



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 τ 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 ξ_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 γ the intensity of degradation.

Assume now that the degradation process takes some time, that is molecules are completely degraded τ 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 τ 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

the total number of mRNA molecules in the stationary state is equal to its expected value,

$$\text{Var}(y) = \langle y \rangle = \langle x \rangle (1 + \gamma \tau), \quad (3.4)$$

where $\langle x \rangle = \frac{k}{\gamma}$ is the expected value of the number of active molecules.

In the limit of small delays, when in the time interval of the length τ only one reaction can take place, (3.2) correctly describes both the social and biological delays and we re-derive (3.4) which is consistent with (2.4).

In the stochastic description of (3.2) we interpret k and γ as intensities of birth (production) and death (degradation) processes. The state of the system at time t is described by the number of mRNA molecules, r . Let $P(r, t)$ be the probability that the system is in the state r at the time t and $P(r, t; m, t - \tau)$ the probability that we have r molecules at time t and m molecules at time $t - \tau$. We use the standard assumptions of birth and death processes, that is events in non-overlapping time intervals are independent, the probability of a reaction is proportional to the length of the time interval, and the probability of two or more reactions is of a lower order and we write

$$\begin{aligned} P(r, t + h) = & khP(r - 1, t) + \gamma h \sum_{m=0}^{\infty} mP(r + 1, t; m, t - \tau) \\ & + (1 - kh)P(r, t) - \gamma h \sum_{m=0}^{\infty} mP(r, t; m, t - \tau). \end{aligned} \quad (3.5)$$

Now we take $P(r, t)$ into the left-hand side, divide (3.5) by h , take the limit $h \rightarrow 0$ and obtain the following Master equation [33]:

$$\begin{aligned} \frac{dP(r, t)}{dt} = & k(P(r - 1, t) - P(r, t)) \\ & + \gamma \sum_{m=0}^{\infty} mP(r + 1, t; m, t - \tau) \\ & - \gamma \sum_{m=0}^{\infty} mP(r, t; m, t - \tau). \end{aligned} \quad (3.6)$$

We introduce the generating function

$$G(u, t; w, t - \tau) = \sum_{r, m=0}^{\infty} f(r, t; m, t - \tau) u^r w^m. \quad (3.7)$$

We differentiate (3.7) with respect to time, use (3.6), then differentiate twice with respect to u , set $u = w = 1$ and obtain

$$\frac{d\langle r(r - 1) \rangle}{dt} = 2k\langle r(t) \rangle + 2\gamma\langle r(t - \tau) \rangle - 2\gamma\langle r(t)r(t - \tau) \rangle. \quad (3.8)$$

In the stationary state we get

$$\langle r(t)r(t - \tau) \rangle = \frac{k}{\gamma} \left(1 + \frac{k}{\gamma} \right). \quad (3.9)$$

We see that the autocorrelation function at the time separation τ is τ independent. The same result was obtained in the delayed random walk in [9].

Now we proceed to obtain the formula for the variance of r . We assume that during the time interval $[t - \tau, t]$ only one reaction can take place. Therefore $r(t)$ can be equal to $r(t - \tau) + 1$ with the probability $k\tau$, to $r(t - \tau) - 1$ with the probability $\gamma r(t - \tau)\tau$, and to $r(t - \tau)$ with the remaining probability. It follows that

$$\langle r(t)r(t - \tau) \rangle = \langle r^2(t - \tau) \rangle (1 - \gamma\tau) + k\tau\langle r(t - \tau) \rangle. \quad (3.10)$$

We combine (3.9) and (3.10), get an expression for $\langle r^2 \rangle$ and therefore for the variance, expand it in τ , keep only a linear term and get

$$\text{Var}(r) = \langle r \rangle (1 + \gamma\tau) = \frac{k}{\gamma} (1 + \gamma\tau). \quad (3.11)$$

