



Agent-based simulations and network analyses reveal the strain structure of falciparum malaria

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Introduction

Background

- The parasite *Plasmodium falciparum* is the causative agent of malaria, a major human health burden in sub-Saharan Africa.
- In endemic areas of high transmission, tens of thousands of genes encode for the major antigen of the parasite (a molecule recognized by the immune system), resulting in an exorbitant number of distinct parasite strains, which cause chronic malaria infections.

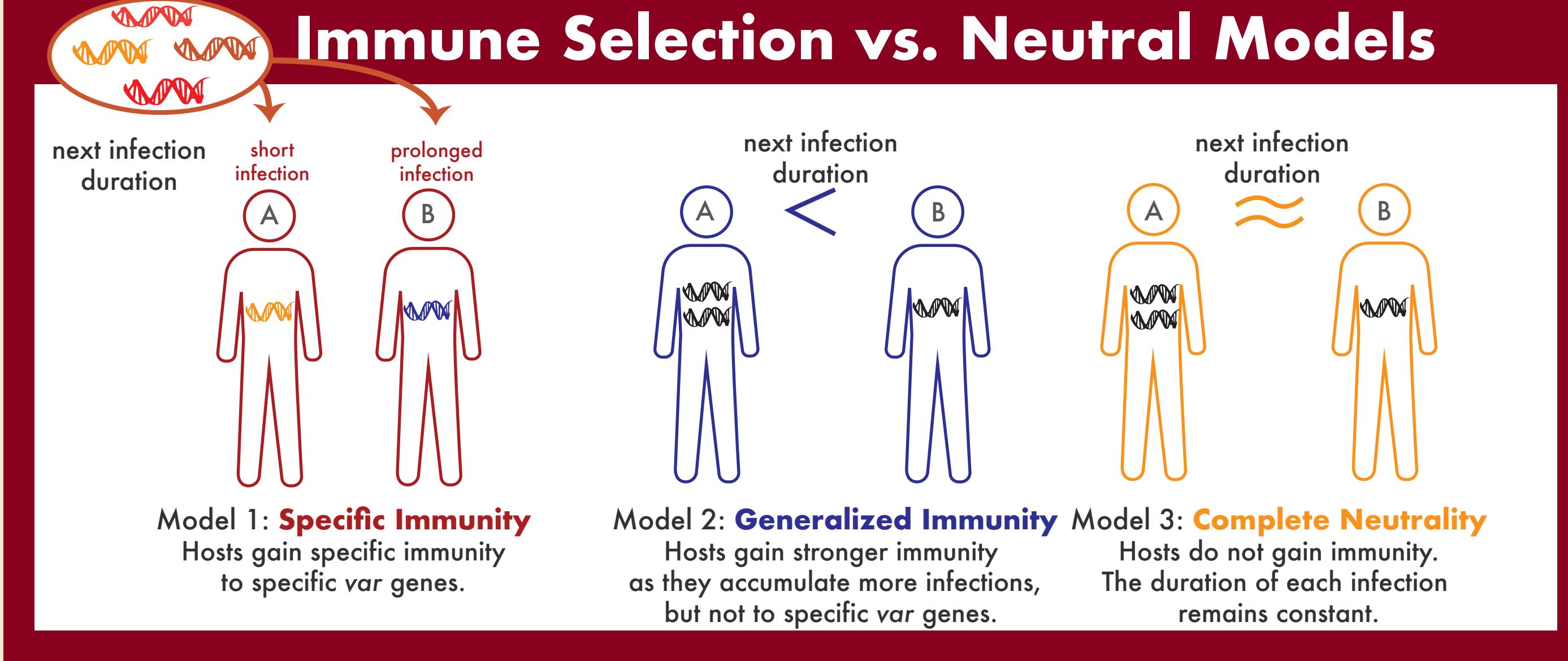
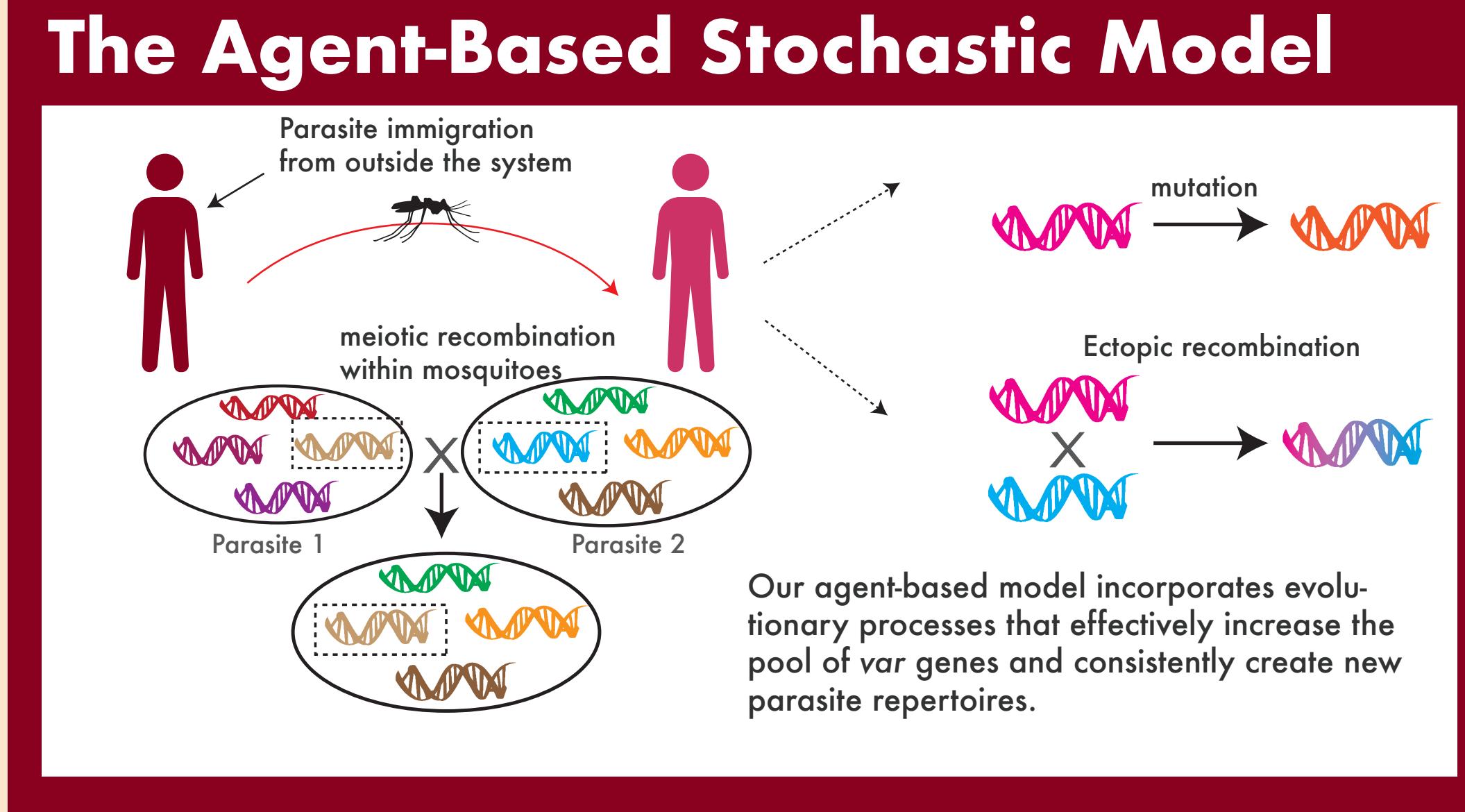
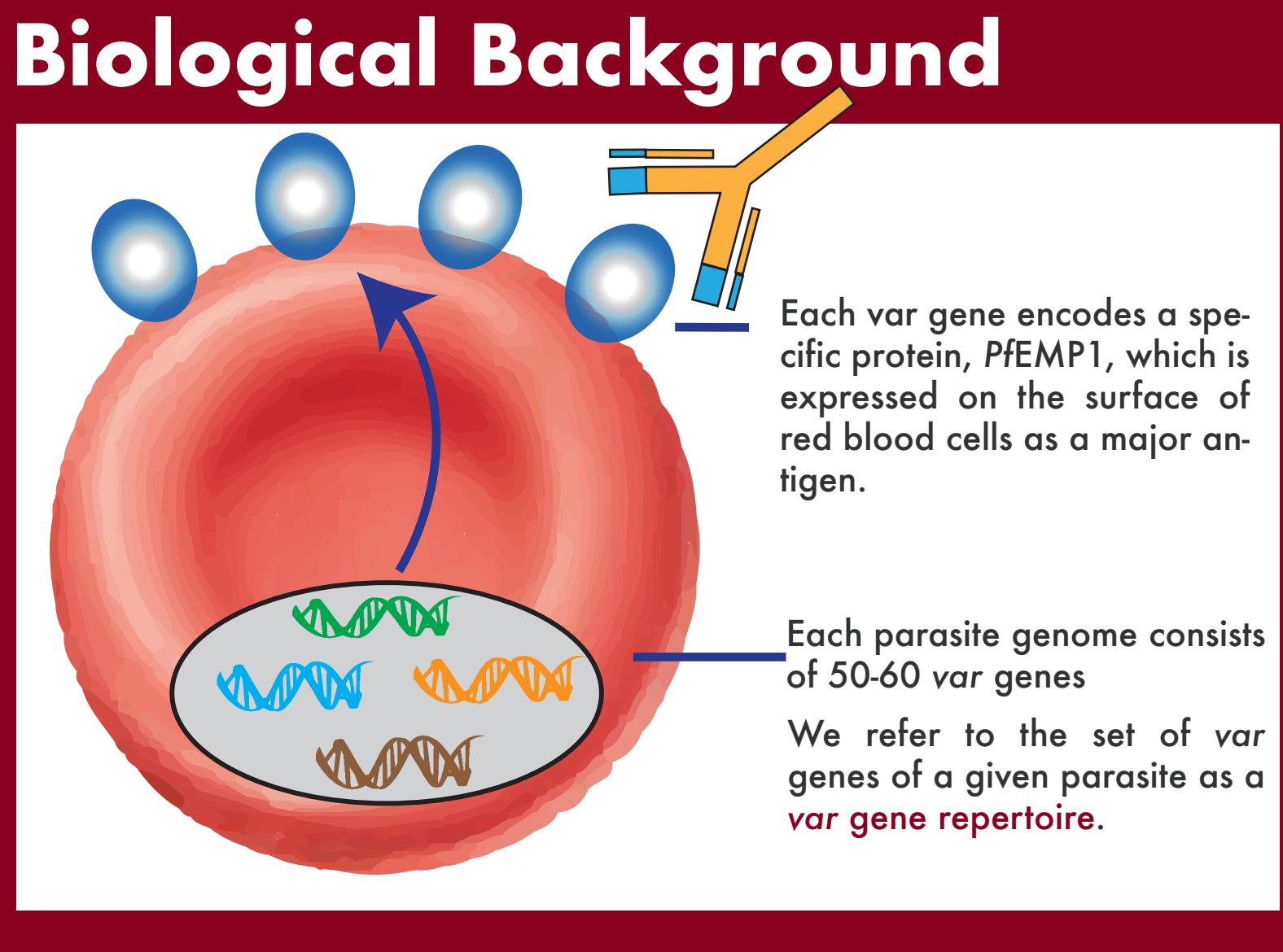
Question

