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Structural Properties of Biological and Ecological Systems

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Abstract

It is astounding how systems in nature can survive under completely different environmental conditions and in the presence of huge parameter variations. Structural analysis aims at explaining why this is possible by studying properties of biological models that hold regardless of parameter values. Here, we discuss selected system properties that have been successfully investigated and explained just looking at the structure, without the need of quantitative information.

Keywords

Dynamical systems · Structural properties · Systems biology

Introduction

Mathematical models of biological and ecological systems are important to help predict their dynamics, as well as to formulate and support hypotheses explaining their behavior (Alon 2006; Edelstein-Keshet 2005). Deterministic models are often employed when the species being modeled are abundant and do not experience stochastic fluctuations (cf. "Deterministic Description of Biochemical Networks" by J. Stelling and H.-M. Kalthenbach and "Stochastic Description of Biochemical Networks" by J. P. Hespanha and M. Khammash). Yet, deterministic models still include uncertain parameters that reflect the complexity of biological environments. Tools from control and dynamical systems theory allow us to draw conclusions on their properties and dynamic behaviors (Cosentino and Bates 2011; Del Vecchio and Murray 2014; Sontag 2005), also in the presence of uncertainty.

We call *structural* a property that is *independent* of the particular parameter values (Blanchini and Franco 2011; Shinar and Feinberg 2010). We consider properties that can be mathematically defined, such as the number of equilibria and their stability, and we survey methods to structurally assess these properties for biological and ecological systems. The qualitative (parameter-free) methods discussed in this entry complement quantitative (numerical) approaches to establish parametric robustness, described in "Robustness

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Analysis of Biological Models" by S. Waldherr and F. Allgöwer.

Systems and Structures

We consider the ordinary differential equation model:

$$\dot{x}(t) = f(x(t), \mu), \tag{1}$$

where $x \in \mathbb{R}^n_+$ is a vector of species concentrations or population densities, $f : \mathbb{R}^n_+ \times \mathbb{R}^q_+ \to \mathbb{R}^n$, and $\mu \in \mathbb{R}^q_+$ is a vector of parameters. Both f and μ may be uncertain or even unknown and time-varying. For instance, protein degradation may be temperature dependent and may be modeled with a linear or saturating function (Sontag 2005); population birth rates depend on variable environmental factors and may be modeled as exponential or logistic growth (May 1974). It is often reasonable to assume that the components of f (f_i, $i = 1, ..., n$) are *monotonic* functions of the x_js, i.e., each $\partial f_i(x, \mu)/\partial x_j$ is sign-definite (either always nonnegative or nonpositive) in the domain of interest; under this assumption, the Jacobian matrix J of the system is also sign-definite and can be mapped to a sign matrix Σ whose element (i, j) is the sign of $\partial f_i(x, \mu)/\partial x_j$. Then, this *sign* matrix Σ captures the *structure* of the system, which remains fixed despite uncertainty or variability in the model.

For (bio)chemical reaction networks (Angeli 2009; Del Vecchio and Murray 2014), the model in (1) can be rewritten as:

$$\dot{x}(t) = Sg(x(t), \mu) + g_0(\mu), \tag{2}$$

where $S \in \mathbb{Z}^{n\times m}$ is a stoichiometry matrix of signed integer entries, $g : \mathbb{R}^n_+ \times \mathbb{R}^q_+ \to \mathbb{R}^m_+$ is a vector of reaction rate functions, and $g_0 : \mathbb{R}^q_+ \to \mathbb{R}^n_+$ models external inputs. When the *law of mass action* applies, the reaction rates can be modeled as polynomial functions of the species concentrations. More in general, the components of g (g_i, $i = 1, ..., m$) are nonnegative functions, *monotonic* in the x_js; they depend on the system state and usually include uncertain or fluctuating parameters. Conversely, matrix S is constant, independent of both states and parameters μ, and represents the *interconnection structure* of the various reactions. System (1) is a particular case of (2) with $S = I$ (the identity), $g = f$, and $g_0 = 0$. The Jacobian of a system of the form (2) is not sign-definite in general, but it always admits the BDC decomposition (Blanchini and Giordano 2014; Giordano et al. 2016):

$$J(x) = BD(x)C, \tag{3}$$

where $D(x)$ is a diagonal matrix carrying on the diagonal the absolute value of the partial derivatives of the vector function g, while B and C are constant matrices that capture the system *structure*.

