Flexible and robust networks

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Abstract   We consider networks with two types of nodes. The v-nodes, called centers, are hyperconnected and interact one to another via many u-nodes, called satellites. This centralized architecture, widespread in gene networks, possesses two fundamental properties. Namely, this organization creates feedback loops that are capable to generate practically any prescribed patterning dynamics, chaotic or periodic, or having a number of equilibrium states. Moreover, this organization is robust with respect to random perturbations of the system.

1   Introduction

Flexibility and robustness are important properties of biological systems. Flexibility means the capacity to adapt with respect to changes of environment whereas robustness is the capacity to support homeostasis in spite of environmental changes. Intriguingly, it seems that biological systems could be in the same time robust and flexible. Development of an organism is robust to variations of initial conditions and environment, species can diversify in order to better satisfy constraints imposed by a varying environment.

We discuss here flexibility and robustness problems for genetical networks of a special topological structure as a model for flexible and robust systems. In these networks, highly connected hubs play the role of organizing centers (centralized networks). The hubs receive and dispatch interactions. Each center interacts with many weakly connected nodes (satellites). Similar ideas, that such a "bow-tie" connectivity can play a role in robustness, have been proposed by (Zhao et al. 2006). In the field of random boolean networks (Kauffman 1969), the phase transitions from chaotic to frozen (robust) phases were related to scale-freeness and heterogeneity of the network by (Aldana 2003). We show that centralized network are capable to produce a number of patterns, while being protected against environment fluctuations.

Network models usually involve interactions between transcription factors (TFs) (Reinitz et al. 1991). In the last years, a great attention has been focused on microRNAs (He and Hannon 2004, Bartel 2009, Hendrikscon et al.

2009, Ihui et al. 2010). MicroRNAs (miRNAs) are short ribonucleic acid (RNA) molecules, on average only 22 nucleotides long and are found in all eukaryotic cells. miRNAs are post-transcriptional regulators that bind to complementary sequences on target messenger RNA transcripts (mRNAs) and repress translation or trigger mRNA cleavage and degradation. Thus, miRNAs have an impact on gene expression and it was shown recently that they contribute to canalization of development (Li et al. 2009). (Shalgi et al. 2007) shows the existence of many genes submitted to extensive miRNA regulation with many TF among these "target hubs". Without excluding other applications, we consider regulation of TF by miRNAs as a possible example of a centralized network. For this particular situation we generalize the TF network models (Reinitz et al. 1991) to take into account miRNA satellites and the centralized architecture. The interaction between network nodes is defined by sigmoidal functions that can be defined by two parameters: the maximum rates of production r_i, and sharpness constants K_i. Other important parameters, play a key role, namely, the degradation constants $\lambda_i > 0$ of centers and satellites.

We obtain a fundamental relation between the main network parameters. This relation ensures maximal robustness of the network with respect to random internal and external fluctuations, given a certain amount of flexibility defined as the number of attractors that are accessible to the network dynamics. Our mathematical results have a transparent biological interpretation: centralized motifs can be simultaneously flexible and robust. One can expect that miRNA molecules, being smaller with respect to TF, are more mobile and react faster to perturbations. This property plays a key role in the flexible and robust functioning of centralized motifs.

The paper is organized as follows. Centralized networks are introduced in Section 2. We also formulate here an important assertion on the flexibility of general centralized networks. We show that these networks are capable to generate practically all dynamics, chaotic or periodic, with any number of equilibrium states. To study robustness with respect to random fluctuations, in Section 3 we consider a toy model of simple centralized TF - miRNA networks with a single center. We show here, by an elementary way, that centralized networks with mutually repressive hub-satellite interaction can produce many different robust patterns.

2   Centralized networks

Centralized networks have been empirically identified in molecular biology, where the centers can be, for example, transcription factors, while the satellite regulators can be small regulatory molecules such as microRNAs (Li et al. 2010). Notice that, in the last decades, the theory of so-called scale-free networks has become very popular. Scale-free networks (Barabasi and Albert 2002, Lesne 2006) occur in many areas, in economics, biology and sociology. In the scale-free networks the probability $P(k)$ that a node is connected with k neighbors, has the asymptotics $Ck^{-\gamma}$, with $\gamma \in (2, 3)$. Such networks typically contain a

few strongly connected nodes and a number of satellite nodes. Hence, scale-free networks are, in a sense, centralized.