We will show now that $\text{Var}(r)$ in (3.11) is exactly the same as in (2.4). The following Langevin equation corresponds to our birth and death process without a time delay (compare (2.1)):

$$\frac{dx}{dt} = k - \gamma x + \sigma \xi_t. \quad (3.12)$$

We integrate (3.12) and get

$$\left(x - \frac{k}{\gamma} \right)^2 = \left(x(0)e^{-\gamma t} + e^{-\gamma t} \int_0^t e^{\gamma s} (k + \sigma \xi(s)) ds - \frac{k}{\gamma} \right)^2. \quad (3.13)$$

In the stationary state, that is in the limit $t \rightarrow \infty$, from the above equation we obtain

$$\left\langle \left(x - \frac{k}{\gamma} \right)^2 \right\rangle = \frac{\sigma^2}{2\gamma}. \quad (3.14)$$

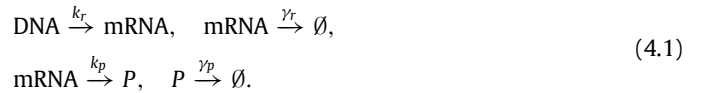
On the other hand, we know that $\text{Var}(x) = \langle x \rangle = \frac{k}{\gamma}$ in the birth and death process, therefore we get

$$\sigma^2 = 2k, \quad (3.15)$$

and finally we see that (2.4) and (3.11) coincide.

4. Gene expression with a delayed degradation

We now consider the classical model of gene expression involving four biochemical processes: transcription, translation, mRNA and protein degradation [21]:



In the stochastic description, deterministic rates of the above reactions are interpreted as intensities of corresponding birth and death processes. The analytical expression for the variance of the number of protein molecules p in the stationary state was derived in [21]:

$$\text{Var}(p) = \langle p \rangle \left(1 + \frac{k_p}{\gamma_r + \gamma_p} \right), \quad (4.2)$$

where $\langle p \rangle = \frac{k_r k_p}{\gamma_r \gamma_p}$ is the expected value of the number of protein molecules.

As in the previous section, we assume that protein degradation takes some time and we model it by a single process with the time delay τ . In [7], the authors used the generating function approach to Master equations and derived the expected value and the variance of the number of protein molecules in the stationary state. Here we re-derive those results in the small τ limit. We might repeat the procedure from the previous section. Instead we will use directly the methodology developed in [7].

Let $r(t)$ be the number of mRNA molecules, $p(t)$ the number of active protein molecules at time t , $d(t)$ the number of delayed protein degradations initiated since the time $t = 0$, and $y(t)$ the total number of protein molecules related to $p(t)$, $d(t)$, and $d(t - \tau)$ in the following way:

$$y(t) = p(t) + d(t) - d(t - \tau). \quad (4.3)$$

It is easy to see that in the stationary state we have $\langle (d(t) - d(t - \tau)) \rangle = \gamma_p \langle p \rangle \tau$. It follows that

$$\langle y \rangle = \langle p \rangle (1 + \gamma_p \tau). \quad (4.4)$$

For the variance of the total number of protein molecules we write

$$\begin{aligned} \text{Var}(y(t)) = & \text{Var}(p(t) + d(t) - d(t - \tau)) \\ = & \text{Var}(p(t)) + \text{Var}(d(t) - d(t - \tau)) \\ & + 2\text{Cov}(p(t)(d(t) - d(t - \tau))). \end{aligned} \quad (4.5)$$

For small time delays, we assume that only one reaction can take place in any time interval $[t - \tau, t]$ and therefore $\langle (d(t) - d(t - \tau))^2 \rangle = \langle d(t) - d(t - \tau) \rangle$. Because $\langle d(t) - d(t - \tau) \rangle^2$ is of the order τ^2 , then for small τ we get that $\text{Var}(d(t - \tau) - d(t)) = \langle d(t) - d(t - \tau) \rangle = \gamma_p \langle p \rangle \tau$.

