A Simulation-Based Approach to the Evolution of the **G**-matrix

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$$\Delta \bar{z} = G \, \beta$$

$\bar{z}$ is a vector of trait means.

β is a vector of directional selection gradients.

G is the genetic variance-covariance matrix.

This equation can be extrapolated to reconstruct the history of selection:

$$\beta_T = G^{-1} \Delta z_T$$

It can also be used to predict the future trajectory of the phenotype.

For this application of quantitative genetics theory to be valid, the estimate of **G** must be representative of **G** over the time period in question. **G** must be stable.

Stability of **G** is an important question

- Empirical comparisons of **G** between populations within a species usually, but not always, produce similar **G**-matrices.

- Studies at higher taxonomic levels (between species or genera) more often reveal differences among **G**-matrices.

- Analytical theory cannot guarantee **G**-matrix stability (Turelli, 1988).

- Analytical theory also cannot guarantee **G**-matrix instability, and it gives little indication of how much **G** will change when it is unstable (and how important these changes may be for evolutionary inferences).
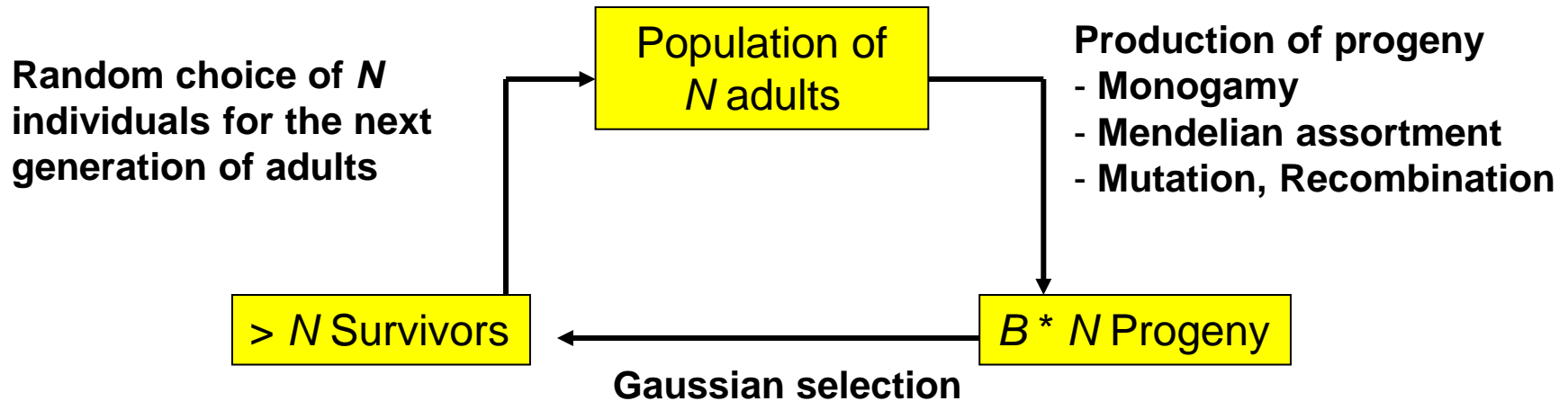
Study Background and Objectives

- Stochastic computer models have been used successfully to study several interesting topics in single-trait quantitative genetics (e.g., maintenance of variation, population persistence in a changing environment).

- Our objective was to use stochastic computer models to investigate the stability of **G** over long periods of evolutionary time.

- More recent work focuses on the evolution of the mutational architecture, the **M**-matrix.

- Models including epistasis are revealing additional insights into the evolution of **G** and **M**.
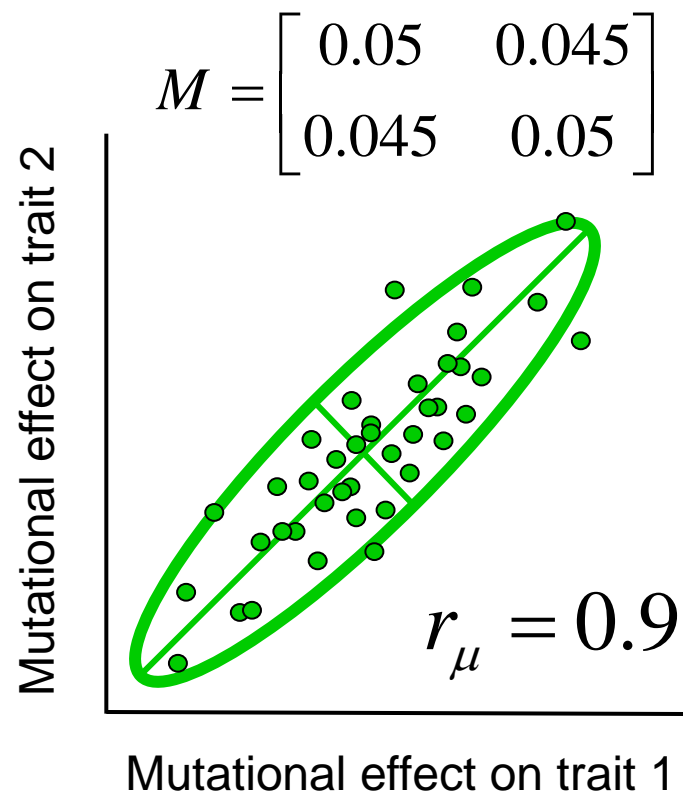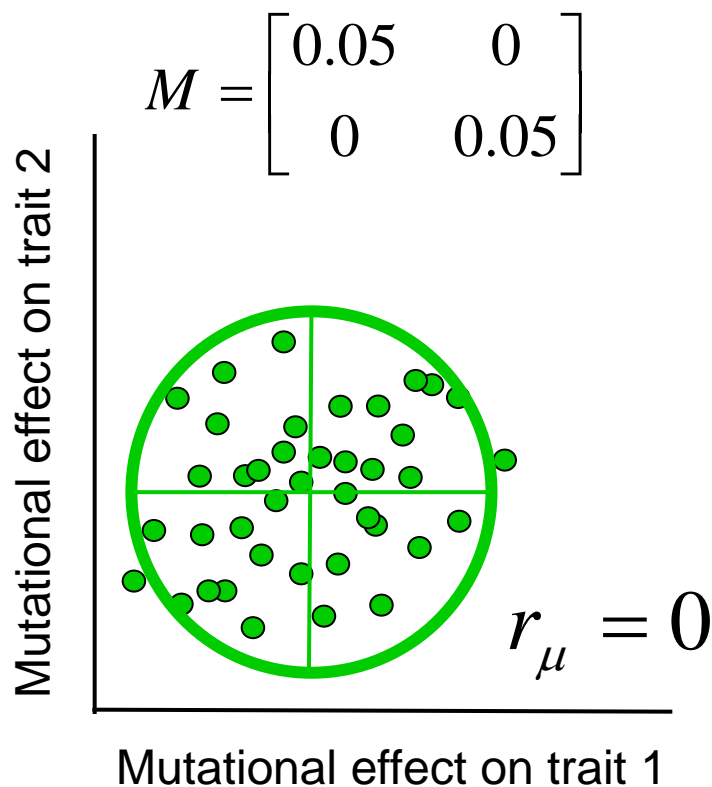
Model details

- *Direct Monte Carlo simulation with each gene and individual specified*

- *Two traits affected by 50 pleiotropic loci*

- *Additive inheritance with no dominance or epistasis*

- *Allelic effects drawn from a bivariate normal distribution with means = 0, variances = 0.05, and mutational correlation r_μ = 0.0-0.9*

- *Mutation rate = 0.0002 per haploid locus*

- *Environmental effects drawn from a bivariate normal distribution with mean = 0, variances = 1*

- *Gaussian individual selection surface, with a specified amount of correlational selection and ω = 9 or 49*

- *Each simulation run equilibrated for 10,000 (non-overlapping) generations, followed by several thousand of experimental generations*

Methods – The Simulation Model (continued)

Random choice of N individuals for the next generation of adults

Population of N adults

Production of progeny
- **Monogamy**
- **Mendelian assortment**
- **Mutation, Recombination**

> N Survivors
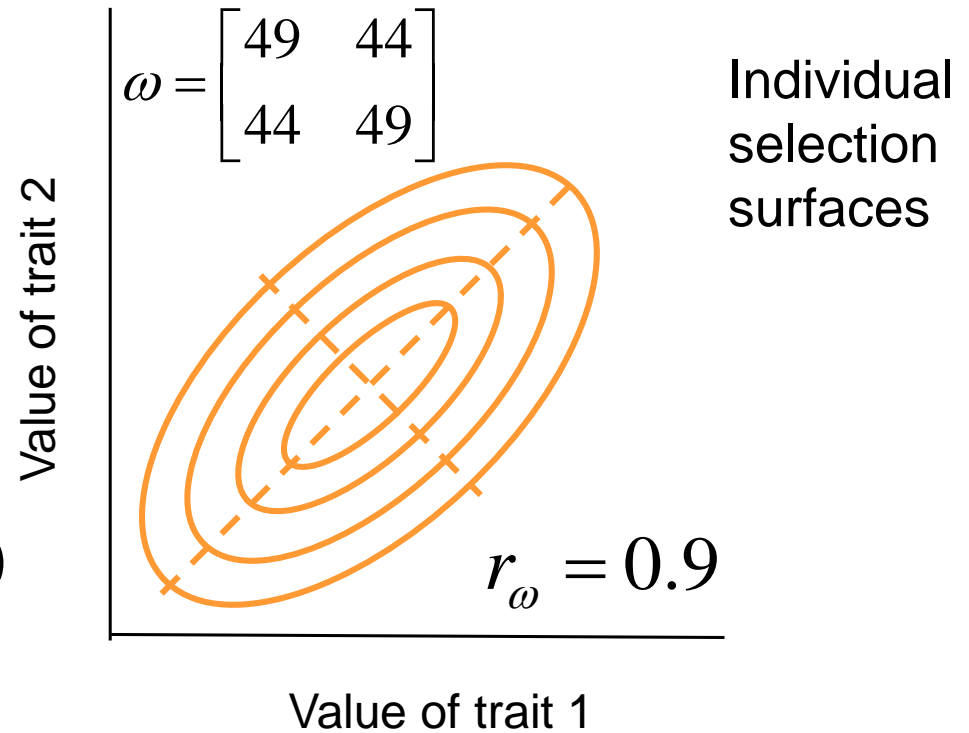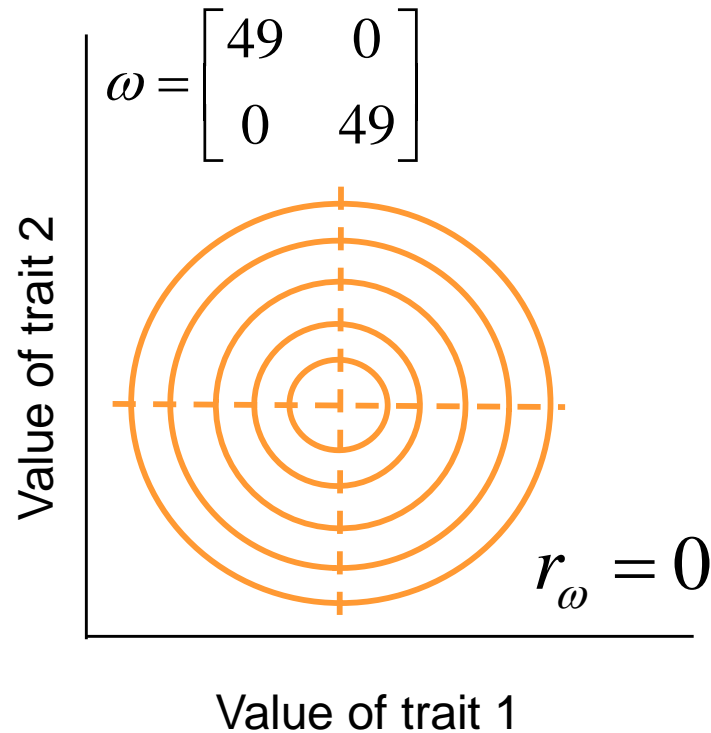
$B * N$ Progeny

Gaussian selection

- Start with a population of genetically identical adults, and run for 10,000 generations to reach a mutation-selection-drift equilibrium.

