Designing communicating colonies of biomimetic microcapsules

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Using computational modeling, we design colonies of biomimetic microcapsules that exploit chemical mechanisms to communicate and alter their local environment. As a result, these synthetic objects can self-organize into various autonomously moving structures and exhibit anti-like tracking behavior. In the simulations, signaling microcapsules release agonist particles, whereas target microcapsules release antagonist particles and the permeabilities of both capsule types depend on the local particle concentration in the surrounding solution. Additionally, the released nanoscopic particles can bind to the underlying substrate and thereby create adhesion gradients that propel the microcapsules to move. Hydrodynamic interactions and the feedback mechanism provided by the dissolved particles are both necessary to achieve the collective dynamic interactions and the feedback mechanism provided by the adhesion gradients that propel the microcapsules to move. 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Recent experiments (31) have verified our two-dimensional (2D) LBM/LSM simulations (32, 33) on the flow-driven movement of compliant capsules through narrow constrictions. Additionally, our 2D simulations for the steady-state motion of rigid particles inside a straight channel show quantitative agreement with corresponding finite element calculations (33). Via these 2D simulations, we showed that two microcapsules can undergo autonomous motion along a line in response to self-generated gradients and hydrodynamic interactions (34). Finally, we validated our three-dimensional (3D) LBM/LSM model by determining the drag force on a periodic array of spheres, as well as simulating the breathing mode oscillations of a single capsule. In both cases, the simulations showed quantitative agreement with analytical theory (27).

Inspired by cellular signaling processes, we herein extend our 3D simulations to encompass two types of adaptive capsules, “signaling” and “target,” which respectively release “agonists” and “antagonists” particles into the surrounding fluid. In cellular communication, dissolved agonists bind to the cell and promote the signaling process (production and release of the signal molecule), whereas antagonists that bind to the cell suppress these processes (35). In our model, the agonist and antagonist particles are designed to perform two functions: control the permeabilities of the capsules and alter the capsule–substrate interactions. Specifically, the permeabilities of both capsules (and hence, the particle release rates) depend on the local concentration of dissolved particles, so that the system exhibits a biomimetic feedback or self-regulating mechanism. Additionally, the released particles can adsorb onto the underlying substrate and thereby modify the wetting properties of the substrate.

**Results and Discussion**

In Fig. 1A, the red sphere is the signaling capsule; the permeability of its shell is initially $P_{s}^{\text{max}}$. The agonist point particles are released from a source within the signaling spheres. These agonists (and antagonists) represent nanoparticles or other submicron reactants; their trajectories obey the following stochastic differential equation (34):

$$d\mathbf{r}(t) = \mathbf{u}(\mathbf{r}(t), t) dt + \sqrt{2D_0} d\mathbf{W}(t).$$

The first term gives the advection due to the local fluid velocity $\mathbf{u}(\mathbf{r}(t), t)$. The second term is the Brownian contribution, with $D_0$ being the particles’ diffusion coefficient and $d\mathbf{W}(t)$ being the differential of a Wiener process with unit variance. We neglect backflow effects (i.e., the impact of the particles motion on the flow field), as well as the interactions between the particles.

The green target capsules (Fig. 1A) also have a permeable shell, which is initially characterized by $P_{t}^{\text{min}}$. When the concentration of diffusing agonists around the target capsules is higher than the threshold value $C_{t}^{\text{thresh}}$, the targets release antagonist, which also diffuse in the solution. Eventually, the concentration of the antagonists around the signaling capsule exceeds a critical threshold $C_{s}^{\text{thresh}}$; subsequently, the permeability of the signaling capsule decreases as shown in Fig. 1D, which depicts the dependence of $P_{s}$ on the respective concentrations of antagonists ($C_{s}$) and agonist ($C_{t}$) in solution.

