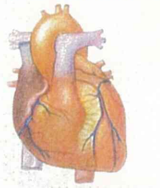
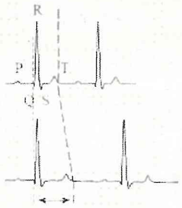
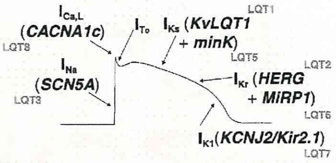
Possible application of cell based toxicology

Prediction of QT elongation

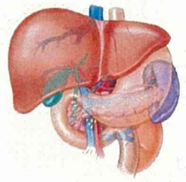




QT elongation is one of the major cause of drug withdrawal. HERG channel is the main target of QT elongation.

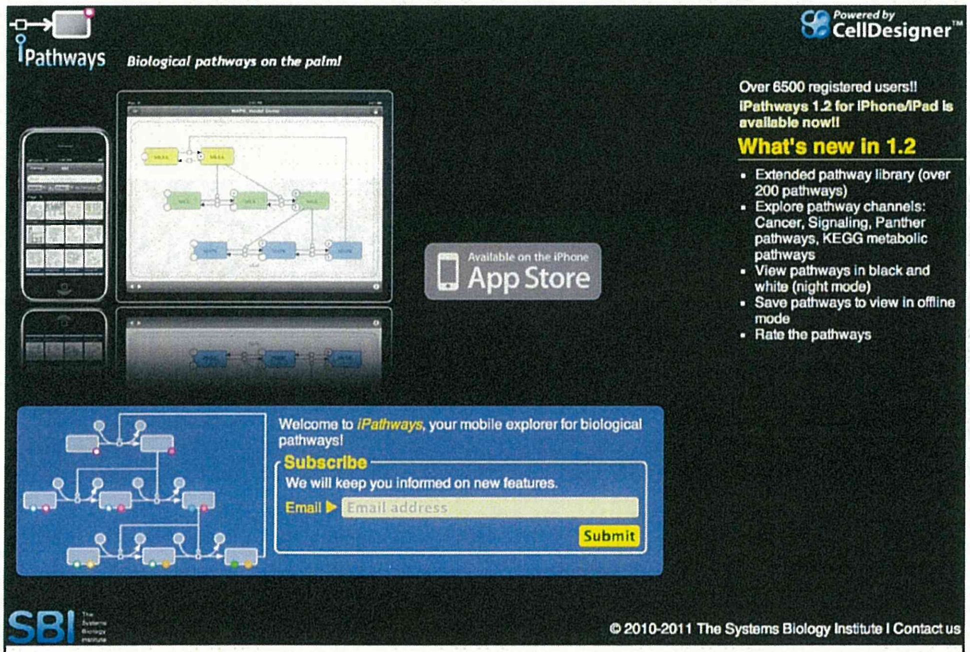


Prediction of Hepatotoxicity



Liver takes central role in the clearance and transformation of chemicals
Step 1 oxidation, reduction, hydrolysis, hydration
Step 2 transferase
Hepatotoxicity means the liver damage induced by chemicals.
Hepatotoxicity is one of the major cause of drug withdrawal.

EMBO Symposium



Biological pathways on the palm!

Over 6500 registered users!!
iPathways 1.2 for iPhone/iPad is available now!!

What's new in 1.2

- Extended pathway library (over 200 pathways)
- Explore pathway channels: Cancer, Signaling, Panther pathways, KEGG metabolic pathways
- View pathways in black and white (night mode)
- Save pathways to view in offline mode
- Rate the pathways

Welcome to *iPathways*, your mobile explorer for biological pathways!

Subscribe

We will keep you informed on new features.

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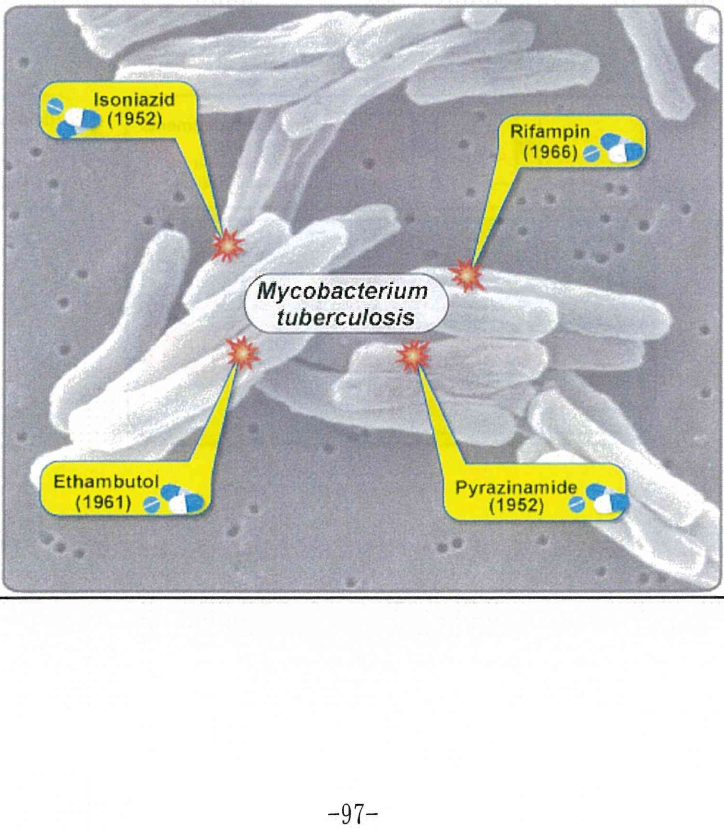
TB: A Disease Neglected



What Is Open Source Drug Discovery
Open Source Drug Discovery(OSDD) is a *CSIR Team India Consortium with Global Partnership* with a vision to provide affordable healthcare to the developing world. more

Message from Chief Mentor
June 2008 marked the 10th anniversary of the complete sequencing of *M. tuberculosis* genome, which was made available as Open Source to the scientific community. more

Student Corner
See how you can contribute to this global initiative.

Open Source Drug Discovery Network Resources

SysBorgTB is the Wiki based OSDD collaboration system and CyberInfrastructure for collaborative Research. more
[Beta version of SysBorg 2.0 is available for preview here]

TBrowse is one of the largest Integrative Genomics resource on *Mycobacterium tuberculosis* H37Rv.more

Computational Resources for Drug Discovery (CRDD) is a comprehensive resources for drug discovery more

Open Source Drug Discovery Collaborative Programs

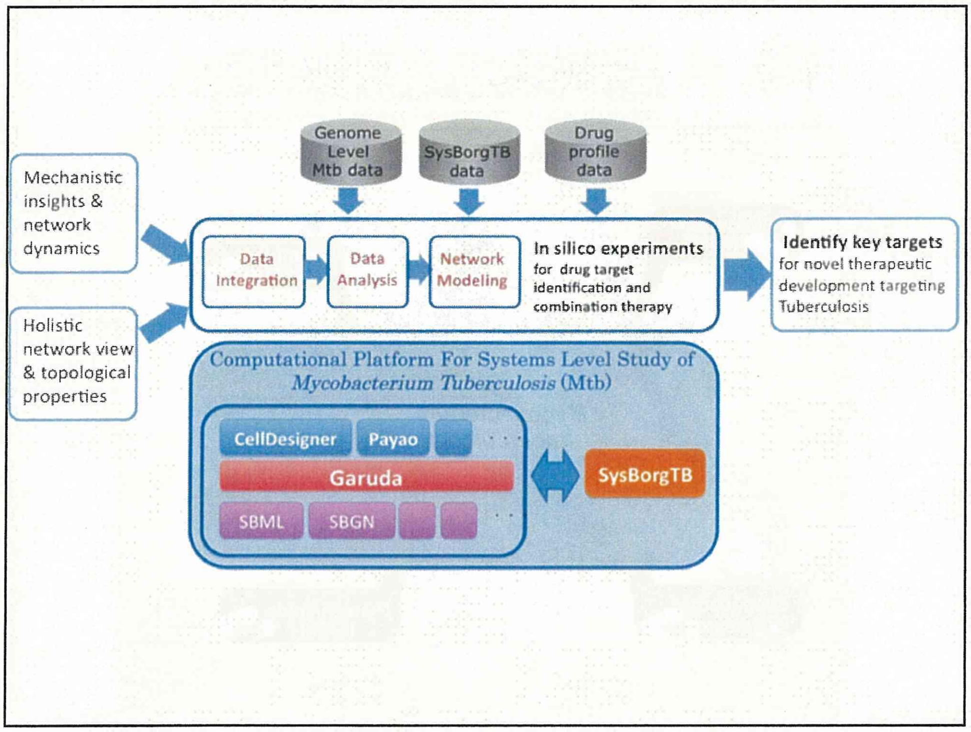
News Updates

Scientists map TB genome NEW DELHI: Scientists from across India today announced the first-ever detail mapping of mycobacterium tuberculosis (MTB), an exercise that may help in producing more effective drugs to combat the ...
Posted an hour ago by Vinod Scaria

