Homología, Evolución, y Bases de Datos

Bioinformática para biotecnología BIT120
2 agosto 2017
Eduardo Castro, PhD
www.castrolab.org

El equipo

- Dr. Daniel Aguayo (daniel.aguayo@unab.cl)
- Dr. Eduardo Castro (eduardo.castro@unab.cl)
- Jonathan Canan (jonathancanan@gmail.com)
- Katterinne Méndez (mendez.katterinne@gmail.com)

Evaluaciones

- La clase se divide en genómica y modelamiento de proteínas

- 3 pruebas (60%) & controles e informes (40%) + examen

- Programa http://tinyurl.com/yastf7pd

El programa

Fecha	**Planificación de actividades**
2 de agosto	Homología y Evolución + Bases de Datos Biológicas y de Literatura + Búsqueda en Bases de Datos
9 de agosto	Alineamiento de Pares de Secuencias, Múltiple y Perfiles (HMM's) + Diseño de Partidores + BLAST
16 de agosto	Ensamblaje de Genomas + Predicción de Genes
23 de agosto	Modelos de Sustitución Nucleotídica y Proteica + Filogenética Molecular
30 de agosto	**Solemne I**
13 de septiembre	Metagenómica, Metatranscriptómica y Microbioma humano
27 de septiembre	Visualización, Comparación y Clasificación de Estructura de Proteínas
4 de octubre	Predicción de Estructura Secundaria y Terciaria de Proteínas
11 de octubre	**Solemne II**
18 de octubre	Búsqueda de proteínas homólogas + Redes de similitud + Modelado por homología
25 de octubre	Bioinformática de enzimas
8 de noviembre	Introducción a la Simulación Molecular
15 de noviembre	Aplicación de la Simulación Molecular en ingeniería de proteínas
22 de noviembre	**Solemne III**
Última semana de noviembre según coordinación UNAB	**Examen**

Bioinformática y Biología Computacional

- **Bioinformática** —> organización, almacenaje, clasificación de información biológica. Desarrollo de métodos, algoritmos, y software para analizar información biológica.

- **Biología Computacional** —> Aplicación de métodos analíticos y teóricos, modelamiento matemático y simulación computacional para el estudio de sistemas biológicos.

So you want to be a computational biologist?

Nick Loman & Mick Watson

Loman, N., & Watson, M. (2013). So you want to be a computational biologist?. *Nature biotechnology*, *31*(11), 996-998.

Propaganda del lab

THE CASTRO LAB

HOME RESEARCH PEOPLE PUBLICATIONS OPPORTUNITIES CONTACT

MICROBIAL GENOMICS

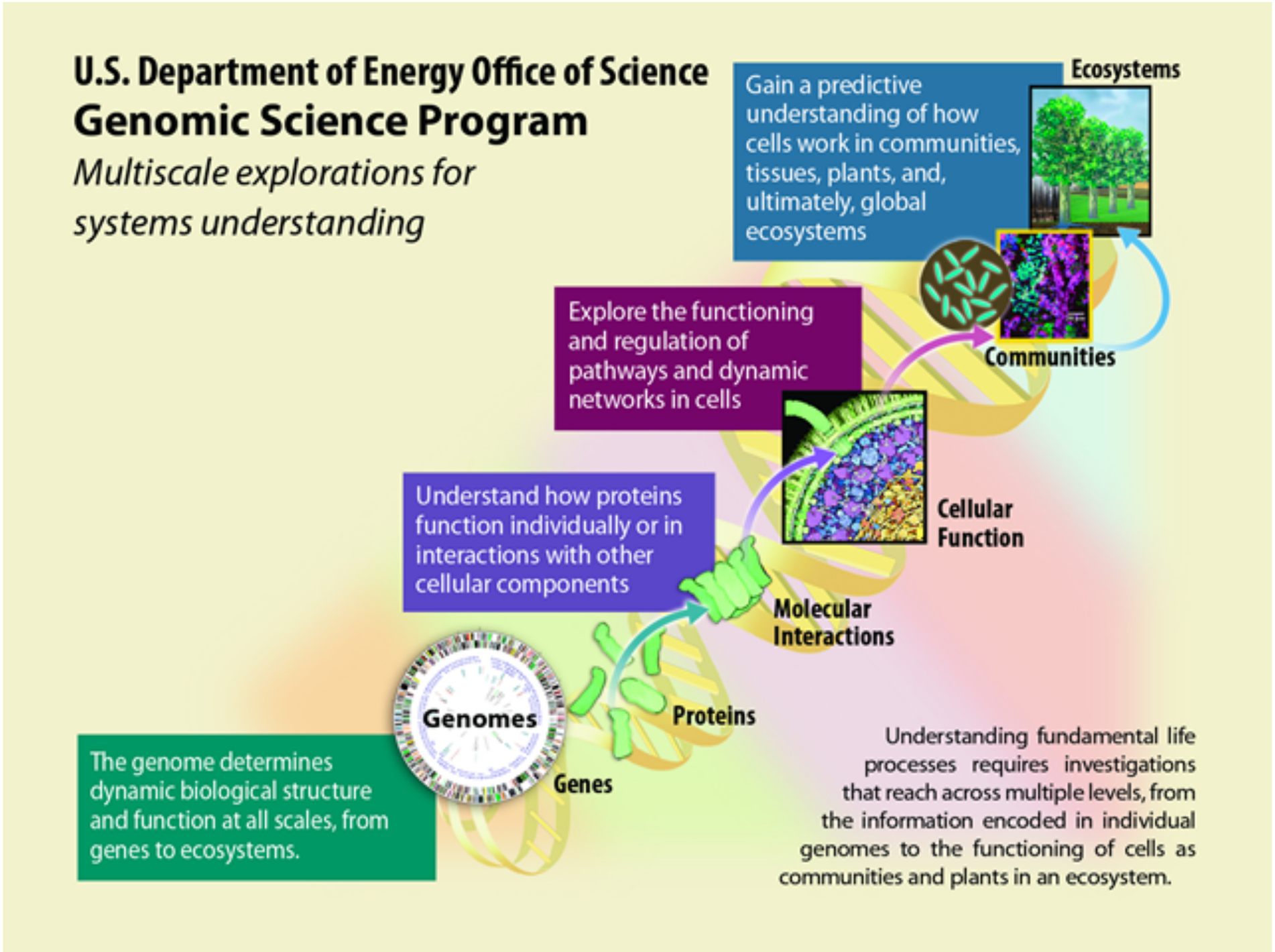
Eduardo Castro-Nallar, PhD
Universidad Andrés Bello
Center for Bioinformatics and Integrative Biology

Microorganisms are the most abundant life form on the planet. They are able to colonize and thrive in most environments ranging from the human body to under water thermal vents. In the Castro Lab, we are interested in understanding the causes and consequences of microbial genetic diversity, and how we can apply this knowledge to gain insights into pathogen diagnostics and discovery, microbial distribution and epidemiology, and novel adaptations.

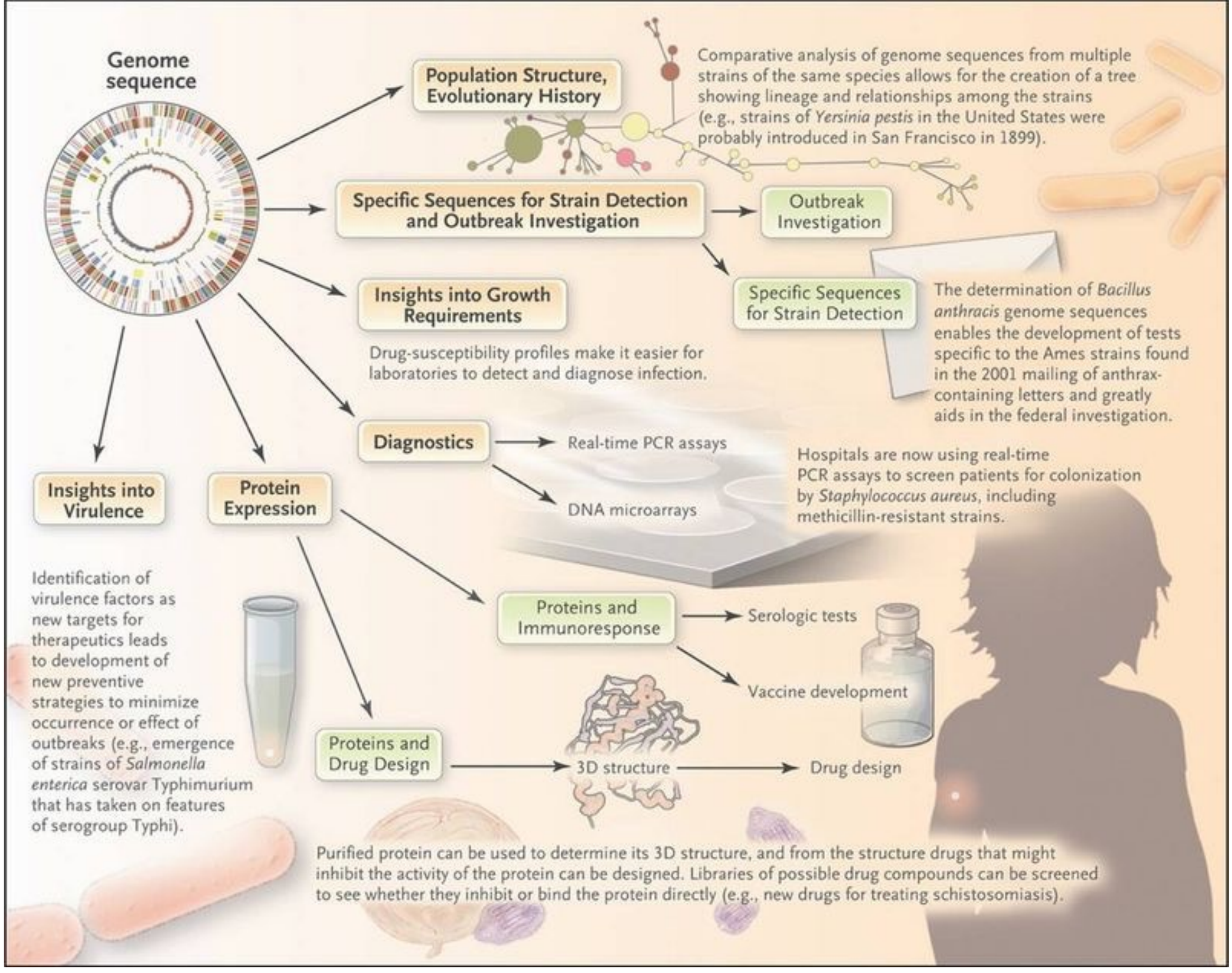
For this, we use molecular and computational biology tools such as high-throughput sequencing, recombinant DNA technology, Bayesian statistics and phylogenetics, transcriptomics and metagenomics.

www.castrolab.org

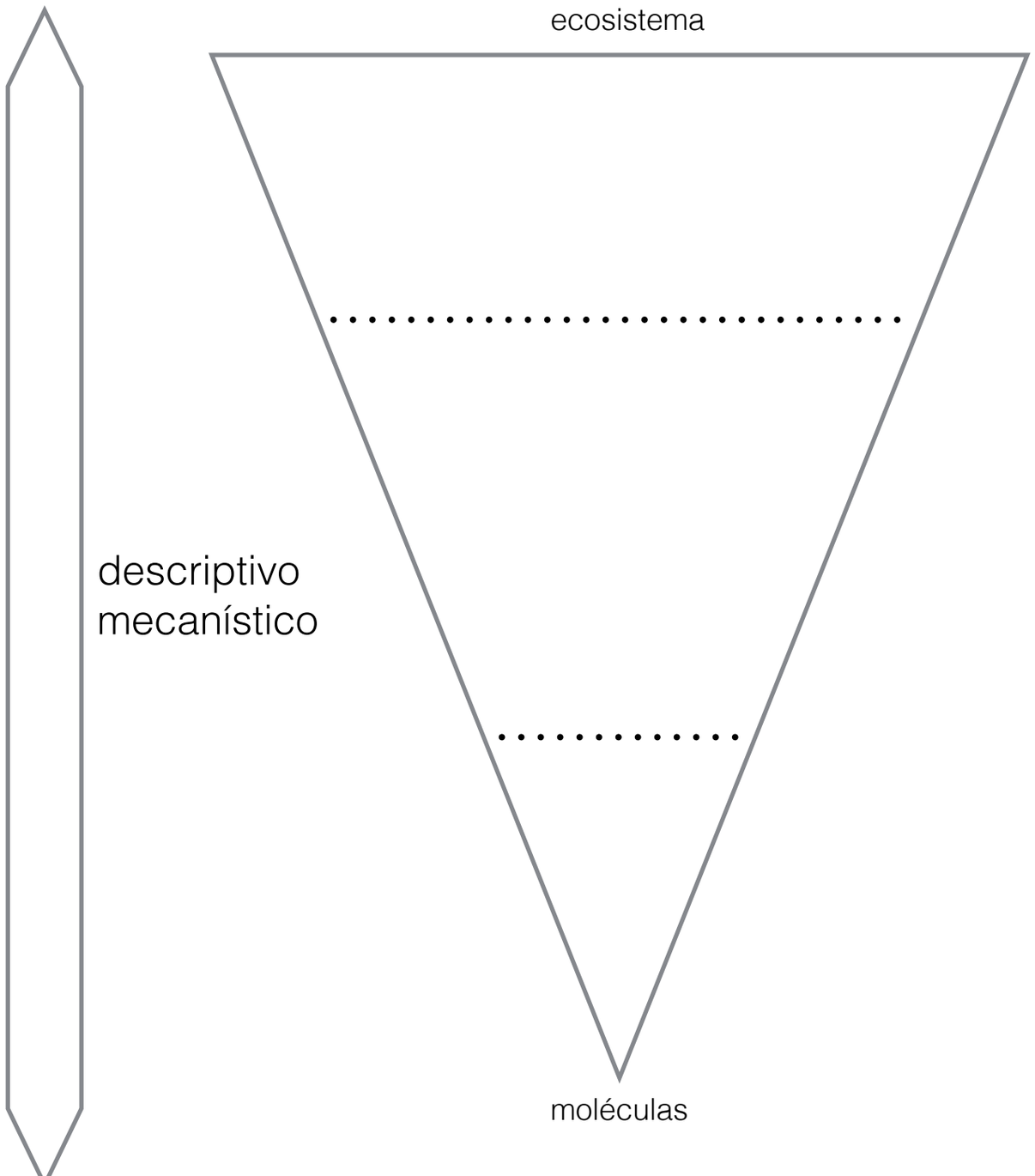
De genes a ecosistemas



http://doegenomestolife.org


Genome sequence
Population Structure, Evolutionary History
Comparative analysis of genome sequences from multiple strains of the same species allows for the creation of a tree showing lineage and relationships among the strains (e.g., strains of *Yersinia pestis* in the United States were probably introduced in San Francisco in 1899).
Specific Sequences for Strain Detection and Outbreak Investigation
Outbreak Investigation
Specific Sequences for Strain Detection
The determination of *Bacillus anthracis* genome sequences enables the development of tests specific to the Ames strains found in the 2001 mailing of anthrax-containing letters and greatly aids in the federal investigation.
Insights into Growth Requirements
Drug-susceptibility profiles make it easier for laboratories to detect and diagnose infection.
Diagnostics
Real-time PCR assays
DNA microarrays
Hospitals are now using real-time PCR assays to screen patients for colonization by *Staphylococcus aureus*, including methicillin-resistant strains.
Insights into Virulence
Protein Expression
Identification of virulence factors as new targets for therapeutics leads to development of new preventive strategies to minimize occurrence or effect of outbreaks (e.g., emergence of strains of *Salmonella enterica* serovar Typhimurium that has taken on features of serogroup Typhi).
Proteins and Immunoresponse
Serologic tests
Vaccine development
Proteins and Drug Design
3D structure
Drug design
Purified protein can be used to determine its 3D structure, and from the structure drugs that might inhibit the activity of the protein can be designed. Libraries of possible drug compounds can be screened to see whether they inhibit or bind the protein directly (e.g., new drugs for treating schistosomiasis).