At this stage, the small fraction of diffusing agonist causes the target capsule to release fewer antagonists because $P_{t}$ also depends on the local concentration of antagonists (see Fig. 1D). This small concentration of antagonist eventually diffuses away and has little effect on the signaling capsule. In this manner, the system is essentially reset, so that the signaling capsule again emits a high concentration of agonists and the entire cycle

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**Fig. 1.** (A)–(C) Oscillations in the permeabilities of immobilized signaling (Right) and target (Left) capsules. Color key shown in (D). Agonist and antagonist are shown in blue and red, respectively. (D) Dependence of $P_{s}$ and $P_{t}$ on the respective concentrations of antagonists ($C_{s}$) and agonists ($C_{t}$) in solution. (E) Periodic oscillations of $C_{t}$ and $C_{s}$ near the capsules.
In Figs. 1 A–C, the different shell permeabilities are color-coded to illustrate this correlated, dynamic behavior. The latter behavior also leads to oscillations in the concentration of agonist and antagonist in the solution (see Fig. 1E).

The capsule–surface interaction is modeled via a nonspecific Morse potential, \( \phi(r) = \varepsilon \exp\left[-\left(\frac{r-r_0}{\kappa}\right)^2\right] \), where \( \varepsilon \) and \( \kappa \) characterize the respective strength and range of the interaction potential. The variable \( r \) represents the distance between lattice nodes on the capsule’s outer surface and the substrate, which is also composed of lattice nodes, and \( r_0 \) is the distance where this force equals zero. In our model, diffusing agonists that bind to the surface increase the strength of the capsule–surface interaction and bound antagonists decrease this quantity. Thus, \( \varepsilon \) is written as \( \varepsilon = \varepsilon \left(1 - \theta + \theta'\right) \), where \( \varepsilon \) is the adhesive strength of the bare surface, \( \theta \) is fractional coverage of the surface by the antagonists and \( \theta' \) is the corresponding value for the agonists.

The adsorbing species create an adhesion gradient along the surface, and if the gradient is sufficiently asymmetric, a capsule is driven by enthalpic forces to spontaneously move from a less adhesive to a more adhesive area (34). To illustrate dynamic interactions in this system, we first consider the two capsules in Fig. 1A that initially sit on a bare surface. At the onset, the signaling capsule emits agonists; the bound agonists leave a symmetric “sticky” blue ring around this capsule (see Fig. 2D). The adhesion profile around the signaling capsule is also symmetric (see Fig. 2A) and at this stage, the capsule does not move. As more agonists deposit on the surface, this ring grows and soon creates an adhesion gradient near the target. Due to this gradient, the target moves closer to the signaling capsule (i.e., in the direction of greater adhesion). The target becomes activated and releases antagonists, which make the surface less sticky. Consequently, the adhesion profile in the region between the target and the signaling capsules is no longer symmetric (Fig. 2B) and now both capsules move away from the less adhesive region (the bump in Fig. 2B) toward the stickier area. The movement of the signaling capsule shifts the location of the maximum in the adhesion gradient (Fig. 2C) and again the pair moves toward the more attractive region around the signaling unit; at this point, the entire process repeats, so that both capsules continue to move as a pair along the plane.

The deposition of both the agonists and antagonists is necessary for the directed movement of the pair in 3D. In contrast, for capsules moving along a line (i.e., in 2D simulations), the self-propelled motion can be achieved with antagonists alone (34).

Even this simple case of two self-propelled capsules moving on a plane exhibits complex dynamics. For example, if \( C_{\text{thresh}} > 10 \) [particles/(LBM lattice unit)], the system exhibits angular instability and the pair initially moves in concentric circles (Fig. 2E). If \( C_{\text{thresh}} < 10 \), then the pair is more stable and moves in a more linear fashion (Fig. 2F). (Here, one LBM lattice unit is comparable to 1 \( \mu \)m, given that the capsule is 10 \( \mu \)m in diameter.)

