

Building computational models in Systems Biology

WTAC

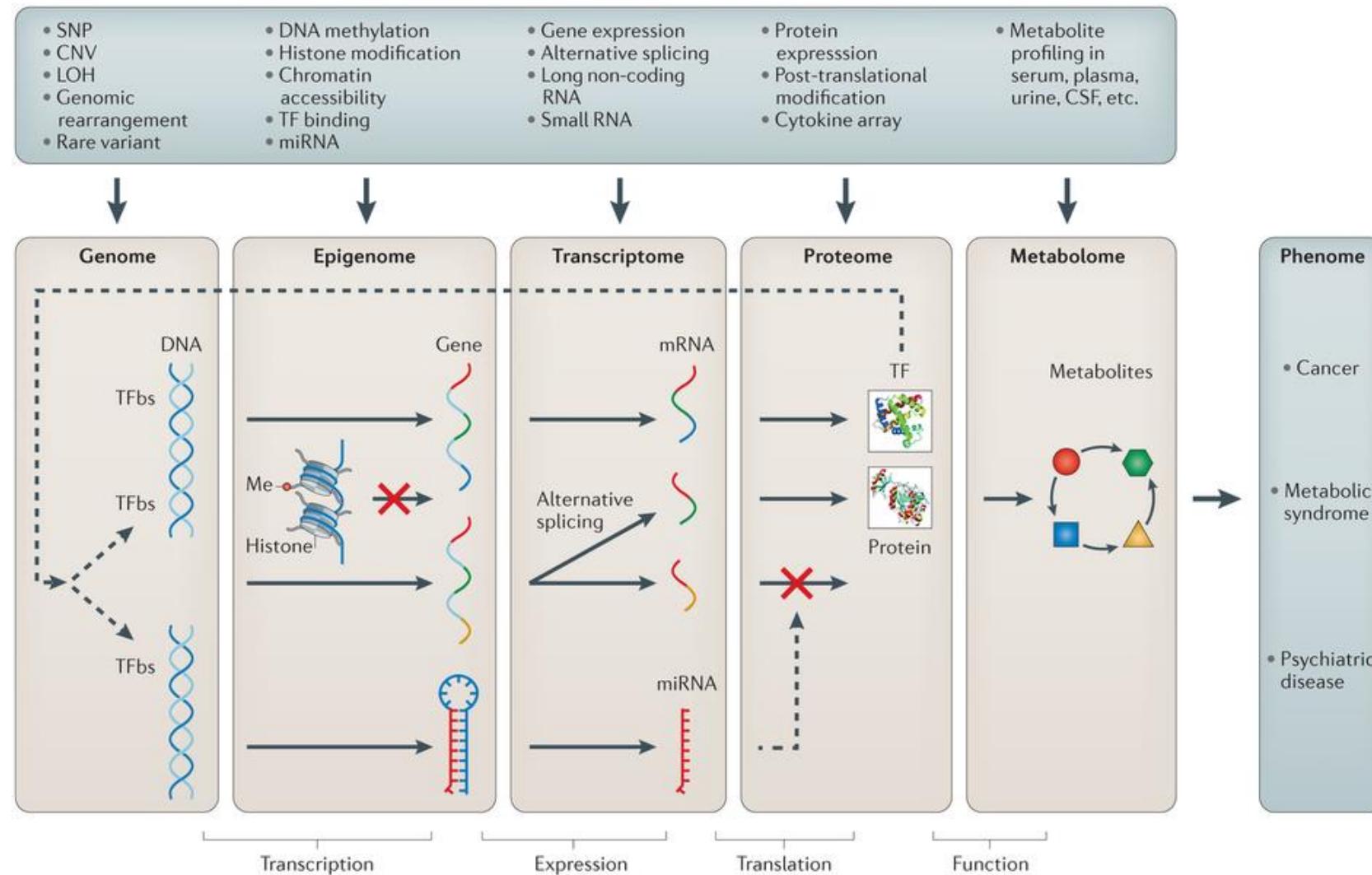
Computational Systems Biology for Complex Human Disease

Dr Anna Niarakis

Hinxton Campus, Monday April 22nd 2024



Organisms: Complex systems

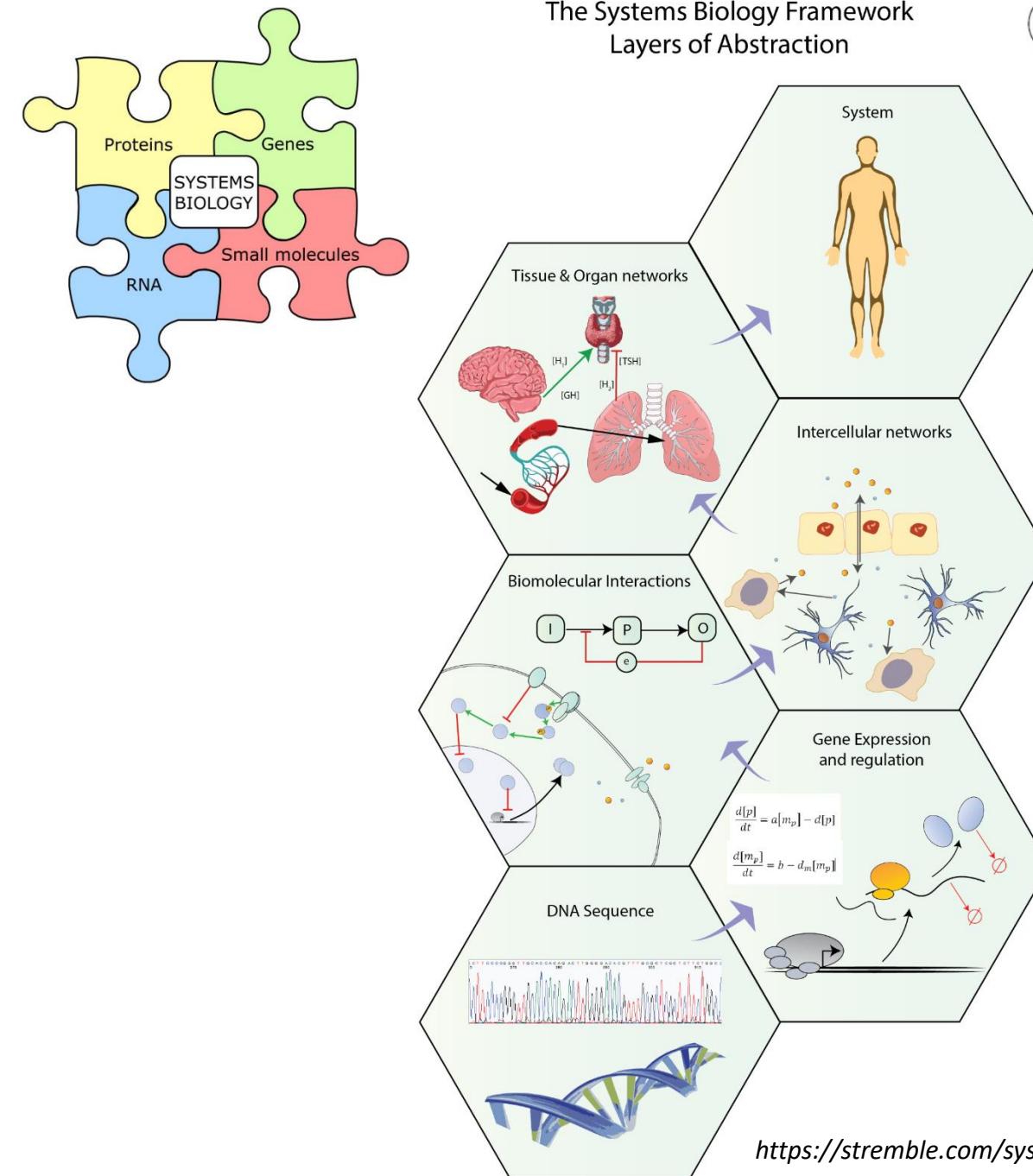


Systems biology: put bits and pieces together

How do the individual parts interact
to yield system behavior?

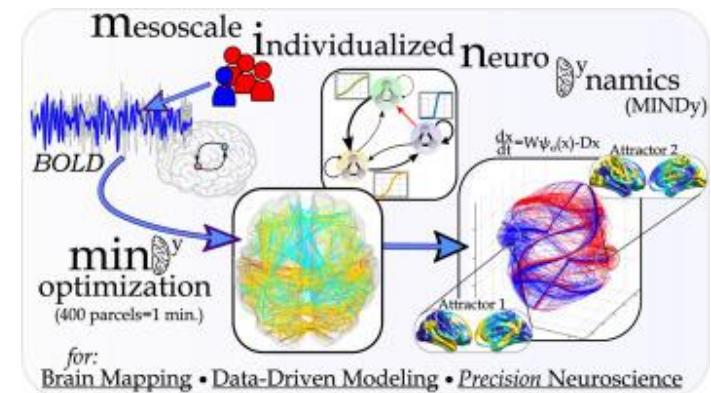
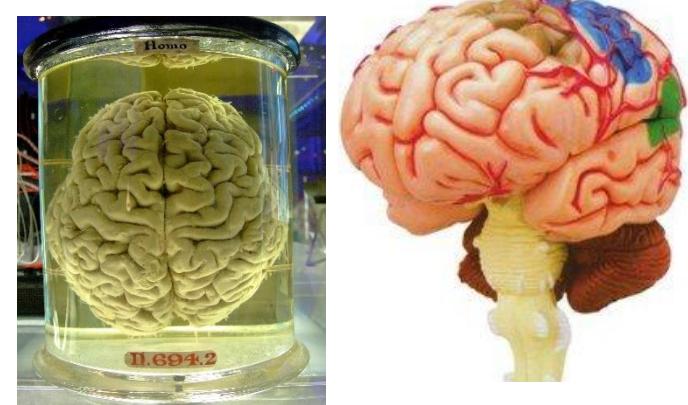
Biology has focused on figuring out
the pieces.

But what happens when you fit
them together?

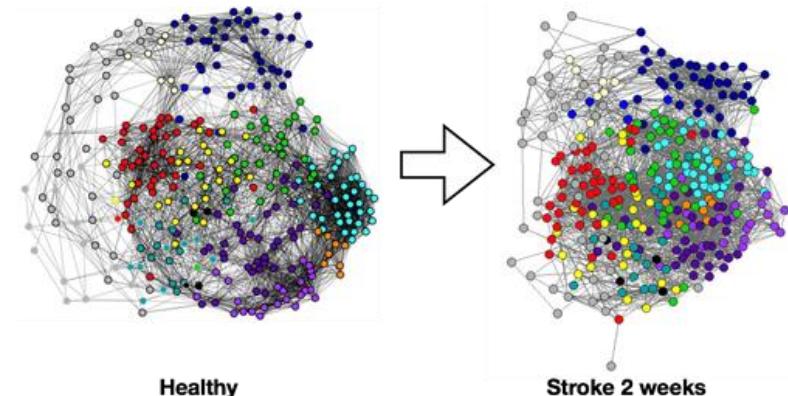


The concept of model in science

- A physical, mathematical, graphical, logical, conceptual, computational representation of an object, event or process or a system of objects, events or processes.
- Abstraction of the « real thing ».
- Helps us study and understand the **system** of interest and the **mechanisms** under which it operates.
- Can also lead to predictions about the system's behaviour.

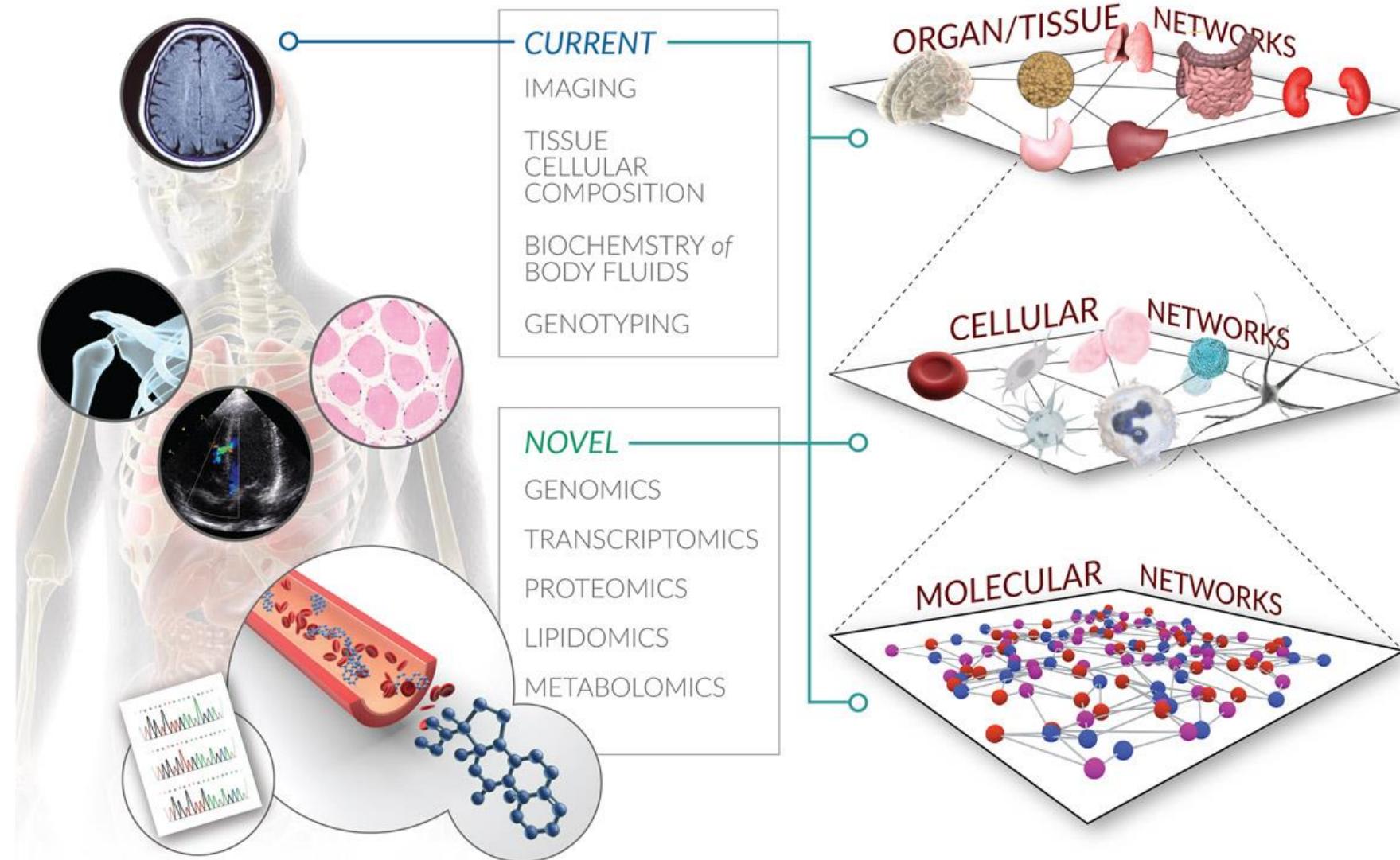


<https://doi.org/10.1016/j.neuroimage.2020.117046>



<https://www.humanbrainproject.eu/en/>

DIAGNOSTIC APPROACHES



Full scale integration

- Key goal of systems biology: construct networks at different cellular levels to investigate cellular machinery.
- Currently no satisfactory method to construct an integrated cellular network.

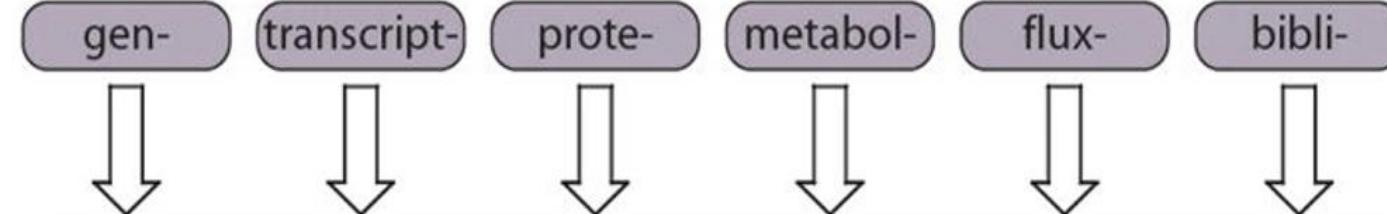
The challenge

- Interpret largescale data sets and extract true information to understand biological systems.
- Computational techniques, which can integrate and combine these large and heterogeneous data sets, will help gain more biological insights.

The Systems Biology paradigm:

Components -> networks -> computational models -> phenotypes

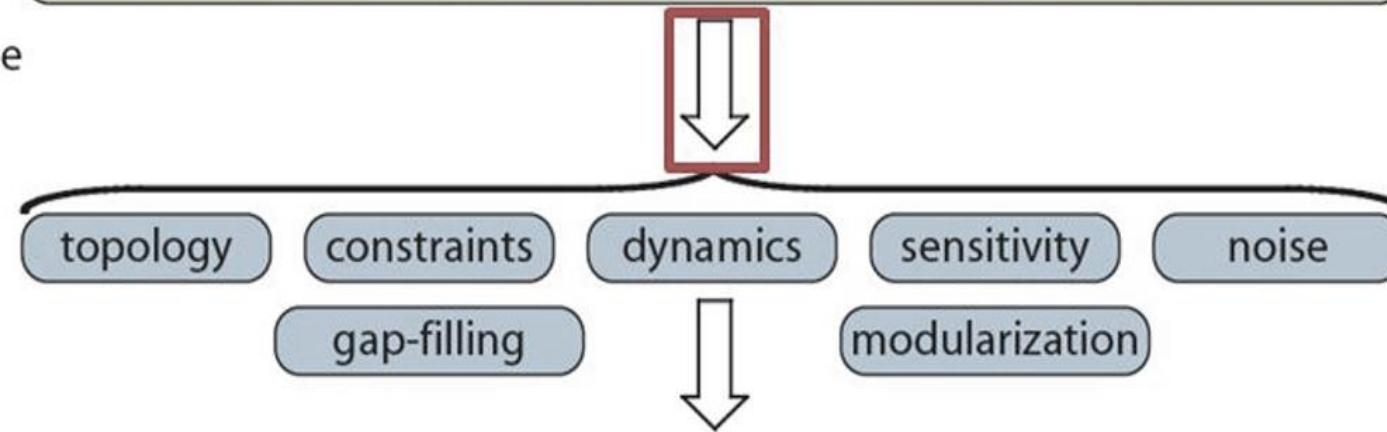
1. Database:
- Plurality of -omics



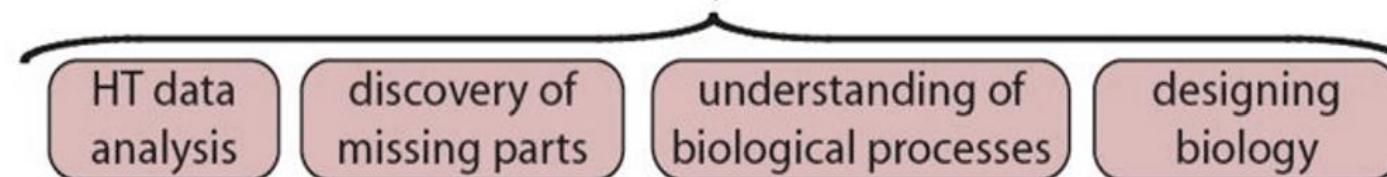
2. Knowledge Base:
- One set of reactions
encoded by a genome



