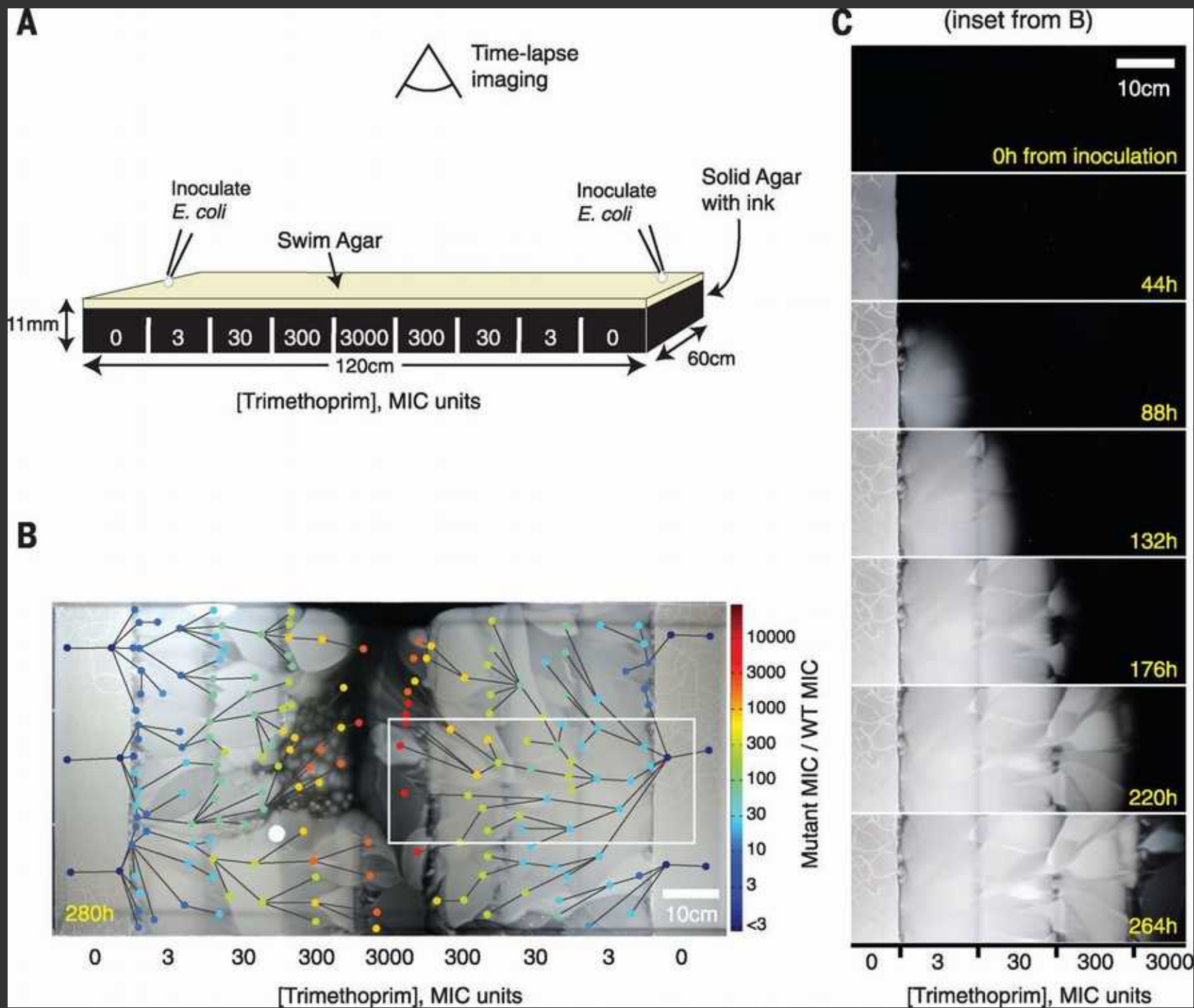


- Variability, heritability, selection coefficient
- Evolution is not goal oriented
- Phylogenies, binomial nomenclature, hierarchies, phylogenetic trees and classification, sister groups
- How phylogenies are constructed: morphology and molecular data, homologies vs. analogies, DNA alignments, outgroups,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

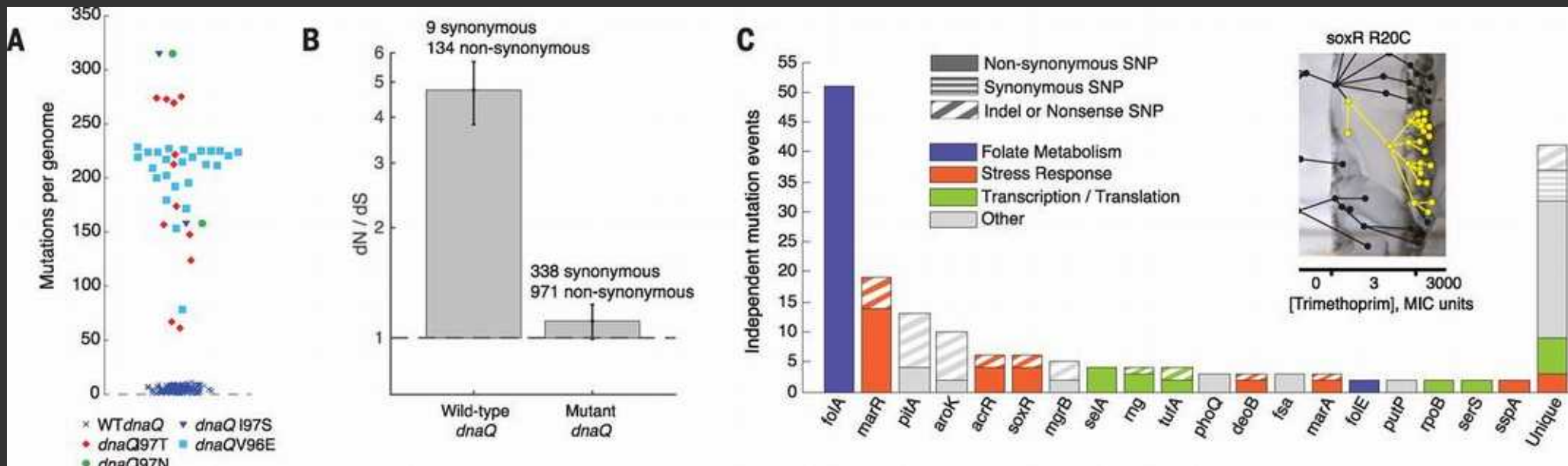
The evolution of bacteria
on a "mega-plate" Petri dish



HARVARD
MEDICAL SCHOOL



Mutation Events captured by genome sequencing



Genetic code is almost universal

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

Synonymous mutation = results in same amino acid

DNA mutation: ATT -> ATA

Is this synonymous???

("silent" mutations)

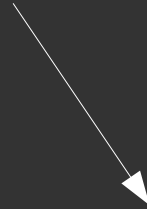
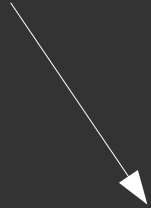
DNA

