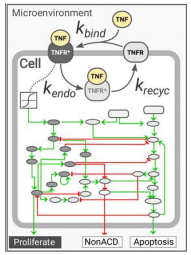
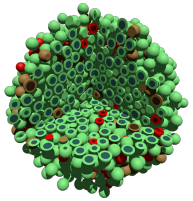
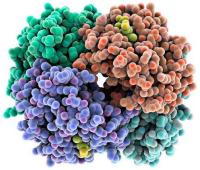
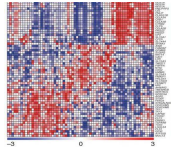




De las redes intracelulares a las simulaciones de sistemas multicelulares





Profesor: Dr. Miguel Ponce de León (miguel.ponce@bs.es) - BSC

Coordinador: Dr. Flavio Pazos (flavio.pazos@gmail.com) - IIBCE/IP

Apoyan:

PEDECIBA MEC-UDELAR

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Institut Pasteur de Montevideo

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Tema 2

Anotación genómica y reconstrucción de redes moleculares

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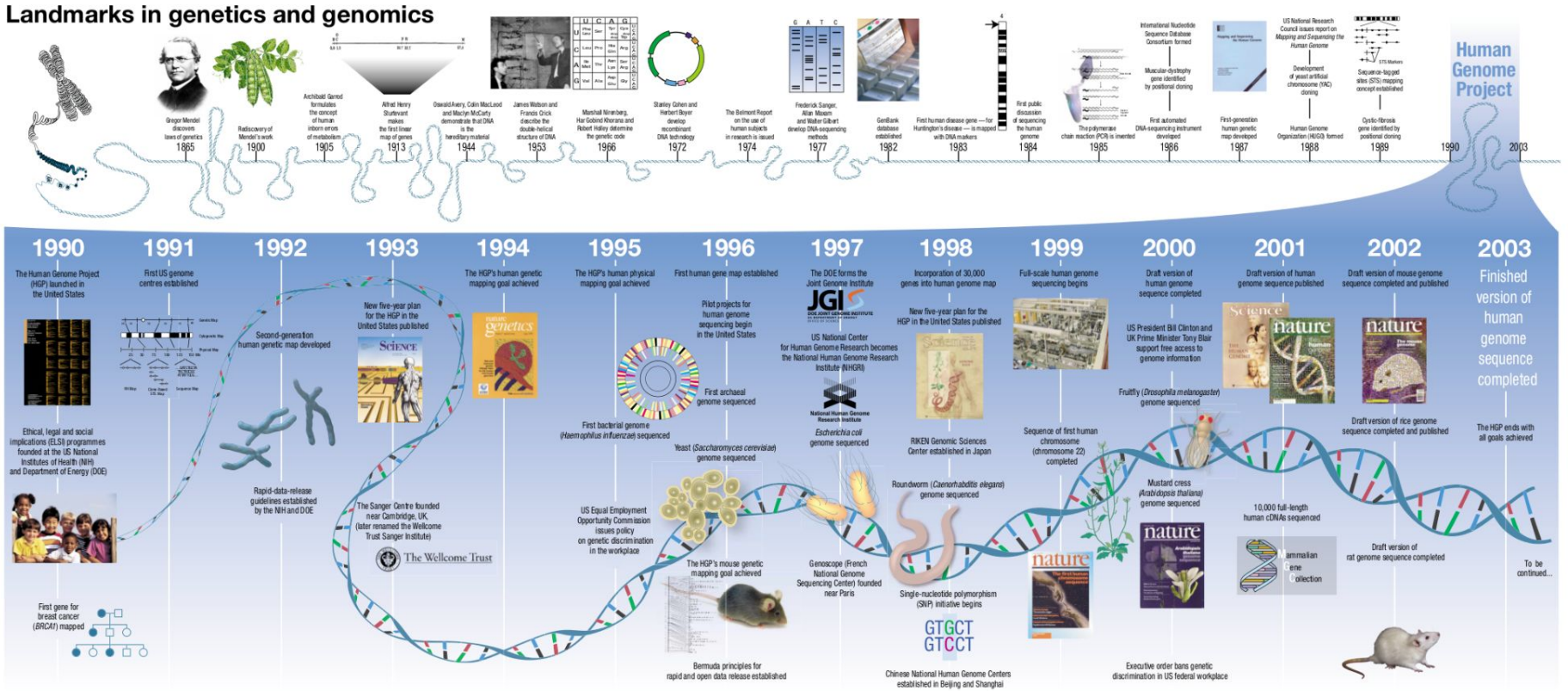
Nace la primera *omica* ⟶ Genómica



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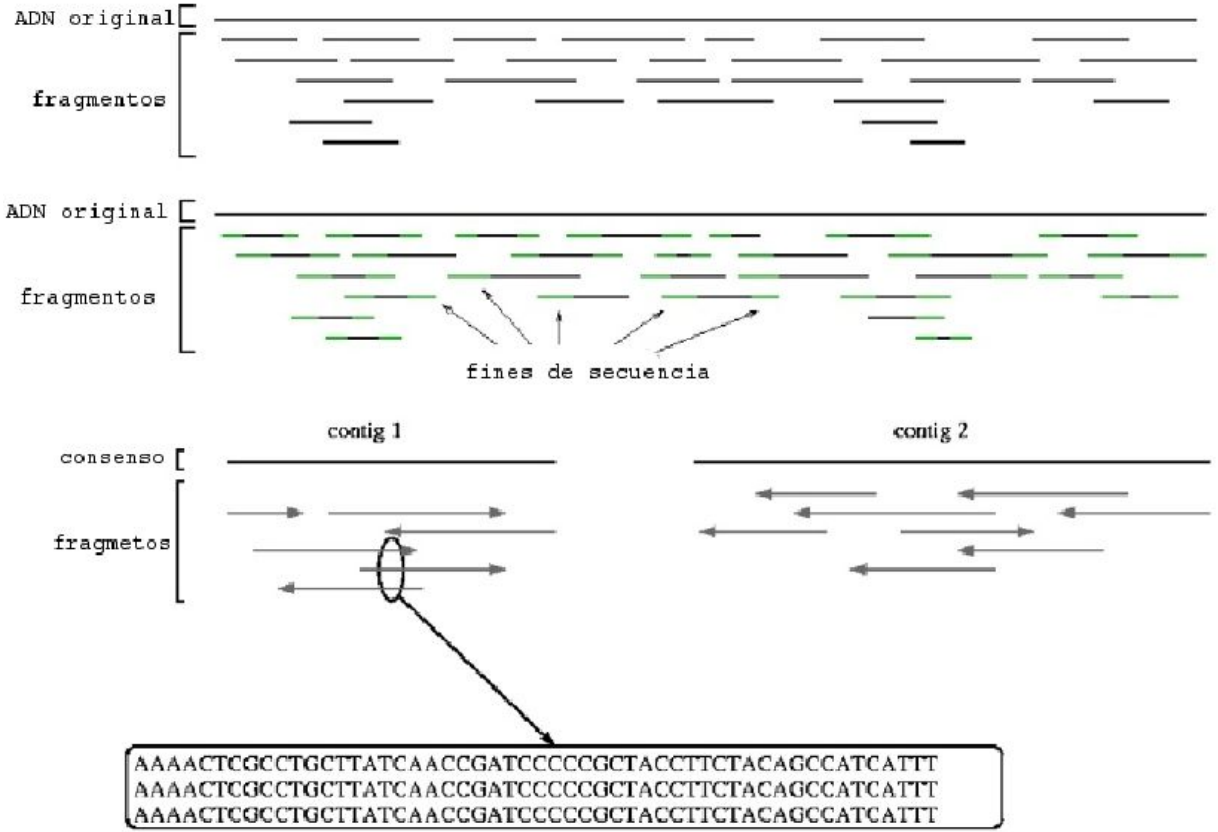
Secuenciación y ensamblado de genomas → nace la bioinformática



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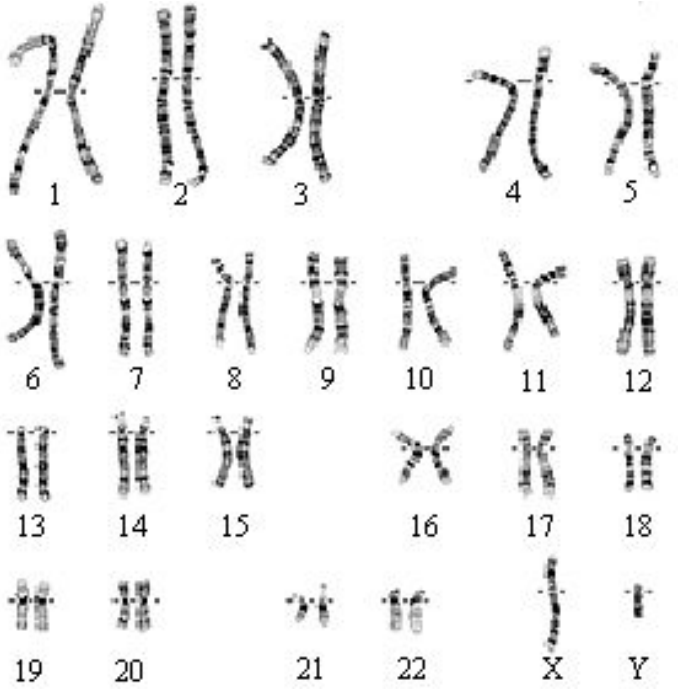
El genoma humano en números (o letras)



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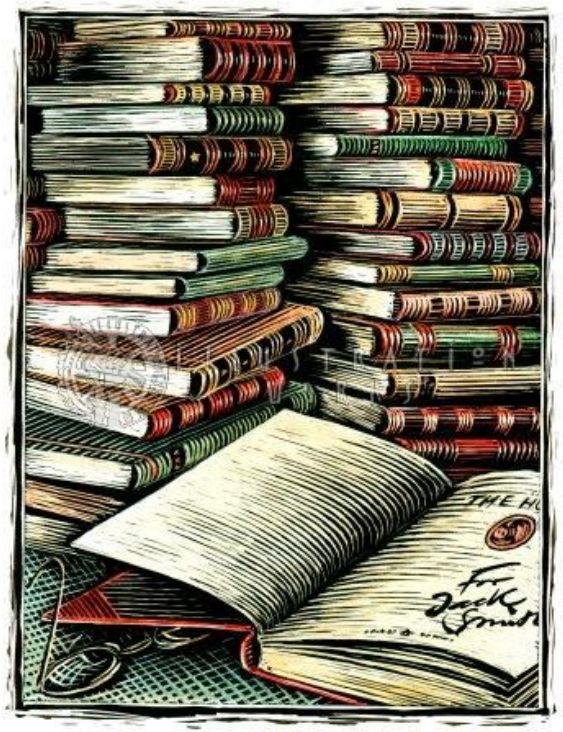

3.000.000.000 pares de bases

200 guías telefónicas de Manhattan
(1000 páginas cada una!!!)

