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Variability and degradation of homeostasis in self-sustained oscillators

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ABSTRACT

Homeostasis is known to be absolutely critical to the sustainability of living organisms. At the heart of homeostasis are various feedback loops, which can control and regulate a system to stay in a most favourable stable state upon the influence of various disturbance. While variability has emerged as a key factor in sustainability, too much variability could however be detrimental. It is thus absolutely crucial to understand the effect of fluctuation in different feedback loops. While modelling technique has achieved a great advancement to understand this issue, too a complicated model however often prevents us from disentangling different many processes.

Here, we propose a novel model to gain a key insight into the effect of variability in feedback on self-sustained oscillation. Specifically, by taking into account variation in model parameters for self-excitation and nonlinear damping, corresponding to positive and negative feedback, respectively, we show how fluctuation in positive or negative feedback weakens the efficiency of feedback and affects self-sustained oscillations, possibly leading to a complete breakdown of self-regulation. While results are generic and could be applied to different self-regulating systems (e.g. self-regulation of neuron activity, normal cell growth, etc.), we present a specific application to heart dynamics. In particular, we show that fluctuation in positive feedback can lead to slow heart by either amplitude death or oscillation death pathway while fluctuation in negative feedback can lead to fast heart beat.

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1. Introduction

Homeostasis is known to be absolutely critical to the sustainability of living organisms (e.g. [1]). Simply put, it means 'not too much, not too little, but just right.' More technically, it represents the ability of a system which can control and regulate itself to stay in a most favourable stable state upon the influence of various disturbance. This is entailed by the presence of two (or more) opposing and complementary forces (or requirements) in a system and by the adjustment of these forces when perturbed to restore a subtle balance through different positive or negative feedback loops. Self-regulation breaks down when a system is no longer under the control of such feedback mechanism, e.g., when one of the forces is overpowered by the other. For instance, normal cells have the ability of self-regulating their growth by maintaining the balance between growth and death, and its breakdown can lead to the overgrowth of cells and consequently tumour cells. Tumour cells can thus result not only from the loss of the ability of inhibiting growth (e.g. the loss of tumour suppressor genes) but also from the activation of uncontrolled growth factor (e.g. the activation of oncogenes) [2].

Another interesting example is self-regulation of neural activity where the balance between excitatory and inhibitory neurons is crucial for the maintenance of normal function of neuron. Either the over-excitation of excitatory neuron or the under-activation of inhibitory of neuron can lead to abnormal brain activity such as eclipse [3]. One more, but not the last, example would be a normal function of heart and heart rhythm as a result of self-regulation, and this will be of our main focus regarding application of our results later in this paper. With myriad of similar examples found in living organisms, self-regulation—a fundamental feature of homeostasis—is also at the heart of the emergence and maintenance of self-organised structures in many other complex systems, including large-scale flows, magnetic fields, and vortices in astrophysical and laboratory fluids, environments, and chemical reactions (e.g. see [4–8]).

Our work is motivated to understand how homeostasis is affected when one of the feedback loops becomes less effective due to stochasticity (fluctuation). While this can be caused by the intrinsic problem with chemical, biological, or physiological process itself (e.g. ion channels, gene expression, tissue damage, etc.), it also seems to be an inevitable consequence of a system involving

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multi-scale processes where fluctuation arises not only from the inhomogeneity and heterogeneity in the system but also from the environmental influence. In view of emerging evidence of variability and stochasticity and their relevance in many systems [5–13], it is timely to undertake a systematic investigation of this issue and quantify the effect of fluctuations in different feedback loops in a self-sustained oscillator.

To this end, we revisit the Van der Pol oscillator and study the effect of fluctuations in the model parameters for positive (self-amplification) and negative feedback (nonlinear damping). We introduce our model in Section 2. Section 3 reports on the effect of modulation in self-amplification. Section 4 presents the results on the modulation in nonlinear damping and the loss (i.e. degradation) of self-regulation. Section 5 discusses implications for heart dynamics. Conclusion and discussion are provided in Section 6. Appendix A and Appendix B include linear stability analysis utilising the Laplace transformation and Mathieu equation. Implication of our results for a long term behaviour in regards to heart variability is briefly discussed in Appendix C. We note that Sections 3 and 4 contain rather detailed mathematical analysis, and readers who are mainly interested in applications are welcome to go to Section 5 after skimming through Section 2.

2. Model

The Van der Pol oscillator is a prototypical mathematical model for self-sustained oscillations. Since originally proposed by Van der Pol to understand oscillations in nonlinear electric circuits, it has been developed further to investigate human heart and the stability of heart dynamics [14–24] and extended to different disciplines (e.g. biology, fluids/plasmas, environments, engineering) [25]. This model is described by the following ordinary differential equation (ODE):

$$\frac{d^2x}{dt^2} + (-\alpha + \beta x^2)\frac{dx}{dt} + \omega_0^2 x = 0. \tag{1}$$

