Data-driven models of sequence landscapes

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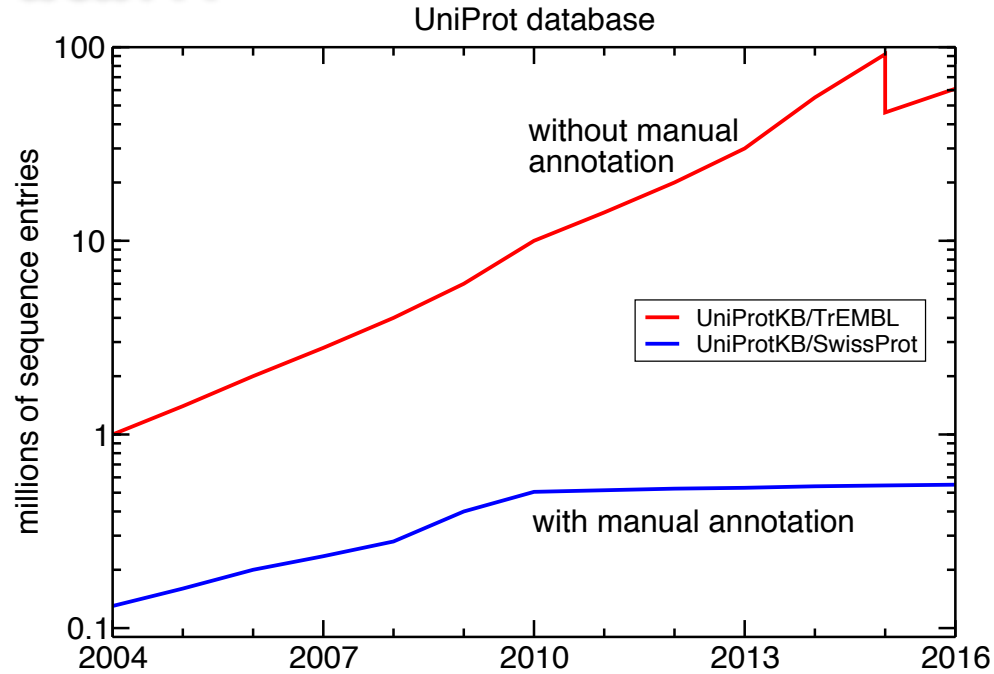
All models are wrong, but some are useful.

[George E.P. Box, 1976]

Data…

Sequence data are rapidly accumulating…



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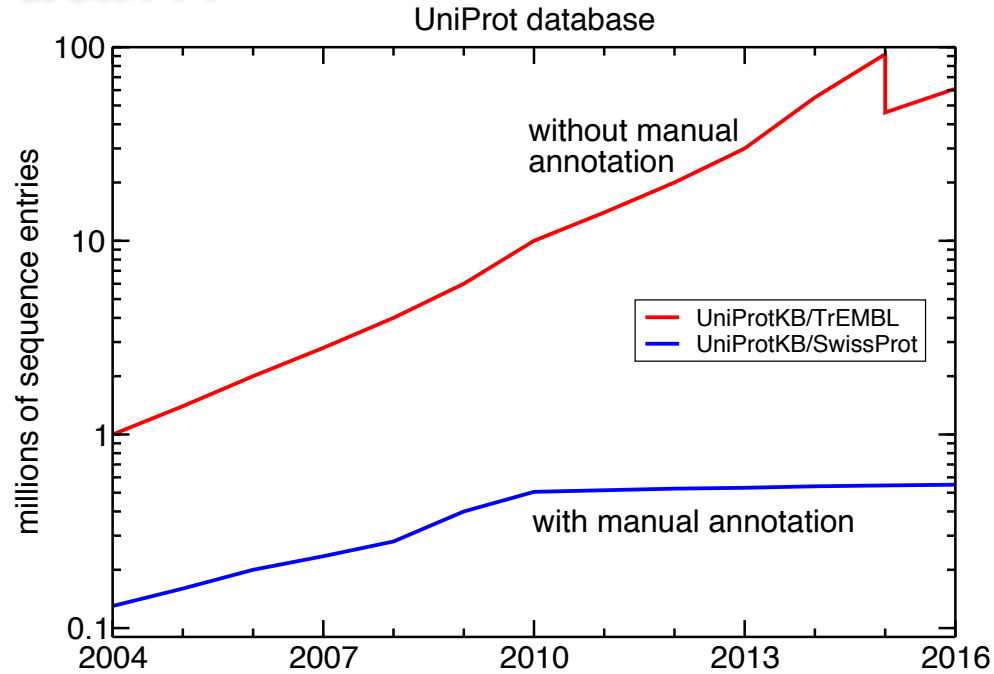
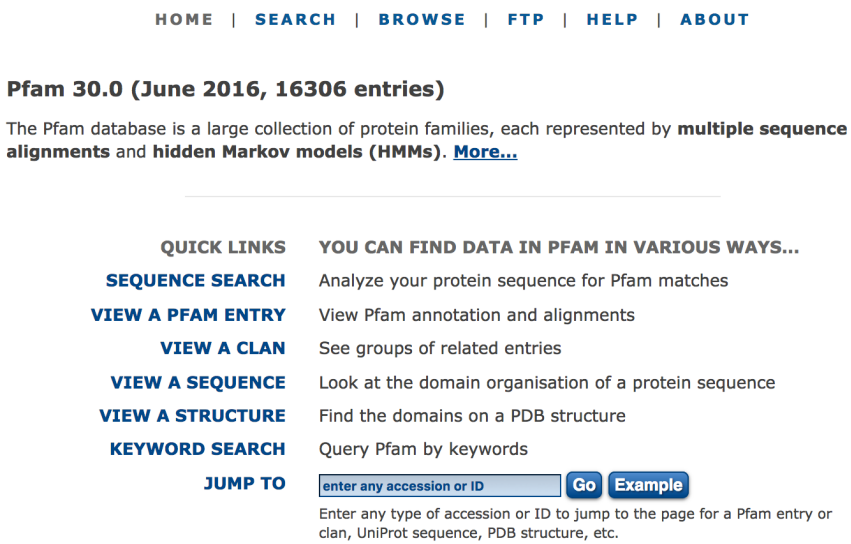


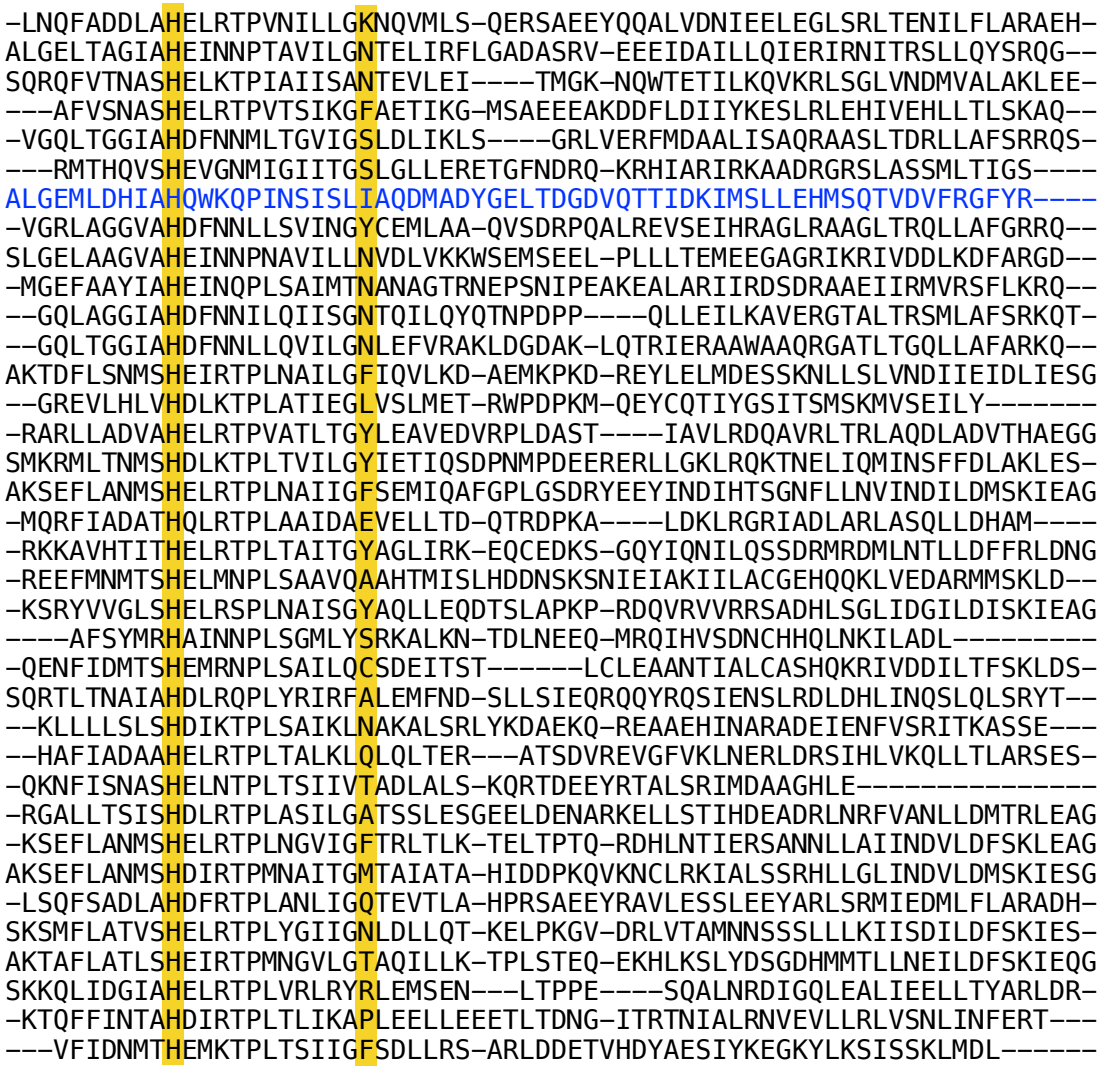


…and organized into **protein families**:

- common evolutionary origin (homologs)
- **conserved biological structure / function**
- **diverged sequences** (20-30% seq ID)
- available as multiple-sequence alignments

➡ **opportunity for data-driven approaches**

Looking for information in :



