



Methods in Drug Development

Protein Structure Prediction

Homology models

(Situation before most recent structure prediction successes)

Protein of unknown
structure

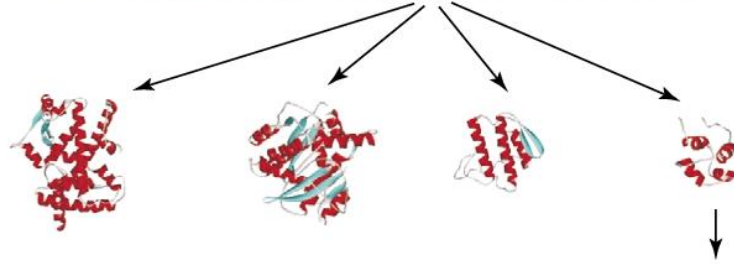


Fold assignment



Target sequence:

MELAFRESLKKMPGK...SKENFSQLEMSRSNYSIESGKSDPTITILEQIVKLTNSTLVVDLI



Target sequence:

Homolog 1, no 3D structure:

Homolog 2, no 3D structure:

Template 1, 3D structure:

Template 2, 3D structure:

.MELAFRESLKKMPGK...SKENFSQLEMSRSNYSIESGKSDPTITILEQIVKLTNSTLVVDLI
...MIGGRKSLGKR...TQEEIASHIGVSRARYSHYENGSE.PDYDTLQKLADYFQVTTDYLLT
...MFSENKKCRKQKRLTQQNMADKLGITAPAYTAYELGSRE.PDYKTLINISNILDVSLDYLLK
MNTQLMGERIARRKKLIRQAALGKMGVGSNVAISQWERSETE.PNGENLLALSKALQCSPDYLLK
...SISSRVKSKRIQLGLNQAELAQKVGTTQQSIEQLENGKTRP...RFLPELASALGVSDWLLN

Homology models

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Protein of unknown structure



Fold assignment



Sequence-structure alignment



Model building
(sidechains, loops)

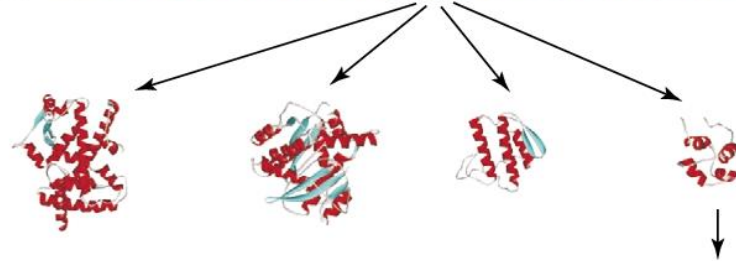


Model refinement



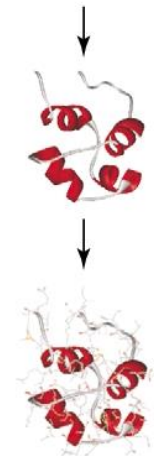
Model assessment

Target sequence: MELAFRESLKMPGK...SKENFSQLEMSRSNYSRIESGKSDPTITLLEQIVKLTNSTLVVDLI



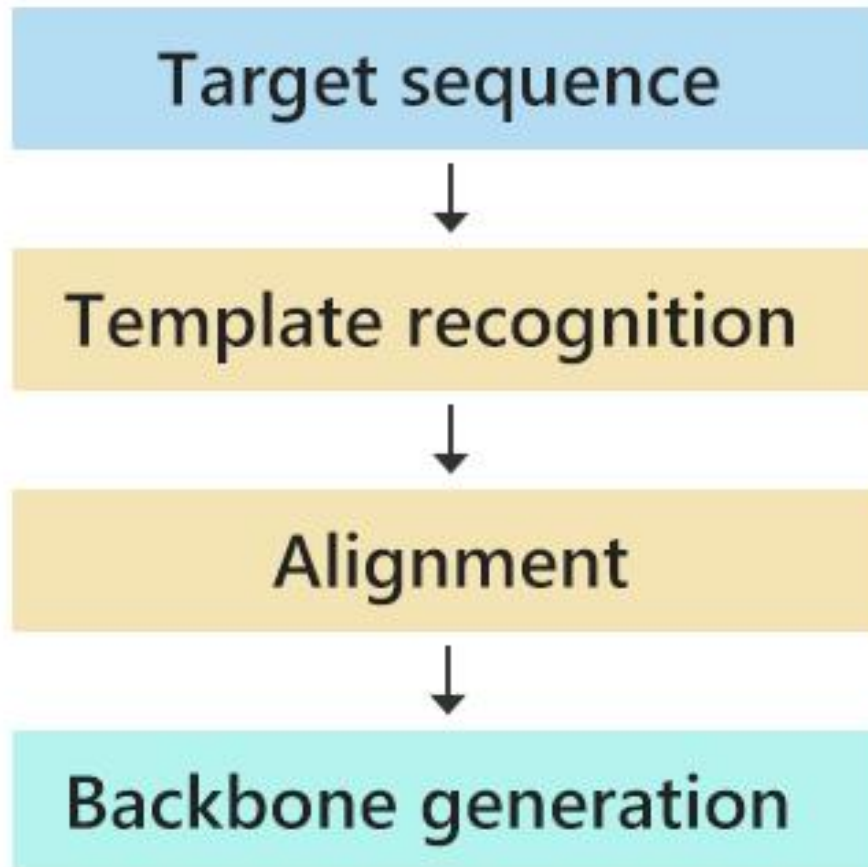
Target sequence:
Homolog 1, no 3D structure:
Homolog 2, no 3D structure:
Template 1, 3D structure:
Template 2, 3D structure:

