

Adaptation dynamics of a polygenic trait

Kavita Jain

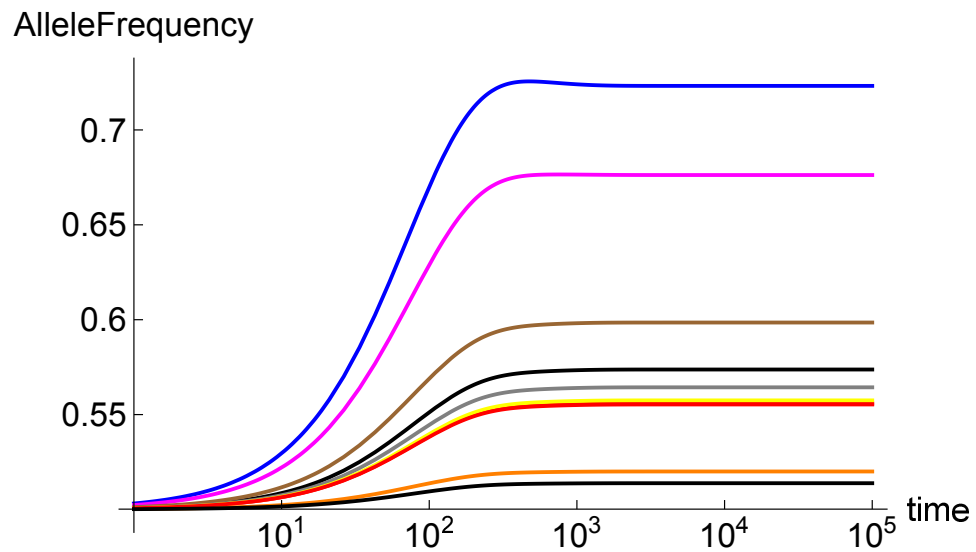
J. Nehru Centre, Bangalore

K. Jain & W. Stephan

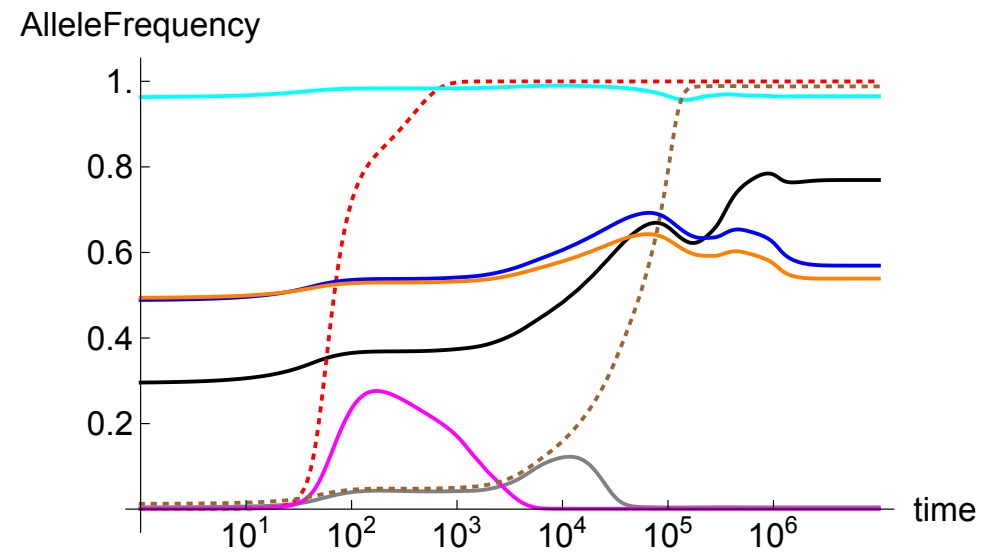
G3 (2015); Genetics (2017); MBE (2017)

K. Jain & A. Devi, EPL (2018)

Modes of polygenic adaptation



Subtle shift in allele frequencies
→ Quantitative-genetic picture



Sweeps in allele frequencies
→ Population-genetic picture

Integrate these approaches into a single framework

Phenotype-Genotype map

How selection acts on phenotype



Phenotype-to-Genotype map



Work out allele frequency dynamics

Phenotypic dynamics



Genotype-to-Phenotype map



But P-G maps are too complicated, not much known

Make simple and reasonable assumptions (e.g., additive map)

Cumulant hierarchy (Bürger 1991)

Mean trait dynamics depend on genetic variance (and higher cumulants)

Variance dynamics depend on skewness (and higher cumulants) ...

- assume variance is roughly constant

(Lande 1983, Turelli & Barton 1990, Rattray & Shapiro 2001,...)

but not always a good approximation

- come up with effective models for specific situations (Chevin & Hospital 2008)

but not general/detailed enough

- numerical simulations of full model

but restricted to few loci (Pavlidis et al. 2012, Franssen et al. 2017, ...)

Today's talk

- consider a detailed model that accommodates both sweeps and shifts

(de Vladar & Barton 2014)

- develop new approximations that allow detailed understanding of dynamics

(Jain & Stephan 2015, 2017)

Model (de Vladar & Barton, 2014)

- Infinitely large population of diploids
- Linkage equilibrium
- Additive phenotype-genotype map
- Quantitative trait determined by finite number of biallelic loci
- Effect sizes γ are locus-depn but do not depend on ℓ
- Trait is under stabilising selection

$$w(z) = 1 - (s/2)(z - z_0)^2$$

Allele frequency dynamics (Wright 1935, Barton 1986)

- Initially population is equilibrated to z_0
- Then phenotypic optimum moves from z_0 to z_f

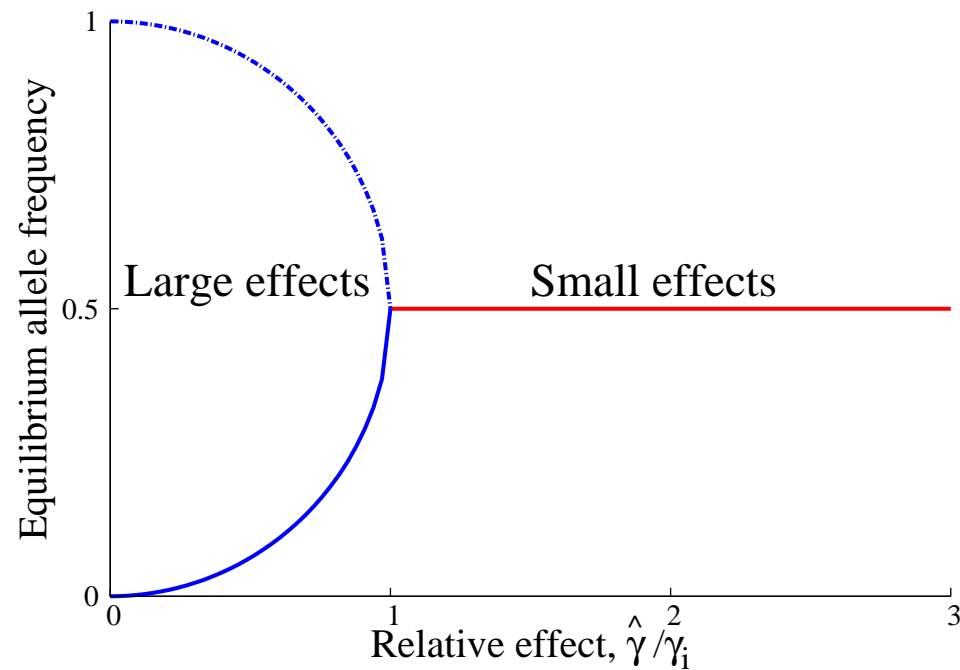
$$\begin{aligned}\dot{p}_i &= \frac{p_i q_i}{2} \frac{\partial \ln \bar{w}}{\partial p_i} + \text{Mutation term} \\ &= \underbrace{-s\gamma_i(\bar{z} - z_f)p_i q_i}_{\text{DIRECTIONAL}} + \underbrace{\frac{s\gamma_i^2}{2} p_i q_i (2p_i - 1)}_{\text{FIXATION}} + \underbrace{\mu(q_i - p_i)}_{\text{MUTATION}}\end{aligned}$$

$$\text{Mean trait, } \bar{z} = \sum_{i=1}^{\ell} \gamma_i p_i - \gamma_i q_i$$

At large times, fixation and mutation matter (de Vladar & Barton 2014)

