Learning Boolean Models of Regulatory Networks Using Improved Particle Swarm Optimization

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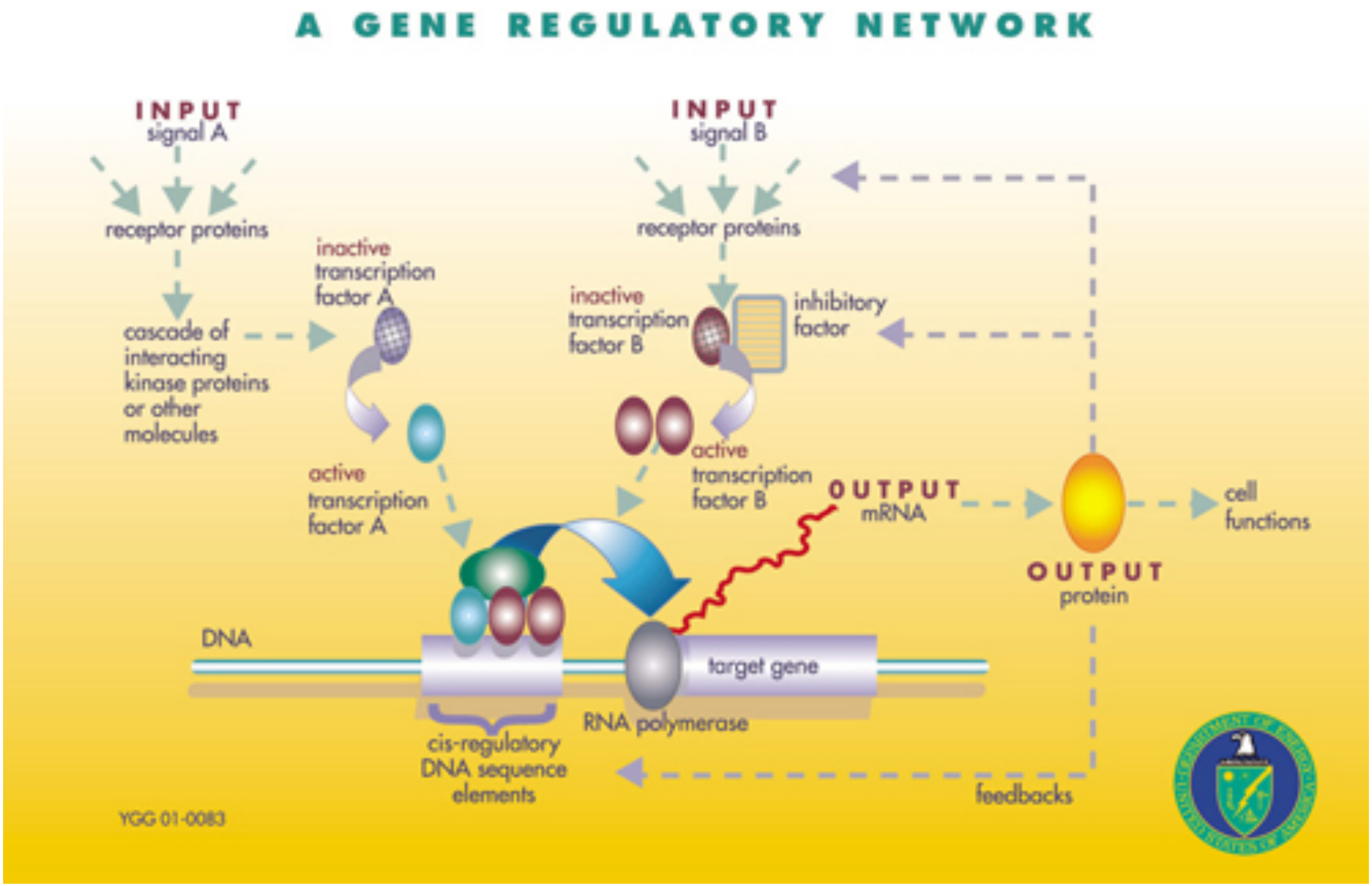
Advisor: Prof. Luay Nakhleh

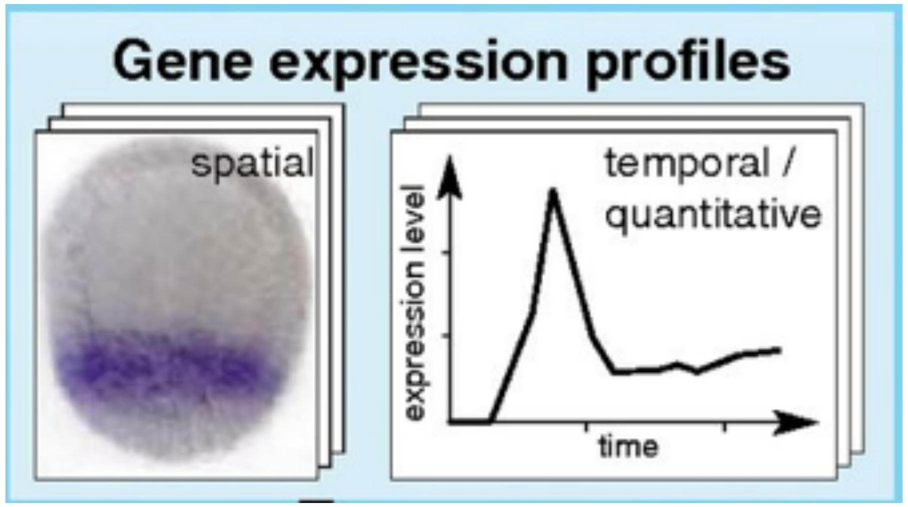
Comp 600
10/28/2013


A GENE REGULATORY NETWORK
INPUT
signal A
receptor proteins
cascade of interacting kinase proteins or other molecules
inactive transcription factor A
active transcription factor A
INPUT
signal B
receptor proteins
inactive transcription factor B
inhibitory factor
active transcription factor B
OUTPUT
mRNA
OUTPUT
protein
cell functions
DNA
target gene
RNA polymerase
cis-regulatory DNA sequence elements
feedbacks
YGG 01-0083

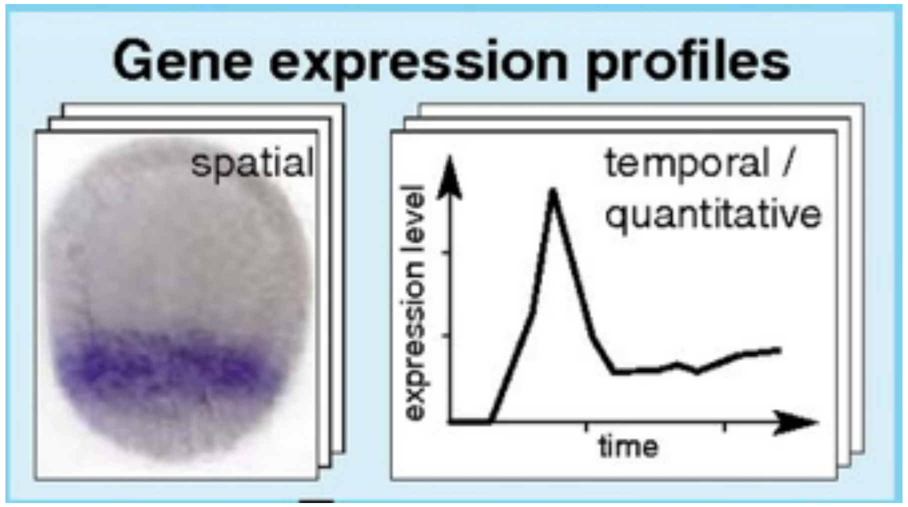
Why are Gene Regulatory Networks (GRN) Important?

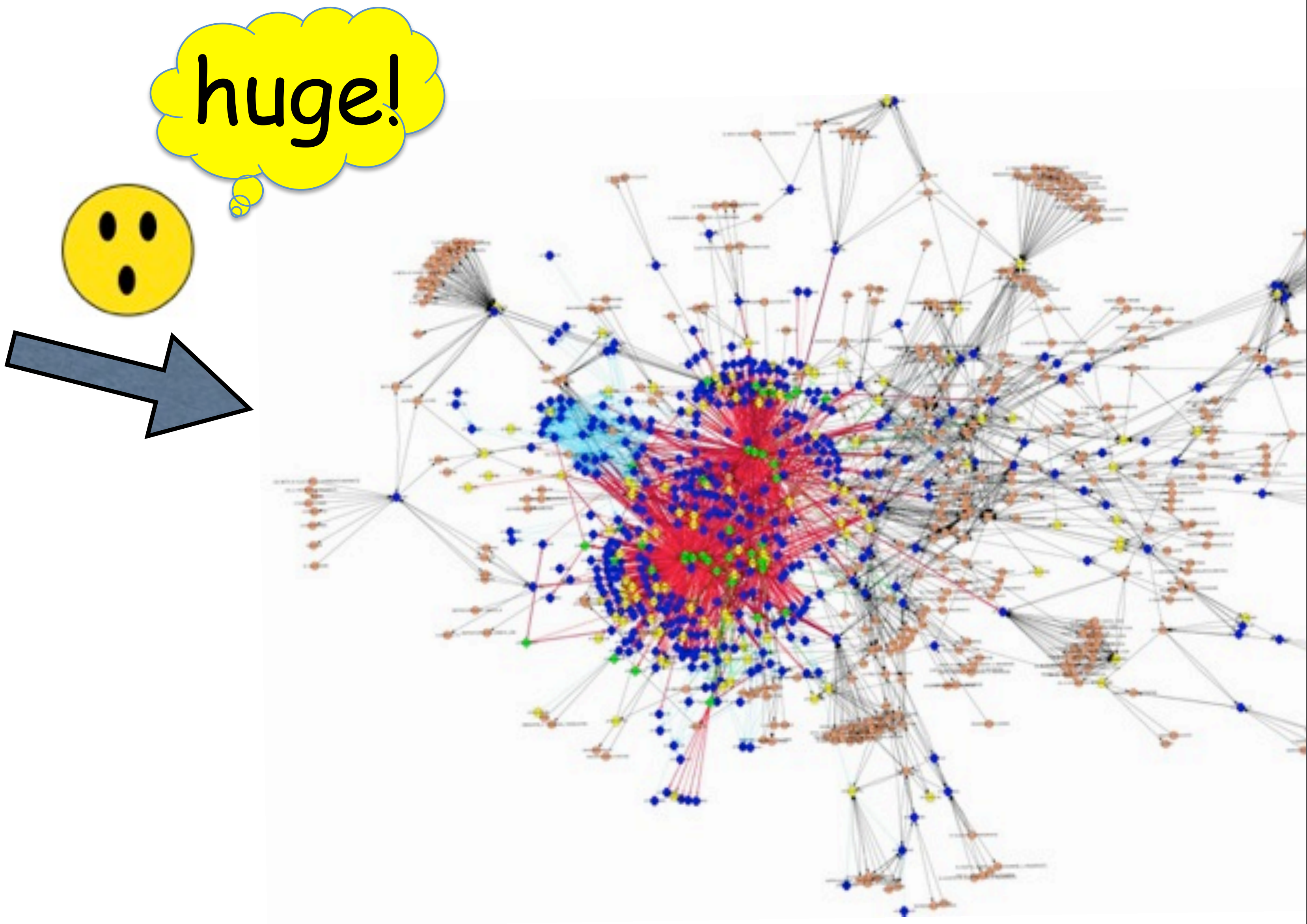
- Essential to the survival and adaptation of the organism.
- Malfunctioning leads to **disease** (e.g: **Cancer, Alzheimer's disease**)
- Potential discovery of triggering mechanism.
- Accurate Diagnosis and proper treatments for disease.
- Targeted **drug development**.

