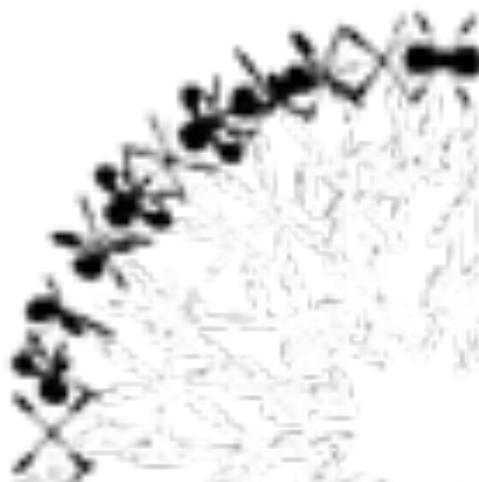


From multi-level data to mechanistic details and predictive
model building for what-if experiments in-silico

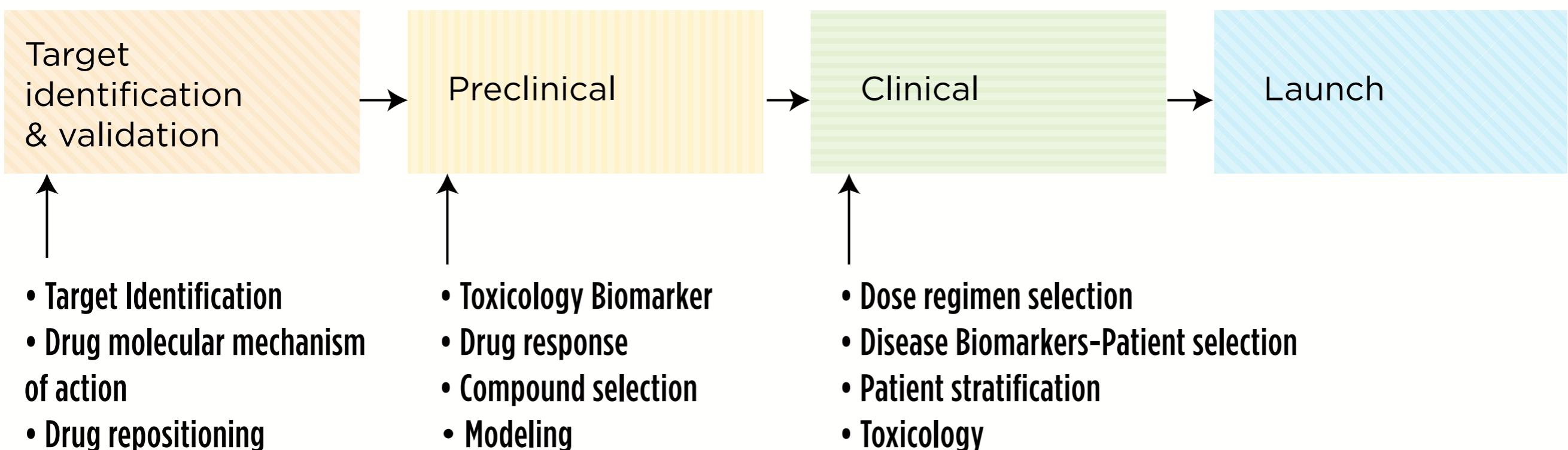
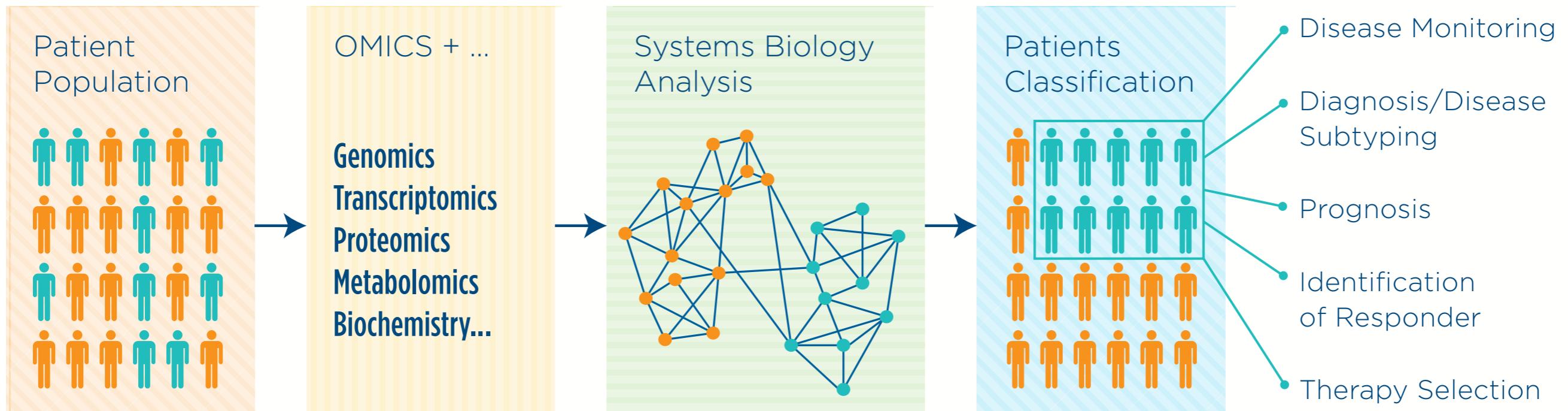


COSBI is

a bioinformatic company
founded in 2005

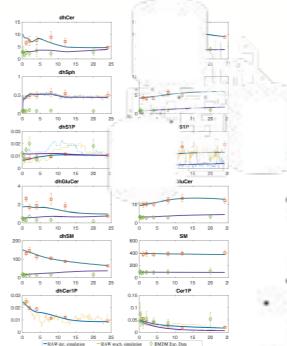
50% Microsoft Research
50% University of Trento

COSBI applications in drug discovery

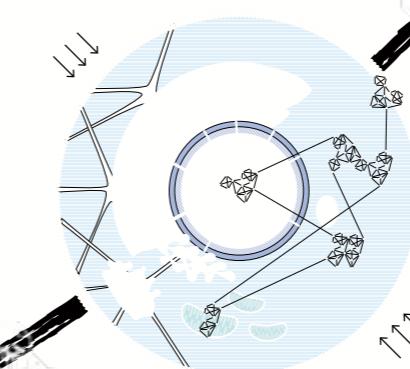


COSBI unique technologies

L	SCUDO SCUDO is a tool for clustering gene expression profiles for discovering clusters of genes with a new type of scale-based signatures	BioNetMotion BioNetMotion provides dynamic and network-based simulation of time course gene data
RSSA Reactive-Based Stochastic Simulation Algorithm	SICOMPRESS Simulation-based qualitative and quantitative prediction of protein complexes	GENER GENER is a tool for performing reduction of ODEs directly based on a strand-displacement
BETAWB Black-box tools to represent and simulate biological entities and their interactions	GRAPH Graph constructs, visualizes, and modifies graphs as well as calculates measures and layouts	KINFER Estimates both structural and rate parameters from time-series data of reaction rates
LIME Language interface for individual-based modeling of molecular dynamics	REDI Redi simulates biochemical systems at the microscopic scale of molecules	WALDO Waldo is a reaction-based tool for easily modeling and simulating biological systems



modeling & simulation



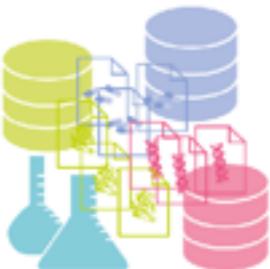
pathway analysis

biomarker identification

knowledge extraction

data integration





Precision literature mining

scientific literature

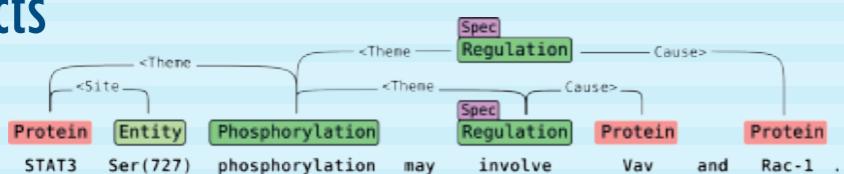


information retrieval

unstructured text

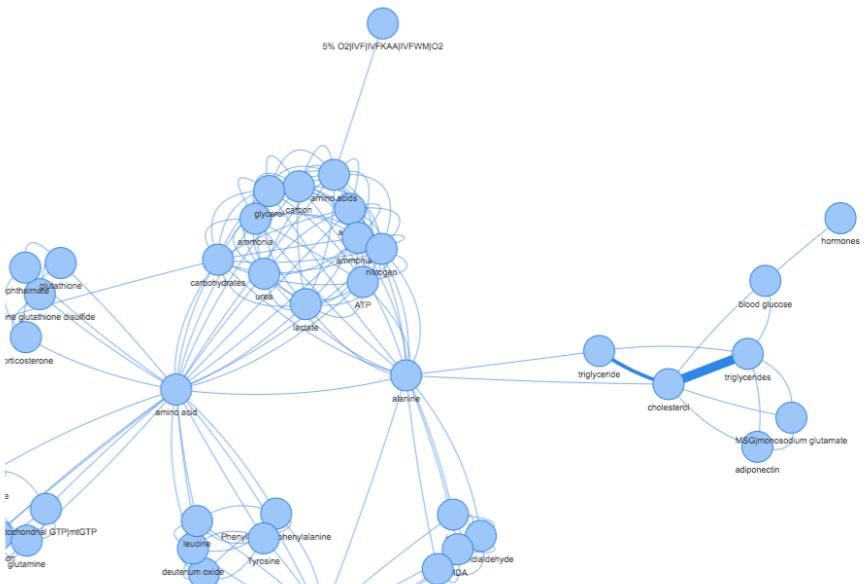
In the present study, signal transducer and activator of transcription 3 (STAT3) Ser(727) phosphorylation and transactivation was investigated in relation to activation of mitogen-activated protein (MAP) kinase family members including extracellular-signal-regulated protein kinase (ERK)-1, c-Jun N-terminal kinase (JNK)-1 and p38 (reactivating kinase) in response to Interleukin (IL)-6 stimulation. Although IL-6 can activate ERK-1 in HepG2 cells, STAT3 transactivation and Ser(727) phosphorylation were not reduced by using the MAP kinase/ERK kinase (MEK) inhibitor PD98059 or by overexpression of dominant-negative Raf. IL-6 did not activate JNK-1 in HepG2 cells and STAT3 was a poor substrate for JNK-1 activated by enzymoin, excluding a role for JNK-1 in IL-6-induced STAT3 activation. However, BEK-1/MKK-4 (where BEK-1 stands for stress activated protein kinase (SAPK)/ERK kinase 1, and MKK-4 stands for MAP kinase kinase 4) was activated in response to IL-6 and overexpression of dominant-negative BEK-1/MKK-4(A-L) reduced both IL-6-induced STAT3 Ser(727) phosphorylation as well as STAT3 transactivation. Subsequently, the BEK-1/MKK-4 upstream components Vav, Rac-1 and MEKK were identified as components of a signal transduction cascade that leads to STAT3 transactivation in response to IL-6 stimulation. Furthermore, inhibition of p38 kinase activity with the inhibitor SB203580 did not block STAT3 Ser(727) phosphorylation but rather increased both basal as well as IL-6-induced STAT3 transactivation, indicating that p38 may act as a negative regulator of IL-6-induced STAT3 transactivation through a presently unknown mechanism. In conclusion, these data indicate that IL-6-induced STAT3 transactivation and Ser(727) phosphorylation is independent of ERK-1 or JNK-1 activity, but involves a gp130 receptor-signalling cascade that includes Vav, Rac-1, MEKK and BEK-1/MKK-4 as signal transduction components.

information extraction [NLP methods]

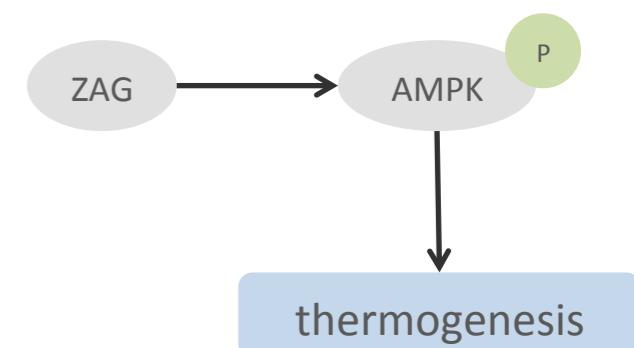


structured facts

knowledge bases,
models, etc.



