Computational Modeling of Protein-Protein Interaction

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Outline

- Binary prediction of Protein-protein Interaction (PPI)
- Analysis of PPI networks
- Structural modeling of PPI
- Physical properties of PPI

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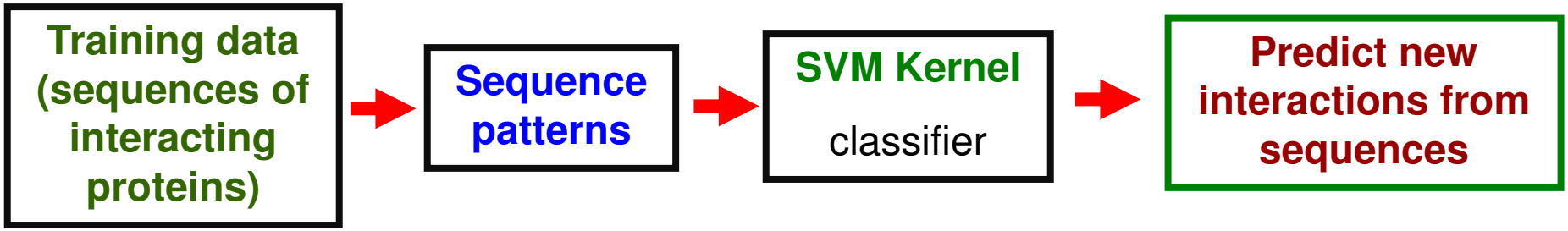
Binary prediction of PPI: General procedure

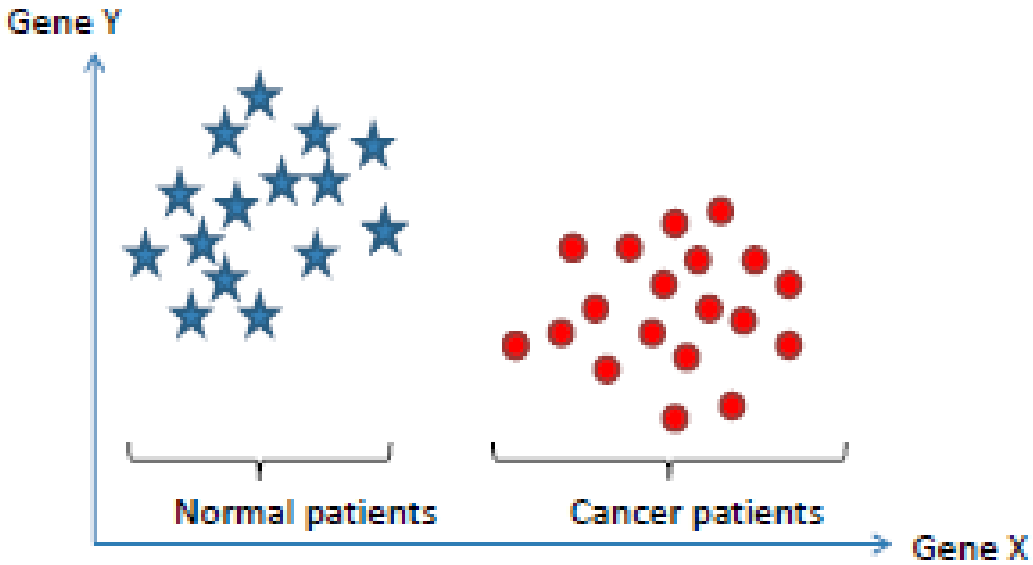


Training set for SVM kernel classifier

= Positive training set (experimental interactions, some for training, some for validation)

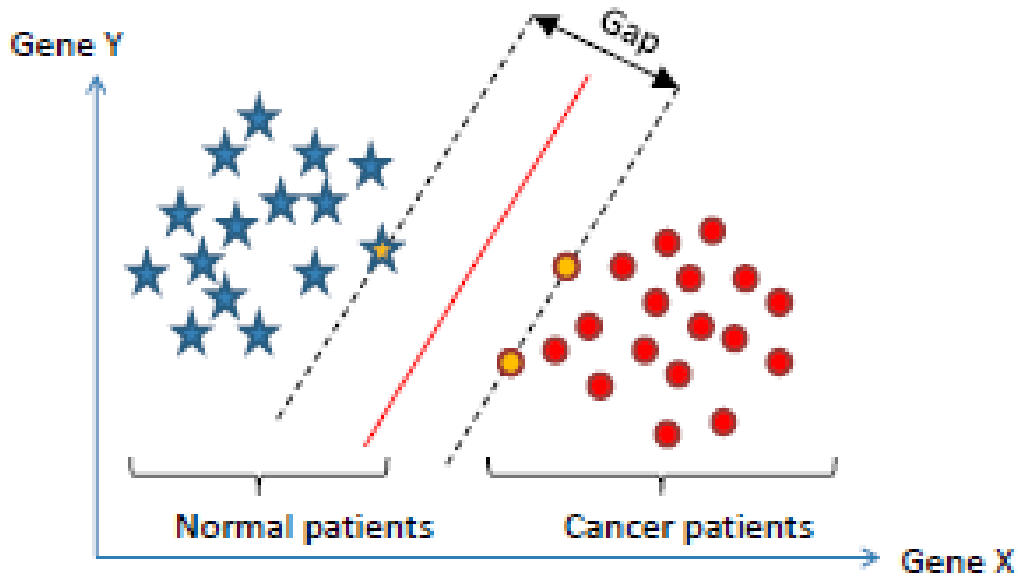
+ Negative training set (mostly random generated pairs)

Main ideas of SVMs



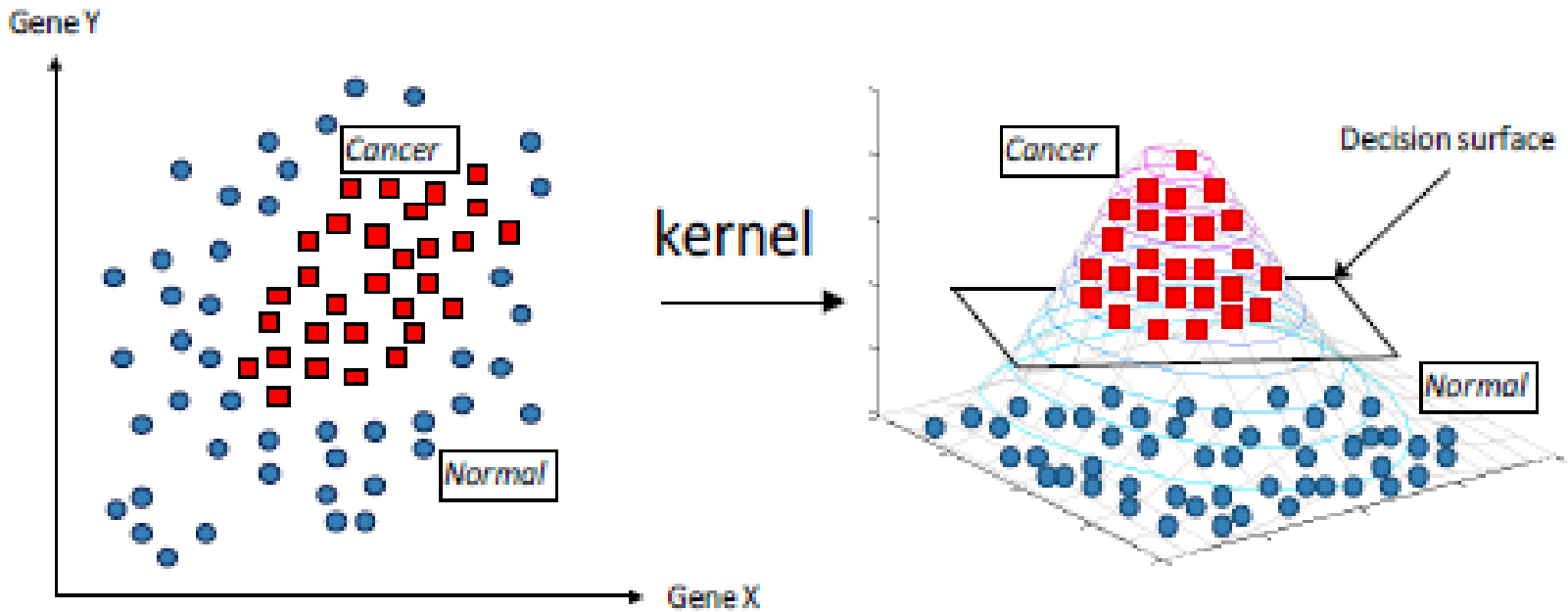
- Consider example dataset described by 2 genes, gene X and gene Y
- Represent patients geometrically (by "vectors")

Main ideas of SVMs



- Find a linear decision surface ("hyperplane") that can separate patient classes <u>and</u> has the largest distance (i.e., largest "gap" or "margin") between border-line patients (i.e., "support vectors");

Main ideas of SVMs



- If such linear decision surface does not exist, the data is mapped into a much higher dimensional space ("feature space") where the separating decision surface is found;
- The feature space is constructed via very clever mathematical projection ("kernel trick").

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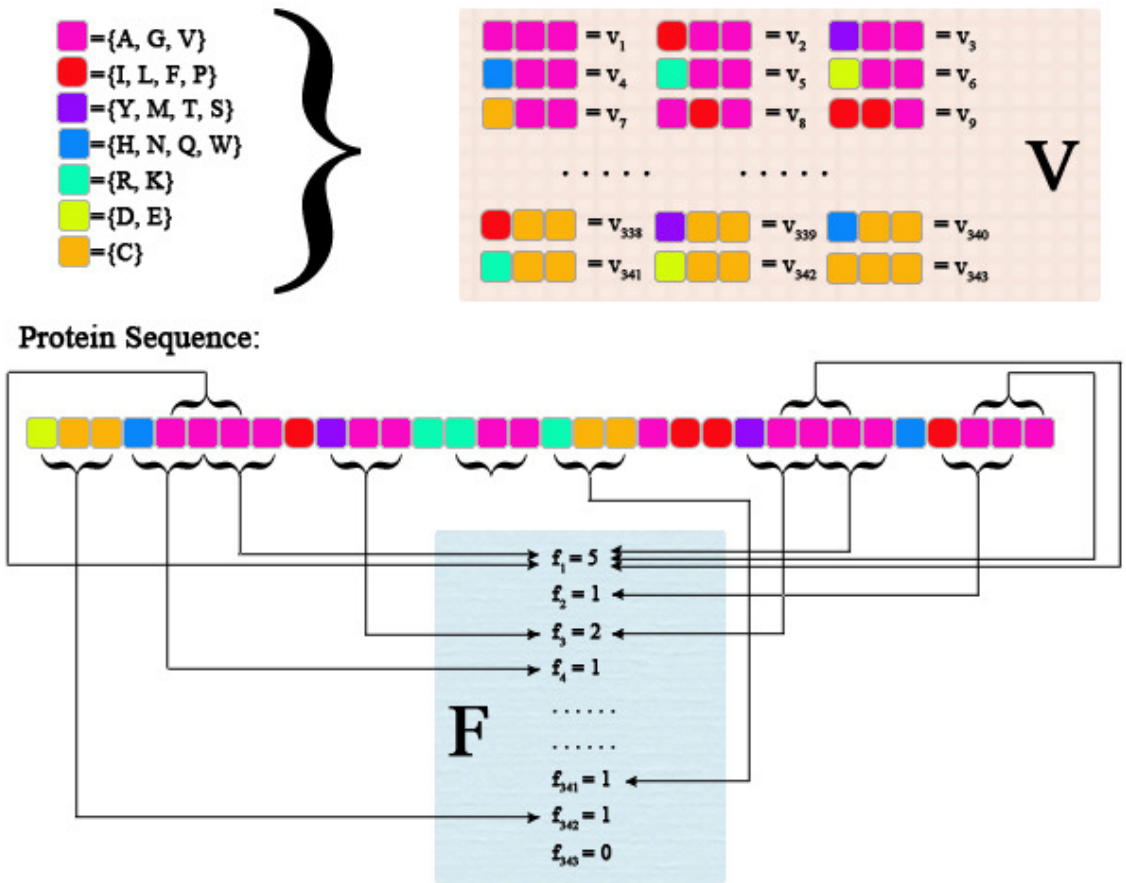
Classification of Amino Acid(AA)

No.	Dipole scale[a]	Volume scale[b]	Class
1	-	-	Ala, Gly, Val
2	-	+	Ile, Leu, Phe, Pro
3	+	+	Tyr, Met, Thr, Ser
4	++	+	His, Asn, Gln, Tpr
5	+++	+	Arg, Lys
6	+'+'+'	+	Asp, Glu
7	+ [c]	+	Cys

Using Conjoint Triads for sequence pattern construction



Reduced-alphabet sequence pattern training:

1. Classify 20 AA types into 7 classes based on their properties (hydrogen bonding, hydrophobic, volumes of sidechains, etc).
2. Build AA triplets using 7 classes, called “conjoint triad” (343 unique types). Save in **V**
3. Calculate frequency of each triad for each protein sequence.

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Kernel Function

- **di** = (**fi** - min {**f**1, **f**2, ..., **f**343})/max{**f**1, **f**2, ..., **f**343}
- $\mathbf{D}_A$={$\mathbf{d}_A$1,$\mathbf{d}_A$2,……,$\mathbf{d}_A$343}
- {$\mathbf{D}_{AB}$} = {$\mathbf{D}_A$}⊕{$\mathbf{D}_B$}: a 686 dimensional vector
- **Kernel Function**:

$$K(\mathbf{D_{AB}}, \mathbf{D_{EF}}) = \exp(-\gamma\|\mathbf{s}\|^2)s = \min\{(\|\mathbf{D_A} - \mathbf{D_E}\|^2 + \|\mathbf{D_B} - \mathbf{D_F}\|^2), (\|\mathbf{D_A} - \mathbf{D_F}\|^2 + \|\mathbf{D_B} - \mathbf{D_E}\|^2)\}.$$

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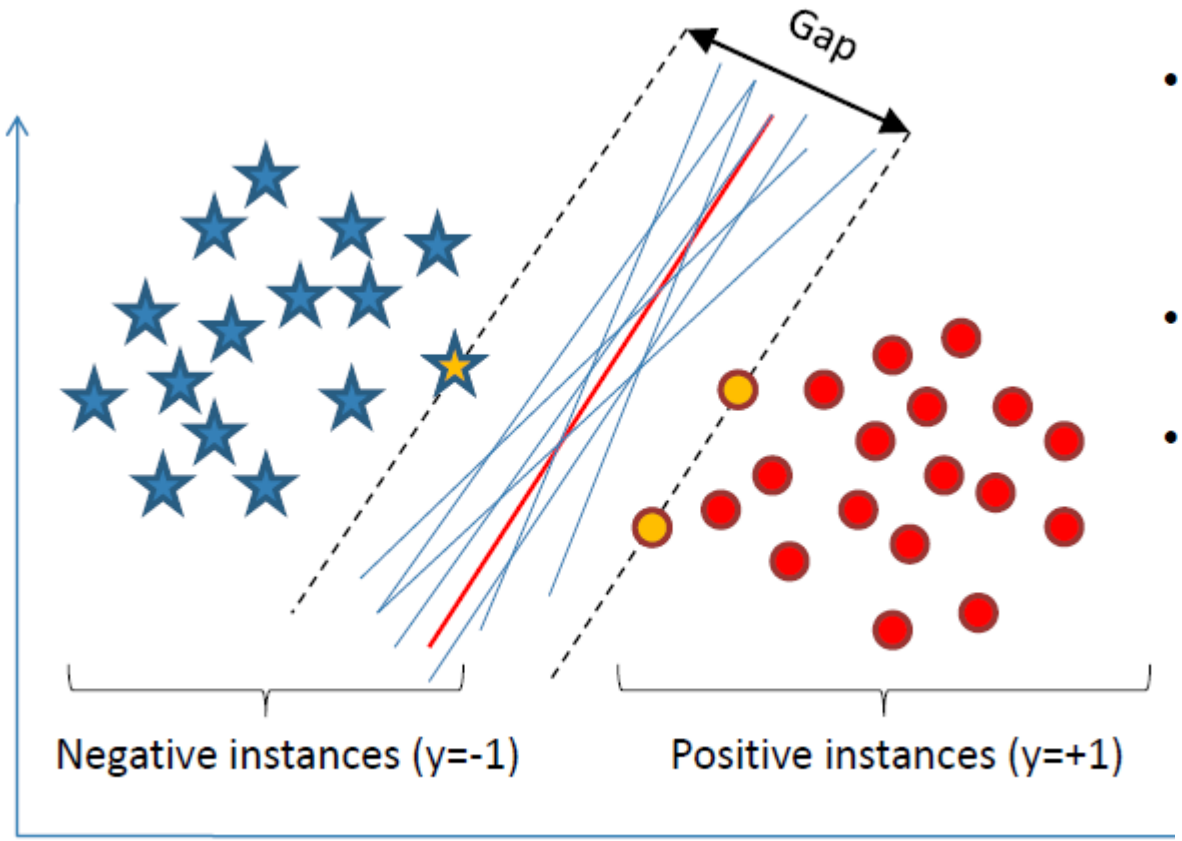
Given training data: $\vec{x}_1, \vec{x}_2, \ldots, \vec{x}_N \in R^n$

$y_1, y_2, \ldots, y_N \in \{-1, +1\}$



- Want to find a classifier (hyperplane) to separate negative instances from the positive ones.
- An infinite number of such hyperplanes exist.
- SVMs finds the hyperplane that maximizes the gap between data points on the boundaries (so-called "support vectors").

