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タンパク質間相互作用ネットワークの推定とその応用に関する研究

Large-scale protein-protein interaction network prediction by an exhaustive rigid docking system MEGADOCK

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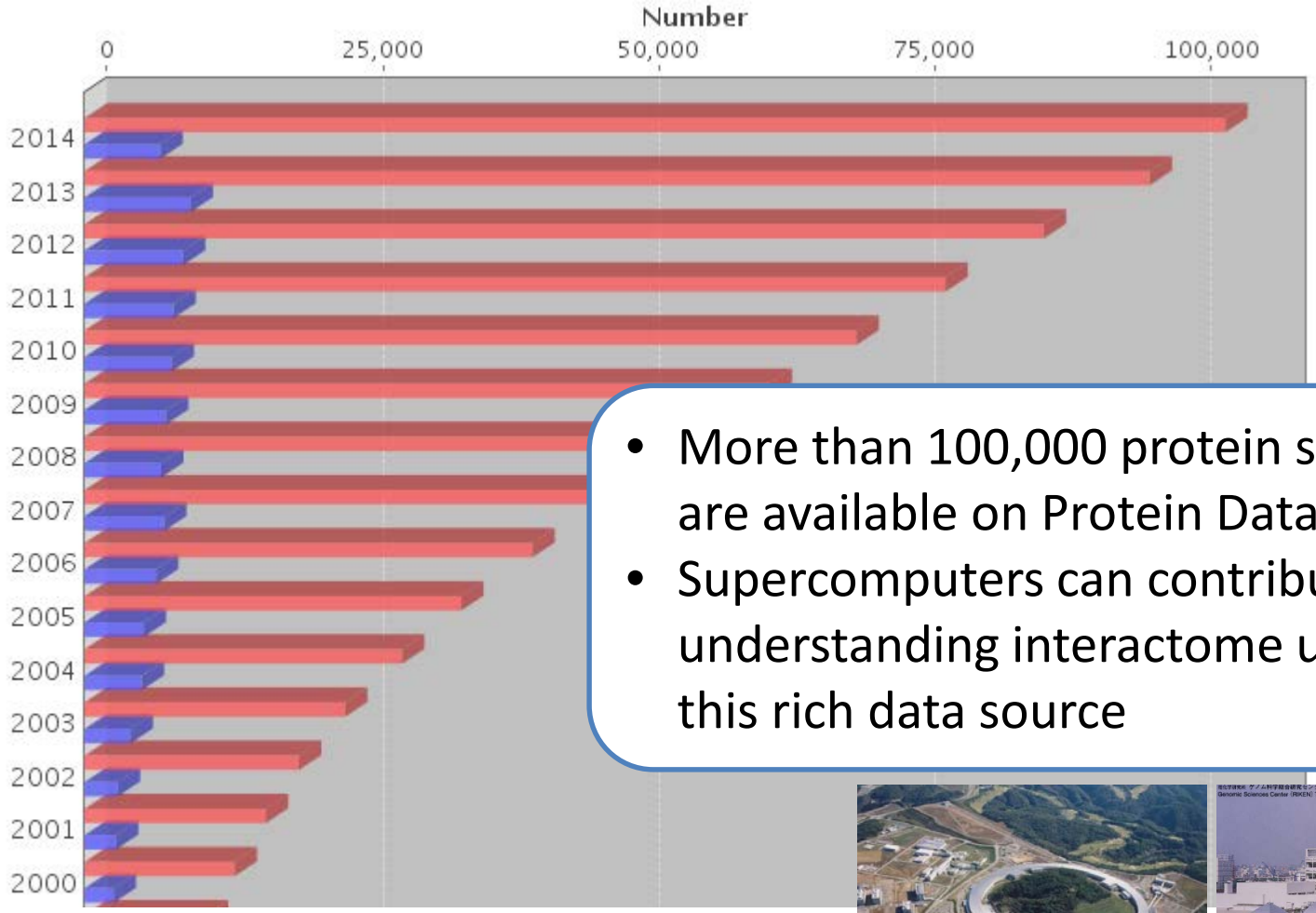
The number of available protein tertiary structures is growing rapidly



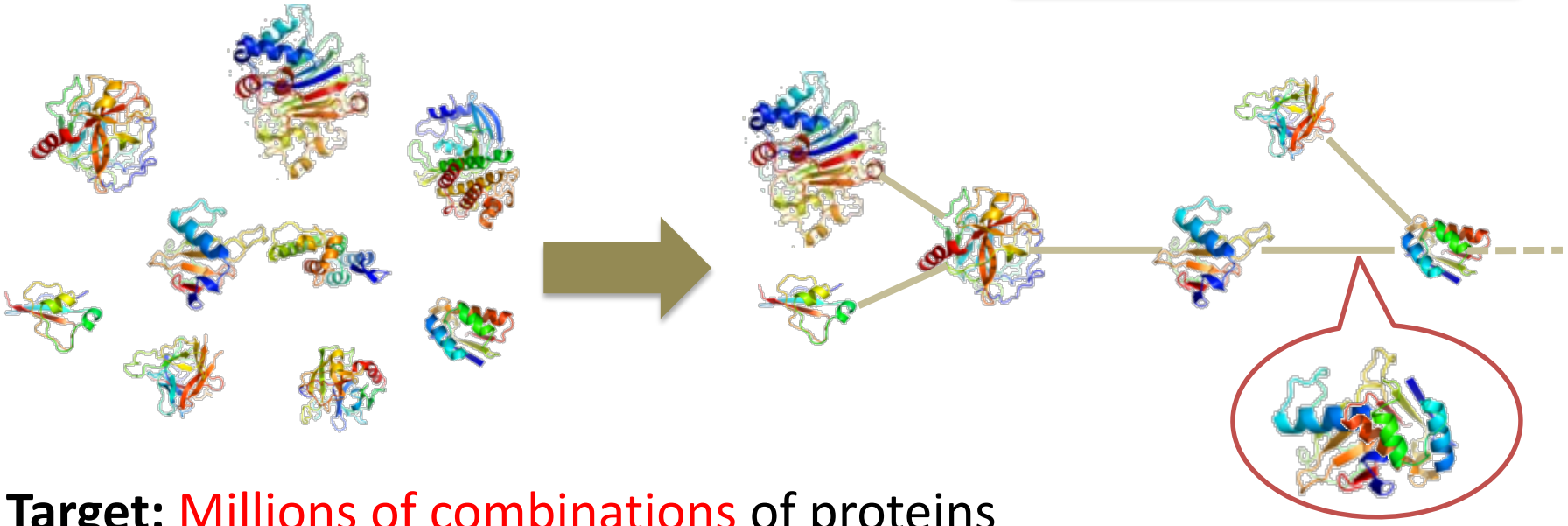
- More than 100,000 protein structures are available on Protein Data Bank
- Supercomputers can contribute understanding interactome utilizing this rich data source

