Parasite (antigenic) diversity
and 'old' and resilient transmission systems

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and

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Hyper-endemic regions : (asymptomatic) infection of all ages

Community gathering
for project participation

Gabon: all children
Ghana: Repeated surveys (2000 people)

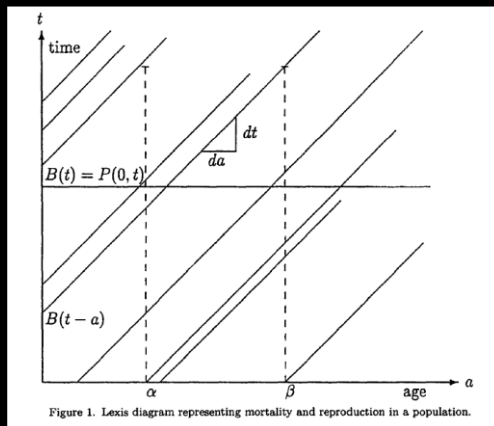**~40-80 % prevalence in asymptomatics**

With **Prof. Karen Day** (Melbourne) and colleagues from Noguchi Memorial Institute (Ghana)

Blood samples and questionnaires in the field

Epidemiological models largely treat age as chronological age

Figure 1. Lexis diagram representing mortality and reproduction in a population.

From Keyfitz and Keyfitz, Math. Comput. Modelling 1997

The McKendrick- von Foerster (partial-differential) equation for structured populations

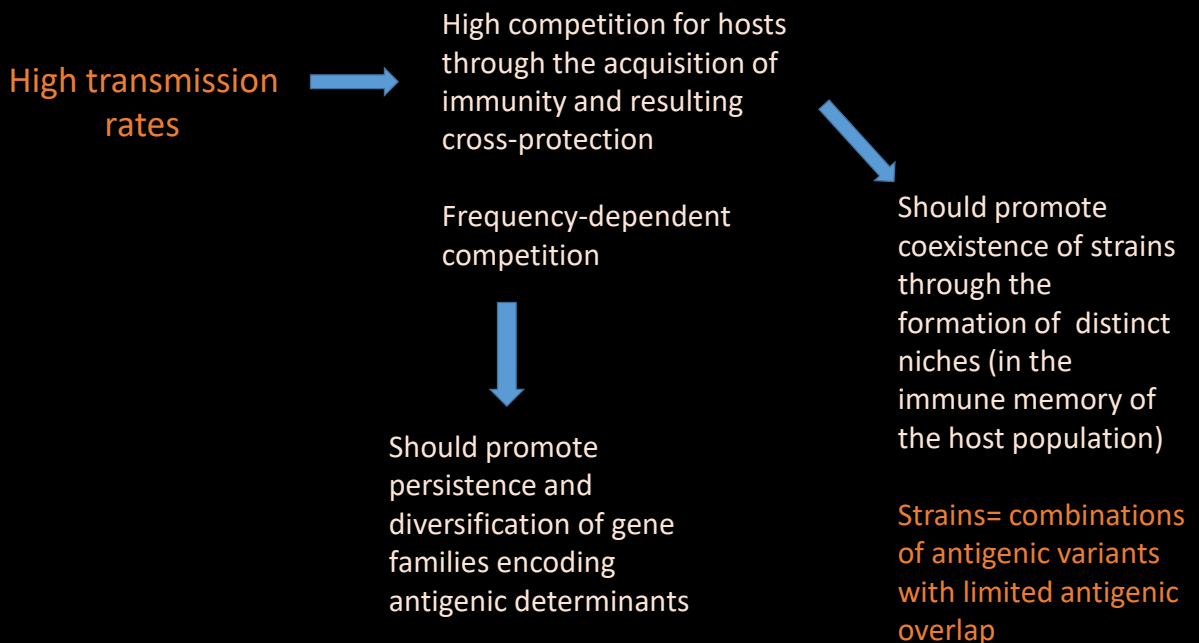$$\frac{\partial P}{\partial t} + \frac{\partial P}{\partial a} + \mu(a)P = 0,$$