3. *In silico* modeling:
- Query Tools

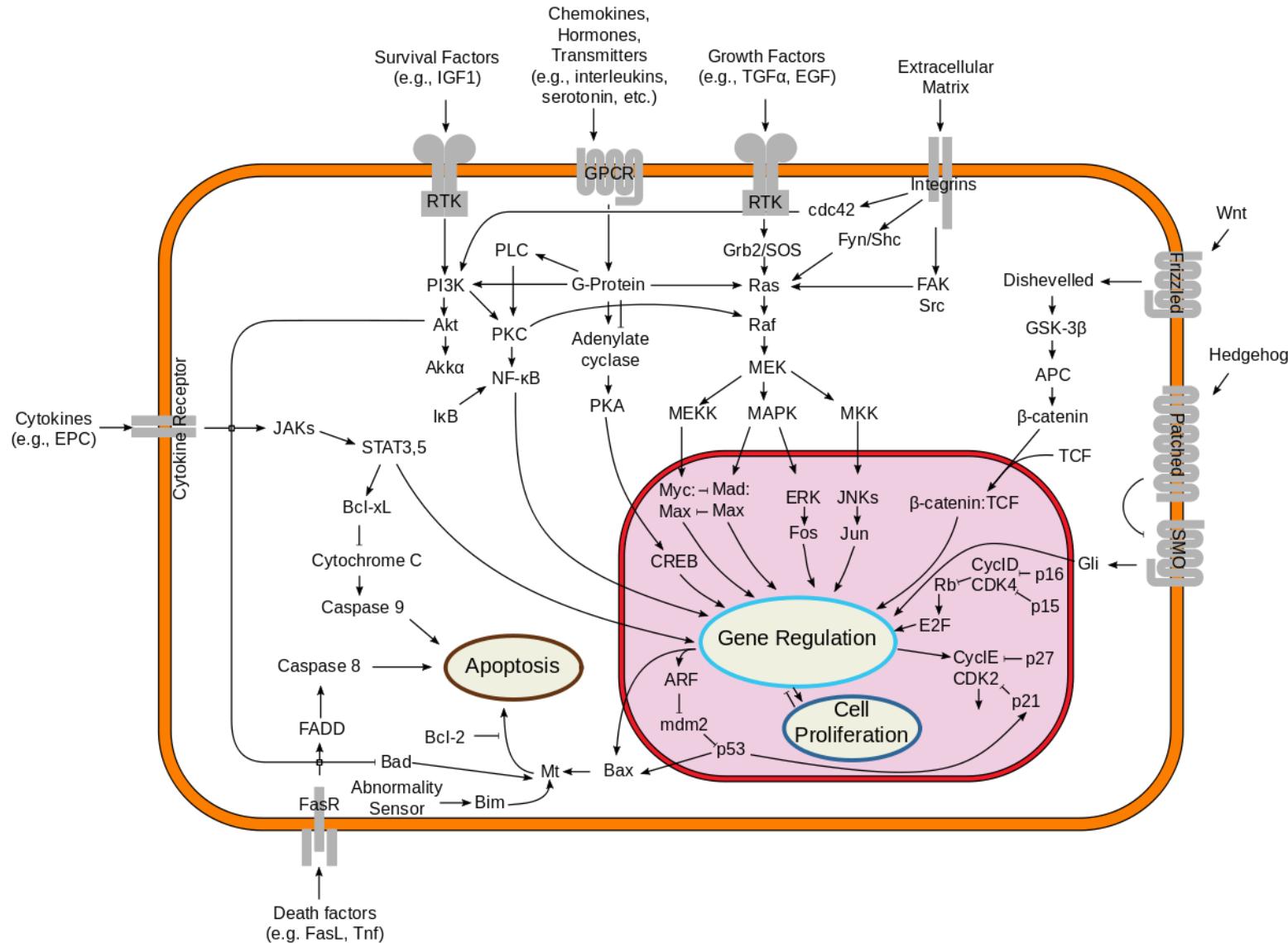


4. Validation, Discovery,
and Use



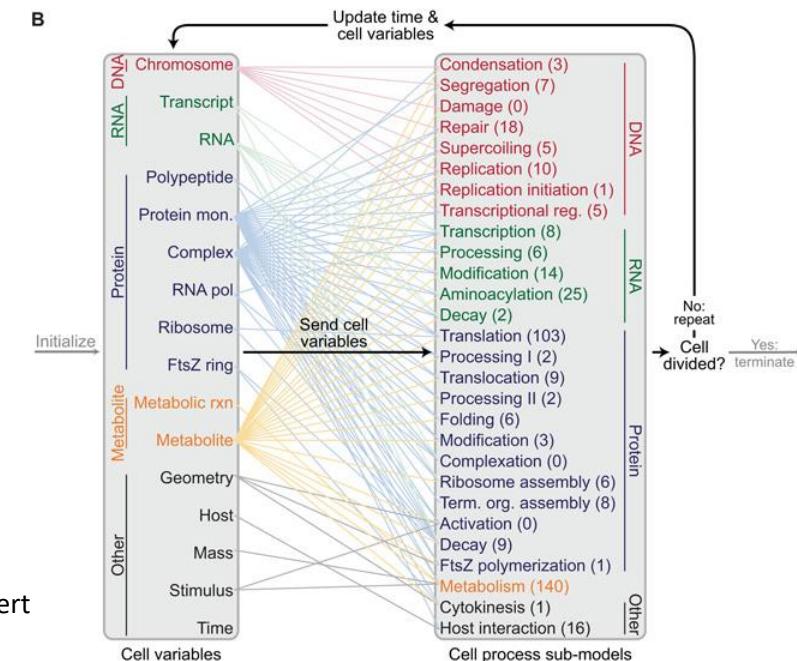
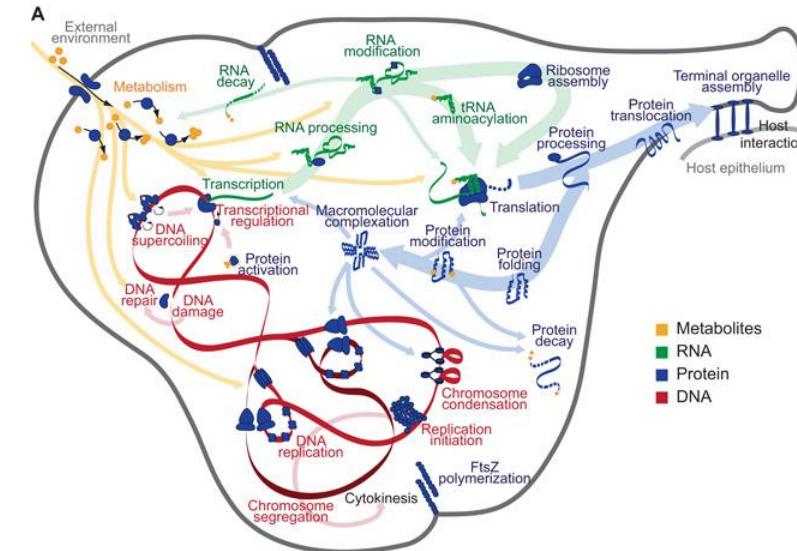
Viewing cells in terms of their underlying network

Organizing biological information in the context of networks is a powerful concept, networks can be seen as graphs.

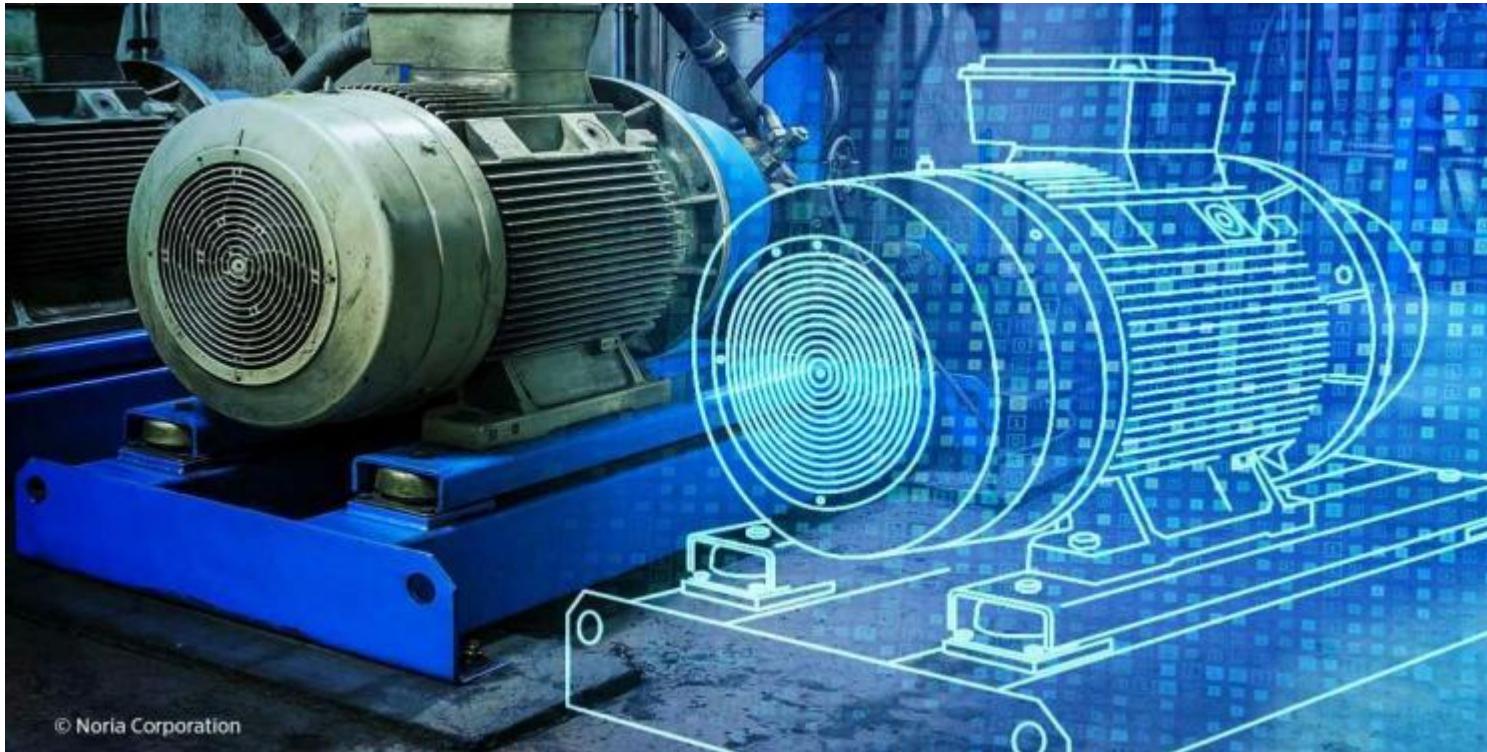


Whole cell model

- *Mycoplasma genitalium*
- Computational Simulation and Analysis
- All simulations were performed with MATLAB R2010b on a 128 core Linux cluster. The predicted dynamics of each cell was logged at each time point and subsequently analyzed using MATLAB.



The concept of a Digital Twin



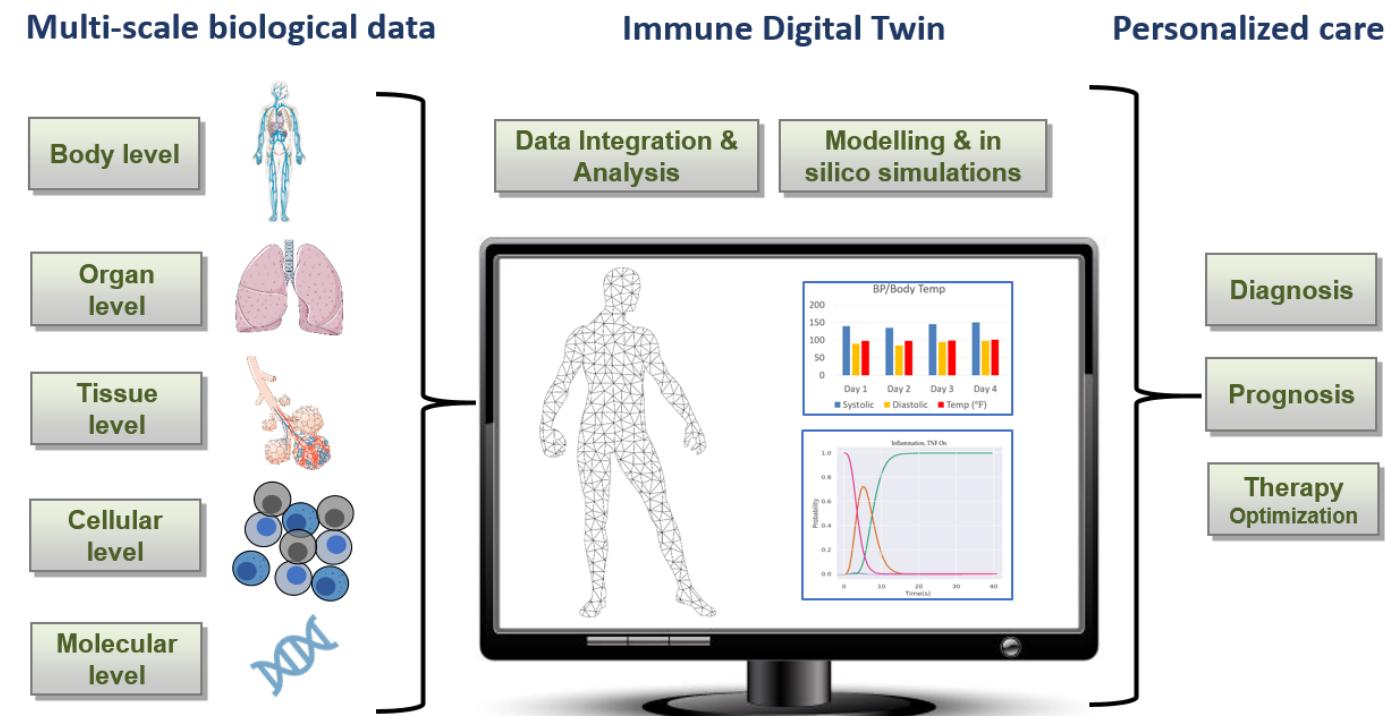
A digital twin is a virtual representation that serves as the real-time digital counterpart of a physical object or process. *Image Credit: Noria Corporation*

Digital Twins are virtual equivalents, or twins, of physical objects.

These digital copies are increasingly popular because they can be used to drive important simulations that haven't been possible until now.

IDT requires advances in three critical areas

1. Develop sufficiently powerful and detailed simulation models of the human immune system.
2. Acquire the appropriate real-world data to train and validate the simulation models.
3. Personalize and customize the simulation models to individual patients and for particular purposes.

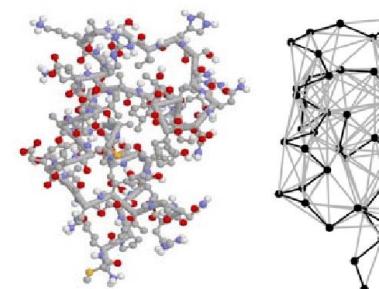
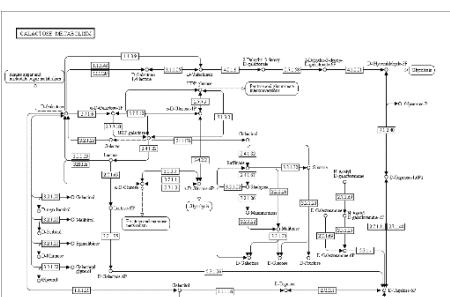
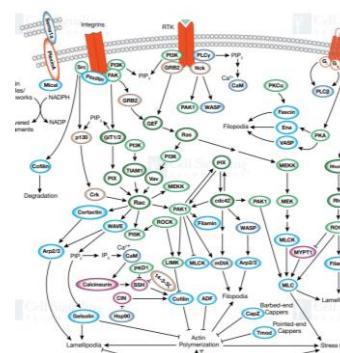
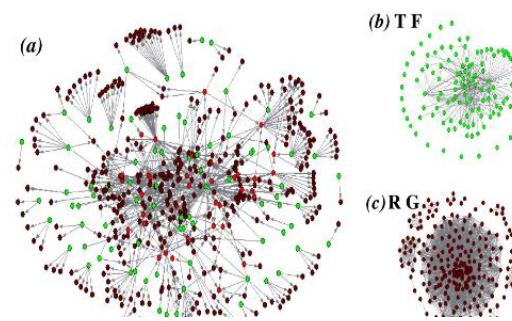
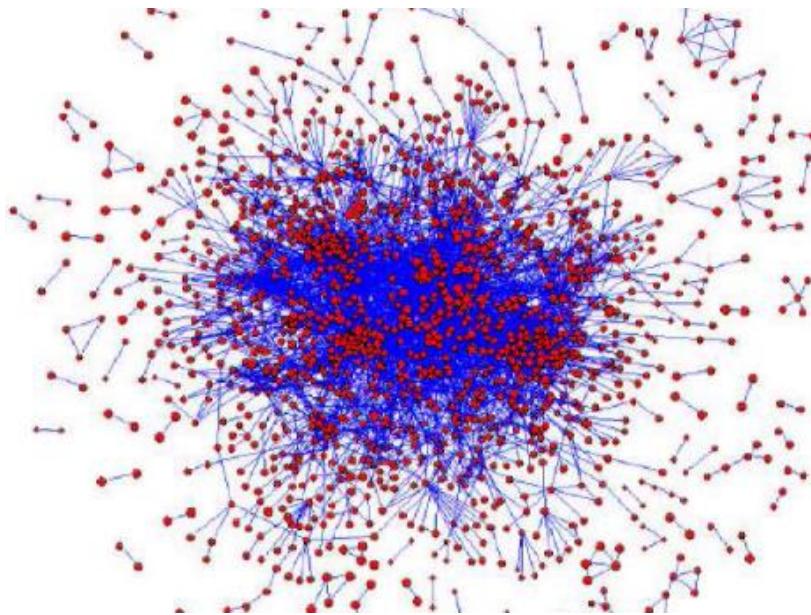


Human body:

- 37.2 trillion cells
- 200 different cell types

Intra-cellular networks

- Transcriptional regulation networks
- Protein structure networks
- Metabolic networks
- Protein-protein interaction (PPI) networks
- Cell signaling networks



How do we construct a network?



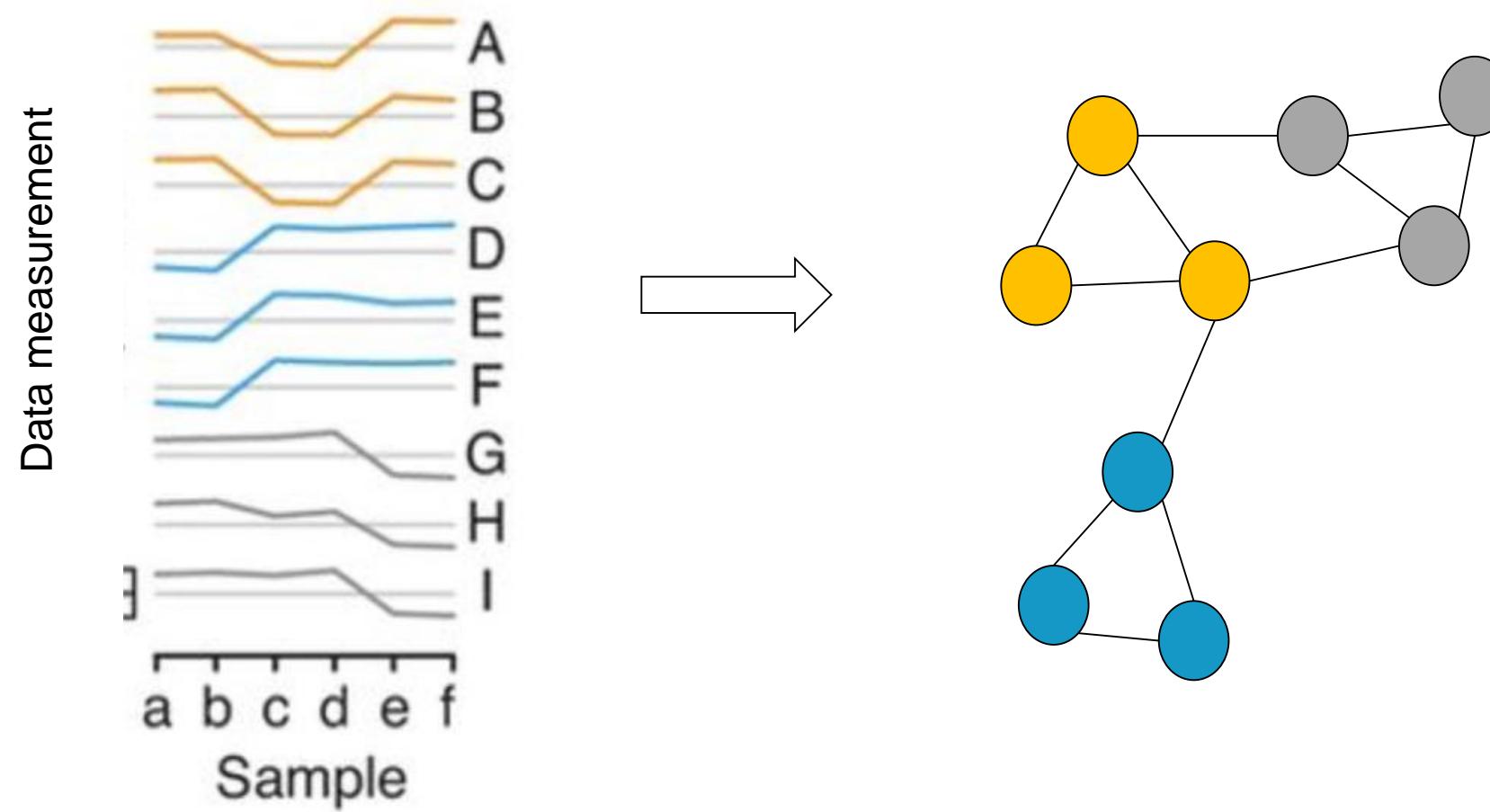
- **Bottom up (from scratch)**
 - Literature based
 - Curation
 - Databases
 - Previous Knowledge
 - From local to global
- **Top down (data driven)**
 - Data dependent
 - Algorithms
 - Inference
 - Reverse engineering



Top down
Data driven network inference

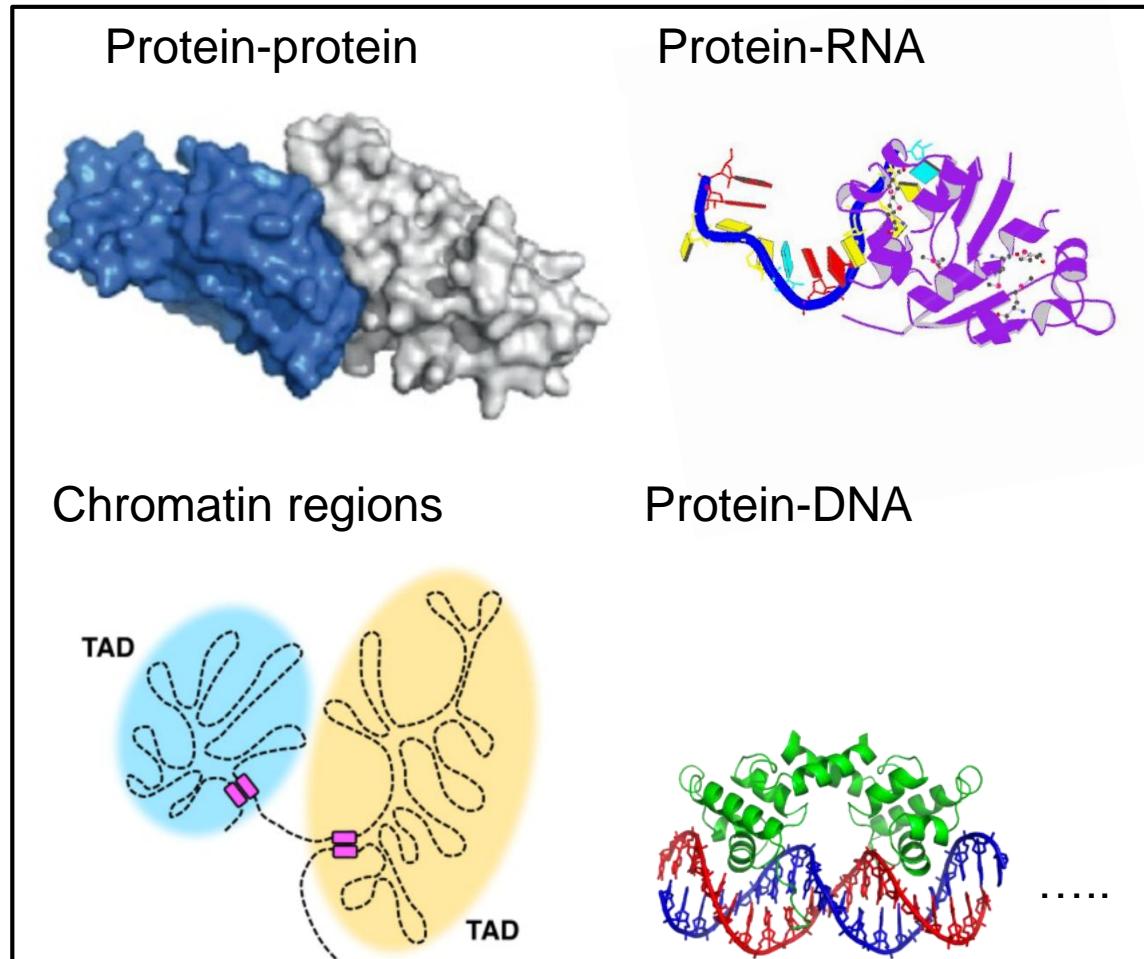
What is network inference?