CSIR to unveil gene map for TB on portal developed by Infosys Jacob koshy writes in LiveMint on the TB Collaborative Research portal developed by InfosysExcerpt:"Akin to a Google map, or a Wikipedia article that can be modified and continually ...
Posted Apr 10, 2010 7:07 PM by Vinod Scaria

Joining forces against TB A partnership involving the US Food and Drug Administration may speed up delivery of new tuberculosis drug combinations, says Priya Shetty."New TB drugs are desperately needed. The existing treatment ...
Posted Apr 4, 2010 1:35 PM by Vinod Scaria

Showing posts 1 - 3 of 22. View more »



Genome Level Mtb data

SysBorgTB data

Drug profile data

Mechanistic insights & network dynamics

Holistic network view & topological properties

Data Integration

Data Analysis

Network Modeling

In silico experiments
for drug target identification and combination therapy

Identify key targets
for novel therapeutic development targeting Tuberculosis

Computational Platform For Systems Level Study of *Mycobacterium Tuberculosis* (Mtb)

CellDesigner

Payao

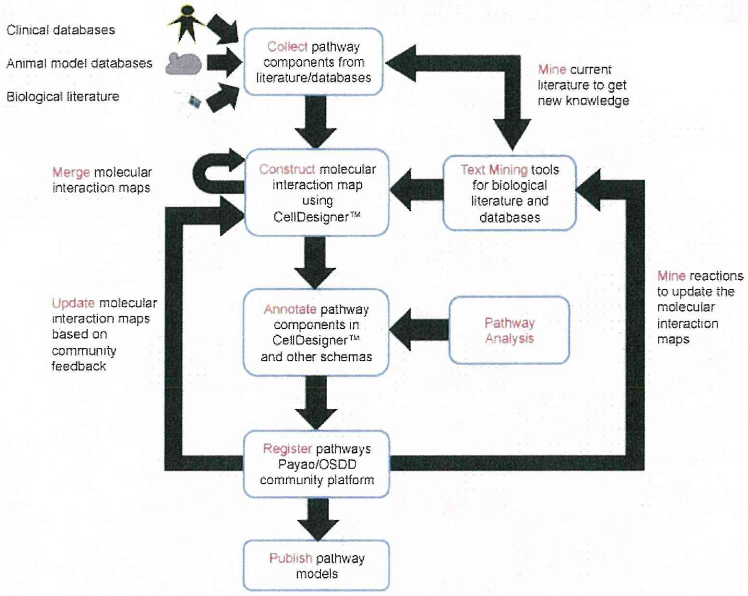
Garuda

SBML

SBGN

SysBorgTB

Open Flow curation of Mtb Metabolome



Clinical databases

Animal model databases

Biological literature

Collect pathway components from literature/databases

Mine current literature to get new knowledge

Merge molecular interaction maps

Construct molecular interaction map using CellDesigner™

Text Mining tools for biological literature and databases

Mine reactions to update the molecular interaction maps

Update molecular interaction maps based on community feedback

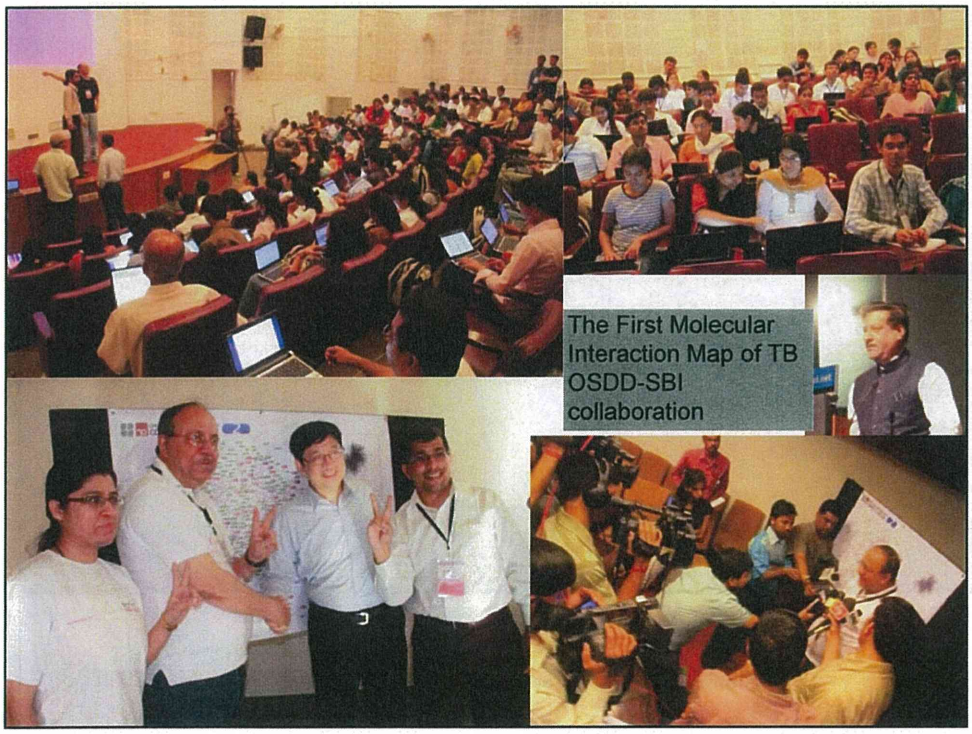
Annotate pathway components in CellDesigner™ and other schemas

Pathway Analysis

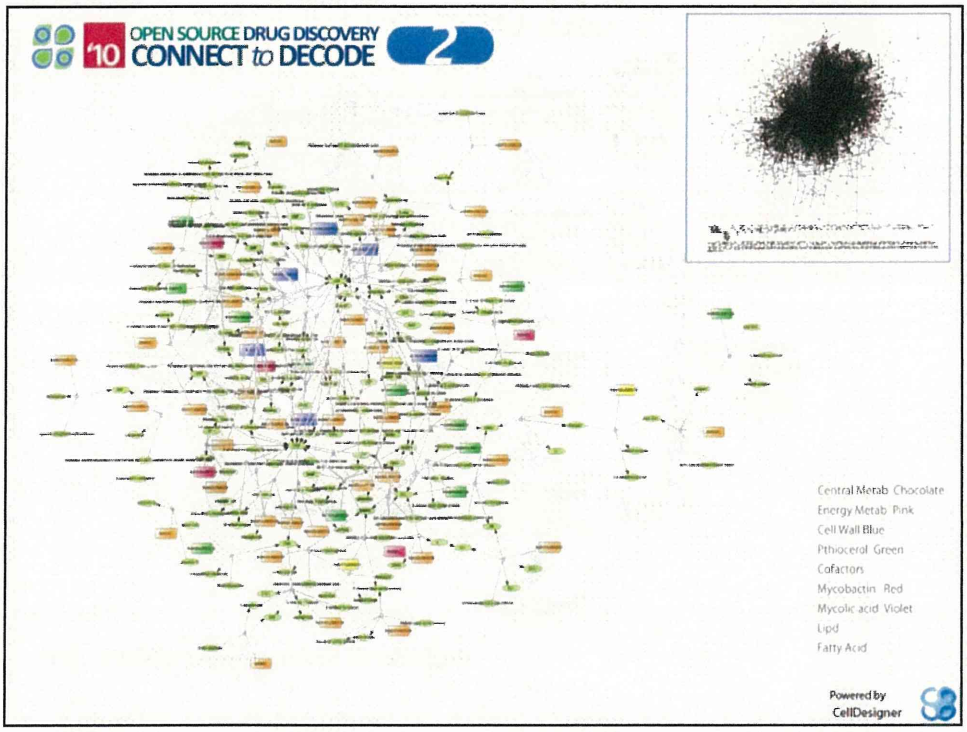
Register pathways Payao/OSDD community platform

