

Exact solution of a stochastic protein dynamics model with delayed degradation

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We study a stochastic model of protein dynamics that explicitly includes delay in the degradation. We rigorously derive the master equation for the processes and solve it exactly. We show that the equations for the mean values obtained differ from others intuitively proposed and that oscillatory behavior is not possible in this system. We discuss the calculation of correlation functions in stochastic systems with delay, stressing the differences with Markovian processes. The exact results allow us to clarify the interplay between stochasticity and delay.

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I. INTRODUCTION

Due to the small number of some of the molecules involved and to the uncontrolled environment, biochemical processes inside a cell usually need to be described by stochastic models [1,2]. Some important basic processes (such as transcription, translation, and specific degradation) are indeed compound multistage reactions involving a large number of steps of similar duration, and in principle, due to the central limit theorem, the time to complete such processes should follow nearly a Gaussian distribution, rather than exponential, with a well-defined characteristic delay time [3]. A description including delay is then needed to obtain a reduced model for this kind of processes. It is well known that delay can change qualitatively the dynamical behavior, allowing, for example, the appearance of oscillations in the evolution of the number of molecules [4–6], and there has been great interest in delay-induced oscillations in biological systems.

Stochastic processes that include delay are analytically difficult due to their non-Markovian character. Most theoretical studies consider a Langevin approach (stochastic differential equations) [8,9] or systems in discrete time [10] (where delay can be accounted for by increasing the number of variables). None of these approaches is completely suitable for describing chemical reactions inside a cell since the former neglects the inherently discrete nature of the molecule levels and the latter considers an arbitrary discretization of time (see [7] for a recent analysis of the accuracy of the chemical Langevin equation). In some cases, the discreteness can be a major source of fluctuations [11].

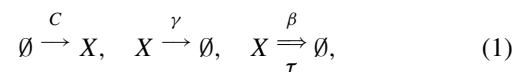
In this work we develop a rigorous derivation of the stochastic description of a protein dynamics model that includes delay in the degradation and solve it exactly. We find that the exact solution for the probabilities leads to equations for the mean values that do not comply with simple intuitive arguments and that oscillatory behavior does not exist (while it is usually believed to be present in this type of system [12]). This clarifies and warns us about the derivation of dynamical equations describing the evolution of the concentrations in cases in which delay plays a role. The exact solution is especially valuable for small system sizes, where approximated schemes typically fail. Due to the low number of molecules inside cells, this regime may be biologically relevant. Our solution extends the results of reference [13] in which the authors consider a particular case that allows for a Markovian description in terms of suitably defined dynamical variables, while such

a Markovian reduction has not been achieved in the more complete case studied here.

This paper is organized as follows: in the next section we define the model, and in Sec. III we derive the corresponding master equation. In Sec. IV we solve the master equation and derive the probabilities and the (macroscopic) equations for the mean values in the case of constant rates. Some technical details are left for the Appendix. In Sec. V we discuss the details of the derivation of the master equation for the conditional probabilities and derive, again in the case of constant rates, the correlation functions of the process. Finally, in Sec. VI we end with a brief discussion of the results.

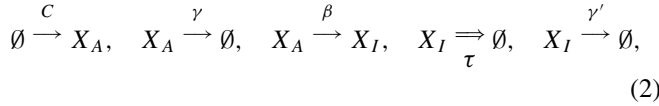
II. MODEL

Proteins usually degrade through complex proteolytic pathways that involve several different steps (such as tagging, binding of auxiliary proteins, recognition by protease, and destruction) [14]. As discussed before, it is then natural to consider a time delay in this process. As a simple model for the dynamics of the number of molecules of a protein X we consider



where, for simplicity and to isolate the effect of delay in degradation, the transcription and translation steps have been lumped into a single stochastic process that occurs at a rate C . This approximation represents accurately protein production only when the product of the mRNA lifetime and the translation rate is small [15], but including the two transcription and translation steps is straightforward, and the role of delay in this compound process should be essentially the same as in the one considered here. The delayed degradation (indicated by a double arrow) is modeled as a reaction that is initiated at a rate β and completed at a time τ after initiation (giving rise to the destruction of the protein). We assume a fixed time delay in this degradation process since this assumption allows for a complete analysis; this approximation is valid when this degradation process is tightly regulated or when it is composed of many steps (the total time should then be Gaussian with a relative standard deviation of $1/\sqrt{m}$, with m being the fixed number of steps); in the general case in which the magnitude of the delay is stochastically distributed, its effect typically decreases [16]. In addition to delayed

degradation, we consider also instantaneous degradation at a rate γ (which can take into account processes such as nonselective degradation, proteins going to the membrane or outside the cell, dilution due to cell growth, etc.). This model of protein dynamics was proposed in Ref. [12], and it was thought that it can lead to periodic oscillations, although the recent analysis of [13,17] in a particular limit showed otherwise. To completely describe the process, one has to specify if a protein that initiates delayed degradation at time t (and thus will disappear at $t + \tau$) can also disappear before the completion of this reaction through instantaneous degradation at a rate γ' , which is not necessarily equal to γ . The process is equivalent to the following two-variable system:



