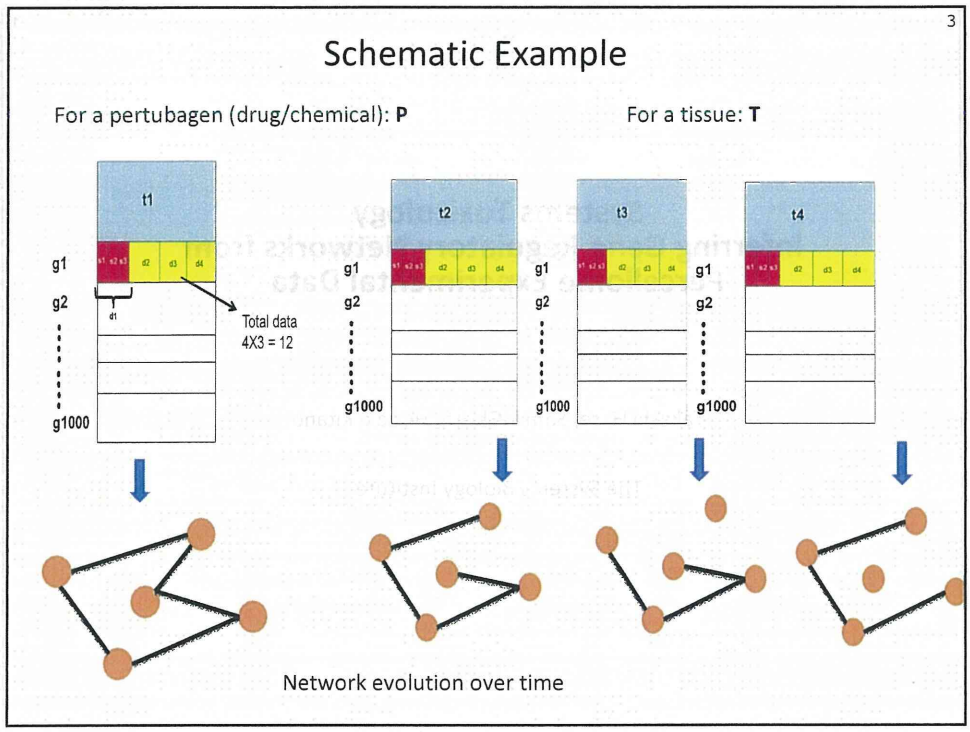
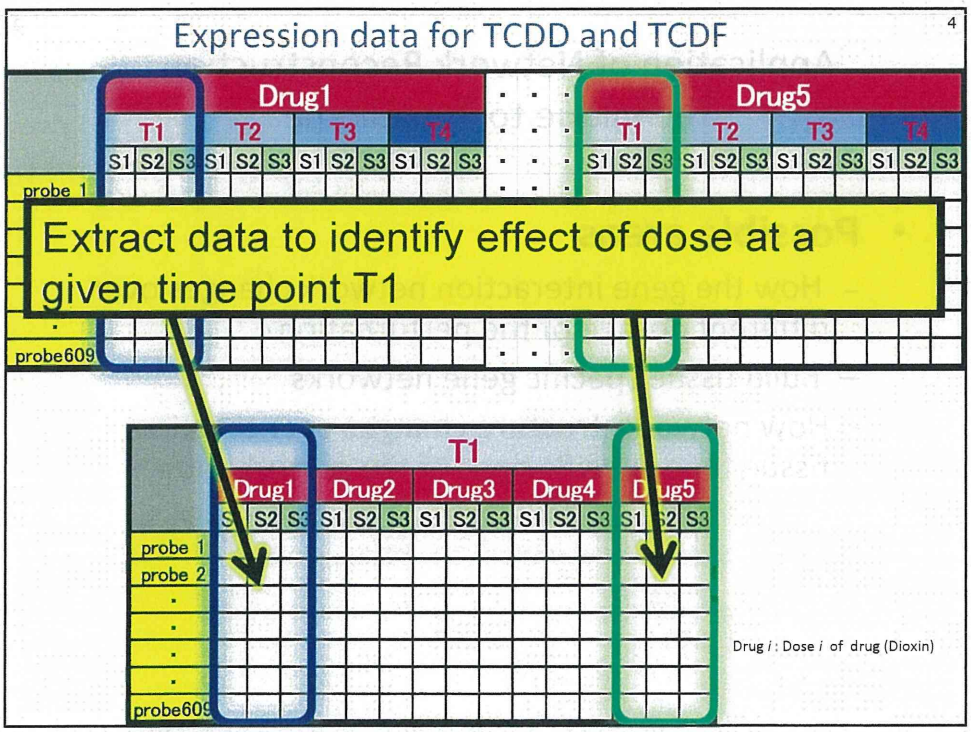

