Stochastic entrainment of a stochastic oscillator

Guanyu Wang and Charles S. Peskin

Phys. Rev. E **92**, 052718 — Published 25 November 2015

DOI: 10.1103/PhysRevE.92.052718

Stochastic Entrainment of a Stochastic Oscillator

Guanyu Wang and Charles S. Peskin
Courant Institute of Mathematical Sciences
New York University, New York, New York 10012, USA

In this work we consider a stochastic oscillator described by a discrete-state continuous-time Markov chain, in which the states are arranged in a circle, and there is a constant probability per unit time of jumping from one state to the next in a specified direction around the circle. At each of a sequence of equally spaced times, the oscillator has a specified probability of being reset to a particular state. The focus of this work is the entrainment of the oscillator by this periodic but stochastic stimulus. We consider a distinguished limit, in which (1) the number of states of the oscillator approaches infinity as does the probability per unit time of jumping from one state to the next, so that the natural mean period of the oscillator remains constant, (2) the resetting probability approaches zero, and (3) the period of the resetting signal approaches a multiple, by a ratio of small integers, of the natural mean period of the oscillator. In this distinguished limit, we use analytic and numerical methods to study the extent to which entrainment occurs.

I. INTRODUCTION

In the study of linear or nonlinear oscillators, an important phenomenon is the synchronization or *entrainment* of the oscillator to a given periodic stimulus. This phenomenon is most often studied in a deterministic context [1–5], in which the oscillator is modeled by a system of ordinary or partial differential equations, and the stimulus is a prescribed periodic driving function. When noise is considered, the noise is typically modeled as an additive term [6–9], so that the oscillator itself is still described by a system of differential equations.

Here, however, we investigate the phenomenon of entrainment in a fully stochastic system, in which the oscillator is described by a discrete-state continuous-time Markov chain, and in which the effect of the stimulus on the oscillator is a reset (that may or may not occur) to a particular state at each of a sequence of equally spaced times.

The motivation for this work comes from the field of circadian rhythms. Biological cells typically contain biochemical oscillators, with natural periods of about 24 hours, in which gene regulation plays a fundamental role. Although these oscillators are often modeled by systems of ordinary differential equations based on macroscopic chemical kinetics [10–13], a more fundamental approach takes into account the discrete and stochastic nature of chemical reactions, so that the state of the system at any particular time is given by the *integer* numbers of molecules of all relevant species that are present at that time, and these integer numbers change in a stepwise manner whenever, by chance, a chemical reaction occurs [12, 14–16].

An important issue in the field of circadian rhythms is the entrainment of these cellular circadian clocks by the external ambient light signal, which has a 24-hour period. Since the influence of light on the cellular circadian oscillators most likely occurs indirectly, through chemical (e.g., hormonal) signals (the details of which are not, at present, known), this, too, is a stochastic process, subject to the same kind of molecular noise that is intrinsic to the clock mechanism itself. Thus, we are led to consider a stochastic oscillator, stochastically entrained.

We do not claim, however, that the particular model considered here is a good model for the circadian clock of any organism. Both the oscillator and the entrainment mechanism in the present paper are drastically oversimplified in comparison to biological reality. Nevertheless, we hope that some of the phenomena revealed here, and also some part of the methodology employed here to analyze those phenomena, will turn out to be useful in the study of circadian rhythms.

II. STOCHASTIC OSCILLATOR

A. An n-State Model

The oscillator we study has n states, state 0, 1, ..., $n-1$. As Figure 1 shows, we arrange them on a circle, so arithmetic on state j will be mod n. The oscillator has a mean period T, and the probability per unit time for a transition from one state to the next is $\frac{n}{T}$. Our entraining stimulus has period S. At any time t which is an integer multiple of S, the oscillator is set to state 0 with probability p.

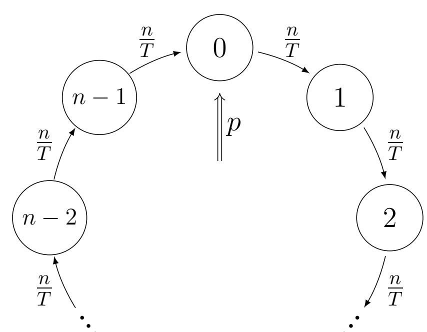

FIG. 1. An n-state oscillator with transition rate $\frac{n}{T}$ and resetting probability p.

