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Comment

Mathematical approaches or agent-based methods? Comment on “Evolutionary game theory using agent-based methods” by Christoph Adami et al.

Corina E. Tarnita

Department of Ecology and Evolutionary Biology, Princeton University, Princeton, NJ 08544, USA

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1. Introduction

Adami et al. [1] review approaches and results obtained within the evolutionary game theory framework and raise a very important question: how much is our understanding of certain phenomena constrained by our ability to write the equations and do the analytics for those phenomena? Using compelling examples, Adami et al. [1] argue that many realistic biological scenarios are often left unstudied due to a lack of a theoretical methodology or the ability to obtain mathematical solutions; they suggest that agent-based simulations are the way to go in those cases, with mathematics being used primarily as a validation tool in the limiting cases where it is feasible.

It is certainly the case that some limits (e.g., weak selection, weak mutation) have been studied disproportionately due to their mathematical tractability. Numerical solutions and simulations for the broader parameter range (e.g. non-weak selection, non-low mutation) have convincingly shown that the intuition built in the limiting cases can be insufficient or even misleading for the understanding of non-limiting cases [1,2]. However, although I agree with the authors that our exploration of realistic biological scenarios should not be limited by the feasibility of mathematical solutions and that agent-based methods reinforced by analytical solutions of limiting cases offer a very powerful way to move forward, I caution that in some cases in which mathematical solutions seem infeasible, this simply reflects a state-of-the-art of our mathematical techniques rather than a provable impossibility of developing new mathematical approaches (or adopting existing ones from other fields) that might allow for mathematical solutions.

That our mathematical techniques evolve to address what at earlier times seemed mathematically infeasible is in many ways already apparent from the review by Adami et al. [1]: although the original formulation of evolutionary game theory only considered infinite well-mixed populations and Evolutionarily Stable Strategies, subsequent advances introduced new measures (e.g., fixation probabilities) to allow the study of finite, not necessarily well-mixed (i.e. structured) populations [3–5]. And it is in fact also true of the main limitation identified by Adami et al. [1], the case of non-weak mutation. When mutation is not weak, strategies do not reach fixation and therefore other measures need to be introduced to explore the dynamics. One possibility in this case is to look at the stationary distribution of such a process (when selection and mutation balance each other out) and determine the abundances of the different

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strategies, which are then compared to their abundances in the absence of selection. To make this concrete, let x be the frequency of one such strategy; we say that this strategy is selected for if

$$\langle x \rangle > \langle x \rangle_0 \quad (1)$$

where $\langle \cdot \rangle$ denotes the average taken over the stationary distribution and $\langle \cdot \rangle_0$ denotes the same average but of the process in the absence of selection. This inequality measures the change in the long-term allele frequency as we move from the neutral equilibrium to the new equilibrium, which balances selection, drift and mutation. This comparison can be employed for any mutation and any intensity of selection. When there are only two strategies (1 and 2 with frequencies x_1 and x_2) it has been shown that in the limit of weak mutation, inequality (1) is equivalent to the familiar comparison of the two fixation probabilities [5], i.e.:

$$\lim_{u \rightarrow 0} \langle x_1 \rangle > 1/2 \iff \rho_1 > \rho_2, \quad (2)$$

a measure employed to determine which strategy is favored over the other. The general inequality (1) applies to both deterministic [6] and probabilistic [7] strategies and it can, for certain processes, be evaluated for any mutation rate. Analytical results have been obtained for any mutation rate for finite well-mixed populations [6,7] as well as for some finite structured populations [8–10], albeit only in the limit of weak selection.

Although there are other important aspects of strategy dynamics and, surely, for some we still lack a mathematical approach, the study of strategy selection via the use of abundances in the stationary distribution offers an example of a new mathematical approach to previously mathematically intractable cases. Since the cases that are challenging mathematically tend to correspond to increased complexity of the phenomena studied and, consequently, to increased complexity of the simulation outcomes, a search for mathematical approaches that can help untangle and interpret those outcomes is most pressing *precisely* in those cases. Therefore, while indeed finding a mathematical approach might not always (or even often) be possible, it is always worthwhile searching for, although not necessarily waiting for.

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