Genetic context dependence diversifies evolving microbial populations

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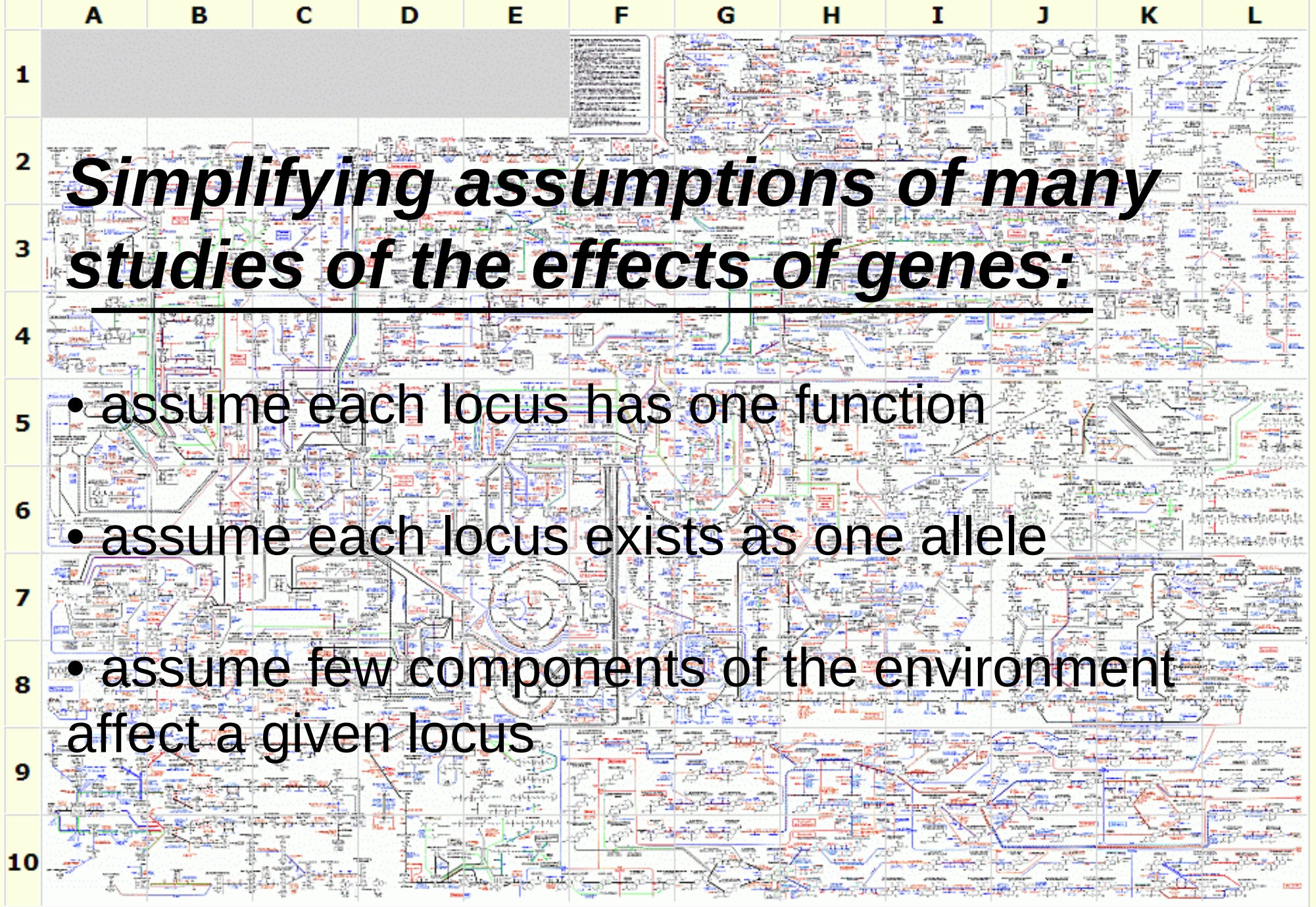


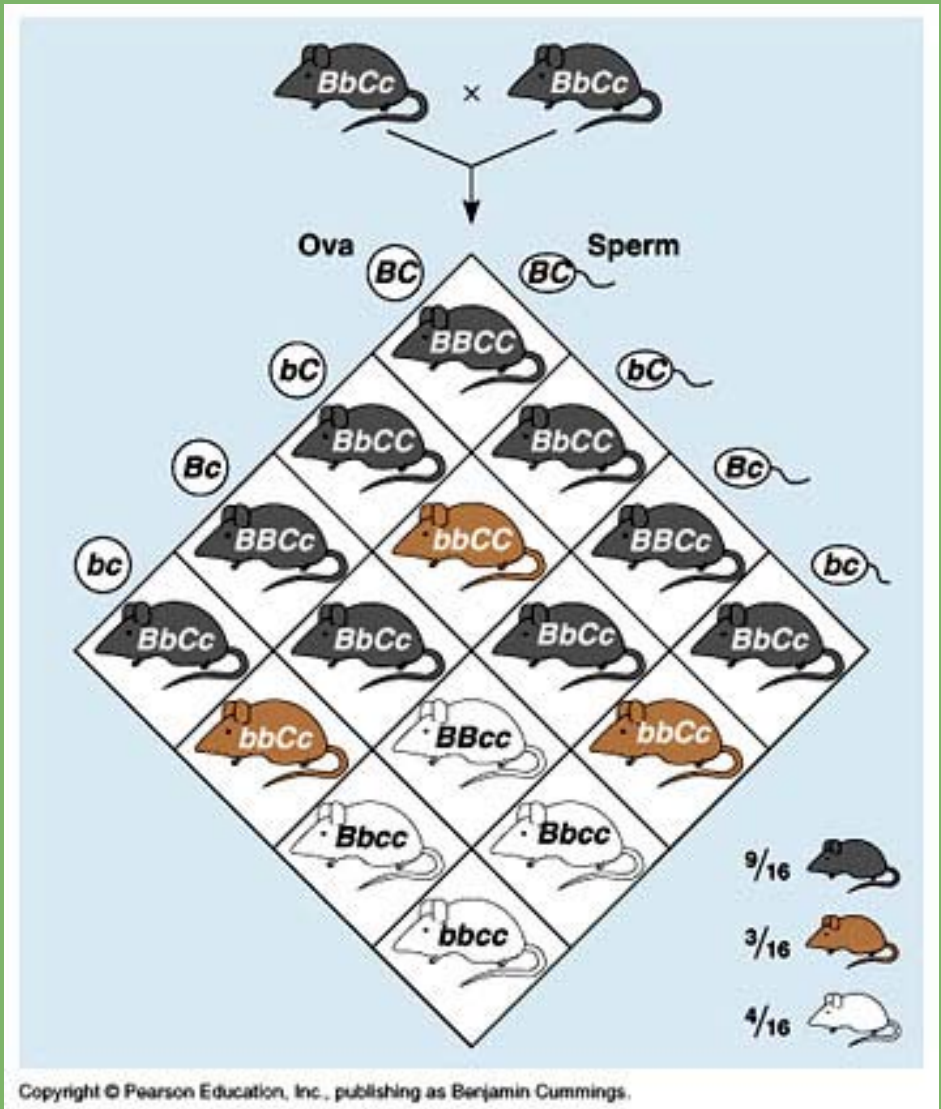
Simplifying assumptions of many studies of the effects of genes:

- assume each locus has one function
- assume each locus exists as one allele
- assume few components of the environment affect a given locus

Context dependence

- *What is it?*
- *How common is it?*
- *How does it arise evolutionarily?*
- *What are its consequences?*

Types of context-dependence



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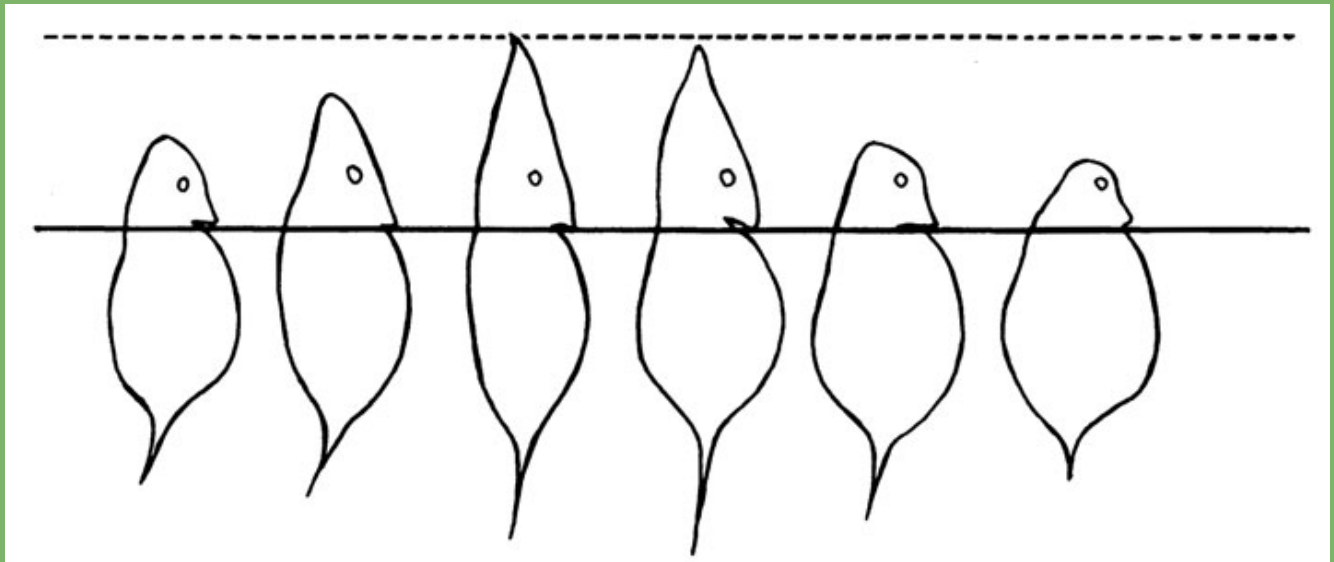
1) Genetic epistasis:
effect of allele at locus C depends on
allele at locus B

BxCx black
bbCx brown
xxcc white

Types of context-dependence



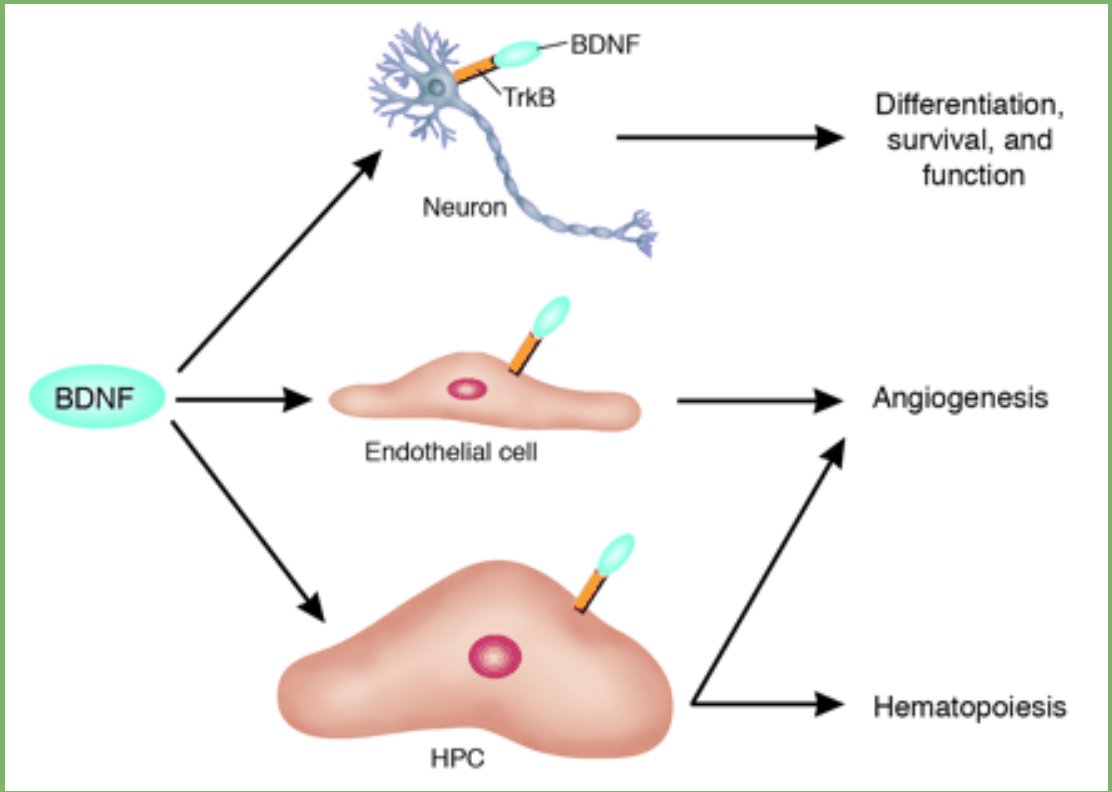
Helmet height in *Daphnia cucullata* as a function of time of year (Dodson 1989, adapted from Woltereck 1909).

2) Phenotypic plasticity:

effect of allele depends on the environment

Daphnia cucullata develop defensive helmets only in response to predation stimulus

Types of context-dependence



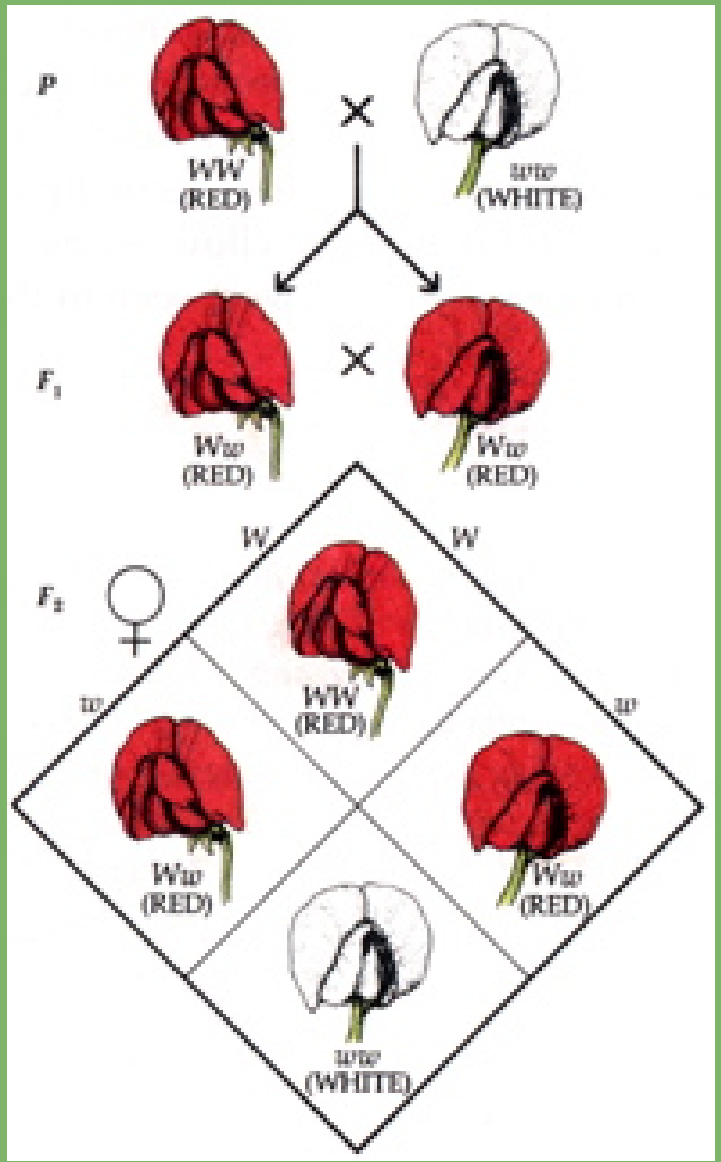
3) Pleiotropy:
Locus affects multiple traits

(function depends on *developmental* or *environmental* context)

The signaling molecule brain derived neurotrophic factor (BDNF) triggers different processes depending on the cell type to which it binds

Duda & Jain. J. Clin. Invest. 115:596–598 (2005)

Types of context-dependence



4) Dominance:
effect of allele depends on other allele at same locus

(a special case of epistasis)

Types of context-dependence

5) Various higher order interactions:

gene x gene x environment

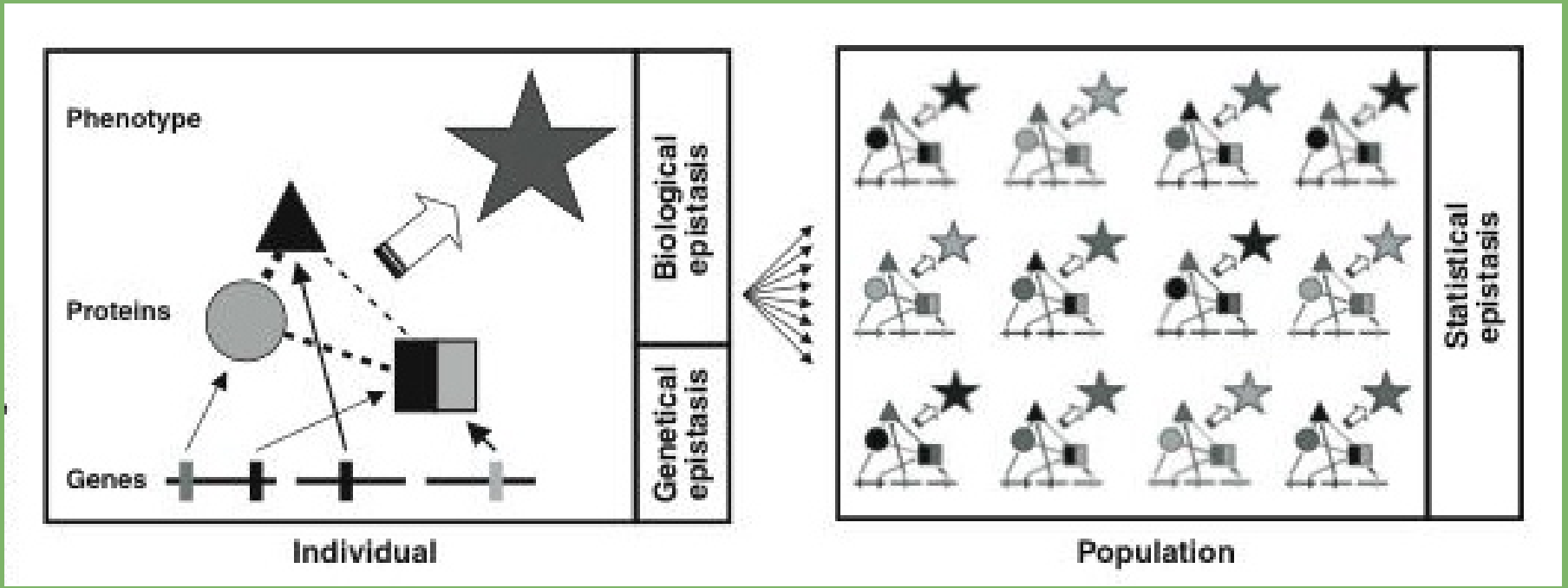
gene x environment x environment

gene x gene x environment x environment

1-5 are variations on a single theme.

Types of context-dependence

Individual vs. population level interactions:



(J. Moore 2005 Nature Genetics 37:13)

Context-dependence and Genetic architecture

- (Average) effects of important genes
- Their genomic positions
- Number of genes
- Individual context dependence
- Contributions population level context dependence to genetic variance

Modified from Zeng et al. 1999 Genet. Res. Camb.

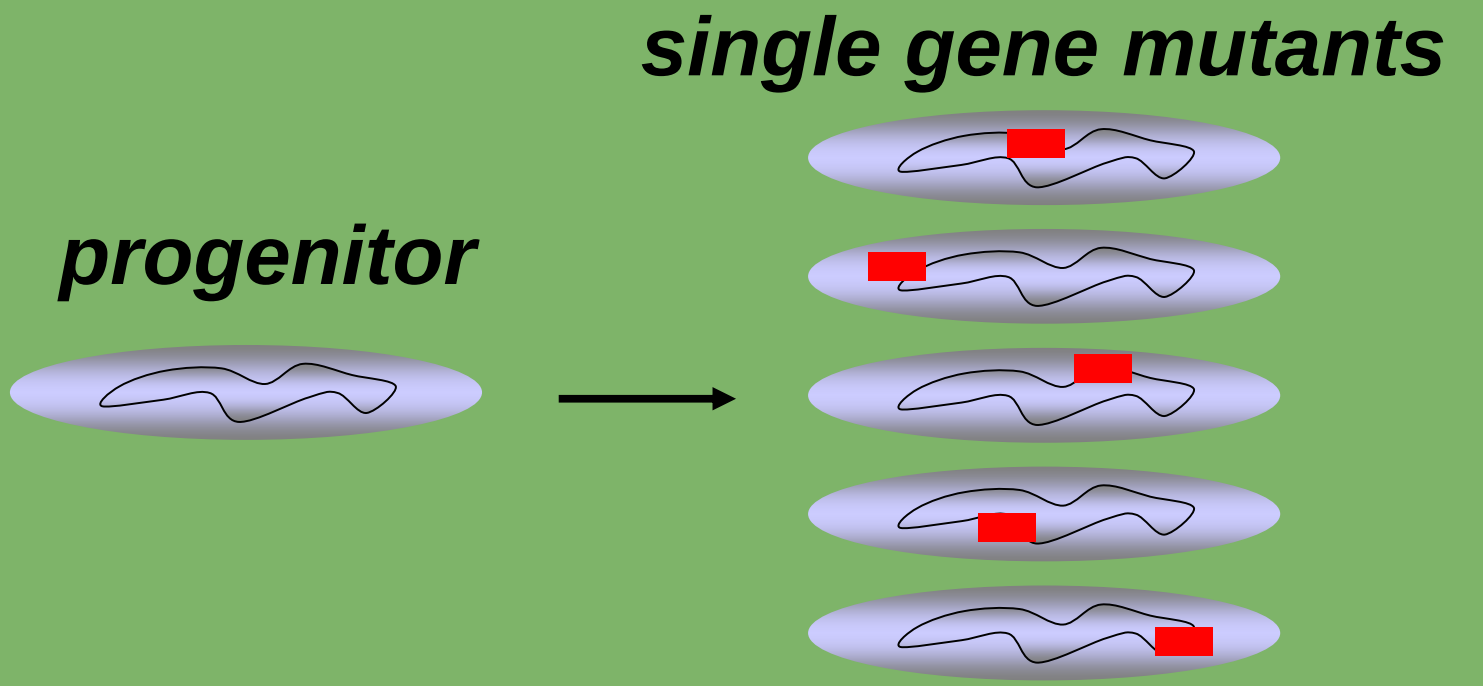
How common is context dependence?

