



# Fitness Landscapes

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**Note: These slides are not *quite* the ones I presented because I've made modest changes hereinto incorporate comments from the audience!**

**DMW**

*The Role of Mutation, Inbreeding, Crossbreeding  
and Selection in Evolution*

Sewall Wright, University of Chicago

Sixth International Conference on Genetics, Ithaca, NY  
1932



Une séance plénière dans la Grande Salle de la Société Royale de Géographie.

# A High Dimensional Domain

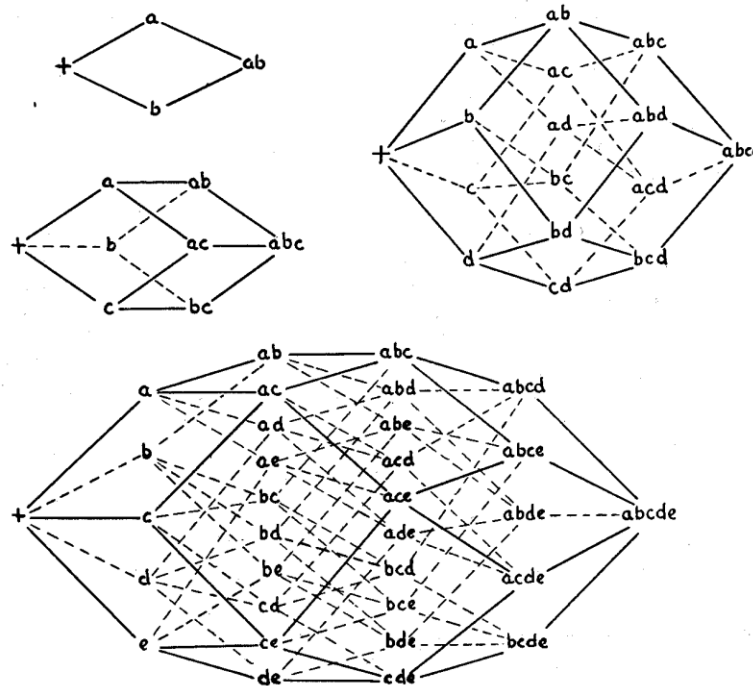


FIGURE 1.—The combinations of from 2 to 5 paired allelomorphs.

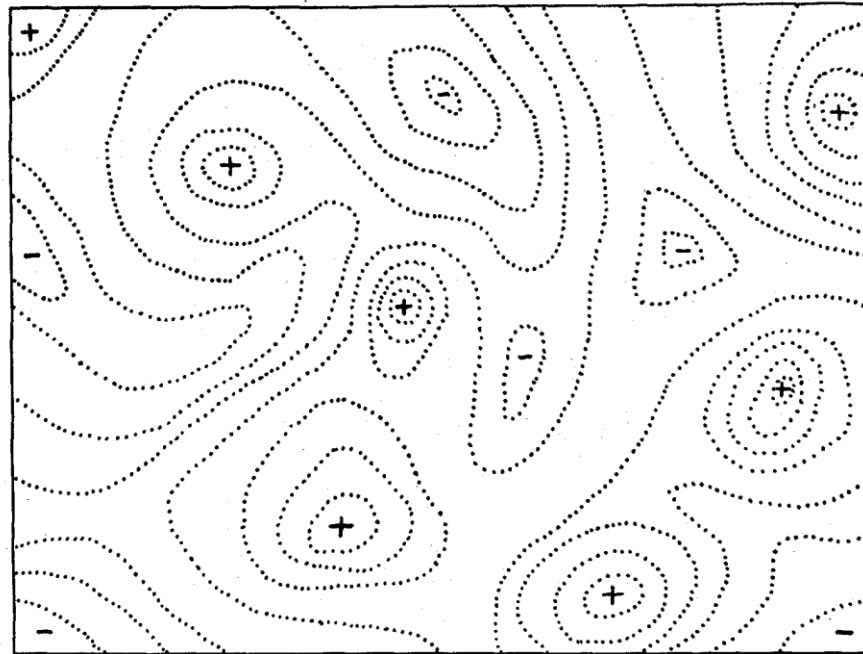
Indeed, one dimension/biallelic locus

(Wright 1932, see also Haldane 1932, Maynard Smith 1970)

# What of the Resulting Surface?

“One possible adaptation falls off more rapidly than others... removes...”

But even in two peaks, increases with possibilities enormous combinations



as maximum combinations number of

there may be case greatly like  $10^{1000}$  will be an harmonious

FIGURE 2.—Diagrammatic representation of the field of gene combinations in two dimensions instead of many thousands. Dotted lines represent contours with respect to adaptiveness.

