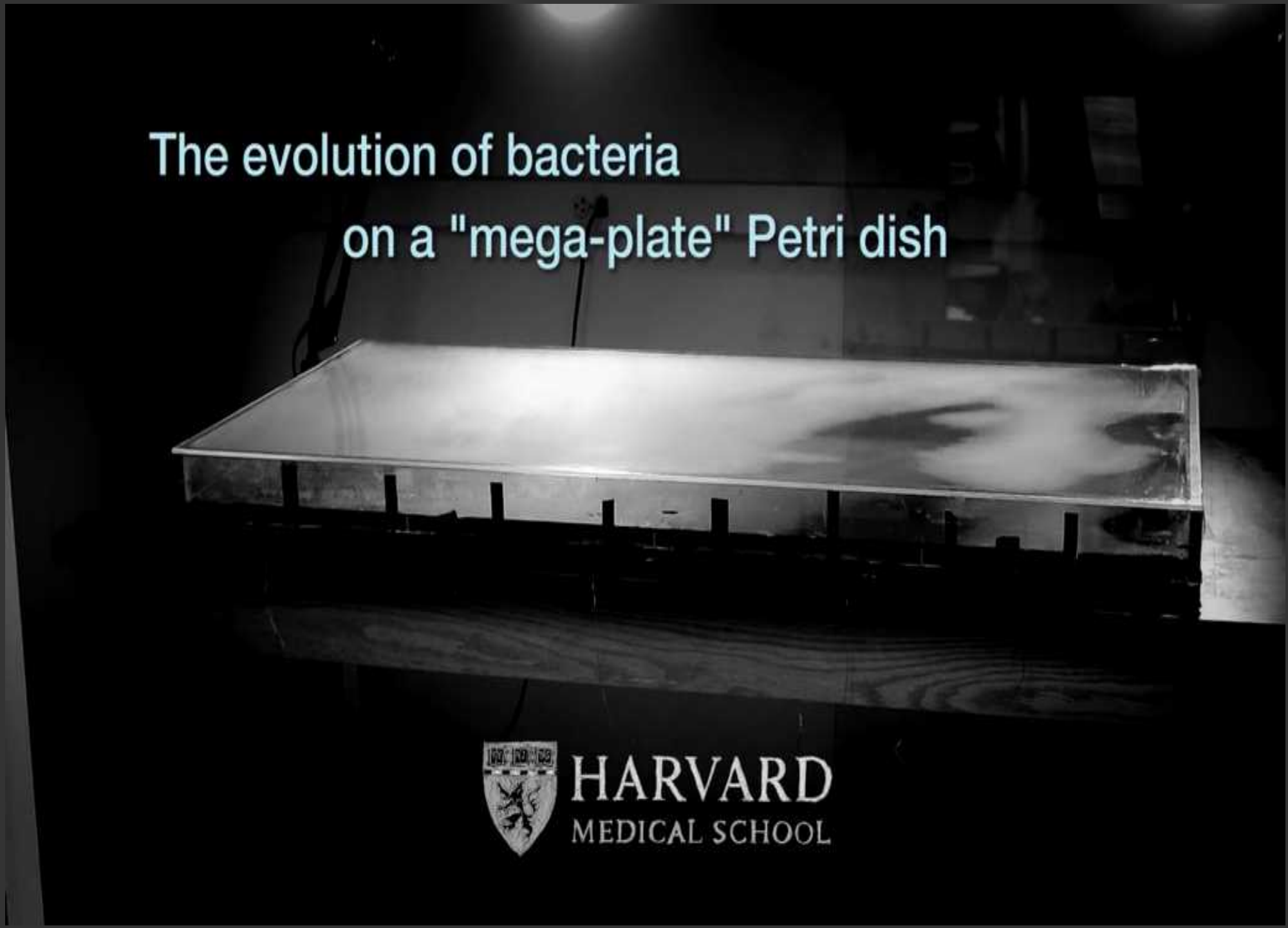
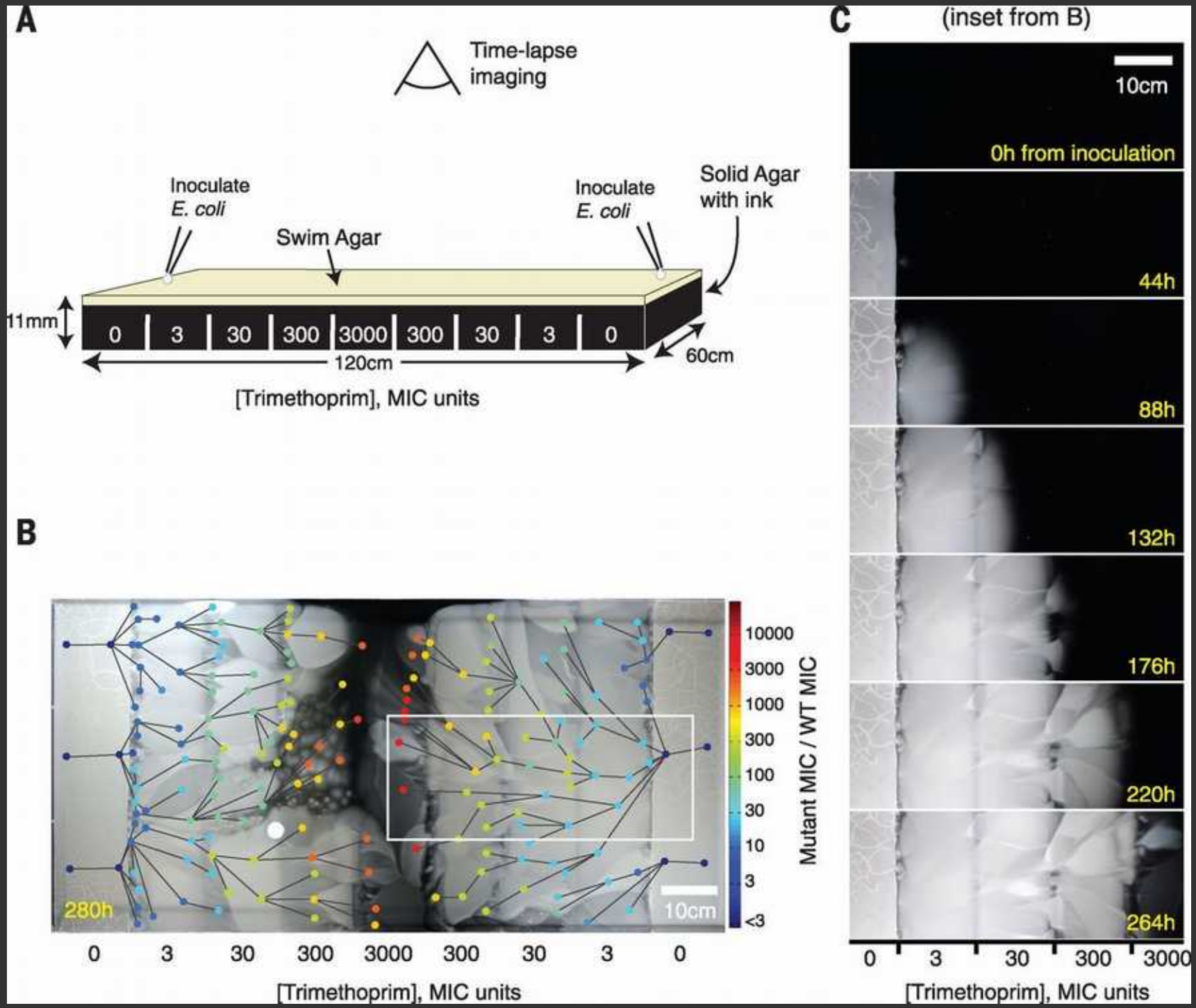
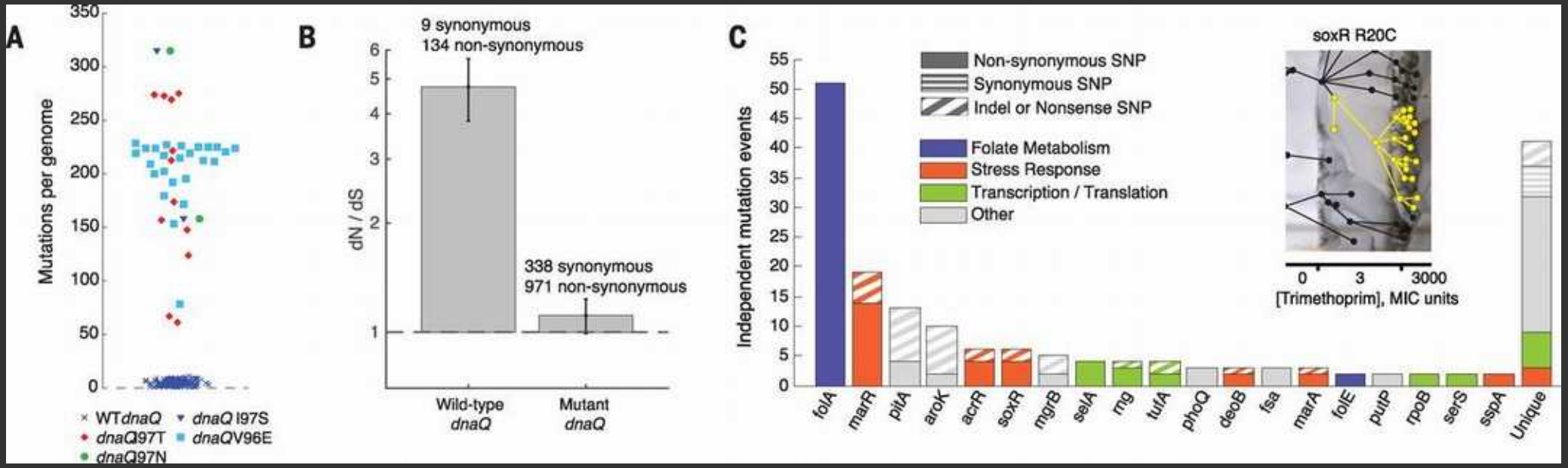
- Variability, heritability, selection coefficient
- Evolution is not goal oriented
- Phylogenies, binomial nomenclature, hierarchies, phylogenetic trees and classification, sister groups
- How phylogenies are constructed: morphology and molecular data, homologies vs. analogies, DNA alignments, outgroups, using them for predictions
- Organisms' evolutionary history is documented in their genomes
- Plasmids and HGT