How common is context-dependence?

- ***Do different ecological parameters cause the same amount of dependence in the effects of alleles?***

Genotypes:

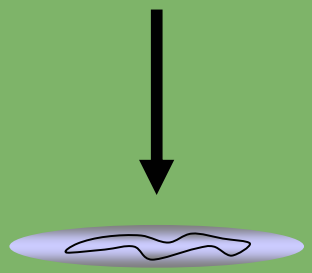
Mutants differ from progenitor at single, randomly located genes



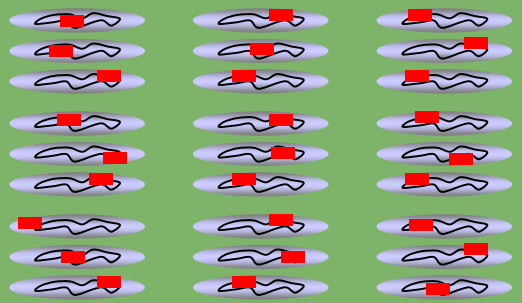
Genotypes:

Environments:

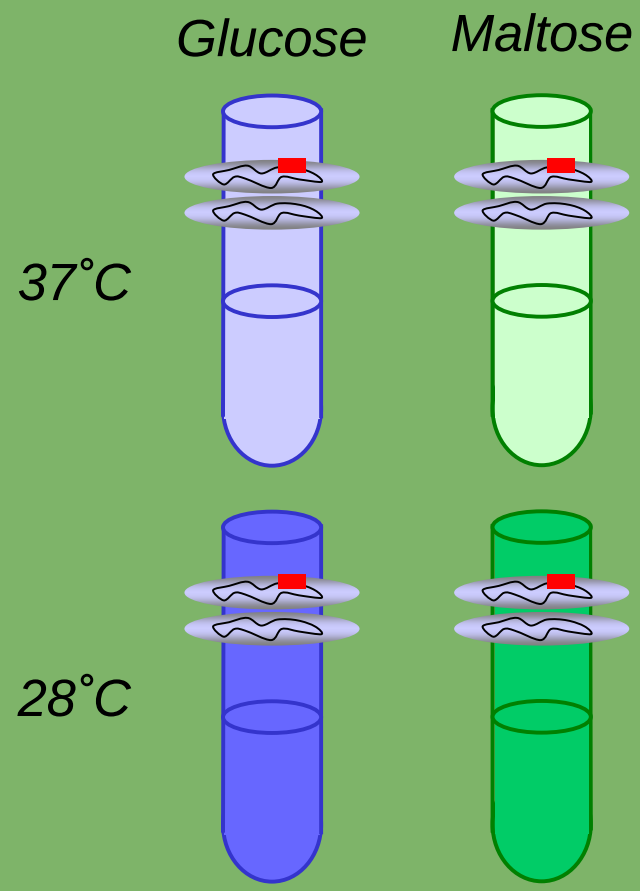
3 experiments

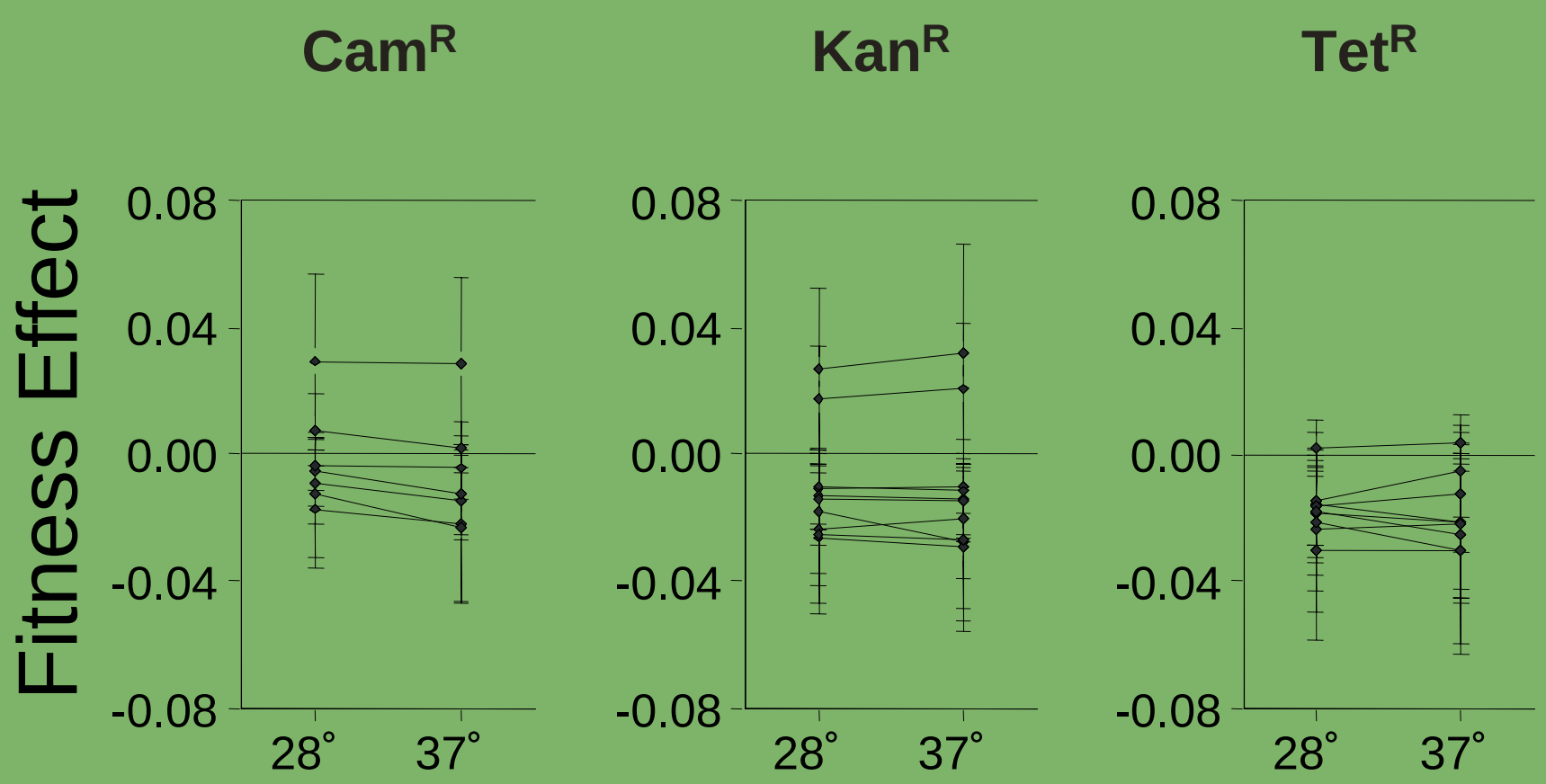


9 mutations / marker

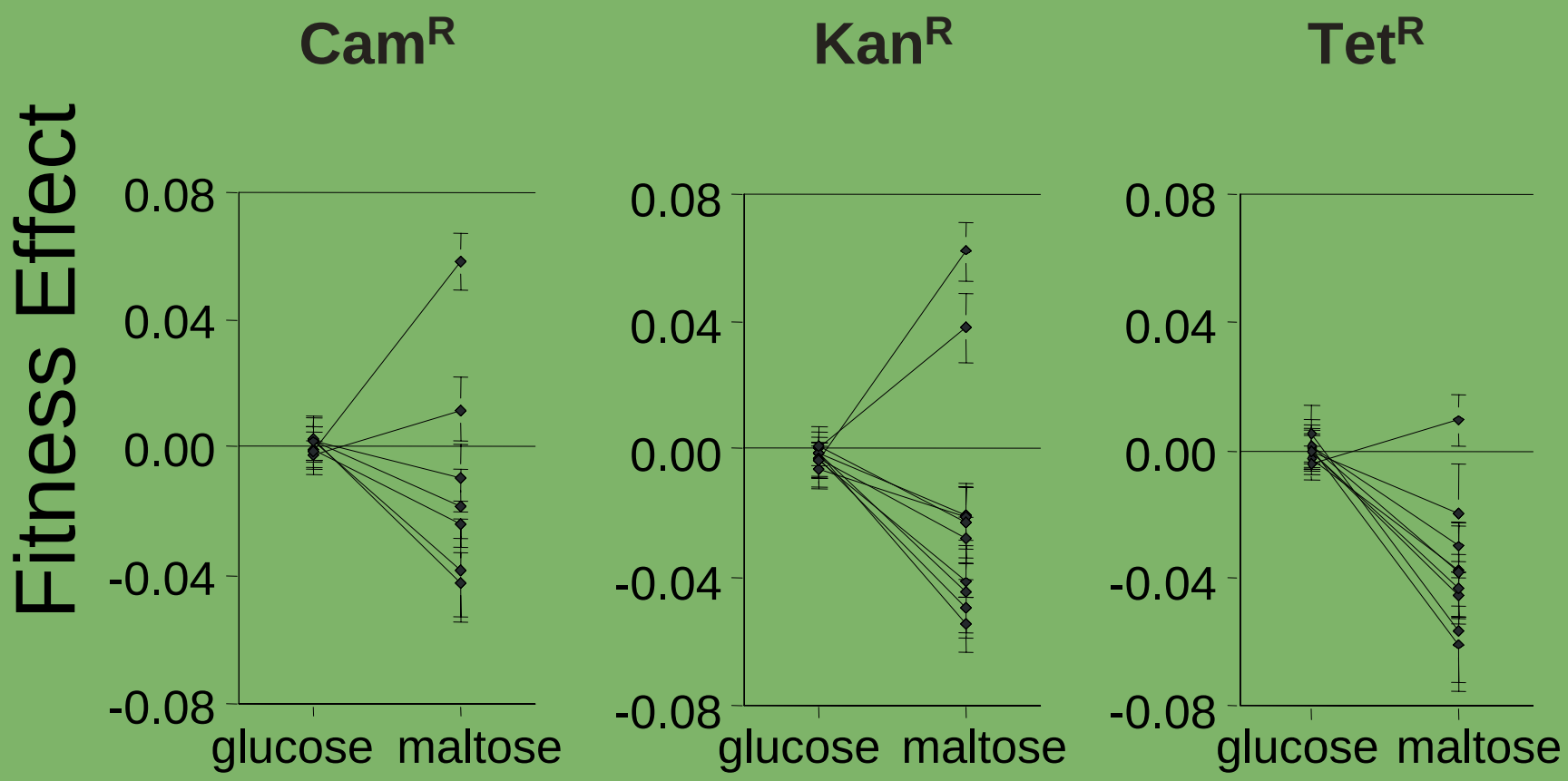


Measure fitness effect of all mutations in 4 environments





Remold and Lenski (2001) PNAS 98:11388



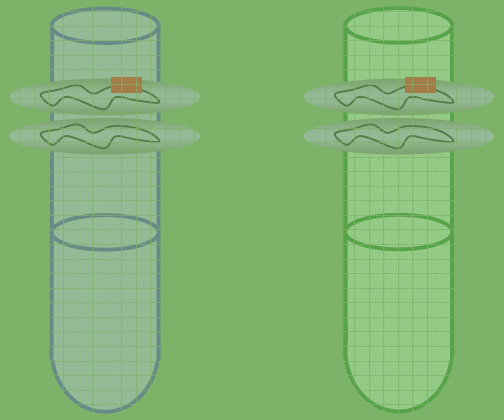
Resources averaged across temperatures

Remold and Lenski (2001) PNAS 98:11388

How common is context-dependence?

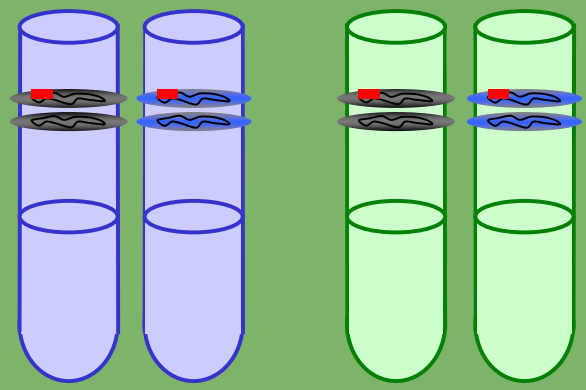
- ***Do ecological environment, genetic environment or both influence the effect of a mutation on fitness?***

Last experiment:
Transplant mutant genotypes into different ecological environments



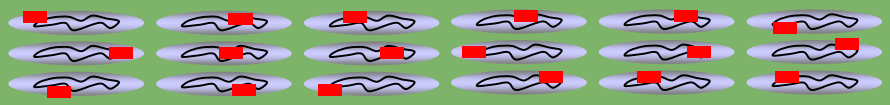
This experiment:
Transplant mutations into different genetic environments

Transplant mutant genotypes into different ecological environments

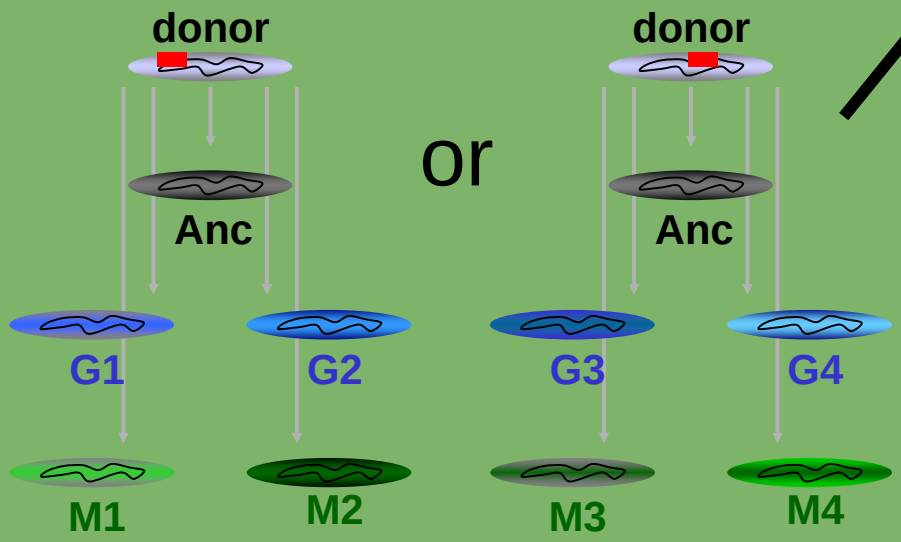


Methods:

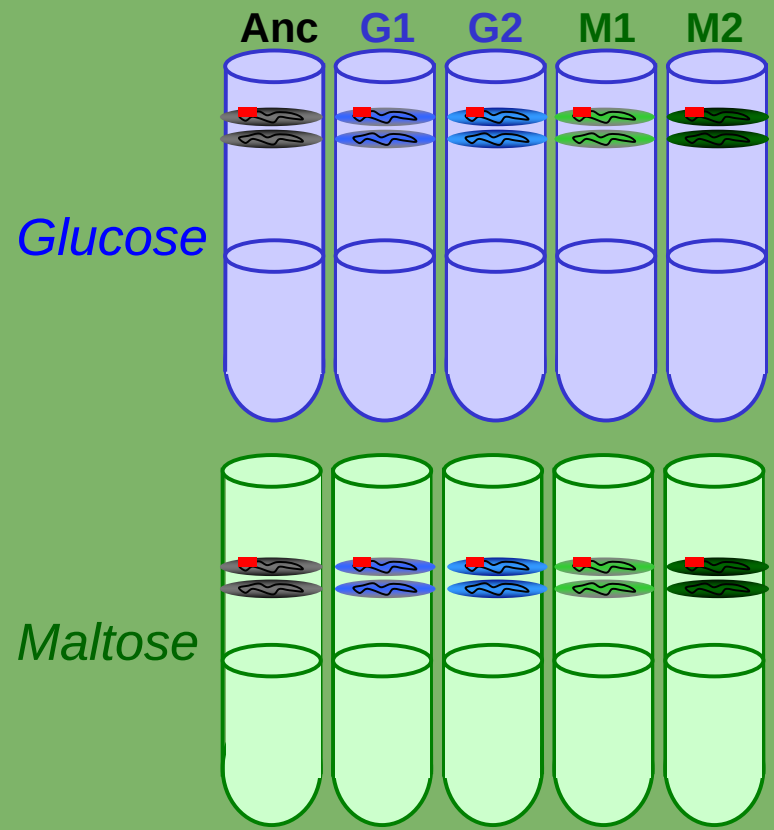
18 mutations



Move each into 5 genetic environments

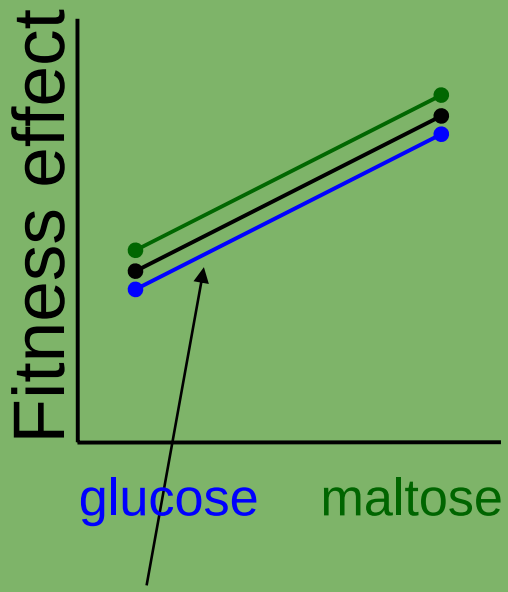


Measure fitness effect in 5 genetic and 2 ecological environments



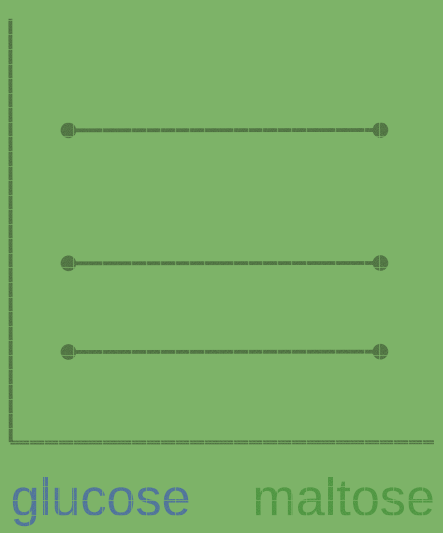
Expected patterns:

Ecological Environment

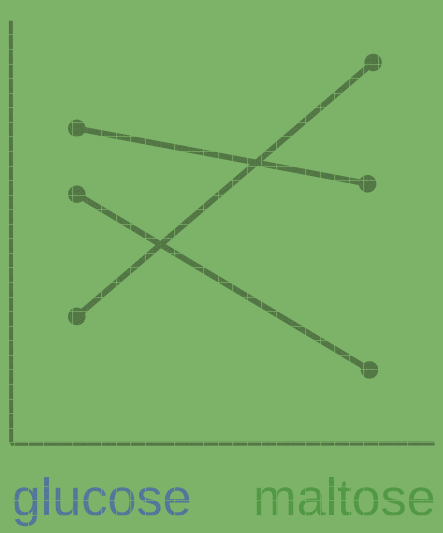


Effect of a single mutation in different genetic environments

Genetic Environment



Both



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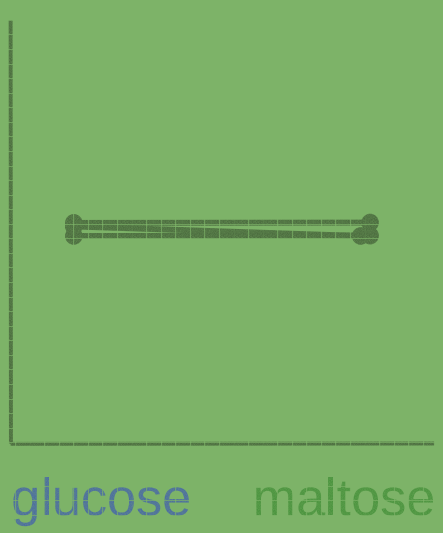
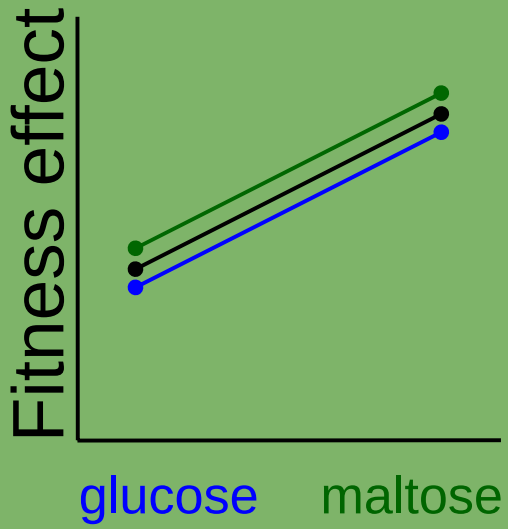
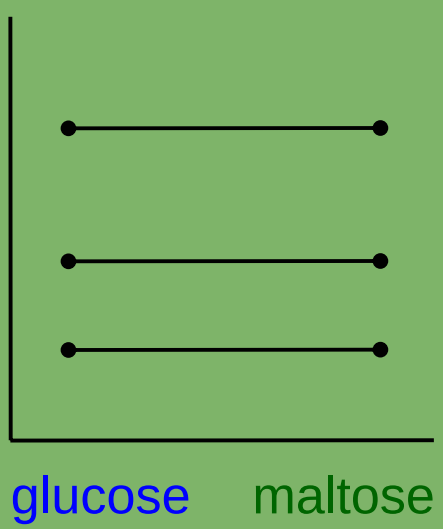


