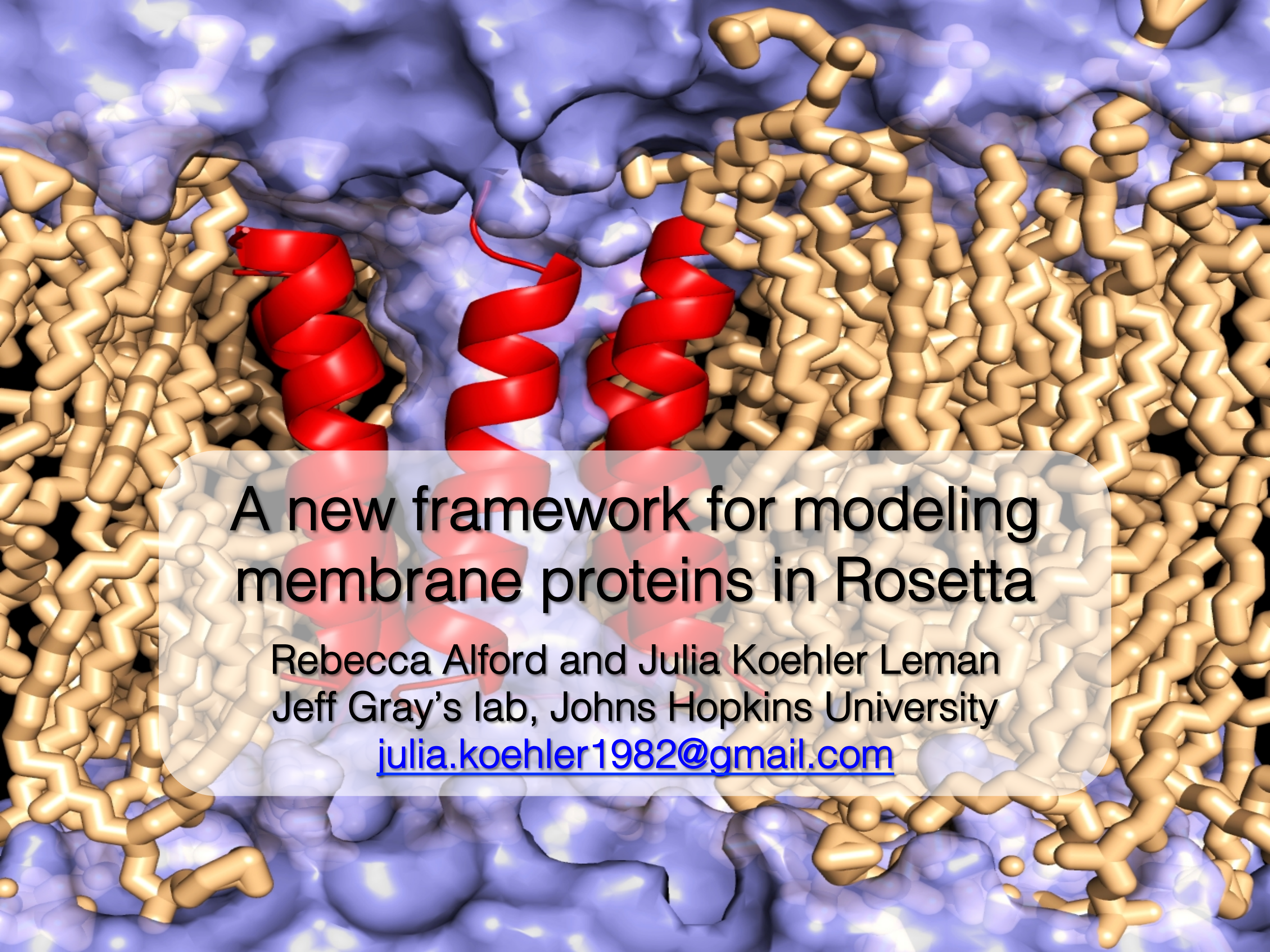




A new framework for modeling membrane proteins in Rosetta

Rebecca Alford and Julia Koehler Leman
Jeff Gray's lab, Johns Hopkins University

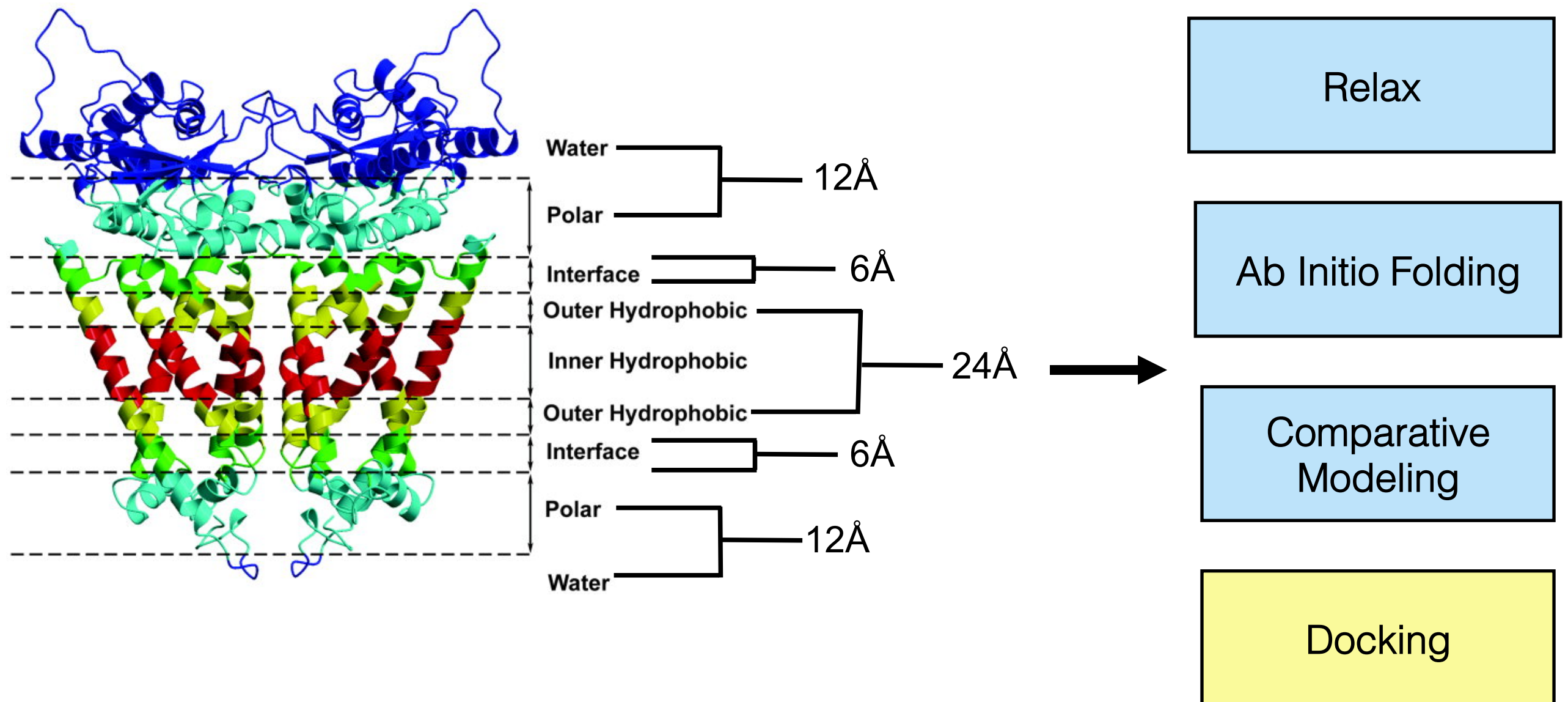
julia.koehler1982@gmail.com

A brief history of the code...

- written and published in 2006 / 2007
- some parts are direct ports from Fortran
- Rosetta code base has changed drastically since
=> new frameworks available now
- need more flexibility, better code design, use for more protocols



