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### Author

Kryazhimskiy, Sergey

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# A simple rule for predicting function of microbial communities

Sergey Kryazhimskiy<sup>1,\*</sup>

<sup>1</sup>Department of Ecology, Behavior and Evolution, University of California San Diego, La Jolla, CA, USA

\*Correspondence: [skryazhi@ucsd.edu](mailto:skryazhi@ucsd.edu)

**Microbial communities perform many important functions, such as carbon sequestration, decomposition, pathogen resistance, etc., but quantitatively predicting functions of new communities remains a major challenge. In this issue of *Cell*, Diaz-Colunga et al report a new simple statistical regularity that enables such predictions.**

How much carbon will marine microbes fix as Earth's climate changes? How do we boost the ability of the gut microbiome to resist invading pathogens? How do we set up industrial bioreactors that maximize biofuel production? To answer this type of questions, we need to understand how the environment structures microbial communities and how community structure determines their function. The study by Diaz-Colunga et al in this issue makes an important advance towards solving the latter problem<sup>1</sup>.

A major challenge with understanding the structure-function relationship in community ecology is that we do not know how community members interact with one another and how these interactions affect species abundances, phenotypes and behavior. Ecologists have been tackling the problem of interactions for over a century and have developed a rich body of theory for pairwise interactions<sup>2</sup>, which usually works well for small communities<sup>3</sup>. However, extending this approach to communities with dozens or hundreds of species—which is relevant in many ecosystems—is not straightforward because models quickly become intractable. Imagine a community with 20 species. To describe all pairwise interactions, one would need on the order of  $20^2 = 400$  parameters. This is already a lot. But recent empirical studies found that pairwise interactions can be modulated by the presence of other species, their abundances or phenotypic states, i.e., there are “higher-order” interactions<sup>4</sup>. To account for all possible higher-order interactions, one would need on the order of  $2^{20} \approx 10^6$  parameters to describe a 20-species community. With such exponential explosion of parameters, it becomes tricky to even simulate large communities, let alone experimentally measure all relevant quantities.

The problem of deciphering the structure-function relationship in ecological communities may seem hopeless. But Diaz-Colunga et al uncover a surprisingly simple path forward, using a statistical approach. Instead of painstakingly measuring all interactions in their experimental system, which consists of eight soil bacteria, they first assemble various “background” communities containing subsets of these species. They measure the

resulting background community function, which in this case is the production of pyoverdines, a class of molecules secreted by some of these bacteria. The next step is crucial. They add each of the eight species to those background communities where this species is absent and measure how each such “species addition” changes the function. Then, Diaz-Colunga et al plot the function of the background community against functional change due to species addition (Figure 1). If higher-order interactions caused pyoverdine production to vary idiosyncratically based on the specific combination of species in the community, this plot would show a random scatter of points. Instead, the authors find that the two quantities are related linearly, with a slope and intercept that depend on the added species. This simple relationship implies that one can statistically predict functions of some new communities without any mechanistic understanding of the underlying interactions. The authors observe similar relationships in five other previously published unrelated microbial and plant datasets, suggesting that this phenomenon is general.

The authors’ approach, while simple, is new in ecology. Diaz-Colunga et al developed it by analogy to an approach that recently showed some success in evolutionary genetics<sup>5,6,7</sup>. For over a century, parallel to ecologists, evolutionary biologists and geneticists have been trying to decipher how the genotype determines phenotypes and fitness, and they have waged their own battles against interactions, albeit between mutations rather than species. They recently observed that the effects of many mutations on fitness scale linearly with the fitness of the “background” genotype, which suggests that some genotype-to-fitness maps have a surprisingly simple statistical structure<sup>8</sup>. In genetics, this phenomenon is termed “global epistasis”, and Diaz-Colunga et al discovered its ecological analog.

