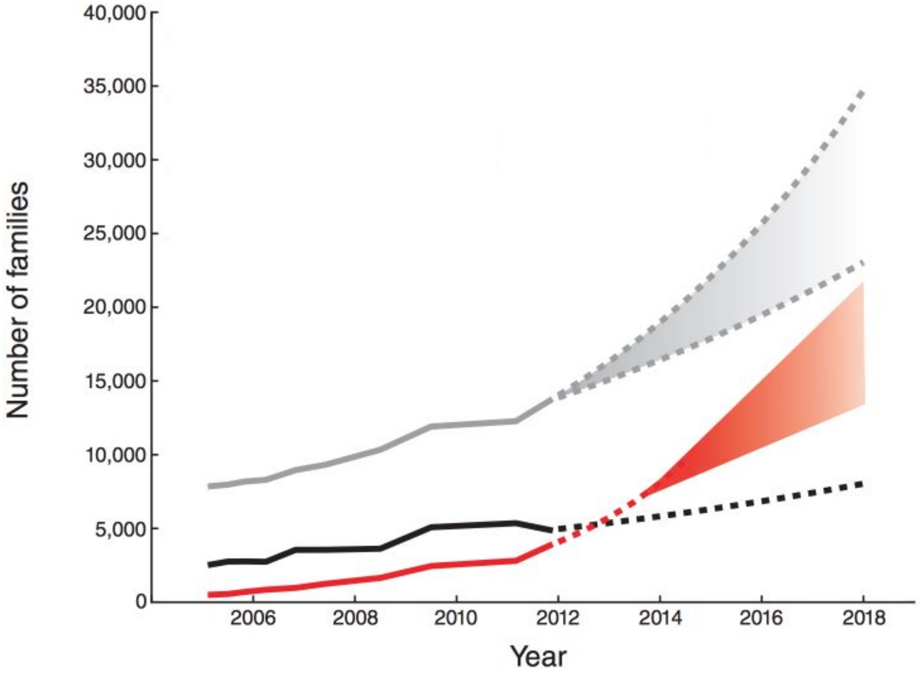
Lecture 11: Protein structure prediction

- Amino acid coevolution
- Residue coupling and contact prediction
  - Maximum-entropy model
- Extensions

Direct vs. indirect interactions



New protein families being discovered by high-throughput sequencing

Experimental structure-determination

Marks (2012) Nat. Biotech.

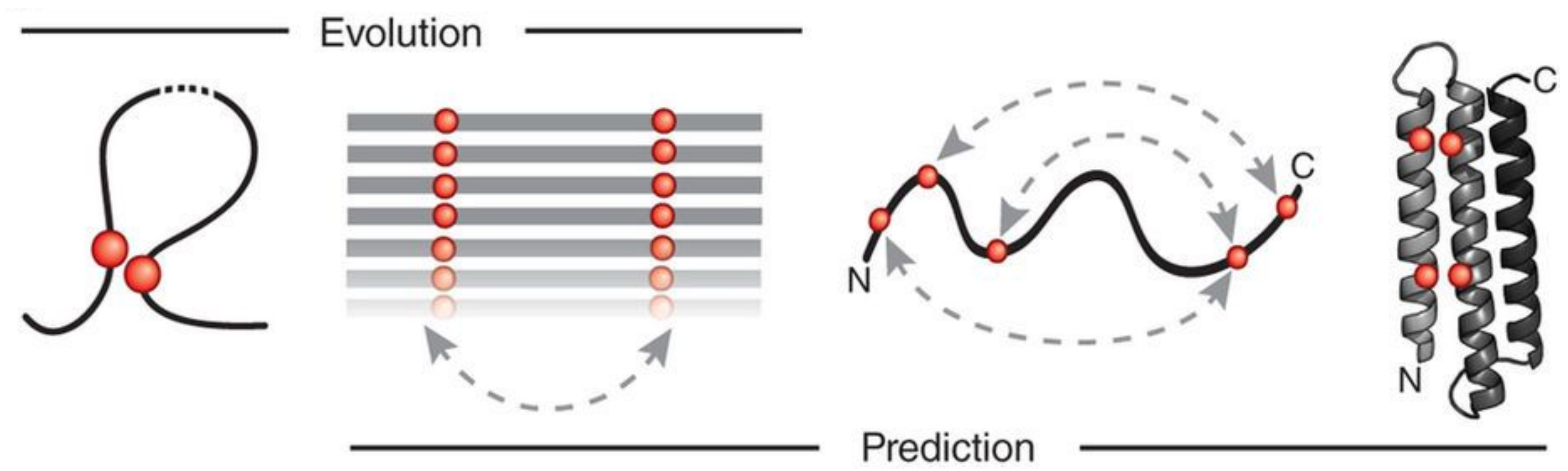
Predicting protein 3D structure from sequence

Evolutionary pressure to maintain favorable interactions b/w physically interacting AA residues in 3D.

Visible record of residue covariation in related protein sequences.

Inverse problem – inferring directly causative residue couplings (evolutionary couplings) from the covariation record – challenging due to transitive correlations & other confounding effects.

ECs can be used to predict the unknown 3D structure of a protein from a set of sequences alone.