where we have split the proteins into two types: X_I are “tagged” molecules that will die precisely at a time τ after being tagged (if still present), and X_A are nontagged particles (so $X = X_A \cup X_I$). In principle, we allow the rates to depend on n_A , the number of X_A particles, but not on n_I , the number of X_I particles, which are considered to be “inert.” One has to include an extra variable because delayed degradation is a “consuming reaction” [18] since as soon as one particle initiates this reaction the number of particles that can initiate it decreases by 1, and so the state of the system changes both when the reaction is initiated and when it is finished, after a time τ . In a recent work [13], the stochastic description was studied in the particular case when tagged proteins cannot undergo instantaneous degradation, $\gamma' = 0$. It turns out that this particular case allows for a Markovian description in terms of suitably defined dynamical variables. Our treatment allows us to pose and solve a non-Markovian problem, and it can be of interest to other processes not allowable to a Markovian description.

III. MASTER EQUATION

To derive the master equation of the process, we start with the following identity, which is valid for any stochastic process (with a numerable set of states; otherwise, the sum should be replaced by an integral):

$$P(n, t + \Delta t) = \sum_{n'} P(n, t + \Delta t; n', t), \quad (3)$$

where $P(n, t)$ is the probability of being at state n at time t and $P(n, t; n', t')$ is the joint probability of being at state n at time t and at state n' at time t' . In most cases of interest, $P(n, t + \Delta t; n', t)$ is $O(\Delta t^0)$ or $O(\Delta t)$ only for a small number of n' (usually depending on n), whereas it is of higher order $o(\Delta t)$ for all the rest. Writing explicitly the terms $O(\Delta t^0)$ and $O(\Delta t)$, dividing by Δt , and taking the limit $\Delta t \rightarrow 0$, one can obtain the master equation of the process [differential equation for $P(n, t)$]. For Markovian processes one can write the joint probabilities as $P(n, t + \Delta t; n', t) = P(n', t)P(n, t + \Delta t|n', t)$, and the conditional probabilities can be readily derived from the rules of the process, and one obtains in this way a closed equation for the one-time probability $P(n, t)$. For non-Markovian ones, in general, the

equation for the one-time probability will depend on higher order joint probability densities $P(n, t; n_1, t_1; \dots; n_m, t_m)$. In some cases (as in the one considered here) it is possible to explicitly write the joint probability densities that appear in the master equation and obtain a closed equation for $P(n, t)$.

In our process, n has two components (n_A and n_I), and the only terms $O(\Delta t^0)$ and $O(\Delta t)$ that appear in Eq. (3) are associated with the following elementary processes schematized in Eq. (2).

(1) The first step is the birth of an X_A particle from the reservoir: $(n_A - 1, n_I) \rightarrow (n_A, n_I)$, with probability $C\Delta t$. The contribution to the right-hand side (rhs) of Eq. (3) is $P(n_A - 1, n_I, t)C\Delta t$.

(2) Second is the death of an X_A particle: $(n_A + 1, n_I) \rightarrow (n_A, n_I)$, with probability $\gamma(n_A + 1)\Delta t$. The contribution to the rhs of Eq. (3) is $P(n_A + 1, n_I, t)\gamma(n_A + 1)\Delta t$.

(3) Next is infection of an X_A particle: $(n_A + 1, n_I - 1) \rightarrow (n_A, n_I)$, with probability $\beta(n_A + 1)\Delta t$. The contribution to the rhs of Eq. (3) is $P(n_A + 1, n_I - 1, t)\beta(n_A + 1)\Delta t$.

(4) Then death of an X_I particle occurs: $(n_A, n_I + 1) \rightarrow (n_A, n_I)$. This might occur by two different reasons: (4a) death by instantaneous decay at rate γ' with probability $\gamma'(n_I + 1)\Delta t$, where the contribution to the rhs of Eq. (3) is $P(n_A, n_I + 1, t)\gamma'(n_I + 1)\Delta t$, and (4b) death after time τ after infection, which is the only non-Markovian contribution. In order to account for this case and according to the previous discussion, we need to write the corresponding contribution to the rhs of Eq. (3) as

$$\sum_{n'_A, n'_I} P(n_A, n_I, t + \Delta t; n_A, n_I + 1, t; \mathcal{S}; \mathcal{I}_{n'_A, n'_I}), \quad (4)$$

where $\mathcal{I}_{n'_A, n'_I} = \{n'_A - 1, n'_I + 1, t - \tau + \Delta t; n'_A, n'_I, t - \tau\}$ denotes the event in which there were n'_A and n'_I particles at time $t - \tau$ and one particle got tagged during the time interval $(t - \tau; t - \tau + \Delta t)$ and \mathcal{S} denotes that the particle tagged during that time interval survived up to time t . We use now the series of conditional probabilities:

