



Systems biology is the study of biology through systematic perturbation, global read-out of the multifaceted response and integration of these data to formulate predictive models¹. Here, we highlight the key steps in the systems biology approach, with a focus on how global data sets are assembled into models of system structure and function. Techniques for model assembly span many layers of abstraction, including statistical mining, alignment across data sets, probabilistic inference, differential

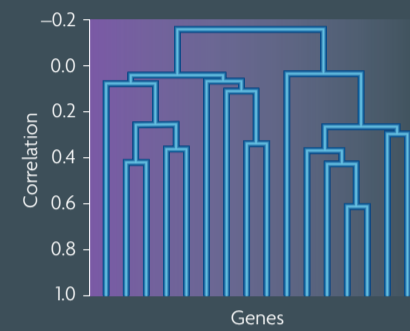
equations and data visualization. These integrative approaches chart the key components and interactions of biological systems over scales ranging from single pathways to whole cells to entire populations of individuals. Major applications of systems biology to biomedical research are to identify genetic risk factors for disease, allow for model-based personalized diagnostics and treatment regimens and suggest new avenues for drug discovery.

Model assembly by data synthesis and integration

Statistical mining

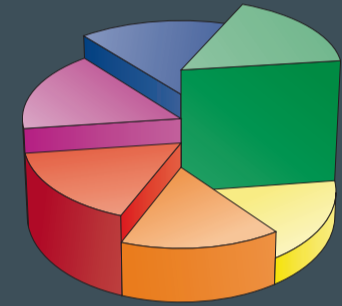
Data filtering and clustering

The most basic form of data integration is to identify statistical overlap between data sets. Another statistical method is clustering, which groups molecules with similar profiles. 'Co-clustering' uses multiple integrated data sets (e.g., mRNA expression & protein networks). Tools: GenePattern, Cluster, JTreeview, MeV



Functional enrichment

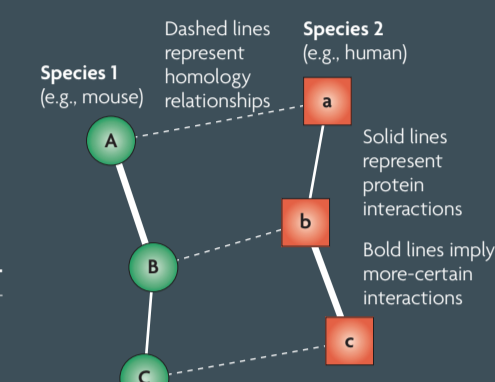
Outstanding measurements define gene sets which can be integrated with databases of known gene functions or pathways, indicating statistically enriched categories. Tools: DAVID, BiNGO, GSEA



Data alignment

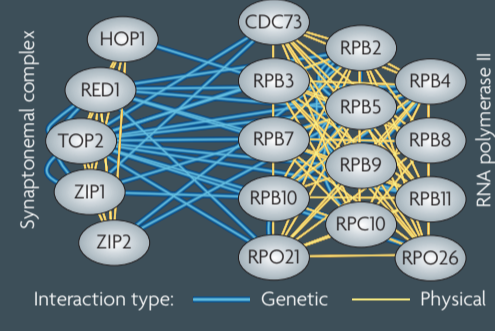
Cross-species

Molecular sequences, states or interactions are aligned across species to identify conserved and diverged clusters. Tools: BLAST, NetworkBLAST (right), IsoRankN



Cross-data type

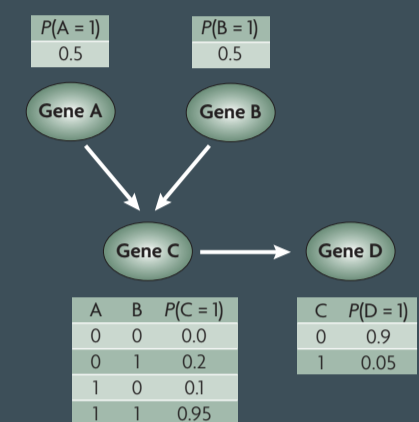
Alignment is also performed across multiple data types, such as mRNA versus protein profiles or networks of physical versus genetic interactions (right)². Molecular causes (e.g., genetic perturbations) are connected to effects (e.g., expression changes) through physical interaction paths³.