¿Dónde encaja la genómica de microorganismos?



comunidades microbianas

asociaciones entre características y fenotipos

poblaciones

epidemiología de brotes y pandemias

organismos, células, moléculas

determinantes de patogenicidad, biosíntesis de moléculas

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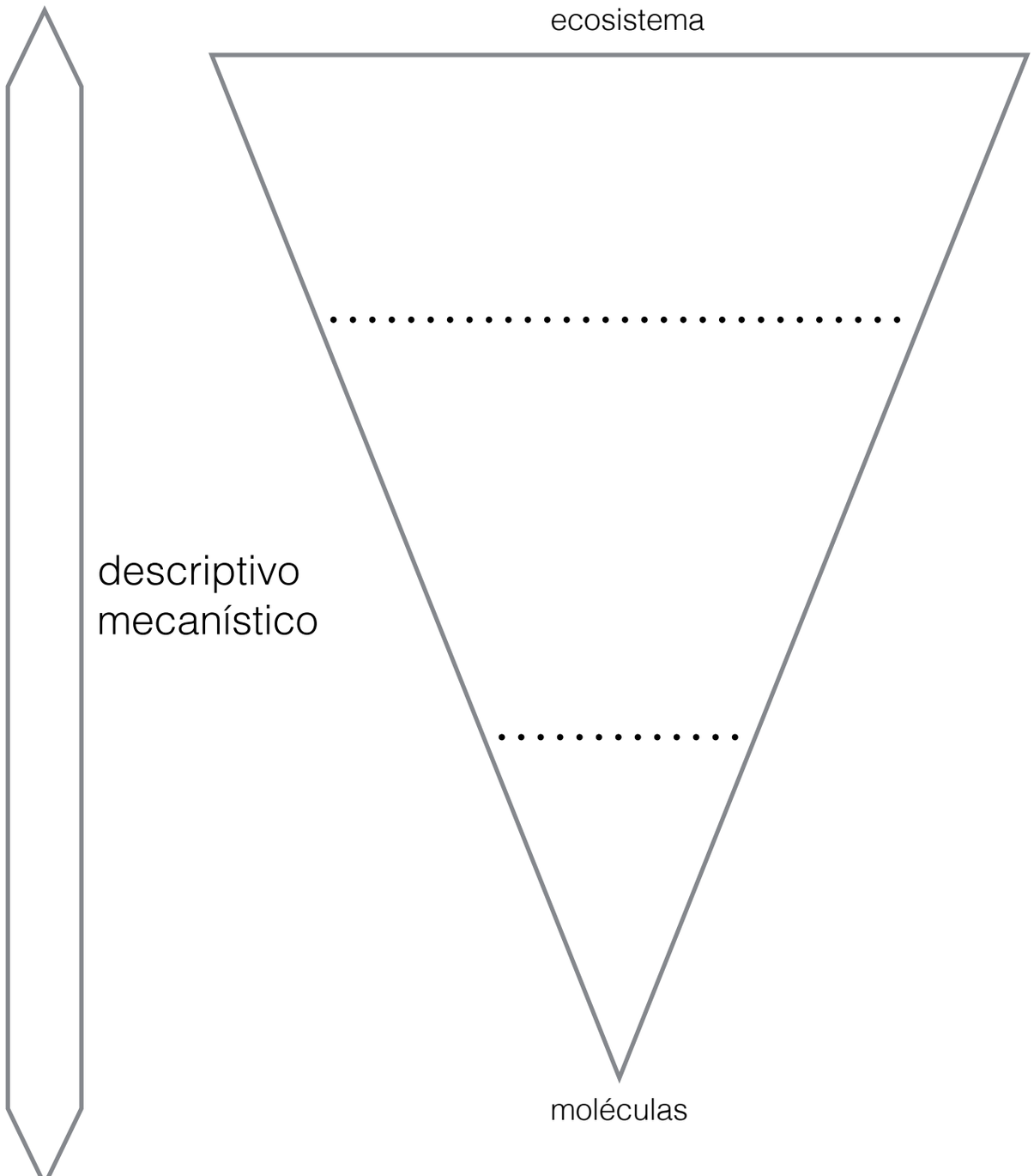

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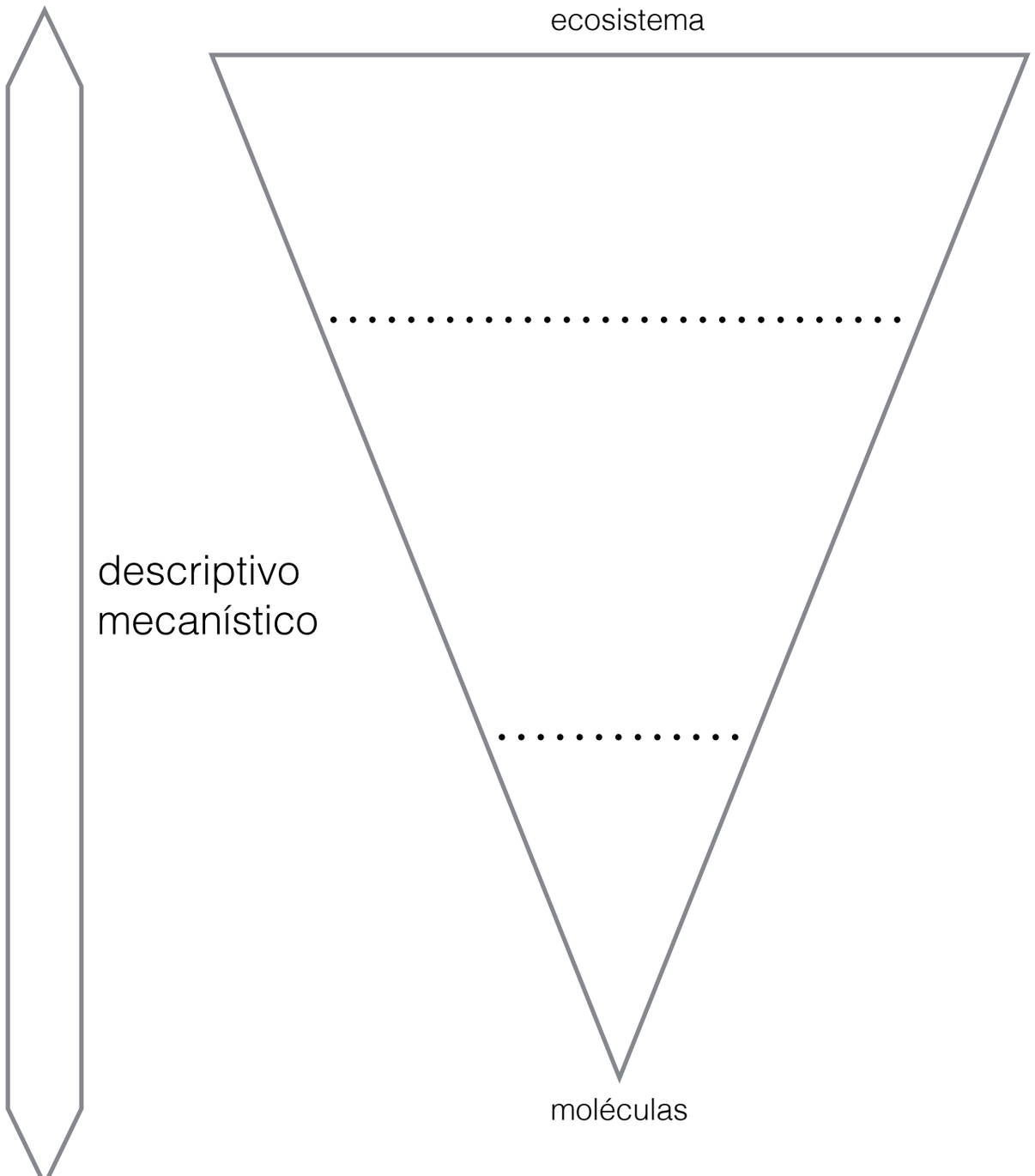

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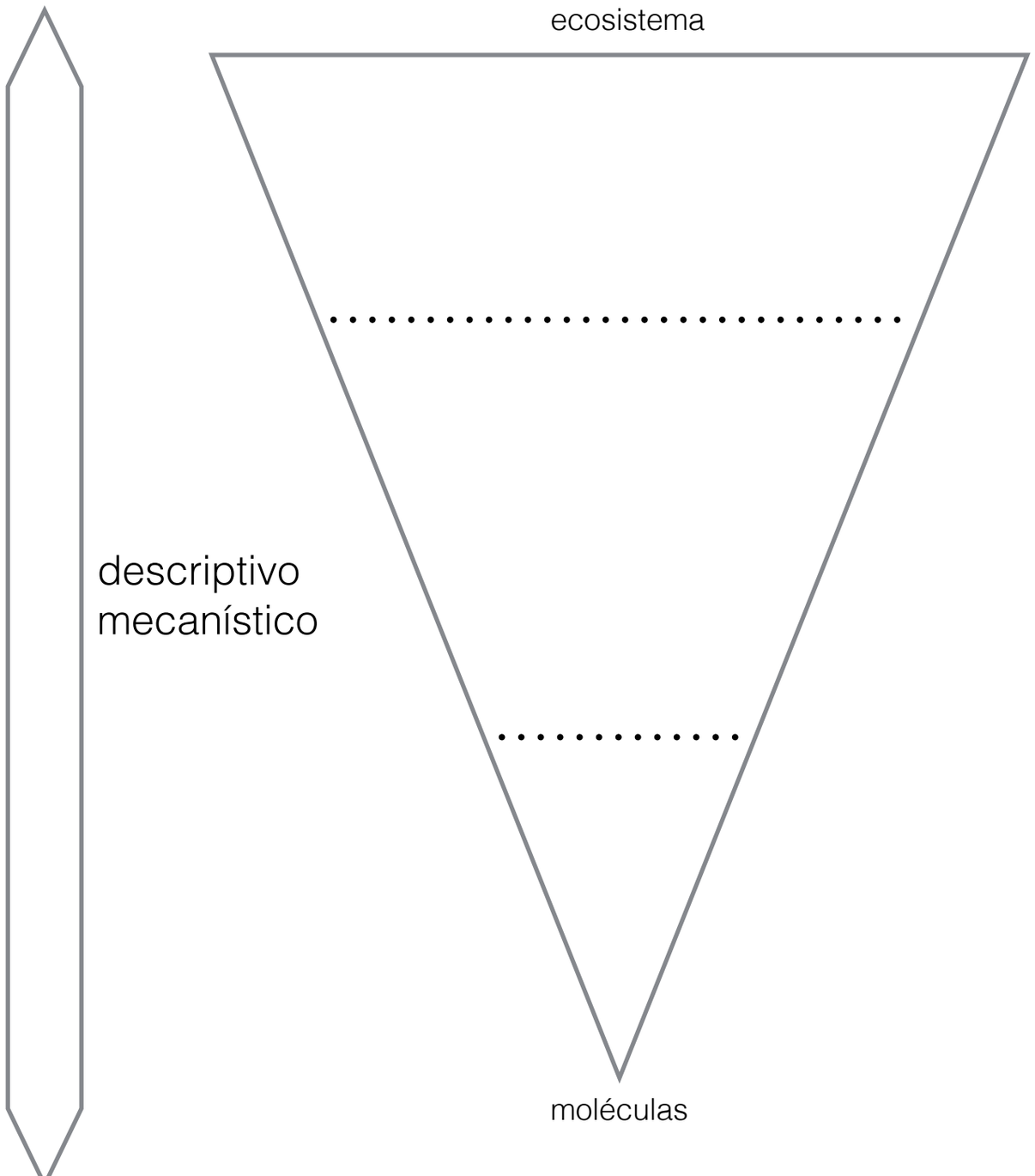

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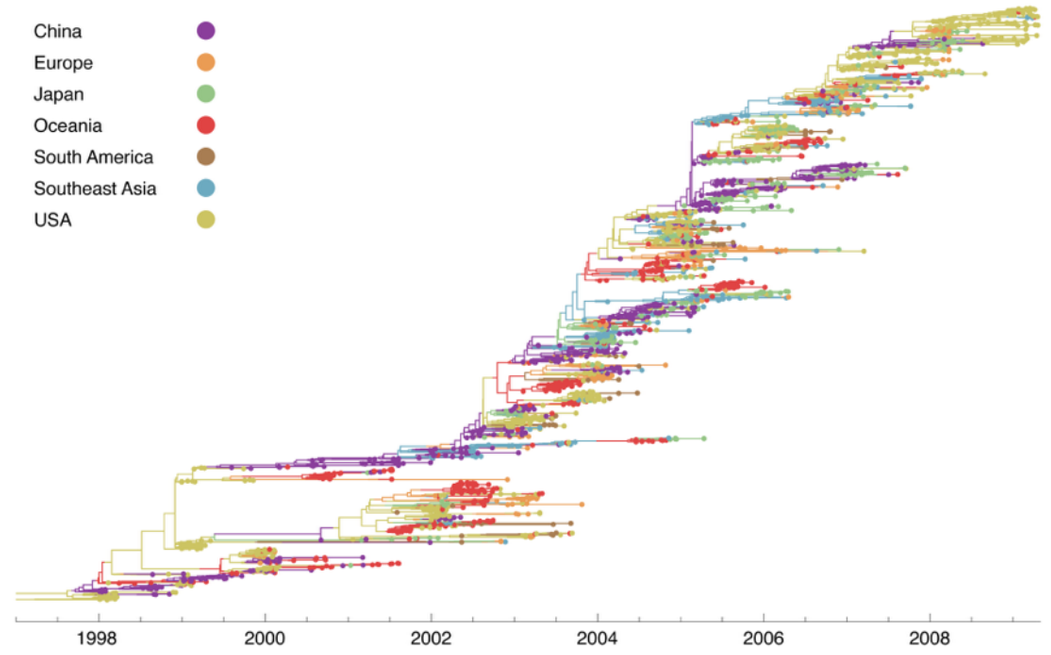
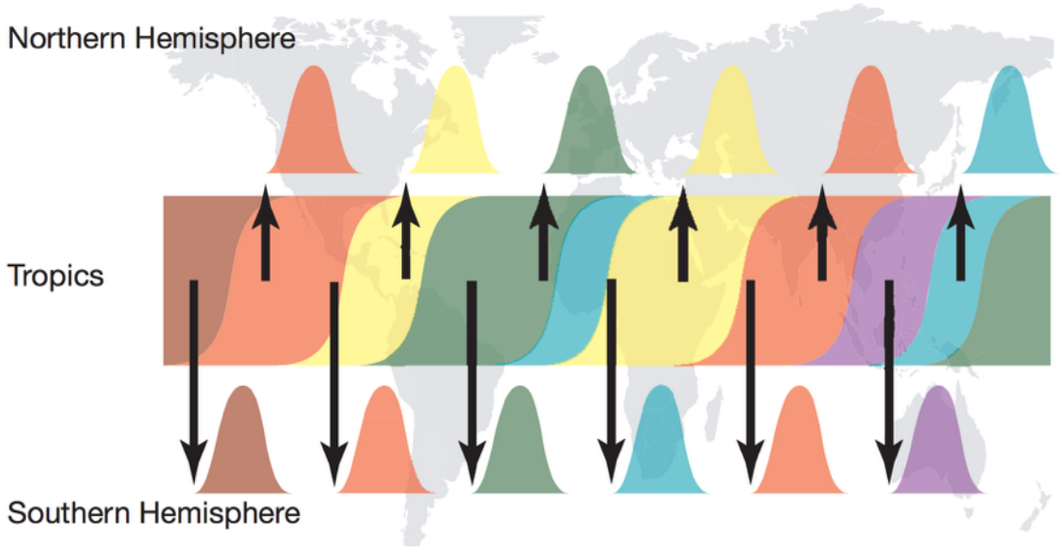
Impacto de la genómica de microorganismos en salud humana y medioambiente

- Epidemiología
- Microbiomas
- Bioprospección





T Bedford, S Cobey, P Beerli, M Pascual, N Ferguson. 2010. Global migration dynamics underlie evolution and persistence of human influenza A (H3N2). PLoS Pathogens. e1000918-e1000918

Rambaut, A., Pybus, O. G., Nelson, M. I., Viboud, C., Taubenberger, J. K., & Holmes, E. C. (2008). The genomic and epidemiological dynamics of human influenza A virus. Nature, 453(7195), 615-619.

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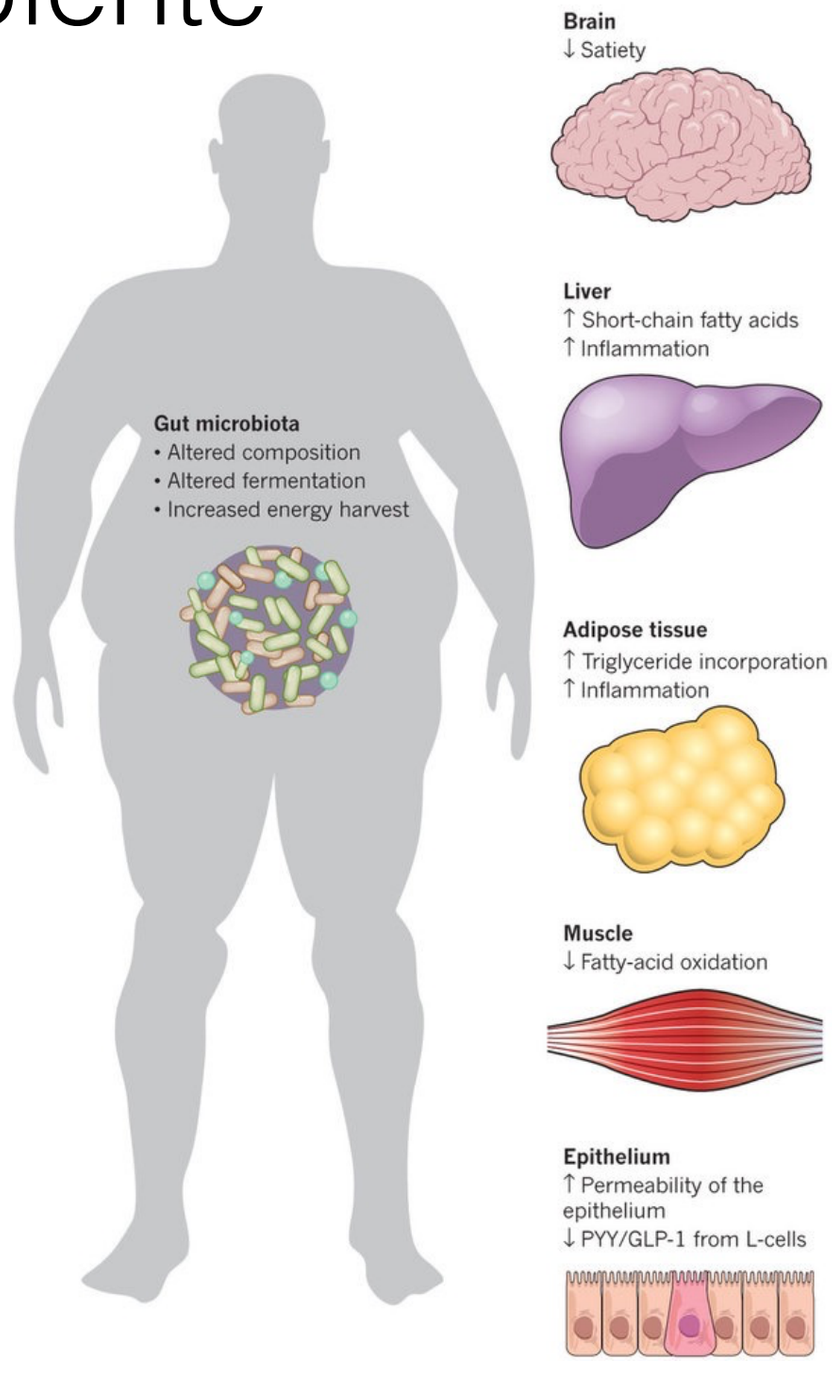

Tremaroli, V., & Bäckhed, F. (2012). Functional interactions between the gut microbiota and host metabolism. Nature, 489(7415), 242-249.

