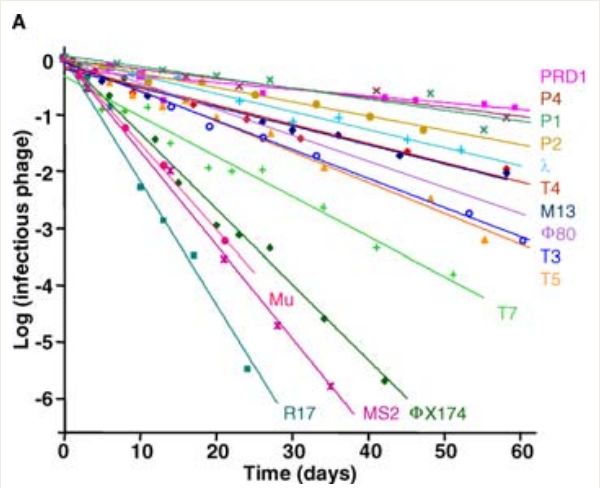
Tradeoffs, coexistence, cooperation

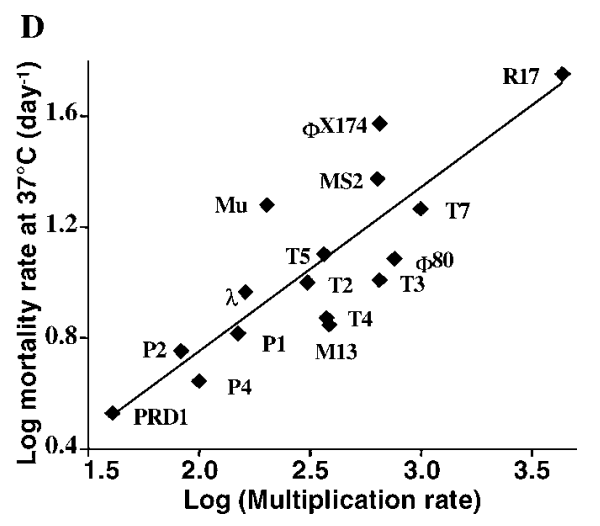
ECOLOGICAL SPECIALIZATION: DECREASING PERFORMANCE IN ALTERNATIVE ENVIRONMENTS WHILE ADAPTING TO CURRENT ENVIRONMENT

* WHAT EVOLUTIONARY FORCES CAPABLE OF DRIVING ECOLOGICAL SPECIALIZATION?

- SELECTION
- DRIFT

Life history tradeoffs in natural phage

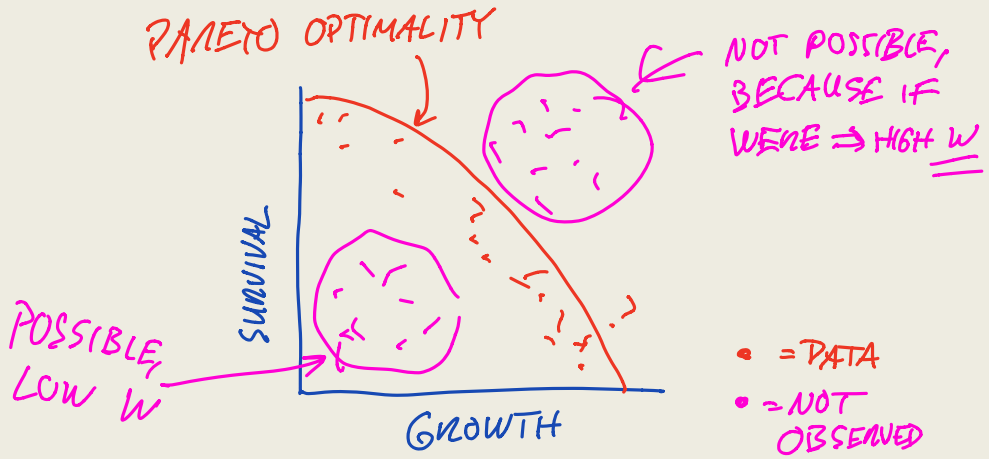




SURVIVAL VS. REPLICATION TRADEOFF?

← TRACKED VIABILITY AS ABILITY TO MAKE "PLAQUE" ON LAWN OF E. coli
- WIDE RANGE OF RATES
- EXPON. DECAY → CONSTANT w/ TIME & "SINGLE STEP"

ASSAYED REPLICATION IN E. coli
- WIDE RANGE



(De Paepe and Taddei, 2006. *PLoS Biology*)

Mutation accumulation vs. antagonistic pleiotropy

ANTAGONISTIC PLEIOTROPY (AP) → SELECTION

- PLEIOTROPY = MUTATION CAUSING MORE THAN ONE PHENOTYPIC EFFECT
- MECHANISTIC TRADEOFF BETWEEN TWO (OR MORE) TRAITS (BY THAT MUTATION)

MUTATION ACCUMULATION (MA) → DRIFT

- NEUTRAL LOSS OF ALTERNATIVE TRAITS DUE TO LACK OF SELECTION FOR THEM
- THIS CAN ACT AT LARGE N FOR UNUSED TRAITS
- REQUIRES VERY SMALL N TO SEE MELTDOWN IN THE SELECTIVE ENVIRONMENT

WHICH SHOULD BE:

FASTER? AP

MORE PARALLELISM? AP
- MTP THAT ADAPT. IN PARALLEL TRAITS
  ↳ CAUSE PARALLEL TRADEOFFS

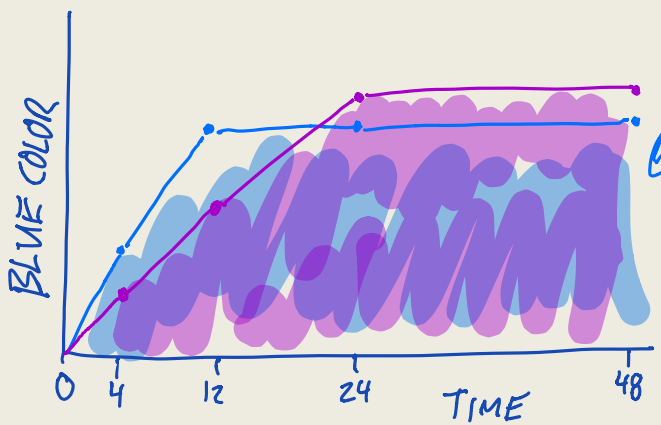
HIGHER IN A MUTATOR STRAIN? MA

* DIRECT TEST: TEST IF MUT. CAUSING $W_B \downarrow$ WAS $W_A \uparrow$ OR $W_A =$

Mutation accumulation vs. antagonistic pleiotropy

- LENSKI LINES IDEAL: EVOLUTION ON JUST* GLUCOSE FOR DECADES

- COOPER & LENSKI
  - ASSAYED STRAINS IN "BIOLOG" PLATES
  - PROPRIETARY 96-WELL PLATES w/ 95 SUBSTRATES, ONE PER WELL
  - CONTAINS DYE THAT TURNS BLUE IF RESPIRATION
  - METRIC: "AREA UNDER CURVE"



ASK:
1. LOSSES IN ALT. ENV. FASTEST WHICH ADAPTATION WAS FASTEST?
2. PARALLELISM IN LOSSES?
3. FASTER LOSS IN MUTATONS?
   ↳ 4 LINES INC. RATE 100x

(Cooper & Lenski, 2000. *Nature*)

Mutation accumulation vs. antagonistic pleiotropy

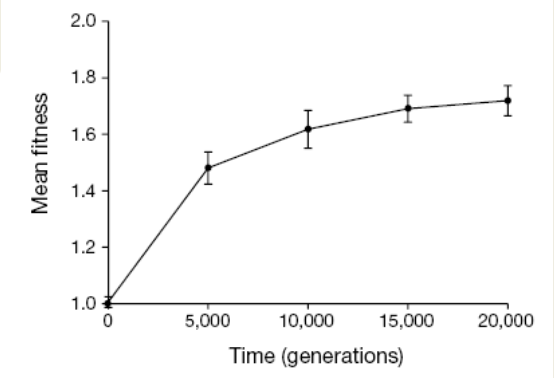
ASK: ① LOSSES IN ALT. ENV. FASTEST WHILE ADAPTATION WAS FASTEST? YES

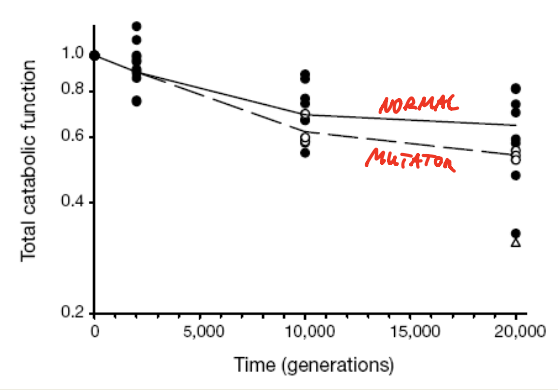
② PARALLELISM IN LOSSES? YES

③ FASTER LOSS IN MUTATORS? ↳ 4 LINES INC. RATE 100x NO

- ANTAGONISTIC PLEIOTROPY
- LOTS OF CATABOLIC DECAY

* DRIVEN BY SELECTION





	Time (generations)		
Carbon source	2,000	10,000	20,000
bromosuccinic acid	7	11	12
D-alanine	1	3	6
D-malic acid	5	12	12
D-ribose	12	12	12
D-saccharic acid	9	11	11
D-serine	12	11	10
D-sorbitol	12	11	11
fructose-6-phosphate	11	10	9
fumaric acid	9	12	12
glucose-1-phosphate	12	11	10
glucose-6-phosphate	11	12	8
glucuronamide	0	4	8
L-asparagine	8	12	12
L-aspartic acid	9	12	12
L-glutamine	12	12	12
L-lactic acid	11	12	10
L-malic acid	7	12	12
malic acid	9	12	12
mono-methylsuccinate	2	12	12
mucic acid	12	8	9
P-hydroxyphenylacetic acid	5	12	11
succinic acid	9	12	12
uridine	12	12	10
Sum of parallel losses	9	16	16