Challenges in Inferring GRN

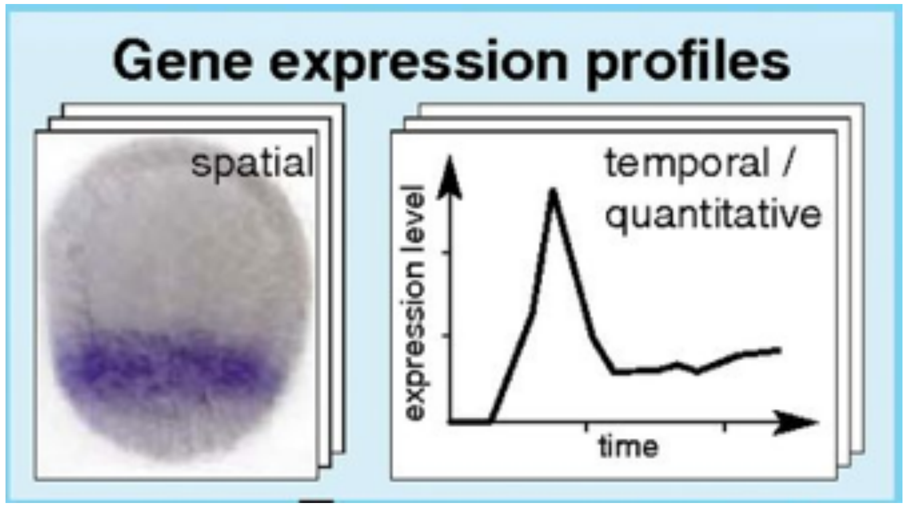


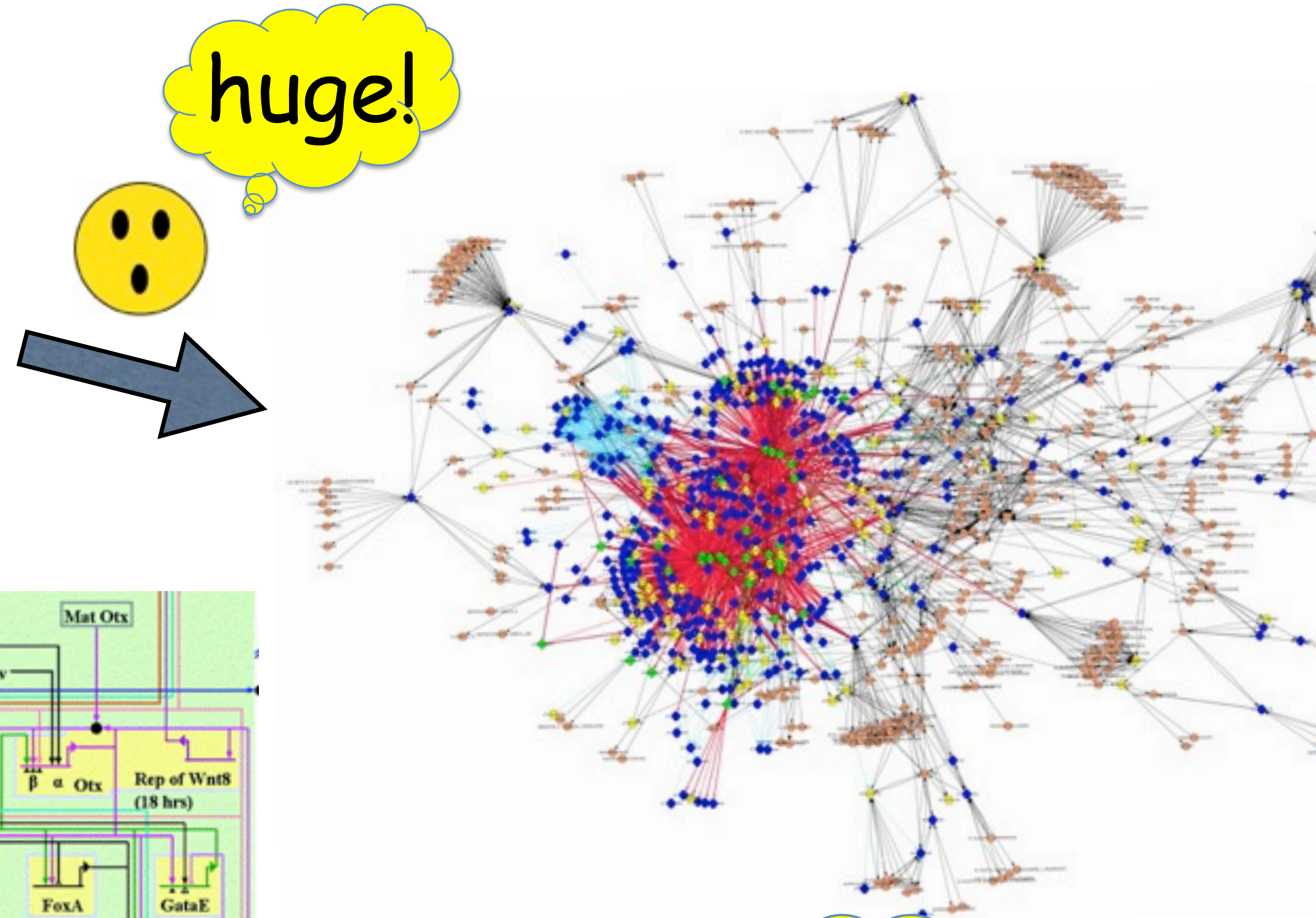
Challenges in Inferring GRN

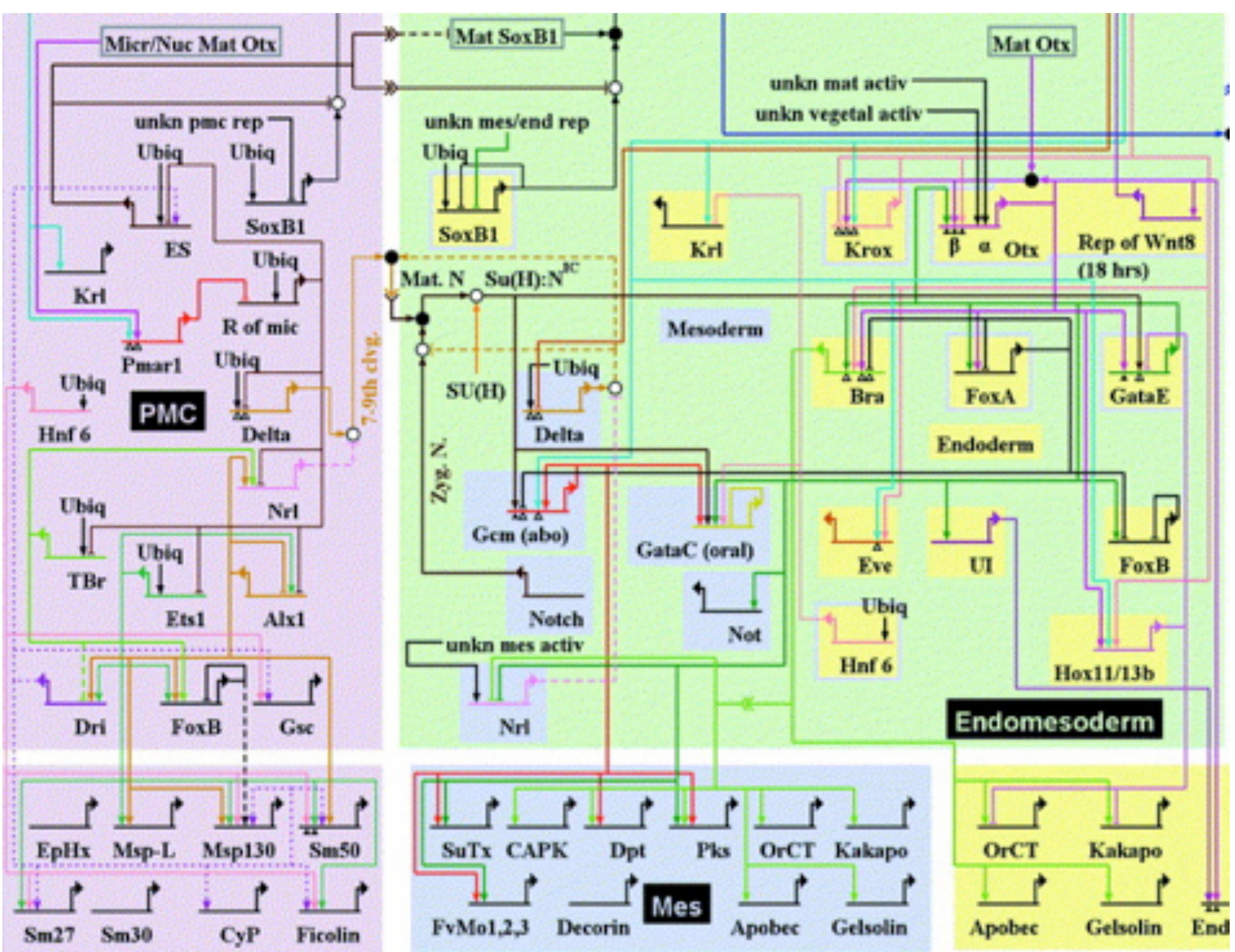




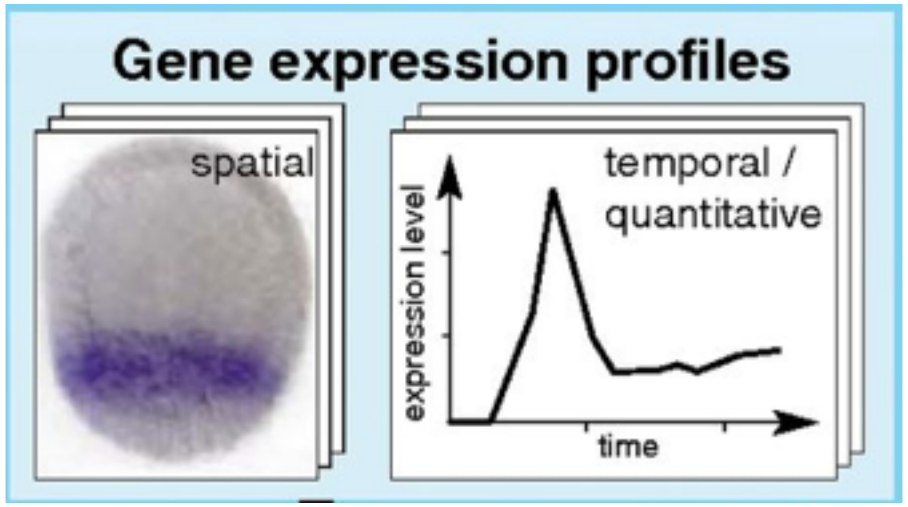
Challenges in Inferring GRN

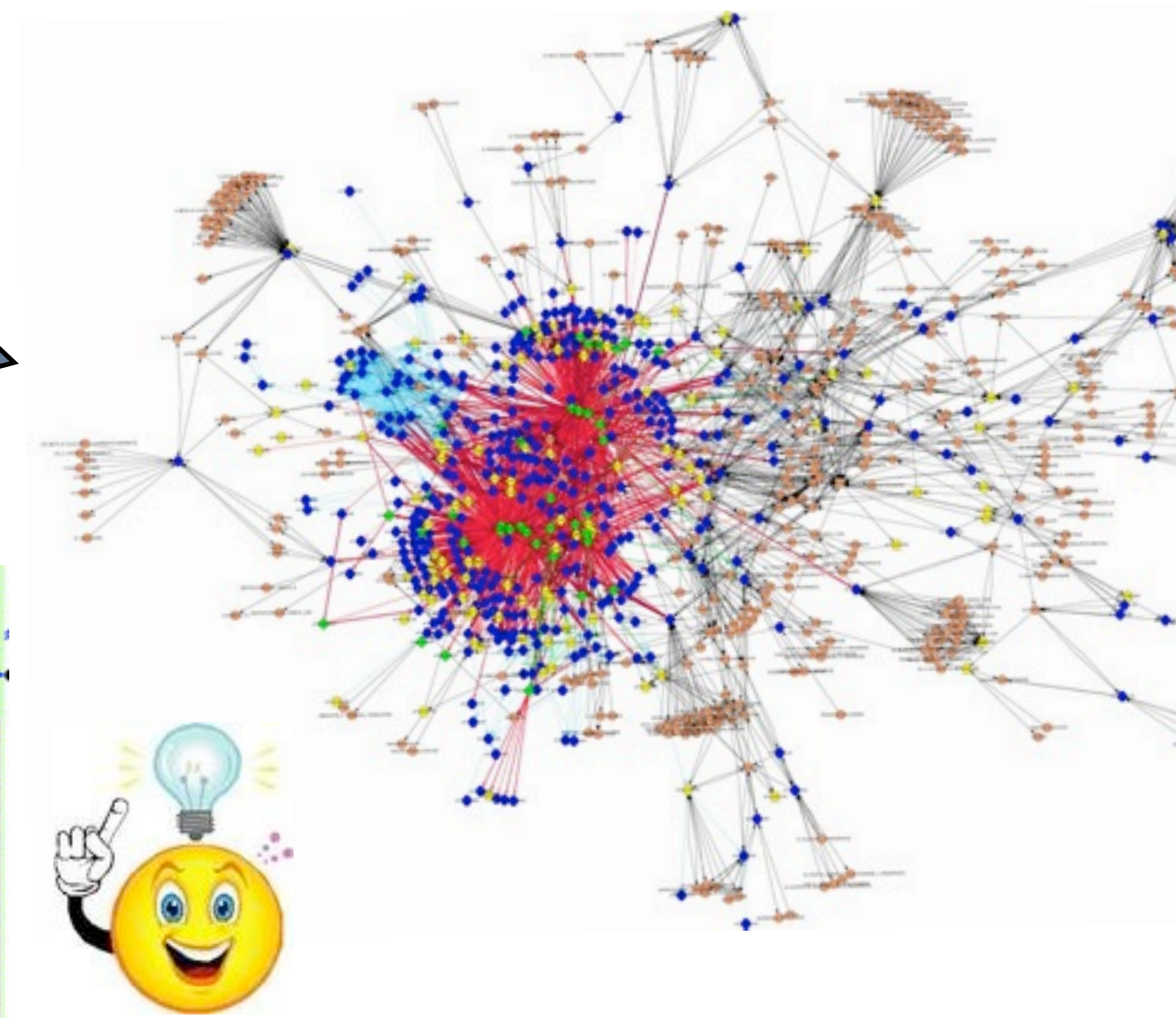


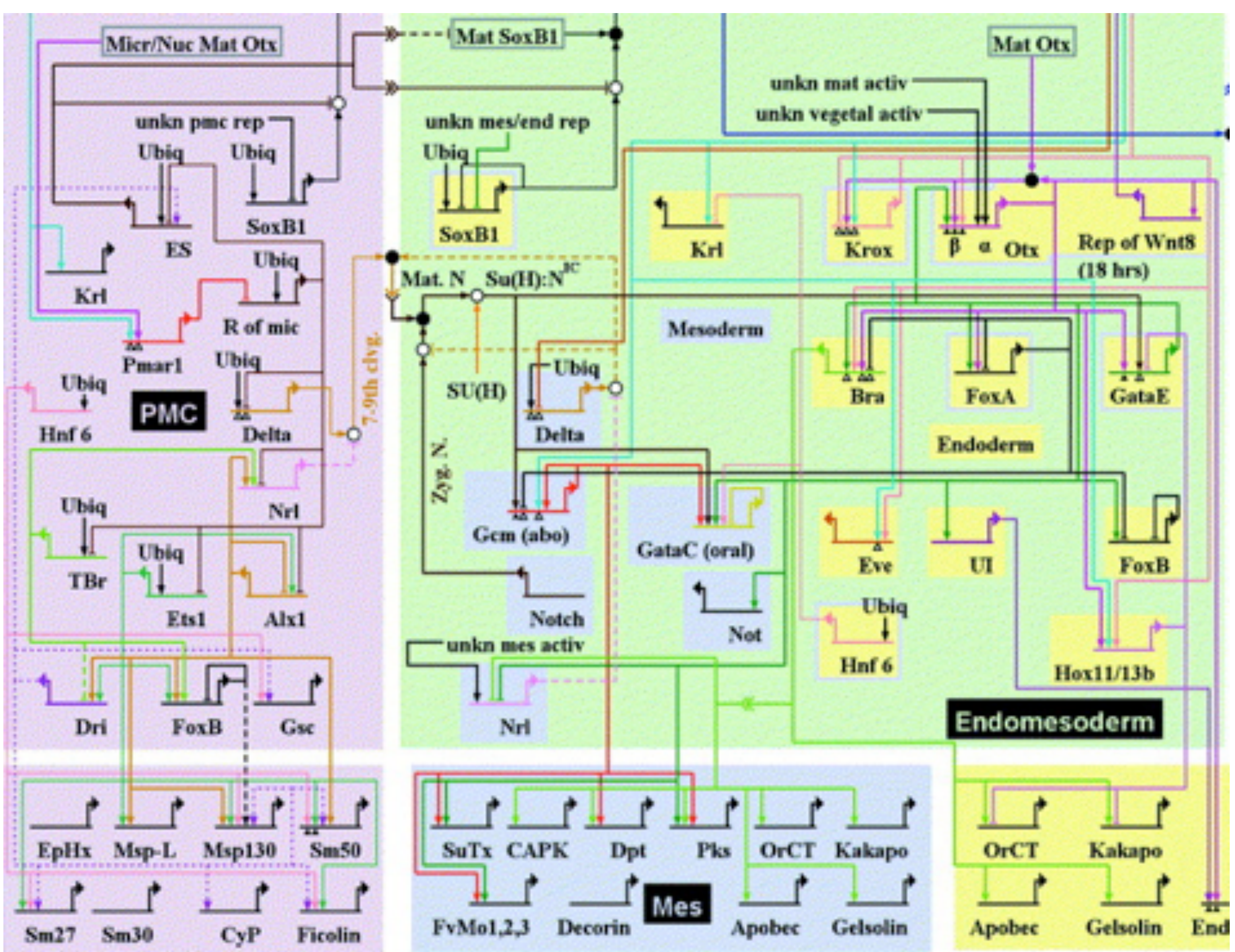




Challenges in Inferring GRN







Remedy:

Modeling Framework

Computational Tool

Modeling Framework for GRN

Linear Models Regression — Lot of Parameters!

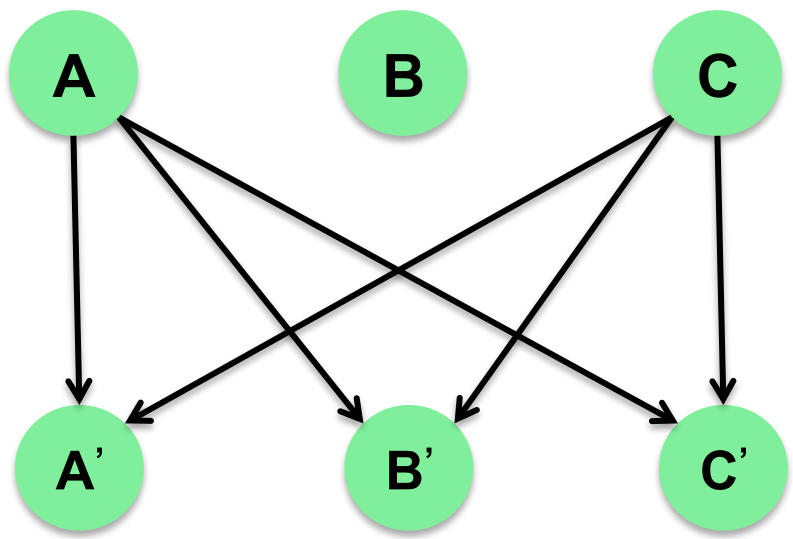
Bayesian Network — No Cycles! No Feedback!

Ordinary Differential Equations — Prior Knowledge of Kinetics??