(Wright 1932)

# And What of the Population Genetics on this Surface?

“In a rugged field of this character, selection will easily carry the species to the nearest peak, but there may be innumerable other peaks which are higher but which are separated by “valleys.” **The problem of evolution as I see it is that of a mechanism by which the species may continually find its way from lower to higher peaks in such a field.**”

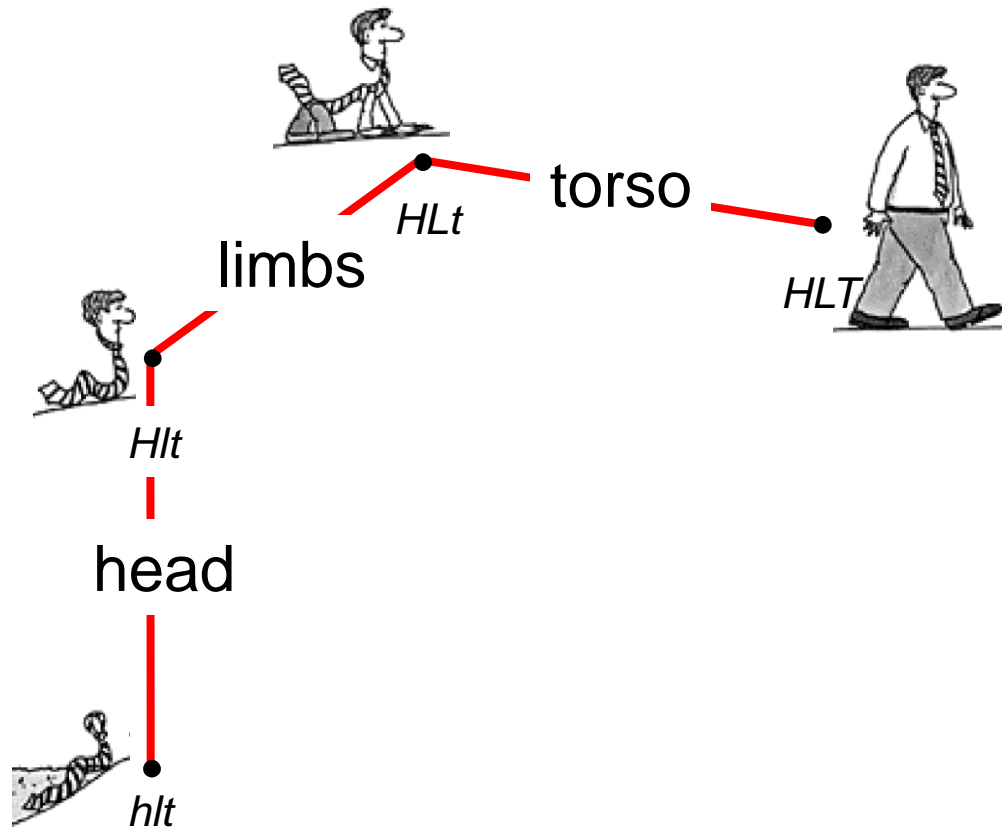
(Wright 1932)

# In Modern Terms



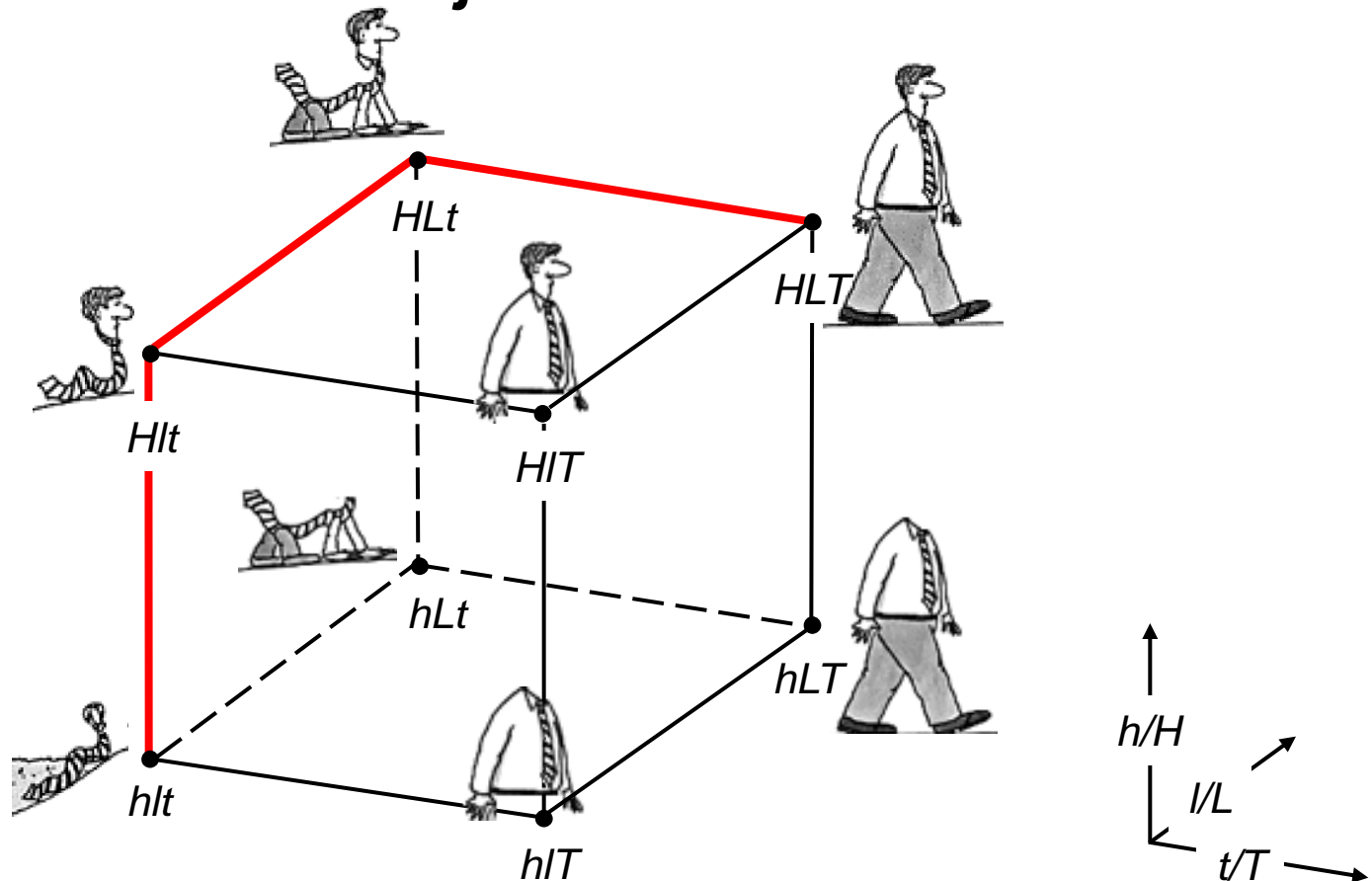
Suppose we're interested in the evolution of the junior businessman from the ancestral necktie?