(Cooper & Lenski, 2000. *Nature*)

Is the assay used really related to fitness?

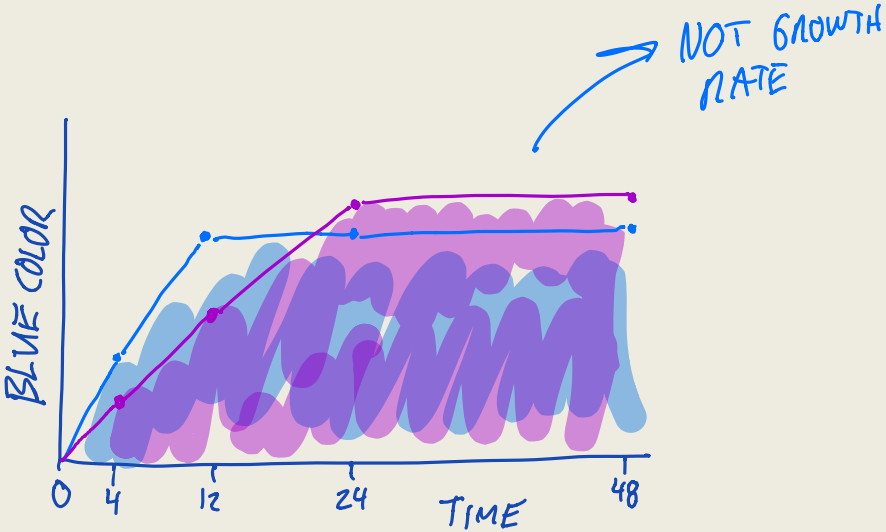
1. 96-WELL vs. FLASK
   ↳ LOW AERATION?
2. DYE CONVERSION vs. CELL DENSITY
   ↳ IS THIS REALLY GROWTH?
3. AUC vs. GROWTH RATE

WE TRIED

48-WELL PLATES

CELL DENSITY

GROWTH RATE

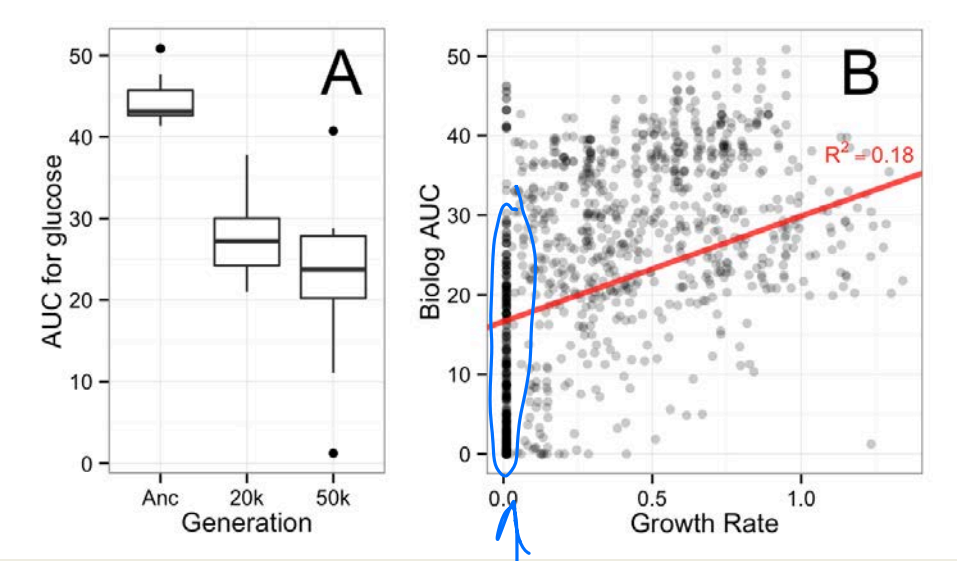


- YIELD IS NOT A FITNESS MEASURE

Is the assay used really related to fitness?

- PERFORMANCE IN GLUCOSE WENT DOWN IN EVOLVED

- THE ONLY CITRATE-UTILIZER HAD SAME AUC AS NON-CIT.

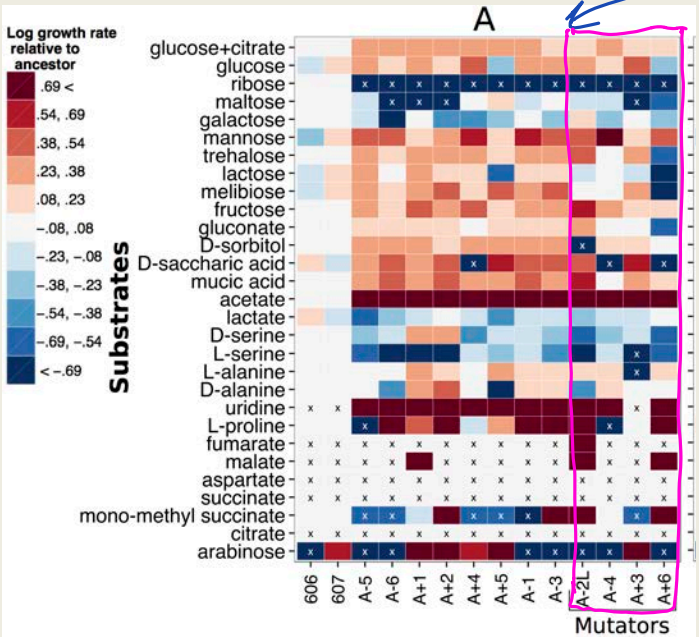


MANY FALSE POSITIVES

* BECAME WORSE AT BIOLOG

(Leiby and Marx, 2014. *PLoS Biology*)

How did growth rate change?

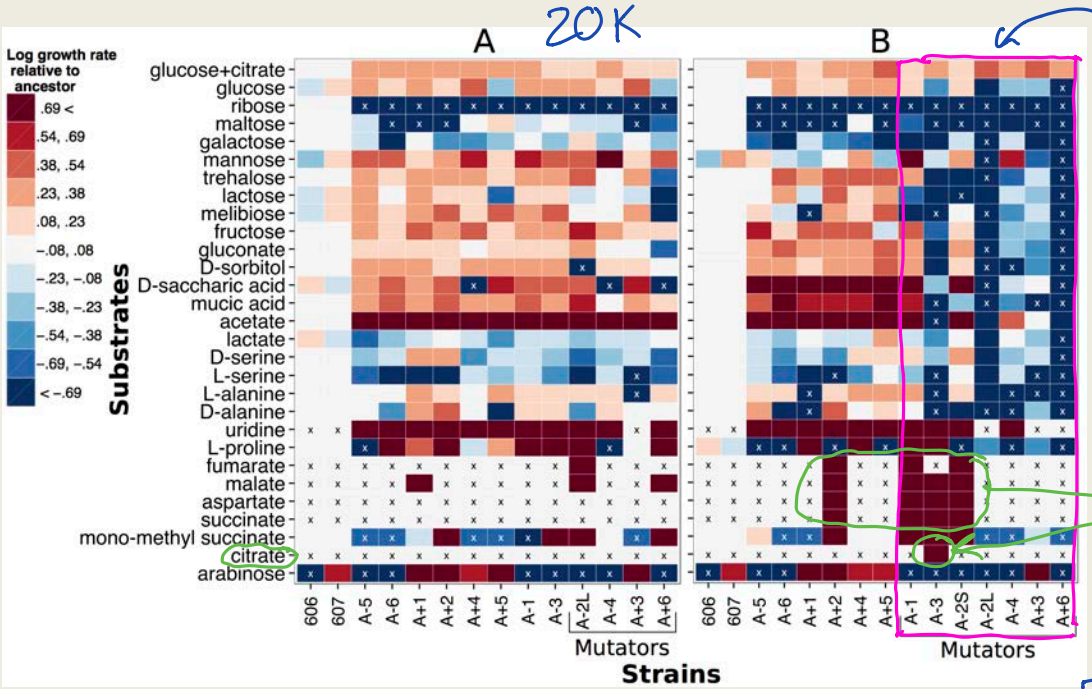


AT 20K GENERATIONS

- MORE GAINS THAN LOSSES
  ↳ "SYNERGISTIC" PLEIOTROPY
- ONLY MODEST PARALLELISM
- MUTATORS: NOT DIFFERENT

(Leiby and Marx, 2014. *PLoS Biology*)

How did growth rate change?



