BMC Systems Biology

BioMed Central

Poster presentation

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# Rate control analysis of the translation initiation pathway in *S. cerevisiae*

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*from* BioSysBio 2007: Systems Biology, Bioinformatics and Synthetic Biology
Manchester, UK. 11–13 January 2007

Published: 8 May 2007

*BMC Systems Biology* 2007, **1**(Suppl 1):P76 doi:10.1186/1752-0509-1-S1-P76

This abstract is available from: http://www.biomedcentral.com/1752-0509/1?issue=S1

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## Introduction

Translation initiation in eukaryotic cells is known to be a complex multi-step process that involves numerous protein factors and which represents an important point of regulation of gene expression. Studies using cell-free extracts and isolated components of the translation machinery have been very informative. However, not all functions of the translation system can be successfully reconstituted *in vitro*, and there is a need for accurate quantitation of rate control *in vivo*.

## Methods

We have set out to generate a quantitative framework for understanding translation control *in vivo*. Applying a process control approach we are defining the response coefficients for all of the eIFs in the initiation pathway. So far we have derived flux-control coefficients for eIF4E, eIF4G, eIF1A and eIF5B in Saccharomyces cerevisiae by placing each of these genes under the control of tetracycline-repressible promoters and comparing changes in the intracellular levels of the respective proteins with changes in cellular protein synthesis rates and in the polysome profiles in a quantitative manner.

## Results

The results provide a precise basis for understanding the contributions of individual factors to translational control, and have already yielded some striking results. For example, eIF4G and eIF1A manifest relatively large response coefficients, reflecting their strong influence on the rate of initiation. The response coefficients of eIF4E and eIF5B are considerably smaller.

## Conclusion

The eukaryotic cap-dependent translation initiation pathway involves a large number of eIFs, some of which are targets for regulatory pathways. In recent years, there has been considerable progress in understanding the basic functions of the individual eIFs. However, little is known about the coordination of their respective modes of action within the initiation pathway. The experimental strategy described here allowed us to perform quantitative rate control analysis *in vivo* for, in the first instance, eIF4E, eIF4G, eIF1A and eIF5B. These factors act at three different steps in the pathway (40S recruitment, scanning and 60S joining). The results reveal that this approach provides valuable information about the balance of rate control exercised by the respective eIFs, at the different steps on the pathway.