RCSB PDB
(as of 2014-09-22)

What we do: Protein-protein interaction (PPI) network prediction using proteins tertiary structure data

Input: Protein structures

Output: PPI networks



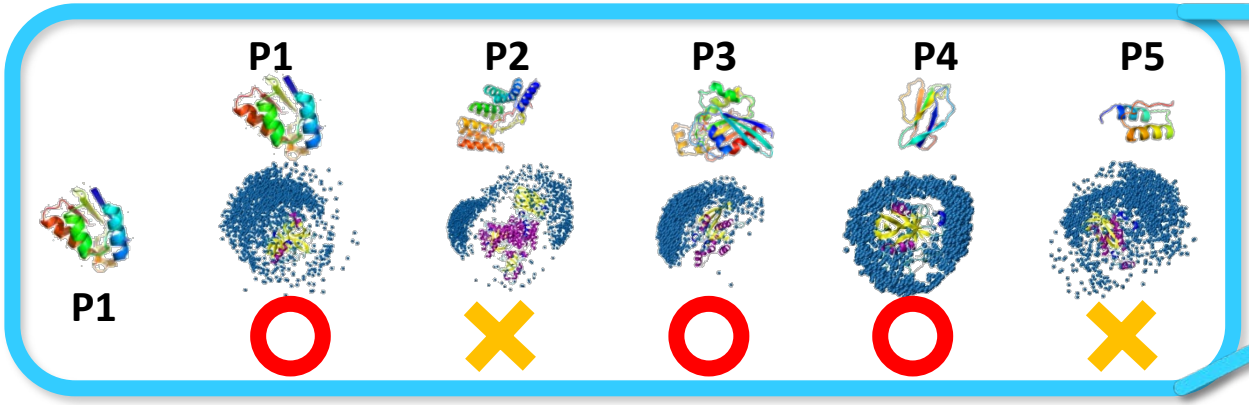
Target: Millions of combinations of proteins

Strategy: Exhaustive rigid docking among target proteins

- Feasible assuming massively parallel computing environments
- Prediction of complex structures can also be provided

MEGADOCK system: PPI network prediction by an ultra-fast rigid-docking tool

Exhaustive docking & post-docking analysis



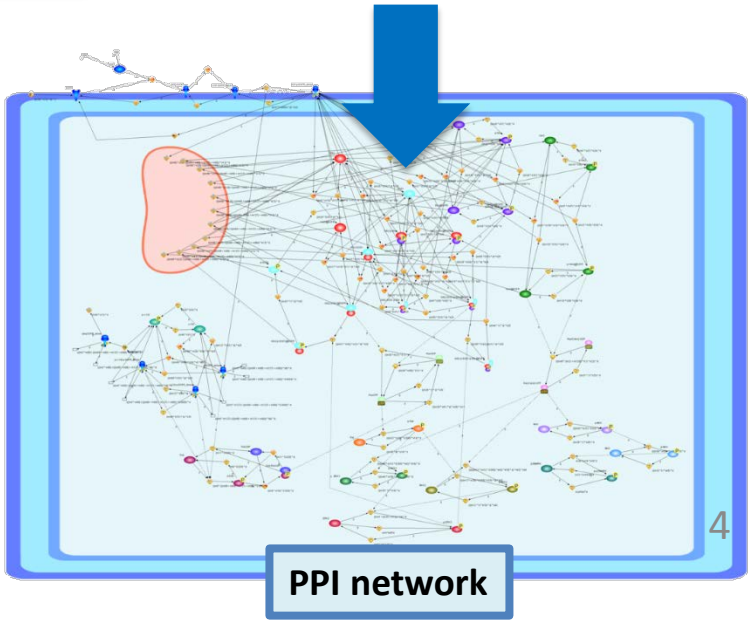
Prediction of binders

	P1	P2	P3	P4	P5
P1	○	×	○	○	×
P2	×	×	×	×	×
P3	○	×	×	○	×
P4	○	×	○	×	○
P5	×	×	×	○	×

MEGADOCK

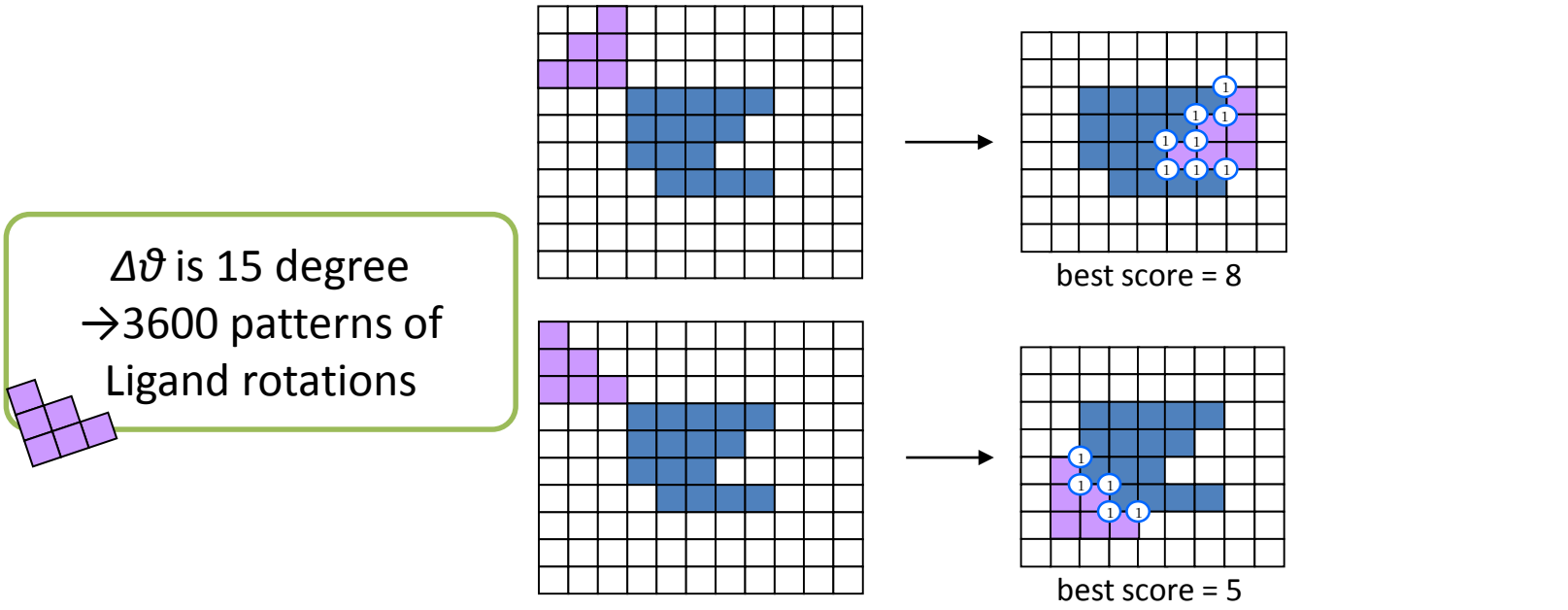
- Rigid-docking software designed for exhaustive docking studies
- Suitable for running on supercomputers
  - K, SCLS, TSUBAME2.5 (CPU/GPU version)
- Open-source
  http://www.bi.cs.titech.ac.jp/megadock/

Ohue, *et al.*, *Bioinformatics*, accepted.



