

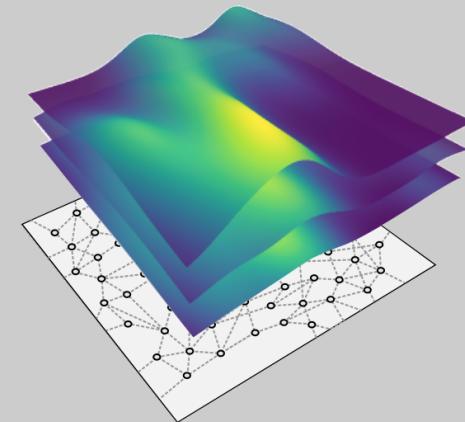
Statistical mapping of structure-function landscapes in microbiomes

Djordje Bajić

Assistant Professor

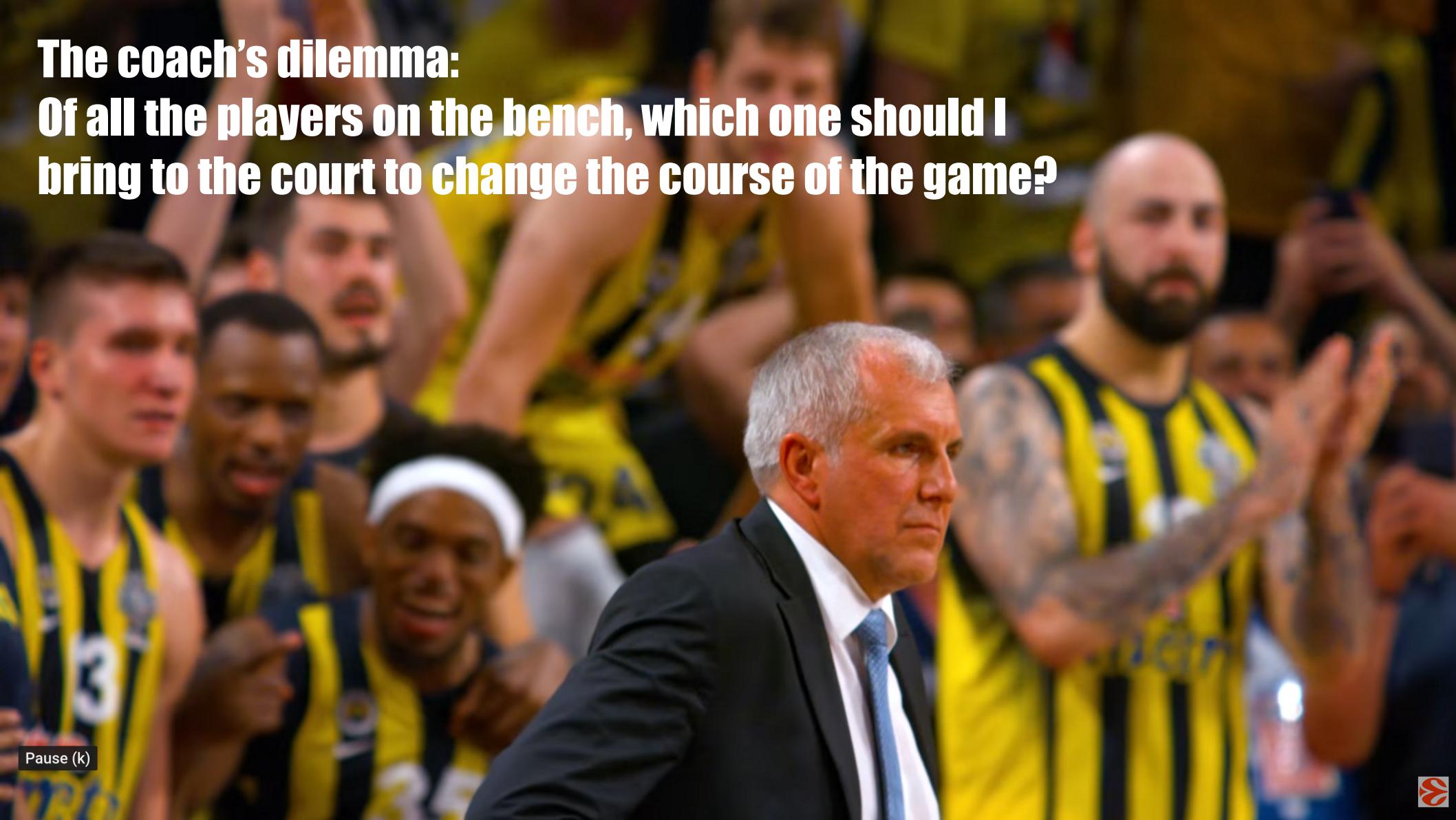
Department of Biotechnology

TU Delft

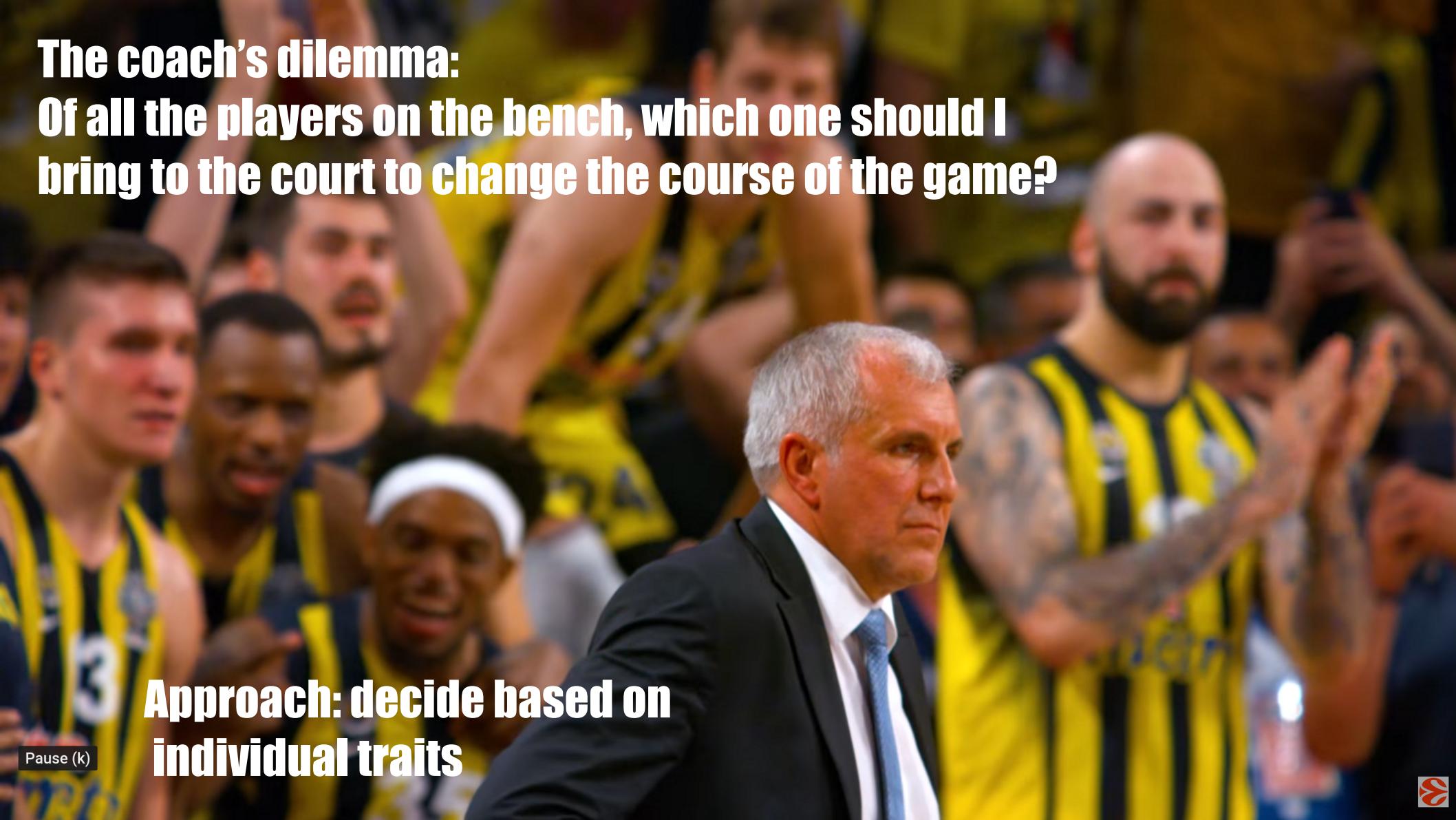


Today goals:

1. Learning what a structure-function landscape is
2. Get to know what is global epistasis
3. Touch some machine learning code
make some predictions
lose the fear ;)



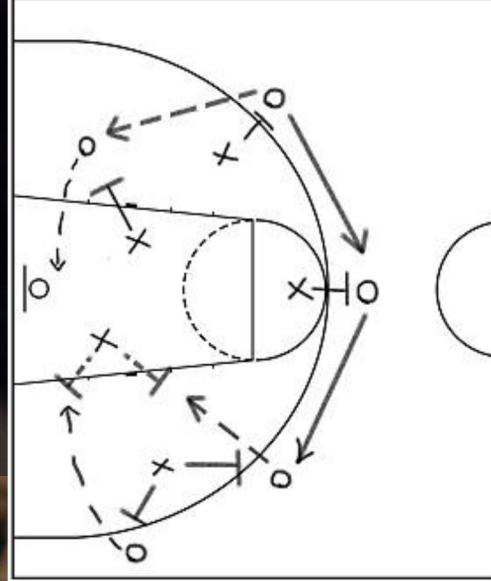
**The coach's dilemma:
Of all the players on the bench, which one should I
bring to the court to change the course of the game?**



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Of all the players on the bench, which one should I
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**Approach: decide based on
individual traits**

BUT: The contribution of a player depends on its interaction with the rest of the team!



In many systems, function arises from interacting components



Applied Soil Ecology
Volume 176, August 2022, 104503

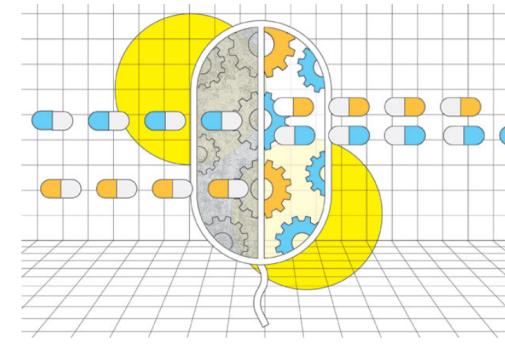
Review
Consortia-based microbial inoculants for sustaining agricultural activities

[Shams Tabrez Khan](#)

An illustration showing a cluster of diverse microorganisms, including bacteria and fungi, labeled 'N 5 μm'. To the right, three bags of 'SBF SMART BIO FERTILIZER' are displayed, with one bag labeled 'BIO COMBACT'.

Combining antibiotics changes their effectiveness

The effectiveness of antibiotics can be altered by combining them with each other, non-antibiotic drugs or even with food additives, EMBL researchers show.



Current Opinion in Chemical Engineering
Volume 22, December 2018, Pages 42-47

Media formulation optimization: current and future opportunities

[Shaun C. Galbraith¹, Hemlata Bhatia², Huolong Liu¹, Seongkyu Yoon^{1,2}](#)

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What combination of components maximizes a desired function?

SBF SMART BIO FERTILIZER

Combining antibiotics changes their effectiveness

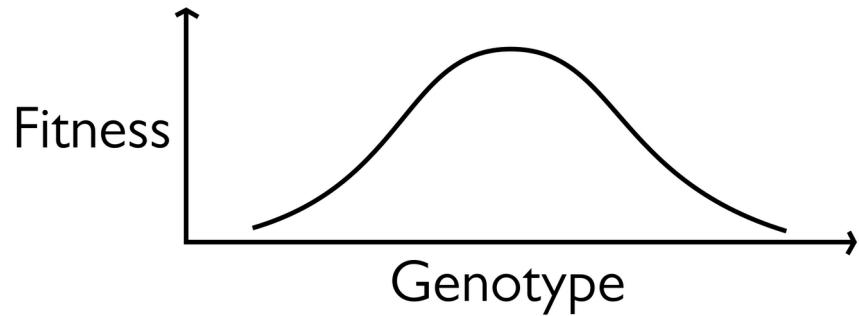
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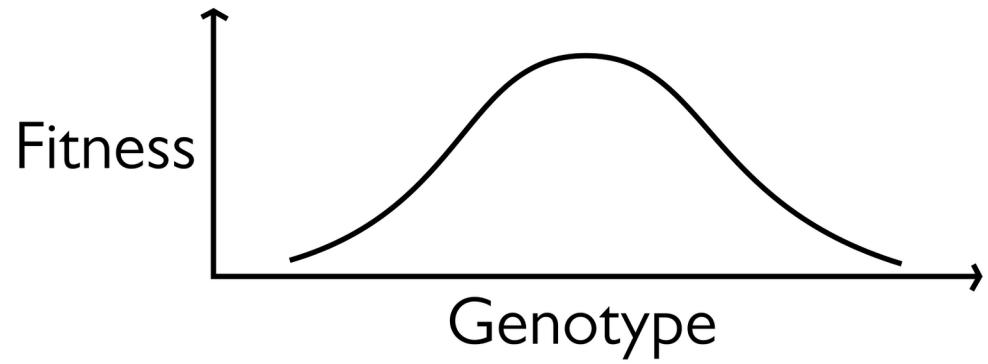
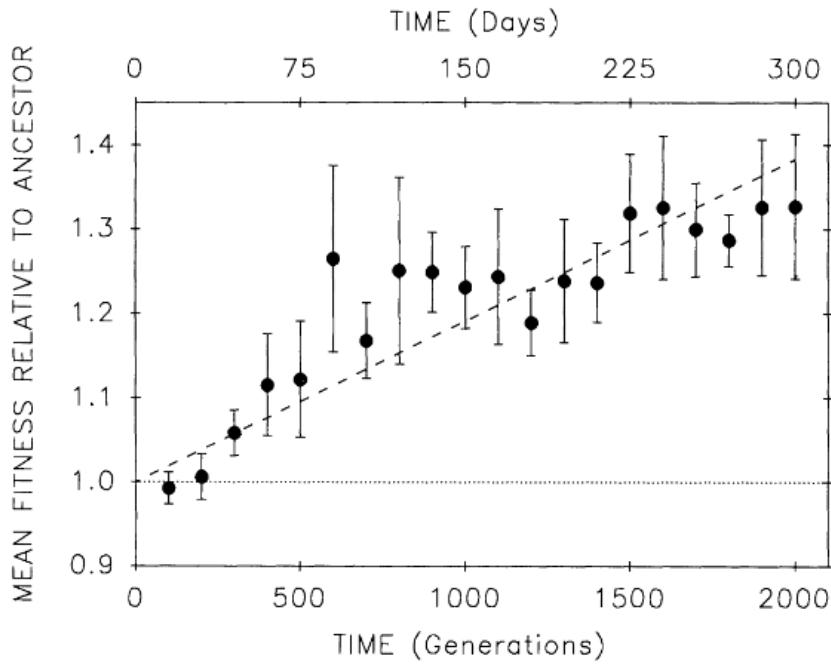
Media formulation optimization: current and future opportunities

Presenting our main tool:

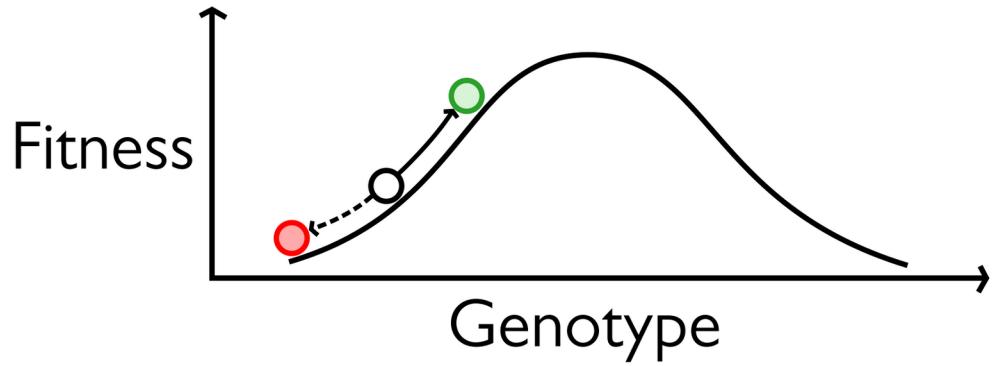
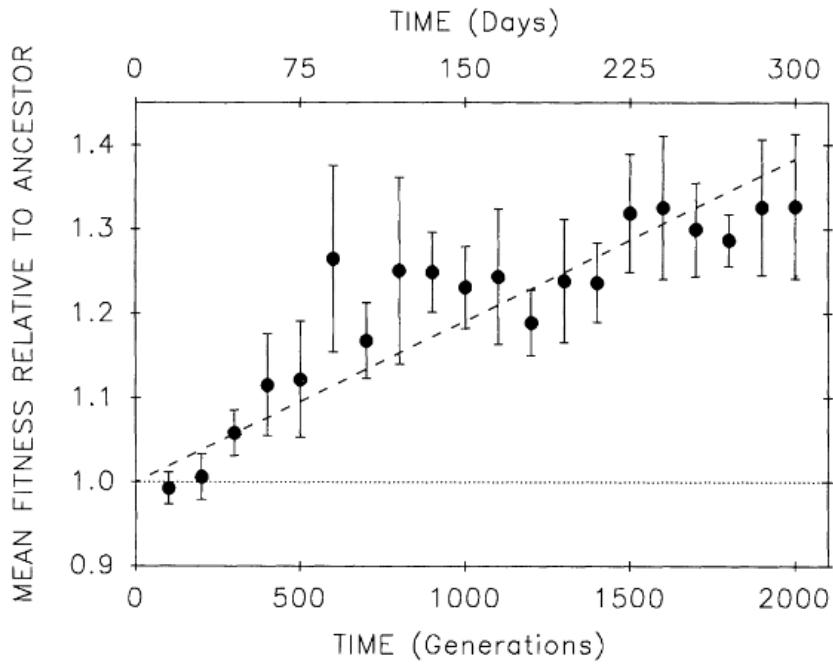
A **fitness landscape** is a map between genotypes and fitness



