Interprotein coevolution: bridging scales from residues to genomes

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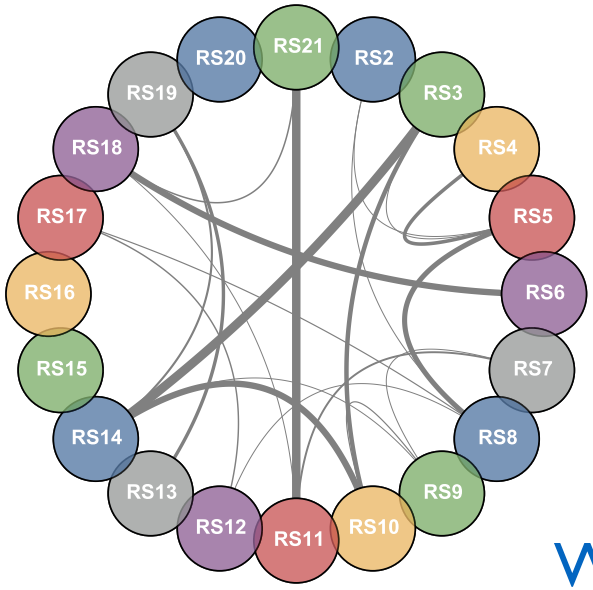
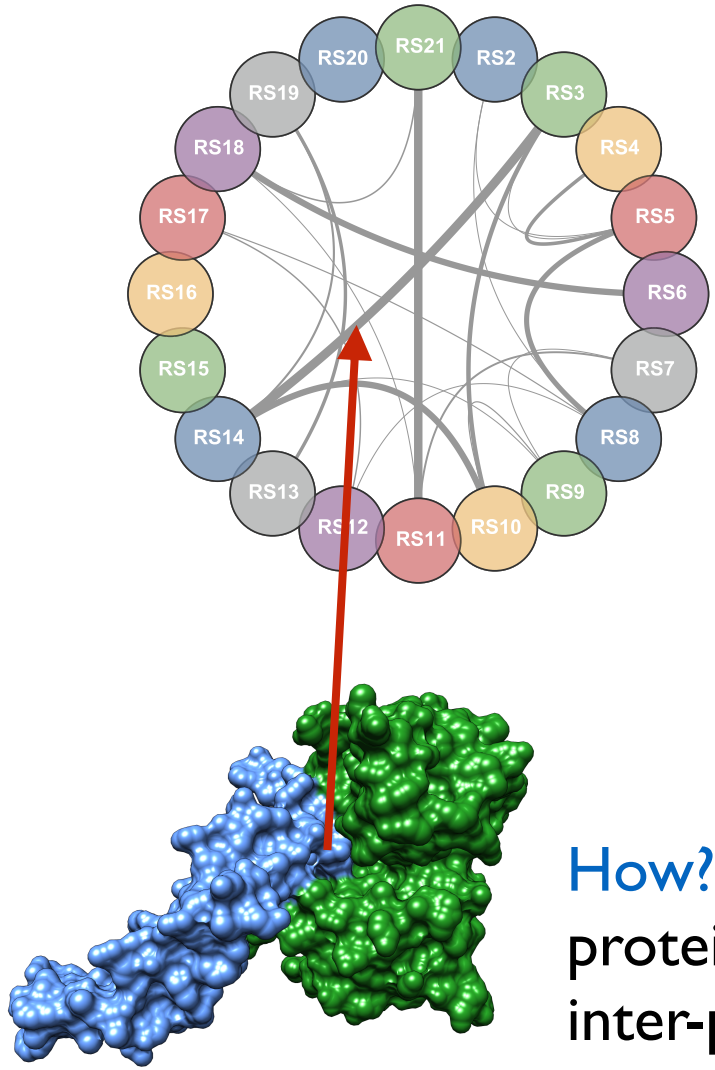
The different scales in protein-protein interaction



Who with whom?

protein-protein interaction networks

The different scales in protein-protein interaction

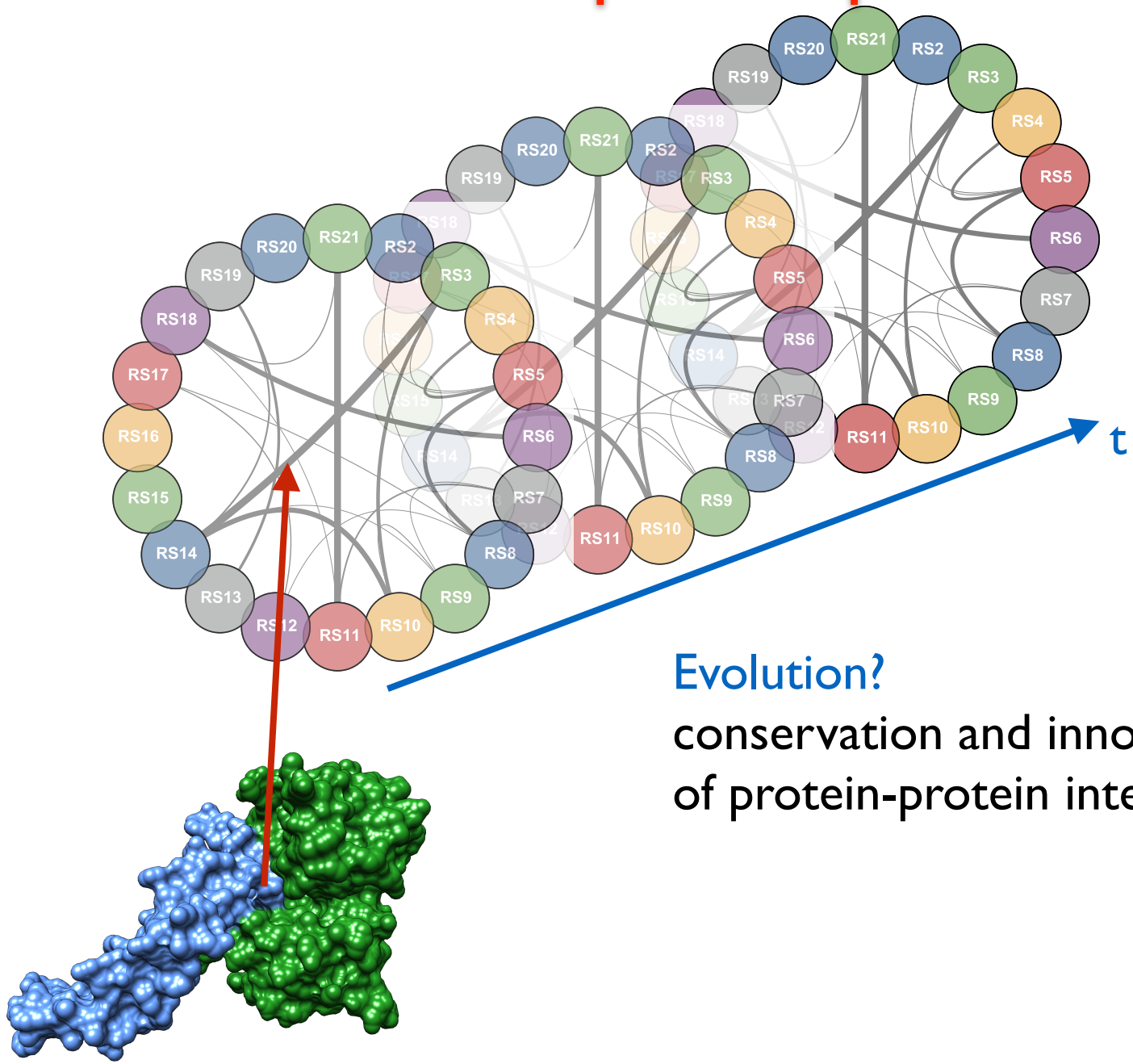


How?

