Computational Analysis of Protein Coevolution and Interaction

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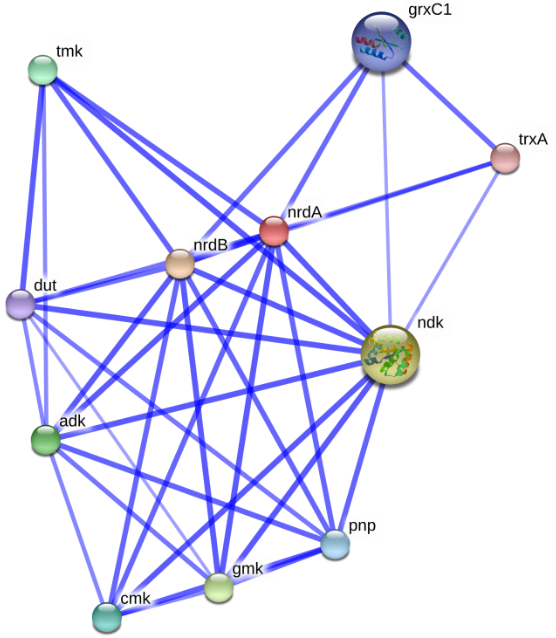
Nova de Lisboa

Outline

1. Introduction
2. Motivation
3. Objectives
4. Results
5. Summary

Protein-protein interactions

- Play a crucial role in biological systems



Protein interactions of RNR (STRING)

Protein-protein interactions

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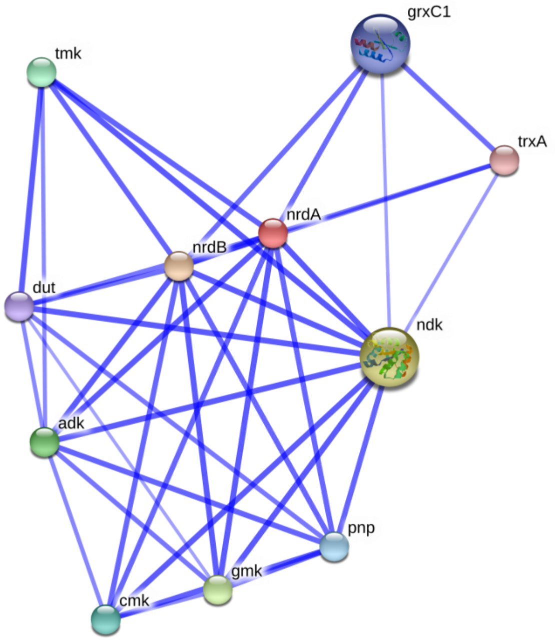
- Invaluable in expanding our understanding of diverse biological processes



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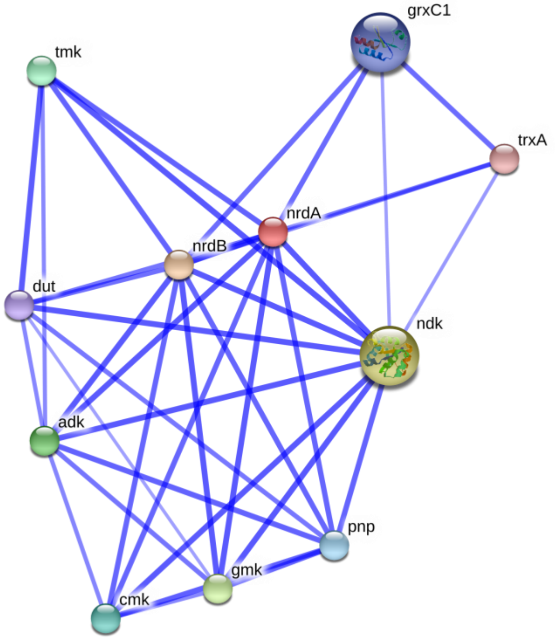

Protein interactions of RNR (STRING)

Protein-protein interactions

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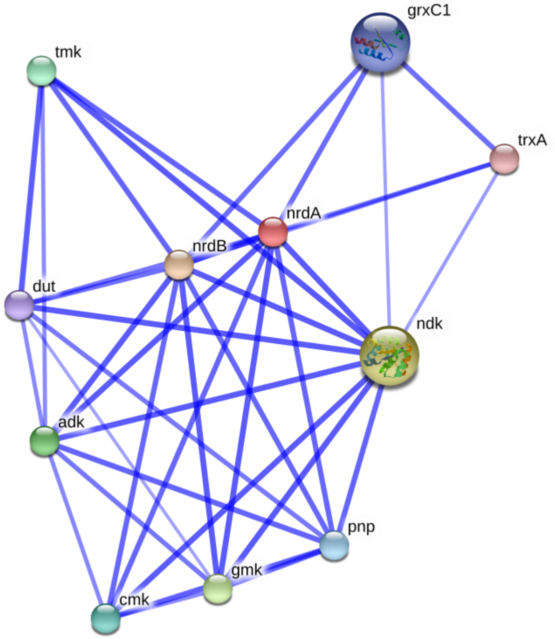
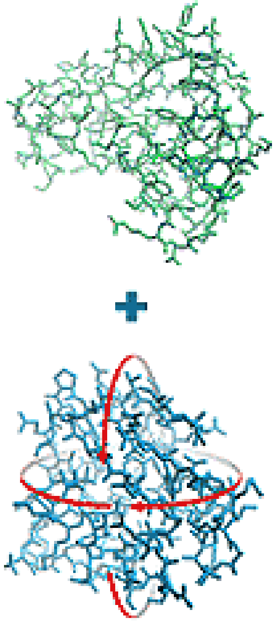
- Invaluable in expanding our understanding of diverse biological processes
- Hard to determine by experimental methods
- Hard to determine by computational methods



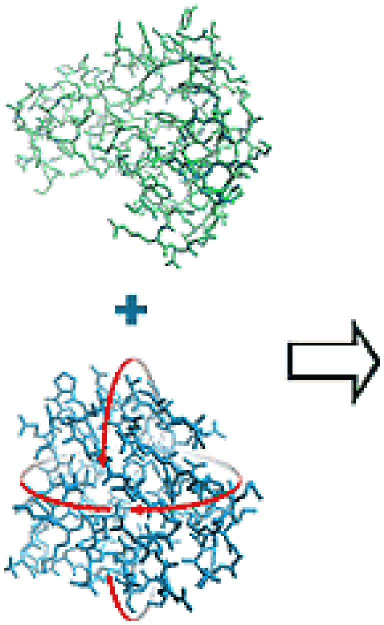
Protein interactions of RNR (STRING)