15	energy metabolism	AZGP1 \\ Zinc-alpha2-glycoprotein \\ ZAG \\ zinc-alpha2-glycoprotein	21457004	OBJECTIVE: Our study aimed to investigate whether ZAG activates AMPKa, an important regulator of energy metabolism, in human skeletal muscle cells (SkMc) \\ DISCUSSION AND CONCLUSION: These results show that ZAG leads to phosphorylation of AMPKa and ACC, thereby activating a pathway central to the regulation of energy metabolism
16	brown fat	AZGP1 \\ Zinc-alpha2-glycoprotein \\ ZAG	14983038	ZAG mRNA was detected by RT-PCR in the mouse WAT depots examined (epididymal, perirenal, s.c., and mammary gland) and in interscapular brown fat \\ Mice bearing the MAC16-tumor displayed substantial losses of body weight and fat mass, which was accompanied by major increases in ZAG mRNA and protein levels in WAT and brown fat
17	fat mass	AZGP1 \\ Zinc-alpha2-glycoprotein \\ ZAG	14983038	Mice bearing the MAC16-tumor displayed substantial losses of body weight and fat mass, which was accompanied by major increases in ZAG mRNA and protein levels in WAT and brown fat
18	fat mass	AZGP1 \\ Zinc-alpha2-glycoprotein \\ ZAG \\ zinc-alpha2-glycoprotein	19549246	The adipokine zinc-alpha2-glycoprotein (ZAG) is downregulated with fat mass expansion in obesity \\ RESULTS: In human subjects, ZAG mRNA level was negatively correlated with BMI ($r = -0.61$, $P < 0.001$, $n = 23$, visceral; $r = -0.6$, $P < 0.05$, $n = 14$, subcutaneous) and fat mass ($r = -0.62$, $P < 0.01$, visceral; $r = -0.6$, $P < 0.05$, subcutaneous)
19	weight loss	AZGP1 \\ Zinc-alpha2-glycoprotein \\ ZAG	20070991	Serum levels of ZAG correlated with serum levels of cholesterol ($P = .00088$) in healthy subjects and during weight loss ($P = .059$)



Precision literature mining

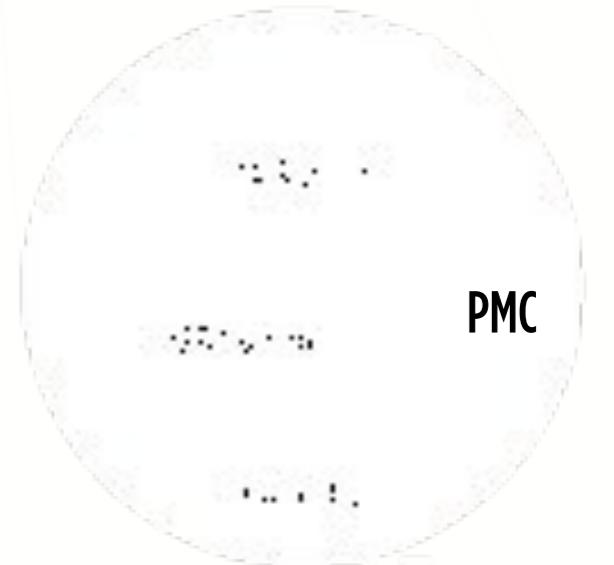
Selected literature sources

- US NLM bibliographic databases
 - PubMed
 - MEDLINE
 - OA Comm, PubMed Central (PMC)
 - Author Manuscript Collection (PMC)
- US Patents > 2002 (~3.7M)
- EU Patents (in progress)
- Clinical Trials (~250K)
- Human-curated MeSH headings



Selected knowledge base sources

- Genes, for ~1K Mammalians - NCBI (~11.1M)
- Proteins - UniProt (~310K)
- Chemicals - PubChem (~320M in progress)
- MeSH Terms - NLM (~270K)
- Diseases - OMIM+CTD (~90K)
- Symptoms - Ontology (~1K)
- Microorganisms taxa (~1.6M)



