Hypothesis-driven interpretable neural network for interactions between genes

Modelling and predicting genotype-fitness maps

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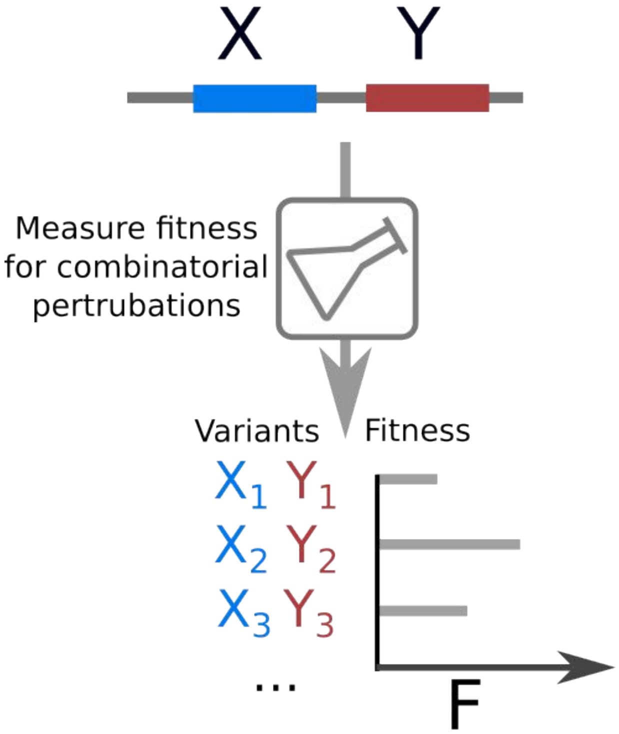
Modelling genotype-fitness maps

- Collection of **mutation-fitness**
- Predictive genotype-fitness model
- Interpretation to build hypotheses
- Biological system engineering



SOTA

- **Mechanistic:**

Explicit modelling of the biological system

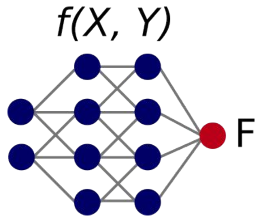
$$F(X,Y) = \left(w + \mu\varphi - \frac{\nu}{1/\eta - \varphi}\right)(1 - \theta_X X - \theta_Y Y)\,,$$

highly interpretable but not streamlined & not scalable

- **Machine learning:**

Statistical modelling of the data

easy modelling & high accuracy but low interpretability



Hypothesis-Driven Modelling

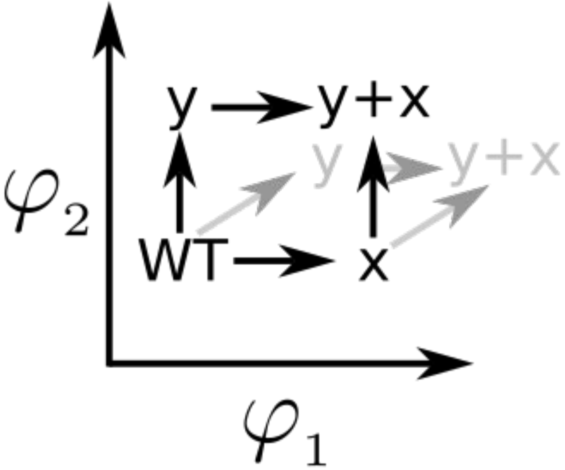
ML ~ Mechanistic

- Phenotype inference
- Identify genetic trade-offs
- Extrapolate outside of the data domain