- Impose the desired model of movement of the optimum.

- Calculate **G-**matrix over the next several thousand generations (repeat 20 times).

- We focus on average single-generation changes in **G**, because we are interested in the effects of model parameters on relative stability of **G**.
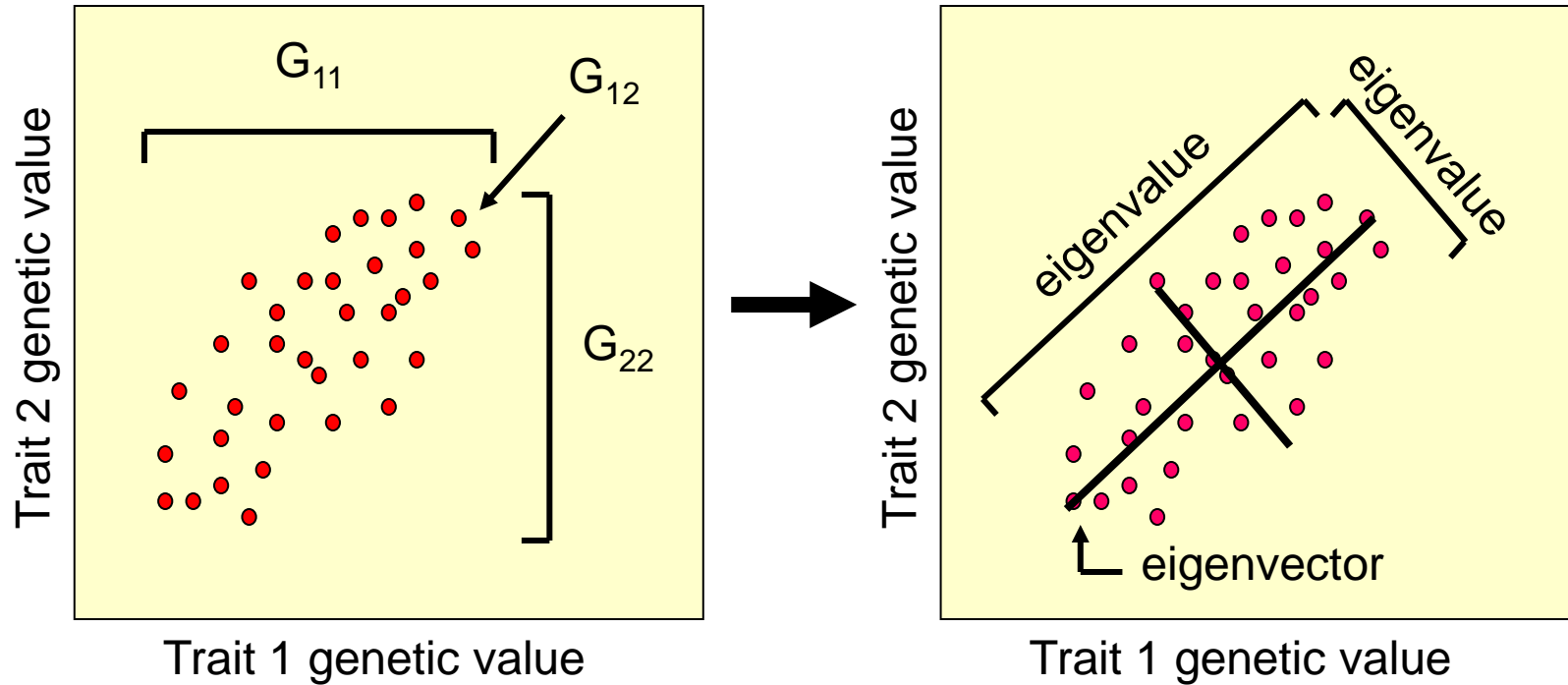
Mutation conventions

$$M = \begin{bmatrix} 0.05 & 0 \\ 0 & 0.05 \end{bmatrix}$$

Mutational effect on trait 2

Mutational effect on trait 1

$r_\mu = 0$

$$M = \begin{bmatrix} 0.05 & 0.045 \\ 0.045 & 0.05 \end{bmatrix}$$

Mutational effect on trait 2

Mutational effect on trait 1

$r_\mu = 0.9$

Selection conventions

$$\omega = \begin{bmatrix} 49 & 0 \\ 0 & 49 \end{bmatrix}$$

$$r_\omega = 0$$

Value of trait 2

Value of trait 1

$$\omega = \begin{bmatrix} 49 & 44 \\ 44 & 49 \end{bmatrix}$$

Individual selection surfaces

$$r_\omega = 0.9$$

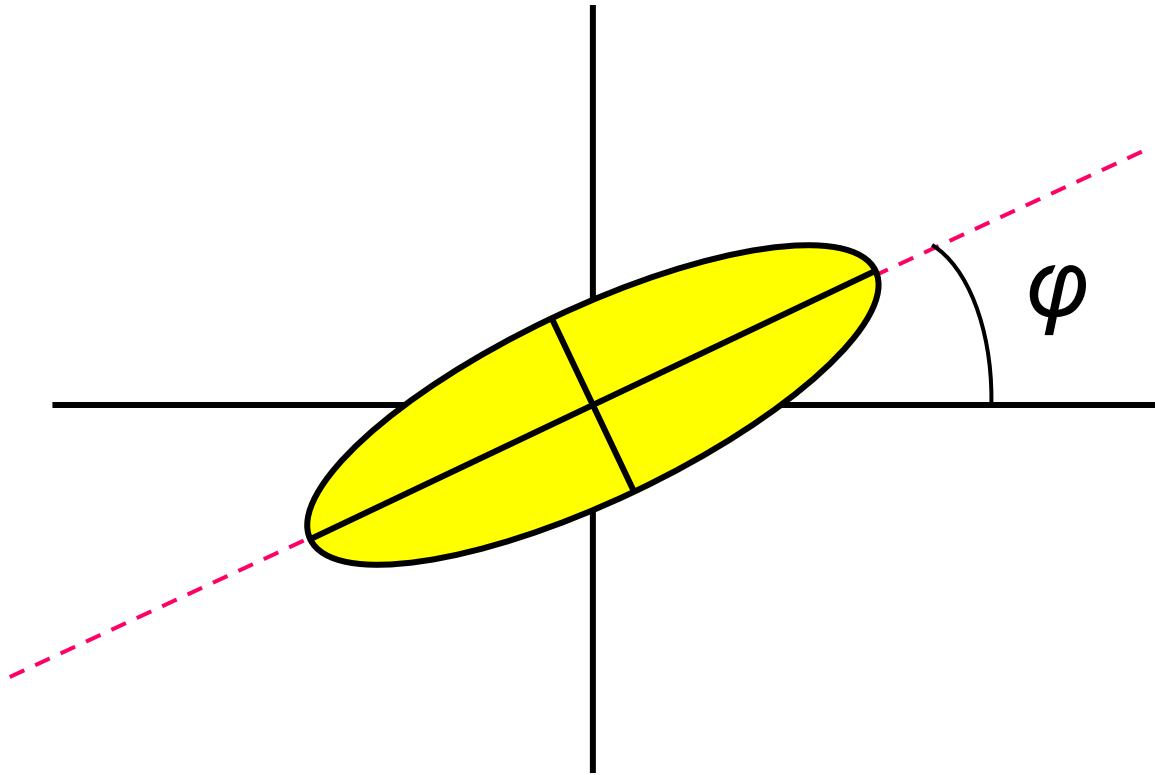Value of trait 2

Value of trait 1

Visualizing the **G**-matrix

$$\mathbf{G} = \begin{bmatrix} G_{11} & G_{12} \\ G_{12} & G_{22} \end{bmatrix}$$

- We already know that genetic variances can change, and such changes will affect the rate (but not the trajectory) of evolution.

- The interesting question in multivariate evolution is whether the trajectory of evolution is constrained by **G**.

- Constraints on the trajectory are imposed by the angle of the leading eigenvector, so we focus on the angle φ.

Stationary Optimum
## (selectional correlation = 0, mutational correlation = 0)
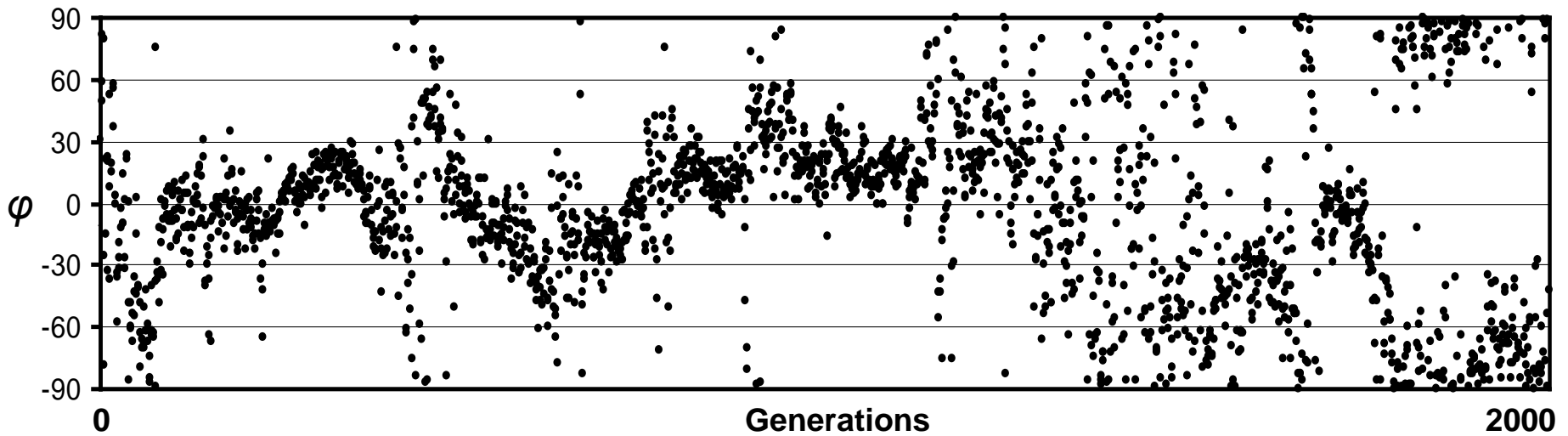
Stronger correlational selection produces a more stable **G**-matrix
(selectional correlation = 0.75, mutational correlation = 0)
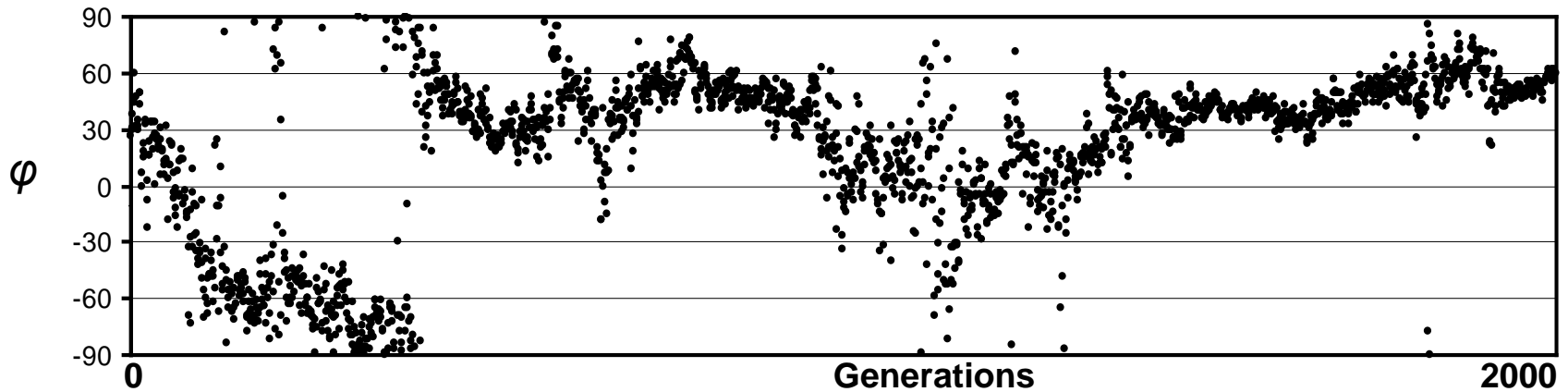
| ω (trait 1)	ω (trait 2)	r (ω)	r (μ)	Δφ
49	49	0	0	9.1
49	49	0.25	0	9.2
49	49	0.50	0	8.9
49	49	0.75	0	7.8
49	49	0.85	0	5.4
49	49	0.90	0	4.3