If the population is well adapted, both polymorphism and fixation are possible

$$p_i^* \approx \begin{cases} 1/2 & , \gamma_i < \hat{\gamma} \quad \text{(small effects)} \\ 0 \text{ or } 1 & , \gamma_i > \hat{\gamma} \quad \text{(large effects)} \end{cases}$$



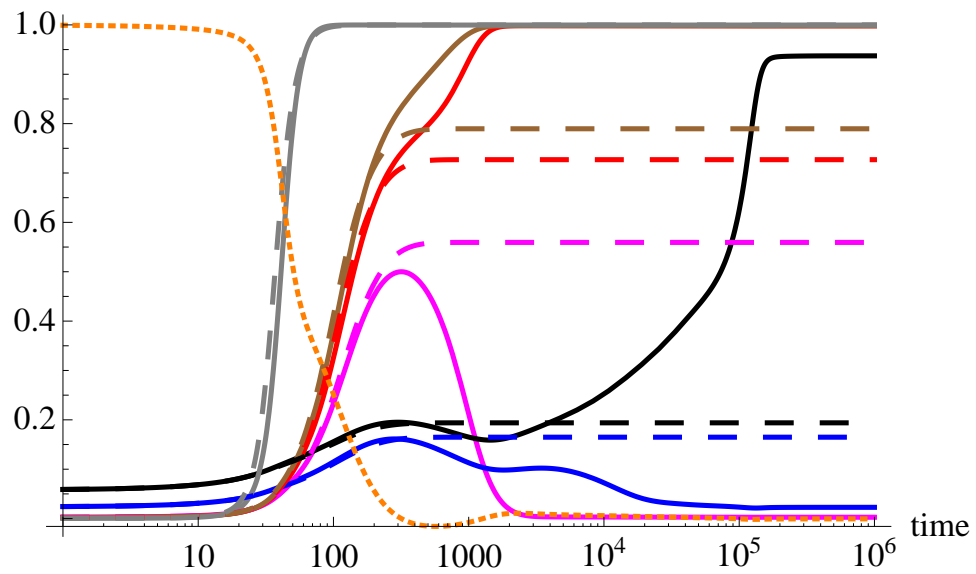
At short times, selection dominates (Jain & Stephan 2015)

$$\dot{p}_i = \underbrace{-s\gamma_i(\bar{z} - z_f)p_iq_i}_{\text{DIRECTIONAL}} + \cancel{\frac{s\gamma_i^2}{2} p_iq_i(2p_i - 1)} + \cancel{\mu(q_i - p_i)}$$

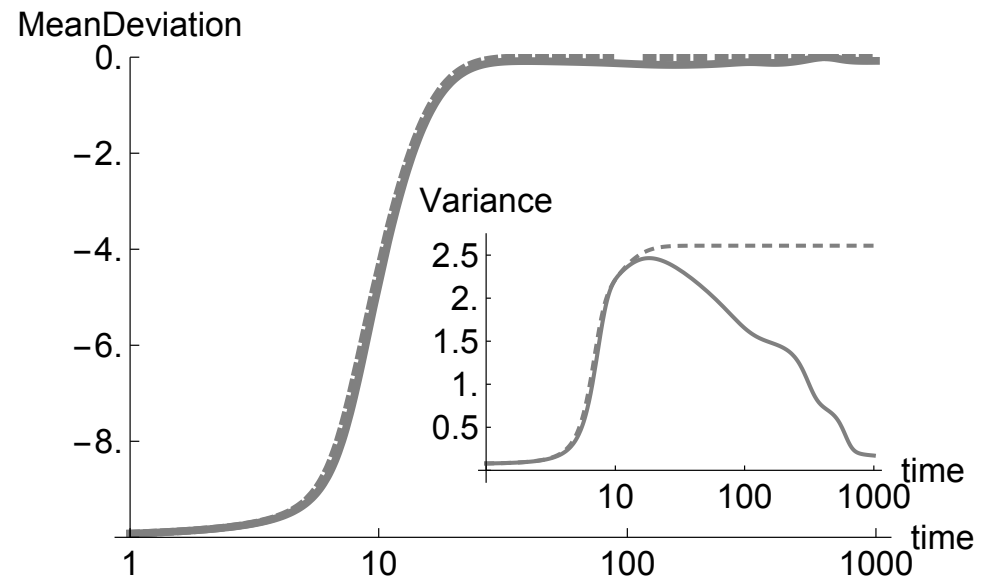
~~FIXATION~~ ~~MUTATION~~

$$\dot{p}_i \approx S_i p_i q_i, \quad S_i = -s\gamma_i(\bar{z} - z_f)$$

Directional selection model



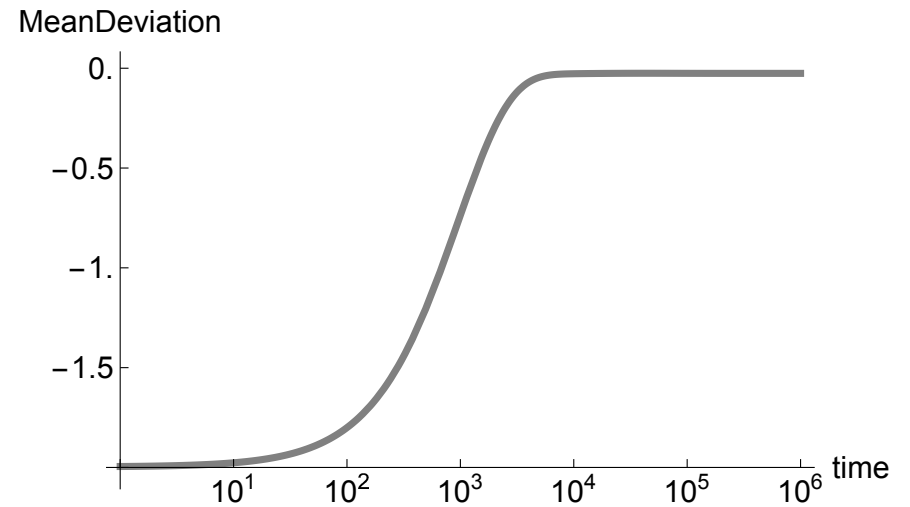
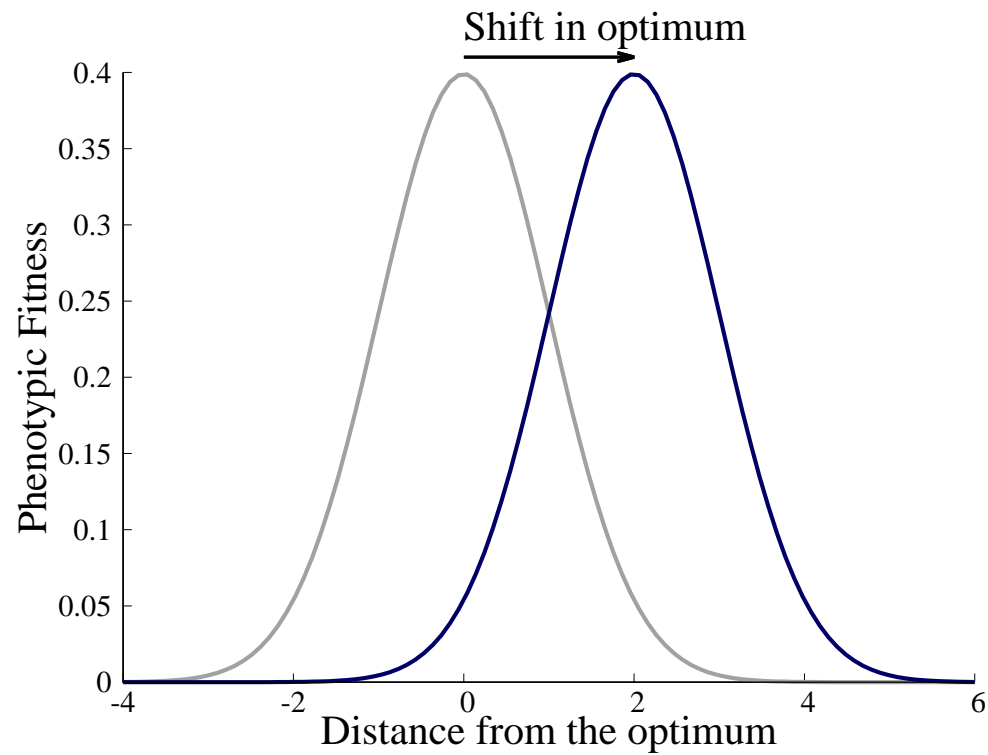
captures bulk of adaptation
(almost always)



