Workshop on Genomics
Český Krumlov, May 22 2023

Comparative Genomics - Morning Session: 09:00-12:00

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UNIL | Université de Lausanne

Swiss Institute of Bioinformatics

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SWISS NATIONAL SCIENCE FOUNDATION

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Instructor Biography-Introduction

2017-	SNF Assistant Professor University of Lausanne	
2015-16	Marie Curie Fellow & Maître assistant University of Geneva *ZDOBNOV*	
2013-14	Marie Curie Outgoing Fellow Massachusetts Institute of Technology *KELLIS*	
2009-12	Postdoctoral Researcher University of Geneva *ZDOBNOV*	
2005-09	Wellcome Trust PhD Imperial College London *CHRISTOPHIDES*	
2004-05	Wellcome Trust MSc Bioinformatics Imperial College London	
2000-04	MBioch Biochemistry University of Oxford	

Instructor Biography-Introduction

OrthoDB

BUSCO

Arthropod Evolutionary Genomics
Insect Immunity Gene Evolution

Orthology Delineation
Quality Assessments

i5k Arthropod Genomics Community

Coordinating the sequencing and analysis of
5'000 insects and other arthropods

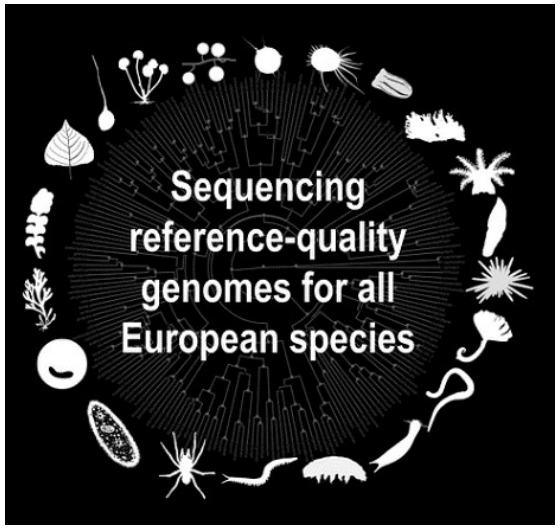
If you use genomics to study arthropods,
you are an i5k member!

i5k pilot project: 28 species
Gene content evolution in the arthropods
Genome Biology 2020

A diverse international group of researchers
Join the community on the i5k Slack Workspace: bit.ly/artgen20

The European Reference Genome Atlas ERGA

EUROPEAN REFERENCE GENOME ATLAS



Coordinating the sequencing and analysis of European eukaryote species

If you are building genome resources for European eukaryotes, you should join!

ERGA Pilot Project: 98 species

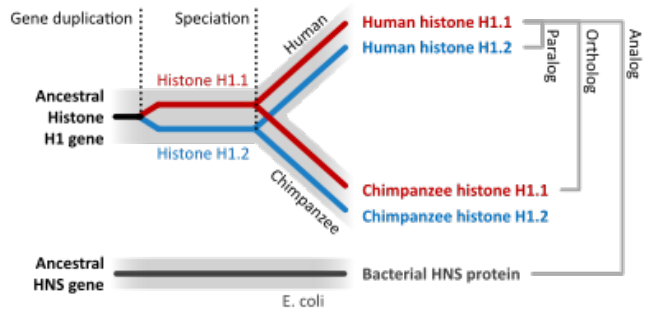
A distributed model of genome generation across 34 countries in Europe

A diverse group of researchers in Europe

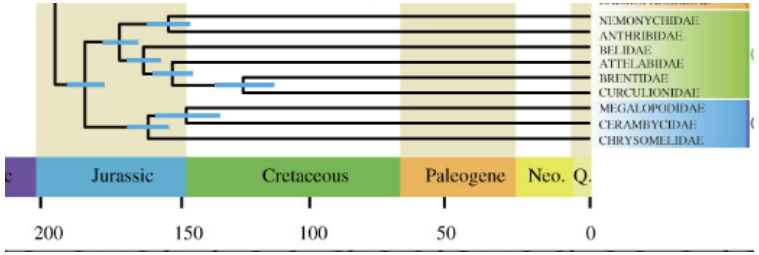
Join the community: www.erga-biodiversity.eu

Comparative Genomics Hands-On: Concepts and Applications

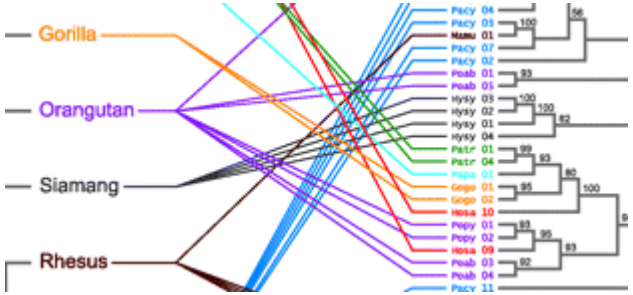
Orthology delineation



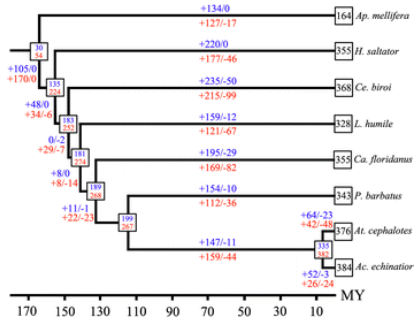
Species tree estimation



Gene-tree–species-tree reconciliation

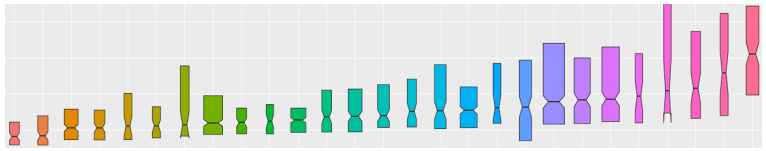


Gene ancestral state reconstruction

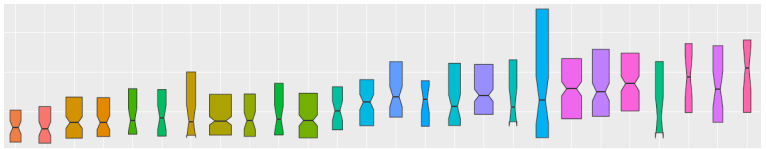


CompGeno: gene family evolutionary dynamics

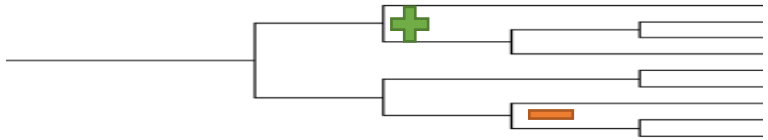
Protein Sequence Divergence



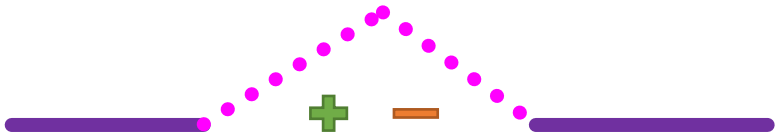
DNA Selection/Constraint



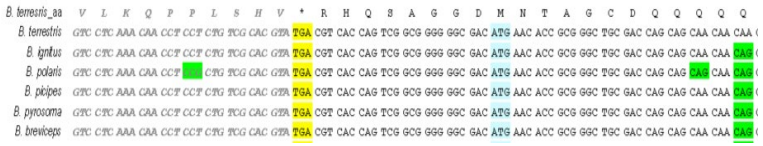
Gene Gain/Loss Rates



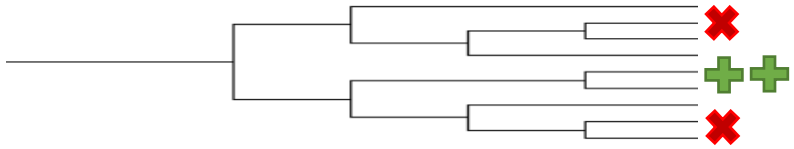
Intron Gain/Loss Rates



Stop-Codon Readthrough



Copy-Number/Universality



Comprehensive quantifications using multiple complementary approaches distinguish conserved/stable from divergent/dynamic gene families

Orthology Delineation

What is orthology?

How do we delineate orthologs?

And why do we need to?
(species/gene trees)

Orthology – what is it?

Homology

Orthology

Orthology – what is it?

Homology

"designates a relationship of **common descent** between any entities, without further specification of the evolutionary scenario"

Orthologs, Paralogs, and Evolutionary Genomics[1]

Eugene V. Koonin

Annu. Rev. Genet. 2005. 39:309–38

Orthology – what is it?

"genes originating from a single ancestral gene in the last common ancestor of the compared genomes"

Orthology

Orthologs, Paralogs, and Evolutionary Genomics[1]

Eugene V. Koonin

Annu. Rev. Genet. 2005. 39:309–38

Orthology – what is it?

"paralogs are
genes related via duplication"

Paralogy

Orthologs, Paralogs, and Evolutionary Genomics[1]

Eugene V. Koonin

Annu. Rev. Genet.
2005. 39:309–38

Orthology – what is it?

