Dynamical strategies for obstacle avoidance duringDictyostelium discoidenum
aggregation: a Multi-agent system model.

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Abstract

Chemotaxis, the movement of an organism in response to chemical stimuli, is a typical feature of many microbiological
systems. In particular, the social amoeba Dictyostelium discoidenumis widely used as a model organism, but it is not
still clear how it behaves in heterogeneous environments. A few models focusing on mechanical features have already
addressed the question; however, we suggest that phenomenological models focusing on the population dynamics may
provide new meaningful data. Consequently, by means of a specific Multi-agent system model, we study the dynamical
features emerging from complex social interactions among individuals belonging to amoeba colonies.

After defining an appropriate metric to quantitatively estimate the gathering process, we find that: a) obstacles play the
role of local topological perturbation, as they alter the flux of chemical signals; b) physical obstacles (blocking the cellular
motion and the chemical flux) and purely chemical obstacles (only interfering with chemical flux) elicit similar dynamical
behaviors; c) a minimal program for robustly gathering simulated cells does not involve mechanisms for obstacle sensing
and avoidance; d) fluctuations of the dynamics concur in preventing multiple stable clusters. Comparing those findings
with previous results, we speculate about the fact that chemotactic cells can avoid obstacles by simply following the
altered chemical gradient. Social interactions are sufficient to guarantee the aggregation of the whole colony past
numerous obstacles.

Keywords: Multi-agent modeling, Collective behavior, Micro-biological systems, Heterogeneous environment, Pattern
formation

1. Introduction

The social amoebaDictyostelium discoidenum, a model
organism in biomedical research (Williams, 2010, Strmecki
et al., 2005), is a well-studied example of chemotactic
life-form (Kessin, 2001, Futrele et al., 1982, Urushihara
2008, Bonner, 1970, Bonner and Savage, 1947, Jowhar and
Janetopoulos, 2013). Chemotaxis involves the detection of
local gradients of chemical signals (spatial detection), the
polarization of the cell and the subsequent movement of
the cell up the gradient (Romeralo et al., 2013, Devreotes
1989). In the absence of nutrition sources, starving cells of
D. discoideumare able to send and to process periodic
stimuli of 3,5-cyclic adenosine monophosphate (cAMP)
that act as chemoattractant (Alcantara and Monk, 1974,
Van Haastert et al., 1981, Nanjundiah, 1988, Robertson
et al., 1972). As a consequence, a scattered colony is able to self-coordinate towards an aggregate bulk (Kessin
2003, Fey et al., 2007). Since directed migration is a common feature in many cell
systems, D. discoideum is widely studied (Muñoz-Braceras et al., 2013) and has inspired problems of decentralized
gathering (Bonabeau et al., 1999, Vlassopoulos and Fates,
2011). Consequently, over the years, many aspects of
chemotactic behavior in amoeboid colonies have been
investigated both from an experimental (Robertson et al.,
1972, Vicker et al., 1984, Darmon et al., 1975, Willard and
Devreotes, 2006) and a theoretical (Marée and Hogeweg,
2001, Dallon and Othmer, 1997, 2004, Palsson and
Othmer, 2000, Nagano, 2000, 1998, Pineda et al., 2015,
Savill and Hogeweg, 1997) point of view. Remarkably,
the colony was shown to perform decentralized gathering in a self-coordinated manner, the aggregation mechanism
being an emergent property arising from local rules. However, past studies are mostly considering colonies in
a homogeneous environment. On the contrary, in vivo conditions are often characterized by heterogeneous envi-
ronments. Only a few studies have already tackled such
issue (Elliott et al., 2012, Grima, 2007) considering the
mechanical and rheological properties of the microbiologi-
cal system at the scale of single cell. On the other hand,
Attempts to investigate the behavior of a whole colony in
a heterogeneous environment rely on Cellular Automata
simulations (Fates, 2008, Hatzikirou and Deutsch, 2008).
Cellular Automata (CA) provide individual-based models
at a population level, but their level of complexity is often not sufficient to grasp important details of a process and can be further improved. A natural extension of CA towards more flexible and realistic models is the Multi Agent Systems (MAS) computational approach. An agent is an individual computer system characterized by an arbitrarily complex architecture for behaviors and is capable of independent action on behalf of its user or owner [Wooldridge, 2002 Weiss, 1999]. In addition to individual realistic representation, additional features of MAS models include embedding of agents into dynamic environment and intracellular decision processes triggered by biochemical cell-cell or cell-matrix interactions [Galle et al., 2009]. Examples of MAS models addressing D. discoideum gathering in homogeneous environments can be found in [Parhizkar and Serugendo, 2018 Proverbio et al., 2019].