protein-protein interfaces

inter-protein residue contacts

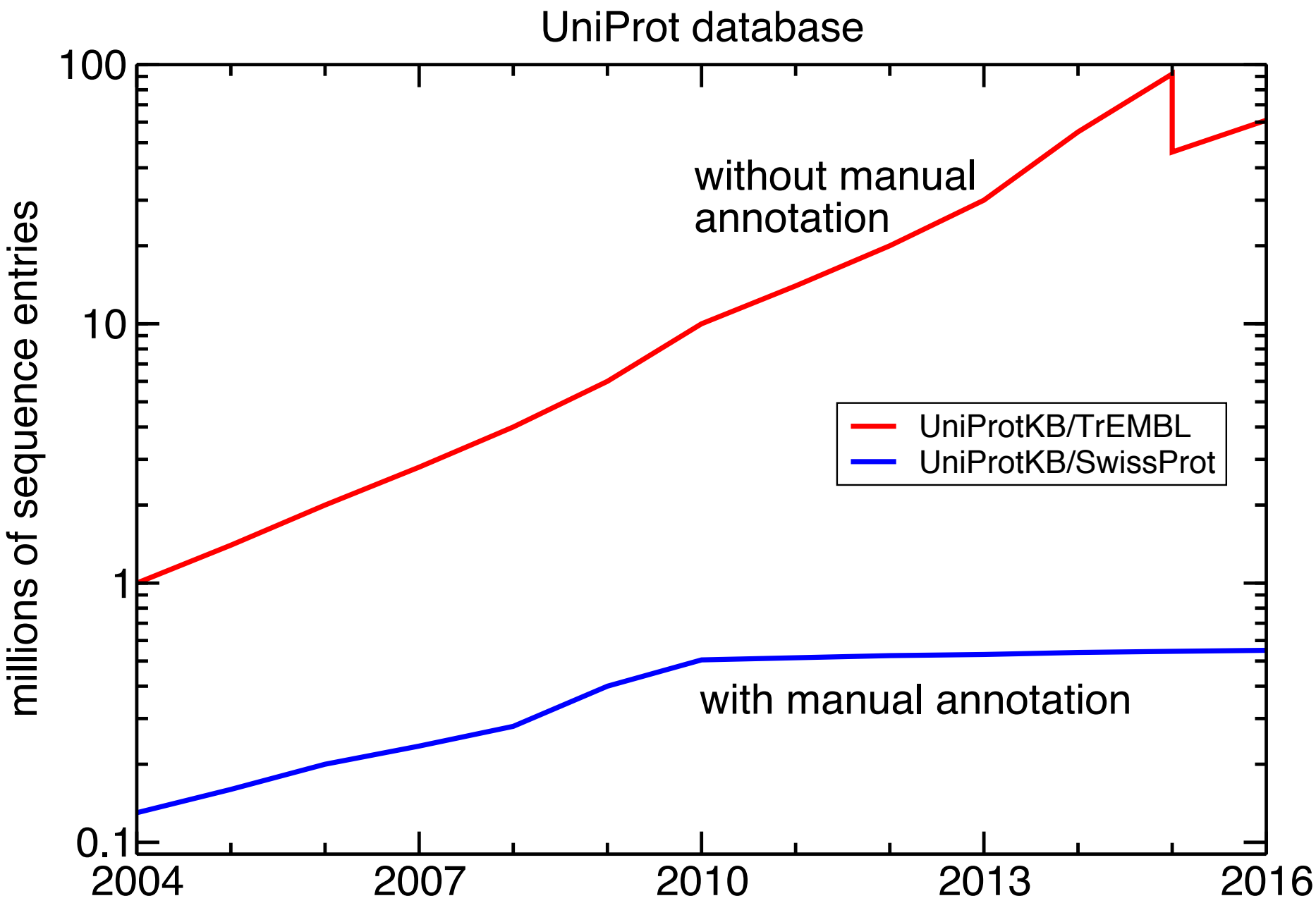
The different scales in protein-protein interaction



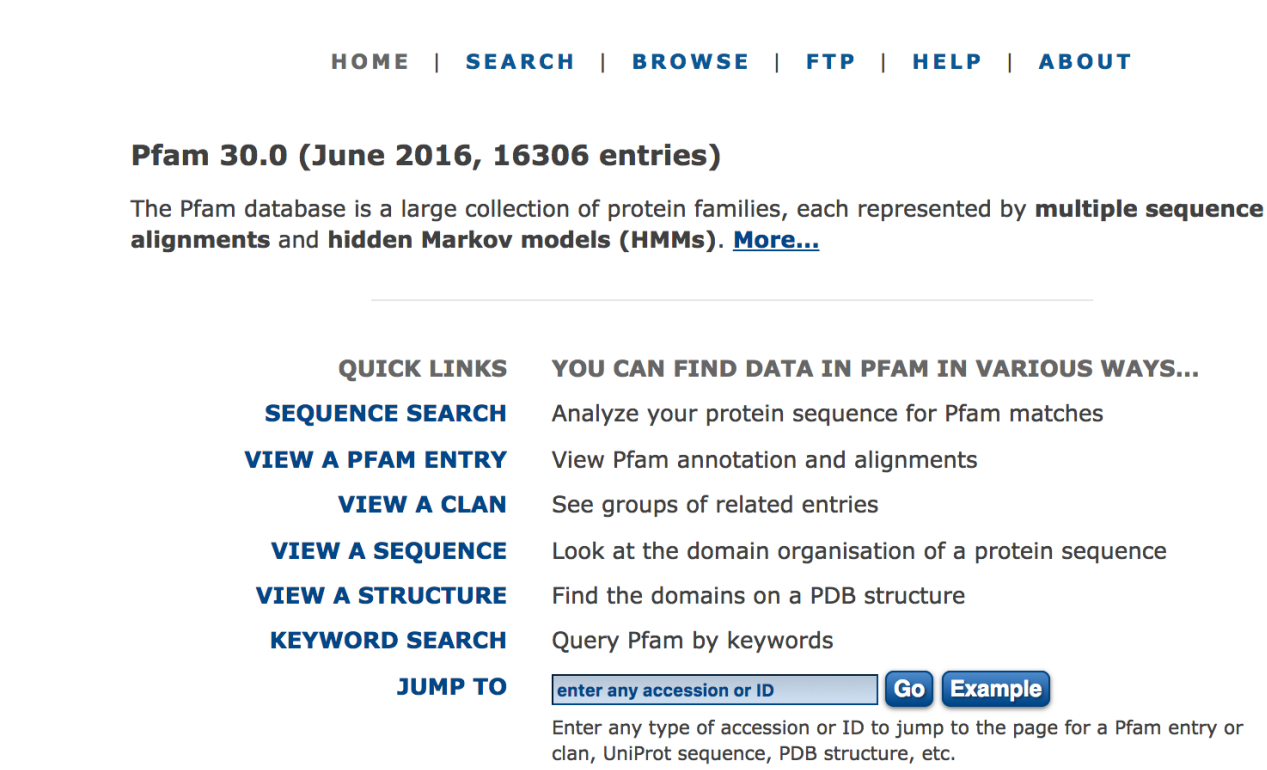
Evolution?

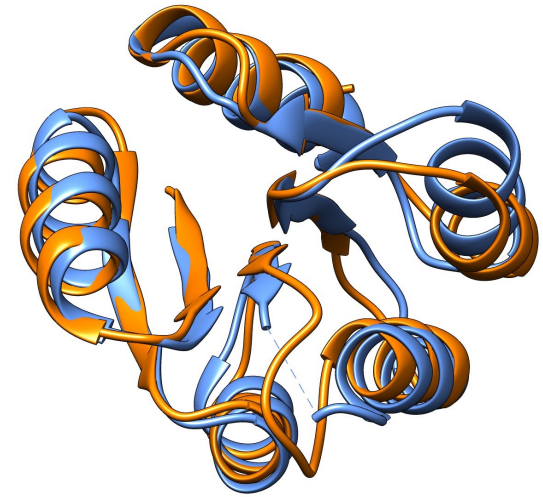
conservation and innovation
of protein-protein interactions

Protein sequence data are accumulating…



…and are classified into homologous protein families





Homologous proteins

- frequently 10^3–10^6 proteins per family
- common evolutionary ancestry
- conserved 3D structure and biological function
- diverged amino-acid sequences (~20-30% sequence identity)
- sequence variability contains information about structure and function
- >5000 families without example structures

Statistical physics

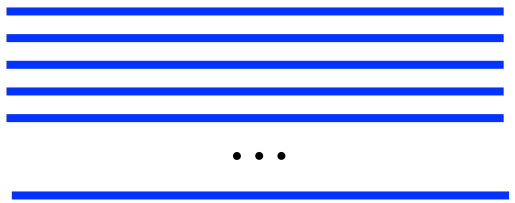
From models over data to thermodynamic observables:

$$P(\overline{S}) \sim e^{-\beta \mathcal{H}(\overline{S})}$$

$$\mathcal{H}(\overline{S}_1) = -\sum_{i<j} J_{ij} S_i S_j - \sum_i h_i S_i$$

sample from model

$$\{\overline{S}^\mu\}_{\mu=1,\ldots,M}$$



$$\langle \mathcal{O}_a(\overline{S}) \rangle_P \simeq \frac{1}{M} \sum_\mu \mathcal{O}_a(\overline{S}^\mu)$$

e.g. $\langle S_i \rangle_P, \langle S_i S_j \rangle_P$

Inverse statistical physics

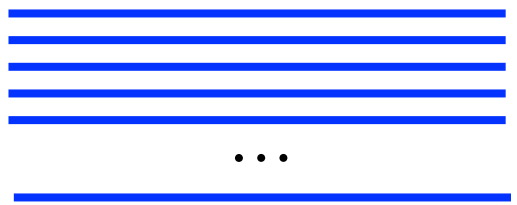
From data over observables to models

$$P(\overline{S}) \sim e^{-\beta \mathcal{H}(\overline{S})}$$

$$\mathcal{H}(\overline{S}_1) = -\sum_{i<j} J_{ij} S_i S_j - \sum_i h_i S_i$$

Data:

$$\{\overline{S}^\mu\}_{\mu=1,\ldots,M}$$



$$\langle \mathcal{O}_a(\overline{S}) \rangle_P \simeq \frac{1}{M} \sum_\mu \mathcal{O}_a(\overline{S}^\mu)$$

e.g. $\langle S_i \rangle_P, \langle S_i S_j \rangle_P$

Inverse statistical physics

How to construct $P(\overline{S}) \sim e^{-\beta \mathcal{H}(\overline{S})}$ from data?

