The effect of epistasis on the response to selection

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Complex traits are inherited in a simple way

- Fleeming Jenkin (1867): "blending inheritance" erodes variation
- Galton (Nature, 1877): offspring are normally distributed around the parental mean, with *constant* variance
- Fisher (1918): consistent with additive effects of very many unlinked genes

The "infinitesimal model"

- for simplicity, neglect non-genetic variance and assume haploids
- offspring normally distributed around mid-parent; variance V_0(1-F)
- F is the probability of identity between genes from the two parents
- Applies to *any* pedigree

Migration and mutation can be included

The infinitesimal limit

$z = \sum_i \alpha_i X_i$, $\overline{z} = \sum_i \alpha_i p_i$, $V = \sum_i \alpha_i^2 p_i(1 - p_i)$

With a selection gradient $\beta = \frac{\partial W}{\partial z}$, $s_i = \beta \alpha_i$ so:

$\Delta z = \sum_i \alpha_i \Delta \mathrm{p}_i = \sum_i \alpha_i s_i p_i(1 - p_i) = \beta \sum_i \alpha_i^2 p_i(1 - p_i) = \beta V$

If Δz, $V \sim 1$, then effects scale as $\alpha \sim \frac{1}{\sqrt{n}}$

$\Delta V = \sum_i \alpha_i^2 (1 - 2 p_i) \Delta \mathrm{p}_i = \beta \sum_i \alpha_i^3 p_i(1 - p_i)(1 - 2 p_i) \sim \frac{1}{\sqrt{n}}$

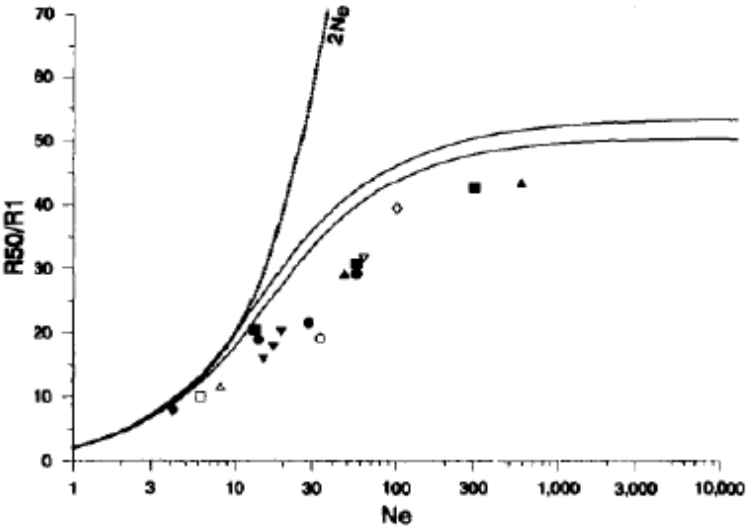
More directly: conditioning on the parents hardly changes the offspring distribution

Robertson's limit

Variance decreases by $\left(1-\frac{1}{N}\right)$ per generation

Hence, total change is:

$$R_\infty = \sum_t \Delta\,\bar{z} = \beta \sum_t V_0\left(1-\frac{1}{N}\right)^t \sim \mathrm{N}\beta V_0 \sim 2\,N\,R_0$$



Weber & Diggins, 1990

The infinitesimal model is *locally* accurate, even though $\underline{Z} = f[\underline{X}]$ is clearly nonlinear

Robertson's limit with epistasis

Trait value can be written as a sum: z = $z_1 + z_2 + z_3 \ldots$

The variance can be written as $V = V_1 + V_2 + V_3 \ldots$; $\Delta z = \beta \mathrm{V}_1$

The additive variance changes as: $V_{t,1} \sim (1 - F_t) \sum_k k\, F_t^{k-1}\, V_{0,k}$

In a population of N haploids, $F_t = 1 - \left(1 - \frac{1}{N}\right)^t$ and:

$R_\infty = \sum_t \Delta \bar{z} = \beta \sum_t V_{t,1} = \mathrm{N} \sum_\mathrm{k} \mathrm{V}_{0,\mathrm{k}} = N\, V_0$

Robertson's limit applies for *any* pattern of gene interaction, provided that selection does not alter the variance components

What if selection is *strong* relative to other processes?

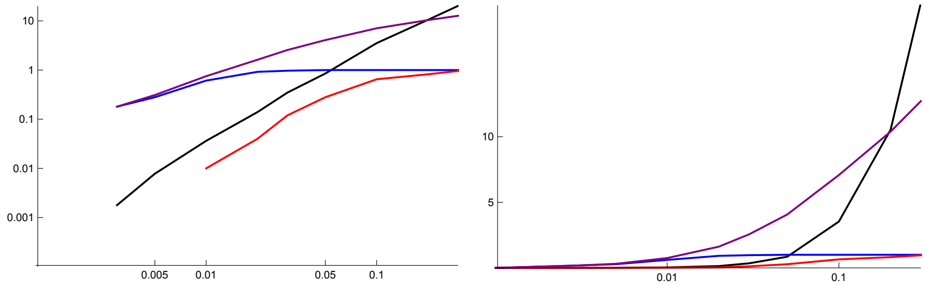
Assume random pairwise epistasis:

$$z = \sum_i \alpha_i \zeta_i + \frac{1}{2} \sum_{i \neq j} \epsilon_{i,j} \zeta_i \zeta_j \quad \text{where } \zeta_i = X_i - p_i^0$$

and define + alleles by their initial advantage, $A_i^0 = \alpha_i$. As alleles sweep through, the additive effects change: $A_i = \alpha_i + \sum_{i \neq j} \epsilon_{i\,j} \left(p_j - p_j^0\right)$

Provided that the additive effects do not change sign, and epistasis is *unbiased* $\left(< \epsilon_{i,j} >= 0\right)$, epistasis has no *expected* effect.

The effect of many independent sweeps is a Gaussian perturbation to A_i
The chance of a 'flip' depends on $\sqrt{n}\ \sigma_\epsilon/\sigma_\alpha$



difference in mean between the global peak and {1, 1 ...}
fraction of replicates where global peak ≠ {1,...}
fraction with >1 peak
Hamming distance between the best peak and {1,...}
plotted against $\sigma_\epsilon/\sigma_\alpha$ with 50 loci

Summary

Complex traits are inherited in a simple way

The *infinitesimal model* applies when many genes contribute to a trait

Then, $R_\infty = 2\,N\,\beta V_{0,G}$: epistasis has little effect if $V_{0,A} \sim V_{0,G}$

When selection dominates, epistasis has no expected effect unless:

- it is *biased*
- it changes the fittest combination of alleles
- $\sqrt{n}\ \sigma_\epsilon >> \sigma_\alpha$

How can we estimate the strength and nature of epistasis??

$\sigma_\epsilon / \sigma_\alpha$	% ≠ {1, …}		distance		$\overline{z}$	
0.001	0.	0.00006	0.	0.	43.9103	43.9103
0.003	0.13	0.13	0.13	0.128137	43.9105	43.9114
0.005	0.32	0.32	0.35	0.34662	43.9203	43.9283
0.01	0.57	0.55	0.7	0.667682	43.9511	43.9854
0.02	0.83	0.84	1.5	1.53967	43.9033	44.018
0.03	0.94	0.95	2.24	2.60558	43.9785	44.2544
0.04	0.97	0.99	3.39	3.2915	43.9385	44.5263
0.05	1.	0.995	4.23	2.58907	43.9363	44.9122