# Adaptation Changes Heritable Phenotypes





# Nucleotide Sequence Space Defines Many Mutationally Equivalent Trajectories

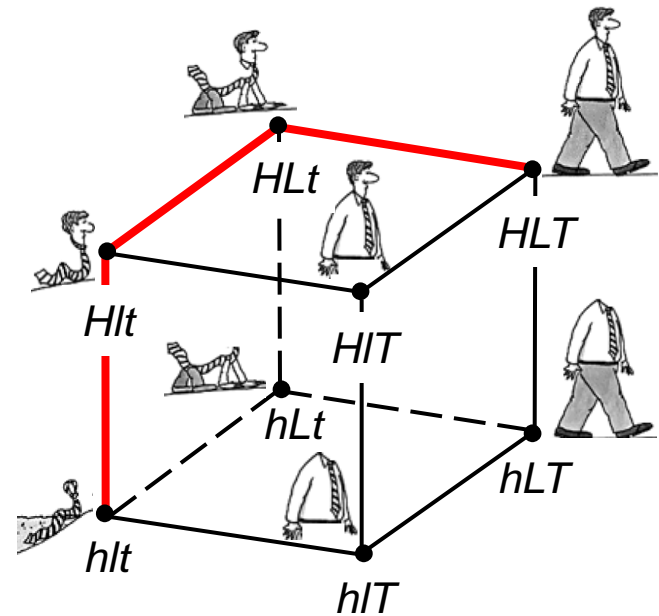


(after Maynard-Smith 1970; see also Wright 1932; Haldane 1932)