In order to model dynamics of centralized networks we adapt a gene circuit model proposed to describe early stages of Drosophila (fruit-fly) morphogenesis (Mjolness et al. 1991, Reinitz and Sharp 1995). To take into account the two types of the nodes, we use distinct variables v_j, u_i for the centers and the satellites. The real matrix entry A_{ij} defines the intensity of the action of a center node j on a satellite node i. This action can be either a repression $A_{ij} < 0$ or an activation $A_{ij} > 0$. Similarly, the matrices $\mathbf{B}$ and $\mathbf{C}$ define the action of the centers on the satellites and the satellites on the centers, respectively. Let us assume that a satellite can not act directly on another satellite (the principle of *divide et impera*). We also assume that satellites respond more rapidly to perturbations and are more diffusive/mobile than the centers. Both these assumptions are natural if we identify satellites as microRNAs.

Let M, N be positive integers, and let $\mathbf{A}, \mathbf{B}$ and $\mathbf{C}$ be matrices of the sizes $N \times M, M \times M$ and $M \times N$ respectively. We denote by $\mathbf{A}_i, \mathbf{B}_j$ and $\mathbf{C}_j$ the rows of these matrices. To simplify formulas, we use the notation

$$\sum_{j=1}^{M} A_{ij} v_j = \mathbf{A}_i v, \quad \sum_{l=1}^{M} B_{jl} v_l = \mathbf{B}_j v, \quad \sum_{k=1}^{N} C_{jk} u_k = \mathbf{C}_j u.$$

Then, the *network model* reads (we exclude diffusion effects):

$$\frac{du_i}{dt} = \tilde{r}_i \sigma \left(\mathbf{A}_i v - \tilde{h}_i \right) - \tilde{\lambda}_i u_i, \tag{1}$$

$$\frac{dv_j}{dt} = r_j \sigma \left(\mathbf{B}_j v + \mathbf{C}_j u - h_j \right) - \lambda_j v_j. \tag{2}$$

We assume that the rate coefficients $r_j, \tilde{r}_i$ are non-negative: $r_i, \tilde{r}_i \geq 0$. Here $i = 1, ..., N$, $j = 1, ..., M$ and σ is a monotone and smooth (at least twice differentiable) *sigmoidal* function such that

$$\sigma(-\infty) = 0, \quad \sigma(+\infty) = 1. \tag{3}$$

Typical examples can be given by the Fermi and Hill functions:

$$\sigma(x) = \frac{1}{1 + \exp(-x)}, \quad \sigma_H(x) = \frac{x^p}{K_a^p + x^p}, \tag{4}$$

where $K_a, p > 0$ are parameters and in the second case $x > 0$. For $x < 0$ we set $\sigma_H(x) = 0$. Analytical and computer simulation results are similar for both variants σ and σ_H.

The parameters $\lambda_i, \tilde{\lambda}_i$ are degradation coefficients, and $h_i, \tilde{h}_i$ are thresholds for activation.

Let us prove that the gene network dynamics defines a dissipative dynamics. In fact, there exists an absorbing set $\mathcal{B}$ defined by

$$\mathcal{B} = \{w = (u, v) : 0 \leq v_j \leq r_j \lambda_j^{-1}, \ 0 \leq u_i \leq \tilde{r}_i \tilde{\lambda}_i^{-1}, \ j = 1, ..., M, \ i = 1, ..., N\}.$$

One can show, by comparison principles for ordinary differential equations, that

$$
\begin{aligned}
0 \le u_i(x,t) &\le \tilde{\phi}_i(x) \exp(-\tilde{\lambda}_i t) + \tilde{r}_i \tilde{\lambda}_i^{-1}(1 - \exp(-\tilde{\lambda}_i t)), \\
0 \le v_i(x,t) &\le \phi_i(x) \exp(-\lambda_i t) + r_i \lambda_i^{-1}(1 - \exp(-\lambda_i t)).
\end{aligned}
\tag{5}
$$

Therefore, solutions of (1), (2) exist for all times t and they enters for the set $\mathcal{B}$ at a time moment t_0 and then stays in this set for all $t > t_0$. So, our system defines a dissipative dynamics and all concentrations are positive if they are positive at the initial moment. In mathematical terms, the Cauchy problem (initial value problem) for our system is well posed.

3 Complex dynamics of centralized networks

Let us show that the centralized networks have a formidable power in dynamics generation. First, we will find an asymptotic simplification of the dynamics, then show that any dynamics, periodic, chaotic, or with a number of stable steady states can be approximated by centralized networks.

3.1 Simplified dynamics when satellites are fast

We suppose here that the u-variables are fast and the v-ones are slow. Then the fast u variables are slaved, for large times, by the slow v modes: one has $u = U(v) + \tilde{u}$, where $\tilde{u}$ is a small correction. This means that, for large times, the satellite dynamics is defined almost completely by the center dynamics.

