Available online at www.sciencedirect.com

ScienceDirect

IFAC PapersOnLine 50-1 (2017) 10944–10949

Pattern Formation in Large-Scale Networks with Asymmetric Connections, ⋆

Andras Gyorgy * **Murat Arcak** **

* Department of Electrical Engineering and Computer Science, UC Berkeley, CA 94702 USA, (e-mail: gyorgy@ berkeley.edu)
** Department of Electrical Engineering and Computer Science, UC Berkeley, CA 94702 USA, (e-mail: arcak@ berkeley.edu)

Abstract: Two of the most common pattern formation mechanisms are Turing-patterning in reaction-diffusion systems and lateral inhibition of neighboring cells. In this paper, we introduce a broad dynamical model of interconnected cells to study the emergence of patterns, with the above mentioned two mechanisms as special cases. This model comprises modules encapsulating the biochemical reactions in individual cells, and interconnections are captured by a weighted directed graph. Leveraging only the static input/output properties of the subsystems and the spectral properties of the adjacency matrix, we characterize the stability of the homogeneous fixed points as well as sufficient conditions for the emergence of spatially non-homogeneous patterns. To obtain these results, we rely on properties of the graphs (bipartiteness, equitable partitions) together with tools from monotone systems theory. As application example, we consider pattern formation in neural networks to illustrate the practical implications of our results. Our results do not restrict the number of cells or reactants, and do not assume symmetric connections between two connected cells.

Keywords: Nonlinear dynamics, pattern formation, large-scale systems, networks.

1. INTRODUCTION

Spatial pattern formation plays a fundamental role in the development of complex self-organized systems, such as multi-cellular organisms Gilbert (2010); Wolpertand and Tickle (2011). The vast majority of theoretical results about the emergence of patterns focus on diffusion-driven instabilities, the so-called Turing-patterning Turing (1952); Gierer and Meinhardt (1972); Dillon et al. (1994); Murray (2003). However, patterning is also facilitated by mechanisms without any diffusible molecules, for instance, in the case of lateral inhibition in the Notch pathway where neighboring cells inhibit each other from converging on the same fate Collier et al. (1996); Gilbert (2010). As lateral inhibition exists both in bacterial and mammalian cells Aoki et al. (2010); Sprinzak et al. (2010, 2011), there is growing attention targeted at understanding pattern formation mechanisms other than Turing-patterning.

Studies of patterning either focus on the continuous case with partial differential equations, or consider network analogues: interconnected dynamical systems where nodes represent systems and edges stand for interconnections (e.g., ecological metapopulations Hanski (1998); Fortuna et al. (2006), spreading of infections over transportation networks Pastor-Satorras and Vespignani (2001); Hufnagel et al. (2004); Colizza et al. (2006), diffusively coupled chemical reactors or cells Othmer and Scriven (1971, 1974); Collier et al. (1996); Horsthemkea et al. (2004); Moore and Horsthemkea (2005)). Since the high-dimension of the resulting problem renders the analysis difficult, studies so far mainly focused on small networks comprising only a few nodes, and resorted to numerical simulations in the case of large-scale networks Collier et al. (1996); Ghosh and Tomlin (2004); Horsthemkea et al. (2004); Moore and Horsthemkea (2005); Sprinzak et al. (2011).

To characterize pattern formation in large-scale networks, we view the network as the interconnection of input/output models Arcak (2013); Ferreira and Arcak (2013). Inputs and outputs correspond to the concentration of species used for communication among cells, the interconnection structure is encoded with a directed and weighted graph: nodes represent cells, edges stand for connection between two nodes, and weights represent the strength of this connection. We do not require the interconnection matrix to be symmetric, our results apply equally to both directed and undirected graphs. We make no assumptions about the sign-structure of the interconnection matrix, thus Turing-patterning and lateral inhibition both emerge as special cases. Although our main motivation is understanding pattern formation in cellular systems, our results characterize patterning in networked systems without any particular restriction to biological systems.

This paper is organized as follows. We first present the mathematical model for studying the emergence of patterns together with the main questions of the paper. In addition to deriving sufficient conditions for the instability of the homogeneous fixed points, we also reveal when spatial patterns emerge. Finally, we illustrate the implications of the results considering neural networks as an application example.

⋆ This wark was supported by the grants NIH NIGMS 1R01GM109460-01 and AFOSR FA9550-14-1-0089.

10.1016/j.ifacol.2017.08.2464

2. MATHEMATICAL MODEL AND NOTATION

Consider a network of identical dynamical systems $i = 1, 2, \ldots, N$, each described by the model

$$\begin{aligned} \dot{x}_i &= f(x_i, u_i), \\ y_i &= h(x_i), \end{aligned} \tag{1}$$

where $x_i \in \mathbb{R}^n$ denotes the state of system i, and $u_i \in \mathbb{R}$ and $y_i \in \mathbb{R}$ represent the input and output of this system, respectively. Introduce x, u and y as the concatenations of x_i, u_i and y_i for $i = 1, 2, \ldots, N$, respectively.