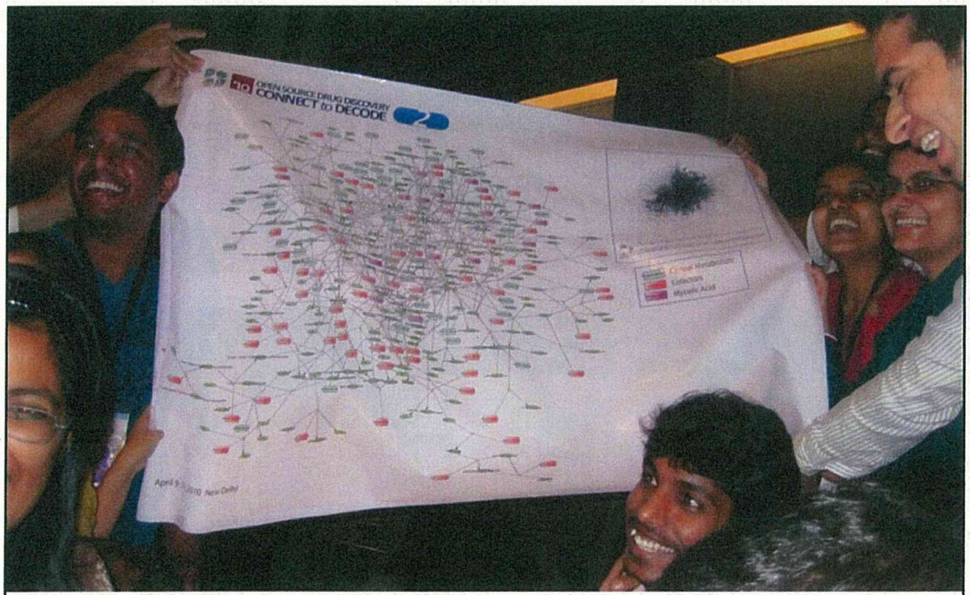
Publish pathway models

Kitano, et al., Nature chemical biology, 2011

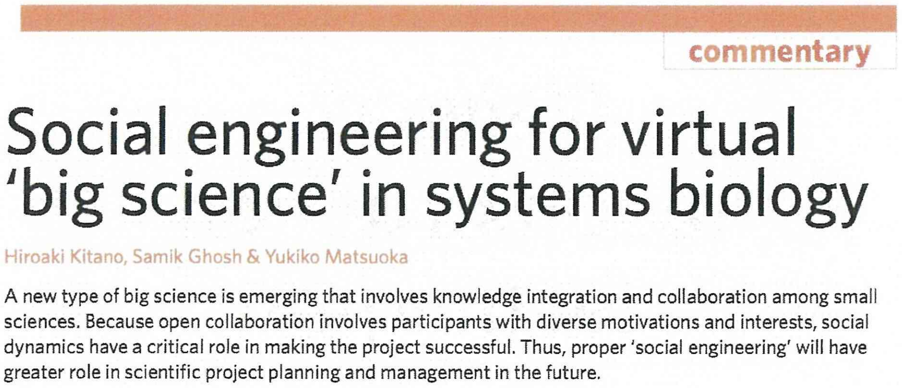


The First Molecular Interaction Map of TB OSDD-SBI collaboration





Kitano, Ghosh, Matsuoka, Nature Chemical Biology, May 2011



commentary

Social engineering for virtual 'big science' in systems biology

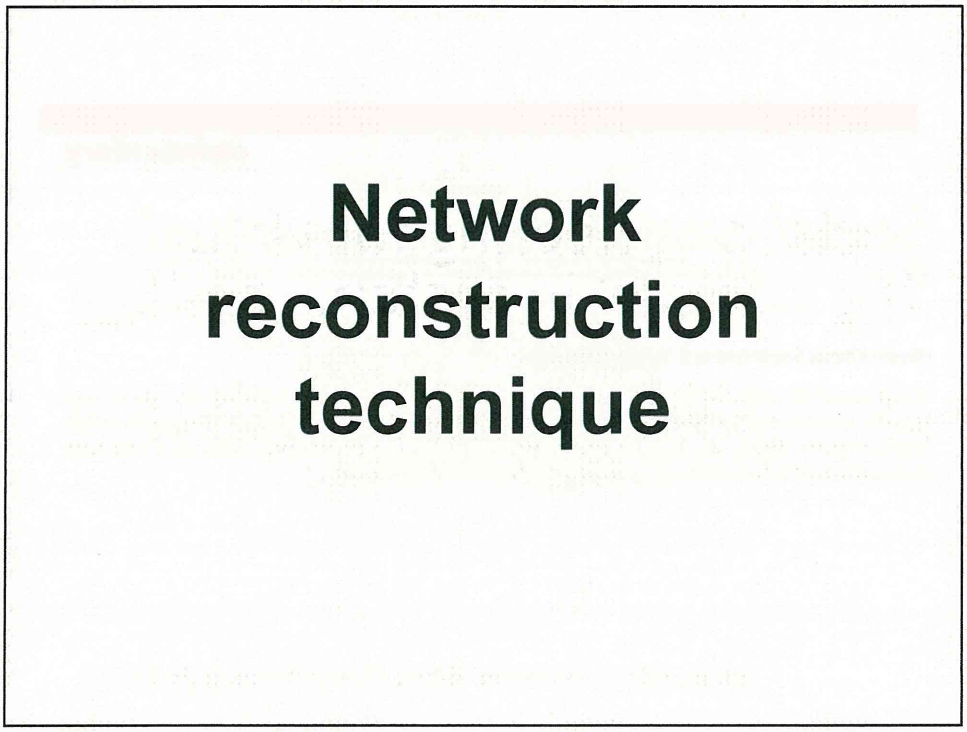
Hiroaki Kitano, Samik Ghosh & Yukiko Matsuoka

A new type of big science is emerging that involves knowledge integration and collaboration among small sciences. Because open collaboration involves participants with diverse motivations and interests, social dynamics have a critical role in making the project successful. Thus, proper 'social engineering' will have greater role in scientific project planning and management in the future.

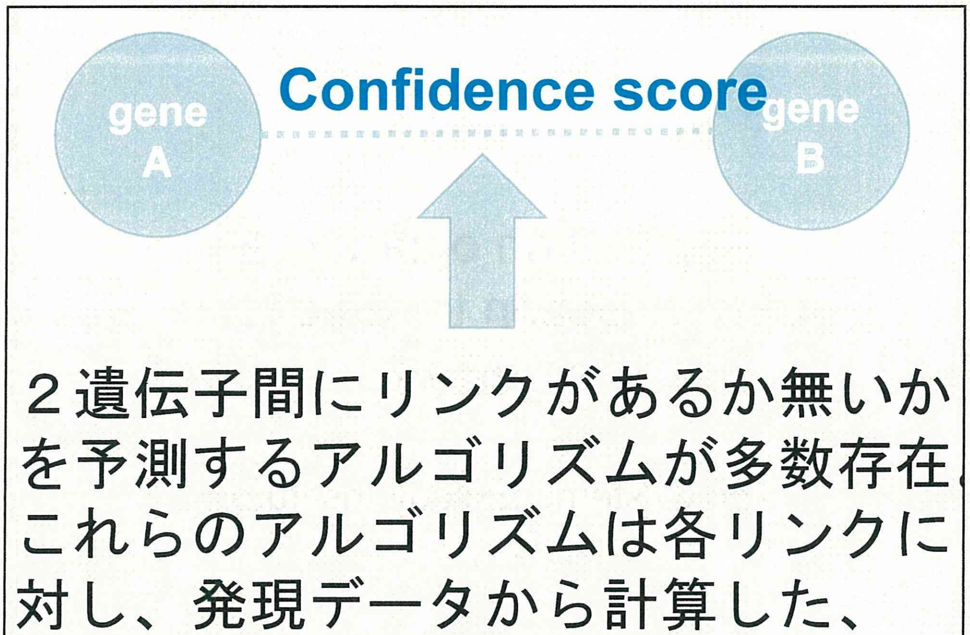
Kitano, Ghosh, Matsuoka, Nature Chemical Biology, May 2011

Application of network reconstruction technique to Percellome

The Systems Biology Institute,
Tokyo



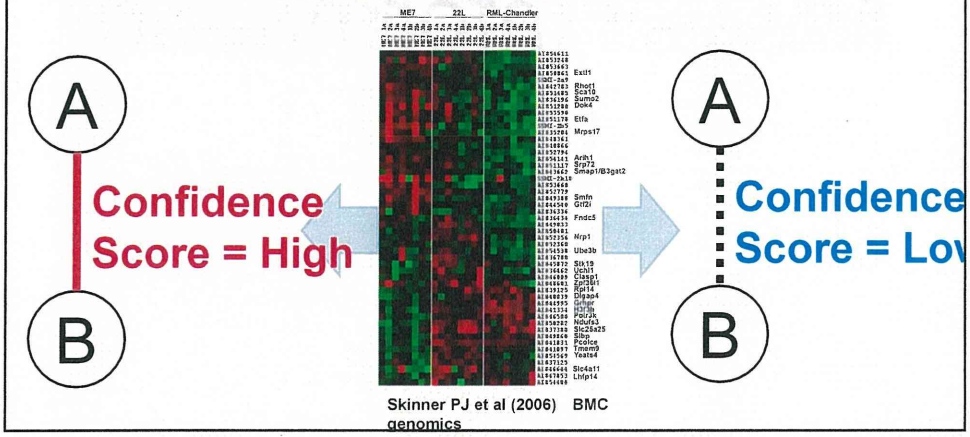
Network reconstruction technique



２遺伝子間にリンクがあるか無いかを予測するアルゴリズムが多数存在。これらのアルゴリズムは各リンクに対し、発現データから計算した、confidence scoreをつける。

Confidence scores from gene expression data

高いconfidence scoresのリンクは、正しい可能性が高く、低いscoreのリンクは正しい可能性が低い。



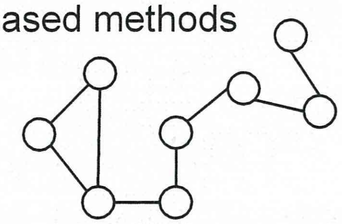
Confidence Score = High

Confidence Score = Lo

Skinner PJ et al (2006) BMC genomics

リンクに対してconfidence scoreを計算するアルゴリズム（Network inference methods）

Mutual information (MI) based methods



Advantage

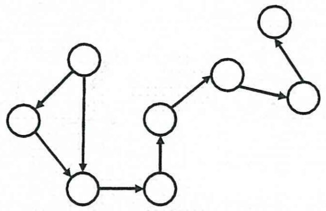
Lower computational cost than BNs

Better performance than BNs in terms of predictive power

Shortcomings

Un-directed graph

Bayesian networks (BN)



Advantage

Directed graph

Shortcomings

Higher computational cost than MIs

Lower performance than MIs in terms of predictive power

Mutual Information

Mutual informationについて

Mutual information between random valuables X and Y; $I(X,Y)$
X and Y represent gene X and Y.

