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Evolutionary History of Gene Regulation in Bacteria

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Analysis of gene regulation in ESPP bacteria relies on comparisons to model organisms, and hence on assumptions about how gene regulation evolves. To test these assumptions we examined the evolutionary histories of transcription factors and of regulatory interactions from the model bacterium *Escherichia coli* K12. We show that although most transcription factors have paralogs, these usually arose by horizontal gene transfer rather than by duplication within the *E. coli* lineage, as previously believed. Most neighbor regulators -- regulators that are adjacent to genes that they regulate -- were acquired by horizontal gene transfer, while most global regulators evolved vertically within the gamma-Proteobacteria. Neighbor regulators are often acquired together with the operon that they regulate, which suggests that the proximity is maintained by repeated transfers, and also aids the prediction of the regulators' function. Because of the complex evolutionary histories of most transcription factors, bidirectional best hits tend to be misleading, and most annotations of bacterial regulators are probably incorrect.

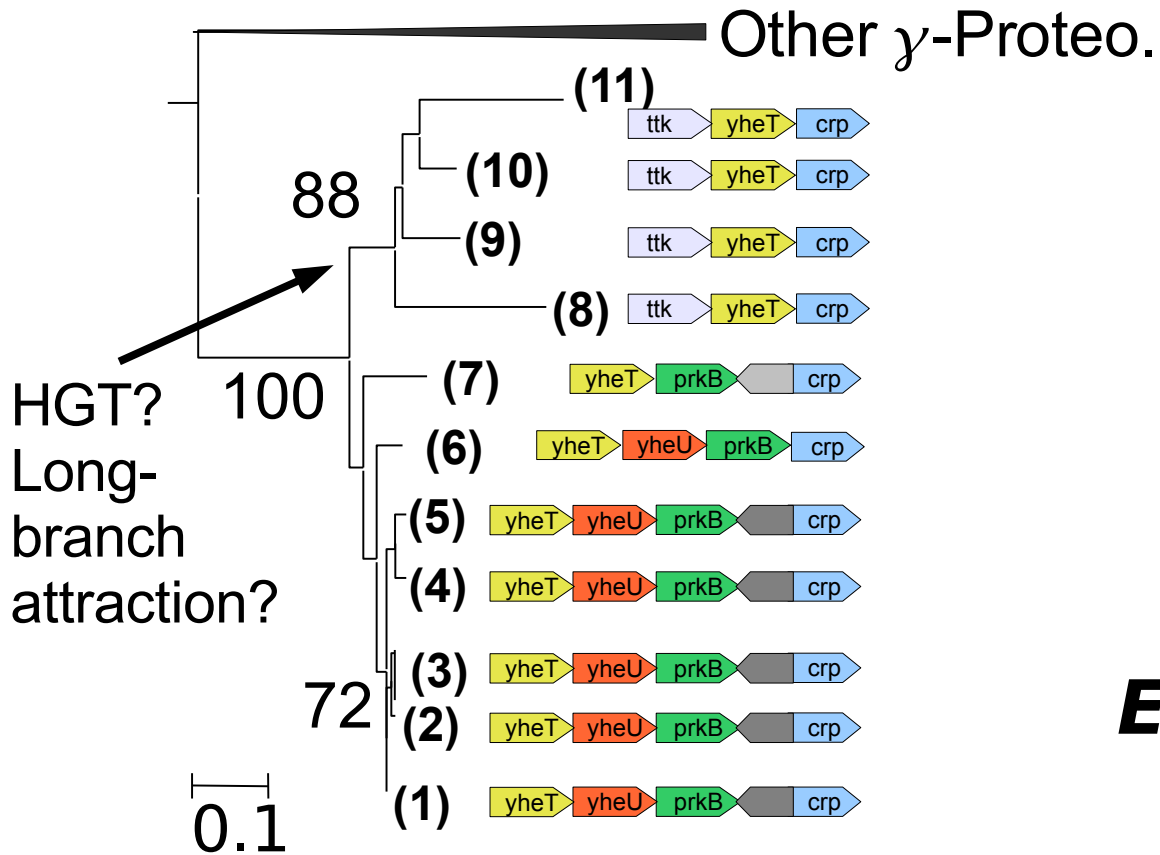
When we analyzed the histories of regulatory interactions, we found that the evolution of regulation by duplication was rare, and surprisingly, many of the regulatory interactions that are shared between paralogs result from convergent evolution. Furthermore, horizontally transferred genes are more likely than other genes to be regulated by multiple regulators, and most of this complex regulation probably evolved after the transfer. Finally, gene regulation is often not conserved, even within the gamma-Proteobacteria. Our results suggest that the bacterial regulatory network is evolving rapidly under positive selection. Such rapid rewiring of gene regulation may be crucial for adaptation to new niches.