1.1. Heterogeneous environments

When considering cell colonies, a homogeneous environment is usually modeled as an Euclidean plane (Env ∈ R²) as suggested by [Baker et al., 2008]. Adding obstacles corresponds to alter the topology of the plane according to their size, shape and position. There are two meaningful types of obstacles that are of biological interest. “Physical” obstacles are such that they prevent cells to cross and absorb the cAMP flux; “Chemical” obstacles absorb cAMP molecules alone, letting amoebas through. The former represents concrete objects, while the latter can be interpreted as chemical species that degrade the cAMP flux locally.

Analytically, physical obstacles are represented as locally reflecting border conditions for Amoeba cells. Let \( J_{Am}(x, t) \) be the component of Amoeba flux that is perpendicular to the obstacle; a “physical” obstacle with size \( S_{obs} = \{\text{length, height}\} \) is defined as a local reflecting boundary condition in the following sense:

\[
\begin{align*}
\frac{\partial J_{Am}(x, t)}{\partial n_m} & = 0 \\
\frac{\partial J_{Am}(x, t)}{\partial n_m} & = n_m \cdot \nabla J_{Am} = 0
\end{align*}
\]

where \( \hat{x} \) is the set of coordinates of points belonging to the obstacle edge that is perpendicular to the normal vector of the flux: \( \hat{x} = \{x' = \{x', y'\} \text{ s.t. } x' \perp n_m\} \) with \( n_m \) being the flux normal vector to the m-th edge of the obstacle. From the perspective of the flux of Amoebas, “chemical” obstacles do not represent any source of topological alteration as they let agents through.

When considering the chemical flux of cAMP molecules, both “physical” and “chemical” obstacles act as local absorbing boundary conditions:

\[
\begin{align*}
\frac{\partial J_{cAMP}(x, t)}{\partial n_m} & = 0 \\
\frac{\partial J_{cAMP}(x, t)}{\partial n_m} & = n_m \cdot \nabla J_{cAMP} = 0
\end{align*}
\]

Usually, environmental heterogeneity occurs on a physical scale that is comparable to that of individual cells [Grima, 2007]. As a consequence, macroscopic continuum models (PDEs) of cell movement have difficulties in solving the problem of heterogeneous domains [Baker et al., 2008]. On the other hand, analytical individual-based models that focus on single cells neglect the complexity of the system: they effectively inquire what happens to the cell movement in response to chemical gradients \( \nabla C = g \hat{z} \) (\( \hat{z} \) being the direction unit vector) around an obstacle, but they do not consider the dynamical interactions among multiple cells behaving as a complex network [Boccaletti et al., 2006 Saetzel et al., 2011 Grüne-Yanoff and Weirich, 2010]. As a matter of fact, D. discoideum colonies consist of a population of simple agents interacting locally with one another and with their environment. Although there is no centralized control structure, local interactions between agents are capable of driving the emergence of global complex behaviors such as multi-stability, collective choices and self-organization [Beni and Wang, 1993 O’Connor and Wong, 2015 Garnier et al., 2007].

1.2. Robustness for biological systems

When considering complex biological systems, the notion of robustness is crucial to assess their dynamical properties quantitatively. Robustness is broadly defined as the ability of a system to maintain its function despite the presence of perturbations [Kitano, 2004]. A way to interpret biological systems is to consider them as computing machines. To their utmost simplification, computing machines deliver an output given an environmental input and a finite set of internal rules (individual program). Computing systems are composed by interacting computing machines. As this notion is congruent to that of MAS [Weiss, 1999], said simulation approach is a natural modeling candidate. Within this framework, robustness can be tested as the ability of a computing system to maintain its function despite alterations of individual programs. This way, we can try to evaluate the minimal program (at individual level) that is sufficient to maintain the emerging function of the whole system (at system level). A minimal program \( P^m \) among a set of possible programs \( P = \{P\} \) each with length \( \text{len}(P) \) corresponding to the number of rules, is formalized as:

\[
P^m = \text{argmin}_{\text{len}(P)} P
\] (1)

