Shaping the Crowd: The Social Life of Cells

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Cells can switch between individual and collective behavior by tuning their communication.

Our daily decisions are influenced by the people around us. We follow their advice, orders, opinions, or trends. We also convey information to others and influence their decisions, e.g., by persuading them or setting an example. Thus, we are sensing the social situation around us and also influencing it at the same time. We form a continuous system with the society: our personal opinions, attitudes, and decisions are coupled to those of the society we live in. Cells in organisms, microbes in populations, or organisms in ecosystems face a similar situation. They are usually not isolated but exist in a tissue, a population, or an ecosystem. They are impacted by the decisions of others in this "society" as much as they influence it.

In this issue, Maire and Youk describe what it means for an individual cell to be part of such a "cellular society" (Maire and Youk, 2015). They simulate the behavior of many cells, arranged on a grid, that are able to produce a diffusive chemical signal. This substance can be sensed by the cells and triggers them to also produce the same chemical signal (Youk and Lim, 2014). The development of the communicating cell population is simulated with a cellular automaton model. Figure 1 shows a similar simulation but with five different cell states, each state producing a specific signal. It turns out that existing in such a "society" leads to the emergence of interesting new properties: the neighborhood of a cell strongly influences which state the cell exists in. A single cell is more likely to switch into the state that is prevalent in its local environment. In this way, individuals can be coupled in their behavior and form a cellular collective (Figure 1B).

Cells have to struggle with many problems. Some of them may be best solved on the individual level, but others are best solved as a collective. Therefore, it is useful for individuals in a social environment to choose the degree to which they act as individuals versus engaging in collectives.

Maire and Youk offer an interesting explanation for how the balance between individual and collective states can be controlled. Cells that communicate by sensing and secreting the same molecule can "decide" the degree to which they want to be part of a "society" by varying the effective range over which this communication takes place. In particular, the cells can control how far the signal molecules diffuse before degrading. For very short-range communication, cells are unable to communicate with others and are basically isolated from the society. However, they can still sense their own chemical signal; this allows them to stabilize their individual physiological states. This circumstance results in significant heterogeneity within the population (Figures 1A and 1B, left). Increasing the range of communication allows cells to share information with an increasing number of other cells. This leads to cellular collectives of increasing size (Figures 1A and 1B, middle and right).

The tuning of social behavior has direct consequences. A high degree of individuality causes a high degree of physiological heterogeneity in a population of cells (Figures 1A and 1B, left). This increases the likelihood for at least some cells to be optimally prepared for unexpected events (bet hedging). Thus, T cells exist in an enormous variety, each responding to a different antigen. This variety maximizes the probability that the immune system will be able to identify a new pathogen. Upon contact with the right antigen, the corresponding T cell has to proliferate, which is supported by producing and self-sensing the same molecules (Meuer et al., 1984).

Moreover, individuality splits the system into many independent working cells. In such a population, local stress stays local and cannot spread through the whole population: the cellular modularity increases resistance toward external disturbances (Figures 1B and 1C, left) (Albert et al., 2000).

On the other hand, forming collectives allows individuals to achieve goals that they could not on their own. It allows the individuals to start concerted actions, bundle their forces, and solve problems as a group, such as the production of public goods, collective defense, or the sharing of labor. For example, slime molds under starvation start to move toward each other guided by chemical communication and form multicellular fruiting bodies that allow them to more effectively spread their spores (Camazine, 2003).

During a collective action, the individual cell completely follows the collective and fulfills a specific task in it. In order to make many individuals act in the same way, a consensus has to be found (Conradt and Roper, 2003). Telling each other the cellular state by communication enables exactly this consensus finding. The individual cell within a population senses the averaged signal from the other cells around it. Making a decision based on this neighborhood average means that the individual cell follows an averaged state of the population. A well-known real-world example is quorum sensing, in which bacteria switch on certain genes only when the cell density (an average value) has reached a certain level (Miller and Bassler, 2001).