A high correlation between mutational effects produces stability
(selectional correlation = 0, mutational correlation = 0.5)
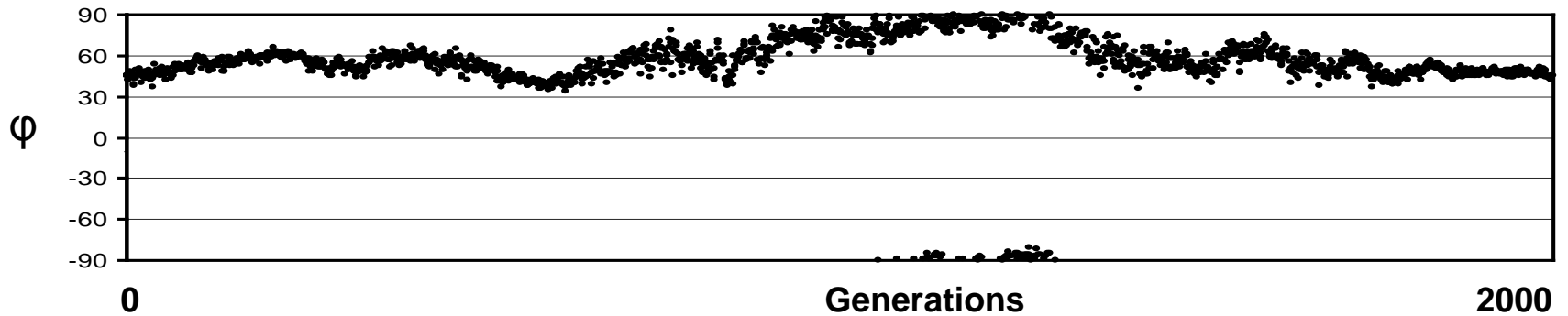
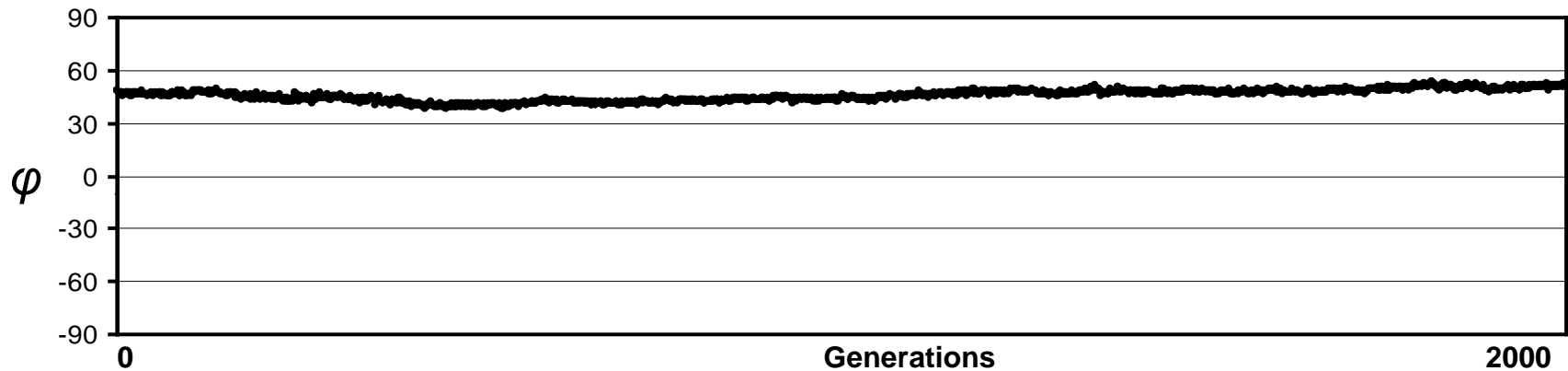| ω (trait 1)	ω (trait 2)	r (ω)	r (μ)	Δφ
49	49	0	0	9.9
49	49	0	0.25	7.9
49	49	0	0.50	3.6
49	49	0	0.75	1.5
49	49	0	0.85	1.1
49	49	0	0.90	0.9

When the selection matrix and mutation matrix are aligned, **G** can be very stable

selectional correlation = 0.75, mutational correlation = 0.5

φ

Generations

0   2000
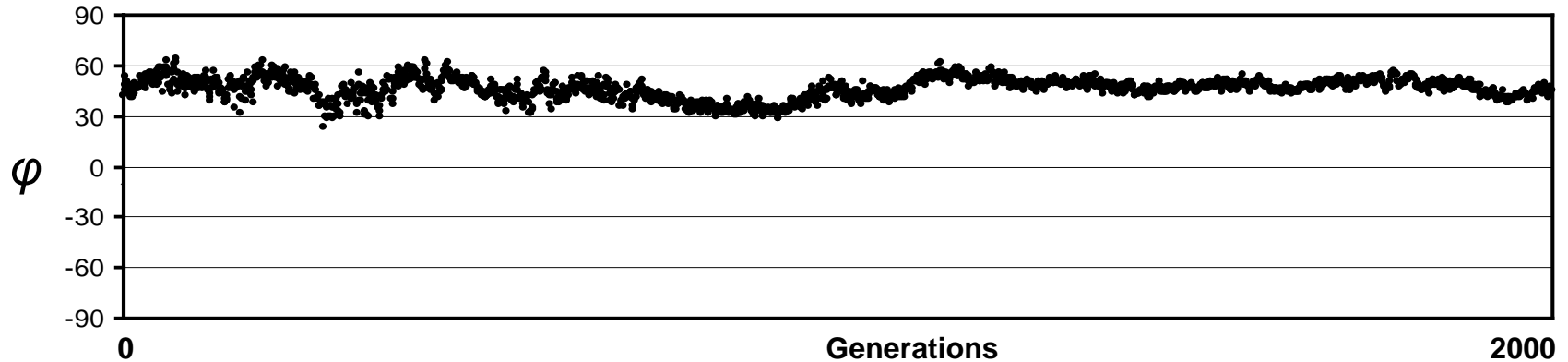
selectional correlation = 0.9, mutational correlation = 0.9

φ

Generations

0   2000

Misalignment causes instability
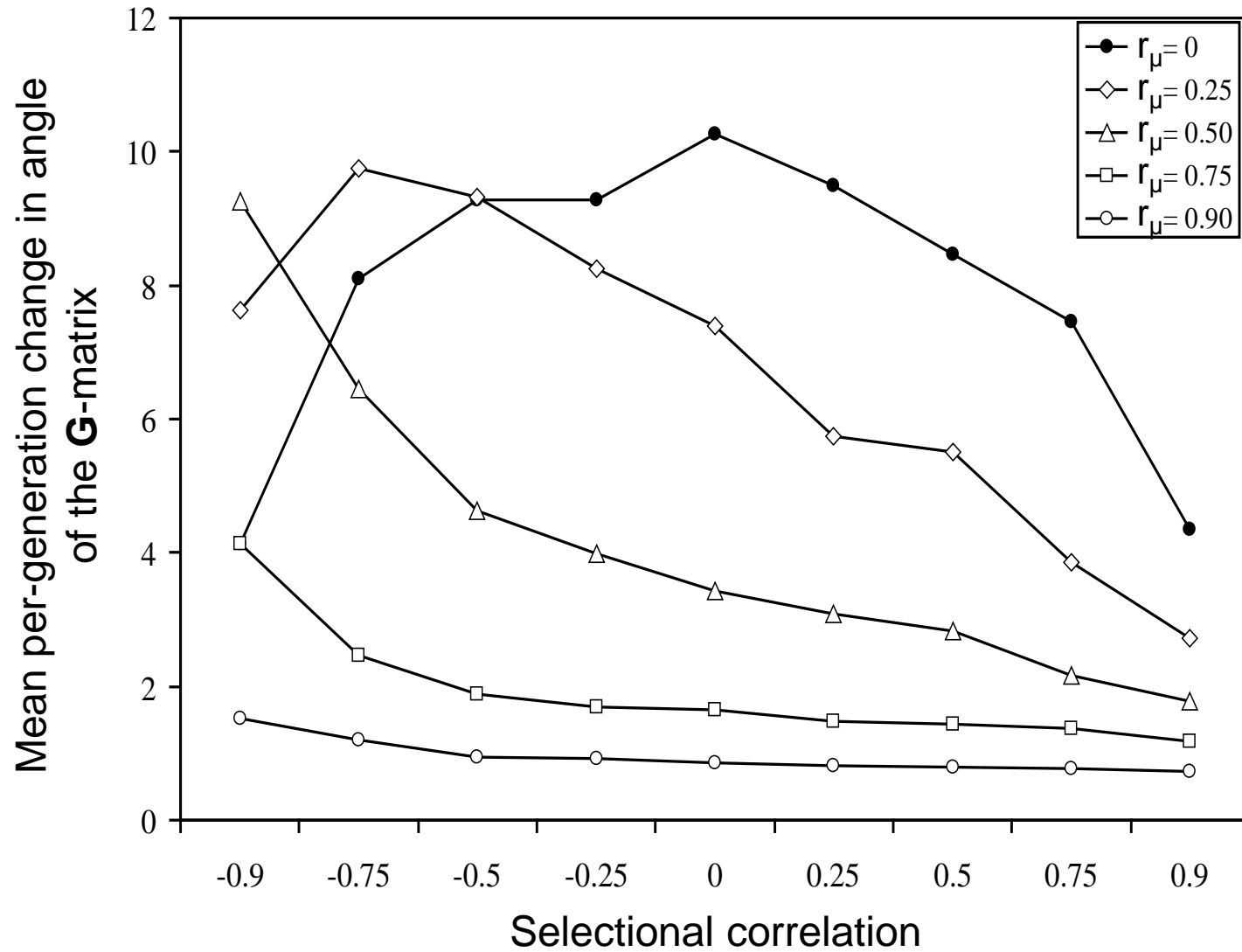
A larger population has a more stable **G**-matrix

ω (trait 1)	ω (trait 2)	r (ω)	r (µ)	N (e)	Δφ
49	49	0	0	1366	8.8
49	49	0.5	0	1366	6.2
49	49	0	0.5	1366	2.7
49	49	0	0	2731	7.6
49	49	0.5	0	2731	2.3
49	49	0	0.5	2731	1.7

Asymmetrical selection intensities or mutational variances produce stability without the need for correlations

ω (trait 1)	ω (trait 2)	r (ω)	r (µ)	α (trait 1)	α (trait 2)	Δφ
49	49	0	0	0.05	0.05	9.9
49	49	0	0	0.05	0.03	7.2
49	49	0	0	0.05	0.02	3.8
49	49	0	0	0.05	0.01	1.9
99	99	0	0	0.05	0.05	9.6
99	4	0	0	0.05	0.05	3.8

Conclusions from a Stationary Optimum

- Correlational selection increases **G**-matrix stability, but not very efficiently unless selection is very strong.

- Mutational correlations do an excellent job of maintaining stability, and can produce extreme **G**-matrix stability.

- **G**-matrices are more stable in large populations, or with asymmetries in trait variances (due to mutation or selection).

- Alignment of mutational and selection matrices increases stability.

-Given the importance of mutations, we need more data on mutational matrices.