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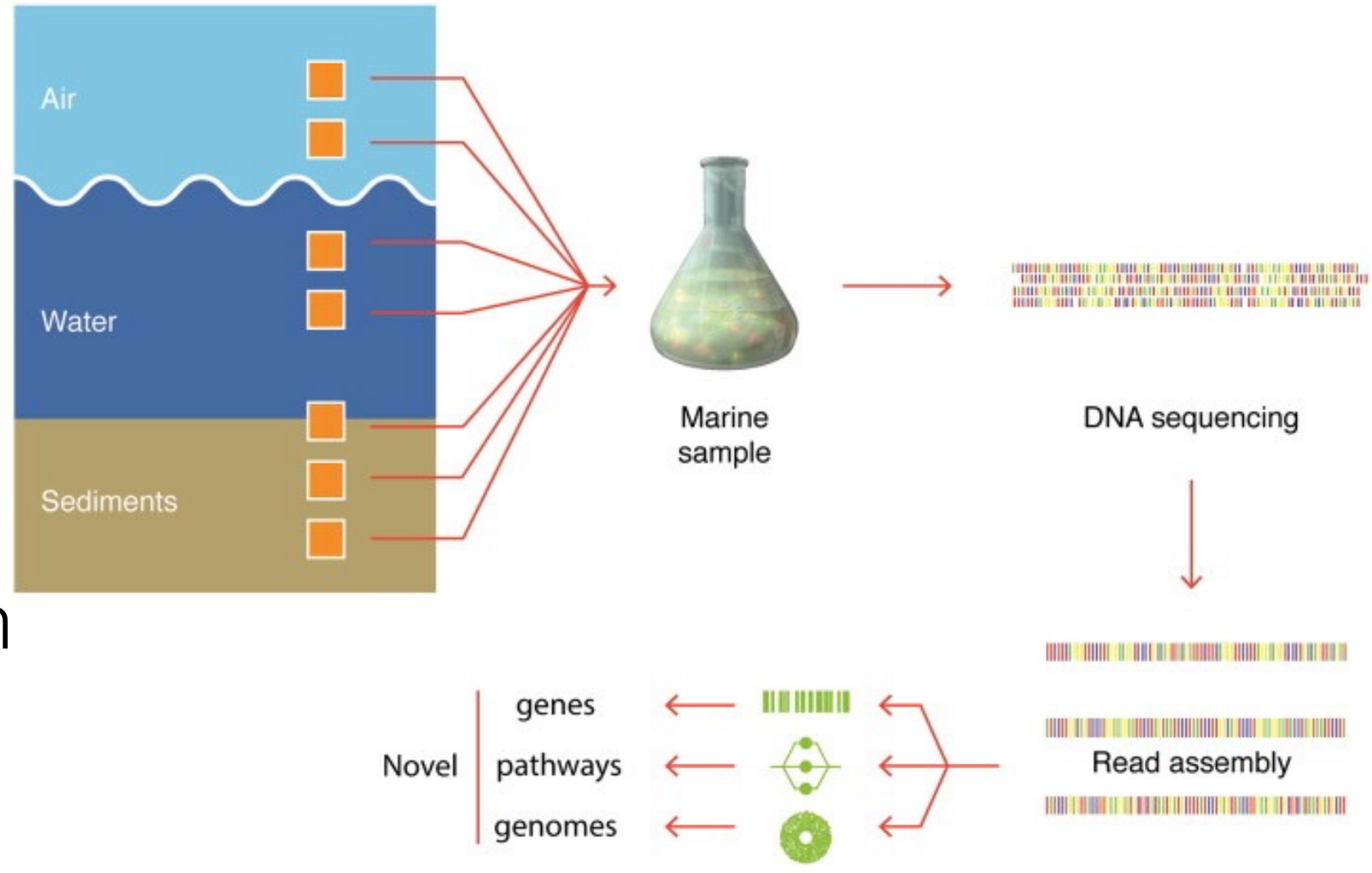
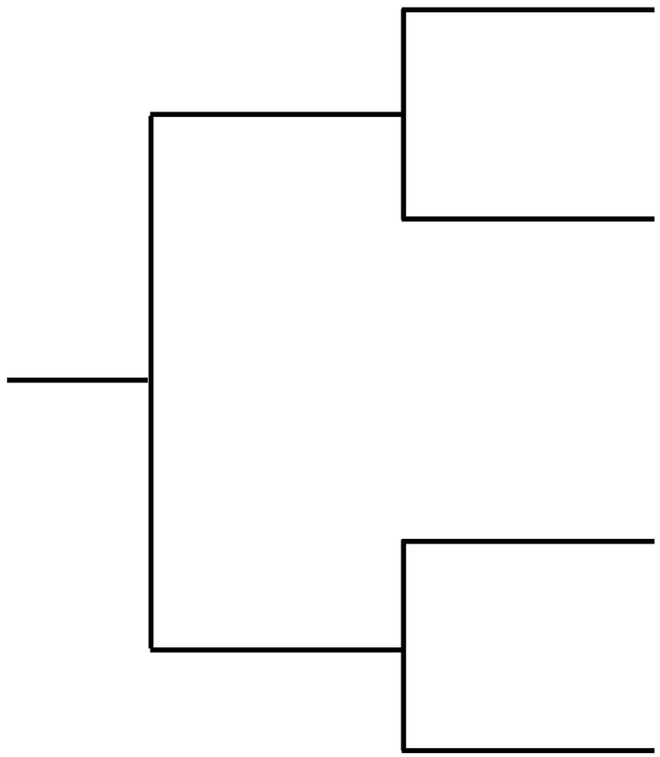


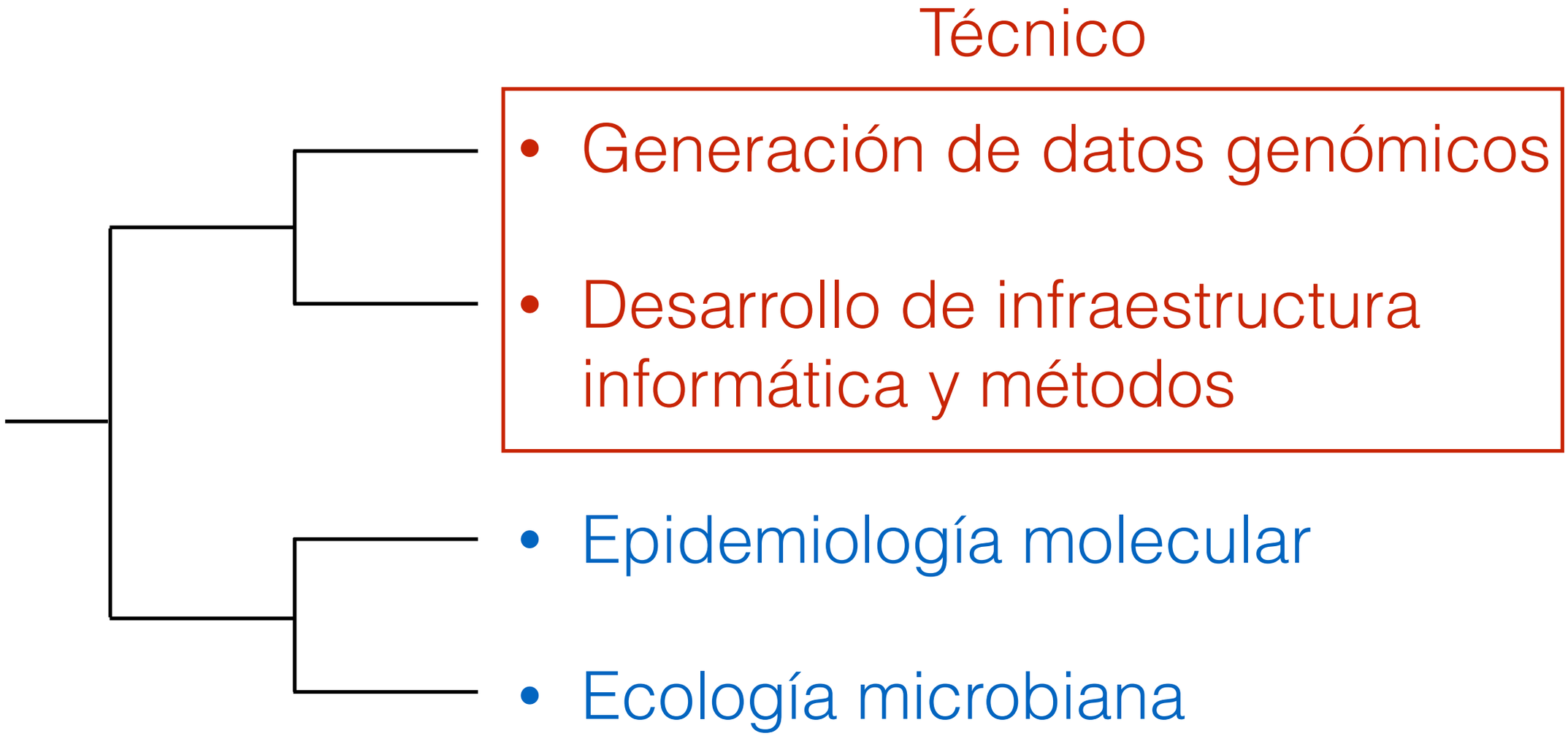
Kodzius, R., & Gojobori, T. (2015). Marine metagenomics as a source for bioprospecting. Marine genomics.

Pilares principales del lab



- Generación de datos genómicos
- Desarrollo de infraestructura informática y métodos
- Epidemiología molecular
- Ecología microbiana

Pilares principales del lab



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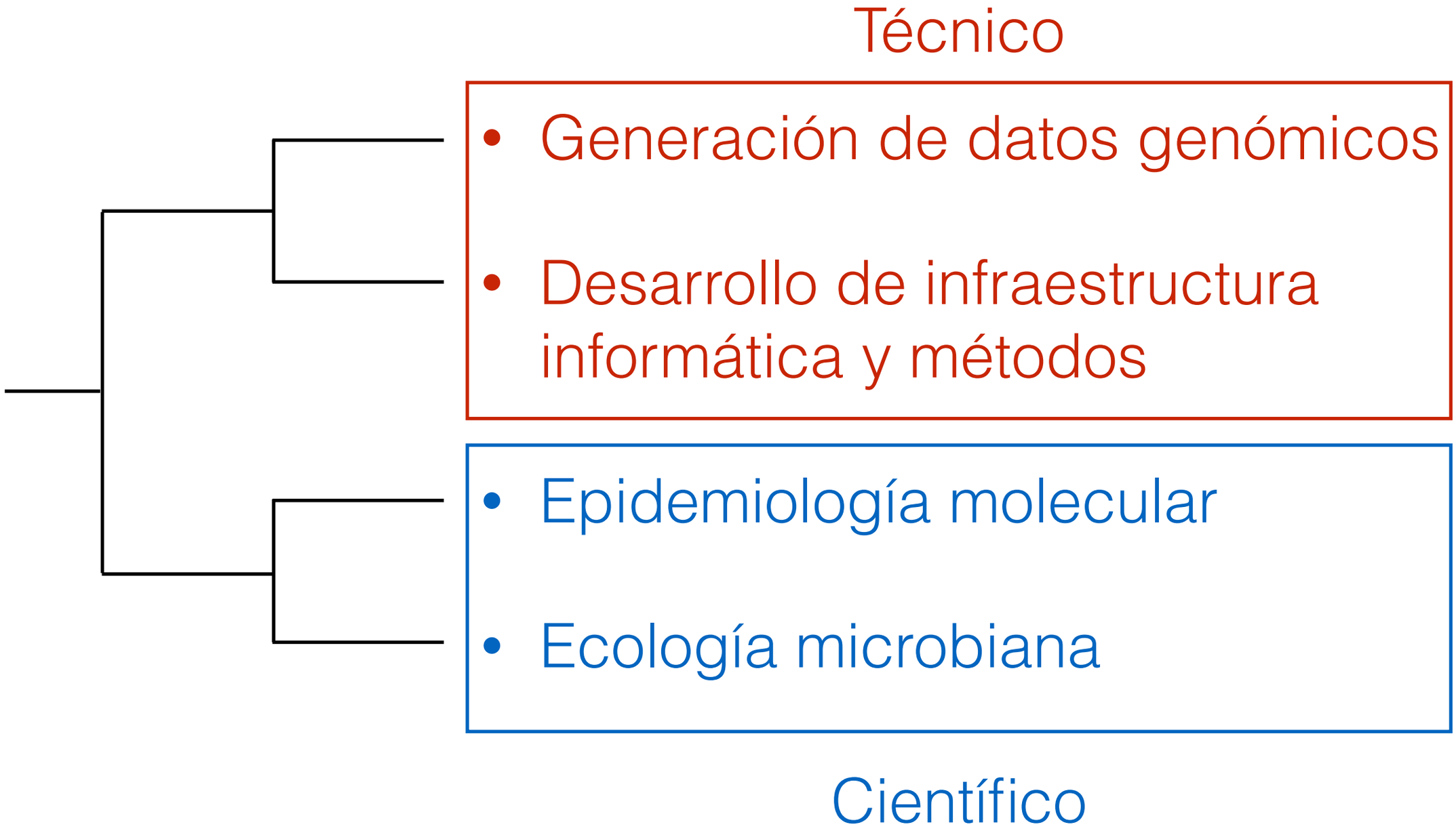


Ahora, la clase…

Objetivos

- Evolución y unidad de las formas de vida
- Homología, paralogía, xenología, etc.
- Organización del conocimiento científico y biológico
- Práctica: uso de bases de datos

Evolución y unidad de las formas de vida

Observación

- Alta biodiversidad
- Sin embargo todos exhiben elementos que los unifican —> organismos comparten ancestros comunes

How to Read the Circle of Life

Primordial life begins at the center and branches out in all directions, leading to the groups of species that exist today (*colored rings*)

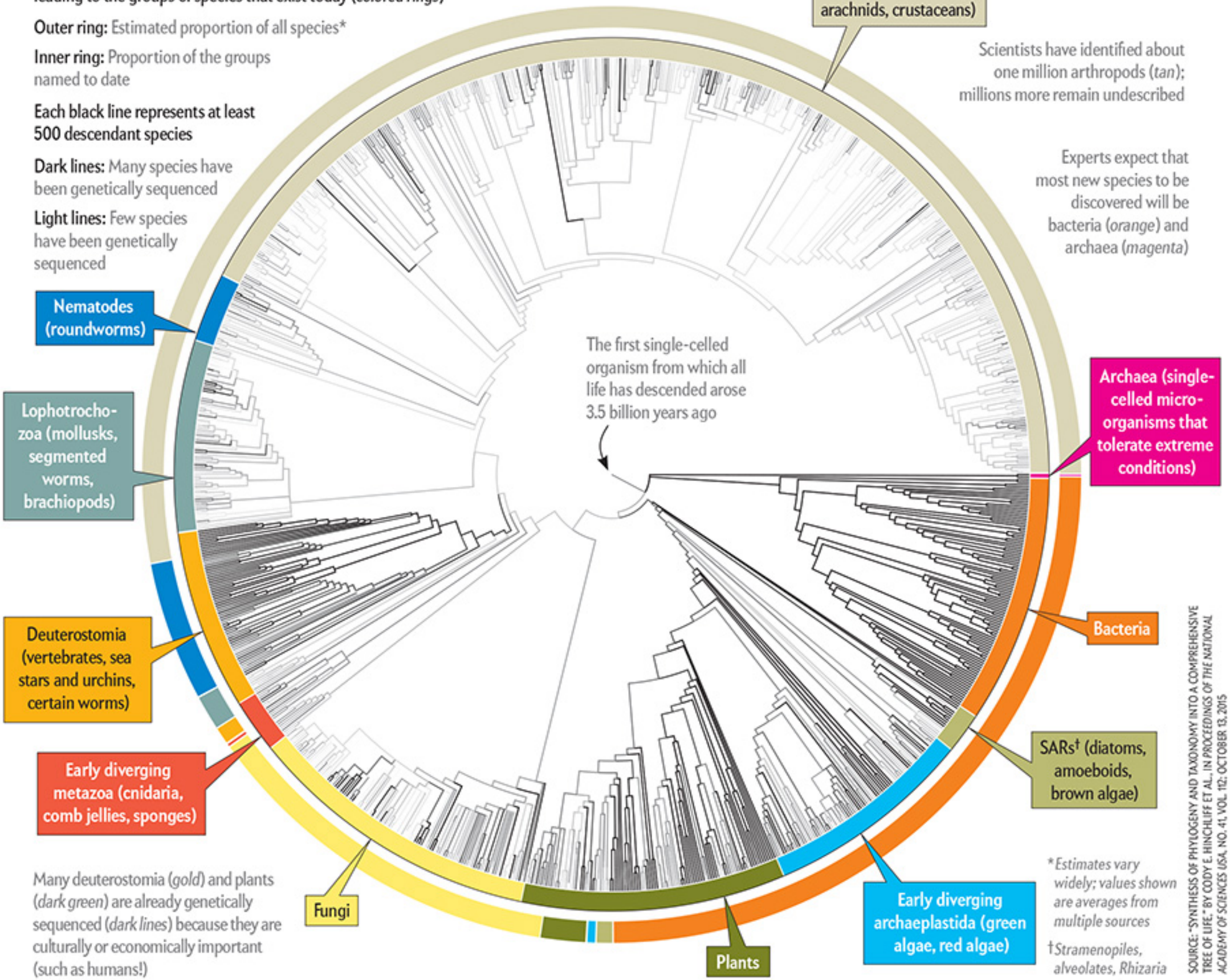
Outer ring: Estimated proportion of all species*