3
Schematic Example
For a pertubagen (drug/chemical): P
For a tissue: T
t1
t2
t3
t4
g1
g2
g1000
Total data
4X3 = 12
Network evolution over time


4
Expression data for TCDD and TCDF
Drug1
Drug5
T1
T2
T3
T4
S1 S2 S3
probe 1
probe609
Extract data to identify effect of dose at a given time point T1
Drug2
Drug3
Drug4
probe 2
Drug i : Dose i of drug (Dioxin)

5

Associations between two genes under a specific time point (T1)

Top 5% links

T1 links

1 bit profile

Gene 1	Gene 2	Rank	Link
A	B	1	1
A	C	2	1
.	.	.	1
.	.	.	1
.	.	.	1
D	E	156062	1
E	F	156063	0
.	.	.	0
.	.	.	0
A	E		0
C	F		0

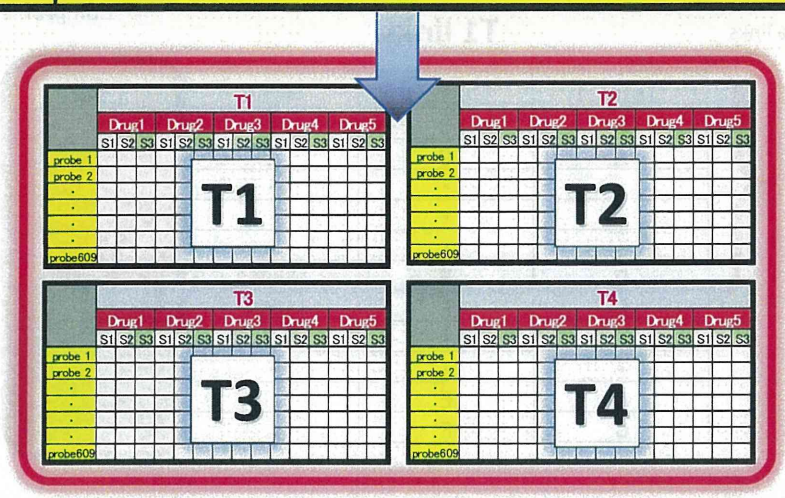
6

Number of links from expression data under a specific time point

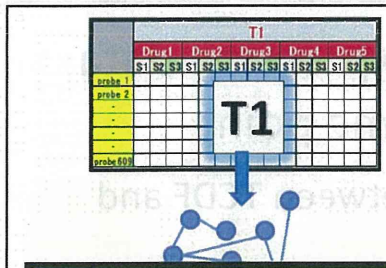
- 2,499 genes are common between TCDF and TCDD datasets.
- By using expression levels of these 2,499 genes, we inferred confidence scores for (2,499 * (2,499-1))/2 associations between two genes.
- We assume that gene links with Top 5% rank (156,062 links) are present under the specific time point.

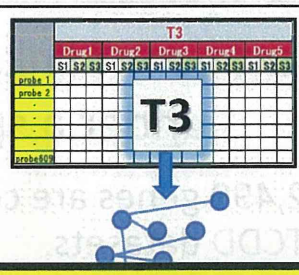
7

Generate data for all the four time points for a compound

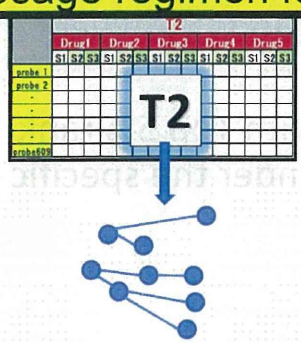


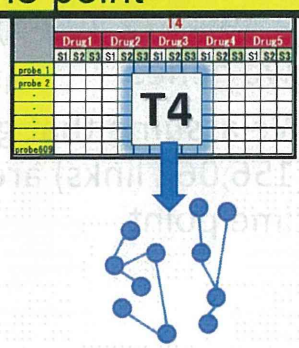
8





Infer associations between genes for the same dosage regimen for each time point





9

Differential regulation under drugs

- Database
  - **2 Compounds**
    - TCDD
    - TCDF
  - **4 Time points**
    - T1
    - T2
    - T3
    - T4