- coherence with data

$$\langle \mathcal{O}_a(\overline{S}) \rangle_P = \frac{1}{M} \sum_{\mu} \mathcal{O}_a(\overline{S}^{\mu})$$

- maximum entropy principle (least constrained model)

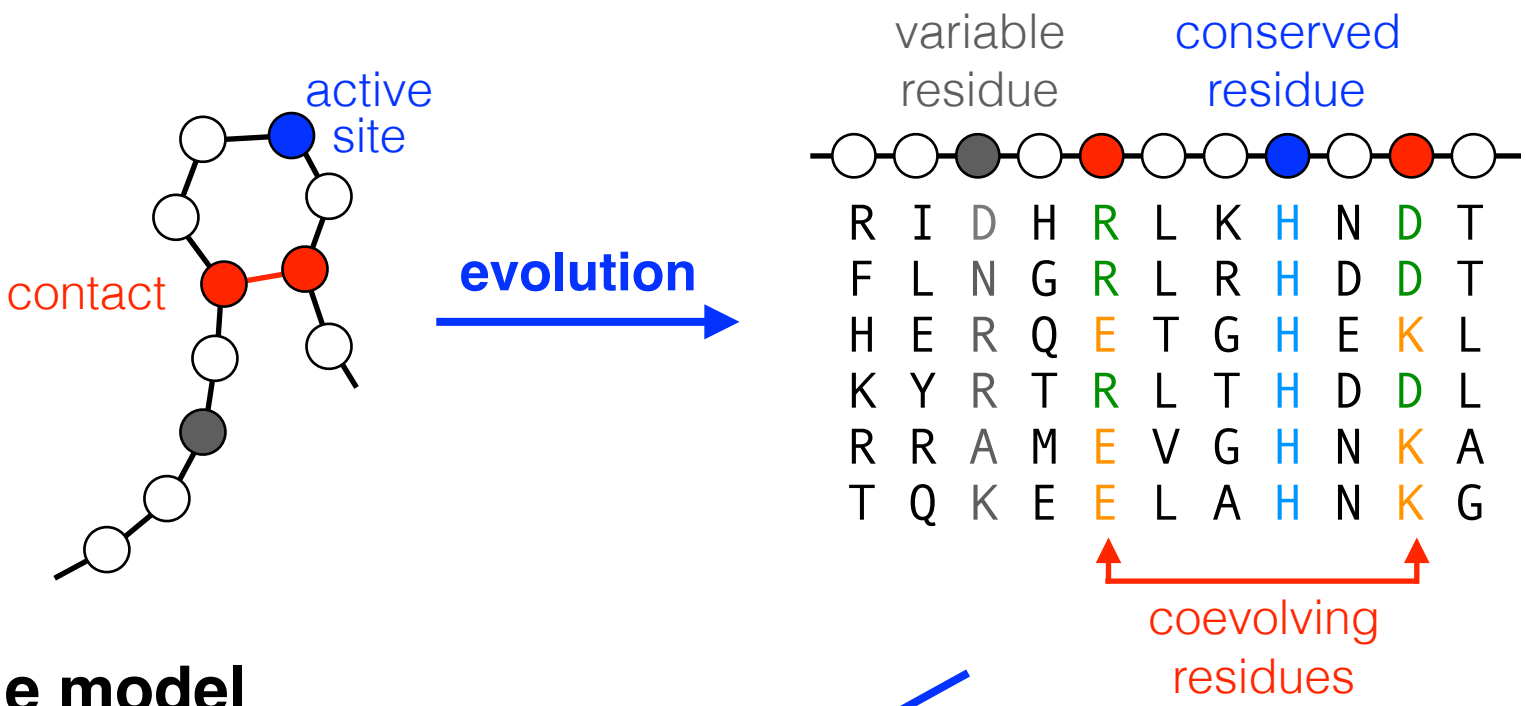
$$-\sum_{\overline{S}} P(\overline{S}) \log P(\overline{S}) \rightarrow \max$$

➡ analytical form of model

$$\mathcal{H}(\overline{S}) = -\sum_{a} \lambda_a(\overline{S}) \mathcal{O}_a(\overline{S})$$

selection of observables
requires priori biological knowledge

Conservation and coevolution in proteins



Profile model

$$P(a_1, ..., a_L) \sim \exp\left\{\sum_i h_i(a_i)\right\}$$

statistical modeling

Direct Coupling Analysis (DCA)

$$P(a_1, ..., a_L)$$

$$\sim \exp\left\{\sum_{i<j} J_{ij}(a_i, a_j) + \sum_i h_i(a_i)\right\}$$

strong couplings -> residue contacts

[Weigt et al, PNAS '09]

[Morcos et al, PNAS '11]

Interactions between protein families

Family 1

```
>F7XUK6_MIDMI/129-211
LAQQLEKRISFRKAAKRLIQNAM.R......M.G..AEGIKIKISGRIG.G.AEIARDQQ
YNEGRVPL..HTLRMMIDYGTAEAH..TTYGRIGVKVWV
>B3SEY6_TRIAD/119-201
VAEQLEKKVSFRKAVKRAISNAM.K......M.G..AKGIKISVSGRLG.G.AEIARTEW
YKEGRVPL..HTLRAIVKYDMAEAH..TIYGLIGVKVWV
>RS3_ORITB/122-204
IAQQLERRQSFKKVMKKAIHASM.K......Q.G..AKGIKIICSGRLG.G.VEIARSES
YKEGRVPL..QTIRADIRYAFAEAI..TTYGVIGVKVWV
>RS3_RICPR/123-205
IAAQLEKRVSFRKAMKTAIQASF.K......Q.G..GQGIRVSCSGRLG.G.AEIARTEW
YIEGRMPL..HTLRADIDYSTAEAI..TTYGVIGVKVWI
>E1X0L6_HALMS/119-201
IASQLEKRVAFRRAMKKVMQSAF.R......A.G..VKGIRVRTAGRLG.G.AEMARAEG
YSERKVPL..HTLRADIDYSTAEAH..TTYGVIGVKVWV
>I7HEJ8_9HELI/120-202
IATQLEKRVAFRRAMKKVMQAAM.K......A.G..AKGIKVKVSGRLA.G.AEMARTEW
YMEGRVPL..HTLRAKIDYGFAEAM..TTYGIIGVKVWI
>M4VDL1_9DELT/120-202
IAMQLEKRISWRRALKKAIAAAT.K......G.G..VRGIKVRVSGRLD.G.AEIARSEW
YNEKSVPL..HTLRADIDYGTAEAL..TAYGIIGMKVWI
>RS3_HYPNA/120-202
IARQLERRASFRRAMKRSIQSAM.R......L.G..AEGVKVVVSGRLG.G.AEIARTEK
YAEGSVPL..HTLRADIDYGTAEAT..TTYGIIGVKVWV
>C0QW02_BRAHW/94-176
VARQLEMRVAFRRAMKSVITQAM.K......K.G..AKGIKVMCSGRLA.G.ADIARTEQ
YKNGSVPL..HTLRANIDYGTAEAL..TTFGIIGIKVWI
>J9Z1W5_9PROT/119-201
IARQLEKRVAFRKAMKKSGQSAI.K......L.G..AKGIKIVCGGRLG.G.AEIARSEK
FSEGSVPL..HTLRADIDYATARAL..TTYGIIGIKVWL
>RS3_MARMM/120-202
IAQQLERRVAFRRAMKRSMQSAM.R......M.G..AKGCKIVCGGRLG.G.AEIARTEQ
YNEGSVPL..HTLRADIDYGTCEAK..TAMGIIGIKVWI
>G0GFA5_SPITZ/122-204
IAGQLEHRASFRRVMKLAVANAM.K......A.G..VQGIKVRVSGRLG.G.AEIARSEV
QMAGRVPL..HTLRADIDYGFAEAR..TTYGVIGVKVWI
>V6DFZ5_9DELT/122-204
ISEQLEKRGSFKKAMKRAALDVM.K.......SG..AKGVKIRCAGRLG.G.AEIARDEW
IRVGSTPL..HTLRSDIDYGFVEAH..TTYGVIGIKVWI
>RS3_NEOSM/120-203
IAFQLEKRSSFRRVIKKAIATVM.R......ESD..VKGVKVACSGRLS.G.AEIARTEV
FKEGSIPL..HTMRADIDYWVAEAH..TTYGVIGVKVWI
>I0III3_PHYMF/124-207
IAEQLAKRASFRRVMKMKAEAAM.N......CGV..CKGVKIMLSGRLG.G.HEMSRSEV
VSLGSIPL..ATLQANVDYGFAISK..TTYGTIGVKVWI
>F0SJ92_RUBBR/120-202
IAQQLGKRGSFRRALKRSMEQVM.D......A.G..AHGVKIELSGRLG.G.AEMSRKEK
GSRGSIPL..STLQRHVDYGYTTAR..TAQGIIGIKVWI
. . .
```