"process of revealing the network structure of a biological system by reasoning backward from observed data."
He et al, 2009



Why do we need network inference?

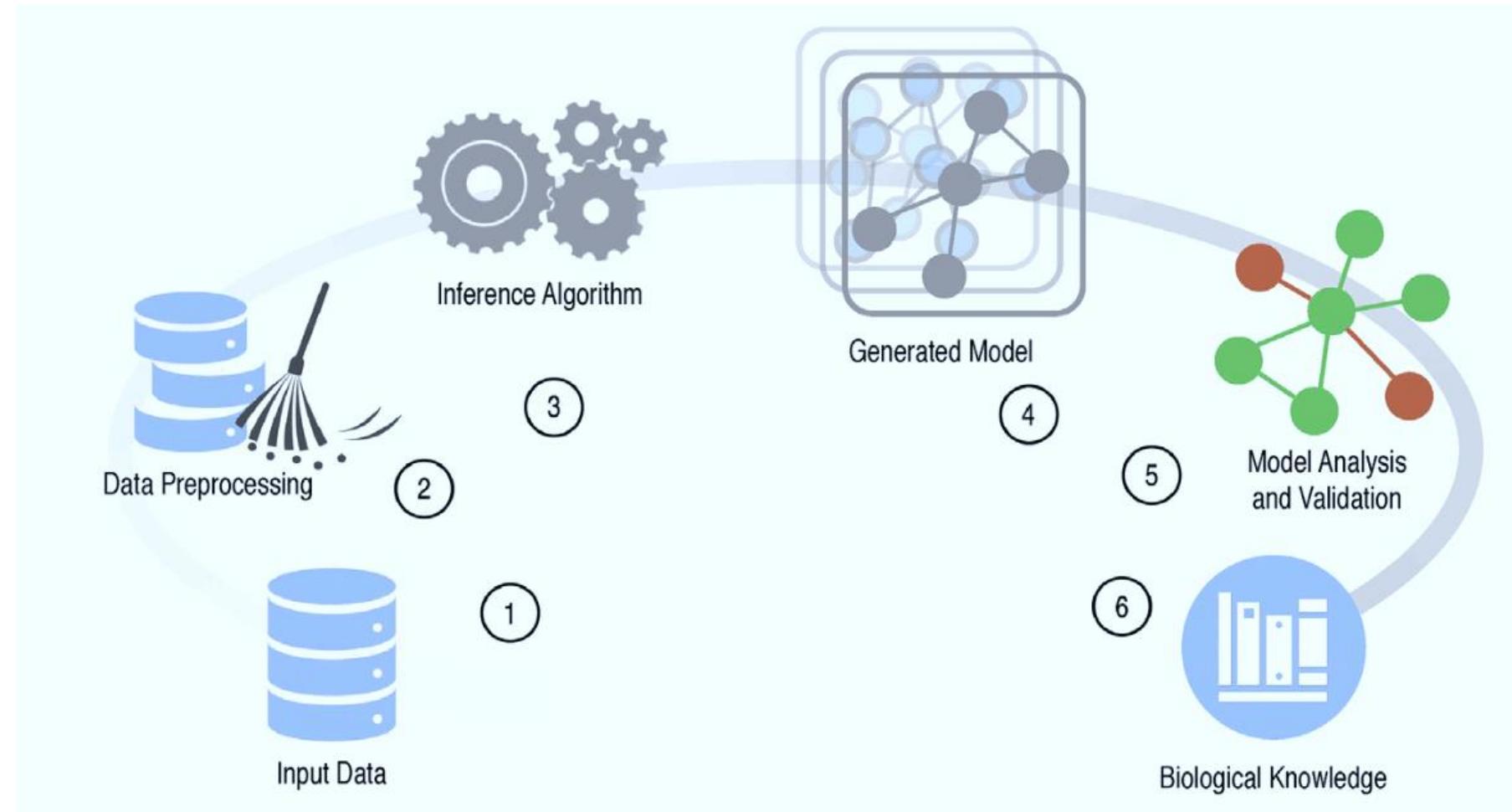
Most/All functions in cells are performed through interactions



Interactions are hard to measure

Abundances are easier to measure

Network inference process



Strengths/weaknesses of network inference types

Computational approach	Strengths	Weaknesses
Information-theory models	<ul style="list-style-type: none">Large GRNs, even out of low expression genesMutual and conditional mutual information approachNot computationally-demandingLow number of samples	<ul style="list-style-type: none">Regulation by multiple genes is not consideredStatic, only suitable for steady-state data
Examples:	REVEAL [36], RELEVANCE [40,84], ARACNE [42], CLR [43], MRNET [44]	
Boolean models	<ul style="list-style-type: none">Capable of inferring large networksGenerally easy to interpretSimplify underlying complex biological phenomenaAllow supervised learning methods	<ul style="list-style-type: none">Deterministic natureDiscretization bottleneck (only on/off states)Problems in handling incomplete or inconsistent expression dataHigh computing timeMost of them use small number of genes
Examples:	RCGA [85], TRaCE + [86], CABeRNET [87]	
ODE models	<ul style="list-style-type: none">Directed signed graphsRealistic dynamicsSuitable for both steady-state and time series expression dataSimplification of the system by means of linear functionsAllow prediction of the behaviour of the network under different conditions once parameters are known	<ul style="list-style-type: none">Not suitable for large networksLinear functions also constrain the dynamic behaviour of cell regulatory functions (e.g. oscillations, multistationarity)Hard to find appropriate values for model parametersNoisy data leads to qualitative instead of quantitative GRN inference
Examples:	SCODE [68], HiDi [69]	
Bayesian models	<ul style="list-style-type: none">Noise and uncertainty handlingDo not require a large number of involved variablesIntegration of prior knowledge and allowance of enrichment analysesStatistical inference of gene network	<ul style="list-style-type: none">Feedback loops are not allowedFail in the inference using time series expression dataCannot cope with large GRNsInherent combinatorial learning
Examples:	F-MAP [88], MDP [89], POMDP [71], QMR-DT [73]	
Neural models	<ul style="list-style-type: none">Recognize an input patternModel any functional relationship inferable from the dataSuitable for both steady-state and time series expression profilesNoise handling and biologically plausibleManage non-linear and dynamic behaviour	<ul style="list-style-type: none">Machine training experiments are hard to perform since every situation requires a different learning rate definitionComputational complexity makes them more suitable for very small systems
Examples:	ANN [27], RNN [78], ELM [83]	

Considerations when choosing approach

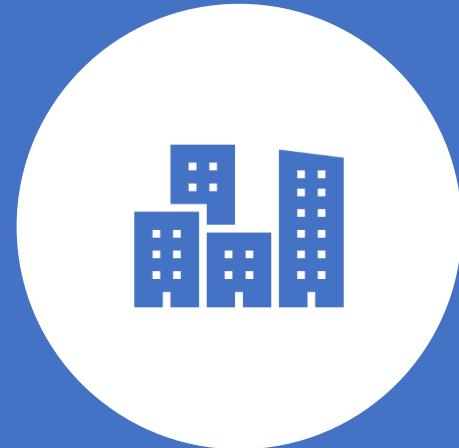
1. Simplicity/interpretability
2. Scalability
3. Assumptions (e.g. can we assume linear relationship?)
4. Sensitivity vs specificity
5. Ability to model feedback loops and combinatorial regulations
6. Availability of data: how much, statistical independency, data points, etc
7. Pitfalls of different network types: e.g. from mRNA to gene regulatory networks:
mRNA abundance is a proxy for activity and presence of regulators, not a direct influence
8. Integrating prior knowledge improves results

Considerations for experimental design / input data

- Network inference is a largely undetermined problem. i.e. has multiple solutions
- To help deconvolute uncertainties, the best experimental design includes
 - Perturbation data
 - Steady-state (more realistic as cheaper) or time course (ideal)
 - Timing for measurements is important
- Bigger scale of network to infer requires more data
- Replicates are needed to remove stochastic error and ensure quality of data

Optimization of networks

- Dimensionality reduction can help focus on ‘interesting’ features/genes
 - E.g. Feature selection: remove genes with low expression or no changes
- Structure/topology optimization against experimental datasets
 - Forward selection (growing network and evaluating)
 - Backward elimination (pruning and evaluating)
- Integration of prior knowledge has been shown to almost always increase accuracy
- Integration of other datasets also has been promising but tools are in early development stage



Bottom up
network construction

		Metabolic	Protein-protein	Regulatory/ Signaling	Organisms	Curation ^a
KEGG	http://www.genome.jp/kegg/	x			many	C
BiGG	http://bigg.ucsd.edu/	x			many	M
BioCyc ^b	http://biocyc.org/	x		x	many	C/M
MetaCyc	http://metacyc.org/	x			many	C/M
Reactome	http://reactome.org/	x	x	x	many	M
BIND	http://www.bindingdb.org/		x		many	E/M
DIP	http://dip.doe-mbi.ucla.edu/		x		many	M
HPRD	http://www.hprd.org/		x		human	M
MINT	http://mint.bio.uniroma2.it/		x		many	M
Biogrid	http://www.thebiogrid.org/		x		many	E
UniHI	http://theoderich.fb3.mdc-berlin.de:8080/unihi/		x		human	E/M
Yeastract	http://www.yeastract.com/			x	yeast	M
TRANSFAC	http://www.gene-regulation.com			x	many	M
TRANSPATH	http://www.gene-regulation.com			x	many	M
RegulonDB	http://regulondb.ccg.unam.mx/			x	many	C/E
NetPath	http://www.netpath.org/			x	human	M

^aM=Manual/Literature, C= Computational, E= Experimental.

^blinks to other *Cyc databases

Many sources available

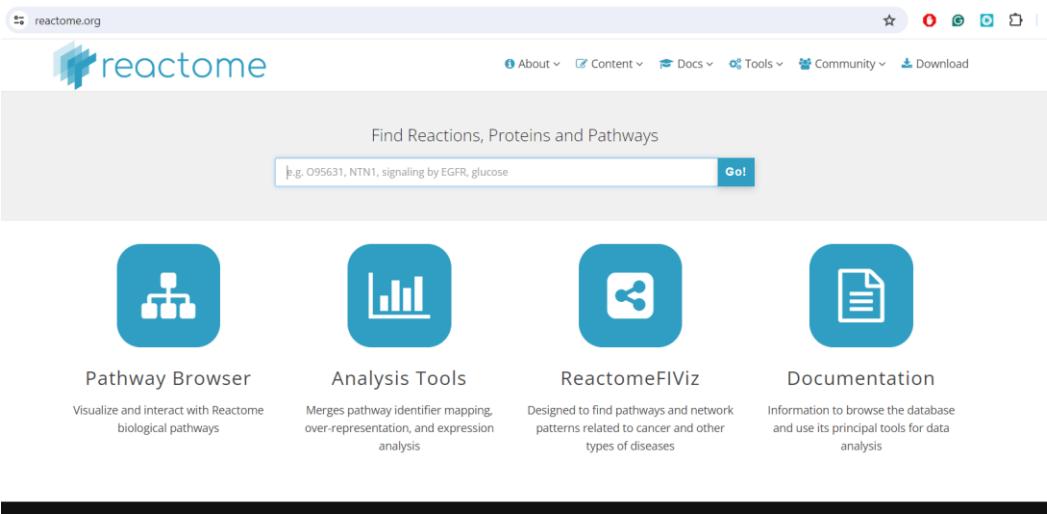
Database Name	URL or Web Address	Comments
HumanCyc (Encyclopedia of Human Metabolic Pathways)	http://humancyc.org/	-MetaCyc adopted to human metabolism -No disease or drug pathways
KEGG (Kyoto Encyclopedia of Genes and Genomes)	http://www.genome.jp/kegg/	-Best known and among the most complete metabolic pathway databases -Covers many organisms -A Few disease and drug pathways
The Medical Biochemistry Page	http://themedicalbiochemistrypage.org/	-Simple metabolic pathway diagrams with extensive explanations -A few drug and disease pathways
MetaCyc (Encyclopedia of Metabolic Pathways)	http://metacyc.org/	-Similar to KEGG in coverage, but different emphasis -Well referenced -No disease or drug pathways
Reactome (A Curated Knowledgebase of Pathways)	http://www.reactome.org/	-Pathway database with more advanced query features -Not as complete as KEGG or MetaCyc
Roche Applied Sciences Biochemical Pathways Chart	http://www.expasy.org/cgi-bin/search-biochem-index	-The old metabolism standard (on line) -Describes most human metabolism
Small Molecule Pathway Database (SMPDB)	http://www.smpdb.ca/	-Pathway database with disease, drug and metabolic pathways for humans -Extensive search, analysis and visualization tools
Wikipathways	http://www.wikipathways.org	-Community annotated pathway database for 19 model organisms -Contains 175 human pathways -Few drug or disease pathways

	CBN	KEGG	Reactome	BioCarta	Wiki-pathways	SPIKE	UCSD signaling gateway	NCI pathway interaction database	NetPath
Species [human (Hs); mouse (Mm); rat (Rn)]	Hs, Mm*, Rn*	>20 species	Hs (curated) +20 species (inferred)	Hs, Mm	>25 species	Hs	Hs, Mm	Hs	Hs
Literature support displayed						✓	✓	✓	✓
At edge level	✓								
At pathway level		✓	✓	✓	✓			✓	✓
Defined biological boundaries									
Species	✓	✓		✓	✓	✓		✓	✓
Tissue	✓								
Disease context	✓	✓			✓				✓
Biological pathways	✓	✓	✓	✓	✓	✓		✓	✓
Manual curation	✓	✓	✓	✓	✓	✓	✓	✓	✓
Data-driven enhancement	✓						✓		✓
Crowd curation	✓			✓	✓				±
Directional edges	✓	✓	✓	✓	✓	✓	✓	✓	✓
Multiple types of entities	✓	✓	✓	✓	✓	✓	✓	✓	✓
Interactive visualization	✓		✓		✓				
Computable	✓	✓	✓						
Available for download	✓	✓	✓		✓	✓	✓	✓	✓
Size	>120 network models	>450 pathway maps	>1400 pathways (Hs)	>350 pathways	>430 pathways	>25 curated pathways	~3500 proteins and their proximal connections	>135 NCI-Nature curated pathways (+Reactome + BioCarta)	>30 curated pathways (immune signaling/cancer)

*coming soon

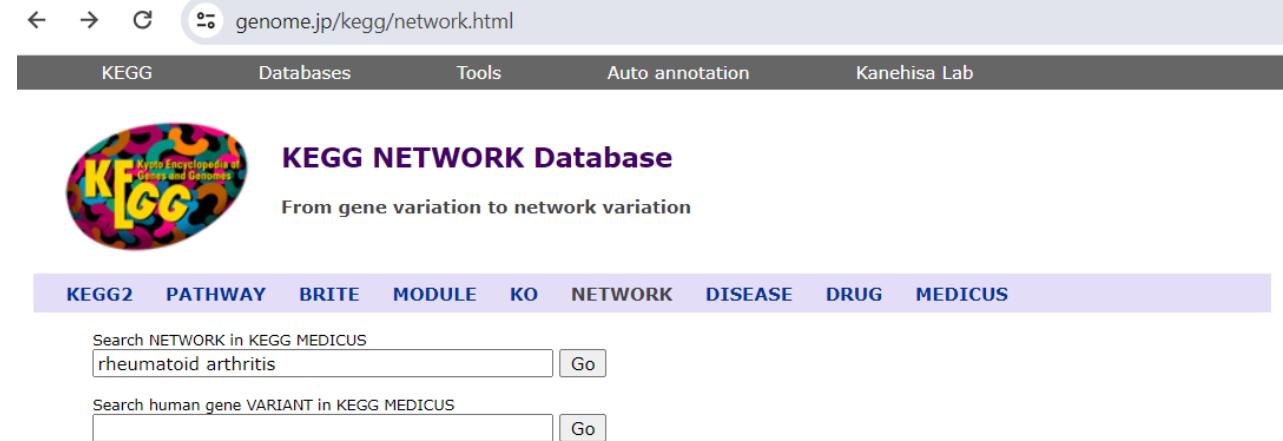
Causal biological network database: a comprehensive platform of causal biological network models focused on the pulmonary and vascular systems

Pathway-bases are now enriched in tools and functionalities

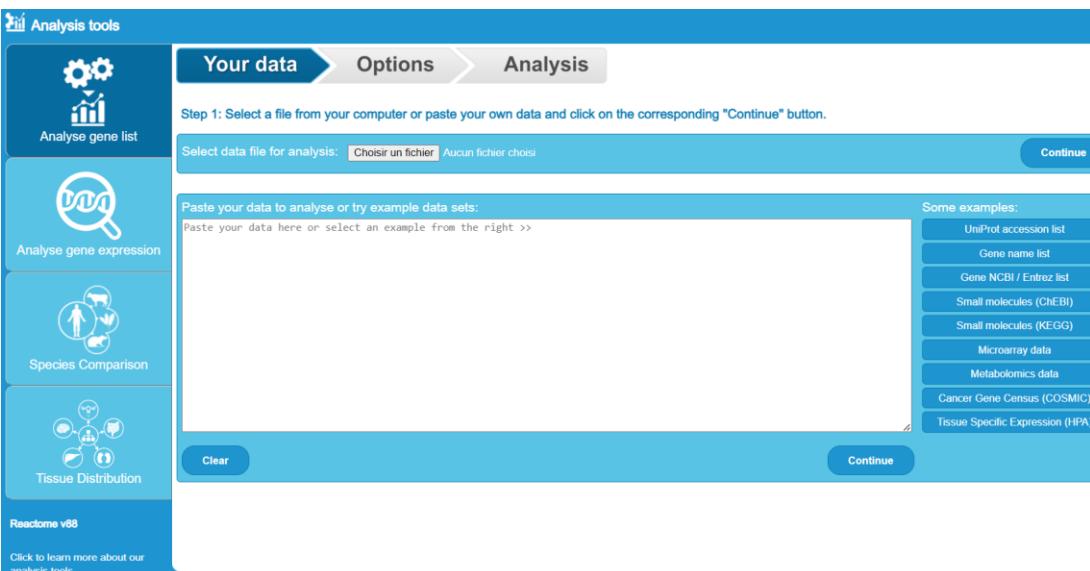


The Reactome website features a search bar at the top with the placeholder "e.g. 095631, NTN1, signaling by EGFR, glucose". Below the search bar are four main navigation icons: Pathway Browser (blue square with white nodes), Analysis Tools (blue square with white bar chart), ReactomeFlViz (blue square with white network nodes), and Documentation (blue square with white document icon). Each icon has a brief description below it.

- Pathway Browser: Visualize and interact with Reactome biological pathways
- Analysis Tools: Merges pathway identifier mapping, over-representation, and expression analysis
- ReactomeFlViz: Designed to find pathways and network patterns related to cancer and other types of diseases
- Documentation: Information to browse the database and use its principal tools for data analysis



The KEGG Network Database homepage features a large "KEGG NETWORK Database" logo with the subtitle "From gene variation to network variation". A navigation bar at the top includes links for KEGG, Databases, Tools, Auto annotation, and Kanehisa Lab. Below the header is a search bar for "Search NETWORK in KEGG MEDICUS" with the query "rheumatoid arthritis". Another search bar below it is for "Search human gene VARIANT in KEGG MEDICUS".