Matrix Σ, matrix S, and the matrix pair B, C are examples of *structures* of a biological model, which are not affected by parameter uncertainty or variability. If a property holds due to the particular structure of the model, regardless of the value of the parameters μ, then it is a *structural property*.

Positivity and Boundedness

Any biological or ecological model should be a positive system, because negative concentrations or population densities are not physically acceptable. If a biological model does not *structurally* satisfy the positivity property, it is not well-posed and should be revised.

System (1) is positive if assuming that $x(0) \geq 0$ (componentwise), then $x(t) \geq 0$ for all $t \geq 0$.

A system of the form

$$\dot{x}_i = f_i(x_1, x_2, \ldots x_n, \mu), \quad i = 1, \ldots, n$$

is positive if and only if, for all k, when $x_k = 0$, its derivative $\dot{x}_k$ is nonnegative:

$$f_k(x_1, x_2, \ldots, x_{k-1}, \underbrace{0}_{x_k}, x_{k+1}, \ldots x_n, \mu) \geq 0.$$

If this condition holds for arbitrary values of μ, then the system is structurally positive. For a *linear* autonomous system $\dot{x} = Ax$, positivity is

equivalent to the fact that A is a Metzler matrix ($A_{ij} \geq 0$ for $i \neq j$).

Boundedness is another important property often (although not always) structurally verified by biological and ecological models. The concentrations of biomolecular species such as proteins and mRNA may fluctuate, but remain bounded in a living cell due to the presence of degradation or secretion mechanisms; similarly, biological species such as predators and preys may experience wide fluctuations, but they rarely exceed thresholds related to the carrying capacity of their ecosystem. In a model of the form (1), we say that the solutions are bounded if, for any initial state $x(0) \geq 0$, there exists a positive constant ξ such that $0 \leq x_i(t) \leq \xi$ for all $t > 0$ and for all i.

The concept of boundedness is directly related to the existence of positively invariant sets; a (bounded) subset $\mathcal{P}$ of the state space is said to be invariant if $x(0) \in \mathcal{P}$ implies that $x(t) \in \mathcal{P}$ for all $t > 0$. Nagumo's theorem provides general necessary and sufficient conditions for a set to be invariant, conditions that may be verified structurally (Blanchini and Miani 2015). The applicability of Nagumo's theorem is very general. Yet, for significant classes of systems, structural boundedness can be assessed by direct inspection. For example, consider the model:

$$\dot{x} = -\Lambda x + Sg(x) + g_0,$$

where Λ is a positive diagonal matrix, modeling the presence of self-degradation for all species, and all the mutual interactions expressed by the entries of g are assumed to be bounded. This system has the form (2), with extended matrix $\tilde{S} = [-\Lambda \ S]$ and extended vector $\tilde{g}(x) = [x \ g(x)]^\top$. If g is a vector of bounded functions, $|[Sg(x) + g_0]_i| \leq \nu$, then

$$\dot{x}_i = [Sg(x) + g_0]_i - \lambda_i x_i \leq \nu - \lambda_i x_i.$$

Hence for all i, if $x_i \geq \xi = \max\{\nu/\lambda_i\}$, we have $\dot{x}_i < 0$, and the variable cannot grow above ξ. The existence of such a bound is a structural property, even though its value depends on the parameters.

Boundedness of the solutions implies the existence of at least an equilibrium, a topic discussed next.

