

# How functional diversity and the role of a gene affect its evolutionary trajectory: large-scale population simulations of gene regulatory networks

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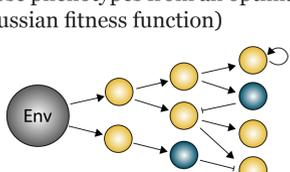
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## Motivation

- The genotype-phenotype relationship is one of the fundamental problems in quantitative and evolutionary biology
- How can we combine approaches from different biological fields to better understand the underlying genetic architecture of complex traits?
- In this study, we used simulations of evolving populations with complex gene regulatory network (GRN) dynamics to describe relationships between the role of a gene in its network, empirically observable quantities about that gene, and the gene's evolutionary trajectory

## GRN Model

- The networks were encoded in the individual genomes by 3 mutation types: structural (the activity of the gene), regulatory (binding sites), and loss-of-function mutations
- The network is activated by an environmental factor and does several iterations
- Gene expression depends on the expression of their activators/suppressors in the previous iteration
- The network produces phenotypes of the individual (the sum of expression of some genes at the last iteration)
- The individual fitness is defined by the differences of those phenotypes from an optimal phenotypes (the Gaussian fitness function)

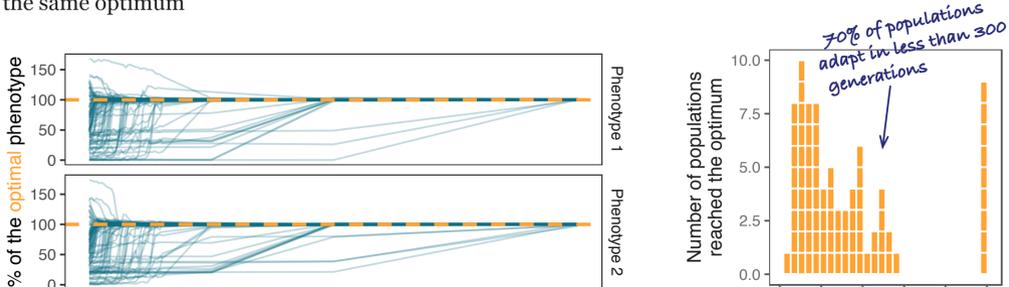


## Simulation parameters

- Individual-based forward time simulations in SLiM 3.3 (Haller & Messer, MBE, 2016)
- A random GRN with 100 genes (75% activators, 25% suppressors) for each simulation
- 10 iterations of the network
- 1 environmental factor
- 2 phenotypes (10 genes each)
- 50Mb genomes with several chromosomes
- Diploid hermaphrodites
- Generations overlap, they live up to age 8
- The population size of 5,000 individuals
- The optimum is 50% of the maximum possible phenotype
- 50,000 generations of burn-in
- Then, 20,000 generations of selection

## Populations adapt

- 60% of simulated populations increased their fitness by improving 2 phenotypes (the figure below)
- Analysis: 100 simulations that successfully adapted - different, random networks, trying to adapt to the same optimum

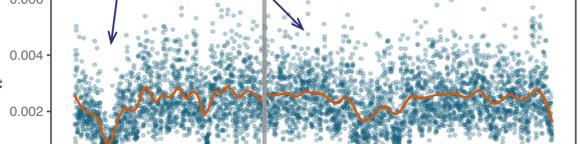


## Flexible framework

The SLiM framework is flexible and allows us to get all kinds of genetic, phenotypic, and demographic information about individuals.

To explore the evolution of the genetic architectures, we measured genetic diversity, additive genetic variance, performed *in silico* molecular biological experiments to assess perturbation sensitivity, and estimated network centrality statistics for each gene at 38 time-points of adaptation.