$$\begin{aligned} & P(n_A, n_I, t + \Delta t; n_A, n_I + 1, t; \mathcal{S}; \mathcal{I}_{n'_A, n'_I}) \\ &= P(n_A, n_I, t + \Delta t | n_A, n_I + 1, t; \mathcal{S}; \mathcal{I}_{n'_A, n'_I}) \\ & \quad \times P(n_A, n_I + 1, t | \mathcal{S}; \mathcal{I}_{n'_A, n'_I}) P(\mathcal{S} | \mathcal{I}_{n'_A, n'_I}) P(\mathcal{I}_{n'_A, n'_I}). \end{aligned} \quad (5)$$

Now, $P(n_A, n_I, t + \Delta t | n_A, n_I + 1, t; \mathcal{S}; \mathcal{I}_{n'_A, n'_I}) = 1$, as the particle that was tagged in $(t - \tau, t - \tau + \Delta t)$ and survived up to t dies with probability 1 during $(t, t + \Delta t)$ according to the rules of the process. The conditional probability of the second line on the rhs is the probability that there are $n_A, n_I + 1$ particles at time t given that there were n'_A, n'_I particles at time $t - \tau$ and one X_A particle was tagged in $(t - \tau, t - \tau + \Delta t)$ and survived up to time t . Since the presence of the tagged particle does not influence the dynamics of births, deaths, and infection of other particles (remember that we have assumed that X_I are “inert” particles such that the different rates do not depend on the number of X_I particles), this conditional probability can be simply obtained by considering the process in which the dynamics of the tagged particle is decoupled from the rest of the particles, i.e., as if removing that particle from the

dynamical process. This leads to

$$P(n_A, n_I + 1, t | \mathcal{S}; \mathcal{I}_{n'_A, n'_I}) = P(n_A, n_I, t | n'_A - 1, n'_I, t - \tau + \Delta t). \quad (6)$$

Furthermore, as all X_I present at $t - \tau$ have died before t [except the one tagged during $(t - \tau, t - \tau + \Delta t)$], this conditional probability is, in fact, independent of n'_I and, for translational invariance, depends only on the time difference τ , so we can write it as $P(n_A, n_I, t | n'_A - 1, t - \tau)$. The next term, $P(\mathcal{S} | \mathcal{I}_{n'_A, n'_I})$, corresponds to the survival probability during a time interval of length τ , or $e^{-\gamma'\tau}$. Finally, $P(\mathcal{I}_{n'_A, n'_I})$ is the infection probability $\beta n'_A \Delta t P(n'_A, n'_I, t - \tau)$. Collecting all the terms, the contribution to the rhs of Eq. (3) is $\sum_{n'_A} P(n_A, n_I, t | n'_A - 1, t - \tau + \Delta t) \beta n'_A P(n'_A, t - \tau) e^{-\gamma'\tau} \Delta t$.

(5) None of the above processes occur in the interval $(t, t + \Delta t)$: $(n_A, n_I) \rightarrow (n_A, n_I)$.

$$\begin{aligned} P(n_A, n_I, t + \Delta t; n_A, n_I, t) &= P(n_A, n_I, t + \Delta t | n_A, n_I, t) P(n_A, n_I, t) \\ &= \left[1 - C \Delta t - (\gamma + \beta) n_A \Delta t - \gamma' n_I \Delta t - \sum_{n'_A, n'_I} P(n_A, n_I, t + \Delta t; \mathcal{S}; \mathcal{I}_{n'_A, n'_I} | n_A, n_I, t) \right] P(n_A, n_I, t) \\ &= [1 - C \Delta t - (\gamma + \beta) n_A \Delta t - \gamma' n_I \Delta t] P(n_A, n_I, t) - \sum_{n'_A, n'_I} P(n_A, n_I, t + \Delta t; n_A, n_I, t; \mathcal{S}; \mathcal{I}_{n'_A, n'_I}). \end{aligned} \quad (7)$$

Treating the last term in the same way as in case (4b), one obtains that the contribution to the rhs of Eq. (3) is

$$\begin{aligned} P(n_A, n_I, t + \Delta t; n_A, n_I, t) &= [1 - C \Delta t - (\gamma + \beta) n_A \Delta t - \gamma' n_I \Delta t] P(n_A, n_I, t) \\ &\quad - \sum_{n'_A} P(n_A, n_I - 1, t | n'_A - 1, t - \tau) \beta n'_A P(n'_A, t - \tau) e^{-\gamma'\tau} \Delta t. \end{aligned} \quad (8)$$