Building on the above system, we now construct the larger assembly shown in Fig. 3A, where the signaling capsule is initially located in the outer layer of a 16-capsule array and \( P_{\text{max}}^t/P_{\text{max}}^t = 1/4 \). (We found that it is important to have the signaling capsule initially in or near the outer layer of an array to observe collective motion.) As the snapshots in Fig. 3B and C (and Movie S1) show, the system self-organizes into a long snake, with the signaling “head” leading a tail of targets. The formation of the adhesion gradients (see Fig. 3F) and the capsules’ motion in response to these gradients (i.e., haptotaxis) are similar to the simpler two-particle case described above. With the larger assembly hydrodynamic interactions play a particularly important role because the capsules are moving through a viscous fluid, which mediates their motion. Specifically, the movement of the first few capsules in the solution generates a net force (34) on the neighboring capsules that drives them to follow the moving chain. (Furthermore, the fluid exerts a frictional force that permits the steady motion of capsules that drives them to follow the moving chain. (Furthermore, the fluid exerts a frictional force that permits the steady motion of these gradients (i.e., haptotaxis) are similar to the simpler two-particle case described above. With the larger assembly hydrodynamic interactions play a particularly important role because the capsules are moving through a viscous fluid, which mediates their motion. Specifically, the movement of the first few capsules in the solution generates a net force (34) on the neighboring capsules that drives them to follow the moving chain. (Furthermore, the fluid exerts a frictional force that permits the steady motion of capsules that drives them to follow the moving chain. (Furthermore, the fluid exerts a frictional force that permits the steady motion of capsules.

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**Fig. 2.** (A)–(C) Changes in the adhesion strength as measured by \( \Delta \theta = \theta - \theta' \) (red line) and subsequent capsule motion. Negative \( \Delta \theta \) corresponds to a more adhesive region. \( S \) marks the signaling capsule and \( T \) marks the target; \( x' \) is the spatial coordinate that is drawn through the capsules’ centers. (D) Adhesion strength on the surface around the moving pair in (C). (E) and (F) Two modes of the pair motion observed in simulations. In these examples, hard wall boundary conditions are applied at the edges of the simulation box. Consequently, in (F), a stable pair is reflected from the edges of the box.
the chain). In fact, if hydrodynamics is turned off (by removing the LBM from the simulation), the motile capsules do not self-organize (see Movie S2).

The feedback mechanism is also critical to the observed behavior; if the permeabilities $P_s$ and $P_t$ are held constant, the capsules do not form a chain, but rather scatter in different directions. This is primarily due to unchecked deposition of the antagonists, which make the surface less sticky. For the self-adjusting capsules, the agonists diffusing in the solution modulate the amount of antagonist released from the targets. For $0.75 < (C_t^*/C_{thresh}) < 1.2$, the permeability of the targets is below the maximum value and thus, the amount of antagonist released into the system is more restricted.

The phase map in Fig. 3D shows that both the formation and length of the snake depend on $P_{max}/P_{max}$ and $C_{thresh}$. When $P_{max}/P_{max} \approx 1$, the capsules do not aggregate due to the high concentration of adsorbed antagonists, which emanate from the highly permeable target capsule. As the permeability of the target capsule is reduced, the system can self-organize into long chains (see Fig. 3E) because the lower permeability (and self-regulating behavior) leads to a reduction of “slippery” antagonists on the surface. (Our simulations indicate that for a given arrangement of signaling and target capsules and set of model parameters, the self-organization is stable with respect to the concentration fluctuations of the agonist and antagonist particles. In other words, the findings depicted in the phase diagram in Fig. 3D are quite robust).

The plot also reveals that there is an optimal range of $C_{thresh}$ that favors the self-organization of self-propelled snakes. If $C_{thresh}$ is too low, then the oscillations seen in Fig. 1 occur too rapidly (relative to timescales for the movement of the capsules) to produce concerted motion. On the other hand, if $C_{thresh}$ is too high, then the local concentration of dissolved agonists might not be sufficiently high to trigger targets to release the antagonists, and motion stops as the surface becomes saturated with the sticky agonists.

We now place two signaling capsules either next to each other or at opposite sides of the array (see Fig. 4) to investigate the potential for cooperation or competition within the system. Depending on the value of $C_{thresh}$ (at fixed $P_{max}/P_{max}$), the system can cooperate to form “two-headed” clusters that increase in size for larger $C_{thresh}$ (Fig. 4A–C). Alternatively, the array can break into two snakes that travel in different directions as the signaling heads compete for target tails (Fig. 4D–F). We anticipate that other “zoologies” can be obtained by varying the placement of the signaling capsules within the array.