Rigid Docking

- Evaluates docking scores mainly based on the complementarity of protein tertiary structure



Katchalski-Katzir E, *et al*. *PNAS*, 1992.

A compact score function of MEGADOCK

Compress three terms into **one complex number**:

- **Shape complementarity**
- **Hydrophobic interaction**
- **Electrostatic interaction**

$$\boldsymbol{S}(\alpha,\beta,\gamma) = \Re\left[\sum_{l=1}^{N}\sum_{m=1}^{N}\sum_{n=1}^{N}\boldsymbol{R}(l,m,n)\boldsymbol{L}(l+\alpha,m+\beta,n+\gamma)\right]$$

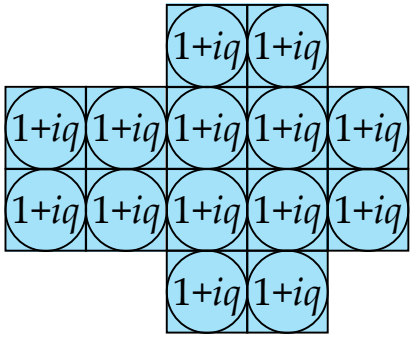
$$\boldsymbol{R}(l,m,n) = G_R(l,m,n) + w_h H(l,m,n) + i\phi(l,m,n)$$

$$\boldsymbol{L}(l,m,n) = G_L(l,m,n) + i w_e q(l,m,n)$$

$$\boldsymbol{S}(\alpha,\beta,\gamma) = \Re\left[\mathrm{IFT}\left[\mathrm{DFT}\left[\boldsymbol{R}(l,m,n)\right]^{*}\mathrm{DFT}\left[\boldsymbol{L}(l,m,n)\right]\right]\right]$$

1+H +$i\phi$	2+H +$i\phi$	3+H +$i\phi$	3+H +$i\phi$	3+H +$i\phi$	2+H +$i\phi$	1+H +$i\phi$
2+H +$i\phi$	-45	-45	-45	-45	-45	2+H +$i\phi$
3+H +$i\phi$	-45	-45	-45	-45	-45	2+H +$i\phi$
3+H +$i\phi$	-45	-45	-45	5+H +$i\phi$	2+H +$i\phi$	1+H +$i\phi$
3+H +$i\phi$	-45	-45	-45	5+H +$i\phi$	2+H +$i\phi$	1+H +$i\phi$
3+H +$i\phi$	-45	-45	-45	-45	-45	2+H +$i\phi$
2+H +$i\phi$	-45	-45	-45	-45	-45	2+H +$i\phi$
1+H +$i\phi$	2+H +$i\phi$	3+H +$i\phi$	3+H +$i\phi$	3+H +$i\phi$	2+H +$i\phi$	1+H +$i\phi$

Receptor protein

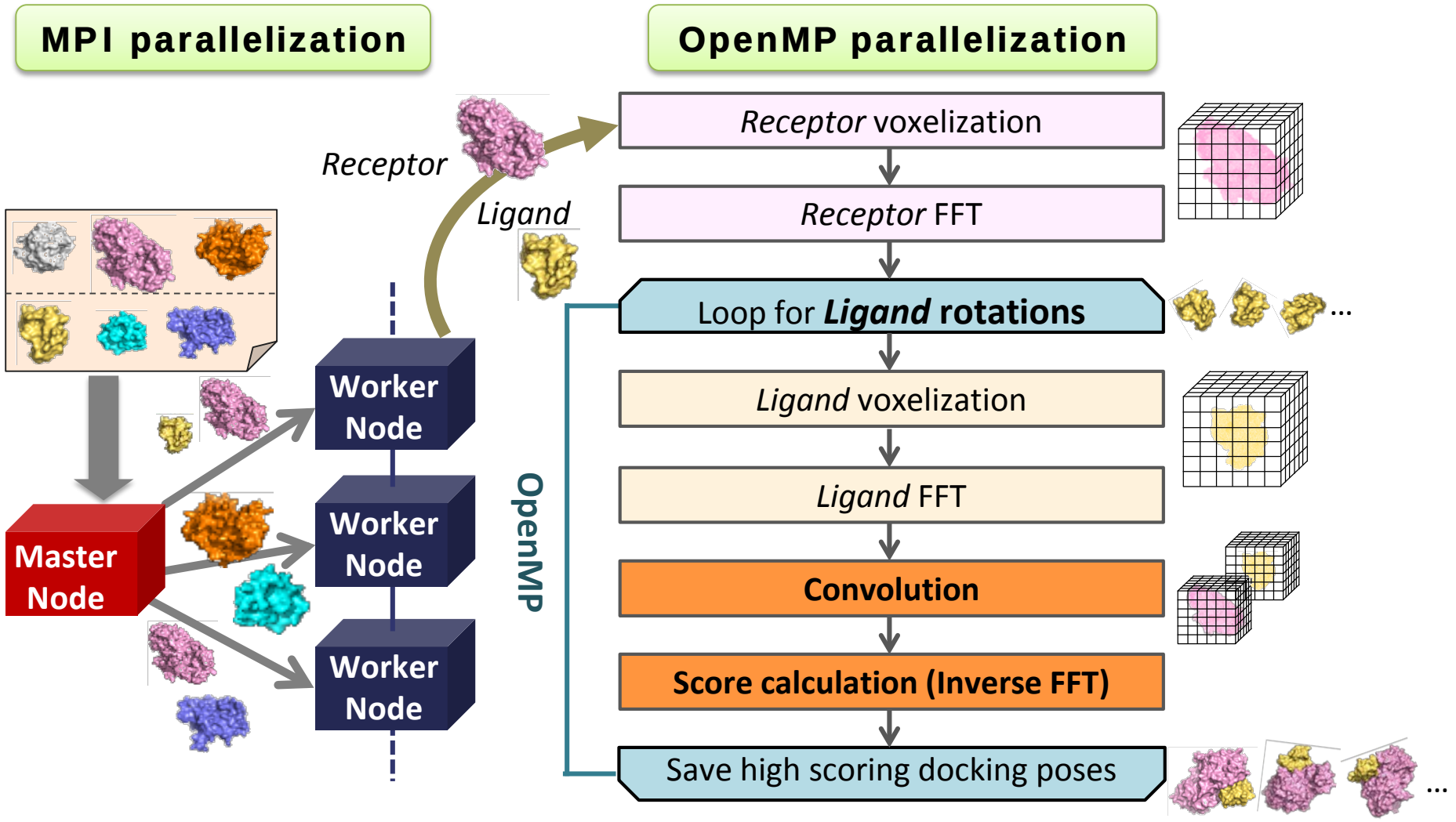


Ligand protein

Convolution can be calculated fast by FFT (Katchalski-Katzir model)