Protein docking



1. Search

Protein docking



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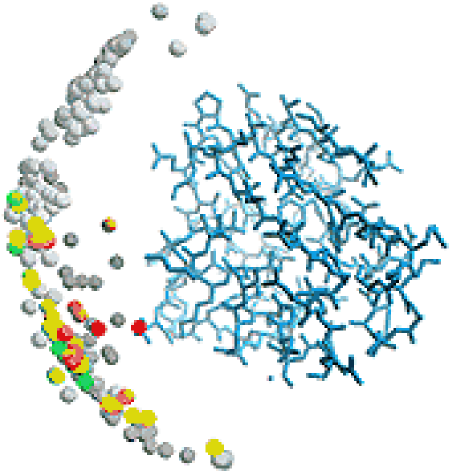
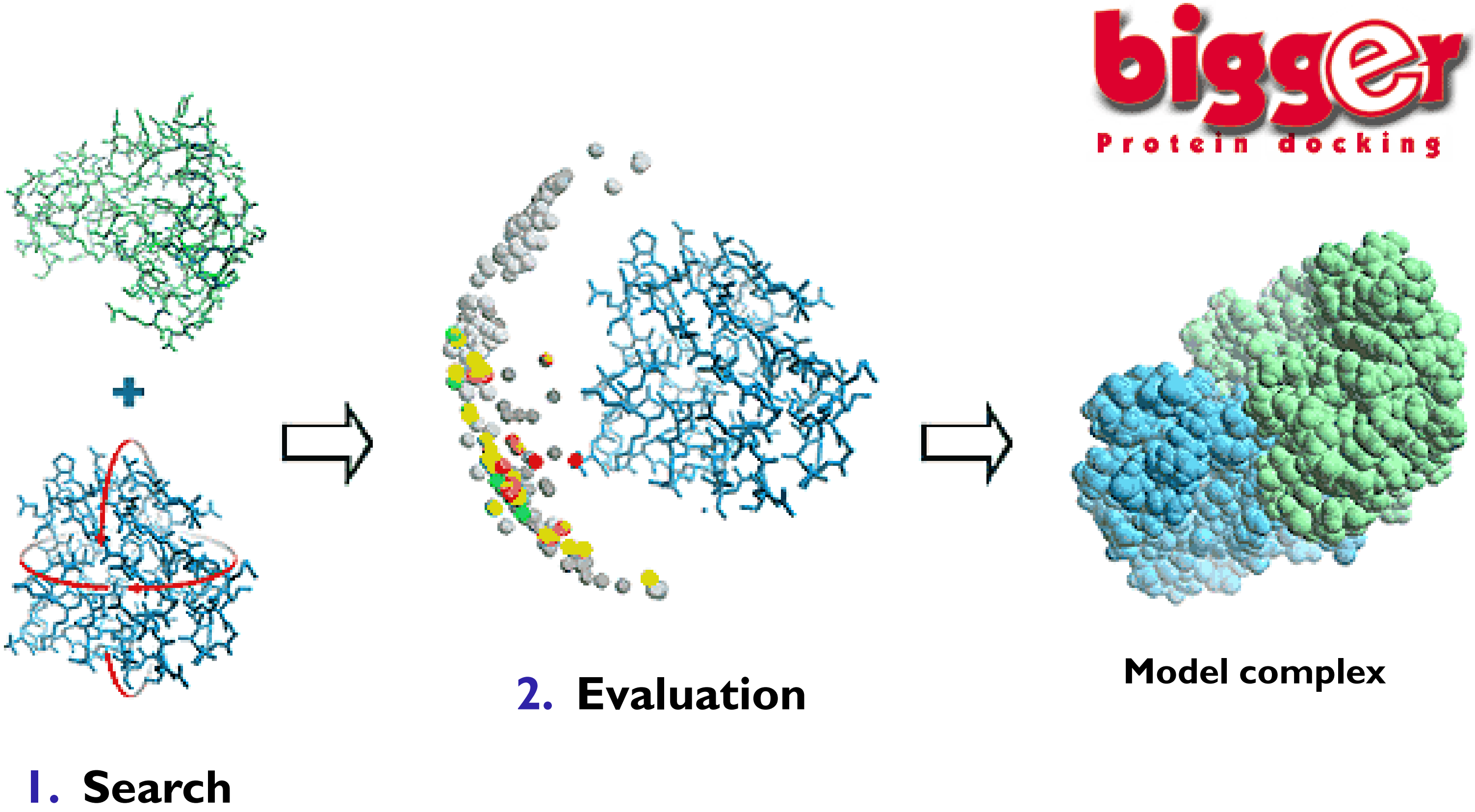


2. Evaluation

Protein docking



1. Search

2. Evaluation

Model complex

Protein coevolution (or correlated mutations)

- Accumulation of sequence changes in one protein triggered by changes in other regions of the same protein or in another protein

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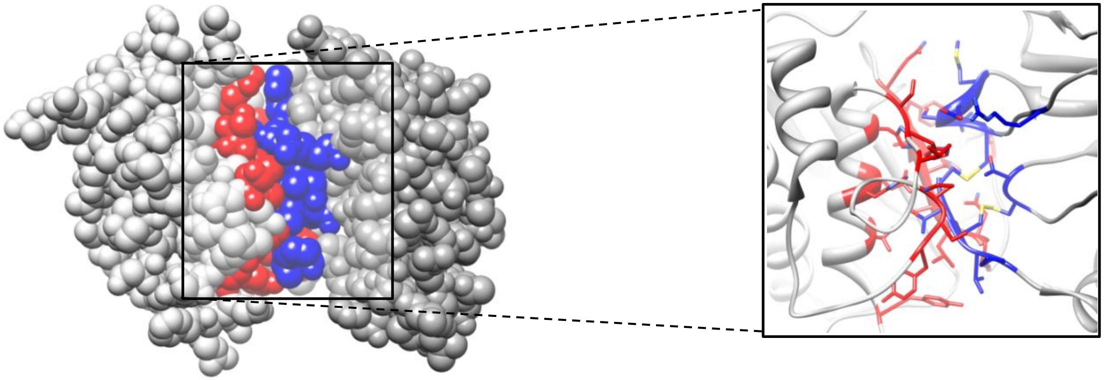
- Applied successfully for:
  - **Prediction of protein interactions**
  - **To guide protein docking**



The "classic" coevolution workflow

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1. **Homologous sequences**

DPSLDRPFISEGTTLKDLIYDMTT

VEGMIKLALSTASGLAHLHMEI

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-----KPGPDLGRDWSVELQEL--
-----EPESDSGRDWSAELPEL--
-----EPEPGSGGDCSEELPEL--
-----DPEPGSGGDCSEELPEL--
PEPEQEPEPDSGGDCSAELPEL--
RKQGLHSMNMMEAACSEPSLDL--
```

2. MSA computation

```
VEGMIKLALSTASGLAHLHMEI
WGSSLRMALSLAQGLAFLHEER
WGSSLRMALSLAQGLAFLHEER
WGSSLRMALSLAQGLAFLHEER
WGSSLSMALSLAEGLAFLHGRR
WGSSLSMALSLAEGLAFLHERR
--SSMSMALSLAQGLAFLHER-
--SSCRLAHSITRGLAYLHTRR
```

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-----DPEPGSGGDCSEELPEL--
PEPEQEPEPDSGGDCSAELPEL--
RKQGLHSMNMMEAACSEPSLDL--
              x
```

2. **MSA computation**

```
VEGMIKLALSTASGLAHLHMEI
WGSSLRMALSLAQGLAFLHEER
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WGSSLSMALSLAEGLAFLHGRR
WGSSLSMALSLAEGLAFLHERR
--SSMSMALSLAQGLAFLHER-
--SSCRLAHSITRGLAYLHTRR
     y
```
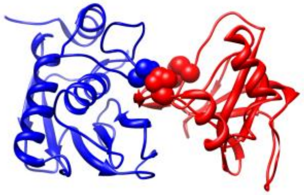

3. **Coevolution analysis**



Methods for finding protein coevolution

- Matrix-based
  - Physicochemical propensities and contact preferences (CPVN, CLM, etc.)
- Correlation-based
  - Correlation coefficient (Pearson's, Spearman's, Quartets, OMES, etc.)
- Statistical-based
  - Perturbation of MSA (MI, SCA, ELSC, etc.)
- Phylogenetic-based
  - Similarity of phylogenetic trees (e.g. Mirrortree, etc.)

Multiple Sequence Alignments

MSA =

```
QFGLFSPEEIRASSVALIR--YPETLENG--VPKESGLVCAGHFGHIELVK
QFGLFSPEEIKRMSVVHVE--YPETMDEQRQRPRTKGLECPGHFGHIELAT
ELGVLDPEIIKKISVCEIV--NVDIYKDG--FPREGGLYCPGHFGHIELAK
QFGVLSPDELKRMSVTEGGIKYPETTE--GGRPKLGGLECPGHFGHIELAK
QFGVLSPDELKRMSVTEGGIKYPETTE--GGRPKLGGLECPGHFGHIELAK
QFGILSPDEIRRMSVTEGGVQFAETME--GGRPKLGGLECPGHFGHIDLAK
QFGILGPEEIKRMSVAH--VEFPEVYE--NGKPKLGGLDCPGHFGHLELAK
QFGILSPEEIRSMSVAK--IEFPETMDESGQRPRVGGLDCPGHFGHIELAK
QFGILSPDEIRQMSVIH----VEHSETTEKGKPKVGGLECPGHFGYLELAK
--------------------------------------ECPGHFGHIELAK
--------------------------------------ECPGHFGFIELAK
QFEIFKERQIKSYAVCLVEHAKSYANA----ADQSGEAECPGHFGYIELAE
QFEVFKEAQIKAYAKCIIEHAKSYEHG----QPVRGGIECPGHFGYVELAE
```