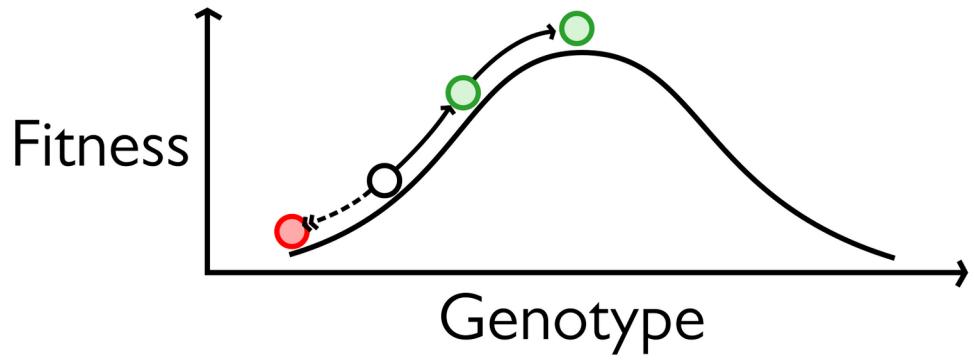
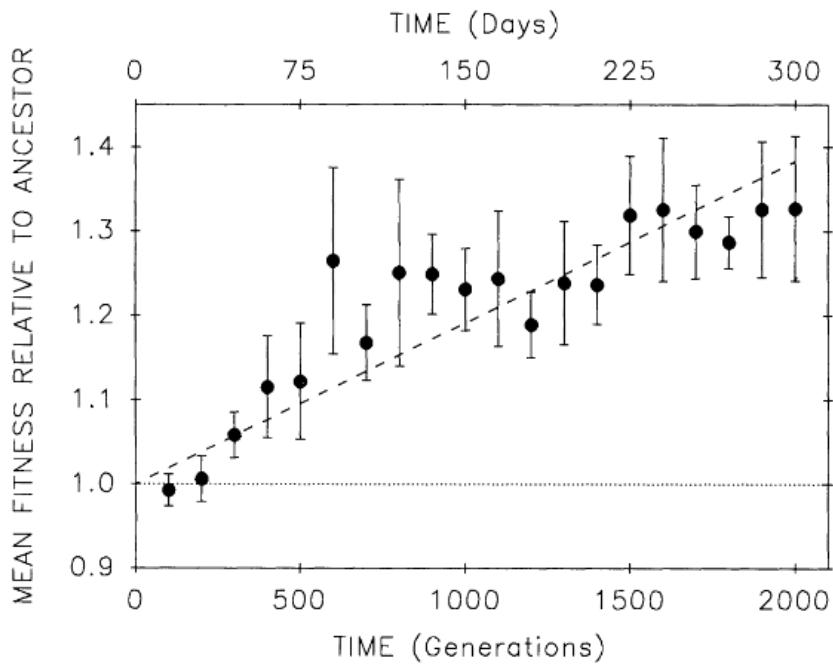
Fitness landscapes have been historically a cornerstone concept to understand and predict evolution



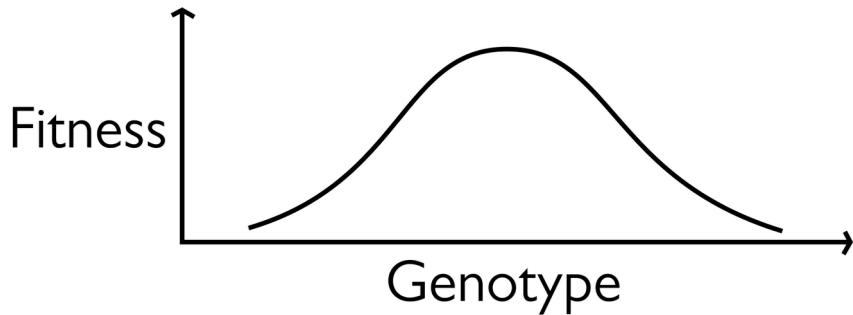
When a spontaneous mutation has higher fitness, it has a chance of fixing. Deleterious mutations get outcompeted



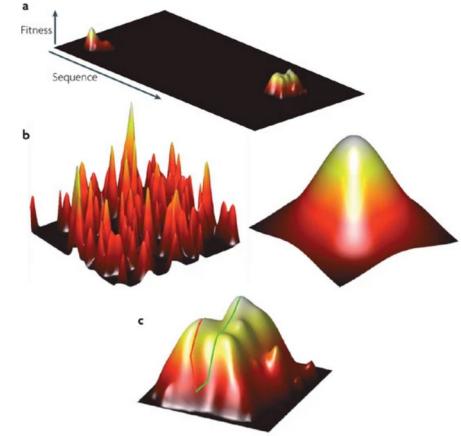
In this way, populations “climb” the peak of the fitness landscape towards genotypes with high fitness



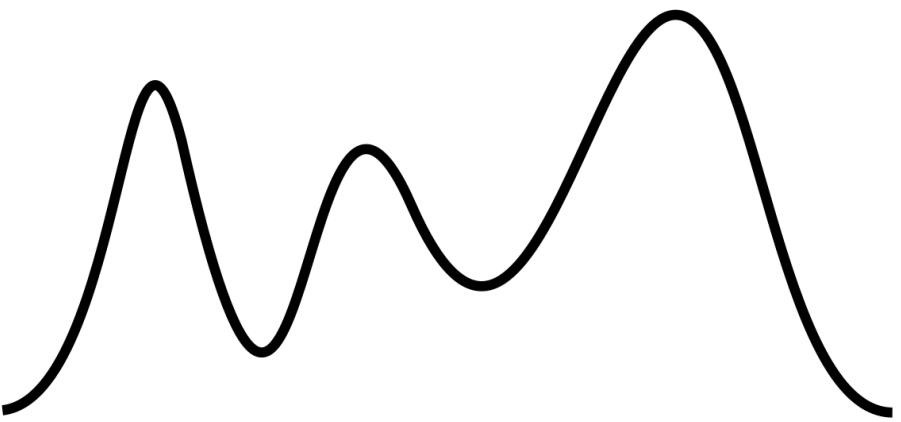
Fitness landscapes have already been useful for engineering, e.g. proteins



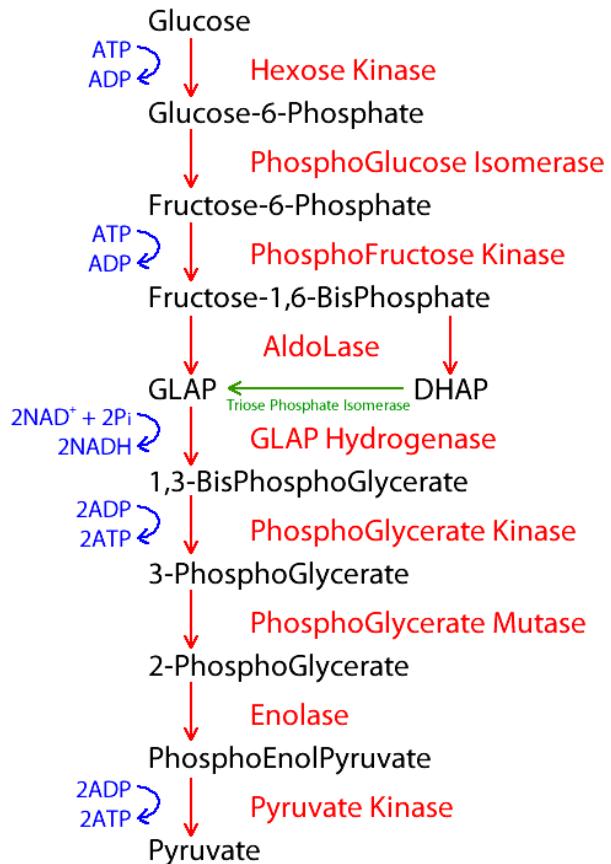
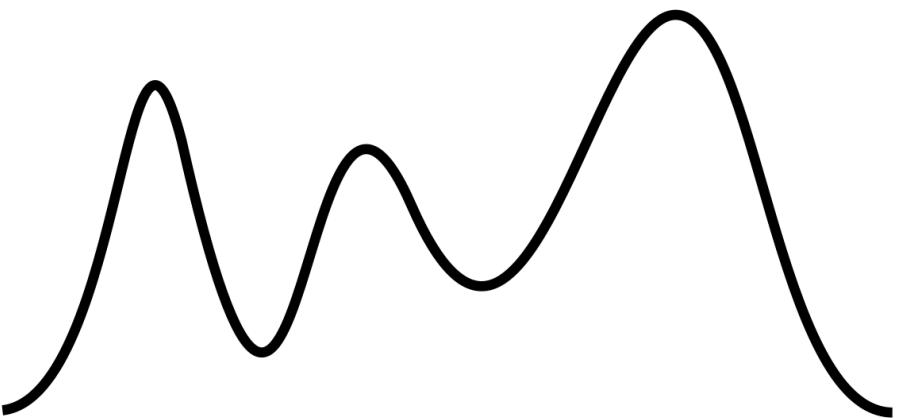
Frances Arnold, Nobel
Prize for the directed
evolution of enzymes



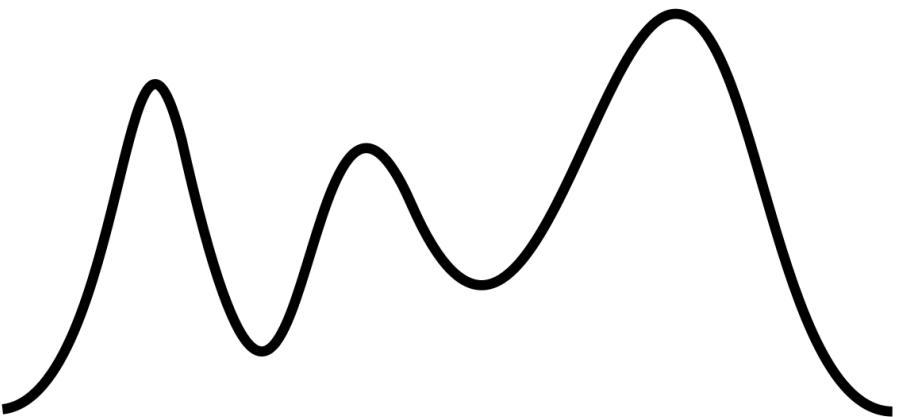
What determines the shape of a fitness landscape?



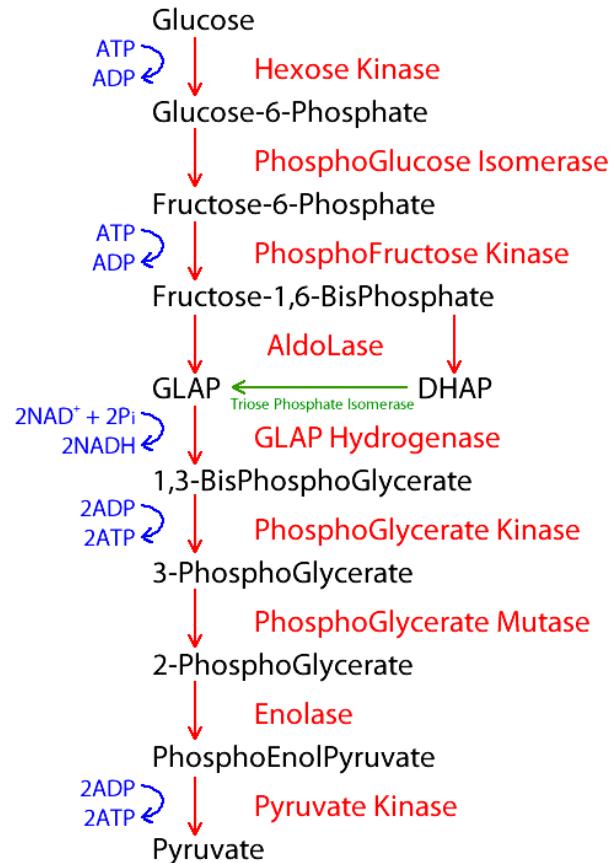
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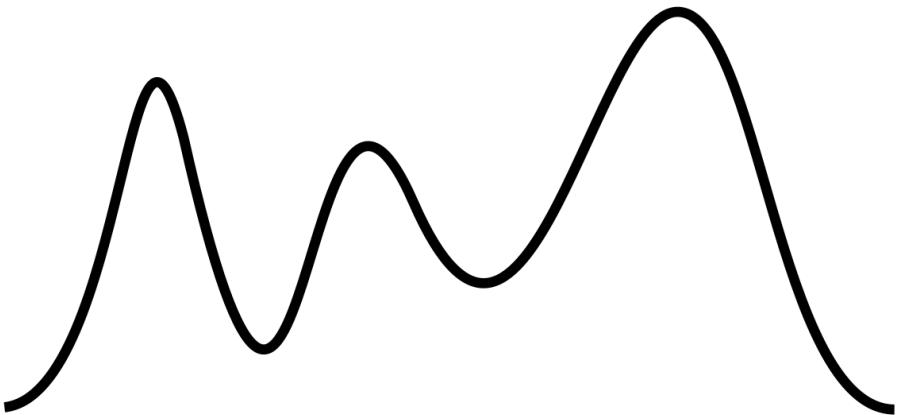
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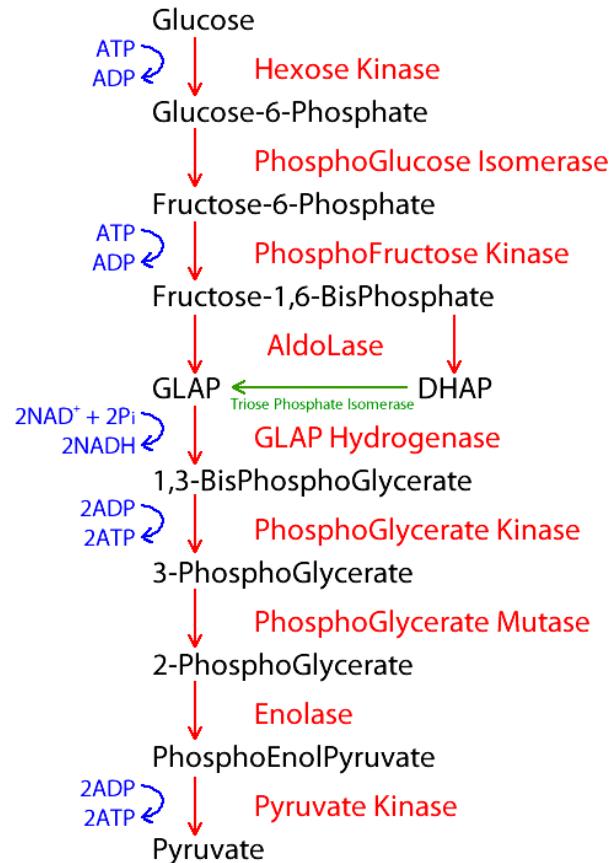
- The environment



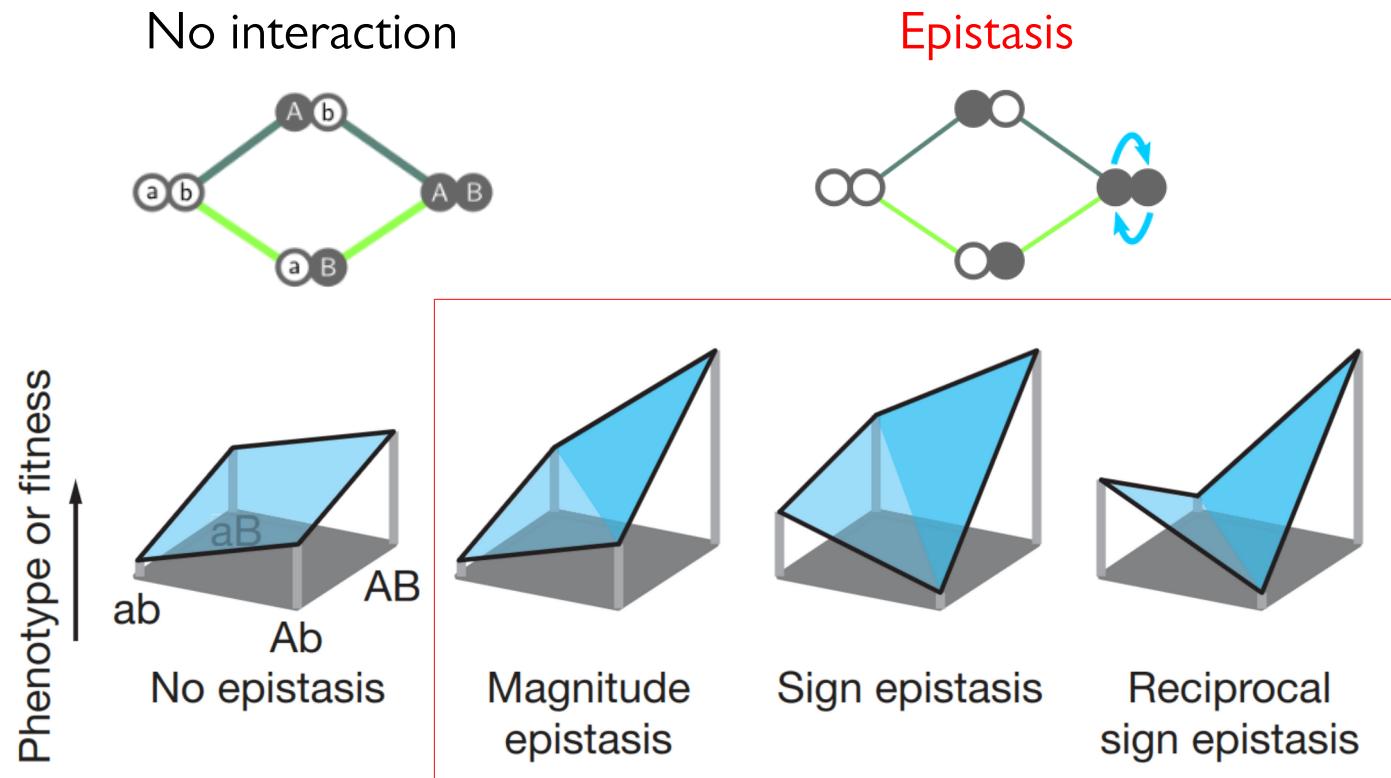
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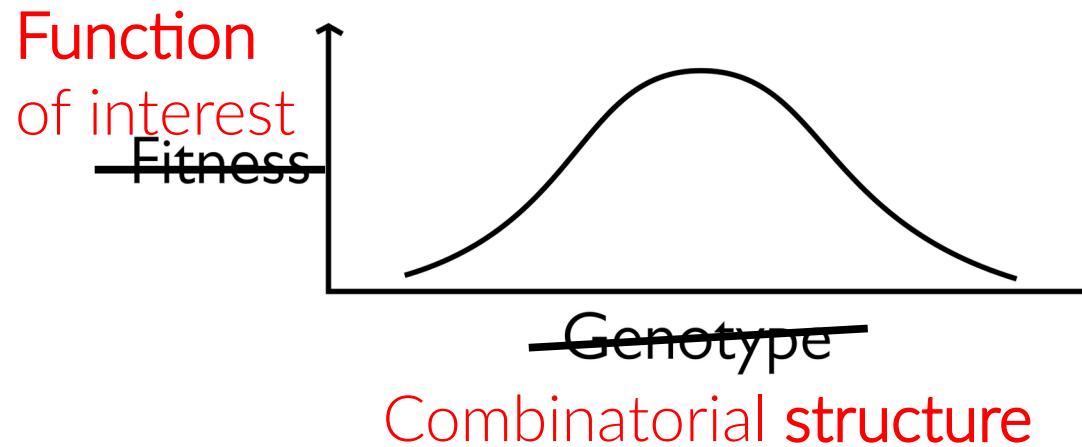
- The environment
- Interactions between mutations - **epistasis**



