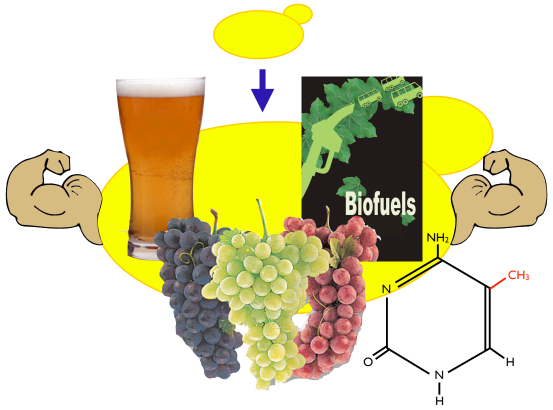

Watching Yeast Change: Using Genomics to Understand the Adaptive Landscape

Gavin Sherlock

sherlock@genome.stanford.edu

February 7th 2011

KITP Program on Microbial and Viral Evolution

The Classic Model of Asexual Evolution (Muller, 1932)

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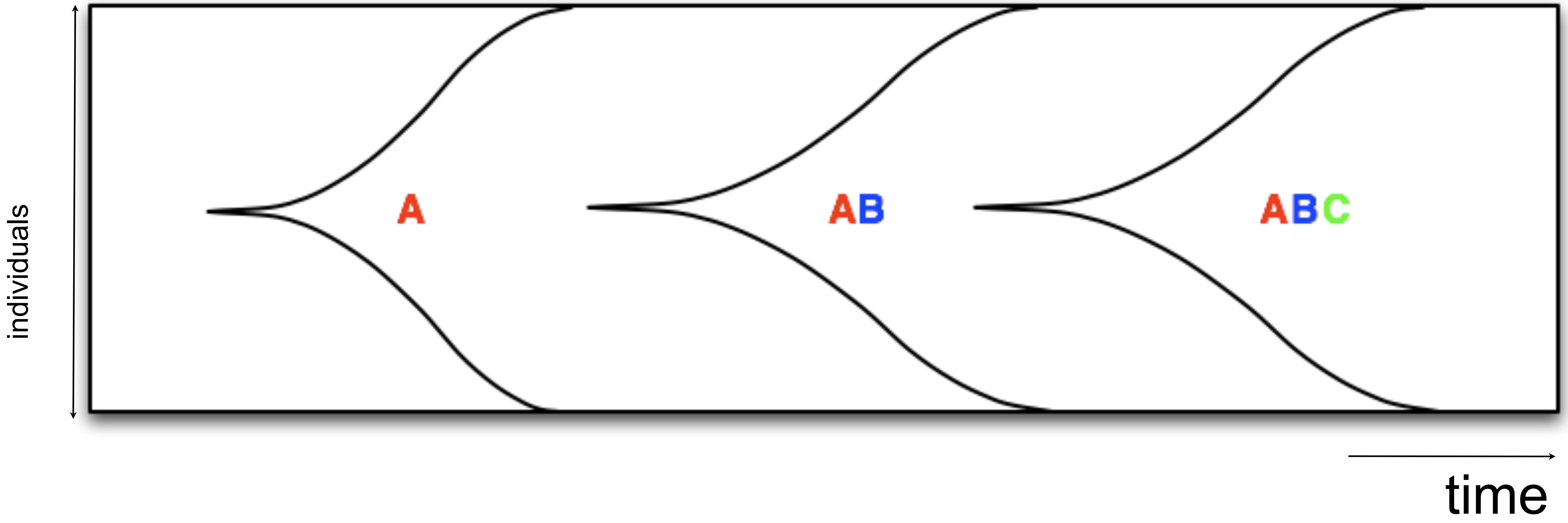
- The population should consist of a single clone, except during periods when an adaptive shift is occurring.
- Known as clonal replacement, and predicts “adaptive sweeps”.

Change in Population Structure Under Classic Model



Adapted from Desai and Fisher, 2007

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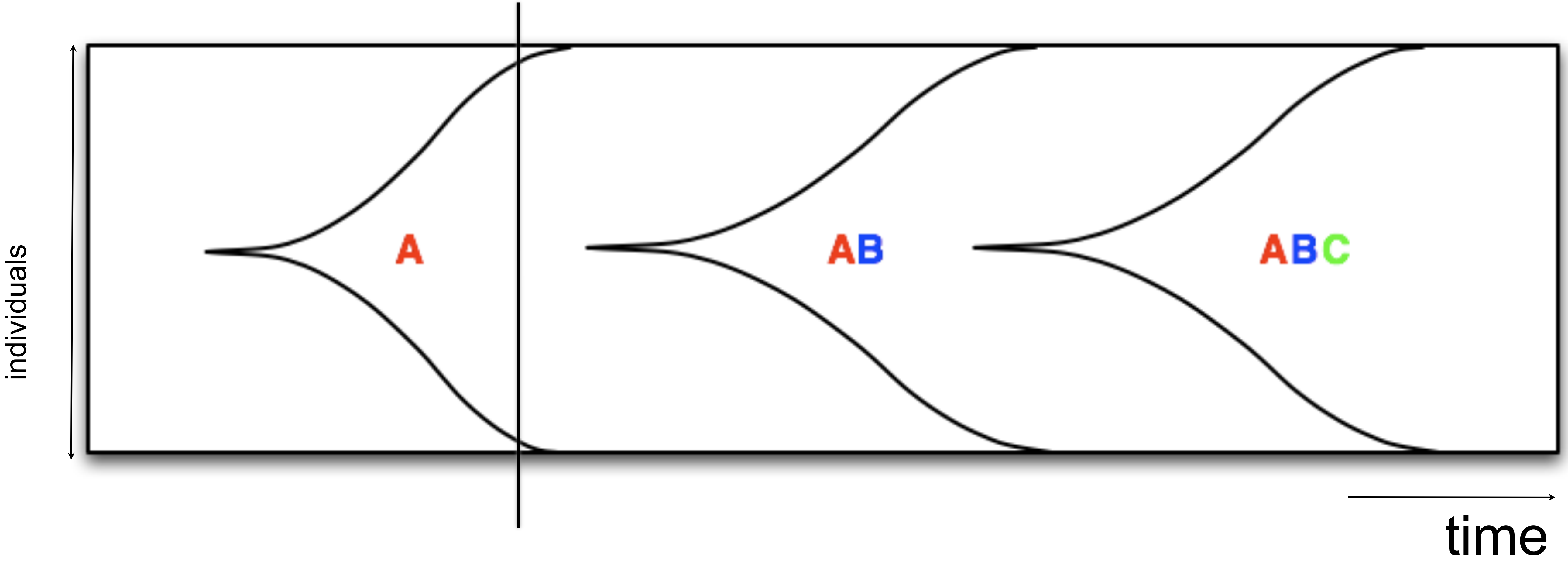

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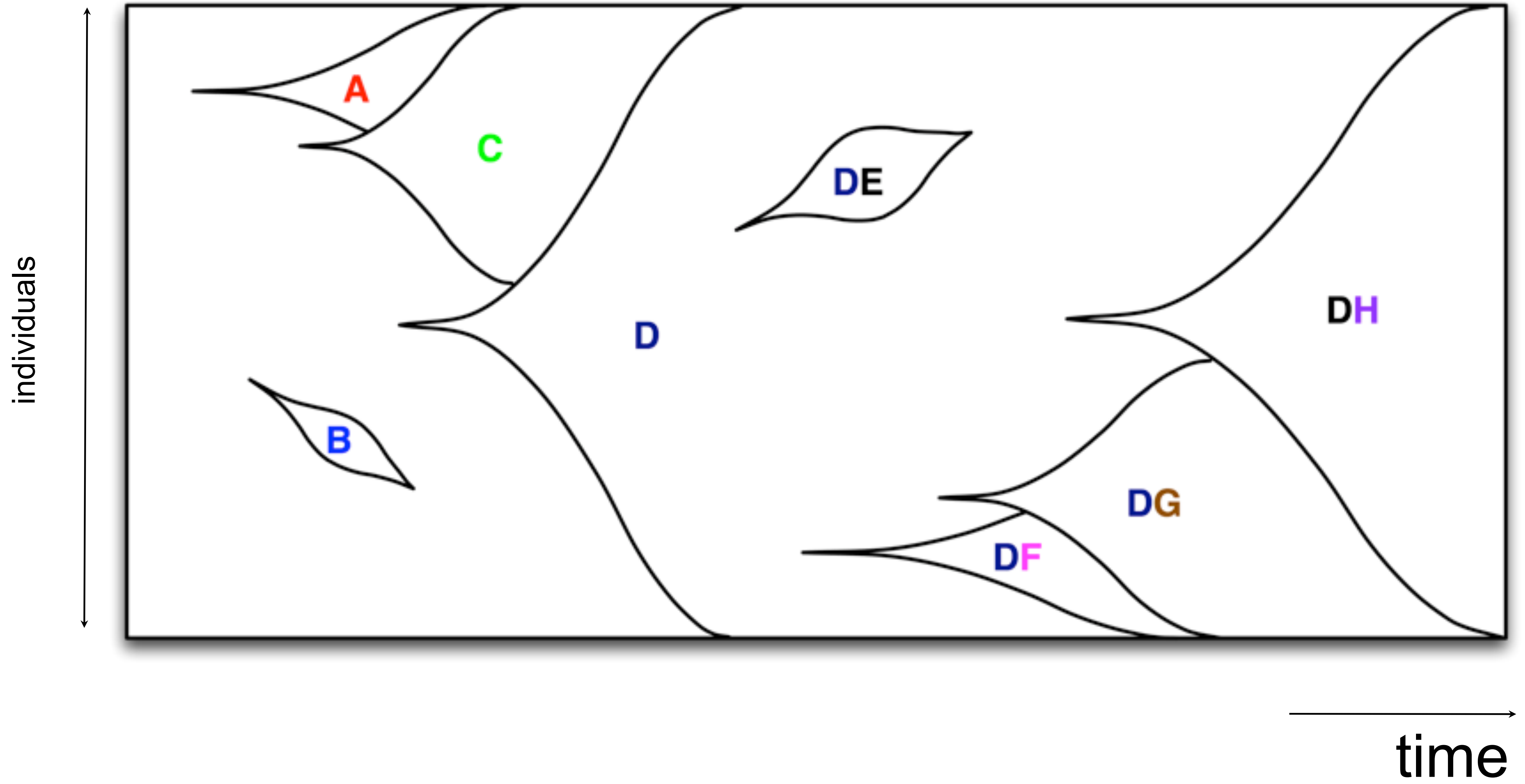
Population structure in the presence of clonal interference



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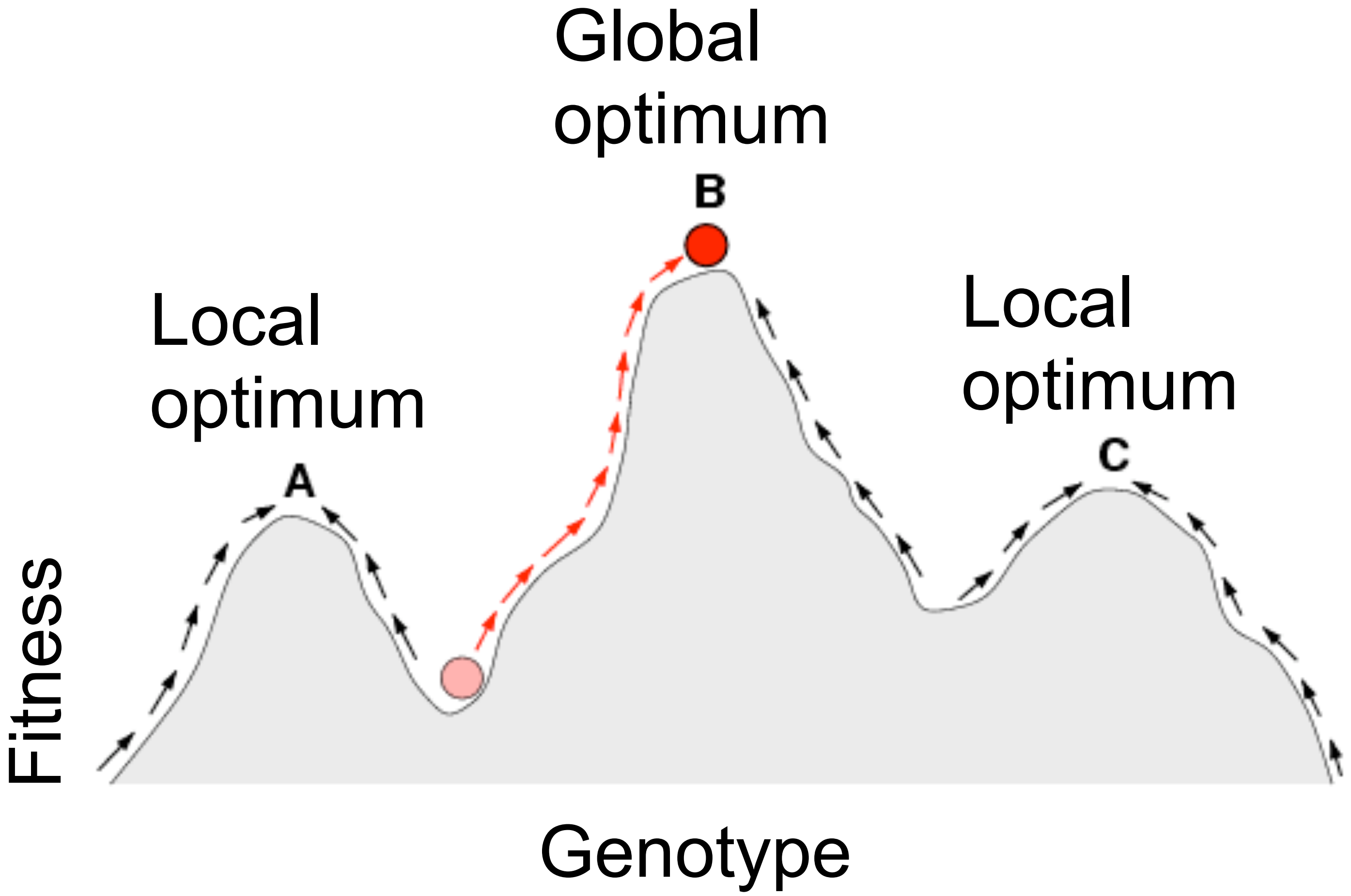
The adaptive landscape and evolutionary trajectory



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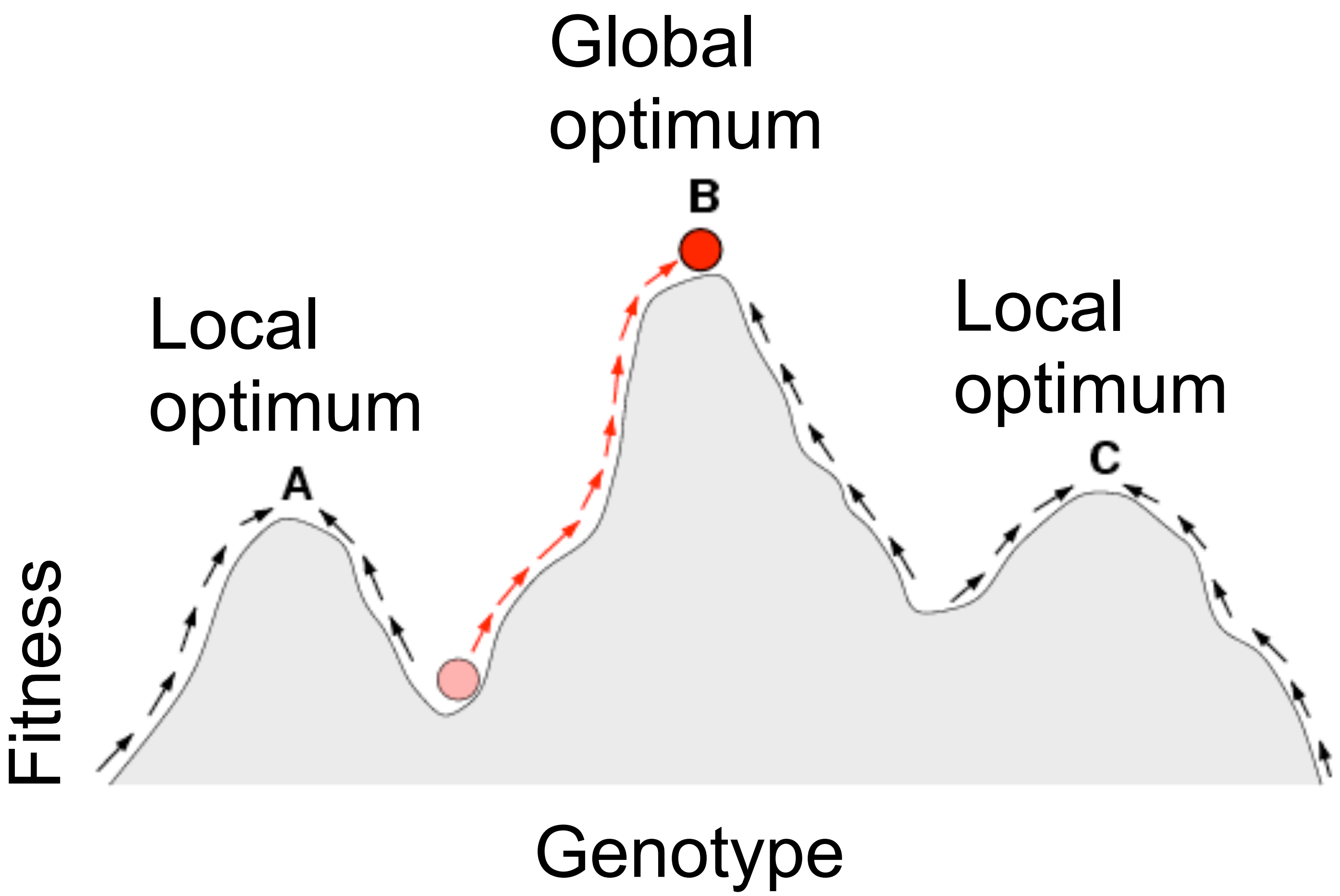

What about in reality?

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Experimental System to Identify, Count and Isolate Clones in an Evolving Population

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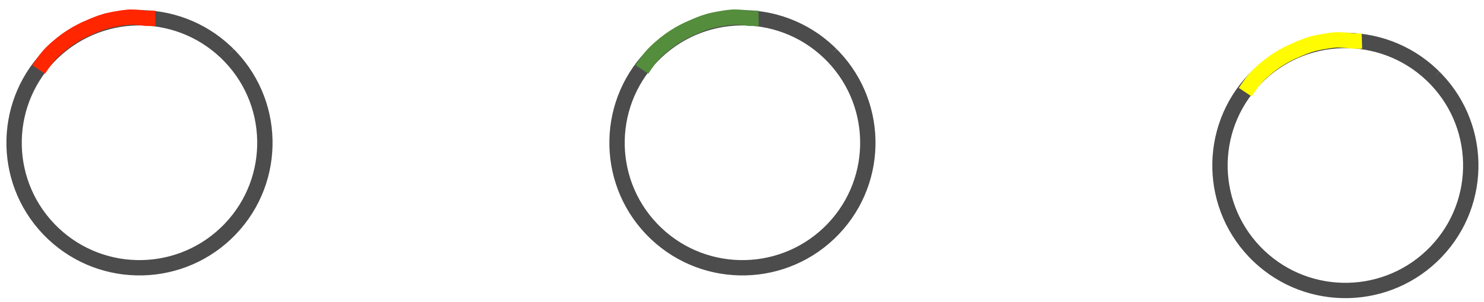
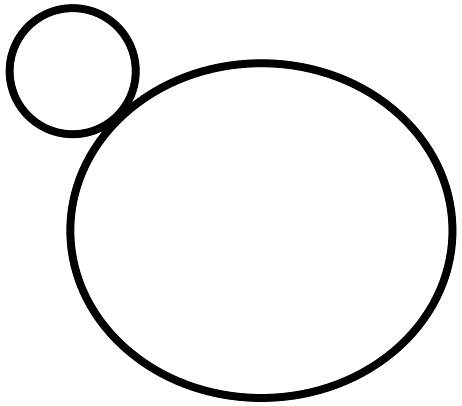


Integrate different fluorescent proteins into yeast cells



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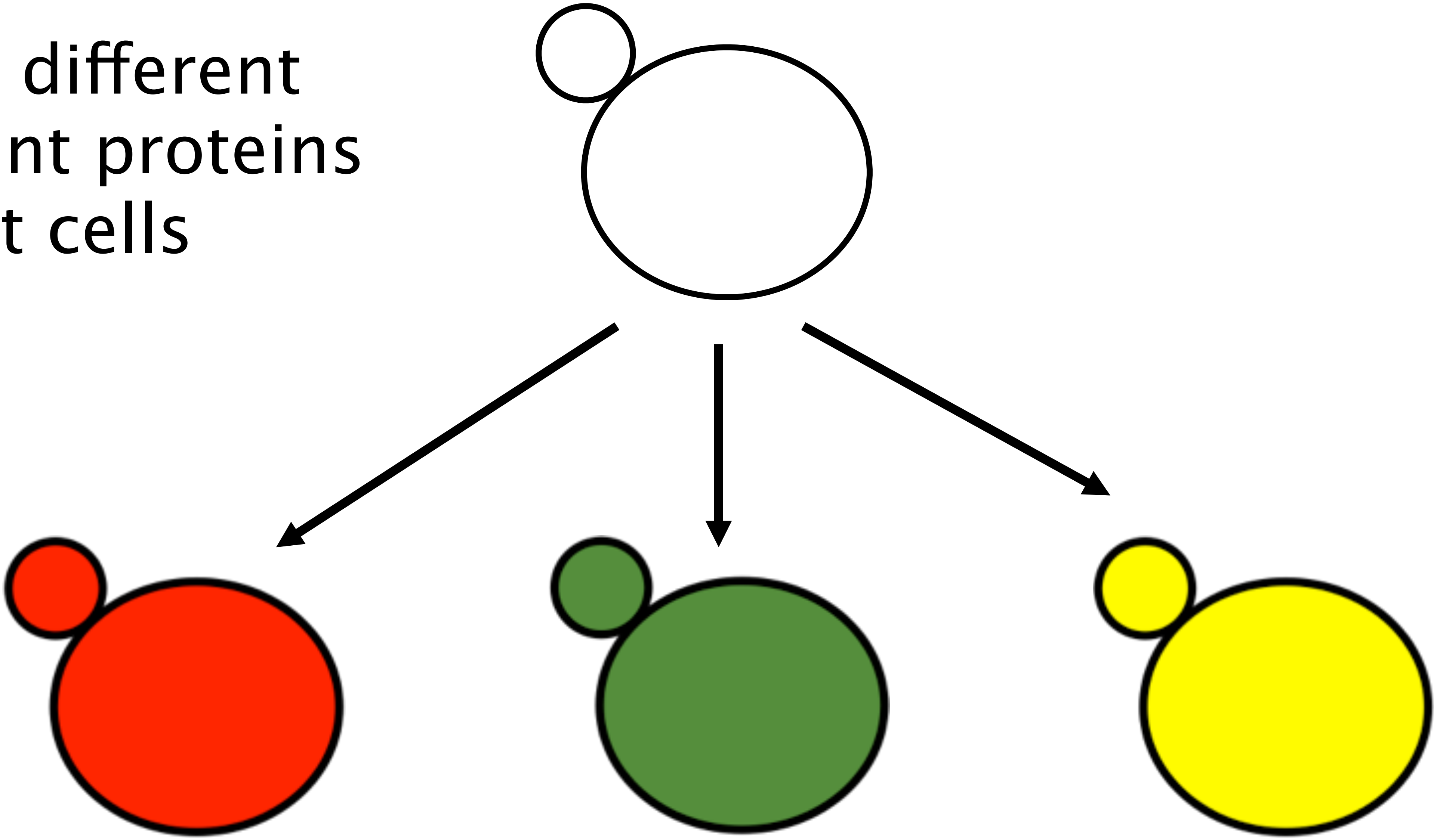
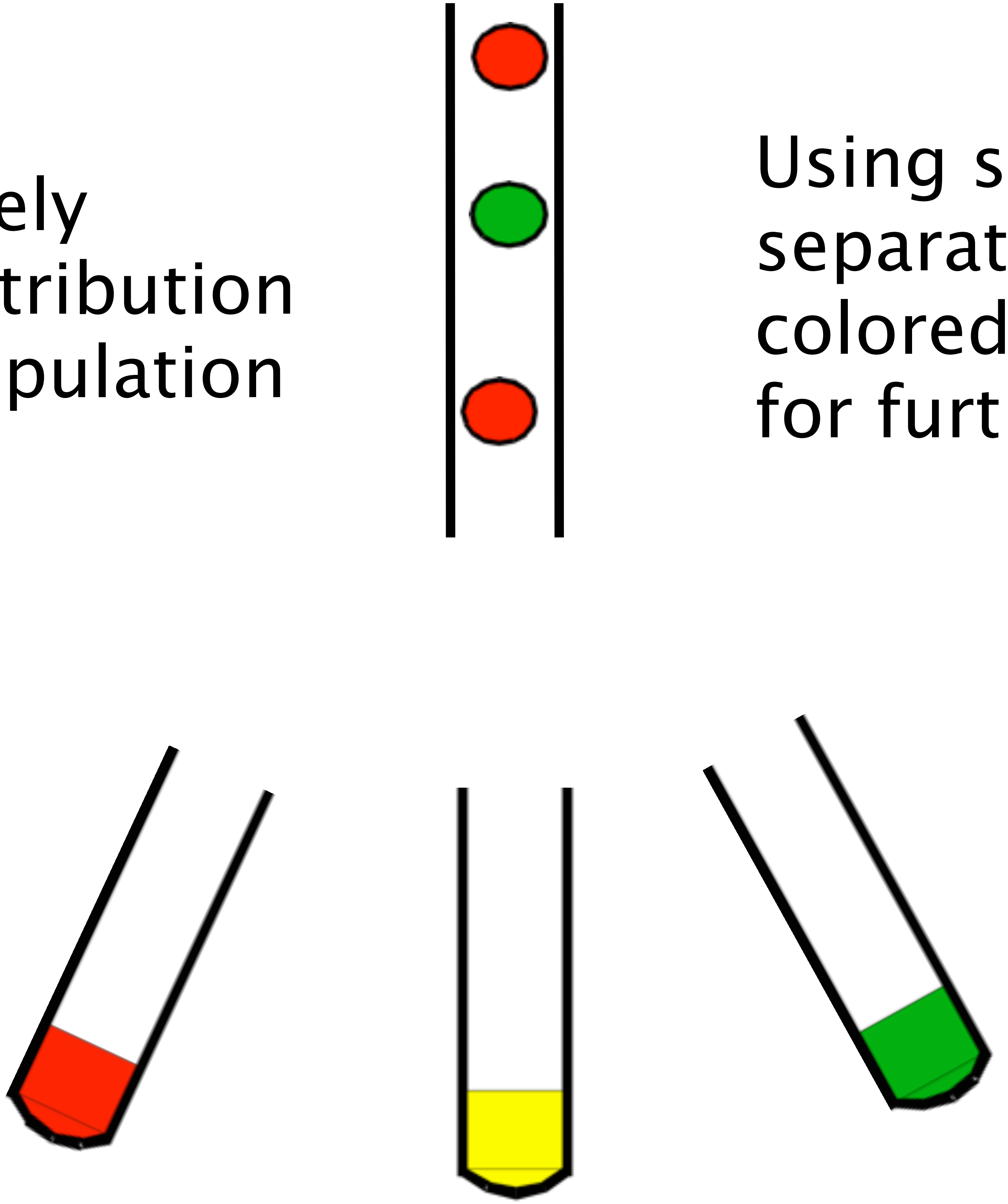