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ELGVLDPEIIKKISVCEIV--NVDIYKDG--FPREGGLYCPGHFGHIELAK
QFGVLSPDELKRMSVTEGGIKYPETTE--GGRPKLGGLECPGHFGHIELAK
QFGVLSPDELKRMSVTEGGIKYPETTE--GGRPKLGGLECPGHFGHIELAK
QFGILSPDEIRRMSVTEGGVQFAETME--GGRPKLGGLECPGHFGHIDLAK
QFGILGPEEIKRMSVAH--VEFPEVYE--NGKPKLGGLDCPGHFGHLELAK
QFGILSPEEIRSMSVAK--IEFPETMDESGQRPRVGGLDCPGHFGHIELAK
QFGILSPDEIRQMSVIH----VEHSETTEKGKPKVGGLECPGHFGYLELAK
--------------------------------------ECPGHFGHIELAK
--------------------------------------ECPGHFGFIELAK
QFEIFKERQIKSYAVCLVEHAKSYANA----ADQSGEAECPGHFGYIELAE
QFEVFKEAQIKAYAKCIIEHAKSYEHG----QPVRGGIECPGHFGYVELAE
```

- Insufficient evolutionary divergence
- Sample size effects
- Small taxa coverage
- False correlations as result of misalignments
- **Underlying assumption of independent mutations**

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- Coevolution data can help predict protein interaction and to guide docking
- BiGGER can use contact information to constraint the search space and improve the quality of the models
- Limitations of MSA, such as the assumption of independent mutations

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➢ The computational analysis of protein coevolution and interaction will focus on:

- Refinement of Multiple Sequence Alignments
- Integration of protein coevolution data in the protein docking workflow
- Development and assessment of different coevolution measures
- Development of new scoring methods to rank docking solutions

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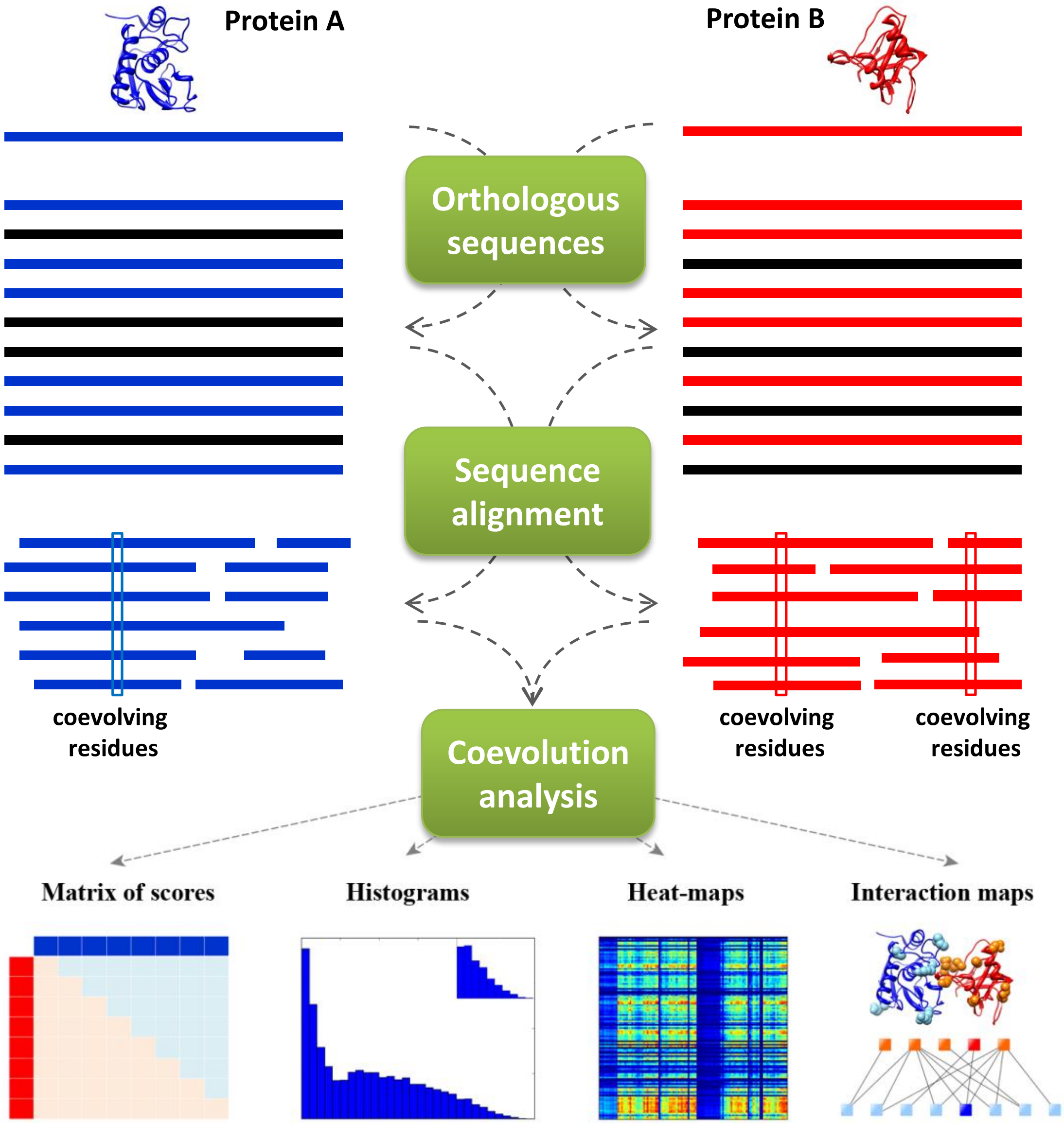
Pycoevol



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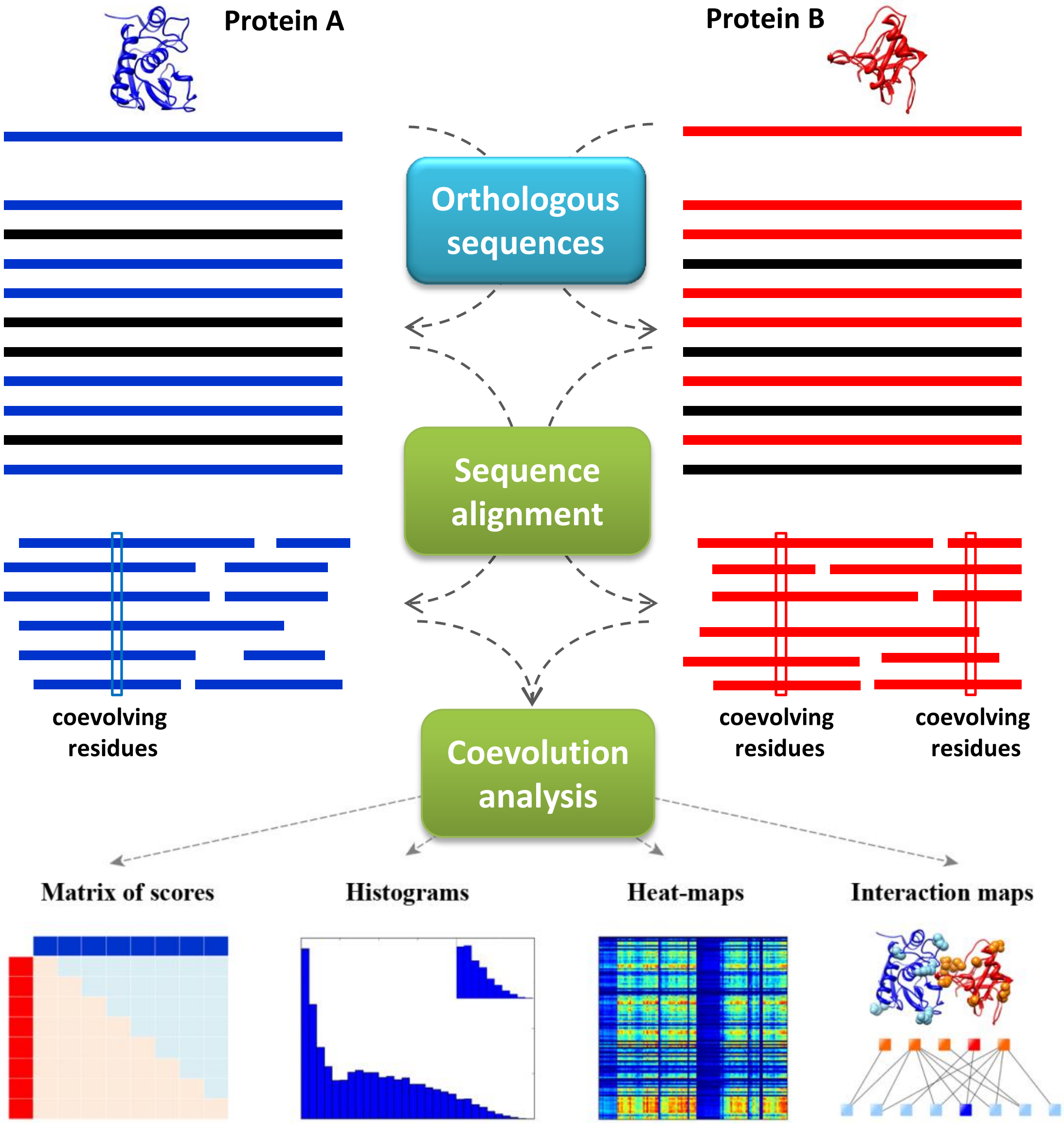

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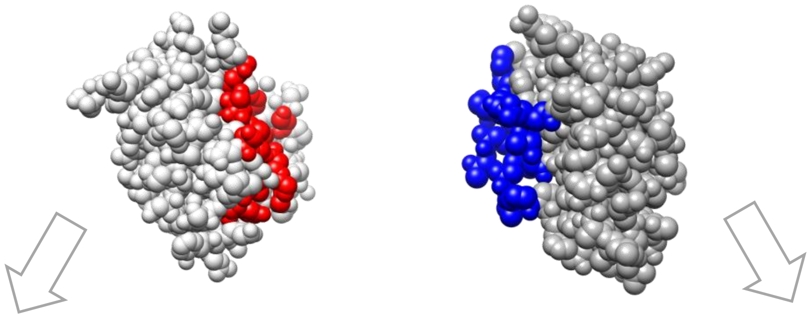
Matching of taxa



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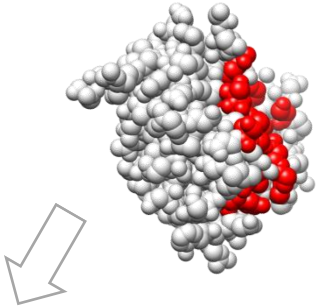

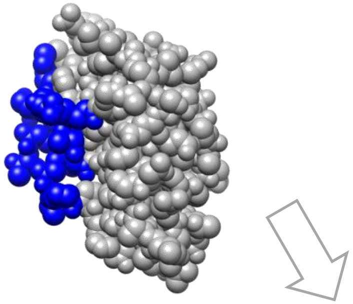

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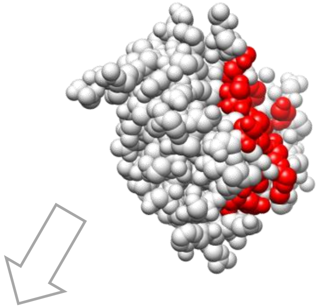

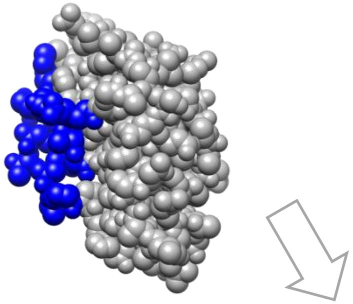

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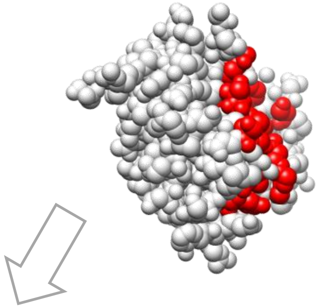

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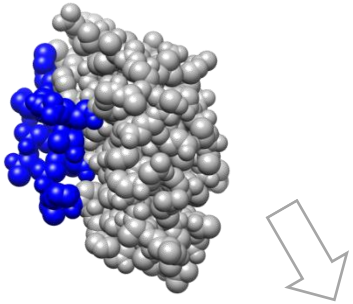

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Pairwise distances and orthologs selection

- p-distance *[Jukes and Cantor, 1969]*

$$d = p = \frac{N_{dif}}{N_{total}}$$

- Jukes-Cantor *[Jukes and Cantor, 1969]*

