Experimental evolution of host-switching and emergence of new viruses

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It's Happening Here.

What governs host use change?

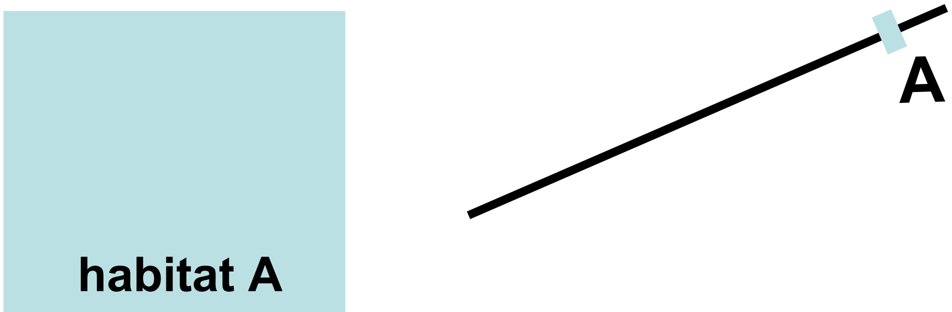
What governs generalism vs specialism?

Link between evolution and genetics of habitat use and ecological diversity

There is a ... profound assumption having to do with the perfectibility of tools. In human affairs we express it by saying “a jack of all trades is a master of none” (McArthur, 1972)

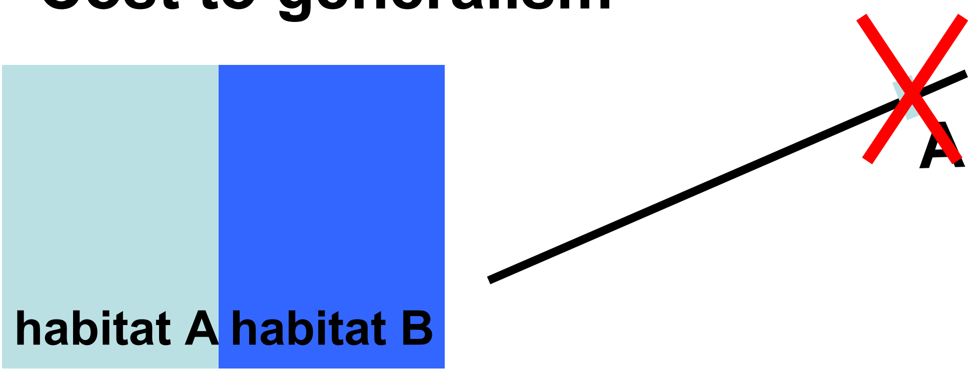
Antagonistic pleiotropy through GxE

Specialism



Fixed due to positive selection.

Cost to generalism



Eliminated due to purifying selection. Generalist hasn't this option and its maximum fitness in habitat A is therefore lower than specialist's.


Tradeoffs are NOT inevitable
OF ALL TRADES
(AND MASTER OF NONE)
SOME OF THE JOBS THAT NEED REPAIR.

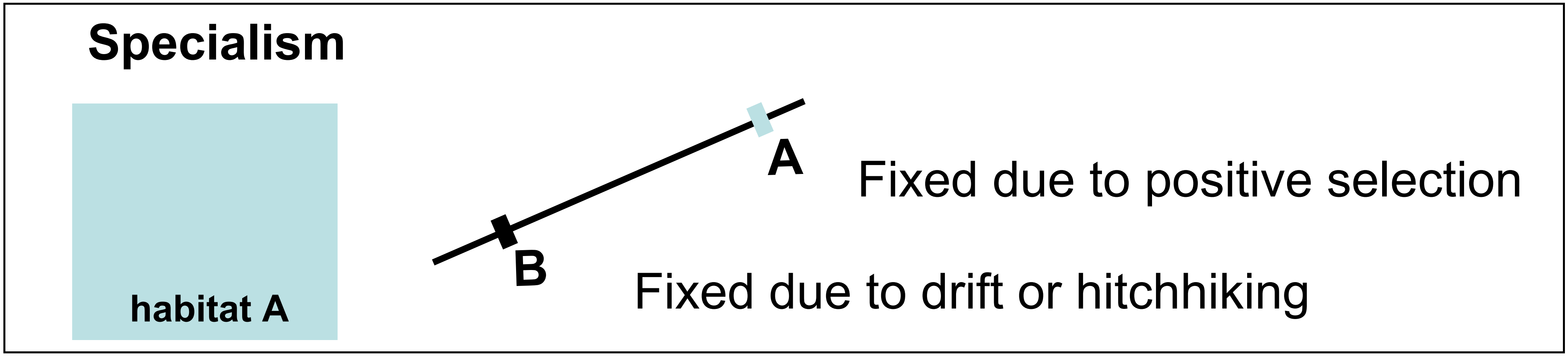
A viable mechanism for specialization must explain:

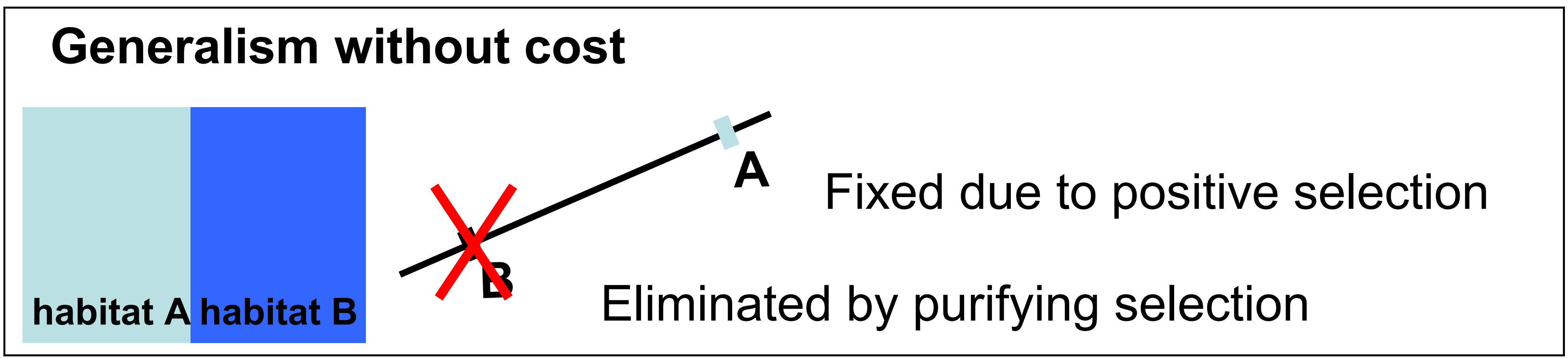
- *The existence of specialist populations*
- *The existence of generalist populations that show no cost of generalism*

Three such potential mechanisms:

- Specialism by directional selection
- Mutation accumulation
- Epistatic antagonistic pleiotropy

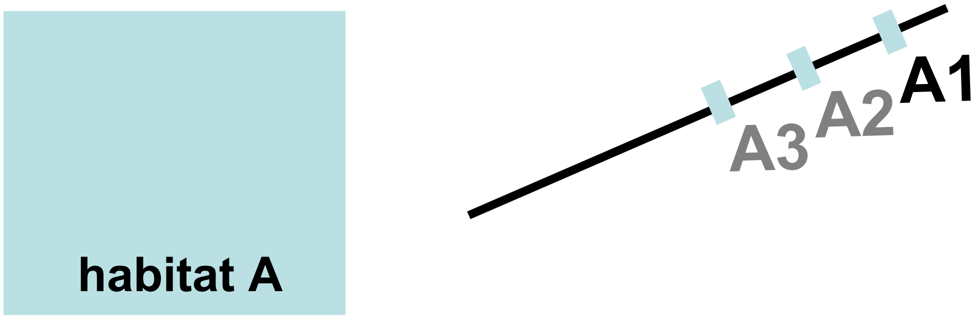
Mutation accumulation (no true genetic tradeoff)





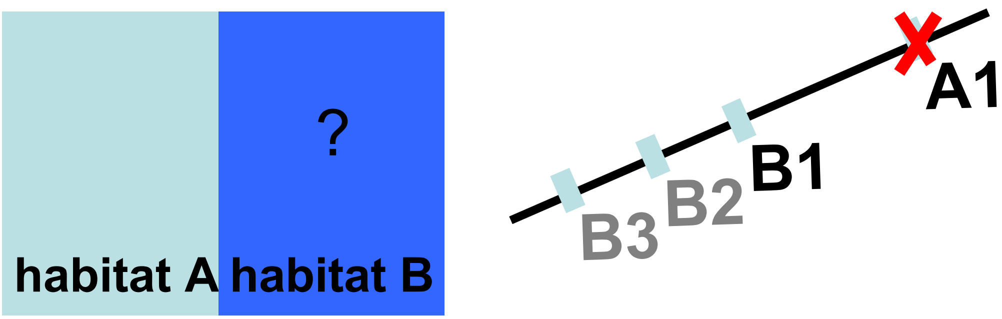
Epistatic antagonistic pleiotropy (GxGxE)

Specialism



Populations heads along an adaptive walk starting with the A1 allele.

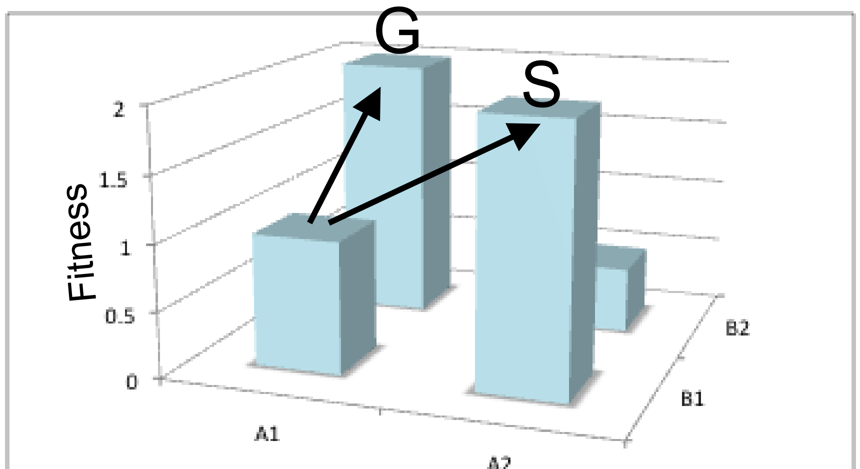
Generalism without cost



The “A” walk is not taken due to chance or purifying selection. Another walk provides access to a phenotype of equal fitness in habitat A.

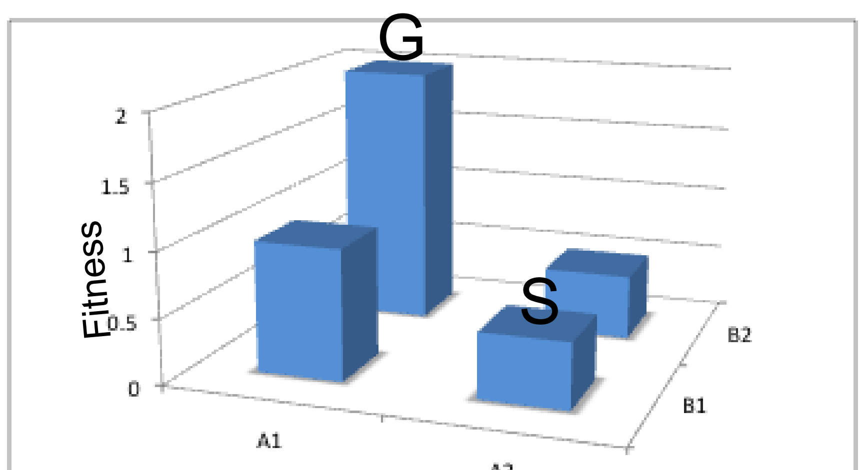
GxGxE drives specialism and generalism without cost

Populations starting at A1B1 and evolving in Environment 1 may move to either A1B2 or A2B1. These loci interact epistatically, so gaining both changes confers no advantage.



