A SIMULATION MODEL FOR THE WHOLE LIFE CYCLE OF THE SLIME MOLD *DICTYOSTELIUM DISCOIDEUM*

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ABSTRACT

Slime molds are fascinating organisms, they can either live as an organism consisting out of a single cell or they can form a multi-cellular organism. Therefore from the biological point of view, the slime molds are studied in order to understand the evolutionary step from a single cell organism to a multi-cellular organism. Studies have shown that the behavior of cooperating single cell organisms exhibits synergistic emergent intelligence, for example finding shortest paths. Just recently, simulation and experiments with a real slime mold (*Physarum polycephalum*) have been used for traveling salesman like problems.

In this work we present a simulation model for the slime mold *Dictyostelium discoideum*. Different to other studies, here the whole life-cycle is modeled and simulated. Very detailed behavioral patterns and parameters are modeled and as result a simulation model is obtained, that shows a behavior very close to the living slime mold. This result is consolidated by extensive verification experiments. As consequence, this model can be used to further study the mechanism of cooperation of single cells, mechanisms of synergy and emergence, and additionally this model offers the possibility to develop more slime mold inspired algorithms.

MOTIVATION

Slime molds are fascinating organisms, that basically are living as single celled amoeba. If the environmental living conditions are bad (mainly if there is not enough food), then the individual amoeba act together in order to ensure the survival of at least some part of the population. In such situation the slime mold forms a social organism (pseudoplasmodium), where the amoeba act as *one* multicellular organism, that moves and reproduces.

Therefore from the biological point of view, slime molds are studied in order to understand the evolutionary step from a single celled organism to a multi-cellular organism. Studies have shown that the behavior of cooperating single celled primitive organisms exhibit synergistic emergent intelligence, for example finding shortest paths. Just recently, simulation and experiments with a real slime mold (*Physarum polycephalum*) have been used for traveling salesman like problems (16; 17). Thus from the computer science point of view, it is interesting to study and learn from the natural mechanisms, that lead to emergent intelligent behavior of a whole system that consists of simple parts.

For this reason we developed a simulation model for the slime mold *Dictyostelium discoideum*. Different to other studies, here the whole life-cycle is modeled and simulated. Very detailed behavioral patterns and parameters are modeled and extensive verification has been done in order to ensure that the resulting model is valid. As consequence, our model can be used in the future to further study the mechanism of cooperation of single cells, mechanisms of synergy and emergence, and to develop more slime mold inspired algorithms exhibiting self-X properties.

In the following the natural life cycle and the most important mechanisms of movement and reproduction of *Dictyostelium discoideum* are summarized. Then it is explained, which of the features are essential for describing the behavior of *Dictyostelium discoideum* and as consequence have been used in order to build a good simulation model. The simulation model is then verified by doing extensive experiments and comparing behavior and quantitative measures of simulation model and real *Dictyostelium discoideum*.

DICTYOSTELIUM DISCOIDEUM BASICS

The study of *Dictyostelium discoideum* has a long history and also the study of collective movement has been focus of research. Special interest was given to the interaction between different amoeba: How do relatively simple single cells communicate? And which mechanisms let them get together and act as a *one* multi-cellular organism?

Early studies about the basic behavior and mechanisms of *Dictyostelium discoideum* can be found in (1; 2; 3; 4). In (2) evidence is given for the chemotaxis bringing the amoeba together.

Summaries and a whole picture of *Dictyostelium discoideum* can be found in recent literature, such as (5) or on a dedicated web page (6).

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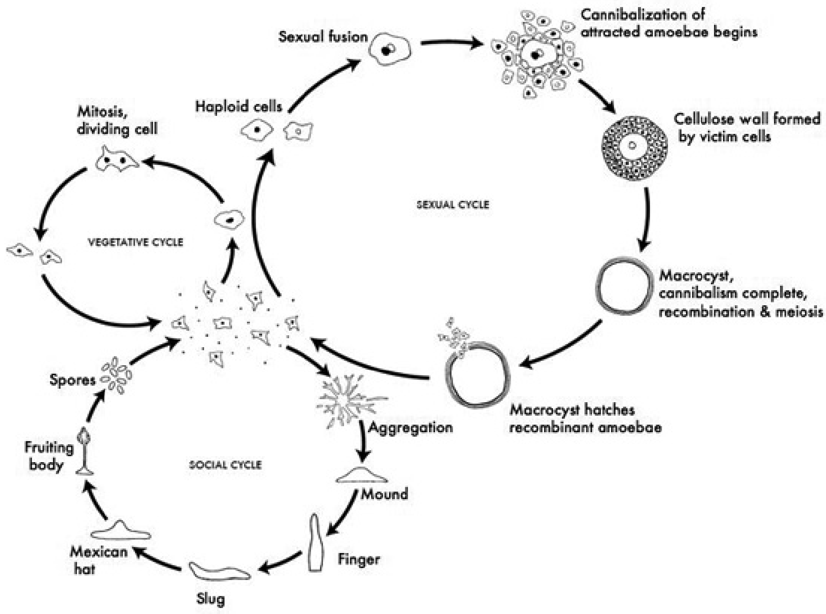