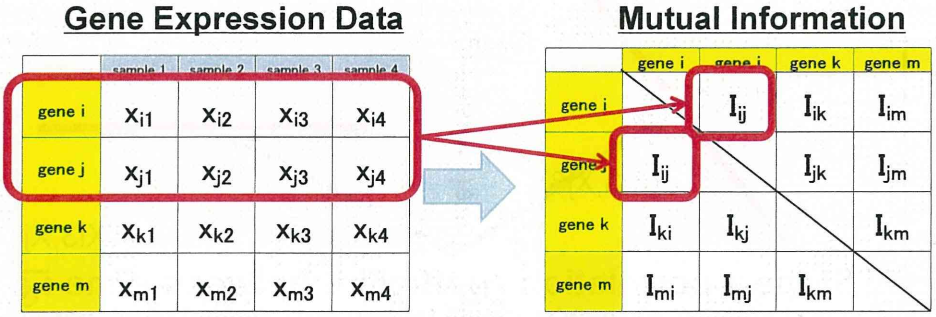
$$I(X,Y)=\sum_{i,j}P(x_i,y_j)\log\frac{P(x_i,y_j)}{P(x_i)P(y_j)}$$

$P(x_i)$ represents probability that expression level of gene X is x_i
$P(x_i,y_j)$ is joint probability.
where i, j represent sample points.
If X and Y are independent to each other, $P(x_i,y_j)=P(x_i)P(y_j)$.
In this case, $I(X,Y)=0$.

Mutual informationについて

Mutual information is a metric that detects statistical dependence between two variables(in this case, expression levels of two genes).
But unlike correlation coefficients, it does not assume continuity, linearity, and etc....

Mutual information between gene i and j; I_{ij}



Gene Expression Data

	sample 1	sample 2	sample 3	sample 4
gene i	x_{i1}	x_{i2}	x_{i3}	x_{i4}
gene j	x_{j1}	x_{j2}	x_{j3}	x_{j4}
gene k	x_{k1}	x_{k2}	x_{k3}	x_{k4}
gene m	x_{m1}	x_{m2}	x_{m3}	x_{m4}

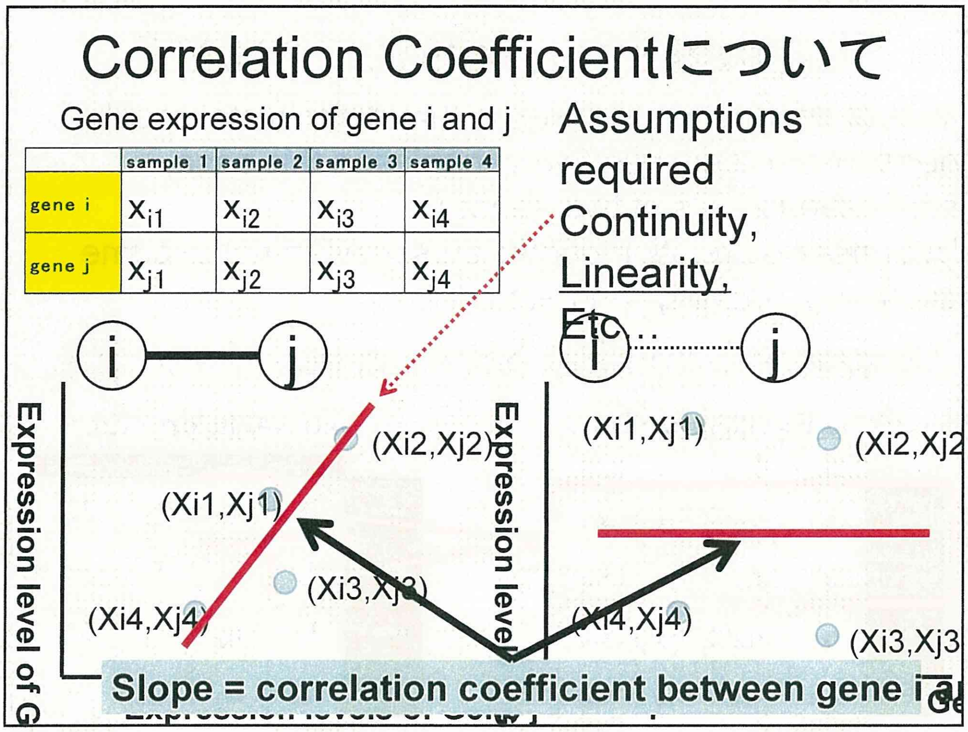
Mutual Information

	gene i	gene j	gene k	gene m
gene i		I_{ij}	I_{ik}	I_{im}
gene j	I_{ij}		I_{jk}	I_{jm}
gene k	I_{ki}	I_{kj}		I_{km}
gene m	I_{mi}	I_{mj}	I_{km}	

Mutual informationを用いてconfidence scoreを計算するアルゴリズムが複数存在する（代表的なものはARACNE、CLR、MRNET、C3NET、そして、RNの５種類）。

これらの５種のアルゴリズムを組み合わせてネットワークの予測（Top1Net）を行う。

Correlation Coefficientについて



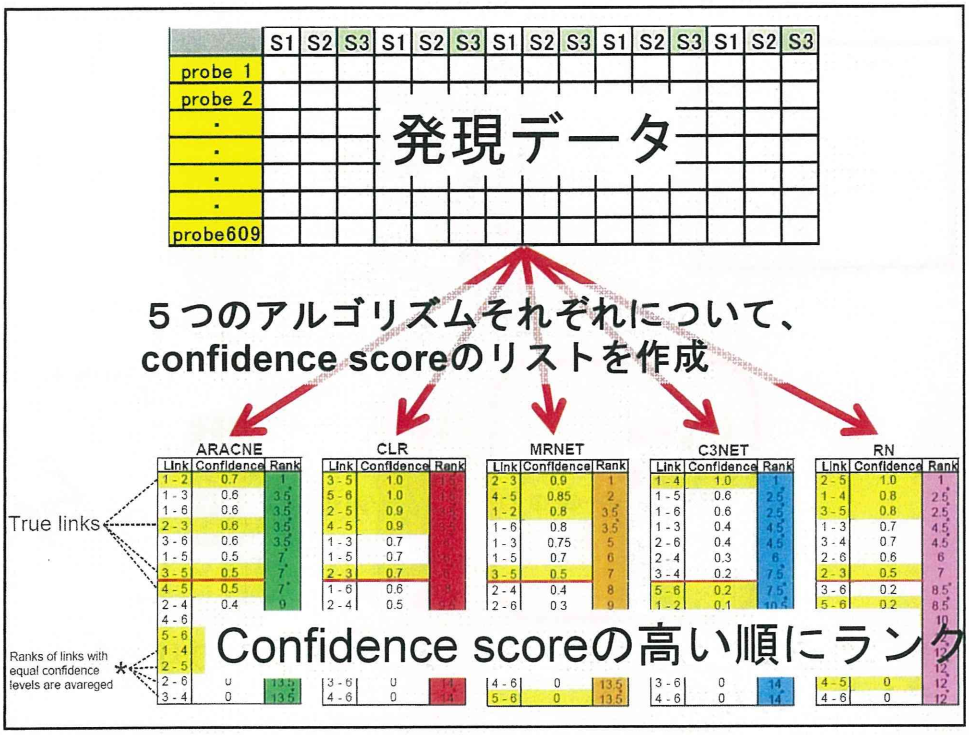
Gene expression of gene i and j

	sample 1	sample 2	sample 3	sample 4
gene i	x_{i1}	x_{i2}	x_{i3}	x_{i4}
gene j	x_{j1}	x_{j2}	x_{j3}	x_{j4}

Assumptions required
Continuity,
Linearity,
Etc…

Slope = correlation coefficient between gene i a

Top1Net法



	S1	S2	S3	S1	S2	S3	S1	S2	S3	S1	S2	S3	S1	S2	S3
probe 1															
probe 2															
·															
·															
·															
·															
probe609															