Kernel Function and parameter adjustment

C=128
Γ=0.25

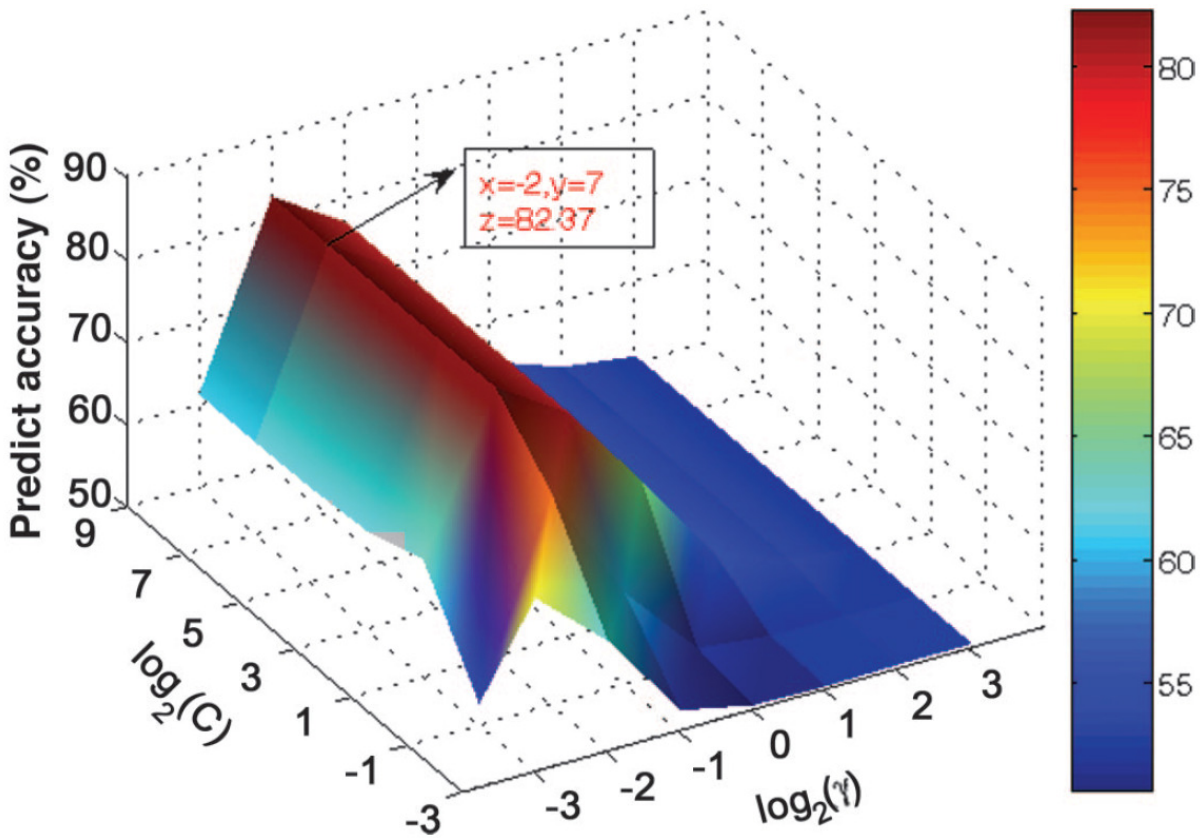


Fig. 1. Accuracy surface of threefold crossover validation on training set versus the variations of parameters C and γ.

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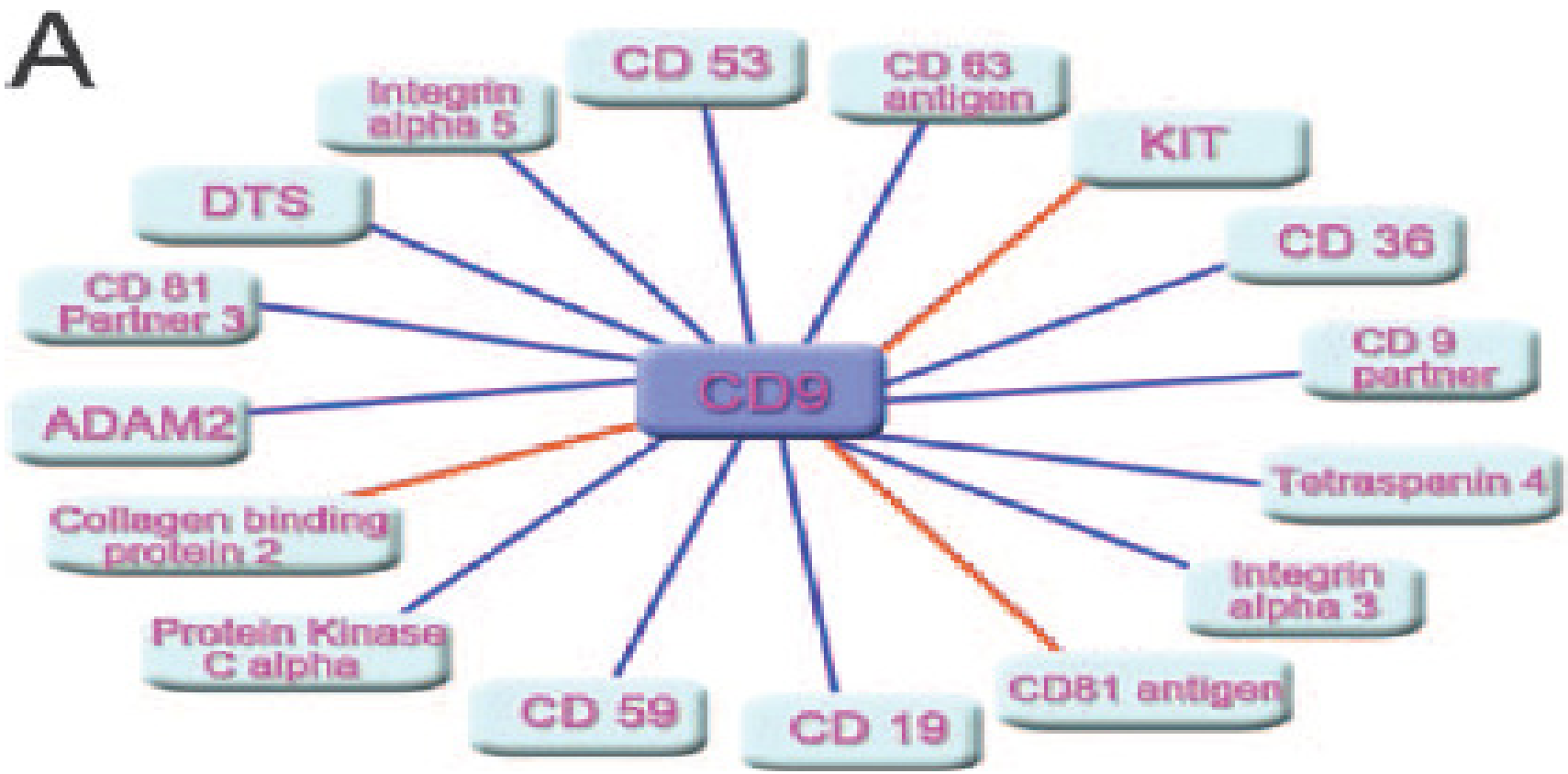
Network Prediction



One-core network

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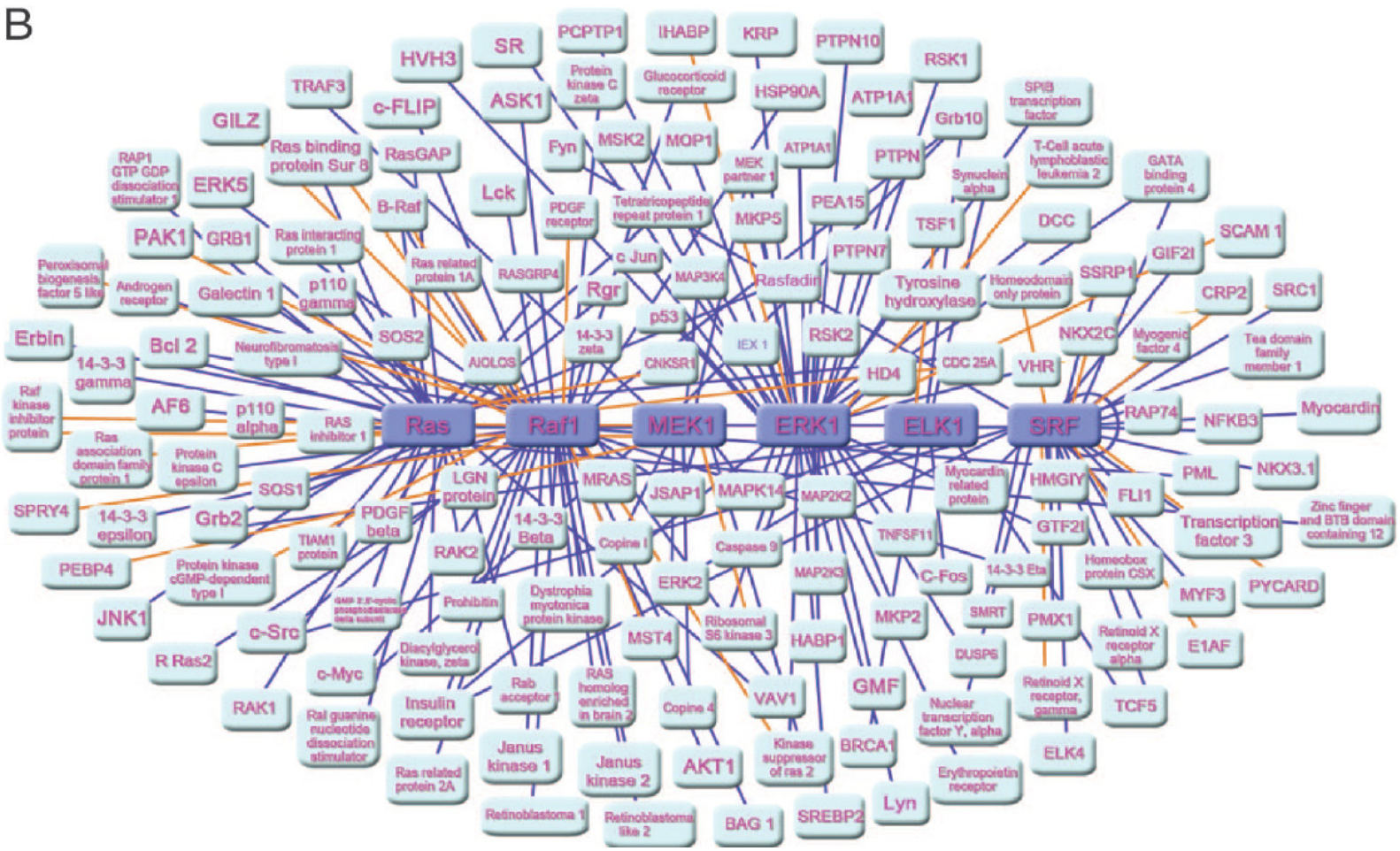
Network Prediction



Multi-core network

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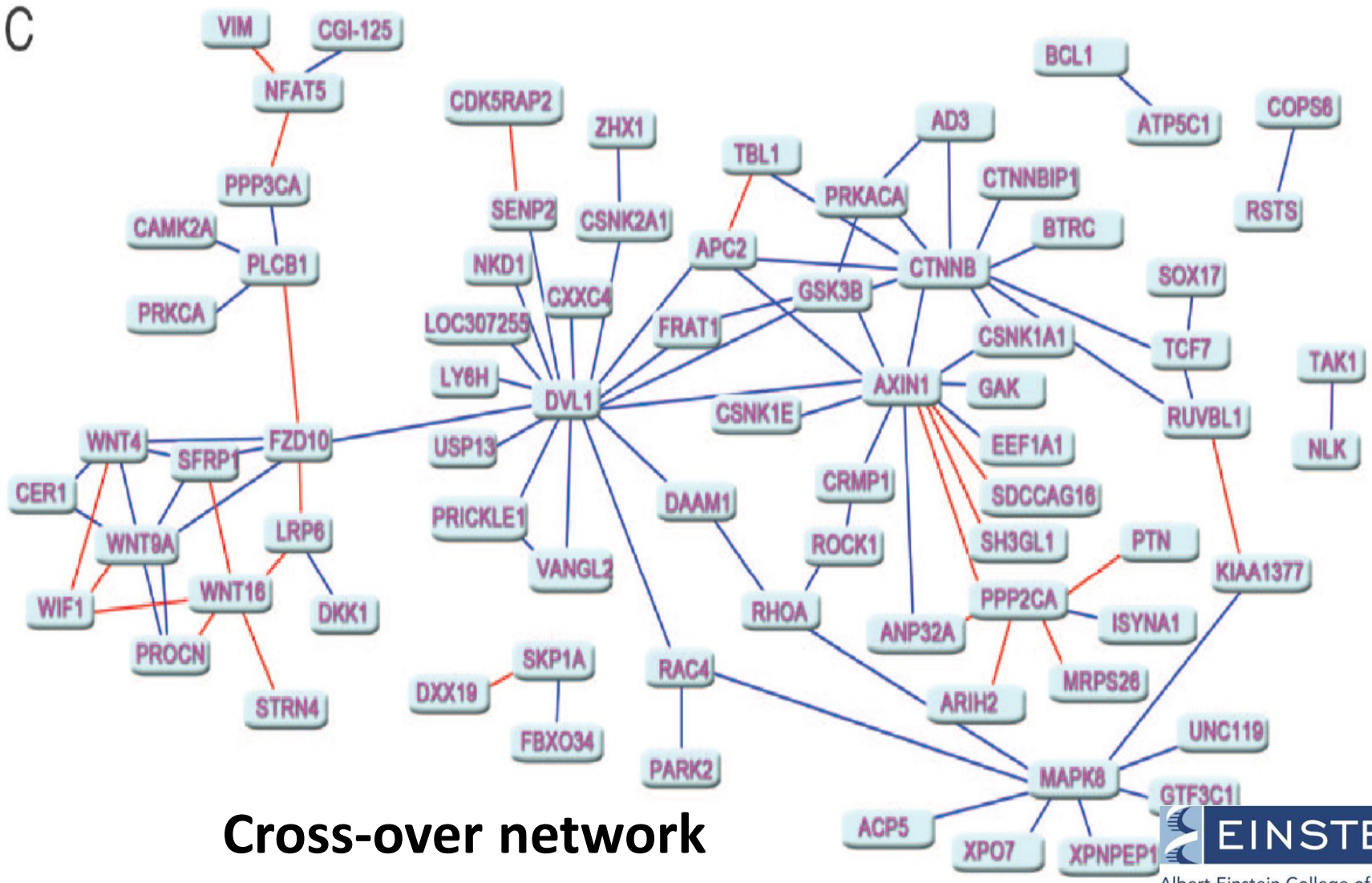
Network Prediction



Cross-over network

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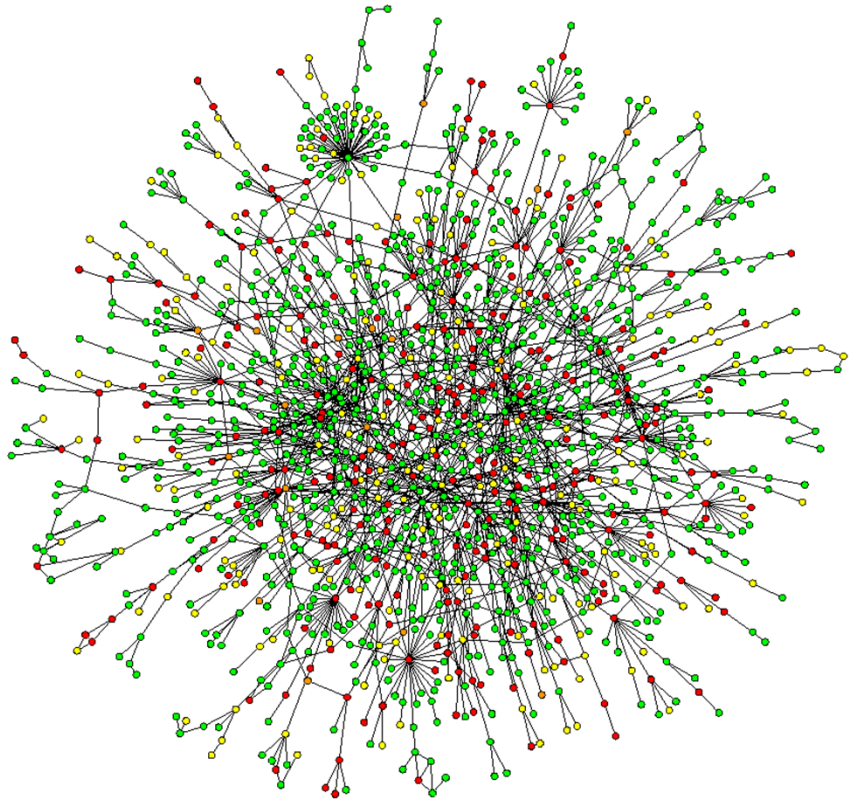
Protein-Protein Interaction Networks?

