

Dynamic modes in biological systems: Why should a biologist care?

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Short summary

Dynamic modes are essential for approximation of biochemical networks and can be viewed as regions in which the change of gene, protein and metabolite levels remains fairly constant for some time. Every interaction between two molecules is active only in certain modes; the topology of the network hence depends on the mode and mixing of modes makes it, *e.g.*, hard to identify functional modules. In general, one should always explicitly state the mode(s) of the system that any model describes or in which experimental data was recorded. We discuss dynamic modes, using two examples: a microarray dataset recorded on *S. cerevisiae*, and a mechanistic nonlinear model of receptor induced apoptosis. (Ref: Nordling et al. 2007, doi:10.1039/b702142a)

Introduction

Interaction between genes, proteins and metabolites is a major topic in modern molecular and cell biology. One, for example, commonly states that gene A upregulates gene B, or that protein A binds to protein B and form an active complex. A statement of this type is a rough simplification, since biological systems are dynamical and contain switching between different modes. We discuss and illustrate the meaning and importance of dynamic modes in biology. This is done using two examples: a microarray dataset recorded on *Saccharomyces cerevisiae* under two different growth conditions (galactose and glucose)¹, and a mechanistic nonlinear model of receptor induced apoptosis².

What is a dynamic mode?

Loosely speaking, any region in which the change of gene, protein and metabolite levels remains approximately constant for some time constitutes a dynamic mode. The apoptosis model² (Figure 1), for example, has two fixed modes: proliferation and apoptosis. Mitosis is conventionally divided into four stages—prophase, metaphase, anaphase and telophase—that all constitute different dynamic modes. Environmental stress and growth conditions can trigger different modes, *e.g.*

yeast grown in galactose has the galactose pathway activated^{1,3} (Figure 2). Formally, we define a dynamic mode as a domain D in state-space such that

$$\bar{x}(t) \in D \subset \mathbb{R}^n \text{ iff } \exists t_L, t_U \text{ such that } \frac{d^2 x_i(t + \tilde{t})}{dt^2} < C \quad \forall \tilde{t} \in]t_L, 0, t_U[\subset \mathbb{R}, t_U - t_L = T \text{ and } \forall i. \quad (1)$$

The constants C and T are selected such that a suitable approximation is obtained, $\bar{x}(t)$ denotes the state of the system at time t and x_i denotes the abundance of a gene, protein or metabolite under study. This definition implies that dynamic mode is a quasi-stationary concept, *i.e.* the system only need to exist in every mode for some time T , and the existence of two basic types of modes: fixed ones where the change in abundance essentially is zero, and transitional ones where it is nonzero.

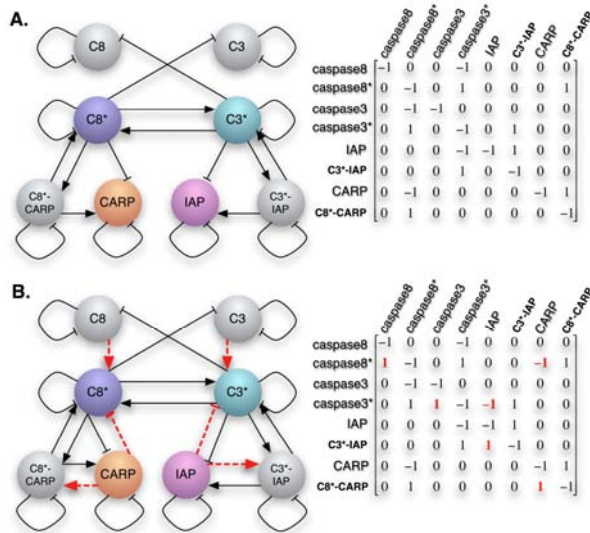


Figure 1: Illustration of two fixed modes in a mechanistic nonlinear model of ordinary differential equations. The extended model of receptor induced apoptosis², linearized in the two steady-states: (A) proliferation and (B) apoptosis. The wiring differs and interactions that only are active in the apoptosis mode are indicated by red dashed lines.

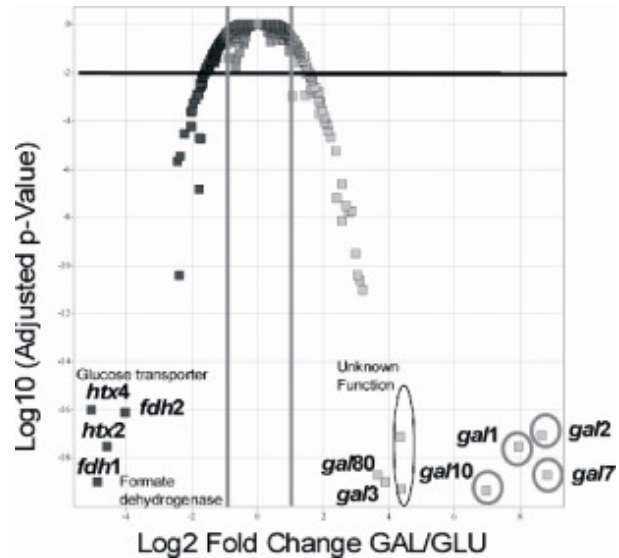


Figure 2: The gene regulatory network of *S. cerevisiae* is in two different dynamic modes depending on if the culture is grown in galactose or glucose. This volcano plot¹ show genes belonging to the galactose pathway (right) as upregulated and glucose related as downregulated (left), when comparing microarrays of a culture grown in galactose with one grown in glucose. The microarray “fingerprint” of the two modes hence differs significantly and can be used to distinguish and characterize them. (Figure reproduced¹ with permission from the author.)

Why care?

Mechanistic nonlinear models have the potential to fully describe the mean behaviour of the system and all modes, *e.g.* the apoptosis model describes two fixed modes. But the amount of precise quantitative measurements needed to construct them limits their application to detailed modelling of small sub-systems, *i.e.* functional modules. We need to approximate in order to get an overall view and even to comprehend the information contained in detailed mechanistic models.

All approximations—Boolean, linear, common statements about up/down regulation—relay on regions where the behaviour of the biological system remains fairly constant, *i.e.* dynamic modes.

The wiring of regulatory networks, *i.e.* its topology, depends on the mode of the system (Figure 1). Every interaction is only active in certain modes of the system, so an upregulation may become no regulation or even downregulation in another mode. It is hence essential to explicitly state the mode that the network describes or in which an interaction was experimentally determined. A functional module only exists in the dynamic mode in which its biologic function is carried out and can therefore only be detected in a network that only describes that mode. A fact worth remembering when models are composed based on interactions documented in databases or literature. Experimental contradictions may be explained by the cell cultures being in different modes.⁴

How to denote the dynamic mode?

In an actual experiment the mode could be denoted by, for example, the cell line, growth medium and all manipulations done to the cells. Conditions that are strictly planned to control the mode of cells. Alternatively characteristic bio-markers of each mode could be used, like a microarray "fingerprint" (Figure 2).

References

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