Finally, by considering two colonies of microcapsules (Fig. 5), we uncover more complex cooperative microbehavior, which evolves because each colony affects the local environment and each, in turn, is affected by this environment. An example of this behavior is shown in Fig. 5A–C: here, the signaling capsules are initially placed so that the colonies could meet or collide. What is distinctive about the images in Fig. 5B–C is that the separate clusters can sense each other (through the surface), combine into a new unit and then continue to move as one group.

To generate Fig. 5D–F, we apply a slightly modified protocol: The colony on the left (C1) is allowed to self-organize whereas the colony on the right (C2) is held dormant (i.e., localized in space with no particle release) for a fixed number of time steps. At a specified time $t_{col}$, however, the chemical mechanisms described above are applied to the capsules in C2. As the latter capsules begin to interact, their motion is influenced by the attractive trail of particles left by the first, already mobile cluster. As seen in Fig. 5D–F, a triad of C2 capsules turns to follow the trail left by the moving C1 cluster. This behavior indicates that our colonies of synthetic capsules are capable of spontaneously coordinating their actions through the trace of particles left on the surface. In this manner, these colonies resemble the behavior of ants and other social insects.

In conclusion, we incorporated a set of model, biomimetic chemical reactions into a system of microcarriers and thereby devised synthetic microscale objects that appear to “collaborate.” In contrast to the self-assembled, motile structures formed from colloids in a magnetic field (9), our snakes organize and move in the absence of an applied stimulus. Furthermore, we do not postulate a priori rules (36, 37) to regulate the interaction of the capsules; rather, the observed collective behavior emerges from the viable chemical and physical phenomena.

Fig. 3. (A)–(C) Formation of a mobile snake; here and below, the signaling capsule is drawn in red and the targets in green. (D) Blue region in phase map pinpoints where mobile three-member clusters (triangles) and snakes (boxes) form and undergo sustained motion. In red region, the moving snakes ultimately come to a halt (in the time scale of the simulation). (E) Histogram for the frequency that a snake contains $N$ capsules. (F) Adhesion profile on the substrate for (C). The size of the simulation box is $L_x \times L_y \times L_z = 200 \times 200 \times 30 \ (\Delta x)^3$. Hard, stationary walls are positioned at $z = 0$ (the substrate) and $z = 30 \Delta x$ (top wall). Periodic boundary conditions are applied along the lateral directions; we used the linked bounce-back boundary conditions (27, 28) at the fluid–wall interface.
Using this model, we can modify the mechanical compliance of the capsules and the substrate, vary the ratio of signaling to target capsules, and alter the relative arrangements of the colonies on the substrate, allowing us to design a rich variety of structures and program complex self-organizing behaviors. Our model also provides a platform for integrating the spatial and temporal behavior of assemblies of biological cells with the reaction pathways associated with the signaling processes. As such, the approach can yield greater insight into the interrelationships between the signaling events, the movement of compliant cells and hydrodynamic interactions. Finally, our findings can provide guidelines for addressing one of the challenges in the design of microfluidic devices: providing a means of autonomously transporting cargo (encapsulated payloads or other capsules) within the fluid-filled microchannels (38).

Methods

In our LBM/LSM (27, 28) computational approach, a capsule’s elastic, solid shell is represented by a triangular network of harmonic springs that connect regularly spaced mass points, or nodes. The spring force \( F_j \) on node \( r_i \) is equal to

\[
F_j(r_i) = -\sum_j k_j [(r_{ij} - r_{ij}^eq) / r_{ij}^eq] r_{ij}
\]

where the summation runs over all nearest- and next-nearest-neighbor nodes. The quantity \( r_{ij} = r_i - r_j \) is the radius vector between the \( i \)th and \( j \)th nodes, \( r_{ij}^eq \) is the equilibrium length of the spring and \( k_j \) is the spring constant. To capture the dynamics of the solid shell, we numerically integrate Newton’s equations of motion, \( M(d^2r_i/dt^2) = F(r_i) \), where \( M \) is the mass of a node. The total force \( F \) acting on a node consists of the following: the sum of the spring forces between the masses (representing the elastic response of the solid shell), the force exerted by the fluid on the shell at the fluid-solid boundary, and the adhesion forces at the solid substrate.

