

Extracellular noise-induced stochastic synchronization in heterogeneous quorum sensing network

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Abstract

Quorum sensing is a bacterial mechanism used to synchronize the coordinated response of a microbial population. Because quorum sensing in Gram-negative bacteria depends on release and detection of a diffusible signaling molecule (autoinducer) among a multicellular group, it is considered a simple form of cell–cell communication for the purposes of mathematical analysis. Stochastic equation systems have provided a common approach to model biochemical or biophysical processes. Recently, the effect of noise to synchronize a specific homogeneous quorum sensing network was successfully modeled using a stochastic equation system with fixed parameters. The question remains of how to model quorum sensing networks in a general setting. To address this question, we first set a stochastic equation system as a general model for a heterogeneous quorum sensing network. Then, using two relevant biophysical characteristics of Gram-negative bacteria (the permeability of the cell membrane to the autoinducer and the symmetry of autoinducer diffusion) we construct the solution of the stochastic equation system at an abstract level. The solution indicates that stable synchronization of a quorum sensing network is robustly induced by an environment with a heterogeneous distribution of extracellular and intracellular noise. The synchronization is independent of the initial state of the system and is solely the result of the connectivity of the cell network established through the effects of extracellular noise.

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1. Introduction

Bacteria produce and release specialized signaling molecules which can coordinate the activity of a local group of the conspecific microorganisms. These molecules can, by analogy to multicellular organisms, be considered as bacterial pheromones. By sensing the signaling molecules, a bacterium can monitor the density of a bacterial population by a process known as “quorum sensing” (Fuqua et al., 1994). Quorum sensing has been demonstrated in numerous species of bacteria and is believed to play a key role in such processes as bioluminescence, biofilm formation, expression of virulence factors, conjugation, sporulation, and synthesis of antibiotics (see

Lazdunski et al., 2004; Taga and Bassler, 2003; Waters and Bassler, 2005; Gera and Srivastava, 2006).

A variety of biochemical pathways in quorum sensing have been documented (Taga and Bassler, 2003; Camilli and Bassler, 2006; Reading and Sperandio, 2006). Signal molecules associated with quorum sensing in Gram-positive bacteria are generally oligopeptides that act on membrane receptors (Okada et al., 2005; Comella and Grossman, 2005; Lyon and Novick, 2004). However, the most fully characterized quorum sensing systems are those of Gram-negative bacteria. As first described by Neelson et al. (1970) in the bioluminescent bacterium *Vibrio fischeri*, many Gram-negative bacteria synthesize a species-typical acylated homoserine lactone (AHL) which is permeable through the membrane (see Fuqua et al., 2001; Fuqua and Greenberg, 2002; Lazdunski et al., 2004; Welch et al., 2005). The biosynthesis of AHL is mediated by synthetases

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which are homologs of the *V. fischeri* LuxI protein involved in regulation of bioluminescence (see Fig. 1). AHL binds specifically to intracellular LuxR-type receptor proteins, which then change in conformation (usually, dimerize), interact with *lux*-box DNA sequences and regulate (usually, activate) transcription of *lux*-type target genes, including *luxR* and *luxI*. AHL is therefore an autoinducer and positive feedback commonly regulates its cellular concentration and production.

Since cell membranes are permeable to AHL, the levels of autoinducer in and around a bacterium will increase when it is surrounded by others and they, too, synthesize the molecule (see Fig. 2). The autoinducer therefore acts as a simple means of biochemical communication within the bacterial population (Fuqua et al., 2001; Taga and Bassler, 2003; Welch et al., 2005; Reading and Sperandio, 2006). In a population, every bacterium releases the autoinducer molecule, which diffuses into the environment. As the molecules diffuse through the environment, they act as a signal to deliver information about population density to all bacteria within the same environment. The physiological state of the bacterium may be changed due to the intracellular regulation of the membrane-permeable autoinducer, for example, to produce light in *V. fischeri*. Quorum sensing in the control of the *lux* genetic system is commonly seen as analogous to cell–cell communication in

multicellular organisms (Keller and Surette, 2006; Taga and Bassler, 2003) and appears as an appropriately simple system useful for mathematical modeling (Terrazas et al., 2005; Chen et al., 2005; Goryachev et al., 2005). In quorum sensing, rather than direct communication, signal molecules (e.g., AHL) are broadcast into the environment and will be subject to fluctuations of local concentrations in the environment. We assume that within a locale, the concentration of the signal molecule may fluctuate according to a single rule. Through the rest of this paper, we will use the term “locale” to mean such a local environment.

Numerous theoretical models for cell–cell communication have been proposed (Elowitz and Leibler, 2000; Elowitz et al., 2002; McMillen et al., 2002; Taga and Bassler, 2003). Since the information is exchanged via a signal molecule which enters the environment and then moves into and out of cells, extracellular noise must have an effect on the communication (Chen et al., 2005; Zhou et al., 2004). Extracellular noise in this context means stochastic variation in the environmental distribution of the autoinducer. The first model for cell–cell communication in which extracellular noise was taken into consideration was proposed by Zhou et al. (2005). This model is homogeneous and well-mixed, which means that all cells are identical and regional fluctuations are ignored (or equivalently, the environment consists of a single locale).