We consider interactions among subsystems of the form

$$u = Py, \tag{2}$$

where the entry $p_{i,j}$ of the matrix $P \in \mathbb{R}^{N\times N}$ represents the strength of the effect of subsystem j on subsystem i. Therefore, we represent the network of interconnected systems by a directed and connected graph (V, P), where V and P denote the set of vertices and the weighted adjacency matrix (assumed to be irreducible), respectively.

In this paper, we study the fixed points of (1)–(2). When does a homogenous fixed point become unstable, setting the stage for patterning? When do spatially non-homogenous patterns emerge? By grouping cells that share the same fate, can we reduce the complexity of the analysis?

While addressing these questions, we consider various subsets of the following main assumptions:

(A1) both $f(\cdot, \cdot)$ and $h(\cdot)$ are continuously differentiable;
(A2) for all $u \in \mathbb{R}$ the set of equations $0 = f(x, u)$ has a solution denoted by $x =: S(u)$, in which case we define $T(u) := h(S(u))$;
(A3) $\left.\frac{\partial f(x,u)}{\partial x}\right|_{(S(u),u)}$ is Hurwitz for all $u \in \mathbb{R}$;
(A4) the maps $S : \mathbb{R} \to \mathbb{R}^n$ and $T : \mathbb{R}^n \to \mathcal{R}$ are continuously differentiable;
(A5) $T(\cdot)$ is bounded and $\frac{\partial T(u)}{\partial u}$ is sign-stable (i.e., either $\frac{\partial T(u)}{\partial u} \leq 0$ or $\frac{\partial T(u)}{\partial u} \geq 0$ for all u);
(A6) $P\mathbf{1}_N = p\mathbf{1}_N$ for some $p \in \mathbb{R}$ (constant row-sum).

Throughout the paper, let e_i denote the i^{th} unit vector and write $M \preceq 0$ and $M \succeq 0$ to denote that all entries of M are non-positive and non-negative, respectively. Finally, $\rho(M)$ and $s(M)$ denote the spectral radius and the largest real part of the eigenvalues of M, respectively, and $\text{diag}(v)$ defines the diagonal matrix composed of the elements of the vector v.

3. RESULTS

Before studying the emergence of patterns, we first focus on the existence of homogeneous fixed points. To this end, we next present an input/output formulation for studying the fixed points of (1)–(2).

Lemma 1. Assume that (A2) holds. If u satisfies

$$\begin{pmatrix} u_1 \\ \vdots \\ u_N \end{pmatrix} = P \begin{pmatrix} T(u_1) \\ \vdots \\ T(u_N) \end{pmatrix} \tag{3}$$

then $x_i = S(u_i)$ is a fixed point of (1)–(2). Conversely, if $S(\cdot)$ in (A2) is unique and x is a fixed point of (1)–(2) then the corresponding u from (2) satisfies (3).

Proof. Both follow from the definition of $T(\cdot)$ in (A2).

Lemma 2. Provided (A2), (A4), (A5) and (A6), $\exists x_0 \in \mathbb{R}^n$ such that $x = \mathbf{1}_N \otimes x_0$ is a fixed point of (1)–(2).

Proof. It is sufficient to show that $\exists u_0 \in \mathbb{R}$ such that $u = \mathbf{1}_N u_0$ satisfies (3), as then $x = \mathbf{1}_N \otimes x_0$ with $x_0 = S(u_0)$ is a fixed point of (1)–(2) from Lemma 1. If u_0 satisfies $u_0 = pT(u_0)$ with $p \in \mathbb{R}$ from (A6) then $u = \mathbf{1}_N u_0$ satisfies (3). Therefore, in what follows we prove that $\exists u_0 \in \mathbb{R}$ such that u_0 satisfies $u_0 = pT(u_0)$.

Since $T(u_i)$ is bounded from (A5), we have $|pT(\cdot)| \leq b$ for some $b \geq 0$. Therefore, it follows from (A4) that the function $F(\cdot) := pT(\cdot)$ is a continuous mapping of the compact convex set $\mathcal{B} := [-b, b]$ into itself (i.e., $F : \mathcal{B} \to \mathcal{B}$). Invoking the Brouwer fixed-point theorem Brouwer (1911) we conclude that there exists $u_0 \in \mathcal{B}$ such that $F(u_0) = u_0$, therefore, u_0 satisfies $u_0 = pT(u_0)$.

In what follows, we assume that the conditions of Lemma 2 are met, thus (1)–(2) has a homogeneous fixed point of the form $x = \mathbf{1}_N \otimes x_0$ for some $x_0 \in \mathbb{R}^n$, and let $u_0 \in \mathbb{R}$ denote the corresponding value of u_i $(i = 1, 2, \ldots, N)$.

3.1 Stability of the Homogeneous Fixed Points

Before studying the emergence of patterns, we first focus on the homogeneous fixed point $x = \mathbf{1}_N \otimes x_0$ of (1)–(2).

Lemma 3. Provided (A1) holds, introduce $A := \frac{\partial f(x_i,u_i)}{\partial x_i}$, $B := \frac{\partial f(x_i,u_i)}{\partial u_i}$, and $C := \frac{\partial h(x_i)}{\partial x_i}$, all evaluated at $x_i = x_0$ and $u_i = u_0$. Let λ_i denote the eigenvalues of P. The fixed point $x = \mathbf{1}_N \otimes x_0$ of (1)–(2) is stable if $A + \lambda_i BC$ are Hurwitz for $i = 1, 2, \ldots, N$, and it is unstable if $A + \lambda_i BC$ has an eigenvalue with positive real part for some i.

