CG920 Genomics

Lesson 11

Systems Biology

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Literature

- Literature sources for Chapter 12:

  - Wilt, F.H., and Hake, S. (2004). Principles of Developmental Biology. (New York ; London: W. W. Norton)
  - Eden, E., Navon, R., Steinfeld, I., Lipson, D., and Yakhini, Z. (2009). GOrilla: a tool for discovery and visualization of enriched GO terms in ranked gene lists. BMC Bioinformatics 10, 48.
  - The Arabidopsis Genome Initiative. (2000). Analysis of the genome sequence of the flowering plant Arabidopsis thaliana. Nature 408, 796-815.
  - Benitez, M. and Hejatko, J. Dynamics of cell-fate determination and patterning in the vascular bundles of Arabidopsis thaliana (submitted)
  - de Luis Balaguer MA, Fisher AP, Clark NM, Fernandez-Espinosa MG, Moller BK, Weijers D, Lohmann JU, Williams C, Lorenzo O, Sozzani R. 2017. Predicting gene regulatory networks by combining spatial and temporal gene expression data in Arabidopsis root stem cells. Proc Natl Acad Sci U S A 114(36): E7632-E7640.

Outline

- Definition of Systems Biology
- Tools
    - Gene Ontology Analysis
    - Bayesian Networks
    - Molecular/Gene Regulatory Networks Modeling
    - Inferring Gene Regulatory Networks from Large Omics Datasets

Definition

Systems biology is the computational and mathematical analysis and modeling of complex biological systems. It is a biology-based interdisciplinary field of study that focuses on complex interactions within biological systems, using a holistic approach (holism instead of the more traditional reductionism) to biological research (Wikipedia).

Definition

Systems biology is the study of biological systems whose behaviour cannot be reduced to the linear sum of their parts' functions. Systems biology does not necessarily involve large numbers of components or vast datasets, as in genomics or connectomics, but often requires quantitative modelling methods borrowed from physics (Nature).

Definition

Nice explanatory video by Dr. Nathan Price,

associate director of the Institute for Systems Biology at https://www.youtube.com/watch?v=OrXRI_8UFHU.

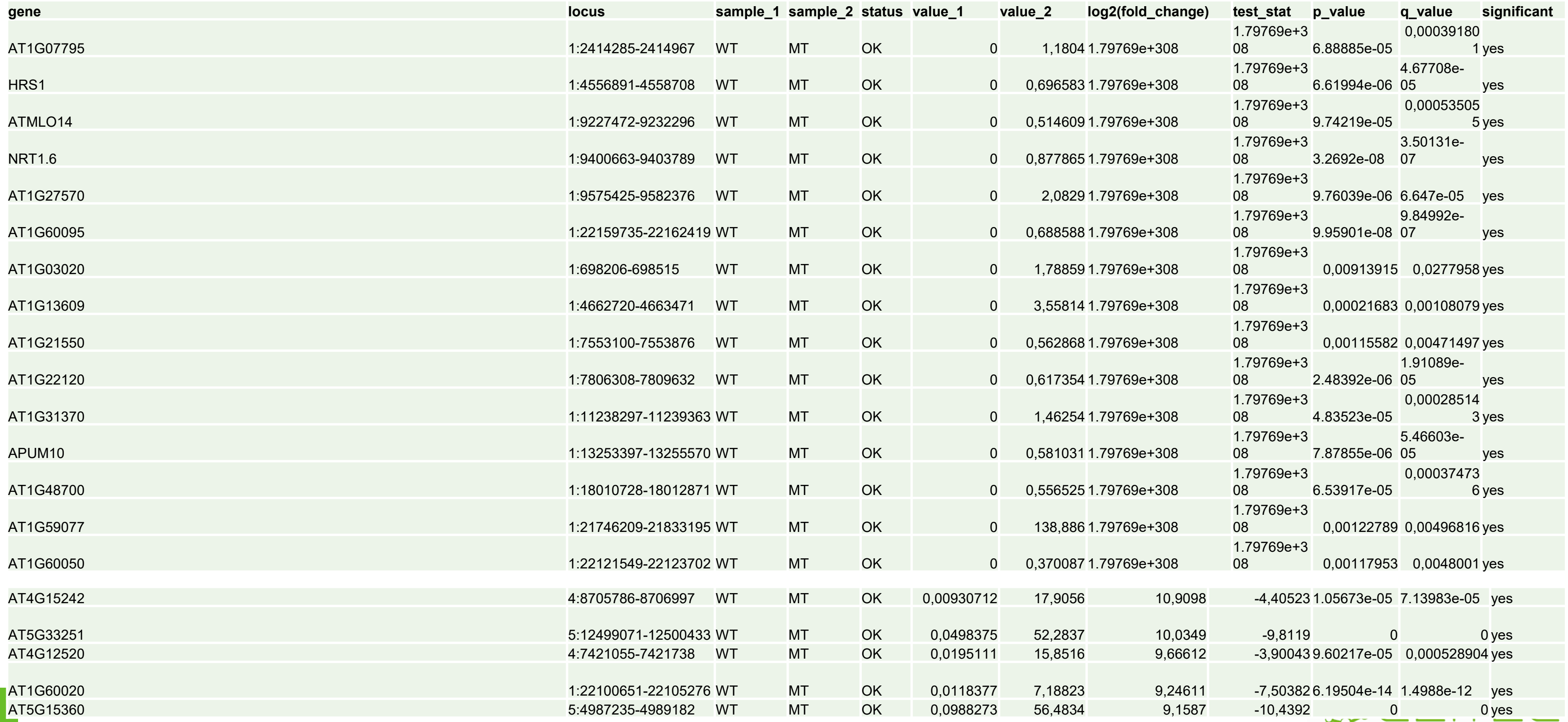
Outline

- Definition of Systems Biology
- Tools
  - Gene Ontology analysis

Results of –omics Studies vs Biologically Relevant Conclusions

- ☐ Results of **–omics studies** represent **huge amount of data**, e.g. genes with differential expression. But how to get any **biologically relevant conclusions** out of it?

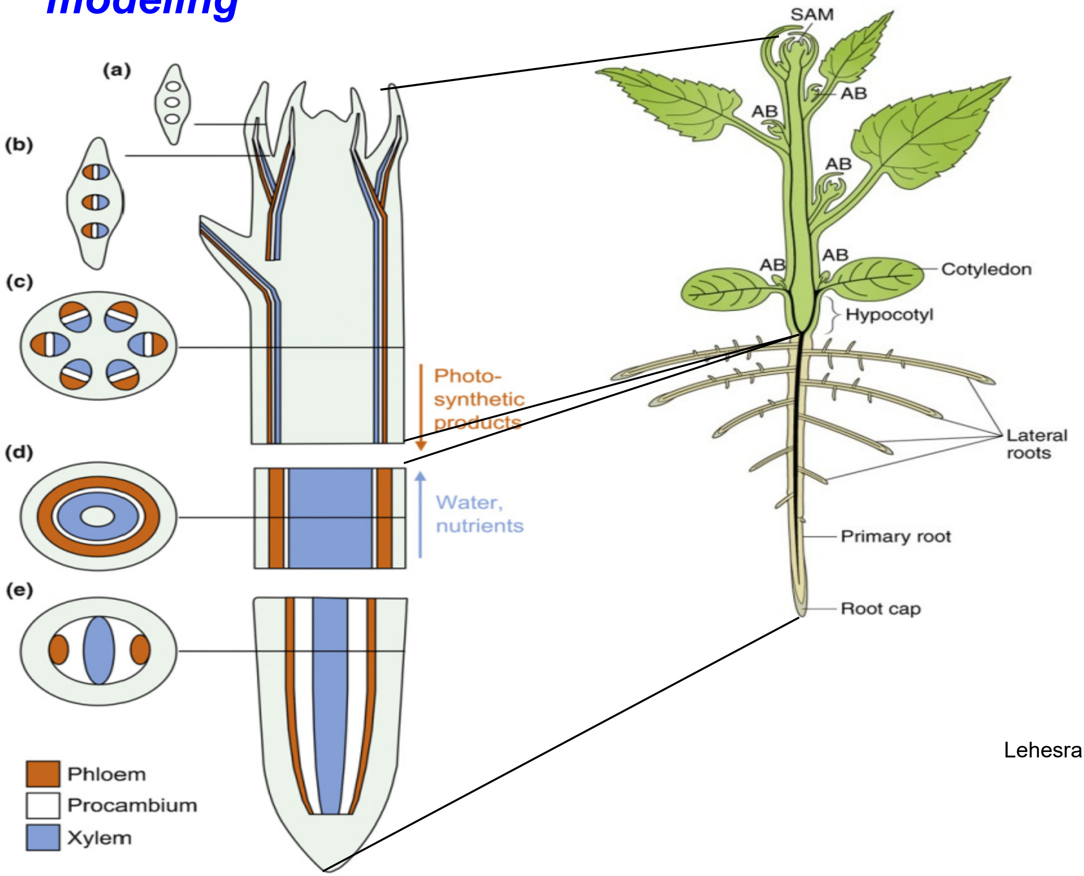
Ddii et al., *unpublished*



gene	locus	sample_1	sample_2	status	value_1	value_2	log2(fold_change)	test_stat	p_value	q_value	significant
AT1G07795	1:2414285-2414967	WT	MT	OK	0	1,1804	1.79769e+308	1.79769e+308	6.88885e-05	0,000391801	yes
HRS1	1:4556891-4558708	WT	MT	OK	0	0,696583	1.79769e+308	1.79769e+308	6.61994e-06	4.67708e-05	yes
ATMLO14	1:9227472-9232296	WT	MT	OK	0	0,514609	1.79769e+308	1.79769e+308	9.74219e-05	0,000535055	yes
NRT1.6	1:9400663-9403789	WT	MT	OK	0	0,877865	1.79769e+308	1.79769e+308	3.2692e-08	3.50131e-07	yes
AT1G27570	1:9575425-9582376	WT	MT	OK	0	2,0829	1.79769e+308	1.79769e+308	9.76039e-06	6.647e-05	yes
AT1G60095	1:22159735-22162419	WT	MT	OK	0	0,688588	1.79769e+308	1.79769e+308	9.95901e-08	9.84992e-07	yes
AT1G03020	1:698206-698515	WT	MT	OK	0	1,78859	1.79769e+308	1.79769e+308	0,00913915	0,0277958	yes
AT1G13609	1:4662720-4663471	WT	MT	OK	0	3,55814	1.79769e+308	1.79769e+308	0,00021683	0,00108079	yes
AT1G21550	1:7553100-7553876	WT	MT	OK	0	0,562868	1.79769e+308	1.79769e+308	0,00115582	0,00471497	yes
AT1G22120	1:7806308-7809632	WT	MT	OK	0	0,617354	1.79769e+308	1.79769e+308	2.48392e-06	1.91089e-05	yes
AT1G31370	1:11238297-11239363	WT	MT	OK	0	1,46254	1.79769e+308	1.79769e+308	4.83523e-05	0,000285143	yes
APUM10	1:13253397-13255570	WT	MT	OK	0	0,581031	1.79769e+308	1.79769e+308	7.87855e-06	5.46603e-05	yes
AT1G48700	1:18010728-18012871	WT	MT	OK	0	0,556525	1.79769e+308	1.79769e+308	6.53917e-05	0,000374736	yes
AT1G59077	1:21746209-21833195	WT	MT	OK	0	138,886	1.79769e+308	1.79769e+308	0,00122789	0,00496816	yes
AT1G60050	1:22121549-22123702	WT	MT	OK	0	0,370087	1.79769e+308	1.79769e+308	0,00117953	0,0048001	yes
AT4G15242	4:8705786-8706997	WT	MT	OK	0,00930712	17,9056	10,9098	-4,40523	1.05673e-05	7.13983e-05	yes
AT5G33251	5:12499071-12500433	WT	MT	OK	0,0498375	52,2837	10,0349	-9,8119	0	0	yes
AT4G12520	4:7421055-7421738	WT	MT	OK	0,0195111	15,8516	9,66612	-3,90043	9.60217e-05	0,000528904	yes
AT1G60020	1:22100651-22105276	WT	MT	OK	0,0118377	7,18823	9,24611	-7,50382	6.19504e-14	1.4988e-12	yes
AT5G15360	5:4987235-4989182	WT	MT	OK	0,0988273	56,4834	9,1587	-10,4392	0	0	yes

Plant Vascular Tissue Development

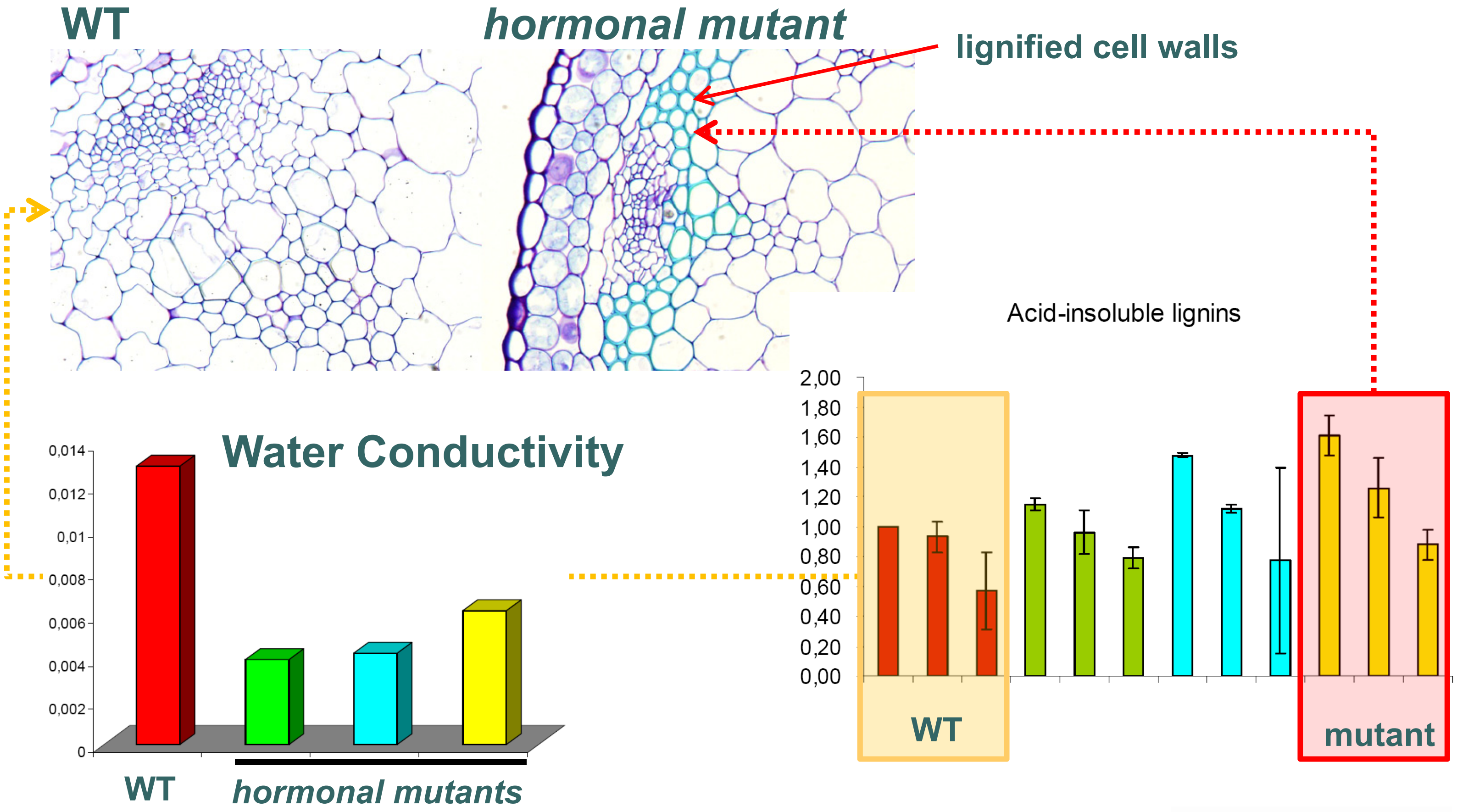
- ☐ ***Vascular tissue*** as a developmental model for ***GO analysis*** and ***MRN modeling***



Lehesranta etal., *Trends in Plant Sci* (2010)

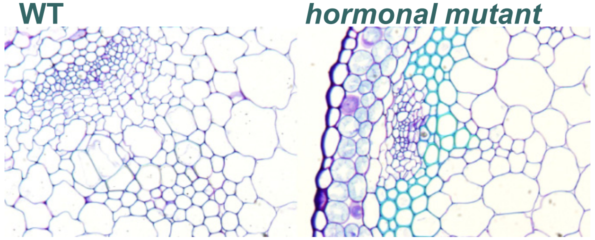
Hormonal Control Over Vascular Tissue Development