strengths

personalised query language

statistical
overrepresentation

annotated txt generation

extended search base

COSBI unique technologies



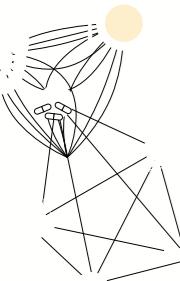
modeling & simulation

pathway analysis

biomarker identification

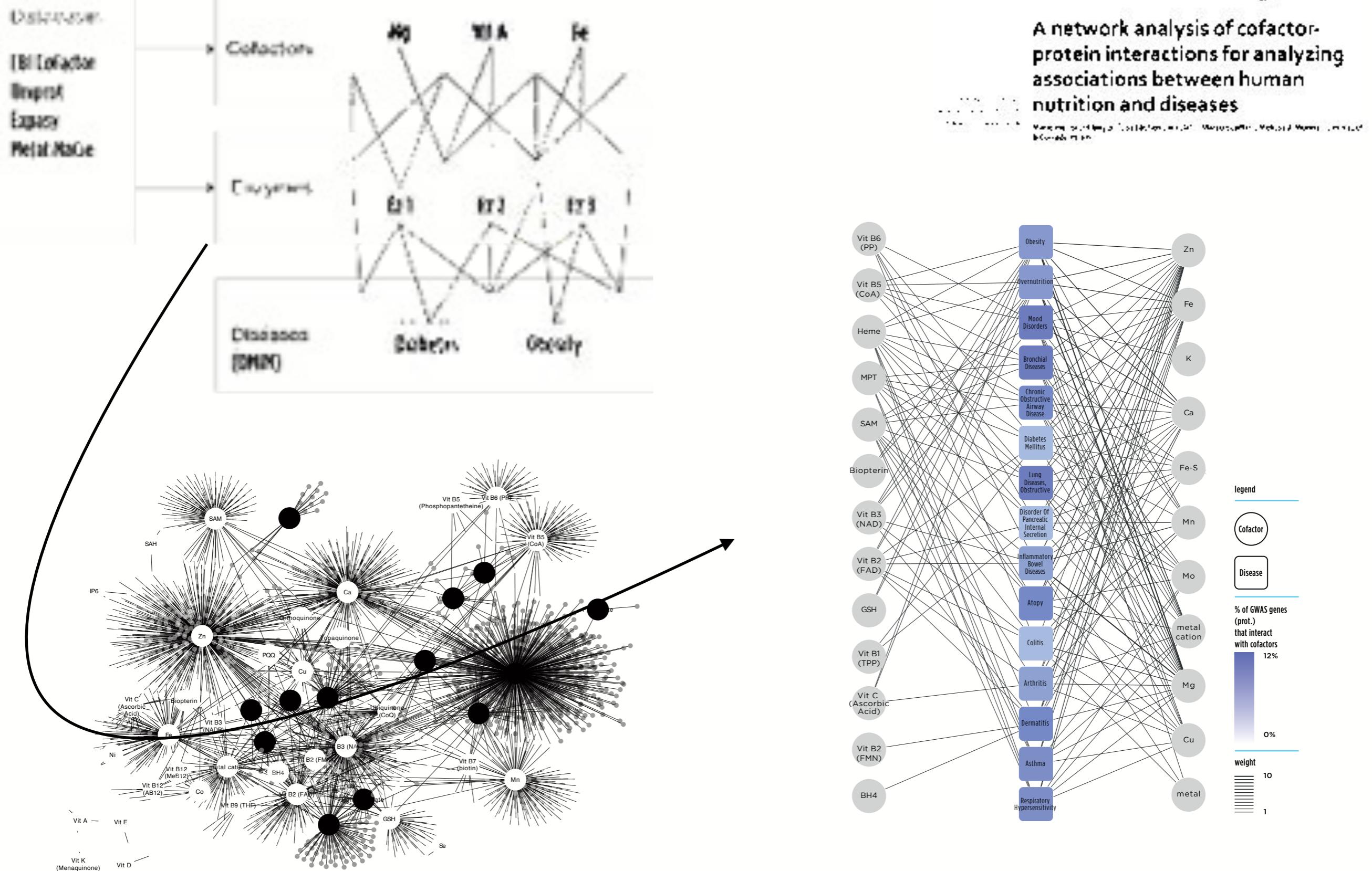
data integration

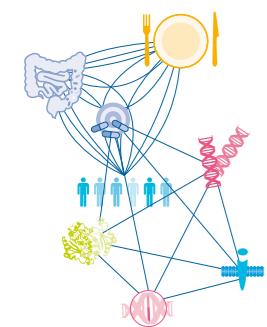
knowledge extraction



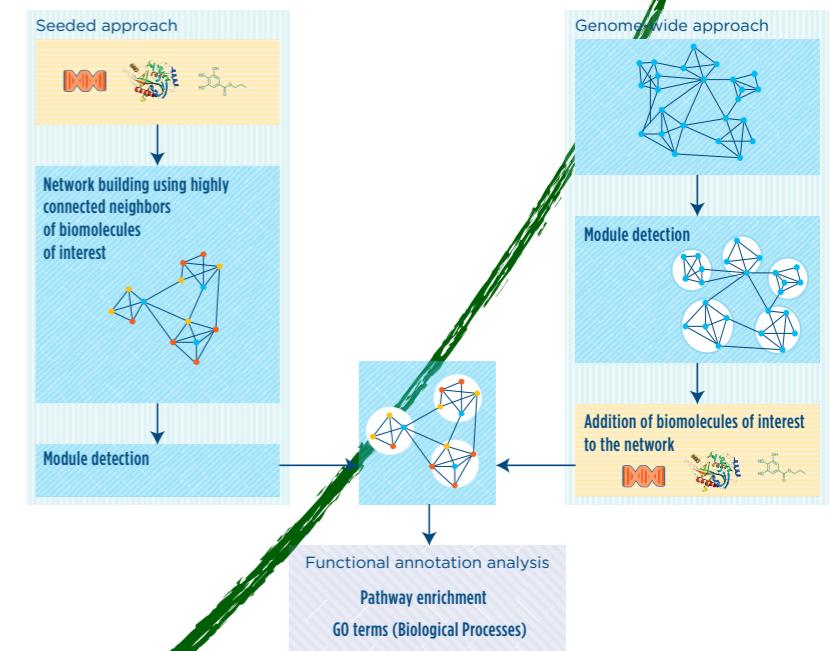
Cofactor - disease interaction

SCIENTIFIC REPORTS

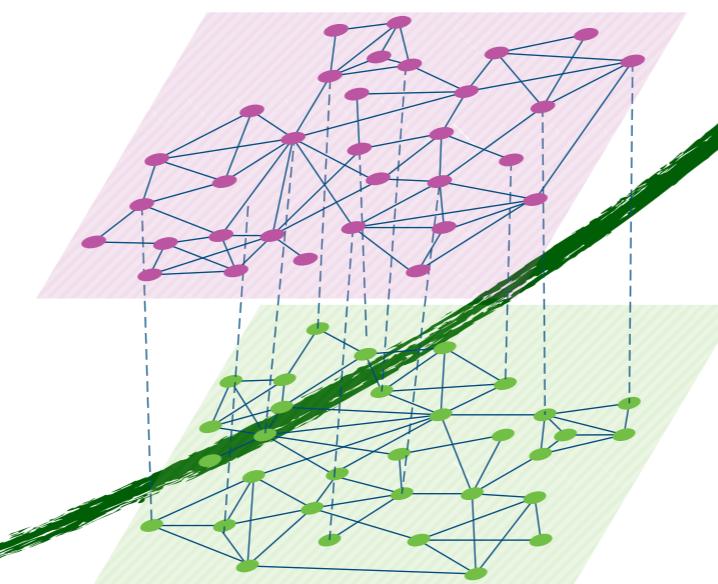




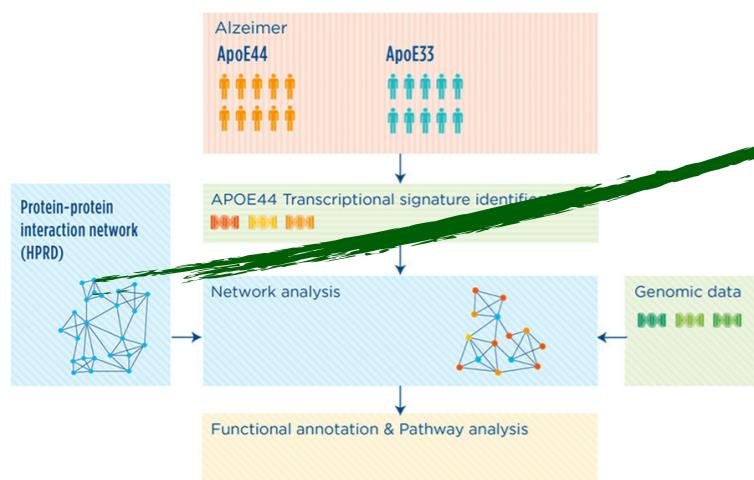
strengths



flexibility



multilayered network

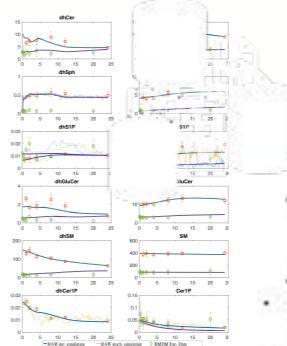


customized pipelines



COSBI unique technologies

L	SCUDO SCUDO is a tool for clustering gene expression profiles for differentially expressed genes and a new type of scale-based signatures	BioNetMotion BioNetMotion provides dynamic and network-based simulation of time course gene data
RSSA Reaction-Based Stochastic Simulation Algorithm	SICOMPRESS Simulation-based, qualitative and quantitative prediction of protein complexes	GENER Gener is a tool for performing reduction on DNA circuits based on a strand-displacement
BETAWB Black-box tools to represent and simulate biological entities and their interactions	GRAPH Graph constructs, visualizes, and modifies graphs as well as calculates measures and layouts	KINFER Estimates both structural and intrinsic model parameters from time-series data of magnetic resonance
LIME Language interface for individual-based modeling of ecosystem dynamics	REDI Redi simulates biochemical systems at the microscopic scale of molecules	WALDO Waldo is a reaction-based tool for easily modeling and visualizing biological systems



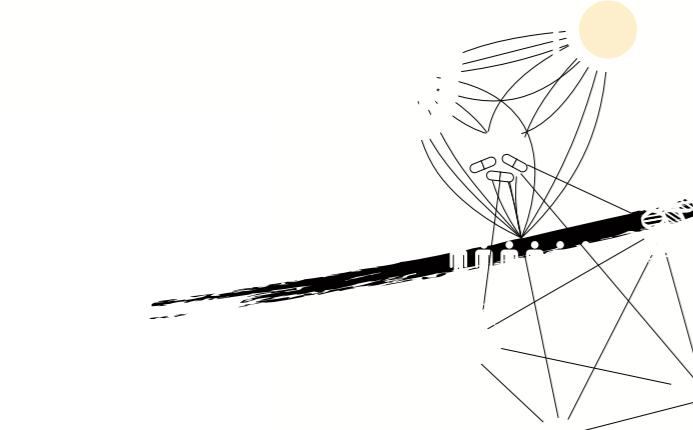
modeling & simulation

pathway analysis

biomarker identification

knowledge extraction

data integration



solution



2012

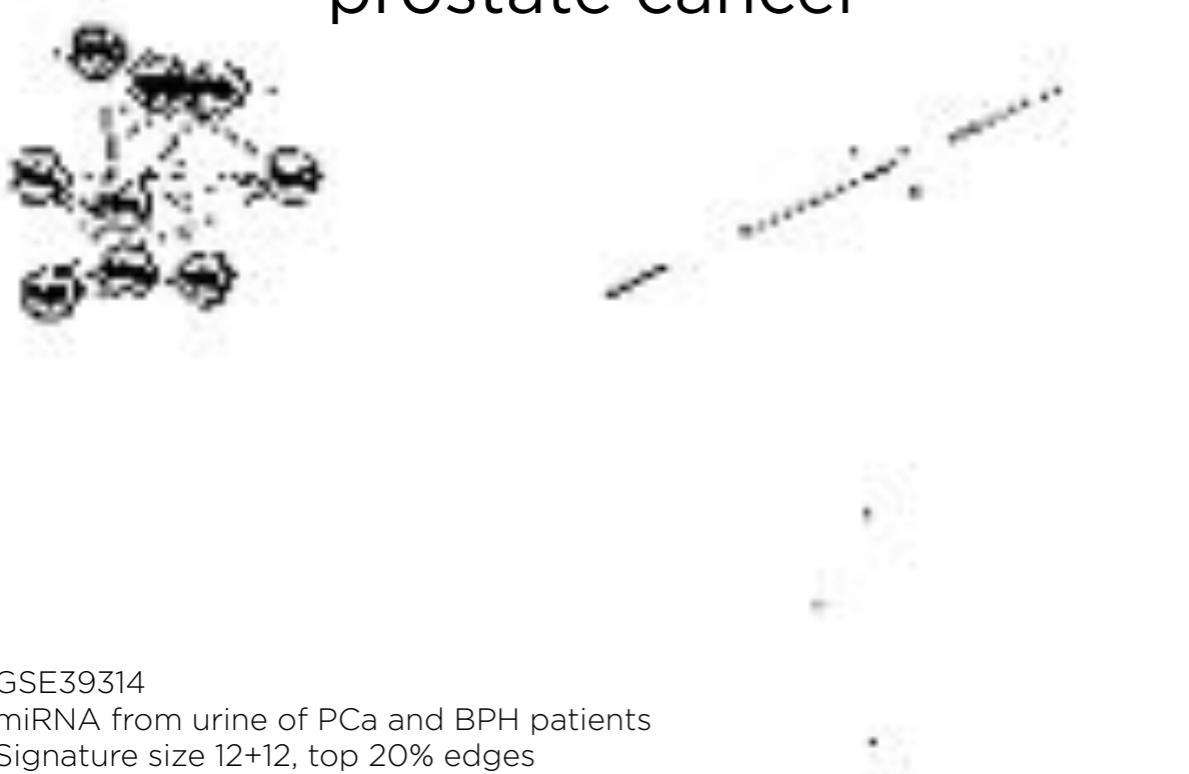


COSBI overall 2nd out of 52 groups, 1st in EU

COSBI 1st out of 52 on the sub-challenge MSD

other examples

prostate cancer

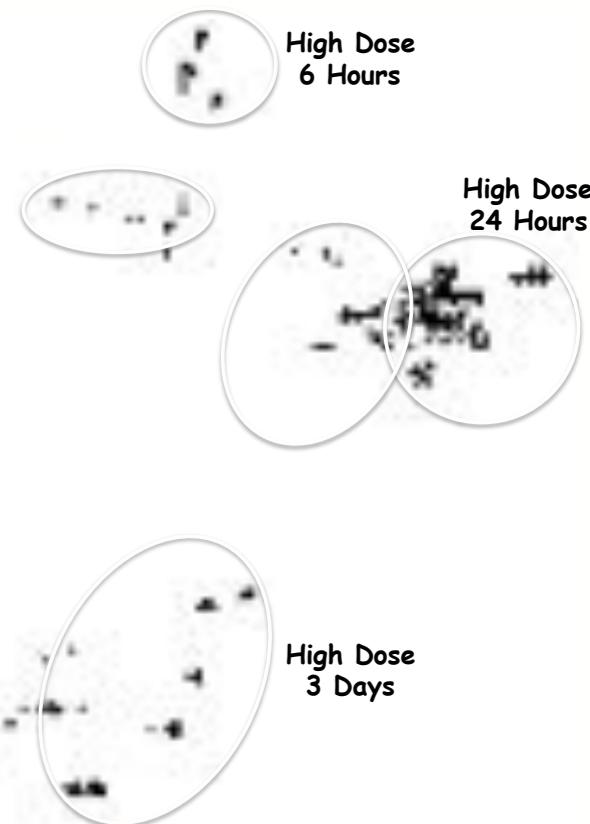


GSE39314
miRNA from urine of PCa and BPH patients
Signature size 12+12, top 20% edges

GSE32891 (FDA, Jefferson, AR)
mRNA from L
signature size: 50+50, top 20% edges

● CONTROL
● ACETAMINOPHEN (100mg/Kg)
● ACETAMINOPHEN (1250mg/Kg)

