The Life Cycle of Operons

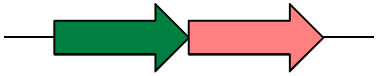
Morgan Price
Eric Alm
Adam Arkin

ERNEST ORLANDO LAWRENCE
BERKELEY NATIONAL LABORATORY

Studying Operon Evolution

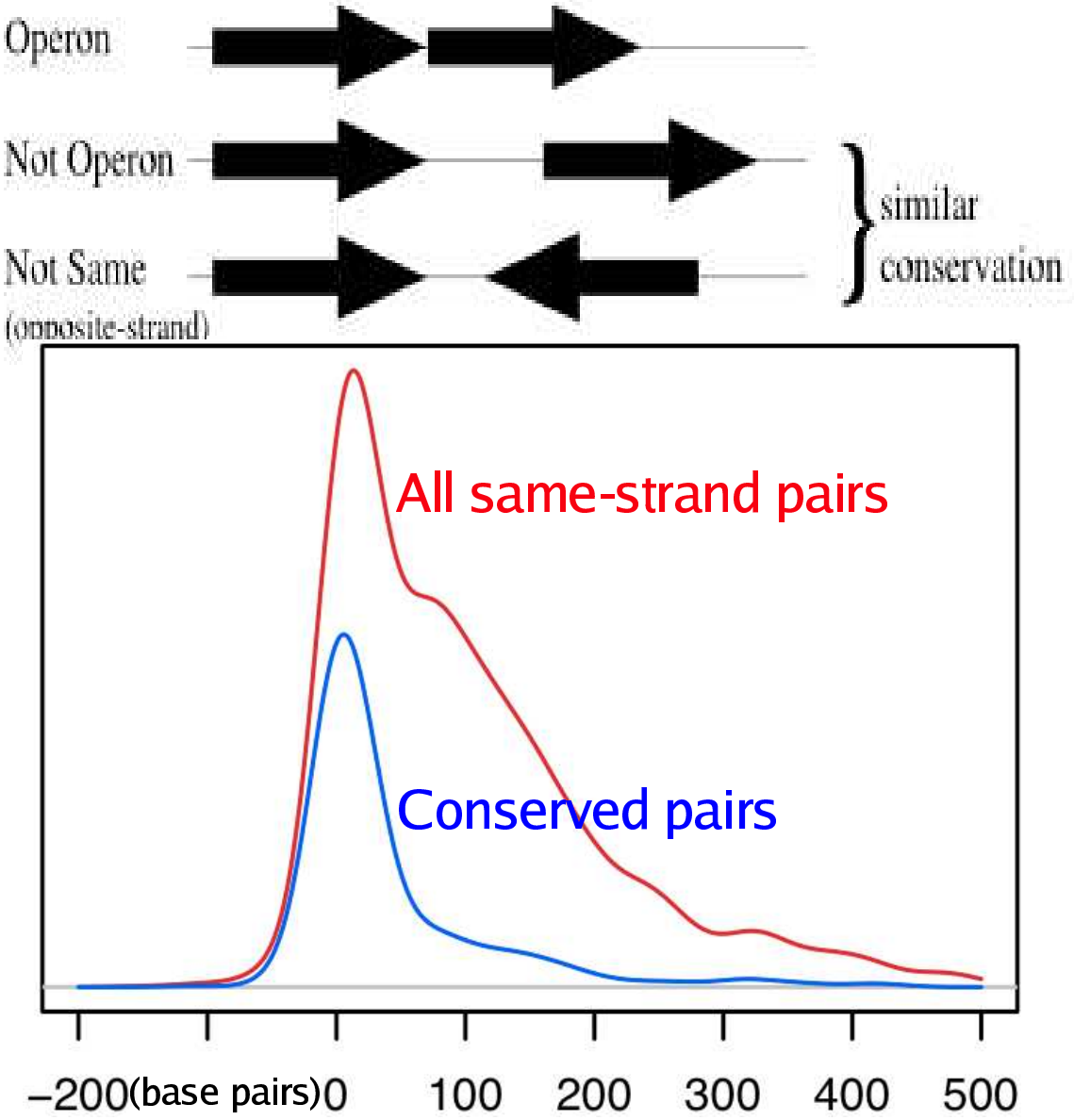
Identify operons & reconstruct their history with comparative genomics

- How do operons form?
- Why are many operons so closely spaced?



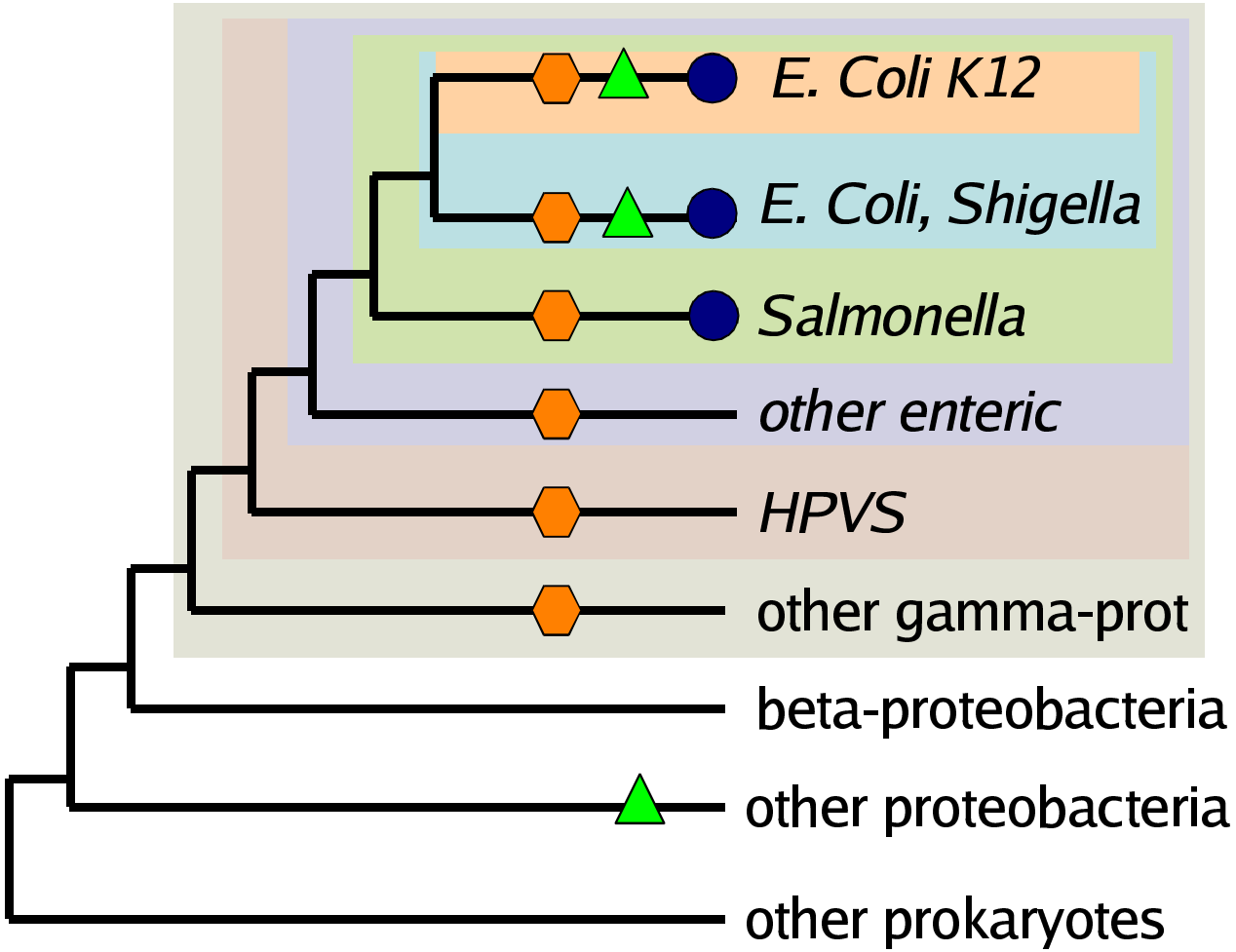
- What drives operon formation & death?
- Is operon evolution neutral or adaptive?

