Spatial Dispersal of Bacterial Colonies Induces a Phase Transition From Local to Global Quorum Sensing

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Bacteria communicate using external chemical signals called autoinducers (AI) in a process known as quorum sensing (QS). QS efficiency is reduced by both limitations of AI diffusion and potential interference from neighboring strains. There is thus a need for theoretical approaches that yield nontrivial quantitative predictions of how spatial community structure shapes information processing in complex microbial ecosystems. As a step in this direction, we apply a reaction-diffusion model to study autoinducer signaling dynamics in a growing bacterial community as a function of the density of metapopulations, or spatially dispersed colonies, in the total system. We predict a non-equilibrium phase transition between a local quorum sensing (LQS) regime at low dispersal, with AI signaling dynamics primarily controlled by the local population density of colonies, and a global quorum sensing (GQS) regime at high dispersal, with the dynamics being governed by the collective metapopulation density. In addition, we propose an observable order parameter for this system, termed the Neighbor Interference Fraction (NIF), which accounts for the ratio of neighbor-produced to self-produced signal at a colony. The transition between LQS to GQS is intimately connected to a tradeoff between the signaling network's latency, or speed of activation, and its throughput, or the total spatial range over which all the components of the system communicate. Levels of dispersal near the phase boundary provide an optimal compromise that enables simultaneously high latency and throughput in a given environment.

Multicellular communities, such as colonies of bacteria, communicate with each other to coordinate changes in their collective group behavior. This communication usually takes the form of the production and secretion of extracellular signaling molecules called autoinducers (AI), as illustrated in Figure 1. Released autoinducers diffuse through the environment, and each cell senses the local concentration of signal to inform changes in gene regulation. This intercellular signaling network, known as quorum sensing (QS), is crucial for a wide array of important microbial processes, including biofilm formation, regulation of virulence and horizontal gene transfer [1–4].

Decades of research have advanced our knowledge of QS, but several subtleties remain unresolved. In particular, AI signals may convey information about many aspects of the cellular network and local environment beyond simply the total number of cells in the system. Far from being reducible to homogeneous, uniform density populations, microbial communities are typically characterized by high spatiotemporal heterogeneity [5]. As a result, a new layer of complexity emerges due to crosstalk between spatially segregated populations. Consequently, there is still controversy over whether the presence of AI molecules is necessarily an indicator of increased local population density, or whether it is a proxy of other variables, such as population dispersal or the rate of mass transfer of chemical signals in the nearby environment [6–9].

The immense complexity of ecological dynamics inspires the question of whether it is possible, in the tradition of condensed matter and statistical physics, to simplify the diverse zoo of ecosystems into a reduced classification of different qualitative phases whose essential characteristics can be captured by coarse-grained phenomenological models. Surprisingly, such an approach frequently yields predictions on relevant macroscopic properties of a system that turn out to be robust to changes in irrelevant microscopic details, resulting in the emergence of the central concepts of universality and renormalization, two key pillars that are a cornerstone of modern physics [10, 11]. Consequently, the study of an artificial toy problem yields predictions of observable ‘fingerprints’ characterizing different possible behaviors in real systems.

Recent years have seen a percolation of this mindset into biology, particularly ecology. A growing community of physicists has been working to catalogue the different classes of collective behavior found in interacting communities of organisms [12–16]. This approach has already successfully yielded insight into a wide variety of ecological problems, with notable recent examples including the effects of invasion in cooperative populations [17], optimal foraging strategies in sheep herds [18], and the properties of microbial signal transduction networks [19–21] and their relationship to long-range spatial pattern formation [22, 23].

In this Letter, we demonstrate the application of such minimalistic modeling to the question of precisely which emergent properties of microbial ecosystems are manifested in spatiotemporal AI signaling patterns. Via numerical simulations of a reaction-diffusion (RD) model, we show that for a community of single-species bacteria, interacting via AI signaling in a finite volume, there is a phase transition in the activation dynamics as a func-
define the NIF as the fraction of signal at the location of the dispersal of the community, or equivalently, the spatial heterogeneity of the cell density. At low dispersal, corresponding to a situation in which the cells aggregate into a few large colonies, the activation is triggered by the supercritical population density of the individual colonies, and therefore, can be described as ‘local’ QS (LQS). At high dispersal, corresponding to a situation in which the cells are spread thinly among many small colonies, activation is instead triggered by the collective metapopulation density, or in other words, by the high concentration of spatially disconnected but mutually interacting colonies. In this regime, the timescale of autoinduction is principally determined by inter-colony signal diffusion, and thus, this state is best described as one of ‘global’ QS (GQS).

