Ticks of a Random clock

P. Jung[1] and P. Talkner[2,a]

[1] Department of Physics and Astronomy, Ohio University, Athens, USA
[2] Institut für Physik Universität Augsburg, 86135 Augsburg, Germany

Abstract. A simple way to convert a purely random sequence of events into a signal with a strong periodic component is proposed. The signal consists of those instants of time at which the length of the random sequence exceeds an integer multiple of a given number. The larger this number the more pronounced the periodic behavior becomes.

1 Introduction

A clock, regardless whether it is an old-fashioned model with a balance spring, a more modern one with a small quartz crystal, or a highly precise atomic clock using hyperfine transitions of Rubidium or Caesium atoms, typically converts a periodic motion of higher frequency into another periodic motion, say that of a pointer, with a lower frequency. We ask here if a periodic signal is essential or whether one can transform a random sequence of events into a periodic signal, or at least into a signal with a strong periodic contribution. We shall discuss this question using the example of a bucket whose water content increases by equally large drops falling randomly into it. Once the water level of the bucket has reached a certain height, the position of the bucket becomes unstable. The bucket turns, releases its water content and moves back into the position in which it can again collect water. The question is whether there are conditions under which the tilting of the bucket happens at almost regular times.

This question of periodicity of a machine in spite of its parts being random has emerged in the context of the mechanism of intracellular calcium oscillations [1]. Intracellular calcium is observed in many cell types, e.g. in astrocytes [2], myocytes, hepatocytes to name just a few, and has important physiologic signaling functions (for a review, see e.g. [3,4]). In recent research it has been found that cellular calcium signals are composed of numerous local calcium release events from internal stores through small clusters of release channels. These local calcium signals, due to the small numbers of channels recruited, *are stochastic in nature* and spatially and temporally limited events. Through the mechanism of calcium-induced calcium release, however, released calcium through one cluster of channels can diffuse to another cluster and induce their opening and subsequent release of calcium. This way, a wave of calcium is generated which can spread through the entire cell. As intracellular calcium waves are often periodic in time, the question arose how purely stochastic events can lead to temporally periodic wave patterns (i.e. a *calcium clock*)(see e.g. [5,6]). The first conceptual model derived from detailed experimental analysis of puffs and subsequent waves [7] asserted that waves are nucleated by an increasing number of stochastically occurring calcium puffs prior to the wave. Falcke et al. [6] analyzed series of calcium spikes of astrocytes and other cells arriving at the conclusion that the spikes are stochastic. Based on a simple model, in which waves are nucleated with a

[a] e-mail: peter.talkner@physik.uni-augsburg.de

time-dependent nucleation rate which vanishes right after a wave is elicited for channel inhibition and exponentially approaches a steady value, they predicted that waves can emerge with some periodicity [8]. Our more general model for a stochastic clock is closer to the original conceptual model for calcium waves put forward in [7]: Puffs (not waves) are generated purely stochastically with a *homogeneous* rate and a wave occurs at the time a given number of puffs have been fired. We will show that waves with a certain periodicity emerge from such a model without any further assumption.

2 When the bucket tilts

If the drops fall independently of each other into the bucket, the times t between subsequent drops are mutually independent and can be characterized by an exponential law

$$P(t) = e^{-\lambda t}\,, \tag{1}$$

specifying the probability that up to time t no drop has fallen yet [9]. Here λ denotes the rate at which drops fall. The probability density function (pdf) of a drop falling at time t immediately follows as

$$\rho(t) = -\frac{dP(t)}{dt} = \lambda e^{-\lambda t}. \tag{2}$$

We assume that exactly N drops are required to fill the bucket and let it tilt. With the mutual independence of "dry" times between drops the pdf $\rho_N(\tau)$ of the filling times τ becomes the convolution of N exponential distributions which is known to be a Gamma distribution with scale parameter λ and shape parameter N [10], i.e. it is

$$\rho_N(\tau) = \lambda \frac{(\lambda\tau)^{N-1}}{(N-1)!} e^{-\lambda\tau}. \tag{3}$$

This is a basic result of renewal theory [11]. In passing we note that the mean value and the variance of the Gamma distribution both are proportional to the shape parameter. Strictly speaking we have

$$\langle\tau\rangle = \lambda N\,, \tag{4}$$

and

$$\sigma_\tau^2 \equiv \langle(\tau - \langle\tau\rangle)^2\rangle = \lambda^2 N. \tag{5}$$