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El genoma humano en números (o letras)

3000 pb ~ 0.0001% del genoma humano (0.06% E. *coli*)

TATGCCGACCATTGCGCTGACTAACAGCATCGCTTTTGCCAACGTGCCGGATGTGGAGCGTGATTTCCCGCGCATTCGTGTGATGGGCACTATCGGCTGGATTGCCGCCGGTCTGGCATGTGGT
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TCAAGCGCCACTTGCTTGATCACC

¿Dónde están los genes?

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El genoma humano en números (o letras)

3000 pb ~ 0.0001% del genoma humano (0.06% E. *coli*)

TATGCCGACCATTGCGCTGACTAACAGCATCGCTTTTGCCAACGTGCCGGATGTGGAGCGTGATTTCCCGCGCATTCGTGTGATGGGCACTATCGGCTGGATTGCCGCCGGTCTGGCATGTGGT
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TCAAGCGCCACTTGCTTGATCACC

¿Dónde están los genes?

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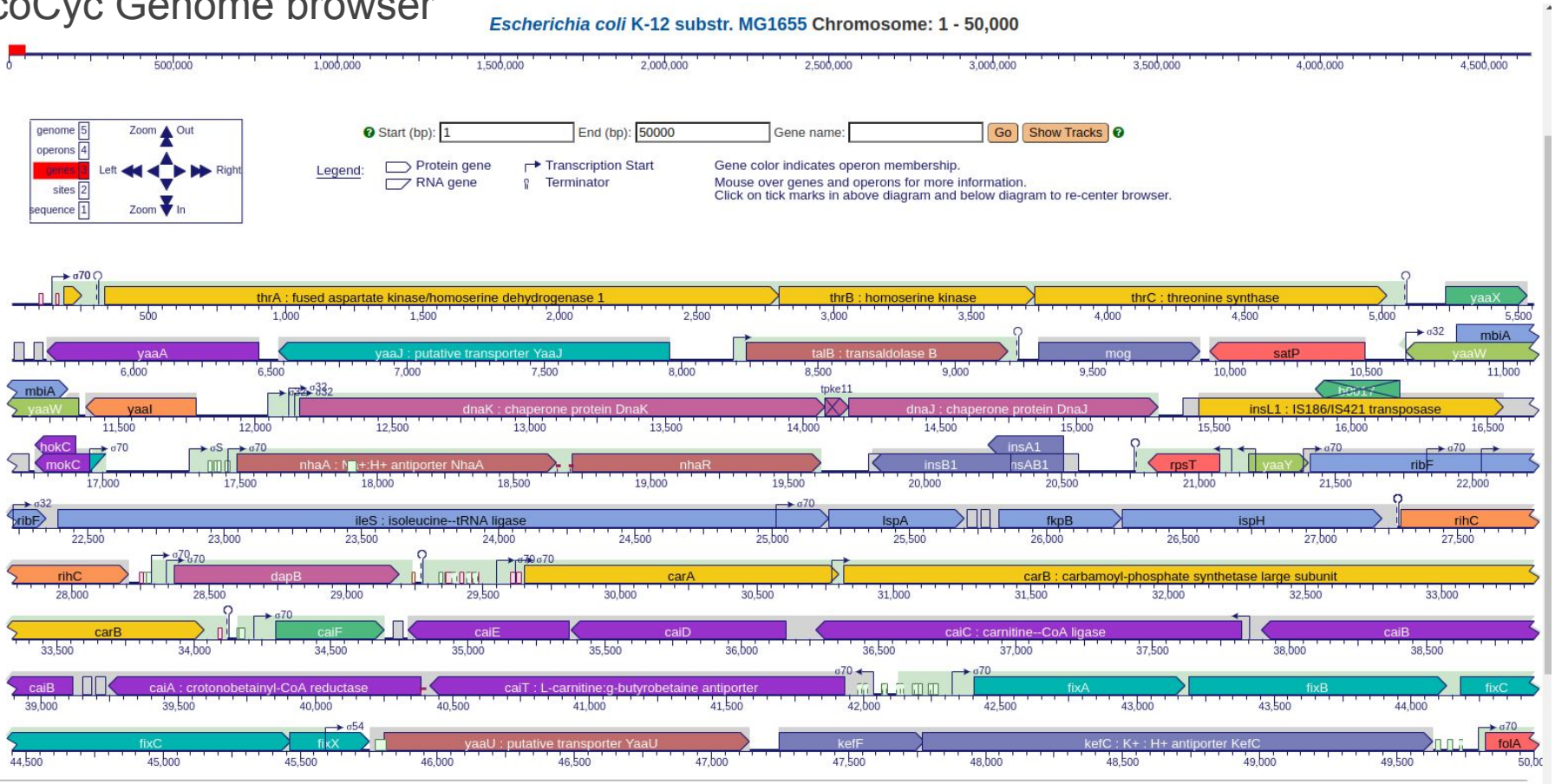
¿Cómo se llega a esto?

https://ecocyc.org/

EcoCyc Genome browser



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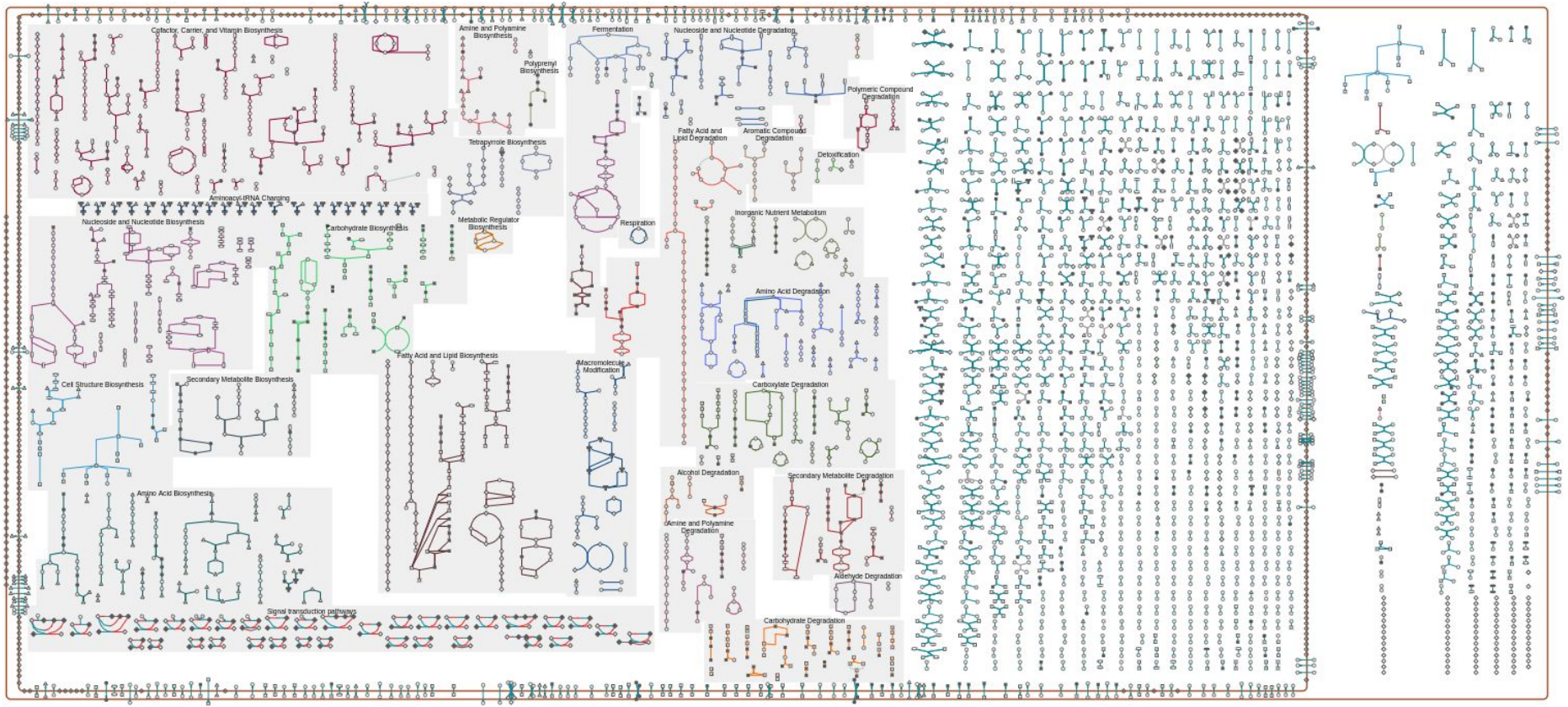
¿Cómo se llega a esto?

https://ecocyc.org/

Metabolic reconstruction of E. coli K12 (MG1655). Metabolic browser (EcoCyc)