Family 2

```
>RS14_NEOSM/47-100
KLNSLPRNSSPARSKNRCSITGR..PRGYY..RKFGI..SRIQLRVLANWGKLPGVVKSS
>I0AI30_IGNAJ/35-88
ALQKLPRNSSVTRLKNRCMFTGR..ARAYY..RKFGV..SRLVLREMALRGEIPGLKKSS
>I6YSF0_MELRP/36-88
.LQLLPRNSAPTRAHNRCLISGR..PRGYY..RKFGI..SRLVLREMALRGEIPGLKKSS
>I0IIH6_PHYMF/34-87
ALSQLPRDASPTRLVTQCAITGR..TRAVY..RKFNV..SRIVLRELALQGKIPGMKKAS
>RS14_CHLT3/35-88
ALRKLPRDSSPTRLKNRCSITGR..AKGVY..KKFGL..CRHILRKYALEGKIPGMKKAS
>RS14_PROA2/35-88
ALSKLPRNSSATRVRNRCVLTGR..GRGVY..EKFGL..CRHMFRKLALEGKIPGVKKAS
>D6XYV1_BACIE/35-88
ALSKLPRDSAPSRLTRRCKATGR..PRGVL..RKFEL..SRIKFRELAHKGQIPGVRKAS
>I0JIY2_HALH3/35-88
ALRKLPRDSSPTRVKRRCELSGR..PRGYM..RKFDM..SRIAFRELAHKGQIPGVKKAS
>RS14_EXIS2/36-88
.LSKLPRNSSAVRLHNRCSITGR..PHGYI..GKFGI..SRIKFRDLAHKGQIPGVKKAS
>RS14_STRR6/36-88
.LSKLPRNASPTRLHNRCRVTGR..PHSVY..RKFGL..SRIAFRELAHKGQIPGVTKAS
>G0VNI1_MEGEL/35-88
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>R7PS46_9FIRM/35-88
ALSKLPRNASPTRLHNRCKLTGR..PHGYL..RKFGV..CRNQFRELAYRGEIPGVRKAS
>F8L373_SIMNZ/47-100
KLNSLPKNSSPIRRRNRCKMTGR..CRGYL..RKFQI..SRLCFREMANDGSIPGVVKAS
>F8L0V7_PARAV/47-100
ALNKMPRDSSPIRLRNRCQLTGR..XRGYL..RKFKL..SRLTFREMALAGLLPGVTKSS
>D6YVK9_WADCW/47-100
QLNKMRRDTSPVRLRNRCQITGR..CRGYL..SKFKV..SRLVFREMASIGMIPGVTKSS
>L7VJR0_9FLAO/35-88
ALQKLPKNSCTVRLRNRCKLTGR..SRGYM..RKFGV..SRISFRNLVNFGLIPGVKKSS