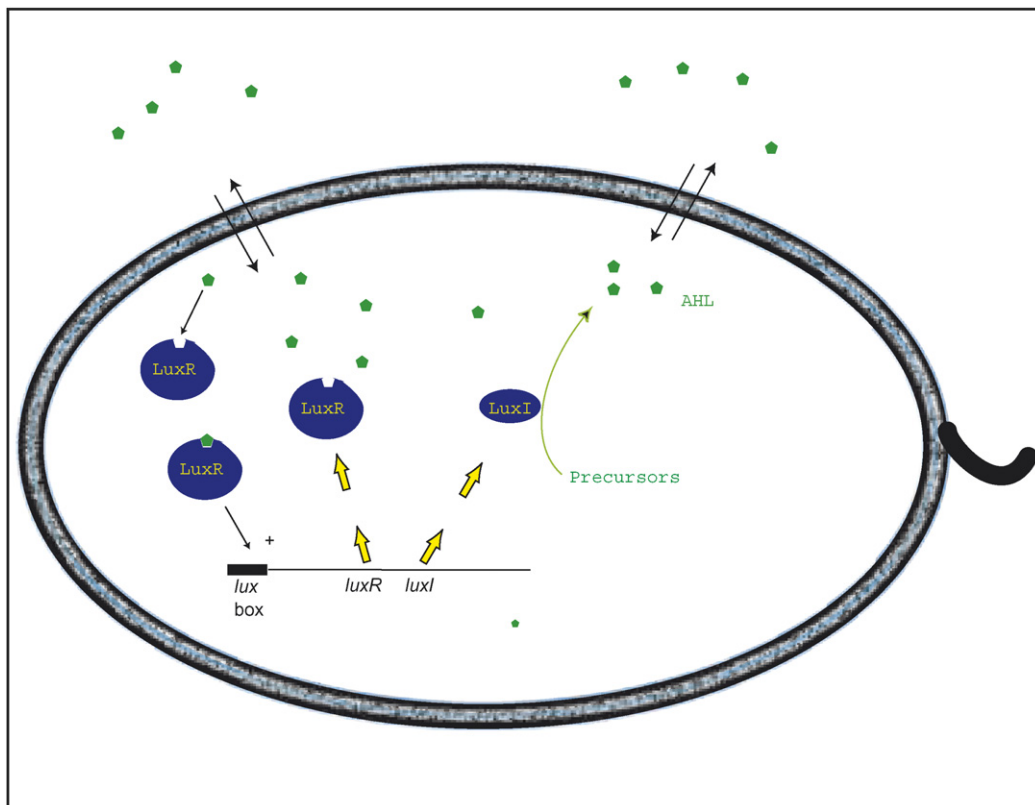


Fig. 1. Regulation of the luminescence system of *Vibrio fischeri*. The simplified diagram uses green pentagons to represent acylated homoserine lactone (AHL), which is freely permeable bi-directionally (black arrows) through the membrane (blue-black outer oval). The dark blue shapes are proteins. LuxR has a recognition site for AHL. The AHL–LuxR complex interacts with the *lux* box on the DNA, activating transcription of *lux* genes including *luxI*. LuxI catalyzes the biosynthesis of AHL. The *V. fischeri* cell has a cilium (on the right).

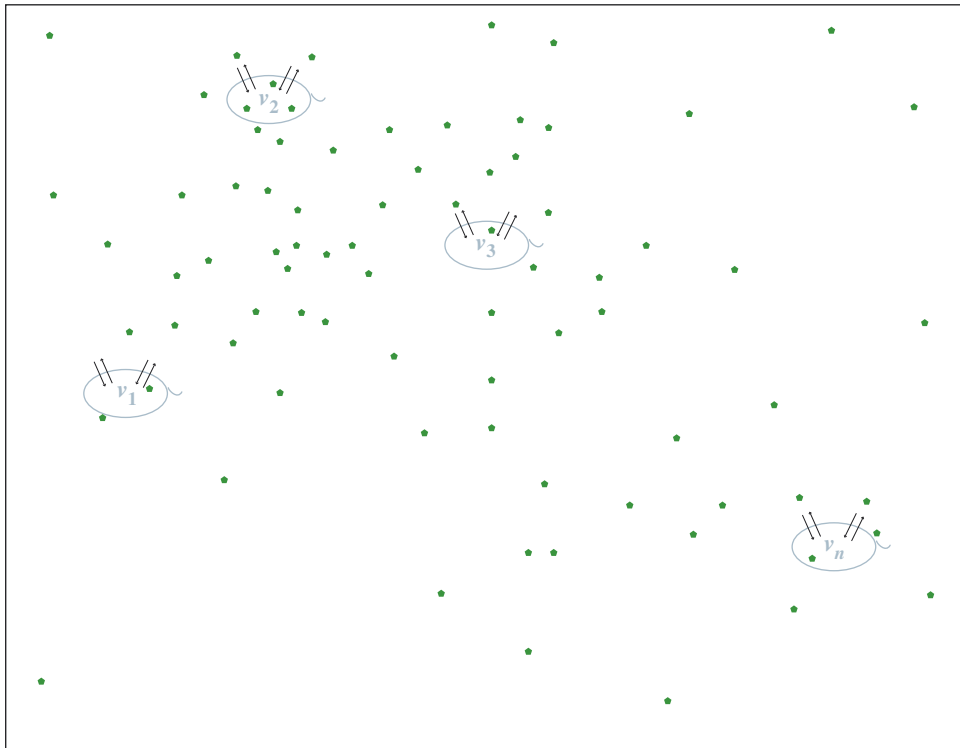


Fig. 2. Heterogeneous extracellular and intracellular autoinducer concentrations. There are n cells (v_1, v_2, v_3, v_n). AHL, indicated by green pentagons, is equally permeable in both directions across the cell membrane.

The consequence of this construction is that n identical cells are coupled by a solitary source of extracellular noise. The Zhou et al. (2005) model possesses both intracellular and extracellular sources of noise. Mathematically, the Zhou et al. (2005) model is captured by a stochastic equation system, and the model demonstrates that the extracellular noise is exploited by the n cells of the population to induce a population synchronization. However, Zhou et al. (2005) defined specific functions and specific numerical coefficients for simulation and analysis within their stochastic equation system to study the behavior of the population. Therefore, the model does not give a general theoretical scheme by which the cells exploit noise to induce synchronization. Nevertheless, as pointed by Springer and Paulsson (2006), the model profoundly changed the perception of the role of noise in quorum sensing and in biological systems in general.

The Zhou et al. (2005) study (as also pointed by the authors) raises an important issue concerning the effects of heterogeneous distribution of extracellular noise in a population of non-identical cells. In this paper, we propose a model to address the two questions below. We consider a quorum sensing network in a general setting: a population of n non-identical cells which reside in a heterogeneous environment consisting of k different locales, in each of which the extracellular noise may differ from others (see Fig. 3). The synchronization of the network is interpreted as follows. The concentrations of the signal molecules in the n cells begin to fluctuate according to a stable and coherent temporal pattern (see the explanation of (9)).

However, absolute concentrations of AHL may still differ between cells due to the stipulations that (a) the cells need not be identical and (b) the locales where the cells reside are heterogeneous. We ask: *In general, what is the mechanism behind the extracellular noise-induced synchronization in a quorum sensing network? How can the concentration of the signal molecule in each of the n cells be quantitatively described when the synchronization occurs?*

2. The model

The intracellular aspect of quorum sensing is the activation of a biochemical pathway regulated by AHL (see Fuqua et al., 2001; Fuqua and Greenberg, 2002; Lazdunski et al., 2004). Since the biochemical reactions are subject to stochastic variation at the molecular level, each cell generates its own intracellular noise (Elowitz and Leibler, 2000; Elowitz et al., 2002; Paulsson, 2004). Using the luminescence system of *V. fischeri* as an example, Fig. 1 illustrates how the circuit in a single cell produces autoinducer (AHL) and how the cell interacts with its locale. Simultaneously, the environment generates extracellular noise within its locales through stochastic variation in release, and the randomness of degradation of AHL. Fig. 2 depicts four cells which reside in an environment, and Fig. 3 further details how the environment consists of k distinct locales of extracellular noise. (Note that for simplicity we have illustrated the relationship between cells and locales from a two-dimensional perspective in Figs. 2–4. However, since the relation between n and k is