Proof. Linearization of (1)–(2) about $x = \mathbf{1}_N \otimes x_0$ yields the Jacobian $I_N \otimes A + P \otimes (BC)$. The stability of $x = \mathbf{1}_N \otimes x_0$ then depends on the eigenvalues of $I_N \otimes A + P \otimes (BC)$. In what follows, we show that these eigenvalues are those of $A + \lambda_i BC$ for $i = 1, 2, \ldots, N$.

To this end, consider the Jordan form $J = W^{-1}PW$ of P (W contains the generalized eigenvectors of P):

$$J = \begin{bmatrix} J_1 & & \\ & \ddots & \\ & & J_k \end{bmatrix},$$

where J_i is the i^{th} Jordan block corresponding to the eigenvalue λ_i of P and has the structure

$$J_i = \begin{bmatrix} \lambda_i & 1 & & \\ & \lambda_i & \ddots & \\ & & \ddots & 1 \\ & & & \lambda_i \end{bmatrix}.$$

The following similarity transformation of the Jacobian yields

$$\begin{aligned} H &= \left(W^{-1} \otimes I_n\right) \left[I_N \otimes A + P \otimes (BC)\right] (W \otimes I_n) \\ &= I_N \otimes A + J \otimes (BC) =: \begin{bmatrix} H_1 & & \\ & \ddots & \\ & & H_k \end{bmatrix}, \end{aligned} \tag{4}$$

where H_i is of the form

$$H_i = \begin{bmatrix} A+\lambda_i BC & BC & & \\ & A+\lambda_i BC & \ddots & \\ & & \ddots & BC \\ & & & A+\lambda_i BC \end{bmatrix}.$$

Considering the block diagonal structure of H in (4), the eigenvalues of H are those of $H_1, H_2, \ldots, H_k$, where the eigenvalues of H_i are those of $A + \lambda_i BC$.

Next, we derive a sufficient condition for the instability of the homogeneous fixed points relying only on the input/output function $T(\cdot)$ and on the eigenvalues of P.

Theorem 4. Assume that (A1), (A2) and (A3) hold. The fixed point $x = \mathbf{1}_N \otimes x_0$ of (1)–(2) is unstable if

$$1 - T'(u_0)\lambda_i < 0 \tag{5}$$

for some real eigenvalue λ_i of P.

Proof. Invoking Lemma 3, it is sufficient to show that (5) implies that $A+\lambda_i BC$ has an eigenvalue with positive real part, where A, B and C are defined in Lemma 3. Since from Arcak (2013) we obtain that $T'(u_0) = -CA^{-1}B$, (5) is equivalent to the condition $1 + \lambda_i CA^{-1}B < 0$. From Sylvester's determinant theorem it follows that

$$(-1)^n \det(A)\det(1 + \lambda_i CA^{-1}B) = (-1)^n \det(A + \lambda_i BC).$$

Next, Claim 2 in Ferreira and Arcak (2013) yields that $(-1)^n \det(A) > 0$ since A is Hurwitz by (A3). From this it then follows that $(-1)^n \det(A + \lambda_i BC) < 0$, so that we conclude that $A + \lambda_i BC$ has a positive real eigenvalue invoking Claim 2 in Ferreira and Arcak (2013).

3.2 Emergence of Patterns

Next, we study the emergence of patterns. To this end, we rely on results from the theory of monotone systems together with the notion of balanced partitioning of graphs Bollobas (1998). To simplify notation, consider $M \in \mathbb{R}^{N\times N}$ and introduce

$$\Psi(M) := M - \sum_{i=1}^{N} \mathrm{diag}(e_i) M \mathrm{diag}(e_i),$$

which is the same as M except it has zeros in the diagonal.

Lemma 5. Given $\dot{z} = f(z)$, $z \in \mathbb{R}^n$, let $J(z)$ denote the Jacobian $J(z) := \frac{\partial f}{\partial z}$ and suppose there exists a bounded, forward invariant set $\mathcal{V} \subset \mathbb{R}^n$ and a non-singular matrix M such that $M^{-1}J(z)M$ is Metzler for all $z \in \mathcal{V}$. Suppose $f(z^*) = 0$ for some $z^* \in \mathcal{V}$ and that

$$M^{-1}J(z^*)M = -\alpha I + Q$$

for some $\alpha \geq 0$ and $Q \succeq 0$ irreducible matrix. If the spectral radius of Q satisfies $\rho(Q) > \alpha$, there exist other equilibrium points in each of the sets $(z^* + \mathcal{K}) \cap \mathcal{V}$ and $(z^* - \mathcal{K}) \cap \mathcal{V}$ other than z^*, where $\mathcal{K}$ is the cone $\mathcal{K} = \{z : M^{-1}z \succeq 0\}$.