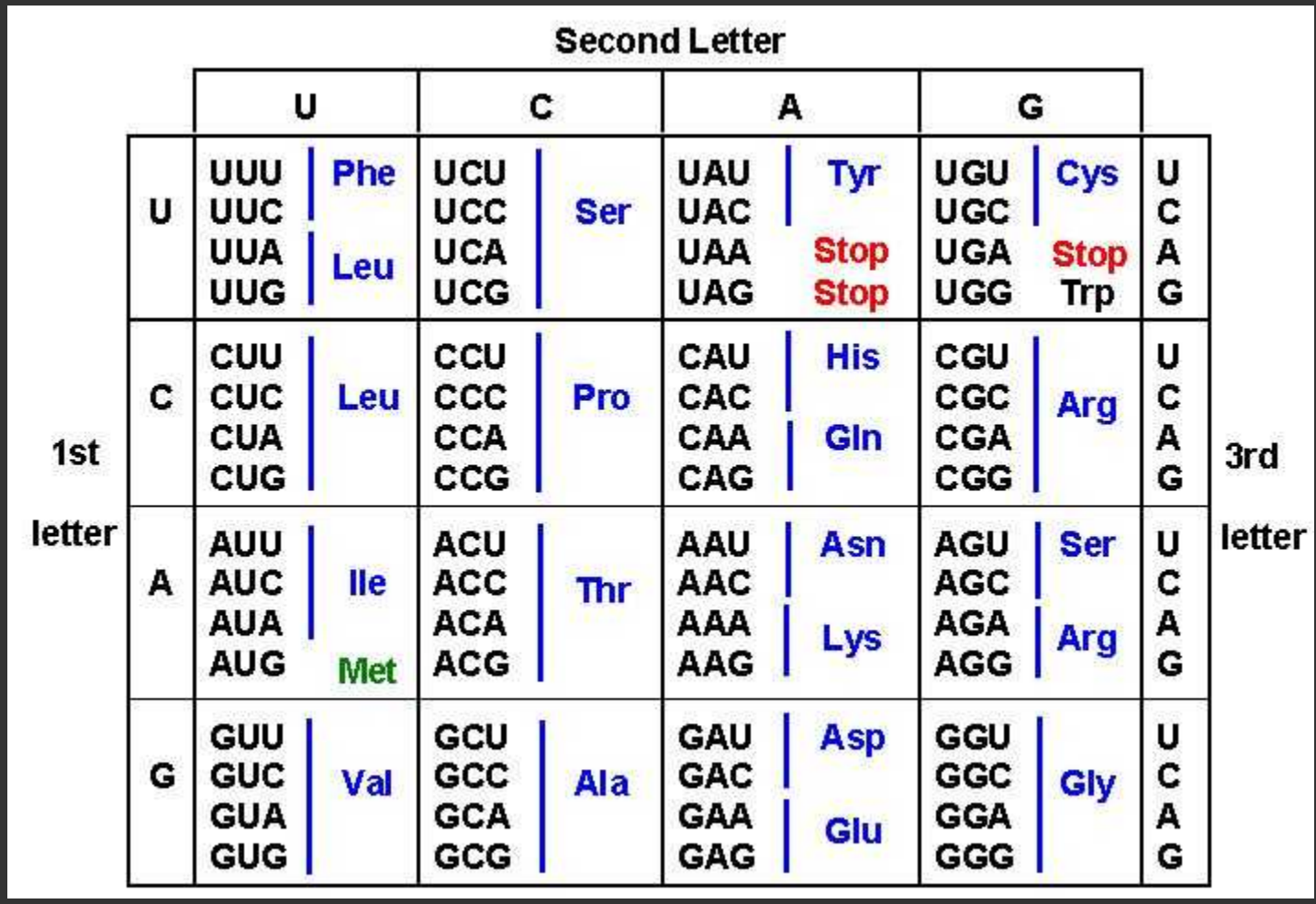

The evolution of bacteria
on a "mega-plate" Petri dish
HARVARD
MEDICAL SCHOOL


A
Time-lapse imaging
Inoculate E. coli
Swim Agar
Inoculate E. coli
Solid Agar with ink
11mm
0 3 30 300 3000 300 30 3 0
120cm
60cm
[Trimethoprim], MIC units
B
280h
10cm
10000
3000
1000
300
100
30
10
3
<3
Mutant MIC / WT MIC
0 3 30 300 3000 300 30 3 0
[Trimethoprim], MIC units
C
(inset from B)
10cm
0h from inoculation
44h
88h
132h
176h
220h
264h
0 3 30 300 3000
[Trimethoprim], MIC units

Mutation Events captured by genome sequencing



Genetic code is almost universal



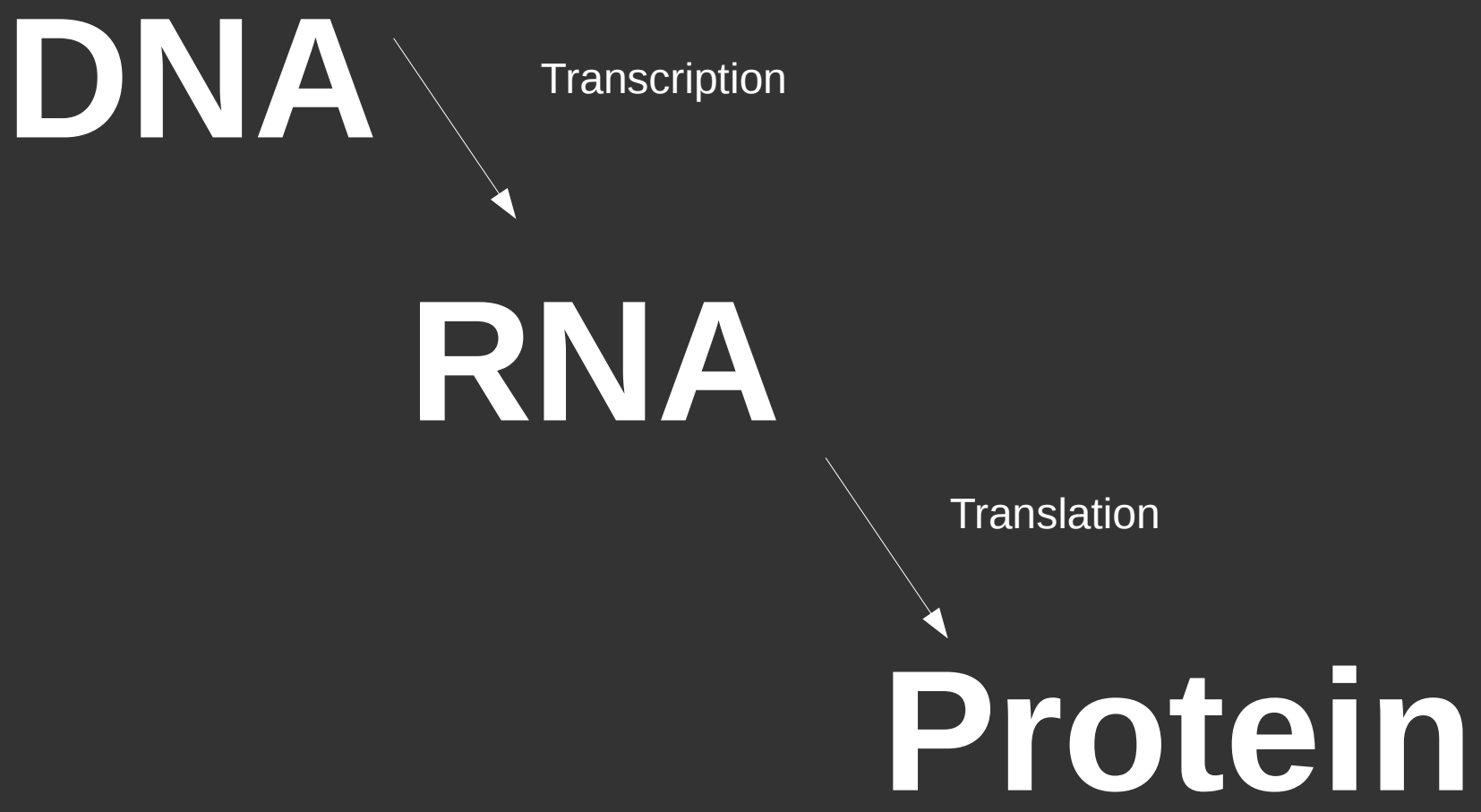
1st letter	Second Letter: U	Second Letter: C	Second Letter: A	Second Letter: G	3rd letter
U	UUU Phe	UCU Ser	UAU Tyr	UGU Cys	U
	UUC Phe	UCC Ser	UAC Tyr	UGC Cys	C
	UUA Leu	UCA Ser	UAA Stop	UGA Stop	A
	UUG Leu	UCG Ser	UAG Stop	UGG Trp	G
C	CUU Leu	CCU Pro	CAU His	CGU Arg	U
	CUC Leu	CCC Pro	CAC His	CGC Arg	C
	CUA Leu	CCA Pro	CAA Gln	CGA Arg	A
	CUG Leu	CCG Pro	CAG Gln	CGG Arg	G
A	AUU Ile	ACU Thr	AAU Asn	AGU Ser	U
	AUC Ile	ACC Thr	AAC Asn	AGC Ser	C
	AUA Ile	ACA Thr	AAA Lys	AGA Arg	A
	AUG Met	ACG Thr	AAG Lys	AGG Arg	G
G	GUU Val	GCU Ala	GAU Asp	GGU Gly	U
	GUC Val	GCC Ala	GAC Asp	GGC Gly	C
	GUA Val	GCA Ala	GAA Glu	GGA Gly	A
	GUG Val	GCG Ala	GAG Glu	GGG Gly	G

Synonymous mutation = results in same amino acid

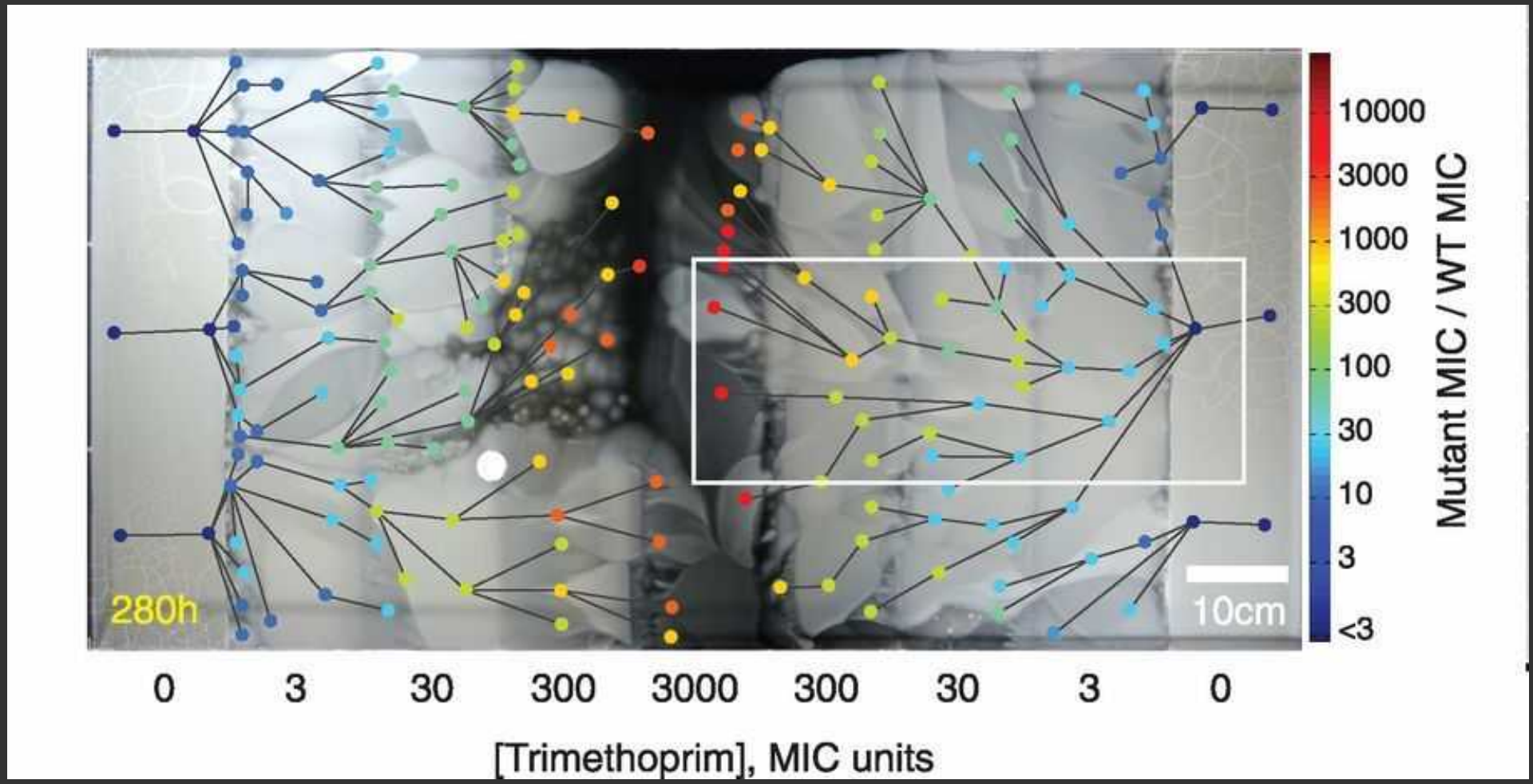
DNA mutation: ATT -> ATA

Is this synonymous???

