



22nd International HIV Dynamics & Evolution

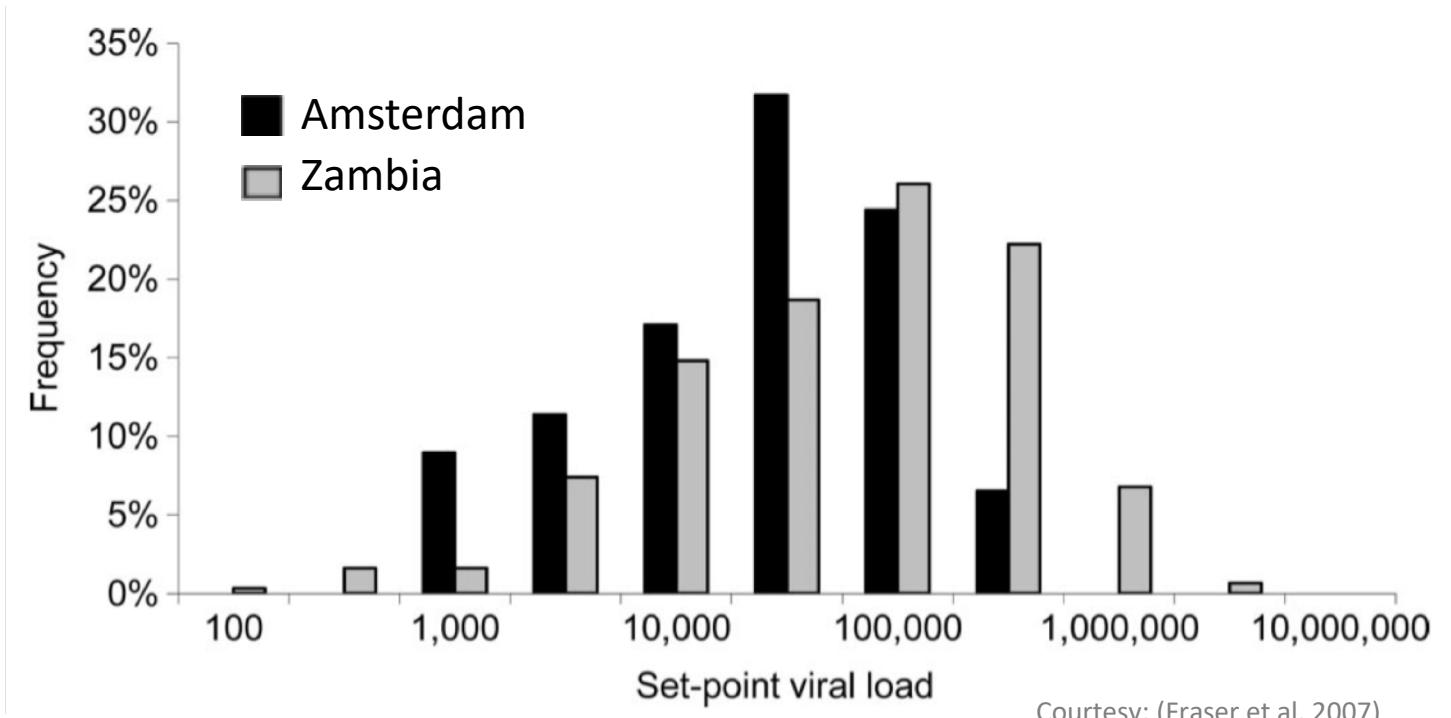
Promoting discussion between HIV specialists

The Spreadability of Pathogen Traits: Bridging Within- and Between-Host Evolution

Venelin Mitov, prof. Tanja Stadler



What shapes the distribution of set-point viral load?



Within-host selection for fittest strain

(Lythgoe et al. 2013, van Dorp et al. 2014 ...)

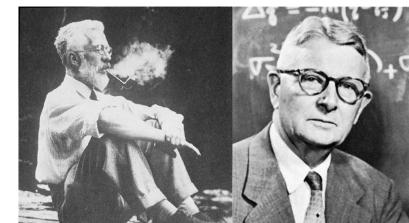
vs

Between-host selection for maximum transmission potential

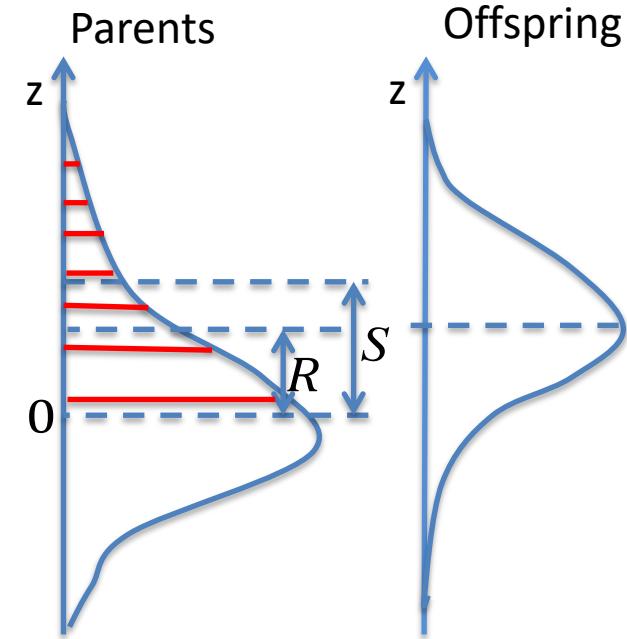
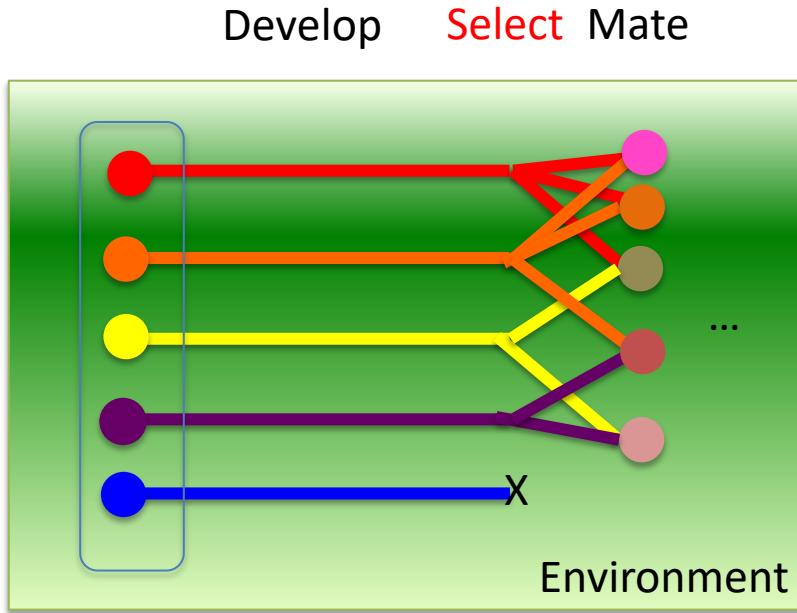
(Fraser et al. 2007)

Selection for transmission potential can have an effect on the observed distribution, only if an amount of information about spVL gets transferred at infection from a donor to a recipient.