$$d = -\frac{19}{20}log(1 - p * \frac{20}{19})$$

- Kimura distance *[Kimura, 1983]*

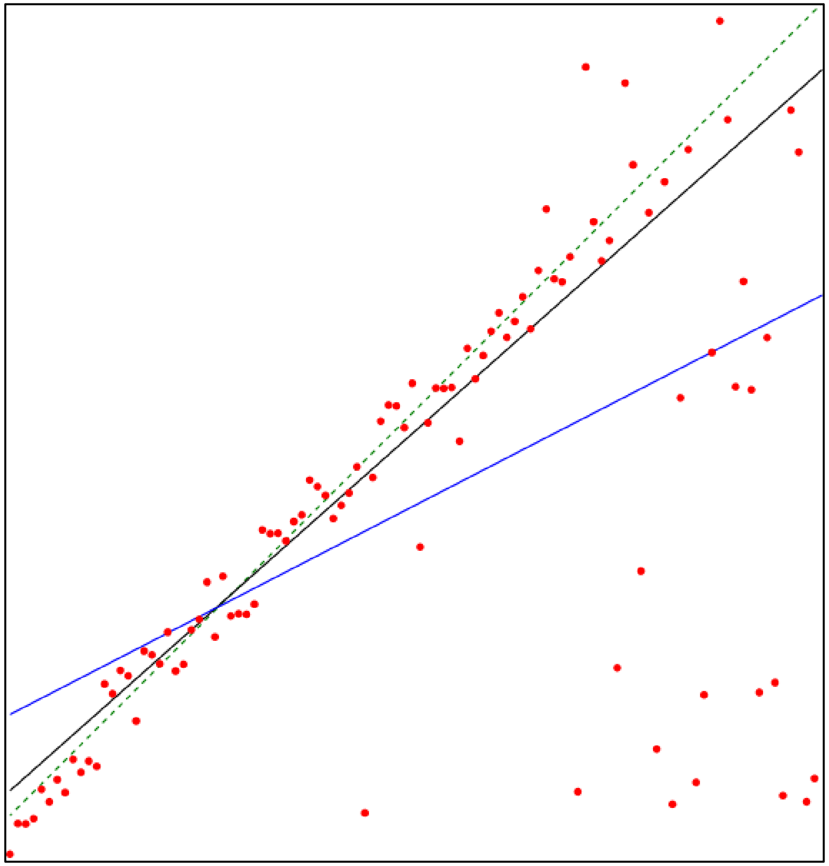
$$d = -ln(1 - p - 0.2^2)$$

- Pairwise score using Dayhoff or PAM matrices [*Gonnet, 2000*]

$$d = \sum \frac{1 - S_{ij}}{S_{ii}} * \frac{1 - S_{ij}}{S_{jj}}$$

Theil-Sen regression and sequence removal

- *Median m of the slopes $(y_j - y_i)/(x_j - x_i)$ determined by all pairs of sample points $\in (x,y)$, which have distinct x-coordinates [Theil, 1950] and [Sen, 1968]*



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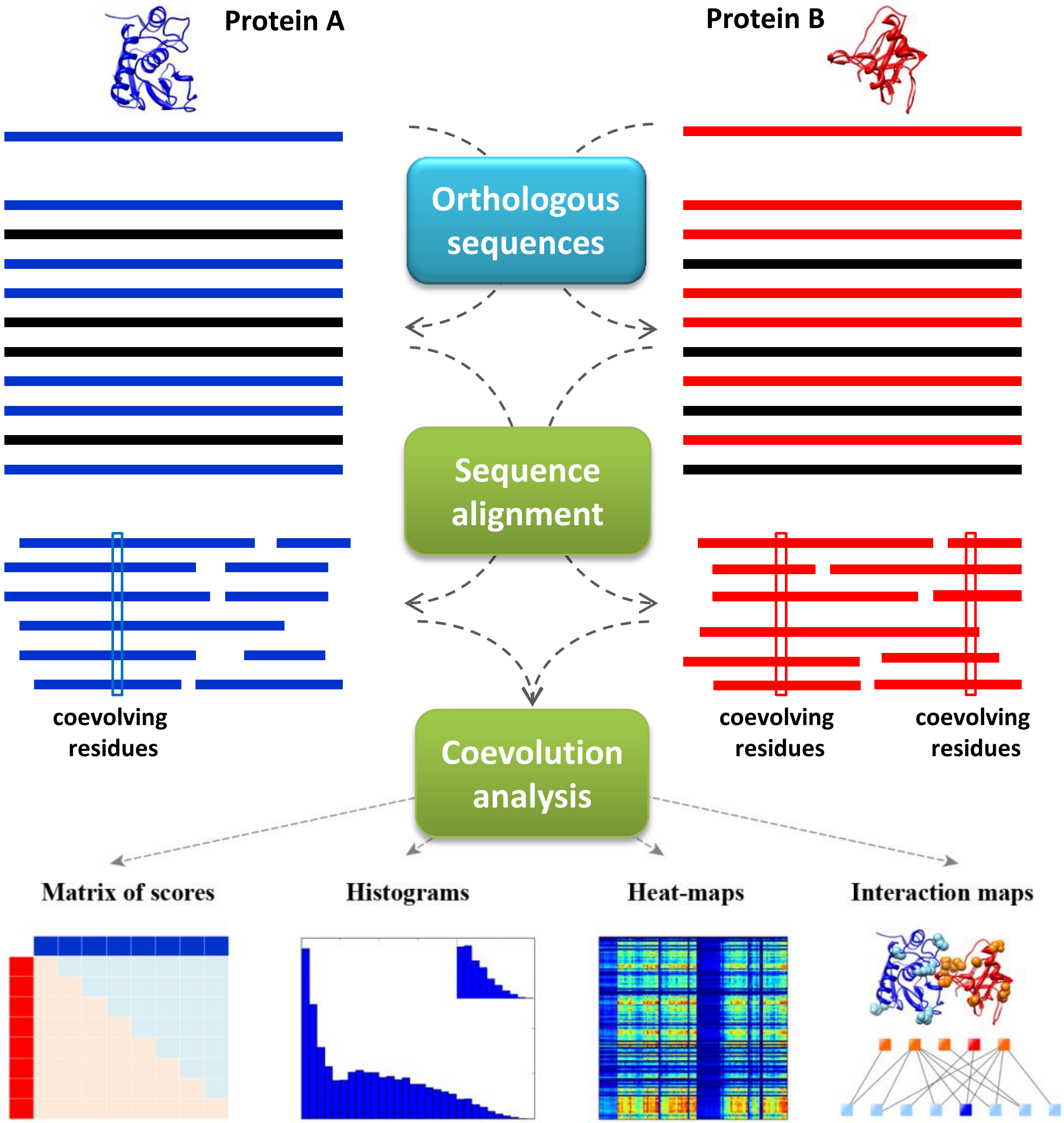

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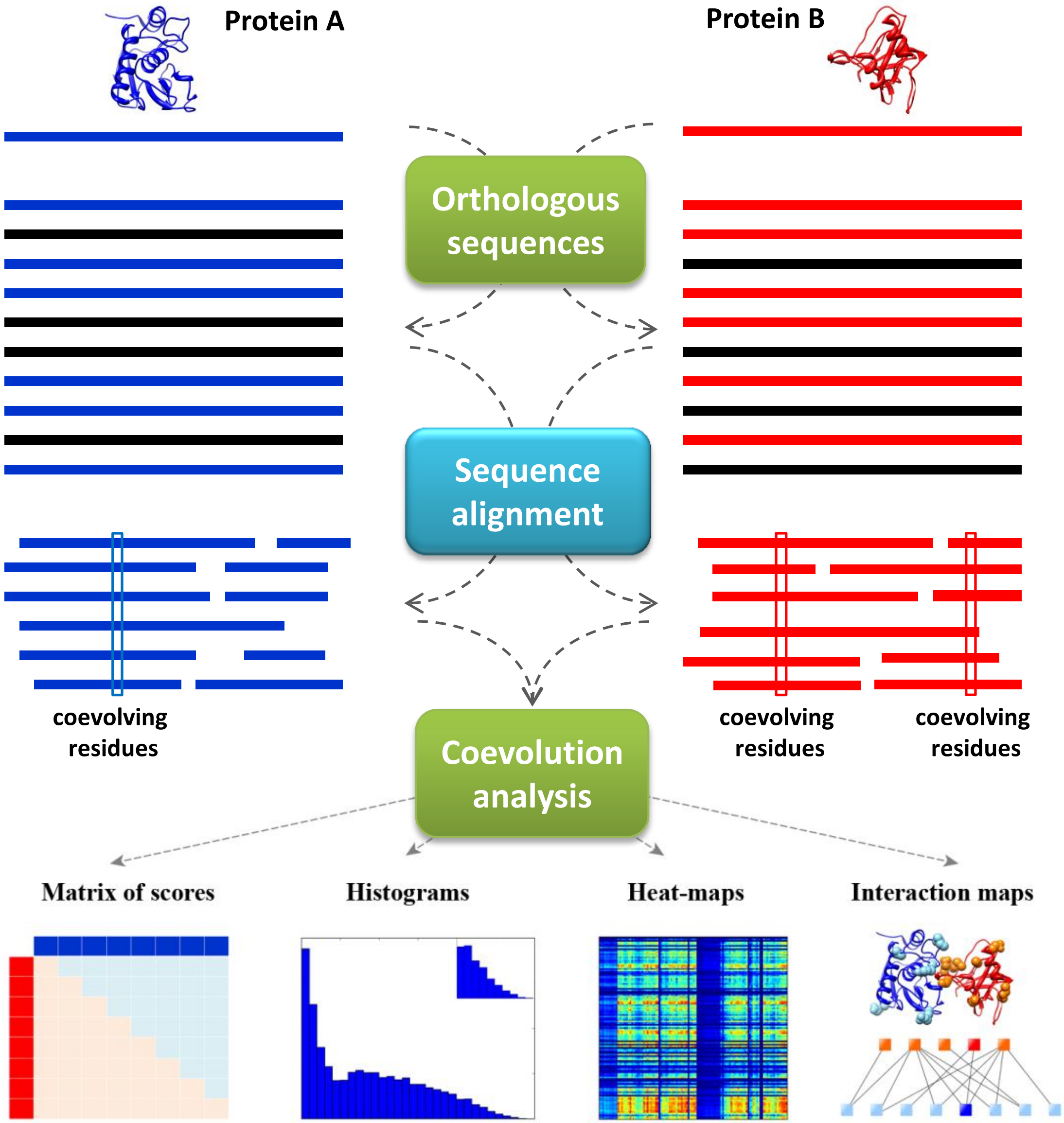

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Refinement of Multiple Sequence Alignments

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QFGILSPDEIRRMSVTEGGVQFAETME--GGRPKLGGLECPGHFGHIDLAK
QFGILGPEEIKRMSVAH--VEFPEVYE--NGKPKLGGLDCPGHFGHLELAK
QFGILSPEEIRSMSVAK--IEFPETMDESGQRPRVGGLDCPGHFGHIELAK
QFGILSPDEIRQMSVIH----VEHSETTEKGKPKVGGLECPGHFGYLELAK
--------------------------------------ECPGHFGHIELAK
--------------------------------------ECPGHFGFIELAK
QFEIFKERQIKSYAVCLVEHAKSYANA----ADQSGEAECPGHFGYIELAE
QFEVFKEAQIKAYAKCIIEHAKSYEHG----QPVRGGIECPGHFGYVELAE
```