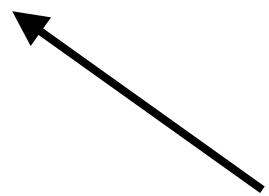
multiple-sequence alignment

- 50-500 positions sequence length
- 10^3-10^5 homologous sequences

Inference of statistical sequence models

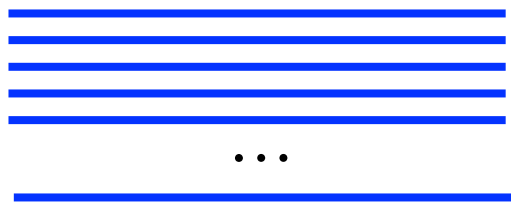
From data to statistical models

$$P(\overline{A}) = P(A_1, ..., A_L)$$



Data – MSA

$$\{\overline{A}^{\mu}\}_{\mu=1...M}$$



Attention:
Data insufficient to do this without modeling

Inference of statistical sequence models

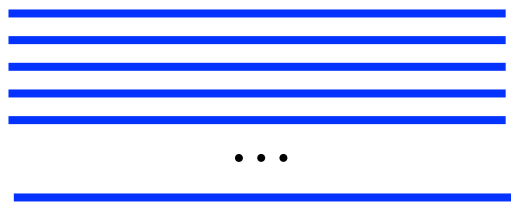
From data over observables to statistical models

$$P(\overline{A}) = \frac{1}{Z} \exp\left\{ \sum_a \lambda_a \mathcal{O}^a(\overline{A}) \right\}$$

maximum entropy model

Data – MSA

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



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

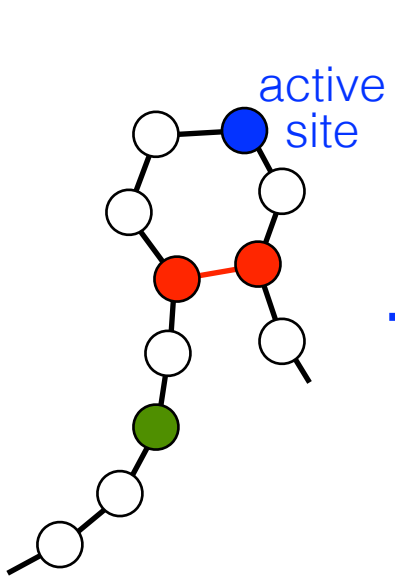
model average

average over data

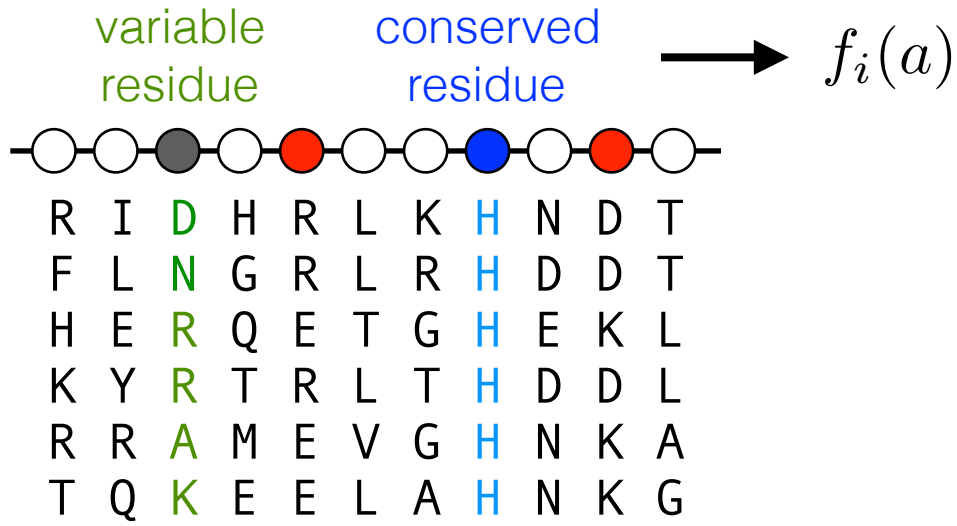
Attention:

- model depends on data only via sample-averaged observables
- selection of observables requires prior biological knowledge

Conservation in proteins



evolution



Profile model – independent residues

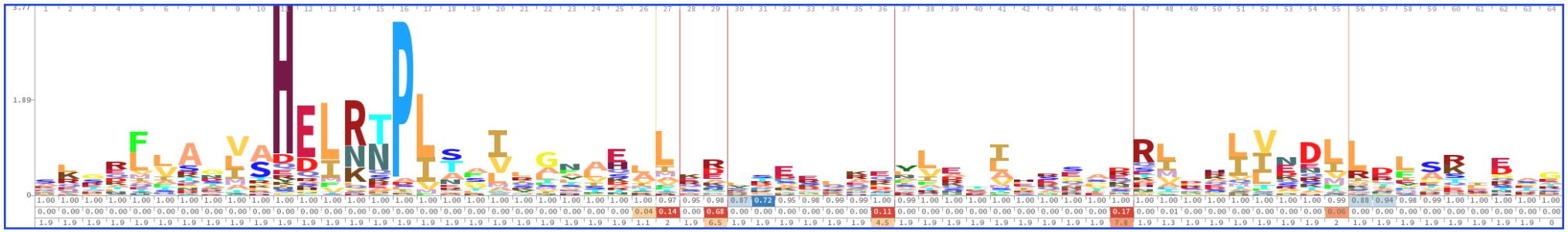
$$P(a_1, ..., a_L) \sim \exp\left\{\sum_i h_i(a_i)\right\}$$

statistical modeling

All models are wrong, but some are useful.

[George E.P. Box, 1976]

Profile models



- identify conserved positions as functionally or structurally important positions
- are used to identify homologous sequences (automatic annotation)
- are used to align sequences

belong to the most successful statistical models in bioinformatics

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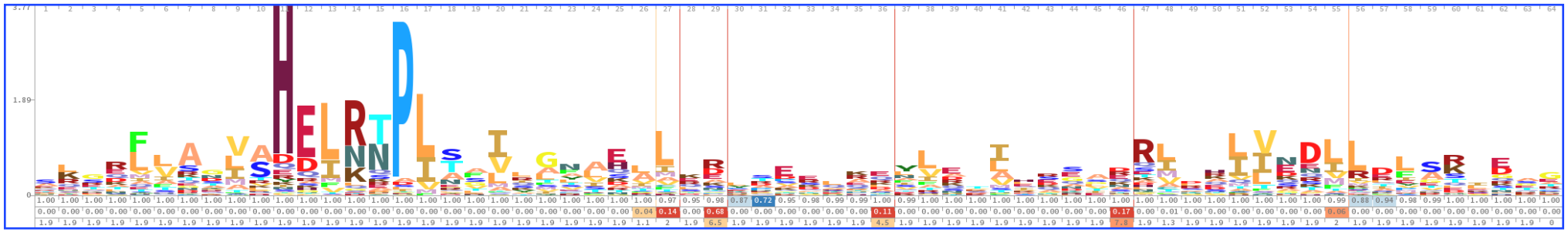
Profile models



- identify conserved positions as functionally or structurally important positions
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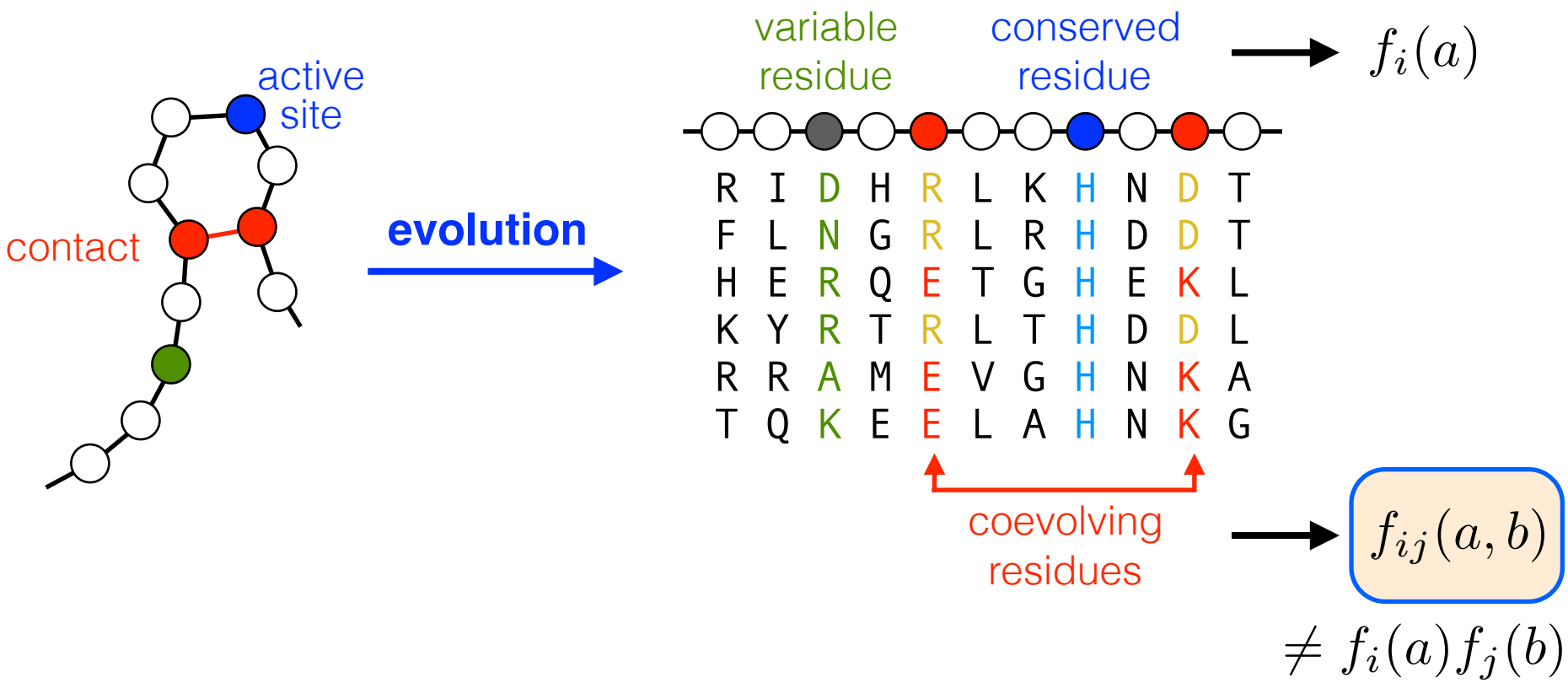
belong to the most successful statistical models in bioinformatics