.MELAFRESLKMPGK...SKENFSQLEMSRSNYSRIESGKSDPTITLLEQIVKLTNSTLVVDLI
...MIGGRKSLGK...TQEEIASHIGVSRARYSHYENGSE.PDYDTLQKLADYFQVTTDYLLT
...MFSENKKCRKQKLTQQNMADLGITAPAYTAYELGSRE.PDYKTLINISNILDVSLDYLLK
MNTQLMGERIARRKKLIRQAALGKMGVGSNVAISQWERSETE.PNGENLLALSKALQCSFDYLLK
...SISSRVKSKRIQLGLNQAEALQKVGTTQQSIEQLENGKTRP...RFLPELASALGVSDWLLN

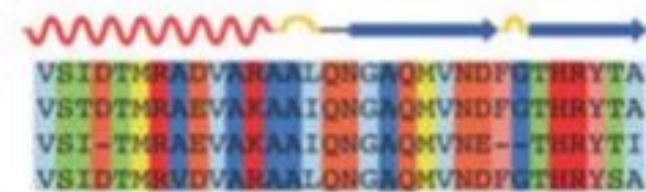
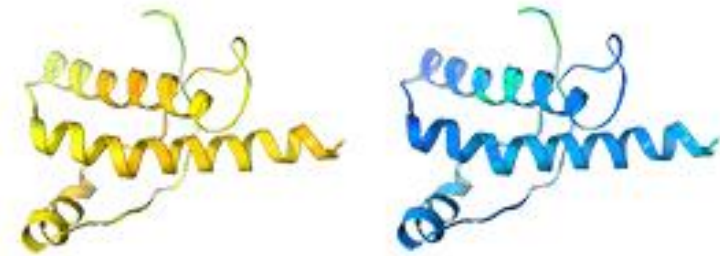