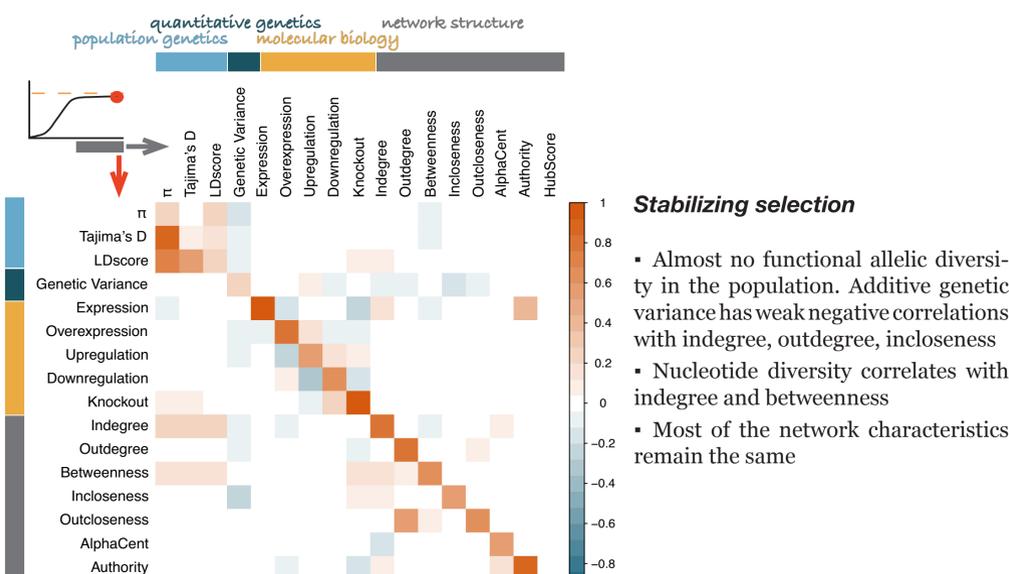
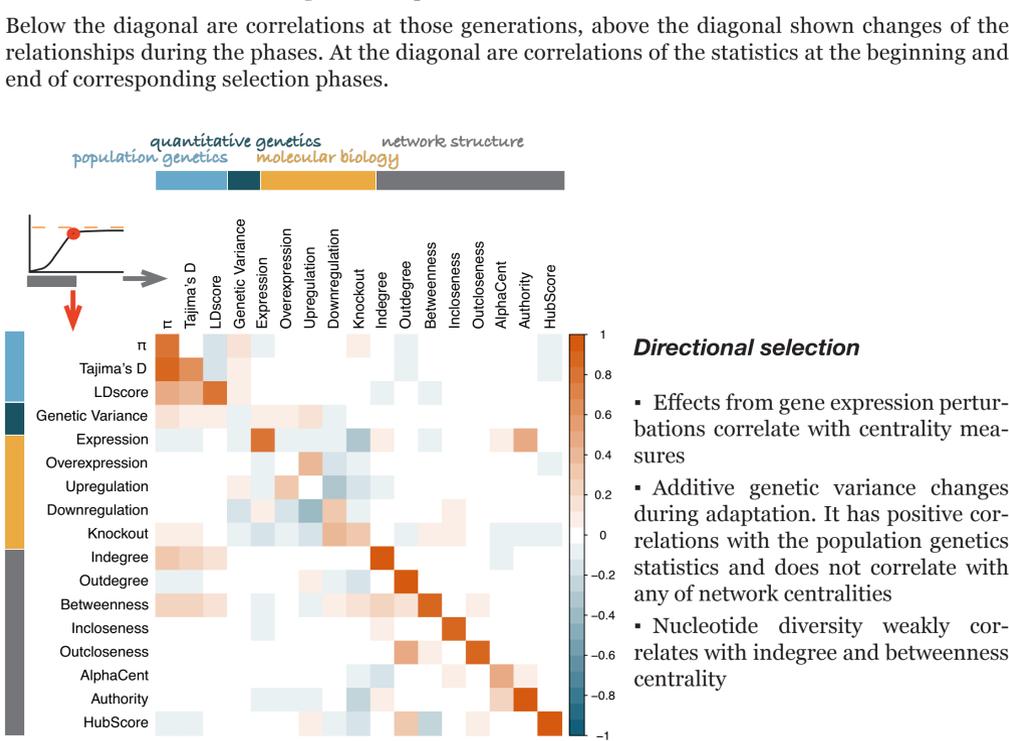
an example of the nucleotide diversity landscape in one population after 200 generations of selection there are sweeps!