} 8 conditions

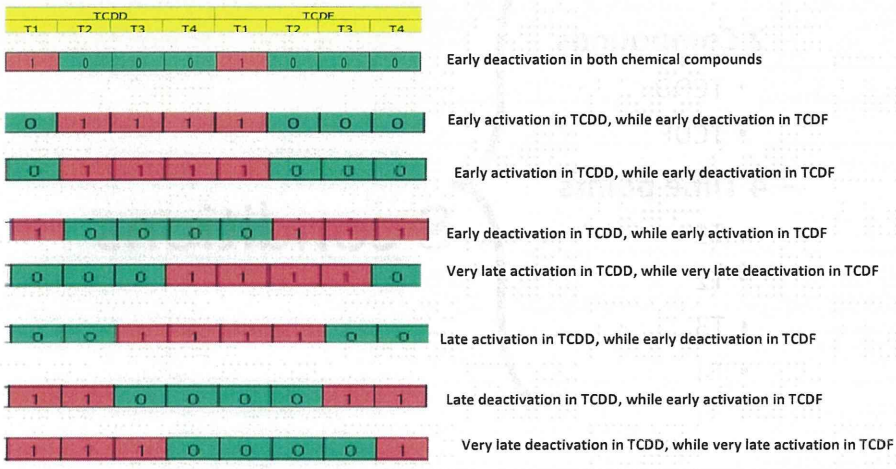
10

Differential regulation under drugs

- For each of the 8 conditions, we generate gene regulatory network considering top 5% associations
- For each association, assign a binary value to represent whether the association is present (1) or absent (0) under the 8 conditions
- Thus a 8 bit **pattern profile** is generated for the two drug regimens representing the 8 conditions
- The **pattern profile** can be used to analyze differential regulation of gene interactions

Pattern profiling of gene regulatory network

- The current analysis presents some of the possible patterns



Pattern profiling of gene regulatory network

Gene 1	Gene 2	TCDD				TCDF			
		T1	T2	T3	T4	T1	T2	T3	T4
Tpm3	Celf1	0	0	0	0	0	1	0	0
Apex1	Celf1	0	0	0	0	0	1	0	0
Ggcx	Celf1	0	1	0	0	0	0	0	0
Zdbf2	Celf1	0	0	0	1	0	0	0	0
Ddx39	Celf1	0	0	1	0	0	0	0	0
Psmc5	Celf1	0	0	0	0	0	1	0	0
Clcn5	Celf1	0	0	1	0	0	0	0	0
Pik3ca	Celf1	0	0	0	0	0	0	1	0
Peli2	Celf1	1	0	0	0	0	0	0	0
Lemd1	Celf1	0	0	1	0	0	0	0	0
Fmo2	Celf1	0	0	0	0	1	0	0	0
Strbp	Celf1	1	0	1	0	0	0	0	0
Slc22a23	Celf1	0	0	0	0	1	0	0	0
Srpk1	Celf1	0	1	0	0	0	1	0	0
Armc8	Celf1	0	0	0	0	0	1	0	0
G6pc	Celf1	0	0	0	0	1	0	0	0
Fkbp1a	Celf1	0	1	0	0	0	0	0	0
Smyd4	Celf1	0	0	0	1	0	0	0	0
Hdgf	Celf1	0	0	0	0	0	1	0	0
Rbm8a	Celf1	0	1	0	0	0	0	0	0
Rhbdd2	Celf1	0	1	0	1	0	0	0	0
Sypl	Celf1	1	0	0	0	0	0	0	0
Mark2	Celf1	0	0	0	0	0	1	0	0

13

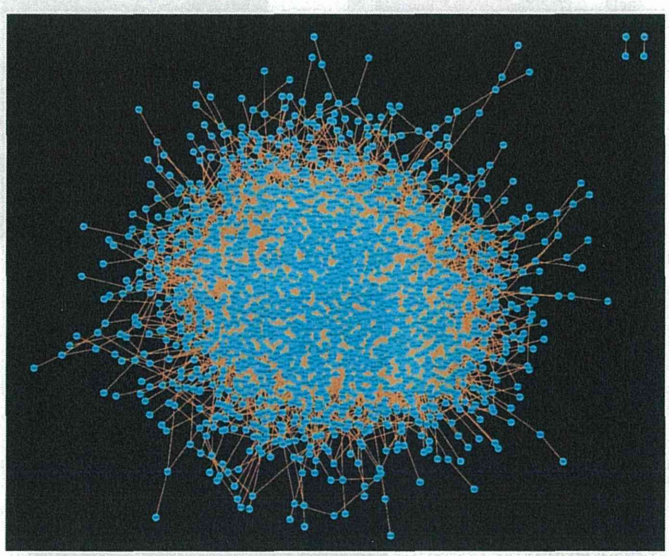
Early deactivation in both chemical compounds.

