The cell-level perspective in social conflicts in Dictyostelium discoideum

Jeremy Van Cleve based on reviews by Peter Conlin and Matthew Herron

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The social amoeba *Dictyostelium discoideum* is an important model system for the study of cooperation and multicellularity as is has both unicellular and aggregative life phases. In the aggregative phase, which typically occurs when nutrients are limiting, individual cells eventually gather together to form a fruiting bodies whose spores may be dispersed to another, better, location and whose stalk cells, which support the spores, die. This extreme form of cooperation has been the focus of numerous studies that have revealed the importance genetic relatedness and kin selection (Hamilton 1964; Lehmann and Rousset 2014) in explaining the maintenance of this cooperative collective behavior (Strassmann et al. 2000; Kuzdzal-Fick et al. 2011; Strassmann and Queller 2011). However, much remains unknown with respect to how the interactions between individual cells, their neighbors, and their environment produce cooperative behavior at the scale of whole groups or collectives. In this preprint, Forget et al. (2021) describe how the *D. discoideum* system is crucial in this respect because it allows these cellular-level interactions to be studied in a systematic and tractable manner.

Spore bias, which is the tendency of a particular genotype or strain to disproportionately migrate to the spore instead of the stalk, is often used to define which strains are "cheaters" (positive spore bias) and which are "cooperative" (negative spore bias). Forget et al. (2021) note that spore bias depends on a number of stochastic factors including external drivers such as variation in environmental (or nutrient) quality and internal drivers like cell-cycle phase at the time of starvation. Spore bias is also affected by the social environment where the fraction of cheater strains in a spore may be limited by the ability of the remaining stalk cells to support the spore. The social environment can also affect cells through their differential responsiveness to the chemical factors that induce

differentiation into stalk cells; responsiveness is partly a function of nutrient quality (Thompson and Kay 2000), which in turn can be a function of cell density. Thus, Forget et al. (2021) highlight a number of mechanisms that could generate frequency-dependent selection that would lead to the stable maintenance of multiple strains with different spore biases; in other words, both cheater and cooperative strains might stably coexist due to these cellular-level interactions.

The cellular-level interactions that Forget et al. (2021) highlight are particularly important because they pose a challenge evolutionary theory: some evolutionary models of social and collective behavior neglect or simplify these interactions. For example, Forget et al. (2021) note that the developmental, behavior, and environmental timescales relevant for *Dictyostelium* fruiting body formation all overlap. Evolutionary analyses often assume some of these timescales, for example developmental and behavior, are separate in order to simplify the analysis of any interactions. Thus, new theoretical work that allows these timescales to overlap may shed light on how cellular-level interactions can produce environmental, physiological, and behavioral feedbacks that drive the evolution of cooperation and other collective behaviors.

References

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Revision round #1

2020-11-12

Social conflicts in Dictyostelium discoideum : a matter of scales

In this manuscript, the authors describe two different conceptual perspectives for understanding the evolution of aggregation and collective behavior in the social amoeba *Dictyostelium discoideum.* The first perspective is the "strain-level" where empirically strain frequencies are used to determine the success of cooperative (less spore bias) or non-cooperative (more spore bias) strategies. The second perspective is the "cell-level" where individual cell fates, spore or stalk, are affected both local biotic and abiotic conditions and by stochastic forces. The paper has a lot of excellent detail about how aggregation and cooperation in *Dictyostelium* functions and might be evolutionarily stable. The "cell-level" perspective highlights a number of important mechanisms that contribute to spore or stalk bias including the cell-cell signaling, cell position,

and cell-cycle stage. These mechanisms suggest there is important and understudied complexity in the experimental results of chimeric mixtures and suggest evolutionary models must account for these mechanistic details in order to truly describe how aggregation evolves and is maintained in *Dictyostelium* lineages.

Two reviewers have read the manuscript and agree that preprint is interesting and provides a valuable perspective. They provides a few important areas for improvement that I think the authors should consider. One area that I would like to highlight specifically is the reviewer's comments about the "the balance of arguments in favor of the strain- level vs. the cell-level perspective". I agree here with the reviewer that manuscript reads a bit more as an exposition on the importance of the cell-level perspective and less of a full comparison of the benefits and drawbacks of both approaches. I also agree that simply signaling this goal earlier in the paper would be a good way to address this issue.