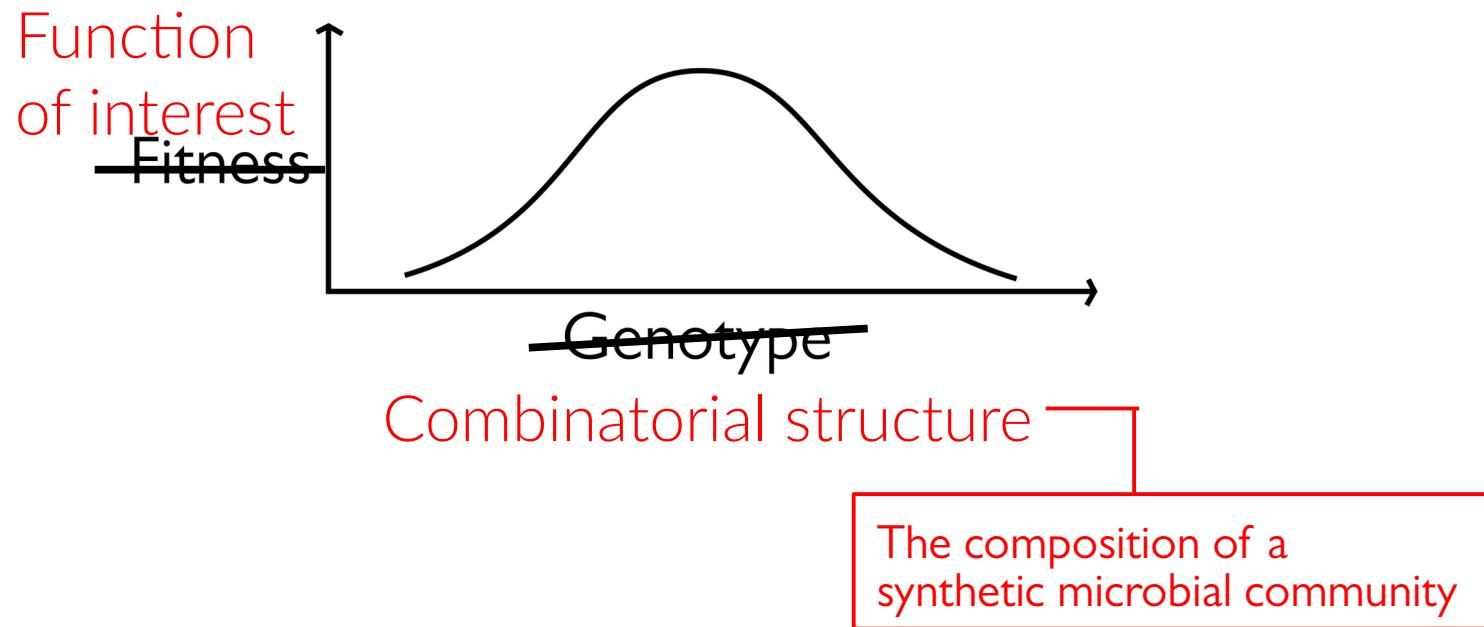
When one mutation affects the fitness of another one, we say there is an **epistatic interaction** among them



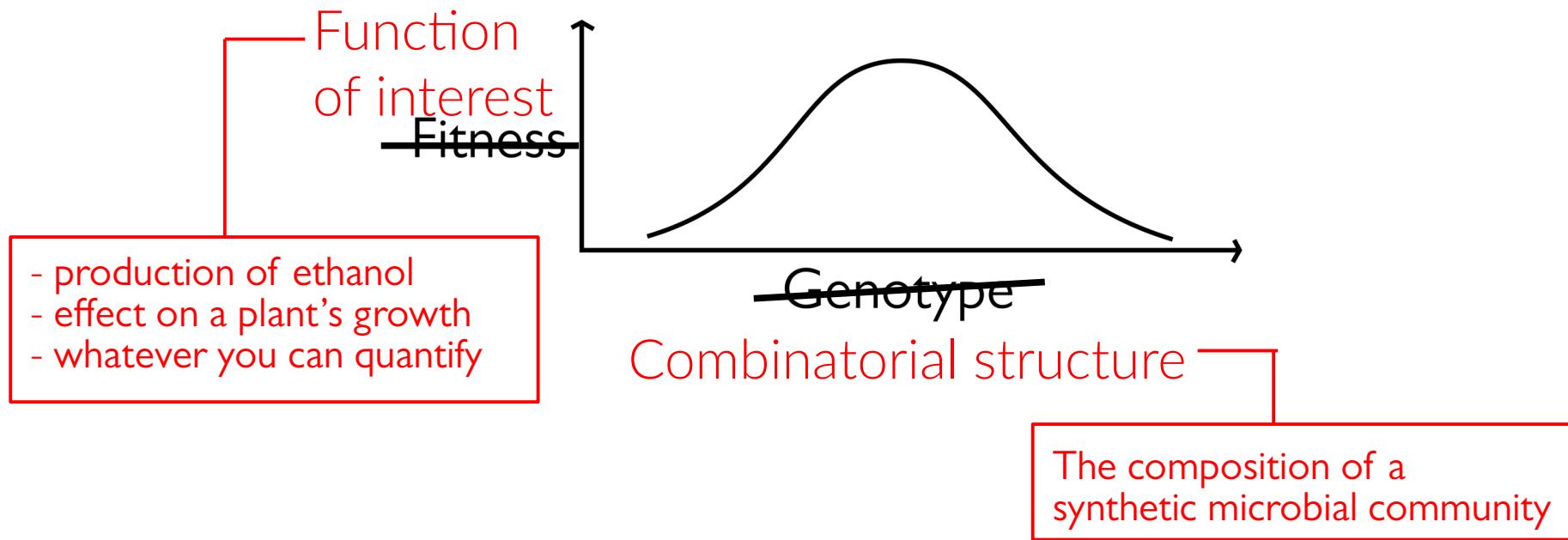
Can we extend the theory of fitness landscapes to engineer other systems with interacting components?



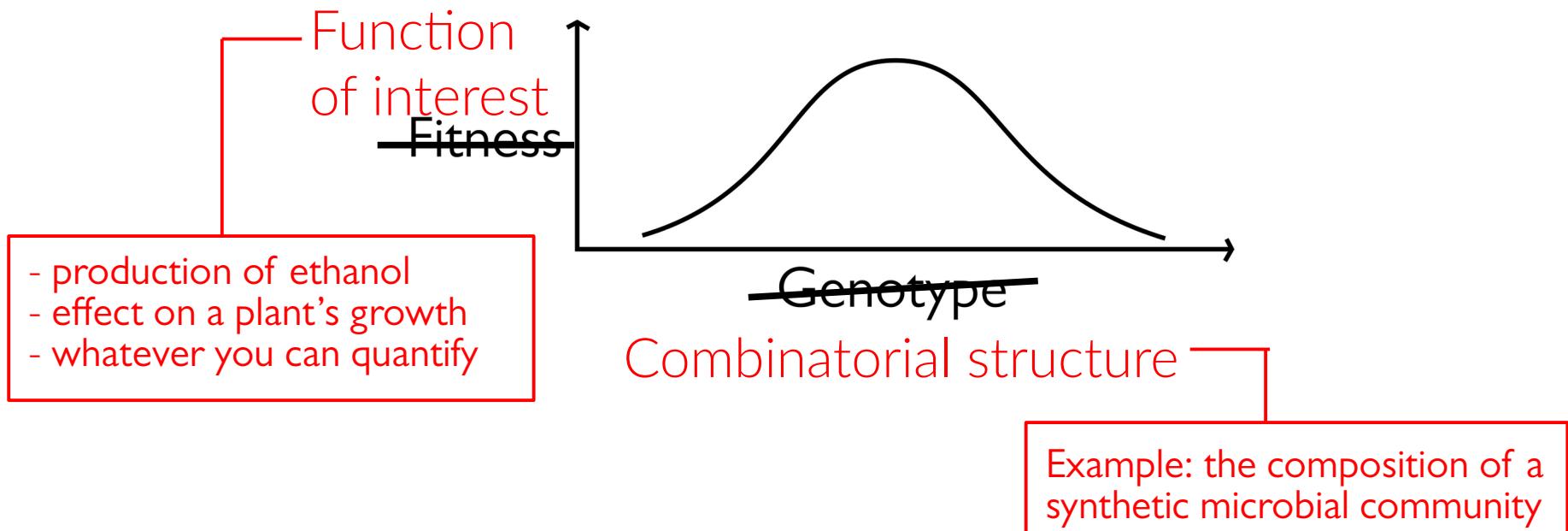
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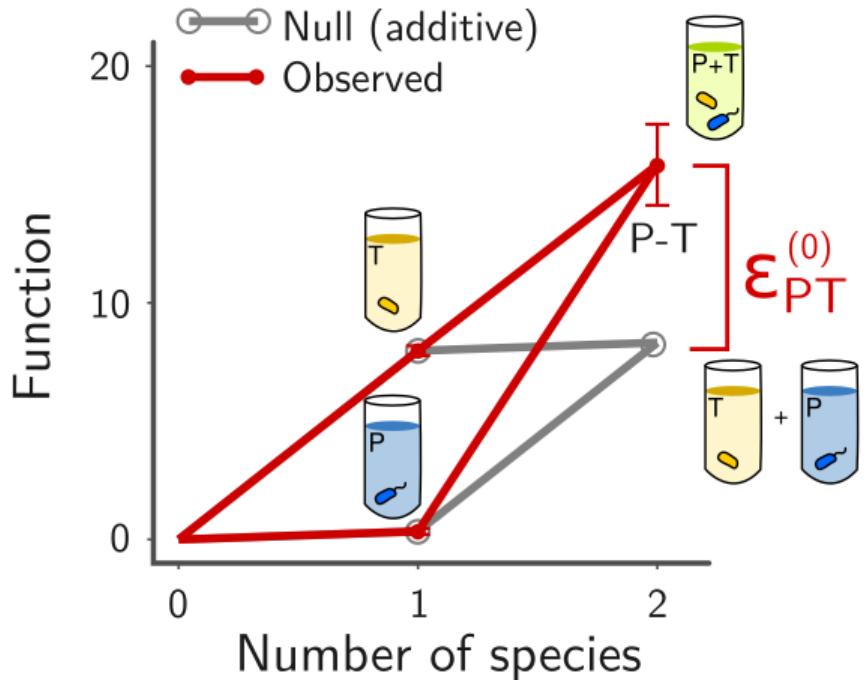
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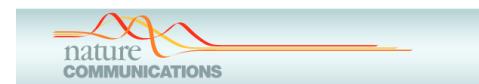
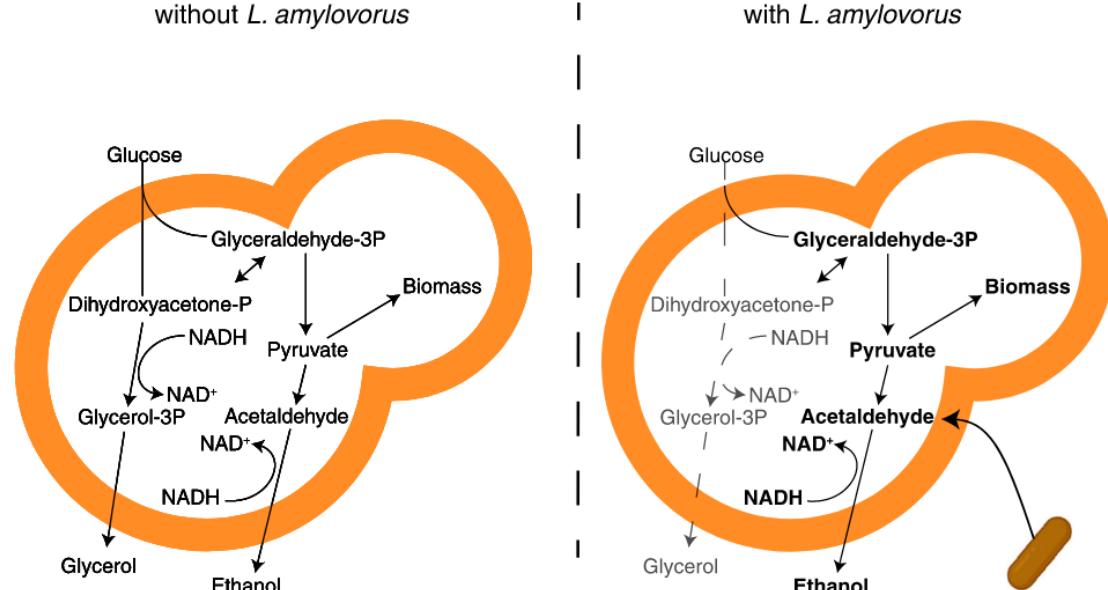
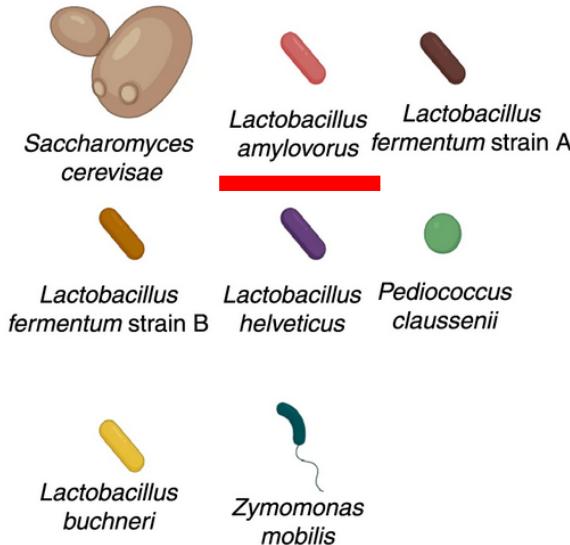
A structure-function landscape



Same as fitness landscapes, structure-function landscapes are also shaped by **interactions**



Structure-function landscape modeling helped identify a potential industrial probiotic



Complex yeast-bacteria interactions affect the yield of industrial ethanol fermentation

Felipe Senne de Oliveira Lino¹, Djordje Bajic^{2,3}, Jean Celestin Charles Vila^{2,3}, Alvaro Sánchez^{2,3} & Morten Otto Alexander Sommer¹



Felipe S. Lino

In systems where function arises from interacting components...



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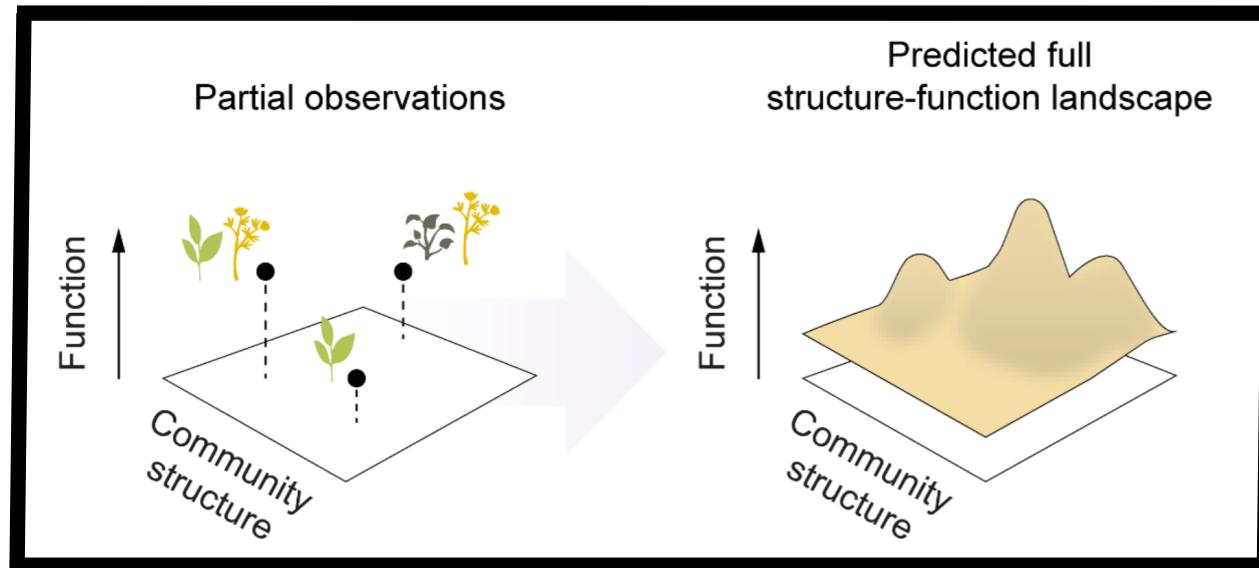


