Use of mathematics to guide target selection in systems pharmacology; application to receptor tyrosine kinase (RTK) pathways

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Abstract

A key element of the drug discovery process is target selection. Although the topic is subject to much discussion and experimental effort, there are no defined quantitative rules around optimal selection. Often 'rules of thumb', that have not been subject to rigorous exploration, are used. In this paper we explore the 'rule of thumb' notion that the molecule that initiates a pathway signal is the optimal target. Given the multi-factorial and complex nature of this question, we have simplified an example pathway to its logical minimum of two steps and used a mathematical model of this to explore the different options in the context of typical small and large molecule drugs. In this paper, we report the conclusions of our analysis and describe the analysis tool and methods used. These provide a platform to enable a more extensive enquiry into this important topic.

Keywords: Receptors, Tyrosine Kinase, Signal transduction, Systems biology, Systems pharmacology, Singular perturbation.

1 Introduction

Whether the optimal molecular target has been selected in a given pathway is often an open question in early drug discovery. However, despite the ubiquitous nature of this question, very few useful rules have been unequivocally identified (cf. Agoram et al. [1], Stock et al. [2] and Benson et al. [3]). Techniques such as sensitivity analysis of mathematical models of systems can be employed (cf. Benson et al [4] and Lebedeva et al. [5]), however these assume accuracy of structure and parameterisation of complex differential models and have yet to become mainstream in drug discovery. Thus, target identification is driven by an intuitive feel for what is right, coupled with empirical demonstration of pharmacological efficacy in pre-clinical drug development. An example of such a gut feel is that targeting the top of a pathway is the optimum point of intervention in the context of efficacy because this is the initiating step.

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