Probabilistic and mathematical modeling

Probabilistic inference

Classification methods (e.g. logistic regression) weigh many different measurements to learn functional links between proteins or other properties⁴. Bayesian networks use changing molecular states over perturbations or time to identify direct causal relationships among genes and can incorporate other data through network 'priors'⁵. Tools: Arachne, Banjo



Network dynamics and fluxes

Information flow through pathways is modeled through differential equations or biophysical simulations, which predict biological outcomes and are fit to measurements and reaction kinetics^{6,6}. Tools: SBW, Cell Designer, Copasi

Network visualization

Data projection

Sets network visuals, e.g., node and edge colors, shapes and sizes, based on biological data, e.g., expression levels, functions (right) or knockout phenotypes.

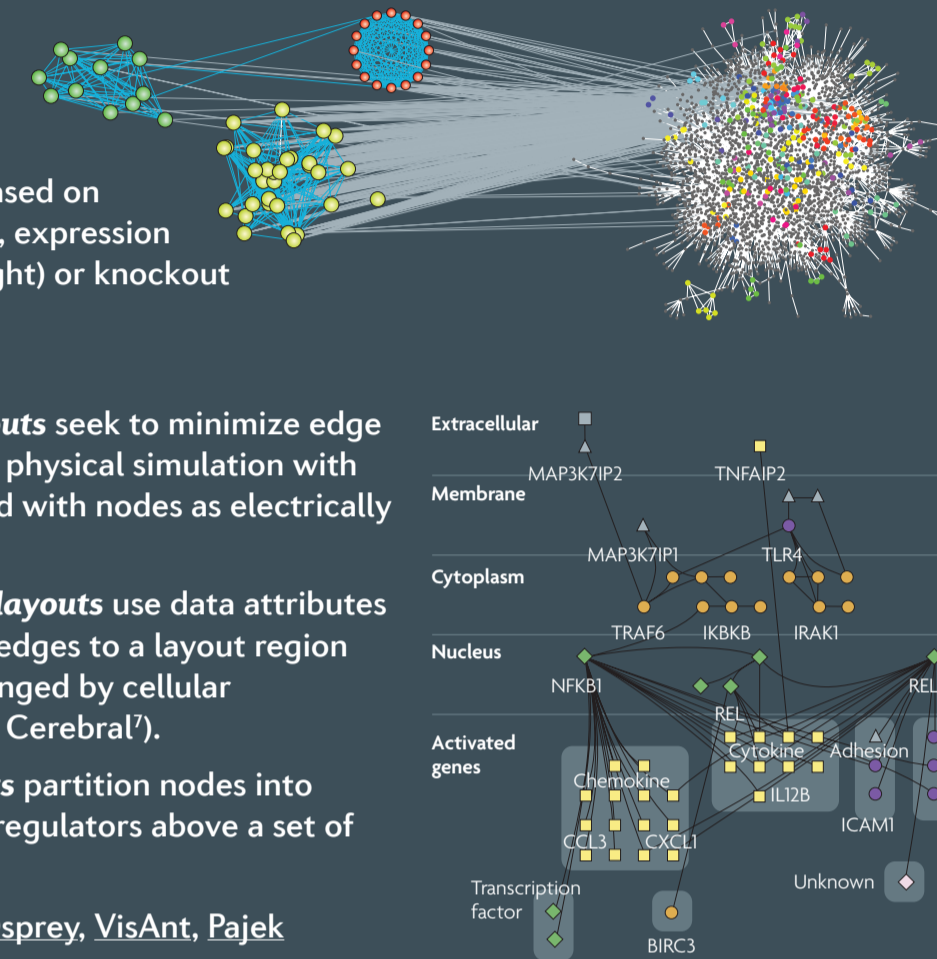
Network layout

Force-directed layouts seek to minimize edge crossings through a physical simulation with edges as springs and with nodes as electrically charged particles.

Attribute-directed layouts use data attributes to attract nodes or edges to a layout region (right, proteins arranged by cellular compartment using Cerebral⁷).

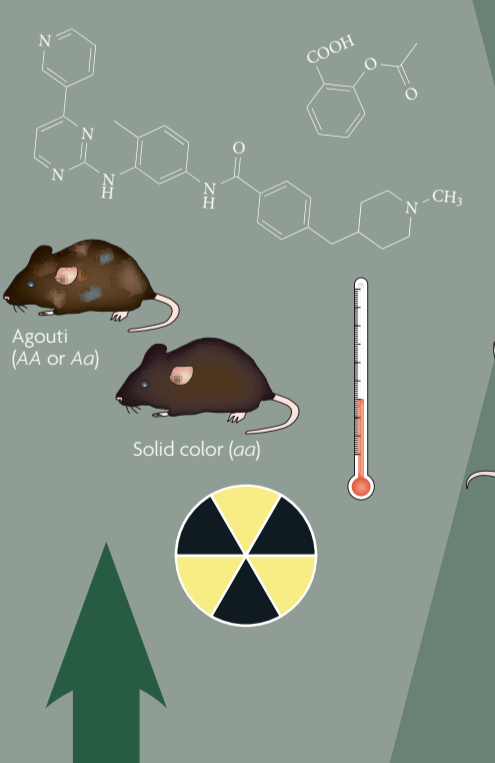
Hierarchical layouts partition nodes into layers, e.g., master regulators above a set of regulated genes.