The A, B and C of Quantitative Genetics

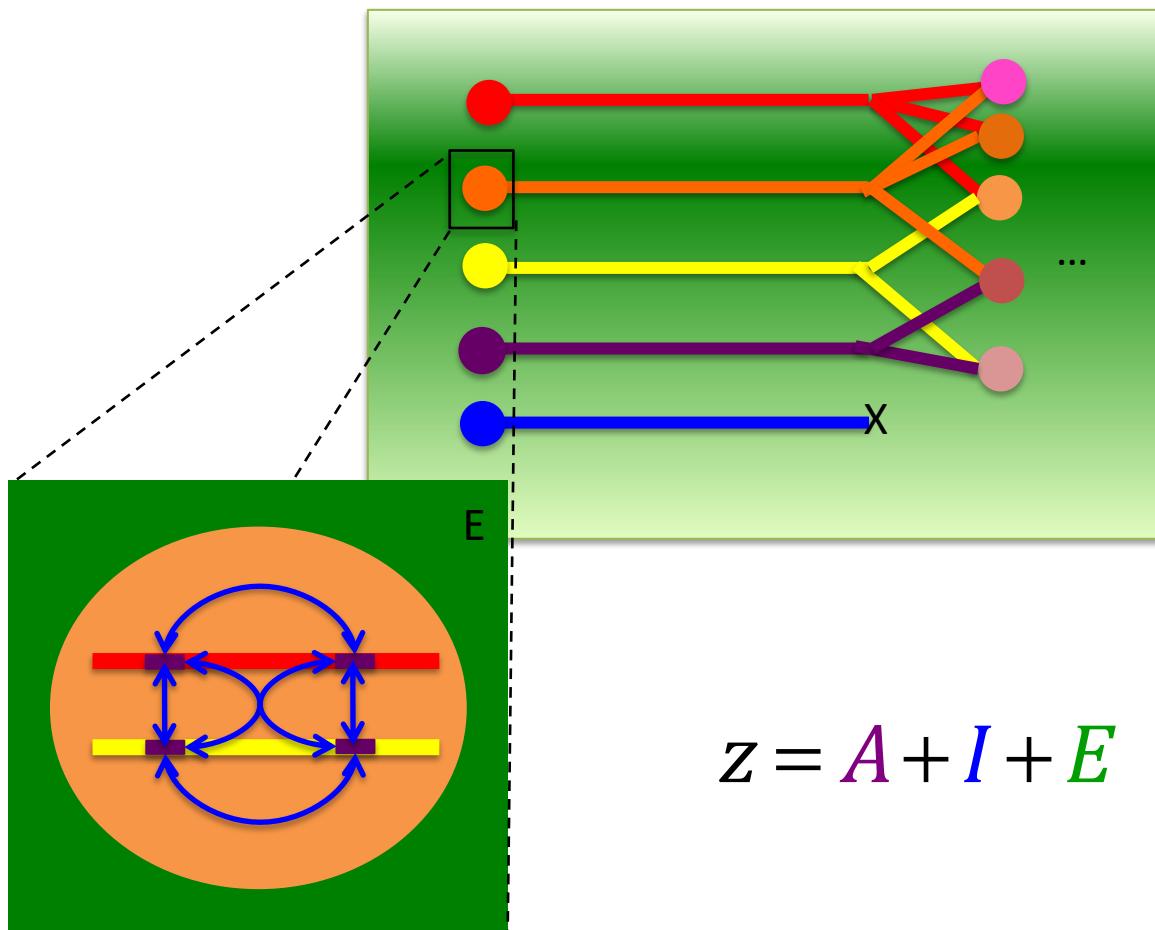


Can we guess properties of the offspring from properties of the parents?

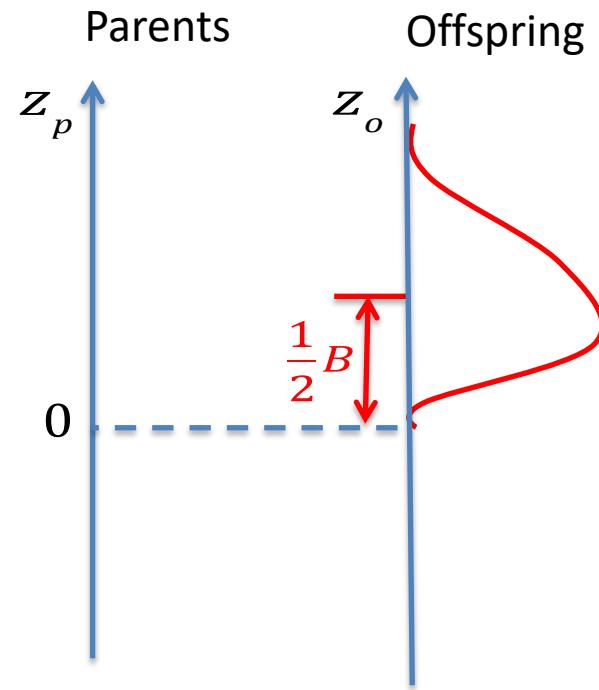
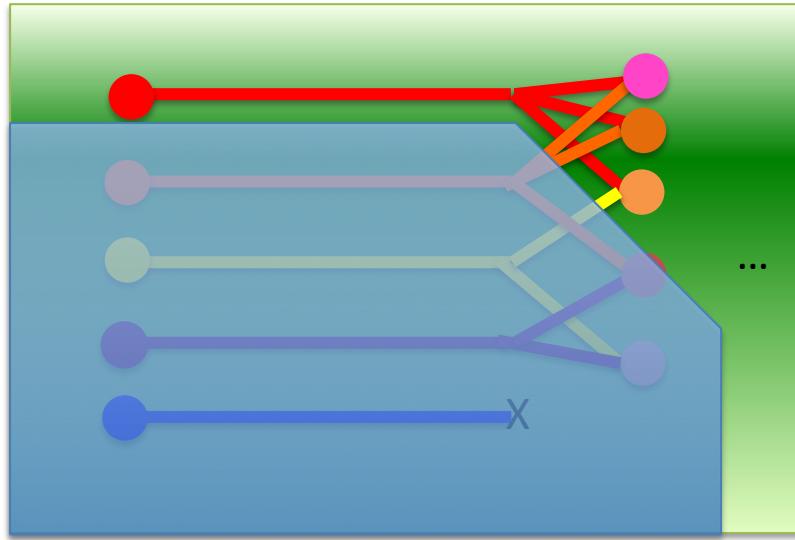


- Measured phenotype: z
- Mean phenotypes:
 - Parent generation: 0 ; Selected parents: S
 - Offspring: R

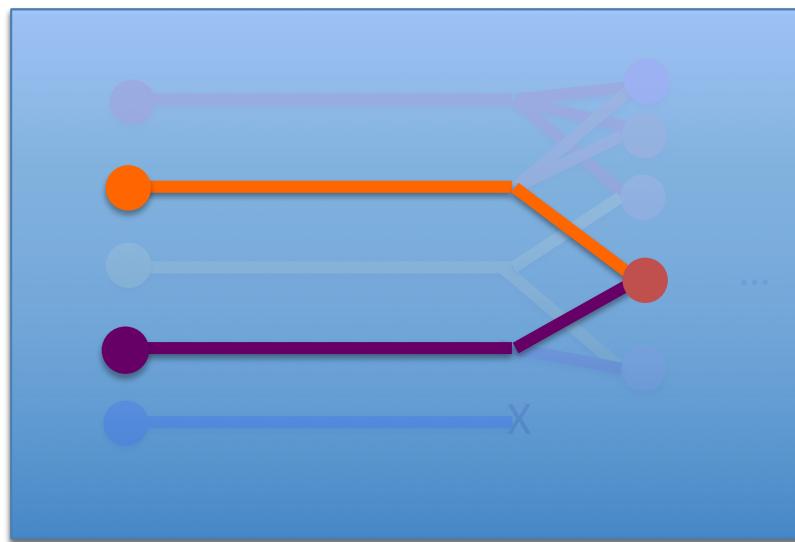
“A” stays for Additive Genetic Value



“B” stays for Breeding Value



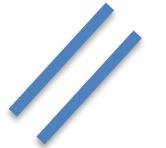
“C” stays for Couple of child and its mid-parent phenotype