Inner ring: Proportion of the groups named to date

Each black line represents at least 500 descendant species

Dark lines: Many species have been genetically sequenced

Light lines: Few species have been genetically sequenced



*Estimates vary widely; values shown are averages from multiple sources

†Stramenopiles, alveolates, Rhizaria

SOURCE: "SYNTHESIS OF PHYLOGENY AND TAXONOMY INTO A COMPREHENSIVE TREE OF LIFE," BY CODY E. HINCHLIFF ET AL., IN *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES USA*, NO. 41, VOL. 112: OCTOBER 13, 2015

Evidencia sobre unidad de la vida

- Código genético
- Registro fósil
- Función y estructura celular —> linea germinal
- Rasgos vestigiales
- Distribución de especies relacionadas

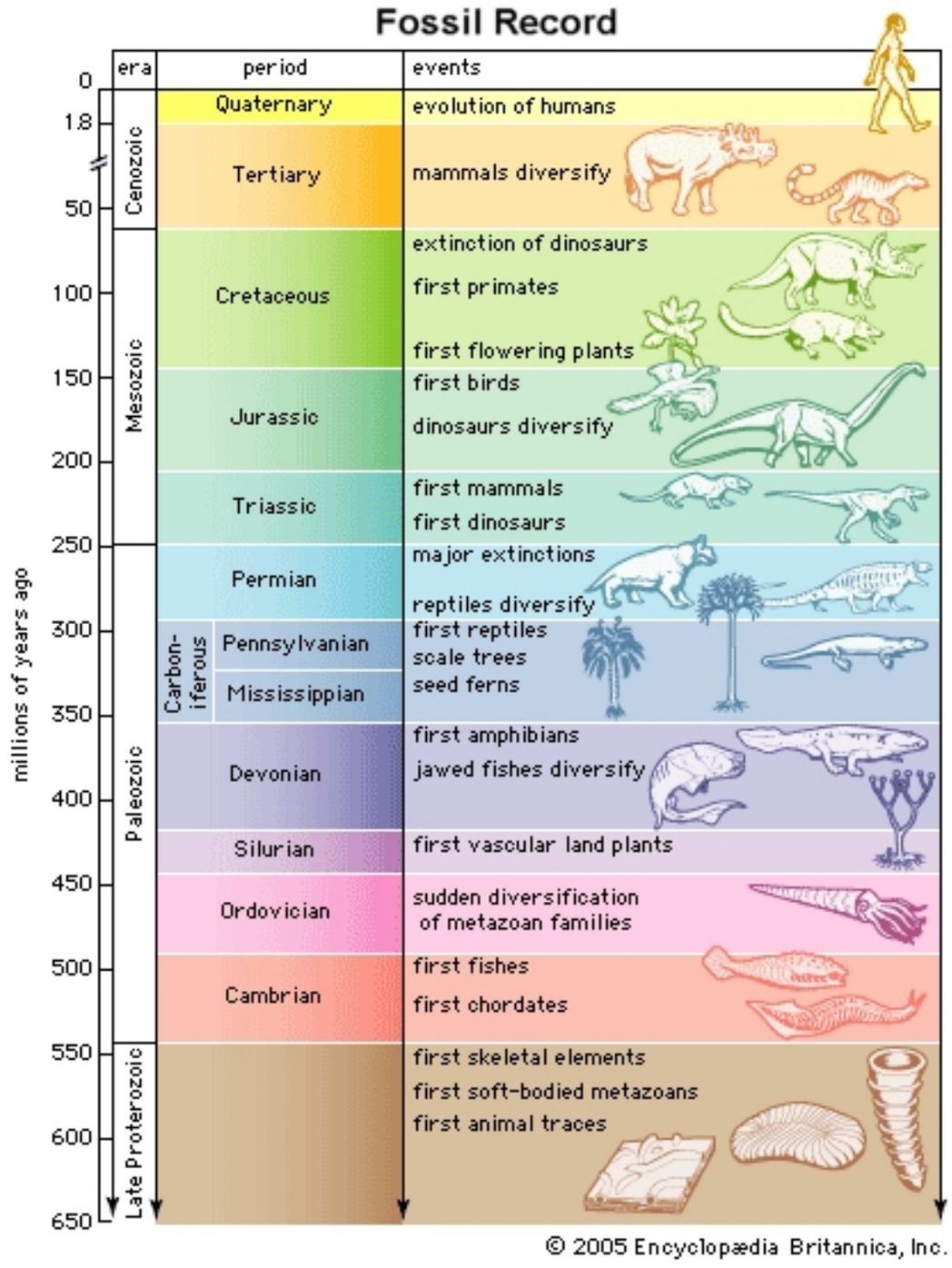
UUU [F] Phe	UCU [S] Ser	UAU [Y] Tyr	UGU [C] Cys
UUC [F] Phe	UCC [S] Ser	UAC [Y] Tyr	UGC [C] Cys
UUA [L] Leu	UCA [S] Ser	UAA [ ] Ter	UGA [ ] Ter
UUG [L] Leu	UCG [S] Ser	UAG [ ] Ter	UGG [W] Trp
CUU [L] Leu	CCU [P] Pro	CAU [H] His	CGU [R] Arg
CUC [L] Leu	CCC [P] Pro	CAC [H] His	CGC [R] Arg
CUA [L] Leu	CCA [P] Pro	CAA [Q] Gln	CGA [R] Arg
CUG [L] Leu	CCG [P] Pro	CAG [Q] Gln	CGG [R] Arg
AUU [I] Ile	ACU [T] Thr	AAU [N] Asn	AGU [S] Ser
AUC [I] Ile	ACC [T] Thr	AAC [N] Asn	AGC [S] Ser
AUA [I] Ile	ACA [T] Thr	AAA [K] Lys	AGA [R] Arg
AUG [M] Met	ACG [T] Thr	AAG [K] Lys	AGG [R] Arg
GUU [V] Val	GCU [A] Ala	GAU [D] Asp	GGU [G] Gly
GUC [V] Val	GCC [A] Ala	GAC [D] Asp	GGC [G] Gly
GUA [V] Val	GCA [A] Ala	GAA [E] Glu	GGA [G] Gly
GUG [V] Val	GCG [A] Ala	GAG [E] Glu	GGG [G] Gly

Código genético

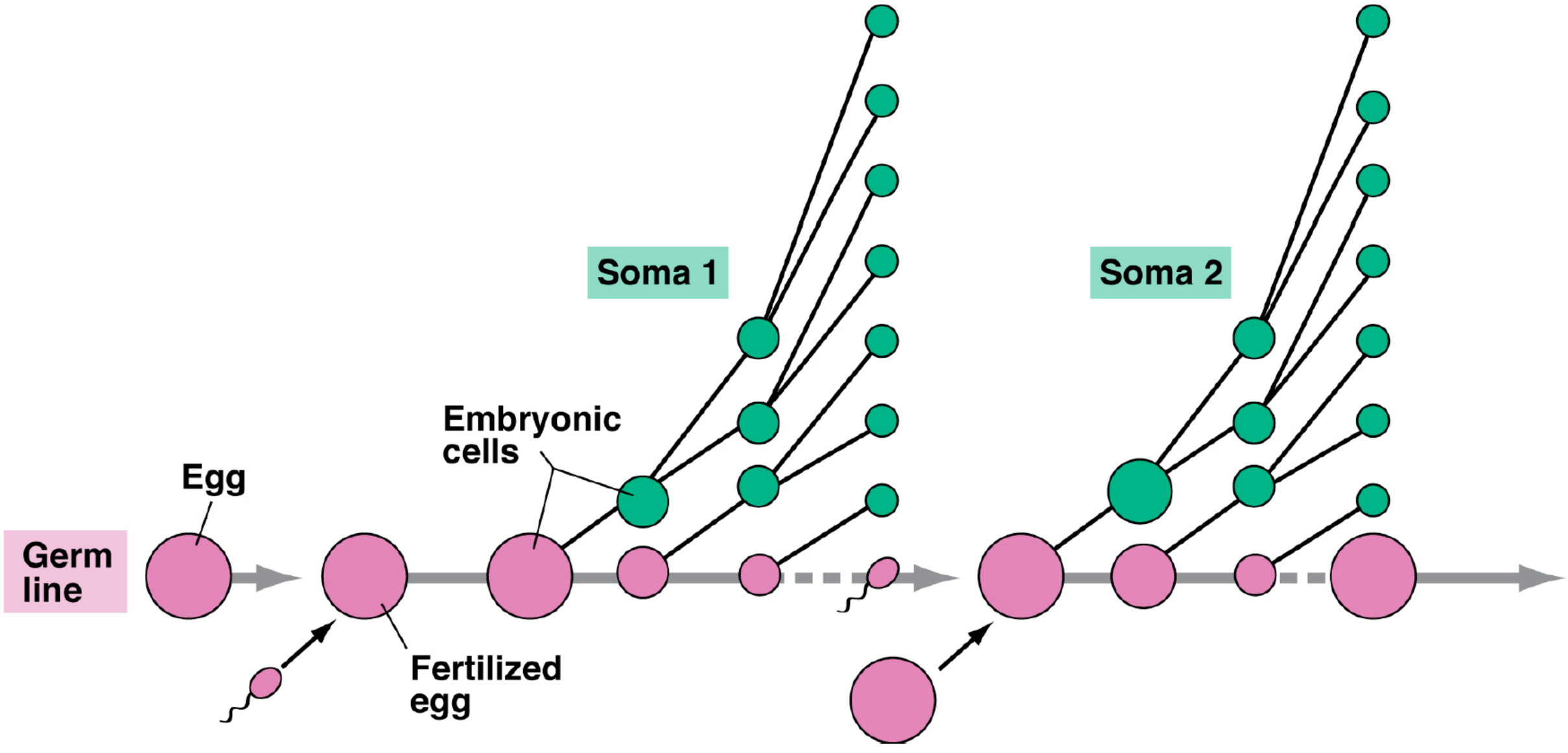
- Sistema común para todas las especies
  - Codones —> aa
  - DNA para almacenar información genética
  - Síntesis de proteínas a través de ribosomas
  - Los mismos 20 aminoácidos

Registro fósil

- Registra la historia de la vida a través del tiempo
- 4 mil millones de años
- Documentan relaciones entre ancestros y descendientes

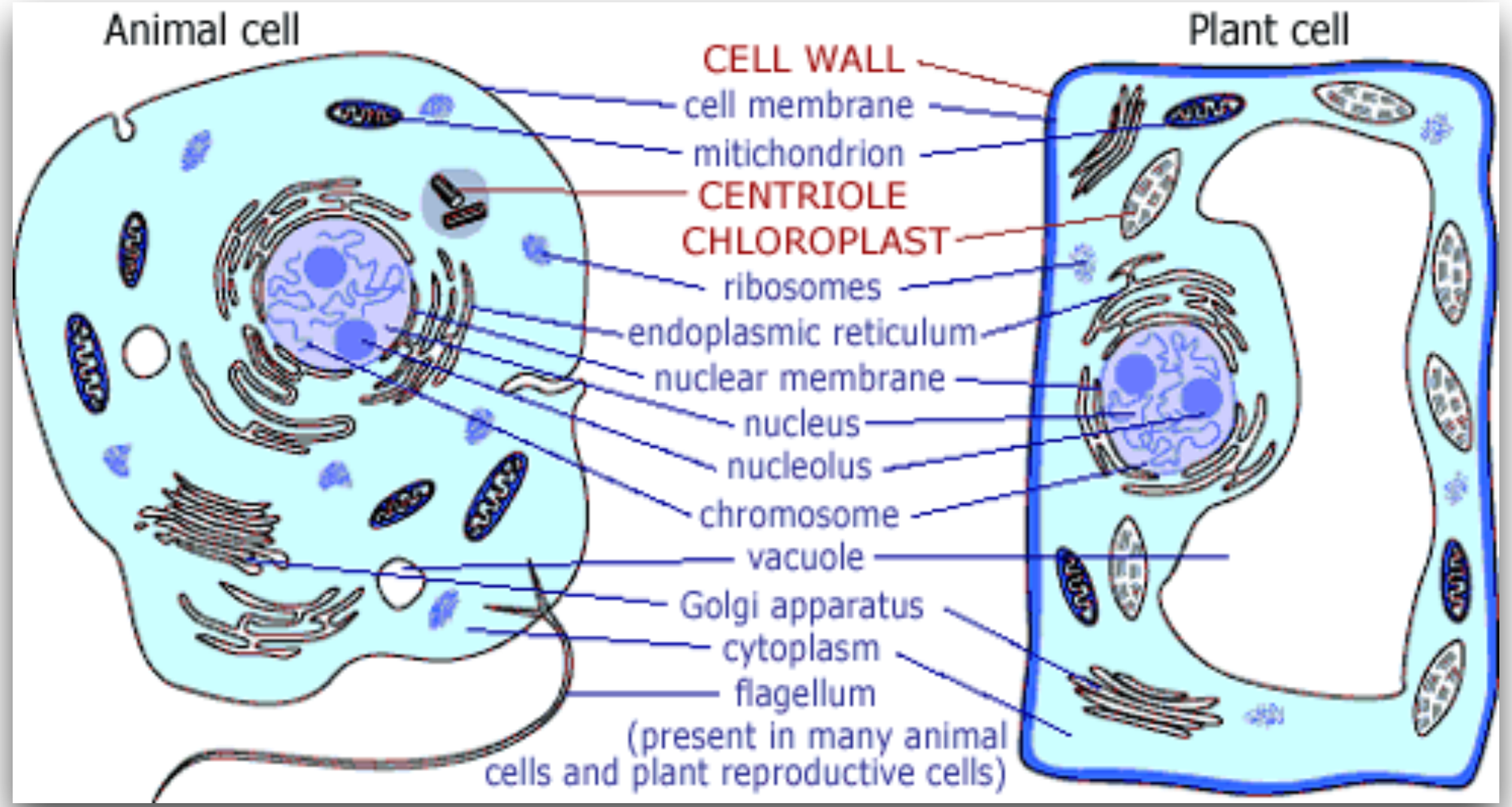


Linea germinal



La linea germinal forma un continuo a través de individuos y generaciones

Estructura y función



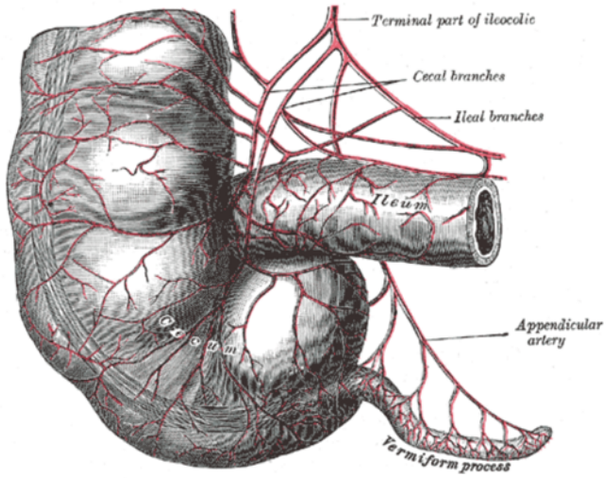
Células de distintos organismos poseen estructuras funcionales similares