Tools: Cytoscape, Osprey, VisAnt, Pajek



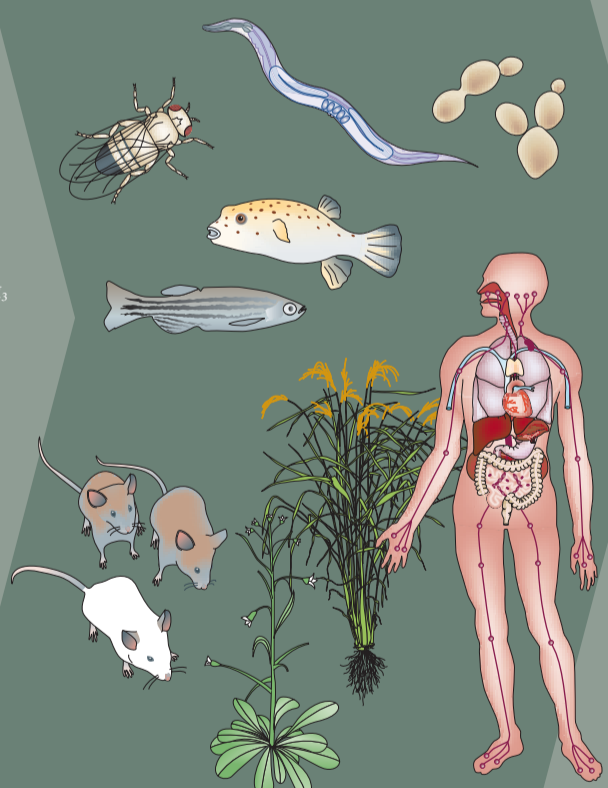
Perturbations

- Chemicals/ small molecules
- Genetic mutations/ RNAi
- Natural variation
- Changing environments
- Shifting time



Biological system

This system under perturbation can range in scale from molecular processes to cells, tissues, single organisms or up to populations of individuals.



Molecular state measurements (nodes)

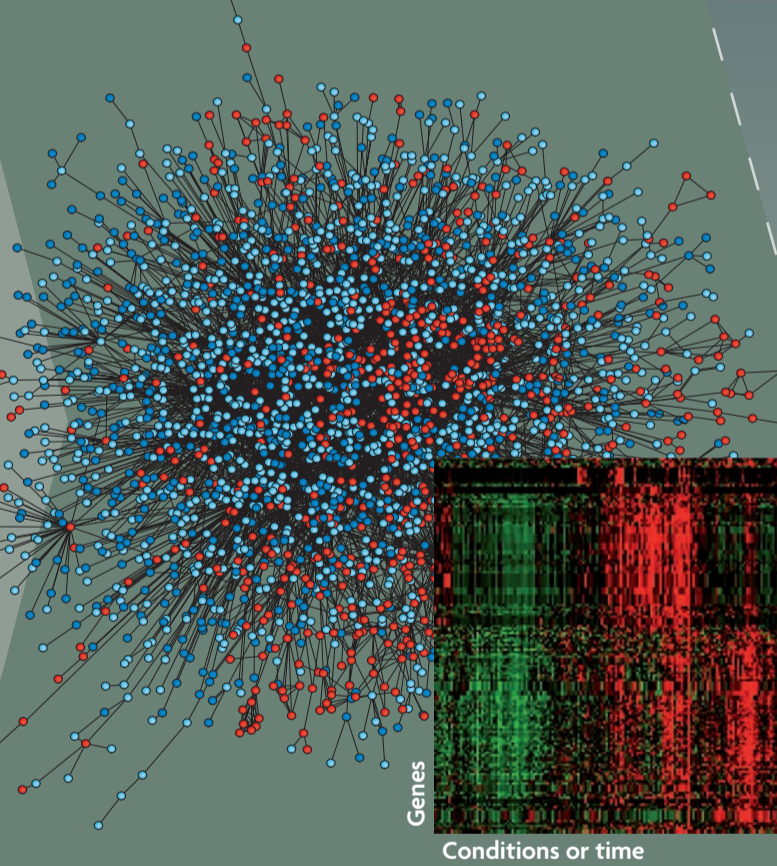
	Large-scale dataset types	Technologies
Genome	Whole-genome DNA sequences, SNPs and CNVs	DNA sequencing, genotyping microarrays
Epigenome	Chromatin modifications and structure	ChIP-seq, methyl-seq, DHS-chip
Transcriptome	Transcript abundances, translation rate and microRNAs	DNA microarrays, RNA-seq, CAGE, GRO-seq, ribosome profiling
Proteome	Protein abundances and modifications	NMR, mass spectrometry, multiparameter FACS
Metabolome	Metabolite profiling	Mass spectrometry, liquid chromatography