The Reactome Analysis Tools interface shows a step-by-step process: "Your data" (selected), "Options", and "Analysis". The "Your data" step includes a "Select data file for analysis" input field and a "Continue" button. The "Analysis" step includes a "Paste your data to analyse or try example data sets" input area and a "Continue" button. On the left sidebar, there are four tool icons: Analyse gene list, Analyse gene expression, Species Comparison, and Tissue Distribution. At the bottom left, there is a link to "Reactome v68" and a note about the analysis tools.

Network Variation Maps

KEGG NETWORK represents a renewed attempt by KEGG to capture knowledge of diseases and drugs in terms of perturbed molecular networks (see Background of [KEGG DISEASE](#)). It accumulates variations of molecular interaction/reaction networks in terms of network variation maps (such as nt06210) consisting of network elements (such as N00014). The notation of network variation maps is as follows.

Network element	Coloring
Reference network	Green
Variant network containing	
Human gene variant	Red
Pathogen gene/protein	Purple
Environmental factor	Blue
Drug-target relation	Navy

Edge	Interaction/reaction
→	Activation
-	Inhibition
=	Complex formation
/	Missing interaction or reaction
↗	Gain of function
⇒	Expression
⊣	Repression
—	Substrate binding to enzyme or transporter
→	Enzymatic reaction or transport process
⇒	Enzyme-enzyme relation of successive reactions

Pathway-bases are now enriched in tools and functionalities

← → ⌂ pantherdb.org



The mission of the PANTHER knowledgebase is to support biomedical and other research by providing comprehensive information about the evolution of protein-coding gene families, particularly protein phylogeny, function and genetic variation impacting that function. [Learn more](#)

PANTHER18.0 Released. [Click for more details.](#)

search keyword All

Home About Data Version Tools API/Services Publications Workspace Downloads FAQ/Help/Tutorial
Current Release: PANTHER 18.0 | 15,693 family

Gene List Analysis Browse Sequence Search Genetic Variant Im

Please refer to our article in [Nature Protocols](#) for detailed instructions on how to use this page.

Help Tips
Steps:

- 1. Select list and list type to analyze
- 2. Select Organism
- 3. Select operation

[Using enhancer data](#)

1. Enter ids and or select file for batch upload. Else enter ids or from workspace for comparing to a reference list.

Enter IDs:
 Aucun fichier choisi

separate IDs by a space or comma

Upload IDs: File format

Please [login](#) to be able to select lists from your workspace.

Select List Type:
 ID List
 Previously exported text search results
 Workspace list
 PANTHER Generic Mapping
 ID's from Reference Proteome Genome Organism for id list

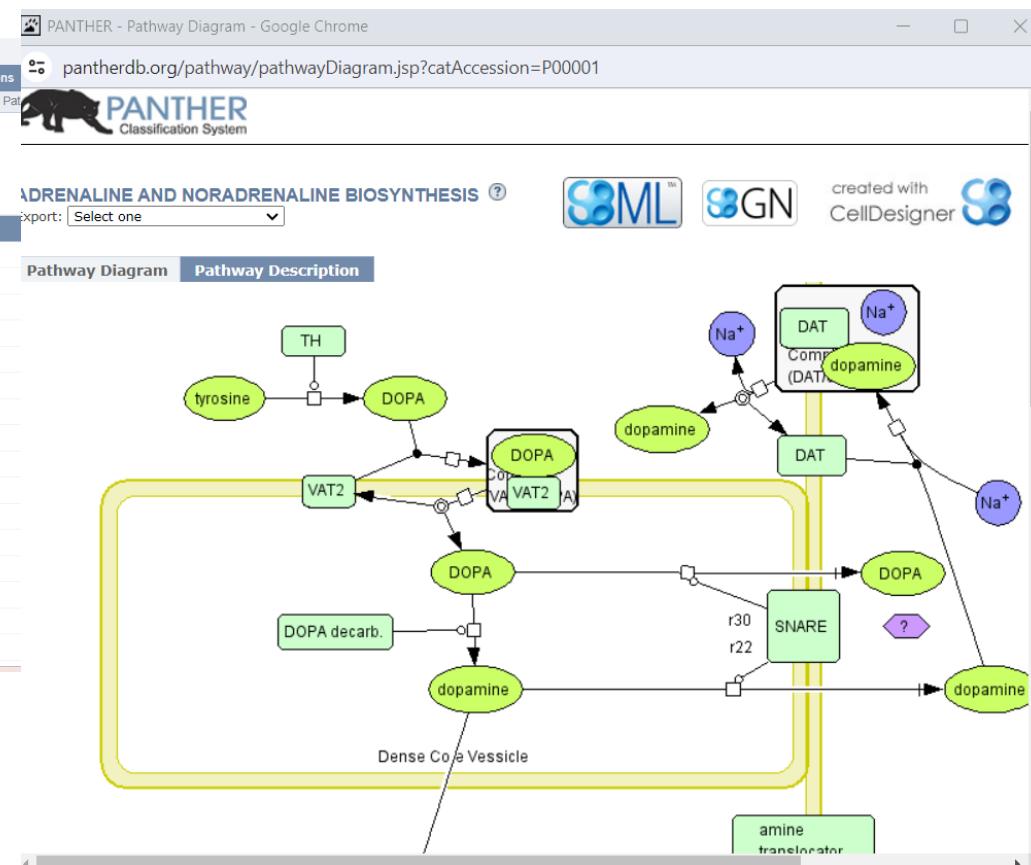
 VCF File Flanking region Search Enhancer Data

2. Select organism.

Homo sapiens
 Mus musculus
 Rattus norvegicus
 Gallus gallus
 Danio rerio



The mission of the PANTHER knowledgebase is to support biomedical and other research by providing comprehensive information about the evolution of protein-coding gene families, particularly protein phylogeny, function and genetic variation impacting that function. [Learn more](#)



Pathway-bases are now enriched in tools and functionalities

wikipathways.org

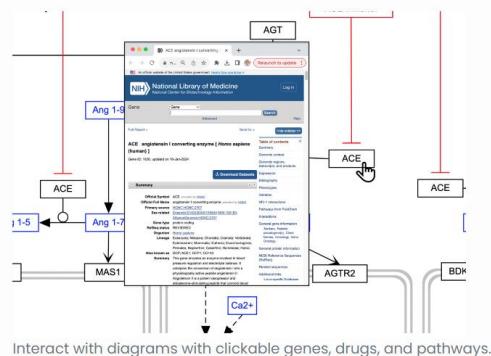


About Search Browse Communities Download Analyze Cite Help Go to Classic Site

WikiPathways is an open science platform for biological pathways contributed, updated, and used by the research community.

[Read more](#) [Video tour](#)

Powered by: PathVisio & BridgeDB



Interact with diagrams with clickable genes, drugs, and pathways.

PathVisio
Biological pathway creation and curation software

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PathVisio biological pathway editor

PathVisio is a free open-source pathway analysis and drawing software which allows drawing, editing, and analyzing biological pathways. It is developed in Java and can be extended with plugins.

PathVisio is the pathway editor for WikiPathways, a community-curated pathway database enabling collaborative pathway editing.

Download and Access

Get pathway information in the format you need, including GPML (XML), GMT, SVG, and more. Programmatically access our content in multiple ways.

[GPML](#) [API](#)
[GMT](#) [SPARQL](#)
[SVG](#) [R](#)
[Archive](#) [Python](#)

signor.uniroma2.it



Signor 3.0
The SIGnaling Network Open Resource

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Search Disease Browser Pathway Browser Advanced Methods

- Homo sapiens
- Mus musculus
- Rattus norvegicus
- Oryctolagus cuniculus

SIGNOR is a repository of manually annotated causal relationships between human proteins, chemicals of biological relevance, stimuli and phenotypes. The search field below allows users to access the entity page detailing all the causal relationships annotated to the query entity. SIGNOR also curates pathways that can be accessed by making choices in the drop down menu below. In addition SIGNOR offers advanced graph tools to explore the human cell network.

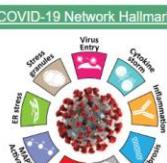
all connect find path

Search tips:
To search for a single entity type its name or ID into the search bar.
For a multi-protein search type their UniProt IDs or Gene Names separated by one of the following delimiters: comma(,), semi-colon(,), space.

Related Projects



News



Tweets from @signor_database Follow



Nothing to see here

**IMEx**

The International Molecular Exchange Consortium

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List of IMEx members

- DIP (Active)
- HPIDB (Active)
- IntAct (Active)
- MBInfo (Active)
- MINT (Active)
- MatrixDB (Active)
- Molecular Connections (Active)
- I2D (Active)
- InnateDB (Active)
- UCL-BHF group, UCL London (Active)
- UniProt group (Active)
- Swiss-Prot group, SIB (Active)
- EMBL-EBI (Active)
- BioGRID (Observer)
- PrimesDB (Observer)
- MPact (I)
- BIND (In)
- MPIDB (

IMEx data

- A non-redundant set of physical molecular interaction data from a broad taxonomic range of organisms.
- Expertly curated from direct submissions, peer-reviewed journals or pre-prints to a consistent high standard.
- Available in standard formats [MITAB](#) or [PSI-MI XML 2.5](#).
- Provided by a network of participating major public domain databases.

Available Interaction Network Data

<http://www.imexconsortium.org/about/>

Integrated Data Sources

Open Source

- Pathway Commons
- BioGRID
- MiMI (Michigan Molecular Interactions)
- STRING (Search Tool for Retrieval of Interacting Genes/Proteins)
- Genes2Network
- VisANT (Integrative Visual Analysis Tool)
- BIOBASE

Proprietary

- IPA (Ingenuity Pathway Analysis)
- MetaCore



VisANT

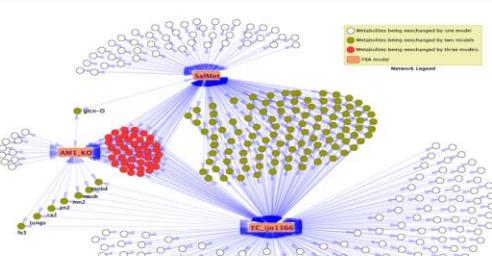
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VisANT 5.0

Visual analyses of metabolic networks in cells and ecosystems

V5 Manual

Download



The visualization displays a complex metabolic network with various nodes representing metabolites and reactions. Three specific pathways are highlighted: 'Salicin' (blue), 'AM1140' (red), and 'EC_001000' (yellow). Nodes are color-coded based on their involvement in multiple models: blue for one model, green for two models, red for three models, and yellow for four models. A legend titled 'Network Legend' provides this key. Below the main network diagram, there is a horizontal row of five smaller network snippets.



Michigan Molecular Interactions

Formerly called the Michigan Protein Database (MIPD). It is currently available [here](#). MiMI is an ongoing project supported by [NCIBI](#). Collaborators include the UM Medical School. Additional sponsors include the [NSF](#), [NIH](#), [MCBI](#), and [Microsoft](#).

MiMI:

Formerly called the Michigan Protein Database (MIPD). It is currently available [here](#). MiMI is an ongoing project supported by [NCIBI](#). Collaborators include the UM Medical School. Additional sponsors include the [NSF](#), [NIH](#), [MCBI](#), and [Microsoft](#).

Biological Texts:

There is a great deal of interest on understanding biological texts automatically. There are also a large number of biological databases dealing with a variety of topics. The goal of our project is to be able to combine these two efforts by storing the information extracted from the text parsing into an XML database with a proper data model. With all the information managed by a database engine, complex queries can be issued and data mining can be applied.

Integrated Protein Information:

Protein data, from sequence and structure to interaction, is being generated through many diverse methodologies; it is stored and reported in numerous forms and multiple places. The magnitude of the data limits researchers abilities to utilize all information generated. Effective integration of protein data can be accomplished through better data modeling. Using an appropriate data model can enable researchers to exploit data more fully. Using [TIMBER](#) as our repository, we are developing a data model which allows fuller usage of the current protein data.

BioGRID 4.4

Welcome to our Database of Protein, Genetic and Chemical Interactions

BioGRID is a biomedical interaction repository with data compiled through comprehensive curation efforts. Our current index is version **4.4.216** and searches **81,370** publications for **2,570,689** protein and genetic interactions, **29,417** chemical interactions and **1,128,339** post translational modifications from major model organism species. All data are **freely** provided via our search index and available for download in many standardized formats.

[BioGRID Statistics](#)  [Latest Downloads](#) 

Q Search BioGRID:

By Protein/Gene

Search by Protein/Gene Identifiers ...

All Organisms

Submit Identifier Search Q

 Advanced Search

 Helpful Search Tips

 Featured Datasets

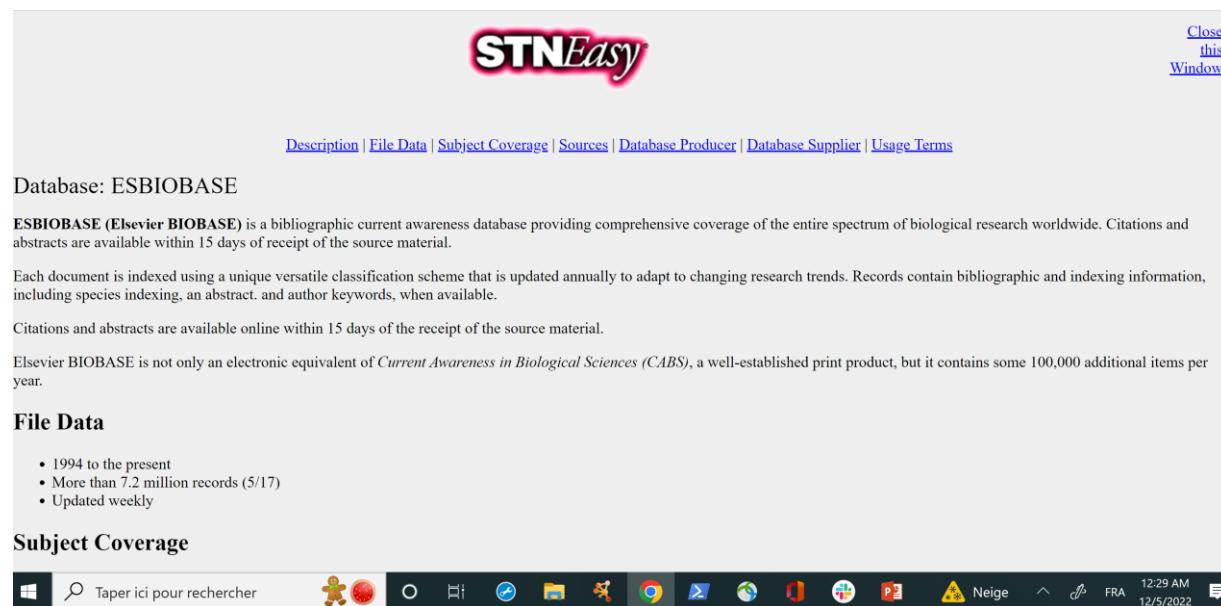
BioGRID COVID-19 Coronavirus Curation Project
Search BioGRID for SARS-CoV-2 Protein Interactions | Download SARS-CoV-2 and Coronavirus-Related Interactions

Related Resources 

BioGRID ORCS - An open repository of CRISPR screens
The BioGRID Open Repository of CRISPR Screens (ORCS) is a publicly accessible database of CRISPR screens compiled through comprehensive curation of all genome-wide CRISPR screen data reported in the biomedical literature. ORCS is updated on a quarterly basis and is fully searchable by

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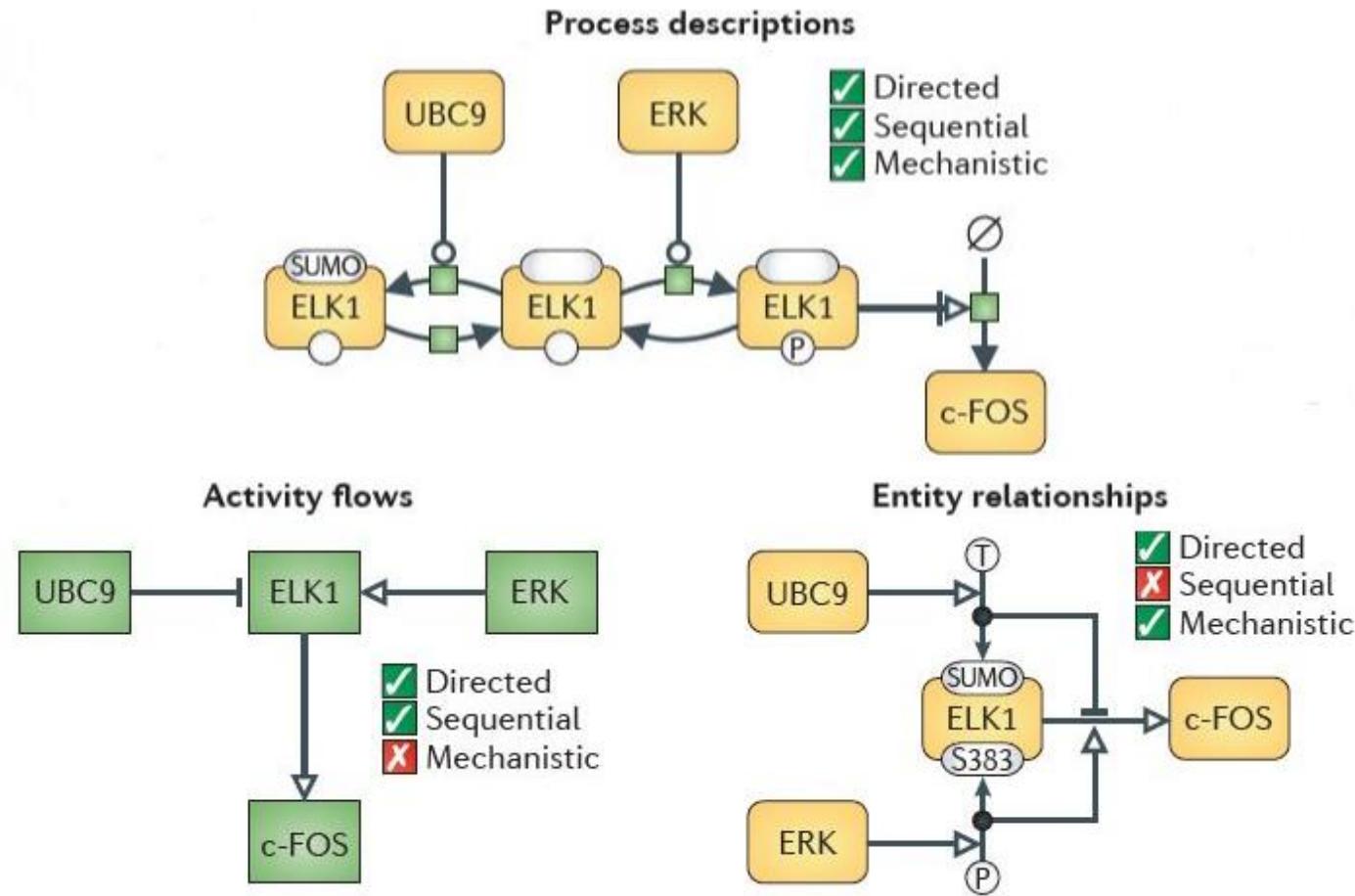


USING FORMALIZED DIAGRAMS TO REPRESENT Biological Networks



Systems Biology Graphical Notation (SBGN)

Describing mechanisms in a systematic fashion

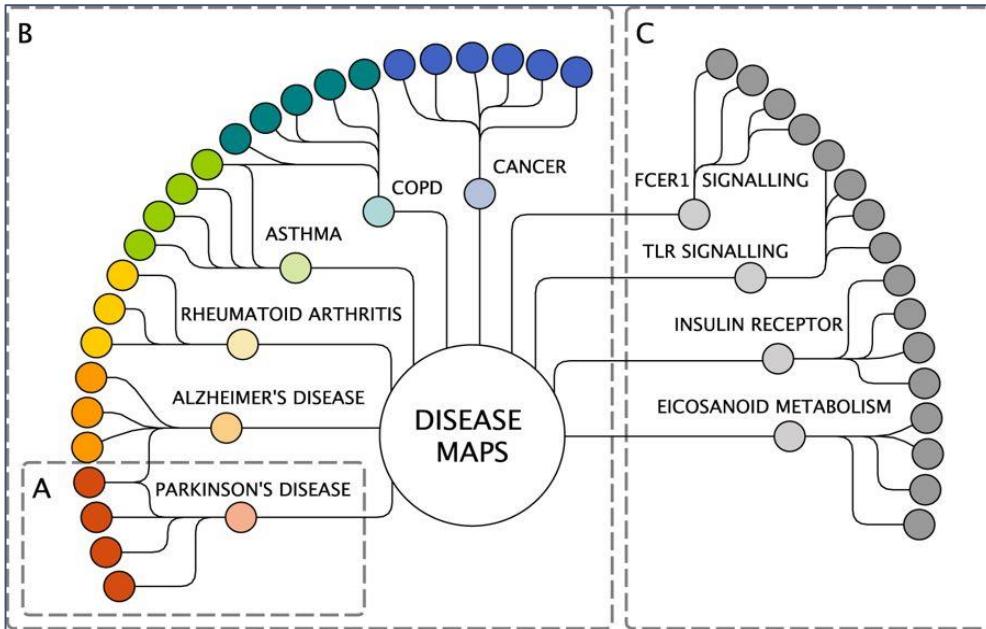


Process description diagrams of biological mechanisms

- Pioneering works of Prof. Hiroaki Kitano.
- Process description representation of signalling networks.
- First comprehensive disease-relevant extensive reconstructions of signalling pathways.
- Cancer Signalling Atlas – Curie Institute -
<https://acsn.curie.fr/ACSN2/ACSN2.html>
- Disease Maps project <https://disease-maps.org/>
- REACTOME – PD like diagrams <https://reactome.org/>

The Disease Maps project

Large-scale open community effort



Key goals

Create

formalized mechanistic networks at different levels to investigate cellular machinery and host pathogen interactions.

