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Modelling and analysis of a gene-regulatory feed-forward loop with basal expression of the second regulator



Louisa Roselius^a, Dirk Langemann^b, Johannes Müller^{c,d}, Burkhard A. Hense^d, Stefan Filges^a, Dieter Jahn^a, Richard Münch^{a,*}

^a Institute of Microbiology and Braunschweig Integrated Centre of Systems Biology, Technische Universität Braunschweig, Spielmannstr. 7, D-38106 Braunschweig, Germany

^b Institute of Computational Mathematics, Pockelsstr. 14, Technische Universität Braunschweig, D-38106 Braunschweig, Germany

^c Centre for Mathematical Sciences, Technische Universität München, Boltzmannstr. 3, D-85747 Garching/Munich, Germany

^d Institute of Computational Biology, Helmholtz Zentrum München - German Research Center for Environmental Health, Ingolstädter Landstr. 1, D-85764 Neuherberg, Germany

HIGHLIGHTS

- We modelled the anaerobic adaptation in *Pseudomonas aeruginosa* using ordinary differential equations.
- The regulatory network is organized as a new kind of feed-forward loop.
- We performed a benefit-cost analysis in various fluctuating environments.
- Environmental adaptation is influenced by response-time, memory and energy storage.
- The observed evolutionary advantage has effects in environmental adaptation and pathogenicity.

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ABSTRACT

Efficient adaptation strategies to changing environmental conditions are essential for bacteria to survive and grow. Fundamental restructuring of their metabolism is usually mediated by corresponding gene regulation. Here, often several different environmental stimuli have to be integrated into a reasonable, energy-efficient response. Fast fluctuations and overshooting have to be filtered out. The gene regulatory network for the anaerobic adaptation of the pathogenic bacterium *Pseudomonas aeruginosa* is organized as a feed-forward loop (FFL), which is a three-gene network motif composed of two transcription factors (Anr for oxygen, NarXL for nitrate) and one target (Nar for nitrate reductase). The upstream transcription factor (Anr) induces the downstream transcription factor (NarXL). Both regulators act together positively by inducing the target (Nar) via a direct and indirect regulation path (coherent type-1 FFL). Since full promoter activity is only achieved when both transcription factors are present the target operon is expressed with a delay. Thus, in response to environmental stimuli (oxygen, nitrate), signals are mediated and processed in a way that short pulses are filtered out. In this study we analyze a special kind of FFL called FFL_k by means of a family of ordinary differential equation models. The secondary FFL regulator (NarXL) is expressed constitutively but further induced in the presence of the upstream stimuli. This FFL modification has substantial influence on the response time and cost-benefit ratio mediated by environmental fluctuations. In order to find conditions where this regulatory network motif might be beneficial, we analyzed various models and environments. We describe the observed evolutionary advantage of FFL_k and its role in environmental adaptation and pathogenicity.

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1. Introduction

Most bacteria are regularly exposed to changing physical and chemical conditions in their environment. In order to survive in a wide range of habitats, it is necessary to adapt to these environmental fluctuations, which is often mediated by transcription regulation networks. In response to external signals, transcription

* Corresponding author. Tel.: +49 531 391 5847.

E-mail address: r.muench@tu-bs.de (R. Münch).

URL: <http://www.comic.tu-bs.de> (R. Münch).

factors are able to change the transcription rate of target genes, which encode proteins or RNAs required for efficient adaptation. Usually multiple signals and regulators are integrated at the target gene promoter in a complex gene regulatory network (GRN). Global analysis of the design principles of microbial GRNs revealed overrepresented sub-networks, the so-called network motifs (Shen-Orr et al., 2002; Alon, 2007).

One of the most abundant network motifs found in microbial systems is the feed-forward loop (FFL). Examples for FFLs are used for the regulation of various sugar utilization systems of *Escherichia coli* (Mangan et al., 2003, 2006; Görke and Stülke, 2008), of flagella production (Kalir et al., 2005) and the induction of the *m*-xylene biodegradation pathway in *Pseudomonas putida* (Silva-Rocha and de Lorenzo, 2011). A nested system of feed-forward loops is found in the sporulation pathway of *Bacillus subtilis* (Eichenberger et al., 2004). Structurally, a FFL is a three-gene network of two transcription factors x and y that act together to regulate the target gene(s)/protein(s) z with the additional property that y is also regulated by x . Thus, there is a direct and indirect path to regulate z . Both regulators usually respond to the external stimuli s_x and s_y (Fig. 1A). Since there are three types of regulatory interactions, which can be either positive or negative (activation or repression), a FFL motif offers eight different possibilities of structural configurations (Mangan and Alon, 2003). The relationship between each FFL topology with its dynamic response behaviour shows a unique probability distribution pattern with differences in its intrinsic plasticity and robustness (Macia et al., 2009; Widder et al., 2012).