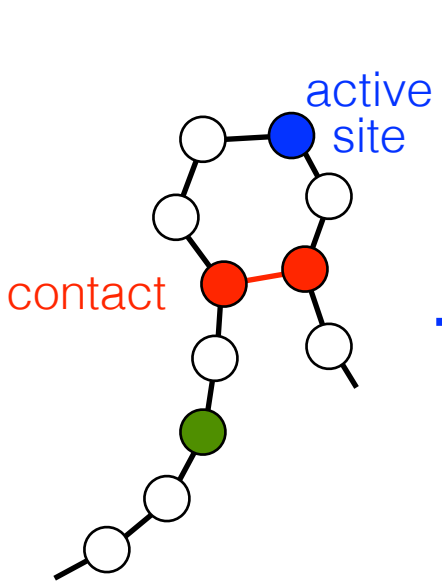
- are intrinsically unable to capture **relations** between positions
  - residue-residue contacts
  - protein-protein interaction

miss important information contained in sequence alignments

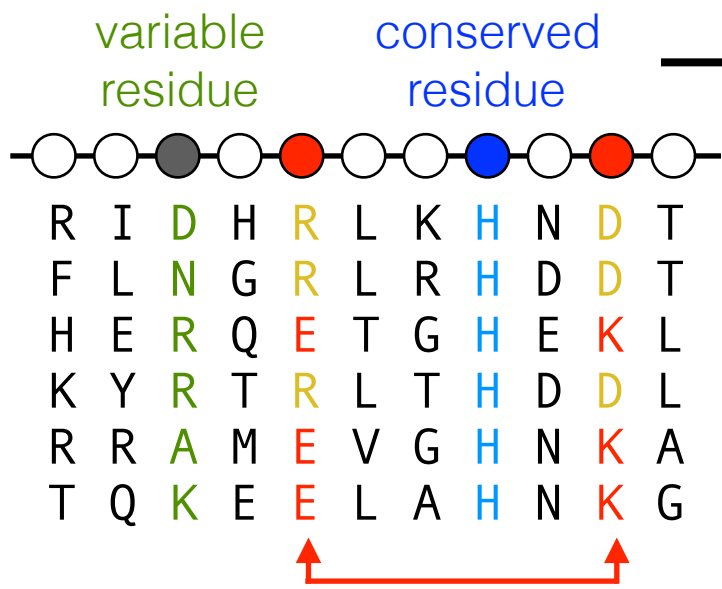
Conservation and coevolution in proteins



Conservation and coevolution in proteins



evolution



$f_i(a)$

$f_{ij}(a,b)$

$\neq f_i(a) f_j(b)$

Profile model – independent residues

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

statistical modeling

Direct Coupling Analysis (DCA) – pairwise residue-residue couplings

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

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

[Weigt et al, PNAS '09]

[Morcos et al, PNAS '11]

Direct coupling analysis (DCA)

- Boltzmann-machine learning:
  - start with initialised parameters (fields/couplings)
  - calculate

$$P_{ij}(A_i, A_j) = \sum_{\{A_k | k \neq i,j\}} P(A_1, ..., A_L)$$

  - update parameters to fit marginals

$$\Delta J_{ij}(a, b) = \varepsilon [f_{ij}(a, b) - P_{ij}(a, b)]$$

  - iterate until sufficiently precise fitting

➡ exact calculation requires exponential time ~ 21^L

➡ approximations (MCMC) needed for computational efficiency

Direct coupling analysis (DCA)

- pseudo-likelihood maximisation
  - replace ensemble average by sample average over sequence data

$$P_1(A_1) = \sum_{\{A_i|i>1\}} P(A_1, ..., A_L)$$

$$= \sum_{\{A_i|i>1\}} P(A_1|A_2, ..., A_L) P(A_2, ..., A_L)$$

$$\simeq \frac{1}{M} \sum_{m=1}^{M} P(A_1|A_2^m, ..., A_L^m)$$

biological sequence data

[Balakrishnan et al., Proteins '11]
[Ekeberg, Lövkvist, Lan, MW, Aurell PRE '13]

Are pairwise DCA couplings useful?

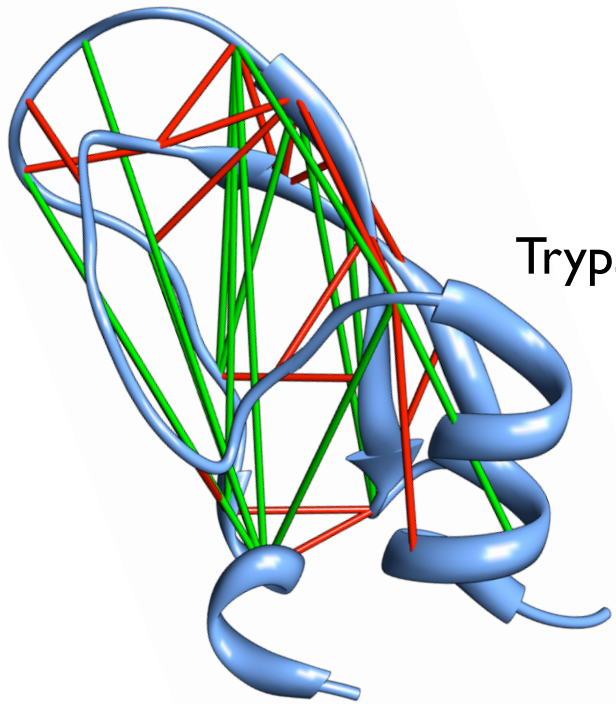
DCA models are **graphical statistical models**:

- defined on a **network** of strongly coupled residues
- provide a **probability** to each sequence (sequence landscape)

What is the **biological information** contained in such models ?

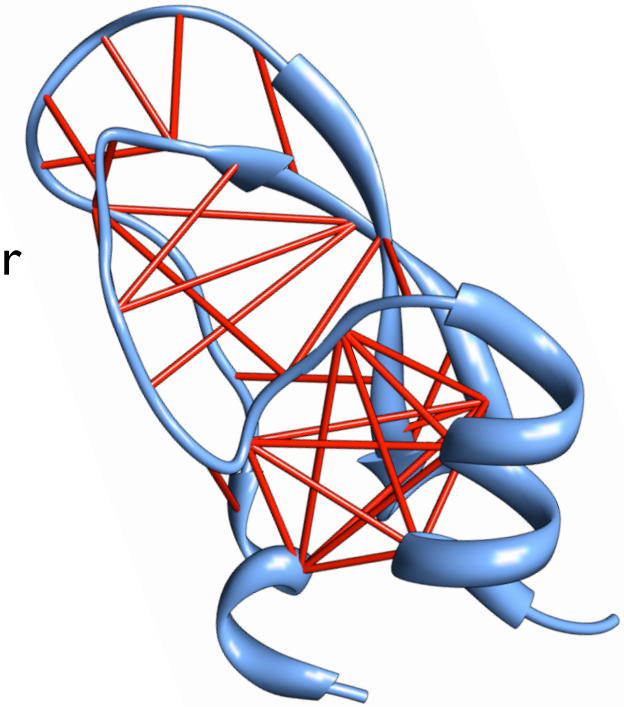
Strong couplings predict residue contacts

30 strongest correlations



Trypsin inhibitor

30 strongest couplings

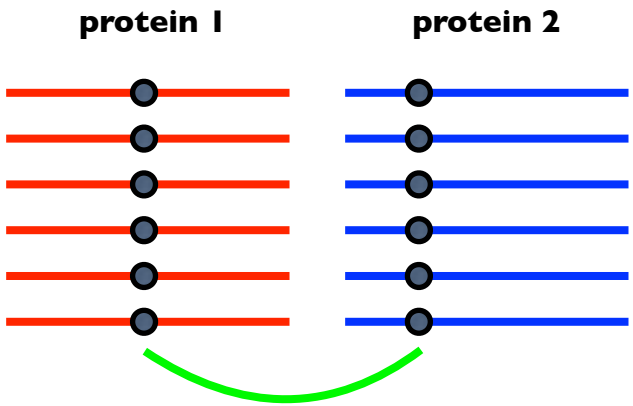


- works across numerous protein families
- accurate prediction for >1000 diverged sequences
- guides 3D protein structure prediction

[Marks et al., PLoS ONE '11]
[Sulkowska, Morcos, MW, Hwa, Onuchic, PNAS '12]
[Hopf et al., Cell '12]
[Nugent, Jones, PNAS '12]
[Ovchinnikov et al., eLife '15]
[Ovchinnikov et al., Science '17]

Prediction of inter-protein residue coevolution

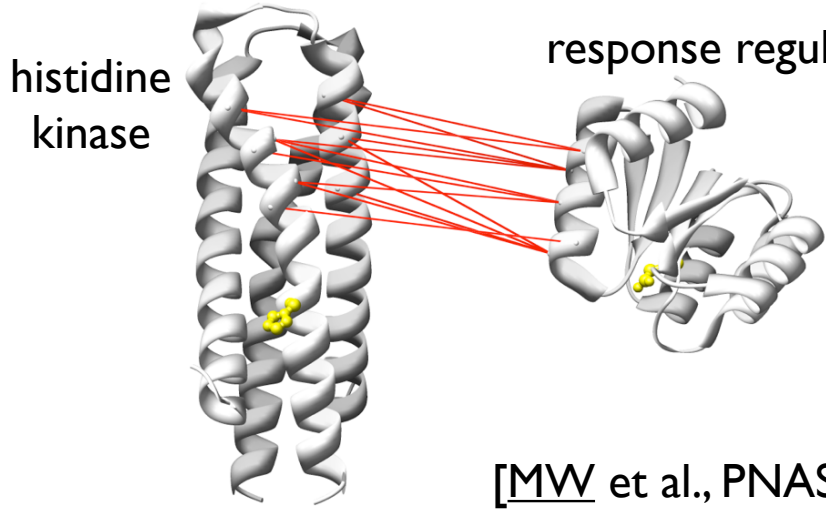
Joint MSA of protein families



inter-protein couplings

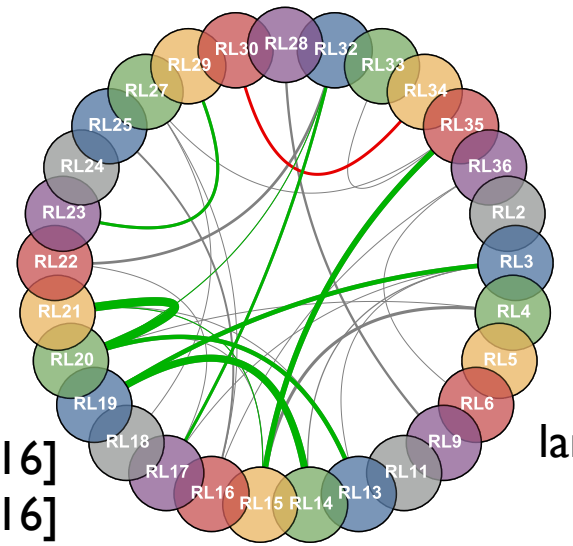
DCA

inter-protein residue contacts



[MW et al., PNAS '09]

protein-protein interaction networks



large ribosomal subunit

[Feinauer, Szurmant, MW, Pagnani, PLoS ONE '16]
[Gueudré, Baldassi, Zamparo, MW, Pagnani, PNAS '16]

Are pairwise DCA couplings useful?