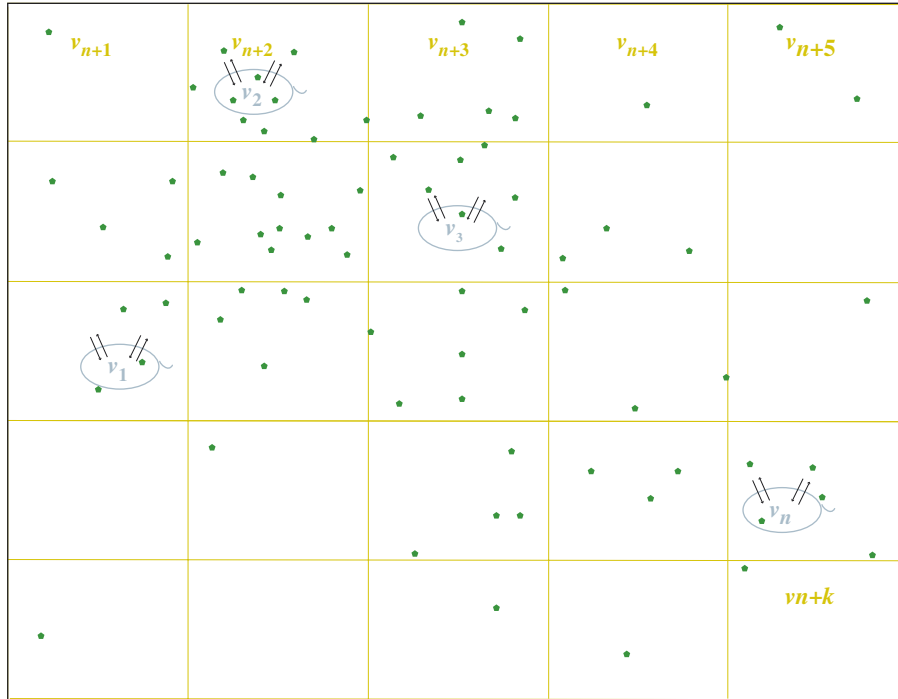


Fig. 3. Regions of extracellular noise in a heterogeneous quorum sensing network. As a first approximation, heterogeneous extracellular distribution of noise can be represented as multiple locales. Within a locale, the concentration of the signal molecule is considered to fluctuate according to a single rule. In this representation, k locales are indicated ($v_{n+1}, v_{n+2}, v_{n+3}, v_{n+3}, v_{n+3}$, and v_{n+k}). For generality, the sources of extracellular noise remain undefined, but presumably include Brownian movement and local variations in degradation of AHL.

not specified, the analysis could just as well apply to a three-dimensional space.) As mentioned in the previous section, within a locale the AHL concentration fluctuates according to a single rule.

Consider a quorum sensing system where n non-identical cells reside in an environment consisting of k locales (see Fig. 3). We will call a cell the i th, $1 \leq i \leq n$, and a locale the j th, $1 \leq j \leq k$. According to Van Kampen (1992) (also, see Zhou et al., 2005), the temporal dynamics $X(t)$ of the AHL concentration in a single cell can be expressed by

$$\frac{dX(t)}{dt} = f(X(t)) + \eta(t), \tag{1}$$

where η characterizes the intracellular noise. Let $X_i(t)$ denote the temporal dynamics of the AHL concentration in the i th cell. We let $Y_j(t)$ denote the temporal dynamics of the AHL concentration in the j th locale; and let $\xi_j(t)$ characterize the extracellular noise in this locale. Now, consider the n cells and k locales as a quorum sensing network (see Fig. 4). Then, in accordance with (1) the dynamics of the AHL concentration in the quorum sensing network is expressed by an equation system reflecting the dynamics of the network

$$\begin{aligned} \frac{dX_i}{dt} &= h_i(X_i, Y_1, \dots, Y_k) + \sigma_i \eta_i, \quad i = 1, \dots, n, \\ \frac{dY_j}{dt} &= g_j(X_1, \dots, X_n, Y_1, \dots, Y_k) + \sigma_j \xi_j, \quad j = 1, \dots, k. \end{aligned} \tag{2}$$

Here, σ_i and σ_j are constants; and h_i and g_j describe, respectively, how the AHL concentration in the i th cell and

j th locale can possibly be affected, respectively, by the k locales and by the n cells plus the k locales. Mathematically, (2) is our proposed model. The setting of (2) follows from the master equation in Zhou et al. (2005). However, there is a significant difference. We consider k locales, meaning that the environment is not well mixed. Thus, we need not introduce a time delay for the cells to reach equilibrium with the environment. Eliminating such a time delay will largely facilitate the analysis of the quorum sensing network presented in this paper.

3. The result

We assume that (2) has a unique solution (see Coffey et al., 2004; Steele, 2000, Theorem 9.1). In other words, given n cells and k locales, there is a unique stochastic process which captures the temporal dynamics of the quorum sensing network regardless of whether synchronization will occur. The question is under what condition this stochastic process will lead to synchronization. We will describe the condition which guarantees that synchronization will occur.

We specify a time unit δ . Consider diffusion of the signal molecule AHL. We assume that the diffusion is uniform in the following sense. For a quorum sensing network, there is a time interval within which any signal molecule is only able to travel between a cell and the locale where the cell resides, or between two neighboring locales. For example, in Fig. 3 we mean exchanges of AHL between cell v_2 and