Now in order to get $\text{Var}(y)$ we need to compute $\text{Cov}(p(t)(d(t) - d(t - \tau)))$ in the stationary state. For small τ we can write $\langle p(t)(d(t) - d(t - \tau)) \rangle$

$$\begin{aligned} &= \sum_{m=0}^{\infty} m P(d(t) - d(t - \tau) = m) P(p(t - \tau) = m + 1) \\ &\quad \times P(p(t - \tau) = m + 1) \\ &= \gamma_p \tau \sum_{m=0}^{\infty} m(m + 1) P(p = m + 1) = \gamma_p \tau (\langle p^2 \rangle - \langle p \rangle). \end{aligned} \quad (4.6)$$

Hence we get that

$$\text{Cov}(p(t)(d(t) - d(t - \tau))) = \langle p \rangle \frac{k_p}{\gamma_r + \gamma_p} \gamma_p \tau \quad (4.7)$$

and finally

$$\text{Var}(y) = \text{Var}(p)(1 + \gamma_p \tau) + \langle p \rangle \frac{k_p}{\gamma_r + \gamma_p} \gamma_p \tau. \quad (4.8)$$

The above formula coincides with the linear approximation of the variance obtained in [7].

We can repeat the above methodology to re-derive (3.11) for the simple production–degradation model. In this case $\text{Cov}(r(t)(d(t) - d(t - \tau))) = 0$ and (3.11) follows immediately.

5. Replicator dynamics

The evolution of populations can often be described within game-theoretic models [34–39]. In such models, players have at their disposal certain strategies and their payoffs in a game depend on strategies chosen both by them and by their opponents. The central concept in game theory is that of a Nash equilibrium. It is an assignment of strategies to players such that no player, for fixed strategies of his opponents, has an incentive to deviate from his current strategy—no change can increase his payoff. The dynamical interpretation of Nash equilibria was provided by several authors [40–42]. They proposed a system of difference or differential replicator equations which describe the time-evolution of fractions of the population playing different strategies. Nash equilibria are stationary points of such dynamics.

Imagine a finite but a very large population of individuals. Assume that they are paired randomly to play a symmetric two-player game with two strategies and the following payoff matrix:

$$U = \begin{matrix} & A & B \\ A & a & b \\ B & c & d, \end{matrix}$$

where U_{kl} , $k, l = A, B$, is a payoff of the first (row) player when he plays the strategy k and the second (column) player plays the strategy l . We assume that both players are the same and hence payoffs of the column player are given by the matrix transposed to U ; such games are called symmetric.

We are interested in fractions of the population playing respective strategies. We assume that individuals receive average payoffs with respect to all possible opponents—they play against the average strategy.

Let $r_i(t)$, $i = A, B$, be the number of individuals playing the strategy A and B respectively at the time t . Then $r(t) = r_A(t) + r_B(t)$ is the total number of players and $x(t) = \frac{r_A(t)}{r(t)}$ is the fraction of the population playing A at time t .

We assume that during the small time interval ϵ , only an ϵ fraction of the population takes part in pairwise competitions, that is plays games. We write

$$r_i(t + \epsilon) = (1 - \epsilon)r_i(t) + \epsilon r_i(t) U_i(t); \quad i = A, B, \quad (5.1)$$

where $U_A(t) = ax(t) + b(1 - x(t))$ and $U_B(t) = cx(t) + d(1 - x(t))$ are average payoffs of individuals playing A and B respectively. We assume that all payoffs are not smaller than 0, hence r_A and r_B are always non-negative and therefore $0 \leq x \leq 1$.

The equation for the total number of players reads

$$r(t + \epsilon) = (1 - \epsilon)r(t) + \epsilon r(t) \bar{U}(t), \quad (5.2)$$

where $\bar{U}(t) = x(t)U_A(t) + (1 - x(t))U_B(t)$ is the average payoff in the population at the time t . When we divide (5.1) by (5.2) we obtain an equation for the frequency of the strategy A ,

$$x(t + \epsilon) - x(t) = \epsilon \frac{x(t)[U_A(t) - \bar{U}(t)]}{1 - \epsilon + \epsilon \bar{U}(t)}. \quad (5.3)$$

