left\langle \nu_\ell, I_k \right\rangle \int_0^t X_\ell^N(s) \, ds 
+ \mu_k \Phi(N) \int_0^t X_k^N(s) \, ds + \frac{\lambda_k}{N} \int_0^t X_1^N(s)X_k^N(s) \, ds. \]
For \(k=n_c\), by definition the process \((X_{n_c}^N(t))\) is non-decreasing,
\[ X_{n_c}^N(t) = \frac{\lambda_{n_c-1}}{N} \int_0^t X_1^N(s)X_{n_c-1}^N(s) \, ds + M_{n_c}^N(t). \]
and
\[
\langle M_{n-1}^N \rangle(t) = \frac{\lambda_{n-1}}{N} \int_0^t X_i^N(s)X_{n-1}^N(s) \, ds.
\]

By looking at the transition rates between the two first coordinates of \((X^N(t))\), one can guess that \((X^N(t))\) should be of the order of \(N/\Phi(N)\) on the normal time scale at least. The following important proposition shows that, on the fast time scale \(t \to \Psi(N)t\), the coordinates with index 2, \ldots, \(n_c-1\) remain negligible with respect to \(N\).

**Proposition 2.** If \((X^N(t))\) is the solution of the SDE (16) with initial state satisfying Condition (1) then, for \(2 \leq k \leq n_c-1\) and any \(\varepsilon > 0\), for the convergence in distribution of processes, the relations
\[
\begin{aligned}
&\lim_{N \to +\infty} \left( \frac{\Phi(N)^{k-1-\varepsilon}}{N} X_k^N(\Psi(N)t) \right) = (0), \quad 2 \leq k \leq n_c, \\
&\lim_{N \to +\infty} \left( \frac{1}{\Phi(N)} \left( X_{n_c+1}^N + \cdots + X_{n_c-1}^N \right)(\Psi(N)t) \right) = (0).
\end{aligned}
\]
hold.

**Proof.** We fix \(\varepsilon \in (0, 1/2)\), define \(\lambda \eqdef \max(\lambda_k, 1 \leq k < n_c)\), \(\mu \eqdef \min(\mu_i/(i-1), 2 \leq i \leq n_c-1)\) and, for \(k=2, \ldots, n_c-1\),
\[
\langle Z^N_k(t) \rangle \eqdef \left( \sum_{i=k}^{n_c-1} (i-1)X_i^N(t) \right).
\]
We start with the case \(k=2\) process \((Z^N_2(t))\). Definition (11) of the infinitesimal generator gives that, when \(X^N(0)=x \in S_N\), this process has positive jumps of size 1 only. Remember that a polymer of size \(n_c\) is in a cemetery state from the point of view of the dynamic of the process \((X^N(t))\). They occur at rate
\[
\frac{x_1}{N} \sum_{i=1}^{n_c-2} \alpha_i \leq \alpha_N^{(2)} \eqdef \lambda N.
\]
Negative jumps of \((Z^N_2(t))\) are at least less than \(-1\) and occur at rate
\[
\frac{\lambda_{n_c-1}}{N} \sum_{i=2}^{n_c-1} \Phi(N) \sum_{i=2}^{n_c-1} \frac{\mu_i}{i-1} (i-1)X_i \geq \delta_N Z^N_2(t),
\]
with \(\delta_N \eqdef \mu \Phi(N)^{1-\varepsilon}\).

With a simple coupling, one can therefore construct a birth and death process process \((L^N_2(t))\), corresponding to an \(M/M/\infty\) queue with arrival rate \(\alpha_N^{(2)}\) and service rate \(\delta_N\), see Chapter 6 of Robert [30], with \(L^N_2(0) = Z^N_2(0)\) and such that the relation \(Z^N_2(t) \leq L^N_2(t)\) holds for all \(t \geq 0\). Let, for \(n \geq 0\),
\[
T^N_n = \inf\{s > 0 : L^N_2(s) \geq n\},
\]
Relation (6.13) of Proposition 6.9 in Robert [30] gives an expression for the Laplace transform of \(T^N_n\), for \(n \in \mathbb{N}\) and \(\xi \geq 0\),
\[
E\left( e^{-\delta_N \xi T^N_n} \right) = \int_0^{+\infty} E\left( (1+r/\beta_N^{(2)}) Z^N_2(0) \mathbb{I}\{Z^N_2(0) < \xi\} \right) r^{\xi-1} e^{-r} \, dr,
\]
with
\[
\beta_N^{(2)} \eqdef \frac{\alpha_N^{(2)}}{\delta_N} = \frac{\lambda}{\mu \Phi(N)^{1-\varepsilon}}.
\]
We assume for the moment that the limit of $(\beta_N^{(2)})$ is not 0, in particular $k_n$ defined by Relation (8) is greater than 2. See Assumption A-2.

If $\Gamma(\cdot)$ is the classical Gamma function,

$$\Gamma(\xi) = \int_0^{+\infty} e^{\xi r} e^{-r} \, dr, \quad \xi > 0,$$

by expanding the integrand of the Laplace transform by using the classical relation $\Gamma(m+1) = m\Gamma(m)$, we get that

$$D_N(\xi) \overset{\text{def.}}{=} \frac{1}{\Gamma(\xi)} \int_0^{+\infty} \left(1 + r/\beta_N^{(2)}\right)^{-\xi} e^{-r} \, dr$$

$$= \sum_{k=0}^{n} \left( \frac{n}{k} \right) \frac{1}{\beta_N^{(2)}} \frac{\Gamma(k+1)}{\Gamma(\xi)} = 1 + \sum_{k=1}^{n} \left( \frac{n}{k} \right) \frac{1}{\beta_N^{(2)}} \prod_{i=0}^{k-1} (1+i).$$

For $x > 0$, we fix $n = 2m_N$ with $m_N = \lceil x/\beta_N^{(2)} \Phi(N) \rfloor = \lceil x/(\lambda/\mu)N/\Phi(N)^{1-\varepsilon} \rfloor$ and denote

$$U_N \overset{\text{def.}}{=} \frac{1}{\mu \Phi(N)^{1-\varepsilon} \Psi(N)} \frac{(2m_N)!}{m_N! m_N^{m_N-1}} \geq \frac{1}{\lambda \Phi(N)^{\varepsilon(m_N-1)-n+2}},$$

due to the assumption of $(\beta_N^{(2)})$, the sequence $(m_N)$ is converging to infinity, and the same property holds for $(U_N)$. We have proved that $(D_N(a/(\delta N \Phi(N))))$ converges to infinity.

Condition (1) for the initial state gives that, for any $\eta > 0$ arbitrarily small, for the convergence in distribution,

$$\lim_{N \to +\infty} \frac{\Phi(N)^{1-\eta}}{N} Z_N^2(0) = 0, \quad \text{so that} \quad \lim_{N \to +\infty} \frac{\Phi(N)^{\varepsilon/2}}{\beta_N^{(2)}} Z_N^2(0) = 0.$$

For $\xi \in \mathbb{R}^+$, by using Lebesgue’s Theorem, we have the relation

$$\lim_{N \to +\infty} \frac{1}{\Gamma(\xi)} \int_0^{+\infty} e^{-(1+x/\beta_N^{(2)})} Z_N^2(0) \, dx \leq \lim_{N \to +\infty} \frac{1}{D_N(\frac{a}{\delta N \Phi(N)})} = 0.$$

Relations (22) and (23) give that, for any $a > 0$ and $x > 0$,

$$\lim_{N \to +\infty} \mathbb{E} \left( e^{-aT_N^{(2)/\Phi(N)}} \mathbb{I} \{ Z_N^2(0) < \beta_N^{(2)} \Phi(N)^{\varepsilon/2} \} \right) \leq \lim_{N \to +\infty} 1/D_N(\frac{a}{\delta N \Phi(N)}) = 0,$$

and

$$\limsup_{N \to +\infty} \mathbb{E} \left( e^{-aT_N^{(2)/\Phi(N)}} \mathbb{I} \{ n > Z_N^2(0) > \beta_N^{(2)} \Phi(N)^{\varepsilon/2} \} \right) \leq \limsup_{N \to +\infty} \mathbb{P} \left( Z_N^2(0) > \beta_N^{(2)} \Phi(N)^{\varepsilon/2} \right) = 0,$$

which gives the relation

$$\lim_{N \to +\infty} \mathbb{E} \left( \exp \left( -a T_N^{(2)/\Phi(N)} \right) \right) = 0.$$
Hence, for any \( t \geq 0 \), the sequence \( \mathbb{P}(T^N_{x+\Phi(N)^{-1-\varepsilon}} \leq t \Phi(N)) \) is converging to 0, equivalently, for \( x > 0 \),
\[
\lim_{N \to +\infty} \mathbb{P} \left( \frac{\Phi(N)^{1-\varepsilon}}{N} \sup_{0 \leq s \leq \Phi(N)} L^N_s \geq x \right) = 0. \tag{24}
\]
The coupling relation between \((L^N_2(t))\) and \((Z^N_2(t))\) gives that the last relation also holds when \((L^N_2(t))\) is replaced by the process \((Z^N_2(t))\).

Assume now that the limit of the sequence \((\beta^N_N)\) is \((\lambda/\mu)N/\Phi(N)^{1-\varepsilon}\) is 0. There exists some constant \( C \) such that \( \delta_N \geq CN \), for all \( N \geq 1 \). Then, with a simple coupling, there exists an \( M/M/\infty \) queue \((L^N_2(t))\) with arrival rate \( \lambda \) and service rate \( C \) such that \( L^N_2(t) \leq L^N_2(Nt) \) holds for all \( t \geq 0 \). Proposition 6.10 of Robert [20] shows that, for any \( \eta > 0 \) and \( x > 0 \),
\[
\lim_{N \to +\infty} \mathbb{P} \left( \frac{1}{\Phi(N)^{\varepsilon}} \sup_{0 \leq s \leq \Phi(N)^{\varepsilon-2}} \tilde{L}^N_s \geq x \right) = 0.
\]
By using again the coupling, this relation also holds for \((Z^N_2(t))\). This completes the proof of our assertion for \( k = 2 \).

Assume that the proposition holds up to \( k < n_c - 1 \). The process \((Z^N_{k+1}(t))\) has also positive jumps of size 1 only, occurring at rate
\[
\frac{x_1}{N} \sum_{i=k}^{n_c - 2} \lambda_i x_i \leq \lambda \sum_{i=k}^{n_c - 2} x_i,
\]
when the process \((X^N(t))\) is in state \( x \in S_N \).

