Self-organization of active particles on random networks

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Collective cell migration in 3D extracellular matrix (ECM) is crucial to many physiological and pathological processes. Migrating cells can generate active pulling forces via actin filament contraction, which are transmitted to the ECM fibers and lead to a dynamically evolving force network in the system. Here, we elucidate the role of such force network in regulating collective cell behaviors using a minimal active-particle-on-network (APN) model, in which active particles can pull the fibers and hop between neighboring nodes of the network following local durotaxis. Our model reveals a dynamic transition as the particle number density approaches a critical value, from an “absorbing” state containing isolated stationary small particle clusters, to an “active” state containing a single large cluster undergoing constant dynamic reorganization. This reorganization is dominated by a subset of highly dynamic “radical” particles in the cluster, whose number also exhibits a transition at the same critical density. The transition is underlain by the percolation of “influence spheres” due to the particle pulling forces. Our results suggest a robust mechanism based on ECM-mediated mechanical coupling for collective cell behaviors in 3D ECM.

FIG. 1: Schematic illustration of the active-particle-on-network (APN) model. Left: Particles on a stress-free network. Middle: Particles contraction leads to a “force network” composed of high-stress fibers (illustrated using red). Right: Particles migration on the ECM network along fibers carrying the largest forces.

Active-particle-on-network model: The 3D ECM is modeled as a discrete network with a “graph” (i.e., node-bond) representation in a cubic simulation domain with linear size L, which is composed of $M_b$ nodes and $M_b$ bonds. The average coordination number $Z$, i.e., the average number of bonds connected to each node, is given by $Z = 2M_b/M_n$. We have used both the periodic boundary (PB) conditions and fixed boundary (FB) conditions (i.e., the nodes within a certain distance $\delta L$ from the boundaries of the simulation domain are fixed)
tem size (e.g., $M_n \sim 5000$) the boundary conditions do not affect the results. In the subsequent discussions, we will mainly present the results obtained using the fixed boundary conditions, under which $M_n$ denotes the number of free (non-fixed) nodes.

Next, $N_p$ active particles (e.g., congruent spheres) are introduced in the network such that each particle occupies a randomly selected un-occupied node (i.e., each node can be occupied by only one particle). The number density $\rho$ of the particles is defined as $\rho = N_p/M_n$, i.e., the fraction of nodes occupied by the active particles. Each particle can generate a contraction, which pulls all of the bonds connected to the node it occupies towards the particle center (i.e., the node) by a fixed amount $\delta l$, leading to different pulling forces in the bonds and thus, a force network in the system. We consider the particles can “migrate” from its original node to an un-occupied neighboring node following local durotaxis, i.e., along the bond with the highest stiffness, which is also the bond that carries the largest pulling force among all neighboring bonds (see Fig. 1 for illustration). The diameter of the particles is not essential in our model and thus, is not explicitly considered here.

The bonds of the network are modeled as elastic elements with only non-zero stretching modulus $E_s$ and free to rotate at the nodes. An active particle can generate pulling forces in the bonds connected to the node it occupies by contraction, i.e., $\delta l$. This contraction leads to a strain $\epsilon_i = \delta l/l_i$ in the bond $i$ with original length $l_i$, and thus, a pulling force $f_s = E_s A \delta l/l_i$, where $A$ is an effective cross-sectional area of the bonds. These pulling forces impose force boundary conditions for the ECM network, and the force-balance network configuration is obtained using an iterative force-based relaxation approach [22].