Homologs

Common Ancestor

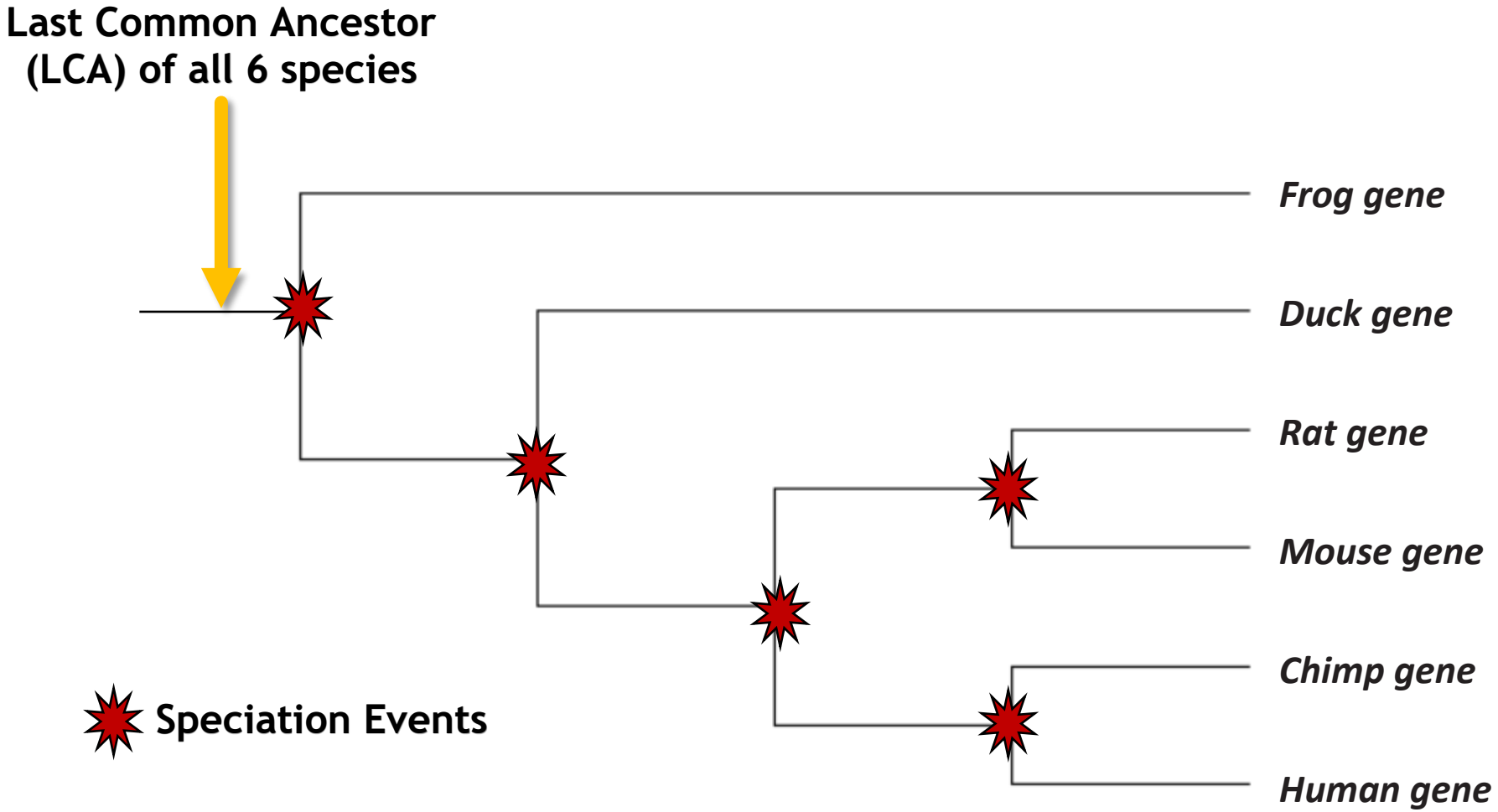
Orthologs

Speciation Event

Paralogs

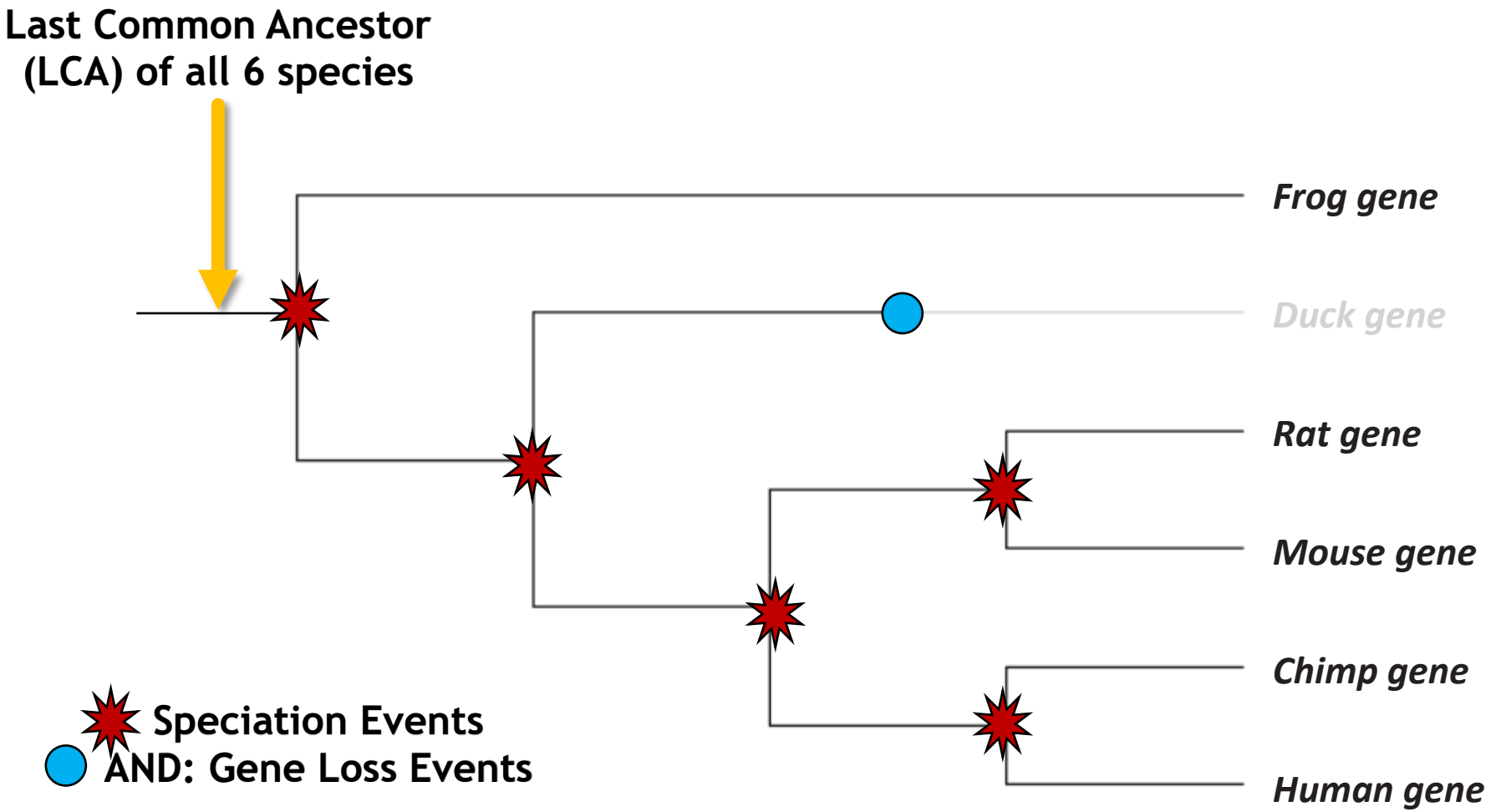
Duplication Event

Orthology – simple scenario



Single-Copy Orthologs

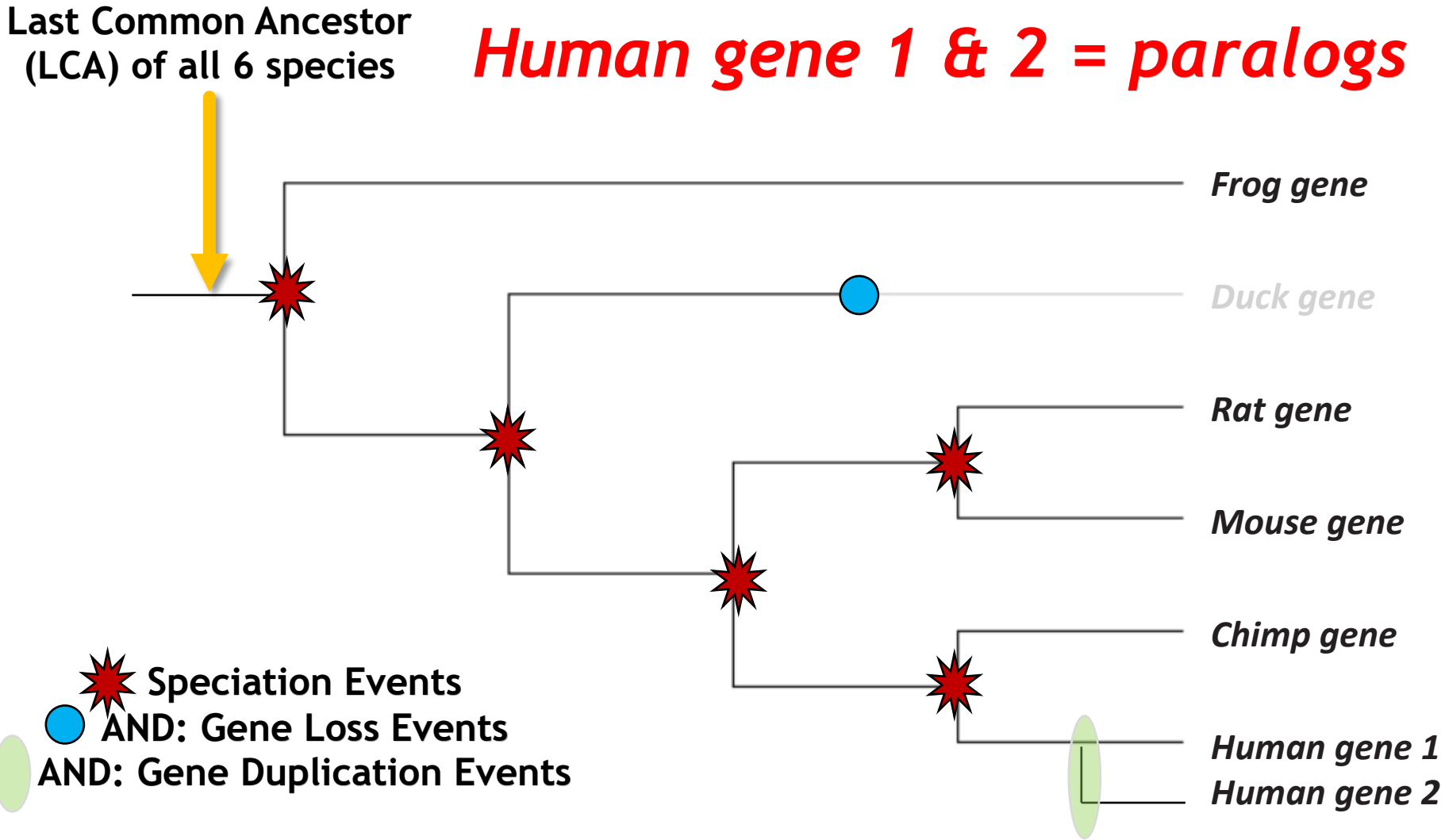
Evolution ≠ simple



Single-Copy Orthologs with Losses

Evolution ≠ simple

Human gene 1 & 2 = paralogs

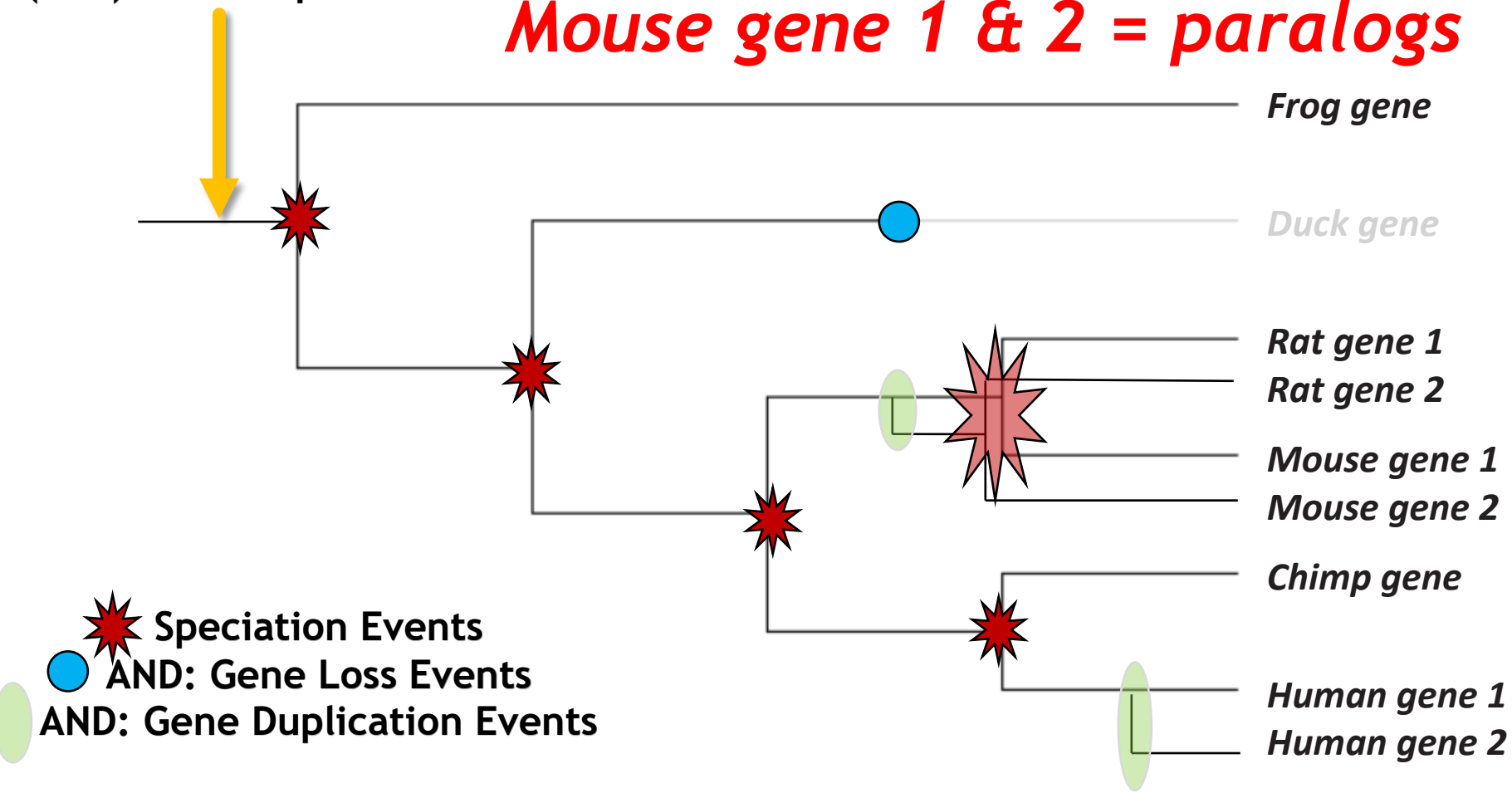


Single-Copy Orthologs with Gains

Evolution ≠ simple

Rat gene 1 & 2 = paralogs

