

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

Adam G. Jones (Texas A&M Univ.)

Stevan J. Arnold (Oregon State Univ.)

Reinhard Bürger (Univ. Vienna)

$$\Delta \bar{\mathbf{z}} = \mathbf{G} \boldsymbol{\beta}$$

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

$\boldsymbol{\beta}$ is a vector of directional selection gradients.

\mathbf{G} is the genetic variance-covariance matrix.

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

$$\boldsymbol{\beta}_T = \mathbf{G}^{-1} \Delta \mathbf{z}_T$$

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 \mathbf{G} must be representative of \mathbf{G} over the time period in question. **\mathbf{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).

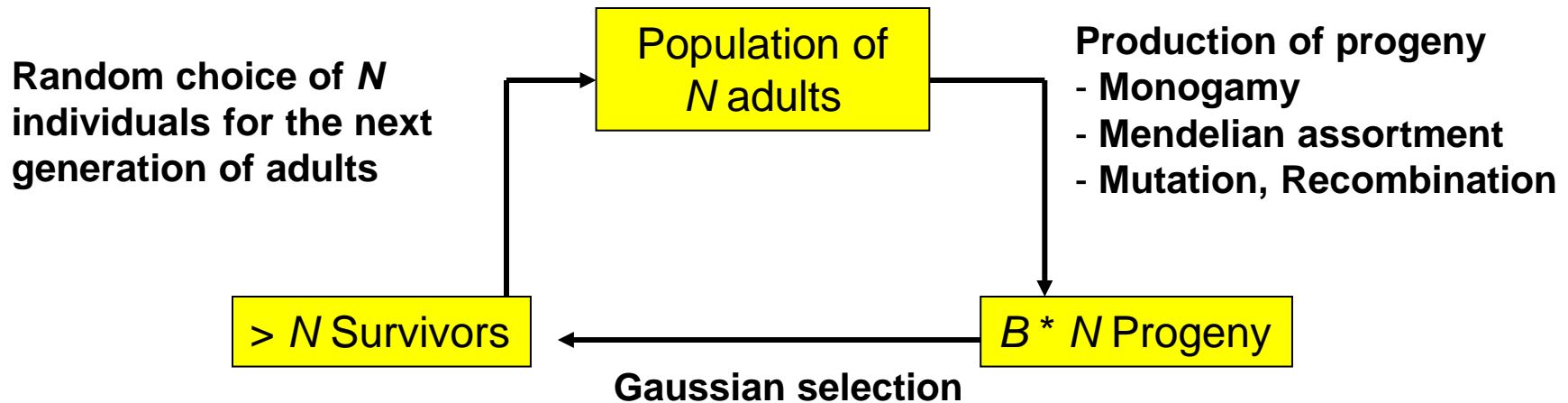
Study Background and Objectives

- 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

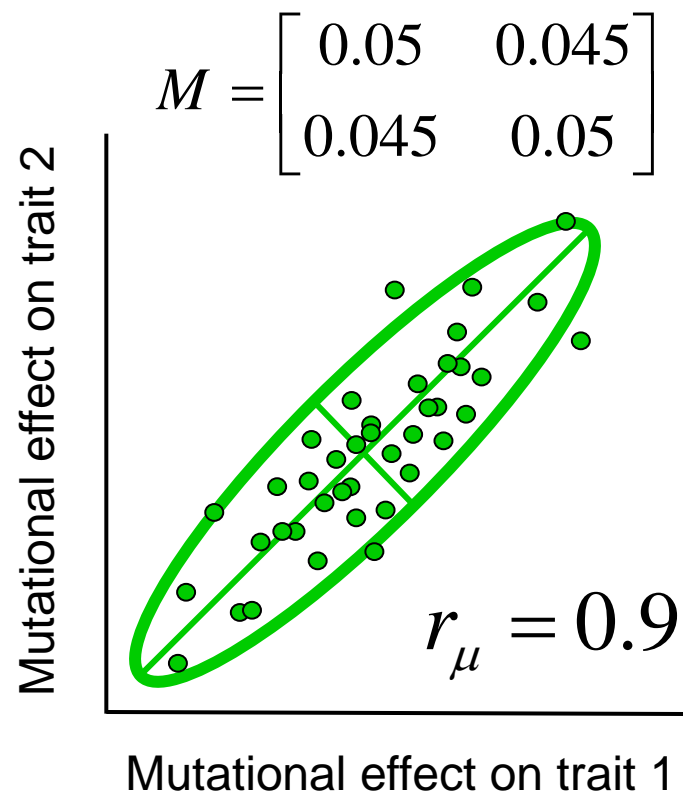
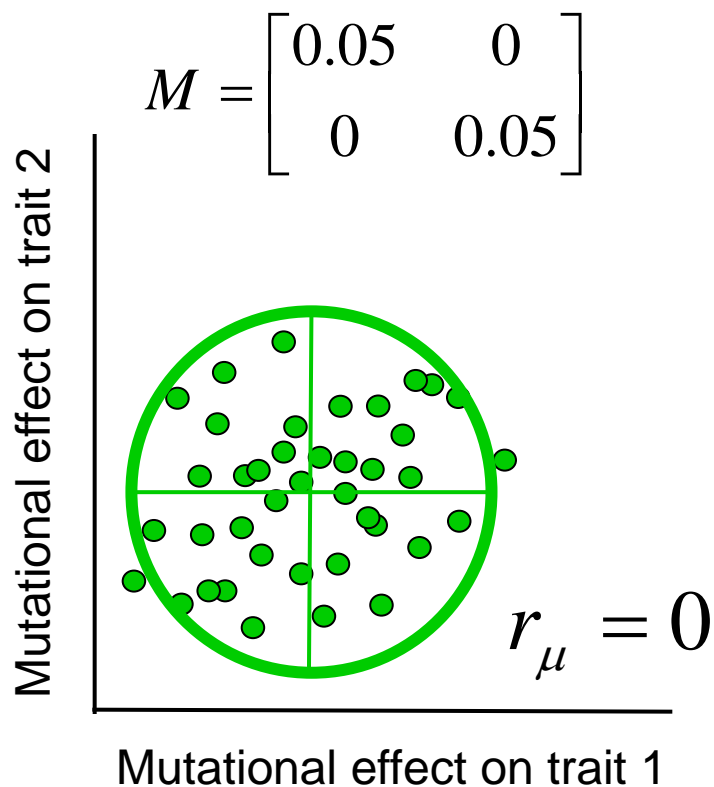
- *Direct Monte Carlo simulation with each gene and individual specified*
- *Two traits affected by 50 pleiotropic loci*
- *Additive inheritance with no dominance or epistasis*
- *Allelic effects drawn from a bivariate normal distribution with means = 0, variances = 0.05, and mutational correlation $r_\mu = 0.0-0.9$*
- *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 $\omega = 9$ or 49*
- *Each simulation run equilibrated for 10,000 (non-overlapping) generations, followed by several thousand of experimental generations*

Methods – The Simulation Model (continued)

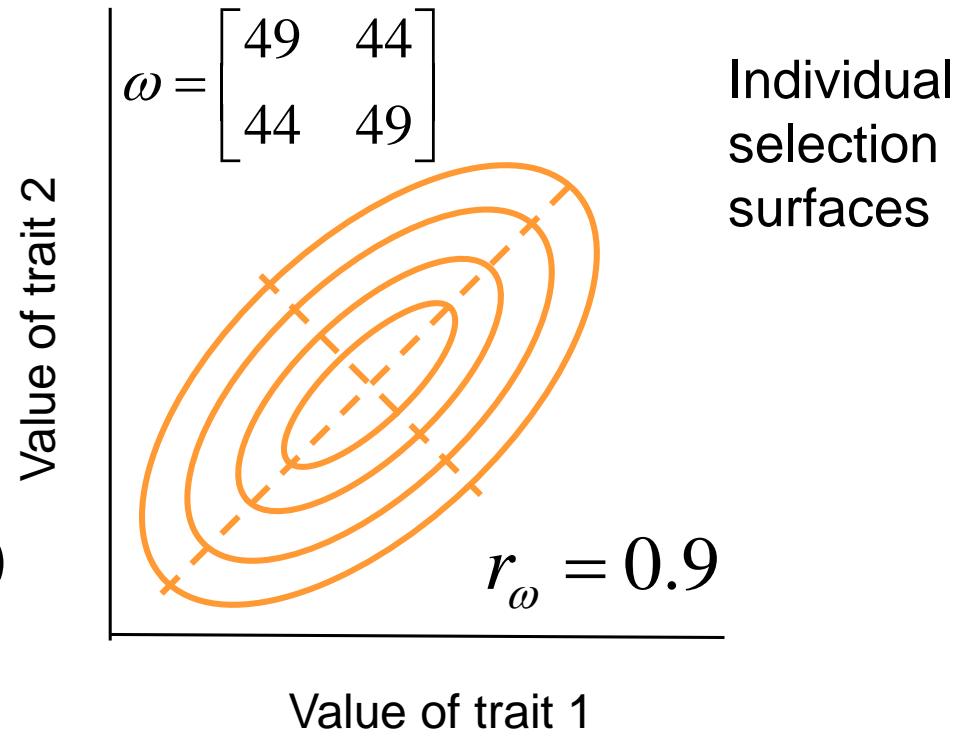
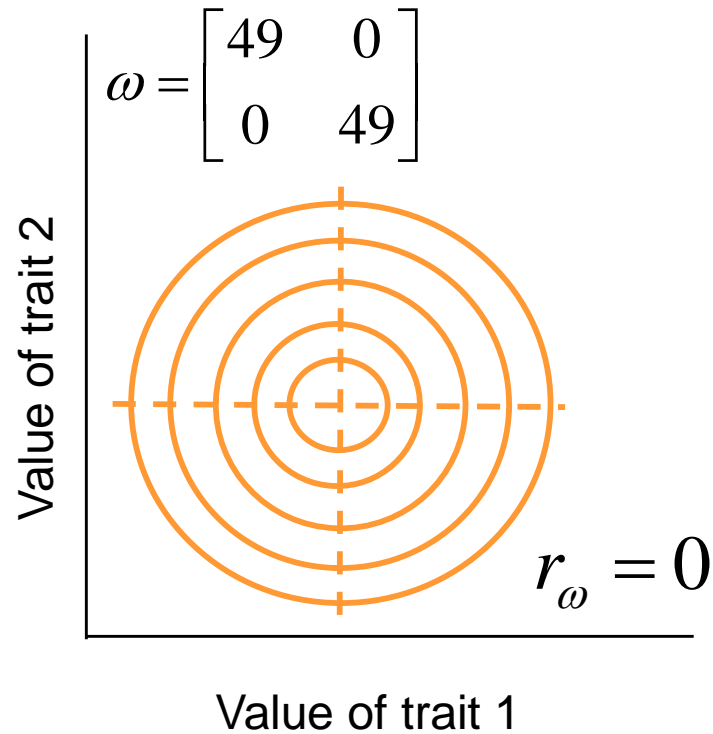


- Start with a population of genetically identical adults, and run for 10,000 generations to reach a mutation-selection-drift equilibrium.
- Impose the desired model of movement of the optimum.
- Calculate **G**-matrix over the next several thousand generations (repeat 20 times).
- We focus on average single-generation changes in **G**, because we are interested in the effects of model parameters on relative stability of **G**.