発現データ

５つのアルゴリズムそれぞれについて、
confidence scoreのリストを作成

ARACNE

Link	Confidence	Rank
1 - 2	0.7	1
1 - 3	0.6	3.5*
1 - 6	0.6	3.5*
2 - 3	0.6	3.5*
3 - 6	0.6	3.5*
1 - 5	0.5	7*
3 - 5	0.5	7*
4 - 5	0.5	7*
2 - 4	0.4	9
4 - 6		
5 - 6		
1 - 4		
2 - 5		
2 - 6	0	13.5*
3 - 4	0	13.5*

CLR

Link	Confidence	Rank
3 - 5	1.0	1.5
5 - 6	1.0	1.5
2 - 5	0.9	3.5
4 - 5	0.9	3.5
1 - 3	0.7	6
1 - 5	0.7	6
2 - 3	0.7	6
1 - 6	0.6	8
2 - 4	0.5	9.5
3 - 6	0	14
4 - 6	0	14

MRNET

Link	Confidence	Rank
2 - 3	0.9	1
4 - 5	0.85	2
1 - 2	0.8	3.5*
1 - 6	0.8	3.5*
1 - 3	0.75	5
1 - 5	0.7	6
3 - 5	0.5	7
2 - 4	0.4	8
2 - 6	0.3	9
4 - 6	0	13.5
5 - 6	0	13.5

C3NET

Link	Confidence	Rank
1 - 4	1.0	1
1 - 5	0.6	2.5*
1 - 6	0.6	2.5*
1 - 3	0.4	4.5*
2 - 6	0.4	4.5*
2 - 4	0.3	6
3 - 4	0.2	7.5*
5 - 6	0.2	7.5*
1 - 2	0.1	10.5*
3 - 6	0	14
4 - 6	0	14*

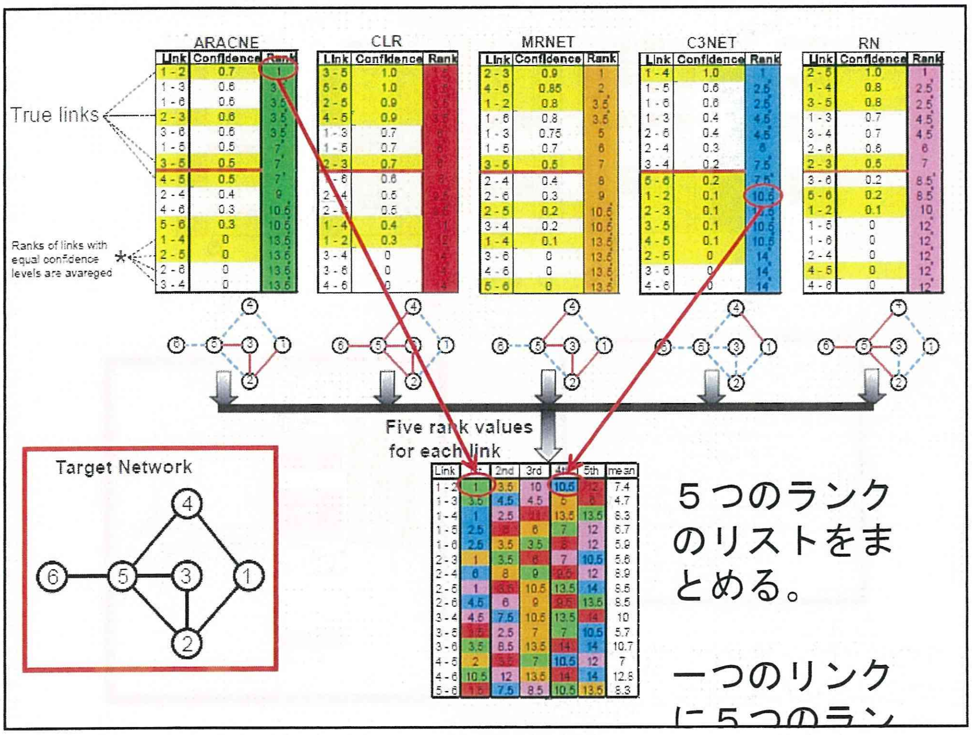
RN

Link	Confidence	Rank
2 - 5	1.0	1
1 - 4	0.8	2.5*
3 - 5	0.8	2.5*
1 - 3	0.7	4.5*
3 - 4	0.7	4.5*
2 - 6	0.6	6
2 - 3	0.5	7
3 - 6	0.2	8.5*
5 - 6	0.2	8.5*
		10
		12*
		12*
		12*
4 - 5	0	12*
4 - 6	0	12*

True links

Ranks of links with equal confidence levels are avareged *

Confidence scoreの高い順にランク



ARACNE

Link	Confidence	Rank
1 - 2	0.7	1
1 - 3	0.6	3.5*
1 - 6	0.6	3.5*
2 - 3	0.6	3.5*
3 - 6	0.6	3.5*
1 - 5	0.5	7*
3 - 5	0.5	7*
4 - 5	0.5	7*
2 - 4	0.4	9
4 - 6	0.3	10.5*
5 - 6	0.3	10.5*
1 - 4	0	13.5*
2 - 5	0	13.5*
2 - 6	0	13.5*
3 - 4	0	13.5*

CLR

Link	Confidence	Rank
3 - 5	1.0	1.5
5 - 6	1.0	1.5
2 - 5	0.9	3.5
4 - 5	0.9	3.5
1 - 3	0.7	6
1 - 5	0.7	6
2 - 3	0.7	6
1 - 6	0.6	8
2 - 4	0.5	9.5
2 - 6	0.5	9.5
1 - 4	0.4	11
1 - 2	0.3	12
3 - 4	0	14
3 - 6	0	14
4 - 6	0	14

MRNET

Link	Confidence	Rank
2 - 3	0.9	1
4 - 5	0.85	2
1 - 2	0.8	3.5*
1 - 6	0.8	3.5*
1 - 3	0.75	5
1 - 5	0.7	6
3 - 5	0.5	7
2 - 4	0.4	8
2 - 6	0.3	9
2 - 5	0.2	10.5*
3 - 4	0.2	10.5*
1 - 4	0.1	13.5*
3 - 6	0	13.5*
4 - 6	0	13.5*
5 - 6	0	13.5*

C3NET

Link	Confidence	Rank
1 - 4	1.0	1
1 - 5	0.6	2.5*
1 - 6	0.6	2.5*
1 - 3	0.4	4.5*
2 - 6	0.4	4.5*
2 - 4	0.3	6
3 - 4	0.2	7.5*
5 - 6	0.2	7.5*
1 - 2	0.1	10.5*
2 - 3	0.1	10.5*
3 - 5	0.1	10.5*
4 - 5	0.1	10.5*
2 - 5	0	14*
3 - 6	0	14*
4 - 6	0	14

RN

Link	Confidence	Rank
2 - 5	1.0	1
1 - 4	0.8	2.5*
3 - 5	0.8	2.5*
1 - 3	0.7	4.5*
3 - 4	0.7	4.5*
2 - 6	0.6	6
2 - 3	0.5	7
3 - 6	0.2	8.5*
5 - 6	0.2	8.5*
1 - 2	0.1	10
1 - 5	0	12*
1 - 6	0	12*
2 - 4	0	12*
4 - 5	0	12*
4 - 6	0	12*