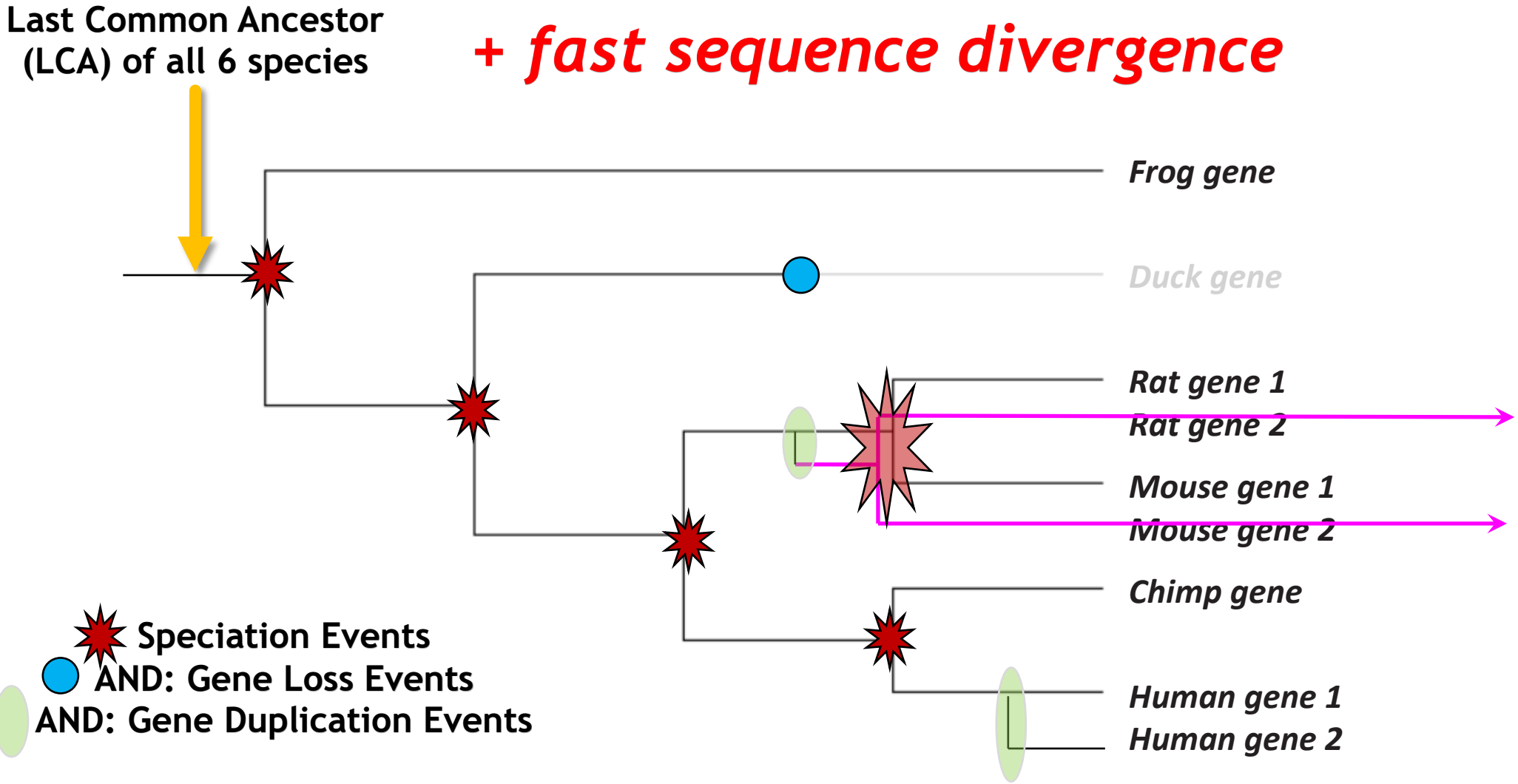
Mouse gene 1 & 2 = paralogs



Single-Copy Orthologs with Gains

Evolution ≠ simple

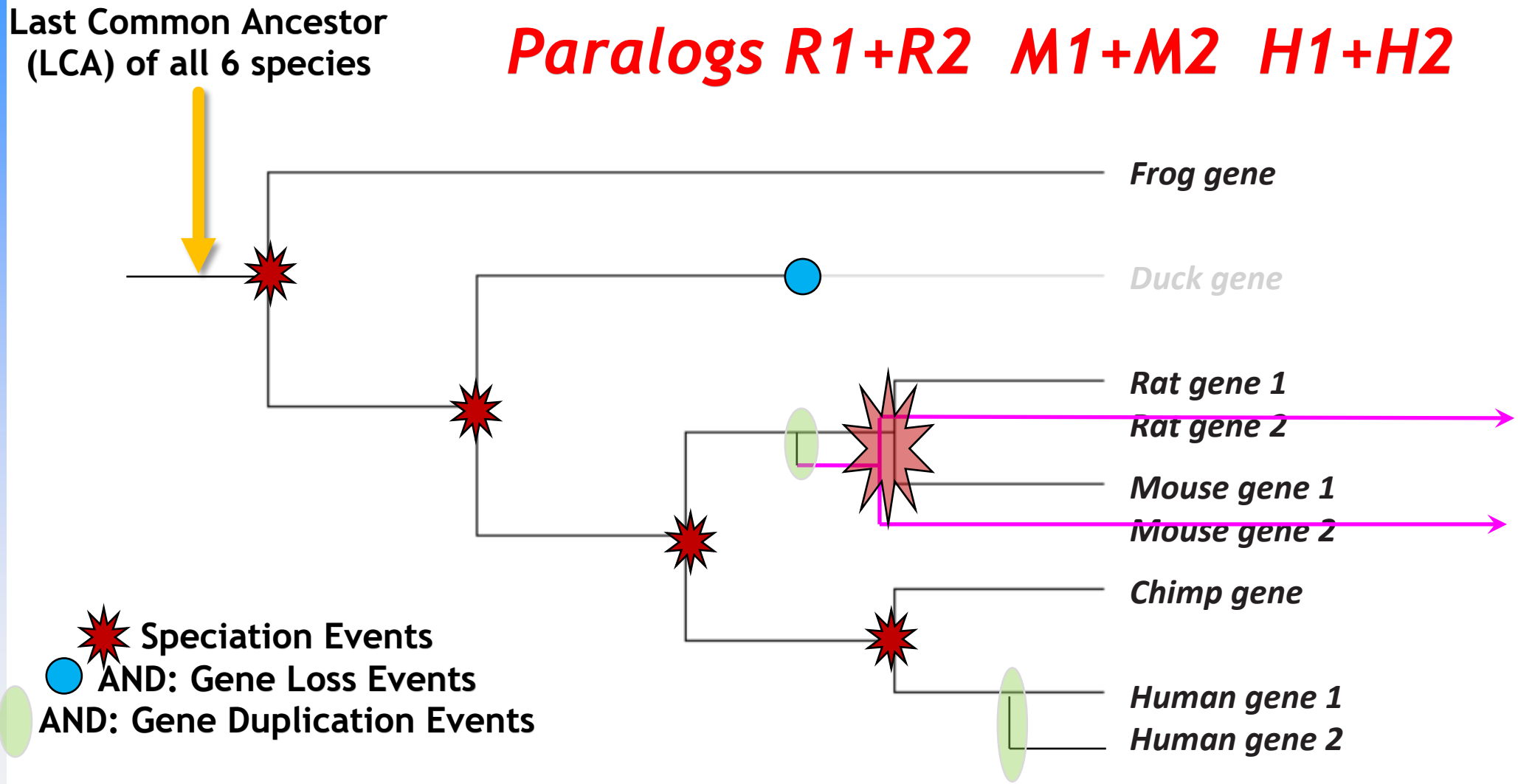
+ fast sequence divergence



Single-Copy Orthologs with Gains

Evolution ≠ simple

Paralogs R1+R2 M1+M2 H1+H2



Orthologs F+R1+R2+M1+M2+C+H1+H2

Orthology – what is it?

Homology

Recognizing similarities as evidence of shared ancestry

Orthology

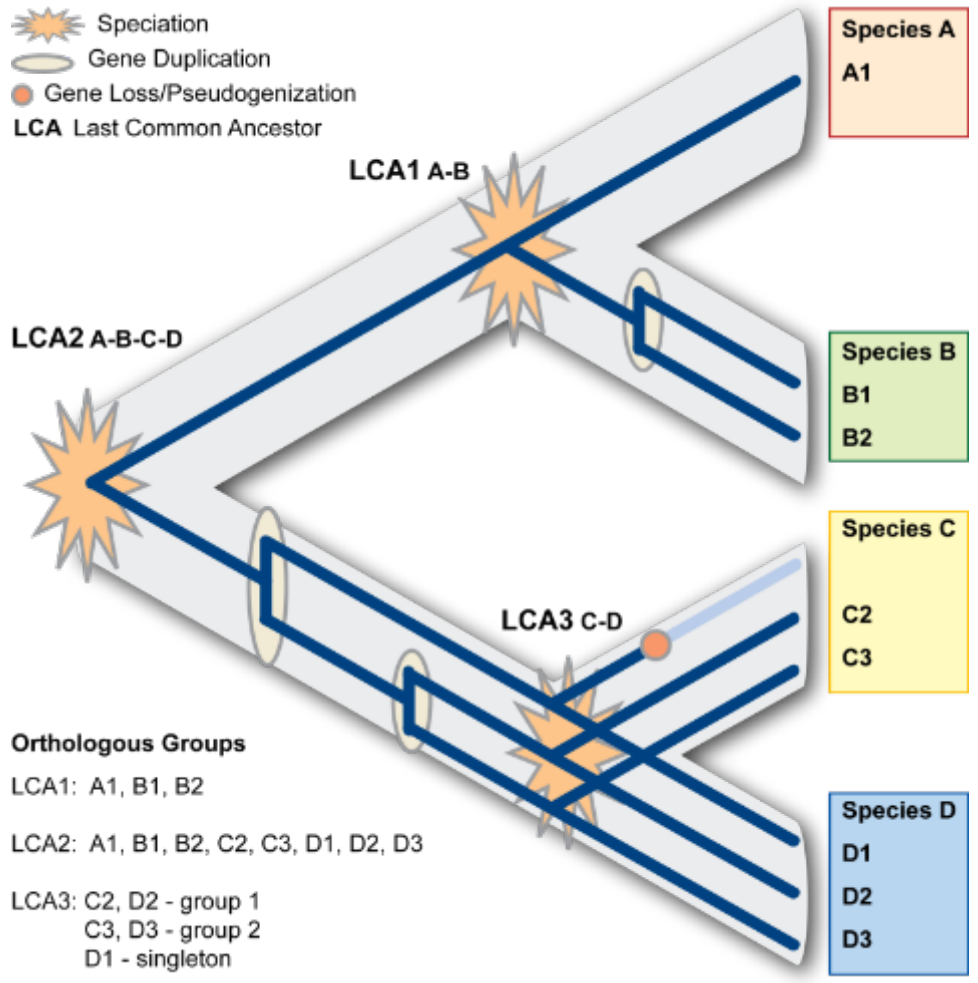
Orthologues arise by vertical descent from a single gene of the last common ancestor