Count and Sort Cells

FACS accurately measures distribution of colored population



Using sorter to separate out each colored population for further studies

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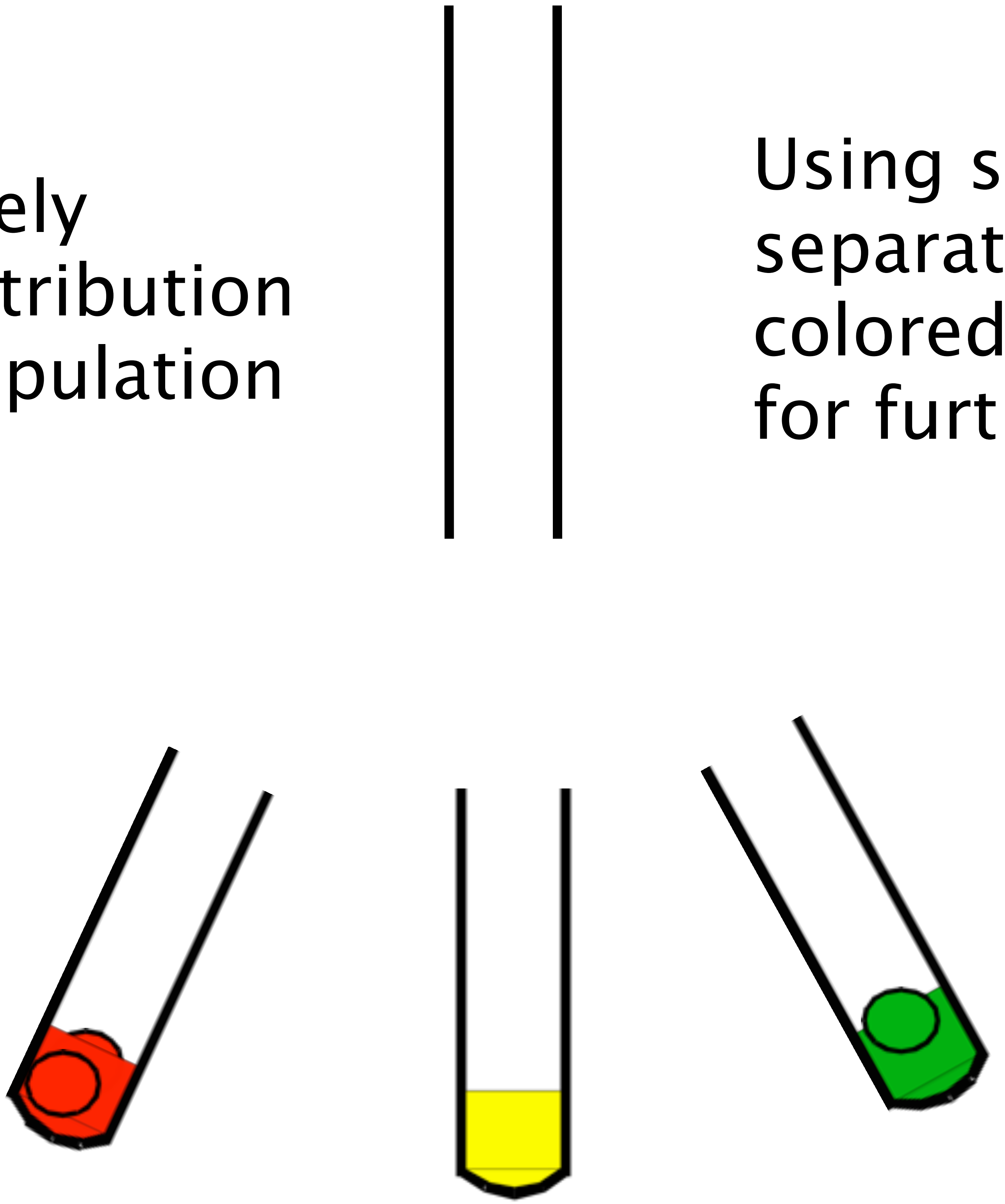

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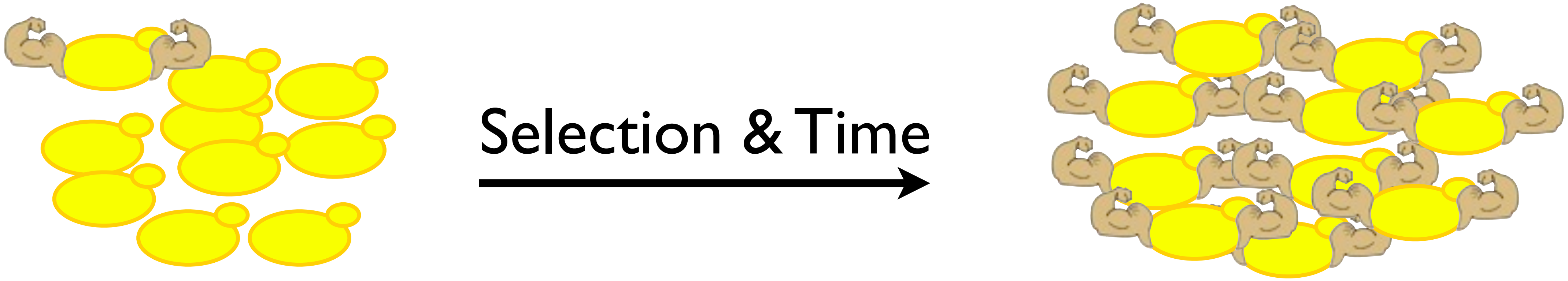
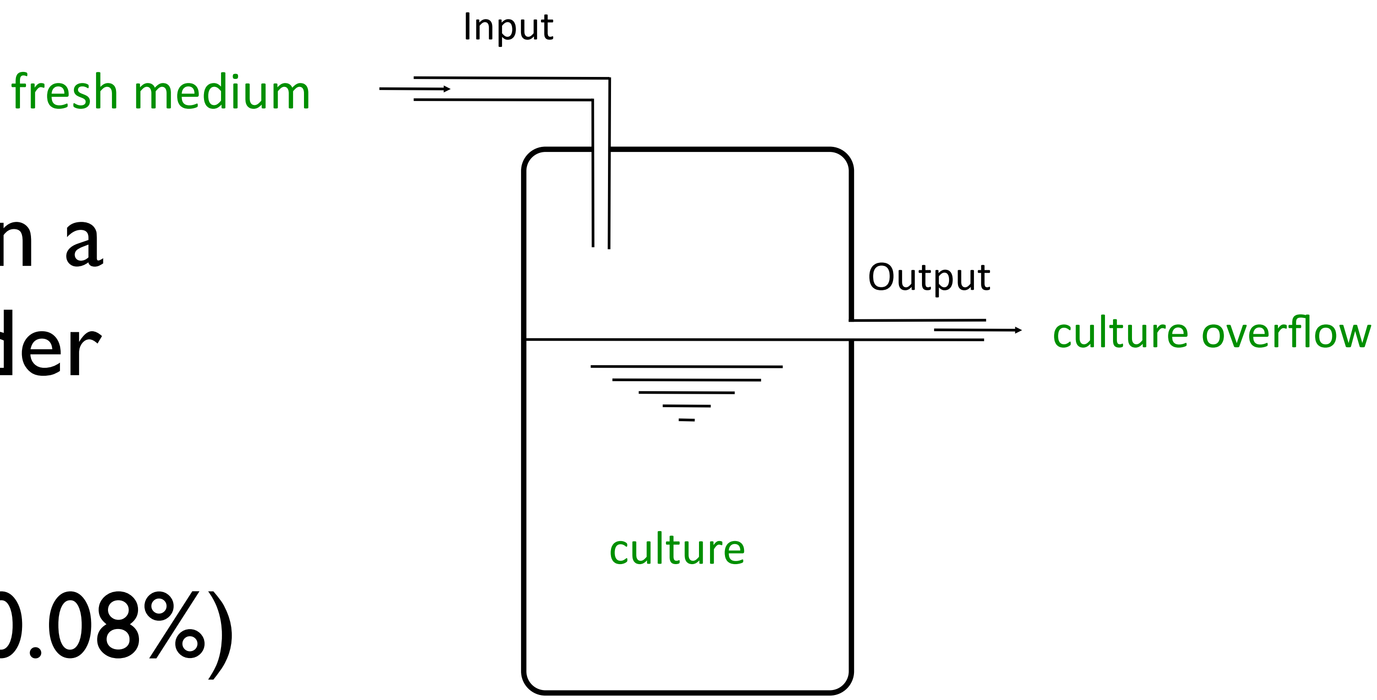
Yeast in chemostats: Selection in action

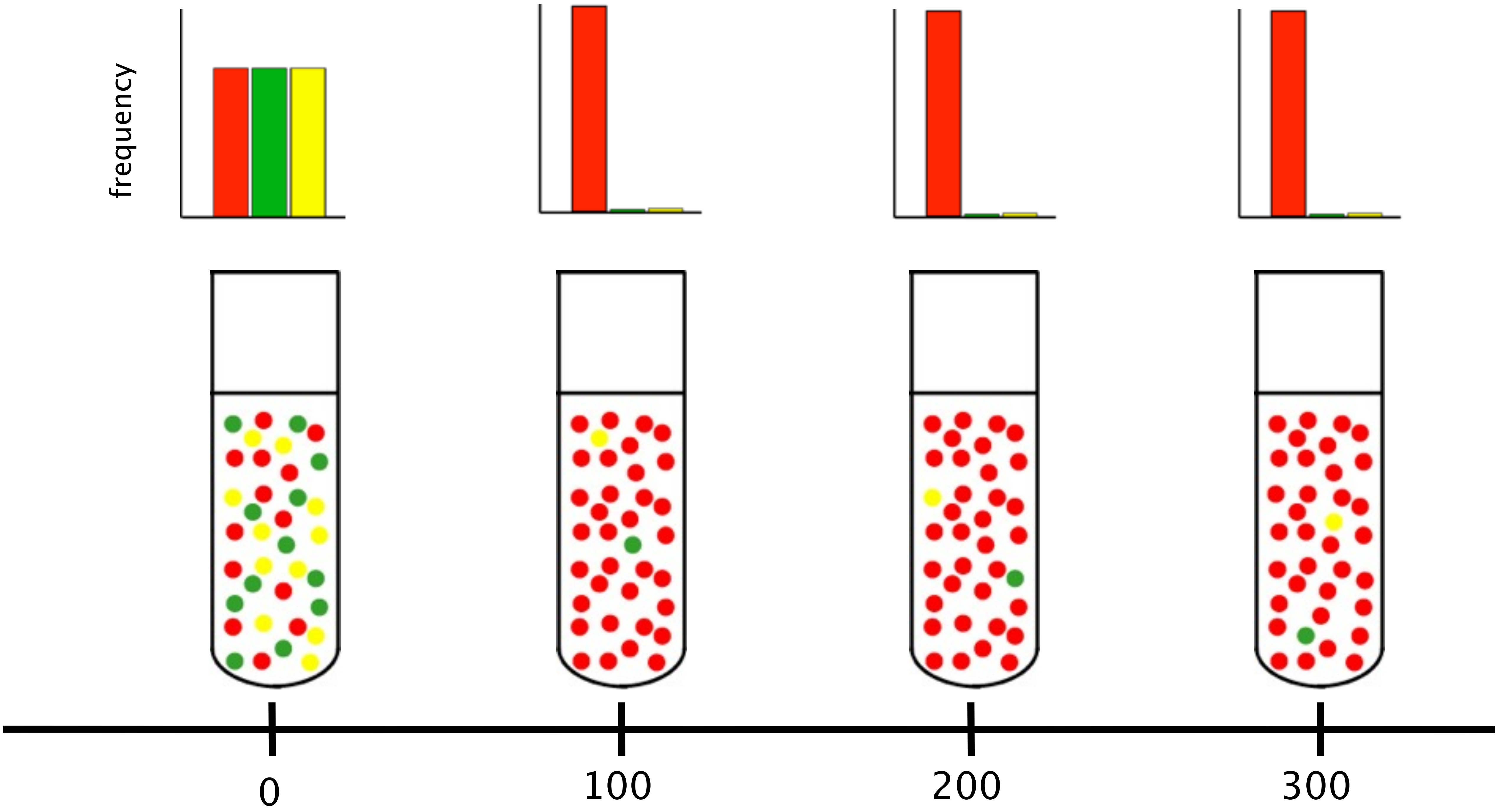




- Continuous cultures maintain a steady-state growth rate under nutrient limitation.
- Limiting nutrient: Glucose (0.08%)
- Asexual *S. cerevisiae*
- Haploids