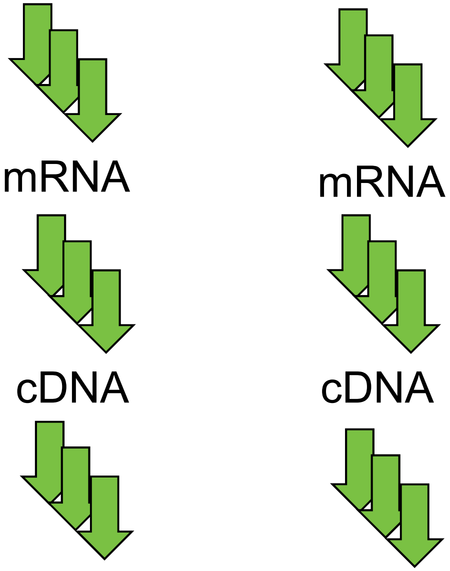
- Plant **Hormones Regulate Lignin Deposition** in Plant Cell Walls and **Xylem Water Conductivity**

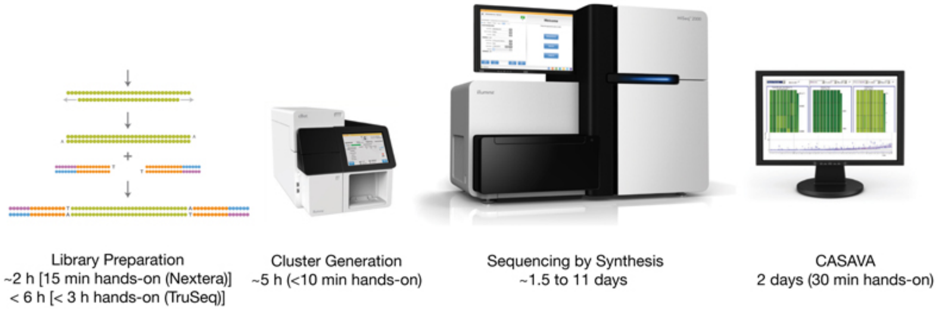


Hormonal Control Over Vascular Tissue Development

- ☐ ***Transcriptional profiling*** via ***RNA sequencing***





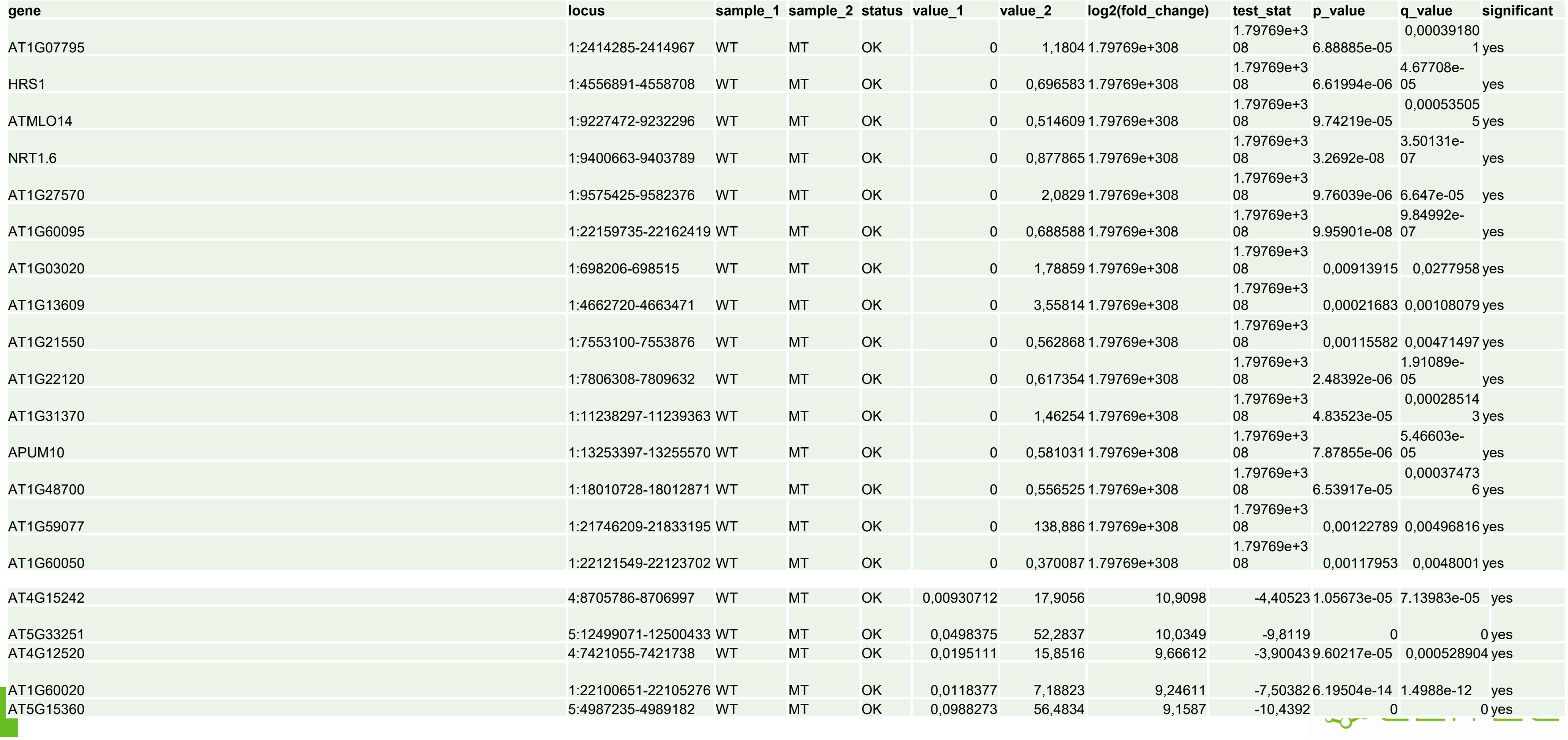


Sequencing by Illumina and
number of transcripts determination

Results of –omics Studies vs Biologically Relevant Conclusions

- ☐ Transcriptional profiling yielded more then **9K differentially regulated genes**…

Ddii et al., *unpublished*



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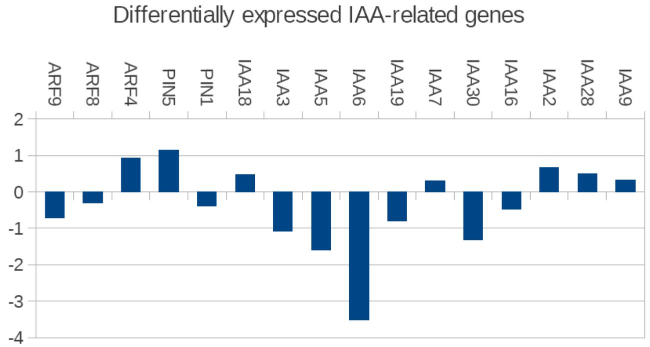
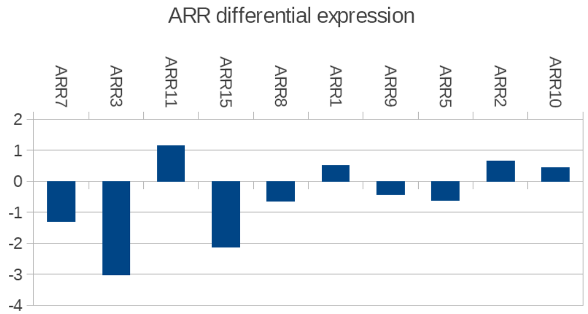
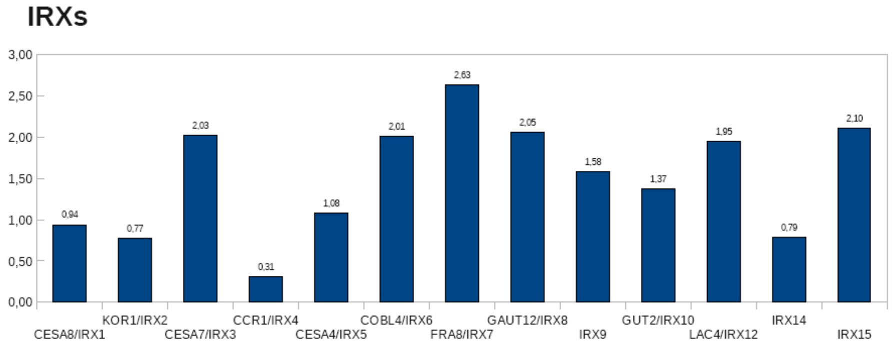
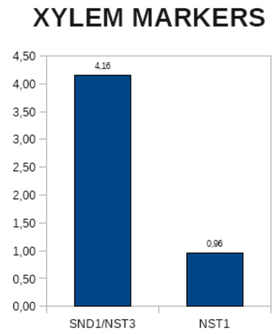
Gene Ontology Analysis

- ☐ One of the possible approaches is to study ***gene ontology***, i.e. previously demonstrated **association** of genes to **biological processes**







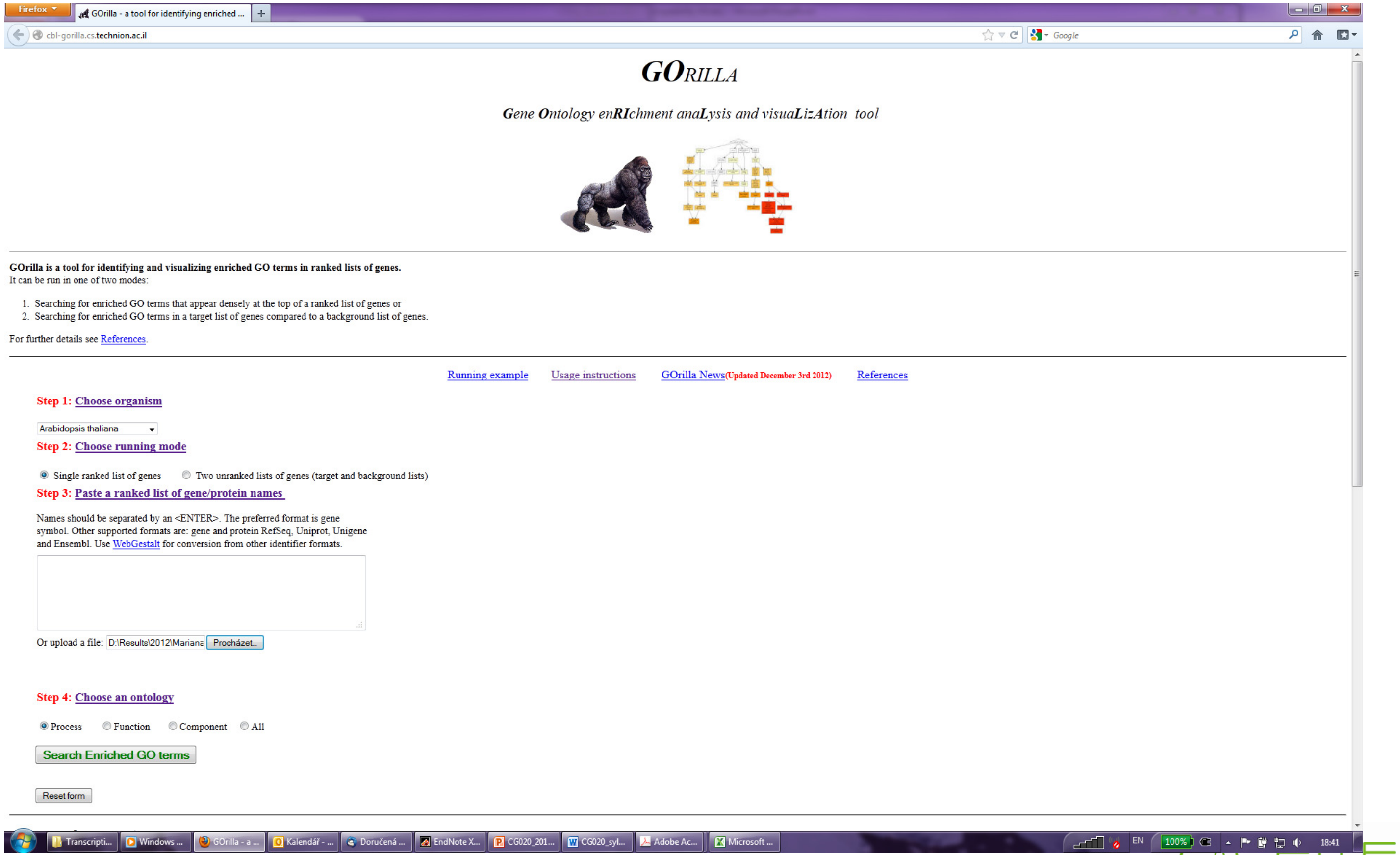


Ddii et al., *unpublished*

Gene Ontology Analysis

- ☐ Several tools allow **statistical evaluation** of **enrichment** for genes **associated with specific processes**

Eden et al., *BMC Biinformatics* (2009)



*GO*RILLA

Gene Ontology enRIchment anaLysis and visuaLizAtion tool

GOrilla is a tool for identifying and visualizing enriched GO terms in ranked lists of genes.
It can be run in one of two modes:

1. Searching for enriched GO terms that appear densely at the top of a ranked list of genes or
2. Searching for enriched GO terms in a target list of genes compared to a background list of genes.

For further details see References.

Running example Usage instructions GOrilla News(Updated December 3rd 2012) References

Step 1: Choose organism

Arabidopsis thaliana

Step 2: Choose running mode

● Single ranked list of genes ○ Two unranked lists of genes (target and background lists)

Step 3: Paste a ranked list of gene/protein names

Names should be separated by an <ENTER>. The preferred format is gene symbol. Other supported formats are: gene and protein RefSeq, Uniprot, Unigene and Ensembl. Use WebGestalt for conversion from other identifier formats.

Or upload a file: D:\Results\2012\Mariana Procházet...