Rapid Evolution of Gene Regulation

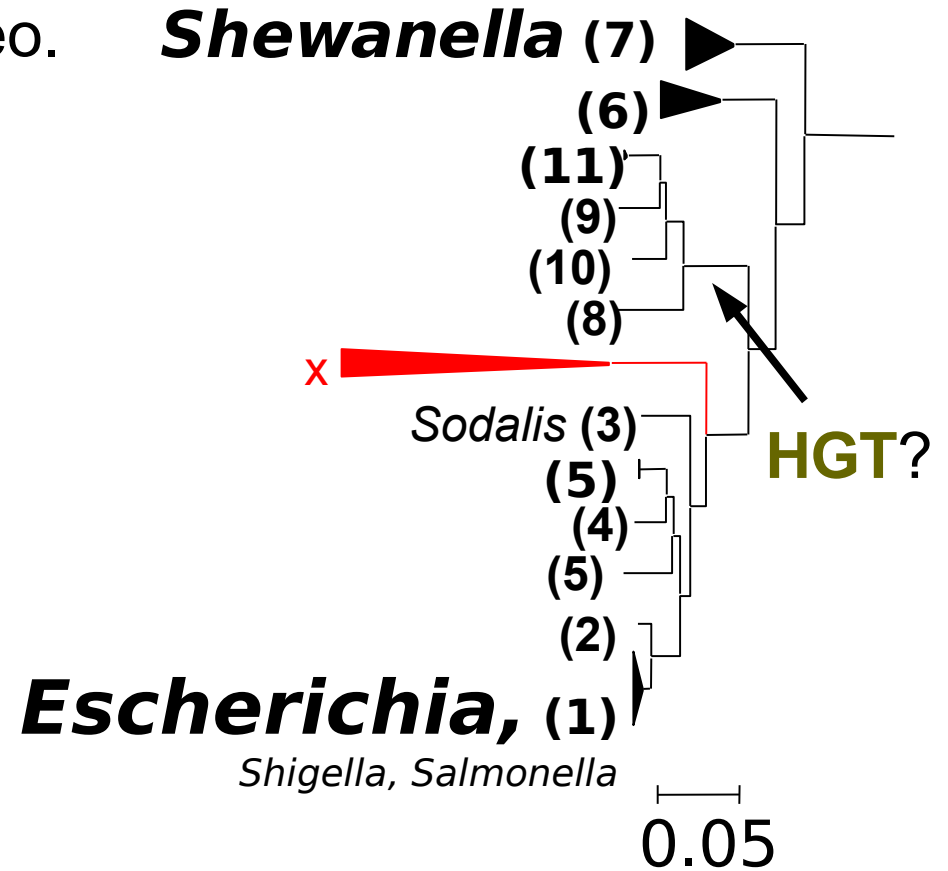
- Transcription factors (TF) have complex histories
 - Rampant transfer (not duplication)
 - “Orthologs” are problematic
 - Annotations are usually incorrect
 - “Neighbor regulation”
 - driven by horizontal gene transfer, aids annotation
 - Global regulators are more conserved
 - but we can predict little about other divisions
- Regulatory interactions not highly conserved

