Computational Protein Stability Prediction

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PUBS

Molecular and systems-level constraints acting on proteins

- Maintain protein stability
- Solubility
- Folding kinetics, lifetime
- Ability to switch between conformations (recognition, molecular machines)
- Binding to desired (multiple) partners
- Avoiding other (undesired) partners

Slide credit: Tanja Kortemme

The effect of a mutant on a protein's stability can be expressed as a $\Delta\Delta G$ value

Definitions:

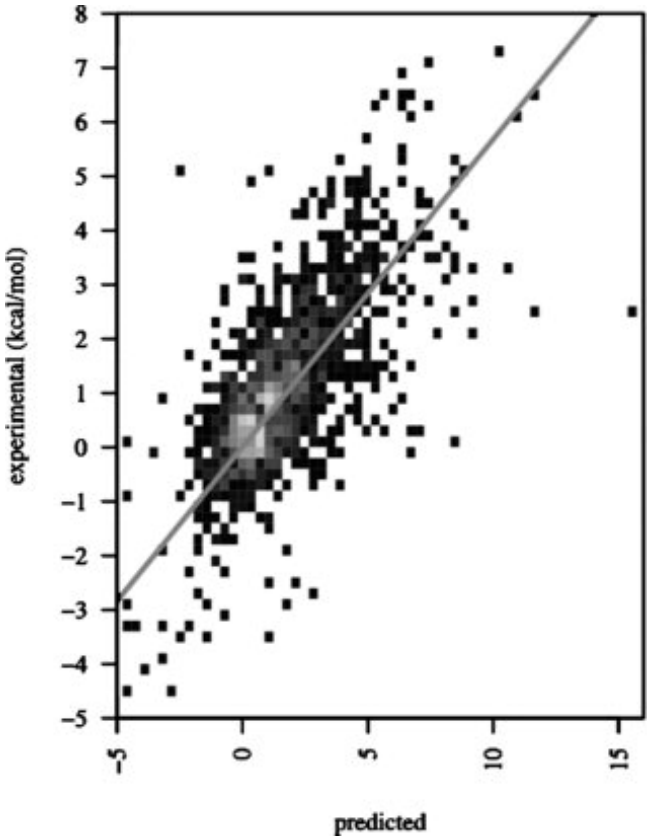
- G — Gibb's free energy
- ΔG – Change in free energy between the unfolded and folded states of a protein

$$\Delta G_{folding} = G_{native\ state} - G_{unfolded\ state} \tag{1}$$

- $\Delta\Delta G$ – Change in free energy of folding caused by a mutation

$$\Delta\Delta G_{I44F} = \Delta G_{folding\ F44} - \Delta G_{folding\ I44} \tag{2}$$

Enter computation: Rosetta $\Delta\Delta G$ Prediction



- Rosetta's predicted $\Delta\Delta G$ value for a single point mutant (starting from a known crystal structure) correlates well with experimental data
- The $\Delta\Delta G$ protocol uses the Rosetta energy function (described last week by Tanja), along with sampling algorithms such as an all side chain "packer", and backbone minimization

Kellogg et al. [1]

Your 1st task: interpret Rosetta's $\Delta\Delta G$ predictions for ubiquitin in the context of your sequencing data