Analysis of the Equilibria

The vector $\bar{x}(\mu) \geq 0$ is an equilibrium for (1) if

$$0 = f(\bar{x}(\mu), \mu)$$

or an equilibrium for (2) if $0 = Sg(\bar{x}(\mu), \mu) + g_0(\mu)$. The equilibria of nonlinear systems like (1) and (2) are generally found via numerical methods. Their stability can be analyzed via standard methods such as Routh-Hurwitz criterion or eigenvalue computation for the linearized system. Unfortunately, in general this requires the knowledge of the parameter values.

Tools from *topological degree theory* (Lloyd 1978) can help structurally establish existence, uniqueness, and, in some cases, stability of equilibria. If the solution of (1) is bounded in a convex set $\mathcal{P}$ that is positively invariant and has a non-empty interior, then at least one equilibrium $\bar{x}$ exists. To analyze how many, assume that no equilibrium is on the boundary of $\mathcal{P}$ and that all equilibria $\bar{x}_k$ are regular, namely, $\det[J(\bar{x}_k)] \neq 0$ for all k. Then it must hold that $\sum_k \text{sign}\{\det[-J(\bar{x}_k)]\} = 1$; see Lloyd (1978). Hence, there cannot be an even number of regular equilibria in the interior of $\mathcal{P}$. If there is an odd number of equilibria, they must obey a rule: for instance, if three regular equilibria exist, exactly one must be such that $\det[-J(\bar{x}_k)] < 0$, hence it must be unstable (because $\det[-J(\bar{x}_k)]$ is the constant term of the corresponding characteristic polynomial and a characteristic polynomial with all positive coefficients is necessary for stability). If $\det[-J(\bar{x})] > 0$ structurally, then the equilibrium must be unique.

Stability of the Equilibria

Analyzing stability of the equilibria is challenging if the parameter values are unknown. However, for important classes of systems, powerful structural results are available. For instance, compartmental systems (Jacquez and Simon 1993),

which can be seen as networks of unimolecular chemical reactions $X_i \rightharpoonup X_j$, have a remarkable intrinsic stability property (Maeda et al. 1978).

Interesting results come from the theory of chemical reactions (Clarke 1980; Feinberg 1987). For example, the structural local stability of an equilibrium can be cast as a D-stability problem (Clarke 1980); a matrix A is D-stable if A is Hurwitz and AD is Hurwitz for any arbitrary diagonal matrix D with positive elements. Also, the famous *deficiency zero theorem* (Feinberg 1987) exploits the algebraic properties of matrix S to provide structural results. The stoichiometric matrix can be decomposed as $S = NM$, where N captures the molarity of each species x_i in each complex (group of species appearing on either side of the reactions whose rates are in vector g), while M is the complex-reaction incidence matrix; then, the deficiency of the network is the structural quantity $\delta = \dim\{\ker(N) \cap \text{range}(M)\}$, which depends only on S and not on the parameters μ. If the network is weakly reversible (if there is a directed path from complex i to complex j, then a path from j to i is also present) and all components of g are of the mass action type (namely, for a chemical reaction $p_1X_1 + p_2X_2 + \ldots p_rX_r \rightharpoonup q_1Y_1 + q_2Y_2 + \ldots q_sY_s$, the rate has the form $g_j = \mu_j x_1^{p_1} x_2^{p_2} \ldots x_r^{p_r}$), the deficiency zero theorem states that, if $\delta = 0$, then there exists within each positive stoichiometric compatibility class (associated with the initial conditions) a single equilibrium, which is locally asymptotically stable. Remarkably, the theorem is proven by showing that the system entropy is a Lyapunov function.

Structural stability of biochemical networks can be assessed via quadratic Lyapunov functions (even parameter dependent) (Clarke 1980) and, also for *general* reaction rates that are not mass action, via non-quadratic Lyapunov functions (Al-Radhawi and Angeli 2016; Blanchini and Franco 2011; Blanchini and Giordano 2014). *Structural* piecewise-linear Lyapunov functions can be systematically built for a general system (2) based on its BDC decomposition (Blanchini and Giordano 2014).