1926

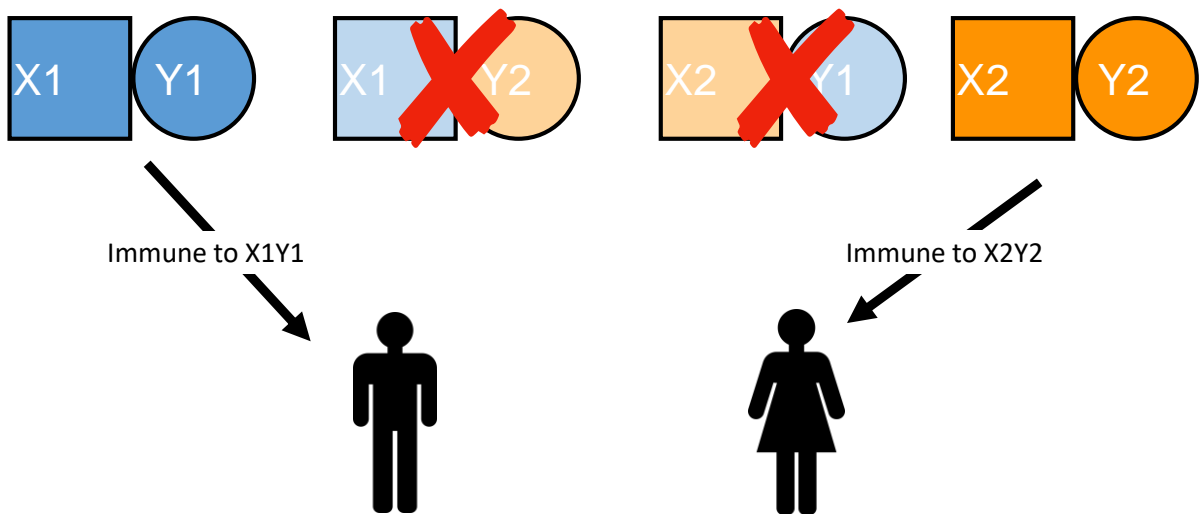## e.g.: model for endemic malaria in Sub-Saharan Africa

$$\frac{\partial S}{\partial t} + \frac{\partial S}{\partial a} = aR - (\lambda(a) + \mu)S$$

$$\frac{\partial I_1}{\partial t} + \frac{\partial I_1}{\partial a} = \lambda(a)S - (\tau_1 + \mu)I_1$$

$$\frac{\partial R}{\partial t} + \frac{\partial R}{\partial a} = \tau_1 I_1 + \tau_2 I_2 - (\lambda(a) + \alpha + \mu)R$$

$$\frac{\partial I_2}{\partial t} + \frac{\partial I_2}{\partial a} = \lambda(a)R - (\tau_2 + \mu)I_2$$

Aguas et al, Plos One 2008

High transmission rates → High competition for hosts through the acquisition of immunity and resulting cross-protection

Frequency-dependent competition

↓

Should promote persistence and diversification of gene families encoding antigenic determinants

Should promote coexistence of strains through the formation of distinct niches (in the immune memory of the host population)

Strains= combinations of antigenic variants with limited antigenic overlap

Strain theory

Immune to X1Y1

Immune to X2Y2

Gupta et al. 1994, 1996, 1999

PfEMP1: a surface protein encoded by a hyperdiverse and multicopy gene family

- Cytoadherence to microvasculature
- Sequestration in different tissues
- Severity of disease

- **Immune evasion**
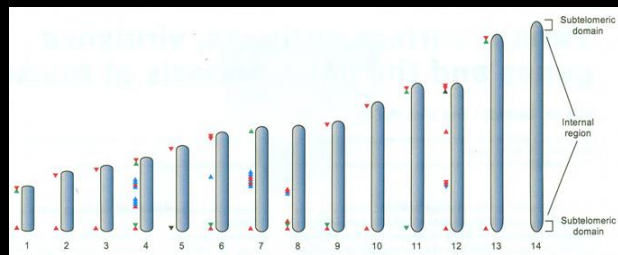
From Deitsch and Hviid, Trends in Parasitology 2004

