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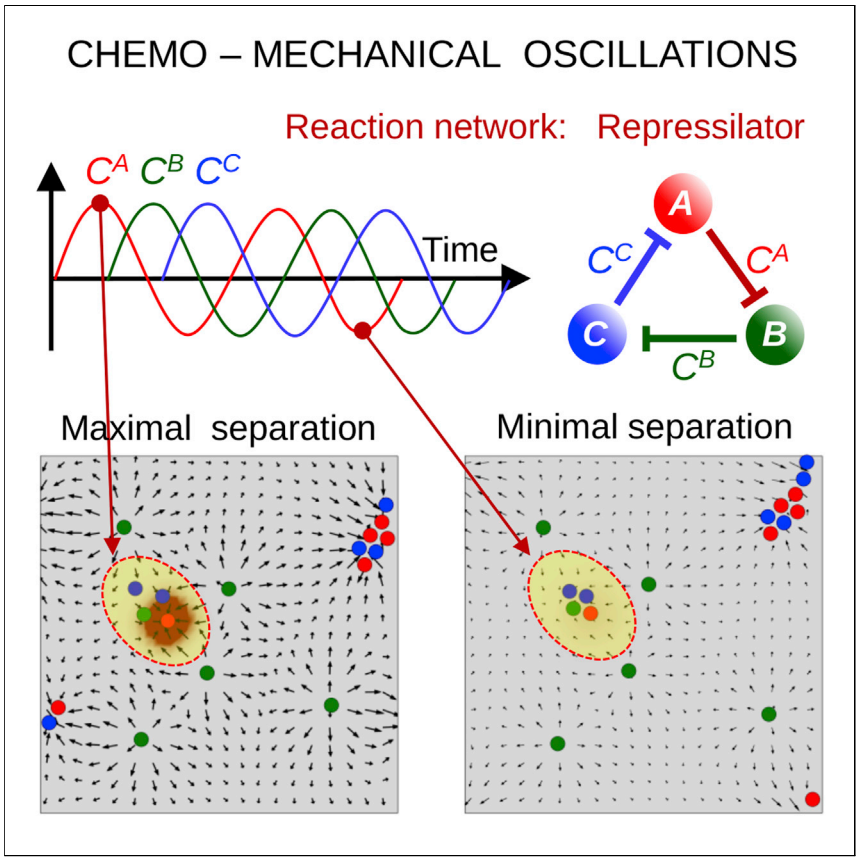
Lifelike behavior of chemically oscillating mobile capsules



Simulations of mobile capsules connected through chemical reaction networks can provide insights into the behavior of early cells, which lacked complex biochemical machinery, but nonetheless assembled into multicellular structures with higher functionality. In the fluidic environment, reactive capsules produce chemical gradients that drive fluid flows and assemble the submerged capsules into colonies. The configuration of the capsules within the clusters determines the collective response of the colony, which can be manifested as chemo-mechanical oscillations of the colony.

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Highlights

Dynamics of mobile catalytic capsules in solution can mimic the behavior of protocells

Chemical reaction networks enable the exchange of signals between separate capsules

Chemical heterogeneities in fluids enable aggregation of capsules into mobile colonies

Reconfigurable clusters produce lifelike collective chemo-mechanical oscillations

3 **Understanding**
Dependency and conditional studies on material behavior

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Lifelike behavior of chemically oscillating mobile capsules

Oleg E. Shklyaev[1,*] and Anna C. Balazs[1,2,*]

SUMMARY

Inspired by the self-organization of unicellular species into multicellular organisms, we use theory and simulation to design a system of mobile, active microcapsules that produce chemicals according to a catalytic reaction network (CRN). In solution, the catalytic reactions generate a force that drives the flow of the surrounding fluid. The convective flow, in turn, transports the capsules to new chemical surroundings with each successive translation. Consequently, the chemical signal produced by a cluster of capsules is critically dependent on the proximity and spatial configuration of the neighboring capsules. If all of the capsules and chemical products involved in the CRN lie within sufficient proximity, then the system develops oscillatory behavior that drives the dynamic self-assembly of capsules into larger clusters that are capable of collective action. These simulations indicate potential chemo-mechanic mechanisms that enable single cellular units, such as ameba, to organize into multicellular life forms.