Assume by induction that the convergence holds for \( k < n_c - 1 \). If \( k \leq k_c \), we therefore have that, for any \( \varepsilon \in (0, 1/2) \) and \( T > 0 \), the relation
\[
\sup_{0 \leq t \leq \Phi(N)T} \sum_{i=k}^{n_c - 2} X^N_i (t) \leq \frac{N}{\Phi(N)^{k-1-2\varepsilon}}
\]
holds with high probability for \( N \) sufficiently large. As before, we introduce an \( M/M/\infty \) process \((L^N_{k+1}(t))\) starting at \( Z^N_{k+1}(0) \) with the service rate \( \delta_N \) defined above, and with the arrival rate \( a^N_{k+1}(x) \), given by \( \lambda N/\Phi(N)^{k-1-2\varepsilon} \), such that for any \( \eta > 0 \), there exists some \( N_0 \) for which the relation
\[
\mathbb{P} \left( Z^N_{k+1}(t) \leq L^N_{k+1}(t), \forall t \in (0, \Phi(N)T) \right) \geq 1 - \eta
\]
holds for all \( N \geq N_0 \). Due to condition [11] for the initial state, \((Z^N_{k+1}(0))/\beta^N_{k+1}(1))\) converges in distribution to 0, where \( \beta^N_{k+1}(1) = \alpha^N_{k+1}(1)/\delta_N = (\lambda/\mu)N/\Phi(N)^{k-3\varepsilon} \). We can now proceed with the same method for \((L^N_{k+1}(t))\) as we did with \((L^N_2(t))\). The case \( k \leq k_c \) is similar. The proposition is proved. \( \square \)

**Proposition 3.** For \( n_c \geq r \geq 2, 1 \leq k \leq ((r-1)/(n_c-2)) \) and \( 2 \leq h \leq n_c - 1 \) then, for the convergence in distribution of continuous processes,
\[
\lim_{N \to +\infty} \left( \frac{1}{N \Phi(N)^{r-2}} \int_0^{\Phi(N)T} X^N_{n_c-k}(u) X^N_h(u) \, du \right) = (0), \tag{25}
\]
\[
\lim_{N \to +\infty} \left( \frac{1}{N \Phi(N)^{r-1}} \int_0^{\Phi(N)T} X^N_{n_c-k}(u) X^N_h(u) \, du \right) = (0). \tag{26}
\]

**Proof.** See Appendix. \( \square \)

We are now ready to establish one of the key technical results used in the proof of the main convergence theorem of this section.
Proposition 4 (Balance Equations). For $k=1, \ldots, n_c-2$, if
\[
\left(\Delta^N_k(t)\right) \overset{\text{def}}{=} \left(\frac{\lambda_{n_c-k-1}}{N} \int_0^t X_1^N(u)^{k+1} X_{n_c-k-1}^N(u) \, du \right) - \mu_{n_c-k} \Phi(N) \int_0^t X_1^N(u)^k X_{n_c-k}^N(u) \, du
\]
then, for the convergence in distribution,
\[
\lim_{N \to +\infty} \left(\frac{1}{(N\Phi(N))^k} \Delta^N_k(\Psi(N)t)\right) = (0).
\]

Proof. By a careful use of the SDE (16), one gets that, for $t \geq 0$ and $m=n_c-k$, where $1 \leq k \leq n_c-2$,
\[
X_1^N(t)^k X_m^N(t) = M^N_{(k)}(t)
\]
\[
+ \frac{\lambda_{m-1}}{N} \int_0^t X_1^N(u)^{k+1} X_{m-1}^N(u) \, du - \mu_m \Phi(N) \int_0^t X_1^N(u)^k X_m^N(u) \, du \right) \Delta^N_k(t)
\]
\[
+ \frac{\lambda_{m-1}}{N} \int_0^t \left( \left( X_1^N(u)-1 \right)^k \right) X_m^N(u) X_{m-1}^N(u) \, du \right) A_1^N(t)
\]
\[
+ \sum_{i \neq m-1, m} \frac{\lambda_i}{N} \int_0^t \left( \left( X_i^N(u)-1 \right)^k \right) X_m^N(u) X_{m-1}^N(u) \, du \right) A_2^N(t)
\]
\[
+ \frac{\lambda_m}{N} \int_0^t \left( \left( X_1^N(u)-1 \right)^k \right) \left( X_m^N(u)-1 \right)^k \, du \right) A_3^N(t)
\]
\[
+ \sum_{i=2}^{m-1} \mu_i \Phi(N) \int_0^t \left( \left( X_i^N(u)+1 \right)^k \right) X_m^N(u) \, du \right) A_4^N(t)
\]
\[
+ \sum_{i=m+1}^{n_c-1} \mu_i \Phi(N) \int_0^t \left( \left( X_i^N(u)+1 \right)^k \right) X_m^N(u) \, du \right) A_5^N(t)
\]
\[
\times \int_0^t \left( \left( X_i^N(u)+1 \right)^k \right) X_m^N(u) \, du \right) A_6^N(t).
\]
The terms $A_i^N(t), i=1, \ldots, 6$, are associated to the compensators of the following transitions, for $x \in S_N$,
\begin{itemize}
  \item $A_N^N(t)$: it is for the transition $x \rightarrow x-e_1-e_{m-1}+e_m$ and with the first term of $\Delta^N_k(t)$
    \[
    \frac{\lambda_{m-1}}{N} \int_0^t X_1^N(u)^{k+1} X_{m-1}^N(u) \, du
    \]
    substracted.
  \item $A_1^N(t)$: transition when the fragmentation of an element of size $m$ gives $y_1$ polymers of size 1 and with the second term of $\Delta^N_k(t)$
    \[
    -\mu_m \Phi(N) \int_0^t X_1^N(u)^k X_m^N(u) \, du
    \]
    substracted.
  \item $A_2^N(t)$: transition $x \rightarrow x-e_1-e_i+e_{i+1}$ for $i \in \{ m-1, m \}$.
  \item $A_3^N(t)$: transition $x \rightarrow x-e_1-e_m+e_{m+1}$.
  \item $A_4^N(t)$: the fragmentation of a polymer of size $2 \leq i < m$ gives $y_1$ polymers of size 1.
  \item $A_5^N(t)$: the fragmentation of a polymer of size $n_c-m$ gives $y_1$ polymers of size 1 and $y_m$ polymers of size $m$.
\end{itemize}
Associated to these transitions, \( (M^N_{(k)}(t)) \) is the corresponding martingale. The above relation can thus be rewritten as

\[
\Delta_k^N(t) = X^N(t)X^N_n_{-k}(t) - M^N_{(k)}(t) - \sum_{i=1}^6 A_i^N(t).
\]

Proposition 2 shows that for \( T \geq 0 \), for \( N \) sufficiently large, with high probability, the relation \( X^N_{n_{-k}}(\Psi(N)t) \leq N/\Phi(N)^{n_{-k}-2} \) holds for all \( t \leq T \). Consequently the relation

\[
\frac{X^N_{1/k}(\Psi(N)t)X^N_{n_{-k}}(\Psi(N)t)}{N^k\Phi(N)^k} \leq \frac{X^N_{n_{-k}}(\Psi(N)t)}{\Phi(N)^k} \leq \frac{N}{\Phi(N)^{n_{-k}-2}}
\]

also holds with high probability in the limit. In particular, due to Assumption A-2, for

\[
M
\]

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\]

also holds with high probability in the limit. In particular, due to Assumption A-2, for

\[
A
\]

We now show that the processes \( (A_i^N(\Psi(N)t)/(N^k\Phi(N)^k)) \), \( i=1,\ldots,6 \), also vanish as \( N \) gets large. Since

\[
A_i^N(t) = \frac{\lambda_{m-1}}{N} \int_0^t B_1 \left( X^N_i(u), X^N_m(u) \right) X^N_i(u)X^N_{m-1}(u) \, du,
\]

with \( B_1(x, z) \equiv \lambda_{m-1} ((x-1)^k - x^k)(z+1) \leq c_1x^{k-1}(z+1) \) for all \( x, z \in \mathbb{N} \) and some convenient constant \( c_1 \), therefore we have

\[
\frac{A_i^N(\Psi(N)t)}{N^k\Phi(N)^k} \leq \frac{c_1}{N\Phi(N)^k} \int_0^{\Psi(N)t} \left( 1 + X^N_{n_{-k}}(u) \right) X^N_{n_{-k-1}}(u) \, du
\]

\[
\leq \frac{c_1}{N\Phi(N)^k} \int_0^{\Psi(N)t} \left( X^N_{n_{-k}}(u)X^N_{n_{-k-1}}(u) + X^N_{n_{-k-1}}(u)^2 \right) \, du.
\]

If \( k < n_2 - 2 \), Relation 26 of Proposition 3 gives that the last process vanishes as \( N \) gets large for the convergence in distribution.

Otherwise, if \( k = n_2 - 2 \),

\[
\frac{A_i^N(\Psi(N)t)}{N^k\Phi(N)^k} \leq \frac{c_1}{N\Phi(N)^{n_{-2}}} \int_0^{\Psi(N)t} \left( X^N_1(u)X^N_2(u) + X^N_1(u) \right) \, du
\]

\[
\leq \frac{c_1}{N\Phi(N)^{n_{-2}}} \int_0^{\Psi(N)t} X^N_1(u)X^N_2(u) \, du + \frac{c_1\Psi(N)t}{\Phi(N)^{n_{-2}}}.
\]

The first term of the right hand side of the last relation is vanishing due to Relation 26 of Proposition 3 and the second term is clearly converging to 0.

Similarly, one can find a constant \( c_2 \) such that

\[
A_2^N(t) \leq c_2\Phi(N) \int_0^t X^N_m(u)^{k-1} \left( X^N_m(u) - 1 \right) X^N_m(u) \, du,
\]

so that

\[
\frac{A_2^N(\Psi(N)t)}{N^k\Phi(N)^k} \leq \frac{c_2}{N\Phi(N)^{k-1}} \int_0^{\Psi(N)t} |X^N_m(u) - 1|X^N_m(u) \, du \leq \frac{c_2}{N\Phi(N)^{k-1}} \int_0^{\Psi(N)t} X^N_{n_{-k}}(u)^2 \, du,
\]

holds. Again Proposition 3 can be used to show that this term vanishes as \( N \) goes to infinity.
Similarly, there are constants $c_i$, $i = 3, \ldots, 6$, such that the relations

$$
\frac{A_3^N (\Psi(N))t}{N^k \Phi(N)^k} \leq \frac{c_3}{N^k \Phi(N)^k} \sum_{i \neq \eta_{n_{c} - k}, n_{c} - k} \int_0^{\Phi(N)t} X^N_{\eta_{n_{c} - k}(u)} X^N_{n_{c} - k}(u) \, du,
$$

$$
\frac{A_4^N (\Psi(N))t}{N^k \Phi(N)^k} \leq \frac{c_4}{N^k \Phi(N)^k} \int_0^{\Phi(N)t} \left( X^N_{\eta_{n_{c} - k}(u)} + X^N_{n_{c} - k}(u) \right) X^N_{n_{c} - k}(u) \, du,
$$

$$
\frac{A_5^N (\Psi(N))t}{N^k \Phi(N)^k} \leq \frac{c_5}{N^k \Phi(N)^k-1} \sum_{i = 2}^{n_{c} - k - 1} \int_0^{\Phi(N)t} X^N_{\eta_{n_{c} - k}(u)} X^N_{n_{c} - k}(u) \, du,
$$

$$
\frac{A_6^N (\Psi(N))t}{N^k \Phi(N)^k} \leq \frac{c_6}{N^k \Phi(N)^k-1} \sum_{i = n_{c} - k + 1}^{n_{c} - 1} \int_0^{\Phi(N)t} \left( X^N_{\eta_{n_{c} - k}(u)} + X^N_{1}(u) + X^N_{n_{c} - k}(u) \right) X^N_{n_{c} - k}(u) \, du
$$

hold and the corresponding terms also vanish at infinity for the convergence in distribution by using Proposition 3.