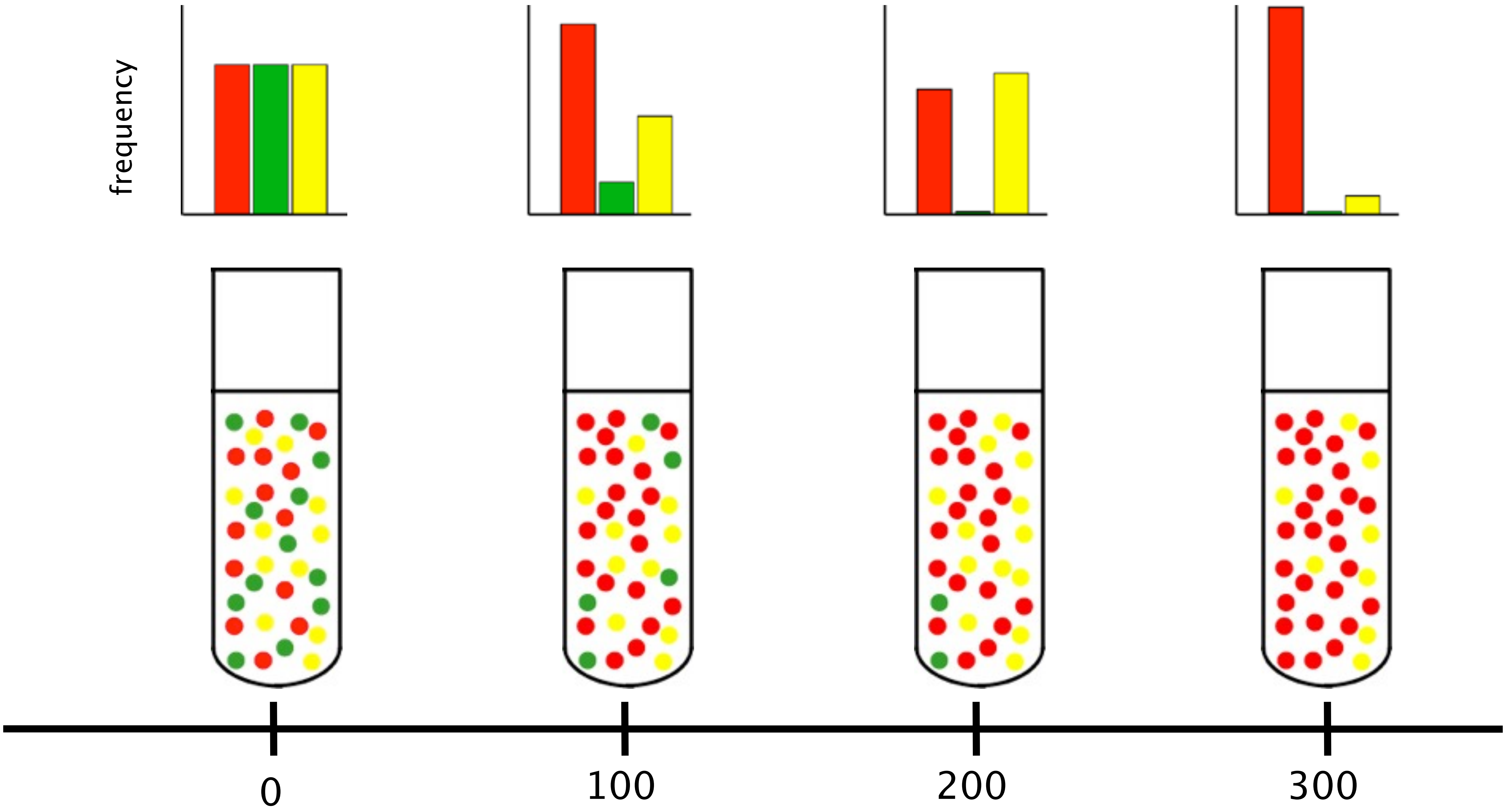
$N = \sim 10^9$

Classical model of clonal replacement



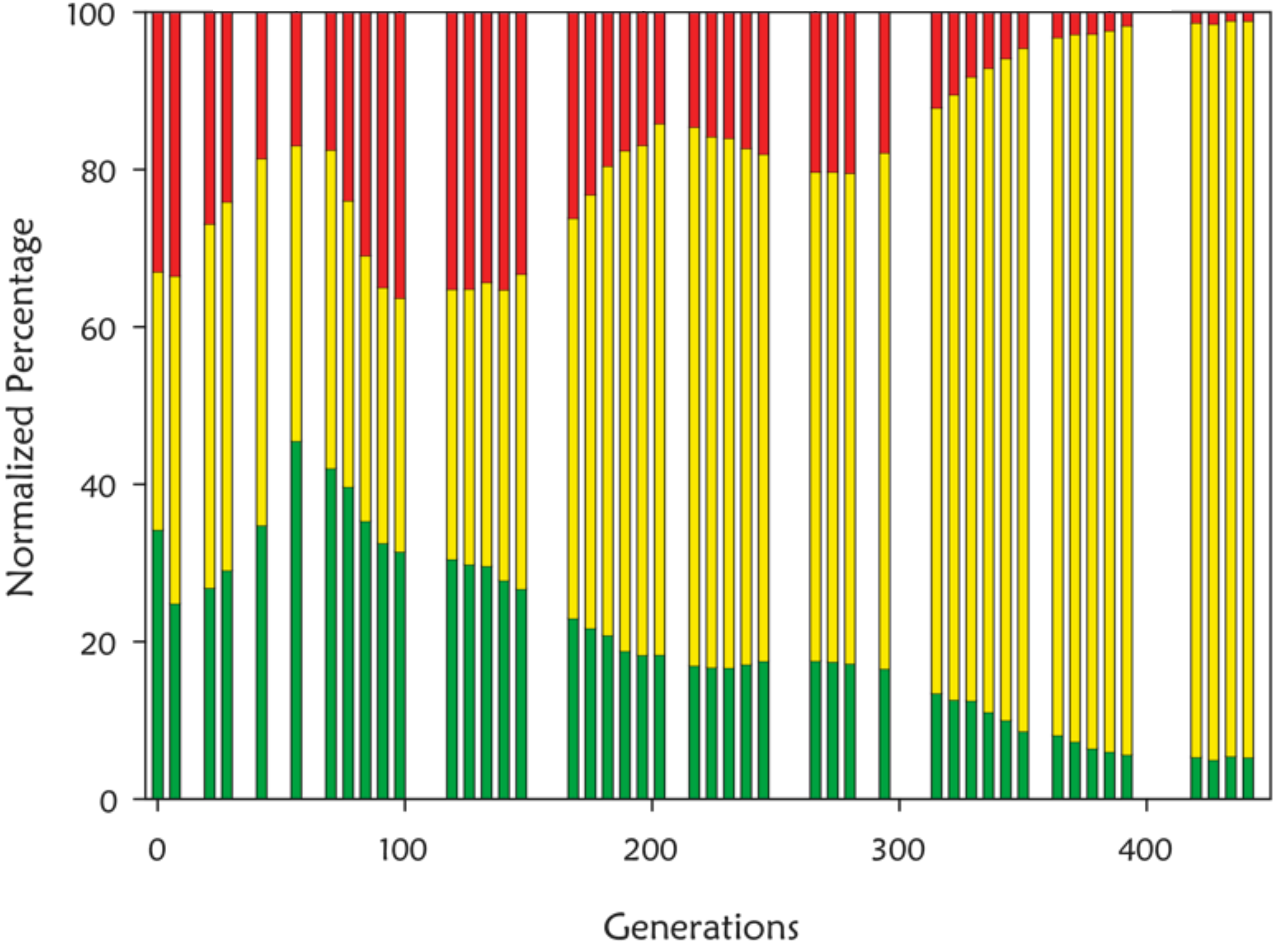
Generations

Evolution in the Presence of Clonal Interference

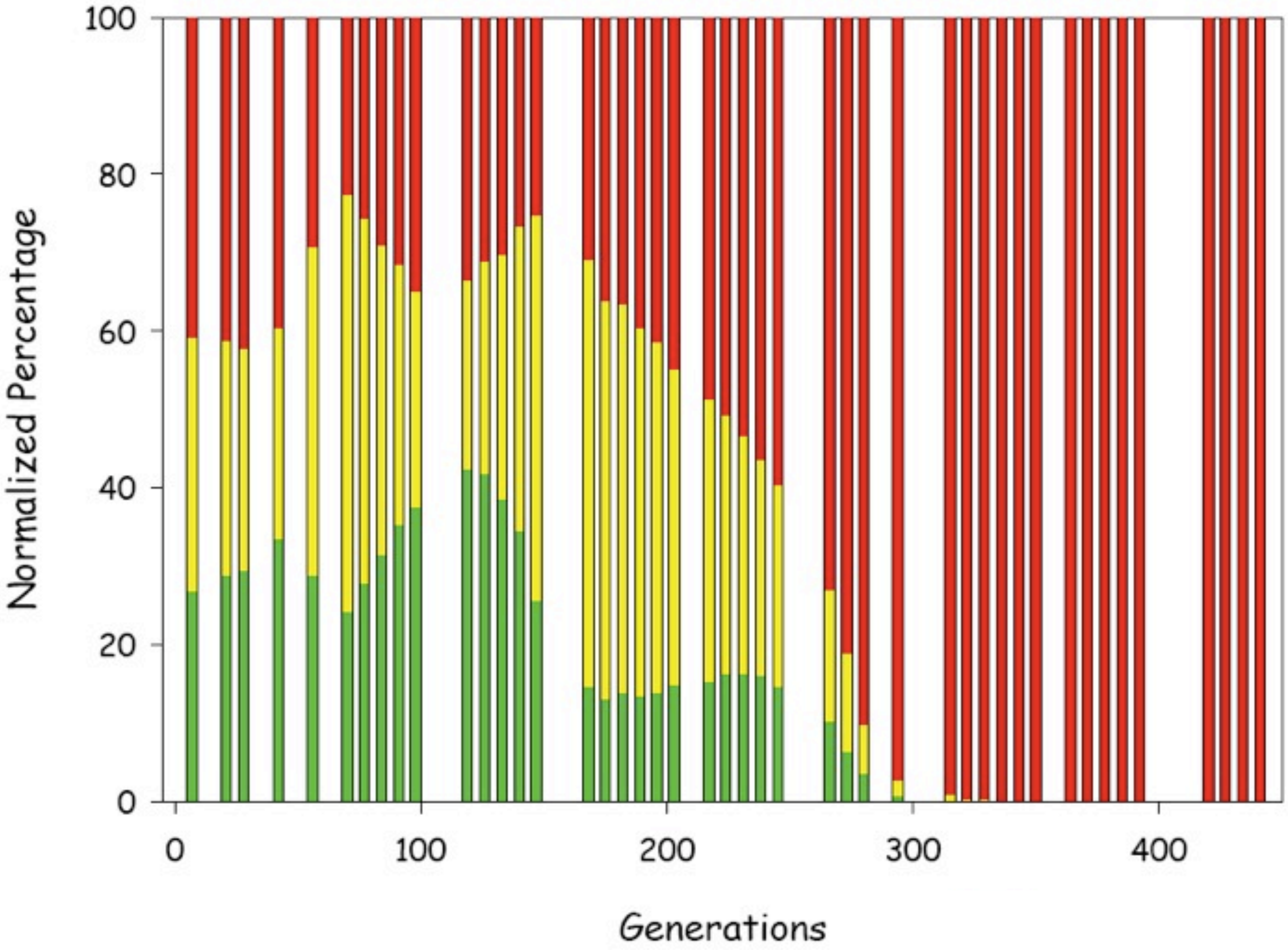


Generations

Results: Experiment #1



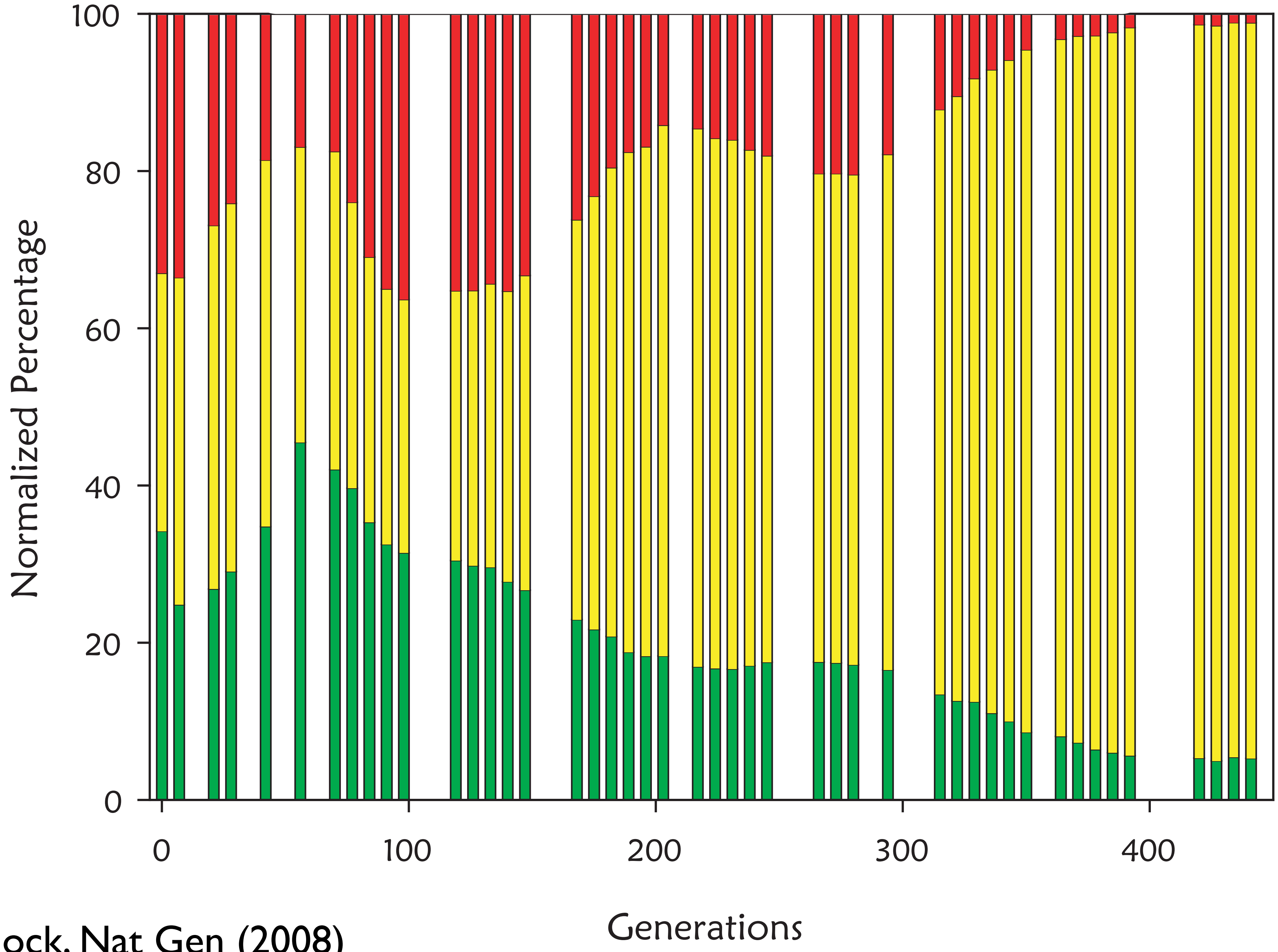
Results: Experiment #2



General Observations

- Adaptive events (observable expansion of a population) roughly every 50-100 generations
  - Similar to previous reports for yeast
- Clonal interference plays an important role in shaping the population structure
- Note - fixation of a color is not necessarily indicative of fixation of an adaptive event.

Sorted Subpopulations



Kao & Sherlock, Nat Gen (2008)

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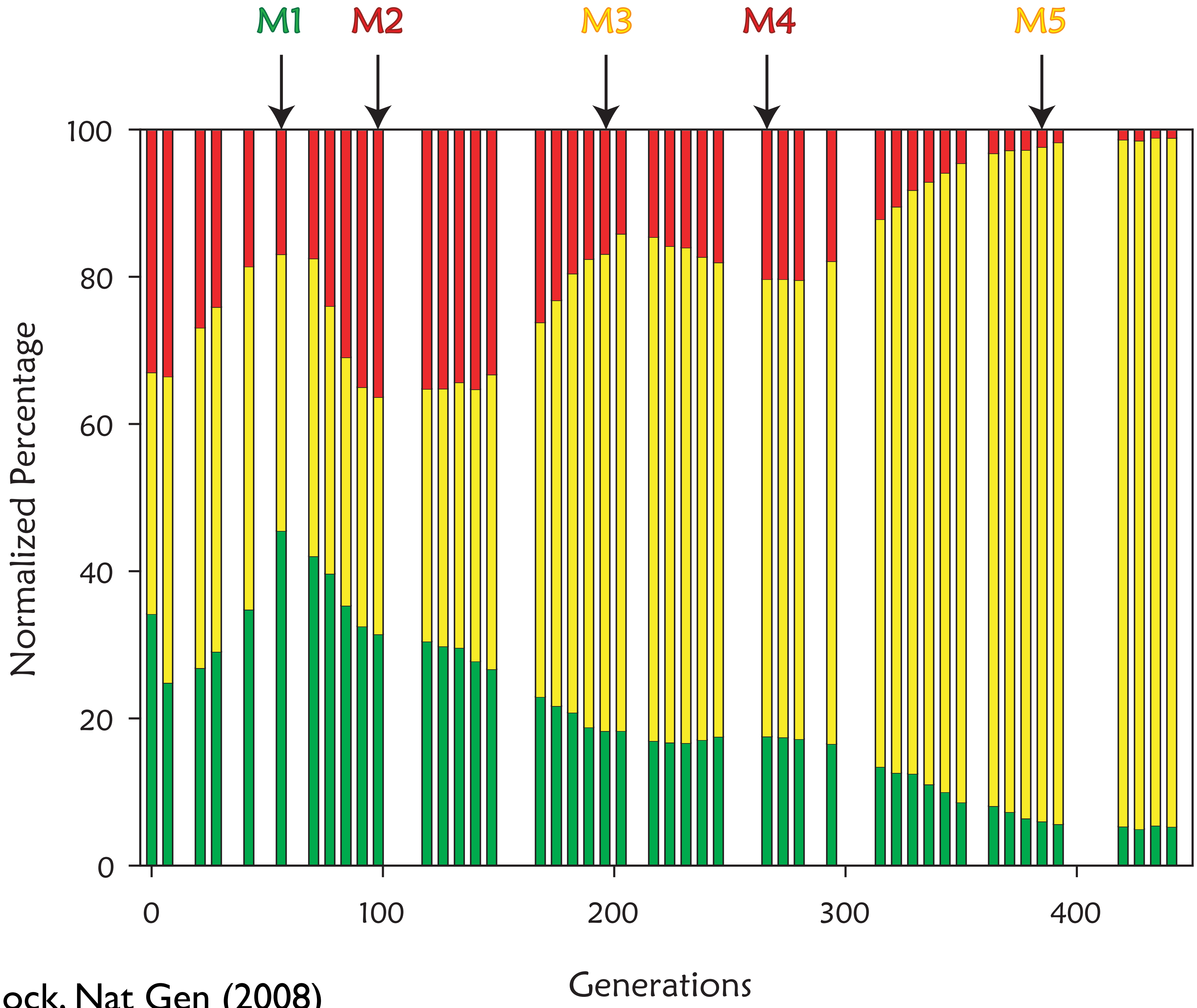

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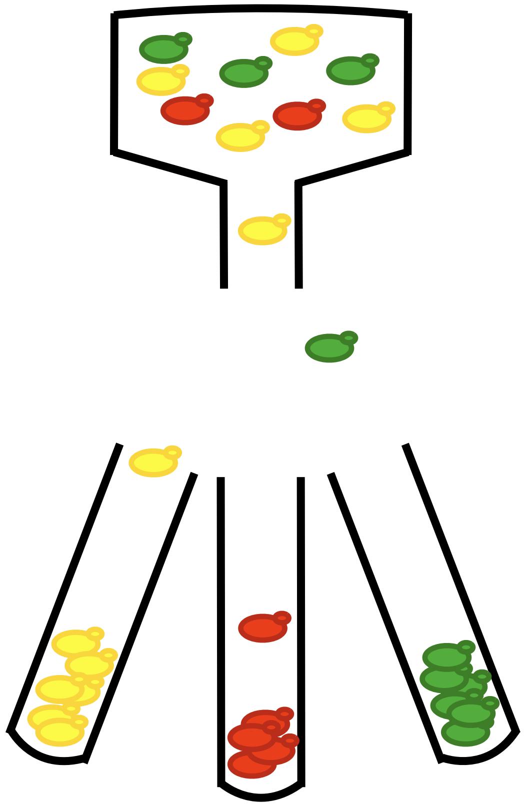
Characterizing Adaptive Clones



Sort

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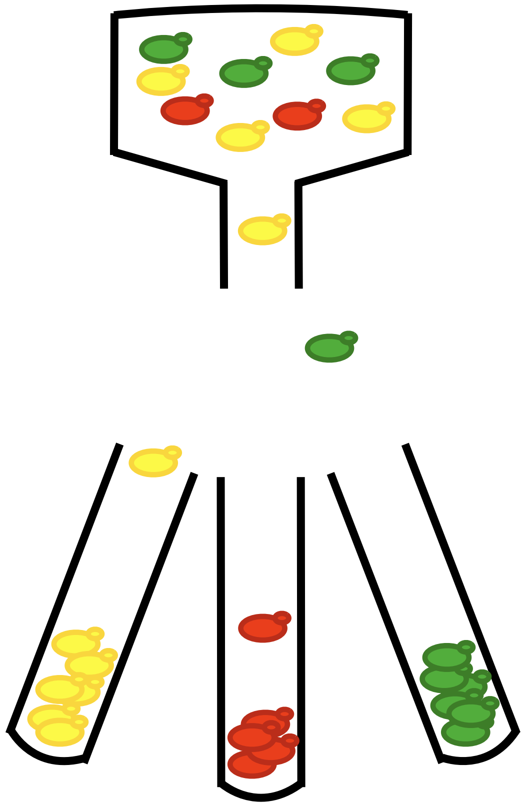

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Isolate 7 clones →

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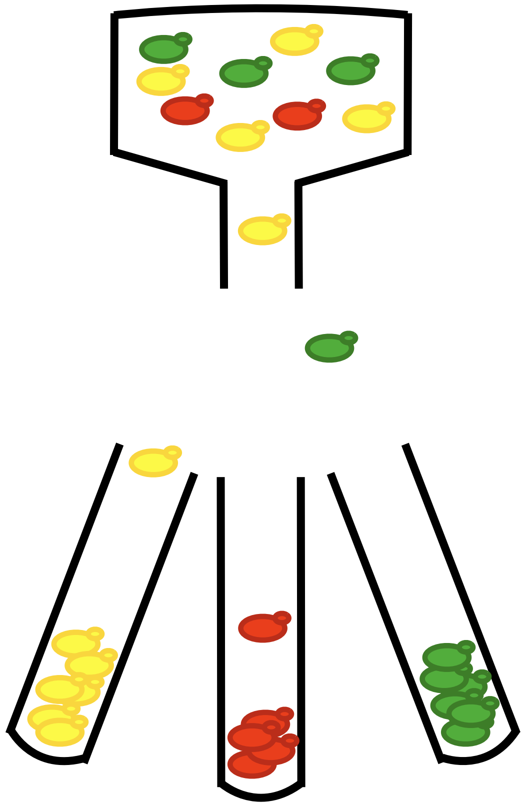

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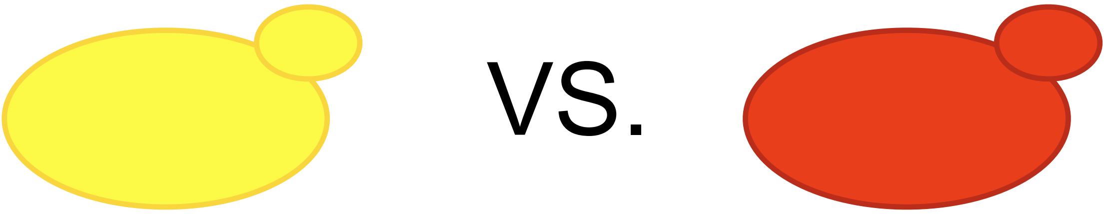
Isolate 7 → clones

Compete in competitive
chemostats



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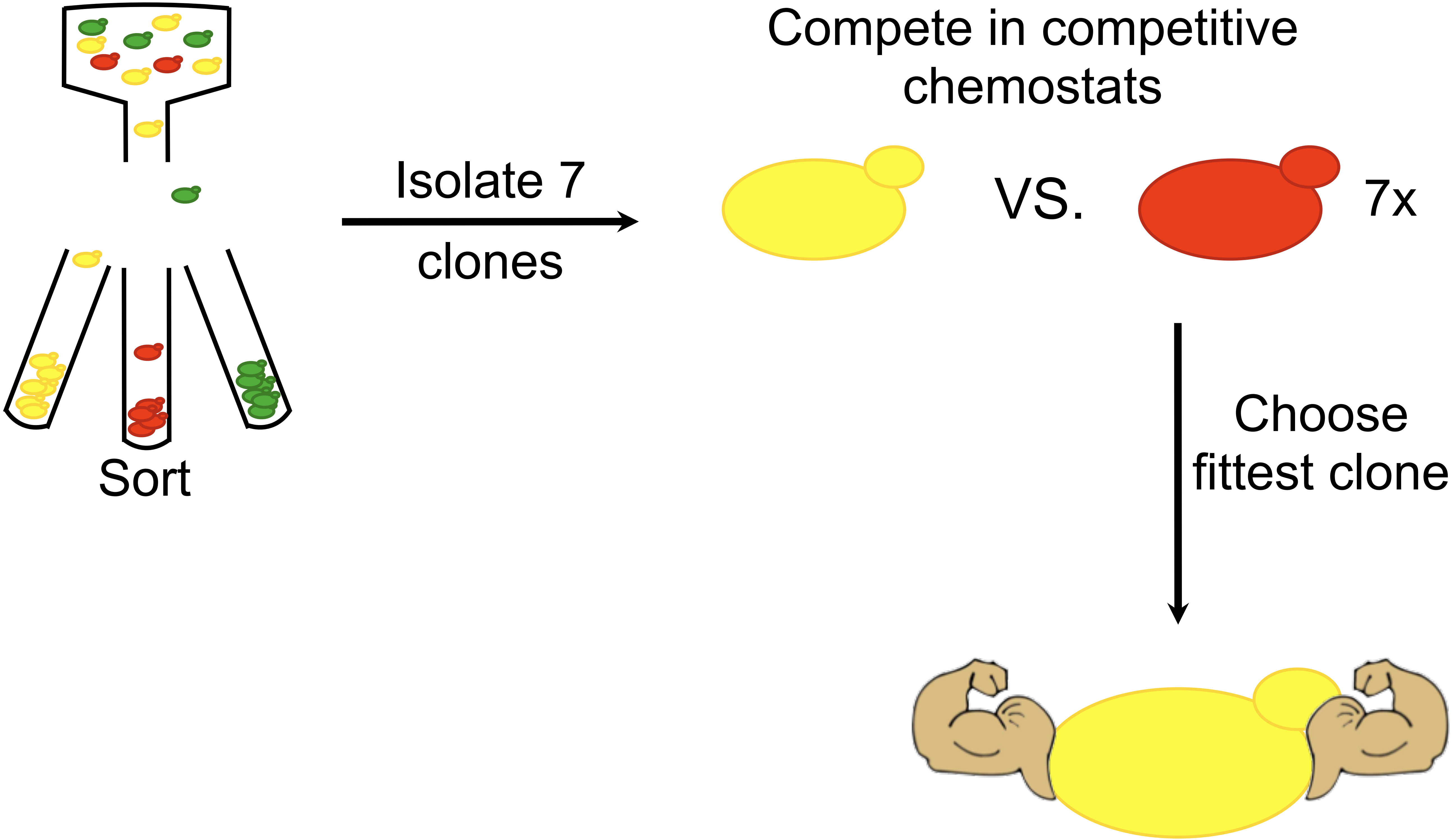

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VS.

7x

Choose fittest clone

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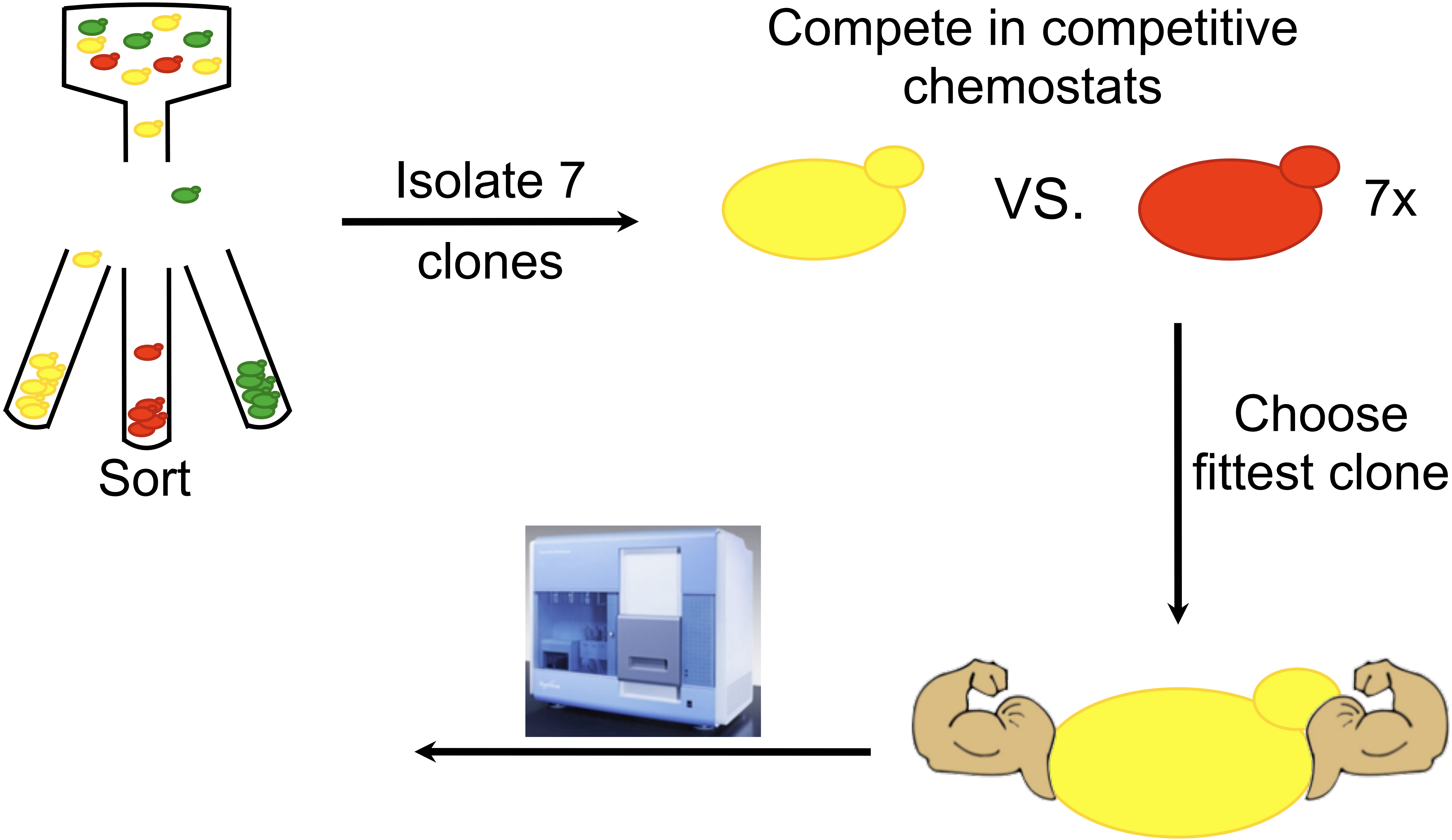