Methods: Predicting Operons



Price *et al.* NAR 2005

Methods: Phylogenetic Inference - Genes



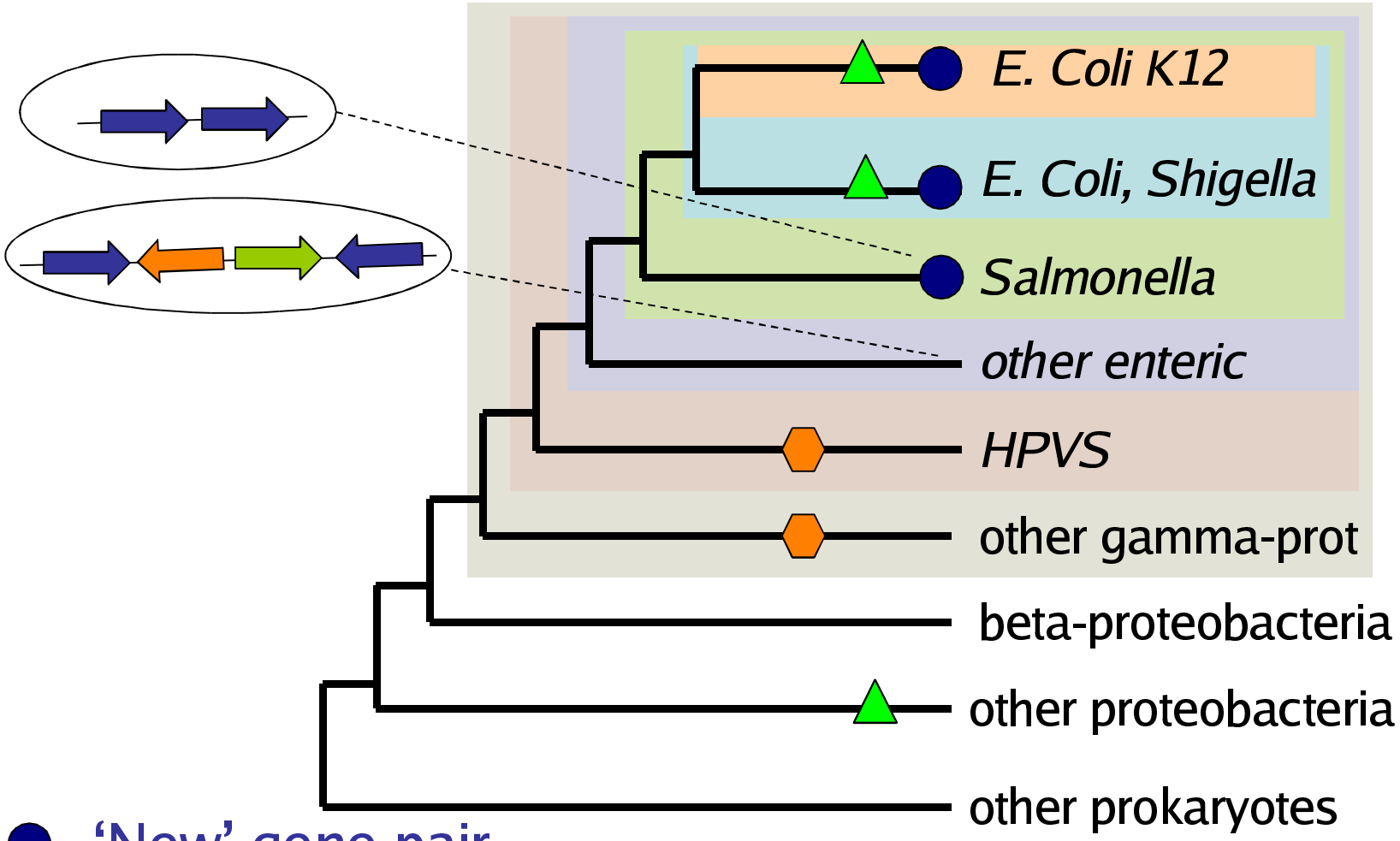
Native

Recent innovation - 'ORFan'