To complete the proof, in view of Relation (28), we have now to show that a similar result for the martingale $(M^N_{(k)}(t))$, i.e. that, for the convergence in distribution,

$$
\lim_{N \to +\infty} \left( \frac{M^N_{(k)}(t)}{N^{k+1} \Phi(N)^{k+1}} \right) (\Psi(N)t) = 0.
$$

From Relation (3.31) of Lemma I.3.30 of Jacod and Shiryaev[10], it is enough to show the following convergence in distribution of the sequence of previsible increasing processes,

$$
\lim_{N \to +\infty} \left( \frac{M^N_{(k)}(t)}{N^{k} \Phi(N)^{k}} \right) (\Psi(N)t) = 0.
$$

Since $(M^N_{(k)}(t))$ is a sum of martingales $(M^N_{i(k)}(t))$, $i \in \{1, \ldots, 6\}$, associated to Poisson processes corresponding to the difference transitions. By orthogonality of these martingales, see Proposition A.10 of Robert[20] for example, due to the independence of the Poisson processes, it is enough to show that the previsible increasing process of each of them vanish when $N$ gets large. We will detail only the case of $(M^N_{1(k)}(t))$, the other martingales can be analyzed in a similar way. For $t \geq 0$, with standard arguments, we have

$$
\left\langle \frac{M^N_{1(k)}(t)}{N^{k} \Phi(N)^{k}} \right\rangle (\Psi(N)t) = \frac{\lambda_{n_{c} - 1}}{N^{2k+1} \Phi(N)^{2k}} \int_0^{\Phi(N)t} \left( X^N_{1}(u) - 1 \right)^k \left( X^N_{n_{c} - k}(u) + 1 \right)^k \left( X^N_{n_{c} - k}(u) \right)^2 X^N_{1}(u) X^N_{n_{c} - k-1}(u) \, du,
$$

with the same notations as before, we get that

$$
\left\langle \frac{M^N_{1(k)}(t)}{N^{k} \Phi(N)^{k}} \right\rangle (\Psi(N)t) \leq \frac{c_1^2}{N^{2k} \Phi(N)^{2k}} \int_0^{\Phi(N)t} \left( X^N_{1}(u) + X^N_{n_{c} - k}(u) \right)^2 X^N_{n_{c} - k-1}(u) \, du
$$

$$
\leq \frac{2c_1^2}{N \Phi(N)^{2k}} \int_0^{\Phi(N)t} \left( X^N_{1} + X^N_{n_{c} - k}(u) \right) X^N_{n_{c} - k-1}(u) \, du.
$$

Again with Proposition 3, we get therefore that the previsible increasing process of $(M^N_{1(k)}(t))$ is converging in distribution to 0 and, consequently the same result holds for the martingale.

By gathering these convergence results in Relation (28), the proof of the proposition is completed. 
\qed
For $k = 1, \ldots, n_c - 2$, denote by $\rho_k = \lambda_k / \mu_k$ and $\overline{p} = \lambda_1 \rho_2 \cdots \rho_{n_c - 1}$. The above proposition shows that the following sequence of processes

$$
\left( \lambda_{n_c - k - 1} \prod_{i=n_c-k}^{n_c-2} \rho_i \frac{1}{N^{k+1} \Phi(N)^c} \int_0^{\Phi(N)t} X_1^N(u)^{k+1} X_{n_c-k-1}^N(u) \, du 
- \lambda_{n_c - k} \prod_{i=n_c-k+1}^{n_c-1} \rho_i \frac{1}{N^{k} \Phi(N)^c} \int_0^{\Phi(N)t} X_1^N(u)^{k} X_{n_c-k}^N(u) \, du \right)
$$

converges in distribution to 0. By summing up all these terms, we obtain the relation

$$\lim_{N \to +\infty} \left( \frac{\overline{p}}{N^{n_c-1} \Phi(N)^{n_c-2}} \int_0^{\Phi(N)t} X_1^N(u)^{n_c} \, du 
- \frac{\lambda_{n_c-1}}{N} \int_0^{\Phi(N)t} X_1^N(u) X_{n_c-1}^N(u) \, du \right) = 0.
$$

The next lemma establishes that, on the time scale $t \to \Psi(N)t$, “most” of the polymers are still of size 1.

**Lemma 1.** The convergence in distribution

$$\lim_{N \to +\infty} \left( \frac{1}{N} X_N^N(\Psi(N)t) \right) = (1, 0, \ldots, 0)
$$

holds.

**Proof.** The estimates of Proposition 2 and the fact that the sum of the coordinates of $X_N^N(t)$ is $N$, show that we just have to prove the convergence result for the last coordinate $(X_{n_c}^N(t))$.

The SDE (20) and Relation (21) give the identity

$$X_{n_c}^N(t) = \lambda_{n_c - 1} \int_0^t \frac{X_1^N(u) X_{n_c-1}^N(u)}{N} \, du + M_{n_c}^N(t),
$$

where $(M_{n_c}^N(t))$ is a martingale. By Relation (29), for $t \geq 0$, for the convergence in distribution, the sequence of processes

$$\left( \frac{\lambda_{n_c-1}}{N} \int_0^{\Phi(N)t} X_1^N(u) X_{n_c-1}^N(u) \, du \right)
$$

has the same limit as

$$\left( \frac{1}{N^{n_c} \Phi(N)^{n_c-2}} \int_0^{\Phi(N)t} X_1^N(u)^{n_c} \, du \right) \left( \frac{1}{N} \int_0^t \left( \frac{X_1^N(\Psi(N)u)}{N} \right)^{n_c} \, du \right),
$$

and, since the coordinates of the last process are upper bounded by $\overline{p}t/N$, we deduce the convergence to (0) of the sequence of processes [31].

The previsible increasing previsible process of the corresponding martingale is given by

$$\left( \left( \frac{M_{n_c}^N}{N} \right) (\Psi(N)t) \right) = \left( \frac{\lambda_{n_c-1}}{N^2} \int_0^{\Phi(N)t} \frac{X_1^N(s) X_{n_c-1}^N(s)}{N} \, ds \right).
$$

With the same argument, by using again Relation (3.31) of Jacod and Shiryaev [15], we get that the sequence of martingales $(M_{n_c}^N(\Psi(N)t))/N$ is converging in distribution to 0. The lemma is proved.

We are now ready to establish the main result of this section.
The sequence of processes $(X^N_{n_c}(N(t)))$ is converging in distribution to a Poisson process on $\mathbb{R}_+$ with rate
\begin{equation}
\overline{\rho} \overset{\text{def.}}{=} \lambda_1 n_c^{-1} \prod_{k=2}^{n_c-1} \frac{\lambda_k}{\mu_k},
\end{equation}
where $\Psi(N) = \Phi(N)^{n_c-2}/N$.

**Proof.** Clearly $(X^N_{n_c}(N(t)))$ is a counting process, i.e. a non-decreasing integer valued process with jumps of size one. By Equation (30), its compensator is given by
\begin{equation}
\left(\lambda_{n_c-1} \int_0^{\Phi(N)t} X^N_1(u)X^N_{n_c-1}(u) \frac{du}{N}\right).
\end{equation}
By Relation (29), this sequence of processes has the same limit as
\begin{equation}
\left(\overline{\rho}^{Nn_c-1+1\Phi(N)n_c-2} \int_0^{\Phi(N)t} X^N_1(u)^{n_c} \frac{du}{N}\right) = \left(\overline{\rho}^{\int_0^t \left(X^N_1 \left(\Psi(N)u\right)\right)^{n_c} \frac{du}{N}\right).
\end{equation}
Lemma 1 shows therefore that the compensator of $(X^N_{n_c}(N(t)))$ is converging in distribution to $(\overline{\rho})$. Theorem 5.1 of Kasahara and Watanabe [18], see also Brown [8], gives the desired convergence in distribution to a Poisson process with rate $\overline{\rho}$. The theorem is proved.

**Proposition 5** (Asymptotic of the First Nucleation Time). If $((U^N(t)))$ is the process defined by Relations [12] and [13] and whose initial state satisfies Relation [9], and $T^N$, defined by Relation [13], is the first time its $n_c$th coordinate $(U_{n_c}(\cdot))$ is non null, then, for the convergence in distribution,
\begin{equation}
\lim_{N \to +\infty} \frac{N}{\Phi(N)^{n_c-2}} T^N = E_{\overline{\rho}},
\end{equation}
$E_{\overline{\rho}}$ is an exponential random variable with parameter $\overline{\rho}$ defined by Relation (32).

**Proof.** Let
\begin{equation}
\tau^N = \inf\{t \geq 0 : X^N_{n_c}(t)=1\},
\end{equation}
then from the SDE’s (12) and (16), one gets the identity
\begin{equation}
\left((U^N_1, \ldots, U^N_{n_c}) \left(t \wedge T^N\right)\right) \overset{\text{dist.}}{=} \left((X^N_1, \ldots, X^N_{n_c}) \left(t \wedge \tau^N\right)\right).
\end{equation}

4. **Asymptotic Growth of Lag Time**

In this section, the evolution of the polymerization process after nucleation is investigated. The main difference with Section 3 lies in the fact that the polymers become more stable after nucleation: a polymer of size $k \geq n_c$ is degraded at rate $\mu_k \Phi(N)$ when $k < n_c$ as in Section 3. See Relation (4). As before we first introduce an auxiliary process to study this phase.

4.1. **A Super-Critical Branching Process**

We will be interested by the evolution of the number of polymers whose size are greater than $n_c$. For $\alpha > 0$ and $\mu > 0$, a Markov process $(Z^{n_c,\mu}(t)) := (Z^{n_c,\mu}_i(t), i \geq n_c)$ will be introduced for this purpose. With a slight abuse of notations, we will consider $(Z^{n_c,\mu}(t))$ as a process in the state space $S_\infty$. Formally, it can be done by assuming that the $n_c-1$ first coordinates are null. We denote by $\|z\|_c$ the sum of the components of the vector $z := (z_i)$ of the set $S_\infty$ of states with finite mass defined by Relation (4),
\begin{equation}
\|z\|_c \overset{\text{def.}}{=} \sum_{i \geq n_c} z_i.
\end{equation}
The generator $\Omega_{\alpha,\mu}$ of the process is given by

$$
\Omega_{\alpha,\mu}(f)(z) = \sum_{k=0}^{\infty} \left[ f(z+e_{k+1}-e_k) - f(z) \right] \alpha z_k + \sum_{k=0}^{\infty} \int_{S_k} \left[ f(z+y-e_k) - f(z) \right] \mu z_k \nu_k(dy)
$$

where, as before, for $i \geq 1$, $e_i$ is the $i$th unit vector of $S_\infty$ and $f$ is a function on $S_\infty$ with finite support. Since coordinates with index greater or equal to $n_c$ are of interest, it is assumed that the function $f$ does not depend on the first $n_c-1$ coordinates.

We give a quick, informal, motivation for the introduction of the Markov process $(Z^{\alpha,\mu}(t))$. It describes in fact the evolution of stable polymers. Assume for the moment that the polymerization rates are independent of the sizes of polymers, i.e. $\lambda_k=\alpha$ for all $k \geq n_c$. A monotonicity argument will be used to have a more general framework.

