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Computing the threshold of the influence of intercellular nanotubes on cell-to-cell communication integrity

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ABSTRACT

We explore how the biochemical substance exchange through tunneling nanotubes (TNTs) affects the functional stability of a multicellular system. We focus on two questions: whether TNTs can either stabilize or destabilize intercellular communication governed by gap junctions (GJs)? and how to determine the threshold at which influence of TNTs destabilize GJ-mediated communication? The goal of this article is to introduce the way in which the concept of pseudospectra can be used to provide the answers.

1. Introduction

Maintaining the functional integrity of cell-to-cell communication in the multicellular systems is one of the prerequisites for achieving their functionality [1–5]. In eukaryotic cells, intercellular communication is primarily mediated locally through gap junctions (GJs) and synapses. However, recent reports demonstrate the existence of a network of intercellular membrane nanotubes enabling long-distance communication [6–8]. Similarly to gap-junctions, these nanotubes can transfer diverse signals between the cells. Also they are detected in prokaryotes where they enable interspecies communication and share of antibiotic resistance [9,10]. It has been shown that in both cases, these tunneling nanotubes (TNTs) can facilitate cell-to-cell communication and intercellular transfer of cytoplasmic molecules, organelles and viruses [8,11–13]. Existence of clusters of TNTs enables formation of complex cellular networks with both local and long-distance interactions based on membrane continuity between TNT-connected cells (Fig. 1). Empirical evidence indicate that they can have important role in many pathophysiological processes, like in activation of natural killer cells, regulation of osteoclastogenesis or in the tumor formation and growth [14–16]. In prokaryotes they can play the important part in transferring virulence from pathogenic to non-pathogenic bacteria [9]. These findings indicate that TNTs significantly contribute in a multitude of physiological processes, in both prokaryotic and eukaryotic cells. What exactly is their role is still unknown, because we do not have enough empirical details about regulation of their formation, directionality of transfer and selectivity of substances that can be transferred via TNTs. However, several recent results points towards close functional link between TNTs, GJs and stress response. First, their formation is induced by stress [17] but direction of their formation depends on cell types. For example, in neurons, cells that undergoes stress will generate more TNTs, while in endothelial cells, stressed cells will synthesize signals that will induce formation of TNTs in non-stressed cells [18]. Second, TNTs can extend through gap junctions [19] modifying GJs functionality. Finally, TNTs are dynamic structures whose formation and decomposition is very sensitive to both intra- and extracellular factors, with lifetimes ranging from several minutes up to 4–5 h [8,13,16]. Their short lifetime suggests that they can promote unstable, transient cell-to-cell communication, in contrast to more stable communication mediated by GJs [20]. Moreover, this transient influence on communication is promoted by stress, when integrity of intercellular communication is of especial interest. Therefore, we believe that it is of importance to systematically explore how the perturbations in communication, induced by the existence

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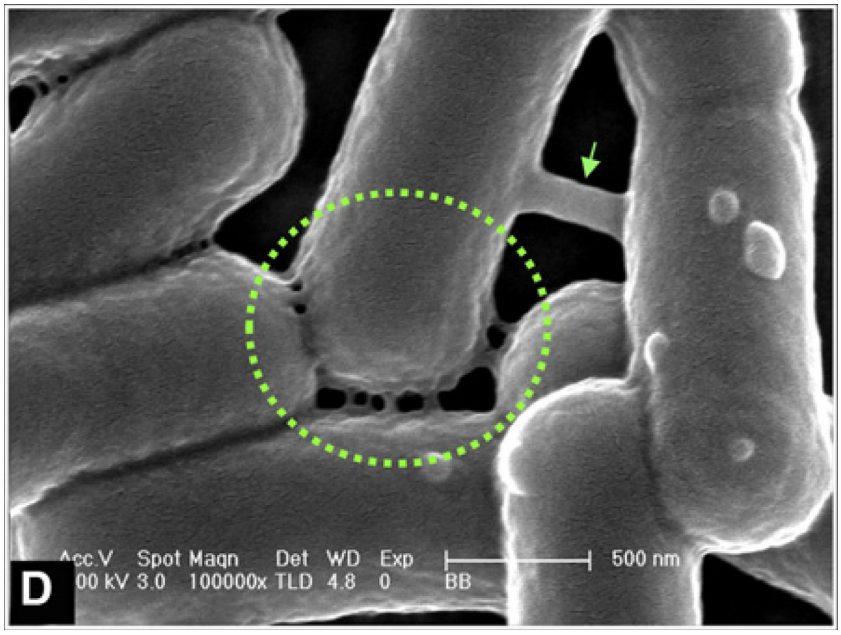

Fig. 1. Example of intercellular TNTs between neighboring, prokaryotic cells. A field of cells with a cluster of smaller TNTs (highlighted by a dashed circle) and a more pronounced larger tube (indicated by an arrow). Reprinted with permission from [9].

of clusters of TNTs, can influence stability of intercellular communication.