("silent" mutations)


DNA
Transcription
RNA
Translation
Protein

Where are mutations happening?
Where are selection events?



Random, heritable mutations are selected by the environment. . . . . natural selection.

Superbugs and the post-antibiotic world

How penicillin works

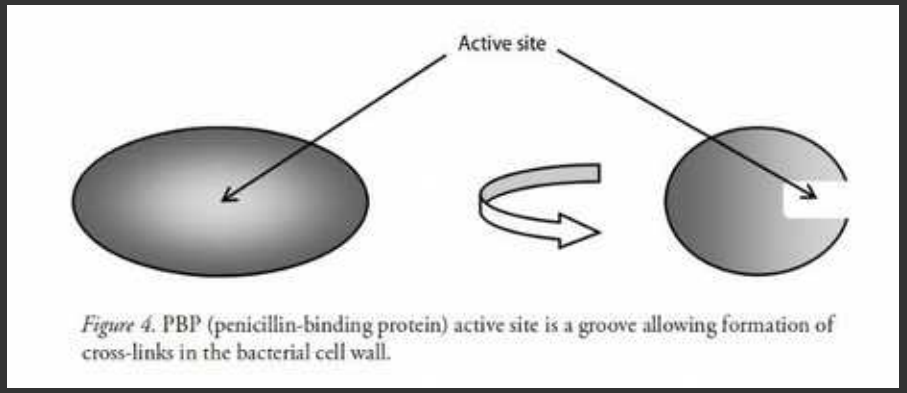


Figure 4. PBP (penicillin-binding protein) active site is a groove allowing formation of cross-links in the bacterial cell wall.

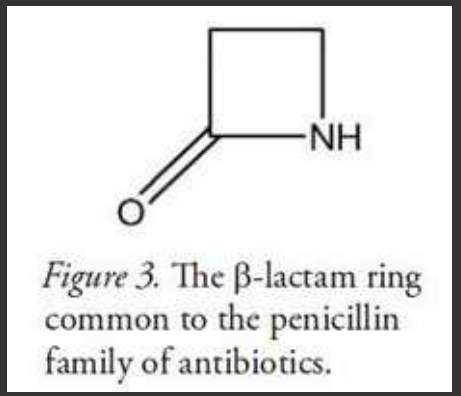


Figure 3. The β-lactam ring common to the penicillin family of antibiotics.

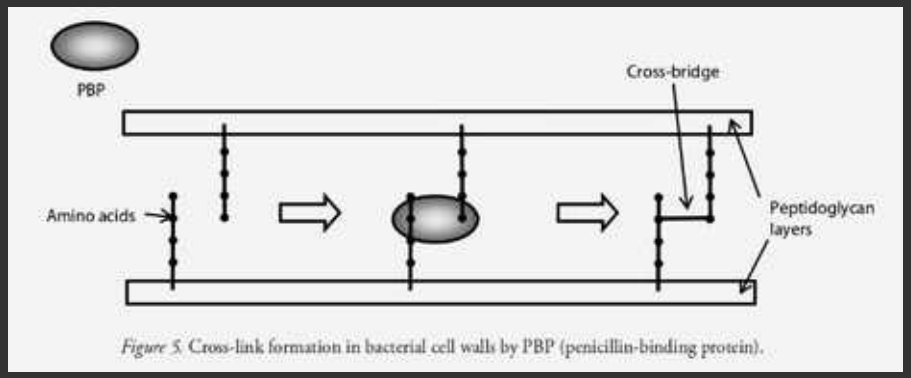
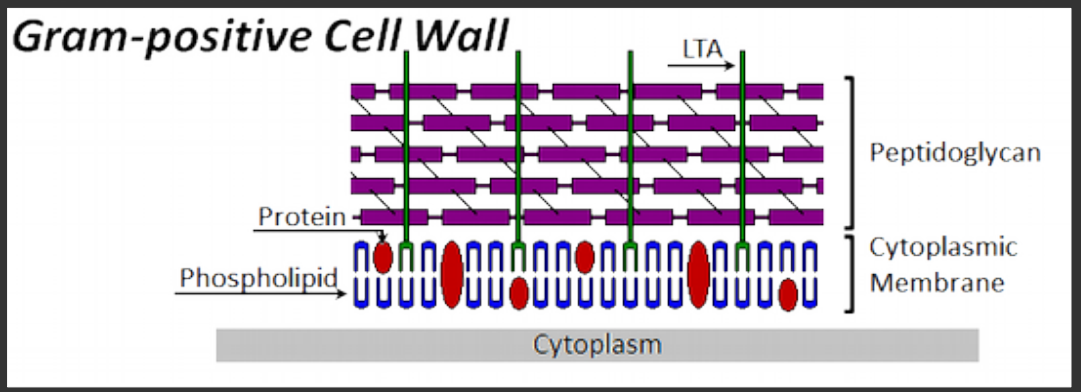
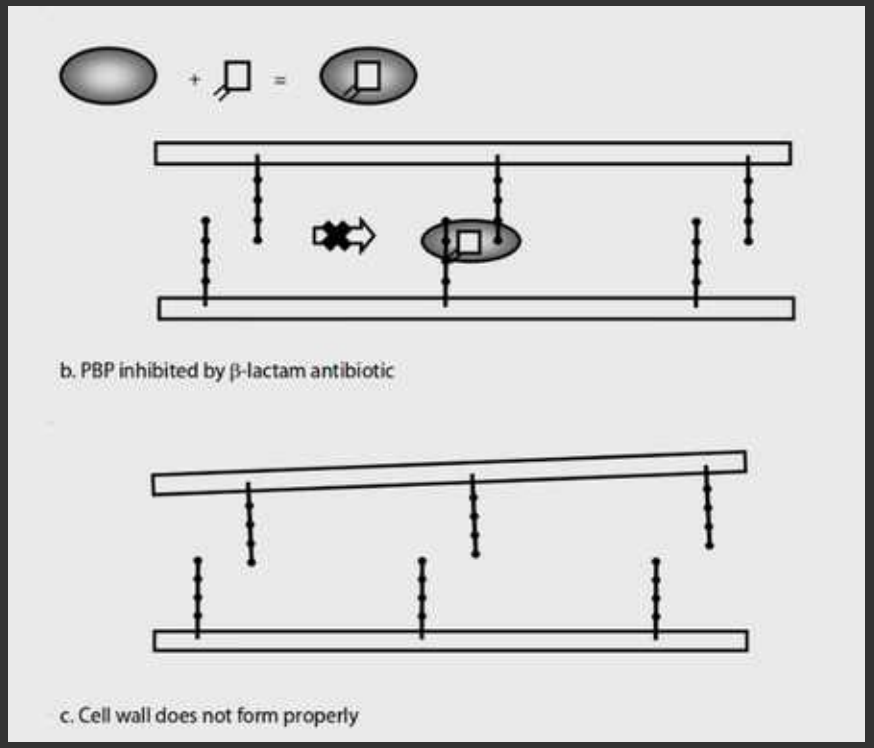


Figure 5. Cross-link formation in bacterial cell walls by PBP (penicillin-binding protein).





Antibiotic resistance

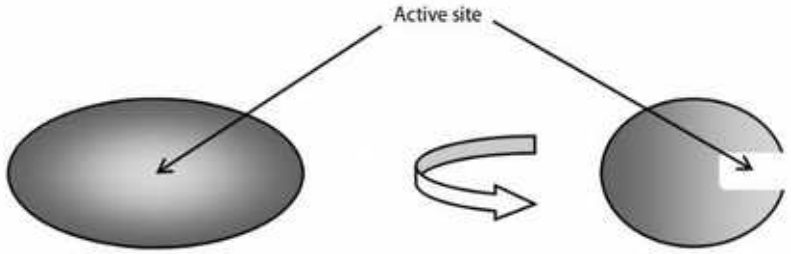


Figure 4. PBP (penicillin-binding protein) active site is a groove allowing formation of cross-links in the bacterial cell wall.

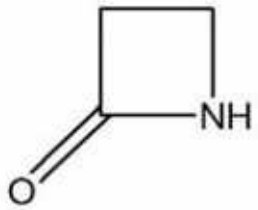


Figure 3. The β-lactam ring common to the penicillin family of antibiotics.

This no longer fits easily in the PBP active site!

Strain	Changes in amino acids of conserved PBP sites making up active penicillin-binding site of PBP:								
	1a			2x			2b		
	370-373[a]	428-430	557-559	337-340	394-397	546-549	385-388	442-445	614-616
R6	STMK[b]	SRN	KTG	STMK	HSSN	LKSG	SVVK	SSNT	KTG
1	-[c]	-	-	-	-	-	-	-	-
2	-	-	-	-	-	VKSG	-	-	-
3	-	-	-	-	-	-	-	SSNA	-
4	-	-	-	-	-	-	-	-	-
5	-	-	-	-	YSSN	-	-	SSNA	-
6	-	-	-	SPMK	-	-	-	SSNA	-
7	-	-	-	-	YSSN	-	-	SSNA	-
8	-	-	-	SPMK	-	-	-	SSNA	-
9	-	-	-	SAMK	-	-	-	SSNA	-
10	-	-	-	SAMK	-	-	-	SSNA	-
11	-	-	-	SAMK	-	VKSG	-	SSNA	-
12	-	-	-	SAMK	-	VKSG	-	SSNA	-
13	SAMK[d]	-	-	SAMK	-	VKSG	-	SSNA	-
14	SAMK	-	-	SAMK	-	VKSG	-	SSNA	-
15	SAMK	-	-	SAMK	-	VKSG	-	SSNA	-
16	SAMK	-	-	SAMK	-	VKSG	-	SSNA	-
17	SSMK	-	-	SAFK	-	VKSG	-	SSNA	-
18	SSMK	-	-	SAFK	-	VKSG	-	SSNA	-

Antimicrob Agents Chemother. 2002 May; 46(5): 1273–1280.
doi: 10.1128/AAC.46.5.1273-1280.2002

MRSA: Methicillin-resistant *Staphylococcus aureus*

Photo Credit: Gregory Moran, M.D.