Proof. Consider the coordinate transformation $w = Mz$, so that $\dot{z} = f(z)$ becomes

$$Mf(M^{-1}w) =: F(w) \tag{6}$$

with Jacobian $DF(w) := M^{-1}J(M^{-1}w)M$. Since this is Metzler, we conclude that (6) is cooperative Smith (1995). In the rest of the proof, we invoke Theorem 4.3.3 in Smith (1995) to show that (6) has equilibrium points in each of the sets $(w^* + \mathcal{K}_w) \cap \mathcal{W}$ and $(w^* - \mathcal{K}_w) \cap \mathcal{W}$, where $\mathcal{K}_w$ is the cone $\mathcal{K}_w = \{w : w \succeq 0\}$, $w^* = Mz^*$ and $\mathcal{W} = \{w : w = Mz,\ z \in \mathcal{V}\}$. From this the conclusion of the claim follows directly considering the coordinate transformation $z = M^{-1}w$.

First, we prove that $s(DF^*) > 0$ where $s(DF^*)$ denotes the largest real part of the eigenvalues of $DF^* := DF(w^*)$, and that there exists an eigenvector $v \gg 0$ such that $DF^*v = s(DF^*)v$. To this end, note that $DF^* = -\alpha I + Q$, so that its eigenvalues are those of $-\alpha I + Q$. Since DF^* is a quasi-positive and irreducible matrix, from Corollary 4.3.2 in Smith (1995), we conclude that there exists an eigenvector $v \gg 0$ such that $DF^*v = s(DF^*)v$. Therefore, $s(DF^*)$ is an eigenvalue of DF^* with eigenvector v. To show that $s(DF^*) > 0$, note that $\rho(Q) > \alpha$ implies that all eigenvalues of DF^* have positive real part, and since since $s(DF^*)$ must be real by its definition, we conclude that $s(DF^*) > 0$.

Second, since $\mathcal{V}$ is bounded and forward invariant for $\dot{z} = f(z)$, so is $\mathcal{W}$ for (6). Since $w^* \in \mathcal{W}$ follows from $z^* \in \mathcal{V}$, we can now invoke Theorem 4.3.3 in Smith (1995) to show that (6) has equilibrium points in each of the sets $(w^* + \mathcal{K}_w) \cap \mathcal{W}$ and $(w^* - \mathcal{K}_w) \cap \mathcal{W}$ other than z^* to conclude the proof.

Definition 6. The graph $\mathcal{G} = (V, W)$ is *balanced* if there is a partition of its set of nodes V into two blocks V_1 and V_2 such that all positive edges connect nodes within V_1 or V_2, and negative edges connect nodes between V_1 and V_2. Furthermore, define the *bipartition vector* b such that $b_i = (-1)^k$ iff $v_i \in V_k$ $(k = 1, 2)$.

Theorem 7. Provided (A2), (A4) and (A5), assume that the graph with irreducible adjacency matrix $\Psi(PT'(u_0))$ is balanced with bipartition vector b. Introduce $u^* := \mathbf{1}_N u_0$ and the cone $\mathcal{K} = \{u : M(u - u^*)b^T \succeq 0\}$ where $M = \mathrm{diag}(b)$. If

$$1 - \lambda_i T'(u_0) < 0 \tag{7}$$

for some real eigenvalue λ_i of P, then both sets $u^* \pm \mathcal{K}$ contain a point $u \neq u^*$ such that $x_i = T(u_i)$ is a fixed point of (1)–(2).

Proof. Introduce the auxiliary dynamical system

$$\dot{u} = -u + P \begin{pmatrix} T(u_1) \\ \vdots \\ T(u_N) \end{pmatrix} =: f(u) \tag{8}$$

and note that the fixed points of (8) are identical to the solutions of (3). Therefore, the fixed points of (8) are fixed points of (1)–(2) from Lemma 1, thus, in the rest of the proof we focus on the fixed points of (8).

First, introduce the coordinate transformation $w := Mu$ and note that $M = M^{-1}$, yielding

$$\dot{w} = -w + MP\Delta(Mw) =: F(w). \tag{9}$$

The Jacobian of (8) is given by $J(u) := -I + P\Delta(u)$ where $\Delta(u) := \mathrm{diag}(T'(u_1)\ \ldots\ T'(u_N))$, so that the Jacobian of (9) is given by $DF(w) := MJ(Mw)M$. We next show that (9) is *cooperative* by proving that $DF(w)$ is Metzler for all $w \in \mathbb{R}^N$. To this end, note that since the graph with irreducible adjacency matrix $\Psi(PT'(u_0))$ is balanced with bipartition vector b, so is $\Psi(P\Delta(u))$ from (A5). Therefore, we have that $b_i b_j p_{i,j} T'(u_j) \geq 0$ for $i \neq j$ and

$i, j = 1, 2, \ldots, N$. It then follows that $DF(w)$ is Metzler for all $w \in \mathbb{R}^N$, thus (9) is cooperative.