Horizontal Gene Transfer - HGT

Price *et al.*,
Genome Res. 2005

Methods: Phylogenetic Inference - Operons



● 'New' gene pair

▲ 'Imported' gene pair

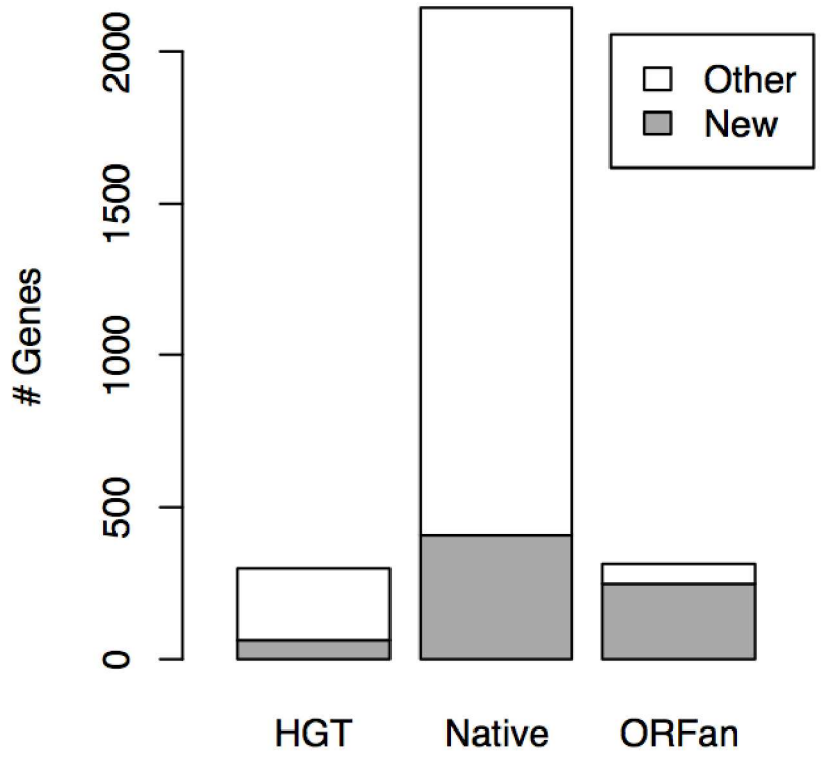
⬢ 'Dead' gene pair

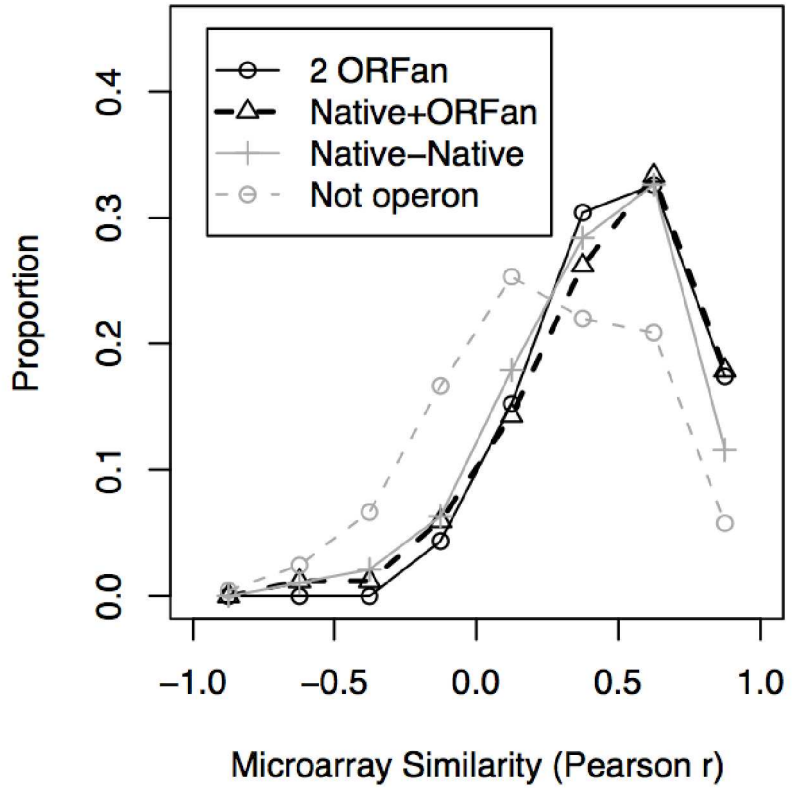
Price *et al.*,
Genome Res. 2005

New Operons

- New operons often “make no sense”
  - Conserved operons usually code for coherent pathways, but not new operons
- How do they form?
  - Known not to require horizontal gene transfer
- New operons vs. modified operons

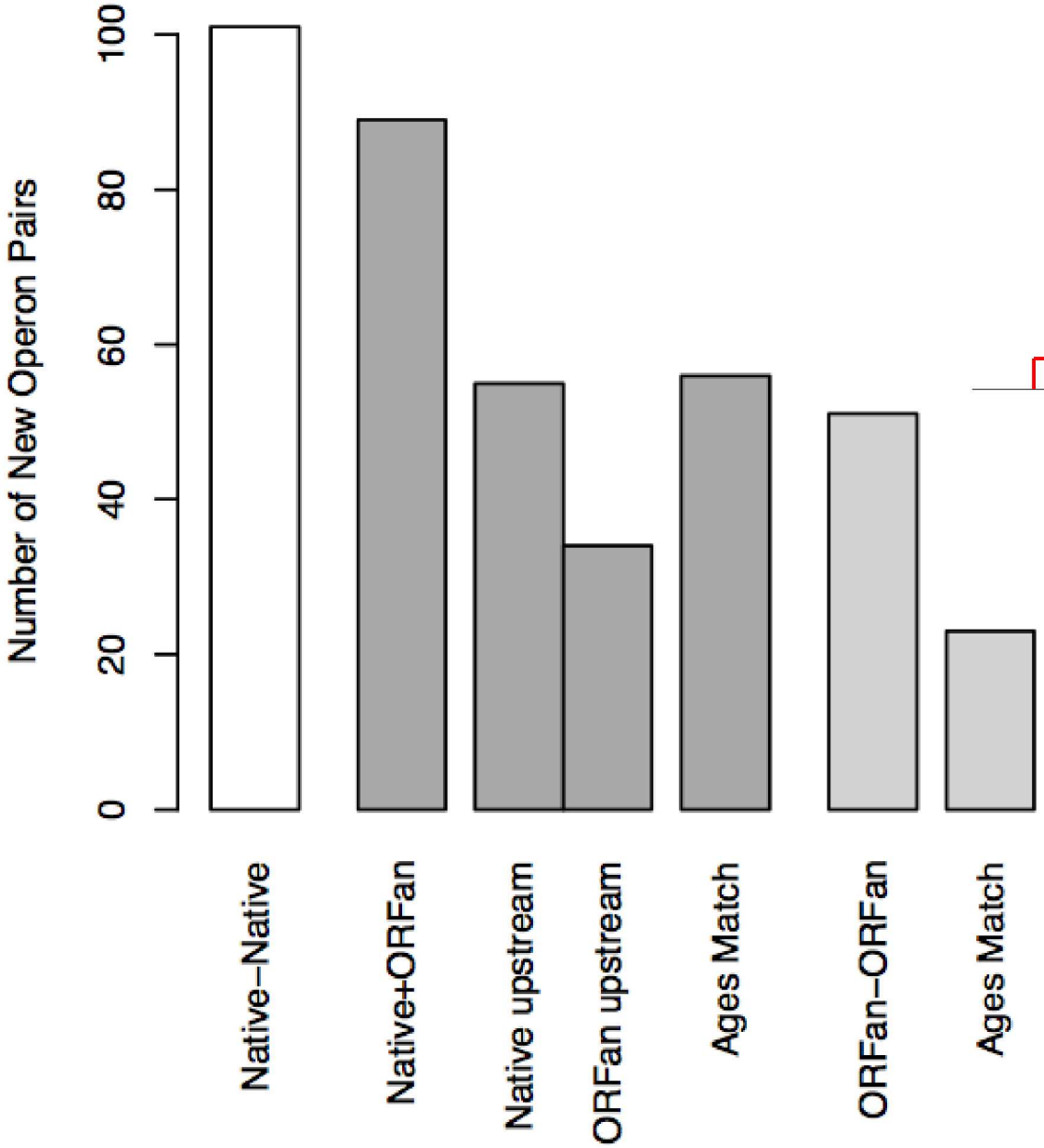
Types of Genes in New Operons

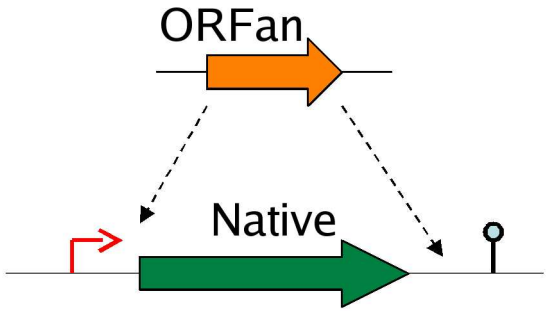




Large proportion of ORFan genes in new operons. Did these operons form at the time of appearance of the ORFan gene?