Step 4: Choose an ontology

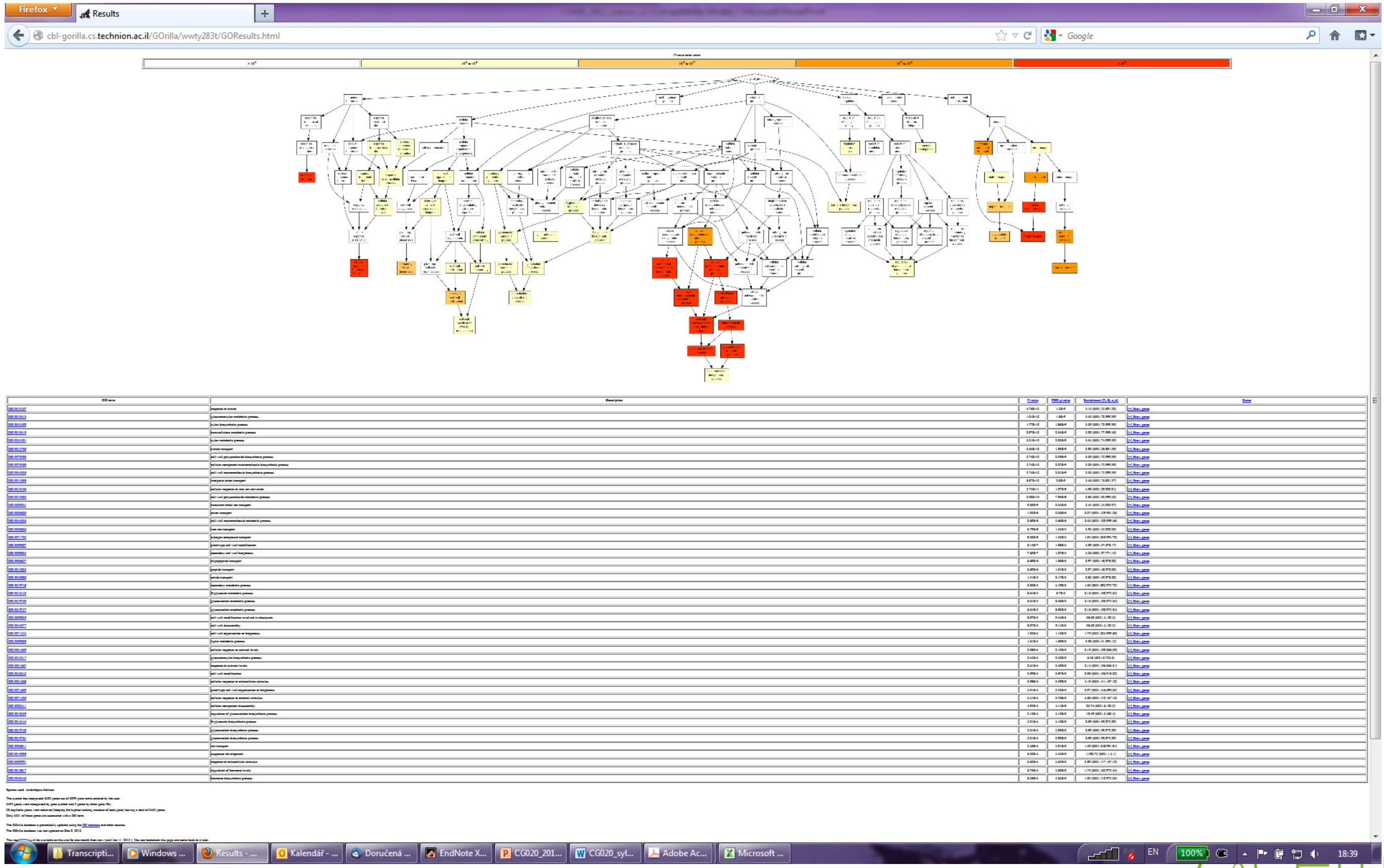
● Process ○ Function ○ Component ○ All

Search Enriched GO terms

Reset form

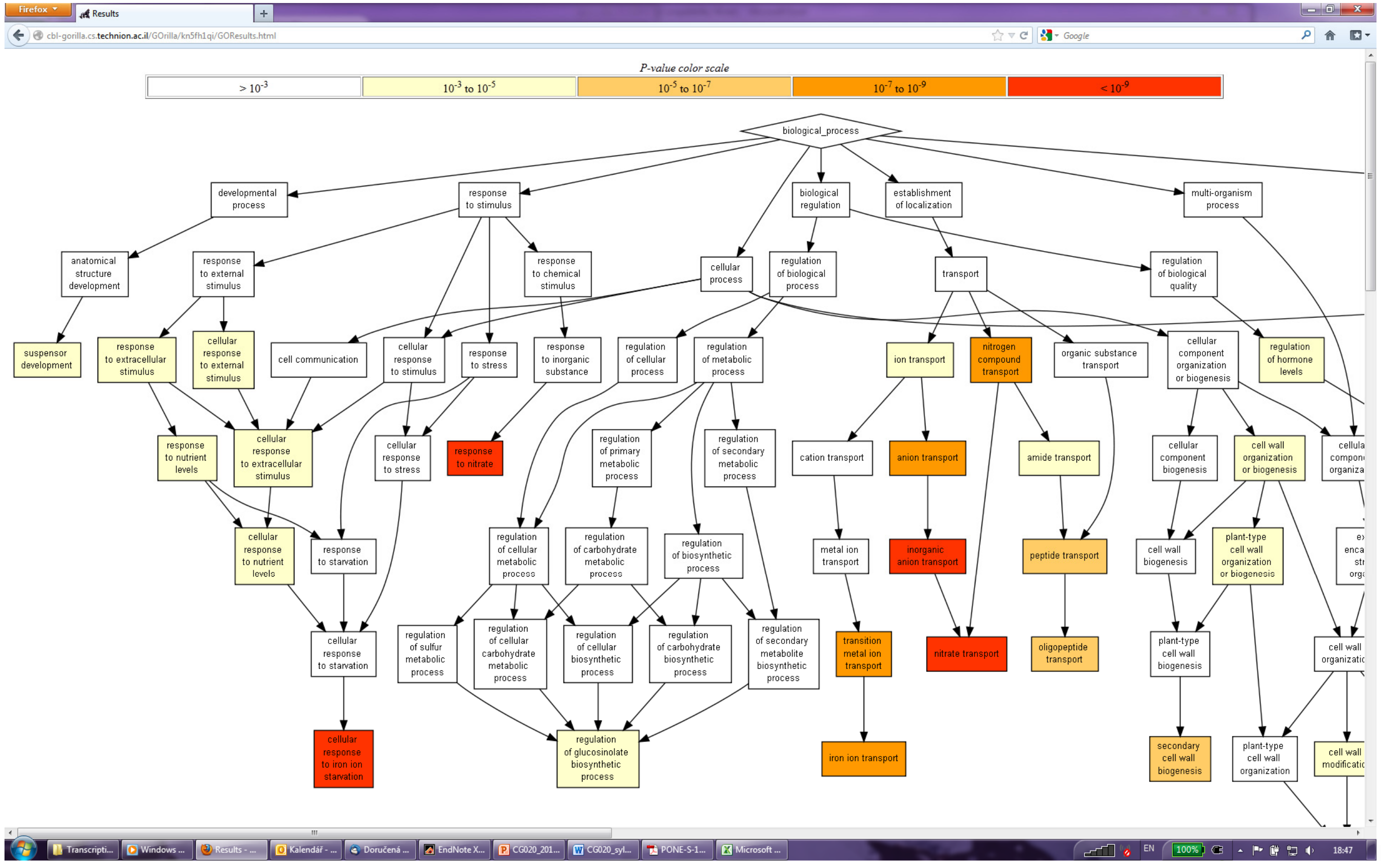
Gene Ontology Analysis

- Several tools allow **statistical evaluation** of **enrichment** for genes **associated with specific processes**



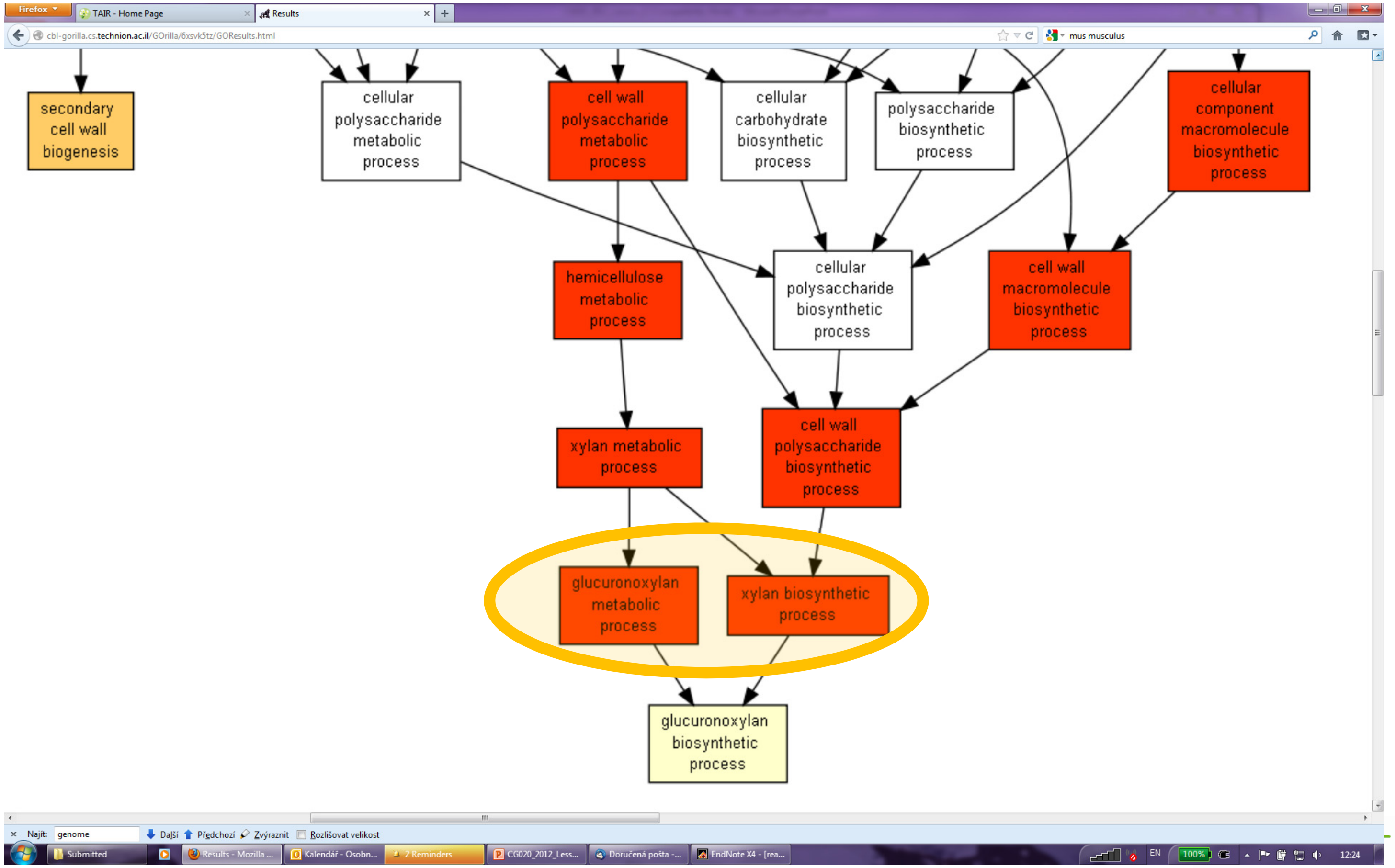
Gene Ontology Analysis

- Several tools allow **statistical evaluation** of **enrichment** for genes **associated with specific processes**



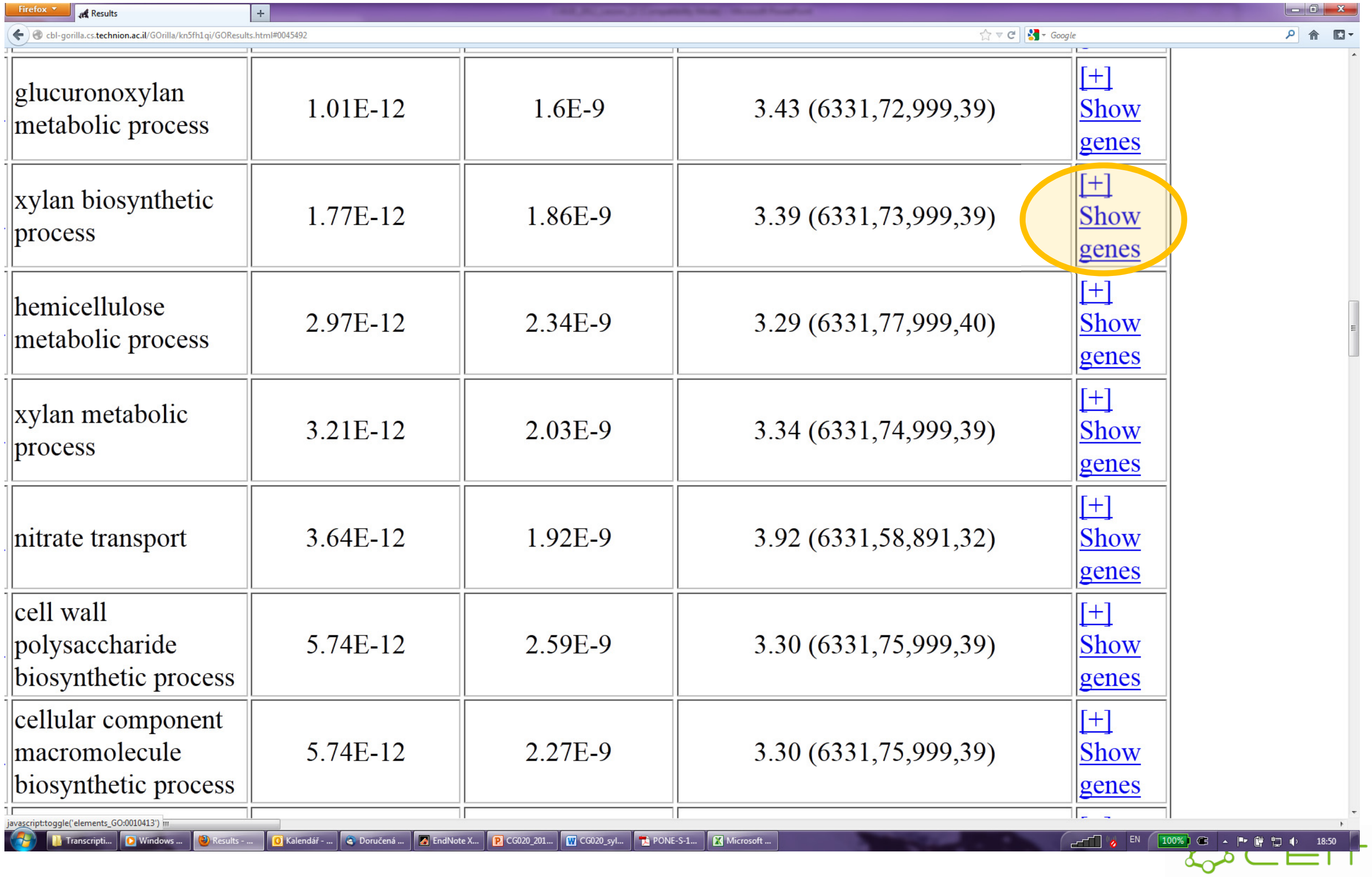
Gene Ontology Analysis

- ☐ Several tools allow **statistical evaluation** of **enrichment** for genes **associated with specific processes**



Gene Ontology Analysis

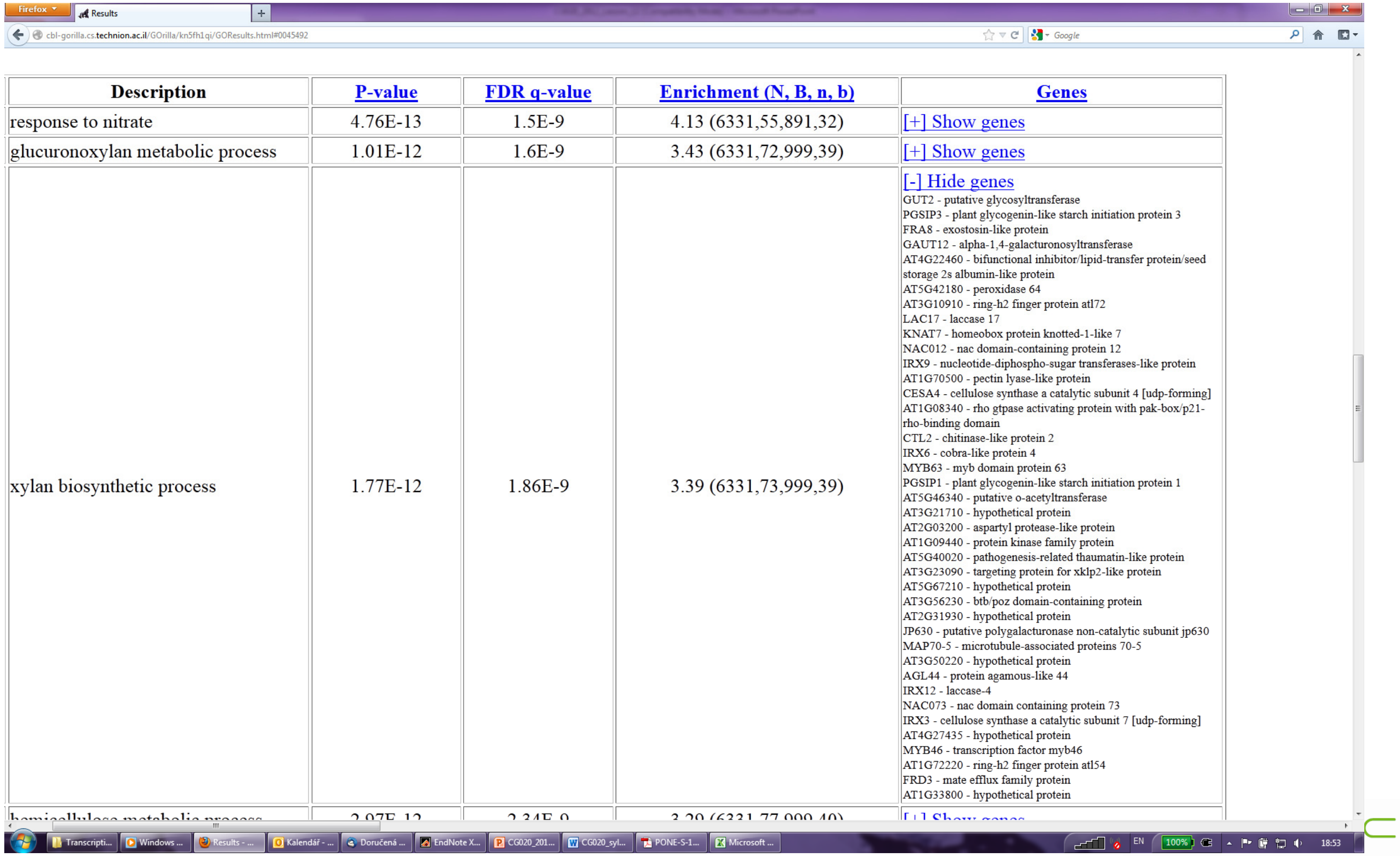
- Several tools allow **statistical evaluation** of **enrichment** for genes **associated with specific processes**



glucuronoxylan metabolic process	1.01E-12	1.6E-9	3.43 (6331,72,999,39)	[+] Show genes
xylan biosynthetic process	1.77E-12	1.86E-9	3.39 (6331,73,999,39)	[+] Show genes
hemicellulose metabolic process	2.97E-12	2.34E-9	3.29 (6331,77,999,40)	[+] Show genes
xylan metabolic process	3.21E-12	2.03E-9	3.34 (6331,74,999,39)	[+] Show genes
nitrate transport	3.64E-12	1.92E-9	3.92 (6331,58,891,32)	[+] Show genes
cell wall polysaccharide biosynthetic process	5.74E-12	2.59E-9	3.30 (6331,75,999,39)	[+] Show genes
cellular component macromolecule biosynthetic process	5.74E-12	2.27E-9	3.30 (6331,75,999,39)	[+] Show genes

Gene Ontology Analysis

- ☐ Several tools allow **statistical evaluation** of **enrichment** for genes **associated with specific processes**



