Emergence of Collective Behavior in Groups of Excitable Catalyst-Loaded Particles: Spatiotemporal Dynamical Quorum Sensing

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Spontaneous spatiotemporal wave activity occurs in groups of excitable particles for groups larger than a critical size. Experiments are carried out with particles loaded with the catalyst of the Belousov-Zhabotinsky reaction that are immersed in catalyst-free reaction mixture. The particles diffusively exchange activator and inhibitor species with the surrounding solution. All particles are nonoscillatory when separated from the other particles; however, target and spiral waves are exhibited in sufficiently large groups. A cellular particle model of the system also exhibits transitions from excitable steady state behavior to spatiotemporal wave activity with increasing group size.

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Many unicellular organisms are able to switch from individual to collective behavior in response to increasing cell numbers or density [1,2]. In this process, known as quorum sensing, cells communicate via the exchange of chemical signaling species through the extracellular solution [3]. Yeast cells, for example, switch from nonoscillatory individual behavior to collective glycolytic oscillations, mediated by the metabolite acetaldehyde, when a critical cell density is attained [4–6]. In certain bacteria, a suprathreshold increase of an autoinducer species in the extracellular solution triggers a positive feedback for cellular autoinducer production and synchronous gene expression [7,8]. The heterogeneity of a population of cells may play an important role in the appearance of collective behavior. In the slime mold Dictyostelium discoideum, a fraction of the population becomes oscillatory, creating pacemakers from which waves of cyclic guanosine monophosphate (cAMP) organize the aggregation of starving cells [9]. In communities of cells such as pancreas beta cells, transitions to oscillatory behavior with increasing population size are thought to be induced by the coupling of heterogeneous individuals [10,11]. Conversely, heterogeneity may also suppress the activity of coupled cells, a phenomenon known as oscillator death [12–15].

In this Letter, we examine the emergence of collective behavior in groups of catalyst-loaded particles immersed in catalyst-free Belousov-Zhabotinsky (BZ) reaction mixture [16]. Each particle behaves as an individual micoreactor capable of either excitable or oscillatory behavior [17–19]. The activator (HBrO\(_2\)) and inhibitor (Br\(^-\)) species produced on each particle are exchanged with the surrounding solution. Heterogeneity of the population arises from the variation in particle diameter (286 ± 32 µm) and particle catalyst concentration (0.36 ± 0.06 mM). Groups of particles above a critical group size display wave activity even though the individual particles are nonoscillatory. The appearance of wave activity is also found to be a collective behavior in a model of the particle system, occurring with a decrease in loss rate of activator averaged over the entire group. In addition, we demonstrate that the natural heterogeneity of the catalyst-loaded particles shifts the critical group size to larger groups for spontaneous wave activity.

Porous cation-exchange beads loaded with the BZ catalyst ferroin (Fe(phen)\(_2\))\(^3+\)) were placed into a petri dish, covered with catalyst-free BZ reaction solution, and monitored from above with a digital camera [17,18]. The behavior of the individual catalyst particles was determined by monitoring sets of up to 200 spatially isolated particles, each at least 5 particle diameters from neighboring particles, at various bromate concentrations [20]. For [BrO\(_3^-\)] ≈ 0.42 M, greater than 97% of the particles were oscillatory, with a range of frequencies that depended on the catalyst loading and diameter. For [BrO\(_3^-\)] ≤ 0.32 M, no individual particles were oscillatory. The behavior of groups of catalyst particles was studied as a function of group size and bromate concentration in solutions in which the individual particles were nonoscillatory ([BrO\(_3^-\)] = 0.30 M, 0.27 M, 0.24 M). Groups were created by arranging the particles to be within one particle diameter of neighboring particles in a quasicircular monolayer. The spatiotemporal dynamics of the group was monitored for 30 min after allowing the system to relax to its asymptotic behavior over a 20 min period.

Single and multiple pacemaker centers as well as spiral wave activity were seen above a critical group size, as shown in Fig. 1. When wave activity was observed in a group of particles, a follow-up procedure was carried out to ensure that the activity was not due to the presence of an individual oscillatory particle. This involved redistributing the particles so they were separated from neighboring particles by at least 5 particle diameters, and the population was then monitored for an additional 30 min for oscillatory activity [20]. The probability of observing wave activity in a group increases with group size n and decreases with...
decreasing $[\text{BrO}_3^-]$, as shown in Fig. 2(a). In over 300 experiments carried out to construct Fig. 2(a), not a single oscillatory particle was found in the follow-up procedure, providing strong evidence that the group wave activity arises as the result of collective dynamics.

Insights into the collective behavior can be gleaned from a cellular particle model based on the three-variable ZBKE model of the BZ reaction [21], with $X_i$, $Y_i$, and $Z_i$ corresponding to the concentrations of the activator $\text{HBrO}_2$, inhibitor $\text{Br}^-$, and the oxidized ferroin catalyst for particle $i$ [22]. The spatial model consists of a 3D array of cells, typically $22 \times 22 \times 4$, with cells of two different types: cells with catalyst concentration, $C_i$, representing the catalyst particles [22], and cells with no catalyst, $C_i = 0$, representing the surrounding solution. An example of the arrangement of the particle cells and solution cells is shown in Fig. 2(b), where 3 layers of solution cells are positioned on top of a monolayer of $n$ particle cells arranged symmetrically in a square configuration. All cells are diffusively coupled via the exchange of species $X$ and $Y$ according to a six-point Laplacian with no-flux boundary conditions [22].