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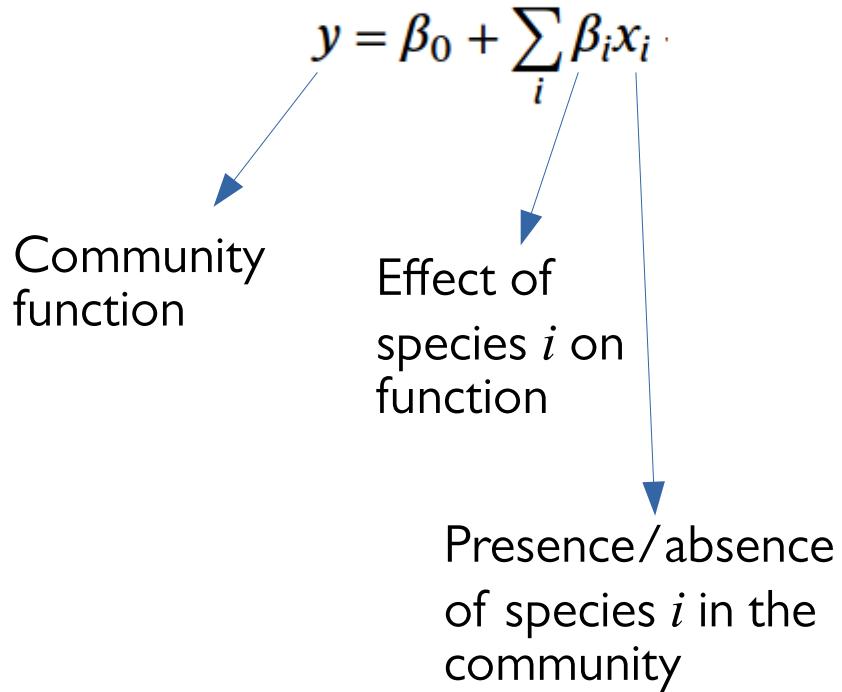
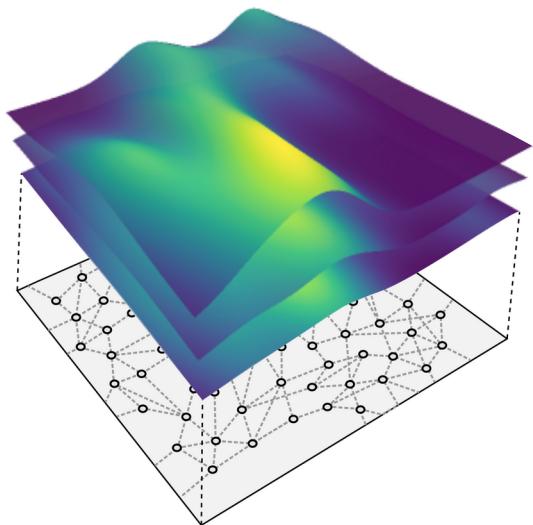
Media formulation optimization: current and future opportunities

Shaun C. Galbraith¹, Hemlata Bhatia², Huolong Liu¹, Seongkyu Yoon^{1,2}

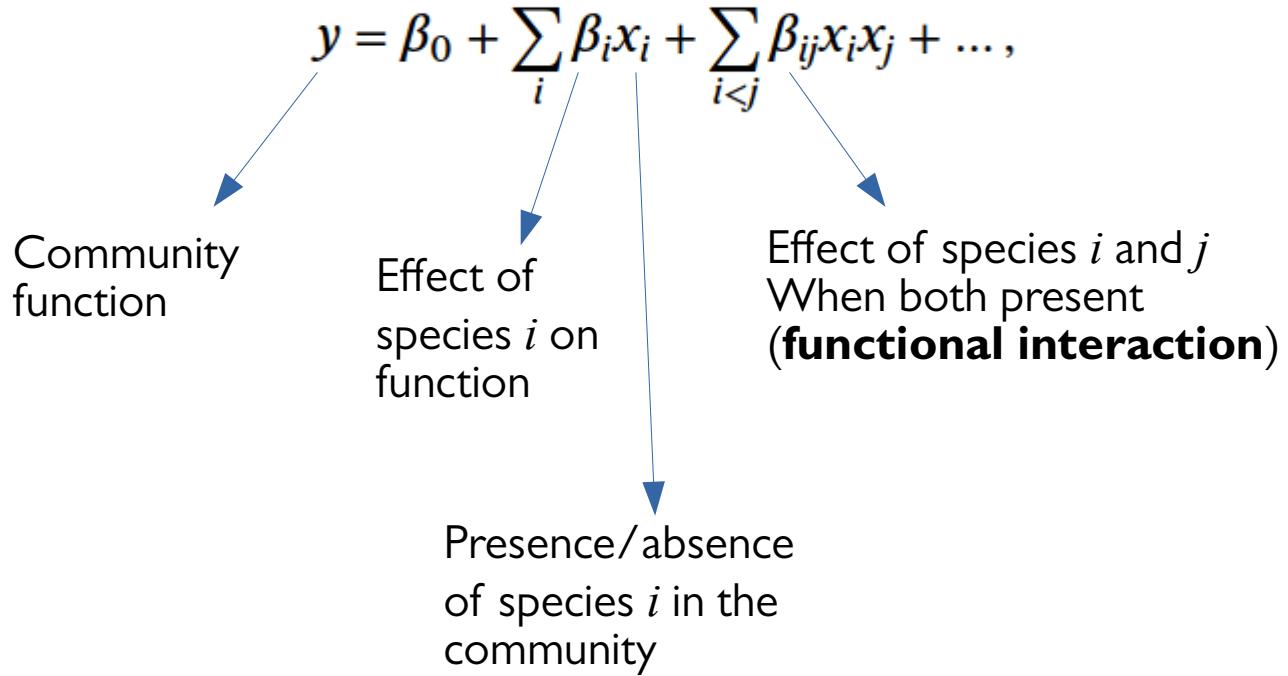
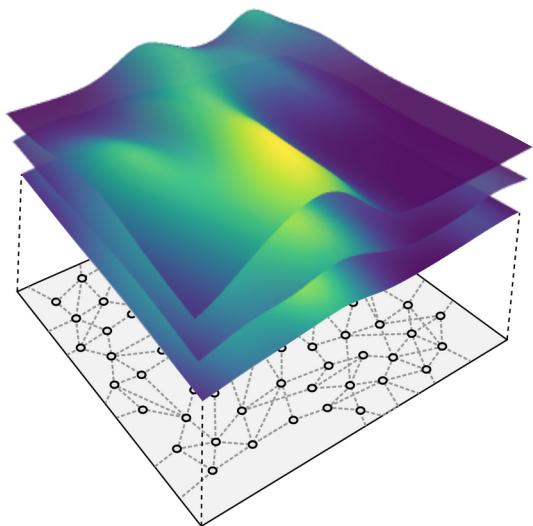
Our goal: predict the structure-function landscape of a microbial community with limited data, because the combinatorial space is infeasible! (2^n)



Simplest statistical approach: regression

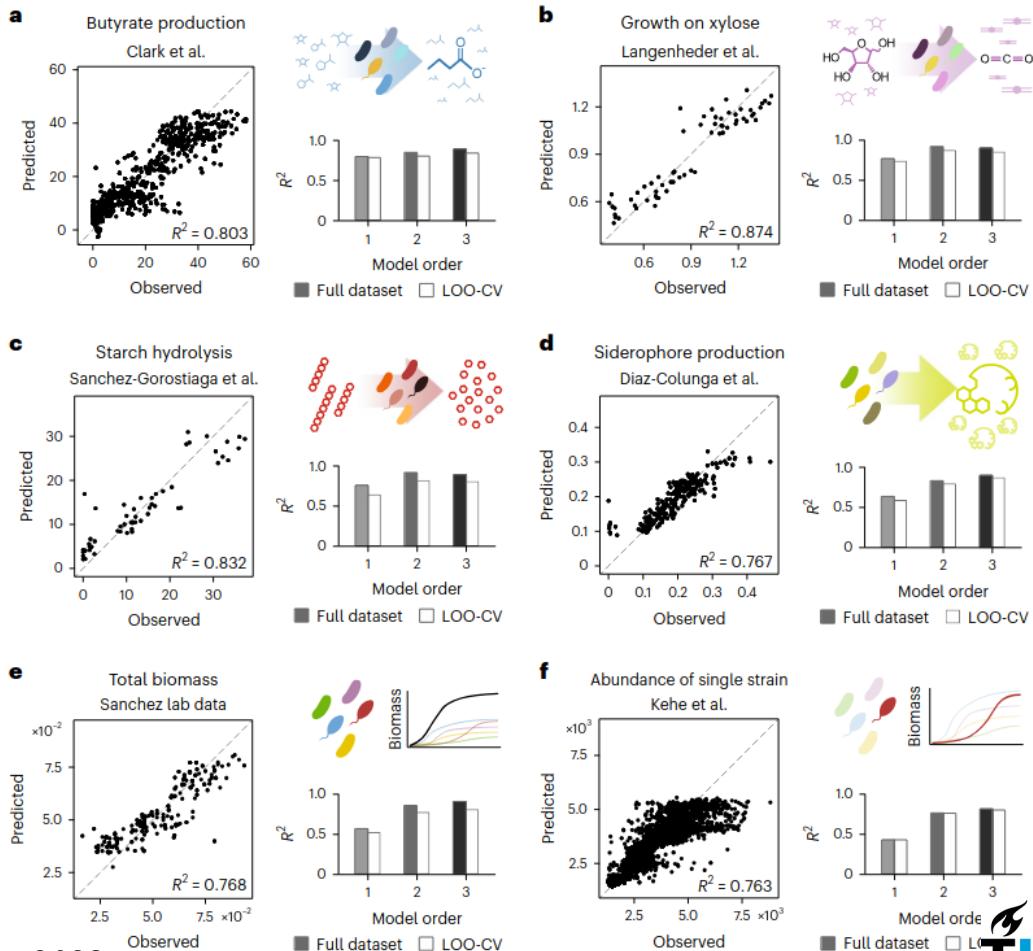
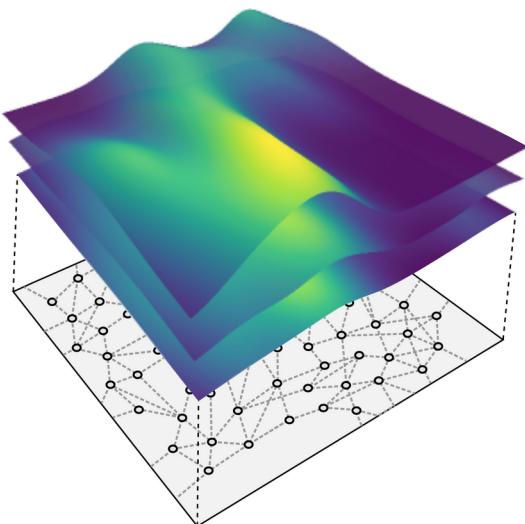


Simplest statistical approach: regression

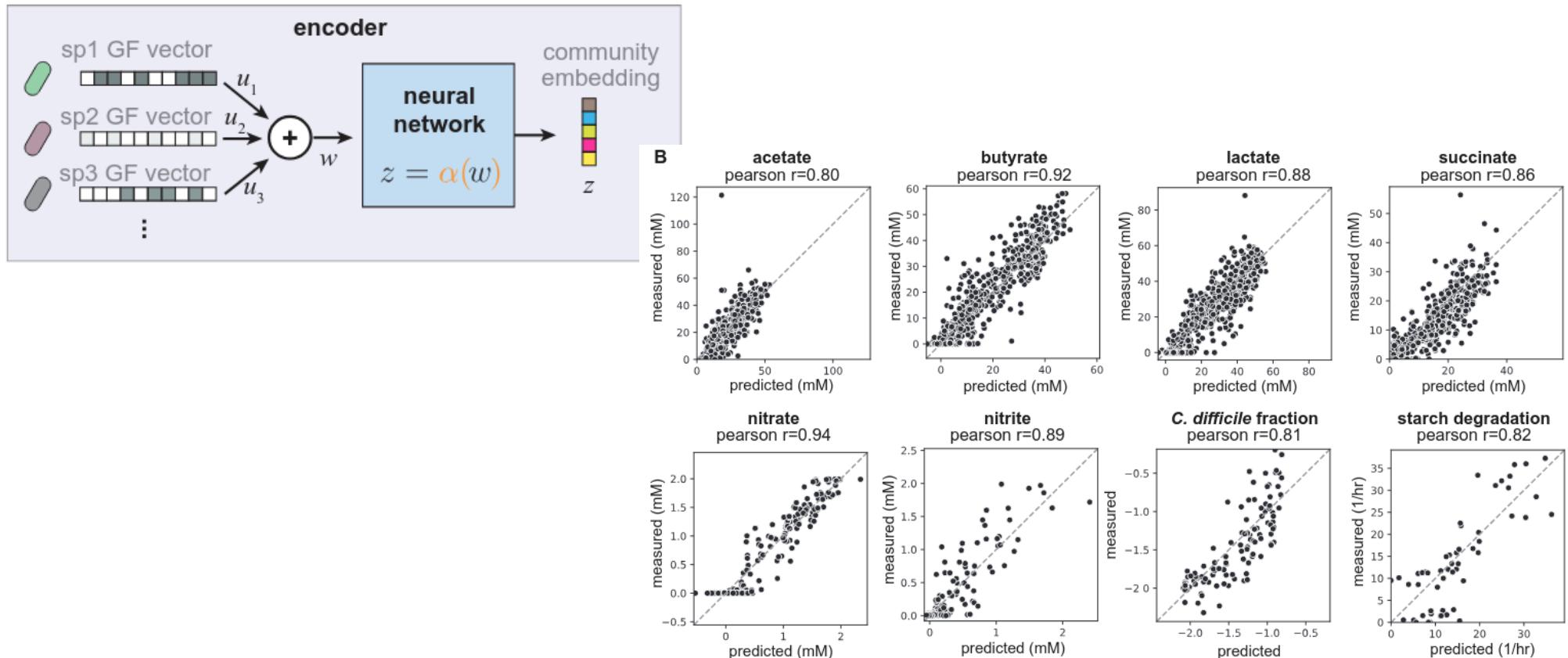


Linear regression works surprisingly well!

$$y = \beta_0 + \sum_i \beta_i x_i + \sum_{i < j} \beta_{ij} x_i x_j + \dots,$$

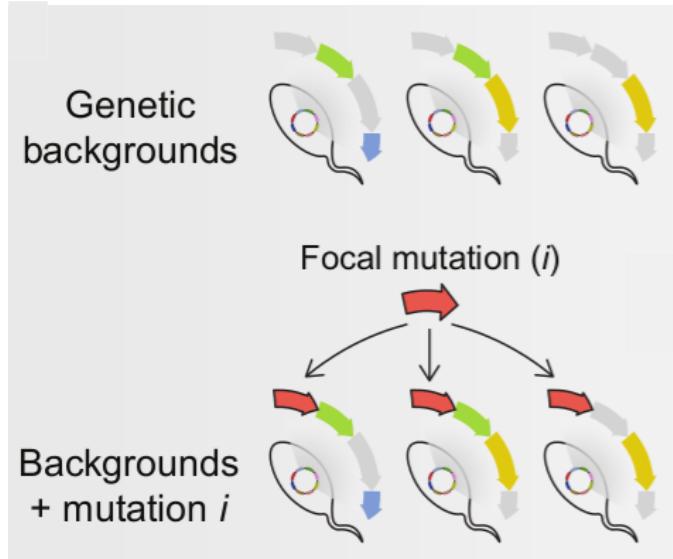


More complex approaches: machine learning

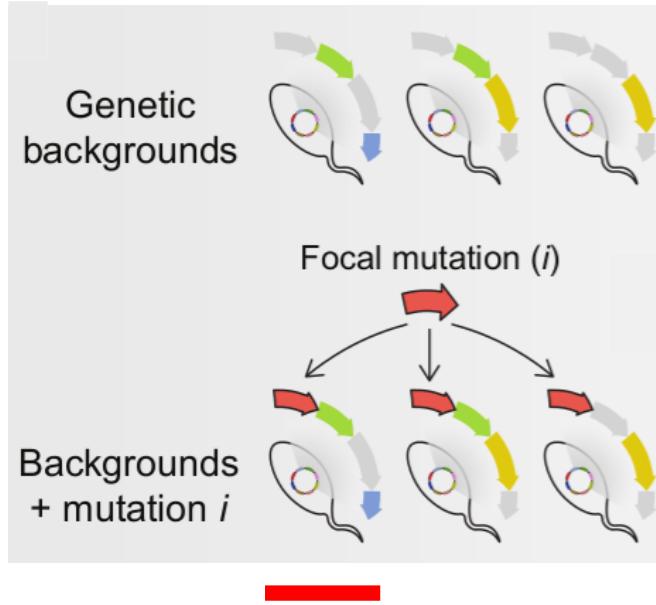


Global epistasis:
A new way to look at interactions

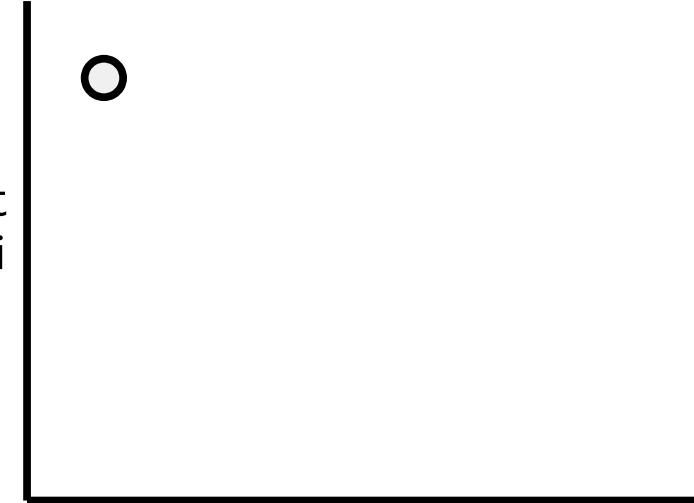
Testing a mutation, one background at a time