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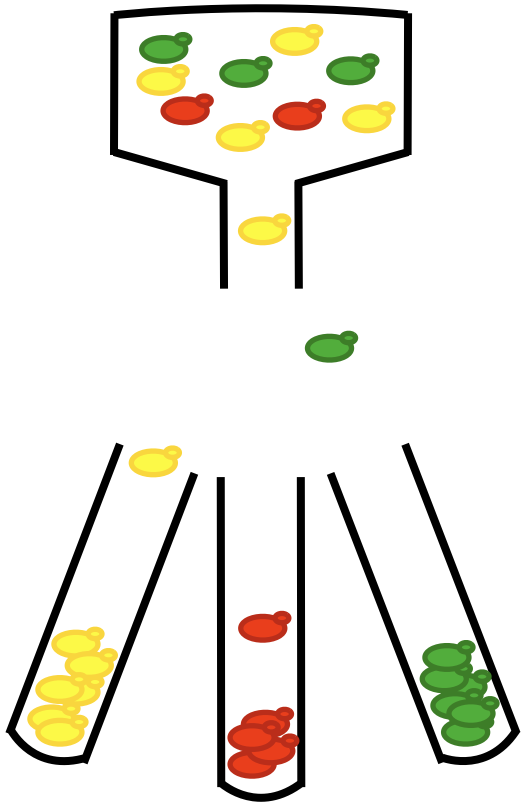

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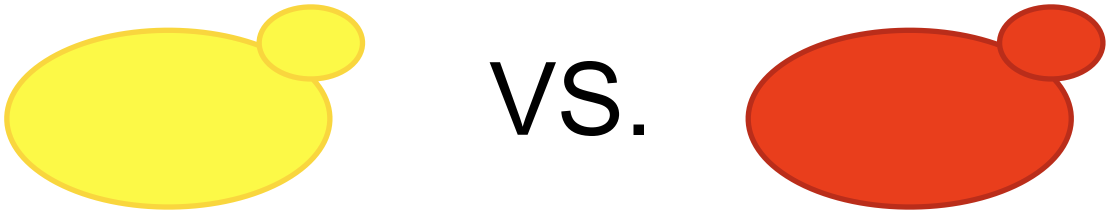

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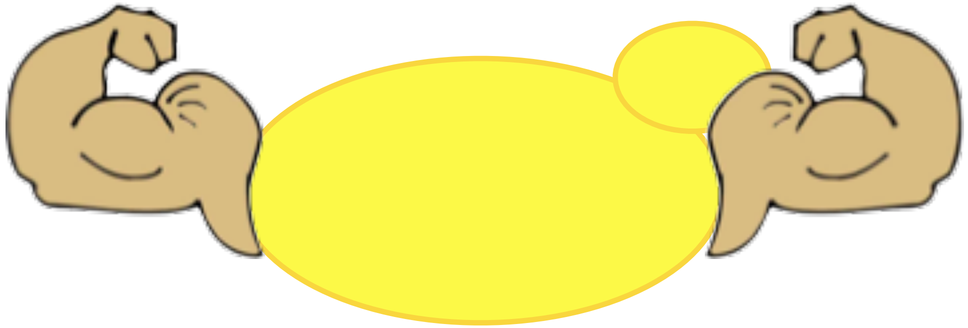
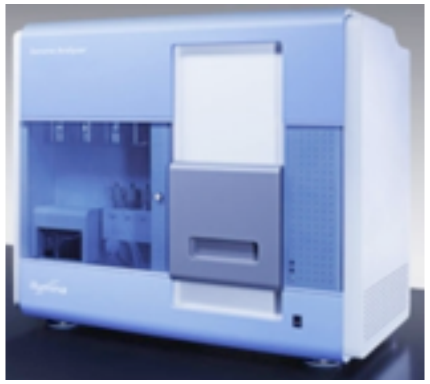
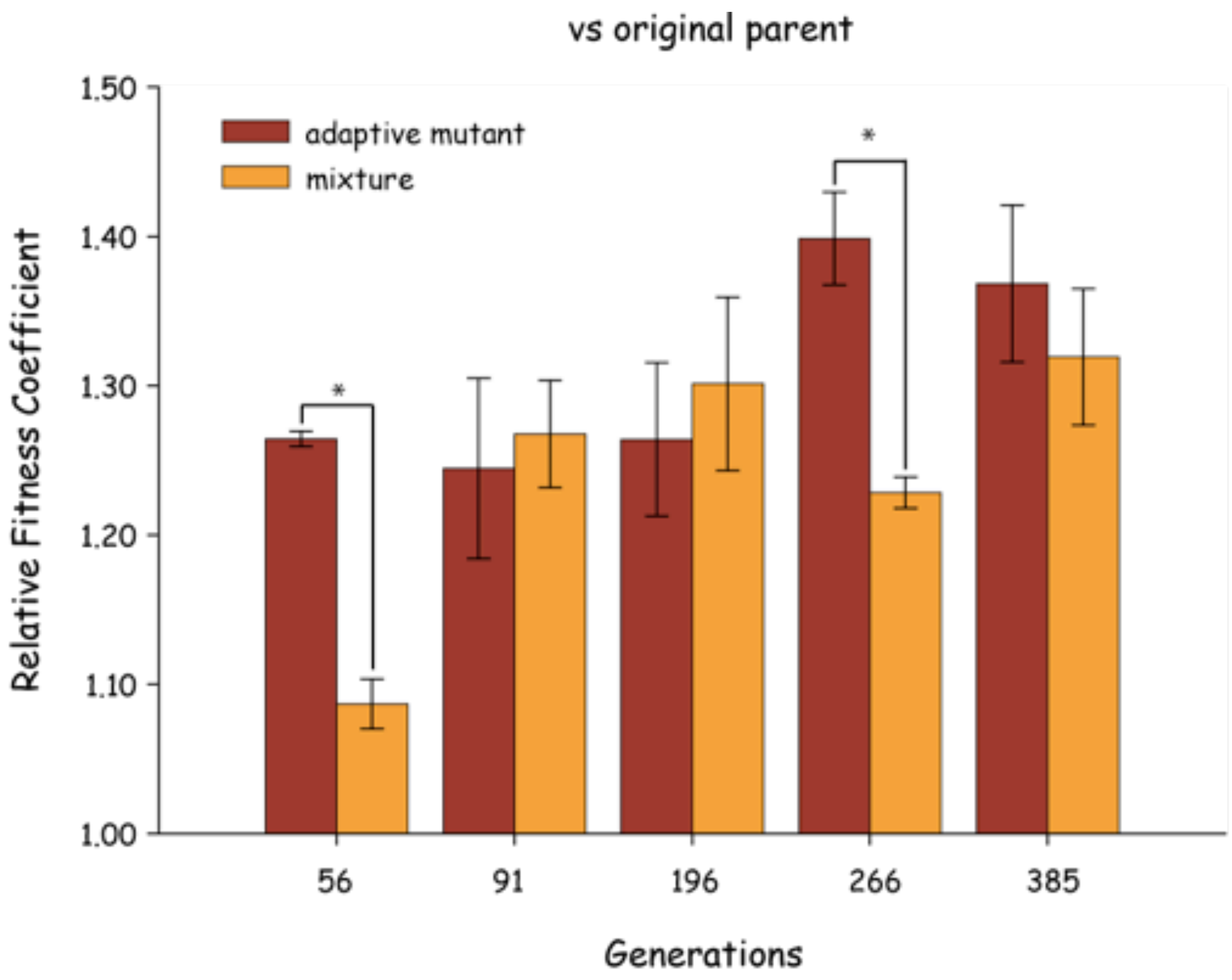




Genome-wide
mutation list

Fitness coefficient against original parents AND against previous adaptive mutant



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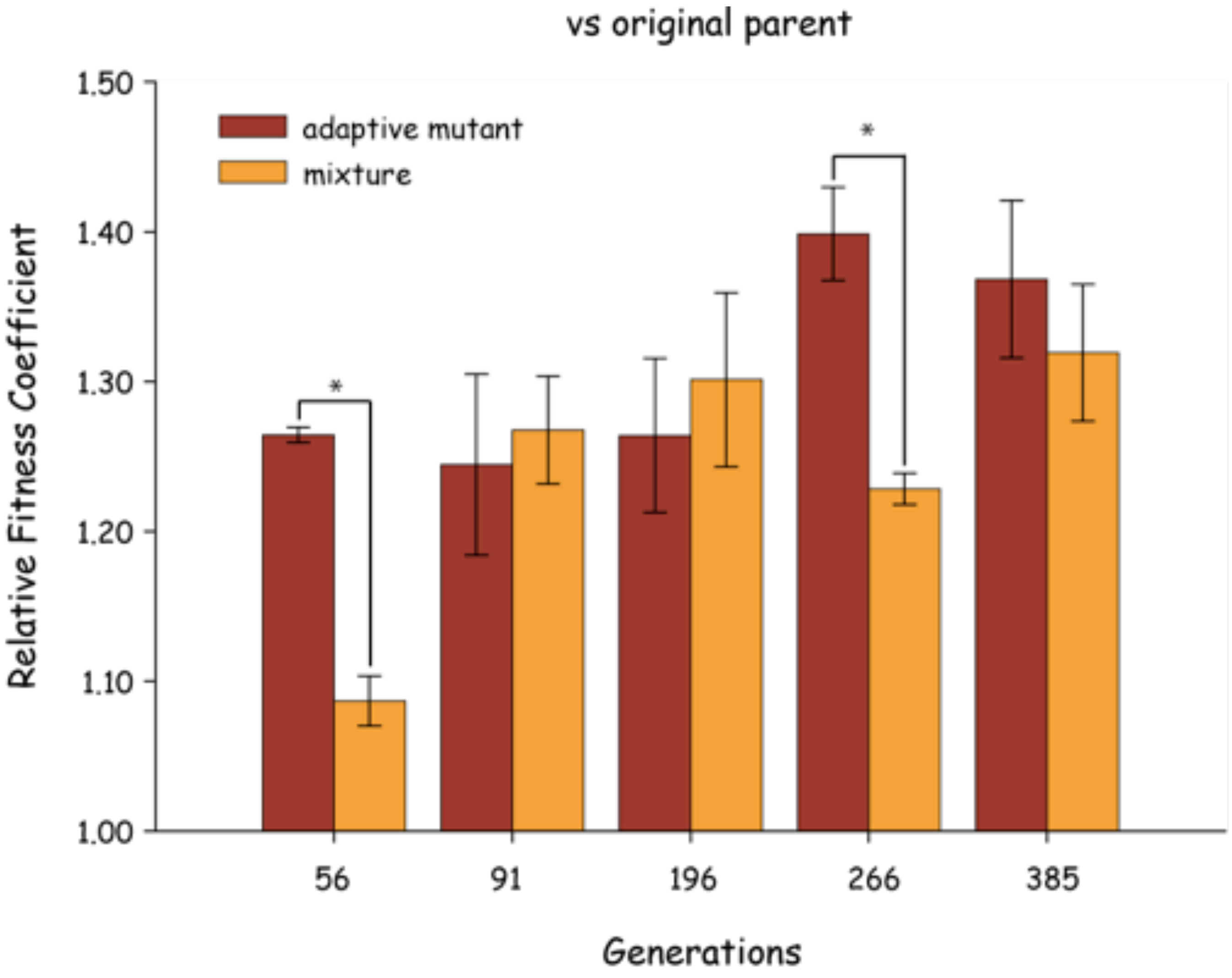
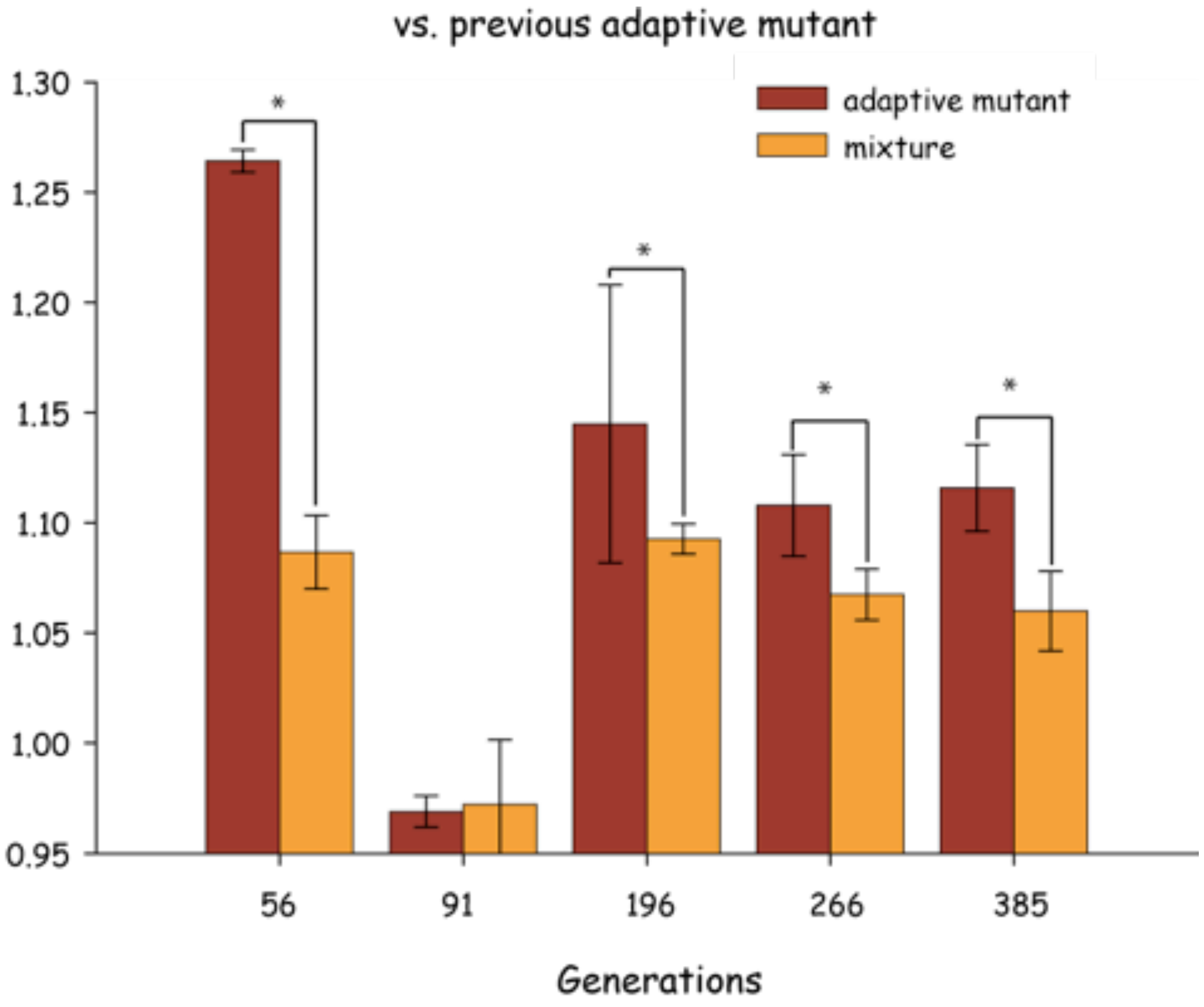

vs original parent


vs. previous adaptive mutant

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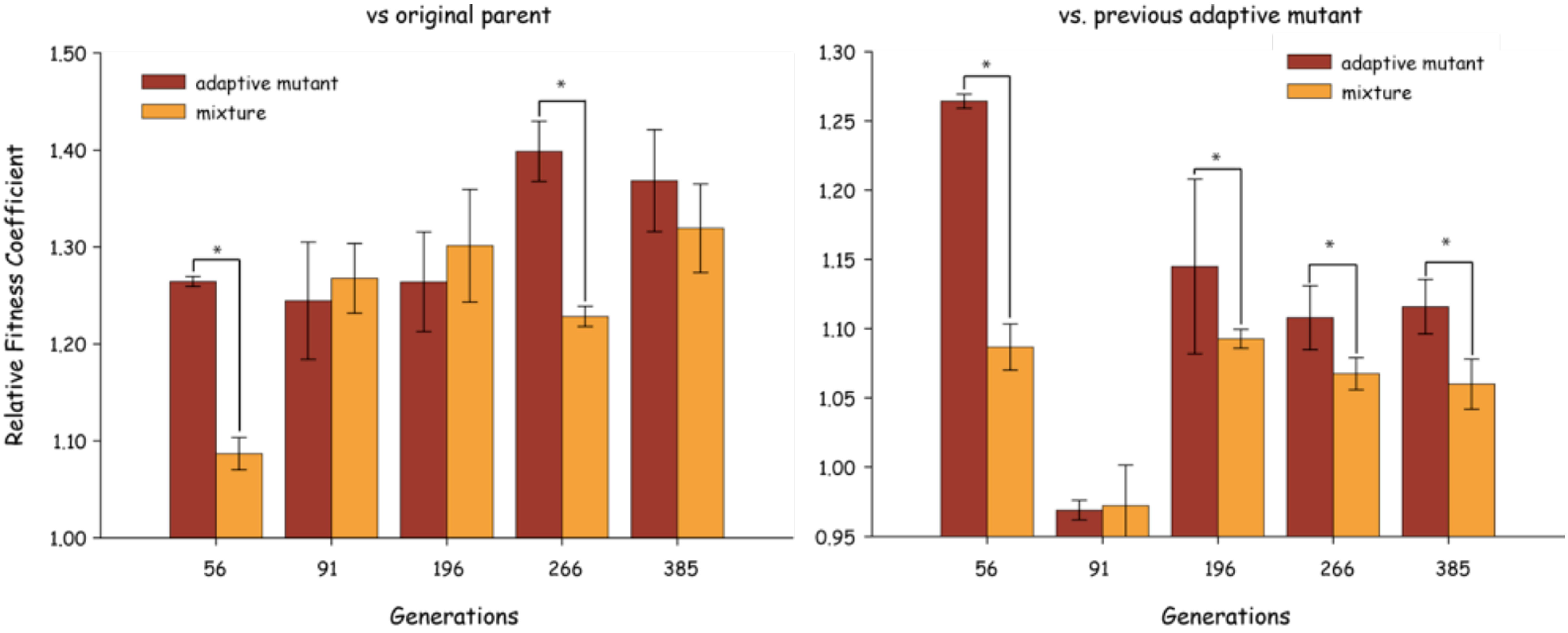


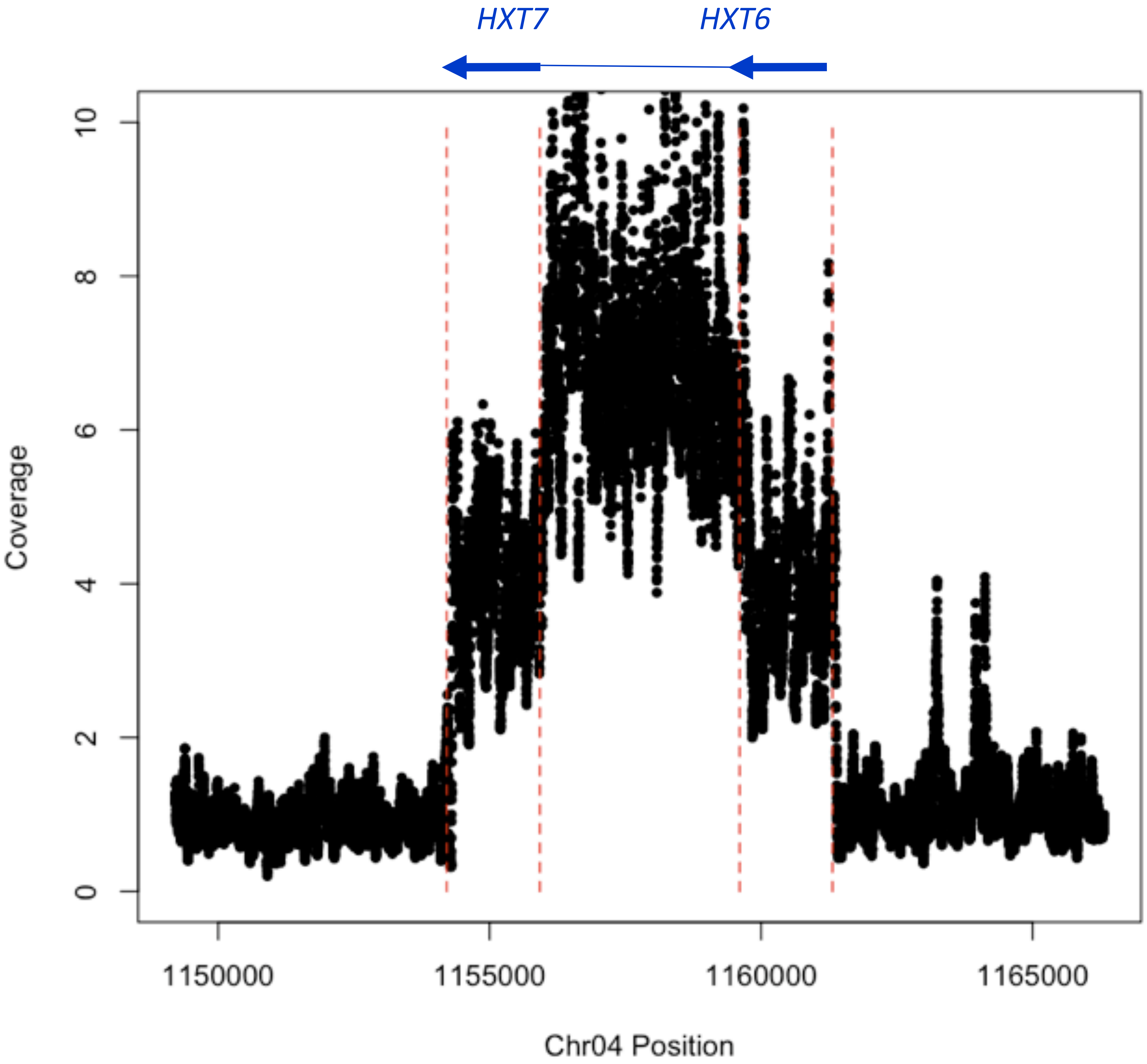
Fitness of subsequent adaptive mutants vs. original parent not necessarily increasing over time.

