The Sino-German Workshop on "Multiscale spatial computational systems biology" (MSCSB2015)

Understanding plant-pathogen interaction through integrative network analyses

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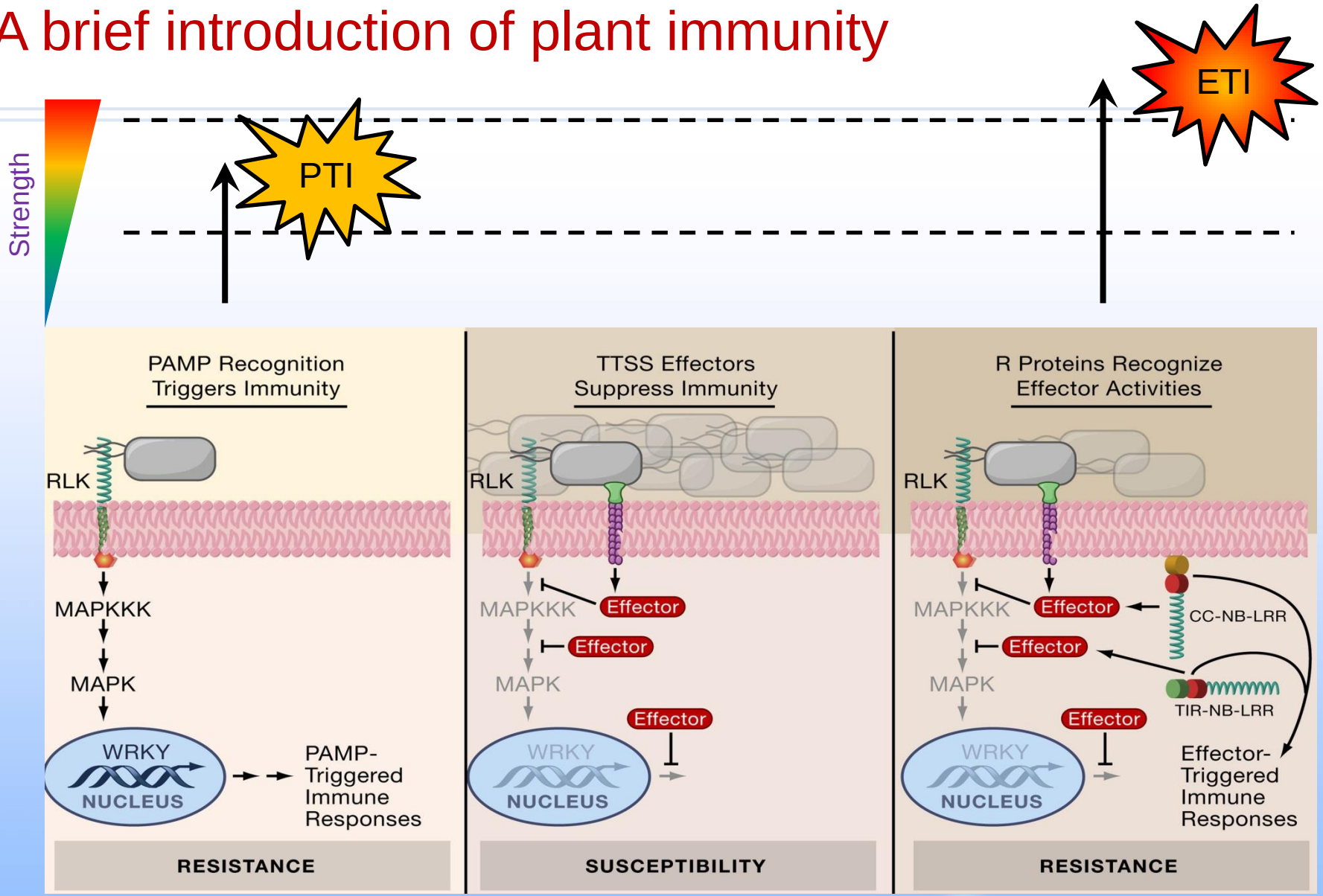
2015-10-09

Pathogens cause plant diseases that threaten crop yield and food security around the world

Hawaiian papaya plot (2011) showing diseased, devastated, nontransformed trees in the foreground and healthy transgenic trees behind

Dangl et al. (2013) Science, 341:746-751.

A brief introduction of plant immunity



*Chisholm et al. (2006). Cell, **124:** 803-814.*

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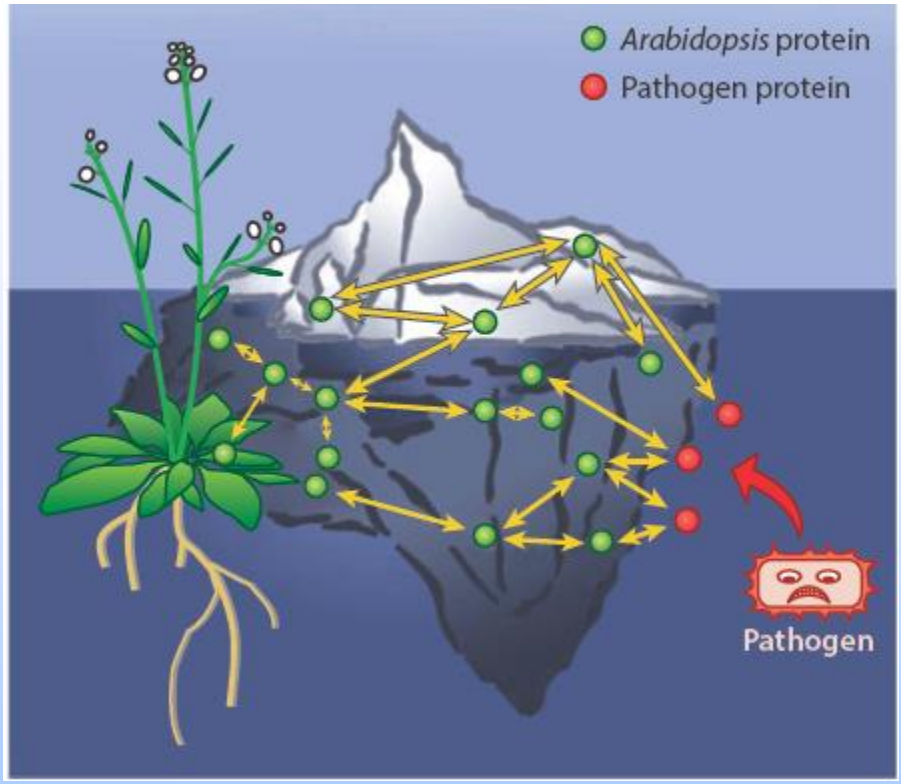
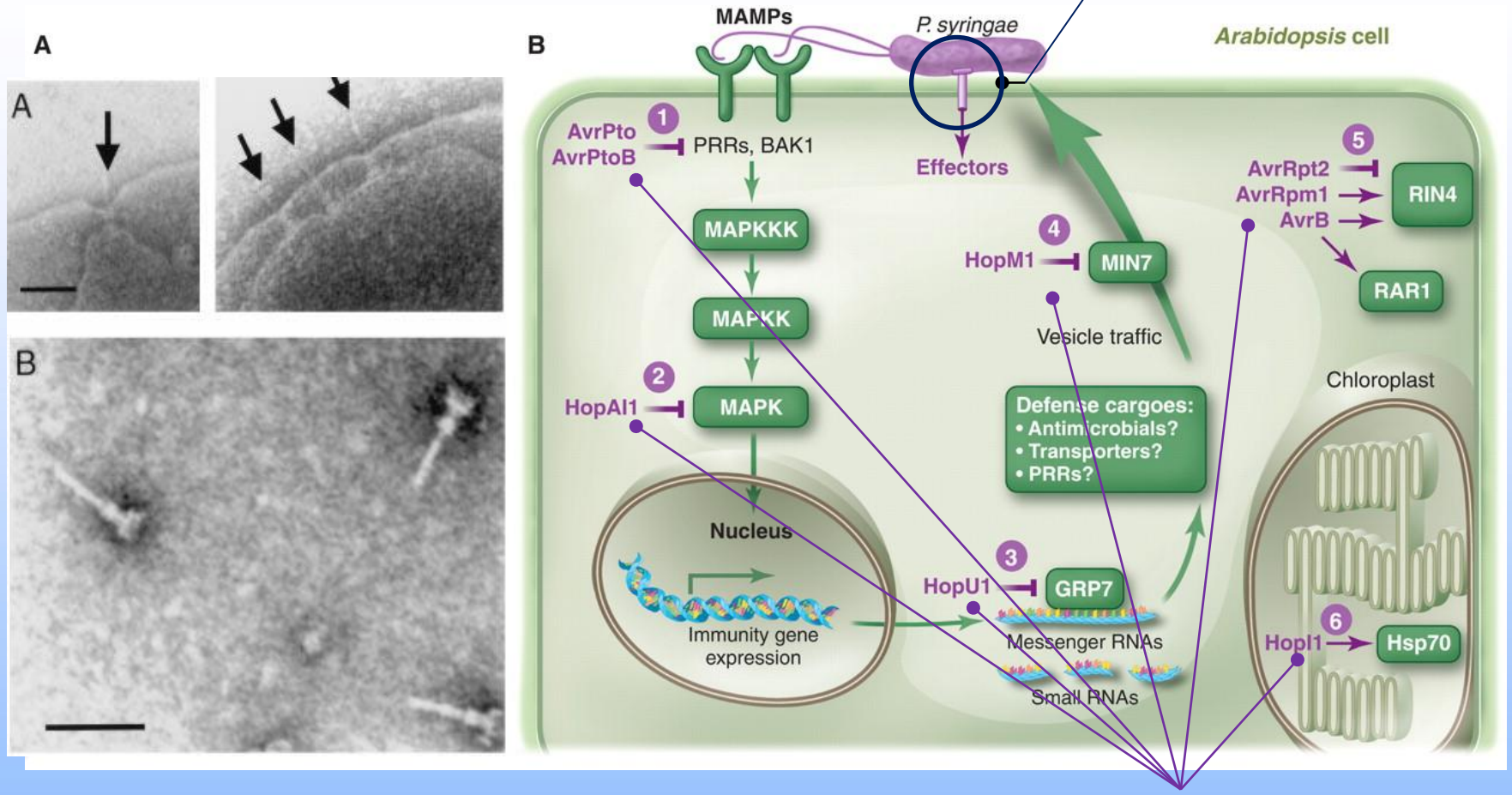
Computational study of plant-pathogen interaction is increasingly important