Boolean Network

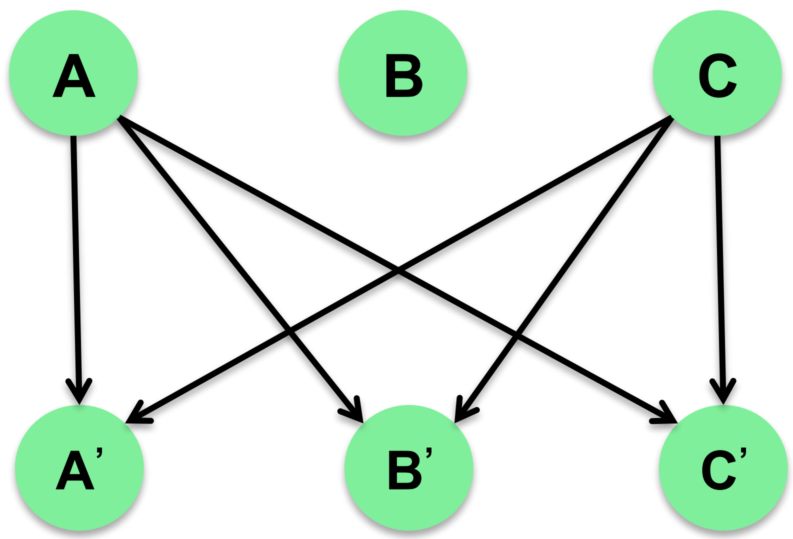
- *Simplicity
- *Capture the Dynamics
- *Capture Steady State Behavior
- *Smaller amount of Data

Boolean Network



A' = not A and C
B' = (not A and not C) or (A and C)
C' = not C or A

Boolean Network



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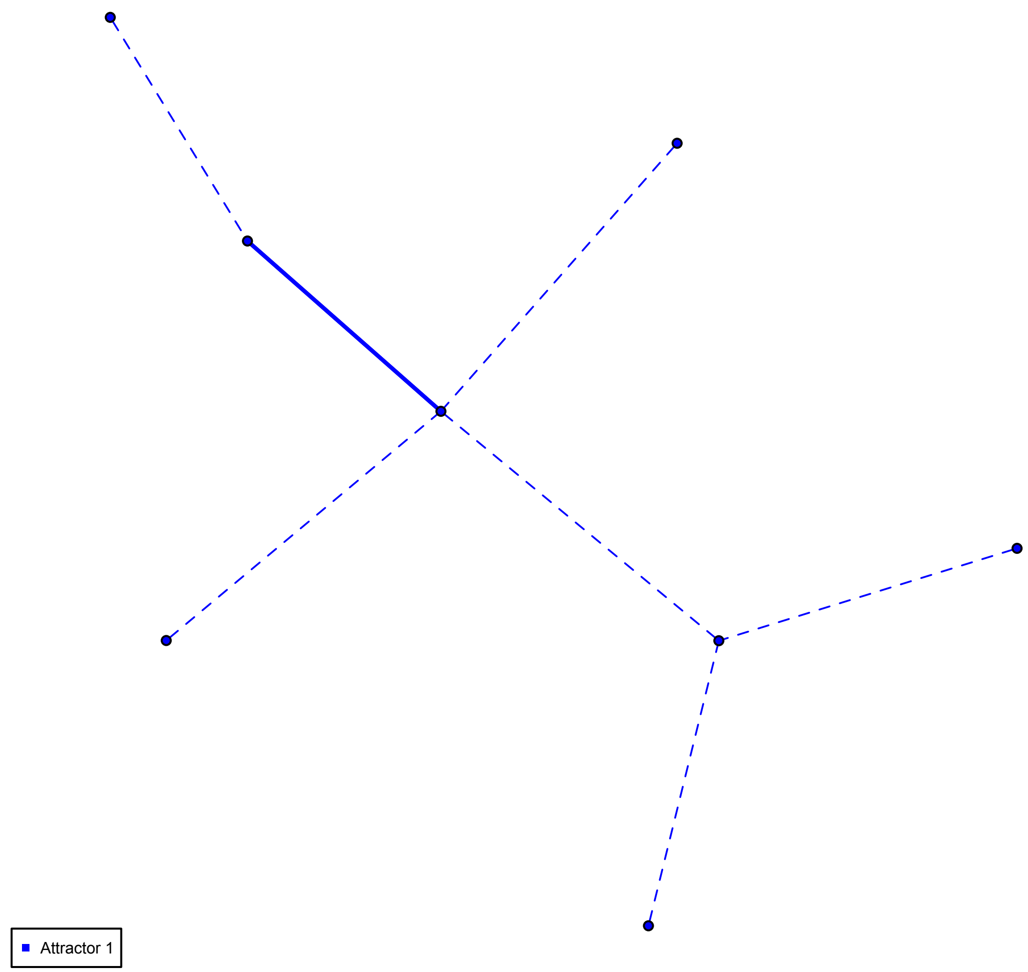
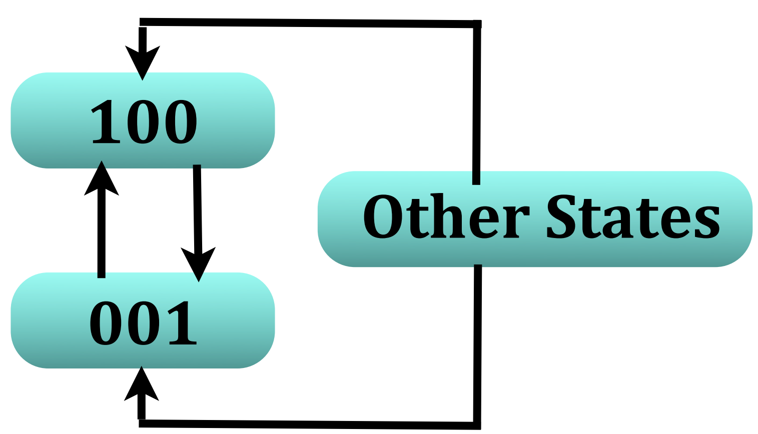
C' = not C or A

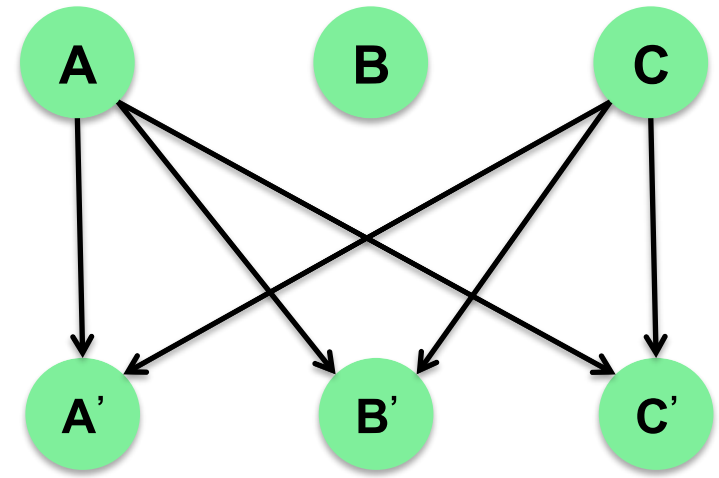
A	B	C	A'	B'	C'
0	0	0	0	1	1
0	0	1	1	0	0
0	1	0	0	1	1
0	1	1	1	0	0
1	0	0	0	0	1
1	0	1	0	1	1
1	1	0	0	0	1
1	1	1	0	1	1

- 1 active/expressed
- 0 inactive/unexpressed
- Steady states are called Attractors

Boolean Network







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A	B	C	A'	B'	C'
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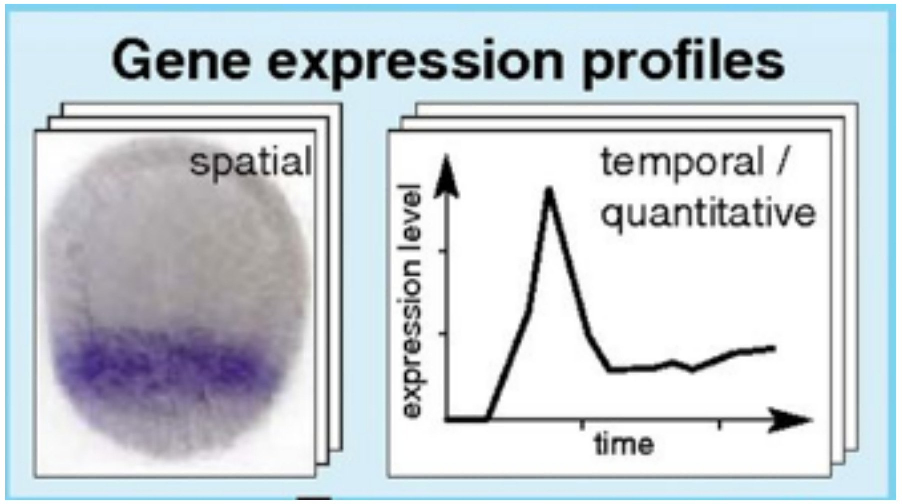
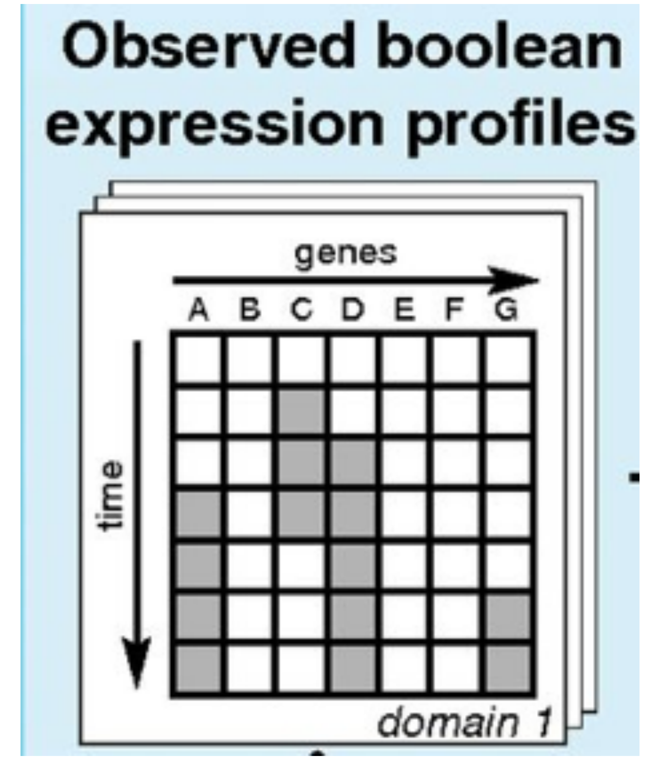
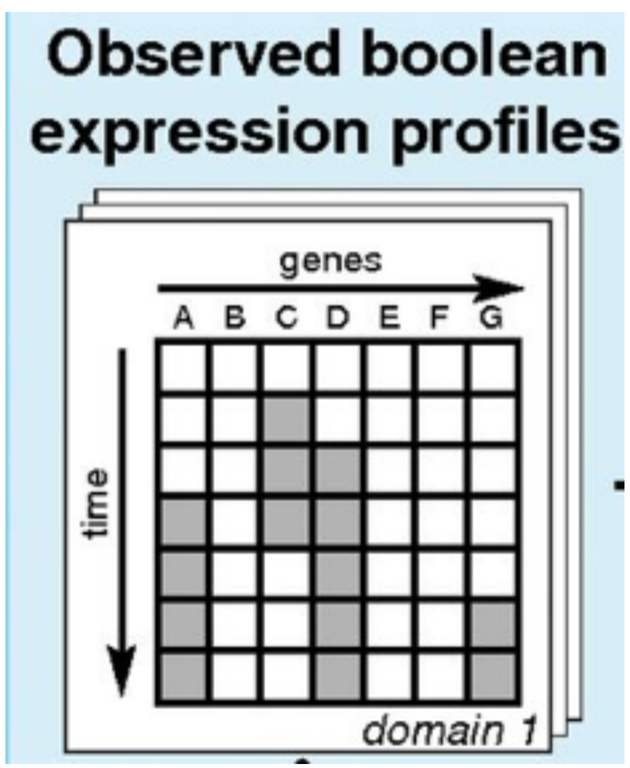
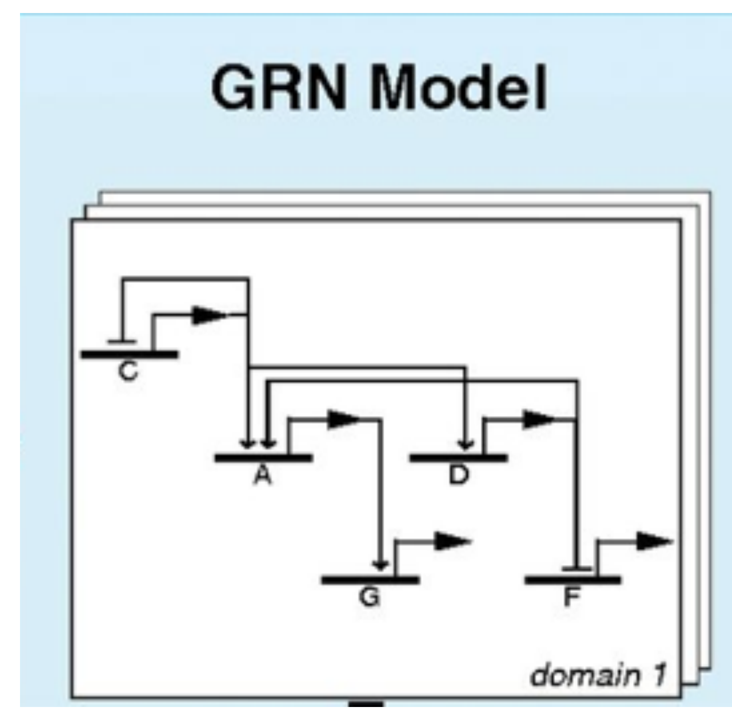
0	1	0	0	1	1
0	1	1	1	0	0
1	0	0	0	0	1
1	0	1	0	1	1
1	1	0	0	0	1
1	1	1	0	1	1