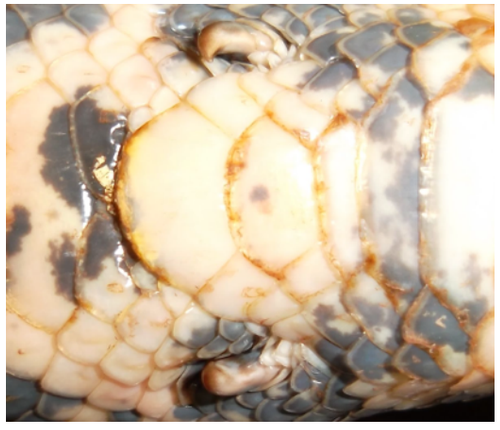
Rasgos vestigiales

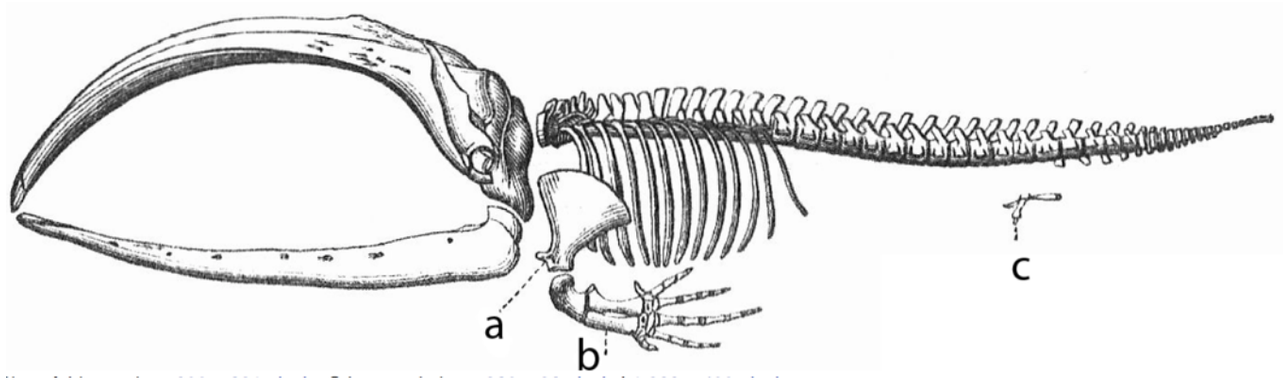
- Estructuras determinadas genéticamente que han sido perdido su función ancestral en una especie pero han sido retenidas durante el proceso evolutivo

- Apéndice, cola, reflejo ante frio

- Patas traseras en boa constrictor, ballena



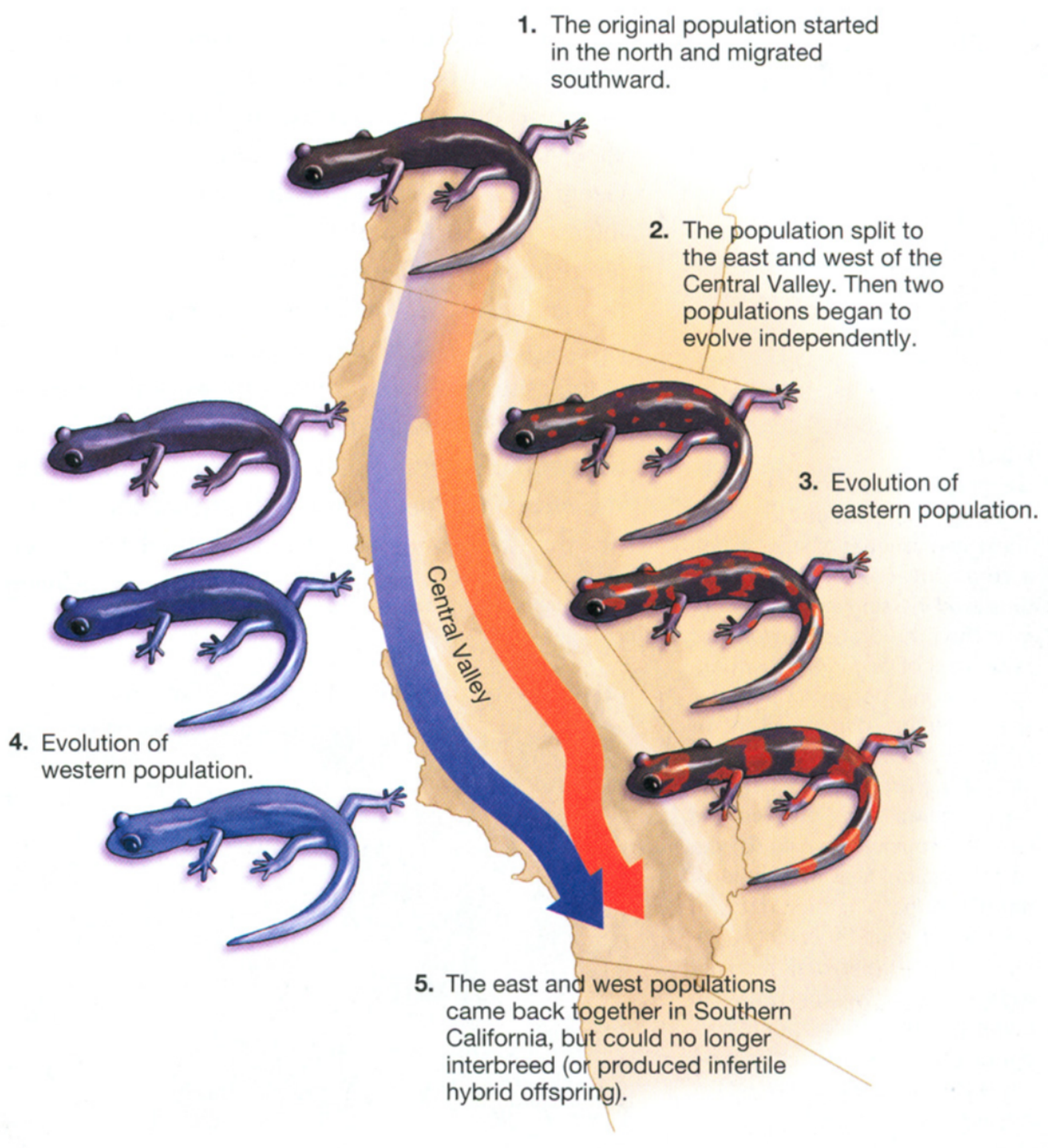




Distribución de especies relacionadas

- Geografía aisla poblaciones y genera especies con origen común

- Especies relacionadas tienden a estar correlacionadas geograficamente

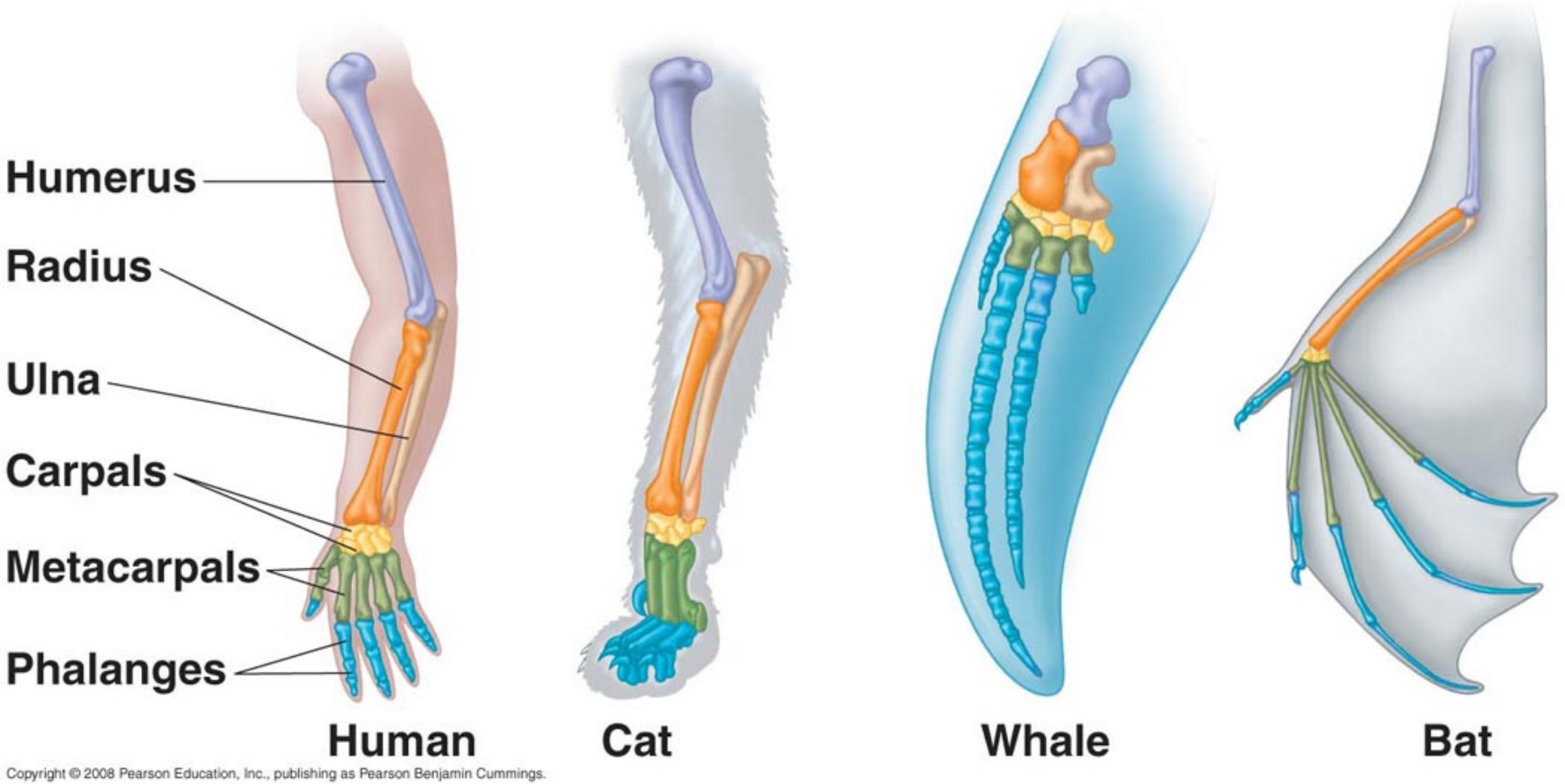


Homología

¿Qué es homología?

- **homología morfológica** —> especies que pertenecen al mismo grupo taxonómico muestran similitudes anatómicas debido a que comparten un ancestro común (no por chance)

Estructuras homólogas



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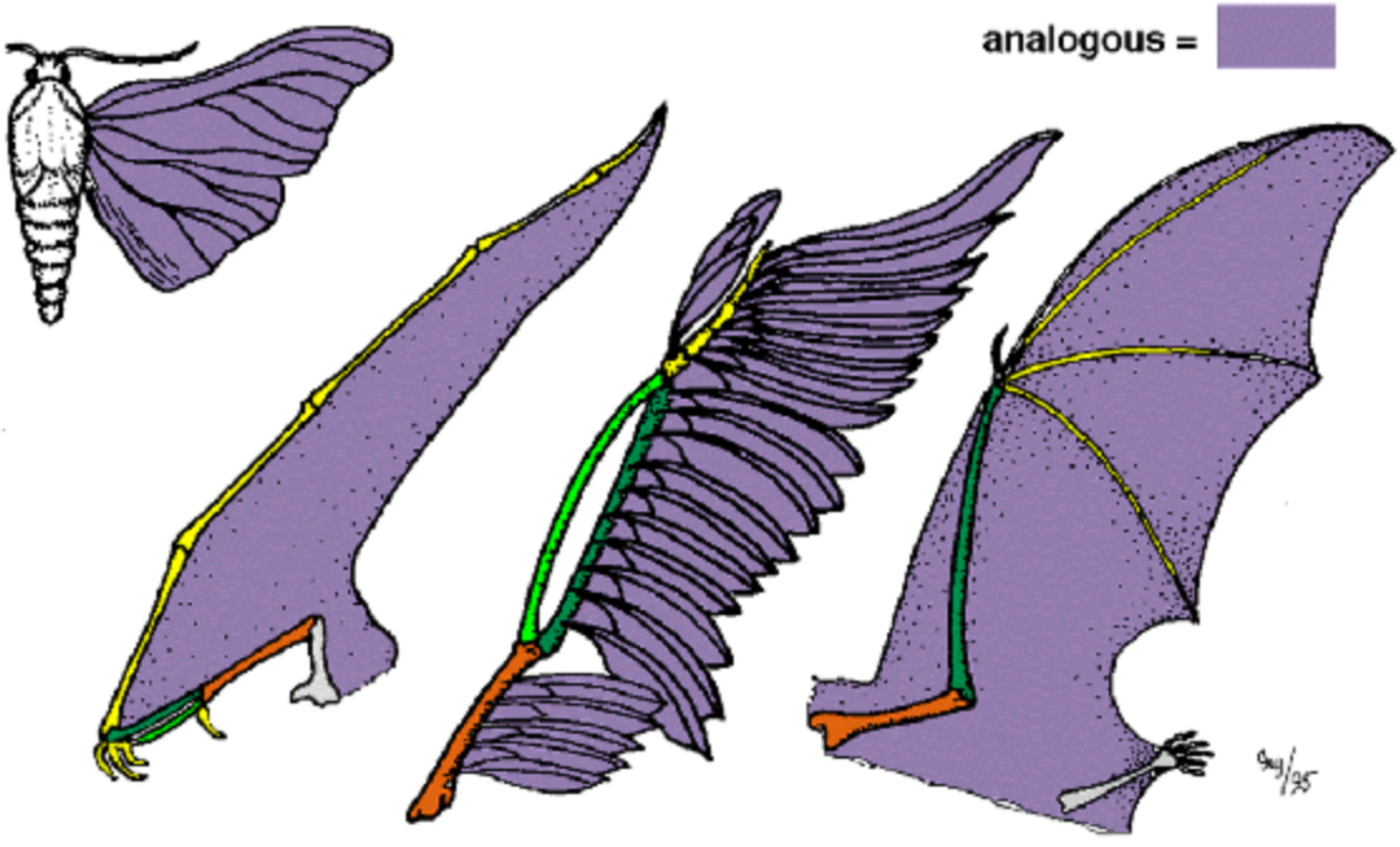
Estructuras análogas



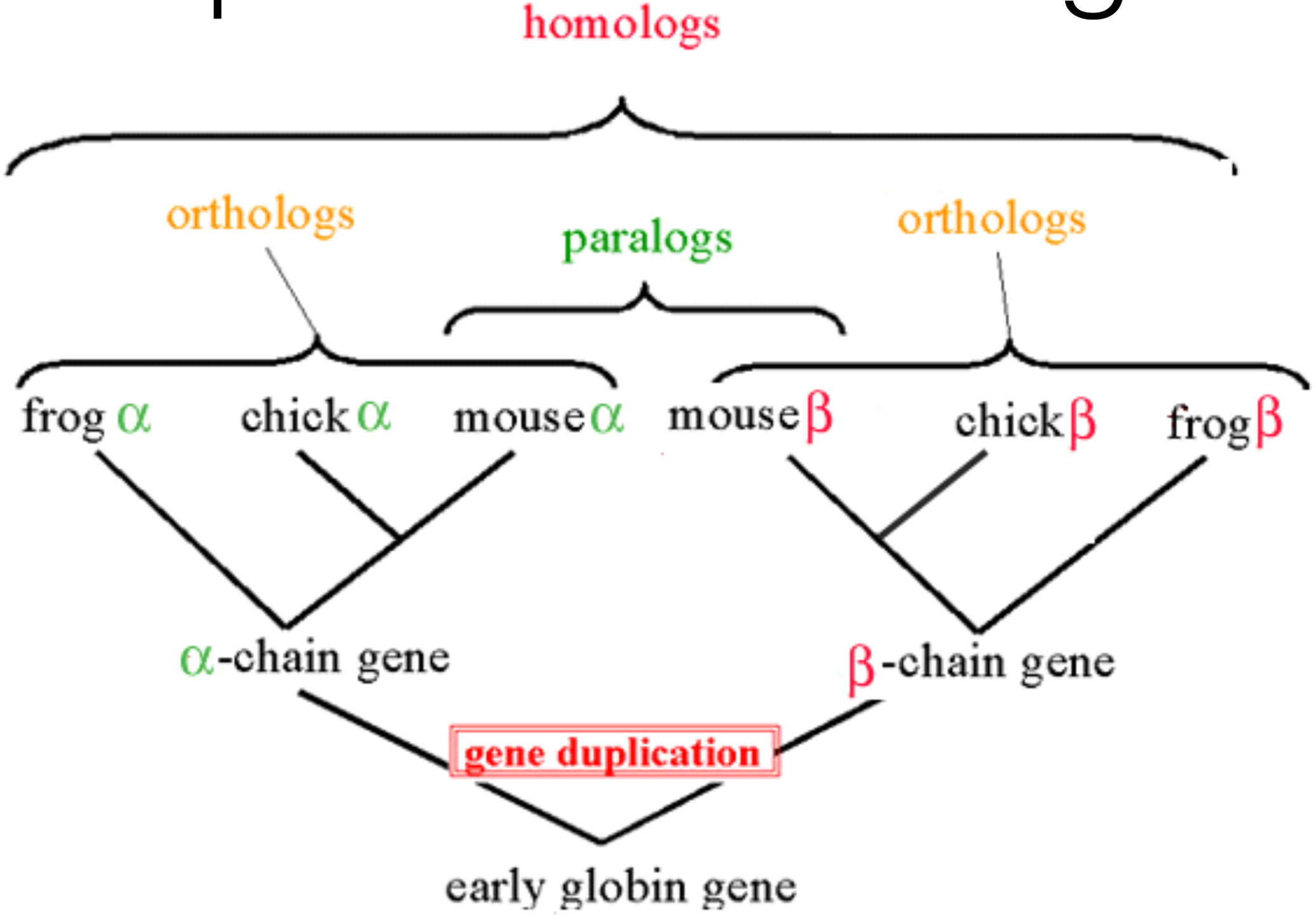
¿Qué es homología?