Example: $C = \langle z, \frac{z+z}{2} \rangle$

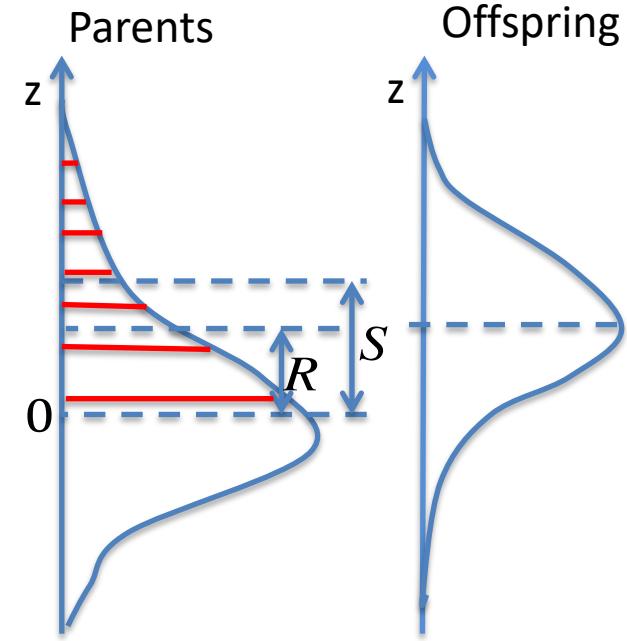
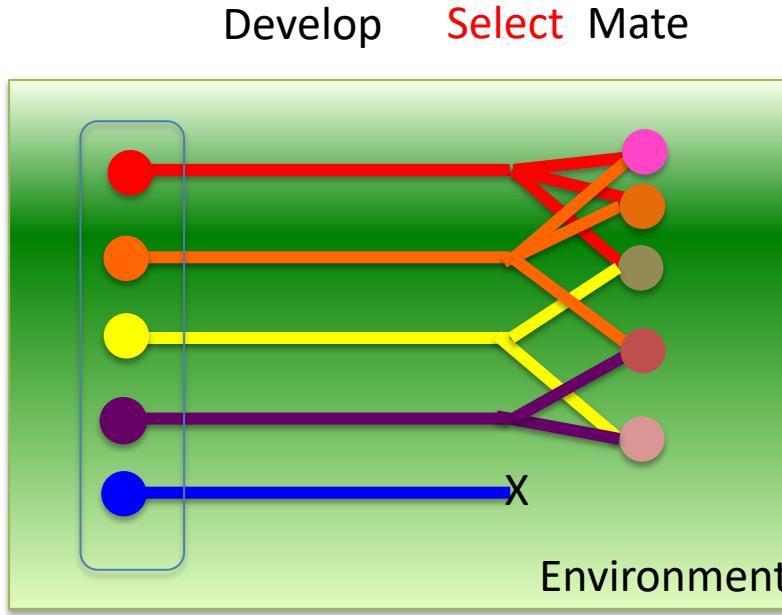
Heritability, Regression Slope and Spreadability

$$\text{Heritability, } h^2 := \frac{\text{Var}(A)}{\text{Var}(z)}$$



$$\text{Regression Slope, } \rho := \frac{\text{Cov}(C)}{\text{Var}(z)} = \frac{\text{Var}(B)}{\text{Var}(z)} =: s^2, \text{Spreadability}$$

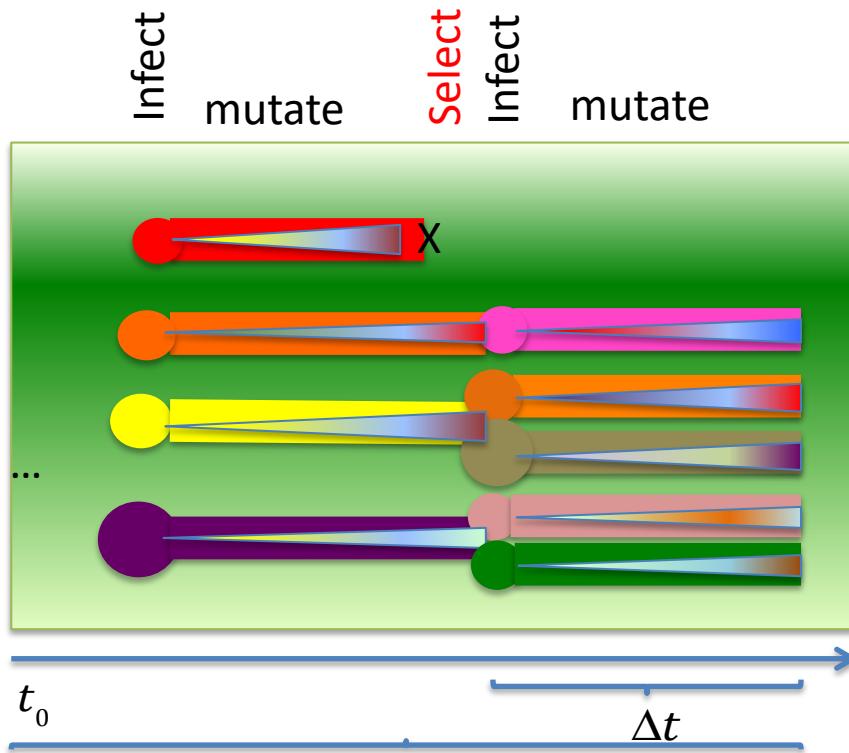
For Traits of Diploid Organisms h^2 Predicts the Response to Selection



$$R = h^2 S$$

However, direct estimation of h^2 is hard.
=> Therefore, estimate h^2 from the regression slope.

Does this work for pathogen traits?



- Can we define A, B and D and respectively h^2 , s^2 and ρ in analogy with diploid organisms? Yes
- Can we predict response to between-host selection from h^2 ? No
- Can we estimate h^2 from ρ ? No

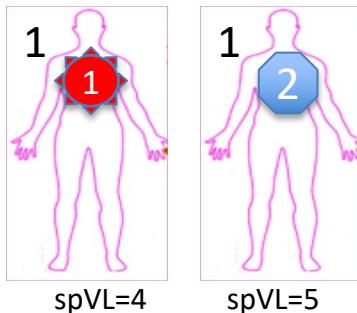
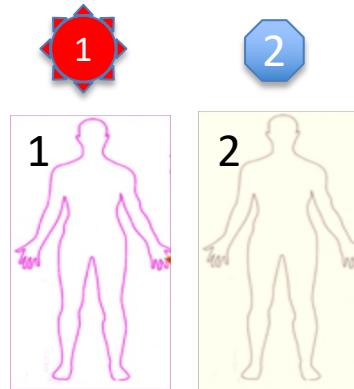
A Toy Model

2 viral strains:

x

2 host types:

=



We observe a population of a fixed size over several generations of transmission.

Within host evolution:

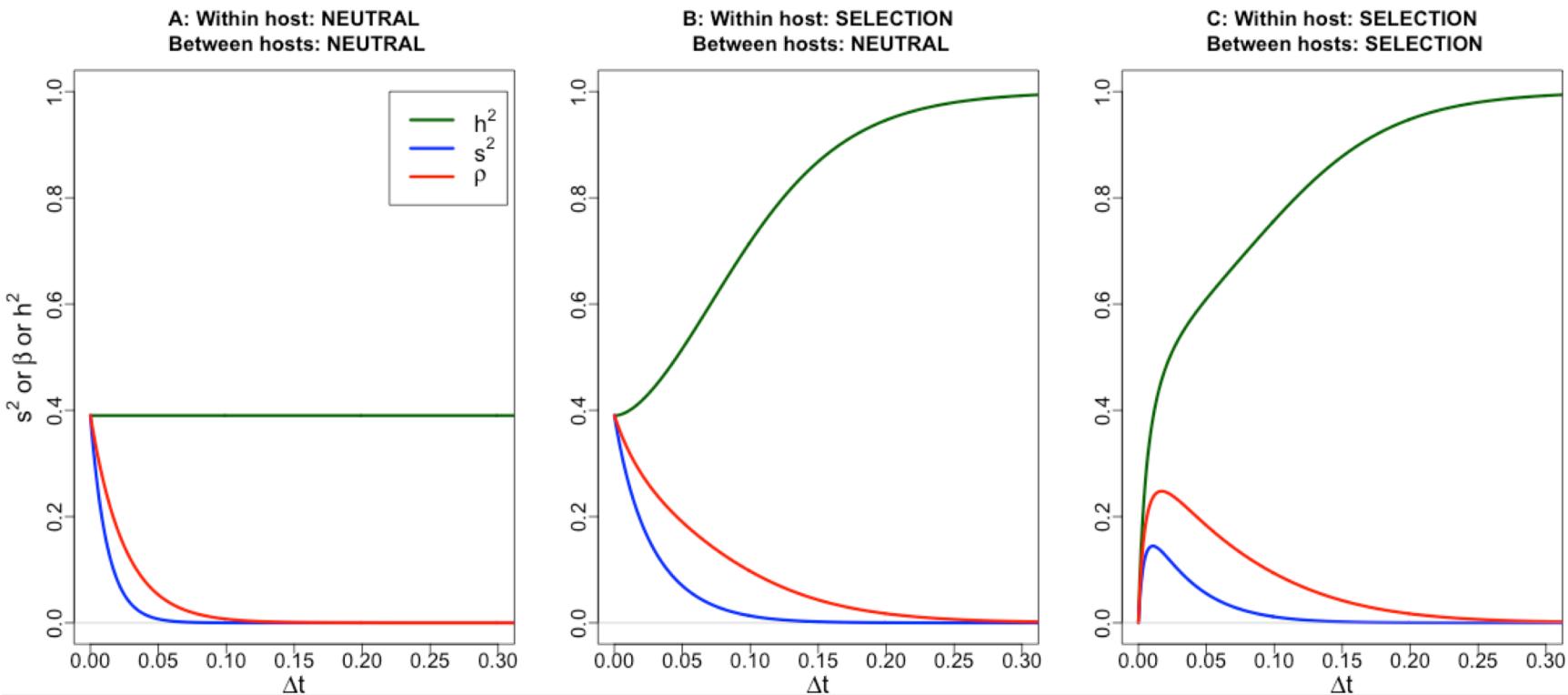
- Neutral : virus mutates randomly in both directions at fixed mutation rate.
- Selection towards the fitter virus with respect to the immune system.