In this Article we explore how the substance exchange through TNTs affects the functional stability of a multicellular system. We suppose that GJs form the main communication line, while formation of TNTs can modify dynamics of communication, keeping GJs intact. Also, in the model, we will consider only TNTs as transient structures. We are aware that both, GJs and TNTs are dynamic structures. Formation of GJs is tightly regulated and their number can significantly change over time. However, in this paper we are only interested on how TNTs can influence already established stable communication. Therefore, the time scale in our model is shorter than the time needed for GJs to be synthesized or degraded. From these starting points we focus on two issues: (i) whether transient clusters of TNTs can either stabilize or destabilize intercellular communication governed by GJs? and (ii) how to determine the threshold at which influence of TNTs destabilize GJ-mediated communication? Therefore, we introduce a model of the substance exchange in a multicellular system, represented by ordinary differential equations, where cell-to-cell communication is mediated by both the GJs and TNTs while metabolic processes in cell follow Michaelis–Menten dynamics. In this model the GJs function governs the time evolution of the intercellular network while the TNTs function simulates the exchange mediated by the TNTs including a scaling parameter for that mediation. So, we consider the influence of TNTs as a functional perturbation of the main communication mediated by GJs. To determine the threshold for which the multicellular system remains stable, despite TNTs influence, we compute the *distance to instability*, cf. [21], using nonconvex optimization algorithm from [22], and we derive numerically cheap lower bounds based on pseudospectral localizations, cf. [23].

2. General model dynamics and pseudospectra

To investigate how TNTs affect the stability of the intercellular communication network, we model the network dynamics as:

$$\dot{x}(t) = \Psi(x(t)) := \Phi(x(t)) + \xi\Theta(x(t)), \tag{1}$$

where $x = [x_1, x_2, \ldots, x_n]^T$. Here $x_i(t) \in [0, 1]$ is the relative concentration of molecules and ions in the cell $i \in N := [1, 2, \ldots, n]$, Φ: $R^n \to R^n$ is a GJs function that governs time evolution of the intercellular network, while Θ: $R^n \to R^n$ models the exchange mediated by TNTs and $\xi > 0$ is a scaling parameter for that mediation. Since many questions remain unanswered about how cargo is transported through TNTs [24] we consider their effect on the model dynamics as an uncertainty described by Θ. The system (1) is generally a nonlinear one whose stability is typically investigated at the equilibrium state $x^\star \in R^n$ as the local asymptotic stability, where $x^\star$ is a state vector such that $\Psi(x^\star) = 0$. An equilibrium state $x^\star$ is locally asymptotically stable if there exists $\epsilon > 0$ such that for every $x(0)$ that is in ϵ neighbourhood of the equilibrium $x^\star$ (i.e., $\|x^\star - x(0)\| < \mu$), it holds that $\lim_{t\to\infty} \|x(t) - x^\star\| = 0$. This local stability property is characterised by the spectra of the Jacobian matrix $A = [\frac{\partial \Psi_i}{\partial x_j}(x^\star)]$ of (1) in the state $x = x^\star$, which can be written as $A = \widehat{A} + \xi\Delta$, where $\widehat{A} = [\frac{\partial \Phi_i}{\partial x_j}(x^\star)]$ corresponds to the exchange through GJs that will be named the measurable communication. The term $\widehat{\Delta} = [\frac{\partial \Theta_i}{\partial x_j}(x^\star)]$ is determined by the transport through TNTs that is generally unknown. Thus, we call it the unmeasurable communication. Furthermore, in order $\xi > 0$ to reflect the scale of TNT mediation we assume that uncertainty parameters are unit scaled in the chosen matrix norm, i.e. $\|\widehat{\Delta}\| = 1$.

To investigate how TNTs can influence stability of communication, we will analyze sensitivity of the spectrum of the measurable communication matrix $\widehat{A}$ upon perturbation $\xi\Delta$. More precisely, we are interested, in general, which scale of TNT's influence ($\xi > 0$) is capable to change asymptotic stability/instability of the network dynamics (1) from what would be expected if TNT's weren't present ($\xi = 0$). Computing the spectra $\Lambda(\widehat{A})$ of the measurable part of the Jacobian, corresponding to GJs interactions and intracellular metabolic processes, we can determine the expected stability $\Lambda(\widehat{A}) \subseteq \mathbb{C}^-$ or instability $\Lambda(\widehat{A}) \not\subseteq \mathbb{C}^-$ of the substance fluxes. However, the unmeasurable part of cellular communication can change this spectral property and lead to the different dynamics of the network. Thus, in general, we distinguish two cases.

First, if GJ network dynamics is stable, i.e., $\Lambda(\widehat{A}) \subseteq \mathbb{C}^-$, then we are interested in computing the critical value of $\xi > 0$ such that the full network (GJ and TNT's) becomes unstable, i.e., $\Lambda(A) \not\subseteq \mathbb{C}^-$.