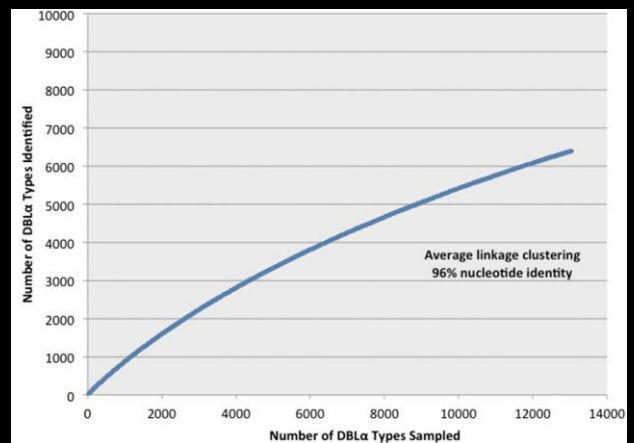A parasite = a repertoire / combination of 50-60 var genes

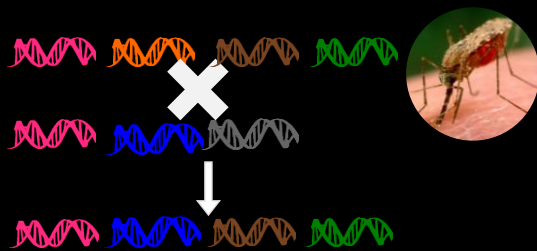# Vast diversity of *var* gene variants in local populations

Cumulative diversity curves
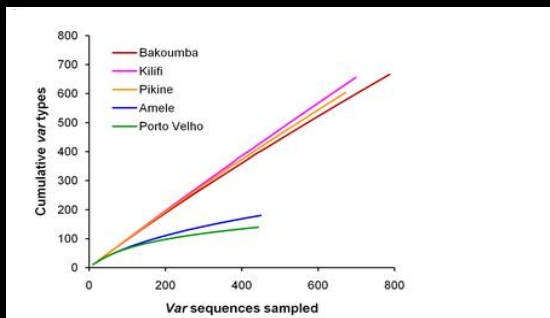
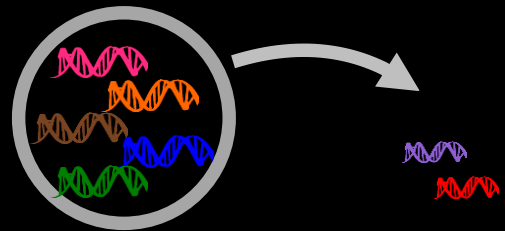Bongo, Ghana

Chen et al., PloS ONE 2011

Day et al. PNAS 2017

Mechanisms of local diversity generation
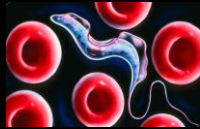
Mitotic recombination
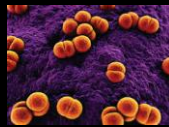
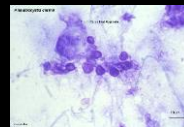Meiotic recombination

Migration

Other parasites relying on 'combinatorics' and multicopy genes for antigenic variation

Protozoa:
Trypanosoma brucei
Vsg ~1000 copies

Bacteria:
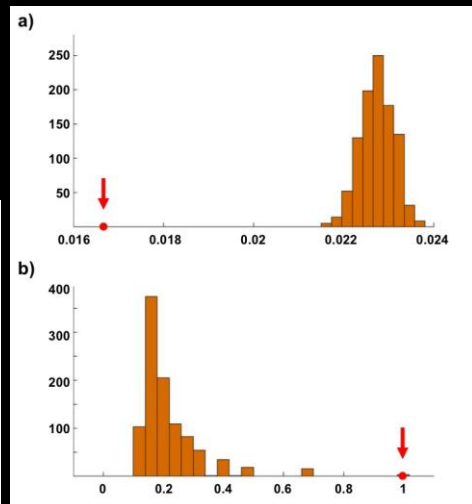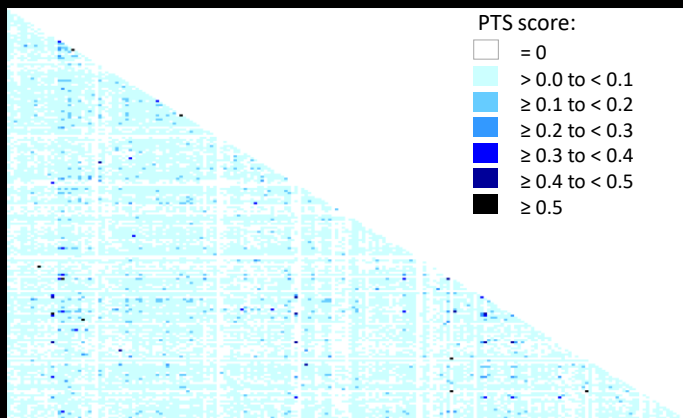*Neisseria meningitidis*
pil ~19 copies