AT 50K GEN.

- MUTATIONS NOW MUCH WORSE
- PARALLELISM MODEST
- FASTER LOSS DESPITE SLOWER ADAPTATION

NOVEL SUBSTRATE USE

* PRIMARY: MA SEEMS MORE DOMINANT THAN AP

FAST LOSSES WHILE ADAPTATION FASTEST?
2000: YES 2014: NO

PARALLELISM?
2000: YES 2014: NOT MUCH

FASTER LOSS IN MUTATIONS?
2000: NOW 2014: YES

(Leiby and Marx, 2014. *PLoS Biology*)

How predict which substrates most likely to experience increases or decreases?

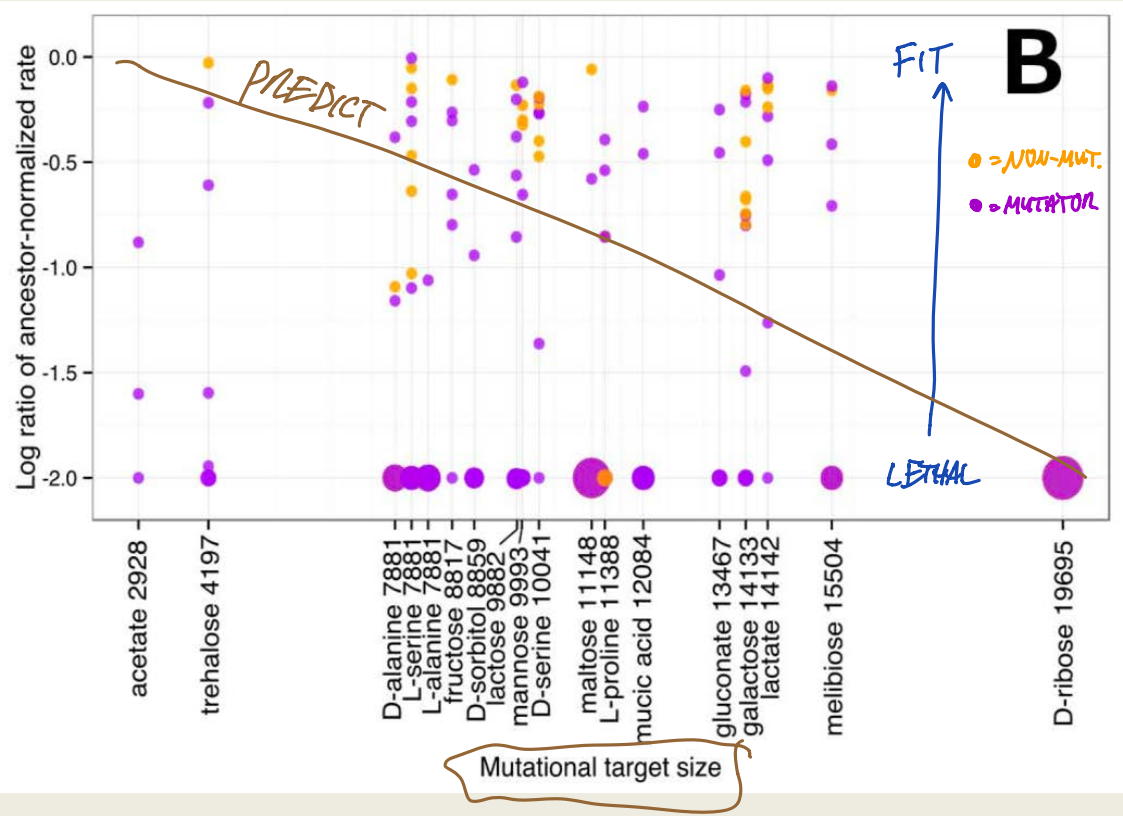
USING SAME ENZ?

SELECTION

- MORE GENES DIF: BIGGER COST, BETTER TO COSE
  BIGGER TARGET FOR MUTATION

- SIMILAR FLUX PATTER: MAGNITUDE OF SHARED FLUXES MORE SIMILAR

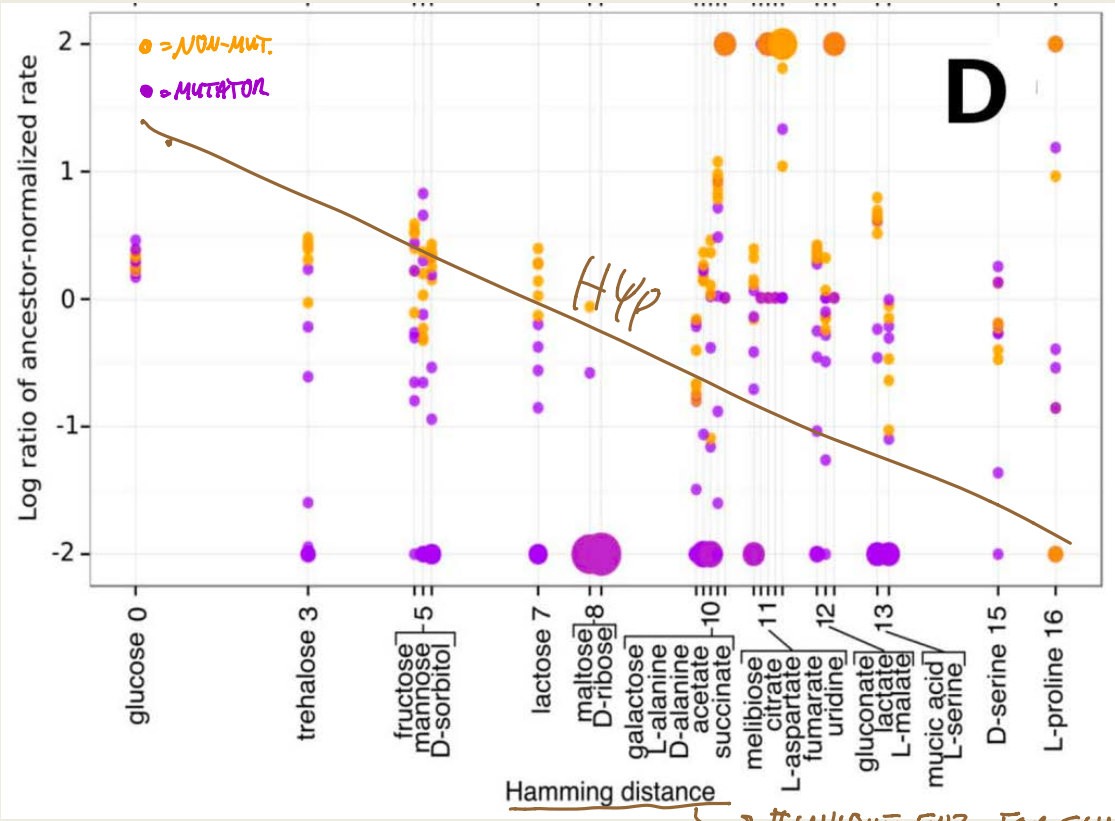
Target size for deleterious mutations?



NO CORREL.

(Leiby and Marx, 2014. *PLoS Biology*)

Similarity in C use to that of glucose?



Z NO

→ # UNIQUE ENZ. FOR GLUCOSE VS. X OR X VS. GLUCOSE

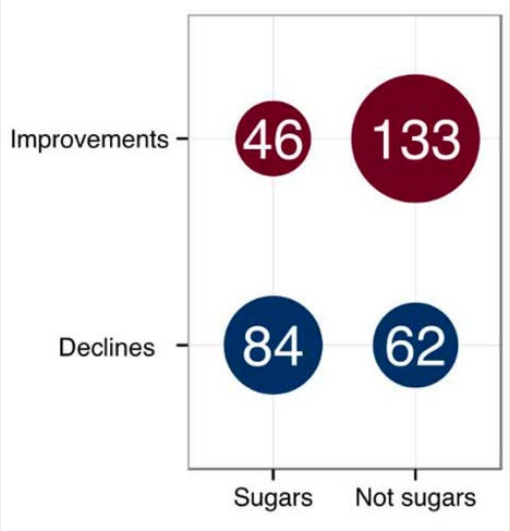
ALTERNATIVE METRICS: EUCLIDIAN DISTANCE btw/ FLUX VECTORS
1 - PEARSON CORRELATION OF FLUX VECTORS
COUNT OF RXNS FOR X & NOT GLUCOSE
↳ $P = 0.04$, $R^2 = 0.02$

(Leiby and Marx, 2014. *PLoS Biology*)

IS IT A SUGAR OR NON-SUGAR?