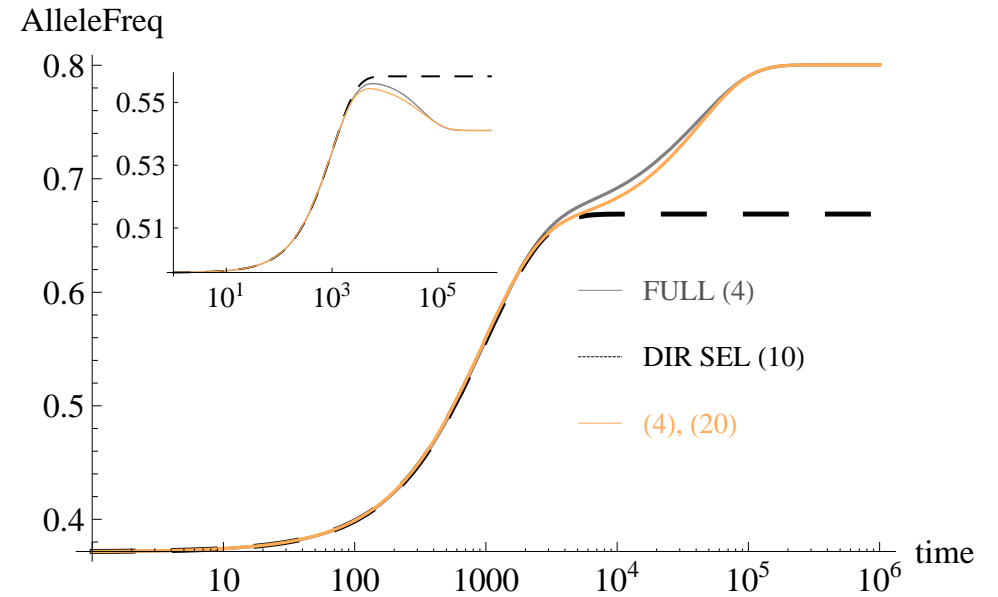
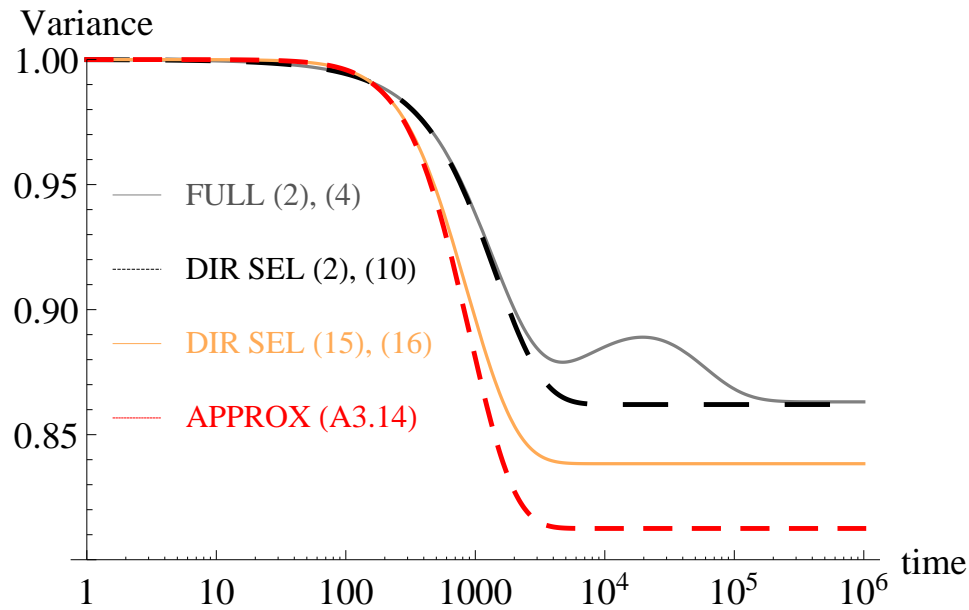
solvable even when variance
changes dramatically

I. Response to a sudden shift in phenotypic optimum

e.g., sudden outbreak of disease



Most effects are small



- Initial genetic variance is large
- Remains roughly constant

- Subtle shifts in minor allele freq
- Sweeps may occur at major loci

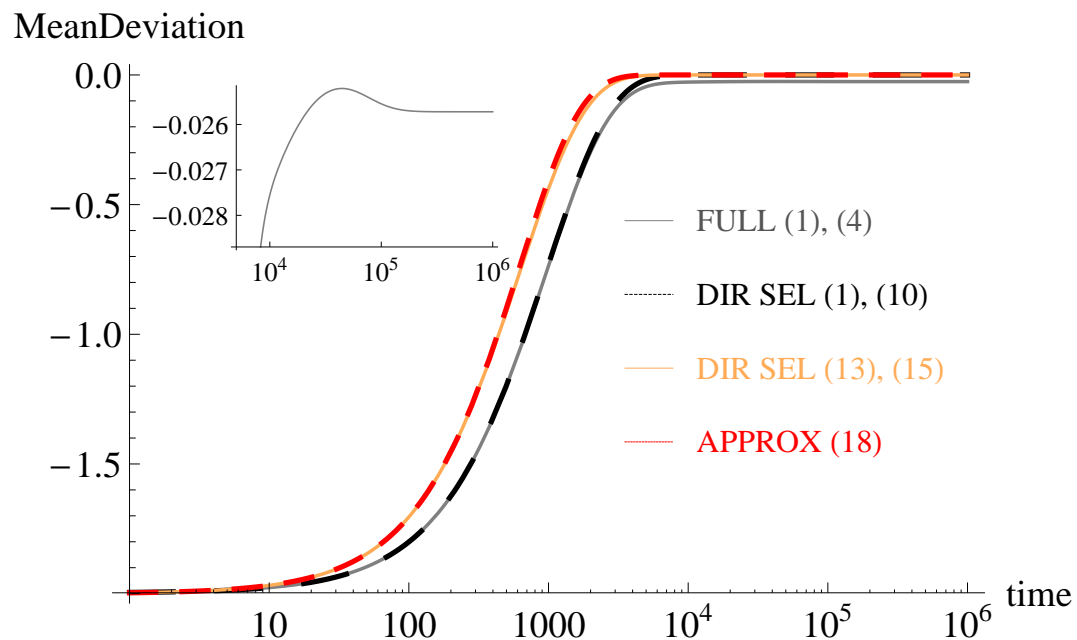
→ Behavior is essentially same as that in infinitesimal model