Between-host evol. :

- Neutral : every individual can infect one recipient on average.
- Selection : The number of infected recipients from a donor depends on viral load.

Analyze the equilibrium frequencies of host-virus combinations for fixed Δt values.

Expected Values of h^2 , ρ and s^2 at Equilibrium



- Mutation during the lifetime of infections breaks the equality between h^2 , ρ and s^2 .
- The spreadability, s^2 , and the regression slope, ρ , tend to vanish as the time-interval between infection events, Δt , increases.
- In the case of within-host adaptation, the heritability, h^2 tends to 1 as Δt increases.

Does this work for pathogen traits?

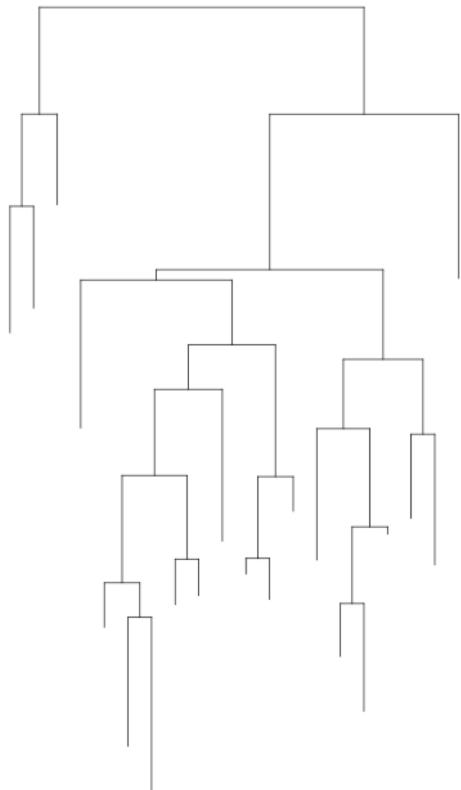
$$\text{Heritability, } h^2 := \frac{\text{Var}(A)}{\text{Var}(z)}$$



$$\text{Regression Slope, } \rho := \frac{\text{Cov}(C)}{\text{Var}(z)} \neq \frac{\text{Var}(B)}{\text{Var}(z)} =: s^2, \text{Spreadability}$$

Can we estimate s^2 ?

Phylogeny-Based Estimation of Spreadability



Assume that the phylogeny approximates the transmission network between patients.

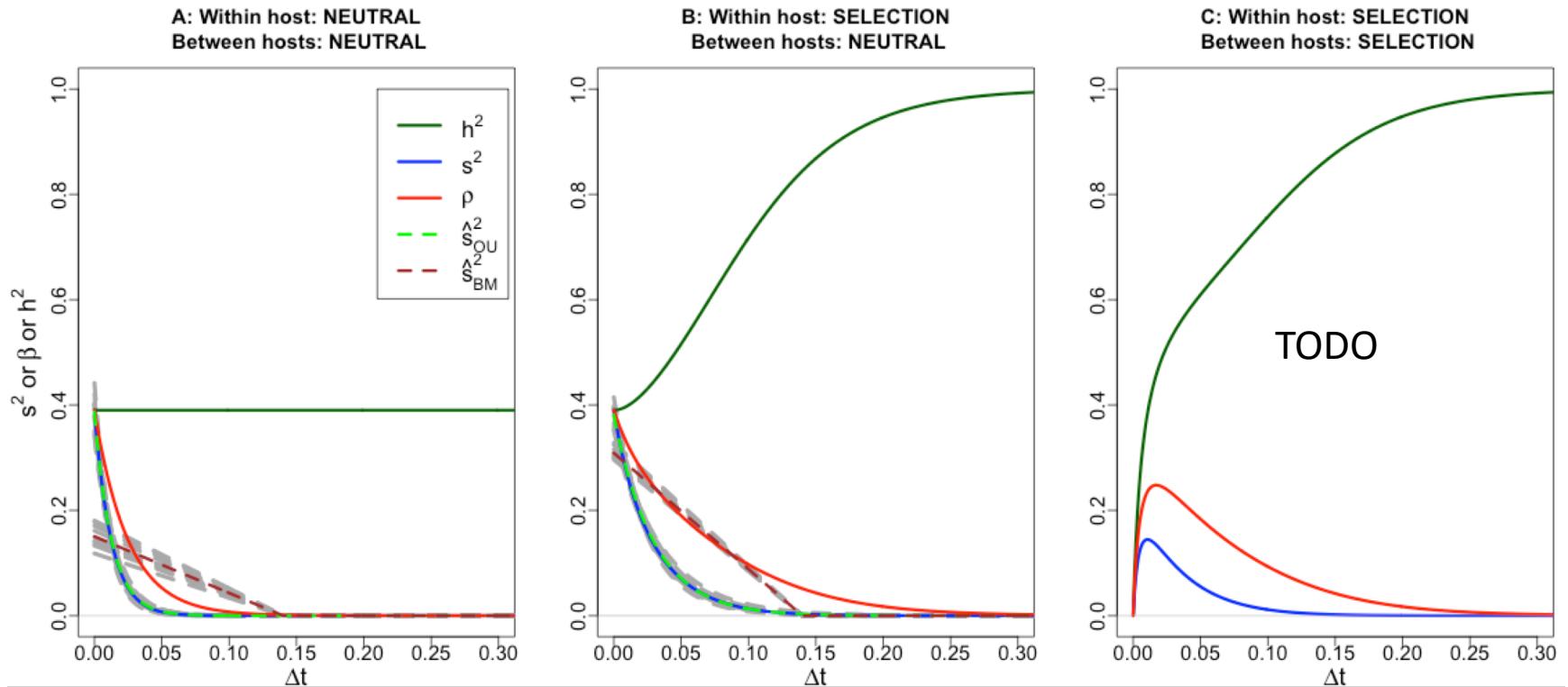
$$Z = g + e$$

Assume that g evolves along the phylogeny according to an Ornstein-Uhlenbeck process.

Use the following formula to estimate spreadability:

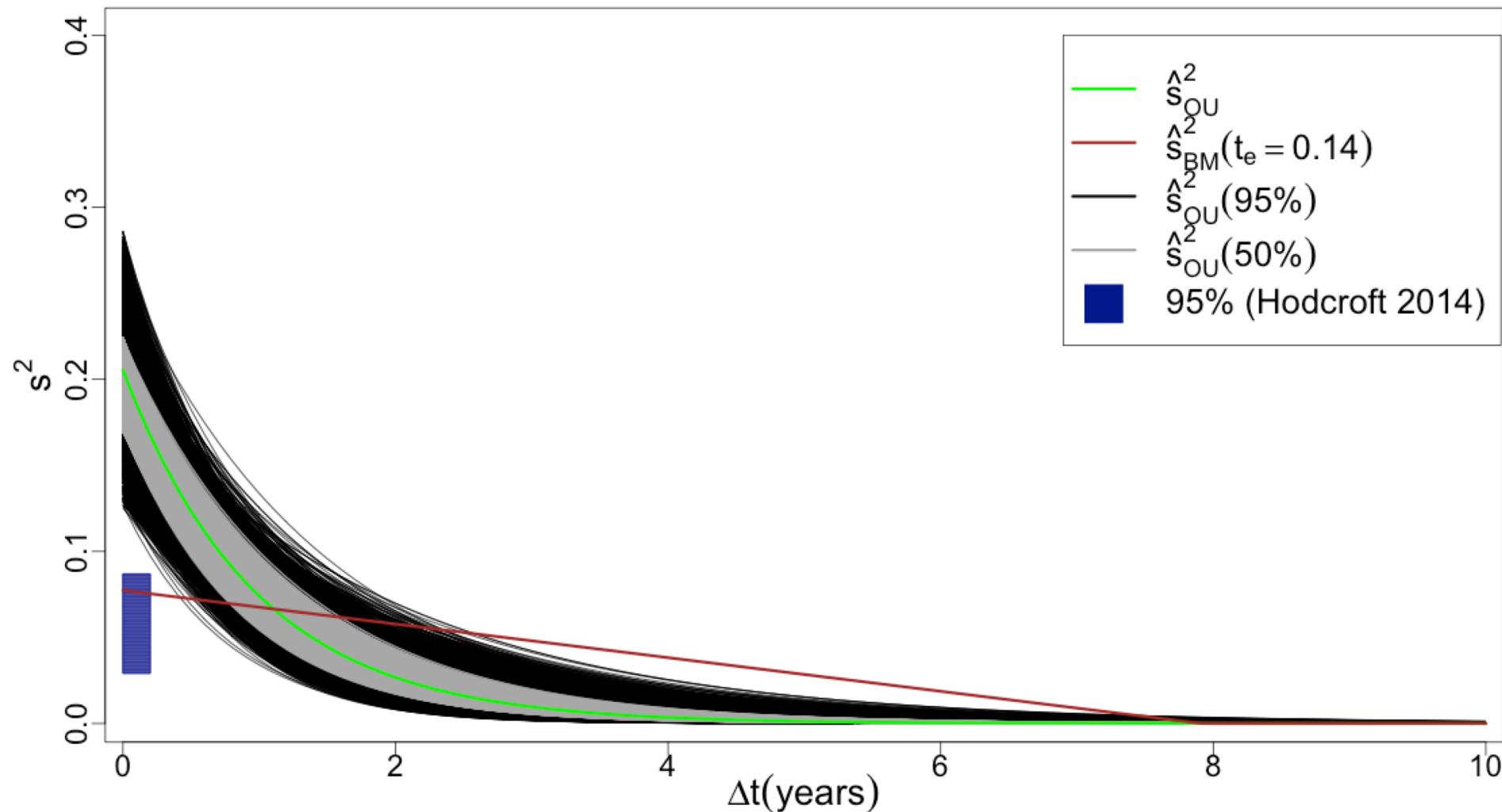
$$\hat{s}^2(\Delta t) = \frac{\sigma_g^2(\infty) - \sigma_g^2(\Delta t)}{\sigma_g^2(\infty) + \sigma_e^2}$$

Expected Values of h^2 , ρ and s^2

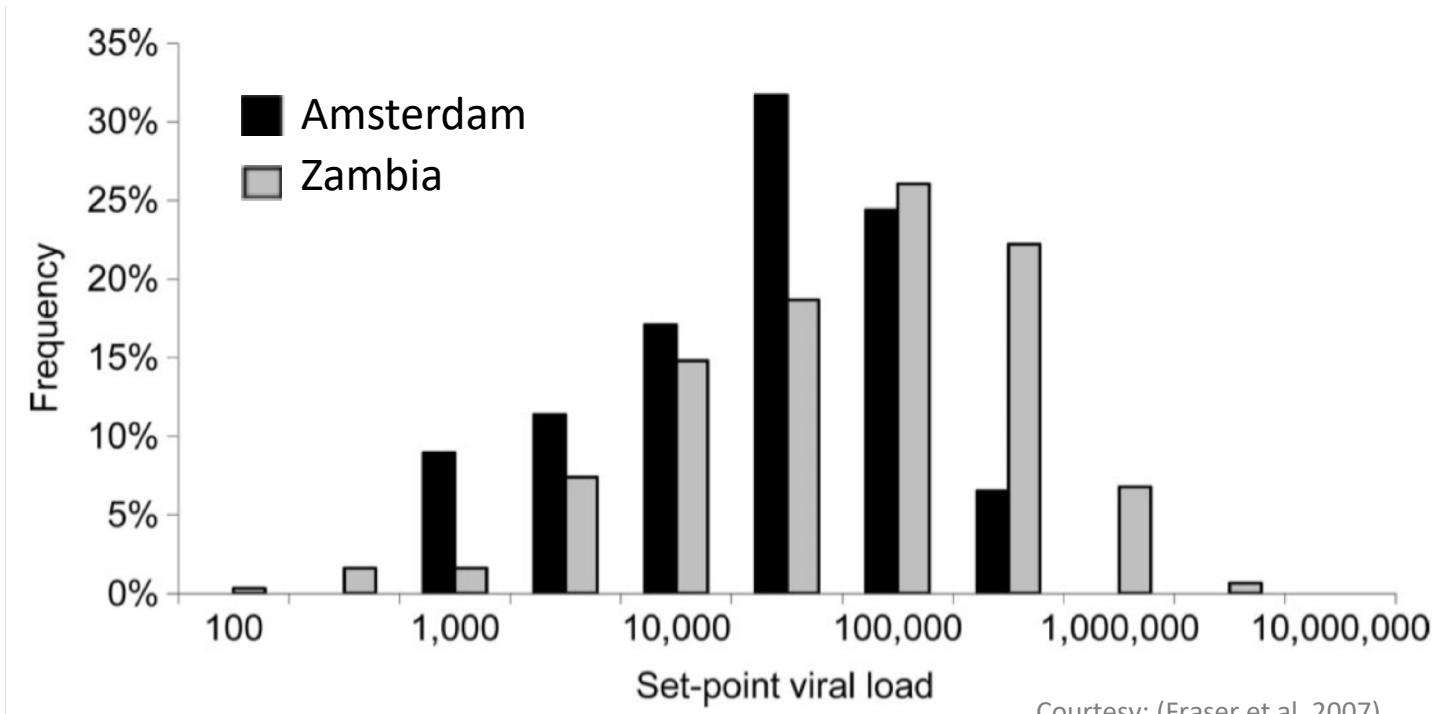


- The PMM / OU based estimation of spreadability seems to be unbiased for case A and B of the toy model.
- The PMM / BM based estimation tends to underestimate spreadability for low Δt , and overestimate it for larger Δt values.

PMM OU/BM Estimates of s^2 of the UK Cohort



What shapes the distribution of set-point viral load?



Courtesy: (Fraser et al. 2007)

Within-host selection for fittest strain

(Lythgoe et al. 2013, van Dorp et al. 2014 ...)

vs

Between-host selection for maximum transmission potential

(Fraser et al. 2007)

Acknowledgements

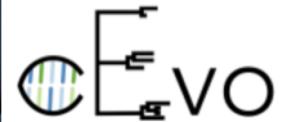
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Bonhoeffer

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ETH Zürich

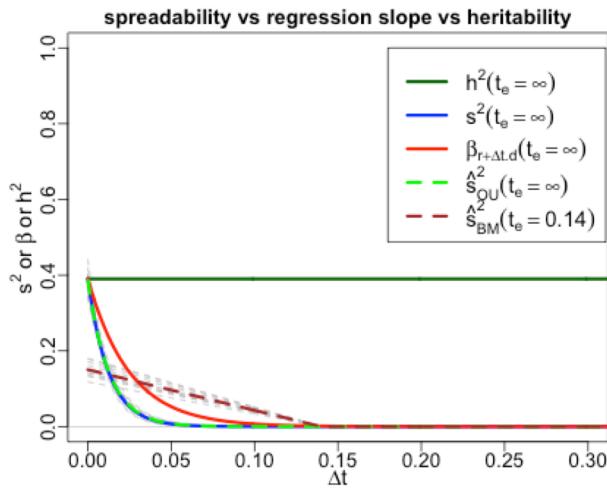


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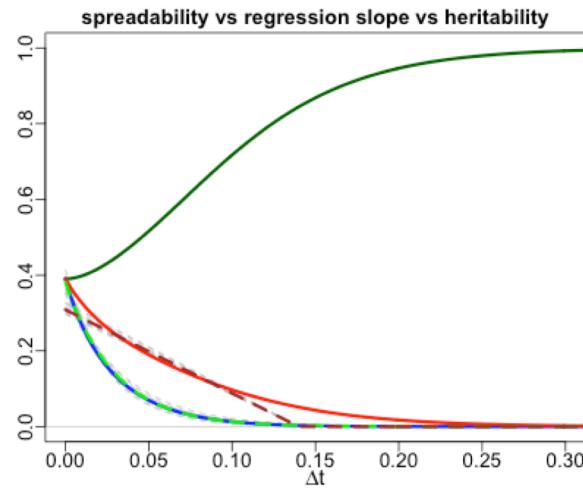
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<http://dx.doi.org/10.1038/nrmicro772>
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Estimates from the our new method