Fungi:
Pneumocystis carinii
msg ~85 copies

➢ Is frequency-dependent competition able to generate strain structure despite high recombination rates and a large pool of variation?

➢ What would be a strain? Are there persistent combinations of variants?

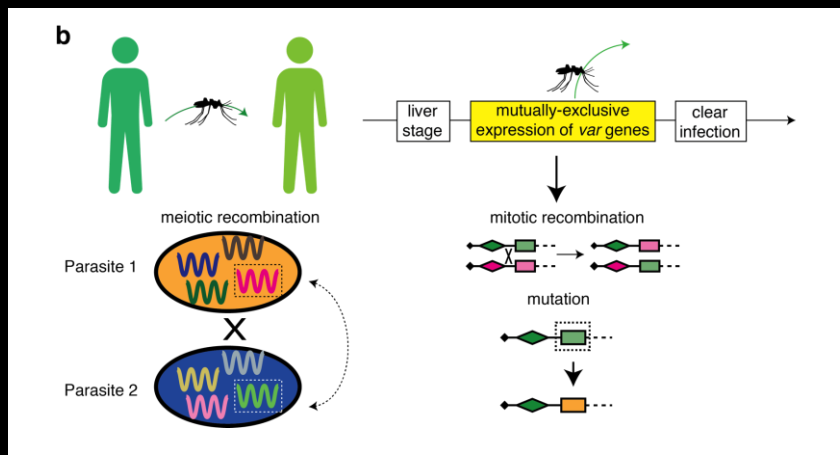➢ (What are empirical signatures of immune selection?)

Non-random structure of repertoires?

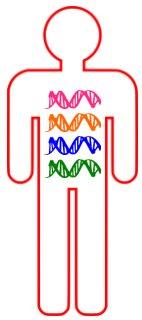$$PTS_{ij} = \frac{N_i \cap N_j}{N_i + N_j}$$

PTS score:
- ☐ = 0
- ☐ > 0.0 to < 0.1
- ☐ ≥ 0.1 to < 0.2
- ☐ ≥ 0.2 to < 0.3
- ☐ ≥ 0.3 to < 0.4
- ☐ ≥ 0.4 to < 0.5
- ■ ≥ 0.5

Day *et al, PNAS 2017*
Rorick *et al, Ecol. & Evol. 2018*

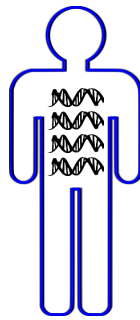# Individual-based formulation: stochastic model