- **Maintain protein stability** — *it should be possible to account for this effect (to some degree) using Rosetta's predicted $\Delta\Delta G$ values*
- Solubility
- Folding kinetics, lifetime
- Ability to switch between conformations (recognition, molecular machines)
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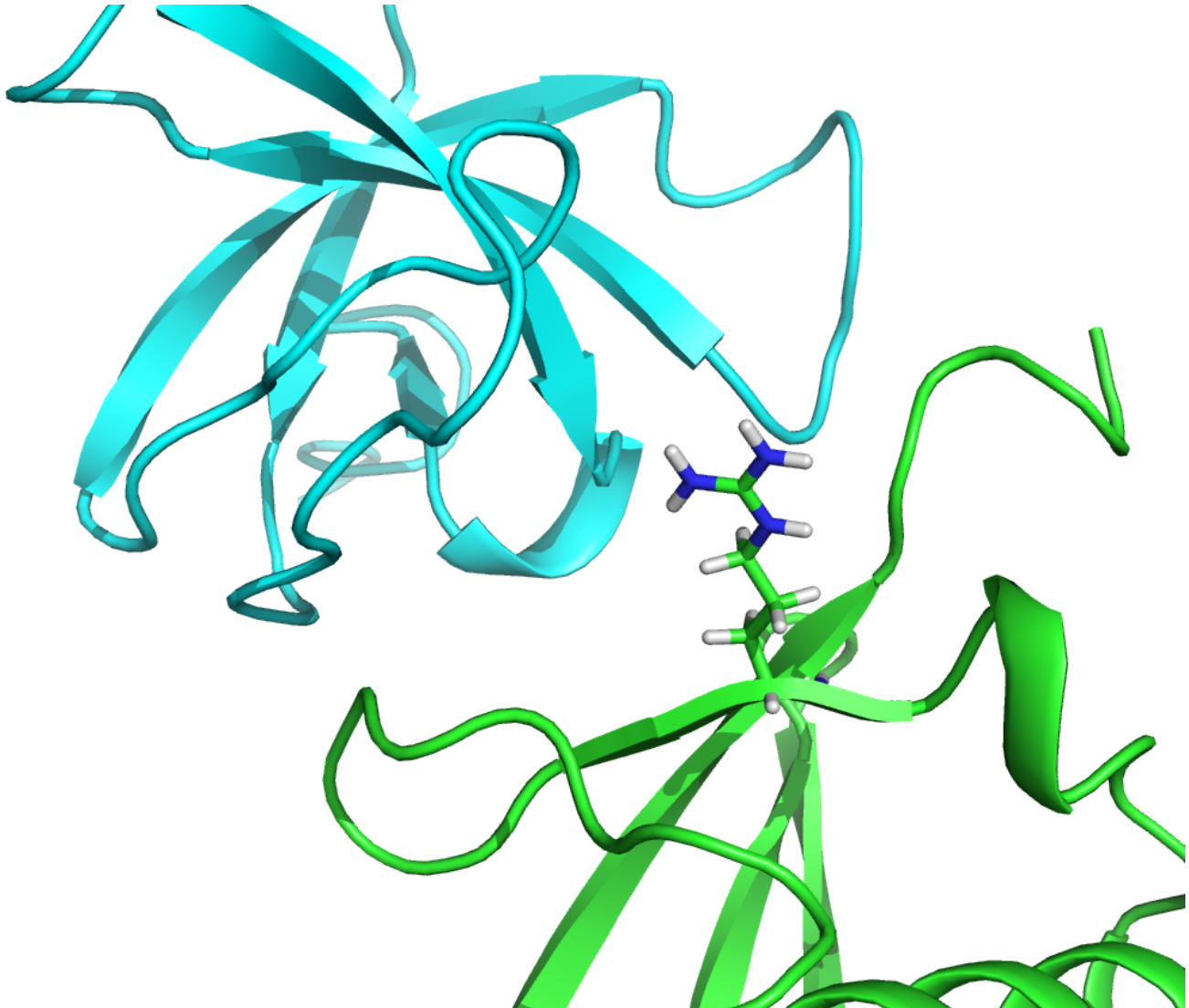
$\Delta\Delta G$ can also be calculated for a residue in a protein complex

$\Delta\Delta G$ can now be thought of as the change in stability of the entire complex.