True links

Ranks of links with equal confidence levels are avareged *

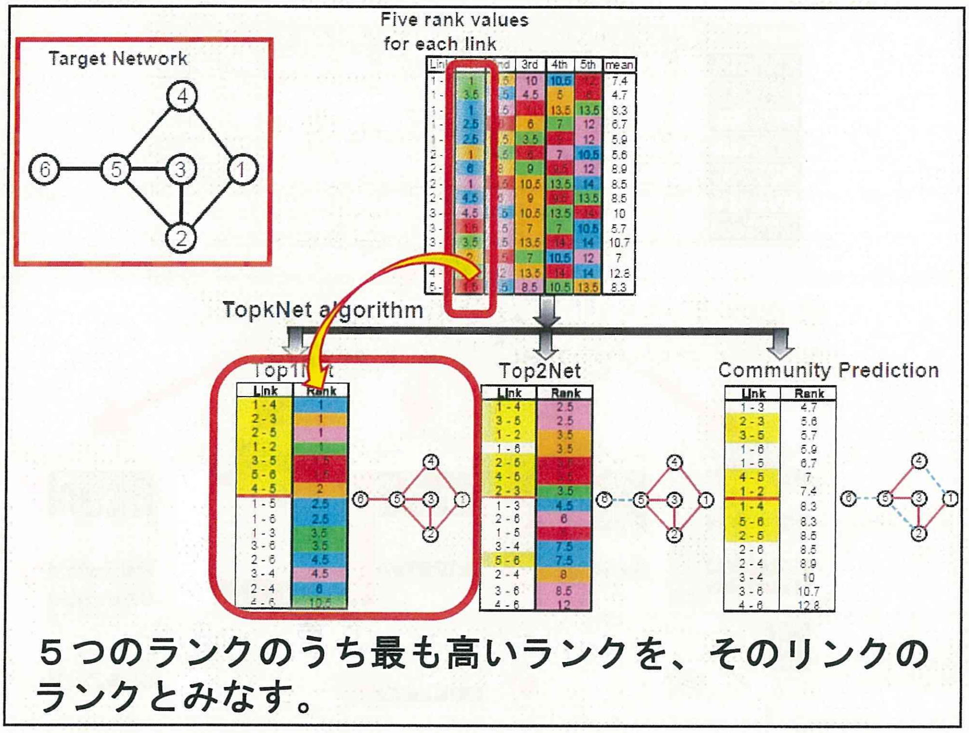
Five rank values for each link

Link	1st	2nd	3rd	4th	5th	mean
1 - 2	1	3.5	10	10.5	12	7.4
1 - 3	3.5	4.5	4.5	5	6	4.7
1 - 4	1	2.5	11	13.5	13.5	8.3
1 - 5	2.5	6	6	7	12	6.7
1 - 6	2.5	3.5	3.5	8	12	5.9
2 - 3	1	3.5	6	7	10.5	5.6
2 - 4	6	8	9	9.5	12	8.9
2 - 5	1	3.5	10.5	13.5	14	8.5
2 - 6	4.5	6	9	9.5	13.5	8.5
3 - 4	4.5	7.5	10.5	13.5	14	10
3 - 5	1.5	2.5	7	7	10.5	5.7
3 - 6	3.5	8.5	13.5	14	14	10.7
4 - 5	2	3.5	7	10.5	12	7
4 - 6	10.5	12	13.5	14	14	12.8
5 - 6	1.5	7.5	8.5	10.5	13.5	8.3

Target Network

５つのランク
のリストをま
とめる。

一つのリンク
に５つのラン



Five rank values
for each link

Lin		nd	3rd	4th	5th	mean
1 -	1	[illegible]	10	10.5	12	7.4
1 -	3.5	[illegible]	4.5	5	6	4.7
1 -	1	[illegible]	[illegible]	13.5	13.5	8.3
1 -	2.5	[illegible]	6	7	12	6.7
1 -	2.5	[illegible]	3.5	[illegible]	12	5.9
2 -	1	[illegible]	6	7	10.5	5.6
2 -	6	[illegible]	9	9.5	12	8.9
2 -	1	[illegible]	10.5	13.5	14	8.5
2 -	4.5	[illegible]	9	9.5	13.5	8.5
3 -	4.5	[illegible]	10.5	13.5	14	10
3 -	1.5	[illegible]	7	7	10.5	5.7
3 -	3.5	[illegible]	13.5	14	14	10.7
	2	[illegible]	7	10.5	12	7
4 -	[illegible]	[illegible]	13.5	14	14	12.8
5 -	1.5	[illegible]	8.5	10.5	13.5	8.3

TopkNet algorithm

Top1Net

Link	Rank
1 - 4	1
2 - 3	1
2 - 5	1
1 - 2	1
3 - 5	1.5
5 - 6	1.5
4 - 5	2
1 - 5	2.5
1 - 6	2.5
1 - 3	3.5
3 - 6	3.5
2 - 6	4.5
3 - 4	4.5
2 - 4	6
4 - 6	10.5

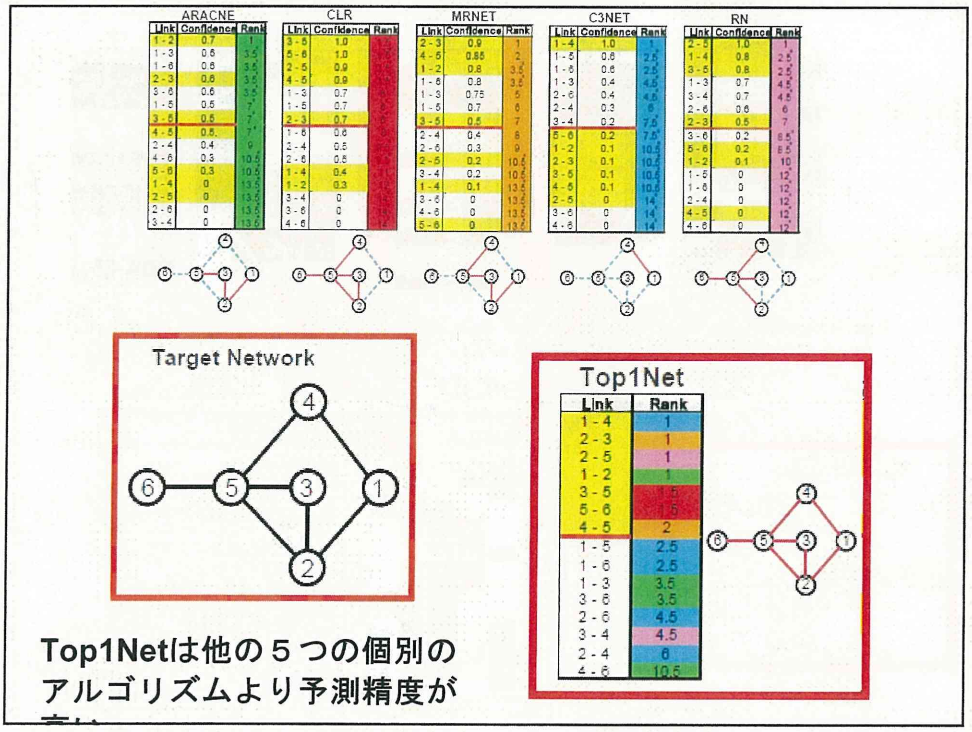
Top2Net

Link	Rank
1 - 4	2.5
3 - 5	2.5
1 - 2	3.5
1 - 6	3.5
2 - 5	3.5
4 - 5	3.5
2 - 3	3.5
1 - 3	4.5
2 - 6	6
1 - 5	[illegible]
3 - 4	7.5
5 - 6	7.5
2 - 4	8
3 - 6	8.5
4 - 6	12

Community Prediction

Link	Rank
1 - 3	4.7
2 - 3	5.6
3 - 5	5.7
1 - 6	5.9
1 - 5	6.7
4 - 5	7
1 - 2	7.4
1 - 4	8.3
5 - 6	8.3
2 - 5	8.5
2 - 6	8.5
2 - 4	8.9
3 - 4	10
3 - 6	10.7
4 - 6	12.8

５つのランクのうち最も高いランクを、そのリンクのランクとみなす。



ARACNE

Link	Confidence	Rank
1 - 2	0.7	1
1 - 3	0.6	3.5
1 - 6	0.6	3.5
2 - 3	0.6	3.5
3 - 6	0.6	3.5
1 - 5	0.5	7
3 - 5	0.5	7
4 - 5	0.5	7
2 - 4	0.4	9
4 - 6	0.3	10.5
5 - 6	0.3	10.5
1 - 4	0	13.5
2 - 5	0	13.5
2 - 6	0	13.5
3 - 4	0	13.5

CLR

Link	Confidence	Rank
3 - 5	1.0	[illegible]
5 - 6	1.0	[illegible]
2 - 5	0.9	[illegible]
4 - 5	0.9	[illegible]
1 - 3	0.7	[illegible]
1 - 5	0.7	[illegible]
2 - 3	0.7	[illegible]
1 - 6	0.6	[illegible]
2 - 4	0.5	[illegible]
2 - 6	0.5	[illegible]
1 - 4	0.4	[illegible]
1 - 2	0.3	[illegible]
3 - 4	0	[illegible]
3 - 6	0	[illegible]
4 - 6	0	[illegible]

MRNET

Link	Confidence	Rank
2 - 3	0.9	1
4 - 5	0.85	2
1 - 2	0.8	3.5
1 - 6	0.8	3.5
1 - 3	0.75	5
1 - 5	0.7	6
3 - 5	0.5	7
2 - 4	0.4	8
2 - 6	0.3	9
2 - 5	0.2	10.5
3 - 4	0.2	10.5
1 - 4	0.1	13.5
3 - 6	0	13.5
4 - 6	0	13.5
5 - 6	0	13.5

C3NET

Link	Confidence	Rank
1 - 4	1.0	1
1 - 5	0.6	2.5
1 - 6	0.6	2.5
1 - 3	0.4	4.5
2 - 6	0.4	4.5
2 - 4	0.3	6
3 - 4	0.2	7.5
5 - 6	0.2	7.5
1 - 2	0.1	10.5
2 - 3	0.1	10.5
3 - 5	0.1	10.5
4 - 5	0.1	10.5
2 - 5	0	14
3 - 6	0	14
4 - 6	0	14

RN

Link	Confidence	Rank
2 - 5	1.0	1
1 - 4	0.8	2.5
3 - 5	0.8	2.5
1 - 3	0.7	4.5
3 - 4	0.7	4.5
2 - 6	0.6	6
2 - 3	0.5	7
3 - 6	0.2	8.5
5 - 6	0.2	8.5
1 - 2	0.1	10
1 - 5	0	12
1 - 6	0	12
2 - 4	0	12
4 - 5	0	12
4 - 6	0	12