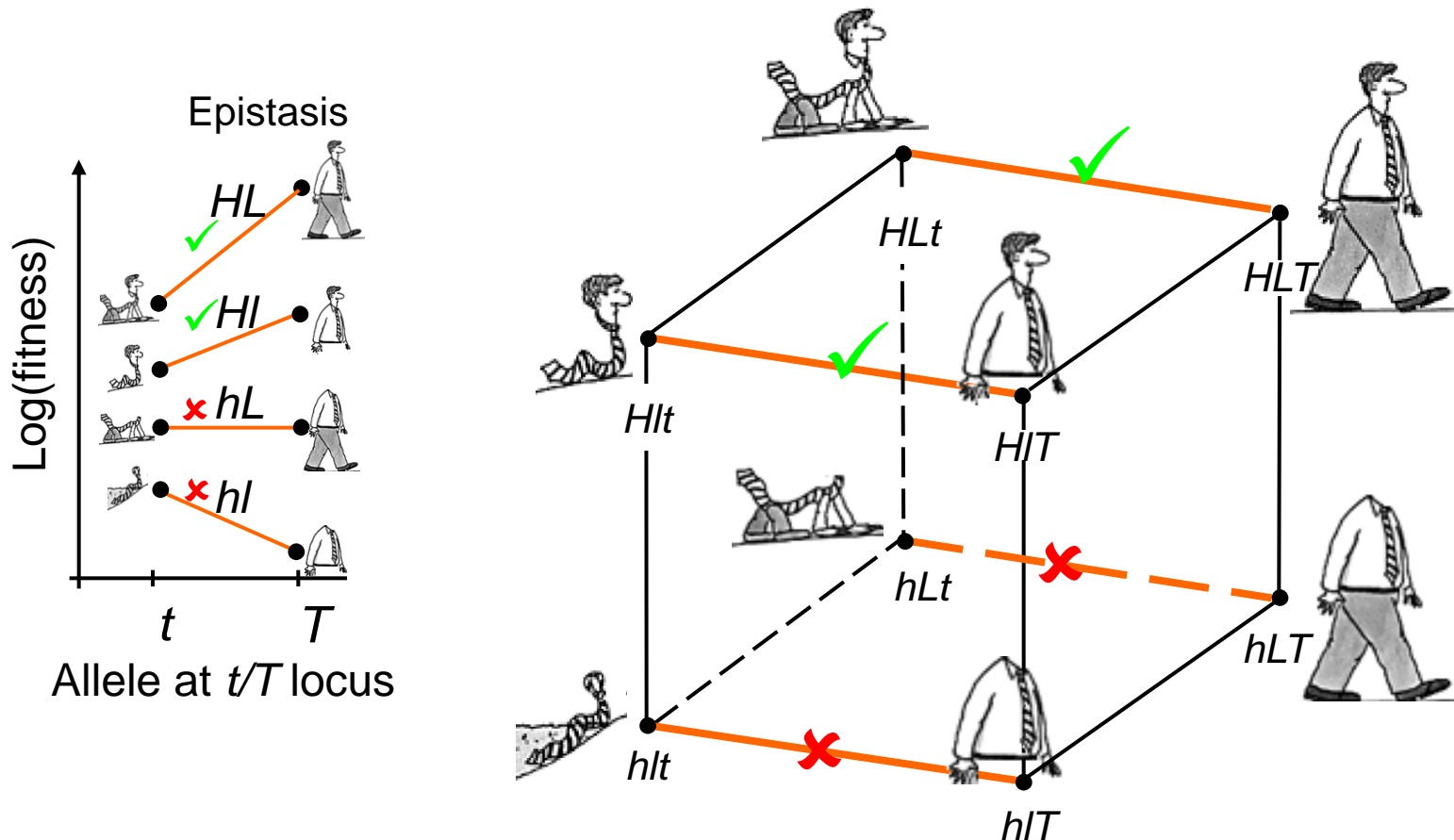
# Question

Are these many mutational trajectories equivalent in the eyes of natural selection? Or is an evolving population constrained to follow a subset of mutational trajectories to reach higher fitness?

NB: framing things in terms of mutational trajectories implicitly makes the strong selection/weak mutation assumption:  $N\mu \ll 1 \ll Ns$ . Or in English, each mutation is fixed or lost before the next mutation appears.



# What Really Matters: Are Mutations Unconditionally Beneficial?



(Weinreich *et al.* 2005, though definitely not news to Wright!)

# Conditionally Beneficial Mutations

Sign epistasis generalizes a very old theoretical problem: is the fitness landscape multipeaked?

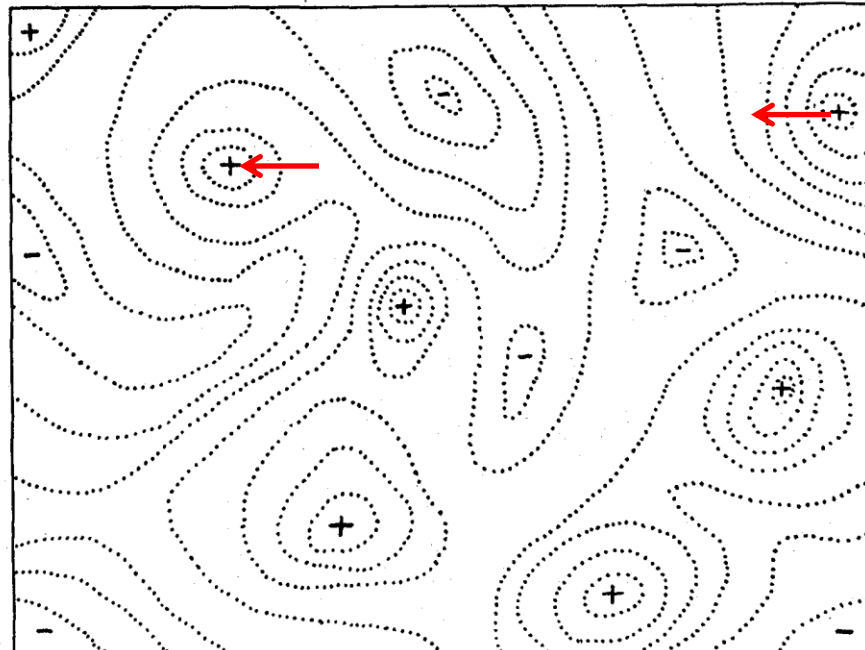
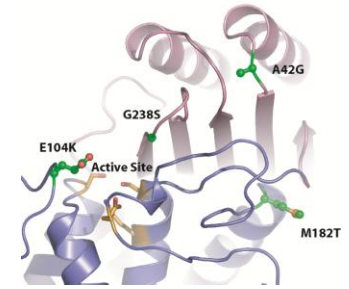


FIGURE 2.—Diagrammatic representation of the field of gene combinations in two dimensions instead of many thousands. Dotted lines represent contours with respect to adaptiveness.