Expected patterns:

Ecological Environment



Genetic Environment



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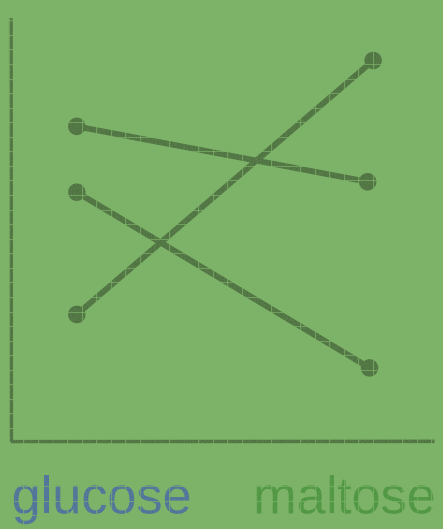
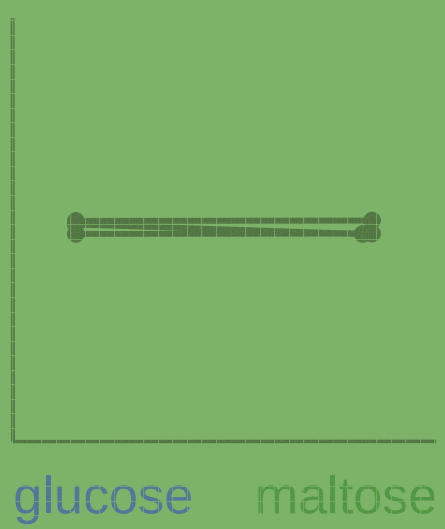
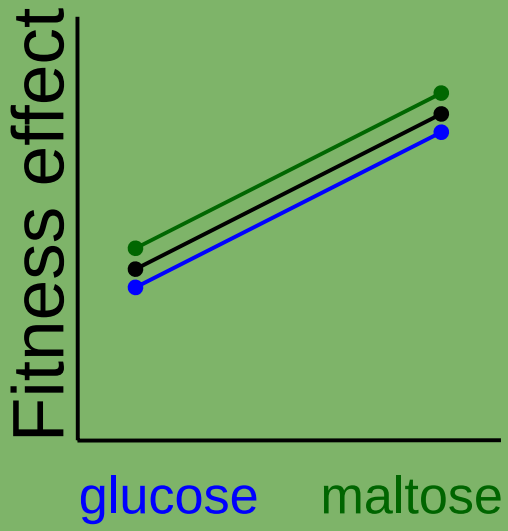


Neither

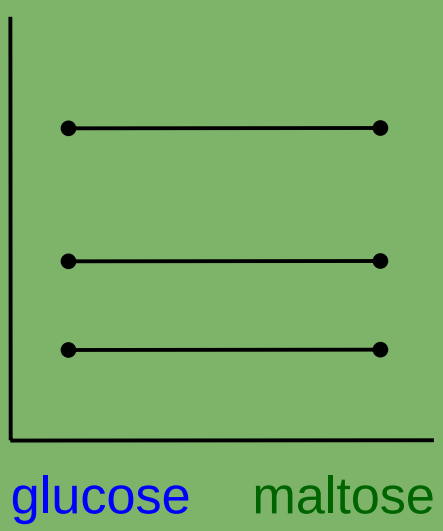


Expected patterns:

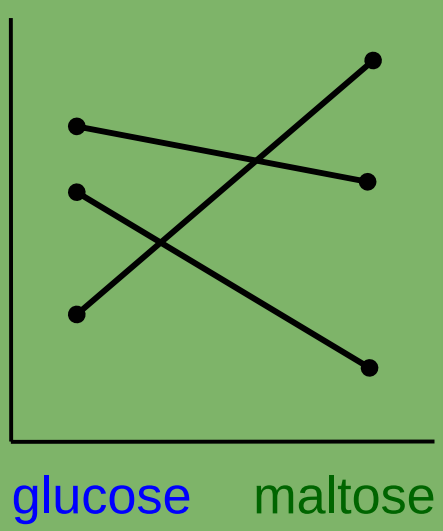
Ecological Environment



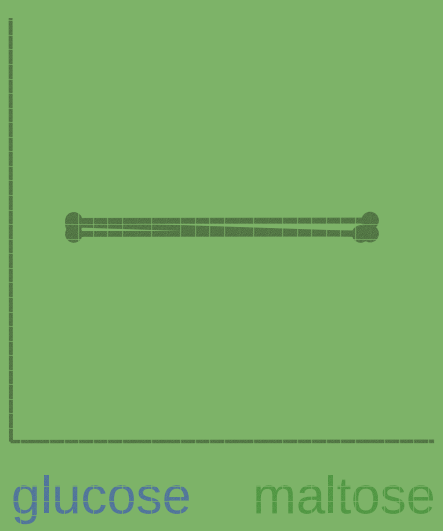
Genetic Environment



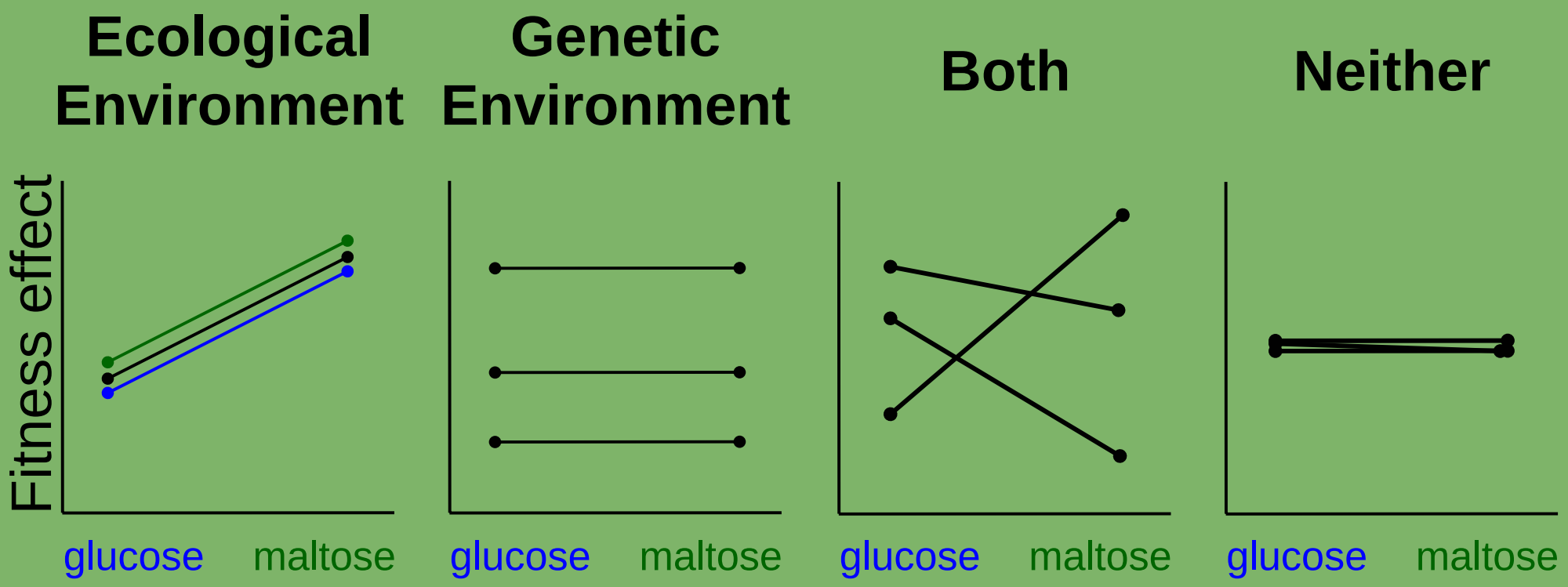
Both



Neither



Expected patterns:

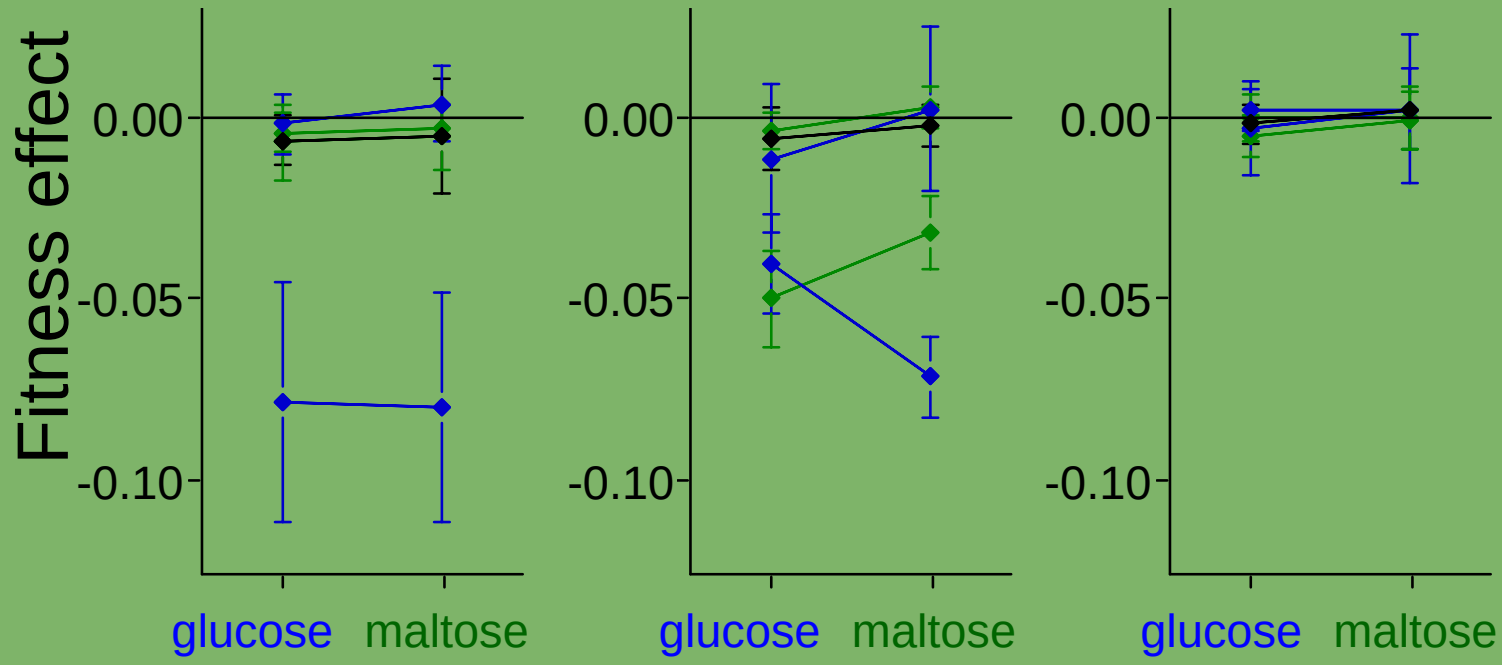


Ecological Environment

Genetic Environment

Both

Neither



0 mutations

3 mutations

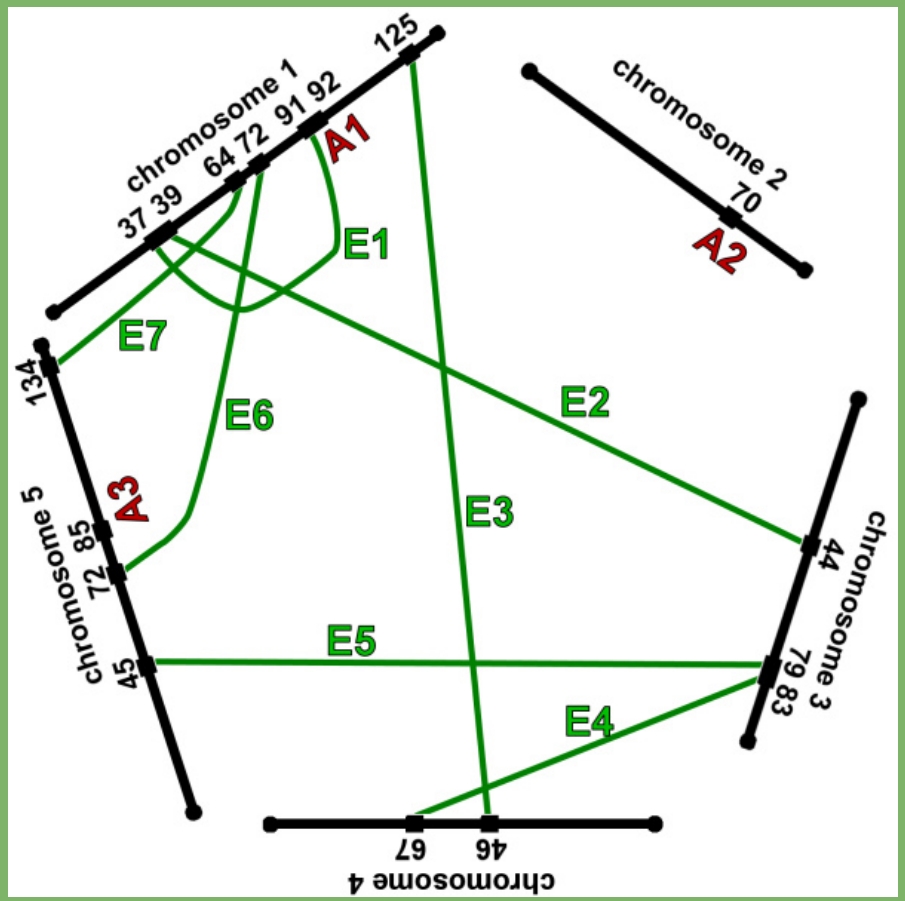
6 mutations

9 mutations

Remold and Lenski (2004) Nature Genetics 36:423

Other kinds of context dependence:

Arabidopsis thaliana



Fruit Number

- **In four fitness components *epistatic* QTL dominate explanation of trait**

- **Locations of QTL differ in greenhouse and field plants (GxGxE)**

(Malmberg et al 2005 Genetics 171:2013)

How does context dependence arise?

How does context-dependence arise in E. coli?

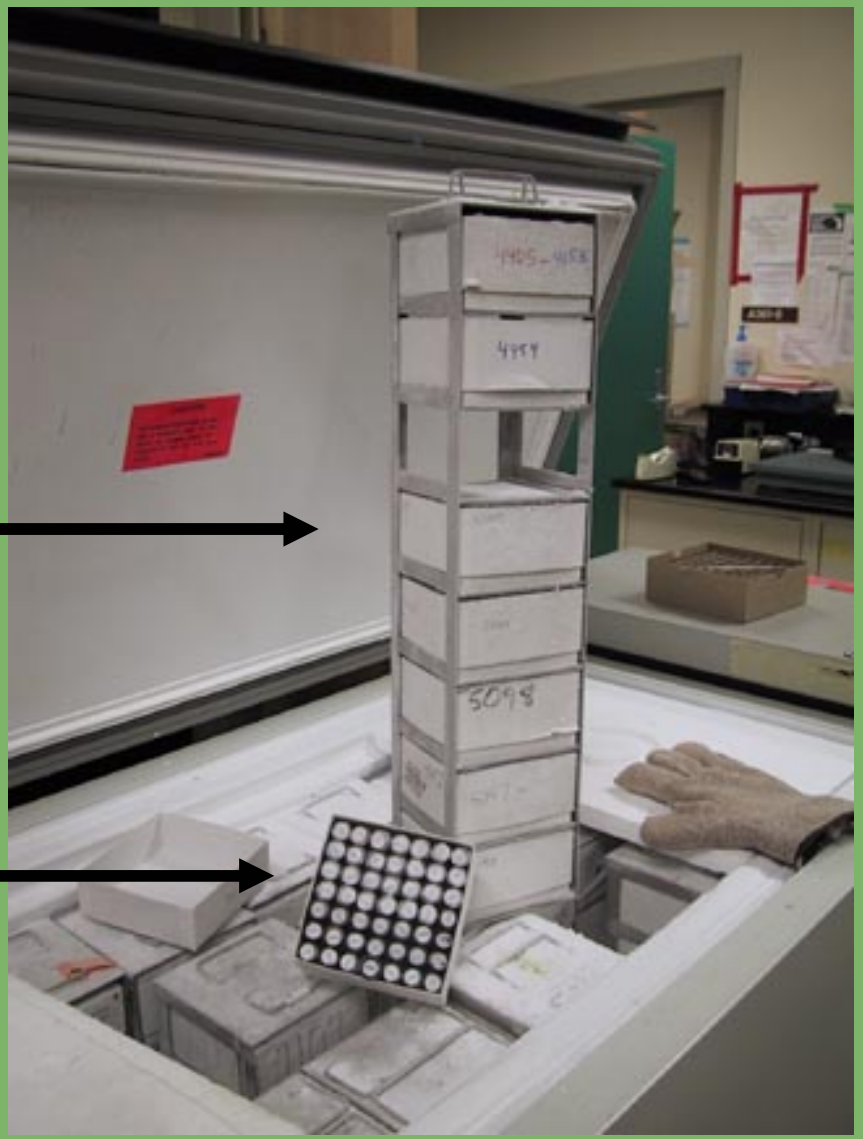
- ***Are differences between genetic environments caused by changes due to response to selection or to random events?***

Long-term evolution in E. coli

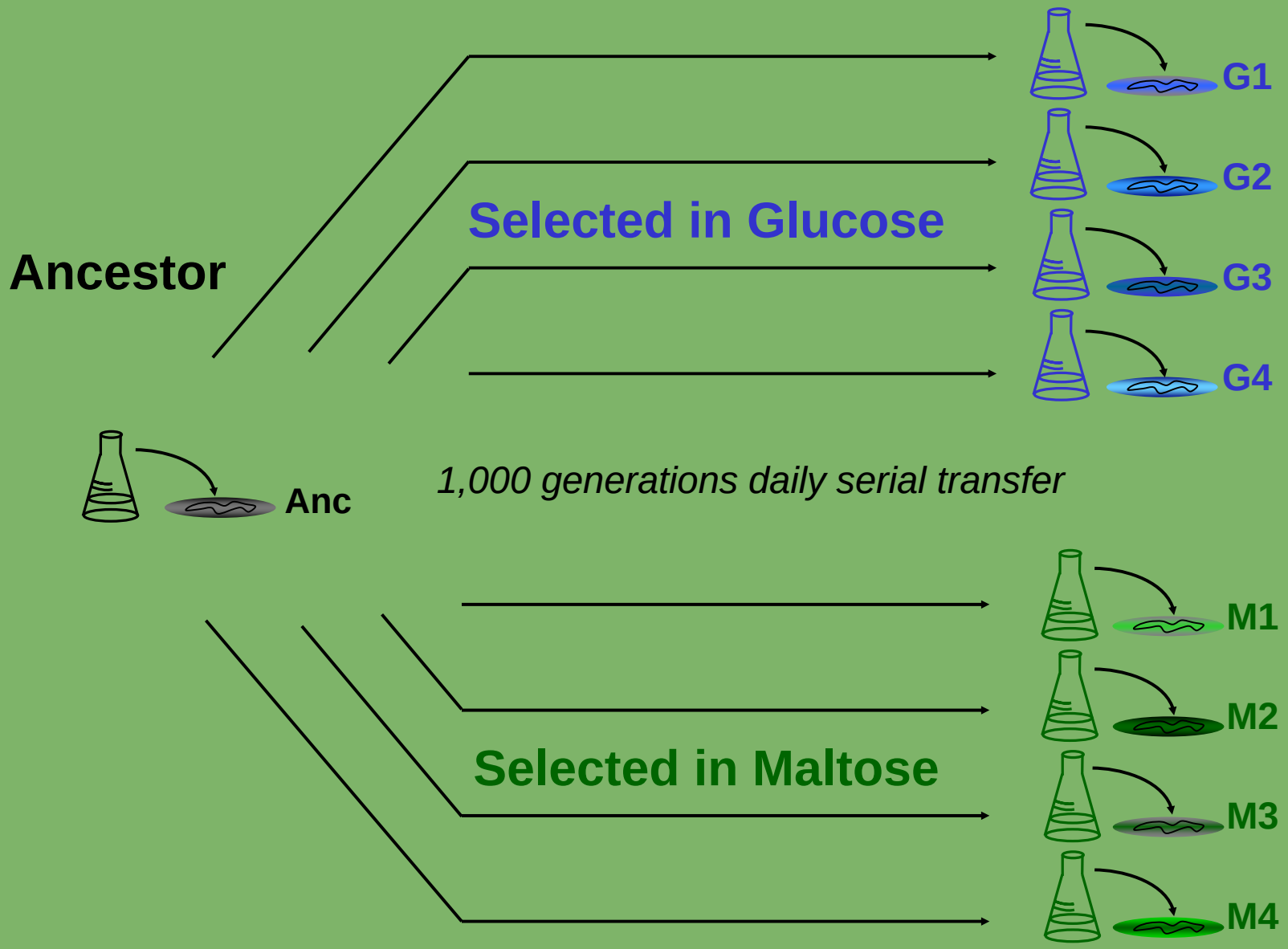
Long-term evolution in E. coli

Fossil record →

Recover genotypes →

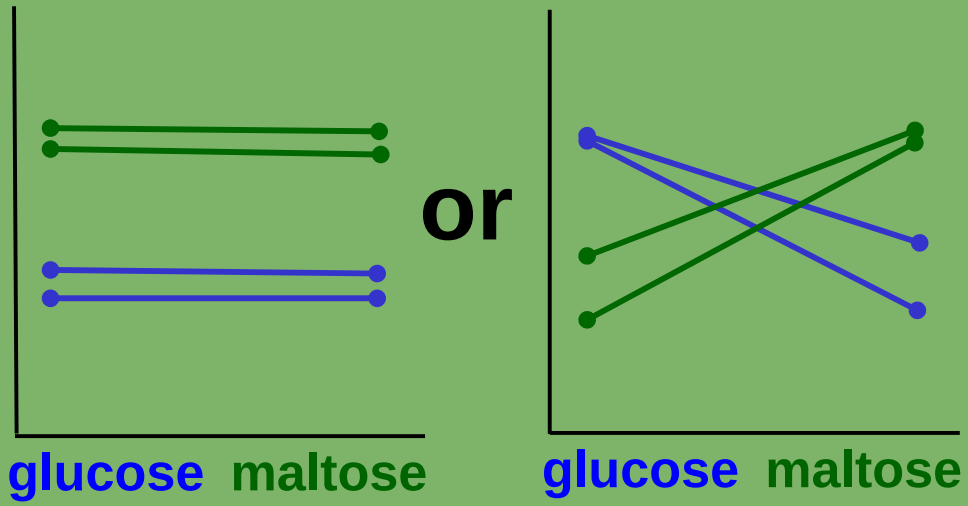


Genetic environments:

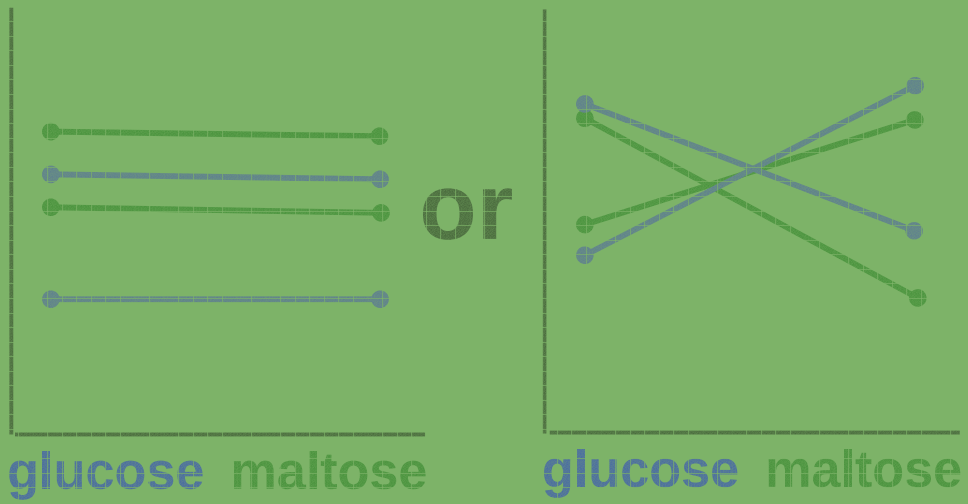


Expected patterns:

Selection

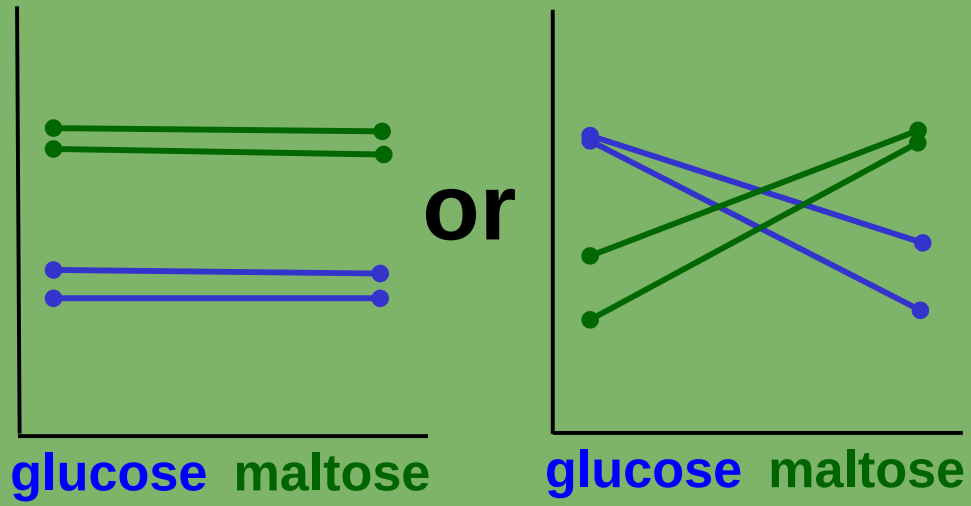


Random contingency

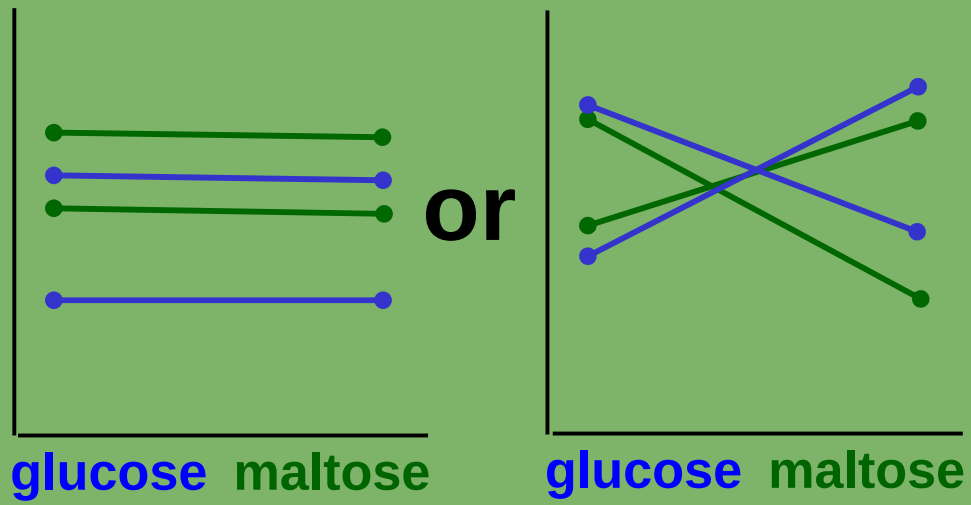


Expected patterns:

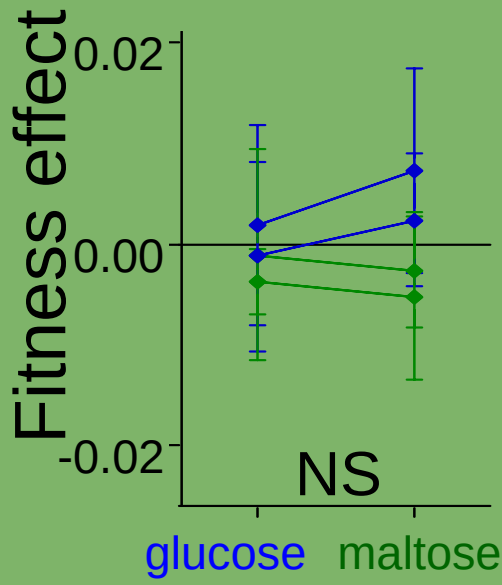
Selection



Random contingency

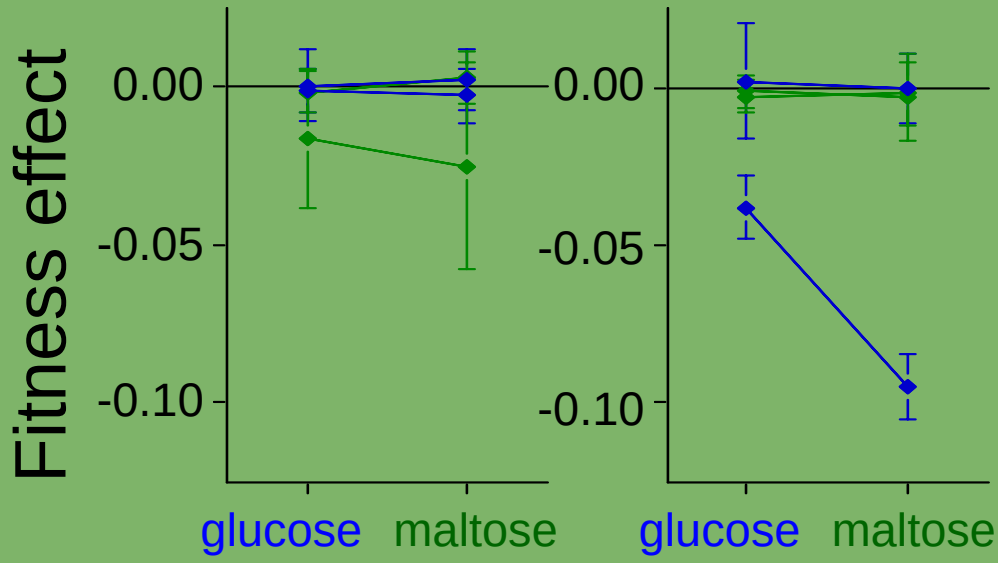


Selection history



0/9 mutations

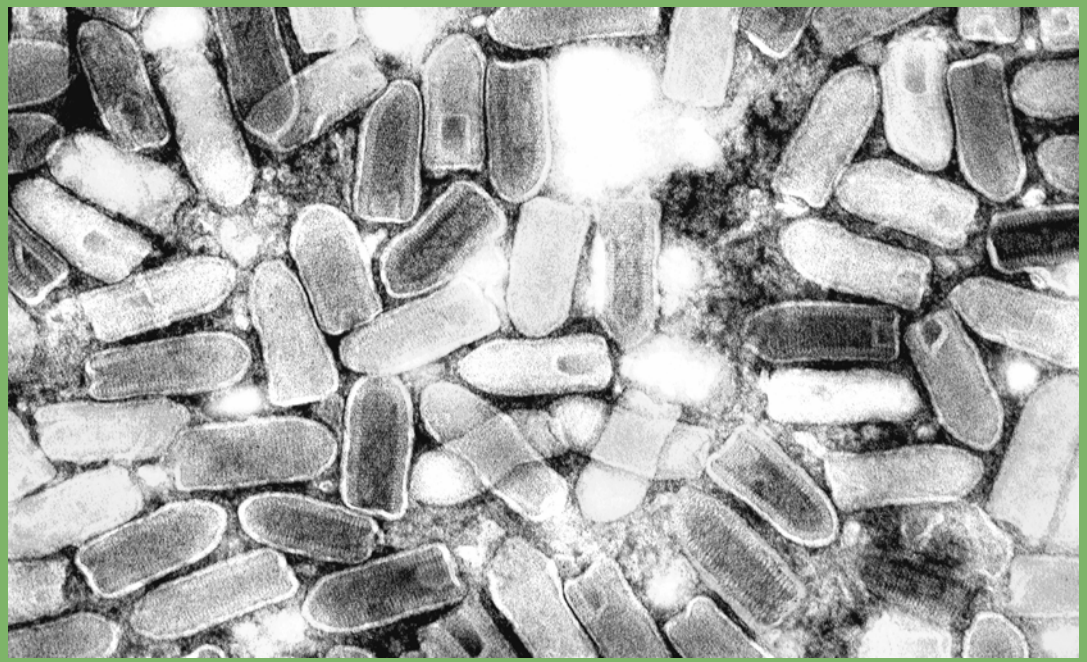
Random contingency



3/9 mutations

Remold and Lenski (2004) Nature Genetics 36:423

How does context-dependence arise in RNA viruses?

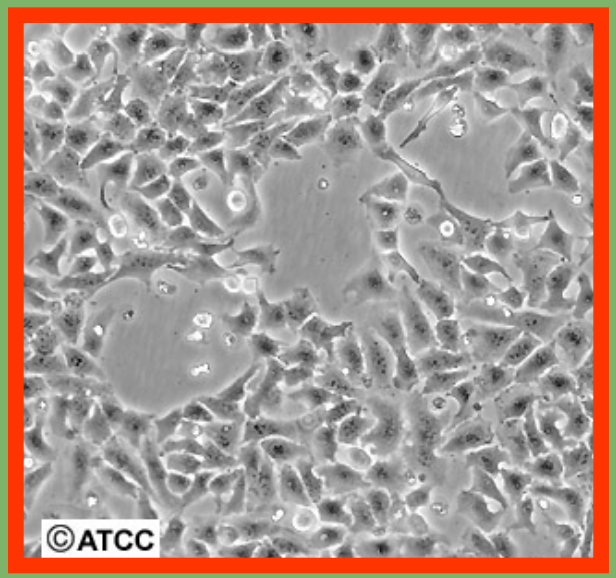


Vesicular stomatitis virus (VSV)

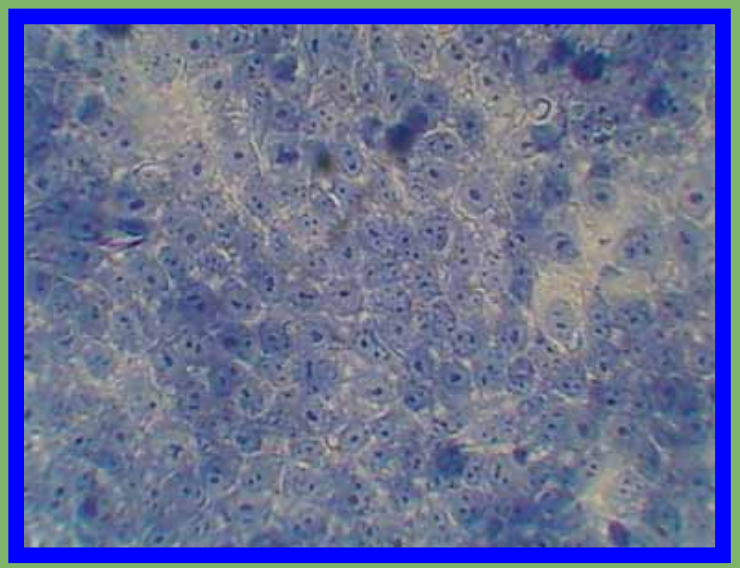
- large population sizes
- very high mutation rates (1.1 mutations/genome)

VSV experimental hosts

mammalian host cells grown in tissue culture

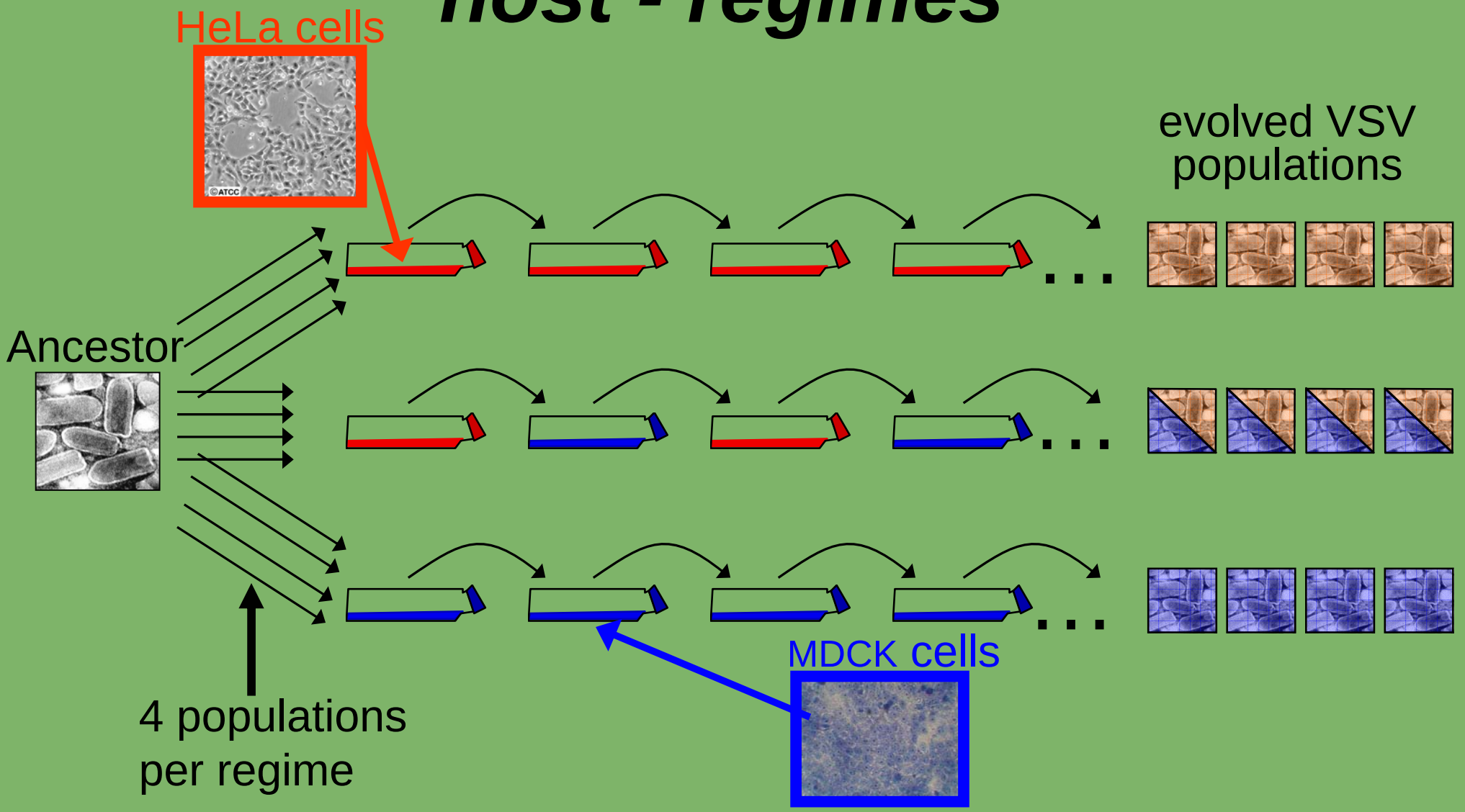


HeLa (human)

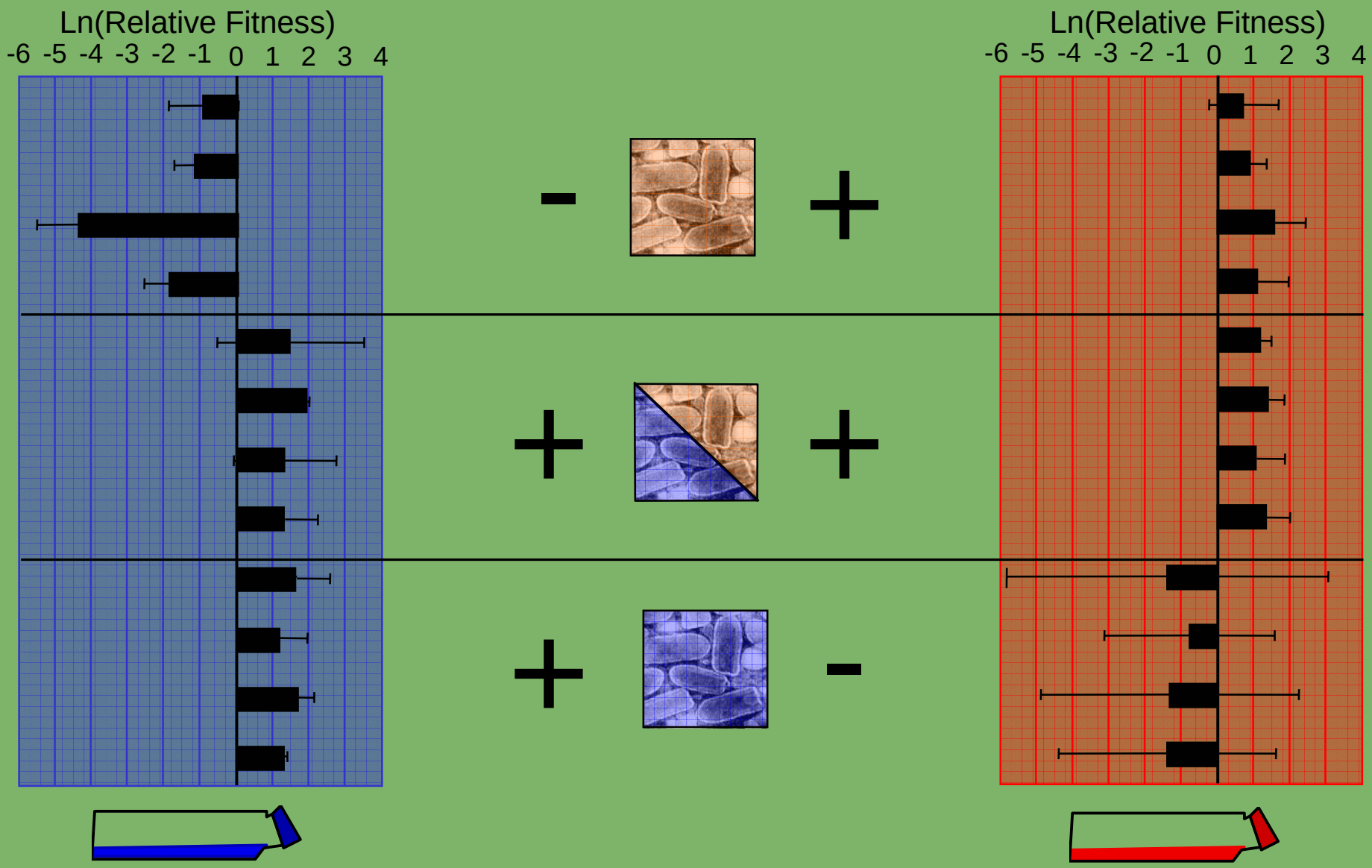


MDCK (canine)

