Dynamic Models of Hormesis and Ageing in Gene Expression Networks

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A system of non-linear ordinary differential equations (ODE) has been established in order to describe the response of a gene regulatory network to environmental signals. It is shown that a double-negative feedback loop in the mTOR pathway can lead to a hormesis-like signal-response characteristic of gene expression levels. Signals with moderate intensity or duration trigger the system to switch to a distinguished stable state that can be related to a putative defense loop. If a certain pulse duration or intensity is exceeded, the defense loop cannot be maintained by the system. The parameters of the model were chosen in such a way that calculated stationary-state values fit to gene expression data measured by RNA-Seq. Using the model, we speculate about processes that possibly contribute to ageing.

Introduction

Living cells respond to external and internal signals by complex mechanisms of gene expression regulation which can hardly be understood in an intuitive way. A stunning, recently disclosed real-world example of such behaviour is the response of cells to reactive oxygen species (ROS)[1]. In contrast to earlier perceptions, it has been demonstrated that a certain amount of ROS ("mild oxidative stress") leads to an improvement of the organisms antioxidant defense. Mathematical models can support the understanding of such complex and non-linear behaviour. Previously described network motifs, found to be present in many real biological networks[2], serve as building blocks of the model.

TSC tuberous sclerosis complex
ERK mitogen-activated protein kinase
Rheb Ras homolog enriched in brain
Akt thymona viral proto-oncogene

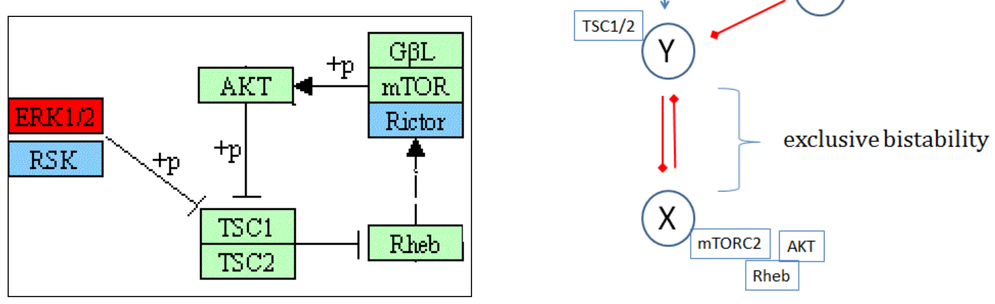


Fig. 1: A part of the mTOR pathway containing a double-negative feedback loop, and a schematic drawing of the derived network motif. The network motif contains a so-called exclusive bistability.

Kinetic Model

The network motif shown above is described by a set of non-linear differential equations. The mutual repression of the TSC genes and the mTORC2-containing complex is controlled by Hill-type functions. The bigger the concentration of the repressor, the bigger is the kinetic coefficient which quantifies the repression. Hill-type functions show a steep increases at x=K, thereby causing a switch-like behavior of the motif.

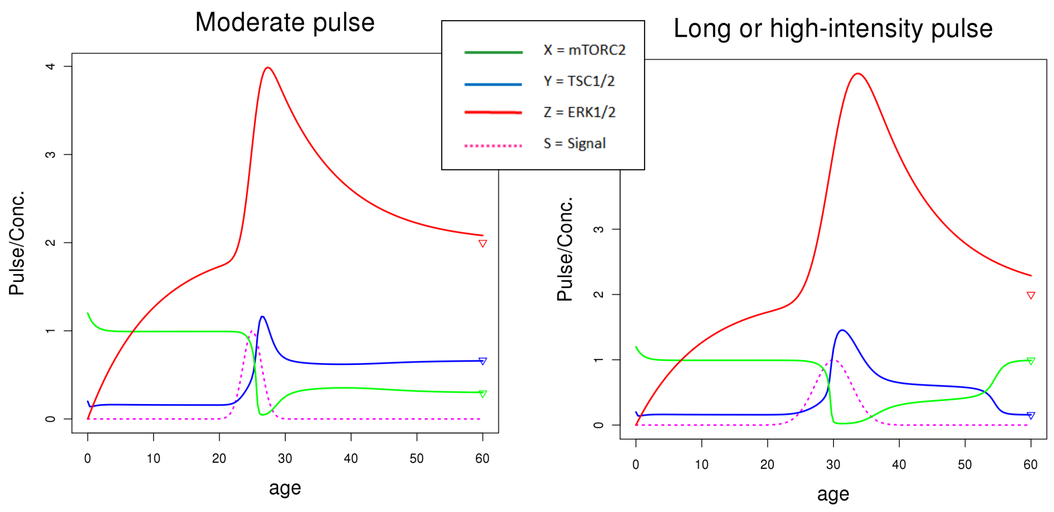
$$\frac{dx}{dt} = \alpha_x - \beta_x \cdot x - \beta_{xy} \cdot h\left(y, K_{xy}\right) \cdot x$$