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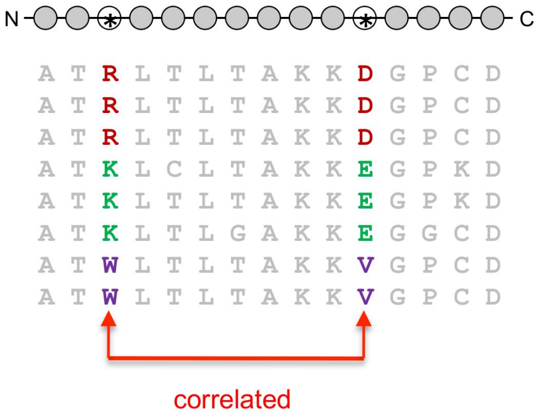
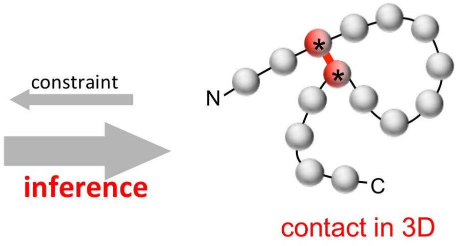
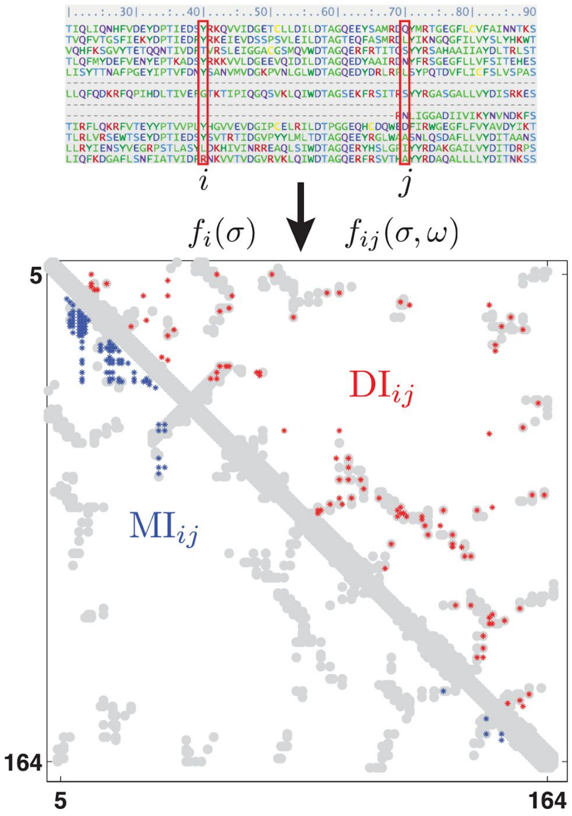
Predicting protein 3D structure from sequence

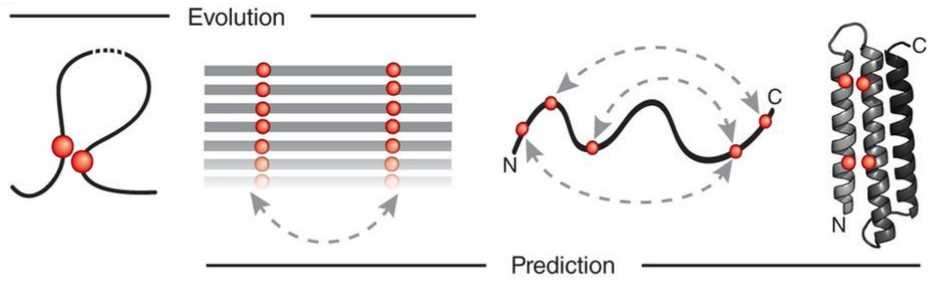






Marks (2011) PLoS One; Marks (2012) Nat. Biotech.
Stein (2015) PLoS Comp. Biol.

Predicting protein 3D structure from sequence



Growth in sequence databases from massively parallel sequencing.

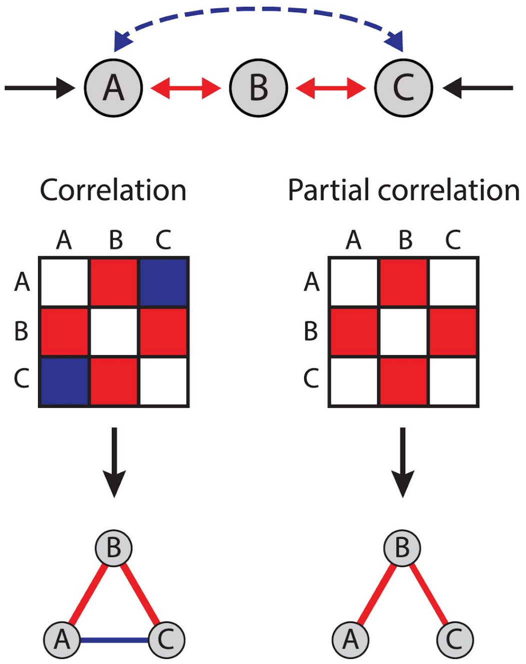
- Availability of sufficient sequences of sufficient diversity.
- Known protein families are growing in size from a few sequences to many thousands of sequences (advances in DNA sequencing tech).

Reduction of conformational search space by cooperative probability models.

- Global probability models account for the fact that interactions along an entire protein chain are mutually interdependent in a way that is inherently cooperative.
- Pair interactions are modified by interactions with other parts of the system and cannot be factored (probabilities are not a simple product of independent terms).
- Compared with molecular dynamics simulations, statistical approaches are many orders of magnitude more efficient in reducing a huge conformational search space to manageable proportions.

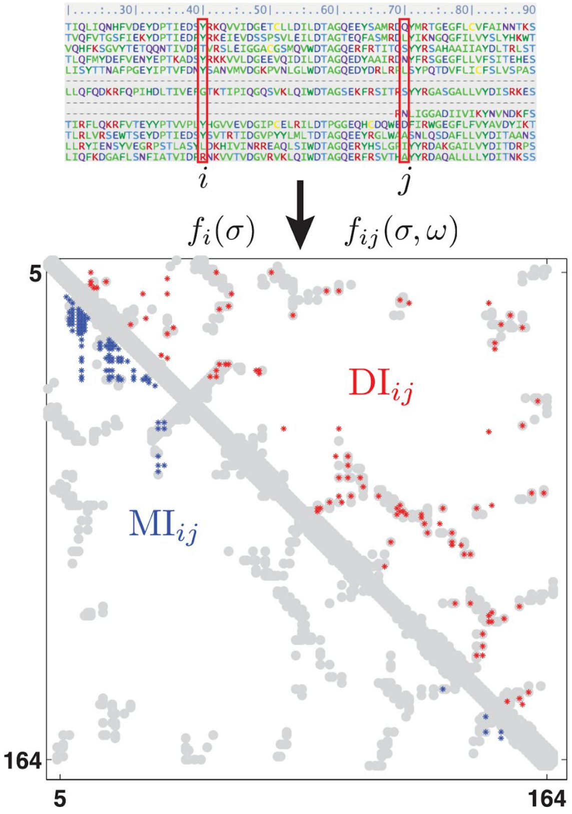
Marks (2012) Nat. Biotech.

