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The role of time delay in adaptive cellular negative feedback systems

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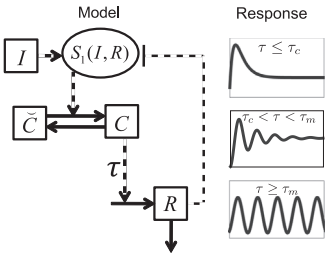
HIGHLIGHTS

- Time delay determines response in biochemical systems containing negative feedbacks.
- We give explicit delay thresholds beyond which the system response patterns change.
- Adaptation of yeast to osmotic stress is optimal.
- A slight change in time delay changes the structural stability of the NF-κB system.

GRAPHICAL ABSTRACT



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ABSTRACT

Adaptation in cellular systems is often mediated by negative feedbacks, which usually come with certain time delays causing several characteristic response patterns including an overdamped response, damped or sustained oscillations. Here, we analyse generic two-dimensional delay differential equations with delayed negative feedback describing the dynamics of biochemical adaptive signal-response networks. We derive explicit thresholds and boundaries showing how time delay determines characteristic response patterns of these networks. Applying our theoretical analyses to concrete data we show that adaptation to osmotic stress in yeast is optimal in the sense of minimizing adaptation time without causing oscillatory behaviour, i.e., a critically damped response. In addition, our framework demonstrates that a slight increase of time delay in the NF-κB system might induce a switch from damped to sustained oscillatory behaviour. Thus, we demonstrate how delay differential equations can be used to explicitly study the delay in biochemical negative feedback systems. Our analysis also provides insight into how time delay may tune biological signal-response patterns and control the systems behaviour.

1. Introduction

Negative feedback control is a fundamental and ubiquitous feature in biological systems (Alon, 2006, 2007; Legewie et al., 2008; Kholodenko et al., 2010; Tyson et al., 2003; Sauro and Kholodenko, 2004; Tsai et al., 2008) that can serve several objectives like, e.g., stabilizing the abundance of biochemical species (Hasty et al., 2002; Alon, 2006; Tyson et al., 2003; Sturm et al., 2010), inducing oscillations (Novak et al., 2007; Tsai et al., 2008; Elowitz and Leibler, 2000; Kholodenko, 2000), modifying response times (Alon, 2007; Macia et al., 2009) and mediating adaptation (Ma et al., 2009; Yi et al., 2000; Ni et al., 2009). In fact, negative feedbacks have been observed in a wealth of biological systems ranging from mammalian cell cycle (Novak et al., 2010; Ferrell et al., 2011) to bacterial adaptation (Kollmann et al., 2005; Yi et al., 2000) and stress response in mammals (Blüthgen, 2010) and yeast (Klipp et al., 2005; Schaber et al., 2012). Negative feedback control principles are even used to engineer artificial biological systems in bacteria and mammalian cells (Stricker et al., 2008; Elowitz and Leibler, 2000; Weber and Fussenegger, 2009).

Another just as wide spread feature of biological systems is time delay between a signal and its response, which comes about by the time needed to transcribe and translate biochemical information into cellular compounds, most importantly proteins

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and/or metabolites (Schaber et al., 2012, 2014; Hoffmann et al., 2002; Bernard et al., 2006).

It is standard theory that negative feedback in conjunction with time delay may lead to oscillatory behaviour (Goodwin, 1963; Griffith, 1968; Mahaffy and Pao, 1984). Oscillations brought about by delayed negative feedback (DNF) have been observed and analysed in a range of biological systems, e.g., the mammalian p53 system (Lahav et al., 2004; Geva-Zatorsky et al., 2006; Purvis et al., 2012), the NF-κB system (Hoffmann et al., 2002; Nelson et al., 2004; Ashall et al., 2009) or the Hes1 transcription factor (Bernard et al., 2006; Monk, 2003). However, the role of oscillations in these systems remains unclear.

Recently, two studies (Nguyen, 2012; Schaber et al., 2014) investigated stability and resistance of DNF systems modelled with three ordinary differential equations (ODEs). However, these studies provide no insight into how time delay influences the behaviour of these systems.

To explicitly study the role of time delay in DNF systems, we modelled a range of DNF systems using two-dimensional differential equations with time delay τ as a parameter. Architectures of considered models mimic biochemical networks differing in the kind of negative feedback and the placement of delay (Fig. 1 and Fig. S1 in the electronic supplementary material). By both theoretical and numerical analyses we are able to explicitly describe the role of time delay in shaping cellular response patterns of biochemical systems. Specifically, we derive explicit delay thresholds and boundaries beyond which the system's response patterns change leading to overdamped, damped oscillatory or sustained oscillatory behaviour.