MRSA history

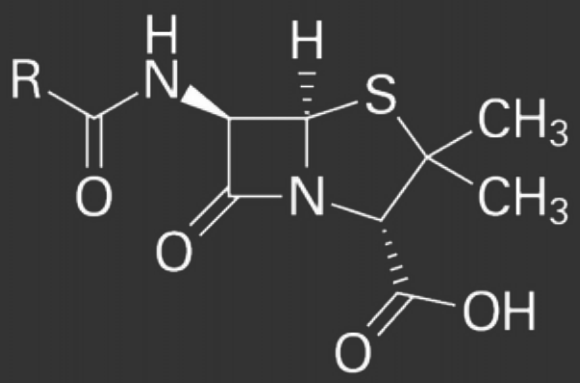
S. aureus was described in the 1880's

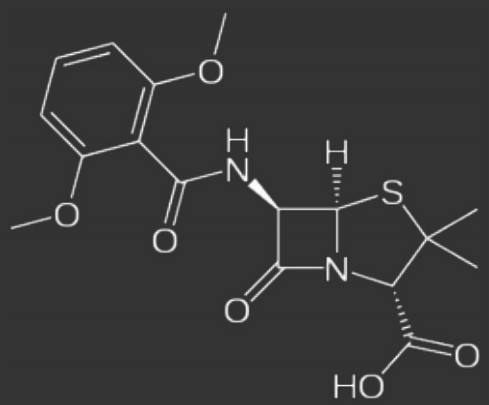
MRSA Discovered in 1961

Term used to describe <u>all</u> *S. aureus* strains resistant to penicillin-like antibiotics

Methicillin was an artificial penicillin compound invented since *S. aureus* was becoming resistant to natural penicillin

"Today, penicillin-susceptible *S. aureus* is a microbiological dinosaur, and a source of amusement when identified."
- N. Lindsey, 1991

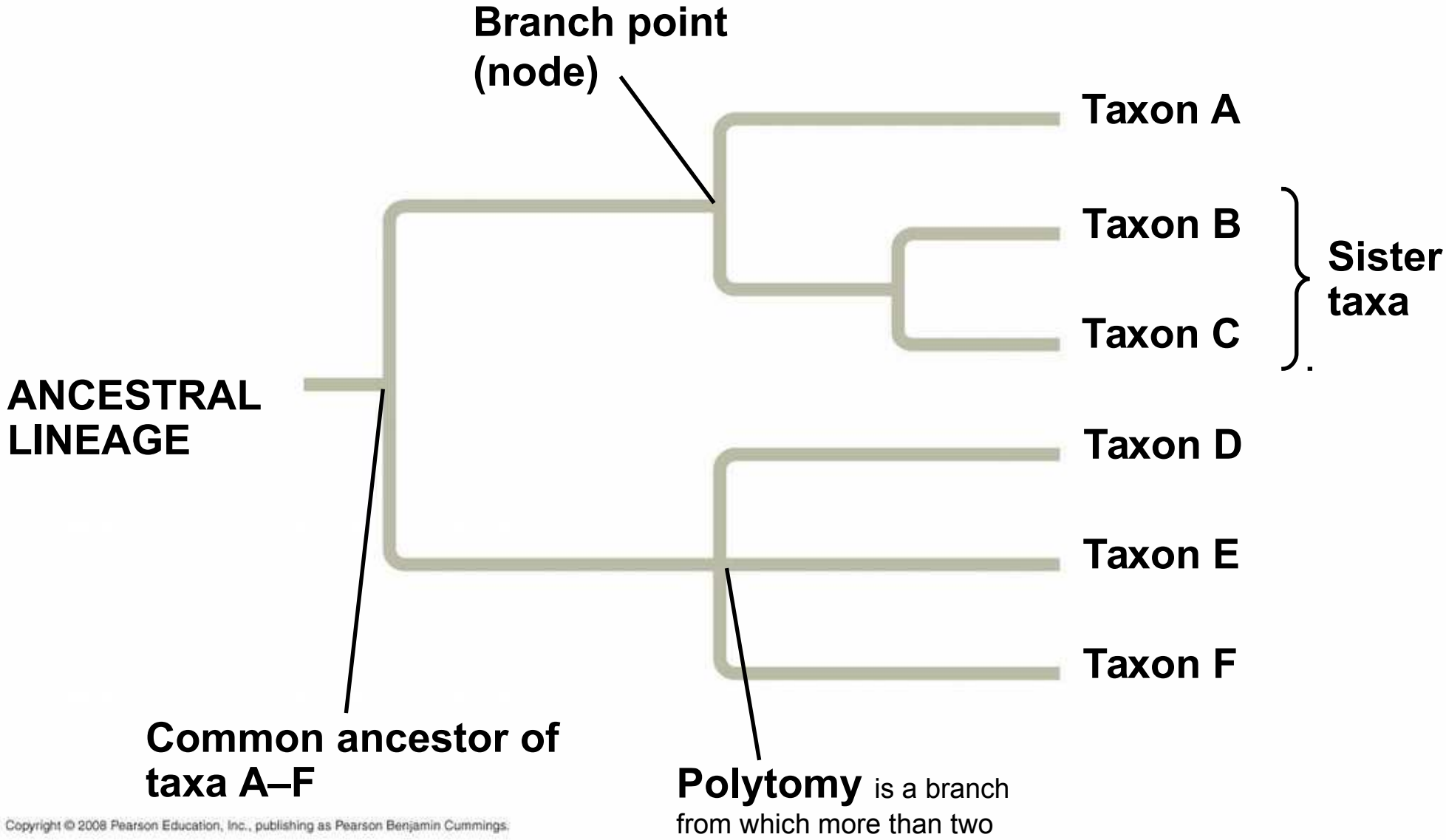




A case study:

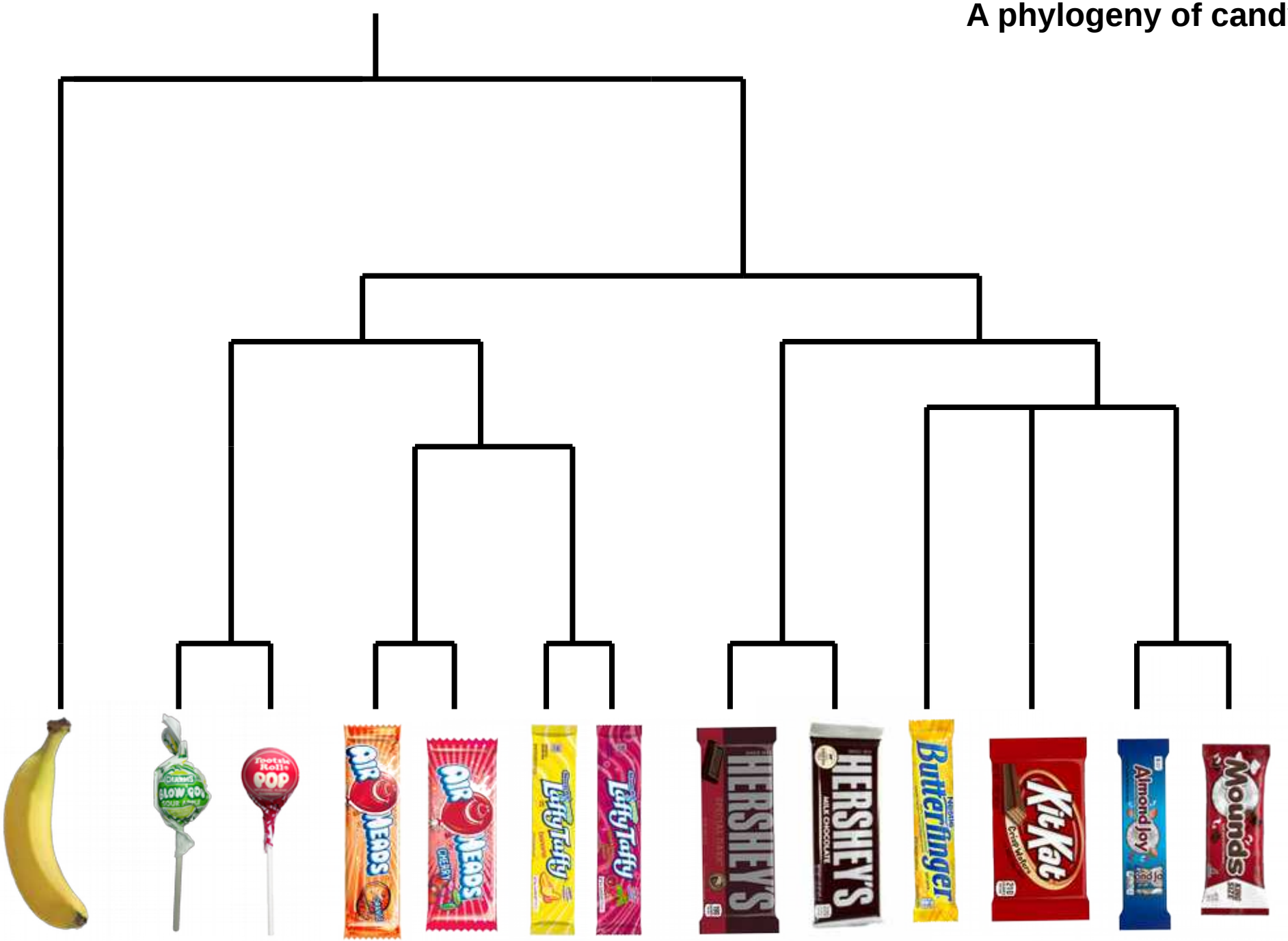
- Say there is an outbreak of MRSA in a hospital in Thailand
- It's a particularly nasty strain, resistant even to last-resort antibiotics
- We need to know where it came from and what is different about it if we have any hope of finding a treatment
- What can we do???

We can look at its phylogeny to see which other strains it's related to.