Vertical Inheritance of Global Regulators in *E. coli*

Gene tree for *crp*



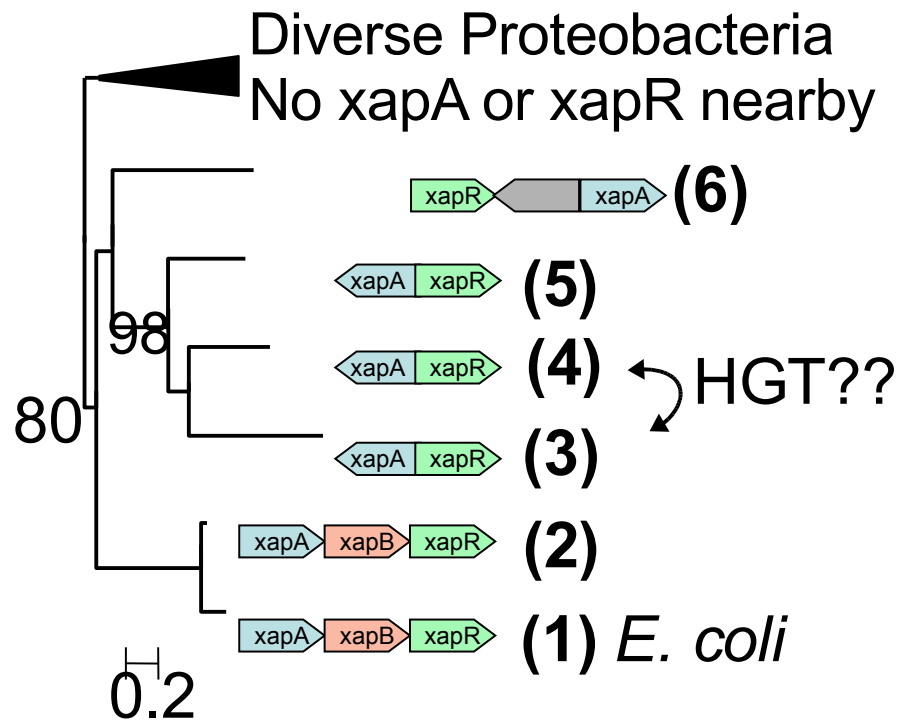
Distribution of *crp*



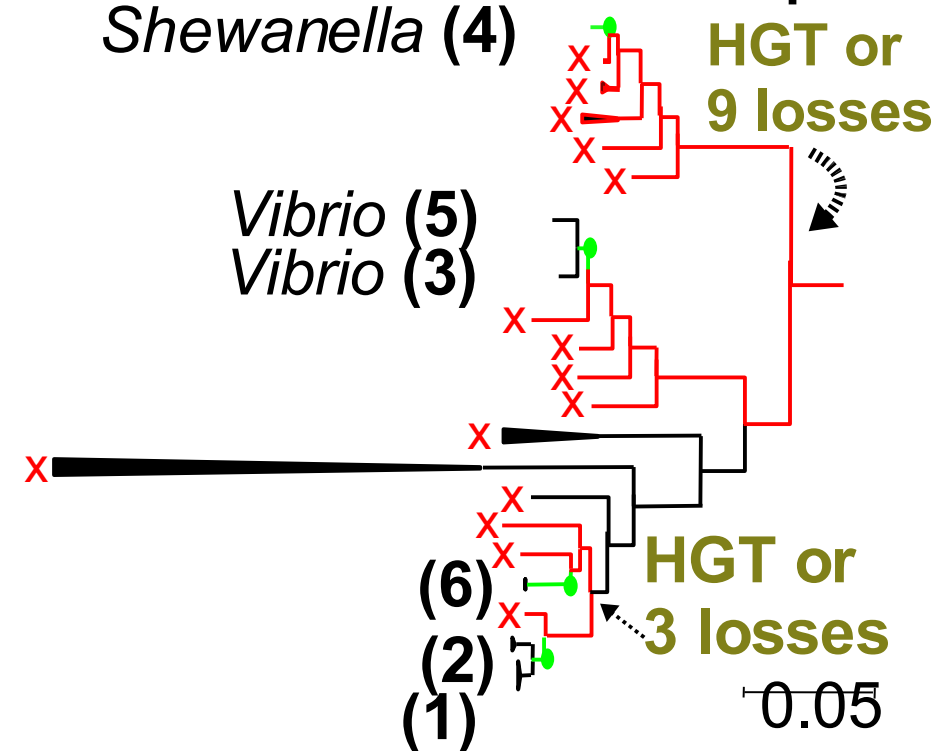