INTRODUCTION

The emergence of multicellular life forms in prebiotic ponds was potentially aided by chemical reaction networks that could orchestrate complex spatiotemporal behavior among the simple cells. For example, such chemical reaction networks (CRNs) could have directed the assembly of primitive, single cells into large colonies and facilitated communication among these cells, prompting the evolution of collective behavior. Potentially, prebiotic ponds contained dispersed inorganic minerals that could trigger localized catalytic reactions, which shifted the relative distribution of chemicals in the solution. This local chemical heterogeneity would benefit certain reaction pathways over others and thereby promote the development of CRNs that led to useful functionality. Inspired by these biological pathways, here, we examine how analogous routes would affect the behavior of responsive, synthetic systems. In particular, we use theory and simulation to design a system of mobile, catalytically active microcapsules that interact through a CRN, which generates chemical heterogeneities in the solution. These chemical gradients produce buoyancy forces that drive fluid flows and transport the immersed capsules. The transported capsules are carried to a new chemical environment, which influences the capsules' subsequent behavior. In other words, the relocated capsules respond to their new surroundings and each successive displacement can elicit new behavior. As we show below, the evolving system exhibits lifelike features, including the assembly, collective motion, and disassembly of multicapsule aggregates, as well as the development of chemical and chemo-mechanical oscillations. In particular, capsules that lie sufficiently far apart generate a stationary distribution of chemicals, while aggregated capsules can produce chemical oscillations. The transition from stationary to oscillatory behavior signifies the development of a multicapsule cluster that

PROGRESS AND POTENTIAL

Growth in the complexity of biological systems typically involves the aggregation of basic structural units into stable colonies and communication among the units to develop collective responses. The evolution of early cells into multicellular organisms was potentially facilitated by simple physicochemical processes in solution, which simultaneously promoted aggregation and communication. We model such synergistic behavior in a system of synthetic microcapsules. Analogous to the cell, communication among the capsules occurs through the exchange of signaling chemicals and development of local chemical gradients that drive fluid flows. The induced flows in turn can transport and assemble capsules into large colonies. Demonstrating this interdependence between aggregation and communication provides new insights into the role of the chemical networks in the evolution of early cellular assemblies and yields new guidelines for designing synthetic active matter with lifelike properties.

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operates as a single "organism," in which interactions among constituent parts lead to the organized, collective behavior of the whole cluster. This type of behavior, characterized by the periodic chemical exchange between different active capsules, can be considered to be the simplest form of communications between cellular units within an organism. Moreover the clusters exhibit shape changes resembling those observed in living ameba and bacteria.[1,2] These simulations indicate the role of the CRN and their coupling to fluid motion in regulating the spatiotemporal behavior of the synthetic capsules and reveal potential mechanisms that led to the development of early multicellular organisms.

The microcapsules are modeled as mobile microscopic beads that produce and consume chemicals, as directed by a simple CRN known as the "repressilator."[3] While the respressilator only involves three chemical reactions interconnected in a cyclic, negative feedback loop, it nonetheless gives rise to complex spatiotemporal chemical dynamics. As applied here, three different types of mobile microcapsules are immersed in a host fluid and catalyze the production of the corresponding chemical species; each species suppresses chemical production in the next capsule within the cycle (Figure 1). Previous modeling studies[4] revealed that capsules governed by this regulatory network can produce oscillations of all three chemical species and generate behavior mimicking biological quorum sensing.[5] The latter models, however, neglected the convective motion of the host fluid, which can greatly affect the collective response of cell colonies.[6,7]

In this study, the fluid motion occurs through a chemical process that is intrinsic to numerous catalytic reactions in solution. As the capsules convert reactants to products, they generate local density variations that drive the fluid to flow through a mechanism referred to as solutal buoyancy.[8] The fluid flows (dashed circles in Figure 1A), in turn, drag the capsules and thereby assemble the capsules into colloidal clusters on the bottom of the chamber.[9] Since the reagent-producing capsules are mobile, the influence of the regulatory network on production depends on the transient position of the capsules. In particular, the types and relative positions of capsules determine whether the concentrations of produced reagents change slowly with time, remaining almost constant, as shown schematically in Figure 1C (dormant type), or exhibit distinct oscillations that display a phase shift between the three components (Figure 1D) (active type). The latter oscillations indicate that all three different types of capsules are present in a single cluster, which permits coherent exchange of reagents. Notably, chemical oscillations of the chemoattractant *cAMP* are vital to the aggregation of unicellular slime mold (*Dictyostelium discoideum*) into multicellular systems.[1,2] These oscillations produce a chemical wave that travels across the aggregating unicellular species; this behavior is also seen in our microcapsular system (discussed further below). Notably, oscillations in biology trigger not only structure formation but also oscillatory behavior (e.g., heartbeat, respiration, neutral activity)[10] also prevents catastrophic runaway processes and maintains homeostatic conditions necessary to preserve biological functionality. Hence, oscillatory behavior is often viewed as a hallmark of lifelike activities.

The microcapsules considered here contribute to the growing list of synthetic active matter, which exhibits complex spatiotemporal behavior and structural organization that yields lifelike characteristics. Examples of these systems include assemblies of self-propelled particles that phase separate and aggregate into two-dimensional clusters on the bottom of fluidic chambers[11] and particles that resemble "living crystals" in the presence of specific reactants in the solution.[12] Such clusters assemble and then continually exchange particles, which can carry material and information between different groups.