To realize this approach, let us assume that the parameters of the system satisfy the following conditions:

$$
|A_{jl}|, |B_{il}|, |C_{ij}|, |\tilde{h}_i|, |h_j| < C_0,
\tag{6}
$$

where $i = 1, 2, ..., N,\ \ i, l = 1, ..., M,\ \ j = 1, ..., N,$

$$
0 < C_1 < \tilde{\lambda}_j,
\tag{7}
$$

and

$$
r_i = \kappa R_i, \quad \tilde{r}_i = \kappa \tilde{R}_i,
\tag{8}
$$

where

$$
|R_i|, |\tilde{R}_i| < C_5, \quad \lambda_i = \kappa \bar{\lambda}_i,\ |\bar{\lambda}| < C_6,
\tag{9}
$$

where κ is a small parameter, and where all positive constants C_k are independent of κ.

Assertion 2.1. *Under assumptions (6), (7), (8) for sufficiently small $\kappa < \kappa_0$ solutions (u, v) of (1), (2) satisfy*

$$
u = U(v(t)) + \tilde{u}(t),
\tag{10}
$$

where the j-th component U_j of U is defined by

$$
-\tilde{\lambda}_j U_j = \kappa G_j(v),
\tag{11}
$$

4

where

$$G_j = \tilde{R}_j \sigma \left(\mathbf{A}_j v(t) - \tilde{h}_j \right)$$

The function $\tilde{u}$ satisfies estimates

$$|\tilde{u}| < c\kappa^2 + R\exp(-\beta t), \quad \beta > 0. \tag{12}$$

The v dynamics for large times $t > C_1 |\log \kappa|$ takes the form

$$\frac{dv_i}{dt} = \kappa F_i(u,v) + w_i, \tag{13}$$

where w_i satisfy

$$|w_i| < c\kappa^2$$

and

$$F_i(u,v) = R_i \sigma \left(\mathbf{B}_i v + \mathbf{C}_i U(v) - h_i \right) - \bar{\lambda}_i v_i.$$

This assertion, known in computational biology as the quasi-steady state assumption, can be proved by well known methods from the theory of differential equations (Henry 1981).

3.2 Realization of prescribed dynamics by networks

Our next goal is to show that dynamics (13) can realize, in a sense, arbitrary dynamics of the centers. To precise this, let us describe the method of realization of the vector fields for dissipative systems (proposed by Poláčik 1991, for applications see, for example, Dancer - Poláčik 1999, Rybakowski 1994, Vakulenko 2000). This method is based on the well developed theory of invariant and inertial manifolds, see Marion 1989, Mane 1977, Constantin, Foias, Nicolaenko and Temam, 1989, Chow-Lu 1988, Babin-Vishik 1988). One can show that there are systems enjoying the following properties:

A *These systems generate global semiflows $S_{\mathcal{P}}^t$ in an ambient phase space H. These semiflows depend on some parameters $\mathcal{P}$ (which could be elements of another parameter space $\mathcal{B}$). They have global attractors and finite dimensional local attracting invariant C^1 (continuously differentiable) - manifolds $\mathcal{M}$, at least for some $\mathcal{P}$.*

B *Dynamics of $S_{\mathcal{P}}^t$ reduced on these invariant manifolds is, in a sense, "almost completely controllable". It can be described as follows. Assume the differential equations*

$$\frac{dp}{dt} = F(p), \quad F \in C^1(B^n) \tag{14}$$

define a dynamical system in the unit ball $B^n \subset \mathbf{R}^n$.

For any prescribed dynamics (14) and any $\delta > 0$, we can choose suitable parameters $\mathcal{P} = \mathcal{P}(n, F, \delta)$ such that

B1 *The semiflow $S_{\mathcal{P}}^t$ has a C^1- smooth locally attracting invariant manifold $\mathcal{M}_{\mathcal{P}}$ diffeomorphic to the ball B^n;*

B2 *The reduced dynamics $S_{\mathcal{P}}^t|_{\mathcal{M_P}}$ is defined by equations*

$$\frac{dp}{dt} = \tilde{F}(p, \mathcal{P}), \quad \tilde{F} \in C^1(B^n) \tag{15}$$

where the estimate

$$|F - \tilde{F}|_{C^1(B^n)} < \delta \tag{16}$$

holds. In other words, one can say that, by $\mathcal{P}$, the dynamics can be specified to within an arbitrarily small error.