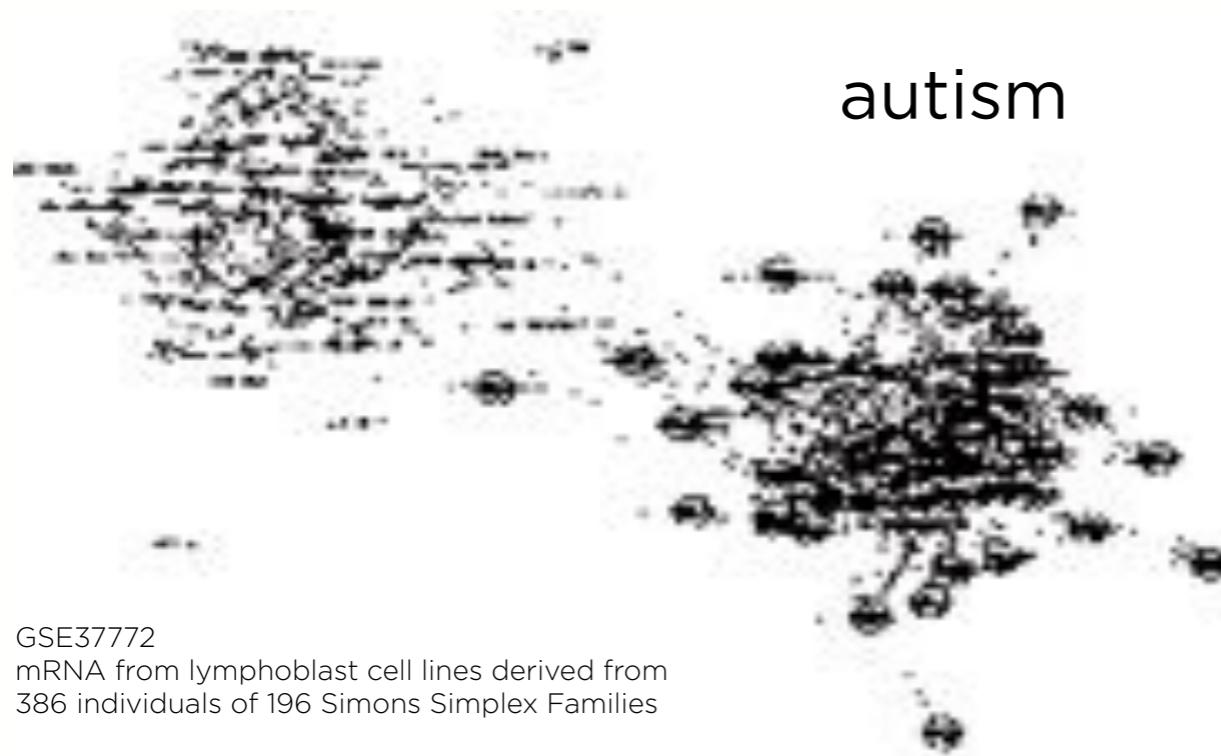
6h
24h
3d
7d



toxicology

mRNA from liver in rats

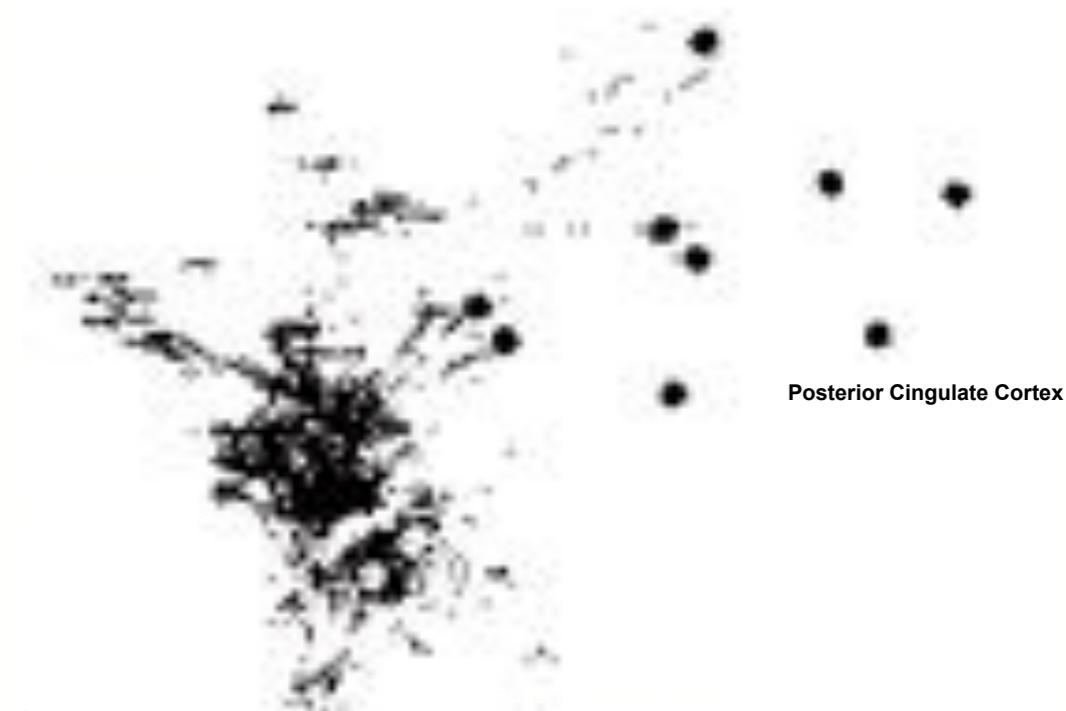
autism



GSE37772
mRNA from lymphoblast cell lines derived from
386 individuals of 196 Simons Simplex Families

Signature size: 25+25, top 20% edges

Microarrays from laser
microdissected neurons



Posterior Cingulate Cortex

AD different brain regions

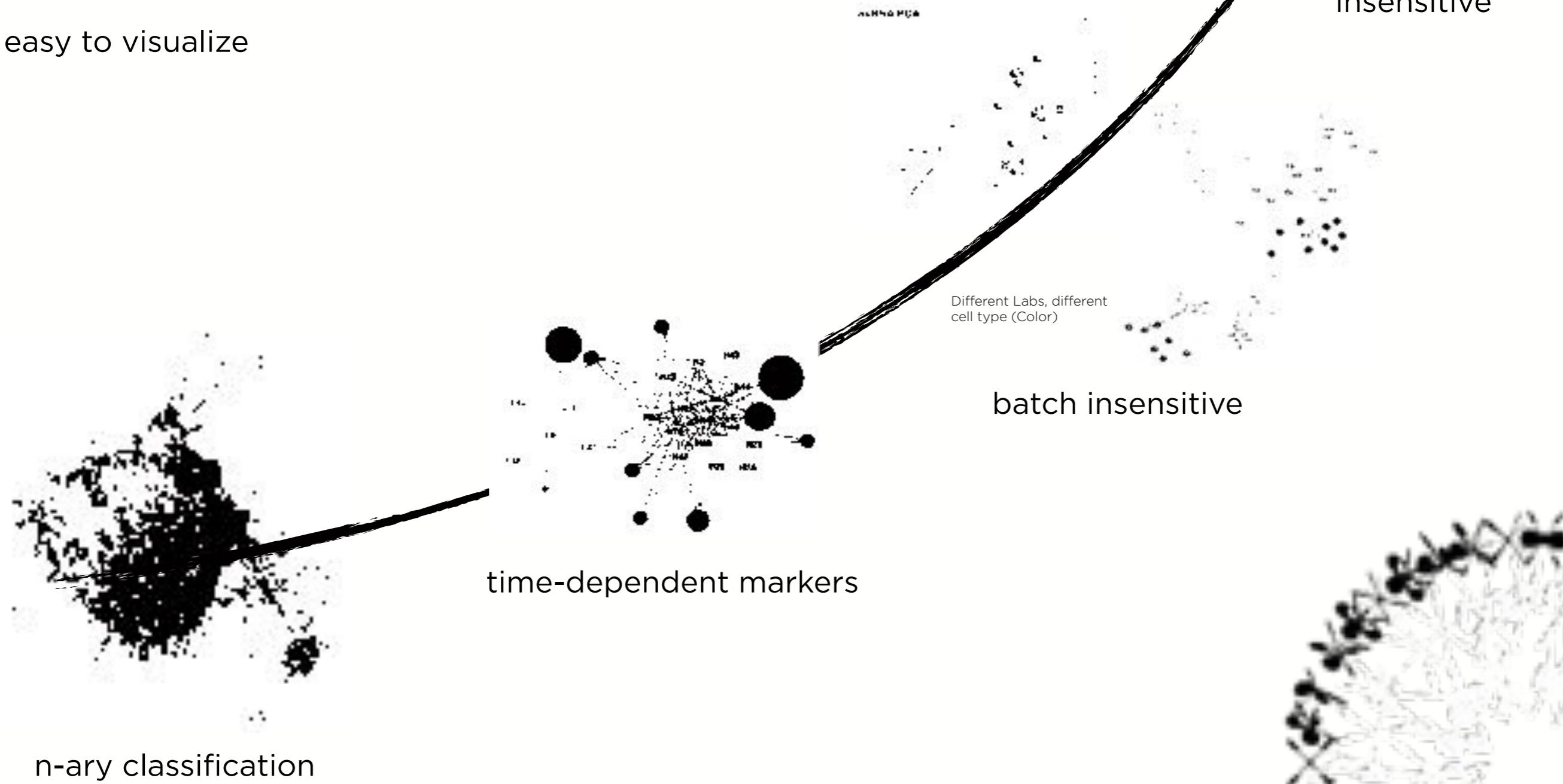
strengths

GSE 32041 cytokines in Parkinsonian syndromes

no need of a priori hypotheses

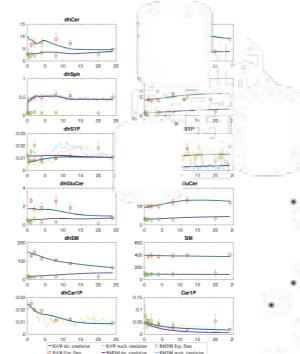
process-based classification – no need to limit the length

easy to visualize

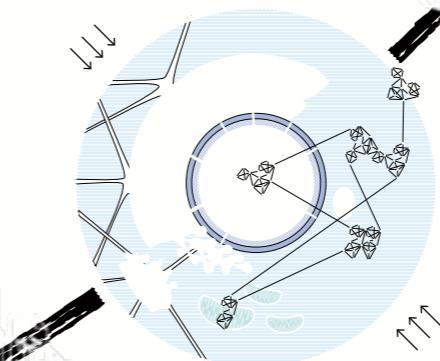


COSBI unique technologies

L	SCUDO SCUDO is a tool for clustering gene expression profiles for different cell types and a new type of scale-based signatures	BioNetMotion BioNetMotion provides dynamic and network-based simulation of time course gene data
RSSA Report-based Stochastic Simulation Algorithm	SICOMPRESS Simulation-based qualitative and quantitative prediction of protein complexes	GENER GENER is a tool for performing reduction on DNA circuits based on a strand-displacement
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LIME Language interface for individual-based modeling of molecular dynamics	REDI Redi simulates biochemical systems at the microscopic scale of molecules	WALDO Waldo is a reaction-based tool for easily modeling and simulating biological systems