Top1Net

Link	Rank
1 - 4	1
2 - 3	1
2 - 5	1
1 - 2	1
3 - 5	1.5
5 - 6	1.5
4 - 5	2
1 - 5	2.5
1 - 6	2.5
1 - 3	3.5
3 - 6	3.5
2 - 6	4.5
3 - 4	4.5
2 - 4	6
4 - 6	10.5

Top1Netは他の５つの個別の
アルゴリズムより予測精度が
高い

TCDD expression dataset

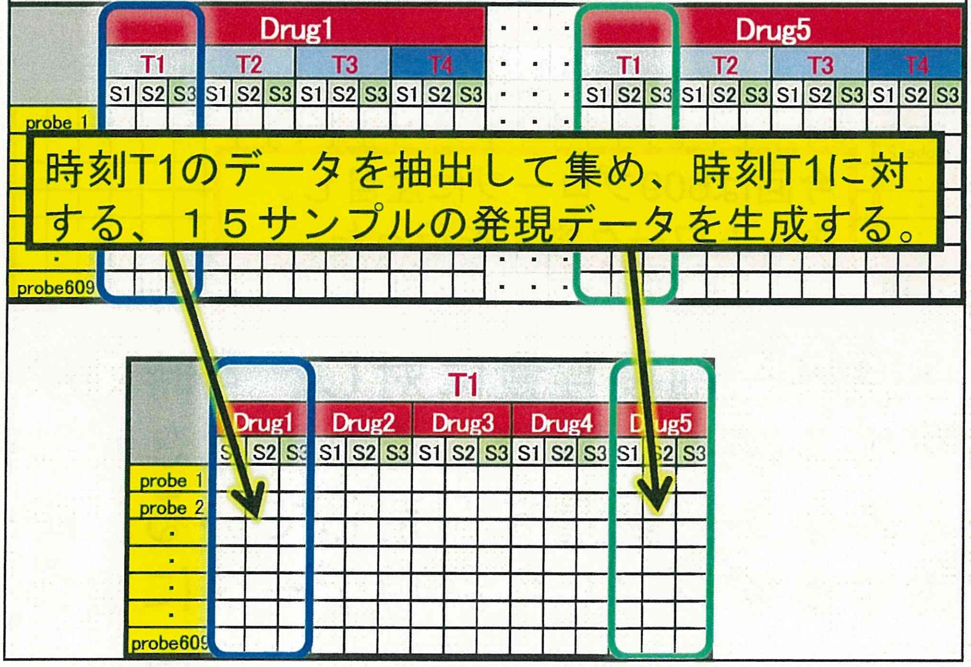
TCDD data

今回は609プローブに注目し、
ネットワーク推定を行った。

５種の薬剤投与量に対し、４時刻のタイムポイントで、それぞれ３サンプルとり発現量を測定している。合計６０サンプルの発現データになる。

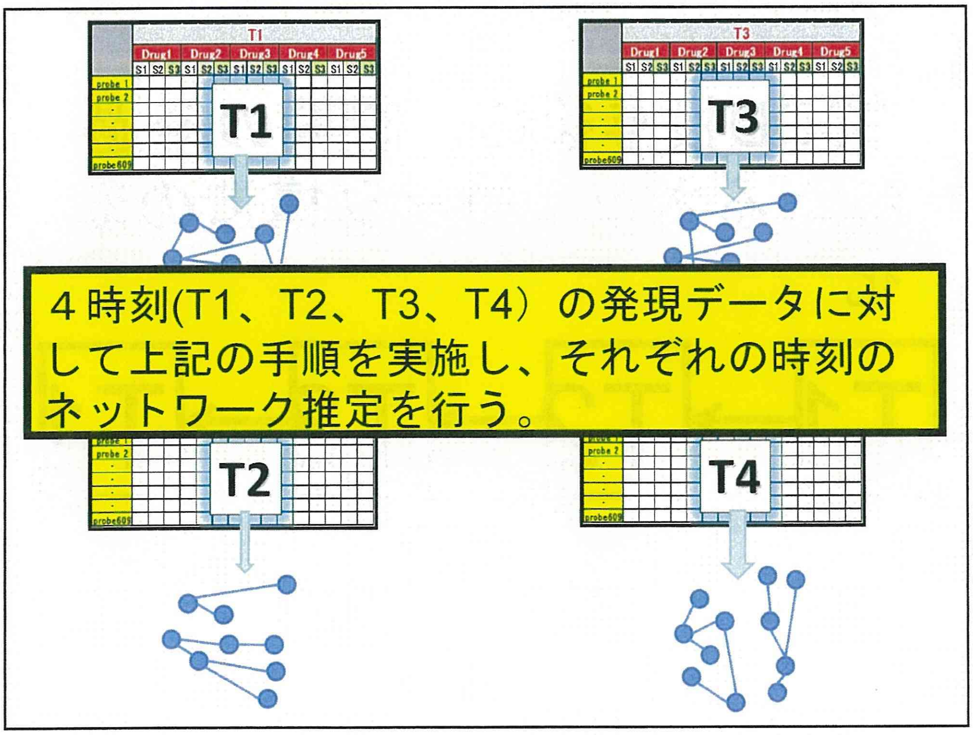
TCDD投与後の、時刻の経過による
ネットワーク構造の変化を探索する。

TCDD data



時刻T1のデータを抽出して集め、時刻T1に対する、１５サンプルの発現データを生成する。