Thus, all dynamics can occur as inertial forms of these systems. Such systems can be named *maximally dynamically flexible, or, for brevity, MDF systems.*

Such dynamics can be *chaotic.* There is a rather wide broad in different definitions of "chaos". In principle, one can use here any concept of chaos. If this chaos is stable under small C^1 -perturbations this kind of chaos occurs in the dynamics of MDF systems. To fix ideas, we use here, following Ruelle and Takens 1971, Newhouse, Ruelle and Takens 1971 Smale 1980, Anosov 1995), such a definition. We say that a finite dimensional dynamics is chaotic if this generates a non-quasiperiodic hyperbolic invariant set Γ. If, moreover, this set Γ is attracting we say that Γ is a chaotic (strange) attractor. (For definition of hyperbolic sets, see Ruelle 1989, Anosov 1995). In this paper, we use only the following basic property of hyperbolic sets, so-called Persistence (Ruelle 1989, Anosov 1995). This means that the hyperbolic sets are, in a sense, stable(robust): if (14) generates the hyperbolic set Γ and δ is sufficiently small, then dynamics (14) also generates another hyperbolic set $\tilde{\Gamma}$. Dynamics (14) and (15) restricted to Γ and $\tilde{\Gamma}$ respectively, are topologically orbitally equivalent (on definition of this equivalence, see Ruelle 1989, Anosov 1995). It is important to mention that a chaos in dissipative systems may be stable, in the sense of structural stability, and although not yet observed in gene networks, structurally stable chaotic itineracy is thought to play a functional role in neuroscience (Rabinovitch 1998).

Therefore, any possible chaotic robust dynamics can be generated by the MDF systems, for example, the Smale horseshoes, Anosov flows, the Ruelle-Takens-Newhouse chaos, see Newhouse, Ruelle, and Takens, 1971, Smale 1980, Ruelle 1989. Some examples of the MDF systems were given in Dancer- Poláčik 1999, Rybakowski 1994, Vakulenko 2000.

Assertion 2.1 allows us to apply this approach to centralized network dynamics. To this end, assume that (8) and (9) hold. Moreover, let us assume

$$\lambda_i = \kappa^2 \bar{\lambda}_i, \quad h_i = \kappa \bar{h}_i \tag{17}$$

where all coefficients $\bar{h}_i$ are uniform in κ as $\kappa \to 0$. We also assume that all direct interactions between centers are absent, $\mathbf{B} = \mathbf{0}$. This constraint is not essential.

Since $U_j = O(\kappa)$ for small κ, we can use the Taylor expansion for σ in (13). Then these equations reduce to

$$\frac{dv_i(\tau)}{d\tau} = \rho_i(\mathbf{C}_i V(v) - \bar{h}_i) - \bar{\lambda}_i v_i + \tilde{w}_i(t), \tag{18}$$

where $\rho_i = \bar{r}_i \sigma'(0)$, $i = 1, 2, ..., M$ and τ is a slow rescaling time: $\tau = \kappa^2 t$. Due to conditions (17), the corrections $\tilde{w}_i$ satisfy

$$|\tilde{w}_i| < c\kappa.$$

Let us focus now our attention to non-perturbed equation (18) with $\tilde{w}_i = 0$. Let us fix the number of centers M. The number of satellites N will be considered as a parameter.

The next important assertion immediately follows from well known approximation theorems of the multilayered network theory, see, for example, Barron 1993, Funahashi and Nakamura 1993.

Assertion 2.2. *Given a number $\delta > 0$, an integer M and a vector field $F = (F_1, ..., F_M)$ defined on the ball $B^M = \{|v| \leq 1\}$, $F_i \in C^1(B^M)$, there are a number N, an $N \times M$ matrix $\mathbf{A}$, an $M \times N$ matrix $\mathbf{C}$ and coefficients h_i, where $i = 1, 2, ..., N$, such that*

$$|F_j(\cdot) - \mathbf{C}_j W(\cdot)|_{C^1(B^M)} < \delta, \tag{19}$$

where

$$W_i(v) = \sigma\left(\mathbf{A}_i v - h_i\right), \tag{20}$$

where $v = (v_1, ..., v_M) \in \mathbf{R}^M$.

This assertion gives us a tool to control network dynamics. Assume $\bar{h}_i = 0$. Then equations (18) with $\tilde{w}_i = 0$ reduce to the Hopfield-like equations for variables $v_i \equiv v_i(\tau)$ that depend only on τ:

$$\frac{dv_l}{d\tau} = \mathbf{K}_l W(v) - \bar{\lambda}_l v_l, \tag{21}$$

where $l = 1, ..., M$, the matrix $\mathbf{K}$ is defined by $K_{lj} = \rho_l C_{lj} R_j \tilde{\lambda}_j^{-1}$. The parameters $\mathcal{P}$ of (21) are $\mathbf{K}$, M, h_j and $\bar{\lambda}_j$.