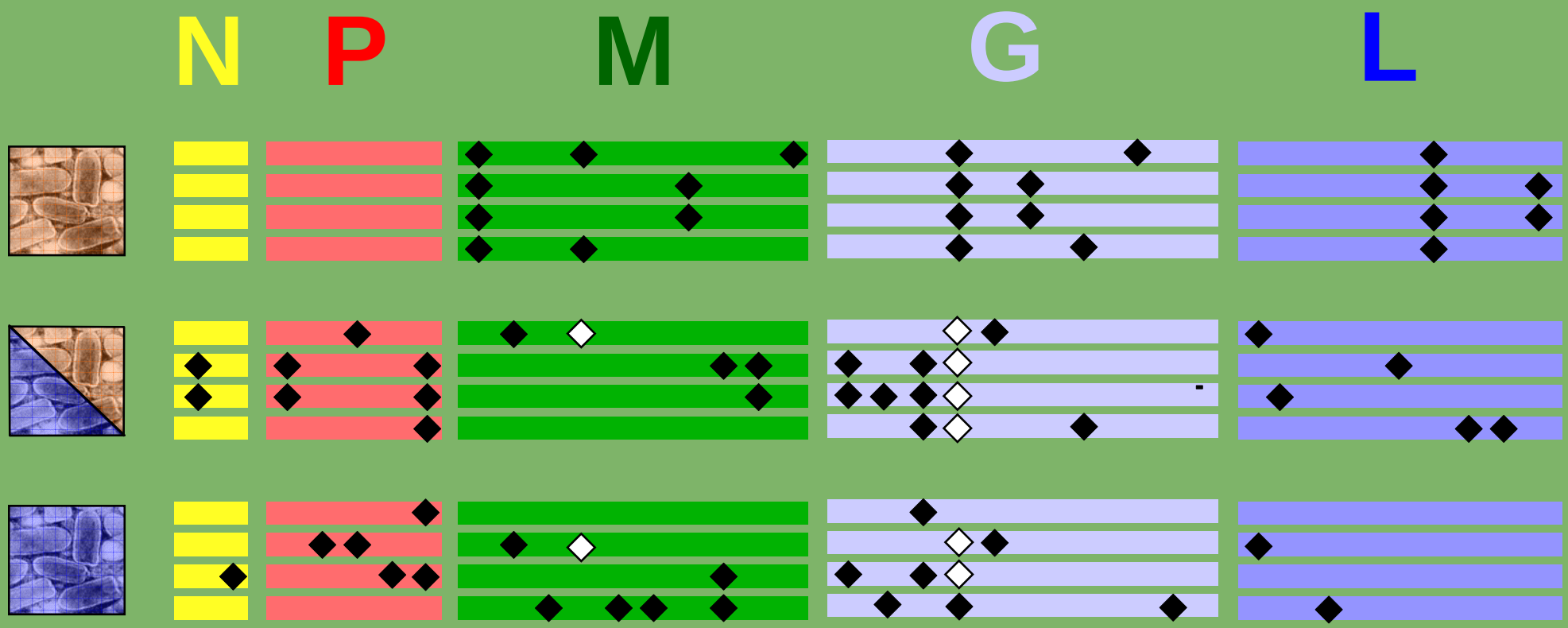
100 generations evolution in new host - regimes

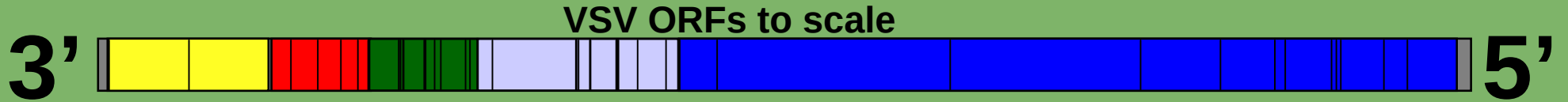


Fitness in differing host environments

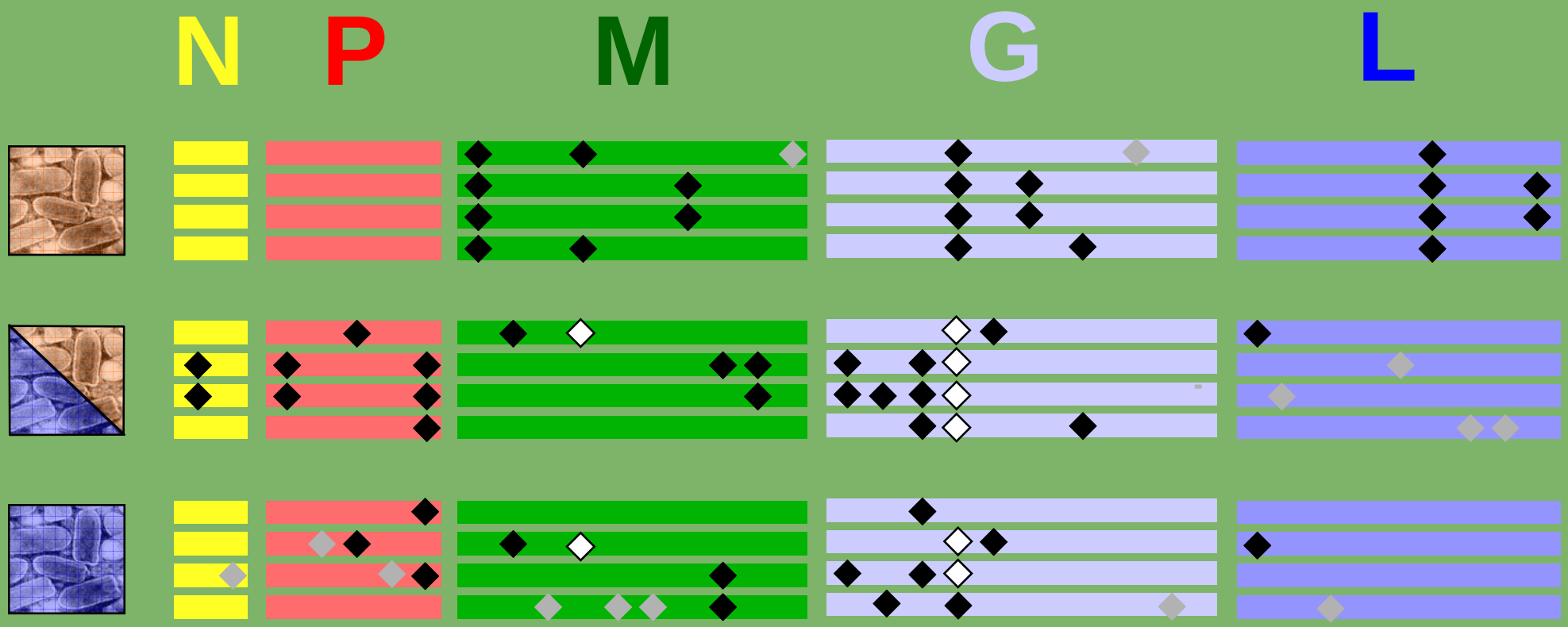


Genetic changes





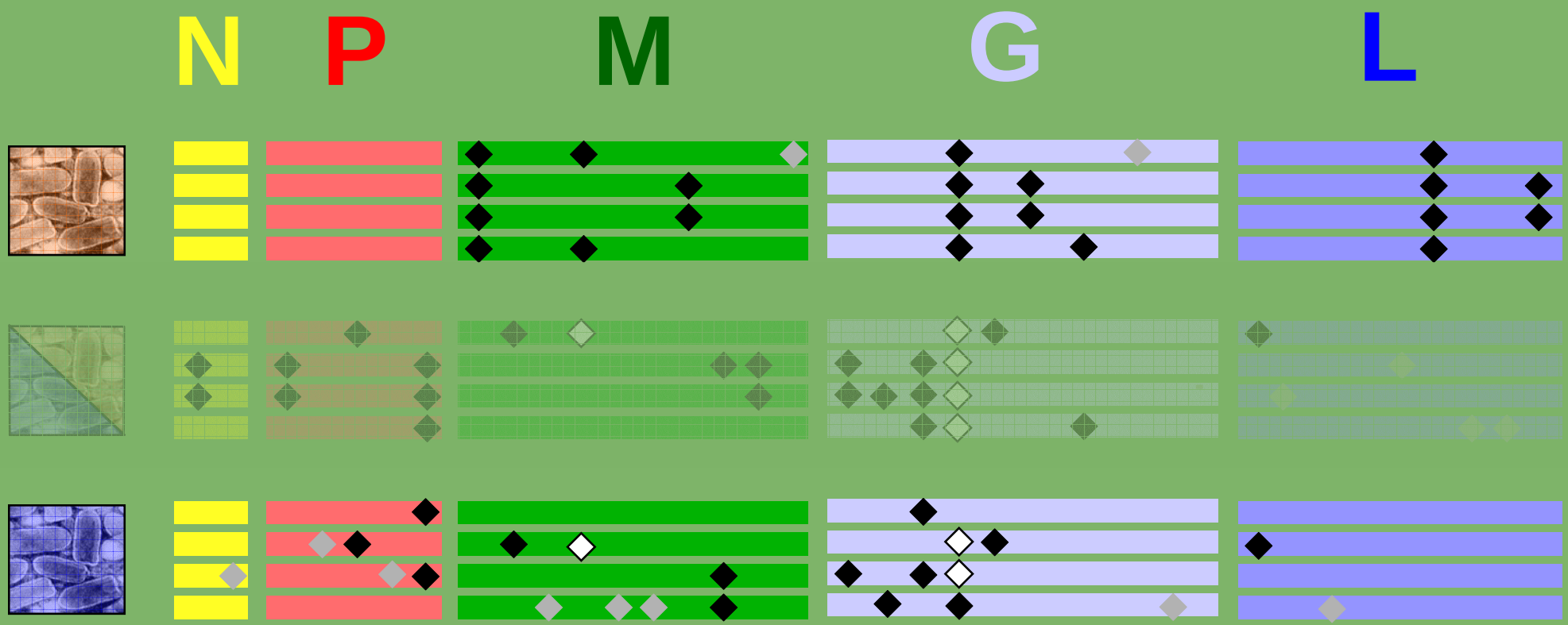
Parallel genetic changes

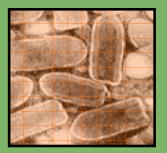
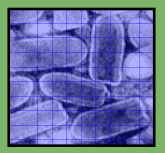


52 of 70 mutations (74%) are at shared sites

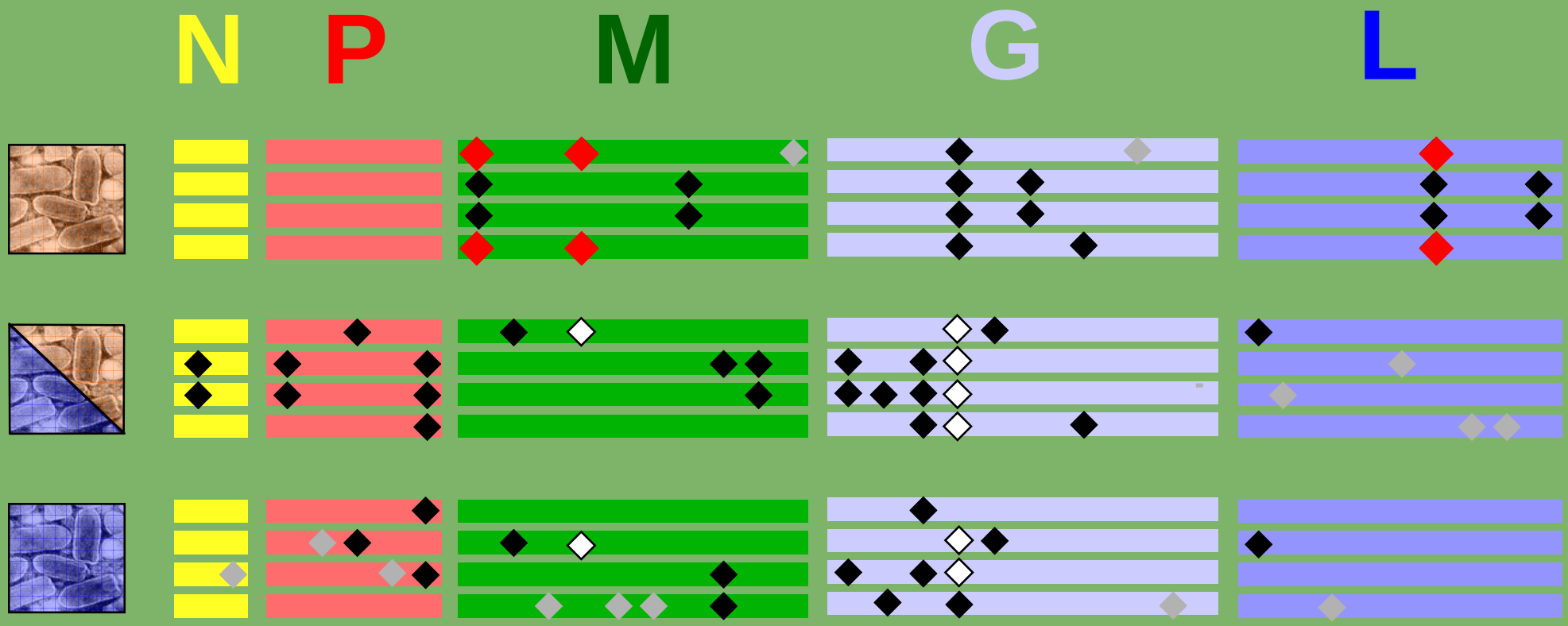
19 of 37 loci (51%) have independent shared alleles

Parallel genetic changes



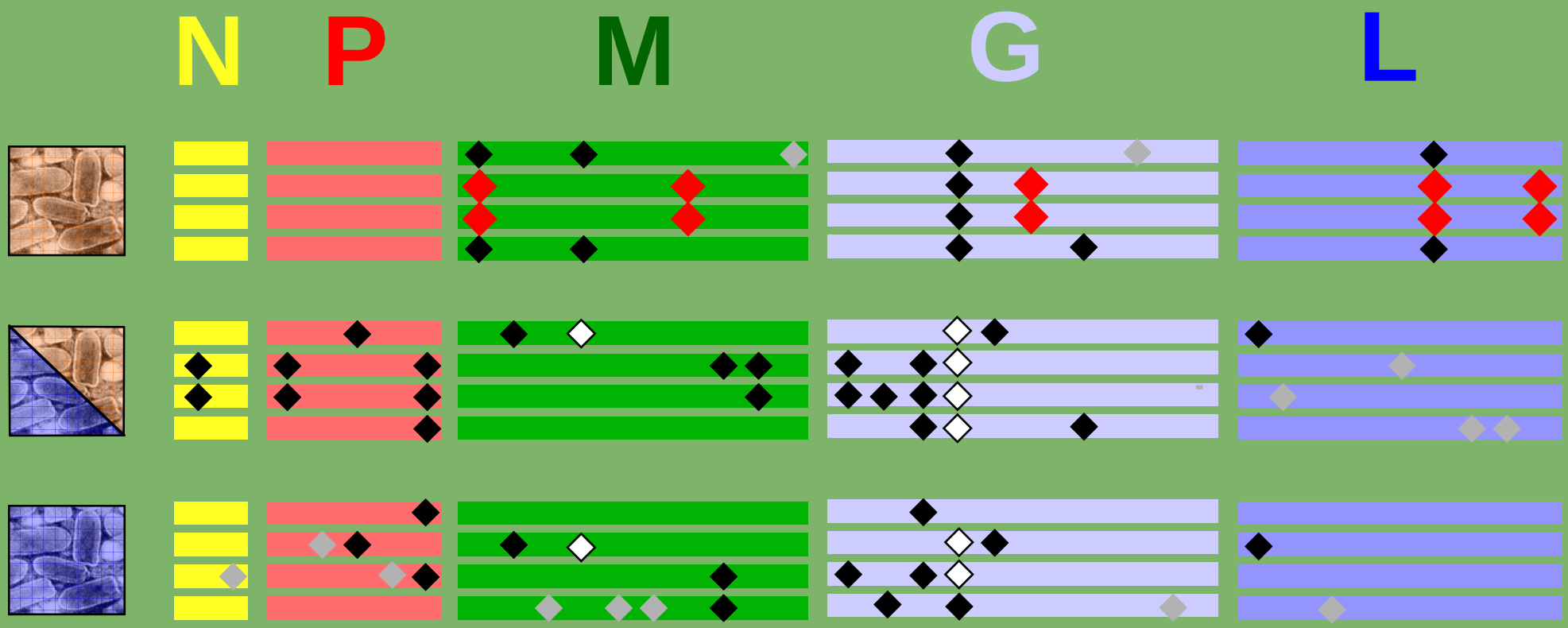
No shared new alleles between  *and* 

Parallel genetic changes



Five sets of co-occurring shared alleles suggest that epistatically interacting groups have become fixed in multiple lineages.

Parallel genetic changes



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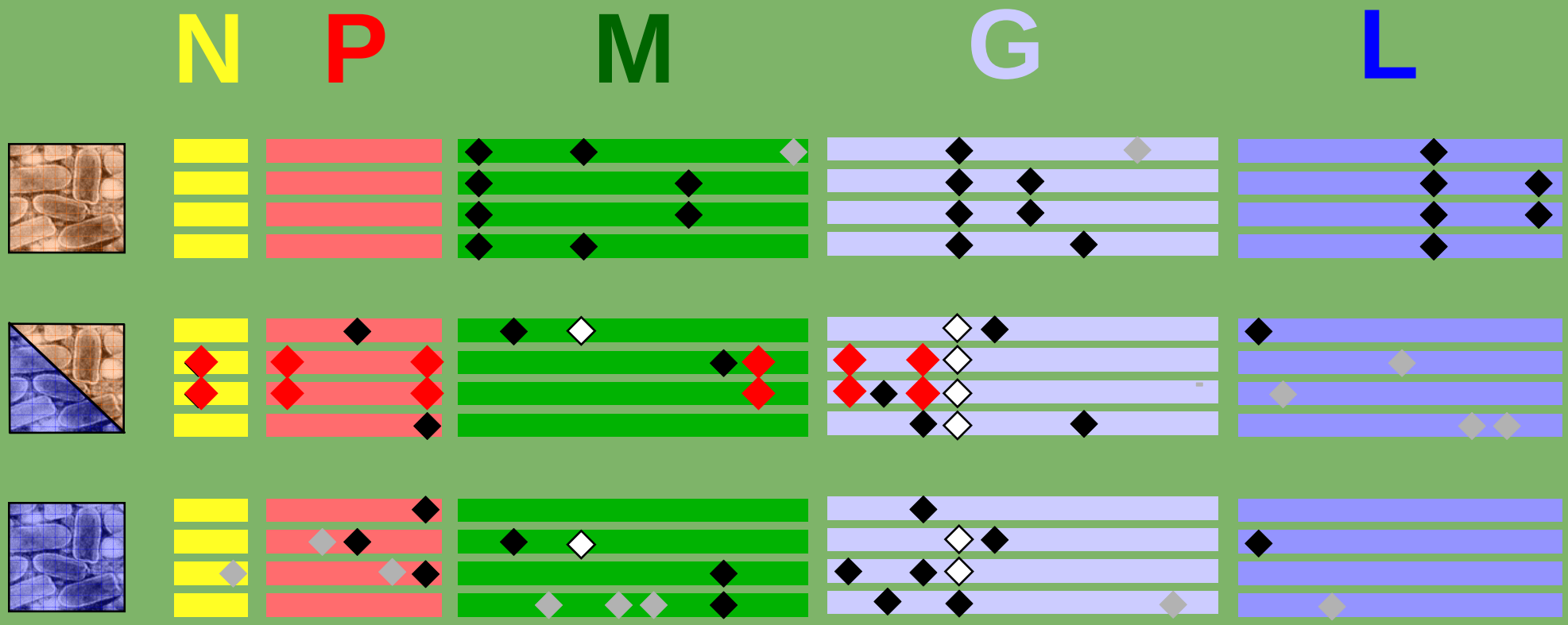
Parallel genetic changes



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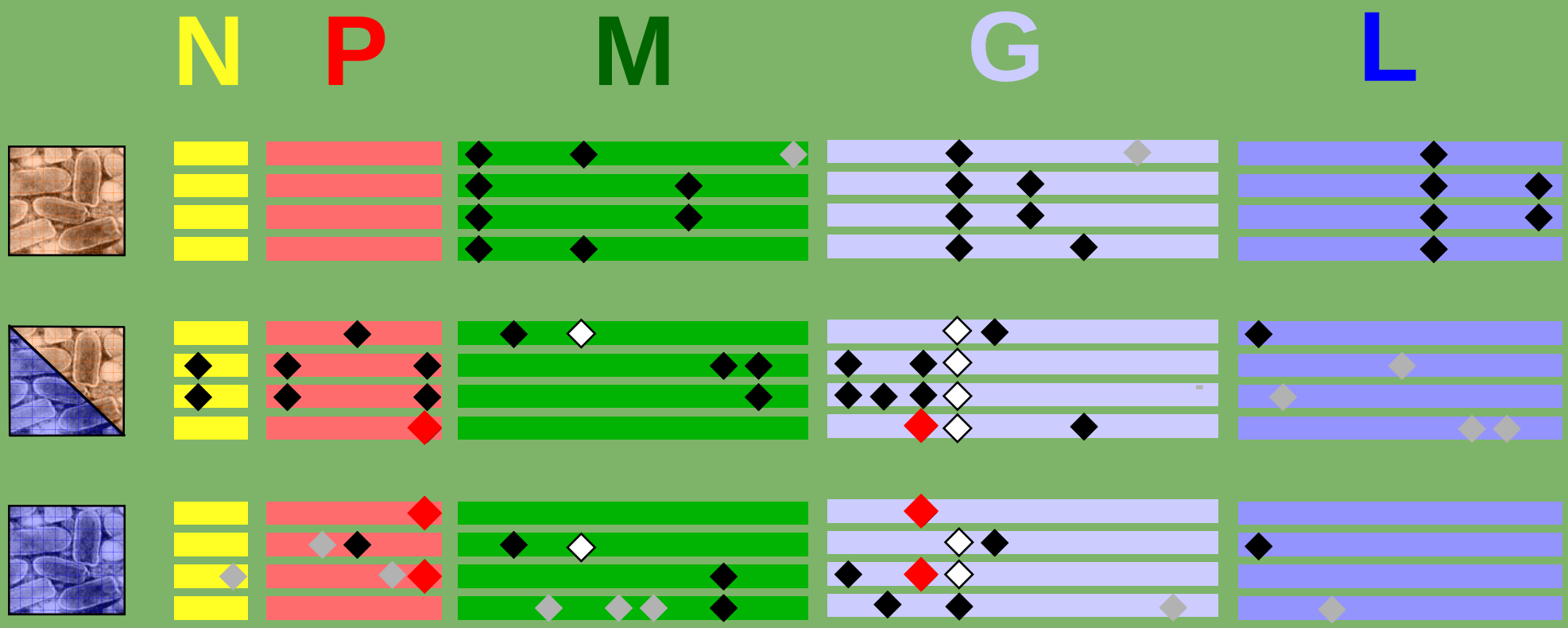
Parallel genetic changes



