CONCENTRATION AND SPECTRAL ROBUSTNESS OF BIOLOGICAL NETWORKS WITH HIERARCHICAL DISTRIBUTION OF TIME SCALES

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Abstract. We discuss here the robustness of the relaxation time using a chemical reaction description of genetic and signalling networks. First, we obtain the following result for linear networks: for large multiscale systems with hierarchical distribution of time scales the variance of the inverse relaxation time (as well as the variance of the stationary rate) is much lower than the variance of the separate constants. Moreover, it can tend to 0 faster than $1/q$, where q is the number of reactions. We argue that similar phenomena are valid in the nonlinear case as well. As a numerical illustration we use a model of signalling network that can be applied to important transcription factors such as NFκB or TGFβ.
Keywords: *Complex network; Relaxation time; Robustness; Signalling network; Chemical kinetics; Limitation; Measure concentration*

Recent progress in molecular biology showed that the development and the functioning of living organisms are controlled by large complex networks, such as genetic and signalling networks. These networks are dynamical and their time scales distribution is log-uniform, which means that there is an hierarchy of characteristic times.

Some numerical studies [1] emphasized the robustness of gene networks functioning, with respect to changes of the constants. This is important for modeling: it shows that a precise knowledge of the constants is not needed. It also brings understanding on how nature deals with unavoidable variability: the regulation structures are robust.

Very little is known on the origin of robustness. In our conception there are two intrinsically related sources of robustness. One has to do with size and concentration of measure on high dimensional metric–measure spaces [3, 2]. The second is related to topology and hierarchy of time scales.

We discuss here the robustness of the relaxation time using a chemical reaction description of genetic and signalling networks. Relaxation time is an important issue in chemical kinetics. It is so for practical reasons because it says how long one has to wait until the end of a process. In biology, the reasons are slightly different. A biological system is a hierarchically structured open system. Any biological model is necessarily a submodel of a bigger one. After a change of the external conditions, a cascade of relaxations takes place and the spatial extension of a minimal model describing this cascade depends on time. It is therefore important to know how the relaxation time depends on the size of the model and how robust is this against variations of the kinetic constants.

First, we obtain some results for linear networks. Let us enumerate reactions in the order of their constants decrease: $k_1 > k_2 > \ldots > k_q$. If kinetic constants are all well separated then we can use $\gg$ instead of $>$. The reaction graph is weakly

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ergodic (further we omit the adverb "weakly"), if for each two vertices (components) A_i, A_j $(i \neq j)$ we can find such a vertex A_k that oriented paths exist from A_i to A_k and from A_j to A_k. One of these paths can be degenerated: it might be $i = k$ or $j = k$. The reaction constant k_r $1 \leq r \leq q$ is the *ergodicity boundary* if the reaction graph for reactions with constants $k_1, k_2, \ldots, k_r$ is ergodic, but for reactions with constants $k_1, k_2, \ldots, k_{r-1}$ it is not. For the relaxation time τ of the whole system the following estimate holds:

$$\overline{a}\frac{1}{k_r} \geq \tau \geq \underline{a}\frac{1}{k_r}, \tag{1}$$

where $\overline{a}, \underline{a} > 0$ are some positive functions of $k_1, k_2, \ldots, k_{r-1}$ (and of the reaction graph topology [4]).

The well known concept of stationary reaction rates *limitation* by "narrow places" or "limiting steps" should be complemented by the *ergodicity boundary* limitation of relaxation time. It should be stressed that the relaxation process is limited not by the classical limiting steps (narrow places), but by absolutely different reactions. The simplest example of this kind is a catalytic cycle: the stationary rate is limited by the slowest reaction (the smallest constant), but the ergodicity boundary is the reaction constant with the second lowest value. In order to change the slowest relaxation time one should coordinately alter the lowest and the second lowest constant.