Hierarchy

Orthology is relative to the species radiation under consideration

Orthologous Groups

All genes descended from a single gene of the last common ancestor



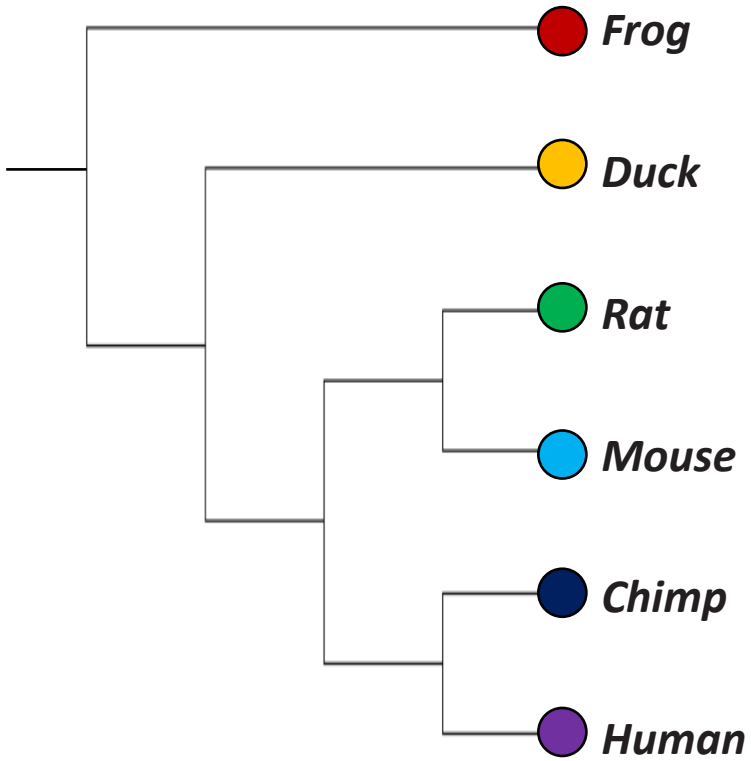
Nucleic Acids Research

OrthoDB: the hierarchical catalog of eukaryotic orthologs in 2011

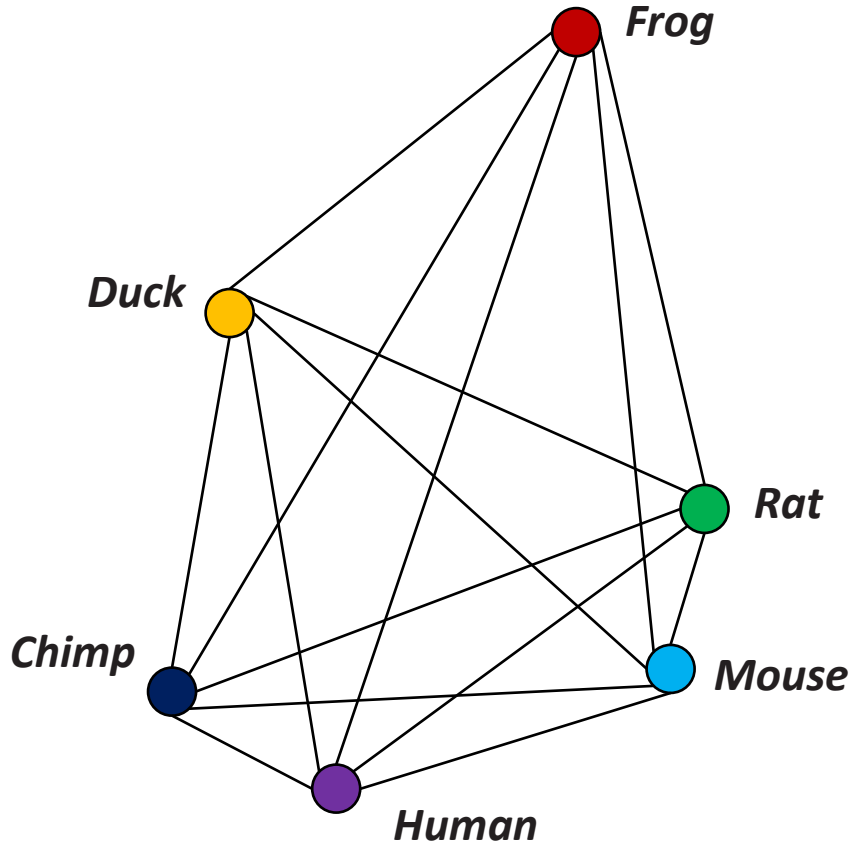
Robert M. Waterhouse[1,2], Evgeny M. Zdobnov[1,2,3], Fredrik Tegenfeldt[1,2], Jia Li[1,2] and Evgenia V. Kriventseva[1,2,*]

How do we delineate Orthology?