17/20 top global regulators are native

Complex Histories of Neighbor Regulators in *E. coli*

Gene tree for xapR



Distribution of xapR

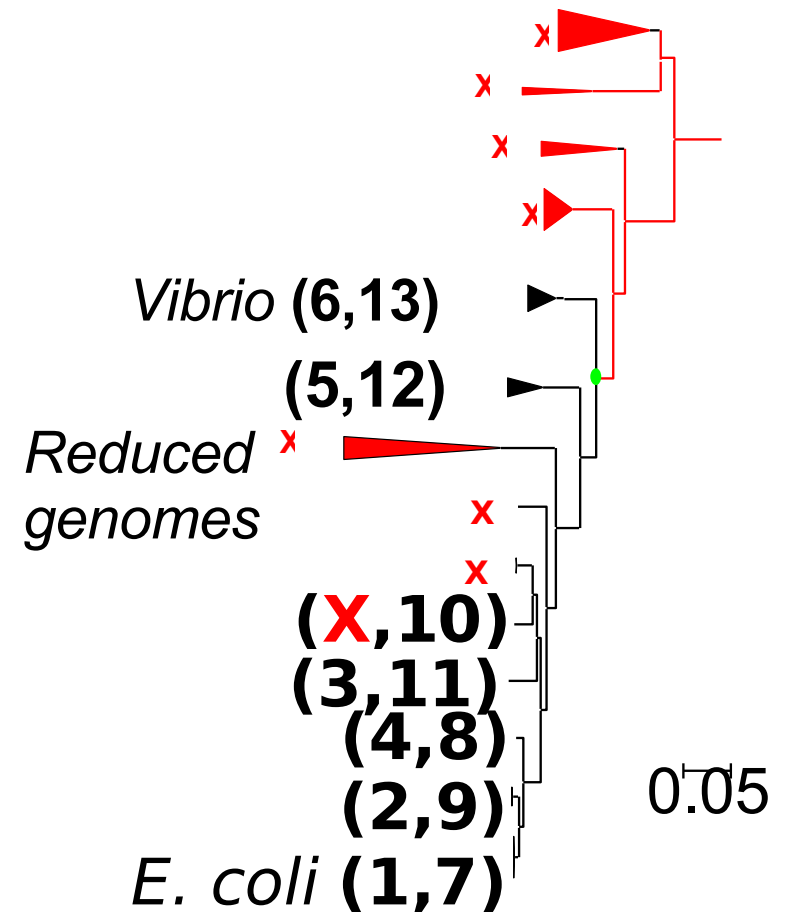
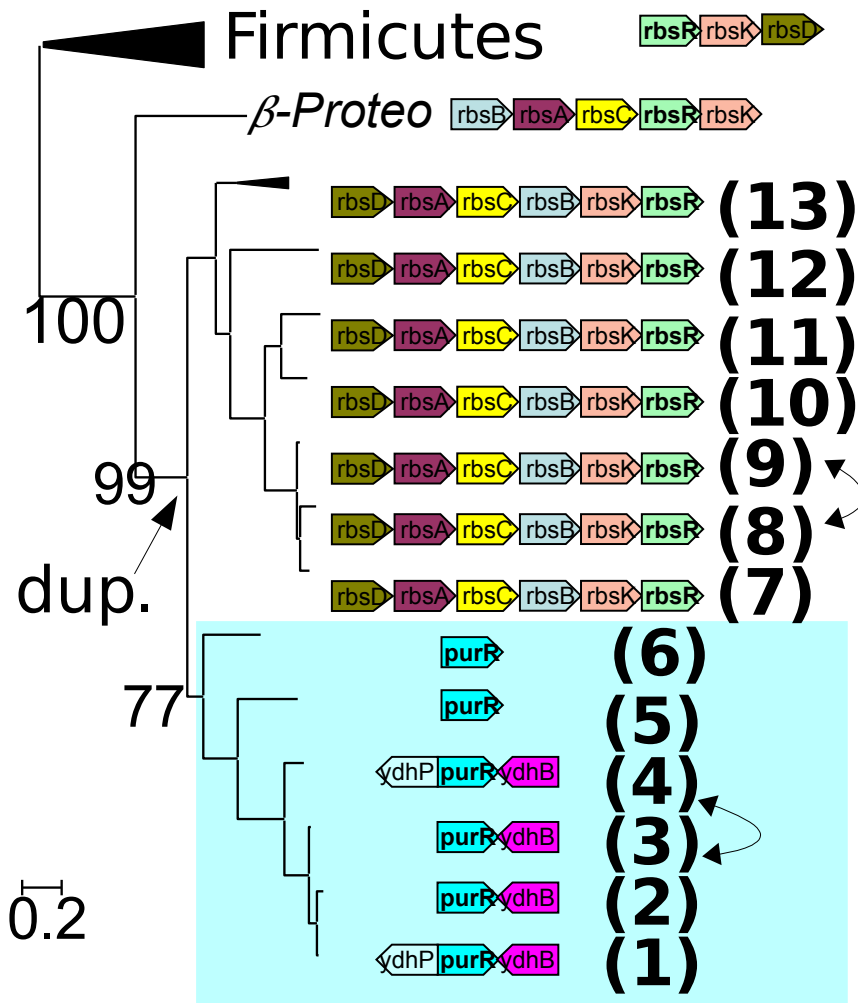