- Constraint Programming

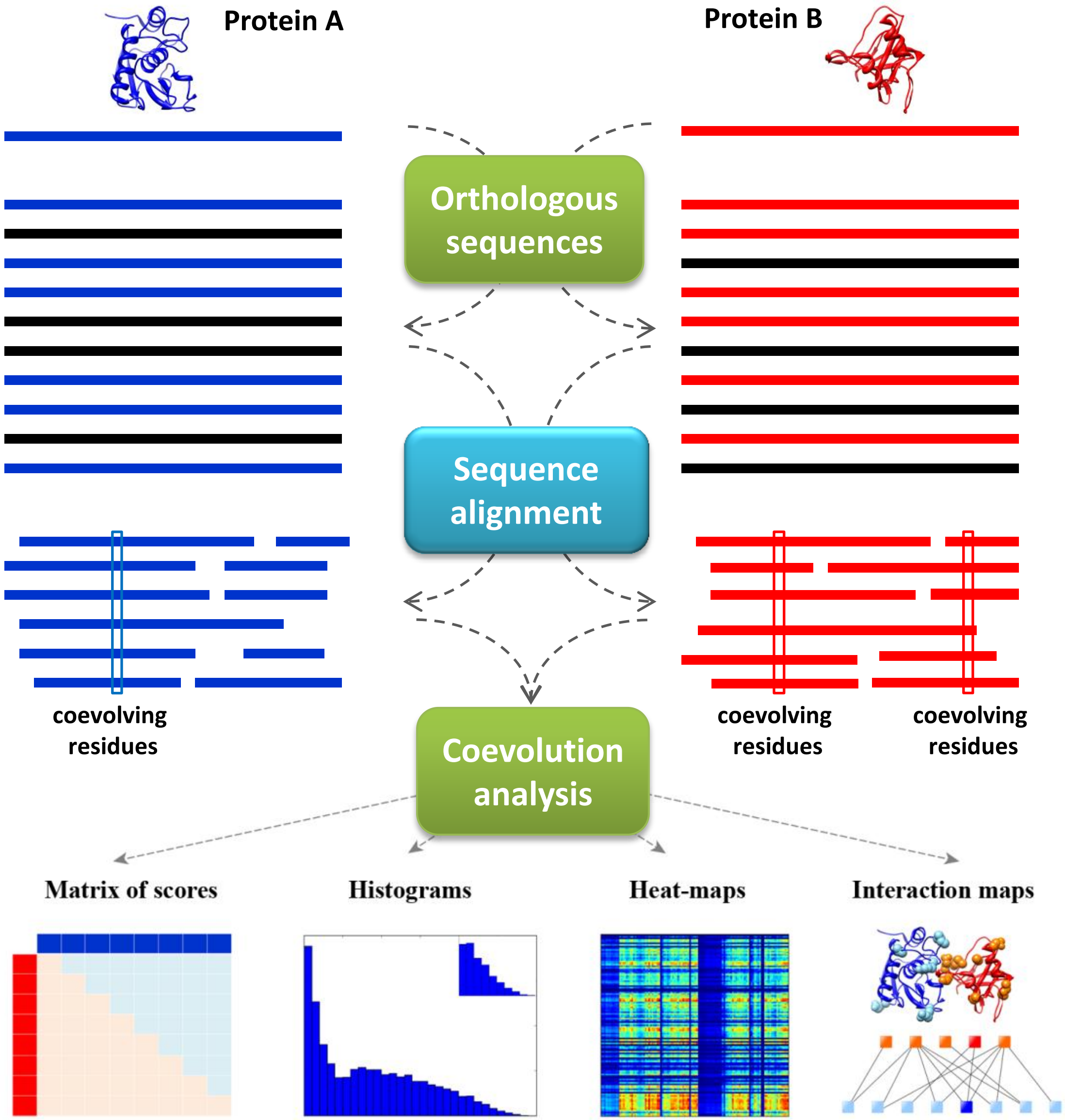
misalignments

Accounts for correlated mutations

```
QFGLFSPEEIRASSVAL--IRYPETLE--NGVPKESGLVCAGHFGHIELVK
QFGLFSPEEIKRMSVVH--VEYPETMDEQRQRPRTKGLECPGHFGHIELAT
QFGILSPEEIRSMSVAK--IEFPETMDESGQRPRVGGLDCPGHFGHIELAK
ELGVLDPEIIKKISVCE--IVNVDIYK--DGFPREGGLYCPGHFGHIELAK
QFGVLSPDELKRMSVTEGGIKYPETTE--GGRPKLGGLECPGHFGHIELAK
QFGVLSPDELKRMSVTEGGIKYPETTE--GGRPKLGGLECPGHFGHIELAK
QFGILSPDEIRRMSVTEGGVQFAETME--GGRPKLGGLECPGHFGHIDLAK
QFGILGPEEIKRMSVAH--VEFPEVYE--NGKPKLGGLDCPGHFGHLELAK
QFGILSPDEIRQMSVIH--VEHSETTE--KGKPKVGGLECPGHFGYLELAK
--------------------------------------ECPGHFGHIELAK
--------------------------------------ECPGHFGFIELAK
QFEIFKERQIKSYAVCL--VEHAKSYA--NAADQSGEAECPGHFGYIELAE
QFEVFKEAQIKAYAKCI--IEHAKSY--EHGQPVRGGIECPGHFGYVELAE
```

Correia, M. Madeira, F., Barahona, P. and Krippahl, L. 2011. **Improving Multiple Sequence Alignments with Constraint Programming and Local Search**. WCB11, pp.37-44.

Pycoevol



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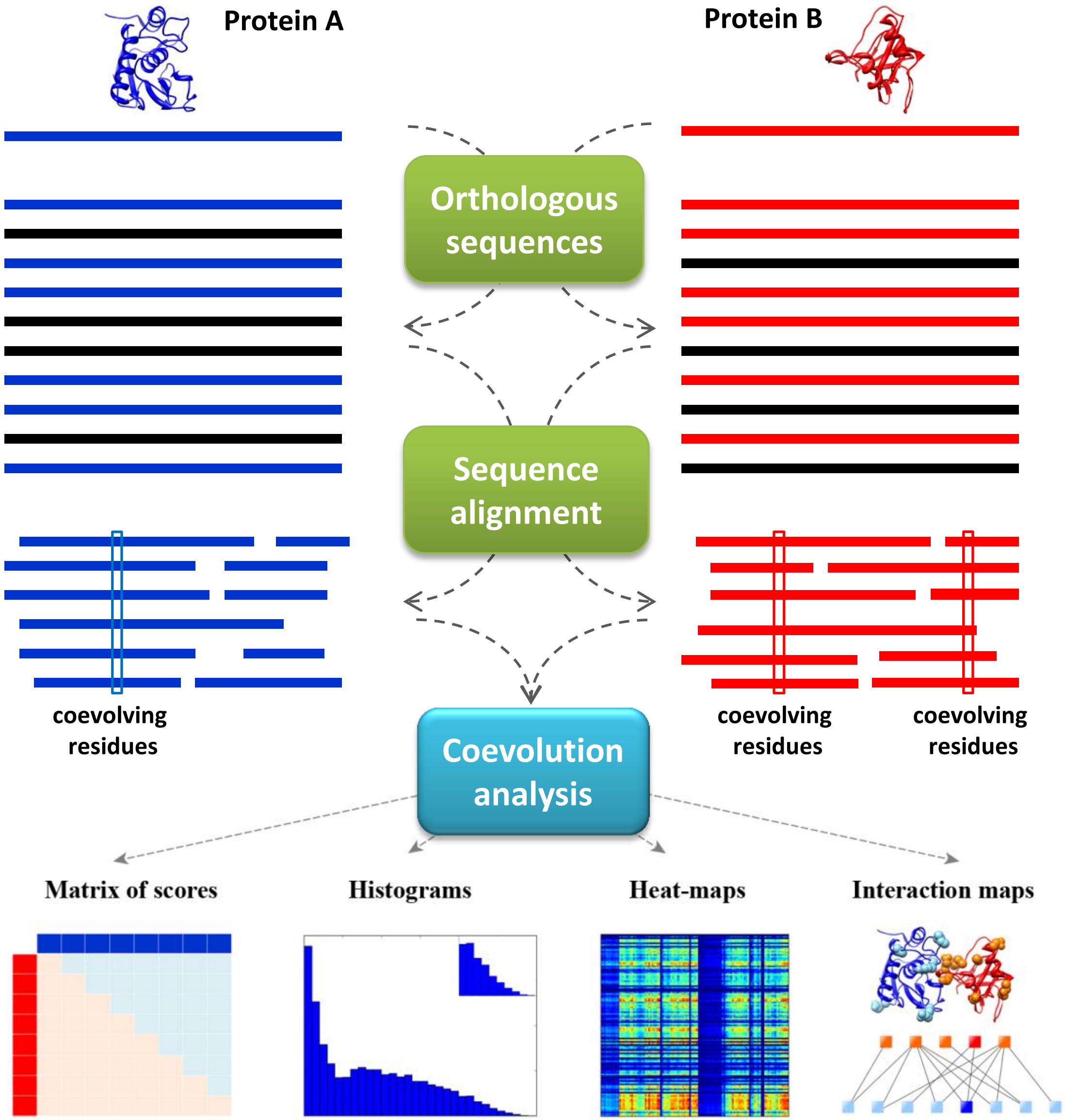

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Methods for finding protein coevolution

- Contact Preferences, Volume Normalized (**CPVN**) *[Glaser et al, 2001]*
- Contact PDB-derived Likelihood Matrix (**CLM**) *[Singer et al, 2002]*
- Residue-residue Volume Normalized (**VOL**) *[Esque et al, 2010]*

$$CM_{x,y} = \sum_{i}^{n} \sum_{j}^{n} \frac{S_{ij}}{n}$$

Methods for finding protein coevolution

- Pearson's correlation (**Pearson**) *[Göbel et al, 1994]*

- Spearman's rank correlation (**Spearman**) *[Pazos et al, 1997]*

- McLachlan Based Substitution Correlation (**McBASC**) *[Fodor and Aldrich, 2004]*

- ***Quartets*** *[Galitsky, 2002]*

$$CM_{x,y} = \frac{1}{N^2} \sum_i \sum_j \frac{W_{ij}(S_{xij} - \langle S_x \rangle)(S_{yij} - \langle S_y \rangle)}{\sigma_x \sigma_y}$$