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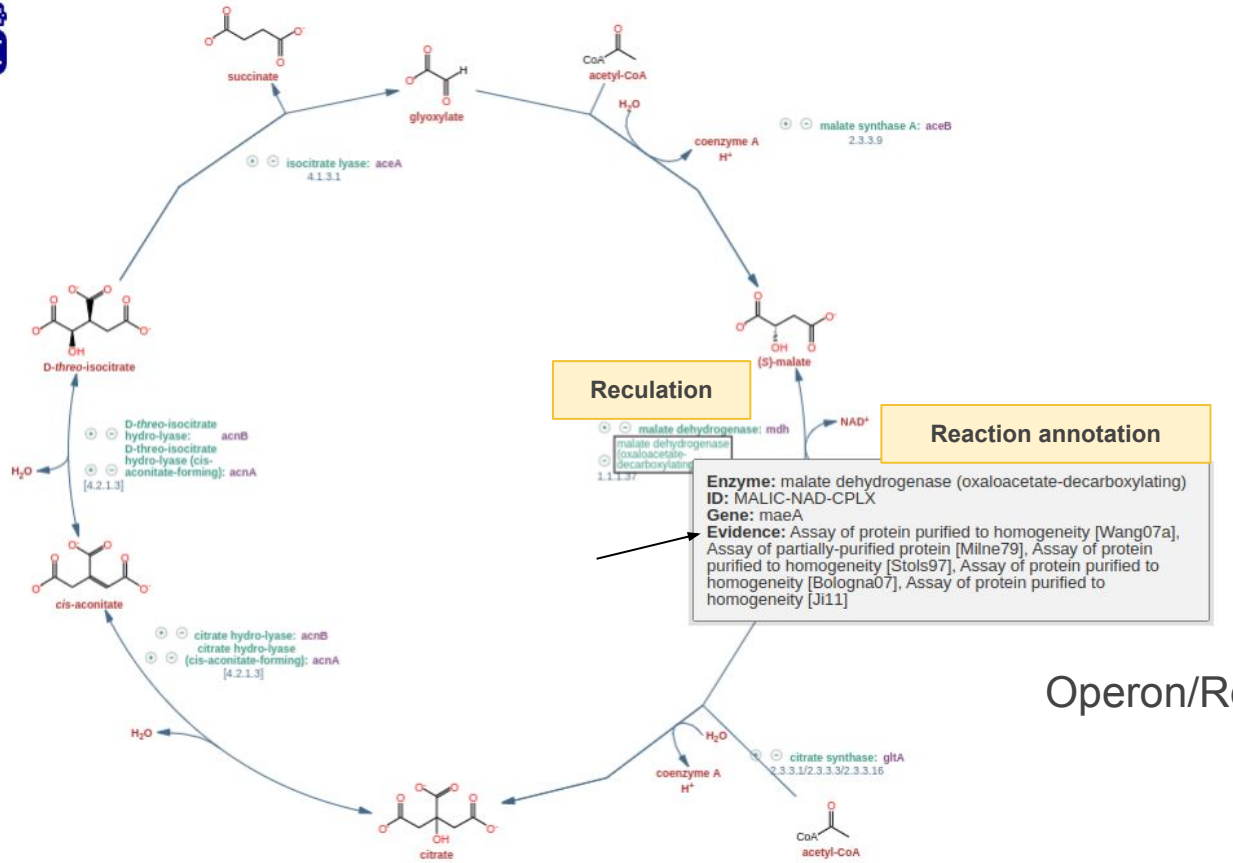
¿Cómo se llega a esto?

https://ecocyc.org/

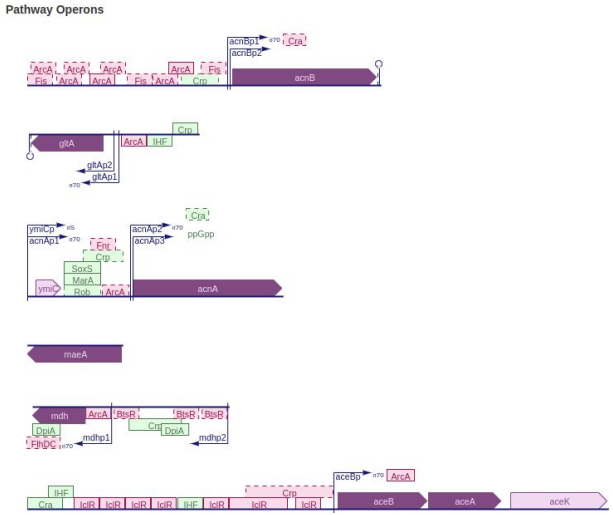


Krebs cycle

Reculation

Reaction annotation

Enzyme: malate dehydrogenase (oxaloacetate-decarboxylating)
ID: MALIC-NAD-CPLX
Gene: maeA
Evidence: Assay of protein purified to homogeneity [Wang07a], Assay of partially-purified protein [Milne79], Assay of protein purified to homogeneity [Stols97], Assay of protein purified to homogeneity [Bologna07], Assay of protein purified to homogeneity [Ji11]



Operon/Regulon structure for the pathway

E. coli K12 (MG1655) Pathway browser (EcoCyc)

GENOME ANNOTATION: FROM SEQUENCE TO BIOLOGY

Lincoln Stein

The genome sequence of an organism is an information resource unlike any that biologists have previously had access to. But the value of the genome is only as good as its annotation. It is the annotation that bridges the gap from the sequence to the biology of the organism. The aim of high-quality annotation is to identify the key features of the genome — in particular, the genes and their products. The tools and resources for annotation are developing rapidly, and the scientific community is becoming increasingly reliant on this information for all aspects of biological research.

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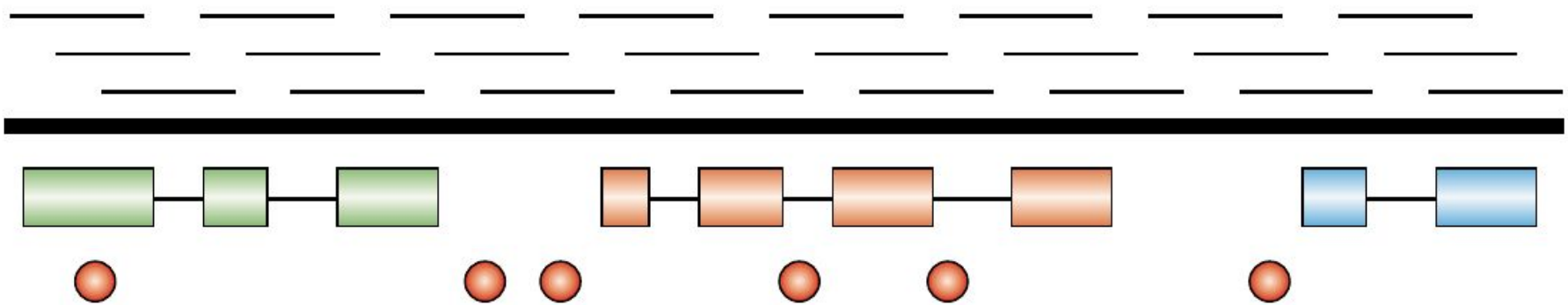
What is genome annotation?

Where?

Nucleotide-level annotation



Structura annotation refers to the process of identifying and annotating various structural features within a genome, such as genes, regulatory elements, and other functional elements (gene finding, promoter prediction, etc).

Adapted from Stein L. 2001.

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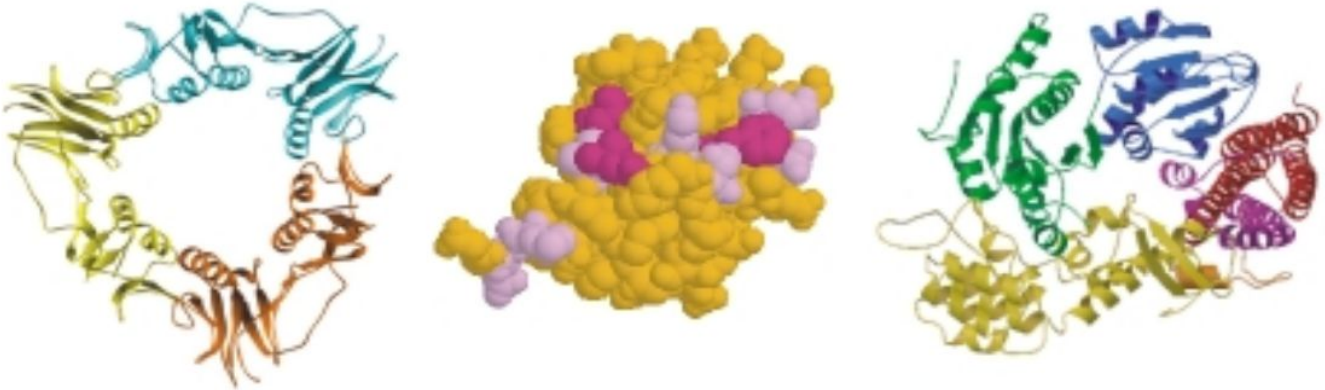
What is genome annotation?

What?
Protein-level annotation



Functional annotation refers to the process of assigning functional information to gene sequences or genomic regions. This information helps researchers understand the biological roles and significance of these sequences (homology-based, domains prediction).

Adapted from Stein L. 2001.