Gene 1	Gene 2	TCDD				TCDF			
		T1	T2	T3	T4	T1	T2	T3	T4
Prmt3	Celf1	1	0	0	0	1	0	0	0
Fzd2	Celf1	1	0	0	0	1	0	0	0
Apoc3	Akr1a1	1	0	0	0	1	0	0	0
Sepp1	Akr1a1	1	0	0	0	1	0	0	0
Uqcrb	Akr1a1	1	0	0	0	1	0	0	0
A230107O07Rik	Akr1a1	1	0	0	0	1	0	0	0
Ttr	Akr1a1	1	0	0	0	1	0	0	0
Cpd	Akr1a1	1	0	0	0	1	0	0	0
Fbxw8	Akr1a1	1	0	0	0	1	0	0	0
Bcap31	Zfp296	1	0	0	0	1	0	0	0
Rdx	Zfp296	1	0	0	0	1	0	0	0
Elavl1	Zfp296	1	0	0	0	1	0	0	0
Lats2	Rom1	1	0	0	0	1	0	0	0
Pa2g4	Rom1	1	0	0	0	1	0	0	0
Gm2769	Rom1	1	0	0	0	1	0	0	0

5275 associations between genes

14

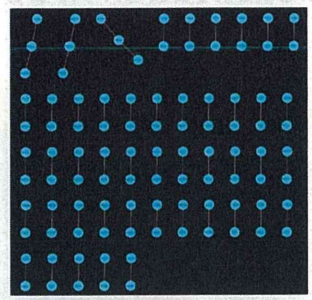
Early deactivation in both chemical compounds.



15

Early activation in TCDD, while early deactivation in TCDF

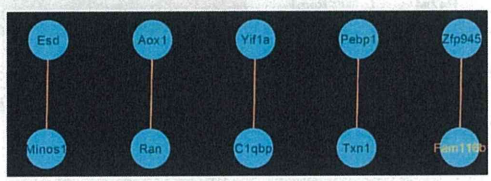
Gene 1	Gene 2	TCDD				TCDF			
		T1	T2	T3	T4	T1	T2	T3	T4
Tomm70a	Strap	0	1	1	1	1	0	0	0
Lamp1	B2m	0	1	1	1	1	0	0	0
Ndufaf4	Top1	0	1	1	1	1	0	0	0
Slc35a1	Dnajc15	0	1	1	1	1	0	0	0
Afmid	Slc16a10	0	1	1	1	1	0	0	0
Cbr3	Meig1	0	1	1	1	1	0	0	0
Cdc34	Ssb	0	1	1	1	1	0	0	0
Pmm1	Antxr2	0	1	1	1	1	0	0	0
Dtx3l	Txnl4a	0	1	1	1	1	0	0	0
Fam65b	Nt5m	0	1	1	1	1	0	0	0
Srsf2	Senp2	0	1	1	1	1	0	0	0
Pitpnc1	Ammecr1l	0	1	1	1	1	0	0	0
Tfap2a	Ctnnd1	0	1	1	1	1	0	0	0
Rpl28	Rps13	0	1	1	1	1	0	0	0
Txnrd1	Plcg1	0	1	1	1	1	0	0	0
Mthfd1	Elovl5	0	1	1	1	1	0	0	0
Tradd	Dsg2	0	1	1	1	1	0	0	0



49 associations

Early deactivation in TCDD, while early activation in TCDF

Gene 1	Gene 2	TCDD				TCDF			
		T1	T2	T3	T4	T1	T2	T3	T4
Zfp945	Fam116b	1	0	0	0	0	1	1	1
Pebp1	Txn1	1	0	0	0	0	1	1	1
Yif1a	C1qbp	1	0	0	0	0	1	1	1
Aox1	Ran	1	0	0	0	0	1	1	1
Esd	Minos1	1	0	0	0	0	1	1	1