- Human hosts gain specific immunity towards the different antigens they have been exposed to. This population memory gives an advantage to rare gene variants and a disadvantage to common ones. It is unclear, however, whether such immune selection acts as a dominant force in structuring parasites' enormous diversity, especially given the opposing mixing effect of high recombination rates.
- We propose the combination of network analyses of genetic similarity with agent-based models that track immune memory in each host, to identify signatures of dominant processes underlying strain structure.
- We test our theoretical predictions using empirical molecular data from Ghana, unique in their depth of population sampling.

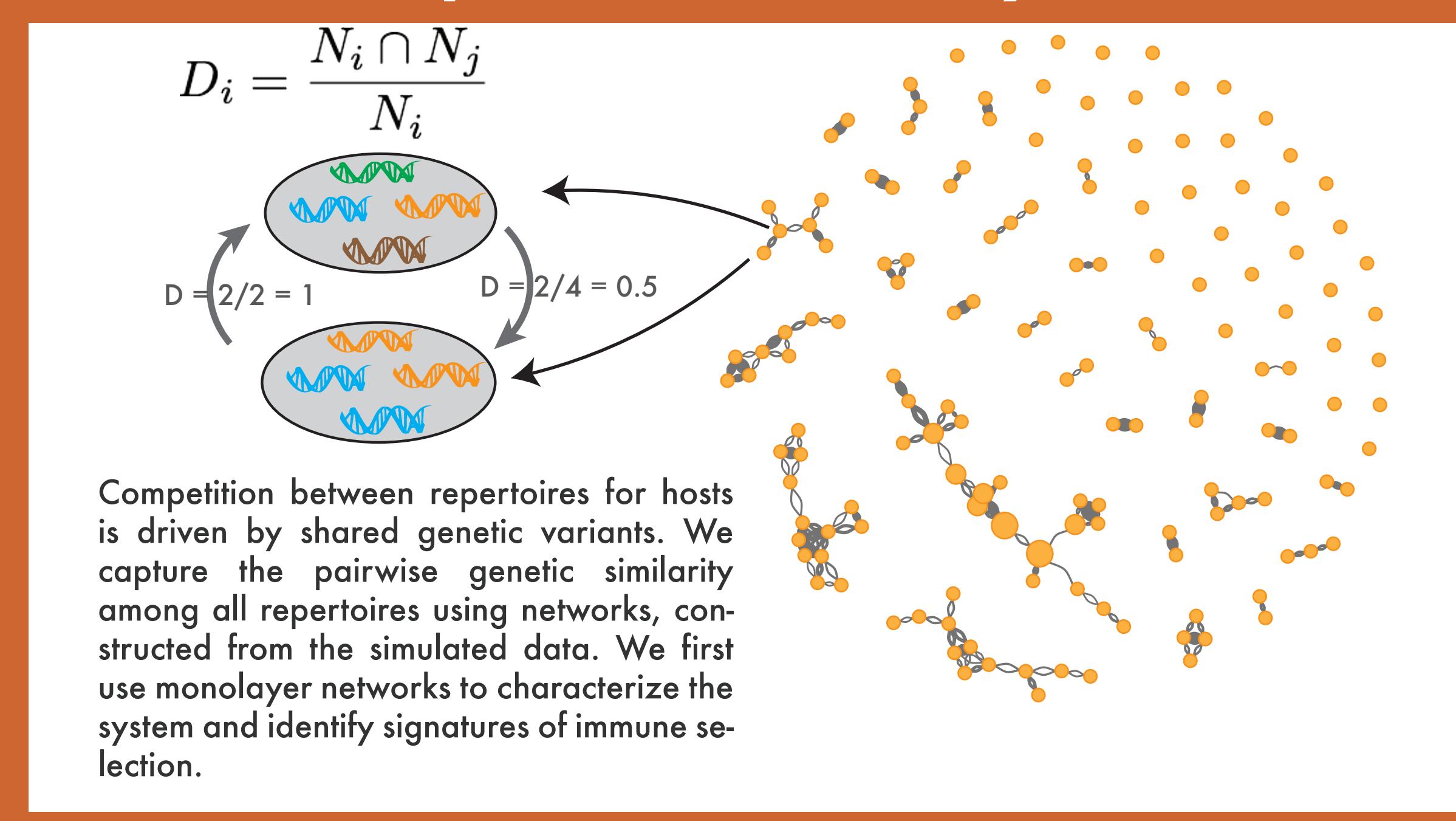
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Aim