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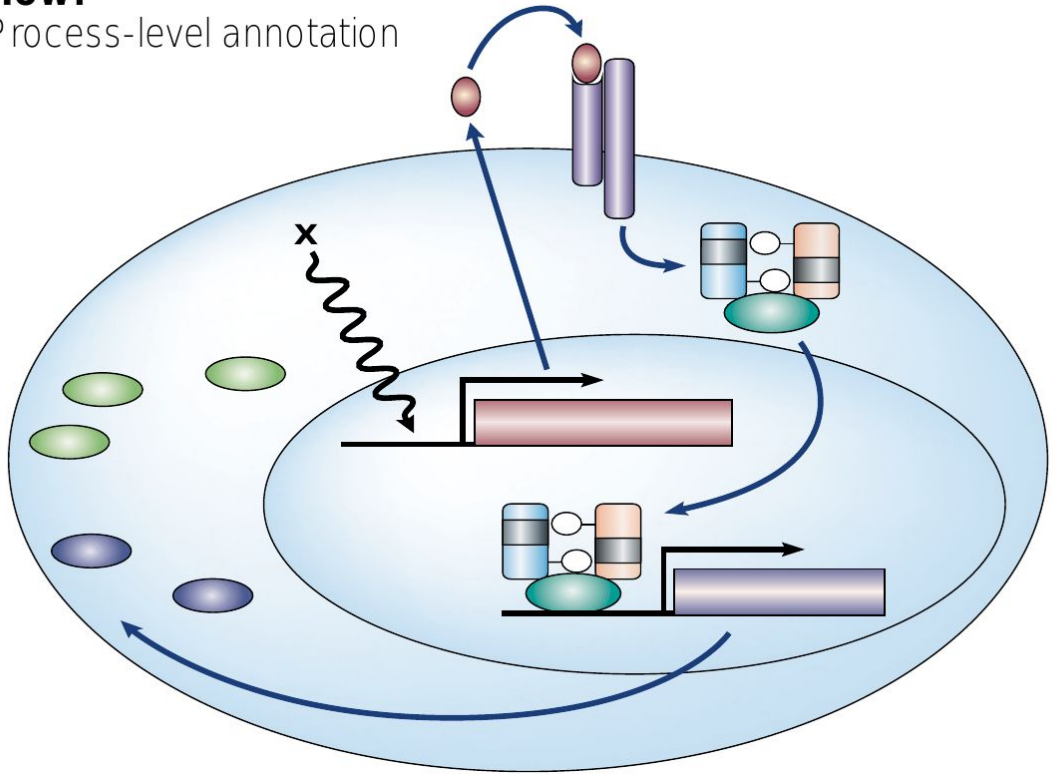
What is genome annotation?

How?
Process-level annotation



Process level annotation refers to the annotation of genes or genomic regions based on their involvement in specific biological processes. This type of annotation provides information about the functions of genes and their roles in cellular processes, pathways, and systems.

Adapted from Stein L. 2001.

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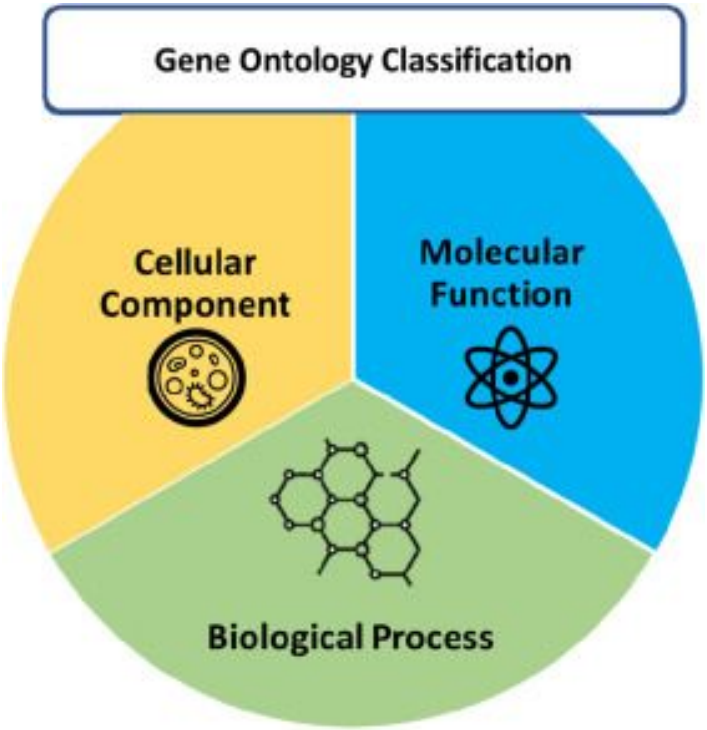
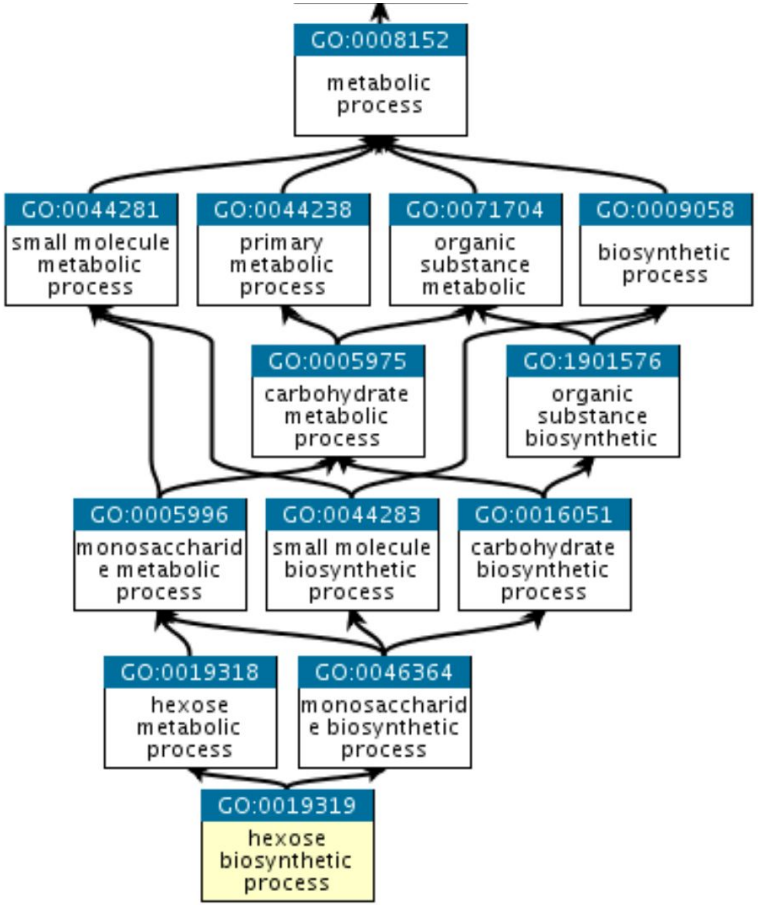
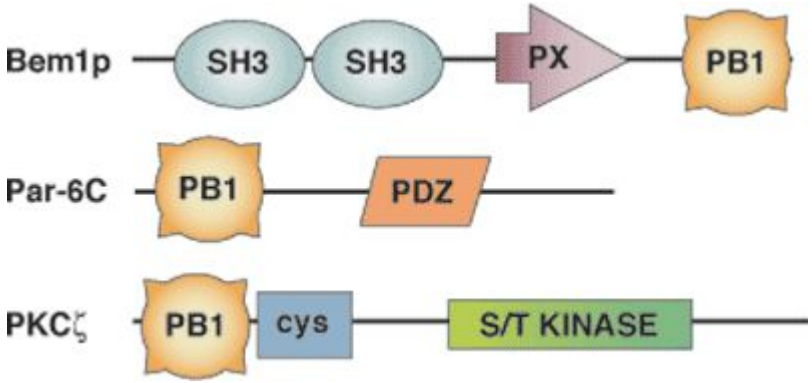
Nombrando entidades y relaciones → ontologías





Buscan estandarizar el uso del lenguaje de las anotaciones (interoperabilidad)

Nombrando entidades y relaciones → ontologías



Molecular function: Molecular-level activities performed by gene products. Molecular function terms describe activities that occur at the molecular level, such as “catalysis” or “transport”.

Cellular Component: The locations relative to cellular structures in which a gene product performs a function, either cellular compartments (e.g., mitochondrion), or stable macromolecular complexes…

Biological process: The larger processes, or ‘biological programs’ accomplished by multiple molecular activities. Examples of broad biological process terms are DNA repair or signal transduction. Examples of more specific terms are pyrimidine nucleobase biosynthetic process or glucose transmembrane transport.

El problema parecería estar resuelto en teoría, pero en la práctica…

BJ www.biochemj.org

BJ Metabolism

Biochem. J. (2010) **425**, 1–11 (Printed in Great Britain) doi:10.1042/BJ20091328

REVIEW ARTICLE

‘Unknown’ proteins and ‘orphan’ enzymes: the missing half of the engineering parts list – and how to find it

Andrew D. HANSON*[1], Anne PRIBAT*, Jeffrey C. WALLER* and Valérie DE CRÉCY-LAGARD†

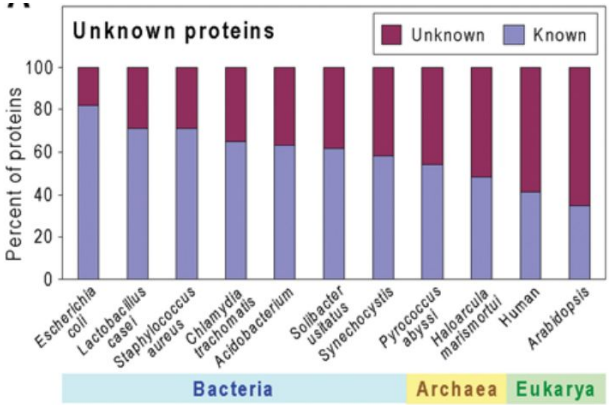
*Horticultural Sciences Department, University of Florida, Gainesville, FL 32611, U.S.A., and †Microbiology and Cell Science Department, University of Florida, Gainesville, FL 32611, U.S.A.