Fitness vs. original parent not proportional to fitness vs. previous adaptive mutant

Solexa Data

	DsRed	M1	M2	M3	M4	M5
Total reads	18,984,170	9,361,251	13,793,258	24,034,054	18,787,801	17,041,684
Mapped reads	13,850,624 (73%)	7,848,858 (84%)	11,174,470 (81%)	18,211,571 (76%)	14,238,716 (76%)	11,998,617 (70%)
Sequencing coverage... ...unique 24-bp regions	38X	22X	30.5X	50X	39X	32X
...nuclear	34.5X	21X	27.4X	48X	37X	31X
...mitochondrial	192X	179X	210X	192X	203X	208X
Physical coverage	99.98%	99.97%	99.97%	99.97%	99.97%	99.97%

Coverage Shows Amplification



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	chr15	G to T		5’ end of Ty1 LTR
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	MTH1	T to A	Leu241 to Stop	Negative regulator of the glucose-sensing signal transduction pathway
M4 Red	*TAF5*	G to T	Gly693 to Val	Subunit (90 kDa) of TFIID and SAGA complexes
	HXT6/7	amp		High-affinity glucose transporter
	RIM15	1 bp del	frame shift	Glucose-repressible protein kinase
	MNN4	A to G	Lys924 to Glu	Putative positive regulator of mannosylphosphate transferase
	chr16	T to G		Intergenic - 5’ of MLC1 & SKI3
M5 Yellow	*GPB2*	LTR ins		Multistep regulator of cAMP-PKA signaling
	HXT6/7	amp		High-affinity glucose transporter
	VMA8	A to C	Glu37 to Ala	Subunit D of the eight-subunit V1 peripheral membrane domain of the vacuolar H+ ATPase
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	BYE1	T to C	Silent at Thr57	Negative regulator of transcription elongation
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–Asexual evolution: no recombination

–Mutations may be adaptive or hitchhikers

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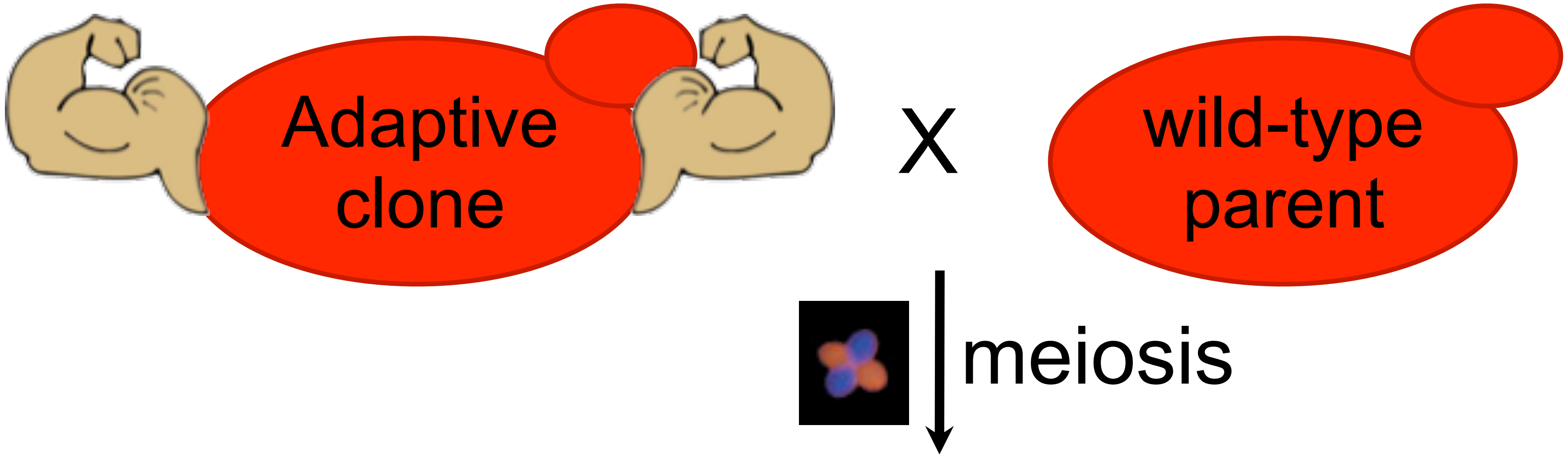

Adaptive clone

X

wild-type parent

meiosis

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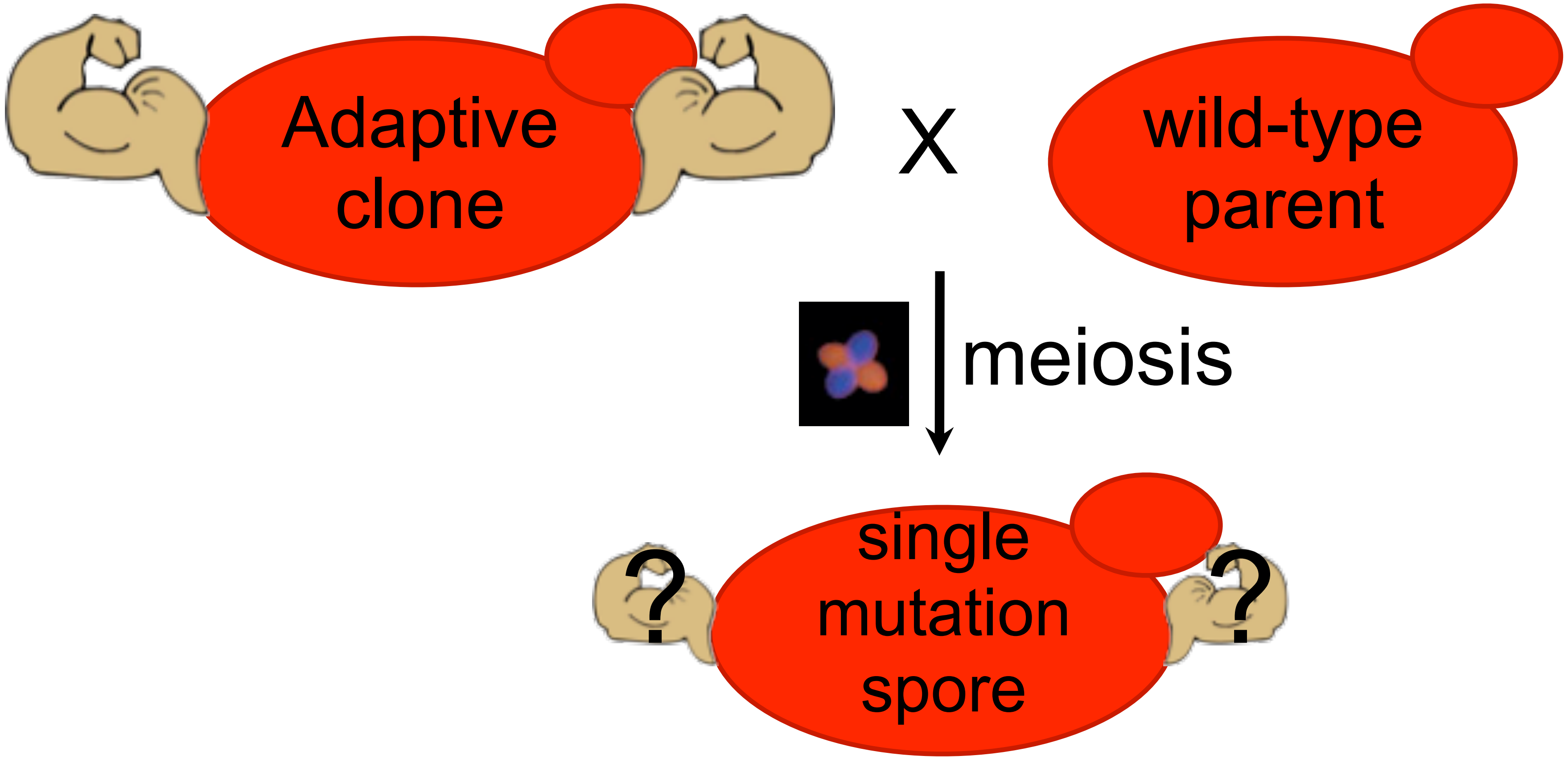

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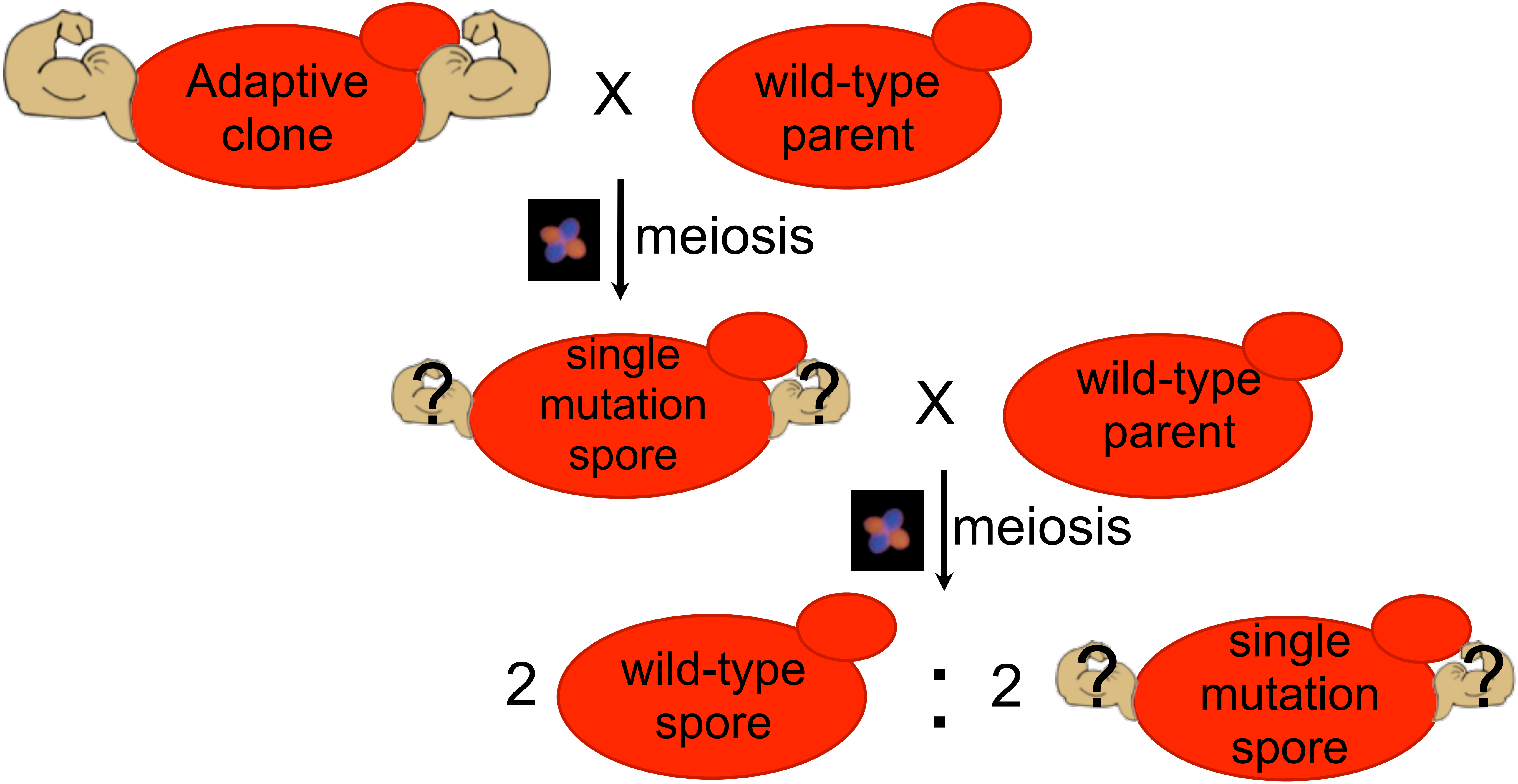


Adaptive clone X wild-type parent

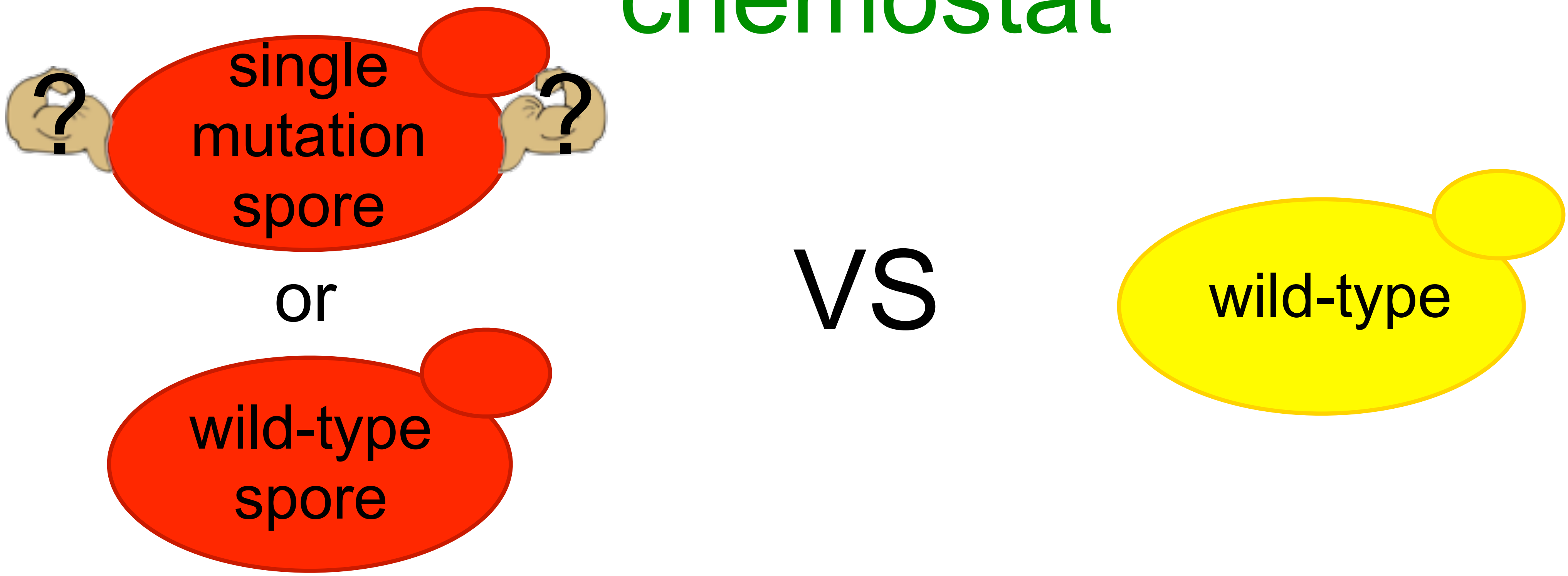
meiosis

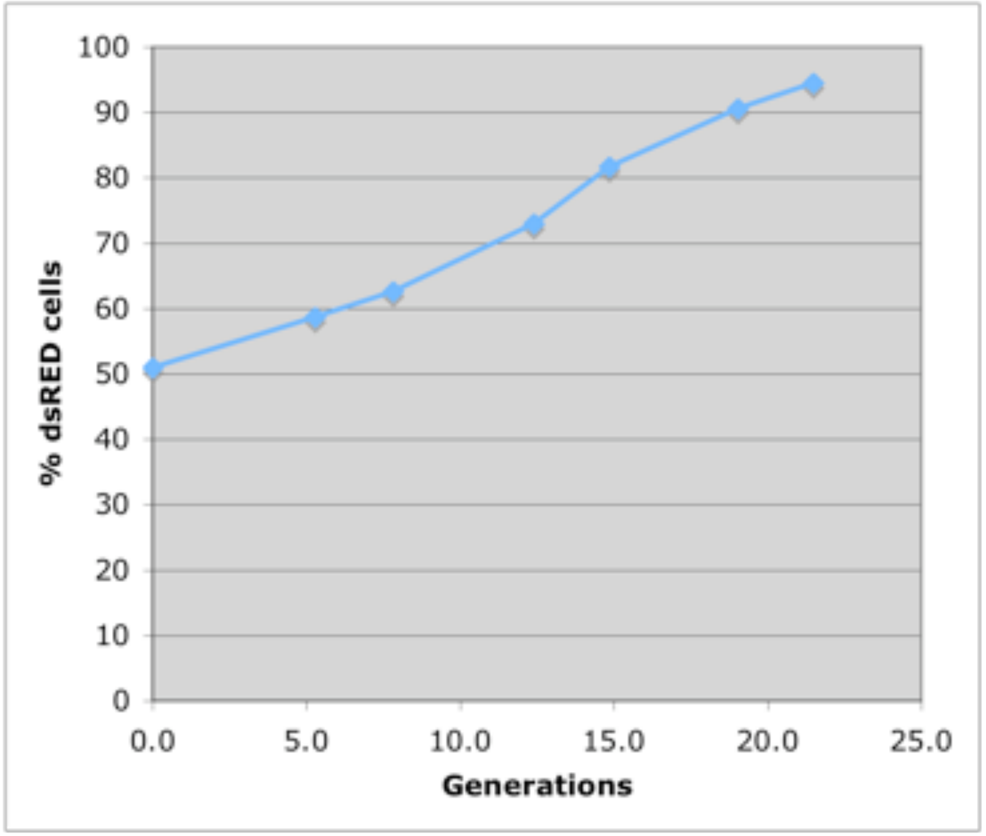
? single mutation spore ? X wild-type parent

meiosis

2 wild-type spore : 2 ? single mutation spore ?

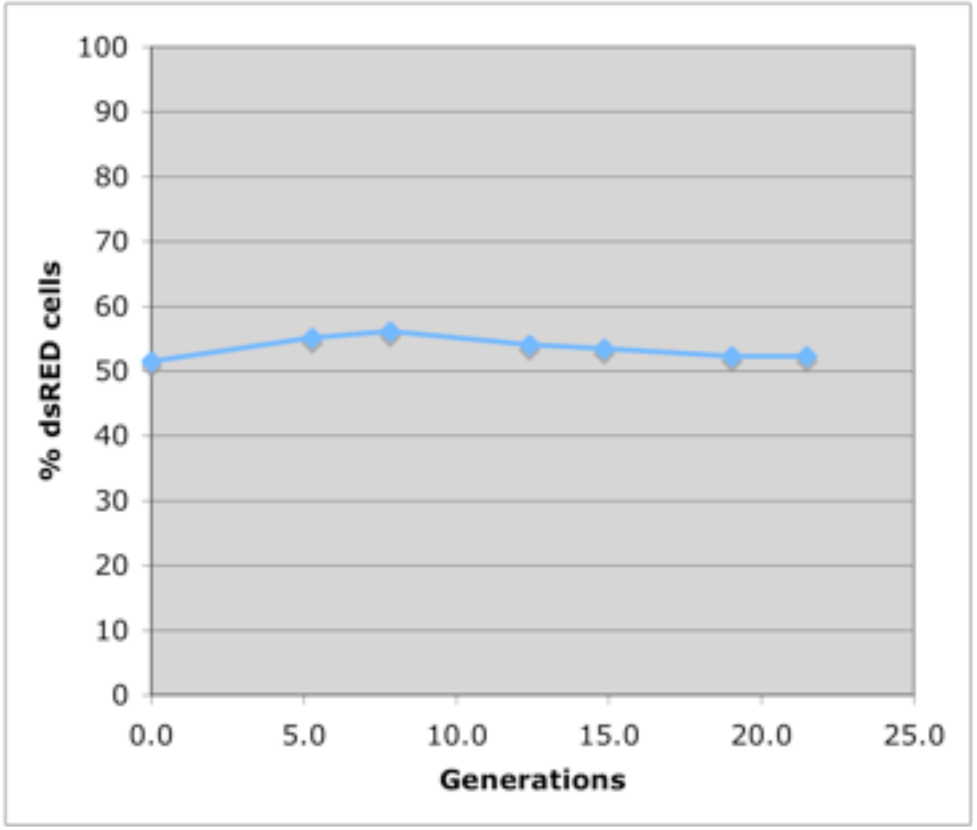
Determining adaptiveness: Competitive chemostat





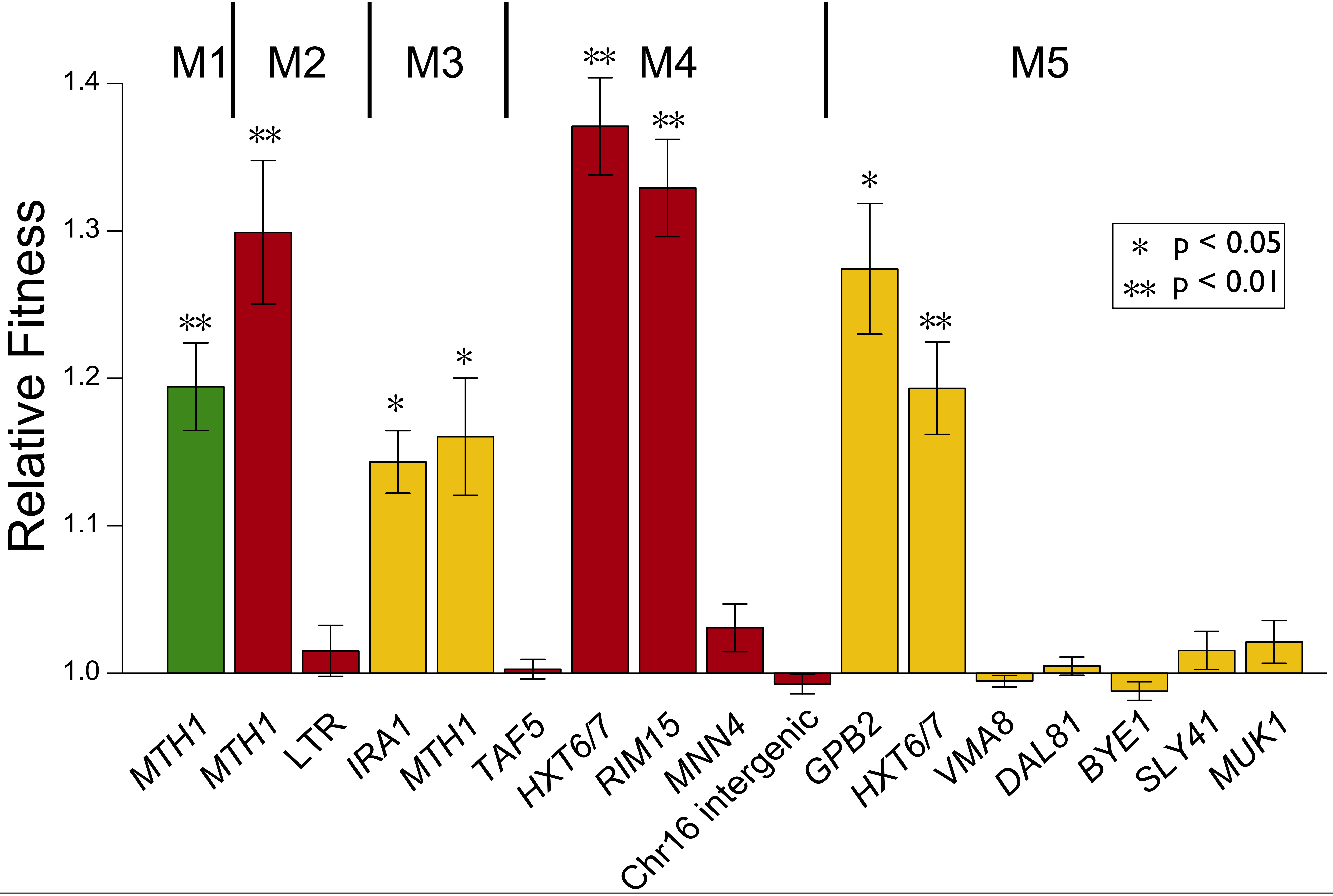
Adaptive mutation

or



Non-adaptive mutation/wt control

Single mutation relative fitnesses: 1-2 measurably adaptive mutations per clone



Clone	**Gene**	**Mutation**	**Amino acid change**	**Comment**
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	MTH1	T to A	Leu241 to Stop	Negative regulator of the glucose-sensing signal transduction pathway
M4 Red	*TAF5*	G to T	Gly693 to Val	Subunit (90 kDa) of TFIID and SAGA complexes
	HXT6/7	amp		High-affinity glucose transporter
	RIM15	1 bp del	frame shift	Glucose-repressible protein kinase
	MNN4	A to G	Lys924 to Glu	Putative positive regulator of mannosylphosphate transferase
	chr16	T to G		Intergenic - 5’ of MLC1 & SKI3
M5 Yellow	*GPB2*	LTR ins		Multistep regulator of cAMP-PKA signaling
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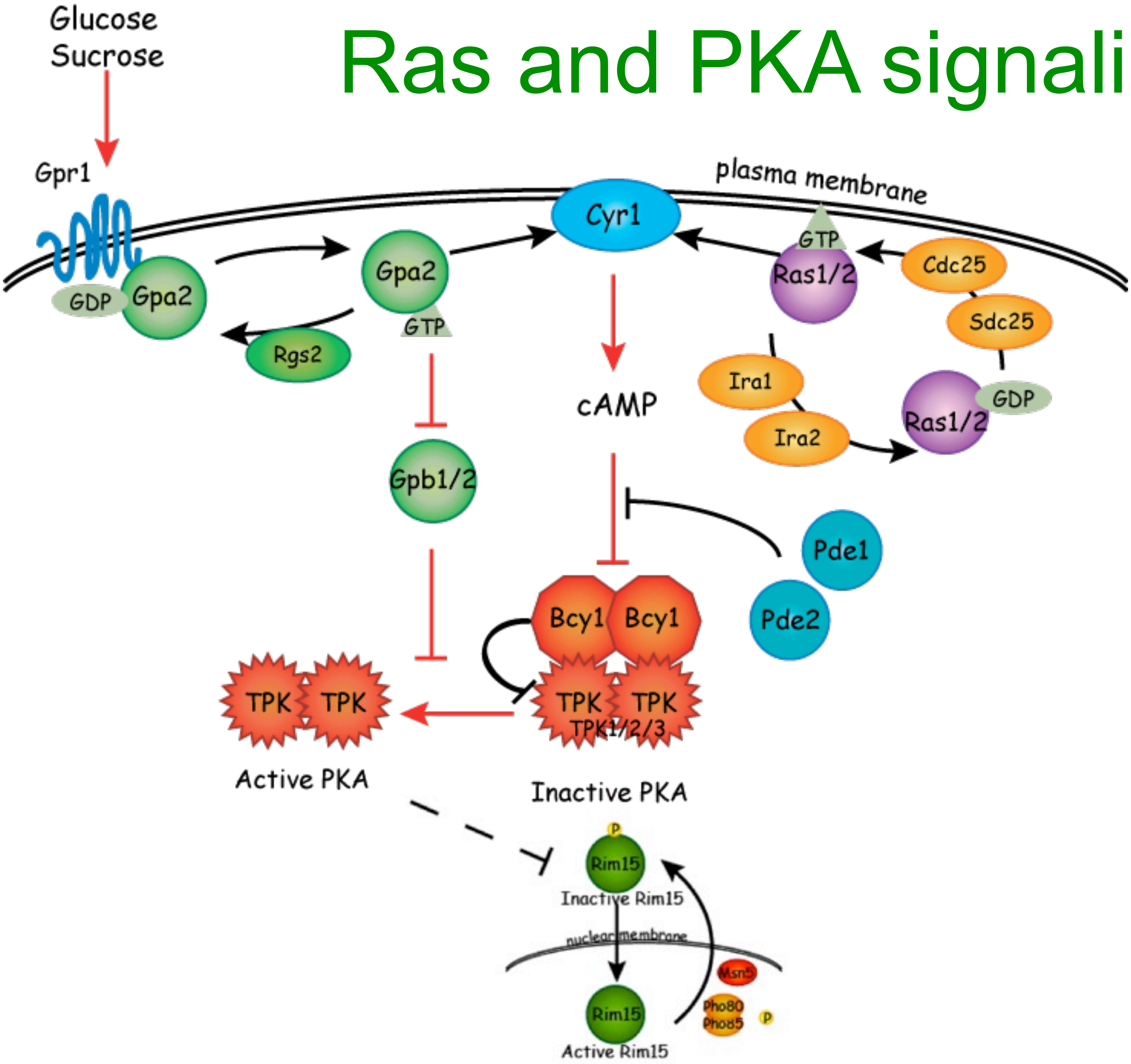
Ras and PKA signaling