- Observed Minus Expected Squared (**OMES**) *[Kass and Horovitz, 2002]*

$$CM_{x,y} = \sum_l^L \frac{(N_{obs} - \frac{C_{xi}C_{yj}}{N_{valid}})^2}{N_{valid}}$$

Methods for finding protein coevolution

- Mutual Information (**MI**) *[Gloor et al, 2005]*

- MI by pair Entropy (**MI/E**) *[Martin et al, 2005]*

- Row and Column Weighed MI (**RCW MI**) *[Gouveia-Oliveira et al, 2007]*

$$MI_{x,y} = \sum_i \sum_j P(x_i y_j) log \frac{P(x_i y_j)}{P(x_i)P(y_j)}$$

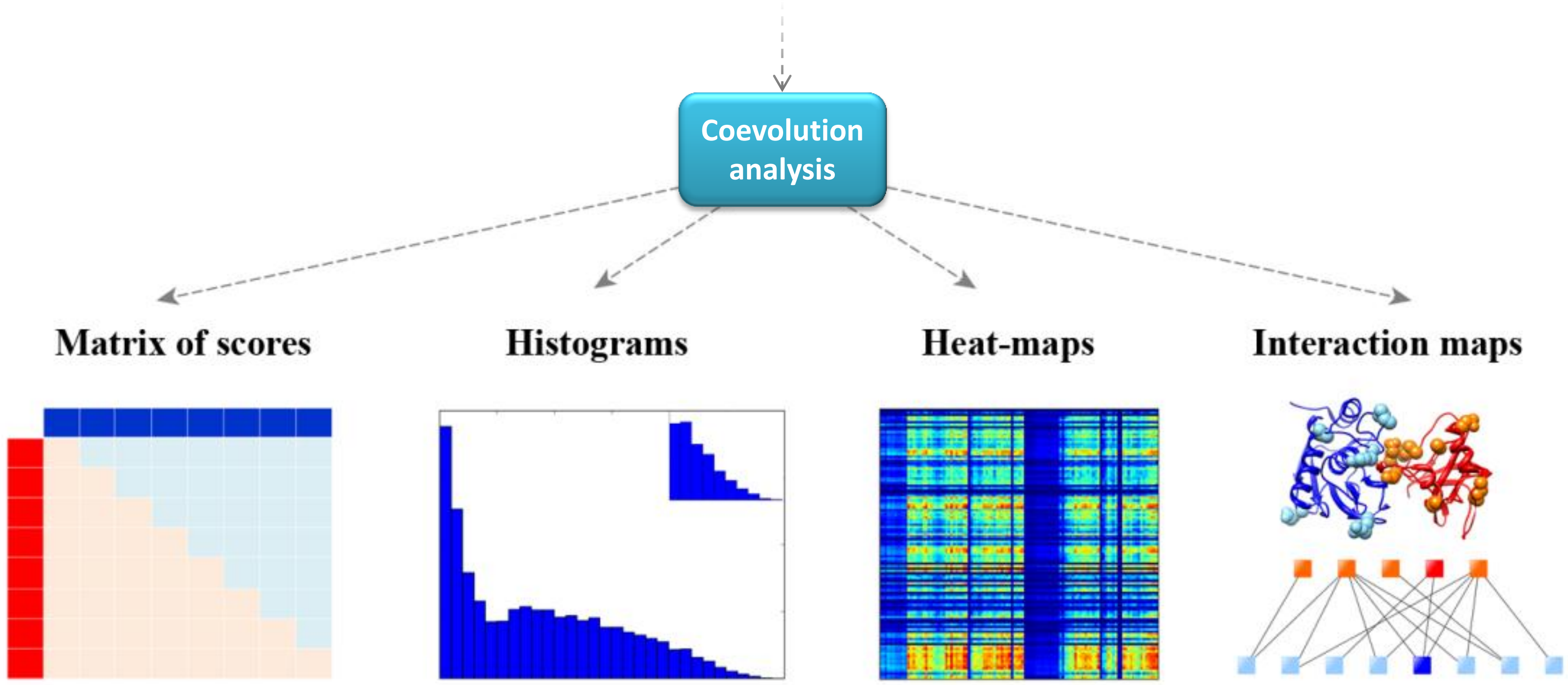
- Statistical Coupling Analysis (**SCA**) *[Lockless and Ranganathan, 1999]*

$$\Delta\Delta G_{x,y} = \sqrt{\sum_i (lnP^i_{x|\delta y} - P^i_x)^2}$$

- Explicit Likelihood of Subset Covariation (**ELSC**) *[Dekker et al, 2004]*

$$\Lambda^y_x = \prod_r^{20} \frac{\binom{N_{r,y}}{n_{r,y}}}{\binom{N_{r,y}}{m_{r,y}}}$$