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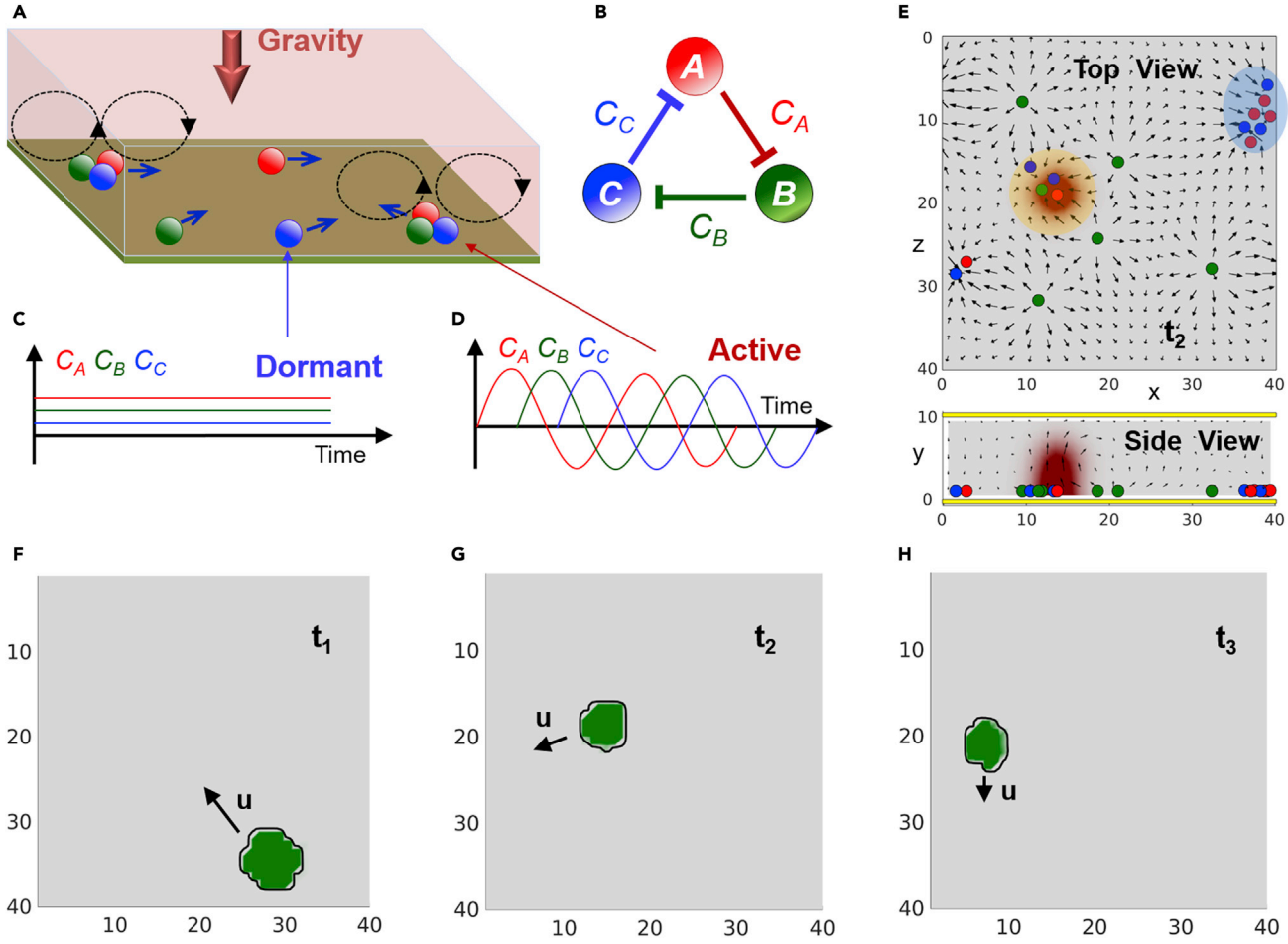

Figure 1. Chemically active capsules form mobile oscillating clusters

(A) Schematic of a fluidic chamber with active capsules that produce chemicals and generate fluid flows shown with black dashed arrows.

(B) Red, blue, and green capsules produce reactants *A*, *B*, and *C*, which inhibit the production of *B*, *C*, and *A* within the repressilator network.

(C) Clusters that consist of capsules of 1 or 2 types do not produce oscillations in the chemical concentrations C_A, C_B, and C_C.

(D) Clusters that include capsules of all 3 types generate oscillations.

(E) Top and side view of the simulation domain that contains dormant (blue circle) and oscillating (orange circle) clusters at time $t = t_2$. Red color shows high concentrations C_A. Black arrows show fluid flows controlled by $\mathbf{b} = (1, -2, 1)$.

(F–H) Positions of the traveling oscillating cluster at $t = t_1$, t_2, and t_3, respectively. Green color outlines the region where amplitude of chemical oscillations $M(\mathbf{r}, \{\mathbf{r}_i\}, t)$ is larger than a threshold. See Video S1 and S4 for more details.