Mutation conventions

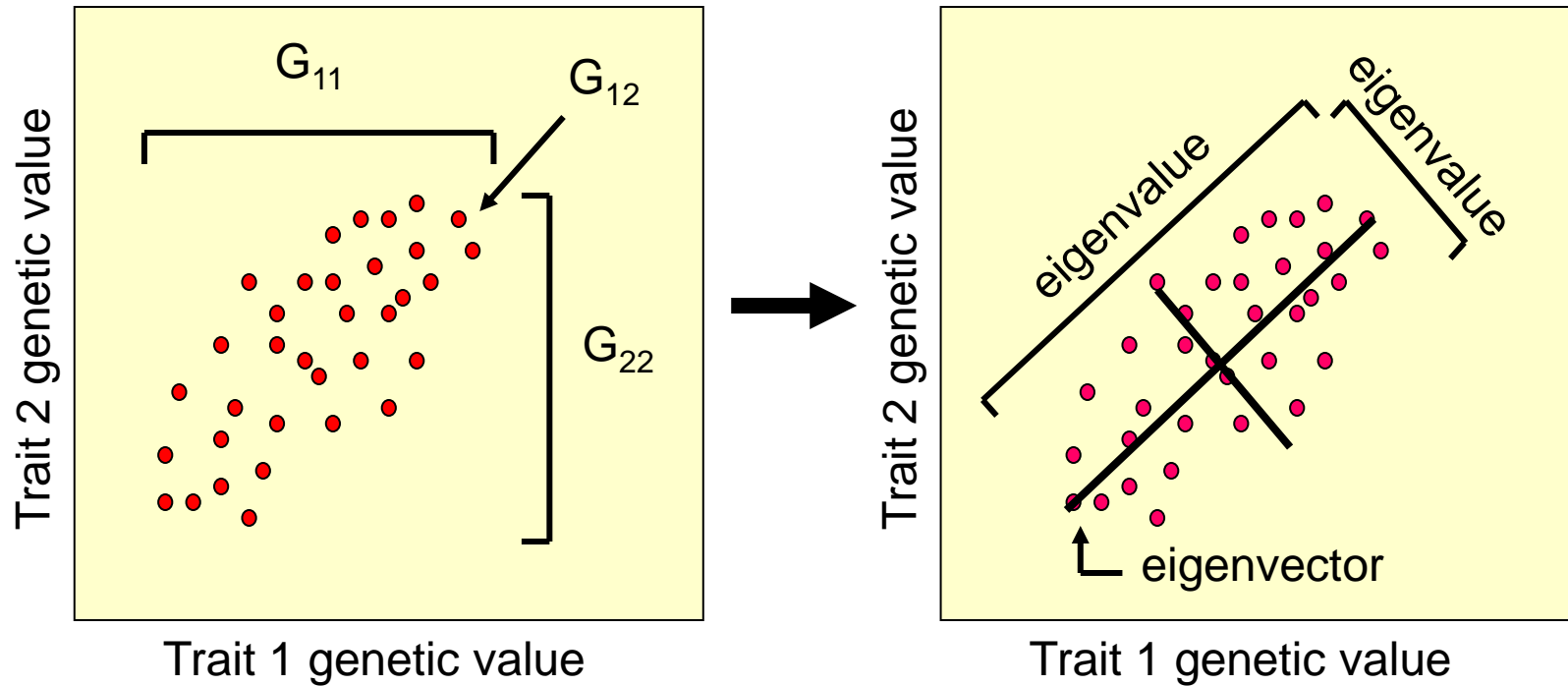


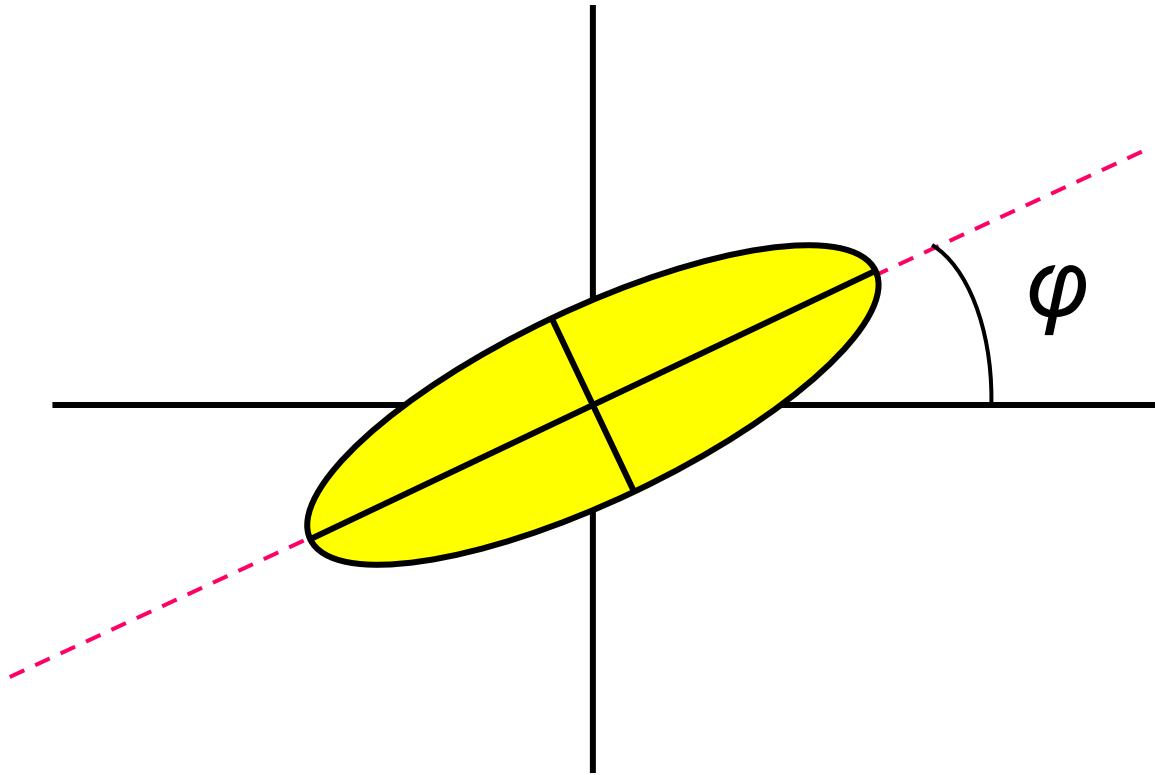
Selection conventions



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 .

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 | Trait 2: |
| Sel. Corr. Traits 1, 2 (hundredths) | 0 | 9 |
| Str. sel'n after peak shift (w2) | 9 | Trait 2: |
| Sel. Corr. after sel'n (hundredths) | 0 | 0 |
| Trait optima shift (real number) | 0.01 | |
| 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

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".

Save the contents of the text window

Run the simulation

Set parameters

Check this box to have the program save each run in a separate ".csv" file – uncheck and recheck the box to change filename

The screenshot shows the 'G-matrix simulations' application window. The title bar includes standard window controls and a 'Picture Tools' button. The menu bar contains 'File' and 'Run'. The toolbar includes icons for saving, running, and a key icon, followed by a checkbox labeled 'Save Individual Runs'. Annotations with arrows point to these elements: 'Save the contents of the text window' points to the save icon; 'Run the simulation' points to the run icon; 'Set parameters' points to the key icon; and the instruction about saving runs points to the 'Save Individual Runs' checkbox.