Homology models

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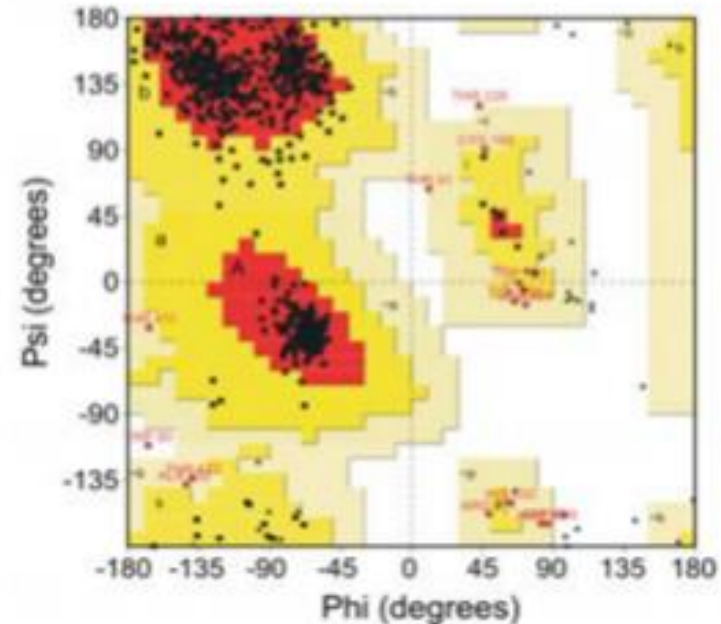
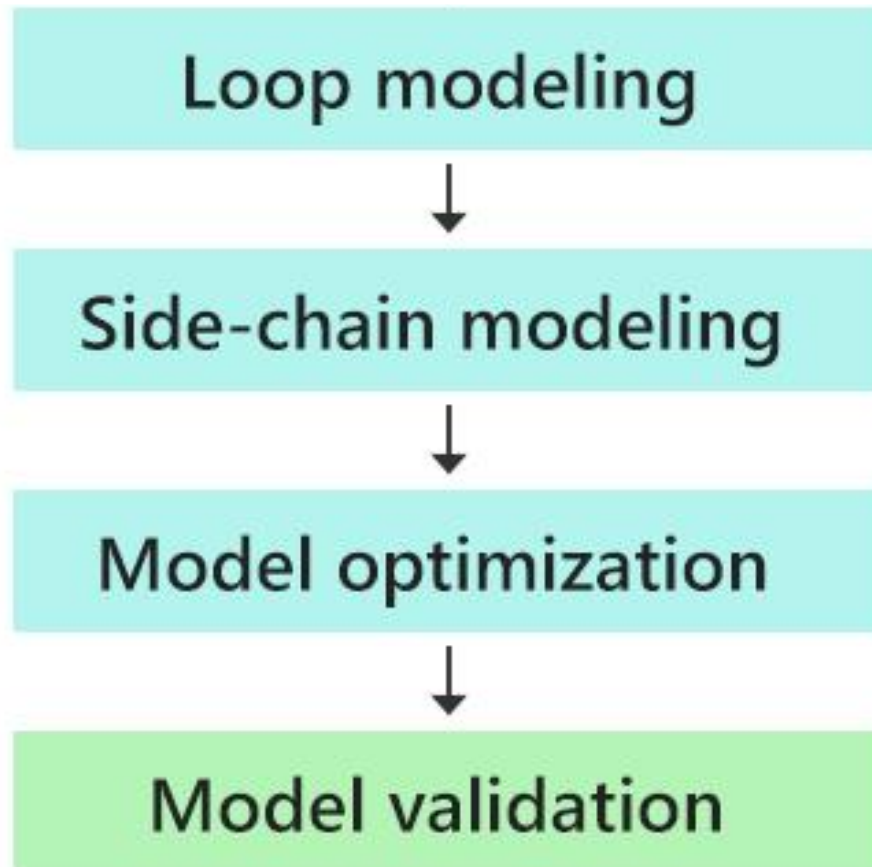
VSIDTMRADVARAALQNGAQMVNDFGTHRYTA



VSIDTMRADVARAALQNGAQMVNDFGTHRYTA
VSTDTMRAEVAKAAIQNGAQMVNDFGTHRYTA
VSI-TMRAEVAKAAIQNGAQMVNE--THRYTI
VSIDTMRADVARAALQNGAQMVNDFGTHRYSA

Homology models

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Recent advances in structure prediction

Groups / strategies that are leading the development / competing:

- AlphaFold (A7D), DeepMind, distance info --> smooth restraints
- Xu, RaptorX, Distance info --> Crystallography and NMR System (CNS)
- Zhang Server
- Baker lab, distance info, angle info, Rosetta