- Co-transfer: ~60% of neighbor regulators, 45% of putative regulators => predictions
- Repeated HGT: ~40% of neighbor reg.

Duplication of rbsR/purR

Gene tree for rbsR, purR

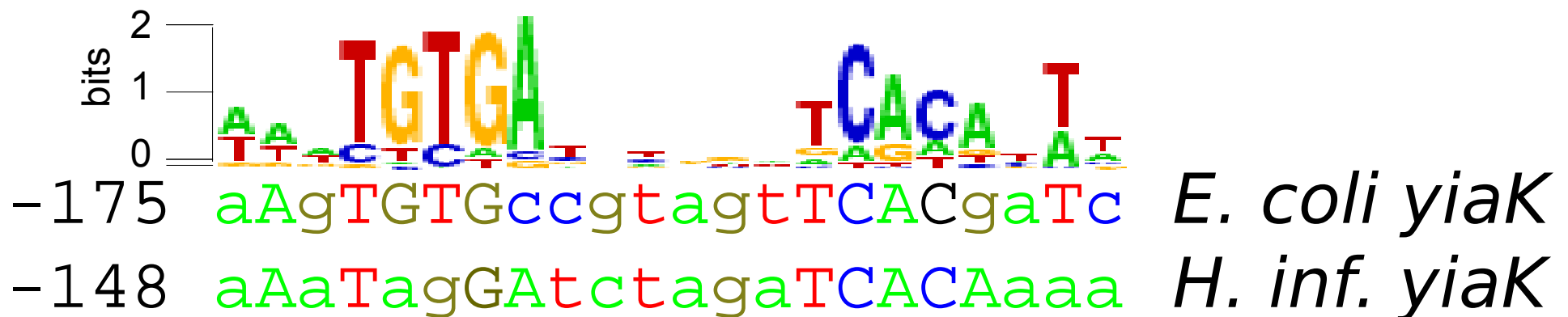
Distribution of rbsR, purR



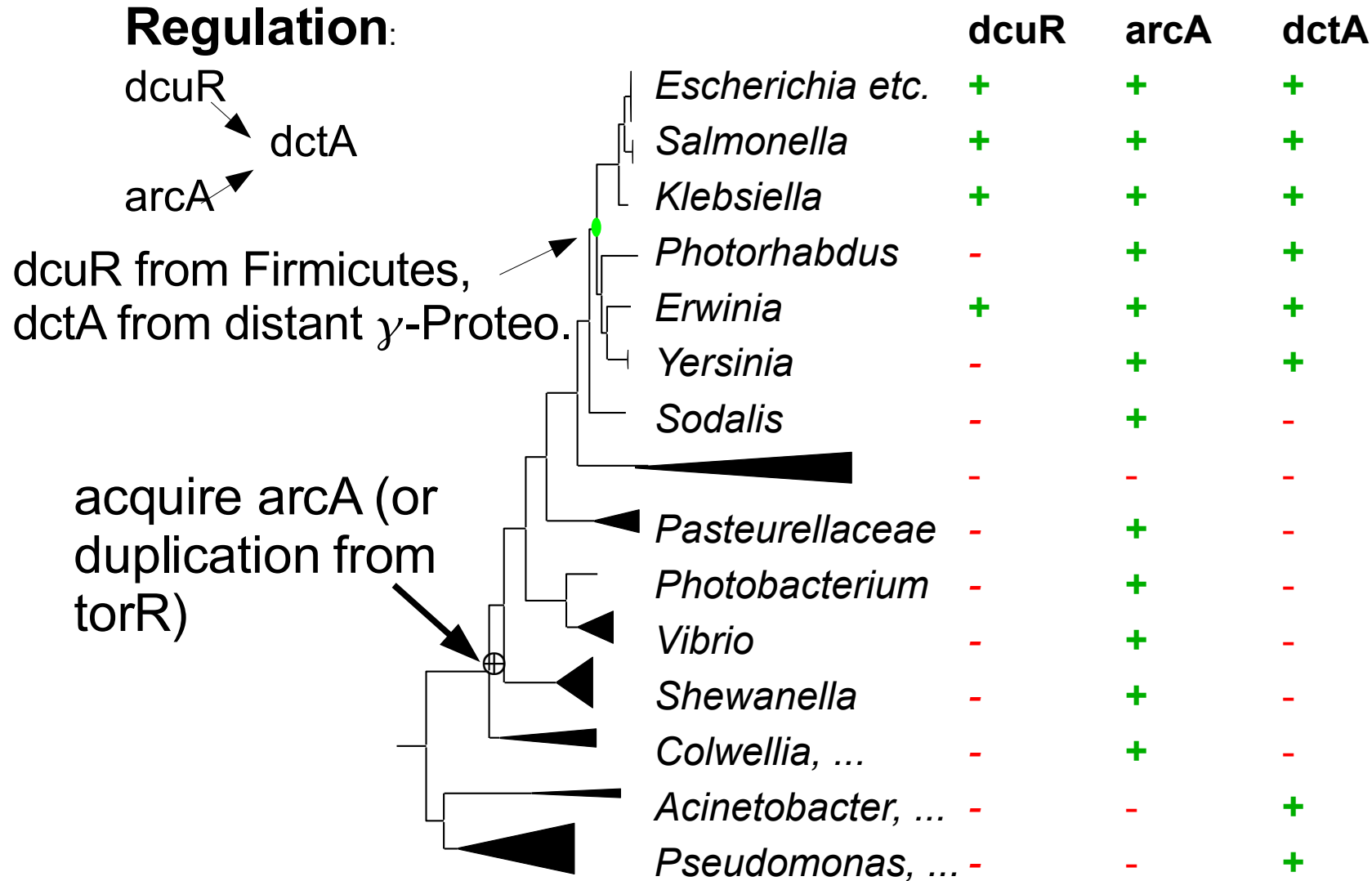
- Dups are rare (13% of *E. coli* TFs)