Moreover, the clusters can undergo oscillatory expansion and contraction cycles.[13] The latter studies, however, involve bimetallic particles or complex biomaterials. In contrast, models describing the behavior of primitive cells are based on vesicles,[14,15] which are separated from the environment by a lipid bilayer, or droplets[16,17] that phase separate from the surrounding solution. Both models demonstrate the functionality of enclosed cores that simultaneously enable specific chemical reactions inside and chemical exchange with the outside surrounding solution, which can contain fuel (nutrients) and building materials for growing cells.

Experiments with different types of droplets filled with the appropriate chemicals revealed that under certain conditions, these droplets can exhibit chemical oscillations,[18] self-propulsion,[19] and chemical exchange,[20] which could be considered as a means of inter-droplet communication.[16] Hence, colonies of droplets display a

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variety of rich dynamic behavior that enables the colony members to assemble, communicate, and develop a collective response to the environmental changes.

The model presented below involves microcapsules that encompass a chemically active inner region, which is distinct from the outer environment and thus can provide a framework for describing biomimetic subunits (e.g., synthetic vesicles, droplets) that can self-assemble into colonies and develop a collective response. In particular, we develop a model in which chemically active capsules use chemical and hydrodynamic interactions to assemble into colonies that can exchange chemicals, materials, and information within and between colonies. Moreover, our results demonstrate that the aggregation of different types of microcapsules into a network can promote the formation of complex biomimetic structures in which the constituent capsules operate as complementary units essential to the survival of the entire colony.

RESULTS

Oscillating clusters of capsules

We integrate concepts from synthetic biology and fluid dynamics to model the dynamic behavior of chemically active capsules (microscopic beads) immersed in a fluid-filled microchamber (Figure 1A). Here, the capsules model microcontainers (e.g., polymersomes) that are fabricated from synthetic materials. The capsules also serve as models for primitive cells that lacked inherent, complex biochemical machinery, but nonetheless eventually assembled into multicellular structures with higher functionality. We assume that there are three types of capsules in the chamber, as shown in Figure 1—N_A (red), N_B (green), and N_C (blue)—with the total number of capsules $N = N_A + N_B + N_C$. Each capsule produces one of the reactants A, B, or C, which are interconnected into a chemical reaction network known as the repressilator.[3,21]

Initially, when $N = (N_A, N_B, N_C)$ capsules are randomly placed in the fluid-filled chamber, they sediment to the bottom surface. We assume that the number of capsules of each type are equal: $N_A = N_B = N_C$. The production of reagents $j = A, B, C$ in the solution is catalyzed by the corresponding capsules—in other words, the capsules serve as the chemical sources (Figure 1B). The differences in the densities of the reactants and products of the reaction give rise to density variations, $\Delta\rho$, and the solutal buoyancy forces that drive the fluid flow, which can organize the capsules into clusters,[9,22] as shown schematically in Figure S1. In the limit where the flow is negligible (small Peclet numbers), the quasi-stationary, spatially separated capsules produce chemical concentrations displaying bell-like distributions, which are centered at the capsule positions $\{\mathbf{r}_i(t)\}$ (with $i = 1 \ldots N$). However, when the separation among all three types of capsules (producing A, B, and C) is below a critical value $\mathbf{r}_c(\Gamma, A, \Pi_j)$, the chemical concentrations $C_j(\mathbf{r}, t)$ can display oscillatory behavior. Typical simulations are shown in Video S1.

The steric repulsion between the capsules controls the minimal separation between the chemical sources, $d_{ij} = |\mathbf{r}_i - \mathbf{r}_j|$, and thus affects the amplitude and period of the chemical oscillations produced by the network. Individual clusters of capsules (characterized by configurations $\{\mathbf{r}_i(t)\}$) can exhibit simultaneous but uncorrelated chemical oscillations. To characterize the net chemical signal produced by the system, we calculate the concentrations $\overline{C}_j(t) = \frac{1}{N_m}\sum_{\alpha}^{N_m} C_j(\mathbf{r}_\alpha, t)$ averaged over mesh points $\mathbf{r}_\alpha$ ($\alpha = 1 \ldots N_m$) of the simulation domain. The quantity $\overline{C}_j(t)$ includes contributions from all stationary and oscillatory chemical sources.

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Before analyzing mobile clusters, we focus on oscillations produced by stationary clusters, where the positions of the constituent capsules are fixed at $\{\mathbf{r}_i\}$. When the characteristic length scale of the system, $L_c = \sqrt{D/\gamma}$, is comparable to the minimal intercapsule separation d_{ij}, the chemical dynamics produced by individual capsules is controlled by the behavior and positions of their nearest neighbors. In the case of $L_c \leq d$, the bell-like distributions of chemicals generated by the sources rapidly decay with the distance from the positions of the capsules $\mathbf{r} - \mathbf{r}_i$. Therefore, the simplest case in which three stationary capsules of different types ((N_A, N_B, N_C) = (1, 1, 1)) are placed equidistantly in a triangular configuration (shown in Figure S2A) provides a reasonable estimate for the oscillation amplitudes and periods produced by larger and more complex clusters. In the case of three capsules, oscillations of concentrations $\overline{C}_j(t)$ have the same amplitude and period $T_j = 2\pi/\omega_j$, but the chemical components are shifted relative to each other by phases $\varphi_j = 2\pi/3$ (Figure S2A), due to the inherent time lag between subsequent reactions in the cyclic network.