Here, α and β are control parameters which represent the efficiency of amplification and nonlinear damping, respectively; ω_0 is the natural frequency of our system in the absence of the amplification and damping (e.g. when $\alpha = \beta = 0$). In terms of self-regulation mentioned previously, α and β represent the efficiency of positive and negative feedback, respectively; the positive feedback $-\alpha\frac{dx}{dt}$ leads to self-amplification (negative damping) with exponential growth of a linear solution while the negative feedback $\beta x^2\frac{dx}{dt}$ due to nonlinear damping limits the growth to a finite value.[1] When a system is well self-regulated, self-amplification and nonlinear damping act together in balance, and lead to self-sustained relaxation oscillation as a limit cycle. This is modelled by using constant positive values for α and β. However, when there is some dysfunction in either positive or negative feedback loop (see Section 4 for further discussion), its efficiency is reduced, causing a mismatch between the two (such as time delay in balance). We model this inefficiency in either feedback by including a time-varying part in α or β, respectively. As noted in Section 1, in continuous systems, Eq. (1) is a mean-field equation for the time-evolution of large-scale observables while control parameters capture the overall effect of unresolved small-scale dynamics.

To gain a key insight into the effect of fluctuations in α and β, we, for simplicity, take α and β to consist of the constant and oscillatory parts as follows:

$$\alpha = \mu_1 + \epsilon_1 \sin(\omega_1 t), \tag{2}$$

$$\beta = \mu_2 + \epsilon_2 \sin(\omega_1 t). \tag{3}$$

Here, μ_1 and μ_2 are constant parts; ϵ_1 and ϵ_2 are the modulation amplitude and ω_1 is the angular frequency of the modulation.[2] By using the unit where the natural frequency $\omega_0 = 1$ (see later), and by varying values of μ_1, μ_2, ϵ_1, ϵ_2, and ω_1, we investigate the effect of the periodic modulation of α and β on limit cycle oscillations in terms of frequency, amplitude, and variability. As our main purpose is to gain a key insight into implications for homeostasis (heart dynamics), we focus on qualitative behaviour of bifurcations upon the change of parameters, leaving a more detailed study on bifurcation sequence for future work. We explore the possibility of the breakdown of self-regulation and highlight a crucial role of efficient feedback in sustainability.

We should note that for nonlinear oscillators, the effect of fluctuations has been studied previously by many authors where fluctuations appear as multiplicative and/or additive noise. In particular, much attention has been paid to the case when the natural frequency ω_0 contains a random part, with a strong interest in parametric instability/resonance, and/or stochastic resonance. In contrast, the effect of fluctuation on parameters α and β has been studied much less (e.g. see [26,27]), which will be the focus of this paper. When α contains fluctuations, the Van der Pol equation is essentially similar to the Mathieu equation [27] as detailed in Appendix B. Also, previous works showed that a periodic additive forcing to the Van der Pol oscillator leads to devil's staircase with chaos sandwiched between adjacent period doublings (e.g. see [28]). In the following, we show that similar devil's staircase also results from a multiplicative noise.

3. Effect of fluctuation in positive feedback

Before presenting nonlinear results, we briefly comment on a linear oscillator in the absence of nonlinear term (i.e. $\beta = 0$) in Eq. (1) to help our understanding in general. As detailed in Appendix A and Appendix B, fluctuation in α can help a linear solution grow exponentially via parametric instability.[3] For $\alpha = \epsilon_1 \sin\omega_1 t$, the critical value of ϵ_1 for the onset of instability depends on ω_1, μ_1 and the frequency ω of excited mode. In Appendix A and Appendix B, we provide some detailed analysis on this parametric resonance and instability by a perturbative analysis on i) a linear dispersion relation derived from the interaction of the two adjacent modes coupled through the periodic modulation and ii) the standard Mathieu equation obtained after the transformation of variables. In particular, we show that the mode of the frequency $\omega = \omega_1/2$ becomes unstable for nonzero ϵ_1 when $\omega_1 = 2\omega_0$, the instability occurring for $2\omega_0 - \frac{1}{2}\epsilon_1 < \omega_1 < 2\omega_0 + \frac{1}{2}\epsilon_1$ (see Eqs. (12) and (24)). Note that while this analysis is strictly valid only for sufficiently small ϵ_1 (e.g. $\epsilon_1/2 < \omega_0$), it will prove useful in understanding a nonlinear response of our system to periodic modulation in the following subsections. For the purpose of elucidating the effect of the modulation in α, we keep $\beta = 1$ in the following subsections.

3.1. $\alpha = \epsilon_1 \sin(\omega_1 t)$ and $\beta = 1$

In the presence of nonlinear damping term ($\beta \neq 0$), an exponentially growing solution saturates to finite amplitude and the solution forms a limit cycle. We note that this limit cycle can be

[1] To be specific, for small $x < \sqrt{\alpha/\beta}$, $-\alpha + \beta x^2$ is negative leading to the growth of x while for large $x > \sqrt{\alpha/\beta}$, $-\alpha + \beta x^2$ becomes positive, causing damping of x.

[2] The signs of ϵ_1 and ϵ_2 do not affect our results.

[3] Note that effect of fluctuation in damping parameter tends to be more robust compared to that in fluctuation in oscillation frequency ω_0. For instance, the previous study [26] has shown that random (Gaussian) fluctuation μ_1 can give rise to the growth of the first moment (e.g. the average x), in contrast to the case of random frequency whose effect appears in higher order moment (e.g. $\langle x^2 \rangle$).

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