Now we divide both sides of (5.3) by ϵ , perform the limit $\epsilon \rightarrow 0$, and obtain the well known differential replicator equation,

$$\frac{dx(t)}{dt} = x(t)[U_A(t) - \bar{U}(t)]. \quad (5.4)$$

The above equation can also be written as

$$\begin{aligned} \frac{dx(t)}{dt} &= x(t)(1 - x(t))[U_A(t) - U_B(t)] \\ &= (a - c + d - b)x(t)(1 - x(t))(x(t) - x^*), \end{aligned} \quad (5.5)$$

where $x^* = (d - b)/(a - c + d - b)$. We will assume now that $c > a$ and $b > d$ so x^* is the unique mixed Nash equilibrium, globally asymptotically stable in (5.4). We will introduce a time delay into discrete Eq. (5.1) in two different ways. The main goal of this section is to demonstrate that the long-time behavior of the population depends on the particular time-delay mechanism.

5.1. Social-type time delay

Here we assume that individuals at time t replicate due to average payoffs obtained by their strategies at time $t - \tau$ for some delay $\tau > 0$. The following equations were proposed in [10]:

$$r_i(t + \epsilon) = (1 - \epsilon)r_i(t) + \epsilon r_i(t) U_i(t - \tau); \quad i = A, B. \quad (5.6)$$

Then for the total number of players we get

$$r(t + \epsilon) = (1 - \epsilon)r(t) + \epsilon r(t) \bar{U}_o(t - \tau), \quad (5.7)$$

where $\bar{U}_o(t - \tau) = x(t)U_A(t - \tau) + (1 - x(t))U_B(t - \tau)$.

Now we proceed as before and get

$$\begin{aligned} x(t + \epsilon) - x(t) &= -\epsilon x(t)(1 - x(t))[x(t - \tau) - x^*] \\ &\quad \times \frac{\delta}{1 - \epsilon + \epsilon \bar{U}_o(t - \tau)}. \end{aligned} \quad (5.8)$$

The corresponding replicator dynamics in the continuous time then reads

$$\frac{dx(t)}{dt} = x(t)[U_A(t - \tau) - \bar{U}_o(t - \tau)] \quad (5.9)$$

and can also be written as

$$\begin{aligned} \frac{dx(t)}{dt} &= x(t)(1 - x(t))[U_A(t - \tau) - U_B(t - \tau)] \\ &= -\delta x(t)(1 - x(t))(x(t - \tau) - x^*). \end{aligned} \quad (5.10)$$

The first equation in (5.10) can also be interpreted as follows. Assume that randomly chosen players imitate randomly chosen opponents. Then the probability that a player who played A would imitate the opponent who played B at time t is exactly $x(t)(1 - x(t))$. The intensity of imitation depends on the delayed information about the difference of corresponding payoffs at time $t - \tau$. We will say that such models have a social-type time delay.

Eq. (5.10) is exactly the time-delay replicator dynamics proposed and analyzed by Tao and Wang [43]. They showed that if

$\tau < \pi(c-a+b-d)/2(c-a)(b-d) = \tau_{cr}$, then x^* is asymptotically stable. When τ passes through τ_{cr} , x^* becomes unstable. In [10], we proved directly (i.e. without referring to the theory of time-delay equations) the following theorem:

Theorem 1. x^* is asymptotically stable in the dynamics (5.8) if τ is sufficiently small and unstable for large enough τ .

5.2. Biological-type time delay

Here we assume that individuals born at time $t - \tau$ are able to take part in contests when they become mature at time t or equivalently they are born τ units of time after their parents played and received payoffs. The following equations were proposed in [10]:

$$r_i(t + \epsilon) = (1 - \epsilon)r_i(t) + \epsilon r_i(t - \tau)U_i(t - \tau); \quad i = A, B. \quad (5.11)$$

Then the equation for the total number of players reads

$$r(t + \epsilon) = (1 - \epsilon)r(t) + \epsilon r(t) \times \left[\frac{x(t)r_A(t - \tau)}{r_A(t)}U_A(t - \tau) + \frac{(1 - x(t))r_B(t - \tau)}{r_B(t)}U_B(t - \tau) \right]. \quad (5.12)$$