Testing a mutation, one background at a time

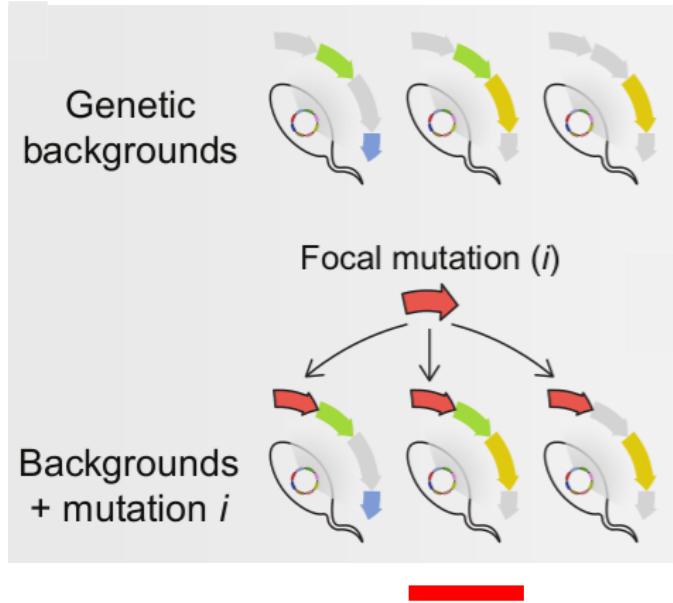


Fitness effect
of mutation i



Fitness of
genetic background

Testing a mutation, one background at a time

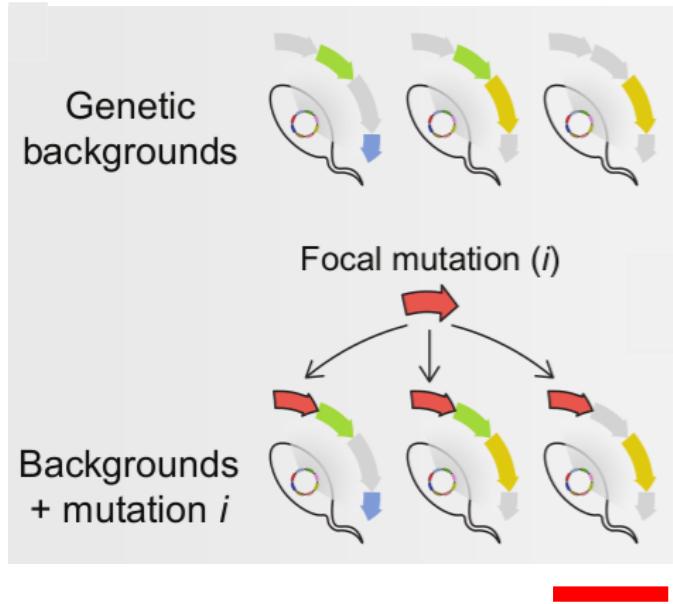


Fitness effect
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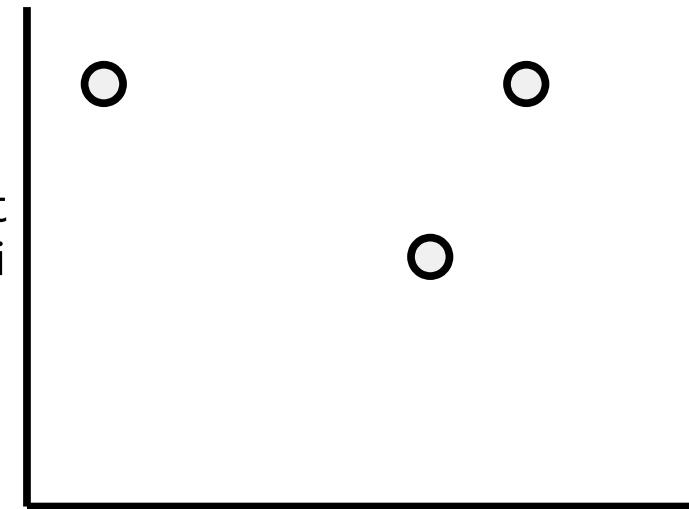


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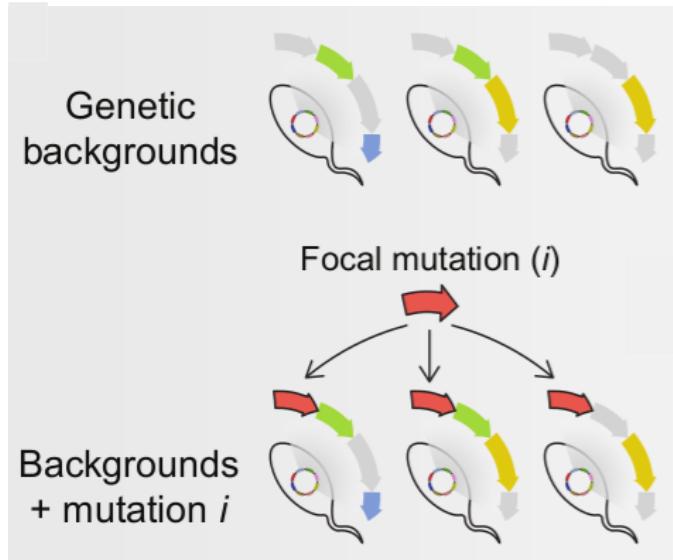


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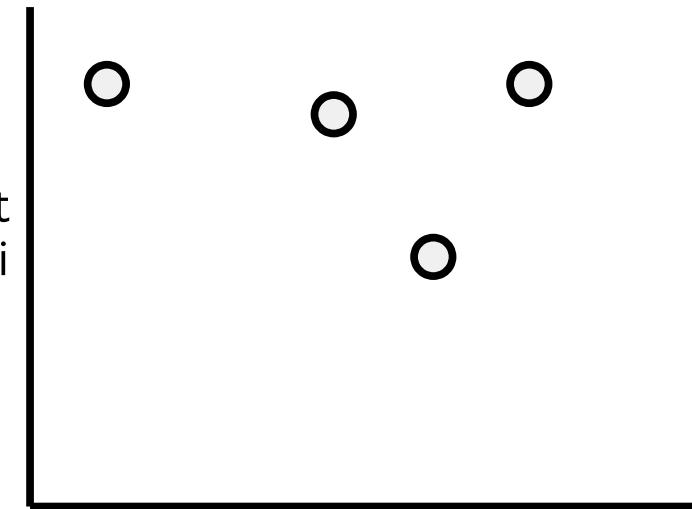


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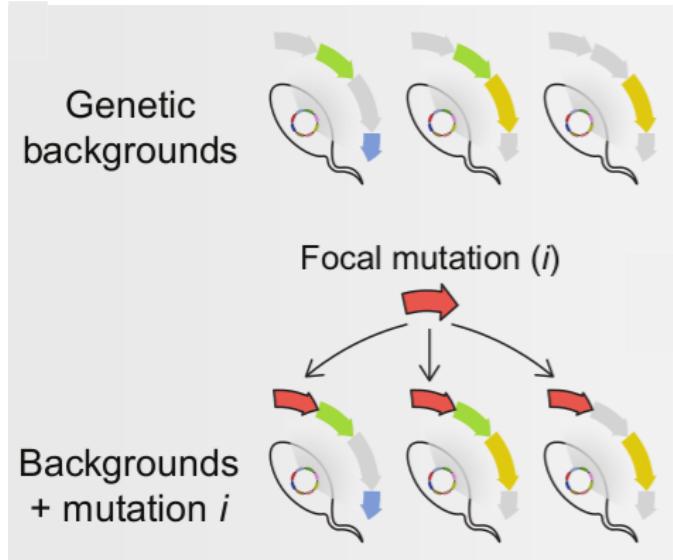


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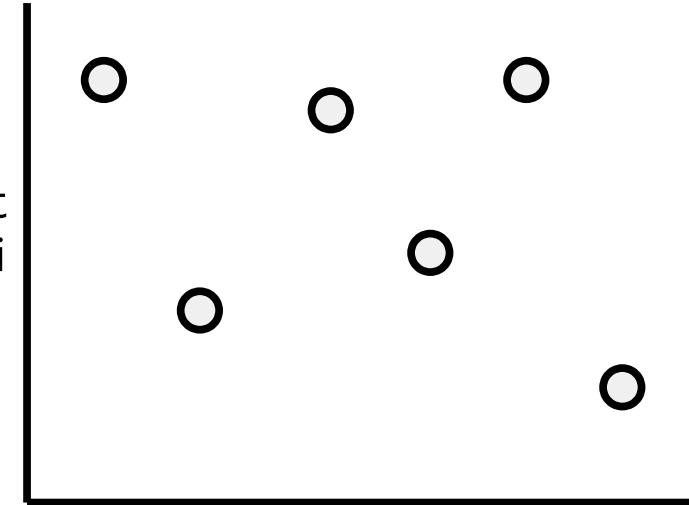


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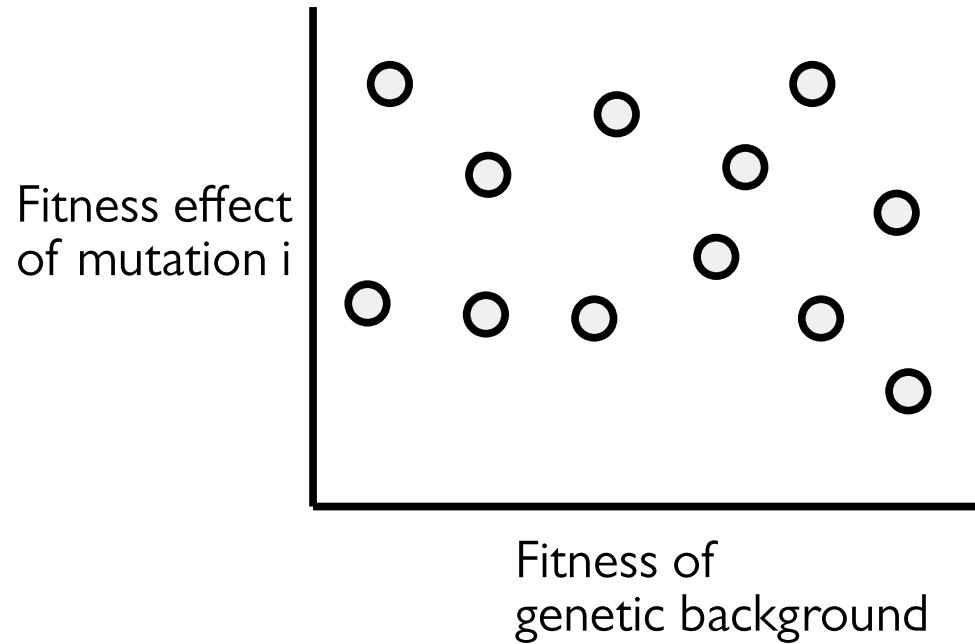
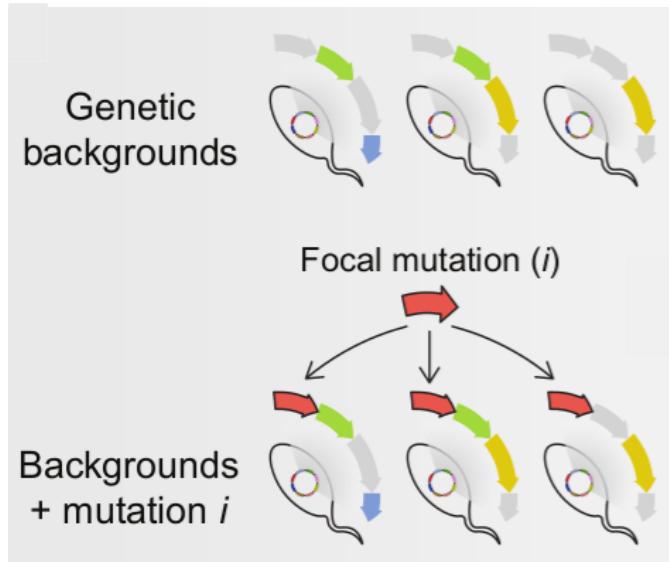


Fitness effect
of mutation *i*

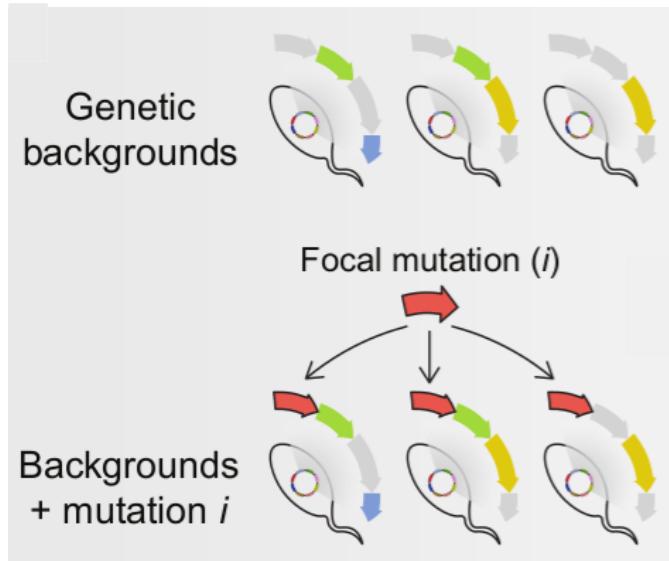


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genetic background

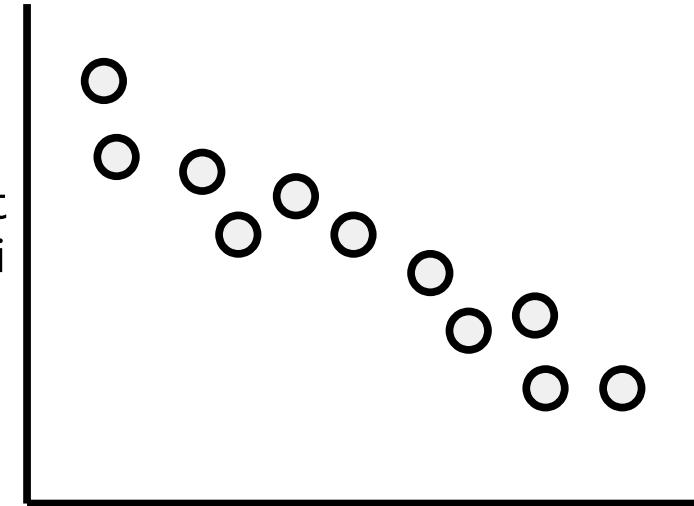
Intuitively, interactions will lead to rugged landscapes, where making predictions is hard



Global epistasis is an emergent linear scaling pattern found in many empirical fitness landscapes

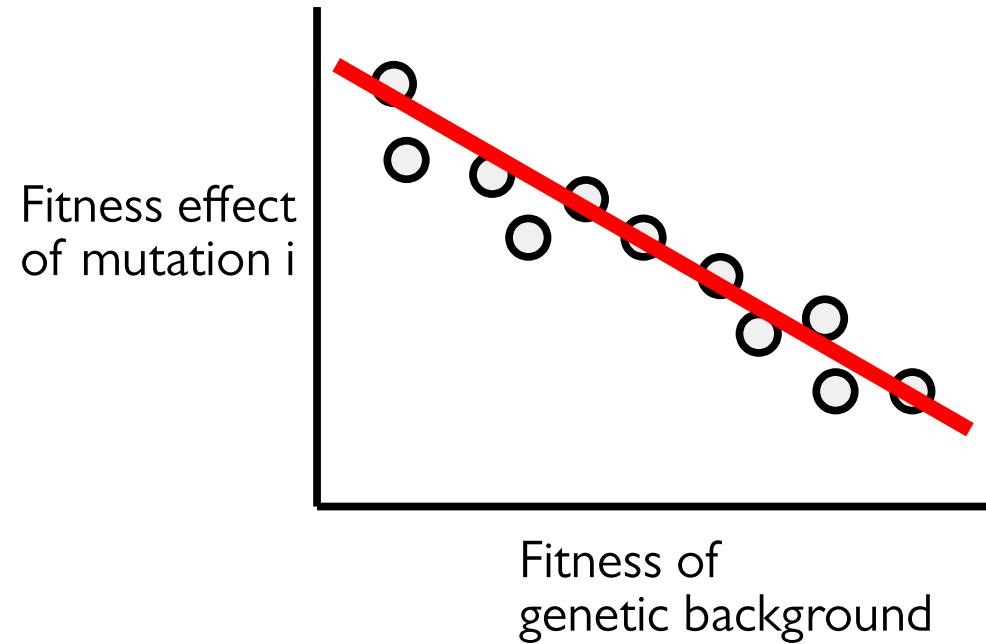
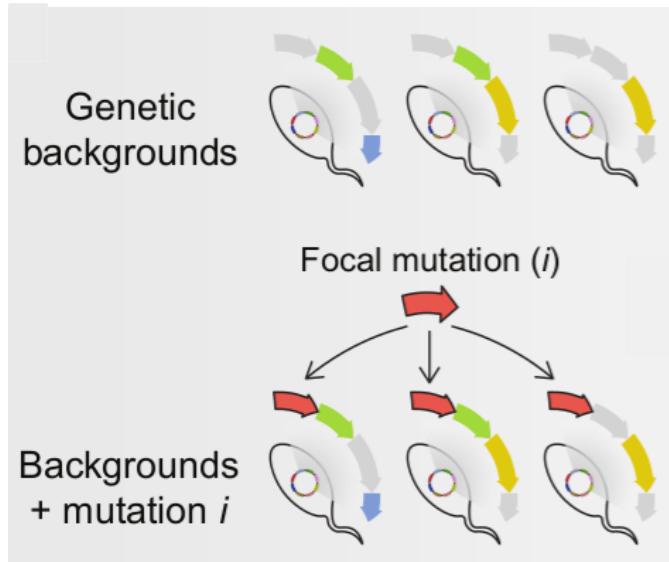


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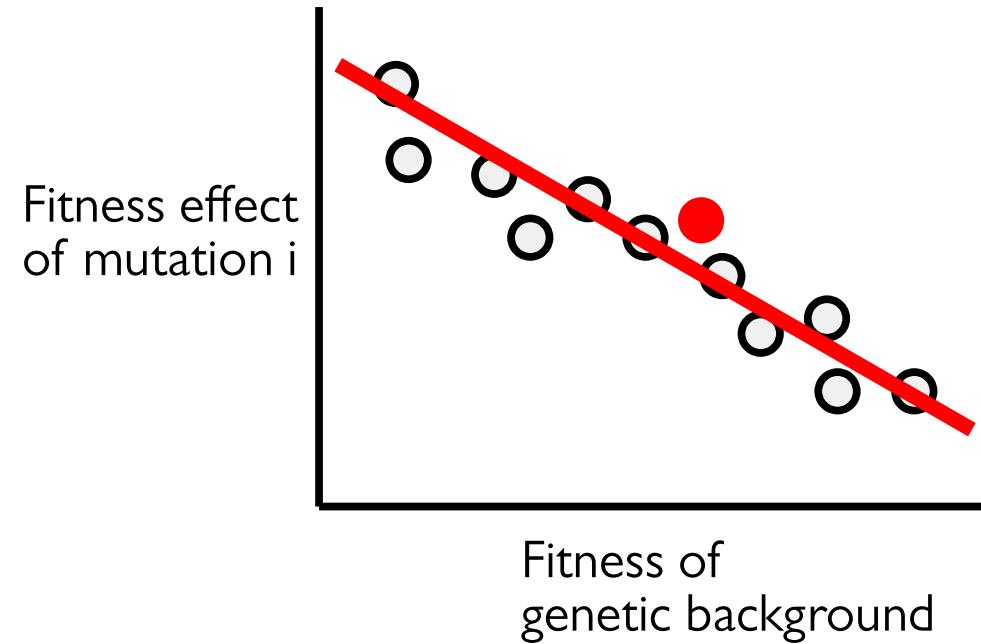
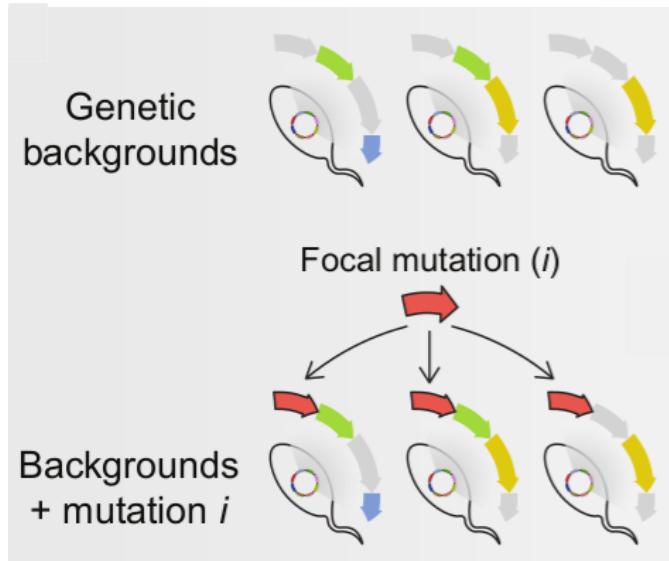