After adding up all contributions to the rhs of Eq. (3), dividing by Δt , and taking the limit $\Delta t \rightarrow 0$, we obtain the master equation of the process:

$$\begin{aligned} \frac{dP(n_A, n_I, t)}{dt} &= (E_A^{-1} - 1) C P(n_A, n_I, t) + (E_A - 1) \gamma n_A P(n_A, n_I, t) \\ &\quad + (E_A E_I^{-1} - 1) \beta n_A P(n_A, n_I, t) + (E_I - 1) \gamma' n_I P(n_A, n_I, t) \\ &\quad + (E_I - 1) \sum_{n'_A=0}^{\infty} P(n_A, n_I - 1, t | n'_A - 1, t - \tau) \beta n'_A P(n'_A, t - \tau) e^{-\gamma'\tau}, \end{aligned} \quad (9)$$

where $E_{A,I}$ are step operators, $E_{A,I}^k f(n_{A,I}) = f(n_{A,I} + k)$, and $P(n_A, t) = \sum_{n_I} P(n_A, n_I, t)$ is the marginal probability. As written, this is an equation for the one-time probability and has to be supplemented with the appropriate initial conditions. The evolution equation for the conditional probability $P(n_A, n_I, t | n_A^0, n_I^0, t_0)$ will be considered in Sec. V. For Markovian processes this equation would be the same as Eq. (9) conditioning all appearing probabilities to (n_A^0, n_I^0, t_0) , but for non-Markovian processes this is not necessarily the case.

The next step is to calculate the conditional probability appearing in Eq. (9). Let $P^*(n_A, n_I, t | n_A^0, n_I^0, 0)$ be the probability that there are n_A particles of X_A type and n_I particles of X_I type at time t given the initial condition that there were n_A^0 and n_I^0 particles at time $t = 0$ and under the condition that particles cannot die through delayed degradation. The key point is to note that

$$P(n_A, n_I, t | n'_A, t - \tau) = P^*(n_A, n_I, \tau | n'_A, 0, 0). \quad (10)$$

This is so because, as noted before, all X_I particles present at any time die before an interval of length τ passes and their presence does not influence the dynamics of births, deaths, and infections of other particles. Note that this equality is only valid as written, as in general $P(n_A, n_I, t | n'_A, t - t') \neq P^*(n_A, n_I, t' | n'_A, 0, 0)$, with the equality only occurring for $t' = \tau$. For $t' < \tau$ not all the tagged particles present at $t - t'$ have died at t ; for $t' > \tau$ some of the particles tagged after $t - t'$ may have died through delayed degradation before t . Therefore, we need to compute $P^*(n_A, n_I, t | n'_A - 1, 0, 0)$ [we simplify the notation to $P^*(n_A, n_I, t | n'_A - 1)$], which follows the same master equation (9) without the last term. For the sake of completeness, we write down the final system of equations:

$$\begin{aligned} \frac{dP(n_A, n_I, t)}{dt} &= (E_A^{-1} - 1) C P(n_A, n_I, t) + (E_A - 1) \gamma n_A P(n_A, n_I, t) + (E_A E_I^{-1} - 1) \beta n_A P(n_A, n_I, t) \\ &\quad + (E_I - 1) \gamma' n_I P(n_A, n_I, t) + (E_I - 1) \sum_{n'_A=0}^{\infty} P^*(n_A, n_I - 1, \tau | n'_A - 1) \beta n'_A P(n'_A, t - \tau) e^{-\gamma'\tau}, \end{aligned} \quad (11)$$

$$\begin{aligned} \frac{dP^*(n_A, n_I, t | n'_A - 1)}{dt} &= (E_A^{-1} - 1) C P^*(n_A, n_I, t | n'_A - 1) + (E_A - 1) \gamma n_A P^*(n_A, n_I, t | n'_A - 1) \\ &\quad + (E_A E_I^{-1} - 1) \beta n_A P^*(n_A, n_I, t | n'_A - 1) + (E_I - 1) \gamma' n_I P^*(n_A, n_I, t | n'_A - 1). \end{aligned} \quad (12)$$

The process defined by Eq. (12) is a standard Markovian process for which exact and approximate schemes have been developed to find its solution. The function $P^*(n_A, n_I, \tau | n'_A - 1)$, obtained by solving Eq. (12) with the appropriate initial condition $P^*(n_A, n_I, 0 | n'_A - 1) = \delta_{n_A, n'_A - 1} \delta_{n_I, 0}$, can be replaced in Eq. (11) and proceed to solve for $P(n_A, n_I, t)$. A very convenient procedure is to derive a differential equation for the generating function $G(s_A, s_I, t) \equiv \sum_{n_A, n_I} s_A^{n_A} s_I^{n_I} P(n_A, n_I, t)$ in terms of the corresponding generating function of the process without delay degradation $G^*(s_A, s_I, t)$; see the Appendix for details. Note that the active variables X_A follow an independent dynamics, as can be seen from the rules of the process (the presence of X_I molecules does not alter at all the dynamics of X_A) or, from a more formal point of view, by noticing that, as derived from Eq. (11), the marginal probabilities for the numbers n_A , $P(n_A, t)$, follow a closed master equation of a birth-death process:

$$\frac{dP(n_A, t)}{dt} = (E_A^{-1} - 1)CP(n_A, t) + (E_A - 1)\gamma n_A P(n_A, t). \quad (13)$$