Interpret

large-scale data sets and extract true information to understand how the disease takes place and progresses.

Develop

computational techniques, which can integrate large and heterogeneous data sets and combine them with prior knowledge.

Build

computational models that can provide insights into the mechanisms of interest.

Molecular interaction maps



Representations of biological processes (disease mechanisms) that are both human and machine-readable.



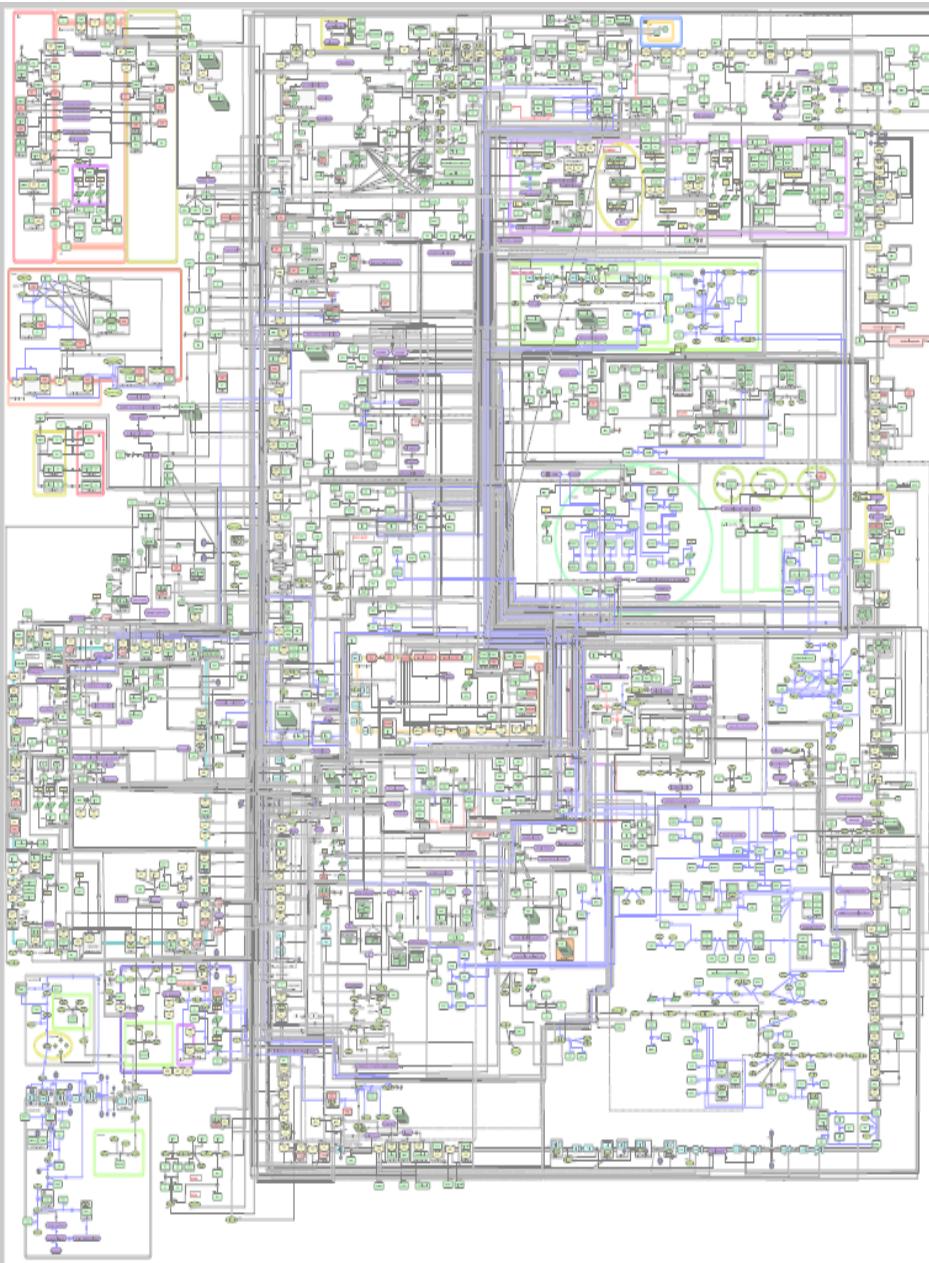
High quality source of knowledge (signalling pathways, gene expression, cellular phenotypes)—template for data visualization.



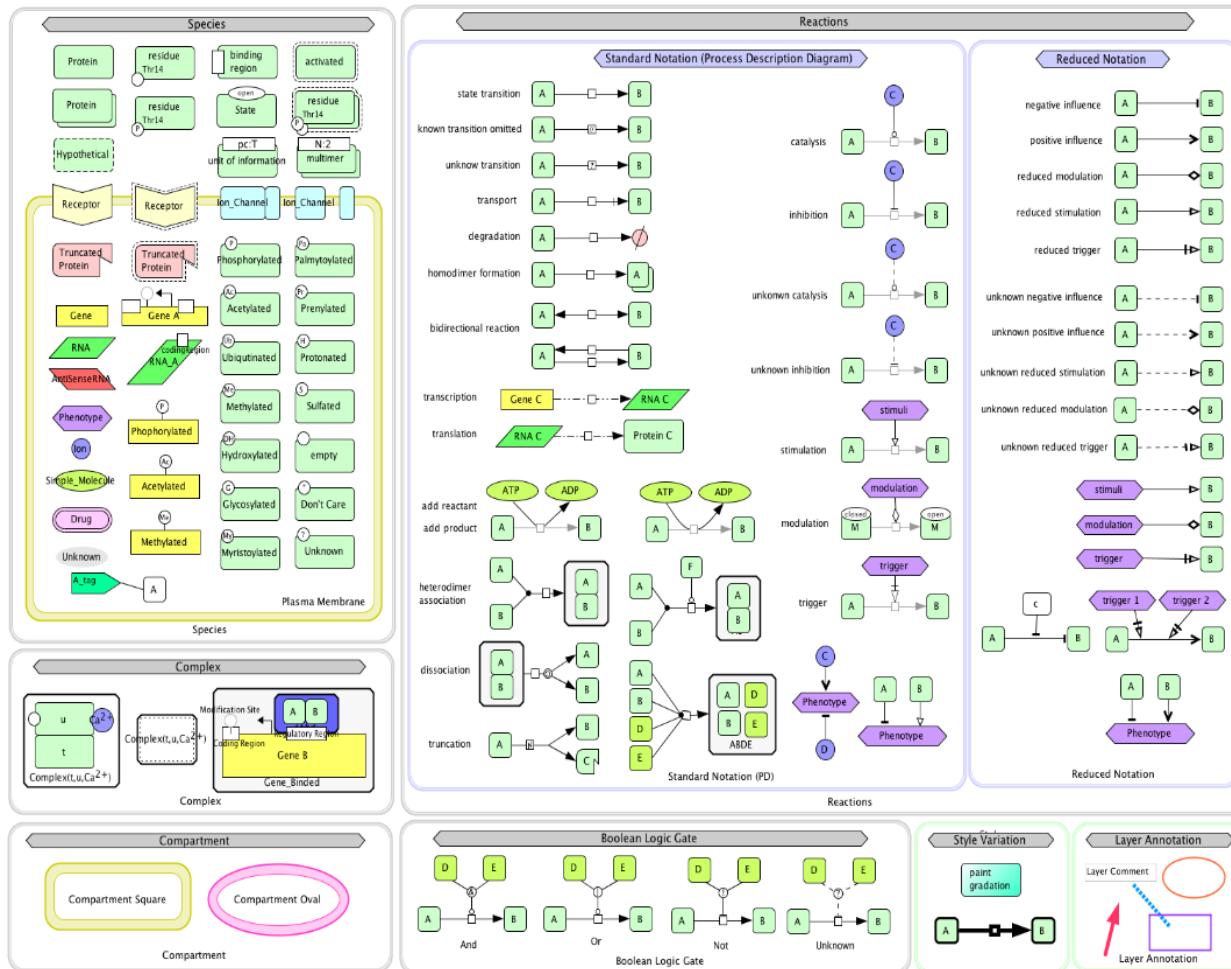
Can be seen and analyzed as **a complex network** (topology/structure).



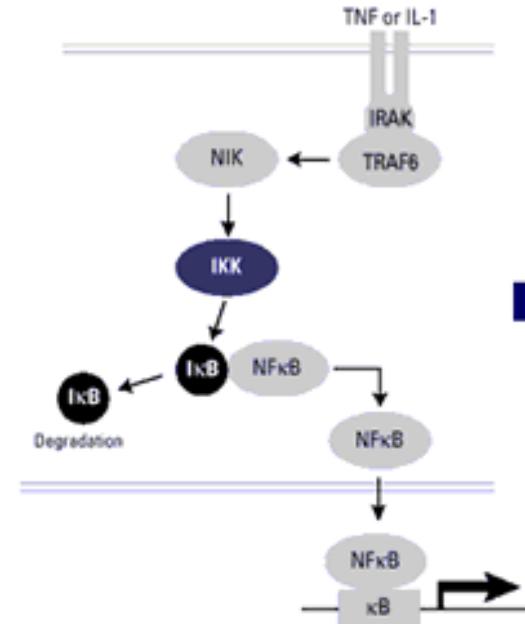
Can serve as a scaffold for a **mathematical model**.



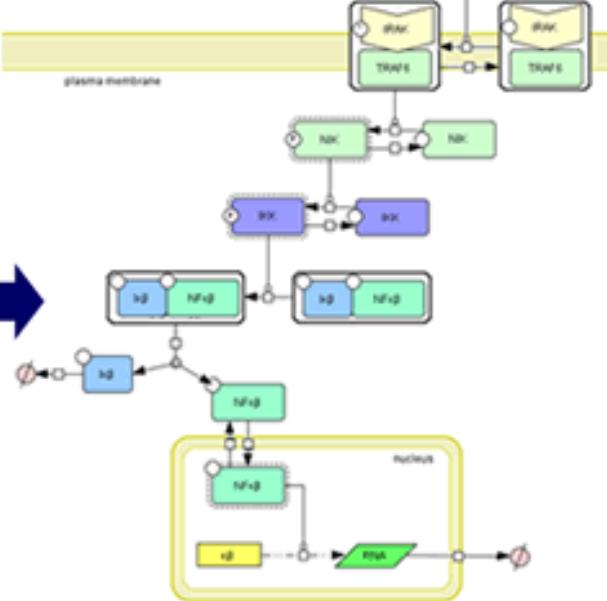
Building molecular maps using CellDesigner



NF κ B Pathway



conventional diagram



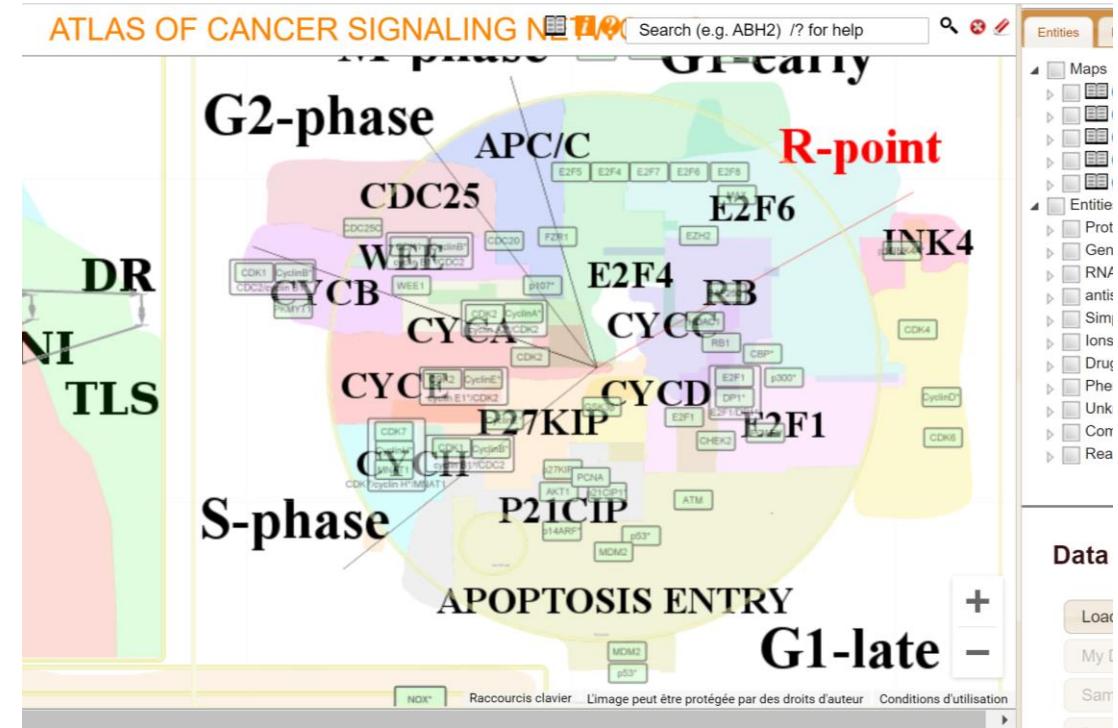
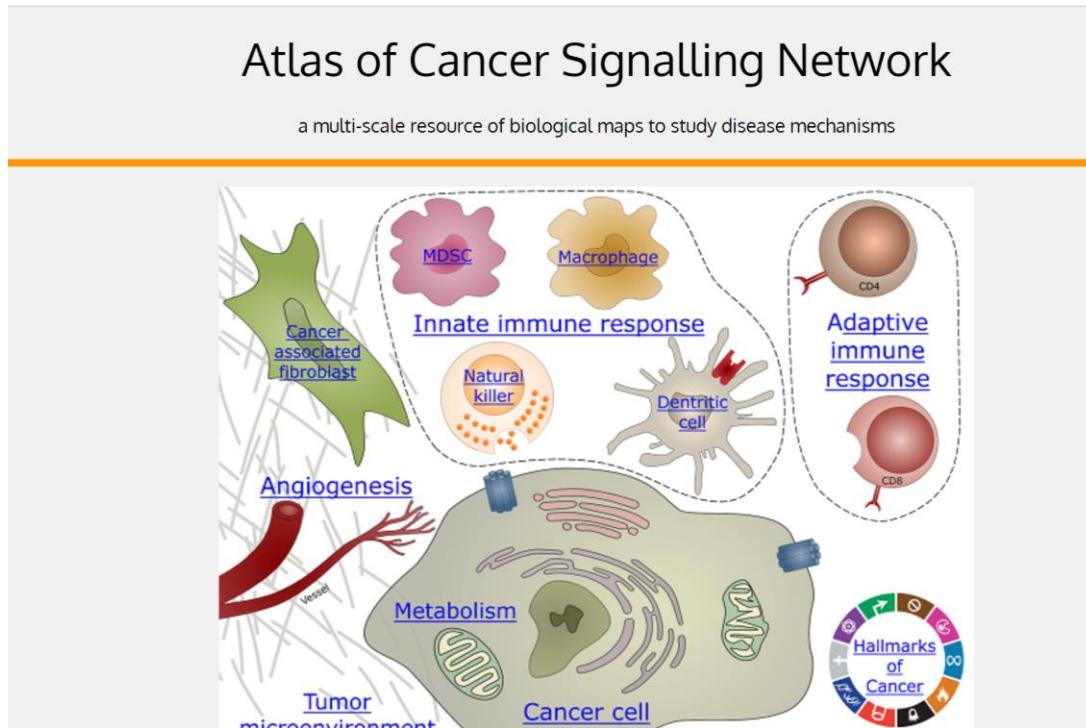
The Parkinson's map

<https://pdmap.uni.lu/Minerva>

- Minerva platform
 - Large scale curation effort
 - Interdisciplinarity
 - PD and AF

Atlas of Cancer Signalling Network

<https://acsn.curie.fr/navicell/maps/acsn/master/index.html>

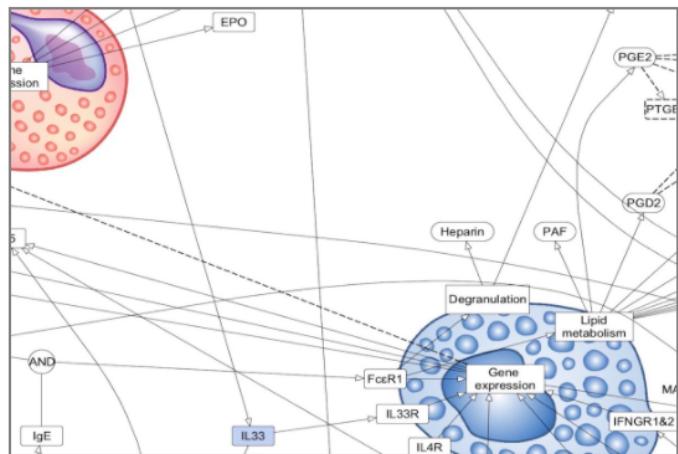


- Large collection of cancer associated pathways
- Navicell
- Large scale effort
- PD and AF

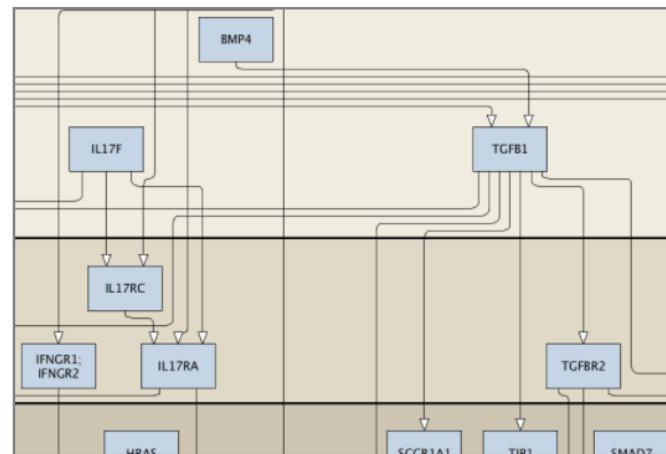
AsthmaMap architecture

The AsthmaMap includes three interconnected layers of granularity: Cellular Interactions (CI), a high-level overview; Molecular Relations (MR), the intermediate level of details; Biochemical Mechanisms (BM), the most detailed layer.