tree-based approaches

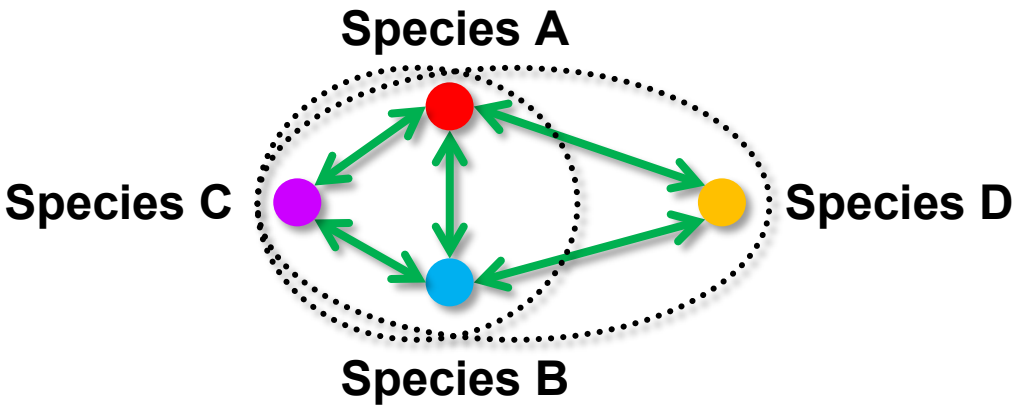


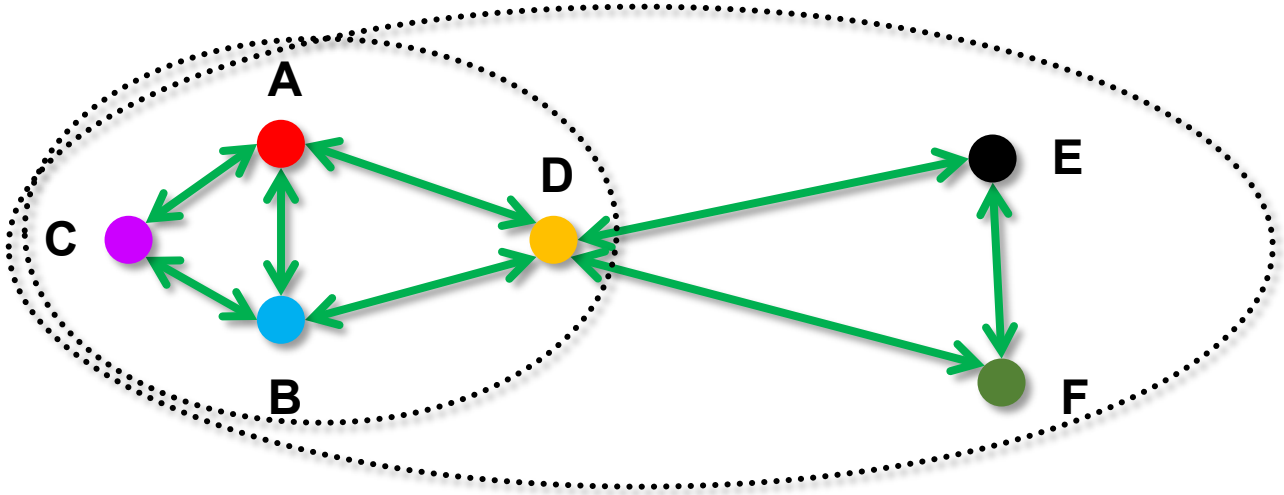
graph-based approaches



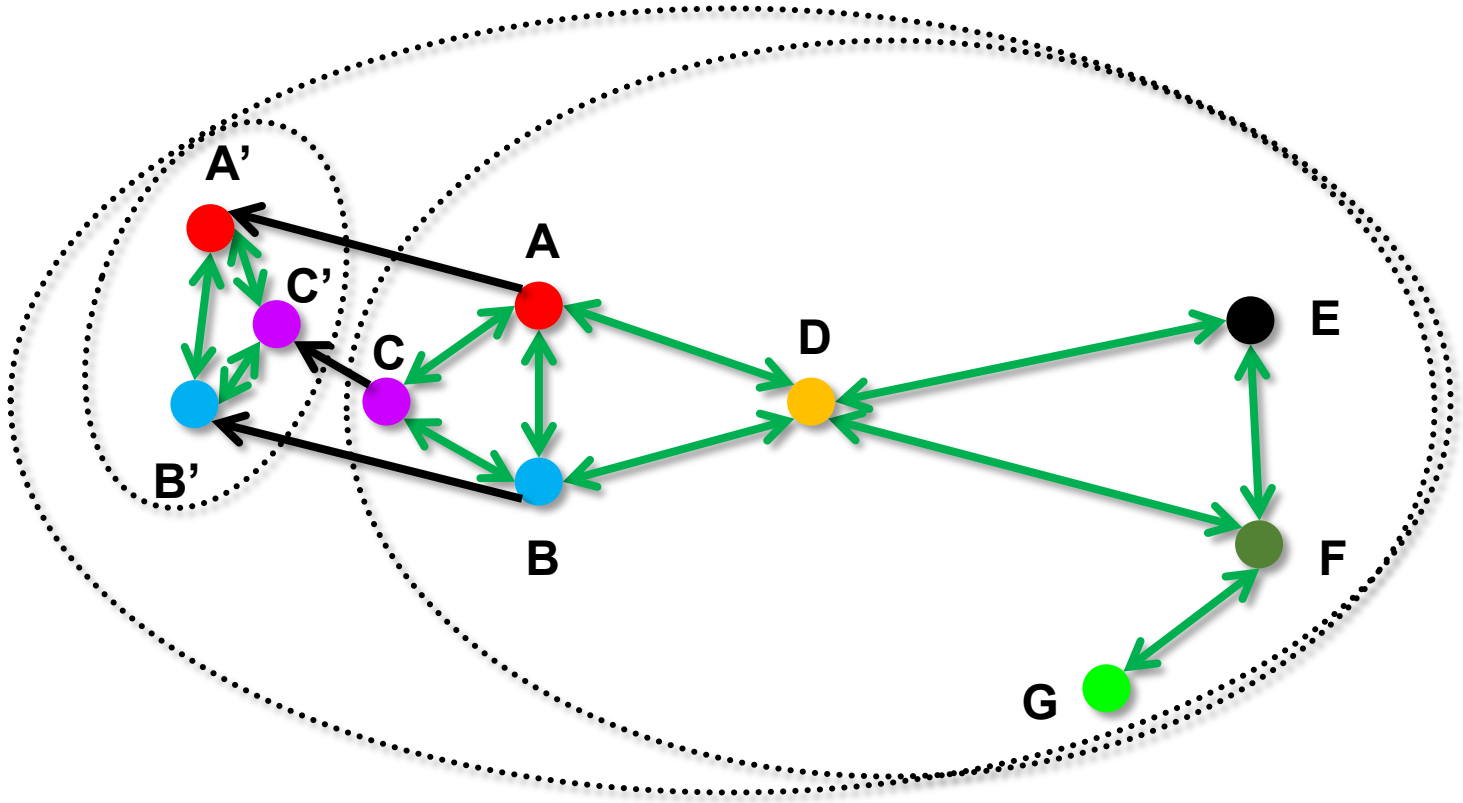
Single-Copy Orthologs

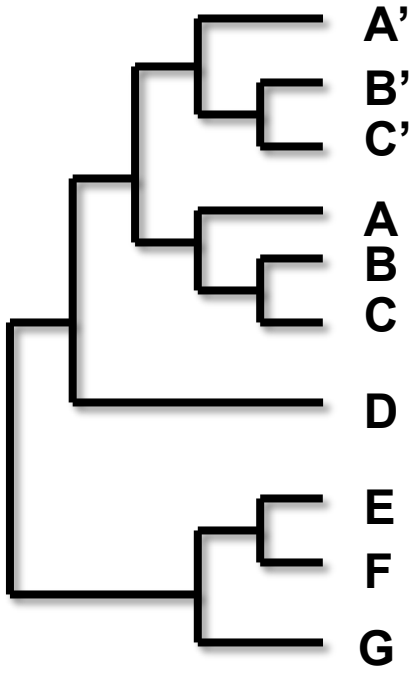
Graph-based best-reciprocal-hits





Within-clade duplications





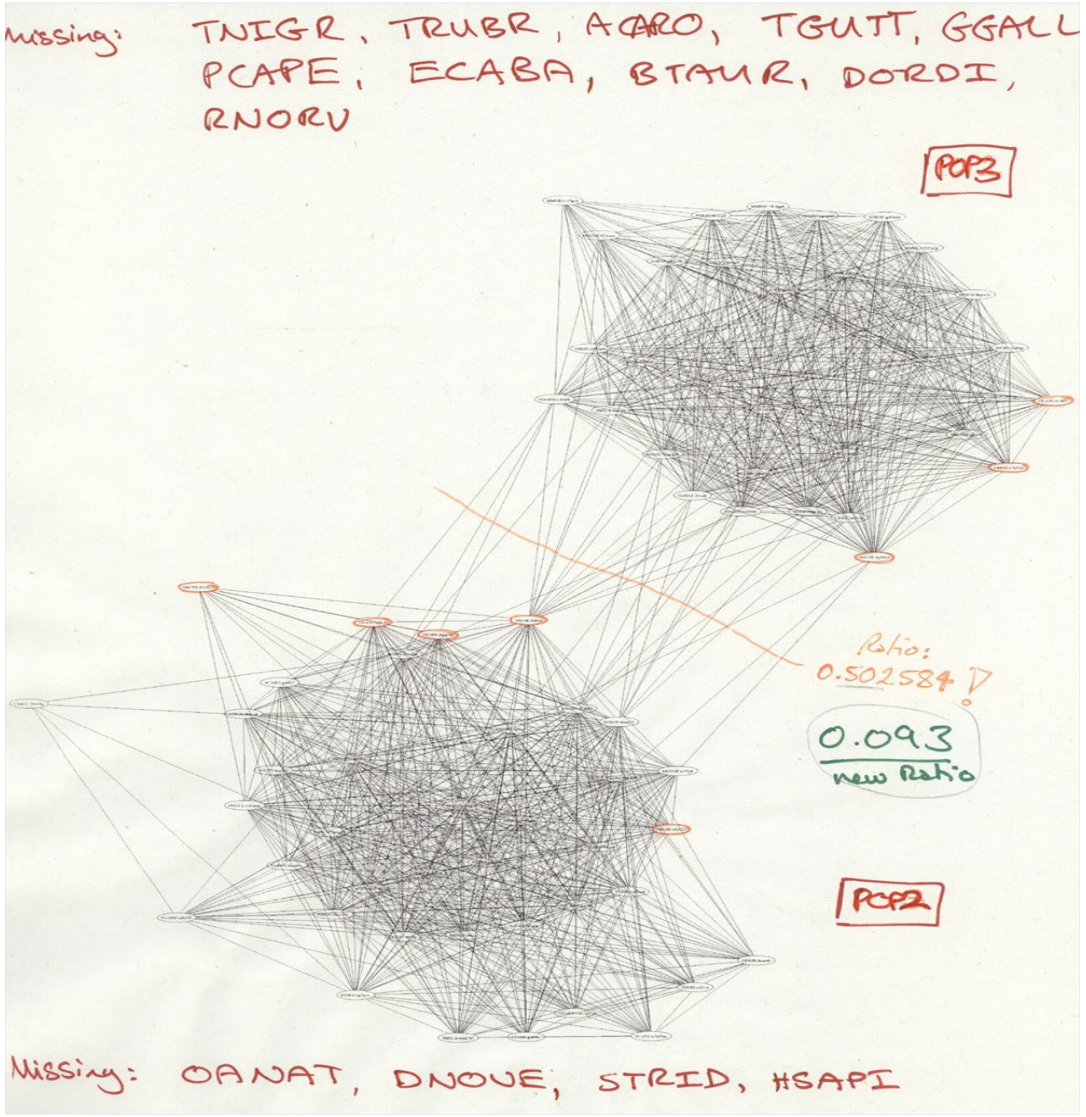
Real-world data can be messy!