Inference of GRN

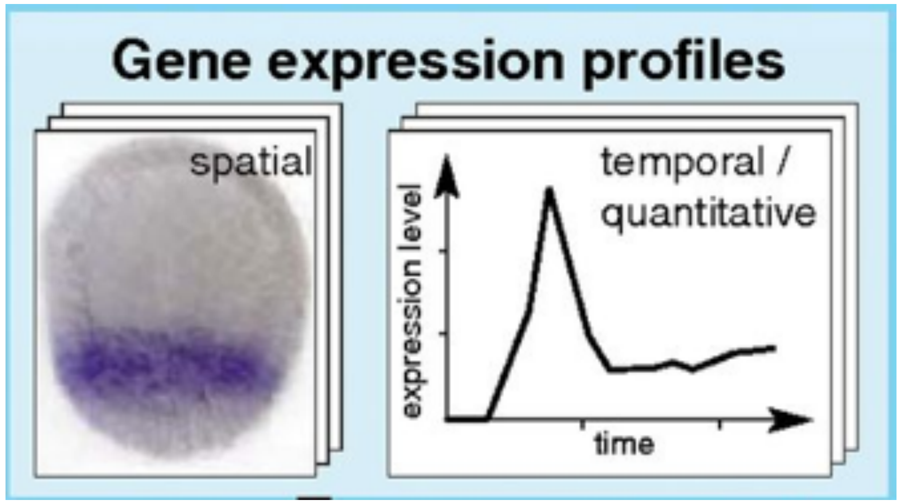






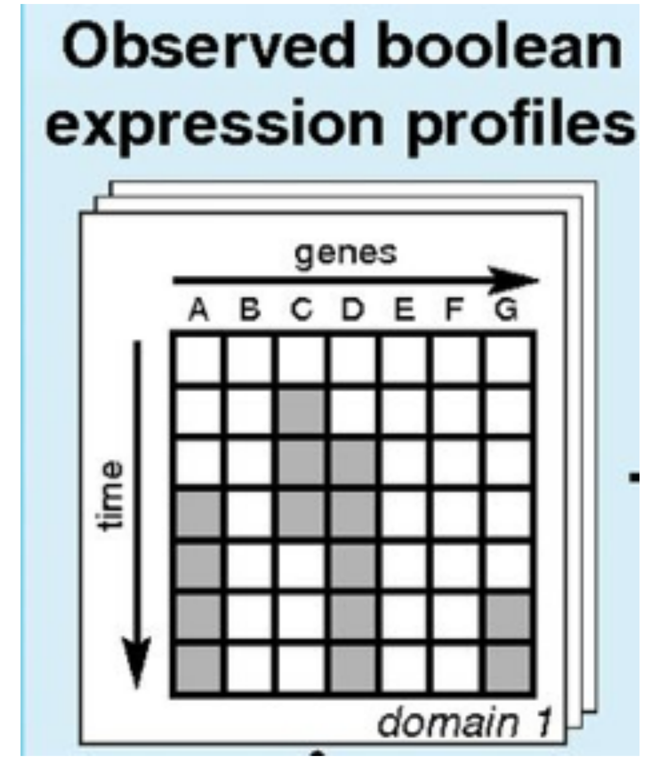


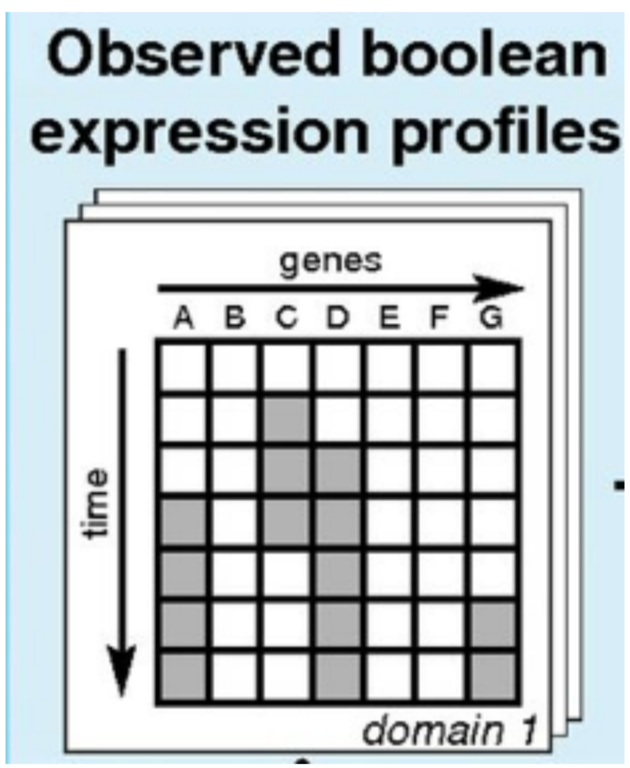
Inference of GRN

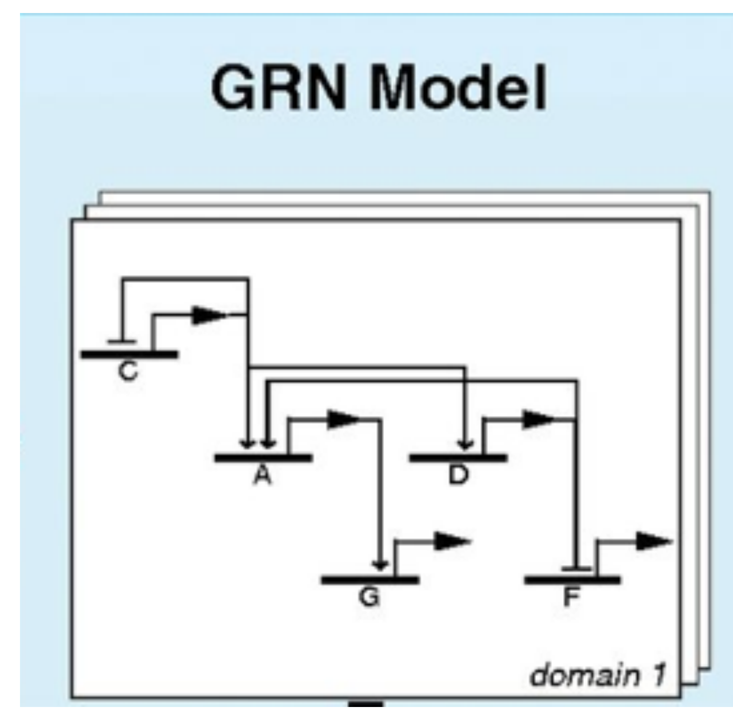


Step 1: Binarization

Iterative Clustering







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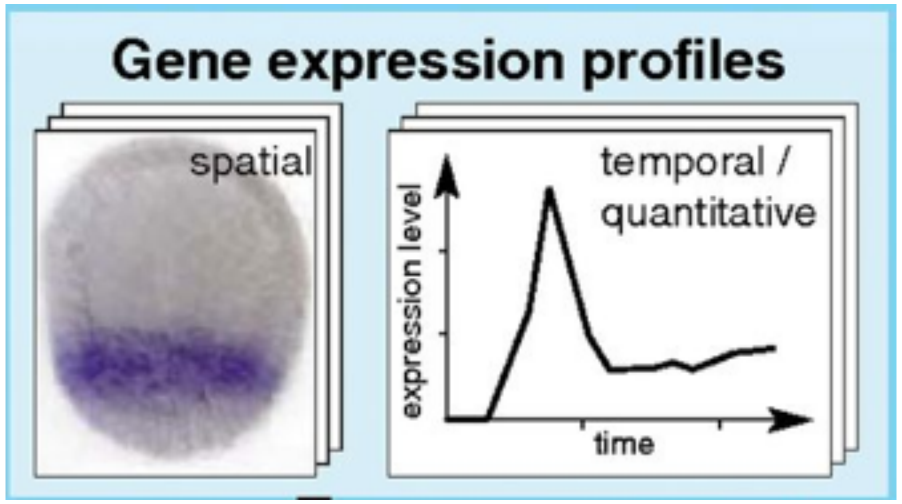

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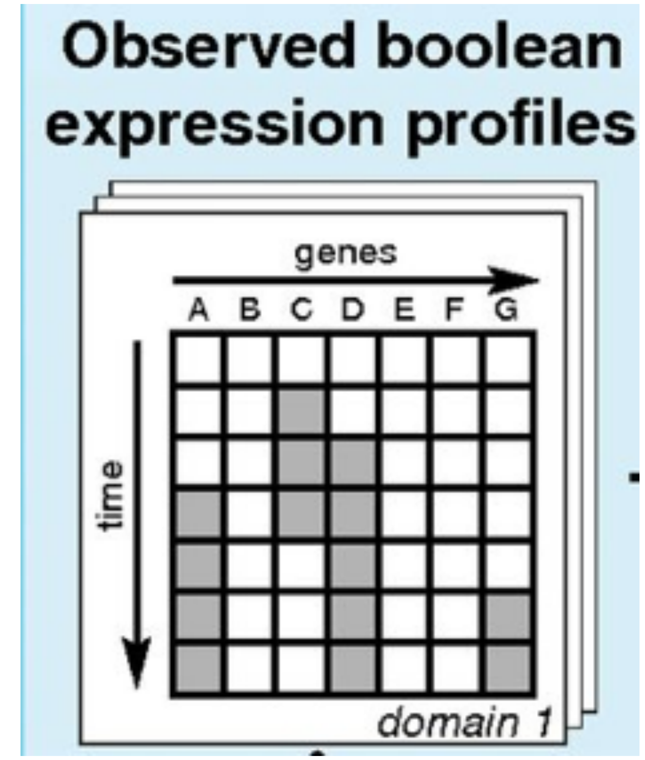
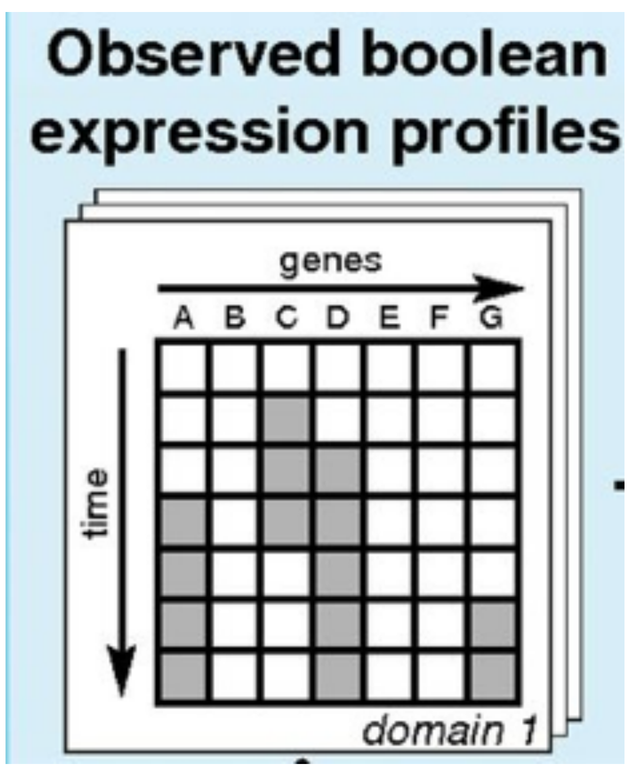
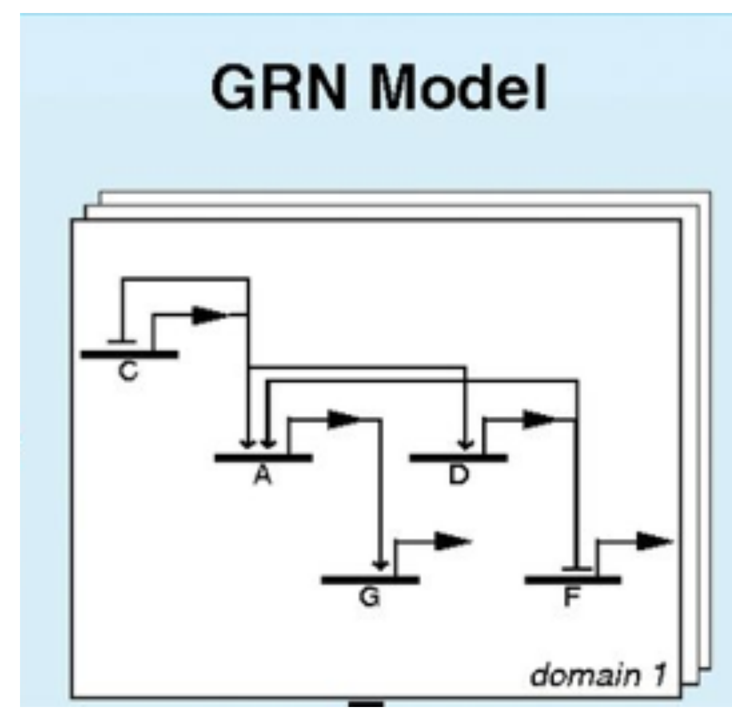




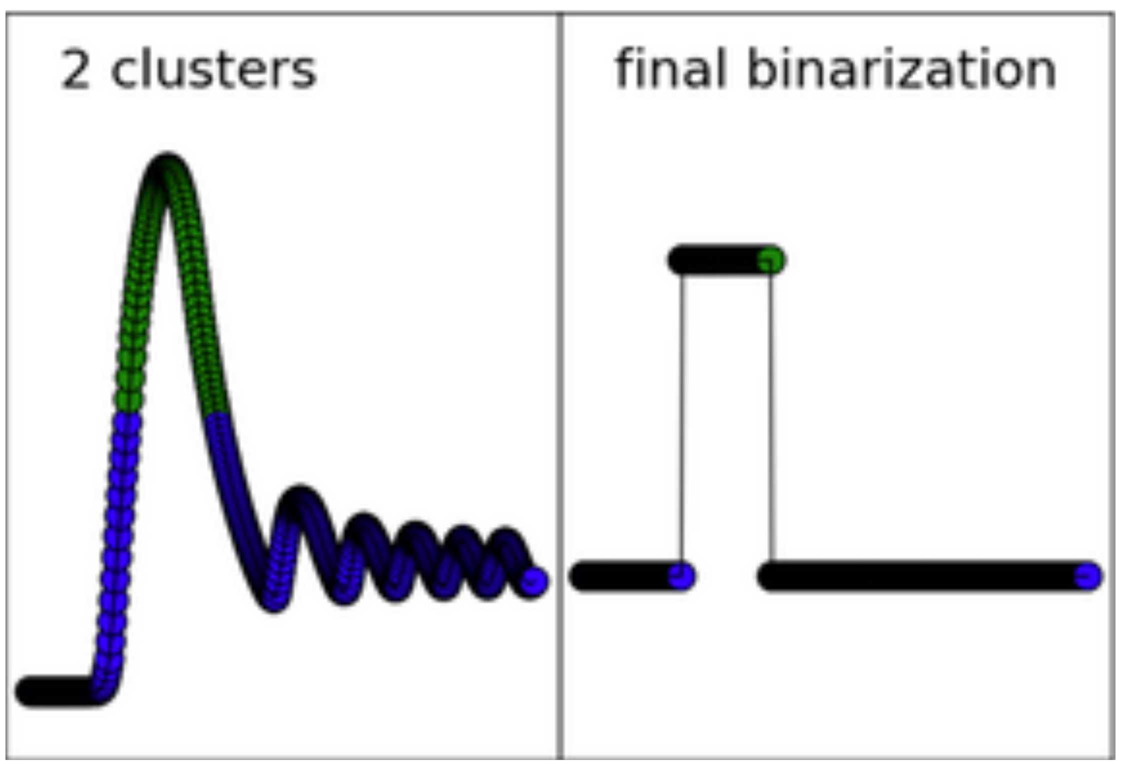
Step 2: Learning

Binary Dynamic Lbest PSO



Binarization using Iterative Clustering

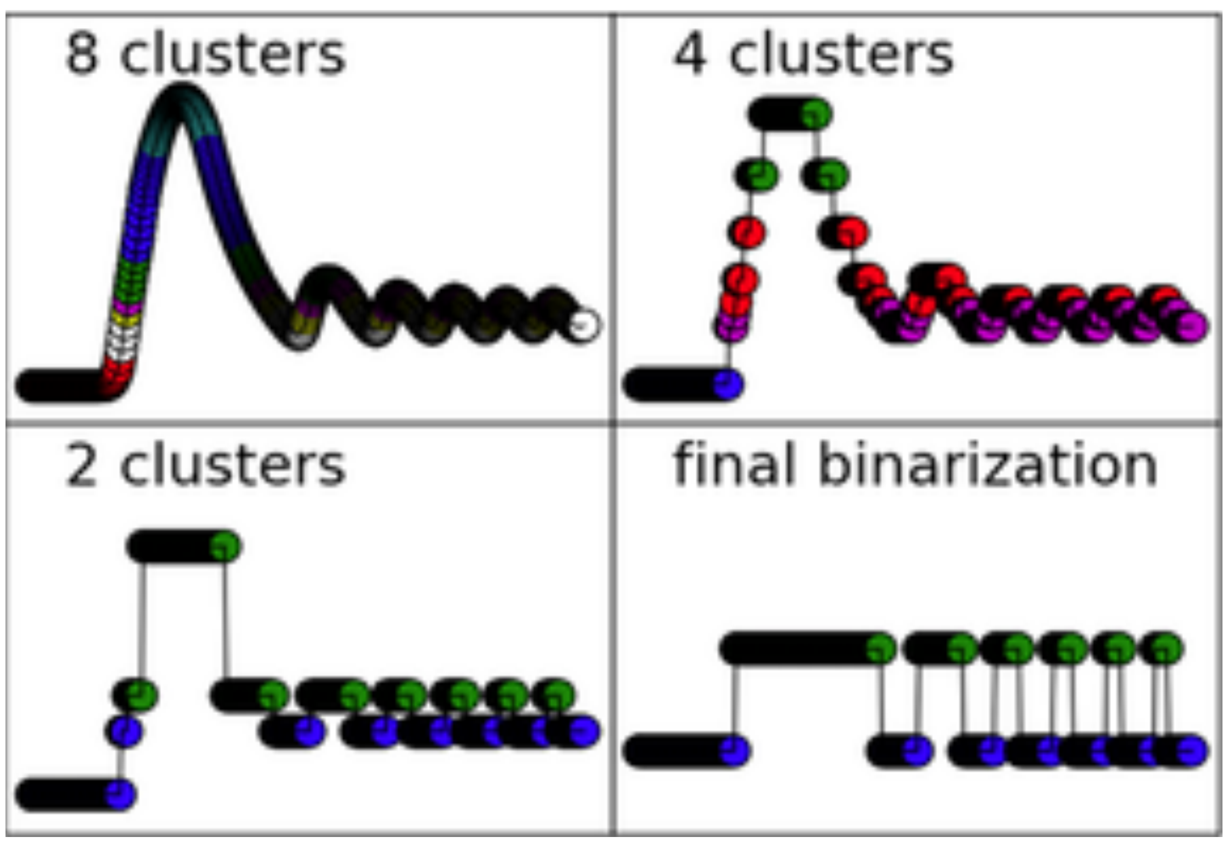
- Input : Time series data for n genes
- Output : Binary time series data
- We want to retain all the information from original data (eg. **Oscillatory dynamics**)



Direct Binarization

Binarization using Iterative Clustering

- Input : Time series data for n genes
- Output : Binary time series data
- We want to retain all the information from original data (eg. **Oscillatory dynamics**)



Iterative Binarization

δ **Depth of Clustering**

Reference: Berestovsky and Nakhleh 2013

Particle Swarm Optimization (PSO)

- Nature-inspired Stochastic Search algorithm.
- Kennedy and Eberhart
- Swarm of particles move around search space looking for best solution.
- Combination of **cognitive** and **social learning.**