The initial state is assumed to be $Z^{\alpha,\mu}(0)=c_{n_c}$ with only one polymer of size $n_c$ present at time 0, as it is the case just after the first nucleation instant. Proposition 6 gives that, at this instant, the number of polymers is small with respect to $N$, i.e. the fraction of monomer is close to 1. A polymer of size greater that $n_c$ grows therefore at a rate close to $\alpha$ as in Relation (34). If the fragmentation of a polymer of size $k \geq n_c$ gives a polymer of size less than $n_c$, then, due to the fast fragmentation rates below $n_c$, this last one is fragmented quickly into monomers and thus vanishes as in Relation (34) since coordinates with index greater or equal to $n_c$ are assumed to be 0 for the process $(Z^{\alpha,\mu}(t))$.

**Proposition 6.** If $Z^{\alpha,\mu}(0)=c_m$ for some $m \geq n_c$, there exist $\kappa_0 \geq 0$, $a_0>0$ and $\eta>0$ such for any $\alpha$ and $\mu>0$ such that $\alpha/\mu \geq \kappa_0$, then the event

$$
\mathcal{F}_{Z^{\alpha,\mu}} = \left\{ \liminf_{t \to +\infty} e^{-a_0 t} \|Z^{\alpha,\mu}(t)\|_c > \eta \right\}
$$

has a positive probability.

**Proof.** The evolution of $(Z^{\alpha,\mu}(t))$ describes the the population of stable polymers generated by an initial polymer with size $m \geq n_c$. Relation (9) of Condition A-3 gives the existence of $\varepsilon>0$ and $k_0 \geq C_0 n_c$ such that if $k \geq k_0$,

$$
\nu_k \left( y : \sum_{i \geq n_c} y_i \geq 2 \right) > \varepsilon.
$$

A stable polymer of size $m \geq n_c$ is fragmented after an exponentially distributed amount of time $E_\mu$ with parameter $\mu$. Just before this instant its size has the same distribution as $M=m+N_\mu([0,E_\mu])$. Recall that only the fragments with size greater than $n_c$ are considered for $(Z^{\alpha,\mu}(t))$. The process $(Z^{\alpha,\mu}(t))$ can then be also seen as a multi-type branching process with the type of an individual being the size of the corresponding polymer. The average number of stable polymers generated by the fragmentation of the polymer of size $M$ is greater than

$$
\mathbb{E} \left( \nu_M \left( y : \sum_{i \geq n_c} y_i \geq 1 \right) \right) + \mathbb{E} \left( \nu_M \left( y : \sum_{i \geq n_c} y_i \geq 2 \right) \right)
$$

$$
\geq \mathbb{P}(M \geq k_0)(1+\varepsilon) = (1+\varepsilon) \left( \frac{\alpha}{\alpha+\mu} \right)^{k_0-n_c}.
$$

By choosing $\alpha/\mu$ sufficiently large, the last quantity is strictly greater than 1. We have thus shown that the process $(\|Z^{\alpha,\mu}(t)\|_c)$ is lower bounded by a continuous time supercritical branching process. The proposition is then a simple consequence of a classical result in this domain, see Chapter V of Athreya and Ney [4] for example. \(\square\)
4.2. Limit Results. now return to the original polymerization process \( (U^N_t(t)) \) with values in the state space \( \mathcal{S}_N \) defined by the SDE (12) and initial state satisfies Condition (I).

We study the asymptotic behavior of the associated lag time \( L^N_\delta \) defined by Relation (14), which is the first time when the mass of stable polymers exceeds \( \delta N \),

\[
L^N_\delta = \inf \left\{ t \geq 0 : \sum_{k=n_c}^{+\infty} kU^N_k(t) \geq \delta N \right\}
\]

The variable \( T^N_\delta \) defined by Relation (15), which is the first time when a stable polymer is created,

\[
T^N_\delta = \inf \left\{ t \geq 0 : U^N_{n_c}(t) = 1 \right\}
\]

is a stopping time such that \( T^N_\delta \leq L^N_\delta \). Let

\[
u^N_k = (\nu^N_k) = U^N(T^N_\delta),
\]

in particular \( u^N_{n_c} = 1 \) and \( u^N_k = 0 \) for \( k > n_c \).

In the rest of this section, we denote by \( (\hat{U}^N(t)) \) the solution of the SDE (12) with initial condition (35) and \( \hat{L}^N_\delta \) the corresponding lag time,

\[
\hat{L}^N_\delta = \inf \left\{ t \geq 0 : \sum_{k=n_c}^{+\infty} k\hat{U}^N_k(t) \geq \delta N \right\},
\]

note that, by the strong Markov property, \( \hat{L}^N_\delta \stackrel{\text{dist.}}{=} L^N_\delta - T^N_\delta \). We have to study the order of magnitude of \( \hat{L}^N_\delta \). We will prove that, with a positive probability, the mass of stable polymers hits the value \( [\delta N] \) in a duration of time of the order of \( \log N \).

The following proposition is the analogue of Proposition 2 but with the additional feature that there may be polymer of size greater than \( n_c \).

**Proposition 7.** For any \( t_0, \varepsilon > 0 \), the convergence in distribution of processes

\[
\lim_{N \to +\infty} \Phi(N)^{k-1-\varepsilon} \sum_{p=k}^{n_c-1} \frac{\Phi(N)}{N} \sum_{i=2}^{n_c-1} \hat{U}^N_i(t), 0 \leq t \leq \min(\hat{L}^N_\delta, \Psi(N)t_0) = (0), \quad 2 \leq k \leq k_c,
\]

\[
\lim_{N \to +\infty} \frac{1}{\Phi(N)^{\varepsilon}} \left( \hat{U}^N_{k-1}(t) + \cdots + \hat{U}^N_{n_c-1}(t) \right), 0 \leq t \leq \min(\hat{L}^N_\delta, \Psi(N)t_0) = (0).
\]

hold.

**Proof.** It should be noted that, due to Propositions 2 and 5 we have, for the convergence in distribution,

\[
\lim_{N \to +\infty} \Phi(N)^{1-\varepsilon} \sum_{i=2}^{n_c-1} (i-1)\hat{U}^N_i(0) = \lim_{N \to +\infty} \frac{\Phi(N)^{1-\varepsilon}}{N} \sum_{i=2}^{n_c-1} (i-1)U^N_i(T^N) = 0.
\]

We introduce the process

\[
(\hat{B}^N_i(t)) \stackrel{\text{def.}}{=} \left( \sum_{i=k}^{n_c-1} (i-1)\hat{U}^N_i(t) \right),
\]

We proceed as in the proof of Proposition 2 for \( k=2 \). On the time interval \([0, \hat{L}^N_\delta]\), it can be stochastically upper bounded by a jump process with initial state \( \hat{B}^N_i(t)(0) \), whose jump rates are given by, for \( x \in \mathbb{N} \),

\[
x \to \begin{cases} 
  x+1 & \text{at rate } \lambda N \\
  x-1 & \text{at rate } \mu_{n_c} \Phi(N)x \\
  x+(n_c-1)C_0 & \text{at rate } \delta N \mu_{n_c}.
\end{cases}
\]
where \( \lambda \) is defined as in the proof of Proposition 2. The last time interval is associated to the fragmentation of polymers of size greater than \( n_c \). Due to the time interval considered, the total mass of these polymers is certainly less than \( \delta N \) and the fragmentation of one of them gives at most \( C_0 \) polymers of size less than \( n_c \) by Relation (6) of Assumption A-3.

Assume that \( k_c \geq 2 \). Let \( a_0= (n_c-1) C_0 \) and \( \lambda_0= \lambda+ \delta \mu_{n_c} \), then, on the time interval \([0, \hat{L}_d^N] \), the process \((\hat{B}_2^N(t))\) is stochastically dominated by the jump process \((Q^N(t))\) with the same initial state and whose jump rates are given by, for \( x \in \mathbb{N} \),

\[
x \to \begin{cases} 
x + a_0 \text{ at rate } \lambda_0 N \\
x - 1 \mu \Phi(N)^{1-\epsilon/2} x.
\end{cases}
\]  

(38)

This is an \( M/M/\infty \) with \( a_0 \) simultaneous arrivals. To prove the lemma, one has to use a similar argument as in the proof of Proposition 2. This is done as follows. One can construct a set of \( a_0 \) processes associated to \( a_0 \) \( M/M/\infty \) queues, \((L_{2,\ell}^N(t))\), \( \ell \in \{1, \ldots, a_0\} \). The queues share the same arrival process with rate \( \mu \Phi(N)^{1-\epsilon/2} \) and initial conditions \( L_{2,1}^N(0)=Q^N(0) \) and \( L_{2,0}^N(0)=0 \), for \( \ell=2, \ldots, a_0 \). A coupling can be done so that \( Q^N(t)=L_{2,1}^N(t)+L_{2,2}^N(t)+\cdots+L_{2,a_0}^N(t) \) holds for all \( t > 0 \).

As in the proof of of Proposition 2 for the convergence in distribution of processes, the relation

\[
\lim_{N \to +\infty} \left( \frac{\Phi(N)^{1-\epsilon}}{N} H(\Psi(N)t) \right) = (0)
\]

holds for all \( H=L_{2,\ell}^N \), \( \ell=1, \ldots, a_0 \) and, consequently, for \( H=Q^N \). By domination, we finally get that

\[
\lim_{N \to +\infty} \left( \frac{\Phi(N)^{1-\epsilon}}{N} \Phi^N(\Psi(N)t) \right) = (0)
\]

holds. The proof for \( k_c < 2 \) and \( 2 < k \leq n_c - 1 \) follows the same kind of arguments as in the proof of Proposition 2.

**Corollary 1.** Under Assumption A-3, for \( \delta_0=\delta > 0 \) and \( t_0 > 0 \), if

\[
\mathcal{E}_N \overset{def}{=} \left\{ \hat{U}_1^N(t) \geq (1-\delta_0) N, \forall t \leq \min(\hat{L}_d^N, \Psi(N)t_0) \right\},
\]

then the sequence \( \mathbb{P}(\mathcal{E}_N) \) is converging to 1.

**Proof.** The conservation of mass gives that, for all \( t \geq 0 \),

\[
\sum_{i=1}^{+\infty} \hat{U}_i^N(t) = \sum_{i=1}^{+\infty} \hat{U}_i^N(0),
\]

and, noting that we have, for \( t \leq \hat{L}_d^N \),

\[
\sum_{i=1}^{+\infty} \hat{U}_i^N(t) \leq \lfloor \delta N \rfloor,
\]

we complete the proof of the lemma by using Relation (36) with \( k=2 \) and \( \epsilon=1/2 \).

**A Coupling.** Let us introduce a Markov process \((Z_{\alpha_0,\mu_{n_c}}^N(t))\) with the initial state \( Z_{\alpha_0,\mu_{n_c}}^0(0)=\varepsilon_{n_c} \) and the generator defined by Relation (34) with \( \alpha_0 \overset{def}{=} \lambda(1-\delta_0) \), where \( \lambda \) is defined in Relation (6).