Braun et al (2013) Annu. Rev. Plant Biol. ***64:****161-187*

- *Database & algorithm development*
- *Network biology*
- *Integration of different omics data*
- *Structural interactome*

Computational identification of type-III secretion effectors from bacterial pathogen genomes



*Boller and He (2009) Science, **324:**742-4*

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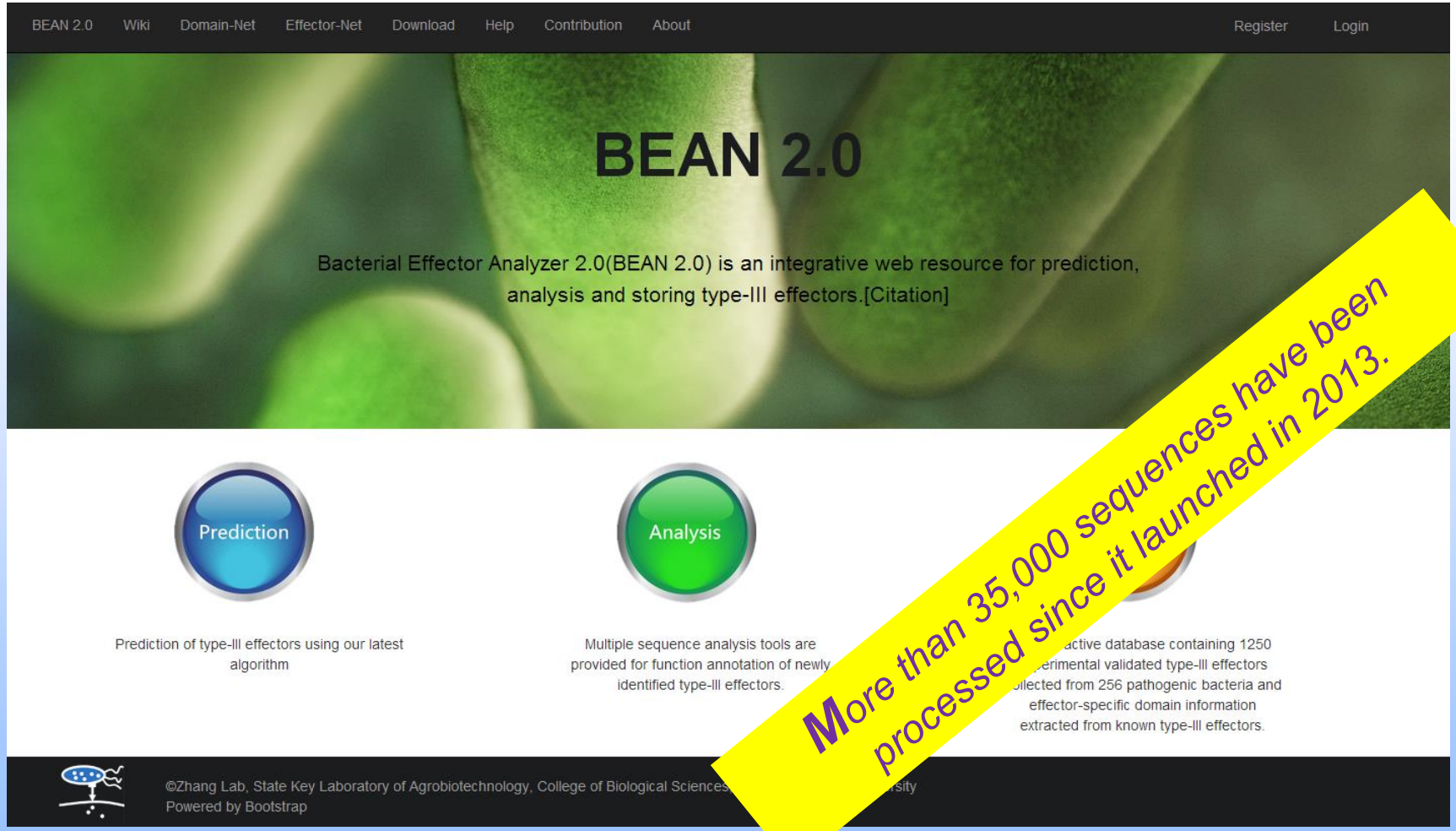
BEAN: A predictor of type-III secretion effectors (http://systbio.cau.edu.cn/bean)



More than 35,000 sequences have been processed since it launched in 2013.

Dong et al (2013), PLoS One, 8(2): e56632.
Dong et al (2015) , Database, bav064.

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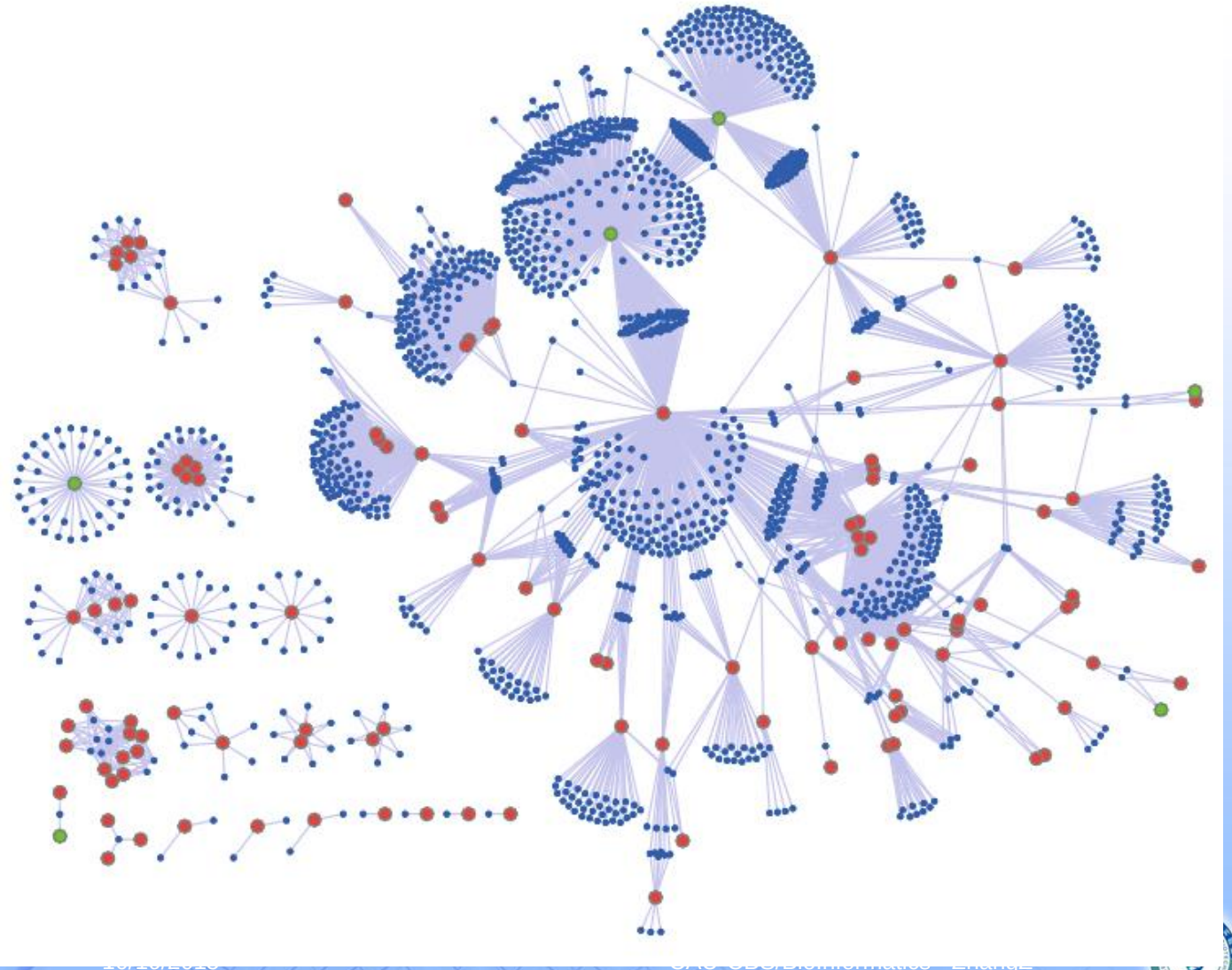
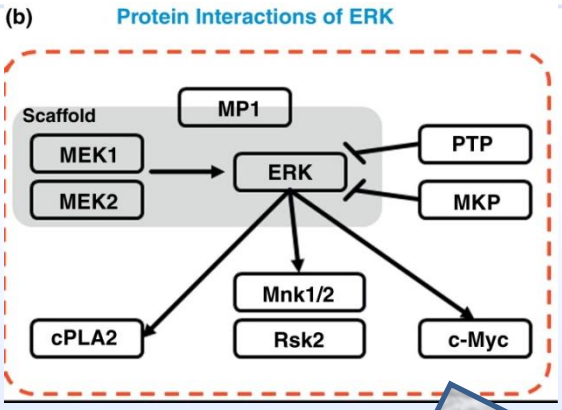
Prediction of plant-pathogen protein interaction networks

