# Parametric robustness in gene networks: reliable functioning with unreliable components

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Robustness, defined as the capacity of a system to function reliably with unreliable components or to adapt to changing external conditions, represents a common feature of living systems. The fittest organisms are those that resist to diseases, to imperfections or damages of regulatory mechanisms, and that can function reliably in various conditions. There are many theories that describe, quantify and explain robustness. Waddington's canalisation [1] was formalised by Thom [2] as structural stability of attractors under perturbations. The canalization by attractors have been recently proven for Drosophila development [3]. The new field of systems biology places robustness in a central position among the living systems organizing principles, identifying redundancy, modularity and negative feedback as sources of robustness [4]. As noticed by von Dassow [6], systems biology models are robust with respect to variations of their parameters. Parametric robustness of models is also expressed by the strong anisotropy of sensitivity coefficients along directions in the parameter space (sloppy sensitivity). Robustness does not exclude fragility [4], as some of the model parameters could have a critical influence on the behavior of the system.

We discuss here system robustness with respect to randomness of the parameters. Our results can be applied to gene networks that function reliably with large variability in the strength of interactions between components. We formally define reliability as small variability of quantities defining network's functioning or output. We want to understand the general principles leading to robust functioning, but also to spot eventual fragility points that can be used to control the network.

Early insights into this problem can be found in the von Neumann's discussion of robust coupling schemes of automata [5]. von Neumann noticed the intrinsic relation between randomness and robustness. Quoting him "without randomness, situations may arise where errors tend to be amplified instead of cancelled out; for example it is possible that the machine remembers its mistakes, and thereafter perpetuates them". To cope with this, von Neumann introduces multiplexing and random perturbations in the design of robust automata.

We distinguish [8,9] three generic types of parametric robustness: simplex concentration, cube concentration and robust/fragile systems (systems with small number of critical parameters). The first two types can be related to the mathematical theory of concentration phenomena in high-dimensional spaces [7]. Model reduction techniques [11,10] can be used to identify critical processes and design rules leading to various robustness situations.

Simplex concentration and dominance effects are largely responsible for "sloppy sensitivity" phenomena, involving inequivalent contributions of elementary dynamical processes to the behavior of the system. Gene networks are multiscale systems, meaning that they involve wide ranges of protein abundances (from one to $10^4$ per cell) and time scales of elementary dynamical processes, for instance biochemical reactions (from $10^{-3}$ to $10^4 s$). Contribution of these elementary dynamical processes to the behavior of the system is highly uneven. Thus, one process is dominating over many others and can be called critical [11]. Mathematically, system's dynamical properties depend on order statistics [9] (combinations of max or min over many parameters or parameter combinations). Order statistics have small variability even if parameter variation range is large, a phenomenon that is called simplex concentration.

Model reduction techniques for multi-scale network models extract the dominant sub-system and identify the critical parameters [11,10]. The model reduction algorithm contains pruning steps that eliminate dominated processes. These processes have little influence on the dynamics, which explains the overall sloppy

sensitivity of the model. As a result, a system with a small number of critical parameters is a paradigm for the robust/fragile concept.

Cube concentration produces reduced variability when many equivalent contributions are added together [9]. This phenomenon generalizes the law of large numbers. Properties showing cube concentration depend on many parameters of the dominant subsystem. An example of property having such behavior is the period of large oscillating networks [9].

We proposed a scenario to test various types of robustness [9]. In this scenario the variability of a given property (quantified by its log-variance) is computed for random variations of the parameters in two cases: i) all $n$ parameters are changed independently with increasing individual log-variance, and ii) $r \leq n$ parameters are randomly chosen and then randomly changed with fixed log-variance for increasing values of the integer $r$. The two resulting plots (log-variance of the property as a function of the log-variance of the parameters in one case, and as a function of the number $r$ of changed parameters in the second case) are discriminating for the three types of generic robustness. We have thus shown that for an oscillating signalling network the period of the oscillations follows cube concentration, the largest relaxation time follows simplex concentration, and the damping time of the oscillation amplitude is robust/fragile [9].

As a new development we present the application of this test to a large set of models from BioModels database for a large set of dynamical properties. We use a similar analysis, in the context of early development stages of Drosophila, to study the robustness of the cis-regulatory modules controlling the expression of even-skipped segmentation genes [12]. These studies illustrate the genericity of the mechanism.

Understanding robustness has fundamental importance as it can guide thinking about biological systems. It is important to known whether the control of a property of a system should be distributed (the case of properties with cube or simplex concentration) or localized on a well chosen target (the case of robust/fragile properties). Our studies also provide tools to identify the various types of robustness and the set of critical parameters which are important for practical applications. These tools complement more traditional sensitivity studies approaches. An even more important practical consequence of our results is the possibility to cope with parametric uncertainty of gene networks in a rational way. Indeed, determination of the dominant subsystems of a given multiscale network depends on the qualitative order relation and not on the precise values of the parameters. Determination of these order relations (qualitative comparison of interaction strengths by experimental techniques or by sequence analysis) allow simplification of the dynamics via model reduction tools and lead to identification of critical parameters that need to be measured more carefully.

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