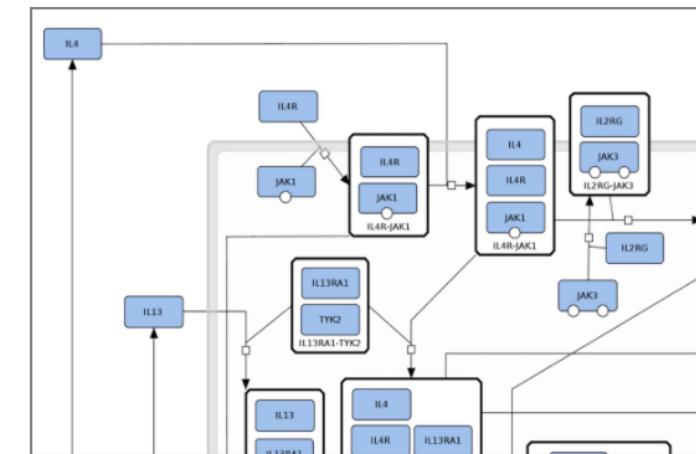
AsthmaMap Cellular Interactions



AsthmaMap Molecular Relations



AsthmaMap Biochemical Mechanisms



The Asthma Map

<https://asthma-map.org/>

- Granularity
- Different layers
- PD
- AF

The RA map

<https://ramap.uni.lu/minerva/>

- SBGN compliant, fully PD
- Detailed annotations using MIRIAM identifiers
- Executable through a map-to-model framework (PD→AF)

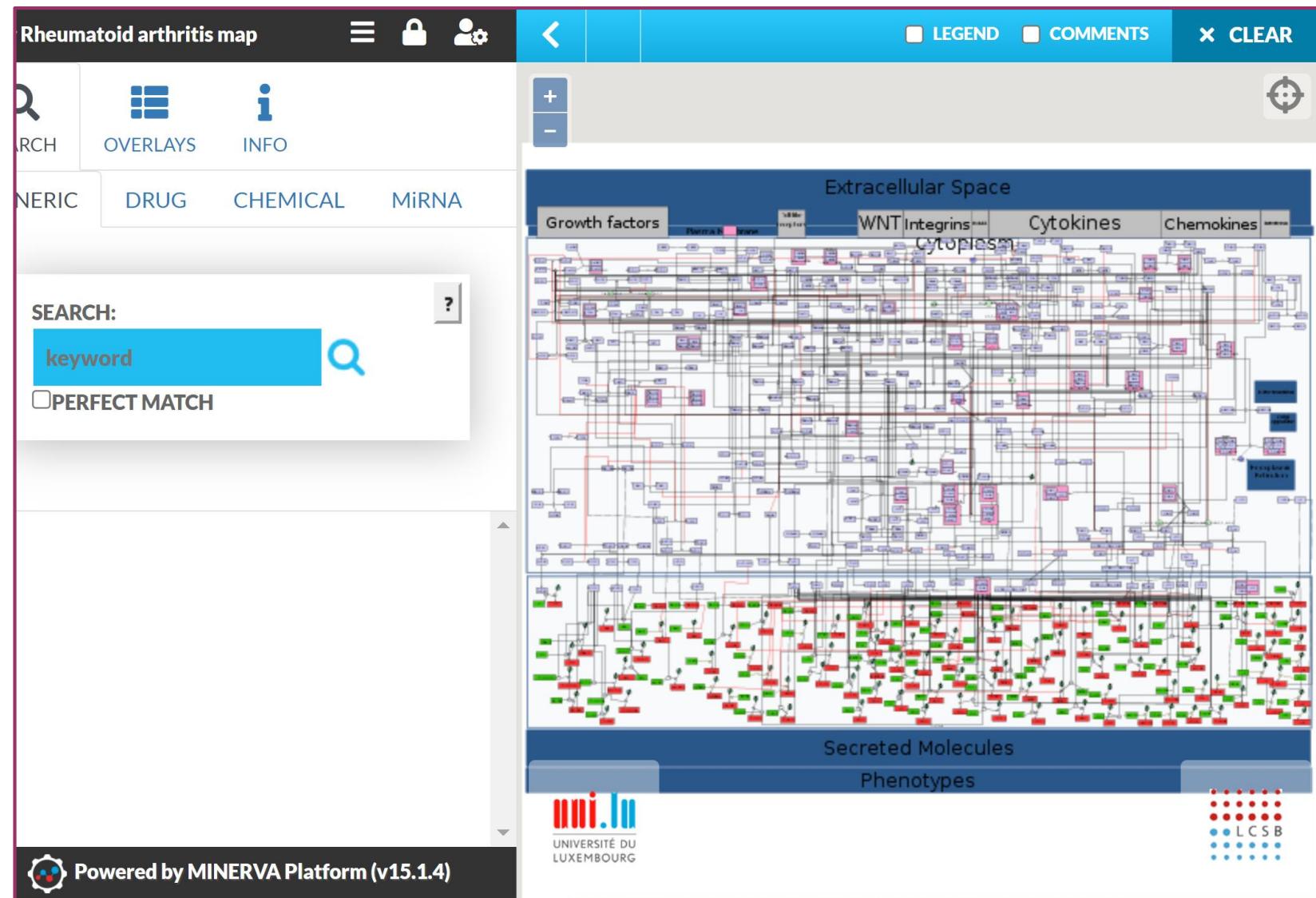
JOURNAL ARTICLE

RA-map: building a state-of-the-art interactive knowledge base for rheumatoid arthritis 

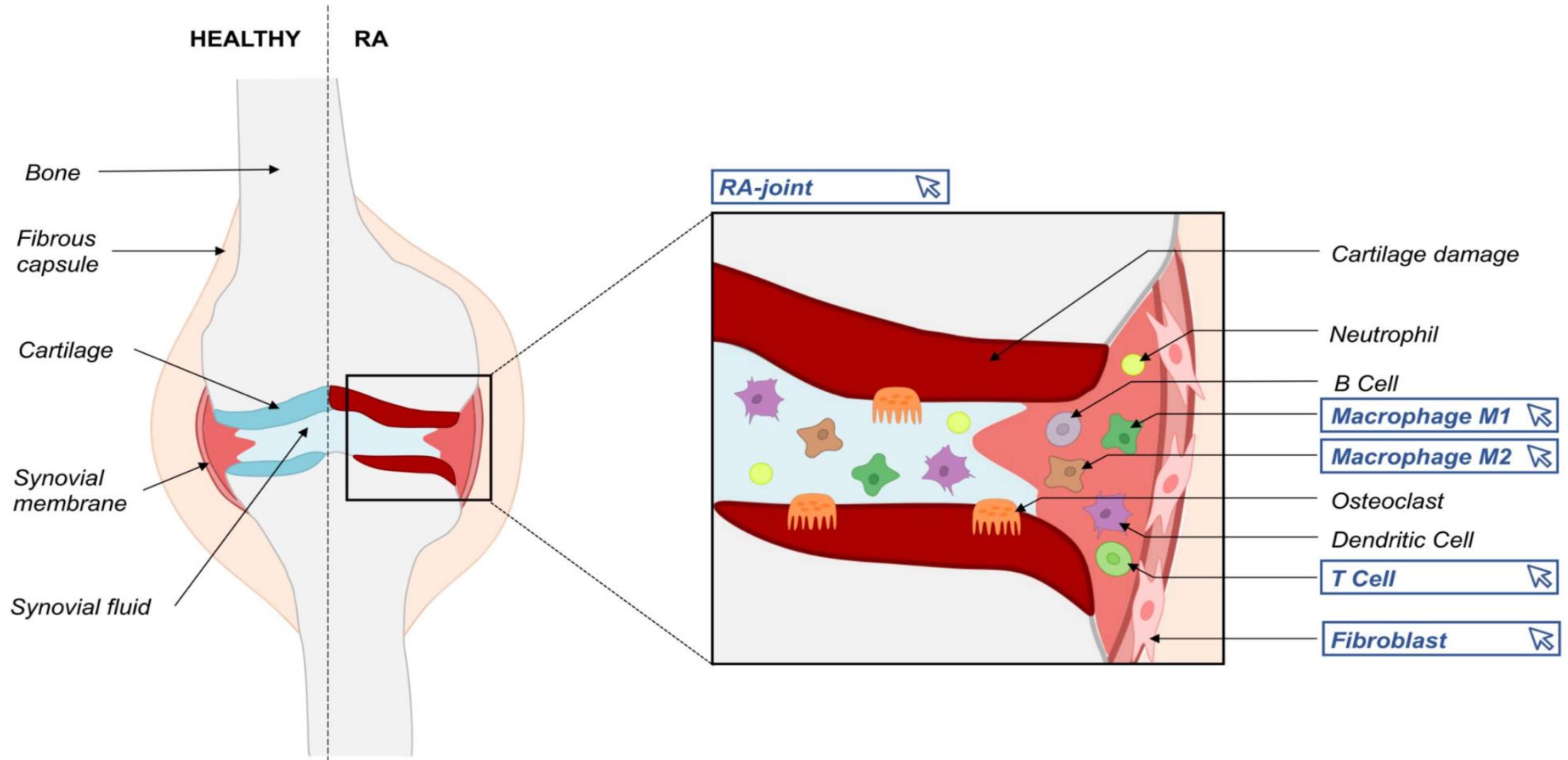
Vidisha Singh, George D Kalliolias, Marek Ostaszewski, Maëva Veyssiére, Eleftherios Pilalidis, Piotr Gawron, Alexander Mazein, Eric Bonnet, Elisabeth Petit-Teixeira, Anna Niarakis 

Database, Volume 2020, 2020, baaa017, <https://doi.org/10.1093/database/baaa017>

Published: 20 April 2020 Article history ▾

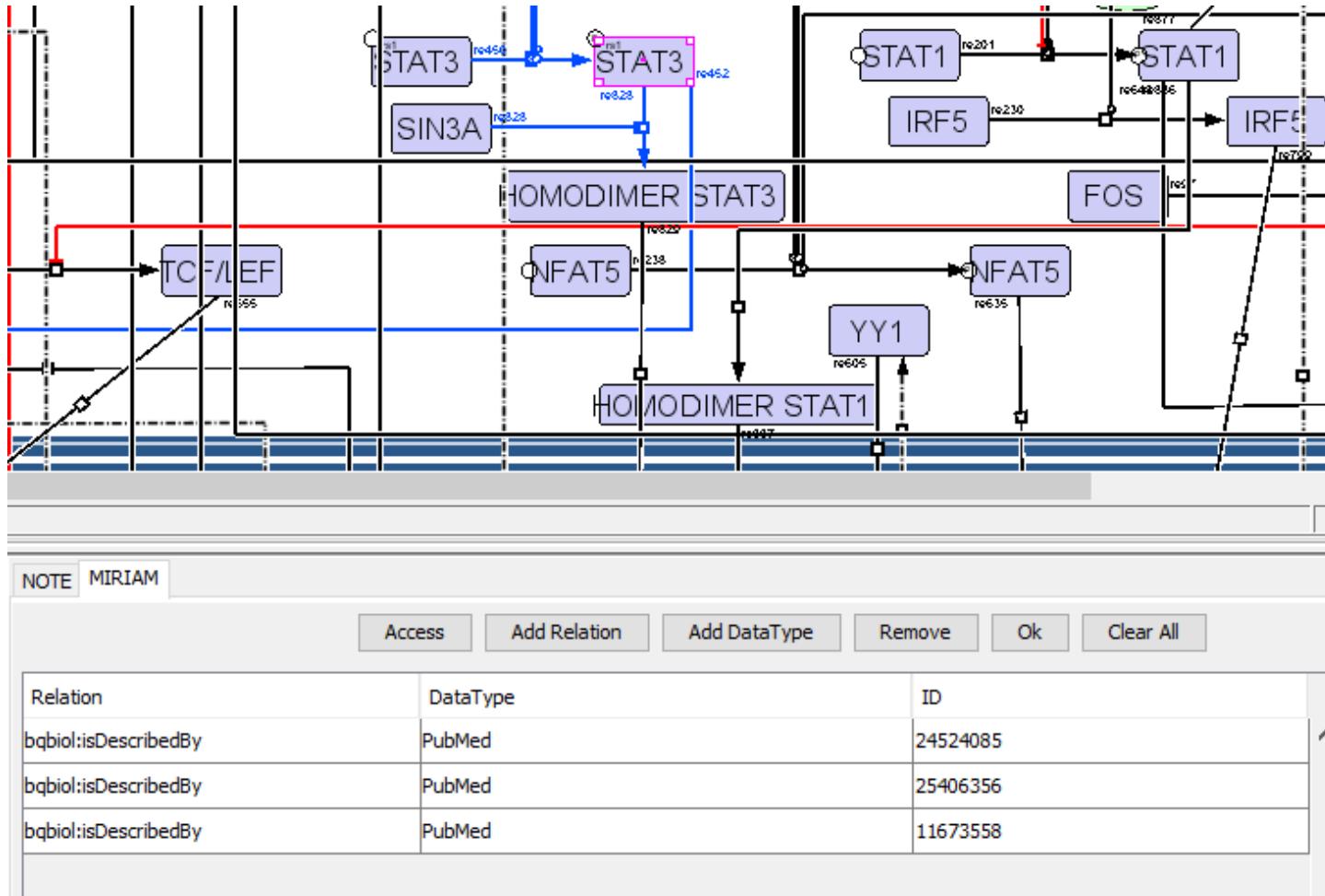


The RA –Atlas



Building molecular maps using CellDesigner

MIRIAM: Minimal Information Required In the Annotation of Models



- Facilitating interoperability and model reusability
- Annotations retrieved in the resulting model

Interactive knowledge base for RA using MINERVA –(Molecular Interaction NEtwoRk VisuAlization) platform

SEARCH OVERLAYS INFO

GENERIC DRUG CHEMICAL MIRNA

SEARCH: IL6

il6

1 RNA: IL6

Compartment: Nucleus
Full name: interleukin 6
Symbol: IL6
Former symbols: IFNB2
Synonyms: BSF2, HGF, HSF, IL-6
Annotations:
Source: Annotated by curator
[1] PUBMED(10688908)
[2] PUBMED(17652167)
[3] PUBMED(2462501)
[4] PUBMED(18281366)
[5] PUBMED(18454843)
[6] PUBMED(24524085)
[7] PUBMED(22870451)
[8] PUBMED(8484679)
[9] PUBMED(12905466)
[10] PUBMED(28494214)
[11] PUBMED(18205922)

Powered by MINERVA Platform

Extracellular Space

Protein: IL6

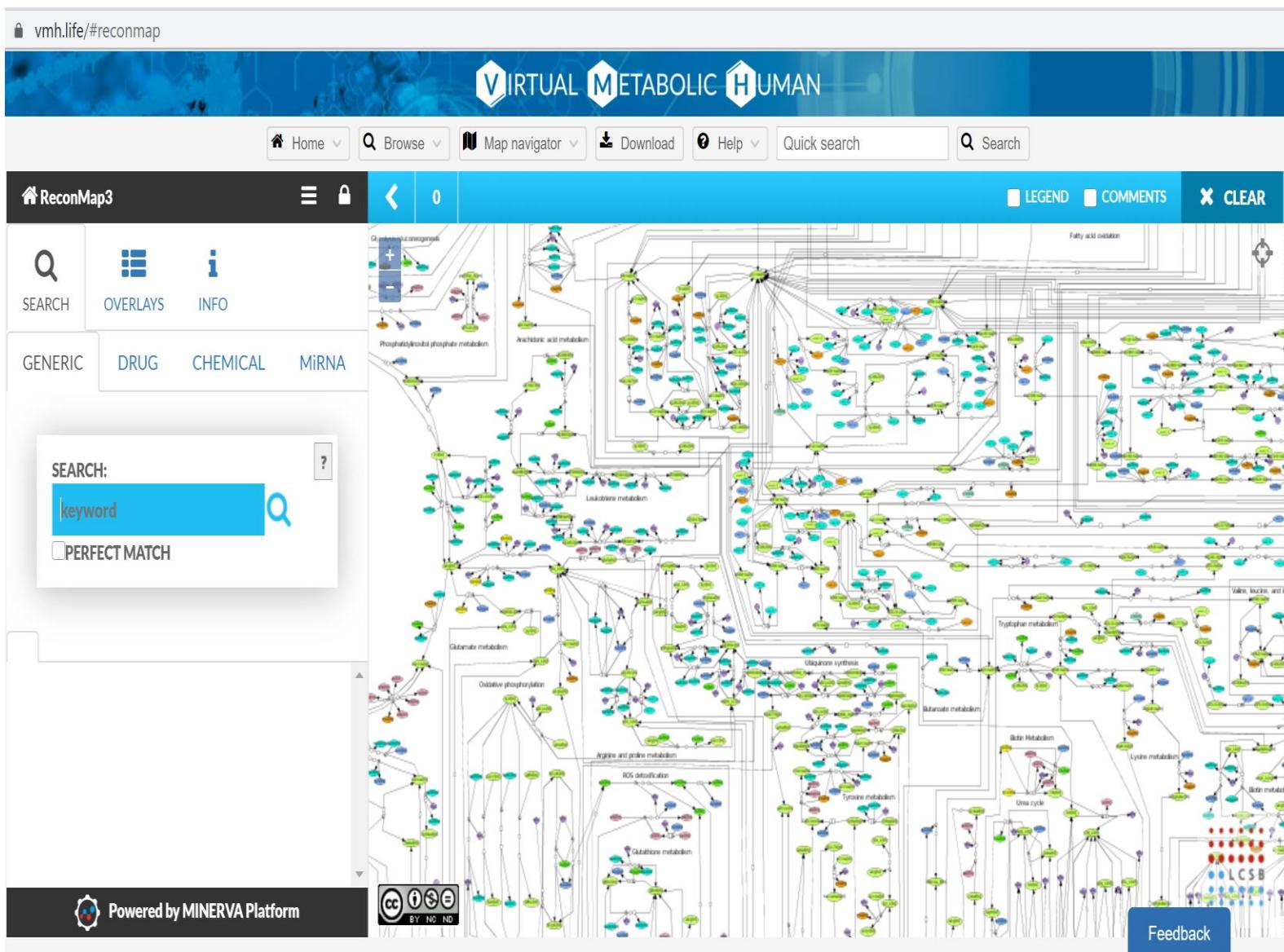
Interacting drugs

Interacting chemicals

Interacting Micro RNAs

The ReconMap

- ReconMap content obtained from the Virtual Metabolic Human database (VMH, <http://vmh.uni.lu>).
- Recon-derived simulation results can be visualized on ReconMap using a new extension to the COBRA Toolbox (Schellenberger et al., 2011).
- User can perform a simulation, e.g. Flux Balance Analysis, using the COBRA toolbox function ‘optimizeCBmodel’, then call the function ‘buildFluxDistLayout’ to write the input file for a context-specific ReconMap Overlay.





CellDesigner™: A modeling tool of biochemical networks



Current Release Version: CellDesigner 4.4.2

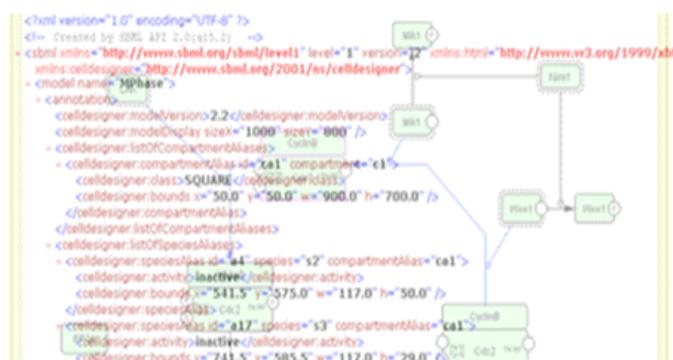
macOS Catalina and Ubuntu 18.04 support + Plugin APIs enhances + BioModels new API support + Garuda enabled + bug fixes. find out more...

You do not have to install JVM separately as it is included in the installer.

Check also:

- [CellDesigner on Garuda platform](#) (Ver4.4.1 Win / Mac)
- [Plugins / Utilities](#)
 - [CellDesigner Plugin API Document](#) (ver4.4.1)
- [Models built with CellDesigner](#)
- [BioModels.net models simulation results with CellDesigner 4.0](#)

What is CellDesigner™



Headlines

[CellDesigner 4.4.2](#) Mac installer updated for Catalina Support (2020/3/30)

[CellDesigner 4.4.2](#) is now available (2019/05/20)

[CellDesigner on Garuda platform](#) (2017/2/14) Garuda enabled Ver4.4 is available as Ver4.4.1 Win / Mac.

[PhysioDesigner 1.0](#) is available. PhysioDesigner can embed CellDesigner's SBML model into its multilevel physiological PHML model. (2014/08/01)

[CellDesigner 4.4](#) is now available (2014/07/12)

Advertisement



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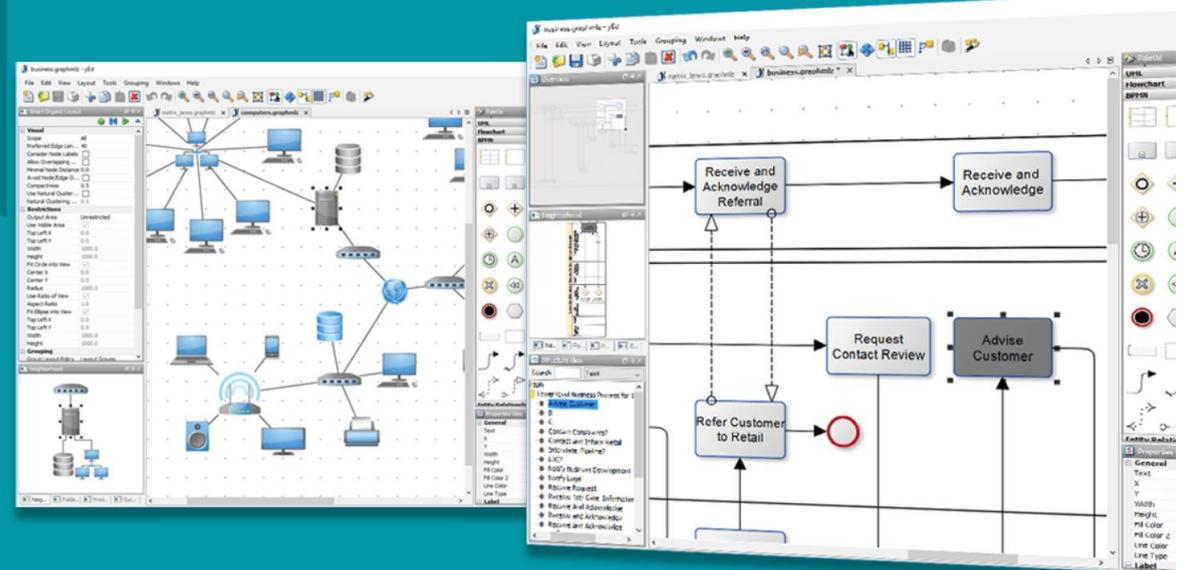


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Pathways Simplified

View, design, and analyze pathways in SBGN and more...

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Welcome to Newt Pathway Viewer & Editor

Newt is a free, web based, open source viewer and editor for pathways in [Systems Biological Graphical Notation \(SBGN\)](#) and [Simple Interaction Format \(SIF\)](#). It was written with a series of libraries and extensions based on [Cytoscape.js](#) with utmost customization in mind.

[Launch **newt**](#)

What distinguishes Newt from other viewers and editors for biological maps can be summarized as:

Search

ENHANCED BY



Latest News

Newt release

April 1, 2020

Newt 3.0 was released to include some [new features](#) such as

Prerequisites for high-quality biochemical interaction maps:

(Inspired by *Systems Biology*, ed. Nielsen and Hofmann, Chapter 8, Wiley -VCH, 2016 and *Community-driven roadmap for integrated disease maps*, Ostaszewski et al., 2018)

- **Accurate** – correctly represents our empirical knowledge.
- **Reusable** – well annotated and referenced.
- **Comprehensive** – accounts for all known reactions within the selected scope.
- **Machine readable** – can be processed and analyzed using computers.

-
- **Executable** – corresponds to a computational model that can be simulated.
 - **Functional** – can explain the known system-level behavior of the biological network.