B. Analysis and Simulation of the Oscillator

Let $P_j(t)$ be the probability of the oscillator being in state j at time t. Then

$$\frac{dP_j}{dt} = \frac{n}{T}\left(P_{j-1} - P_j\right) \tag{1}$$

with mod n arithmetic on j. Equation (1) holds on any interval of time of the form

$$rS < t < (r+1)S \tag{2}$$

where r is any non-negative integer. At each of the special times $t = rS$, we have the jump condition

$$P_j(rS^+) = (1-p)\,P_j(rS^-) + p\,\delta_{j0} \tag{3}$$

Now we look for solutions of the system (1-3) that are periodic with period S, which means

$$P_j(t) = P_j(t+S) \tag{4}$$

In that case, we only need to consider the interval $(0, S)$, and Equation (3) becomes

$$P_j(0) = (1-p)\,P_j(S) + p\,\delta_{j0} \tag{5}$$

where 0 here means 0^+, and S means S^-.

1. *Solution by Discrete Fourier Transform*

Let

$$\hat{P}_k(t) = \sum_{j=0}^{n-1} P_j(t)\, e^{-i\frac{2\pi}{n}jk} \tag{6}$$

$$P_j(t) = \frac{1}{n}\sum_{k=0}^{n-1} \hat{P}_k(t)\, e^{i\frac{2\pi}{n}jk} \tag{7}$$

Note that

$$1 = \sum_{j=0}^{n-1} \delta_{j0}\, e^{-i\frac{2\pi}{n}jk} \tag{8}$$

$$\delta_{j0} = \frac{1}{n}\sum_{k=0}^{n-1} 1 \cdot e^{i\frac{2\pi}{n}jk} \tag{9}$$

Substituting these expressions into (1-5), we get

$$\frac{d\hat{P}_k}{dt} = \frac{n}{T}\,(e^{-i\frac{2\pi}{n}k} - 1)\,\hat{P}_k \tag{10}$$

$$\hat{P}_k(0) = (1-p)\,\hat{P}_k(S) + p \tag{11}$$

The solution of (10) is

$$\hat{P}_k(t) = \hat{P}_k(0)\,\exp((e^{-i\frac{2\pi}{n}k} - 1)\,\frac{nt}{T}) \tag{12}$$

$$\Rightarrow \hat{P}_k(S) = \hat{P}_k(0)\,\exp((e^{-i\frac{2\pi}{n}k} - 1)\,\frac{nS}{T}) \tag{13}$$

$$\xRightarrow{(11)} \hat{P}_k(0) = \frac{p}{1-(1-p)\,\exp((e^{-i\frac{2\pi}{n}k} - 1)\,\frac{nS}{T})} \tag{14}$$

$$\xRightarrow{(12)} \hat{P}_k(t) = \frac{p\,\exp((e^{-i\frac{2\pi}{n}k} - 1)\,\frac{nt}{T})}{1-(1-p)\,\exp((e^{-i\frac{2\pi}{n}k} - 1)\,\frac{nS}{T})} \tag{15}$$

Then, taking the inverse discrete Fourier transform will give us the solution $P_j(t)$ for $t \in (0, S)$.

2. *Stochastic Simulation*

Instead of looking for a solution formula, we can also investigate the behavior of the system by simulating it stochastically, so we simulate L independent systems with initial state random so that their behaviors will not be biased. We set the probability of each state at the initial time as a random number normalized so that the sum of these numbers is 1, and then we use these probabilities when we select one state as the starting state randomly. Then if we simulate a large enough number of systems, we can expect that at each time step $t = 0, \Delta t, 2\Delta t, ...$, the fraction of systems being in state j should be a good approximation of $P_j(t)$. Here we are not in the periodic steady state, so we compute $P_j(t)$ by solving the system (1-3) by Euler's method.

To compare the stochastic simulation result with the numerical solution, at each time step, we make a histogram of the fraction described above for each state j, with the curve P_j solved by Euler's method superimposed, as shown in Figure 2. Figure 2 verifies that the observed fraction is approximately equal to the computed probability.