He *et al*. Nature Communications 2018

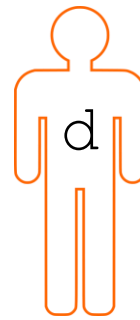# Dynamic process-based neutral models

Number of *var* epitopes seen

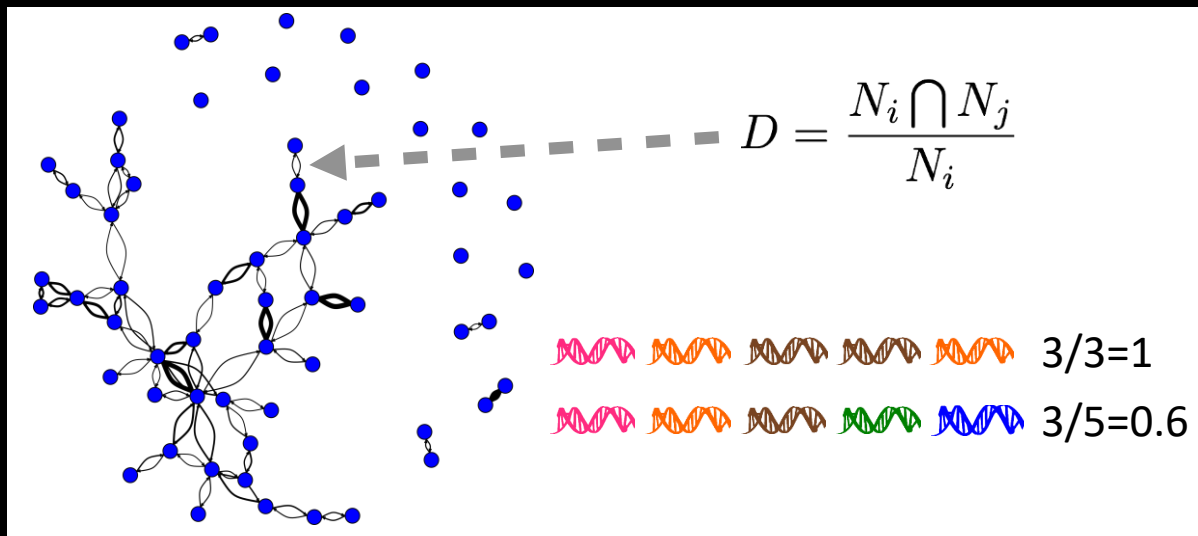Immune selection

Number of infections

Generalized immunity

Constant

Complete neutrality

Networks of genetic similarity of repertoires

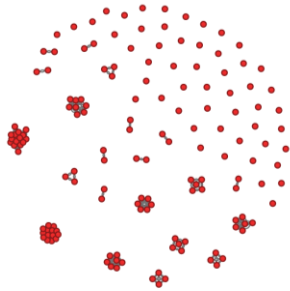$$D = \frac{N_i \bigcap N_j}{N_i}$$

3/3=1

3/5=0.6

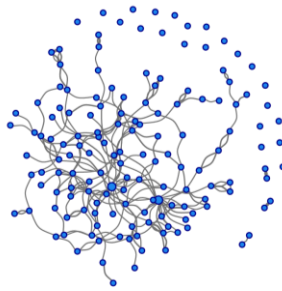He et al., Nature Communications 2018

Network properties reveal distinctive signatures of selection
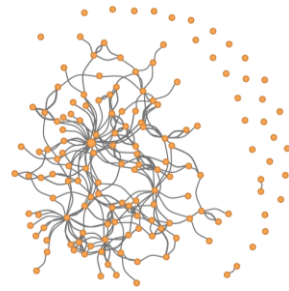

Medium var diversity (South Asia/Pacific)

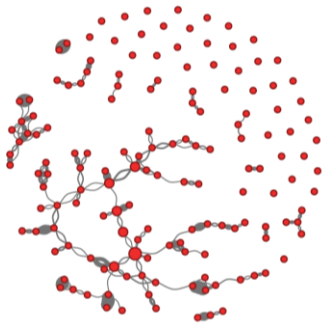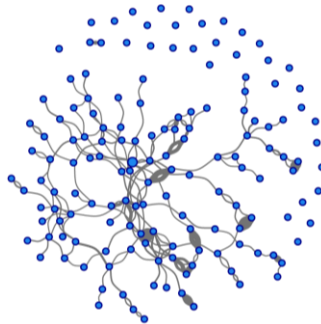1-Immune Selection   2-Generalized Immunity   3-Neutrality
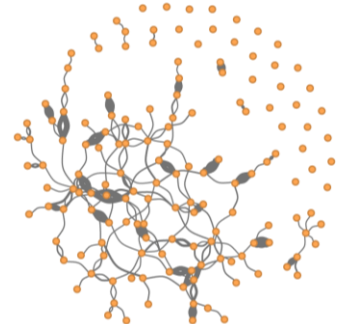
High diversity
(characteristic of West Africa)