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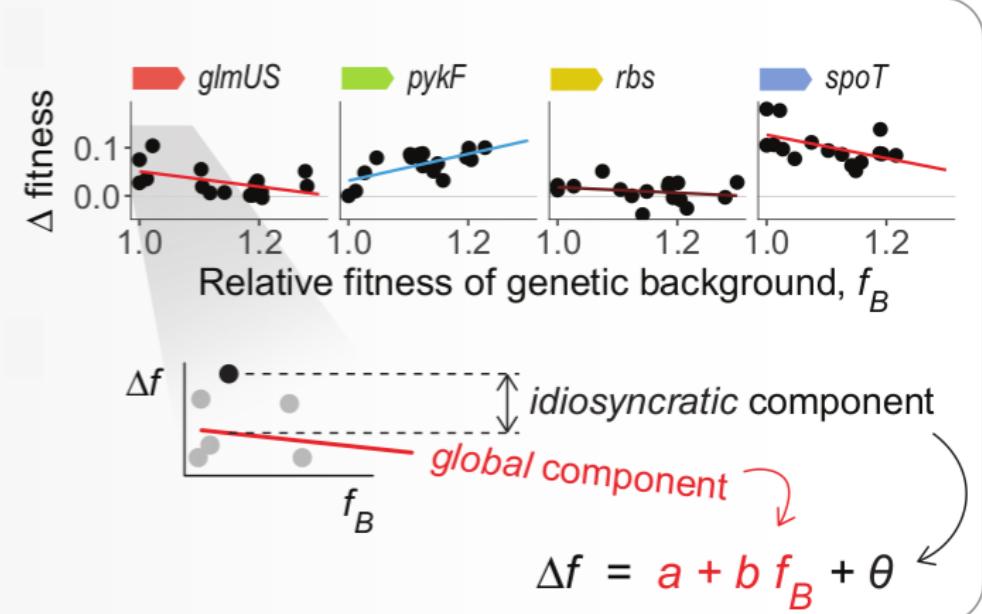
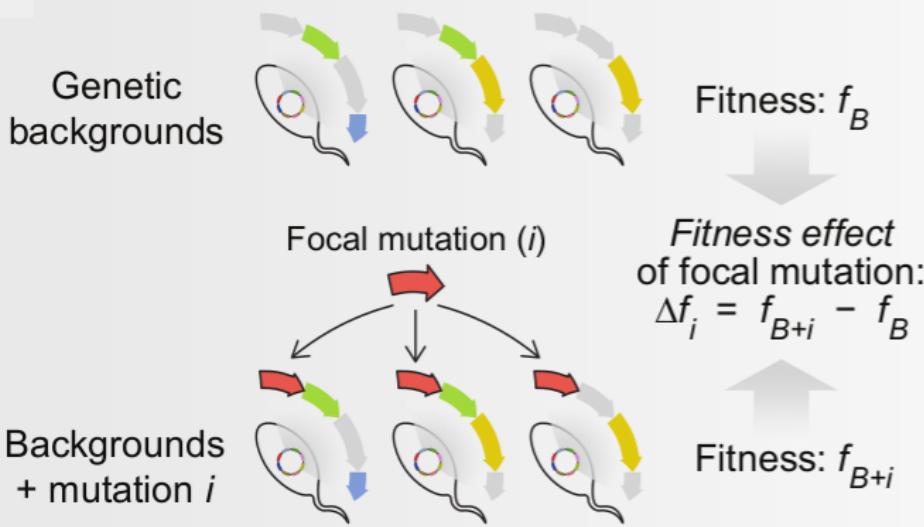
Global epistasis is an emergent linear scaling pattern found in many empirical fitness landscapes



Global epistasis can help us make predictions



Global epistasis is very common in empirical fitness landscapes



Does global epistasis exist also in structure function landscapes of microbial communities?



Juan Diaz
Colunga
(IPLA, CSIC)



Abby
Skwara
(Yale)



Álvaro
Sánchez
(CBGP, CSIC)

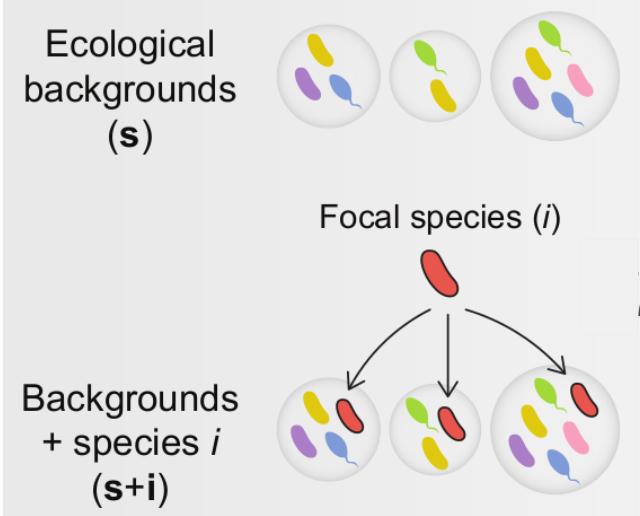
Theory

Global epistasis and the emergence of function in microbial consortia

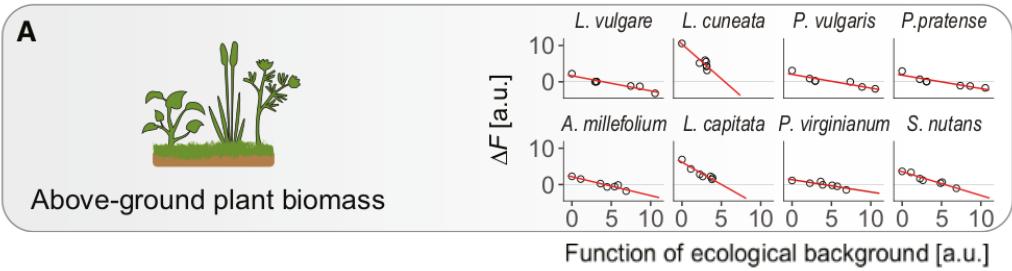
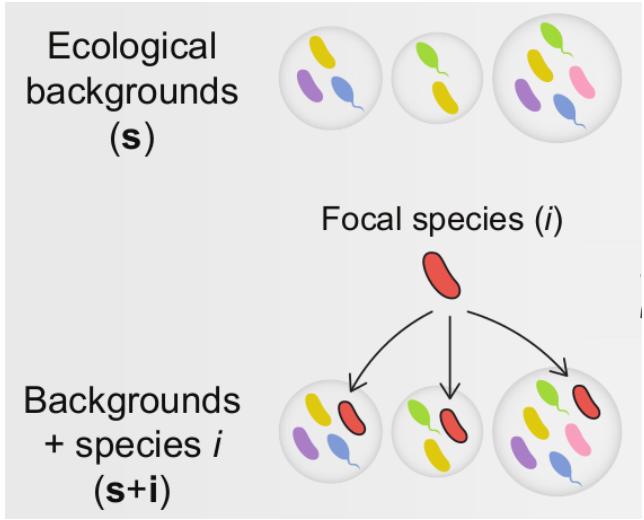
Juan Diaz-Colunga,^{1,2,3,4,7,*} Abigail Skwara,^{1,2,7} Jean C.C. Vila,^{1,2,5} Djordje Bajic,^{1,2,6,*} and Alvaro Sanchez^{1,2,3,4,8,*}

Cell

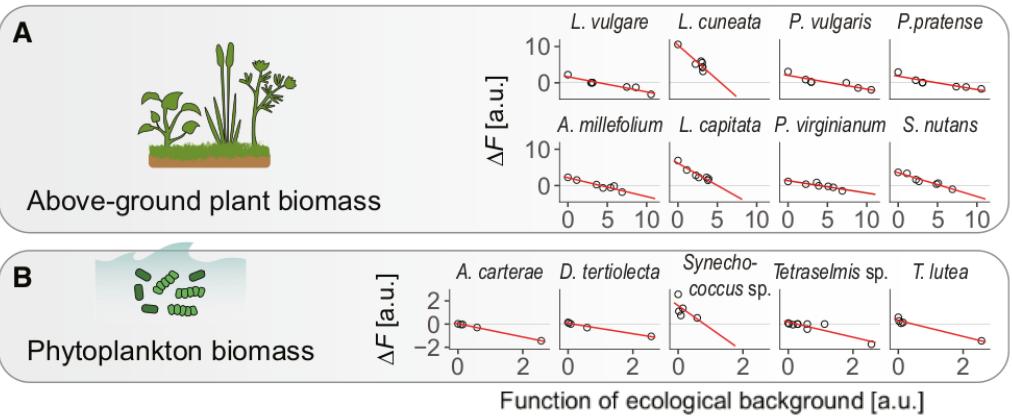
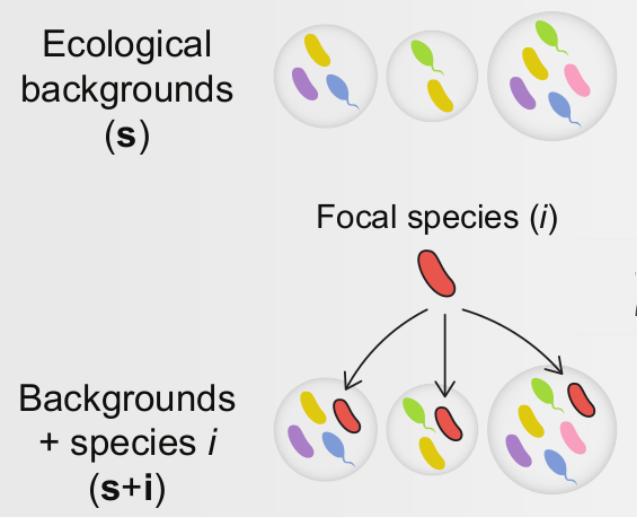
Is there global epistasis
also in ecological
structure-function
landscapes?



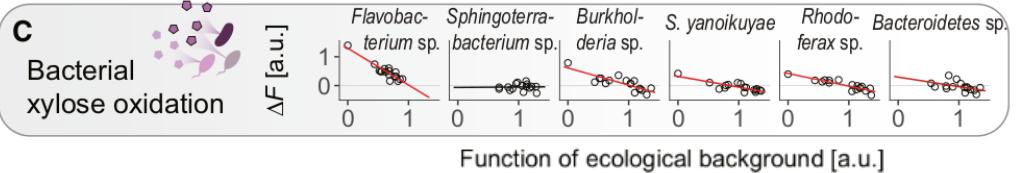
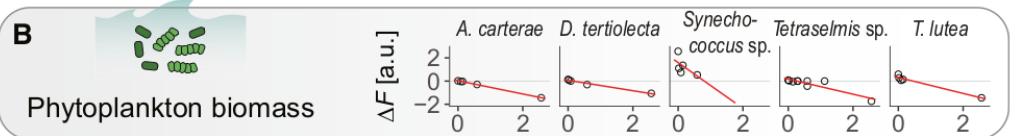
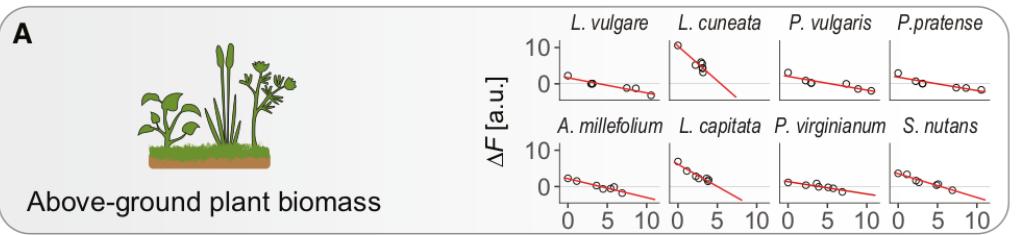
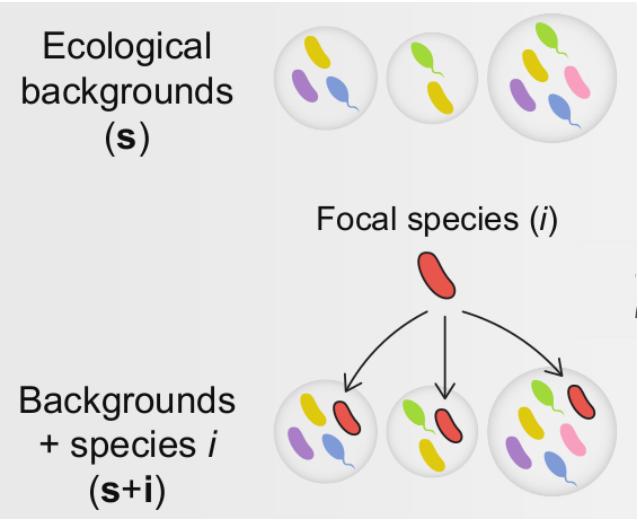
Is there global epistasis also in ecological structure-function landscapes?



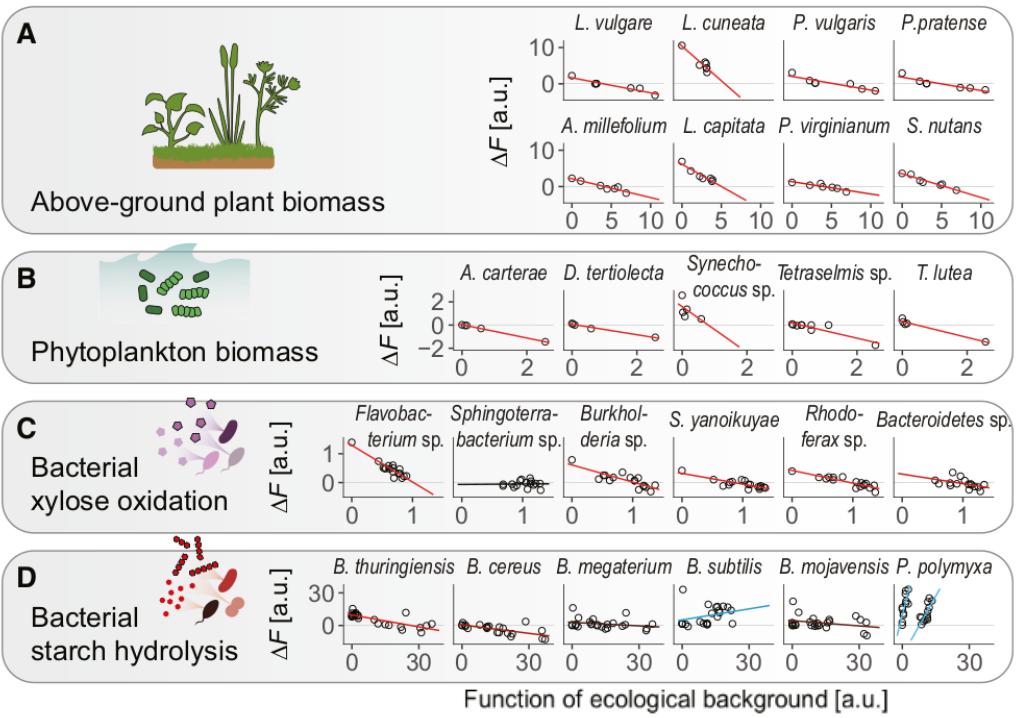
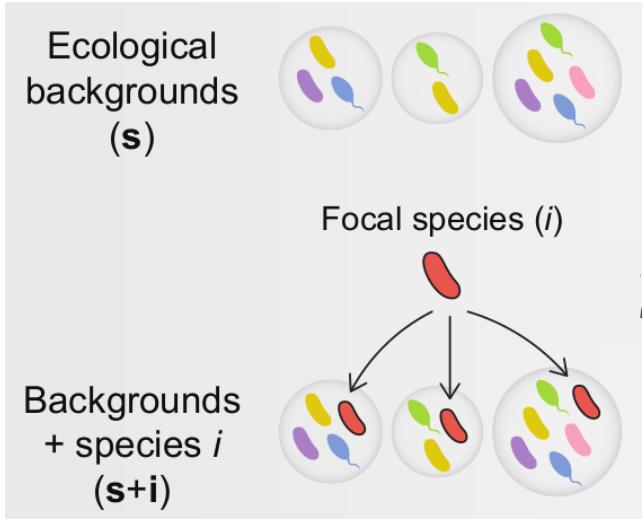
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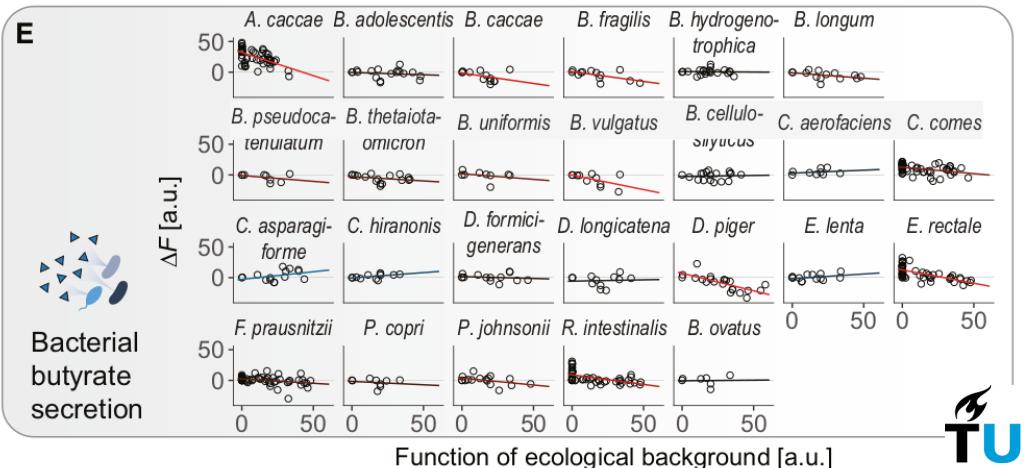
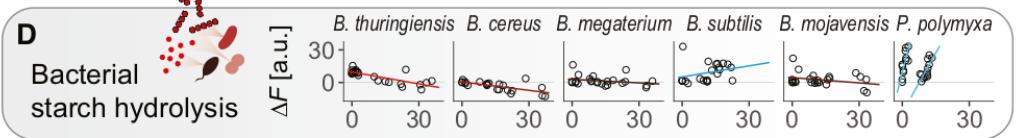
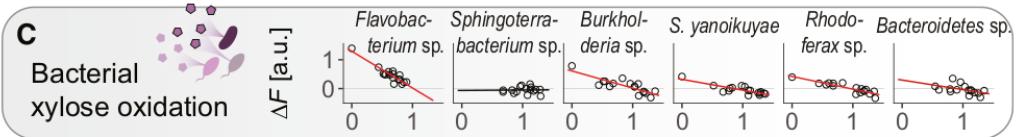
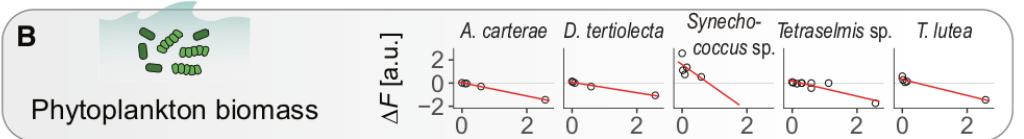
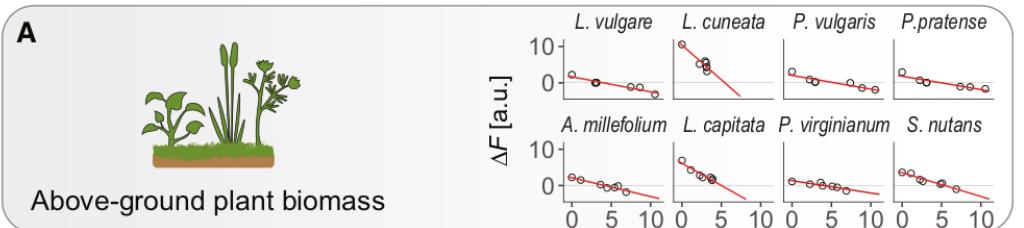
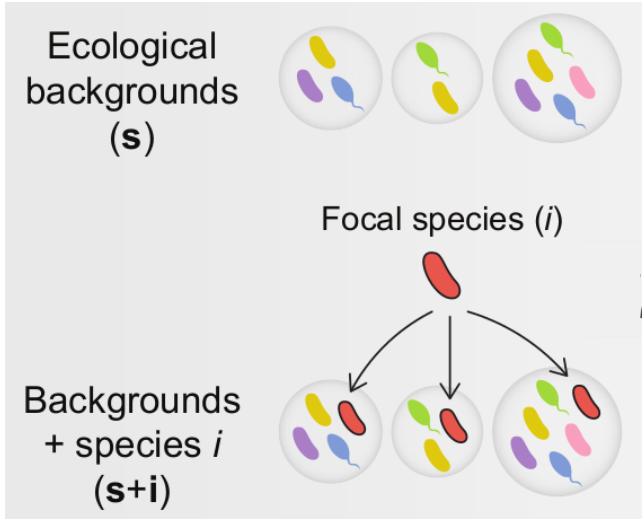
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Is there global epistasis also in ecological structure-function landscapes?