To provide a more mechanistic interpretation for their observation, the authors turned to a recently developed genetic theory<sup>6,7</sup>. They found that species whose pairwise interactions are on average negative have a negative global-epistasis slope (Figure 1). In fact, the majority of species examined by the authors show this pattern. But a small minority, about 5%, tend to interact positively with other members and, as a result, have a positive slope, i.e., their addition improves community function with “increasing returns”. Importantly, neither genetic nor ecological global epistasis can be fully reduced to pairwise interactions. Instead, to explain these global patterns, pairwise interactions must be averaged across all genetic or ecological backgrounds. In other words, higher-order interactions matter, but knowing their average effect appear to be sufficient.

The work by Diaz-Colunga et al has important practical and conceptual implications. From the practical perspective, ecological global epistasis could become a powerful tool for predicting functions of new microbial communities or even designing communities that perform certain functions optimally. In fact, the authors provide a proof-of-principle demonstration of this application. Starting with a community whose function is known, they

sequentially add new species and compute the predicted function of new communities. The consistency of their predictions with experimental measurements is striking.

Conceptually, this work offers hope that the problem of interactions in ecology may not be as intractable as some have feared. It suggests that at least some community-level properties can be described by low-dimensional effective models<sup>9,10</sup>, despite the fact they depend on a multitude of between-species interactions, or perhaps because of this dependence. However, when and why the approach of Diaz-Colunga et al works so well requires further research. It may work only in communities where higher-order interactions are sparse or weak. Or, perhaps interactions need to be numerous and uncorrelated so that their combined effects are governed by the central limit theorem<sup>6</sup>.

Finally, the authors' discovery highlights the value and promise of interdisciplinary research. They noticed essential similarities between mathematical formalisms in ecology and genetics, took them seriously, and probed them in the lab. Interestingly, another recent work also drew upon these similarities to understand community assembly<sup>10</sup>. These studies bolster the idea that diverse complex systems—cells, ecological communities and perhaps others—share deep commonalities, whose discovery can be accelerated by interdisciplinary cross-pollination.

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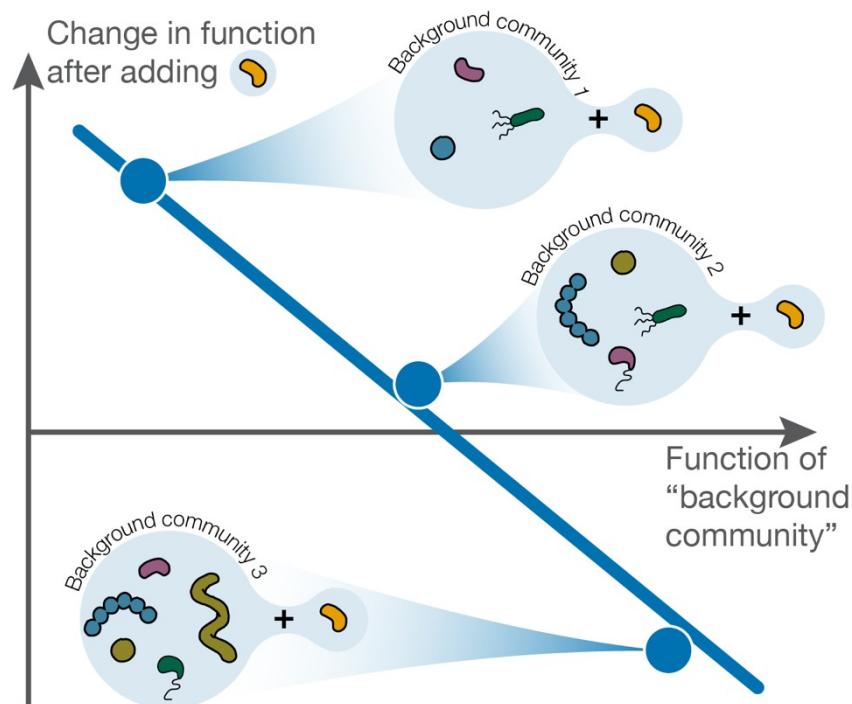
## **DECLARATION OF INTERESTS**

The author declares no competing interests.

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**Figure 1. Global epistasis in community ecology. The change in ecological function after an addition of a particular species scales linearly with the function of the “background community” to which the species is added.**