The chemical signal produced by clusters containing more than three stationary capsules $N = (N^A, N^B, N^C)$ depends on the relative positions $\{\mathbf{r}_i\}$ of the chemical sources and their types (as discussed in Note S1 and illustrated in Figure S2). The oscillation amplitudes of the averaged concentrations $\overline{C}_j(t)$ increase with the number N of participating capsules (chemical sources), while the oscillation periods remain approximately the same as N is increased. Capsules that are located sufficiently far from the oscillating clusters contribute a constant value into the averaged chemical signals $\overline{C}_j(t)$ (Figures S2E and S2F).

Due to the decay of reagents (characterized by the dimensionless parameter Γ) away from the chemical sources, the chemical oscillations are localized around the capsules in the clusters and are absent in the surrounding solution. For example, Figure S3 shows the spatial extent of the oscillatory region produced by a cluster with 6 = (2, 2, 2) capsules. Within the oscillatory region, the three different types of capsules constitute the essential components that enable a coordinated exchange of chemicals within and between clusters. This periodic chemical exchange can be regarded as the simplest form of communication among primitive life forms. As noted above, the periodic fluctuations of *cAMP* produced by ameba form the communication that instigates the self-organization of single units into multicellular organisms.[1,2] In analogy, the chemical oscillations instigated by the three different types of capsules can be viewed as a basic form of communication within this synthetic system.

The chemical dynamics produced by the oscillating clusters are qualitatively different from the slowly varying changes in the reagent concentrations exhibited by isolated capsules that are scattered across the domain. The region separating the inner oscillatory domain from the outer non-oscillating region provides a natural boundary that defines an active "synthetic organism." The thickness of the boundary is characterized by the diffusive length scale $\sqrt{D/\gamma} = r^*\sqrt{S/\Gamma}$. This boundary provides an alternative and potentially useful means of modeling the compartmentalization in primitive cellular systems. The latter systems are usually modeled as vesicles and droplets where isolated cores are separated from the environment by a protective materials layer.[16,17] As discussed below, our model yields lifelike behavior even without invoking a firm boundary between the inner and outer environments.

The above examples of stationary oscillating clusters of capsules were not affected by the fluid flow generated by the chemical reactions. When the capsules are mobile,

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however, the positions $\{\mathbf{r}_i(t)\}$ of N chemically interacting capsules are coupled to the chemically generated flows, which can drive the capsule assembly that is necessary to induce spontaneous oscillatory behavior. The chemical oscillations from the mobile chemical sources can be characterized by the instantaneous local amplitudes $M(\mathbf{r}, t)$ and periods $T_L(\mathbf{r}, t)$. Examples of clusters that generate oscillating and stationary distributions of chemicals are outlined in orange and blue in Figure 1E, which displays the top and side views of the simulation domain at time $t = t_2$. To trace the motion of the oscillating clusters, we monitor the local amplitude $M(\mathbf{r}, t) = \max_{0 \le t \le T_L}(C_A(\mathbf{r}, t)) - \min_{0 \le t \le T_L}(C_A(\mathbf{r}, t))$ of chemical oscillations calculated over a local period, T_L, which is the time elapsed between two successive maxima in the concentration $C_A(\mathbf{r}, t)$ at the position $\mathbf{r}$. Regions where the amplitude $M(\mathbf{r}, t)$ is larger than a threshold value M_S are marked in green in Figures 1F–1H and outline the body of the synthetic organism, which traverses the computation domain with a velocity $\mathbf{v}(t)$. This procedure allows us to visualize only "alive" clusters that oscillate and to exclude passive islands, which nonetheless provide the raw building material for subsequent cluster formation.

Importantly, when there are several distinct mobile oscillating clusters in the domain, the clusters communicate via both hydrodynamic and chemical mechanisms. With respect to the role of hydrodynamics, the inward fluid flows (Figure S1) generated by each cluster bring neighbors sufficiently close to enable the exchange of chemical signals between the clusters. The chemical mechanism goes into effect when the separation between clusters is less than some critical distance; then, the regulatory network associated with the clusters affects the mutual chemical production and thereby influences the oscillatory behavior of the group. An example of the synchronization of chemical oscillation produced by two approaching clusters is demonstrated in Figure S4 and Video S2.

