



# Stochasticity and time delays in gene expression and evolutionary game theory

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## ABSTRACT

We discuss effects of stochasticity and time delays in simple models of population dynamics. In social-type models, where individuals react to the information concerning the state of the population at some earlier time, sufficiently large time delays may cause oscillations. In biological-type models, where some changes already take place in the population at an earlier time, oscillations might not be present for any time delay. We illustrate this idea in models of delayed random walks, gene expression, and population dynamics of evolutionary game theory.

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## 1. Introduction

Many socio-economic and biological processes can be modeled as systems of interacting objects. One may then try to derive their global behavior from individual interactions between their basic entities such as animals in ecological and evolutionary models, RNA and protein molecules in biochemical reactions of gene expression and regulation, and people in social processes. If the number of interacting objects is small, to describe and analyze the time evolution of such systems we should use stochastic modeling.

It was usually assumed that reactions take place instantaneously and effects of individual interactions are immediate. In reality, all biochemical processes take a certain time and there is a substantial time delay between the beginning of a reaction and the appearance of new products in the system. Similarly, in ecological models results of interactions between individuals may appear in the future, and in social models, individuals or players may act, that is choose appropriate strategies, on the basis of the information concerning events in the past.

It is well known that time delays may cause oscillations in solutions of ordinary differential equations [1–5]. The main goal of this paper is to show that the presence of oscillations depends on particular causes of a time delay. We divide models with time delays into two families. In social-type models, where individuals react to the information concerning the state of the population at some earlier time, we should expect oscillations. On the other hand, in biological-type models, where some changes already take

place in the population at an earlier time, oscillations might not be present for any time delay. We illustrate our idea with two examples: gene expression with a delayed degradation and an evolutionary game with the stable coexistence of two strategies.

It was argued recently in [6] that combined effects of the time delay of protein degradation and stochasticity may cause an oscillatory behavior in simple models of gene expression. It was shown in [7] that if one assumes that a process of degradation is consuming, that is molecules which started to degrade cannot take part in other processes, then oscillatory behavior is no longer present in such systems. The key point here is that although protein molecules will completely degrade at some time in the future, they have already changed the state of the system at an earlier time. We say that such models are of biological type. However, if we change the model and allow protein molecules to be chosen many times for degradation, that is we do not see any change at an earlier time, then we obtain formally a delayed random walk of a social type [8,9]. In such a random walk, oscillations are present for sufficiently large delays. We compare here these two models and show that they are equivalent in the limit of small time delays. We derive an analytical expression for the variance of the number of protein molecules in a simple model of gene expression with a time-delay degradation.

We will also discuss two evolutionary game theory models with stationary coexistence of two strategies in the replicator dynamics [10,11]. In the social-type model, players imitate opponents taking into account average payoffs of games played some time ago. In the biological-type model, new players are born from parents who played in the past. We show that in the first type of dynamics, the stationary point is asymptotically stable for small time delays and becomes unstable for big ones. In the second type of dynamics,

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however, the stationary point is asymptotically stable for any time delay.

## 2. Random walk with a time delay

One of the simplest models involving both stochasticity and time delays is a delayed random walk [8,9]. In such a walk, transition probabilities at time  $t$  depend on the position of the walker at time  $t - \tau$ . In [8], a delayed random walk was considered, where in the absence of delays, the transition toward the origin (a stable point) is more probable than the outward transition, otherwise transition probabilities are position independent. The authors shown that the mean square displacement of the walker, that is the variance, approaches a stationary value in an oscillatory manner for large time delays and in a monotonic way for small ones. Moreover, this stationary value is a linear function of the delay and the coefficient of proportionality is a linear function of the transition probability. In [9], the transition probability towards the origin was assumed to increase linearly with the distance to the origin up to the distance above which it was set constant as in the previous model. It was proved that in the stationary state, the autocorrelation function of the position of the walker,  $\langle X_t X_{t-\tau} \rangle$ , is  $\tau$  independent and  $\langle X_t X_{t-u} \rangle$  has an oscillatory behavior as a function of  $u$  for large delays. Continuous (in time and space) analogs of delayed random walks were analyzed in [9,12,13]. The following Langevin equation was considered,

$$\frac{dx}{dt} = -\beta x(t - \tau) + \xi_t, \quad (2.1)$$

where  $x$  is a continuous variable denoting the position of the walker and  $\xi_t$  is a time uncorrelated random shock, that is  $\langle \xi_t \xi_s \rangle = \delta(t - s)$ . In the rigorous presentation, the above equation has the form of the Itô equation,

$$dx = -\beta x(t - \tau)dt + dW, \quad (2.2)$$

where  $W$  is the standard Wiener process with the zero expected value and the unit variance.