- For some suites of characters, the **G**-matrix is probably very stable over long spans of evolutionary time, while for other it is probably extremely unstable.
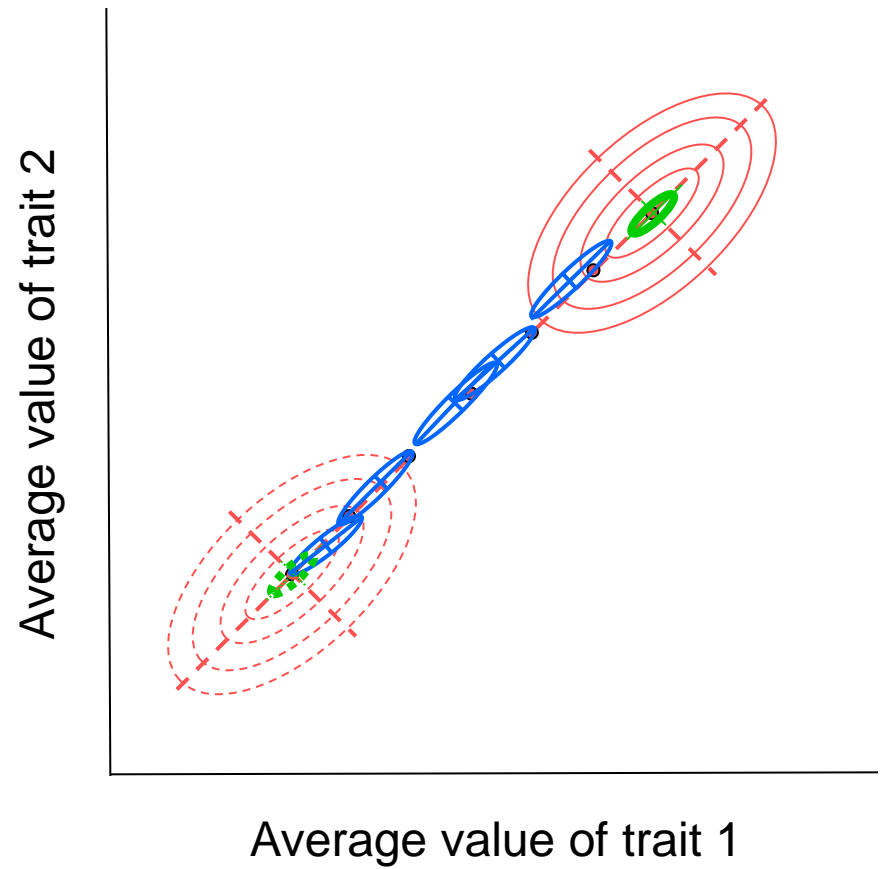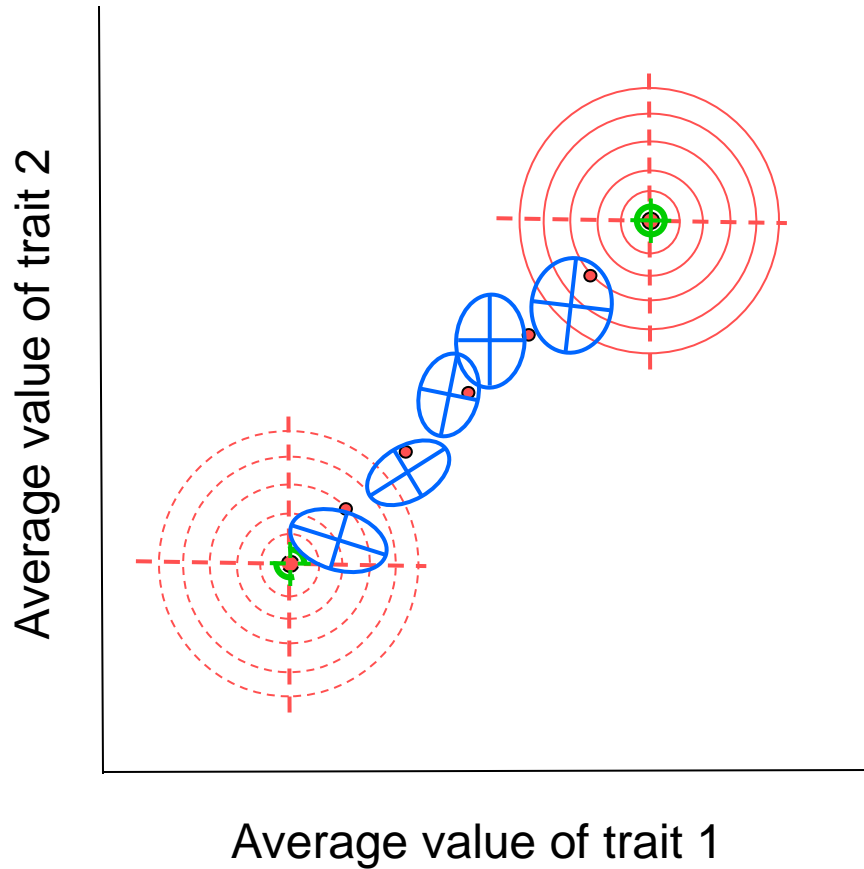
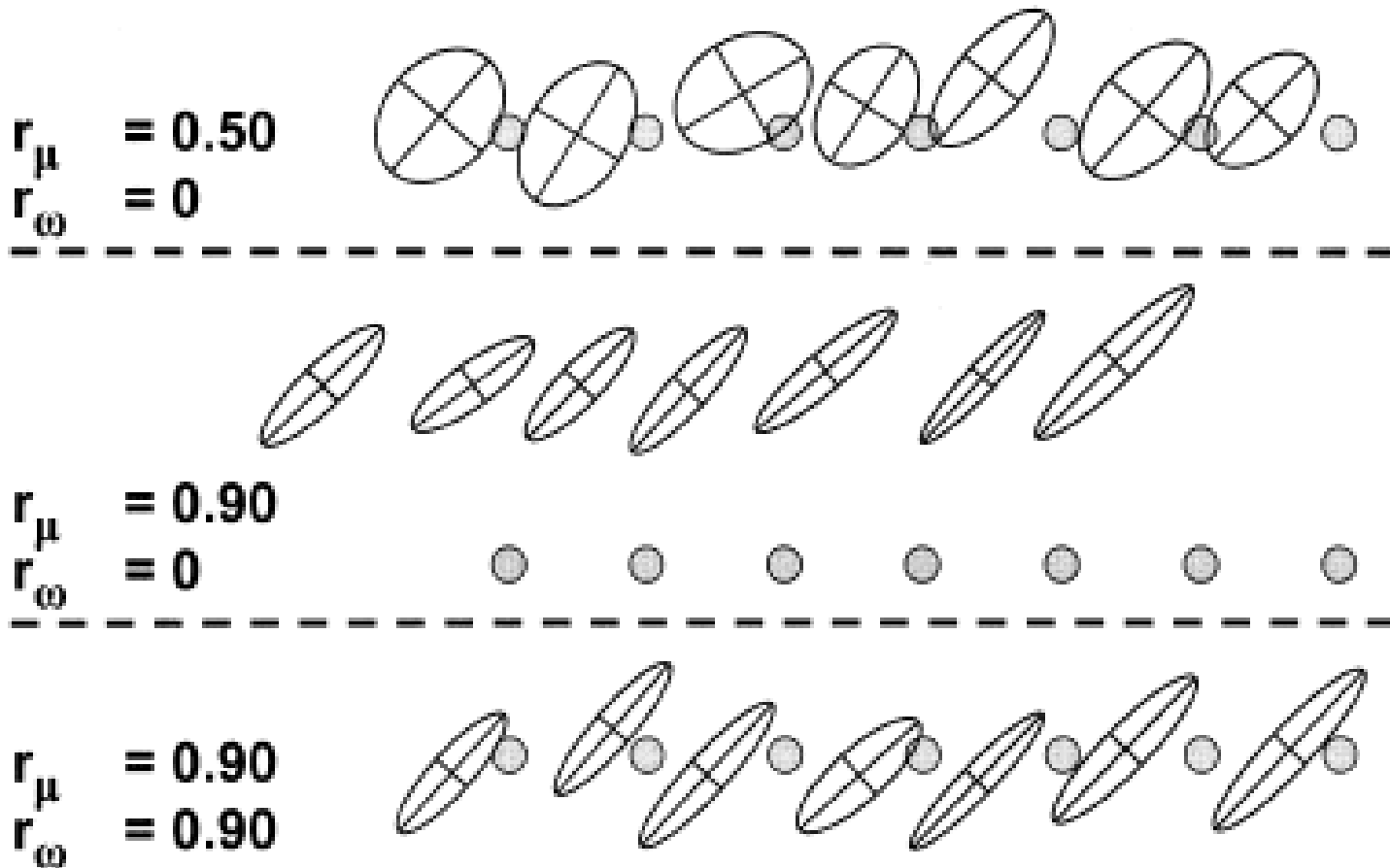# What happens when the optimum moves?
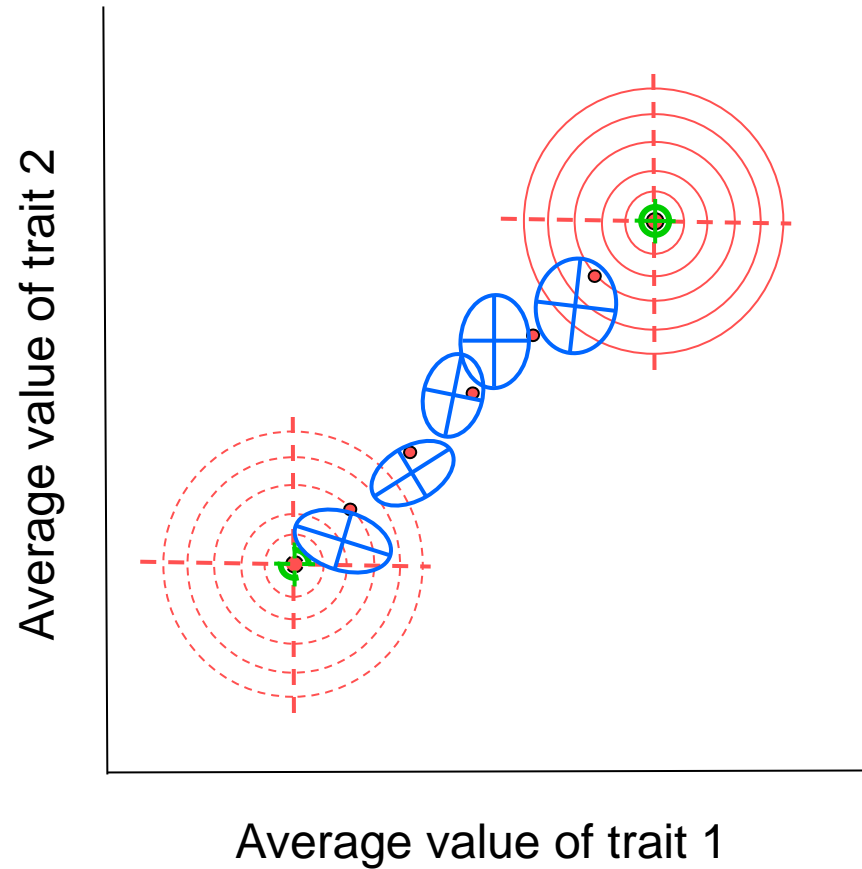
In the absence of mutational or selectional correlations, peak movement stabilizes the orientation of the **G**-matrix

r_ω	r_μ	$\Delta\theta$	ΔG_{11}	ΔG_{22}	Δr_g	$\Delta\lambda_1$	$\Delta\lambda_2$	$\Delta\Sigma$	$\Delta\varepsilon$	$\Delta\varphi$
0	0	●	0.037	0.037	0.026	0.036	0.037	0.027	0.050	9.0
0	0	↗	0.036	0.036	0.024	0.036	0.036	0.027	0.051	3.7
0	0	→	0.036	0.036	0.025	0.036	0.036	0.027	0.051	3.4
0	0	↘	0.036	0.036	0.024	0.036	0.036	0.026	0.051	3.8

Peak movement along a genetic line of least resistance stabilizes the **G**-matrix