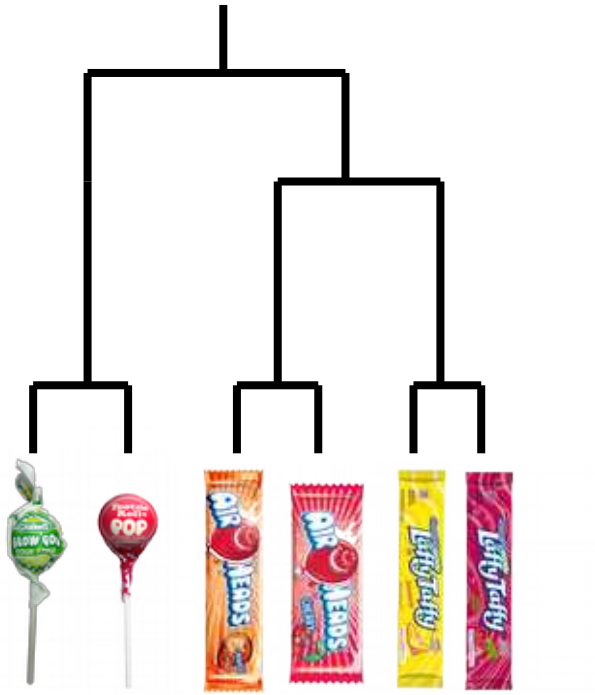


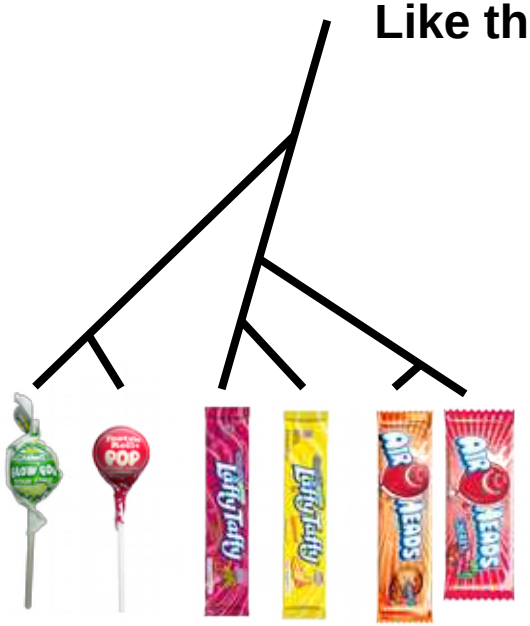
A phylogeny of candy

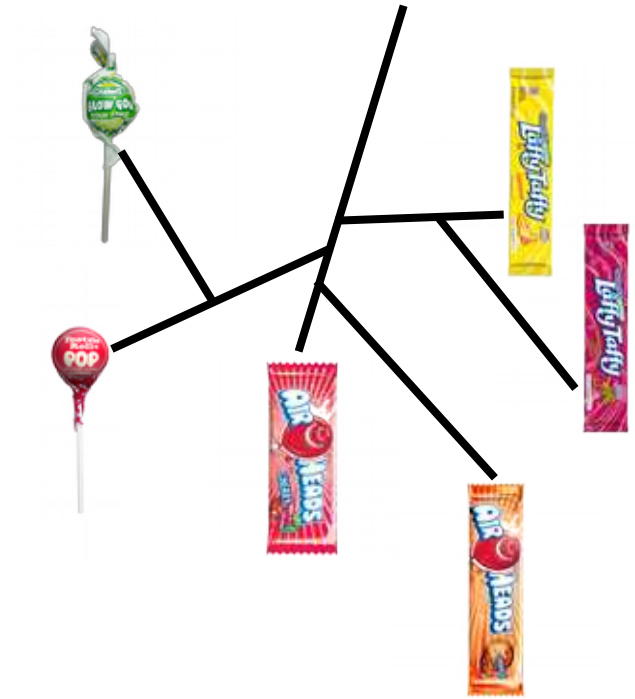
A phylogeny of candy

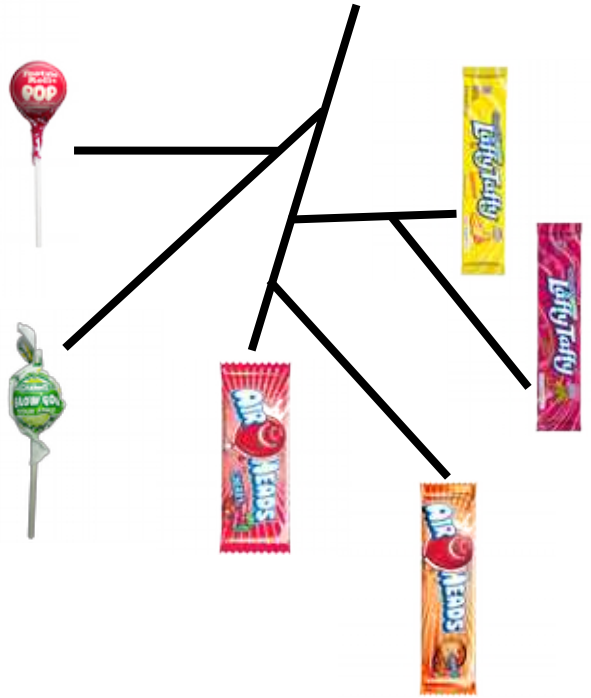


One of these things is not Like the others . . .