- **homología molecular**—> especies que pertenecen al mismo grupo taxonómico muestran similitudes en DNA, RNA y proteínas debido a que comparten un ancestro común (no por chance)

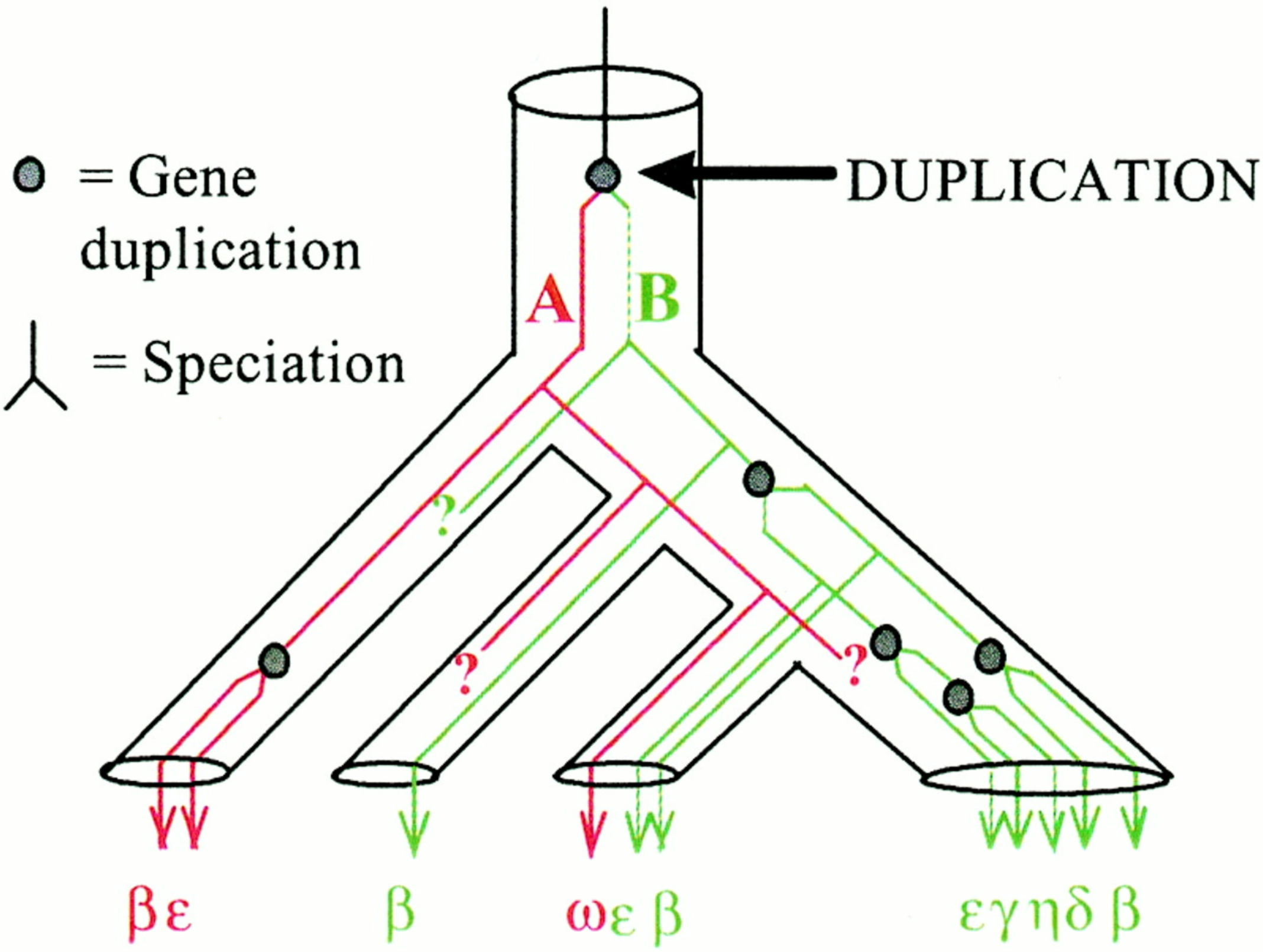
Tipos de homología

- Ortólogos
- Paralógos
- Xenólogos

Tipos de homología



Ancestral β-globin gene

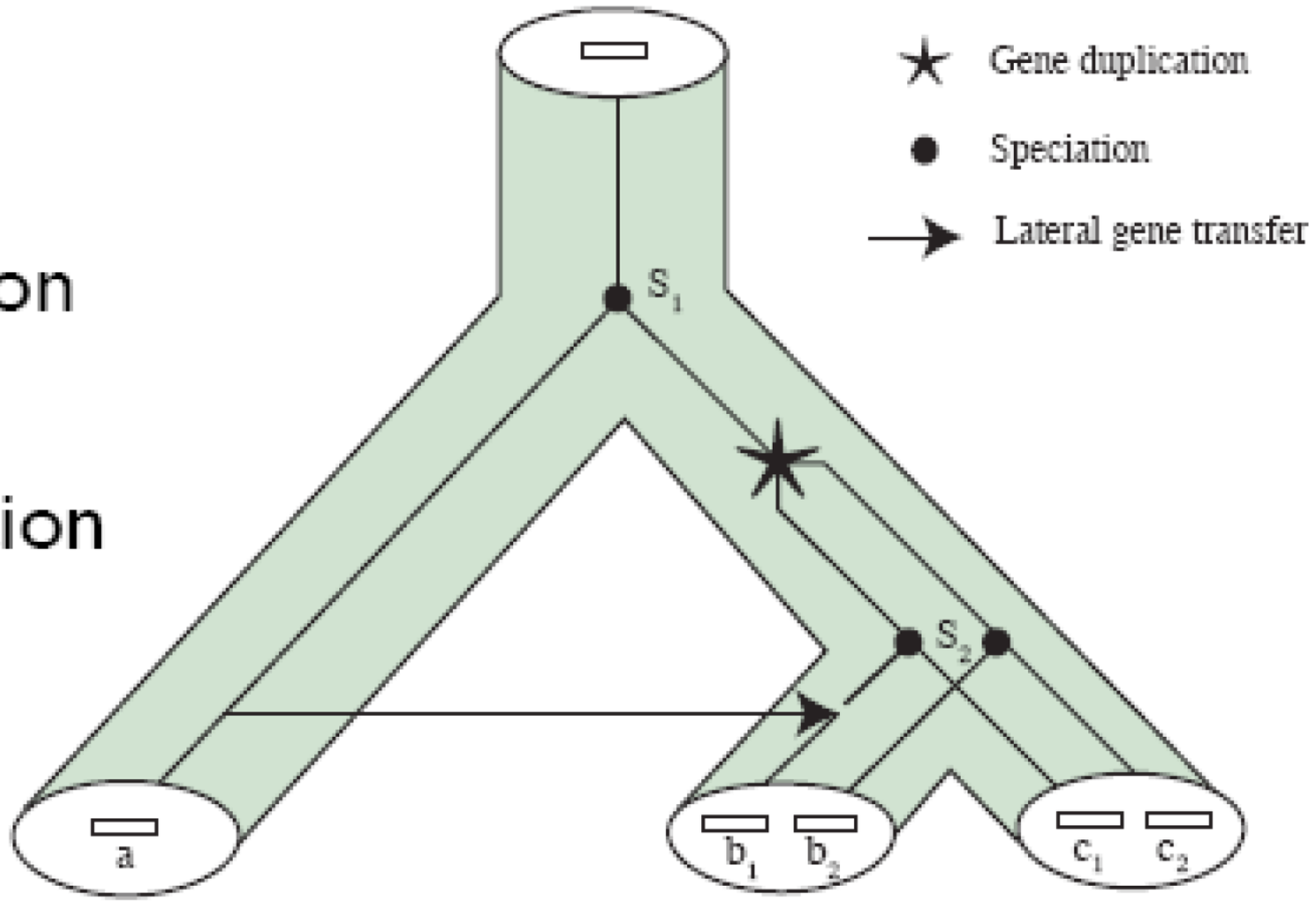


Tipos de homología

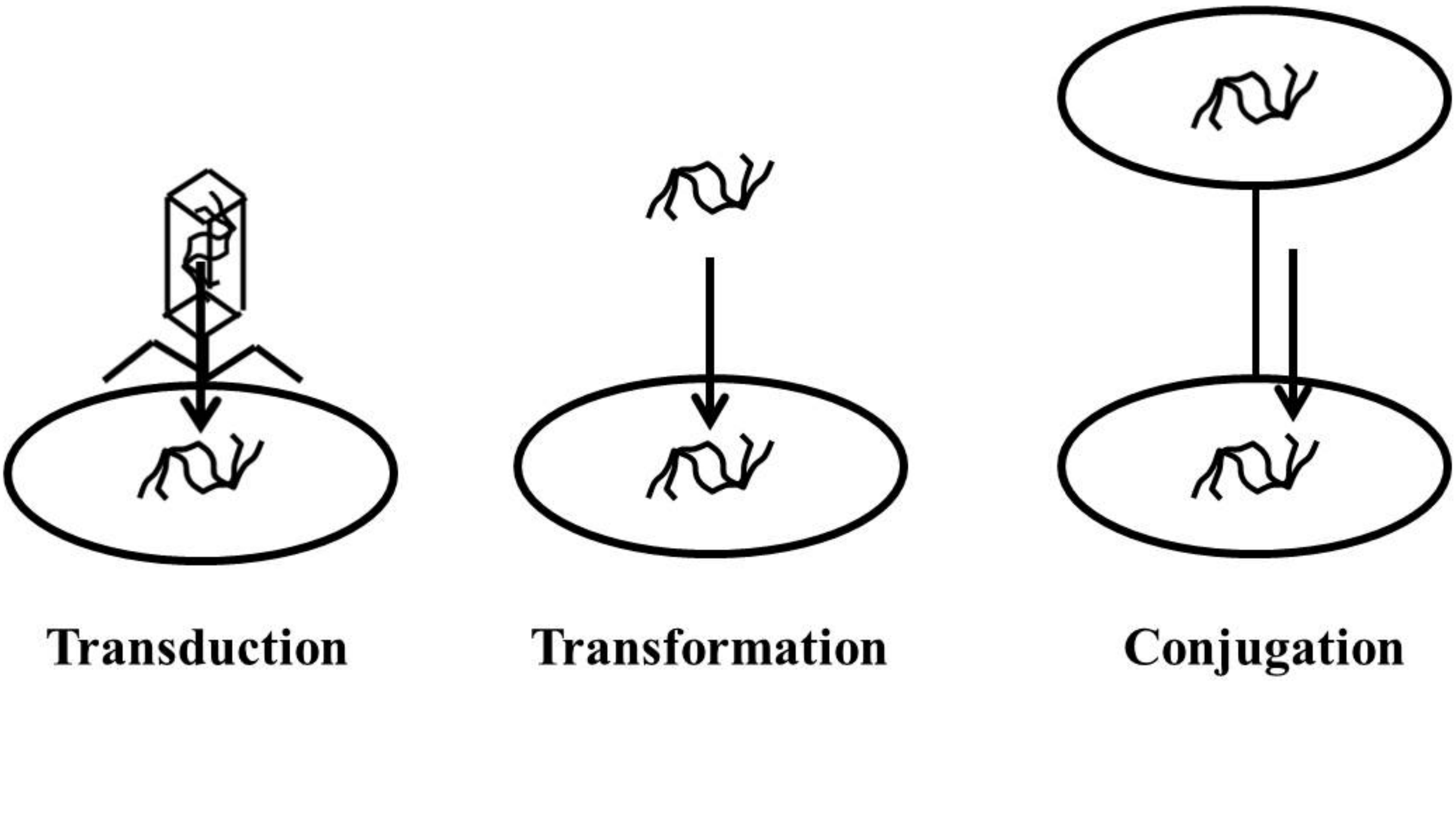
Two genes (or characters) are *homologs* if they have a common ancestor.

Main Subtypes

- *Orthologs*: through speciation
- *Paralogs*: through duplication
- *Xenologs*: through lateral transfer



Xenólogos en bacteria



Transduction **Transformation** **Conjugation**

Bases de datos

¿Por qué necesitamos bases de datos?

- Biología es una ciencia cuantitativa
- Experimentos de alto rendimiento como secuenciamiento masivo producen vastas cantidades de datos
- Necesitamos clasificar, almacenar, buscar información biológica para transformar información en conocimiento

¿Qué pueden hacer las bases de datos?

- Hacer datos disponibles para científicos alrededor del mundo (human-readable)

- Hacer datos disponibles para que puedan ser analizados por algoritmos (machine-readable)

Tipos de bases de datos

- Primarias: Resultados experimentales directos.
  Secundarias: Resultados de análisis

- Nucleótidos y proteínas

- Dominios y motivos

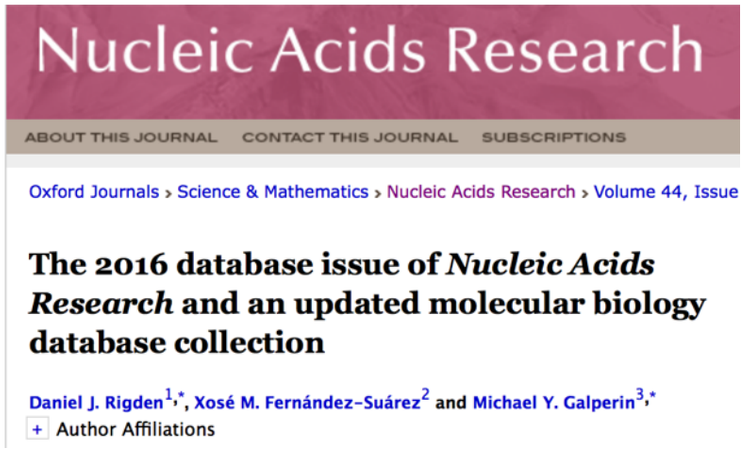
- Estructuras 3D

- Expresión génica

- Rutas metabólicas

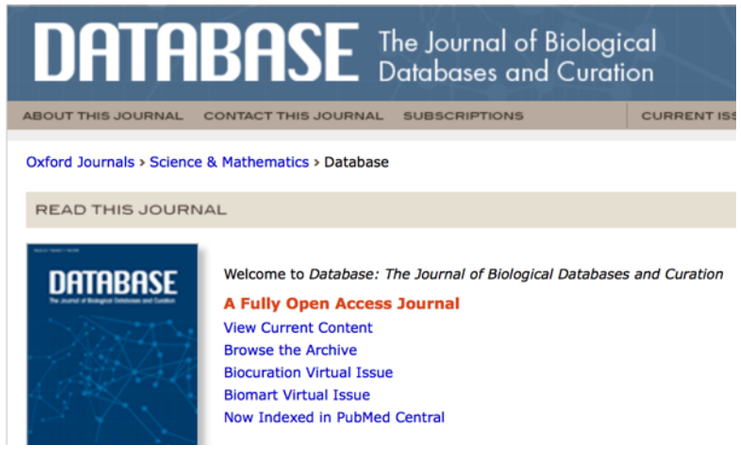
¿Cómo encuentro la base de datos que necesito?

- NAR database issue
- Database Journal



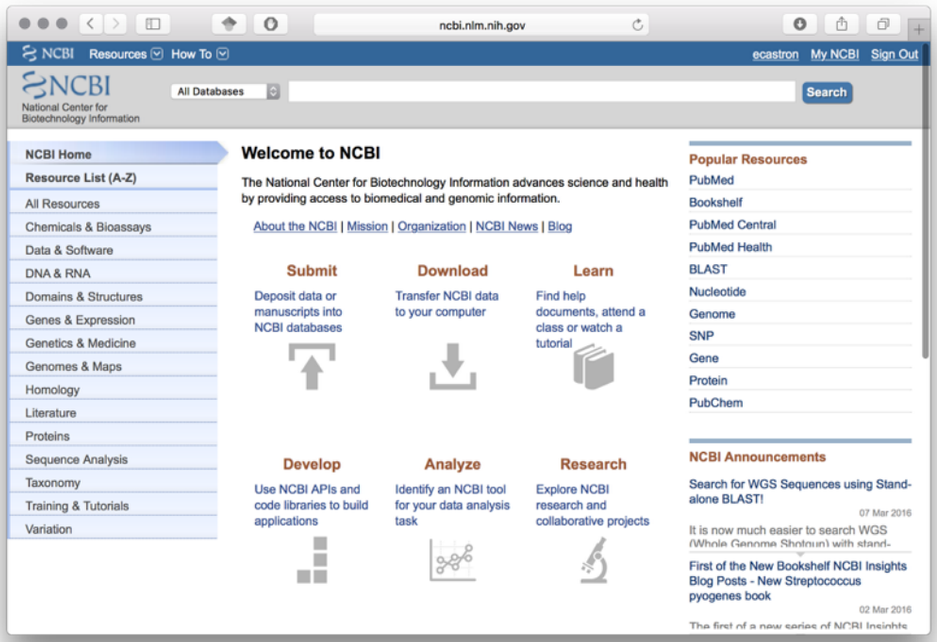
NAR Database Summary Paper Category List

Nucleotide Sequence Databases
RNA sequence databases
Protein sequence databases
Structure Databases
Genomics Databases (non-vertebrate)
Metabolic and Signaling Pathways
Human and other Vertebrate Genomes
Human Genes and Diseases
Microarray Data and other Gene Expression Databases
Proteomics Resources
Other Molecular Biology Databases
Organelle databases
Plant databases
Immunological databases
Cell biology

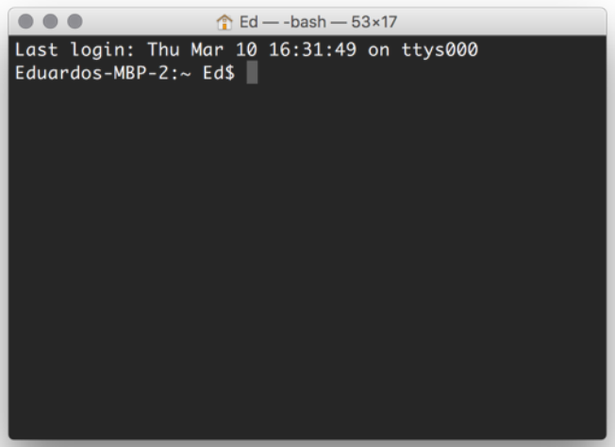


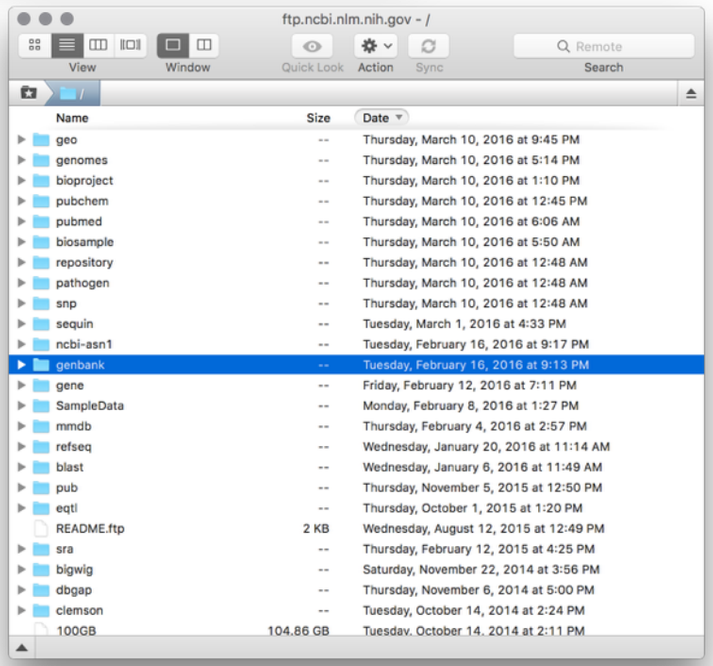
¿Cómo accedo a los datos contenidos en bases de datos?