Effect of convective flows on assembly of capsules

The hydrodynamic interactions between capsules play a crucial role in the processes of cluster aggregation and propulsion. The generated fluid velocities and rates of cluster assembly are controlled by the magnitude of the Grashof numbers Gr and vector $\mathbf{b} = (b_A, b_B, b_C)$, which specifies the buoyancy forces produced by each chemical. We focus on two exemplar situations: the generated convective flows either attract all capsules toward one another or introduce repulsion between some of the capsules. The first exemplar situation is that we fix $\mathbf{b} = (1, 1, 1)$ and model the situation in which all three types of capsules produce less dense products (chemical A, B, or C) and thereby generate inward flows that drag neighboring capsules toward one another (Figure S1). The aggregation process resembles coarsening dynamics as the randomly placed capsules approach their neighbors to form small islands, which later merge into larger clusters. Unlike coarsening, however, the repressilator network acting on the capsules ensures that chemical oscillations emerge once the clusters attain an appropriate composition and configuration.

Figure 2 shows an example of the coarsening dynamics that accompany the chemical oscillations for $18 = (6, 6, 6)$ capsules. Figure 2A displays the evolutions of the averaged chemical concentrations $\overline{C}_j(t)$ ($j = A, B, C$) with red ($\overline{C}_A$), green ($\overline{C}_B$), and blue ($\overline{C}_C$) lines. A few, small clusters are formed as randomly placed capsules are dragged toward one another (Figure 2B). The single oscillating cluster includes all three types of capsules and for emphasis is outlined in orange. During this early stage, these small clusters move relatively quickly and rapidly change configurations. The duration of the oscillatory

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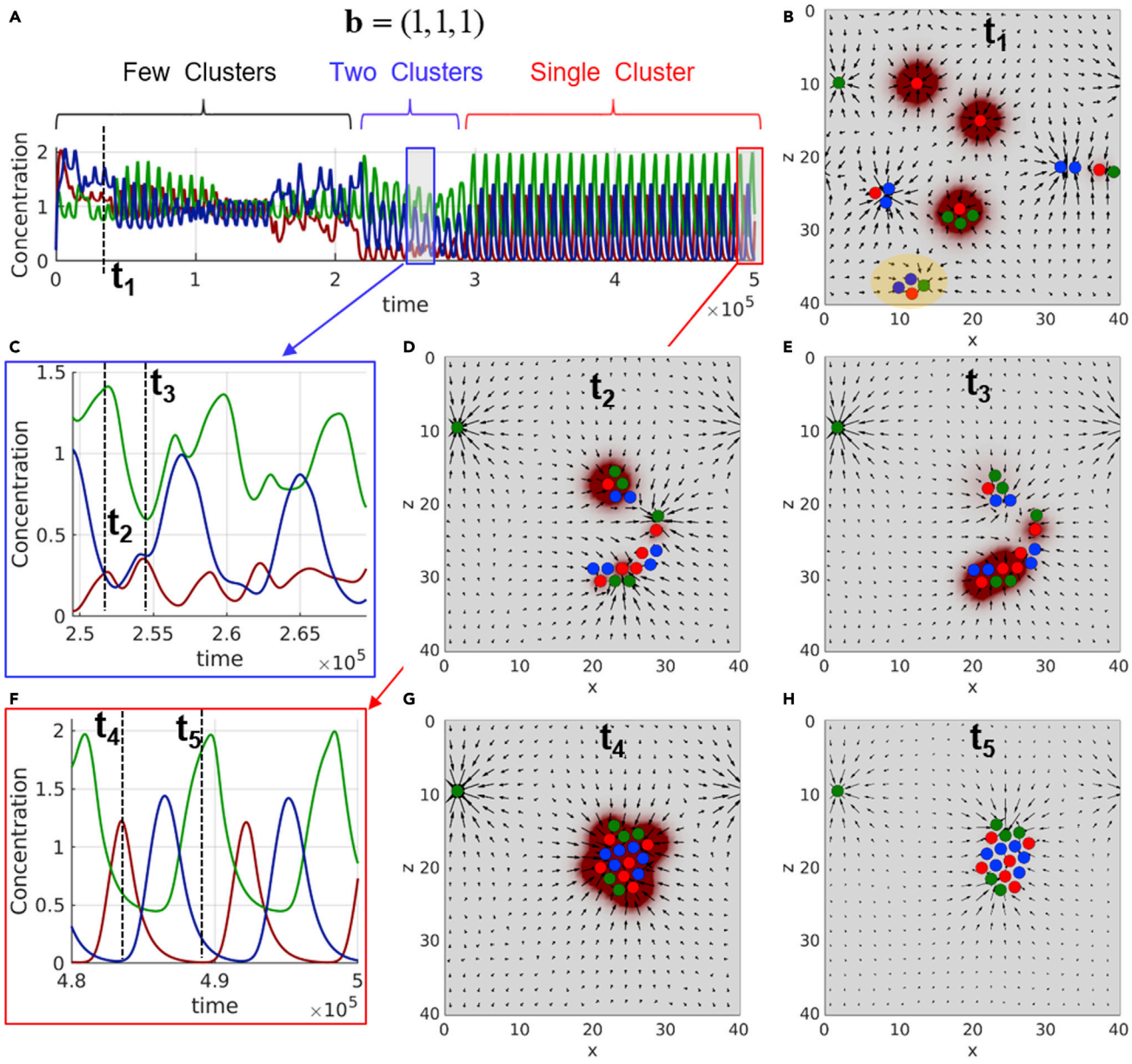

Figure 2. Coarsening dynamics of oscillating clusters with 18 = (6, 6, 6) active capsules

The dynamics are controlled by $\mathbf{b} = (1,1,1)$.