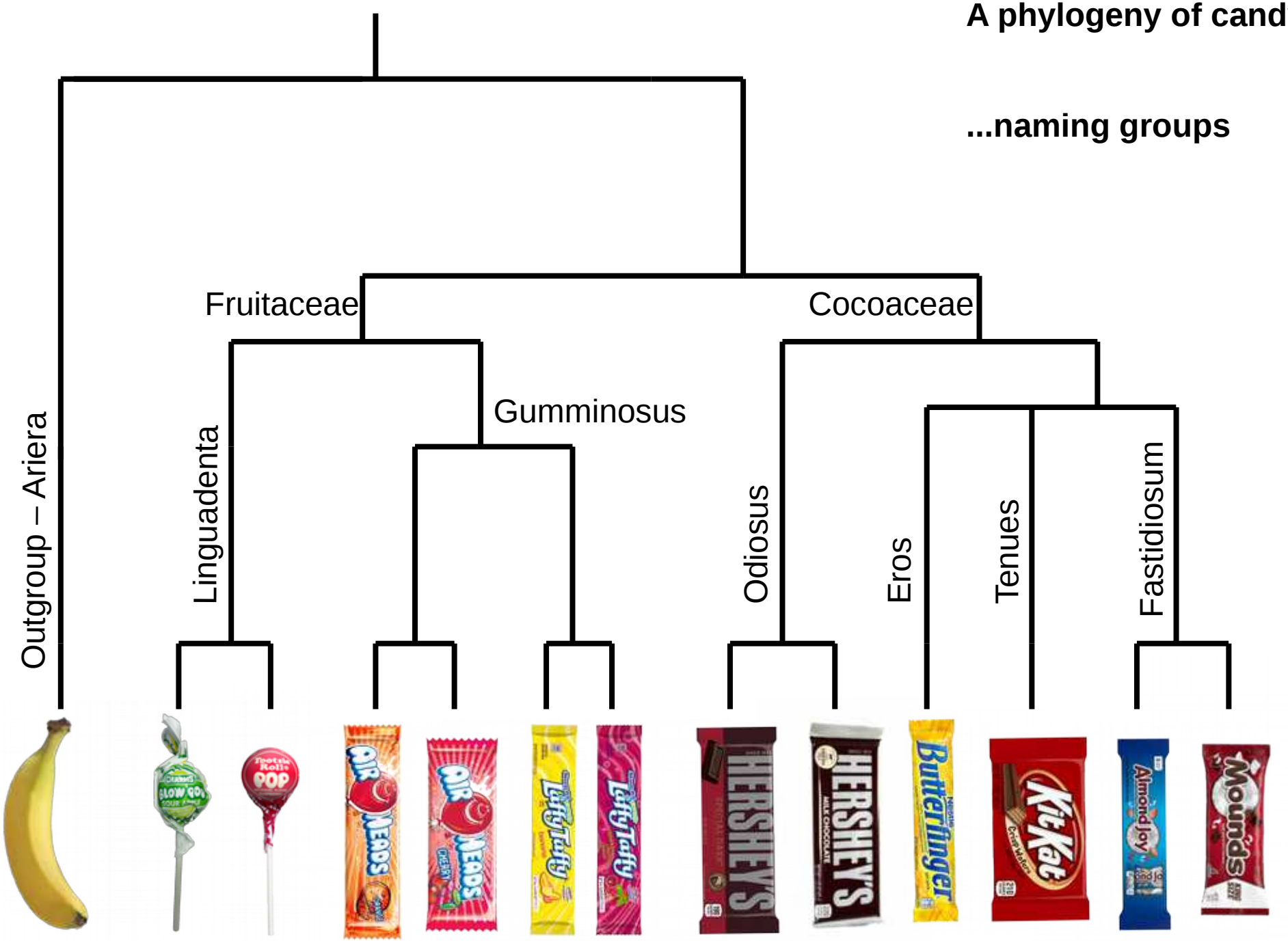






A phylogeny of candy

...naming groups



A phylogeny of candy

...MONOPHYLETIC

Outgroup – Ariera

Fruitaceae

Linguadenta

Gumminosus

Cocoaceae

Odiosus

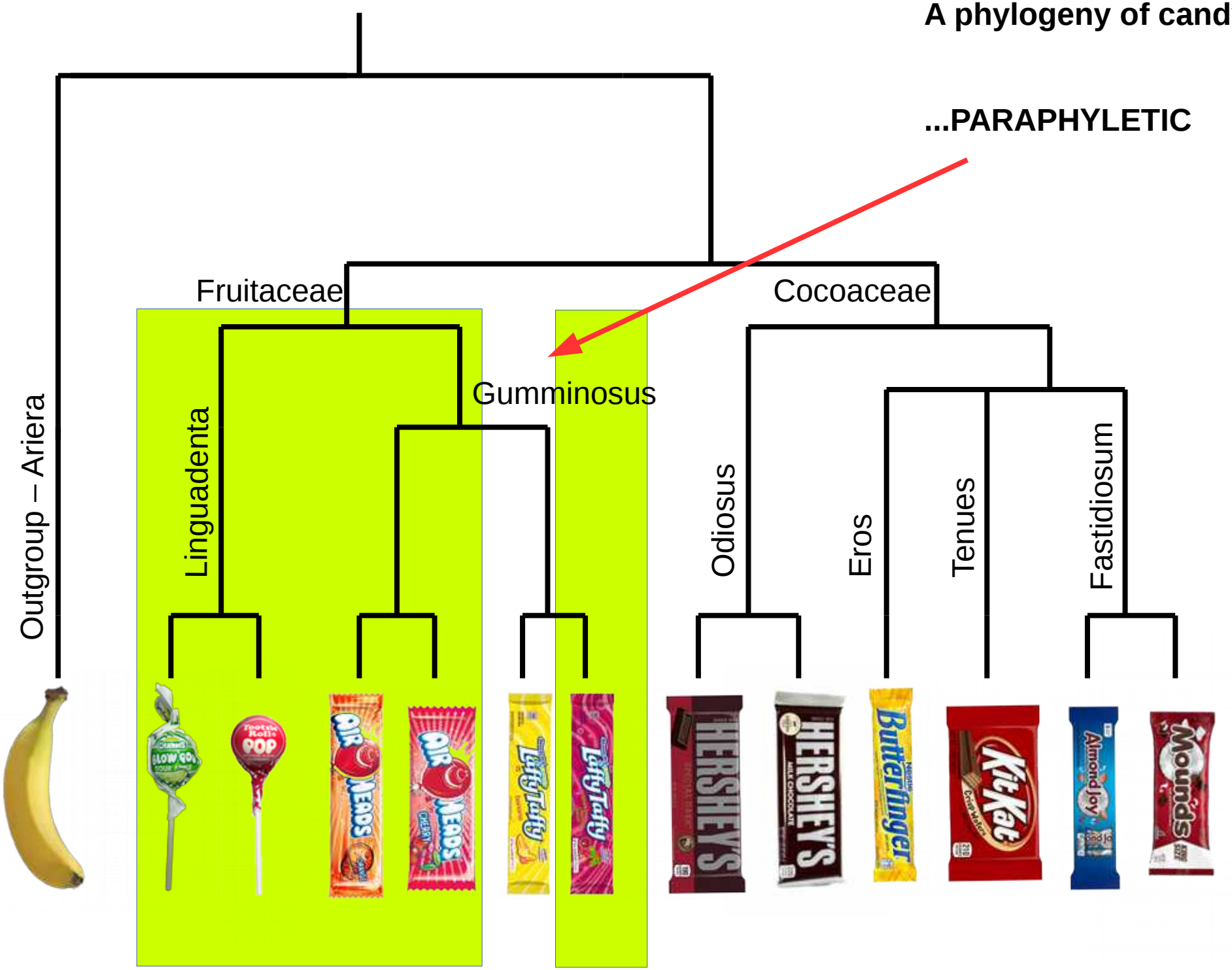
Eros

Tenues

Fastidiosum

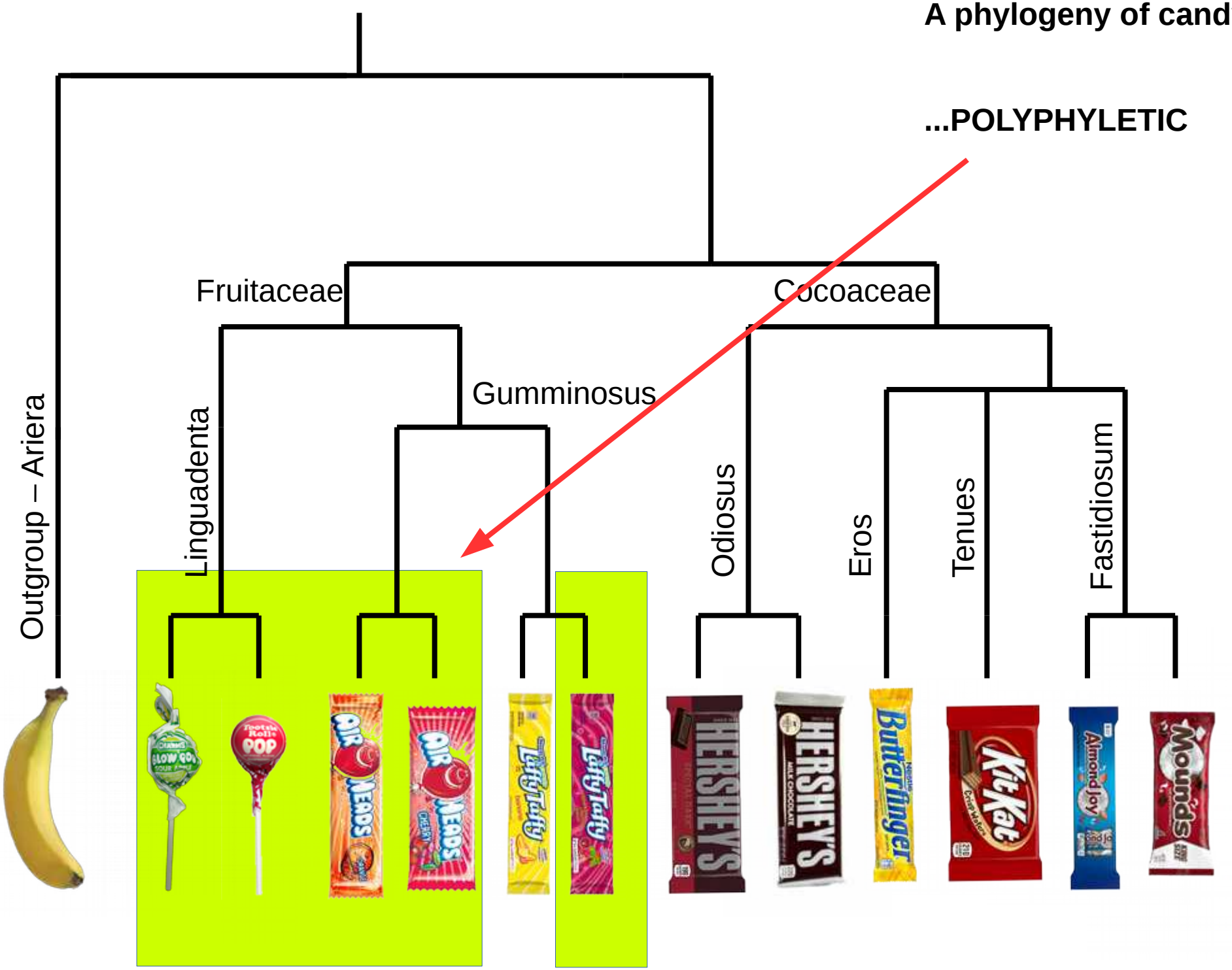
A phylogeny of candy

...PARAPHYLETIC



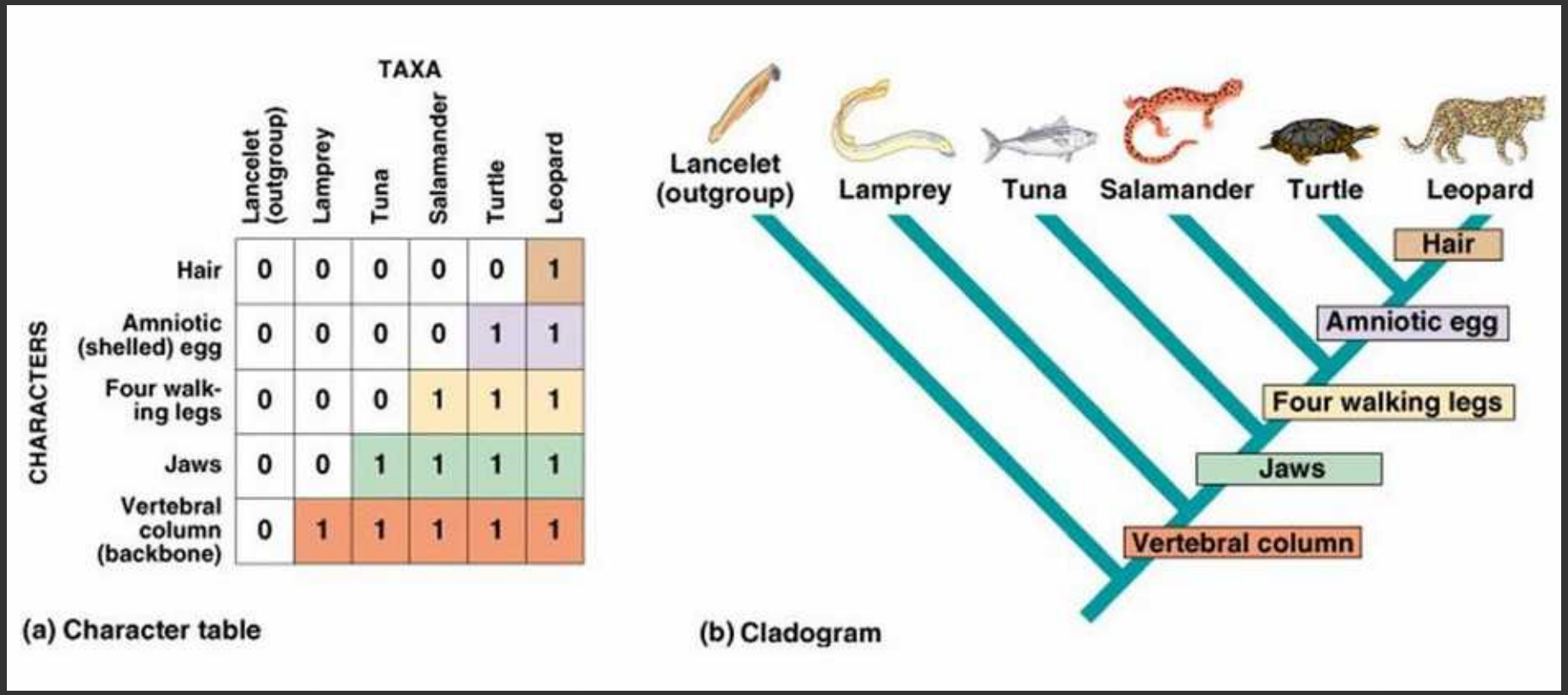
A phylogeny of candy

...POLYPHYLETIC



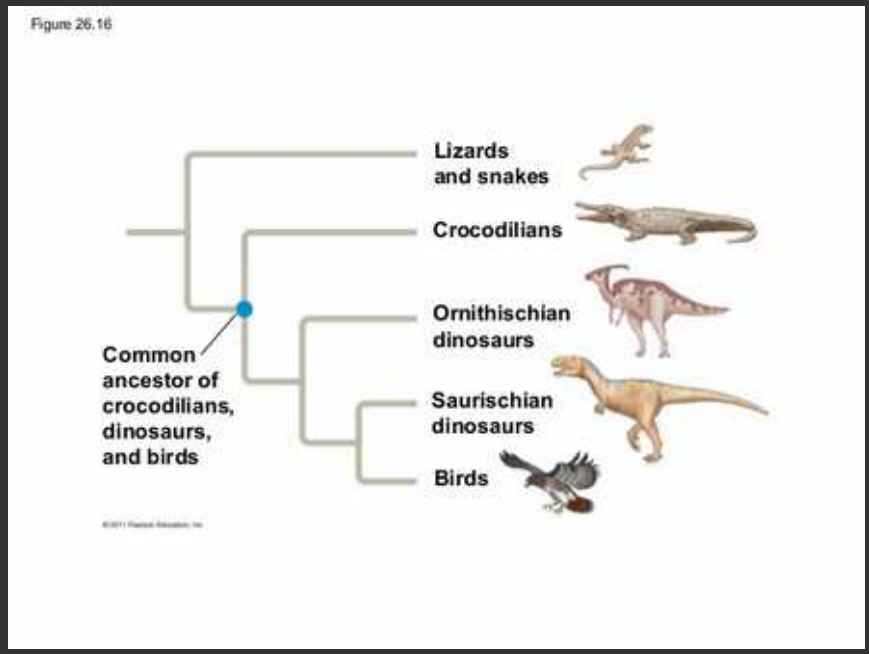
How to determine phylogeny:

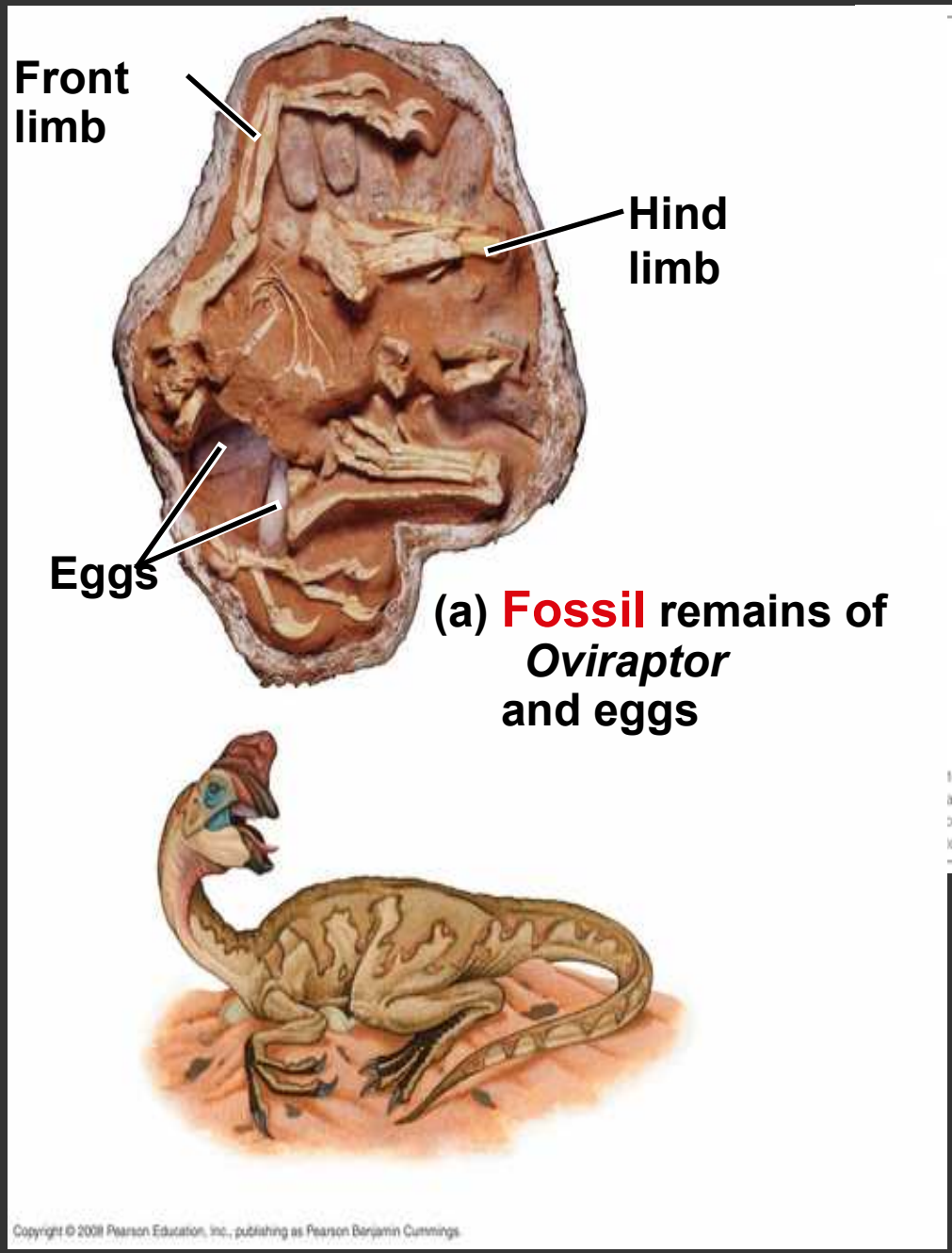
- Morphological traits
- Molecular traits