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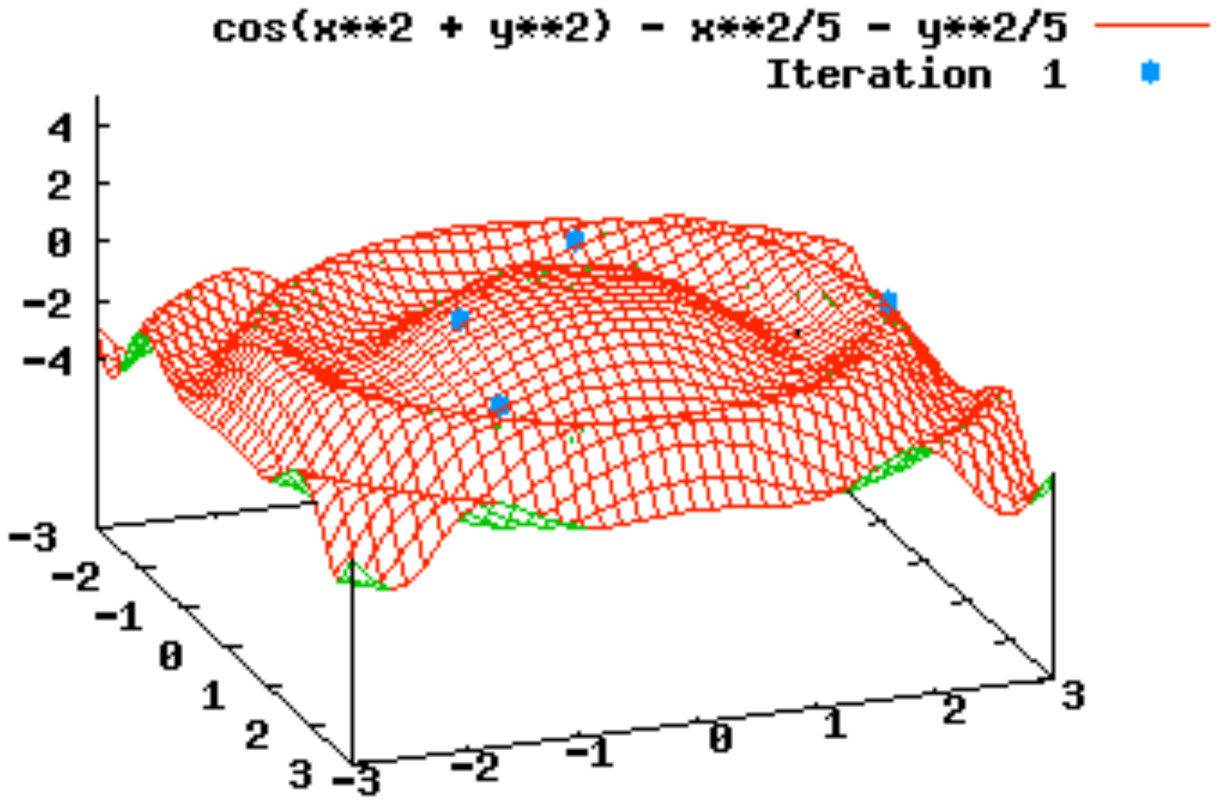
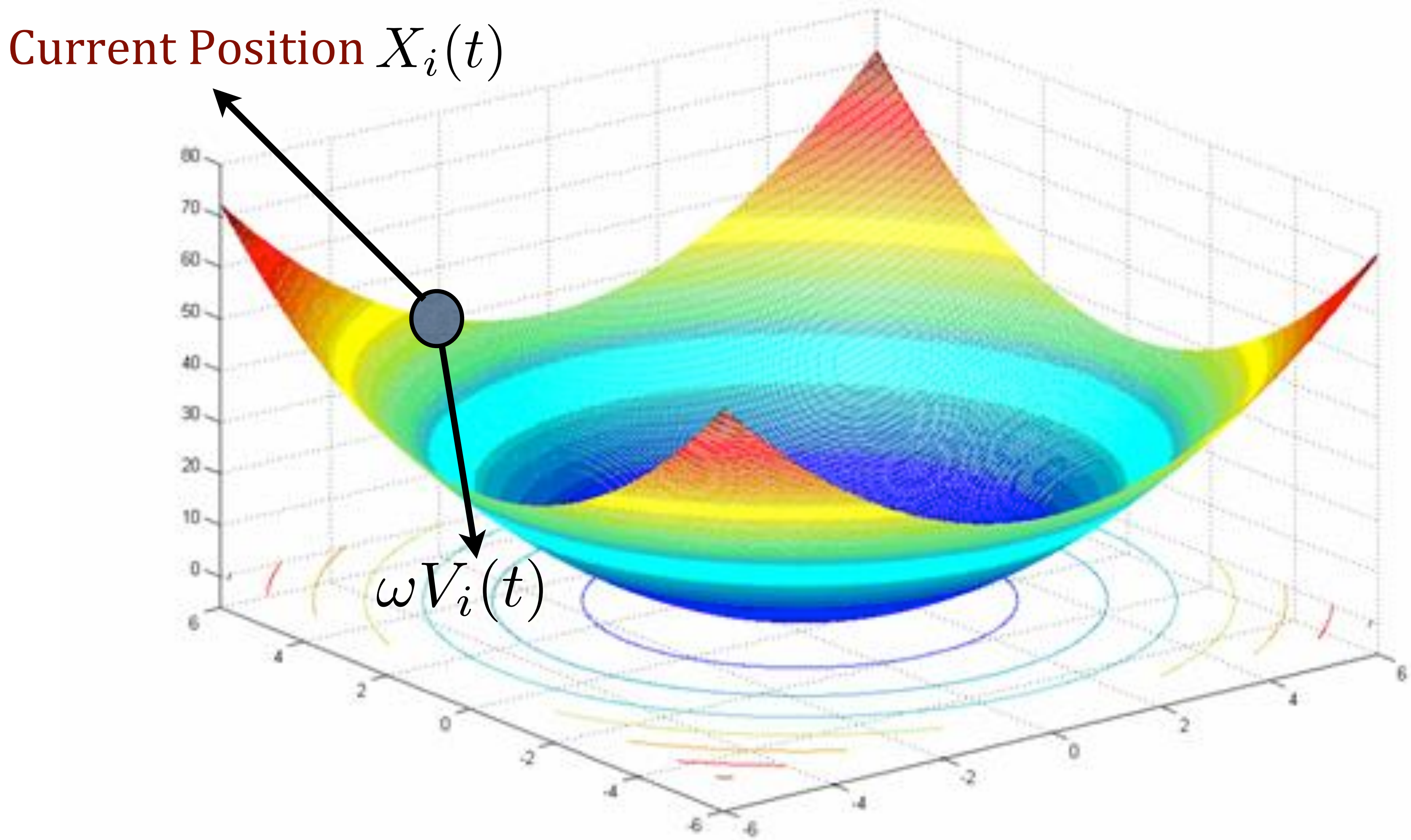


How Cognitive and Social Learning are Combined?



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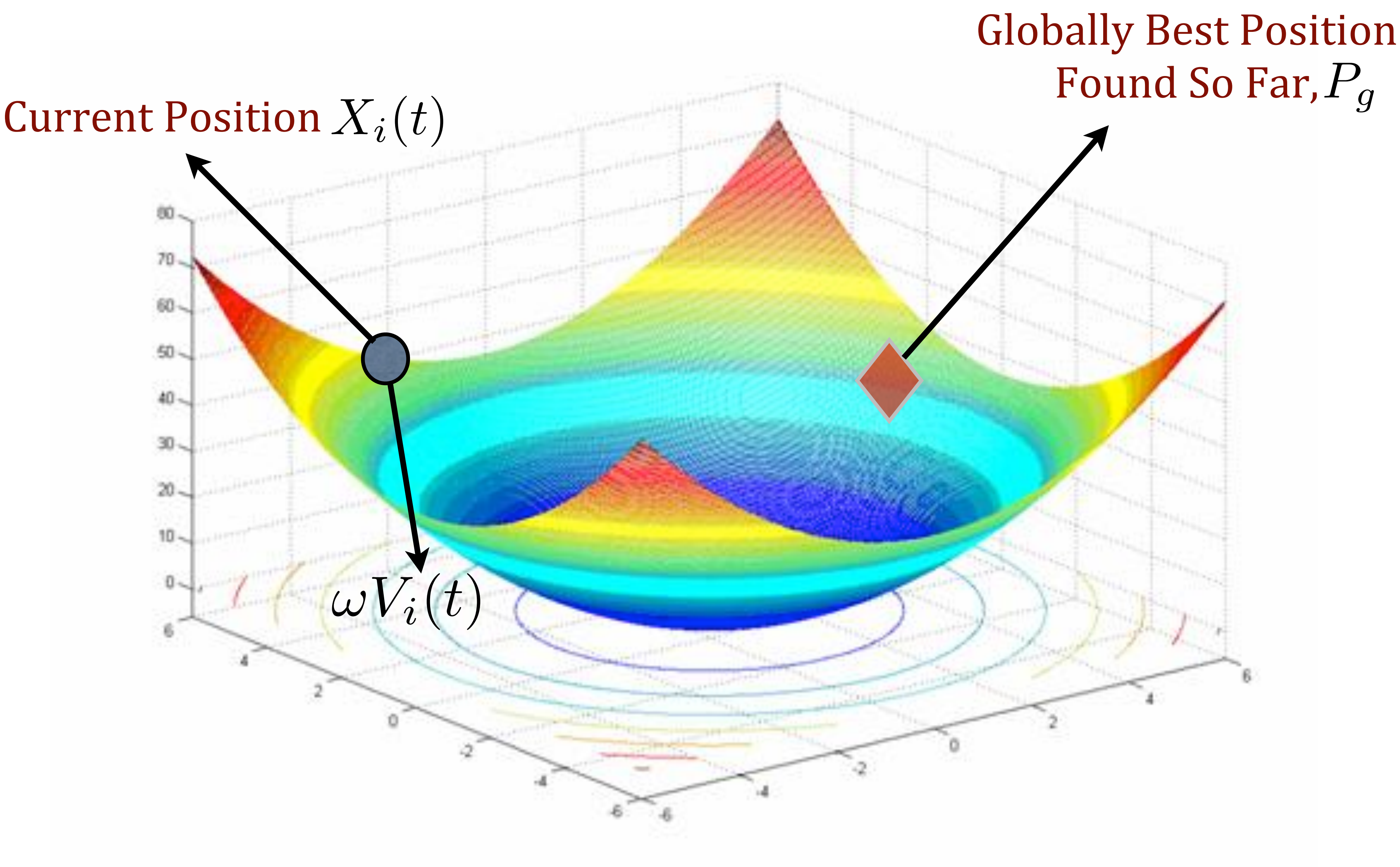

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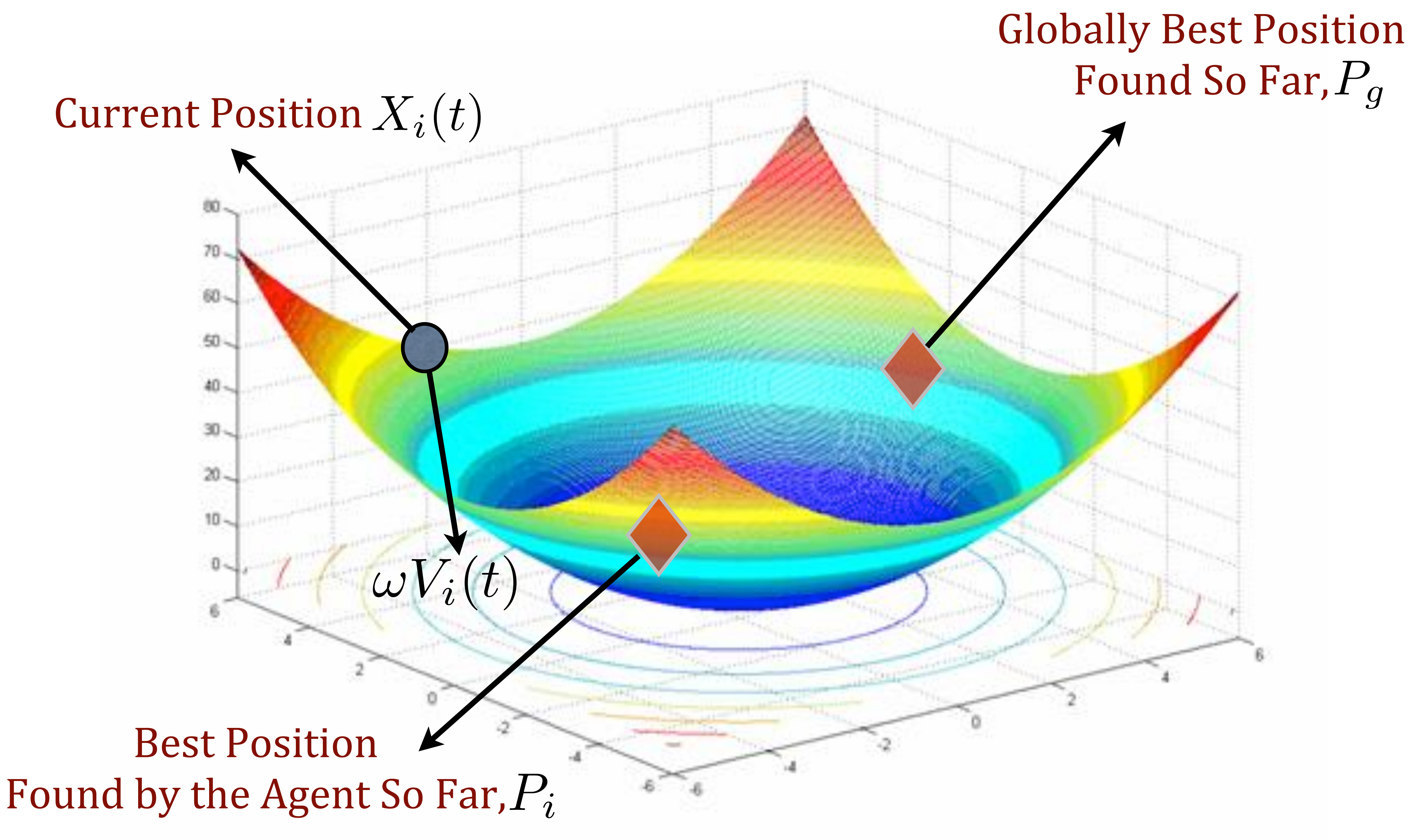

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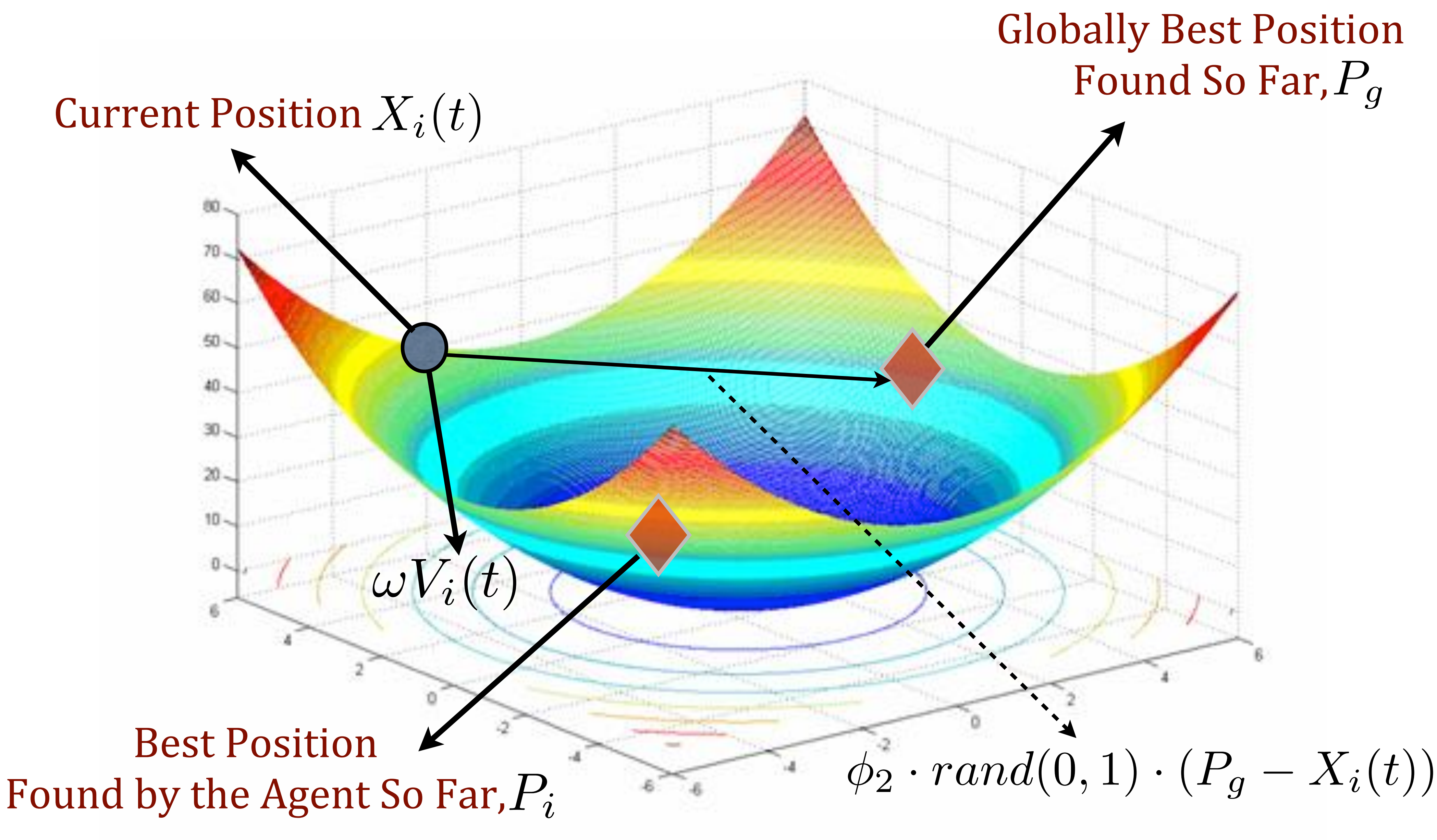