Second, we focus on the bounded forward invariant set $\mathcal{V}$ in Lemma 5. From (A5) we have that $\exists \bar{T} > 0$ such that $|T(\cdot)| \leq \bar{T}$. With this, introduce $\bar{w} := \max(|u_0|, \|P\|_1 \bar{T})$ and the set $\mathcal{W} := [-\bar{w}, \bar{w}]^N$. We next show $\mathcal{V} := M\mathcal{W}$ is forward invariant for (8). To see this, note that from (9) we obtain that

$$\dot{w}_i = -w_i + b_i \sum_{j=1}^{N} p_{i,j} T(b_j w_j),$$

where $|b_i \sum_{j=1}^{N} p_{i,j} T(b_j w_j)| \leq \|P\|_1 \bar{T}$. This yields then that $F_w(\bar{w}\mathbf{1}_N) \leq 0$ and $F_w(-\bar{w}\mathbf{1}_N) \geq 0$ from (9). Given that (9) is cooperative, thus monotone with respect to the standard orthant cone $\mathbb{R}^N_{\geq 0}$, we conclude that the hypercube $\mathcal{W}$ is forward invariant and it contains the equilibrium point Mu^* as $\bar{w} \geq |u_0|$. Therefore, $\mathcal{V} = M\mathcal{W}$ is bounded, forward invariant and it contains u^*.

Third, note that $M^{-1}J(u^*)M = -I + M^{-1}PT'(u_0)M$. We already proved above that $D := M^{-1}PT'(u_0)M$ is Metzler. Let $d_{i,j}$ denote the entries of D ($i, j = 1,2,\ldots,$N), introduce $d := \min_i d_{i,i}$ and $Q := D - dI$ together with $\alpha := 1 - d$. With this, we obtain that $M^{-1}J(u^*)M = -\alpha I + Q$ such that $Q \succeq 0$ is irreducible (since P is). Therefore, to invoke Lemma 5, all there is left to show is that $\rho(Q) > \alpha$.

To this end, note that the eigenvalues of D are $\lambda_j T'(u_0)$ and since D is Metzler from above, we invoke Corollary 4.3.2 in Smith (1995) to conclude that $s(D) = \lambda_i T'(u_0)$ for some i such that λ_i is real. Therefore, the condition in (7) yields that $s(D) > 1$. Furthermore, from $Q = D - dI$ it follows that $s(Q) = s(D) - d$, and since $\alpha = 1 - d$ we obtain that $s(Q) > \alpha$. Finally, from the Perron-Frobenius theorem (Theorem 4.3.1 in Smith (1995)) we have that $\rho(Q) = s(Q)$, thus $\rho(Q) > \alpha$.

Now we can invoke Lemma 5 with $\mathcal{V}$, M and Q defined above to conclude that both sets $u^* \pm \mathcal{K}$ contain a fixed point $u \neq u^*$ of (8). This is equivalent to having solutions u of (3) in both sets $u^* \pm \mathcal{K}$ different from u^*. Finally, we conclude from Lemma 1 that such solutions $u = (u_1\ \ldots\ u_N)^T$ yield fixed points $x = (T(u_1)\ \ldots\ T(u_N))^T$ of (1)–(2).

3.3 Patterns with Groups

Finally, we search for equilibrium points of (1)–(2) in which subsystems are grouped into classes $O_1, O_2, \ldots, O_r$ such that $x_i = x_j$ if $i, j \in O_k$. Such a solution yields patterns in which subsystems of the same class have identical steady states. To find these solutions, we rely on the notion of equitable partitions of graphs Bollobas (1998).

Definition 8. For a weighted and directed graph (V, P) with adjacency matrix P, a partition π of the vertex set V into classes $O_1, O_2, \ldots, O_r$ is said to be *equitable* if there exist $\bar{p}_{i,j}$ for $i, j = 1, 2, \ldots, r$ such that

$$\bar{p}_{i,j} = \sum_{v \in O_j} p_{u,v} \qquad \forall u \in O_i. \tag{10}$$

Let the reduced adjacency matrix $\bar{P} \in \mathbb{R}^{r \times r}$ be formed by the entries $\bar{p}_{i,j}$.

Theorem 9. Provided (A2), (A4) and (A5), let π be an equitable partition of the vertices V of the graph (V, P) into classes $O_1, O_2, \ldots, O_r$ and let $\bar{P}$ denote the resulting reduced adjacency matrix. Assume that $\Psi(\bar{P}T'(u_0))$ is irreducible and balanced with bipartition vector $\bar{b}$. Introduce $u^* := \mathbf{1}_r u_0$ and the cone $\mathcal{K} = \{\bar{u} : (\bar{u} - u^*)\bar{b}^T \succeq 0\}$. If

$$1 - \bar{\lambda}_i T'(u_0) < 0, \tag{11}$$

for some real eigenvalue $\bar{\lambda}_i$ of $\bar{P}$ then both sets $u^* \pm \mathcal{K}$ contain a point $\bar{u} \neq u^*$ such that $x_i = T(\bar{u}_j)$ for $i \in O_j$ is a fixed point of (1)–(2).

Proof. Consider the reduced set of equations

$$\begin{pmatrix} \bar{u}_1 \\ \vdots \\ \bar{u}_r \end{pmatrix} = \bar{P} \begin{pmatrix} T(\bar{u}_1) \\ \vdots \\ T(\bar{u}_r) \end{pmatrix}. \tag{12}$$

Following the same steps as in the proof of Theorem 7, we conclude that (12) has equilibrium points $\bar{u} \neq u^*$ in both sets $u^* \pm \mathcal{K}$. Exploiting the fact that π is an equitable partition of (V, P), a solution $\bar{u}$ of (12) also defines a solution u of (3) in which $u_i = \bar{u}_j$ for all $i \in O_j$, so that $x_i = T(\bar{u}_j)$ for $i \in O_j$, concluding the proof.