More generally, the characteristic function $\Theta_N(\omega)$ of the filling times becomes

$$\begin{aligned}\Theta_N(\omega) &= \int_0^\infty d\tau e^{i\omega\tau} \rho_N(\tau) \\ &= \left(1 - i\frac{\omega}{\lambda}\right)^{-N}.\end{aligned} \tag{6}$$

With the assumption that the time needed to empty the bucket can be neglected in comparison to the mean time between two drops, the bucket tilts at subsequent times t_n following from

$$t_{n+1} = t_n + \tau_n,\ t_0 = 0\,, \tag{7}$$

or equivalently

$$t_n = \sum_{k=0}^{n-1} \tau_k\,, \tag{8}$$

where the increments τ_n are the times it takes to refill the bucket after it was emptied at time t_n and hence are distributed according to the Gamma distribution $\rho_N(\tau)$.

3 Mean value and correlation function of the signal

The sequence of times t_n constitutes a signal $S(t)$ given by

$$S(t) = \sum_{n=1}^{\infty} \delta(t - t_n)\,. \tag{9}$$

As most important characteristics, we determine the mean value, the auto-correlation function and the power spectral density of this signal and discuss the dependence of these quantities on the number N required to trigger a tick of the clock.

3.1 Mean value

The mean value of the signal is determined by

$$\langle S(t)\rangle = \sum_{n=1}^{\infty} \langle \delta(t - t_n)\rangle, \tag{10}$$

where

$$\begin{aligned}\langle \delta(t - t_n)\rangle &= \langle \delta(t - \sum_{k=0}^{n-1} \tau_k)\rangle \\ &= \int d^n\tau \delta(t - \sum_{k=0}^{n-1} \tau_k) \prod_{k=0}^{n-1} \rho_N(\tau_k) \\ &= \rho_N^{\otimes n}(t).\end{aligned} \tag{11}$$

The n-fold convolution of $\rho_N(\tau)$, $\rho_N^{\bigotimes n}(t)$, transforms into the n-th power of the characteristic function upon Fourier transformation, $\Theta_N^n(\omega) = 1/(1 + i\omega/\lambda)^{(N+1)n}$. The inverse Fourier transformation then yields

$$\rho_N^{\otimes n}(t) = \lambda \frac{(\lambda t)^{Nn-1}}{(Nn-1)!} e^{-\lambda t}. \tag{12}$$

Combining with Eq. (10) and performing the sum by means of Ref. [12] one obtains

$$\begin{aligned}\langle S(t)\rangle &= \lambda e^{-\lambda t} \sum_{n=1}^{\infty} \frac{(\lambda t)^{Nn-1}}{(Nn-1)!} \\ &= \lambda(\tau t)^{N-1} e^{-\lambda t} \sum_{n=0}^{\infty} \frac{(\lambda t)^{Nl}}{[Nl + N - 1]!} \\ &= \frac{\lambda}{N} \sum_{k=1}^{N} \cos\left[\frac{2\pi k}{N} + \lambda t \sin\frac{2\pi k}{N}\right] \exp\left[-\lambda t \left(1 - \cos\frac{2\pi k}{N}\right)\right].\end{aligned} \tag{13}$$

At large times the term with $k = N$ dominates the sum which then simplifies to the single exponential $e^{\lambda t}$. Therefore the average signal approaches a constant value at large times, which

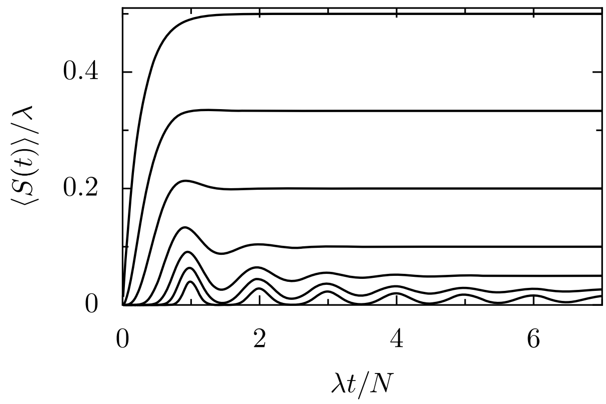

Fig. 1. The average signals $\langle S(t)\rangle/\lambda$ as a function of the scaled time $\lambda t/N$ for $N = 2, 3, 5, 10, 20, 40$ and $N = 100$ (from top to bottom). With increasing N the overall value of the average signal decreases and at the same time develops an increasingly pronounced oscillatory structure.