Perturbation of the Equilibrium

A biological system can be subject to unknown or uncertain inputs/perturbations, whose structural effect can be analyzed as follows. Suppose that the system is at some (unknown) stable steady-state $\bar{x}$, corresponding to some nominal (unknown) value $\bar{\mu}$ of the parameters, and consider a relevant system output $y = Hx$, where H is a row vector. Assume that one of the parameters suddenly becomes $\bar{\mu}_j + u$, with u positive (without loss of generality) and not too large (not to compromise stability). After a transient, the system settles at a new equilibrium $\bar{x} + z(\infty)$ and a new output $\bar{y} + v(\infty)$. We have a *structural influence* if the sign of the steady-state output variation, $v(\infty)$, induced by the perturbation does not depend on the parameters $\bar{\mu}$ (Dambacher et al. 2002). Then,

$$\text{sign}[v(\infty)] \in \{+, -, 0, ?\},$$

corresponding to the cases when the steady-state output variation is always positive, always negative, always zero, or indeterminate (i.e., it depends on the parameters). For systems of the form (2), structural influences can be assessed based on the BDC decomposition (3). We can investigate the *structural steady-state influence* of a constant input variation $u > 0$ (which is the parameter we are perturbing) on the output variation v by analyzing the steady-state output of the system:

$$\dot{z} = BDCz + Eu, \quad v = Hz, \quad D \text{ positive diagonal},$$

where $z = x - \bar{x}$. The structural input-output influence of u on v can be assessed based on the sign of

$$\phi(D) = \det \begin{bmatrix} -BDC & -E \\ H & 0 \end{bmatrix} = \frac{v(\infty)}{u}.$$

As shown in Giordano et al. (2016), function $\phi(D_1, D_2, \ldots, D_m)$ is positive (negative) for all $D_k > 0$ if and only if $\phi(1, 1, \ldots, 1) > 0$ (< 0) and $\phi(\hat{D}_1, \hat{D}_2, \ldots, \hat{D}_m) \geq 0$ (≤ 0) for all possible choices of $\hat{D}_k \in \{0, 1\}$, while it is zero

if and only if it is zero for all possible choices of $\hat{D}_k \in \{0, 1\}$. It is undetermined otherwise.

When both E and H have a single nonzero element, say $E_j = 1$, $H_i = 1$, we can investigate the steady-state influence on variable i due to an input affecting the equation of variable j. The structural influence matrix collects all possible (i, j) pairs (Giordano et al. 2016). A zero steady-state influence is associated with perfect adaptation, a remarkable feature of some biological systems that transiently respond to a persistent input change and eventually return to the original equilibrium (Alon 2006; Briat et al. 2016; Steuer et al. 2011).

Structural Feedback Loops

We use simple examples to illustrate the effects of structural feedback loops, and of their sign, in systems of the form (1). Feedback, present in most biological dynamical systems, enables all homeostatic processes, as well as complex dynamic behaviors such as bistability (or multi-stability) and oscillations. As conjectured in Thomas (1981), positive feedback is a necessary condition for bistability, while negative feedback is a necessary condition for oscillations. These conjectures were proved in Gouze (1998) and Snoussi (1998). We consider a two-node gene network:

$$\tau_a \dot{a} = -a + f_b(b), \qquad \tau_b \dot{b} = -b + f_a(a) + u,$$

where a and b are concentrations of molecular species and u is an external signal. Functions $f_b(b)$ and $f_a(a)$ model the production rate of species a and b and are monotonically increasing Hill-type functions:

$$f(x) = \alpha \frac{x^p}{\beta + x^p} + \gamma,$$

where α is the maximal production rate, β is a threshold, p measures the sharpness of the sigmoid, and γ represents a basal production rate; for $x \gg \beta$, $f(x)$ saturates reaching the value $\gamma + \alpha$. The factors τ_a and τ_b are introduced to rescale time so that the degradation rate of a and b is normalized (unitary). Species a and b mutually activate, generating a positive-feedback loop.