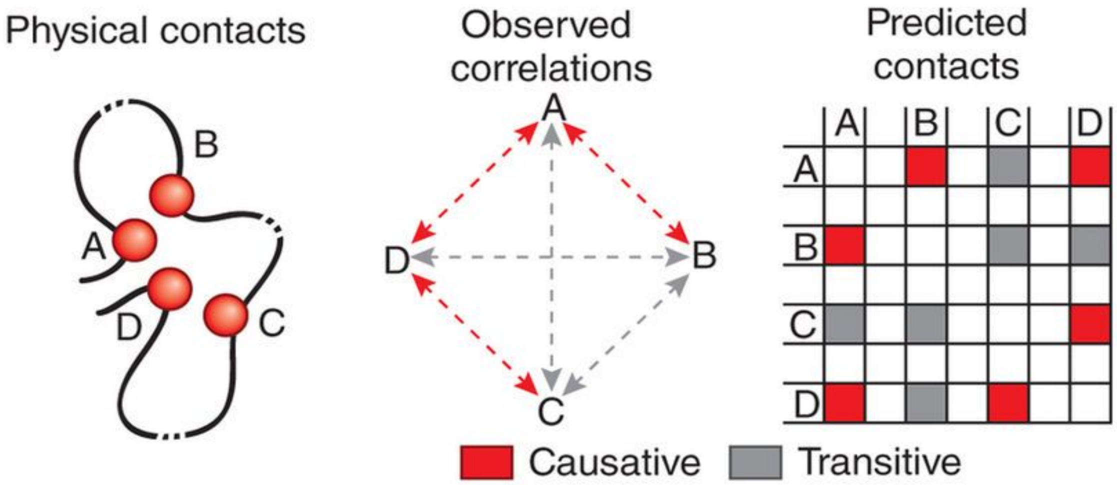
Direct vs. indirect interactions



Stein (2015) PLoS Comp. Biol.

Direct vs. indirect interactions





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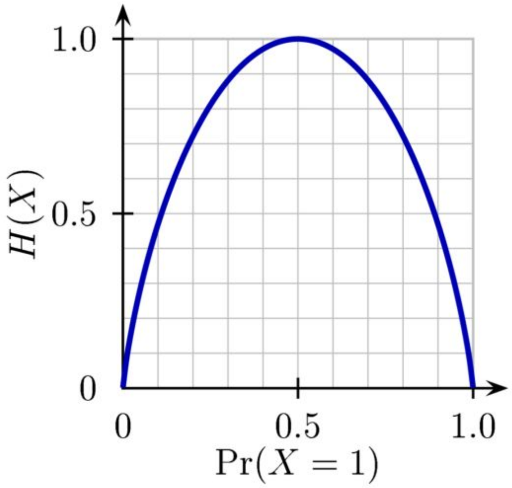
Information theory

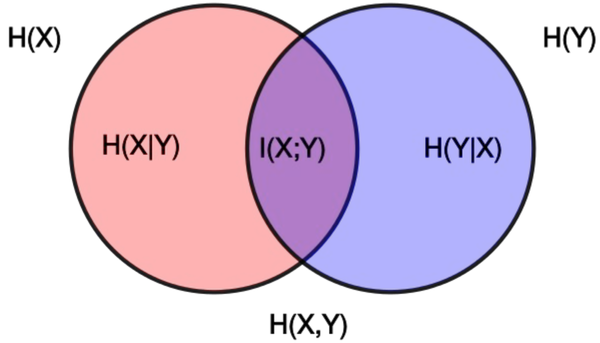
Entropy (H): the average amount of information produced by a stochastic source of data.

Mutual information: MI two random variables **I(X, Y)** quantifies the amount of information obtained about one random variable, through the other random variable.

$$\mathrm{H}(X) = -\sum_{i=1}^{n} \mathrm{P}(x_i) \log_b \mathrm{P}(x_i)$$

$$I(X;Y) = \sum_{x,y} p(x,y) \log \frac{p(x,y)}{p(x)p(y)} = \mathrm{H}(Y) - \mathrm{H}(Y|X)$$





Wikipedia

Global probabilistic models of residue coupling (maximum-entropy)

$$\mathbf{x} = (x_1, \ldots, x_L) \in \Omega^L$$

$$\downarrow$$

Pairwise maximum-entropy distribution

$$P(x_1, \ldots, x_L) = \frac{1}{Z} \exp\left(\sum_i h_i(x_i) + \sum_{i<j} e_{ij}(x_i, x_j)\right)$$

$$\downarrow$$

Parameter inference

- mean-field (MF)

$$e_{ij}^{\mathrm{MF}}(\sigma, \omega) = -\left(C^{-1}\right)_{ij}(\sigma, \omega)$$

- sparse maximum-likelihood (SML)

$$e_{ij}^{\mathrm{SML}}(\sigma, \omega) = -\left(C_{1,\lambda}^{-1}\right)_{ij}(\sigma, \omega)$$

- pseudolikelihood maximization (PLM)

$$\left\{\boldsymbol{h}^{\mathrm{PLM}}(\boldsymbol{\sigma}), \boldsymbol{e}^{\mathrm{PLM}}(\boldsymbol{\sigma}, \boldsymbol{\omega})\right\} = \underset{\boldsymbol{h}(\boldsymbol{\sigma}), \boldsymbol{e}(\boldsymbol{\sigma}, \boldsymbol{\omega})}{\arg\min} \left\{-\ln l_{\mathrm{PL}} + \lambda_{\boldsymbol{h}} \|\boldsymbol{h}\|_2^2 + \lambda_{\boldsymbol{e}} \|\boldsymbol{e}\|_2^2\right\}$$

$$\downarrow$$

Pair scoring functions

- direct information

$$\mathrm{DI}_{ij} = \sum_{\sigma,\omega} P_{ij}^{\mathrm{dir}}(\sigma, \omega) \ln\left(\frac{P_{ij}^{\mathrm{dir}}(\sigma, \omega)}{f_i(\sigma) f_j(\omega)}\right)$$

- Frobenius norm

$$\|e_{ij}\|_{\mathrm{F}} = \left(\sum_{\sigma,\omega} e_{ij}(\sigma, \omega)^2\right)^{1/2}$$

- average product-corrected Frobenius norm

$$\mathrm{APC\text{-}FN}_{ij} = \|e_{ij}\|_{\mathrm{F}} - \frac{\|e_{i\cdot}\|_{\mathrm{F}} \|e_{\cdot j}\|_{\mathrm{F}}}{\|e_{\cdot\cdot}\|_{\mathrm{F}}}$$

Stein (2015) PLoS Comp. Biol.

Global probabilistic models of residue coupling (maximum-entropy)

$$a = (a_1, a_2 .., a_N)$$

A sequence made of monomers a_i taking values from a given alphabet

$$P(a|J,h) = \frac{1}{Z} \exp\left(\sum_{i=1}^{N-1} \sum_{j=i+1}^{N} J_{ij}(a_i, a_j) + \sum_{i=1}^{N} h_i(a_i) \right)$$

Probability of a sequence within the model.

h(a_i): parameters that represent the propensity of symbol to be found at a certain position.