Real example:

POP3 missing from 10 vertebrates

POP2 missing from 4 vertebrates

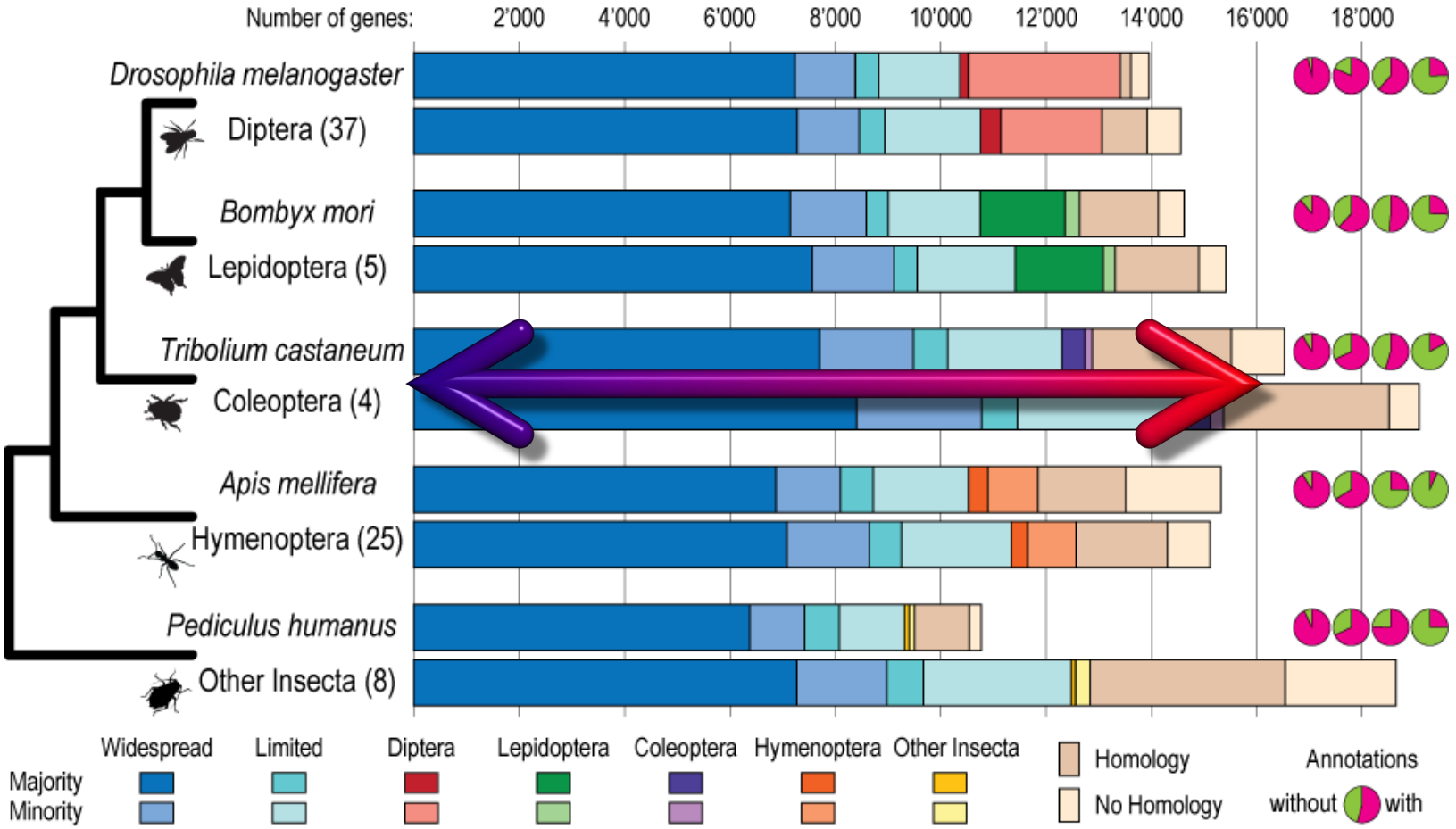
Two orthologous groups start to merge into one



Orthology – why do we need it?

1) Tracing the **Evolutionary Histories** of all genes in extant species

2) Building **Hypotheses on Gene Function** informed by evolution



Orthology ≠ Function … BUT …

By tracing the **Evolutionary Histories** of all genes in extant species

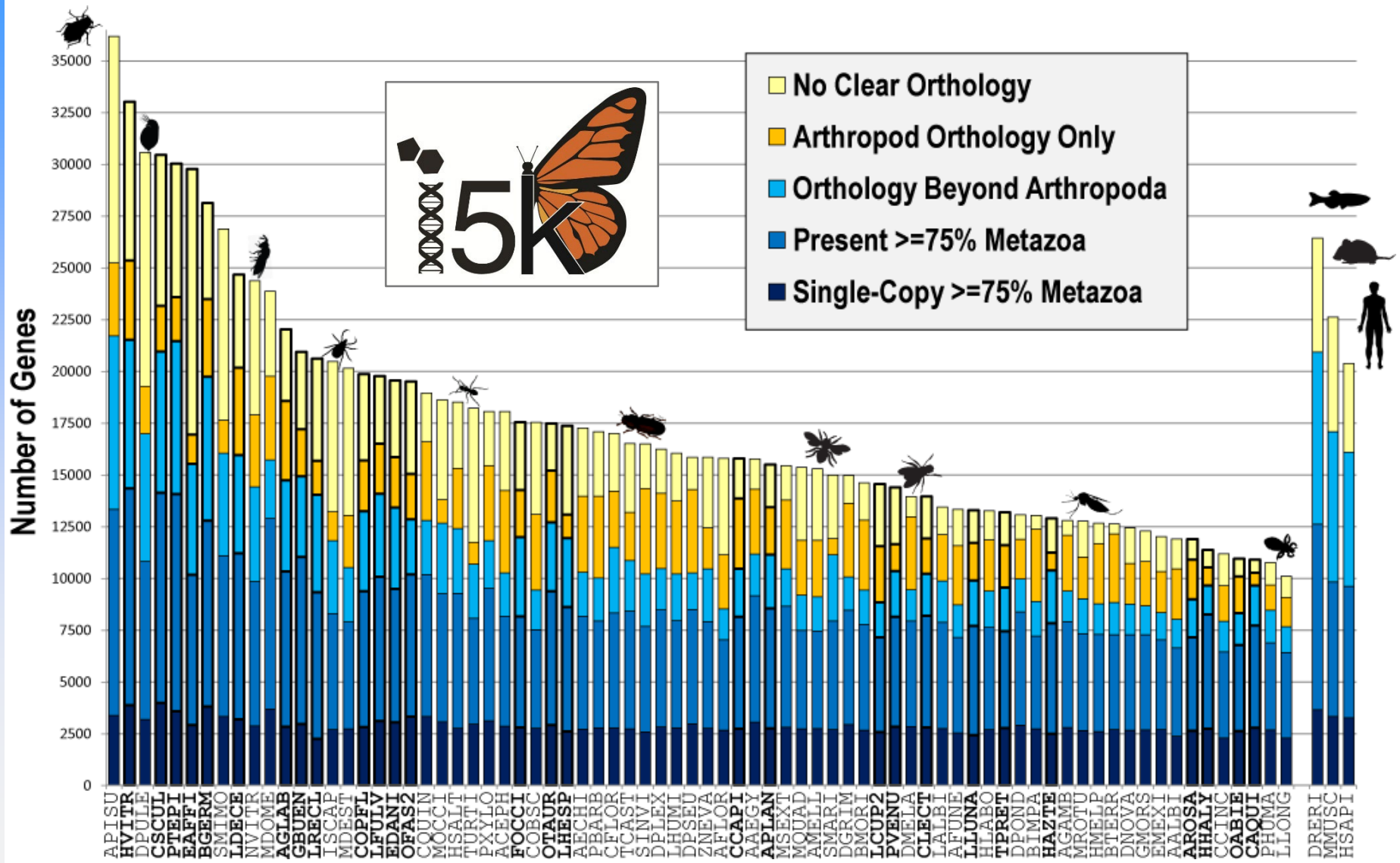
We can build **Hypotheses on Gene Function** informed by evolution

"validity of the conjecture on **functional equivalency** of orthologs is crucial for reliable annotation of newly sequenced genomes and, more generally, for the progress of functional genomics.

The huge majority of genes in the sequenced genomes will **never be studied experimentally**, so for most genomes **transfer of functional information** between orthologs is the only means of detailed functional characterization."