Output results



Coevolution analysis

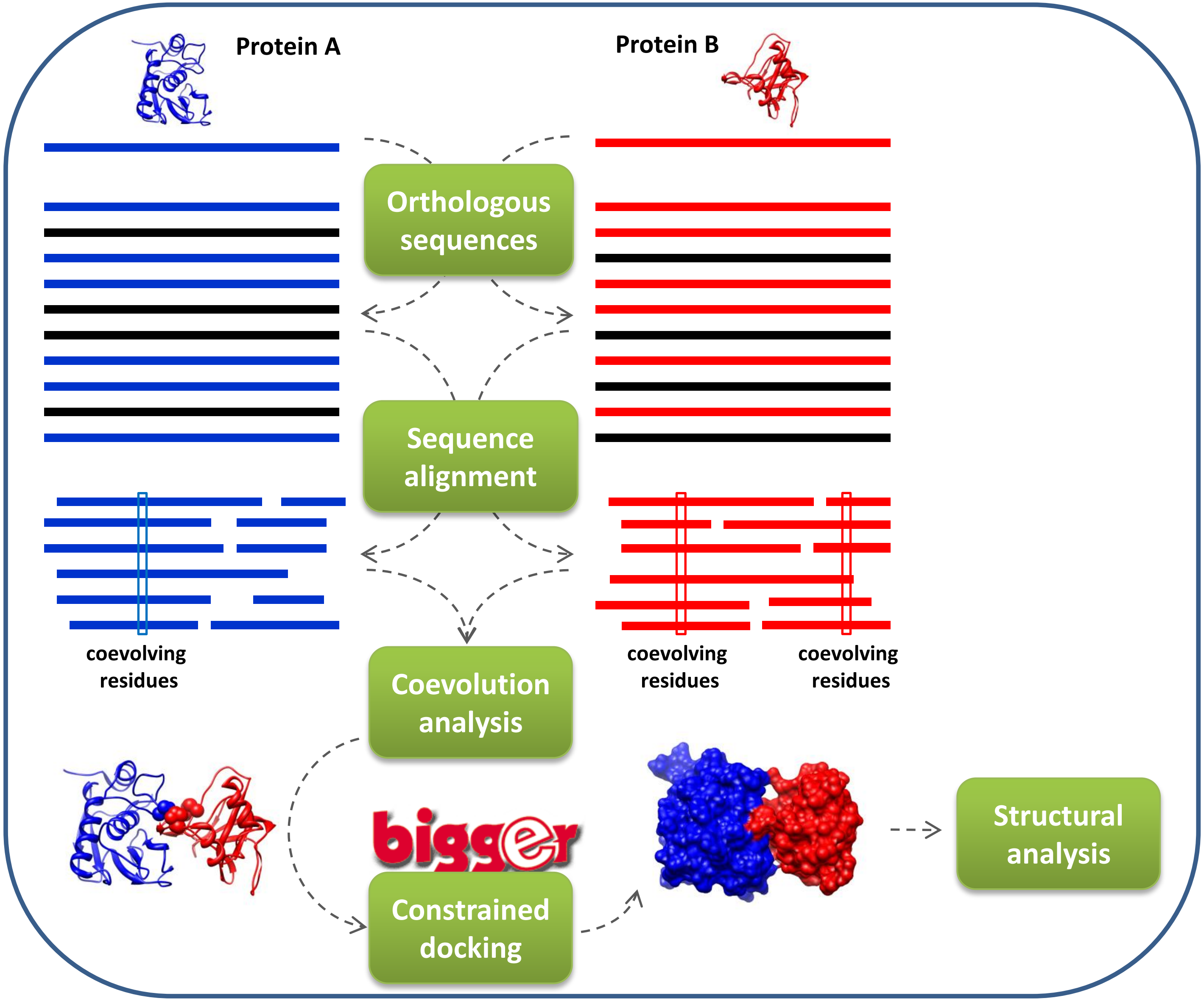
Matrix of scores

Histograms

Heat-maps

Interaction maps

Development of an integrated system



Protein A

Protein B

Orthologous sequences

Sequence alignment

coevolving residues

coevolving residues

coevolving residues

Coevolution analysis

bigger

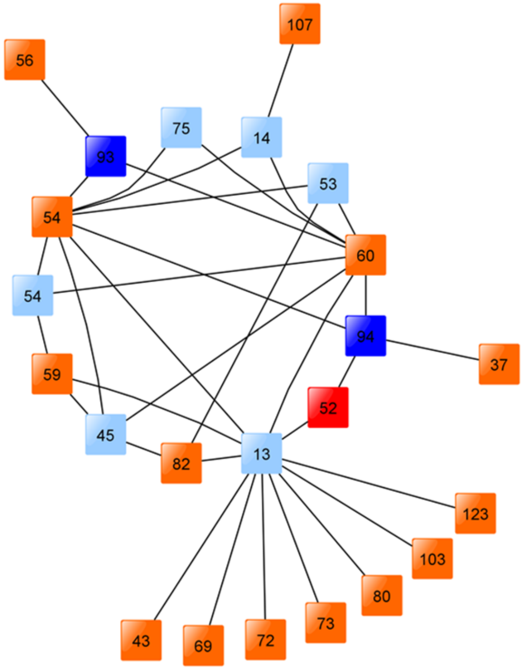
Constrained docking

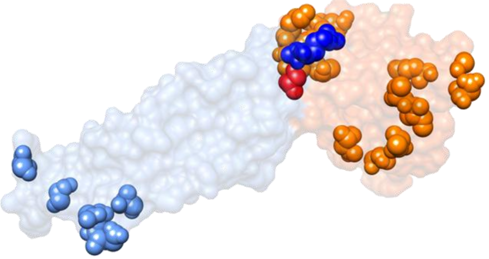
Structural analysis

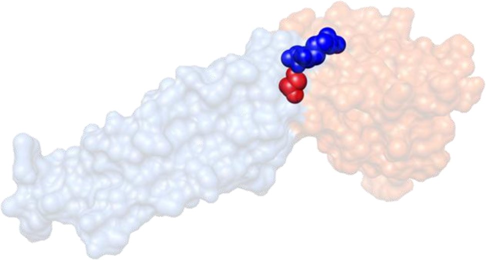
Example

Protein complex TGF-β3/TGF-β receptor type II (1ktz)

- Most residues were at the surface level
- 3 out of 23 residues were at the interface
- 8 residues from TGF-β3
- 15 residues from TGB-β receptor

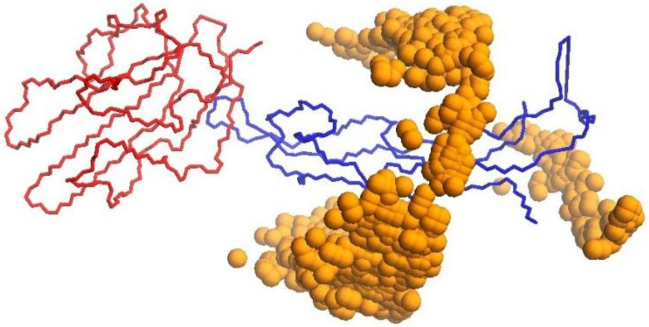






Improving protein-protein docking

- Possible pairs of contacts = 11772
- Tested contacts = 120
- Reduced the search space to 0.01% of possible contact points



Difficult complex to model

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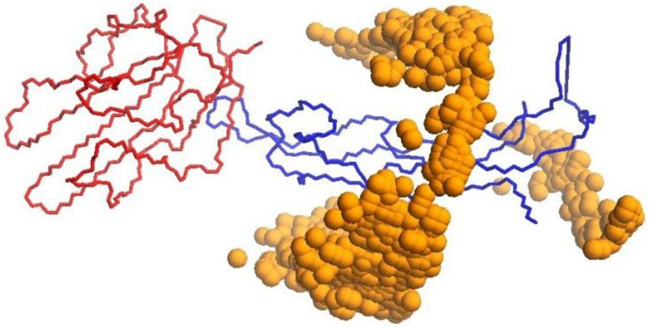

Difficult complex to model

- Given the complexity of protein-protein docking, finding even only one positive interface contact can help constraint the search space and improve the accuracy of constrained docking algorithms such as BiGGER [*Palma et al, 2000*]

Evaluation of coevolution methods

- Survey which method is better suited for the identification of interface contact points using a large protein complex dataset (unpublished)

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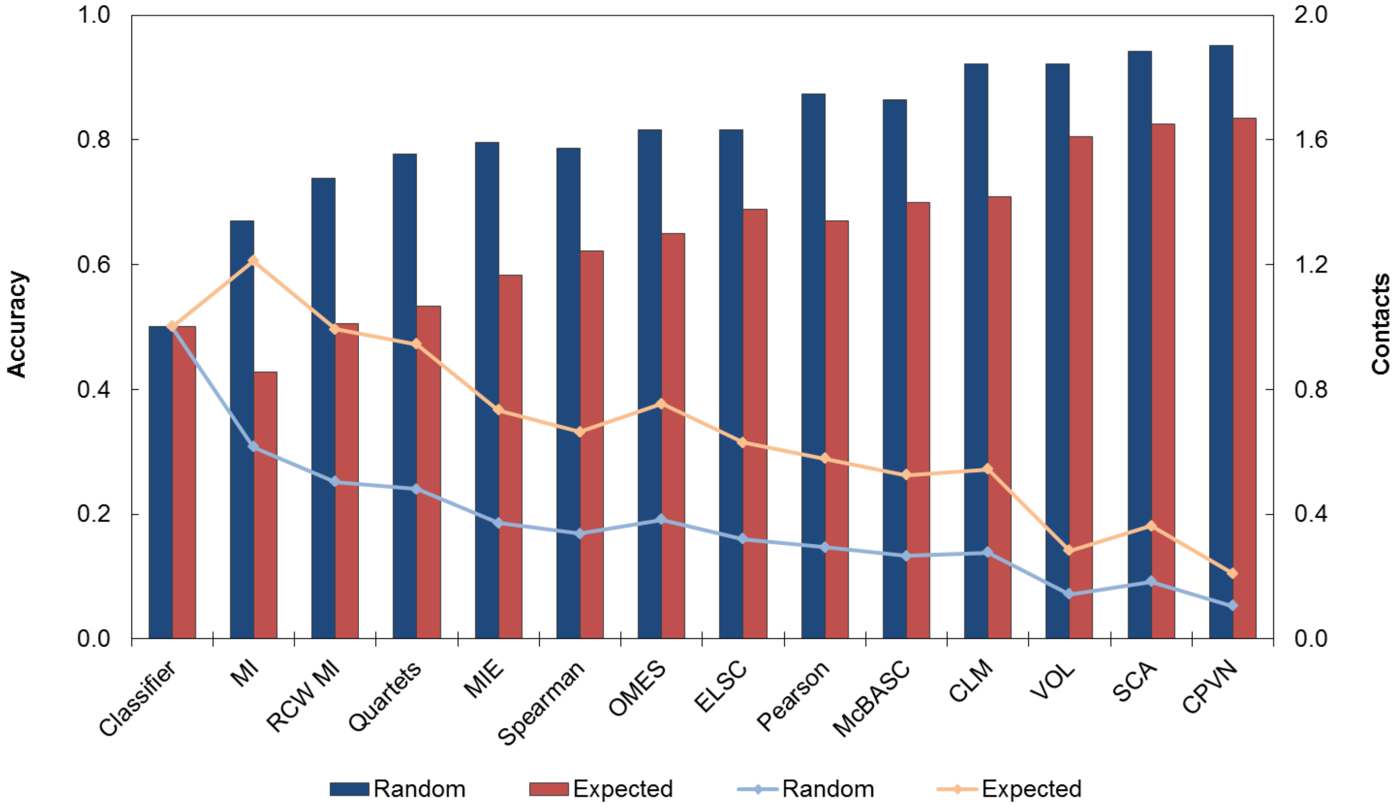

Outline

1. Introduction
2. Motivation
3. Objectives
4. Results
5. Summary

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- Source code at https://github.com/fmadeira/pycoevol

Thanks for your attention!

Computational Analysis of Protein Coevolution and Interaction

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