How can we use global epistasis to make predictions?

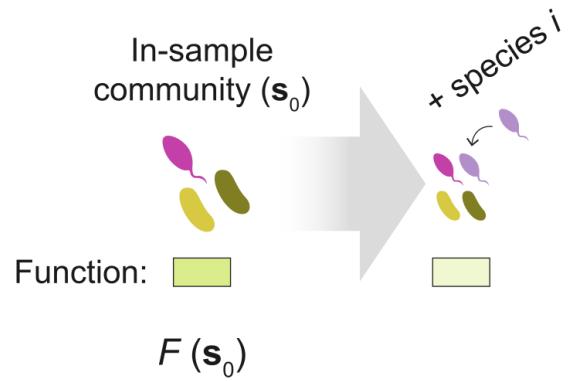
In-sample
community (\mathbf{s}_0)



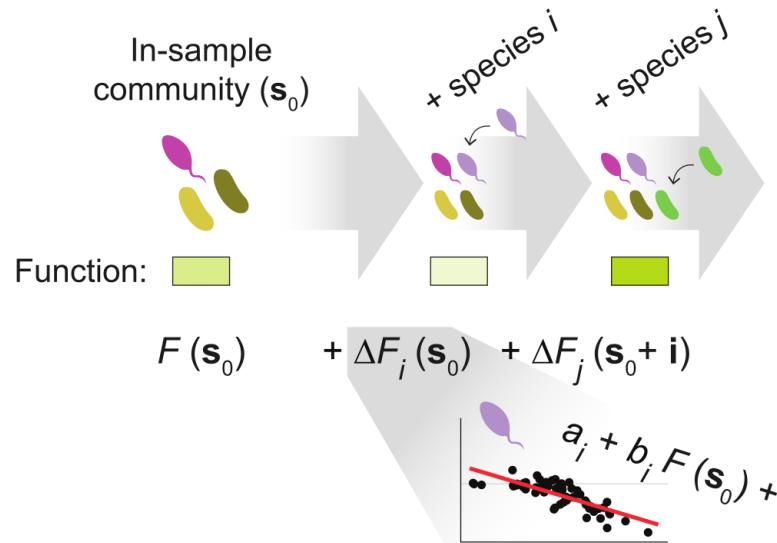
Function: 

$$F(\mathbf{s}_0)$$

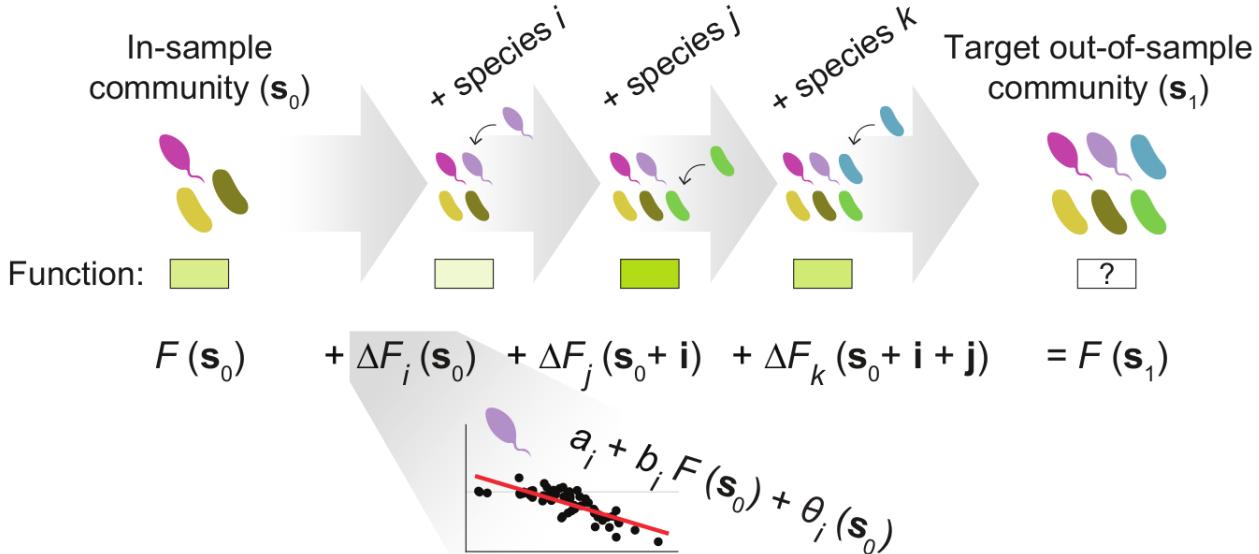
How can we use global epistasis to make predictions?



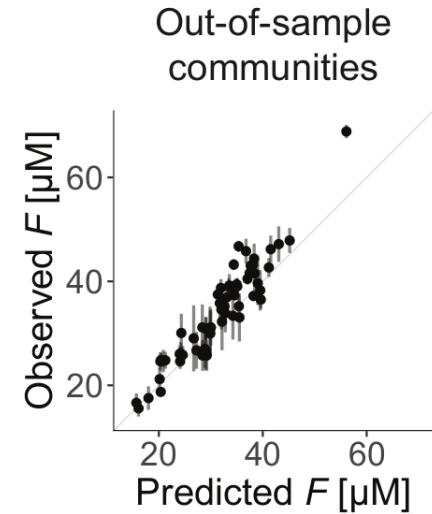
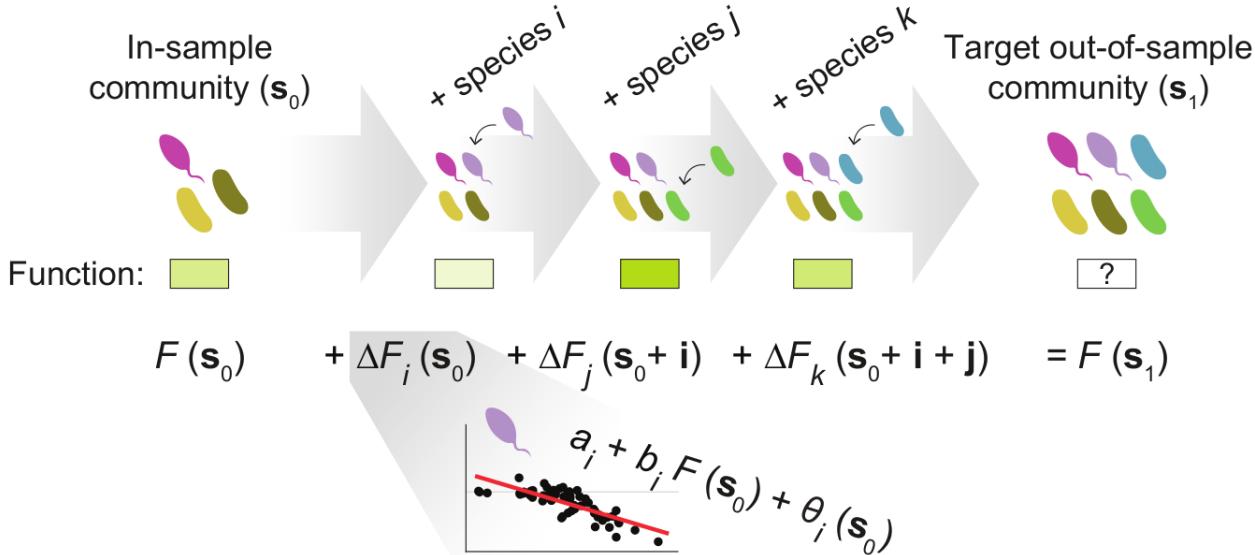
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How can we use global epistasis to make predictions?

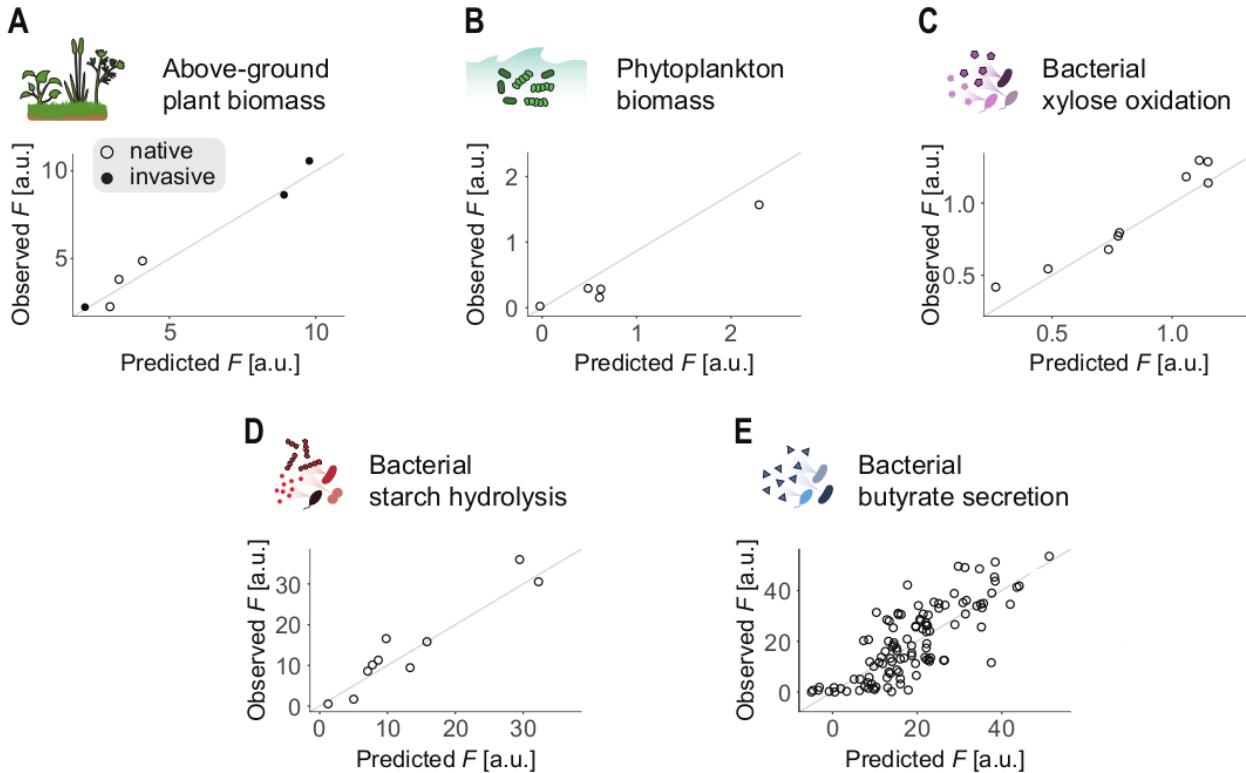


How can we use global epistasis to make predictions?

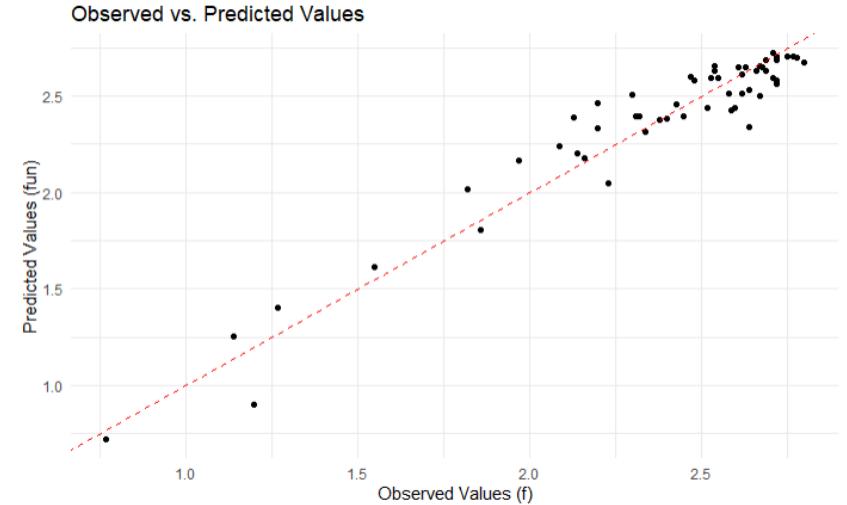
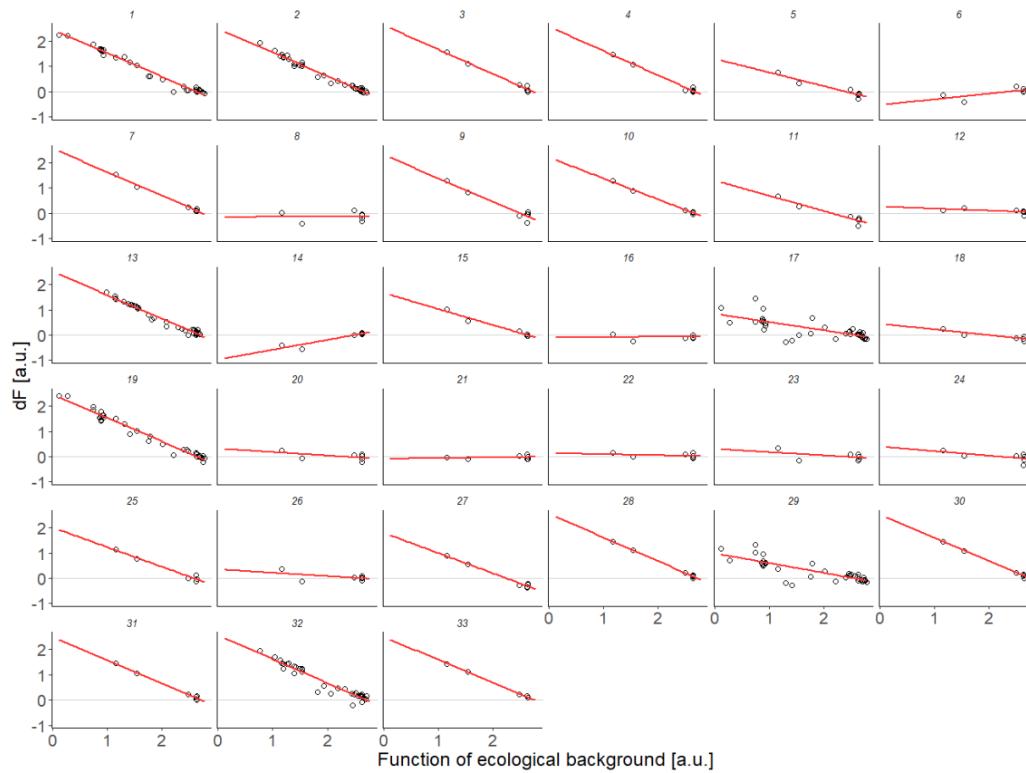


F = Pyoverdine production,
 $R^2=0.81$

Global epistasis shows very promising predictive power



Global epistasis is able to predict acidification in synthetic soymilk-fermenting communities



Uros Gojković



Nemanja
Stanisavljevic
(IMGGE)