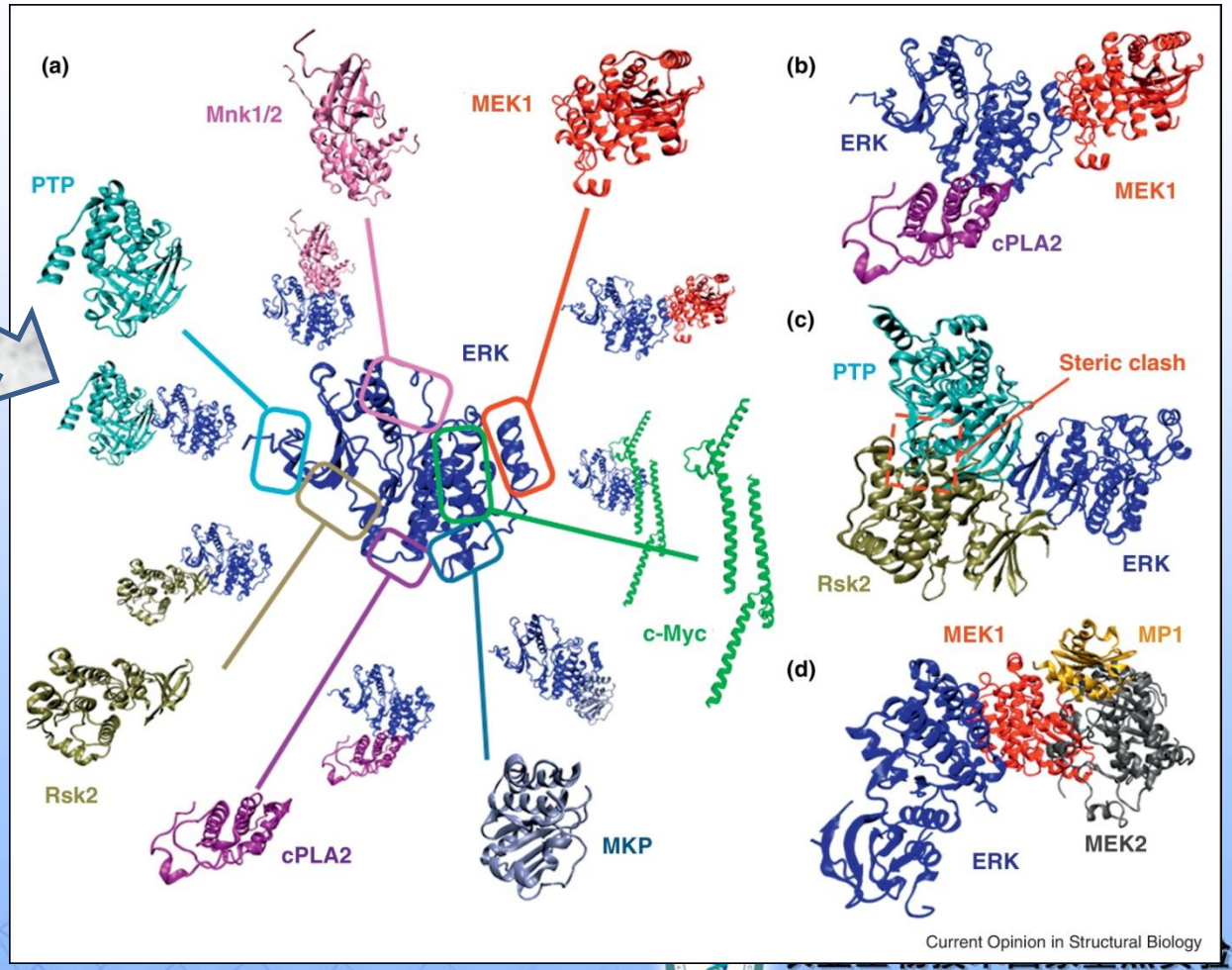


- *The interolog method*
- *The domain-based method*

*Li et al (2012) Amino acids, **42:** 2363–2371*

Construction of plant-pathogen structural interactome





Kuzu G, et al (2012). Curr Opin Struct Biol. ***22(3):*** *367-77.*

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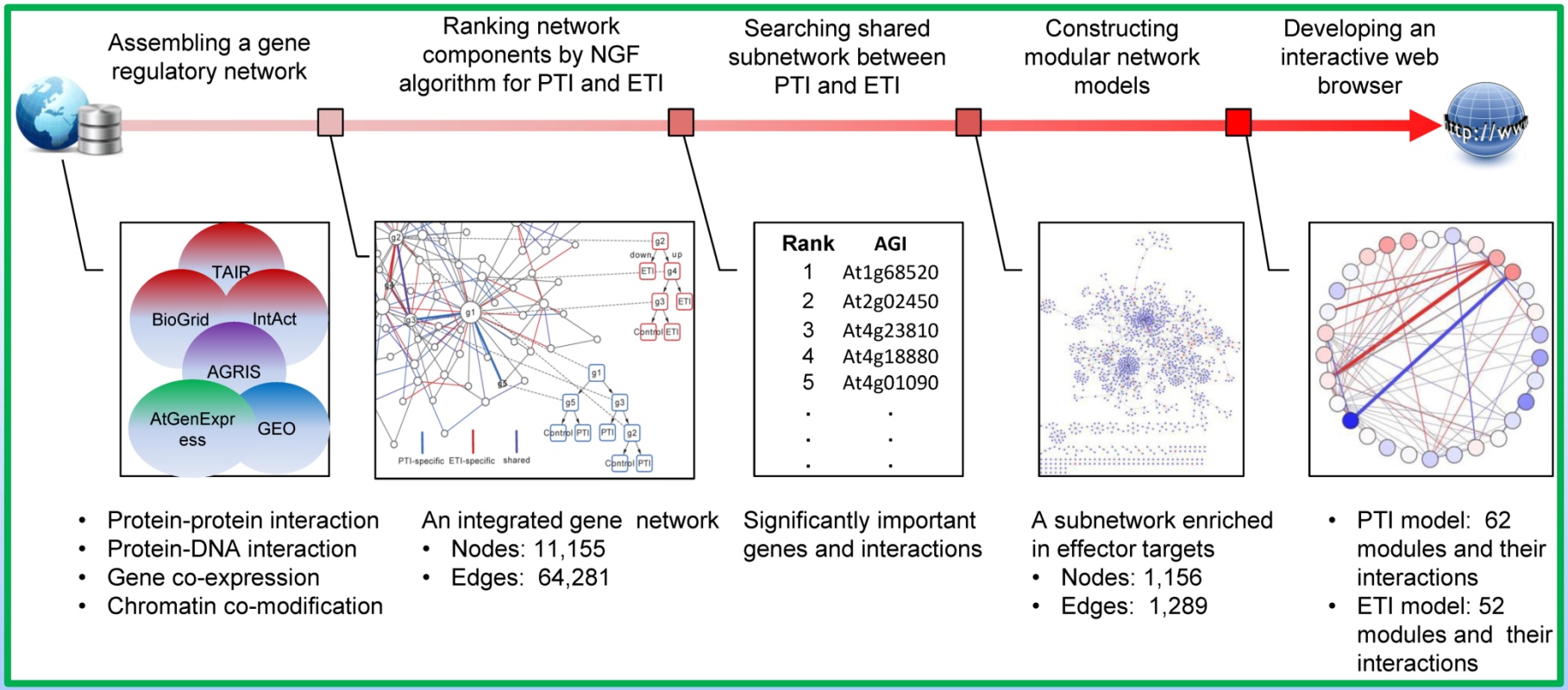
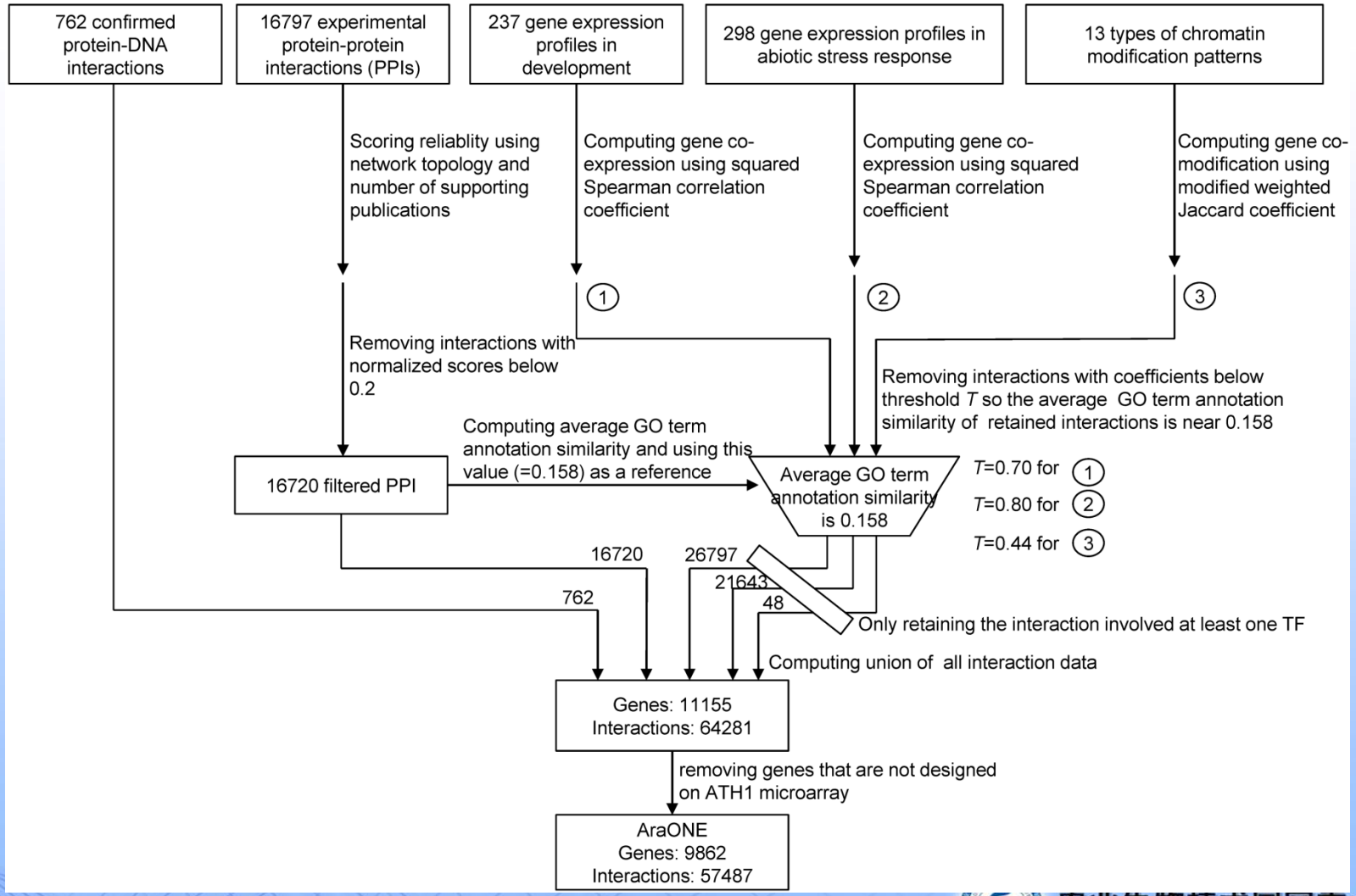
Integrative analyses of gene network organization in *Arabidopsis* immune responses

Arabidopsis thaliana
Pseudomonas syringae

Methodological overview of the integrative network analyses



Assembly of an Integrated Gene Network of Arabidopsis (AraONE)