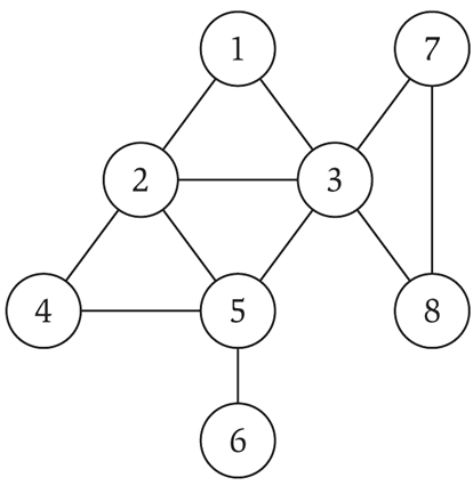
- Protein are nodes
- Interactions are edges



Yeast PPI ne

Introduction to graph theory

- **Graph** – mathematical object consisting of a set of:
  - V = **nodes** (vertices, points).
  - E = **edges** (links, arcs) between pairs of nodes.
  - Denoted by $G = (V, E)$.
  - Captures pairwise relationship between objects.
  - **Graph size** parameters: $n = |V|$, $m = |E|$.



V = { 1, 2, 3, 4, 5, 6, 7, 8 }

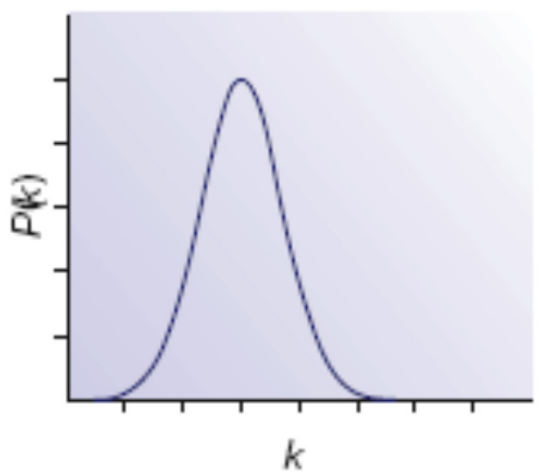
E = { {1,2}, {1,3}, {2,3}, {2,4}, {2,5}, {3,5}, {3,7}, {3,8}, {4,5}, {5,6} }

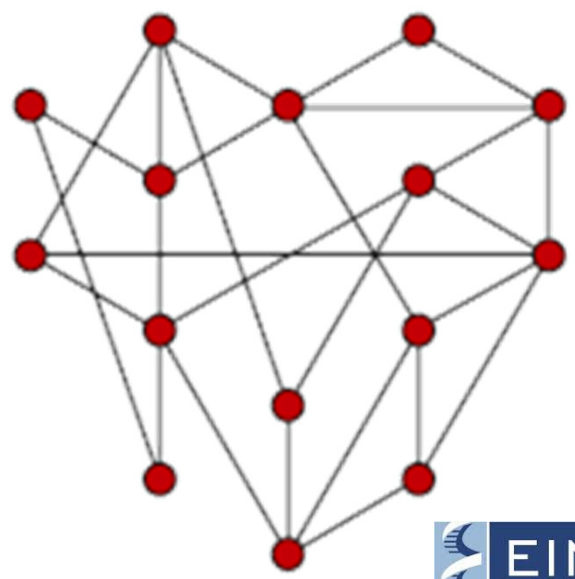
n = 8

m = 11

Random network

- Connect each pair of node with prob p
- Expect value of edge is $pN(N\text{-}1)/2$
- Poisson distribution
  - The node with high degree is rare





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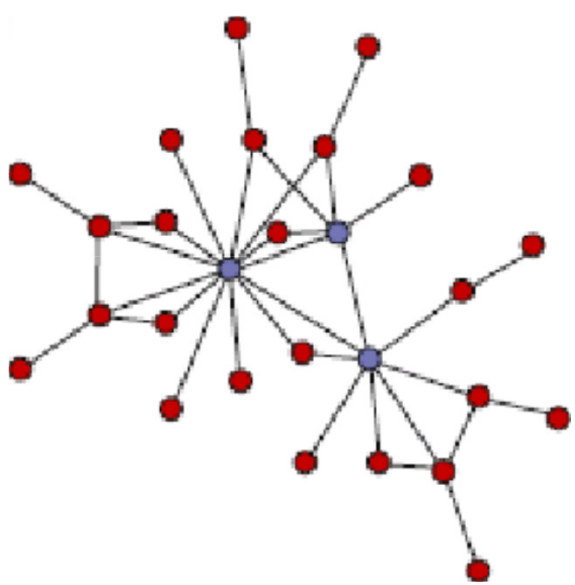
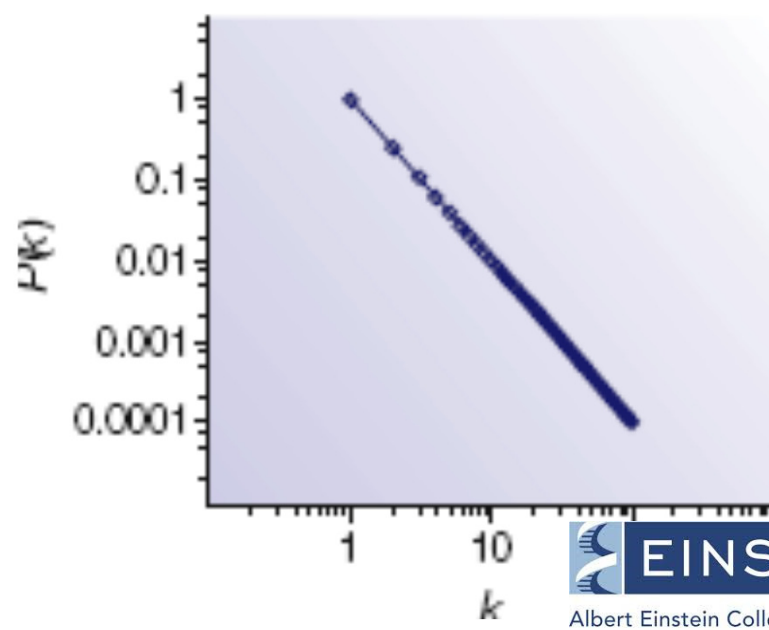
Scale-free network

- Power-law degree distribution
- Hubs and nodes
- When a node add into network, it prefer to link to hubs





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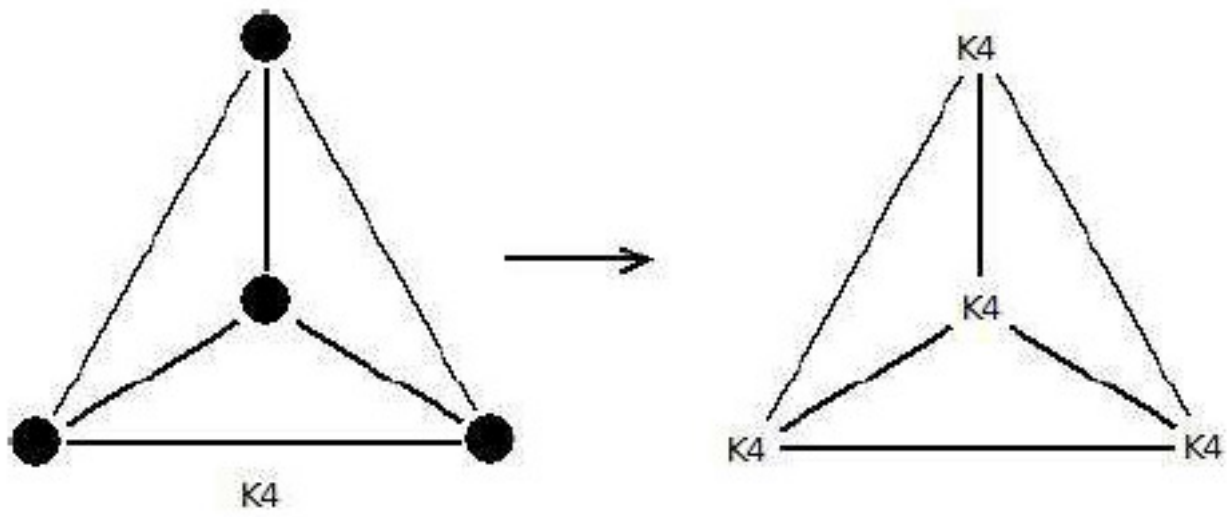
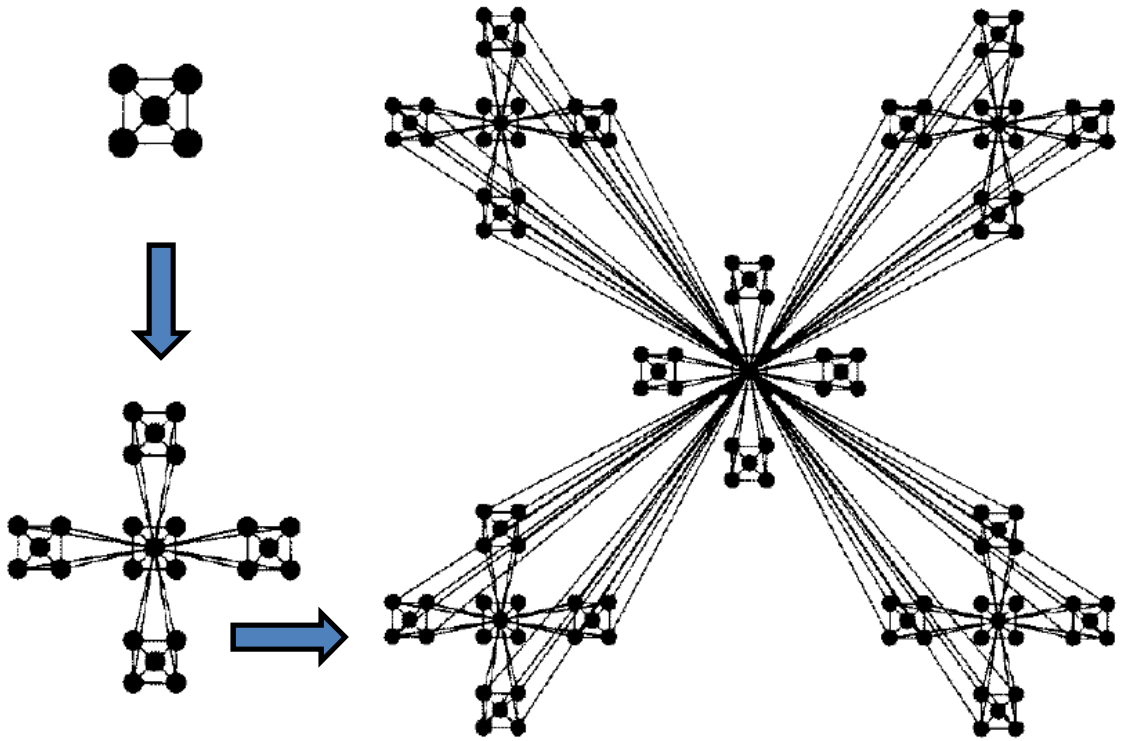
Hierarchical network

- Preserves network “modularity” via a fractal-like generation of the network



Hierarchical network



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Types of Network Comparisons

- 3 types (modes) of comparative methods:
  1. **Network alignment**
  2. **Network integration**
  3. **Network querying**

Types of Network Comparisons

1. Network alignment:

   - The process of comparison of two or more networks of <u>the same type</u> to identify regions of similarity and dissimilarity

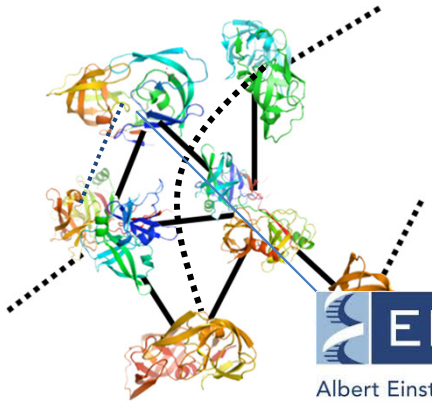
   - Commonly applied to detect subnetworks that are conserved across species and hence likely to present true functional modules

Types of Network Comparisons

2. Network integration:

- The process of combining networks encompassing <u>interactions of different types</u> over <u>the same set of elements</u> (e.g., PPI and genetic interactions) to study their interrelations

- Can assist in uncovering protein modules supported by interactions of different types



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Types of Network Comparisons

- A grand challenge:

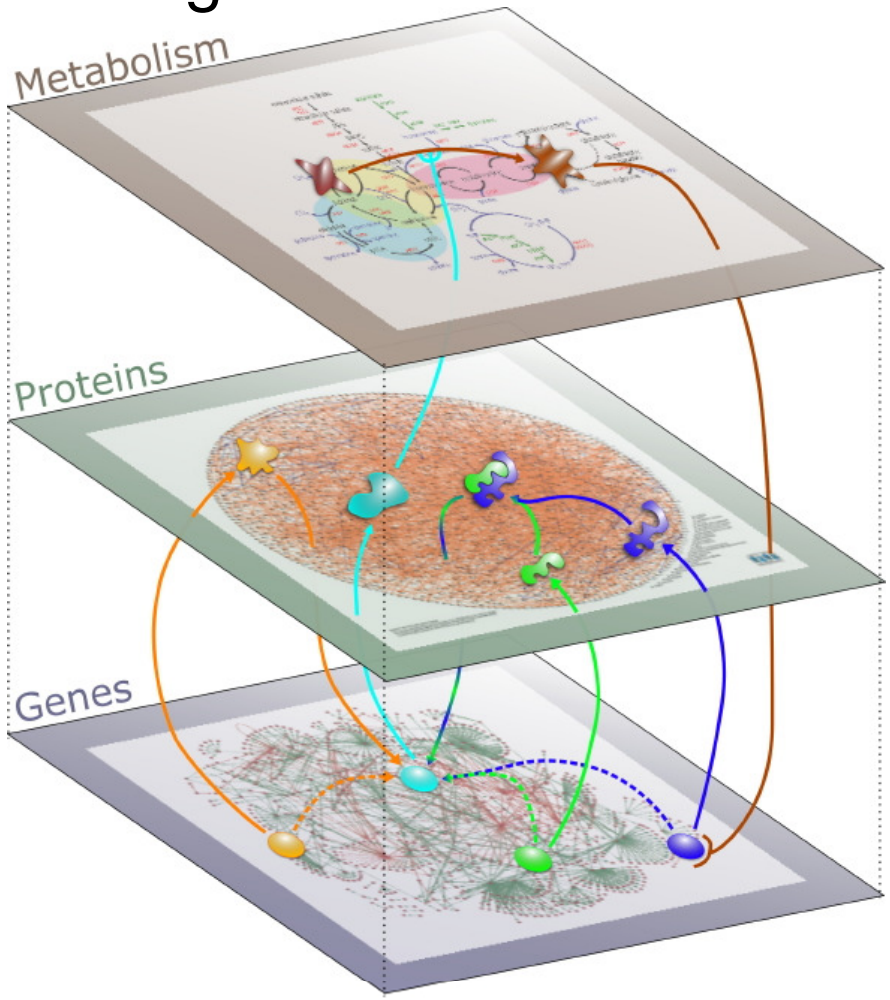

Image from: http://www-dsv.cea.fr/en/institutes/institute-of-biology-and-technology-saclay-il

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Types of Network Comparisons

3. Network querying:

- A given network is searched for subnetworks that are similar to a subnetwork query of interest

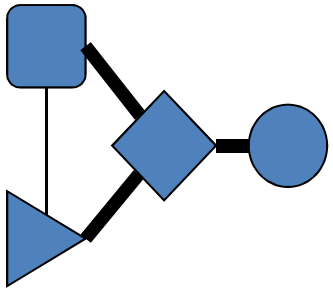
- This basic database search operation is aimed at transferring biological knowledge within and across species

- Currently limited to very sparse graphs, e.g., trees

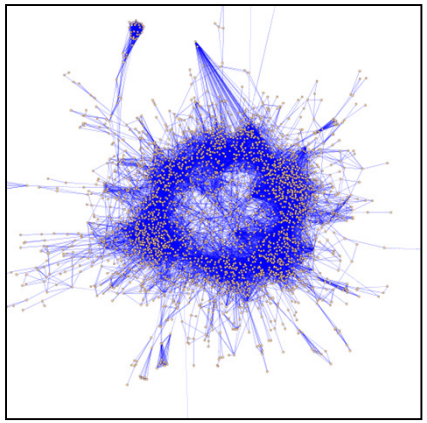
Types of Network Comparisons

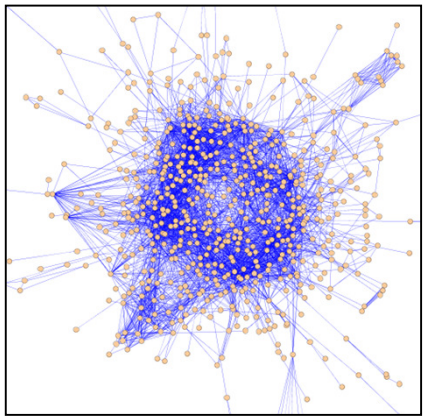
3. Network querying
   - Useful application for biologists: given a candidate module, align to a database of networks ("query-to-database")

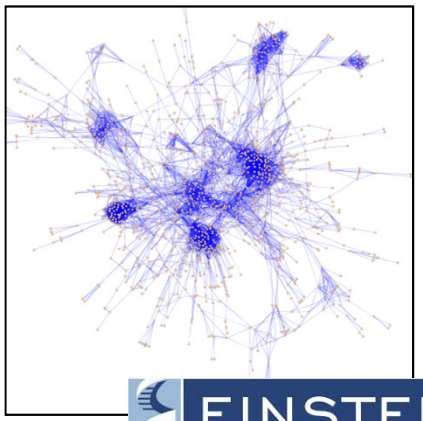
Query:



Database:







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Types of Network Comparisons

Summary

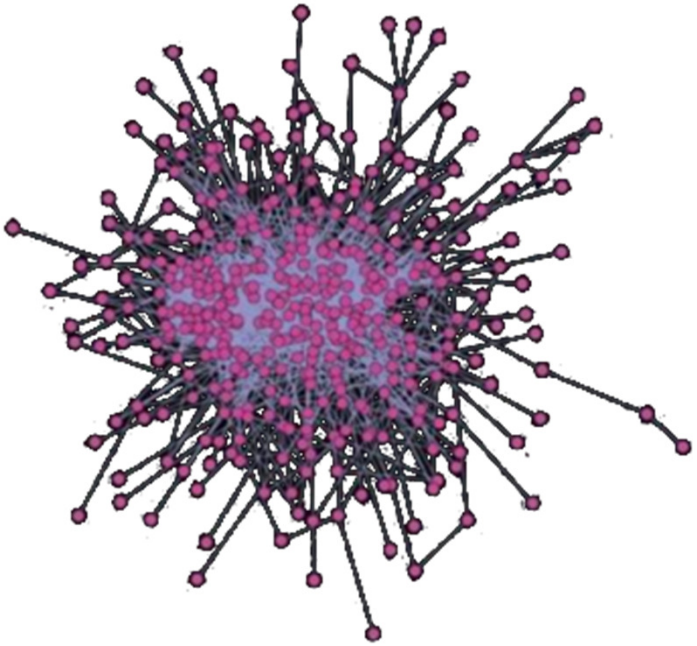
Table 1 Modes of network comparison

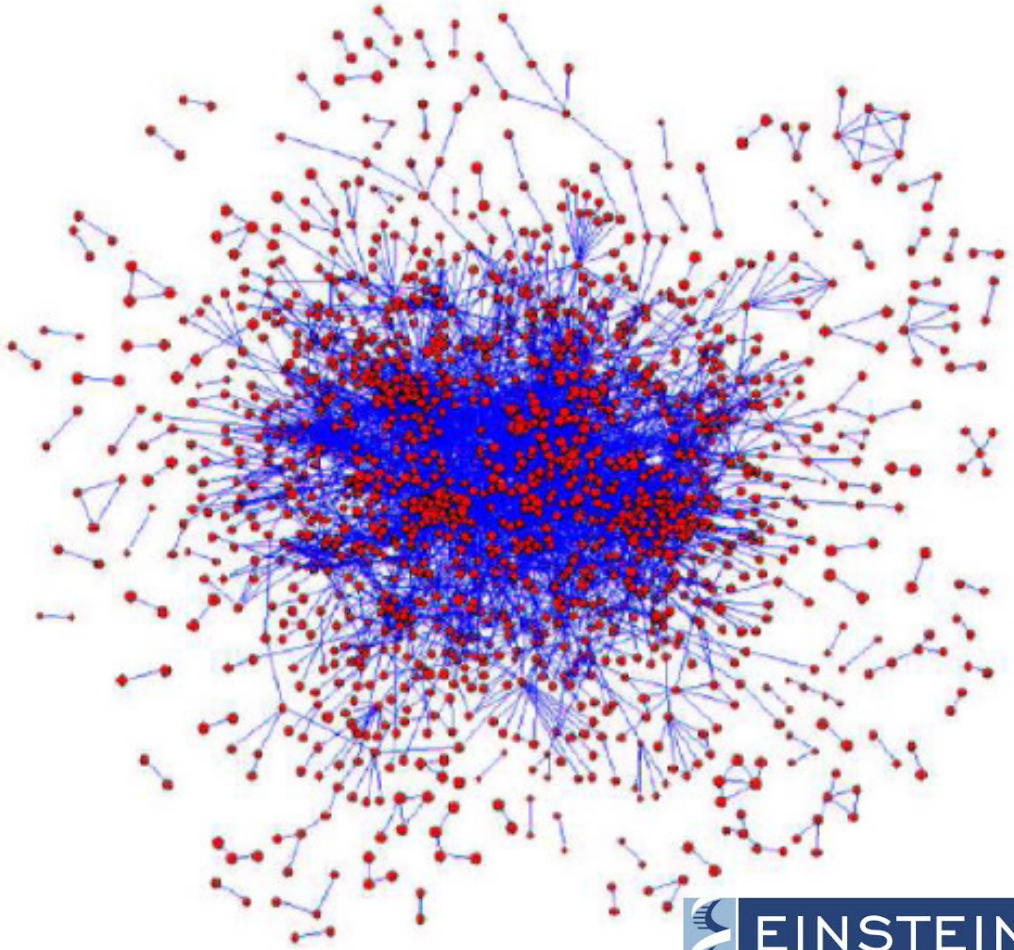
Mode	Common application	Main goals	Some current limitations
Alignment	At least two networks of the same type across species	Identification of functional (conserved) protein modules; study of network evolution; interaction prediction	Limited to few (five or fewer) species
Integration	At least two networks of different types for the same species	Identification of modules (supported by several networks); study of interrelations between data types; interaction prediction	No agreed-upon way to combine scores over different networks
Querying	Subnetwork module versus a network	Identification of duplicated/conserved instances of the module; knowledge transfer	Query is limited to a tree topology

Sharan and Ideker (2006) *Nature Biotechnology* **24**(4): 427-433

Network Alignment

- Finding structural similarities between two networks





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Network Alignment

- Methods vary in these aspects:
  A. Global vs. local
  B. Pairwise vs. multiple
  C. Functional vs. topological information

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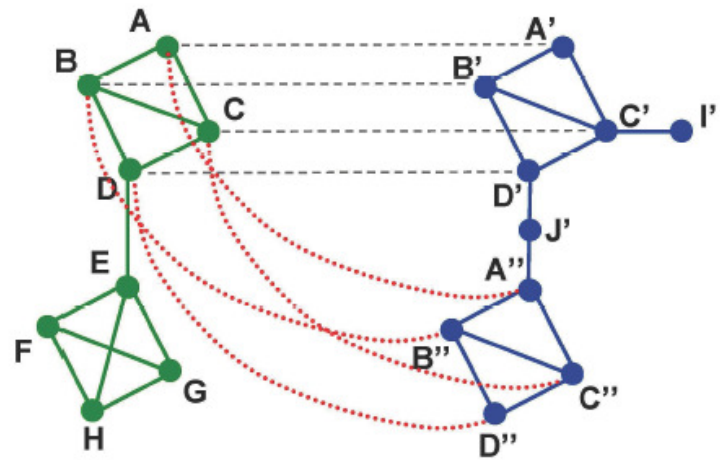

A. <u>Local alignment</u>:

- Mappings are chosen independently for each region of similarity
- Can be ambiguous, with one node having different pairings in different local alignments
- Example algorithms:

  PathBLAST, NetworkBLAST, MaWISh, Graemlin

Network Alignment

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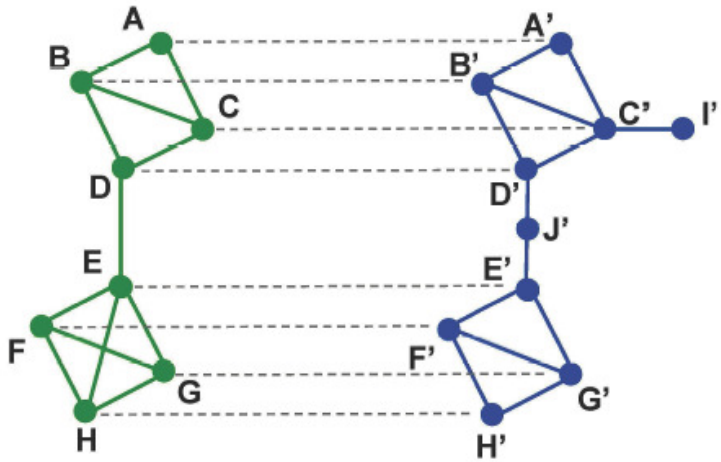

A. <u>Global alignment</u>:

- Provides a unique alignment from every node in the smaller network to exactly one node in the larger network
- May lead to inoptimal matchings in some local regions
- Example algorithms:

  IsoRank, IsoRankN, Graemlin 2, GRAAL, H-GRAAL

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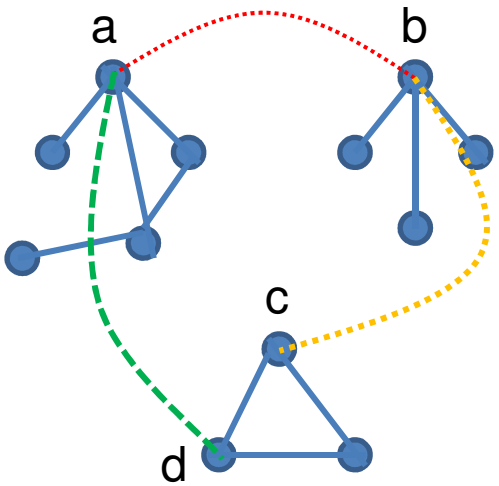

B. <u>Pairwise alignment</u>:

- Two networks aligned
- Example algorithms:
  GRAAL, H-GRAAL, PathBLAST, MaWISh, IsoRank

<u>Multiple alignment</u>:

- More than two networks aligned
- Computationally more difficult than pairwise alignment
- Example algorithms:
  Greamlin, Extended PathBLAST, Extended IsoRank

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Network Alignment

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C. <u>Functional information</u>

- Information external to network topology (e.g., protein sequence) used to define "similarity" between nodes
- Careful: mixing different biological data types, that might agree or contradict

<u>Topological information</u>

- Only network topology used to define node "similarity"
- Good – since it answers how much and what type of biological information can be extracted from topology only

Network Alignment

- In general, the network alignment problem is computationally hard (generalizing subgraph isomorphism)
- Hence, heuristic approaches are devised

- For now, let us assume that we have a heuristic algorithm for network alignment
- How do we measure the quality of its resulting alignments?