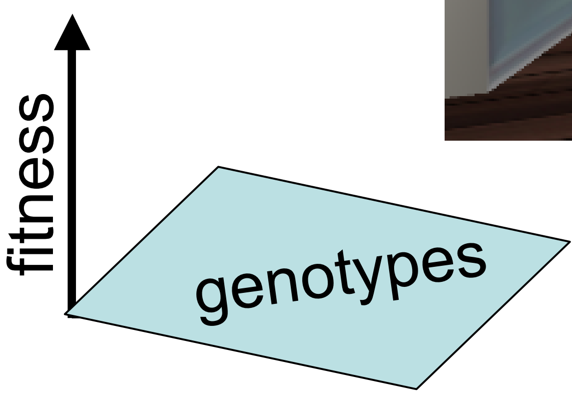
Environment 1

Populations at A1B2 are generalists while those at A2B1 are specialists with respect to this pair of environments.



Environment 2

Genotypes differ in the degree to which the fitness associated with them changes with the environment



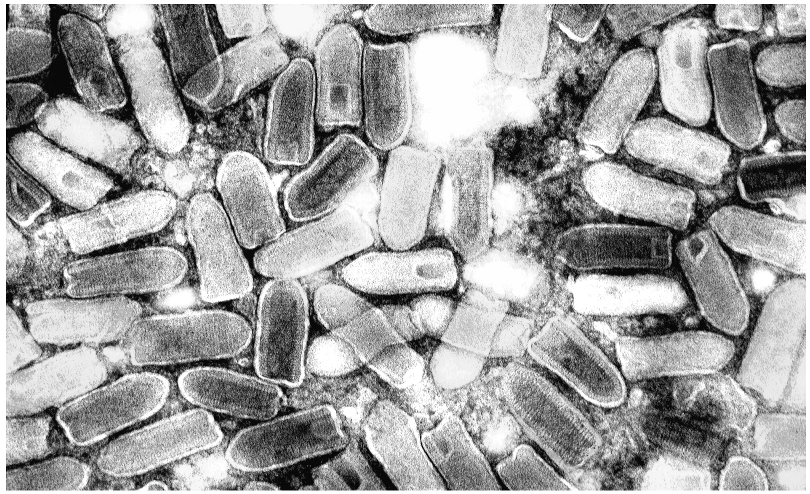
OVERVIEW:

Mutation accumulation and epistatic pleiotropy in viral host adaptation

Consequences for ecological host shifts

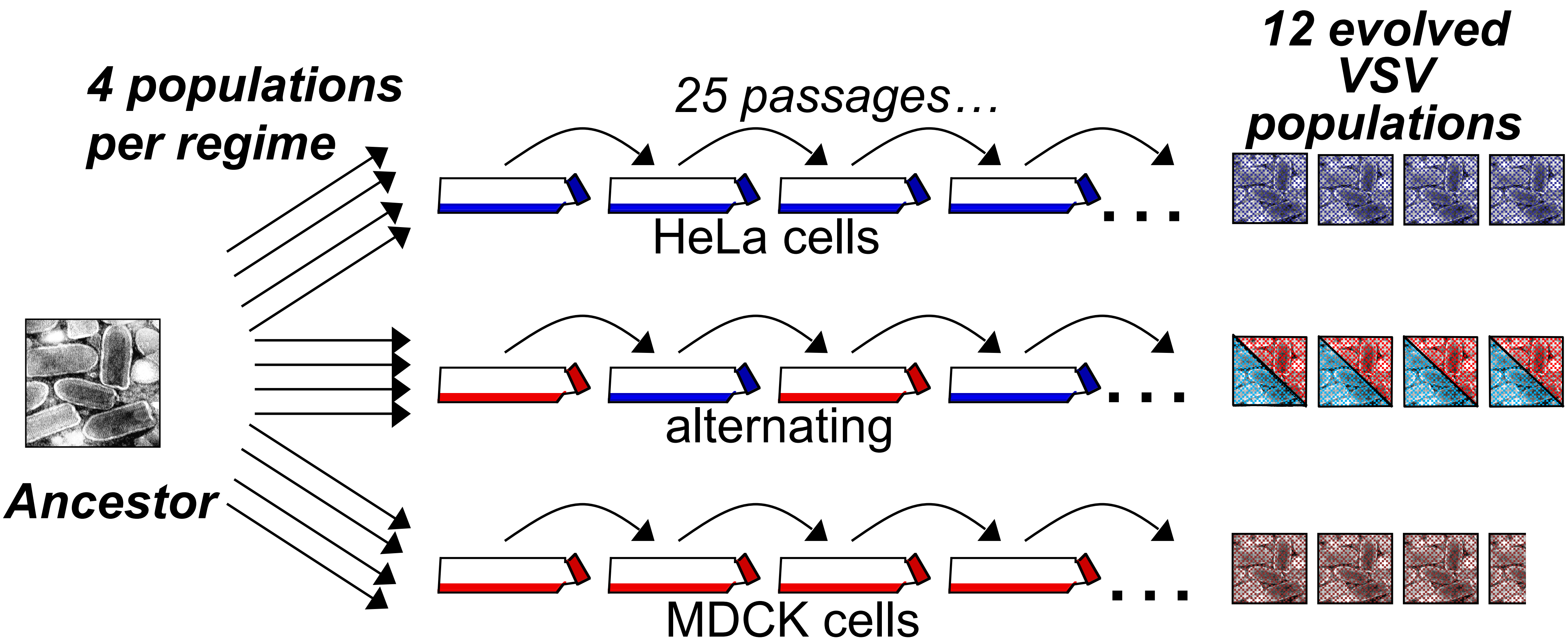
Consequences for evolutionary host shifts

Vesicular stomatitis virus (VSV)



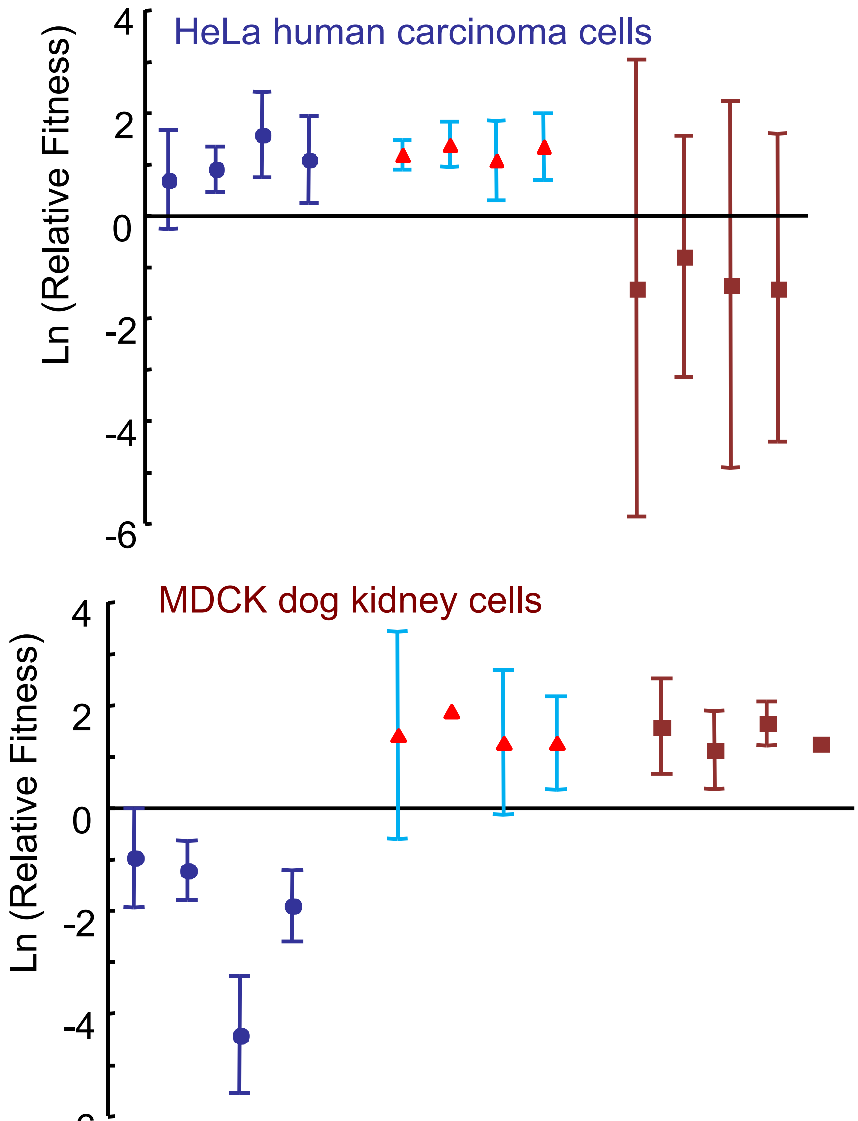
- negative sense RNA virus
- broad host range in nature
- model system in molecular virology
- model system in virus evolution
- possible oncolytic agent

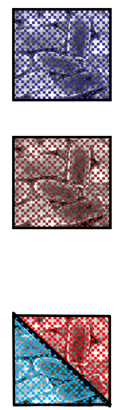
100 generations evolution in new host - regimes



Turner & Elena 2000 Genetics

How does host-use environment affect fitness?





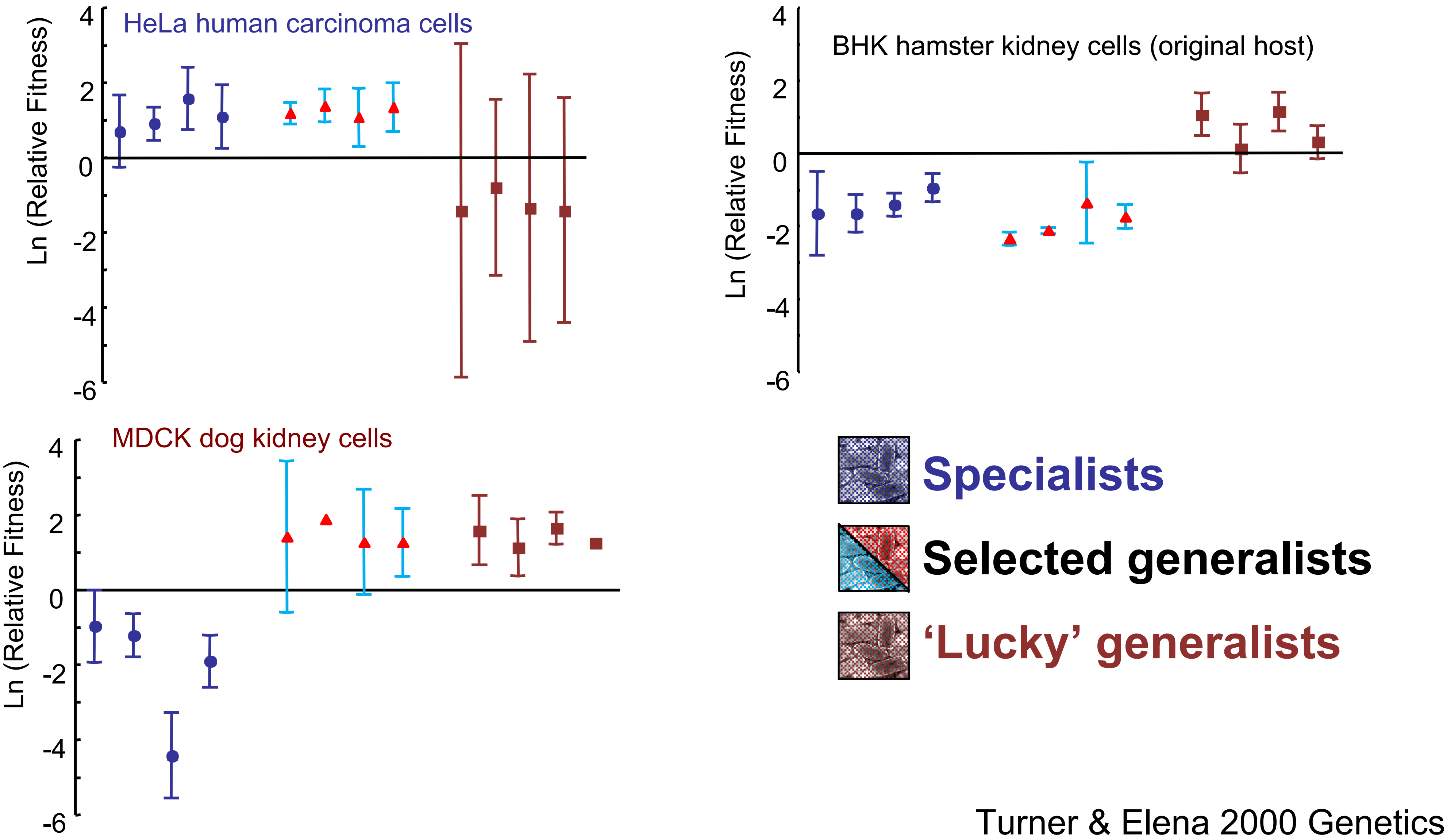
Good on HeLa, not on MDCK

Good on MDCK, not on HeLa

As good on both HeLa and MDCK as either single-host selected population.