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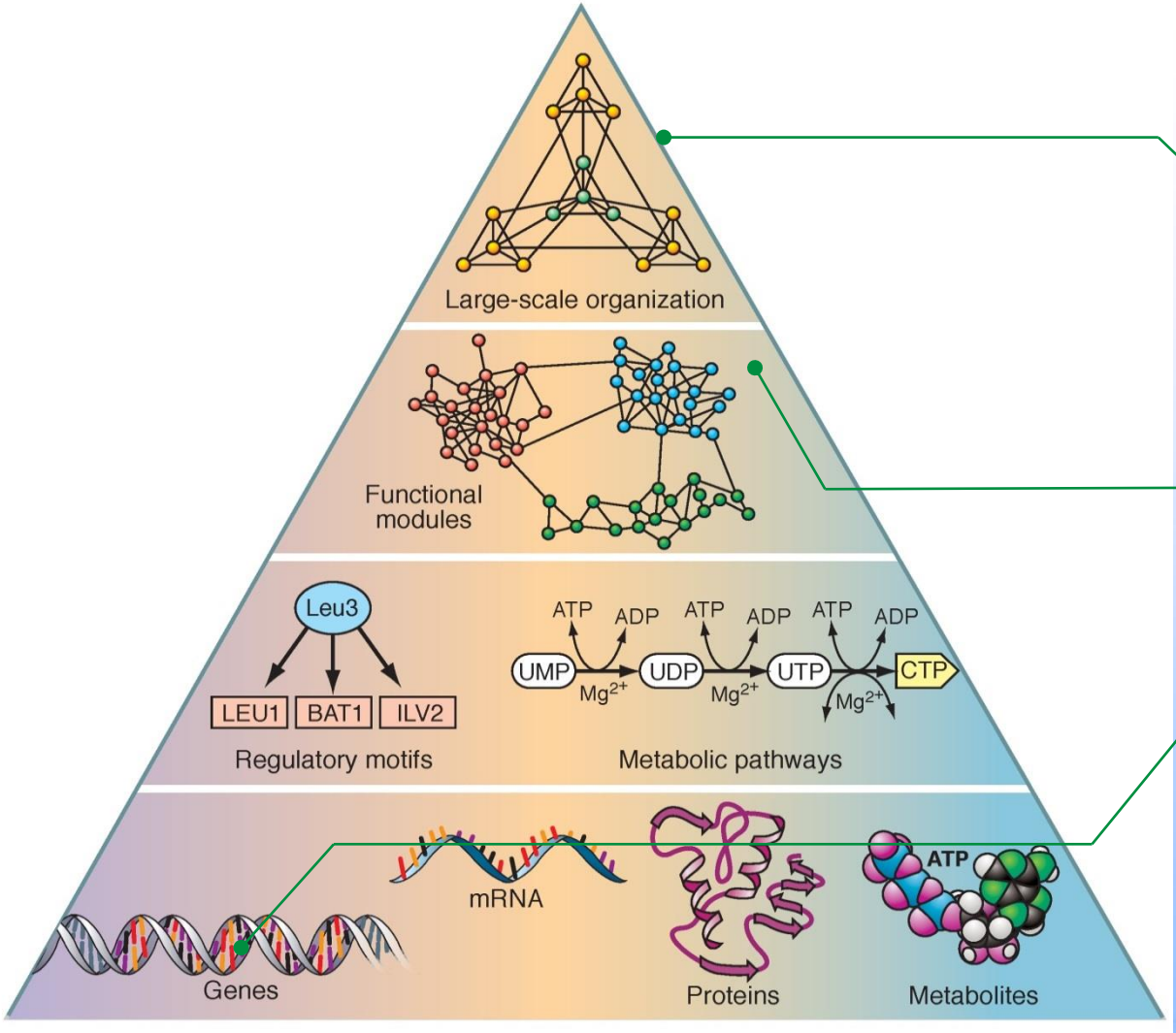
Comparison of PTI and ETI at three network resolutions



3 At the global network level

2 At the subnetwork level

1 At the node/edge level

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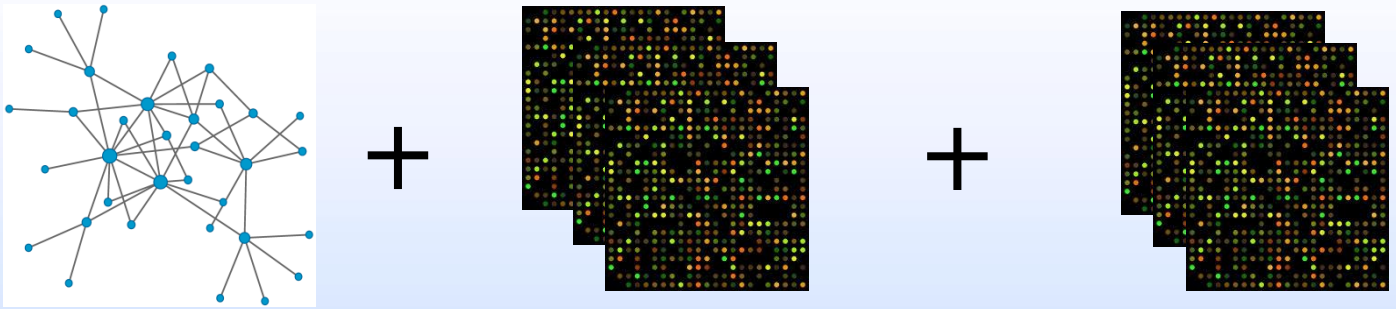
The input of Network-Guided Forest (NGF)

AraONE + PTI/ETI + control

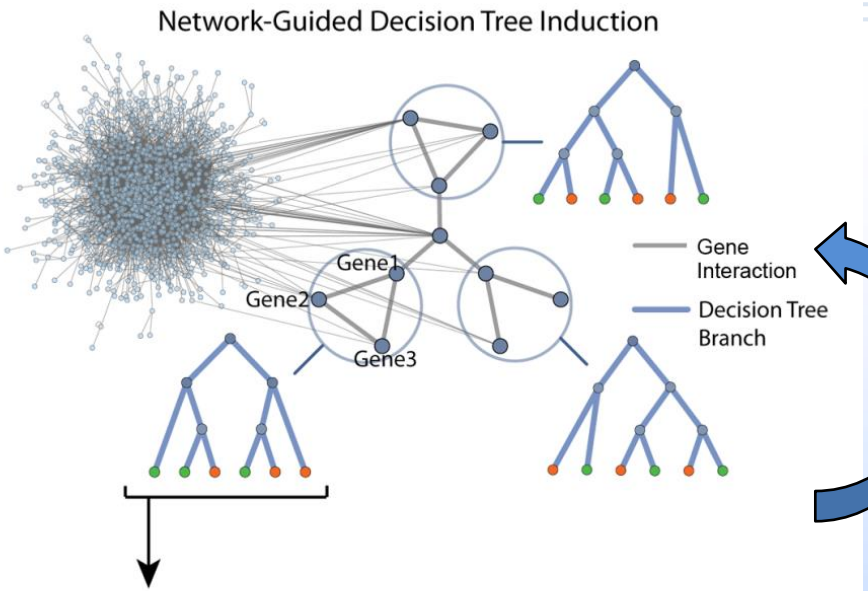


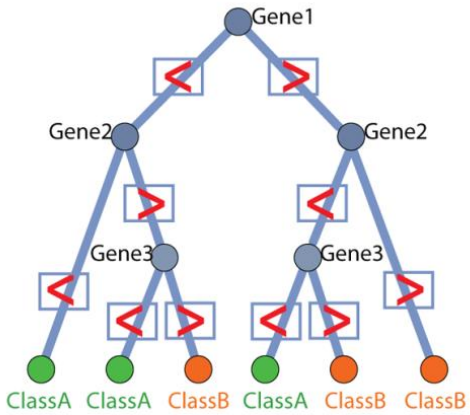
PTI : 69 gene expression profiles after different *P. syringae* PAMP treatments

ETI: 36 gene expression profiles in response to *P. syringae* carrying effector genes

Control: 65 gene expression profiles

The core idea of NGF





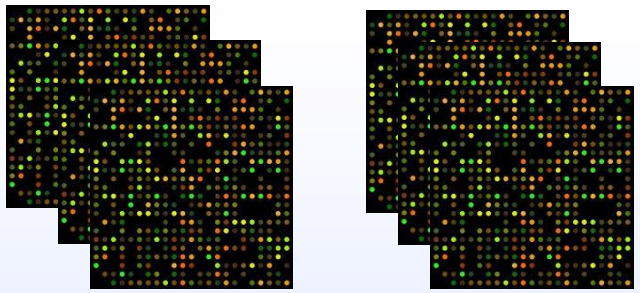
Decision Tree

Gene1	Gene2	Gene3	OUTPUT
DOWN	DOWN	DOWN	ClassA
DOWN	DOWN	UP	ClassA
DOWN	UP	DOWN	ClassA
DOWN	UP	UP	ClassB
UP	DOWN	DOWN	ClassA
UP	DOWN	UP	ClassB
UP	UP	DOWN	ClassB
UP	UP	UP	ClassB

(>) UP-REGULATED
(<) DOWN-REGULATED

Logic Function

PTI/ETI control group



repeat many times to generate many decision trees with different start points

- Developed from Random Forest
- The network is used to guide the growth of each decision tree

