Journal of Theoretical Biology 357 (2014) 245–267

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Memory effects in biochemical networks as the natural counterpart of extrinsic noise

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HIGHLIGHTS

- We study dynamics of subnetworks embedded in large networks by projection techniques.
- The conceptual and quantitative need to include memory terms is demonstrated.
- We obtain memory functions for the full nonlinear dynamics in PINs.
- Application to EGFR signalling allows dominant memory channels to be identified.

ARTICLE INFO

Article history:
Received 4 February 2014
Received in revised form
22 May 2014
Accepted 3 June 2014
Available online 11 June 2014

Keywords:
Subnetworks
Model reduction
Memory function
Protein interaction networks

ABSTRACT

We show that in the generic situation where a biological network, e.g. a protein interaction network, is in fact a subnetwork embedded in a larger "bulk" network, the presence of the bulk causes not just extrinsic noise but also *memory effects*. This means that the dynamics of the subnetwork will depend not only on its present state, but also its past. We use projection techniques to get explicit expressions for the *memory functions* that encode such memory effects, for generic protein interaction networks involving binary and unary reactions such as complex formation and phosphorylation. Remarkably, in the limit of low intrinsic copy-number noise such expressions can be obtained even for nonlinear dependences on the past. We illustrate the method with examples from a protein interaction network around epidermal growth factor receptor (EGFR), which is relevant to cancer signalling. These examples demonstrate that inclusion of memory terms is not only important conceptually but also leads to substantially higher quantitative accuracy in the predicted subnetwork dynamics.

1. Introduction

Biological networks are often complex and models are required to try and understand their behaviour (Bhalla, 2003). This has stimulated an ongoing research effort into the construction of reduced models that allow one to focus on subnetworks of a larger system. Such subnetworks may carry out biologically important functions, or be of interest because they capture parts of the system where there is less uncertainty in the network structure or dynamical parameters such as reaction rates. The example network considered here is epidermal growth factor receptor (EGFR) signalling, which is a relatively small and well-studied network (Kholodenko et al., 1999) and contains a number of subnetworks, such as Src homology and collagen domain protein (Shc) and Shc-interacting proteins. An understanding of the properties of such subnetworks can be used to help rationalise the behaviour of a larger network (Ackermann et al., 2012; Conradi et al., 2007; Shojaie and Michailidis, 2010).

The above considerations motivate the analysis of subnetwork dynamics by model reduction, where one starts from a description of a large network and reduces this to an effective description of the subnetwork. Further motivation comes from the fact that almost any biological network that we choose to model is incomplete, and in reality is a subnetwork embedded in a larger "bulk" network. It is then important to understand what, in principle, is the appropriate way of describing the dynamics in such a subnetwork. This is the aim of this paper, and our main result is that such a description must in principle always involve memory effects in addition to the well-studied extrinsic noise caused by the presence of the bulk (Swain et al., 2002; Paulsson,

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http://dx.doi.org/10.1016/j.jtbi.2014.06.002
0022-5193/

2004). We focus in our analysis on the specific example of protein interaction networks with unary and binary reactions, but expect that our qualitative conclusions are rather general, as suggested by the generic nature of the intuitive explanation of memory effects: the state of the subnetwork in the past will influence the bulk, and this will feed back into the subnetwork dynamics in the present (Fig. 1).

We apply the method to investigate the dynamics of a subnetwork model of epidermal growth factor signalling (Normanno et al., 2006). We show that the subnetwork dynamics, in the presence of Shc and Shc-interacting proteins, are more accurately modelled by including memory terms originating from the Shc-centred bulk network in which the subnetwork is embedded. The models we use obey conservation laws so that no increased gene expression or destabilisation is incorporated. The analysis thus serves as a first step towards quantitative modelling of experimentally tractable perturbations and observable responses of both time courses and steady state concentrations (Rubin and Sollich, 2014), which may include signalling pathways with multiple ligands such as the ErbB signalling network (Birtwistle et al., 2007).

There is a substantial literature on methods of model reduction that attempt to simplify an initial large model down to a subnetwork description. The aim is to do this whilst retaining the main features of the behaviour of the original system (Okino and Mavrovouniotis, 1998; Radulescu et al., 2012). These methods are often based on (a) sensitivity analysis, (b) timescale separation, (c) splitting the system into modules or (d) lumping together components to obtain a smaller number of parameters or variables. In most of these approaches, it is assumed that the subnetwork can be freely chosen to make the model reduction most effective. We consider the more difficult task of finding a reduced description for a subnetwork that is fixed in advance, e.g. because of its relevance to the overall biological question being asked, or by experimental constraints on which molecular species can feasibly be monitored.