Transcription

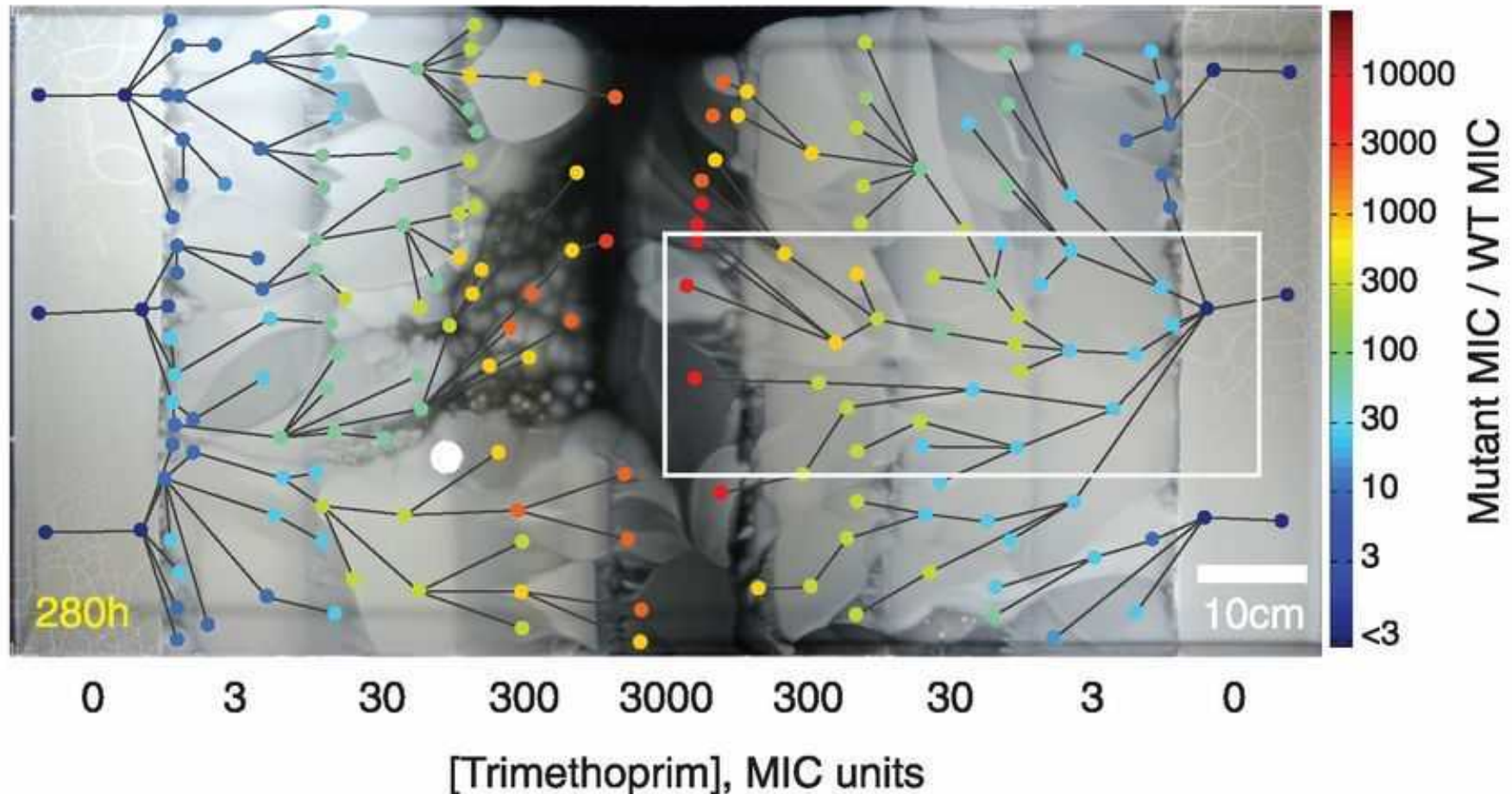
RNA

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

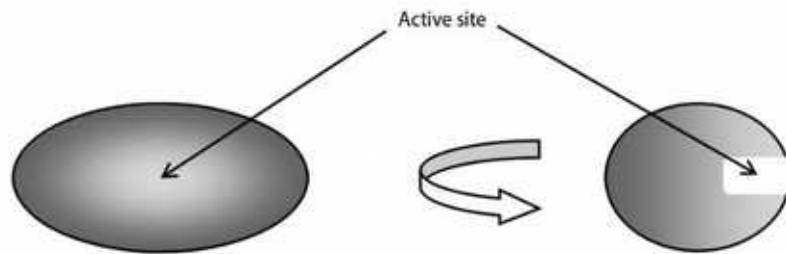


Figure 4. PBP (penicillin-binding protein) active site is a groove allowing formation of cross-links in the bacterial cell wall.

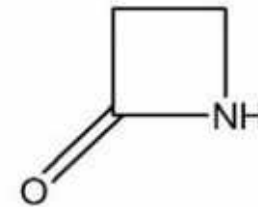


Figure 3. The β -lactam ring common to the penicillin family of antibiotics.

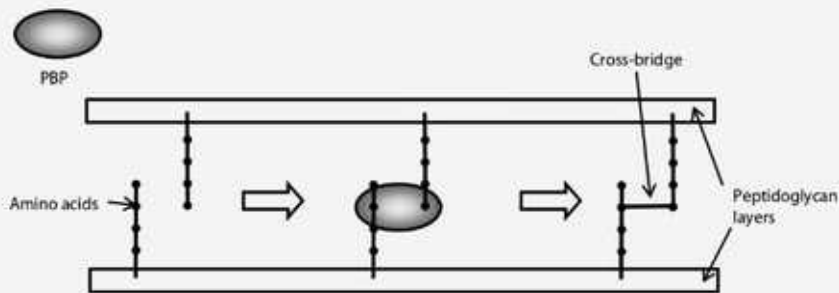
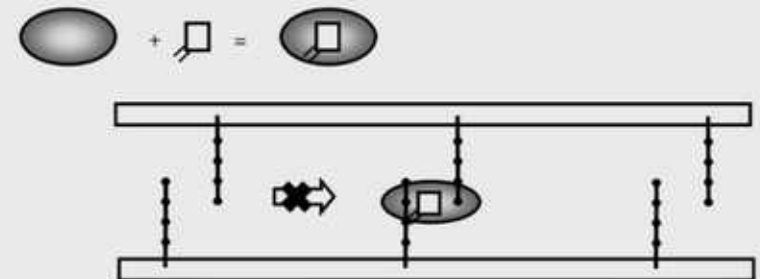
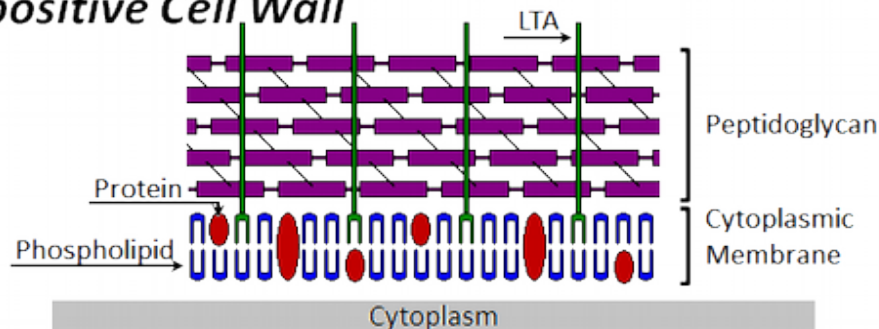
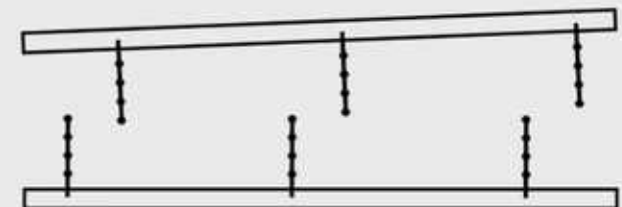


Figure 5. Cross-link formation in bacterial cell walls by PBP (penicillin-binding protein).

Gram-positive Cell Wall



b. PBP inhibited by β -lactam antibiotic



c. Cell wall does not form properly

Antibiotic resistance

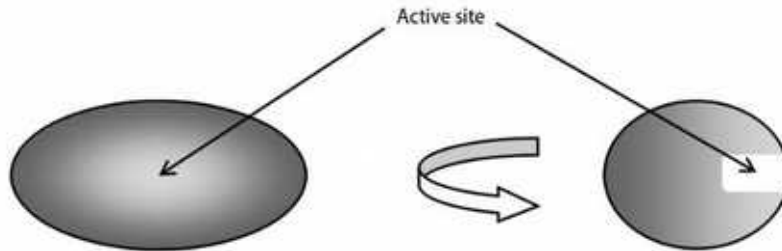


Figure 4. PBP (penicillin-binding protein) active site is a groove allowing formation of cross-links in the bacterial cell wall.

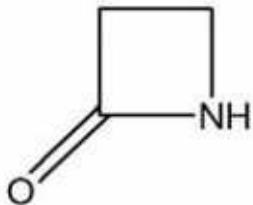


Figure 3. The β -lactam ring common to the penicillin family of antibiotics.

This no longer fits easily in the PBP active site!

Changes in amino acids of conserved PBP sites making up active penicillin-binding site of PBP:

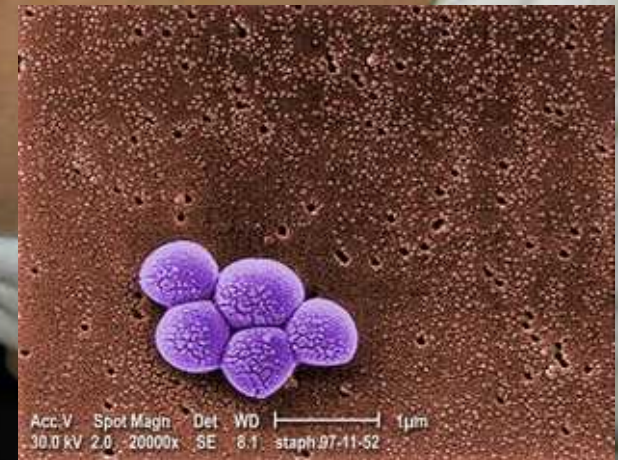
| Strain | 1a | | | 2x | | | 2b | | |
|--------|----------------------|---------|---------|---------|---------|---------|---------|---------|---------|
| | 370-373 ^a | 428-430 | 557-559 | 337-340 | 394-397 | 546-549 | 385-388 | 442-445 | 614-616 |
| R6 | STMK ^b | SRN | KTG | STMK | HSSN | LKSG | SVVK | SSNT | KTG |
| 1 | - | - | - | - | - | - | - | - | - |
| 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

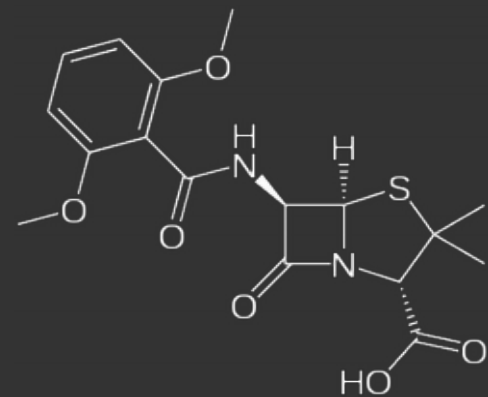
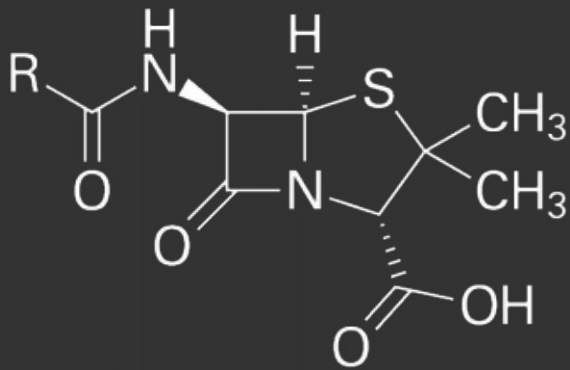
MRSA Discovered in 1961

Term used to describe all *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."