ClassA: PTI (or ETI)
ClassB: control group

*Dutkowski and Ideker (2011) PLoS Comput Biol. **7:** e1002180.*

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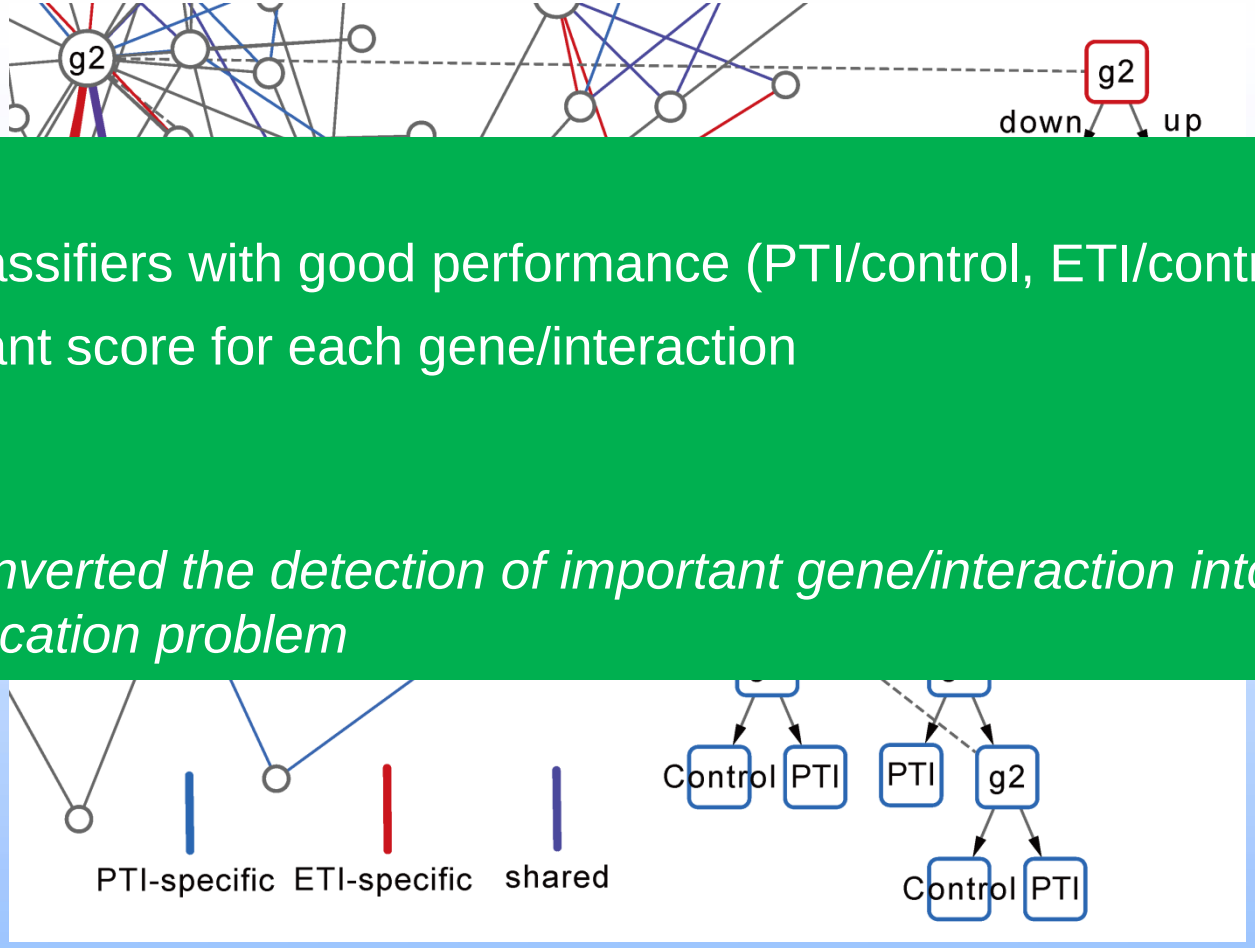
The output of NGF



Output:

- Two classifiers with good performance (PTI/control, ETI/control)
- Important score for each gene/interaction

Highlight:

- *We converted the detection of important gene/interaction into a classification problem*

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Top 20 genes in PTI versus control

AGI #	Name	Function in Plant Immunity	NGF IS
At1g68520	B-box domain protein 14, BBX14	SA mediated signaling pathway	0.660
At2g02450	long vegetative phase1, LOV1	unknown	0.573
At4g23810	WRKY DNA-binding protein 53, WRKY53	coordinates with WRKY… …l resistance	0.453
At4g18880	heat shock transcription factorA4A, HSFA4A	response to chi… …MPK3/MPK6 signaling	0.382
At4g01090		unkno…	0.379
At1g72610	germin-like protein GLP1	u…	0.377
At2g24570	WRKY DNA-binding protein 17, WRKY17	… …al resistance	0.361
At5g18150			0.346
At1g14370	PBS1-like 2 pr… PBL2	… AvrPphB; pbl2 mutant showed …antly reduced callose deposition in flg22 …d elf18 treatment	0.340
At1g69770	ch…	involved in defense response-related DNA methylation	0.303
At3g260…		unknown	0.276
At3g4678…	…onally active	unknown	0.275
At5g04870	…dependent protein …se 1, CPK1	control onset of cell death triggered by RPS2 and RPM1	0.271
At2g38470	…WRKY DNA-binding protein 33, WRKY33	key transcriptional regulator of and hormonal and metabolic responses to necrotroph	0.268
At1g34310	auxin response factor 12, ARF12	unknown	0.259
At3g17700	cyclic nucleotide gated channel 20, CNGC20	regulation of plant-type hypersensitive response	0.257
At2g29100	glutamate receptor 2.9, GLR2.9	unknown	0.255
At5g05190		unknown	0.255
At4g02410	lectin-like protein kinase 1, LPK1	confer Arabidopsis pathogen resistance when overexpression	0.250

Some immune gene candidates deserve further experimental validation.

Top 20 genes in ETI versus control

AGI #	Name	Function in Plant Immunity	NGF IS
At3g44720	arogenate dehydratase 4, ADT4	regulation of plant-type hypersensitive response	0.275
At3g57150	homologue of NAP57, NAP57	unknown	0.270
At5g46760	MYC3	mediate JA response	0.215
At1g63100		unknown	0.212
At2g02450	long vegetative phase 1, LOV1	unknown	0.212
At2g13650	Golgi nucleotide sugar transporter 1, GONST1	gonst1 plants have a dwarfed phenotype and a constitutive hypersensitive response with elevated salicylic acid levels	0.199
At1g59590	ZCF37	unknown	0.197
At2g30250	WRKY DNA-binding protein 25, WRKY25	negative regulator of SA-mediated defense responses	0.174
At1g14370	PBSL1-like protein kinase 2A, PBL2	cleaved by AvrPphB; pbl2 mutant showed significantly reduced callose deposition in flg22 andelf18 treatment	0.173
At5g52010		unknown	0.173
At3g22780	chinese for "ugly" TSO1	unknown	0.169
At3g59220	PRN1	unknown	0.165
At4g18880	heat shock transcription factor A4A, HSF A4A	response to chitin; substrate of the MPK3/MPK6 signaling	0.160
At3g56400	WRKY DNA-binding protein 70, WRKY70	convergence between SA and JA signaling	0.158
At1g67690		unknown	0.155
At2g38470	WRKY DNA-binding protein 33, WRKY33	key transcriptional regulator of hormonal and metabolic responses to necrotroph	0.149
At1g31190	myo-inositol monophosphatase like 1, IMPL1	unknown	0.149
At5g20950		unknown	0.147
At4g19030	NOD26-like major intrinsic protein 1, NLM1	regulation of defense response	0.146
At1g71260	whiry 2, WHY2	defense response	0.146
At1g64280	non-expresser of PR genes 1, NPR1	master regulator of SA-mediated systemic acquired resistance	0.145

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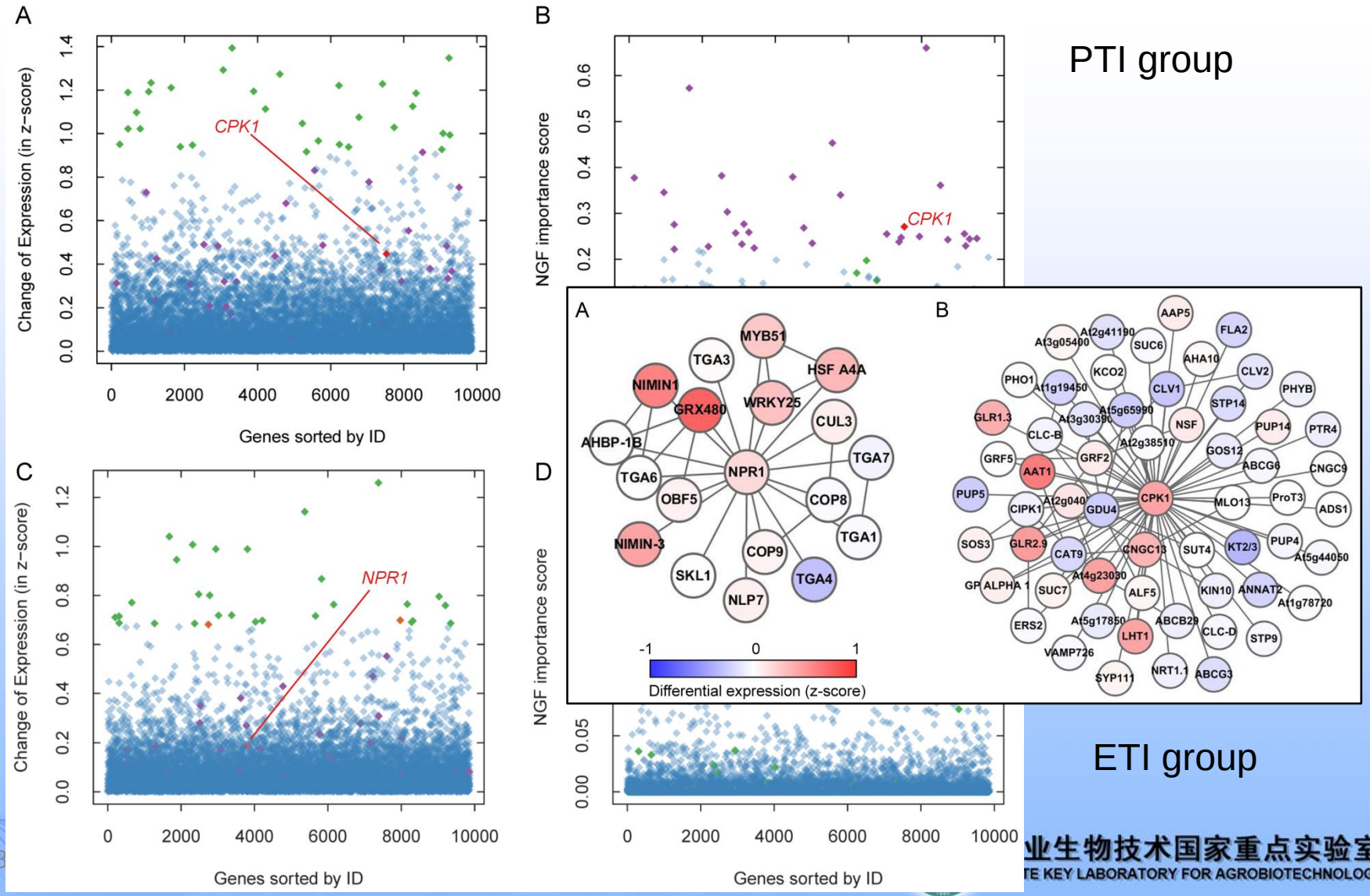
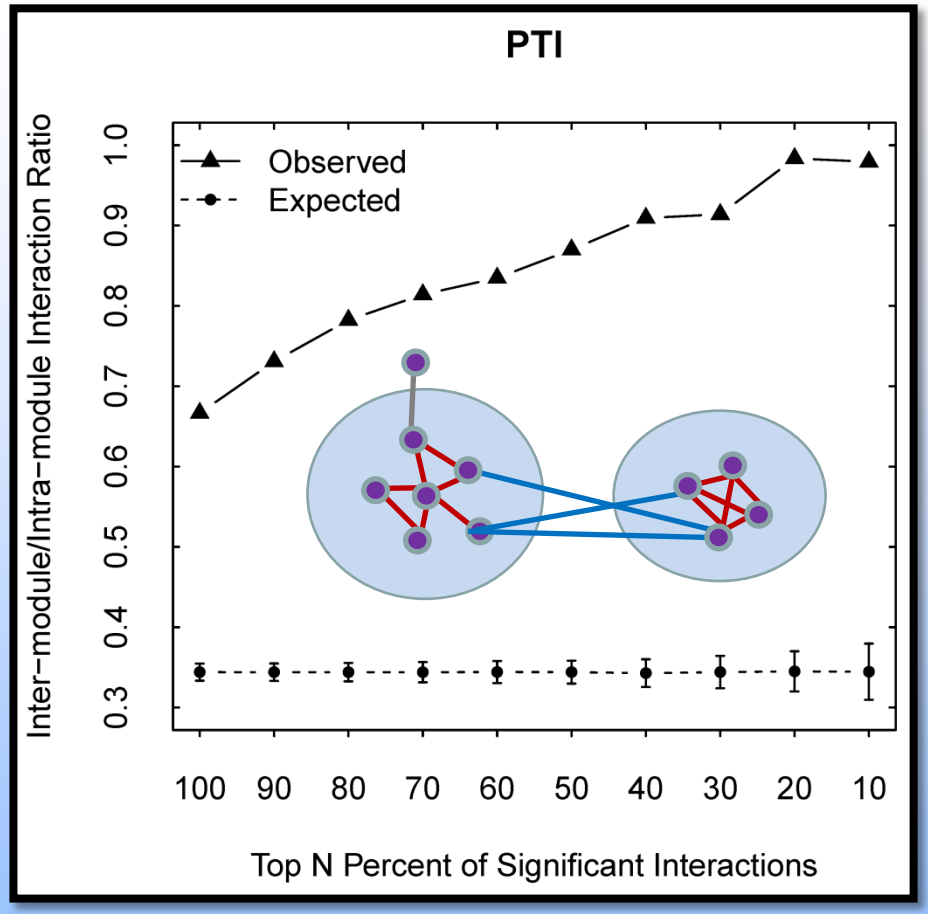
Comparison of NGF with differential expression analysis