- Non-overlapping functions (~half of dups)

Sources of the CRP Regulon

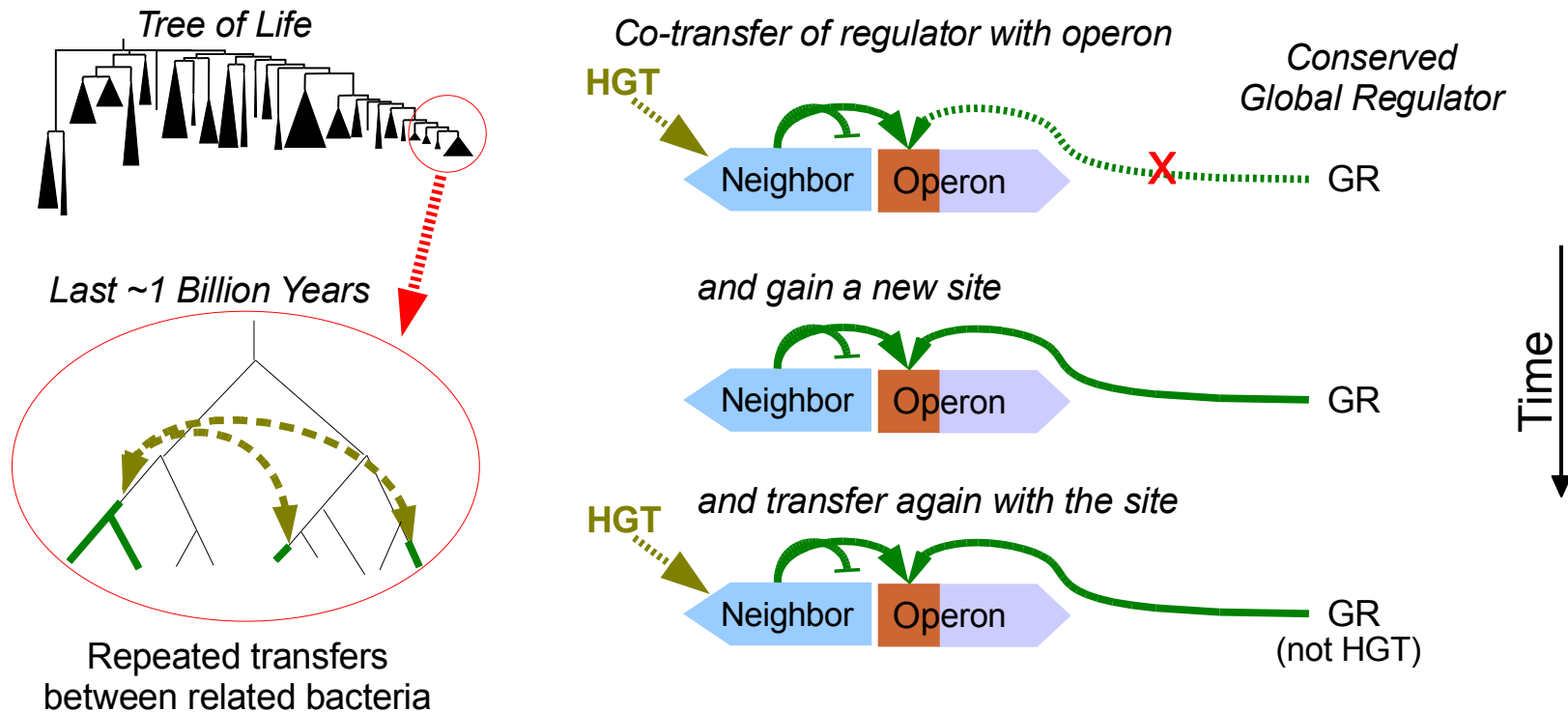
- From distant bacteria w/o CRP (~80%)
- From related bacteria with CRP (~20%)
 - CRP site conserved across HGT in 4/12
- Sites usually not conserved across HGT (6/20 for global regulators)
 - except for co-transfer (presumably)