Shuhui Wang

One phenotype — one latent variable

- 1 **gene** ↔ 1 **phenotype** ↔ 1 **latent variable**



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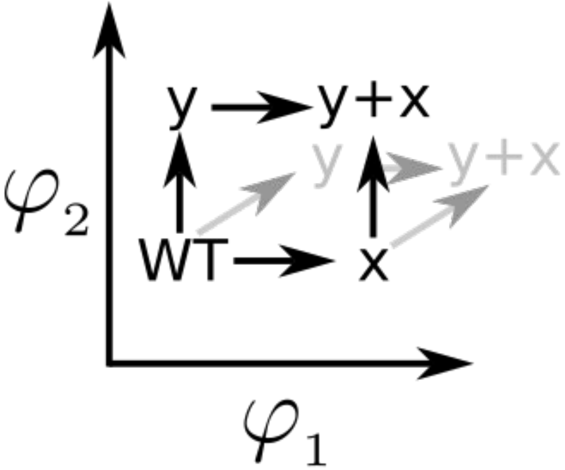

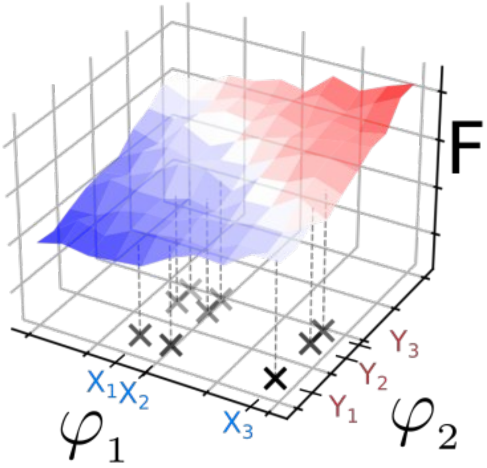

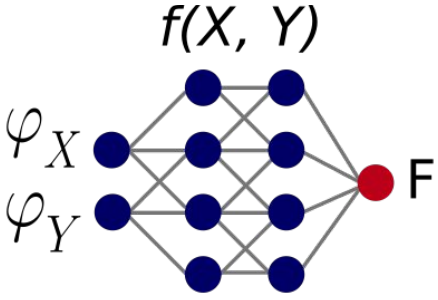

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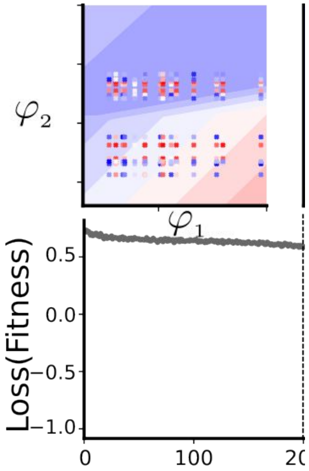

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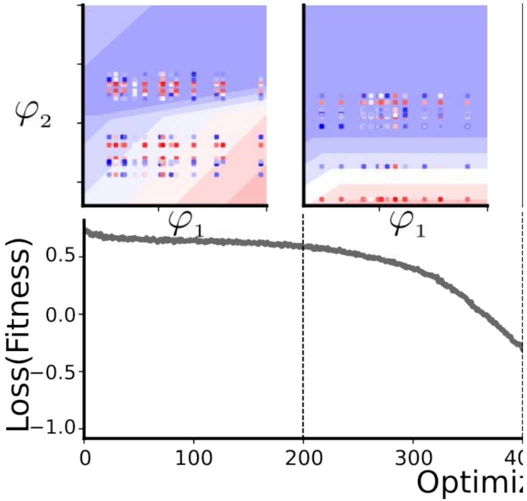