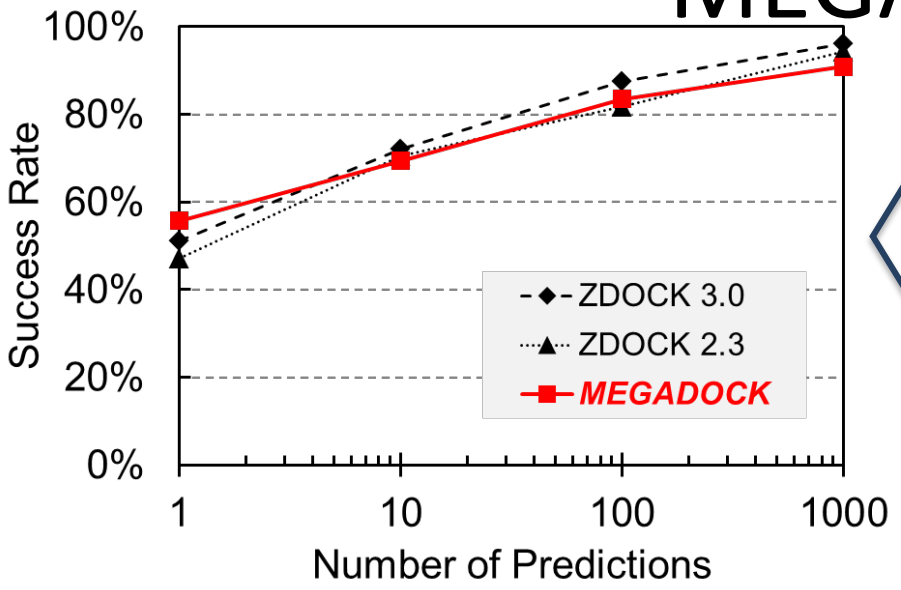
Ohue *et al.*, *Lecture Note in Bioinformatics*, 2012.

Implementation by hybrid parallelization



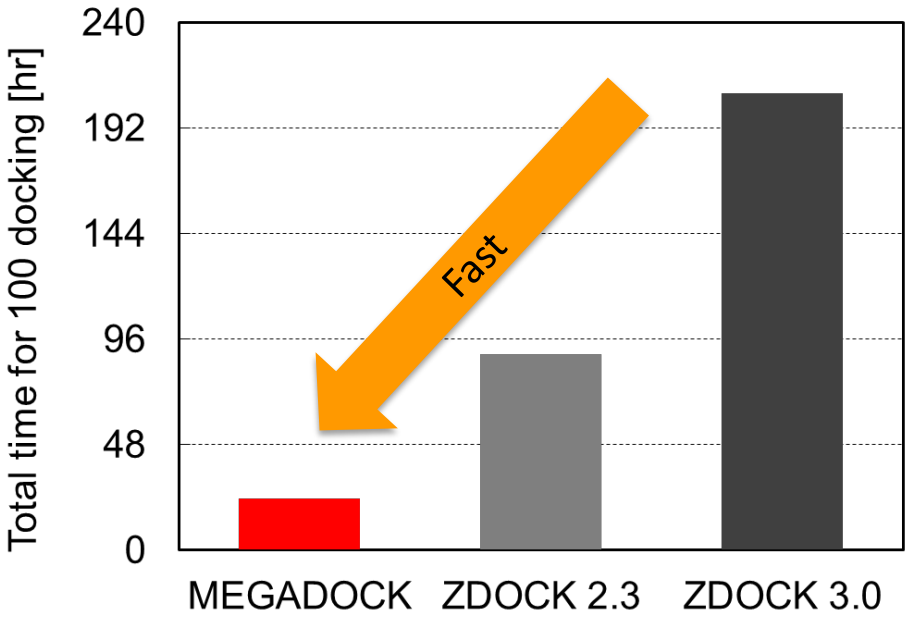
Matsuzaki, *et al.*, *Source Code Biol Med*, 2013.

Performance of protein docking by MEGADOCK



Docking accuracy was **comparable** to conventional tools
(Benchmark 4.0, 176 bound complexes)

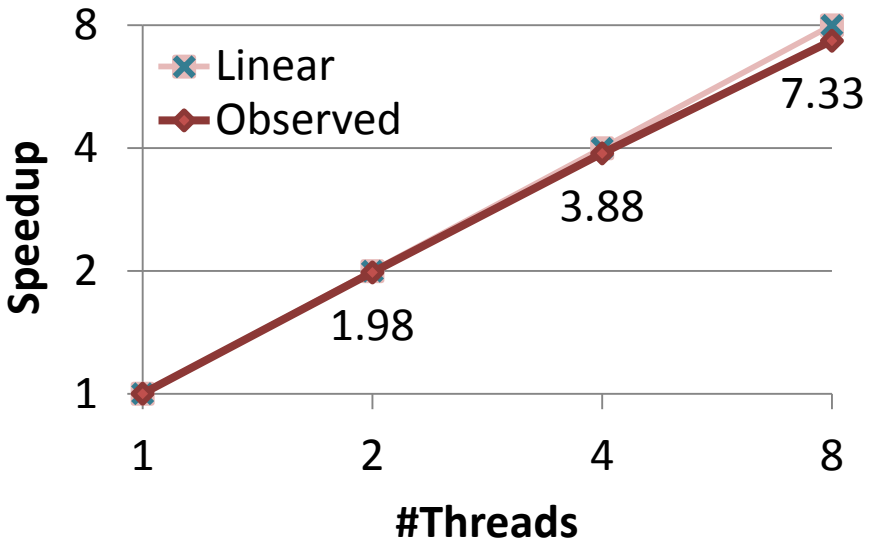
8.8 times speedup
compared to ZDOCK 3.0
(single node, single thread)