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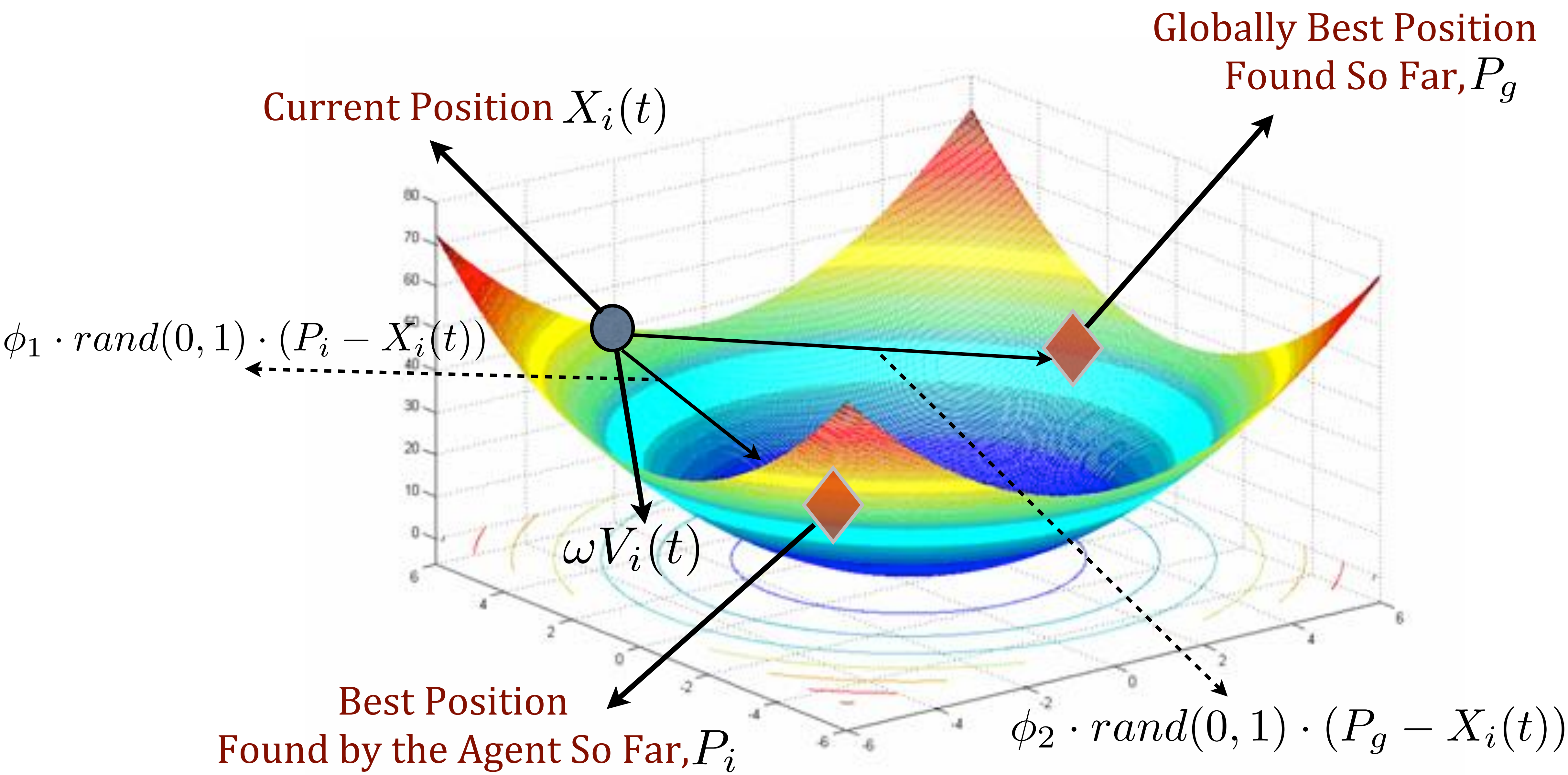

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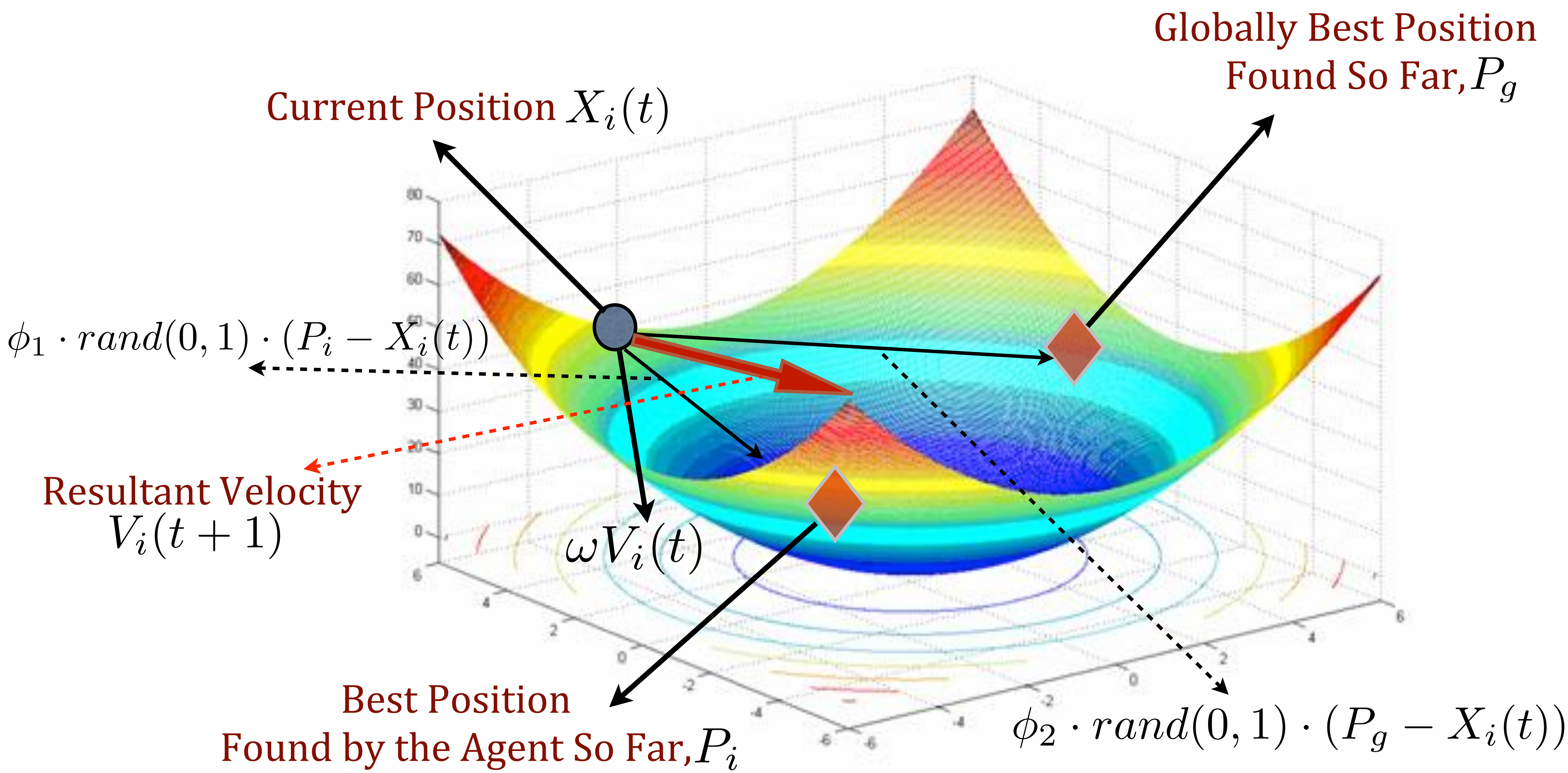

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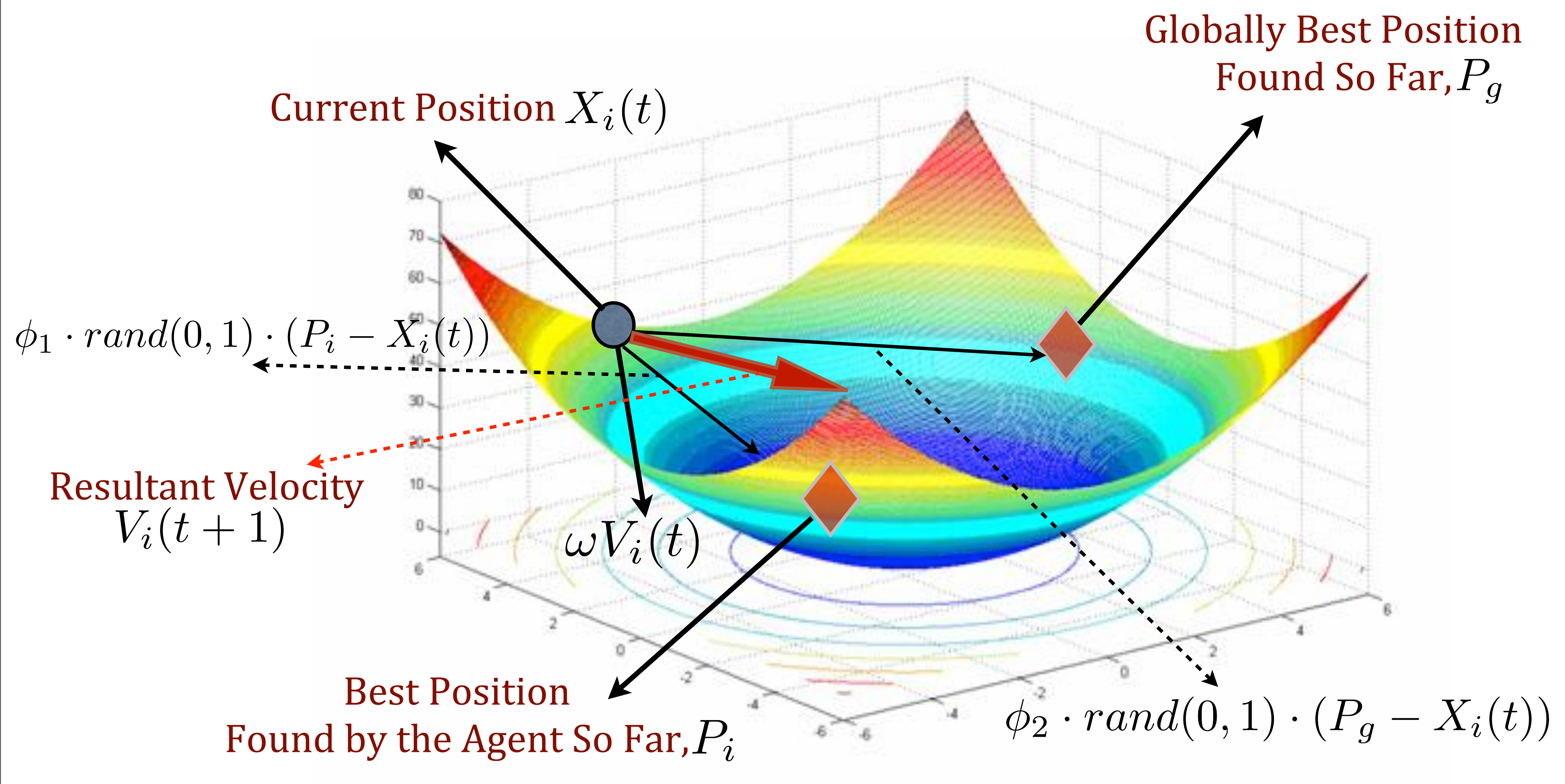


$$X_i(t+1) = X_i(t) + V_i(t+1)$$

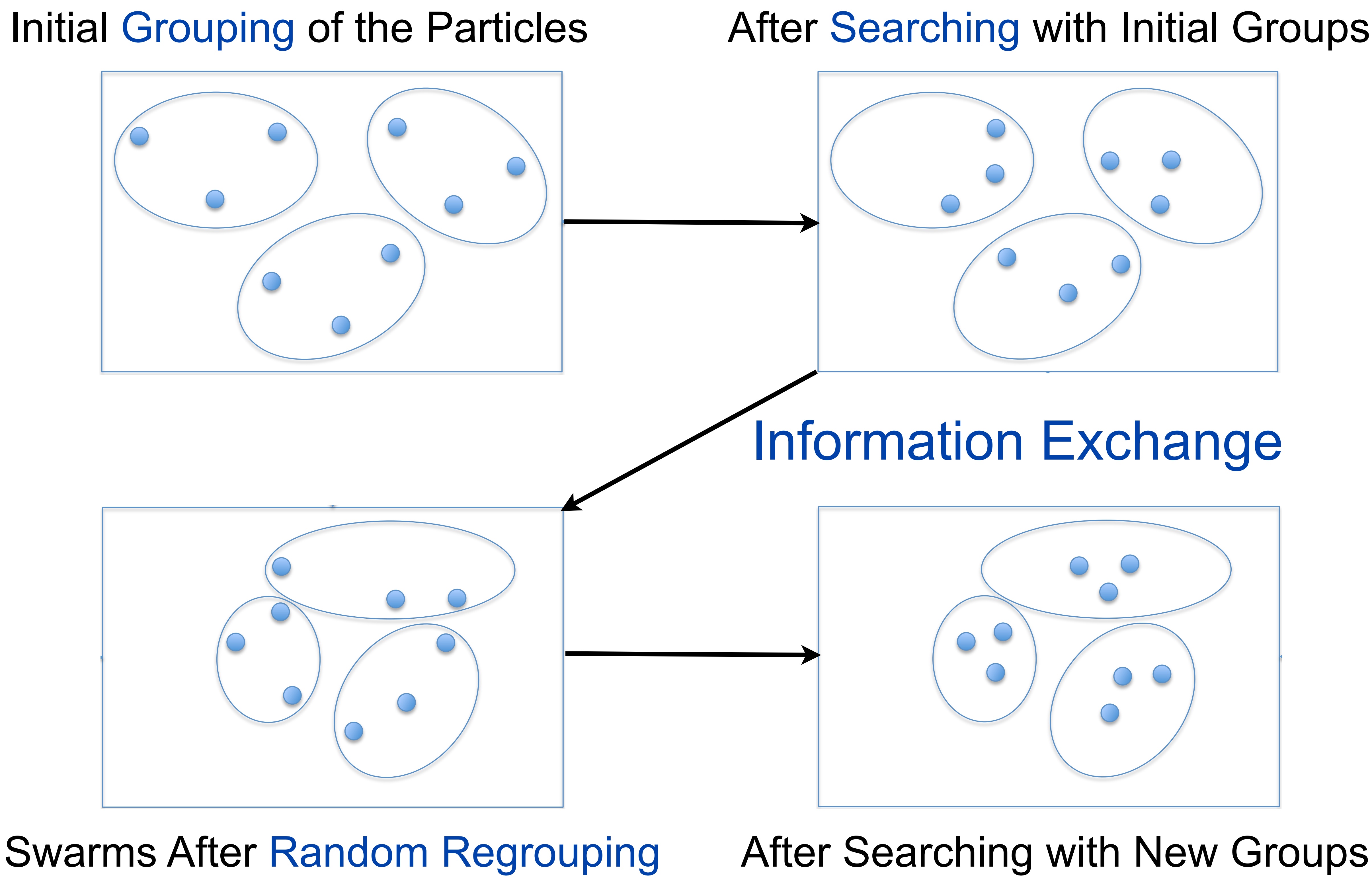
Local Neighborhood Based PSO

- Limitation of *gbest* PSO:
  - Premature convergence to local optima.
- Solution : *lbest* PSO
  - Best position achieved within the **neighborhood** influences a particle's velocity.

$$V_i(t+1) = \omega.V_i(t) + \phi_1.rand(0,1).(P_i - X_i(t)) + \phi_2.rand(0,1).(L_i - X_i(t))$$

  - L_i is best position achieved within the neighborhood.

Dynamic *lbest* PSO (D-LPSO)



How to Use D-LPSO for Learning Boolean Network?