$$\frac{dy}{dt} = I_y \cdot S(t) + \alpha_y - \beta_y \cdot y - \beta_{yx} \cdot h\left(x, K_{yx}\right) \cdot y - \beta_{yz} \cdot h\left(z, K_{yz}\right) \cdot y$$

$$\frac{dz}{dt} = I_z \cdot S(t) + \alpha_z - \beta_z \cdot z$$

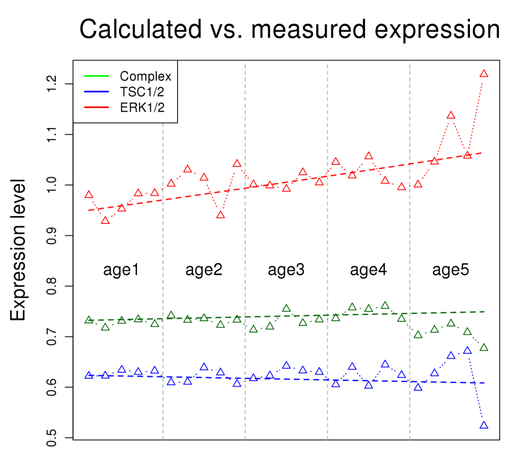
$$h(x, K, n) = \frac{\left(\frac{x}{K}\right)^n}{1 + \left(\frac{x}{K}\right)^n}$$

Fig. 2: System of ODE for the network motif shown above.



On a so far simple level, the model is able to display a hormesis-like signal-response characteristic: signals with moderate intensity or duration trigger the system to switch to a distinguished stable state that can be related to a putative defense loop, conducting adaption of the network. However, if a certain pulse duration or intensity is exceeded, the defense loop perishes. This qualitative behaviour is preserved for a wide range of model parameters. In summary, the defense enzyme is only active when the triggering signal has a proper intensity or duration.

Fig. 3: Calculated temporal variation of the enzyme concentrations for two different pulse durations.



To model ageing effects, calculated equilibrium values are considered. The observed changes of gene expression in the mTOR pathway can be described by a quasi-stationary drift of the parameters of the ODE system (Fig. 4). It can be hypothesized that a connection between ageing and hormesis exists. Long-lived individuals might be in the defense state for a greater proportion of their lifetime. By increasing degradation, the bistable nature of the network motif and thereby the ability to switch to the defense state can be lost (Fig.5).

Fig. 4: Calculated and measured steady-state values of expression for some genes of the mTOR pathway.

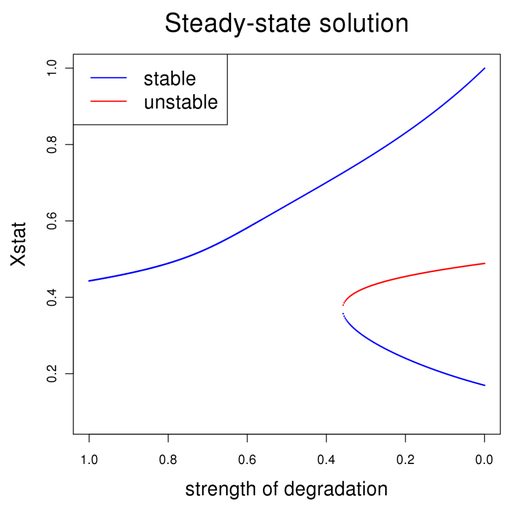


Fig. 5: Loss of bistable behaviour for high levels of intrinsic degradation.

[1] Ristow M., Zarse K. (2010). Experimental Gerontology **45** (6), 410-418.
[2] Mangan S., Alon U. (2003). PNAS **100** (21), 11980-5.