Description	P-value	FDR q-value	Enrichment (N, B, n, b)	Genes
response to nitrate	4.76E-13	1.5E-9	4.13 (6331,55,891,32)	[+] Show genes
glucuronoxylan metabolic process	1.01E-12	1.6E-9	3.43 (6331,72,999,39)	[+] Show genes
xylan biosynthetic process	1.77E-12	1.86E-9	3.39 (6331,73,999,39)	[-] Hide genes GUT2 - putative glycosyltransferase PGSIP3 - plant glycogenin-like starch initiation protein 3 FRA8 - exostosin-like protein GAUT12 - alpha-1,4-galacturonosyltransferase AT4G22460 - bifunctional inhibitor/lipid-transfer protein/seed storage 2s albumin-like protein AT5G42180 - peroxidase 64 AT3G10910 - ring-h2 finger protein atl72 LAC17 - laccase 17 KNAT7 - homeobox protein knotted-1-like 7 NAC012 - nac domain-containing protein 12 IRX9 - nucleotide-diphospho-sugar transferases-like protein AT1G70500 - pectin lyase-like protein CESA4 - cellulose synthase a catalytic subunit 4 [udp-forming] AT1G08340 - rho gtpase activating protein with pak-box/p21-rho-binding domain CTL2 - chitinase-like protein 2 IRX6 - cobra-like protein 4 MYB63 - myb domain protein 63 PGSIP1 - plant glycogenin-like starch initiation protein 1 AT5G46340 - putative o-acetyltransferase AT3G21710 - hypothetical protein AT2G03200 - aspartyl protease-like protein AT1G09440 - protein kinase family protein AT5G40020 - pathogenesis-related thaumatin-like protein AT3G23090 - targeting protein for xklp2-like protein AT5G67210 - hypothetical protein AT3G56230 - btb/poz domain-containing protein AT2G31930 - hypothetical protein JP630 - putative polygalacturonase non-catalytic subunit jp630 MAP70-5 - microtubule-associated proteins 70-5 AT3G50220 - hypothetical protein AGL44 - protein agamous-like 44 IRX12 - laccase-4 NAC073 - nac domain containing protein 73 IRX3 - cellulose synthase a catalytic subunit 7 [udp-forming] AT4G27435 - hypothetical protein MYB46 - transcription factor myb46 AT1G72220 - ring-h2 finger protein atl54 FRD3 - mate efflux family protein AT1G33800 - hypothetical protein
hemicellulose metabolic process	2.97E-12	2.34E-9	3.29 (6331,77,999,40)	[+] Show genes

Outline

- Definition of Systems Biology
- Tools
    - Gene Ontology analysis
    - Bayesian Networks

Bayesian Networks

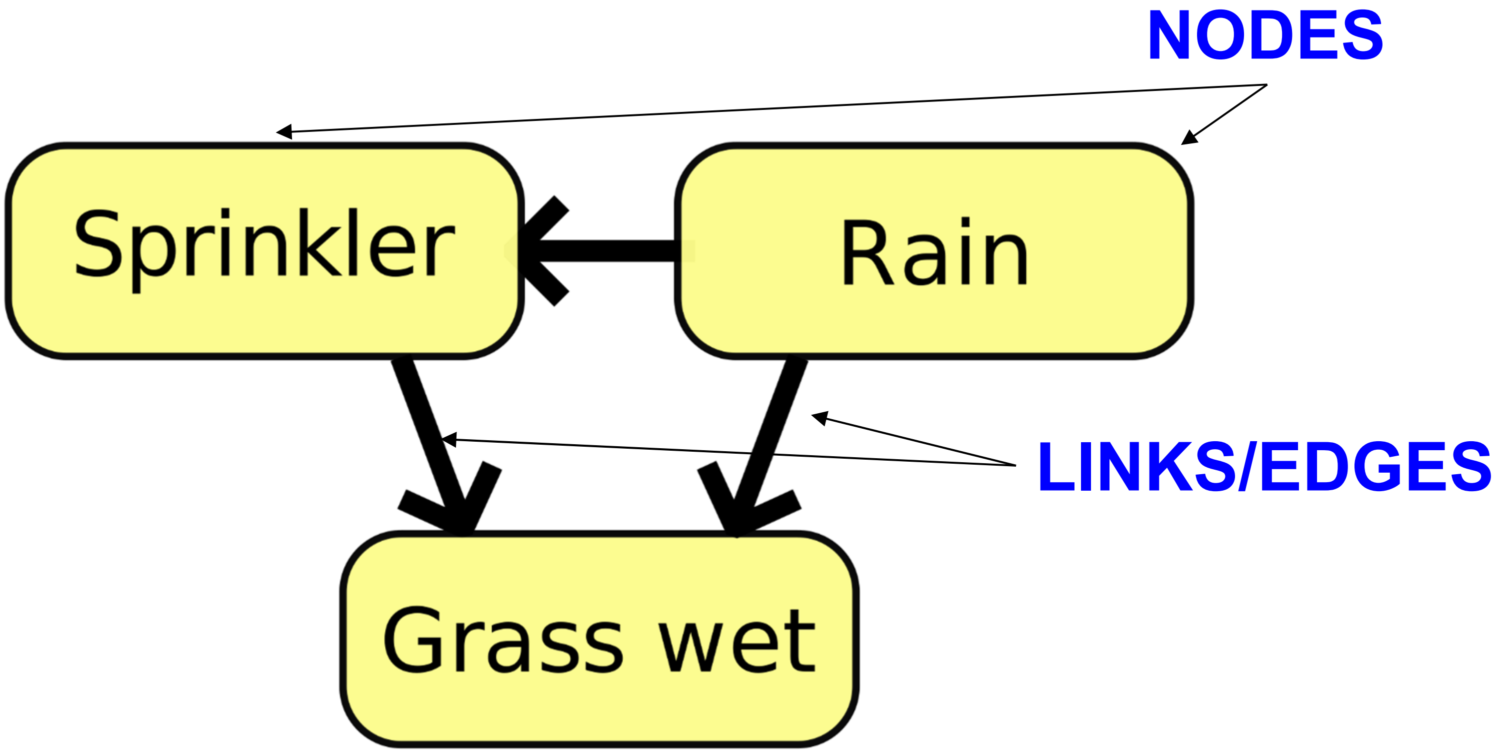
- What are Bayesian networks?
    - **Probabilistic Graphical Model that can be used to build models from data and/or expert opinion**

https://www.youtube.com/watch?v=4fcqyzVJwH

Bayesian Networks

- What are **Bayesian Networks**?
  - **Probabilistic Graphical Model** that can be used to **build models from data** and/or **expert opinion**
  - can be used for a wide range of tasks including **prediction, anomaly detection, diagnostics, automated insight, reasoning, time series prediction** and **decision making under uncertainty**
- **NODES**
  - each node represents a **variable** such as someone's height, age or gender. A variable might be discrete, such as Gender = {Female, Male} or might be continuous such as someone's age
- **LINKS**
  - added **between nodes** to indicate that **one node** directly **influences** the **other**

Bayesian Networks



NODES

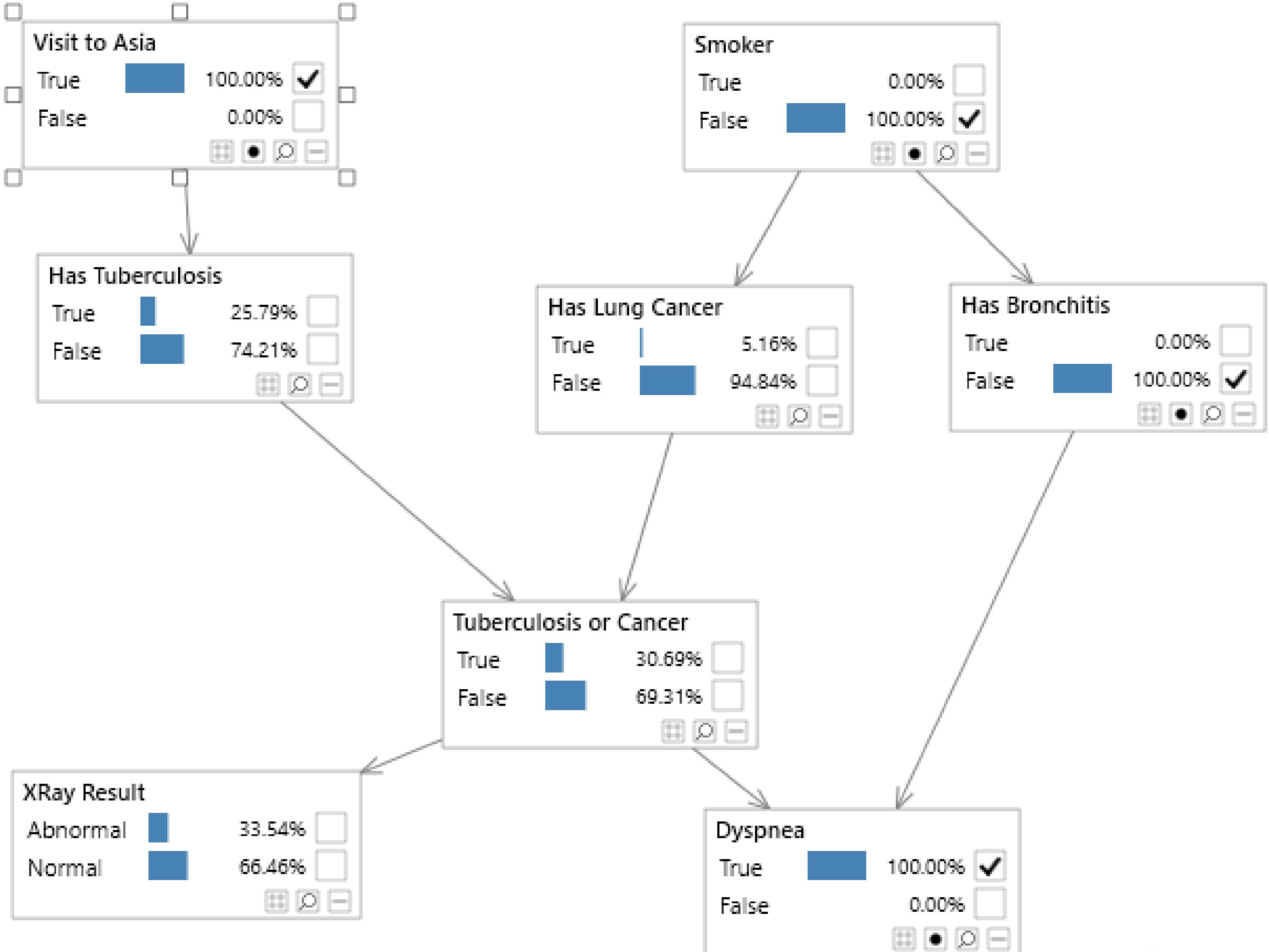
Sprinkler

Rain

LINKS/EDGES

Grass wet

Asia Bayesian Network



Visit to Asia
True 100.00% ☑
False 0.00% ☐

Smoker
True 0.00% ☐
False 100.00% ☑

Has Tuberculosis
True 25.79% ☐
False 74.21% ☐

Has Lung Cancer
True 5.16% ☐
False 94.84% ☐

Has Bronchitis
True 0.00% ☐
False 100.00% ☑

Tuberculosis or Cancer
True 30.69% ☐
False 69.31% ☐

XRay Result
Abnormal 33.54% ☐
Normal 66.46% ☐

Dyspnea
True 100.00% ☑
False 0.00% ☐

https://www.bayesserver.com/

Outline

- Definition of Systems Biology
- Tools
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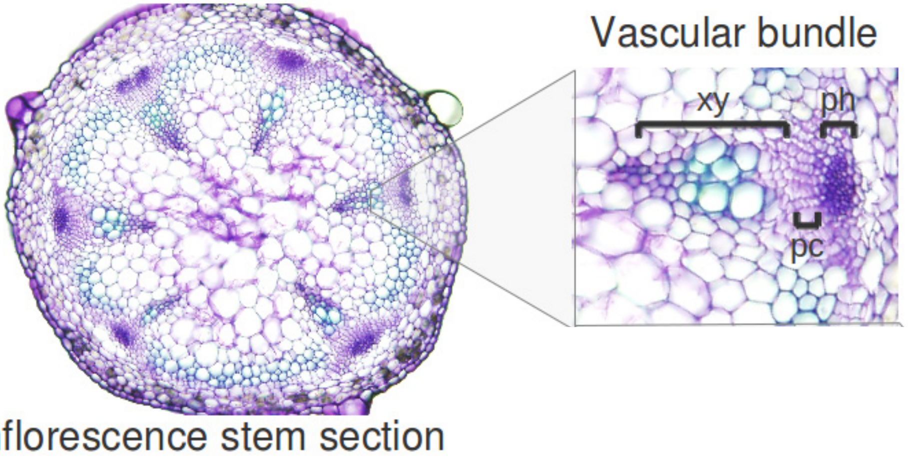
  - Bayesian Networks
  - Molecular/Gene Regulatory Networks Modeling

Molecular Regulatory Networks Modeling

- ***Vascular tissue*** as a developmental model for ***MRN modeling***



Benitez and Hejatko, *PLoS One,* 2013

Molecular Regulatory Networks Modeling

- **Literature search** for published data and **creating small database**

Interaction	**Evidence**	**References**
A-ARRs –| CK signaling	Double and higher order type-A ARR mutants show increased sensitivity to CK. Spatial patterns of A-type ARR gene expression and CK response are consistent with partially redundant function of these genes in CK signaling. A-type ARRs decreases B-type ARR6-LUC. Note: In certain contexts, however, some A-ARRs appear to have effects antagonistic to other A-ARRs.	[27] [27] [13] [27]
AHP6 –| AHP	ahp6 partially recovers the mutant phenotype of the CK receptor WOL. Using an in vitro phosphotransfer system, it was shown that, unlike the AHPs, native AHP6 was unable to accept a phosphoryl group. Nevertheless, AHP6 is able to inhibit phosphotransfer from other AHPs to ARRs.	[9] [9]

Benitez and Hejatko, *PLoS One*, 2013

Molecular Regulatory Networks Modeling

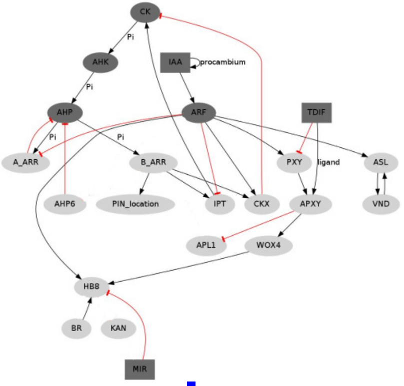
- ☐ Formulating ***logical rules*** defining the ***model dynamics***

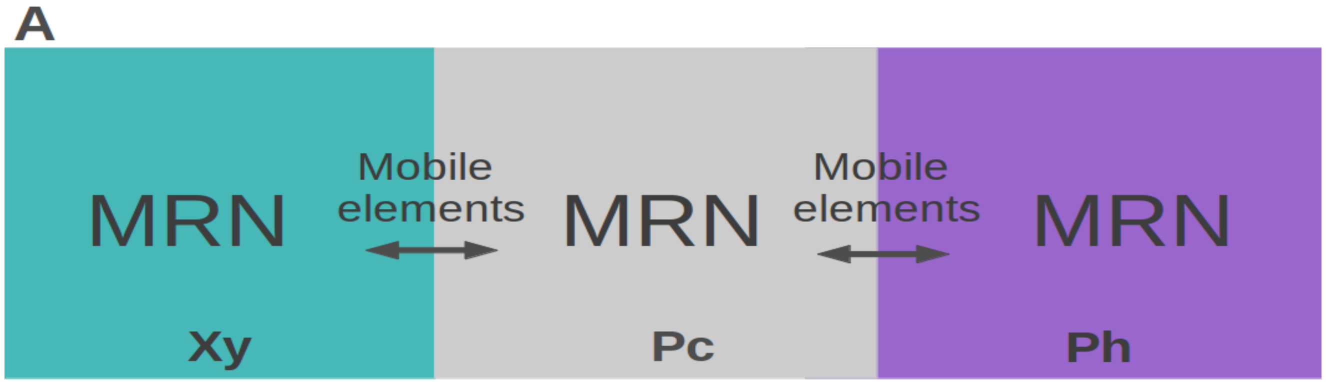
Network node	**Dynamical rule**
CK	2 If ipt=1 and ckx=0 1 If ipt=1 and ckx=1 0 else
CKX	1 If barr>0 or arf=2 0 else
AHKs	ahk=ck
AHPs	2 If ahk=2 and ahp6=0 and aarr=0 1 If ahk=2 and (ahp6+aarr<2) 1 If ahk=1 and ahp6<1 0 else
B-Type ARRs	1 If ahp>0 0 else
A-Type ARRs	1 If arf<2 and ahp>0 0 else