Adding a dynamical layer

“Why build models?” Jay Bailey

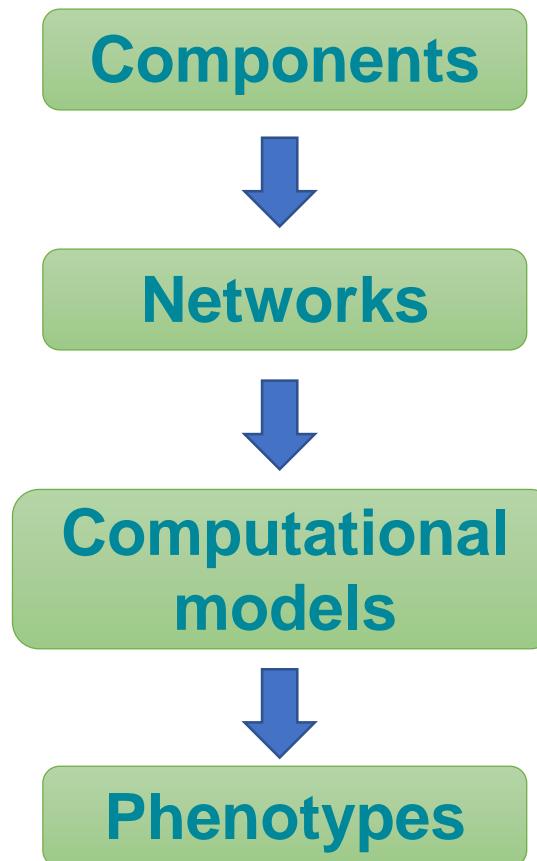
- To organize disparate information into a coherent whole.
- To think (and calculate) logically about what components and interactions are important in a complex system.
- To discover new strategies.
- To make important corrections to the conventional wisdom.
- To understand the essential qualitative features.



Computational models

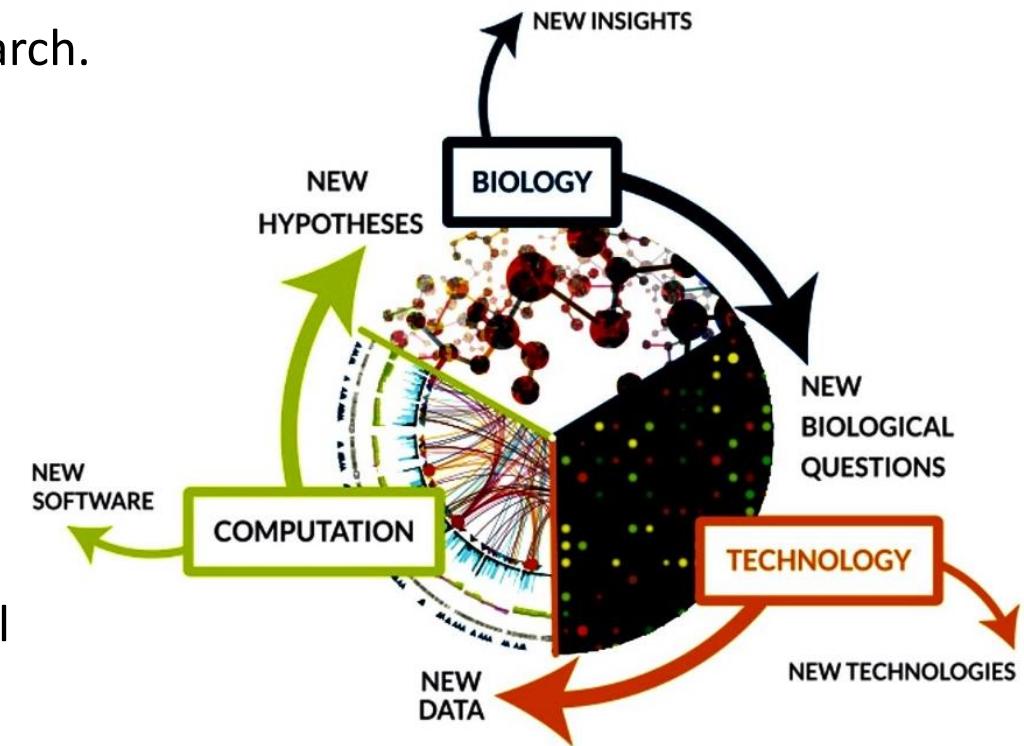
- Models are used to represent actual quantitative/qualitative relations between the molecules in the system.
- Abstract representations of biological processes
- Have an inherent execution scheme attached to the model.

Central dogma of computational systems biology



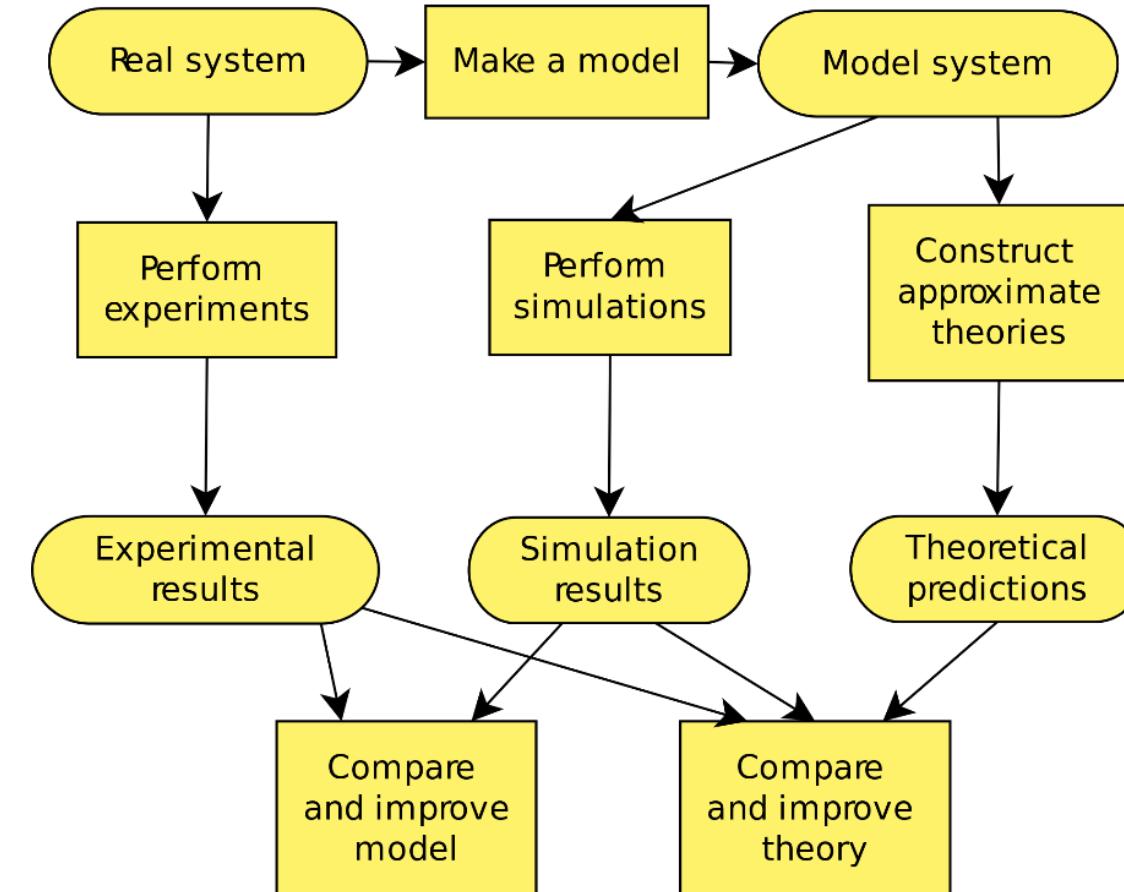
Model building: a step by step process

- Generation of the structural model based on a literature search.
- Compilation of a calibration dataset using experimentally validated biological knowledge.
- Model fitting to the experimental data.
- *In silico* simulations to generate predictions.
- Validation of predictions through experimental testing.
- Model refinement by feeding newly generated experimental data back to the model.
- Generation of novel hypotheses.
- Reiteration.



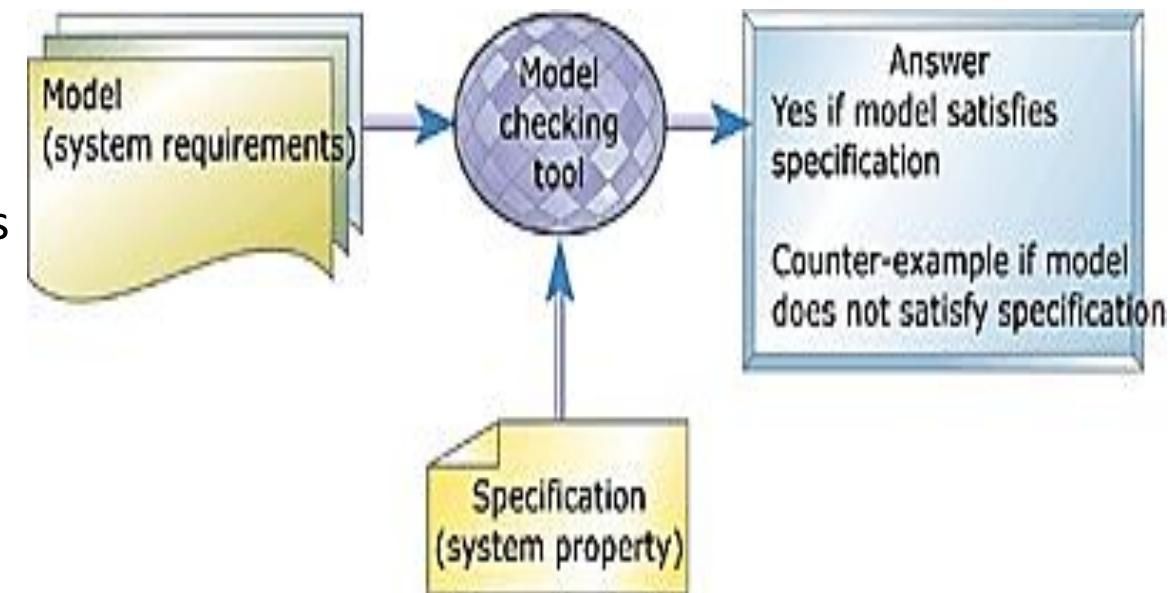
“In theory, there is no difference between theory and practice.

But in practice, there is.” “The Yale Literary Magazine”, February 1882; Benjamin Brewster



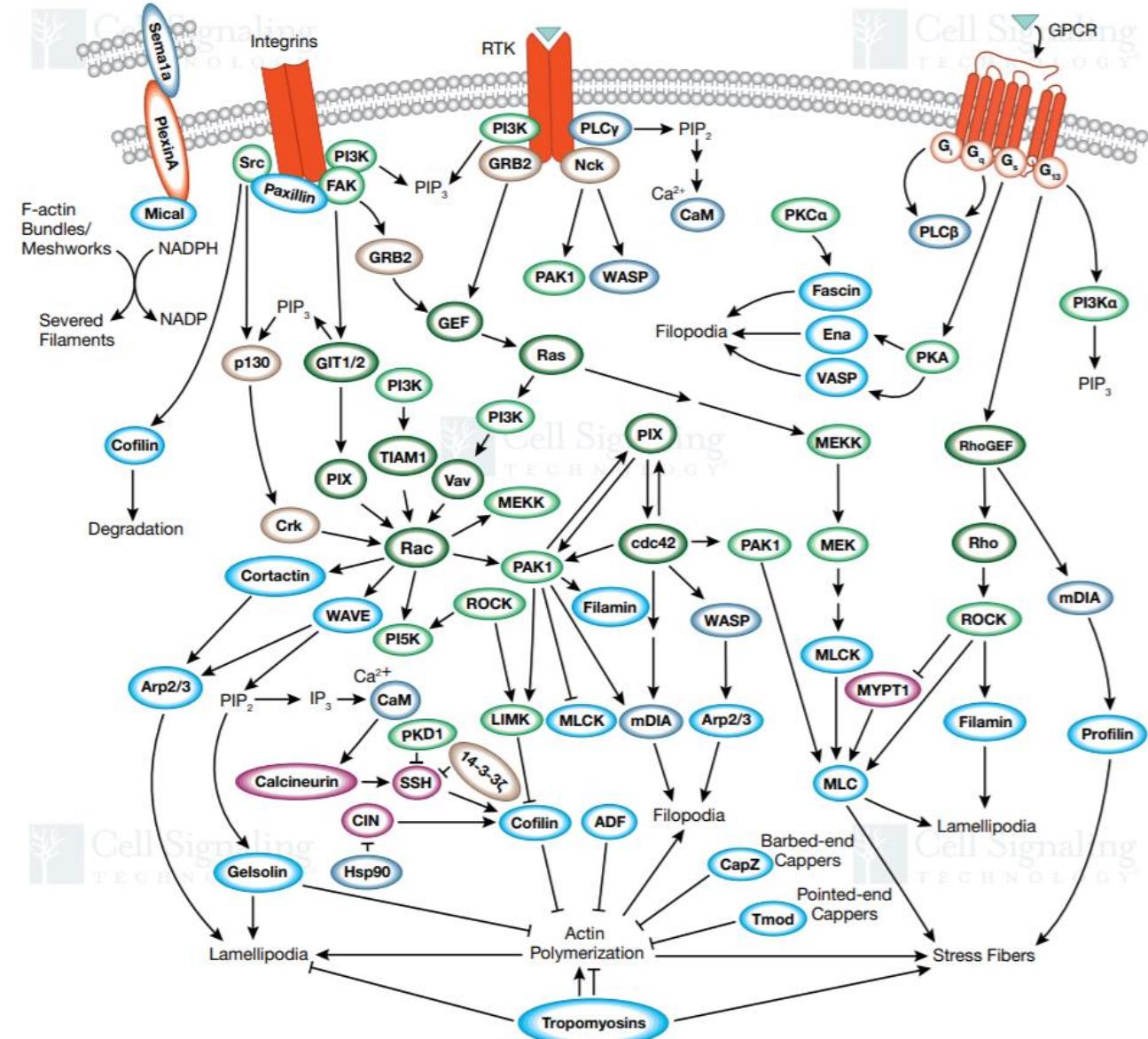
Model checking techniques - Comparing mechanistic models to specifications

- A formal model of the system under study is constructed.
- Experimental evidence is formalized as specifications (observations).
- Model checking is used to ensure that the model reproduces the experimental observations.
- **Mismatch with experimental observations:** model should be refined by additional information.
- **Match with experimental observations:** could lead to further querying and testing of the model to suggest further experimental studies.



Reachability analysis

- Extra-cellular molecules trigger a response inside the cell by initiating a signal at special membrane receptors.
- Signal is transmitted to reporters/targets through various chains of interactions among proteins.
- Understanding whether such a signal can reach from membrane receptors to reporters is essential in studying the cell response to extra-cellular events.



COMPUTATIONAL (BIO) MODELING METHODOLOGIES → LEARNING METHODOLOGIES

Hypothesis-driven

(Mostly) Data-driven

PROCESS ALGEBRA An example in Beta Binder $((\beta(x, \Delta_E)[E]) \parallel (\beta(y, \Delta_I)[I]))$ \downarrow join operator $\beta^a(x, \Delta_E)\beta^a(y, \Delta_I)(E \parallel I)$ $\beta(\cdot)$ active binding site $\beta^a(\cdot)$ hidden binding site \parallel parallel operator Enzyme (E) Inhibitor (I)	RULE-BASED SYSTEMS $EGFR(ECD!1, aa1092\sim Y).EGFR(ECD!1, aa1092\sim Y)$ \downarrow join operator k_1 k_2 \downarrow (An example in BioNetGen) $EGFR(ECD!1, aa1092\sim pY).EGFR(ECD!1, aa1092\sim Y)$	PETRI NETS PLACE TRANSITION NOT ENABLED TOKEN TRANSITION ENABLED Reaction A Reaction B Reaction C Signal Transduction Network	SUPERVISED LEARNING Clinical data: demographic, genetic, cognitive assessment data MRI, CT, PET Deep Learning Feature extraction: $f_w(\text{data})$ Classifier Train (train N) Prediction Validate performance (pred, test)
LOGIC-BASED $r1(brt2.1) \stackrel{\text{def}}{=} \forall t, n. T(t) \otimes$ $C(n, breast, 1, [TGF\beta]) \multimap$ $T(t + d_{11}(f)) \otimes$ $A(n), f \in 0..2 =$ 	FLUX BALANCE + OPTIMISATION Vector of Fluxes Metabolic network Cellular target 2 Pareto front Cellular target 1 Multomics	CONTINUOUS TIME AND HIDDEN MARKOV CHAINS a) Alignment of protein sequences b) Maximum likelihood c) Set of protein structures and their evolutionary histories d) Structure predictions, prediction of evolutionary rates	VARIATIONAL AUTOENCODER (VAE) probabilistic framework Input Encoder $q_\phi(z x) = \mathcal{N}(z; \mu, \text{diag}(\sigma^2))$ Latent representation Decoder $p_\theta(x z) = \prod_{i=1}^n p_\theta(x_i z) = \prod_{i=1}^n x_i^{a_i}(1-x_i)^{1-a_i}$
LATTICE-BASED 	CHEMICAL MASTER EQUATION $\beta = \alpha + \Gamma_1 + \Gamma_2 + \gamma_p$ $\alpha = \beta + \Gamma_2 - \gamma_p$	AGENT-BASED Signaling Molecule (Communicating Agent) Receptor (Reactive Agent) Messengers (Cooperative Agents) Nucleus (Reactive Agent) Signal Transduction	UNSUPERVISED LEARNING Unsupervised neural models developed: <ul style="list-style-type: none"> DiffVAE Disentangled-DiffVAE Graph-DiffVAE $q_\phi(z x) = \mathcal{N}(z; \mu, \text{diag}(\sigma^2))$ $p_\theta(x z) = \prod_{i=1}^n p_\theta(x_i z) = \prod_{i=1}^n x_i^{a_i}(1-x_i)^{1-a_i}$
ORNSTEIN-UHLENBECK Branching Phylogeny 	COMPLEX NETWORKS Omic layer 1 Omic layer 2	GAME THEORY Player 1 Player 2 Altruism Cooperation Spite Selfishness	BAYESIAN LEARNING $\ell(\beta_Z) = \arg \min_{\beta_Z} \left(\sum_{i=1}^n \delta_i \left(\mathbf{x}_{Z,i}^T \beta_Z - \log \left[\sum_{j \in R(i)} \exp(\mathbf{x}_{Z,j}^T \beta_Z) \right] \right) + P_\lambda(\beta_Z) \right)$ Network-based Cox Regression models $M' = \begin{pmatrix} M_{11} & M_{12} & \dots & M_{1p} \\ M_{21} & M_{22} & \dots & M_{2p} \\ \vdots & \vdots & \ddots & \vdots \\ M_{p1} & M_{p2} & \dots & M_{pp} \end{pmatrix}$ Network function Penalties $P_{\lambda,\alpha}(\beta)$
			REINFORCEMENT LEARNING State Action Reward Environment

Interpretability/ non linearity/parameter estimation

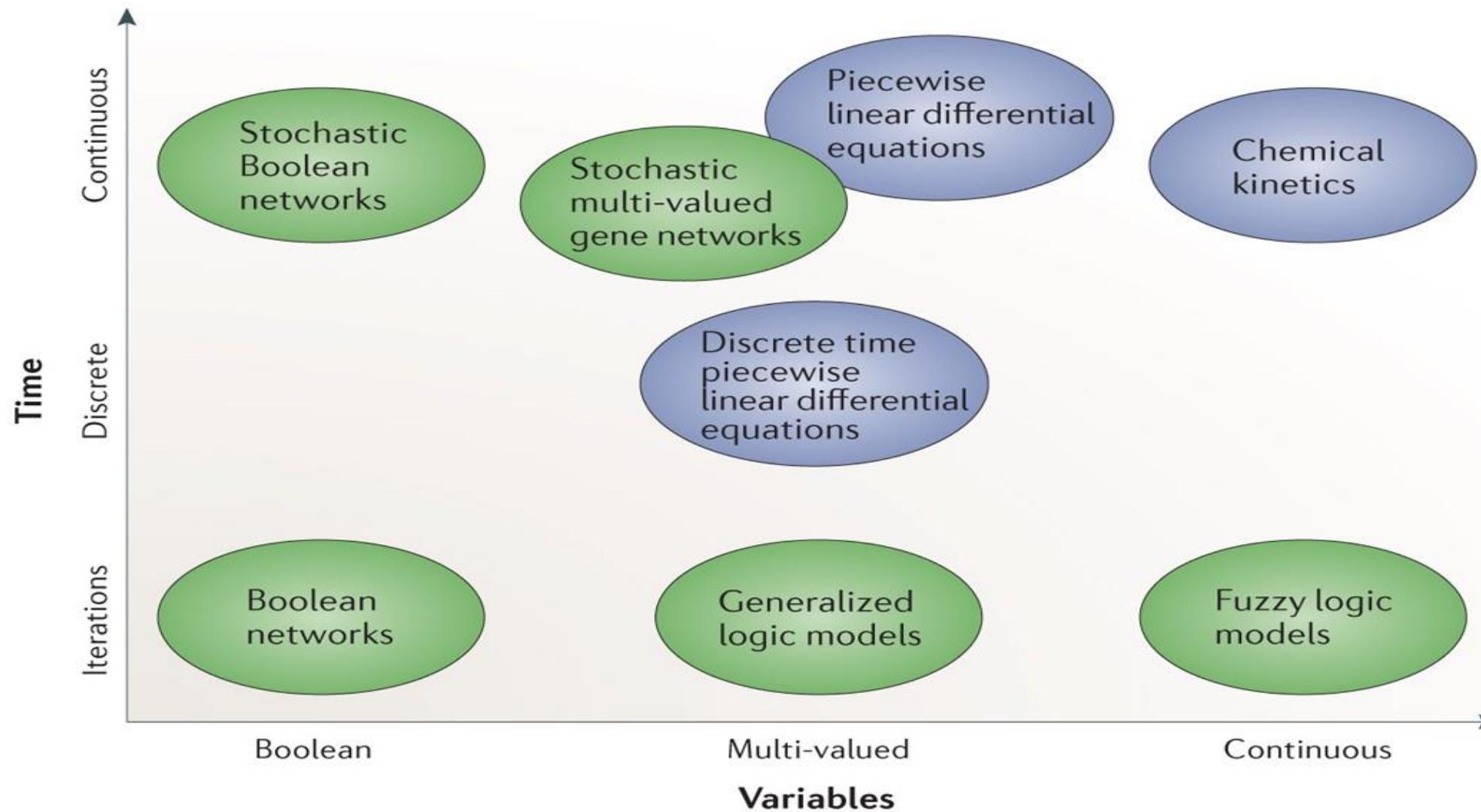
Quantitative versus qualitative models

Table 1

Comparison matrix of quantitative and qualitative models

	Quantitative model	Logic model
Suitable for	Time series	Phenotypes
Time representation	Linear representation	Abstract iterations
Variables	Quantitative	Qualitative
Mechanism representation	Yes	No
What can we do?	Compute concentrations and durations; evaluate the effect of parameter values	Compute state transitions and attractors (steady-states and cyclic attractors)
Data necessary to build the model	Molecular species, genes, interactions, biochemical processes	Activities, defined phenotypes, rules linking those
Data to parameterize and validate the model	Amount of molecular species, timecourses, quantitative phenotype	Perturbations of activities such as RNA interference, inhibitors, qualitative phenotypes
Advantages	Quantitative, precise; direct comparison with quantitative measurements; large existing toolkit	Easy to build; easy to compose; easy simulation of perturbations
Weaknesses	Requires quantitative knowledge of initial conditions and kinetics	Cannot provide quantitative predictions; difficult to choose between alternative behaviours