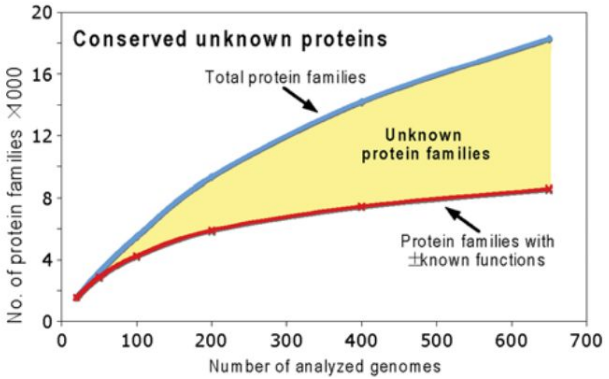
'Unknown' proteins and orphan enzymes

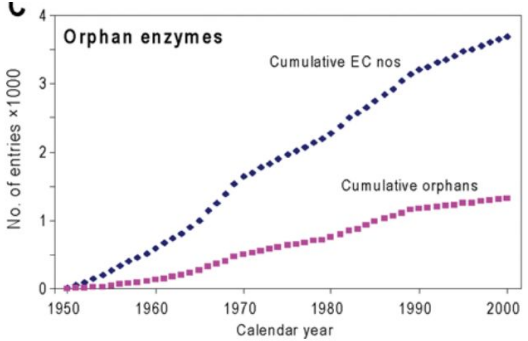
The elephant in the room

Two classes:

- **Hypothetical protein / putative conserved:** Sequences that "looks" like genes, are conserved across liange but nobody knows their function (in the most brad sense).
- **Orphan functions:** known functions (e.g. enzymatic activity) that nobody knows a candidate gene encoding that function.







Adapted from Hanson et 2010.

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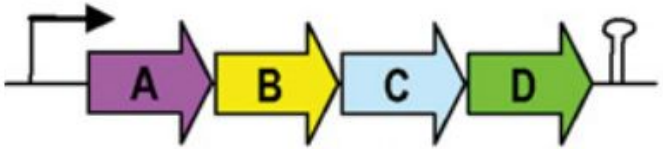
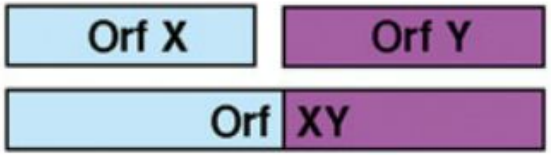
The predictive power of comparative genomics

The 'guilt by association' principle

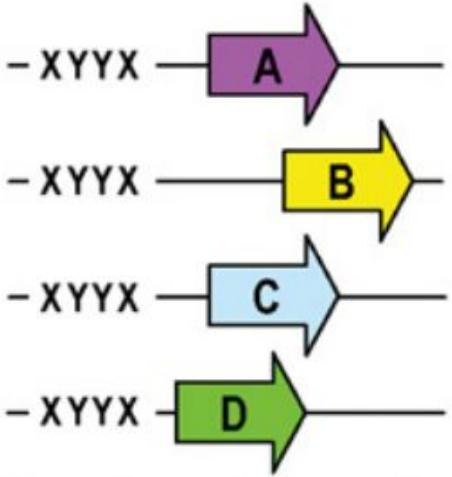
Types of associations in comparative genomics: **genomic evidence**



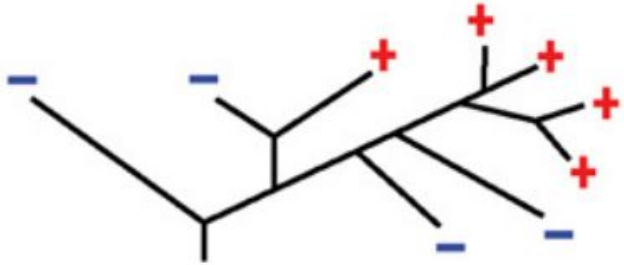
Gene clustering



Gene fusion



Shared regulatory sites



Phylogenetic occurrence

Adapted from Hanson et 2010.

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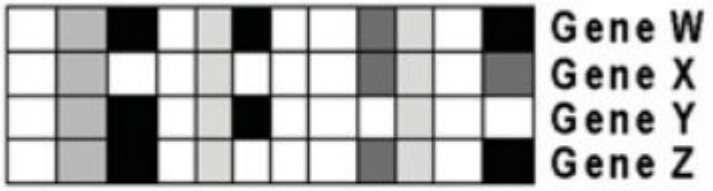
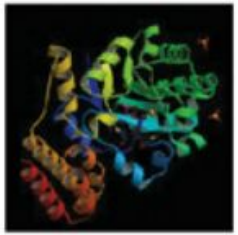
The predictive power of comparative genomics

The 'guilt by association' principle

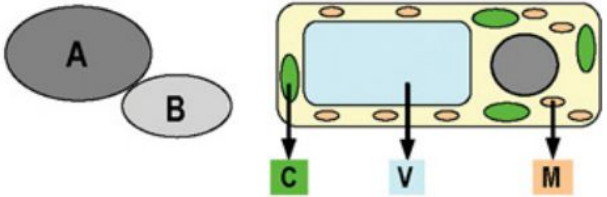
Associations based on post-genomic resources: **post-genomic evidence**



Co-expression

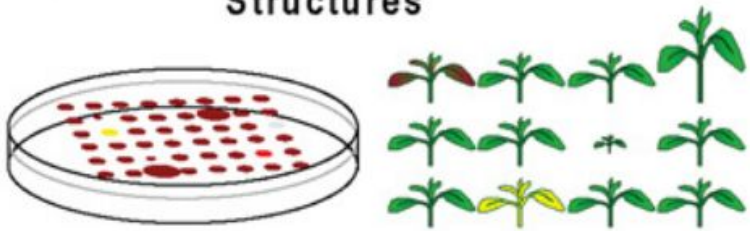


Structures



Protein-protein interactions

Organelle proteomes



Essentiality & other phenome data

Adapted from Hanson et 2010.

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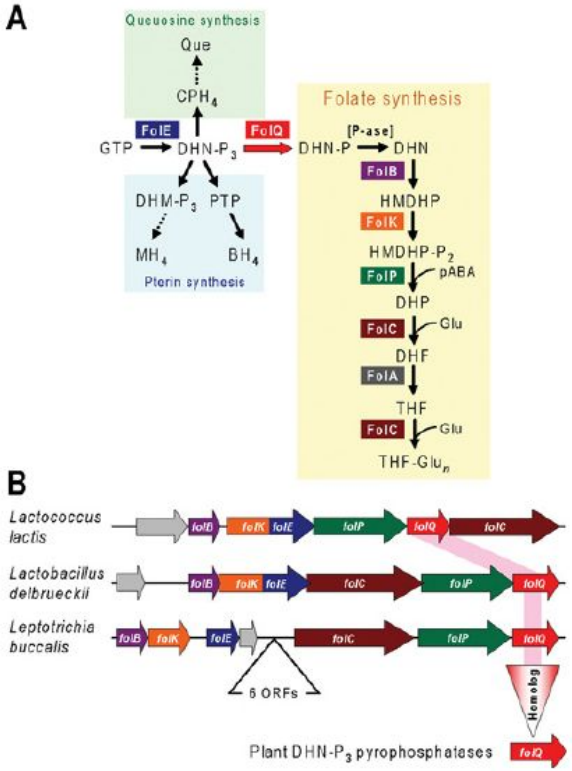
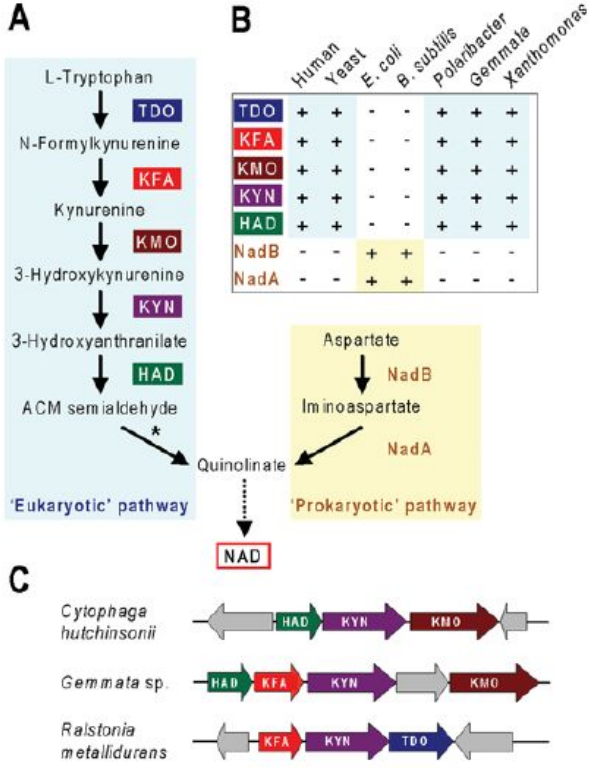
Examples



