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FEEDBACK-FEEDFORWARD CONTROL IN EMT SIGNALLING PATHWAY MODEL

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ABSTRACT

Introduction

Positive and negative feedback loops are well-established concepts in building and analysis of cell signalling pathways' models. However, control theory and engineering experience have led to the development of advanced structures as more viable options in many problems. The complexity of biological interactions suggests that more complex control structures may be found in their models.

One of the basic structures, used widely in industrial applications, is a feedback-feedforward structure, which joins the benefits of standard feedback control with feedforward's ability to quickly react to disturbances in the system. It includes two controllers: one responsible for standard feedback reaction and the second for filtering the input signal and directly supplying it to the plant. One of the key features of such a structure is the high sensitivity of its output to changes in the feedforward path when compared to changes in the feedback. Should such a structure be found in a signalling pathway model, this characteristic can be used for preliminary filtering of parameters for sensitivity analysis, as more potent drug targets will be present in the feedforward path.

Epithelial-mesenchymal transition (EMT) is considered crucial in the process of acquiring metastatic capabilities by the tumour, therefore finding effective therapy targets in its signalling pathway can be of great merit. Model of EMT developed by Lu, et al. [1] was chosen to search for components structurally and functionally similar to the technical feedback-feedforward control structure. It describes interaction between 2 proteins - Snail and Zeb, their mRNAs and 2 microRNAs - miR-34 and miR-200. The main advantage of that model, in the context of this work, was its small size (only 6 differential equations) however, the model being well verified in the literature is not without significance.

Methods

The search for a given structure can be divided into stages: representing interactions between molecules (variables) as a directed graph of connections, searching for preliminary candidates based on the graph of connections, verifying candidates by checking if key summing junctions are represented in the equations. As an additional, final verification of the method, sensitivity analysis is performed to check the key behavioural trait of the structure - high sensitivity to changes in the feedforward path. Sensitivity was checked using two methods - time domain based [2] and frequency domain based [3].

Results

First stage of the analysis found 14 candidates for a feedback-feedforward structure, based solely on the similarity of connections' graph. All candidate structures were built on 6 core feedback loops, though for each core feedback loop, pairs of candidates are found, for which molecules assigned to the roles of feedback controller and plant are switched.

Next stage of analysis - verification of key summing junctions - led to the rejection of 8 out of 14 candidates. Those 6 candidates that passed the stage are similar to each other in terms of roles assigned to types of molecules, i.e. protein levels act as input signal, and feedback loop is based on interactions between mRNA and miRNA.

Final stage - sensitivity analysis - took into account 6 parameters for each candidate, paired in such a way that for each parameter in the feedback path there was a parameter with the same interpretation (e.g. production rate, or degradation rate) in the feedforward path. Verification of the behaviour in terms of sensitivity was therefore based on comparison of those pairs.

In the tests, only 3 candidates performed in a desired way - having higher sensitivity for changes in the feedforward path. All of them had the core feedback loop built with miRNA level acting as a controller and mRNA level acting as a plant.

Discussion

The results of the sensitivity analysis required a closer look at the 6 candidates that passed the first two stages. All of the candidates follow a common structural pattern, shown schematically in Fig. 1, with two additional interactions (marked in red) modifying the feedback loop. Depending on whether

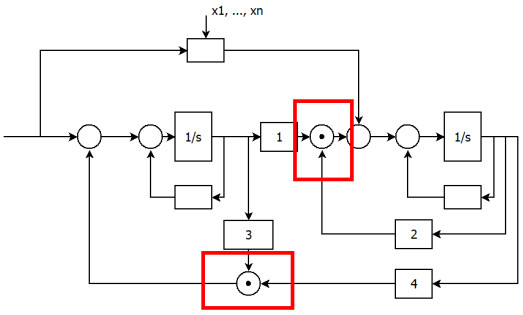

Figure 1. Structural pattern of candidates found

the role of a controller was assigned to miRNA or mRNA, either blocks 1 and 3 or blocks 2 and 4 were filled by a function that was nearly constant in the operating range of the model, while the other two were a constant equal to 1. When block 3 was equal to 1 and block 4 was a nearly constant function (as was the case for mRNA as a controller) the feedback loop was almost insensitive to changes of output, breaking the structure's fundamental assumption.

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