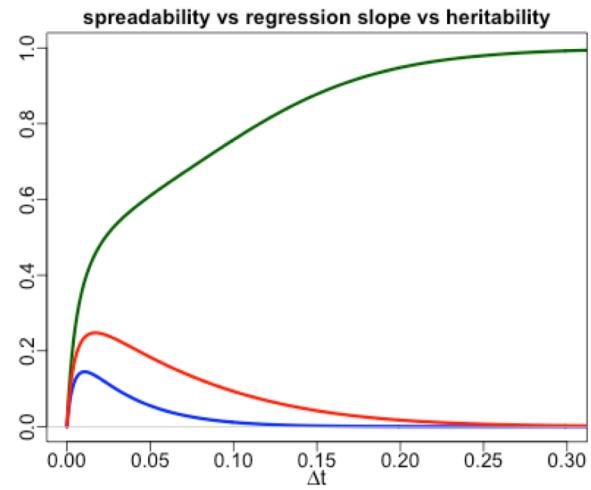
A: Within host: NEUTRAL; Between hosts: NEUTRAL



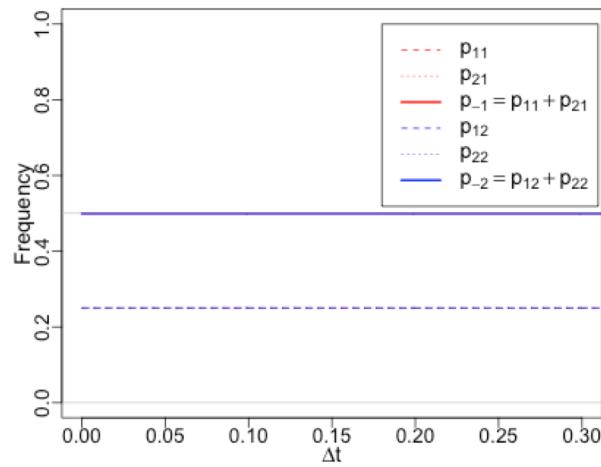
B: Within host: SELECTION; Between hosts: NEUTRAL



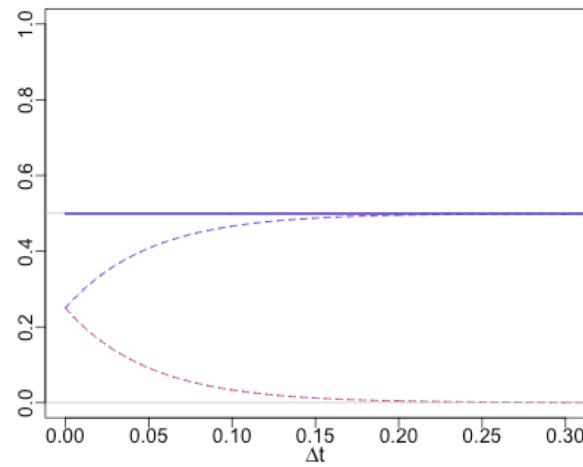
C: Within host: SELECTION; Between hosts: SELECTION



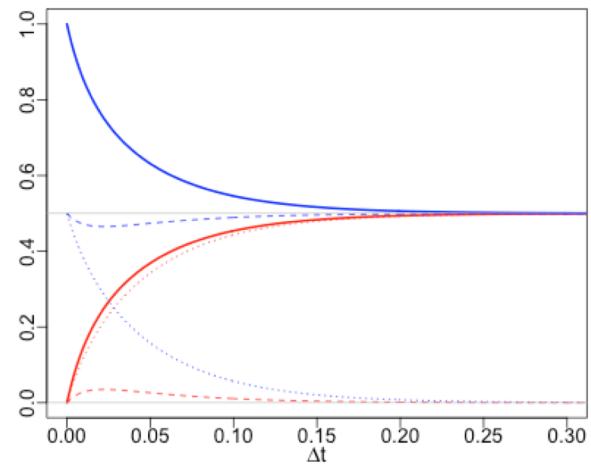
Individual frequencies at equilibrium



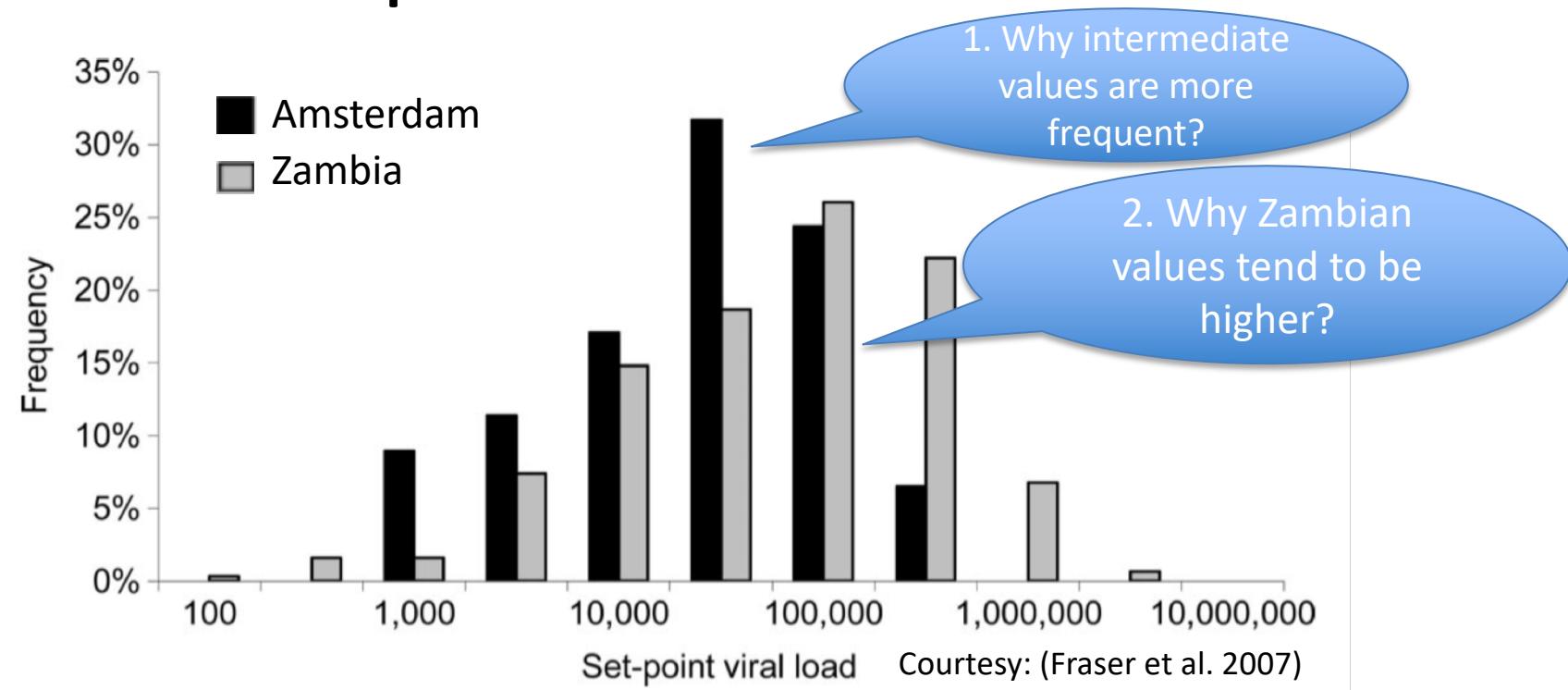
Individual frequencies at equilibrium



Individual frequencies at equilibrium



What shapes the distribution of set-point viral load?