Average value of trait 2

Average value of trait 1

Average value of trait 2

Average value of trait 1

Strong genetic correlations can produce a flying-kite effect

$r_\mu = 0.50$
$r_\omega = 0$

$r_\mu = 0.90$
$r_\omega = 0$

$r_\mu = 0.90$
$r_\omega = 0.90$

Direction of optimum movement →

Reconstruction of net-β
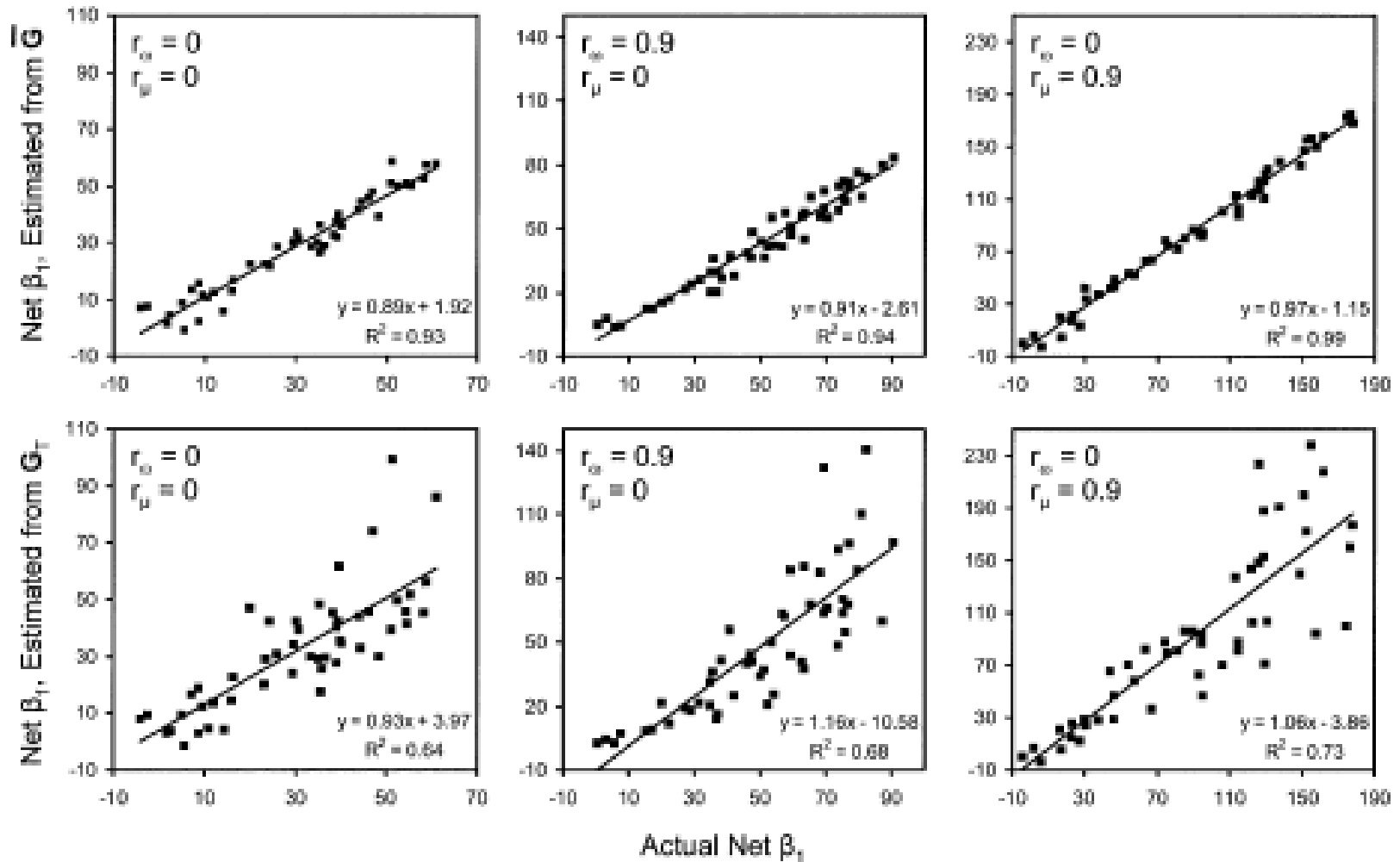
More realistic models of movement of the optimum

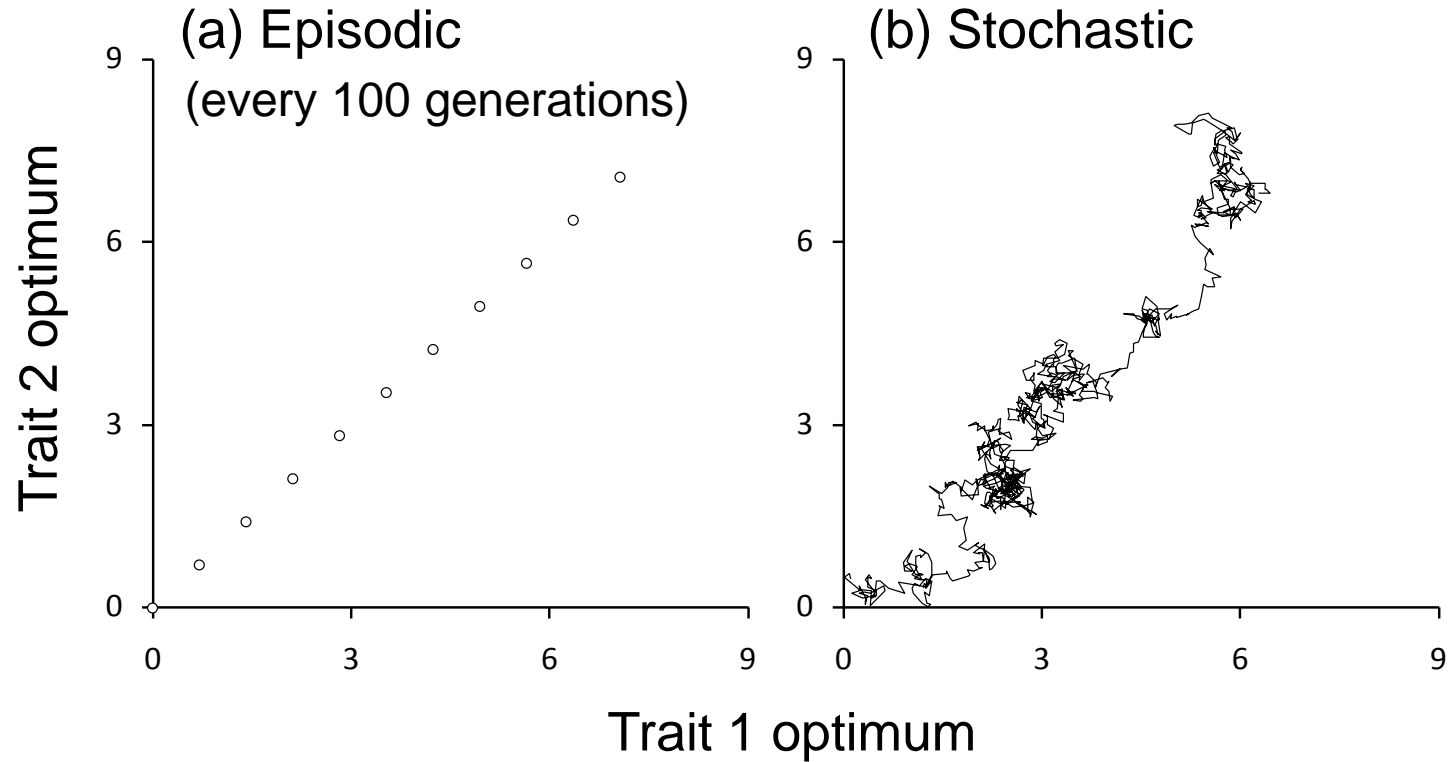# Steadily moving optimum
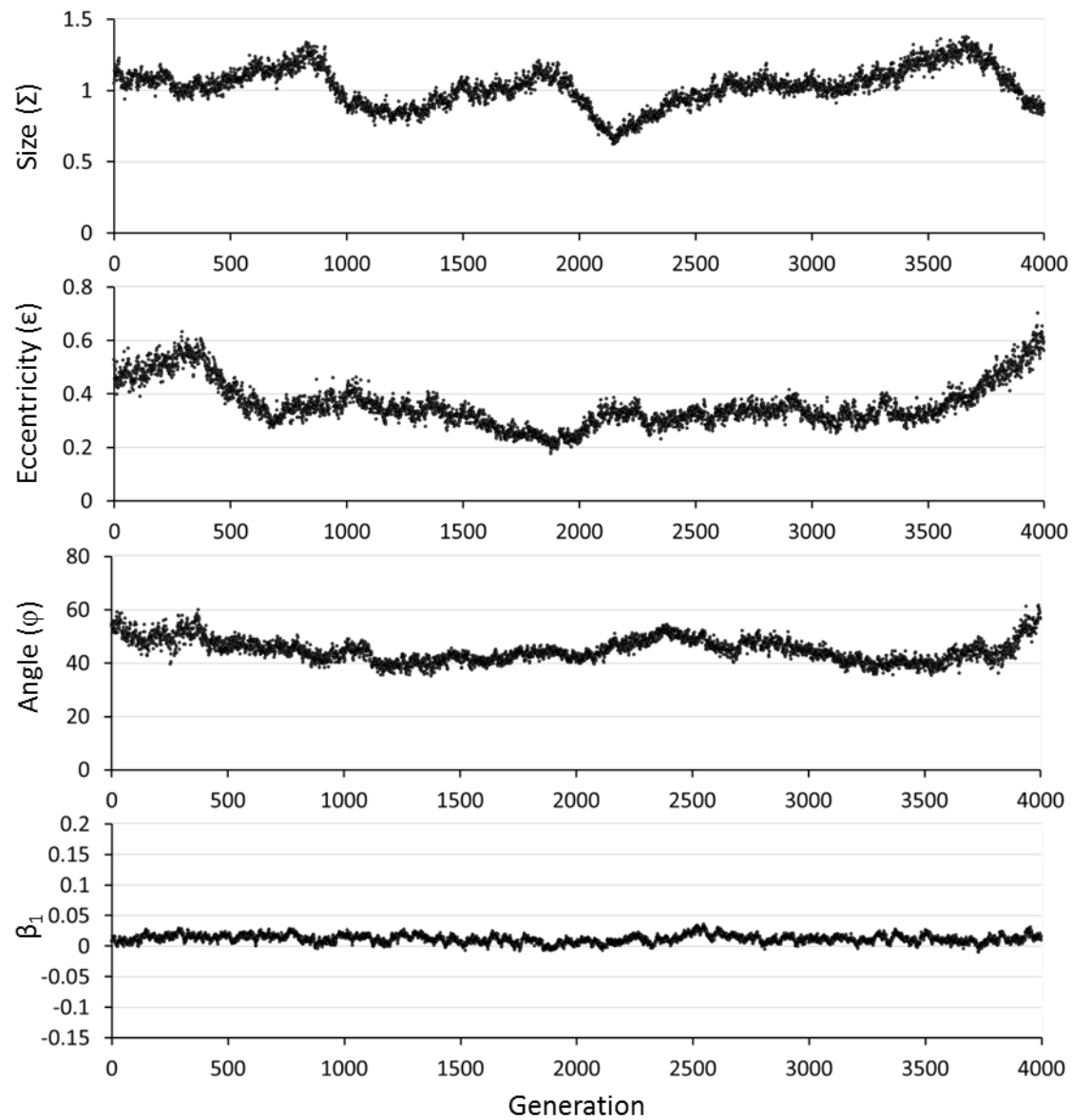
Episodically moving optimum