Sensitivity analysis tries to determine which molecular species are insignificant to the dynamic system of interest (Huang et al., 2010). A parameter is classified as insignificant if it has a low sensitivity, in which its precise value does not have a large effect on the concentrations of the rest of the species in the network. Low sensitivity parameters are then eliminated or replaced by a smaller number of effective species. However, sometimes it is necessary to keep a low sensitivity parameter to ensure that the results are biologically valid.

Timescale separation techniques are used to focus on the species that contribute most to the long-time dynamics of a system, by removing molecular species whose dynamics takes place on much shorter timescales. This is reasonable because biochemical processes occur on a range of timescales; changes in gene expression levels, for example, may take place over hours whereas protein signalling takes seconds. Timescale separation approaches have been used by e.g. Gardiner (1984) and Thomas et al. (2012), with the subnetwork then containing all the slow molecular species and the bulk the fast ones. Thus, while these authors used projection techniques as we do, memory effects did not arise: they become negligible if the bulk is fast enough to respond effectively instantaneously – on the timescale of the subnetwork dynamics – to the state of the subnetwork. Here we consider signalling networks where the timescales of the dynamics of the subnetwork and the bulk are comparable, so that timescale separation methods are not directly applicable.

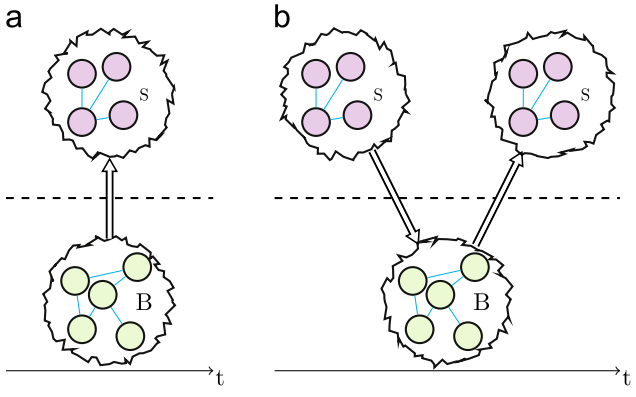

Fig. 1. Extrinsic noise versus memory. (a) Extrinsic noise on the subnetwork S arises from fluctuations of the bulk B that are uncontrolled and generally uncontrollable via experimental conditions. (b) Memory effects arise because the behaviour of S in the past will generically influence B, and this effect will feed back to S at a later time: the time evolution of S depends on its own past.

Another way to reduce the system is to split it into modules where each module has a different function and a limited number of interactions with the other modules (Hartwell et al., 1999). Conzelmann et al. (2004) apply dimensional reduction to the modules so that the modules have reduced complexity but show similar input and output behaviour.

Lumping together variables with similar features also allows one to reduce the size of a model (Sunnaker et al., 2011; Conzelmann et al., 2004); however, lumping components together may make it difficult to interpret the results because the lumped variables may not retain their original meaning. Similarly Liebermeister et al. (2005) reduce the bulk surrounding a chosen subnetwork, whilst the subnetwork is kept in its original form. As one might expect, accounting for the bulk in this way, i.e. considering the environment surrounding the subnetwork, yields a reduced model that is more accurate than modelling just the isolated subnetwork. Our work extends this result by showing that the inclusion of memory effects arising from the bulk gives a significantly more accurate description of the subnetwork dynamics. Apri et al. (2012) remove or modify reactions and parameters based on their effect on the output behaviour of the system. They consider which parameters can be removed or lumped together to obtain output data correct to within a certain tolerance. Although no detailed prior biological knowledge of the system is needed, there must be some qualitative understanding of the system dynamics to ensure that no species which are generally considered to be an important part of the network dynamics are removed.

Our approach starts from kinetic equations for the concentrations of a set of molecular species in a large protein interaction network, allowing for small amounts of intrinsic noise caused by fluctuations in the copy number of each species as shown in Fig. 2(a). We then use a projection operator formalism to obtain a set of dynamical equations for selected variables from the network, which define the chosen subnetwork. This approach retains information from the remainder of the larger network, i.e. the bulk, and allows us to obtain a reduced set of equations for the subnetwork (Fig. 2(b)). These projected equations contain extrinsic noise arising from the bulk dynamics as expected, but crucially the noise is accompanied by memory terms (Fig. 1). The memory terms are represented mathematically as integrals over the past history of the subnetwork, modulated by *memory functions*. These are the focus of our analysis. In Section 2 we explain the projection approach and how it can be applied to protein interaction networks. We also illustrate the method with a simple example that already captures some general properties of memory functions (Fig. 2(c)). Next, in Section 3 we obtain closed-form expressions for memory functions in protein interaction network dynamics and discuss and illustrate some of their properties, e.g. the amplitudes and what they tell us about reactions between the subnetwork and the bulk. Finally in Section 4 we apply our approach to the