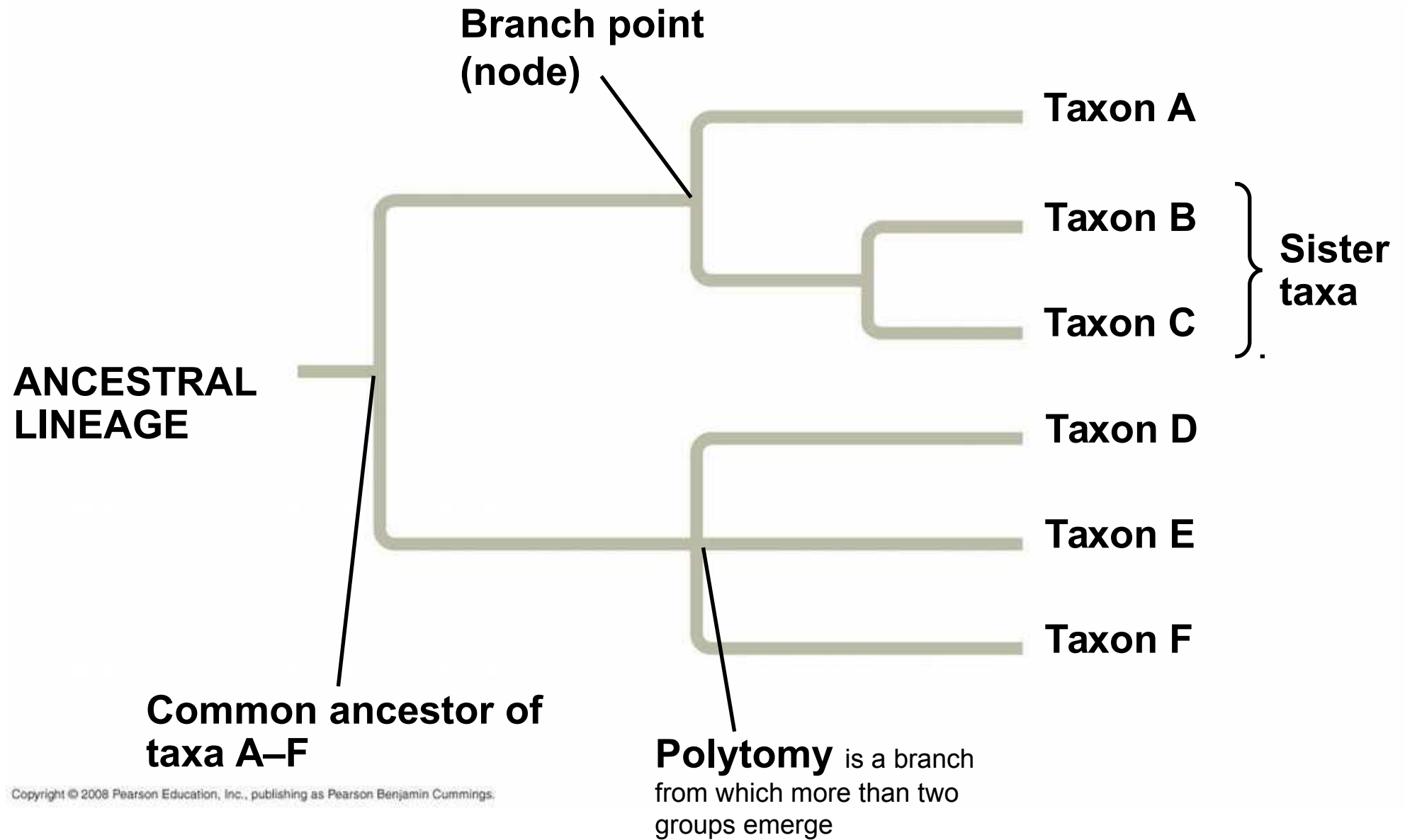
- N. Lindsey, 1991



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???

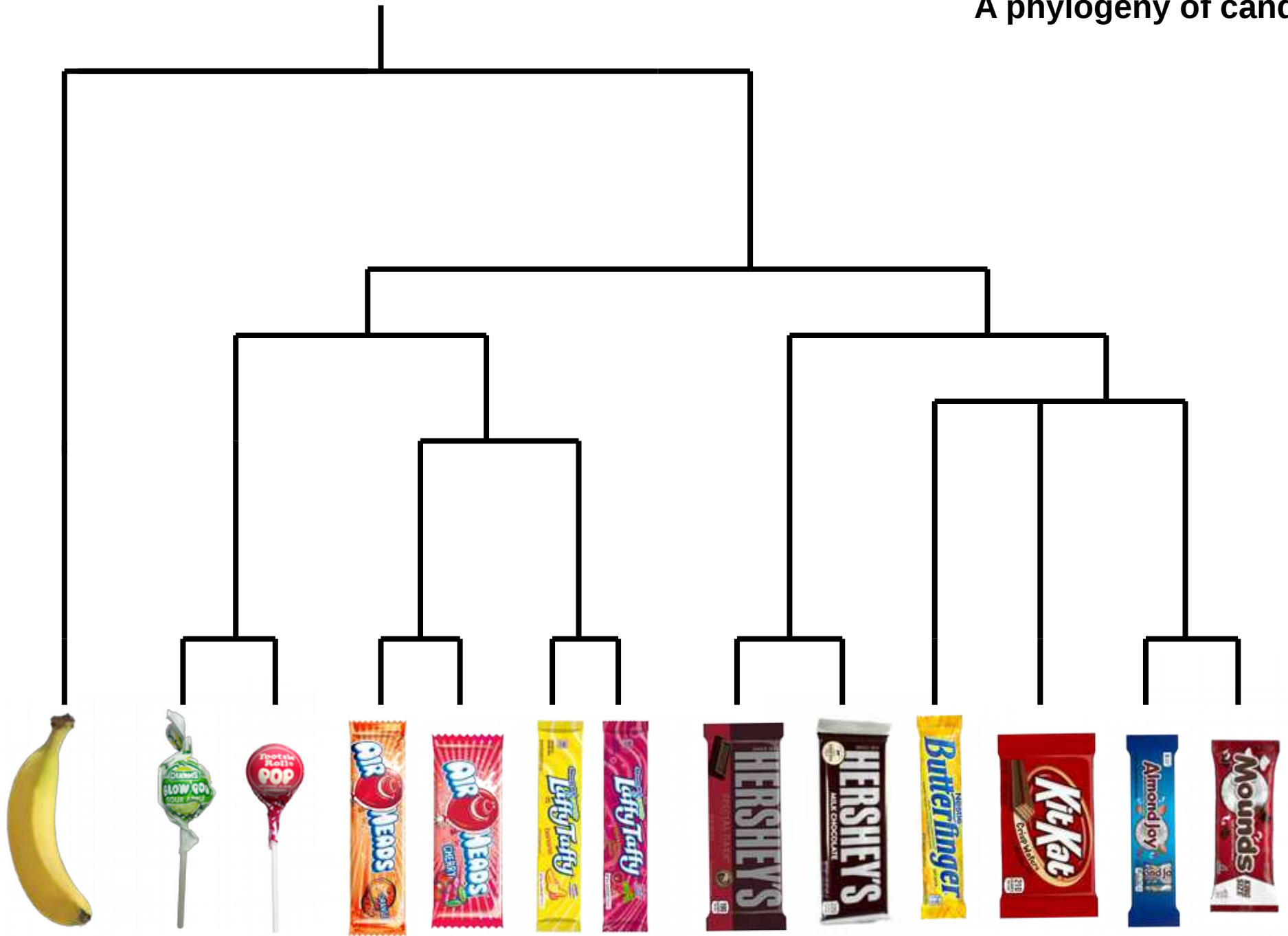
We can look at its phylogeny to see which other strains it's related to.



