Ill-conditioning – a property of bio-networks

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***Short Abstract* — Analysis of large gene expression datasets shows that they all share the same feature; the variance is concentrated to significantly fewer orthogonal directions than the applied perturbations span. Given that all perturbations are of same magnitude, this shows that the underlying networks are ill-conditioned. We establish ill-conditioning as a generic property of biochemical networks, resulting from the fact that all networks need to provide both signal amplification and disturbance attenuation. One consequence of ill-conditioning is the commonly observed co-expression of genes.**

I. Introduction

Knowledge of generic properties of networks is of outmost importance in modelling, analysis and synthesis of biochemical networks. One such property is scaling in random networks [1], which has had a profound impact on the way we view, analyse, construct and model complex networks [2]. Here we present another generic property – ill-conditioning – that has strong implications for the dynamics of the system. Observations that the measured response matrix of gene expression changes is ill-conditioned have led to the introduction of characteristic modes [3]. The notion of co-expressed genes [4] is also a consequence of an ill-conditioned response matrix. An ill-conditioned response matrix, however, only implies that the underlying network is ill-conditioned under certain conditions. We show that ill-conditioning is a generic property of biochemical networks caused by specific combinations of interaction strengths and feedback structures.

II. Definition and Results

The network A is a mapping from the space of all possible perturbations to corresponding responses of the n state variables, $A:P\rightarrow Y$. Here P denotes the direct effect of a change of the experimental conditions on each state, i.e. gene, protein, metabolite, while Y denotes the response of each state. The network matrix A can be viewed as an adjacency matrix of a directed graph with the sign and weight of each edge as its elements. We define the network as ill-conditioned if and only if A has a high condition number, i.e. the ratio of the largest and smallest singular value is high. Ill-conditioning implies the co-existence of perturbations leading to weak responses, i.e. weak gain directions, and other leading to strong responses, i.e. high gain directions. This will cause ill-conditioning of the response matrix if the applied perturbations are uniform. However, the response matrix may be ill-conditioned even though the network is not. For instance, if we assume m steady-state experiments then $Y=-A^{-1}P$, and Y will be ill-conditioned if either A or P is ill-conditioned. If $m<n$ then Y is ill-conditioned because P does not span the state space.

The probability that two randomly chosen perturbations of same magnitude yield a similar response increases with the ill-conditioning of the network. Two genes are co-expressed if they have a similar expression pattern for many different perturbations; hence ill-conditioning implies co-expression. On the other hand, all responses of a perfectly conditioned network, condition number one, are equally probable, but in a large network co-expressed genes will still be observed since the number of experiments is less than the number of genes. Thus co-expression does imply an ill-conditioned response matrix, but not ill-conditioning of the network.

We postulate that ill-conditioning is a generic property of biochemical networks and put forward strong support.

We have analysed a large number of the gene expression datasets in the COXPRESdb database [5]. In all cases where the perturbations have similar magnitude, the network shows all characteristics of an ill-conditioned network.

Every cell need to obtain homeostasis, characterised by an internal environment far from thermodynamic equilibrium with the surrounding environment. This requires mechanisms for sensing, signalling, decision making, active transport, processing, etc. Amplification in signal pathways, like MAPK, EGF, and Integrin, constitute strong gain directions. Simultaneously, toxic substances must be maintained at low levels, independent of environmental perturbations, thus their production must constitute weak gain directions.

III. Conclusion

Ill-conditioning is a network property with significant implications for the network dynamics. We present evidence in support of ill-conditioning as a generic property of biochemical networks.

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