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Signatures of nonlinearity in single cell noise-induced oscillations

Philipp Thomas [a,b,c], Arthur V. Straube [c], Jens Timmer [d], Christian Fleck [f,g], Ramon Grima [a,e,*]

[a] School of Biological Sciences, University of Edinburgh, United Kingdom
[b] School of Mathematics, University of Edinburgh, United Kingdom
[c] Department of Physics, Humboldt University of Berlin, Germany
[d] BIOSS Centre for Biological Signalling Studies, University of Freiburg, Germany
[e] Freiburg Institute for Advanced Studies, University of Freiburg, Germany
[f] Laboratory for Systems and Synthetic Biology, Wageningen University, Netherlands
[g] Centre for Biological Systems Analysis (ZBSA), University of Freiburg, Germany

HIGHLIGHTS

- We develop a general theory of noise-induced oscillations in subcellular volumes.
- The theory provides the power spectrum in closed form for any monostable network.
- The spectra close to a Hopf bifurcation have three universal features.
- The predicted features are seen in experimental single cell data.
- Simulations of circadian and mitotic oscillators verify the theory's accuracy.

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ABSTRACT

A class of theoretical models seeks to explain rhythmic single cell data by postulating that they are generated by intrinsic noise in biochemical systems whose deterministic models exhibit only damped oscillations. The main features of such noise-induced oscillations are quantified by the power spectrum which measures the dependence of the oscillatory signal's power with frequency. In this paper we derive an approximate closed-form expression for the power spectrum of any monostable biochemical system close to a Hopf bifurcation, where noise-induced oscillations are most pronounced. Unlike the commonly used linear noise approximation which is valid in the macroscopic limit of large volumes, our theory is valid over a wide range of volumes and hence affords a more suitable description of single cell noise-induced oscillations. Our theory predicts that the spectra have three universal features: (i) a dominant peak at some frequency, (ii) a smaller peak at twice the frequency of the dominant peak and (iii) a peak at zero frequency. Of these, the linear noise approximation predicts only the first feature while the remaining two stem from the combination of intrinsic noise and nonlinearity in the law of mass action. The theoretical expressions are shown to accurately match the power spectra determined from stochastic simulations of mitotic and circadian oscillators. Furthermore it is shown how recently acquired single cell rhythmic fibroblast data displays all the features predicted by our theory and that the experimental spectrum is well described by our theory but not by the conventional linear noise approximation.

1. Introduction

Cellular rhythms are ubiquitous throughout many tissues of the body (Mohawk et al., 2012). The central pacemaker of the mammalian circadian clock located in the suprachiasmatic nucleus is thought to be entrained to a light-dark cycle and to reset the expression of clock genes in peripheral tissues in vivo (Mohawk et al., 2012). For example, 10% of the transcriptome and 20% of the proteome in mouse liver are expressed rhythmically (Panda et al., 2002; Reddy et al., 2006). Similar fractions have been found to be under circadian control in the human metabolome indicating that rhythmic expression of clock genes controls many downstream pathways (Dallmann et al., 2012).

In the absence of pacemaker control, isolated peripheral clocks function as sustained but independently phased cell autonomous 24 h-oscillators under constant light conditions (Welsh et al., 2004; Nagoshi et al., 2004). In consequence initially synchronized

* Corresponding author at: C. H. Waddington Building, Mayfield Road, University of Edinburgh, EH9 3JD, UK. Tel.: +44 131 651 9060.
E-mail address: Ramon.Grima@ed.ac.uk (R. Grima).

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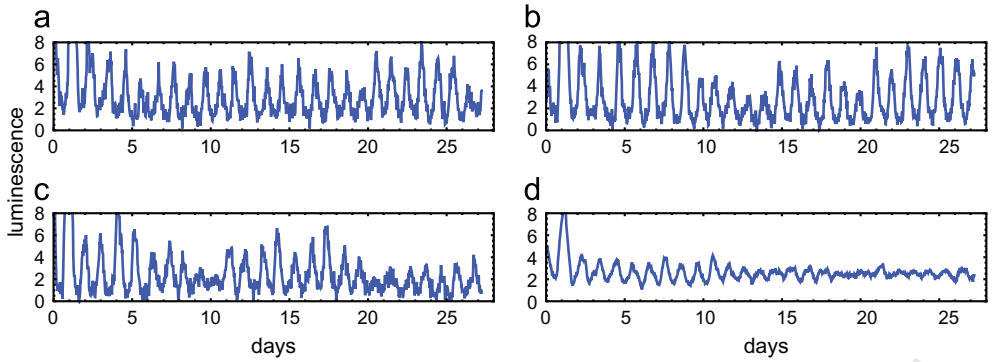

Fig. 1. Single cell circadian oscillations in individual fibroblast cells over two weeks after medium change reproduced from experimental dataset S1 in Leise et al. (2012). (a–c) Single time course of protein luminescence of first three individual fibroblast cells shows sustained oscillations. (d) Population average over the first 20 cells shows a dampening of the oscillations due to dephasing of individual cell rhythms.

cell cultures display only damped oscillations on the ensemble level due to a gradual dephasing of individual cellular clocks (Welsh et al., 2004; Westermark et al., 2009). Fig. 1 illustrates this phenomenon by comparing three time traces of protein luminescence (a–c) from single fibroblast cells against the averaged response of a culture of 20 cells shown in (d). The images have been reproduced from dataset S1 in Leise et al. (2012).