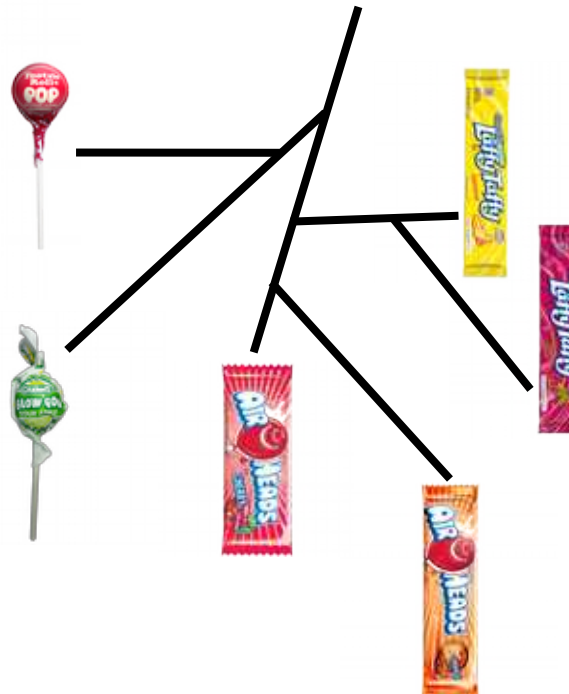
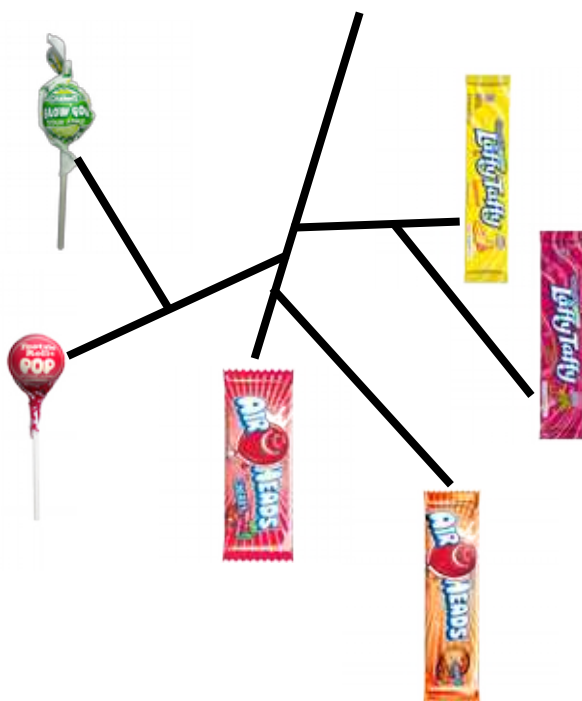
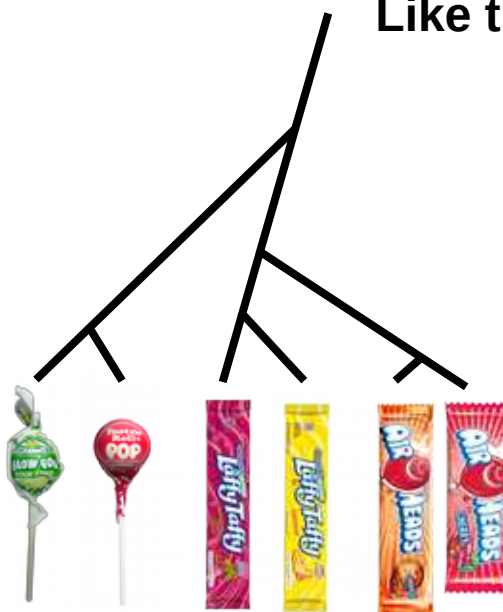
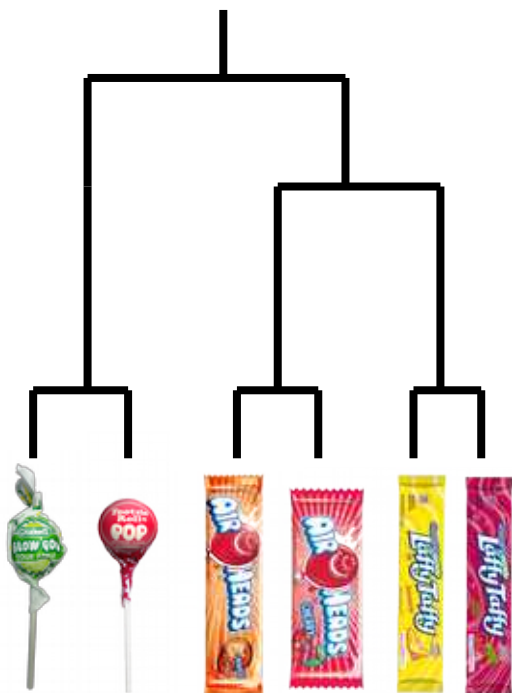
A phylogeny of candy



A phylogeny of candy

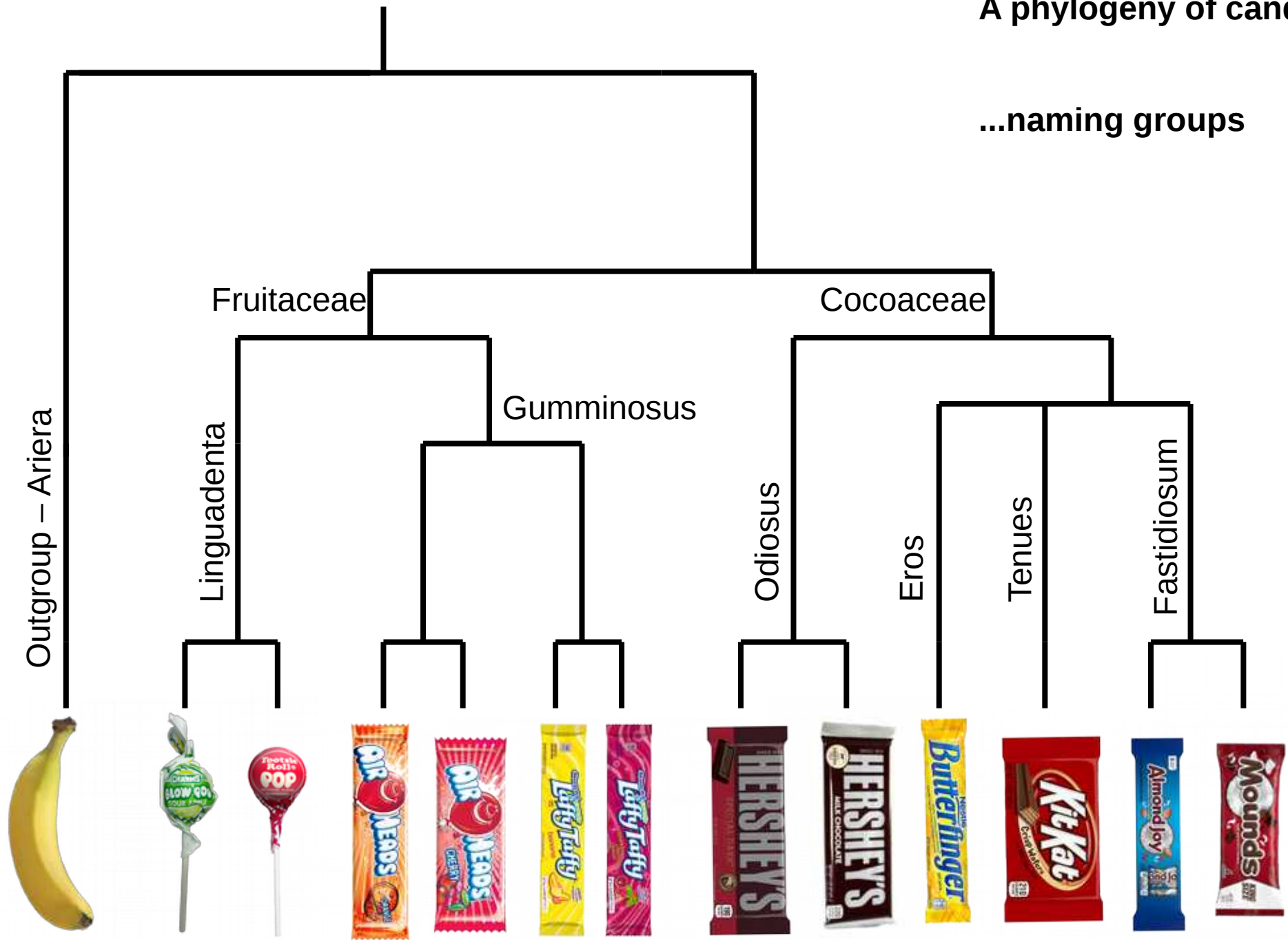


One of these things is not
Like the others . . .