In the present context, \( P \) is the set of programs composed by biologically validated rules (e.g. cAMP relay, nutrition sensing . . .) plus additional hypothetical mechanisms (e.g. obstacle sensing). The system function corresponds to its ability to achieve decentralized gathering within time scales that are biologically consistent (e.g. as reported by Fey et al. [2007]). We then conjecture that social interactions among cells are sufficient to ensure robust behavior.
towards coordinated cell movement and obstacle avoidance, without additional mechanisms for obstacle detection and avoidance.

1.3. Aim and overview

The present work aims at investigating the aggregation of chemotactic colonies in heterogeneous environments with obstacles. In particular, as cellular mechanisms for obstacle sensing and avoidance are still poorly understood (Grima, 2007), testing concurrent hypothesis in a computational testbed will provide insights on the main processes involved. Concurrent hypothesis are modeled as different programs \( P_i \in P \). By using a Multi-agent system model, we study the efficiency of chemotaxis in achieving controlled and robust cell migration, focusing on dynamical features and self-organization at a population level (Camazine, 2003).

To complete the investigation on how obstacle affect the dynamics, both “physical” and “chemical” obstacles are considered and their impact assessed.

The paper is structured as follows. First, we defend the model choice and we describe the implementation of the MAS model and its environment. Second, we define a topology-independent quantitative measurement to follow the complex evolution of the colony. Third, we present the results: how obstacles (and their type) affect the dynamics and what are the minimal behaviors for cells towards efficient decentralized gathering. Finally, we notice that obstacles elicit multiple stable clusters of cells, we explore the effect of individual fluctuations on the formation of said clusters.

We remark that the present modeling approach is effective both in single-obstacle and multi-obstacle settings and is easily biologically interpretable. Hence, we believe helping researchers to explore additional realistic configurations and test system robustness efficiently.

2. Methods

2.1. The Multi Agent systems model

In order to perform simulations and analysis, we extend an existing MAS-based computational framework that was purposefully designed to address \( D. \) discoideum behavior and that has already been tested and validated (Proverbio et al., 2019). The model simulates the desired dynamics after stating individual behavioral rules and setting biologically consistent parameters. Four main agents compose the model architecture: Environment Env (a squared closed dim \( \times \) dim domain, divided into cells with associated food sources \( b(t) \) possibly growing over time), Amoeba agents Am (proactive agents representing individual cells), cAMP signals cAMP (vectorial packages of chemical signal) and Obstacles Obs.

Agents Amoeba are implemented with individual behaviors embedded in a complex architecture: given the set of configurations \( \{ E_g \} \) of the environment Env, the agent is a tuple \( Am = \langle \text{Inspect, Internal, Action} \rangle \). \( \text{Inspect} = \{ U_i^g : E_g \to \text{per} \} \) looks at \( E_g \) (locally) and maps it into internal perception per. \( \text{Update} = \{ U_i^g : \text{per} \to S_j \} \) may update the states according to the perceptions. \( \text{Action} = \{ A_j^g : S_j \to E_{g'} \} \) is the set of feasible actions on Env according to the current state of the agent. In Fig. 1 the decision-making flowchart for a single agent is reported.

Values for variables and parameters of the model come from settings described in (Proverbio et al., 2019) and are derived from validated biological literature. See Table 1 for simulation values of density \( \rho \) and number of agents \( N \), for agents’ speed \( v_A \), cAMP diffusion drift \( v_c \), cAMP shooting period \( t_s \) and internal “agitation” noise \( P_A \). The latter is the probability that an individual mis-processes the chemical signal due to asymmetric binding receptor occupancy (Van Haastert et al., 1981); it is inserted to improve realism of simulations as stochastic perturbations are often present in biological systems. This way, stochastic perturbations and individual failures can be easily included and controlled by tuning the respective parameters.