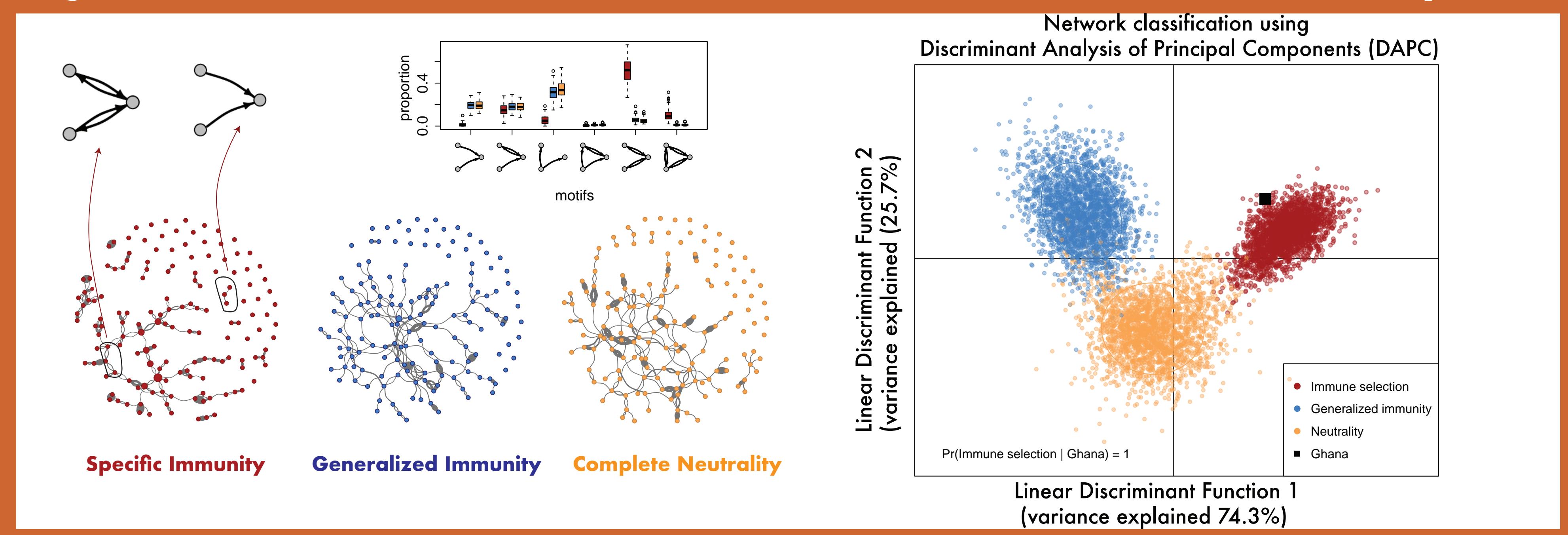
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Var Gene Repertoire Similarity Networks

