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Dynamical Systems

Robustness in biological regulatory network III: Application to genetic networks controlling the morphogenesis

Robustesse dans les réseaux de régulation biologique III : Applications biologiques aux réseaux génétiques contrôlant la morphogénèse

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ARTICLE INFO

Article history: Received 18 November 2011 Accepted 4 January 2012 Available online 29 February 2012

Presented by the Editorial Board

ABSTRACT

This Note deals with the mathematical notions of entropy and stability rate in interaction graphs of genetic networks, in the particular context of the genetic threshold Boolean random regulatory networks (getBrens). It is proved that in certain circumstances of particular connectance, the entropy of the invariant measure of the dynamical system can be considered both as a complexity and a stability index, by exploiting the link between these two notions, fundamental to characterize the resistance of a biological system against endogenous or exogenous perturbations, as in the case of the *n*-switches. Examples of biological networks are then given showing the practical interest of the mathematical notions of complexity and stability in the case of the control of the morphogenesis.

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RÉSUMÉ

Cette Note utilise les notions mathématiques existant entre entropie et vitesse de retour à l'équilibre dans les graphes d'interaction des réseaux génétiques de manière générale, appliquées ici au cas particulier des réseaux de régulation génétique booléens probabilistes à seuil (appelés getBrens). Il est prouvé que, dans certaines circonstances de connectivité particulière, l'entropie de la mesure invariante du système dynamique peut être considérée à la fois comme un indice de complexité et de stabilité, en montrant explicitement le lien existant entre ces deux notions fondamentales, afin de mieux caractériser la résistance d'un système biologique à des perturbations endogènes ou exogènes, comme dans le cas des *n*-switches. Des exemples de réseaux sont ensuite traités, montrant l'intérêt pratique des notions de complexité et stabilité introduites dans cet article. Ils concernent le contrôle de la morphogénèse.

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1. Introduction

The notion of stability in a genetic regulatory network is quantified by the rate at which the system returns to its attractor regime [3,4,6,5,17] after exogenous and/or endogenous perturbations, this rate being correlated to the evolutionary

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¹⁶³¹⁻⁰⁷³X/\$ – see front matter © 2012 Académie des sciences. Published by Elsevier Masson SAS. All rights reserved. doi:10.1016/j.crma.2012.01.002



	Sequential updating		Parallel updating		
Nature	Attractor	ABRS	Attractor	ABRS	AD
Fixed point 1	000000000000000000000000000000000000000	1.56%	000000000000000000000000000000000000000	$\approx 0.00\%$	0.75
Fixed point 2	0011111001101110	96.88%	0011111001101110	99.66%	4.14
Fixed point 3	0000010000001100	1.56%	0000010000001100	pprox 0.00%	0.5
Limit cycle 1	None	-	0011010001101100	0.34%	2.45
			0000111000001110		

Fig. 1. Top: Interaction signed digraph modeling the genetic regulation network of feather morphogenesis. Activation (resp. inhibition) is represented by a black-headed (resp. white-headed) arc. Bottom: Attractors of the network for sequential and parallel schedules, with T = 0. Nodes order is: miRNA 141, EphA3, p53, Vav3, Stk11, Wnt2, RhoA, Smad3, SrC, Id3, Cyclin D1, Zfhx3, Sox11, β -catenin, cMyc and β -catenin/LEF/TCF/BL9/CBP.

entropy of the network [9]. We will in this paper apply the main concepts developed in [9,10], underlying the relationship between complexity and stability in the context of a particular genetic threshold Boolean regulatory network (getBren), the network controlling the feather morphogenesis in chicken.