Current Membrane Framework only supports selected protocols

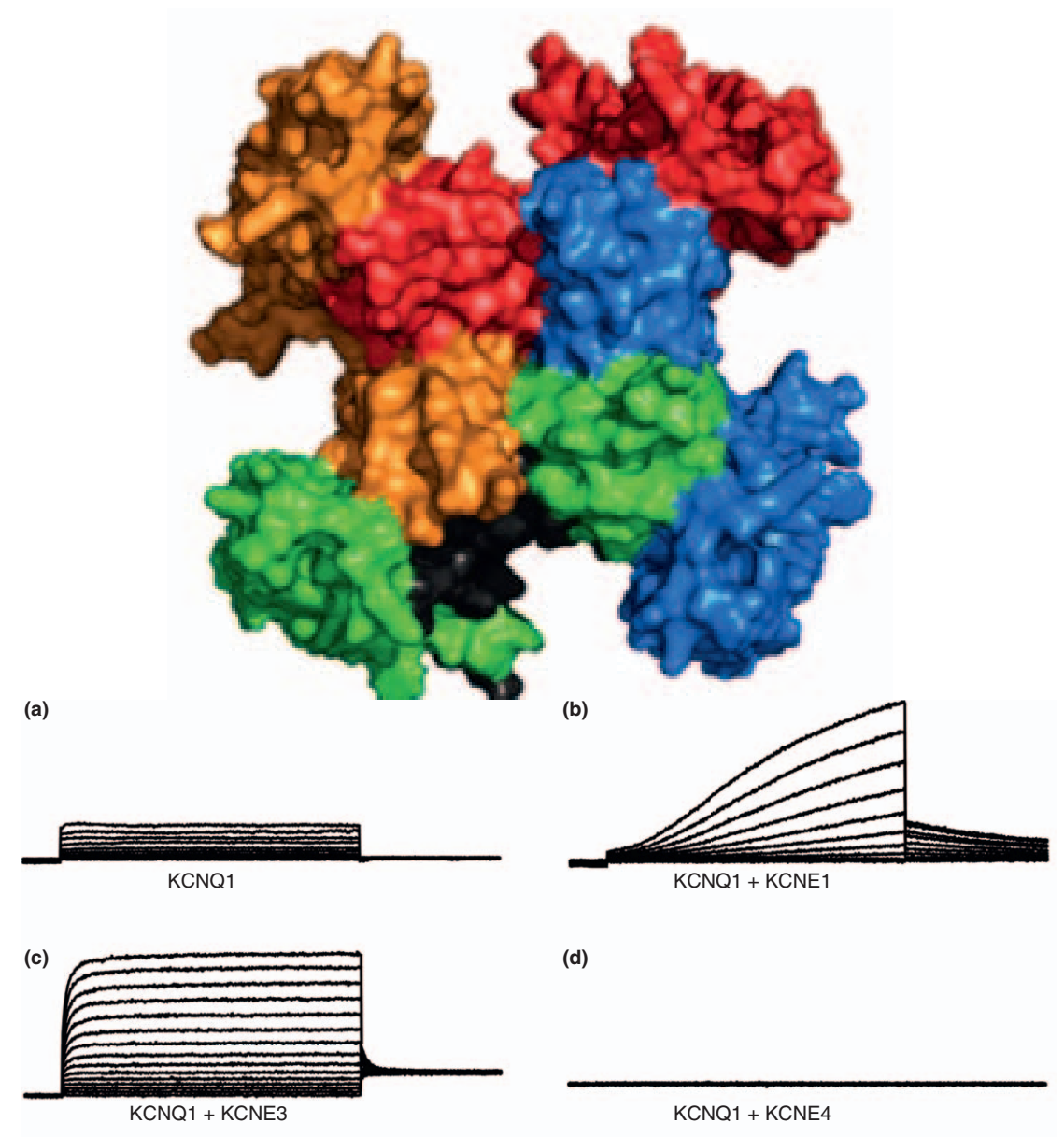
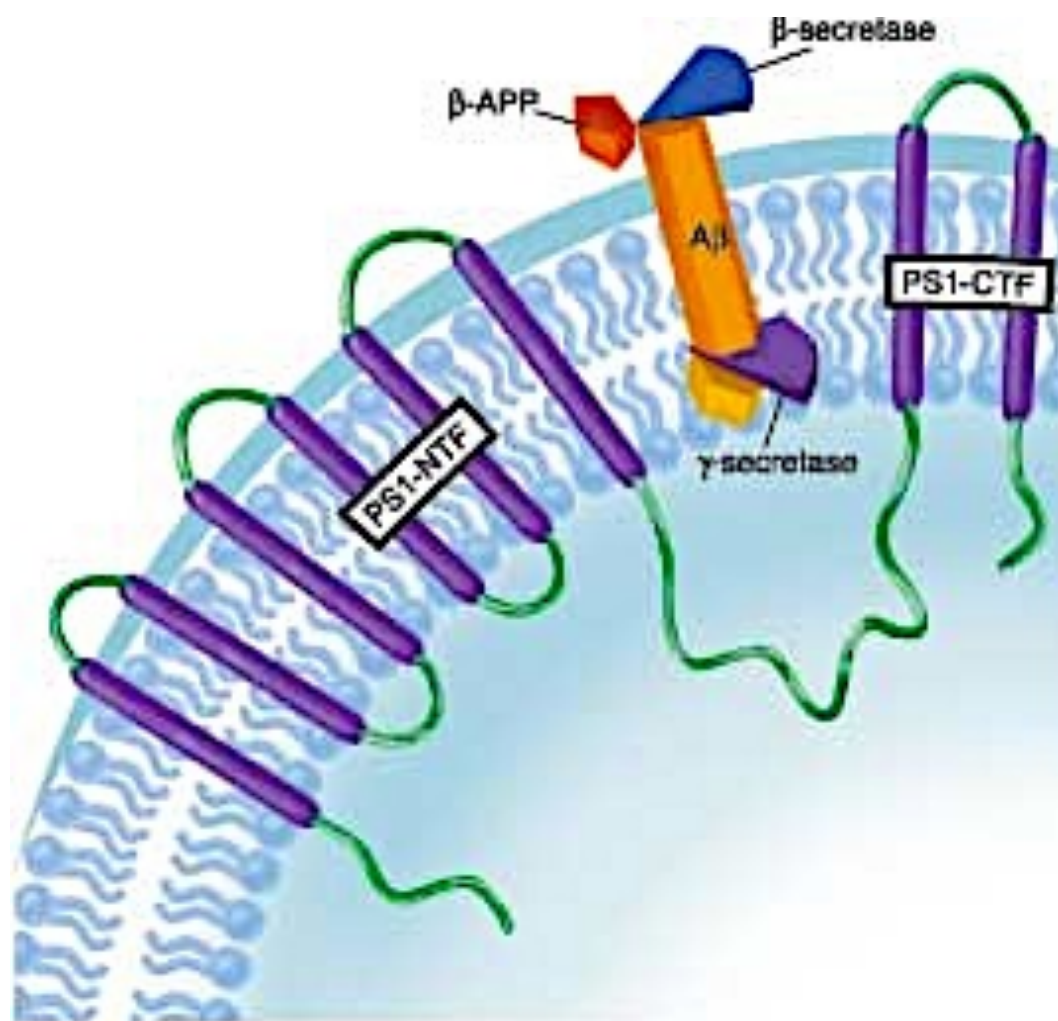