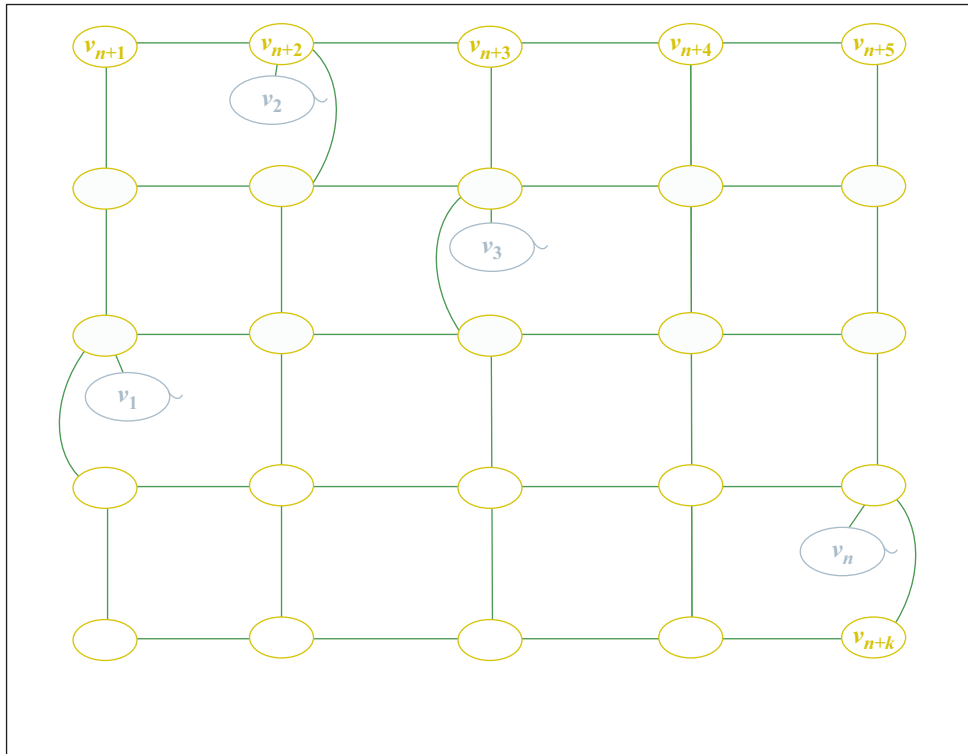


Fig. 4. Graphical representation of a heterogeneous quorum sensing network. As in Figs. 2 and 3, there are n cells (which are not necessarily identical), and k locales of extracellular noise, representing the environment where the four cells reside. There is no direct connection between any two cells; however, the locales are interconnected (solid blue lines). Each cell communicates with a single locale (solid blue lines). For example, cell v_2 communicates only with v_{n+2} .

locale v_{n+2} , v_{n+1} and v_{n+2} , v_{n+2} and v_{n+3} , etc. We let δ be such a time interval. One might have noticed that there are different choices for δ . If $0 < \delta'$ is chosen, then some $0 < \delta' < \delta$ would be an alternative choice. Thus, δ is a parameter of the proposed model, which will play an important role in the main theoretical result of this paper, Theorem 1. Notice that in reality δ is very small.

Denote by $x_i(t)$ and $y_j(t)$ the AHL concentration in the i th cell and in the j th locale at time $t\delta$, $t = 1, 2, \dots, s$, respectively. Notice that $x_i(t)$ and $y_j(t)$ have a stochastic nature and are mathematically considered random variables. We introduce

$$X_i \stackrel{\text{def}}{=} \{x_i(t) : t = 1, 2, \dots, s\} \tag{3}$$

and

$$Y_j \stackrel{\text{def}}{=} \{y_j(t) : t = 1, 2, \dots, s\}. \tag{4}$$

And we consider a vector-valued discrete stochastic process

$$\{(x_1(t) \dots x_n(t) y_1(t) \dots y_k(t))^\top : t = 1, 2, \dots, s\}, \tag{5}$$

where $(\cdot)^\top$ stands for the transposition of a vector (\cdot) . $x_i(t)$ can be viewed as the observed value of AHL concentration in the i th cell. Thus, (5) traces the observed values of AHL concentration in the n cells over time $t\delta$, $t = 1, 2, \dots, s$. Consider $(x_i(t+1) - x_i(t))$ the difference in the AHL concentration in the i th cell between time $t\delta$ and $(t+1)\delta$. Notice that $(x_i(t+1) - x_i(t))$ is also a random variable.

Since δ is very small, we expect that the random variable takes a small range. Suppose that there are constants $M > 0$ and $p > \frac{1}{2}$ such that for all $1 \leq i \leq n$ and for all $1 \leq t \leq s$

$$|x_i(t+1) - x_i(t)| \leq M \cdot \delta^p. \tag{6}$$

X_i in (2) characterizes how a biochemical process (the AHL concentration in a cell) progresses over time. Accordingly, x_i in (3) is used to look up the AHL concentration levels in the i th cell instant-by-instant along all possible paths (temporal traces) in the process. Any path in a biochemical process is relatively smooth over time. Therefore, we can reasonably assume that all paths are in a Hölder class $A^p(M)$ with $p > \frac{1}{2}$. Here, we recall that the Hölder classes are defined as follows: Let us denote all possible real-valued functions by h . Then, for $0 < p \leq 1$, $A^p(M) \stackrel{\text{def}}{=} \{h : \forall x_1, x_2, (|h(x_1) - h(x_2)| \leq M|x_1 - x_2|^p)\}$; and for $1 < p$, $A^p(M) \stackrel{\text{def}}{=} \{h : \forall x |h'(x)| \leq M, h^{[p]}$ exists, and $\forall x_1, x_2, (|h^{[p]}(x_1) - h^{[p]}(x_2)| \leq M|x_1 - x_2|^{p-[p]})\}$. Thus, we can assume that M and p in (6) are absolute constants for all possible choices of δ .

(6) is also applied to all y_j . The restriction imposed by (6) is mild. A path in a Hölder class $A^p(M)$ means it represents a continuous temporal trace; however, when $p < 1$, the path may not be differentiable.

Suppose that the condition (6) is satisfied. Then we have the following theorem. A proof for this theorem is in Section 4. Let $E[\cdot]$ denote the mean of a random variable.

Theorem 1. Let $s = \delta^{-\alpha}$ for some $0 < \alpha < 1$. Then, for all $\varepsilon > 0$

$$\Pr \left\{ \max_{1 \leq i \leq n} \{|x_i(s) - E[x_i(s)]|\} \leq \varepsilon \right\} \geq 1 - 2n \exp \left(-\frac{\varepsilon^2}{2M^2 \cdot \delta^{2p-\alpha}} \right). \tag{7}$$

This theorem has some important implications as follows. Letting $\varepsilon = \delta^{(2p-\alpha)/3}$ in (7) we have

$$\Pr \left\{ \max_{1 \leq i \leq n} \{|x_i(s) - E[x_i(s)]|\} \leq \delta^{(2p-\alpha)/3} \right\} \geq 1 - 2n \exp \left(-\frac{1}{2M^2 \cdot \delta^{(2p-\alpha)/3}} \right). \tag{8}$$

As mentioned in Section 1, numerous theoretical models for cell–cell communication have been proposed. The model proposed in this paper is the first in which extracellular noise, non-identical cells and not well mixed environment are considered. The model is closer to the realistic natural condition, and brings the following three new insights, (A1)–(A3), into quorum sensing.

(A1) *The synchronization is stable:* M and p are determined by the biochemical process, i.e., essentially by the type of cell under consideration; and n is the number of cells in the quorum sensing network. Now, we fix α . Recall that δ is specified as a time interval within which any signal molecule is only able to travel between a cell and the locale where the cell resides, or between two neighboring locales. Thus, though it is very small, δ has a lower bound $\lambda \approx 0$. Throughout the rest of this paper, we will fix δ as the lower bound λ . From the viewpoint of theoretical biology, it is important that (8) can be used to explain that the synchronization is stable, as is observed experimentally. That is, once synchronization occurs in a quorum sensing network, it will persist as long as there are no changes in the environment. We first consider how to represent δ at different time scales. For example, for simplicity let us assume that δ is 1 s; then it is $\frac{1}{3600} \approx 0.00028$ h. The larger the scale is, the smaller the δ is. We can mathematically normalize the whole scale as 1 and introduce a parameter m so that δ is actually represented by $1/m$. In the example above, if $m = 1$ at the scale of seconds; then $m \approx 0.00028$ at the scale of hours. Then, letting $\delta = 1/m$, with (8) we have

$$\Pr \left\{ \max_{1 \leq i \leq n} \{|x_i(s) - E[x_i(s)]|\} \leq \left(\frac{1}{m}\right)^{(2p-\alpha)/3} \right\} \geq 1 - 2n \exp \left(-\frac{m^{(2p-\alpha)/3}}{2M^2} \right). \tag{9}$$

The value of m increases as the time scale gets large. With increasing m , (a) the left side of (9) indicates all x_i are rapidly getting close to $E[x_i]$; and (b) the right side of (9) means that the probability for (a) to happen converges to 1 exponentially fast. We therefore conclude that the synchronization is stable once it occurs.