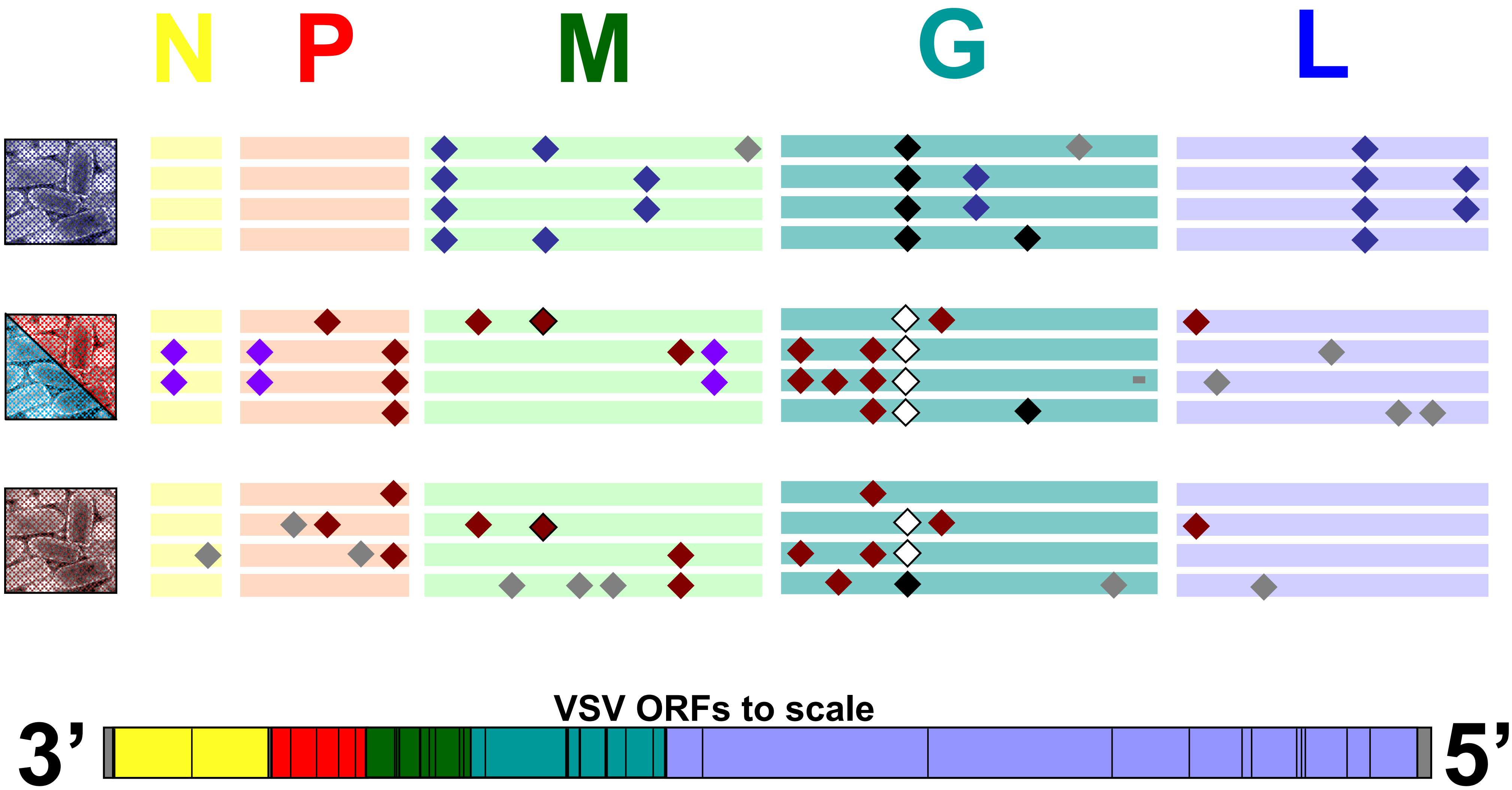
Turner & Elena 2000 Genetics

How does host-use environment affect fitness?



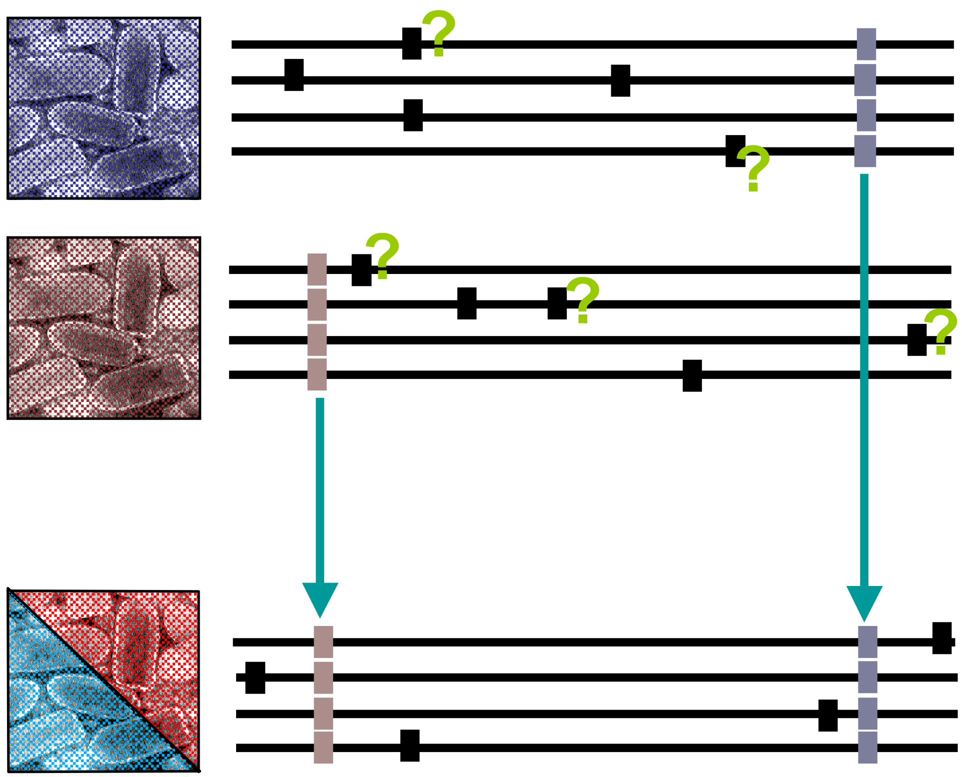
Turner & Elena 2000 Genetics

Genetic changes



Remold, Rambaut & Turner, 2008

Expectation under mutation accumulation



Apparent tradeoff avoided

same loci responsible for adaptation in

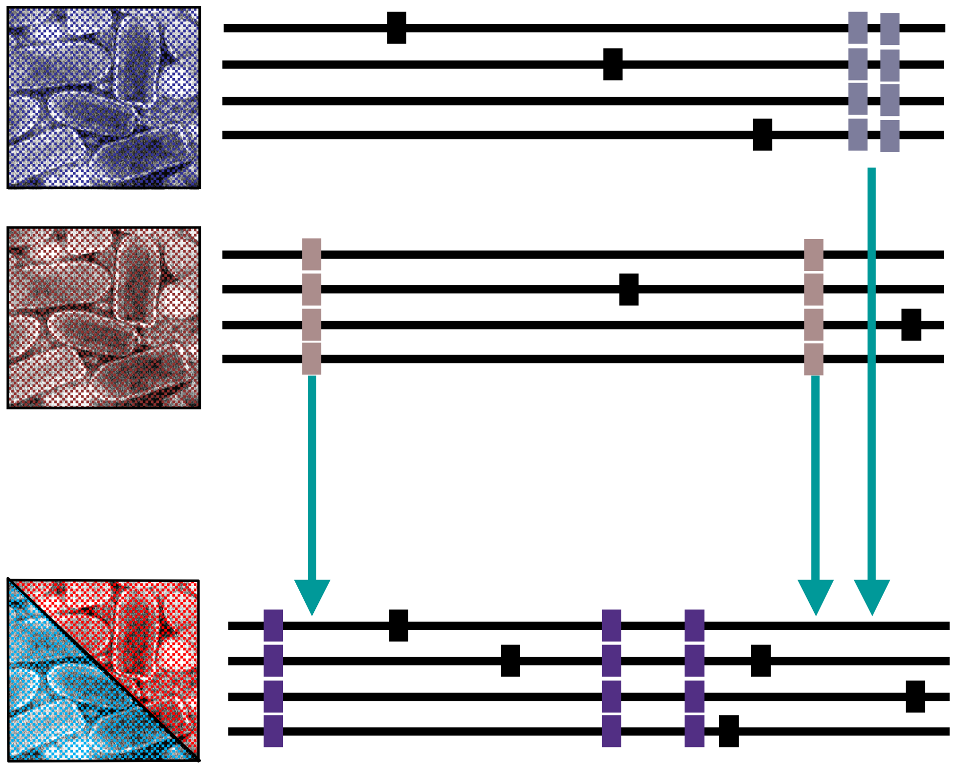
HeLa

and

MDCK

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

Expectation under epistatic pleiotropy (GxGxE)



Tradeoff avoided

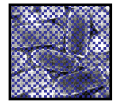
different loci responsible for adaptation in

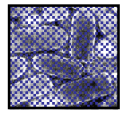
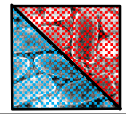
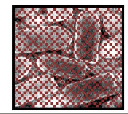
single

vs

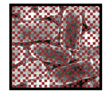
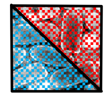
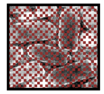
Alternating hosts

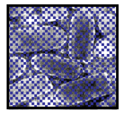
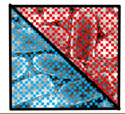
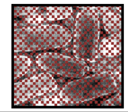
Assumption: P(potential beneficial mutation arises and becomes fixed in at least some lineages) is ***high***

Inferred epistasis in evolved VSV suggests epistatic pleiotropy in 

Set	Locus	ORF	HeLa H1	HeLa H2	HeLa H3	HeLa H4	Alternating A1	Alternating A2	Alternating A3	Alternating A4	MDCK M1	MDCK M2	MDCK M3	MDCK M4	Prob.
A	$G_{2686}\rightarrow A$	M		•	•										0.03
	$A_{4167}\rightarrow G$	G		•	•										
	$G_{10048}\rightarrow U$	L		•	•										
B	$U_{2401}\rightarrow C$	M	•	•	•	•									1.00
	$C_{9597}\rightarrow U$	L	•	•	•	•									
C	$C_{696}\rightarrow U$	N						•	•						0.03 or 0.001
	$G_{1521}\rightarrow A$	P						•	•						
	$U_{2937}\rightarrow G$	M						•	•						
D	$C_{2151}\rightarrow U$	P						•	•	•	•		•		0.02
	$G_{3846}\rightarrow A$	G						•	•	•	•		•		
E	$U_{1927}\rightarrow G$	P					•					•			<0.0001
	$A_{2413}\rightarrow G$	M					•					•			
	$A_{2431}\rightarrow C$	M					•					•			
	$U_{3856}\rightarrow C$	G					•					•			
	$C_{4981}\rightarrow U$	L					•					•			

Shared epistatic sets in  and  suggest lower fitness of  on MDCK is due to mutation accumulation.