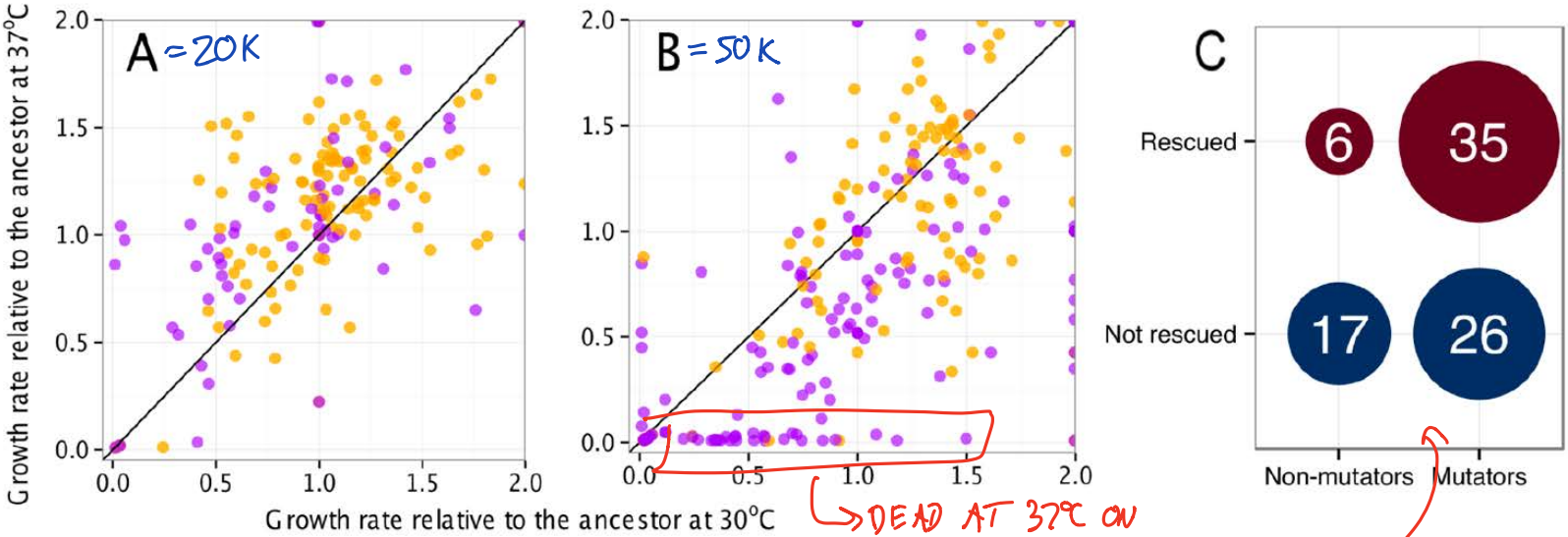
- SIGNIFICANT ASSOCIATION w/ BEING A SUGAR
  - ↳ IN WRONG DIRECTION

* TRADEOFFS IN SUGAR TRANSPORT



(Leiby and Marx, 2014. *PLoS Biology*)

Any generality to LOF mutations?



DEAD AT 37°C ON THAT SUBSTRATE, BUT OK AT 30°C

20K:

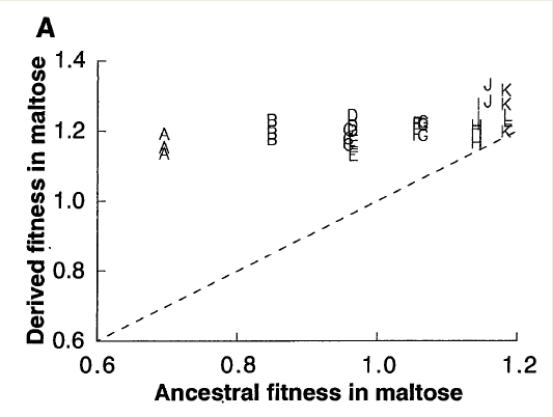
50K:

→ LOTS OF DECLINE IN MUTATIONS DUE TO DESTABILIZATION OF UNUSED PROT. IN GLUCOSE

(Leiby and Marx, 2014. *PLoS Biology*)

How permanent are tradeoffs?

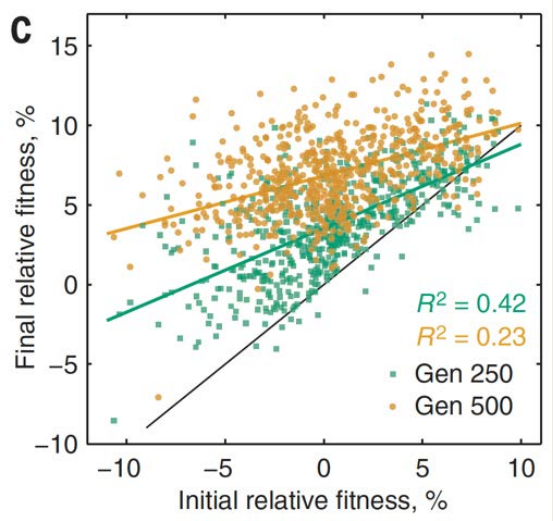
- IF LOSE FITNESS IN Y WHILE ADAPTING TO X, CAN WE BE RECOVERED EASILY?
  - VAISHALI'S WORMS
  - KRISHNA'S YEAST
  - MY ENGINEERED Methylobacterium



- EARLY LINEAGES FROM LENSKI

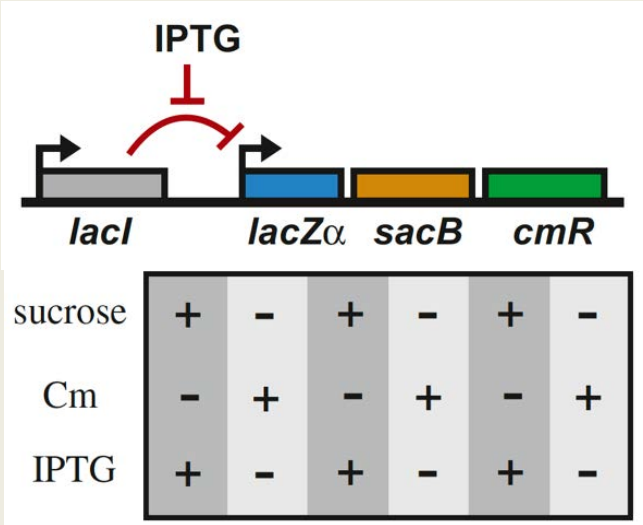
- DESAI YEAST LINES

* RAPID AMELIORATION



(Travisano & Lenski, 1995. *Science*; Kryazhimskiy et al., 2014. *Science*)

Tradeoffs in reversing regulatory logic



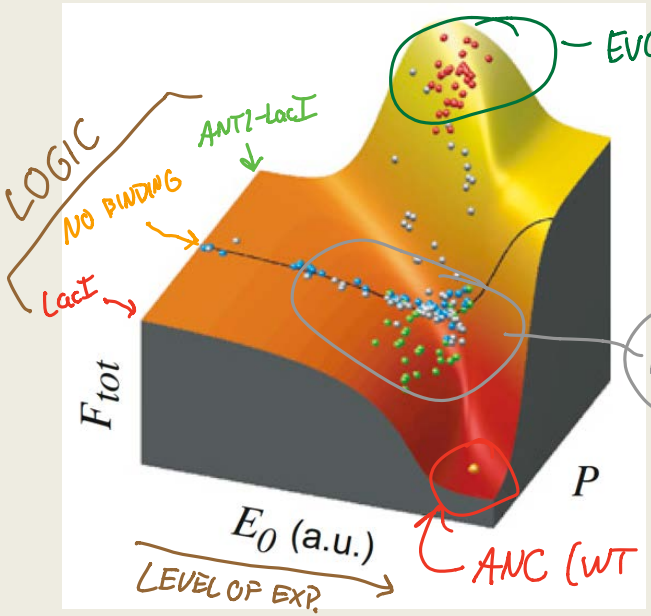
	IPTG (INDUCER) −	IPTG (INDUCER) +
LacI	BINDS (OFF)	NO BINDING (ON)
ANTI-LacI	NO BINDING (ON)	BINDS (OFF)