(A2) *The synchronization is an intrinsic property of the quorum sensing network:* As discussed in Section 1, synchronization occurs when the concentrations of the signal molecules in the n cells begin to fluctuate according to a stable and coherent temporal pattern (i.e., are close to the expectation, $E[x_i(s)]$). However, since the cells are different, $E[x_i(s)]$ will differ by cell. In Section 4 we will show that in (9) as $m \uparrow \infty$

$$(E[x_1(s)], \dots, E[x_n(s)], E[y_{n+1}(s)], \dots, E[y_{n+k}(s)])^T \rightarrow \text{the principal eigenvector of a matrix that captures the Jacobian of (2).}$$

Also, we will show that $E[x_i]$ are dependent only on the matrix, and are independent of the initial levels of AHL concentration levels in the cells. This and (A1) together indicate that the synchronization is a state determined only by the network itself.

(A3) *The synchronization is driven by a universal mechanism:* The proof of Theorem 1 only uses two relevant biophysical characteristics of the quorum sensing system, and a mathematical theorem about stochastic process with independent increments which demonstrates how the two characteristics influence synchronization.

4. Analysis

4.1. A proof of Theorem 1

We will apply some basics of stochastic integration. An insightful introduction to the theory can be found in Chung and Williams (1990). With the Girsanov theorem, we have that if it exists, the solution of (2) is a stochastic process with independent (non-homogenous, in general) increments. As a consequence of the Girsanov theorem we have the following. Let $T_0 = s\delta$ and $m = s$ in (3) and (4). Consider the time interval $[0, T_0]$ which is divided into subintervals $[(l-1)T_0/m, lT_0/m]$, $l = 1, 2, \dots, m$. Define a random variable $d_l^{(i)}$ for the accumulation of X_i in (2) during the time period $[(l-1)T_0/m, lT_0/m]$. Then, $d_l^{(i)}$ are independent. This is no more than saying that the probabilistic behavior of the paths that constitute the solution of (2) are independent over non-overlapped subintervals $[(l_\tau-1)T_0/m, l_\tau T_0/m]$ for any $1 \leq \dots < l_{\tau-1} < l_\tau < \dots \leq m$. By definition we have $x_i(t) = \sum_{l=1}^t d_l^{(i)}$, $1 \leq i \leq n$, that is, $x_i(t)$ can be expressed by the sum of t independent random variables $d_l^{(i)}$, $l = 1, \dots, t$. The same conclusion can be made to $y_j(t)$. This leads to a simple proof of Theorem 1 (in Appendix).

However, Theorem 1 alone does not reveal the mechanism behind the quorum sensing. One would expect that, in general, such a mechanism should depend on the following: some biophysical characteristics of bacteria and the signal molecule AHL; and the network structure where the quorum sensing occurs. In the rest of this section, we will show that the two biophysical characteristics are (i) the cell membrane permeability of bacteria and (ii) the symmetry

of signal molecule diffusion. Furthermore, the network is required to be connected; that is, the bacteria share a common environment, though the local conditions in the environment may be different.

4.2. Representing (2) via a graph

We represent the equation system (2) via a weighted undirected graph G with $(n + k)$ nodes and edges defined by a matrix A (see Fig. 4). We let the first n nodes v_l , $l = 1, \dots, n$, denote the n cells, and let the last k nodes v_l , $l = (n + 1), \dots, (n + k)$, denote the k locales. Each edge characterizes the diffusion of the signal molecule AHL between its two end nodes. With the entries $a_{l_1 l_2}$ of a matrix A , we define the edge between two nodes v_{l_1} and v_{l_2} , $1 \leq l_1, l_2 \leq (n + k)$. There are four cases:

Case 1. $1 \leq l_1, l_2 \leq n$: Both v_{l_1} and v_{l_2} are cells. Since there is no direct connection between two cells or a cell onto itself, $a_{l_1 l_2} = 0$; i.e., there is no edge between v_{l_1} and v_{l_2} . All communications among the cells are via locales.

Case 2. $[1 \leq l_1 \leq n] \wedge [(n + 1) \leq l_2 \leq (n + k)]$ or $[(n + 1) \leq l_1 \leq (n + k)] \wedge [1 \leq l_2 \leq n]$: One node is a cell and the other is the locale where the cell resides. We let $a_{l_1 l_2} = 0$ if within the unit time δ there is no direct exchange of the signal molecule between v_{l_1} and v_{l_2} ; otherwise, we define $a_{l_1 l_2} > 0$ as the diffusion rate between v_{l_1} and v_{l_2} .

Case 3. $(n + 1) \leq l_1 \neq l_2 \leq (n + k)$: Two nodes are different locales. We let $a_{l_1 l_2} = 0$ if within the unit time δ there is no direct exchange of the signal molecule between v_{l_1} and v_{l_2} ; otherwise, we define $a_{l_1 l_2} > 0$ as the diffusion rate between v_{l_1} and v_{l_2} .

Case 4. $(n + 1) \leq l_1 = l_2 \leq (n + k)$: Two nodes are the same locale. We let $a_{l_1 l_2} = 0$.

In addition, three operators U , R and D on G are needed. Operator U characterizes diffusion of the signal molecule between cell and locale, or between two locales. Suppose that at time $t\delta$, the expectations of the concentration of the signal molecule in the l_1 th cell and in the l_2 th locale are, respectively, d_1 and d_2 . U operates as follows: At time $(t + 1)\delta$, the expected amount of the signal molecule that moved from the cell to the extracellular locale (or from the locale to the cell) will be $a_{l_1 l_2} \cdot d_1$ (or, respectively, $a_{l_2 l_1} \cdot d_2$). We suppose that

$$a_{l_1 l_2} = a_{l_2 l_1} \quad \text{for all } 1 \leq l_1, l_2 \leq (n + k), \tag{10}$$

which means that the diffusion of the signal molecule between a cell and a locale simply obeys a basic physical characteristic, *the symmetry of cell membrane permeability*. Furthermore, *the diffusion of the signal molecule between two locales is also symmetrical*.