## Evolution of GRN features

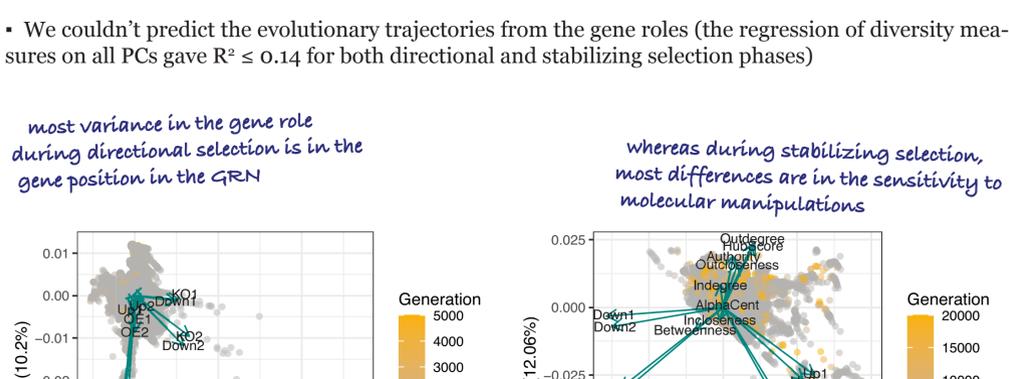
Correlations of statistics for the directional selection phase were measured at the generation where populations reached the optimum (both mean phenotypes were different by less than 2% from the optimum), and for the stabilizing selection phase at the end of simulations.

Below the diagonal are correlations at those generations, above the diagonal shown changes of the relationships during the phases. At the diagonal are correlations of the statistics at the beginning and end of corresponding selection phases.



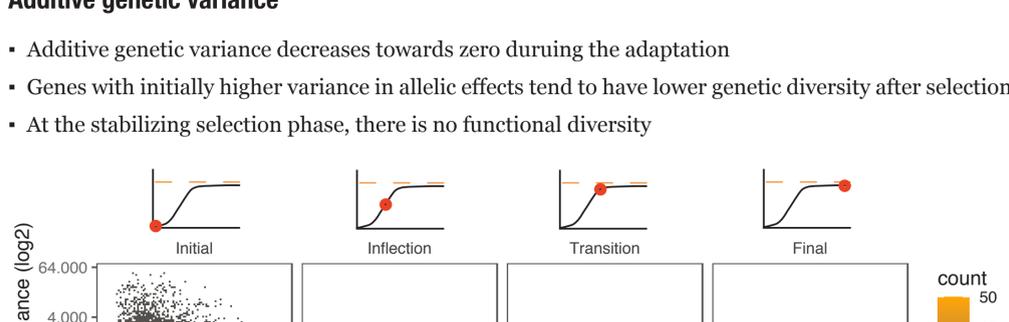
## Roles of the genes

- We quantified the 'role' of a gene using 16 variables combining both the effects of gene expression perturbations on phenotype and the network centrality measures. The position of all genes in a PCA of these variables across all networks is shown below.
- We couldn't predict the evolutionary trajectories from the gene roles (the regression of diversity measures on all PCs gave  $R^2 \leq 0.14$  for both directional and stabilizing selection phases)



## Additive genetic variance

- Additive genetic variance decreases towards zero during the adaptation
- Genes with initially higher variance in allelic effects tend to have lower genetic diversity after selection
- At the stabilizing selection phase, there is no functional diversity



## Conclusions

- Selection reduces nucleotide and functional diversity in populations
- We cannot predict evolutionary trajectories of the genes from their functions
- Evolutionary trajectories are highly dependent on availability of functional genetic variation