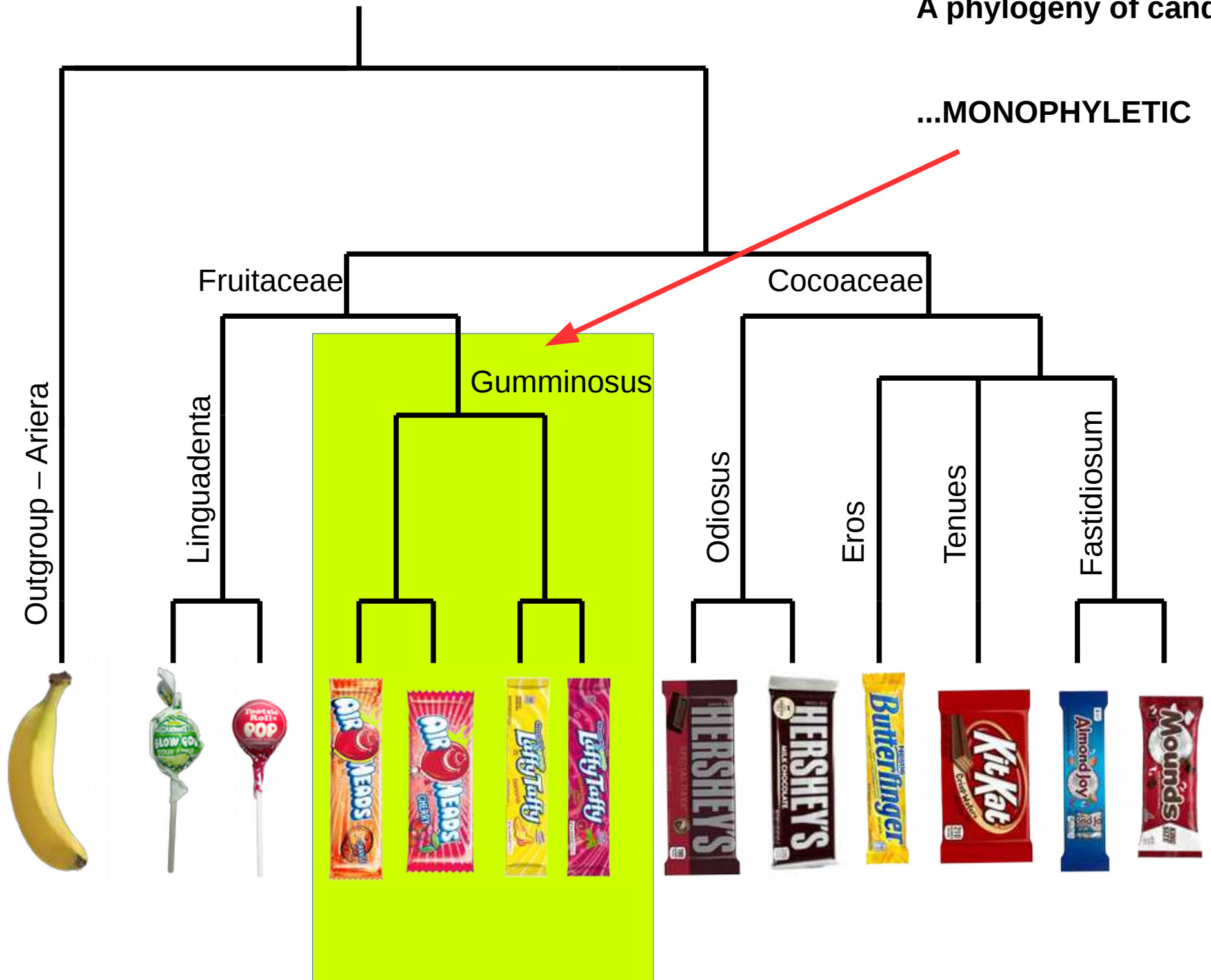


A phylogeny of candy

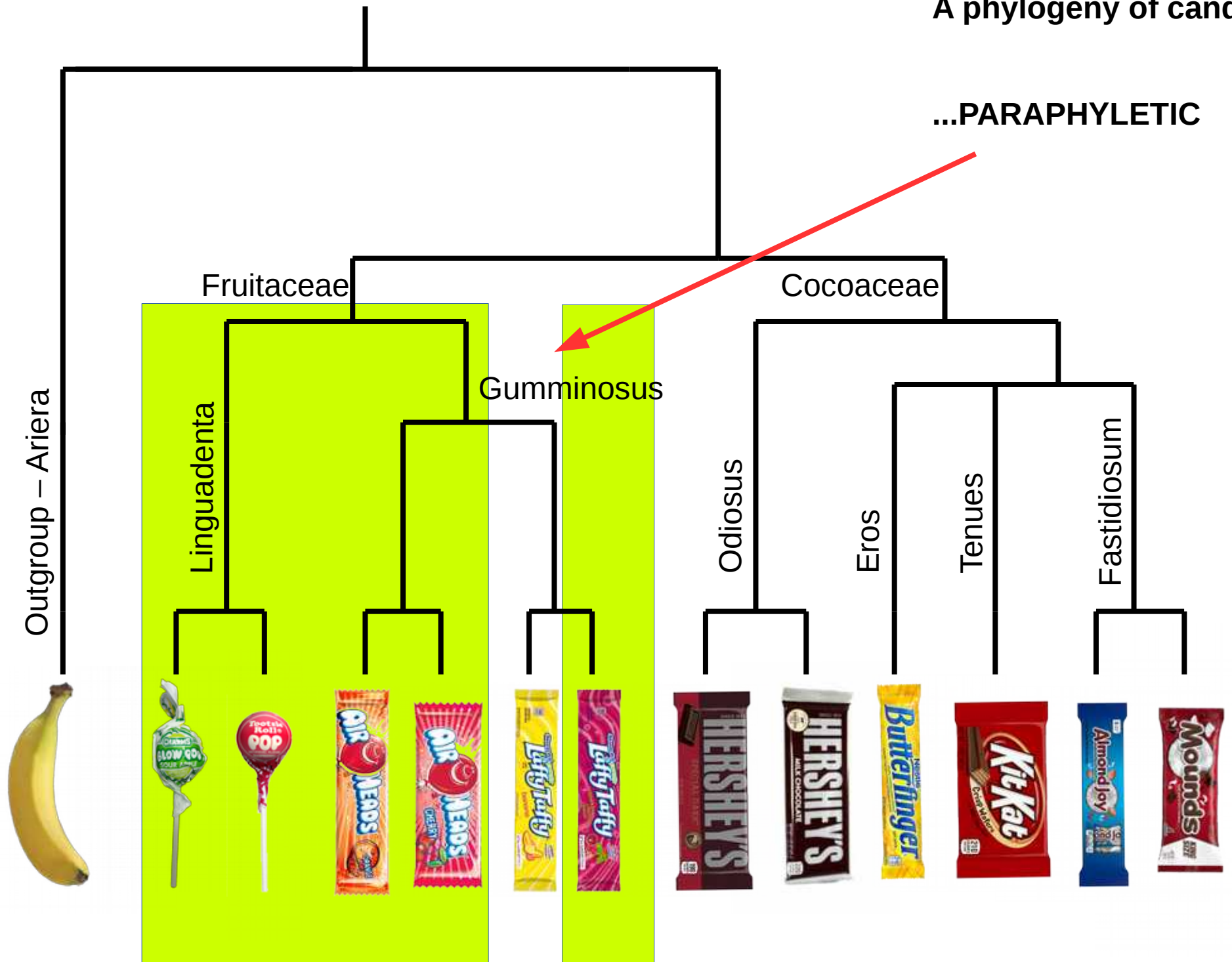
...naming groups



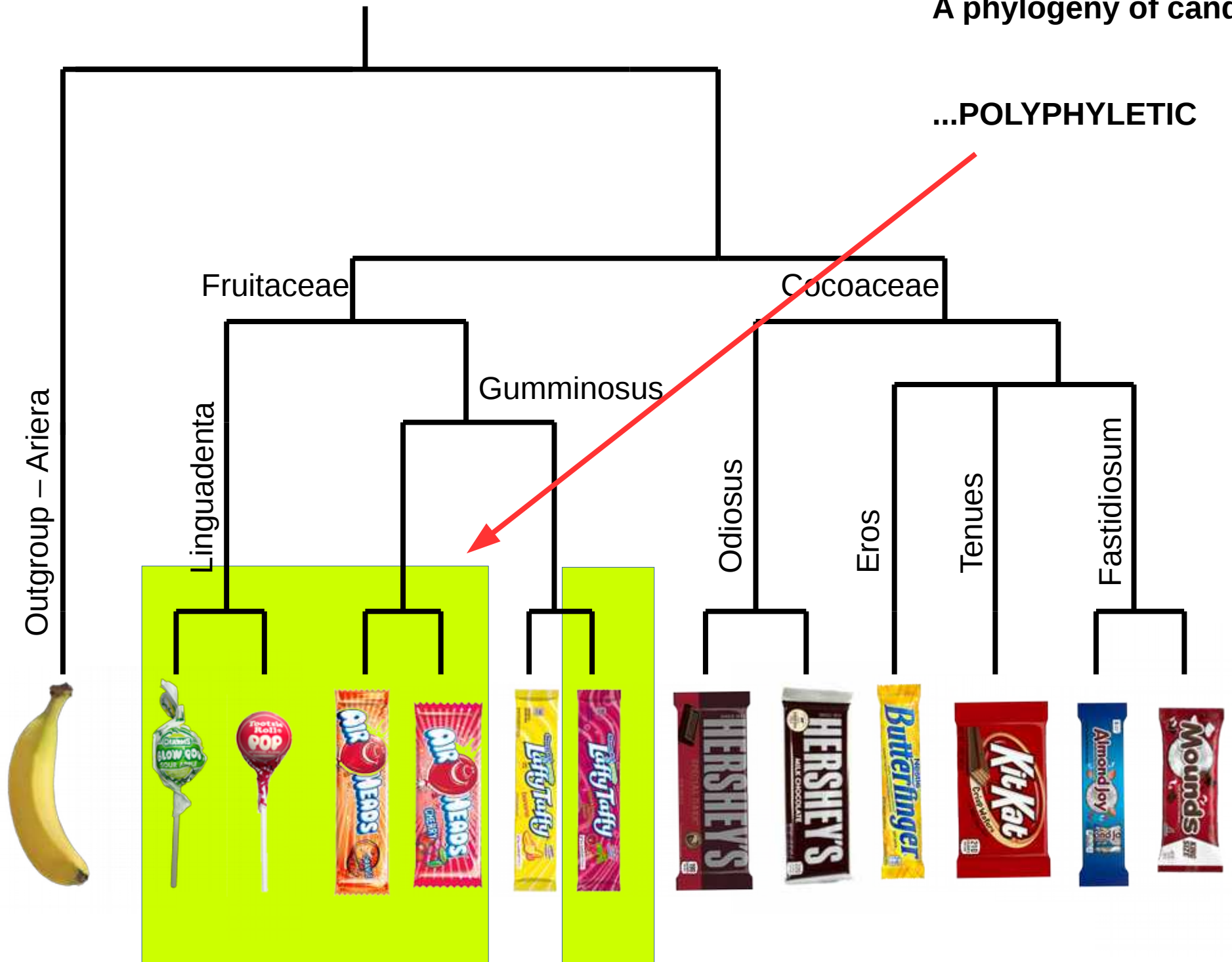
A phylogeny of candy



A phylogeny of candy



A phylogeny of candy

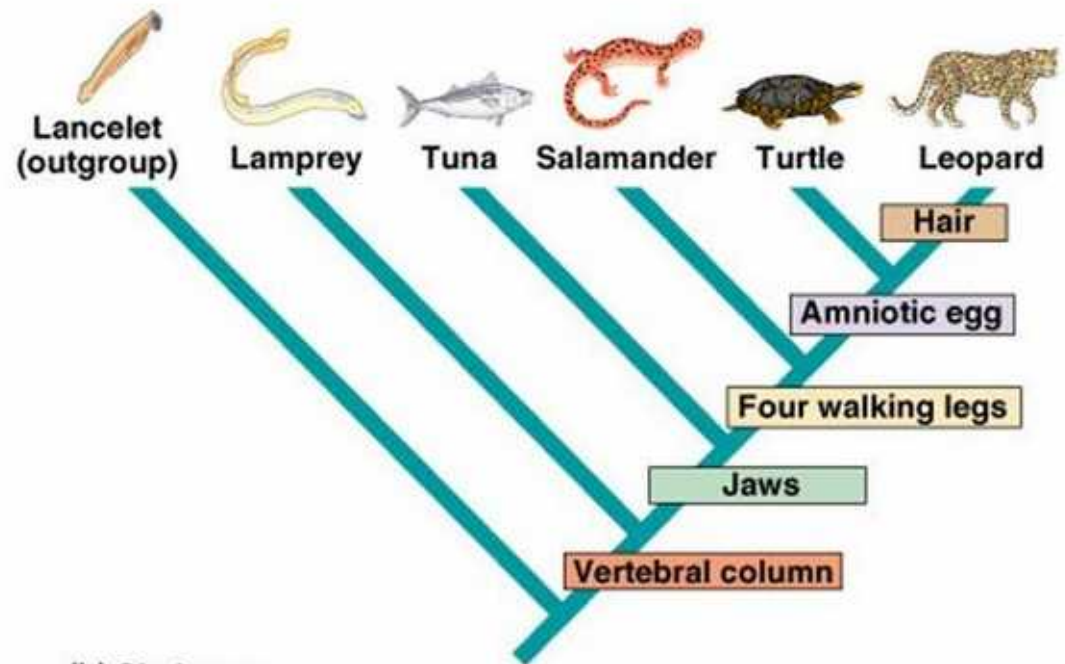


How to determine phylogeny:

- Morphological traits
- Molecular traits

| CHARACTERS | TAXA | | | | | |
|-----------------------------|---------------------|---------|------|------------|--------|---------|
| | Lancelet (outgroup) | Lamprey | Tuna | Salamander | Turtle | Leopard |
| Hair | 0 | 0 | 0 | 0 | 0 | 1 |
| Amniotic (shelled) egg | 0 | 0 | 0 | 0 | 1 | 1 |
| Four walking legs | 0 | 0 | 0 | 1 | 1 | 1 |
| Jaws | 0 | 0 | 1 | 1 | 1 | 1 |
| Vertebral column (backbone) | 0 | 1 | 1 | 1 | 1 | 1 |

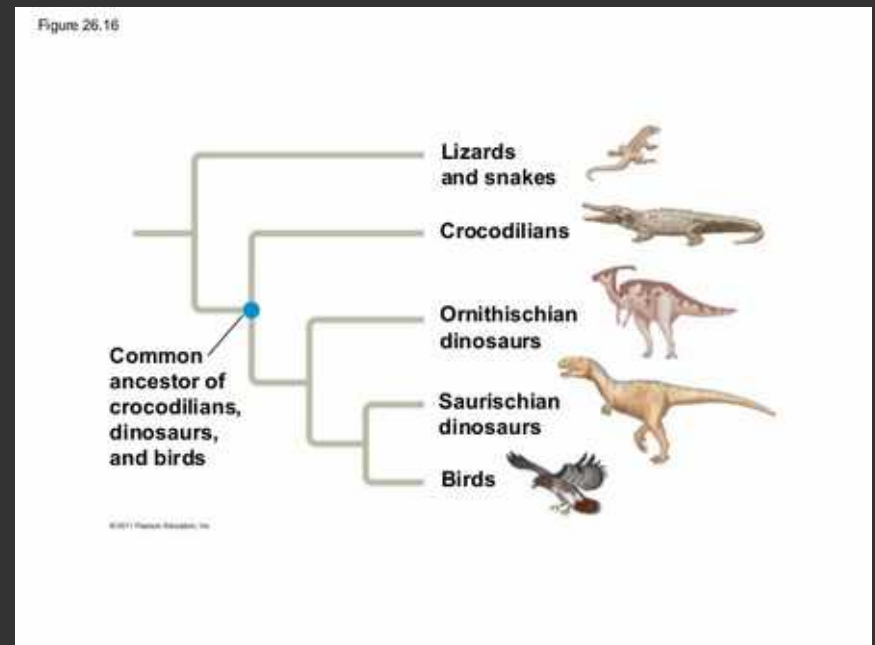