Simulations of homogeneous populations of particles, with the catalyst concentration $C_i = 0.0053 \text{ M}$, were carried out with the $\text{BrO}_3^-$ concentration $A$ selected so that the isolated particles were excitable but nonoscillatory. For a particular value of $A$, two distinct types of behavior are seen: all particles remain in a steady state for smaller group sizes, and spatiotemporal wave activity is exhibited above a critical group size. Figure 2(c) shows the probability of observing wave activity with increasing group size $n$ for $A = 0.2430 \text{ M}$ (red solid line), $0.2425 \text{ M}$ (blue dashed line), and $0.2420 \text{ M}$ (green dotted line). The probability of observing wave activity in a group increases with increasing $n$ and decreases with decreasing $A$. We describe below how population heterogeneity gives rise to probabilities that more accurately reflect the experimentally observed probabilities shown in Fig. 2(a).

Spatial distributions of the steady state concentrations $X$ and $Y$ are shown in Fig. 2(d) for the group of excitable particles in Fig. 2(b). The concentrations of both the activator $\text{HBrO}_2$ and the inhibitor $\text{Br}^-$ are significantly higher for the particle cells than in the surrounding solution cells, with the maximum $[\text{Br}^-]$ occurring at the central particle cell. There is a shallow minimum in $[\text{HBrO}_2]$ over the collection of particles that also occurs at the central particle. For groups larger than a critical group size, $n_{\text{crit}}$, the central particle acts as a pacemaker from which waves propagate outward over the group. As shown in Fig. 2(c), the critical group size for this transition decreases as
bromate concentration increases: for $A = 0.2420$ M, 0.2425 M, and 0.2430 M, the value of $n_{\text{crit}} = 36$, 20, and 6.

The transition to wave activity with increasing $n$ is not accompanied by an increase in activator concentration at the central pacemaker cell. Figure 3(a) shows that the average [HBrO$_2$] in the solution remains approximately constant with increasing $n$, while there is a decrease in the average [HBrO$_2$] of the catalyst particles. However, the average loss rate of HBrO$_2$ from the particles to the surrounding solution decreases, as shown in Fig. 3(b). Similar trends are observed for [HBrO$_2$] on the central particle cell and in the solution cell directly above, as shown in Fig. 3(c). The loss rate of activator from the central particle cell, however, is approximately constant for groups of 9 or more particle cells, as shown in Fig. 3(d). The appearance of spatiotemporal wave activity is associated with a decrease in the loss rate of activator averaged over all particles. The decreasing activator loss rate follows the decrease in the average number of solution cells in contact with particle cells as the group size increases. The vertical dotted lines in Figs. 3(a)–3(d) show the critical group size, $n = n_{\text{crit}}$, where the behavior changes from an excitatory steady state to spatiotemporal wave activity. The particle cell and solution cell concentrations, as well as the average loss rate of activator, are more difficult to interpret for $n \geq n_{\text{crit}}$, as they are time-averaged values for the system undergoing spatiotemporal wave activity.

The introduction of variation in excitability of the particle cells influences the sharpness of the transition to wave activity with increasing $n$. We introduce variation in the particle population by selecting the catalyst concentration of each particle from a normal distribution. The mean, $C_{\text{mean}}$, and standard deviation, $C_{\sigma}$, of the distribution are chosen to reflect the experimentally observed frequencies of isolated particles with $A > A_{\text{crit}} = 0.32$ M (see Fig. 1A in [18]). It is important to note that none of the isolated particle cells are oscillatory with the values of $A$ used in the simulations of collective behavior. Figure 4(a) shows the probability of wave activity in groups with heterogeneous populations of particle cells. We see that the effect of heterogeneity is to reduce the likelihood of wave activity for a given group size $n$, and the probability as a function of $n$ is much like that observed in the experiments shown in Fig. 2(a). Another feature like the experimental wave activity is single or multiple pacemakers occurring close to the center particle cell of the group, but not necessarily at the center cell.

The impact of excitability heterogeneity is further illustrated in Fig. 4(b). For a system with $n = 49$ and $A = 0.242$ M, wave activity occurs when $C_{\sigma} \leq 3.7 \times 10^{-4}$ M, whereas no activity is found for $C_{\sigma} \geq 6.0 \times 10^{-4}$ M. The decreasing probability of observing activity with increasing heterogeneity is related to the phenomenon of “oscillator death,” in which locally coupled oscillatory cells...