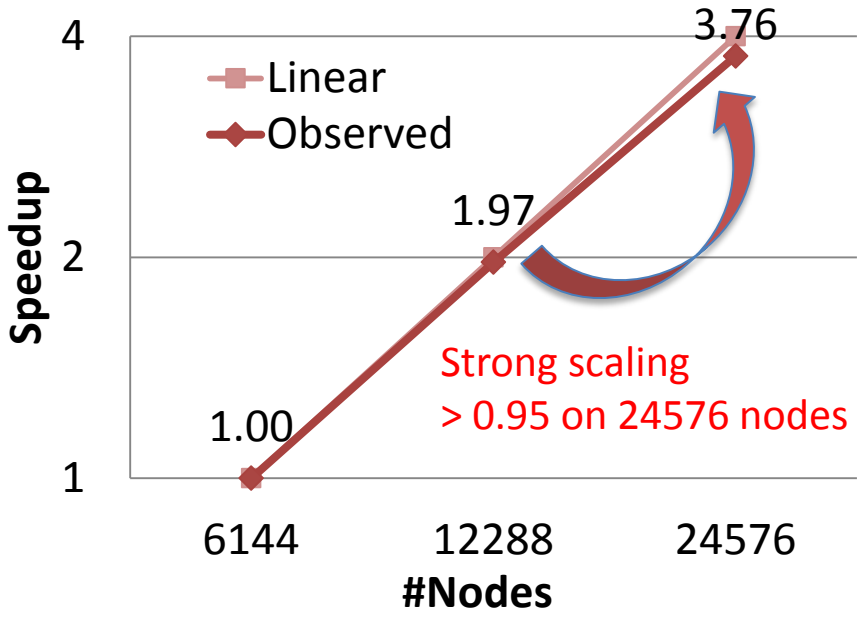
Ohue, *et al.*, *Lecture Note in Bioinformatics*, 2012.

Scalability on K computer

OpenMP parallelization



MPI parallelization

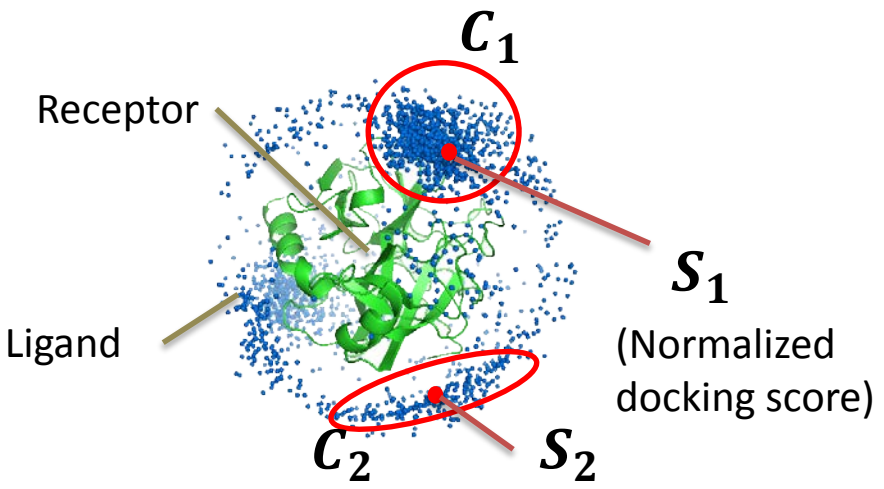


- Less but sufficient scalability (strong scaling 0.91) was observed with 82,944 nodes.

Matsuzaki, *et al.*, *Source Code Biol Med*, 2013.

Prediction method 1: clustering based

- Get 2,000 high scoring models by docking of each protein pair
- Conduct clustering based on structure similarity
- Define the highest docking score (normalized) of the data included in the cluster C_i : s_i
- Define cluster population (normalized) : m_i
- Select populated clusters C' with threshold m^* of population of the cluster $C' = \{C_i \mid m_i > m^*\}$
- Decide PPI score E
- Evaluate each pair of protein combination as interacting if E is higher then the threshold E^*

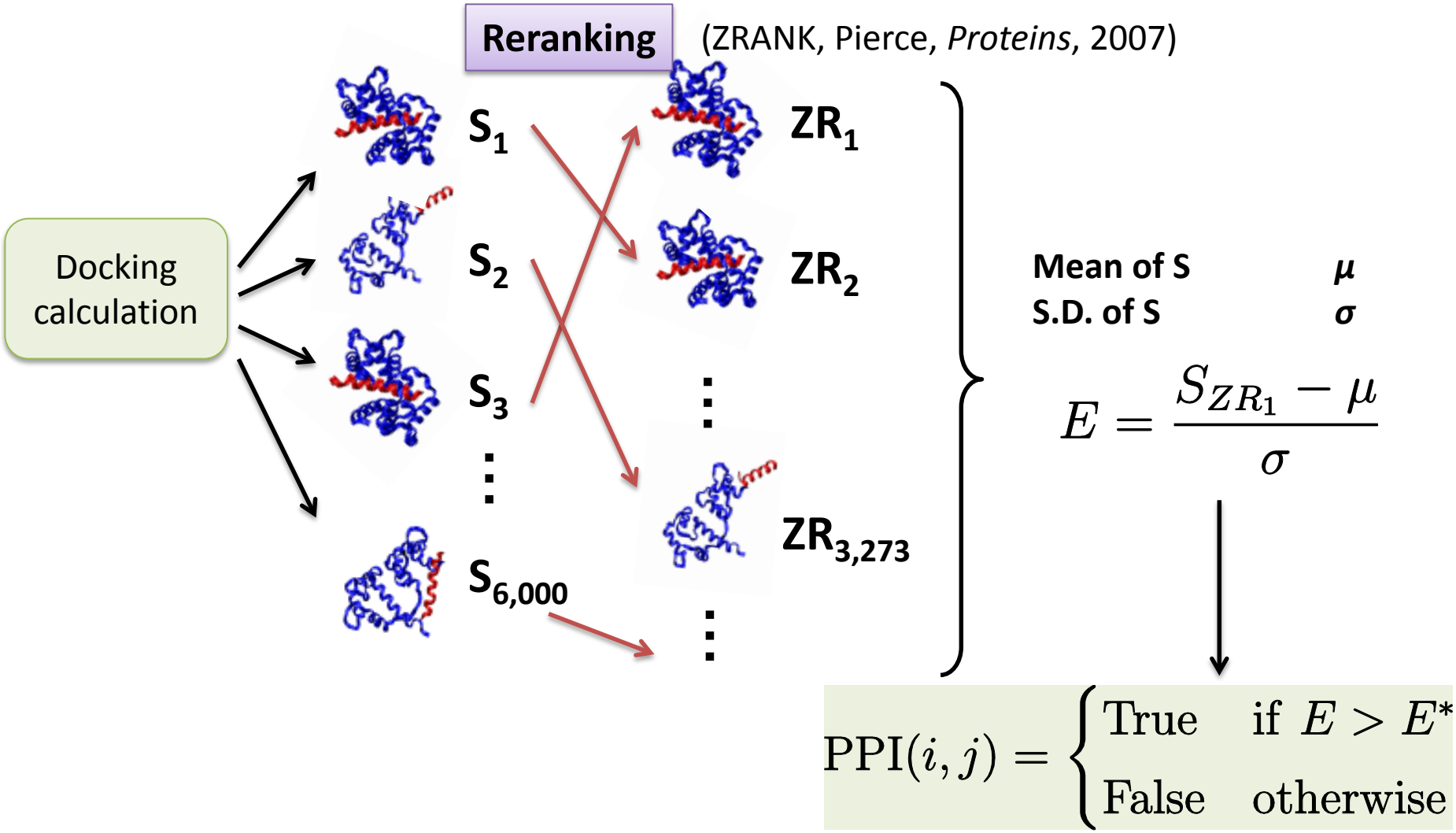


$$E = \begin{cases} max\ s_i,\ i \in C' & \text{if } C' \neq \varnothing \\ 0 & \text{otherwise} \end{cases}$$

$$interaction = \begin{cases} true & \text{if } E > E^* \\ false & \text{otherwise} \end{cases}$$