# A Fitness Landscape



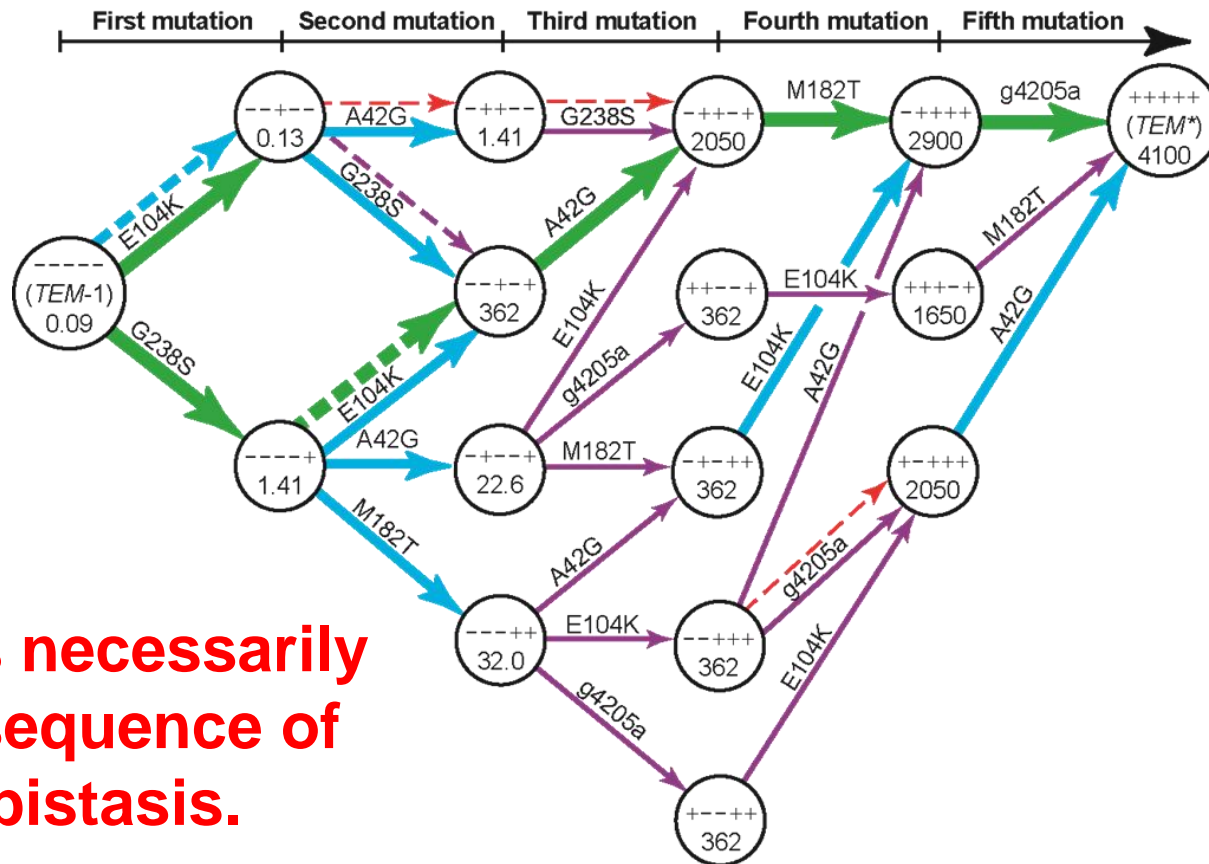
Mutational State					Resistance ( $\mu\text{g/ml}$ )			
g4205a	A42G	E104K	M182T	G238S	Allele	Rep 1	Rep 2	Rep 3
-	-	-	-	-	<i>TEM-1</i>	0.0884	0.0884	0.0884
-	-	-	-	+		1.41	1.41	1.41
-	-	-	+	-		0.0711	0.0884	0.0711
-	-	-	+	+		32.0	32.0	32.0
-	-	+	-	-		0.130	0.130	0.130
-	-	+	-	+		362.	362.	362.
⋮	⋮	⋮	⋮	⋮		⋮	⋮	⋮
+	+	+	+	-		1.41	1.41	2.0
+	+	+	+	+	<i>TEM*</i>	4096.	4096.	4096.



**f: Genotype**  $\longrightarrow$  **Fitness**

(Weinreich et al. 2006)

# Only 18 of 120 trajectories are selectively accessible



**This is necessarily a consequence of sign epistasis.**

# (A Current Research Interest of Mine)



Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

ScienceDirect



Should evolutionary geneticists worry about higher-order epistasis?

Daniel M Weinreich<sup>1</sup>, Yinghong Lan<sup>1</sup>, C Scott Wylie<sup>1</sup> and Robert B Heckendorn<sup>2</sup>

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Current Opinion in Genetics & Development 2013, 23:700–707

[www.sciencedirect.com](http://www.sciencedirect.com)

We now have ~20 combinatorially complete empirical fitness landscapes. What statistical generalities are emerging?

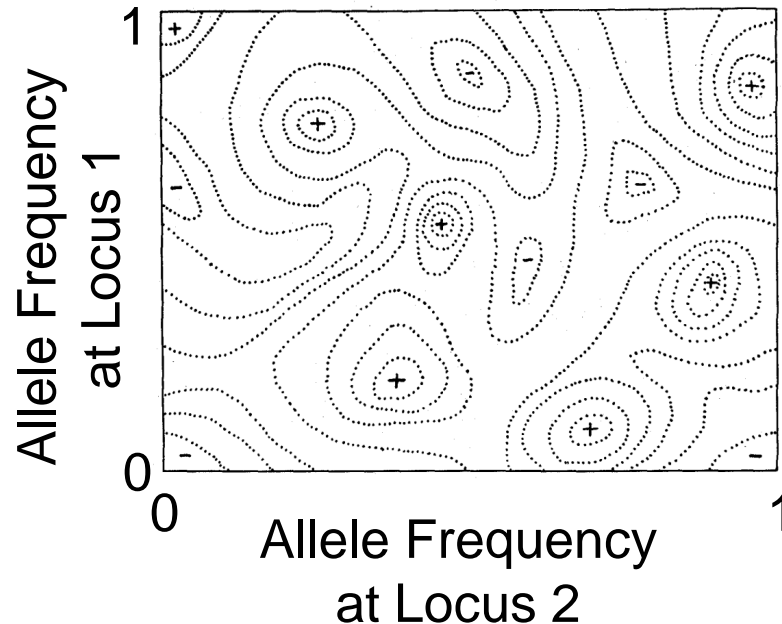
# Sequence Space Landscape Limitations

- Can't trivially handle frequency dependent selection
- Experiments grow exponentially in  $L$ .
- Though not necessary, we often assume
  - populations are almost always genetically monomorphic;
  - environment is constant;
  - no diploids, dominance or recombination.