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**FIG. 3** (color). Behavior of particle model as a function of the group size $n$ of identical particles with $C_i = 0.0053$ M and $A = 0.242$ M. (a) Average steady state concentration of HBrO$_2$ on group particles (solid line) with increasing $n$ and in the solution cells directly above the particle cells (dashed line, scaled by factor of 2.4). (b) Average loss rate of HBrO$_2$ from $n$ particles to the surrounding solution. The average loss rate is determined as the average of the diffusive loss from each particle cell. (c) Steady state concentration of HBrO$_2$ on the central particle (solid line) with increasing $n$ and in the solution cell directly above the particle cell (dashed line, scaled by factor of 2.4). (d) Loss rate of HBrO$_2$ from the central particle. The vertical dashed line in each plot represents the value of $n_{\text{crit}}$, above which spatiotemporal wave activity occurs. For steady state group or particle behavior, $n \leq n_{\text{crit}}$, each point corresponds to a square or nearly square group of $n$ particles ($1 \times 2$, $2 \times 3$, etc.). For spatiotemporal behavior, $n > n_{\text{crit}}$, each point corresponds to a time average for the group or particle in such groups of $n$ particles. The curves for $n \geq n_{\text{crit}}$ are scaled by a factor of 4.4.

**FIG. 4** (color). (a) Probability of wave activity with increasing group size $n$. Each point is based on 50 simulations, each with a Gaussian distribution of particle cell catalyst concentrations: $C_{\text{mean}} = 0.0053$ M, $C_{\sigma} = 0.0006$ M. The three curves correspond to $A = 0.2430$ M (red solid line), 0.2425 M (blue dashed line), and 0.2420 M (green dotted line). (b) Probability of wave activity with increasing $C_{\sigma}$, where each point is calculated as in (a) with $C_{\text{mean}} = 0.0053$ M, $A = 0.2420$ M, and $n = 49$. 
cease to oscillate [12,23]. For the heterogeneous particle population, the larger the value of $C_{\alpha \tau}$, the greater the likelihood of large differences between neighbors and the less likely a particle cell will become a pacemaker.

In the homogeneous model system, activity is initiated at the central particle cell; however, pacemaker activity occurs in other locations with the introduction of heterogeneity. Studies of coupled (noisy) excitable elements have demonstrated that a small degree of diversity may give rise to phase transitions from steady state behavior to synchronous oscillations of the elements [24,25]. Other studies of noise-free excitable elements have shown that heterogeneity due to different intrinsic steady states may result in an oscillatory response of the elements [10]. In the excitable particle system studied here, the heterogeneity decreases the probability of excitation and spatiotemporal wave activity [14,23].

Quorum sensing transitions are often explained in terms of a buildup of an autoinducer species in the extracellular solution [2,3,7]. However, Dockery and Keener [8] have interpreted the transition as the result of decreases in the loss rate of the autoinducer species in model studies of quorum sensing in bacteria. We also find the transition to be associated with a decrease in the loss rate of activator in our system of locally coupled excitable particles. A more detailed analysis, examining the combined effects of the activator and inhibitor species, shows that the average relative loss rate of activator to inhibitor is another key indicator. This ratio is found to decrease on increasing $n$ toward the transition to wave activity. The transition arises with a decreasing loss rate averaged over all particles rather than from a particular pacemaker particle leading to the wave activity. Despite only local coupling, each particle affects the overall group behavior for $n \approx n_{\text{crit}}$ since a critical group size is necessary for one of the particles to become a pacemaker.

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[20] Independent experiments showed that beads separated from other beads by more than three bead diameters displayed no evidence of interbead interactions.
[22] The rate equations for $X_i$, $Y_i$, and $Z_i$ for particle $i$: $\frac{dX_i}{dt} = -R_2 + R_3 - R_5 - R_6 + R_7 + D \Delta X_i$, $\frac{dY_i}{dt} = -R_2 + R_3 + qR_6 + R_7 + D \Delta Y_i$, $\frac{dZ_i}{dt} = R_6 - R_7$, where $R_2 = k_1 h_0 X_i Y_i$, $R_3 = k_2 h_0 A Y_i$, $R_4 = 2k_3 X_i^2$, $R_5 = k_4 h_0 A X_i$, $R_6 = k_5 U_{xx}(C_i - Z_i)$, $R_7 = k_6 B Z_i$, $R_8 = k_8 B Z_i$, and $R_9 = k_9 B$. $D$ is the diffusion coefficient, $B = 0.2 \, M$, $h_0 = 0.73 \, M$, $q = 0.72$, $k_2 = 4.81 \times 10^6 \, M^2 \, s^{-1}$, $k_3 = 16.03 \, M^2 \, s^{-1}$. The bromate concentration is $A$, and the catalyst concentration $C_i$ represents the sum of the oxidized and reduced forms of the catalyst, $[\text{Fe(phen)}^{3+}]^+ + [\text{Fe(phen)}^{2+}]^-$, for particle $i$. All other constants and $U_{xx} = f(X_i, Y_i, Z_i)$ as in [21]. The system is integrated using an Euler scheme with time step $dt = 0.001 \, s$, diffusion coefficient $D = 2.5 \times 10^{-3} \, mm^2 \, s^{-1}$, and a spatial grid size equal to the mean particle size of 0.3 mm. No change in behavior was found when the integration was carried out with the value of $dt$ lowered by tenfold and 100-fold.