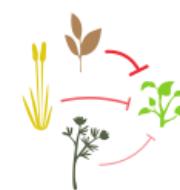
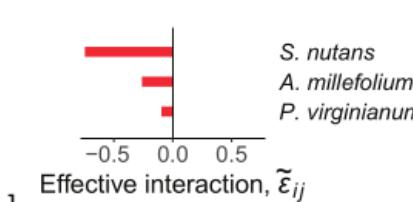
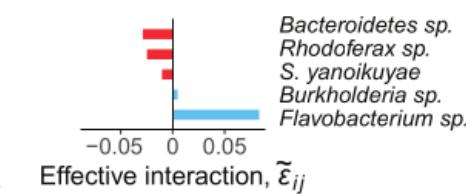
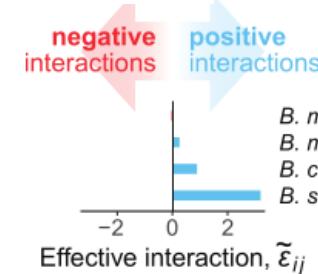
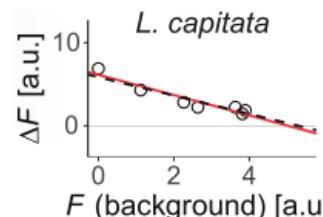
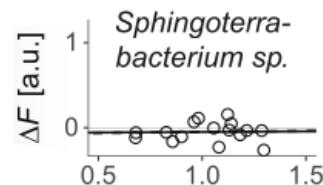
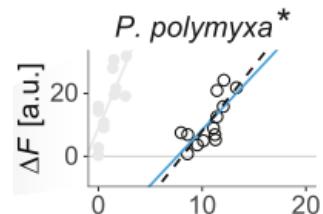


Nemanja
Kljajević
(IMGGE)

Global epistasis is a spotlight to identify relevant interactions

slope of species i
expected from theory

$$b_i \approx \sum_{j \neq i} \tilde{\varepsilon}_{ij}$$

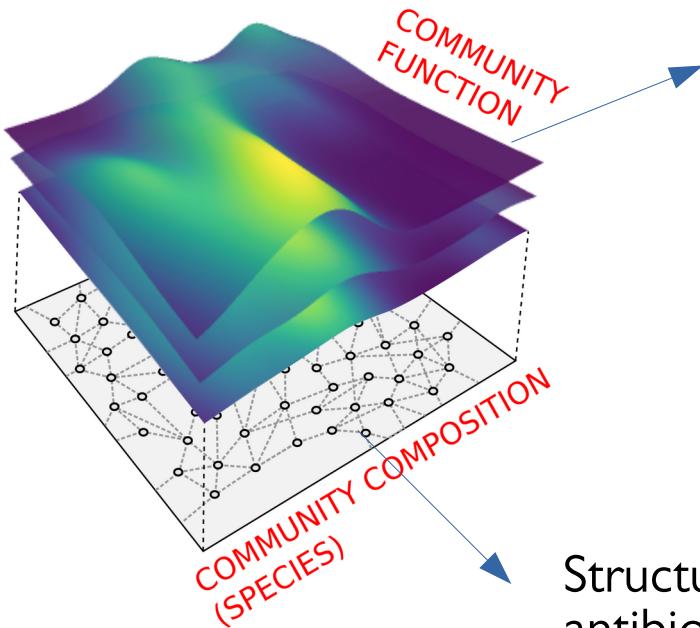


n

— Expectation from theory
— Empirical FEEs

* $B. thuringiensis$
present in background

Can we generalize this even further,
beyond microbial communities?



Function: How much it kills
Staphylococcus aureus?

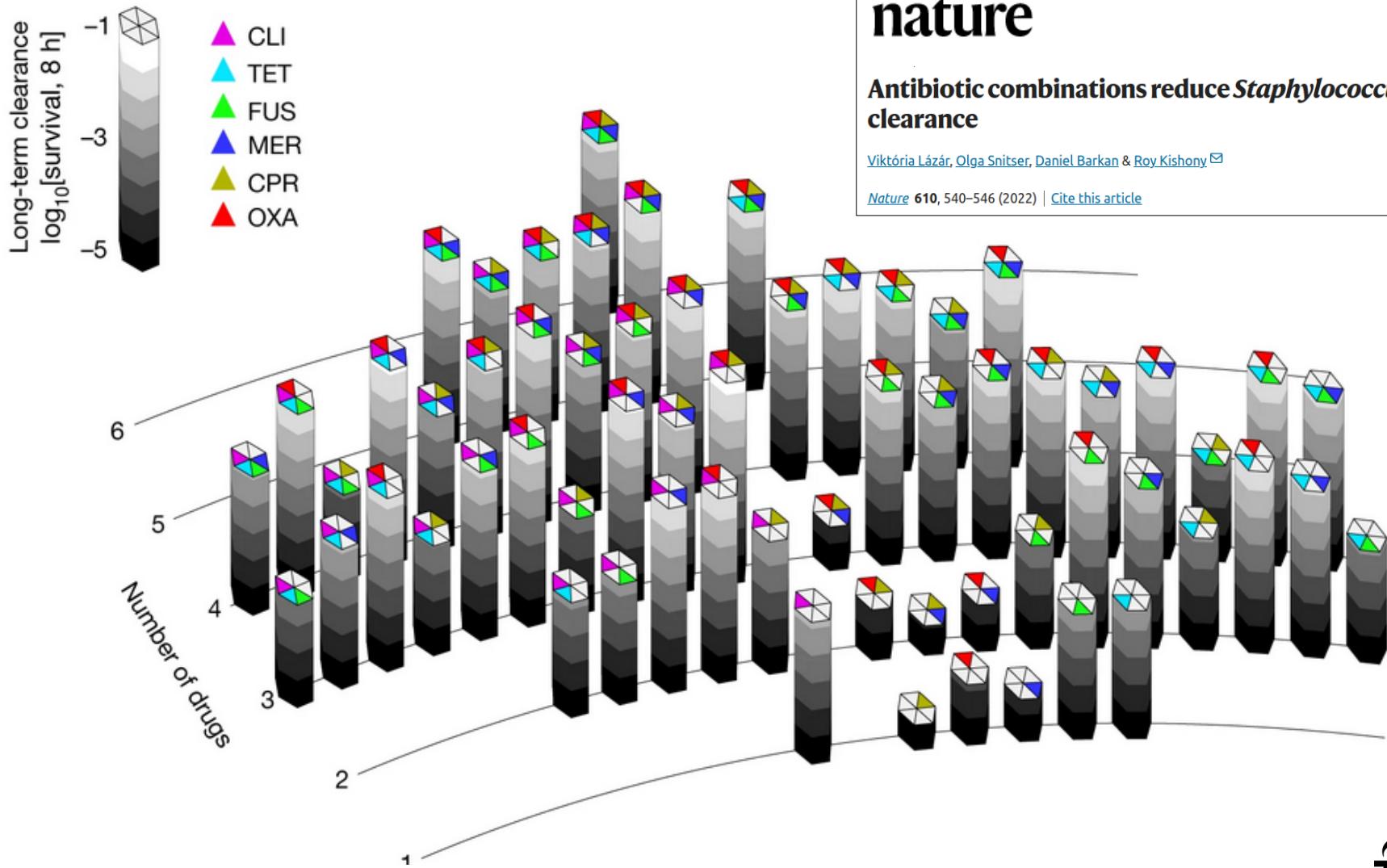
Structure: composition of an
antibiotic cocktail



Floris
Klein Obbink



Minke
Gabriëls



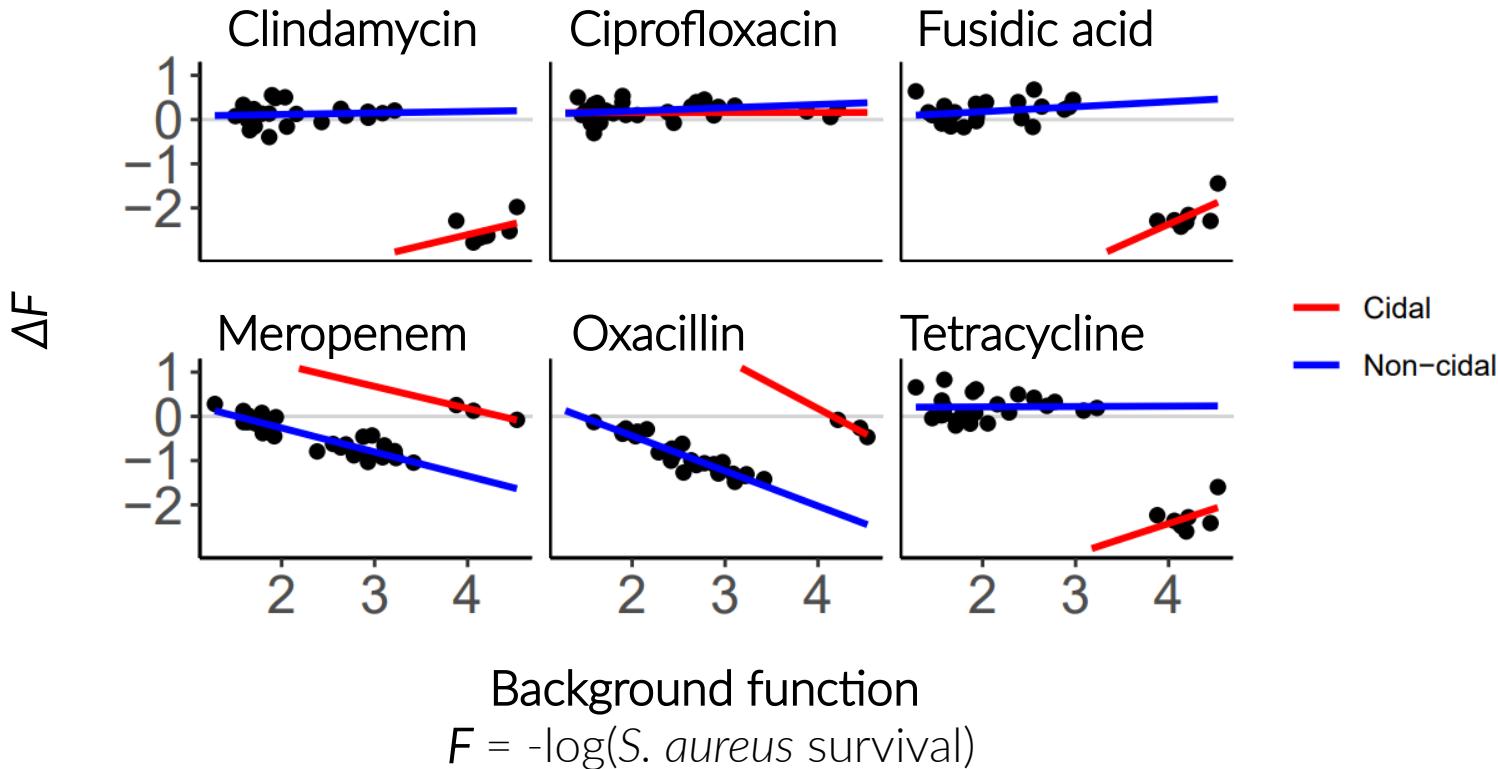
nature

Antibiotic combinations reduce *Staphylococcus aureus* clearance

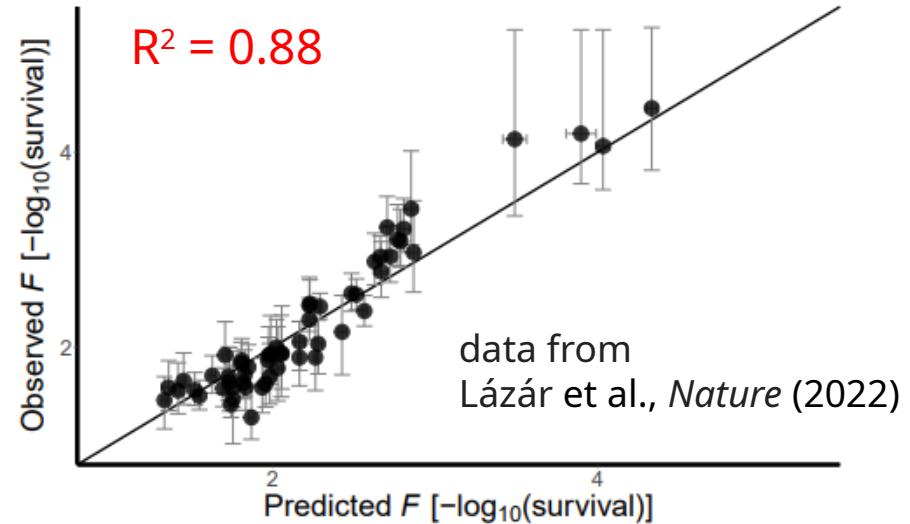
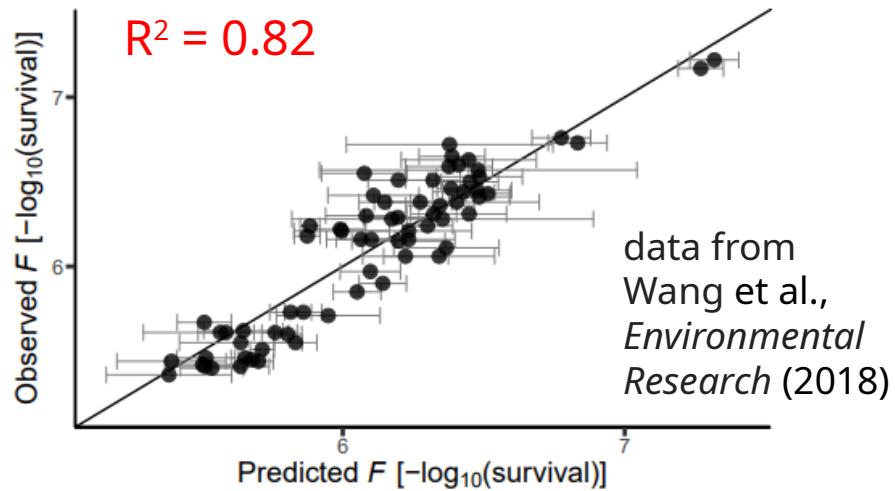
Viktória Lázár, Olga Snitser, Daniel Barkan & Roy Kishony

Nature 610, 540–546 (2022) | [Cite this article](#)

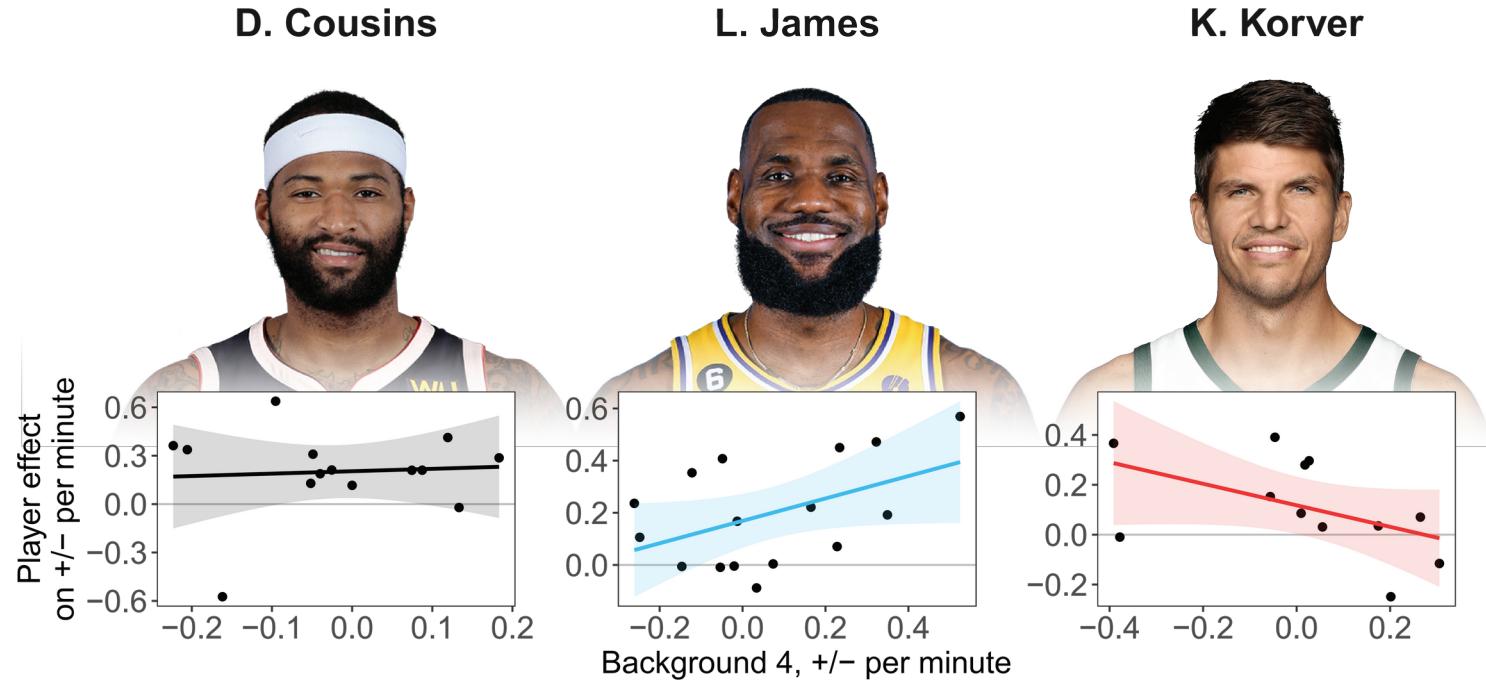
Antibiotic combinations exhibit global epistasis in their effects on *Staphylococcus aureus* clearance



The effect of unknown antibiotic cocktails can be predicted using global epistasis!



And we can take it even further!



(Real data for NBA season 2015-16)

Collaborators

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Abby Skwara (Yale University, USA)
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Nemanja Kljajević (IMGGE, Serbia)
Viktoria Lazar (BRC, Szeged, Hungary)
Ivica Dimkić (University of Belgrade, Serbia)
Ilija Dukovski (Boston University, USA)
Daniel Segre (Boston University, USA)
Sotaro Takano (AIST, Japan)
Jean Vila (Stanford, USA)
Ludovic Jourdin (TU Delft, The Netherlands)
Jean-Marc Daran (TU Delft, Netherlands)
Robbert Kleerebezem (TU Delft, Netherlands)

Group @  TU Delft



Minke
Gabriëls



Uroš
Gojković



Rienk
Van Vliet

Funding



Thank you!

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Funding

Zero Emission Biotechnology Program @



Thank you!

Group @  **TU**Delft



Minke
Gabriëls



Uroš
Gojković



Rienk
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Practical Exercise

Statistical prediction and optimization of microbial community functions



Courtesy of: Juan Díaz-Colunga

Microbial Systems Biology Lab (MSBlab), Spanish National Research Council

10 minute break?