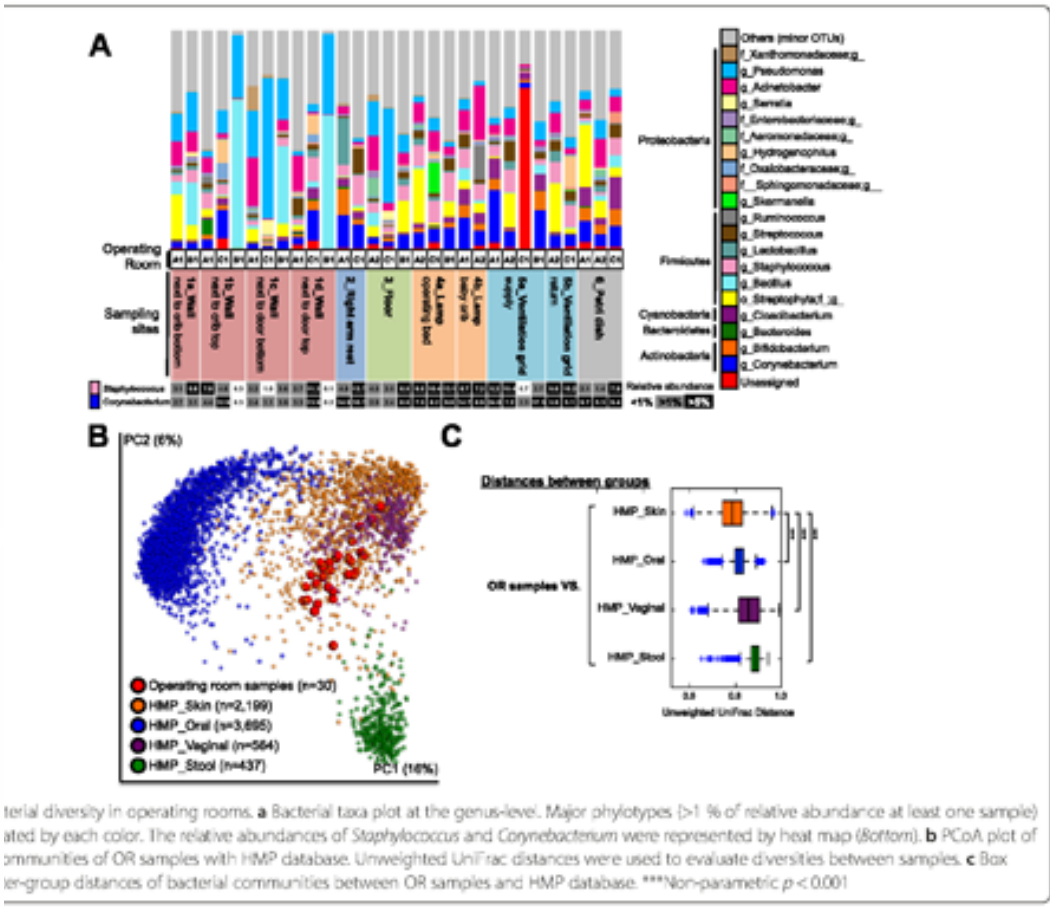


What else are phylogenies good for?

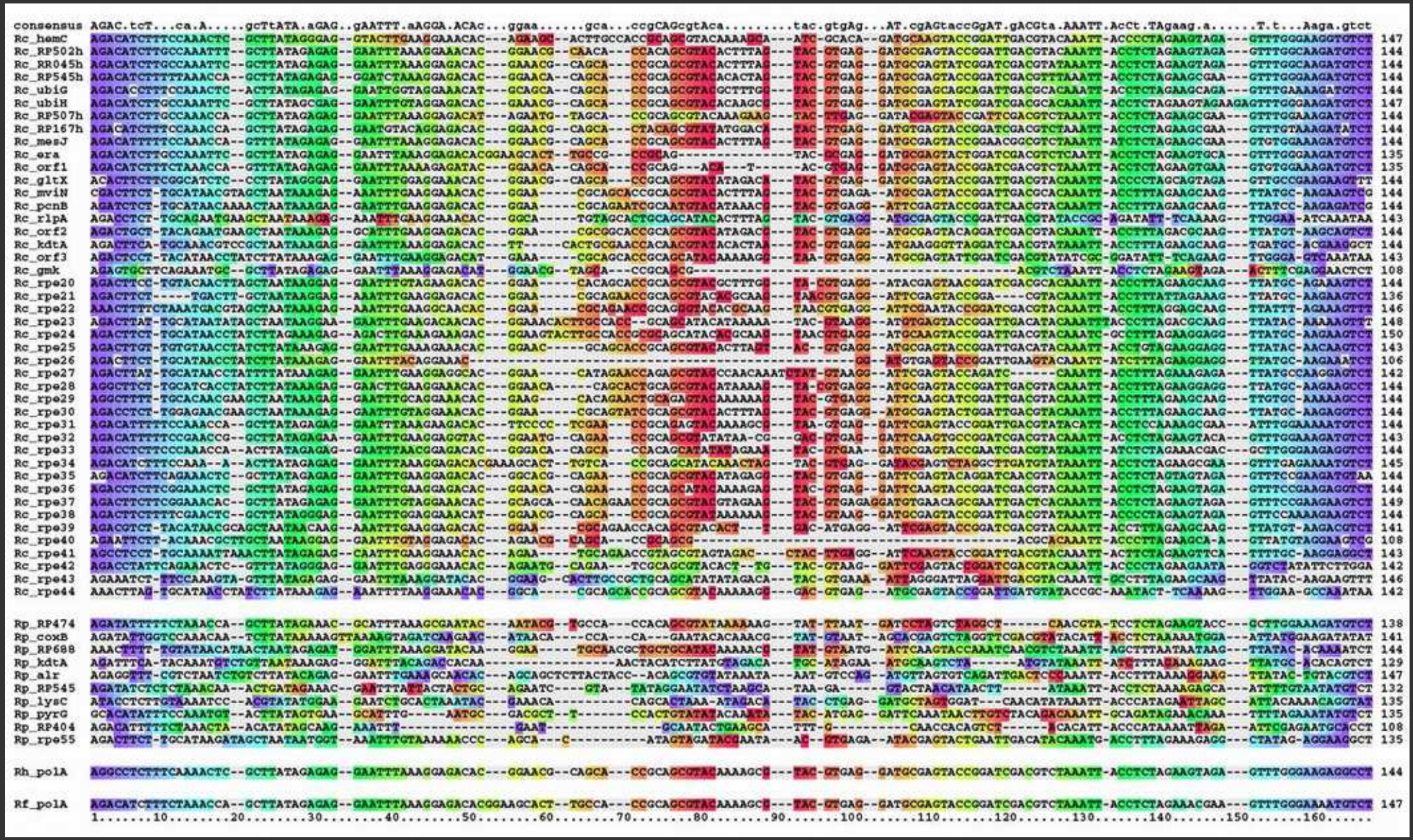
- They are hypotheses and the best hypothesis is the one that best fits all the available data
- They generate predictions! All valid hypotheses do this.
- Predictions can be tested

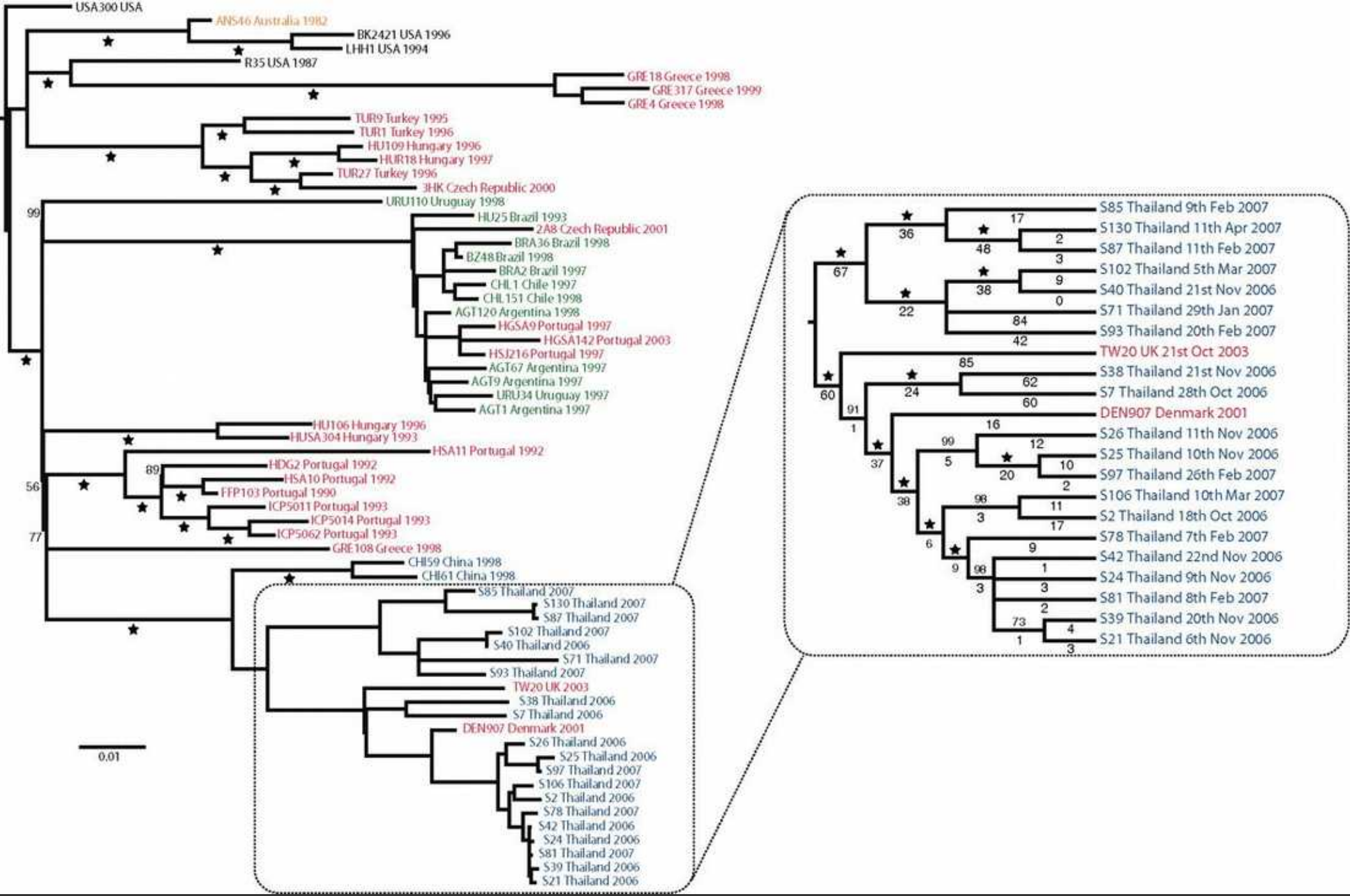





1 % of relative abundance at least one sample) ated by each color. The relative abundances of *Staphylococcus* and *Corynebacterium* were represented by heat map (*Bottom*). **b** PCoA plot of ommunities of OR samples with HMP database. Unweighted UniFrac distances were used to evaluate diversities between samples. **c** Box er-group distances of bacterial communities between OR samples and HMP database. ***Non-parametric $p < 0.001$