Network Alignment

- **<u>Key algorithmic components</u>** of network alignment algorithms:
  - Node similarity measure
  - Rapid identification of high-scoring alignments from among the exponentially large set of possible alignments

Network Alignment

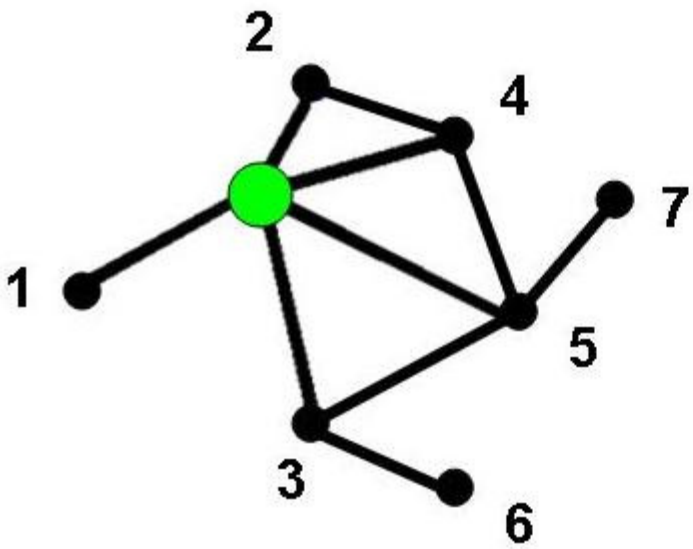
- How is **“similarity” between nodes** defined?
  - Using information external to network topology, e.g., the sequence alignment score
    - Homology, E-values, sequence similarity vs. sequence identity…
  - Using only network topology, e.g., node degree,
  - Using a combination of the two

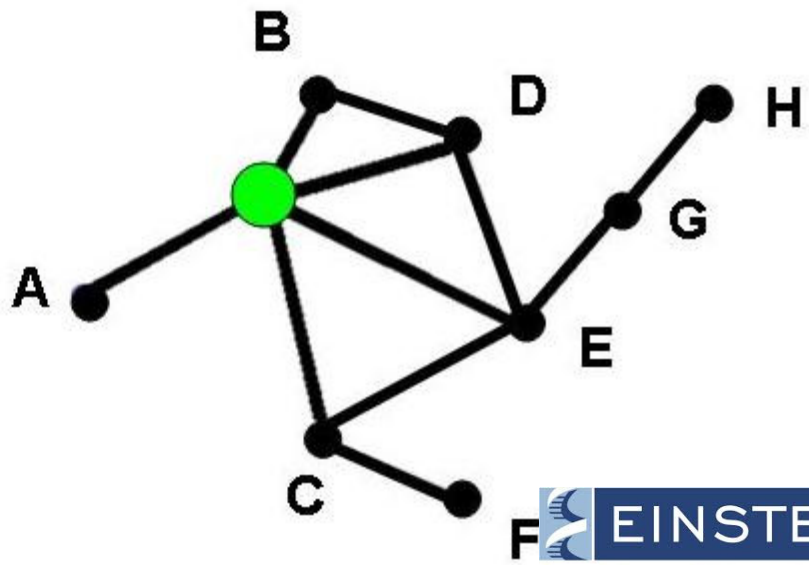
Network Alignment

- How to identify <u>high-scoring alignments</u>?
  - Idea: seeded alignment
    - Inspired by seeded sequence alignment (BLAST)
    - Identify regions of network in which “the best” alignments likely to be found

Network Alignment

- How to identify <u>high-scoring alignments</u>?
  - Greedy ***seed and extend*** approaches
    - Use the most "similar" nodes across the two networks as "anchors" or **"seed nodes"**
    - "Extend around" the seed nodes in a greedy fashion





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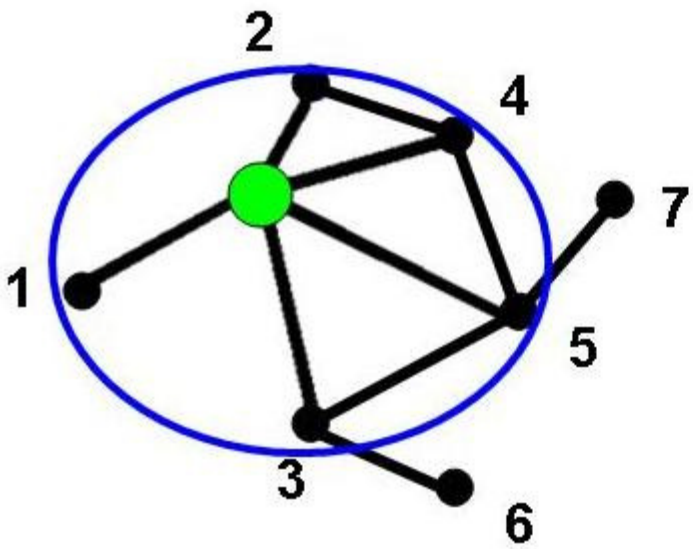

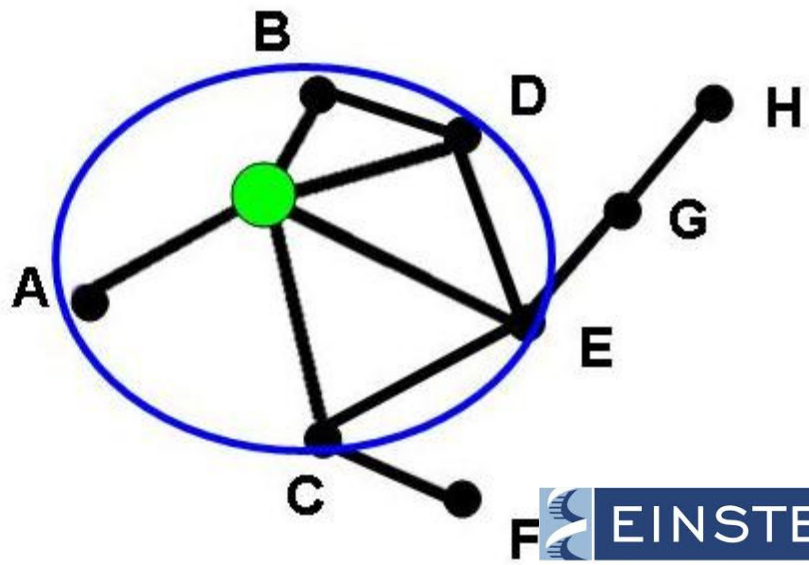

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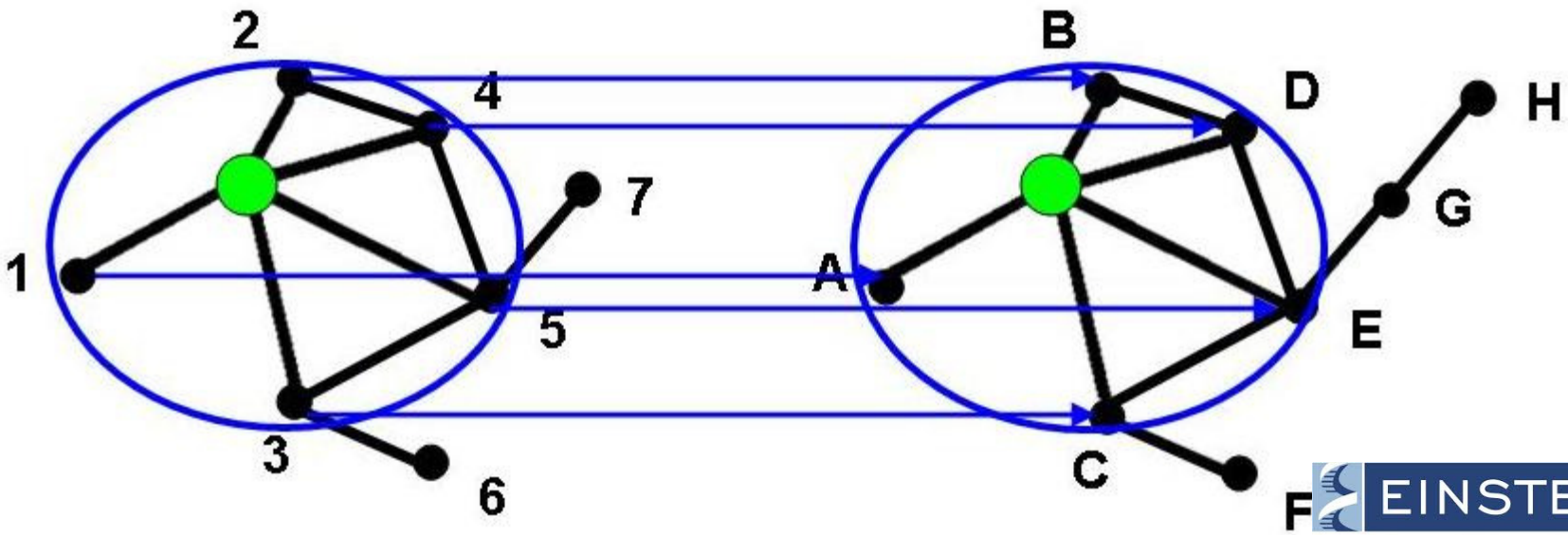

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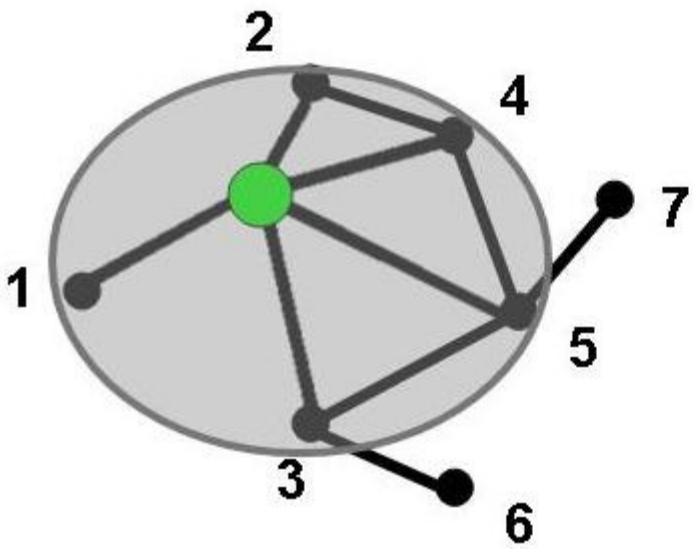

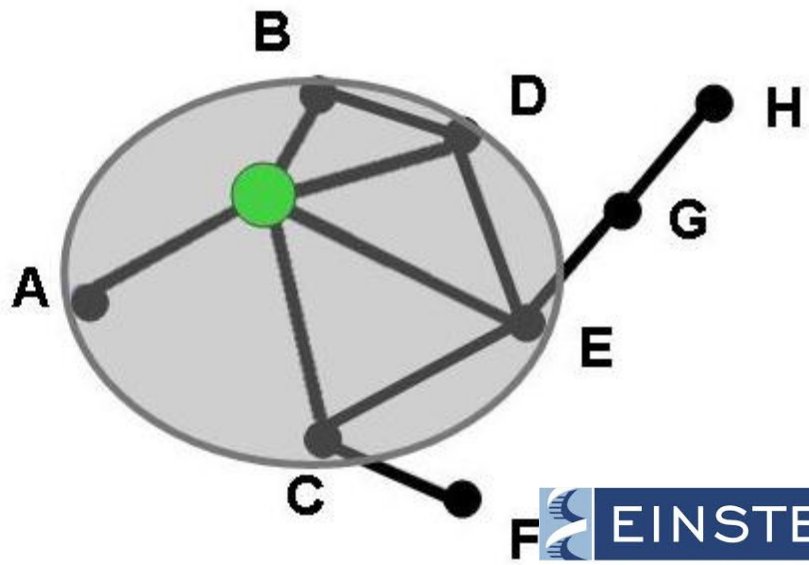

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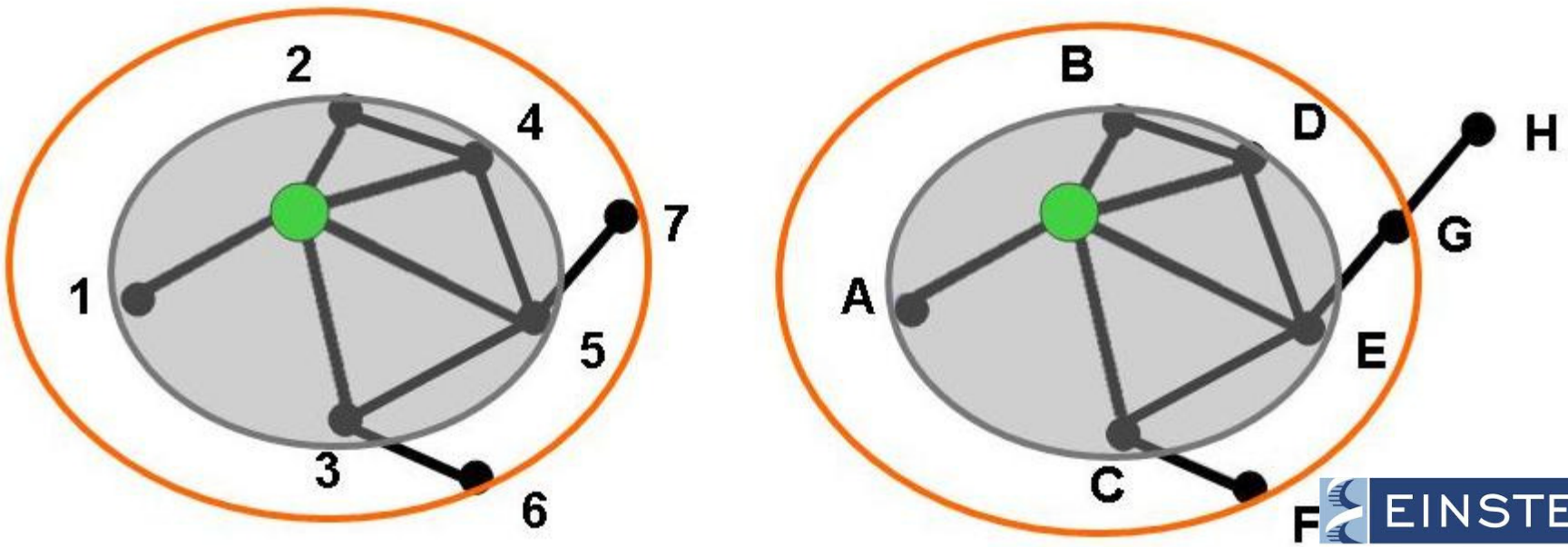
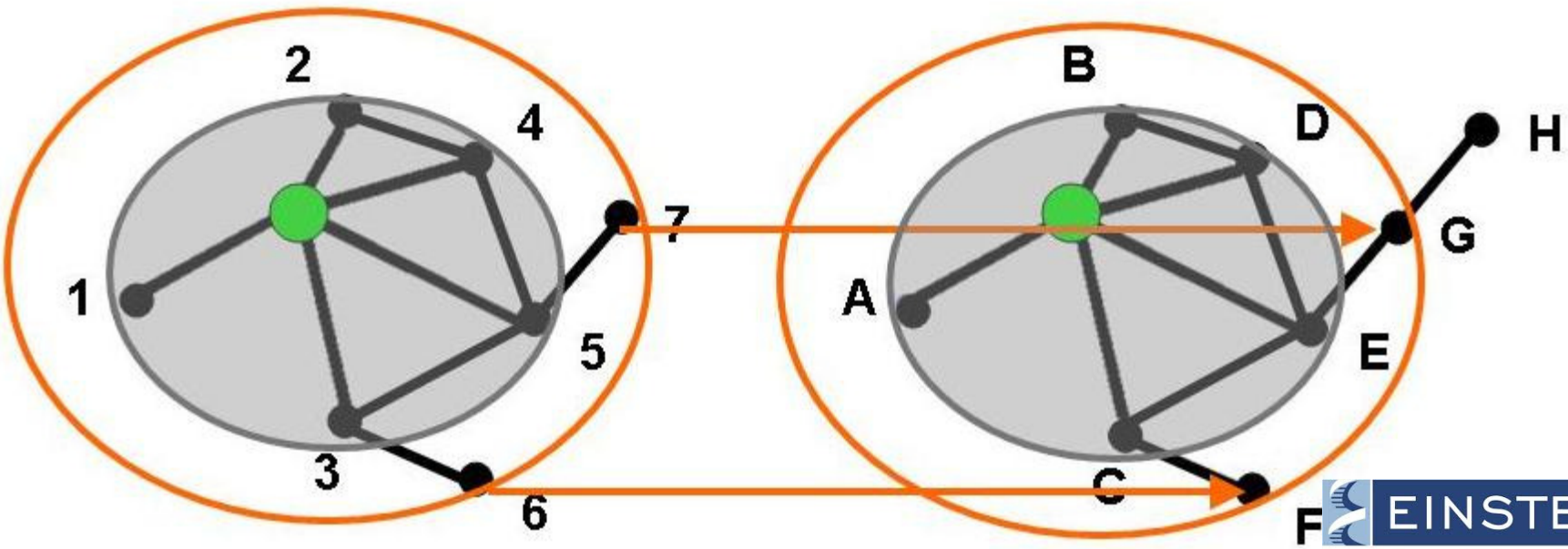


Network Alignment

- How to identify <u>high-scoring alignments</u>?
  - Greedy ***seed and extend*** approaches
    - Use the most "similar" nodes across the two networks as "anchors" or **"seed nodes"**
    - "Extend around" the seed nodes in a greedy fashion



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Take home message

- Binary prediction of Protein-protein Interaction (PPI)
- Analysis of PPI networks
  - Different topologies of network
  - Different type of network comparison
  - Basic ideas of network alignment
- Structural modeling of PPI
- Physical properties of PPI