J(a_i, a_j): represent an interaction, quantifying how compatible the symbols at both positions are with each other.

Wikipedia

Global probabilistic models of residue coupling (maximum-entropy)

$$a = (a_1, a_2.., a_N)$$

$$P(a|J,h) = \frac{1}{Z} \exp\left(\sum_{i=1}^{N-1} \sum_{j=i+1}^{N} J_{ij}(a_i, a_j) + \sum_{i=1}^{N} h_i(a_i)\right)$$

The idea of maximum-entropy: For a given set of sample covariances and frequencies, the model represents the **distribution with the maximal entropy** of all distributions reproducing those covariances and frequencies.

$$\begin{aligned} F[P] = &- \sum_a P(a) \log P(a) \\ &+ \sum_{i<j} \sum_{x,y} \lambda_{ij}(x,y)\Big(P_{ij}(x,y) - f_{ij}(x,y)\Big) \\ &+ \sum_i \sum_x \lambda_i(x)\Big(P_i(x) - f_i(x)\Big) \\ &+ \Omega\left(1 - \sum_a P(a)\right). \end{aligned}$$

The unique distribution ***P*** that maximizes the functional to the *left*.

$f_i(a)$: frequency of finding symbol ***a*** at position ***i***.

$f_{ij}(a, b)$: frequency of finding symbols ***a*** & ***b*** at positions ***i*** and ***j*** in the same sequence.

Wikipedia

Global probabilistic models of residue coupling (maximum-entropy)

$$a = (a_1, a_2.., a_N)$$

$$P(a|J,h) = \frac{1}{Z}\exp\left(\sum_{i=1}^{N-1}\sum_{j=i+1}^{N} J_{ij}(a_i, a_j) + \sum_{i=1}^{N} h_i(a_i)\right)$$

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$$F_i = \frac{1}{N}\sum_{j\neq i}^{N} F_{ij}$$

$$F_{ij}^{APC} = F_{ij} - \frac{F_i F_j}{F}$$

$$F = \frac{1}{N^2 - N}\sum_{i,j,i\neq j}^{N} F_{ij}$$

The idea of maximum-entropy: For a given set of sample covariances and frequencies, the model represents the **distribution with the maximal entropy** of all distributions reproducing those covariances and frequencies.

The unique distribution ***P*** that maximizes the functional to the *left*.

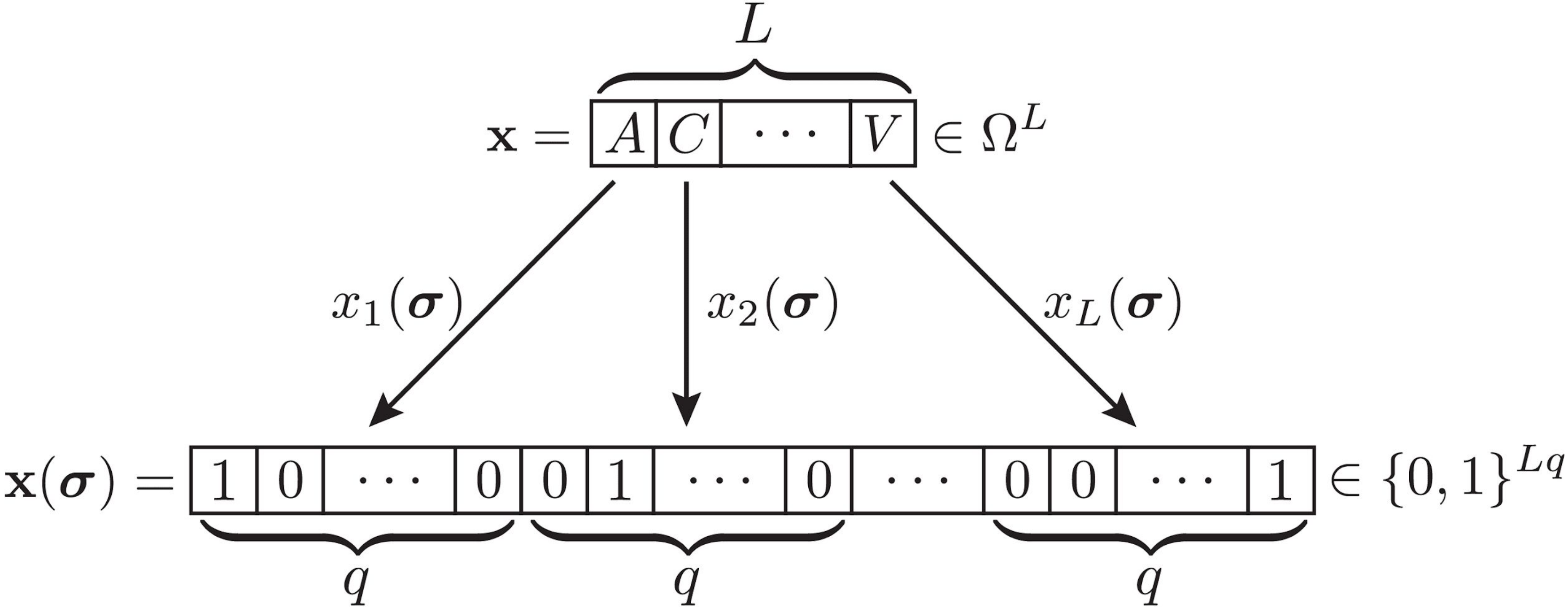
Final step:

- average product correction (APC).

Wikipedia

Global probabilistic models of residue coupling

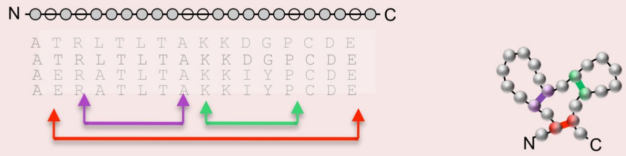
Binary embedding of amino acid sequence



Stein (2015) PLoS Comp. Biol.