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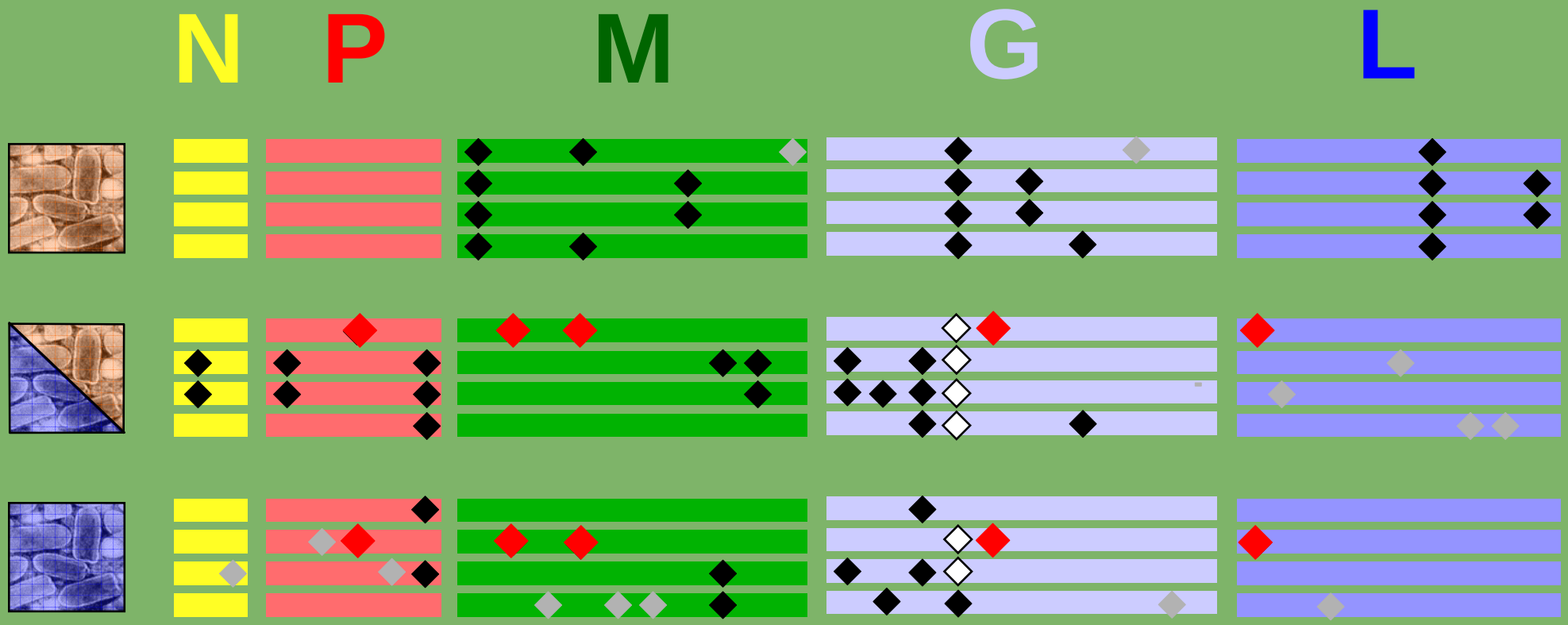
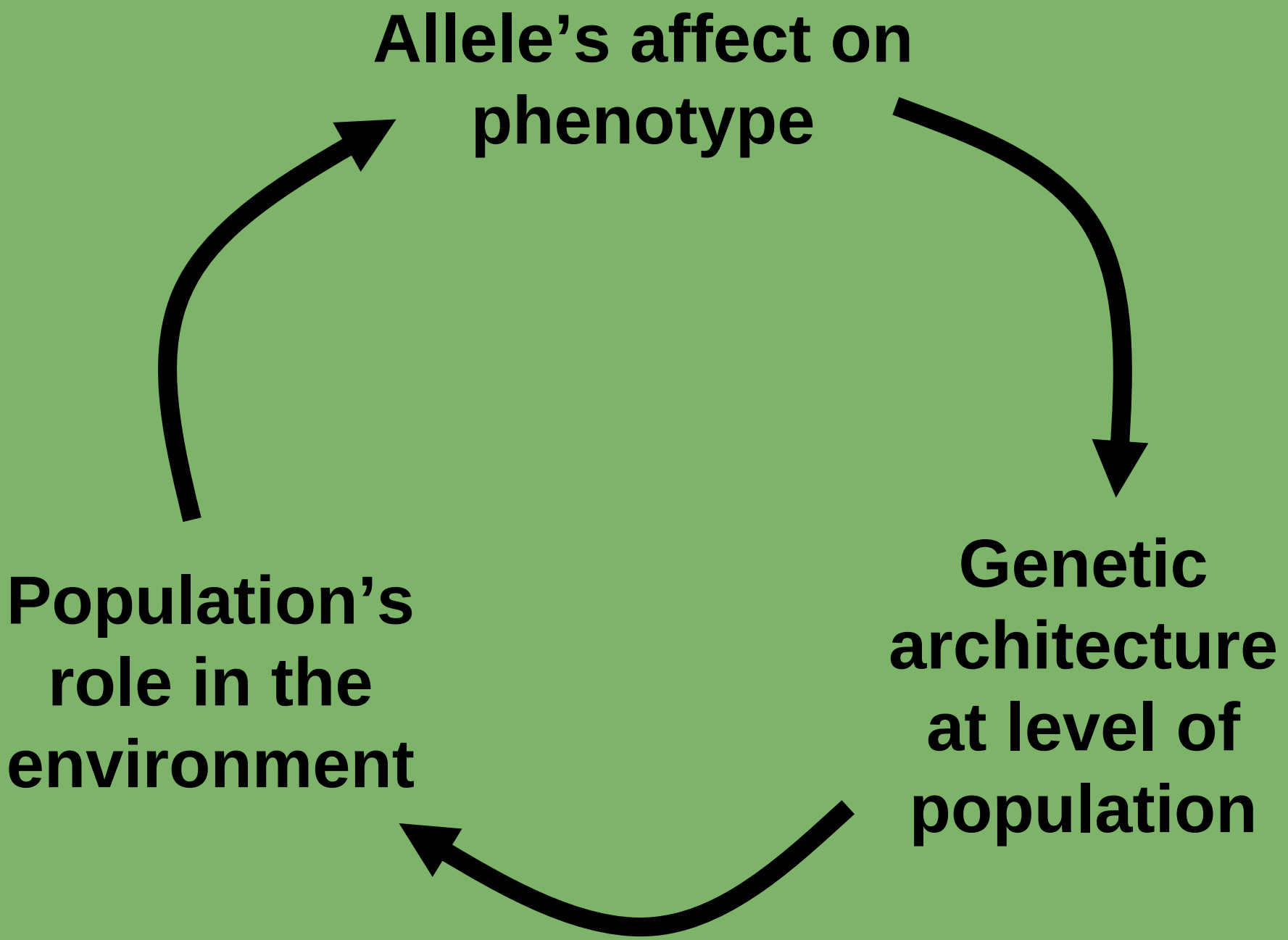
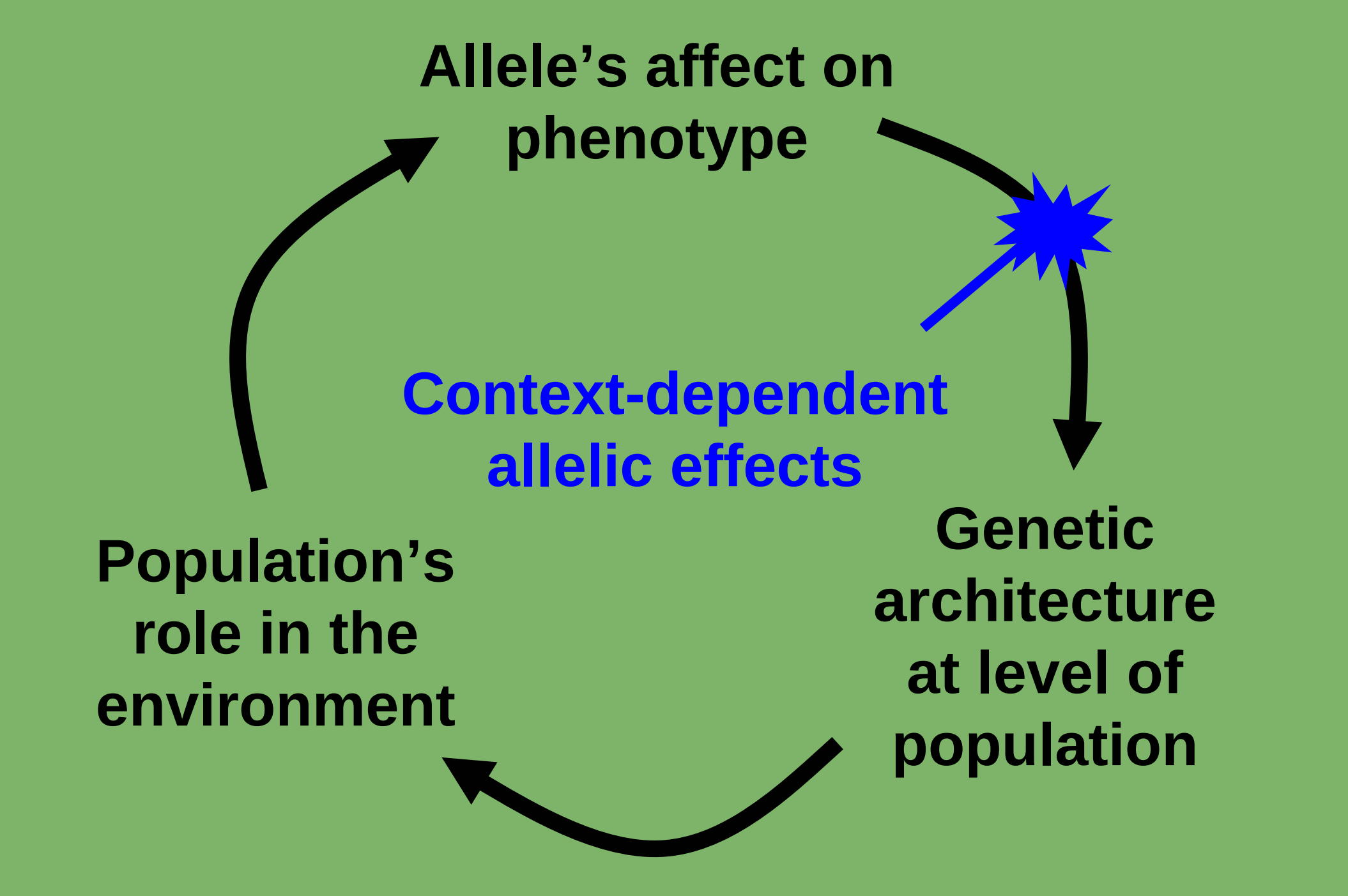
Parallel genetic changes

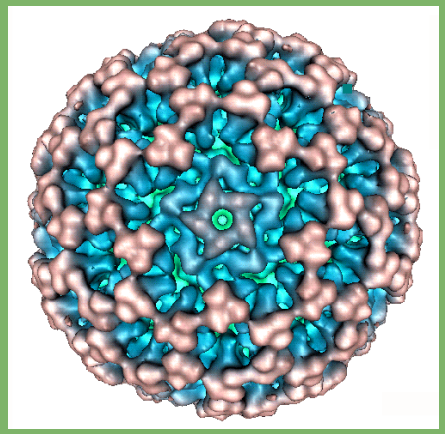


Five sets of co-occurring shared alleles suggest that epistatically interacting groups have become fixed in multiple lineages.

What are the consequences of context dependence?

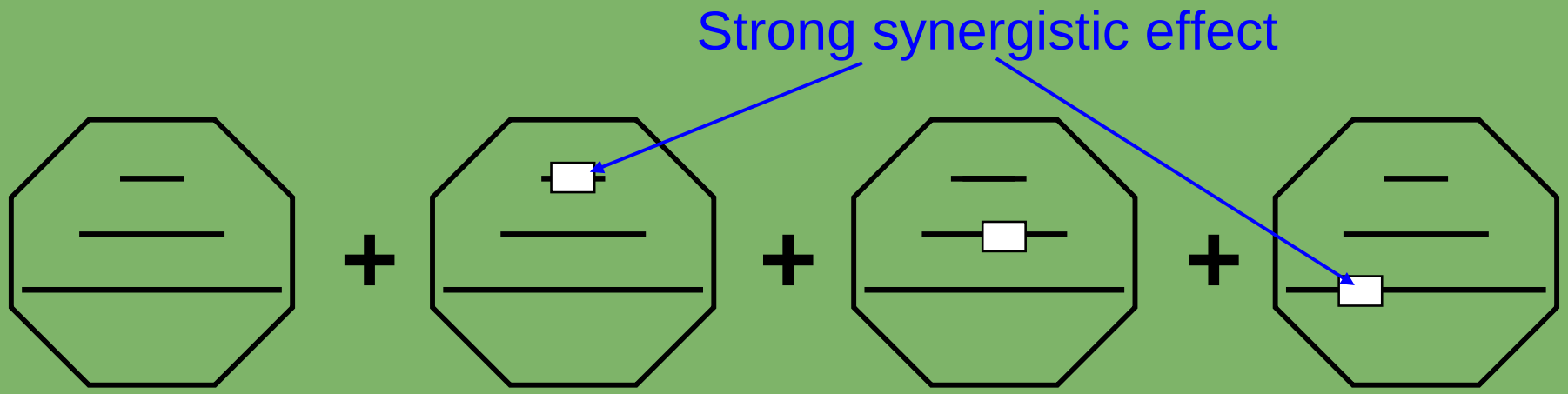

Allele’s affect on phenotype
Genetic architecture at level of population
Population’s role in the environment


Allele's affect on phenotype
Genetic architecture at level of population
Population's role in the environment
Context-dependent allelic effects



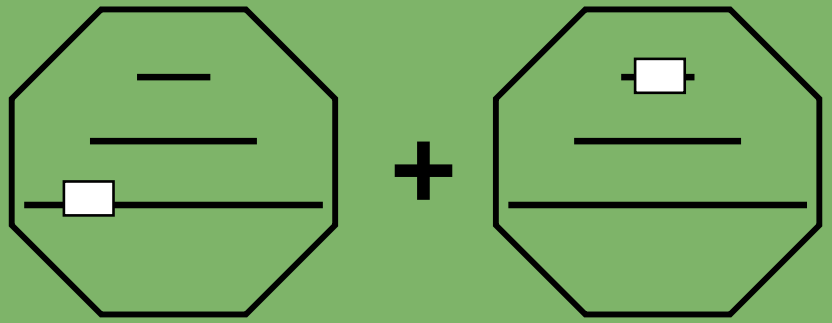
Phage ϕ6 of *Pseudomonas phaseolicola*

How will co-infection and epistasis affect the rate of loss of deleterious alleles?



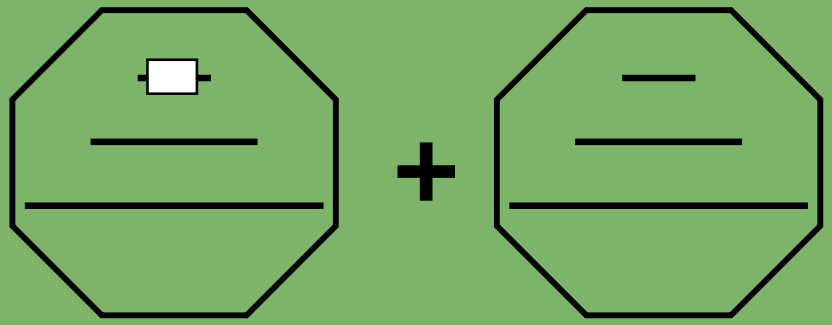
*Replicate mixed populations infect hosts at **low** and **high** multiplicity of infection.*

Froissart et al 2004 Genetics 168:9



Sex:

Reassortment of synergistically epistatic mutations could speed their elimination from the population

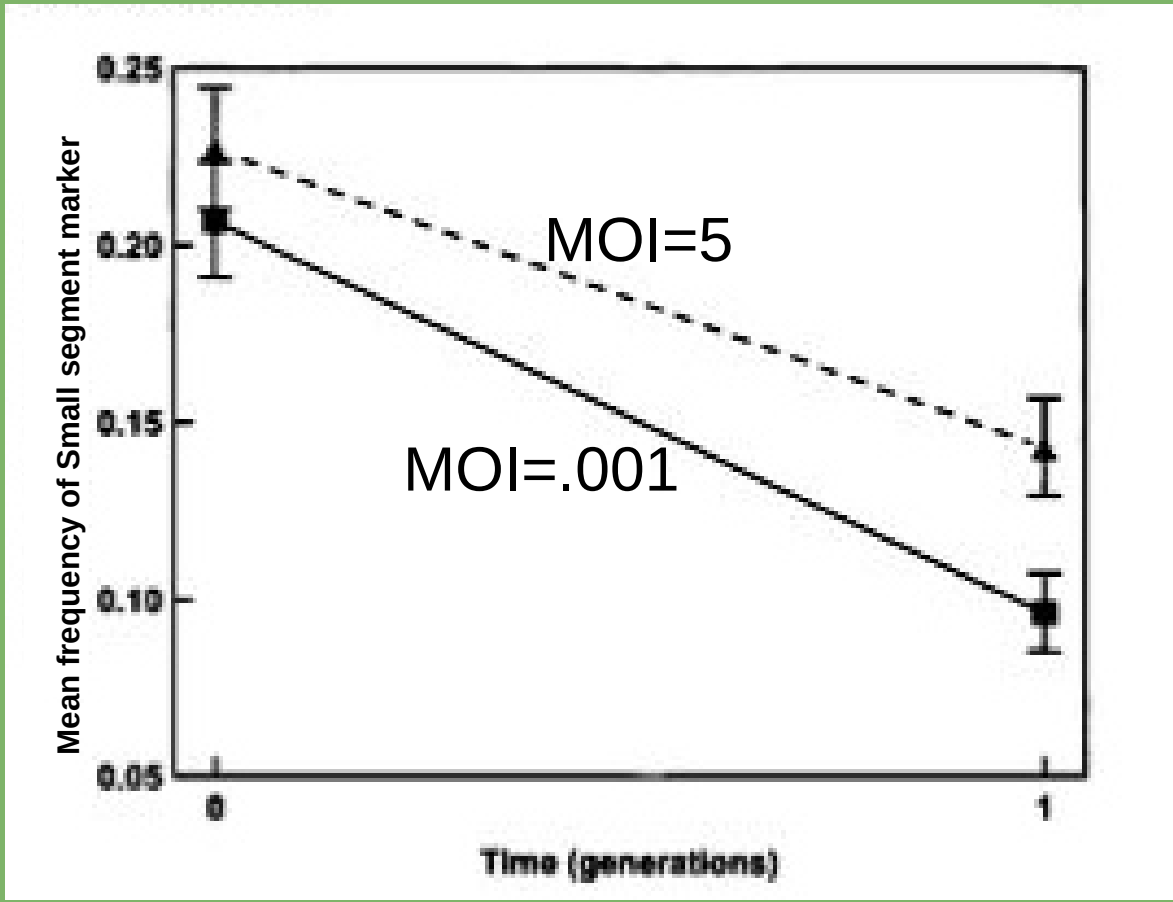


Complementation:

Presence of the WT gene product due to co-infection could decrease the mutation's cost and slow its elimination

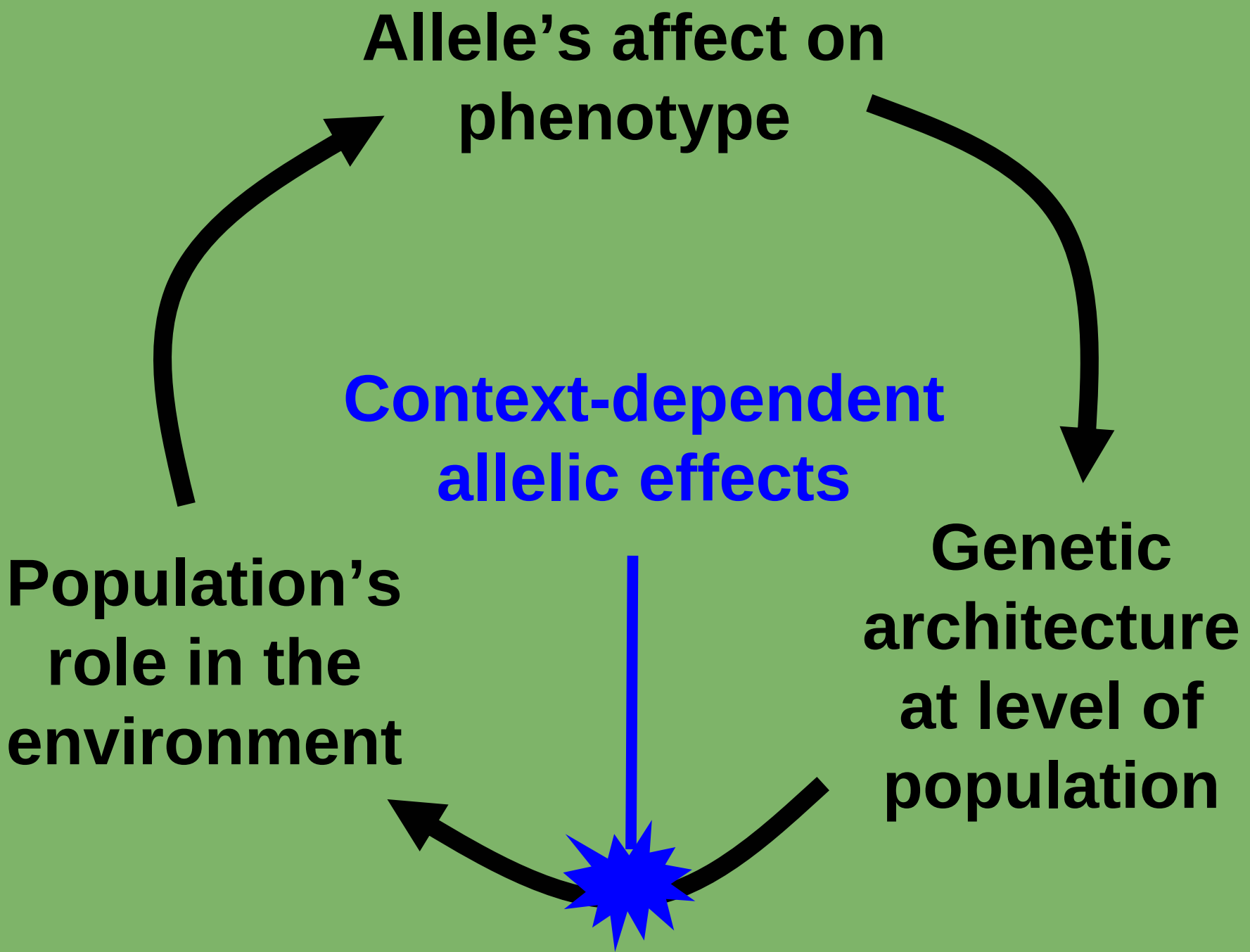
Froissart et al 2004 Genetics 168:9

Stronger selection against the mutation in the absence of co-infection than in its presence.