Cyclical changes in the genetic variance in response to episodic movement of the optimum
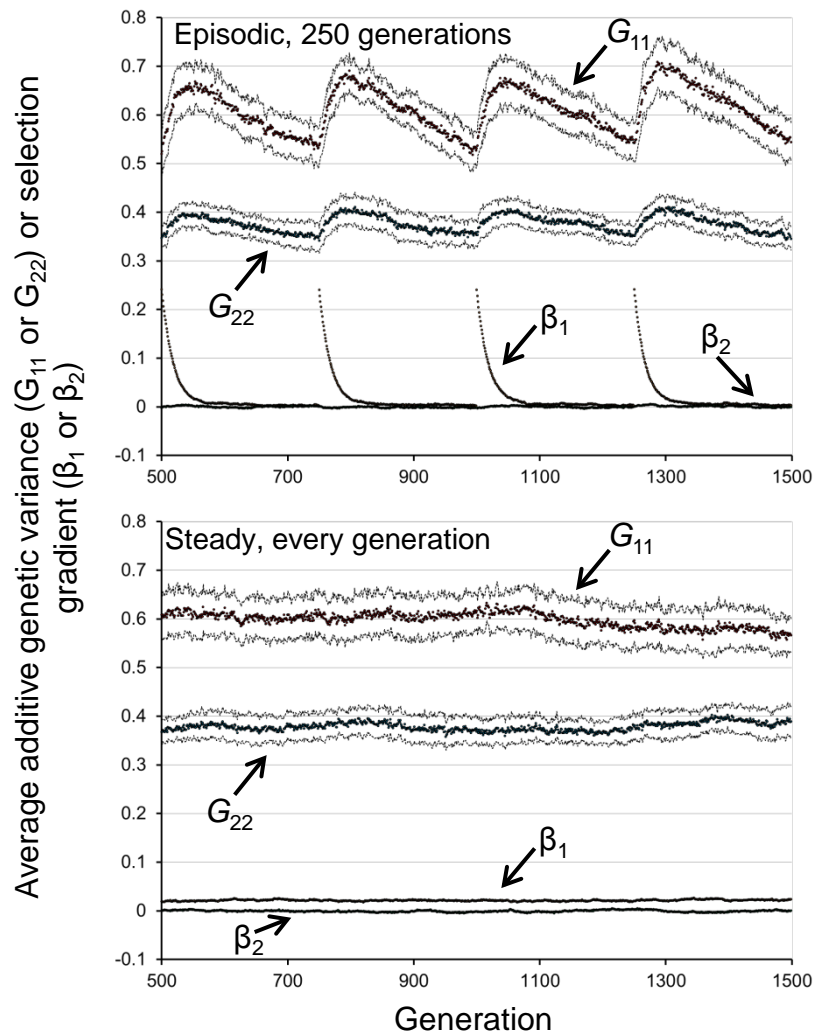
Effects of steady (or episodic) compared to stochastic peak movement

Steady movement, $r_\omega=0$, $r_\mu=0$

Stochastic, $r_\omega=0$, $r_\mu=0$, $\sigma_\theta^2=0.02$

Direction of peak movement

Static optimum

Moving optimum

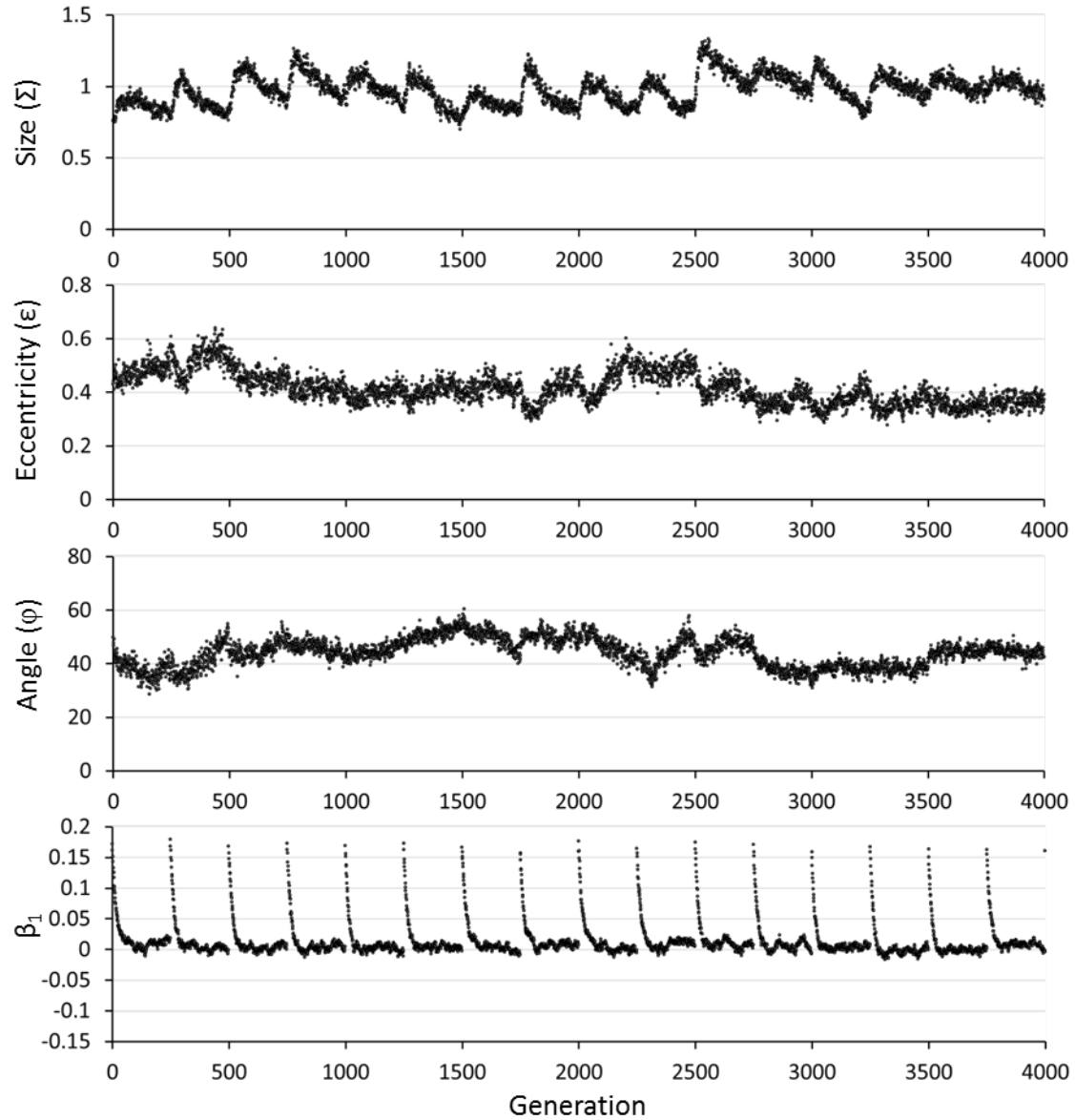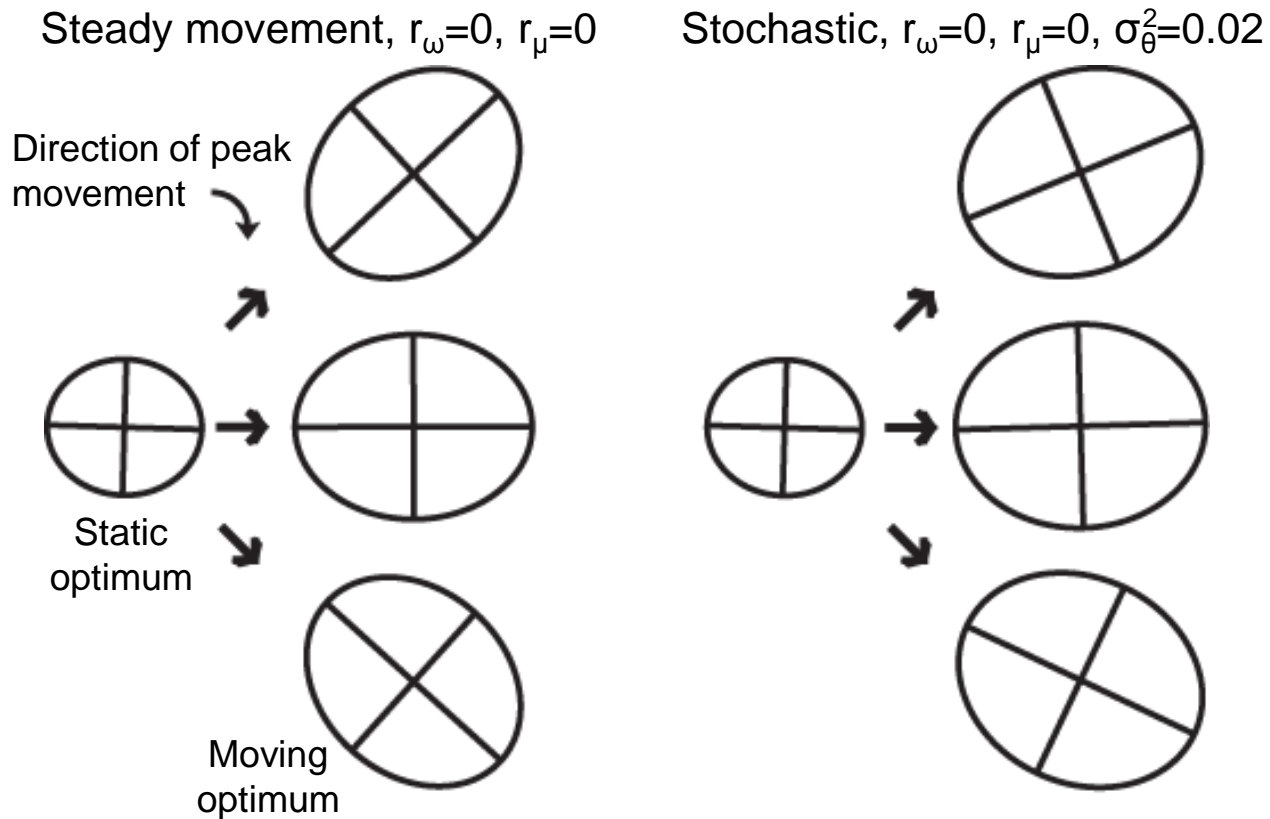# Episodic vs. stochastic

Episodic movement = smooth movement
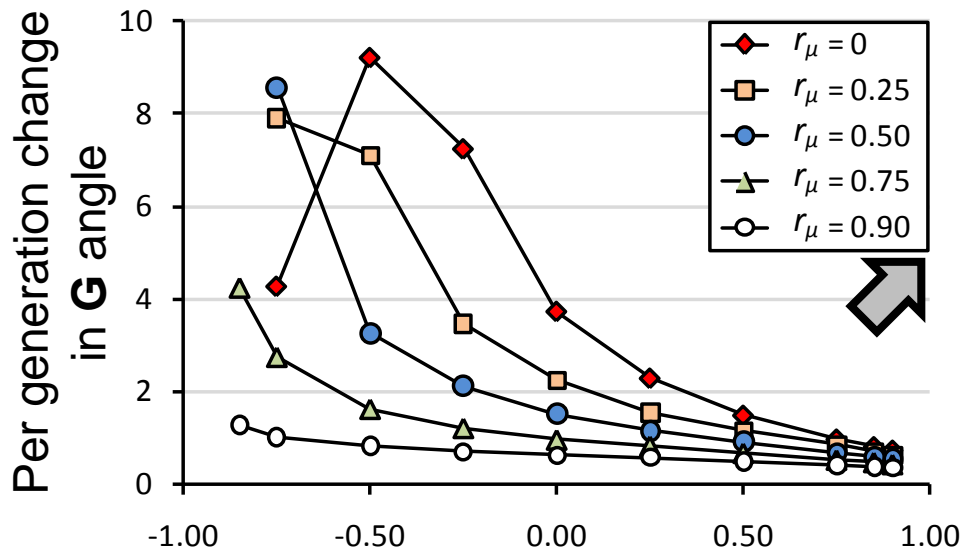
Stochastic movement

Stochastic peak movement destabilizes **G** under stability-conferring parameter combinations and stabilizes **G** under destabilizing parameter combinations.