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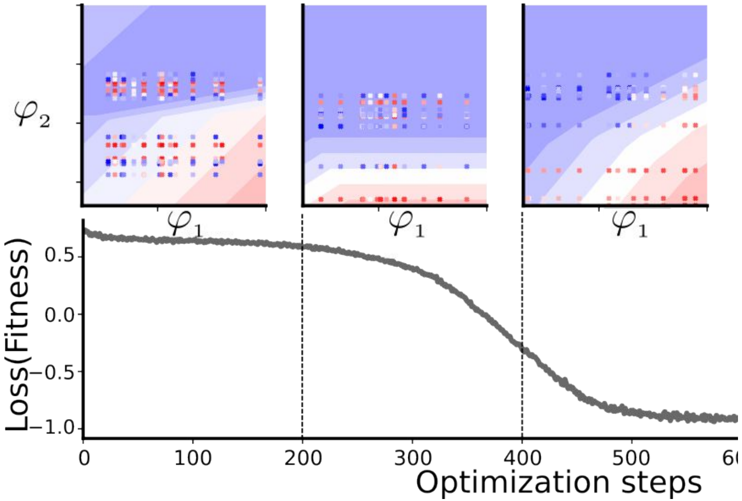

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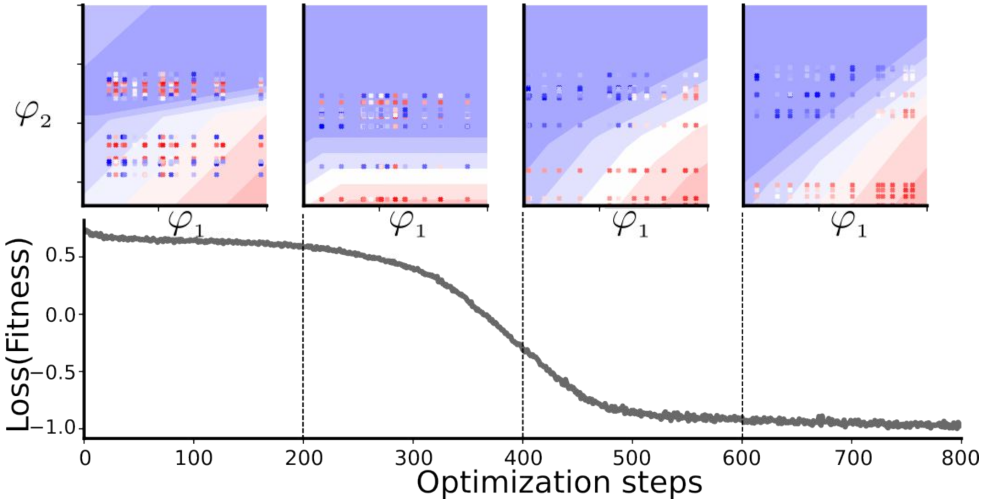
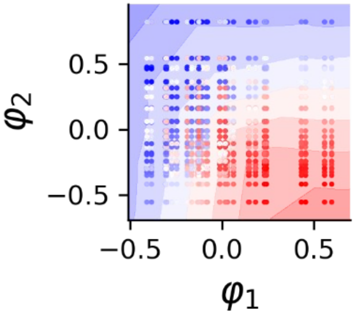
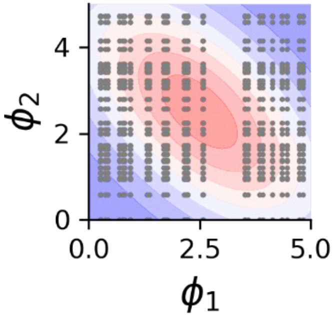


The challenge of non-monotonous landscapes



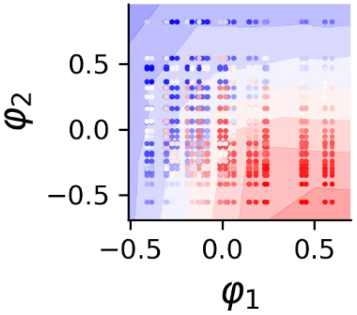
Naive model



Artificial data

The challenge of non-monotonous landscapes

- Construct a graph of mutations
- Spectral initialization (Laplacian)



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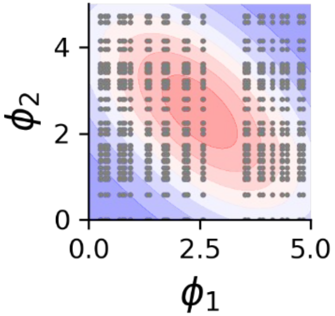