1-Immune Selection   **2-Generalized Immunity**   **3-Neutrality**

Ghana data is classified with immune selection networks

Discriminant analysis of principal components

LD2

LD1

Pr(Immune selection | Ghana) = 1

- Immune selection
- Generalized immunity
- Neutrality
- Ghana
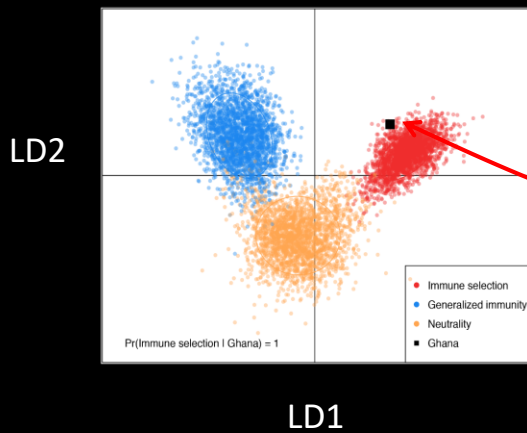
Ghana data:
two seasons / isolates with
multiplicity of infection = 1

- S1
- S2
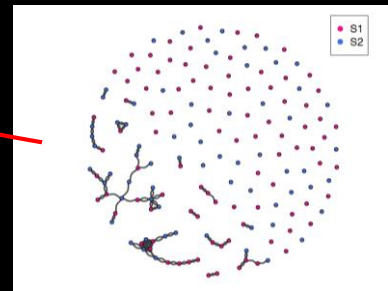
He *et al.*, *Nature Communications 2018*

Network structure in time?

Pilosof *et al. in review.*
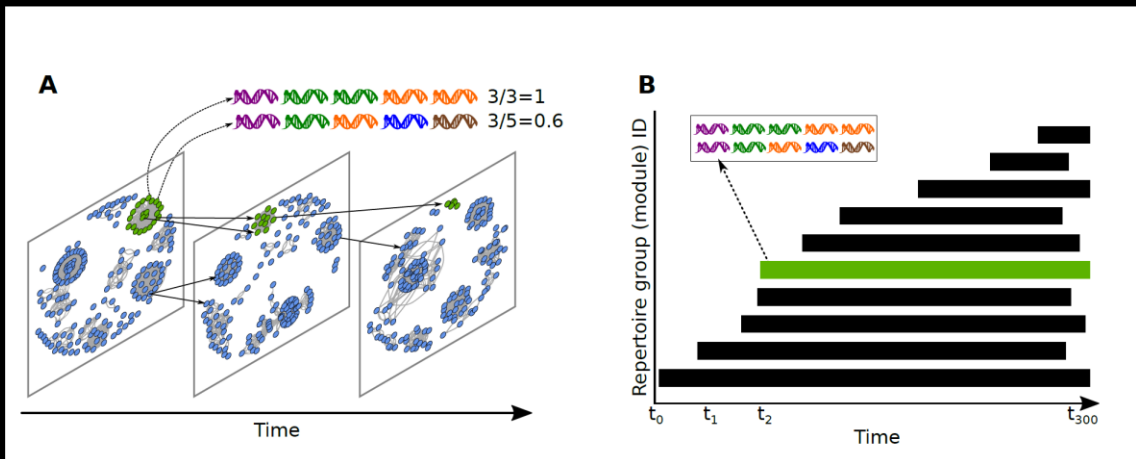
Identifying Modular Flows on Multilayer Networks Reveals Highly Overlapping Organization in Interconnected Systems

Manlio De Domenico,[1] Andrea Lancichinetti,[2] Alex Arenas,[1] and Martin Rosvall[2]