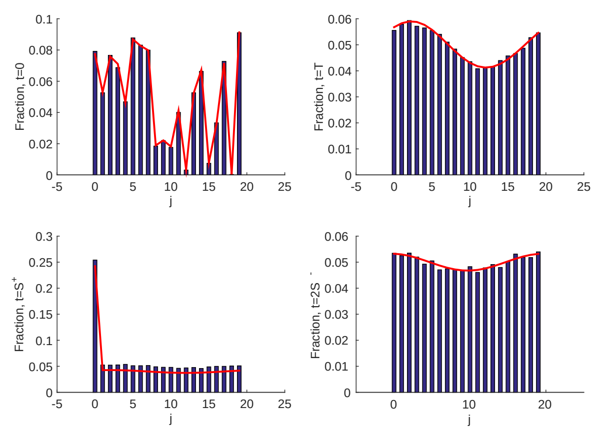

FIG. 2. (Color online) Comparison of the fraction of systems in state j at time t and the probability $P_j(t)$ of the oscillator being in state j at time $t = 0, T, S^+$, and $2S^-$. We simulate 80000 oscillators with $n = 20, T = 50$s, $S = 100.25$s, and $p = 0.2$. The bars represent the fractions, and the curve is the plot of P_j. Here $P_j(t)$ is the numerical solution of Equations (1-3). The total time simulated is $2S$. Agreement is enforced at $t = 0$ by setting $P_j(0)$ equal to the actual fraction of systems that were started in state j.

C. The Limit as $n \to \infty$

The waiting time for the oscillator to jump from one state to the next is an exponential random variable with rate $\frac{n}{T}$, so the period of the oscillator is the sum of n independent and identically distributed exponential random variables, which has the gamma distribution with shape parameter n and rate $\frac{n}{T}$. Figure 3 is a plot of the probability density function of the period, for various values of n.

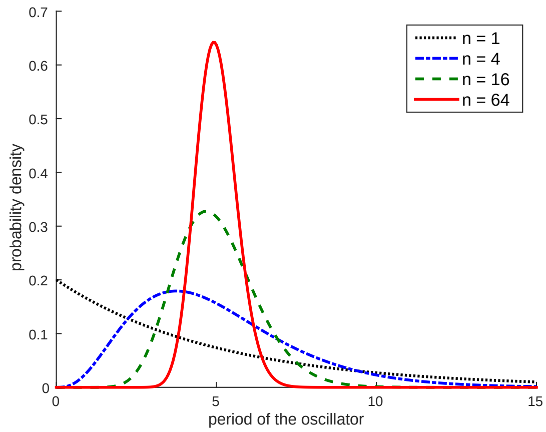

FIG. 3. (Color online) Probability density functions of the period of the oscillator with $n = 1, 4, 16$, and 64 states.

The variance of the period is $n\left(\frac{T}{n}\right)^2 = \frac{T^2}{n}$. Thus as the number of states increases, the period of the system becomes less variable. This makes it easier for a stimulus at the correct period to entrain the oscillator, but it also makes the entrainment more sensitive to any mismatch between the period of the stimulus and the period of the oscillator. If we fix p and let $n \to \infty$, the result will be perfect entrainment when the period of the stimulus is close to an integer multiple of the period of the oscillator. (See Appendix for details.) To avoid this degenerate case, we introduce a weaker entrainment signal, i.e. a smaller resetting probability. Thus we consider a distinguished limit in which $n \to \infty$ with

$$p = \frac{\alpha}{n} \tag{16}$$

where α is a positive real number. We use $\alpha = 20$ for the results shown below. For larger α, the result would be qualitatively the same but with stronger entrainment. Also, since the variability of the period of the oscillator becomes smaller as $n \to \infty$, we need to make the period of the entrainment signal closer to an integer multiple of that of the oscillator in order for the entrainent to be effective. Thus, we set

$$S = (m + \frac{\beta}{n})\, T \tag{17}$$

where m is a positive integer and β is a real parameter. Later, we shall replace the integer m by a ratio of small integers $\frac{m}{l}$, see Section IIIB.

To study the above distinguished limit, we first make the taylor expansion of $e^{-i\frac{2\pi}{n}k}$ to get

$$(e^{-i\frac{2\pi}{n}k} - 1)\, n = -i2\pi k - \frac{2\pi^2 k^2}{n} + \ldots \tag{18}$$

$$\xRightarrow{(15)} \hat{P}_k(t) \sim \frac{\frac{\alpha}{n}\, e^{-i2\pi k\frac{t}{T}}\, e^{-\frac{2\pi^2k^2}{n}\frac{t}{T}}}{1-(1-\frac{\alpha}{n})\, Q} \tag{19}$$

for large n, where

$$Q \sim e^{-i2\pi k(m+\frac{\beta}{n})}\, e^{-\frac{2\pi^2k^2}{n}(m+\frac{\beta}{n})} \tag{20}$$

$$= e^{-i2\pi k\frac{\beta}{n}}\, e^{-\frac{2\pi^2k^2}{n}(m+\frac{\beta}{n})} \tag{21}$$

$$\sim (1 - i2\pi k\frac{\beta}{n})\,(1 - \frac{2\pi^2k^2m}{n}) \tag{22}$$

$$\sim 1 - \frac{1}{n}\,(i2\pi k\beta + 2\pi^2k^2m) \tag{23}$$

$$\Rightarrow 1 - (1-\frac{\alpha}{n})\, Q \sim \frac{1}{n}\,(i2\pi k\beta + 2\pi^2k^2m + \alpha) \tag{24}$$