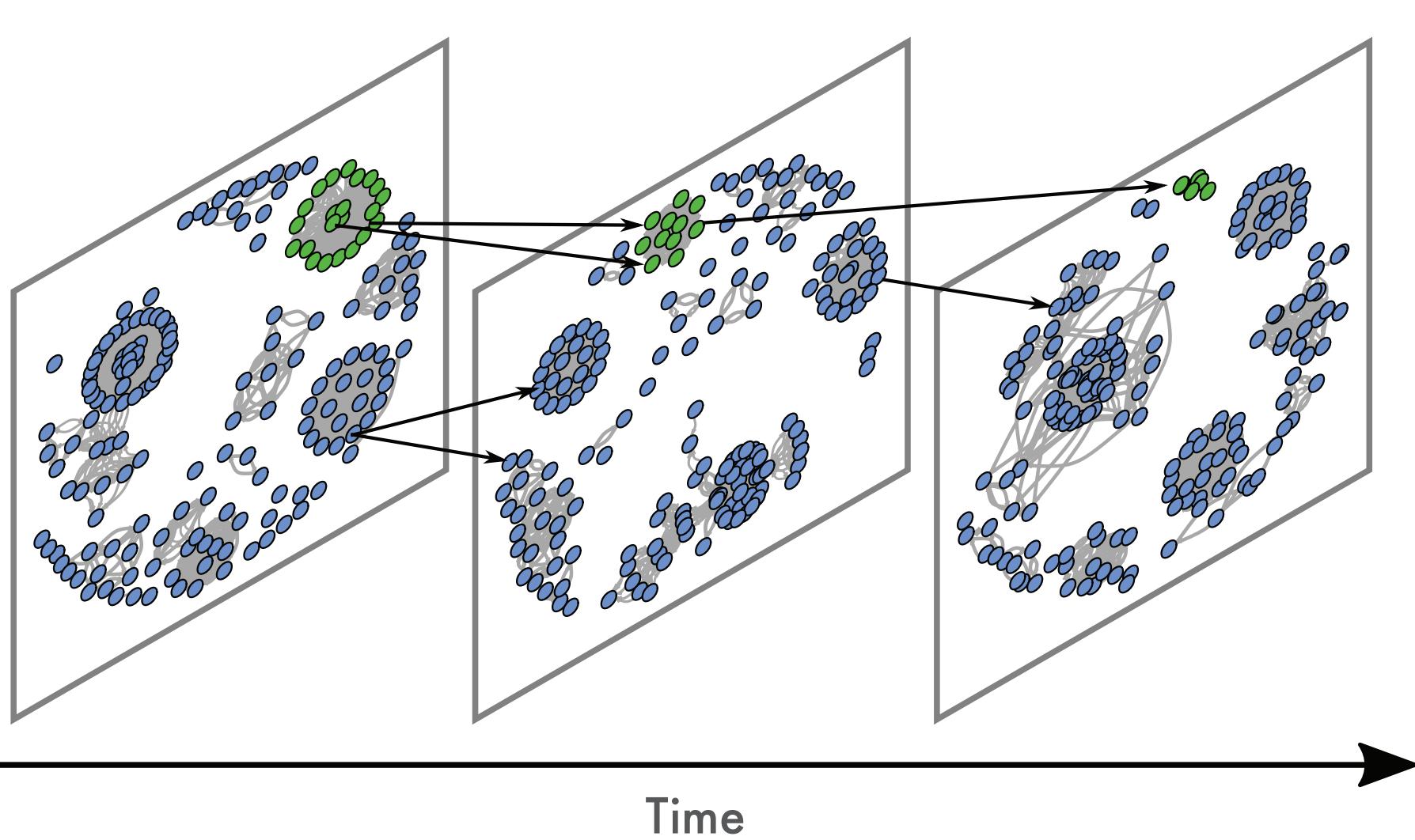


Signatures of Immune Selection Identified Based on Network Properties



Definition of Temporal Networks

We use multilayer networks to describe the evolution of the population structure in time. Interlayer edges are defined in the same way as intralayer edges, but are unidirectional.