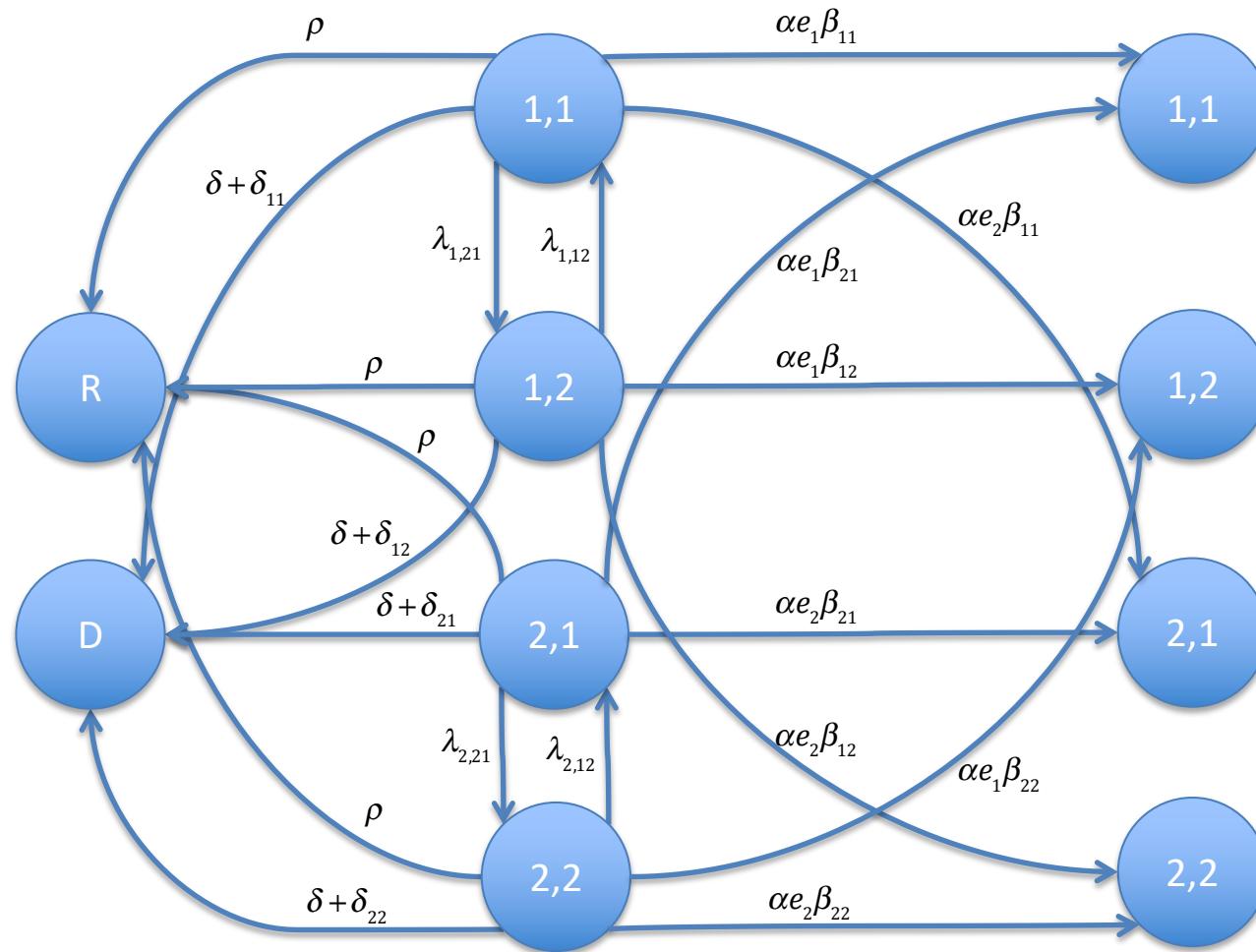


- Role of between-host selection for maximum transmission potential (Fraser et al. 2007) vs. short-sightedness of HIV-1 evolution (Lythgoe et al. 2013, van Dorp et al. 2014)?
=> NARROW-SENSE HERITABILITY, h^2 , as a criterion: e.g. Hodcroft et al. 2014

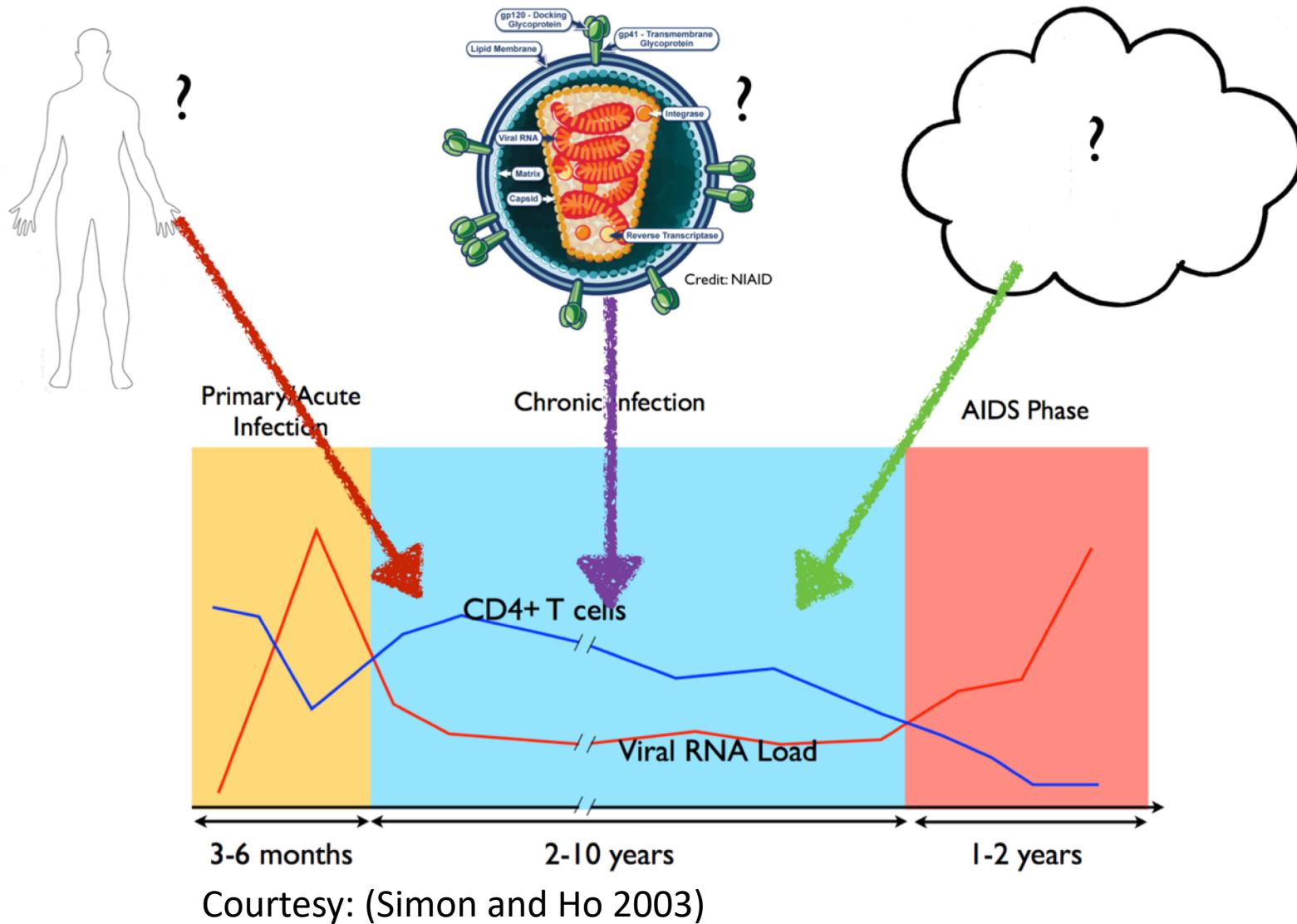
Summary

- When there is mutation during the lifetime of individuals, h^2 of pathogen traits cannot be estimated by donor-recipient regression or PMM methods...
- ...nor does it predict the evolutionary outcome of between and within host selection!
- Estimators of heritability from consecutive generations can predict evolutionary outcome, however they are not estimators of heritability but of the spreadability of the trait.
- In the case of uniform transmission potential, our new phylogenetic method for estimating spreadability provides very accurate estimates. This method still needs to be tested in the case of non-uniform transmission potential.
- The estimated spreadability of the UK-data goes from 0.2 to 0 within an evolutionary pol distance of 0.05 nucleotide substitutions/year.

An ODE Model of a 2x2 system



What determines the duration of the asymptomatic phase?