Shifting from individual to collective behavior changes not only the decision making of a cell, but also how it is recognizing its environment. Because of their limited size, individual cells can only

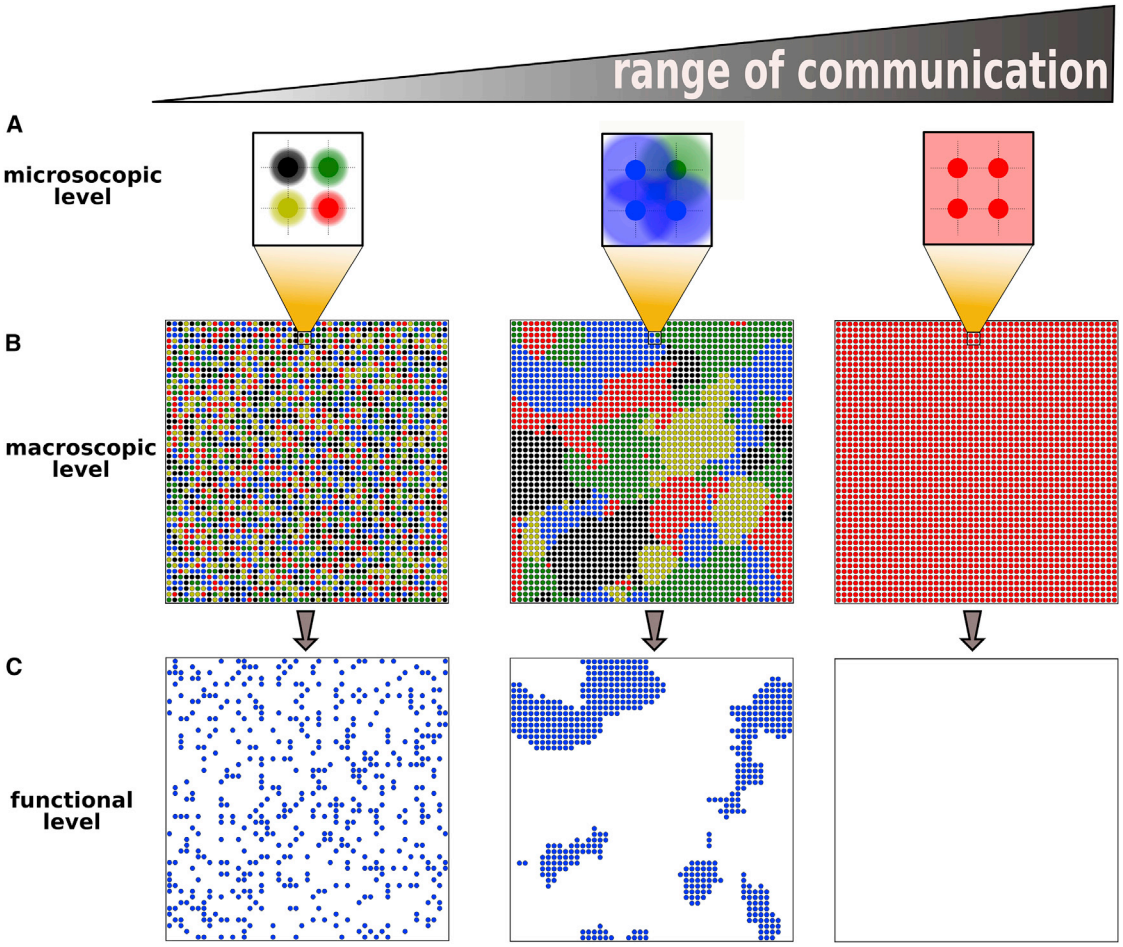

Figure 1. Cellular Automaton Model of Communicating Cells Arranged on a Grid

(A) The cells communicate by secreting and sensing chemical signals, whereas every phenotypical state has a different signal molecule. Cells switch into the phenotypical state of which they sense the highest signal concentration. For a small communication range (e.g., fast degradation compared to diffusion), the cells only sense their own signal and stay in their original state. Increasing the range of communication causes them to be more and more influenced by its neighbors.

(B) Accordingly, the area over which the cells are coupled in their behavior increases with communication range, and homogeneous patches appear.

(C) If the different cell types have different functions (e.g., only the blue cell is able to deal with a certain environmental situation), the strong dispersal of different cell types allows a similar good response over the entire population. However, upon cluster formation, areas that show optimal response exist, but so do areas without any response—which in the most extreme case, where all cells are synchronized, can lead to a complete loss of the blue cell function.

sense their close environment, which offers only local, subjective, and potentially error-prone information. In contrast, a population of spatially arranged individuals each senses a different part of space; by combining these local pieces of information via communication, the population achieves a much more complete picture of the environment and can compensate for individual errors (Couzin, 2007).