A negative-feedback loop could be generated by modifying the effect of b on a (without loss of generality):

$$\tau_a \dot{a} = -a + g_b(b), \qquad \tau_b \dot{b} = -b + f_a(a) + u,$$

where $f_a(a)$ is defined as above (activator), while $g_b(b)$ is a decreasing Hill-type function (inhibition):

$$g(x) = \delta \frac{1}{\phi + x^p} + \epsilon,$$

with similar definitions of the parameters. Both systems are positive and evolve in bounded sets: this may be verified as suggested in section "Positivity and Boundedness". The feedback loops generated by these systems are clearly identifiable when inspecting the Jacobian matrices, which are, respectively:

$$J_P = \begin{bmatrix} -1/\tau_a & f_b'(b)/\tau_a \\ f_a'(a)\tau_b & -1/\tau_b \end{bmatrix},$$

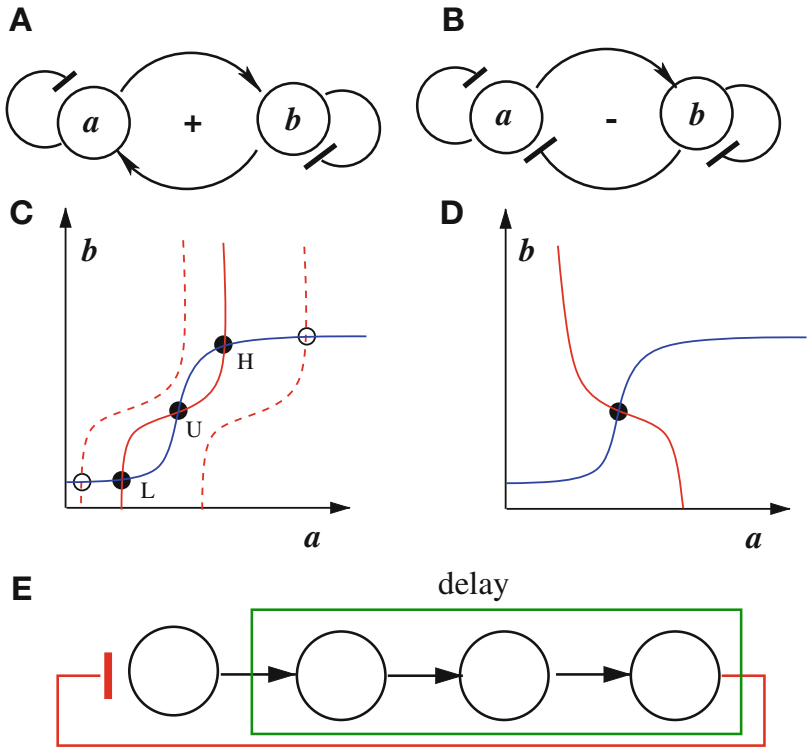
$$J_N = \begin{bmatrix} -1/\tau_a & g_b'(b)/\tau_a \\ f_a'(a)/\tau_b & -1/\tau_b \end{bmatrix}.$$

Due to the monotonicity of Hill functions, since f_a and f_b are increasing while g_b is decreasing, the Jacobians can be mapped to the sign matrices:

$$\Sigma_P = \begin{bmatrix} - & + \\ + & - \end{bmatrix}, \quad \Sigma_N = \begin{bmatrix} - & - \\ + & - \end{bmatrix}.$$

These matrices can be associated with the graphs shown in Fig. 1A, B, whose nodes represent the species and whose arcs represent the signed influence of each species on the other (pointed arrows indicate positive influence; hammerhead arrows indicate negative influence) corresponding to the nonzero Jacobian entries. The feedback loops in these systems are structural, i.e., they are present for arbitrary choices of the parameters.