This crossover, furthermore, is intimately related to a fundamental tradeoff between two proxies of signaling efficiency: 1) the speed with which the community initially activates, or the ‘latency’ of the signaling network, and 2) the total range of space that eventually becomes activated at asymptotically long times, or the overall network ‘throughput’. The results suggest that an intermediate amount of dispersal near the phase transition presents the optimal compromise, enabling simultaneous high latency and high throughput performance in a given resource-constrained environment.

To further illuminate the nature of the transition, we identify an explicit order parameter for the system, which we denote the ‘Neighbor Interference Fraction’ (NIF). We define the NIF as the fraction of signal at the location of the center colony of the system that originates from any sources other than the center colony itself - in essence, as the intensity of cross-talk from neighboring colonies. The value of this NIF, at the instant the system begins to activate, is observed to sharply increase as the system transitions from LQS to GQS behavior, displaying qualitatively distinct behavior on each side of the transition, and justifying the choice of NIF as an order parameter.

The dynamics of the autoinducer concentration $n_{AI}$ are governed by the spatiotemporal cell density profile $n_{cell}$ via the reaction-diffusion equation

$$\left( \frac{\partial}{\partial t} - D \nabla^2 + \lambda \right) n_{AI} = r(n_{AI}) n_{cell}(\vec{x}, t),$$

where $D$ and $\lambda$ are respectively the AI signal diffusivity and decay, and $r$ is the local, AI-concentration-dependent signaling rate of the cells, given by

$$r(n_{AI}) = r_b + (r_a - r_b) \theta(n_{AI}(\vec{x}, t) - n_{AI_{crit}}).$$

Here, $r_b$ is the basal AI production rate of the cells in the absence of any activation, while $n_{AI_{crit}}$ is the threshold AI concentration for cells to transition to an activated state, with an amplified AI production rate $r_a$. We take the activation to be instantaneous, modeling it via the Heaviside theta function $\theta$, as is common practice (see, e.g., [27]).

With this setup, the spatiotemporal density of the cellular community $n_{cell}$ can be interpreted as an input driving signal that generates the spatiotemporal AI profile $n_{AI}$ as an output response signal. This response, being inherently nonlinear due to the positive feedback between AI concentration and signal production, is in general not analytically solvable for an arbitrary cellular input. Nevertheless, the equations are simple enough for accurate numerical integration in a wide range of relevant scenarios.

Accordingly, we design and perform a series of computational ‘experiments’ to isolate the effects of spatial dispersal, or metapopulation density, on AI signaling. At time $t = 0$, we instantaneously colonize a quasi-2D region...

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**TABLE I: The parameters used in this work.** The properties of the AI signals and their interactions with quorum sensing species are adapted from [23], while the spatiotemporal distribution of cells is set to reproduce typical cell-colony packing densities and inter-colony spacings.

| Quantity                      | Units          | Value   |
|-------------------------------|---------------|---------|
| Signal Diffusivity ($D$)      | $\mu$m$^2$/sec| 160     |
| Signal Decay Rate ($\lambda$) | molecules/sec | 0.01    |
| Basal Production Rate ($r_b$) | molecules/hr  | 500     |
| Activated Production Rate ($r_a$) | molecules/hr | 3000    |
| Activation Threshold ($n_{AI_{crit}}$) | molecules/µm$^3$ | 100   |
| Initial No. of Cells (Total)  | $10^5$ cells  | 1       |
| Max. No. of Cells (Total)     | $10^5$ cells  | 6561    |
| Doubling Time (Total)         | mins          | 30      |
FIG. 2: (Left) In our simulations, we keep the initial and final number of cells in a confined region of space fixed between different replicates, but varying the spatial dispersal of the population, by spreading it out into successively larger sets of ever smaller colonies. This can be parameterized by the effective periodicity of the system $j$ or, equivalently, by the number of colonies $N$. (Right) We display some representative snapshots of the dynamics of the spatial AI concentration profile along the $x$-axis (defined as the horizontal bisection axis of the system) for some sample time points, with the concentration displayed as a signal intensity, in decibel units (dB) defined by $n_{AI}(dB) = 10 \log\left(\frac{n_{AI}(nM)}{n_{AI_{crit}}}\right)$, where $n_{AI}(nM)$ is the autoinducer concentration in nM units and $n_{AI_{crit}}$ is the threshold concentration for activation (100 nM).