In order to achieve such a collective sensing, the individuals have to be arranged in space, and indeed, the formation of social collectives is very often accompanied by the formation of spatial structure: schools of fish, swarms of birds, herds of mammals, colonies of social insects, or the above-mentioned slime mold each exhibit a rich variety of collective structural dynamics (Parrish and Edelstein-Keshet, 1999). In all of those cases, simple communication rules between individuals lead to the emergence of higher-order structures.

Maire and Youk observe a similar emergence of spatial structure in their model. The length over which the communication takes place influences the size of emerging clusters of synchronous behavior (Figure 1B). This emergent spatial structure is in line with other work that used communicating cellular automata to describe pattern formation in ecosystems or developing organisms (Ermentrout and Edelstein-Keshet, 1993), showing the strong connection between communication and self-organized spatial order.

Often pattern formation is described as an interplay between activating and inhibiting communication like in the famous Turing patterns. However, the model by Maire and Youks shows that positive interactions together with a lower detection threshold are sufficient to lead to pattern formation. Although the emerging patterns are—contrary to Turing patterns—not strictly defined in their size, position,

and shape, the simplicity of Maire and Youks' mechanism could make it of general importance in natural systems.

Establishing spatial collectives may be of importance in the structural formation of tissues, bacterial communities, and ecosystems. The presented framework shows how individuals can tune their role in those processes and thus the processes themselves and therefore provides a path toward understanding those complex systems.

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Studying Autism in Context

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Studying autism genes in the context of the protein complexes to which they belong illustrates the potential of network-centric approaches for understanding complex genetic disease.

Autism spectrum disorders (ASD) are a set of related neurodevelopmental diseases with shared phenotypes such as impaired language skills and social cognition. Although ASD is quite prevalent, having been reported to affect ~1% of the population (Miles, 2011), its causes remain poorly understood. This can be largely attributed to the complexity of the disease, which so far has been linked to a diverse set of associated genes. In this issue of *Cell Systems*, Li et al. (2015) examine ASD-associated genes in the context of protein complexes to explore underlying mechanisms of the disease and to suggest shared etiologies between forms of ASD associated with other conditions (syndromic ASD) and those forms for which the cause is unknown (idiopathic ASD).

The genetic basis of autism is highly complex and heterogeneous. In an attempt to identify risk genes, recent efforts have used increasingly large cohort sizes (De Rubeis et al., 2014; Iossifov et al., 2014) and sophisticated statistical techniques to integrate transmitted, de novo, and case-control genetic variation (De Rubeis et al., 2014). While this has led to the discovery of key ASD genes, including voltage-gated ion channels, histone modifiers, and chromatin remodelers (De Rubeis et al., 2014), the physical organization of these genes, especially in relevant cell types, remains unknown. Furthermore, since the observed number of mutations in individual genes is only slightly higher than expected, polygenic models are needed to accurately identify ASD risk genes (Neale et al., 2012). Because it has been shown that ASD genes form highly interconnected protein networks (Neale et al., 2012; O'Roak et al., 2012), Li et al. take the next step and carefully elucidate these networks in neuron-like cells used as models in autism research.

The authors characterize protein complexes involving previously identified ASD genes. Using a published resource of human protein complexes, they find that histone deactylases HDAC1 and HDAC2 in the NuRD chromatin-remodeling complex interact with orthologs of ASD genes in the embryonic mouse brain and positively regulate downstream ASD genes during early brain development.

Next, Li et al. extend this result by using *HDAC1* as well as five idiopathic ASD risk genes (*ANK2*, *CHD8*, *CUL3*, *DYRK1A*, *POGZ*) and a syndromic ASD risk gene (*FMR1*) as "baits" to pull down protein complexes, which were then identified using mass spectrometry. This is the first systematic study to identify protein complexes involving autism-related genes in a cultured neuronal cell line, yielding 119 high-confidence interactions. Comparisons to two independent gene expression datasets confirmed that the interacting proteins are in fact co-expressed in human brain tissue, supporting the idea that this cell-type-specific network may be highly valuable in understanding the physical basis of how ASD genes work.

As an example, the authors find that the I304N mutation on the *FMR1*-encoded RNA-binding protein FMRP significantly perturbs the underlying interactome network. Since FMRP-regulated