Episodic and stochastic peak movement increase the risk of population extinction

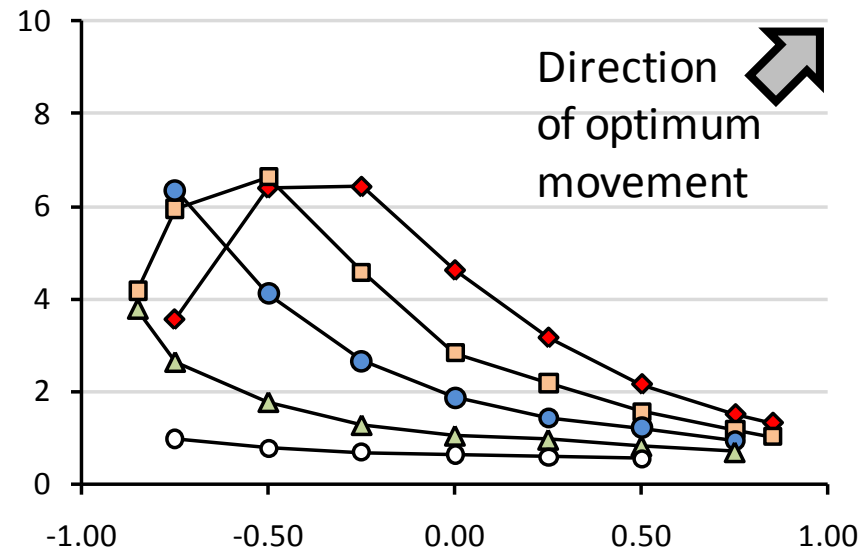| Model of Peak Movement			Parameters of selection and mutation			
Mode of and interval between peak movement (generations)	$\sigma_{\theta 1}^2 = \sigma_{\theta 2}^2$	$\Delta\theta$	$r_\omega = 0.75$ $r_\mu = 0$	$r_\omega = 0.75$ $r_\mu = 0.5$	$r_\omega = 0.9$ $r_\mu = 0.9$	$r_\omega = -0.75$ $r_\mu = 0.5$
Steady (1)	0	↗				
Steady (1)	0	→				
Steady (1)	0	↘				
Episodic (100)	0	↗				
Episodic (100)	0	→			ex	
Episodic (100)	0	↘			ex	
Episodic (250)	0	↗			ex	ex
Episodic (250)	0	→	ex	ex	ex	ex
Episodic (250)	0	↘	ex	ex	ex	
Stochastic (1)	0.01	↗			ex	
Stochastic (1)	0.01	→			ex	
Stochastic (1)	0.01	↘			ex	
Stochastic (1)	0.02	↗	ex	ex	ex	
Stochastic (1)	0.02	→	ex	ex	ex	
Stochastic (1)	0.02	↘	ex	ex	ex	

Conclusions

(1) The dynamics of the **G**-matrix under an episodically or stochastically moving optimum are similar in many ways to those under a smoothly moving optimum.

(2) Strong correlational selection and mutational correlations promote stability.

(3) Movement of the optimum along genetic lines of least resistance promotes stability.

(4) Alignment of mutation, selection and the **G**-matrix increase stability.

(5) Movement of the bivariate optimum stabilizes the **G**-matrix by increasing additive genetic variance in the direction the optimum moves.

(6) Both stochastic and episodic models of peak movement increase the risk of population extinction.

Conclusions

(7) Episodic movement of the optimum results in cycles in the additive genetic variance, the eccentricity of the **G**-matrix, and the per-generation stability of the angle.

(8) Stochastic movement of the optimum tempers stabilizing and destabilizing effects of the direction of peak movement on the **G**-matrix.

(9) Stochastic movement of the optimum increases additive genetic variance in the population relative to a steadily or episodically moving optimum.

(10) Selection skews the phenotypic distribution in a way that increases lag compared to expectations assuming a Gaussian distribution of breeding values. This phenomenon also results in underestimates of net-**β**.

(11) Many other interesting questions remain to be addressed with simulation-based models.

Epistasis and the evolution of **M**

- The mutational architecture, summarized by the **M**-matrix, plays a huge role in generating evolutionary constraints

- What evolutionary phenomena shape the mutational architecture?

- Epistatic interactions provide a realistic, natural way for the M-matrix to evolve

Epistasis – The Multilinear Model

- Our model of epistasis is a multivariate extension of the multilinear model of Hansen and Wagner (2001):

  Additive model:

  $$z = a_1 + a_2 + a_3 + \ldots + e$$

  Multilinear model:

  $$z = a_1 + a_2 + \varepsilon a_1 a_2 + \ldots + e$$

  It's only slightly more complex for the multivariate case

Epistasis Results

- Does epistasis increase genetic variation?

ε variance	r_ω	V_1	V_2	r_V	G_1	G_2	r_G	% additive
0	0	0.53	0.51	0.02	0.52	0.50	0.02	100
0.1	0	0.59	0.59	0.01	0.54	0.54	-0.01	92
1.0	0	0.75	0.79	0.00	0.60	0.63	0.01	80
10.0	0	0.75	0.74	0.01	0.46	0.44	-0.01	61
0	0.75	0.41	0.39	0.27	0.41	0.39	0.28	100
0.1	0.75	0.44	0.44	0.31	0.40	0.41	0.37	91
1.0	0.75	0.45	0.44	0.28	0.36	0.35	0.37	80
10.0	0.75	0.42	0.40	0.19	0.25	0.25	0.31	61

Generations = 5000, N = 512, ω = 49, μ = 0.0005

Epistasis Results

- Does epistasis increase genetic variation?

ε variance	r_ω	V_1	V_2	r_V	G_1	G_2	r_G	% additive
0	0	0.53	0.51	0.02	0.52	0.50	0.02	100
0.1	0	0.59	0.59	0.01	0.54	0.54	-0.01	92
1.0	0	0.75	0.79	0.00	0.60	0.63	0.01	80
10.0	0	0.75	0.74	0.01	0.46	0.44	-0.01	61
0	0.75	0.41	0.39	0.27	0.41	0.39	0.28	100
0.1	0.75	0.44	0.44	0.31	0.40	0.41	0.37	91
1.0	0.75	0.45	0.44	0.28	0.36	0.35	0.37	80
10.0	0.75	0.42	0.40	0.19	0.25	0.25	0.31	61

Generations = 5000, N = 512, ω = 49, μ = 0.0005

Epistasis Results

- Epistasis allows selection to shape the distribution of new mutations

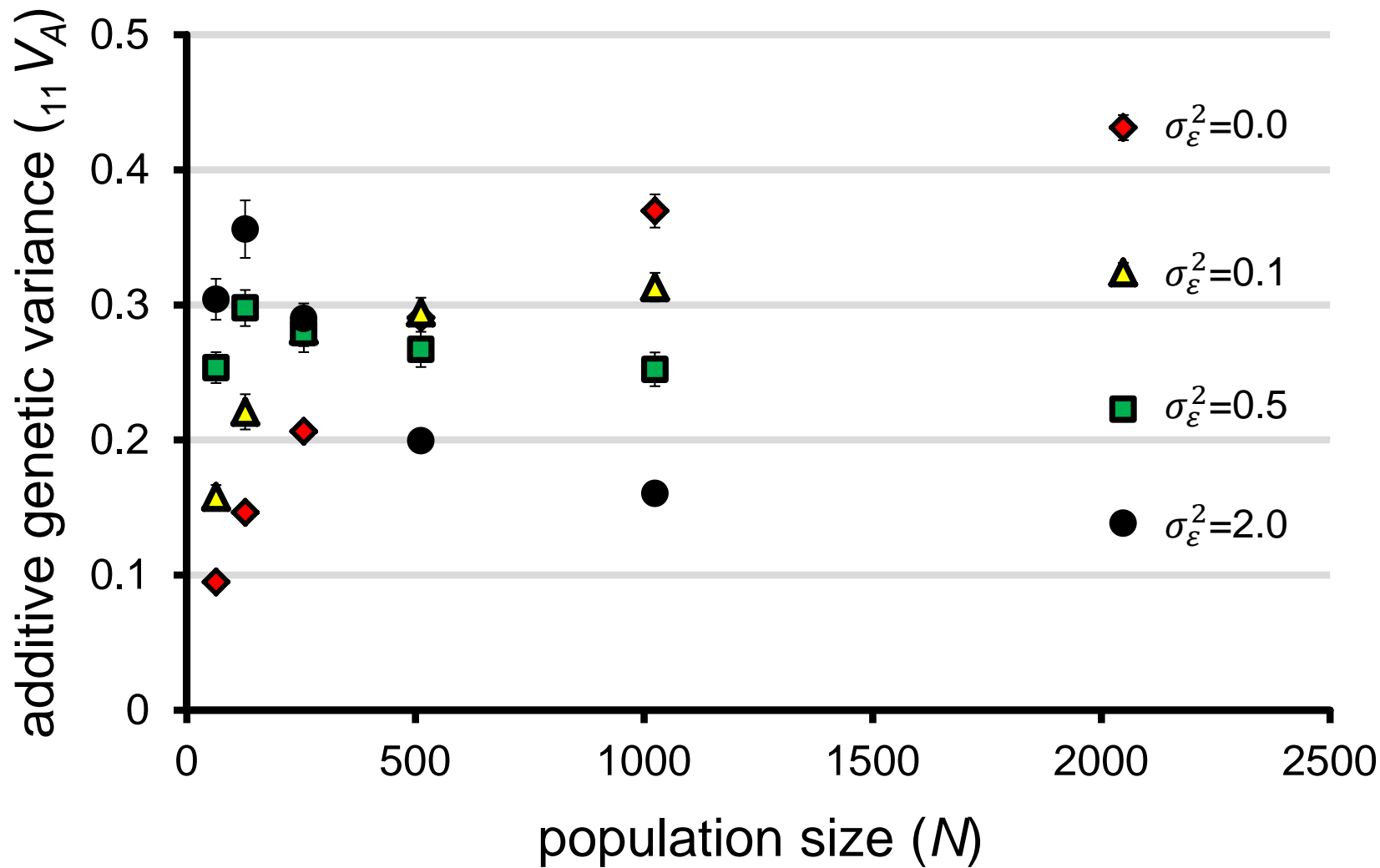| N	r_ω	V_1	V_2	r_V	M_1	M_2	r_μ
128	0	0.77	0.79	0.05	0.71	0.82	0.02
256	0	0.80	0.84	-0.02	0.46	0.50	-0.01
1024	0	0.70	0.70	0.00	0.17	0.16	-0.01
2048	0	0.68	0.65	-0.02	0.14	0.14	-0.01
128	0.90	0.33	0.32	0.41	0.43	0.42	0.08
256	0.90	0.33	0.33	0.45	0.24	0.26	0.14
1024	0.90	0.28	0.28	0.40	0.11	0.12	0.16
2048	0.90	0.26	0.27	0.40	0.10	0.10	0.18