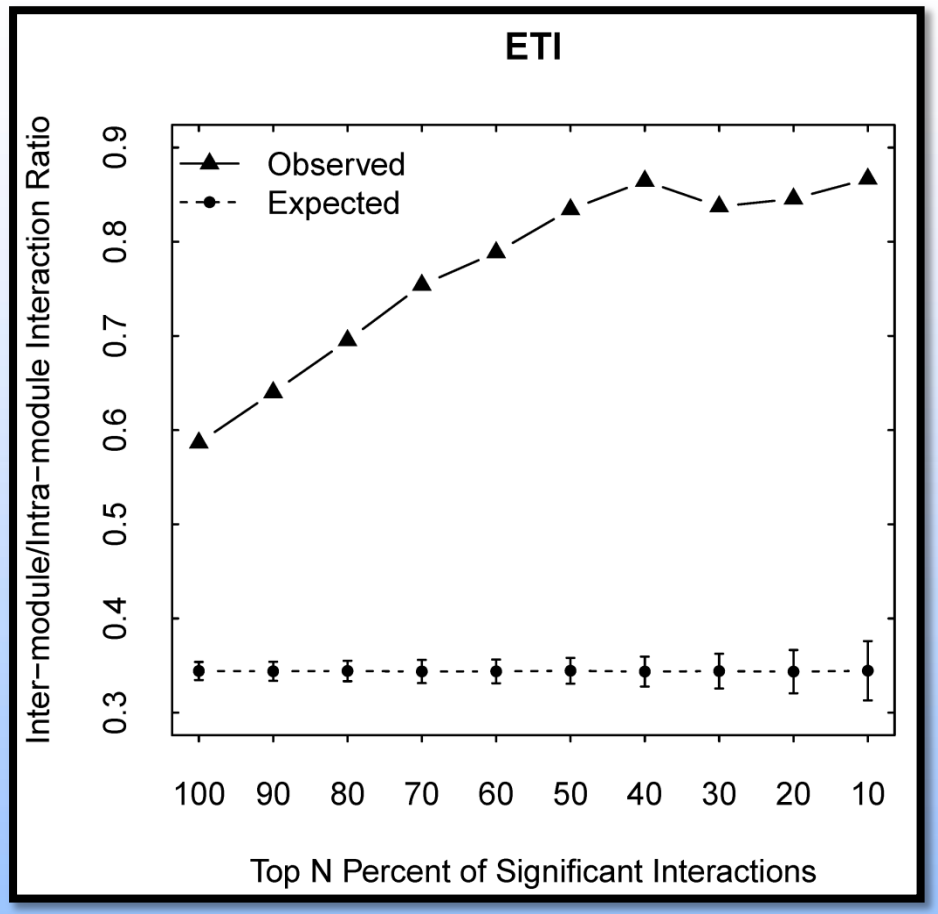


PTI group

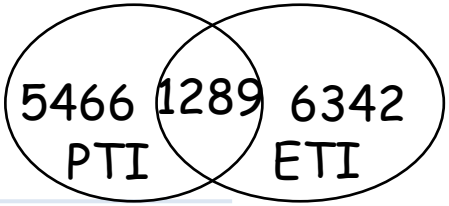
ETI group

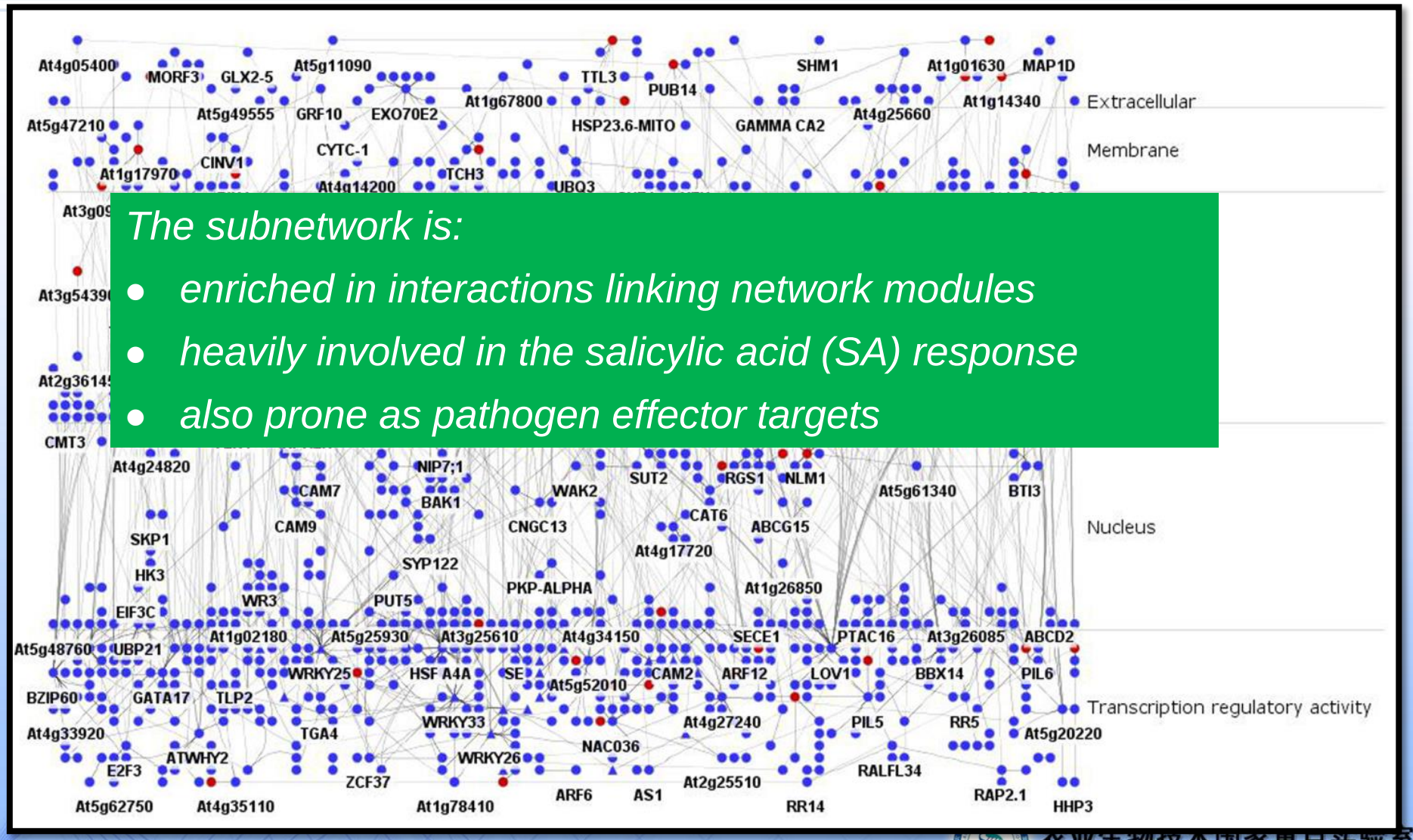
Significantly important gene interactions tend to link different network modules