2. Entropy and robustness in getBrens

Let $\mu = (\mu_{\beta}) = (\mu(\{\beta\}))$ be the stationary distribution or invariant measure (over the space of configurations $\Omega = \{0, 1\}^n$, if the network has *n* genes) of the Markov probability transition matrix $P = (P_{\gamma}^{\beta})_{\gamma,\beta\in\Omega}$ of a getBren observed asymptotically from an initial measure uniform on Ω . Then, the evolutionary entropy *H* serving as robustness index of the getBrens can be explicitly calculated [10]: $H = -\Sigma_{\gamma,\beta\in\Omega}\mu_{\beta}P_{\gamma}^{\beta}\log P_{\gamma}^{\beta}$. The main complexity parameter of *B*(*A*), the attraction basin of an attractor *A* (i.e., the set of all initial conditions hav-

The main complexity parameter of B(A), the attraction basin of an attractor A (i.e., the set of all initial conditions having A as asymptotic behavior) is its Attraction Basin Relative Size (ABRS), defined by: ABRS(A) = $\Sigma_{x \in B(A)} \mu_x = \mu(B(A))$. When T = 0, the invariant measure μ is concentrated on the m attractors of the deterministic dynamics and $H = -\Sigma_{k=1,m}\mu(A_k)\log\mu(A_k)$ and when $T = +\infty$, μ is scattered uniformly over Ω and $H = n\log 2$. A rough estimation of Hinvolves the attractor entropy [9,10], easier to calculate:

 $E_{attractor} = -\Sigma_{k=1,m \leq 2^n} \text{ABRS}(A_k) \log(\text{ABRS}(A_k))$

There exists an intermediary temperature *T* between 0 and $+\infty$, for which for any $\beta \in B(A)$, the transition probability from β to γ , that is P_{γ}^{β} , is scattered rather uniformly over B(A), then:

$$H \approx \Sigma_{k=1,m \le 2^n} \text{ABRS}(A_k) \log(2^n \text{ABRS}(A_k)) = n \log 2 - E_{attractor}$$

Then, the attractor entropy of the network controlling the feather morphogenesis in chicken [16], whose interaction graph is pictured in Fig. 1 top panel, may be calculated for parallel updating: $H = 16 \times 0.3 - E_{attractor} = 4.8 - 9.9 \times 10^{-3}$. We can notice that $E_{attractor}$ decreases from parallel to sequential schedule (from 7×10^{-2} to 9.9×10^{-3}), showing that the updating mode has an influence on the robustness of the network.

3. The *n*-switches

The *n*-switches are often used to model morphogenetic processes both in vegetal and animal development [1,2,17,16, 14,13]. In the case of the parallel update schedule of an *n*-switch having an autocatalysis compensating the threshold

 $(w_{ii} = \theta_i)$ and a constant inhibitory weight w < 0 for interactions between each pair of distinct vertices of the network, we can calculate explicitly the transition probability M_{xy} , the stationary measure μ and the evolutionary entropy H [9,10], in the case where $\theta_i = 0$ and w small (or T large): $\forall x, y \in \Omega$, $M_{xy} = \prod_{i=1,...,n} [P_{i,1}^x \mathbb{1}_{\{i \in y\}} + P_{i,0}^x \mathbb{1}_{\{i \notin y\}}]$ where $\forall \alpha \in \{0, 1\}$, $\beta \in \Omega$, $P_{i,\alpha}^{\beta}(\{x_i(t+1) = \alpha \mid x(t) = \beta\}) = \exp(\alpha \Sigma_{j=1,n} w \beta_j) / [1 + \exp(\Sigma_{j=1,n} w \beta_j)], \ \mu_x = \Sigma_{y \in \Omega} \exp(\Sigma_{i \in x, j \in y} w x_i y_j) / Z$, where $Z = \Sigma_{z \in \Omega} \Sigma_{y \in \Omega} \exp(\Sigma_{k \in z, j \in y} w z_k y_j)$, and $H = -\Sigma_{x,y \in \Omega} \mu_x M_{xy} \log M_{xy}$.