DCA models are **graphical statistical models**:

- defined on a **network** of strongly coupled residues
- provide a **probability** to each sequence (sequence landscape)

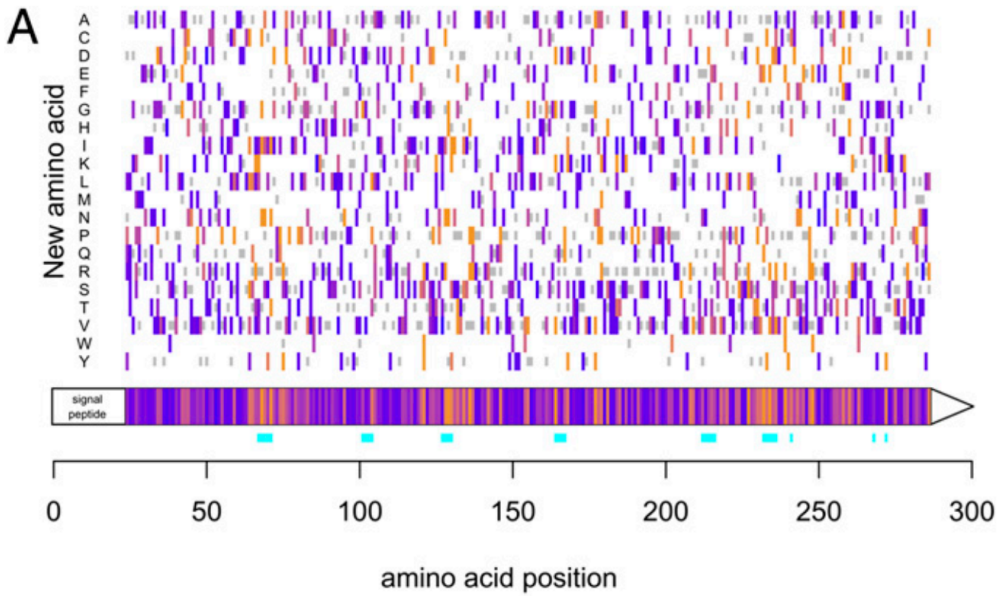
What is the **biological information** contained in such models ?

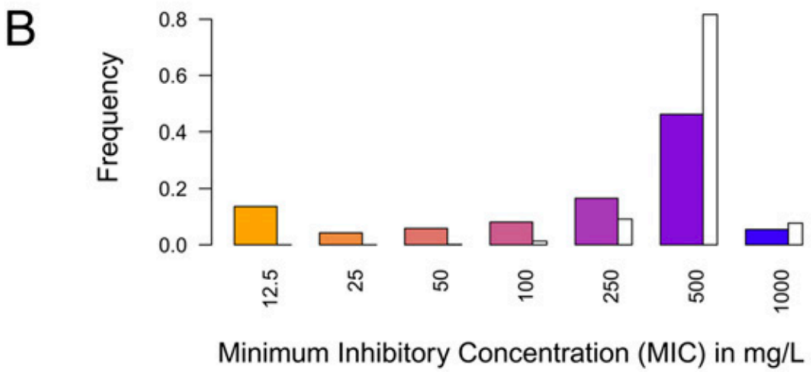
Measuring mutational effects in proteins

Capturing the mutational landscape of the beta-lactamase TEM-1

PNAS 110 (2013) 13067

Hervé Jacquier[a,b,c,1], André Birgy[a,b], Hervé Le Nagard[a,b,d,e], Yves Mechulam[f], Emmanuelle Schmitt[f], Jérémy Glodt[a,b], Beatrice Bercot[c,g], Emmanuelle Petit[h], Julie Poulain[h], Guilène Barnaud[i], Pierre-Alexis Gros[a,b,j], and Olivier Tenaillon[a,b,1]





Deep mutational scanning of proteins

TEM-1 protein

- causes antibiotic resistance

generated ~10^4 random mutants

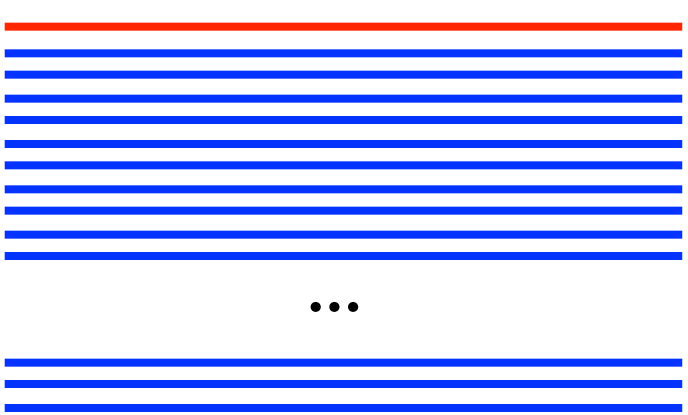
- 1,700 without mutation
- 990 distinct single AA changes

measured resistance to amoxicillin

- minimum inhibitory concentration as proxy for fitness

Landscape inference by Direct-Coupling Analysis

Beta-lactamase2 family (PF13354)



~2,500 diverged sequences

Statistical landscape inference (DCA)

$$P(A_1, ..., A_L)$$

$$\sim \exp\left\{ \sum_{i,j=1}^{L} e_{ij}(A_i, A_j) + \sum_{i=1}^{L} h_i(A_i) \right\}$$

Score for mutant AA sequences

$$\Delta\Phi = \log\left\{ \frac{P(\text{mutant})}{P(\text{wildtype})} \right\}$$

Evolutionary constraints
across diverged homologs

[Figliuzzi, Jacquier, Schug, Tenaillon, MW, *Mol Biol Evol* '16]

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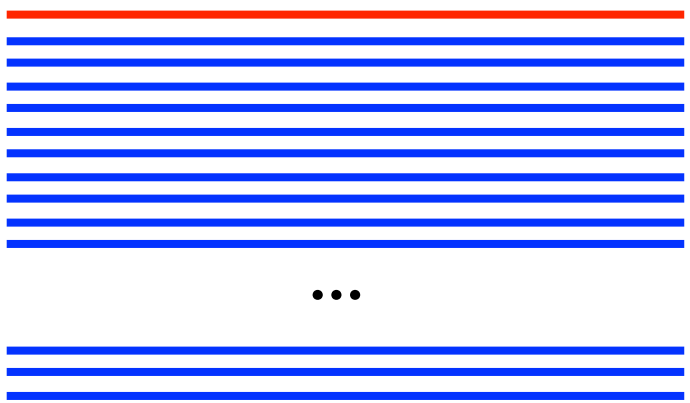

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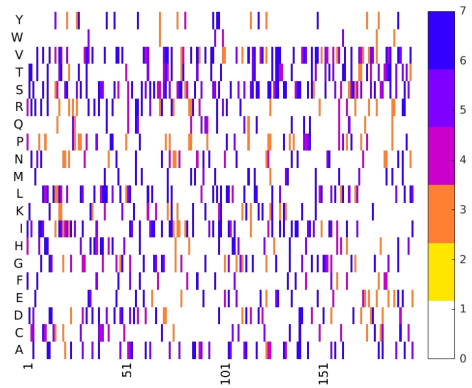

MIC changes of TEM-1
due to single-AA changes

?