The capsule’s spherical shell is formed from two concentric layers of LSM nodes; each layer contains \( N = 122 \) nodes. These two layers are separated by a distance of \( \Delta x_{LSM} = 1.5 x_c \), where \( \Delta x_{LSM} \) is the lattice spacing between nearest nodes in the LSM and \( x_c \) is the spacing in the LBM. The outer radius of the shell was taken to be \( R = 5 x_c \). We specify \( k_1 \) and \( k_2 \), which are the spring constants in the orthogonal and the diagonal directions, respectively; for \( k_1/2 = k_2 \), we calculate the Young’s modulus of the shell as \( (30) E = 5k/2\Delta x_{LSM} \).

As noted above, the LBM is an efficient solver for the Navier–Stokes equation (SI Text). The Reynolds number \( (Re) \) in our system is \( Re \sim 10^5 - 10^6 \); i.e., the flow is in the Stokes regime. We chose the lattice Boltzmann model because it allows us capture the fluid–structure interactions and complex geometries in an efficient manner. In particular, in our LBM/LSM simulations, the fluid and solid phases interact through appropriate boundary conditions (27, 28). In particular, lattice spring nodes that are situated at the solid–fluid interface impose their velocities on the surrounding fluids; the velocities are transmitted through a linked bounce-back rule (27, 28) to those LBM distribution functions that intersect the moving solid boundary. In turn, LS nodes at the solid–fluid interface experience forces due to the fluid pressure and viscous stresses at that boundary. We calculate the latter force based on the momentum exchange between the LBM particle and solid boundary, and then distribute this quantity as a load to the neighboring LS nodes.

Herein, we focus on the motion of rigid capsules. Given that \( V \) is the capsule velocity and \( \mu \) is the fluid viscosity, we specifically consider cases where both the dimensionless capillary number, \( Ca = V^2/4 \Delta x_{LSM}^2 \), and the capsule–surface interaction strength, \( \Phi = \mu V^2/4 \Delta x_{LSM}^2 \), are small and, hence, the capsules’ shapes are close to spherical. We set the interaction strength to \( \Phi = 10^{-2} \) and check that in simulations \( Ca < 10^{-4} \).

Fig. 4. Self-organization for different arrangements of signaling capsules. Small, mobile clusters (B) and (E) form at \( C_{thresh} = 7.5 \). Large two-headed cluster (C) or two snakes (F) form at \( C_{thresh} = 12.5 \). Here, \( P_{max}/P_{thresh} = 1/4 \).

Fig. 5. Interaction of two colonies. (A)–(C): Two mobile groups interact to form a new cluster. (D) and (F) Colony on the left (C1) starts moving at time \( t = 0 \), whereas the colony on the right (C2) is held dormant for \( t = 500 \) time steps. Eventually C2 capsules follow the trail made by C1 capsules. See color bar for the adhesion strength on the substrate.
The permeabilities of the capsules shells (and, hence, the particle release rates) depend on the local concentration of dissolved particles. To capture the microcapsules' response to the variations in the concentration of agonist, $C_1$, and antagonist particles, $C_2$, we model the dependence of the permeability of the capsules' shells in the form of smoothed step functions:

$$P_t^s = \frac{1}{2} P_{max} \left( 1 - \tanh\left( \frac{C_t - C_{thresh}}{\Delta C} \right) \right),$$

$$P_t^r = \frac{1}{2} P_{max} \left( 1 + \tanh\left( \frac{C_t - C_{thresh}}{\Delta C} \right) \right).$$

Here, $P_{max}^s$ and $P_{max}^r$ are the maximum permeabilities of the signaling and target capsules' shells, respectively. The sharpness of the transition from a "dormant" state with zero permeability of the capsule's shells to an "active" state with maximum permeability was taken equal to a small value $\Delta C = 0.1 \times C_{thresh}$. We also set the threshold concentration for this transition, $C_{thresh}$, equal for the signaling and target capsules.

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