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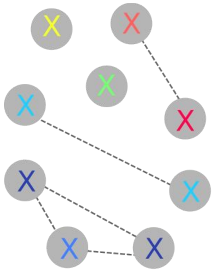

Similarity graph

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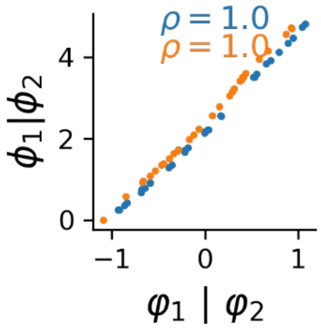

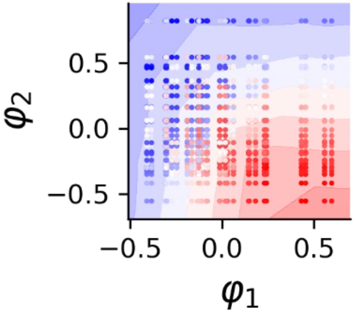

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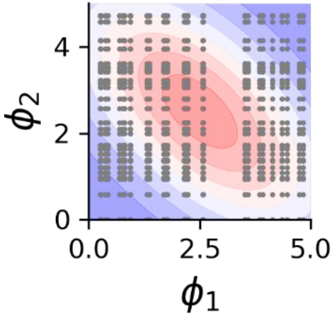

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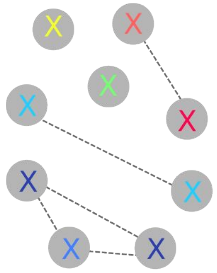
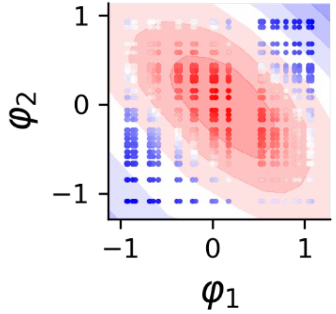


Similarity graph



Spectral initialization

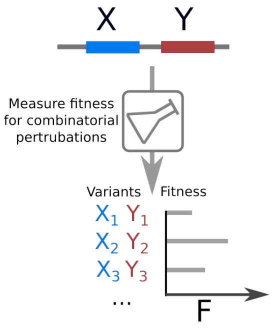
Phenotype inference

Latent variation = phenotypic variation

- Artificial fitness landscape:

$$F(X,Y) = \left(w + \mu\varphi - \frac{\nu}{1/\eta - \varphi}\right)(1 - \theta_X \boxed{X} - \theta_Y \boxed{Y}) \,,$$

Kemble *et al* 2020



- Assign numerical **phenotypic values**

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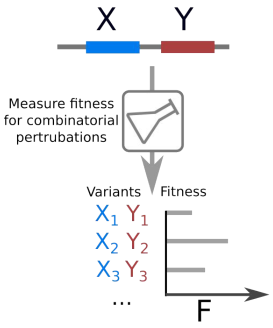