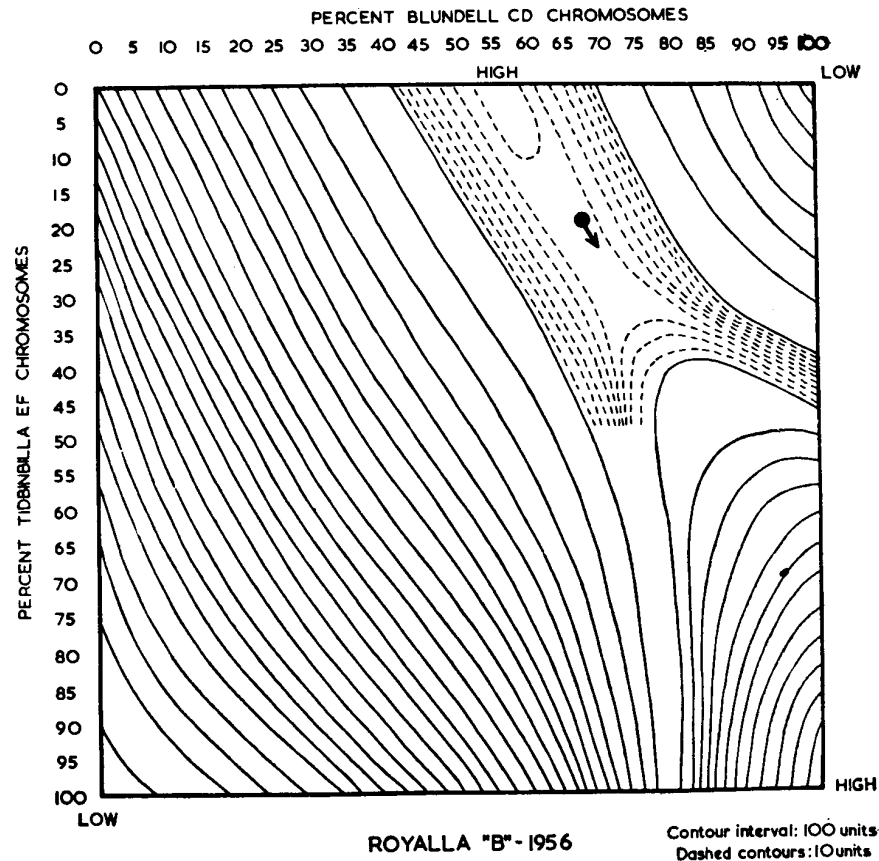


# What were those axes again?



- Wright and others sometimes instead projected population mean fitness over allele frequency space.
- This fills in the interstices between points on discrete fitness landscape

# What were those axes again?



(Lewontin and White 1960)

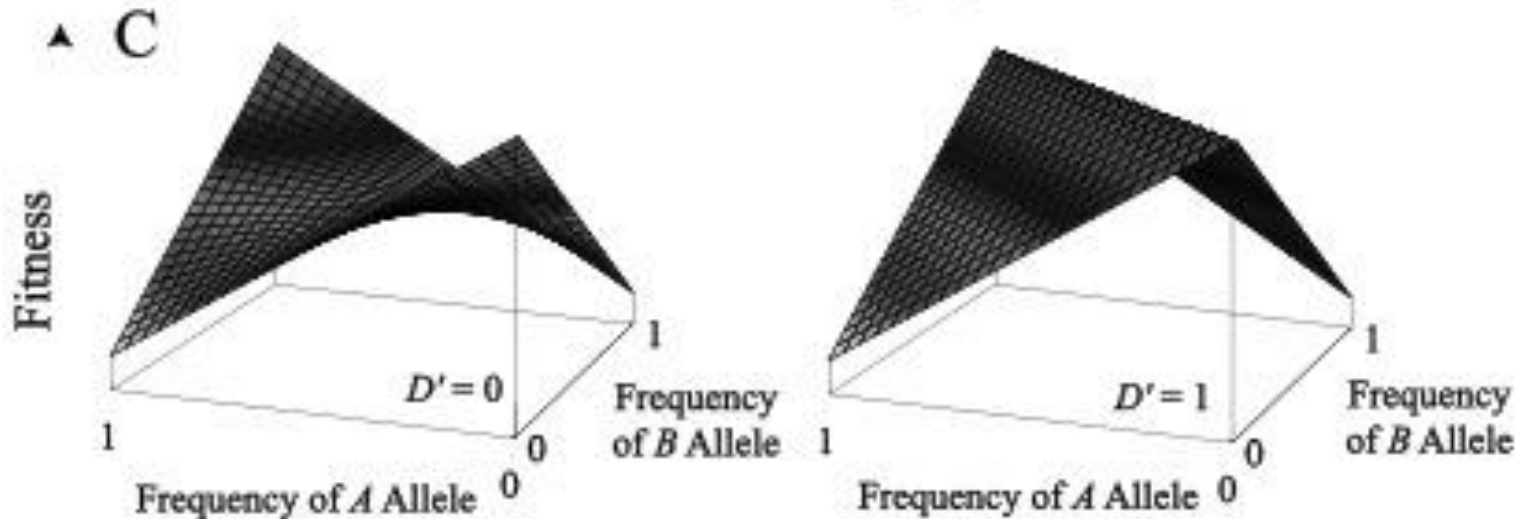
# Population Mean Fitness Landscape

Articulates with RA (not Daniel) Fisher's 1932 Fundamental Theorem of Natural Selection:

“The rate of increase in mean fitness in a population due to natural selection acting on allele frequencies is exactly equal to its genetic variance in fitness.”