Global probabilistic models of residue coupling (maximum-entropy)

Align evolutionary diverged sequences



Calculate covariance matrix for each pair of sequence positions for all pairs of amino acids (A,B)

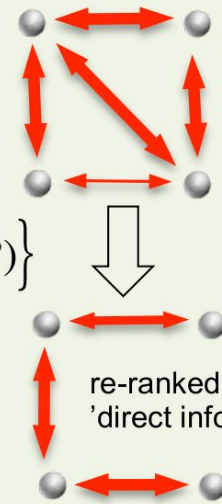
$$C_{ij}(A,B) = f_{ij}(A,B) - f_i(A)P_j(B)$$

$$C_{ij}^{-1}(A,B) = -e_{ij}(A,B)_{i \neq j}$$

$$P_{ij}^{Dir}(A,B) = \frac{1}{Z}\exp\left\{e_{ij}(A,B) + \tilde{h}_i(A) + \tilde{h}_j(B)\right\}$$

Identify maximally informative pair couplings using **statistical model** of entire protein to infer residue-residue co-evolution

$$DI_{ij} = \sum_{A,B=1}^{q} P_{ij}^{Dir}(A,B)\ln\frac{P_{ij}^{Dir}(A,B)}{f_i(A)f_j(B)}$$



high ranking **transitive** 'indirect correlations'

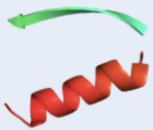
re-ranked correlations 'direct information' = DI

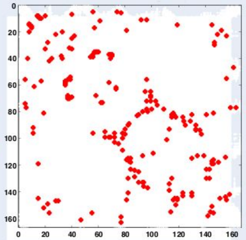
Marks (2011) PLoS One

From contacts to structure

Analyze the highest scoring pairs to produce ranked list of residue pairs which we predict to be close in 3D space. Use these pairs as predicted close “evolutionary inferred contacts” , EICs, in folding calculations

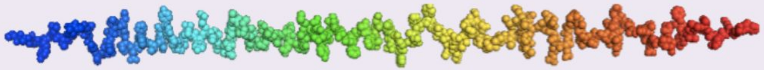
assign (resid 143 and name CA) (resid 123 and name CA) 4 4 3
assign (resid 16 and name CA) (resid 10 and name CA) 4 4 3
assign (resid 141 and name CA) (resid 82 and name CA) 4 4 3
assign (resid 129 and name CA) (resid 87 and name CA) 4 4 3
assign (resid 92 and name CA) (resid 11 and name CA) 4 4 3
assign (resid 116 and name CA) (resid 81 and name CA) 4 4 3



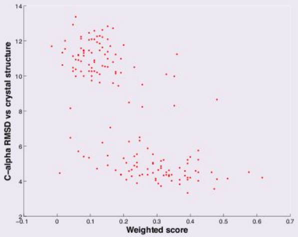


predicted contacts (EICs)

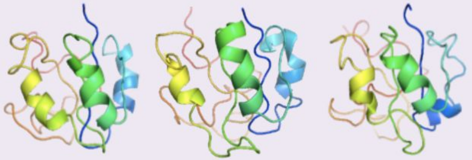
Start with extended structure
use **distance geometry** and **simulated annealing** with predicted constraints, EICs, to fold the chain



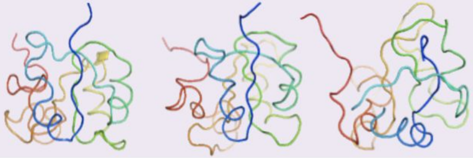
Rank predicted structures using quality measure of backbone alpha torsion and beta sheet twist