**Proposition 8** (Coupling). For \( t_0 > 0 \) and \( \delta \in (0, \delta_0) \), under Assumptions A*, one can construct a coupling of the two processes \((Z_{\alpha_0,\mu_{n_c}}^N(t), t \geq 0)\) and \((\hat{U}^N(t), t \geq 0)\) such that, on the event \( \mathcal{E}_N \) of Corollary 4, the relation

\[
\sum_{k \geq n} Z_{\alpha_0,\mu_{n_c}}^k(t) \leq \sum_{k \geq n} \hat{U}_k^N(t), \ \forall t \geq n_c,
\]

holds for all \( 0 \leq t \leq \min(\hat{L}_d^N, \Psi(N)t_0) \).
Proof. At time 0, there is exactly a polymer of size $n_c$ for $(\hat{U}^N(t))$ and for $(Z^{a_0,\mu_{n_c}}(t))$. For $t \geq 0$, recall, Relation (33), that

$$\|Z^{a_0,\mu_{n_c}}(t)\|_c = \sum_{n \geq n_c} Z^{a_0,\mu_{n_c}}(t)$$

is the number of polymers for $(Z^{a_0,\mu_{n_c}}(t))$.

If this last quantity is not 0, we denote by $A_p(t)$, $1 \leq p \leq \|Z^{a_0,\mu_{n_c}}(t)\|_c$ the respective sizes of the corresponding polymers. The order of the sizes is arbitrary. One will show that one can construct a coupling with the following property: on the event $\mathcal{E}_N$, for $0 \leq t < \min(\hat{L}^N, \Psi(N)t_0)$, we can associate $\|Z^{a_0,\mu_{n_c}}(t)\|_c$ distinct polymers described by the vector $\hat{U}^N(t)$, whose sizes are given respectively by $B_p(t)$, $1 \leq p \leq \|Z^{a_0,\mu_{n_c}}(t)\|_c$, and such that the relation $A_p(t) \leq B_p(t)$ holds for all $1 \leq p \leq \|Z^{a_0,\mu_{n_c}}(t)\|_c$. This property implies that Relation (39) holds. It is proved by induction on the number of jumps of $(Z^{a_0,\mu_{n_c}}(t))$ and $(\hat{U}^N(t))$. It clearly holds at time 0.

Assume that this relation holds at some fixed time $0 \leq t < \min(\hat{L}^N, \Psi(N)t_0)$, we will show that one can construct a version of the two processes after that time so that the relation will also hold after the next jump of $(Z^{a_0,\mu_{n_c}}(t))$ and $(\hat{U}^N(t))$. We now give the construction of the next jump.

1. A monomer addition to the polymer of size $A_i(t-)$ occurs at rate $\alpha_0$. Remark that

$$\alpha_0 \leq \lambda_{B_i(t-)} \frac{\hat{U}^N_i(t-)}{N}.$$

Indeed, by definition, $\lambda_{B_i(t-)} \geq 1$ and, on the event $\mathcal{E}_N$, one has the relation $\hat{U}^N_i(t-) \geq \lambda(1-\delta_0)N$.

The coupling is done so that a monomer addition to the polymer of size $B_i(t)$ is also occurring at that time for the process $(\hat{U}^N(t))$.

2. A monomer addition to the polymer of size $B_i(t-)$ occurs at rate given by

$$\lambda_{B_i(t-)} \frac{\hat{U}^N_i(t-)}{N} = \alpha_0.$$

There is no change for the process $(Z^{a_0,\mu_{n_c}}(t))$ with this event.

3. If $A_i(t-) = k$ and $B_i(t-) = k'$, $n_c \leq k \leq k'$.

At rate $\mu_{n_c}$, both polymers of size $k$ [resp. of size $k'$] are fragmented as $A_i$, $A_i^n$ [resp. $B_i$, $B_i^n$] according to the distribution $\nu_k$ [resp. $\nu_{k'}$]. By Assumption A-4, the random variables $(A_i^n)$ and $(B_i^n)$ can be chosen so that, for any $1 \leq i \leq n_A$, there exists some $1 \leq m_i \leq n_B$ such that $A_i^n \leq B_i^{m_i}$ and all indices $m_i$, $i = 1, \ldots, n_A$ are distinct. Note that we keep the $A_i^n$, $1 \leq i \leq n_A$, whose values are greater or equal to $n_c$.

4. All jumps involving the other polymers of $(\hat{U}^N(t))$ are done as in the original setting.

With this construction, it is easily seen that $(\hat{U}^N(t))$ and $(Z^{a_0,\mu_{n_c}}(t))$ are indeed Markov processes with the generator (31) and (34) respectively. Moreover, each of the transitions described above preserve the desired relation. The proposition is proved. \hfill $\square$

Proposition 9. Under Assumptions A*, if $\lambda \geq \kappa_0 \mu_{n_c}$, $\kappa_0$ is defined in Proposition 6 and $\hat{L}$ by Relation (6), then for any $\delta < 1 - \kappa_0 \mu_{n_c}/\lambda$, there exist positive constant $p_0$ and $K$, and $N_0$ such that, for any $N \geq N_0$,

$$\mathbb{P} \left( \frac{\hat{L}}{\log N} \leq K \right) \geq p_0.$$

Proof. In the following, all statements are understood on the event $\mathcal{E}_N$ defined in Corollary 4; this result shows that this event has a probability close to 1 as $N$ gets large. For
$K>0$, note that, due to Condition (1) of Assumption A-2, for $N$ sufficiently large then $K \log N \leq t_0 \Psi(N)$. We fix $\delta_0 \in (0, 1-\kappa_0 \mu_0/\lambda)$ and $\alpha_0 = \lambda(1-\delta_0)$.

From Proposition 6 it can be assumed that there exists a Markov process $(Z^{n_0, \mu_n}_{\cdot}(t))$ with generator defined by Relation (34) and initial point $c_n$ such that the relation

$$\|Z^{n_0, \mu_n}_{\cdot}(t)\|_c = \sum_{k \geq n_c} Z^{n_0, \mu_n}_{k}(t) \leq \sum_{k \geq n_c} \tilde{U}^N_k(t),$$

holds for all $t \leq \tilde{L}^N_\delta$. Since, for $t \geq 0$,

$$\sum_{k \geq n_c} \tilde{U}^N_k(t) \leq \sum_{k \geq n_c} U^N_k(t)$$

$$\mathcal{H}_N \stackrel{\text{def.}}{=} \left\{ \tilde{L}^N_\delta > K \log N \right\} \subset \left\{ \|Z^{n_0, \mu_n}_{\cdot}(K \log N)\|_c \leq |\delta N| \right\},$$

since $\lambda(1-\delta_0) > \mu_0$, with the notations of Proposition 6 one can take $K = 2/a_0$ then

$$F_{Z^{n_0, \mu_n}_{\cdot}} \cap \mathcal{H}_N = \emptyset,$$

as soon as $N > 2\delta_0/\eta$, where the event $F_{Z^{n_0, \mu_n}_{\cdot}}$ is defined in Proposition 6 hence

$$\liminf_{N \to +\infty} P \left( E_N \cap F_{Z^{n_0, \mu_n}_{\cdot}} \cap \left\{ \tilde{L}^N_\delta \leq K \log N \right\} \right) = P(F_{Z^{n_0, \mu_n}_{\cdot}}) > 0.$$  

The proposition is proved. \hfill \square

**Theorem 2** (Growth Rate for the Lag Time). **Under Assumptions A**, if $\lambda > \kappa_0 \mu_0$, the constant $\kappa_0$ is defined in Proposition 4 and $\lambda$ by Relation (6), then, if $\delta \in (0, 1-\kappa_0 \mu_0/\lambda)$ and for $\varepsilon > 0$, there exist $K_1$ and $K_2$ such that

$$\liminf_{N \to +\infty} P \left( K_1 \leq \frac{L^N_\delta}{\Psi(N)} \leq K_2 \right) > 1-\varepsilon,$$

where $\Psi(N) = \Phi(N)^{n_c-2}/N$.

**Proof.** The existence of the $K_1$ is a simple consequence of the fact that $L^N_\delta \geq T^N$ and Proposition 6.

For $i \in \mathbb{N}$, $E_{i,\pi}$ will denote an exponentially distributed random variables with parameter $\overline{\beta}$ defined by Relation (22).

By Proposition 5 and the strong Markov property of $(U^N(t))$, at time $T^N_{1,\pi}$ a polymer of size $n_c$ is created. Proposition 5 gives that $T^N_{\pi}/\Psi(N)$ converges in distribution to $E_{1,\pi}$. According to Proposition 6, there exists some $N_0$ such that, for $N \geq N_0$, with probability at least $p_0$, there is a fraction $\delta$ of monomers is polymerized into stable polymers before time $R^N_{1,\pi} \defeq T^N + K \log N$.

If this does not happen, there are two possibilities:

1. There is at least one stable polymer at time $R^N_{1,\pi}$. One can construct another coupling with an independent process $(\tilde{Z}^{n_0, \mu_n}_{\cdot}(t))$ with the same distribution as $(Z^{n_0, \mu_n}_{\cdot}(t))$. Again, there exists $N_1$ such that, if $N \geq N_1$, with probability at least $p_0$ that a fraction $\delta$ of monomers is polymerized into stable polymers before time $R^N_{\delta} \defeq R^N_{1,\pi} + K \log N$.

2. There are no stable polymers at time $R^N_{1,\pi}$. Due to Proposition 6 there exists some $N_1$ such that if $N \geq N_1$, the state $\tilde{U}^N(R^N_{1,\pi})$ satisfies Condition (I). If $R^N_{1,\pi} + T^N_{2,\pi}$ is the time of the first nucleation time after time $R^N_{1,\pi}$, Proposition 5 gives that $T^N_{2,\pi}/\Psi(N)$ converges in distribution to $E_{2,\pi}$.

This decomposition shows that the lag time $L^N_\delta$ can be stochastically upper-bounded by a random variable

$$S^N \defeq \sum_{i=1}^{1+G_{p_0}} (T^N_{i} + K \log N),$$

where

$$G_{p_0} \defeq \left\{ \frac{L^N_\delta}{\Psi(N)} \leq K_2 \right\}.$$
where $G_{n_0}$ is a geometrically distributed random variable with parameter $p_0$ independent of a sequence of random variables $(T_i^N)$ such that, for $i \geq 1$, the sequence $(T_i^N)$ converges in distribution to $E_{0,\gamma}$. It is easy to prove that the sequence of random variables $(S^N / \Psi(N))$ is tight. The theorem is therefore proved.

□

When $\Phi(N) = N^\gamma$, $N \geq 1$. Assumption A-2 requires that the nucleus size satisfies $n_0 > 2 + 1 / \gamma$, the above theorem gives that the lag time is in this case of the order of $N^{(n_0 - 2) - 1}$.

