Modeling Cell-to-Cell Communication Networks Using Response-Time Distributions

Graphical Abstract

Highlights
- Scalable modeling framework for modeling cell-to-cell communication networks
- Intracellular, input-to-output processing described by response-time distributions
- Emergent behaviors of cell-to-cell communication network motifs are identified
- Response-time modeling is applied to published cytokine secretion data

Authors
Kevin Thurley, Lani F. Wu, Steven J. Altschuler

Correspondence
kevin.thurley@drfz.de (K.T.), lani.wu@ucsf.edu (L.F.W.), steven.altschuler@ucsf.edu (S.J.A.)

In Brief
Interacting cellular communities have critical roles in biological functions such as tissue development or immune responses. Cell-to-cell communication networks comprise both intra- and intercellular processes, making detailed mathematical models intractable. Here, we develop a scalable framework for modeling extra-cellular communication networks that treats intracellular signal transduction networks as “black boxes” with characterized input-to-output response relationships. We discover that a range of dynamic cell-population behaviors, including cellular synchronization, delays, and bimodal responses, can emerge from simple cell-to-cell communication networks.
Modeling Cell-to-Cell Communication Networks Using Response-Time Distributions

Kevin Thurley,1,2,3,* Lani F. Wu,1,* and Steven J. Altschuler1,3,*

1Department of Pharmaceutical Chemistry, University of California San Francisco, San Francisco, CA 94158, USA
2Present address: German Rheumatism Research Center (DRFZ), a Leibniz Institute, 10117 Berlin, Germany
3Lead Contact
*Correspondence: kevin.thurley@drfz.de (K.T.), lani.wu@ucsf.edu (L.F.W.), steven.altschuler@ucsf.edu (S.J.A.)

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SUMMARY
Cell-to-cell communication networks have critical roles in coordinating diverse organismal processes, such as tissue development or immune cell response. However, compared with intracellular signal transduction networks, the function and engineering principles of cell-to-cell communication networks are far less understood. Major complications include: cells are themselves regulated by complex intracellular signaling networks; individual cells are heterogeneous; and output of any one cell can recursively become an additional input signal to other cells. Here, we make use of a framework that treats intracellular signal transduction networks as “black boxes” with characterized input-to-output response relationships. We study simple cell-to-cell communication circuit motifs and find conditions that generate bimodal responses in time, as well as mechanisms for independently controlling synchronization and delay of cell-population responses. We apply our modeling approach to explain otherwise puzzling data on cytokine secretion onset times in T cells. Our approach can be used to predict communication network structure using experimentally accessible input-to-output measurements and without detailed knowledge of intermediate steps.

INTRODUCTION
In multicellular organisms, cells live in communities and constantly exchange signaling molecules. Prominent examples of short-range communication are diffusible ligands shaping immune responses (Schwartz et al., 2015) and the tumor microenvironment (Balkwill et al., 2012), notch-delta-mediated signals (Guruharsha et al., 2012), and microvesicles (Raposo and Stoorvogel, 2013). In the mammalian immune system, cell-to-cell communication can involve multiple cell types (e.g., T cells, neutrophils, macrophages, and epithelial cells) communicating through tens of different types of cytokine species (Burmeister et al., 2014; Schwartz et al., 2015). In many cases, cytokines secreted by one cell type act in a relay on other cell types, as well as affect the original cell type. An important example is interferon gamma (IFN-γ), which is secreted by Th1 cells (a subclass of T cells), stimulates macrophages, and also induces the differentiation of T cells toward Th1 cells. The levels of various cytokine species vary by an order of magnitude or more between supernatants of isolated cells and cell populations (Schrier et al., 2016; Shalek et al., 2014; Xue et al., 2015), suggesting pronounced effects of cell-to-cell communication on the cytokine milieu.

Within a cell, extensive research has identified many molecules and pathways involved in signal transduction and, in many cases, has also developed an understanding of their function. In particular, the identification and analysis of generic network motifs has led to an understanding of how certain interaction topologies can function to suppress noise, amplify signals, or provide robustness (Alon, 2007; Alon et al., 1999; Heinrich et al., 2002; Hornung and Barkai, 2008; Shen-Orr et al., 2002). For this purpose, mathematical models of simplified systems have often been an important driving force, which have helped to reveal engineering principles such as feedback control and perfect adaptation (Altschuler et al., 2008; Fritsche-Guenther et al., 2011; Ma et al., 2009).

At the level of communication among cells, the mapping from general network motif to function is poorly understood. In cell-to-cell communication networks, each node is a type of cell and each type of cell processes input signals through intracellular networks to elicit an output; outputs are a cell-state change and (potentially) an input signal to other cell types or even its own cell type. Thus, cell-to-cell communication networks are complex: they are “networks of networks”; they can contain different cell types with different input-to-output relationships; the response times of cells—even within one type—to identical input stimuli is heterogeneous; and output of any one cell can recursively become an additional input signal to other cells.

Whereas the well-studied rules of chemical kinetics can be applied to model the building blocks of intracellular networks (e.g., proteins, metabolites, etc.), it is unclear how best to model cell-to-cell communication networks. Existing studies of cell-to-cell communication have largely focused on specific cases—such as the cytokines interleukin-2 (IL-2) (Feinerman et al., 2010; Fuhrmann et al., 2016; Thurley et al., 2015; Waysbort et al., 2013), IFN-γ (Helmstetter et al., 2015; Schulz et al., 2015), or tumor necrosis factor alpha (TNF-α) (Paszek et al., 2010; Tay et al., 2010). However, in most settings, most if not all intracellular network parameters are unmeasured or inaccessible with current experimental approaches. Thus, there is a
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