becomes

$$S_\infty \equiv \lim_{t\to\infty} \langle S(t)\rangle = \frac{\lambda}{N}\,. \tag{14}$$

For large N, the mean value $\langle S(t)\rangle$ exhibits damped oscillations (see Fig. 1) with a decreasing damping constant with increasing N. At large times the frequency and the damping rate of this damped oscillatory motion are given by $\sin 2\pi/N \approx 2\pi/N$ and $1 - \cos(2\pi/N) \approx 2\pi^2/N^2$, respectively where the approximate results apply for large values of N.

3.2 Correlation function

The correlation function of the signal is defined as

$$\begin{aligned}\langle S(t+s)S(t)\rangle &= \sum_{n,m} \langle \delta(t+s-t_n)\delta(t-t_m)\rangle \\ &= \sum_{n,m} \langle \delta(s-t_n+t_m)\delta(t-t_m)\rangle \\ &= \delta(s)\sum_n \langle \delta(t-t_m)\rangle + {\sum_{n,m}}' \langle \delta(s-t_n+t_m)\delta(t-t_m)\rangle,\end{aligned} \tag{15}$$

where we split the double sum into its diagonal and off-diagonal contributions. Here the prime at the double sum indicates the omission of all terms with $n = m$. In the following we restrict ourselves to positive values of the time laps s. Since we are mainly interested in the asymptotic limit of large times t in which the correlation function becomes symmetric in s this does not present any restriction of generality. The first term on the right hand side of the last line of Eq. (15) can be expressed in terms of the mean value of the signal, see Eq. (10). We now consider the second term on the rhs of Eq. (15). Since $s > 0$, t_n must be larger than t_m and hence only terms with $n > m$ contribute to the sum. These terms can be written as

$$\begin{aligned}\langle \delta(s-t_n+t_m)\delta(t-t_m)\rangle &= \left\langle \delta\left(s - \sum_{k=m}^{n-1}\tau_k\right)\delta\left(t-\sum_{k=0}^{m-1}\tau_k\right)\right\rangle \\ &= \left\langle \delta\left(s - \sum_{k=m}^{n-1}\tau_k\right)\right\rangle\left\langle\delta\left(t-\sum_{k=0}^{m-1}\tau_k\right)\right\rangle \\ &= \rho_N^{\otimes(n-m)}(s)\rho_N^{\otimes m}(t).\end{aligned} \tag{16}$$

They factorize because the sums of the increments τ_k entering the arguments of the two delta-functions run over disjoint sets and consequently are independent of each other. Hence, for positive delays s the signal correlation function becomes

$$\begin{aligned}\langle S(t+s)S(t)\rangle &= \langle S(t)\rangle\delta(s) + \sum_{n>m}\left\langle\delta\left(s-\sum_{k=m}^{n-1}\tau_k\right)\right\rangle\left\langle\delta\left(t-\sum_{k=0}^{m-1}\tau_k\right)\right\rangle \\ &= \langle S(t)\rangle\delta(s) + \sum_{l=1}^{\infty}\left\langle\delta\left(s-\sum_{k=0}^{l-1}\tau_k\right)\right\rangle\sum_{m=1}^{\infty}\left\langle\delta\left(t-\sum_{k=0}^{m-1}\tau_k\right)\right\rangle \\ &= \langle S(t)\rangle(\delta(s)+\langle S(s)\rangle). \end{aligned} \tag{17}$$

Since the first factor of the second sum on the right hand side of the first line, $\langle\delta(s-\sum_{k=m}^{n-1}\tau_k)\rangle$ only depends on $n-m$ one can rearrange this double sum such that it factorizes by introducing instead of n the index $l = n-m$ as new summation index.