(A) Oscillations of concentrations $\overline{C}_j(t)$ ($j = A,B,C$) averaged across the domain.

(B) Early stage ($t = t_1$) of beads assembling into clusters.

(C–E) Chemical oscillations with bead configurations at times t_2 and t_3 are shown in (D) and (E), respectively.

(F–H) Chemical oscillations with bead configurations at times t_4 and t_5 are shown in (G) and (H), respectively. Capsules that produce chemicals *A*, *B*, and *C* are depicted as red, green, and blue spheres, respectively. Regions of high concentration C_A of chemical *A* are shown in red. Black arrows indicate directions of local fluid velocities $\mathbf{u}(\mathbf{r},t)$. See Video S3 for details.

dynamics produced by a few clusters is indicated by the black horizontal bracket in Figure 2A.

Eventually, the system forms two clusters, and each cluster now includes all three types of capsules necessary for chemical oscillations. The clusters oscillate independently, operating out of phase, as shown in Figures 2C–2E. The blue brackets in

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Figure 2A indicate the duration of this stage, and Figure 2C reveals details of the oscillatory process. Panels 2D and 2E show instances in which either the upper or lower (with respect to the z axis) cluster produces maximal concentrations $C_A(\mathbf{r}, t)$ of chemical *A* (red spots). As the generated flows drag the clusters toward one another, their oscillations become synchronized, in a process similar to the one described in Figure S4.

After the clusters merge into a single island, it slowly drifts upward toward lower *z* values (see Video S3) and produces regular oscillations outlined by the red bracket in Figure 2A. The details of the steady oscillatory process are provided in Figure 2F. Figures 2G and 2H show snapshots with a maximal ($t = t_4$) and minimal ($t = t_5$) production of the reagent *A* (red spot). A more complete description of the dynamics for clusters with $18 = (6, 6, 6)$ is summarized in Figure S5.

The chemical oscillations produced by the clusters and characterized by the averaged chemical signals $\overline{C}_j(t)$ reflect their instantaneous compositions. The chemical interactions between nearest neighbors determine the details of the chemical oscillations, such as amplitude and frequency. However, remote capsules (producing a steady chemical distribution) contribute to an increase in the average value of $\overline{C}_j(t)$. In particular, a stray green capsule (Figures 2G and 2H) produces an excessive amount of chemical *B* (green line in Figure 2F), because all of the sources of the inhibiting reagents (other capsules) are located too far away.

As a second exemplar situation (Figure 3), we incorporate the production of more dense chemicals, which effectively cause repulsive interactions between certain capsules. In particular, we assume that the red and blue capsules produce less dense products (*A* and *C*), while the green capsule produces the denser product, *B*. This scenario is modeled by setting $\mathbf{b} = (1, -2, 1)$. The components of vector $\mathbf{b}$ are chosen to ensure that cluster formation is still possible despite the repulsion between capsules. The heavier chemical (*B*) generates an outward flow, which moves downward above the green capsule as shown in Figure S1. Along the bottom surface, the flow repels neighbors away from the green capsule. The assembly of the clusters now involves a competition between an attraction toward red and blue capsules, and simultaneous repulsion from the green units. The competition hinders the aggregation, and therefore, relative to the homogeneous situation with $\mathbf{b} = (1, 1, 1)$, the heterogeneous case controlled by $\mathbf{b} = (1, -2, 1)$ requires a larger number of capsules *N* to ensure the formation of clusters and subsequent chemical oscillations.

Note that in the purely repulsive situation, $N = (N_A, N_B, N_C)$, clusters are not formed. The capsules repel their neighbors and form an irregular lattice with approximately equidistant spacings.

In the above second case, $\mathbf{b} = (1, -2, 1)$, the capsules dynamically assemble into transient clusters, which can later fall apart, after collisions with other clusters or capsules. Moreover, capsules grouped in one cluster can later leave and become absorbed into another cluster. In the cases involving repulsive hydrodynamic interactions (Figure 3), chemical oscillations can be accompanied by spatial oscillations in the positions of capsules and result in periodic changes of the cluster configuration. Qualitatively, the latter coupling between the chemical and mechanical oscillations resembles the biological chemo-mechanical transduction involved in generating a periodic heartbeat.