- COOL SCHEME TO REWARD OR PENALIZE TRANSCRIPTION

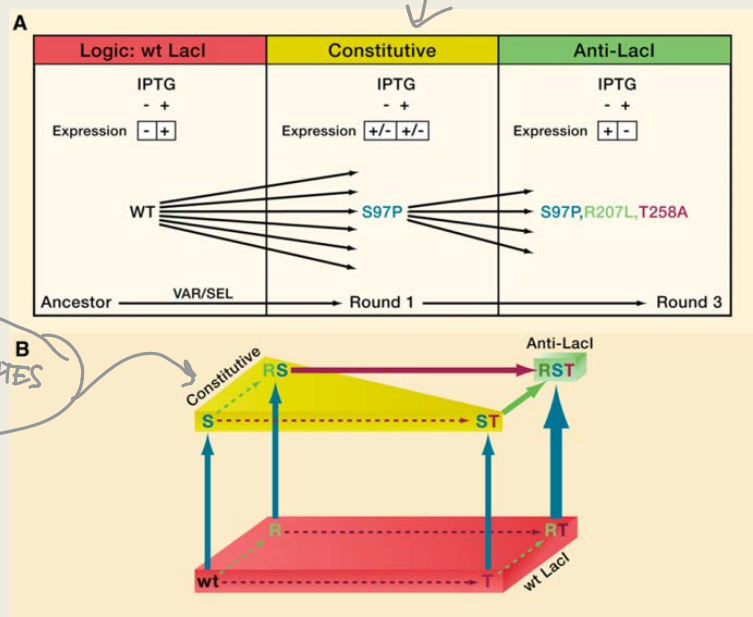
- HARD TO EVOLVE OPPOSITE PHENOTYPE?

(Poelwijk et al., 2011. *Cell*)

Tradeoffs in reversing regulatory logic



INTERMEDIATES



- NEITHER STEP TO REVERSED "ANTI-LacI" (S or T) COULD DO SO ON OWN
  - ↳ PASSED THROUGH CONSTITUTIVE PHEN (or REMAIN DELETERIOUS)

(Poelwijk et al., 2011. *Cell*; Marx, 2011. *Cell*)

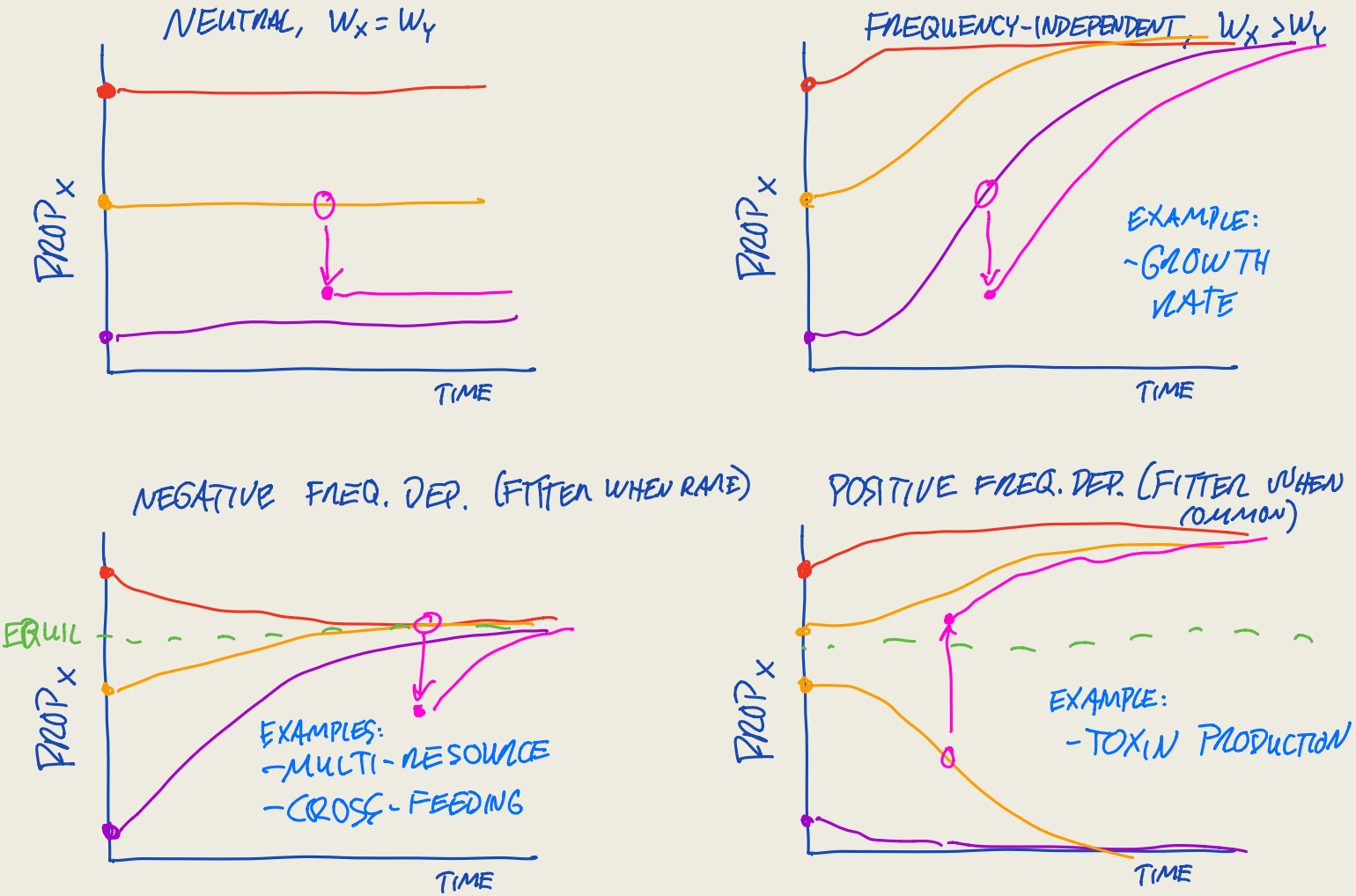
Coexistence requires particular type of fitness interaction

- WHAT IS REQUIRED FOR ECOLOGICAL SPECIALIZATION TO PERMIT COEXISTENCE?

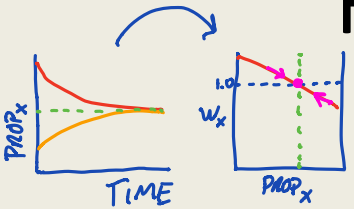
COEXISTENCE - STABLE MAINTENANCE OF ≥2 GENOTYPES (OR SPECIES)

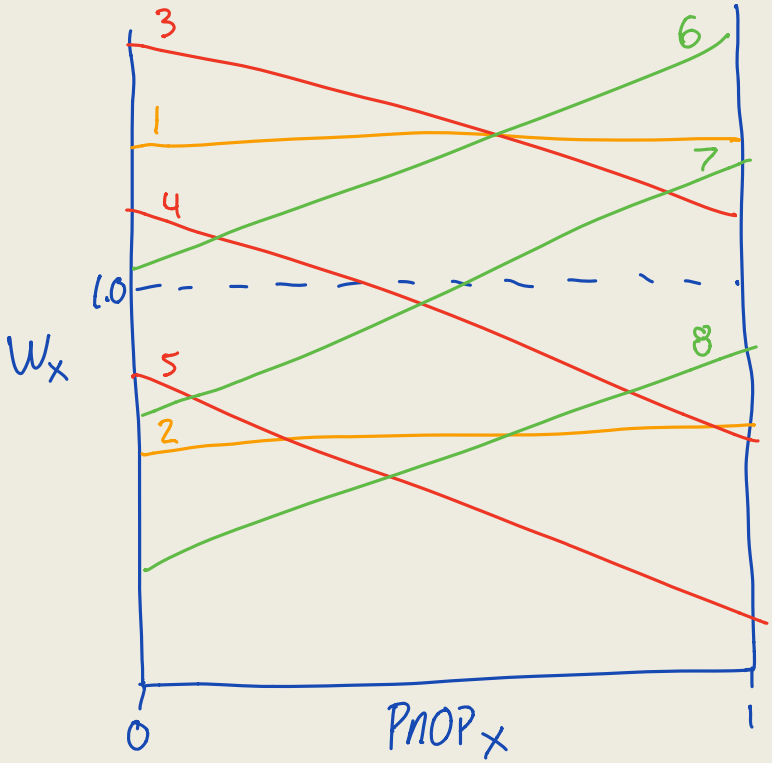
- NOT JUST ≥2 THERE
  - → MUTATION SELECTION BALANCE
  - → NEUTRAL (CRYPTIC) VARIATION
  - → CLONAL INTERFERENCE w/ OTHER BENEFICIAL LINEAGES
  - → MIGRATION

Potential interaction types



How test for coexistence?





PATTERN	FREQ-DEP?	CROSS 1.0	WINNER
1	NO	N	X
2	NO	N	Y
3	NEG.	N	X
4	NEG.	Y	X & Y
5	NEG.	N	Y
6	POS.	N	X
7	POS.	Y	X OR Y (DEP. X_0)
8	POS.	N	Y

Genomic evidence for coexistence?