A missing folate biosynthesis enzyme



Tryptophan to quinolinate in NAD biosynthetic pathway

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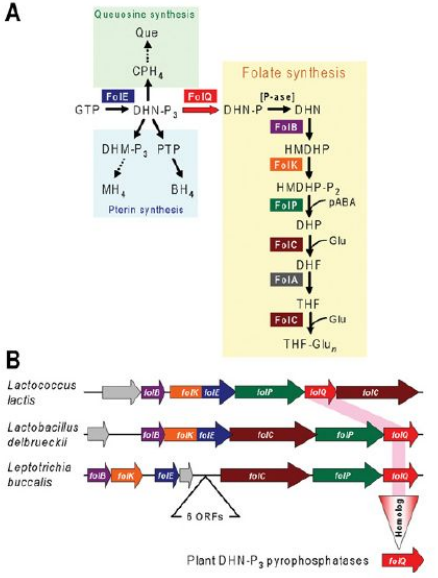
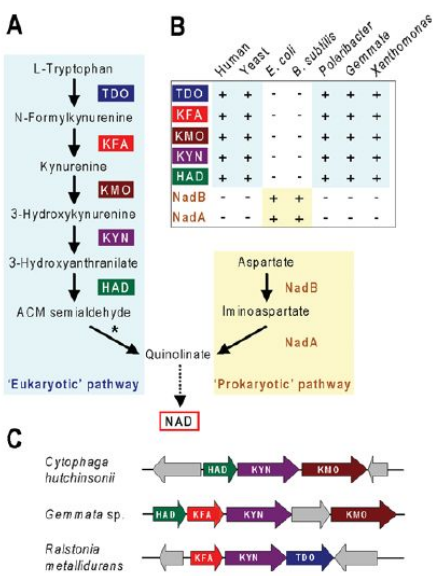
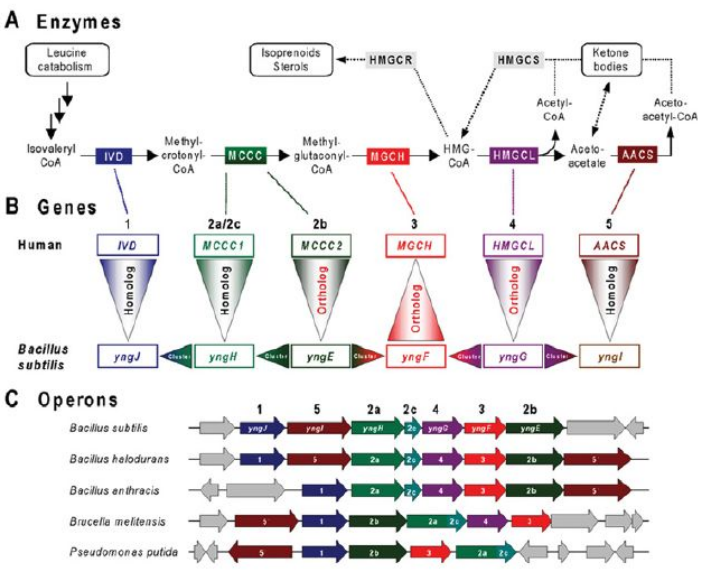
The predictive power of comparative genomics: the 'guilt by association' principle

Example 1: a missing folate biosynthesis enzyme

Example 2: the tryptophan to quinolinate route in NAD synthesis







Machine Learning Based Approaches

A. L. Samuel

Some Studies in Machine Learning Using the Game of Checkers

1959

Abstract: Two machine-learning procedures have been investigated in some detail using the game of checkers. Enough work has been done to verify the fact that a computer can be programmed so that it will learn to play a better game of checkers than can be played by the person who wrote the program. Furthermore, it can learn to do this in a remarkably short period of time (8 or 10 hours of machine-playing time) when given only the rules of the game, a sense of direction, and a redundant and incomplete list of parameters which are thought to have something to do with the game, but whose correct signs and relative weights are unknown and unspecified. The principles of machine learning verified by these experiments are, of course, applicable to many other situations.

Volume 93, 1992

Previous Article | Next Article

From the journal:
Faraday Discussions

Modelling the structure and function of enzymes by machine learning

Michael J. E. Sternberg, Richard A. Lewis, Ross D. King and Stephen Muggleton

Abstract

A machine learning program, GOLEM, has been applied to two problems: (1) the prediction of protein secondary structure from sequence and (2) modelling a quantitative structure-

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machine learning

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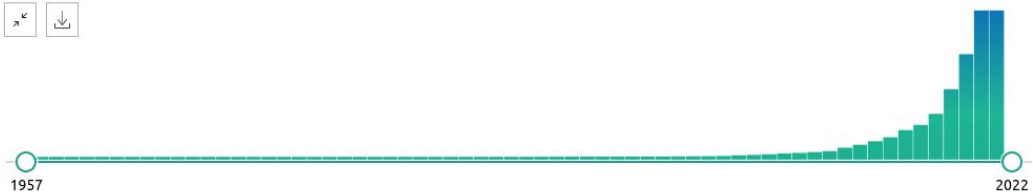

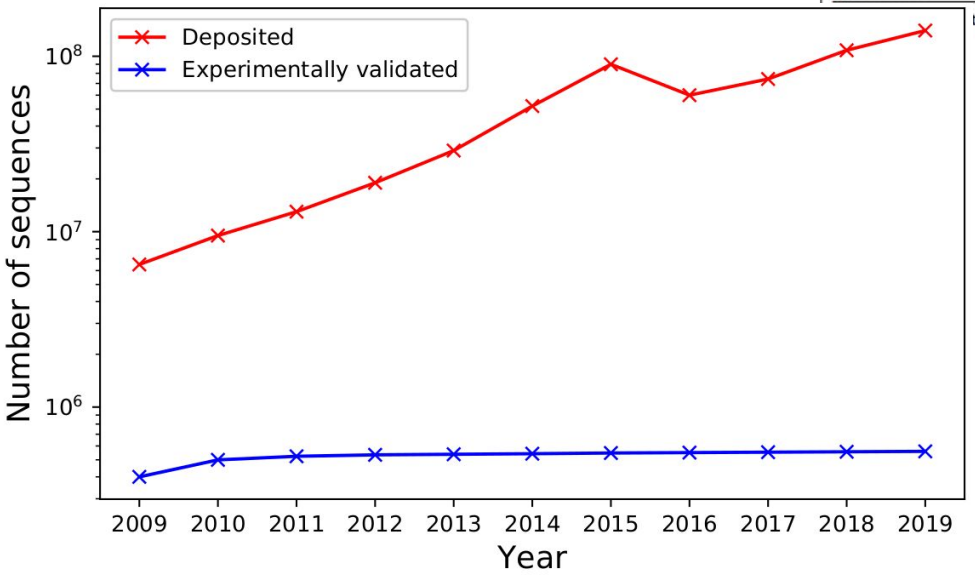

Article

Unraveling the functional dark matter through global metagenomics

https://doi.org/10.1038/s41586-023-06583-7
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Open access

Georgios A. Pavlopoulos[1,2,3✉], Fotis A. Baltoumas[1], Sirui Liu[4], Oguz Selvitopi[5], Antonio Pedro Camargo[2], Stephen Nayfach[2], Ariful Azad[6], Simon Roux[2], Lee Call[2], Natalia N. Ivanova[2], I. Min Chen[2], David Paez-Espino[2], Evangelos Karatzas[1], Novel Metagenome Protein Families Consortium*, Ioannis Iliopoulos[7], Konstantinos Konstantinidis[8], James M. Tiedje[9], Jennifer Pett-Ridge[10], David Baker[11,12,13], Axel Visel[2], Christos A. Ouzounis[2,14,15], Sergey Ovchinnikov[4], Aydin Buluç[5,16] & Nikos C. Kyrpides[2✉]

Metagenomes encode an enormous diversity of proteins, reflecting a multiplicity of functions and activities[1,2]. Exploration of this vast sequence space has been limited to a comparative analysis against reference microbial genomes and protein families derived from those genomes. Here, to examine the scale of yet untapped functional diversity beyond what is currently possible through the lens of reference genomes, we develop a computational approach to generate reference-free protein families from the sequence space in metagenomes. We analyse 26,931 metagenomes and identify 1.17 billion protein sequences longer than 35 amino acids with no similarity to any sequences from 102,491 reference genomes or the Pfam database[3]. Using massively parallel graph-based clustering, we group these proteins into 106,198 novel sequence clusters with more than 100 members, doubling the number of protein families obtained from the reference genomes clustered using the same approach. We

Bonetta & Valentino, 2019

General workflow

Genes with known functions

Training & evaluation

Sequence features
Structural features
Expression patterns
Interaction networks
Phylogenies
Gene location

Feature engineering, feature selection, embeddings

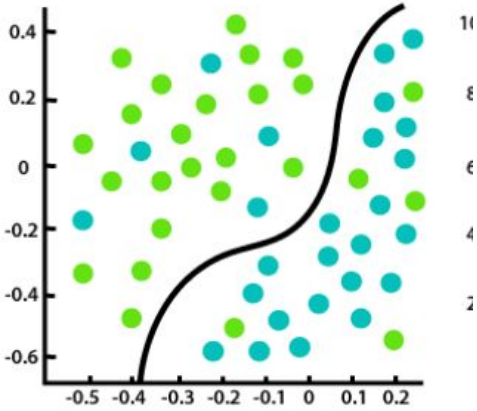
ML model

Algorithms & architectures

Functional predictions

List of candidate genes

Experimental validation



Some characteristics of gene function prediction as a classification problem

- Multiclass classification: large number of functional classes.
- Multilabel classification: multiple annotations for each gene.
- Labels at different level of reliability.
- Hierarchical relationships between classes (structured output).
- Unbalanced classification.
- Different strategies to choose negative examples.
- Multiple sources of relevant data available.
- Data are usually complex and noisy.