good scores

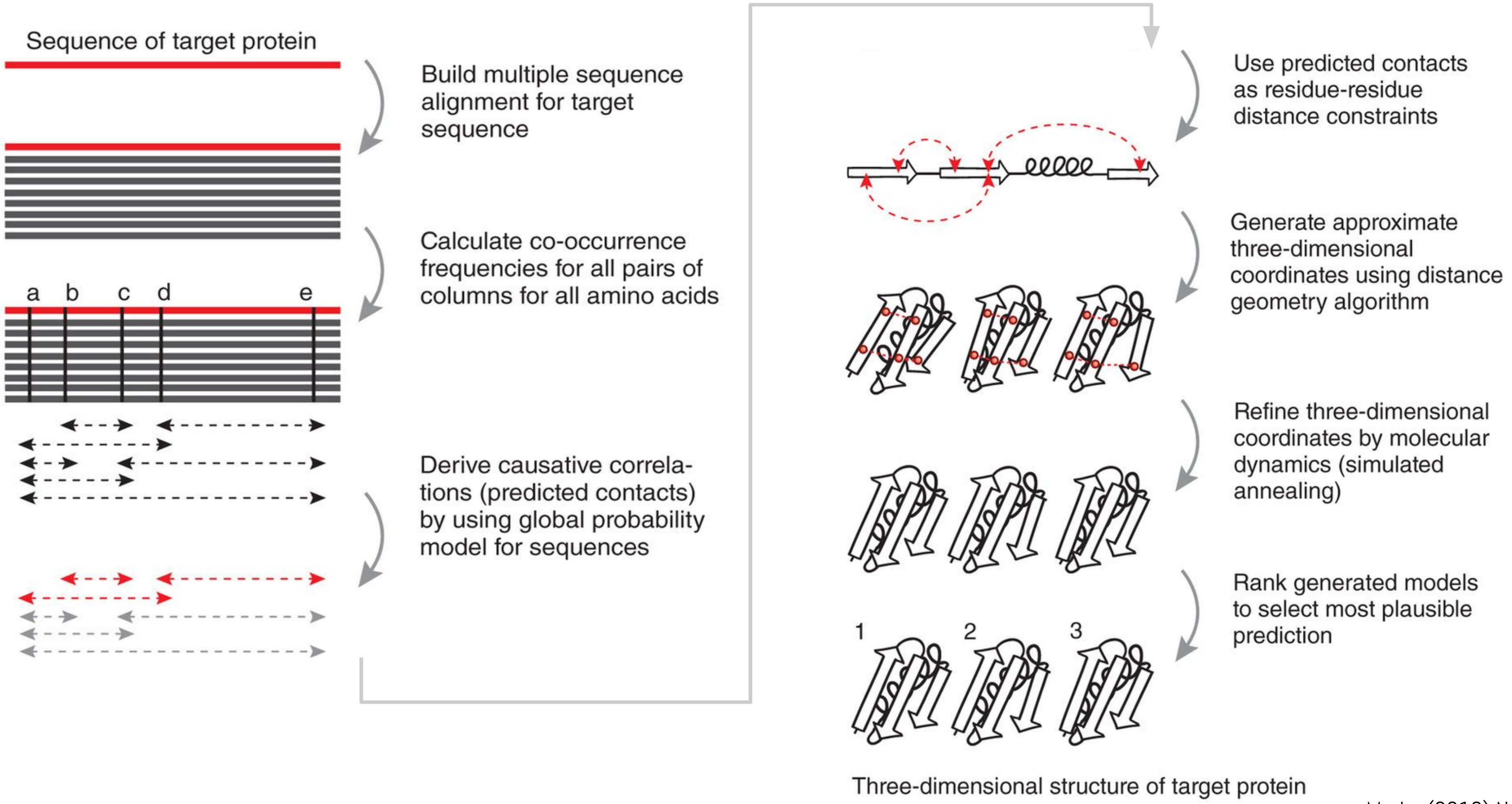


bad scores



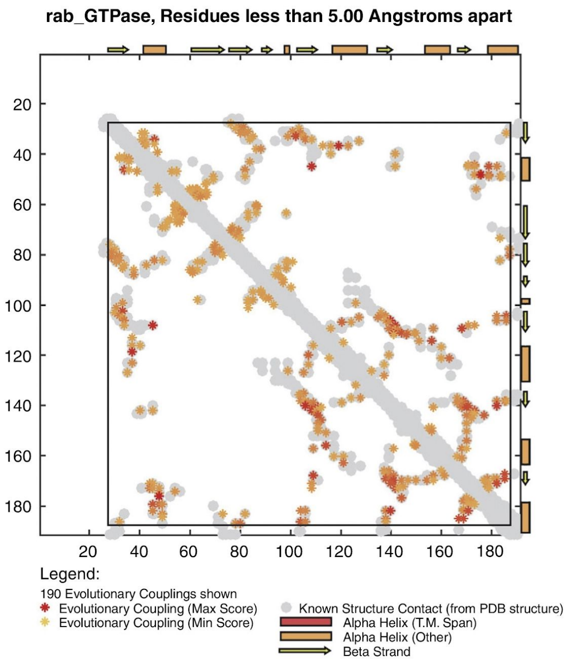
Marks (2011) PLoS One

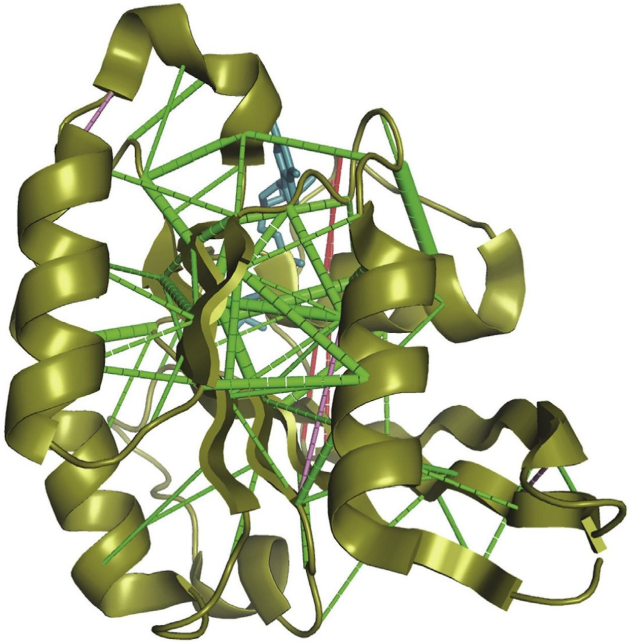
Predicting protein 3D structure from sequence



Marks (2012) Nat. Biotech.

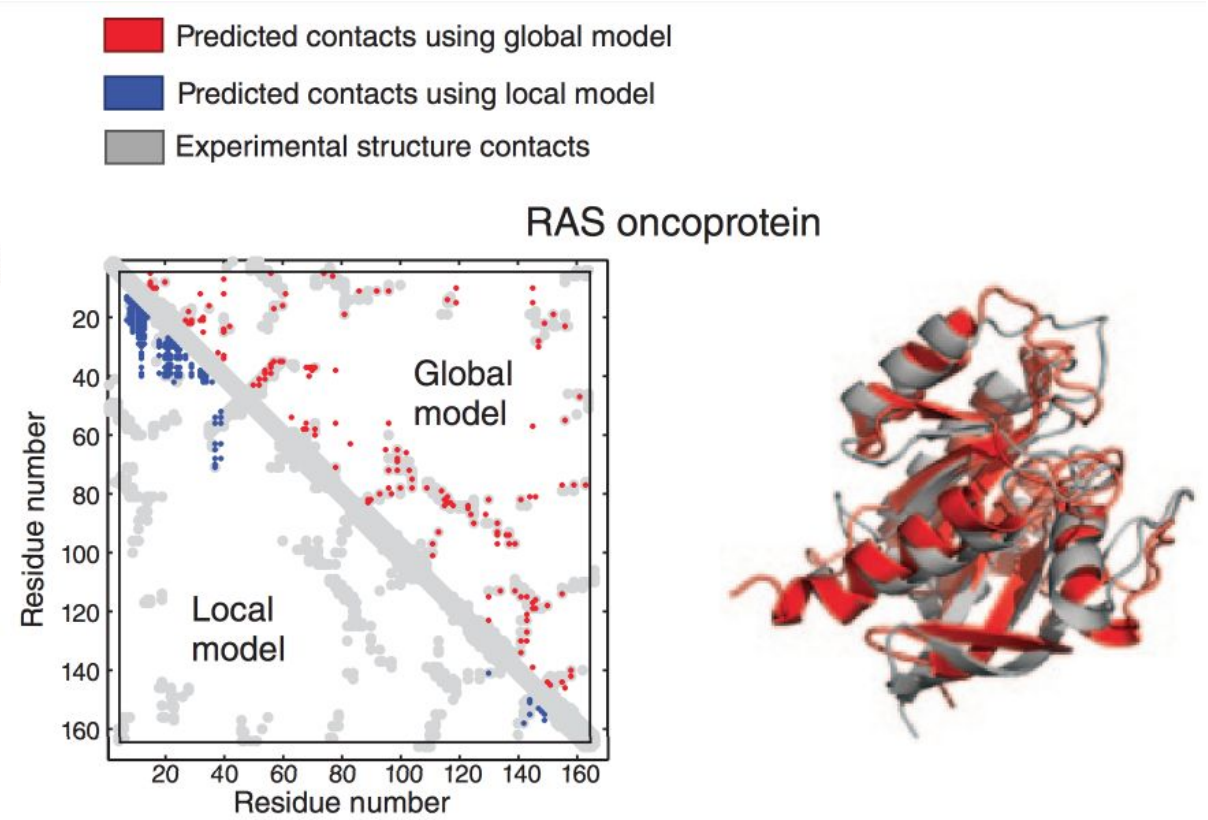
Predictions of 3D structures based on evolutionary coupling





Newald (2016) Curr. Opin. Struct. Biol.