References

1. David Aldous, *Probability approximations via the Poisson clumping heuristic*, Springer-Verlag, New York, 1989.
2. David J. Aldous, *Deterministic and stochastic models for coalescence (aggregation and coagulation): a review of the mean-field theory for probabilists*, Bernoulli 5 (1999), no. 1, 3–48.
3. David F. Anderson and Thomas G. Kurtz, *Continuous time Markov chain models for chemical reaction networks*, Design and Analysis of Biomolecular Circuits (Heinz Koeppl, Gianluca Setti, Mario di Bernardo, and Douglas Densmore, eds.), Springer New York, 2011, pp. 3–42.
4. Krishna B. Athreya and Peter E. Ney, *Branching processes*, Springer-Verlag, New York, 1972, Die Grundlehren der mathematischen Wissenschaften, Band 196.
5. J. M. Ball, J. Carr, and O. Penrose, *The Becker-Döring cluster equations: basic properties and asymptotic behaviour of solutions*, Comm. Math. Phys. 104 (1986), no. 4, 657–692. MR 841675
6. R. Becker and W. Döring, *Kinetiesche behandlung der keimbildung in bersttigten dmpfen*, Annalen der Physik 416 (1935), no. 8, 719–752.
7. Jean Bertoin, *Random fragmentation and coagulation processes*, Cambridge Studies in Advanced Mathematics, vol. 102, Cambridge University Press, Cambridge, 2006.
8. Tim Brown, *A martingale approach to the Poisson convergence of simple point processes*, The Annals of Probability 6 (1978), no. 4, 615–628.
9. Marie Doumic, Sarah Eugène, and Philippe Robert, *Asymptotics of stochastic protein assembly models*, SIAM Journal on Applied Mathematics 76 (2016), no. 6, 2333–2352.
10. Nicholas Ercolani, Sabine Jansen, and Daniel Ueltschi, *Stochastic processes in physics and chemistry*, 38, Journal of the Mathematical Society of Japan (1987), no. 2, 703–735.
11. Bert Fristedt, *The structure of random partitions of large integers*, Transactions of the American Mathematical Society 337 (1993), no. 2, 703–735.
12. James Hofrichter, *Kinetics of nucleic acid polymerization: II. nucleation rates determined from stochastic fluctuations in polymerization progress curves*, Journal of Molecular Biology 189 (1986), no. 3, 553–571.
13. Martin Jacobsen, *Limit theorems for stochastic processes*, Grundlehren der mathematischen Wissenschaften (Fundamental Principles of Mathematical Sciences), vol. 288, Springer-Verlag, Berlin, 1987.
14. Intae Jeon, *Existence of gelling solutions for coagulation-fragmentation equations*, Communications in mathematical physics 194 (1998), no. 3, 541–567.
15. NG Van Kampen, *Stochastic processes in physics and chemistry*, North Holland, 2007.
16. Yuji Kasahara and Shinzo Watanabe, *Limit theorems for point processes and their functionals*, Journal of the Mathematical Society of Japan 38 (1986), no. 3, 543–574.
17. D. Kashchiev, *Protein polymerization into fibrils from the viewpoint of nucleation theory*, Biophys. J. 109 (2015), no. 10, 2126–2136.
18. Aimee M Morris, Murielle A Watzky, and Richard G Finke, *Protein aggregation kinetics, mechanism, and curve-fitting: a review of the literature*, Biochimica et Biophysica Acta (BBA)-Proteins and Proteomics 1794 (2009), no. 3, 375–397.
19. J. D. Murray, *Mathematical biology. I*, third ed., Interdisciplinary Applied Mathematics, vol. 17, Springer-Verlag, New York, 2002. An introduction.
20. Jim Pitman, *Exchangeable and partially exchangeable random partitions*, Probability Theory and Related Fields 102 (1995), no. 2, 145–158.
21. Stephanie Prigent, Hadjer Wafaa Halfaf, H. T. Banks, M. Hoffmann, Human Rezaei, and Marie Doumic, *Size distribution of amyloid brils. Mathematical models and experimental data*, International Journal of Pure and Applied Mathematics 93 (2014), no. 6, 845–878.
29. Laurent Pujo-Menjouet, *Étude de modèles mathématiques issus de la biologie du cycle cellulaire et de la dynamique des protéines*, Habilitation à diriger des recherches, Université Claude Bernard Lyon 1 - Institut Camille Jordan, December 2016.

30. Philippe Robert, *Stochastic networks and queues*, Stochastic Modelling and Applied Probability Series, Springer-Verlag, New York, 2003.

31. Wen Sun, *A functional central limit theorem for becker-döring model*, Preprint, October 2017.

32. Wen Sun, Mathieu Feuillet, and Philippe Robert, *Analysis of large unreliable stochastic networks*, Annals of Applied Probability 26 (2016), no. 5, 2959–3000.

33. Juraj Szavits-Nossan, Kym Eden, Ryan J. Morris, Caït E. MacPhee, Martin R. Evans, and Rosalind J. Allen, *Inherent variability in the kinetics of autocatalytic protein self-assembly*, Physical Review Letters 113 (2014), 098101.

34. Albrecht Wegner and Juergen Engel, *Kinetics of the cooperative association of actin to actin filament*, Biophysical Chemistry 3 (1975), no. 3, 215–225.

35. W-F Xue, S W Homans, and S E Radford, *Systematic analysis of nucleation-dependent polymerization reveals new insights into the mechanism of amyloid self-assembly*, PNAS 105 (2008), 8926–8931.

36. Romain Yvinec, Samuel Bernard, Erwan Hingant, and Laurent Pujo-Menjouet, *First passage times in homogeneous nucleation: Dependence on the total number of particles*, The Journal of Chemical Physics 144 (2016), no. 3, 034106.

37. Romain Yvinec, Maria R. D’Orsogna, and Tom Chou, *First passage times in homogeneous nucleation and self-assembly*, The Journal of Chemical Physics 137 (2012), no. 24, 244107.
5. Appendix

5.1. Biological Background. The protein polymerization processes investigated in this paper are believed to be the main phenomena at the origin of several neuro-degenerative diseases such as Alzheimer’s, Parkinson’s and Huntington’s diseases for example. The general picture of this setting is the following. At some moment, for some reasons, within a neural cell a fraction of the proteins of a given type are produced in an anomalous state, defined as misfolded state. Recall that if a protein is a sequence of amino-acids, its three-dimensional structure determines also its functional properties.

A misfolded protein has the same sequence of amino-acids but a different spatial architecture. It turns out that misfolded proteins tend to aggregate to form fibrils, also called polymers. These fibrils are believed to have a toxic impact in the cell, on its membrane in particular, leading to its death. The prion protein PrP\textsuperscript{SC} is an example of such protein that can be polymerized when it is in the state PrP\textsuperscript{SC}. The corresponding disease is the Bovine Spongiform Encephalopathy (BSE), also known as the mad cow disease. This (rough) description is not completely accurate or complete, moreover some aspects are disputed, but it is used in a large part of the current literature. See the interesting historical survey Pujo-Menjouet [29]. Other biological processes such as actin filamentation, or yet industrial processes exhibit similar mechanisms, see Wegner and Engel [34].

The Variability of the Polymerization Process. Neuro-degenerative diseases are quite diverse. They can be infectious, like the BSE, others are not, like Alzheimer (apparently). Nevertheless they all exhibit large, variable, time spans for the development of the disease, from several years to 10 years.

When experiments are done in vitro with convenient types of proteins/monomers and with no initial polymers, a related phenomenon is observed. The fraction of monomers consumed by the polymerization process exhibit an \textit{S}-curve behavior: it stays at 0 for several hours, and quickly reaches 1, the state where most of monomers are polymerized. The other key feature of these experiments concerns the variability of the instant of the take-off phase of the \textit{S}-curve from an experiment to another. See Szavits-Nossan et al. [33] and Xue et al. [35]. See Figure 2 where twelve experiments are represented, the instant when half of the proteins are polymerized varies from 7.3h. to 10.1h. with an average of 8.75h.

The initial step of the chain reactions giving rise to polymers consists in the spontaneous formation of a so-called \textit{nucleus}, that is, the simplest possible polymer able to ignite the reaction of polymerization. This early phase is called \textit{nucleation}, and is still far from being understood.

5.2. Marked Poisson Point Processes. We first recall briefly some elementary aspects of stochastic calculus with marked Poisson point processes. They are used throughout the paper. See Jacobsen [14] and Last and Brandt [23] for more details. Let \( \mathcal{N}_\lambda \) be a Poisson point process on \( \mathbb{R}_+ \) with parameter \( \lambda \) and an independent sequence \( (U_n) \) of i.i.d. random variables on some locally compact space \( H \), \( \mu \) denotes the common distribution of these variables. The marked Poisson point process \( \mathcal{N}^{\mathcal{U}}_\lambda \) is defined as a point process on \( \mathbb{R}_+ \times H \), by

\[
\mathcal{N}^{\mathcal{U}}_\lambda = \sum_{n \in \mathbb{N}} \delta(t_n, U_n),
\]

if \( f \) is a non-negative measurable function on \( \mathbb{R}_+ \times H \), one defines, for \( t \geq 0 \),

\[
\int_0^t f(s, u) \mathcal{N}^{\mathcal{U}}_\lambda (ds, du) = \sum_{n \in \mathbb{N}} f(t_n, U_n) 1 \{ t_n \leq t \}
\]

and, if \( F \in \mathcal{B}(H) \) is a Borelian subset of \( H \),

\[
\mathcal{N}^{\mathcal{U}}_\lambda ([0, t] \times F) = \int_0^t 1 \{ u \in F \} \mathcal{N}^{\mathcal{U}}_\lambda (ds, du) = \sum_{n \in \mathbb{N}} 1 \{ t_n \leq t, U_n \in F \}.
\]
The natural filtration associated to $\mathcal{N}_X^U$ is $(\mathcal{F}_t)$, with, for $t \geq 0$,

$$
\mathcal{F}_t = \sigma \left( \mathcal{N}_X^U([0, s] \times F) : s \leq t, F \in B(H) \right).
$$

**Proposition 10.** If $g$ is a càdlàg function on $\mathbb{R}_+$ and $h$ is Borel on $H$ such that

$$
\int_0^t g(s)^2 \, ds < +\infty, \quad \forall t \geq 0 \text{ and } \int_H h(u)^2 \nu(du) < +\infty,
$$

then the process

$$
(M(t)) \overset{\text{def}}{=} \left( \int_0^t g(s) h(u) \mathcal{N}_X^U(ds, du) - \lambda \int_H h(u) \nu(du) \int_0^t g(s) \, ds \right)
$$

is a square integrable martingale with respect to the filtration $(\mathcal{F}_t)$, its previsible increasing process is given by

$$
⟨(M)⟩(t) = \lambda \int_H h^2(u) \nu(du) \int_0^t f(s)^2 \, ds
$$

In the paper, since we are dealing with several Poisson point processes, the (implicit) definition of the filtration $(\mathcal{F}_t)$ is extended so that it includes all of them.

### 5.3. Proof of Proposition 3

In this section we prove Relations \[25\] and \[26\] of the proposition by induction on $r$ varying from $n_c$ to 2. The various stochastic integral equations used are listed in Section 5.3.1 below.

When $r = n_c$ and $k \leq n_c - 2$, one has

$$
\left( \frac{1}{N \Phi(N)^{n_c-2}} \int_0^{\Psi(N)} X_{n_c-k}^N(u) X_h^n(u) \, du \right) = \left( \int_0^t \frac{X_{n_c-k}^N}{N} X_h^n(\Psi(N)u) \, du \right).
$$

Proposition 2 shows that this process converges in distribution to 0 when $N$ goes to infinity for all $k = 1, \ldots, n_c - 2$ and $2 \leq h \leq n_c - 1$. Relation \[26\] also holds in this case.