modeling & simulation



pathway analysis



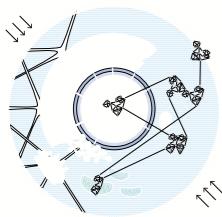
biomarker identification



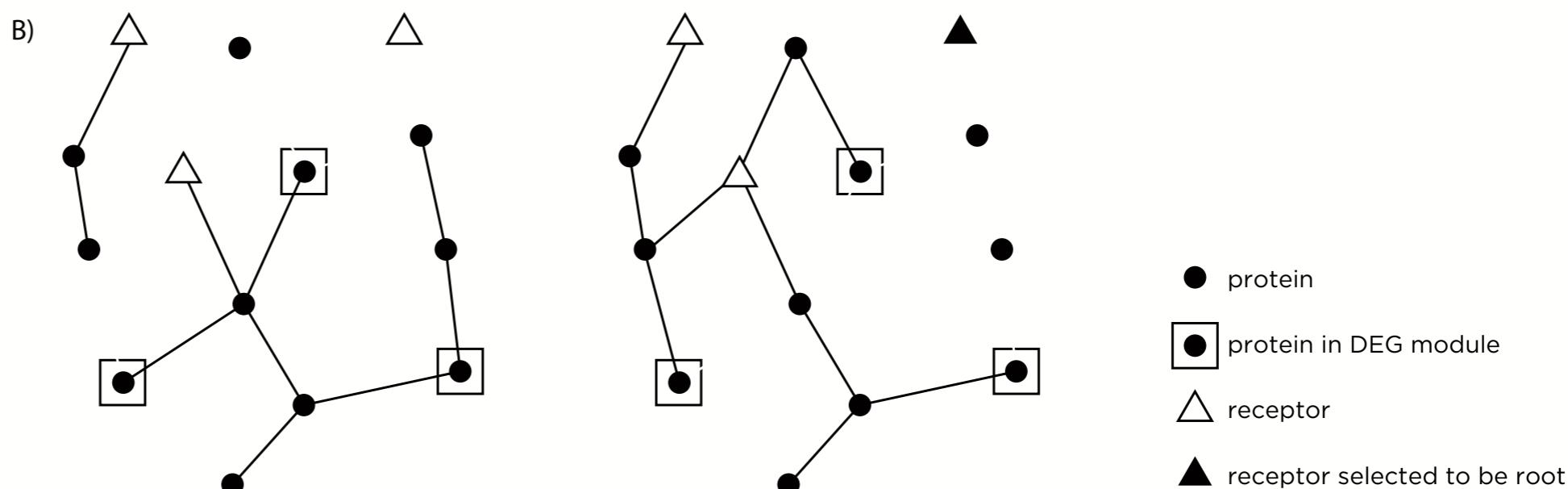
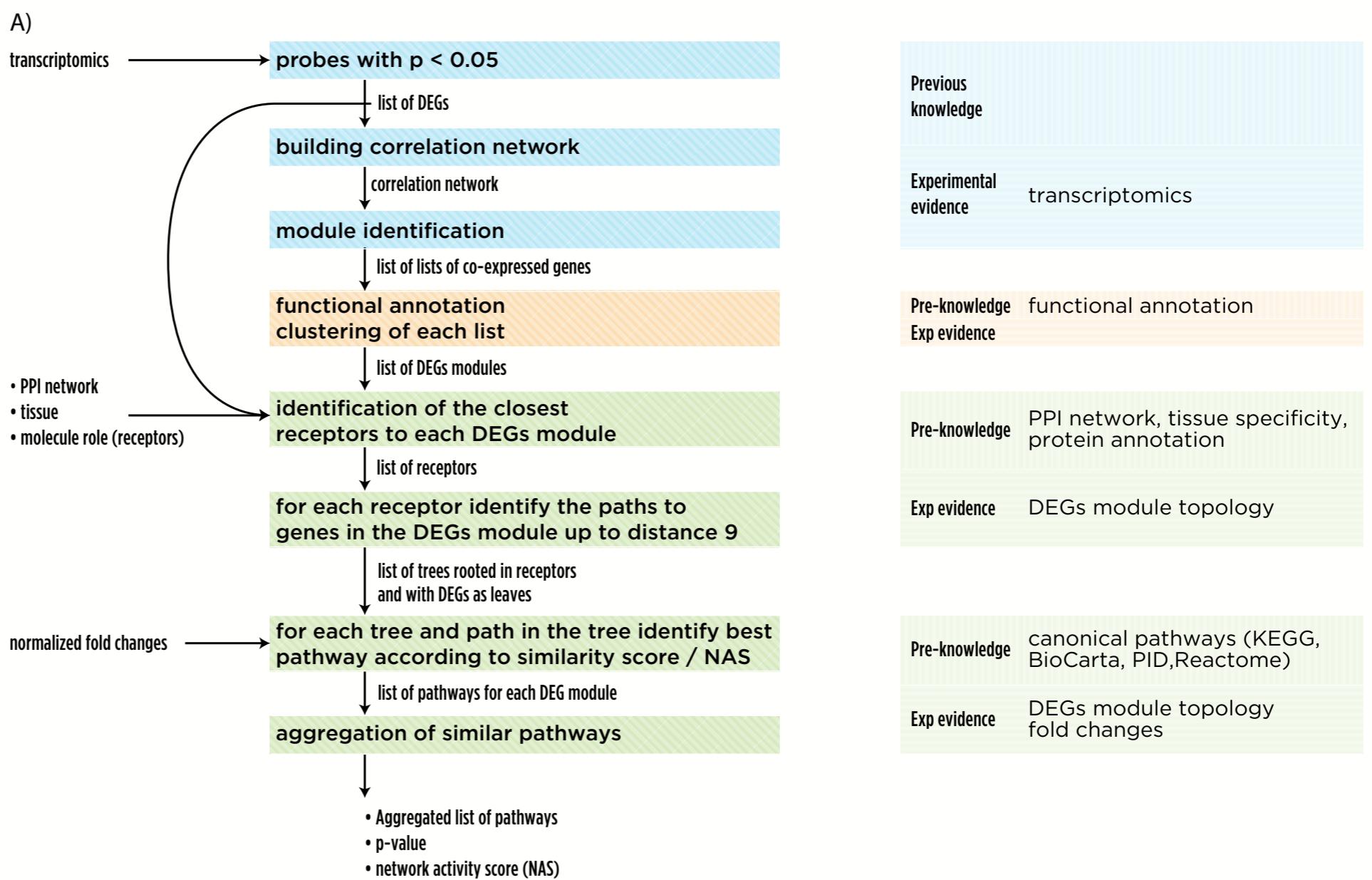
knowledge extraction

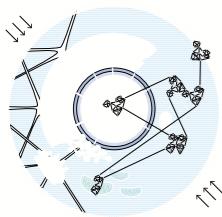
data integration





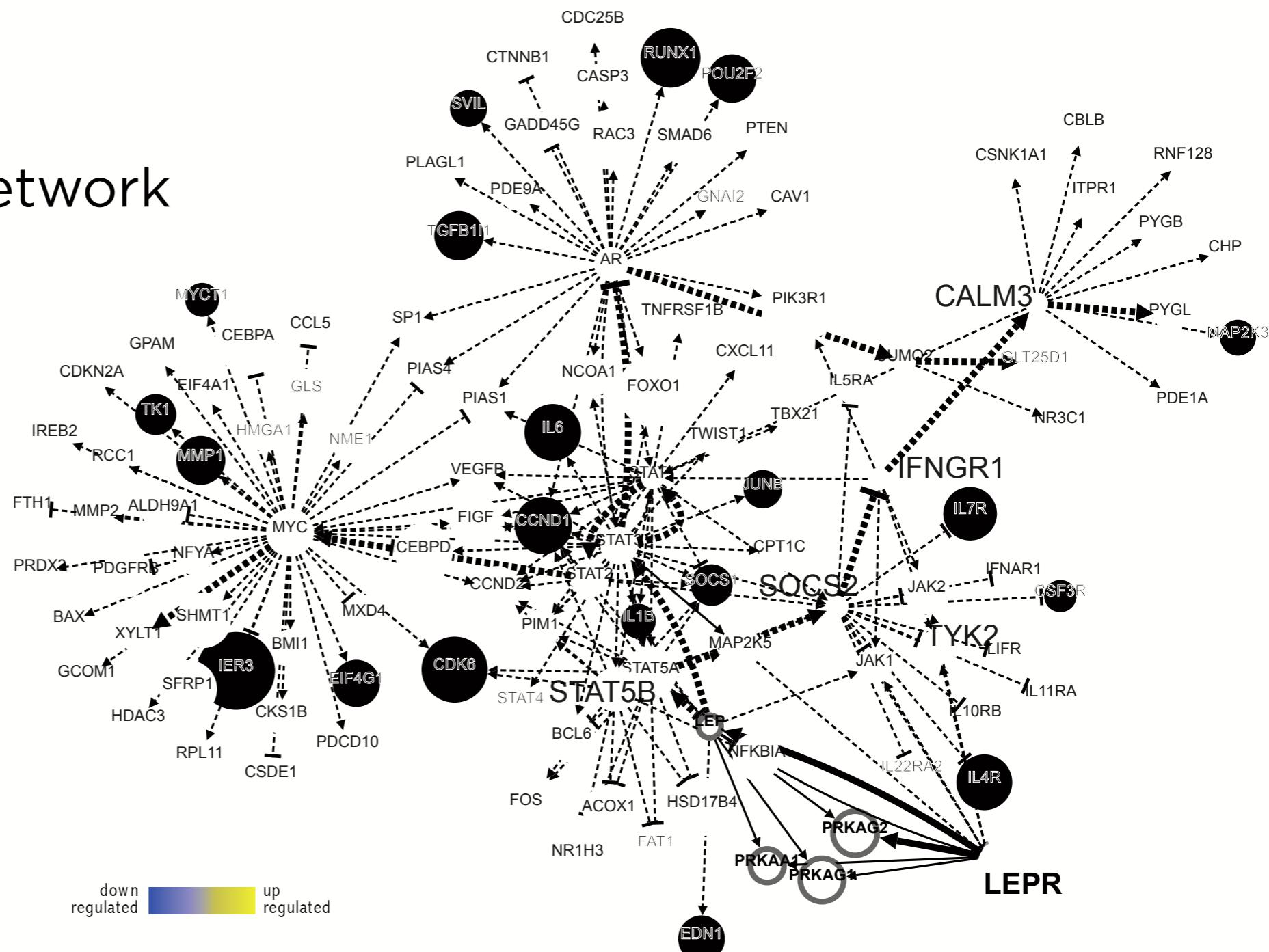
algorithm





visualization

active network



○ Molecules belonging to the canonical pathway.

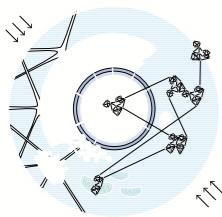
Receptor.

● Molecules - color codes for up- and down-regulation; size increases logarithmically with the inverse of significance p-value.

— Solid lines connect nodes belonging to the canonical pathway.

— Thick lines denote the active network determined by NASFinder.

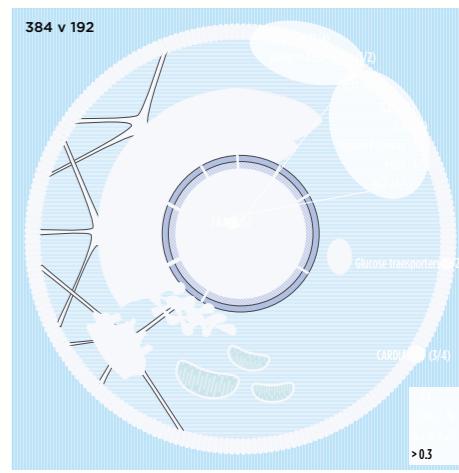
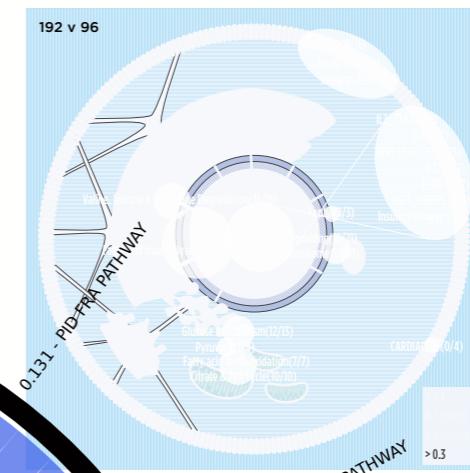
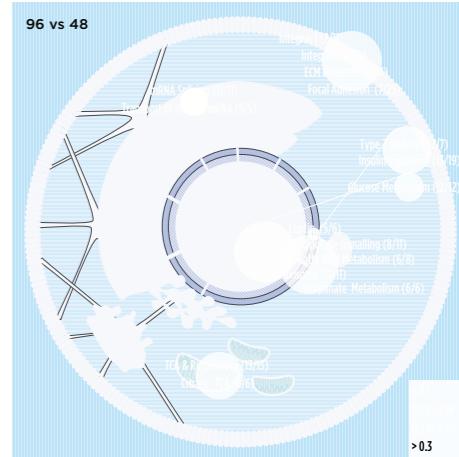
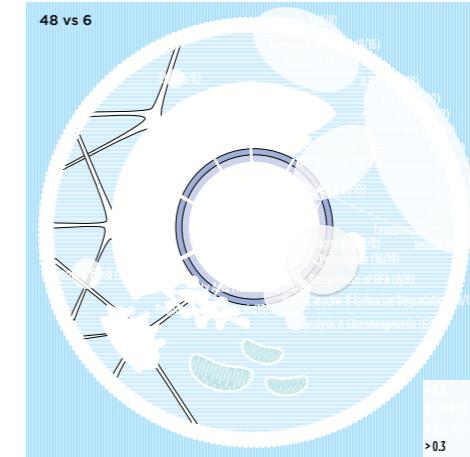
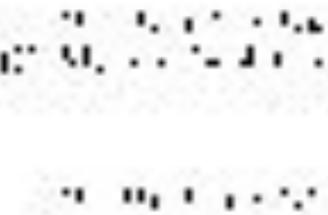
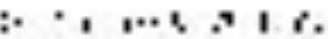
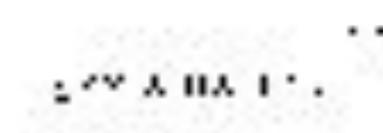
- - Dashed lines denote interactions outside the canonical pathway determined by building the 1-neighbor network from the active network identified by NASFinder.