>C7NDL0_LEPBD/41-94
ELSKLPRNASPTRVRNRCQINGR..PRGYM..REFGI..SRVMFRQLAGEGVIPGVKKSS
>RS14_FUSNN/41-94
ELNKLPKDSSAVRKRNRCQLDGR..PRGYM..REFGI..SRVKFRQLAGAGVIPGVKKSS
>K0P015_9BACT/35-88
ALDKLPKNSSPVRLRNRCNITGR..ARGYI..RRFGI..SRLVFRKWALEGKLPGIRKAS
>RS14_AMOA5/35-88
ALDKLPKNASPVRVRNRCKITGR..ARGYM..RKFGI..SRIVFREWAAQGKIPGVIKAS
>I4ALV0_FLELS/42-94
.LDKLPKDSSPVRLHNRCRLTGR..PRGYM..RRFGI..CRVVFREMANDGKIPGVTKSS
>RS14_SALRD/35-88
ELQKLPRDSSPVRQNNRCELCGR..QRGYL..RKFGV..CRICFRELALEGKIPGIRKAS
>C7PU84_CHIPD/35-88
ELDQLPRNASPVRLHNRCQLSGR..PKGYM..RHFGM..CRNMFRDLALAGKIPGVRKAS
>F4KWV6_HALH1/35-88
ELDKLPRNSNPIRMHNRCQLTGR..PKGYM..RQFGL..CRVKFREMALYGKIPGITKSS
. . .
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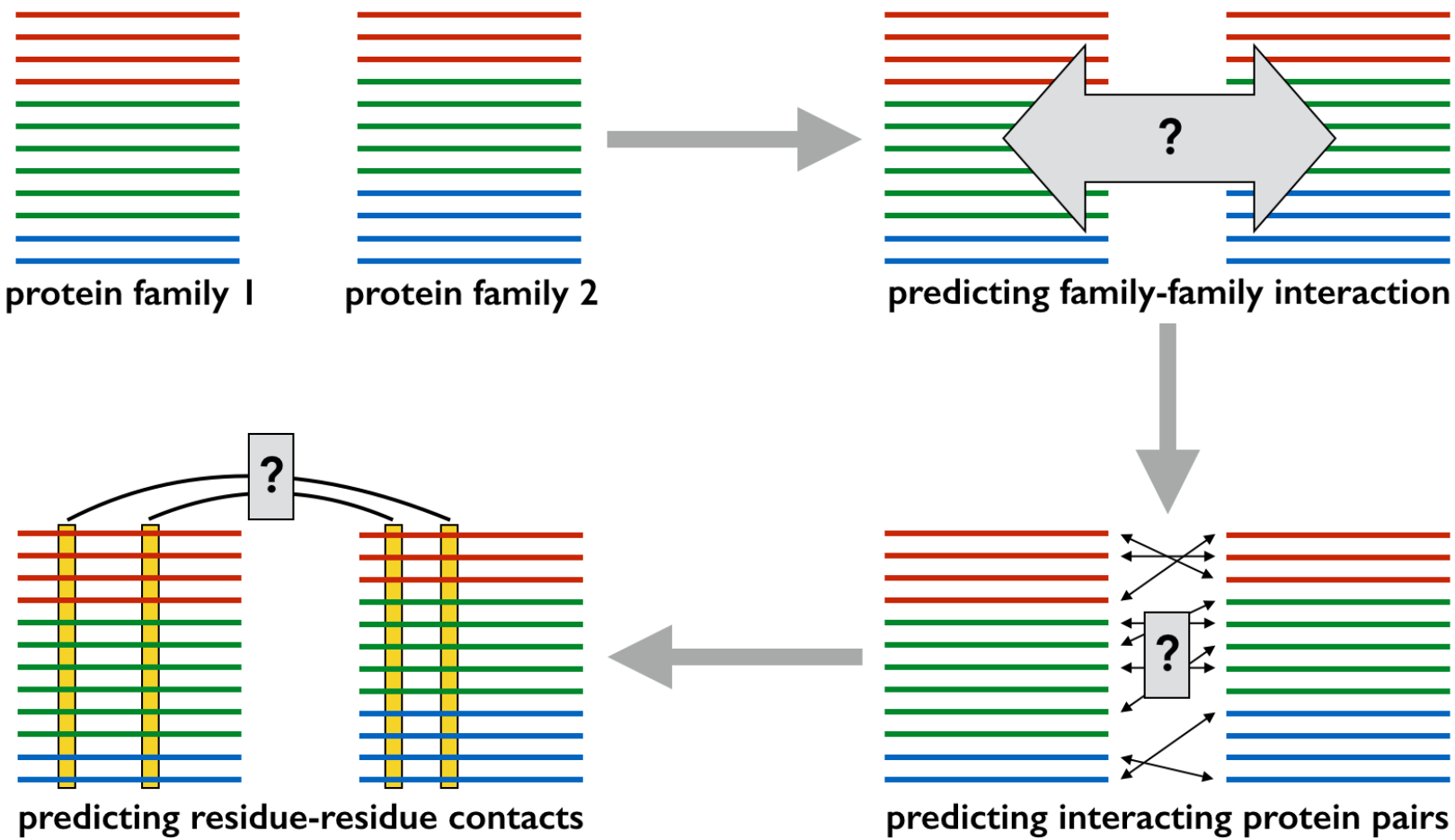
Interactions between protein families



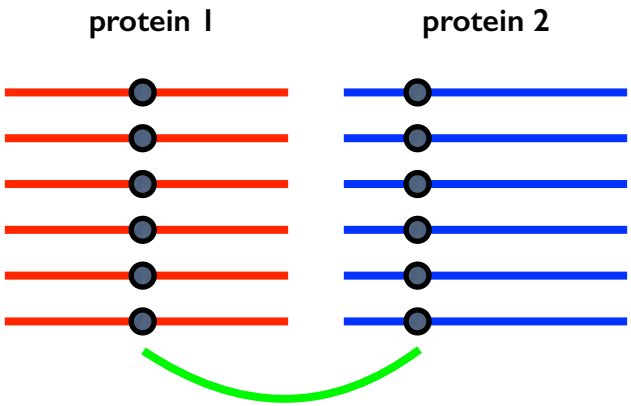
What can we learn from the empirical sequence variability:

- do the families interact?
- which specific proteins interact?
- which residues are in contact?

➡ relation between protein structure/function and evolution

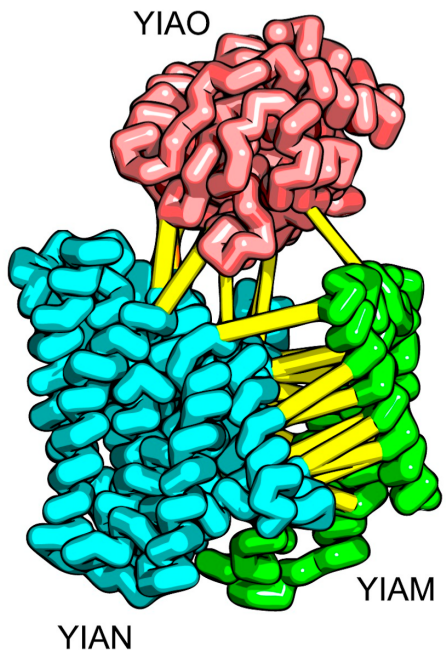
Prediction of inter-protein residue contacts

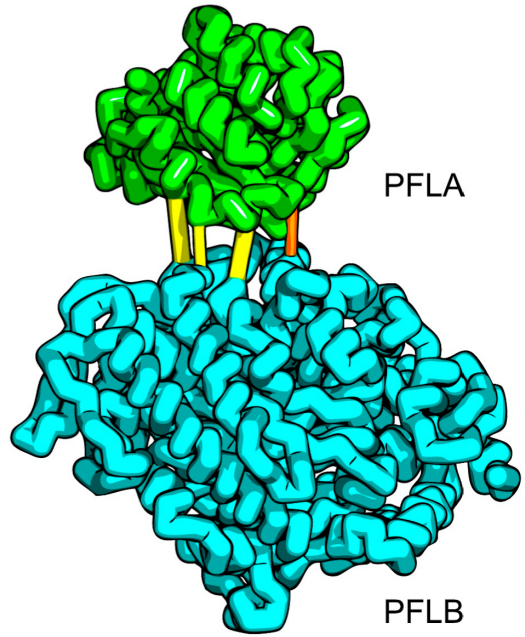
joint MSA of protein families



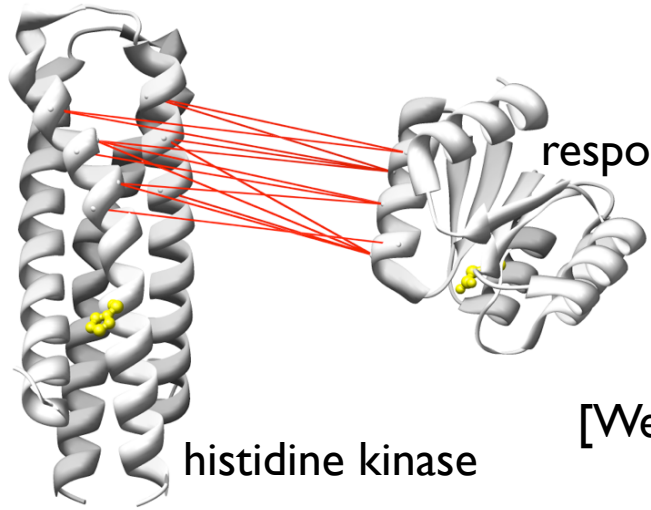
DCA