We note that many factors can affect the interactions between the dynamic force network and the collective dynamics of the active particles in our APN model. These may include the geometry/topology and mechanical properties of the network, as well as the number density, spatial distribution and the contractibility (i.e., $\delta l$) of the active particles. In this work, we mainly focus on disordered isostatic networks (i.e., $Z = 6$) derived from maximally random jammed packings of congruent hard spheres [23]. It is straightforward to generalize this study to random network models derived from confocal images of collagen gels [20]. In addition, we use simple linear elastic network models (see Methods). This allows us to investigate the system in the elastic regime [27], in which the force network is mainly determined by the number density and spatial distribution of the active particles, and largely independent of particle contractibility. Our model can readily incorporate more realistic mechanical models for the ECM, taking into account non-linear responses of the fibers [28, 29] and plasticity [13]. Moreover, in an actual cell-ECM system, the cell migration might not be sensitive to individual stiffer fibers, but determined by certain meso-scale stiff structures emerged due to cell remodeling, such as bundles of high-stress fibers. Nonetheless, we believe that the general organizational principles of active particles on random networks obtained here are relevant to and can provide insights on the actual cell-ECM systems.

**Dynamic phase transition in the APN system:**
We now describe the observed collective dynamics of the active particles on the random networks. In our simulations, we systematically vary the particle number density $\rho \in (0.05, 0.95)$. For each $\rho$, the particles are initially randomly introduced in the network and the system is allowed to evolve according to the aforementioned APN dynamics. At low densities (i.e., $\rho < \rho_c \approx 0.114$), the particles rapidly aggregates into multiple isolated small clusters, which are randomly distributed within the ECM (see Fig. 2a and 2b). Here, we consider two particles belong to the same “cluster” if they occupy the two nodes connected by the same bond. As $\rho$ approaches $\rho_c$ from below, the maximal cluster size $n_c$ (i.e., the number of particles in the largest cluster of the system) increases dramatically (see Fig. 2c), indicating the majority of the particles are connected to form a single large cluster in the system.

In addition, we find that the isolated small clusters associated with $\rho < \rho_c$ are stationary, i.e., the particles in the clusters either do not move at all or hop between two adjacent nodes (typically at the boundary of a cluster). On the other hand, the dominant large clusters formed for $\rho > \rho_c$ undergo constant dynamic reorganization. To further quantify the dynamics of the clusters, we count the number of distinct nodes $m_s$, visited by a particle dur-
note that the different particle densities are shown in Fig. 3a. We refer to these highly dynamic particles as “radicals”. (b) Representative trajectories for 10 randomly selected radicals (i.e., highly dynamic particles) for different \( \rho \). (c) The number of radicals \( N_r \) as a function of \( \rho \), which exhibits a clear transition at \( \rho_c \approx 0.114 \) (indicated by the dashed line). This is consistent with the transition observed in the maximal cluster size \( n_c \) as \( \rho \) increases (see Fig. 2c). The inset shows the log-scale plot of \( N_r \) for \( \rho > \rho_c \).

The absorbing-to-active transition has also been observed in a wide spectrum of “random-organizing” physical systems, such as periodically driven colloids [31,32], granular materials and amorphous solids [34–36], vortices [37] and skyrmion systems [38].

**Influence sphere due to active pulling forces:** We now investigate the mechanisms for the observed transition. Once a particle pulls the fibers, a stress gradient is built up surrounding this particle. When another particle “senses” the pulling force [21], it will tend to move up the stress gradient towards the contracting particle due to local durotaxis. This would lead to an effective mutual pulling between the particles.

It is reasonable to assume that the pulling forces generated by a specific particle can only influence other particles within a certain distance \( R_l \). Due to the intrinsic network heterogeneity, \( R_l \) may vary for different particles. Here, we take a “mean-field” approach and assign the same effective \( R_l \) to all the particles in the system and introduce the concept of the influence sphere, which is a spherical region with radius \( R_l \) centered at a contractile particle (see the inset of Fig. 4).

The influence-sphere radius \( R_l \) is estimated from the cluster statistics of the APN systems at low \( \rho \), i.e., those containing multiple small isolated stationary clusters in the final state. This is based on the assumption at low \( \rho \), only particles which are within the influence region of one another would eventually aggregate. In particular, we first identify the particles within the same cluster in the final state of the system. Then the system

\[
N_c \sim (\rho - \rho_c)^\alpha, \quad \text{where the critical exponent } \alpha \approx 6.6 \pm 0.1.
\]

In addition, we find that \( N_c \sim (\rho - \rho_c)^\beta \), where the critical exponent \( \beta \approx 1.63 \pm 0.04 \). The numerical values of \( \alpha \), \( \beta \) and \( \rho_c \) are obtained by fitting the simulation data. We also note that the \( \rho_c \) value is much lower than the site percolation threshold for the network (\( \approx 0.310 \)) [30].