visualization

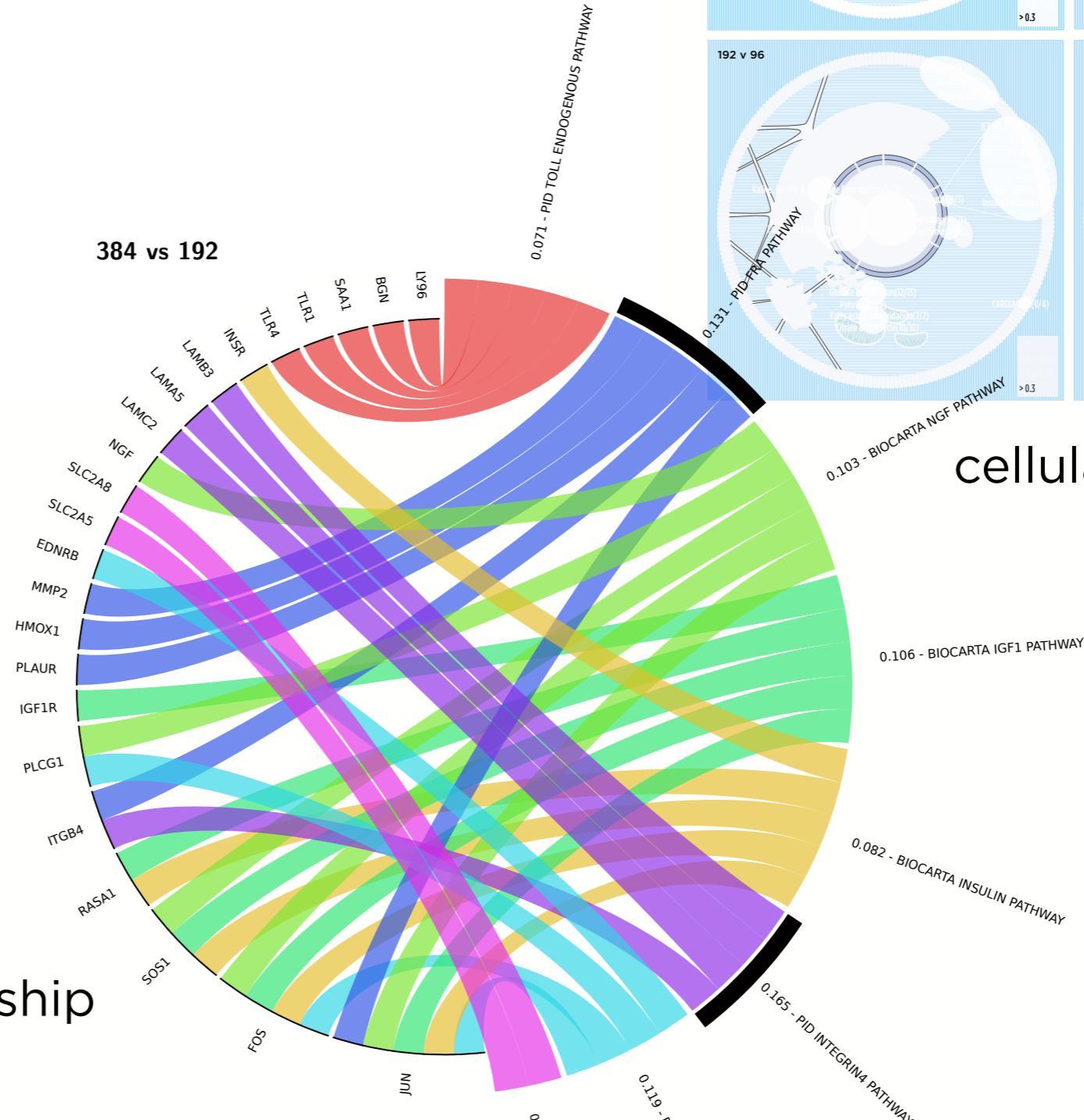
cond 11384 11192 11196 11148

NAS



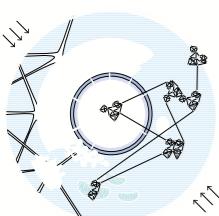
pathway activity level

384 vs 192

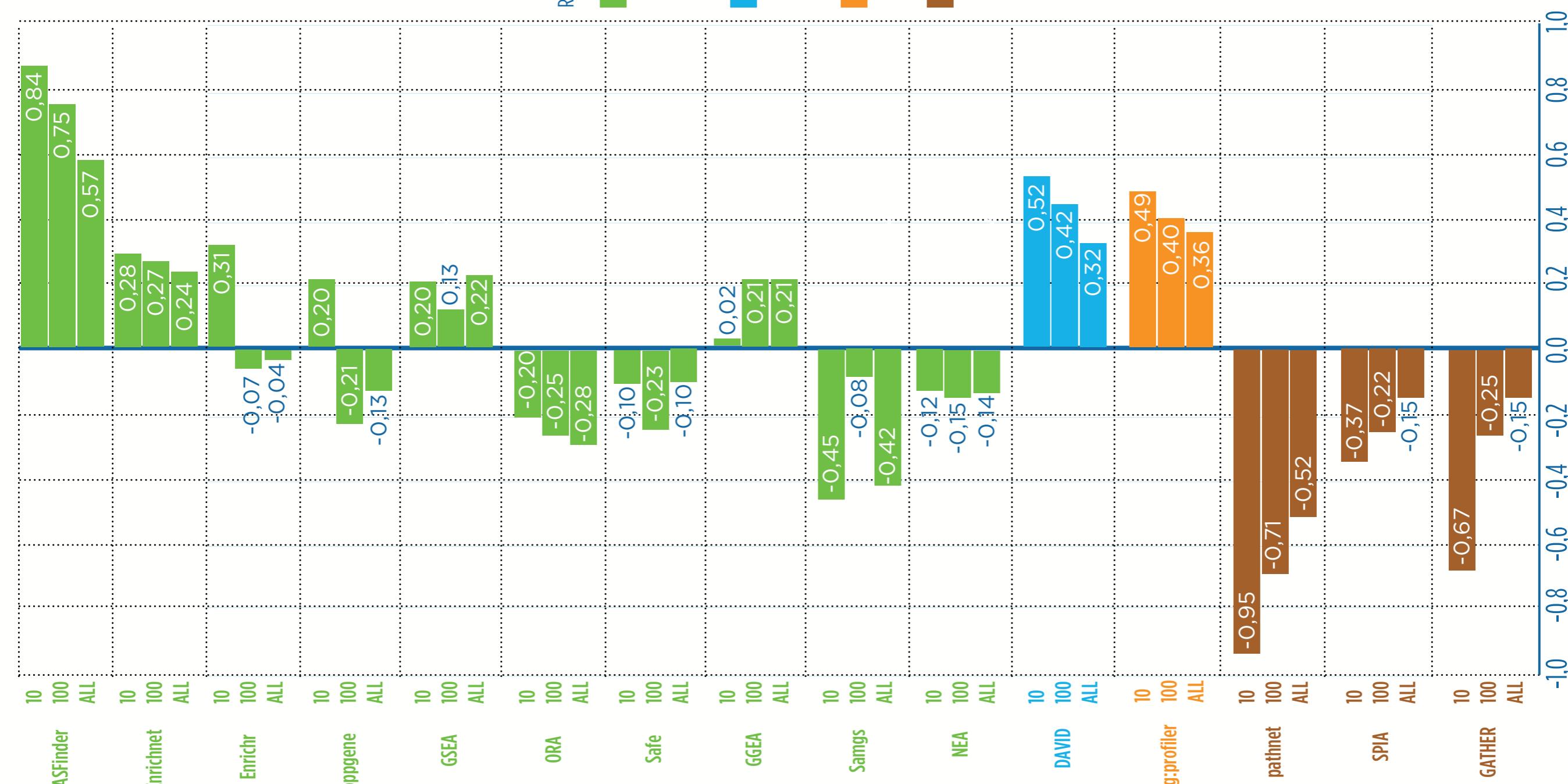


cellular localization

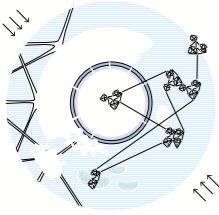
gene-pathway relationship



cumulative performance



avg Z-score on precision, sensitivity, specificity, accuracy

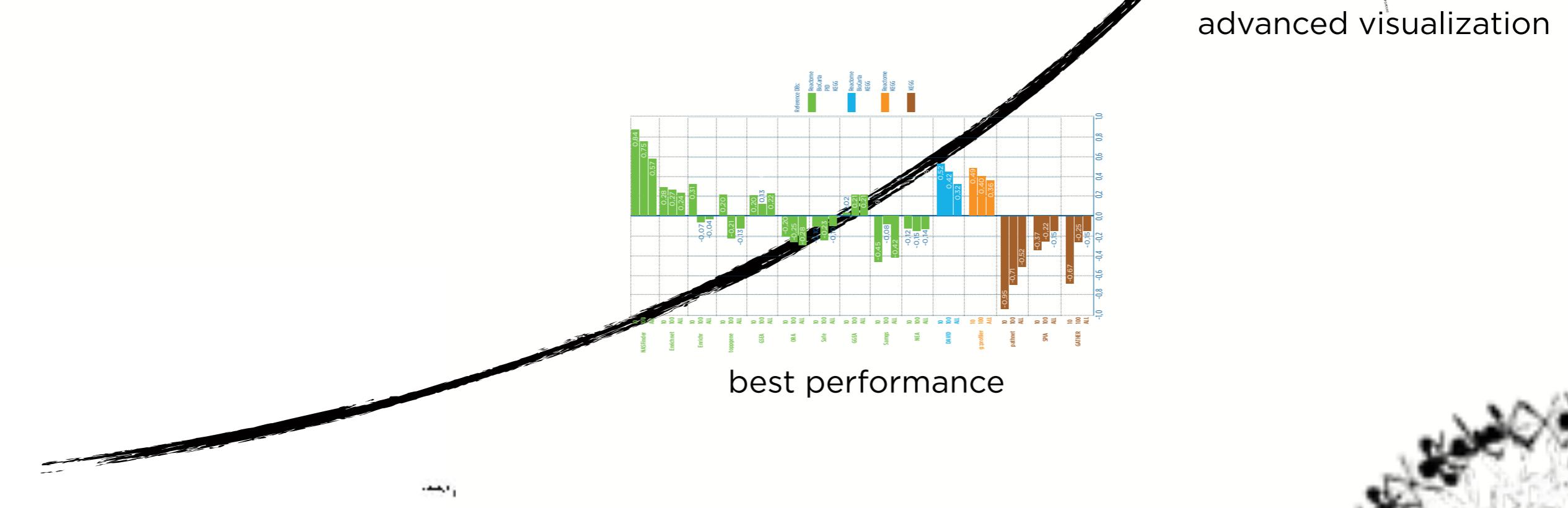


strengths

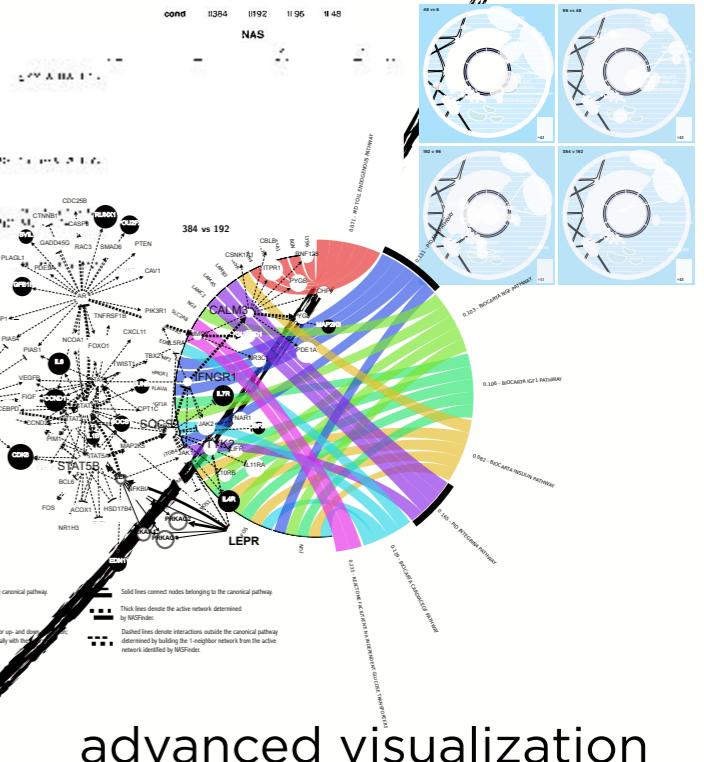
prioritize pathways

bridge biomarkers with modeling and simulation

multiple data-types



flexible / customizable



advanced visualization

COSBI unique technologies

L	SCUDO An imperative, domain specific language to stochastically simulate biological algorithms.	BioNetMotion BioNetMotion provides dynamic and network-based simulation of time course gene expression data.
RSSA	SICOMPRESS Repetition-based Stochastic Simulation Algorithm	GENER Gener is a tool for performing reduction on DNA networks based on a strand-displacement
BETAWB	GRAPH Graph constructs, visualizes, and modifies graphs as well as calculates measures and layouts	KINFER Estimates both structural and rate-model parameters from time-series data of magnetic abundance
LIME	REDI Real-time simulation of biochemical systems at the microscopic scale of molecules	WALDO Waldo is a reaction-based tool for easily modeling and simulating biological systems

data integration

biomarker identification

knowledge extraction

pathway analysis

modeling & simulation

modeling languages

Case Studies

C. Priami. *The Stochastic pi-calculus*. **The Computer Journal**, 38(6): 578-589, 1995.

C. Priami, A. Regev, E. Shapiro, W. Silvermann. *Application of a stochastic name-passing calculus to representation and simulation of molecular processes*. **Information Processing Letters**, 80:25-31, 2001.