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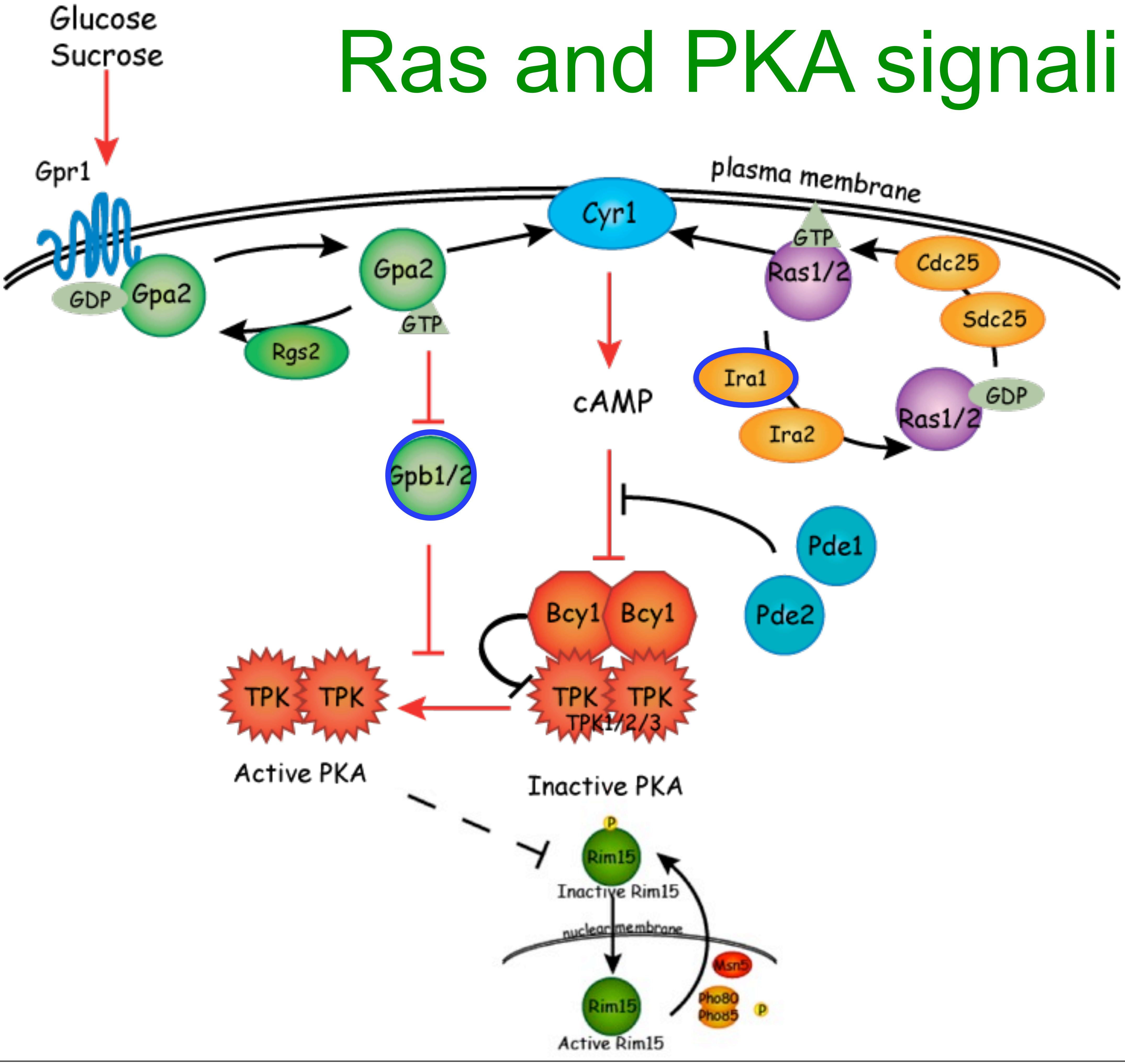

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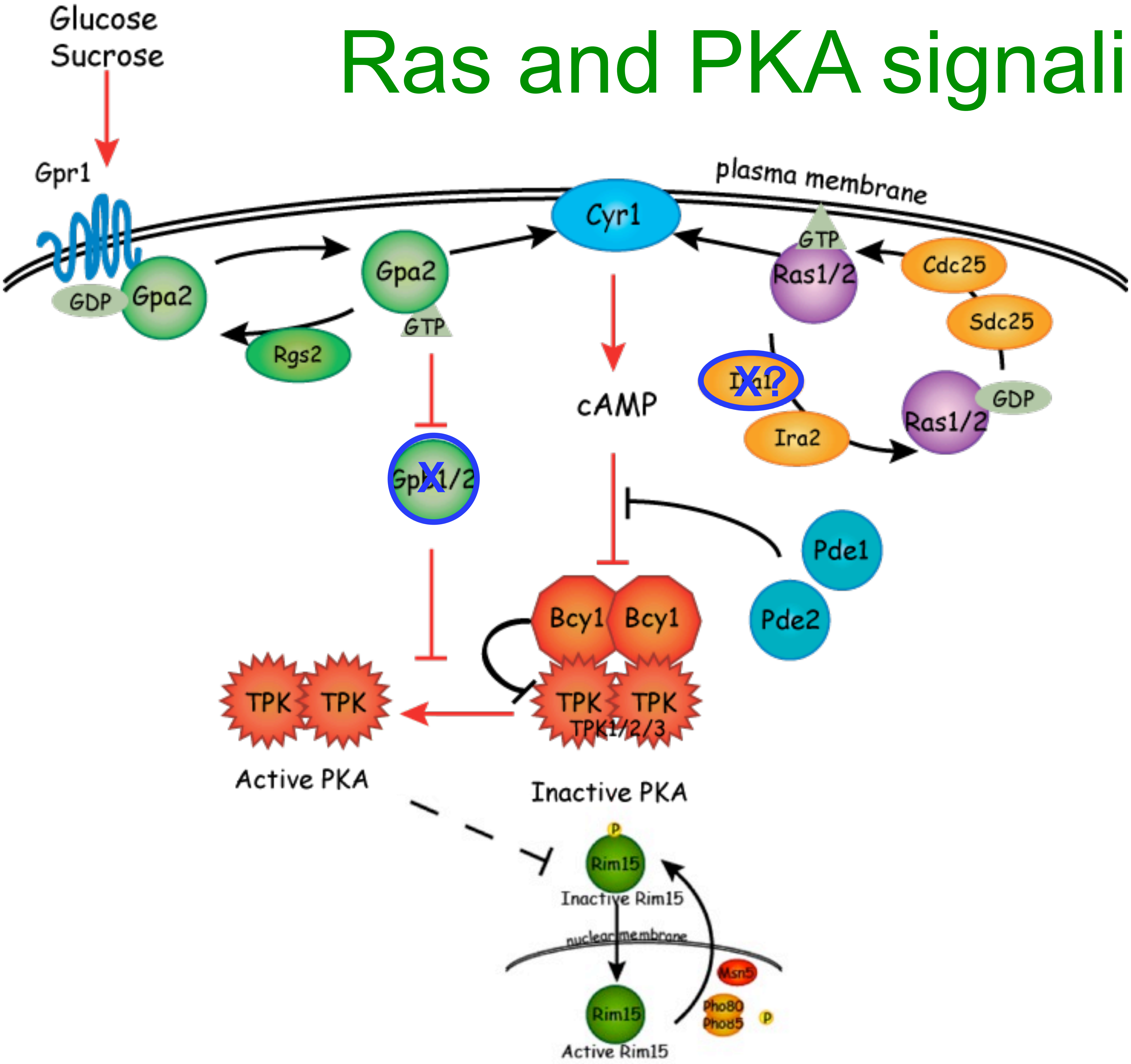

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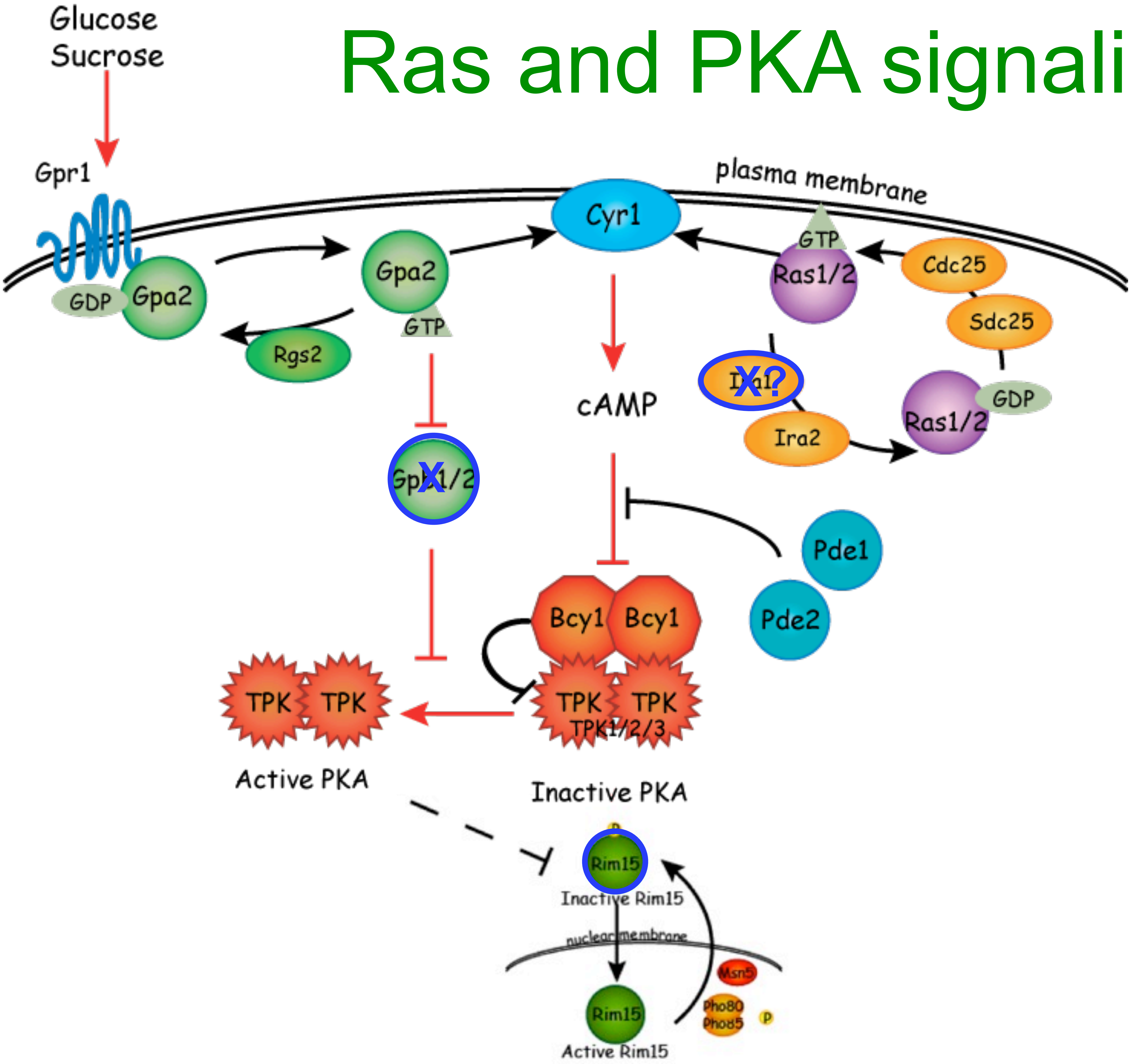

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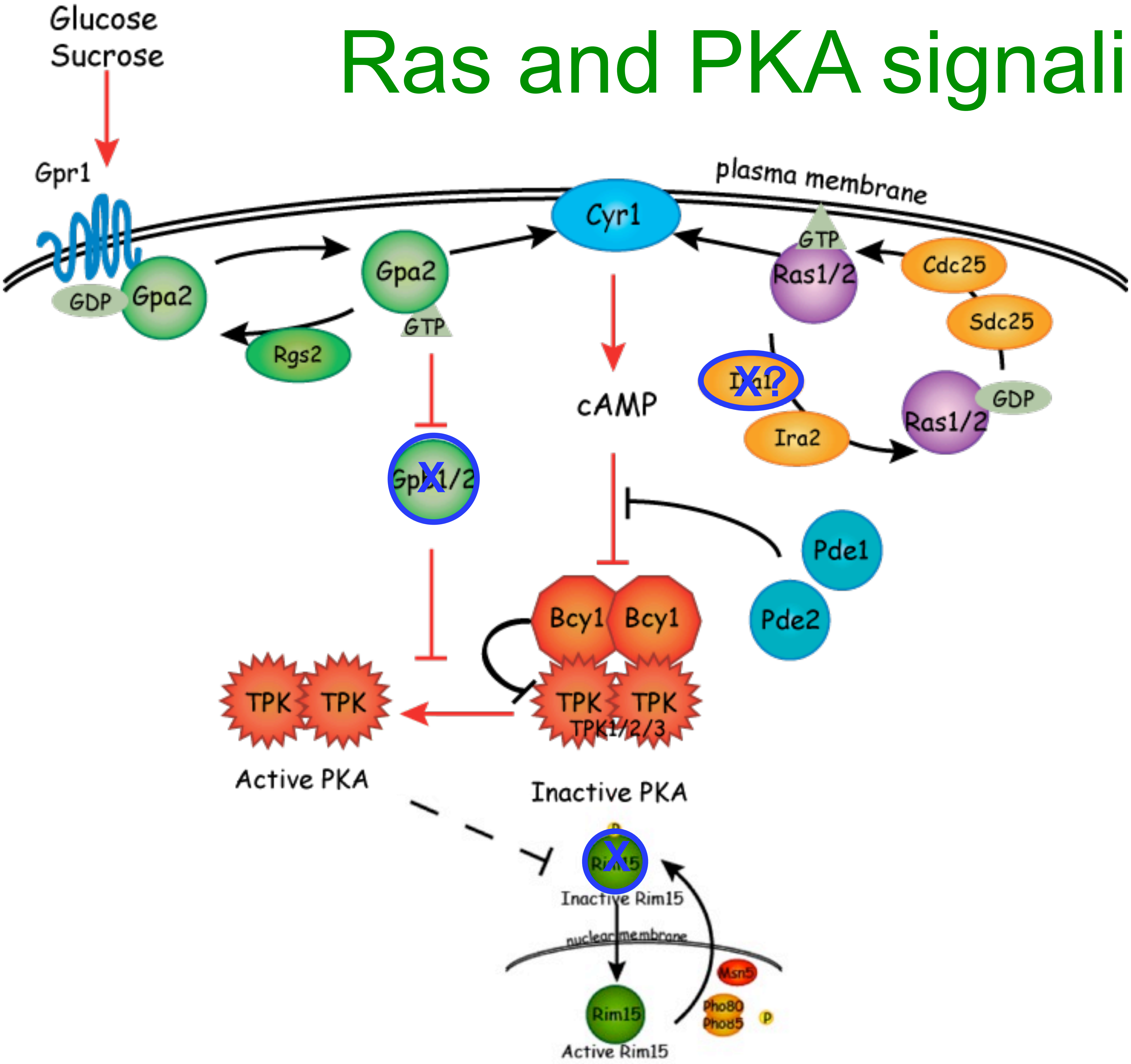

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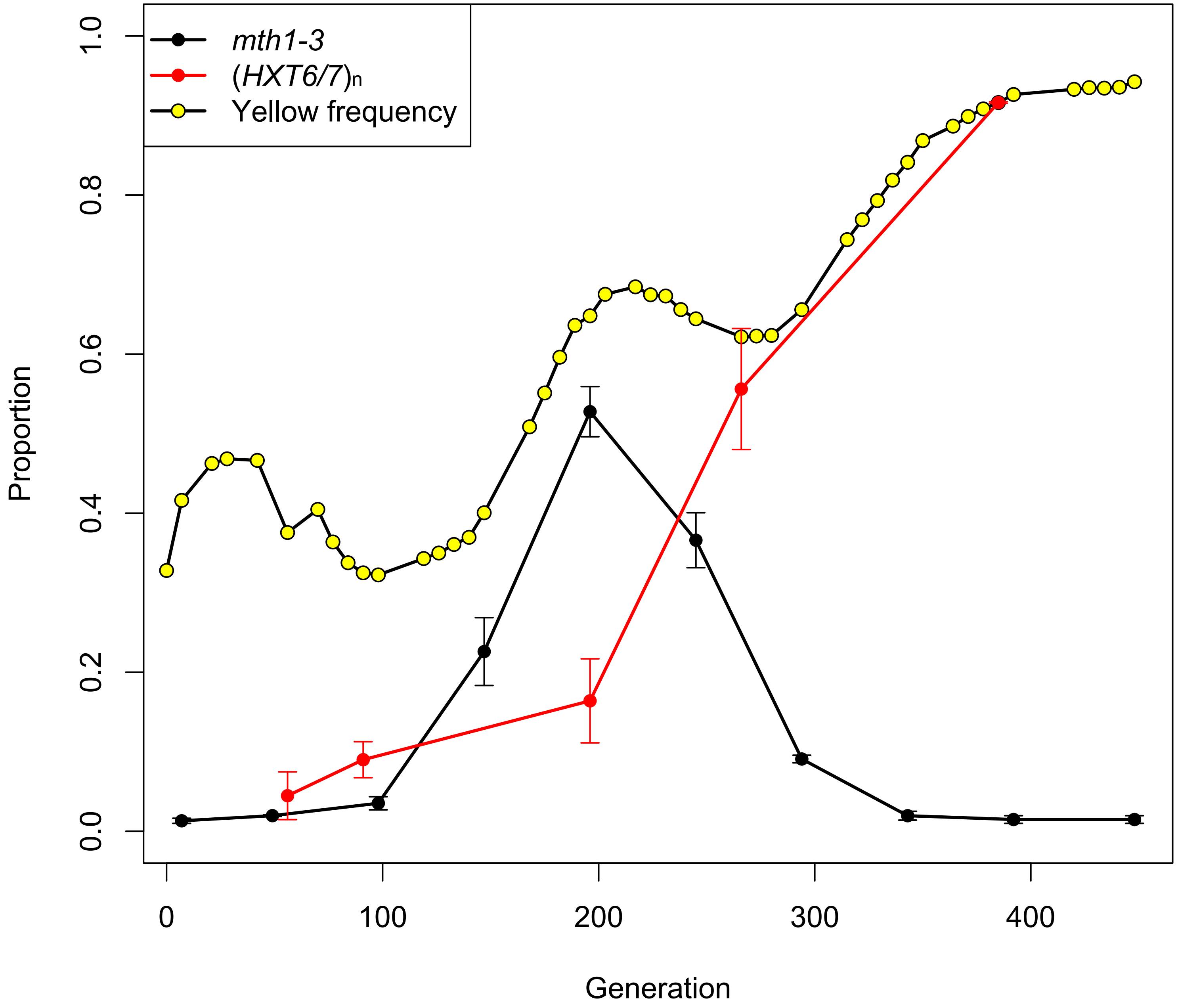
Hypothesis: *mth1* and (*HXT6/7*)$_n$ mutations are mutually exclusive because of reciprocal sign epistasis.

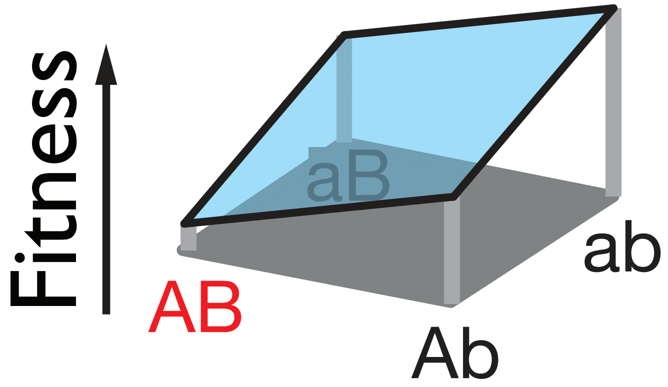
Do *mth1* and (*HXT6/7*)$_n$ determine evolutionary trajectory by constraining the fitness landscape?