Figure 1: Life-cycle of *Dictyostelium discoideum*(creative commons license, by David Brown and Joan E. Strassmann)

Life-cycle of *Dictyostelium Discoideum*
In the biological taxonomy *Dictyostelium discoideum* belongs to the single celled *myxomycota* (= slime-molds), there to the *acrasiomcycota* (cellular slime-molds).

The normal appearance is a single celled amoeba with a size of 8 - 12 μm. Chromosome two (out of six, with ca. 8000 to 10000 genes) suggests that *Dictyostelium discoideum* has closer relationship to animals than to plants. The movement of *Dictyostelium discoideum* is a reaction to chemical stimuli (chemotaxis), the stimulus normally being the excrement of bacteria, the main food source of *Dictyostelium discoideum*. This attraction can span over 5 μm if many bacteria are present. A second stimulus are chemicals that are emitted by other amoeba that are hungry. If none of those stimuli is present the movement is directed by the next source of light and if the light is diffuse or non-existent, then the movement of *Dictyostelium discoideum* is random.

For the movement *Dictyostelium discoideum* builds pseudopodia.

The reproduction is mainly asexual by cell division (although also the possibility of sexual reproduction is possible, however rarely). Between two divisions an amoeba has to eat approximately 1000 bacteria, the final division needs a duration of approximately three minutes.

The life-cycle consists of three phases (see Fig. 1 for a detailed illustration):

- growth and reproduction
- interphase (phase of hunger)
- aggregation phase

If enough food is present *Dictyostelium discoideum* eats and reproduces and moves towards more food. If even by movement no more food can be found the amoeba's state changes into 'hunger' and emits cAMP (cyclic adenosine monophosphate, discovered by (2) in 1947 and identified 1967 by (3)).

Amoeba that are not hungry do not react on cAMP very much. While being hungry the reaction sensitivity to cAMP increases and with a small delay the cAMP concentration is amplified by hungry cells that, additionally to being hungry, sense cAMP.

By this stimulus, the amoeba enters the aggregation phase, which is characterized by all hungry amoeba coming together and that ends with building a fruiting body and finally releasing the spores. The minimum population density for aggregation is 400 amoeba per mm^2.

The aggregation phase can be divided in five subphases (see Fig. 2):

- Streaming
- Mound
- Slug
- Mexican hat
- Fruiting body/Sorokarp

The aggregation phase culminates the spore out of the fruiting body. Spores are spread out and carried by wind and other external factors, fall down and start growing new populations of *Dictyostelium discoideum*, the life-cycle starts again.

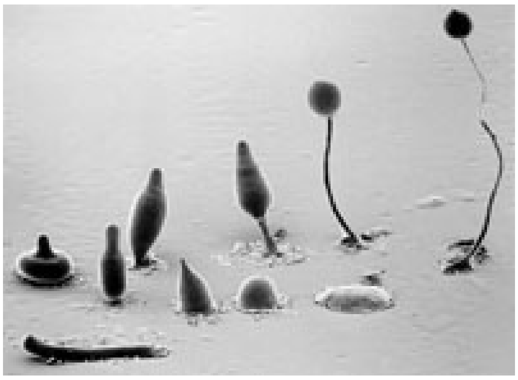

Figure 2: *Dictyostelium discoideum* from aggregation to spore out Copyright granted by, M.J. Grimson and R.L. Blanton, Biological Sciences Electron Microscopy Laboratory, Texas Tech University.

STATE OF THE ART

As early as in the 70s, researchers tried to find a mathematical description of the behavior of *Dictyostelium discoideum* such as in (8). Later on, especially the spiral geometry of the aggregation patterns have been of interest (9). In (7) a model for the individual as well as the collective movement of *Dictyostelium discoideum* has been developed.

However, each of the previous works only simulates *one* aspect of the life-cycle, neither work includes a simulation model for the *whole* life-cycle of *Dictyostelium discoideum*. This is what we present in the remainder.

SIMULATION MODEL

Our simulation model consists of a basically two-dimensional grid where amoeba can move around. In the grid also information about light and wind, food (bacteria) and chemical stimuli (cAMP signaling hunger, folic acid signaling food) is stored. The level of geometrical detail is one μm. The level of detail concerning the timing is derived from the speed of *Dictyostelium discoideum* which is two μm/min. Thus the smallest time duration is an interval of 30 seconds which we chose as cycle time of the simulation.