Thus by Equation (19),

$$\lim_{n\to\infty} \hat{P}_k(t) = \frac{\alpha e^{-i2\pi k\frac{t}{T}}}{i2\pi k\beta + 2\pi^2k^2m + \alpha} \tag{25}$$

Now define $\rho(x,t)$ by

$$\rho(x,t) = \sum_{k=-\infty}^{\infty} \frac{\alpha e^{i2\pi k(x-\frac{t}{T})}}{i2\pi k\beta + 2\pi^2k^2m + \alpha} \tag{26}$$

Note that $\rho(x,t)$ is periodic in x with period 1, and periodic in t with period T.

The sense in which $\rho(x,t)$ serves as the limit of $P_j(t)$ as $n \to \infty$ is discussed as follows. Here we consider only even n, but the case for odd n can be argued in essentially the same way. Also, for clarity, we make the value of n explicit as a superscript, so the dependence on n is evident. Then we can write Equation (6) and (7) as

$$\hat{P_k^n}(t) = \sum_{j=0}^{n-1} P_j^n(t)\, e^{-i\frac{2\pi}{n}jk} \tag{27}$$

$$P_j^n(t) = \frac{1}{n}\sum_{k=0}^{n-1} \hat{P_k^n}(t)\, e^{i\frac{2\pi}{n}jk} \tag{28}$$

Note that Equation (27) defines $\hat{P_k^n}(t)$ as periodic in k with period n. Therefore $P_j^n(t)$ can be rewritten as

$$P_j^n(t) = \frac{1}{n}\sum_{k=-\frac{n}{2}}^{\frac{n}{2}}{}^{\mathrm{T}}\, \hat{P_k^n}(t)\, e^{i\frac{2\pi}{n}jk} \tag{29}$$

where Σ^{T} denotes a trapezoided sum, in other words, there is a coefficient $\frac{1}{2}$ in the first and last term. Now define

$$\rho^n(x,t) = \sum_{k=-\frac{n}{2}}^{\frac{n}{2}}{}^{\mathrm{T}}\, \hat{P_k^n}(t)\, e^{i2\pi kx} \tag{30}$$

For each t, this is the Fourier series of a real, periodic function of x with period 1. Note that

$$\frac{1}{n}\,\rho^n(\frac{j}{n},t) = P_j^n(t) \tag{31}$$

This tells us how to extract $P_j^n(t)$ from $\rho^n(x,t)$. On the other hand, taking the limit $n \to \infty$ of $\rho^n(x,t)$, we see that

$$\lim_{n\to\infty} \rho^n(x,t) = \rho(x,t) \tag{32}$$

Thus we expect that for large n

$$P_j^n(t) \approx \frac{1}{n}\,\rho(\frac{j}{n},t) \tag{33}$$

Figure 4 shows the result for an 150-state oscillator, where for each time step t, we make a histogram of the exact probability computed by discrete Fourier transform for each state j, with the approximation function $\frac{1}{n}\,\rho(\frac{j}{n},t)$ superimposed. We can see that the two plots match well if n is sufficiently large.

III. ANALYSIS OF THE DISTINGUISHED LIMIT

In order to measure the entrainment better, we now seek an explicit formula for $\rho(x,t)$. Clearly, from Equation (26),

$$\rho(x,t) = \rho_0(x - \frac{t}{T}) \tag{34}$$

where

$$\rho_0(x) = \sum_{k=-\infty}^{\infty} \frac{\alpha e^{i2\pi kx}}{i2\pi k\beta + 2\pi^2k^2m + \alpha} \tag{35}$$

Notice that $\rho_0(x)$ solves the ordinary differential equation

$$-\frac{m}{2}\frac{d^2\rho_0(x)}{dx^2} + \beta\frac{d\rho_0(x)}{dx} + \alpha\rho_0(x) = \alpha\sum_{k=-\infty}^{\infty}\delta(x-k) \tag{36}$$