Proposition 1. For an n-switch with $(w_{ii} = \theta_i)$ and a constant inhibitory weight w < 0 and for interactions sufficiently small, we have the following estimation of the evolutionary entropy H:

 $H \approx n \log 2 - w^2 n(n-1)/16 + o(w)$ and $\partial H/\partial w = -wC_n^2/4 + O(w)$

Proof. In the case of the parallel update schedule, by identifying Ω with the set of subsets of $\{1, ..., n\}$ and x with the subset of genes in state 1 (i.e. $x \equiv \{i \in \{1, ..., n\}/x_i = 1\}$), we can write:

$$\begin{split} M_{xy} &= e^{w(|x|.|y|-|x\cap y|)} / \left[\left(1 + e^{w|x|} \right)^{n-|x|} \left(1 + e^{w(|x|-1)} \right)^{|x|} \right] \text{ and } \\ \mu_x &= \sum_{j=0,|x|} C^j_{|x|} \sum_{k-j=|y|-j=0,n-|x|} C^{k-j}_{n-|x|} e^{w(|x|.(k-j+j)-j)} / Z = \sum_{j=0,|x|} C^j_{|x|} e^{w(|x|-1)j} \left(1 + e^{w|x|} \right)^{n-|x|} / Z \\ &= \left(1 + e^{w(|x|-1)} \right)^{|x|} \left(1 + e^{w|x|} \right)^{n-|x|} / Z, \text{ where } Z = \sum_{z \in \Omega} \left(1 + e^{w(|z|-1)} \right)^{|z|} \left(1 + e^{w|z|} \right)^{n-|z|} \end{split}$$

Let denote $L(w, x) = (1 + e^{w|x|})^{n-|x|} (1 + e^{w(|x|-1)})^{|x|}$, then $\mu_x = L(w, x) / \Sigma_{z \in \Omega} L(w, z)$ and

$$\begin{split} H_{x} &= -\sum_{j=0,|x|} C_{|x|}^{j} \sum_{k=|y|-j=0,n-|x|} C_{n-|x|}^{k} e^{w(|x|(k+j)-j)} \left[w \left(|x|(k+j)-j \right) - \log L(w,x) \right] / L(w,x) \\ &= \sum_{j=0,|x|} C_{|x|}^{j} e^{wj(|x|-1)} \left[\left(1 + e^{w|x|} \right)^{n-|x|} \left[\log L(w,x) - wj(|x|-1) \right] - \left(1 + e^{w|x|} \right)^{n-|x|-1} (n-|x|) w|x| \right] / L(w,x) \\ &= L(w,x) \left[\log L(w,x) - w|x| \left(|x|-1 \right) \left(1 + e^{w(|x|-1)} \right)^{-1} - w|x| (n-|x|) \left(1 + e^{w|x|} \right)^{n-2} \right] / L(w,x) \\ &= \log L(w,x) - w|x| \left(|x|-1 \right) \left(1 + e^{w(|x|-1)} \right)^{-1} - w|x| (n-|x|) \left(1 + e^{w|x|} \right)^{n-2} \end{split}$$

Then, we can calculate *H*:

$$\begin{split} H &= -\Sigma_{x,y\in\Omega}\mu_{x}M_{xy}\log M_{xy} = \Sigma_{x\in\Omega}L(w,x)H_{x}/\Sigma_{z\in\Omega}L(w,z) \\ &= \Sigma_{x\in\Omega}L(w,x) \Big[-\log L(w,x) + w|x| \big(|x|-1\big) \big(1 + e^{w(|x|-1)}\big)^{-1} + w|x| \big(n-|x|\big) \big(1 + e^{w|x|}\big)^{-1} \Big]/\Sigma_{z\in\Omega}L(w,z) \\ &= -\Sigma_{i=0,n}C_{n}^{i}L(w,i) \Big[-\log L(w,i) + wi(i-1) \big(1 + e^{w(i-1)}\big)^{-1} + wi(n-i) \big(1 + e^{wi}\big)^{-1} \Big]/\Sigma_{z\in\Omega}L(w,z) \end{split}$$