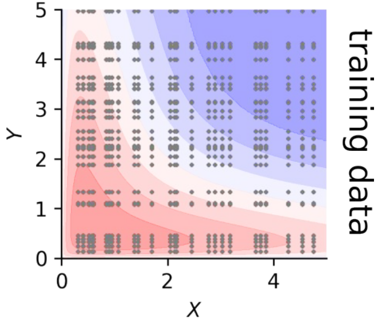

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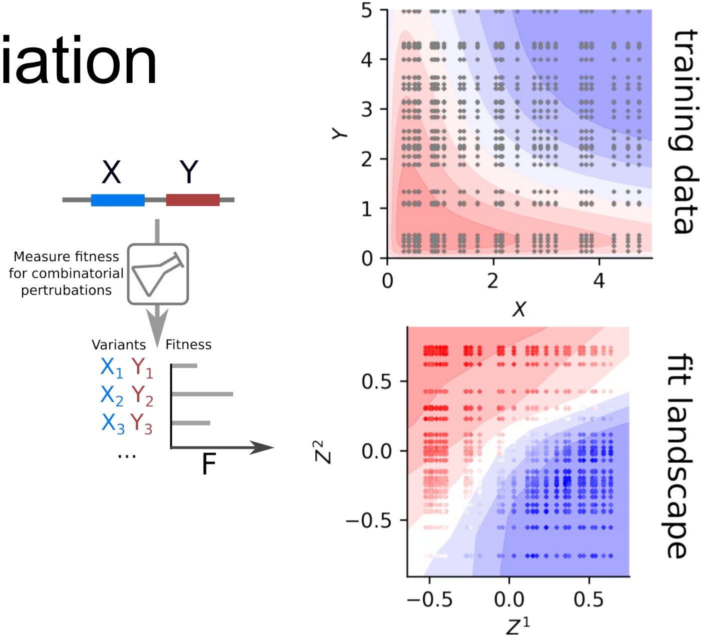

Measure fitness for combinatorial pertrubations

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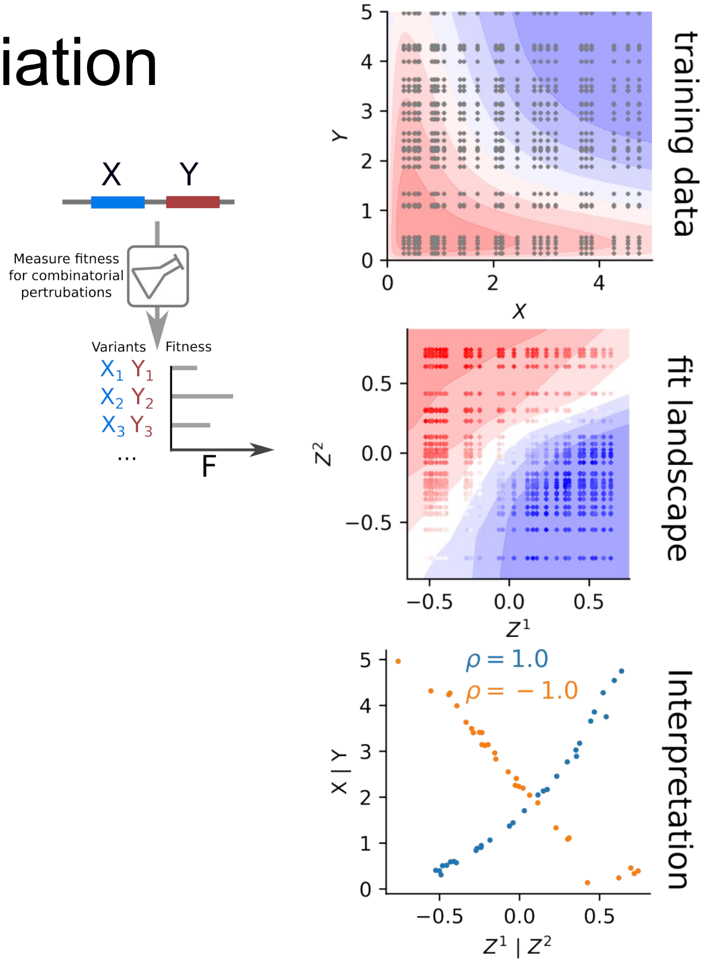
- Assign numerical **phenotypic values**