Vegetative Phase

In this phase, *Dictyostelium discoideum* moves around, searches food and reproduces, when enough food has been consumed. Since in the grid information about food and the corresponding chemical signal is stored, an amoeba can smell the direction of the nearest food and move in that direction. If no food is near, the movement is random.

If food is met, a waiting time corresponding to the time of phagocitosis (eating) is implemented. Since the real phagocitosis needs approximately 90 seconds, it corresponds to three simulation cycles. After that, the food disappears from the grid and the food counter of the amoeba having eaten is increased.

If enough food has been consumed (mean value for that is 1000 bacteria), a cell division is started. That means that the amoeba is divided into two amoeba being placed in the grid.

After a certain number of cycles (240 cycles corresponding to approx. two hours for real *Dictyostelium discoideum*) with no food the state will be changed to hungry and after a certain delay (1 hour thus 120 cycles) *Dictyostelium discoideum* will not move towards food but is sensitive to cAMP and moves into the direction of the highest cAMP concentration instead of searching for food. However, if food is meet by chance, it will be consumed.

Mound Phase

As mentioned before, hungry amoeba stream together, following the cAMP signal of other hungry individuals. Through the pressure from all sides to the center, the amoeba are lifted in the third dimension, which is also modeled here.

If the majority of surrounding hungry amoeba have been streaming to one place the so-called mound phase is reached. That means that a mound-like accumulation is built up. If enough amoeba are together or after a certain time, the next phase is started: the slug phase.

Slug Phase

In this phase, the gathered amoeba start to move and act as one multicellular organism. They start moving, mainly towards the next light source, in order to find the best place for the spore out. It is called slug phase, because the moving accumulation of amoeba looks like a microscopic slug (snail without house).

The collective movement is mainly steered by the cAMP concentration while the position of the individuals inside the slug is determined by the DIF (Differencing Inducing Factor (15)) concentration (this is important when different clones of *Dictyostelium discoideum* are studied), which also starts the building of the spore stalk, when a certain limit is reached.

Mexican Hat Phase

When a certain level of DIF concentration is reached the amoeba stop moving. The pressure of the outer amoeba lets the stalk grow into the height. The cells in the middle start building the stalk, harden and die. Other cells wander up the stalk and build the fruiting body. Only these cells reproduce by spore out. Spore out is like an explosion, the cells are distributed around the stalk nearly randomly, additionally moved by the wind.

VERIFICATION

In order to prove that our simulation model is accurate and represents the behavior of the real *Dictyostelium discoideum*, we conducted a thorough verification of the

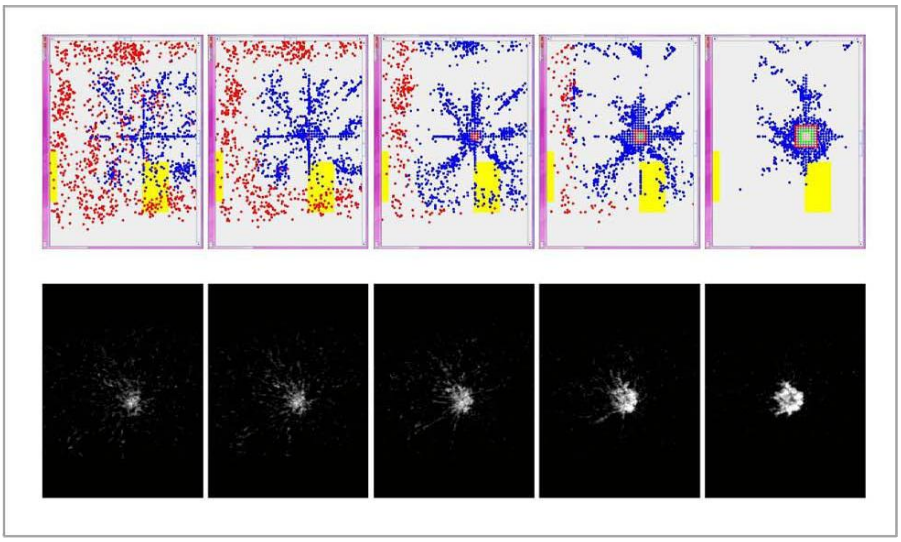

Figure 3: Verification of the aggregation phase

simulation model. Only then, the model can be used for further studies.

First we do optical verification, that is we compare by sight the behavior of the real and the artificial slime mold.

See Fig. 3 for a comparison of the aggregation phase of the simulation (upper pictures) and pictures of the real *Dictyostelium discoideum*. Note that also the timing of the set of pictures is comparable. One can see that the simulation shows the same behavior, that is the same aggregation patterns (streaming like) at the same points in time as the real movement and streaming patterns of *Dictyostelium discoideum*.