In general, for large multiscale systems we observe concentration effects: the variance of the inverse relaxation time (as well as the variance of the stationary rate) is much lower than the variance of the separate constants. Moreover, here we meet a "simplex–type" concentration ([2], pp. 234–236) and the variance of the relaxation time can tend to 0 faster than $1/q$, where q is the number of reactions. For simplest linear reaction mechanisms with random constants k the estimate $\mathrm{Var}(1/\tau) \sim \mathrm{Var}(k)/q^2$ is proven.

We argue that similar phenomena are valid in the nonlinear case as well. As an illustration we use a rather generic model of signalling network that can be applied to important transcription factors such as NFκB or TGFβ. The model consists of five reactions:

(1) $R + F \leftrightarrow C$
(2) $C + K \leftrightarrow F$
(3) $2F^* \rightarrow 2F^* + R$
(4) $R \rightarrow$
(5) $F \leftrightarrow F^*$

F is a transcription factor that forms a complex C with the repressor R. The complex is localized in the cytosol. The signal is represented by a kinase K that phosphorylates the repressor and frees the transcription factor. Nuclear F^* comes from cytoplasmic F by transport and controls the transcription of various genes among which the repressor R.

In order to study the robustness of the system, we have performed five operations. In each one of these operations the reaction constants k_i, k_i^r of the forward and of the reversed reaction i have been divided by a scale factor. The effects of these operations on the value of F^* at stationarity and on the relaxation time τ have been represented in Fig.1 in the presence and in the absence of a signal. Although the constants have been changed on four decades, the relaxation time have large plateaus where it is constant and its total variation is smaller than two decades. Without signal, robustness is less pronounced.

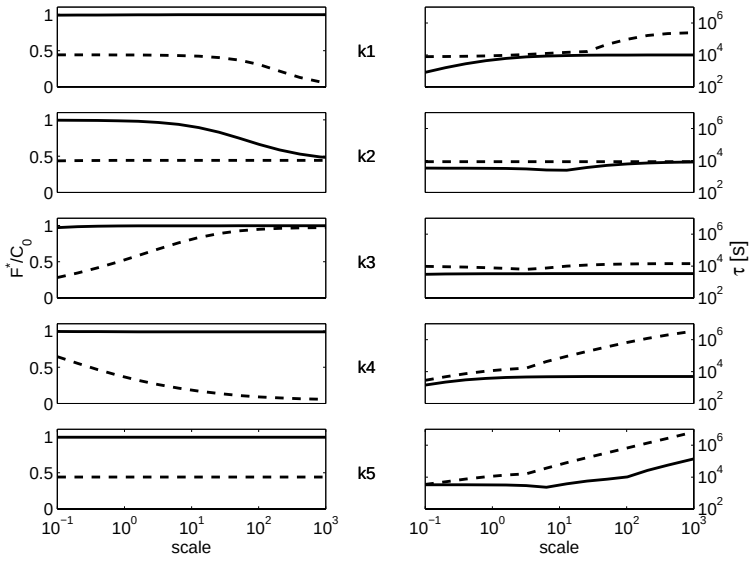

FIGURE 1. Robustness of the steady state and of the relaxation time τ of the signalling network. The response to the signal is the concentration F^* of transcription factor in the nucleus. Dynamics evolves on conserved hyperplanes $F + F^* + C = C_0$ according to the reactions described in the text and to the law of mass action. The presence ($K \neq 0$) and the absence ($K = 0$) of a signal are represented by a continuous and a dotted line, respectively. Each subfigure correspond to a different reaction whose constants were divided by *scale*. Unscaled constants are those of the reference [5].

Obviously, results as general as Eq. 1 do not work in the nonlinear case. For instance, the relaxation time diverges near a saddle-node bifurcation point. In this case there are no concentration effects. Our simple model suggests that with some restrictions, concentration of the relaxation time might work in the nonlinear case as well. We do not know yet which are the restricting conditions and how to connect these effects to topology.

The observed phenomena can give a clue to robustness of relaxation characteristics of multidimensional networks with hierarchical distribution of time scales. It suggests that for systems with wide distributions of reaction rate constants, the relaxation time of the whole system is much more stable than the relaxation times of individual small fragments. In particular, the relaxation time of the whole system is much more stable than the relaxation times of the individual reactions.

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