The sign matrix Σ_P has only positive loops; therefore, the corresponding system is a *strong*



Structural Properties of Biological and Ecological Systems, Fig. 1 Graph representation of a two-node positive-feedback loop (**A**) and negative-feedback loop (**B**) system; pointed arrows represent positive influences, and hammerhead arrows represent negative influences. Nullclines and equilibria for the positive-feedback loop (**C**) and the negative-feedback loop (**D**) system. A negative-feedback loop including at least three nodes, or a time delay (**E**), is necessary to have oscillations

candidate multistationary system (Blanchini et al. 2014; Mincheva and Craciun 2008): if, by perturbing a parameter, we destabilize an equilibrium, then instability is generated by a dominant real eigenvalue that becomes positive (any transition to instability is exponential). In fact, instability of an equilibrium for this system implies $\det(-J_P) < 0$ in that equilibrium; however, according to the degree theory arguments in section "Analysis of the Equilibria", this implies the existence of (at least) other two equilibria with $\det(-J_P) > 0$.

Conversely, matrix J_N only has negative loops, so the corresponding system is a *strong candidate oscillator* (Blanchini et al. 2014; Mincheva and Craciun 2008): if, by perturbing a parameter, we destabilize an equilibrium, then instability is generated by a pair of dominant complex eigenvalues whose real part becomes positive (any transition to instability is oscillatory). Also, the system admits a single equilibrium because $\det(-J_N) > 0$ structurally. In this special (2×2) case, the unique equilibrium is always asymptotically stable, as we will find out soon.

Indeed, a strong candidate oscillator (multistationary system) does not necessarily oscillate (exhibit multiple equilibria); however, the onset of *instability* (if any) is necessarily associated with sustained oscillations (appearance of more equilibria).

In addition to the above information about the admissible dynamics, obtained through degree theory arguments, the low order of the two considered systems enables a more direct and specific qualitative analysis of the equilibria and their stability.

The equilibrium conditions for the positive-feedback system are:

$$-a + f_b(b) = 0, \qquad -b + f_a(a) + u = 0.$$

Their solutions correspond to the intersections of the two curves illustrated in Fig. 1C. Depending on the value of u, we may have either one or three intersections (we consider tangentiality as two coincident solutions). For small u, there is a single equilibrium (L) corresponding to low levels of both variables. For large u, there is a single equilibrium (H) corresponding to high levels of both variables. For intermediate values of u, we may have tree equilibria, and the intermediate one (U) is unstable. This configuration yields a bistable device that can act as a "switch": from the equilibrium U, if we increase u, we move the system to the upper equilibrium H, while, if we decrease u, we move the system to the lower equilibrium L. The situation remains unchanged if we restore u to the nominal bistable level. In the negative-feedback system, similar reasonings show the presence of a single equilibrium, as shown in Fig. 1D, regardless of the parameters.

To investigate the stability of the equilibria, we first find the characteristic polynomial associated with J_P:

$$\Phi_P(\lambda) = \lambda^2 + (1/\tau_a + 1/\tau_b)\lambda + (1 - f_a' f_b')/(\tau_a \tau_b).$$

It can be checked that:

(a) at the equilibria L and H, $(1-f_a' f_b')/(\tau_a \tau_b) > 0$; hence, the roots of $\Phi_P(\lambda)$ (the eigenvalues of J_P) have negative real part, since $(1/\tau_a + 1/\tau_b) > 0$;
(b) at the equilibrium U, $(1 - f_a' f_b')/(\tau_a \tau_b) < 0$; hence, there exists a positive real root.

Similarly, the characteristic polynomial of J_N is:

$$\Phi_N(\lambda) = \lambda^2 + (1/\tau_a + 1/\tau_b)\lambda + (1 - g_b' f_a')/(\tau_a \tau_b).$$

Since $g_b' f_a' < 0$, all the coefficients of the polynomial are positive; therefore, all the eigenvalues have negative real part, and the unique equilibrium is asymptotically stable for any value of the parameters.