C. Priami. *Language-based performance prediction of distributed and mobile systems*. **Information and Computation**, 175:119-145, 2002.

L. Dematté, C. Priami, A. Romanel. *The BlenX Language: a tutorial*. In **Formal Methods for Computational Systems Biology**, (M. Bernardo, P. Degano, G. Zavattaro, Eds.), **LNCS 5016**, 313-365, Springer, 2008.

L. Dematté, C. Priami, A. Romanel. *The Beta Workbench: a computational tool to study the dynamics of biological systems*. **Briefings in Bioinformatics**, 9(5): 437-449, 2008.

L. Dematté, R. Larcher, A. Palmisano, C. Priami, A. Romanel. *Programming Biology in BlenX*. In **Systems Biology for Signaling Networks** 1:777-821, S. Choi, Ed., Springer, 2010.

D. Nikolic, C. Priami, R. Zunino. *A Rule-based and Imperative Language for Biochemical Modeling and Simulation*. Proceedings of **SEFM'12, LNCS**, Springer, 2012.

C. Priami, P. Quaglia, R. Zunino. *An imperative language of self-modifying graphs for biological systems*. Proceedings of **ACM SAC'12**, 1903-1909, ACM, 2012.

L

2012

BlenX
2008

Beta
binders
2004

Stochastic
pi-calculus
1995

C. Priami and P. Quaglia. *Beta binders for biological interactions*. Proceedings of CMSB04, **LNBI 3082**, 21-34, 2005.

C. Priami, P. Quaglia. *Operational patterns in Beta-binders*. **Transactions on Computational Systems Biology**, I:LNBI 3380, 50-65, 2005.

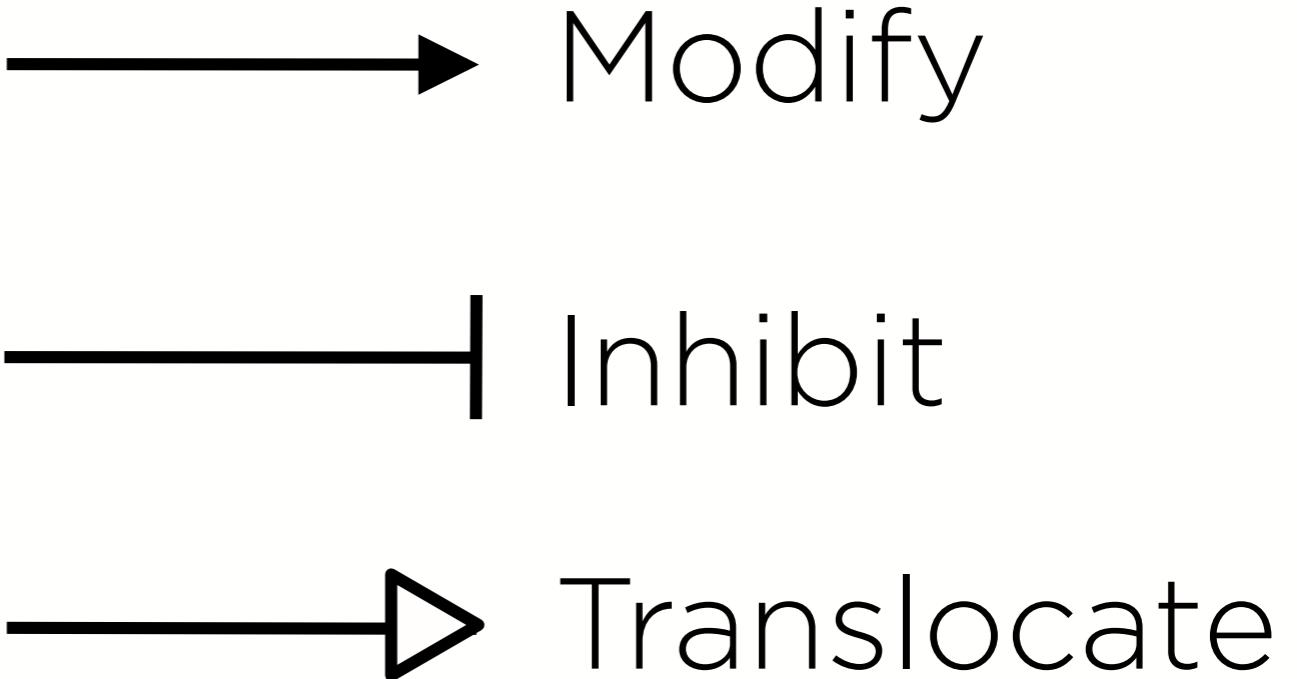
Implementation

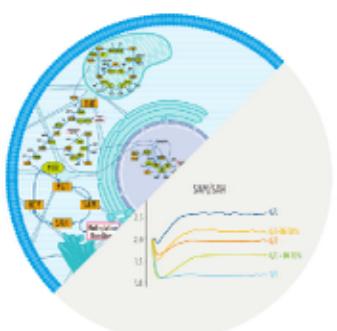
bStyle

Syndrome of “a new symbol”

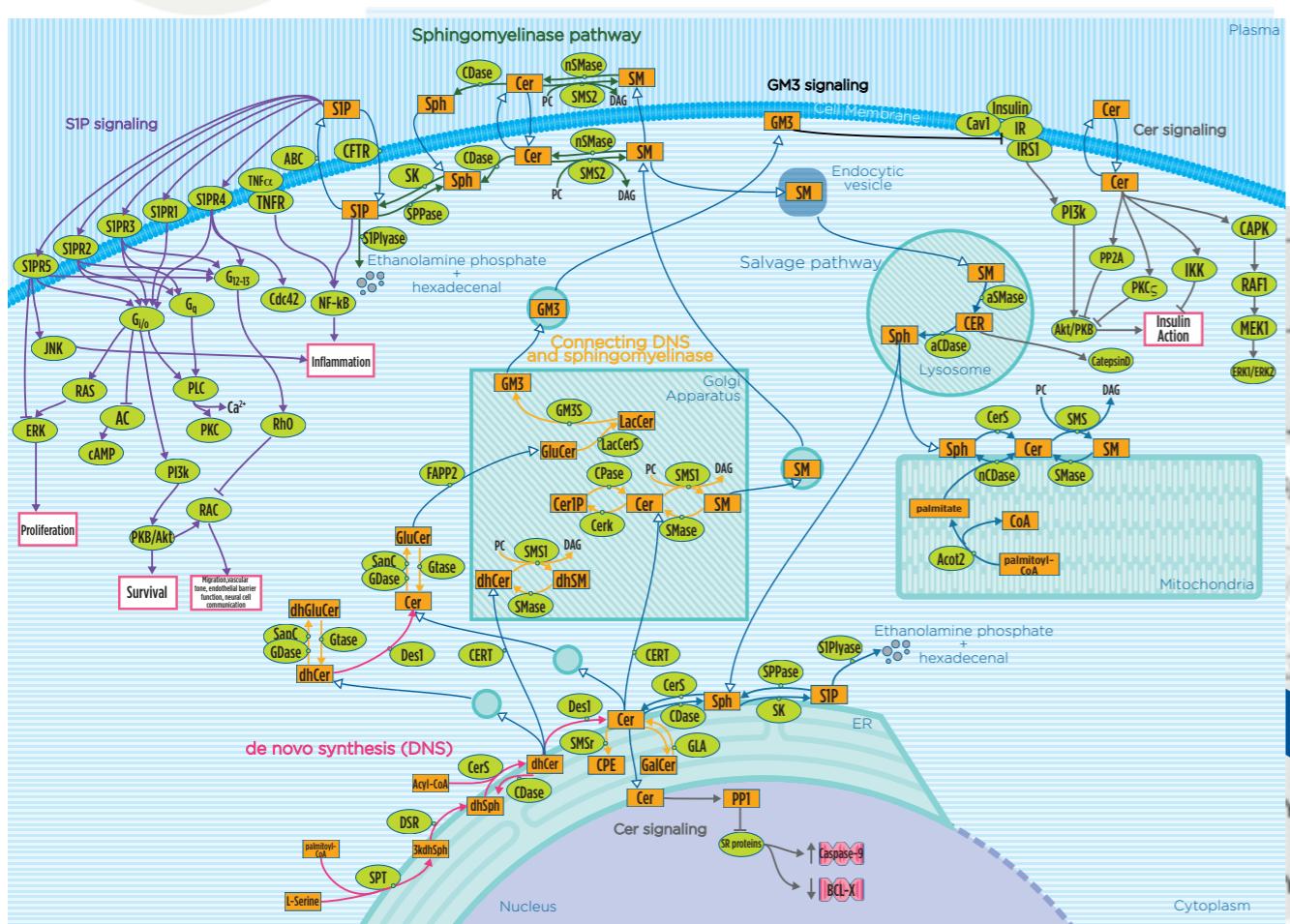
+

Better = New functionalities





making simulation accessible



analysis of
biological systems

Modeling is fast becoming fundamental to understanding the processes that define biological systems. High-throughput technologies are producing increasing quantities of data that require an ever-expanding toolkit for their effective analysis and interpretation. Analysis of high-throughput data in the context of a molecular interaction network is particularly informative as it has the potential to reveal the most relevant network modules with respect to a phenotype or biological process of interest.

Analysis of Biological Systems collects classical material on analysis, modeling and simulation, thereby acting as a unique point of reference. The joint application of statistical techniques to extract knowledge from big data and map it into mechanistic models is a current challenge of the field, and the reader will learn how to build and use models even if they have no computing or math background. An in-depth analysis of the currently available technologies, and a comparison between them, is also included. Unlike other reference books, this in-depth analysis is extended to the field of language-based modeling. The overall result is an indispensable, self-contained and systematic approach to a rapidly expanding field of science.