In this case one can formulate the following result.

Assertion 2.3. *Let us consider a C^1-smooth vector field $Q(p)$ defined on a ball $B_R \subset \mathbf{R}^M$ and directed strictly inside this ball at the boundary ∂B^M:*

$$F(p) \cdot p < 0, \quad p \in \partial B^M. \tag{22}$$

Then, for each $\delta > 0$, there is a choice of parameters $\mathcal{P}$ such that (21) δ -realizes system (14). This means that (21) is a MDF system.

This follows from Assertions 2.1 and 2.2.

4   A toy model of centralized network

In this section we consider a simple centralized network that, nonetheless, can produce a number of point attractors (stable steady states). Due to its simple structure, we can investigate here the robustness of this system.

Let us consider a central node interacting with many satellites. This motif can appear as a subnetwork in a larger scale-free network. In order to study robustness, we add noise to the model. We consider two types of stochastic perturbations. The first type of perturbations is a Langevin type additive noise that can simulate intrinsic stochastic fluctuations of gene expression dynamics. The choice of additive noise is for the sake of simplicity, however more general multiplicative noise can be used with no change of the results. The second type of noise is a shot-like perturbation that can simulate the external contributions to noise, caused by the environment. Furthermore, we replace the sigmoid in (2) by a linear function. This is justified in TF - miRNAs networks, where the action of satellites (miRNA's) on centers (TF's) is post-transcriptional and produces a modulation of the production rate of the center protein. This modulation can be modeled by a soft sigmoid or even by a linear function. Moreover, to simplify our model, we assume that all satellites are, in a sense, equivalent.

The network dynamics can be described then by the following equations:

$$\frac{du_i}{dt} = -\lambda u_i + f_i(v) + \xi_i(t), \tag{23}$$

$$\frac{dv}{dt} = -\nu v + Q(u) + \xi_0(t), \tag{24}$$

where f_i, Q are defined by

$$Q(u) = a_0 + a \sum_{i=1}^{n} u_i, \quad f_i(u) = r\sigma(b(v - h_i)),$$

Here ξ_i are noises, the coefficient $\lambda > 0$ is a satellite mobility (degradation rate), $r > 0$ is the satellite maximum production rate, b defines a sharpness of center action on the satellites, $\nu > 0$ is a center mobility (degradation rate), a is the strength of the satellites feedback action on the center.

We consider the following type of noises: non-correlated white noise

$$\langle \xi_i(t), \xi_j(t') \rangle = \beta_i \delta_{ij} \delta(t - t') \tag{25}$$

where $\beta_i > 0$ are intensities, and shot-like noise

$$\xi_i(t) = \beta_i \eta_i \delta(t - \tau_j) \tag{26}$$

where τ_j are random shot times following a Poisson process, β_i are noise amplitude coefficients, and η_i are random variables distributed uniformly on $[0, 1]$. In numerical simulations we set $\delta(t - \tau_j) = 1$ with a probability $p_0 << 1$ and $\delta(t - \tau_j) = 0$ with the probability $1 - p_0$, where $\tau_j = j\delta t$, δt is a time step. Such noises ξ_i can summarize the effect of a strong environment fluctuations on the satellite and center expression.

We study the problem under the following

Assumption. *Let the derivatives of f_i and Q satisfy*

$$f_i^{'}(v)Q'(u) > 0 \ for \ all \ i, u, v.$$

8

Then one can show, following (Hirsch, 1988) that the dynamics is monotone, and, therefore, all trajectories converge to equilibria. The numerical simulations confirm this fact. Notice that the above assumption is not needed when satellites are fast, because in this case the asymptotic dynamics is one dimensional and in dimension one all the attractors are stable steady states (point attractors). Although this simple system can not generate chaos or periodic behavior, the number of point attractors can be arbitrarily large, and thus this system is nonetheless flexible.

4.1 Multistationarity of the toy model

Let us fix the signs of the satellite actions on the center assuming that $a < 0$. This restriction is fulfilled in gene networks, where the centers are transcription factors (TF) and the satellites are microRNAs (indeed, usually microRNA can only repress transcription factors). Let us show that the toy model admits coexistence of any number of point attractors.