For the frequency of the first strategy we get the equation

$$x(t + \epsilon) - x(t) = \epsilon \frac{x(t - \tau)U_A(t - \tau) - x(t)\bar{U}(t - \tau)}{(1 - \epsilon)\frac{r(t)}{r(t - \tau)} + \epsilon\bar{U}(t - \tau)}, \quad (5.13)$$

where $\bar{U}(t - \tau) = x(t - \tau)U_A(t - \tau) + (1 - x(t - \tau))U_B(t - \tau)$.

The following theorem was proved in [10]:

Theorem 2. x^* is asymptotically stable in the dynamics (5.13) for any value of the time delay τ .

We see that large time delays cause oscillations in the social-type model and in the corresponding biological-type model, the stationary state does not lose stability for any time delay.

It is important to study the combined effects of stochasticity and time delays in such models. We hope to present some results in the near future.

6. Discussion

It is well known that time delays may cause oscillations in solutions of ordinary differential equations. Usually a unique globally asymptotically stable stationary point loses the stability for large time delays. More precisely, there exists a critical time delay at which the system undergoes the Hopf bifurcation and a stable limit cycle appears. Here we demonstrated that the presence of oscillations depends on particular causes of a time delay. In particular, 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 physical change already takes place in the population at an earlier time, oscillations might not be present for any time delay.

We compared a delayed random walk model (a social-type model with oscillations) to a corresponding production–degradation model (biological-type model without oscillations). We derived an analytical expressions for the variance of the number of protein molecules in a simple model of gene expression with a small time delay degradation. We also presented two population dynamics models – evolutionary games – with and without oscillations.

It is important to study more complex systems with time delays, especially combined effects of time delays and stochasticity, and in particular the possibility of stable oscillations in such systems.