Strong inter-protein couplings predict contacts



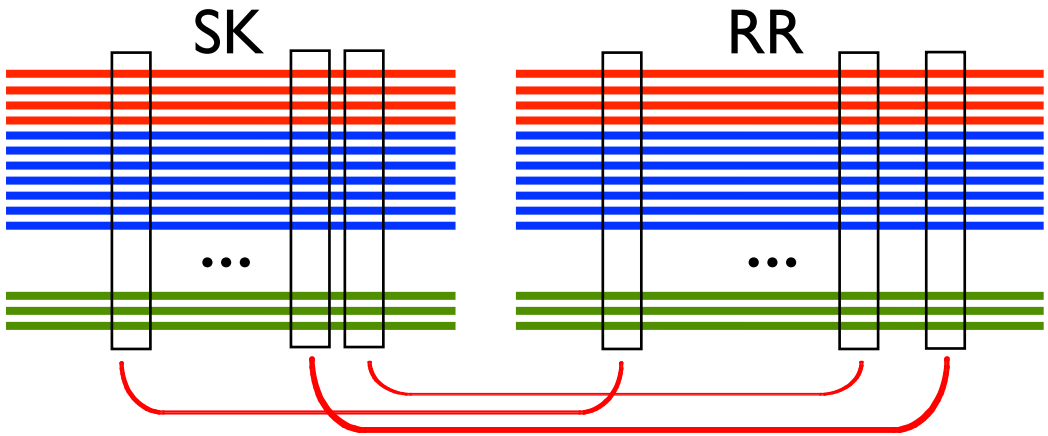


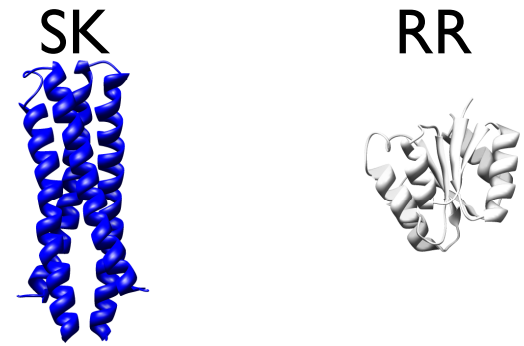
[Ovchinnikov et al., *eLife* '14]



[Weigt et al., PNAS '09]

In silico prediction of high-resolution structures of transient protein complexes

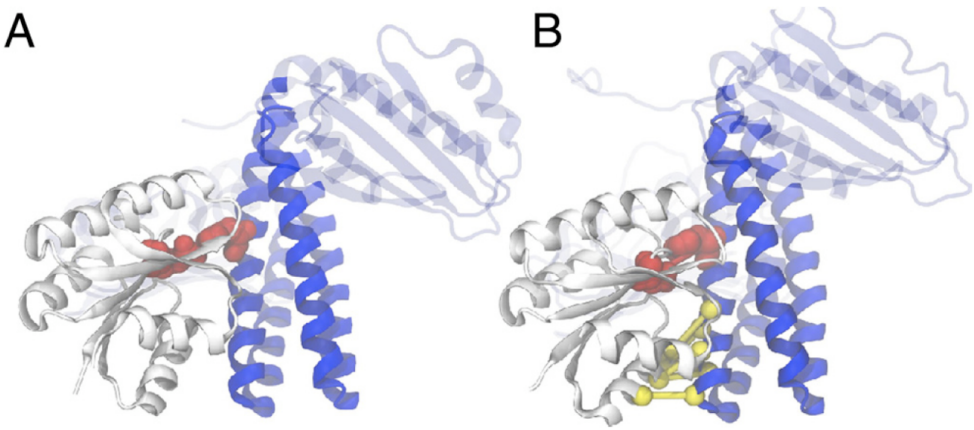




DCA identifies residue contacts

protein monomer structures

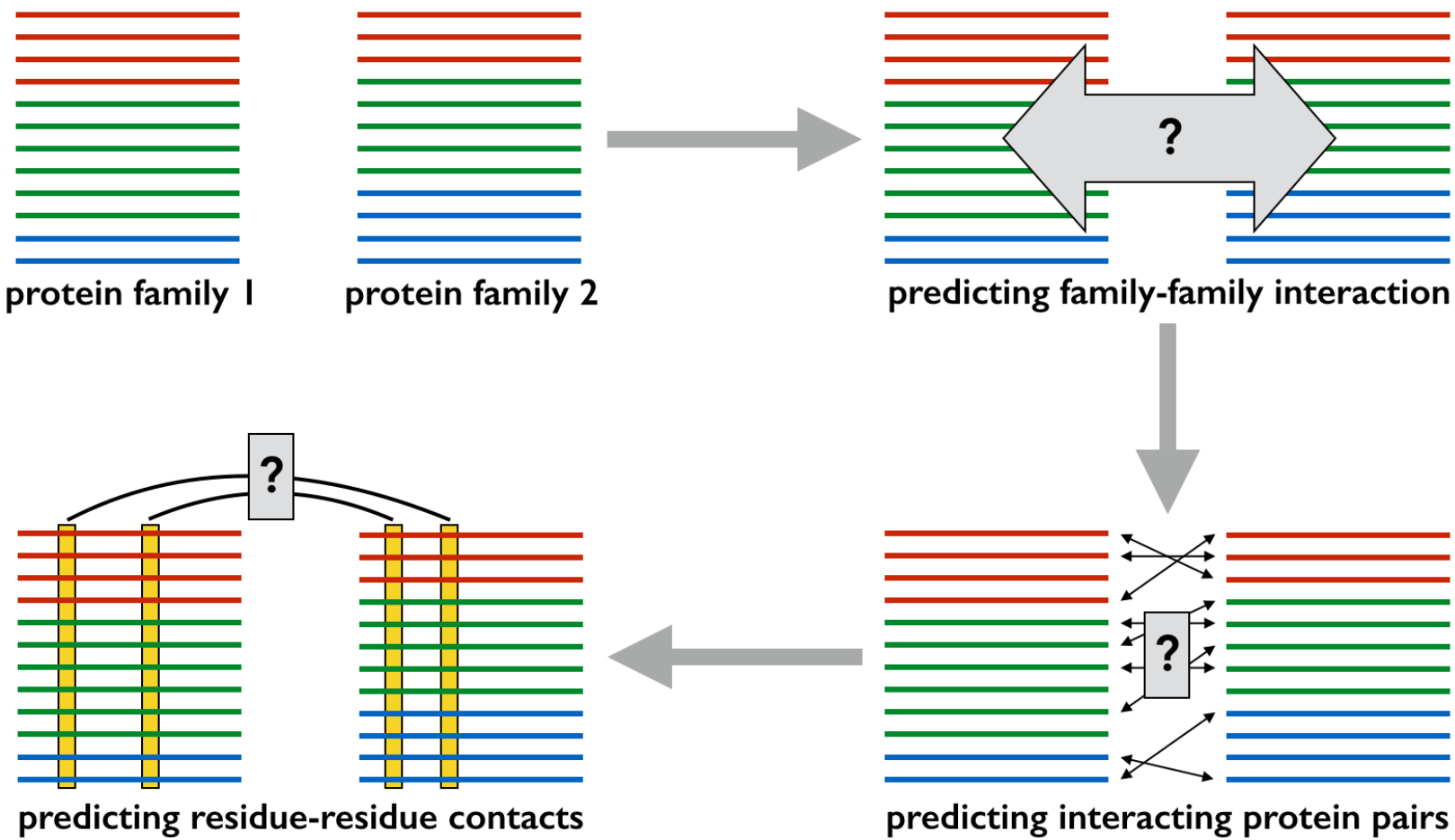
guided molecular dynamics simulations →



Spo0B/0F: co-crystal [Zapf *et al.* (2000)] vs. our model

[Schug, MW, Onuchic, Hwa, Szurmant, PNAS '09]

Interactions between protein families



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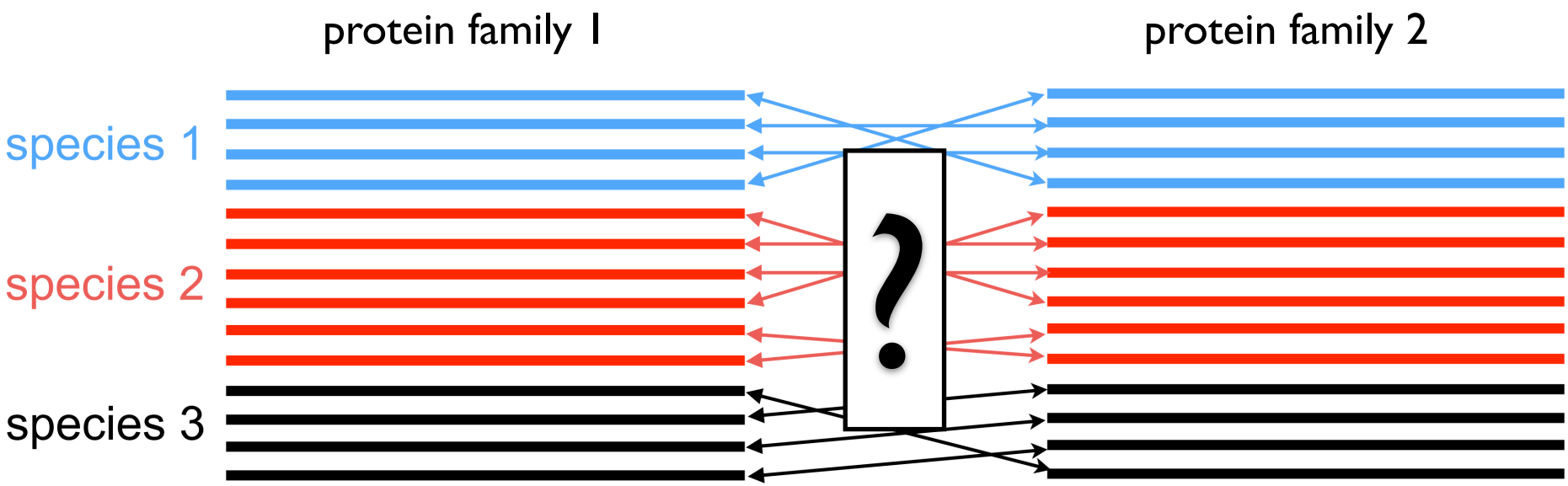
➡ relation between protein structure/function and evolution

Specific interactions and paralog matching



General idea:

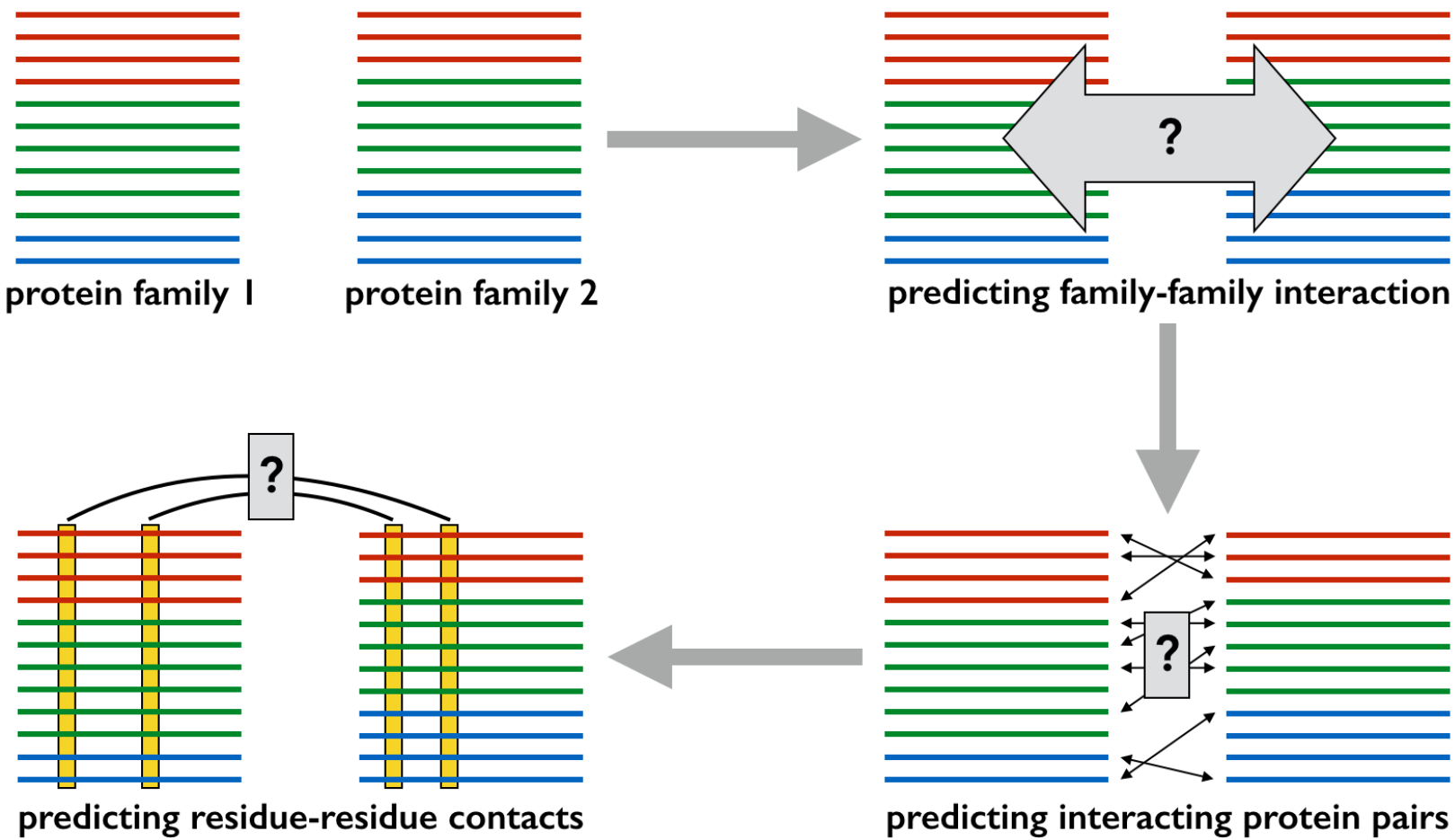
- correct matching shows inter-protein covariation
- random matching has no inter-protein covariation

➡ maximise inter-protein covariation computationally

- reach 80-90% of accuracy in test cases
- simultaneous prediction of interacting paralogs and inter-protein contacts

[Gueudré, Baldassi, Zamparo, MW, Pagnani, *PNAS* '16]
[Bitbol, Dwyer, Colwell, Wingreen, *PNAS* '16]