Benitez and Hejatko, *PLoS One*, 2013

Molecular Regulatory Networks Modeling

- ☐ Specifying ***mobile elements*** and their model behaviour





MRN

Mobile elements

MRN

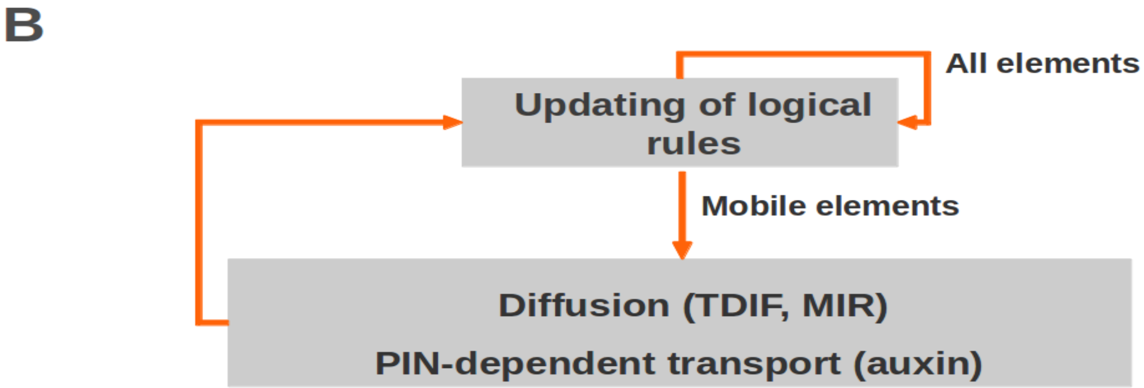
Mobile elements

MRN

Xy

Pc

Ph



All elements

Updating of logical rules

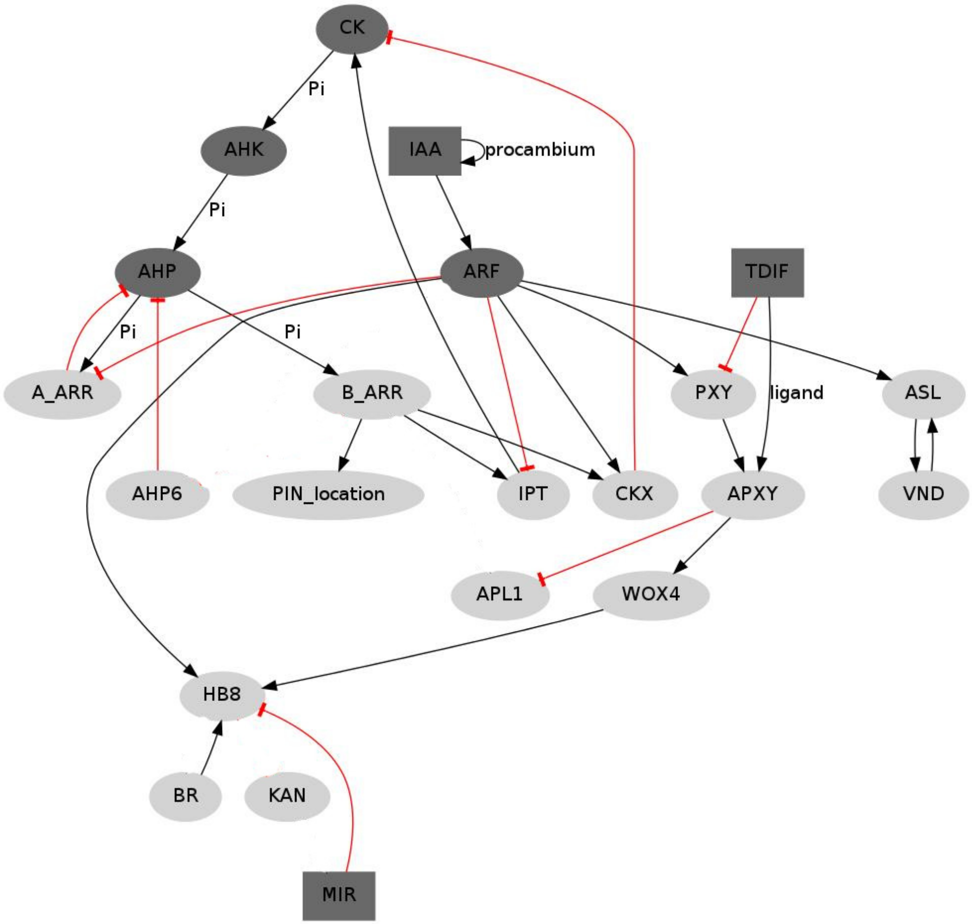
Mobile elements

Diffusion (TDIF, MIR)

PIN-dependent transport (auxin)

Molecular Regulatory Networks Modeling

- Preparing the ***first version*** of the model and its ***testing***



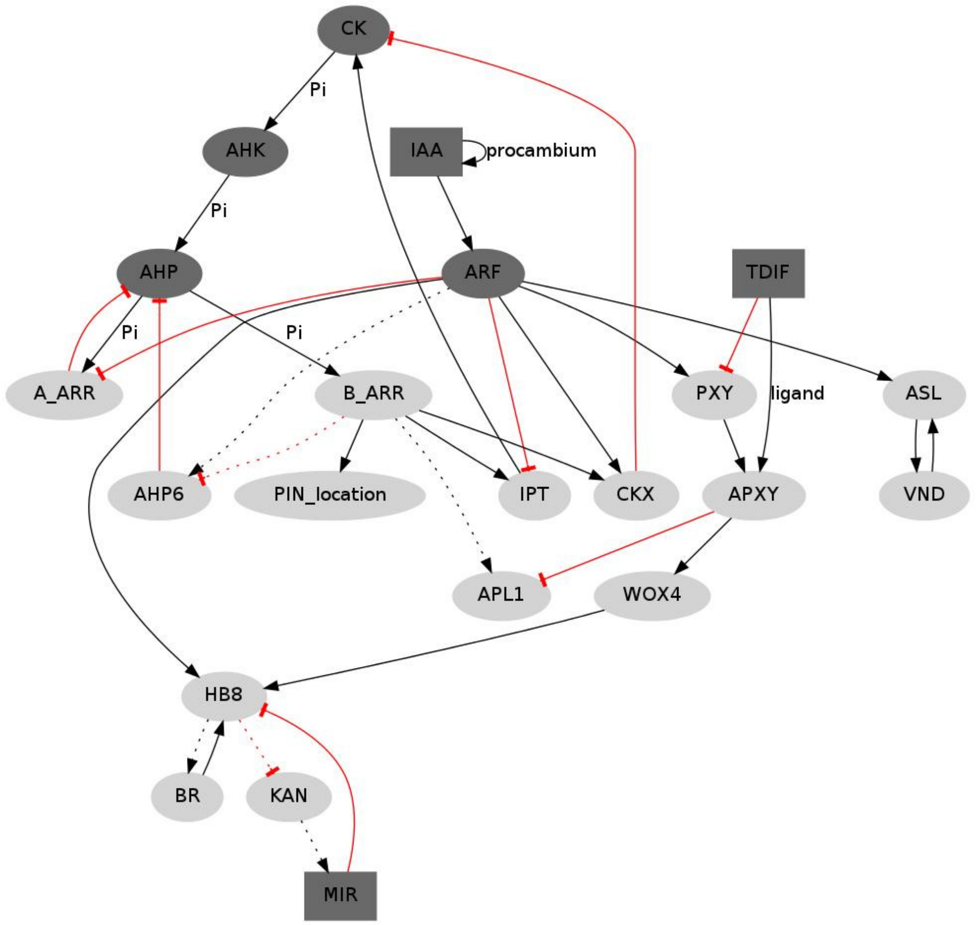
Molecular Regulatory Networks Modeling

- Specifying of missing interactions via ***informed predictions***

Interaction	**Evidence**	**References**
CK → PIN7 radial localization	Predicted interaction (could be direct or indirect)	
	Informed by the following data:	
	During the specification of root vascular cells in Arabidopsis thaliana, CK regulates the radial localization of PIN7.	[18]
	Expression of PIN7:GFP and PIN7::GUS is upregulated by CK with no significant influence of ethylene.	[18,20]
	In the root, CK signaling is required for the CK regulation of PIN1, PIN3, and PIN7. Their expression is altered in wol, cre1, ahk3 and ahp6 mutants.	[19]
CK→ APL	Predicted interaction (could be direct or indirect)	
	Consistent with the fact that APL overexpression prevents or delays xylem cell differentiation, as does CKs.	[21]
	Partially supported by microarray data and phloem-specific expression patterns of CK response factors.	(TAIR, ExpressionSet: 1005823559, [22])

Molecular Regulatory Networks Modeling

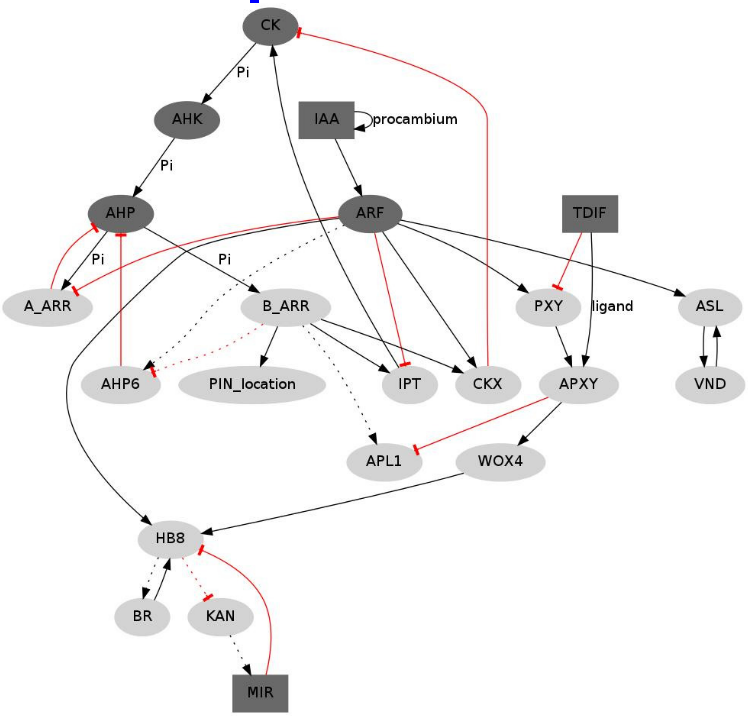
- Preparing the ***next version*** of the model and its ***testing***

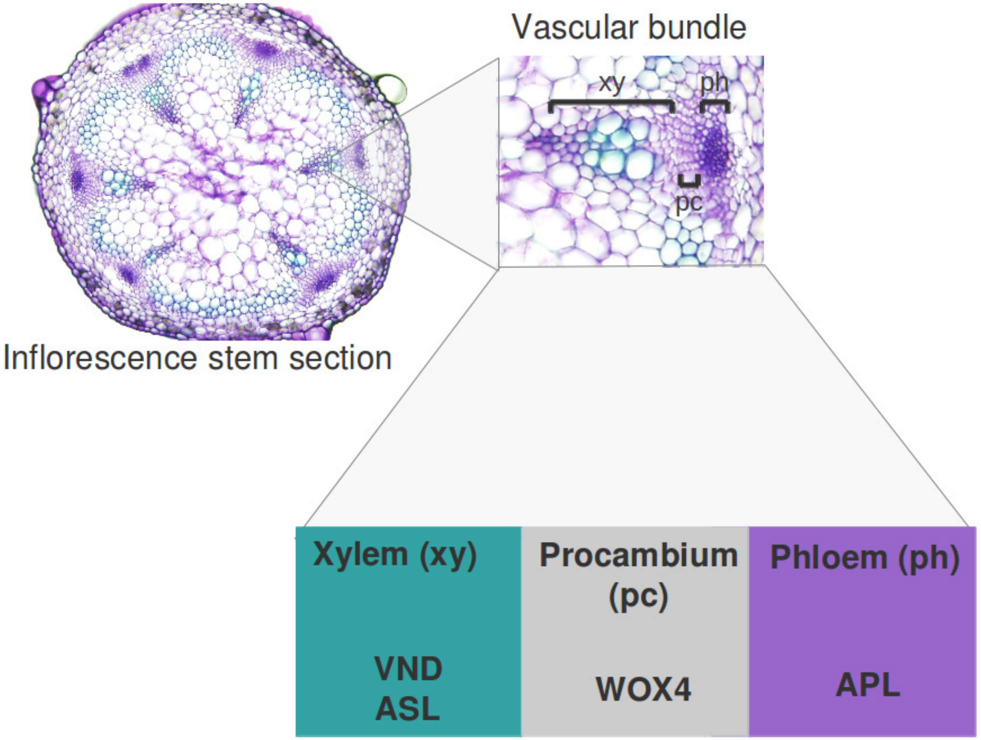


Benitez and Hejatko, *PLoS One*, 2013

Molecular Regulatory Networks Modeling

- ☐ ***Good model*** should be able to ***simulate reality***



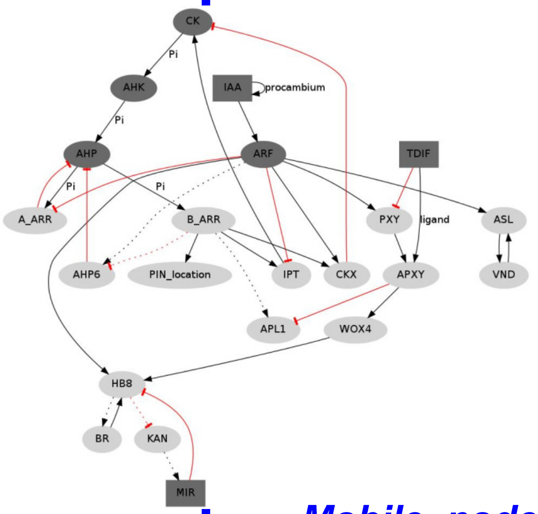


Xylem (xy)	Procambium (pc)	Phloem (ph)
VND ASL	WOX4	APL

Benitez and Hejatko, *PLoS One*, 2013

Molecular Regulatory Networks Modeling

- Formulating ***equations*** describing the ***relationships*** in the model



logical rule function

state in the time *t*

Static **nodes:** $g_n(t+1)=F_n(g_{n1}(t),g_{n2}(t),\ldots,g_{nk}(t))$

state in the time *t+1*

Amount if TDIF or MIR165 in cell *i*

Mobile nodes: $g_{(t+1)T\,[i]}= H(g_{(t)\,[i]}+ D\,(g_{(t)\,[i+1]}+g_{(t)\,[i-1]} - N(g_{(t)\,[i]}))-b)$