Generations = 5000, ε variance = 1.0, ω = 49, μ = 0.0005
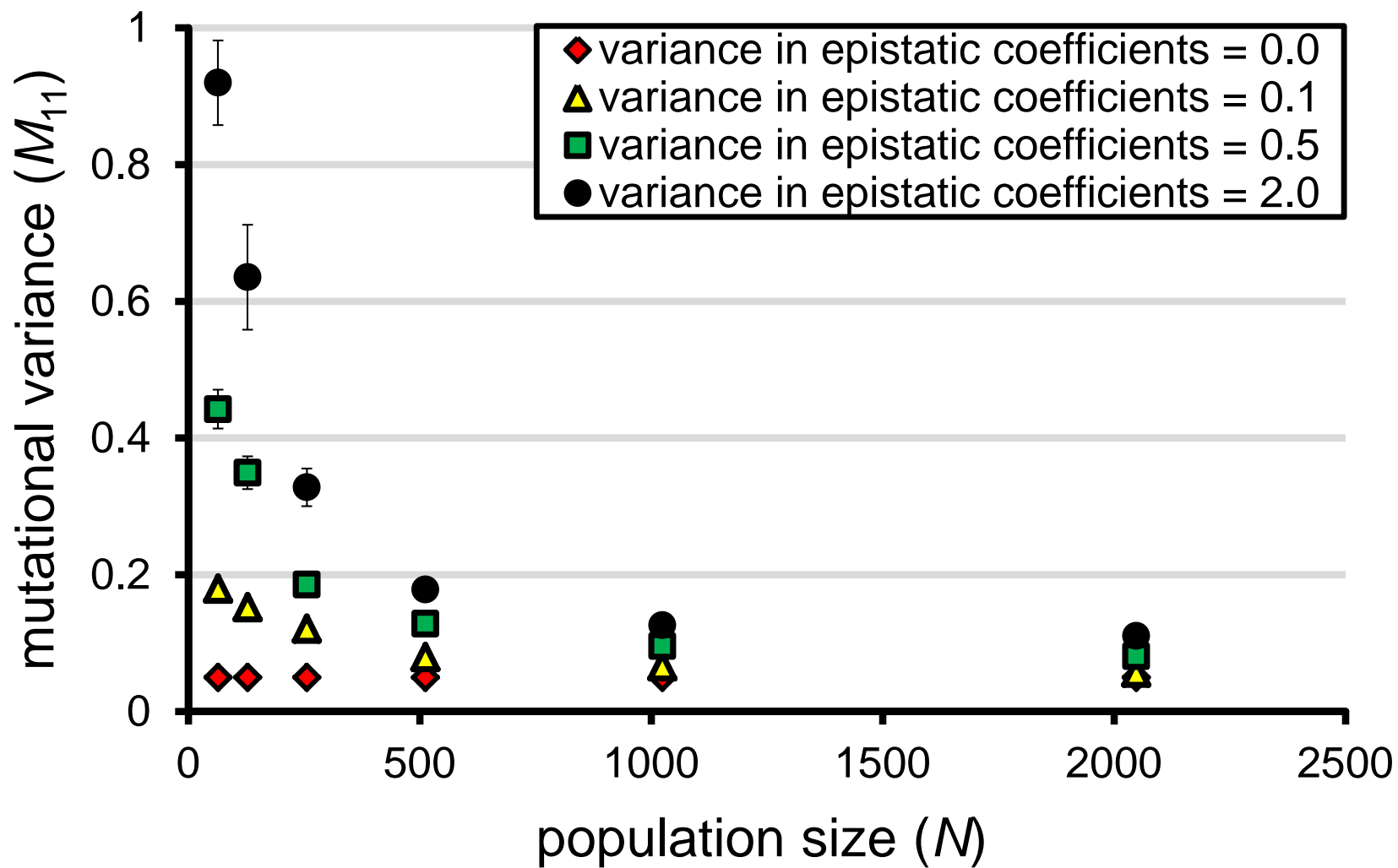
Epistasis Results

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N	r_ω	V_1	V_2	r_V	M_1	M_2	r_μ
128	0	0.77	0.79	0.05	0.71	0.82	0.02
256	0	0.80	0.84	-0.02	0.46	0.50	-0.01
1024	0	0.70	0.70	0.00	0.17	0.16	-0.01
2048	0	0.68	0.65	-0.02	0.14	0.14	-0.01
128	0.90	0.33	0.32	0.41	0.43	0.42	0.08
256	0.90	0.33	0.33	0.45	0.24	0.26	0.14
1024	0.90	0.28	0.28	0.40	0.11	0.12	0.16
2048	0.90	0.26	0.27	0.40	0.10	0.10	0.18

Generations = 5000, ε variance = 1.0, ω = 49, μ = 0.0005

$$\omega = \begin{bmatrix} 93 & 0 \\ 0 & 5 \end{bmatrix}$$

$$G = \begin{bmatrix} 0.262 & 0.000 \\ 0.000 & 0.079 \end{bmatrix}$$

$$M = \begin{bmatrix} 0.103 & 0.000 \\ 0.000 & 0.072 \end{bmatrix}$$

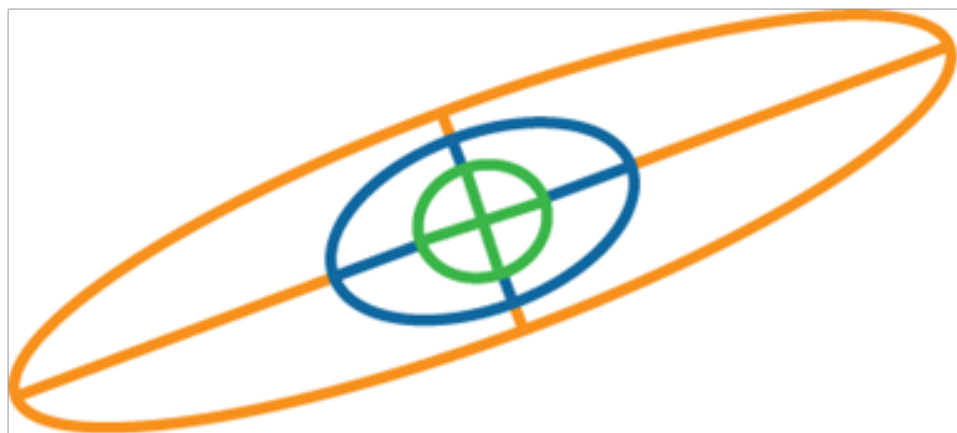$$\omega = \begin{bmatrix} 82 & 30.0 \\ 30.0 & 16 \end{bmatrix}$$

$$G = \begin{bmatrix} 0.239 & 0.060 \\ 0.060 & 0.102 \end{bmatrix}$$

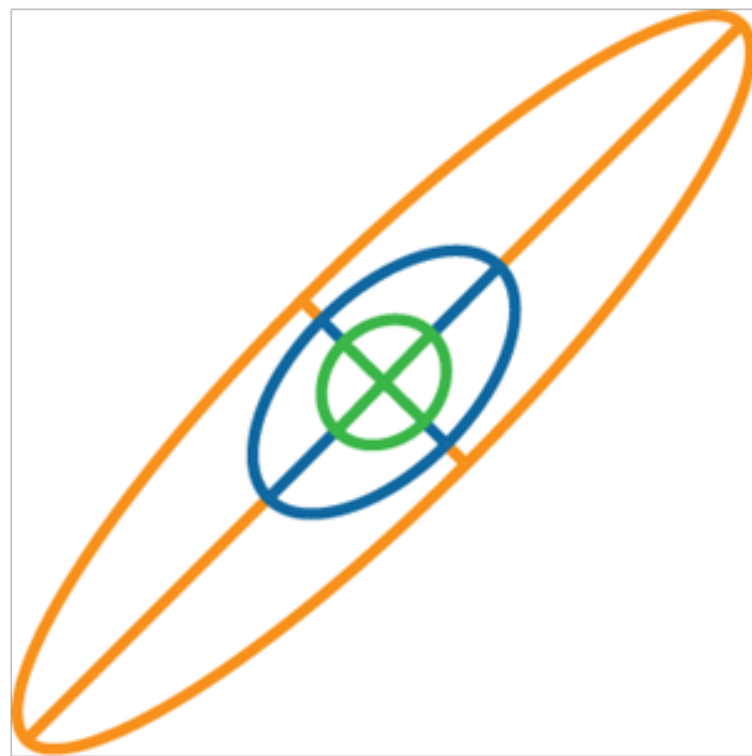$$M = \begin{bmatrix} 0.097 & 0.008 \\ 0.008 & 0.075 \end{bmatrix}$$

$$\omega = \begin{bmatrix} 49 & 44.1 \\ 44.1 & 49 \end{bmatrix}$$

$$G = \begin{bmatrix} 0.174 & 0.096 \\ 0.096 & 0.175 \end{bmatrix}$$

$$M = \begin{bmatrix} 0.089 & 0.016 \\ 0.016 & 0.090 \end{bmatrix}$$

Conclusions from the Model

- Epistasis allows natural selection to shape the mutational architecture of traits.

- Smaller populations evolve larger mutational variances.

- Smaller populations harbor more genetic variance than larger populations in this model.

- Triple alignment: the selection surface, **G**-matrix, and **M**-matrix evolve to be in nearly perfect alignment.

Implications

- High apparent additive genetic variation doesn't necessarily imply that the underlying genetic architecture involves only independent, additive loci (much of the additive genetic variance can arise from epistatic terms).

- Mutational variances and covariances can be shaped by selection when epistasis enters the picture.

- For traits affected by large numbers of genes there could be hundreds or thousands of epistatic interactions, which may be difficult to diagnose in genome-wide association studies or QTL mapping studies.

- The mutational architecture, which we like to think of as separate from natural selection, could itself be a product of historical patterns of selection.

Using the Simulation Program

- A fully factorial approach is prohibitively time consuming, because the model has too many parameters

- Think in terms of experimental design, with controls and treatments

- Start with a core set of parameters and vary one or two parameters at a time

- The default values provide a reasonable starting place (but possibly remove stochasticity, use a stationary optimum, and increase curvature of the selection surface by setting ω to 9 instead of 49)

Simulation Parameters

Number of Loci	50
Number of Offspring per Adult	2
No. Females in Population	128
Mutation Rate (per 1,000,000)	200
Number of Traits	2
No. of Experimental Generations	1000	Trait 2:
Mutation Variance (in hundredths)	5	5
Strength of selection (w2)	9	9
No. Initial Gens (Stationary Opt)	1000
No. Complete Replications	5
Mut. Corr. Traits 1, 2 (hundredths)	75
Sel. Corr. Traits 1, 2 (hundredths)	0	Trait 2:
Str. sel'n after peak shift (w2)	9	9
Sel. Corr. after sel'n (hundredths)	0	Trait 2:
Trait optima shift (real number)	0.01	0
Calc. G every ___ generation(s)	1
Move peak at generation	1
Calc. equil. values over ___ gens	500
Draw G every ___ generations	0	(0 = animate)
Drawing scale constant	20
Size of image (X, Y dimensions)	1000	500
Location of starting optimum (x, y)	200	250
No. Initial Gens (Moving Optimum)	0	Trait 2:
Var. in Optimum Position (real no.)	0.0005	0.0005

○ Move Peak Once
● Move Peak Repeatedly

☐ Begin with no genetic var.

Okay   Cancel

Annotations:

If you make the number of loci too small, the program will probably crash because you won't maintain any genetic variance

Each female has 2x this number of offspring

The sex ratio is equal and you're changing the number of females

This mutation rate is 0.0002 – too small will result in no variance

Mutational variances for traits 1 and 2 (5 means 0.05)

Smaller values result in a steeper selection surface

How many simulation runs under these parameter values? Not the number of generations, which are set separately.

Mutational correlation – very important – can be between -100 and 100

Selectional correlation – set both values, generally to the same number

How far does the optimum move for trait 1 and trait 2?

What generation (Move Peak Once) or how often (Move Peak Repeatedly) does the optimum move?

These parameters set the graphical window's properties – experiment

If you want some generations of a moving optimum, with no data collected, set them here

Stochasticity in the position of the optimum – set this to zero for starters

Once – the bivariate optimum moves once at generation "Move peak at generation" by "Trait Optima Shift Units". Repeatedly – the peak moves every "Move peak at generation" generations by the "Trait Optima Shift".

G-matrix simulations

File   Run

☐ Save Individual Runs

```
Parameter Values:
2      Loci
2      Offspring per adult
128    Females in population
200    Mutations per 1,000,000
2      Traits
1000   Experimental generations
5      Mutational variance trait 1 (in hundredths)
9      w2 (trait 1) during stabilizing selection
1000   Initial generations of stab. sel'n
5      Total repetitions
75     Mutational correlation (in hundredths)
0      Stab. selection correlation (in hundredths)
9      w2 (trait 2) during stabilizing selection
5      Mutational variance trait 2 (in hundredths)
9      w2 (trait 1) after peak shift
9      w2 (trait 2) after peak shift
0      Selection correlation after shift (hundredths)
0.01   Trait 1 optimum shift
0      Trait 2 optimum shift
0.0005     Trait 1 optimum variance
0.0005     Trait 2 optimum variance
1      Interval between calculations of G
1      Generation at which peak shift occurred
       Peak moves multiple times.
Gen   Opt(1)    Opt(2)    z-bar(1)   z-bar(2)   P(11)     P(22)     P(12)     G(11)     G(22)
```

3/5 running. Path: Null

G-matrix image