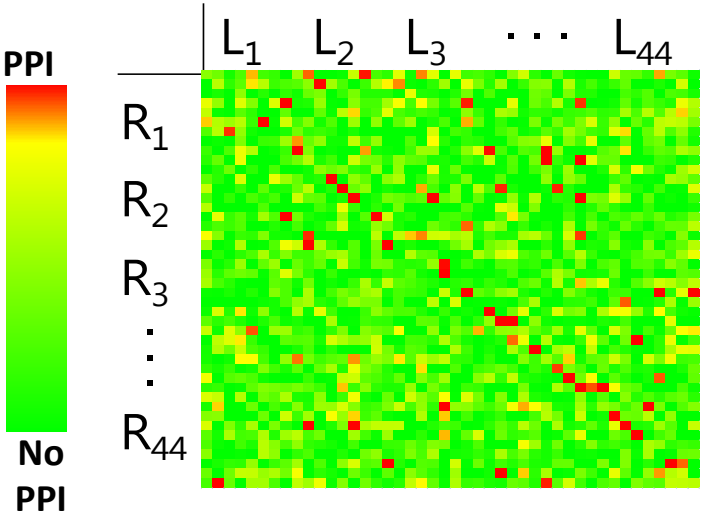
Matsuzaki, *et al., J Bioinform Comput Biol, 2009.*

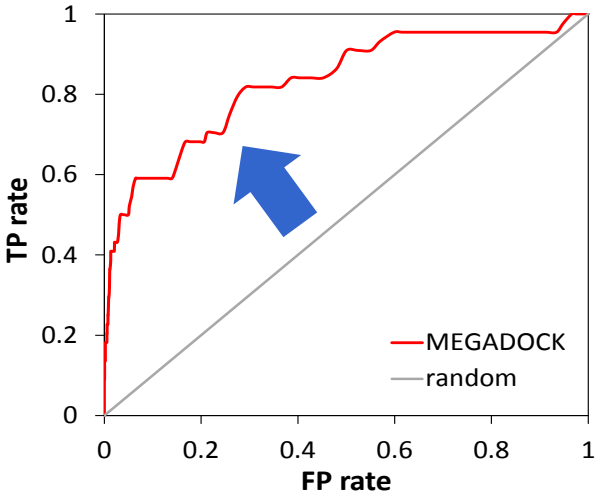
Prediction method 2: reranking based

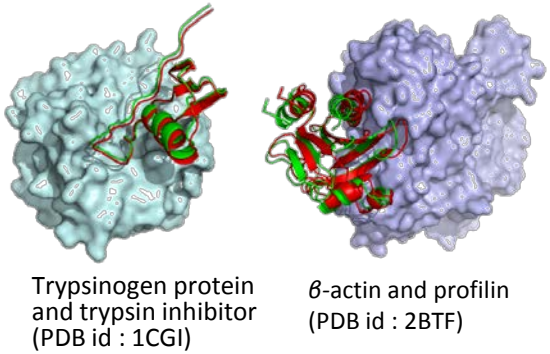


Ohue, *et al.*, *Protein Pept Lett*, in press.

PPI prediction using general benchmark data







Binding partner prediction from 44x44=1936 dockings and post-docking (Diagonal: interacting pairs)

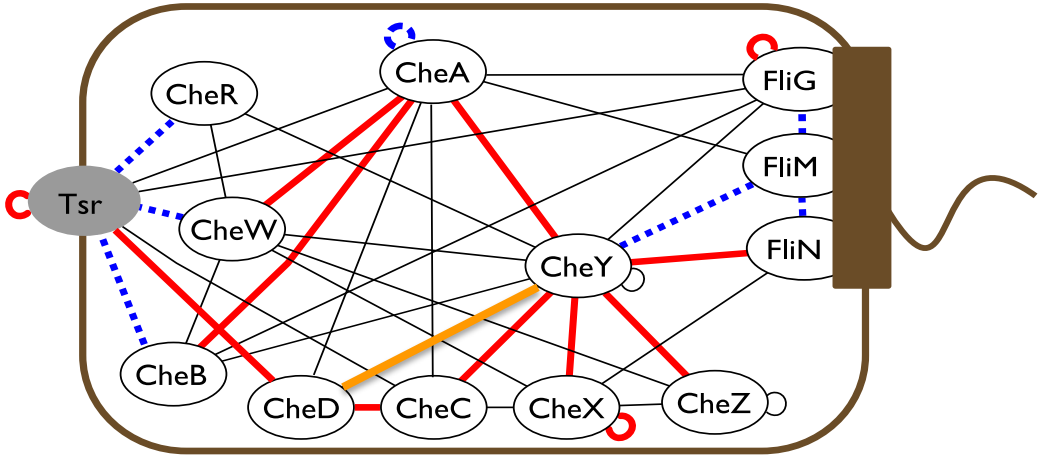
F-measure : 0.42

$$F\text{-measure} = \frac{2 \cdot \mathrm{TP}}{(\mathrm{TP}+\mathrm{FP})+(\mathrm{TP}+\mathrm{FN})}$$

PPI prediction by MEGADOCK achieved better than random performance on general benchmark dataset (monomer pair from protein-protein docking benchmark 2.0, Mintseris *et al*, *Proteins*, 2005.)

Matsuzaki, *et al.*, *J Bioinform Comput Biol*, 2009.
Ohue, *et al.*, *Protein Pept Lett*, *2014*.

Application to bacterial chemotaxis pathway

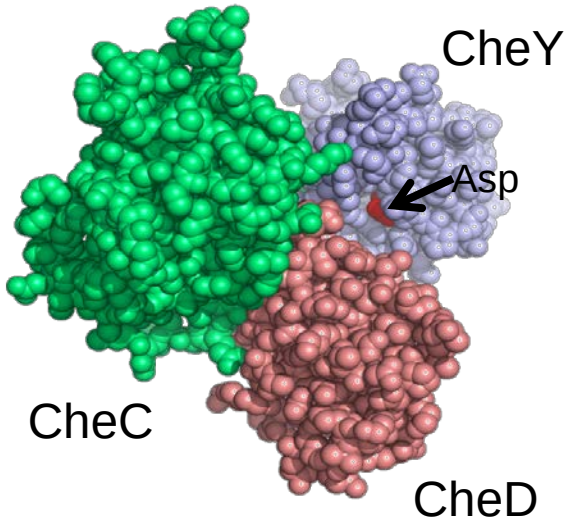


: True Positive
: False Negative
: False Positive

13 proteins
(101 structures)

F-measure : 0.44

Acceptable performance was shown on a real biology pathway reconstruction problem.