Allele Frequencies also Suggest Epistasis

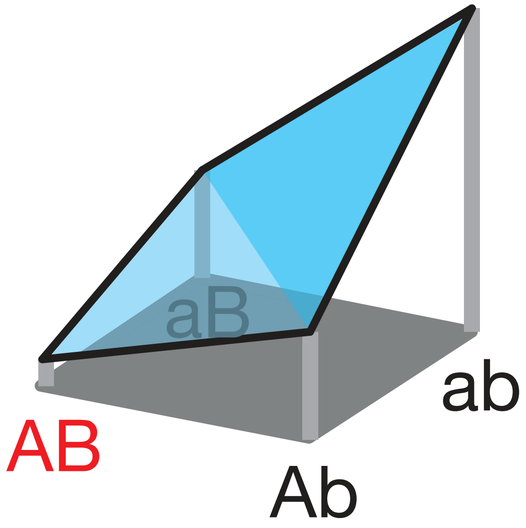


Sign epistasis constrains evolutionary trajectories

AB = wild-type



No epistasis



Magnitude epistasis

Adapted from Poelwijk et al, *Nature,* (2007). Theory by Weinreich et al, *Evolution,* (2005)

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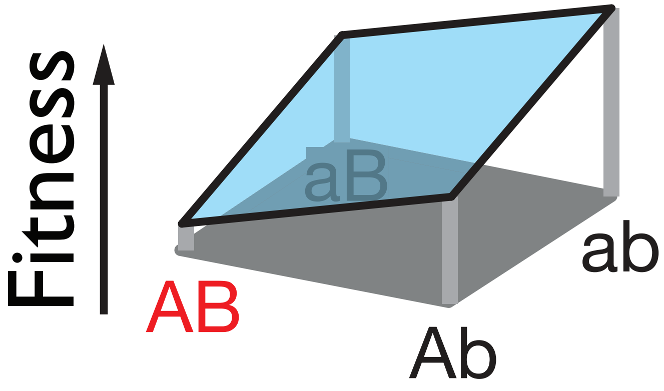

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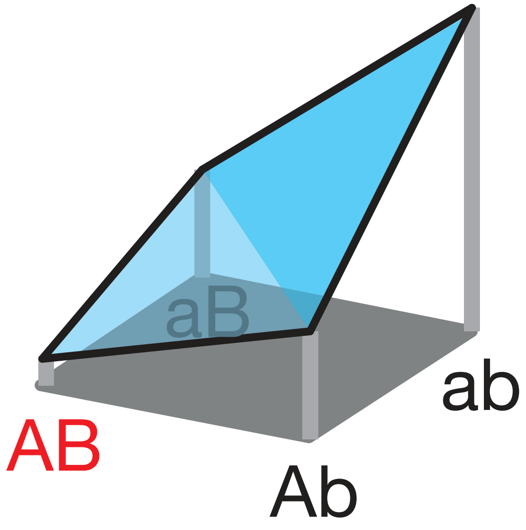

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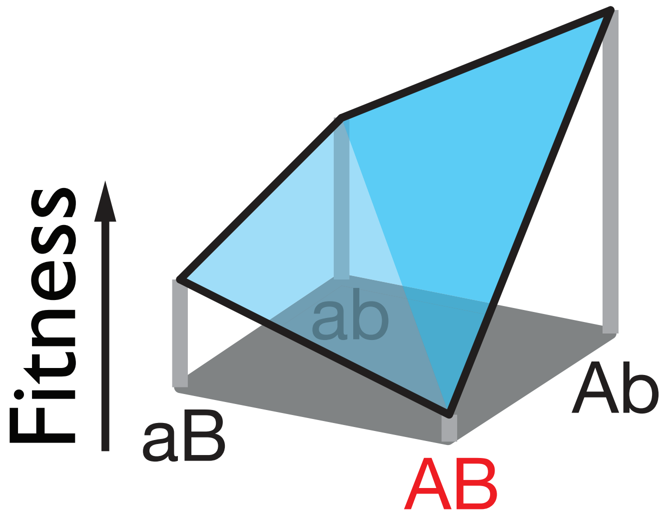
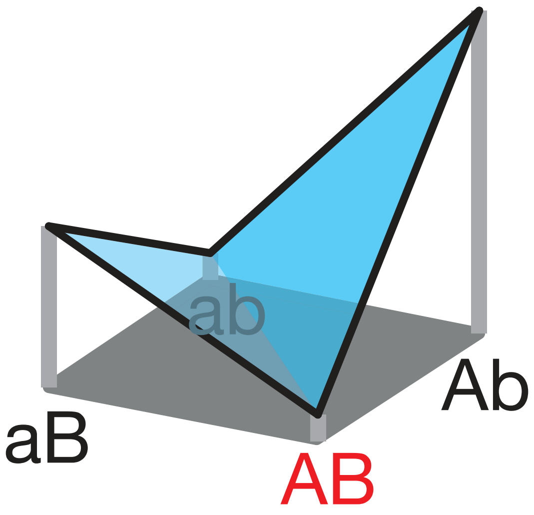


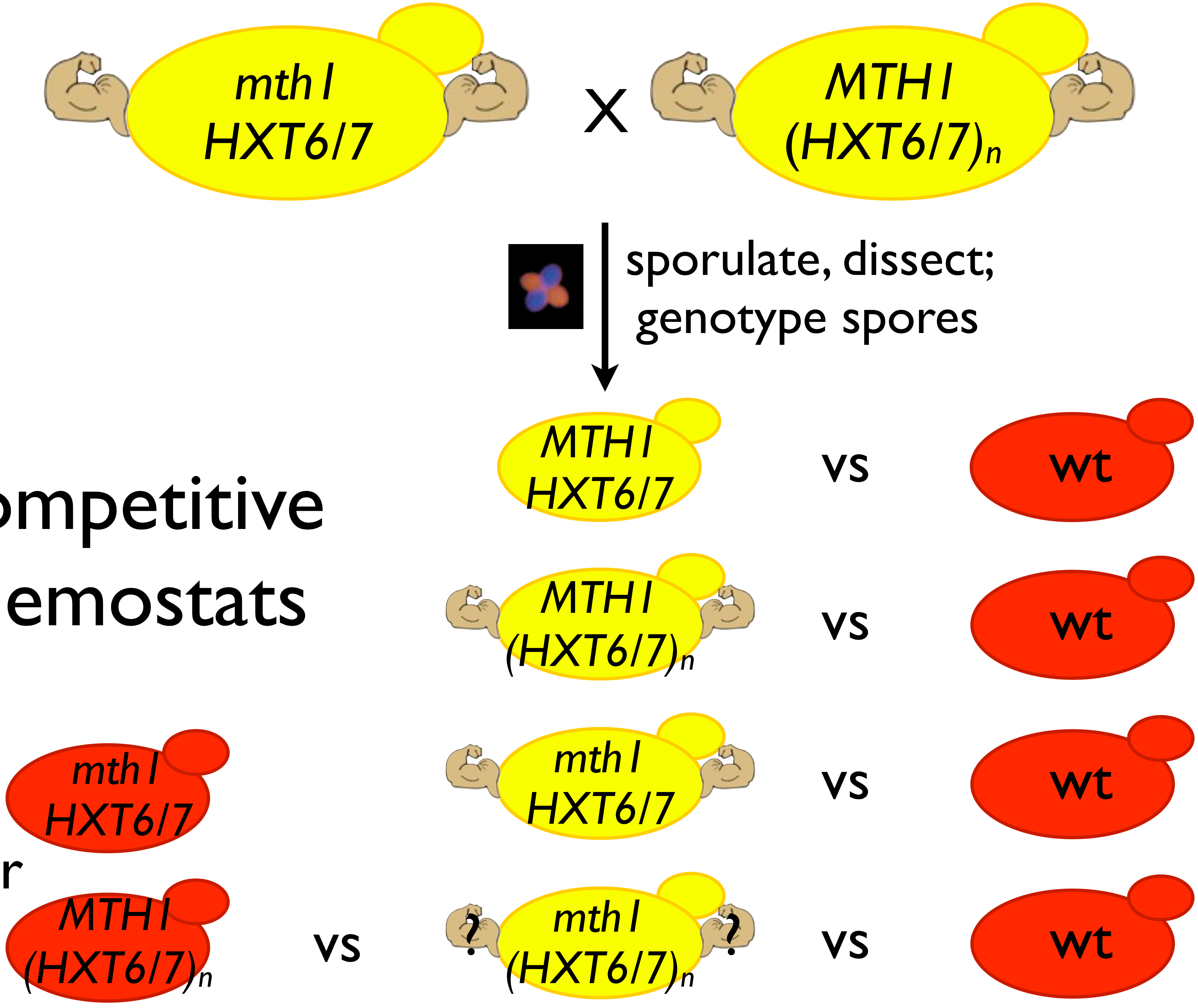
Sign epistasis



Reciprocal sign epistasis

Adapted from Poelwijk et al, *Nature,* (2007). Theory by Weinreich et al, *Evolution,* (2005)

Methods: Reciprocal sign epistasis between *mth1* and $(HXT6/7)_n$?



mth1
HXT6/7
X
MTH1
$(HXT6/7)_n$

sporulate, dissect;
genotype spores

Competitive chemostats

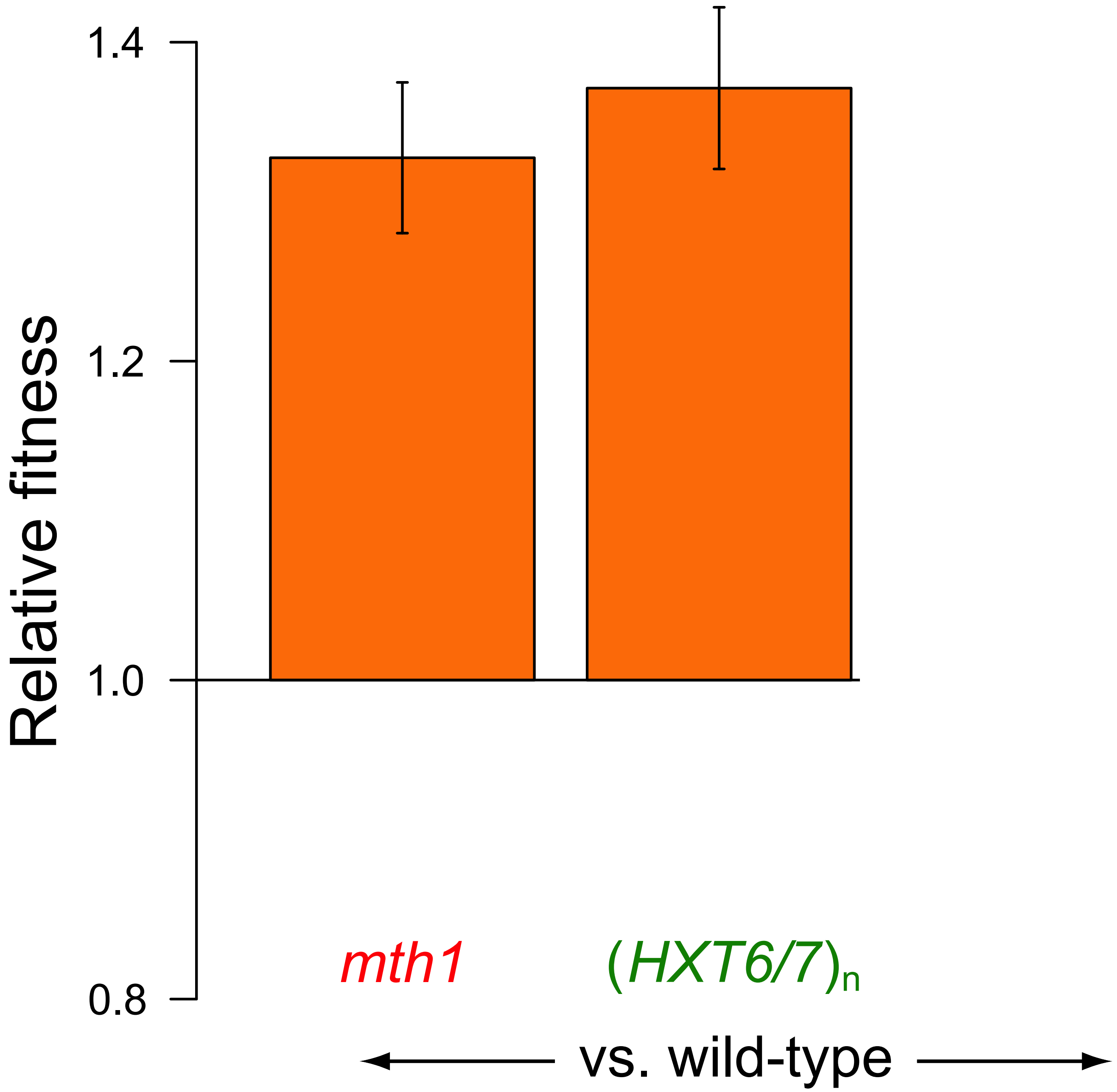
MTH1 *HXT6/7* vs wt

MTH1 $(HXT6/7)_n$ vs wt

mth1 *HXT6/7* vs wt

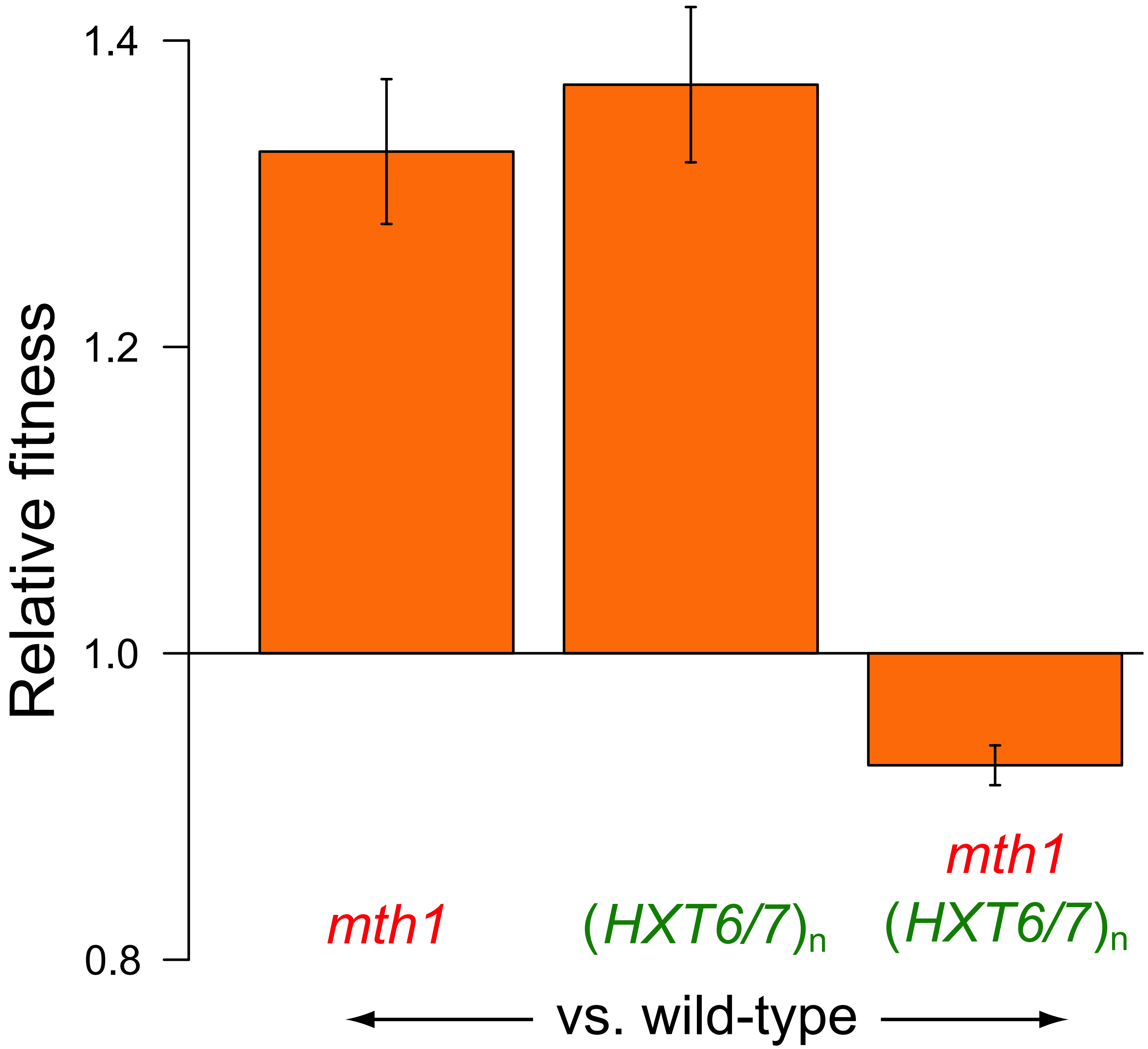
mth1 *HXT6/7*
or
MTH1 $(HXT6/7)_n$
vs
? *mth1* $(HXT6/7)_n$? vs wt

Reciprocal sign epistasis between *mth1* and *(HXT6/7)*$_n$



All: $p<0.001$

Reciprocal sign epistasis between *mth1* and *(HXT6/7)ₙ*



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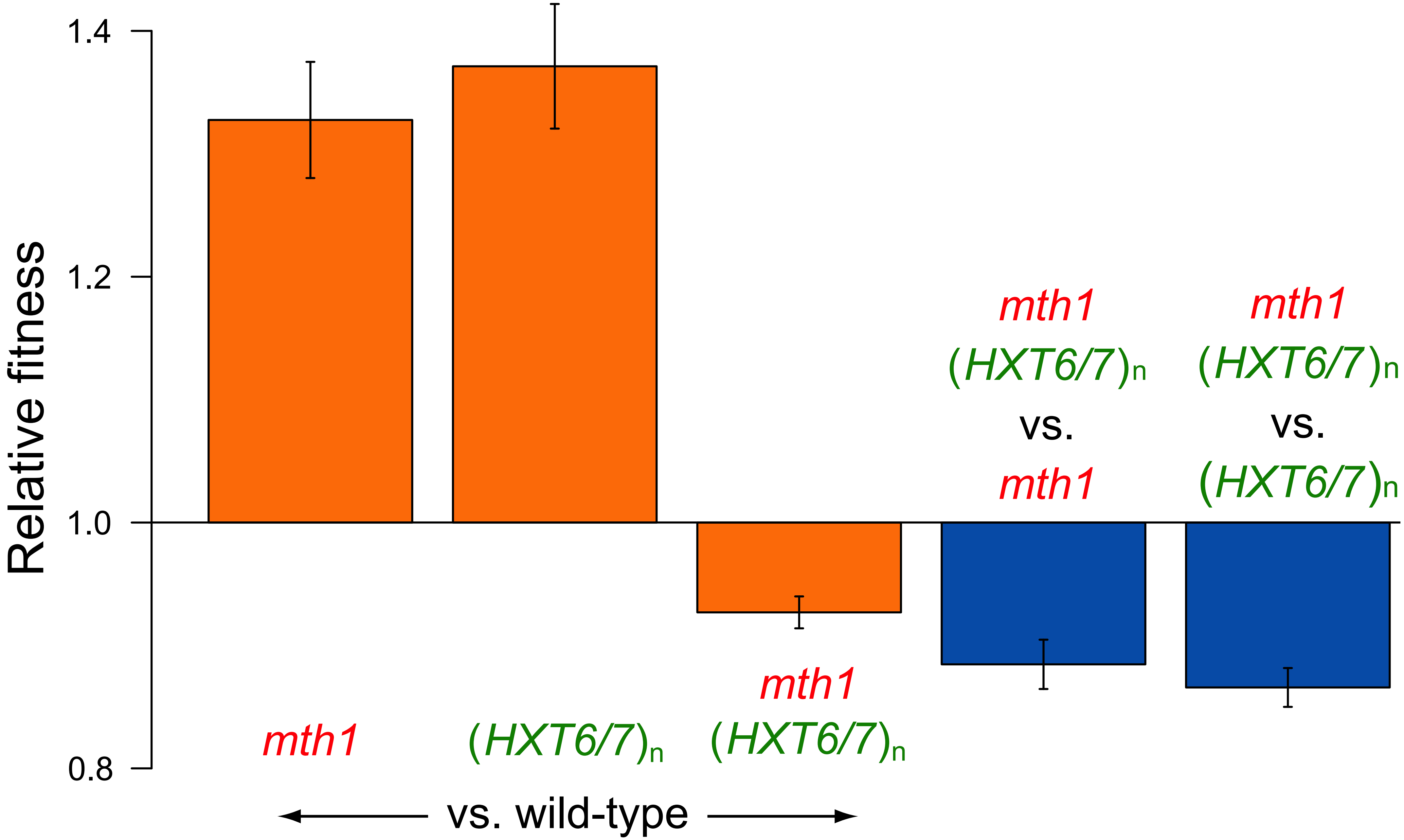

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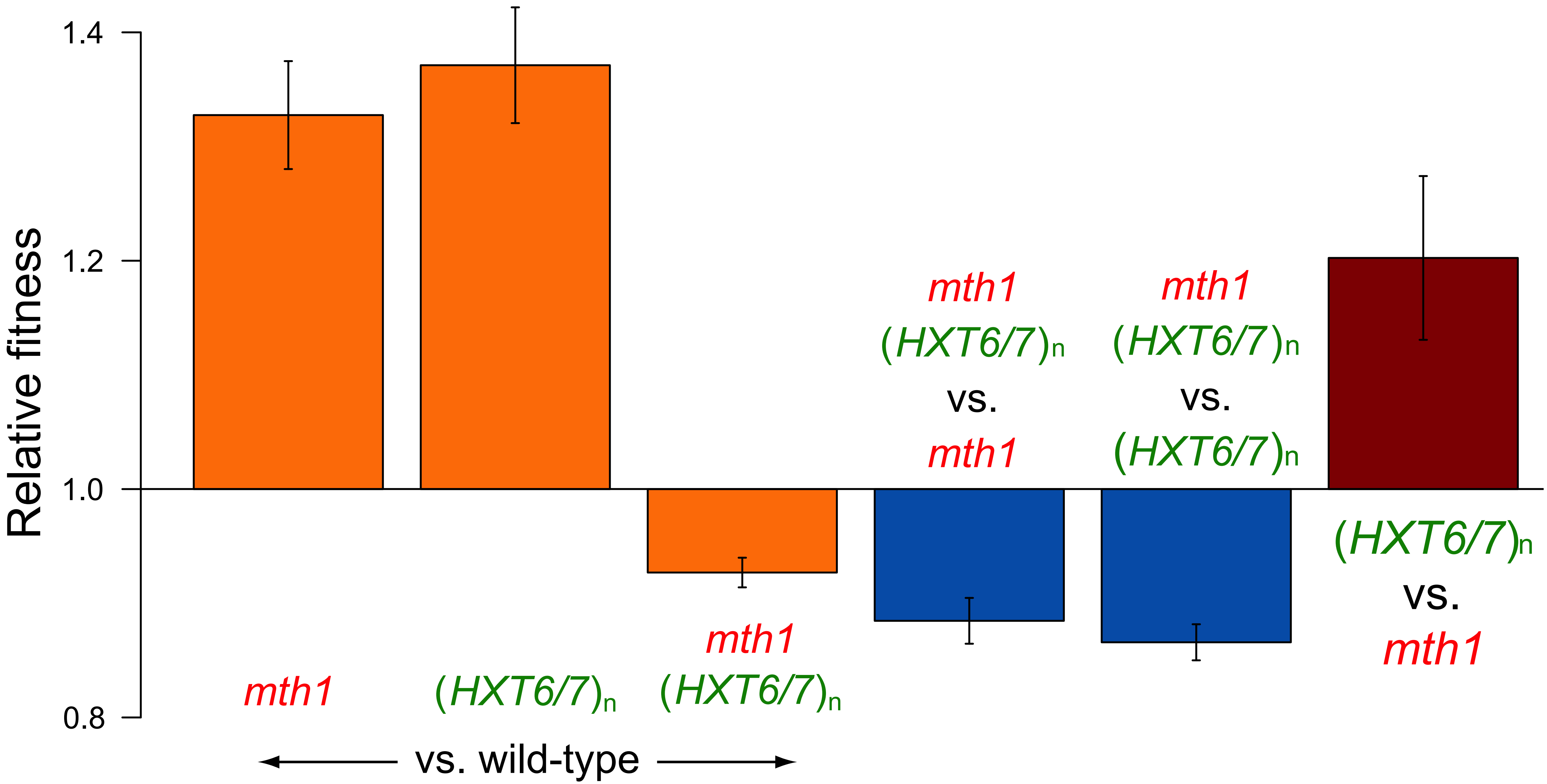

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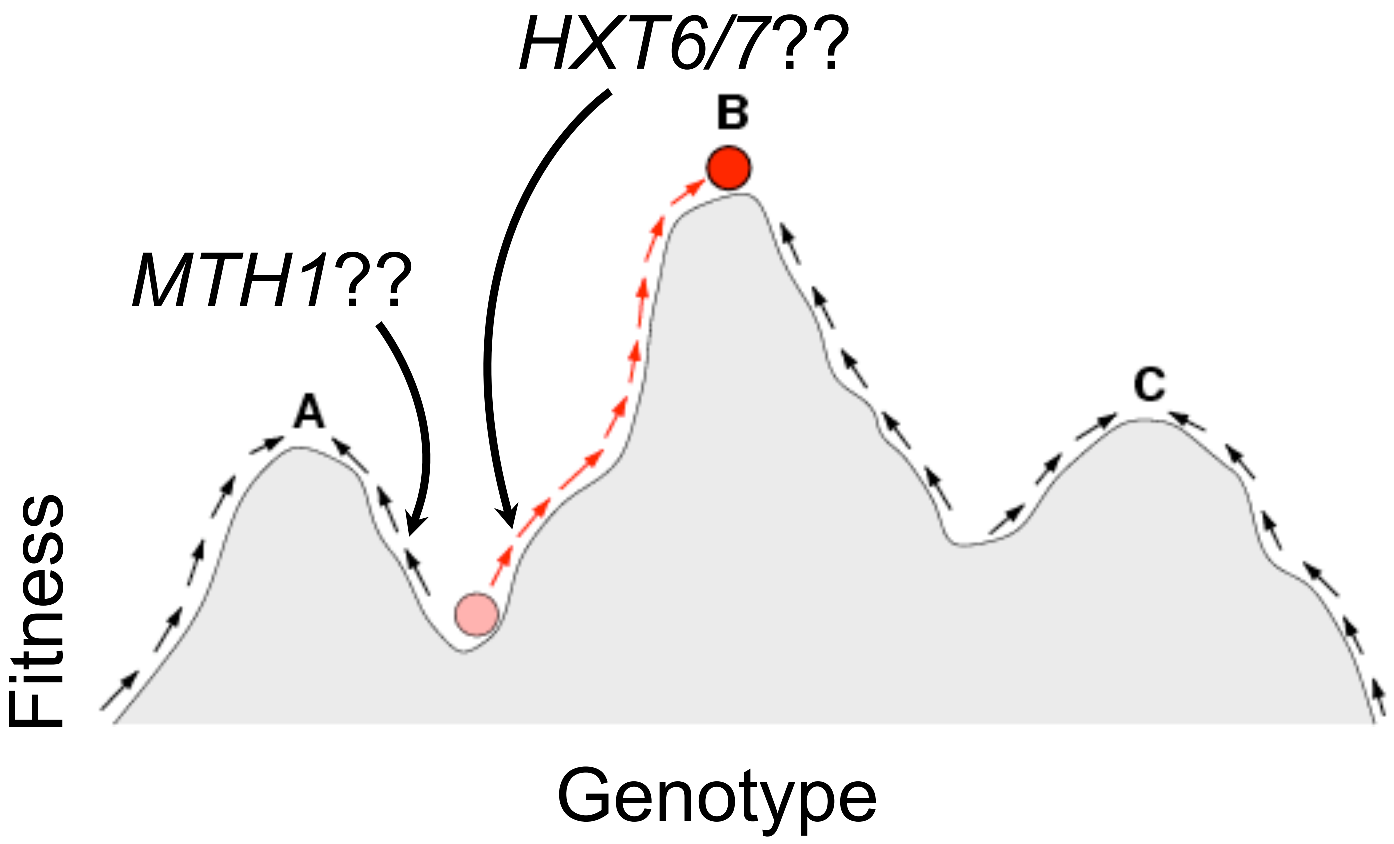
Fitness Landscape?