OPEN ACCESS Freely available online

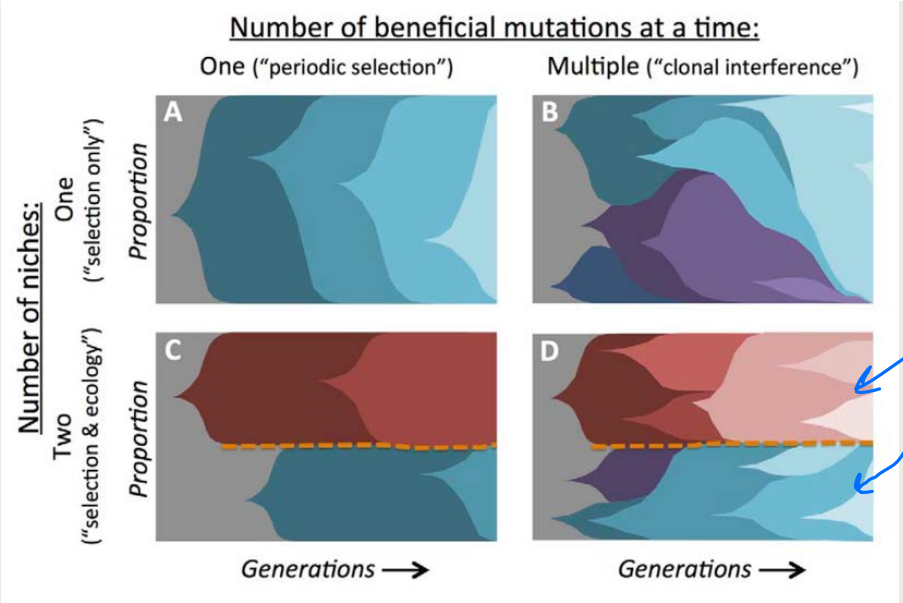
PLOS | BIOLOGY

Primer

Can You Sequence Ecology? Metagenomics of Adaptive Diversification

Christopher J. Marx[1,2]*

1 Department of Organismic and Evolutionary Biology, Harvard University, Cambridge, Massachusetts, United States of America, 2 Faculty of Arts and Sciences Center for Systems Biology, Harvard University, Cambridge, Massachusetts, United States of America

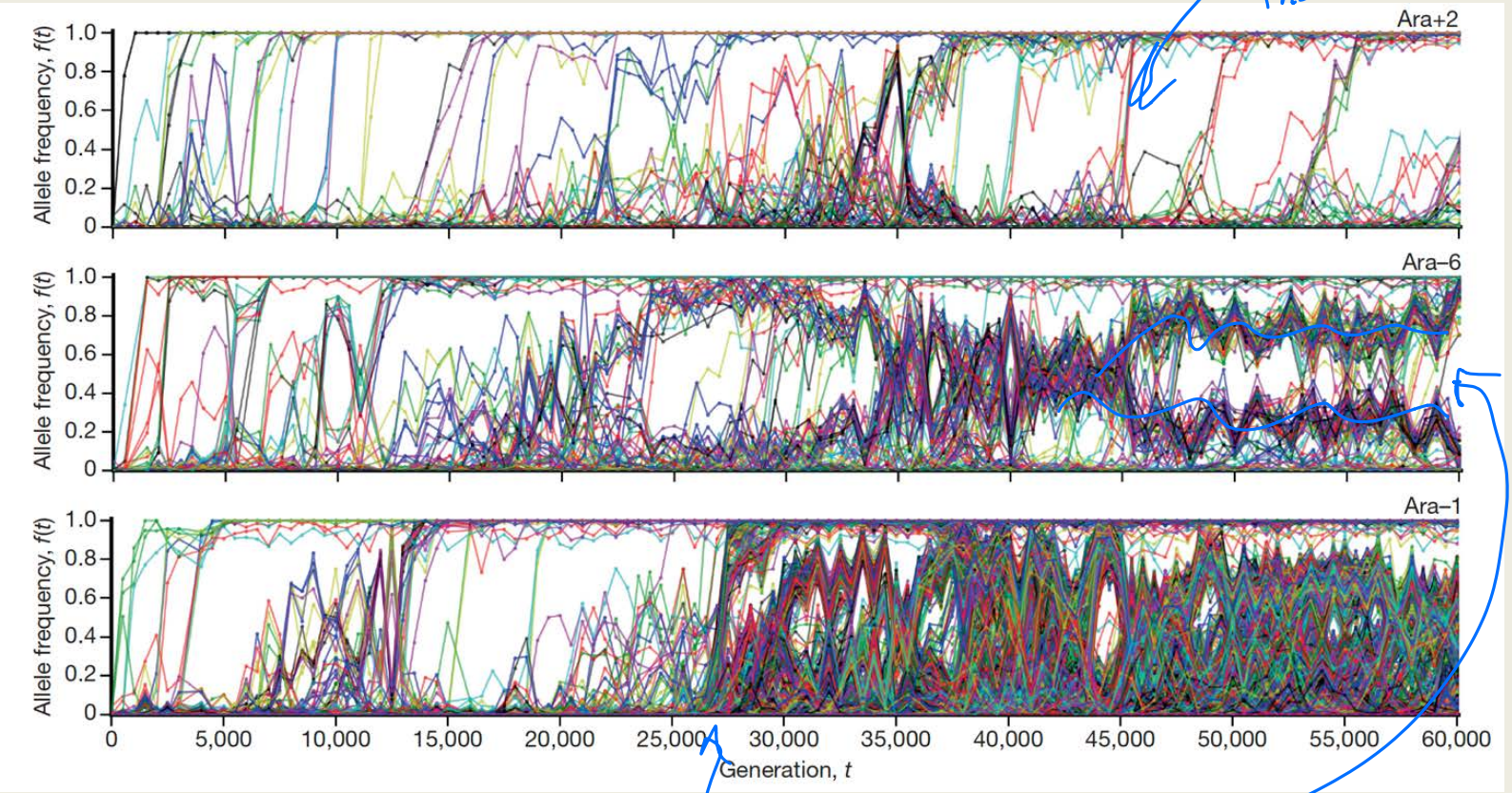


SELECTION DYNAMICS HELD TO W/IN EACH SUBPOPULATION

(Marx, 2013. *PLOS Biology*)

Co-existence in Lenski lines

NO EVID CE FREQ.DEP



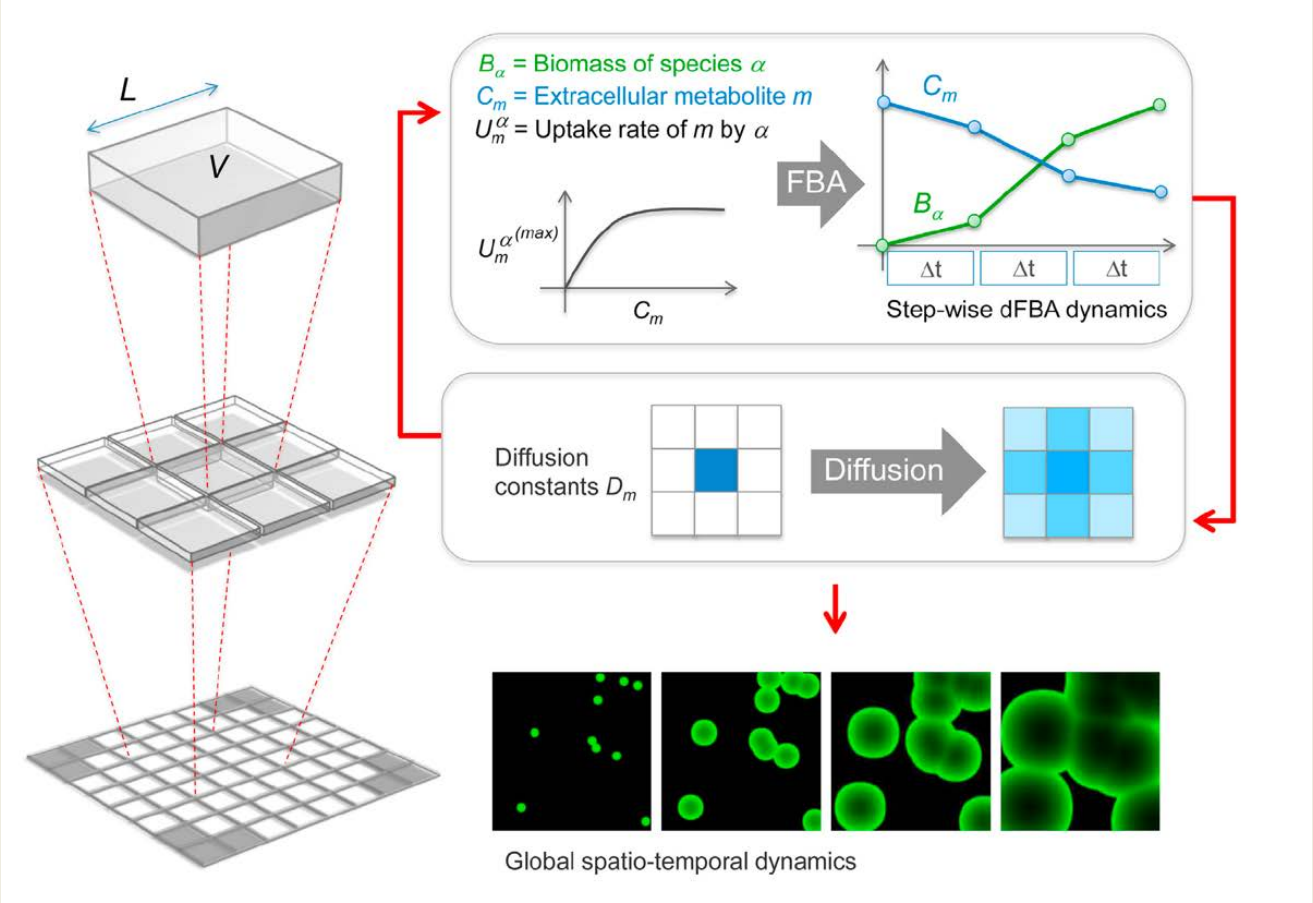
MUTATION

TWO DISTINCT "ECOTYPES"