of space, of dimensions $8 \times 8 \times 0.01 \text{ cm}^3$, with an initial population of approximately $10^5$ cells, and have the cells exponentially grow, with doubling time 30 minutes, until they have multiplied to approximately 7000 times their initial size, at which point the growth is saturated.

We perform several replicates of this simulation. In the first replicate, the cells are perfectly localized into a circular colony at the center of the quasi-2D region, with a colony packing density of one cell per $\mu m^3$. This corresponds to a situation of minimal dispersal, with only one homogeneous colony and no spatially distributed metapopulations. The cells produce, sense, and activate AI signals undergoing diffusion and decay according to equations (1)-(2), with parameter values displayed in Table I. The system is then numerically integrated for 12 hours to yield a discretized output spatiotemporal AI signaling profile $n_{AI}(\vec{x}, t)$. Calculations are performed with the aid of the BSIM software package [28]; for additional details on the setup of the simulation, we refer the reader to the Supplementary Information.

For subsequent replicates of the simulation, the setup is nearly identical, with the only difference being in the number of colonies $N$ that the cells separate into, or equivalently, the effective spatial periodicity $j$ of the colonies in the system. In addition to our original one-colony simulation, with $j = N = 1$, we run trials with $j = 3, 5, 7, 9, 11, 13$ and 15, corresponding respectively to $N = 9, 25, 49, 81, 121, 169$ and 225 colonies, distributed in symmetric square grids as shown in Figure 2. Inter-colony spacings are chosen such that in all cases, the square grid of colonies occupies a $5 \times 5 \times 0.01 \text{ cm}^3$ sub-space of the larger region, sufficiently distant from the boundaries of the system for any AI signal reflection at the boundary to be negligible. In all cases, the packing densities, initial total number of cells and final number of cells at full growth are the same as in the single-colony simulation. Consequently, the different replicates gradually tune the system from a state of a few large colonies, to one of many smaller colonies, with a corresponding increase in the concentration of interacting ‘patches’ of spatially extended metapopulations.

We may define a region of space as being ‘activated’ if its concentration of AI signal is above a reference ‘threshold’ concentration of 100 nM, beyond the threshold for which a cell activates quorum sensing. Figure 3 illustrates the fraction of space that gets activated over time for each of the different replicates. At low colony number $N$, corresponding to a small number of highly clustered colonies, the system is in a regime of local quorum sensing (LQS), where regions near the individual colonies receive enough locally produced signal to enable rapid activation, in a manner that is largely independent of the activity of neighboring colonies. Meanwhile, beyond $N = 81$, corresponding to a lattice periodicity greater than $j = 9$, the system is in a regime of global quorum sensing (GQS), where activation is necessarily communal in nature, triggered instead by the collective sharing of AI signal that slowly diffuses into a common pool.

Communities in the LQS regime have a fast time to initial activation, but are restricted to relatively short-range communication, suffering from substantial ‘redundancy’ due to an oversupply of colonies signaling near the colony...
FIG. 3: By plotting the total fraction of space (Top) in the 8 cm × 8 cm × 10 µm volume in which QS has been activated, we can see that the spatiotemporal signaling dynamics of the system undergo a transition in cooperativity between N = 81 and N = 121 colonies. This illustrates the general principle that there is a tradeoff (Bottom) between the speed of initial activation (faster for more clustered, large colonies) and the overall long-term spatial range reached by signaling (larger for more distributed, smaller colonies).