Molecular interaction measurements (edges)

	Data types	Technologies
Physical	Protein-protein	Immuno-precipitation (IP), co-affinity purification, yeast two-hybrid, protein arrays, kinase-substrate measurements
	Protein-DNA, protein-RNA	Genome-wide chromatin immuno-precipitation (ChIP), DNA binding arrays
	Protein-small molecule, reaction fluxes	Isotope labeling, mass spectrometry
Genetic and functional	Synthetic lethality, epistasis	Synthetic genetic arrays (SGA) combinatorial RNAi, population genetics
	Cause-effect relationships	Genetic perturbation (gene knockout, RNAi) followed by phenotyping (microarrays, cellular imaging); trans eQTLs (expression quantitative trait loci)

Molecular databases

New measurements are stored alongside existing data, including functional annotations.

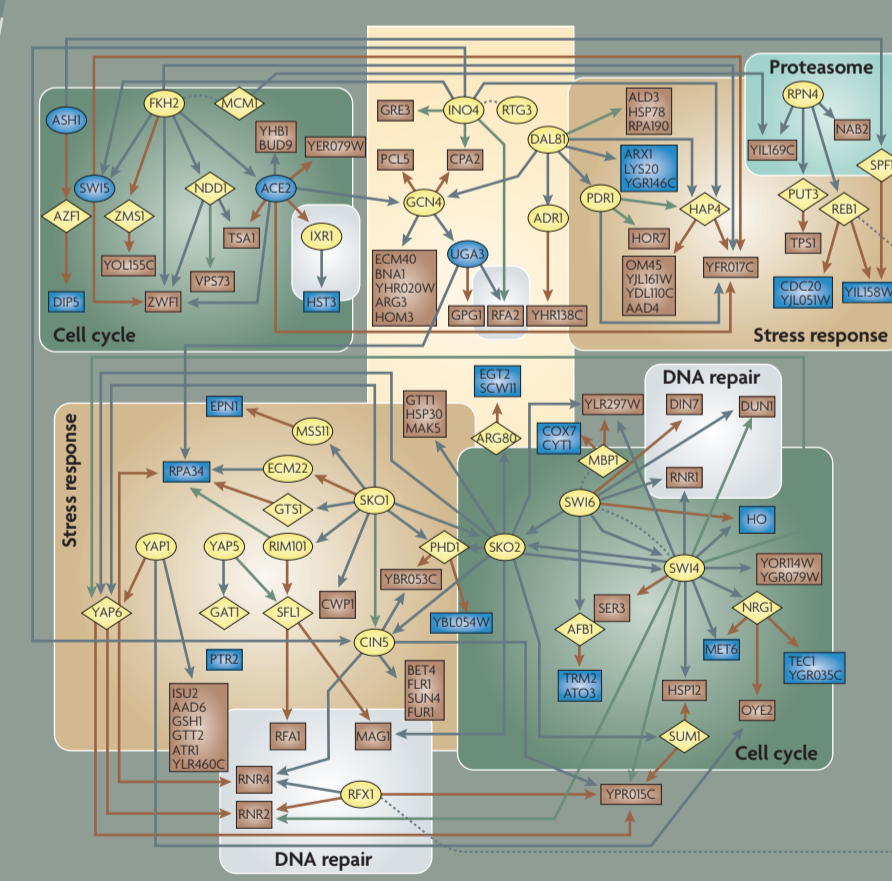


	Annotations	States	Interactions
Selected molecular databases	GO, KEGG, REACTOME, NetPath, UCSC Genome Browser	Genbank, GEO, ArrayExpress, Proteome Commons	BioGRID, HPRD, IntAct, TRANSFAC, STRING, iHOP, functionalnet.org

Model assembly

Library of network models

The critical task of model assembly extracts and integrates the diverse datasets stored in databases into network models that are descriptive, predictive and executable.



Model refinement and validation

An iterative process by which cellular models are refined based on the goodness-of-fit between predictions and data, giving rise to further experimentation.

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