We may be tempted to conclude that negative feedback stabilizes the system; however, this is not a generalizable conclusion. Let us modify this model to include the additional species c:

$$\tau_a \dot{a} = -a + g_c(c),$$
$$\tau_b \dot{b} = -b + f_a(a),$$
$$\tau_c \dot{c} = -c + f_b(b) + u.$$

The eigenvalues of the Jacobian associated with this system are the roots of the equation

$$(\tau_a \lambda + 1)(\tau_b \lambda + 1)(\tau_c \lambda + 1) + \kappa = 0,$$

where $\kappa = -f_a' f_b' g_c' > 0$. These roots cannot be real positive, consistent with the fact that we have a negative loop only. Standard root locus or Routh-Hurwitz analysis shows that, if κ is sufficiently large, two roots move to the right half of the complex plane, so a necessary requirement to have oscillations is that the loop includes at least three first-order sub-systems in series or a single "delay" element whose effect is comparable to that of a longer chain (see Fig. 1E). Smaller values of κ are sufficient to destabilize the system when the time constants τ_i are similar, while the most favorable situation to ensure stability is when one of these constants, say τ_1, is much larger than the others (Blanchini et al. 2018b).

Aggregation Can Simplify the Structural Analysis of Complex Networks

The methods and examples we discussed so far are easy to apply to small systems. Yet, comprehensive models of biological processes involve many species, making it difficult to use analytical methods. A route toward the simplification of large systems is "aggregation." Consider a system of the form

$$\dot{x} = f(x) + Fu, \quad y = Gx \tag{4}$$

where, for simplicity, F and G are column and row vectors, while u and y are scalars. A fundamental property that can be exploited is *monotonicity* (see also "▸ Monotone Systems in Biology" by D. Angeli). If system (4) is input-output monotone (Angeli and Sontag 2003; Hirsch and Smith 2005), it is order-preserving, i.e., given two initial states, $x^a(0)$ and $x^b(0)$, such that $x^a(0) \geq x^b(0)$ componentwise, and two inputs $u^a(t) \geq u^b(t)$, the two corresponding solutions $x^a(t)$ and $x^b(t)$ satisfy $x^a(t) \geq x^b(t)$ (componentwise) and the outputs satisfy $y^a(t) \geq y^b(t)$. Input-output monotonicity is guaranteed if F and G are positive vectors and the Jacobian J of $f(x)$ is a Metzler matrix (namely, $J_{ij} \geq 0$ for $i \neq j$). If we assume stability, the order-preserving property of a monotone system makes its behavior qualitatively comparable to that of a first-order system; therefore, a high-order model can be collapsed to a single node (see Blanchini et al. (2018a) and the references therein). Aggregation of several nodes associated with monotone sub-systems allows us to drastically reduce the complexity of a large network and then apply the structural analysis tools described earlier to the reduced system.

Discussion and Future Directions

Structural analysis reveals parameter-free properties of natural systems and explains how they can keep performing their life-preserving function in the most different environmental conditions. Many challenges related to structural analysis are still open, such as the full characterization of structurally stable chemical reaction networks with arbitrary kinetics. Structural perturbation analysis could go beyond constant inputs to include, e.g., periodic input signals and consider not only steady-state effects but also the short-term system response.

Aggregating sub-systems that enjoy particular properties and can be collapsed into a single node enables the structural analysis of large-scale complex systems through model simplification; to this aim, properties of interest besides monotonicity could be exploited, such as the positive-impulse-response property (Blanchini et al. 2018a).

Structural analysis not only can establish that a property holds for a given system even under huge parametric uncertainties, but it can also reveal that a property is necessarily ensured by a certain *structure*. This allows us not only to explain observed phenomena but also to falsify models by comparing structural predictions to experimental results. Finally, structural analysis can be precious to design de novo artificial biomolecular circuits (see ▸ "Synthetic Biology" by D. Del Vecchio and R. M. Murray) that are guaranteed to exhibit the desired qualitative function, despite perturbations, in view of their structure.

Cross-References

- ▸ Deterministic Description of Biochemical Networks
- ▸ Monotone Systems in Biology
- ▸ Robustness Analysis of Biological Models
- ▸ Stochastic Description of Biochemical Networks
- ▸ Synthetic Biology

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