ADAPTIVE DIVERSIFICATION

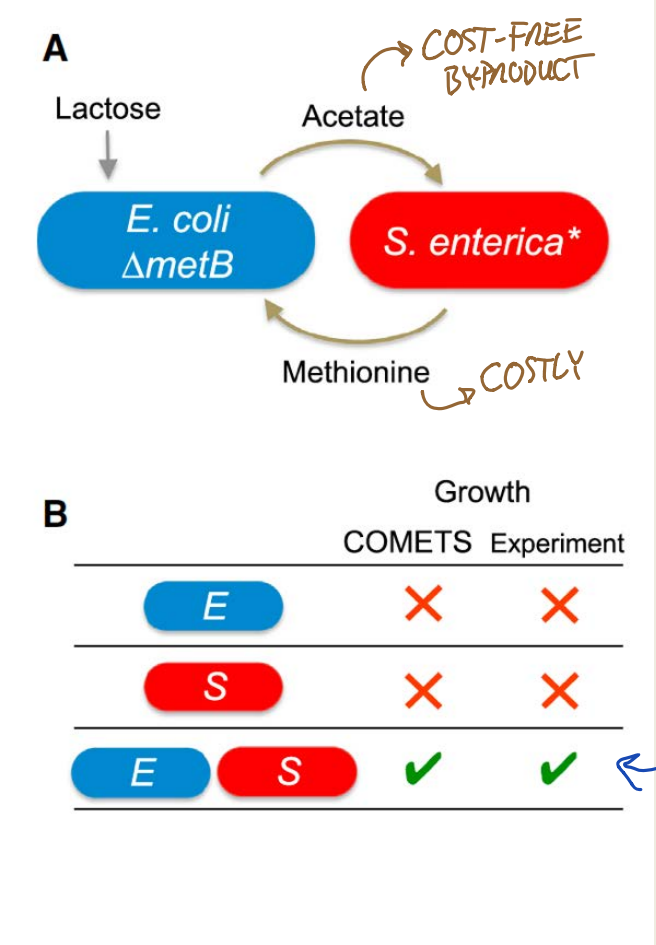
(Good et al., 2017. *Nature*)

Use of FBA to predict co-existence in multi-species community



(Harcombe et al., 2014. *Cell Reports*)

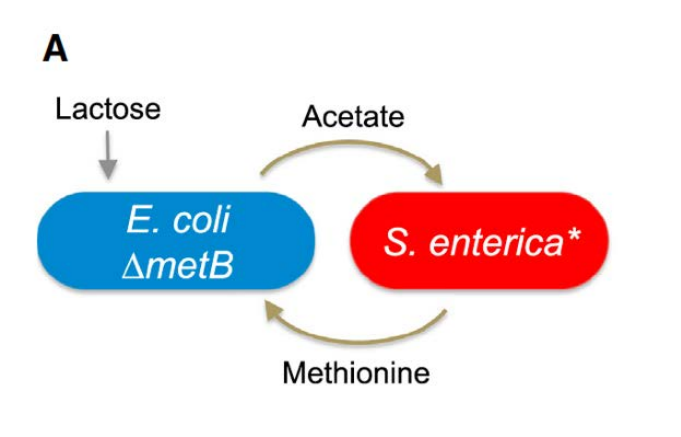
Use of FBA to predict co-existence in multi-species community

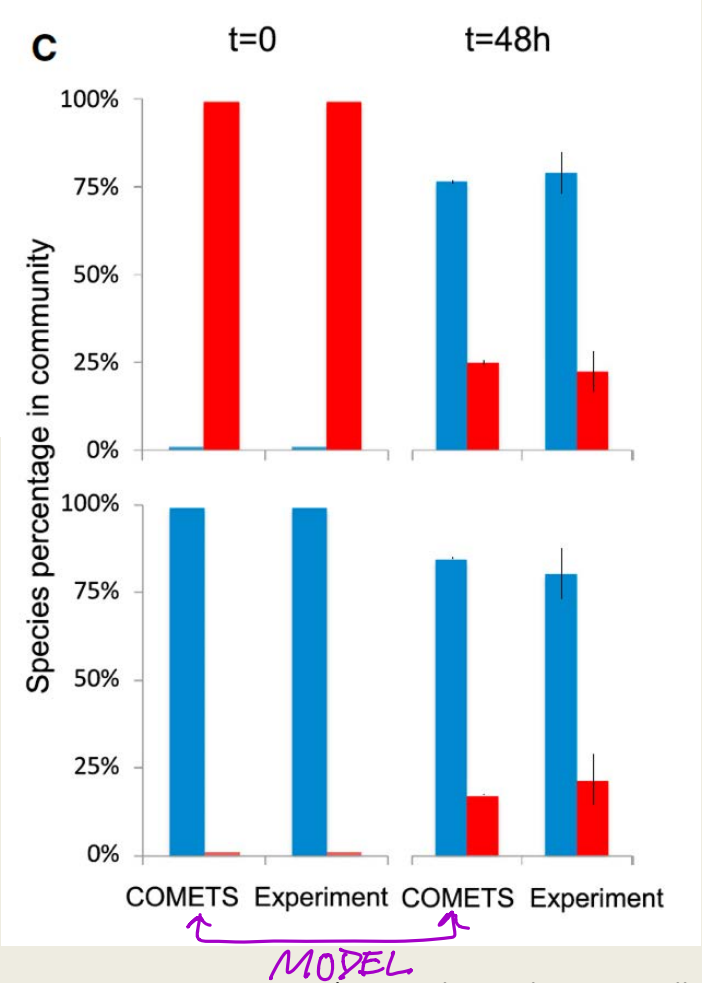


- EACH REQUIRES FOOD OR A NUTRIENT FROM EACH OTHER
- NEED BOTH

(Harcombe et al., 2014. *Cell Reports*)

Use of FBA to predict co-existence in multi-species community



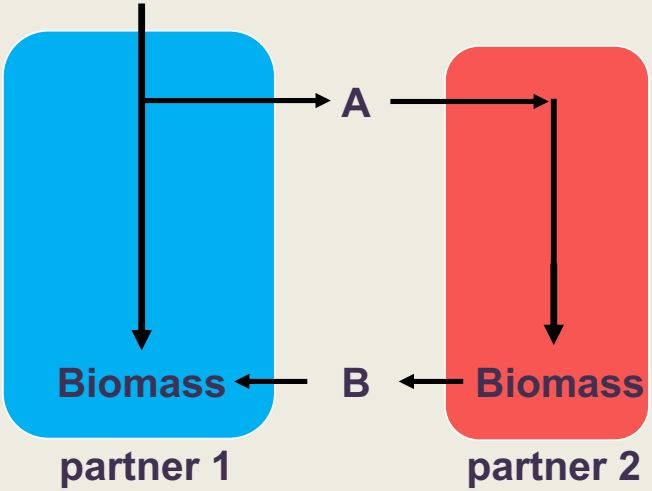


- EQUILIBRIUM WELL-PREDICTED

- ALSO SUCCESSFUL w/ OBLIGATE 3-WAY SYNTHETIC COMMUNITY

(Harcombe et al., 2014. *Cell Reports*)

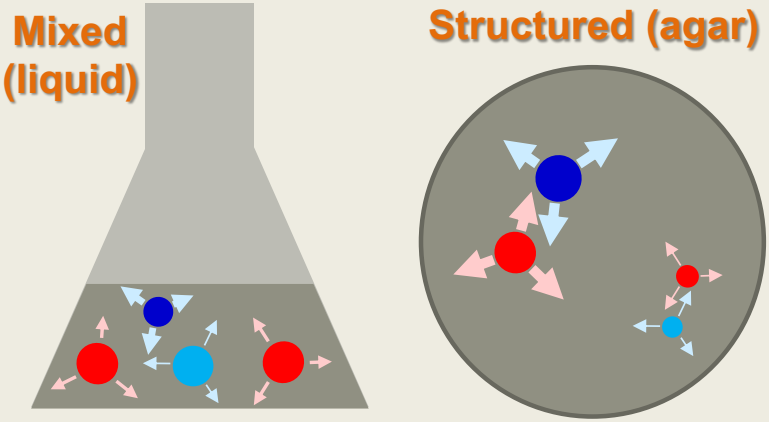
Costly cooperation requires structured interactions to evolve



- How direct more benefits to cooperators?
  - One way: Spatial structure…

- If costly, how can this emerge in the face of cheaters?