Now suppose, by induction, that for all $r > t$ and $1 \leq k < r \wedge (n_c - 1)$, $2 \leq h \leq n_c - 1$, one has the convergences in distribution \[25\] and \[26\]. On will prove that this property

**Figure 2.** Twelve experiments for the time evolution of fraction of the mass of polymers with size greater 2. From data published in Xue et al. \[35\], see also Eugene et al. \[11\].
holds for \( r = \ell \) and for \( k \) from 1 to \((r-1)\wedge(n_c-2)\). Take \( k=1 \) and we will first prove the convergence \( (25) \) for \( h=n_c-1 \) and Convergence \( (26) \), then Convergence \( (25) \) by induction on \( h \), from \( n_c-1 \) to 2.

Take \( k=1 \) and \( h=n_c-1 \). Since \( X_j^N(t) \leq N \) for all \( j \geq 1 \), then for \( i=n_c-1, n_c-2 \)

\[
\left( \frac{1}{N\Phi(N)^{r-1}} \right)^2 \int_0^{\Phi(N)t} \left( 2X_{n_c-1}^N(u) \pm 1 \right)^2 X_i^N(u)X_i^N(u) \frac{du}{N} \\
\leq \frac{(2N+1)^2}{N^2\Phi(N)^{r-2}} \int_0^{\Phi(N)t} X_i^N(u)X_i^N(u) \frac{du}{N} \leq \frac{9}{N\Phi(N)^r} \int_0^{\Phi(N)t} X_i^N(u)X_i^N(u) \frac{du}{N},
\]

as a process, the last term converges to 0 in distribution by Relation \( (26) \) of the induction. Similarly, the term

\[
\left( \frac{1}{N\Phi(N)^{r-1}} \right)^2 \int_0^{\Phi(N)t} \Phi(N)X_{n_c-1}^N(u) \left( 2X_{n_c-1}^N(u) - 1 \right)^2 \frac{du}{N}
\]

\[
\leq \frac{4}{N\Phi(N)^{r-2}} \int_0^{\Phi(N)t} X_i^{N-1}(u)^2 \frac{du}{N} \leq \frac{4}{N\Phi(N)^{r-1}} \int_0^{\Phi(N)t} X_i^{N-1}(u)^2 \frac{du}{N}
\]

converges to 0 in distribution as a process by Relation \( (25) \) of the induction. Recall that \( r = \ell \). Therefore, one gets the previsible increasing process, see Relation \( (42) \), of the martingale

\[
\left( \frac{1}{N\Phi(N)^{r-1}} \right)^{M_{h, n_c-1, n_c-1}(\Phi(N)t)}
\]

is converging to 0 as \( N \) goes to infinity. By Doob’s inequality, we obtain that this martingale is thus vanishing for \( N \) large.

Similarly, for \( h \in \{n_c-2, n_c-1\} \), the induction assumption gives the convergence in distribution

\[
\lim_{N \to +\infty} \left( \frac{1}{N\Phi(N)^{r-1}} \int_0^{\Phi(N)t} \left( 2X_{n_c-1}^N(u) \pm 1 \right) X_i^N(u)X_i^N(u) \frac{du}{N} \right) = (0).
\]

From Proposition \( 2 \) we get that, for the convergence in distribution,

\[
\lim_{N \to +\infty} \left( \frac{1}{N\Phi(N)^{r-1}} X_{n_c-1}^N(\Phi(N)t)^2 \right) = (0).
\]

By gathering these results in Equation \( (41) \) of Section \( 3.3.1 \), one finally gets that

\[
\lim_{N \to +\infty} \left( \frac{1}{N\Phi(N)^{r-2}} \int_0^{\Phi(N)t} \left( 2X_{n_c-1}^N(u) - 1 \right) X_i^{N-1}(u) \frac{du}{N} \right) = (0).
\]

For \( x \in \mathbb{N} \) the relation \( x^2 \leq (2x-1)x \) gives therefore that

\[
\lim_{N \to +\infty} \left( \frac{1}{N\Phi(N)^{r-2}} \int_0^{\Phi(N)t} X_i^{N-1}(u)X_i^N(u) \frac{du}{N} \right) = (0),
\]

for \( h=n_c-1 \).

Take \( k=1 \) and \( h=1 \). By using Relation \( (16) \), one gets By Relation \( (26) \) of the induction for \( r+1 \), for any \( j=1, \ldots, n_c-1, \ i=n_c-1, n_c-2 \) the processes

\[
\left( \frac{1}{N\Phi(N)^r} \int_0^{\Phi(N)t} \frac{X_j^N(u)}{N} X_i^N(u) X_i^N(u) \frac{du}{N} \right) \leq \left( \frac{1}{N\Phi(N)^r} \int_0^{\Phi(N)t} X_i^N(u)X_i^N(u) \frac{du}{N} \right)
\]

converge in distribution to \( (0) \) when \( N \) gets large. By Relation \( (25) \) of the induction for \( r=\ell+1 \), for any \( j=2, \ldots, n_c-1 \), the processes

\[
\left( \frac{\Phi(N)}{N\Phi(N)^r} \int_0^{\Phi(N)t} X_j^N(u)X_{n_c-1}^N(u) \frac{du}{N} \right)
\]
converge in distribution to (0) when N is converging to infinity. By using similar approach as in the previous case, by replacing \( t \) by \( \Psi(N)t \) and by multiplying Relation (45) of Section 5.3.1 by \( 1/(N\Phi(N)^{r}) \), we obtain the convergence (26) for \( r=\ell \) when \( k=1 \).

Now, we prove Relation (25) by induction on \( h \), from \( n_{e}-1 \) to 2. Assume it holds for all \( h \in \{ h'+1, \ldots, n_{e}-1 \} \). If Identity (46) of Section 5.3.1 is multiplied by \( 1/(N\Phi(N)^{r-1}) \) and if \( t \) is replaced by \( \Psi(N)t \), then we show that several of its terms vanish in the limit. They are examined one by one.

a) By Proposition 3 and the fact that \( r \geq 2 \), one has

\[
\lim_{N \to +\infty} \left( \frac{1}{N\Phi(N)^{r-1}} N_{n_{e}-1} \cdot X_{h}^{N}(\Psi(N)t) \right) = (0).
\]

b) For \( h \in \{ n_{e}-1, n_{e}-2 \} \),

\[
\frac{1}{N\Phi(N)^{r-1}} \int_{0}^{\Psi(N)t} \frac{X_{h}^{N}(u)X_{1}^{N}(u)X_{h}^{N}(u)}{N} \, du \leq \frac{1}{N\Phi(N)^{r-1}} \int_{0}^{\Psi(N)t} X_{h}^{N}(u)X_{h}^{N}(u) \, du.
\]

Relation (25) of the induction shows that the last term of this inequality converges in distribution to 0 when \( N \) gets large.

c) For \( h=1 \),

\[
\frac{1}{N\Phi(N)^{r-1}} \int_{0}^{\Psi(N)t} \frac{X_{h}^{N}(u)X_{h}^{N}(u)X_{1}^{N}(u)}{N} \, du \leq \frac{1}{N\Phi(N)^{r-1}} \int_{0}^{\Psi(N)t} X_{h}^{N}(u)X_{1}^{N}(u) \, du,
\]

the recurrence relation (26) for \( r \) gives that the last term of this relation vanishes as \( N \) goes to infinity.

d) For all \( n_{e}-1 \geq h+1 \), the recurrence assumption gives

\[
\lim_{N \to +\infty} \left( \frac{1}{N\Phi(N)^{r-2}} \int_{0}^{\Psi(N)t} X_{1}^{N}(u)X_{h}^{N}(u) \, du \right) = (0).
\]

e) The martingale. The relation

\[
\left\langle \frac{1}{N\Phi(N)^{r-1}} M_{n_{e}-1,h}^{N}(\Psi(N)t) \right\rangle = \frac{1}{N^{2}\Phi(N)^{2r-2}} \left\langle M_{n_{e}-1,h}^{N} \right\rangle (\Psi(N)t)
\]

and, in the same way as before, by checking each term of the expression (50) of \( \left\langle M_{n_{e}-1,h}^{N} \right\rangle (t) \), one also gets the convergence in distribution

\[
\lim_{N \to +\infty} \left( \frac{1}{N\Phi(N)^{r-1}} M_{n_{e}-1,h}^{N}(\Psi(N)t) \right) = (0).
\]

One gets finally that the remaining term of Relation (46) of Section 5.3.1 is also vanishing, the convergence in distribution

\[
\lim_{N \to +\infty} \left( \frac{1}{N\Phi(N)^{r-2}} \int_{0}^{\Psi(N)t} X_{h}^{N}(u)X_{h}^{N}(u) \, du \right) = (0)
\]

holds, i.e. Relation (25) is true for \( h \). This gives the proof of this recurrence scheme for \( k=1 \) and all \( n_{e}-1 \geq h \geq 2 \).

To proceed the induction on \( k \), from 1 to \( r-1 \), one uses Equations (43) and (44), (45) and (47), and also (49) and (50) in Section 5.3.1 below for the processes

\[
\left( \frac{X_{n_{e}-2,h}(\Psi(N)t)^{2}}{N\Phi(N)^{r-1}} \right), \quad \left( \frac{X_{1}^{N}X_{h}^{N}(\Psi(N)t)}{N\Phi(N)^{r}} \right), \quad \left( \frac{X_{n_{e}-1,h}^{N}(\Psi(N)t)}{N\Phi(N)^{r-1}} \right),
\]

and, with the same method which has been used for the first step one gets that, for \( 1 \leq k \leq (r-1) \land (n_{e}-2) \) and \( 2 \leq h \leq n_{e}-1 \). The proposition is proved.
5.3.1. Some Stochastic Integral Equations. For the sake of completeness, we detail the various equations used in the previous proof. They are obtained by using repeatedly SDE \([16]\), via stochastic calculus with marked Poisson processes, see Section 5.2. See the proof of Proposition 4 for an example of such a derivation.