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Outline

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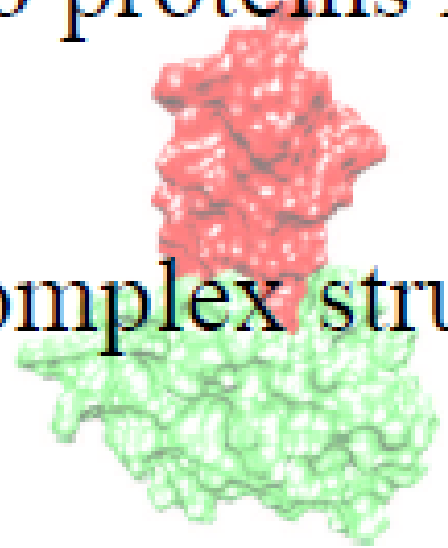
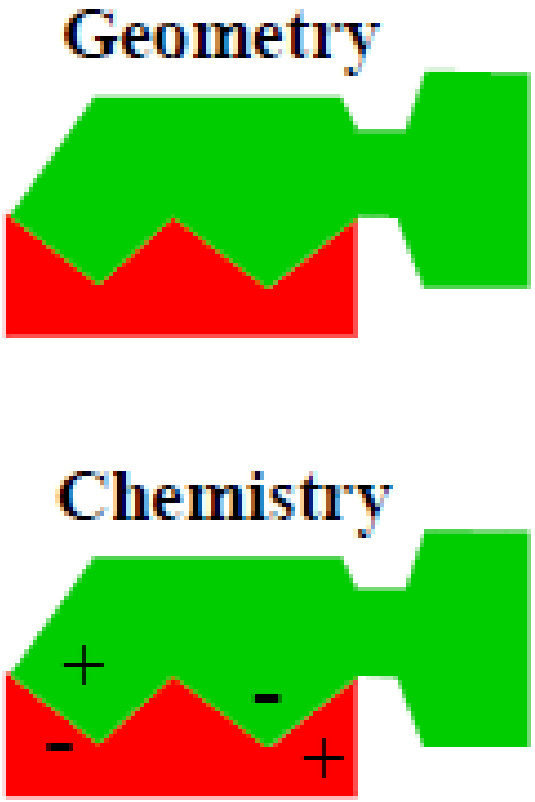
Protein-Protein Docking

- Given two proteins **A** and **B**



- Predict complex structure **AB**

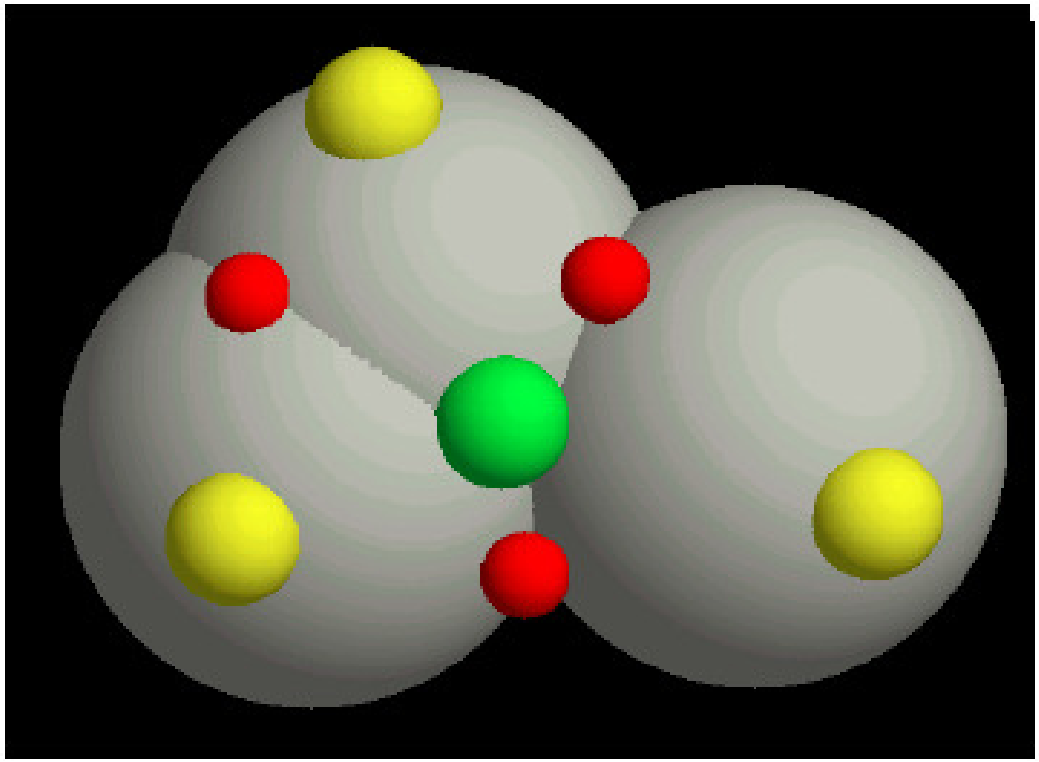
Lock-and-Key Principle



Docking Algorithm Scheme

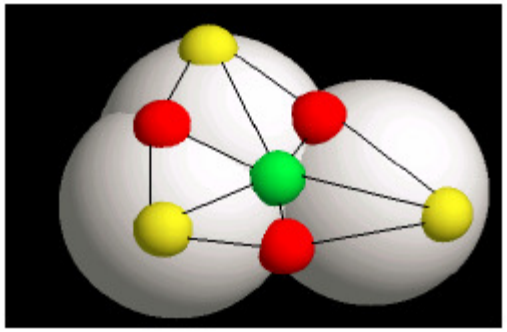
- Part 1: **Molecular surface representation**
- Part 2: Features selection
- Part 3: Matching of critical features
- Part 4: Filtering and scoring of candidate transformations

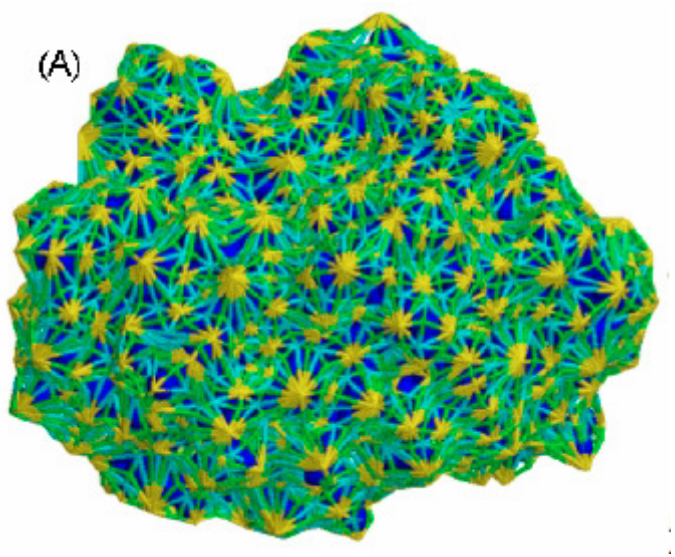
1. Surface Representation



Sparse Surface Graph – G_{top}

- Caps (yellow), pits (green), belts (red):





- G_{top} – Surface topology graph:

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Docking Algorithm Scheme

- Part 1: Molecular surface representation
- **Part 2: Features selection**
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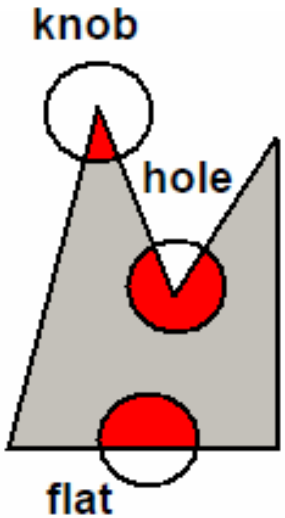
2.1 Coarse Curvature calculation
2.2 Division to surface patches of similar curvature

2.1 Curvature Calculation

- Shape function is a measure of local curvature.

- 'knobs' and 'holes' are local minima and maxima (<1/3 or >2/3), 'flats' – the rest of the points (70%).

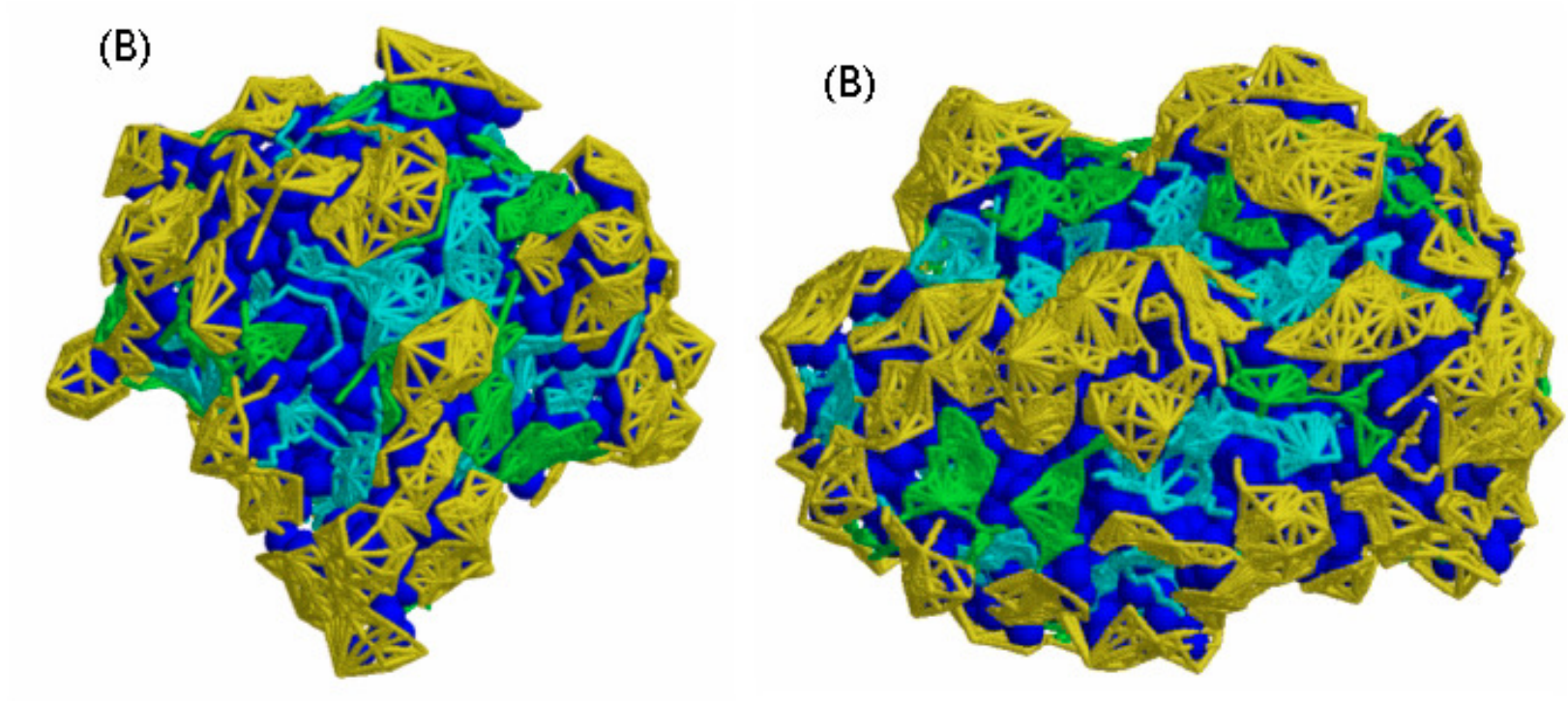


2.2 Patch Detection

Goal: divide the surface into connected, non-intersecting, equal sized patches of critical points with similar curvature.

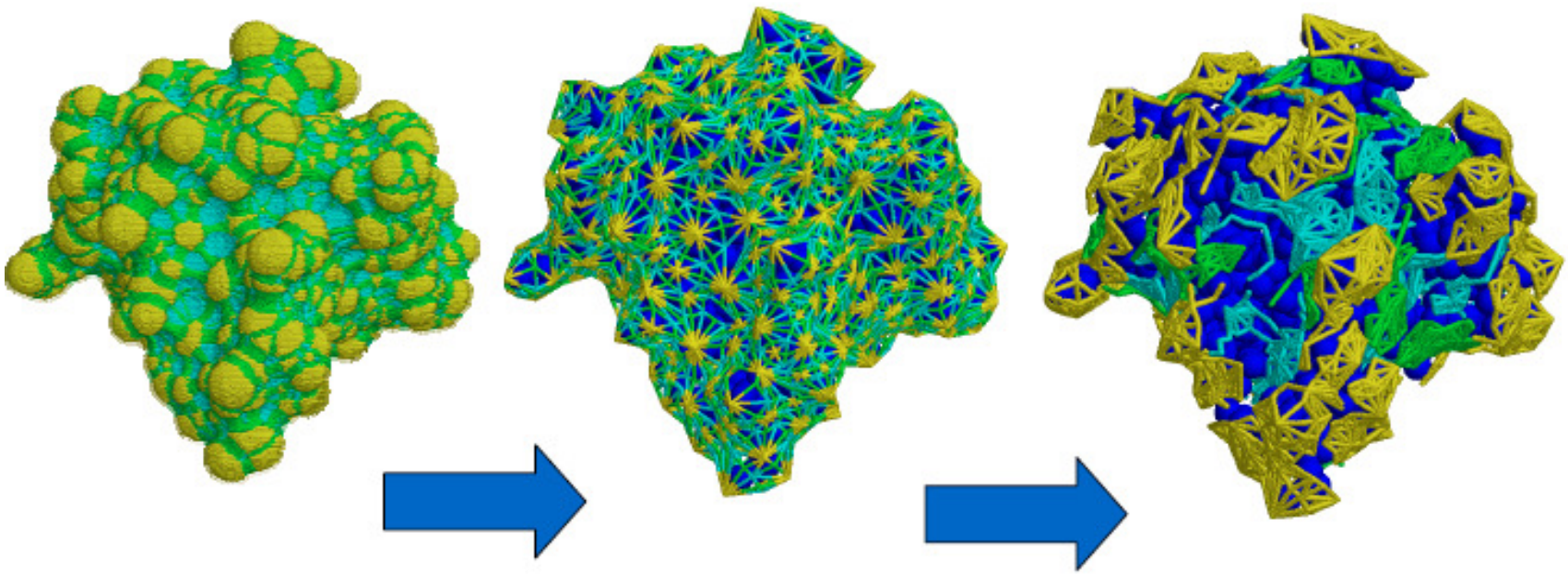
- **connected** – the points of the patch correspond to a connected sub-graph of G_{top}.
- **similar curvature** – all the points of the patch correspond to only one type: knobs, flats or holes.
- **equal sized** – to assure better matching we want shape features of almost the same size.