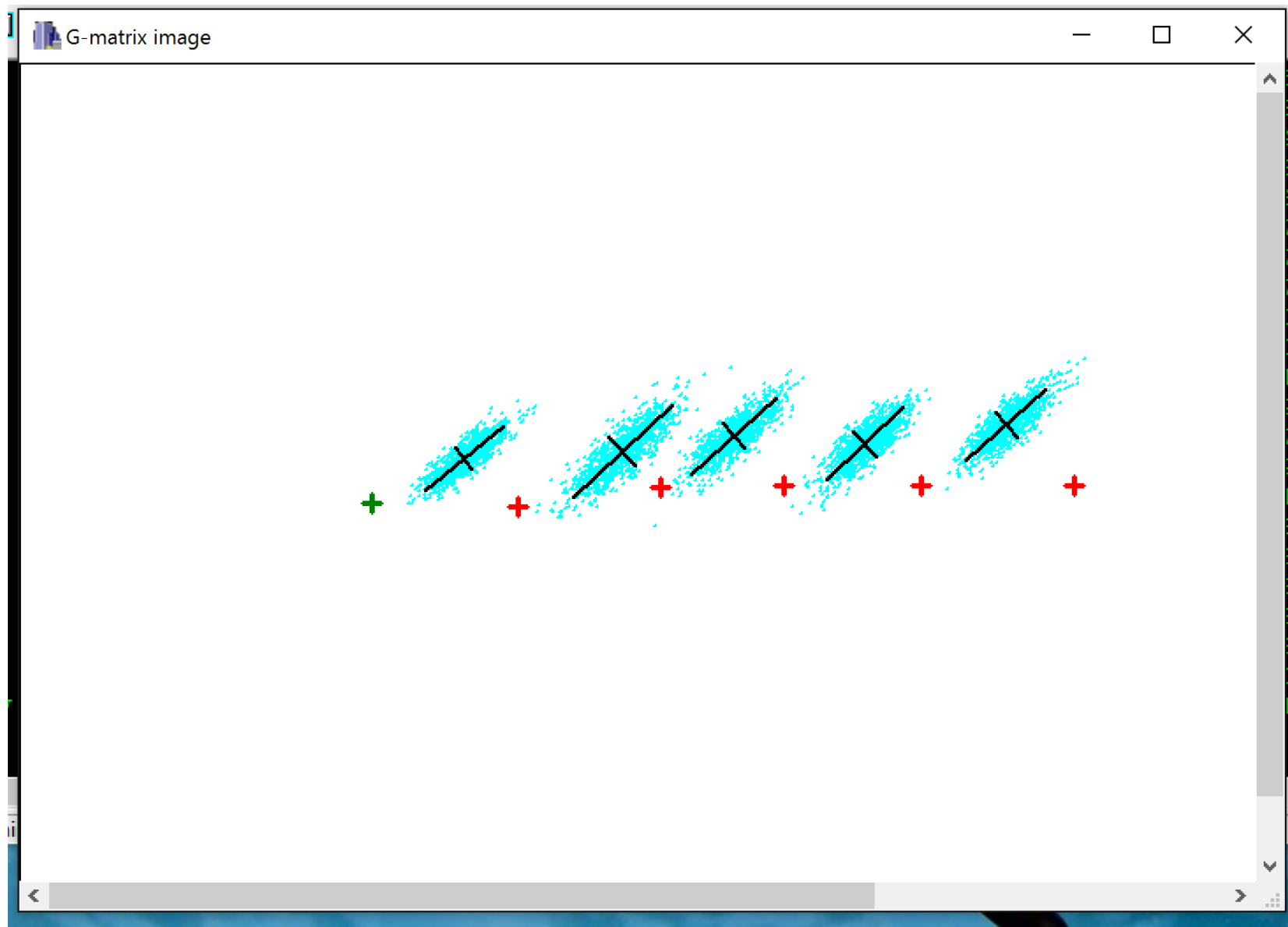
Parameter Values:

```
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) |
|-----|--------|--------|----------|----------|-------|-------|-------|-------|-------|
| < | | | | | | | | | > |

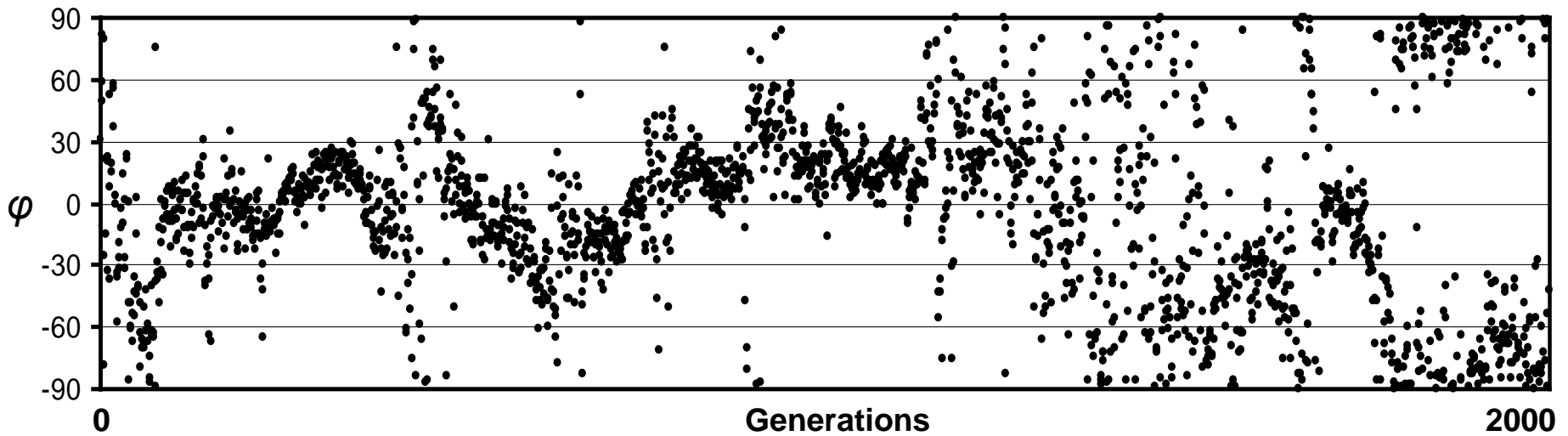
3/5 running. Path: Null



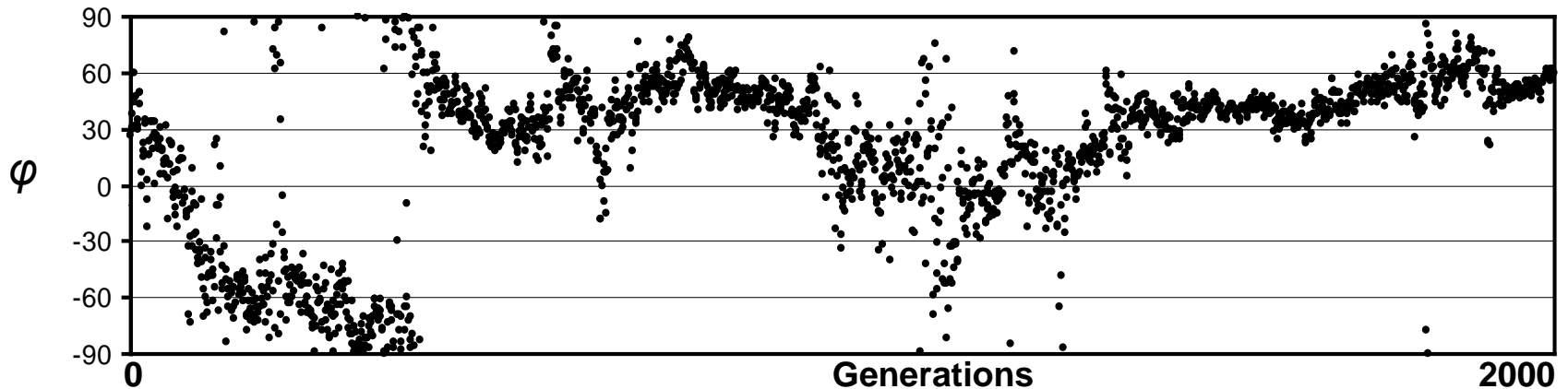


Stationary Optimum

(selectional correlation = 0, mutational correlation = 0)

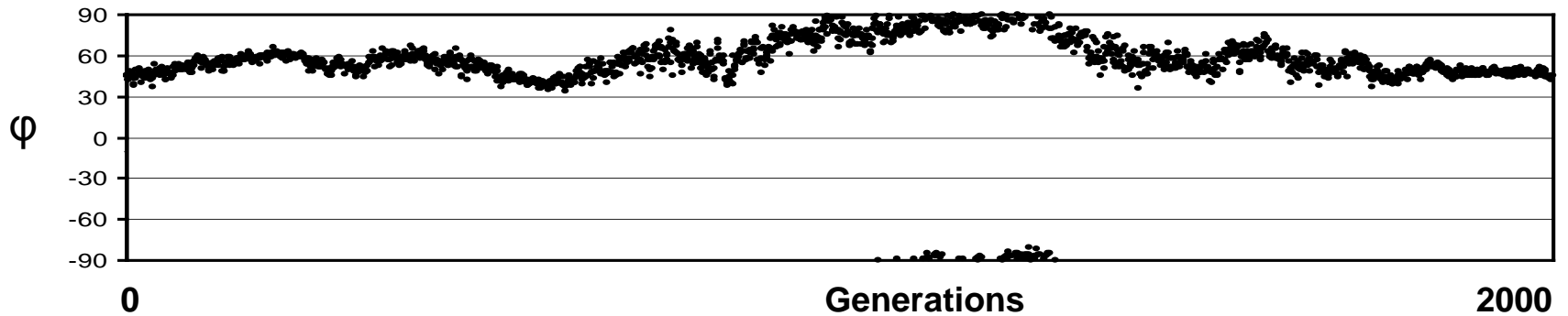


Stronger correlational selection produces a more stable **G**-matrix
(selectional correlation = 0.75, mutational correlation = 0)



| ω (trait 1) | ω (trait 2) | $r(\omega)$ | $r(\mu)$ | $\Delta\phi$ |
|--------------------|--------------------|-------------|----------|--------------|
| 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 |

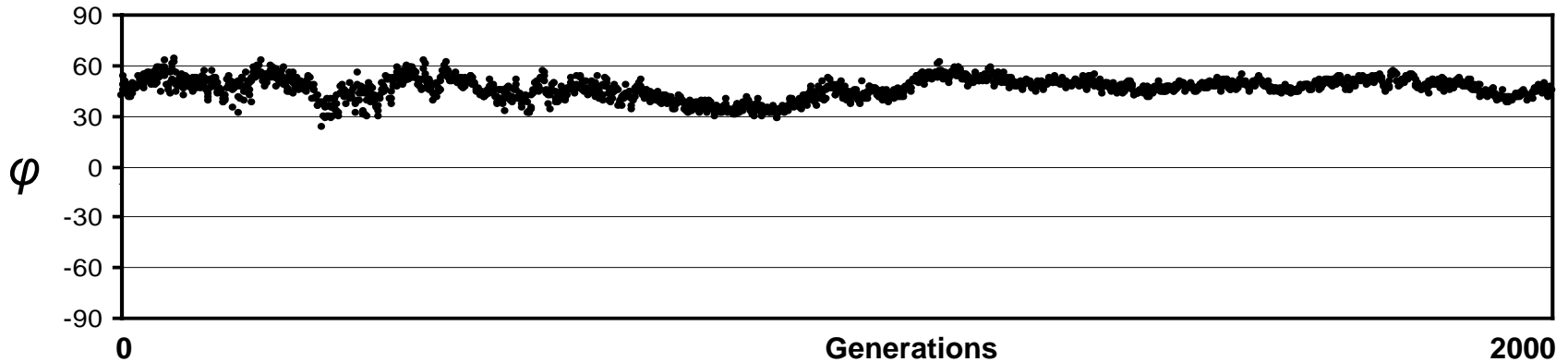
A high correlation between mutational effects produces stability
(selectional correlation = 0, mutational correlation = 0.5)