(a) Character table



(b) Cladogram

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

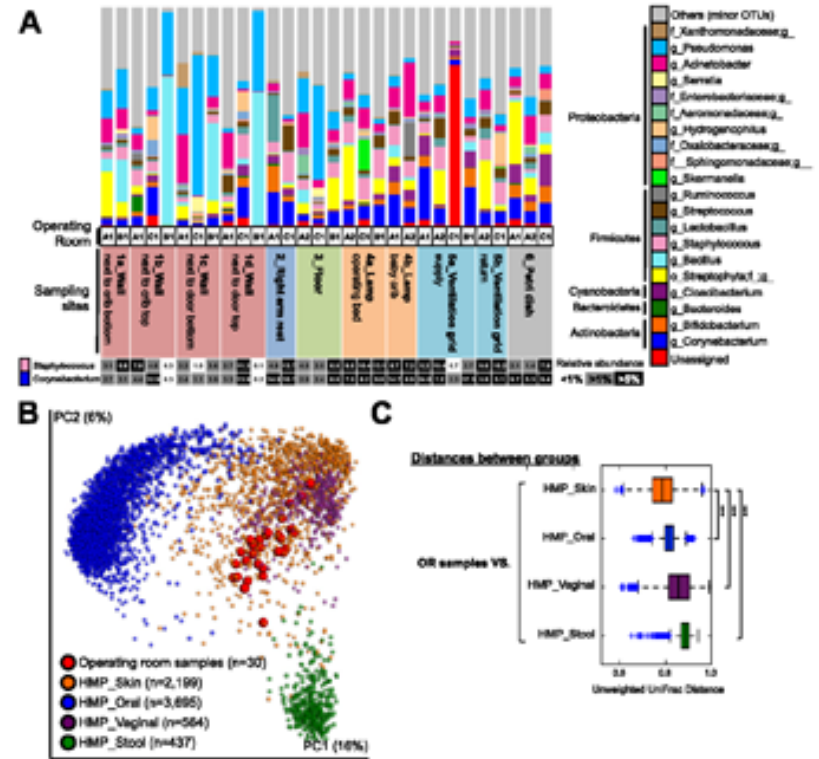


Front limb

Hind limb

Eggs

(a) **Fossil** remains of *Oviraptor* and eggs



terial diversity in operating rooms. **a** Bacterial taxa plot at the genus-level. Major phylotypes (>1 % of relative abundance at least one sample) are represented by each color. The relative abundances of *Staphylococcus* and *Corynebacterium* were represented by heat map (bottom). **b** PCoA plot of bacterial communities of OR samples with HMP database. Unweighted UniFrac distances were used to evaluate diversities between samples. **c** Box plot inter-group distances of bacterial communities between OR samples and HMP database. ***Non-parametric $p < 0.001$