# Limitations of Population Mean Fitness Landscape

- In the presence of epistasis, population mean fitness is not uniquely determined by allele frequencies except in the high-recombination limit.

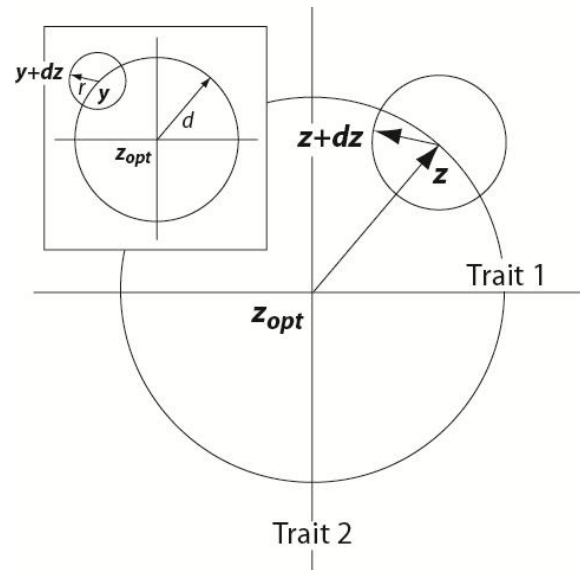




# Phenotypic Fitness Landscape

- Projects organismal fitness over organismal phenotype.
- Nonlinear fitness function gives rise to epistasis for fitness even in the absence of epistasis for phenotype.
- Often yield nice theoretical results in the absence of explicit genetics.

# E.g. Fisher's Geometric Model



- Fitness declines monotonically from optimum ' $z_{opt}$ '
- $\Pr\{\text{beneficial mutation}\}$  goes up as size of mutational effect goes down (Fisher 1930)