Score for mutant AA sequences

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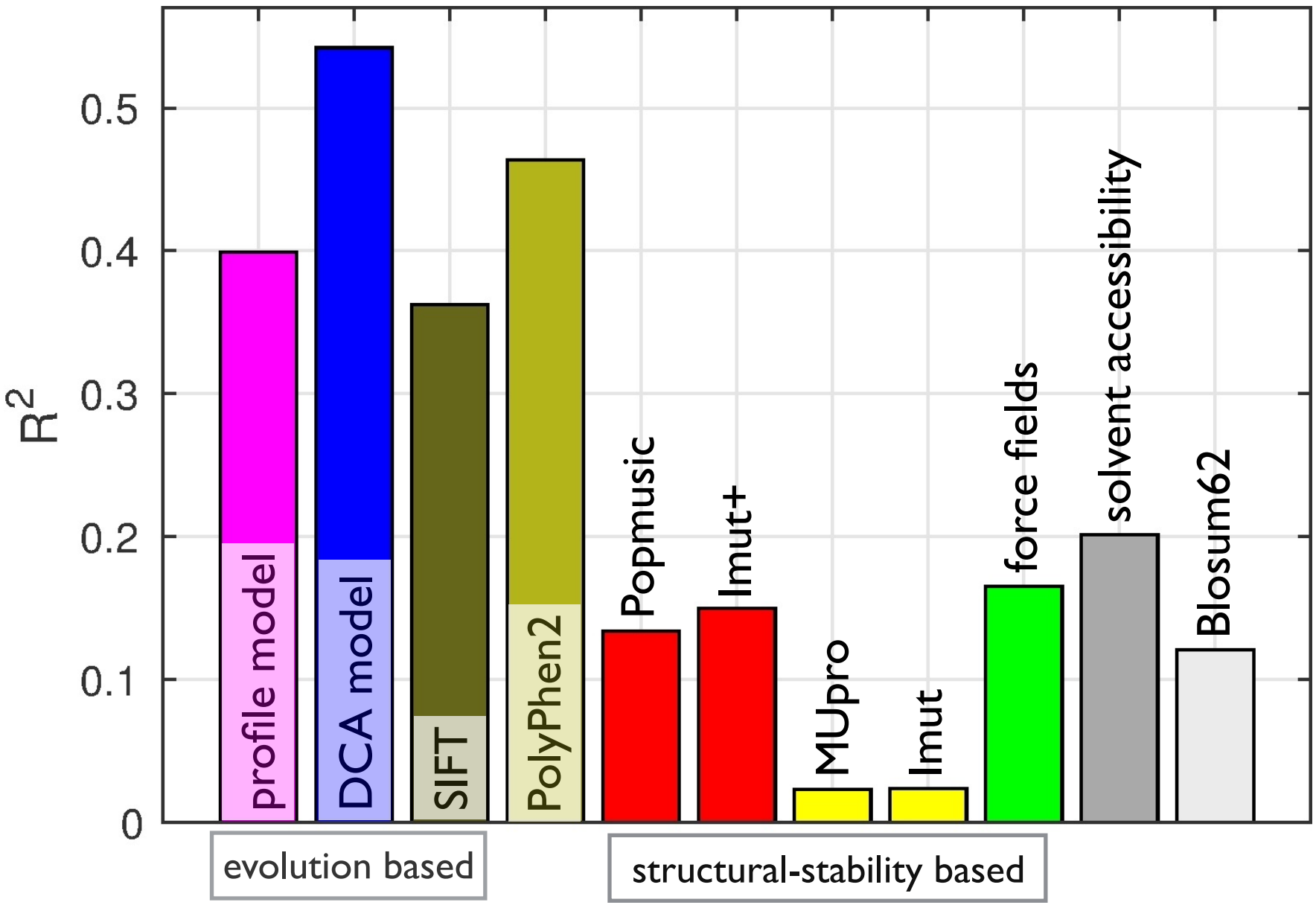
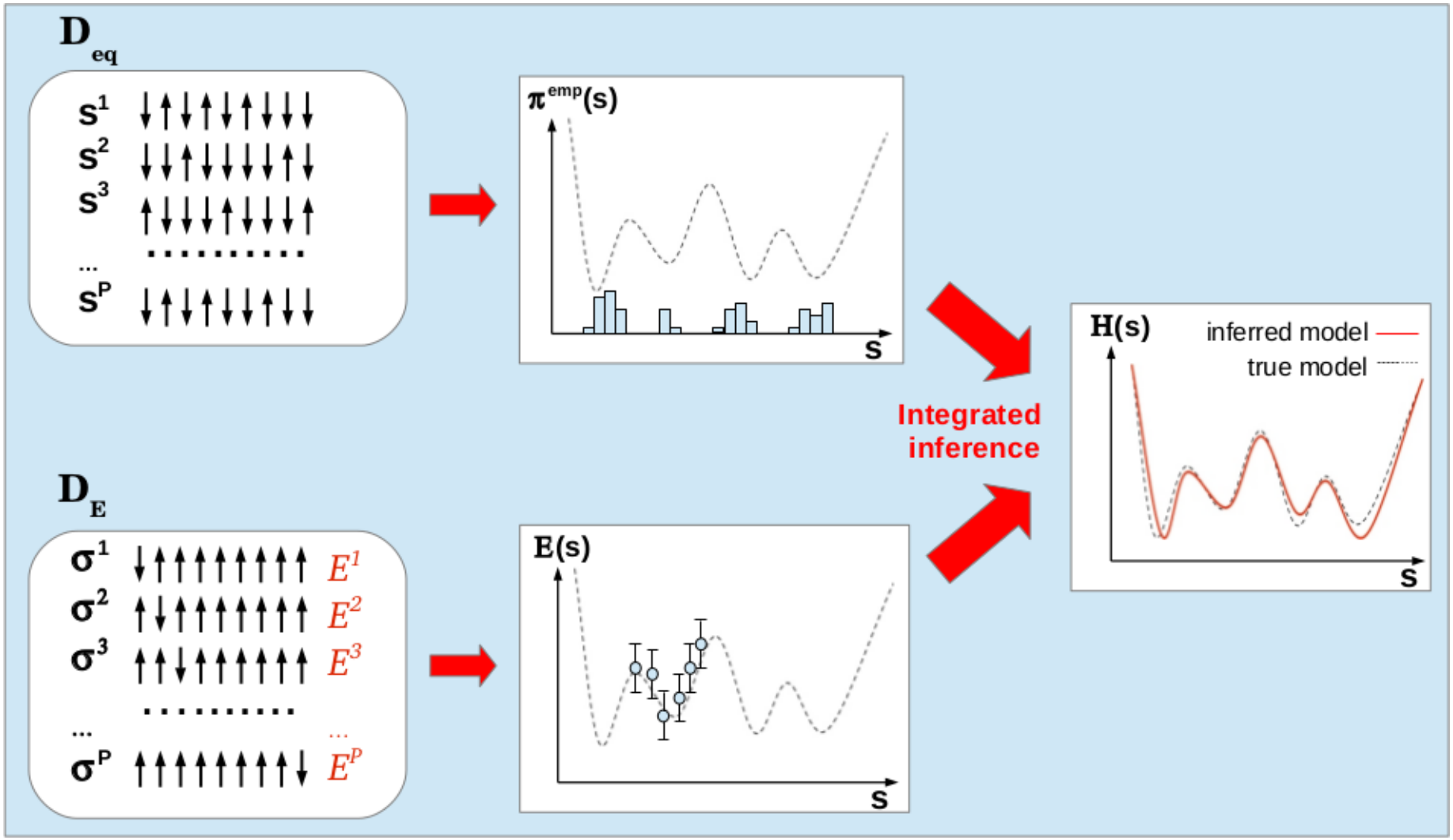
Predicting mutational effects in proteins



[Figliuzzi, Jacquier, Schug, Tenaillon, MW, *Mol Biol Evol* '16]

Integrating heterogenous data in landscape inference

MSA: sequence data



DMS: mutational data

[Barrat-Charlaix,Figliuzzi, MW, *Sci Rep* '16]

Integrating heterogenous data in landscape inference

Statistical model

$$P(\overline{A}|\mathbf{J},\mathbf{h}) = \frac{1}{Z}\exp\left\{\sum_{a<b} J_{ij}(A_i,A_j) + \sum_a h_i(A_i)\right\} = \frac{1}{Z}\exp\left\{-\mathcal{H}(\overline{A})\right\}$$

Probability of MSA

$$P(\{\overline{A}^\mu\}_\mu|\mathbf{J},\mathbf{h}) = \exp\left\{-\sum_\mu \mathcal{H}(\overline{A}^\mu) - M\ln Z\right\}$$

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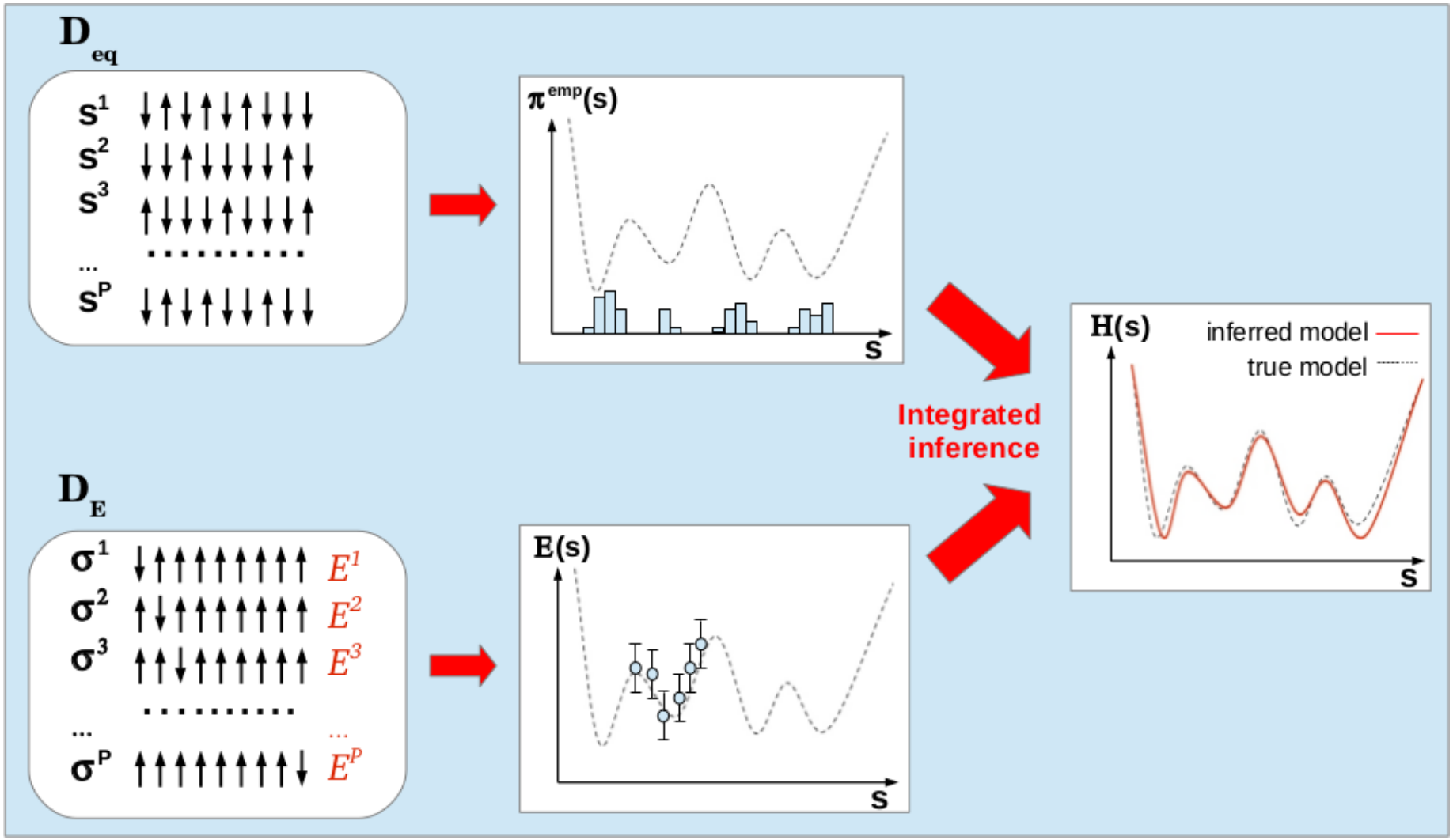