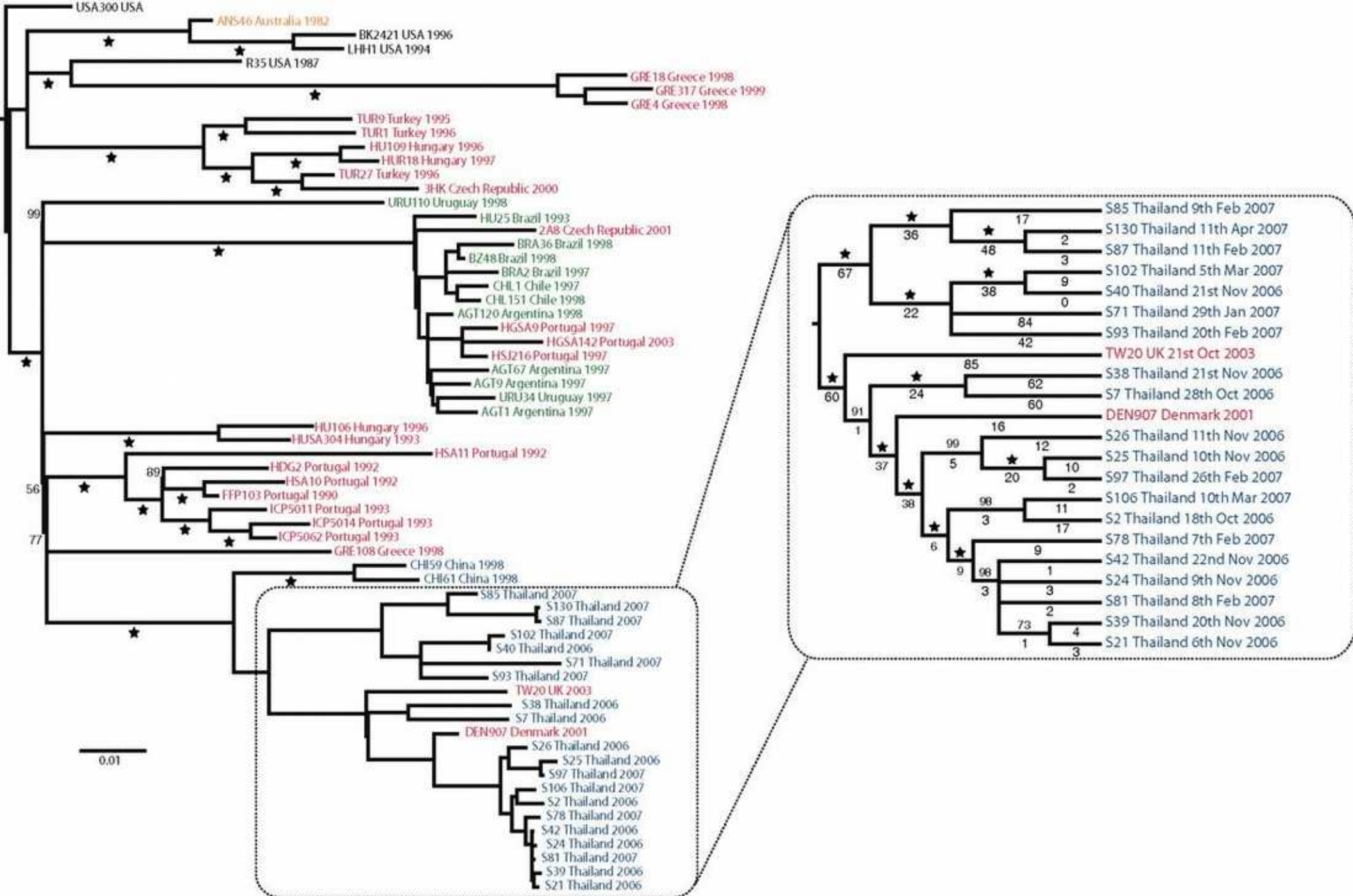
[illegible]

Rp_RP474 AGATATTTTCTAAACCA--GCTTATAGAAG--GCTTTAAAGCGAATAC--AATAGC--TGGCA--CCACAAGCTATAAAAAAG--TATTTAAT--GATCCTGTCAGGCT--CAACGTA--TCCTCTGAAGTACC--GCTTGGAAAGATGTC 138
 Rp_coxb AGAATTTGGTCCAAACAA--TCCTATAAAAGGTTAAAGTAGATCAAGAAC--ATAACA--CCA--GA--GAATACACAAACG--TATGTAAT--AGCAGAGCTGTAGGTTGAGCGTACAT--AGCTCTAAAAAGGA--ATTATGGAAGATATAT 140
 Rp_RP688 AAACTTTT--TGATATAACATACTAATAGAGAT--GGATTTAAGAAGTACAA--GGA--TGCAACGCGTGGTGCATCAAAAAAC--TATGTAATG--ATTCAAGTACCAAAATCAAGCTCAAAATG--AGCTTTAATAATAGT--TTATAC--ACAAATGT 144
 Rp_kdta AGATTTCACACAAATCTGCTTAATAAGAG--GGATTTCACAGACCAAA--AACTACATCTTATAGACA--TGCATAGAA--ATGCCAGCTCTA--ATGTATATAAT--ATCTTTAAAGAGAG--TTATGC--ACACAGTCT 129
 Rp_alr AGAGGCTT--CGCTTAATCTGCTTATACAGAG--GAATTTGAAGCAACAC--AGCAAGCTTACTAGCC--ACAGCGGTATATAATA--AATGTCCG--ATTGTAGTGTAGATGAGCTCAAAAT--ACCTTTAAAGCAAG--TTATAC--GTACAGTCT 147
 Rp_RP545 AGATATCTCTTAACAA--ACTGATAGAAC--GAATTTTACTACTGCG--AGAATC--GTA--TATAGGAATCTTAAGCA--TAA--GA--GTACTATAGTAACCTT--ATAAAT--ACCTCTAAAAAGAGCA--ATTTGTATATAGTCT 132
 Rp_lysc ATACCTCTTGTAAATCC--ACGTATATGGA--GAATCTGCACATAATAC--GAACA--CAGCACTAAAATAGAC--TACCTGAG--GATGCTAGGGAT--CAACATATAAAT--ACCCATAGATTTAGC--ATTACAAACAGGTA 135
 Rp_pyrg GCACATATTTCCAAATGT--ACTTATAGTGA--GCAATTC--AATGC--GACCGT--T--CAAGTGTATACAACT--TACATGAG--GATGCAATAACTGTGTACACAAATG--GCAGATAGAAACAA--TTTGAAGAATATGCT 135
 Rp_RP404 AGACATCTTTAAACTA--ACATATAGCA--AAATTT--GAAT--GCAATCTAGGAAGCA--TTTG--CAACCAAGTCT--CACATT--ACCCATAAAATAGA--ATTGGGAAGATGCTGCT 108
 Rp_rp55 AGACTTCT--TGCATAAGTAGCTAATAATGCT--AAATTTGTAAAAAAACC--AGCA--C--ATAGTGATACGAATA--AT--GTGAGA--ATACGAGTACTGAATGCATCAAAATG--ACCTTTGAAGAGGC--CTATAG--AGGAAGGCT 133

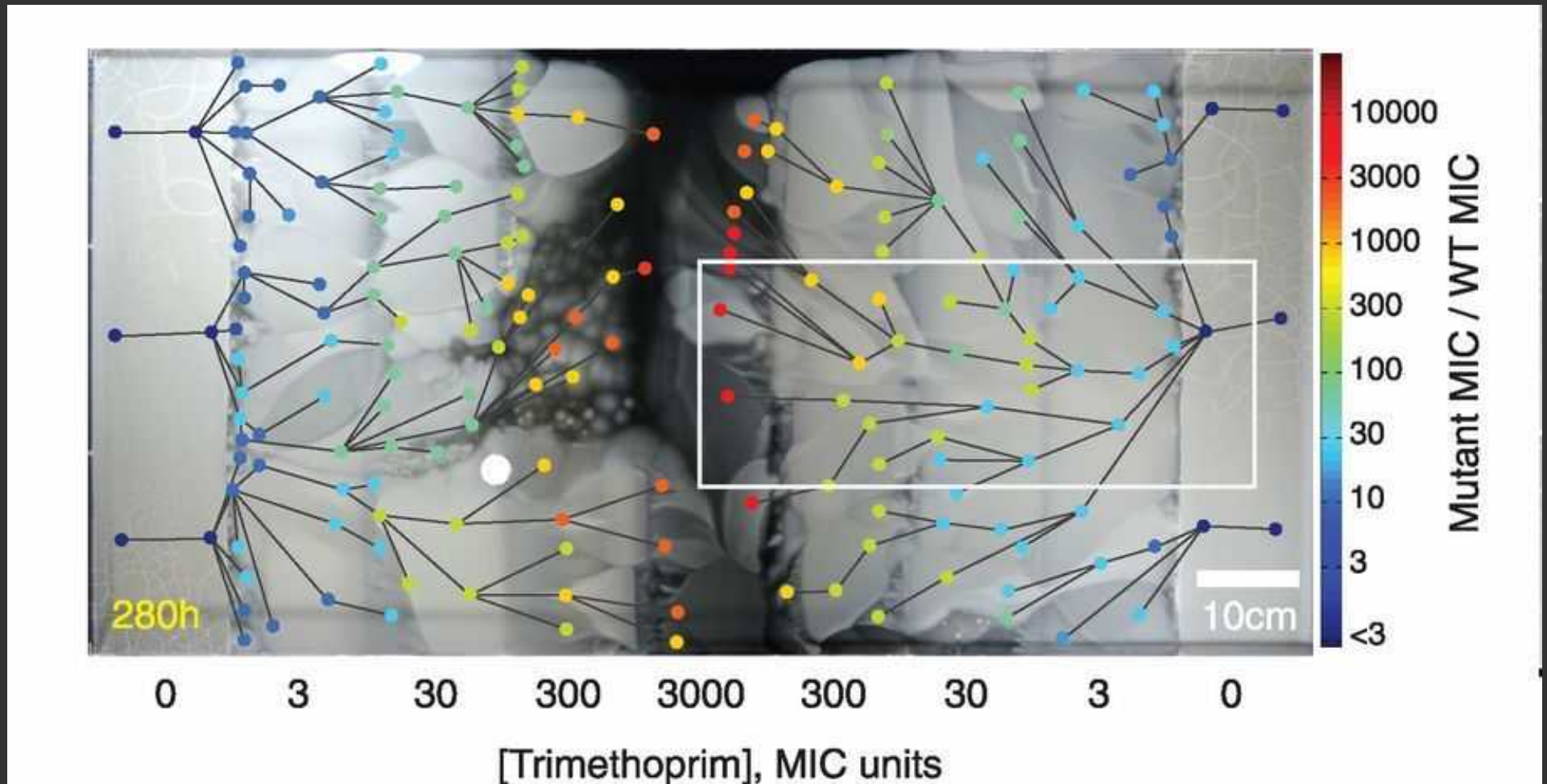
Rh_pola **AGGCCCTCTTTCAAAACTC--GCTTATAGAG--GAATTTAAAGGAGACAC--GGAACG--CAGCA--CCGCA****CGGTAC**AAAAGC**G--TAC-TTGAG--GATGCGAGTACCGGATCGACGTCATAAAT-ACCTCTAGAAAGTAGA---GTTTGGGAAGAGGCC** 144