Birth of an Operon: Native-ORFan Pairs





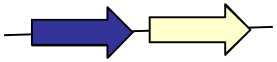
Birth of an Operon: Native-Native Pairs

Examine gene order of new *E. coli* operons in *Vibrio*

Delete intervening genes (6 cases)

Vibrio

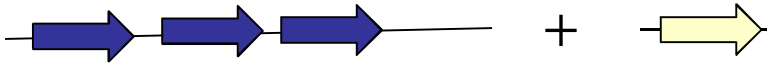
E. coli



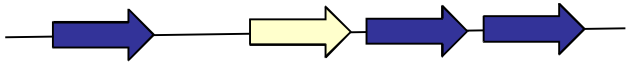
Importance of chance in operon evolution?

Large-scale genome rearrangements (4 cases)

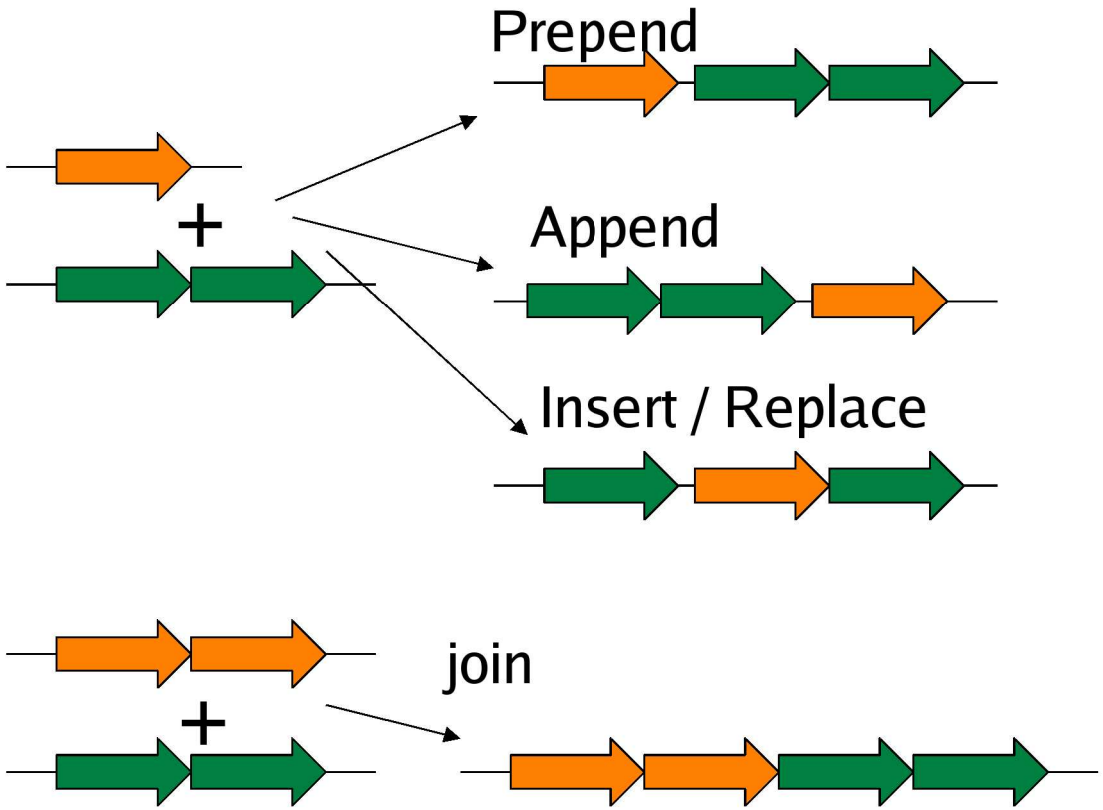
Vibrio

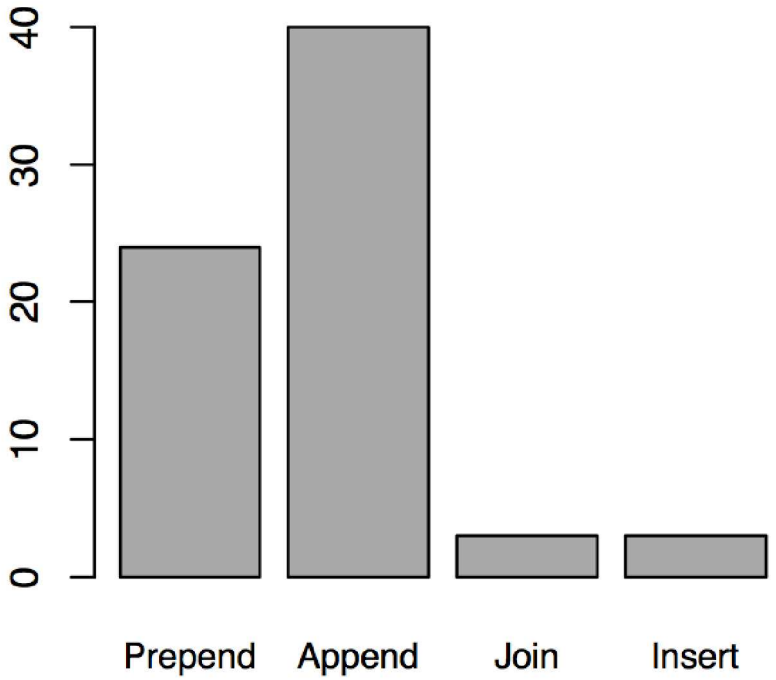


E. coli



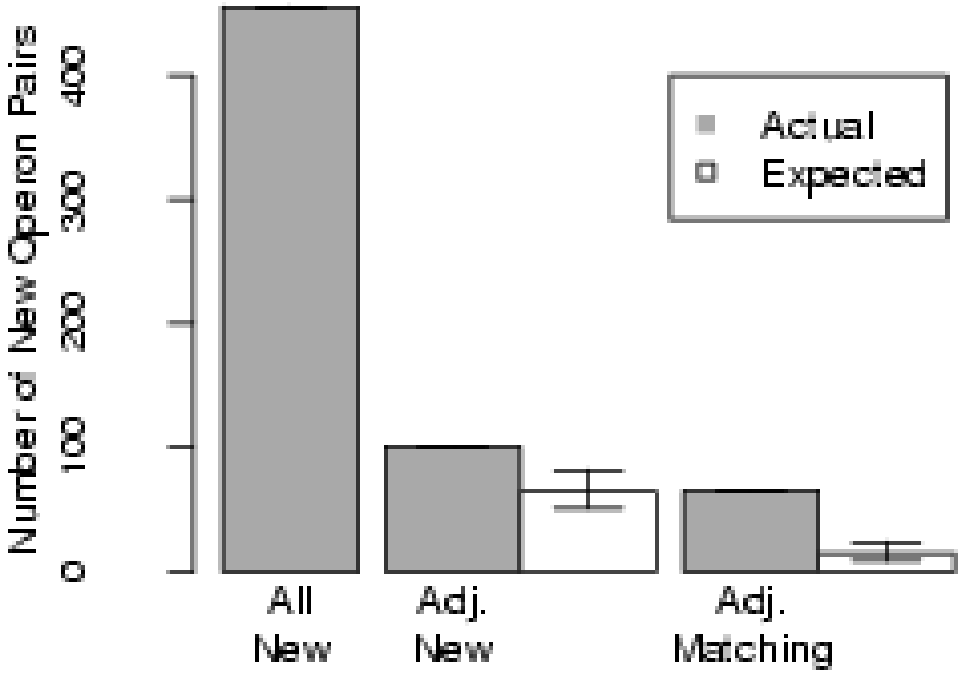
Modifications to Operons: Mechanisms





Accelerated Evolution of Some Operons

- Often see adjacent new pairs AB + BC = ABC
- The ages of AB and BC often match



Accelerated evolution implies positive selection?