Let us make a transformation reducing (23) and (24) to a system of two equations introducing a new variable Z by

$$Z = \sum_{j=1}^{N} u_j, \quad G(v) = \sum_{j=1}^{N} r\sigma(b(v - h_j)).$$

Then, by summarizing eqs. (23), one obtains

$$\frac{dZ}{dt} = -\lambda Z + G(v), \tag{27}$$

$$\frac{dv}{dt} = -\nu v + a_0 + aZ. \tag{28}$$

This system is relatively simple and it can be studied analytically and numerically. Since all trajectories are convergent we obtain that the attractor consists of equilibria defined by

$$\lambda Z + F(Z) = 0, \quad F(Z) = G(\nu^{-1}(a_0 + aZ)). \tag{29}$$

Let $\mathcal{P} = \{b, h_i, N, a_0, a\}$ be free parameters that can be adjusted. Like to the previous section, we can "control" the nonlinearity F by $\mathcal{P}$ and use the fact that $F(Z)$ can approximate arbitrary smooth functions. The following assertion shows that the system is multi-stationarity with an arbitrary number of point attractors:

Assertion 3.1. *Let N be a positive integer. Then there are coefficients $b, \lambda > 0, r > 0$, where $i = 1, ..., N$, $\nu > 0$ and h_i, a_0, a in such a way that equation (29) has at least $n + 1$ stable roots that can be placed in any given positions in the Z-space.*

The main idea of the proof can be illustrated by Fig. 1 and holds in both cases of the Fermi and the Hill sigmoids. Let us make a variable change $w =$

$\lambda Z/r$. The steady states are solutions of the equation $rw = F(w)$, where the function $F(w)$ is close to a step function with N steps; each step is given by the function $\sigma(\gamma(w - \bar{h}_i))$ that is close to Heaviside step function for large γ. Here γ is a parameter that defines the sigmoid sharpness:

$$\gamma = abr(\nu\lambda)^{-1}. \tag{30}$$

The steady states of the system are given by the intersections between the graph of $F(w)$ and the straight line of slope r. An elementary argument shows that the intersections lying on horizontal segments of the graph of $F(w)$ are stable attractors, whereas the intersections on ascending vertical segments correspond to repellers.

The position of the i-th step in w-space is $\bar{h}_i$ and its height is r. Under an appropriate choice of $\bar{h}_i$ this entails our assertion (see Fig. 1). In the neural network theory, γ is known as *gain parameter*. This quantity, defined as the product of rates on sharpness divided on the product of degradation coefficients, gives the maximal possible density of the equilibrium states in w-space.

It is useful to note that one gets $n + 1$ attractors on the horizontal segments of the step function provided that $\bar{h}_i$ decrease with i.

Notice that the main condition to obtain flexibility (multistationarity) is the sharpness of the sigmoidal function, meaning that the gain parameter γ should be large. The construction is robust: we can vary $w_i, b, \bar{h}_i$ but the number of equilibria is conserved.

4.2 Robustness and stability of attractors

The roots of Eq.(29) are point attractors and then they are dynamically stable, otherwise, they are repellers and unstable. In Fig. 1, attractors correspond to intersections of the straight line $y = rw$ with the curve $y = F(w)$, lying on horizontal segments of the graph of F. A simple argument suggests that the positions of these attractors are robust with respect to variations of the thresholds $\bar{h}_i$. Indeed, a perturbation of $\bar{h}_i$ induces a horizontal shift of the step $\sigma(\gamma(w - \bar{h}_i))$, and the positions of the attractors are only slightly affected.

More insight into robustness of the centralized toy model can be obtained by considering the noisy case $\xi_i \neq 0$.

First, let us consider the case of the Langevin noise (25). We are interested in the robustness of the number and positions of the attractors with respect to noises $\xi_i(t)$. Near a point attractor, the equations (27), (28) can be linearized. The linearized dynamics is defined by the following matrix $\mathbf{H}$:

$$\begin{pmatrix} -\lambda & \mu \\ a & -\nu \end{pmatrix}$$

where $\mu = G'(v_{eq})$. For large γ and for stable stationary states μ is small, $\mu = G'(v_{eq}) \to 0$ as $\gamma \to \infty$. Let us assume that the noises ξ_i are independent white noises. Using standard results from the theory of linear stochastic differential
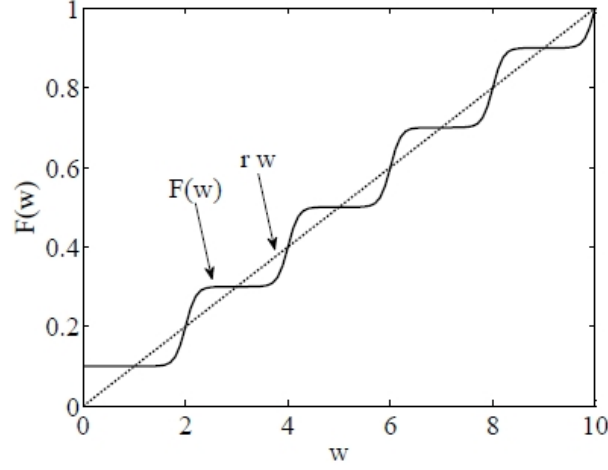
Figure 1: Intersections of the curve $y = F(w)$ and the straight line $y = rw$ correspond to steady states; intersections on horizontal segments of the graph of F correspond to stable steady states.

equations, see, for example, Keizer 1987, it follows that small deviations $\delta Z, \delta v$ from the equilibrium are normally distributed with the density

$$\rho(\delta Z, \delta v) = const \exp(-X \cdot \mathbf{M}^{-1} \cdot X^{tr}), \quad X = (\delta Z, \delta v), \tag{31}$$

where $\mathbf{M}$ is a symmetric, positively defined, 2×2 covariation matrix with entries $m_{11}, m_{22}, m_{12} = m_{21}$. This matrix can be defined by the well known relation (the fluctuation-dissipation theorem):

$$\mathbf{HM} + \mathbf{MH}^{tr} = -\mathbf{B}, \tag{32}$$

where $\mathbf{B} = diag(B_1^2, B_2^2)$ and, since the noises are non-correlated, $B_1 = \sqrt{\sum_{i=1}^{N} \beta_i^2}$, $B_2 = \beta_0$.

As a result, a characteristic fluctuation amplitude F_A is proportional to the maximum $\max\{\theta_1^{1/2}, \theta_2^{1/2}\}$ where θ_i are eigenvalues of $\mathbf{M}$. Eq. (32) can be resolved explicitly and θ_i can be found.

Now we can investigate the following problem: how to tune the parameters λ, ν and a to obtain the minimal fluctuation amplitude F_A with respect to the noise under a given multistationarity level (this means $\gamma = \gamma_0 >> 1$ is fixed but we can vary the degradation rates ν, λ). This optimization problem can be resolved numerically. The results, which describe the optimal λ_{opt}, ν_{opt} as functions of γ, are as follows.

The case **A**), $B_2 >> B_1$, the center is under a stronger noise than the satellites. Then the center degradation rate ν_{opt} should be large, and λ_{opt} is a small, decreasing in γ function.

The case **B**), $B_2 \leq B_1$, the center is under smaller noise than the satellites. Then the center degradation rate ν_{opt} should be smaller, $\lambda_{opt} > \nu_{opt}$, and the both parameters are decreasing in γ. This situation is illustrated by Fig. 2.
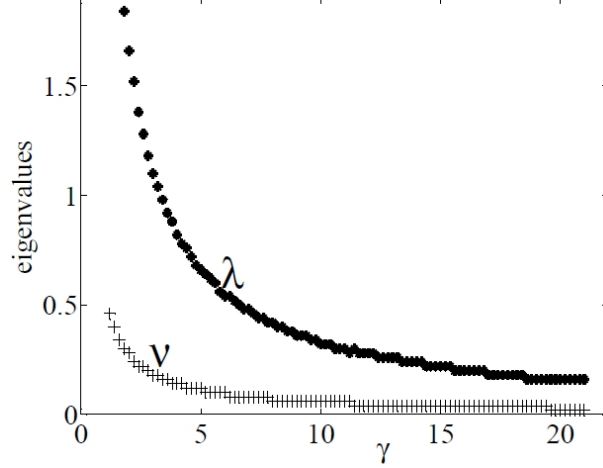

Figure 2: Optimal degradation parameters ν_{opt}, λ_{opt} (minimizing the eigenvalues of the matrix **H**) as functions of the gain parameter γ in the case $B_2 \leq B_1$, when the center is under smaller noise than the satellites.

The classical ideas of the invariant manifold theory, discussed in the preceding section, allow us to systematize these results. The centralized network can function under two main and quite opposite regimes. The first one arises when $\lambda >> \nu$. Then the satellite dynamics is slaved by the center motion. The center dominates and such a regime can be named *power of the center*. This regime is stable if β_0 is small, but β_i are large (the noises act on satellites mainly, case **B**). Considering that the noise intensity is larger for those components that are expressed in larger copy numbers, the case should be representative for miRNA-TF networks, when miRNA are in smaller copy numbers than the transcription factors. In this case the noise perturb satellite states (u_i) but, since the satellites are controlled by the center state v, satellites return to the normal states and dynamics is robust, the noise does not damage the attractor. The opposite regime is when $\lambda << \nu$. Then, opposite to the previous situation, the center dynamics is slaved by the satellites motion. Such a regime can be named *satellite democracy*. This regime is stable when β_0 is large, but β_i are small (the noise acts stronger on the center, case **A**). Here the noise can perturb the center state (v) but this state can be restored by satellites. The large time dynamics is robust, again the noise does not damage the attractor.

