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Letters Response

Response to Goldman and Brown: Making sense of microbial consortia using ecology and evolution

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In their commentary on our review, 'Engineering microbial consortia: a new frontier in synthetic biology' [1], Goldman and Brown [2] encourage a synthesis that makes complete sense – the field of evolutionary and ecological theory has great potential to inform the design of engineered microbes and microbial consortia. The authors also raise several issues that allow us to clarify some points that we made in the review.

Goldman and Brown emphasize that the evolutionary outcomes of the simple engineered systems in Figures 2–4 of our review are easy to predict, and social evolution theory is helpful in making such predictions. As we emphasize in the review, these synthetic consortia highlight the different types of ecological interactions that can be implemented in principle. In none of the examples did the engineers attempt to make the consortia genetically stable; on the contrary, they might have purposefully used effectors with dramatic negative survival effects to demonstrate the designed function more clearly. For instance, Balagaddé *et al.* [3] specifically chose a more toxic version of the CcdB protein in the predator–prey system to promote population oscillations. All of the organisms in these examples gain great evolutionary advantage by mutating to escape the engineered control. As suggested by Goldman and Brown, future design and optimization of these types of gene circuits will benefit from the application of evolutionary theories.

Goldman and Brown stress that predicting the evolutionary outcomes of engineered microbial consortia will require 'careful classification of the nature of the underlying traits' of the consortia. It might be true that 'artificial assemblages of engineered organisms are less likely to display the robustness associated with natural, diverse assemblages'. Elucidating the limitations of artificial assemblages will require unambiguous definition of 'robustness' and more controlled studies in future research. The ability to design robust synthetic consortia for applications is contingent upon full classification of the natural environments in which the consortia will be used. Such classification will require new work to predict evolutionary trajectories of large mixed populations in complex environments through time. Toward this end, simple model systems in manipulable environments constitute a starting point for productive collaboration among ecological and evolutionary theorists, microbiologists and synthetic biologists. If natural consortia are more robust, perhaps evolutionary theorists and microbiologists can identify natural consortia that might be amenable and stable to engineered change by synthetic biologists. This echoes the 'top down' engineering approach proposed by Goldman and Brown, and it underscores the need, as we state in the review, for extension of techniques like directed evolution to enable fine-tuning of the performance of mixed populations.

Goldman and Brown take issue with our definition of 'communication' between microbes. By speaking of various modes of interaction between microbes as 'communication', we do not claim that each mechanism poses the same evolutionary dilemma for a population. Here, 'communication' refers to the category of physical interactions in which the source, carrier and receiver of the information are identifiable. Further analysis of evolutionary outcomes will require classification within this broad category.

Overall, we appreciate the enthusiasm of Goldman and Brown in suggesting that ecological and evolutionary theory might be brought to bear on the problems associated with engineering microbial consortia, and we look forward to fruitful collaboration between these fields in the future.

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