Notice that by definition, $a_{l_1 l}$ quantifies the proportions of the amount of AHL that moved from inside of the l_1 th cell to the l th locale during the same time interval $[t\delta, (t + 1)\delta]$. Thus, for any $1 \leq l_1 \leq n$ and for all $(n + 1) \leq l \leq (n + k)$, we have $a_{l_1 l} \geq 0$ and $1 - \sum_{l=n+1}^{n+k} a_{l_1 l} \geq 0$. By a similar argument, we have $a_{l_1 l} \geq 0$ and

$1 - \sum_{l=1}^{n+k} a_{l_1 l} \geq 0$ for any $(n + 1) \leq l_1 \leq (n + k)$ and for all $1 \leq l \leq (n + k)$. These relations will be used in Section 4.3.

Operator R characterizes the rate of production of the signal molecule in a cell. Suppose that at time $t\delta$, the expectation of the concentration of the signal molecule in the l_1 th cell is d . Then, the expected amount of the signal molecule that was produced in the l_1 th cell during the duration from $t\delta$ to $(t + 1)\delta$ will be $\beta_{l_1} \cdot d$.

Operator D captures the degradation rate of the signal molecule in the cells or extracellular locales. We assume that D is a variable $D(t)$ of time $t\delta$, satisfying $0 < D(t) < 1$. For $1 \leq t < s$, the degradation rate $D(t)$ operates as follows. Suppose that in a cell, from time $t\delta$ to $(t + 1)\delta$, the expectation of the concentration of the signal molecule would become d (at time $(t + 1)\delta$) by exchanging the signal molecule with its locale and by also producing the signal molecule. Then, due to degradation, the actual amount is $D(t) \cdot d$. Within an extracellular locale, $D(t)$ has the same effect.

Using the matrix A and the operators U and R , we define another matrix A^* . Let

$$a_{l_1 l_2}^* = \begin{cases} a_{l_1 l_2} + (1 - \sum_{l=n+1}^{n+k} a_{l_1 l}) + \beta_{l_1} & \text{if } 1 \leq l_1 \leq n \\ & \text{and } l_1 = l_2, \\ a_{l_1 l_2} + (1 - \sum_{l=1}^{n+k} a_{l_1 l}) & \text{if } (n + 1) \leq l_1 \leq (n + k) \\ & \text{and } l_1 = l_2, \\ a_{l_1 l_2} & \text{otherwise.} \end{cases} \tag{11}$$

Then, let

$$A^* \stackrel{\text{def}}{=} (a_{l_1 l_2}^*)_{(n+k) \times (n+k)}.$$

4.3. A technical lemma required for the analysis

Define for $t = 1, 2, \dots, s$,

$$\tilde{x}_i(t) \stackrel{\text{def}}{=} E[x_i(t)] \quad \text{and} \quad \tilde{y}_j(t) \stackrel{\text{def}}{=} E[y_j(t)].$$

Then we consider a sequence of $(n + k)$ -vectors:

$$\begin{pmatrix} \tilde{x}_1(1) \\ \vdots \\ \tilde{x}_n(1) \\ \tilde{y}_1(1) \\ \vdots \\ \tilde{y}_k(1) \end{pmatrix} \begin{pmatrix} \tilde{x}_1(2) \\ \vdots \\ \tilde{x}_n(2) \\ \tilde{y}_1(2) \\ \vdots \\ \tilde{y}_k(2) \end{pmatrix} \cdots \begin{pmatrix} \tilde{x}_1(t) \\ \vdots \\ \tilde{x}_n(t) \\ \tilde{y}_1(t) \\ \vdots \\ \tilde{y}_k(t) \end{pmatrix} \cdots \begin{pmatrix} \tilde{x}_1(s) \\ \vdots \\ \tilde{x}_n(s) \\ \tilde{y}_1(s) \\ \vdots \\ \tilde{y}_k(s) \end{pmatrix}. \tag{12}$$

Notice that this sequence of $(n + k)$ -vectors is numerical (not random), which describes how the means of $x_i(t)$ and $y_j(t)$ progress over time. In what follows, for $t = 1, \dots, s$, we let

$$\mathcal{V}(t) \stackrel{\text{def}}{=} (\tilde{x}_1(t) \cdots \tilde{x}_n(t) \tilde{y}_1(t) \cdots \tilde{y}_k(t))^T,$$

where $(\cdot)^T$ stands for transposition. We have the mathematical operation corresponding to the transition from

$\mathcal{V}(t)$ to $\mathcal{V}(t + 1)$ is

$$\mathcal{V}(t + 1) = D(t) \cdot (A^* \times \mathcal{V}(t)) \quad \text{for all } 1 \leq t < s. \quad (13)$$

We will prove (13) shortly. For the moment, let us assume that (13) holds. Then, we have

$$\mathcal{V}(s) = \left(\prod_{t=1}^{s-1} D(t) \right) \cdot (A^*)^{s-1} \times \mathcal{V}(1). \quad (14)$$

In what follows, we will use a result in elementary matrix theory. We refer the reader to [Horn and Johnson \(1985\)](#) for a reference. By definition, the matrix A^* is symmetric. Furthermore, A^* is non-negative, i.e., all its entries $a_{l_1 l_2}^*$ are non-negative numbers. Indeed, by definition the matrix A is non-negative. Then, by (11) we have for all $1 \leq l_1 \neq l_2 \leq (n + k)$, $a_{l_1 l_2}^* = a_{l_1 l_2}$ are non-negative. In the case of $1 \leq l_1 = l_2 \leq n$, we have that $a_{l_1 l_2} = 0$, $\beta > 0$ (by definition). And as argued in Section 4.2, for any $1 \leq l_1 \leq n$ and for all $(n + 1) \leq l \leq (n + k)$, we have $a_{l_1 l} \geq 0$ and $1 - \sum_{l=n+1}^{n+k} a_{l_1 l} \geq 0$. This yields $a_{l_1 l_2}^* > 0$ for all $1 \leq l_1 = l_2 \leq n$. With an argument similar to the above, we can have $a_{l_1 l_2}^* \geq 0$ for all $(n + 1) \leq l_1 = l_2 \leq (n + k)$. Thus, A^* is a non-negative symmetric matrix with positive entries $a_{l_1 l_2}^*$, $1 \leq l_1 = l_2 \leq n$, on the diagonal. Therefore, all $(n + k)$ eigenvalues of A^* are real, which we denote by $\lambda_1 \geq \lambda_2 \geq \dots \geq \lambda_{n+k}$, and the largest eigenvalue λ_1 is positive. When the multiplicity of λ_1 is 1, i.e., $\lambda_1 > \lambda_2$, all eigenvectors of λ_1 are parallel. Thus, one of these eigenvectors can be chosen as the basis for the eigenspace of λ_1 , and the chosen vector is the principal eigenvector. In this case, by (14) we have that as $s \rightarrow \infty$, $\mathcal{V}(s)$ converges to a vector parallel to the principal vector, if $\mathcal{V}(1)$ is a non-zero vector and has all components non-negative.