4. APPLICATION EXAMPLE

We next focus on the emergence of patterns in neural networks to demonstrate how our results can be employed when studying pattern formation in networks of the form (1)–(2).

Consider the interconnection of N leaky integrate-and-fire neurons Koch and Segev (1999), described by

$$\begin{aligned} \dot{x}_i &= -ax_i + g(u_i), \\ y_i &= x_i, \\ u &= Py \end{aligned} \tag{13}$$

with $a > 0$ and where $g(\cdot)$ is an increasing function such that $g(0) = 0$. In what follows we consider

$$g(u_i) = G \frac{\exp\left(\frac{2\mu}{G}u_i\right) - 1}{\exp\left(\frac{2\mu}{G}u_i\right) + 1} \tag{14}$$

to model the saturated nature of the interconnection channels. For simplicity, we focus on the case when $P\mathbf{1}_N = \mathbf{0}_N$ so that the origin is a fixed point of (13), thus $x_0 = u_0 = 0$.

As a concrete example, introduce the asymmetric interconnection matrix

$$P = \begin{bmatrix} 1 & -1 & & \\ & \ddots & \ddots & \\ & & \ddots & -1 \\ -1 & & & 1 \end{bmatrix}, \tag{15}$$

describing the interconnection of N neurons in a ring structure such that each neuron activates itself and inhibits its neighbor on the right-hand side, and assume that N is even. Theorem 4 then yields that the origin is a stable fixed point of (13)–(14) if $\mu < a/2$ (Fig. 1, left panel).

We next demonstrate that (up to rotation along the ring) a unique stable pattern emerges in (13)–(15) when $\mu > a/2$. Moreover, we show that this unique pattern is such that $x_1 = -x_2 = x_3 = \ldots = x_{N-1} = -x_N \neq 0$, thus we call

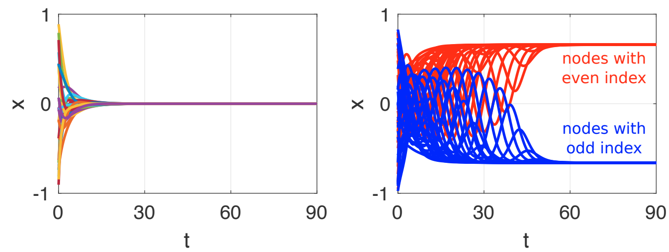

Fig. 1. Pattern formation in neural networks. The origin is globally asymptotically stable when $\mu < a/2$ (left panel, simulation parameters: $N = 50$, $a = 1$, $G = 1$, $\mu = 0.4$). A unique alternating steady state pattern emerges when $\mu > a/2$ (right panel, simulation parameters: $N = 50$, $a = 1$, $G = 1$, $\mu = 0.4$).

it an alternating pattern (Fig. 1, right panel). Building on the results presented in the preceding sections, we first show that such a pattern exists and it is unique (up to rotation), then we prove that it is stable.

Invoking Theorem 9, we first prove that (13)–(15) has two fixed points other than the origin: one such that $x_{2k-1} \geq 0$ and $x_{2k} \leq 0$; and another such that $x_{2k-1} \leq 0$ and $x_{2k} \geq 0$ for $k = 1, \ldots, N/2$. To this end, note first that the partition π of the vertices into $O_1 = \{1, 3, \ldots, N-1\}$ and $O_2 = \{2, 4, \ldots, N\}$ is equitable. The eigenvalues of the corresponding reduced adjacency matrix

$$\bar{P} = \begin{bmatrix} 1 & -1 \\ -1 & 1 \end{bmatrix}$$

are $\bar{\lambda}_1 = 0$ and $\bar{\lambda}_2 = 2$. Second, the matrix

$$\Psi(\bar{P}T'(u_0)) = \begin{bmatrix} 0 & -\mu/a \\ -\mu/a & 0 \end{bmatrix}$$

is irreducible and balanced with bipartition vector $\bar{b} = (1 \ -1)^T$. Third, since $u_0 = 0$, we obtain that $u^* := \mathbf{1}_r u_0$ is the origin, yielding the cone $\mathcal{K} := \{\bar{u} : (\bar{u} - u^*)\bar{b}^T \succeq 0\} = \{\bar{u} : \bar{u}_1 \geq 0, \ \bar{u}_2 \leq 0\}$. Therefore, from Theorem 9 it follows that if $\mu > a/2$ then there exist $\bar{u}_1 \geq 0$ and $\bar{u}_2 \leq 0$ not simultaneously zero such that for $i = 1, 2, \ldots, N$ both

$$x_i = \begin{cases} T(\bar{u}_1) & i \text{ even} \\ T(\bar{u}_2) & i \text{ odd} \end{cases} \tag{16}$$

and

$$x_i = \begin{cases} T(\bar{u}_1) & i \text{ odd} \\ T(\bar{u}_2) & i \text{ even} \end{cases} \tag{17}$$

are fixed points of (13)–(15), where $T(\bar{u}_1) \geq 0$ and $T(\bar{u}_2) \leq 0$ are not simultaneously zero.