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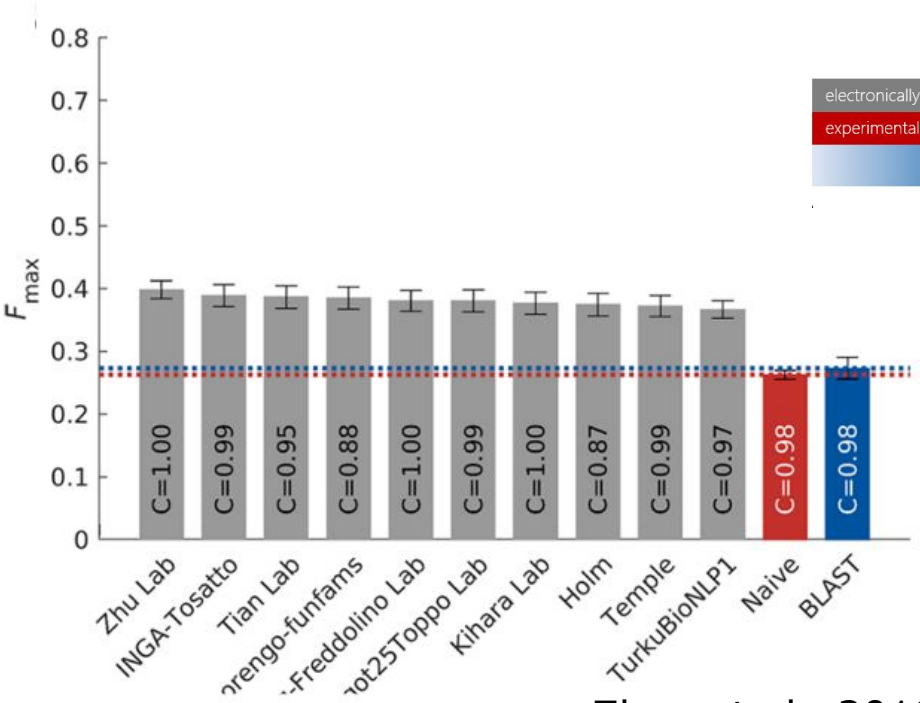
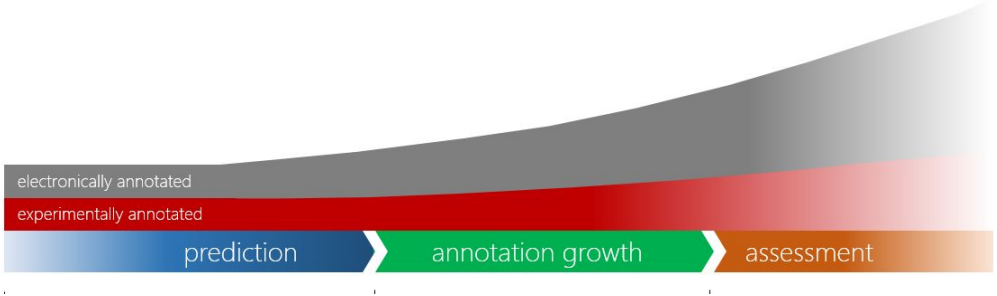
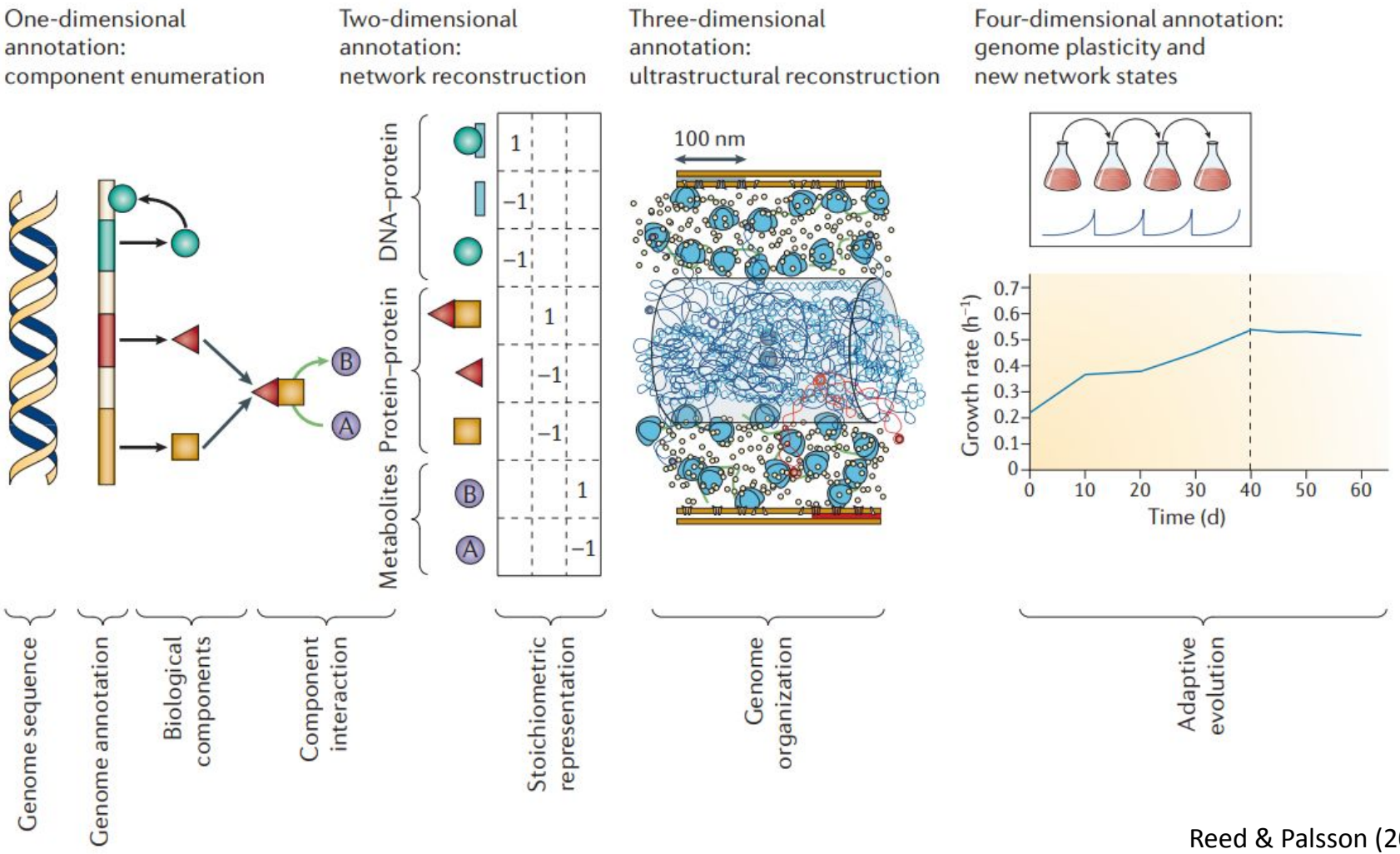
An open problem



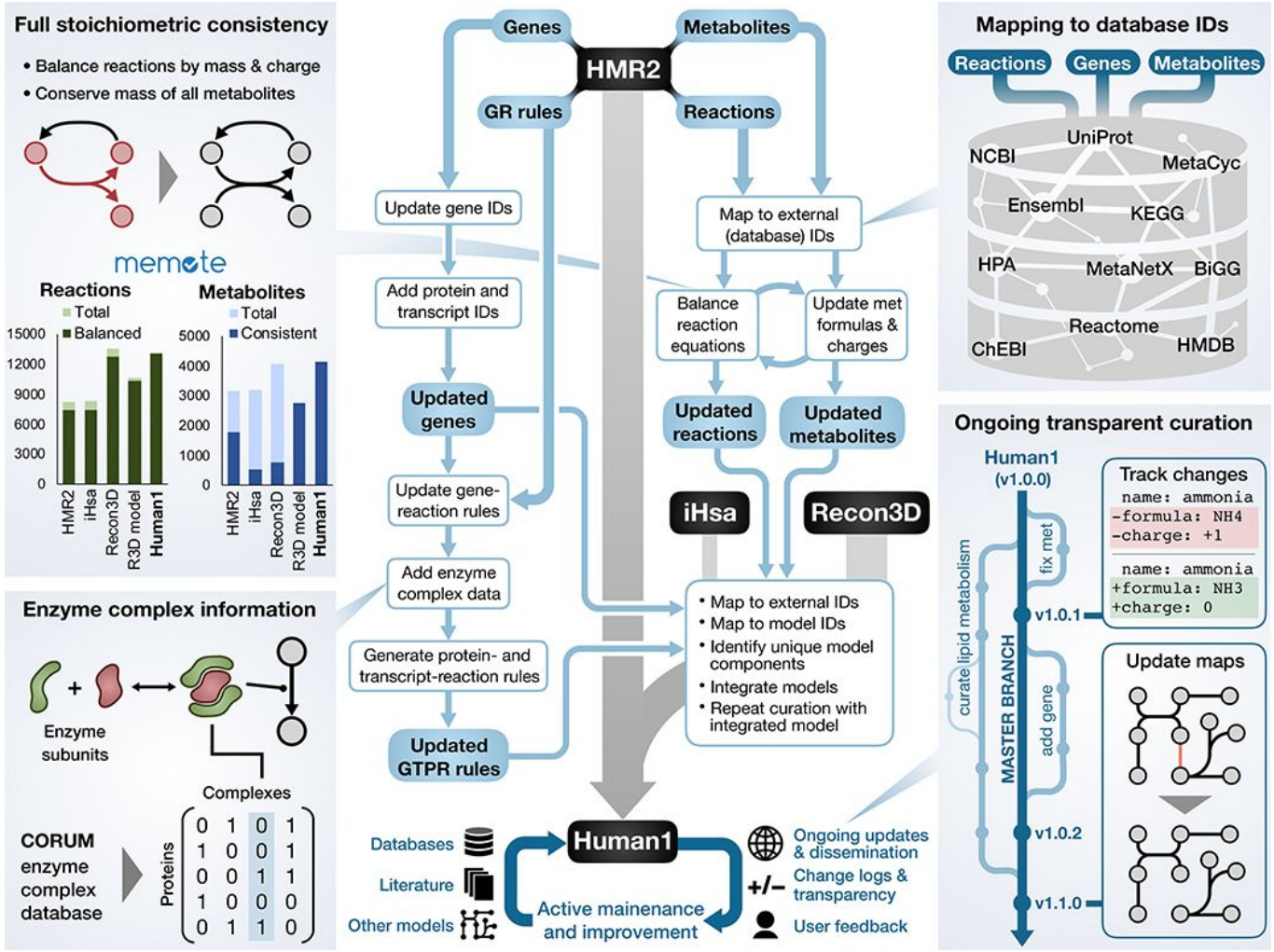


Zhou et al., 2019

Reconstructing Molecular networks



Reed & Palsson (2006)



Robinson et al. (2021)