One place that I think the manuscript needs more substantial modification is in its description of the mathematical theory in relationship to the strain vs cell-level perspective. On page 9 in section 3, the authors suggest pure strategy models are sufficient for the strain-level perspective and mixed strategy models are necessary for the cell-level perspective. In actuality, the cell-level perspective doesn't necessitate the use of mixed strategies any more than the strain-level does. A pure strategy can be deterministic or probabilistic. In fact, many models of cooperation use a continuous variable to measure the level of cooperation, which conceptually is no different than if that same variable measures a continuous probability of cooperating. Mixed strategies become relevant when one considers the possibility of a mixture of discrete pure strategies. But in many cases this is indistinguishable from a continuous of pure strategies where the strategy is a probability. The second issue on page 9 is that the paragraph suggests that simply by using a mixed strategy, certain models allow coexistence of different behaviors (stalk vs spore I assume). However, these models really show an equilibrium with both behaviors because they setup a game that is no longer a simple prisoner's dilemma (PD); rather, these games are likely snowdrift (SD) games where a mixed strategy or intermediate value is stable. In other words, its the change of the game structure in these models, not their consideration of mixed strategies per se, that leads to coexistence. This applies to n-players games too where some n-players games result in PD like games and others have nonlinearities that lead to SD like outcomes, but being an n-player game per se doesn't result in nonlinearities (e.g., "Such games naturally introduce frequency-dependent payoffs and non-linearities" on page 10). In a few other places the authors suggest that multiplayer games add additional complexity that requires new game theoretic approaches rather than traditional deterministic approaches (the paragraph on page 21 starting "In evolutionary game theory"). This also isn't true (see for example Peña et al 2014 J Theor Biol and Peña and Nöldeke 2015 J Theor Biol). In general, the authors should take more care about connecting any specific feature of the strain or cell perspective to a technical limitation of a specific game theoretic approach or model; its much more likely that specific models made specific biological assumptions such as regarding the payoff structure of the game the organisms play that resulted in the model's predictions rather than a specific technical aspect of the model analysis.

Specific comments

- Page 5: "many rounds of the game". In evolutionary game theory, this really is many generations.
- Page 5: "cost" and "benefit" should be qualified by "fitness" (i.e., fitness cost and fitness benefit).
- Page 6: where citing Fletcher and Doebeli 2009, the authors should also cite Queller 1992 Evolution.
- Page 7: "assemble locally" should be "assemble from locally".
- Page 9: "still contrasted". Not clear what this means.
- Page 12: "lead Maeda" should be "led Maeda".
- Page 13: "back of the slug" and "rear form the stalk". What is different between "back" and "rear"?
- Page 17: "Fruiting bodies with large heads may be more prone to collapse and would then reduce the potential to disperse of both strains, thus undercutting the reproductive success of the cheater itself." This kind of feature is exactly what sets up the payoffs for a SD game instead of a PD game!

- Page 18: "allows to" should be "allows us to".
- Page 18: "Variation...respectively. I don't think this is an accurate description of the indirect genetic effects approach.
- Page 19: "statistical description of the outcome of interactions does not inform on the underlying processes.". This seems to reference multilevel selection or kin selection approaches. These approaches are not purely statistical and usually do build on mechanistic biological assumptions.
- Page 21: "In evolutionary game theory...processes". I'd ditch this whole paragraph.
- Page 22: "allow nowadays" should be "allow us nowadays"

Additional requirements of the managing board:
As indicated in the 'How does it work?' section and in the code of conduct, please make sure that:
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Preprint DOI: 10.20944/preprints202008.0554.v1

Reviewed by [Peter Conlin](), 2020-10-22 17:00
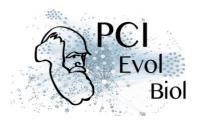
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Reviewed by [Matthew Herron](), 2020-10-15 06:07

The preprint contrasts two approaches to modeling social conflicts in the social amoebae, one based on strain-level descriptions and one based on cell-level descriptions. Numerous examples are given of cell-level processes that might, if ignored, mislead evolutionary predictions based on strain-level models. This is an important distinction, and as such the preprint makes a valuable contribution. In addition, descriptions of aggregation behavior, mechanisms, and genetics are sufficiently thorough that the preprint serves as an adequate review of these aspects of Dictyostelium biology aside from its central argument. Depending on the authors' goals (and possibly on the journal they might submit it to), these descriptions could be substantially shortened without undermining the preprint's central message.
In the Discussion the authors briefly address the conditions under which the cell-level approach is likely to yield different evolutionary predictions than the strain-level approach, and this is one point that I think would be worth expanding on. Doing so could also be left as a future direction, but formally defining the conditions or assumptions under which the two approaches yield equivalent predictions would substantially increase the value of the work.

Minor comments:
Introduction, paragraph 1: "defended by predators" should probably be "defended against predators".
Introduction, paragraph 3: the abbreviation cAMP has not previously been used and should probably be

spelled out here. Introduction, paragraph 4: "Giving up one's own descent" is an unusual wording, and I'm not sure it conveys the authors' intent. "Giving up one's own descendants" might be preferable.

Introduction, paragraph 6: the cheating strategy in game theory is usually referred to as "defect" rather than "defective". Section 2, paragraph 3: it may be worth noting that the Fletcher & Doebeli model breaks with the foregoing description of kin selection in that cooperators need not share an allele at a particular locus, i.e. it does not require identity by descent.

Last paragraph in the 'genetic assortment' section: social amoebae biologists probably understand the significance of washing whole dishes before spore count, but I don't. 4th paragraph of the Cell phenotype through development section: "cells at the back of the slug tend to turn into spores, whereas most of those at the rear form the stalk." I suspect one of these should refer to the front.

Author's reply:

[Download author's reply (PDF file)](#)