Summary – The Birth of Operons

- Many Native-ORFan new operons
  - Formed by insertion of ORFan?
  - A way to express the ORFan?
- Native-Native pairs form by both deleting intervening genes and by rearrangement
  - Deletion highlights the chance nature of evolution
  - But related genes may already be clustered
- Rapid evolution of some operons
  - Multiple modifications in a short evolutionary time
  - Positive selection

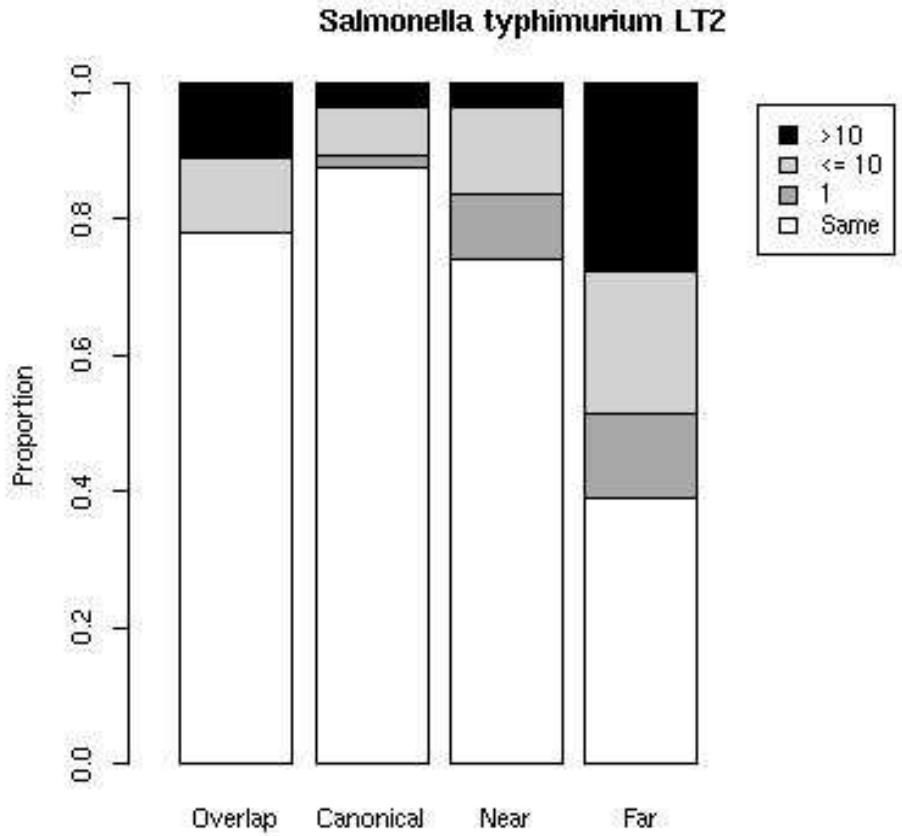
Operon Spacing

- Genes in operons tend to be close together
  - Primary way to predict operons
- Often the start and stop codons overlap ("canonical spacing")
  - TG***ATG*** ***ATG***A
- Deletion pressure or efficient translation?

Spacing Evolves Rapidly

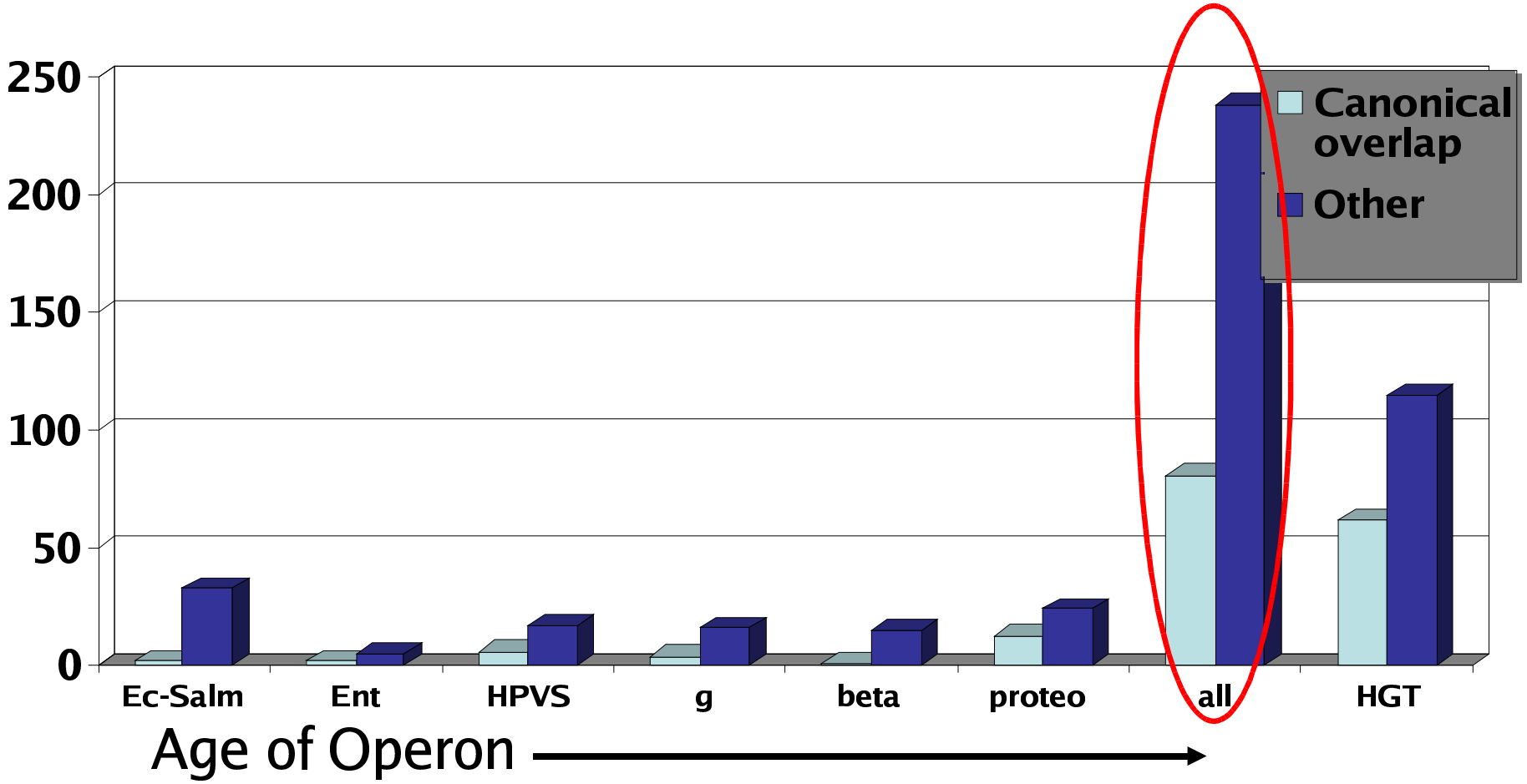
Often changes between *E. coli* and *Salmonella*

not under strong selection



Spacing in *E. coli*

Operon Spacing: Compaction over time?