In this case, complementation is stronger than sex.

Froissart et al 2004 Genetics 168:9

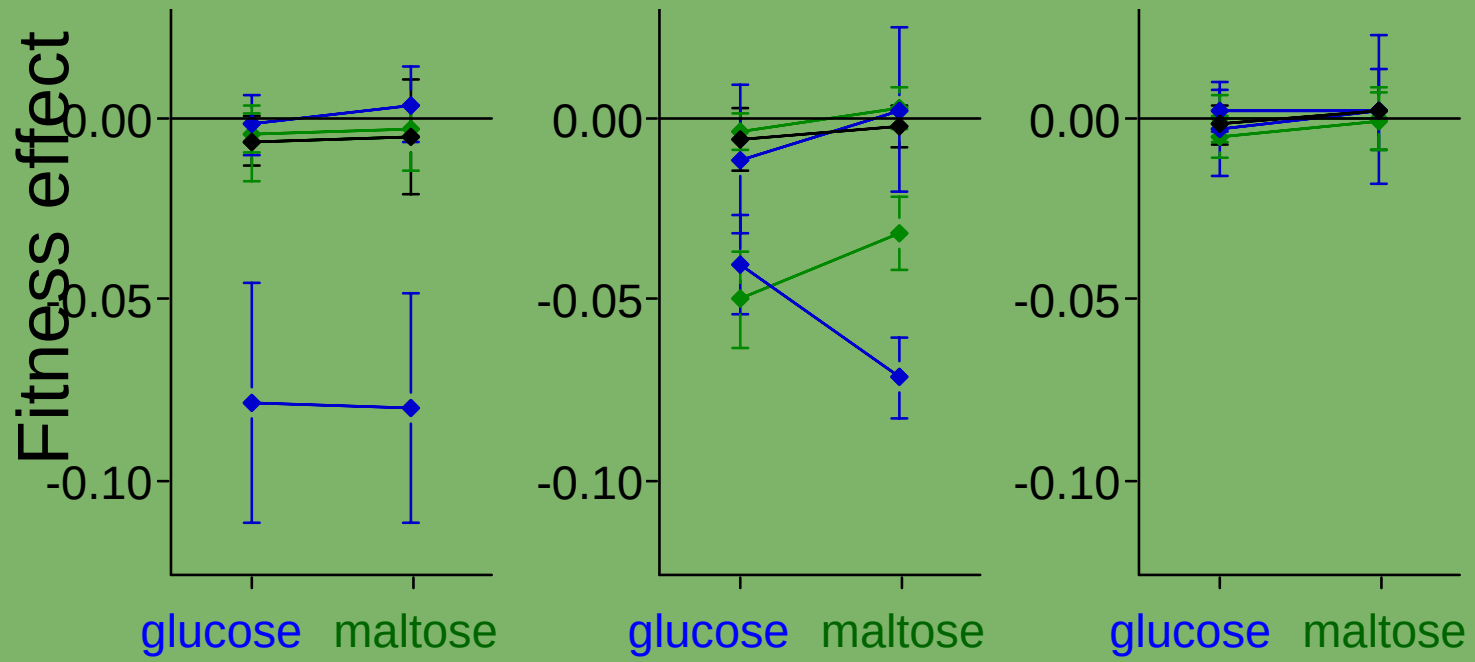

Allele's affect on phenotype
Context-dependent allelic effects
Genetic architecture at level of population
Population's role in the environment

Ecological Environment

Genetic Environment

Both

Neither



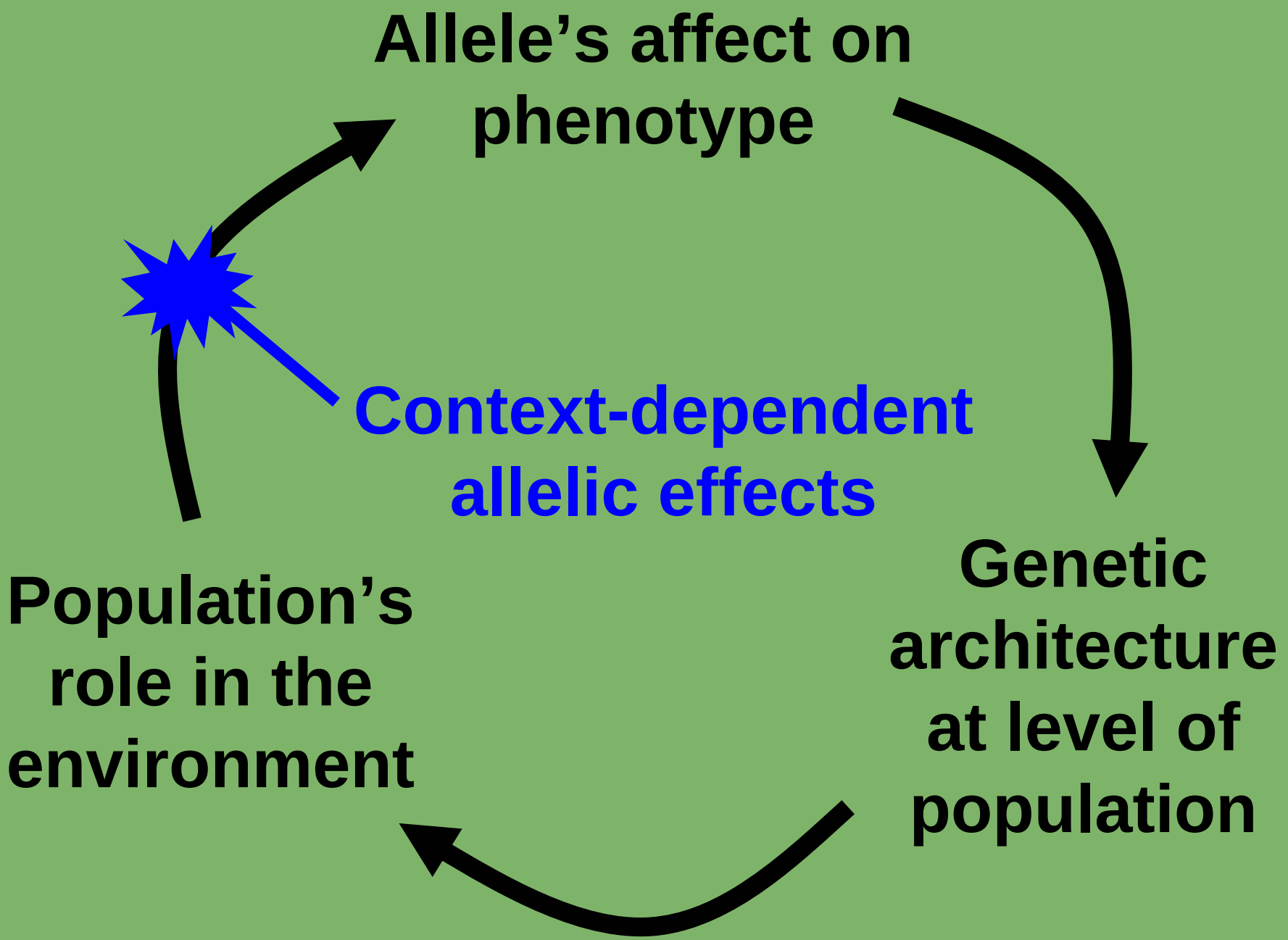
0 mutations

3 mutations

6 mutations

9 mutations

In the absence of gene flow, E coli populations rapidly diverge in the genetic architecture, even in the presence of parallel selection.


Allele's affect on phenotype
Genetic architecture at level of population
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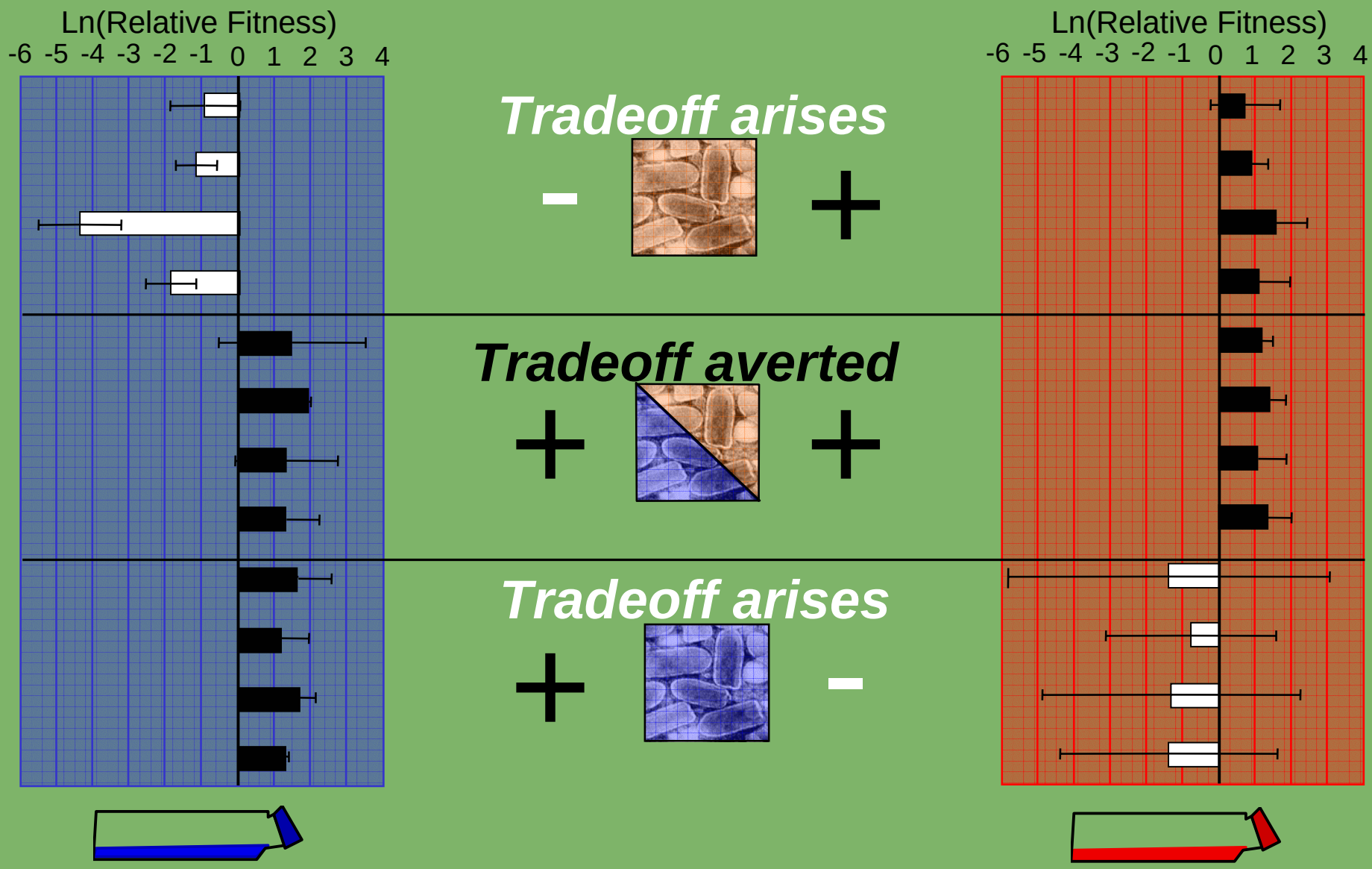
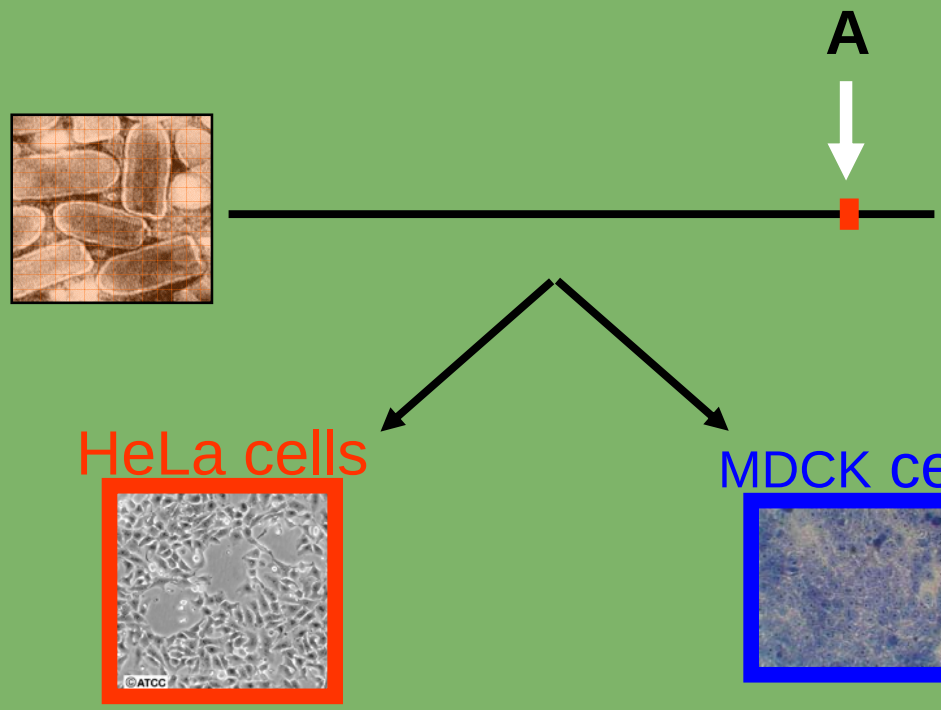
Why do tradeoffs arise?



Antagonistic pleiotropy

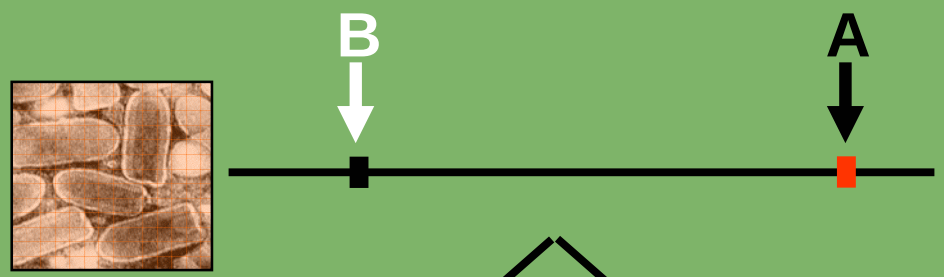


A increases fitness

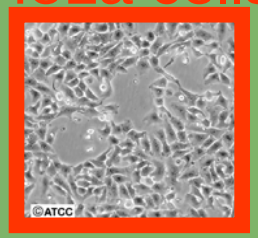
A decreases fitness

True functional linkage

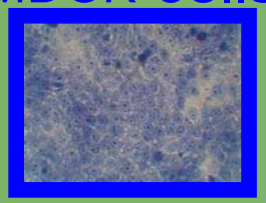
Mutation accumulation



HeLa cells



MDCK cells



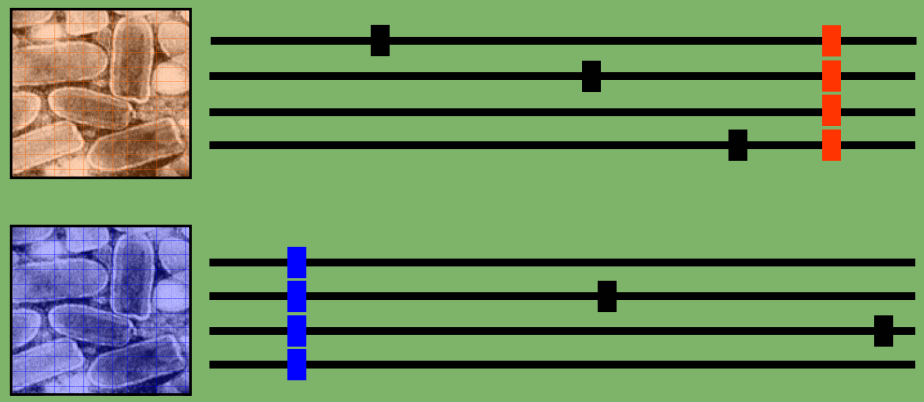
A *Increases fitness*
B *Neutral*

A *Neutral*
B *Decreases fitness*

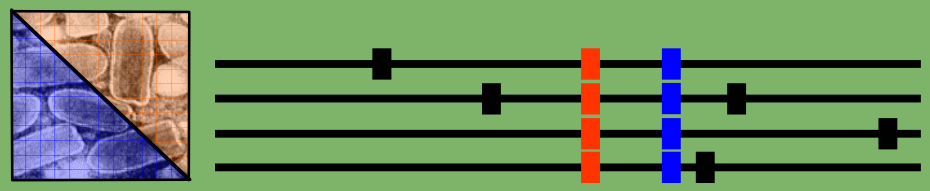
Not true functional linkage

Expectation under antagonistic pleiotropy

Tradeoff arises



Tradeoff avoided



different loci responsible for adaptation in

single

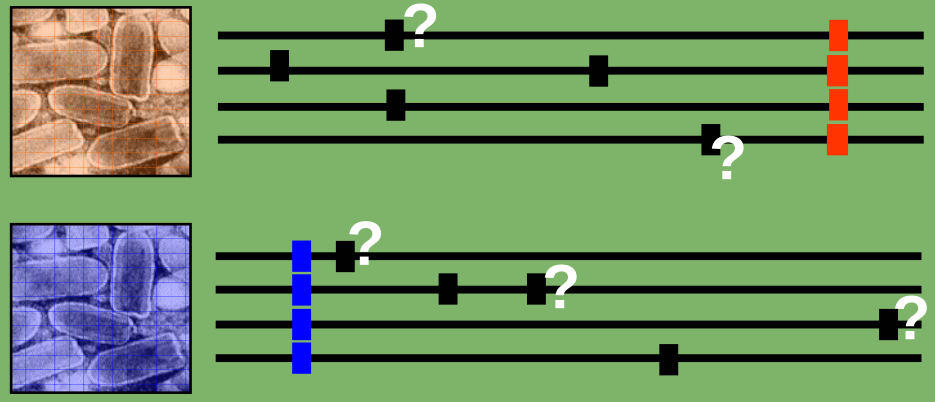
vs

Alternating hosts

Assumption: P(potential beneficial mutation arises and becomes fixed in at least some lineages) is ***high***