state in the time *t+1*

constant corresponding to a degradation term

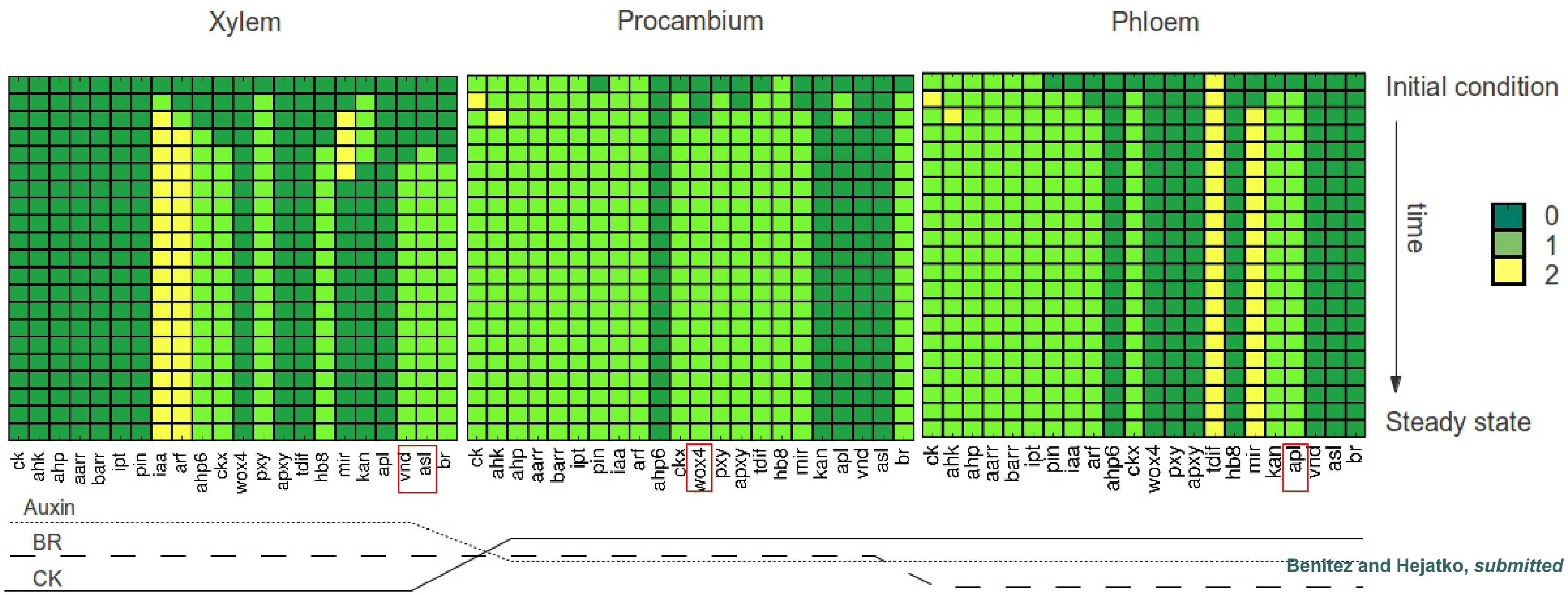
proportion of movable element

Molecular Regulatory Networks Modeling

- ☐ ***Good model*** should be able to ***simulate reality***

Static **nodes:** $g_n(t+1)=F_n(g_{n1}(t),g_{n2}(t),\dots, g_{nk}(t))$

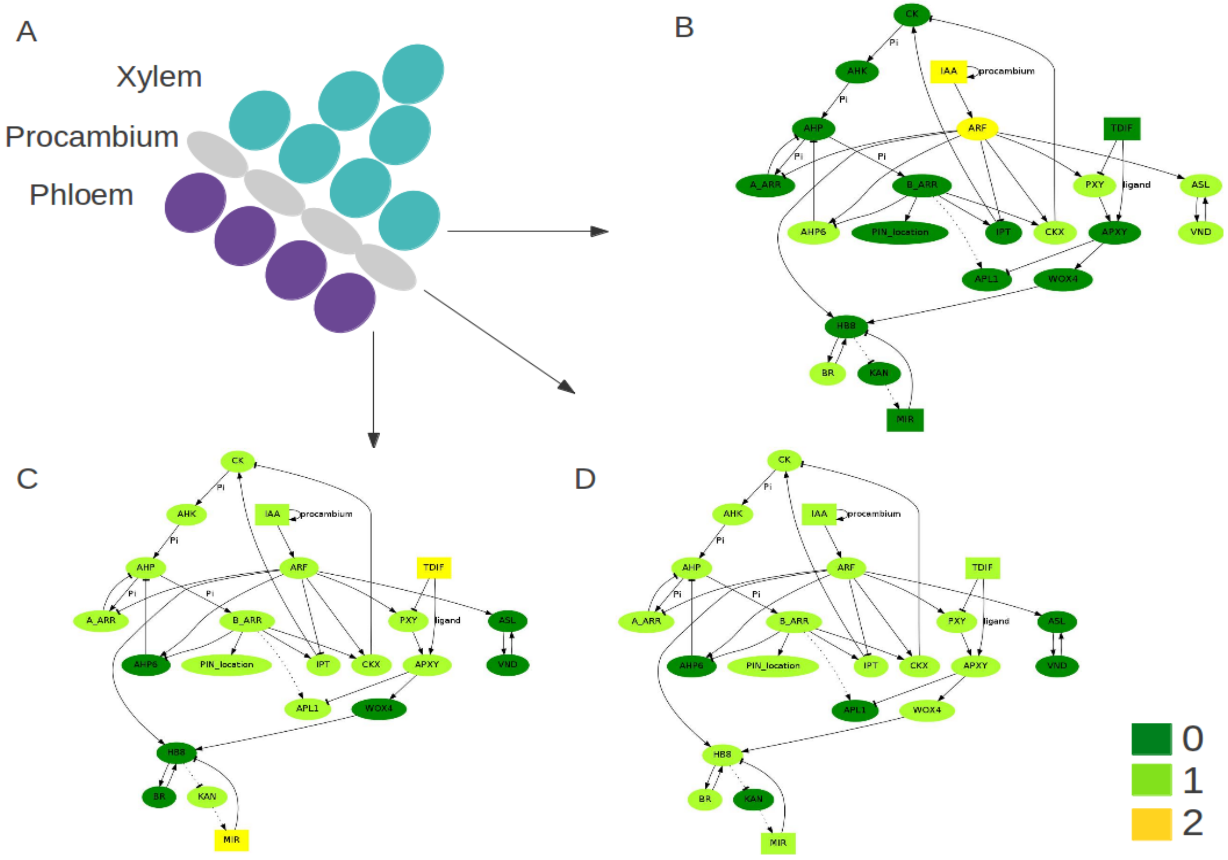
Mobile nodes**:** $g_{(t+1)T\,[i]} = H(g_{(t)\,[i]} + D\,(g_{(t)\,[i+1]}+g_{(t)\,[i-1]} - N(g_{(t)\,[i]}))-b)$



Benítez and Hejatko, *submitted*

Molecular Regulatory Networks Modeling

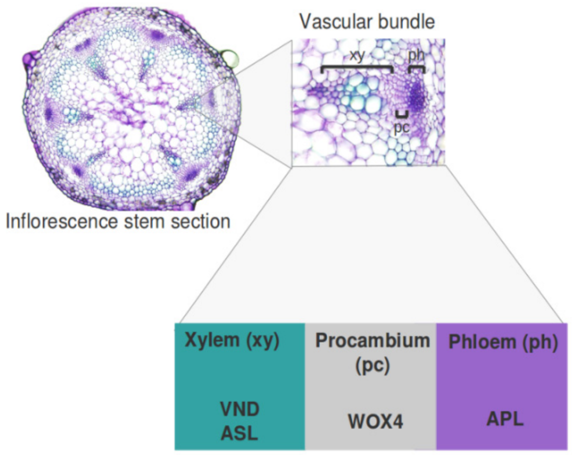
- The **good model** should be able to **simulate reality**

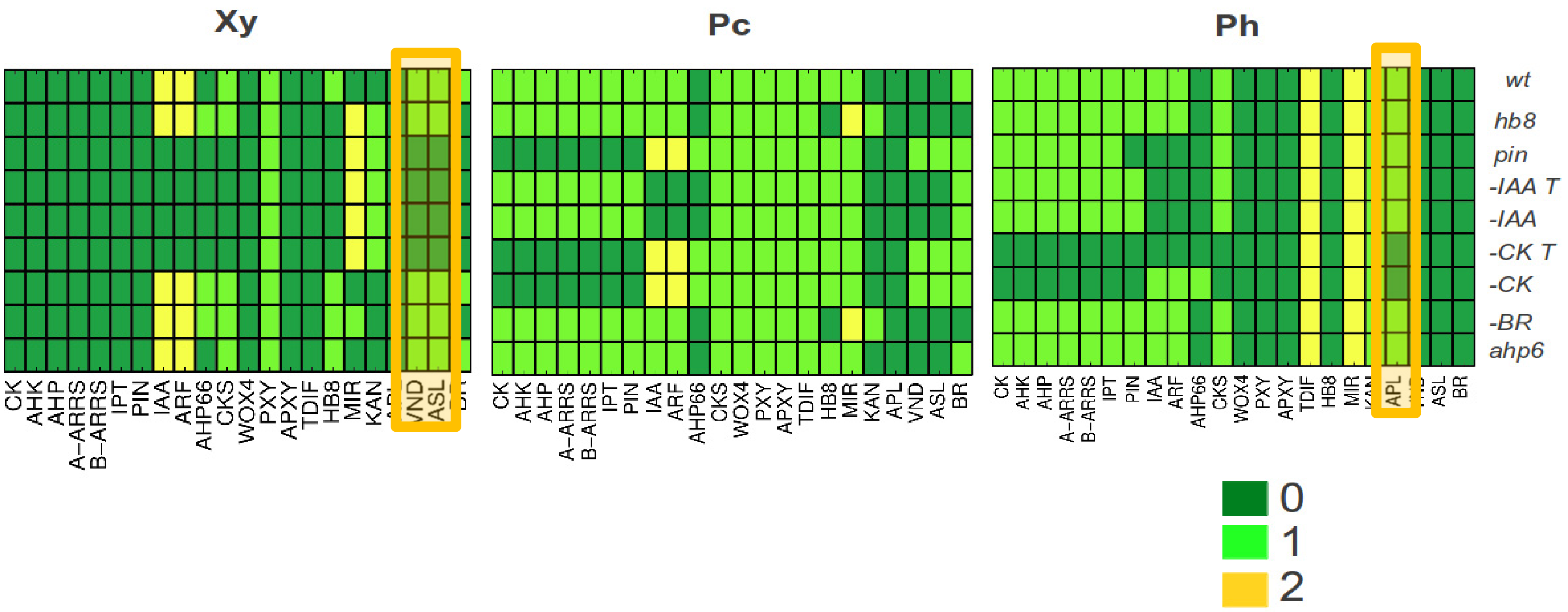


Benitez and Hejatko, *submitted*

Molecular Regulatory Networks Modeling

□ Simulation of ***mutants***

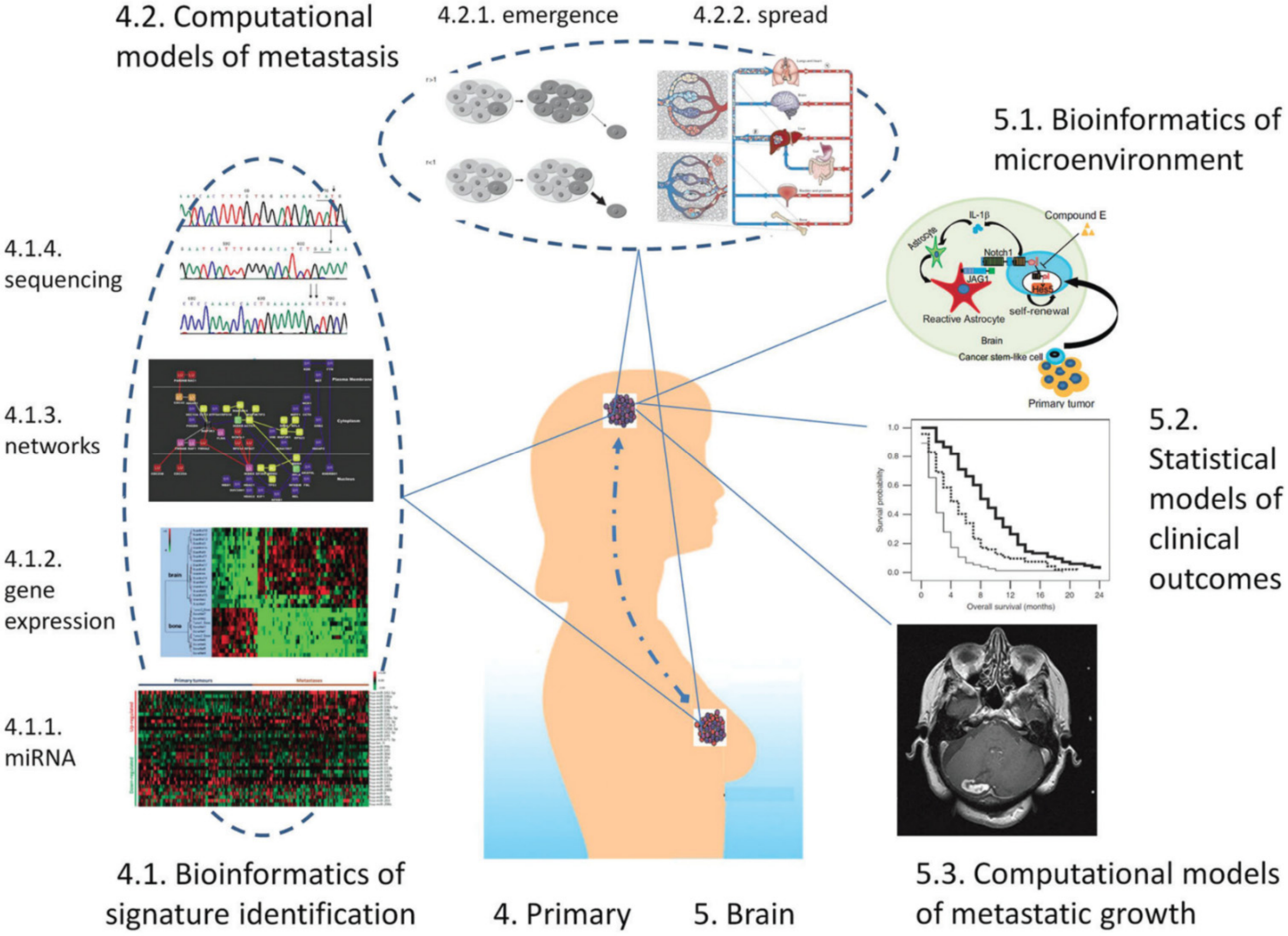




Outline

- Definition of Systems Biology
- Tools
  - Gene Ontology analysis
  - Bayesian Networks
  - Molecular/Gene Regulatory Networks Modeling
  - Inferring Gene Regulatory Networks from Large Omics Datasets

Systems Biology in Cancer Research



4.2. Computational models of metastasis

4.2.1. emergence

4.2.2. spread

5.1. Bioinformatics of microenvironment

4.1.4. sequencing

4.1.3. networks

4.1.2. gene expression

4.1.1. miRNA

5.2. Statistical models of clinical outcomes

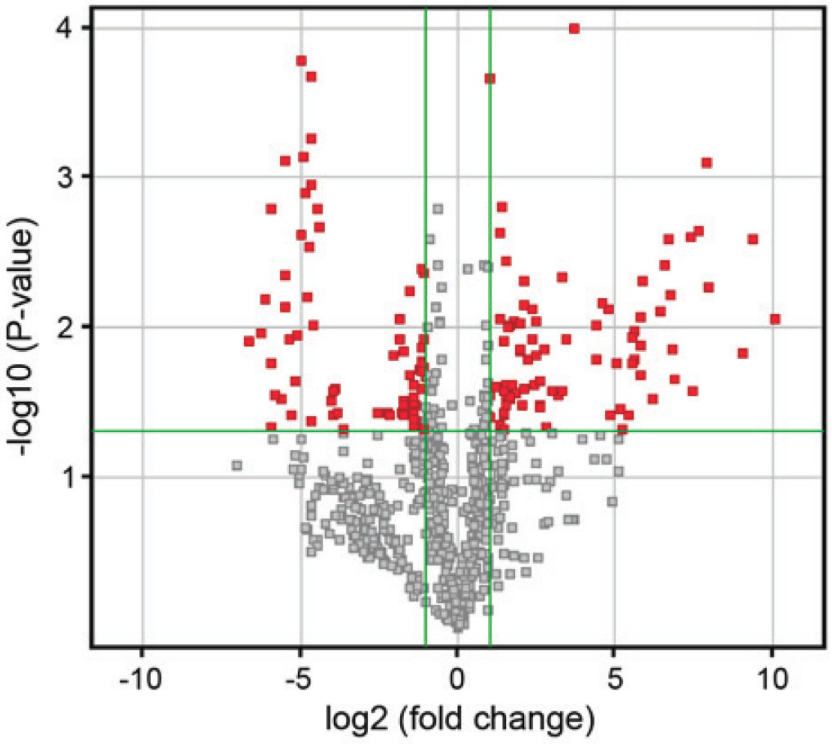
4.1. Bioinformatics of signature identification