# Fisher's Geometric Model

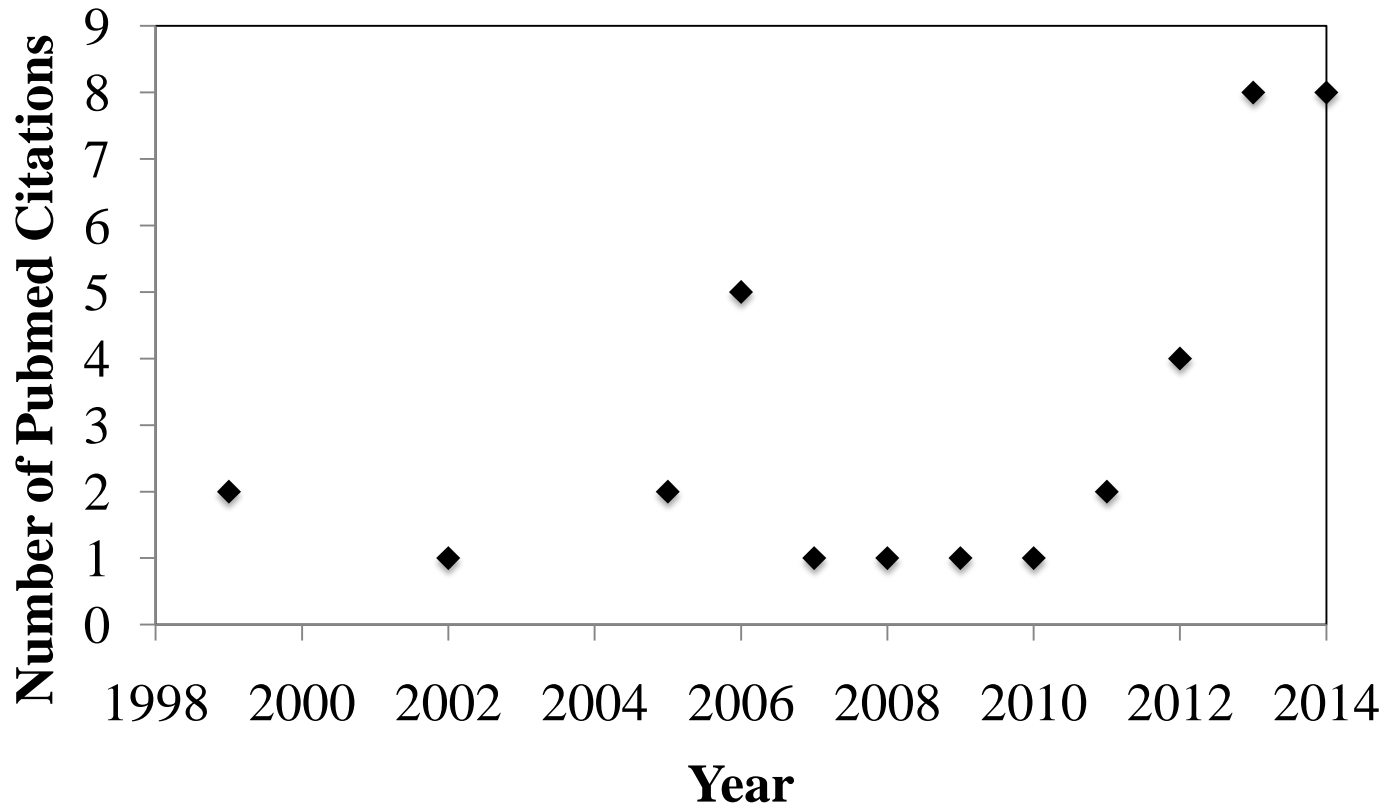
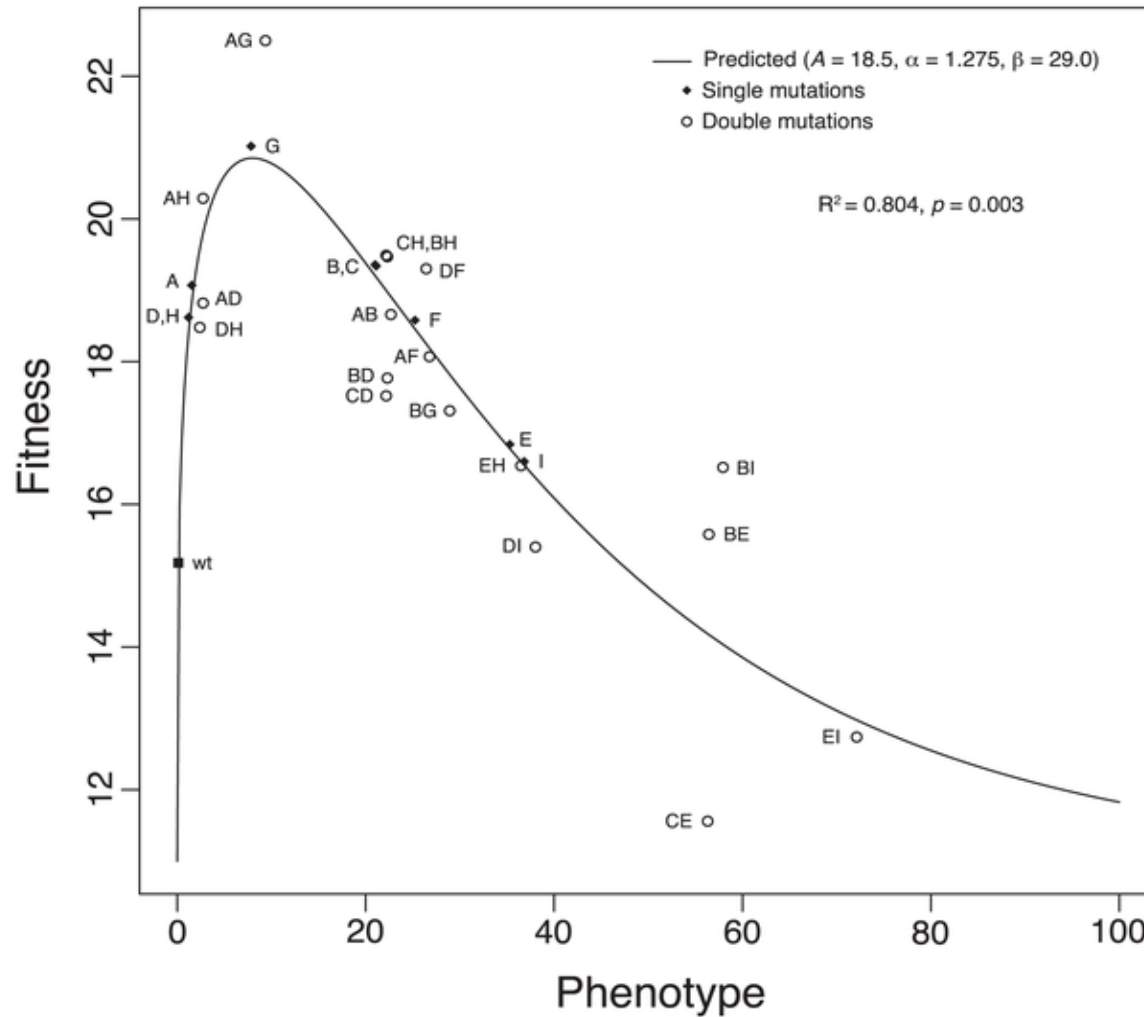


Figure 3. The phenotype-to-fitness map.



Rokyta DR, Joyce P, Caudle SB, Miller C, et al. (2011) Epistasis between Beneficial Mutations and the Phenotype-to-Fitness Map for a ssDNA Virus. *PLoS Genet* 7(6): e1002075.  
doi:10.1371/journal.pgen.1002075  
<http://www.plosgenetics.org/article/info:doi/10.1371/journal.pgen.1002075>



# Three kinds of landscapes

- Discrete map from sequence space to organismal fitness
  - This is the most common usage.
- Continuous map from allele frequencies to population mean fitness
  - Not dynamically sufficient when epistasis is present.
- Continuous map from phenotype space to organismal fitness
  - Often an elegant theoretical framework.