In our study, we are interested in the so-called type-1 coherent FFL where all regulatory interactions are positive. It was shown that this type of FFL has the potential to act as a delay element since the second regulator has first to accumulate for successful transcription of the target gene(s) (Mangan and Alon, 2003; Kalir et al., 2005; Wall et al., 2005). Consequently, these circuits can act as filter for unwanted responses to fluctuating inputs. In contrast to previous studies we analyze a special case of the type-1 coherent FFL where the second regulator y shows a significant basal expression level denoted by k . Therefore, we named this regulatory circuit FFL_k . While FFL_k leads to a permanent cost factor due to the production of the regulator y it is expected that the

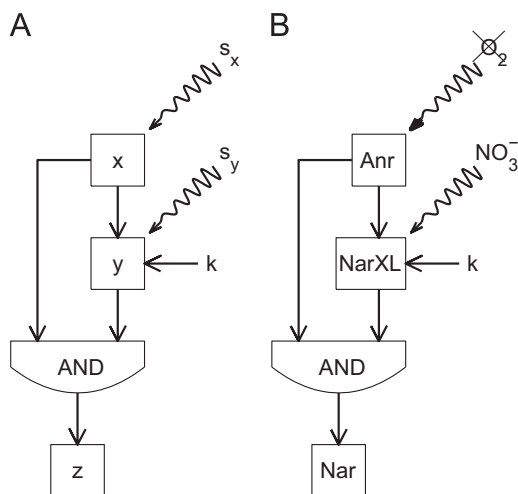


Fig. 1. (A) General structure of a type-1 coherent feed-forward loop motif. Regulator x activated by stimulus s_x induces the expression of regulator y which is activated by stimulus s_y . Both regulators act together in inducing the target gene (z) and corresponding protein(s) designated as z . Optionally, y has a basal expression rate of k . (B) Anaerobic induction of the denitrification genes of *P. aeruginosa* in the presence of nitrate and absence of oxygen via the regulators Anr and the two-component system NarXL. NarXL has a basal half-maximal expression which is presented by the parameter k .

pulse filtering is reduced to shorter pulses since the delay time to the onset of z is significantly decreased. FFL_k -type regulation was previously described for *E. coli*, where the arabinose responsive regulator AraC shows a significant basal expression level (Mangan et al., 2003). In this study we refer to an FFL_k involved in anaerobic adaptation of the opportunistic pathogen *Pseudomonas aeruginosa*. During an environmental shift to anoxic conditions this organism can efficiently adapt to dissimilatory denitrification which is a respiratory process where nitrate is used instead of oxygen as electron acceptor for energy generation. While, oxygen is the energetically most favourable electron acceptor, dissimilatory nitrate respiration is the system with highest energy yields in anaerobic environments (Strohm et al., 2007). The two environmental signals “loss of oxygen” and “presence of nitrate” are sensed by the regulator Anr and the two-component system NarXL, respectively. It has been shown in previous analyses that the *narXL* operon is constitutively expressed under aerobic conditions and is induced about two-fold after anaerobic induction (Fig. 1B) (Schreiber et al., 2007). We argue that the resulting decreased response time to anaerobic pulses might be a tradeoff between the essential need for energy production versus the cost-intensive biosynthesis of the nitrate reducing enzyme apparatus. Such a balancing of cost and increased fitness seems to play a major role in the evolutionary selection of protein expression levels and network motifs (Lan and Tu, 2013; Dekel et al., 2005; Shachrai et al., 2010).

In this context, we analyzed various models in order to find conditions where a FFL_k is generally beneficial in comparison to a FFL without a basal expression. An optimal net-benefit relation with a non-trivial, i.e. non-vanishing and non-complete, basal expression mirrors an evolutionary advantage of a FFL_k . The paper is organized as follows: first the modelling approach of the feed-forward loop is generally introduced in Section 2. In the following Section 3 a linear modelling approach is discussed. There, we show that the use of linear influence functions is not suitable to demonstrate a non-trivial optimal net-benefit relation. The first argument for an evolutionary advantage is found in Section 4 using a nonlinear model with an optimal net-benefit function. However, the short delay time and ability of fast target production accounts for significant costs in this model. Directly after a signal switch to anaerobic phases the instantaneous net-benefit of this model is negative, which is not suitable to explain an evolutionary advantage because such a situation would eventually lead to cell death. This model is able to explain the advantage of the basal expression but not the evolutionary stability of the whole system. Consequently, Section 5 extends the model by an energy storing mechanism that integrates the mentioned costs and turns their utilization into the advantage of a rapid change to anaerobic respiration. This model with an energy store allows for a better understanding of the essential role of the basal expression. However, the use of linear influence functions again does not provide arguments for any optimality of a non-vanishing and non-complete basal expression. Finally, the model with the energy store and the nonlinearities were combined, and we will present a simple mathematical model underlining the evolutionary advantage of the basal expression. We conclude with numerical simulation results and a discussion in the context of anaerobic adaptation and pathogenicity of *P. aeruginosa*.

2. Modelling the feed-forward loop

The generalized feed-forward-loop model contains a system of three differential equations corresponding to the two regulators x and y and the target z . For simplicity, transcription and translation were modelled as one process, so the state variables

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