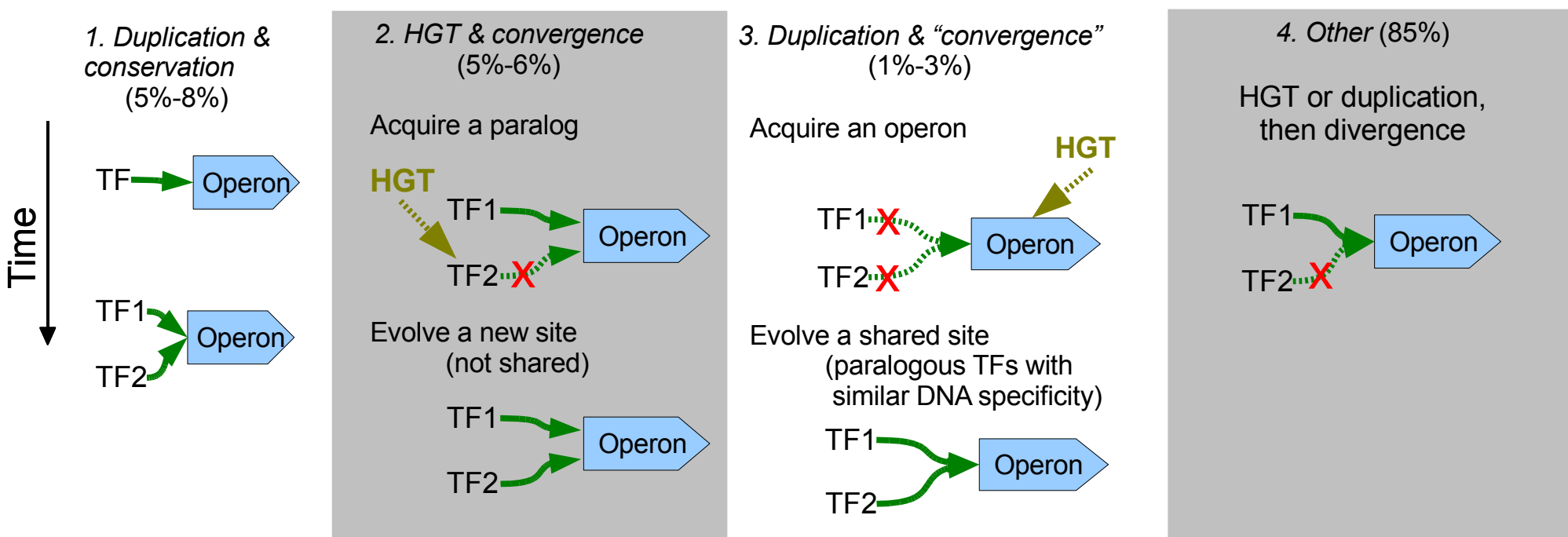
Apparent Evolution of Regulation by Duplication is Convergent