At the end of the streaming/aggregation phase *Dictyostelium discoideum* builds a mound (see Fig. 4). Afterwards it moves slug-like into direction of better environmental conditions, that is towards light (see Fig. 5). (In all pictures: (not) hungry cells are blue (red), the light source is yellow, the third dimension is also color coded in the center of the mound).

Quantitative Verification

After comparing the real and simulated behavior mainly by sight, we now do detailed measurements of the timing of the development of *Dictyostelium discoideum*.

The most imminent quantitative properties characterizing a population of *Dictyostelium discoideum* are the durations of the different phases. In the nature the aggregation takes 9 to 13 hours depending on the size of the population, environmental conditions and distance of individuals.

In the verification scenarios 2310 aggregation cycles have been simulated and the durations of the phases have been measured and the mean value has been calculated and verified by the Chi Square test.

It can be seen in table 1 that the simulation results are well within the natural durations, also regarding the confidence intervals.

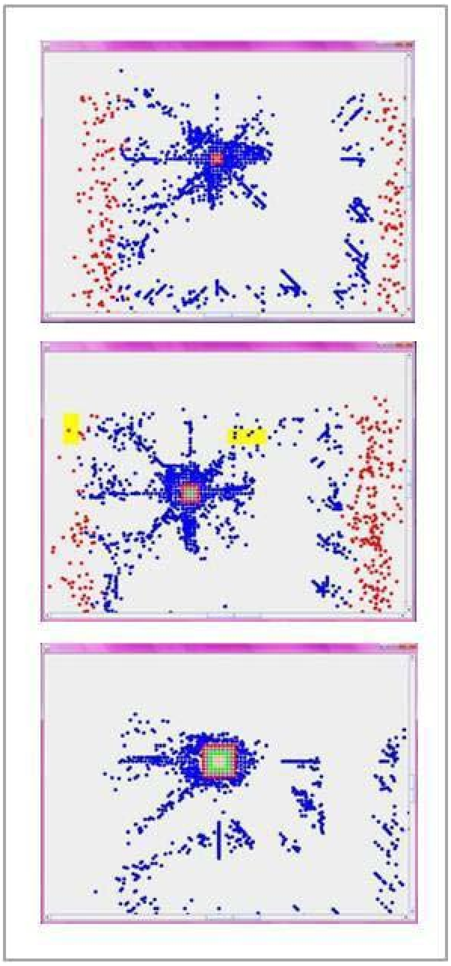

Figure 4: Simulation of forming the mound

Table 1: Verification of phases of the life-cycle

	Aggregation	Slug	Mexican Hat
Mean duration/min	696	174	238
Mean duration/h	11.6	2.9	3.96
95%-confidence interval (min)	694-699	207 - 213	237 - 240
Mean natural value from literature	9-13 hours	up to 5 hours	4-5 hours

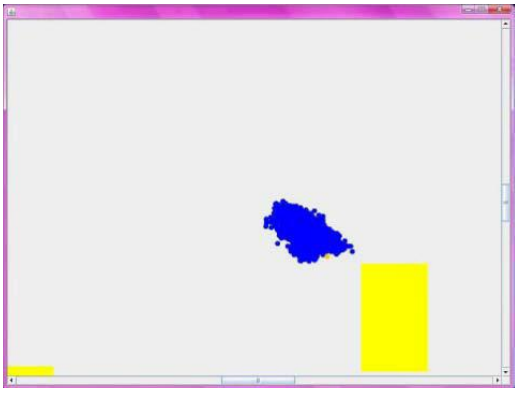

Figure 5: Simulation of slug movement towards light

The durations of the phases in a natural environment differ depending on the detailed environmental conditions. Considering the natural deviations of the timing of the phases, the simulated lengths of the phases is always within the natural bandwidth of the time values.

So as result we can state, that with high probability our simulation model captures the qualitative as well as the quantitative behavior of the whole life-cycle of *Dictyostelium discoideum*.

CONCLUSION

In this work we showed a simulation model for the whole life cycle of *Dictyostelium discoideum*. The verification shows that the results are well within the natural parameters. *Dictyostelium discoideum* has gained increasing interest as model organism for biologists as well as computer scientist in order to study the mechanisms of synergy and emergent intelligent behavior out of simple single parts. With our model we hope to better understand these mechanisms and derive new algorithms for the networked world that make things easier to inter-operate. In future work we will use the the model to study mechanisms of group selection and also try to derive computational algorithms from the behavior of *Dictyostelium discoideum*.

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AUTHOR BIOGRAPHIES

MATTHIAS BECKER got his diploma in computer science from University Würzburg in 1996 and his Ph.D. from University Bremen in 2000. Since then he is researcher and lecturer at University Hannover in the fields of Petri Nets, simulation of discrete event systems, heuristic optimization and biological systems

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