Set	Locus	ORF	HeLa H1	HeLa H2	HeLa H3	HeLa H4	Alternating A1	Alternating A2	Alternating A3	Alternating A4	MDCK M1	MDCK M2	MDCK M3	MDCK M4	Prob.
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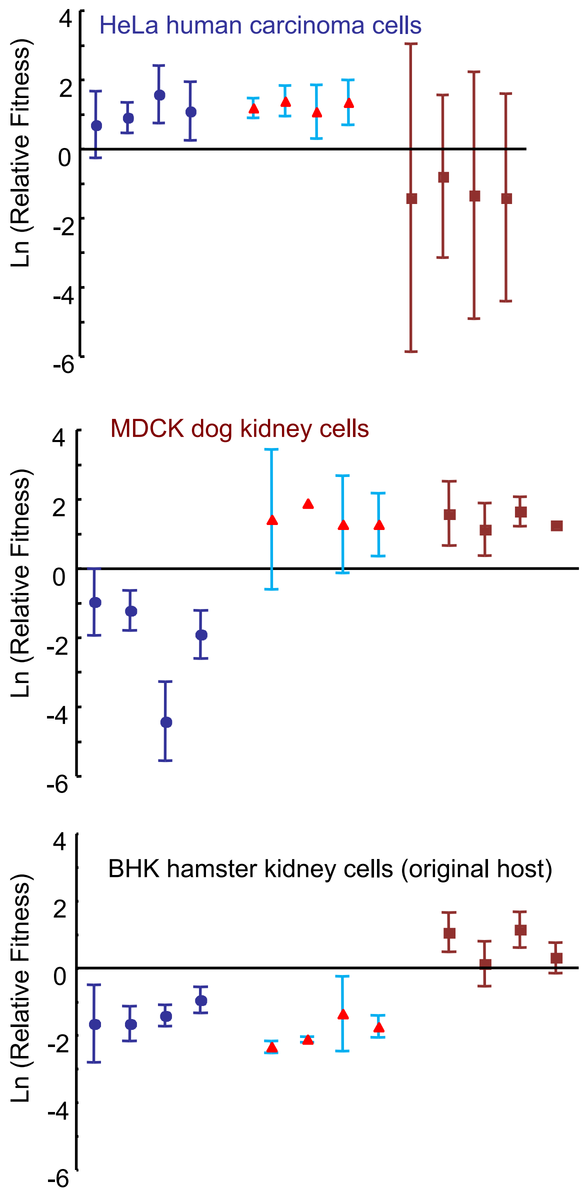
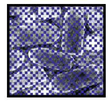
B	$U_{2401}\rightarrow C$	M	•	•	•	•									1.00
	$C_{9597}\rightarrow U$	L	•	•	•	•									
C	$C_{696}\rightarrow U$	N						•	•						0.03 or 0.001
	$G_{1521}\rightarrow A$	P						•	•						
	$U_{2937}\rightarrow G$	M						•	•						
D	$C_{2151}\rightarrow U$	P						•	•	•	•		•		0.02
	$G_{3846}\rightarrow A$	G						•	•	•	•		•		
E	$U_{1927}\rightarrow G$	P					•					•			<0.0001
	$A_{2413}\rightarrow G$	M					•					•			
	$A_{2431}\rightarrow C$	M					•					•			
	$U_{3856}\rightarrow C$	G					•					•			
	$C_{4981}\rightarrow U$	L					•					•			

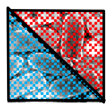
Genome changes asociated with host adaptation



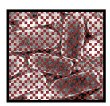


Specialists

Evidence for antagonistic epistatic pleiotropy. There are other genetic solutions that achieve equal fitness on HeLa without cost on other assayed cell lines.

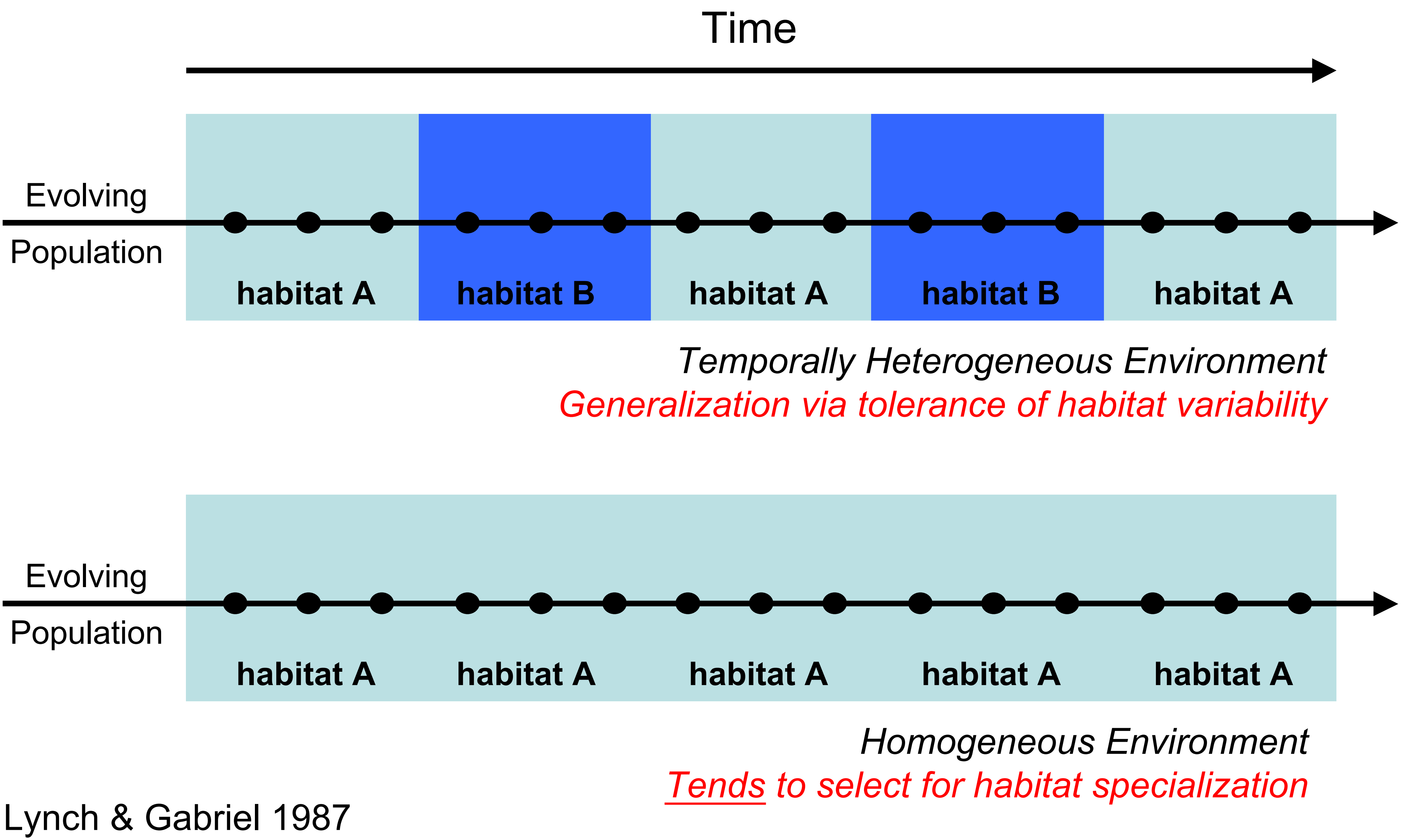


Selected generalists



‘Lucky’ generalists

Evidence for mutation accumulation and epistatic sets. Two epistatic sets are shared between these two types of specialists, one is not (it is in selected generalists only).


Time
Evolving
Population
habitat A
habitat B
habitat A
habitat B
habitat A
Temporally Heterogeneous Environment
Generalization via tolerance of habitat variability
Evolving
Population
habitat A
habitat A
habitat A
habitat A
habitat A
Homogeneous Environment
Tends to select for habitat specialization
Lynch & Gabriel 1987

OVERVIEW:

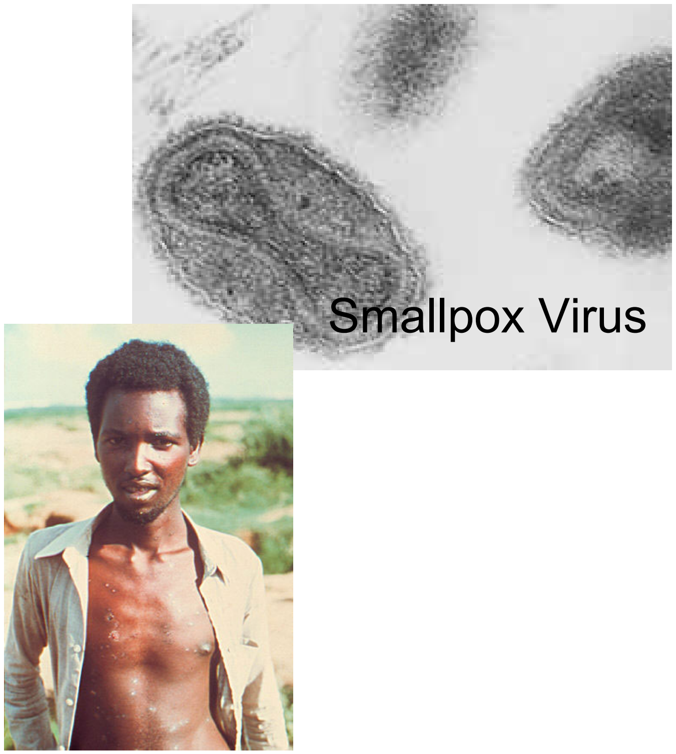
Mutation accumulation and epistatic pleiotropy in viral host adaptation

Consequences for ecological host shifts

Consequences for evolutionary host shifts

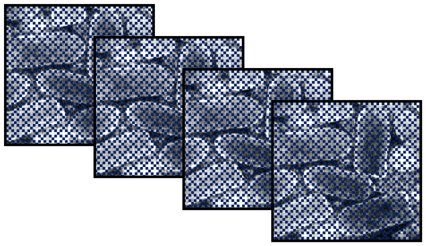
How easily can a virus population expand into use of a novel host?

How does past host use patterns affect future patterns?

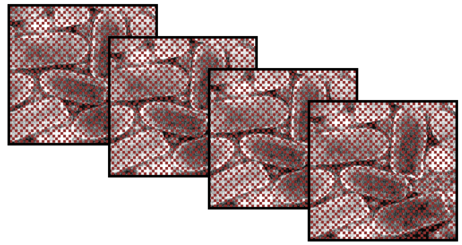


<u>Prediction:</u> populations selected for tolerance to host heterogeneity (selected generalists) will be most able to emerge in a new host.