IV. SOLUTION IN THE CASE OF CONSTANT RATES

Up to now, we have been rather general. The only assumption needed is that the rates can depend only on the number of active particles n_A . We now provide the exact solution in the case of constant rates. In this case P^* corresponds to a simple birth-death Poisson process. As shown in the Appendix, it turns out that if the initial condition $P(n_A, n_I, 0)$ follows a Poisson distribution (which includes the case that starts with no molecules at all at $t = 0$) then the generating function at arbitrary time is $G(s_A, s_I, t) = e^{x_A(t)(s_A - 1) + x_I(t)(s_I - 1)}$. This shows that the joint probability of n_A and n_I is the product of independent Poisson distributions, with mean values and variances $\langle n_A(t) \rangle = \sigma_{n_A}^2(t) = x_A(t)$, $\langle n_I(t) \rangle = \sigma_{n_I}^2(t) = x_I(t)$. It follows that the total number of X particles, $n = n_A + n_I$, also obeys at all times a Poisson distribution with parameter $x(t) = x_A(t) + x_I(t)$. If we start with an initial condition different from the Poisson-distributed one, the time-dependent solution is not Poissonian, but this form is recovered in the steady state with mean values $\langle n_{A,I} \rangle_{st}$. The mean values satisfy differential equations including delay terms:

$$\begin{aligned} \frac{dx_A(t)}{dt} &= C - ax_A(t), \\ \frac{dx_I(t)}{dt} &= -\gamma' x_I(t) + \beta[x_A(t) - e^{-\gamma'\tau} x_A(t - \tau)], \end{aligned} \quad (14)$$

with $a \equiv \beta + \gamma$. The solution with initial condition $x_A(t \leq 0) = 0$, $x_I(t = 0) = 0$ is

$$\begin{aligned} x_A(t) &= \frac{C}{a}(1 - e^{-at}), \\ x_I(t) &= \begin{cases} \frac{C\beta}{a-\gamma'} \left[\frac{1-e^{-\gamma't}}{\gamma'} - \frac{1-e^{-at}}{a} \right], & 0 \leq t \leq \tau, \\ \frac{C\beta}{a} \left[\frac{1-e^{-\gamma'\tau}}{\gamma'} + \frac{(1-e^{\tau(a-\gamma')})}{a-\gamma'} e^{-at} \right], & t \geq \tau. \end{cases} \end{aligned} \quad (15)$$

The steady-state values are $\langle n_A \rangle_{st} = C/a$, $\langle n_I \rangle_{st} = C\beta(1 - e^{-\gamma'\tau})/(a\gamma')$.

It is important to note that it is not possible to write a closed equation for the evolution of the total number of particles $x(t) = x_A(t) + x_I(t)$. In the case $\gamma = \gamma'$ we arrive at $\dot{x}(t) = C - \gamma x(t) - \beta e^{-\gamma'\tau} x_A(t - \tau)$, and in the case $\gamma' = 0$ we get $\dot{x}(t) = C - \gamma x_A(t) - \beta x_A(t - \tau)$, which differs in both cases from the closed result $\dot{x}(t) = C - \gamma x(t) - \beta x(t - \tau)$ used in Ref. [12]. A different process that leads to this closed form of the rate equations corresponds to delayed production and linear negative feedback:

$$0 \xrightleftharpoons[\tau]{C-\beta n} X, \quad X \xrightarrow{\gamma} 0. \quad (16)$$

However, in this case the creation rate $C - \beta n$ may become negative, and so the process is ill defined [16].

V. TIME CORRELATIONS

We now turn to the calculation of the time correlations. For this, we will write a master equation for the conditional probability $P(n_A, n_I, t | n_A^0, n_I^0, t_0)$ and derive evolution equations for the conditional averages $\langle n_{A,I}, t | n_A^0, n_I^0, t_0 \rangle$. As noted before, for a Markovian process, $P(n, t)$ and $P(n, t | n^0, t_0)$ satisfy identical master equations but with different initial conditions. For non-Markovian processes, however, in principle one has to specify the whole history before t_0 . In our system, the problem is that the dynamics from t_0 depends on when the n_I^0 particles were created. We are mainly interested in the steady state. The term that causes difficulties is the one corresponding to delayed degradation. To obtain the proper contribution to the master equation and in the line of the previous arguments, we take a starting point similar to Eq. (5):

$$\begin{aligned} P(n_A, n_I, t + \Delta t; n_A, n_I + 1, t; \mathcal{S}; \mathcal{I} | n_A^0, n_I^0, t_0) \\ = 1 \times P(n_A, n_I + 1, t | \mathcal{S}; \mathcal{I}; n_A^0, n_I^0, t_0) P(\mathcal{S}; \mathcal{I} | n_A^0, n_I^0, t_0), \end{aligned} \quad (17)$$

with $\mathcal{I} = \bigcup_{n'_A, n'_I} \mathcal{I}_{n'_A, n'_I}$ being the event in which a particle was tagged during the interval $(t - \tau, t - \tau + \Delta t)$, independent of the number of particles present at that time.