PRX 2015

Persistence of modules is enhanced by host immunity

Full model

Neutral model

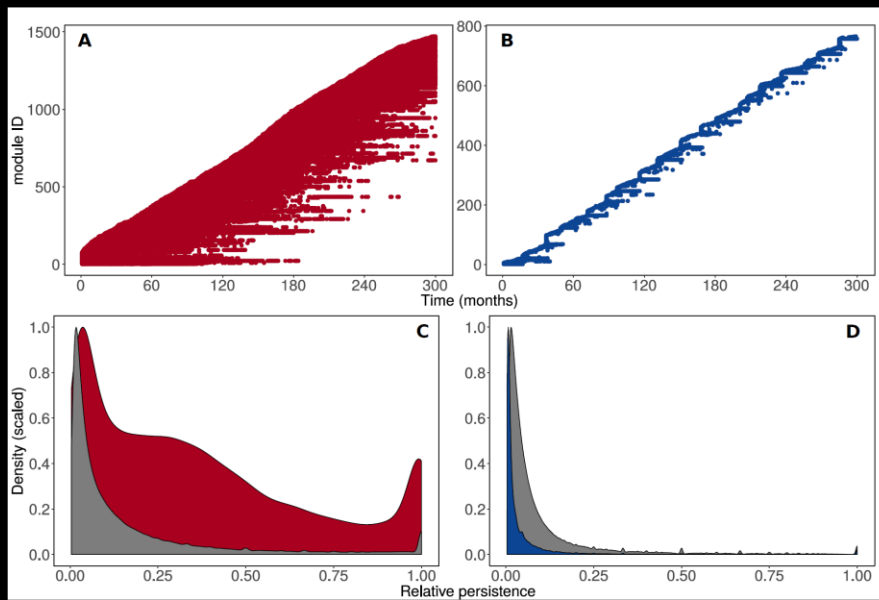## Some conclusions and questions:

➢ Antigenic diversity underlies the large reservoir of infection in individuals of all ages.

➢ The vast genetic diversity of *P. falciparum* repertoires in local populations is enabled by frequency-dependent competition between parasites through host immunity.

➢ A rich structure of antigenic diversity emerges that is both non-random and non-neutral. When analyzed over time, this structure allows us to recover clusters of parasites that would constitute strains.

➢ The same selection force that underlies the long persistence ('age') of *var* genes over evolutionary times influences the persistence of strains over epidemiological/ecological times.

➢ Balancing selection generates and maintains diversity at multiple levels of organization.

➢ The vast diversity of strains goes hand-in-hand with the vast diversity of the gene pool from which the system is assembled.

Endemicity (high transmission) involves by default a high-dimensional 'trait' space in which simple niche partitioning is no longer possible

Still: a structured antigenic diversity

INFLUENCE ON THE DYNAMICS OF ELIMINATION?

WHAT ARE COARSE-GRAINED REPRESENTATIONS OF THE TRANSMISSION SYSTEM?
(generalized vs. specific memory).

Under superinfection: a **critical transition** with alternative steady states
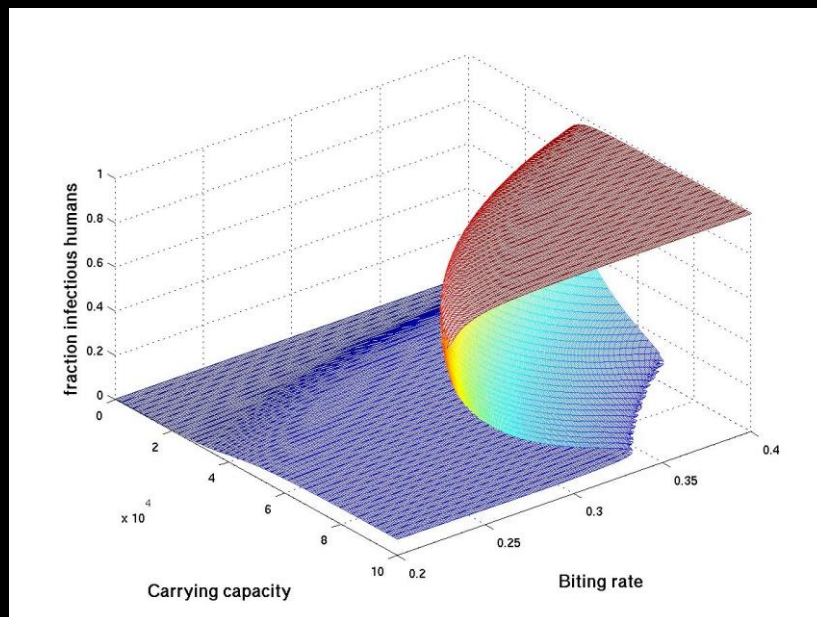
Gracias

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Shazia Ruybal, UMelb

Kathryn Tiedje, UMelb

NIH-NSF Ecology of Infectious Diseases