For \(t \geq 0\),

\[
X_{n-1}^N(t) = X_{n-1}^N(0)^2 + M_{n-1,n-1}^N(t)
+ \lambda_{n-1} \int_0^t (2X_{n-1}^N(u)+1) \frac{X_{n-2}^N(u)X_{n-1}^N(u)}{N} \, du
+ \int_0^t (-2X_{n-1}^N(u)+1) \left( \mu_{n-1} \Phi(N)X_{n-1}^N(u) + \lambda_{n-1} \frac{X_{n-1}^N(u)X_{n-1}^N(u)}{N} \right) \, du
\]

where \((M_{n-1,n-1}^N(t))\) is a martingale whose previsible increasing process is given by

\[
\left< M_{n-1,n-1}^N \right>(t) = \lambda_{n-1} \int_0^t (2X_{n-1}^N(u)+1)^2 \frac{X_{n-1}^N(u)X_{n-1}^N(u)}{N} \, du
+ \int_0^t (-2X_{n-1}^N(u)+1)^2 \left( \mu_{n-1} \Phi(N)X_{n-1}^N(u) + \lambda_{n-1} \frac{X_{n-1}^N(u)X_{n-1}^N(u)}{N} \right) \, du.
\]

For \(2 \leq k \leq n-2\) and \(t \geq 0\),

\[
X_{n-k}^N(t)^2 = X_{n-k}^N(0)^2 + M_{n-k,n-k}^N(t)
+ \lambda_{n-k} \int_0^t (2X_{n-k}^N(u)+1) \frac{X_{n-k-1}^N(u)X_{n-k}^N(u)}{N} \, du
+ \sum_{i=n-k+1}^{n-1} \mu_i \Phi(N) \int_0^t \int_{y \in S_i} \left( 2X_{n-k}^N(u)y_{n-k} + y_{n-k}^2 \right) \nu_i(dy)X_i^N(u) \, du
+ \int_0^t \left( -2X_{n-k}^N(u) \right) \left( \mu_{n-k} \Phi(N)X_{n-k}^N(u) + \lambda_{n-k} \frac{X_{n-k}^N(u)X_{n-k}^N(u)}{N} \right) \, du,
\]

\((M_{n-k,n-k}^N(t))\) is a martingale whose previsible increasing process is given by

\[
\left< M_{n-k,n-k}^N \right>(t) = \lambda_{n-k} \int_0^t (2X_{n-k}^N(u)+1)^2 \frac{X_{n-k-1}^N(u)X_{n-k}^N(u)}{N} \, du
+ \sum_{i=n-k+1}^{n-1} \mu_i \Phi(N) \int_0^t \int_{y \in S_i} \left( 2X_{n-k}^N(u)y_{n-k} + y_{n-k}^2 \right)^2 \nu_i(dy)X_i^N(u) \, du
+ \int_0^t \left( -2X_{n-k}^N(u) \right) \left( \mu_{n-k} \Phi(N)X_{n-k}^N(u) + \lambda_{n-k} \frac{X_{n-k}^N(u)X_{n-k}^N(u)}{N} \right) \, du.
\]

For \(t \geq 0\),

\[
X_{n-1}^N(t)X_1^N(t) = X_{n-1}^N(0)X_1^N(0) + M_{n-1,1}^N(t)
+ \int_0^t X_1^N(u) \left( \lambda_{n-2} \frac{X_{n-2}^N(u)}{N}X_1^N(u) - \lambda_{n-1} \frac{X_{n-2}^N(u)X_1^N(u)}{N} \right) \, du
+ \mu_{n-1} \Phi(N) \int_0^t \left[ -X_1^N(u) + \nu_{n-1} \left( \frac{X_{n-1}^N(u)}{N} - 1 \right) \right] X_{n-1}^N(u) \, du
+ \int_0^t X_{n-1}^N(u) \left( \sum_{j=1}^{n-1} (1 + I_{j=1}) \lambda_j \frac{X_j^N(u)}{N}X_1^N(u) + \sum_{i=2}^{n-2} \mu_i \Phi(N)X_i^N(u) \nu_i \right) \, du
+ \int_0^t \left( -\lambda_{n-2} \frac{X_{n-2}^N(u)X_1^N(u)}{N} + \lambda_{n-1} \frac{X_{n-1}^N(u)X_1^N(u)}{N} \right) \, du,
\]

where \((M_{n-1,1}^N(t))\) is a martingale.

For \(2 \leq h \leq n-2\) and \(t \geq 0\),


(46) \[ X_{h-1}^N(t)X_N^N(t) = X_{h-1}^N(0)X_N^N(0) + M_{h-1}^N(t) \]
\[ + \int_0^t X_N^N(u) \left( \lambda_{N-2} \frac{X_{h-2}^N(u)X_N^N(u)}{N} - \lambda_{N-1} \frac{X_{h-1}^N(u)X_N^N(u)}{N} \right) du \]
\[ + \mu_{N-1} \Phi(N) \int_0^t \left[ -X_N^N(u) + \nu_{N-1}(u) \left( X_{h-1}^N(u) - 1 \right) \right] X_{h-1}^N(u) du \]
\[ + \int_0^t X_N^N(u) \left( \lambda_{N-1} \frac{X_{h-2}^N(u)X_N^N(u)}{N} - \lambda_N X_N^N(u) \right) \]
\[ \mu_N \Phi(N)X_N^N(u) + \sum_{i=N+1}^{N-2} \mu_i \Phi(N)X_i^N(u) \nu_i \]
\[ \mathbb{1}_{\{h=N+2\}} \lambda_{N-2} \int_0^t \frac{X_{h-2}^N(u)X_N^N(u)}{N} du, \]

where \((M_{h-1}^N(t))\) is a martingale.

Additional identities used to complete the proof of the proposition.

For \(1 < h < N + 1\) and \(t \geq 0\),
\[ X_i^N(t)X_N^N(t) = X_i^N(0)X_N^N(0) + M_i^N(t) \]
\[ + \lambda_i \int_0^t \left( X_i^N(u) - 1 - \mathbb{1}_{\{i=N+2\}} \right) \frac{X_{i-1}^N(u)X_i^N(u)}{N} du \]
\[ + \lambda_N \int_0^t \left( 1 - X_1^N(u) \right) \frac{X_N^N(u)X_N^N(u)}{N} du \]
\[ - \sum_{j=2}^{N-1} \lambda_j \int_0^t X_N^N(u) \frac{X_j^N(u)X_N^N(u)}{N} du - 2\lambda_1 \int_0^t X_N^N(u) \frac{X_1^N(u)^2}{N} \mathbb{1}_{\{X_1^N(u) \geq 2\}} du \]
\[ + \sum_{i=2}^{N-1} \mu_i \Phi(N) \int_0^t \int_S \left[ y_1 X_h^N(u) + y_i \left( X_i^N(u) + y_1 \right) \mathbb{1}_{\{i=h\}} \right] \]
\[ - \mathbb{1}_{\{i=N\}} \Lambda_1 \int_0^t \frac{X_{h-2}^N(u)X_N^N(u)\mathbb{1}_{\{i=N\}}}{N} du, \]

where \((M_i^N(t))\) is a martingale whose predictable increasing process is given by
\[ \mathbb{E} \left\{ M_i^N(t) \right\} = \sum_{j \neq i, j < N+1} \frac{\lambda_j}{N} \int_0^t X_j^N(u)^2 X_i^N(u) X_i^N(u) du \]
\[ + \lambda_i \int_0^t \left( 1 - X_i^N(u) - X_N^N(u) \right) \frac{X_{i-1}^N(u)X_i^N(u)^2}{N} du \]
\[ + \mathbb{1}_{\{h=N+2\}} \left( \lambda_i \int_0^t X_N^N(u) X_i^N(u)^2 N \sum_{n \geq 2} \mathbb{1}_{\{X_N^N(u) \geq 2\}} du \right) \]
\[ + \mathbb{1}_{\{i=N\}} \left( \lambda_i \int_0^t X_{i-1}^N(u) X_i^N(u)^2 N \sum_{n \geq 2} \mathbb{1}_{\{X_i^N(u) \geq 2\}} du \right) \]
\[ + \lambda_{N-1} \int_0^t \left( X_i^N(u) - X_N^N(u) - 1 \right) ^2 \frac{X_{N-1}^N(u)X_i^N(u)}{N} du \]
\[ + \sum_{i=2}^{N-1} \mu_i \Phi(N) \int_{[0,t] \times S_i} \left[ y_1 X_h^N(u) + y_i \left( X_i^N(u) + y_1 \right) \mathbb{1}_{\{i=N\}} \right] \]
\[ - \mathbb{1}_{\{i=N\}} \Lambda_1 \int_0^t \frac{X_{h-2}^N(u)X_N^N(u)\mathbb{1}_{\{i=N\}}}{N} du, \]
For \( 2 \leq k \leq n_c - 2, 2 \leq h < n_c - k \) and \( t \geq 0 \),

\[
X_{n_c-k}^{N}(t) X_{h}^{N}(t) = X_{n_c-k}^{N}(0) X_{h}^{N}(0) + M_{n_c-k,h}^{N}(t)
\]

\[
+ \int_{0}^{t} X_{h}^{N}(u) \left( \lambda_{n_c-k-1} \frac{X_{n_c-k-1}(u) X_{1}^{N}(u)}{N} - \lambda_{n_c-k} \frac{X_{n_c-k}(u) X_{1}^{N}(u)}{N} \right) du
\]

\[
+ \mu_{n_c-k} \Phi(N) \int_{0}^{t} \left( -X_{h}^{N}(u) + \langle \nu_{n_c-k}, I_h \rangle \right) X_{n_c-k}^{N}(u) du
\]

\[
+ \int_{0}^{t} X_{n_c-k}^{N}(u) \left( \lambda_{h-1} \frac{X_{h-1}(u) X_{1}^{N}(u)}{N} - \lambda_{h} \frac{X_{h}(u) X_{1}^{N}(u)}{N} \right)
\]

\[
- \mu_{h} \Phi(N) X_{h}^{N}(u) + \sum_{i=h+1}^{n_c-k-1} \mu_{i} \Phi(N) X_{i}^{N}(u) \langle \nu_{i}, I_{h} \rangle
\]

\[
+ \int_{0}^{t} \sum_{i=n_c-k+1}^{n_c-1} \mu_{i} \Phi(N) X_{i}^{N}(u) \left( \langle \nu_{i}, I_{h} \rangle X_{n_c-k}^{N}(u) + \langle \nu_{i}, I_{n_c-k} \rangle X_{h}^{N}(u) \right) du
\]

\[
- \mathbb{1}_{\{ h = n_c-k-1 \}} \lambda_{n_c-k-1} \int_{0}^{t} \frac{X_{n_c-k-1}(u) X_{1}^{N}(u)}{N} du
\]

where \( \langle M_{n_c-k,h}^{N}(t) \rangle \) is a martingale whose previsible increasing process is given by

\[
\langle M_{n_c-k,h}^{N}(t) \rangle = \mathbb{1}_{\{ h = n_c-k-1 \}} \lambda_{n_c-k-1} \int_{0}^{t} \frac{X_{n_c-k-1}(u) X_{1}^{N}(u)}{N} du
\]

\[
+ \int_{0}^{t} X_{h}^{N}(u)^{2} \left( \lambda_{n_c-k-1} \frac{X_{n_c-k-1}(u) X_{1}^{N}(u)}{N} \mathbb{1}_{\{ h < n_c-k-1 \}} + \lambda_{n_c-k} \frac{X_{n_c-k}(u) X_{1}^{N}(u)}{N} \right) du
\]

\[
+ \mu_{n_c-k} \Phi(N) \int_{0}^{t} \int_{y \in S_{n_c-k}} \left( X_{h}^{N}(u) - y_{h} X_{n_c-k}^{N}(u) - 1 \right)^{2} X_{n_c-k}^{N}(u) \nu_{n_c-k}(dy) du
\]

\[
+ \int_{0}^{t} X_{n_c-k}^{N}(u)^{2} \left( \lambda_{h-1} \frac{X_{h-1}(u) X_{1}^{N}(u)}{N} + \lambda_{h} \frac{X_{h}(u) X_{1}^{N}(u)}{N} \mathbb{1}_{\{ h < n_c-k-1 \}} \right)
\]

\[
+ \mu_{h} \Phi(N) X_{h}^{N}(u) + \sum_{i=h+1}^{n_c-k-1} \mu_{i} \Phi(N) X_{i}^{N}(u) \langle \nu_{i}, I_{h}^{2} \rangle du
\]

\[
+ \sum_{n_c-k+1}^{n_c-1} \mu_{i} \Phi(N) \int_{S_{i}} \int_{0}^{t} \left( y_{h} X_{n_c-k}^{N}(u) + y_{n_c-k} X_{h}^{N}(u) + y_{h} y_{n_c-k} \right)^{2} X_{i}^{N}(u) \nu_{i}(dy) du.
\]