- Interface gráfica —>



- “Puerta de atrás” FTP, scripting —> ftp.ncbi.nlm.nih.gov

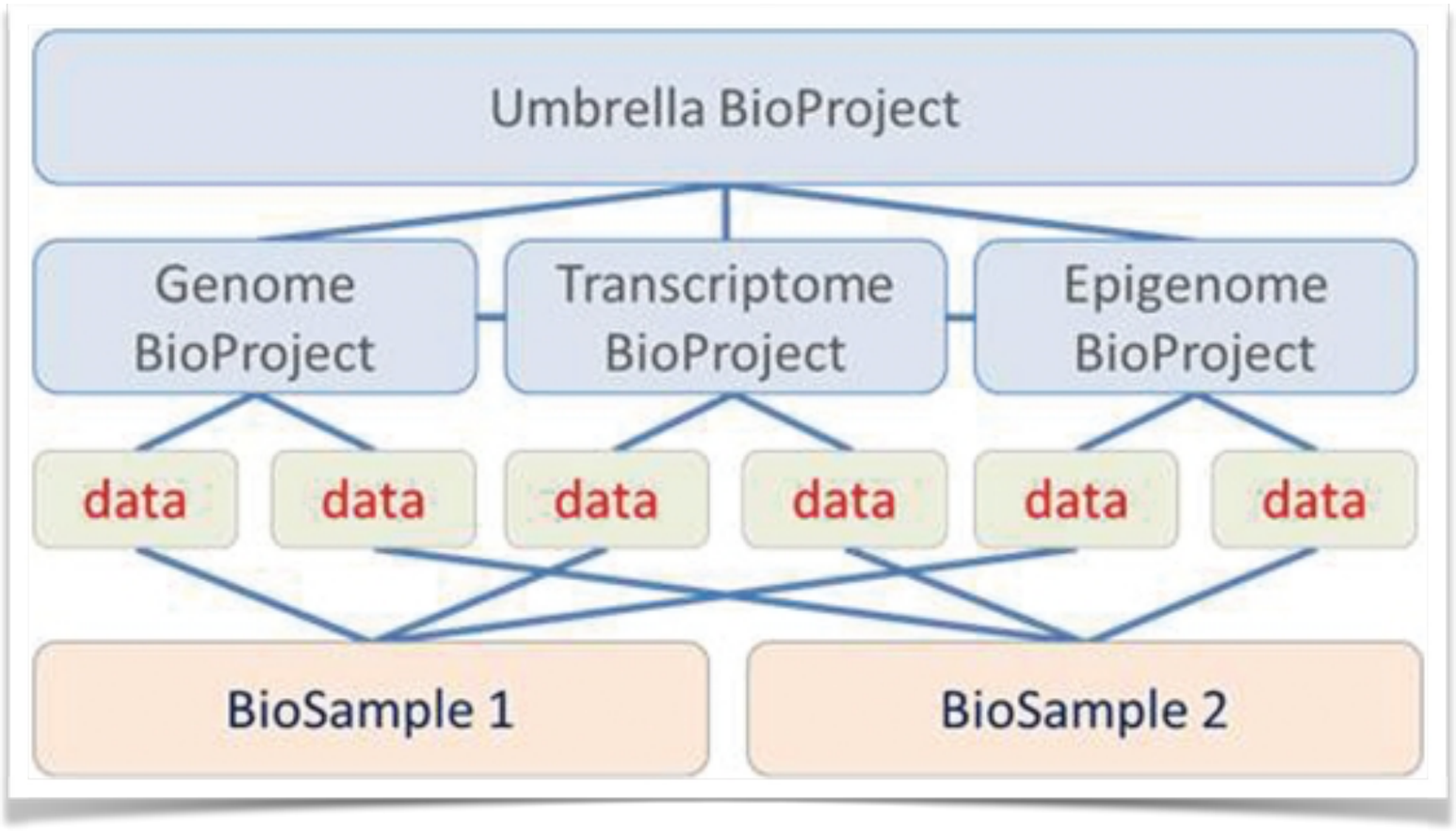




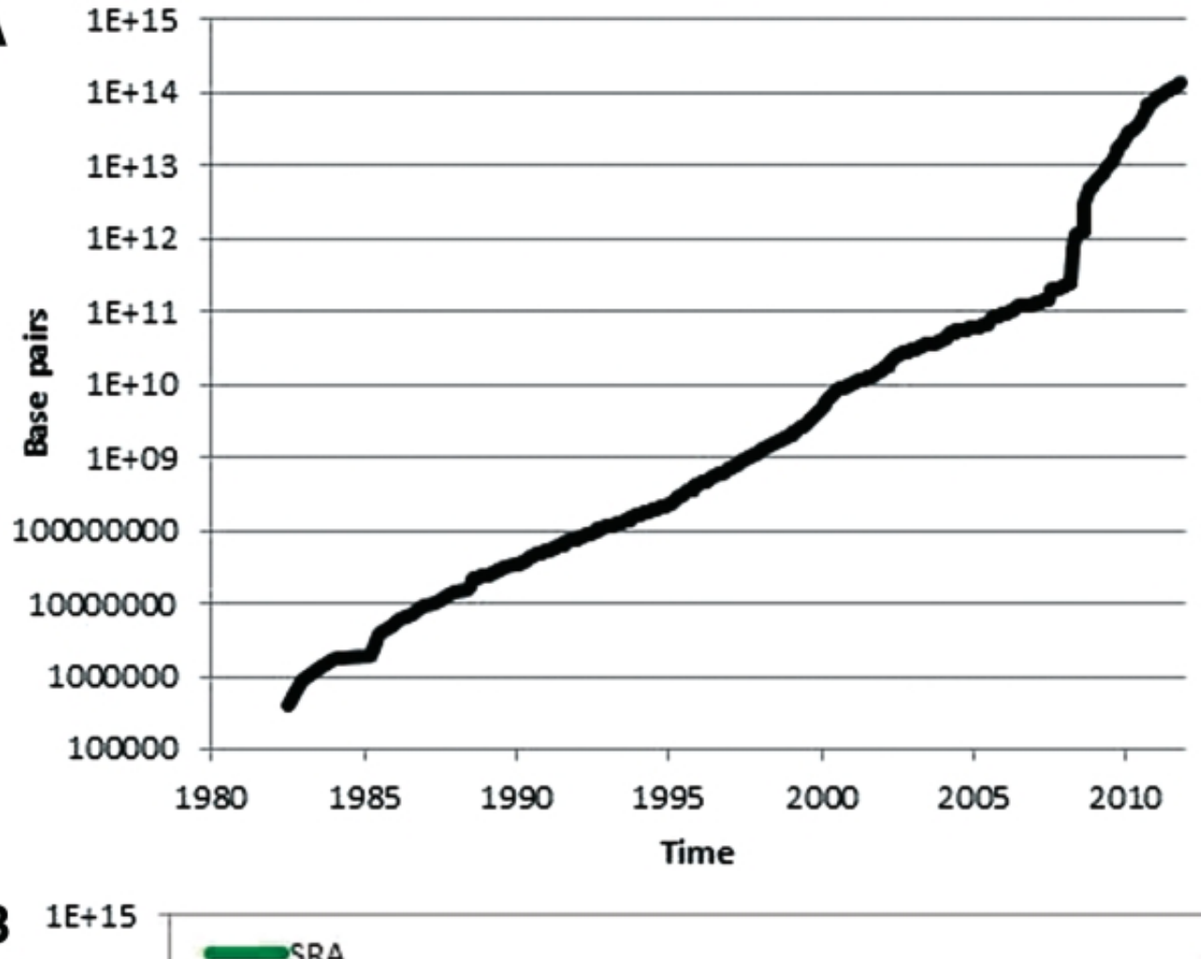
Ejemplo más popular

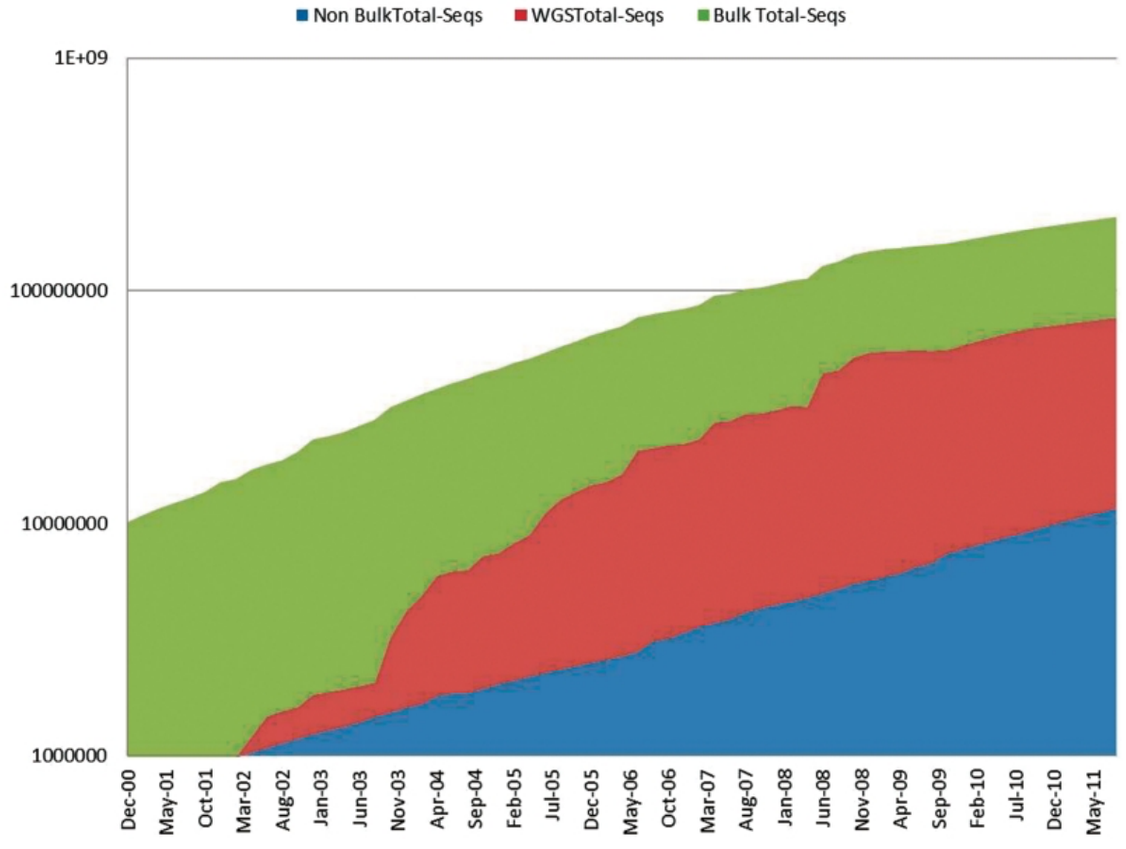
- International Nucleotide Sequence Database Collaboration (INSDC)

- 30 años de antigüedad

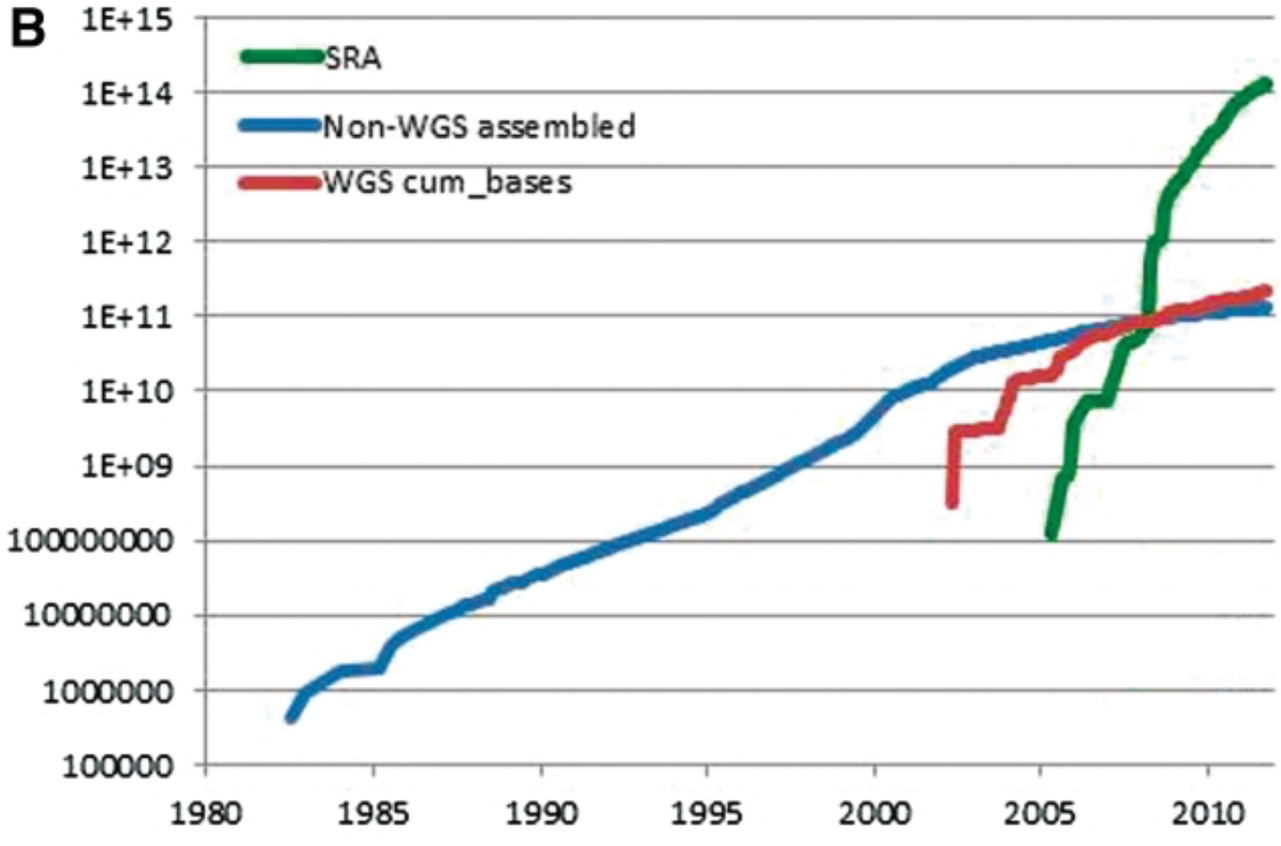


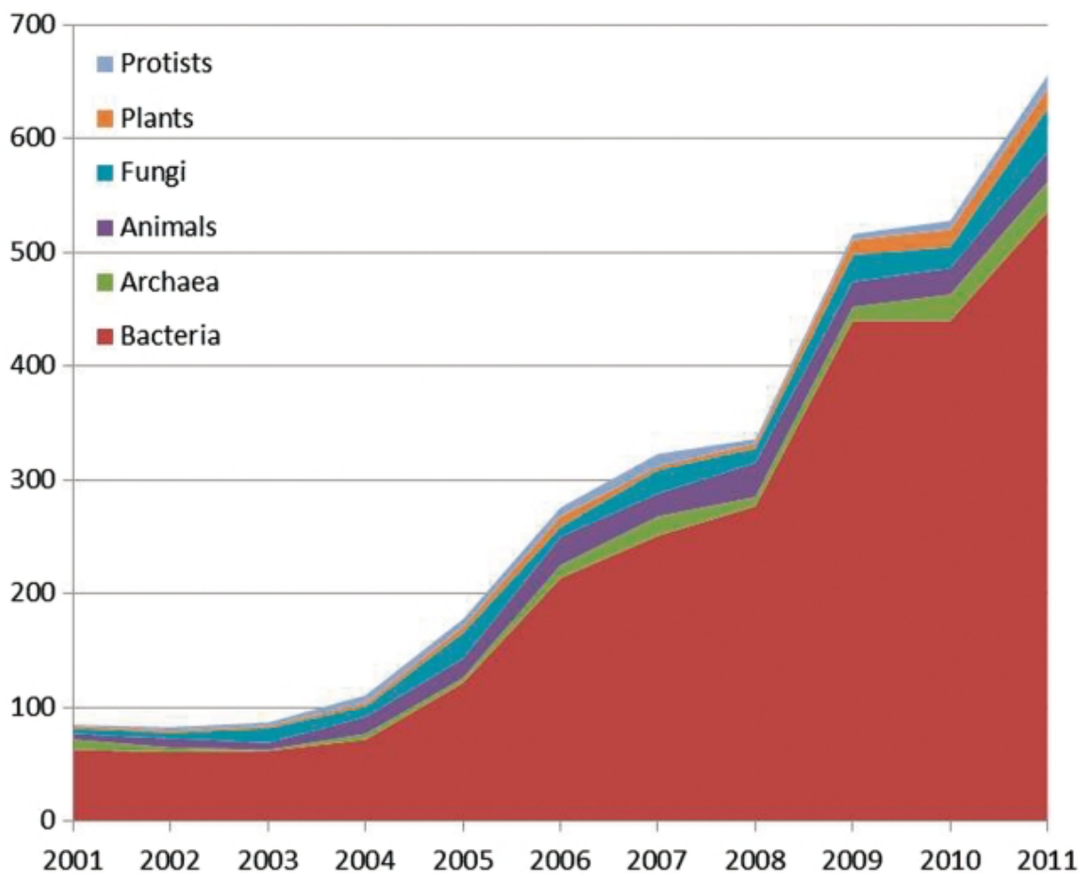
A


1E+15
1E+14
1E+13
1E+12
1E+11
1E+10
1E+09
100000000
10000000
1000000
100000
Base pairs
1980
1985
1990
1995
2000
2005
2010
Time