Table 1: Meaningful parameters and variables for simulations (set to be biologically consistent). Values from (Proverbio et al., 2019).

| \( \rho \) [cell \( \text{mm}^{-3} \)] | \( N \) | \( v_A \) [unit \( \text{s}^{-1} \)] | \( v_c \) [unit \( \text{s}^{-1} \)] | \( t_s \) [s] | \( P_A \) |
|---|---|---|---|---|---|
| 563 | 2640 | 1.4 | 4.7 | 10 | 0.001 |

We mentioned that chemical signals are modeled as discrete cAMP packages (tokens). It has been shown (Proverbio et al., 2019) that the vectorial message sharing approach generates results that are consistent to those obtained with the typical diffusion of chemicals. In fact, we can relate a chemical gradient \( \nabla C = g \hat{z} \) with a probability gradient. In this case, of the probability that a starving amoeba processes the information carried by an absorbed cAMP token \( P_{amoeba}(I_{\text{staying}} : E_g \to \text{per}) \). At the same time, such strategy is cheaper than that of diffuse chemicals in terms of computational cost (Nemec, 2010; Wang et al., 2010), thus allowing better scaling for large populations.

Heterogeneity is modeled by inserting objects Obs in the
environment. In the present work, obstacles are rectangular with arbitrary length and height. As described above, obstacles can be either “physical” or “chemical”. Following the simulation framework, they are modeled with local rules, depending on their kind $k_{\text{obs}}$. Both obstacles act as sink for cAMP molecules:

Algorithm 1: Absorb cAMP

```
if cAMP overlaps obstacle then
    delete cAMP token;
end
```

Moreover, Amoeba agents can not cross “physical” obstacles, while no restriction is given on “chemical” ones:

Algorithm 2: Reflect Amoeba

```
v_A^+ = v_A \cdot n_m;
if k_{\text{obs}} == \text{phys} then
    if Amoeba overlaps obstacle then
        v_A^- = -v_A^+;
    end
end
```

Fig. 2 shows an example setting of heterogeneous environment with embedded agents (green circles), cAMP tokens (blue dots) and obstacles (grey). Food sources are color coded and can evolve during simulation cycles. In the figure, orange is for $b(t) = 1$, white for $b(t) = 0$.

The model focuses on the first aggregating stages of the gathering process (“streaming” process [Romeralo et al. 2013]) and it does not implement adhesion forces between neighbor cells, thus relying on social mechanisms to maintain cell-cell cohesion. Nonetheless, we believe that it represents an appropriate tool to investigate the dynamical properties of complex colonies while coping with topological perturbations due to obstacles. The code is freely
available from the GitHub repository https://github.com/daniele-proverbio/amoeba

2.2. Defining quantitative measurements

Traditional metrics to quantify the aggregation of a scattered colony are: “Box count”, namely the dimension of a box containing all cells (Fates 2008), and the marginal Variance (Proverbio et al. 2019), accounting for the average spread of the colony around the central bulk. However, such measurements are solely valid in homogeneous environments, as they are susceptible to topological characteristics and fail to track aggregation in multiple clusters.

In order to quantify the aggregation stages in heterogeneous environments, we then suggest a “mean local gathering factor” metric. In particular, the desired metric needs to be monotonically increasing in time if the colony is expected to be aggregated in time.

3. In the position space, the “neighborhood area” of the agent is given by:

\[ A_i = \{(x', y') \text{ s.t.} \ (x_i - x')^2 + (y_i - y')^2 \leq R_i^2\}. \quad (2) \]

where \( (x_i, y_i) \) are the cell center coordinates. At the same time, the physical area occupied by the agent is given by:

\[ A_j = \{(x'', y'') \text{ s.t.} \ (x_j - x'')^2 + (y_j - y'')^2 \leq R_j^2\}. \quad (3) \]

3. The set \( I_n(t) \) of j-amoebas that are neighbors (at time \( t \)) of the i-th agent is the set of j-agents whose physical area intersects the i-th “neighbor area” at time \( t \), that is:

\[ I_n(t) = \{\{Am_j\}, \ j = 1..n \text{ s.t.} [Am_j \cap Am_i^*](t) \neq \emptyset\} \quad (4) \]

4. The number of neighbor cells for the i-th amoeba is thus given by:

\[ N_i^{in}(t) = \dim (I_n(t)) \quad (5) \]

where \( \dim \) represents the dimension of the set. \( N_i^{in}(t) \) is the local gathering factor and increases the deeper the i-th amoeba is in the gathering pattern and/or in the final aggregate.