In the limit of large times t the signal correlation function becomes

$$\begin{aligned}\langle S(s)S\rangle &= \lim_{t\to\infty}\langle S(t+s)S(t)\rangle \\ &= S_\infty(\delta(s)+\langle S(|s|\rangle), \end{aligned} \tag{18}$$

where the delay time may take any positive or negative value.

The power spectral density $\mathcal{S}(\omega)$ then follows as the Fourier transformation of the autocorrelation function. It becomes

$$\begin{aligned}\mathcal{S}(\omega) &= \int_{-\infty}^{\infty} ds e^{i\omega s}\langle(S(s)-S_\infty)(S-S_\infty)\rangle \\ &= \frac{\lambda}{N}\left[1+2\frac{q^N\cos N\varphi - 1}{q^{2N}+1-2q^N\cos N\varphi}\right], \end{aligned} \tag{19}$$

where

$$\varphi = \arcsin\frac{\omega/\lambda}{\sqrt{1+(\omega/\lambda)^2}}, \tag{20}$$

$$q = \sqrt{1+(\omega/\lambda)^2}\,. \tag{21}$$

For small frequencies ω the power spectral density can be expanded into a power series in ω/λ which up to the leading term is

$$\mathcal{S}(\omega) \approx \frac{\lambda}{N^2}\left[1+\frac{N^2}{12}\left(1-\frac{1}{N^2}\right)\left(\frac{\omega}{\lambda}\right)^2\right]. \tag{22}$$

Hence, the power spectral density has a pronounced minimum at $\omega = 0$. Figure 2 shows the power spectral density for different values of N. Most significantly, it exhibits peaks of the height $S(\omega_n) = \lambda/(\pi^2 n^2)$ at the frequencies $\omega_n = 2\pi(n/N)\lambda$ for large N and sufficiently small integers n. For a more detailed discussion see the Appendix A.

4 Discussion

The times when the bucket empties, i.e. the ticks of our clock, are random for small buckets which can contain only small numbers of drops. The power spectral density is relatively flat correspondingly. For larger buckets, the emptying times, although still random, acquire some periodicity, leading to peaks in the power spectral density at frequencies $f_n = \omega_n/(2\pi) = n(\lambda/N)$. The first peak at f_1 corresponds to the average time it takes for a bucket that can

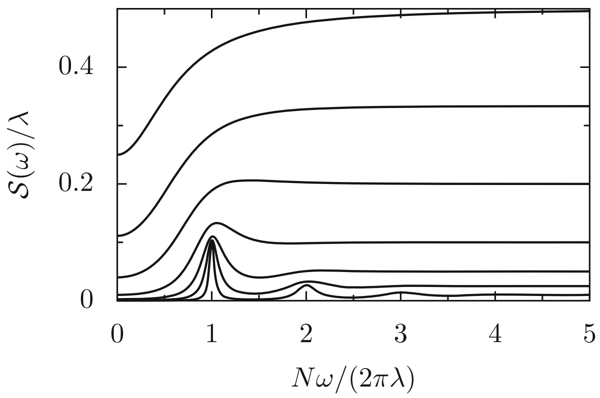

Fig. 2. The power spectral density $\mathcal{S}(\omega)/\lambda$ as a function of $N\omega/(2\pi\lambda)$ for $N = 2, 3, 5, 10, 20, 40, 100$ from top to bottom. With increasing N the power spectral density decreases both in the region between $\omega = 0$ and the first peak, between successive peaks and in the asymptotic region for large values of ω. At the same time the peaks narrow and approach heights independent of N.

carry N drops to fill, i.e. $\langle\tau\rangle = N/\lambda$. Quite surprising, if the bucket is big enough, peaks at higher harmonics $f_n = n\lambda/N$ indicate preferred bucket emptying times $\tau_n = \lambda(N/n)$ smaller than $\langle\tau\rangle$. The peak heights of the power spectral density, however, remain finite indicating that the clock will not tick perfectly periodic. In fact, the mean time interval between consecutive spikes, i.e. $\langle\tau\rangle = N/\lambda$ and the variance, i.e. $\sigma^2 = \langle\tau^2\rangle - \langle\tau\rangle^2 = N/\lambda^2$ are proportional to N, indicating random behavior.