We demonstrate that our theoretical results can be used to study concrete cellular systems both adaptive as well as oscillatory. This is based on the fact that our models are capable to recapitulate measured dynamics of these systems in a quantitative manner. Thus, our theoretical result can be parametrized to study real systems. We show that despite its simplicity our theoretical framework facilitates novel insights into the functioning of the HOG pathway mediating osmo-adaptation in yeast (Macia et al., 2009), as well as NF-κB oscillations in mammalian cells (Hoffmann et al., 2002). Specifically, we show that adaptation to osmotic stress in yeast is optimal in the sense of minimizing adaptation time without causing oscillatory behaviour, i.e., a critically damped response. Additionally, a slight increase of time delay in NF-κB system might induce a switch from damped to sustained oscillatory behaviour.

Thus, we demonstrate how delay differential equations can be used to explicitly study the role of delay in biochemical negative feedback systems, and, to this end, we derive specific theory and formulas. In addition, our analysis provides insight into how time delay may tune biological signal-response patterns and control the systems behaviour.

2. Materials and methods

2.1. Description of experimental data

We used previously published data to parametrize and analyse concrete cellular systems.

For the HOG pathway we took data from Macia et al. (2009) as described in Schaber et al. (2014). The dataset consists of time series of phosphorylated Hog1 under several hyper-osmotic shock conditions for wild-type yeast and different mutants for up to 2 h after hyper-osmotic shock.

The dataset that we used to parametrize the NF-κB model was extracted from Fig. S1 of the supplementary material of Hoffmann et al. (2002). This figure shows an oscillatory profile of nuclear NF-κB in IκBβ-/- IκBϵ-/- mice fibroblasts in response to TNF-α stimulation. For extracting data we used the software called Plot Digitizer located at http://plotdigitizer.sourceforge.net/. We loaded the figure in the software, calibrated axes and digitized values of the plot by clicking the mouse on each data point. The program automatically defined coordinates of data points, which we saved and re-used.

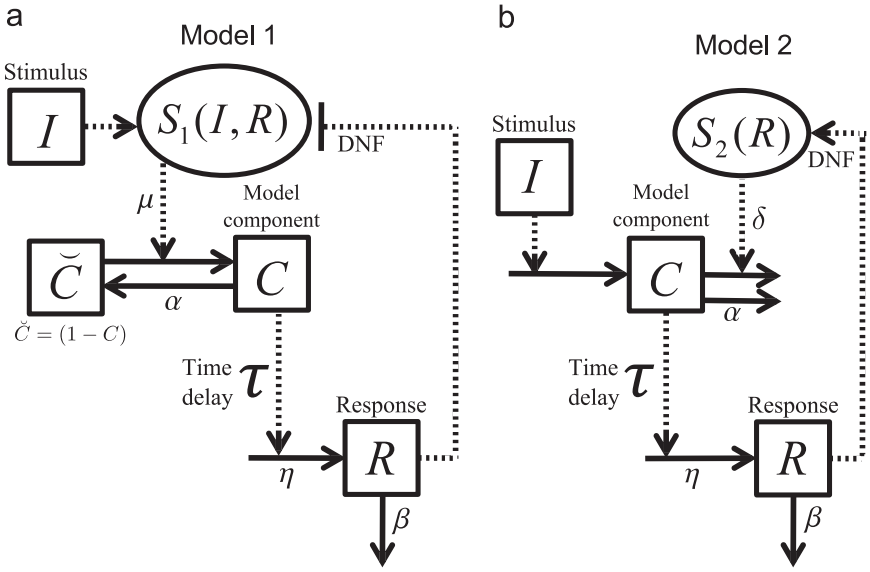

Fig. 1. Generic signal-response models with time delay τ. Squares indicate model variables, circles indicate model functions. Arrows between and to components indicate biochemical reactions (solid arrows). Arrows on arrows indicate modifying influences and arrows to functions indicate the respective influence on the function (dotted arrows). The models differ in the architecture of the delayed negative feedback (DNF) as well as by presence of signalling components C. (a) Model 1 with input-inhibition mimicking a signalling network. (b) Model 2 with output-activation mimicking a transcription network. In both models the time delay τ is before activation of the response variable R.