Predictions of 3D structures based on evolutionary coupling



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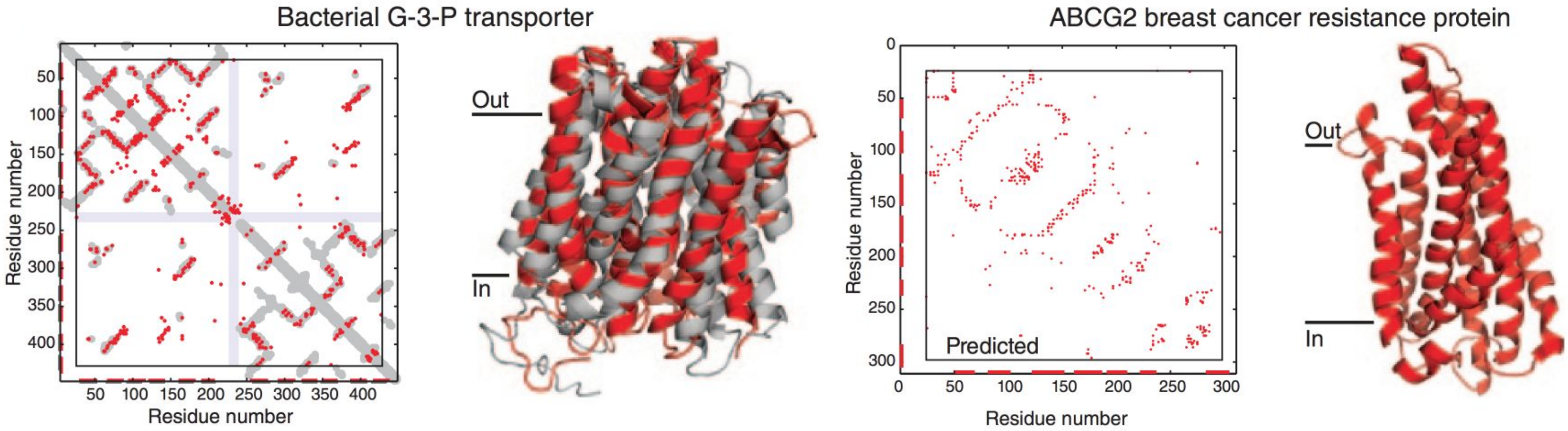

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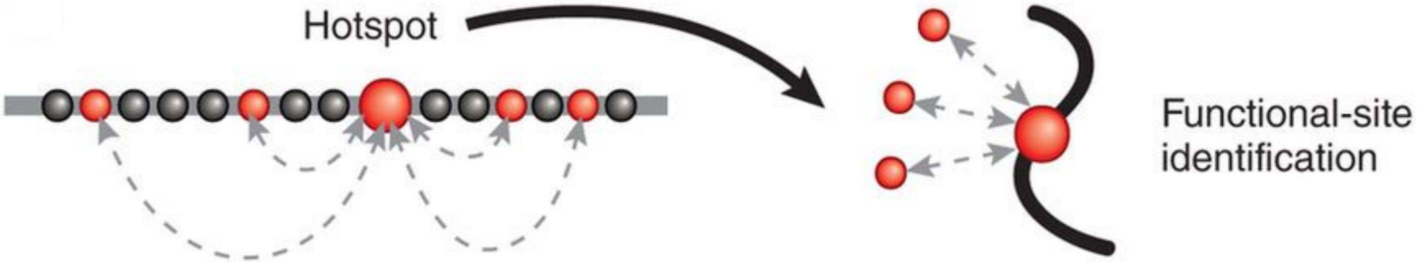
Detecting functional hotspots

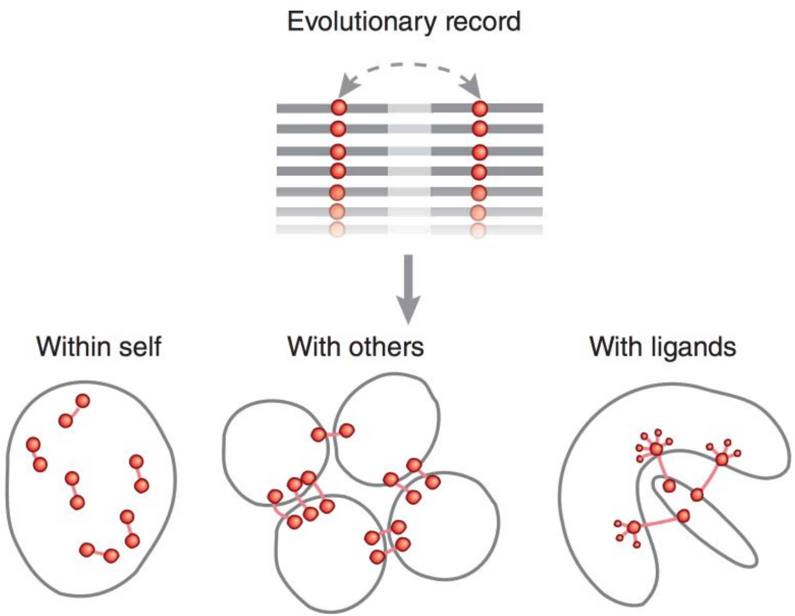
Residues subject to a high number of evolutionary pair constraints represent likely functional hotspots.