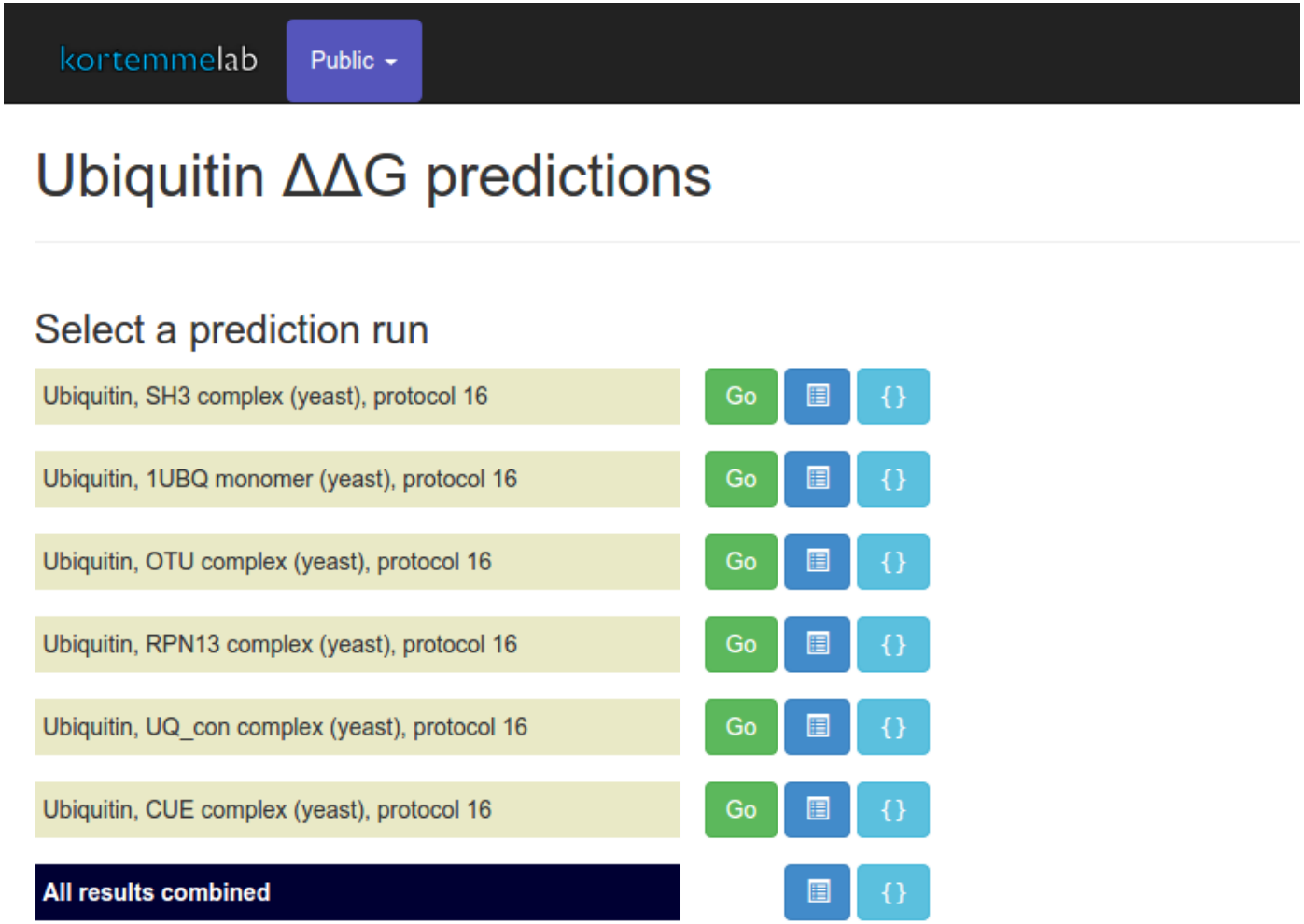
Your next task: interpret Rosetta's $\Delta\Delta G$ predictions for ubiquitin in the context of your fitness data

- Maintain protein stability
- Solubility
- Folding kinetics, lifetime
- Ability to switch between conformations (recognition, molecular machines)
- **Binding to desired (multiple) partners** – How well does a change in stability for ubiquitin and a bound partner correlate with fitness? Why?
- Avoiding other (undesired) partners

Some ubiquitin/partner complexes you will be able to investigate

Identifier	PDB ID	Perturbation of interest	Yeast gene
1UBQ	1UBQ	All	WT Ubiquitin
SH3	2JT4	Caffeine	Many, including CDC25, CYK3, FUS1
OTU	3BY4	DTT	OTU1
RPN13	2Z59	MG123	RPN13
UQ_con	2GMI	Hydroxy Urea	Ubc13, Mms2
CUE	2LVO	DMSO	CUE1 (HRD1)

Website demo



Summary: Your tasks

1. Download the Rosetta $\Delta\Delta G$ prediction data from the website (http://url.ipqb.org/rosettaddg) for the ubiquitin monomer
   - Compare this data with your fitness data for the unperturbed condition. Generate hypotheses about how well/why/where predicted stabilities relate to fitness effects.
2. Download the Rosetta $\Delta\Delta G$ prediction data for all available complexes, analyze, and hypothesize!
3. Reread Roscoe et al. [2] if you need additional inspiration.

On Wednesday teams will do a short presentation of initial results, and Samuel will begin the multi-constraint design activity

References

[1] Elizabeth H. Kellogg, Andrew Leaver-Fay, and David Baker. Role of conformational sampling in computing mutation-induced changes in protein structure and stability. *Proteins: Structure, Function, and Bioinformatics*, 79(3):830–838, March 2011. ISSN 08873585. doi: 10.1002/prot.22921. URL http://onlinelibrary.wiley.com/enhanced/doi/10.1002/prot.22921/.

[2] Benjamin P. Roscoe, Kelly M. Thayer, Konstantin B. Zeldovich, David Fushman, and Daniel N. A. Bolon. Analyses of the effects of all ubiquitin point mutants on yeast growth rate. *Journal of Molecular Biology*, 425 (8):1363–1377, April 2013. ISSN 0022-2836. doi: 10.1016/j.jmb.2013.01.032. URL http://www.sciencedirect.com/science/article/pii/S0022283613000636.