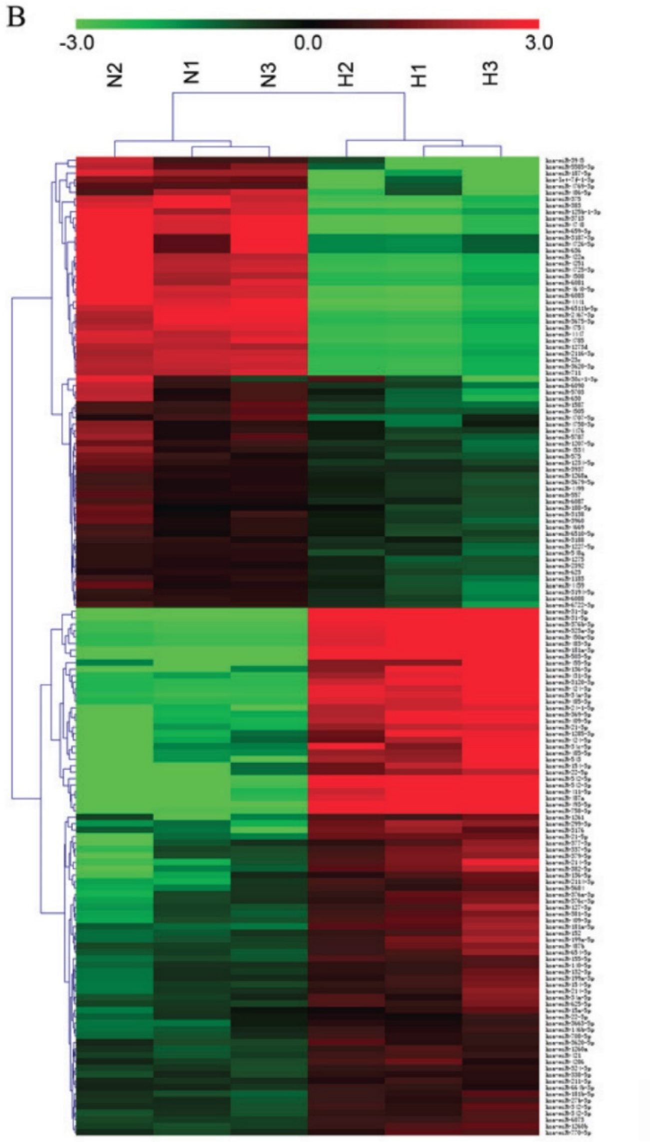
4. Primary

5. Brain

5.3. Computational models of metastatic growth

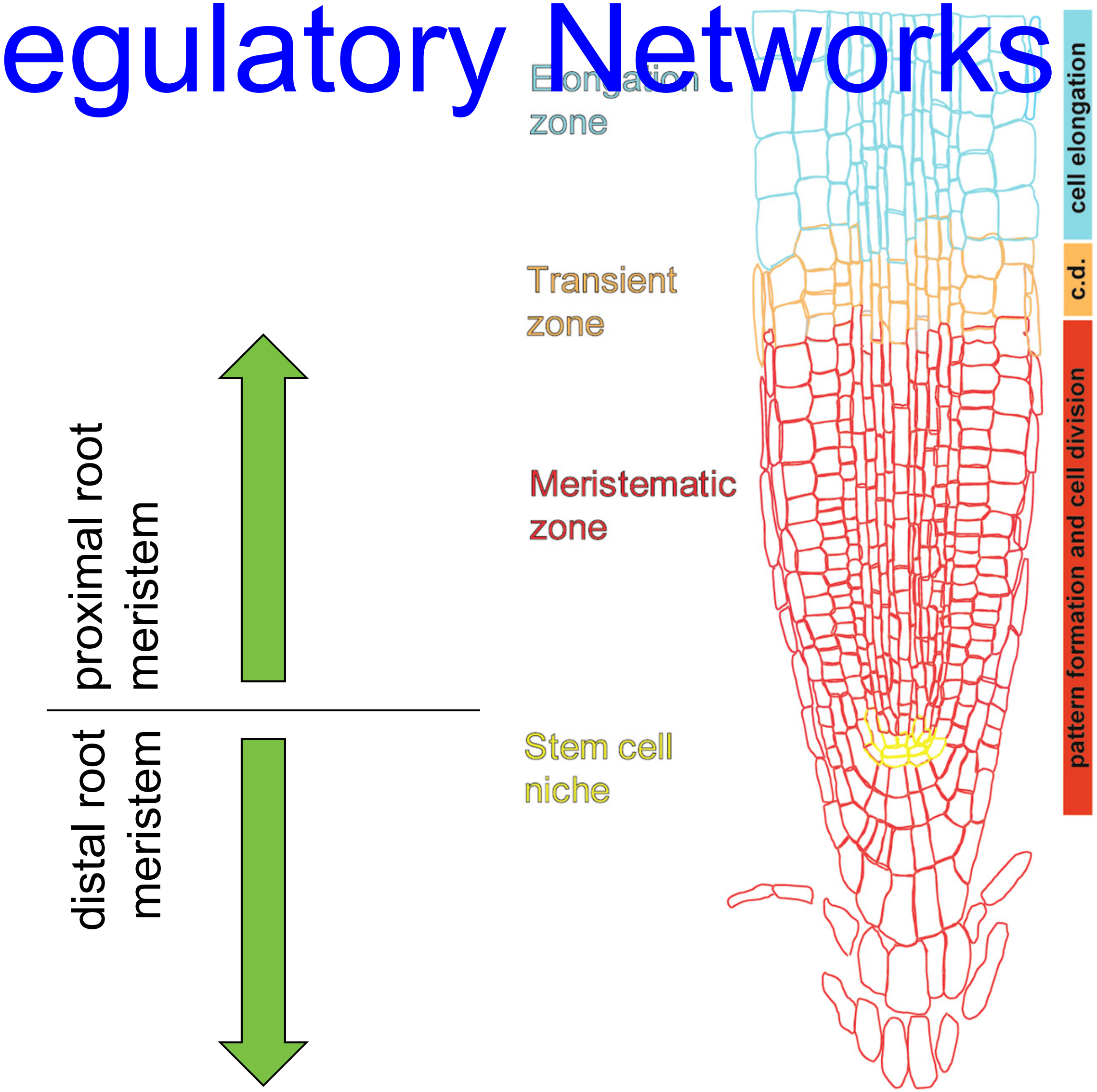
miRNA/mRNA Profiling





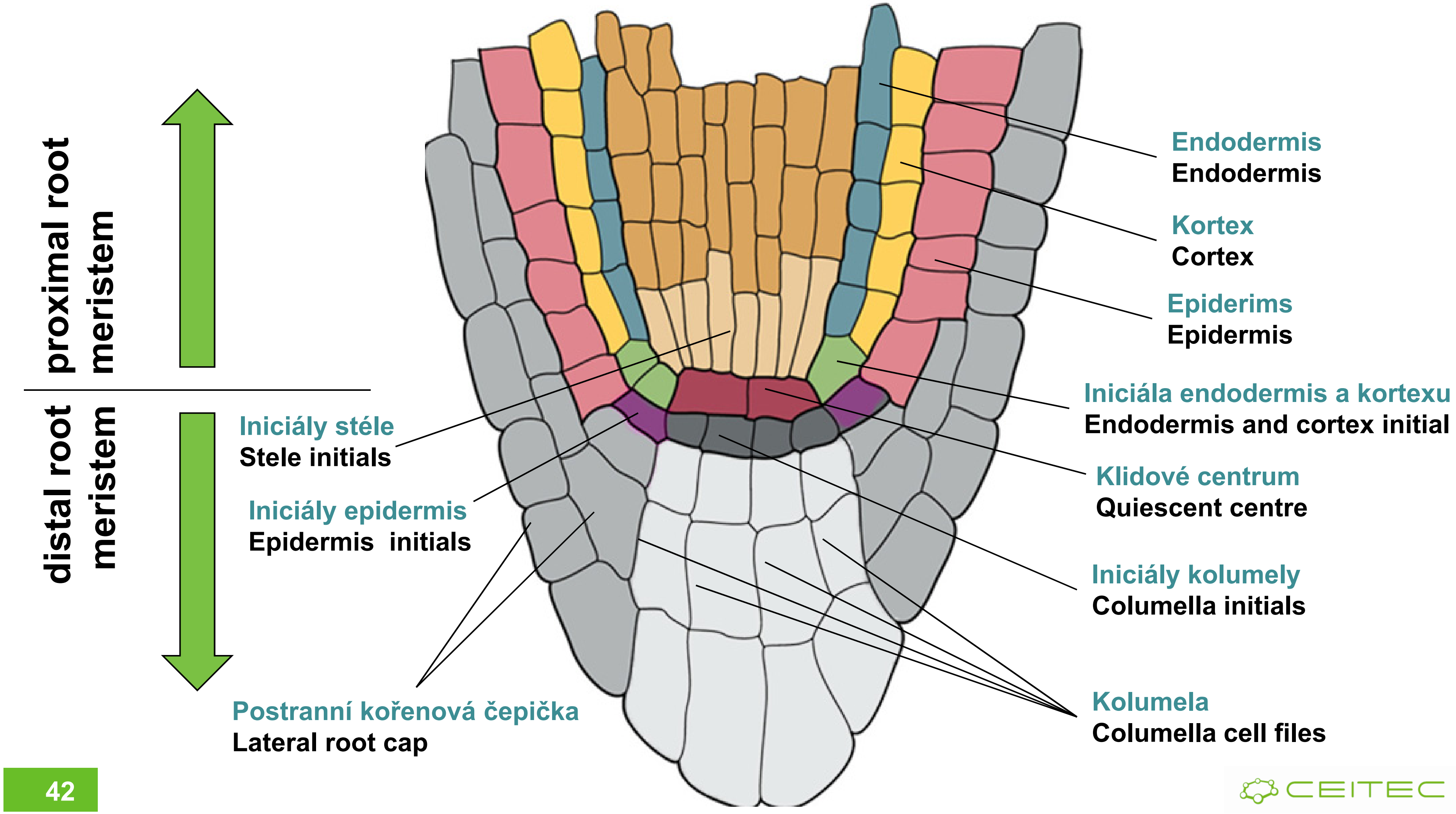
Guo et al., *Mol Med Reports,* 2017

Inferring Gene Regulatory Networks



Benkova and Hejatko, *Plant Mol Biol* (2008)

Gene Regulatory Networks



proximal root meristem

distal root meristem

Iniciály stéle
Stele initials

Iniciály epidermis
Epidermis initials

Postranní kořenová čepička
Lateral root cap

Endodermis
Endodermis

Kortex
Cortex

Epiderims
Epidermis

Iniciála endodermis a kortexu
Endodermis and cortex initial

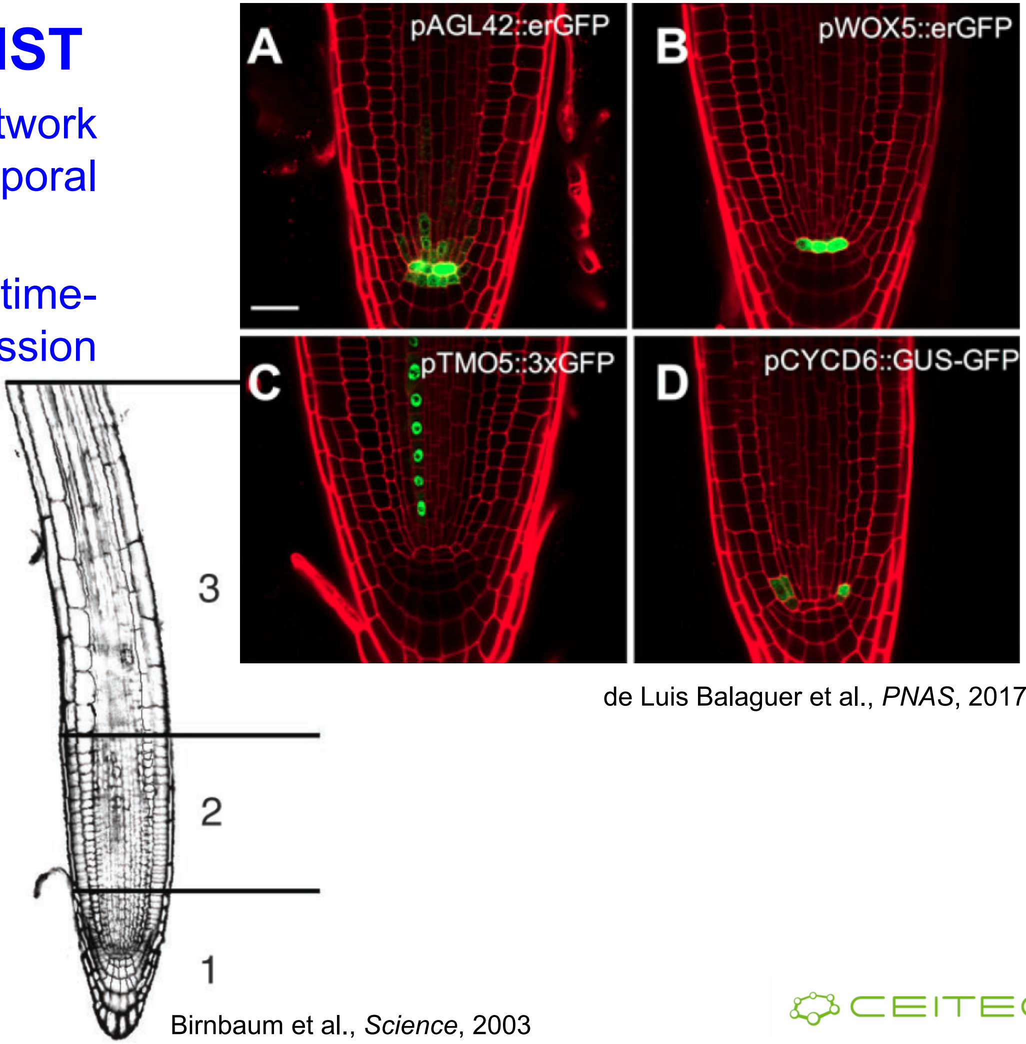
Klidové centrum
Quiescent centre

Iniciály kolumely
Columella initials

Kolumela
Columella cell files

Gene Regulatory Networks - GENIST

- Inferring GRNs via **GENIST**
    - **GE**ne regulatory **N**etwork **I**nference from **S**patio**T**emporal data algorithm
    - Combining spatial- and time-specific gene expression profiles



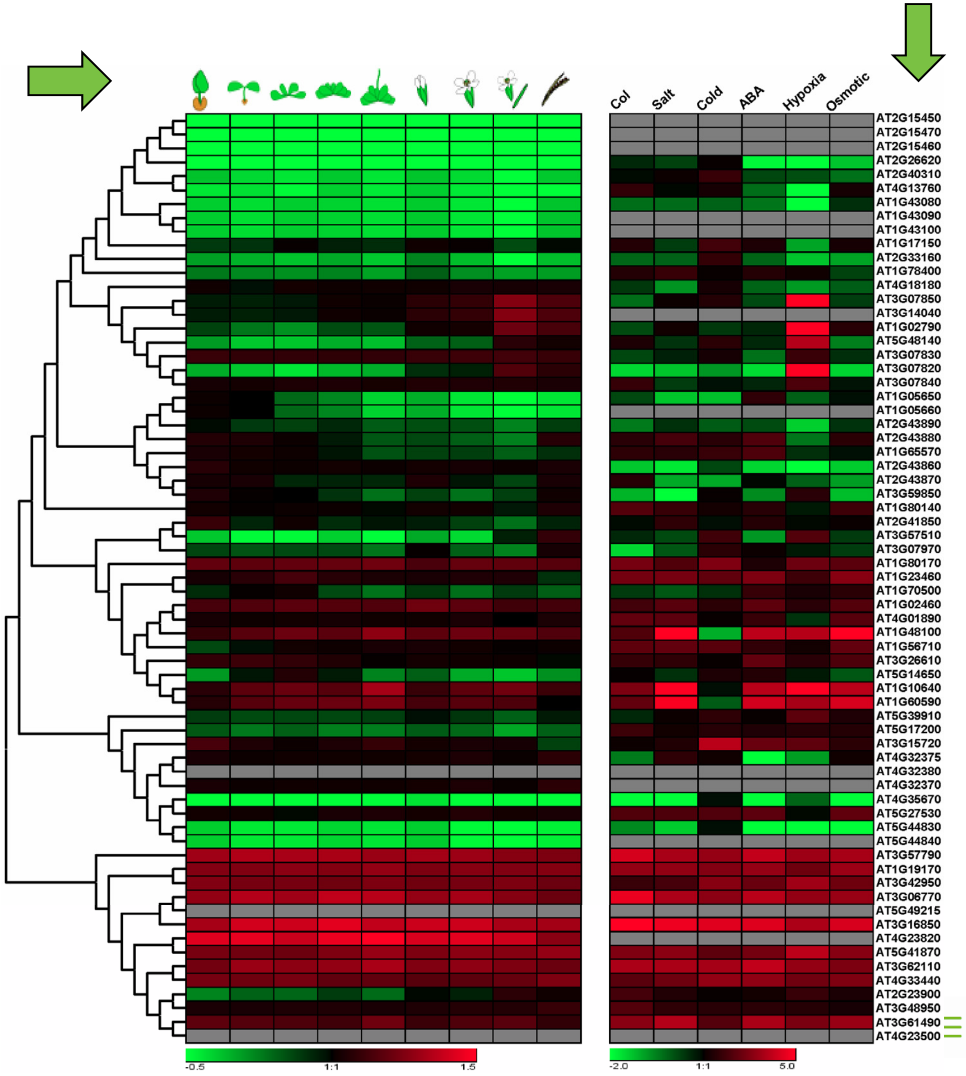
de Luis Balaguer et al., *PNAS*, 2017

Birnbaum et al., *Science*, 2003

Combining Large Omics Datasets

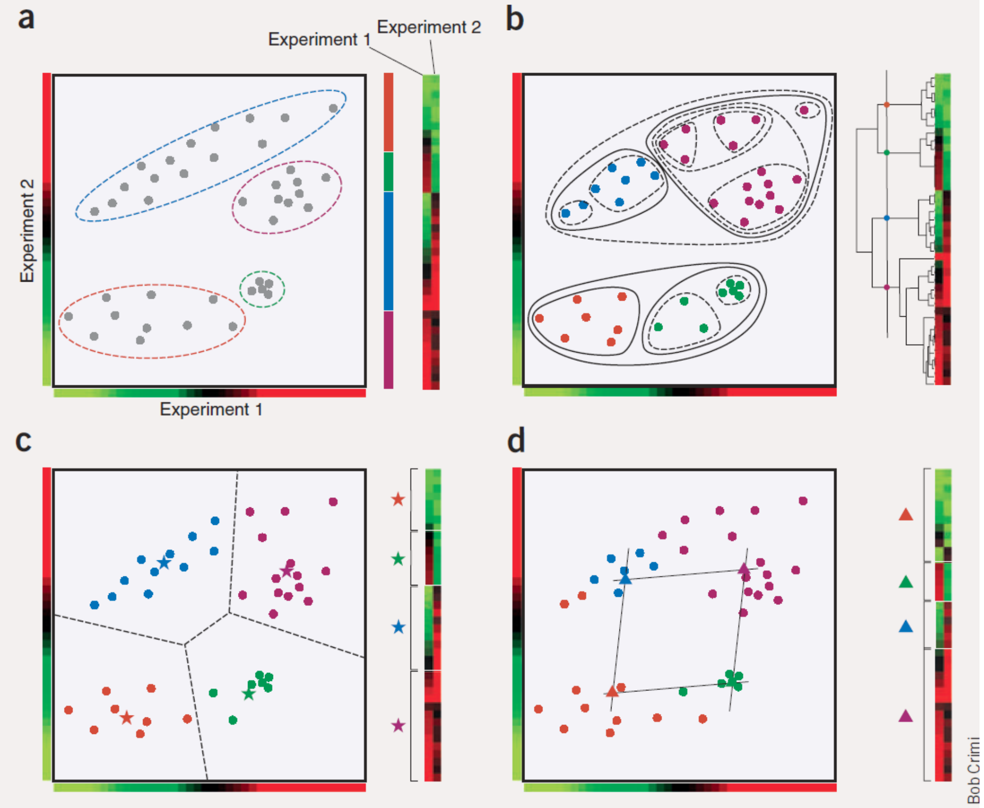
GENES

TISSUE/TIME



Gene Regulatory Networks - GENIST

- Inferring GRNs via **GENIST**
    - **Clustering of genes**
        - Expression similarity under various conditions/genetic backgrounds, time points, …
    - **Inferring intra-cluster connections**
        - **Selection** of potential **regulators** and **co-regulators**
            - Based on the time correlation in the change of expression and/or user specification
        - **Dynamic Bayesian Network modeling**