Expectation under mutation accumulation

Apparent tradeoff arises



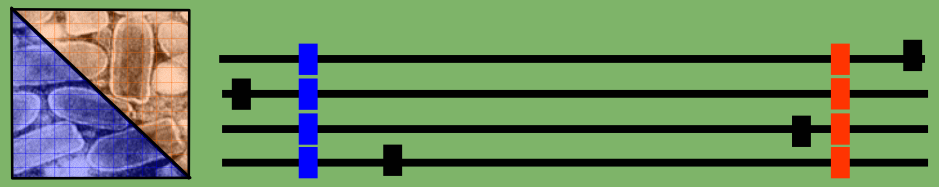
same loci responsible for adaptation in

HeLa

and

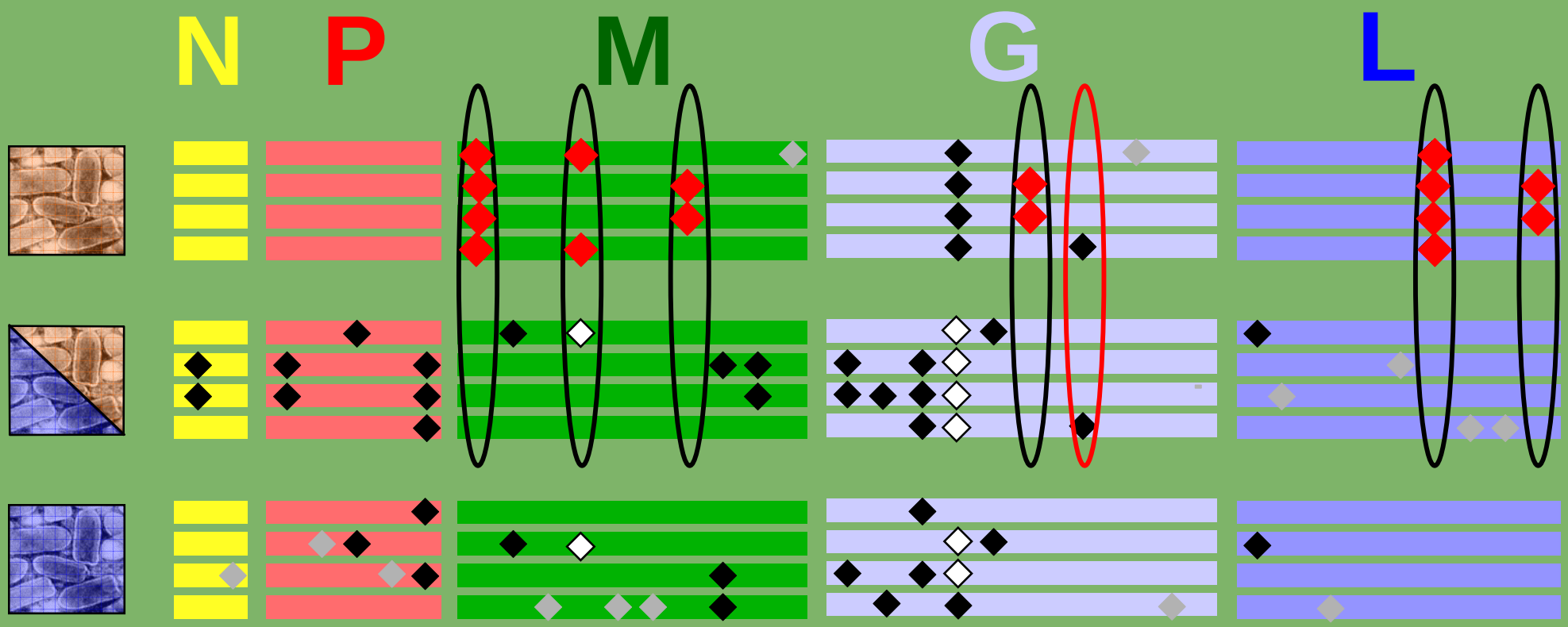
MDCK

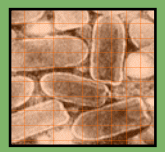
Apparent tradeoff avoided



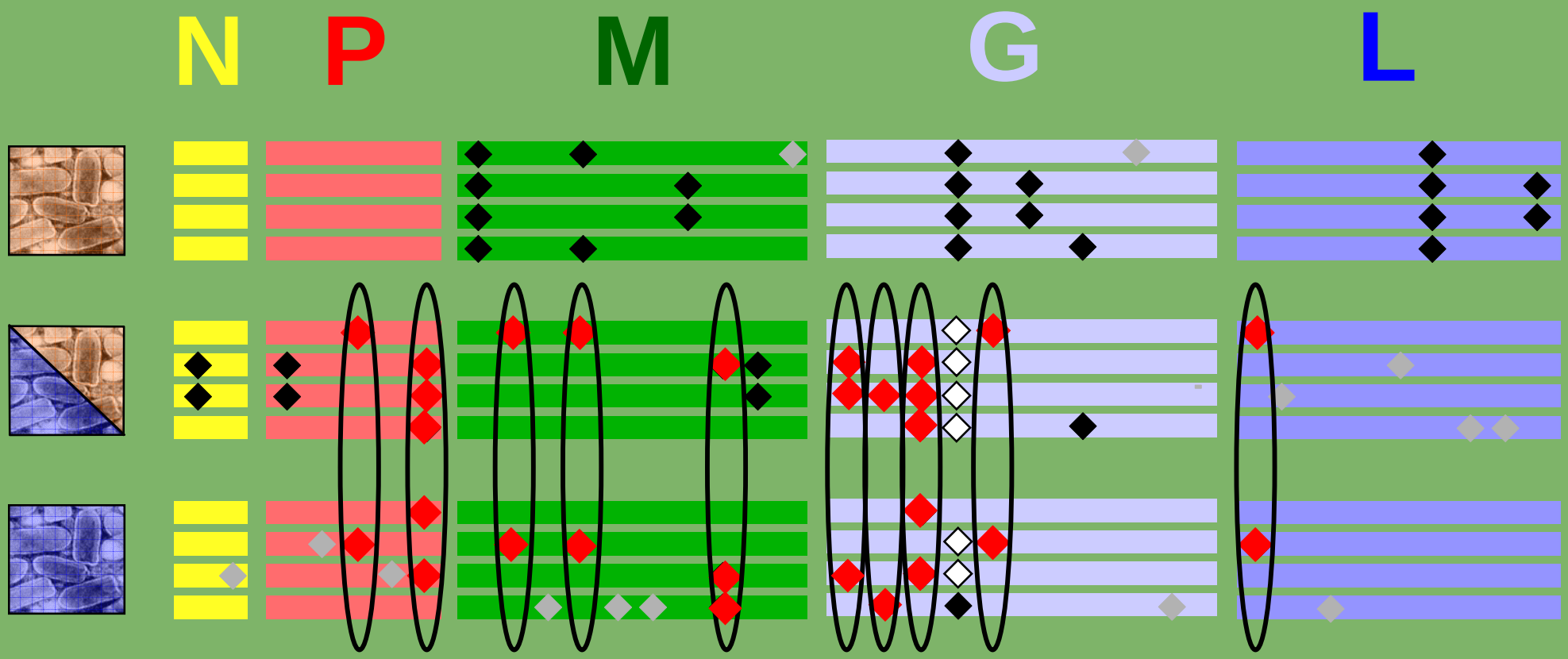
loci responsible for **cost** *in alternate host not identifiable*

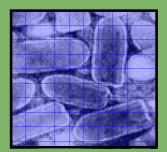
Tradeoffs: General trends



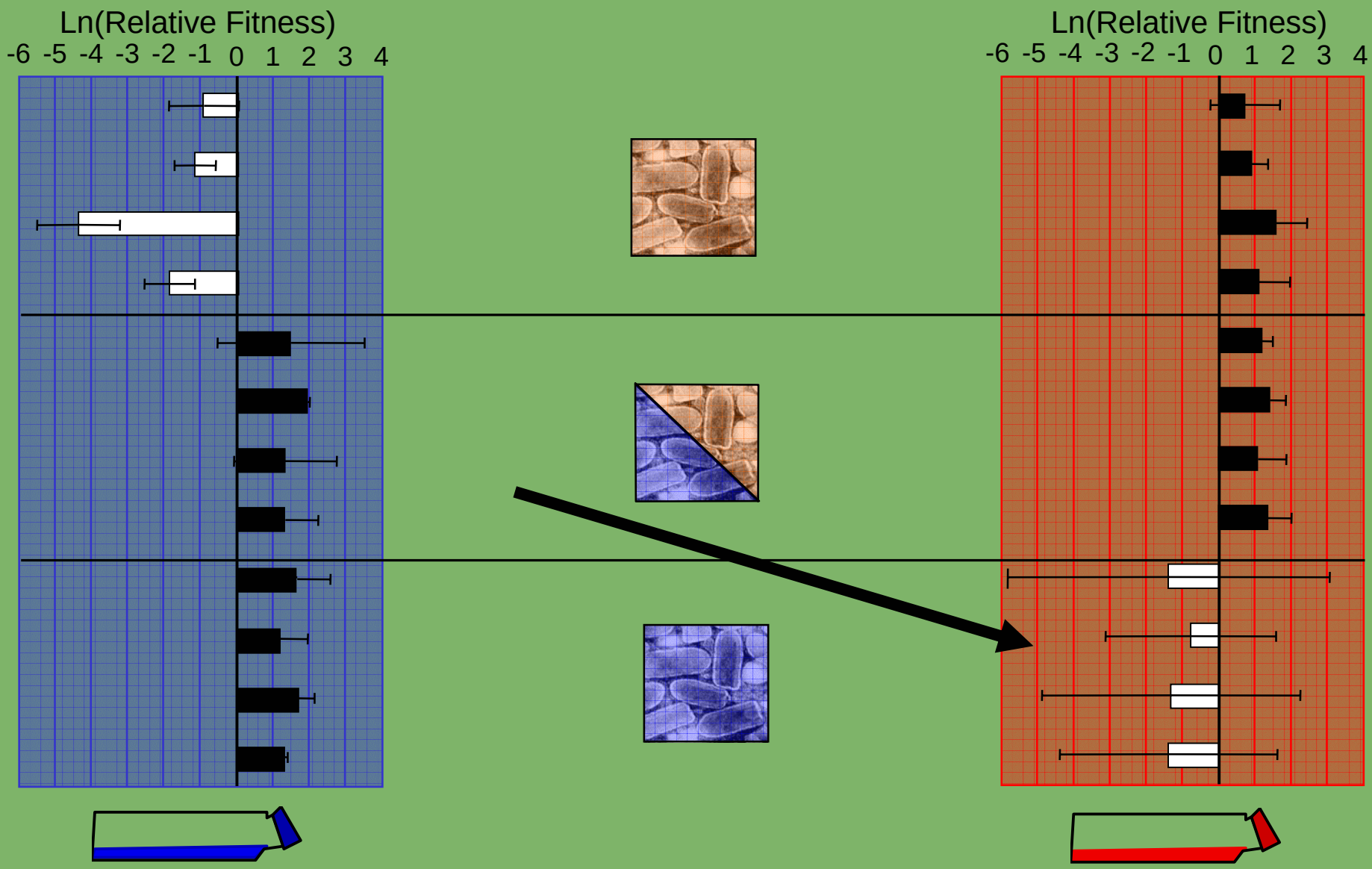
In  *populations pattern of substitutions consistent with antagonistic pleiotropy*

Tradeoffs: General trends



In  *populations pattern of substitutions consistent with mutation accumulation*

High variances - rapid adaptation?



Context dependence

- Broadly speaking, context dependence occurs when the effect of an allele on other factor(s).

- May be very common, and higher order interactions may be most common.

- Both contingency and selection can contribute to the evolution of context dependence.

- Context dependence can increase diversity among populations and can affect the probability of colonization of new niches.

Acknowledgments

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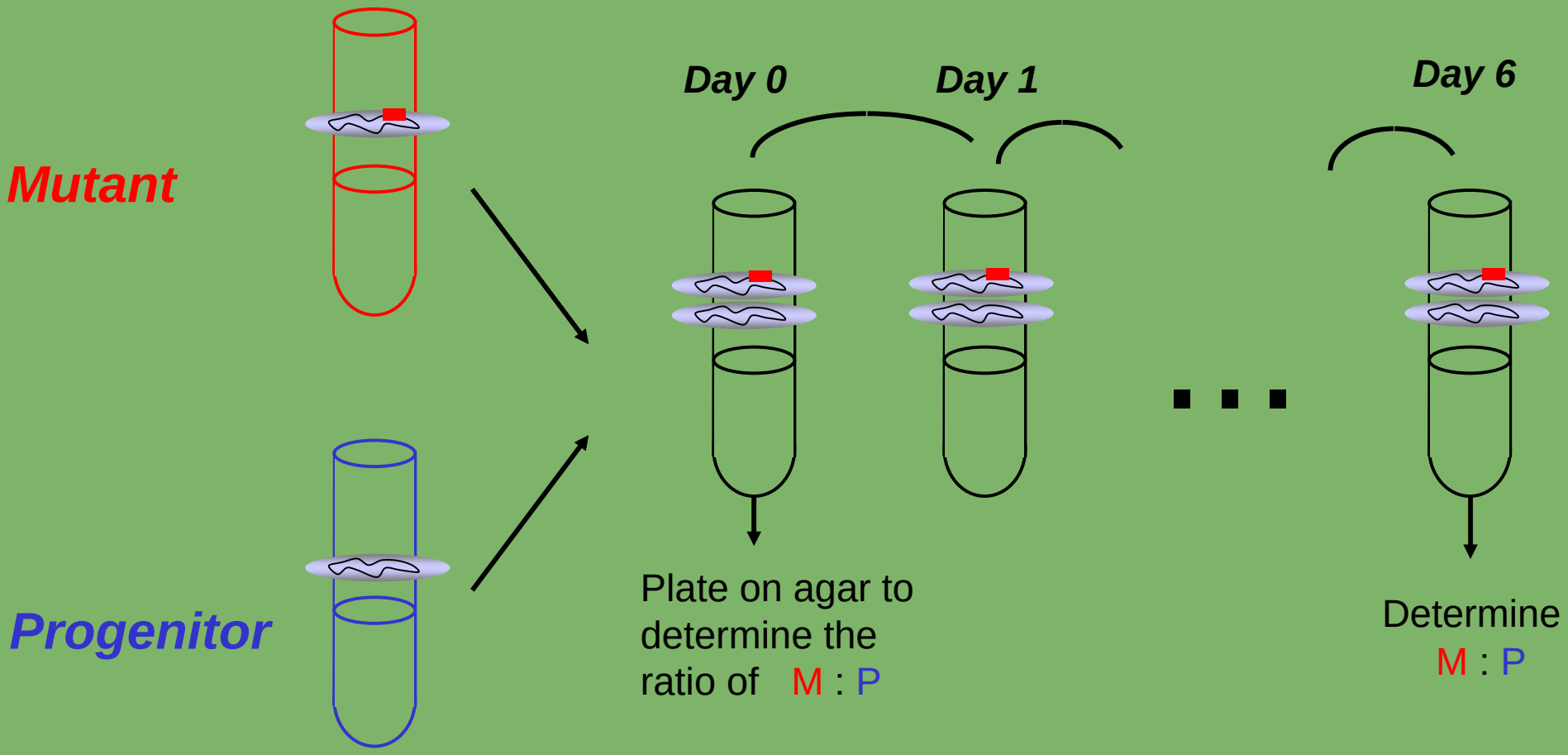
VSV

Paul Turner
Isabel Novella
YIBS
Anna Fuller Fund
NSF

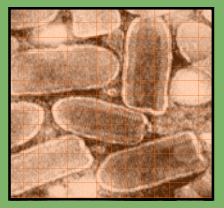
Fitness measured in direct competition:



$$\text{Fitness effect} = 1 - \text{Relative fitness} = 1 - \frac{\ln [\, N_M(\text{Day 6}) \times 10^6 / N_M(\text{Day 0}) \,]}{\ln [\, N_P(\text{Day 6}) \times 10^6 / N_P(\text{Day 0}) \,]}$$

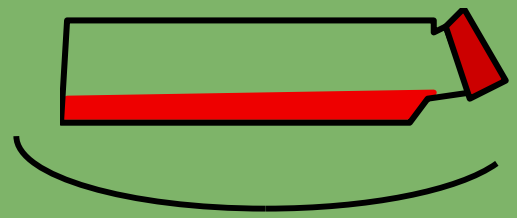
Fitness measured in direct competition:

Evolved Genotype



Ancestor (with neutral marker)

mix



Day 0

Determine R_0
initial ratio ***E : A***

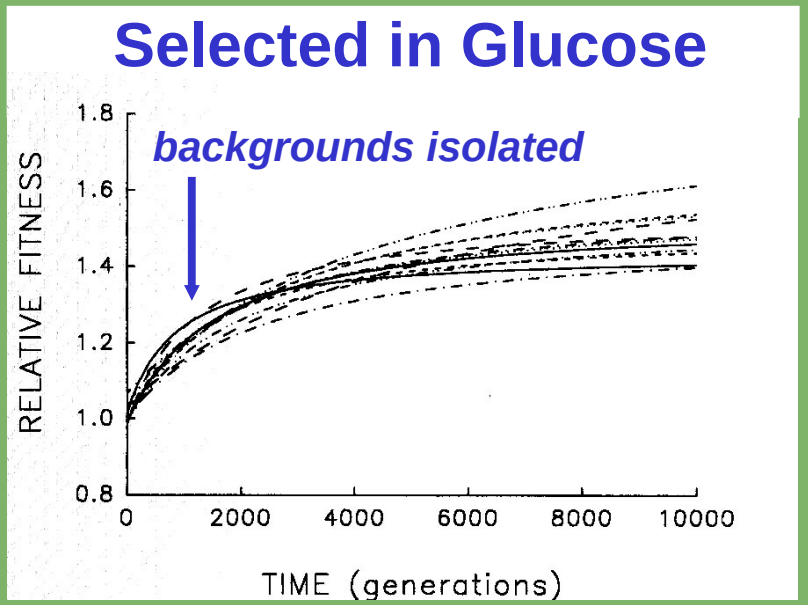
Day 1

Determine R_t
final ratio ***E : A***

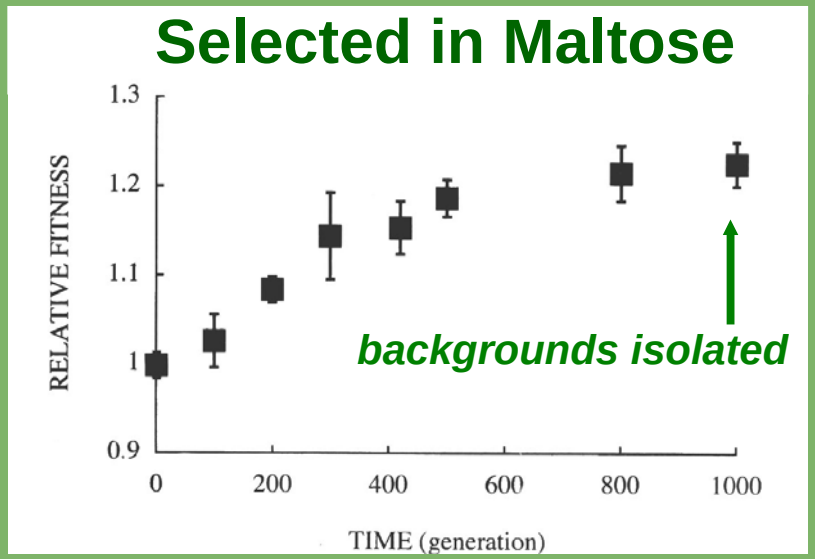
$$\textit{ln (Relative fitness)} = \frac{\textit{ln}(R_t) - \textit{ln}(R_0)}{t}$$

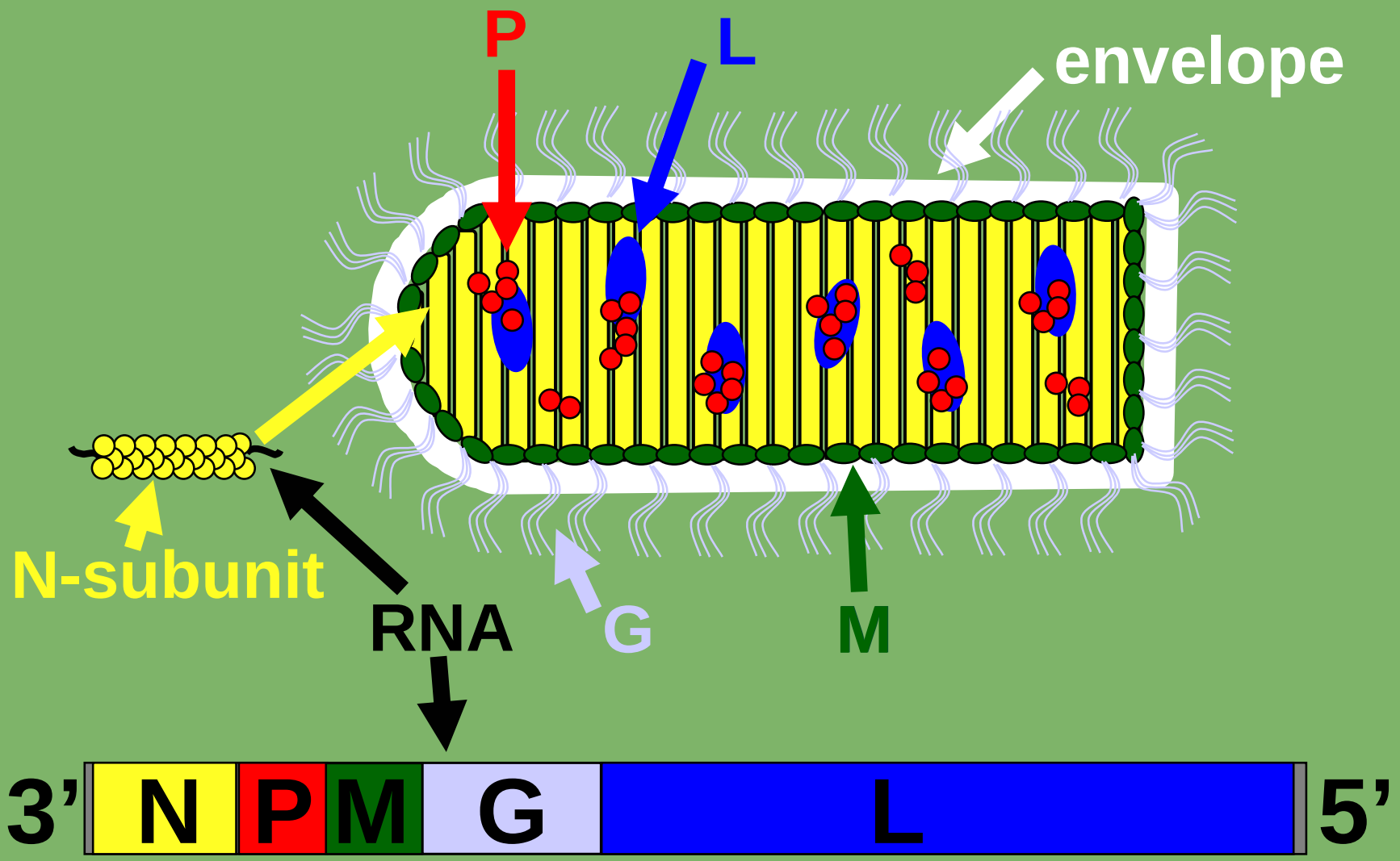
Genetic environments:

similar increases in fitness



Lenski, and Travisano (1994) PNAS 91:6808



Travisano (1997) Genetics 146:471

VSV Structure and Genome