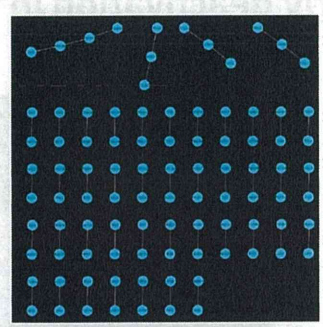


5 associations

16

Late activation in TCDD, while early deactivation in TCDF

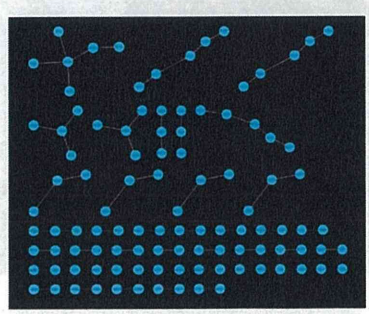
Gene 1	Gene 2	TCDD				TCDF			
		T1	T2	T3	T4	T1	T2	T3	T4
Ublcp1	Peli2	0	0	1	1	1	1	0	0
Ptplad1	Nop10	0	0	1	1	1	1	0	0
Ctnna1	Gnpnat1	0	0	1	1	1	1	0	0
Lancl1	Epb4.1l2	0	0	1	1	1	1	0	0
Gabarapl2	Cct2	0	0	1	1	1	1	0	0
Ndufs3	Ptcd3	0	0	1	1	1	1	0	0
Dcxr	Cd59a	0	0	1	1	1	1	0	0
Tsc22d3	Eda	0	0	1	1	1	1	0	0
Coasy	Abce1	0	0	1	1	1	1	0	0
Mycbp	Cyhr1	0	0	1	1	1	1	0	0
Prkab1	Lasp1	0	0	1	1	1	1	0	0
Bhlhe40	Birc3	0	0	1	1	1	1	0	0
Marco	Rpusd4	0	0	1	1	1	1	0	0



48 associations

Very late activation in TCDD, while very late deactivation in TCDF

Gene 1	Gene 2	TCDD				TCDF			
		T1	T2	T3	T4	T1	T2	T3	T4
Prss53	Mfap2	0	0	0	1	1	1	1	0
Tm9sf3	Mfap2	0	0	0	1	1	1	1	0
Zfp292	Mfap2	0	0	0	1	1	1	1	0
Ptges3	Nop10	0	0	0	1	1	1	1	0
Acox2	Rnf11	0	0	0	1	1	1	1	0
Cyhr1	Mrpl44	0	0	0	1	1	1	1	0
Papola	Cmah	0	0	0	1	1	1	1	0
Rpl10a	Cct2	0	0	0	1	1	1	1	0
Rpl26	Cct2	0	0	0	1	1	1	1	0
Uqcr10	Ptcd3	0	0	0	1	1	1	1	0
Fahd2a	Cd59a	0	0	0	1	1	1	1	0
Slc25a39	Obfc2a	0	0	0	1	1	1	1	0
Ankrd13c	Obfc2a	0	0	0	1	1	1	1	0
Herc4	Akap10	0	0	0	1	1	1	1	0
Arglu1	Tpd52	0	0	0	1	1	1	1	0



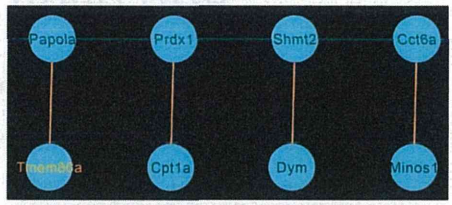
63 associations

17

Late deactivation in TCDD, while early activation in TCDF

Gene 1	Gene 2	TCDD				TCDF			
		T1	T2	T3	T4	T1	T2	T3	T4
Cct6a	Minos1	1	1	0	0	0	0	1	1
Shmt2	Dym	1	1	0	0	0	0	1	1
Prdx1	Cpt1a	1	1	0	0	0	0	1	1
Papola	Tmem86a	1	1	0	0	0	0	1	1

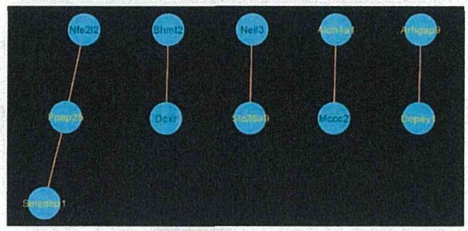
4 links



Very late deactivation in TCDD, while very late activation in TCDF

Gene 1	Gene 2	TCDD				TCDF			
		T1	T2	T3	T4	T1	T2	T3	T4
Arhgap9	Dopey1	1	1	1	0	0	0	0	1
Aldh4a1	Mccc2	1	1	1	0	0	0	0	1
Neil3	Slc38a9	1	1	1	0	0	0	0	1
Ppap2b	Nfe2l2	1	1	1	0	0	0	0	1
Shmt2	Dcxr	1	1	1	0	0	0	0	1
Ppap2b	Selenbp1	1	1	1	0	0	0	0	1