Similar results are illustrated in the case of a shot noise in Fig. 3.

So, we obtain an interesting connection between robustness, multistationarity and network rate: to support robustness and multistationarity in a noisy situation, we should decrease the degradation constants. Multistationarity of

molecular switches is important in decision making processes in differentiation, development, and immune response of the organisms. Our finding means that noise protected switches are necessarily slow.
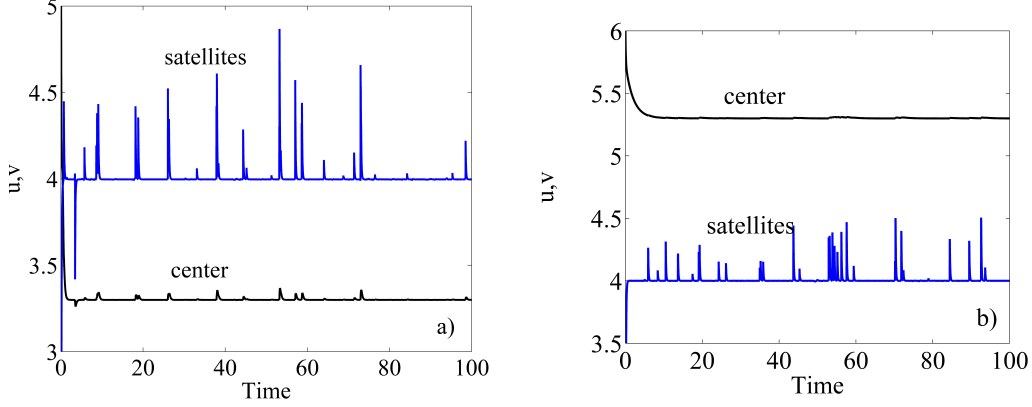

Figure 3: Numerical simulations of the system's trajectories under shot noise. The parameters were as follows: $N = 6$, $\sigma(z) = \sigma_H(z)$ with $p = 4$, $b = 20$, $K_a = 1$, $h_i = i$, $r = 1$, $\lambda = 5$, $a_0 = 0.3\nu$, $x \in [0, 10]$ and $t \in [0, 120]$. The parameter $\beta_i = 0$ for all i beside $i = 3$, where $\beta_3 = 50$. The two functioning regimes correspond to different values of ν, a, namely, $a = 50$, $\nu = 5$ (satellites democracy (SD), a)), and $a = 5$, $\nu = 0.5$ (power of the center (PC), b)). In the both cases the system shows multistationarity. For the chosen initial data trajectories converge to an attractor $v \approx 5.3$ as $t >> 1$ in the PC regime and also in the SD regime $v \to 3.3$. This means that the fast center loses the attractor control, while the slow center controls dynamics even under large deviations.

5   Conclusion

We have considered networks with two types of nodes. The v-nodes, called centers, are hyperconnected and interact one to another via many u-nodes, called satellites. We show, by recently advanced mathematical methods, that this centralized network architecture, allows us to control network dynamics to create complicated dynamical regimes. This network organization creates feedback loops that are capable to generate practically all kinds of dynamics, chaotic or periodic, or having a number of equilibrium states. This strong flexibility could be crucial for adaptive biological functions of these networks.

Using the simple example of a motif with a single center, we also argued that centralized networks can perform trade-offs between flexibility and robustness. To support both flexibility and robustness in a noisy situation, the network should function in a slow manner, i.e, we propose slow-down as a way to increase stability.

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Which of the nodes should be slowed-down depends on the fluctuations. Basic ideas from the invariant manifold theory show that if the noises act on the satellites, then, in order to conserve dynamics and the attractor structure, the center should be slow and controls the satellites (we called this regime *power of the center*). In the opposite case, when the noise acts on the center, the satellites should be slow in order to control the center and the global dynamics (we called this regime *satellites democracy*).

We did not consider here extrinsic noise or parametric variability of the system, that we plan to study in the future. We also think that the slow-down effect could be observed in all systems where there is a separation into slow and fast variables, independently of architecture.

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