Annu. Rev. Genet.
2005. 39:309–38

Evolutionary histories: classes



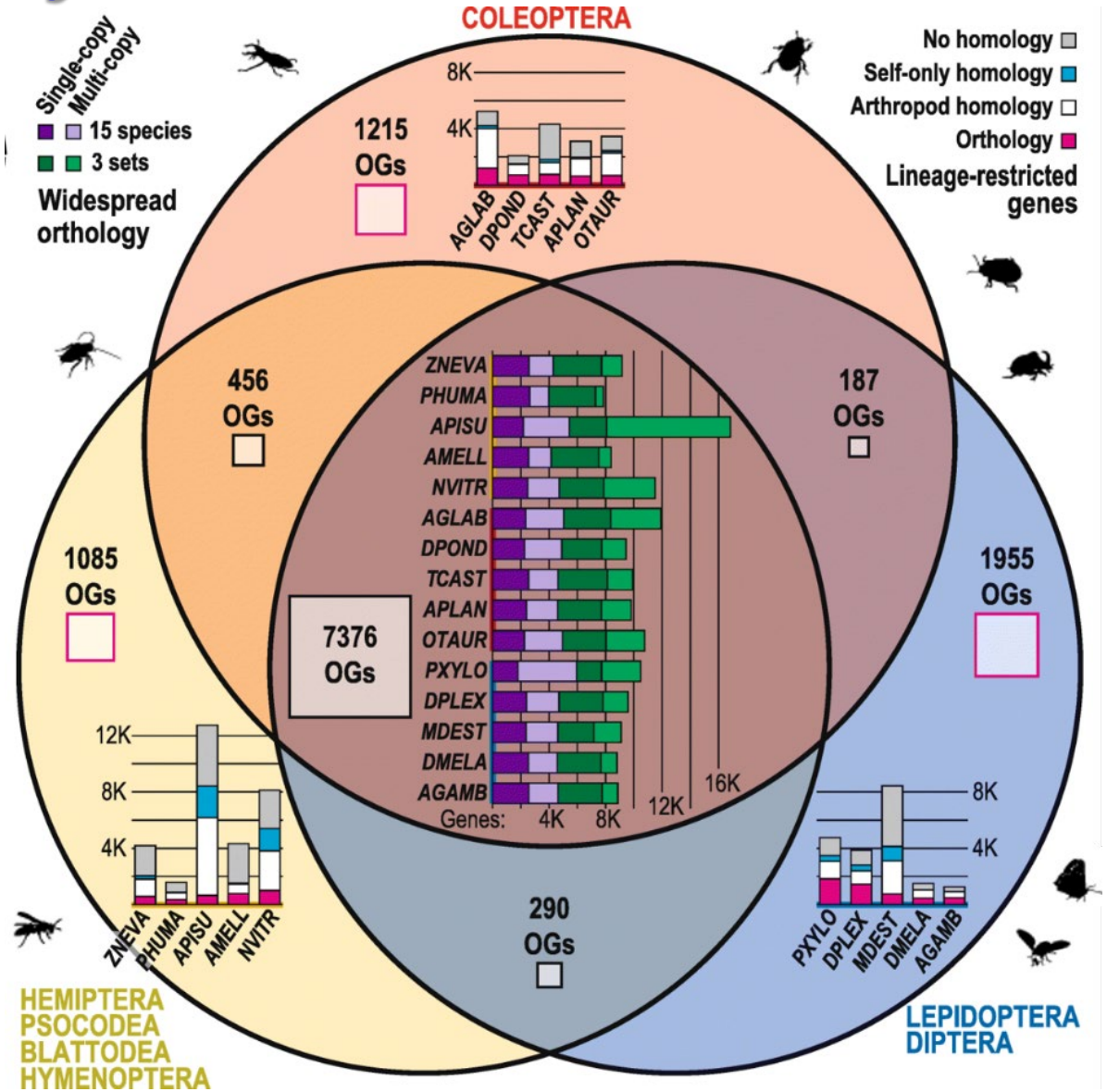
Unique

Variable

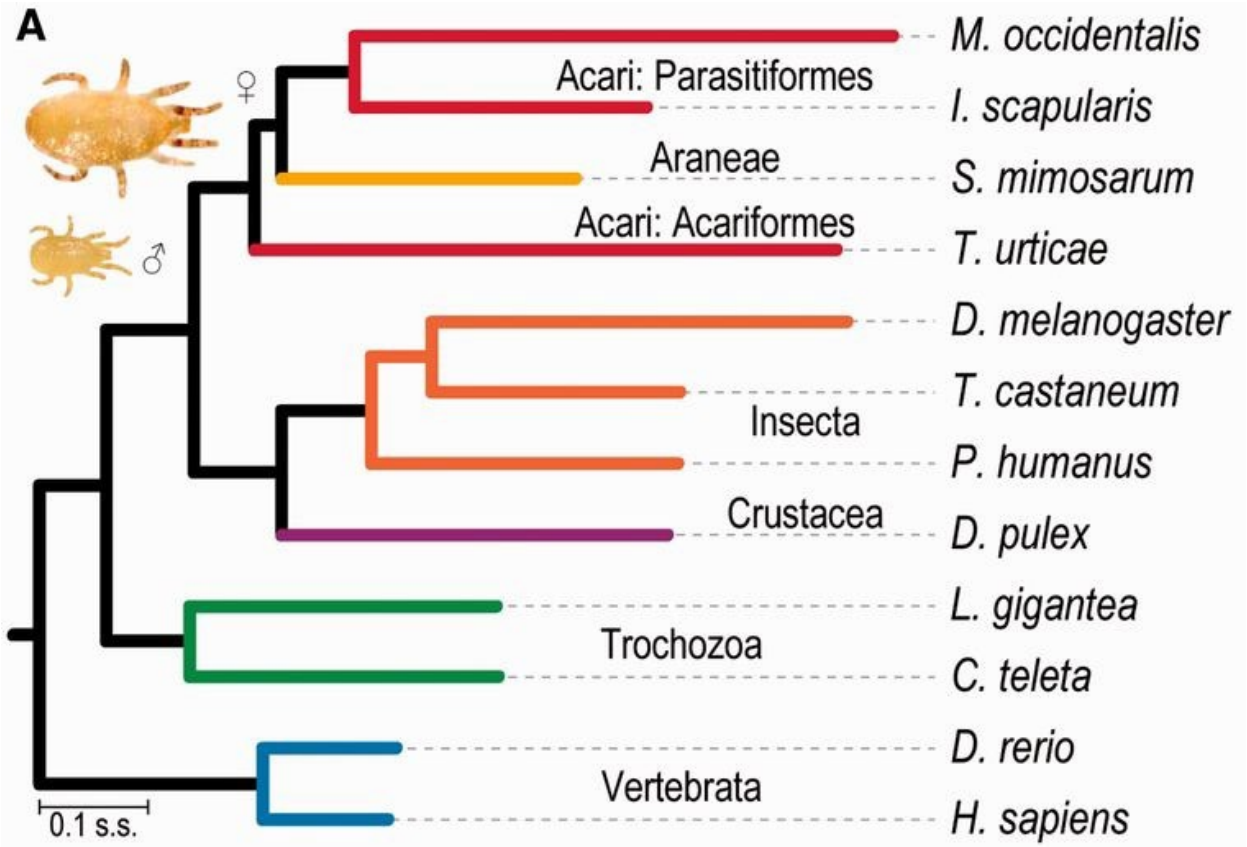
Common

Evolutionary histories: classes

Clade-specific
& variable-count
orthologues

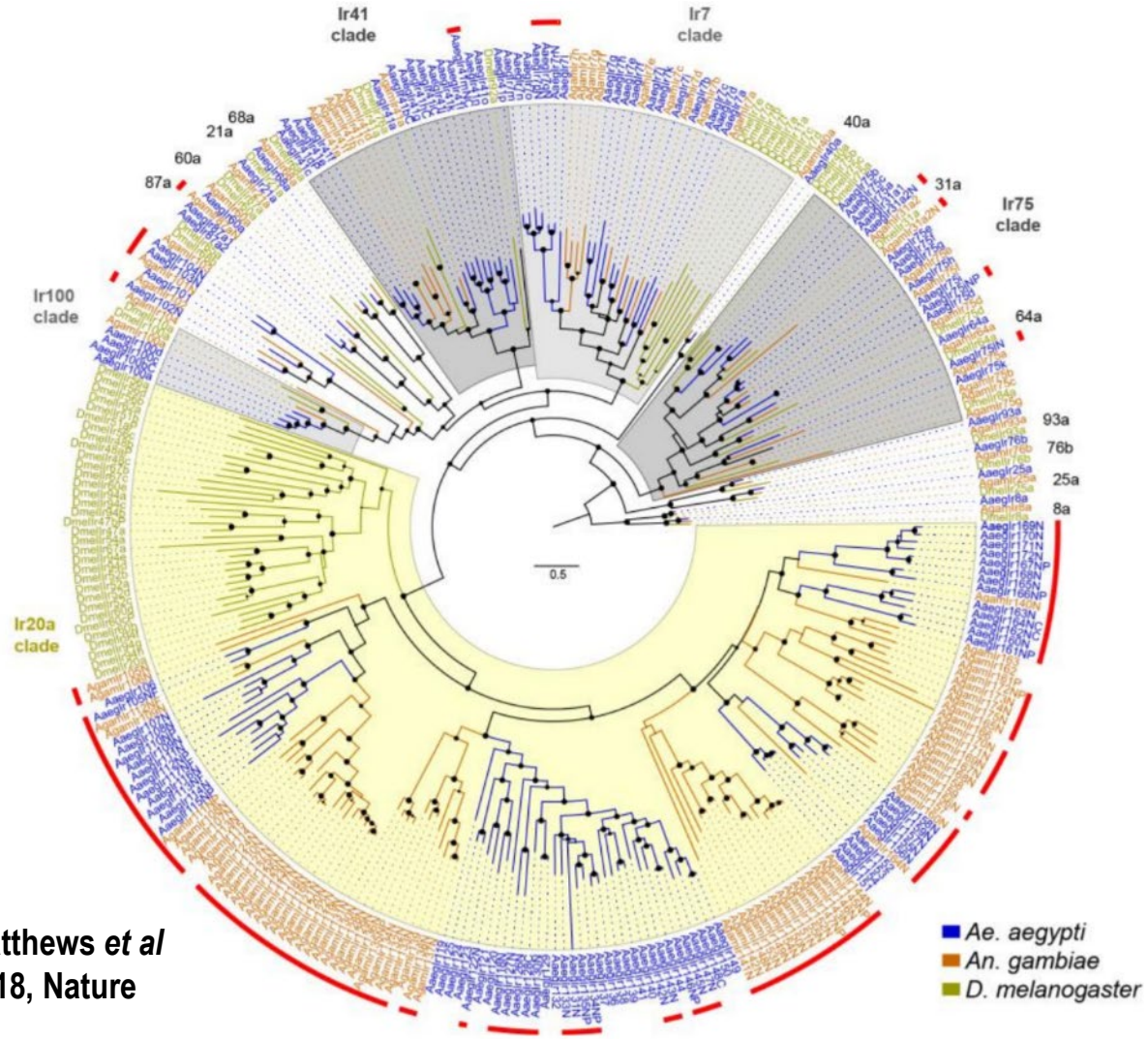


Species Tree Estimation



Phylogenomics with single-copy orthologues

Gene Family Tree Building

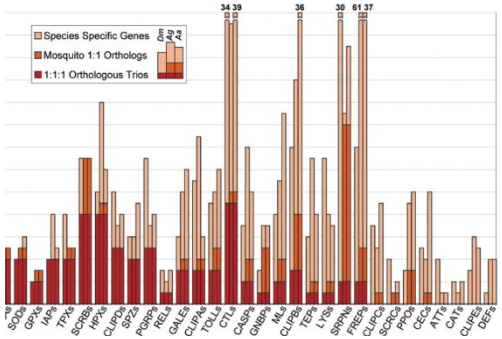


Matthews *et al*
2018, Nature

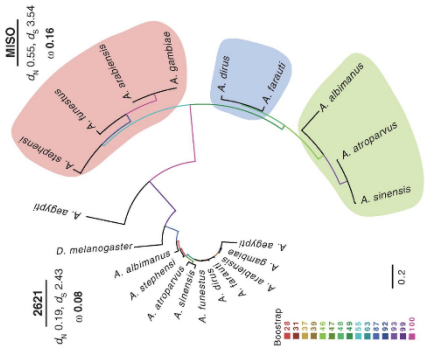
Dynamically evolving families

Many of the most biologically interesting genes and gene families show highly dynamic evolutionary histories