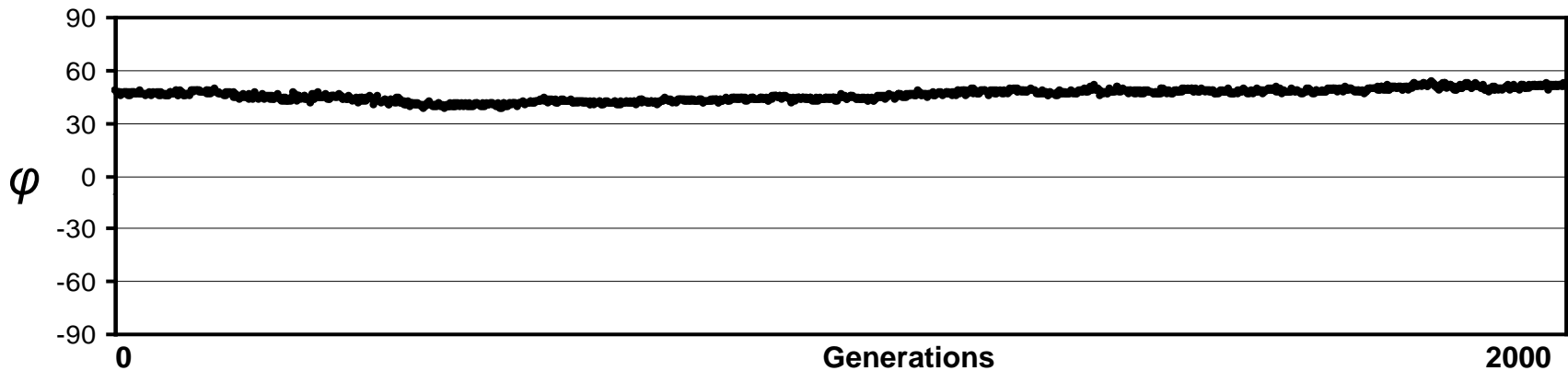
| ω (trait 1) | ω (trait 2) | $r(\omega)$ | $r(\mu)$ | $\Delta\phi$ |
|--------------------|--------------------|-------------|----------|--------------|
| 49 | 49 | 0 | 0 | 9.9 |
| 49 | 49 | 0 | 0.25 | 7.9 |
| 49 | 49 | 0 | 0.50 | 3.6 |
| 49 | 49 | 0 | 0.75 | 1.5 |
| 49 | 49 | 0 | 0.85 | 1.1 |
| 49 | 49 | 0 | 0.90 | 0.9 |

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

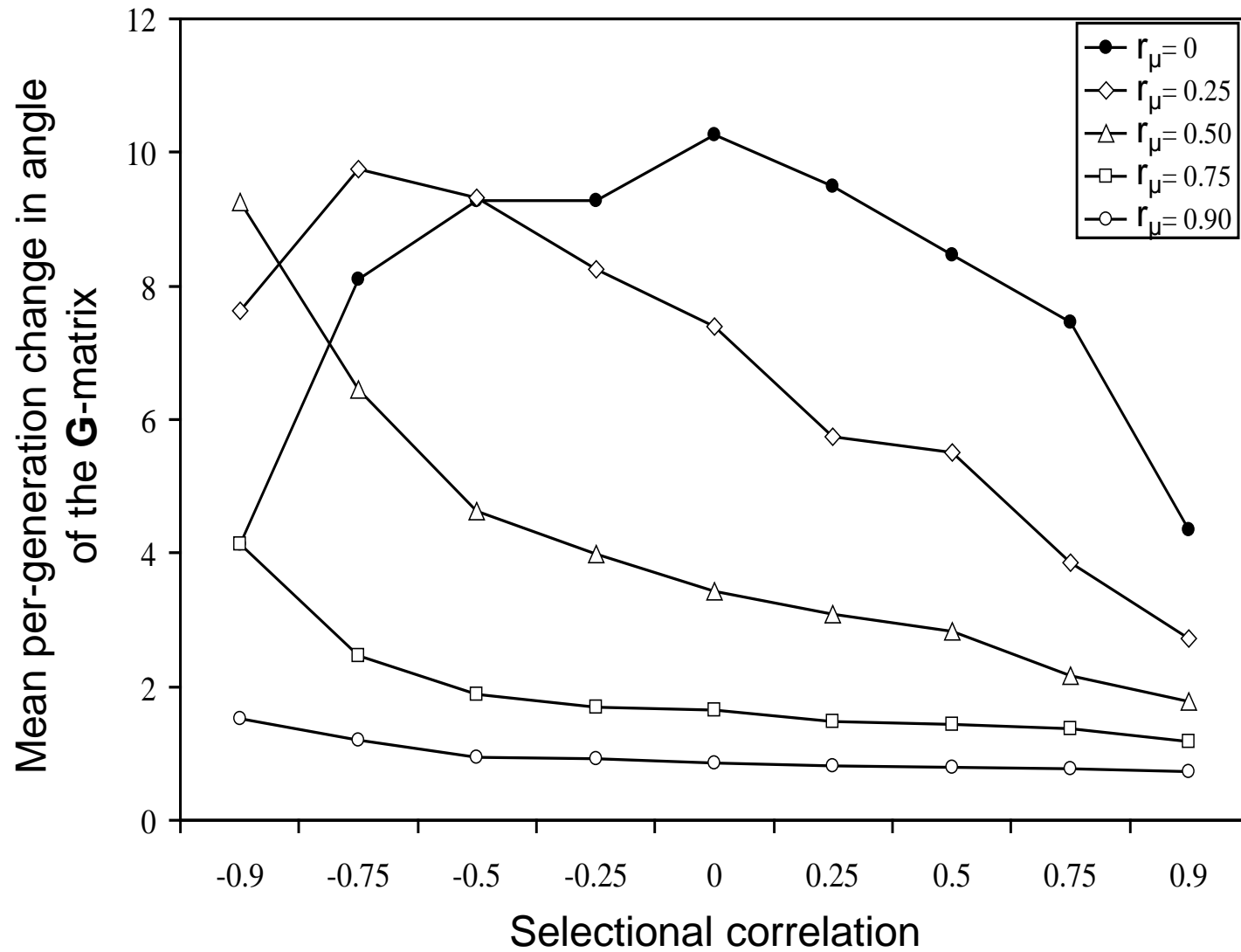
selectional correlation = 0.75, mutational correlation = 0.5



selectional correlation = 0.9, mutational correlation = 0.9



Misalignment causes instability



A larger population has a more stable **G**-matrix

| ω (trait 1) | ω (trait 2) | $r(\omega)$ | $r(\mu)$ | $N(e)$ | $\Delta\phi$ |
|--------------------|--------------------|-------------|----------|--------|--------------|
| 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 |

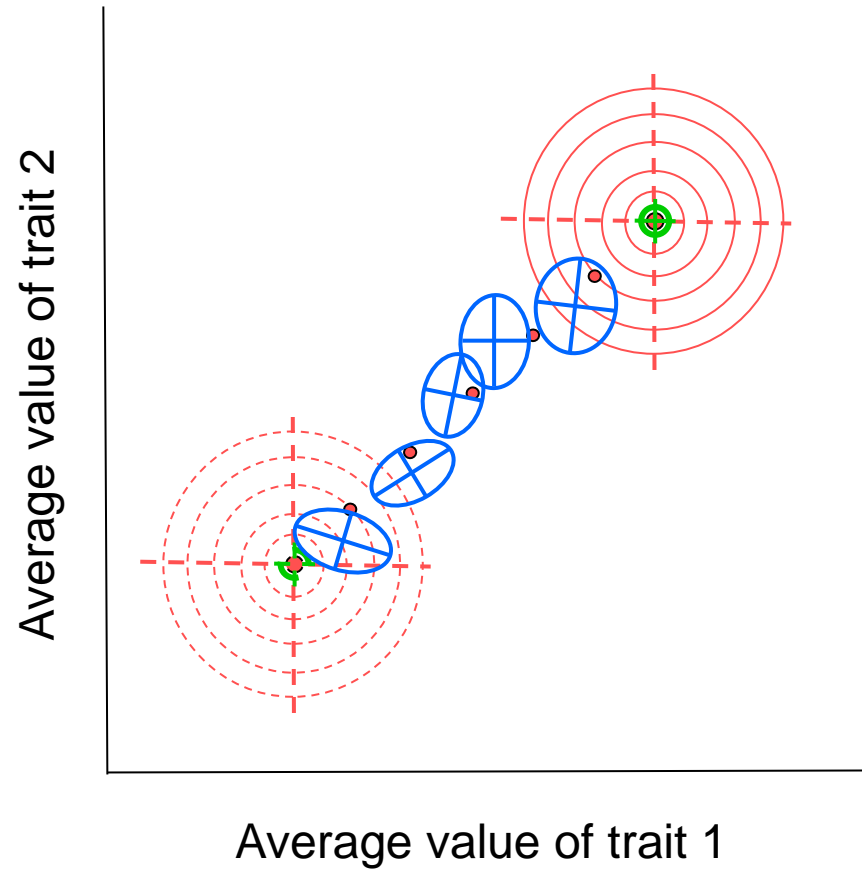