The way our random clock model works is similar to the principle action of the integrate-and-fire model of a neuron [1]: The filling of the bucket by a prescribed number of drops corresponds to the charging of a membrane capacitance by a current up to a threshold value of the membrane voltage. The ticks of the clock relate to the firing of the neuron. While in the integrate-and-fire model the charging current is mostly assumed as a continuous process, which may be deterministic or random, the drops of our clock discretely fall one after the other in a random way. A steady discharging of the membrane taken into account in leaky integrate-and-fire models would correspond to a steady loss rate of the water content of the bucket. This latter effect though is not taken into account in our model.

Finally, we would like to connect our “random clock” to the emergence of calcium oscillations. To this end, we note that the probability density of dry periods i.e. time intervals in between consecutive ticks, can equivalently be characterized by a “hazard”, or time dependent rate defined as the negative logarithmic derivative of the probability $P_N(\tau) = \int_\tau^\infty \rho_N(s)ds$ of an uninterrupted dry period of duration τ. This probability can be expressed as

$$P_N(\tau) = \frac{\lambda}{(N-1)!}\Gamma(N, \lambda\tau), \tag{23}$$

where $\Gamma(a, z)$ denotes the incomplete Gamma-function [13]. The time dependent rate $k_N(\tau)$ then becomes

$$\begin{aligned} k_N(\tau) &= -\frac{d \ln P_N(\tau)}{d\tau} \\ &= \lambda(\lambda\tau)^{N-1}e^{-\lambda\tau}/\Gamma(N, \lambda\tau), \end{aligned} \tag{24}$$

and is shown in Fig. 3. It vanishes at $\tau = 0$ and stays very small up to times $\tau = N/\lambda$ where it rapidly starts to grow. Asymptotically it approaches the constant value λ as $k_N(\tau) \approx \lambda(1 - (N-1)/(\lambda\tau))$. This time-dependent hazard-rate corresponds to the time-dependent nucleation rate for the calcium waves in the model in [6,8]. The characteristic times-scale of our hazard rate Eq. (24), i.e. N/λ is the inverse frequency of the fundamental harmonic in the power spectral density, i.e. the time-scale in the hazard rate determines the periodicity of the

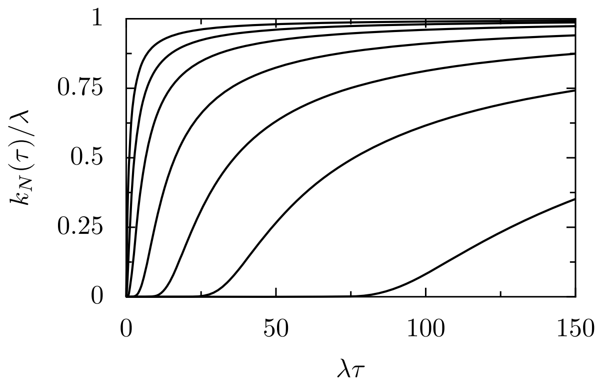

Fig. 3. The time dependent rate $k_N(\tau)/\lambda$ as a function of the dimensionless time λt for $N = 2, 3, 5, 10, 20, 40, 100$ from top to bottom. Note that the refractory time during which the rate is almost zero grows with N. Asymptotically the rate approaches the value λ being independent of N.

calcium clock. Hence, by starting with an ad-hoc time-dependent hazard rate (as in [6,8]), the resulting periodicity is dictated by this choice. In our model, however, interpreted in the context of calcium signaling, the hazard rate in Eq. (24) is an *emerging feature of the stochastically generated calcium puffs* as originally proposed in [7].

We would like to thank our friend Lutz Schimansky-Geier for his continued efforts to investigate the interplay of noise and nonlinear dynamics. P.T. acknowledges financial support by the DFG project HA 1517/28-1. P.J. thanks the National Science Foundation for support through grant IOS-0744798.