5. To obtain a mean local gathering factor, we average \( N_i^{in}(t) \) over the number of amoebas \( N \):

\[ R(t) = \frac{1}{N} \sum_{i=1}^{N} N_i^{in}(t) \quad (6) \]

Note that \( R \) will not be normalized, since the maximum value it can reach at the end of the simulation time \( t_{max} \) is itself informative about the “strength” of the gathering process.

In a homogeneous environment, mean local gathering factor \( R \) is precisely the inverse of the marginal Variance \( \operatorname{var}_x \), as the former quantifies how much agents are packed together while the latter measures how spread the colony is. Fig. 3 shows the agreement between data (from repeated simulations) and the following fit relationship:

\[ R = a + \frac{b}{\operatorname{var}_x + c} \quad (7) \]

![Figure 3: Mean local gathering factor R as defined in this section against marginal Variance as used by Proverbio et al. (2019). Data come from repeated simulations in homogeneous environments. As expected, when obstacles are absent, the two metrics are inverse one of the other, as guaranteed by the hyperbolic fit (values reported).](image)

2.3. Simulation protocol and remarks

Simulations and subsequent analysis are based on the following protocol.

1. Consider the parameter space \( \mathbb{P}_S \) defined by the number, size, location and kind of obstacles: \( \mathbb{P}_S = \{n_{obs} \times S_{obs} \times \bar{x}_0 \in \text{Env} \times k_{obs}\} \). Remember that they are initially considered of rectangular shape. The first
3. Obstacles as local source of perturbation

By following the above protocol, we first inquire whether obstacles indeed represent local sources of perturbation. We run repeated simulations of the same setting, which was randomly chosen from $\mathcal{P}^S$, measuring $(N(t) \pm \sigma_N(t))$ and also considering simulated animations. $k_{obs}$ was varied from "physical" to "chemical". As we see in Fig. 4 obstacles perturb the colony dynamics locally. On the left-hand half of the domain, we observe that obstacles circumscribe sub-domains with different cell densities, thus eliciting metastable clusters. On the contrary, in the right-hand side (obstacle-free region) we recognise the usual streaming behavior towards the aggregate, as reported in previous studies (Dallon and Othmer, 1997, Palsson and Othmer, 2000, Proverbio et al., 2019). Moreover, as shown in Fig. 5 the measure $\aleph$ is monotonically increasing, as we would expect in case of a steadily aggregating colony. This fact quantifies that clusters have been formed despite the presence of obstacles, which do not cause the cells to remain scattered but prevent the formation of a global aggregate.
grammed to augment over time.

\[ b(t + 1) - b(t) = \begin{cases} -1, & \text{if Am is eating,} \\ 0, & \text{otherwise} \end{cases} \]

Hence, during the simulation, white space indicates regions that have been explored by amoebas, while orange ones have not. In Fig. 4 we observe that Am agents explored most of the domain during the aggregation, but they seldom went close to obstacles. In addition, we observe that physical and chemical obstacles elicit aggregating behaviors that are not statistically distinguishable (see Fig. 5). On the one hand, it suggests that, colony-wise, chemical and physical obstacles elicit the same confining effects by disrupting the flow of cAMP chemicals that guide the cells. On the other hand, this evidence asks for a more detailed investigation of the individual programs (at cellular level) that guide amoebas towards robust gathering.

4. Emerging behavior for obstacle avoidance

Given the previous findings regarding the impact of obstacles on the gathering process, we now ask what is the minimal program \( P^m \) that guarantees a robust aggregation process. We recall that performing MAS simulations corresponds to check for the emergence of complex phenomena (coordinated aggregation past obstacles) from microscopic rules (individual programs for Amoeba agents). Hence, \( P^m \) refers to a program at cell level leading to robust aggregation of the whole colony (population scale). Here, \( \text{robust} \) only refers to the fact that cells form clusters without being scattered all over the environment. Whether clusters are unique or manifold is not currently inquired. To do so, we update the \( \text{Move} \) rule for amoeba agents (see Fig. 3). This results in having two concurrent programs for the agent Amoeba. \( P1 \) corresponds to the original set of rules for Am: an agent’s movement is always up gradient. \( P2 \) corresponds to the updated \( \text{Move} \) statement: an agent first checks for nearby obstacles and avoids them. In pseudocode, \( P1 \) and \( P2 \) read as follows:

```python
def P1
    inherit from
    Am = \{Inspect, Internal, Action\}
end

def P2
    inherit from
    Am = \{Inspect, Internal, Action\}
    update Move:
        isObs = checkFor(nearbyObstacle)
        if isObs == true:
            avoidObstacle
end
```

Note that the two separated programs are dual to Algorithm 2, apart from the fact that they are cell-oriented. Implementation is reported in the publicly available code.