FIG. 3: (a) Statistics of the number of distinct nodes \( m_s \) visited by a particle for \( s = 24 \) successive steps for different number densities \( \rho \). As \( \rho \) approaches \( \rho_c \) from below, a subset of highly dynamic particles emerge which are able to visit many distinct nodes for a given number of steps and are referred to as “radicals”. (b) Representative trajectories for 10 randomly selected radicals (i.e., highly dynamic particles) for different \( \rho \). (c) The number of radicals \( N_r \) as a function of \( \rho \), which exhibits a clear transition at \( \rho_c \approx 0.114 \) (indicated by the dashed line). This is consistent with the transition observed in the maximal cluster size \( n_c \) as \( \rho \) increases (see Fig. 2c). The inset shows the log-scale plot of \( N_r \) for \( \rho > \rho_c \).

FIG. 4: Percolation probability analysis indicates a percolation transition of overlapping influence spheres with radius \( R_l = 0.104L \) at \( \rho^* \approx 0.109 \), which agrees well with the critical density \( \rho_c \approx 0.114 \) for the dynamic phase transition in the APN system. Inset: Schematic illustration of the concept of the influence region (yellow circles), characterizing the range of the pulling forces (red) due to particle (red) contraction.

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is “re-winded” to the initial state, and the intra-cluster nearest-neighbor distances $d_n$ are computed for all clusters. We then use the mean nearest-neighbor distance $\bar{d}_n$ to estimate $R_I \approx 0.104L$ (where $L$ is the linear system size), which is roughly twice of the average fiber length (see SI for fiber length distributions).

**Mean field theory: Percolation of influence sphere:** We now investigate the percolation of the influence spheres as $\rho$ increases. For a given $\rho$, we randomly place particles on the ECM network. Instead of allowing the particles to move according to the APN dynamics, we place a virtual sphere with radius $R_I = 0.104L$ at each particle, representing the influence spheres. We subsequently identify the clusters formed by the influence spheres, based on which the percolation of the system can be determined.

Fig. 4 shows the percolation probability analysis for the system (see SI for details), from which a percolation transition and the associated critical density (i.e., percolation threshold) $\rho^* \approx 0.109$ can be clearly identified. Interestingly, the percolation transition of the influence spheres coincides with the dynamic transition of the active particles at $\rho_c \approx 0.114$. This suggests that the dynamic transition of the active particles from the “absorbing” state to the “active” state is underlaid by and can be understood as the percolation transition of the influence spheres.

We also investigate the collective dynamics of active particles on other network models, including the networks derived from the diamond lattice, as well as random networks reconstructed based on confocal images (see SI for details). We find that although the critical transition density $\rho_c$ depends on the geometry and topology of the networks, the dynamic transition and the aggregation behaviors of the active particles occur in all of the studied model networks. This suggests the feedback loop between the evolving force network and particle dynamics provides a robust mechanism for regulating collective migratory behaviors. In future work, we will also explore the effects of fiber alignment and external mechanical cues.

Finally, we emphasize again that this minimal model does not take into account crucial mechanisms in actual cell migration such as ECM remodeling (e.g., orientation, bundling and degradation) and cell-cell adhesion. Interestingly, our studies indicate that, at least for the APN systems, the local durotaxis for the active particles is sufficient to induce and stabilize aggregations, even without adhesion. Nonetheless, we expect that the insights on the collective behaviors of active particles regulated by the dynamically evolving force network obtained here are helpful in understanding the collective dynamics emerged in actual multi-cellular-ECM systems, as well as in other active-particle systems dominated by environment-mediated particle-particle interactions.

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