Is this Relevant to Wild Yeast?

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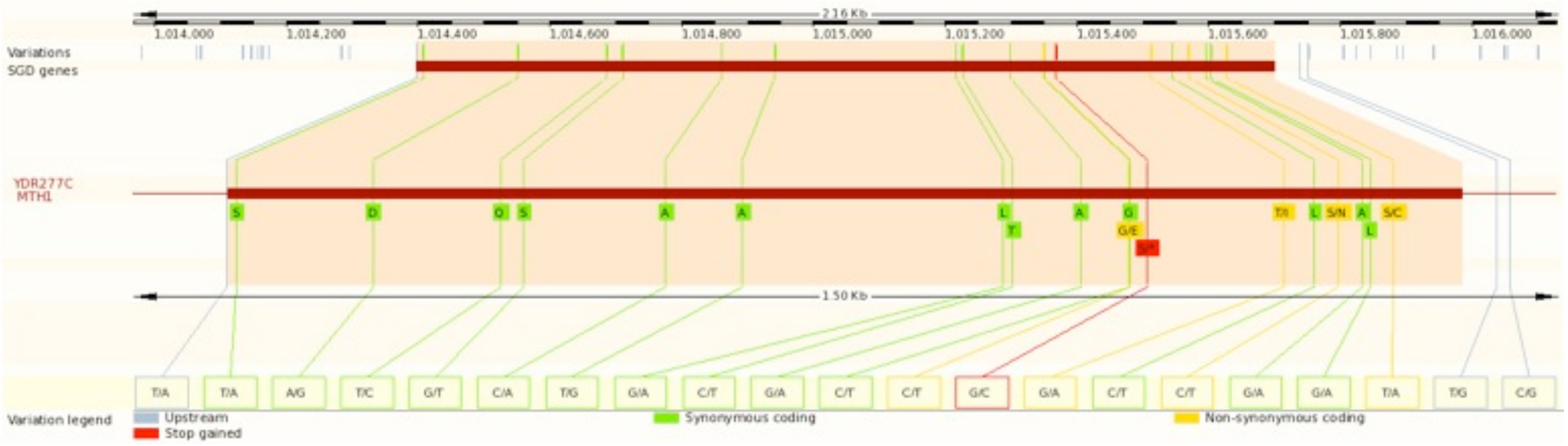
MTH1



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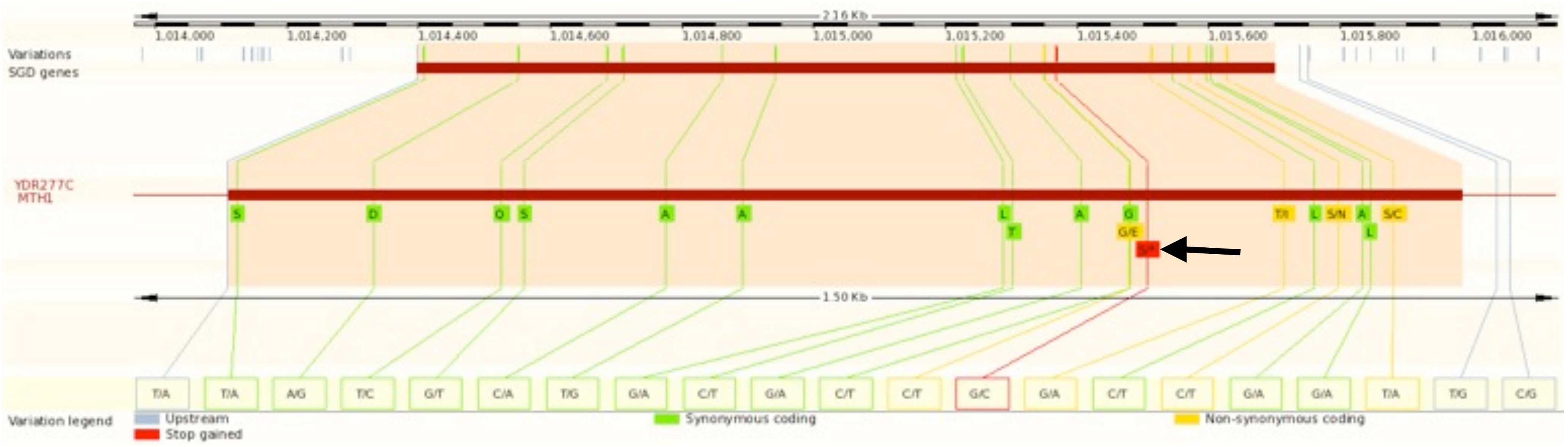

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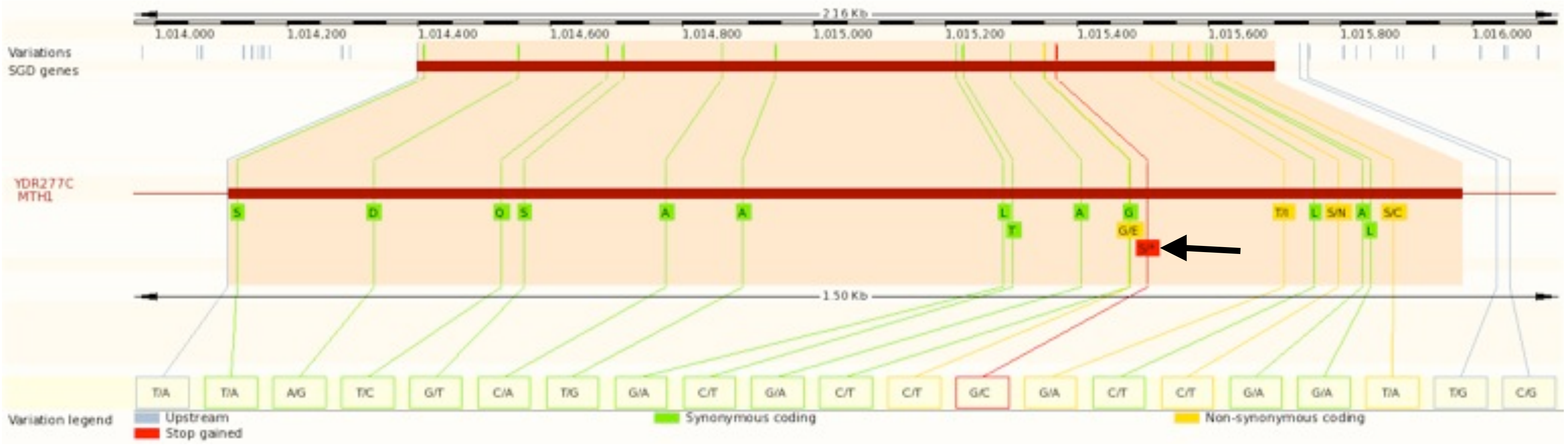
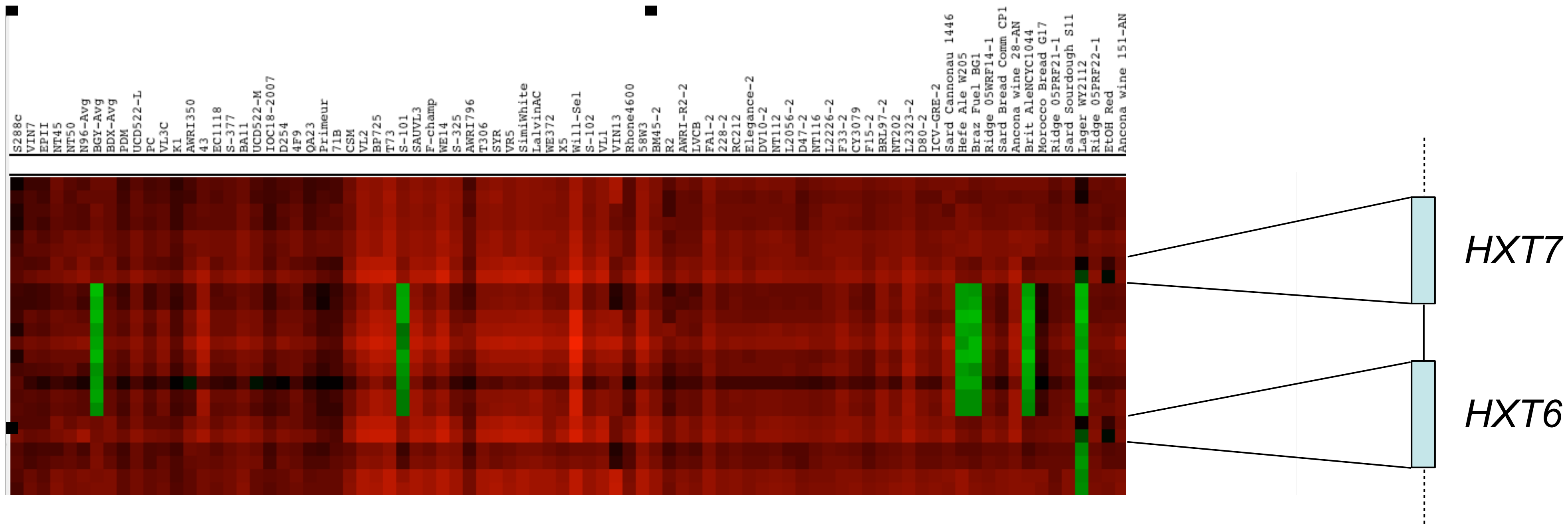


HXT6/7



What about other inter-clonal epistasis relationships?

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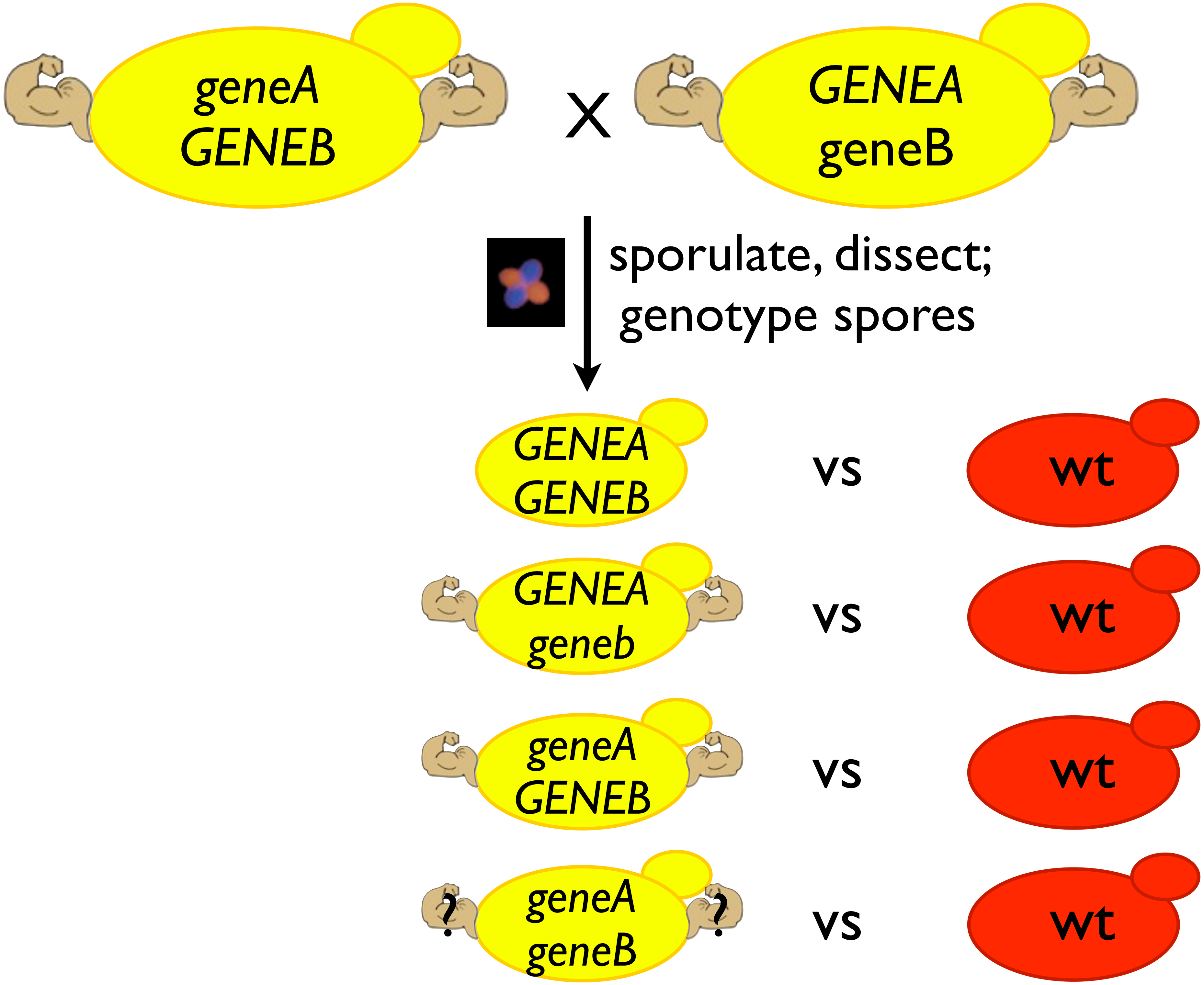


geneA
GENEB
x
GENEA
geneB

sporulate, dissect;
genotype spores

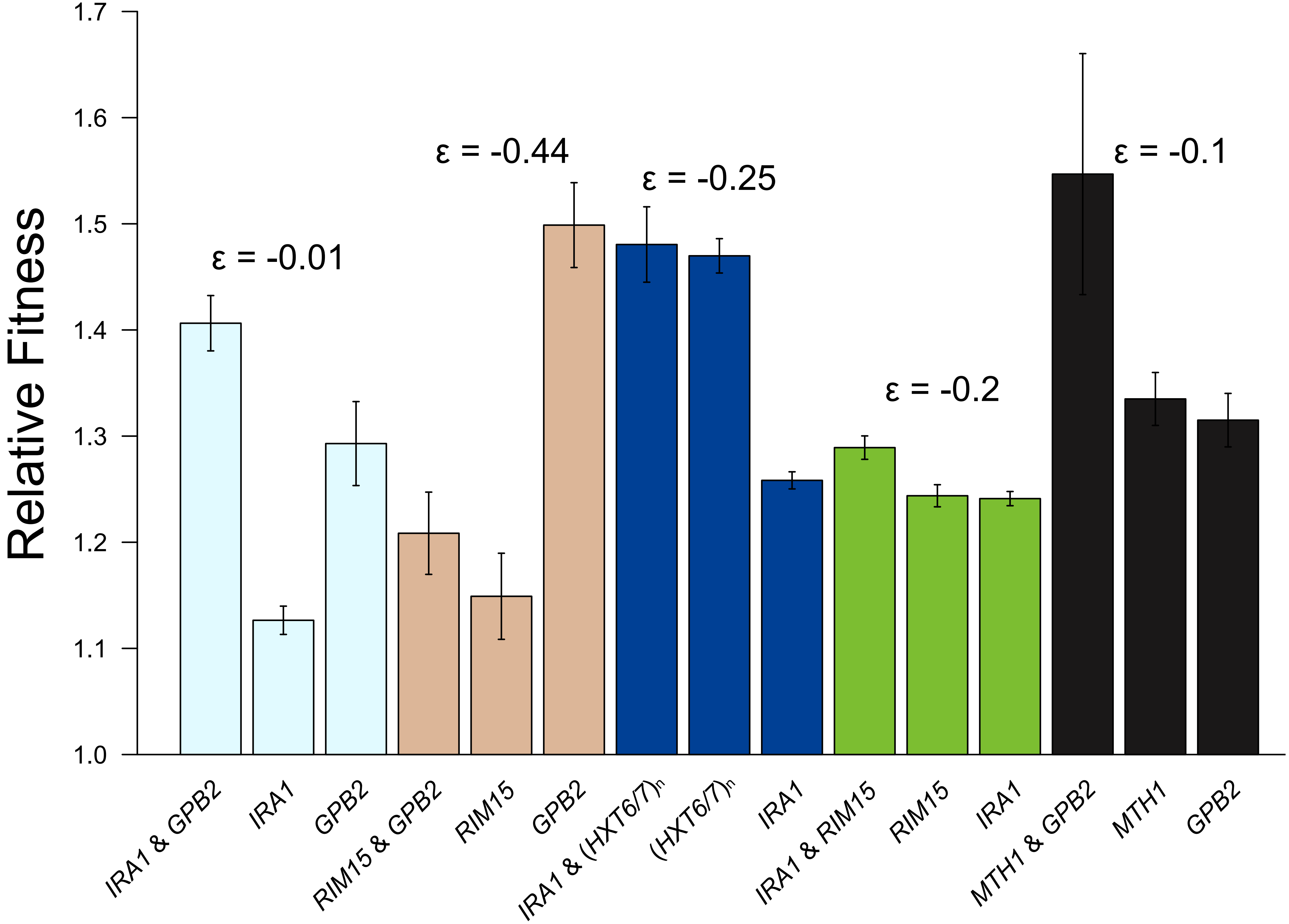
GENEA
GENEB
vs
wt

GENEA
geneb
vs
wt

geneA
GENEB
vs
wt

?
geneA
geneB
?
vs
wt

Sign and Negative Epistasis are Prevalent



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Summary

- Clonal interference an important effect in adaptive evolution of yeast
  - Population dynamics
  - Allele frequencies
  - Several adaptive mutations lost or nearly lost due to other adaptive mutations
- Signaling through the Ras pathway an important target of adaptation
- Mutually exclusive mutations play a role in defining the adaptive landscape

Future Work/Questions

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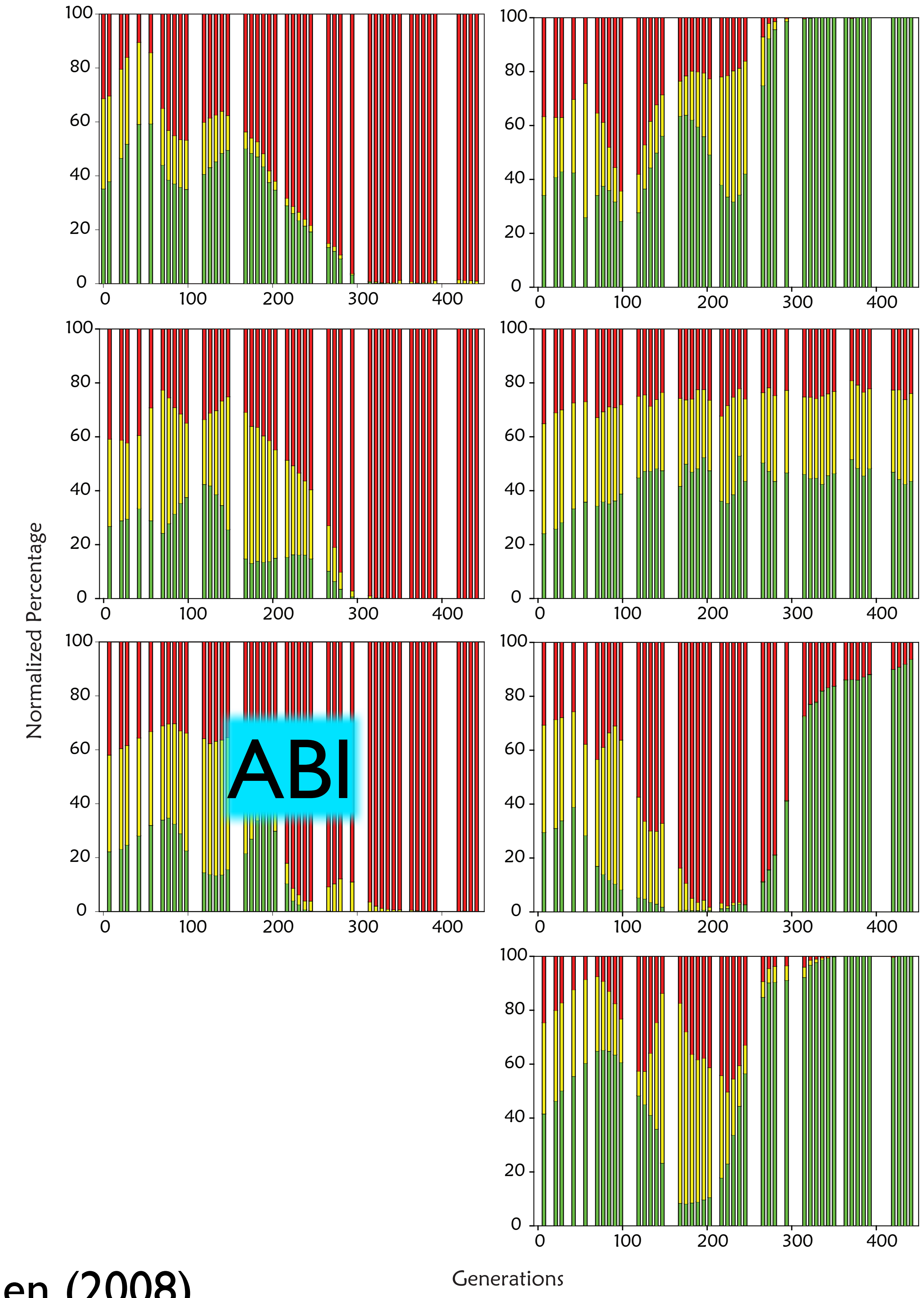
- Are some “hitchhikers” adaptive in the presence of other mutations?
- How general are the adaptations?
  - In other conditions
- What fraction of the adaptive landscape have we explored?
  - Other evolved populations
  - Haploid vs. Diploid

Seven additional populations

0.08%
glucose
$N = \sim 10^9$



0.008%
glucose
$N = \sim 10^8$

Kao & Sherlock, Nat Gen (2008)

Acknowledgments

Jared Wenger

Dan Kvitek

Michael

Katy Kao - Texas A&M

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Yuya Kobayashi

Barbara Dunn

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NATIONAL INSTITUTES OF HEALTH