Most effects are small

- Initial genetic variance drives bulk of adaptation

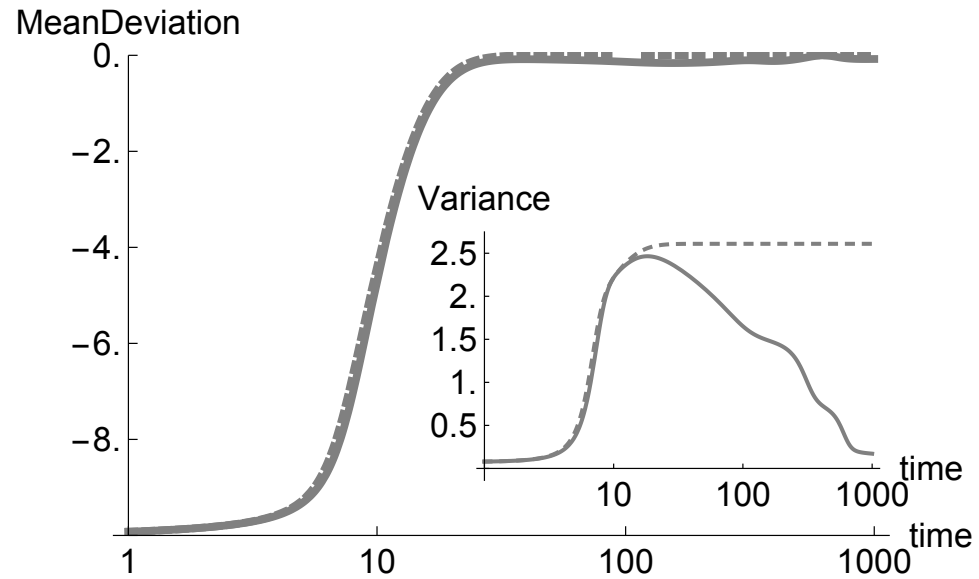
$$\text{Mean deviation} \approx -z_f e^{-s\sigma_g^2 t} = -z_f e^{-sl\bar{\gamma}^2 t}$$

- At long times, true stationary state reached

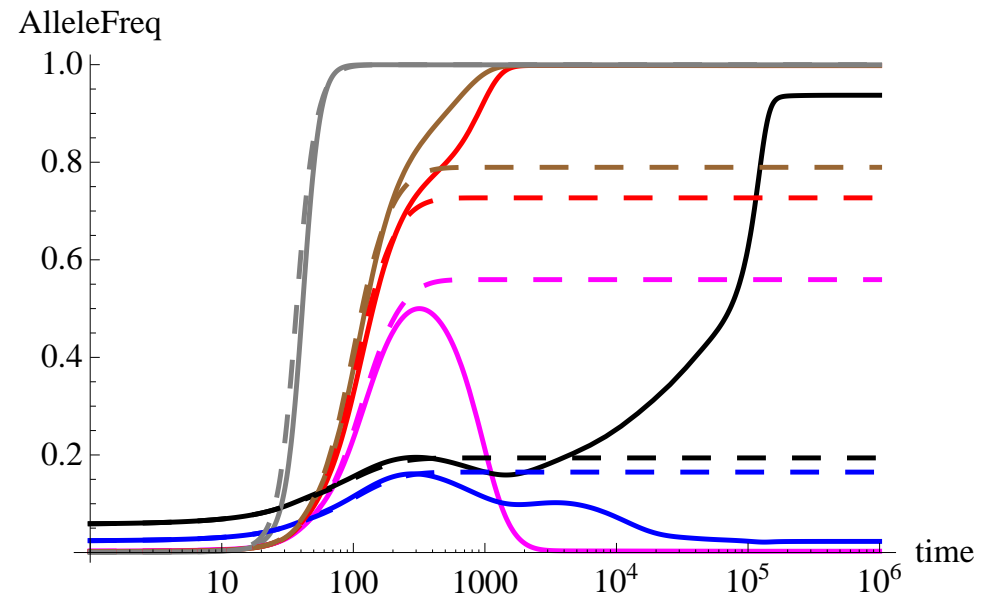


Numerical solution for $\hat{\gamma} = 0.13$, $\bar{\gamma} = 0.04$, $z_f = 2$, $\ell = 200$

Most effects are large



- Initial genetic variance is small
- Increases dramatically

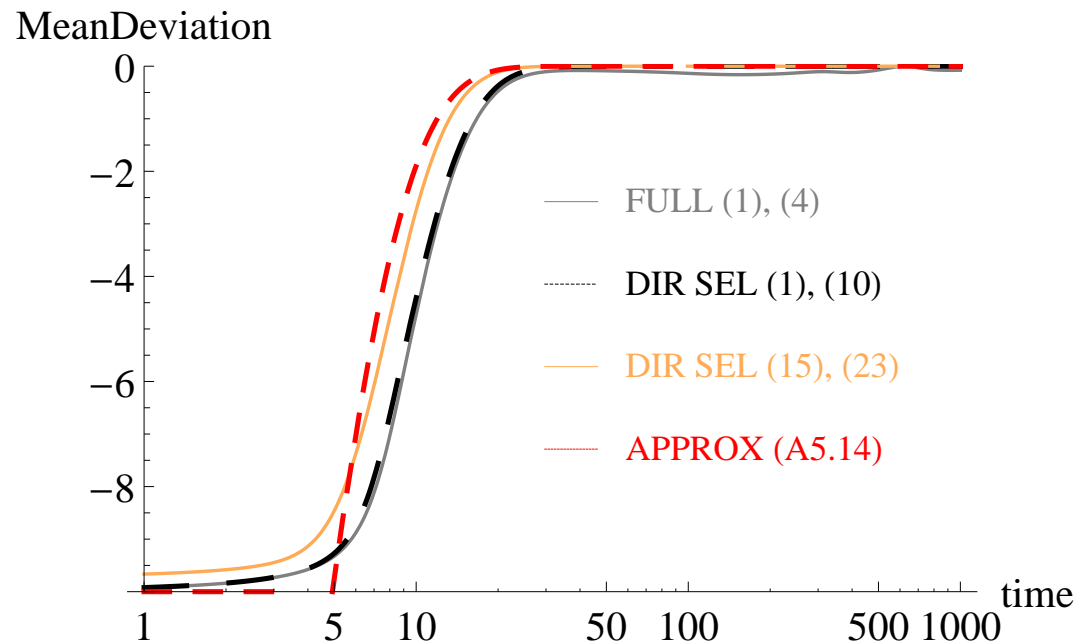


- Sweeps at major allele freq
- At both short and long times

When most effects are large

Mean deviation decreases as $\sim e^{-sz_f \bar{\gamma} \frac{(\ln \ell)^2}{\ln \alpha} t}$