Position Vector of a Particle:

$$v_{11}v_{12}..v_{1k}f_1 \mid v_{21}v_{22}..v_{2k}f_2 \mid \; . \; . \; . \; . \; . \; . \; \mid v_{n1}v_{n2}..v_{nk}f_n$$

Candidate Boolean Network

Genes are encoded in Binary

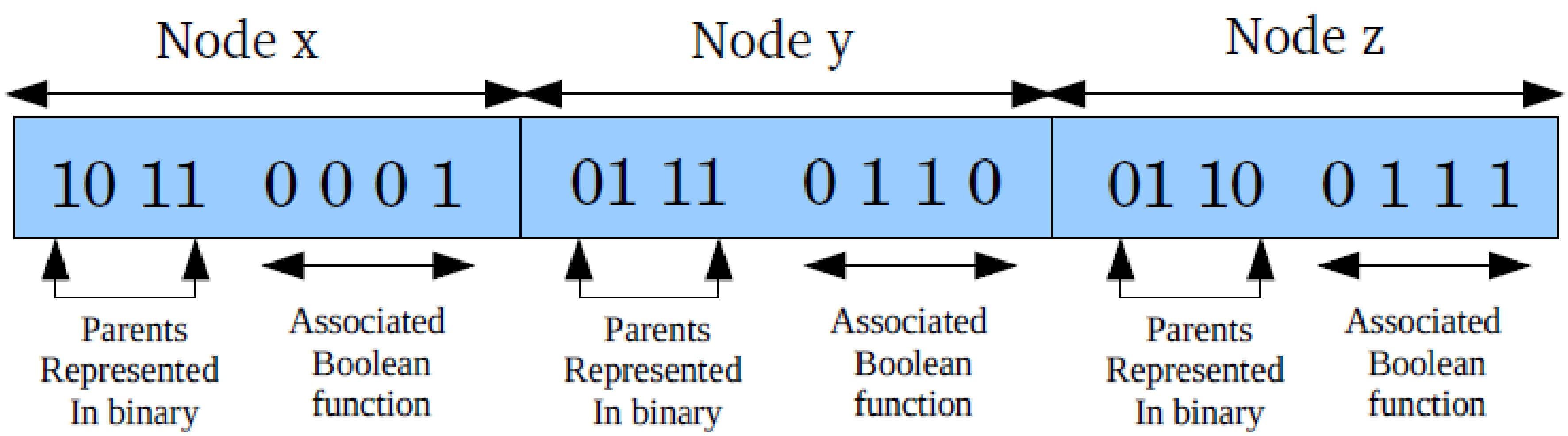
n genes

k inputs/gene

How to Use D-LPSO for Learning Boolean Network?

Position Vector of a Particle:

e.g: $n = 3, k = 2$



x : 01
y : 10
z : 11

x	y	z	x^*	y^*	z^*
0	0	0	0	0	0
0	0	1	0	1	0
0	1	0	0	0	1
0	1	1	1	1	1
1	0	0	0	1	1
1	0	1	0	0	1
1	1	0	0	1	1
1	1	1	1	0	1

How to handle Binary Data in PSO?

- Velocity of a particle gives the rate of change of bit's value.
- Two additional velocity vectors for each particle
- V_{i1} and V_{i0}, represents the change in velocity.
- Updated with the help of perturbations due to personal and social learning.

$$\text{If } pbest_i^d = 1 \text{ then } d_{i1,pbest}^d = c_1 r_1 (pbest_i^d - x_i^d) \text{ and } d_{i0,pbest}^d = -c_1 r_1 (pbest_i^d - x_i^d)$$

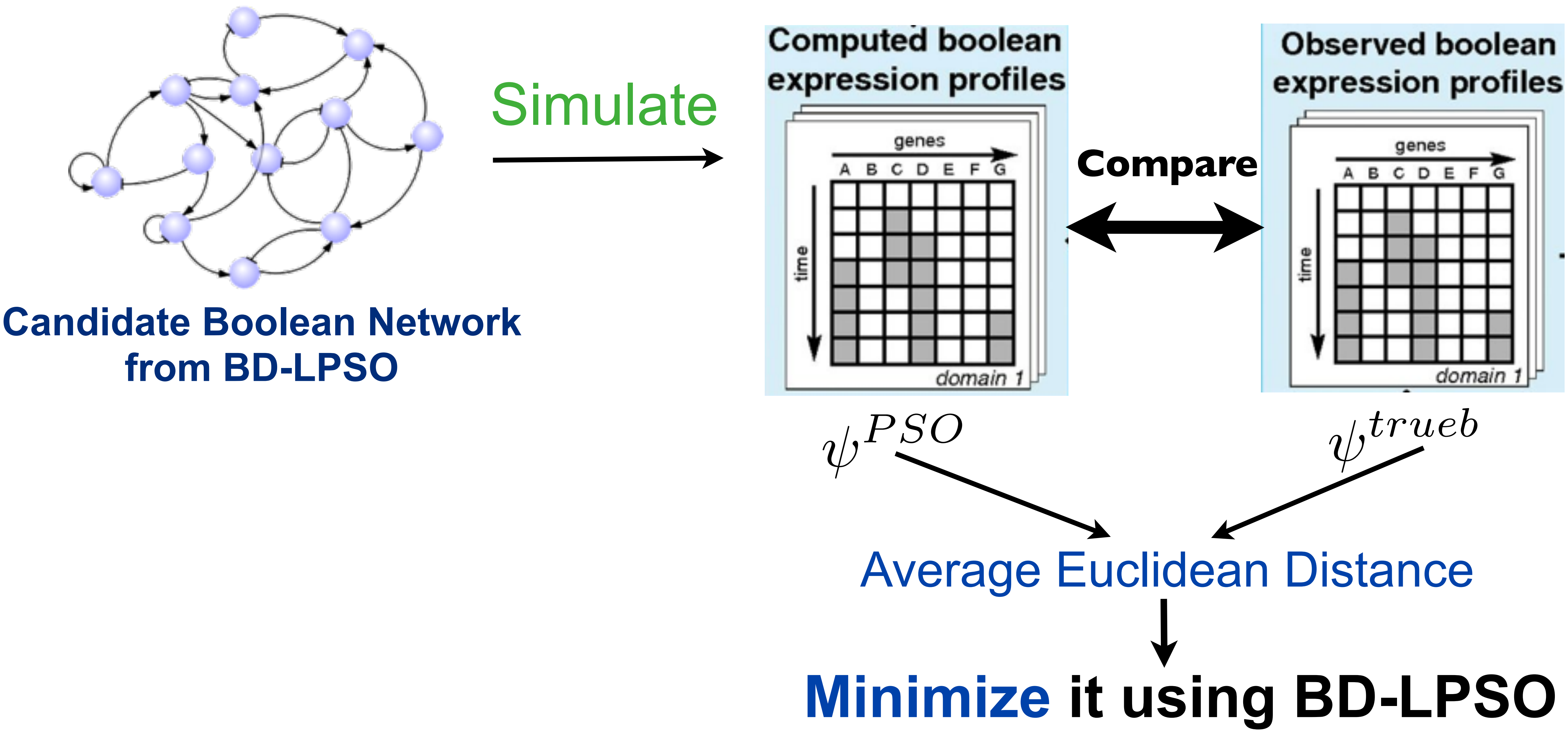
$$\text{If } pbest_i^d = 0 \text{ then } d_{i1,pbest}^d = -c_1 r_1 (pbest_i^d - x_i^d) \text{ and } d_{i0,pbest}^d = c_1 r_1 (pbest_i^d - x_i^d)$$

$$\text{If } lbest_i^d = 1 \text{ then } d_{i1,lbest}^d = c_2 r_2 (lbest_i^d - x_i^d) \text{ and } d_{i0,lbest}^d = -c_2 r_2 (lbest_i^d - x_i^d)$$

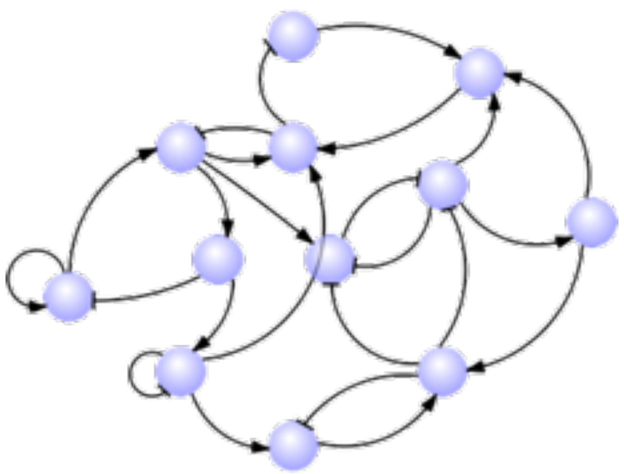
$$\text{If } lbest_i^d = 0 \text{ then } d_{i1,lbest}^d = -c_2 r_2 (lbest_i^d - x_i^d) \text{ and } d_{i0,lbest}^d = c_2 r_2 (lbest_i^d - x_i^d)$$

We call the resulting algorithm as **BD-LPSO**

Fitness Metric

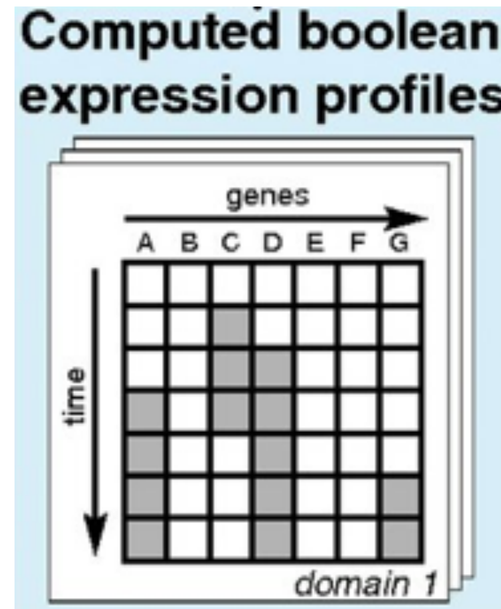


Fitness Metric

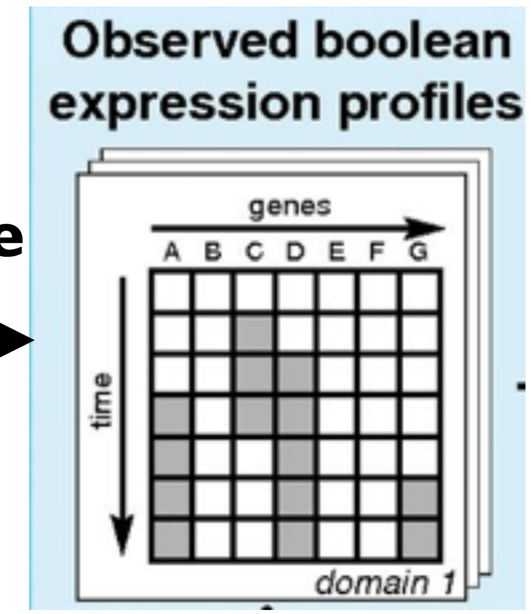


Candidate Boolean Network
from BD-LPSO

Simulate



Compare



ψ^{PSO} ψ^{trueb}

Average Euclidean Distance

Minimize it using BD-LPSO

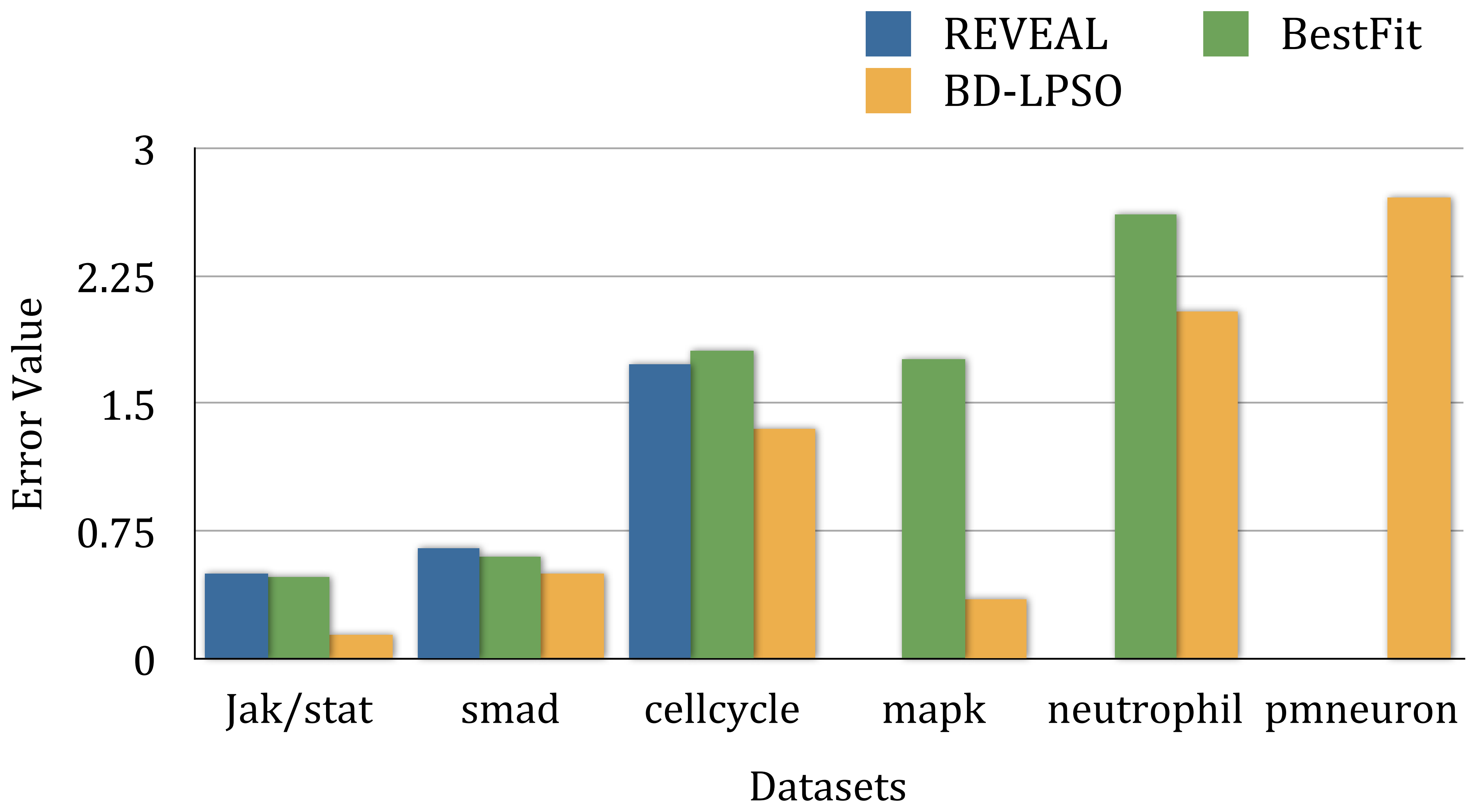
Simulation Scheme:

1. Synchronous
2. Asynchronous

Experimental Results

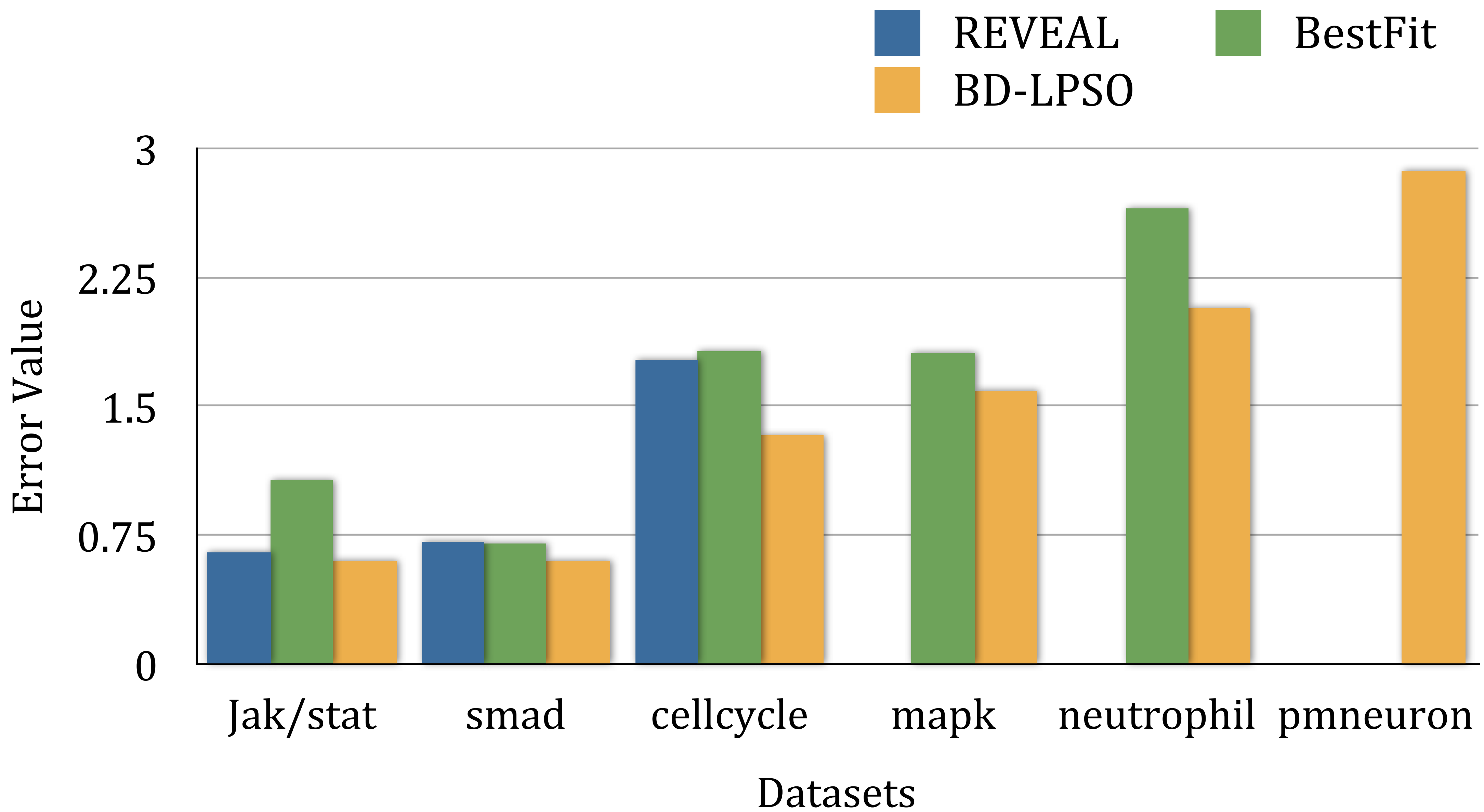
Error value is measured in terms of average Euclidean distance