Next, we prove that apart from the origin, the only fixed points of (13)–(15) are those in (16)–(17). To this end, consider first the unique solution $x^* > 0$ of

$$x^* = \frac{G}{a} \frac{\exp(\frac{4\mu}{G}x^*) - 1}{\exp(\frac{4\mu}{G}x^*) + 1} \tag{18}$$

and note that with $\bar{u}_1 := 2x^* > 0$ and $\bar{u}_2 := -2x^* < 0$ we have $x^* = T(\bar{u}_1) > 0$ and $-x^* = T(\bar{u}_2) < 0$. Since $|g(u_i)| < G$ we have that $\dot{x}_i$ can only be zero if $|x_i| < G/a$, therefore, what is left to show is that if $x_i \in (0, x^*)$ or $x_i \in (x^*, G/a)$ then x can not be a fixed point of (13)–(15). To this end, note that

$$x_{i+1} = x_i + \frac{G}{2\mu} \ln\left(\frac{\frac{G}{a} - x_i}{\frac{G}{a} + x_i}\right) =: L(x_i), \tag{19}$$

so that for x to be a fixed point we must have that

$$x_i = (\underbrace{L \circ L \circ \cdots \circ L}_{N})(x_i).$$

From (19) it follows that $|L(x^*)| = x^*$ and we obtain that $|L(x_i)| < x_i$ for $|x_i| < x^*$ and $|L(x_i)| > x_i$ for $x^* < |x_i| < G/a$. Therefore, we must have $|x_i| = x^*$ for x to be a fixed point, and then from (19) it follows that either $x_i = (-1)^i x^*$ or $x_i = (-1)^{i+1} x^*$ for $i = 1, 2, \ldots, N$.

Finally, we show that the alternating patterns in (16)–(17) are stable fixed points of (13)–(15). To this end, define $\alpha := 2\mu/a$ and $v := 2ax^*/G$ such that from (18) we have that $v = (e^{2\alpha v} - 1)/(e^{2\alpha v} + 1)$, and let $v = V(\alpha)$ denote its positive solution. Define

$$h(\alpha) := \frac{2\alpha e^{\alpha V(\alpha)}}{(e^{2\alpha V(\alpha)} + 1)^2},$$

yielding $g'(\bar{u}_1) = g'(\bar{u}_2) = g'(\pm 2x^*) = ah(\alpha)$. Since $0 < h(\alpha) < 0.5$ for $\alpha > 1$ (verified numerically), this then implies that with $\tilde{P} := ah(\alpha)P$ its spectral radius $\rho(\tilde{P})$ is such that $\rho(\tilde{P}) = ah(\alpha)\rho(P) < a$. Considering the following lemma, this then yields that the alternating patterns in (16)–(17) are stable fixed point of (13)–(15).

Lemma 10. Let x^* denote a fixed point of

$$\begin{aligned} \dot{x}_i &= Ax_i + Bg(u_i), \\ y_i &= Cx_i, \\ u &= Py, \end{aligned} \tag{20}$$

where $A \in \mathbb{R}^{n \times n}$, $B \in \mathbb{R}^{n \times k}$, $C \in \mathbb{R}^{1 \times n}$, $P \in \mathbb{R}^{N \times N}$ and $g(\cdot) : \mathbb{R} \to \mathbb{R}^k$ is differentiable. Introduce $u^* := P(I_N \otimes C)x^*$ and let $\tilde{\lambda}_i$ denote the eigenvalues of $\tilde{P} := \mathrm{diag}(g'(u_1^*) \ \ldots \ g'(u_N^*))P$. The fixed point x^* is stable if $A + \tilde{\lambda}_i BC$ are Hurwitz for $i = 1, 2, \ldots, N$ and it is unstable if $A + \tilde{\lambda}_i BC$ has an eigenvalue with positive real part for some i.

Proof. The linearization of (20) about the fixed point x^* yields the Jacobian $I_N \otimes A + \tilde{P} \otimes (BC)$. We can then show that the eigenvalues of the above Jacobian are those of $A + \tilde{\lambda}_i BC$ similar to the proof of Lemma 3.

5. DISCUSSION

In this paper, we presented analytical results for pattern formation in large-scale networks even with asymmetric connections between nodes. Therefore, the results presented here significantly advance our understanding of patterning in a general setting by overcoming the dimensional constraints of earlier studies.

By relying on the static input/output characteristic of each cell and the algebraic properties of the interconnection graph, we first characterized the stability of the homogeneous fixed points. Second, we provided sufficient conditions for the emergence of non-homogeneous patterns when the graphs representing the interconnection structure are bipartite. Following this, we demonstrated that equitable partitions provide templates for patterns such that cells share the same fate within partition. Finally, we demonstrated how to use our results in the case of neural networks and reaction-diffusion systems.

The most limiting assumption of the results presented here are about the interconnection structure. We relied heavily on the fact that the graphs representing the connections among cells are bipartite. This allowed us to leverage results from monotone systems theory to conclude the emergence of non-homogeneous steady state patterns. To overcome this limitation, a generalization to a larger class of graphs needs to be developed.