- Effect size (not initial variance) is the driving force
- Only a few large-effect loci are important

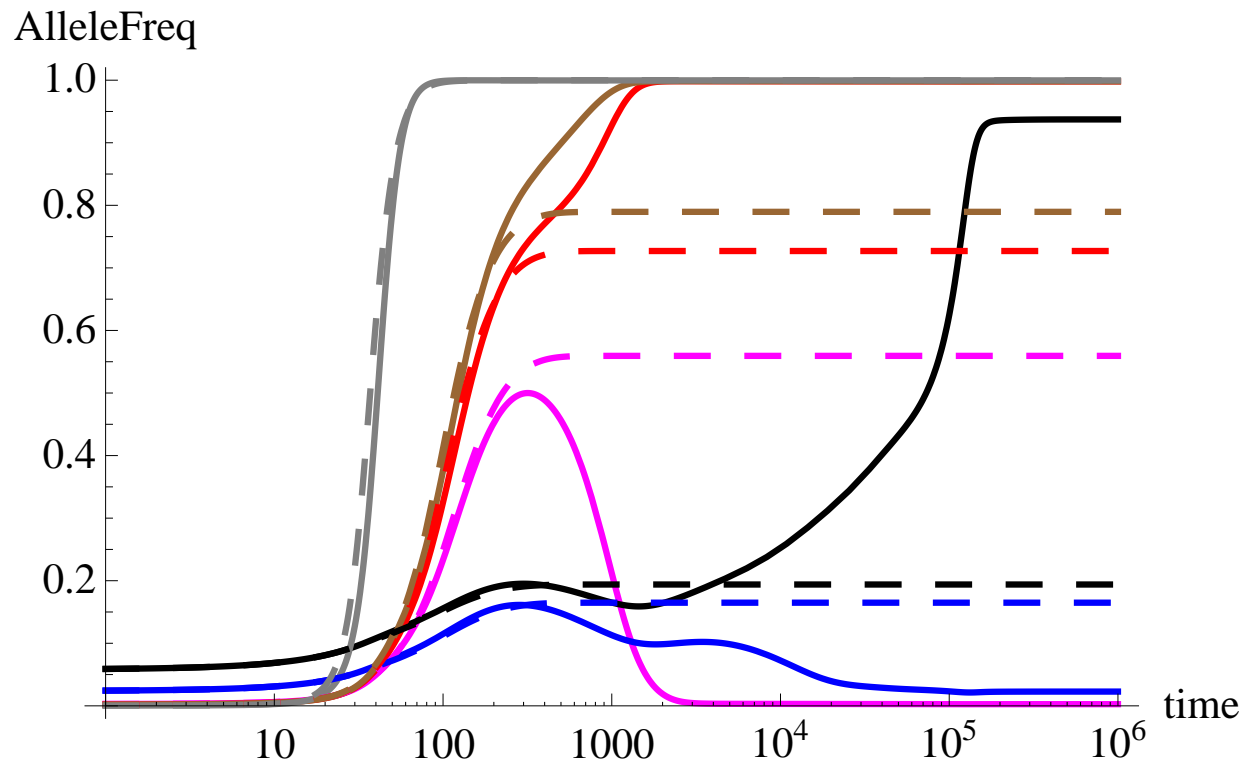


Numerical solution for $\hat{\gamma} = 0.03$, $\bar{\gamma} = 0.3$, $z_f = 10$, $\ell = 200$

When do selective sweeps occur at major loci?

when major allele freq at end of directional selection $> 1/2$

$$\dot{p}_i = \cancel{-s\gamma_i(\bar{z} - z_f)p_iq_i} + \frac{s\gamma_i^2}{2}p_iq_i(2p_i - 1) + \cancel{\mu(q_i - p_i)}$$



When do selective sweeps occur? (Jain & Stephan 2017)

For exponentially distributed effects:

- when most effects are large, selective sweeps can occur at short times since moderately large effect sizes needed

$$\gamma_i > \frac{2\bar{\gamma}}{\ln\left(\frac{2\bar{\gamma}}{\hat{\gamma}}\right)} \ln\left(\frac{\ell\bar{\gamma}}{z_f}\right) \ln\left(\frac{2\gamma_i}{\hat{\gamma}}\right)$$

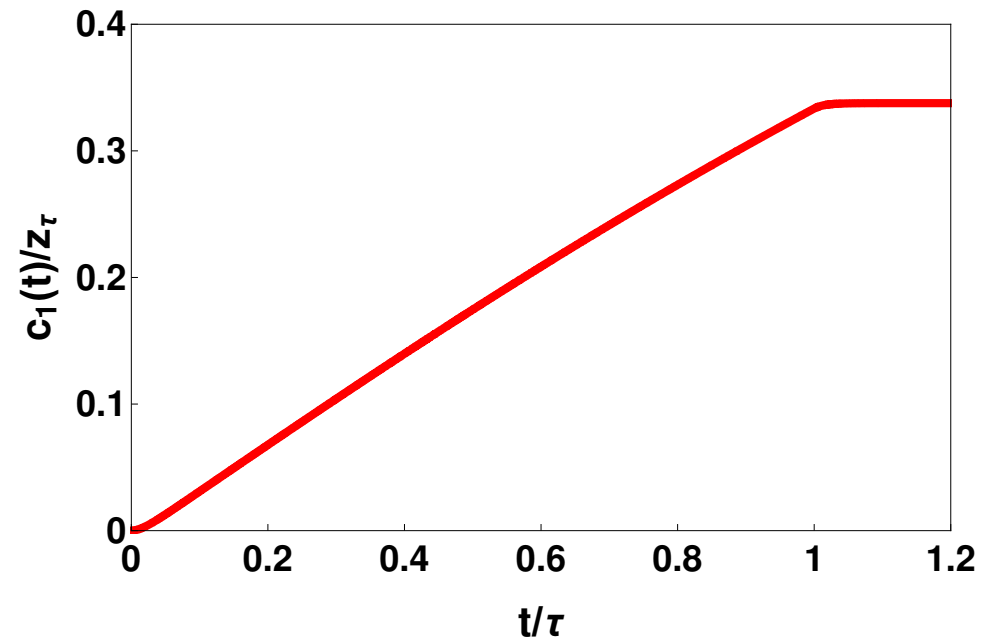
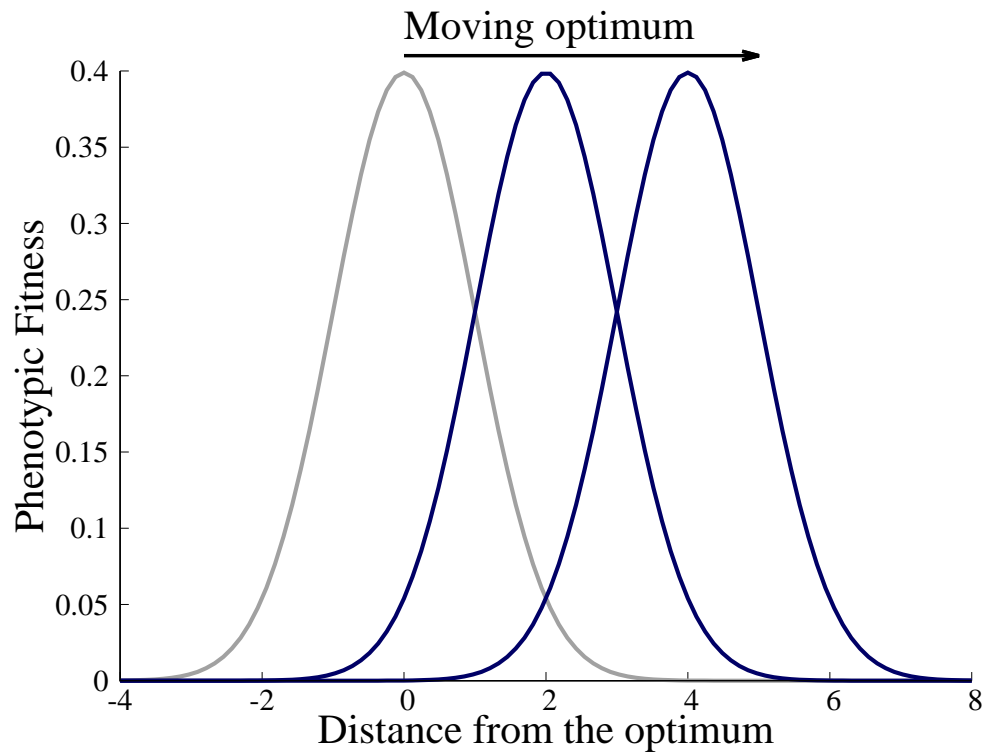
- when most effects are small, sweeps are prevented since quite large effect sizes needed