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References

- [1] Györi I, Ladas G. Oscillation theory of delay differential equations with applications. Clarendon; 1991.
- [2] Gopalsamy K. Stability and oscillations in delay differential equations of population. Springer; 1992.
- [3] Kuang Y. Delay differential equations with applications in population dynamics. Academic Press Inc.; 1993.
- [4] Hale J. Theory of functional differential equations. New York: Springer; 1997.
- [5] Foryś U. Biological delay systems and the Mikhailov criterion of stability. J Biol Syst 2004;12:1–16.
- [6] Bratsun D, Volfson D, Tsimring LS, Hasty J. Delay-induced stochastic oscillations in gene regulation. Proc Natl Acad Sci USA 2005;102:14593–8.
- [7] Miękisz J, Poleszczuk J, Bodnar M, Foryś U. Stochastic models of gene expression with time delays. Preprint. 2010.
- [8] Ohira T, Milton JG. Delayed random walks. Phys Rev E 1995;52:3277–80.
- [9] Ohira T. Oscillatory correlation of delayed random walks. Phys Rev E 1997;55:R1255–8.
- [10] Alboszta J, Miękisz J. Stability of evolutionarily stable strategies in discrete replicator dynamics. J Theoret Biol 2004;231:175–9.
- [11] Miękisz J. Evolutionary game theory and population dynamics. In: Capasso V, Lachowicz M, editors. Multiscale problems in the life sciences, from microscopic to macroscopic. Lecture notes in mathematics, vol. 1940. 2008. p. 269–316.
- [12] Küchler U, Mensch B. Langevin stochastic differential equation extended by a time-delayed term. Stoch Stoch Rep 1992;40:23–42.
- [13] Ohira T, Yamane T. Delayed stochastic systems. Phys Rev E 2000;61:1247–57.
- [14] Guillouzic S, L'Heureux I, Longtin A. Small delay approximation of stochastic delay differential equations. Phys Rev E 1999;59:3970–82.
- [15] Bodnar M. On the nonnegativity of solutions of delay differential equations. Appl Math Lett 2000;13:91–5.
- [16] Barrio M, Burrage K, Leier A, Tian T. Oscillatory regulation of Hes1: discrete stochastic delay modelling and simulation. PLOS Comput Biol 2006;2:1017–29.
- [17] Cai X. Exact stochastic simulation of coupled chemical reactions with delays. J Chem Phys 2007;126:124108-1-.
- [18] Berg OG. A model for the statistical fluctuations of protein numbers in a microbial population. J Theoret Biol 1978;71:587–603.
- [19] McAdams HH, Arkin A. Stochastic mechanisms in gene expression. Proc Natl Acad Sci USA 1997;94:814–9.
- [20] Kepler T, Elston T. Stochasticity in transcriptional regulation: origins, consequences, and mathematical representations. Biophys J 2001;81:316–36.
- [21] Thattai M, van Oudenaarden A. Intrinsic noise in gene regulatory networks. Proc Natl Acad Sci USA 2001;98:8614–9.
- [22] Swain PS, Elowitz MB, Siggia ED. Intrinsic and extrinsic contributions to stochasticity in gene expression. Proc Natl Acad Sci USA 2002;99:12795–800.
- [23] Paulsson J. Summing up the noise in gene networks. Nature 2004;427:415–8.
- [24] Paulsson J. Models of stochastic gene expression. Phys Life Rev 2005;2:157–75.
- [25] Hornos JEM, Schultz D, Innocentini GCP, Wang J, Walczak AM, Onuchic JN, Wolynes PG. Self-regulating gene: an exact solution. Phys Rev E 2005;72:051907.
- [26] Komorowski M, Miękisz J, Kierzek A. Translational repression contributes greater noise to gene expression than transcriptional repression. Biophys J 2009;96:372–84.
- [27] Gillespie DT. Exact stochastic simulation of coupled chemical reactions. J Phys Chem 1997;81:2340–61.
- [28] Mao X, Yuan C, Zou J. Stochastic differential delay equations. J Math Anal Appl 2005;304:296–320.
- [29] Lei J, Mackey MC. Stochastic differential delay equation, moment stability, and application to hematopoietic stem cell regulation system. SIAM J Appl Math 2007;67:387–407.
- [30] Tian T, Burrage K, Burrage PM, Carletti M. Stochastic delay differential equations for genetic regulatory networks. J Comput Appl Math 2007;205:696–707.
- [31] Galla T. Intrinsic fluctuations in stochastic delay systems: theoretical description and application to a simple model of gene regulation. Phys Rev E 2009;80:021909.
- [32] Ribeiro AS. Stochastic and delayed stochastic models of gene expression and regulation. Math Biosci 2010;223:1–11.
- [33] van Kampen NG. Stochastic processes in physics and chemistry. 2nd ed. Amsterdam: Elsevier; 1997.
- [34] Maynard Smith J. Evolution and the theory of games. Cambridge: Cambridge University Press; 1982.
- [35] Weibull J. Evolutionary game theory. Cambridge (USA): MIT Press; 1995.
- [36] Hofbauer J, Sigmund K. Evolutionary games and population dynamics. Cambridge: Cambridge University Press; 1998.
- [37] Hofbauer J, Sigmund K. Evolutionary game dynamics. Bull Amer Math Soc 2003;40:479–519.

- [38] Nowak MA, Sigmund K. Evolutionary dynamics of biological games. *Science* 2004;303:793–9.
- [39] Nowak MA. *Evolutionary dynamics*. Cambridge (USA): Harvard University Press; 2006.
- [40] Taylor PD, Jonker LB. Evolutionarily stable strategy and game dynamics. *Math Biosci* 1978;40:145–56.
- [41] Hofbauer J, Schuster P, Sigmund K. A note on evolutionarily stable strategies and game dynamics. *J Theoret Biol* 1979;81:609–12.
- [42] Zeeman E. Dynamics of the evolution of animal conflicts. *J Theoret Biol* 1981;89:249–70.
- [43] Tao Y, Wang Z. Effect of time delay and evolutionarily stable strategy. *J Theoret Biol* 1997;187:111–6.