Asymmetrical selection intensities or mutational variances produce stability without the need for correlations

| ω (trait 1) | ω (trait 2) | $r(\omega)$ | $r(\mu)$ | α (trait 1) | α (trait 2) | $\Delta\phi$ |
|--------------------|--------------------|-------------|----------|--------------------|--------------------|--------------|
| 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.

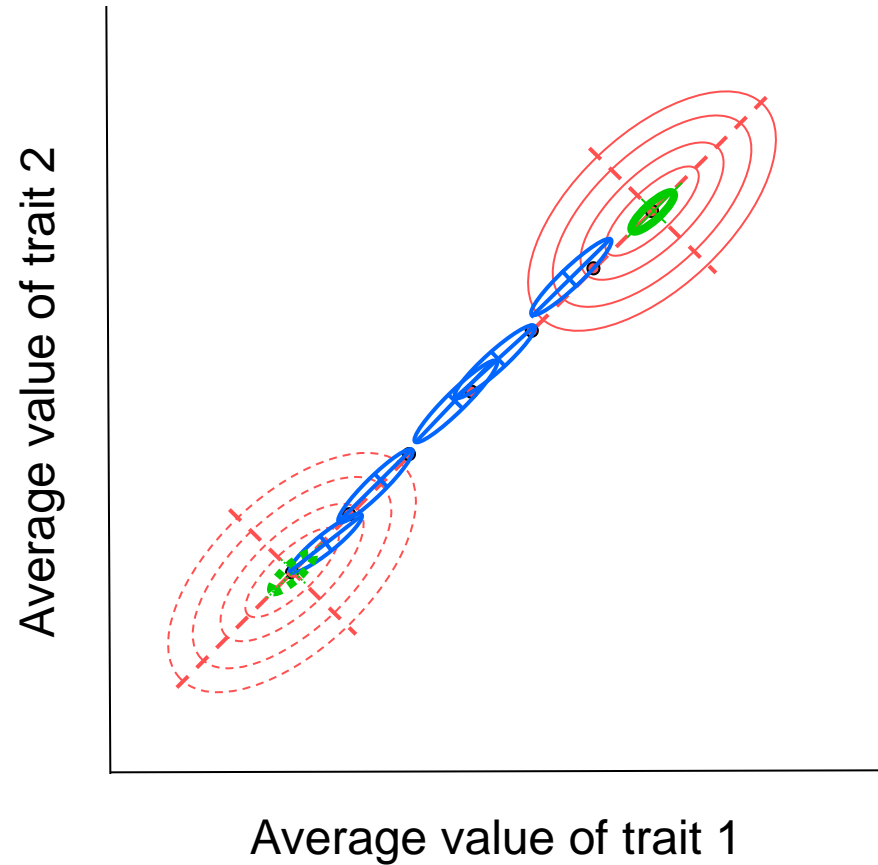
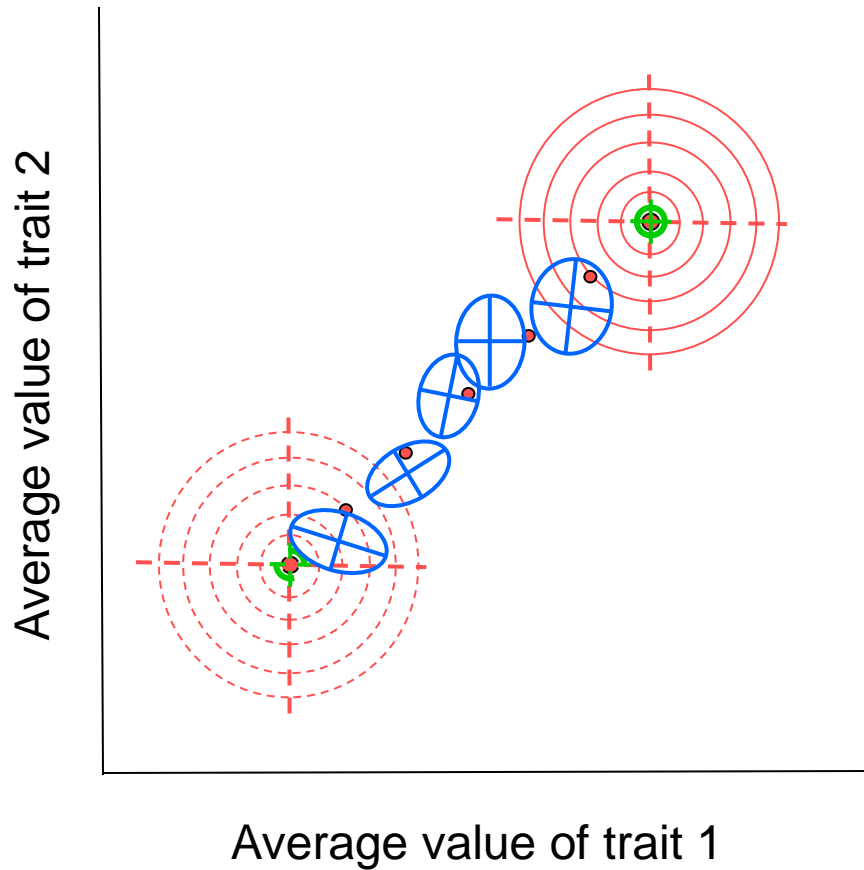
What happens when the optimum moves?



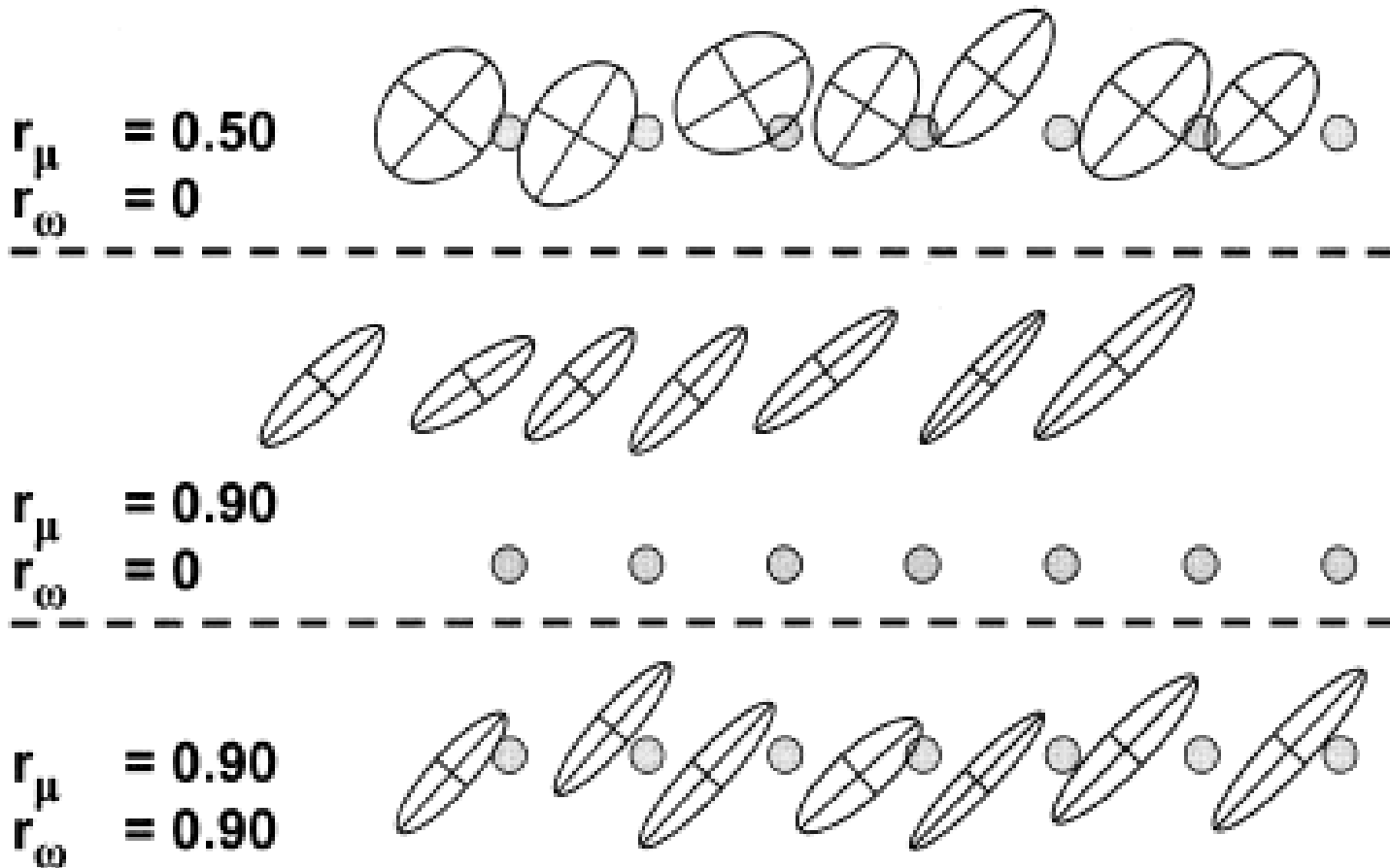
In the absence of mutational or selectional correlations, peak movement stabilizes the orientation of the **G**-matrix

| 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

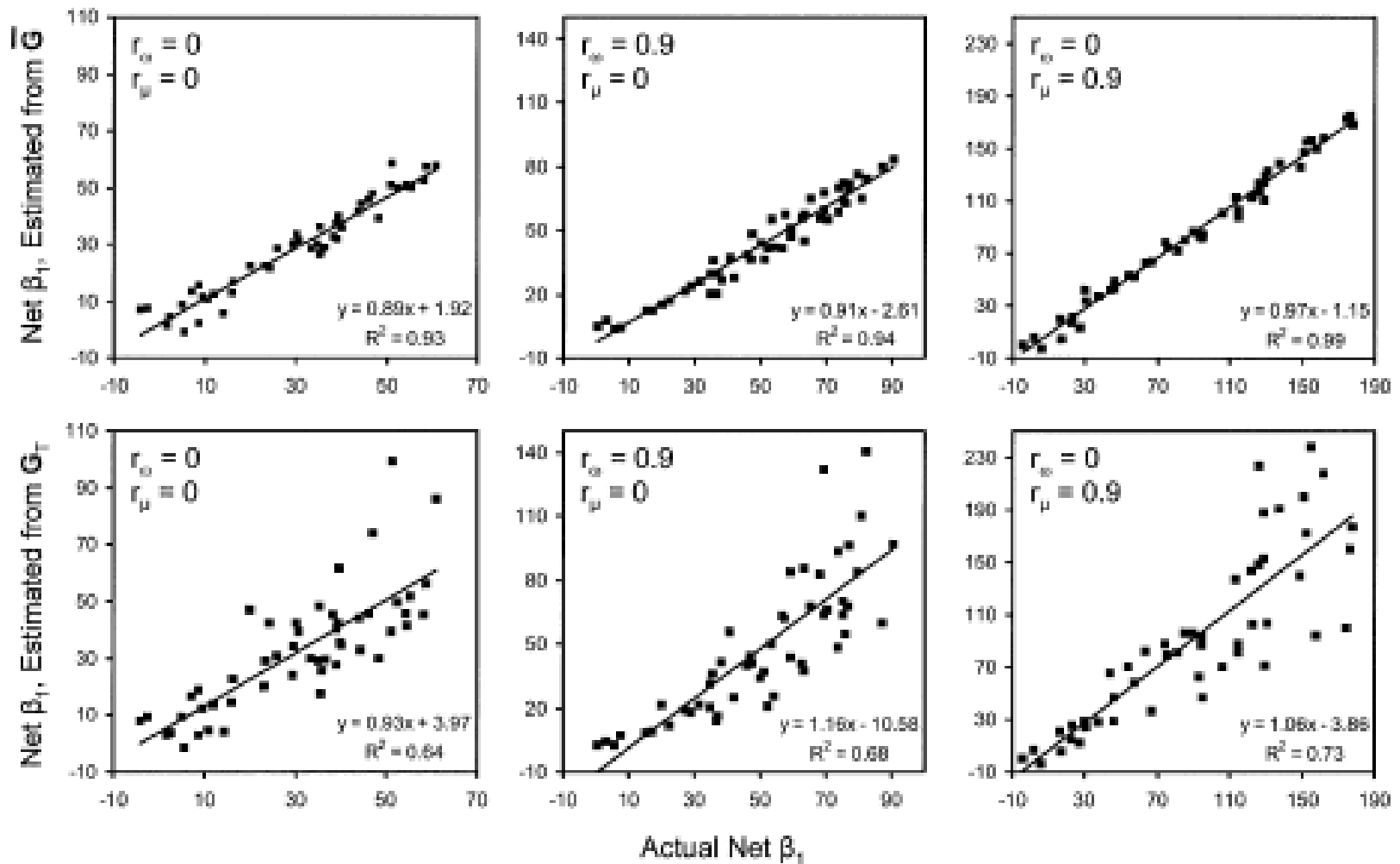


Strong genetic correlations can produce a flying-kite effect

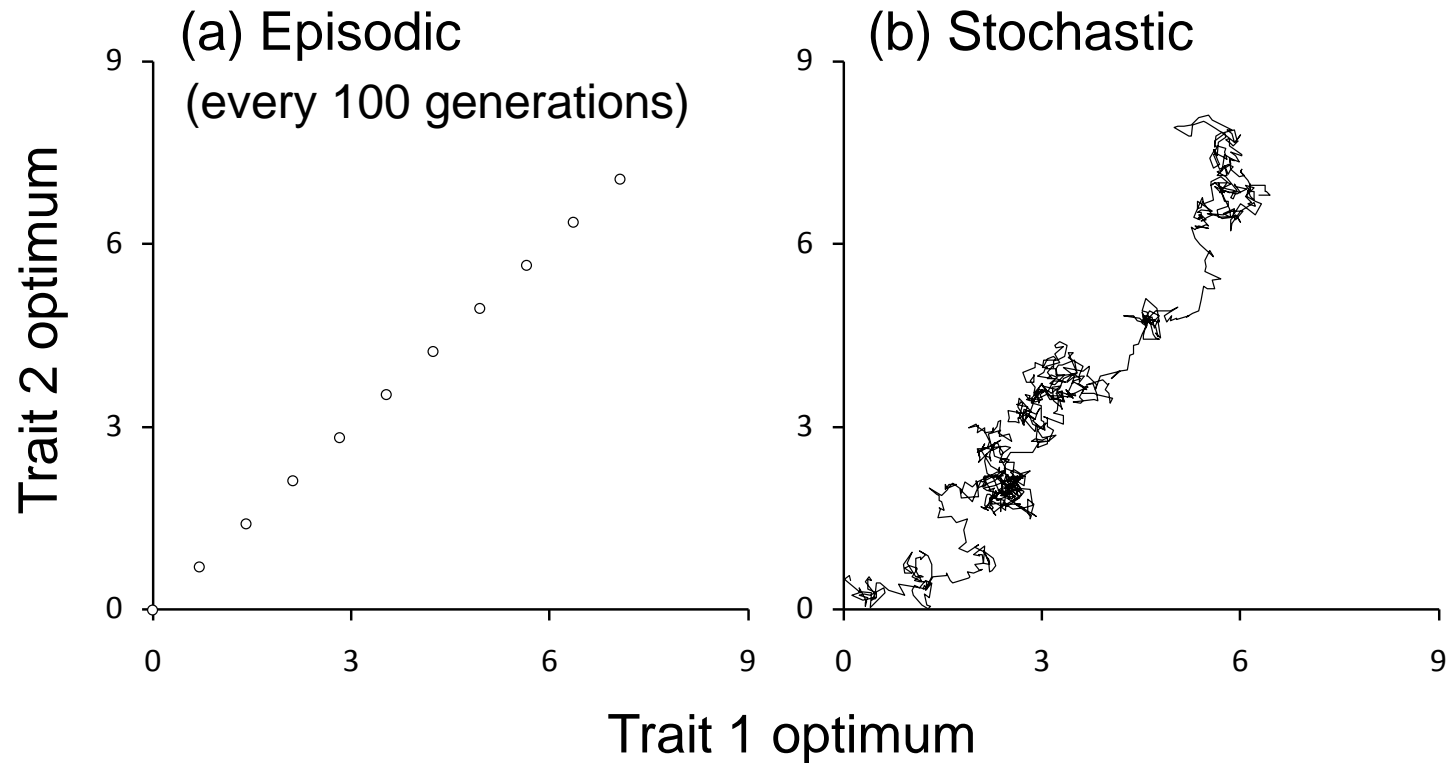


Direction of optimum movement →

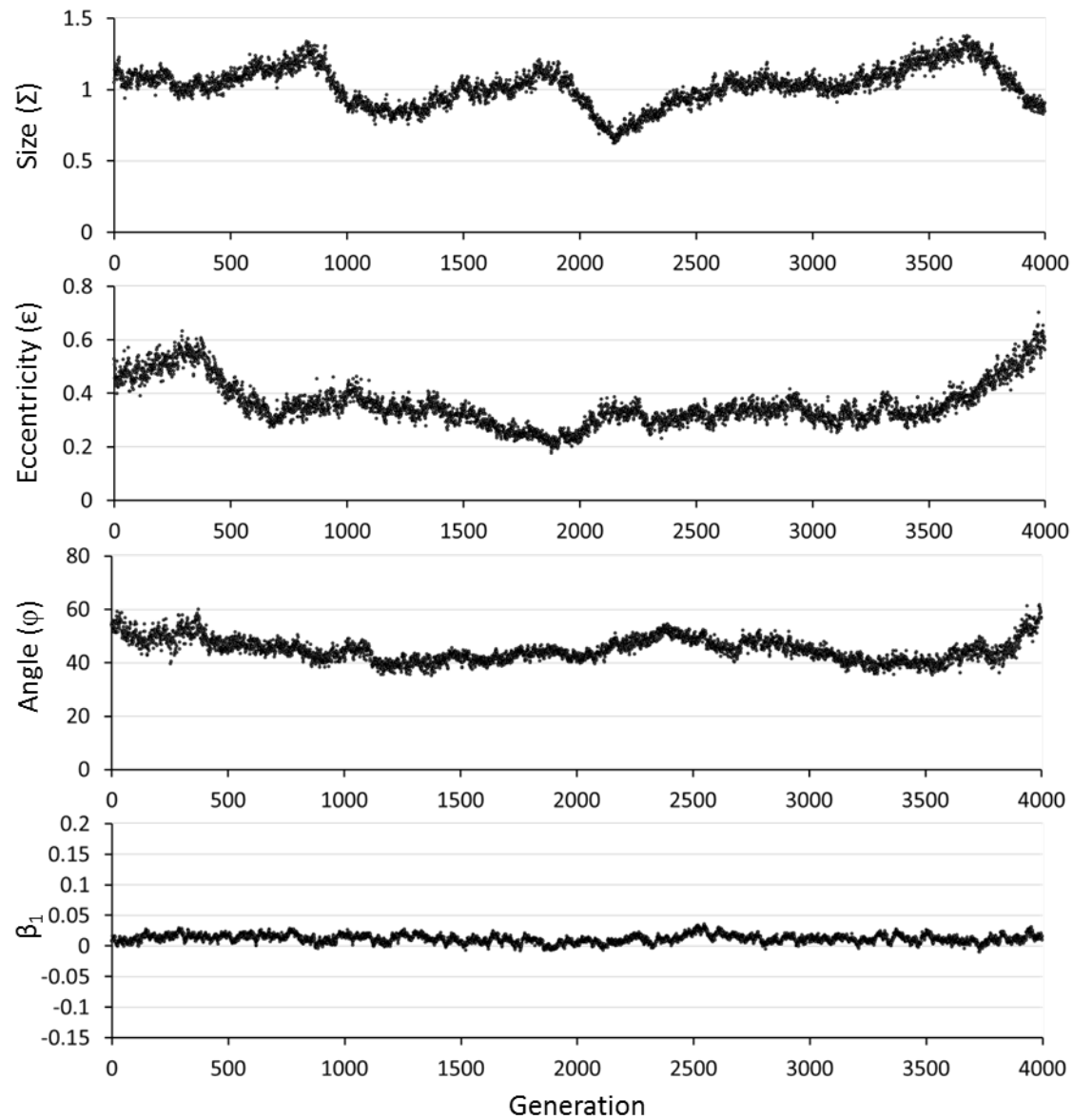
Reconstruction of net- β



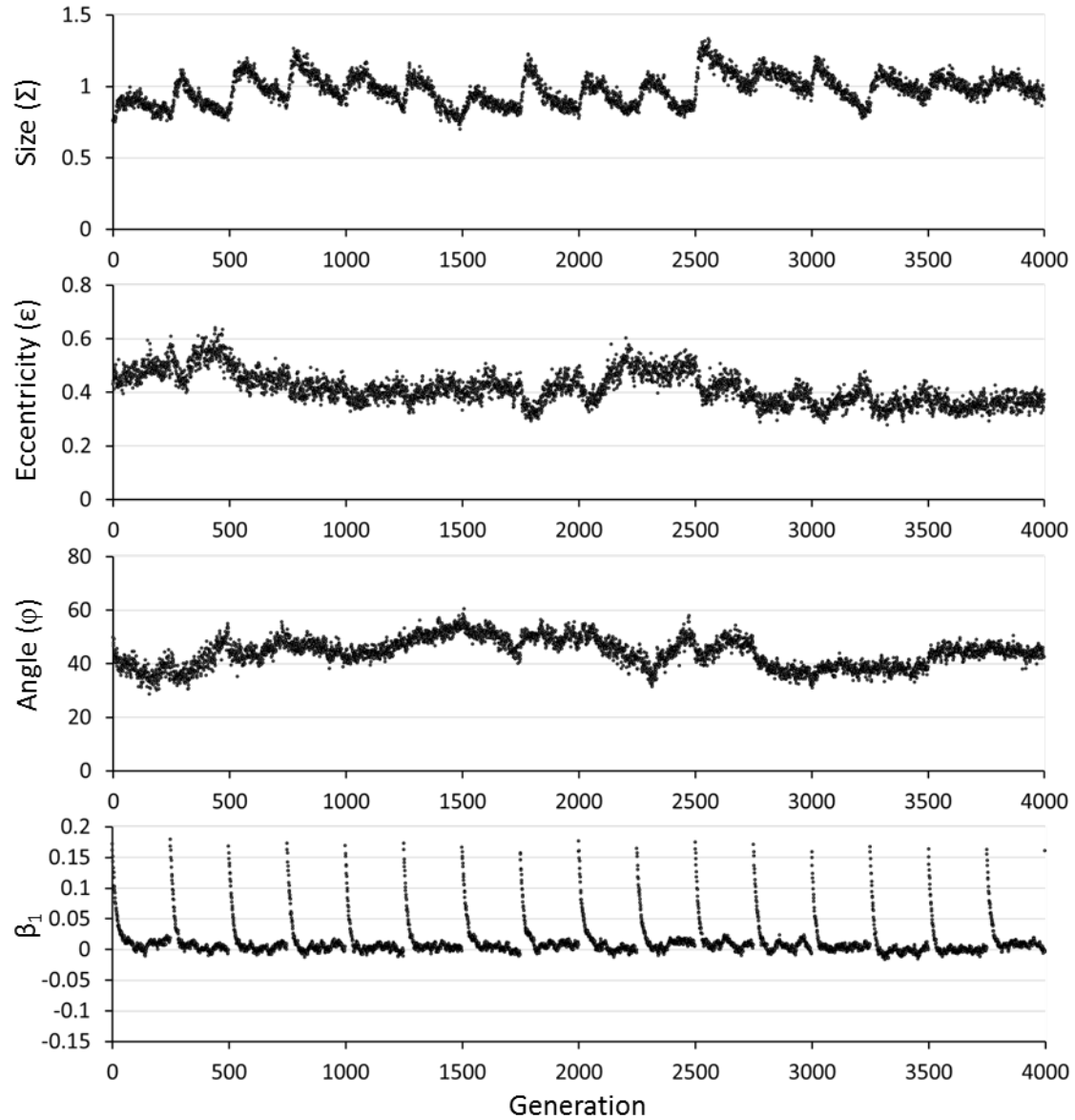