One has to distinguish the intervals $t - t_0 < \tau$ and $t - t_0 > \tau$. In the former, following the reasoning of Eq. (6), we see that the first conditional probability on the rhs of Eq. (17) equals $P(n_A, n_I, t | n_A^0, n_I^0 - 1, t_0)$ since, as noted before, one of the X_I particles present at time t_0 will stay until time t and its presence does not influence the dynamics of creations and deaths of other particles. Next, we use Bayes' theorem:

$$\begin{aligned} P(\mathcal{S}; \mathcal{I} | n_A^0, n_I^0, t_0) &= \sum_{n'_A, n'_I} P(\mathcal{S}; \mathcal{I}_{n'_A, n'_I} | n_A^0, n_I^0, t_0) \\ &= \sum_{n'_A, n'_I} P(n_A^0, n_I^0, t_0 | \mathcal{S}; \mathcal{I}_{n'_A, n'_I}) \frac{P(\mathcal{S}; \mathcal{I}_{n'_A, n'_I})}{P(n_A^0, n_I^0, t_0)}. \end{aligned} \quad (18)$$

An argument similar to the one used in deriving Eq. (6) shows that $P(n_A^0, n_I^0, t_0 | \mathcal{S}; \mathcal{I}_{n'_A, n'_I}) = P(n_A^0, n_I^0 - 1, t_0 | n'_A - 1, n'_I, t - \tau)$, which can be written as $P(n'_A - 1, n'_I, t - \tau | n_A^0, n_I^0 - 1, t_0) P(n_A^0, n_I^0 - 1, t_0) / P(n'_A - 1, n'_I, t - \tau)$. We use also that

$P(\mathcal{S}; \mathcal{I}_{n'_A, n'_I}) = n'_A P(n'_A, n'_I, t - \tau) e^{-\gamma' \tau} \beta \Delta t$ to obtain

$$P(\mathcal{S}; \mathcal{I}_{n'_A, n'_I} | n_A^0, n_I^0, t_0) = \sum_{n'_A, n'_I} P(n'_A - 1, n'_I, t - \tau | n_A^0, n_I^0 - 1, t_0) n'_A \beta e^{-\gamma' \tau} \Delta t \frac{P(n'_A, n'_I, t - \tau)}{P(n'_A - 1, n'_I, t - \tau)} \frac{P(n_A^0, n_I^0 - 1, t_0)}{P(n_A^0, n_I^0, t_0)}. \quad (19)$$

We know that in the steady state, if the rates are constant, n_A and n_I follow independent Poisson distributions. This allows us to compute the ratios of probabilities in this expression:

$$\frac{P(n'_A, n'_I, t - \tau)}{P(n'_A - 1, n'_I, t - \tau)} = \frac{\langle n_A \rangle_{st}}{n'_A}, \quad (20)$$

$$\frac{P(n_A^0, n_I^0 - 1, t_0)}{P(n_A^0, n_I^0, t_0)} = \frac{n_I^0}{\langle n_I \rangle_{st}}, \quad (21)$$

which leads to

$$P(\mathcal{S}; \mathcal{I}_{n'_A, n'_I} | n_A^0, n_I^0, t_0) = \sum_{n'_A, n'_I} P(n'_A - 1, n'_I, t - \tau | n_A^0, n_I^0 - 1, t_0) \beta e^{-\gamma' \tau} \Delta t \frac{\langle n_A \rangle_{st}}{\langle n_I \rangle_{st}} n_I^0 \quad (22)$$

$$= \beta e^{-\gamma' \tau} \Delta t \frac{\langle n_A \rangle_{st}}{\langle n_I \rangle_{st}} n_I^0, \quad (23)$$

where we have used $\sum_{n'_A, n'_I} P(n'_A - 1, n'_I, t - \tau | n_A^0, n_I^0 - 1, t_0) = 1$. Putting all the pieces together, we find that the delay degradation term in the master equation for the conditional probability for $t - t_0 < \tau$ is

$$(E_I - 1) P(n_A, n_I - 1, t | n_A^0, n_I^0 - 1, t_0) \frac{\gamma'}{e^{\gamma' \tau} - 1} n_I^0. \quad (24)$$

On the other hand, for $t - t_0 > \tau$, expression (17) equals

$$\sum_{n'_A, n'_I} P(n_A, n_I, t | n'_A - 1, n'_I, t - \tau; n_A^0, n_I^0, t_0) e^{-\gamma' \tau} n'_A \beta \Delta t P(n'_A, n'_I, t - \tau | n_A^0, n_I^0, t_0), \quad (25)$$

which is the same as the delay-degradation term in the master equation (9) but conditioning all probabilities to n_A^0, n_I^0 at time t_0 , as happens in Markovian processes.