In this case, we are not interested in maintaining two sub-domains as in Sec. 3, so obstacles with different shape and size are randomly scattered all over the environment. To test for mechanisms for obstacle sensing and avoidance, obstacles are always of “physical” kind. Repeated MAS simulations are then performed, testing both programs in different settings. Fig. 7 shows the evolution of a simulation without updated \( \text{Move} \): we observe the ability of the colony to overcome obstacles and to stream toward multiple clusters even in the absence of specific mechanisms. In fact, similarly to what reported in Fig. 4, cells follow chemical gradients away from obstacles. More quantitatively, we measured \( N(t) \) for repeated simulations in different settings, while changing program. Results are reported in Fig. 6. We observe that evolution of the colony whose individuals follow \( P^1 \) is not statistically distinguishable from that ruled by \( P^2 \). This evidence is strengthened by a \( Z \) test. Other considered settings in the parameter space \( PS \) give the same result.

Previous works (Grima, 2007, Elliott et al., 2012) suggested that cells are not required to own specific sensing mechanisms, as they can in many cases avoid the obstacle by following the perturbed chemical gradient in its vicinity. Such hypothesis was preliminary tested with single-cell individual-based models. Using a multi-cell scheme, we suggest that similar results can be obtained when considering the whole complex system: at a population level, cells do not even came close to obstacles as they are guided by social interactions through message sharing. From the “perspective of the colony”, its microscopic components (individual amoeba cells) are sufficiently equipped with \( P1 = P^m \) to get the emergence (at population scale) of coordinated aggregation past an obstacle.

A speculative biological interpretation is the following: in order for a colony to robustly aggregate, it is not necessary for a cell to develop specific mechanisms for obstacle avoidance. Cells seem to be guided by chemicals that,
Figure 7: Several snapshots during the evolution of a colony. They refer to the experimental set whose measurements are reported in Fig. 5. In order to magnify the spontaneous formation of multiple clusters, simulations were let run after the streaming interval considered in the above analysis ($400 < t < 1300$). Obstacles are randomly scattered in the whole domain. (a) Setting the experiment with constant food sources in Env; (b) $t = 500$: after an initial transient, streams appear; (c) At $t = 1500$ early aggregation after streaming is almost completed. (d) $t > 1500$: Multiple clusters are clearly recognizable: there are three main attractors around which amoebas are gathering. Note that cells have explored almost all the space (they ate all bacteria that were deployed initially.)

once being absorbed by obstacles, highlight the best paths for chemotaxis-directed migration. The self-aggregating patterns of the colony as a whole not only guide single cells towards stable clusters, but they also elicit collective choices to avoid obstacles.

5. Fluctuations drive the system out of local minima

As described in the above section, cells tend to form multiple clusters when obstacles are present. Fig. 7 shows this phenomenon. Borrowing vocabulary from statistical mechanics, multiple clusters correspond to different attractors, that are local minima of a hypothetical energy landscape for the system. Hence, obstacles contribute to barrier potentials between these minima. It is now interesting to inquire if it is possible to get a single cluster corresponding to a global minimum.

In statistical mechanics, noise is known to push system states out of local attractors. Also, in simulations of biological systems, fluctuations around a mean behavior are known to elicit better explorations of the space (Garrier et al. 2007, Eberhart et al. 2001). Therefore, MAS simulations are now performed to check if fluctuations alone are sufficient to drive the colony towards a single cluster, and how often. As a preliminary search, we consider fluctuations due to the colony being “off-scale”.

It is known that, for a MAS simulation to be repeatable and stable, number $N$ and density $\rho$ of agents have to considered (Proverbio et al. 2019). Initial values listed in Table 1 respect the conditions for the system to be considered in a scale-free regime. On the contrary, “off-scale” systems are such that individual fluctuations dominate the dynamics. They can not be considered for systematic studies as above, but they are perfect to test noisy settings in heterogeneous environments.