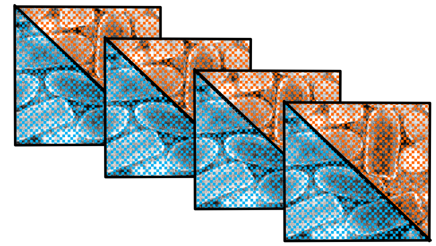
Compare ***growth*** *(titer) of*



vs



vs



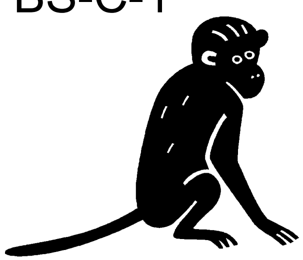
Specialists

Lucky generalists

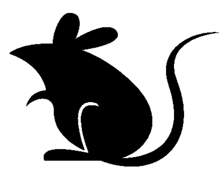
Selected generalists

on

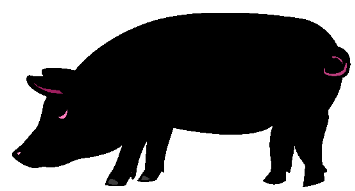
BS-C-1



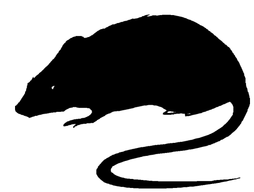
NCTC Clone 929



PK-15



C6



Turner, Alto, Morales & Remold 2010

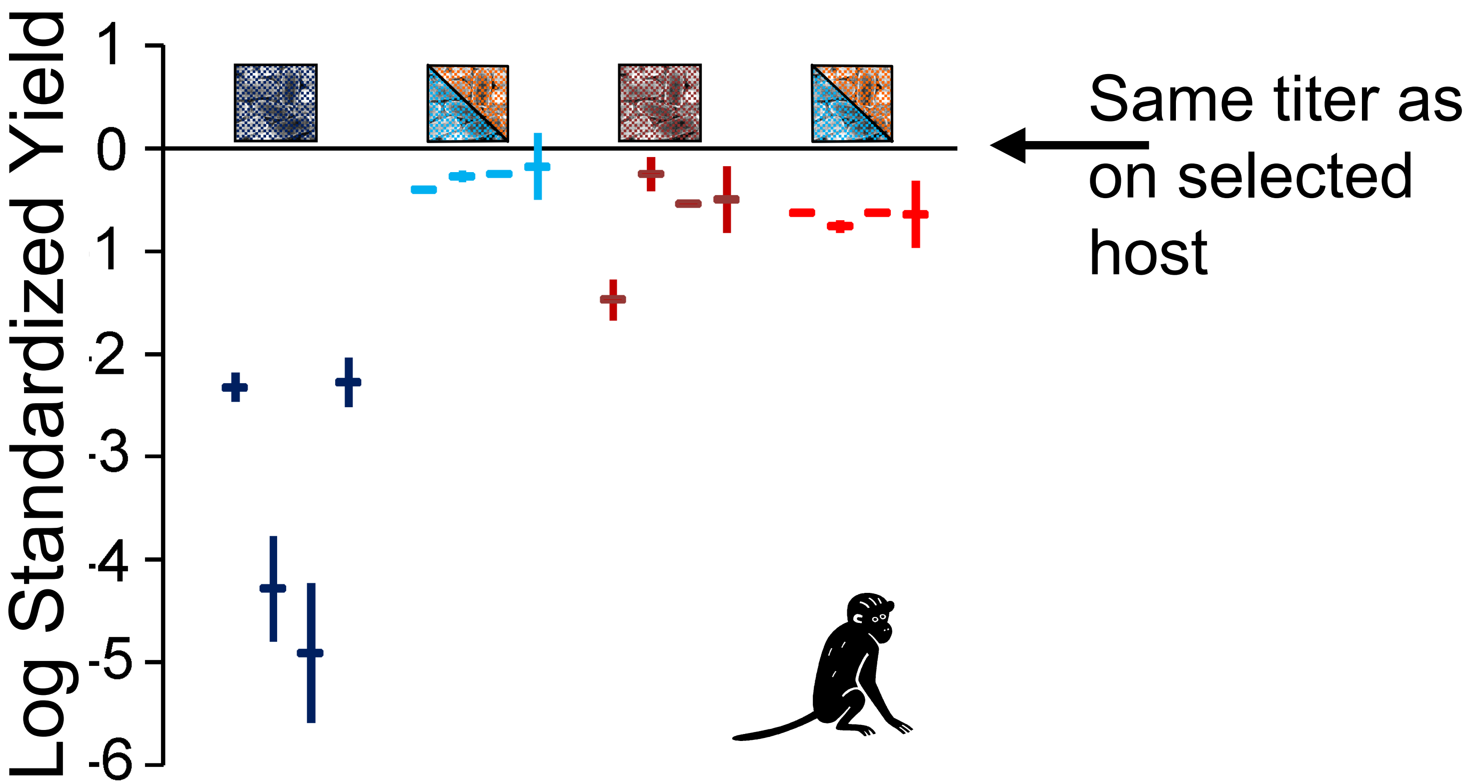
Evolutionary conditions that result in higher potential for emergence will cause:

1) higher mean population growth on new hosts

2) lower among-population variance in growth on new hosts

3) lower population variance in growth across new hosts

Turner, Alto, Morales & Remold 2010



Specialists (HeLa adapted)

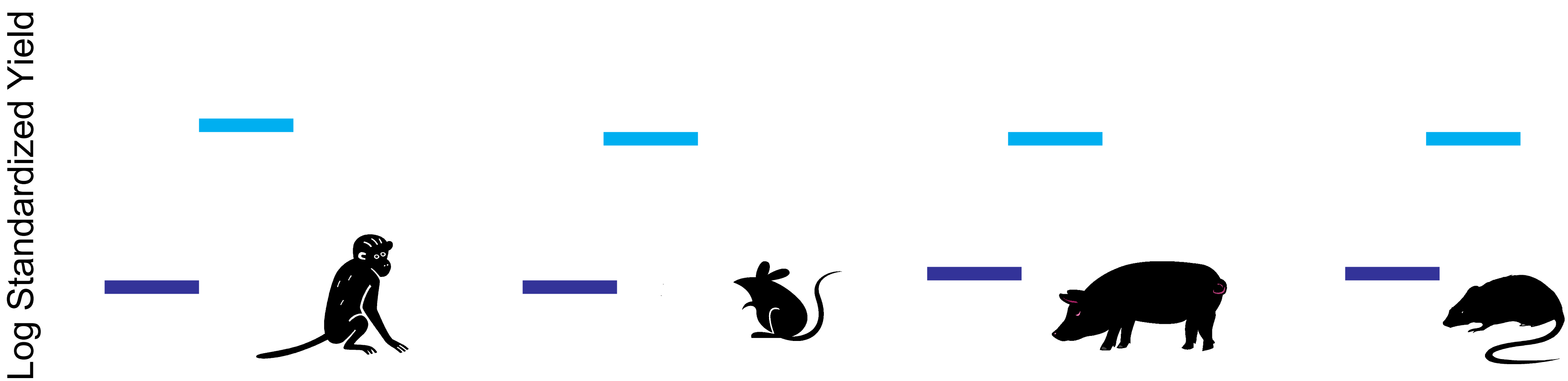
Selected generalist (Alternating adapted) standardized to titer on HeLa

Lucky generalists (MDCK Adapted)

Selected generalist (Alternating adapted) standardized to titer on MDCK

Turner, Alto, Morales & Remold 2010

Higher mean growth on new hosts prediction:

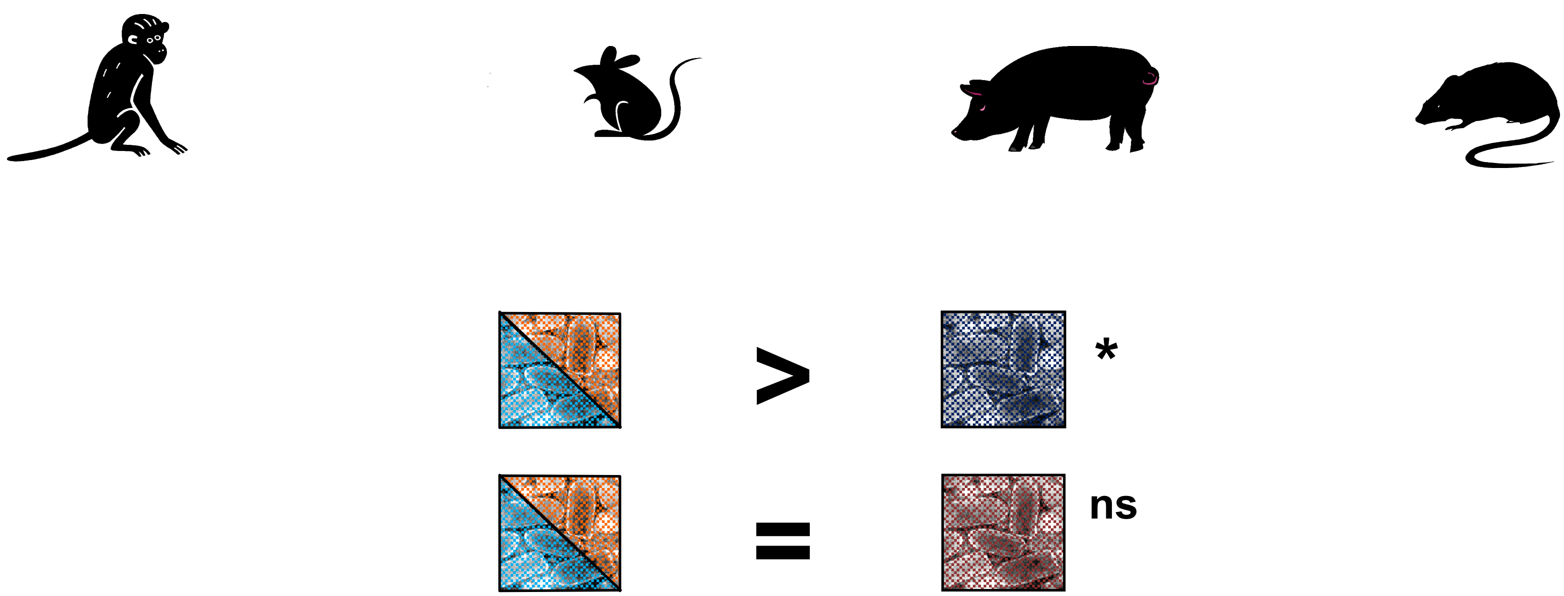


The mean titer of selected generalists (regardless of population or novel host) will be higher.

Turner, Alto, Morales & Remold 2010

Higher mean growth on new hosts prediction:

Log Standardized Yield



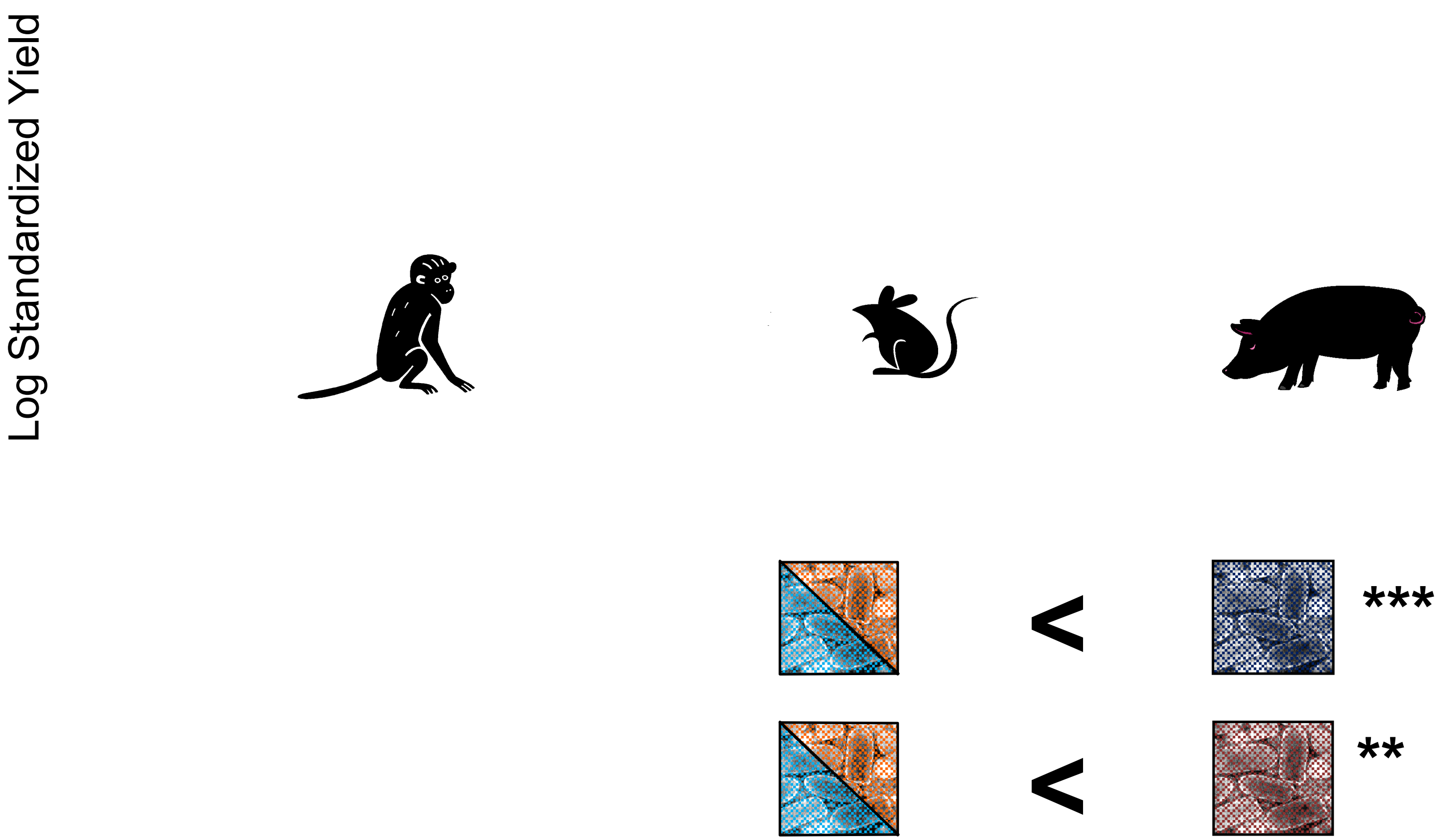
Turner, Alto, Morales & Remold 2010

Lower among-population variance prediction:

The variance among selected generalists populations (regardless of novel host) will be lower.