Thus we look for a continuous $\rho_0(x)$ with period 1 of the form

$$\rho_0(x) = Ae^{\lambda_1 x} + Be^{\lambda_2 x} \tag{37}$$

where λ_1, λ_2 are the two roots of the characteristic equation $-\frac{m}{2}\lambda^2 + \beta\lambda + \alpha = 0$; and A, B are constants. We can find A and B using the periodicity and boundary condition satisfied by $\rho_0(x)$. Since $\rho_0(x)$ is 1-periodic, we have

$$\rho_0(0) = \rho_0(1) \tag{38}$$

And if we integrate Equation (36) in a small neighborhood around 0, we get

$$\rho_0{}'(0^+) - \rho_0{}'(0^-) = -\frac{2\alpha}{m} \tag{39}$$

$$\Rightarrow \rho_0{}'(0) - \rho_0{}'(1) = \lambda_1\lambda_2 \tag{40}$$

Combining Equations (38) and (40), we can solve for A and B. This gives us an explicit formula for $\rho_0(x)$, which is

$$\rho_0(x) = \frac{\dfrac{e^{\lambda_1 x}}{e^{\lambda_1}-1} - \dfrac{e^{\lambda_2 x}}{e^{\lambda_2}-1}}{\dfrac{1}{\lambda_1} - \dfrac{1}{\lambda_2}} \tag{41}$$

A. Measurement of Entrainment

Note that expression (41) is invariant under interchange of λ_1 and λ_2. Without loss of generality, we choose $\lambda_2 < 0 < \lambda_1$ so that both the numerator and denominator are sums of positive terms. As a check, it is easy to verify that

$$\int_0^1 \rho_0(x)\,dx = 1 \tag{42}$$

Thus $\rho_0(x)$ is a probability density function on $(0,1)$. It follows that

$$\rho_0^{max} = \max_{x\in[0,1]} \rho_0(x) \geq 1 \tag{43}$$

$$\|\rho_0\| = \sqrt{\int_0^1 \rho_0^2(x)\,dx} \geq 1 \tag{44}$$

with equality only if ρ_0 is constant. Either of these norms, more specifically how much they exceed 1, can be used as an measurement of the extent to which the oscillator is entrained. From Equation (41), we can then derive a formula for ρ_0^{max} or $\|\rho_0\|$. Here we will only discuss ρ_0^{max}, since $\|\rho_0\|$ gives us similar results.

Because λ_1 and λ_2 have opposite sign, it follows from the expression (41) that $\rho_0(x)$ is a convex function on $(0,1)$. Its maximum on $[0,1]$ can be therefore achieved only at the boundary points $x=0$ or 1. Thus

$$\rho_0^{max} = \rho_0(1) = \rho_0(0) = \frac{\dfrac{1}{e^{\lambda_1}-1} - \dfrac{1}{e^{\lambda_2}-1}}{\dfrac{1}{\lambda_1} - \dfrac{1}{\lambda_2}} \tag{45}$$

We claim that ρ_0^{max} is maximized, for any particular m, by setting β to 0. To see this we again use the Fourier series, Equation (35), in a different way.

$$\rho_0^{max} = \rho_0(0) = \sum_{k=-\infty}^{\infty} \frac{\alpha}{i2\pi k\beta + 2\pi^2k^2m + \alpha} \tag{46}$$

$$= 1 + 2\alpha\sum_{k=1}^{\infty} \frac{2\pi^2k^2m + \alpha}{(2\pi k\beta)^2 + (2\pi^2k^2m + \alpha)^2} \tag{47}$$

It is obvious from this formula that for any fixed m, the maximum happens when $\beta = 0$.

B. Generalization to the Case in Which $\frac{S}{T} \approx \frac{m}{l}$, Where m and l Are Small Integers

It is important to note that up to now, we have only considered the case in which m is a positive integer. This corresponds, for $m > 1$, to a subharmonic stimulus, since the period of the stimulus is an integer multiple of the natural period of the oscillator. More generally, we could consider the case in which the period of the stimulus is approximately rationally related to the natural period of the oscillator by replacing m

