**Major Comments**

Introduction didn’t properly set people up for the big takeway (several people didn’t get it from the results alone, either)

I’m leaning towards a short intro, something like:

The extent to which mutations affect a variety of phenotypes matters to evolution

Shorten

Environment/condition distinction was confusing (just stick to one)

“evolution condition” also confusing – this needs to be more clearly explained (and also what “batches” are)

Maybe we should rethink SVD placement? At the beginning of section 1?

Importance of subtle perturbations was not clear

**INTRODUCTION**

I think we could shorten the introduction and focus less on this semi-false contrast between universal pleiotropy and large effect mutations.

Just go with something like at the end?

Cis/trans did not work for people at all

People did like the last paragraph

**Figure 1**

**Part A**

Had relatively mixed takes, some people liked it but thought a few things lacked:

1. Different weightings in different environments (could easily include another “fitness” box with colored arrows to each and show variation)

**Part B**

People got really confused by the matrix entries (partly b/c of 4x4 nature of both of them). Need to cue this better. Also maybe re-think what the matrix notation is? (one suggestion is using p for phenotype and w for weighint of the environment)

Should we do something about the fact that SVD actually has a third matrix? Maybe briefly acknowledge in main text with details in the methods (people who know SVD may think it’s weird there are ony 2 matrices, as per Chuan’s comment).

Peppered moth example is now incorrect as written (non-melanic was under selection post-industrial)

Maybe rethink a few things:

**RESULTS**

**Figure 2**

Time needs label in panel A

**Figure 3**

Nobody cared about the fact that our approaches worked in simulation. Maybe just talk about that only in the methods? [at the very least they thought we were talking about real data already, because we sort of do]

**Figure 4**

Needs A and B shown.

Streamline diploids into high-fitness diploids (including those w/ extra mutations)

Cut down on # mutants with color in Figure 4. (maybe just show the canonical 4?)

Need supplemental figure (or additional to main Figure 4) showing drop in explanatory power for large number of components (pick a number)

Need to point out why we show the 4 conditions we do in B.

**Figure 5**

Need labels on the points on A. Maybe just focus on 3 conditions in two components? Just need to show: components capture mutant behavior, and it’s context-dependent (both which mutants show up and which conditions have any importance)

**Minor stuff:**

Talk about relationship between effect size and pleiotropy in discussion?

i.e. mutations (at least these ones) tend to be locally modular – this explains why large effect mtuations might be possible despite early inclinations that they might otherwise not be.

Adaptation is a process that selects for mutations (organisms) whose traits are best suited to a given environment. If mutations only affect a single trait, then this process is straightforward, and mutations that affect the trait in the correct direction will be adaptive. However, this process is more complicated when mutations affect many traits that matter to fitness, as the net effect of the traits must be beneficial.

Because of this complication, there is a lot of work trying to understand the phenotypic effects of mutations and uncovering the genotype-phenotype-fitness map. The important piece of this puzzle is that, while it’s possible for mutations to affect many phenotypes, it could be that only a subset of of these pphenotypes matter to fitness.

This super hard (need to understand effect of genotype on phenotype AND how those matter to fitness in a given environment)