Cheater: taking advantage of public goods with less (or no) investment



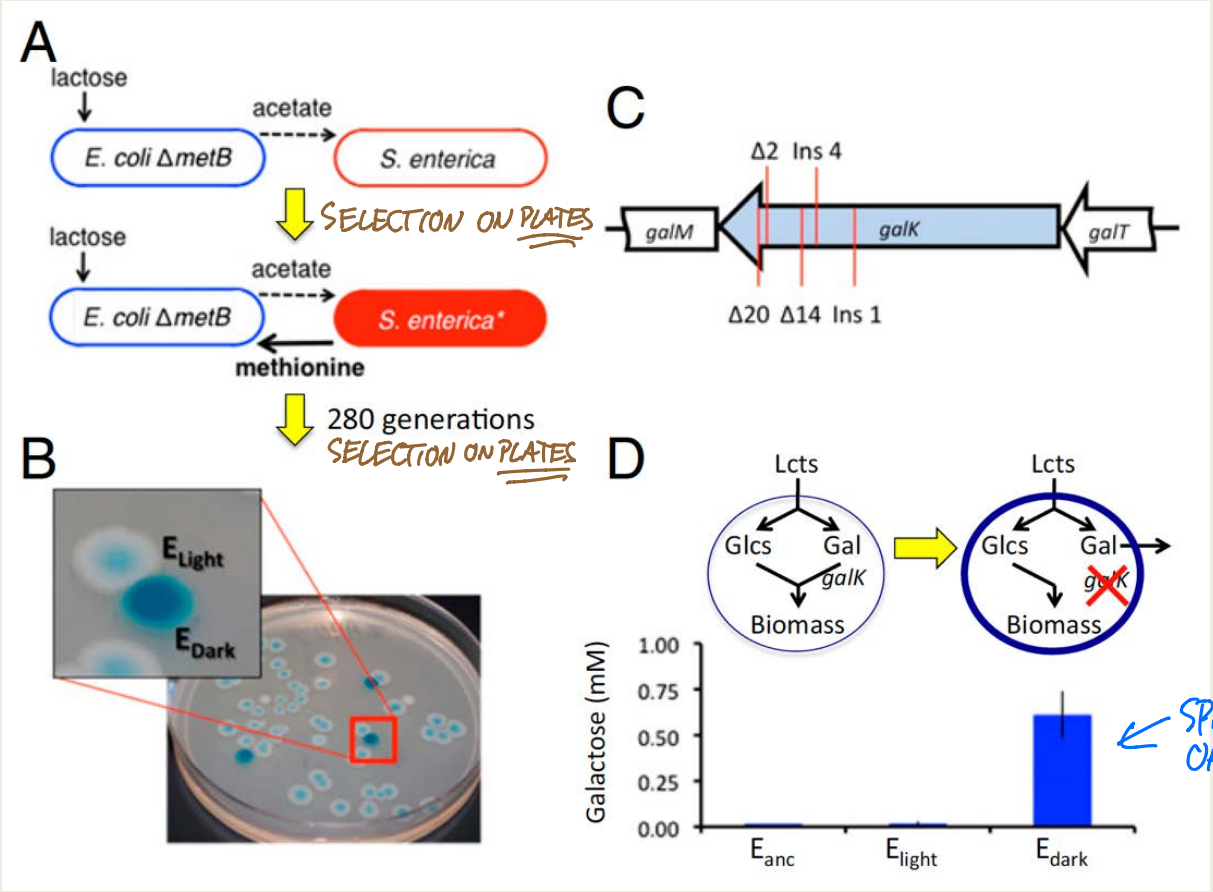
Interactions global	Interactions local
No correlation of benefit & production (cheating wins)	Benefit correlated with production (cooperation wins*)

Cooperation is an advantage if:

1. benefits (b) > costs (c)
2. $b_C - c_C > b_D - c_D$

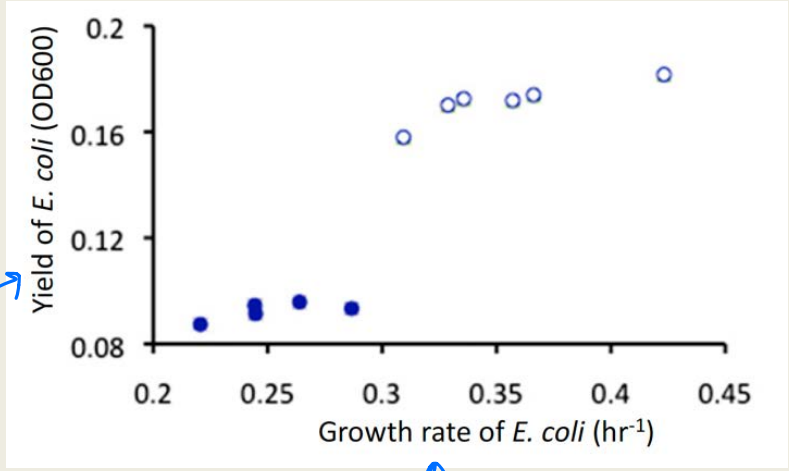
C = cooperator ● ; D = defector ●

Novel cooperation by *E. coli*



(Harcombe et al., 2018. *PNAS*)

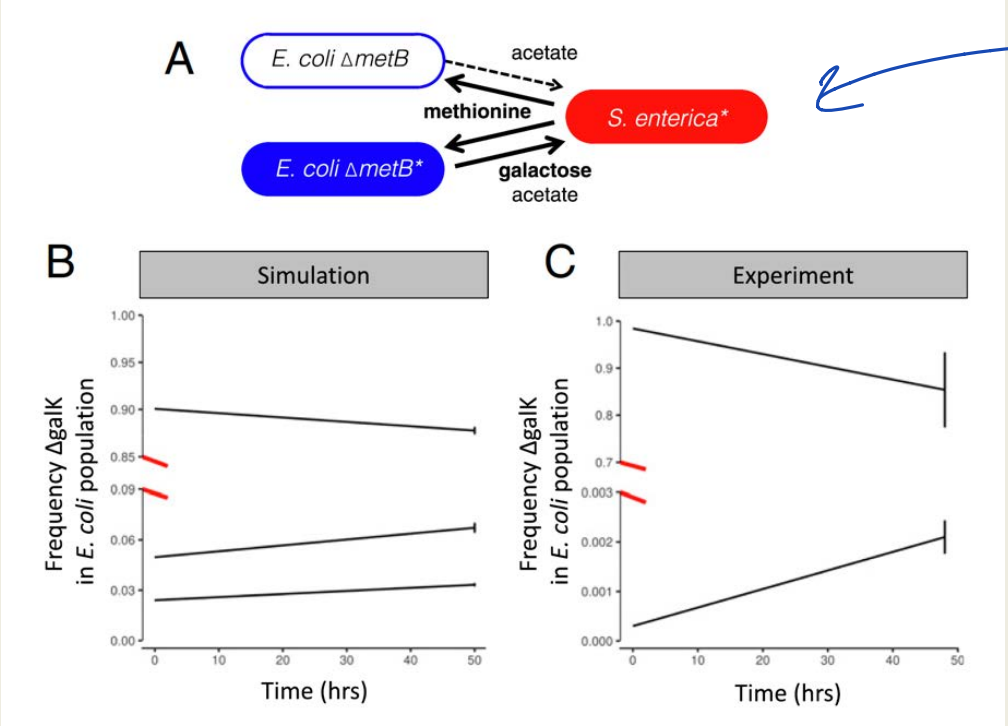
Galactose production costly



- BOTH GROWTH RATE & YIELD LOWER FOR GALACTOSE PRODUCERS

(Harcombe et al., 2018. *PNAS*)

FBA predicts cooperators will coexist



MODEL w/ THREE TYPES
↳ LOOK AT SELECTION btw/ E.coli AT LOW, HIGH FREQ.

- OBSERVE NEGATIVE FREQUENCY-DEP. FITNESS FOR GALACTOSE PRODUCER
  ↳ LEADS TO COEXISTENCE OF BOTH E.coli w/ S. enterica

(Harcombe et al., 2018. *PNAS*)