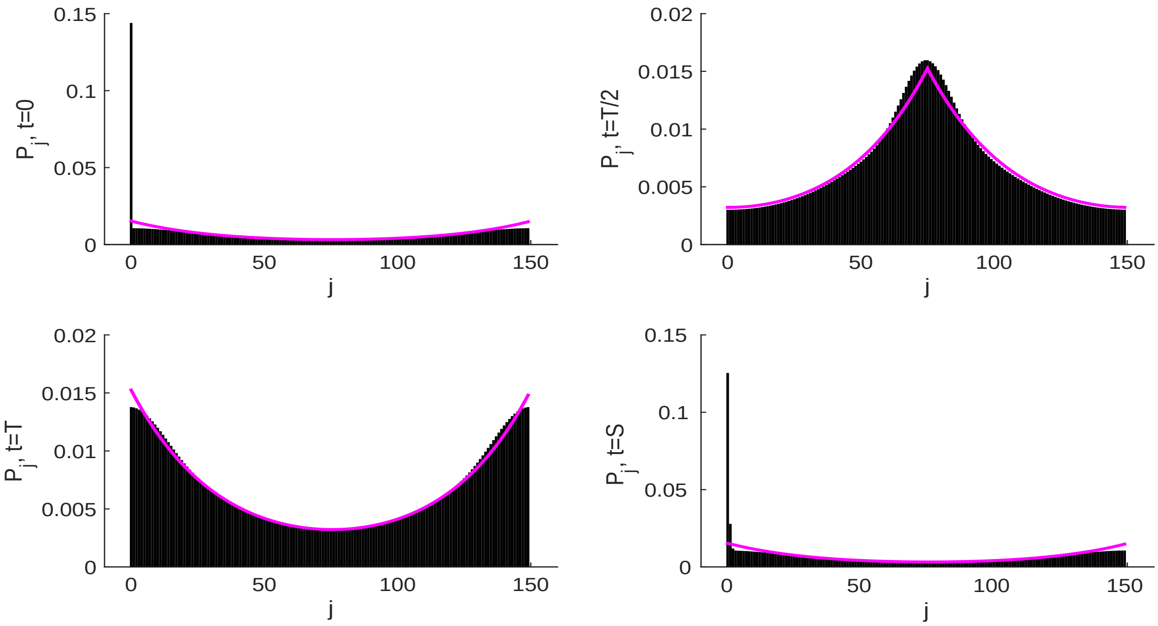

FIG. 4. (Color online) Comparison of the solution by discrete Fourier transform and the approximate expression given in Equation (33) at times $t = 0, \frac{T}{2}, T,$ and S. The oscillator has 150 states with $\alpha = 20, \beta = 0.1, m = 2,$ and $T = 50$s. The bars represent the exact solution P_j obtained by discrete Fourier transform, and the curve is the plot of $\frac{1}{n}\,\rho(\frac{j}{n}, t)$.

with $\frac{m}{l}$, where m and l are both positive integers, and $\frac{m}{l}$ is in lowest terms. Thus the stimulus has period S of the form

$$S = (\frac{m}{l} + \frac{\beta}{n})\,T \tag{48}$$

and we discuss the same distinguished limit as before.

Now Equation (19) is still valid but with a different Q,

$$Q \sim e^{-i2\pi k\frac{m}{l}}\, e^{-i2\pi k\frac{\beta}{n}}\, e^{-\frac{2\pi^2k^2}{n}(\frac{m}{l}+\frac{\beta}{n})} \tag{49}$$

$$\sim e^{-i2\pi k\frac{m}{l}}\,(1 - i2\pi k\frac{\beta}{n})\,(1 - \frac{2\pi^2k^2}{n}\frac{m}{l}) \tag{50}$$

$$\sim e^{-i2\pi k\frac{m}{l}}\,(1 - \frac{1}{n}\,(i2\pi k\beta + 2\pi^2k^2\frac{m}{l})) \tag{51}$$

for large n. Thus we get

$$\begin{aligned} &1 - (1 - \frac{\alpha}{n})Q \\ \sim &1 - e^{-i2\pi k\frac{m}{l}} + \frac{1}{n}\,e^{-i2\pi k\frac{m}{l}}\,(i2\pi k\beta + 2\pi^2k^2\frac{m}{l} + \alpha) \end{aligned} \tag{52}$$

If k is an integer multiple of l, then $e^{-i2\pi k\frac{m}{l}} = 1$. Everything is the same as before except that m has been replaced by $\frac{m}{l}$. We have

$$\lim_{n\to\infty} \hat{P}_k(t) = \frac{\alpha e^{-i2\pi k\frac{t}{T}}}{i2\pi k\beta + 2\pi^2k^2\frac{m}{l} + \alpha} \tag{53}$$