$$E_{total} = E_{env} + E_{pair} + E_{density} + E_{clash}$$

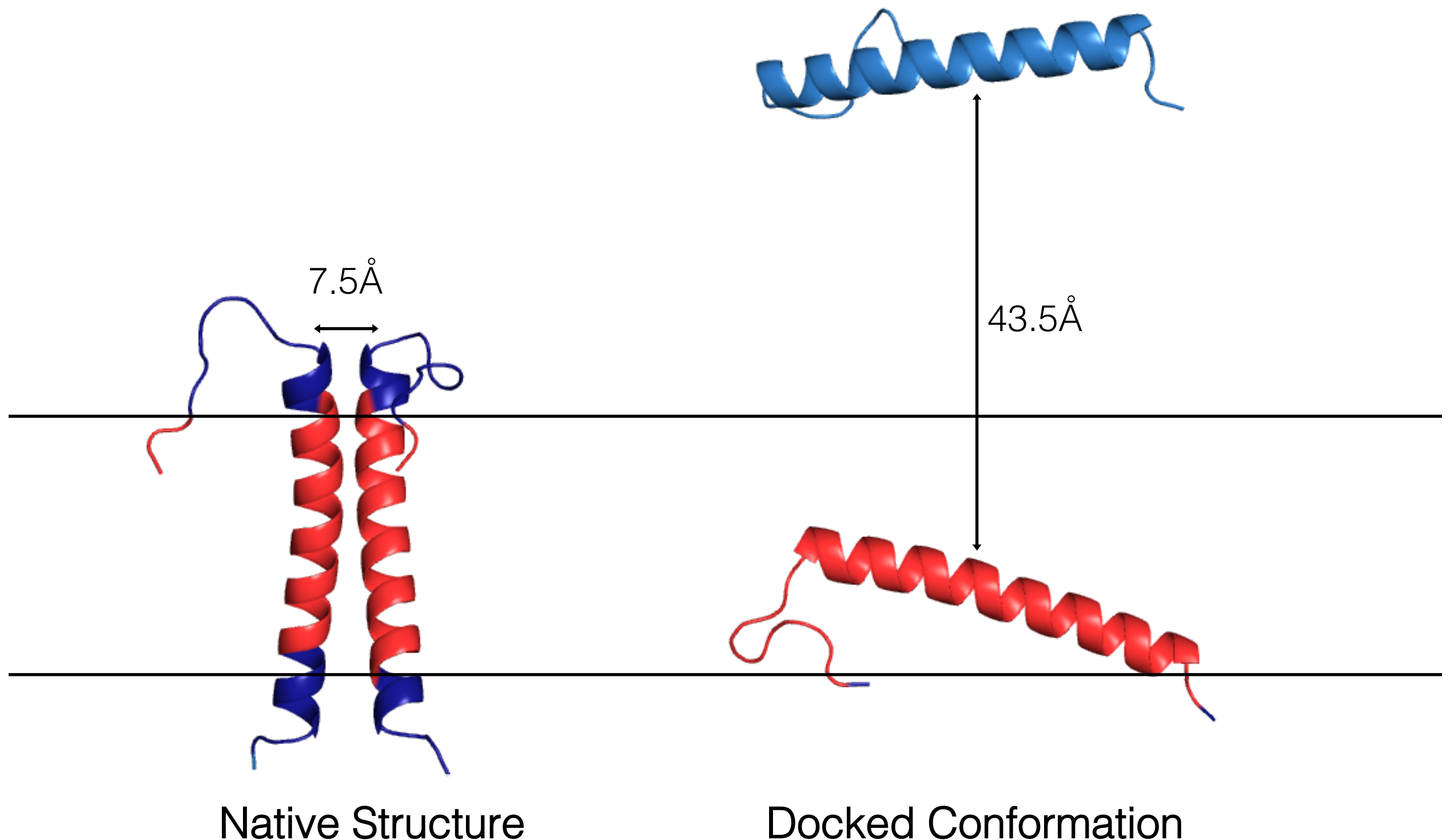
Motivation: We want to know how proteins interact within the membrane