(A) Niche-Specific Neighbor Regulators vs. Conserved Global Regulators



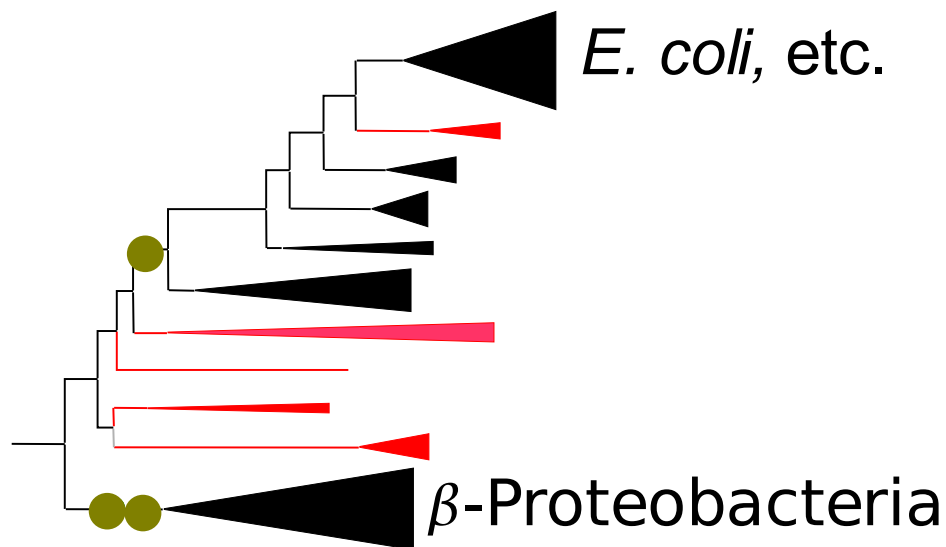
(B) Rapid & Convergent Evolution of Regulatory Interactions



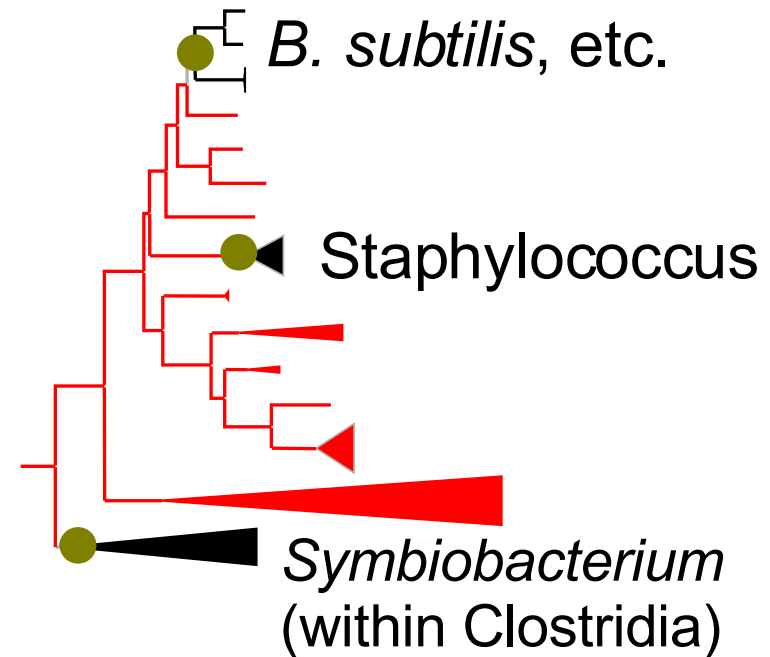
BBHs of TFs Have Different Functions

- Different pathways & stimuli
 - *E. coli* *betI*: choline -> osmotic stress
 - *B. subtilis* *pksA*: polyketide synthase

***betI*: HGT or 3 losses**



***pksA*: 2 HGT or >5 losses**



17/26 different functions between *E. coli*, *B. subtilis*

9/20 different between *E. coli* and other divisions of Proteobacteria