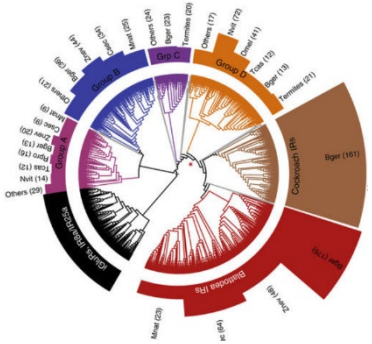
IMMUNITY



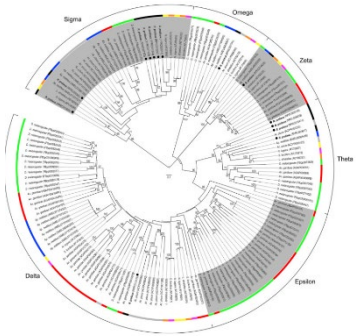
REPRODUCTION



CHEMOSENSATION

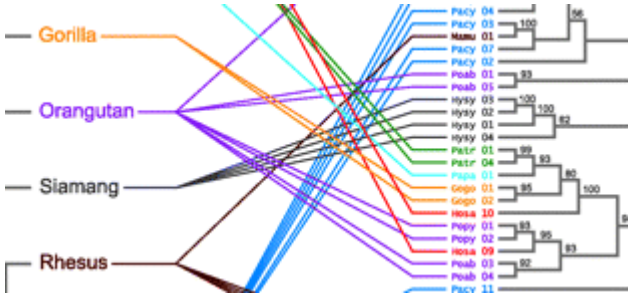


DETOXIFICATION

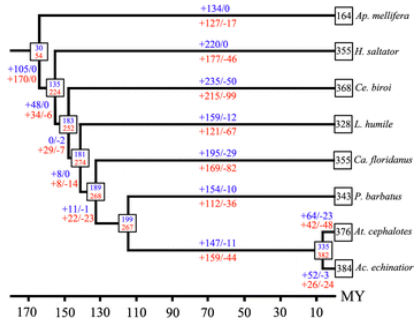


Inferring gene evolutionary histories

Gene-tree–species-tree reconciliation



Gene ancestral state reconstruction



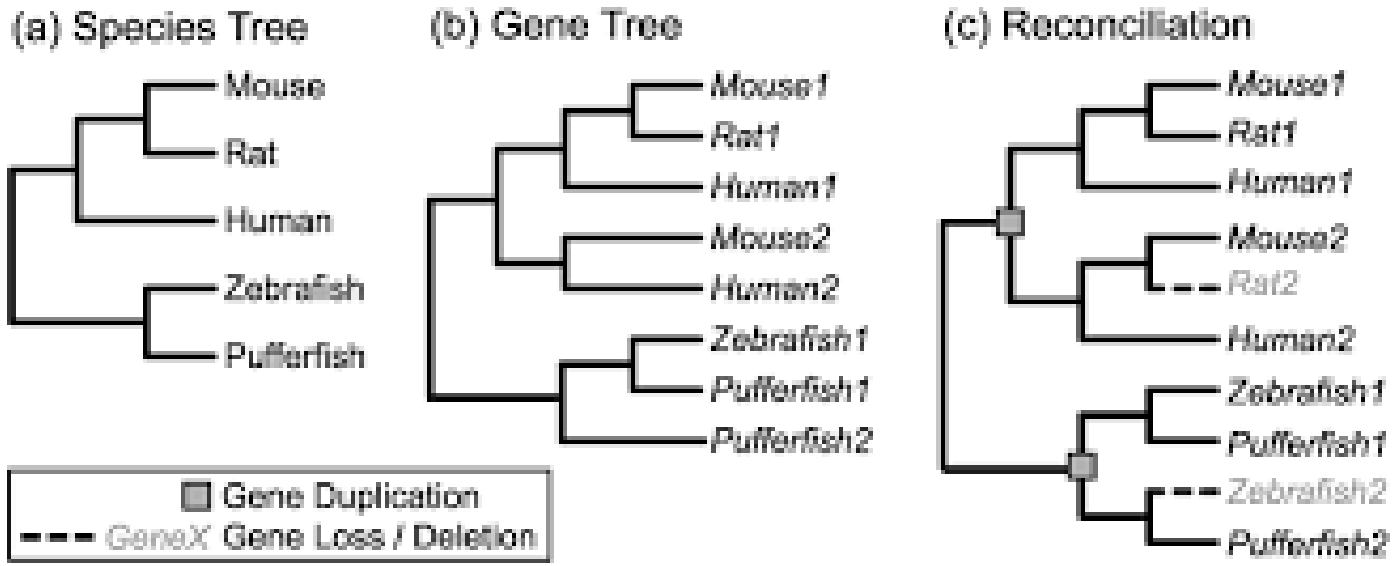
INPUTS

- Confident species phylogeny
- Individual gene trees
  - From orthologous groups
  - From homologous gene families

- Confident species phylogeny
- Counts of orthologues per species
  - From orthologous groups
  - From homologous gene families

Gene-tree-species-tree reconciliation

A gene tree-species tree reconciliation explains the evolution of a gene tree within the species tree given a model of gene-family evolution



Given all possible duplication and loss events that are compatible

- Compute the minimum "cost" resolution
- Impacted by assumptions on costs for duplication and losses

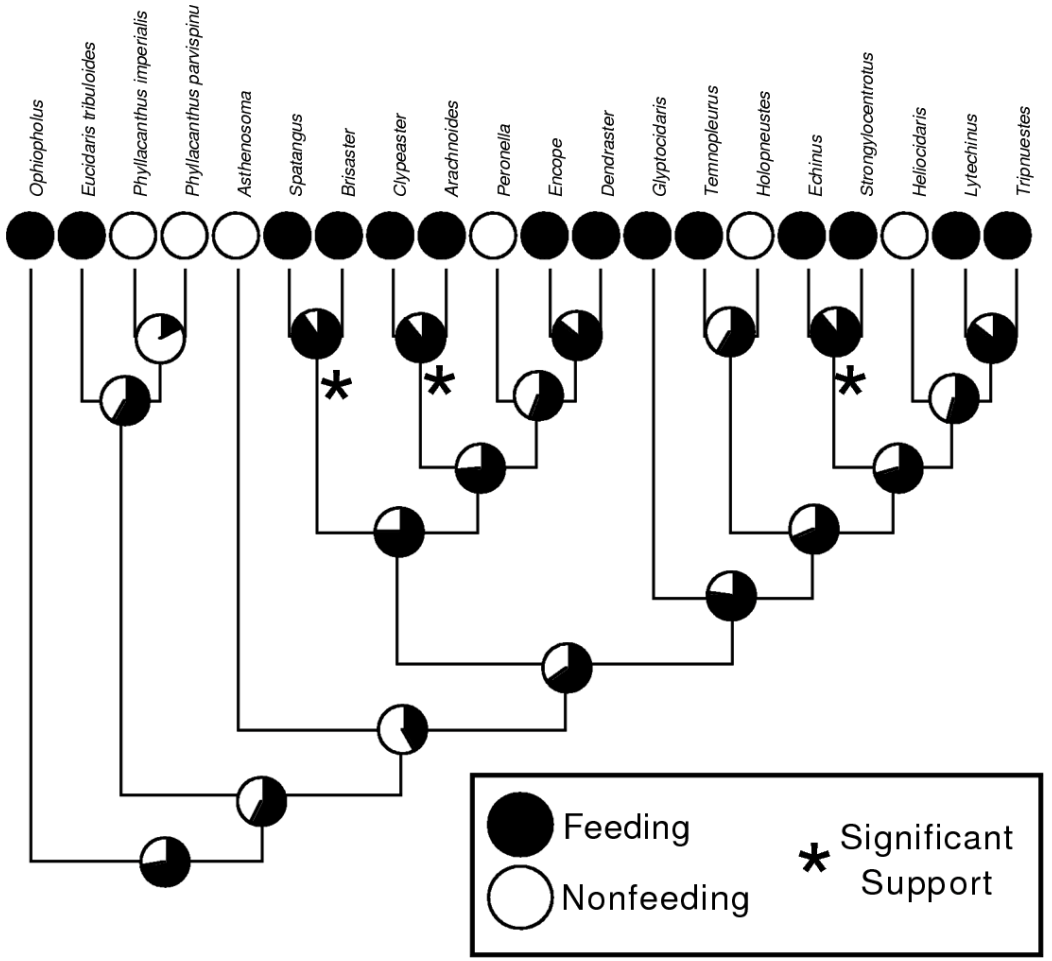
Gene ancestral state reconstruction

Ancestral state reconstruction in general is the extrapolation back in time from measured characteristics of individuals to their common ancestors

Ancestral gene content reconstruction follows the same principles:

- Extant characters are gene counts

- A gene **birth and death** process is used to model gene gain and loss across a user-specified phylogenetic tree



Inferring gene evolutionary histories

Reconciliation or Reconstruction is used to map evolutionary events
– gene gains and losses onto a species phylogeny

Understanding how these event relate to the biology and evolution
of the organisms being studied then requires additional data

- phenotype data like organismal traits (metabolism, ecology, etc)
- functional genomics data like expression / functional annotations

The first steps of data analysis are almost universal:
[1] delineation of families and/or orthologous groups
[2] building a robust species phylogeny

Orthology Delineation

What is orthology?

How do we delineate orthologs?

And why do we need to?
(species/gene trees)

Break time