Examples of Patches for trypsin and trypsin inhibitor



Yellow – knob patches, cyan – hole patches, green – flat patches

Shape Representation Part



Docking Algorithm Scheme

- Part 1: Molecular surface representation
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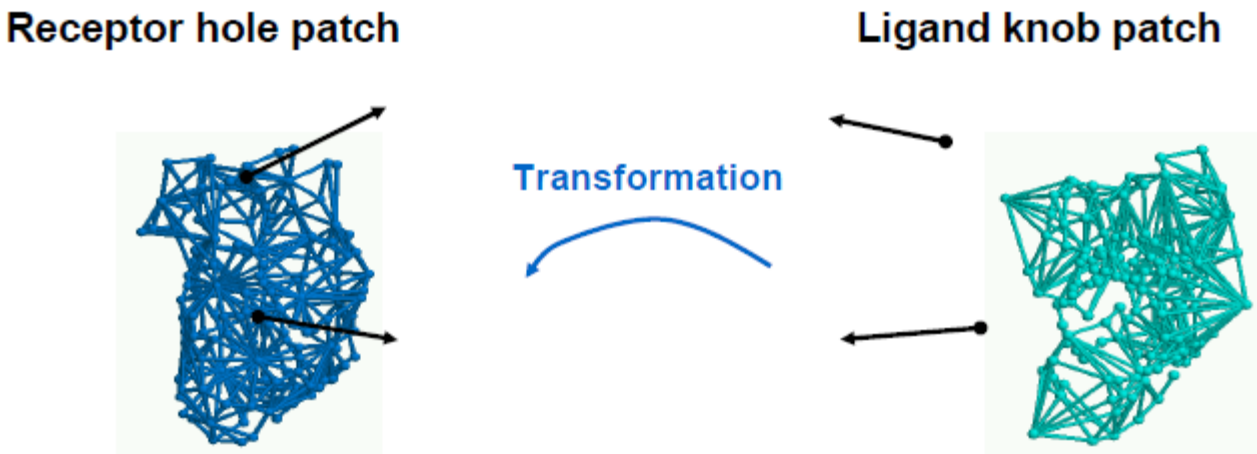
3. Matching of patches

The aim is to align knob patches with hole patches, and flat patches with any patch. We use two types of matching:

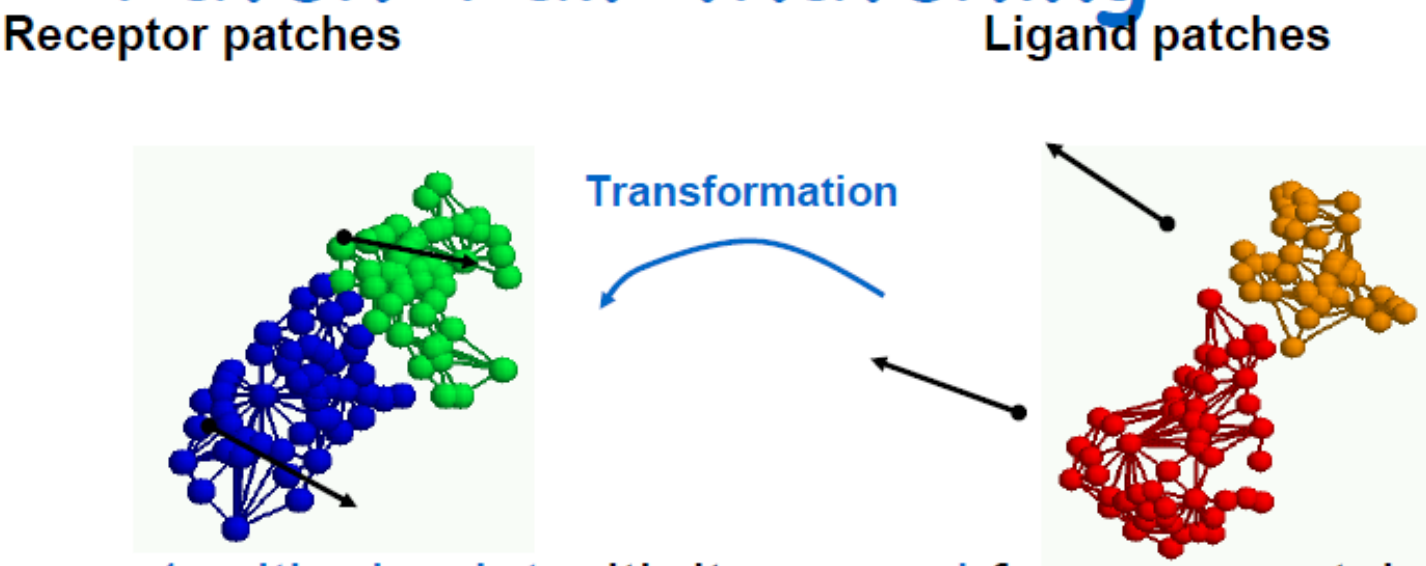
- **Single Patch Matching** – one patch from the receptor is matched with one patch from the ligand. Used in protein-drug cases.
- **Patch-Pair Matching** – two patches from the receptor are matched with two patches from the ligand. Used in protein-protein cases.

Single Patch Matching



- **Base:** a pair of critical points with their normals from one patch.
- Match every base from a receptor patch with all the bases from complementary ligand patches.
- Compute the transformation for each pair of matched bases.

Patch-Pair Matching

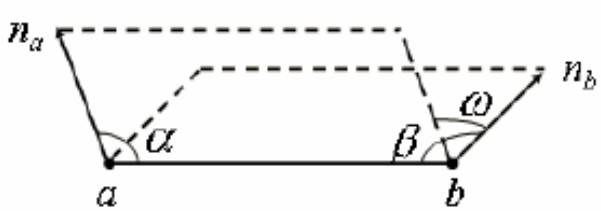


- **Base:** 1 critical point with its normal from one patch and 1 critical point with its normal from a neighboring patch.
- Match every base from the receptor patches with all the bases from complementary ligand patches.
- Compute the transformation for each pair of matched bases.

Base Compatibility

The **signature** of the base is defined as follows:

1. Euclidean and geodesic **distances** between the points: **dE, dG**
2. The angles **α, β** between the [a,b] segment and the normals
3. The torsion angle **ω** between the planes



dE, dG, α, β, ω

Two bases are compatible if their signatures match

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Geometric Hashing

- **Preprocessing:** the bases are built for all ligand patches (single or pairs) and stored in hash table according to base signature.
- **Recognition:** for each receptor base access the hash-table with base signature. The transformations set is computed for all compatible bases.

Docking Algorithm Scheme

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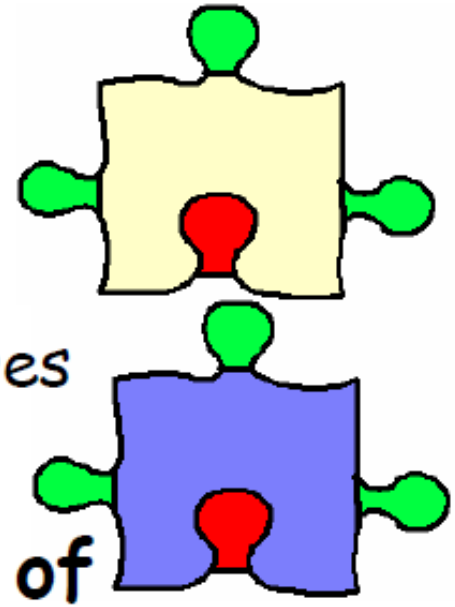


Filtering Transformations with Steric Clashes

- Since the transformations were computed by local shape features matching they may include unacceptable steric clashes.

Scoring Shape Complementarity

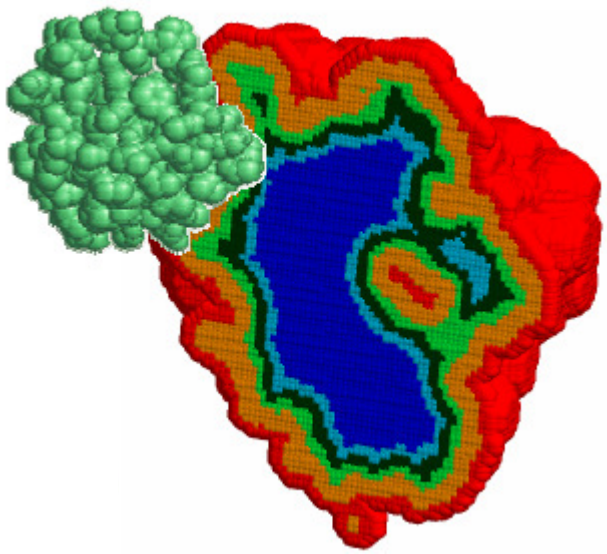
- The scoring is necessary to rank the remaining solutions.
- The surface of the receptor is divided into five shells according to the distance function: **S1 - S5**

[-5.0,-3.6), [-3.6,-2.2), [-2.2, -1.0), [-1.0,1.0), [1.0→).

- The number of ligand surface points in every shell is counted.
- Each shell is given a weight: **W1 - W5**

-10, -6, -2, 1, 0.

- The geometric score is a weighted sum of the number of ligand surface points **N** inside every shell:



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Flexible Docking - general methodology

- Rigid subpart docking :
  - Split the flexible molecule into rigid subparts.
  - Dock independently each subpart.
  - Pair the top hypotheses for each subpart to detect hinge consistency.
- Anchor fragment method :
  - Position a ‘preferred’ anchor fragment.
  - Rotate sequentially the flexible bonds to position the other fragments.

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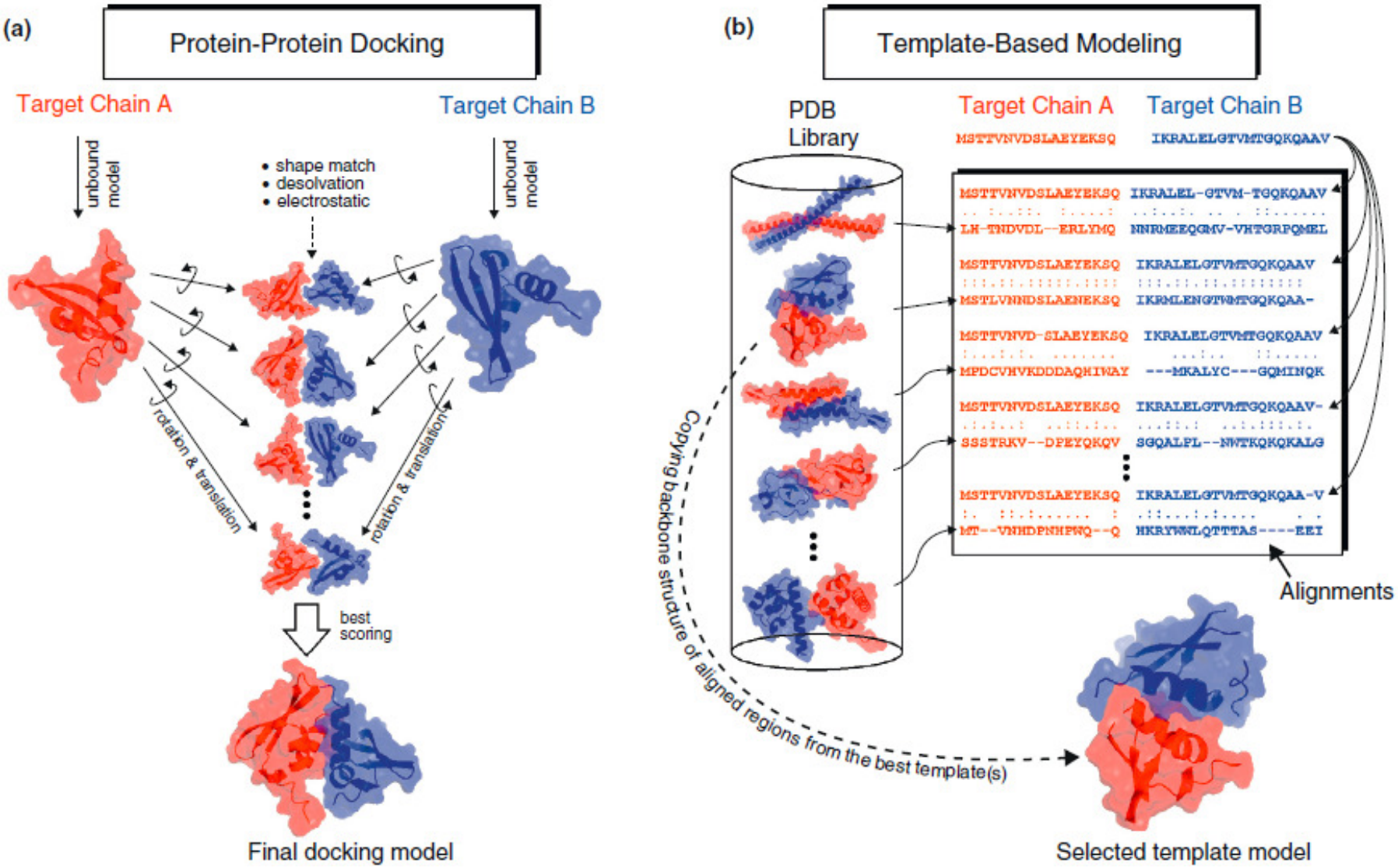

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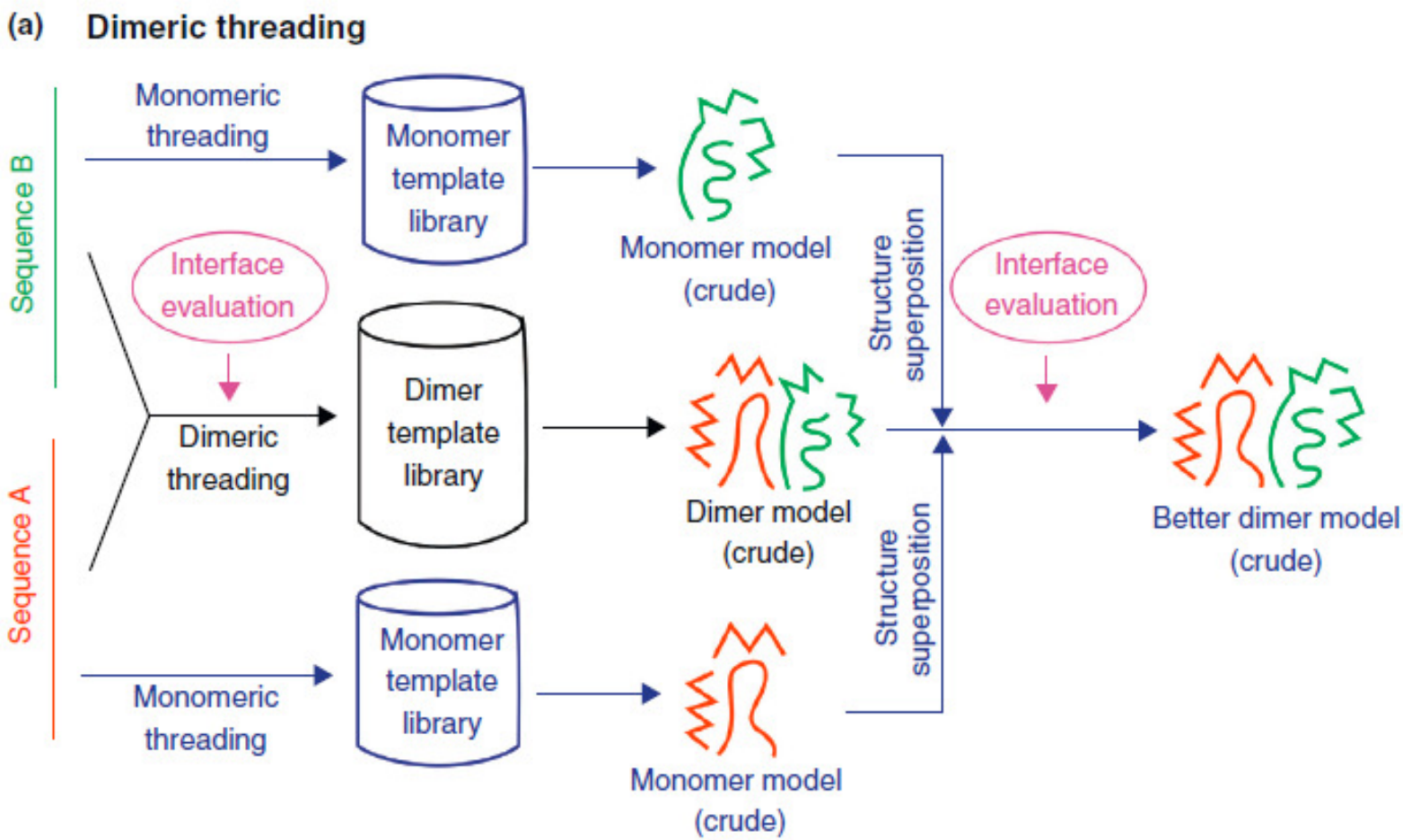
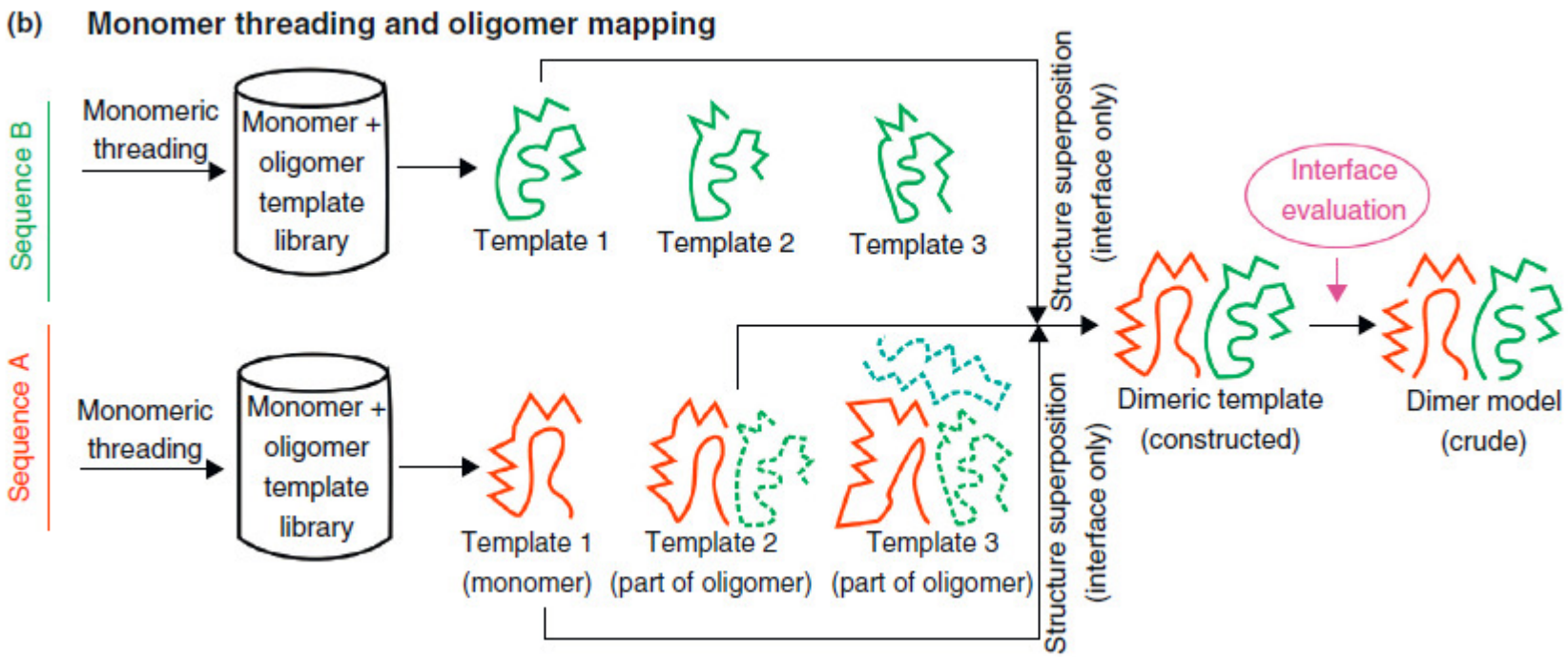
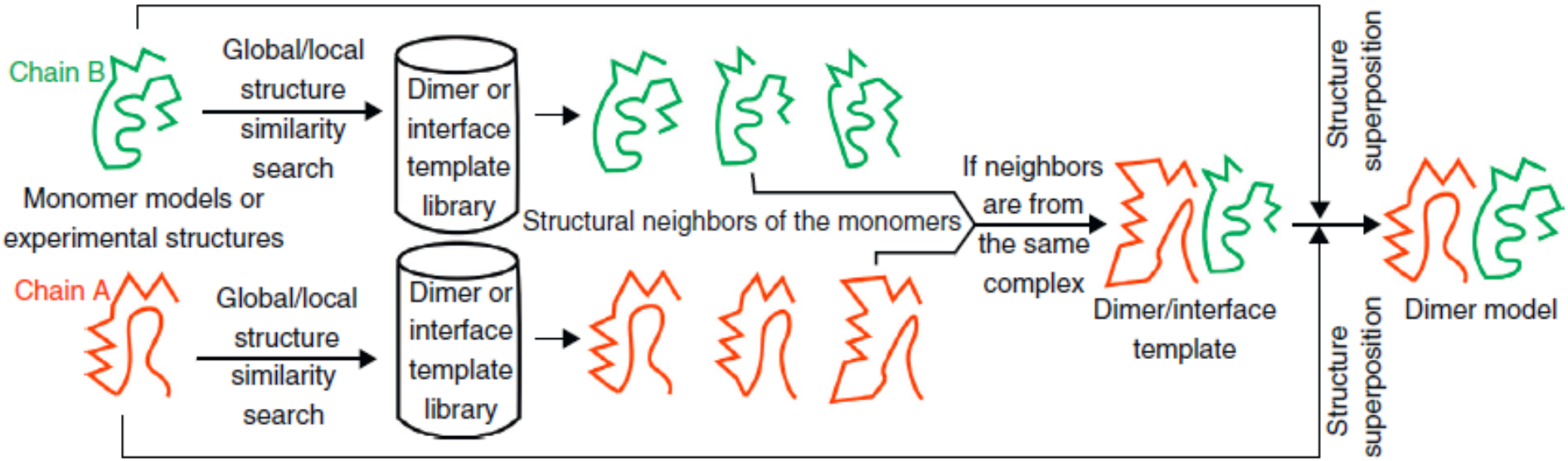
Template-based modeling: general methodology