Using (24) and (25) in the corresponding time intervals, we obtain the evolution of the conditional averages in the steady state:

$$\begin{aligned} \frac{d\langle n_A, t | n_A^0, n_I^0, t_0 \rangle}{dt} &= C - a \langle n_A, t | n_A^0, n_I^0, t_0 \rangle, \\ \frac{d\langle n_I, t | n_A^0, n_I^0, t_0 \rangle}{dt} &= \begin{cases} -\gamma \langle n_I, t | n_A^0, n_I^0, t_0 \rangle + \beta \langle n_A, t | n_A^0, n_I^0, t_0 \rangle - \frac{\gamma'}{e^{\gamma' \tau} - 1} n_I^0, & t_0 \leq t \leq t_0 + \tau, \\ -\gamma \langle n_I, t | n_A^0, n_I^0, t_0 \rangle + \beta (\langle n_A, t | n_A^0, n_I^0, t_0 \rangle - e^{-\gamma' \tau} \langle n_A, t - \tau | n_A^0, n_I^0, t_0 \rangle), & t \geq t_0 + \tau. \end{cases} \end{aligned} \quad (26)$$

The steady-state correlations $K_{UV}(t) \equiv \langle n_U(t' + t) n_V(t') \rangle_{st} - \langle n_U \rangle_{st} \langle n_V \rangle_{st}$ can be obtained by integrating the previous equations (26) and averaging over initial conditions in the steady state. The result is

$$K_{AA}(t) = \langle n_A \rangle_{st} e^{-at}, \quad (27)$$

$$K_{II}(t) = \begin{cases} \langle n_I \rangle_{st} \frac{e^{-\gamma' t} - e^{-\gamma t}}{1 - e^{-\gamma' \tau}}, & 0 \leq t \leq \tau, \\ 0, & t \geq \tau, \end{cases} \quad (28)$$

$$K_{IA}(t) = \begin{cases} \frac{C\beta}{a} \frac{e^{-\gamma' t} - e^{-at}}{a - \gamma'}, & 0 \leq t \leq \tau, \\ \frac{C\beta}{a} \frac{e^{(a-\gamma')\tau} - 1}{a - \gamma'} e^{-at}, & t \geq \tau, \end{cases} \quad (29)$$

$$K_{AI}(t) = 0. \quad (30)$$

The autocorrelation function for the total number of particles $n = n_A + n_I$ is $K(t) = K_{AA}(t) + K_{II}(t) + K_{IA}(t) + K_{AI}(t)$. Note that in the case $\gamma' = 0$ the correlation for the X_I particles decays linearly in time instead of the typical exponential decay [as can be seen from taking the limit $\gamma' \rightarrow 0$ in Eq. (28)]. For arbitrary γ' the correlation function for the X_I particles drops strictly to zero at $t = \tau$.

An analysis of the previous expressions shows that, in all cases, the autocorrelation functions $K_{AA}(t)$, $K_{II}(t)$, and $K(t)$ decrease monotonically in time, so there is no signature of stochastic oscillations, contrary to what was claimed in Ref. [12] and in agreement with what was found in the particular case $\gamma' = 0$ considered in Ref. [13]. These exact theoretical expressions are in excellent agreement with the results of extensive numerical simulations of the stochastic process (2) using a conveniently modified form of Gillespie's

algorithm [19,20]. This agreement provides an independent check of the correctness of the theoretical calculations. It is important to realize that particles that are tagged at, say, time t and are then scheduled to die at time $t + \tau$ can nevertheless die instantaneously at a rate γ' during the interval $(t, t + \tau)$. If this is the case, in the stochastic simulation one has to remove that particle from the list of scheduled events to happen at $t + \tau$. Otherwise, one is removing a particle that was already removed. Stochastic oscillations do appear if one, erroneously, removes twice these particles. In the case $\gamma' = 0$ one has to take into account that only “untagged” proteins (and not the whole population) can be degraded instantaneously. These considerations lead to the introduction of two variables X_A and X_I .

VI. DISCUSSION

In this work, we have studied a stochastic model of protein level dynamics that includes delay in the degradation. The exact solution shows that no oscillations are present in the system, contrary to previous results [12,21] and in agreement with a recent analysis in a simplified version of the stochastic model that allows for a Markovian reduction [13]. This implies that the presence of delay in degradation alone cannot give rise to oscillations. Our analysis is based on the assumption of a fixed delay, but the effect of a stochastically distributed delay typically decreases as the fluctuations in the delay size increase [16]. Since the delayed degradation is a consuming reaction (the state of the system changes both when the reaction is initiated and when it is completed after the delay time), one needs to consider two variables when analyzing the system. Not doing so produces erroneous results such as the appearance of oscillations.