The mathematical lemma below is required for analysis of our proposed model. A proof for this lemma is in Appendix.

Lemma 2. *We have (i) the mathematical operation corresponding to the transition from $\mathcal{V}(t)$ to $\mathcal{V}(t + 1)$ is (13); and (ii) the multiplicity of λ_1 is 1 provided that the graph G is connected; in this case we can have the principle eigenvector with its all components being positive.*

Recall, by definition, that $\mathcal{V}(1)$ is the vector comprising the expected values of concentration of AHL in each cell and locale. Following Lemma 2, we can conclude that as long as the initial vector $\mathcal{V}(1)$ is non-negative, as time passes, the vector $\mathcal{V}(s)$ converges to a $(n + k)$ -vector which has all its components positive and is parallel to the principle eigenvector. Let us call this $(n + k)$ -vector the target vector. Now, we argue that the target vector is unique in the following sense. Since, the multiplicity of the largest eigenvalue is 1, the direction of the eigenvectors of the largest eigenvalue is determined. Let

$$(c_1, c_2, \dots, c_n, e_1, \dots, e_{n+k}) \quad (15)$$

represent this direction. This implies that over time, the dynamic of the quorum sensing network converges to a coherent and stable state: the expected values $E[x_i(s)]$ and

$E[y_j(s)]$ of the AHL concentration in cells and locales are such that

$$\begin{aligned} & (E[x_1(s)], \dots, E[x_n(s)], E[y_{n+1}(s)], \dots, E[y_{n+k}(s)])^T \\ & \rightarrow \lambda(s) \cdot (c_1, c_2, \dots, c_n, e_1, \dots, e_{n+k}). \end{aligned}$$

The expected values therefore converge to a vector of defined direction and variable length $\lambda(s)$, meaning that the expected patterns of temporal fluctuations in AHL concentration are the same from cell to cell (and from locale to locale). In particular, when all cells are identical and the locales are homogeneous, the direction in (15) will be $(1, 1, 1, \dots, 1)$, indicating that all expected values are identical.

According to Theorem 1, the actual values of the AHL concentration of cells are very close to their expectations. Therefore, the actual patterns of temporal fluctuations in AHL concentration are very similar between cells (and between locales), although absolute concentrations can vary by cell or locale. In the specific instance when all cells are identical and the locales are homogeneous, the actual concentrations of AHL in the cells will be identical as in [Zhou et al. \(2005\)](#).

5. Conclusions

Despite the fact that noise has null information, biological organisms and systems can use noise to extract information from the environment. Previous models of quorum sensing have been specific, in that the equations and parameters were explicitly set ([Zhou et al., 2005](#)). We have shown that quorum sensing can be modeled in a general setting, without requiring either a homogenous extracellular environment or identical cells.

In the new model, we showed that extracellular noise is required for synchronization to occur in a population of cells. Without extracellular noise, the cells would continue to show independent activity due to the intracellular noise. The effect of extracellular noise is to produce a stochastic process which leads to a stable and coherent temporal pattern (see the explanation of (9)). However, absolute concentrations of AHL may still differ between cells due to the stipulations of heterogenous extracellular environment and non-identical cells.

The result (9) defines a general law for synchronization in a quorum sensing network, without defining parameters. We note that the time to synchronization should be measurable to a desired degree of certainty in an experimental situation where number of cells and environmental volume are controlled. Using (9), it would therefore be feasible to calculate δ , which should be directly related to biophysical measurements of the rate of diffusion of AHL.

Furthermore, our new model clearly predicts that *it is possible to introduce strong noise to disrupt quorum sensing*. Indeed, our proposed model is a stochastic

differential equation (see (2)); and our result requires that this equation has both a unique solution and that the solution is in a Hölder class (see the first paragraph in Section 3). According to the theory of stochastic differential equation, when the noise terms $\sigma_i \eta_i$ and $\sigma_j \xi_j$ are strong, the equation may still have a unique solution, but the solution will no longer be in any Hölder class. With strong noise, then, synchronization may not occur, i.e., quorum sensing would fail. An increase in temperature will increase Brownian motion of signal molecules, thereby increasing molecular noise and potentially disrupting quorum sensing. It would therefore be of great interest to apply the current model to an analysis of the effects of fever in reducing quorum sensing leading to virulence of an infection.

Clearly, novel clinical therapies and other important applications are likely to result from a fuller understanding of quorum sensing and the effects of perturbation of the underlying mechanisms (Alfaro et al., 2004; Anguige et al., 2004; Andre and Godelle, 2005; Qazi et al., 2006; Dong and Zhang, 2005).

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Appendix

Proof of Theorem 1. Recall a classic inequality in probability theory by Hoeffding (1963). Let X_1, \dots, X_m be independent random variables with $b_1 \leq X_i \leq b_2$ ($i = 1, \dots, m$). Then for all $\varepsilon > 0$,

$$\Pr \left\{ \left| \sum_{i=1}^m (X_i - E[X_i]) \right| \leq \varepsilon \right\} \geq 1 - 2 \exp \left(- \frac{2\varepsilon^2}{m(b_2 - b_1)^2} \right).$$

We apply the inequality above to $x_i(t) = \sum_{l=1}^t d_l^{(i)}$. By (6) we have $|d_l^{(i)}| \leq M \cdot \delta^p$ for all $1 \leq t \leq s$. Moreover, as argued in Section 4.1, $d_l^{(i)}$ ($= x_i(t+1) - x_i(t)$) are independent random variables. Now, taking $b_1 = -M \cdot \delta^p$ and $b_2 = M \cdot \delta^p$, and letting $m = s = \delta^{-\alpha}$ (s is assumed to be an integer before Eq. (3) in Section 3), we have for all $\varepsilon > 0$

$$\Pr \{ |x_i(s) - E[x_i(s)]| \leq \varepsilon \} \geq 1 - 2 \exp \left(- \frac{\varepsilon^2}{2M^2 \cdot \delta^{2p-\alpha}} \right)$$

for each $1 \leq i \leq n$, which leads to

$$\Pr \{ |x_i(s) - E[x_i(s)]| > \varepsilon \} \leq 2 \exp \left(- \frac{\varepsilon^2}{2M^2 \cdot \delta^{2p-\alpha}} \right)$$

for each $1 \leq i \leq n$. Thus, we have

$$\begin{aligned} & \Pr \left\{ \bigcup_{i=1}^n \{ |x_i(s) - E[x_i(s)]| > \varepsilon \} \right\} \\ & \leq \sum_{i=1}^n \Pr \{ |x_i(s) - E[x_i(s)]| > \varepsilon \} \\ & \leq 2n \exp \left(- \frac{\varepsilon^2}{2M^2 \cdot \delta^{2p-\alpha}} \right) \end{aligned}$$

and hence,

$$\begin{aligned} & \Pr \left\{ \max_{1 \leq i \leq n} |x_i(s) - E[x_i(s)]| > \varepsilon \leq \varepsilon \right\} \\ & = \Pr \left\{ \overline{\bigcup_{i=1}^n \{ |x_i(s) - E[x_i(s)]| > \varepsilon \}} \right\} \\ & = 1 - \Pr \left\{ \bigcup_{i=1}^n \{ |x_i(s) - E[x_i(s)]| > \varepsilon \} \right\} \\ & \geq 1 - 2n \exp \left(- \frac{\varepsilon^2}{2M^2 \cdot \delta^{2p-\alpha}} \right). \end{aligned}$$