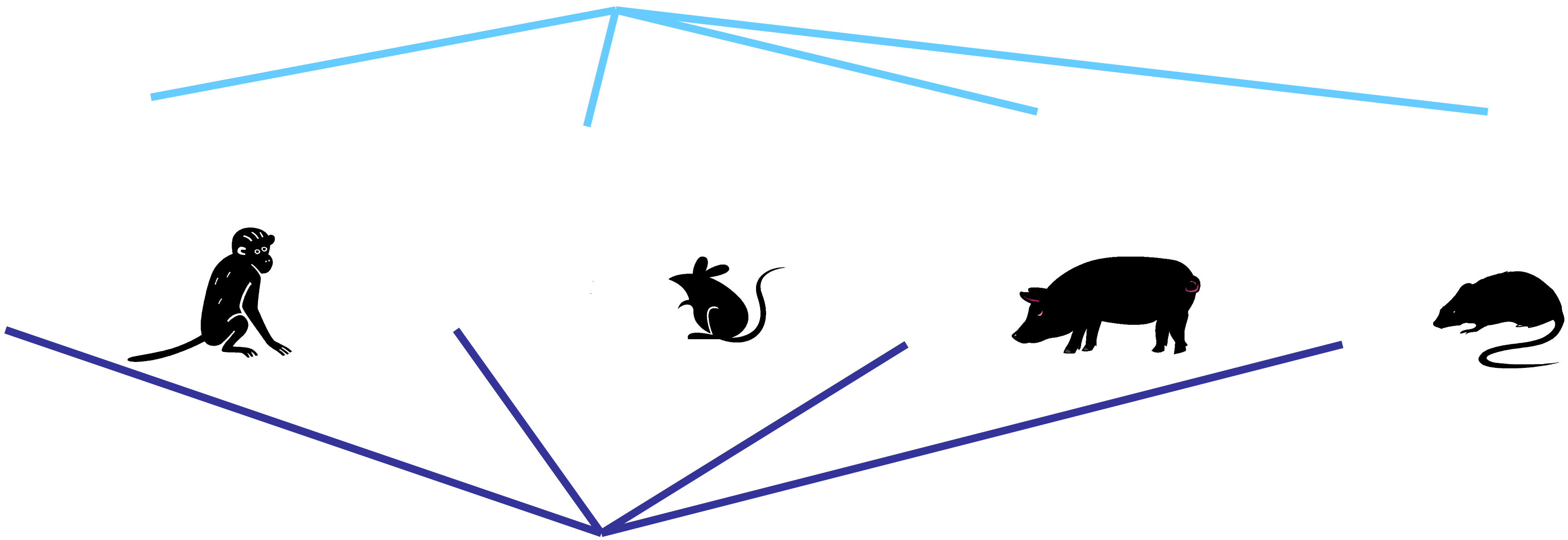
Turner, Alto, Morales & Remold 2010

Lower among-population variance prediction:



Turner, Alto, Morales & Remold 2010

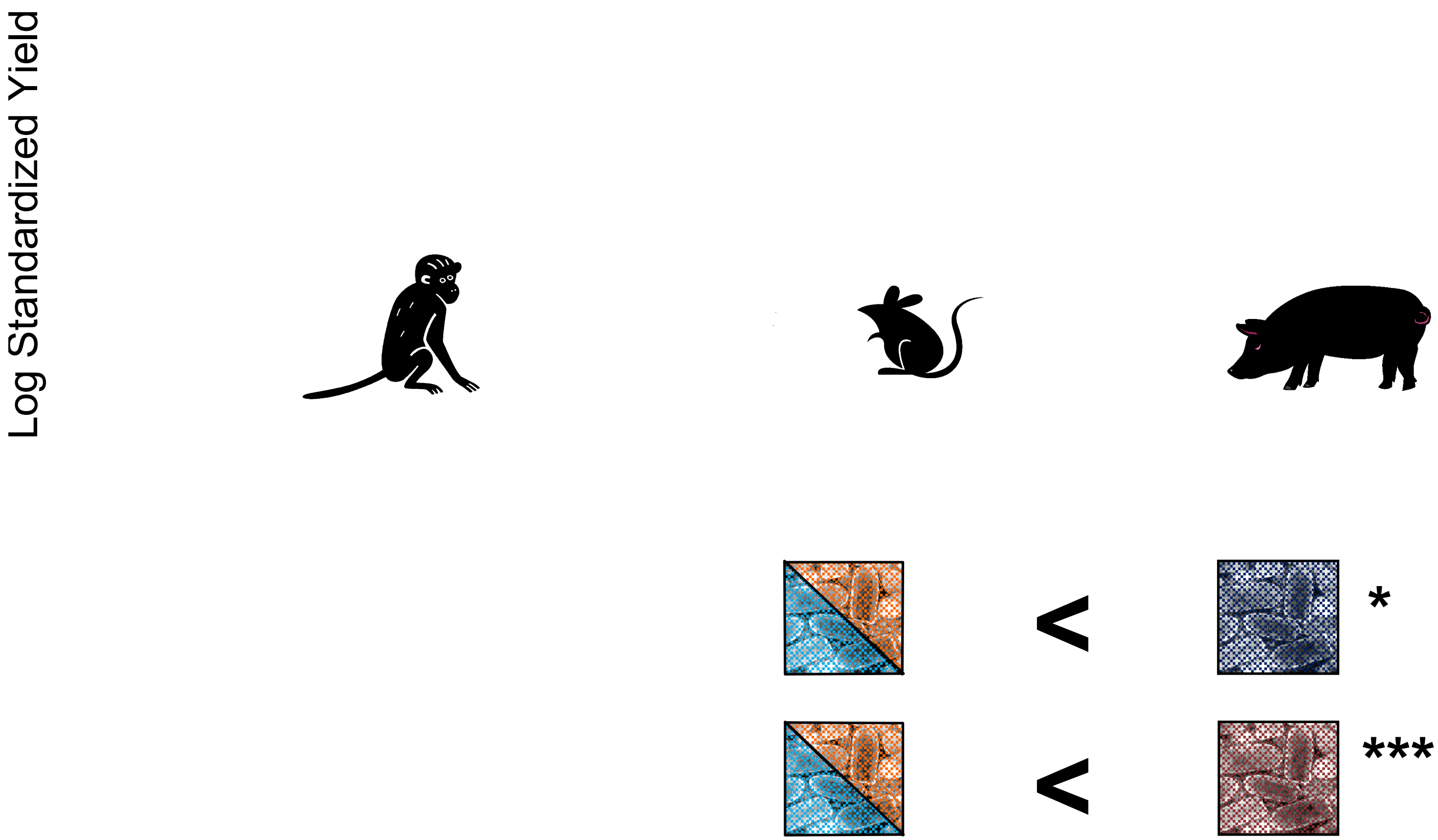
Lower population variance across new hosts prediction:



The variance of each selected generalists population across novel hosts hosts will be lower.

Turner, Alto, Morales & Remold 2010

Lower population variance across new hosts prediction:



Turner, Alto, Morales & Remold 2010

Why do selected and lucky generalists differ in emergence potential?

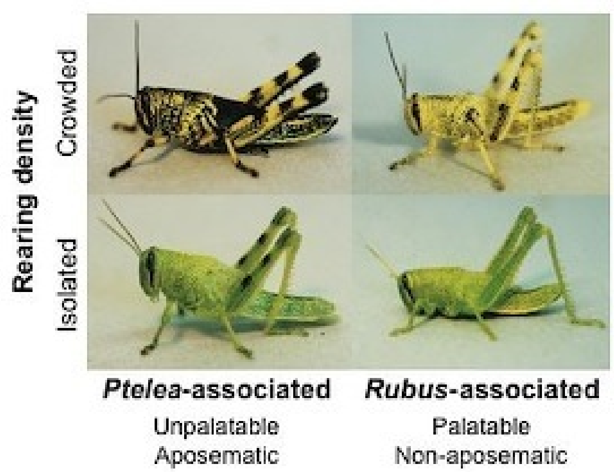
Two types of genes can increase fitness on multiple hosts:

Pleiotropic genes with benefit in multiple environments

These genes will be under positive selection on both types of populations.

Plasticity genes

These only favored in the ecological conditions of the selected generalists.



Density Dependent warning coloration: Sword (2002) Proc Royal Soc Lond B

OVERVIEW:

Mutation accumulation and epistatic pleiotropy in viral host adaptation

Consequences for ecological host shifts

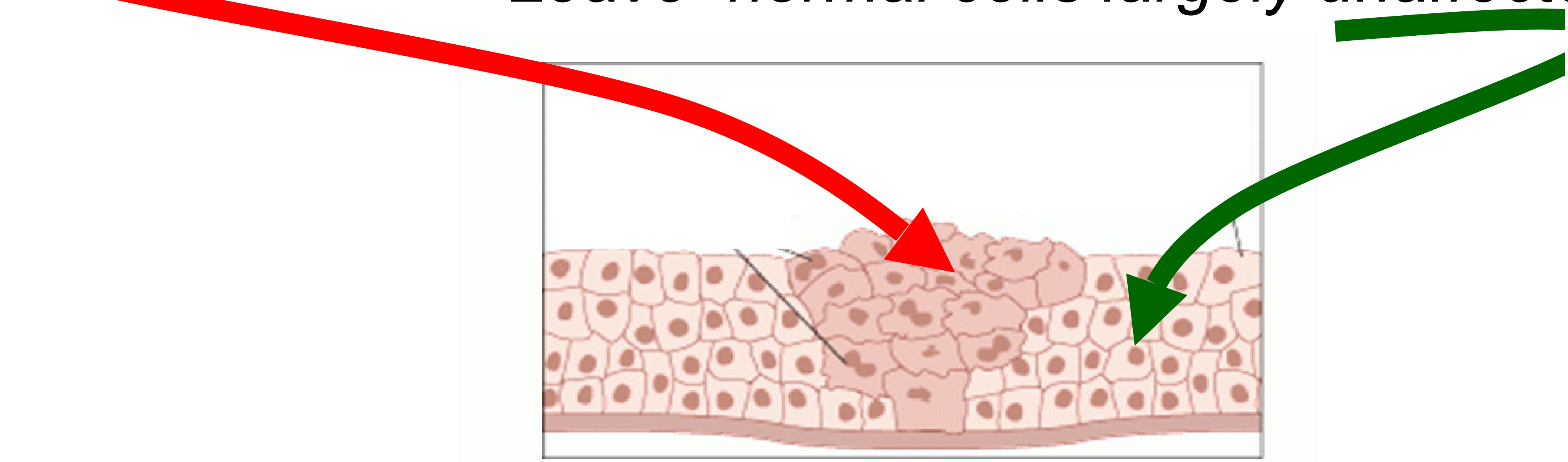
Consequences for evolutionary host shifts