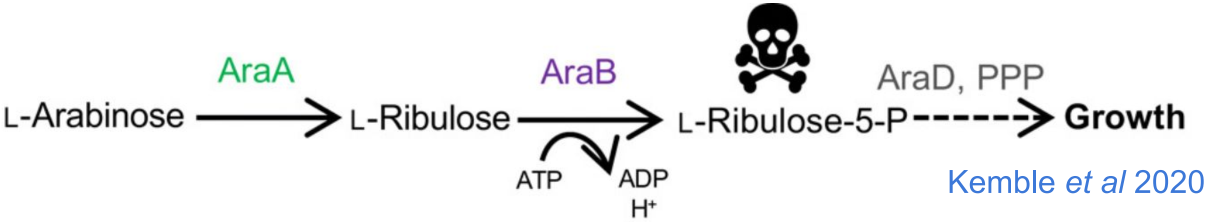
- **Latent variables ∝ phenotype**



Measure fitness for combinatorial pertrubations

Identify trade-offs

Identify a genetic trade-off



Kemble *et al* 2020

- **2 genes** influencing growth
- **Fitness** measured: **growth** (sequencing/barcoding)

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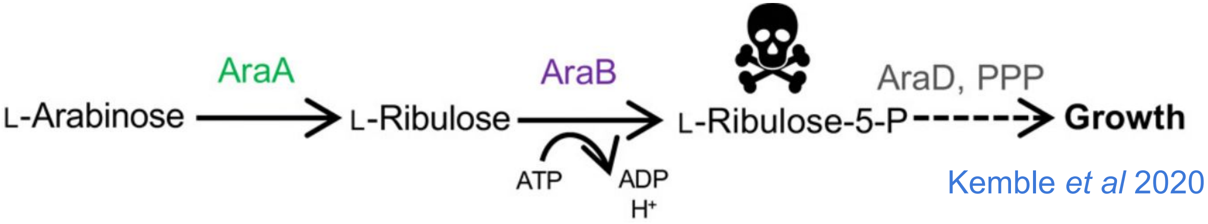

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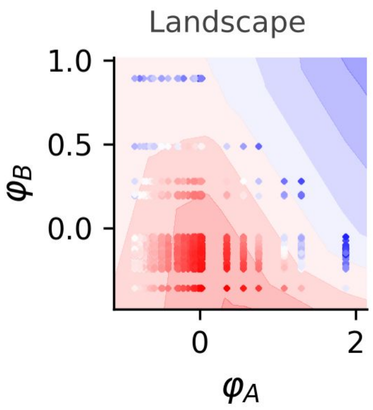

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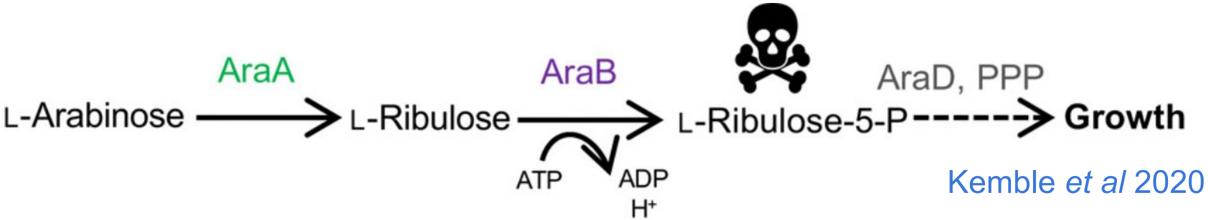