Therefore, if *w* is small, we have:

$$L(w,i) = (1 + e^{wi})^{n-i} (1 + e^{w(i-1)})^{l}$$

$$\approx 2^{n} [1 + i(n-1)w/2 + i^{2}(n-i)w^{2}/4 + i(i-1)^{2}w^{2}/4 + i^{2}(n-i)(i-1)w^{2}/4]$$

and, therefore,

$$\begin{split} & Z = \sum_{z \in \Omega} L(w, z) \approx 2^{2n}, \qquad \mu_i \approx \left[1 + i(n-1)w/2 \right] / 2^n \\ & \log L(w, i) \approx n \log 2 + i(n-1)w/2 - i^2(n-1)^2 w^2 / 4 + i^2(n-i)w^2 / 4 + i(i-1)^2 w^2 / 4 \\ & H \approx -\sum_{i=0,n} C_n^i \left[-\log L(w, i) + 2^{-1}wi(i-1) \left(1 - w(i-1)/2 \right) + 2^{-1}wi(n-i)(1-wi/2) \right] / 2^n \\ & \approx \left(n 2^n \log 2 - w^2 n(n-1) 2^{n-3} - w^2 n^3(n-1) 2^{n-3} \right) / 2^n = n \log 2 - w^2 n(n-1) / 16 - w^2 n(n-1) (n^2 + 1/2) / 8 \end{split}$$

and hence $\partial H/\partial w = -wC_n^2/4 + O(w) = -w \operatorname{var} G - \operatorname{cov}(H, G)$, where G is the global cross-frustration (cf. [10]).

Remarks. (1) The Markov matrix M in case of sequential updating verifies: $M_{xy} = \prod_{i=1,...,n} M_{xy,i}$, where $M_{xy,i} = P_{i,1}^{[x \cap (N \setminus I)] \cup [y \cap I]} \mathbb{1}_{\{i \notin y\}} + P_{i,0}^{[x \cap (N \setminus I)] \cup [y \cap I]} \mathbb{1}_{\{i \notin y\}}$. Each matrix M_i has the same subdominant eigenvalue approximately equal to $2e^{w(n-1)/2}$ and same Gibbs measure as eigenvector [8], then the subdominant eigenvalue λ_1 of M verifies: $-\log \lambda_1 \approx n \log 2 + wn(n-1)/2$, about the value of H in parallel updating (cf. also [12,7] for comparing parallel and sequential free energies).

(2) The robustness increases with *n* when *w* is small (or *T* large), which is not surprising because the number of deterministic fixed configurations in an *n*-switch equals *n*, then, when *n* tends to infinity, the number of attraction basins tends also to infinity, contributing to augment *H* and to increase $\partial H/\partial w$.

It is interesting to notice that in the case of the *n*-switches, the derivative $\partial H/\partial w$ is depending on the frustration of the network like in Propositions 2–4 of [10]. This observation comes from the fact that *n*-switches are discrete Boolean potential systems [11] (contrarily to networks with only isolated circuits which are purely Hamiltonian [15]), as proved in Proposition 2 below, i.e., a system defined on the discrete state space Ω by

$$x_i(t+1) = h(-\Delta P/\Delta x_i + x_i(t)) \quad \text{or} \quad \Delta x_i/\Delta t = h(-\Delta P/\Delta x_i + x_i(t)) - x_i(t) \tag{1}$$

where $\Delta t = 1$ and *P* is a real function (e.g. a polynomial with real coefficients valued in \Re) on Ω and *h* a function from \Re to Ω , with boundary conditions ensuring that the flow remains in Ω . The second formulation of (1) is then the discrete equivalent of $dx_i/dt = -\partial P/\partial x_i$. In the Boolean case, we will choose for *h* the Heaviside function H : H(s) = 1, if s > 0, and H(s) = 0, if not. If $P(x) = \Sigma_k({}^txA_kx)x_k + {}^txWx + Bx$, where $A = (a_{ijk})$ is an interaction tensor (cf. [8] for an introduction to the triplet interactions), with $A_k = (a_{ij})_k$ as marginal matrices and $a_{iii} = 0$, $W = (w_{ij})$ as interaction matrix and $B = (b_i)$ as threshold line vector, the partial space derivatives of *P* are:

$$\Delta P / \Delta x_i = \Sigma_{j,k} (a_{ijk} + a_{jki} + a_{jki}) x_j x_k + \Sigma_j (w_{ij} + w_{ji}) x_j + b_i + \left[w_{ii} + \Sigma_{j \neq i} (a_{ijj} + a_{jij} + a_{jji}) x_j \right] \Delta x_i \tag{2}$$