Appendix A: Large N-asymptotics of the power spectral density

In order to discuss the mathematical properties of the power spectral density $\mathcal{S}(\omega)$ given by Eq. (19) it is convenient to use the angle φ defined by Eq. (20) as the independent variable instead of ω. One then obtains for the scaled power spectral density $F(\varphi)$ the expression

$$\begin{aligned} F(\varphi) &\equiv S(\lambda \tan\varphi)/\lambda \\ &= \frac{1-\cos^{2N}\phi}{N\,(1+\cos^{2N}\phi - 2\cos^{N}\phi\cos N\phi)}, \end{aligned} \tag{25}$$

where $\varphi \in (0, \pi/2)$. Replacing $\cos N\varphi$ by 1 one obtains the upper bound

$$\frac{1}{N}\frac{1+\cos^{N}\varphi}{1-\cos^{N}\varphi} \geq F(\varphi), \tag{26}$$

which touches $F(\varphi)$ at

$$\varphi_n = 2\pi n/N. \tag{27}$$

At these contact points the values of $F(\varphi_n)$ and the first two derivatives of $F(\varphi)$ are

$$F(\varphi_n) = \frac{1}{N}\frac{1+\cos^{N}\varphi_n}{1+\cos^{N}\varphi_n} \approx \frac{1}{\pi^2 n^2}, \tag{28}$$

$$\frac{dF(\varphi_n)}{d\varphi} = -\frac{\sin\varphi_n\cos^{N-1}\varphi_n}{(1-\cos^{N}\varphi_n)^2} \approx -\frac{N}{\pi^3 n^3}, \tag{29}$$

$$\frac{d^2F(\varphi_n)}{d\varphi^2} = -\frac{4\cos^N\varphi_n\left[N\cos 2\varphi_n\left(1+\cos^N\varphi_n\right)-\left(1-\cos^N\varphi_n\right)\right]}{\left(1+\cos 2\varphi_n\right)\left(1-\cos^N\varphi_n\right)^3} \approx -\frac{N^4}{2\pi^6 n^6}, \qquad (30)$$

where we indicated the asymptotic behavior for large values of N. The parabolic approximation to $F(\varphi)$ in the vicinity of φ_n then has a maximum at $\varphi_n^* = \varphi_n - 2\pi^3n^3/N^3$ with $F(\varphi_n^*) = (1+2\pi^3n^3/N^3)/(\pi^2n^2)$ for large N including leading corrections in n/N. For $n/N \ll 1$ the terms of order n^3/N^3 can be neglected and hence in the large N limit the maxima of the power spectral density are located at $\omega_n \approx \lambda\varphi_n = 2\lambda\pi n/N$ and take the values $S(\omega_n) = \lambda/(\pi^2n^2)$.

References

1. B. Lindner, J. Garcia-Ojalvo, A. Neiman, L. Schimansky-Geier, Phys. Rep. **392**, 321 (2004)
2. A.H. Cornell-Bell, S.M. Finkbeiner, M.S. Cooper, S.J. Smith, Science **247**, 470 (1990)
3. D.E. Clapham, Cell **131**, 1047 (2007)
4. M.J. Berridge, M.D. Bootman, H. Llewelyn Roderick, Nature Rev. Mol. Cell Biol. **4**, 517 (2003)
5. J.W. Shuai, P. Jung, Proc. Natl. Acad. Sci. U. S. A. 100:506-10. (2003).(2001)
6. A. Skupin, H. Kettenmann, U. Winkler, M. Wartenberg, H. Sauer, S.C. Tovey, C.W. Taylor, M. Falcke, Biophys. J. **94**, 2404 (2008)
7. J.S. Marchant, I. Parker, EMBO J. **20**, 62 (2001)
8. A. Skupin, M. Falcke, Chaos **19**, 037111 (2009)
9. For such a purely random process the conditional probability $P(t|s)$ of a dry period of duration τ conditioned on a preceding dry period of length s is independent of the duration s. Hence, $P(t|s) = P(t)$. On the other hand, Bayes rule implies $P(t|s) = P(t+s)/P(s)$ and therefore one obtains with $P(t+s) = P(t)P(s)$ a functional equation with exponential functions as the only continuous solutions [10]
10. W. Feller, *An Introduction to Probability Theory and Its Applications*, Vols. I and II (John Willey, New York, 1966)
11. D.R. Cox, *Renewal Theory* (Methuen, London, 1962)
12. A.B. Prudnikov, Yu.A. Brychkov, O.I. Marichev, *Integrals and Series*, Vol. 1 (Gordon and Breach, New York, 1992), p. 703, formula 5.27.1
13. M. Abramowitz, I.A. Stegun, *Handbook of Mathematical Functions* (Natitional Bureau of Standards, Washington, 1972)