VSV experimental evolution: implications for oncolytic virus design

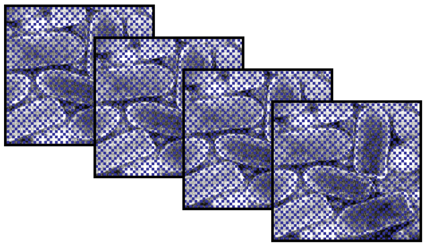
Oncolytic viruses

Infect, replicate in and destroy cancer cells

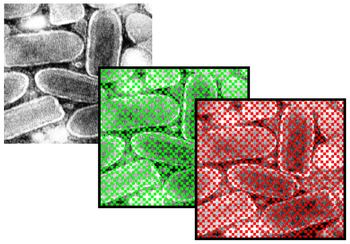
Leave normal cells largely unaffected



*Compare **growth** and **cell killing***



vs



HeLa-adapted VSV

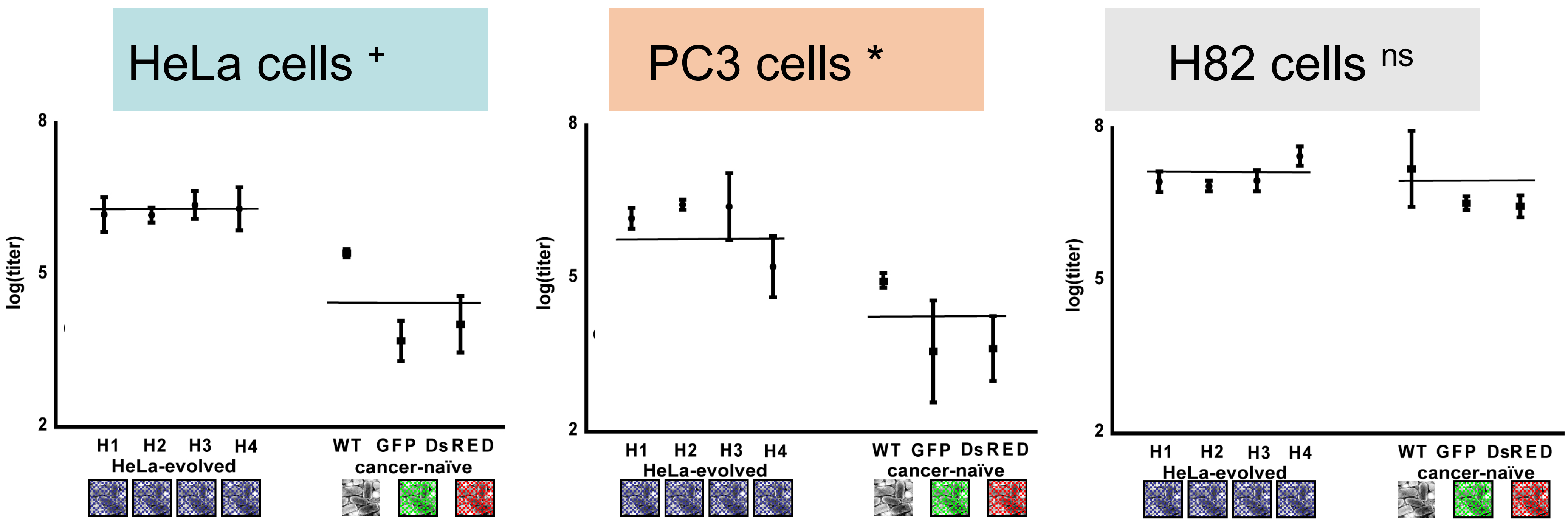
Cancer-naïve VSV genotypes

on

HeLa (cervical carcinoma)	**PC3 (prostate carcinoma)**	**H82 (small cell lung carcinoma)**

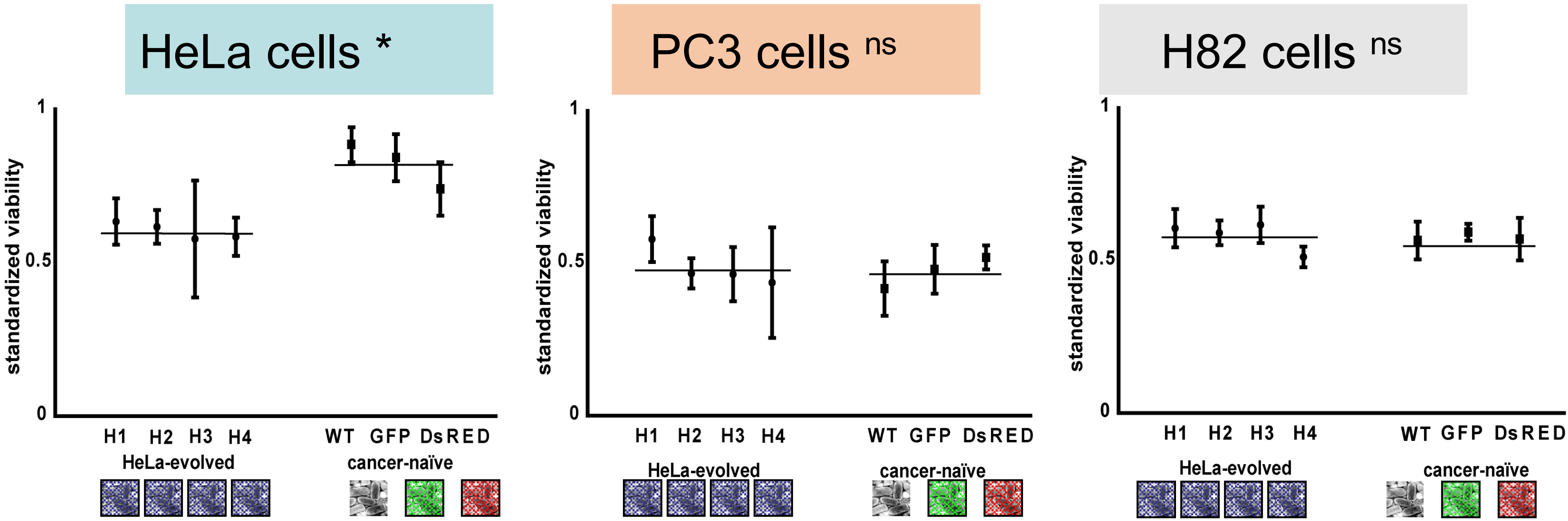
Willett and Remold *in prep*

HeLa-evolved populations grew to higher titers on HeLa cells and on PC3 cells, but not on H82 cells



Willett and Remold *in prep*

While HeLa-evolved populations reduced HeLa cell populations significantly more than the HeLa-naïve viruses did, there were no such difference on the two novel cancer cell lines



Willett and Remold *in prep*

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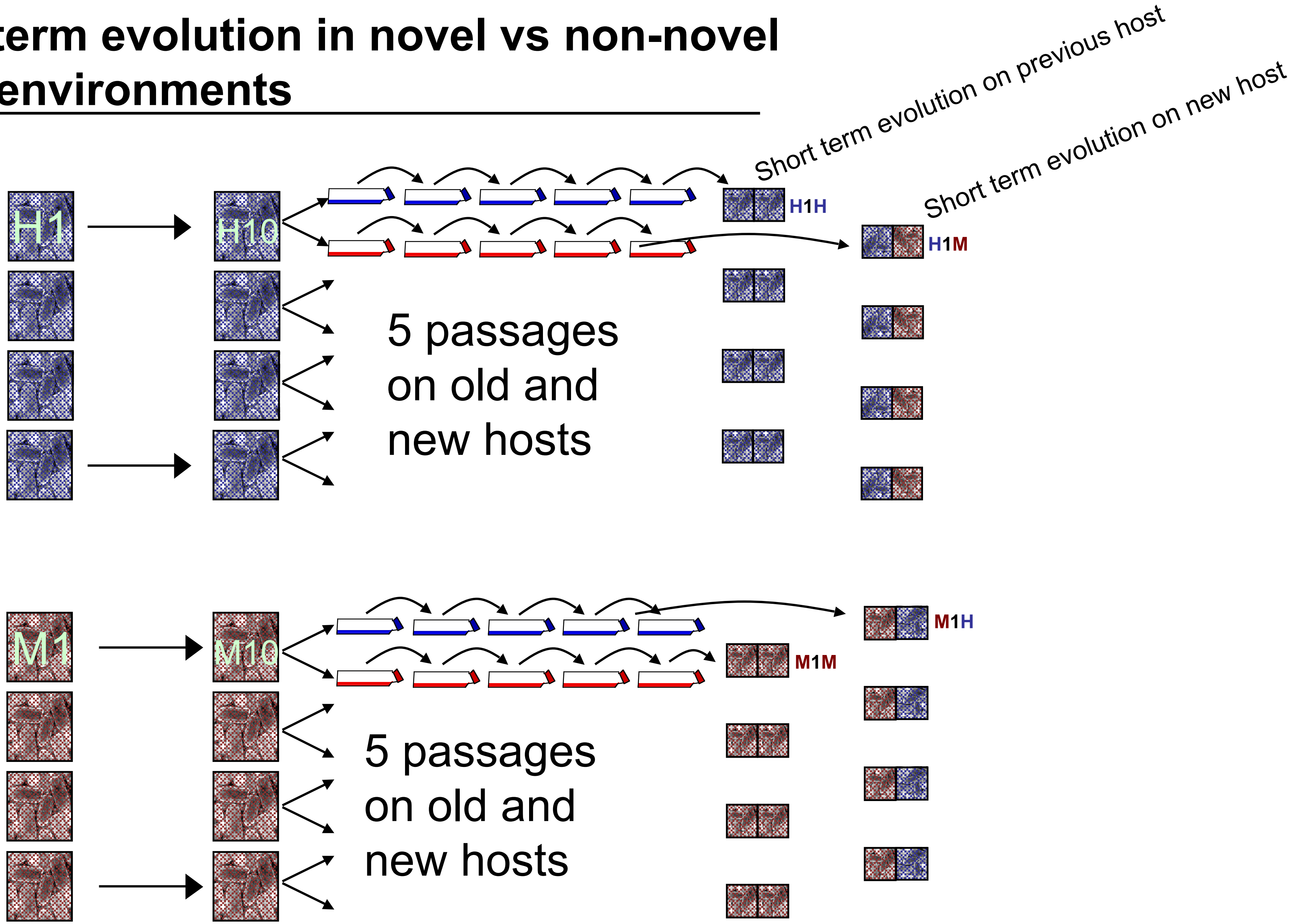
Consequences for ecological host shifts

Consequences for evolutionary host shifts

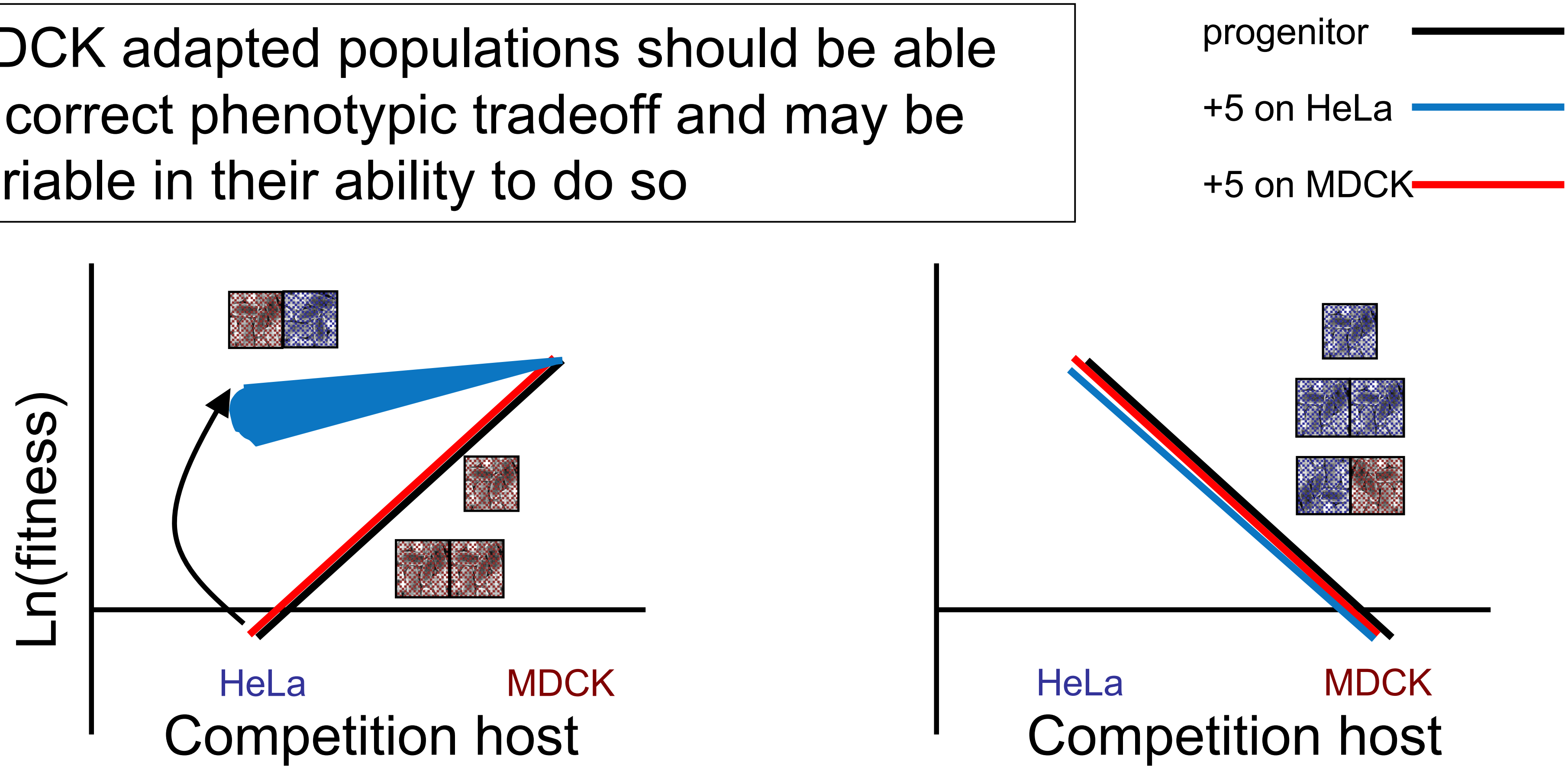
How does the genetic changes causing host adaptation affect the ability to respond to environmental changes evolutionarily?