Interactions between protein families



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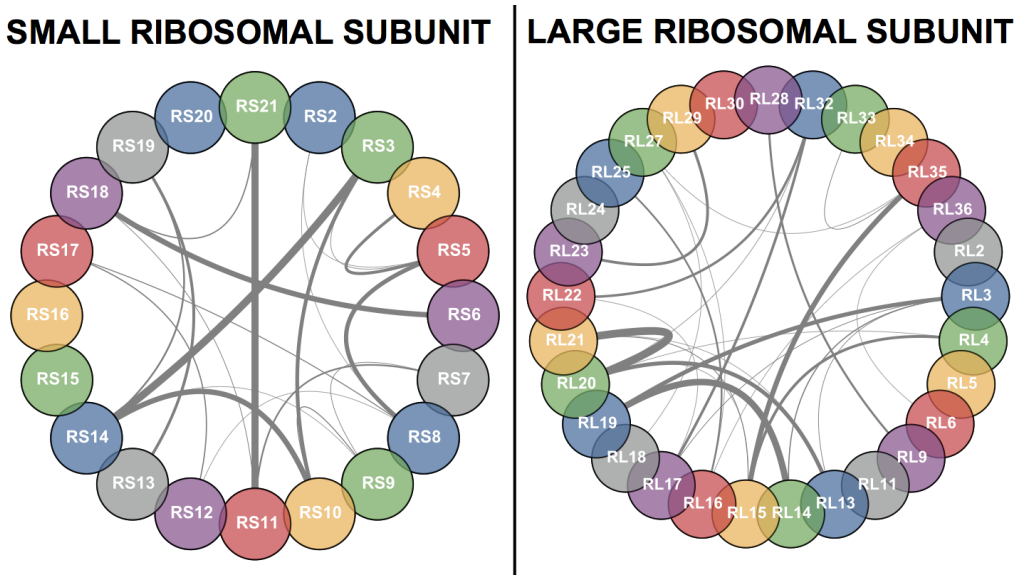
Inference of protein-protein interaction networks



Bacterial ribosomal proteins

Small ribosomal subunit

- 20 proteins
- 21 interactions (11% of 190 pairs)

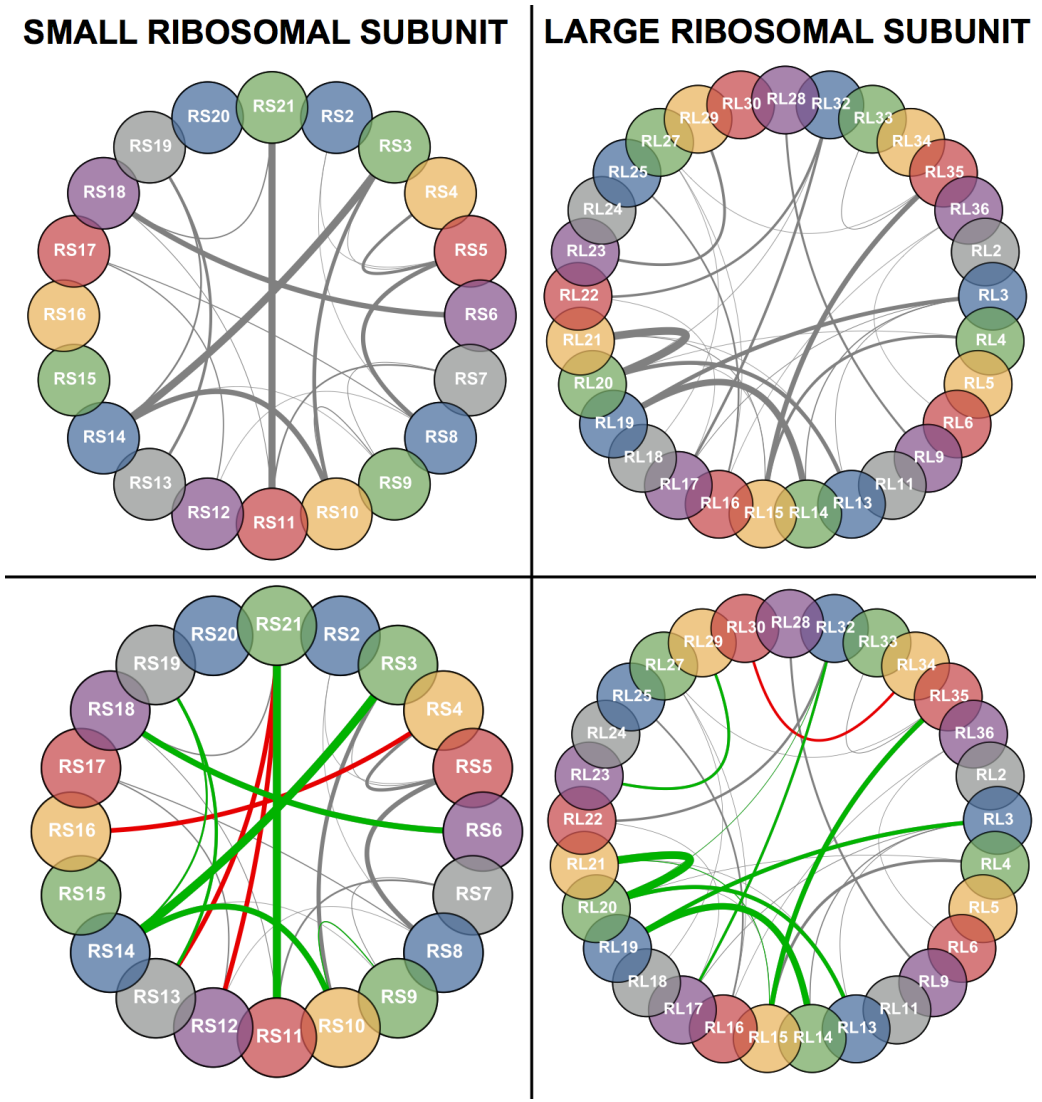
Large ribosomal subunit

- 29 proteins
- 29 interactions (7% of 406 pairs)

▸ sparse interaction network

[Feinauer, Szurmant, MW, Pagnani, *PLoS ONE* '16]

Inference of protein-protein interaction networks



Bacterial ribosomal proteins

Pairwise DCA (1000-3000 seqs.)

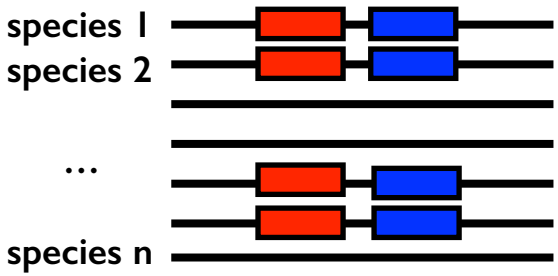
Top 10 predictions for each subunit

- 16 true positive interactions (80% TP vs. 8% in random prediction)
- find most large interfaces
- fail to detect small interfaces
- false predictions appear in smaller alignments

▸ larger alignments needed

[Feinauer, Szurmant, MW, Pagnani, *PLoS ONE* '16]
cf. also [Uguzzoni, Lovis, Oteri, Schug, Szurmant, MW, *PNAS* '17]

Exploring genomic scales

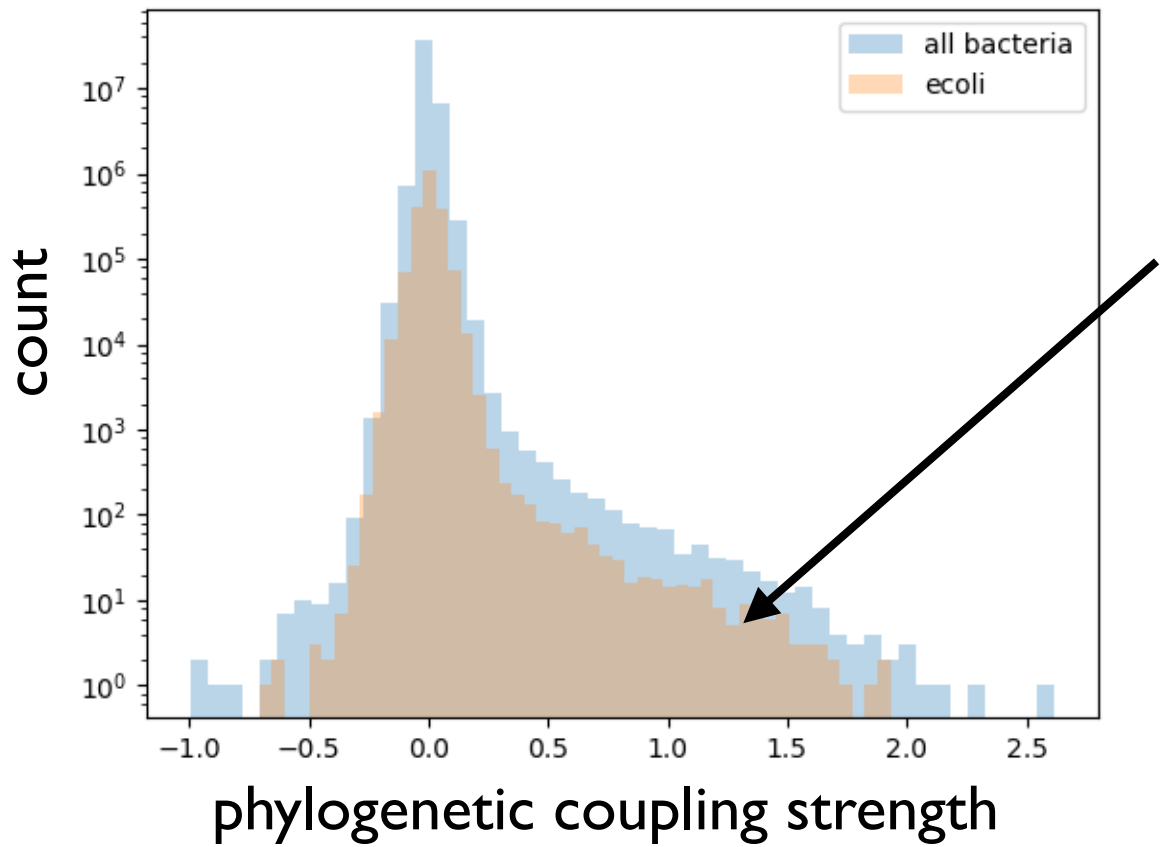


correlated presence / absence of interacting proteins

– phylogenetic profiles [Pellegrini et al. 1999]

– correlated phylogenetic trees [Pazos et al. 2001]

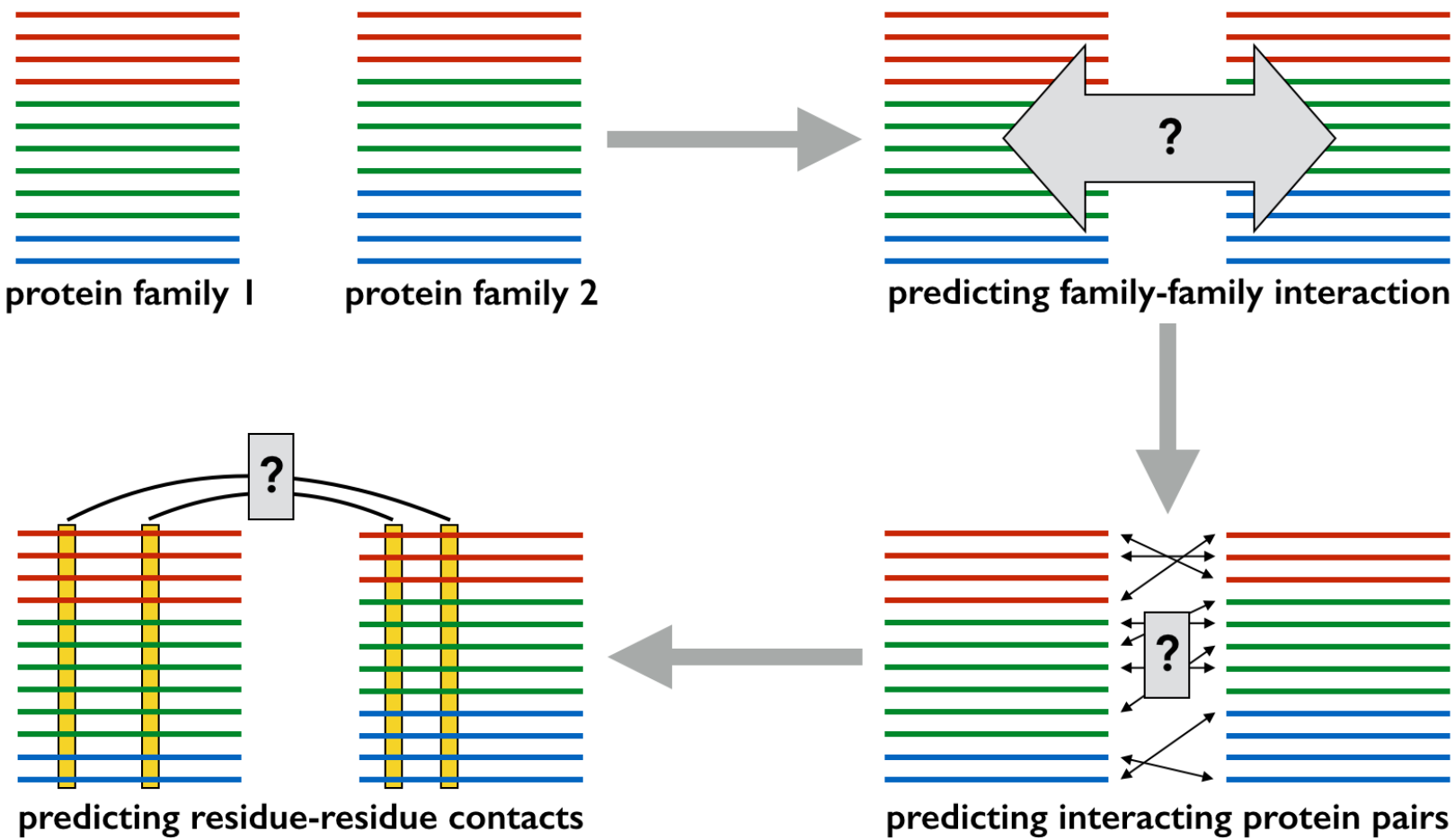
– phylogenetic coupling analysis [Croce et al., in prep]



Tail of ~1000 strong couplings

- 80% known relations (interaction, colocalisation)
- 20% new predictions

Interactions between protein families



What can we learn from the empirical sequence variability:

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➡ towards a structurally resolved & evolutionary conserved interactome

Thanks to:

The group in Paris:

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Kai Shimagaki
Edwin Rodriguez

Francesco Oteri

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Guido Uguzzoni
Alice Coucke
Matteo Figliuzzi
Christoph Feinauer

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Hendrik Szurmant (Western U LA)
Alexander Schug (KIT Karlsruhe)
Jose Onuchic (Rice U, Austin)
Faruck Morcos (UT Dallas)
Angel E. Dago (Scripps La Jolla)
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Erik Aurell (KTH Stockholm)
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Rémi Monasson (ENS)
Simona Cocco (ENS)
Olivier Tenaillon (Inserm Paris)

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Agence Nationale de la Recherche ANR

îledeFrance Demain s'invente ici

ICS Institut du calcul et de la simulation

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