Effect of deletion pressure?

Overlaps Can Easily Form by Deletion

Both canonical overlaps and greater overlaps, e.g.

rfaF-rfaC

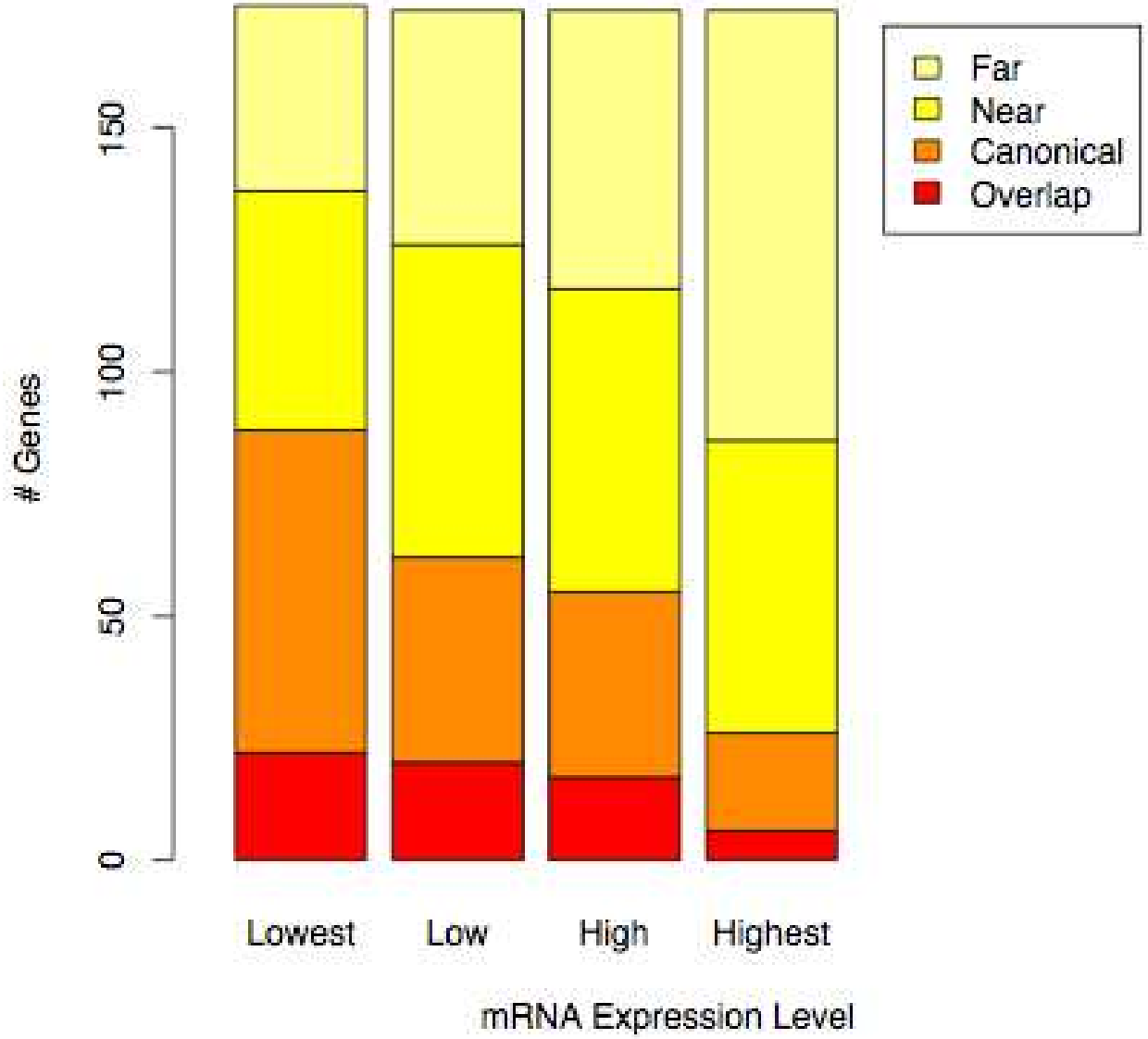
AAAtAATGGCGCTGCATGA *E. coli*

AAAc-ATGGCGCTGCATGA *Salmonella*

These deletions often cause small (neutral?) coding changes

Rarity of larger overlaps suggest selection against them

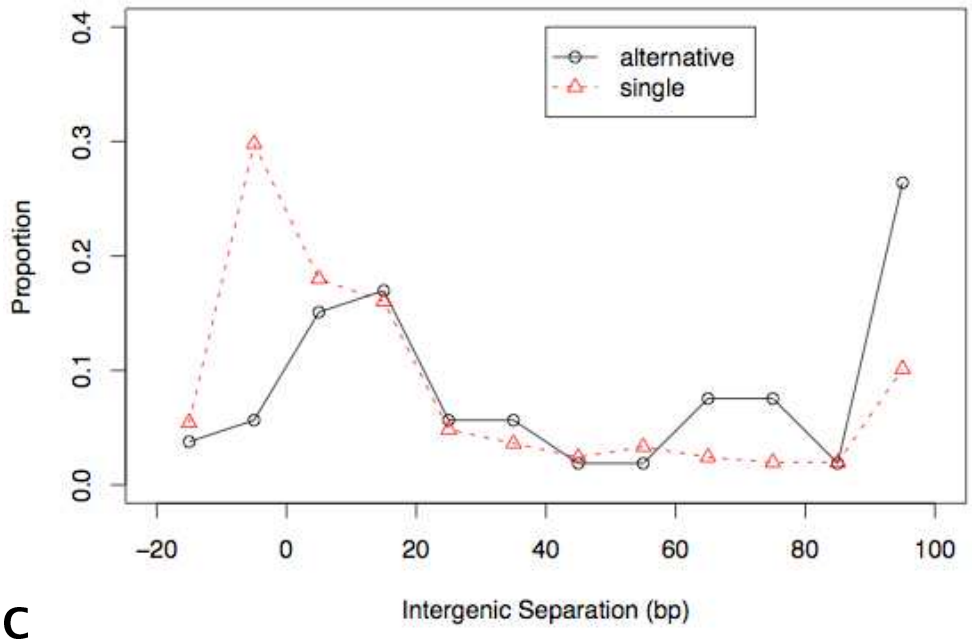
Highly Expressed Operons Often Have Wide Intergenic Spacings