$$\gamma_i > 2\bar{\gamma} \frac{\ell\bar{\gamma}}{z_f} \ln\left(\frac{2\gamma_i}{\hat{\gamma}}\right)$$

Simpler model (Lande 1983) gives same results (Chevin & Hospital 2008)

II. Response to a slowly moving phenotypic optimum

e.g., global warming



Most effects are small

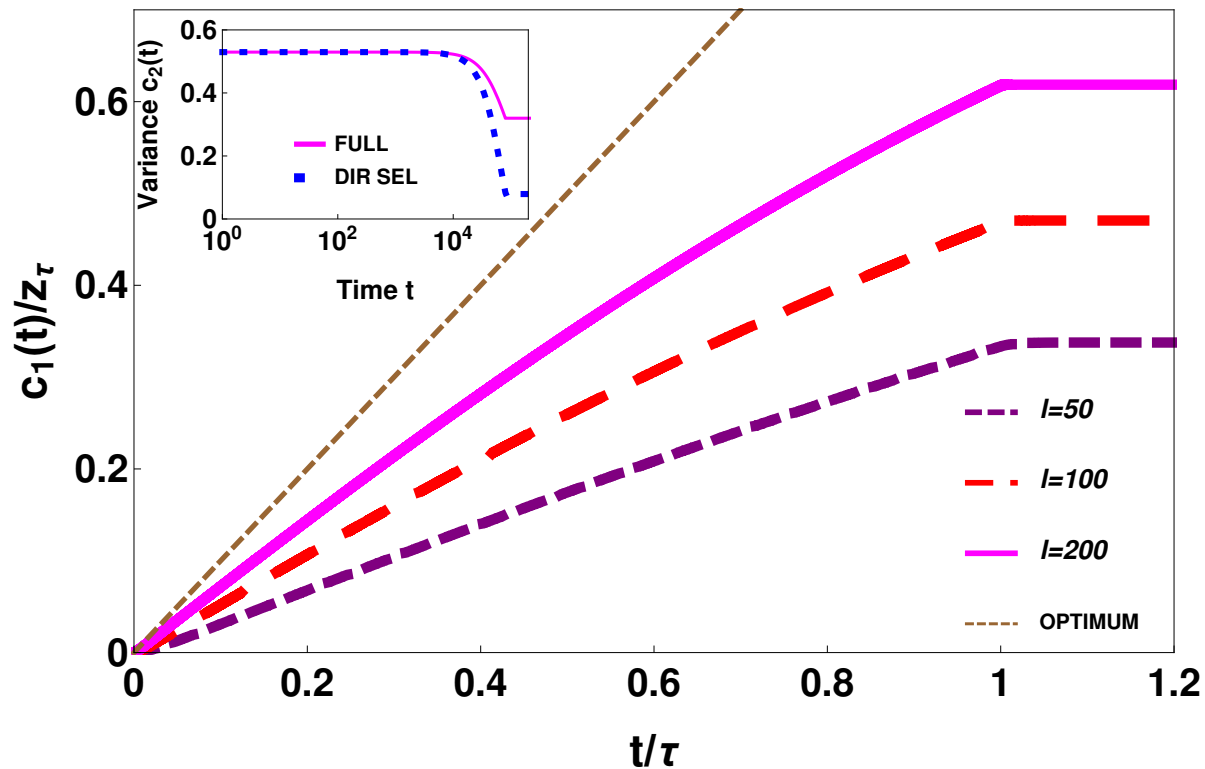
Is the behavior same as that in infinitesimal model in which mean trait moves with speed of optimum and maintains constant lag?

$$\bar{z}(t) = vt - \frac{v}{s\sigma_g^2} \quad (\text{Bürger \& Lynch 1995})$$

Most effects are small (Jain & Devi 2018)

As before, genetic variance remains constant

But mean trait moves slower than optimum



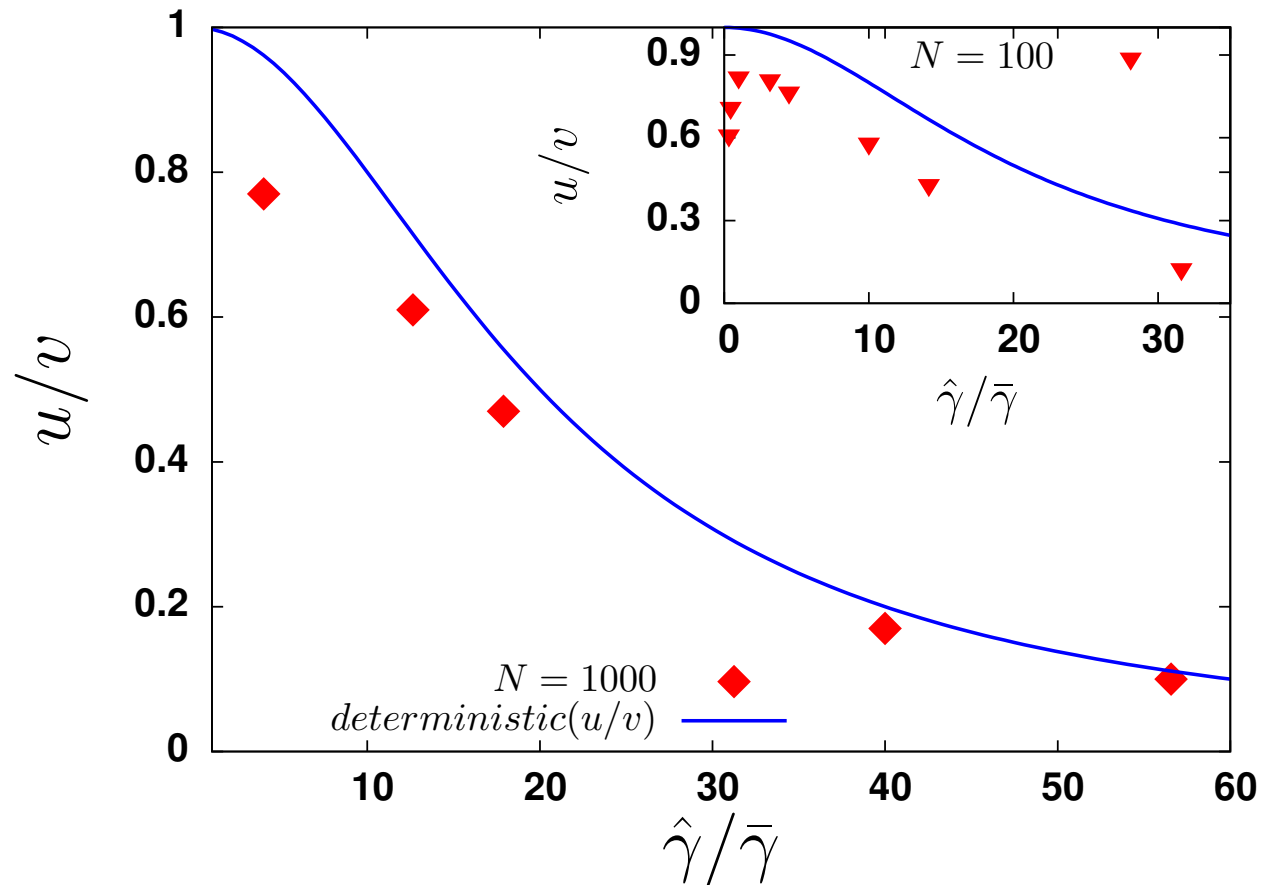
Full model captured by directional selection+ mutation