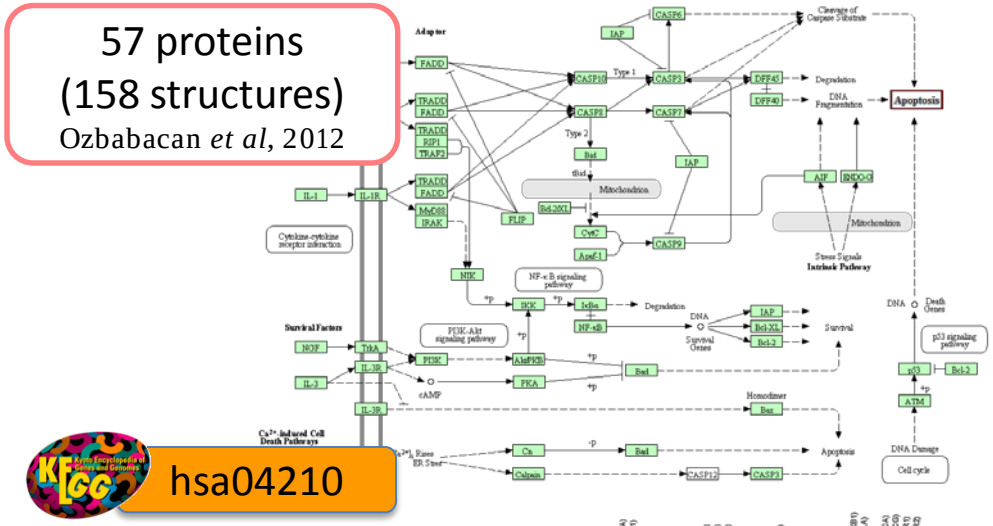


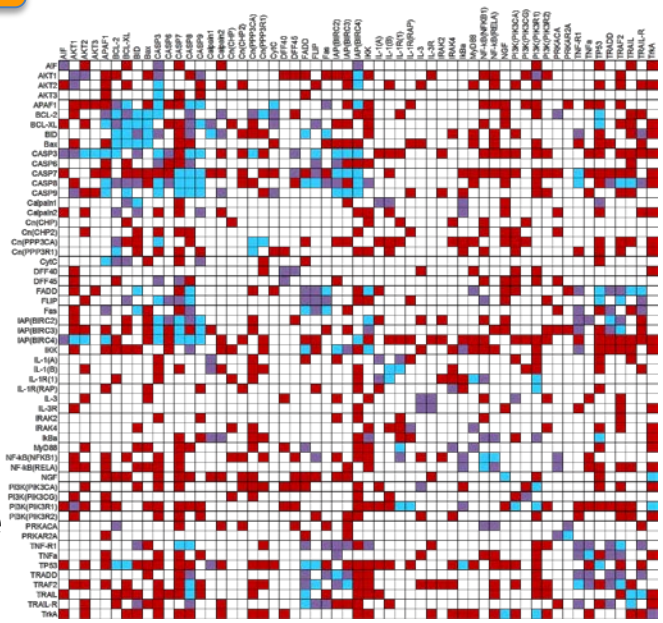
A suggestion of CheY-CheC interaction by using "False-positive" pair CheY-CheD as a mediator

Matsuzaki, *et al.*, *J Bioinform Comput Biol*, 2009.

Application to human apoptosis pathway

57 proteins
(158 structures)
Ozbabacan *et al*, 2012





True Positive

False Positive

False Negative

F-measure : 0.28

PPI prediction by docking without any other knowledge showed comparable results to template-based search of interaction partners (F-measure 0.30, Ozbabacan *et al.*, *J Struct Biol*, 2012).

Prediction	Interacting	No Interaction
Positive	88	364
Negative	96	1105

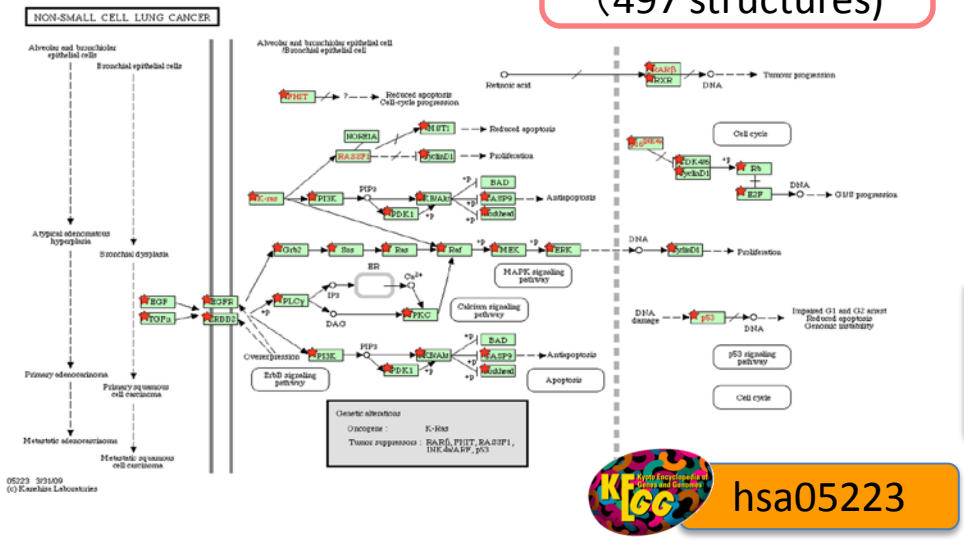
Ohue, *et al.*, *BMC Proc.*, *2013*.

Application to non-small cell lung cancer pathway

- Completed large-scale exhaustive docking
  - 497 structures, all-to-all docking
    ＝247,009 structure pairs
- Achieved high PPI prediction performance
  - Precision 0.29
  - Recall 0.47
  - F-measure 0.36

PPI prediction of about 250 thousand structure pairs showed comparable performance to the application to bacterial chemotaxis (10 thousand pairs).