Imperial College Press
www.icpress.co.uk

analysis of biological systems

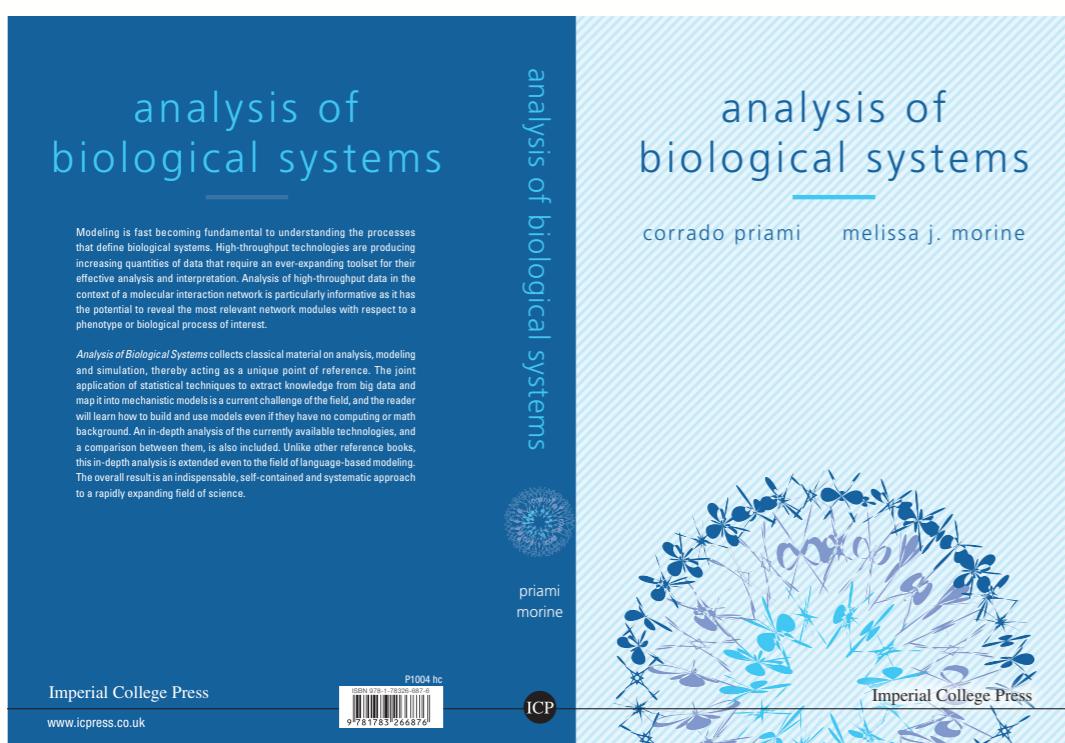
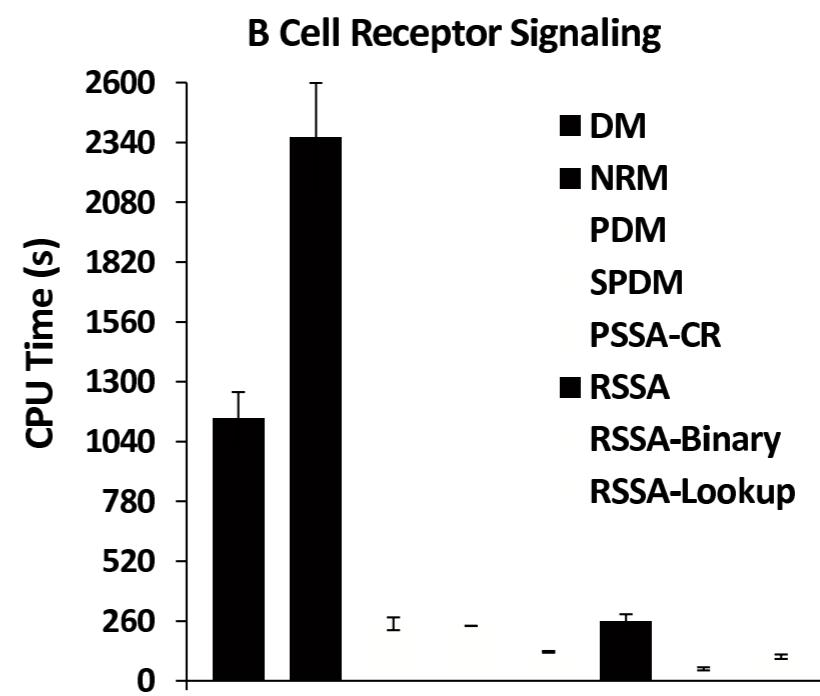
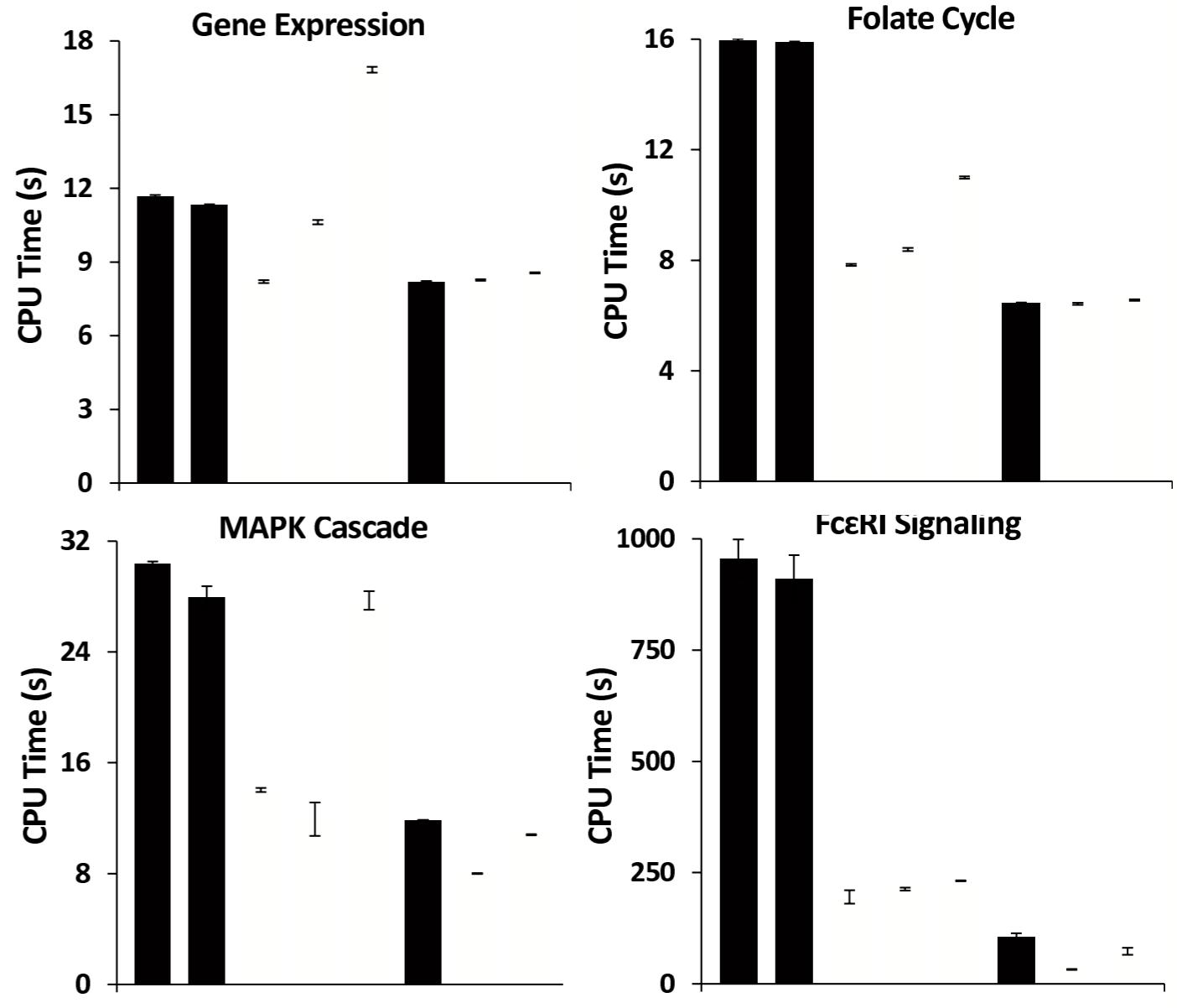
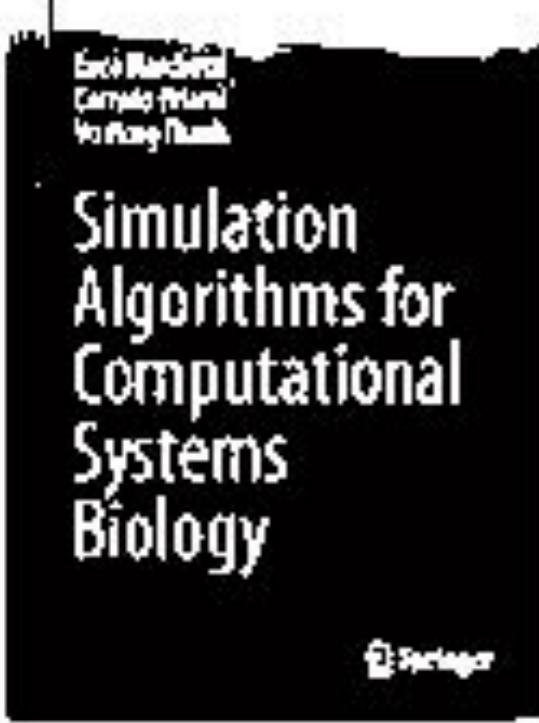
analysis of
biological systems

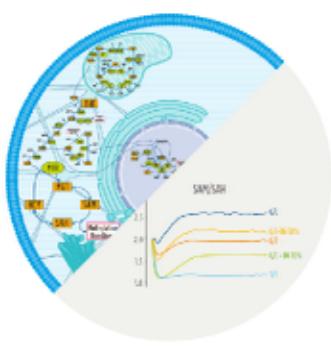
corrado priami melissa j. morine



CREDITS: “Insert a coin, avoid Klingons” Atari philosophy

performance





strengths

many application to real cases

hierarchical modeling

deterministic, stochastic, hybrid

Case Studies

L. Dematté, C. Priami, A. Romanel. *The BioX Language: a tutorial*. In Formal Methods for Computational Systems Biology, (M. Bernardo, P. Degano, G. Zavattaro, Eds.), LNCS, 2008.

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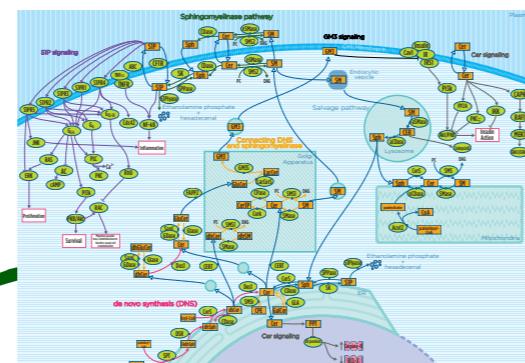
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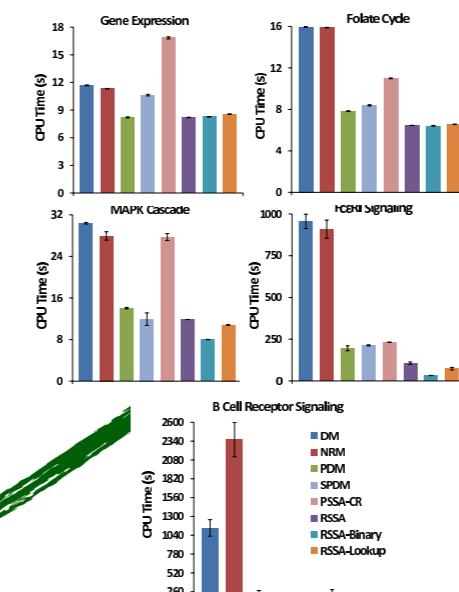
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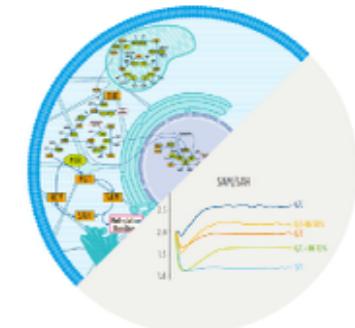


smallest graphical modeling language

huge experience in modeling language



fastest stochastic and hybrid simulation algorithms



integrated platform data-analysis / simulation



Thank you for your time