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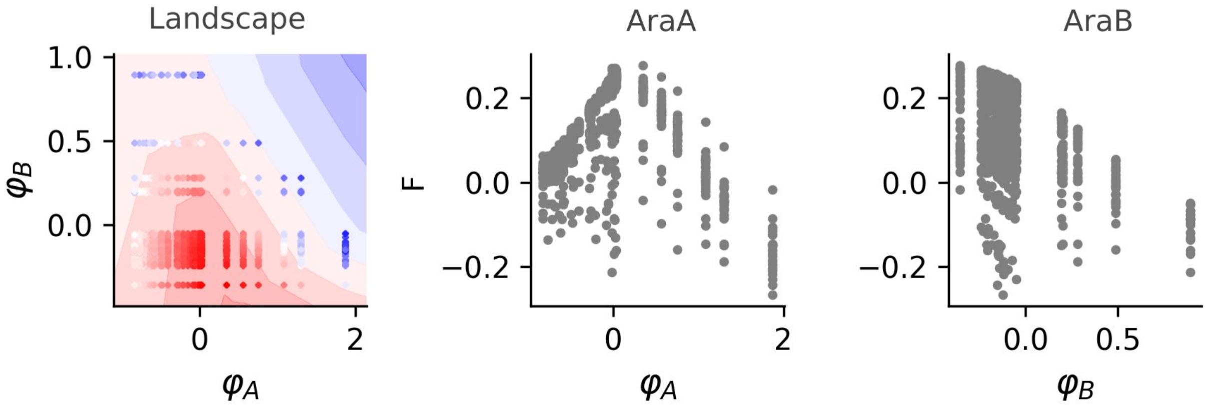
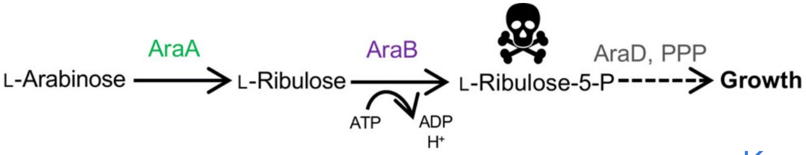


Recovery of biophysical/mechanistic insights



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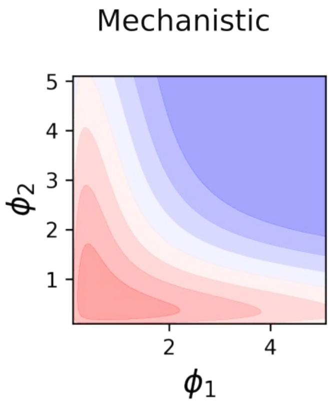
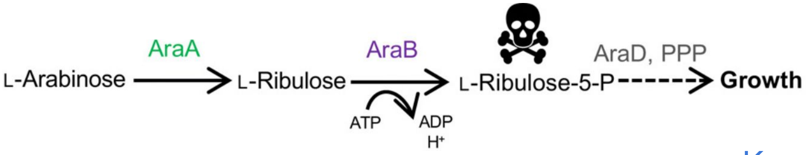
- **Previous biophysical modelling**
- **Latent variable correlated to earlier hypotheses**


Mechanistic

Recovery of biophysical/mechanistic insights



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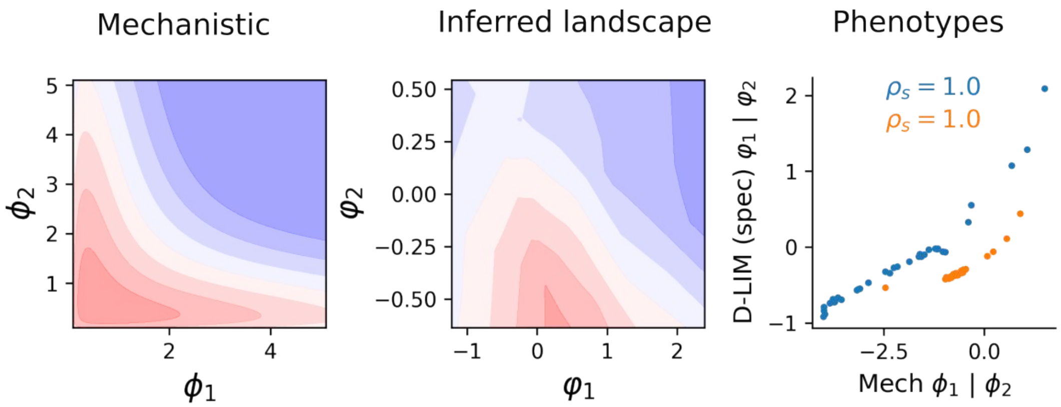
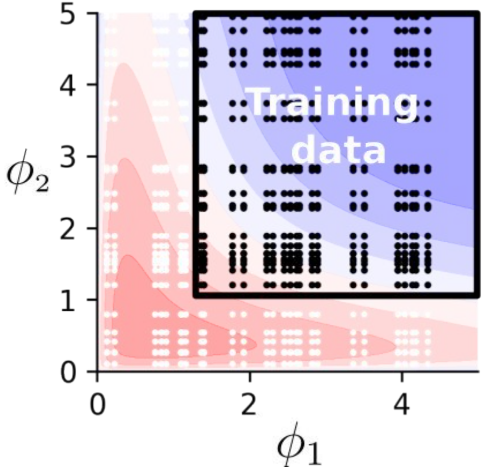