Otherwise, $e^{-i2\pi k\frac{m}{l}} \neq 1$, and in this case it is easy to verify that

$$\lim_{n\to\infty} \hat{P}_k(t) = 0 \tag{54}$$

Thus we only need to consider k's such that $k = lK$ where K is an integer, and then Equation (35) becomes

$$\rho_0(x, m, l, \beta) = \sum_{K=-\infty}^{\infty} \frac{\alpha e^{i2\pi Klx}}{i2\pi Kl\beta + 2\pi^2K^2l^2\frac{m}{l} + \alpha} \tag{55}$$

Now let

$$lx = X \tag{56}$$

$$l\beta = B \tag{57}$$

$$lm = M \tag{58}$$

Then

$$\rho_0(x, m, l, \beta) = \sum_{K=-\infty}^{\infty} \frac{\alpha e^{i2\pi KX}}{i2\pi KB + 2\pi^2K^2M + \alpha} \tag{59}$$

$$= \rho_0(X, M, 1, B) \tag{60}$$

$$= \rho_0(lx, lm, 1, l\beta) \tag{61}$$

and we are back to the previous case. Now we have generalized our result to the case of any rational $\frac{m}{l}$. To visualize the results, we plot ρ_0^{max} versus β, for various values of $\frac{m}{l}$ in Figure 5. It is clear that the maximum always occurs at $\beta = 0$, and the entrainment is the strongest when $S = T$.

IV. CONCLUSIONS

As we have shown by analysis and simulation, familiar phenomena of entrainment occur even in the somewhat unfamiliar setting of a discrete-state stochastic oscillator under the

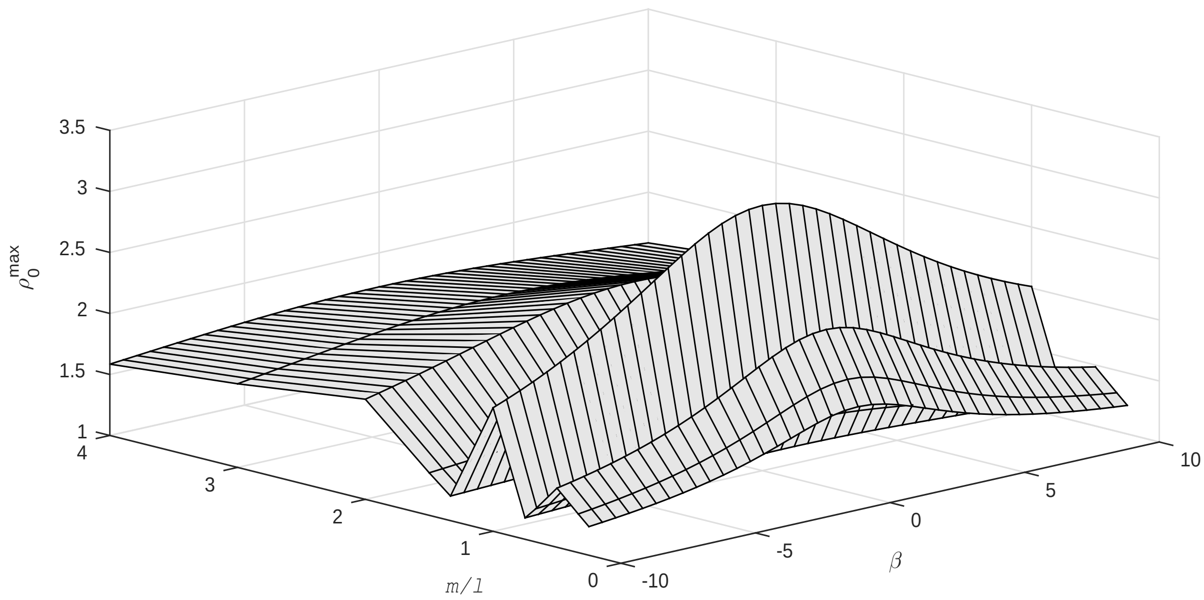

FIG. 5. (Color online) ρ_0^{max} for $\beta \in [-10, 10]$ and $\frac{m}{l}$ with both m and l ranging from 1 to 4.

influence of a stochastic entraining stimulus. In particular, entrainment is strongest when the natural period of the oscillator matches the period of the entraining stimulus, but entrainment can also occur when the ratio of these periods is approximately equal to a ratio of small integers.