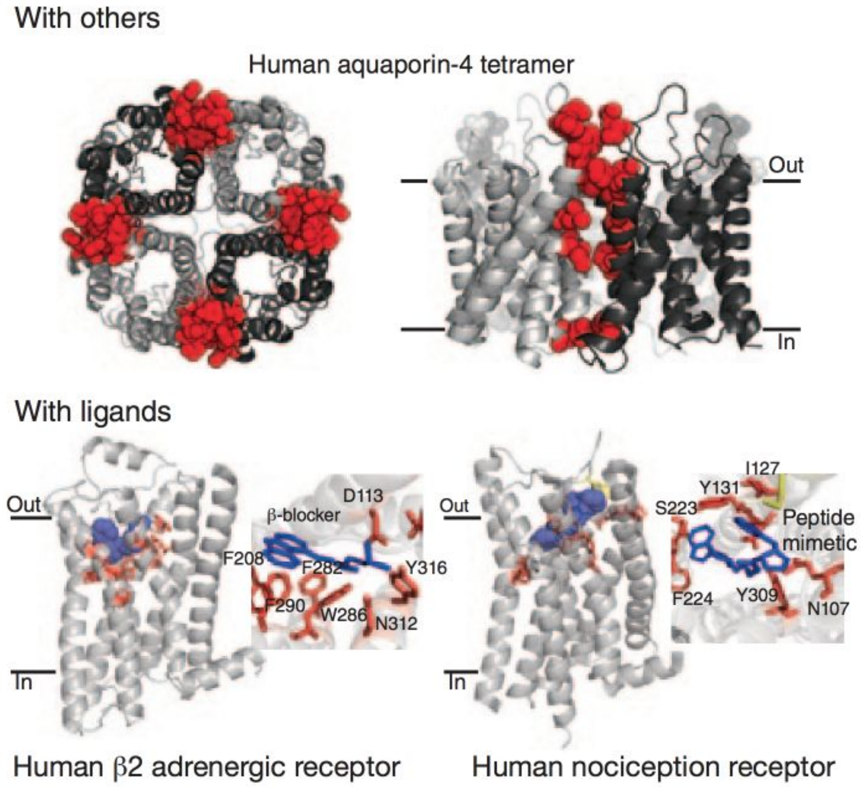
- Such highly constrained residues include residues in functional sites (for e.g., interaction with external ligands).
- Not detectable by analysis of single-residue conservation.



Marks (2012) Nat. Biotech.

Predicting protein-protein & protein-ligand interactions





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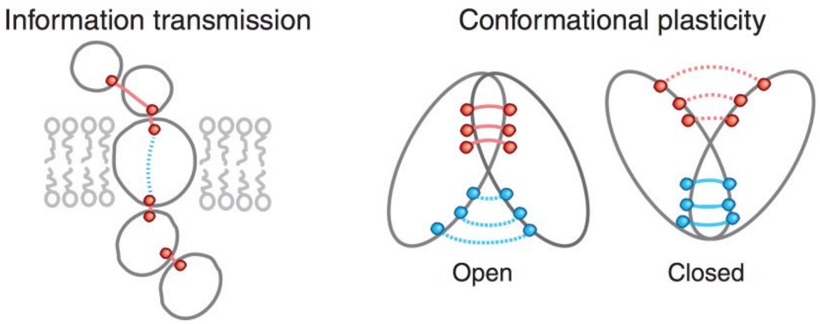
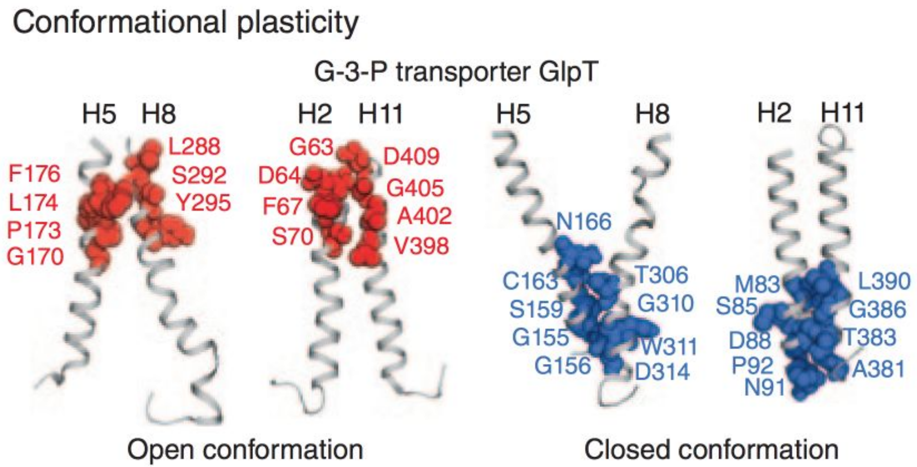
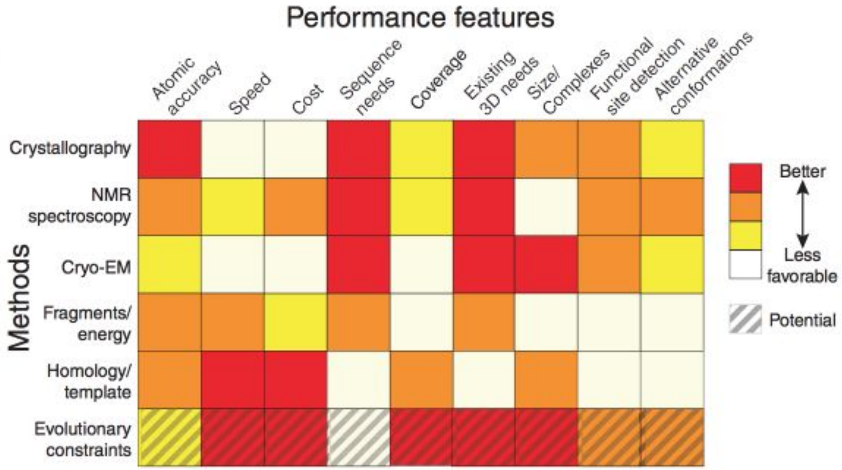
Predicting conformational changes

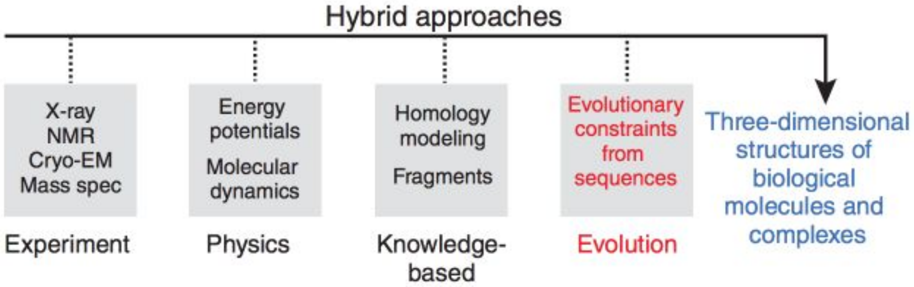




Marks (2012) Nat. Biotech.

Hybrid approaches for determining protein 3D structure





Marks (2012) Nat. Biotech.