Ellis & Wilcox 2009 Cad. Saúde Pública

Sort term evolution in novel vs non-novel host environments



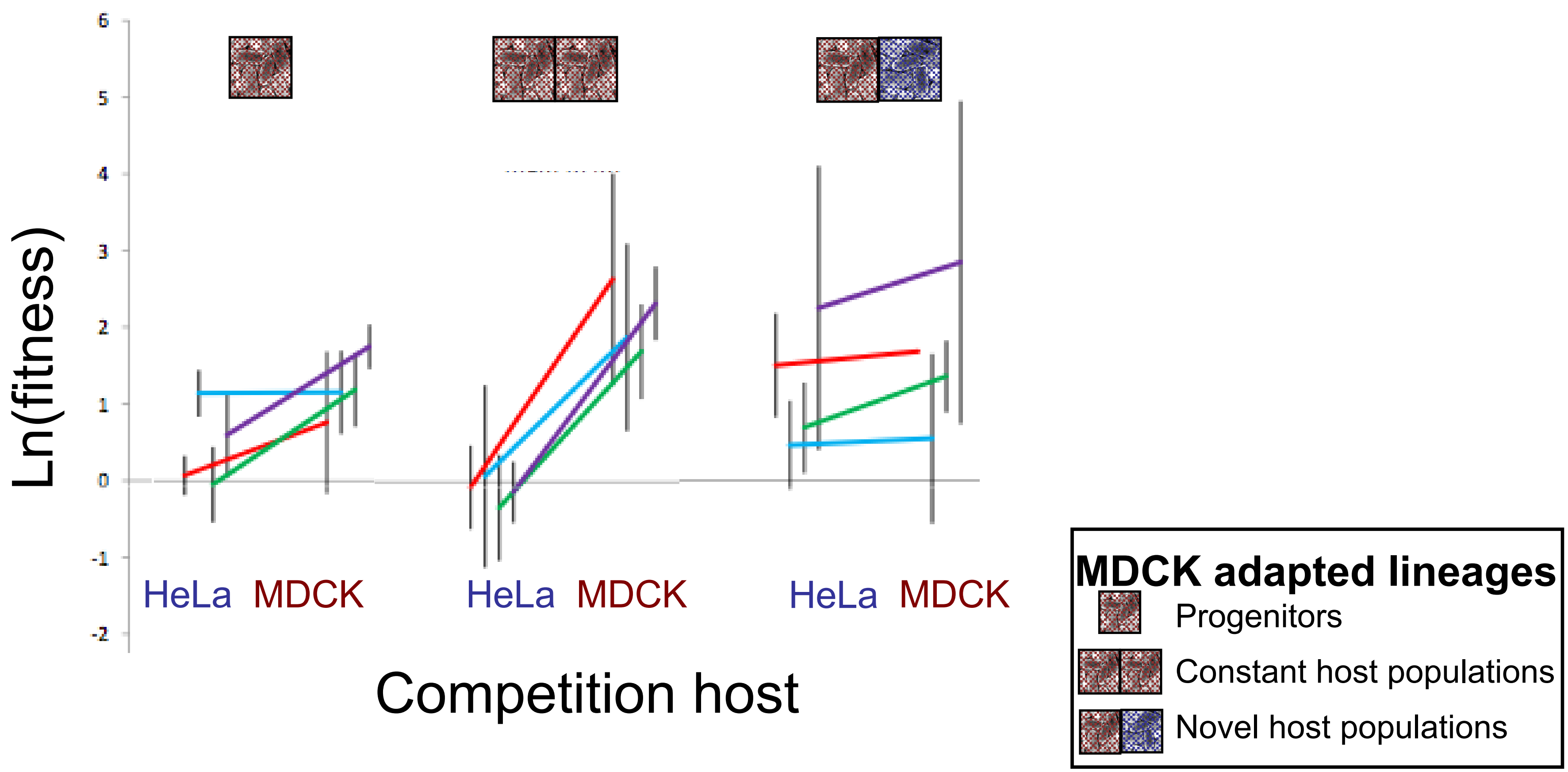
MDCK adapted populations should be able to correct phenotypic tradeoff and may be variable in their ability to do so



If the HeLa adapted populations' tradeoff is due to GxGxE, breaking it should require change at multiple loci. Short term they should be "evolutionarily stuck".

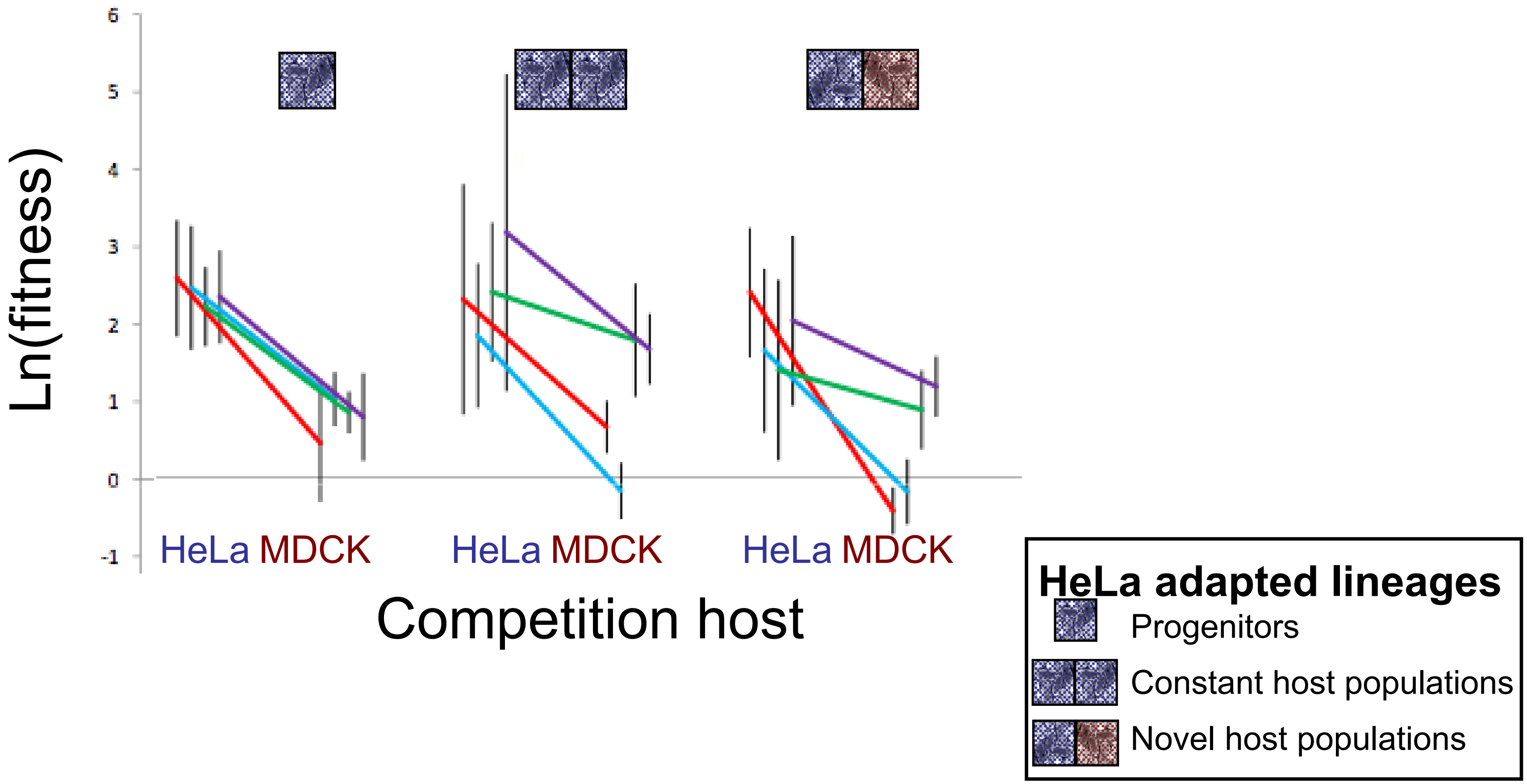
Mean fitness of MDCK lineages on novel hosts do not evolve to significantly less pleiotropy relative to the progenitors, but do so relative to the constant host control populations.

Variance among hosts increases after evolution on HeLa.



Mean fitness of HeLa lineages do not differ from progenitor on either competition host, after evolution on either HeLa or MDCK.

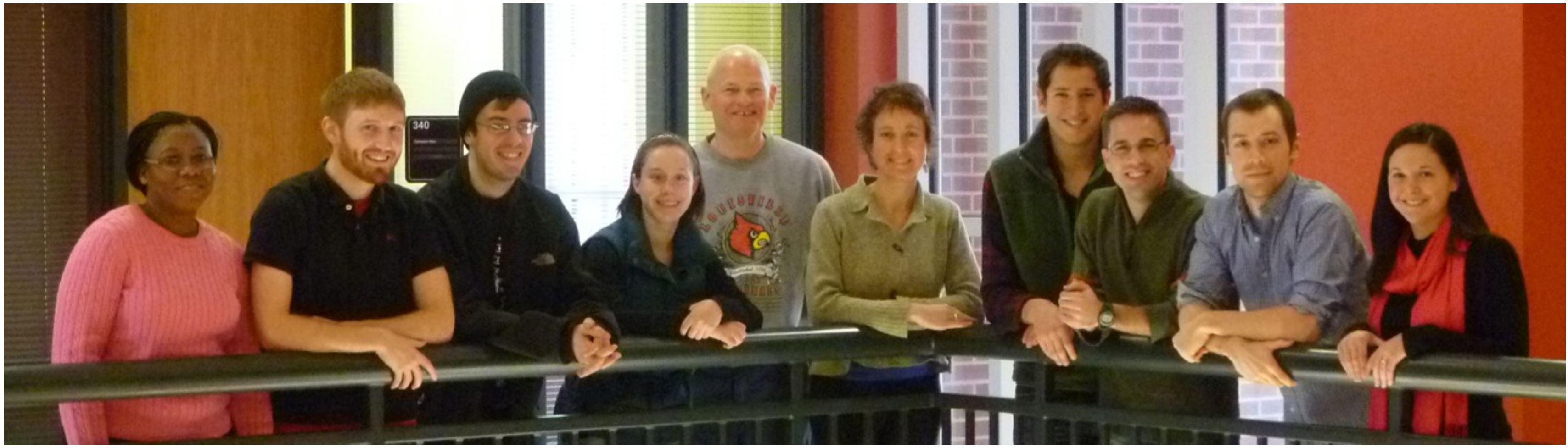
Variance increases under both short term evolutions, especially in the selected hosts.



Up next:

What are the ecological conditions under which specialism by GxGxE evolves, vs those under which generalists bearing no cost evolve?

- variable scale of temporal variability
- variable degrees of similarity between hosts experienced



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