４時刻(T1、T2、T3、T4）それぞれに対して１５サンプルの発現データを生成。これら４つの発現データから、それぞれの時刻のネットワーク推定を行う。

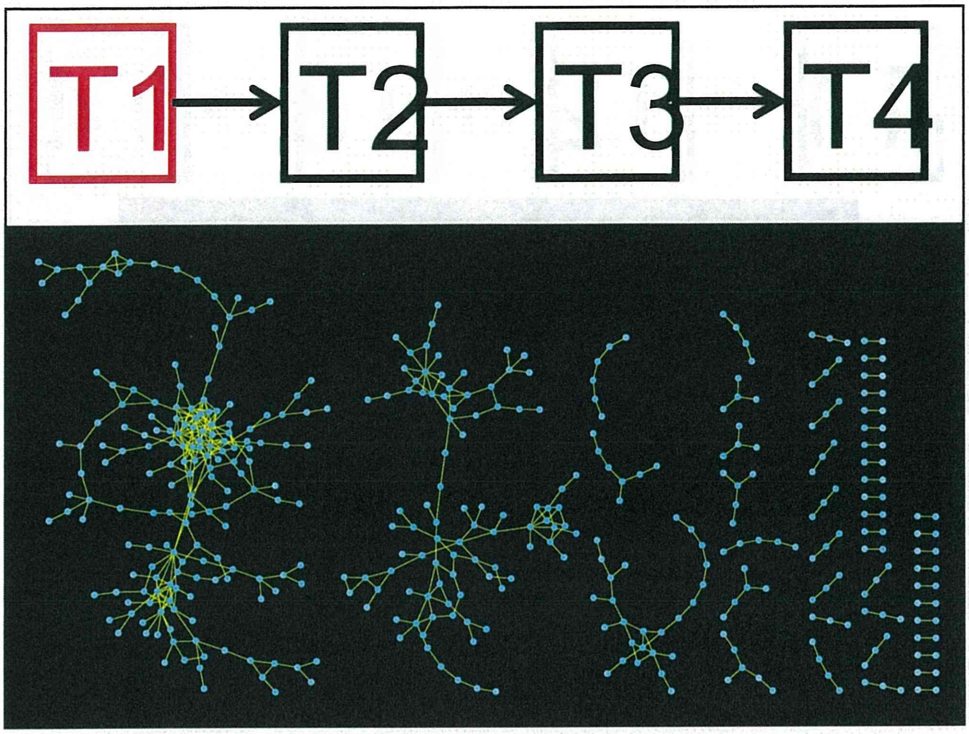


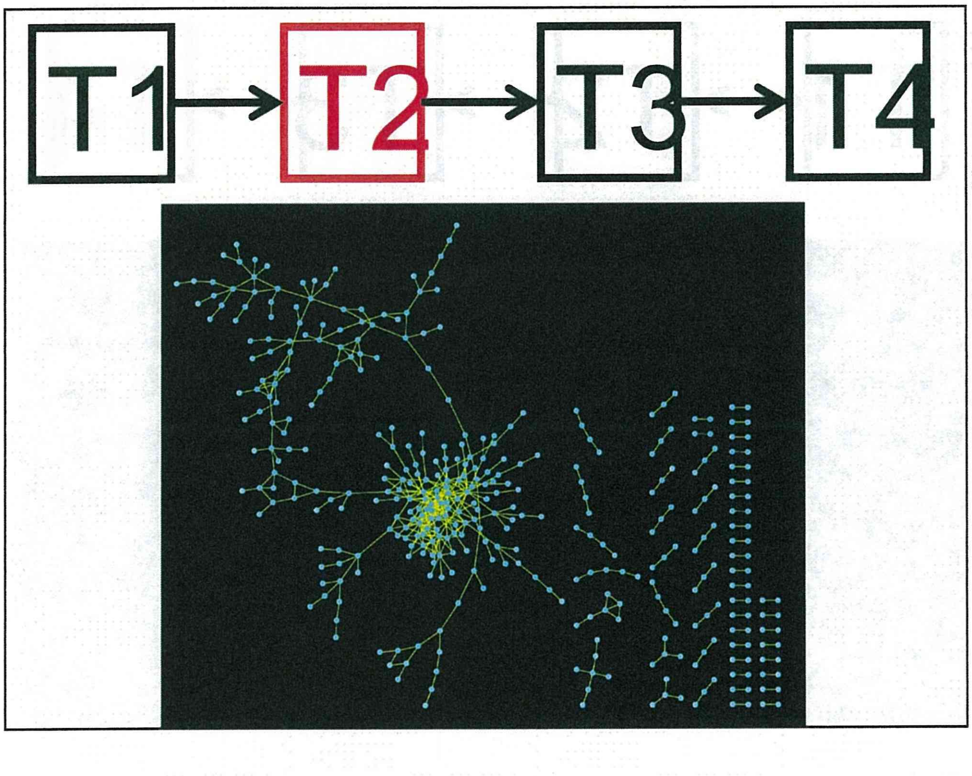
４時刻(T1、T2、T3、T4）の発現データに対して上記の手順を実施し、それぞれの時刻のネットワーク推定を行う。

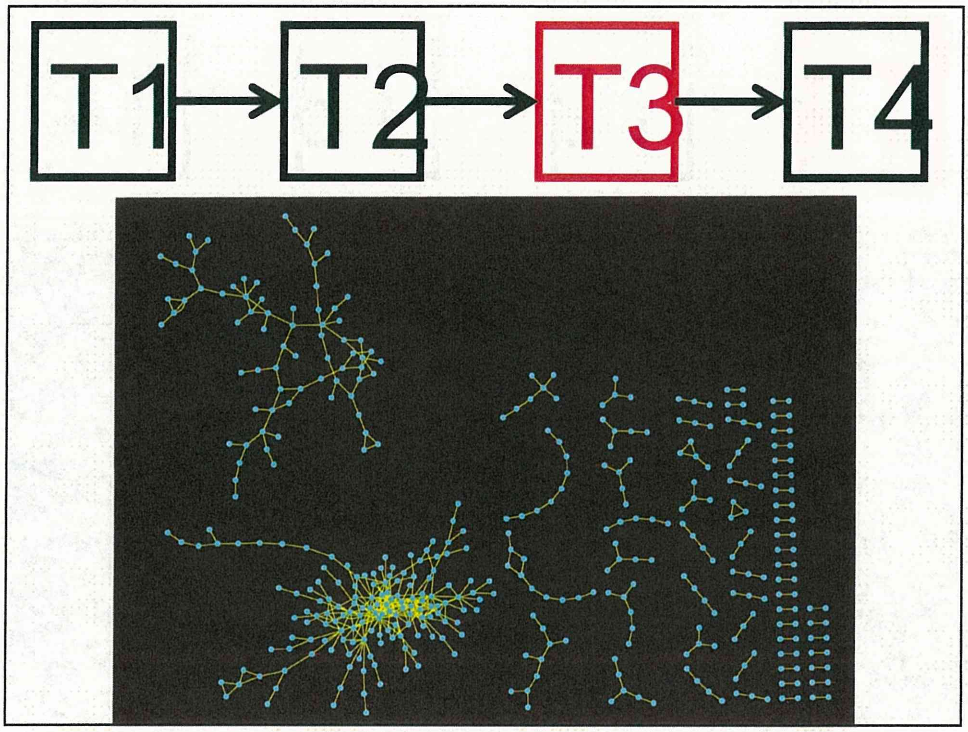
Results1

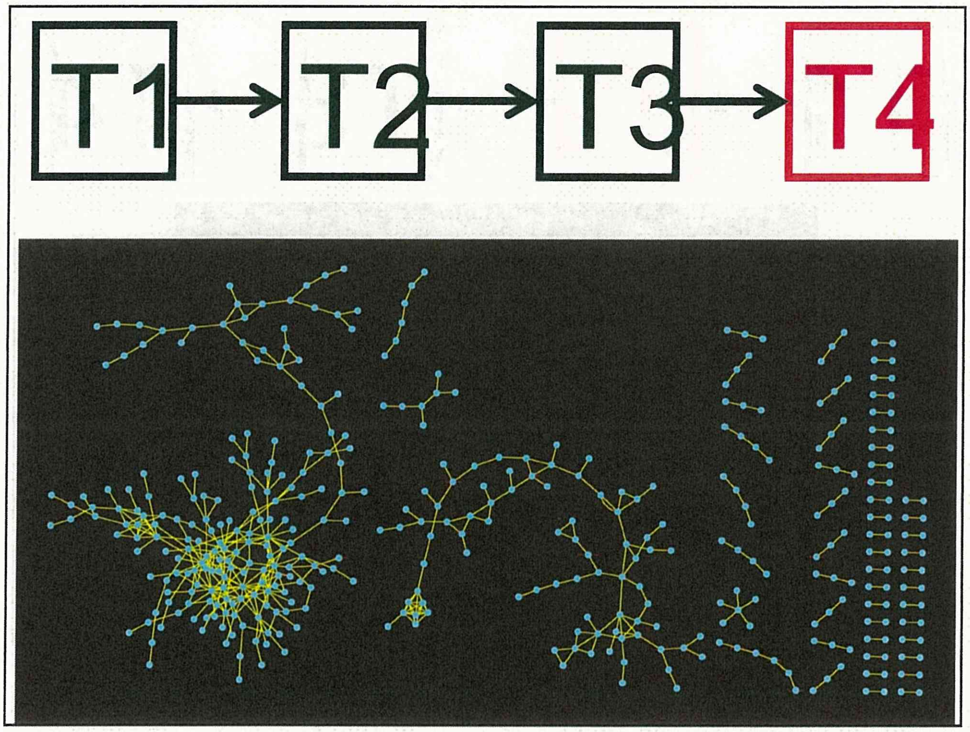
TCDD投与後の、時間の経過によるネットワーク構造の変化

T1 → T2 → T3 → T1

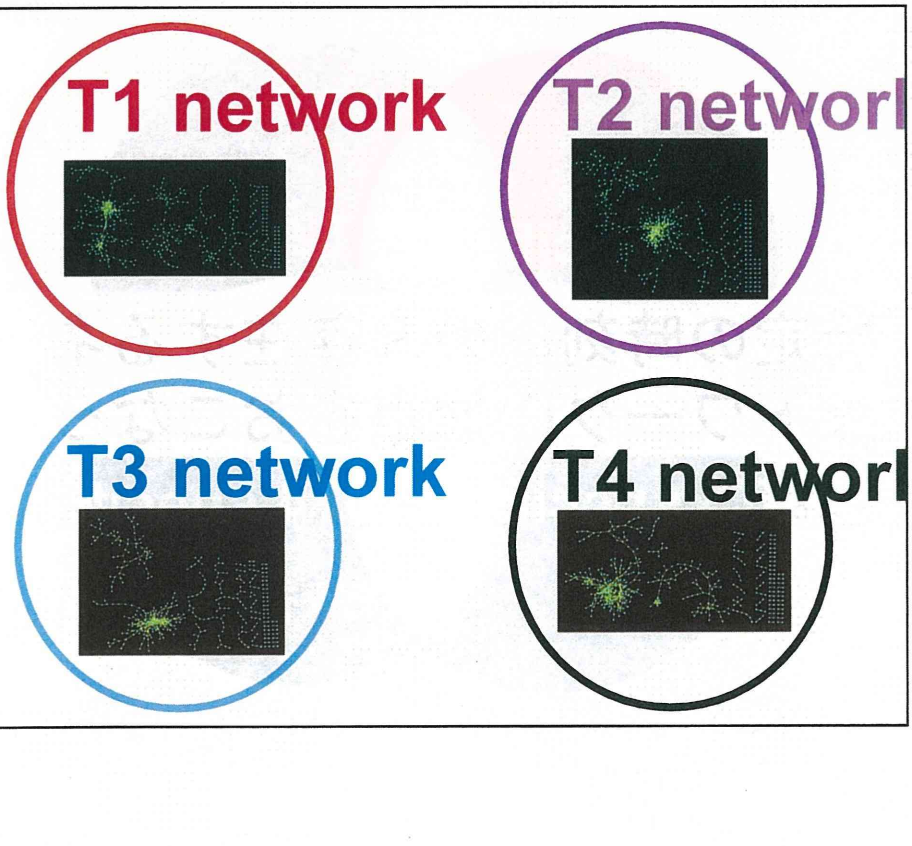

T1
T2
T3
T4


T1
T2
T3
T4


T1
T2
T3
T4


T1
T2
T3
T4

Results2



T1 network

T2 networ

T3 network

T4 networ