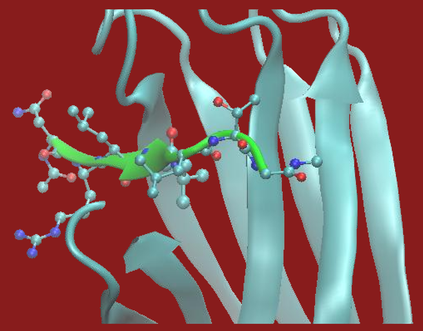
University of Massachusetts Amherst



Physical Origins of DnaK-Substrate Binding Revealed through Physics-based Model: PALADIN

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Introduction

Molecular chaperone **DnaK** aids cellular **Quality Control** by binding to misfolded proteins.

Big Question:
What is the physical nature of DnaK's selective preferences?

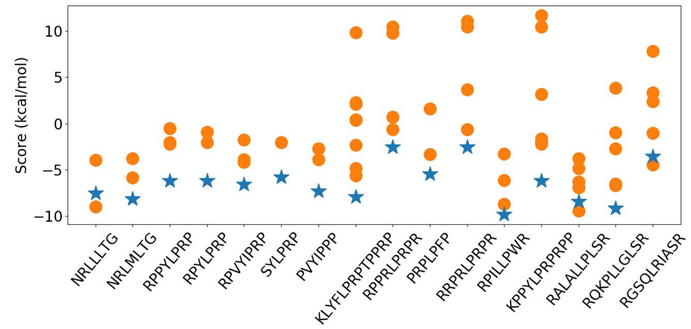
PALADIN: Physics-based model of DnaK-substrate binding

PALADIN is highly extensible and can distinguish peptides in both orientations.

PALADIN model form:

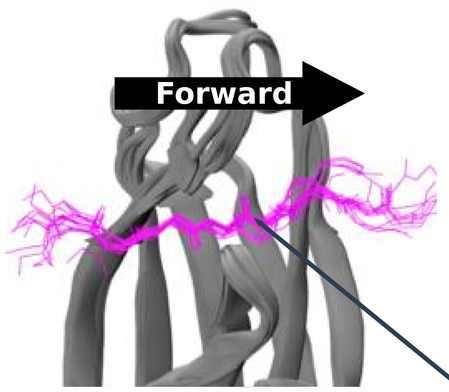
$$\Delta E\left(\text{5-mer}\right)=\sum_{sites} w_{site} \sum_{terms} w_{term} E^{res}_{\text{site,term}}$$

PALADIN has high resolution



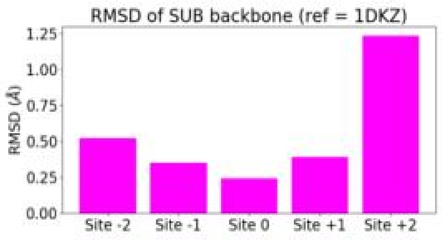
Where blue star is lowest in energy = correct prediction

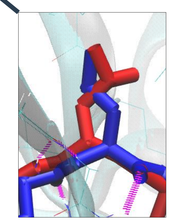
Consistent Binding Pose



Overlay of many **Substrates** and **DnaK** binding domains. Pose is invariant of:

- Sidechain
- Orientation

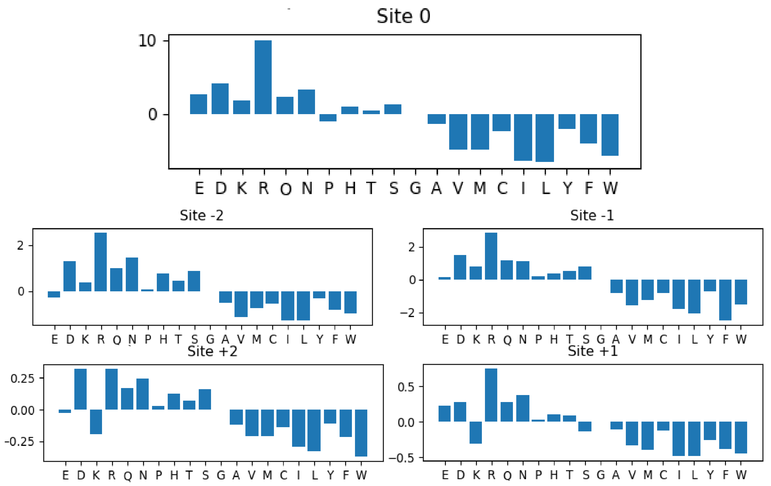




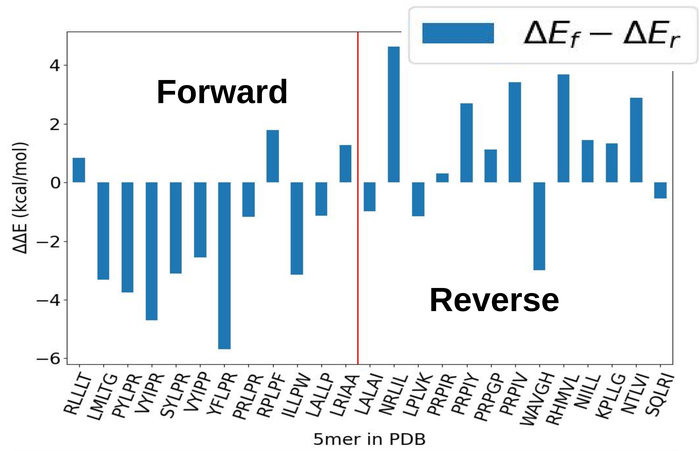
Forward
Reverse
Leu @ Site 0

Physical Interaction Terms

Basis-set **MD simulations** to sample interactions between DnaK and substrates in **binding pose** yield terms that combine effects of:
sterics, **electrostatics** and **solvation**.



PALADIN distinguishes orientations!



Applications

- Extend to other Hsp70 homologs
- Iteratively design new binding motifs with desired affinity

References:

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2.Clerico, et al. (2019) Biochem J.,476(11):1653-1677
3.Zahn, et al. (2013) J. Mol. Biol. 425, 2463–2479
4.Clerico, et al. (in prep.)

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