What is significant here is that these results are obtained directly from the stochastic model, in a suitable distinguished limit. The noise in our system is intrinsic to the system itself, and we model it that way. There is also noise in the entraining signal, and it, too is modeled directly as given. At no point in our analysis or simulation do we consider noise as a separate stochastic process interacting with an otherwise deterministic system. We believe that this point of view, with its emphasis on intrinsic noise, will become increasingly important in the mathematical modeling of biological systems in which fluctuations play an important role.

ACKNOWLEDGMENTS

We thank Adam Stinchcombe for preliminary work on this problem. GW was supported by a MacCracken Fellowship from New York University. CSP was supported in part by the Systems Biology Center New York under NIH grant P50-GM071558.

Appendix

Let $p = p_0$ be fixed and $S = (m + \frac{\beta}{n})\, T$, where $m \in \mathbb{Z}^+$, $\beta \in \mathbb{R}$. By Equations (15) and (18), for large n

$$\hat{P}_k(t) \sim \frac{p_0\, e^{-i2\pi k \frac{t}{T}}\, e^{-\frac{2\pi^2 k^2}{n}\frac{t}{T}}}{1-(1-p_0)\, Q} \tag{A.1}$$

where

$$Q \sim e^{-i2\pi k (m+\frac{\beta}{n})}\, e^{-\frac{2\pi^2 k^2}{n}(m+\frac{\beta}{n})} \tag{A.2}$$

$$= e^{-i2\pi k \frac{\beta}{n}}\, e^{-\frac{2\pi^2 k^2}{n}(m+\frac{\beta}{n})} \tag{A.3}$$

$$\sim (1 - i2\pi k \frac{\beta}{n})\, (1 - \frac{2\pi^2 k^2 m}{n}) \tag{A.4}$$

$$\sim 1 - \frac{1}{n}\, (i2\pi k\beta + 2\pi^2 k^2 m) \tag{A.5}$$

$$\Rightarrow 1 - (1-p_0)\, Q \sim \frac{1}{n}\, (i2\pi k\beta + 2\pi^2 k^2 m - p_0) + p_0 \tag{A.6}$$

Thus by Equation (A.1),

$$\lim_{n\to\infty} \hat{P}_k(t) = e^{-i2\pi k \frac{t}{T}} \tag{A.7}$$

Following the notations of $\rho(x,t)$ and $\rho_0(x)$ from Equations (26) and (34), respectively, we get

$$\rho_0(x) = \sum_{k=-\infty}^{\infty} e^{i2\pi k x} \tag{A.8}$$

$$= \sum_{k=-\infty}^{\infty} \delta(x-k) \tag{A.9}$$

Clearly, from this formula, ρ_0^{max} is infinity and the result will be perfect entrainment.

[1] S. H. Strogatz, *Nonlinear Dynamics and Chaos* (Perseus Books, Cambridge, MA, 1994).
[2] G. B. Ermentrout and J. Rinzel, Am. J. Physiol. **246**, R102 (1983).
[3] G. B. Ermentrout, J. Math. Biol. **29**, 571 (1991).
[4] F. C. Hoppensteadt and J. P. Keener, J. Math. Biol. **15**, 339 (1982).
[5] B. W. Knight, J. Gen. Physiol. **59**, 734 (1972).
[6] Z. Schuss, SIAM J. Rev. **22**, 119 (1980).
[7] L. Markus and A. Weerasinghe, J. Differ. Equations **71**, 288 (1988).
[8] X. Mao, *Stochastic Differential Equations and Applications* (Horwood Pub., Chichester, 2008).
[9] H. Risken, *The Fokker-Planck Equation* (Springer-Verlag, Berlin, Heidelberg, 1996).
[10] D. B. Forger and C. S. Peskin, Proc. Natl. Acad. Sci. USA **100**, 14806 (2003).
[11] A. Goldbeter, Proc. R. Soc. Lond. B. **261**, 319 (1995).
[12] D. Gonze, J. Halloy, and A. Goldbeter, J. Biol. Phys. **28**, 637 (2002).
[13] J. C. Leloup and A. Goldbeter, Proc. Natl. Acad. Sci. USA **100**, 7051 (2003).
[14] D. B. Forger and C. S. Peskin, Proc. Natl. Acad. Sci. USA **102**, 321 (2005).
[15] D. T. Gillespie, J. Phys. Chem. **81**, 2340 (1977).
[16] D. Gonze, J. Halloy, and A. Goldbeter, Proc. Natl. Acad. Sci. USA **99**, 673 (2002).