DNA Alignment

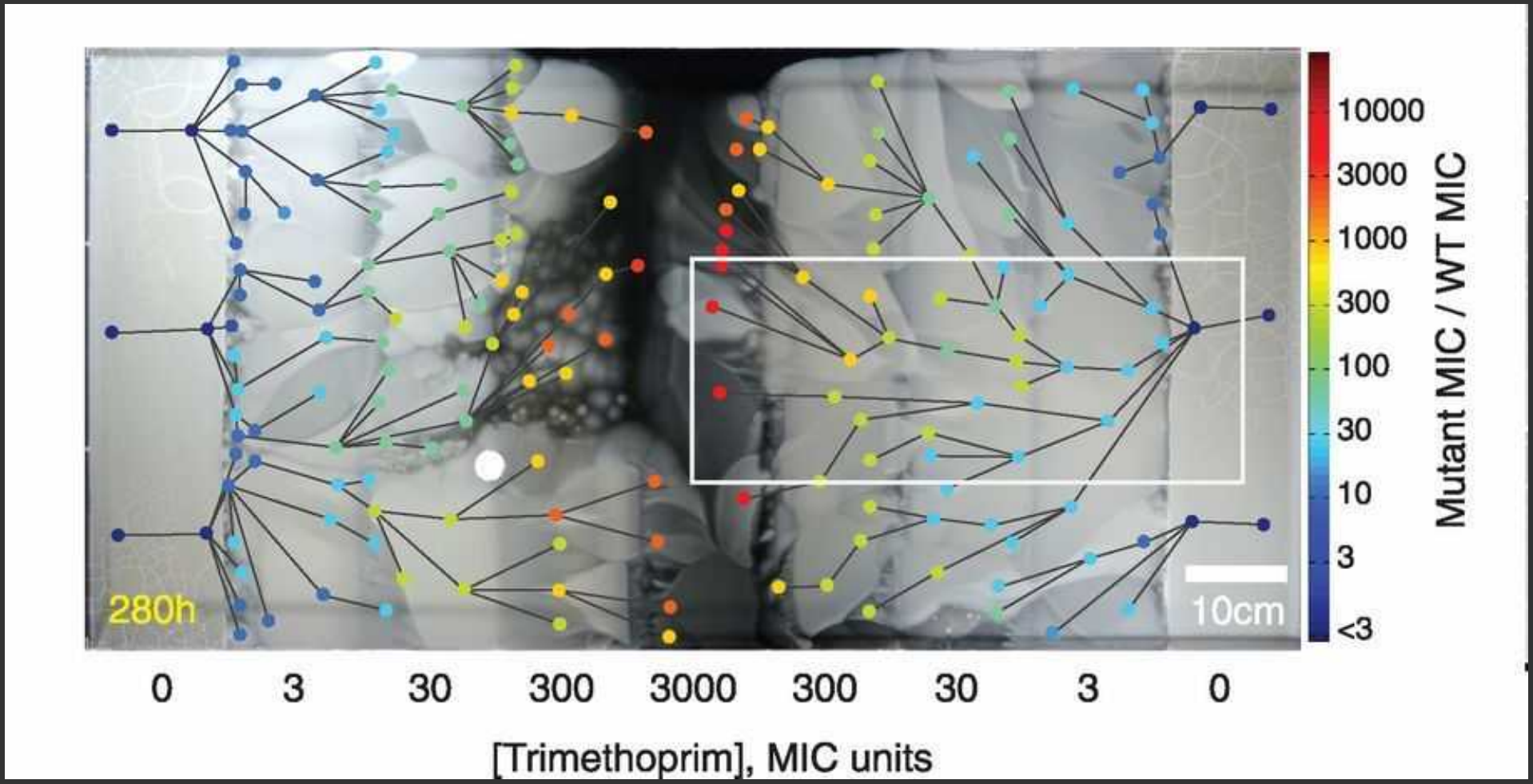




Science 22 Jan 2010:
Vol. 327, Issue 5964, pp. 469-474
DOI: 10.1126/science.1182395

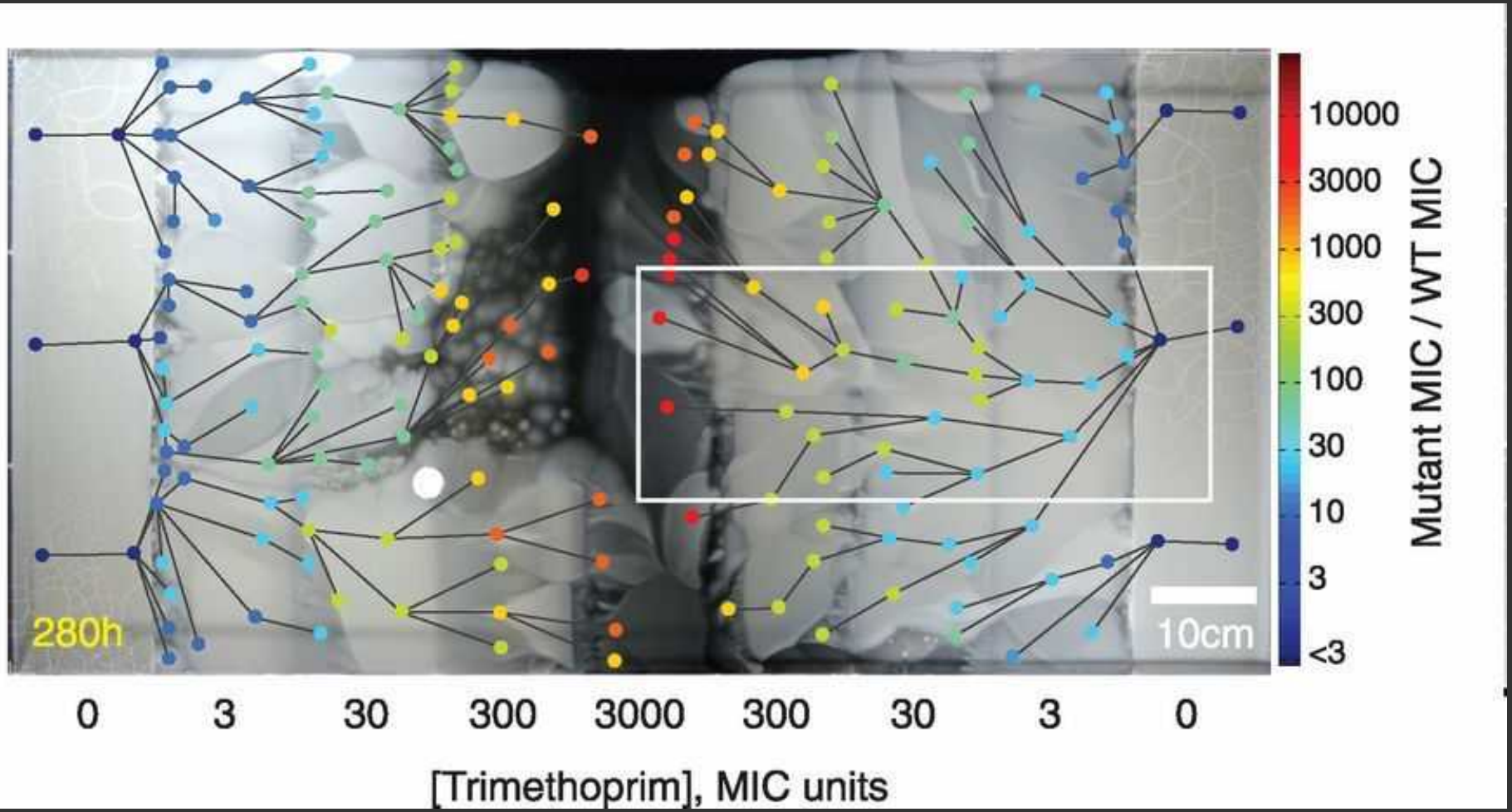
MRSA Phylogeny, colored by location

Look familiar???



Organisms' evolutionary histories are documented in their genomes

What if we re-wound the clock?



The Burgess Shale

SJ Gould used this formation to ponder whether life would have evolved in the same progression again if we could magically rewind the clock

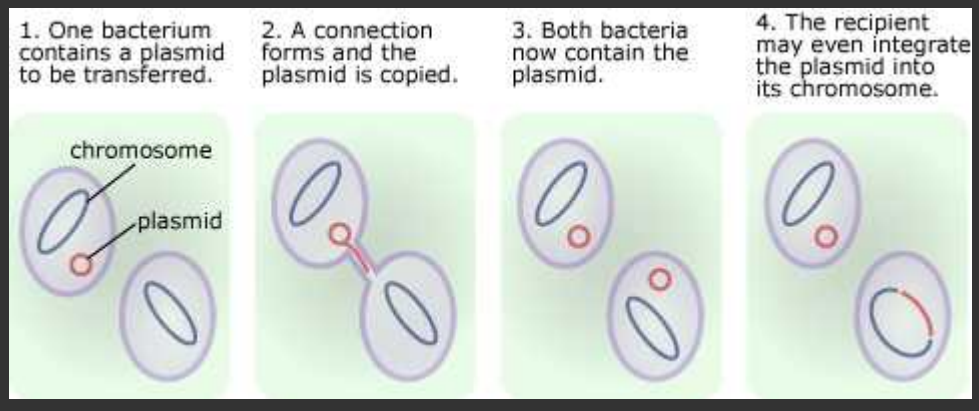
Fossils all around the world follow the same pattern: More "primitive" organisms in older rocks, more complex organisms in newer rocks.

Okay, but what to do about antibiotic resistant pathogens?

Evolution in bacteria is very rapid: fast generation times and plasmids (HGT)

Antibiotics are expensive to develop

Newly developed antibiotics are shelved for emergencies



Where is MRSA found?

?

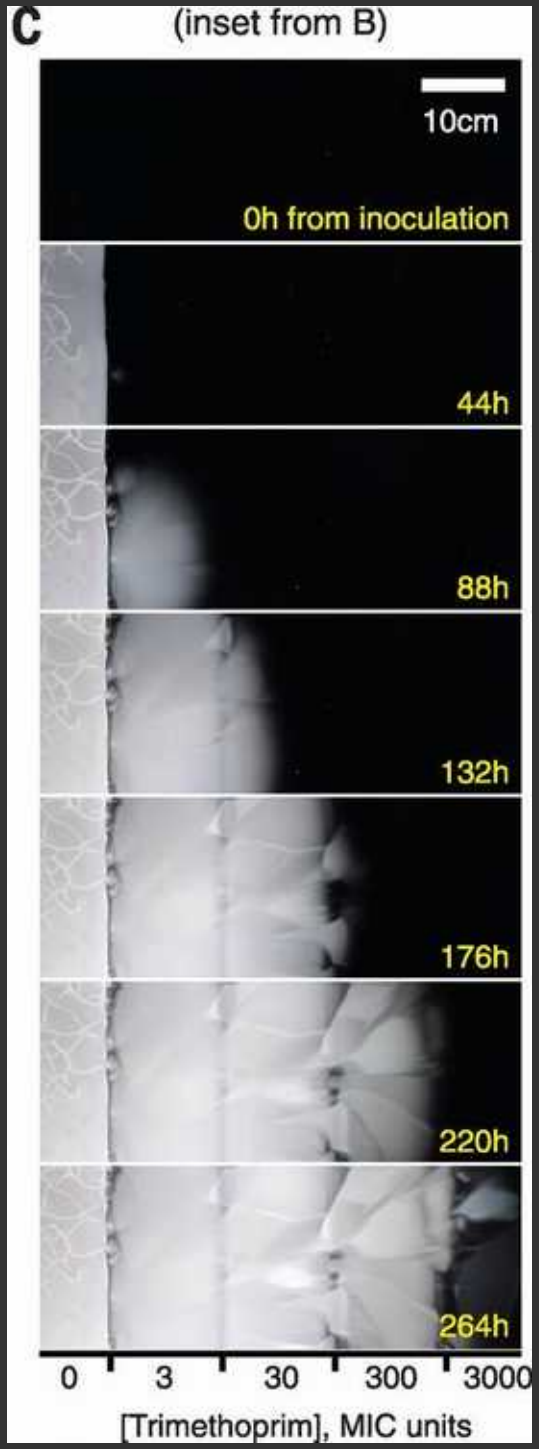
If the following conditions are met, evolution MUST occur:

Variation (from mutations/recombinations)

Heritability of those variations

Some selective force acting on that variability

Remember: Mutations are not generated because they are "needed!"



Where is variation coming from?

Is it heritable?

What are the selective forces at work?

Evolution from the gene's-eye perspective

Analogous genes: similar because of convergent evolution

Homologous genes: similar because of shared descent

- Orthologs: Speciation
- Paralogs: Gene duplication (in same species)