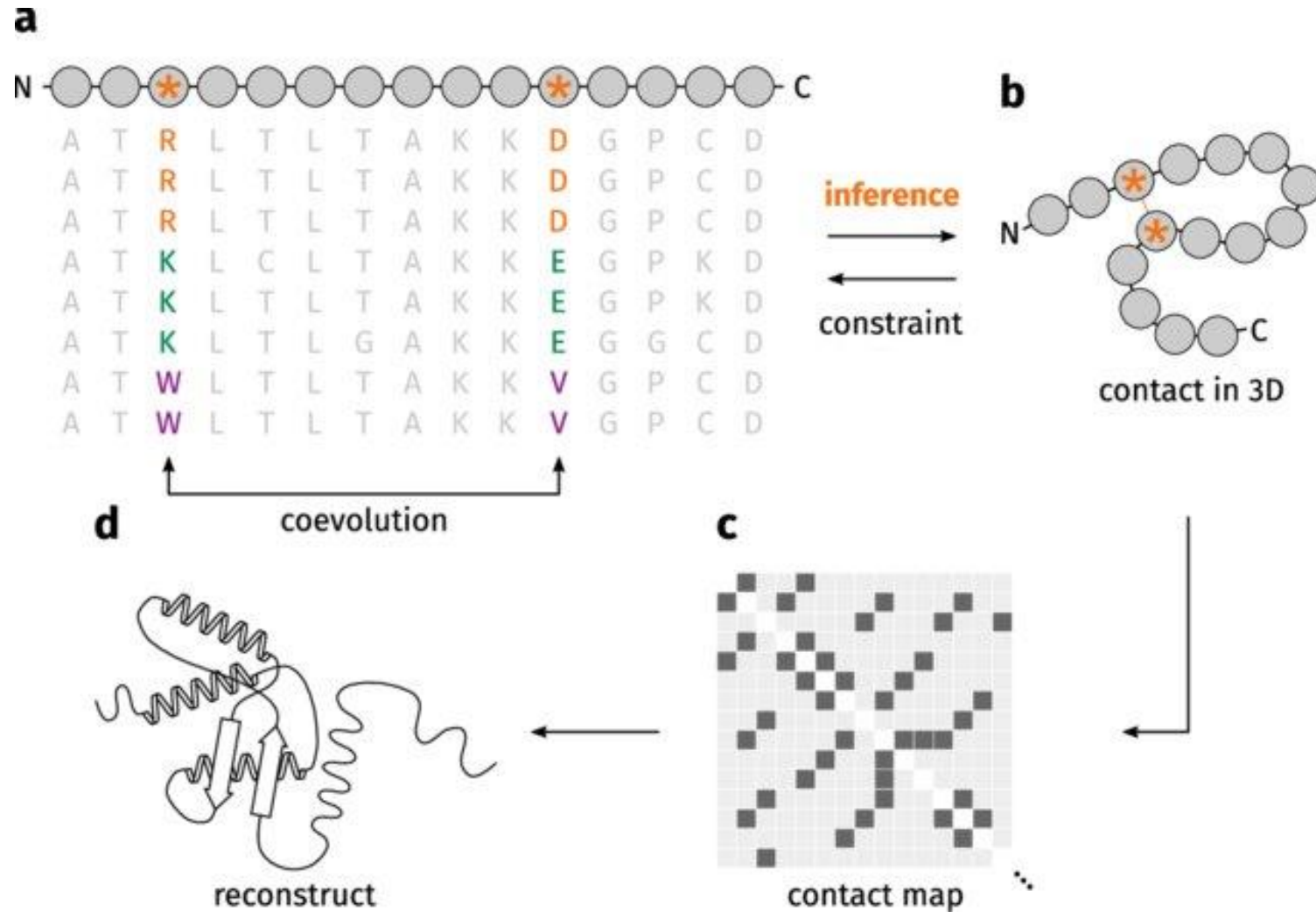
Multiple sequence alignment

Protein Mdm4 (MDM4) UniProt 
Homo sapiens

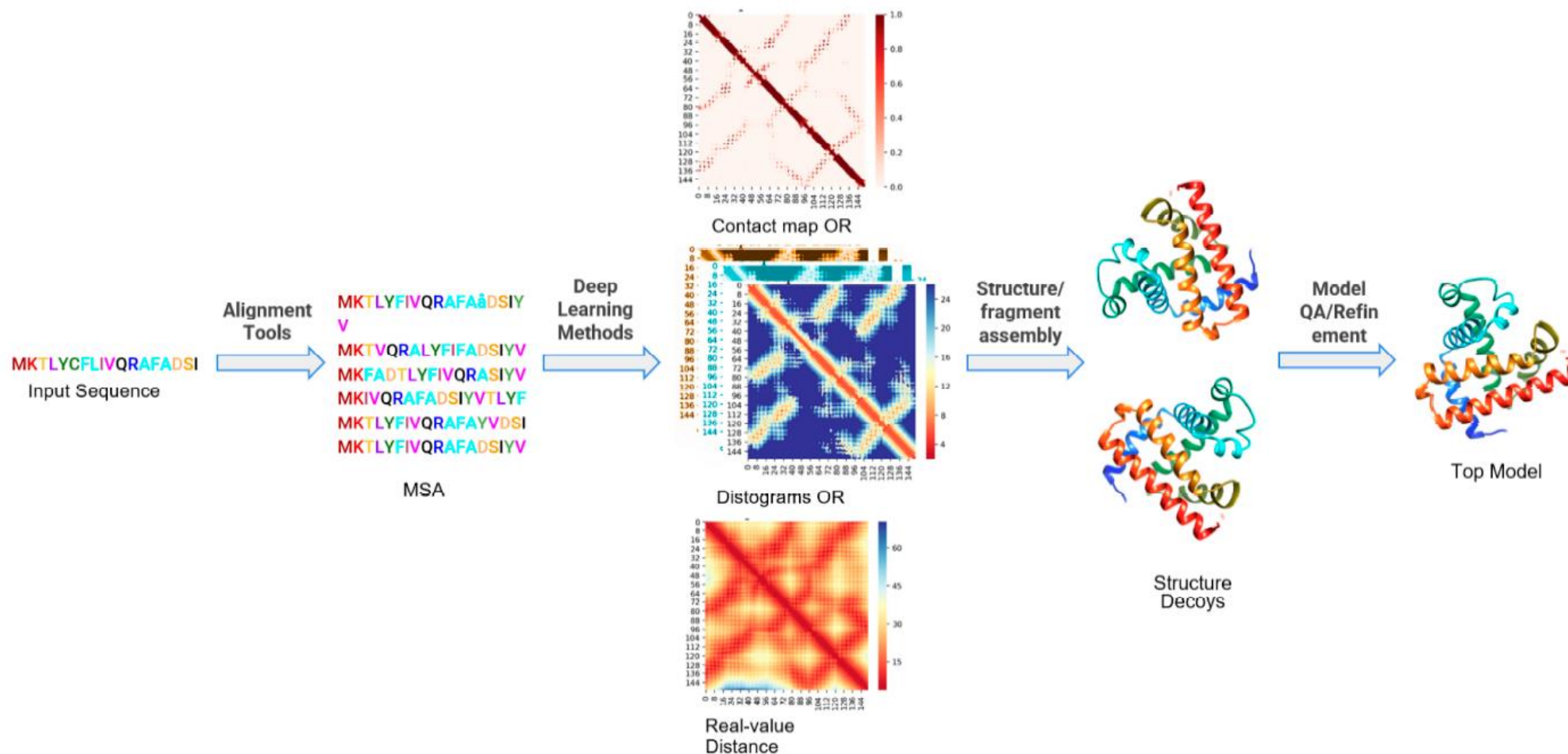