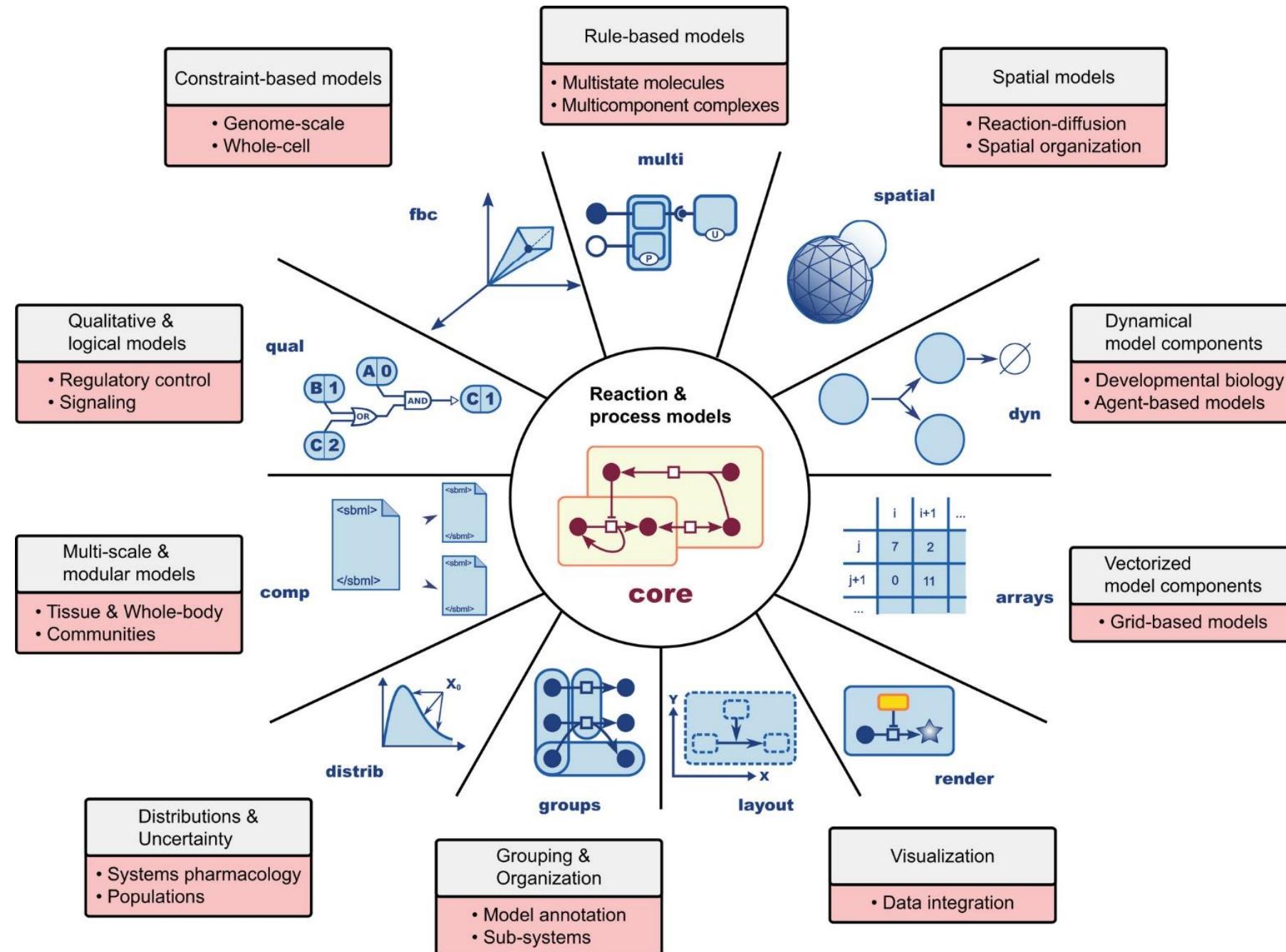
Granularity of time representation and variable values for various modelling approaches.



Many different modelling approaches – one common language?



- A format to encode mathematical models that is used in systems biology.
- Initially focused on non-spatial, reaction-based biochemical models.
- Packages covering different modelling approaches (qual).
- Supported by software libraries in different programming languages .
- Can be imported or exported by a variety of modelling and simulation tools.
- Does not store experimental data, or simulation descriptions.
- Based on xml format, intended to be machine and not human-readable.



🔍 SEARCH

OVERLAYS
SUBMAPS
INFO
+
-

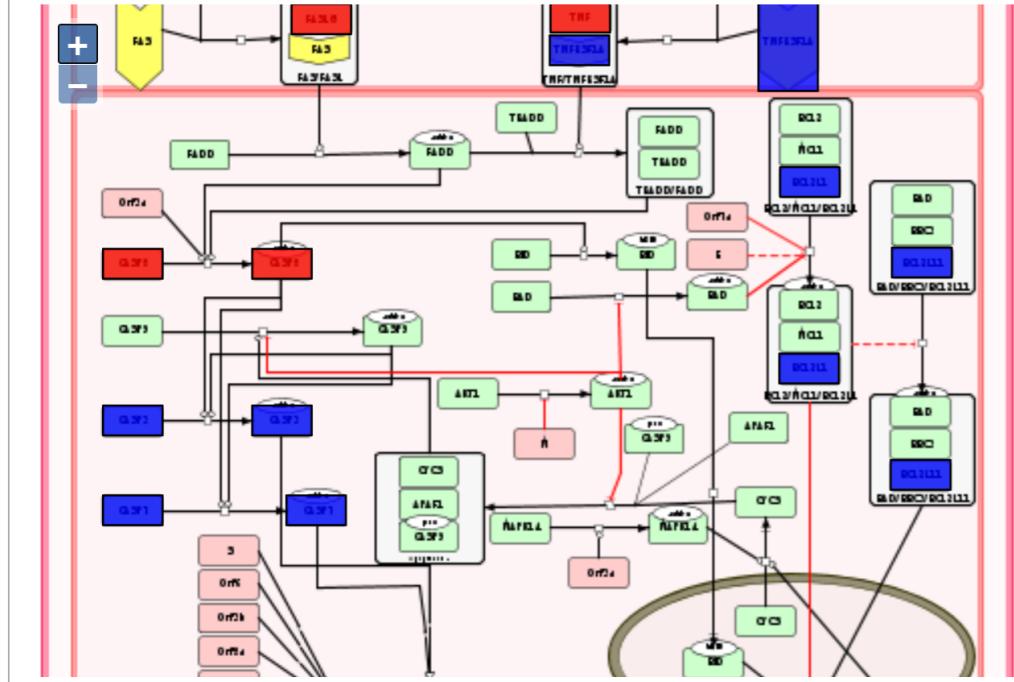
Human host

SARS-CoV-2

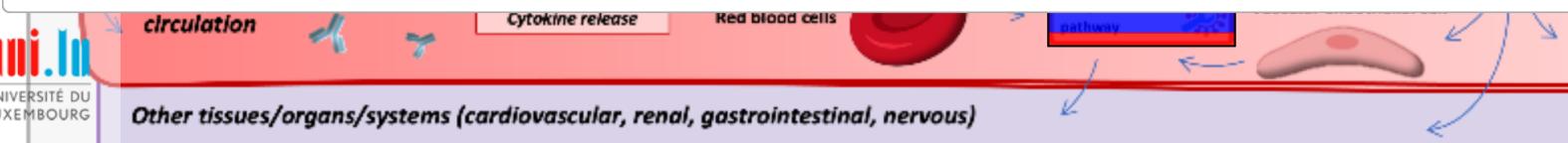
Target cell


COVID-19
Disease Map

APOPTOSIS PATHWAY


UNIVERSITÉ DU
LUXEMBOURG

Other tissues/organs/systems (cardiovascular, renal, gastrointestinal, nervous)


🌐 Powered by MINERVA Platform (v15.1.4)

The COVID-19 Disease Map

<https://covid19map.elixir-luxembourg.org/minerva/>

The content

	Source		
	Individual diagrams	Reactome	WikiPathways
Diagram contents	21 diagrams 1334 interactions 4272 molecular entities 397 publications	2 diagrams 101 interactions 489 molecular entities 227 publications	19 diagrams 401 interactions 738 molecular entities 61 publications
Access	Gitlab git-r3lab.uni.lu/covid/models	SARS-CoV-1 and SARS-CoV-2 infections collection reactome.org/PathwayBrowser/#/R-HSA-9679506	COVID pathways collection covid.wikipathways.org
Exploration	The MINERVA Platform [21] covid19map.elixir-luxembourg.org Guide: covid.pages.uni.lu/minerva-guide	Native web interface Guide: covid.pages.uni.lu/reactome-guide	Native web interface Guide: covid.pages.uni.lu/wikipathways-guide
Biocuration guidelines	Community ⁴	Community ⁵ Platform-specific ⁵	Community ⁶ Platform-specific ⁶
Diagram Editors	CellDesigner ⁷ , Newt ⁸ SBGN-ED [22], yEd+ySBGN ⁹	Reactome pathway editor ⁵	PathVisio [23]
Formats	CellDesigner SBML [24] SBGNML [25,26]	Internal, SBML and SBGNML compliant	GPML [23]

Article | 19 October 2021 | OPEN ACCESS

TRANSPARENT PROCESS

COVID19 Disease Map, a computational knowledge repository of virus-host interaction mechanisms

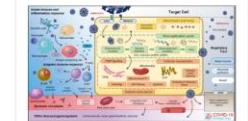
Marek Ostaszewski, Anna Niarakis, Alexander Mazeln, Ima Kuperstein, Robert Phair, Aurelio Orta-Resendiz, Vidisha Singh, Sara Sadat Aghamiri, Marcio Luis Acebedo, Enrico Glaab, Andreas Ruepp, Cisela Fobo, Corinna Montrone, Barbara Brauner, Coar Frishman, Luis Cristóbal Monraz Córmez, Julia Somers, Matti Hoch, Shalendra Kumar Gupta, Julia Scheel, Hanns Börlinghaus, Tobias Czauderna, Falk Schreiber, Arnau Montagud, Miguel Ponce de Leon, Akira Funahashi, Yusuke Hiki, Noriko Hiro, Takahiro Yamada, Andreas Dräger, Alina Renz, Muhammed Naveed, Zsolt Bocksei, Francesco Messina, Daniela Börnigen, Liam Ferguson, Marta Conti, Marius Ramell, Vanesa Nakonecní, Jakob Vanhoefen, Leonard Schmieser, Muying Wang, Emily E Ackerman, Jason E Shoemaker, Jeremy Zucker, Kristie Oxford, Jeremy Teuton, Ebrou Kocakaya, Gökcem Yağmur Summak, Kristina Hanspers, Martina Kutman, Susan Coort, Lars Eijssen, Friederike Ehrhart, Devasahayam Arunka Balaya Rex, Denise Sinter, Marvin Martens, Nhung Pham, Robin Haw, Bijay Jassal, Lisa Mattheus, Marija Orlic-Milacic, Andrea Senff-Ribeiro, Karen Rothfels, Veronica Shamovsky, Ralf Stephan, Cristoffer Sevilla, Thawfeek Varusal, Jean-Marie Ravel, Rupsika Fraser, Vera Ortseifen, Silvia Marchesi, Plotr Gavron, Ewa Smula, Laurent Heirendt, Venkata Satagopam, Guannming Wu, Anders Riutta, Martin Goleblewski, Stuart Owen, Carole Coble, Xiaoming Hu, Rupert W Overall, Dieter Mäler, Angela Bauch, Benjamin M Gyori, John A Bachmann, Carlos Vega, Valentin Gróves, Miguel Vazquez, Pablo Porras, Luana Licata, Marta Iannuccelli, Francesca Sacco, Anastasia Nesterova, Anton Yuryev, Anita de Waard, Denes Turel, Augustin Luna, Ozgun Babur, Sylvain Soliman, Alberto Valdeolivas, Marina Esteban-Medina, María Peña-Chiles, Kinza Rian, Tomás Hellkar, Bhanwar Lal Punya, Desso Modos, Agatha Treveil, Marton Olber, Bertrand De Meulder, Stéphane Balleriu, Aurelien Dugourd, Aurelien Naldi, Vincent Noël, Laurence Calzone, Chris Sander, Emre Demir, Tamás Korcsmaros, Tom C Freeman, Franck Augé, Jacques S Beckmann, Jan Hasenauer, Olaf Wolkenhauer, Egon L Willighagen, Alexander R Pico, Chris T Evelo, Marc E Gillespie, Lincoln D Stein, Henning Hermjakob, Peter D'Eustachio, Julio Saez-Rodríguez, Joaquín Dopazo, Alfonso Valencia, Hiroaki Kitano, Emmanuel Barillot, Charles Auffray, Rudi Balling, Reinhard Schneider, the COVID-19 Disease Map Community

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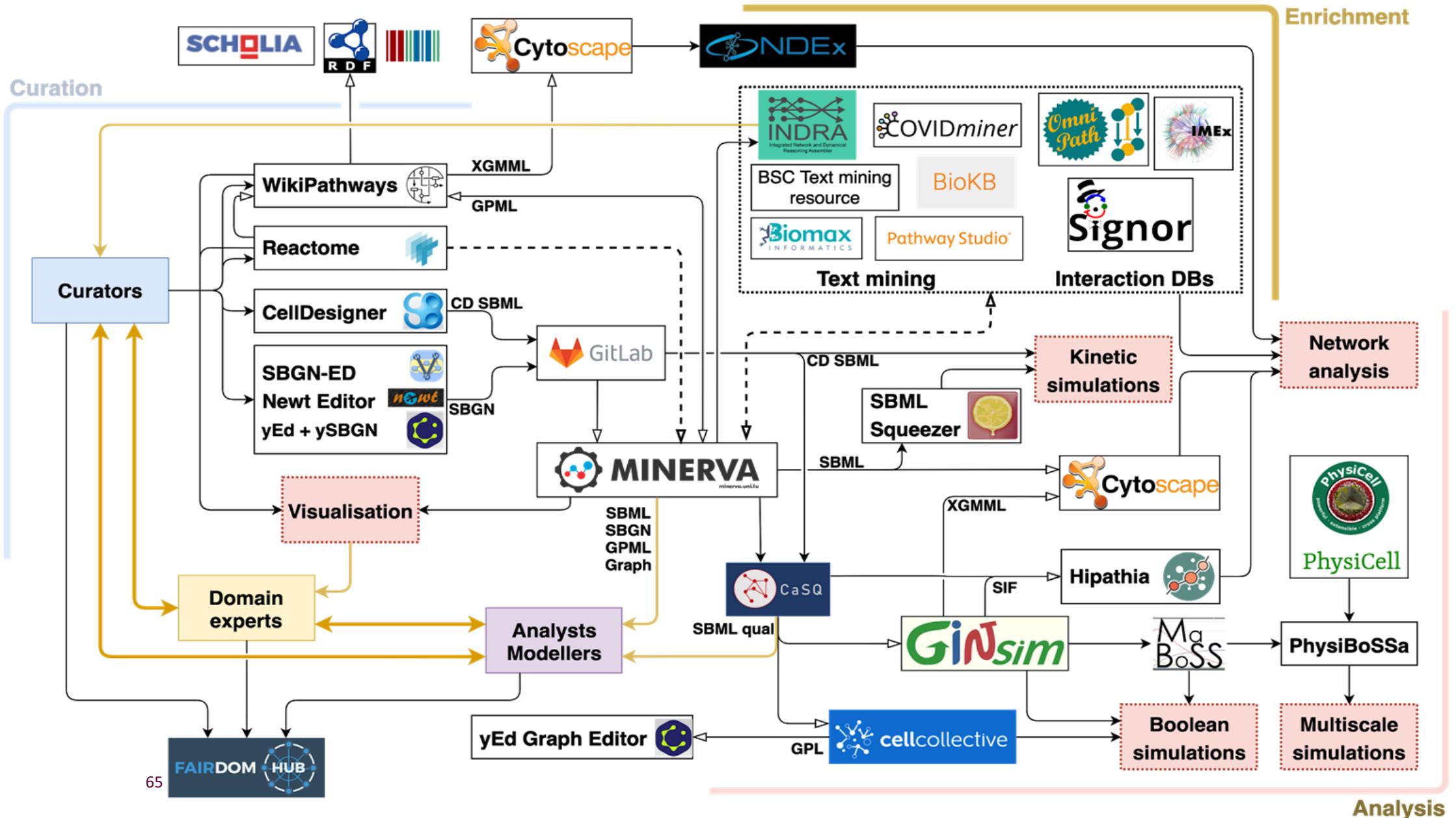


Figure 2.
The structure and content of the COVID-19 Disease Map



An overview of the areas of focus of the C19DMap biocuration. Go to

The COVID19 Disease Map ecosystem



Multiscale & multicellular models

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ORIGINAL RESEARCH article

Front. Immunol., 13 February 2024
Sec. Systems Immunology
Volume 14 - 2023 | <https://doi.org/10.3389/fimmu.2023.1282859>

Drug-target identification in COVID-19 disease mechanisms using computational systems biology approaches

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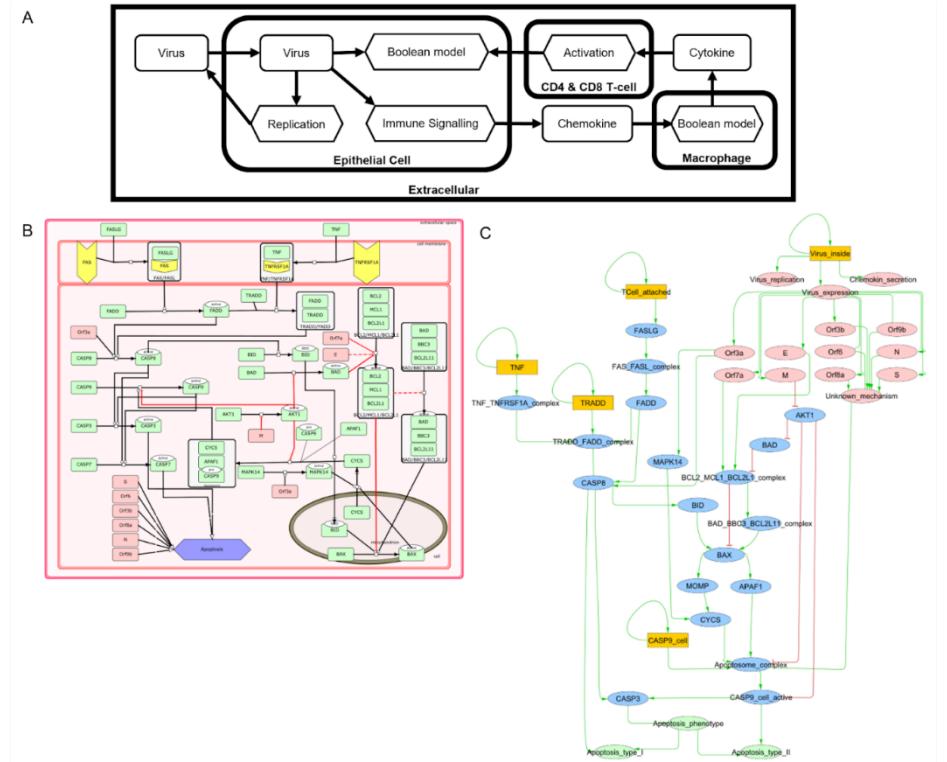
Data availability statement

Ethics statement

Author contributions

Funding

Acknowledgments



An example of simulations

Simulation of wild type and mutants using PhysiBoSS. Our framework can simulate wild-type epithelial cells state (A)

and wild-type immune cells recruitment (B)

and study the effect of knockouts such as FADD's in the epithelial cells' apoptosis (C)

or such as p38's in the immune cells recruitment (D).