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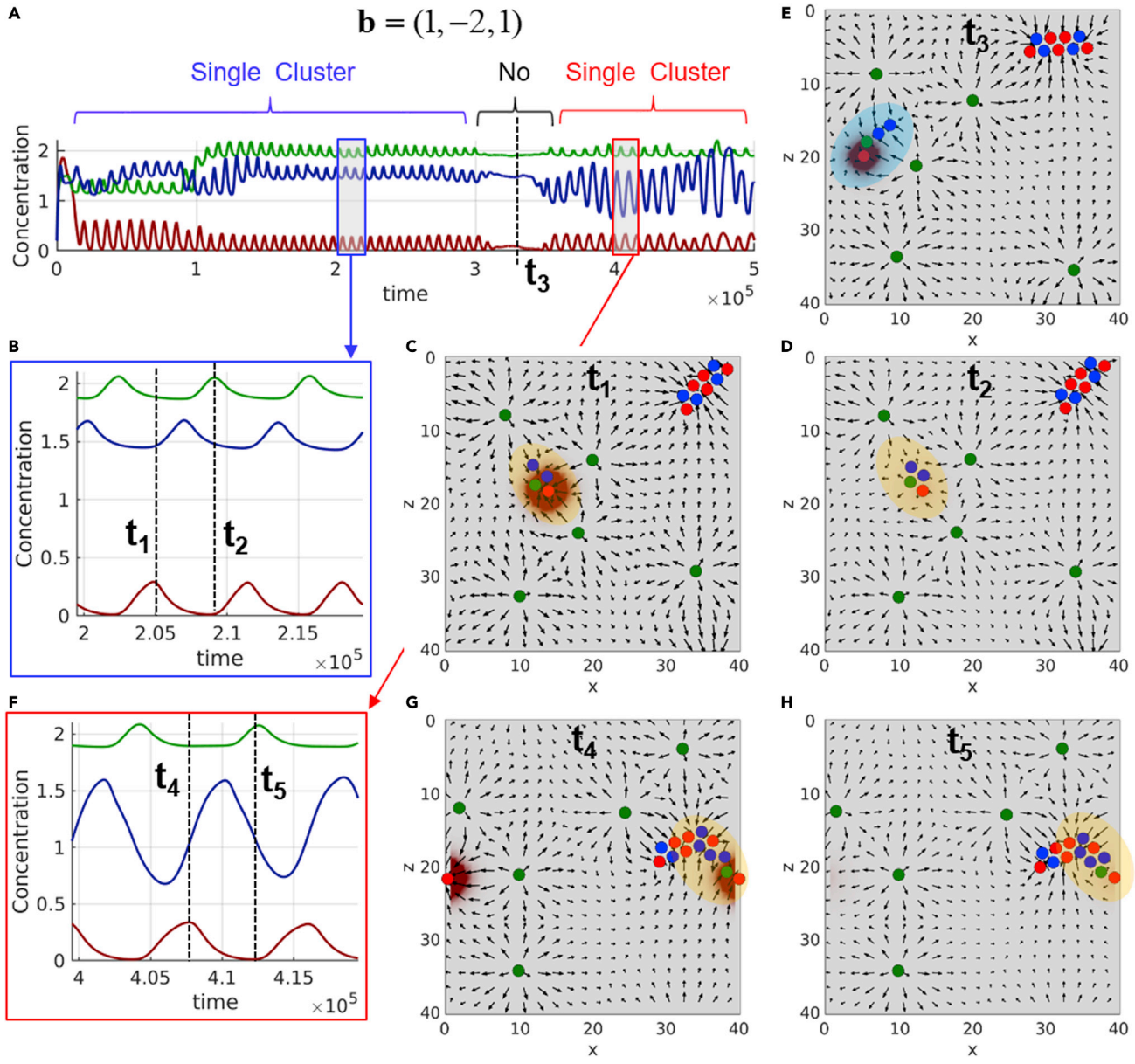

Figure 3. Dynamics of 18 = (6, 6, 6) capsules that produce chemo-mechanical oscillations

The behavior is controlled by $\mathbf{b} = (1, -2, 1)$.

(A) Oscillations of concentrations $\overline{C}_j(t)$ ($j = A, B, C$) averaged across the domain.

(B–D) Chemical oscillations with bead configurations at times t_1 and t_2 are shown in (C) and (D), respectively. Tetramer that performs chemo-mechanical oscillations is outlined in orange.

(E) Configuration of the mobile active capsules that does not produce chemical oscillations ($t = t_3$).

(F–H) Chemical oscillations with bead configurations at times t_4 and t_5 are shown in (G) and (H), respectively. Capsules that produce chemicals *A*, *B*, and *C* are depicted as red, green, and blue spheres, respectively. Regions of high concentration C_A of chemical *A* are shown in red. Black arrows indicate the directions of local fluid velocities $\mathbf{u}(\mathbf{r}, t)$. See Video S4 for details.

Figure 3 shows the example of such chemo-mechanical coupling in the synthetic system in which the dynamics of 18 = (6, 6, 6) capsules are controlled by $\mathbf{b} = (1, -2, 1)$. The evolution of the averaged chemical concentrations $\overline{C}_j(t)$ is shown in Figure 3A. After an initial transition, randomly placed capsules (shown in Figure S6B) aggregate into a small oscillating cluster (highlighted in orange), which