Extrapolate beyond training data

Latent ↔Phenotype map

- No data for high fitness

- Measure phenotypic values
  (Single measures ↔combinatorial measures)



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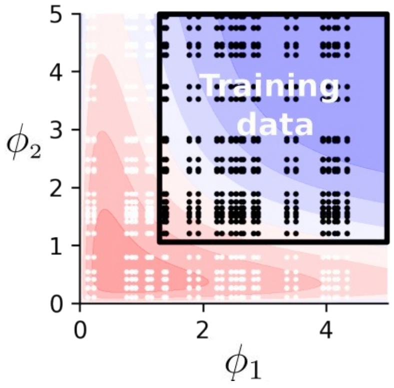

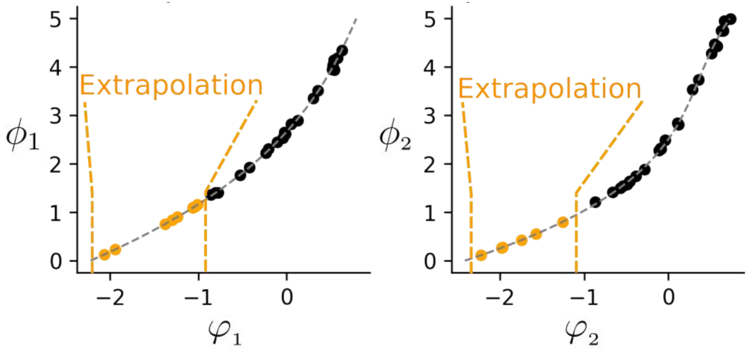

Latent ↔Phenotype map

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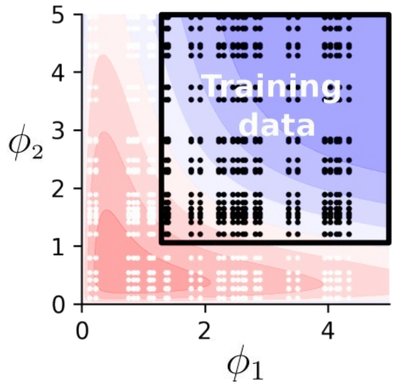
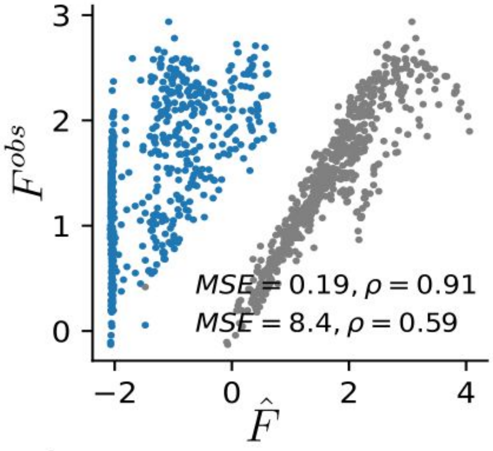
- Infer fitness



Fitting quality



Thank you !

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