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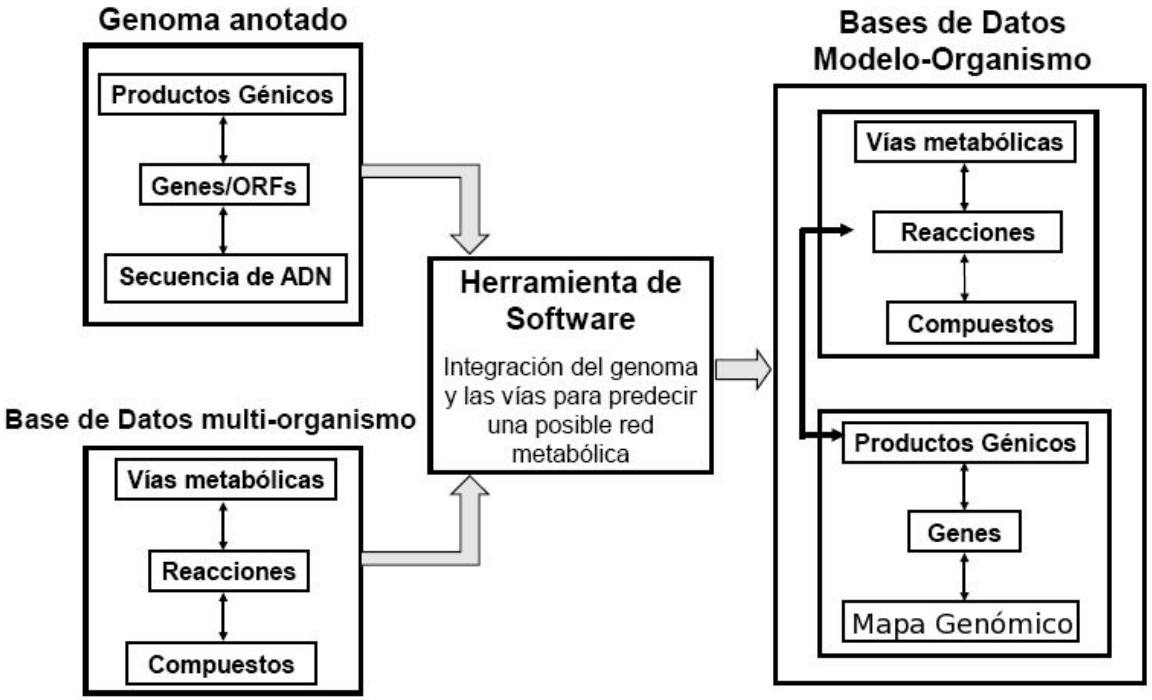
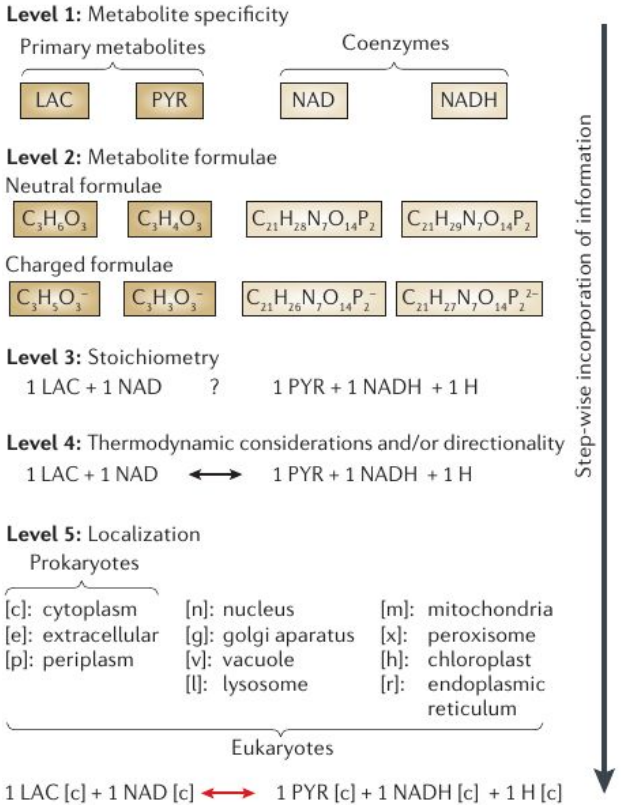
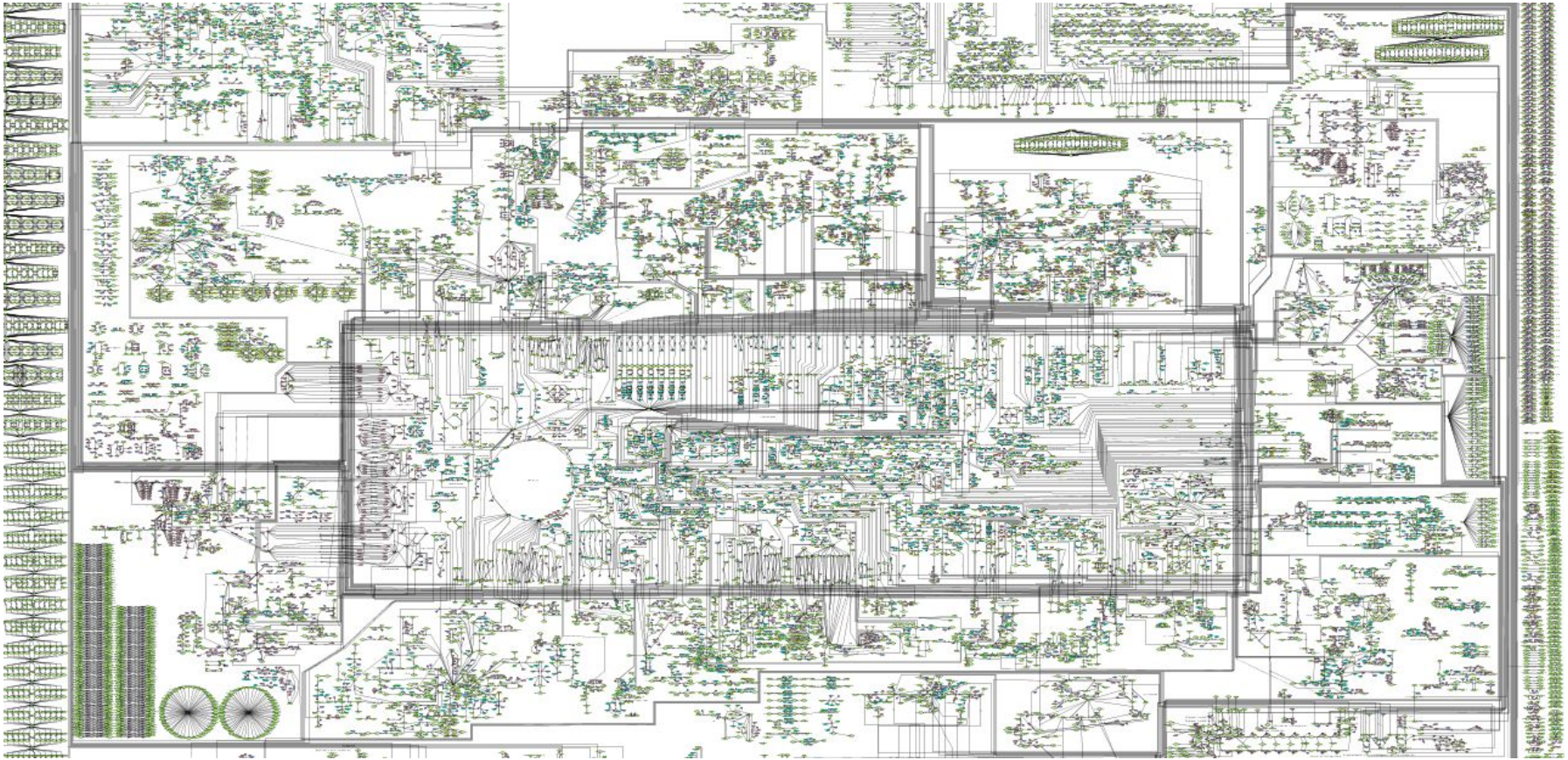
Reconstrucción metabólica





Virtual Human Metabolic:



https://www.vmh.life/minerva/

Genome-Scale Model of Human Metabolism

Table 1

Statistics of currently published generic human GEMs.

Generic GEMs	Genes	Metabolites[a]	Reactions[a]	Features
RECON1	1496	1509	3744	Manually reconstructed from bibliomics data
EHMN	2322	2671	2823	Manually reconstructed from bibliomics data
RECON2	1789	2626	7440	Merging EHMN and HepatoNet1 with RECON1
RECON 2.2	1675	5324	7785	Reconstructed by integrating previous versions, with emphasis on mass and charge balance
HMR1.0	1512	3397	4144	Reconstructed based on RECON1, EHMN, HumanCyc and KEGG
HMR2.0	3765	3160	8181	Reconstructed based on HMR1, with additional emphasis on lipid metabolism by integrating iAdipocytes1809, KEGG, Lipidomics Gateway
Recon3D	2248	5835	10600	Reconstructed based on RECON2 and includes mapping to 3D structure of proteins through PDB ids
Human1	3625	10138 (4164)	13417	Integrated and extensively curated the most recent human metabolic models to construct a consensus GEM, Human1

- Several options available (all derived from RECON1)
- Human1 is most recent version

Modified from Swainston, N., et al (2016). Metabolomics, 12(7), 109.

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Discusión

¿Qué entendemos por “anotar”?

Función molecular; contexto y contribución al fenotipo; historia evolutiva..

¿Se reduce a enumerar y describir componentes y sus interacciones?

¿Qué pasa con las interacciones?

¿Cuando consideramos que una entidad o proceso está anotada?

Función molecular; contexto y contribución al fenotipo; historia evolutiva..

¿Se podrá completar el catálogo algún día?

¿Tiene sentido la pregunta anterior?

¿Open ended evolution?

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Referencias

Anotación de genomas y reconstrucción de redes

- Genome annotation from sequence to biology (Stein - 2001)
- Unknown proteins and orphan enzymes the missing half of the engineering parts list – and how to find it (Hanson et al - 2010)
- The model organism as a system: integrating 'omics' data sets (Joyce & Palsson, 2006)
- Toward multidimensional genome annotation (Reed et. al, 2006)

Perspectivas desde el pasado reciente

- From molecular to modular cell biology (Hartwell et al - 1999)
- What lies beyond bioinformatics? (Palsson - 1997)