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Probability of MSA

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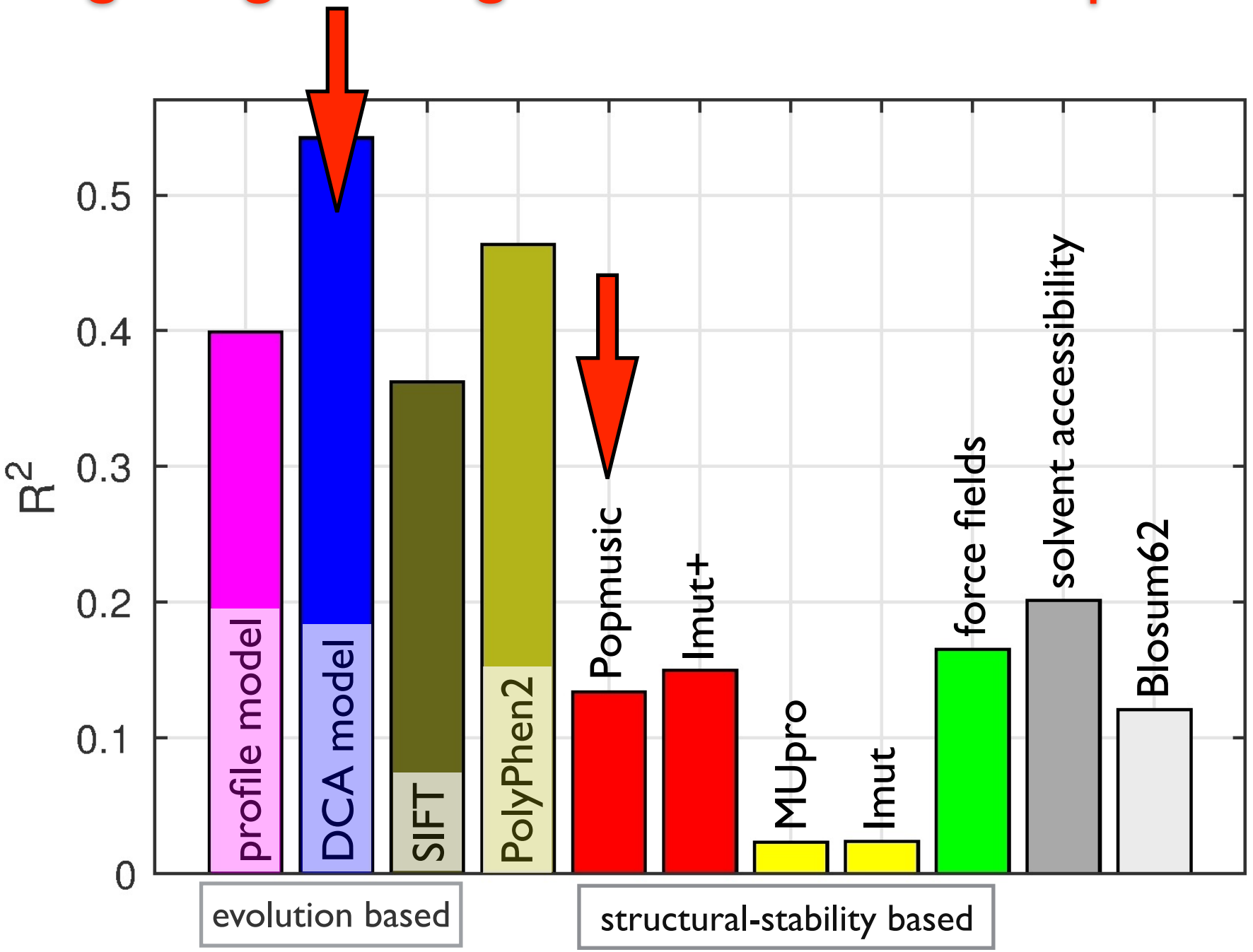
Mutational data - Gaussian experimental noise

$$P(\{E^a\}_a|\{\overline{A}^a\}_a,\mathbf{J},\mathbf{h})) = \frac{1}{(2\pi\Delta^2)^{P/2}}\exp\left\{-\frac{1}{2\Delta^2}\sum_a\left(E^a - \mathcal{H}(\overline{A}^a)\right)^2\right\}$$

Log-likelihood of model parameters

$$\mathcal{L}(\mathbf{J},\mathbf{h}|data) = \log P(\{\overline{A}^\mu\}_\mu|\mathbf{J},\mathbf{h}) + \log P(\{E^a\}_a|\{\overline{A}^a\}_a,\mathbf{J},\mathbf{h})$$

Integrating heterogenous data in landscape inference



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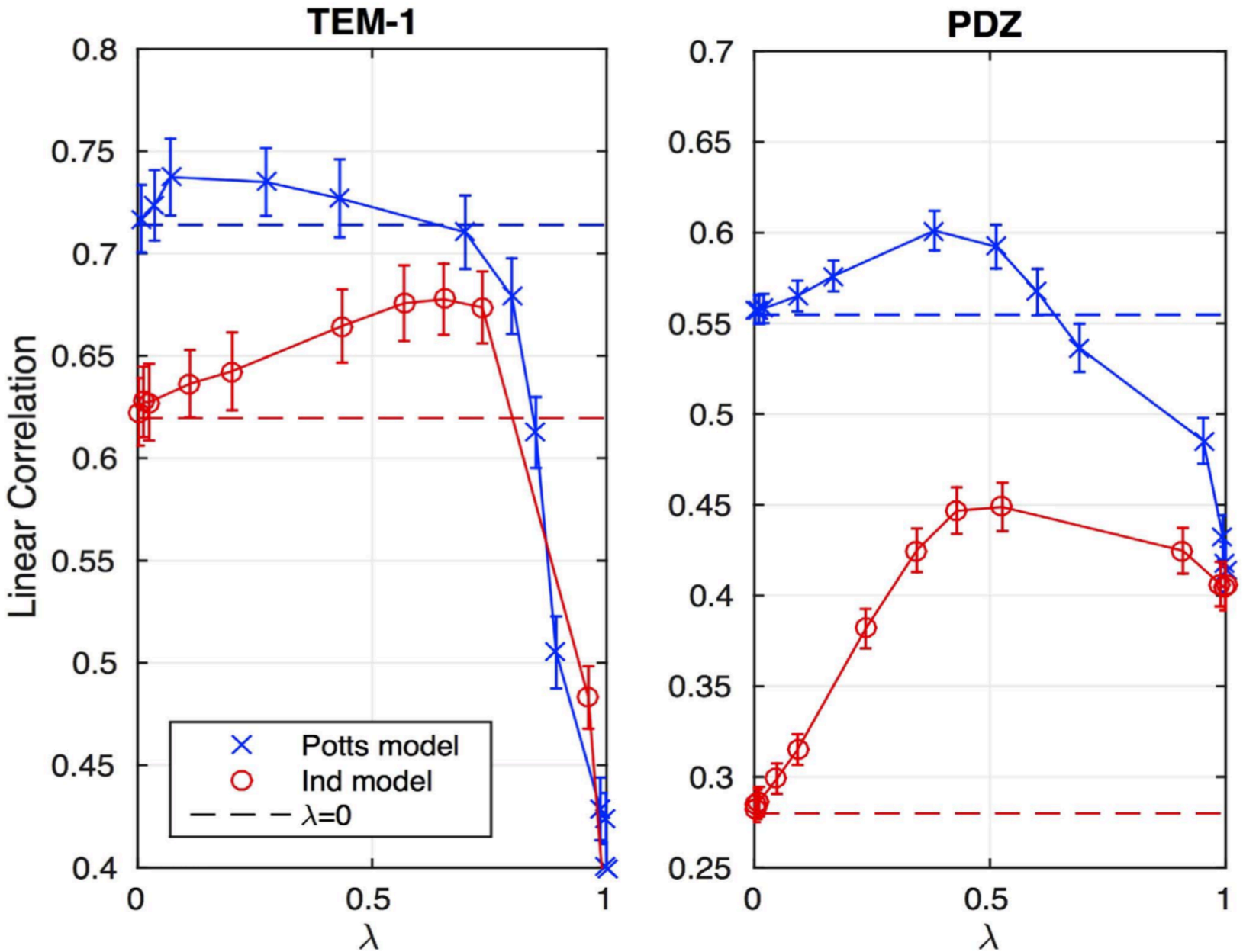

[Barrat-Charlaix,Figliuzzi, MW, *Sci Rep* '16]

Are pairwise DCA couplings useful?

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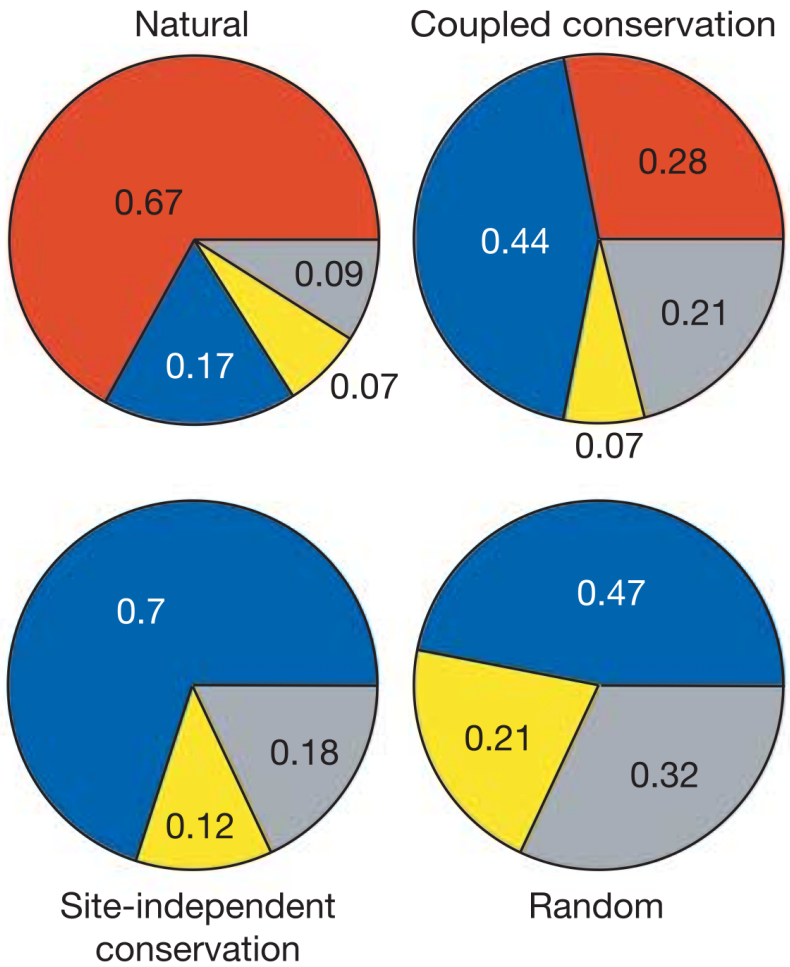
What is the **biological information** contained in such models ?

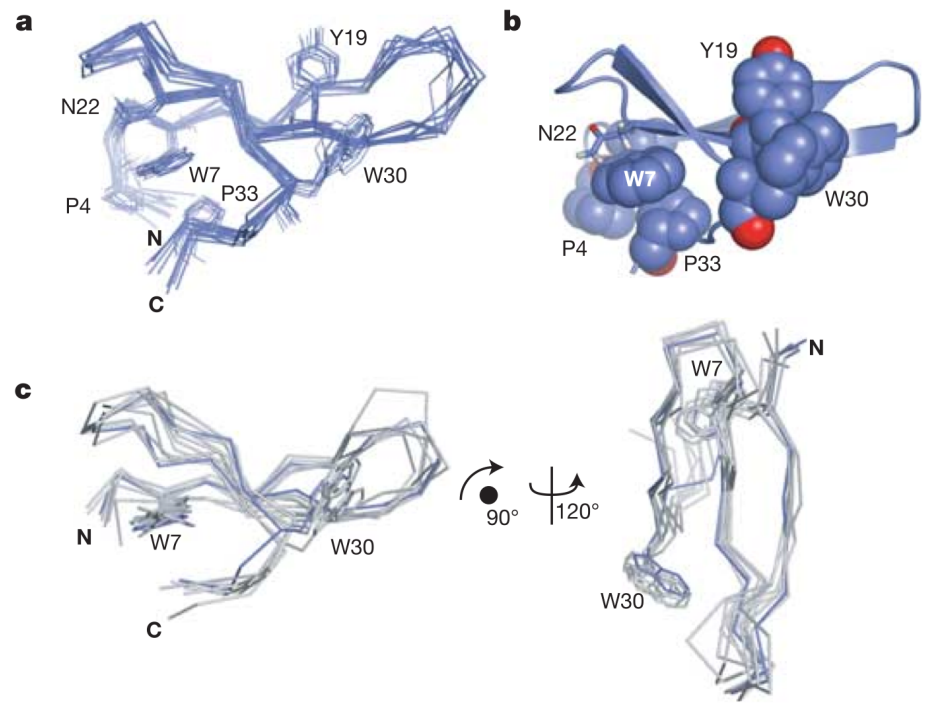
Are pairwise couplings sufficient?