$$\frac{u}{v} = \frac{1}{1 + \frac{1}{\ell} \left(\frac{\hat{\gamma}}{2\bar{\gamma}} \right)^2}$$

Most effects are small (Devi & Jain, unpubl.)

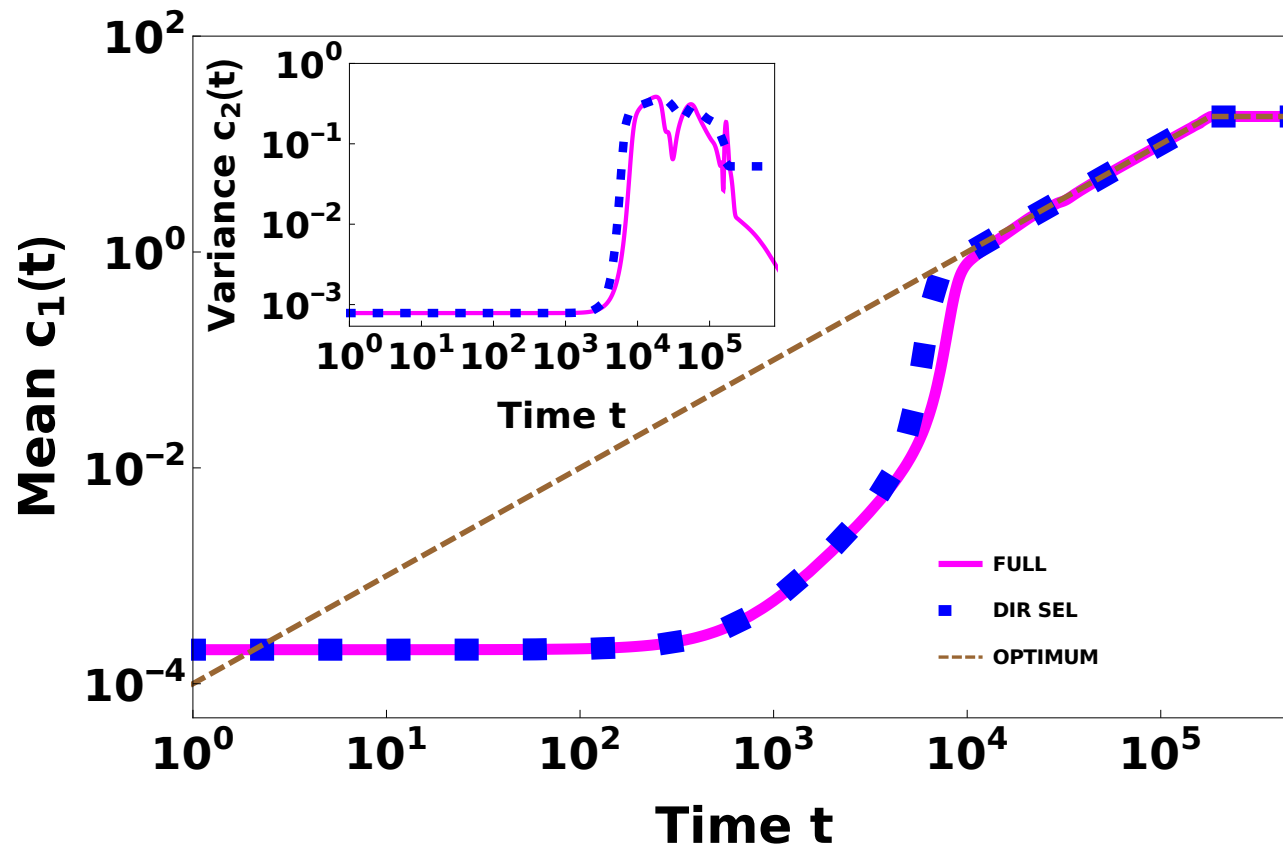
Unlike infinitesimal model, finite loci and recurrent mutations included

Finite pop. size? Speed is slow for stochastic populations also



Most effects are large

- Negligible mutations \rightarrow mean trait moves with the speed of optimum
- Changing genetic variance \rightarrow lag larger than in infinitesimal model



Key results

- When effects are small, recurrent mutations can change the behavior from that of infinitesimal model
- When effects are large, genetic variance does not remain constant unlike in infinitesimal model; it increases dramatically and is an indicator of sweeps

Open questions

- Linkage (although QLE terms can be added)
- Asymmetric mutations (but equilibria not known)
- Periodic, fluctuating optimum
- Random genetic drift
- Multiple traits (pleiotropic effects)

Directional selection model is solvable (Jain & Stephan, 2017)

- $$\dot{p}_i = -s\gamma_i p_i q_i \Delta c_1(\{p_1, \dots, p_\ell\})$$
$$\dot{p}_j = -s\gamma_j p_j q_j \Delta c_1(\{p_1, \dots, p_\ell\})$$

Allows to express the allele frequencies in terms of just one of them

$$p_j = F_j(p_i), \quad j \neq i$$
$$\dot{p}_i = -s\gamma_i p_i q_i \Delta c_1(\mathcal{F}(p_i))$$

- Variance, skewness... can be found using mean

$$\dot{c}_1 = -s\Delta c_1 c_2$$
$$\dot{c}_2 = -s\Delta c_1 c_3$$

No arbitrary truncation needed !