- Dimeric threading
- Monomer threading and oligomer mapping
- Template-based docking





(c) **Template-based docking**



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  - Kinetic rates
  - Binding affinity

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Kinetic parameters

The speed at which a complex AB dissociates is determined by its **dissociation rate constant** k_{dissoc} (s^{-1}):

$$k_{\text{dissoc}}\ [\text{AB}] = \frac{-d[\text{AB}]}{dt}$$

The speed at which a complex AB forms is determined by its **association rate constant** k_{assoc} ($M^{-1}s^{-1}$):

$$k_{\text{assoc}}[\text{A}][\text{B}] = \frac{+d[\text{AB}]}{dt}$$

At equilibrium: $d[AB]/dt = 0$

$$k_{dissoc}\,[AB] = k_{ass}\,[A][B]$$

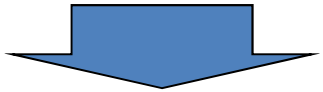
$$k_{dissoc}/k_{assoc} = [A][B]/[AB] = K_d$$

Surface plasmon resonance (SPR)

- SPR measures the change of the refractive index at the backside of a metal film when protein A binds to protein B immobilized on this film
- Using SPR, one can determine K_d, k_{assoc} and k_{dissoc}

Brownian Dynamics (BD)

- The dynamic contributions of the solvent are incorporated as a dissipative random force (Einstein's derivation on 1905). Therefore, water molecules are not treated explicitly.
- Since BD algorithm is derived under the conditions that solvent damping is large and the inertial memory is lost in a very short time, longer time-steps can be used.



- BD method is suitable for long time simulation.

Algorithm of BD

The Langevin equation can be expressed as

$$m_i \frac{\mathrm{d}^2 \mathbf{r}_i}{\mathrm{d}t^2} = -\zeta_i \frac{\mathrm{d}\mathbf{r}_i}{\mathrm{d}t} + \mathbf{F}_i + \mathbf{R}_i \qquad \textbf{(1)}$$

Here, $\mathbf{r}_i$ and m_i represent the position and mass of atom i, respectively. ζ_i is a frictional coefficient and is determined by the Stokes' law, that is, $\zeta_i = 6\pi a_i^{\mathrm{Stokes}}\eta$ in which a_i^{Stokes} is a Stokes radius of atom i and η is the viscosity of water. $\mathbf{F}_i$ is the systematic force on atom i. $\mathbf{R}_i$ is a random force on atom i having a zero mean $\langle \mathbf{R}_i(t) \rangle = 0$ and a variance $\langle \mathbf{R}_i(t)\mathbf{R}_j(t) \rangle = 6\zeta_i kT\delta_{ij}\delta(t)$; this derives from the effects of solvent.

For the overdamped limit, we set the left of eq.1 to zero,

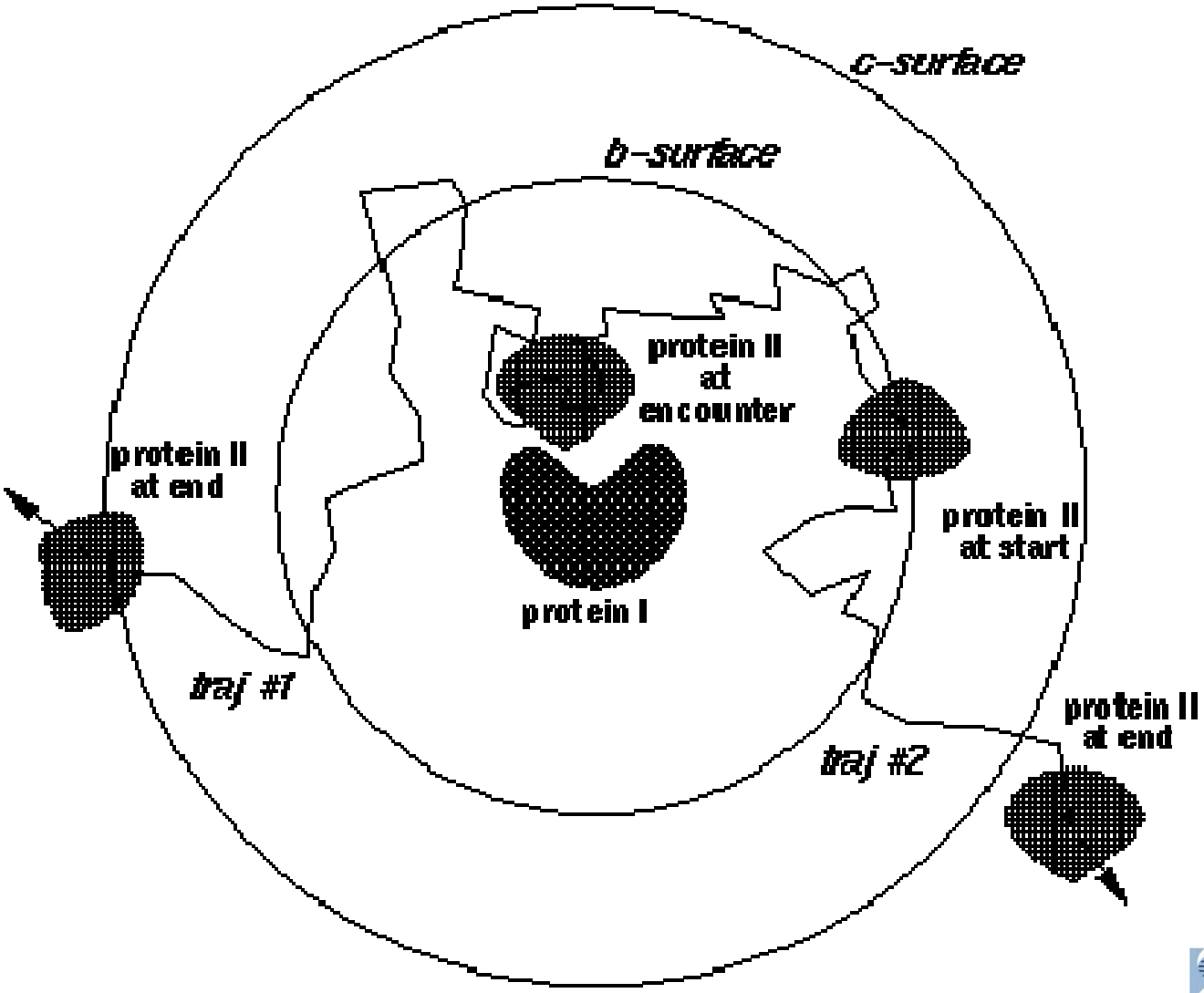
$$\zeta_i \frac{\mathrm{d}\mathbf{r}_i}{\mathrm{d}t} = \mathbf{F}_i + \mathbf{R}_i \qquad \textbf{(2)}$$

The integrated equation of eq. 8 is called Brownian dynamics;

$$\mathbf{r}_i(t+\Delta t) = \mathbf{r}_i(t) + \frac{\mathbf{F}_i(t)}{\zeta_i}\Delta t + \sqrt{\frac{2k_{\mathrm{B}}T}{\zeta_i}\Delta t}\,\boldsymbol{\omega}_i \qquad \textbf{(3)}$$

where Δt is a time step and $\boldsymbol{\omega}_i$ is a random noise vector obtained from Gaussian distribution.

Brownian dynamic simulation of protein association



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Equilibrium parameters

The strength of an interaction is usually given as the **equilibrium dissociation constant**, K_d:

$$K_d = \frac{[A][B]}{[AB]}$$

Relationship between K_d and Gibbs free energy change ΔG upon binding

$$\Delta G = \Delta G^0 + RT \ln [AB]/[A][B]$$

Under equilibrium conditions ($\Delta G = 0$):

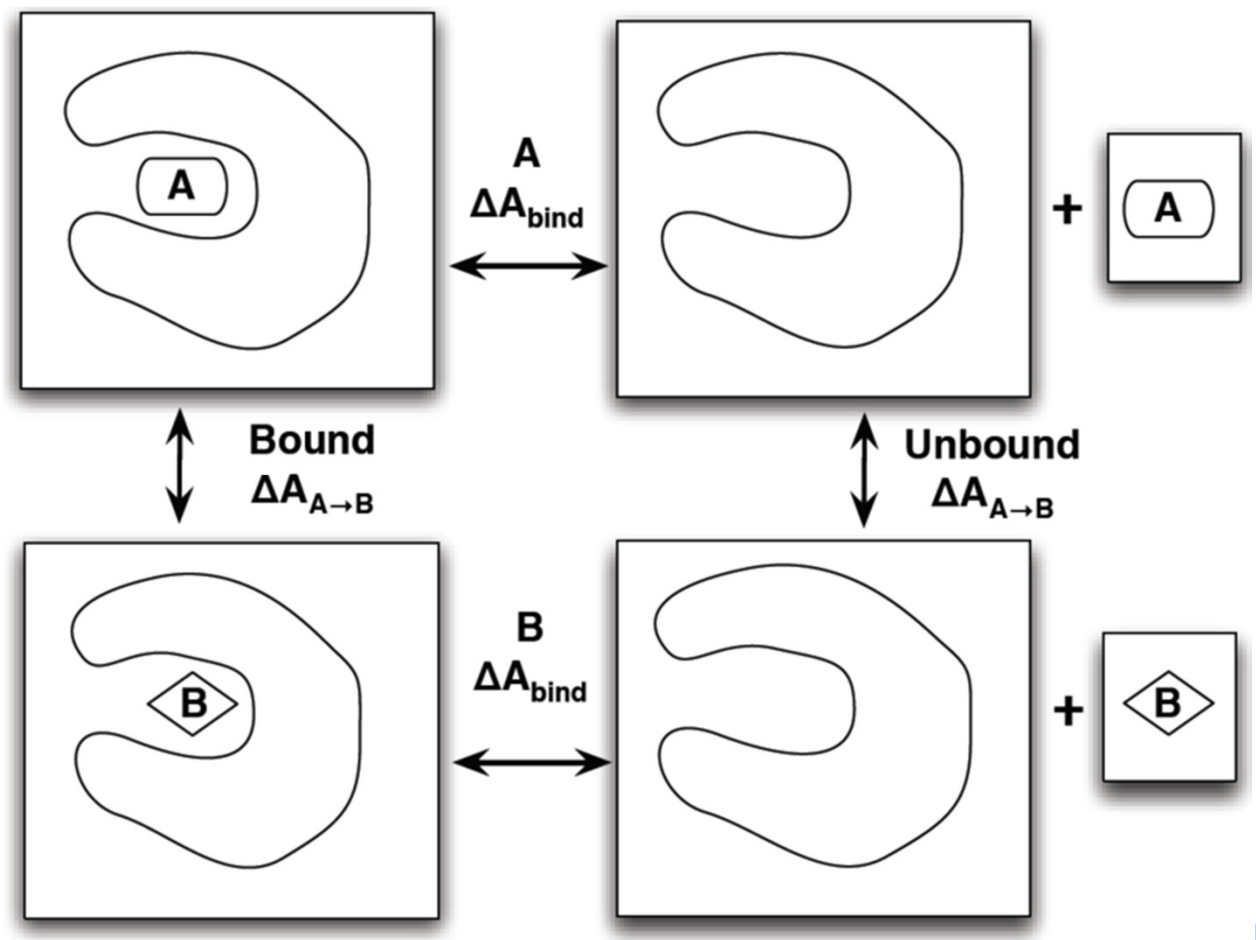
$$\Delta G^0 = -RT \ln \frac{[AB]}{[A][B]}$$

$$\Delta G^0 = -RT \ln K_a = -RT \ln\left(\frac{1}{K_d}\right) = RT \ln K_d$$

Isothermal titration calorimetry (ITC)

- ITC measures ΔH, which is the heat that is released or absorbed when the complex AB associates from A and B
- Using ΔH as the binding signal, one can determine K_d, the reaction stoichiometry (n), and the reaction entropy (ΔS)

Computational simulation of binding affinity: thermodynamic cycles



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