As there are many instances with multiple channels of communication, a promising future research direction is the extension of the results presented here to multigraphs. A particularly interesting problem arises when we allow different interconnection structures for different channels of communication. While this is not typical in biological systems, where the interconnection channels are often the same for all communicating species, it is certainly common in social networks where different types of ties among people can have fundamentally dissimilar underlying interonnection structure.

REFERENCES

Aoki, K., Diner, E., de Roodenbeke, C., Burgess, B., Poole, S., Braaten, B., Jones, A., Webb, J., Hayes, C., Cotter, P., and Low, D. (2010). A widespread family of polymorphic contact-dependent toxin delivery systems in bacteria. *Nature*, 468, 439–442.

Arcak, M. (2013). Pattern formation by lateral inhibition in large-scale networks of cells. *IEEE Transactions on Automatic Control*, 58(5), 1250–1262.

Bollobas, B. (1998). *Modern Graph Theory*. Springer, New York, NY.

Brouwer, L.E.J. (1911). Uber abbildungen von mannigfaltigkeiten. *Mathematische Annalen 71*, 97–115.

Colizza, V., Barrat, A., Barthelemy, M., and Vespignani, A. (2006). The role of the airline transportation network in the prediction and predictability of global epidemics. *PNAS*, 103, 2015–2020.

Collier, J.R., Monk, N.A., Maini, P.K., and Lewis, J.H. (1996). Pattern formation by lateral inhibition with feedback: A mathematical model of delta-notch intercellular signalling. *Journal of Theoretical Biology*, 183, 429–446.

Dillon, R., Maini, P.K., and Othmer, H.G. (1994). Pattern formation in generalized turing systems. *Journal of Mathematical Biology*, 32, 345–393.

Ferreira, A.S.R. and Arcak, M. (2013). A graph partitioning approach to predicting patterns in lateral inhibition systems. *SIAM Journal on Applied Dynamical Systems*, 12(4), 2012–2031.

Fortuna, M.A., Gomez-Rodriguez, C., and Bascompte, J. (2006). Spatial network structure and amphibian persistence in stochastic environments. *Proceedings of the Royal Society B: Biological Sciences*, 273, 1429–1434.

Ghosh, R. and Tomlin, J.C. (2004). Symbolic reachable set computation of piecewise affine hybrid automata and its application to biological modeling: Delta-notch protein signaling. *IET Systems Biol*, 1, 170–183.

Gierer, A. and Meinhardt, H. (1972). A theory of biological pattern formation. *Kybernetik*, 12, 30–39.

Gilbert, S.F. (2010). *Developmental Biology (9th edition)*. Sinauer Associates, Sunderland, MA.

Hanski, I. (1998). Metapopulation dynamics. *Nature*, 396, 41–49.

Horsthemkea, W., Lamb, K., and Moore, P.K. (2004). Network topology and turing instabilities in small arrays of diffusively coupled reactors. *Physics Letters A*, 328, 444–451.

Hufnagel, L., Brockmann, D., and Geisel, T. (2004). Forecast and control of epidemics in a globalized world. *PNAS*, 101, 15124–15129.

Koch, C. and Segev, I. (1999). *Methods in neuronal modeling : from ions to networks (2nd ed.)*. MIT Press, Cambridge, MA.

Moore, P.K. and Horsthemkea, W. (2005). Localized patterns in homogeneous networks of diffusively coupled reactors. *Physica D: Nonlinear Phenomena*, 206, 121–144.

Murray, J.D. (2003). *Mathematical Biology II: Spatial Models and Biomedical Applications*. Springer, New York, NY.

Othmer, H.G. and Scriven, L.E. (1971). Instability and dynamic pattern in cellular networks. *Journal of Theoretical Biology*, 32, 507–537.

Othmer, H.G. and Scriven, L.E. (1974). Non-linear aspects of dynamic pattern in cellular networks. *Journal of Theoretical Biology*, 43, 83–112.

Pastor-Satorras, R. and Vespignani, A. (2001). Epidemic spreading in scale-free networks. *Physical Review Letters*, 86, 3200–3203.

Smith, H.L. (1995). *Monotone dynamical systems: An introduction to the theory of competitive and cooperative systems*. Mathematical Surveys and Monographs, vol. 41, American Mathematical Society, Providence, RI.

Sprinzak, D., Lakhanpal, A., Bon, L.L., Garcia-Ojalvo, J., and Elowitz, M. (2011). Mutual inactivation of notch receptors and ligands facili-tates developmental patterning. *PLoS Computational Biology*, 7(6).

Sprinzak, D., Lakhanpal, A., Bon, L.L., Santat, L., Fontes, M., Anderson, G., Garcia-Ojalvo, J., and Elowitz, M. (2010). Cis-interactions between notch and delta generate mutually exclusive signalling states. *Nature*, 465, 86–90.

Turing, A.M. (1952). The chemical basis of morphogenesis. *Philosophical Transactions of the Royal Society of London*, 237, 37–72.

Wolpertand, L. and Tickle, C. (2011). *Principles of Development (4th edition)*. Oxford University Press, London, UK.