LETTER

Reply to Gerlee and Altrock: Diffusion and population size in game theory models of cancer

Evolutionary game theory can help explain the dynamics of growth factor production by cancer cells as an example of cooperation for the production of a public good. The diffusion range of the growth factor determines the size of the group of cells sharing the public good. We tested the predictions of the theory using cells producing insulin-like growth factor II (IGF-II) (1).

Gerlee and Altrock (2) comment that "nowhere in the article is group size justified empirically" and, based on their "approximation of the diffusion coefficient of IGFs (10^{-6} cm^2/s)," they suggest that IGF-II will diffuse to the whole population, which "would invalidate the model" (because "producing is selected against in large populations"). We are puzzled by these comments. Growth factors like IGF-II bind to cell surface receptors as they diffuse from the source, leading to a limited effective diffusion range, which also depends on complex (and not fully understood) interactions with IGF binding proteins. We are not aware of the value reported by Gerlee and Altrock (who provide no justification and no reference). Instead of choosing a specific diffusion range, in the original paper (1) we show results for different possible values. Our model does predict that when the diffusion range (hence group size) is large enough, the producer cells will go extinct (figure 5 in ref. 1; we only need to assume that diffusion range is large enough, not necessarily that the growth factor diffuses to the whole population). This group-size effect is what Gerlee and Altrock (2) suggest and is well known in the theory of public goods. In some of our experiments, the producer cells indeed go extinct. We do not see, therefore, why the model would be invalid.

Gerlee and Altrock (2) also suggest that "the proposed model might behave differently if the population size is allowed to increase." As we show in figure S4 of ref. 1, however, there is no significant difference at equilibrium when population size increases.

Finally, Gerlee and Altrock show (in figure 1 of ref. 2) a case in which a single unstable mixed equilibrium occurs, and they seem to imply that this contradicts our results. The same result occurs in our model, however (figure S2 in ref. 1; high values of h), and is easily explained by models of nonlinear public goods (see figure 2D in ref. 3). It is not clear what Gerlee and Altrock (2) mean by "the ratio of growth rate production rate over growth rate consumption rate"; if, based on their definition of $\gamma = \rho/\delta$, they mean "the ratio of growth *factor* production rate over growth *factor* consumption rate," their figure seems to show that a mixed equilibrium would occur for a larger diffusion range (which contradicts the argument about group size). Therefore, we are not sure what the issue is here.

Surely it seems hasty to conclude that evolutionary game theory "should not be applied generally for understanding tumor growth dynamics" (2). Game theory is not "heuristic"; it has led to precise and applicable results that are recognized as fundamental in other fields (4). If used properly, there is no reason why it could not be applied to the study of cancer dynamics.

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1 Archetti M, Ferraro DA, Christofori G (2015) Heterogeneity for IGF-II production maintained by public goods dynamics in neuroendocrine pancreatic cancer. *Proc Natl Acad Sci USA* 112(6): 1833–1838.

2 Gerlee P, Altrock PM (2015) Complexity and stability in growing cancer cell populations. *Proc Natl Acad Sci USA* 112:E2742–E2743.

3 Archetti M, Scheuring I (2012) Review: Game theory of public goods in one-shot social dilemmas without assortment. *J Theor Biol* 299:9–20.

4 Economic Sciences Prize Committee of the Royal Swedish Academy of Sciences (2014) Scientific Background on the Sveriges Riksbank Prize in Economic Sciences in Memory of Alfred Nobel 2014: Jean Tirole: Market Power and Regulation. Available at www.nobelprize.org/nobel_prizes/economic-sciences/laureates/2014/advanced-economicsciences2014.pdf. Accessed March 29, 2015.

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