It is still under debate what is the underlying single cell mechanism responsible for producing oscillations. In the absence of noise, populations of synchronized self-sustained oscillators exhibit in-phase oscillations of constant amplitude while populations of damped oscillators show an in-phase decaying amplitude. In both cases, taking into account the molecular fluctuations stemming from the stochastic nature of the underlying biochemical reactions leads to a population of cells with sustained (noisy) oscillations and with cell-to-cell variation in the phase. Hence presently experimental single cell data can be explained by both noisy self-sustained and damped oscillator models (Westermark et al., 2009).

The fact that molecular noise induces a deterministically damped oscillator to exhibit sustained oscillations has led to this phenomenon being called noise-induced oscillations (NIOs) (Vilar et al., 2002; McKane et al., 2007). The amplitude of these oscillations is proportional to $1/\sqrt{N}$ where N is the mean number of molecules. Hence NIOs have been deemed important for reactions involving a typically small number of molecules such as those occurring inside cells (Grima and Schnell, 2008). Similar mechanisms to generate NIOs have been described as coherence resonance with non-excitable dynamics in the contexts of epidemics (Kuske et al., 2007), predator–prey interactions (Rozenfeld et al., 2001) and lasers models (Ushakov et al., 2005).

The power spectrum of concentration fluctuations has been the main measure used to quantify NIOs, both experimentally and theoretically, to date (Gang et al., 1993; Hou and Xin, 2003; Welsh et al., 2004; Davis and Roussel, 206; Li and Lang, 2008; Geva-Zatorsky et al., 2010; Ko et al., 2010). Briefly speaking the power spectrum measures how the square amplitude of a signal is distributed with frequency. In particular, peaks in the power spectrum indicate the presence of NIOs. For systems composed of purely first-order reactions, exact expressions for the power spectrum of concentration fluctuations can be derived from the chemical master equation (CME) (the accepted mesoscopic description of biochemical kinetics) (Warren et al., 2006; Simpson et al., 2004). However, most biochemical systems of interest do not fall in the latter category since they are composed of a large number of bimolecular reactions arising from oligomer binding, cooperativity, allostery or phosphorylation of proteins (Novák and Tyson, 2008). A popular means to obtain approximate expressions for the power spectra of systems composed of both unimolecular and bimolecular reactions is the linear noise approximation (LNA) of the CME (Van Kampen, 1976; Dauxois et al., 2009; McKane et al., 2007; Qian, 2011; Toner and Grima, 2013) whereby the probability distribution solution of the CME is approximated by a Gaussian. It is, however, the case that the LNA provides a good approximation to the CME only in the limit of large volumes at constant concentrations, i.e., the limit of large molecule numbers. Given that molecule numbers of several key intracellular players are in the range of few tens to few thousands (Schwanhäusser et al., 2011), it is plausible that the predictions of the LNA maybe limited in scope for biological systems. Indeed recent studies (Grima, 2009, 2010, 2012; Thomas et al., 2010; Ramaswamy et al., 2012) have shown that the mean concentrations and variances of interacting chemical species present in low molecule number can be considerably different than those given by the LNA; these effects originate from the combination of intrinsic noise and nonlinearity in the law of mass action. Similarly analytical studies of two-variable epidemic (Chaffee and Kuske, 2011) and predator–prey models (Scott, 2012) revealed NIOs with more than one frequency that are not captured by linear analysis. While it is clear that the LNA must miss some of the crucial features of single cell NIOs, athorough investigation of these effects has not been carried out to-date.

In this paper we obtain the leading order correction to the LNA's prediction of the power spectrum of the fluctuations for a general biochemical reaction pathway whose corresponding deterministic system is just below a super-critical Hopf bifurcation. We show that this novel nonlinear contribution to the power spectrum yields additional peaks at zero frequency and at twice the frequency of the peak predicted by the LNA. The analytical results are verified by comparison with experimental single cell data of rhythmic fibroblast cells and with detailed stochastic simulations of an oscillator controlling mitosis and of a transcriptional feedback oscillator.

2. Preliminaries: linear theory of noise-induced oscillations

2.1. The standard description of stochastic chemical kinetics

We consider a general chemical system consisting of a number N of distinct chemical species interacting via R chemical reactions of the type

$$s_{1j}X_1 + \cdots + s_{Nj}X_N \xrightarrow{k_j} r_{1j}X_1 + \cdots + r_{Nj}X_N \tag{1}$$

occurring in a volume of mesoscopic size Ω. Here j is an index running from 1 to R, X_i denotes chemical species i, s_{ij} and r_{ij} are the stoichiometric coefficients and k_j is the rate constant of the jth reaction. Under well-mixed conditions there are two descriptions

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