Rf_pola **AGACATCTTTCTAAACCA--GCTTATAGAG--GAATTTAAAGGAGACCGGAAGCACT--TGCCA--CCGCA****CGGTAC**AAAAGC**G--TAC-TTGAG--GATGCGAGTACCGGATCGACGTCATAAAT-ACCTCTAGAAACGAA---GTTTGGGAAATGTCT** 147

1 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160

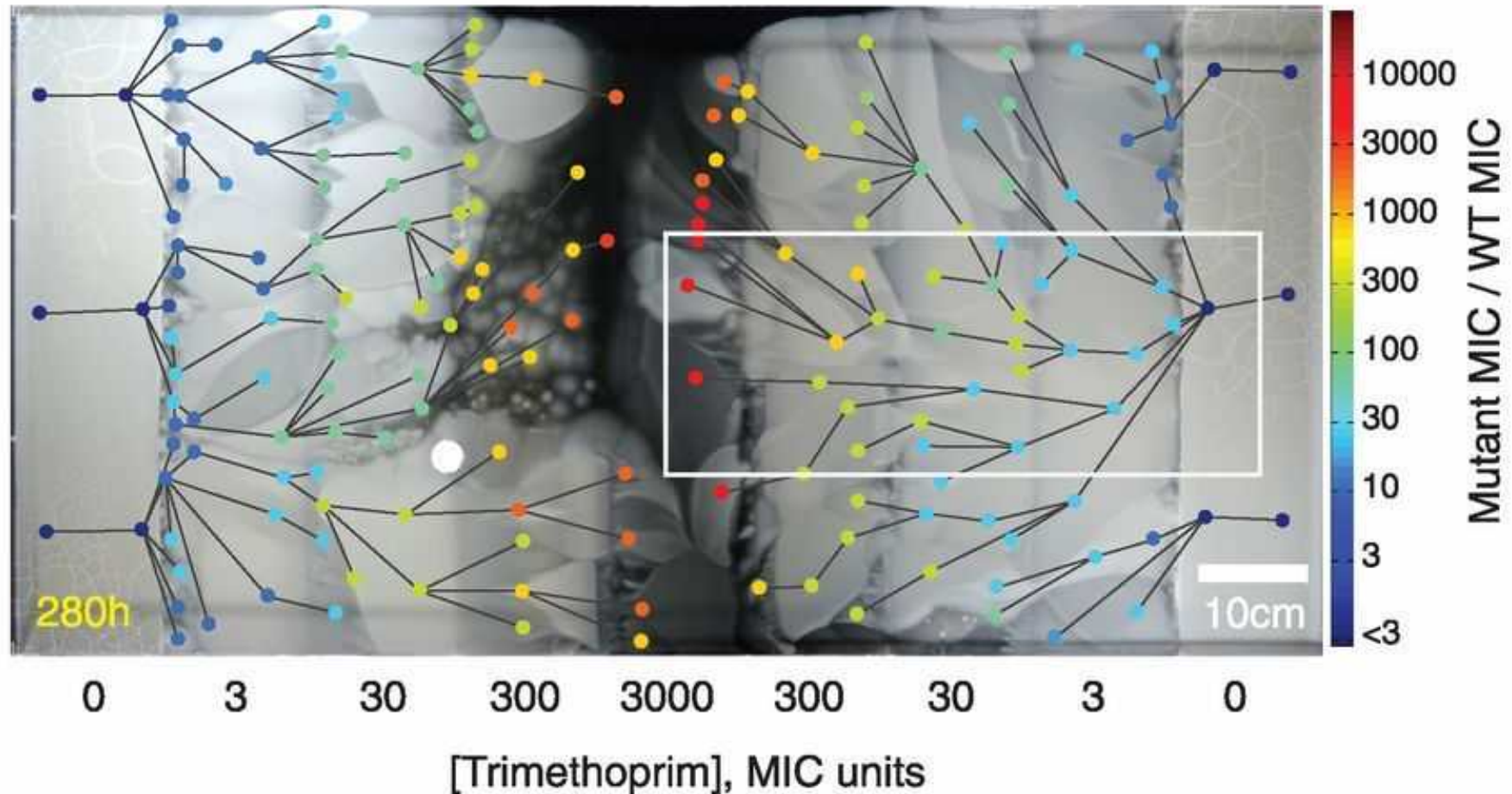


Look familiar???

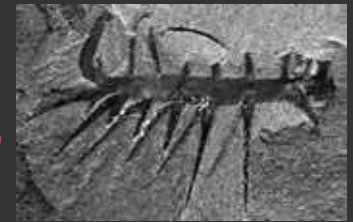


Organisms' evolutionary histories are documented in their genomes

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

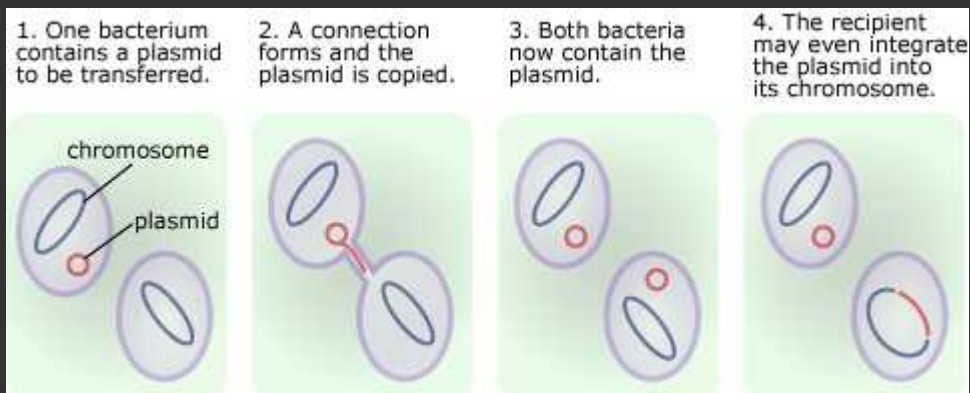
Fossils all around the world follow the same pattern:
More "primitive" organisms in older rocks, more complex organisms in newer rocks.

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?





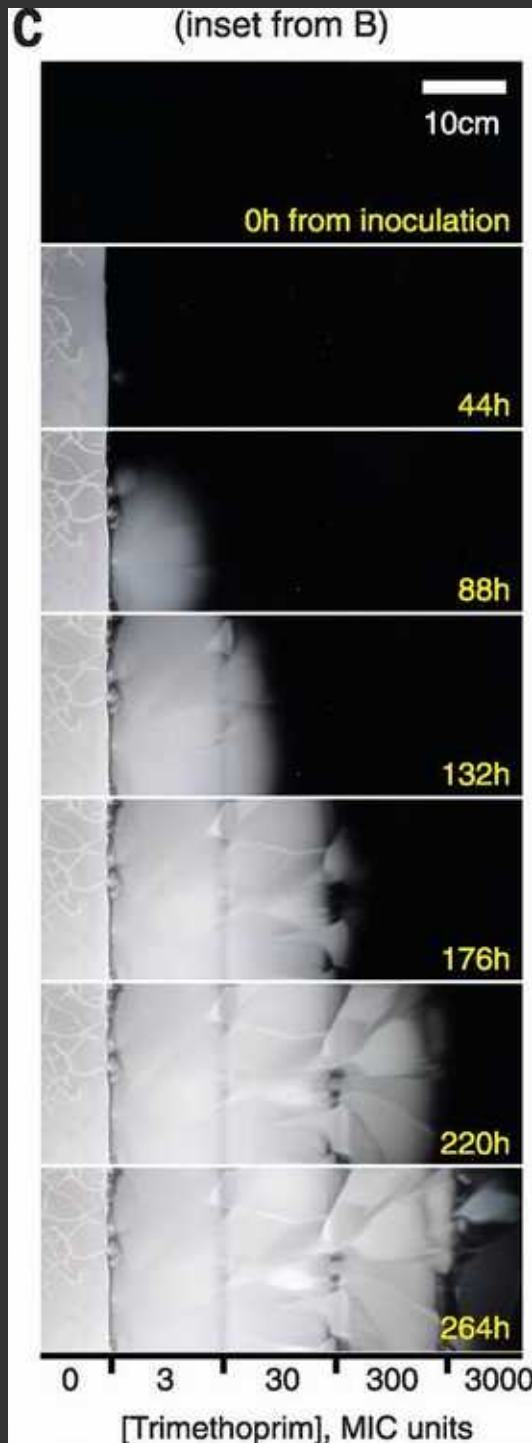
If the following conditions are met,
evolution **MUST** occur:

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)