We then set new simulations on off-scale configurations by changing density and numerosity values (for instance, $\rho = \frac{200}{100^2}, N = 200$). See Proverbio et al. (2019) (Fig. 11) for all values $\{N, \rho\}$ that define an “off-scale” regime. Different settings and different configurations of obstacle number and placement are then tested. Fig. 8 shows an example simulation in which the “off-scale” colony aggregates in a single cluster. Table 2 summarizes how many times (in percentage, out of 200 simulations) multiple clusters are formed, depending on the system regime (“on” or “off” scale) and how many obstacles are present in the domain (1 or multiple).

Table 2: Chances [%] to get multiple stable clusters (at least 2). Data from multiple (200) simulations with different obstacles configurations.

| Obstacles | on-scale | off-scale |
|-----------|----------|-----------|
| 1 obstacle| 15       | 3         |
| multiple obs | 70      | 30        |

Table 2 reports that noisy systems (“off-scale”) are more likely to converge to single clusters than “on-scale” ones, which are less prone to individual fluctuations. Moreover, values in Table 2 show that a single obstacle produces less multiple clusters than multiple obstacles. This suggests that obstacles act as potential barriers between energy minima, thus stabilizing local attractors. However, in highly heterogeneous environments, fluctuations alone are not sufficient to achieve robust and repeatable decentralized gathering in a single cluster. Collective behavior towards aggregation seems to result from a delicate trade-off between robust chemotaxis and random fluctuations as suggested by previous experimental works (Dallon et al. 2011).

6. Conclusion

The main aim of this project was to investigate how colonies of chemotactical cells behave in the presence of obstacles, as often happens in vivo. To do so, we chose the social amoeba Dictyostelium discoideum as model organism and we studied its aggregation process. Since
we decided to focus on dynamical features elicited by nonlinear social interactions, rather than on individual mechanical properties, we used a Multi Agent System model that had been purposefully designed, implemented and validated. A suitable metric (the mean local gathering factor $\mathcal{N}$) was also defined.

By analyzing chemical and physical obstacles, we noticed that their main impact on the system is to perturb the chemical flux. A group of cells in collision with an obstacle can in many cases avoid it by simply following signals coming from other directions. In fact, as far as the present model is concerned, agents Amoeba are able to aggregate robustly both when having or lacking specific rules for obstacle sensing and avoidance. Such evidence suggests that, from a population point of view, social interactions are effective to drive the colony past obstacles. In fact, big colonies are only locally perturbed by the presence of obstacles and emergent dynamics is sufficient for robust decentralized gathering in heterogeneous environments. Additional individual abilities might elicit better efficiency, but such is not the case observed in the present simulations. This may suggest why specialized biological mechanisms for avoiding obstacles are only known for a few cells and organisms [Grima, 2007].

Moreover, preliminary results suggest that a fluctuating system can better explore the state space and overcome obstacles with less probability of forming multiple clusters. On the other hand, as known in the literature [Fates, 2008; Proverbio et al., 2019], perturbed colonies are less likely to follow the chemical gradient, so an efficient gathering process should present a trade-off between chemotactical stability and random exploration. This is typically suggested in the field of system control [Iglesias and Ingalls, 2010].

Often, organisms that live in colonies have little concern for an individual fate, whereas they are evolutionary competitive as a whole population [Bonabeau et al., 1999]. Therefore, focusing on the emergence of collective behaviors from individual programs provide additional information on the development of such colonies. We believe that MAS models, that couple cell and population scale, are useful when addressing complex microbiological systems in heterogeneous environments. Further in vivo and in vitro studies are recommended to test the hypothesis made in this article and to improve our knowledge on behavior of cellular motility in heterogeneous environments.

**Code**

The code to perform MAS simulations is freely accessible at the following GitHub repository: [https://github.com/daniele-proverbio/amoeba](https://github.com/daniele-proverbio/amoeba). Statistical analysis was performed with Python open libraries.

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**Author contributions**

D.P and M.M. designed and conceived this project. D.P. performed the experiments and the analysis. D.P. and M.M. interpreted the results and wrote the manuscript. All authors contributed to and approved the manuscript.
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