Synchronous Simulation:

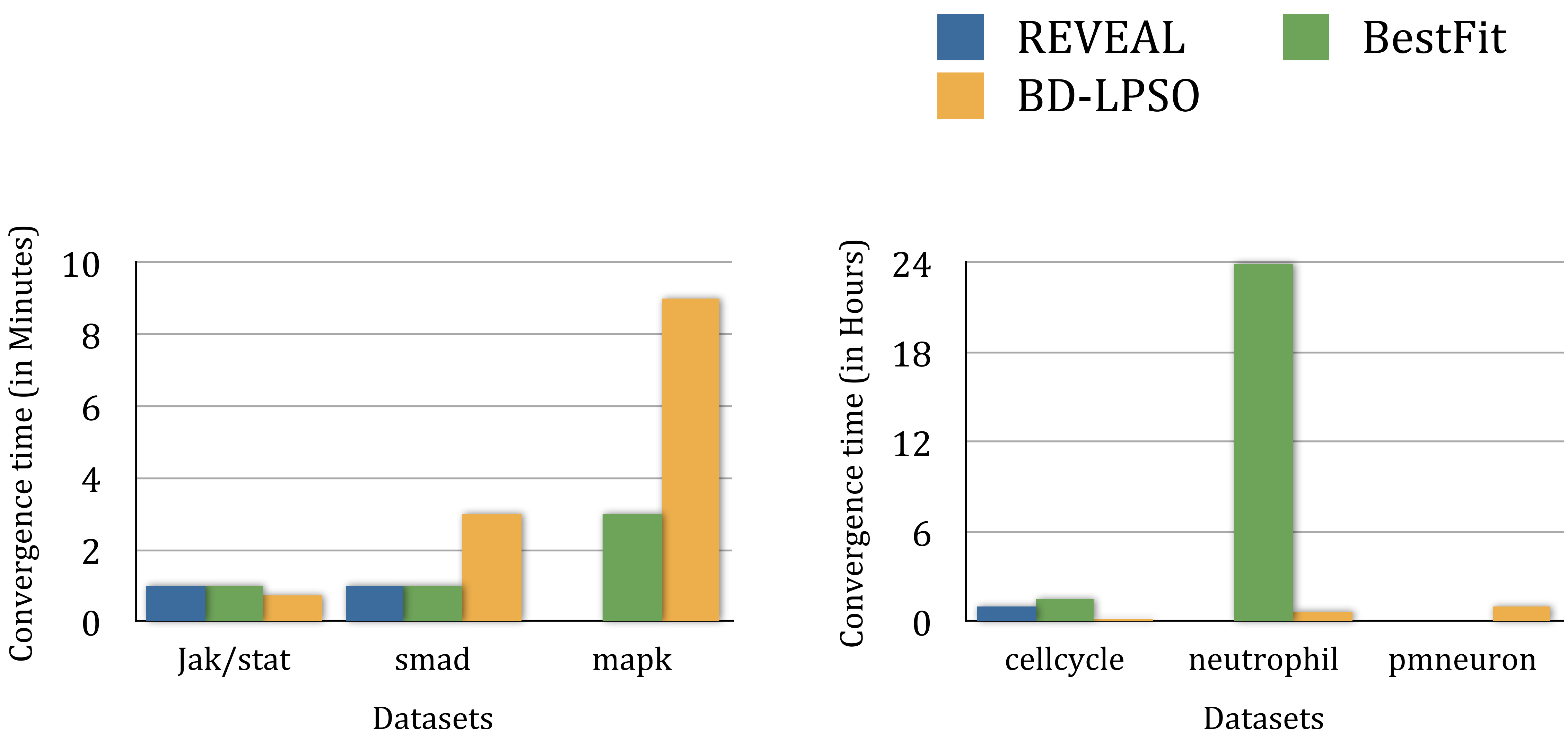


Experimental Results

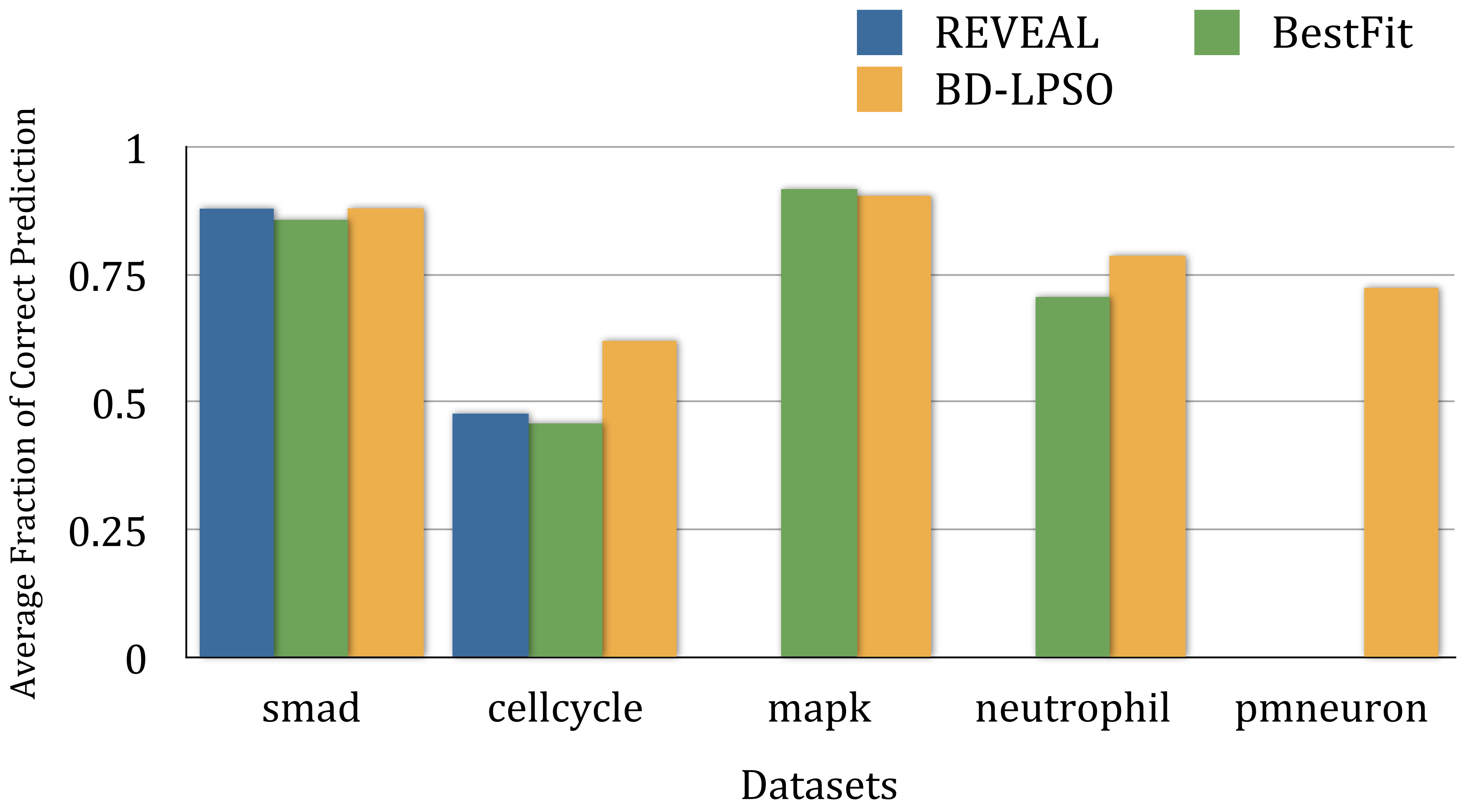
Asynchronous Simulation:



Comparison of Runtime

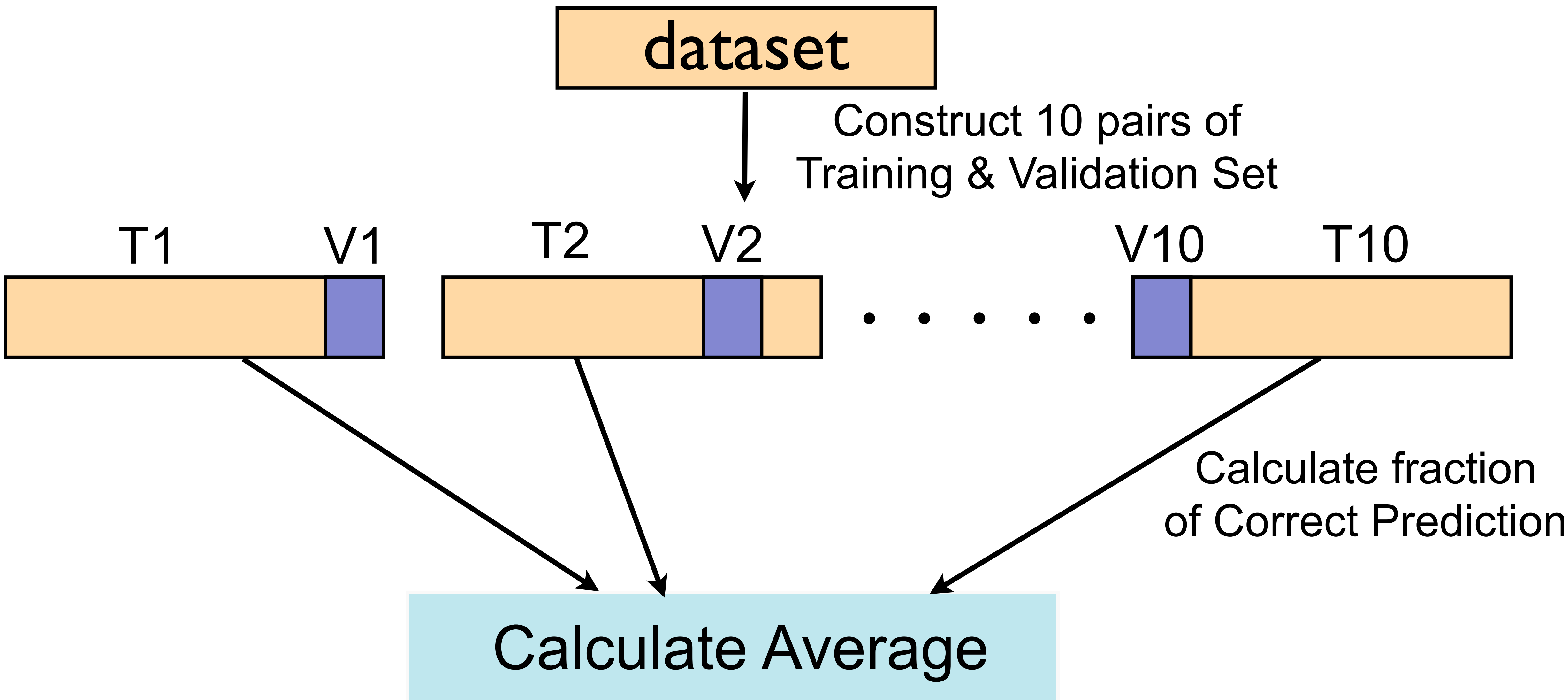


Comparison of Predictive Power



How to Calculate Predictive Power?

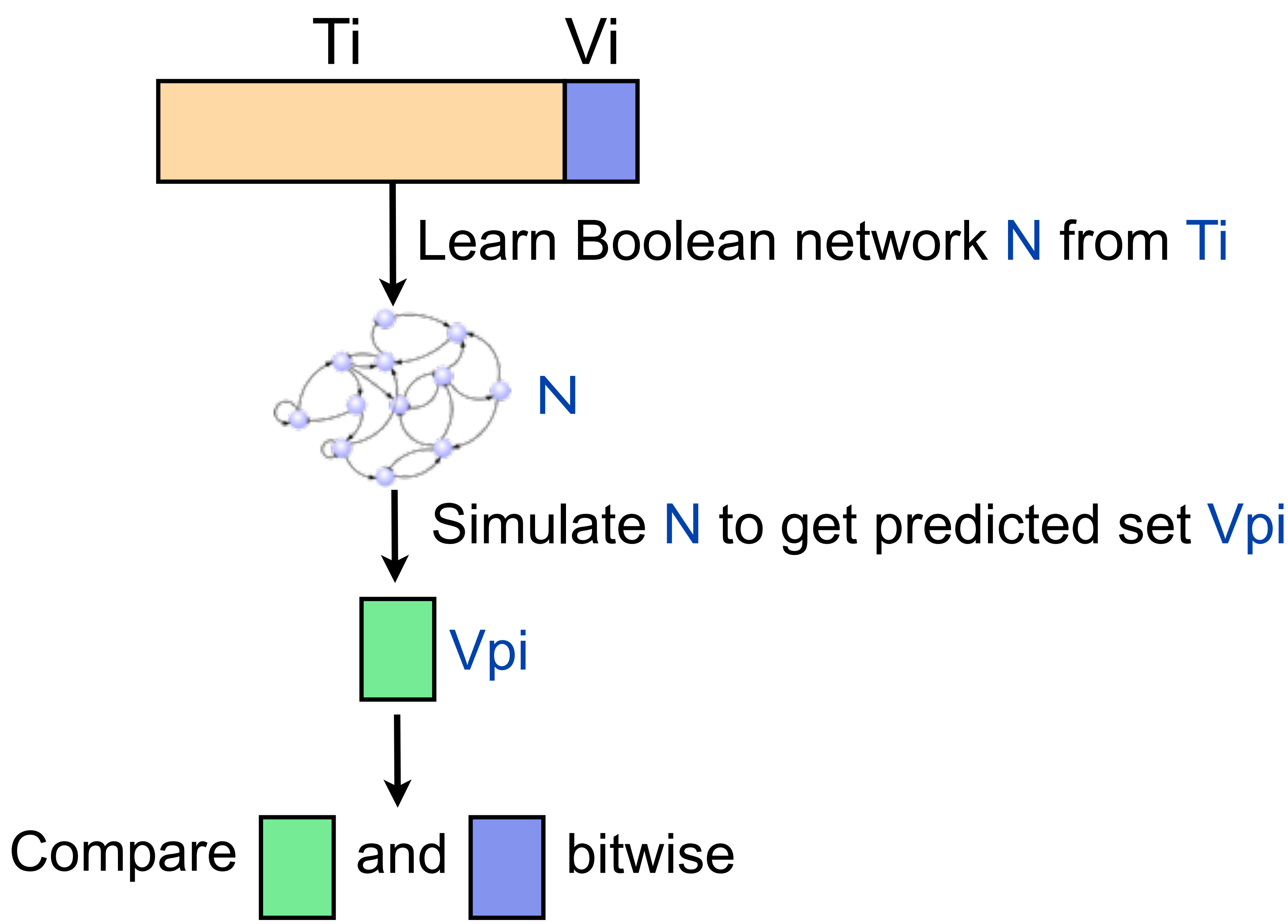
10 fold Cross Validation



Average over 10 runs

How to Calculate Predictive Power?

Fraction of Correct Prediction for a pair of Tr-Val Set :



Value is between 0 and 1

Future Work

- Integrated model of cellular network (signaling, metabolic and Gene Regulatory Networks).
- Learn more complex models (ODE). Supervised Learning using domain knowledge.
- Use of Gene knockout data along with time series data to infer the networks (two stage learning).

Conclusion

- BD-LPSO is an efficient algorithm for learning GRN from time series data.
- Better to learn BN in terms of
  - Accuracy
  - Predictive Power
  - Convergence Time.
- Specifically suitable for larger network with Complex dynamics.