We have also analyzed the derivation of master equations and the time correlations in systems with delay, pointing out the differences with Markovian processes. Our approach allows one to deal with more general systems than the one used in Ref. [13] and may be of interest for studying other non-Markovian processes. Exact results are especially valuable in small systems where approximated schemes typically fail (see Ref. [7] for a recent analysis of the accuracy of the chemical Langevin equation and [22,23] for exact solutions in other stochastic models of gene expression). They are also important for studying the validity of assumptions and approximations to be used in more complicated systems.

In a broader context, due to the important role of stochasticity and delay in many biological, physical, and technological systems, the present work seems to be relevant as a case where exact results can be obtained, allowing us to clarify the combined effect of stochasticity and delay.

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APPENDIX: CALCULATION OF THE PROBABILITIES

Let us define the generating function of $P^*(n_A, n_I, t | n_A^0, n_I^0, 0)$ as $G^*(s_A, s_I, t) \equiv \sum_{n_A=0}^{\infty} \sum_{n_I=0}^{\infty} s_A^{n_A} s_I^{n_I} P^*(n_A, n_I, t | n_A^0, n_I^0, 0)$. Using standard techniques, it follows from the master equation (12) that the generating function obeys the partial differential equation

$$\frac{\partial G^*}{\partial t} = [\gamma(1 - s_A) + \beta(s_I - s_A)] \frac{\partial G^*}{\partial s_A} + \gamma'(1 - s_I) \frac{\partial G^*}{\partial s_I} + C(s_A - 1)G^* \quad (\text{A1})$$

with initial condition $G^*(s_A, s_I, 0) = s_A^{n_A^0} s_I^{n_I^0}$. Using the method of the characteristics, one can find that the solution in the case of the initial condition $n_A^0 = n'_A - 1, n_I^0 = 0$ [as needed in master equation (9)] can be written as

$$G^*(s_A, s_I, t) = [1 + \Phi(s_A, s_I, t)]^{n'_A - 1} \times \exp \left[C \int_0^t dt' \Phi(s_A, s_I, t') \right], \quad (\text{A2})$$

where

$$\Phi(s_A, s_I, t) = (s_A - 1)e^{-at} + (s_I - 1) \frac{\beta}{a - \gamma'} (e^{-\gamma't} - e^{-at}). \quad (\text{A3})$$

It follows from Eq. (11) that the generating function for the original delayed process $G(s_A, s_I, t) \equiv \sum_{n_A=0}^{\infty} \sum_{n_I=0}^{\infty} s_A^{n_A} s_I^{n_I} P(n_A, n_I, t)$ obeys

$$\begin{aligned} \frac{\partial G}{\partial t} &= [\gamma(1 - s_A) + \beta(s_I - s_A)] \frac{\partial G}{\partial s_A} + \gamma'(1 - s_I) \frac{\partial G}{\partial s_I} \\ &+ C(s_A - 1)G + \beta e^{-\gamma'\tau} (1 - s_I) \\ &\times \sum_{n'_A=0} G^*(s_A, s_I, \tau) n'_A P(n'_A, t - \tau), \end{aligned} \quad (\text{A4})$$

We assume $n_A(t) = n_I(t) = 0$ for $t < 0$ so that both the master equation (9) and the equation for the generating function (A4) are valid for $t > 0$. The number of X_A particles follows a Poisson distribution at all times $P(n_A, t) = \frac{x_A(t)^{n_A}}{n_A!} e^{-x_A(t)}$, with $x_A(t)$ being the average value given in Eq. (15) [assuming the initial condition is $n_A(0) = 0$]. Using Eq. (A2), it is possible to perform the sum over the n'_A variable to obtain the equation

$$\begin{aligned} \frac{\partial G}{\partial t} &= [\gamma(1 - s_A) + \beta(s_I - s_A)] \frac{\partial G}{\partial s_A} + \gamma'(1 - s_I) \frac{\partial G}{\partial s_I} \\ &+ C(s_A - 1)G + \beta e^{-\gamma'\tau} (1 - s_I) x_A(t - \tau) \\ &\times \exp \left[x_A(t - \tau) \Phi(s_A, s_I, \tau) + C \int_0^\tau dt' \Phi(s_A, s_I, t') \right]. \end{aligned} \quad (\text{A5})$$

One can check by direct substitution that the Poisson distribution $G(s_A, s_I, t) = e^{x_A(t)(s_A - 1) + x_I(t)(s_I - 1)}$ is a solution of this equation if $x_A(t)$ and $x_I(t)$ obey the differential equations (14). Therefore, n_A and n_I follow independent Poisson distributions at all times [assuming $n_A(0) = n_I(0) = 0$]. It follows that the total number of X particles $n = n_A + n_I$ also obeys at all times a Poisson distribution with parameter $x(t) = x_A(t) + x_I(t)$. If we start with an initial condition different from $n_A(0) = n_I(0) = 0$ (or n_A being Poisson distributed), the time-dependent solution is not Poissonian, but this form is recovered in the steady state.

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