Searching function through docking

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Target: Lipoprotein YxeF

- Organism: Bacillus Subtilis (gram +)
- Bacterial Lipoproteins:
  - Secretory
  - Membrane-associated
  - N-terminal lipobox (signal peptide) cleaved
    -> anchored to cell membrane (usually outside)
Structure: 2joz

- NMR (20 structures)
- (Most of) signal peptide left off
- His-tag at C-terminus
- Lipocalin structure
Comparison YxeF – BLC (E. Coli)
Comparison BLC - YxeF

- BLC (solid)
- YxeF (mesh)
- Neutral / - / +
Searching for natural ligands

1. Compile libraries of potential binders
   a. Lipids from \textit{(B. subtilis)} cell membranes
   b. Compounds involved in lipid metabolism
   c. all of KEGG and HMD

2. Dock into protein structures
How to validate?

- Redock complexed ligand
- BLC apo
- Reference ligand
- Docking: first rank
- Docking: best result
How to validate?

- Dock BLC ligands to BLC complex / apo

- title: ampicillin CHEBI:28971
- title: 1-oleoyl-2-hydroxy-sn-glycero-

- title: retinol CHEBI:50211

- title: 1-palmitoyl-2-hydroxy-sn-glycero...
- title: arachidonate CHEBI:32395
- title: sn-glycero-3-phosphoethanolamine...

- title: complexed ligand 2aco liggrep
- title: palmitoleic acid CHEBI:28716
- title: cis-vaccenic acid CHEBI:50464

- title: myristic acid CHEBI:28875
- title: oleate CHEBI:30823
How to validate?

- Dock BLC ligands to BLC complex / apo
  - Normal docking: correlation ???

![Graphs showing docking score vs log Kd for complex and apo](image)
How to validate?

• Dock BLC ligands to BLC complex / apo
  – Normal docking: correlation ???
  – Induced fit docking: best binders scored best

Induced Fit - complex

Induced fit - apo
How to validate?

Dock BLC ligands to BLC complex /apo– Normal docking: No correlation!– Induced fit docking: best binders scored best– Enrichment?

score distribution

docking score

fraction screened

tested Compounds membrane lipids lipid metabolism
Workflow on YxeF

- Dock data sets to all conformations
- Select best pose over all conformations
- Cluster results
Lipids in YxeF

Glide SP

-10  -8  -6  -4  -2  0  2

-10  -8  -6  -4  -2  0  2

fraction screened
glide score

lipid metabolism  membrane lipid
Kegg/HMD in YxeF
Kegg/HMD top scoring in YxeF
Kegg/HMD top efficient in YxeF
Next steps

• Cluster KEGG/HMD results
• Investigate role of disordered parts
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