centers beyond what is necessary for activation. Activation in regions beyond the local vicinity of the colonies is substantially degraded by the slow rate of inter-colony signal diffusion, and thus, the rapid time to initiation of local activity comes at the cost of a longer waiting time for more global levels of activation that cover a higher fraction of space. On the contrary, GQS in spatially extended metapopulations is slower, but reduces the degree of inefficient and redundant `waste' signaling, by trying to ensure that each region of space gets only what it needs to be activated, and allowing the community to communicate information to a broader spatial range. These tradeoffs are illustrated in the bottom image of Figure 3, which shows that if one is primarily interested in rapid initiation, it is preferable to be in the LQS regime, but that if one is interested in a substantial fraction of space receiving the signal in a reasonable amount of time, it is preferable to be near the GQS regime.

To further probe the degree of crosstalk, and thus the `communality' of the signaling, it is useful to separating the set of all AI signals into two distinguishable groups: 1) Those that originated from the center colony, \( n_{\text{center}}^{AI} \), which we may take to be located at the origin \( \vec{x} = 0 \), and 2) Those that originated from any of the other neighboring colony, \( n_{\text{neighbors}}^{AI} \). Then, if we denote the instant that center colony activates as \( t_{\text{act}} \), the Neighbor Interference Fraction (NIF) is defined as

\[
NIF = \frac{n_{\text{center}}^{AI}(0, t_{\text{act}})}{n_{\text{center}}^{AI}(0, t_{\text{act}}) + n_{\text{neighbors}}^{AI}(0, t_{\text{act}})}. \tag{3}
\]

The NIF is a natural measure of the degree of inter-colony communication, as it is intuitive to expect that a transition between the LQS and GQS regimes of signaling would be associated with a corresponding increase in the NIF, and indeed, this is what is observed in Figure 4. Therefore, NIF emerges as a natural order parameter for this transition. Additionally, we note that the point at which the NIF begins to increase, corresponding to \( j = 9 \) or \( N = 81 \) colonies, is identical to the point in Figure 3 at which the system most quickly activates 20% of space. This illustrates that the onset of the phase transition is directly correlated with the point at which the system yields the best overall compromise between network latency (favored in the LQS regime) and network throughput (favored in the GQS regime), indicating that being near the phase boundary is desirable to have an optimal level of overall signaling efficiency and functionality. In addition, we note that the NIF, as an order parameter has the advantage of being a theoretical quantity that can potentially be indirectly related to inferences made on data from single-particle tracking experiments [29].

FIG. 4: (Top) By labeling signal originating from the center colony as a chemically equivalent pseudosignal, red in the diagram, one can determine the relative abundance of signal that originates from the center colony itself vs. interference generated via crosstalk from neighbors. (Bottom) The calculations performed in this work predict that this `Neighborhood Interference Fraction', at the moment of activation, serves as an order parameter for this system, sharply increasing as the system transitions from a LQS to a GQS regime.
The overall nature of this crossover can be concisely summarized by coarse-graining the results into a discretized network representation. We sample a discrete set of points, including the colony centers, and label each point as either a possible ‘node’ (if a colony is centered at that point) or an ‘edge’ (if otherwise). Then, we can observe how the separate activation dynamics of nodes and edges of the network change across the crossover point. Figure 5 highlights the observed dramatic changes in behavior - the enhanced sharpness and cooperativity of the transition are notably present in the GQS state, and notably absent in the LQS state.

In summary, the results of this work clearly point to the prediction of an experimentally observable transition between LQS and GQS behavior. We further note that there is, a priori, no immediately obvious reason why the qualitative effects present in our simplified model should not be robust to more realistic complications (e.g., enhanced disorder, a range of more complex growth kinetics, higher-order interactions and feedback between signals and sources), as long as these complications are sufficiently ‘weak’ to be treated as small perturbations. At the same time, however, we expect that beyond the ‘perturbative’ regime, incorporation of these higher layers of detail will give rise to qualitatively new physical phenomena that cannot be accounted for by this minimal models. Nevertheless, we hope that the present work will inspire and accelerate the application of simple biophysical modeling to unexplored questions in microbial ecology.

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