6 links



18

Summary

- Ability to infer gene regulatory networks is a key problem in many biomedical research areas
- Systems Toxicology endeavors to capture the effect of various drugs and chemical at network level
- The Systems Toxicology project will provide one of the first applications of inference techniques to large scale toxicology databases with wide range of chemicals
- The integration of Percellome data and associated regulatory network on the Garuda Platform will provide a unique global resource for systems toxicology studies

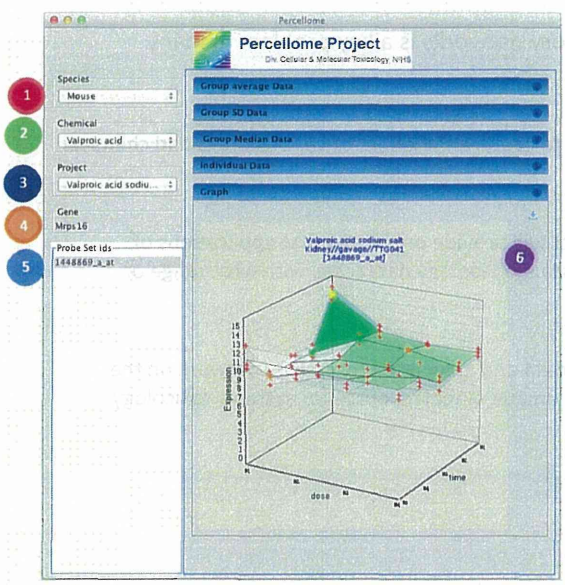
19

Percellome & Garuda

- The Percellome database has been Garuda-enabled and provides API to Garuda
- Percellome Garuda gadget
  - –Provide user interface to access and interact with Percellome data
  - –Select species, chemical/drugs of interest
  - –Map genes of interest to Probe Ids
  - –Save data from Percellome database in tabular format
  - –Save 3D images from Percellome database
  - –Linked with CellDesigner to analyze genes and proteins from pathway maps
- The Percellome gadget on Garuda would be available in Garuda 1.0 release

20

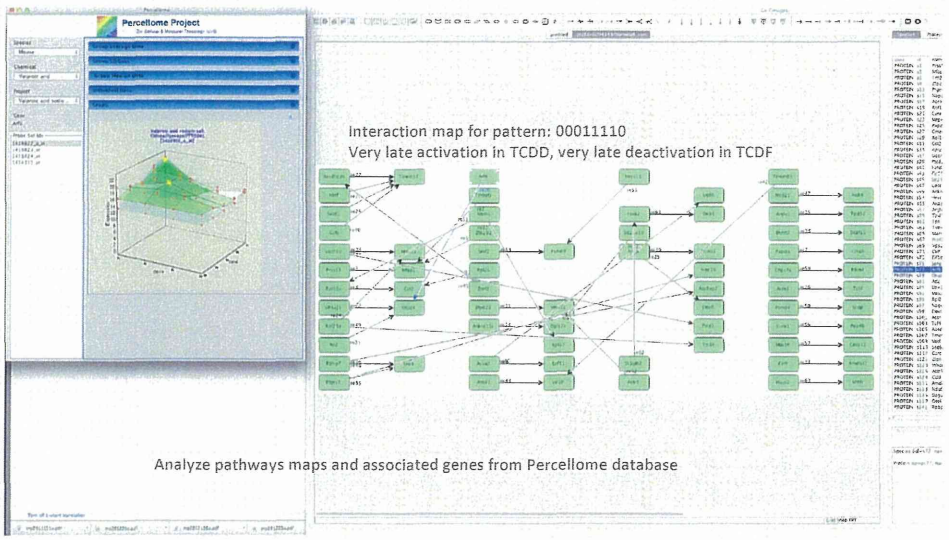
Percellome & Garuda



1. Species of interest selection
2. *Chemical or drug selection*
3. Percellome Project selection
4. Gene of interest
5. List of probes associated with the gene
6. Results obtained from Percellome

21

Percellome & Garuda



Analyze pathways maps and associated genes from Percellome database

22

Discussions