Non BulkTotal-Seqs
WGSTotal-Seqs
Bulk Total-Seqs
1E+09
100000000
10000000
1000000
Dec-00
May-01
Oct-01
Mar-02
Aug-02
Jan-03
Jun-03
Nov-03
Apr-04
Sep-04
Feb-05
Jul-05
Dec-05
May-06
Oct-06
Mar-07
Aug-07
Jan-08
Jun-08
Nov-08
Apr-09
Sep-09
Feb-10
Jul-10
Dec-10
May-11

B


1E+15
1E+14
1E+13
1E+12
1E+11
1E+10
1E+09
100000000
10000000
1000000
100000
SRA
Non-WGS assembled
WGS cum_bases
1980
1985
1990
1995
2000
2005
2010

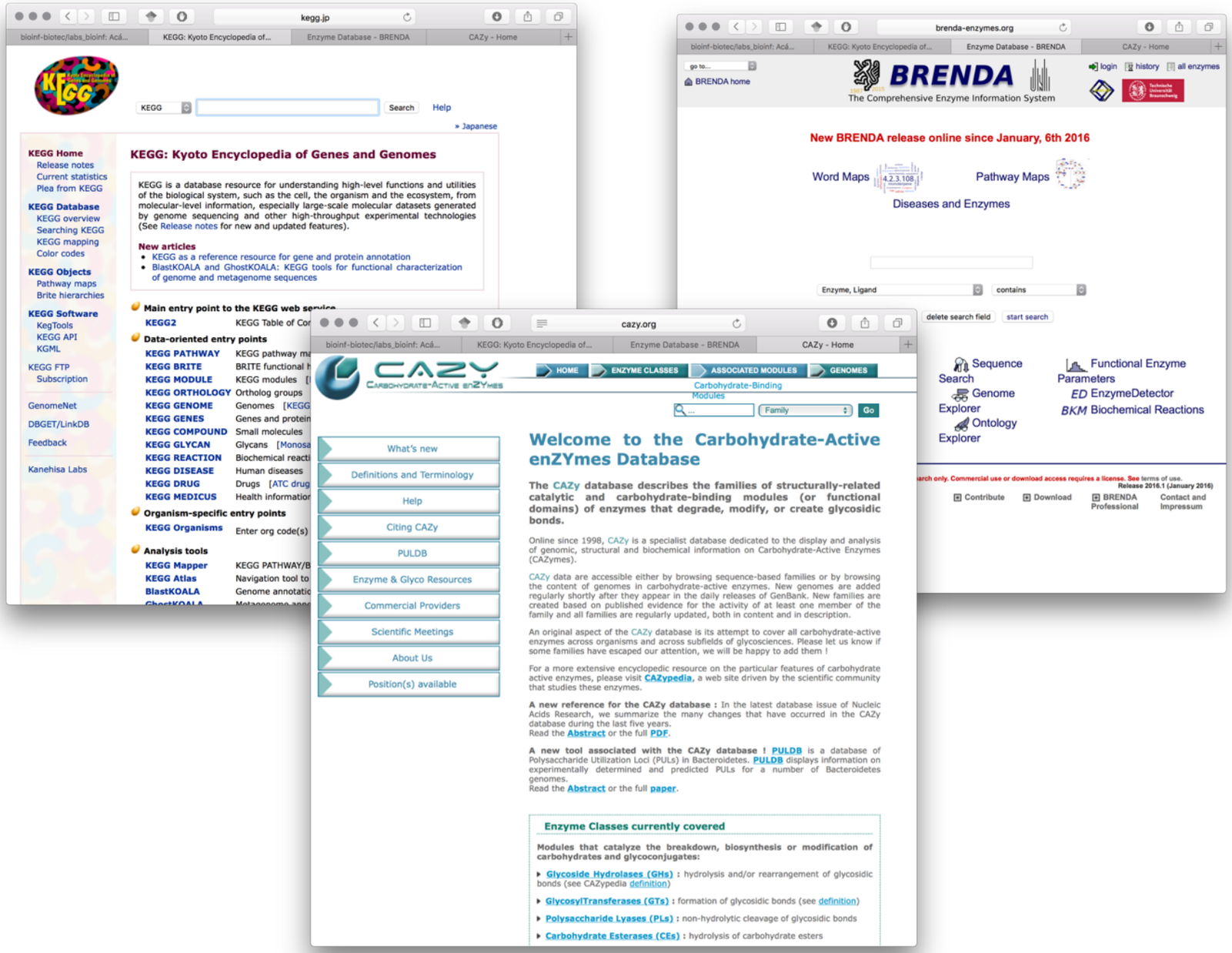

700
600
500
400
300
200
100
0
Protists
Plants
Fungi
Animals
Archaea
Bacteria
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011

Clases especiales de bases de datos

- No curadas
  - NCBI nt, TrEMBL
- Curadas (con diferentes niveles de evidencia)
  - Swiss-Prot, PIR
- Especializadas
  - PeptidesAtlas —> espectros de masas de péptidos

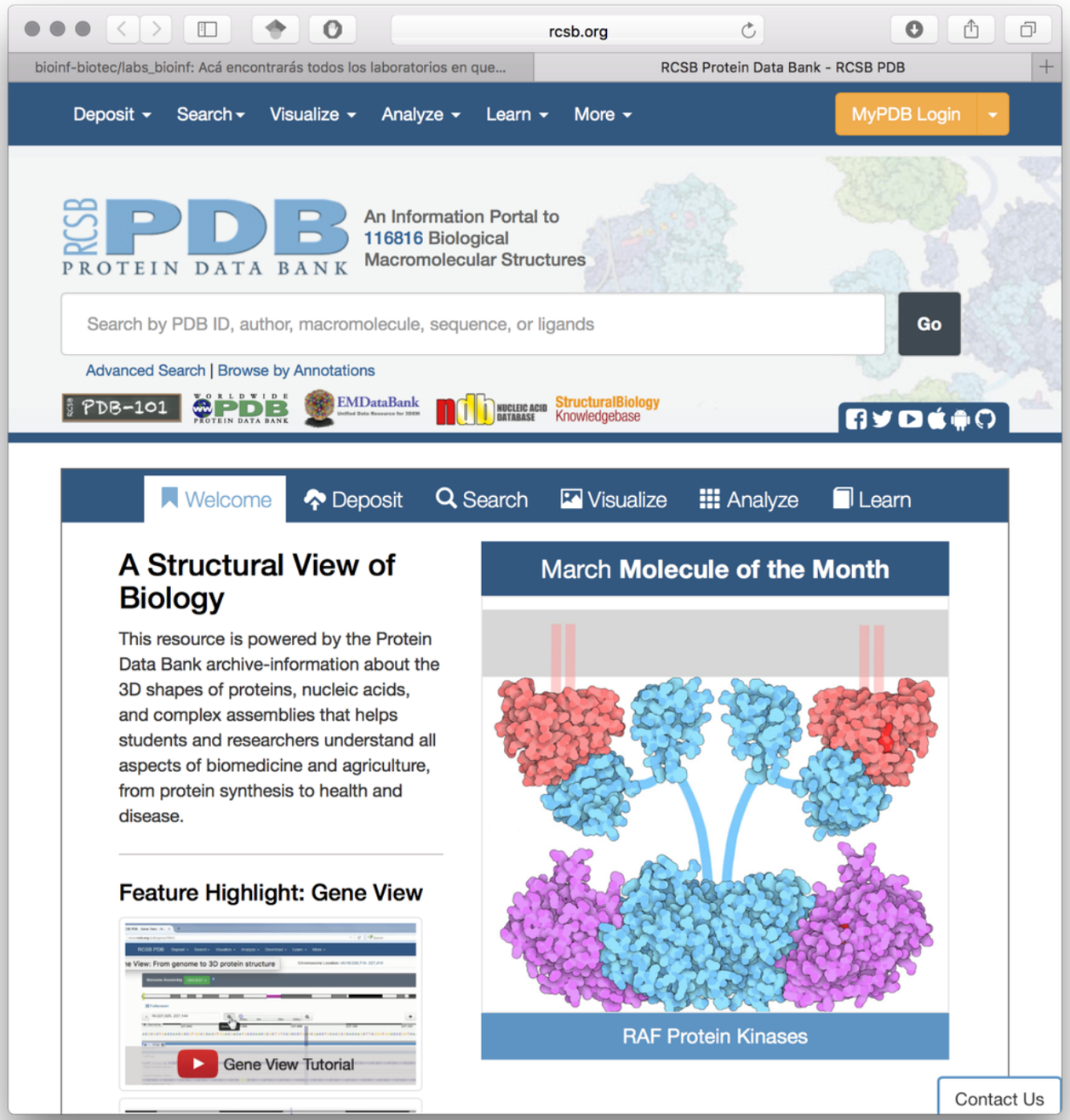
… de enzimas

- KEGG
- BRENDA
- CAZymes



… de proteínas

- Protein Data Bank

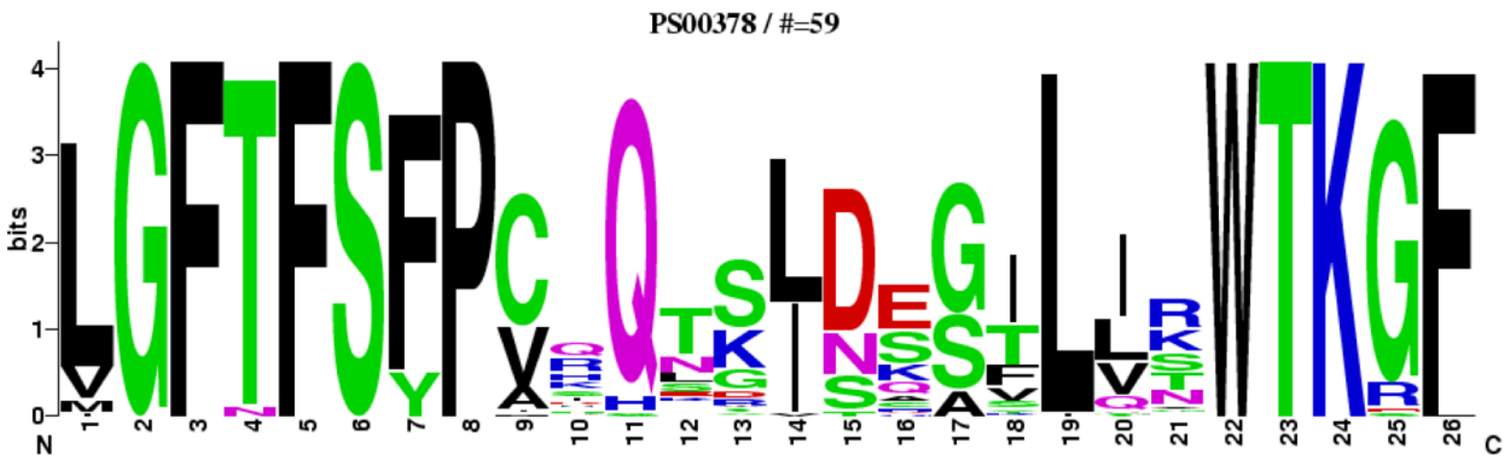


Bases de datos secundarias

- PROSITE
- Pfams
- Rfams
- PRINTS

PROSITE [HEXOKINASES PS00378]

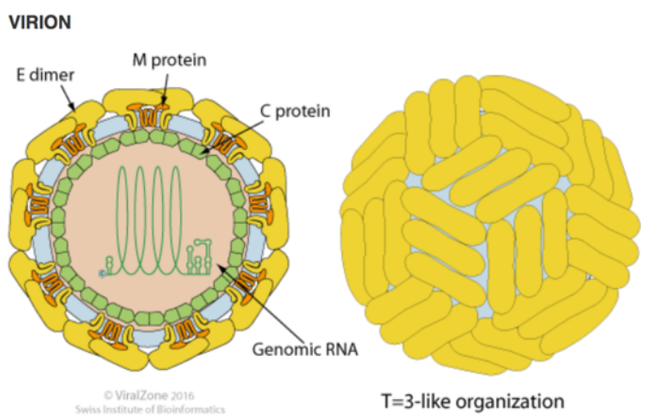
- Database of protein domains, families and functional sites
- Hexokinases signature: Pattern [LIVM]-G-F-[TN]-F-S-[FY]-P-x(5)-[LIVM]-[DNST]-x(3)-[LIVM]-x(2)-W-T-K-x- [LF].



y taxonomia

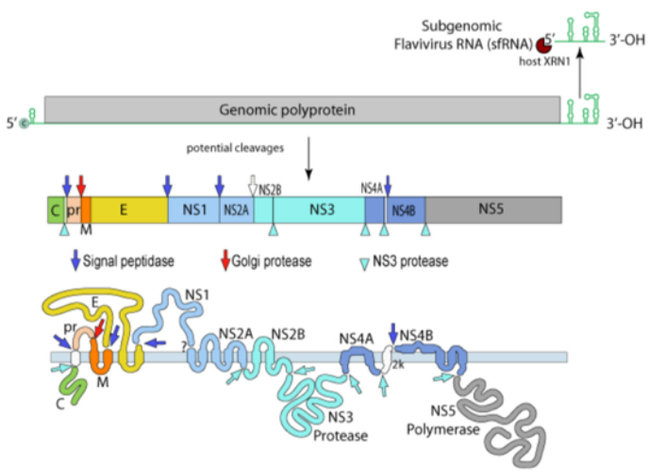
- UniProt Taxonomy
- NCBI Taxonomy
- ViralZone

Zika virus (strain Mr 766)



Enveloped, spherical, about 50 nm in diameter. The surface proteins are arranged in an icosahedral-like symmetry.

GENOME



Monopartite, linear, ssRNA(+) genome of of 10,794 bp. The genome 5' end has a methylated nucleotide cap for canonical cellular translation. The 3' terminus is not polyadenylated but forms a loop structure. This secondary structure leads to the formation of a subgenomic flavivirus RNA (sfRNA) through genomic RNA degradation by host XRN1. sfRNA is essential for pathogenicity, and may play a role in inhibiting host RIG-I antiviral activity as shown for Dengue virus.

GENE EXPRESSION

The virion RNA is infectious and serves as both the genome and the viral messenger RNA. The whole genome is translated in a polyprotein 3,419 aa long, which is processed co- and post-translationally by host and viral proteases.

REPLICATION

CYTOPLASMIC in mammals, **NUCLEAR** in insects?

1. Attachement of the viral envelope protein E to host receptors mediates internalization into the host cell by apoptotic mimicry
2. Fusion of virus membrane with host endosomal membrane. RNA genome is released into the cytoplasm.
3. The positive-sense genomic ssRNA is translated into a polyprotein, which is cleaved into all structural and non structural proteins (to yield the replication proteins).
4. Replication takes place at the surface of endoplasmic reticulum in cytoplasmic viral factories. A dsRNA genome is synthesized from the genomic ssRNA(+).
5. The dsRNA genome is transcribed/replicated thereby providing viral mRNAs/new ssRNA(+) genomes.
6. Virus assembly occurs at the endoplasmic reticulum. The virion buds via the host ESCRT complexes at the endoplasmic reticulum, is transported to the Golgi apparatus.
7. The prM protein is cleaved in the Golgi, thereby maturing the virion which is fusion competent.
8. Release of new virions by exocytosis.


Salary vs years
colored according to position
Salary
Future (years)
Positions
Masters / PhD / Entry Level
PI / Group Leader
Post Doc / Research Scientist
Professor / Senior Managment
Senior Post doc / Senior Scientist

Ahora, el lab…

https://github.com/bioinf-biotec