Haeseleer, *Computational Biology*, 2005

Gene Regulatory Networks - GENIST

- Inferring GRNs via **GENIST**
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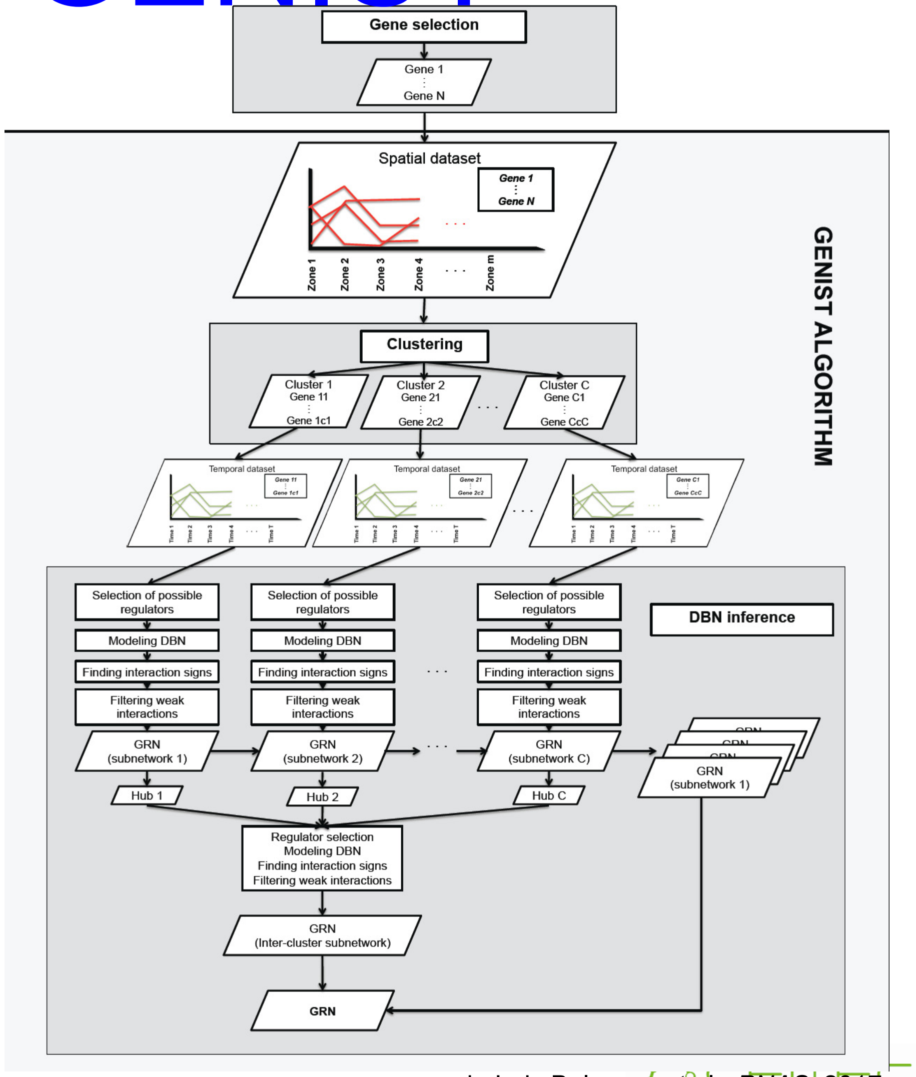
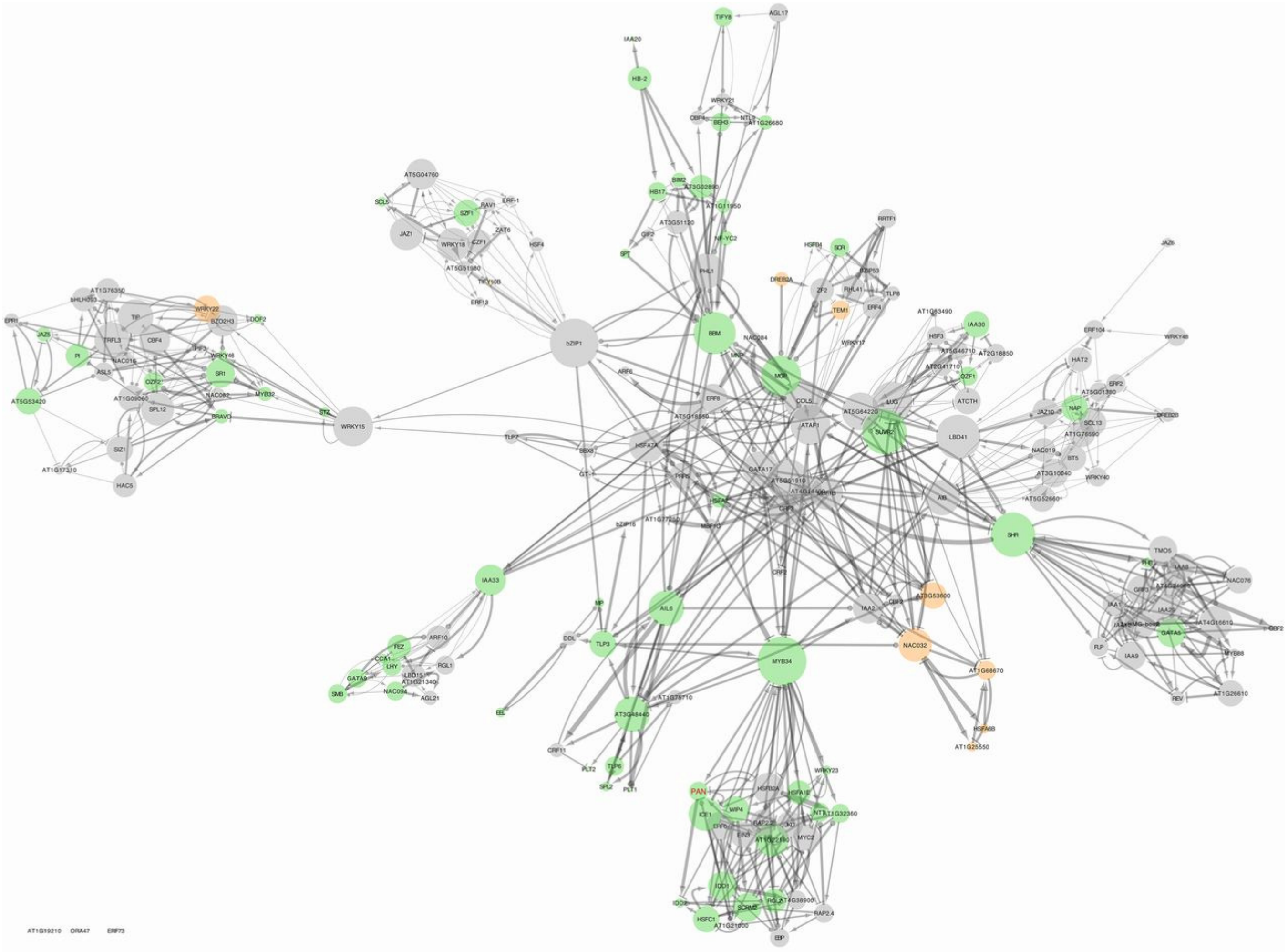


de Luis Balaguer et al., *PNAS*, 2017

Gene Regulatory Networks - GENIST



de Luis Balaguer et al., *PNAS*, 2017

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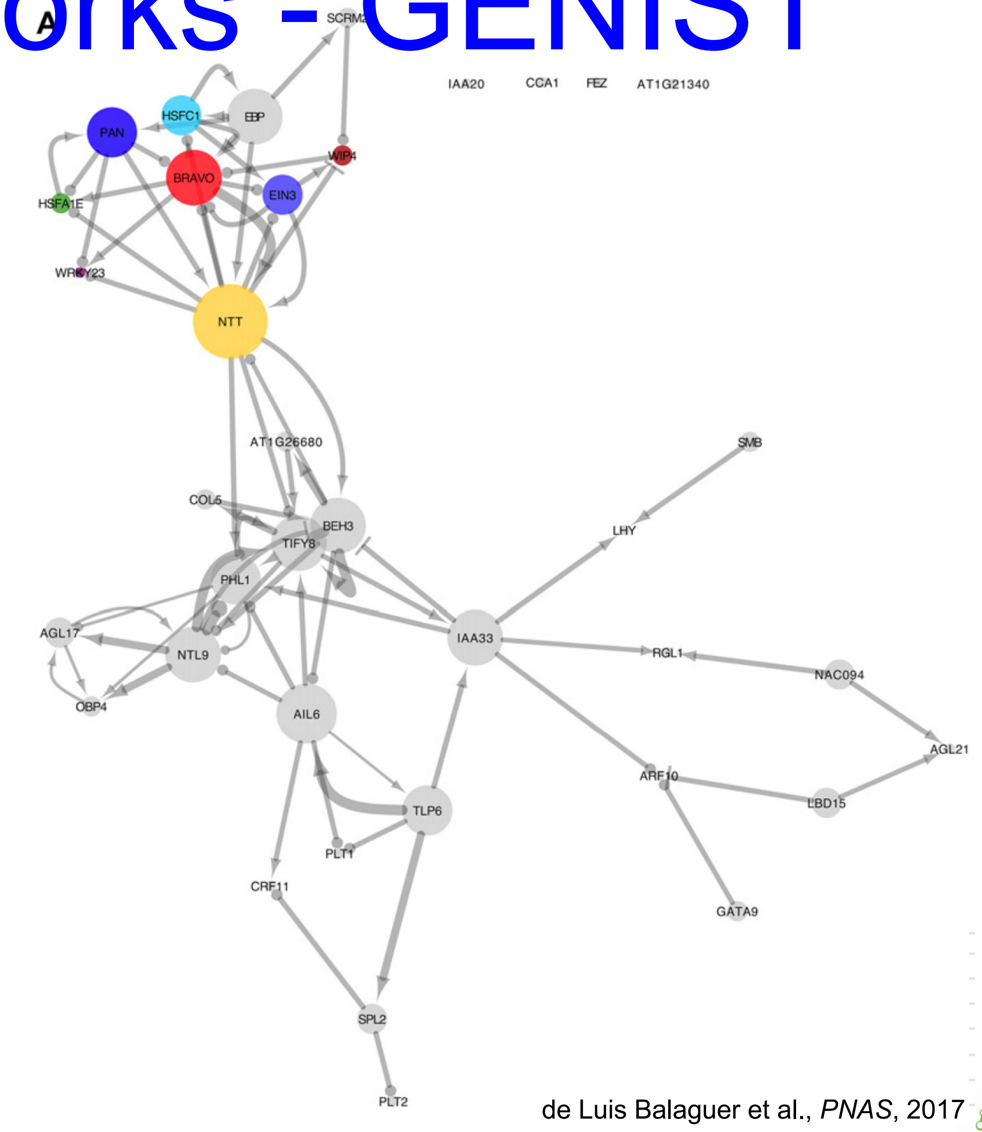
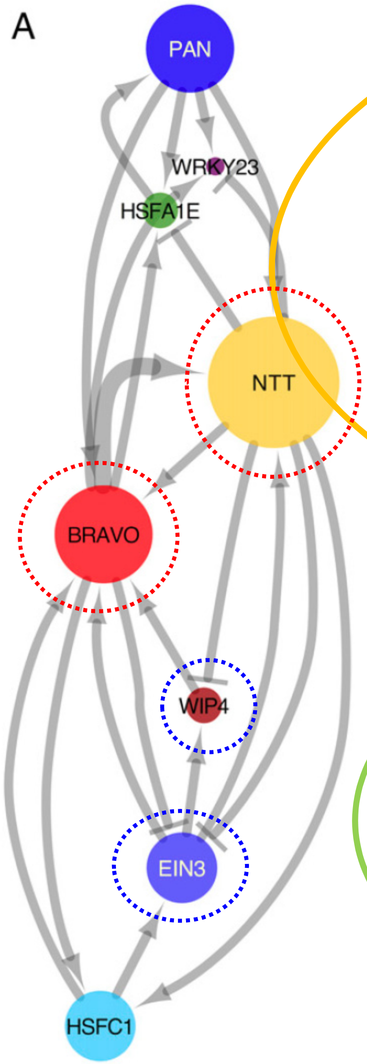
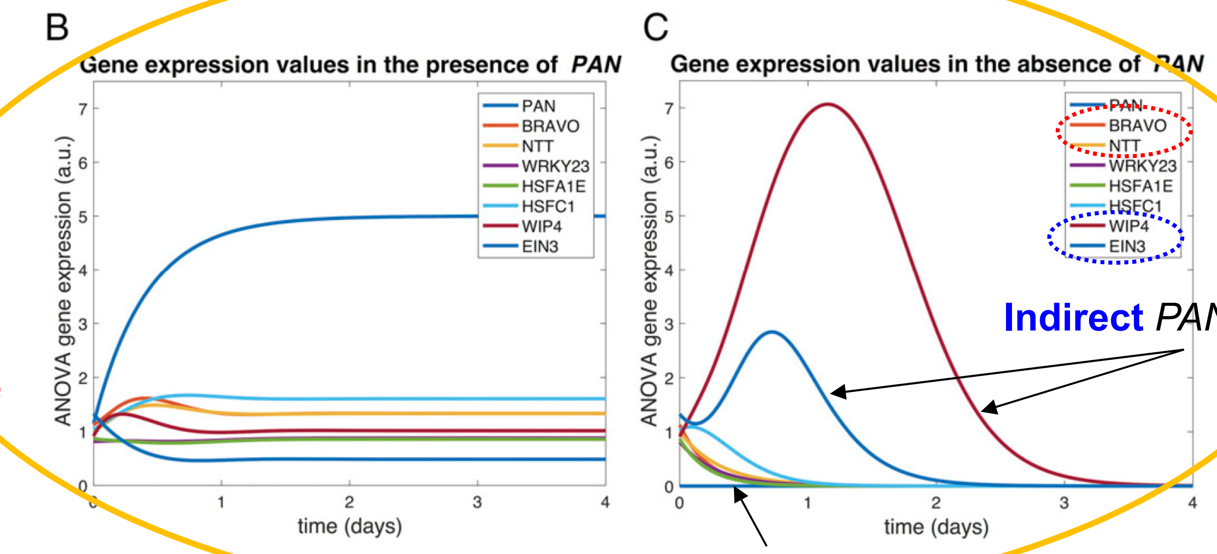


de Luis Balaguer et al., *PNAS*, 2017

Gene Regulatory Networks - GENIST

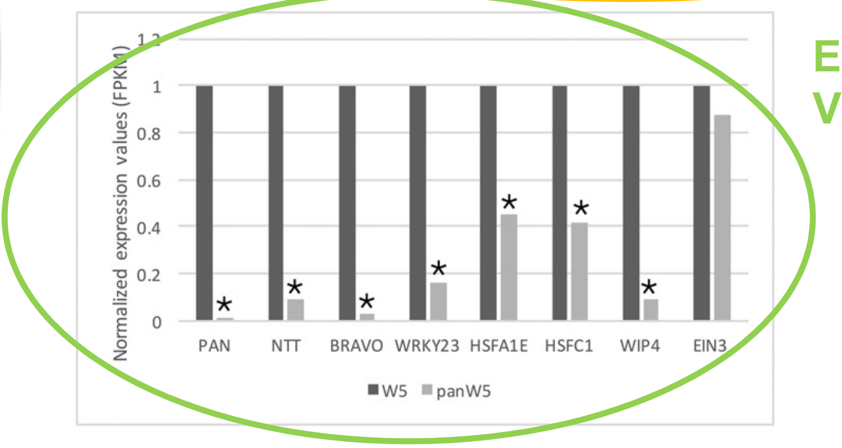
MODEL PREDICTION





Indirect *PAN* targets

feed-back loops



EXPERIMENTAL VERIFICATION

CEITEC

Summary

- Definition of Systems Biology
- Tools
  - Gene Ontology analysis
  - Bayesian Networks
  - Molecular/Gene Regulatory Networks Modeling
  - Inferring Gene Regulatory Networks from Large Omics Datasets

Discussion