The shared subnetwork between PTI and ETI

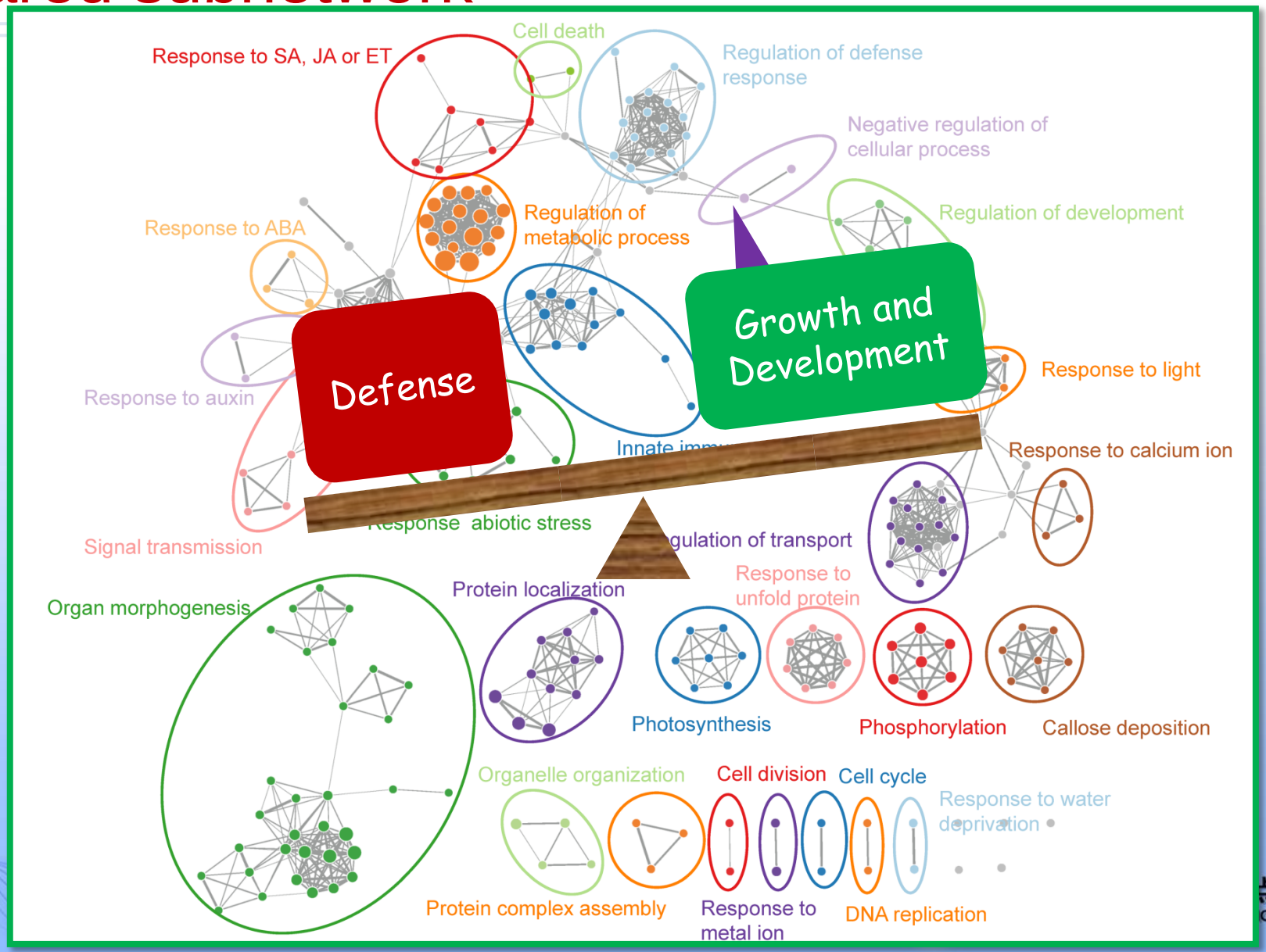




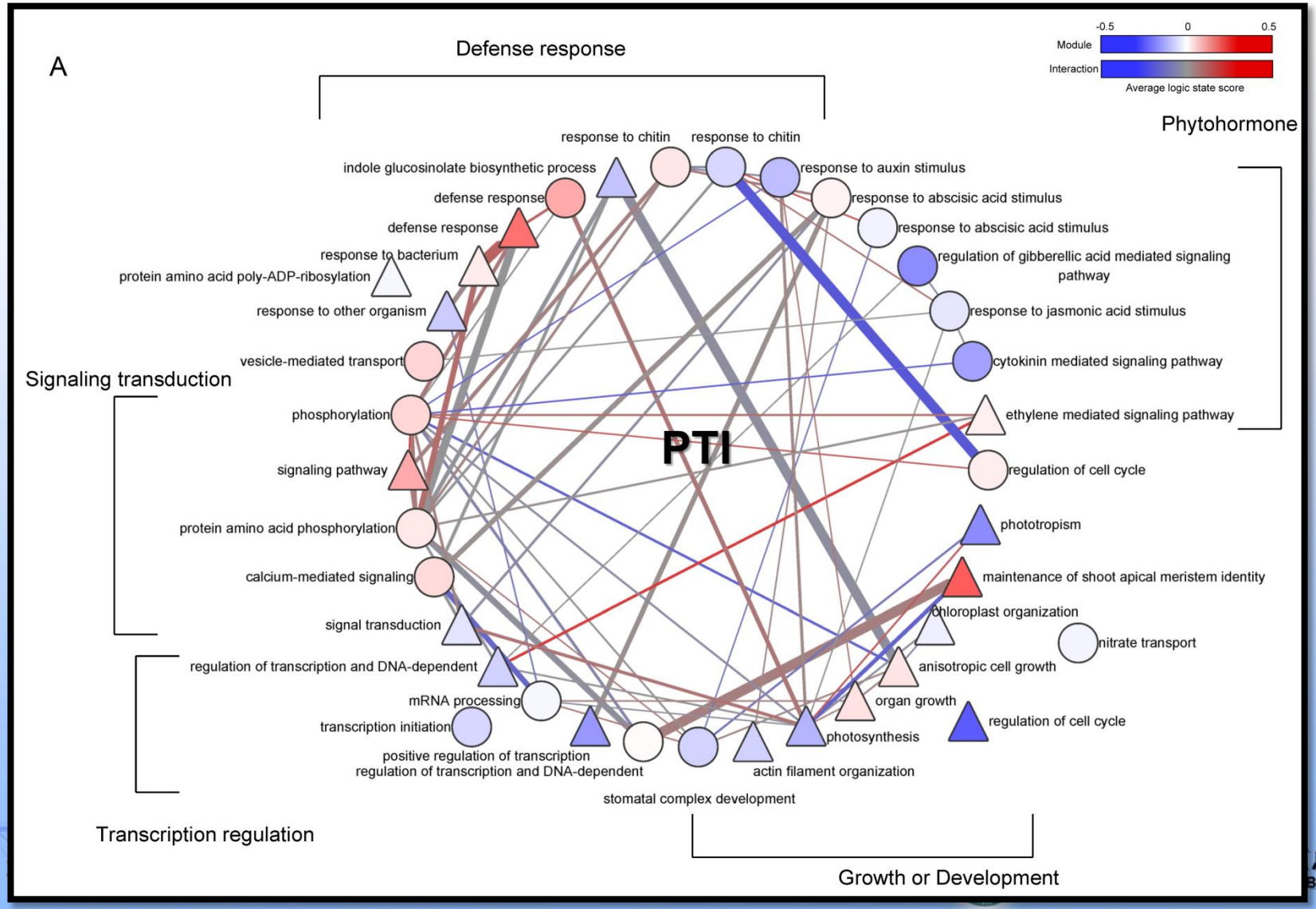
The subnetwork is:

- *enriched in interactions linking network modules*
- *heavily involved in the salicylic acid (SA) response*
- *also prone as pathogen effector targets*