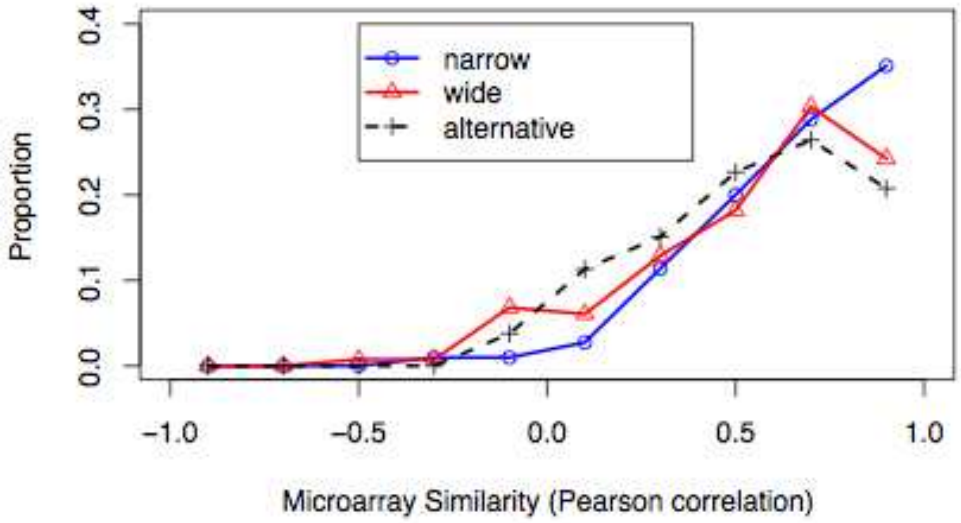


Known Alternative Transcripts Are Similar to 'Wide' Operons

47/156 'wide' operons have conserved intergenic footprints

13/15 manually inspected footprints were reported previously in the literature





Summary – Operon Spacing

- Separations evolve rapidly
  - May not be under strong selection
- Canonical overlaps form by deletion
  - Deletion pressure, perhaps efficient translation
- Larger overlaps form easily
  - Removed by selection
- Highly expressed operons have wide spacings to allow complex regulation
  - Stronger selection to regulate more highly expressed genes

Functional Significance of Operon Evolution

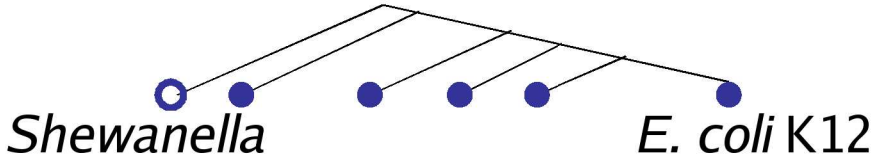
- Many new operons "make no sense" (contain genes in unrelated pathways)
- Operons are more likely to be conserved if they are functionally coherent
- New incoherent operons can be viewed as
  - Niche-specific adaptations
  - Neutral

Consequences of Operon Evolution

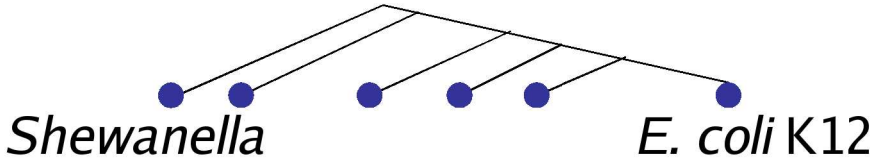
- Does operon formation or death lead to big changes in expression patterns?
  - Genes from highly conserved operons are coregulated even if the operon is split apart

- We can't study gene expression in ancestor, but we **can** study expression in close relatives