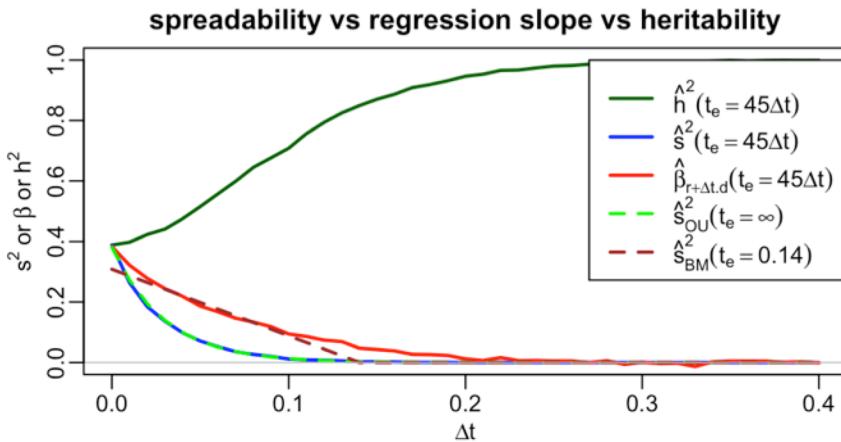
A Discrete Generation Model

- m types of immune systems (environments);
- n viral alleles at a 1 locus;
- Mutation rate matrix for each environment e :

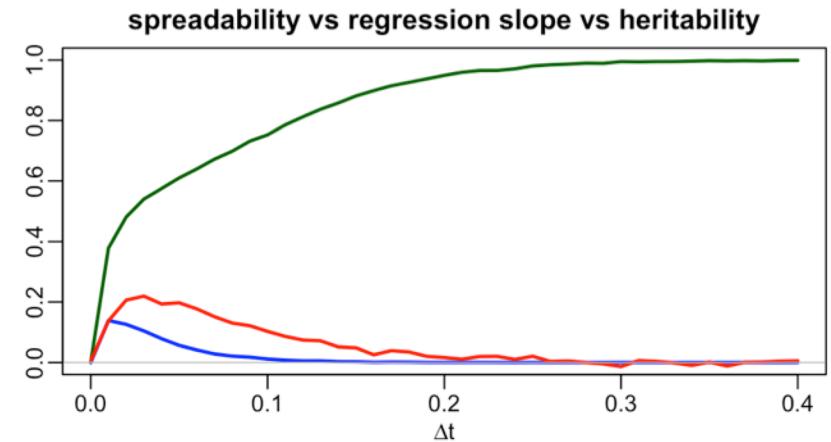
$$Q_e = \begin{pmatrix} -\lambda_{e,1} & \dots & \lambda_{e,1 \rightarrow n} \\ \vdots & \ddots & \vdots \\ \lambda_{e,n \rightarrow 1} & \dots & -\lambda_{e,n} \end{pmatrix}, \lambda_{e,i} = \sum_{j \neq i} \lambda_{e,j \rightarrow i}$$

Results of the simulation

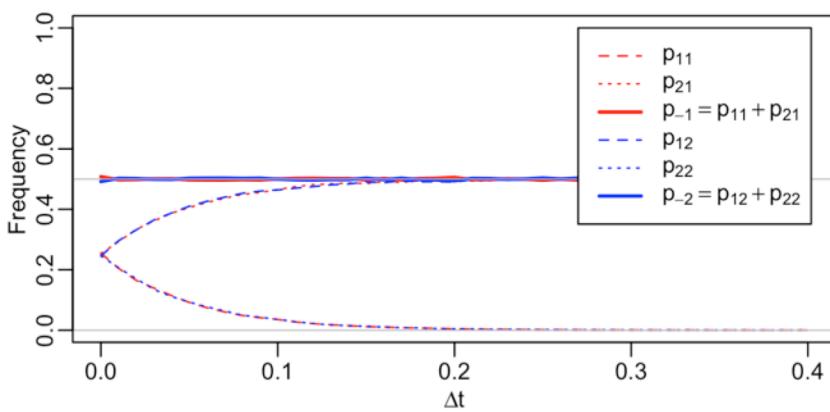
A: Within-hosts: SELECTION; Between hosts: NEUTRAL



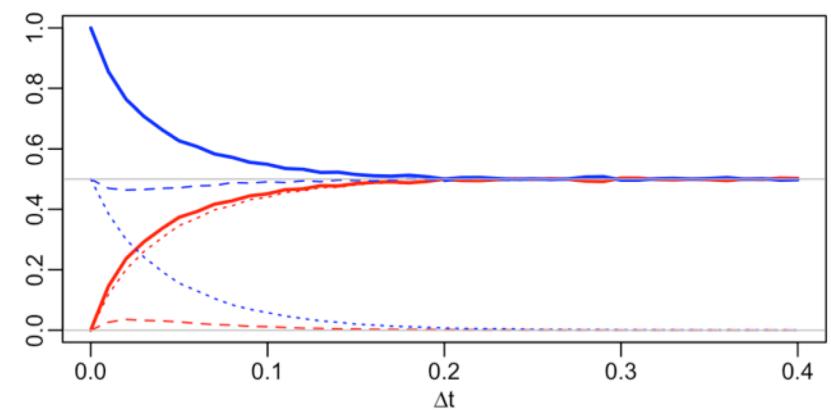
B: Within-hosts: SELECTION / Between hosts: SELECTION



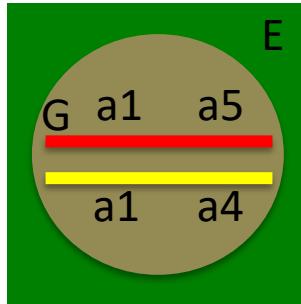
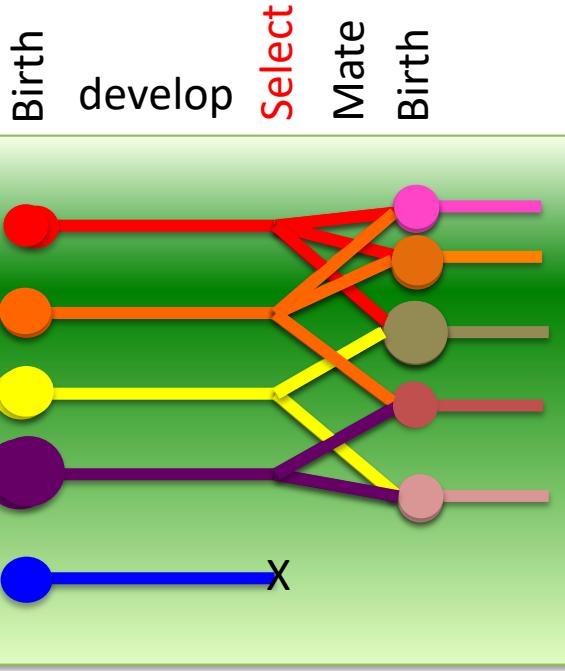
Individual frequencies



Individual frequencies



h^2 and its estimators

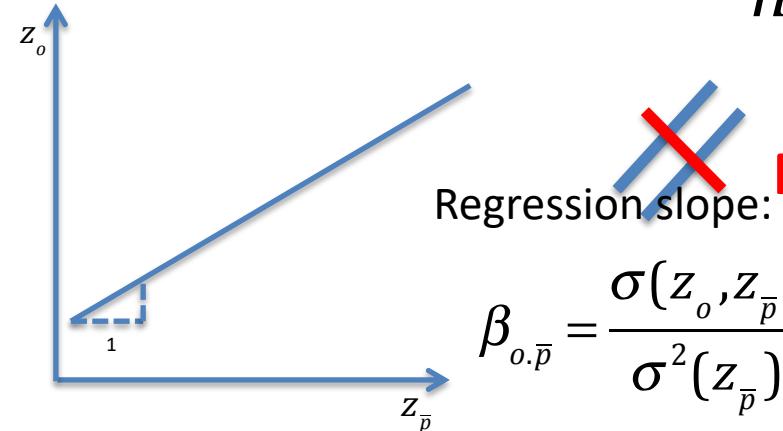


$$Z = G + E$$

Alleles: a_1, a_2, a_3 - at locus 1
 a_4, a_5 - at locus 2

Gene contents:
 $N_1=2, N_2=0, N_3=0;$
 $N_4=1, N_5=1;$

$$G = \mu_G + \underbrace{\sum_{1 \leq i \leq 5} \alpha_i N_i}_{A} + e$$



$$h^2 = \frac{\sigma^2(A)}{\sigma^2(z)}$$

Regression slope: **MUTATION**

$$\beta_{o.\bar{p}} = \frac{\sigma(z_o, z_{\bar{p}})}{\sigma^2(z_{\bar{p}})}$$

Spreadability:

$$s^2 = \frac{\sigma^2(B)}{\sigma^2(z)}$$