Then, the discrete potential system associated to *P* is defined by $\Delta x_i / \Delta t = \Delta x_i = -\Delta P / \Delta x_i = -\Sigma_{j,k} (a_{ijk} + a_{jik} + a_{jki}) x_j x_k - \Sigma_j (w_{ij} + w_{ji}) x_j - b_i - [w_{ii} + \Sigma_{j \neq i} (a_{ijj} + a_{jij} + a_{jji}) x_j] \Delta x_i$. Hence, we have: $\Delta x_i = -[\Sigma_{j,k} (a_{ijk} + a_{jik} + a_{jki}) x_j (t) x_k(t) + \Sigma_j (w_{ij} + w_{ji}) x_j(t) + b_i] / [1 + w_{ii} + \Sigma_{j \neq i} (a_{ijj} + a_{jij} + a_{jji}) x_j(t)]$ and $x_i(t+1) = H(\Delta x_i + x_i(t)) = H(-\Delta P / \Delta x_i + x_i(t))$, where *H* is the Heaviside function. From (2) we derive (3): $x_i(t+1) = H(-[\Sigma_{j,k} (a_{ijk} + a_{jik} + a_{jki}) x_j(t) + \Sigma_j (w_{ij} + w_{ji}) x_j(t)] + b_i] / [1 + w_{ii} + \Sigma_{j \neq i} (a_{ijj} + a_{jij}) x_j(t)] + x_i(t)).$

Proposition 2. Consider an n-switch network as a Boolean potential system where A = 0, $P(x) = {}^{t}xWx + Bx$, with $w_{ii} = -b_i \ge 0$ and each sub-matrix on any subset J of indices in $\{1, ..., n\}$ of W is non-positive. Then P decreases on the trajectories of the potential system $x_i(t + 1) = H(-\Delta P/\Delta x_i + x_i(t))$ for any updating mode of the dynamics (sequential, block sequential and parallel). This system is a getBren [10], whose stable fixed configurations correspond to the minima of P.

Proof. It is easy to check that from (2): $\Delta P / \Delta x_i = \Sigma_j (w_{ij} + w_{ji}) x_j + b_i + w_{ii} \Delta x_i$, and from (3) and $w_{ii} = -b_i$: $x_i(t+1) = H(-\Delta P / \Delta x_i + x_i(t)) = H(-[\Sigma_j(w_{ij} + w_{ji})x_j(t) + b_i]/[1 + w_{ii}] + x_i(t)) = H(-\Sigma_{j \neq i}(w_{ij} + w_{ji})x_j(t) + b_i)$. Then, for any updating mode where only the states change on the subset *J* between *t* and t + 1: $P(x(t+1)) - P(x(t)) = -\Sigma_{i \in J} \Delta x_i^2 (1 + w_{ii}) + \Sigma_{(i,j) \in J \times J} w_{ij} \Delta x_i \Delta x_j \leq 0$, the result coming from the non-positivity of the sub-matrices of *W* or from [5]. \Box

4. Conclusion

We have presented in this Note several examples of practical usage of the complexity parameter H (evolutionary entropy), by applying the theoretical results of [9,10] to a specific genetic network regulating feather morphogenesis in chicken. A generalization of the present approach to non-linear genetic regulatory networks with more than pair interactions (triplet, quadruplet, etc.) met in regulation by protein complexes as transcription factors, can be found in [8].

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