The functional distribution of genes in the shared subnetwork



Modular network model of PTI



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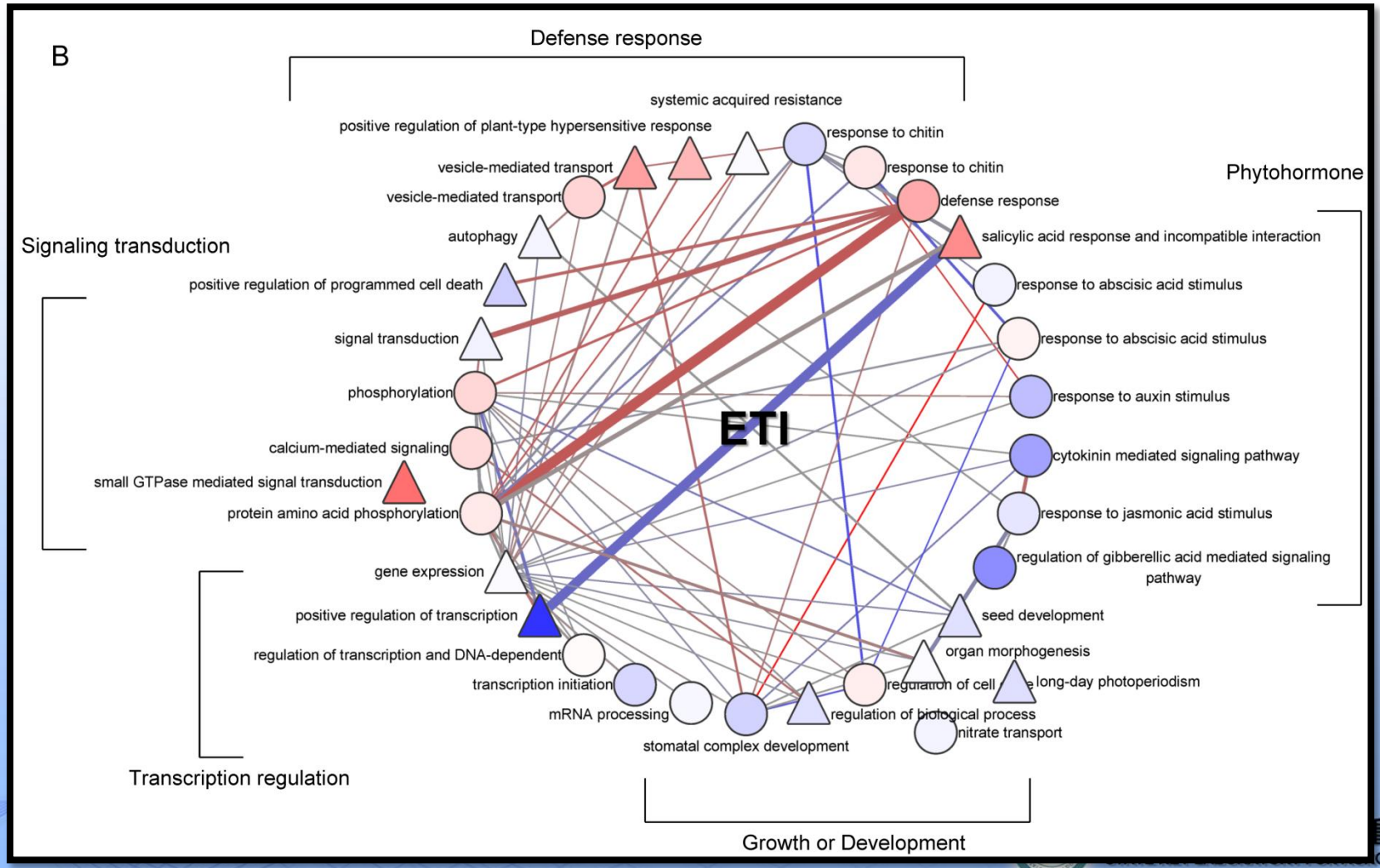
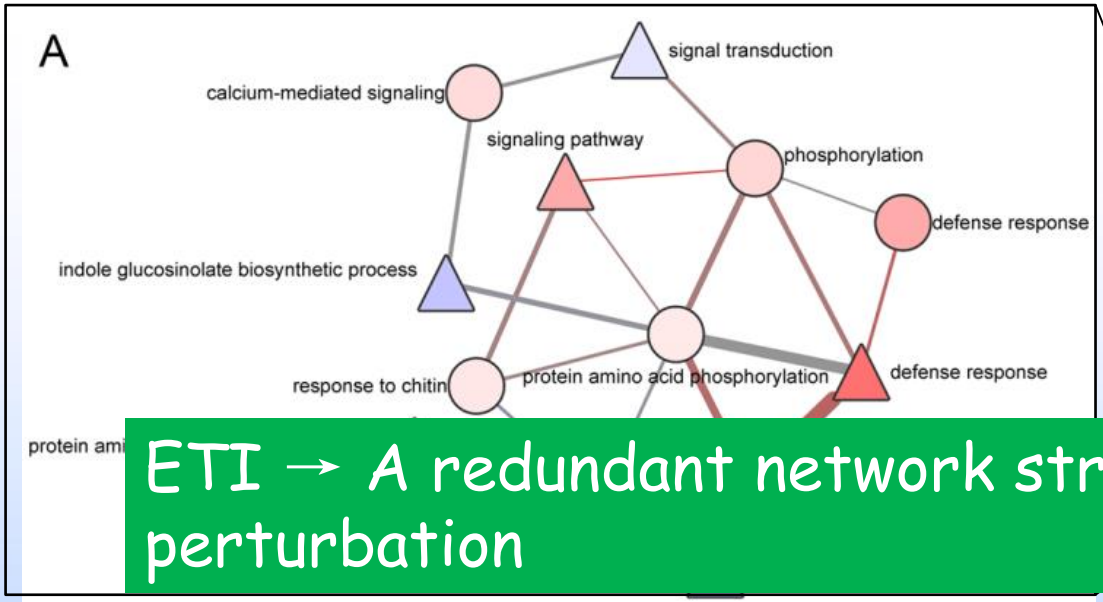
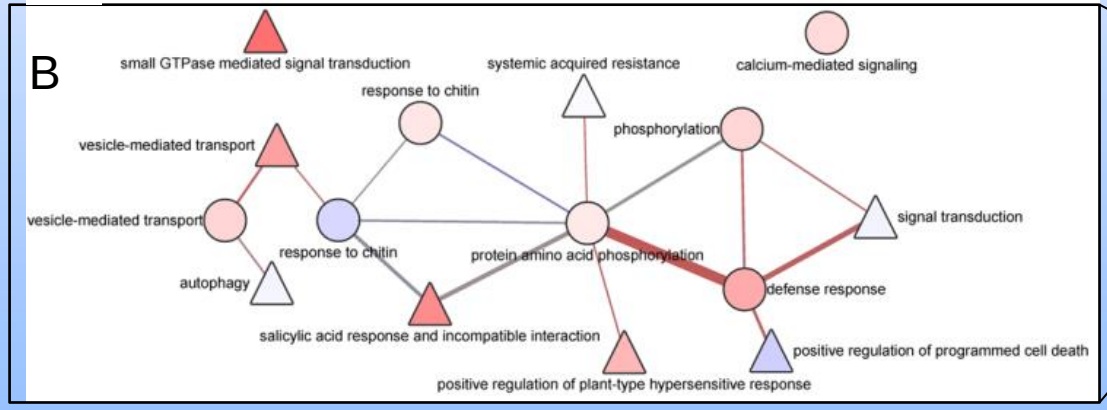
Modular network model of ETI

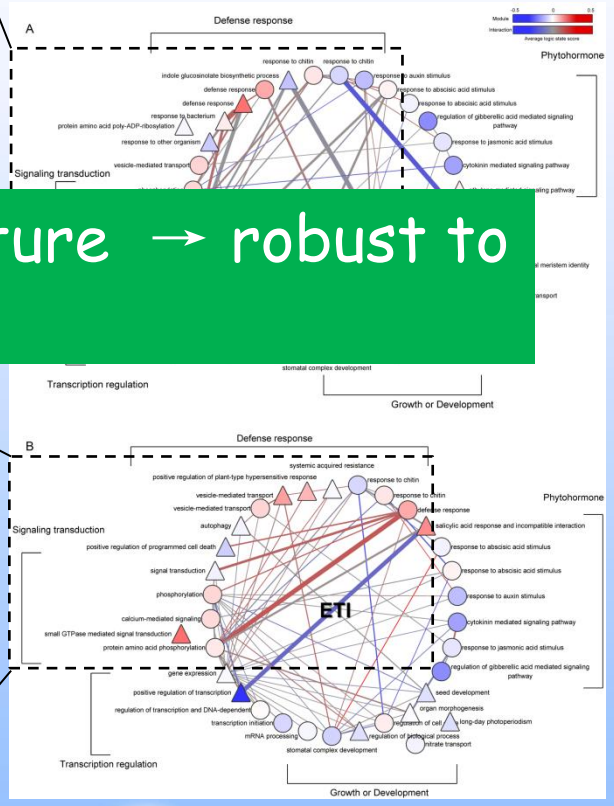


A relatively independent organization of defense modules distinguishes ETI from PTI

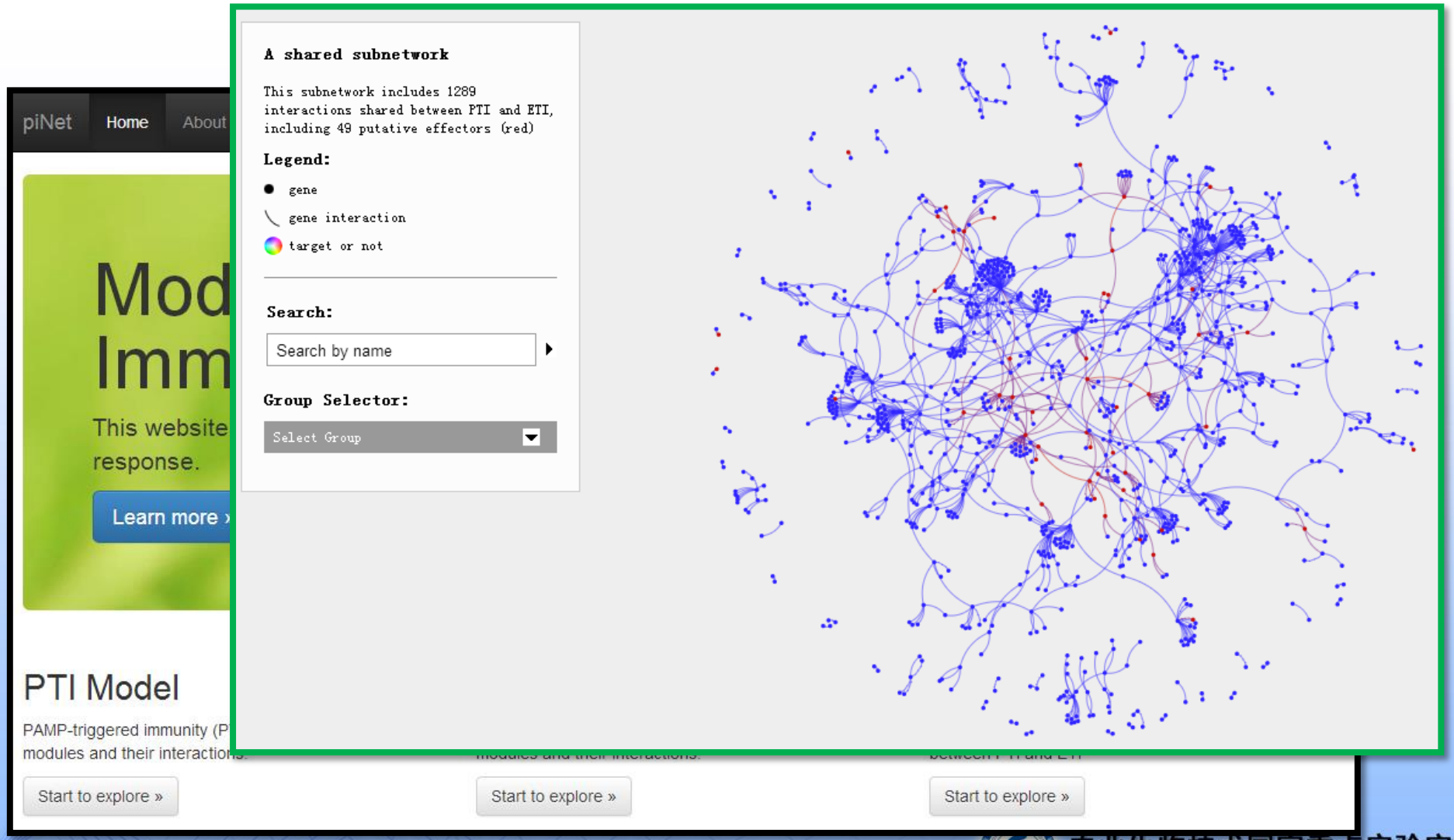


ETI → A redundant network structure → robust to perturbation





Network visualization (http://systbio.cau.edu.cn/pinet/home.php)

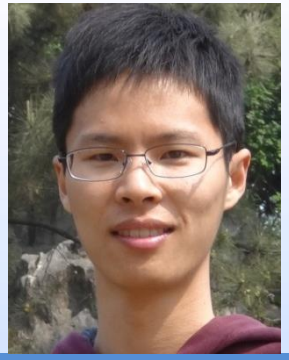


Dong et al (2015) *Plant Physiol*, **167:**1186-1203.

Conclusions

- *Computational study of plant-pathogen interaction is an important research topic.*
- *We constructed a comprehensive gene network of Arabidopsis (AraONE).*
- *Using the gene expression data and AraONE as input, the NGF algorithm was employed to identify key genes/interactions involved in the immune response.*
- *We identified a subnetwork shared between PTI and ETI and confirmed the biological importance of the subnetwork.*
- *We further identified immune response-related network modules and compared the different organization of these modules in PTI and ETI.*

Acknowledgments



Dr. Xiaobao Dong

http://systbio.cau.edu.cn

- **Funding Source**
  - *National Natural Science Foundation of China (31271414 & 31471249)*

Thank you for your attention!