44 proteins
(497 structures)



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Prediction	Interacting	No Interaction
Positive	53	131
Negative	59	747

Counts are based on protein species

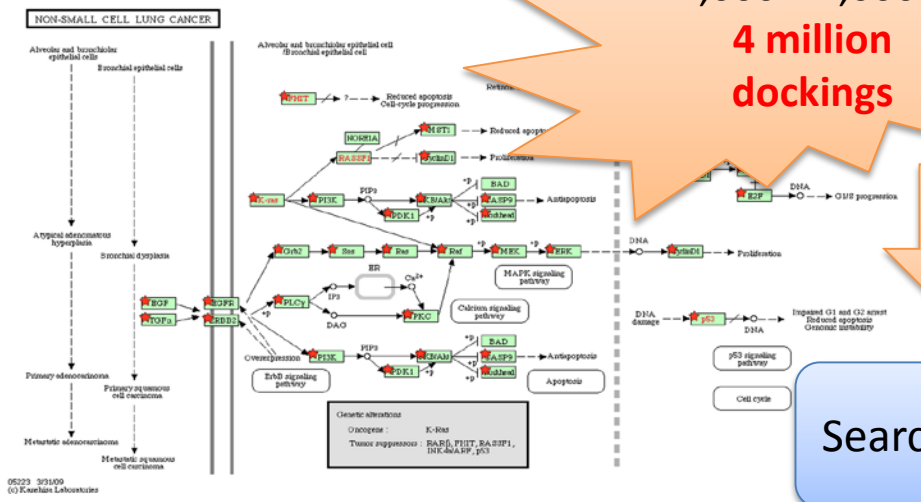
Application to lung-cancer drug related proteins

EGFR pathway related to non-small cell lung cancer

+

Proteins related to Gefitinib estimated by Miyano lab., The Univ. of Tokyo, from microarray analysis

44 proteins
(497 structures)



2,000 x 2,000 =
4 million dockings

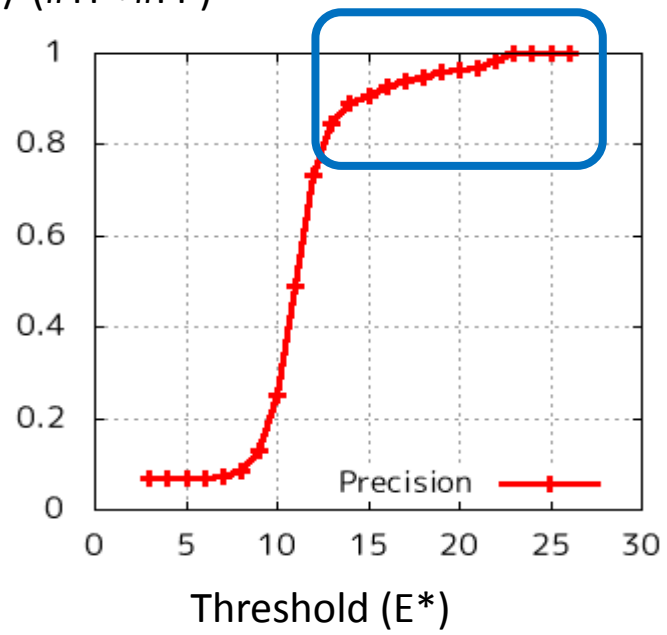
294 proteins
(1424 structures)

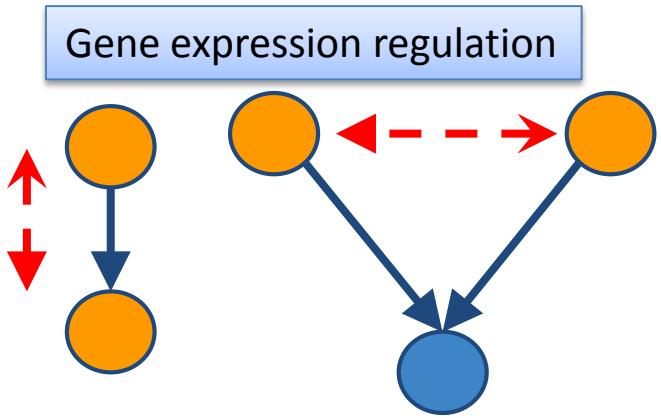
#TP / (#TP+#FP)

Search novel cancer related PPIs

PPI prediction result

Precision
#TP / (#TP+#FP)





- Using threshold of E* = 13.0
  - 3873 structure pairs
  - 175 protein pairs
  - Evaluated the prediction by 6 public databases (MIPS, DIP, IntAct, HPRD, BioGRID, MINT)
  - Undefined positives
    35 pairs
- Looked up these pairs on cancer gene regulatory networks derived by correlation of transcription data
  - Selected highly correlated pairs
  - Obtained 11 pairs

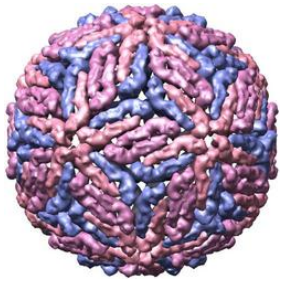
Evaluation of 7 potential PPIs by SPR

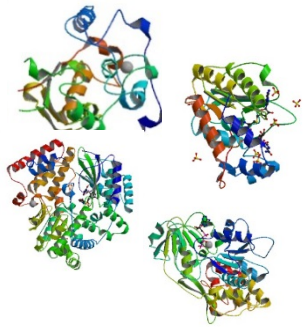
- 7 pairs were sent to assay using surface plasmon resonance (SPR) spectroscopy
  - Reference Biolabs Inc., Korea
  - Device: Reichert SR7500DC
- Binding affinities were measured except from 1 pair

Reference Biolobs Inc.

[Ongoing] Virus-human PPI prediction

4 major enzymes of Dengue virus





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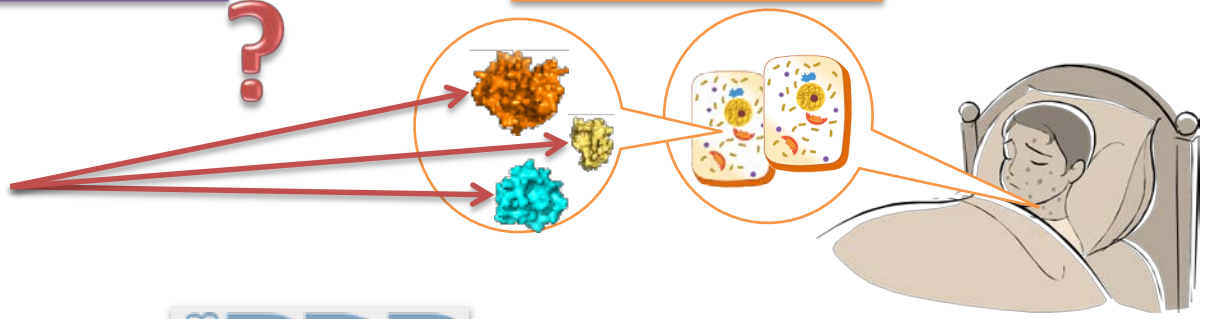
Human proteins



Collected human proteins data:

- ✓ >25 residues
- ✓ X-ray resolution better than 3.25 Å
- ✓ No mutation

Enzyme
Protease
Methyltransferase
Polymerase
Helicase

#Proteins (UniProt IDs)	3,353
#Structure data (PDB-chains)	30,544

(2013-06-15)

$4 \times 30{,}544 = 122{,}176$ dockings
Suggested 28 potential interactions

References

(Papers contributed by MEGADOCK group)

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