A general result for the allele frequency

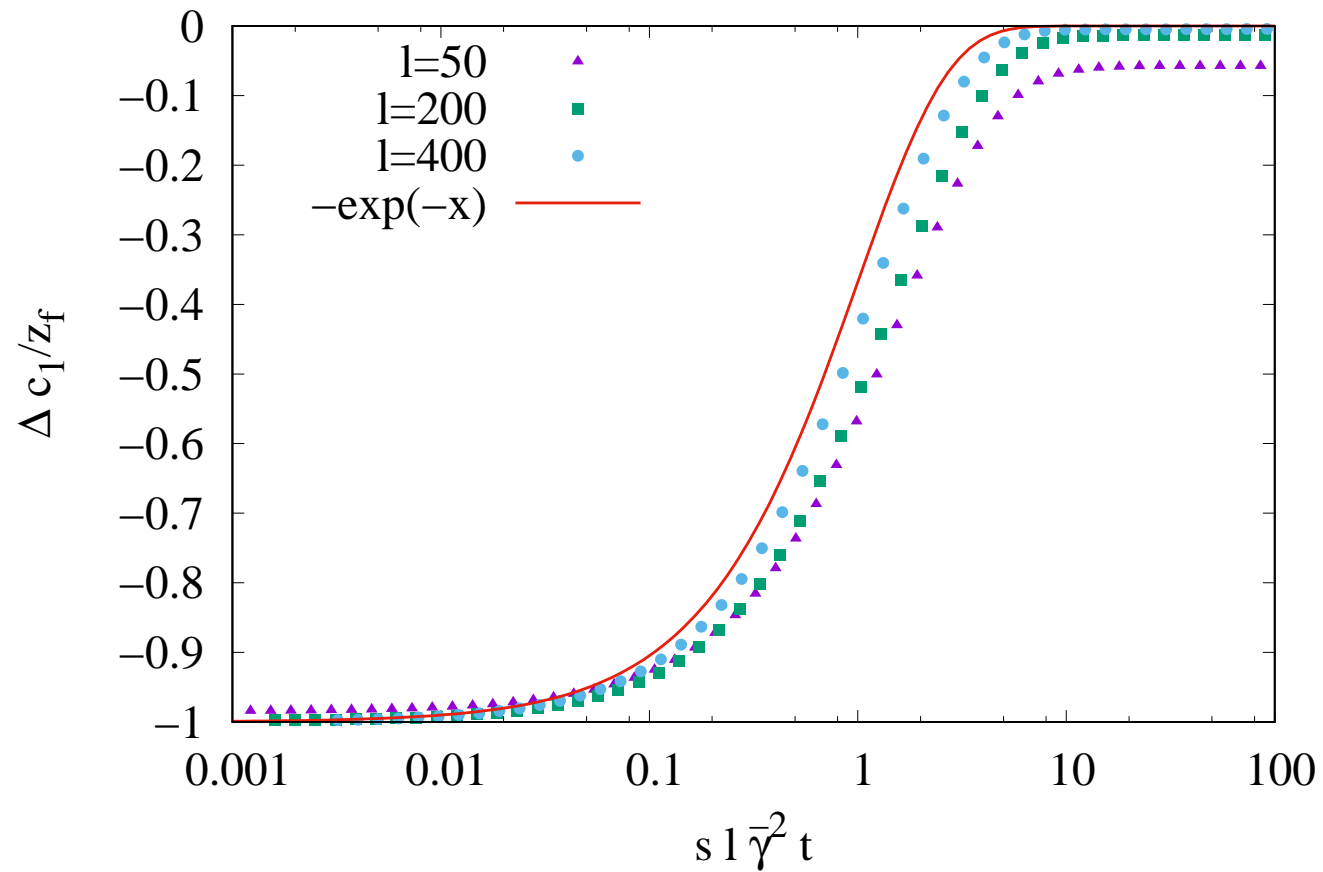
$$\dot{p}_i = -s\gamma_i p_i q_i (c_1 - z_f)$$

At short times, all + alleles increase in frequency

Suggestion: consider many loci simultaneously instead of individual SNPs

Our approximations are good if the number of loci are large

$$\Delta c_1(t) = -z_f \exp(-s l \bar{\gamma}^2 t)$$



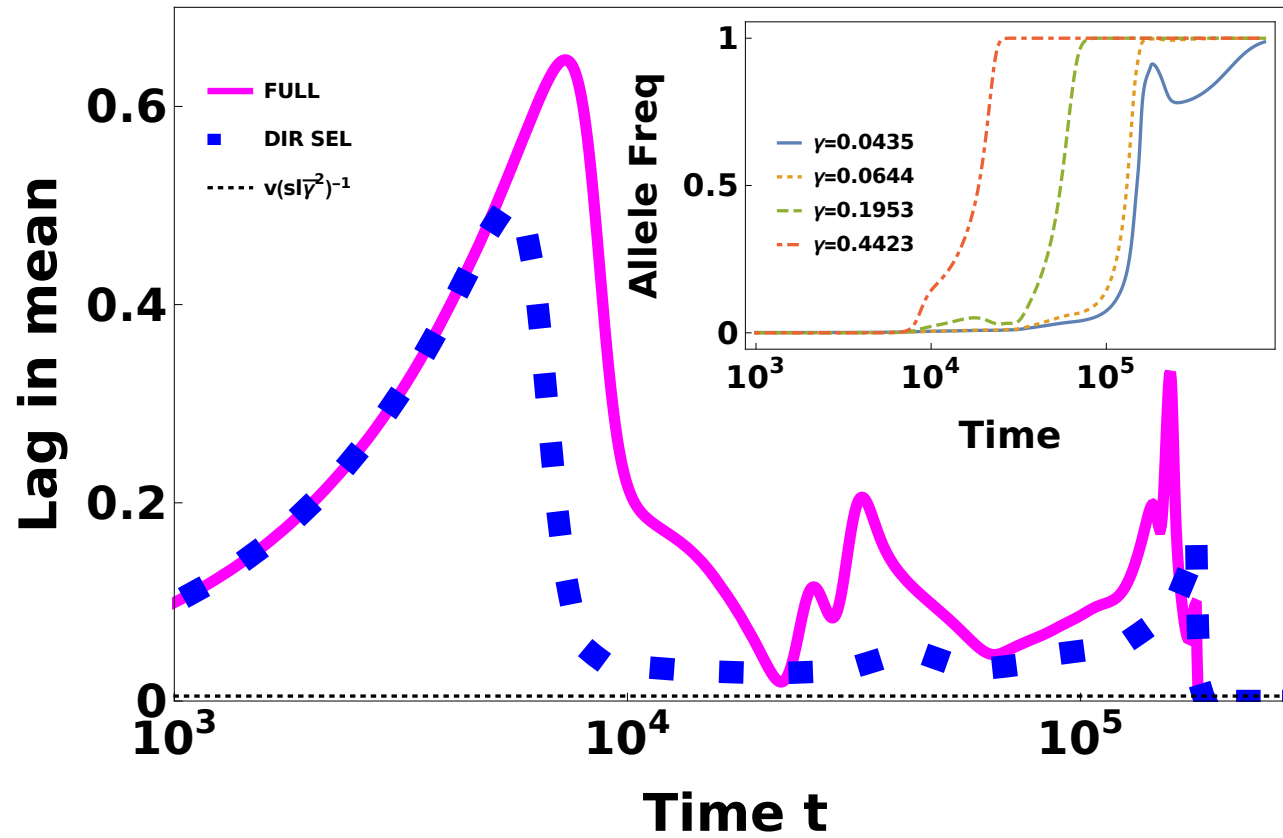
Stationary genetic variance (de Vladar & Barton, 2014; Jain & Stephan, 2015)

$$c_2^* = \underbrace{\frac{8\mu}{s} n_l}_{\text{major loci}} + \underbrace{\frac{1}{2} \sum_{\gamma_i < \hat{\gamma}} \gamma_i^2}_{\text{minor loci}}$$
$$= \begin{cases} l\bar{\gamma}^2 & , \bar{\gamma} < \hat{\gamma} & \text{(small effects)} \\ l\hat{\gamma}^2 & , \bar{\gamma} > \hat{\gamma} & \text{(large effects)} \end{cases}$$

small effects : polymorphic equilibria hence large initial variance

large effects : near-fixation hence small initial variance

Large effects and moving optimum



Mixed effects and moving optimum

Mean trait moves with speed of optimum with constant lag