More realistic models of movement of the optimum



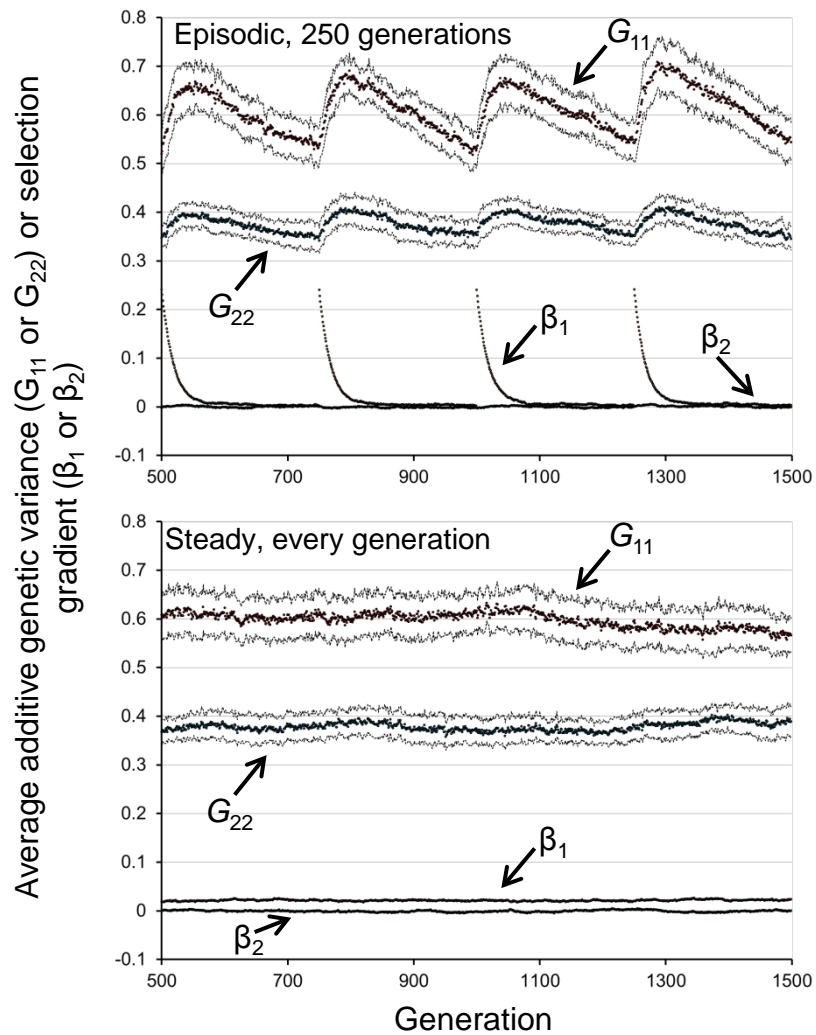
Steadily moving optimum



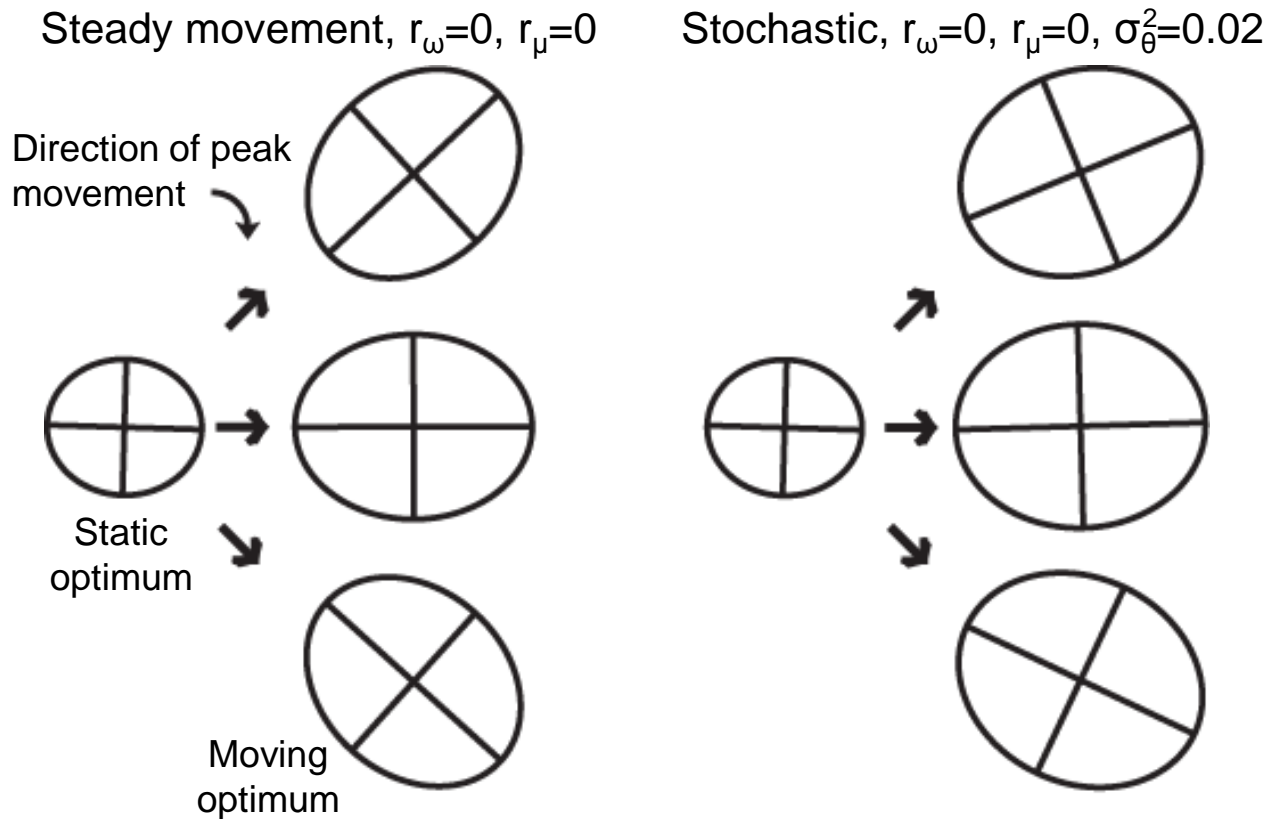
Episodically moving optimum



Cyclical changes in the genetic variance in response to episodic movement of the optimum

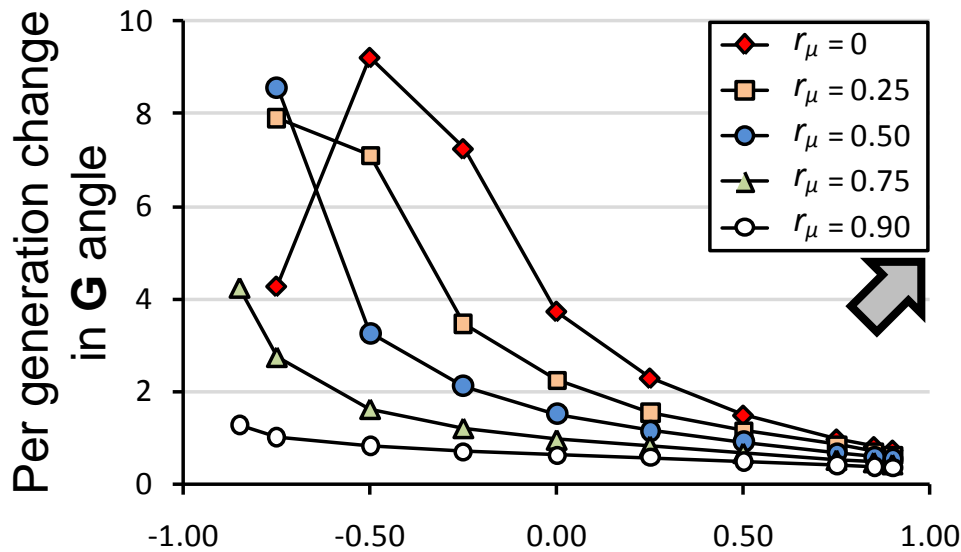


Effects of steady (or episodic) compared to stochastic peak movement

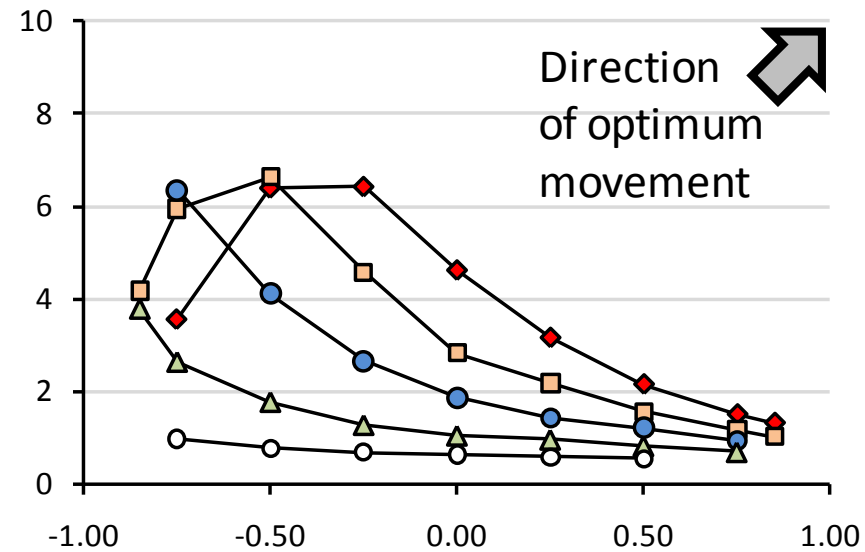


Episodic vs. stochastic

Episodic movement = smooth movement



Stochastic movement



Degree of correlational selection

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) | $\sigma_{\theta 1}^2 = \sigma_{\theta 2}^2$ | $\Delta\theta$ | $r_{\omega} = 0.75$ | $r_{\omega} = 0.75$ | $r_{\omega} = 0.9$ | $r_{\omega} = -0.75$ |
| | | | $r_{\mu} = 0$ | $r_{\mu} = 0.5$ | $r_{\mu} = 0.9$ | $r_{\mu} = 0.5$ |
| Steady (1) | 0 | \nearrow | | | | |
| Steady (1) | 0 | \rightarrow | | | | |
| Steady (1) | 0 | \searrow | | | | |