In [12], the stationary variance of such a process was calculated,

$$\text{Var}(x) = \frac{1 + \sin \beta \tau}{2\beta \cos \beta \tau}. \quad (2.3)$$

For small time delays, the linearization of (2.3) gives us

$$\text{Var}(x) = \frac{1}{2\beta} (1 + \beta \tau). \quad (2.4)$$

Small-delay expansions and corresponding Fokker–Planck equations were analyzed in [13,14] where original delay systems were approximated by non-delayed stochastic differential equations.

In the following section we take a different approach. To describe fluctuations in finite systems of objects/individuals, we model their time evolution by appropriate birth and death processes. We will discuss simple stochastic models of gene expression. In our first model, mRNA molecules are produced and are subject to a time delay degradation. We will compare such a stochastic process with the delayed random walk described above and discuss fundamental differences between these two models. We will show that in the limit of small delays both models are equivalent and we will re-derive (2.4).

## 3. Delayed degradation

In the simplest production–degradation system, mRNA molecules are produced and degrade with constant intensities. Let us denote by  $x(t)$  the concentration of mRNA molecules at time  $t$ . The classical equation of chemical kinetics, i.e. the time evolution of  $x(t)$ , then reads:

$$\frac{dx}{dt} = k - \gamma x(t), \quad (3.1)$$

where  $k$  is the intensity of production and  $\gamma$  the intensity of degradation.

Assume now that the degradation process takes some time, that is molecules are completely degraded  $\tau$  units of time after the delayed degradation is triggered. We are tempted to model such a phenomenon by the following time-delay differential equation [6]:

$$\frac{dx}{dt} = k - \gamma x(t - \tau). \quad (3.2)$$

After a simple change of the variable  $x$ , the shift  $x \rightarrow x - k/\gamma$ , we obtain a deterministic term in (2.1).

Delayed random walk models and Langevin equations like (2.1) correctly describe real processes if the rate of change of the size of the population at time  $t$  depends on the size of the population at some earlier time  $t - \tau$  but there is no change in the population at time  $t - \tau$ . We may refer to such models as of social type.

On the contrary, in our production–degradation model, some molecules undergo a change at time  $t - \tau$ —they start to degrade, therefore they cannot be chosen for degradation again so in a sense they are not active and cannot be taken again into account in calculating the future rate of change of the size of the population. The differential equation (3.2) does not take this into account. Degrading molecules affect the concentration at the future time and in the meantime they may again take part in another process of degradation. Therefore they may be subtracted from the system several times and this may make the size of the population negative which is unacceptable in biological models. This is a frequent problem that solutions of time-delay differential equations with positive initial conditions may become negative [15].

In [7] we developed a new methodology to deal with time delays in biological systems. It is based on the division of reactions into consuming and non-consuming ones [16,17]. We applied it to simple gene expression models with a delayed degradation. When a molecule starts to degrade then we consider it inactive (it cannot take part in another reaction) but it is still in the system and hence it is visible. Such reactions are called consuming. Let us denote by  $x$  the concentration of active molecules and by  $y$  the concentration of all molecules present in the system. We arrive at the following equations for  $x$  and  $y$ :

$$\begin{aligned} \frac{dx}{dt} &= k - \gamma x(t), \\ \frac{dy}{dt} &= k - \gamma x(t - \tau). \end{aligned} \quad (3.3)$$

Such a system of equations can be easily solved; it does not exhibit any cyclic behavior [7] as opposed to (3.2) where for some critical  $\tau$  the population undergoes the Hopf bifurcation and there appears a limit cycle [1–5].

In many cases, biochemical processes take place in small volumes and may involve only a few molecules. The deterministic approach dealing with macroscopic concentrations of molecules is then inappropriate. A small number of molecules taking part in gene expression results in significant random fluctuations. To take into account such fluctuations, many stochastic models involving Master, Fokker–Planck, and Langevin equations were analyzed [18–26] and appropriate birth and death processes were simulated by the Gillespie algorithm [27].

Stochastic dynamics with time delays were recently investigated in [6,8,9,12–14,28–32]. In [6], the authors argued that combined stochasticity and time delay cause oscillations in gene expression with a delayed degradation.

In [7], we used a generating function approach to Master equations corresponding to (3.3) and showed that the variance of

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