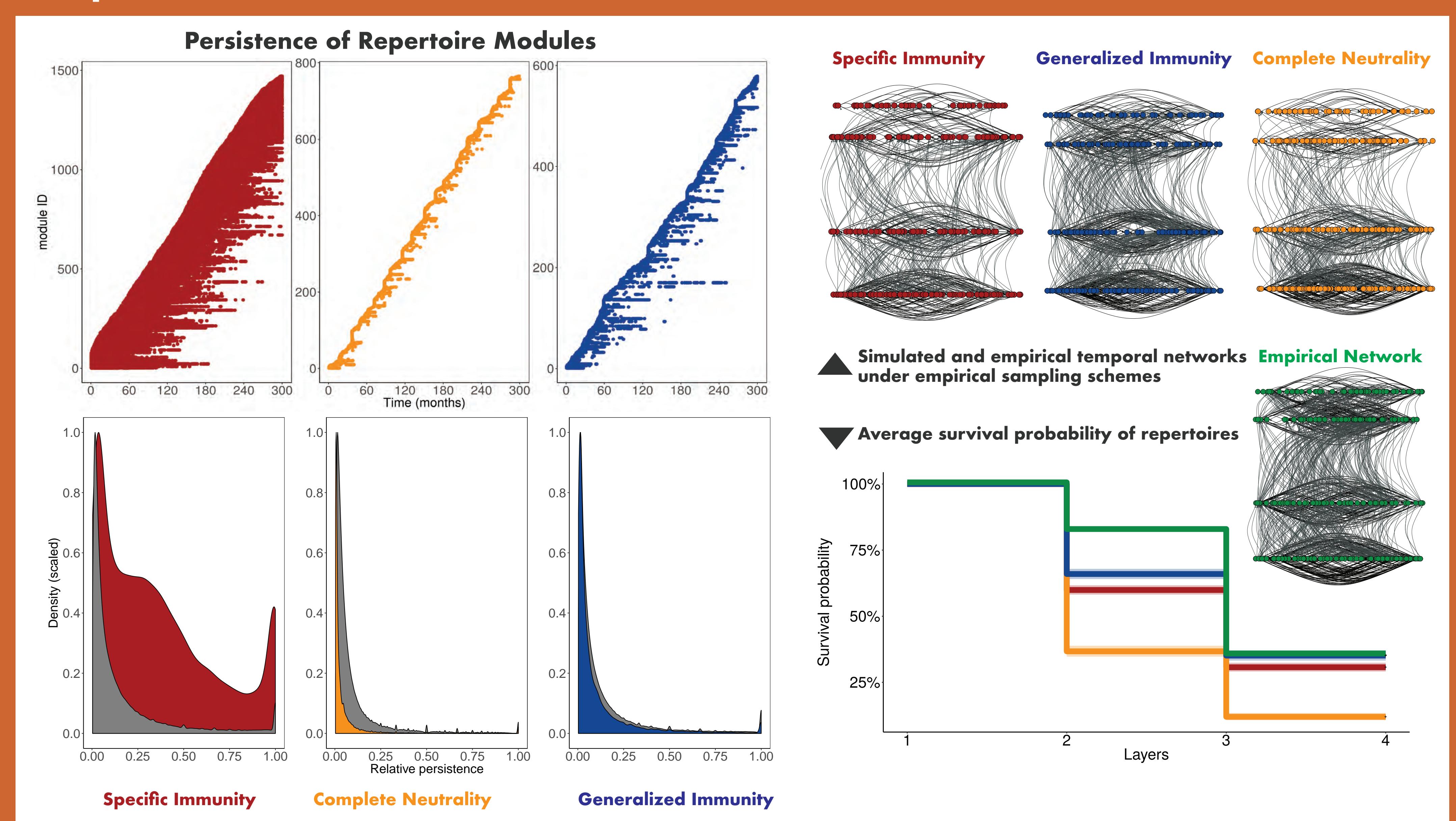


We look for temporal structure by analyzing the partitioning of the network into modules with Infomap (<http://www.mapequation.org>).

A module represents a group of repertoires which are more similar to each other than to other repertoires in the network, and persist in time.

We quantify the persistence of the modules. Persistence is a key biological property because immune selection should promote long-lived modules.

Temporal Networks Reveal Niche Persistence Under Immune Selection



Conclusions

- Networks of repertoire similarity show distinctive signatures of immune selection when compared to networks obtained with neutral models.
- Temporal multilayer networks reveal longer persistence of repertoire modules in the immune selection model than in its neutral counterparts.
- Modules represent specific niches in the antigenic space of the human population, and therefore persist much longer than their repertoire members, which change faster due to evolution.
- Application of these network analyses to empirical isolates from asymptomatic infections from local populations in Ghana provides unequivocal evidence for an important role of immune selection at both static and temporal levels.
- Frequency-dependent competition between parasites for hosts (i.e., immune selection) enables the coexistence of a large number of gene variants and strains, with patterns of limiting similarity that differ from typical niches at lower dimensionality.
- Monitoring var gene diversity and structure in responses to control efforts becomes central to understanding malaria epidemiology.

Acknowledgments

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