Alignments:  qfo          



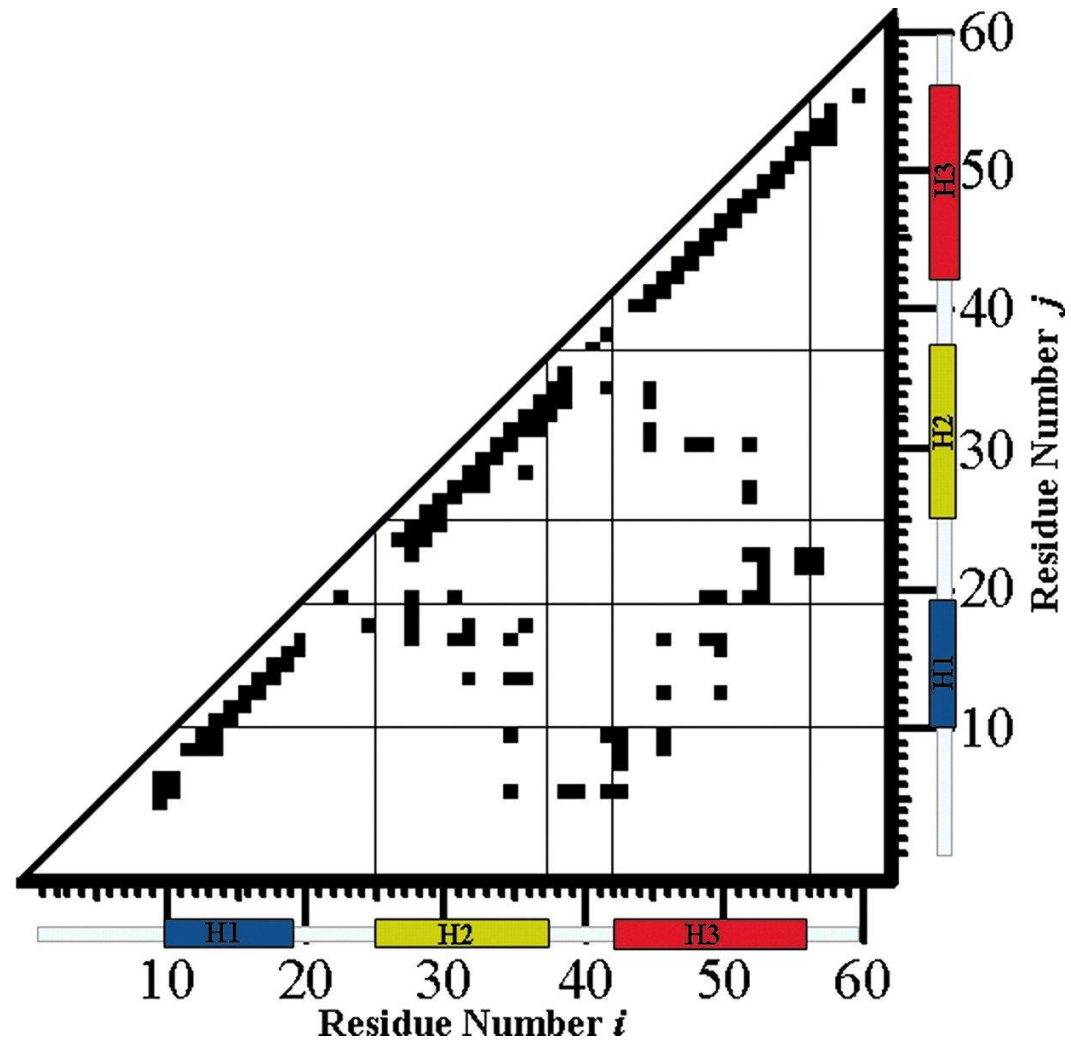
Co-evolution data --> Contact map



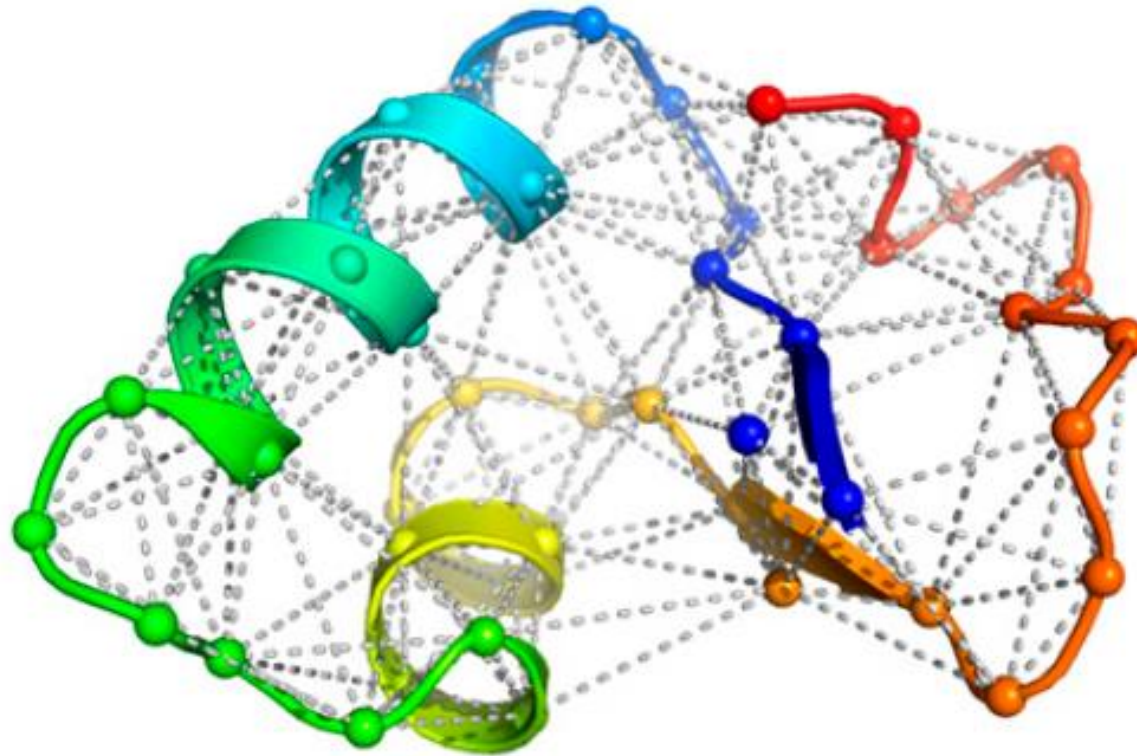
Sequence similarities --> Contact map



Contact map



Structure calculation



AI component

- Use of «deep neural networks»
- Better predict contact maps