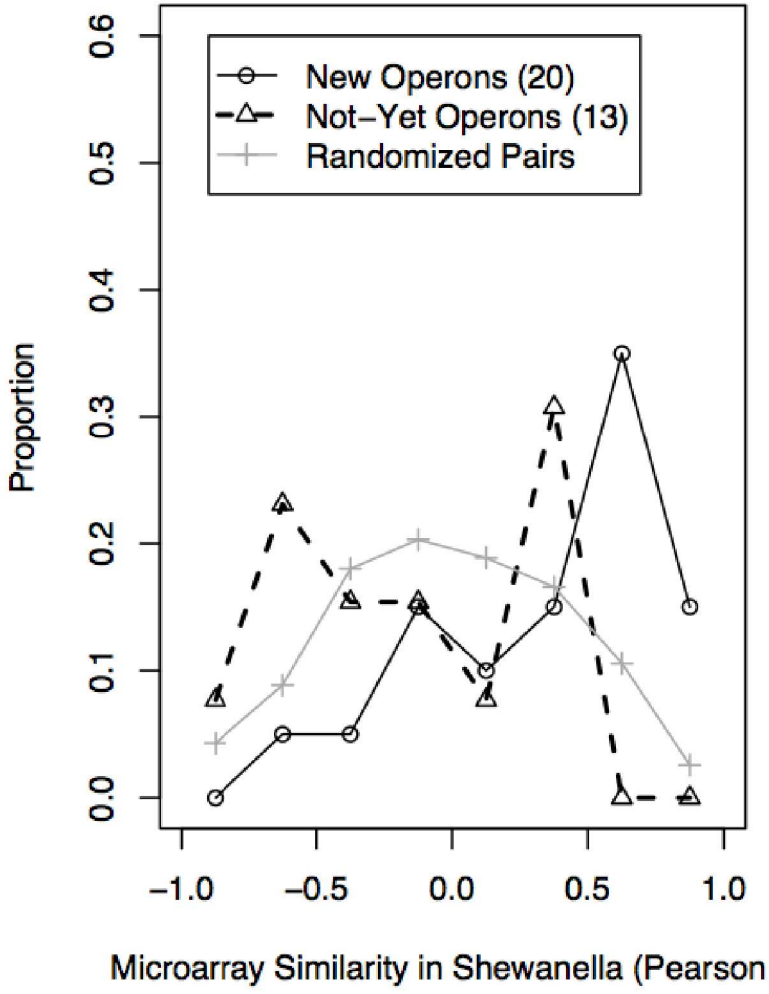
“Not-Yet” Operons Are Not Coexpressed



“Not-yet” operon

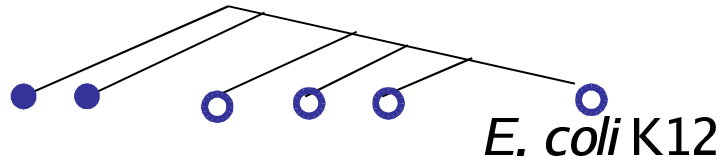


“Already” operon

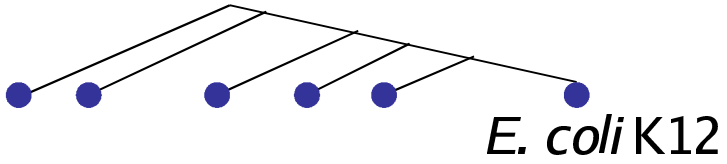


Operon formation has a big effect

Dead Operons Are Weakly Coexrpressed

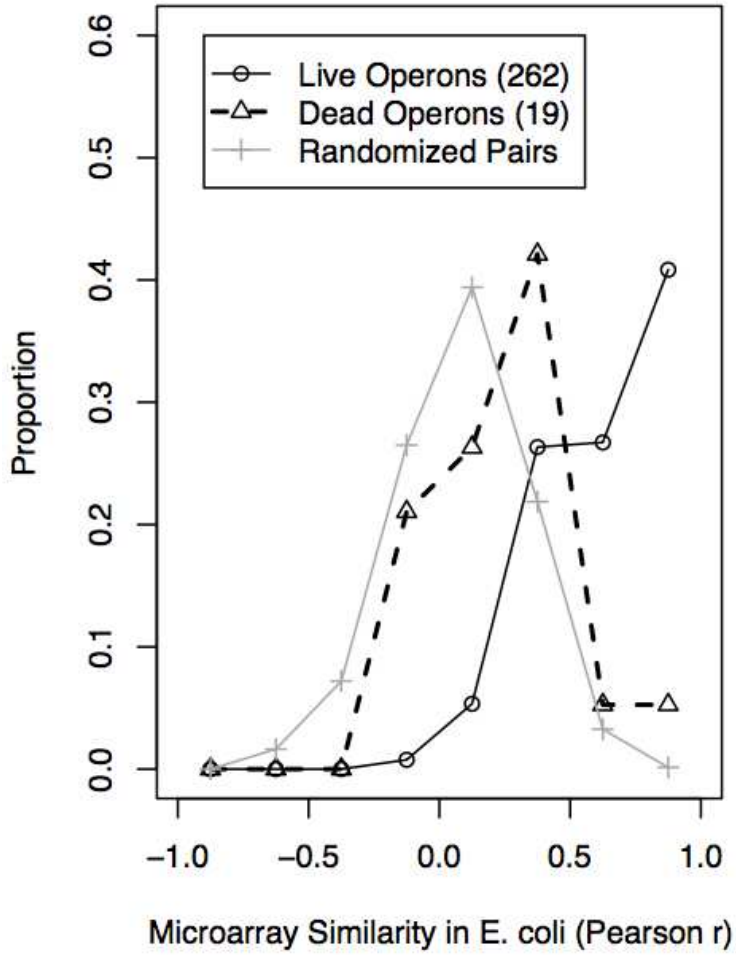


Dead operon



Live operon

Can only identify conserved dead operons => more functionally related than new operon pairs

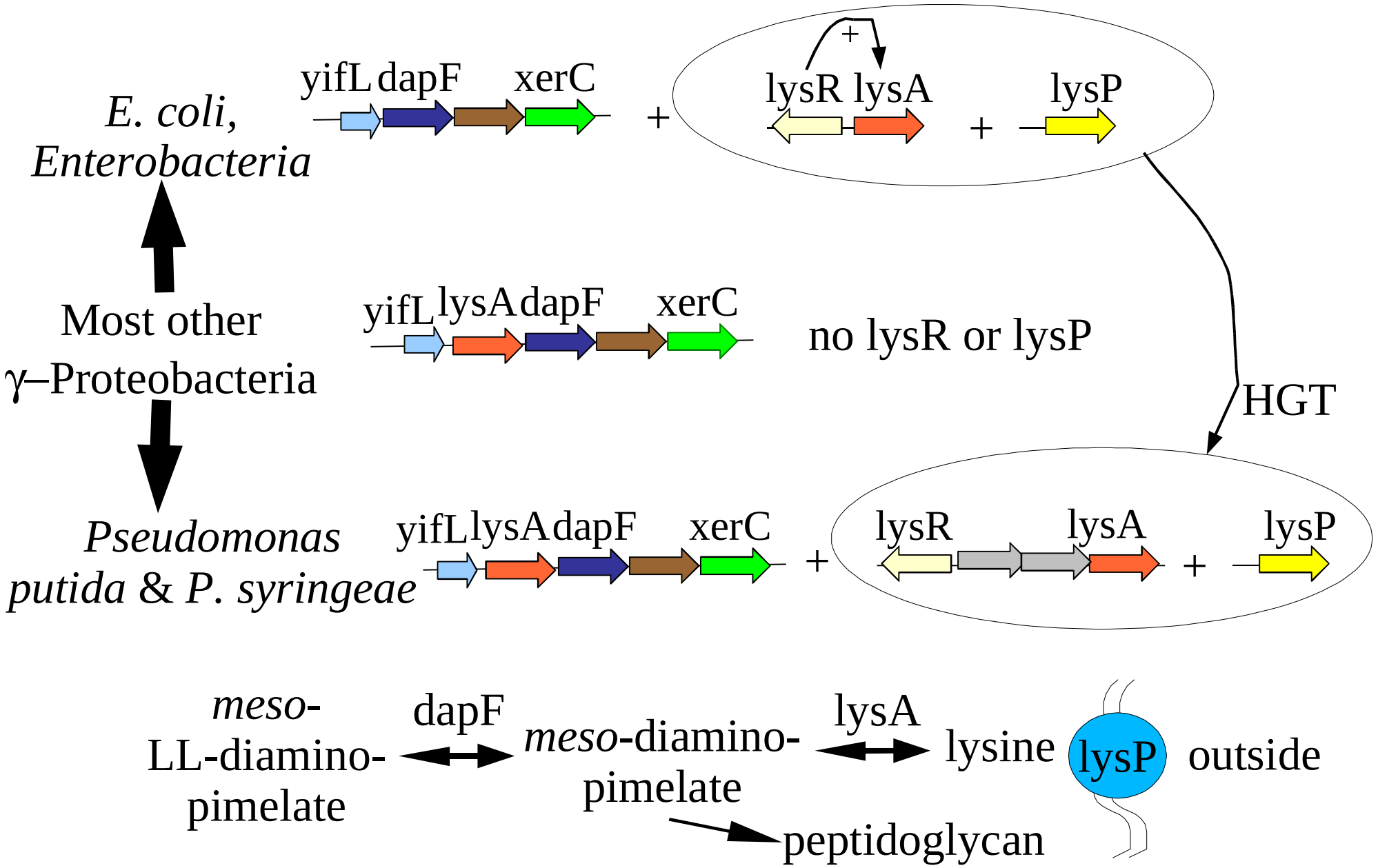


Operon death has a big effect

Summary – Consequences of Operon Evolution

- Operon evolution has large effects on expression patterns
- Gene expression is under strong selection
  - Most *E. coli* regulatory sequences are under strong negative selection
  - The complexity of gene regulation suggests strong positive selection
- Operon evolution is probably under strong selection
  - many less-conserved operons are niche-specific adaptations

lysA-dapF – A Niche-Specific Operon?



Conclusions: The Life Cycle of Operons