This completes a proof for the theorem. \square

Proof of Lemma 2. First, we prove (i). Consider the l_1 th cell, $1 \leq l_1 \leq n$. By the definitions of operators U and R in Section 4.2, from time t to $(t+1)$, the expected amount of the signal molecule that this cell receives is

$$\sum_{l=n+1}^{n+k} a_{ll_1} \cdot \tilde{y}_l(t); \tag{16}$$

the expected amount of the signal molecule that this cell sends to extra-cellular locales is

$$\sum_{l=n+1}^{n+k} a_{l_1 l} \cdot \tilde{x}_{l_1}(t); \tag{17}$$

and the expected amount of the signal molecule that is produced by this cell is

$$\beta_{l_1} \cdot \tilde{x}_{l_1}(t). \tag{18}$$

Utilizing the fact that $a_{l_1 l_2} = a_{l_2 l_1}$ for all $1 \leq l_1, l_2 \leq (n+k)$ and $a_{l_1 l_2} = 0$ for all $1 \leq l_1, l_2 \leq n$, by (16), (17), (18), and the definition of operator D in Section 4.2, we have

$$\begin{aligned} \tilde{x}_{l_1}(t+1) = D(t) \cdot & \left[\sum_{l=1}^n a_{l_1 l} \cdot \tilde{x}_l(t) + \sum_{l=n+1}^{n+k} a_{l_1 l} \cdot \tilde{y}_l(t) \right. \\ & \left. + \left(1 - \sum_{l=n+1}^{n+k} a_{l_1 l} + \beta_{l_1} \right) \cdot \tilde{x}_{l_1}(t) \right]. \end{aligned} \tag{19}$$

By a similar argument, we can have for the l_2 th locale $(n + 1) \leq l_2 \leq (n + k)$

$$\begin{aligned} \widetilde{y}_{l_2}(t + 1) = & D(t) \cdot \left[\sum_{l=1}^n a_{l_2 l} \cdot \widetilde{x}_l(t) + \sum_{l=n+1}^{n+k} a_{l_2 l} \cdot \widetilde{y}_l(t) \right. \\ & \left. + \left(1 - \sum_{l=1}^{n+k} a_{l_2 l} \right) \cdot \widetilde{y}_{l_2}(t) \right]. \end{aligned} \quad (20)$$

(13) follows from (19), (20) and (11).

Now, we prove (ii) by three steps as follows. We denote an eigenvector of the largest eigenvalue λ_1 by $V^{(\lambda_1)} = (v_1^{(\lambda_1)} \dots v_l^{(\lambda_1)} \dots v_{n+k}^{(\lambda_1)})^T$.

Step 1: We claim that there is $V^{(\lambda_1)}$ such that all $v_l^{(\lambda_1)} \geq 0$ and at least one $v_l^{(\lambda_1)}$ is positive. Indeed, let us take $\mathcal{V}(1)$ as a vector with all positive components. By (14) we have that as $s \rightarrow \infty$, $\mathcal{V}(s)$ converges to a vector V^* parallel to an eigenvector of λ_1 . Since A^* is non-negative and $D(t) > 0$, all components of V^* must be non-negative and at least one component positive. We let $V^{(\lambda_1)} = V^*$, proving the claim.

Step 2: We claim that when the graph G is connected, we have that if all $v_l^{(\lambda_1)} \geq 0$ and at least one $v_{l_0}^{(\lambda_1)} > 0$ then all $v_l^{(\lambda_1)} > 0$. Indeed, since the graph G is connected, there is a path between the l_0 th and l th nodes for any $1 \leq l \neq l_0 \leq (n + k)$. This, by elementary graph theory and the definition of A^* , implies there is positive integer k such that the l th component $c_l(k)$ of the vector $(A^*)^k \times V^{(\lambda_1)}$ is positive. On the other hand, since $V^{(\lambda_1)}$ is an eigenvector of λ_1 , we have $(A^*)^k \times V^{(\lambda_1)} = \lambda_1^k \cdot V^{(\lambda_1)}$. That is, we have $\lambda_1^k \cdot v_l^{(\lambda_1)} = c_l(k) > 0$, which indicates that $v_l^{(\lambda_1)} > 0$ (because λ_1 is positive).

Step 3: We prove (ii) by contradiction. Suppose that the multiplicity of λ_1 is greater than 1. Then there are two linearly independent eigenvectors $V^{(\lambda_1)} = (v_1^{(\lambda_1)} \dots v_l^{(\lambda_1)} \dots v_{n+k}^{(\lambda_1)})^T$ and $U^{(\lambda_1)} = (u_1^{(\lambda_1)} \dots u_l^{(\lambda_1)} \dots u_{n+k}^{(\lambda_1)})^T$. Based on Steps 1 and 2, we can assume that all $v_l^{(\lambda_1)} > 0$. Thus, we can find $\varepsilon > 0$ such that all $w_l^{(\lambda_1)} \stackrel{\text{def}}{=} v_l^{(\lambda_1)} + \varepsilon \cdot u_l^{(\lambda_1)} > 0$. Let $W^{(\lambda_1)} \stackrel{\text{def}}{=} (w_1^{(\lambda_1)} \dots w_l^{(\lambda_1)} \dots w_{n+k}^{(\lambda_1)})^T$. By definition, $W^{(\lambda_1)}$ is an eigenvector of λ_1 . Now, we have two linearly independent eigenvectors $V^{(\lambda_1)}$ and $W^{(\lambda_1)}$ such that both have all their components positive. Let

$$\rho \stackrel{\text{def}}{=} \min \left\{ \frac{v_l^{(\lambda_1)}}{w_l^{(\lambda_1)}} : l = 1, \dots, (n + k) \right\} \quad (21)$$

and define $Z^{(\lambda_1)} \stackrel{\text{def}}{=} V^{(\lambda_1)} - \rho \cdot W^{(\lambda_1)}$. Since $V^{(\lambda_1)}$ and $W^{(\lambda_1)}$ are linearly independent, $Z^{(\lambda_1)}$ is a non-zero vector, and hence is an eigenvector of λ_1 . By definition, all components of $Z^{(\lambda_1)}$ are non-negative. However, by (21) there is at least one component of $Z^{(\lambda_1)}$ that is zero, contradicting the claim proved in Step 2. \square

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