Idea: scramble multiple-sequence alignments of homologs to conserve

- global amino-acid frequencies (no site specificity)
- site independent conservation (protein profile) → only local fields, no couplings
- pairwise amino-acid co-occurrences → pairwise residue-residue couplings



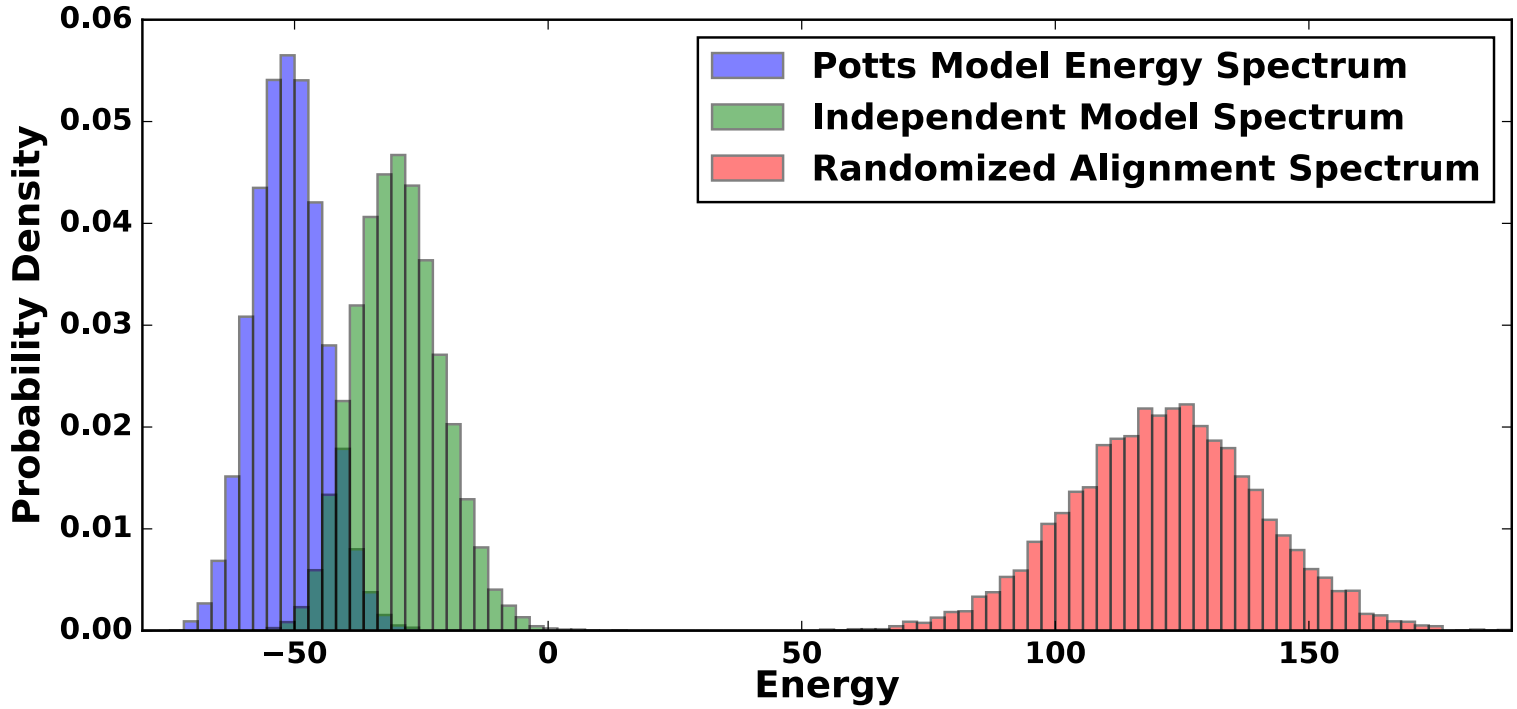
NMR structure of artificial protein (WW domain)

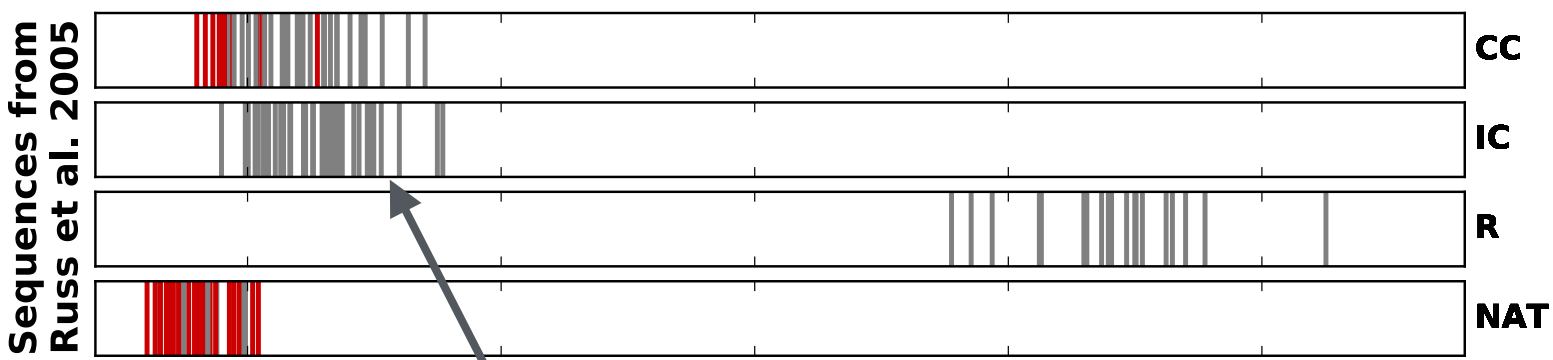


structural alignment with 6 natural WW domains

[M Socolich et al., *Nature* 437, 512 (2005)]

Predicting folding sequences of the WW domain





non folding

folding

high probability

low probability

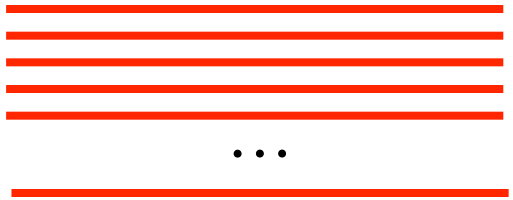
Data-driven statistical design

From data over observables and models to data

$$P(\overline{S}) \sim \exp\left\{\sum_a \lambda_a \mathcal{O}^a(\overline{S})\right\}$$

Output data:

$$\{\overline{X}^\nu\}_{\nu=1,\ldots,N}$$



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

Input data:

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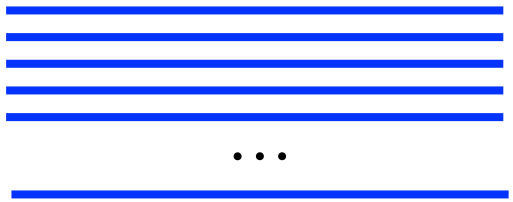

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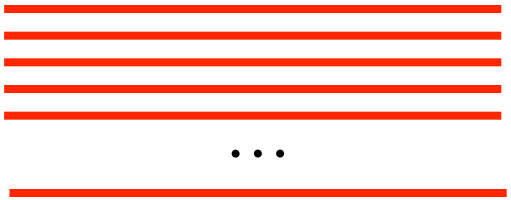
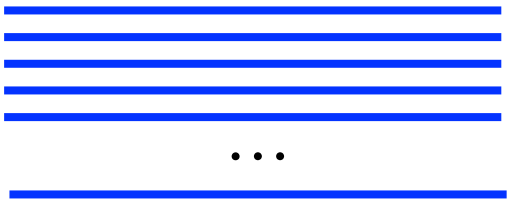


generative model?

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

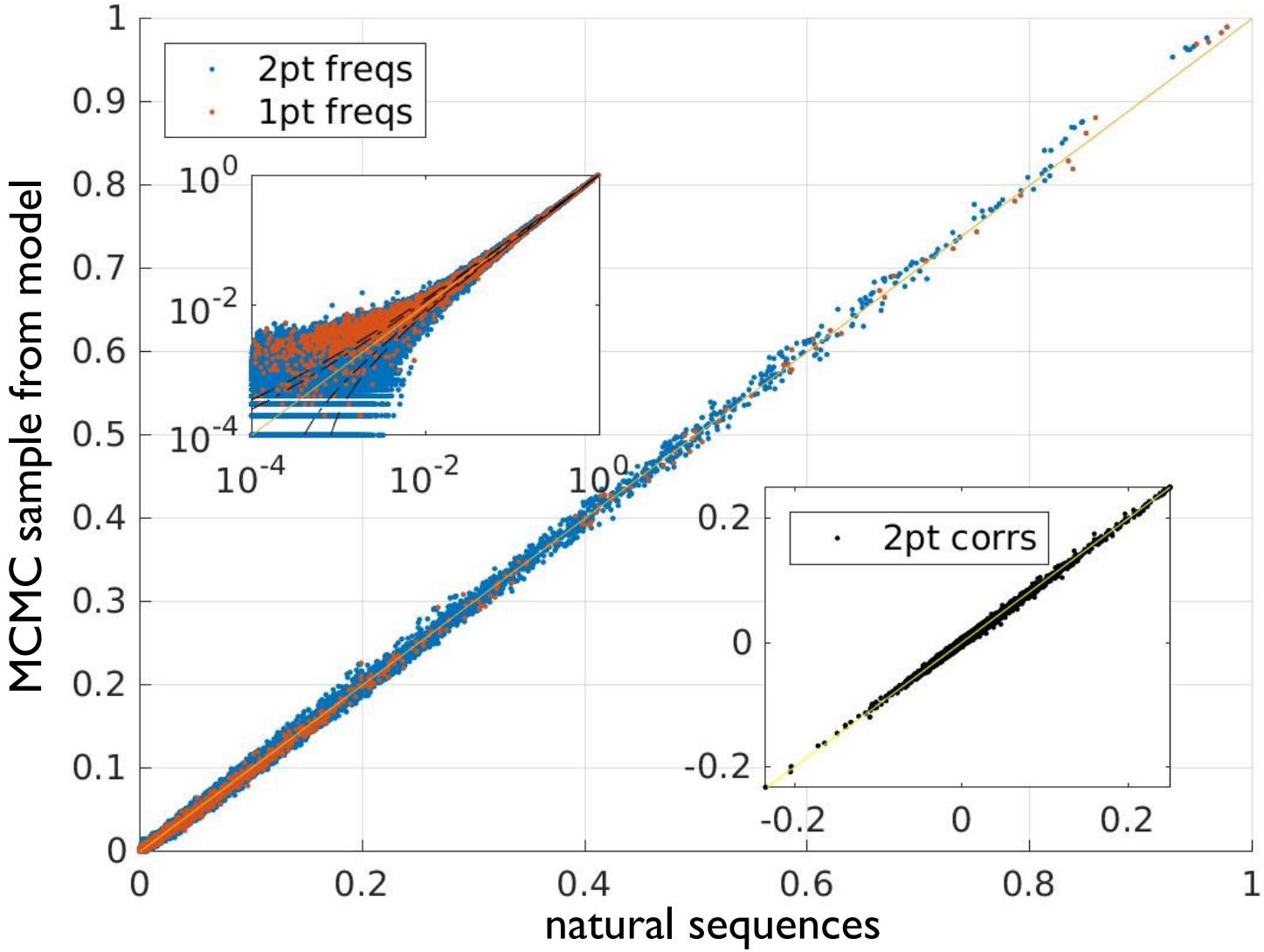
Input data:

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



DCA reaches very precise fitting

response regulator (PF00072)

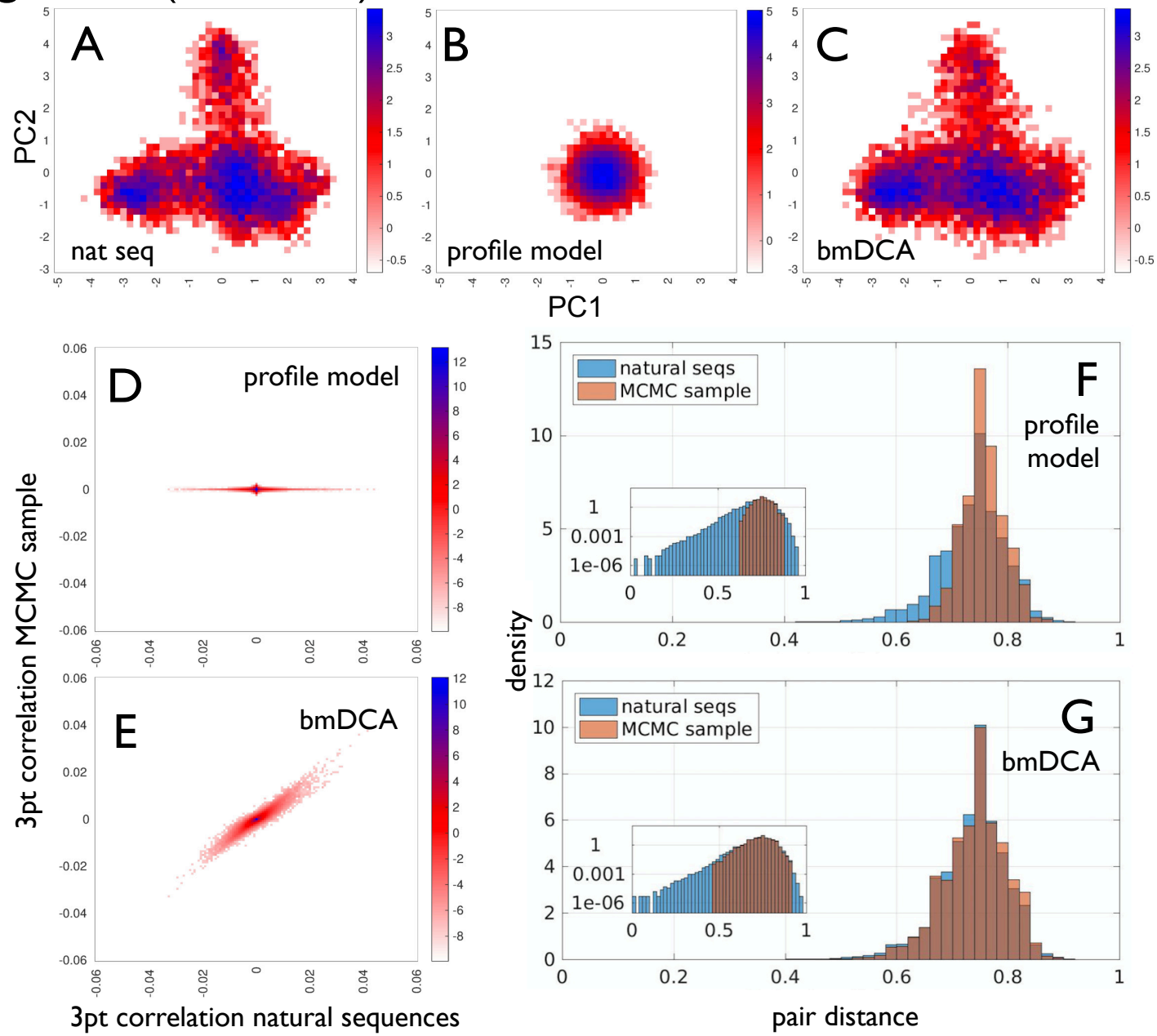


➡ tested for many protein families

[Figliuzzi, Barrat-Charlaix, MW, *Mol. Biol. Evol.* 2018]

DCA reproduces non-fitted quantities

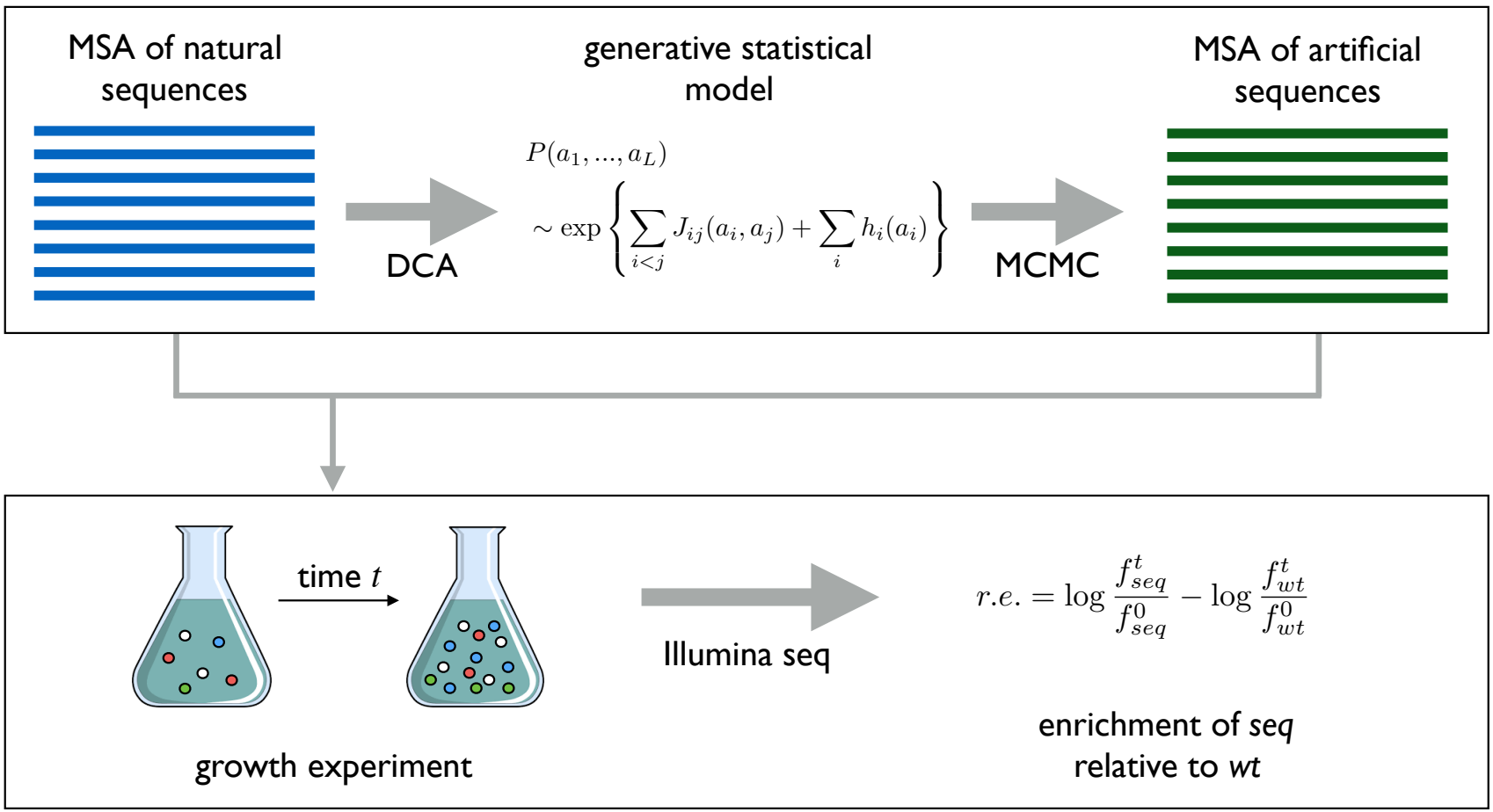
response regulator (PF00072)



➡ tested for many protein families

[Figliuzzi, Barrat-Charlaix, MW, Mol. Biol. Evol. 2018]

Coevolution-guided protein design



data-driven statistical sequence design

experimental validation of natural and designed sequences

experiments by B. Russ, R. Ranganathan

…all models are wrong, but some are useful.

[George E.P. Box, 1976]

Biological sequence evolution

≠

MCMC sampling from Potts models

…all models are wrong, but some are useful.

[George E.P. Box, 1976]

However DCA allows for

- protein structure prediction – strong couplings accurately predict contacts
- mutational effect prediction – statistical model as sequence landscape
- generative statistical modeling – pairwise couplings seem necessary and sufficient to capture biological sequence diversity

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However DCA allows for

- protein structure prediction – strong couplings accurately predict contacts
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A few current limitations

- many parameters vs. limited data – strong regularization against overfitting
  ➡ parsimonous modeling / dimensional reduction ?
- correlated data – DCA fits functional and phylogenetic correlations
  ➡ inference from non-i.i.d. samples ?
- better models may be even more useful…
  ➡ systematic selection of statistically relevant observables ?
- uses multiple-sequence alignment based on profile models
  ➡ more accurate methods using couplings for alignment ?
- sequences modeled as strings over abstract 21-letter alphabet
  ➡ prior biological knowledge / integrative modeling ?

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