| Episodic (100) | 0 | \nearrow | | | | |
| Episodic (100) | 0 | \rightarrow | | | ex | |
| Episodic (100) | 0 | \searrow | | | ex | |
| Episodic (250) | 0 | \nearrow | | | ex | ex |
| Episodic (250) | 0 | \rightarrow | ex | ex | ex | ex |
| Episodic (250) | 0 | \searrow | ex | ex | ex | |
| Stochastic (1) | 0.01 | \nearrow | | | ex | |
| Stochastic (1) | 0.01 | \rightarrow | | | ex | |
| Stochastic (1) | 0.01 | \searrow | | | ex | |
| Stochastic (1) | 0.02 | \nearrow | ex | ex | ex | |
| Stochastic (1) | 0.02 | \rightarrow | ex | ex | ex | |
| Stochastic (1) | 0.02 | \searrow | 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:

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

Multilinear model:

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

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, $N = 512$, $\omega = 49$, $\mu = 0.0005$

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, $N = 512$, $\omega = 49$, $\mu = 0.0005$

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 |

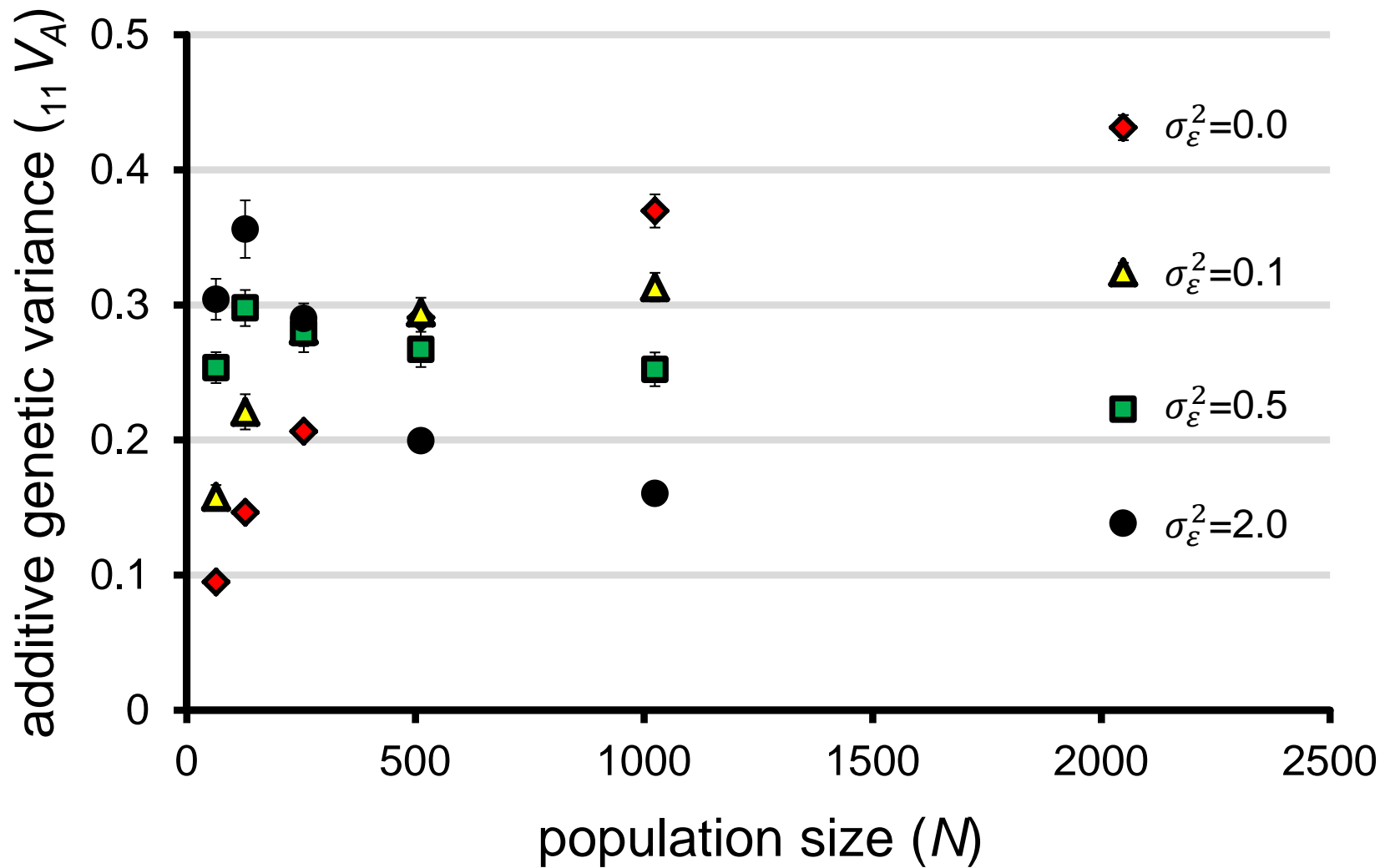
Generations = 5000, ε variance = 1.0, $\omega = 49$, $\mu = 0.0005$

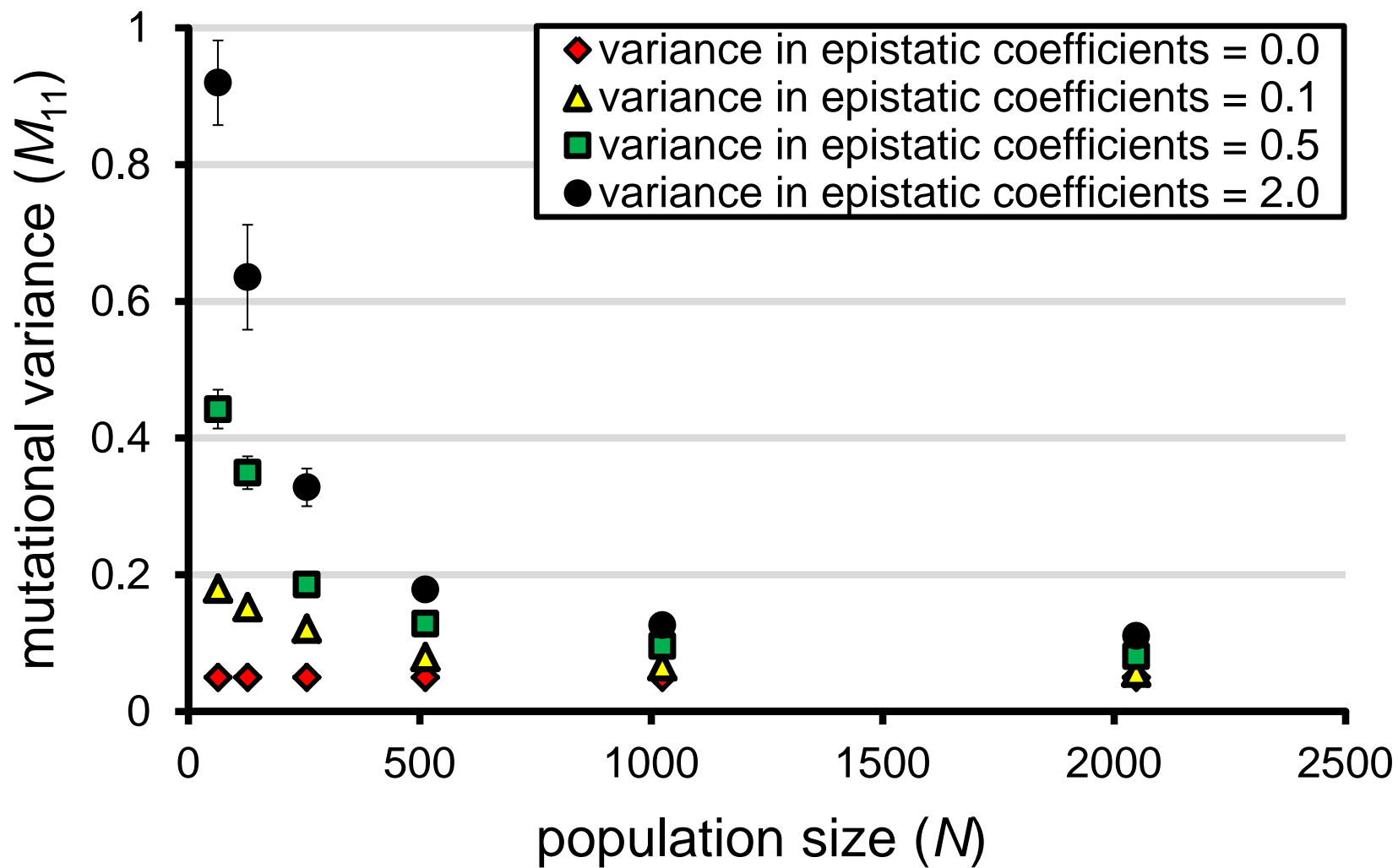
Epistasis Results

- 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, $\omega = 49$, $\mu = 0.0005$





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

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

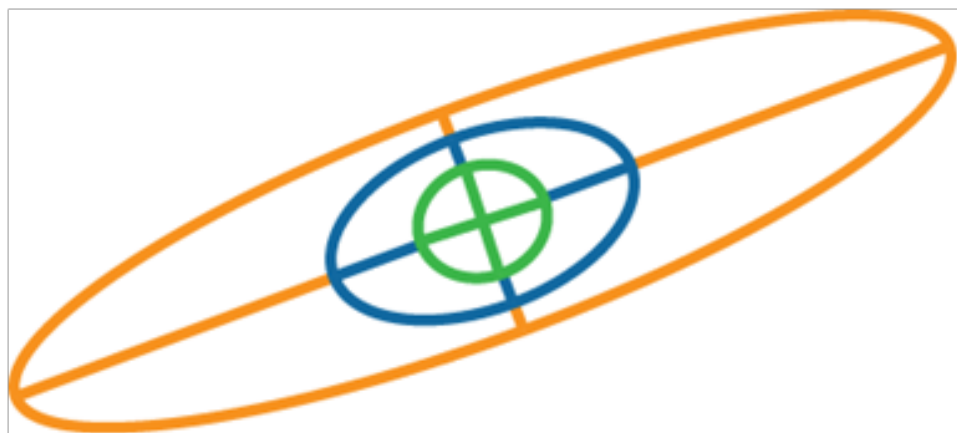
$$\mathbf{M} = \begin{bmatrix} 0.103 & 0.000 \\ 0.000 & 0.072 \end{bmatrix}$$



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

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

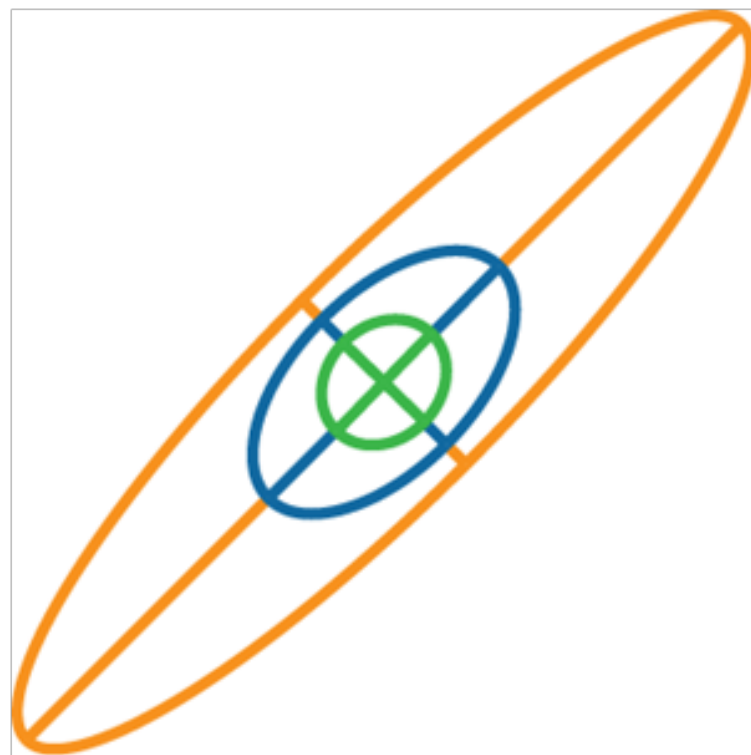
$$\mathbf{M} = \begin{bmatrix} 0.097 & 0.008 \\ 0.008 & 0.075 \end{bmatrix}$$



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

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

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



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.