γ -secretase and APP

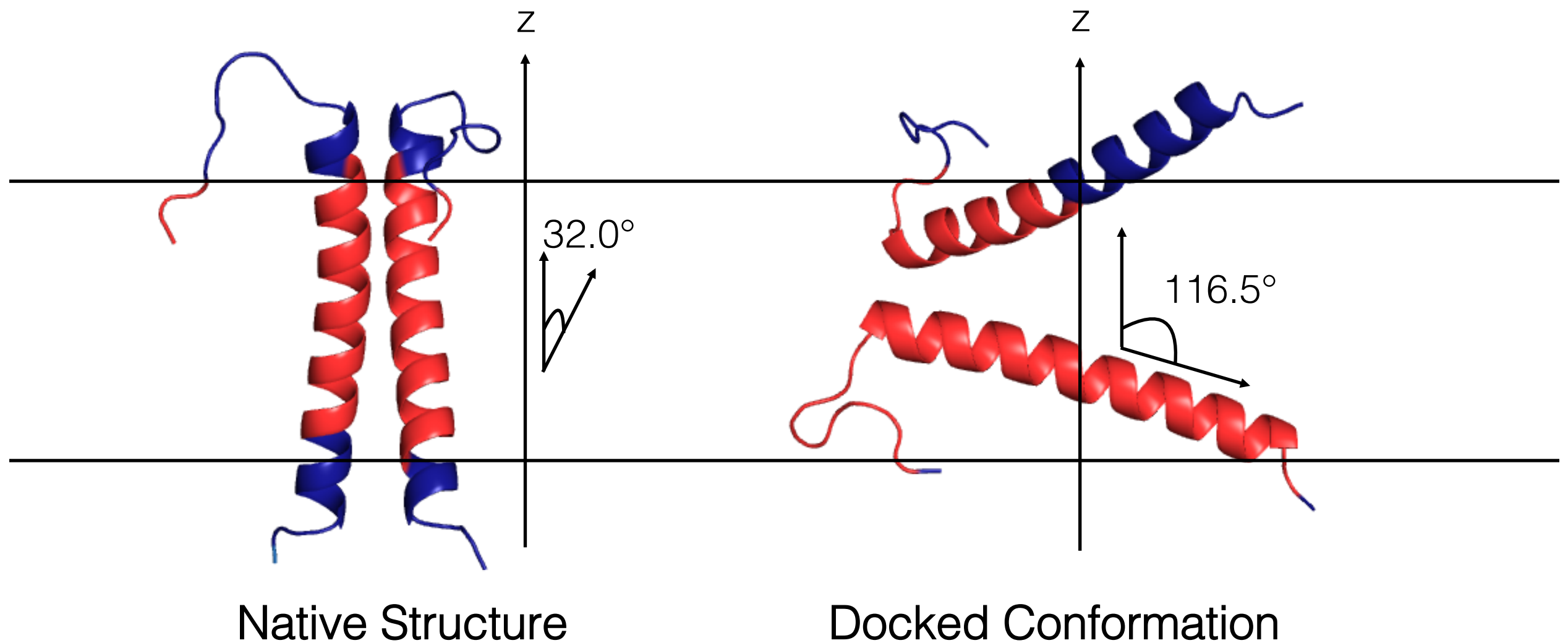
KCNQ1 and KCNE1



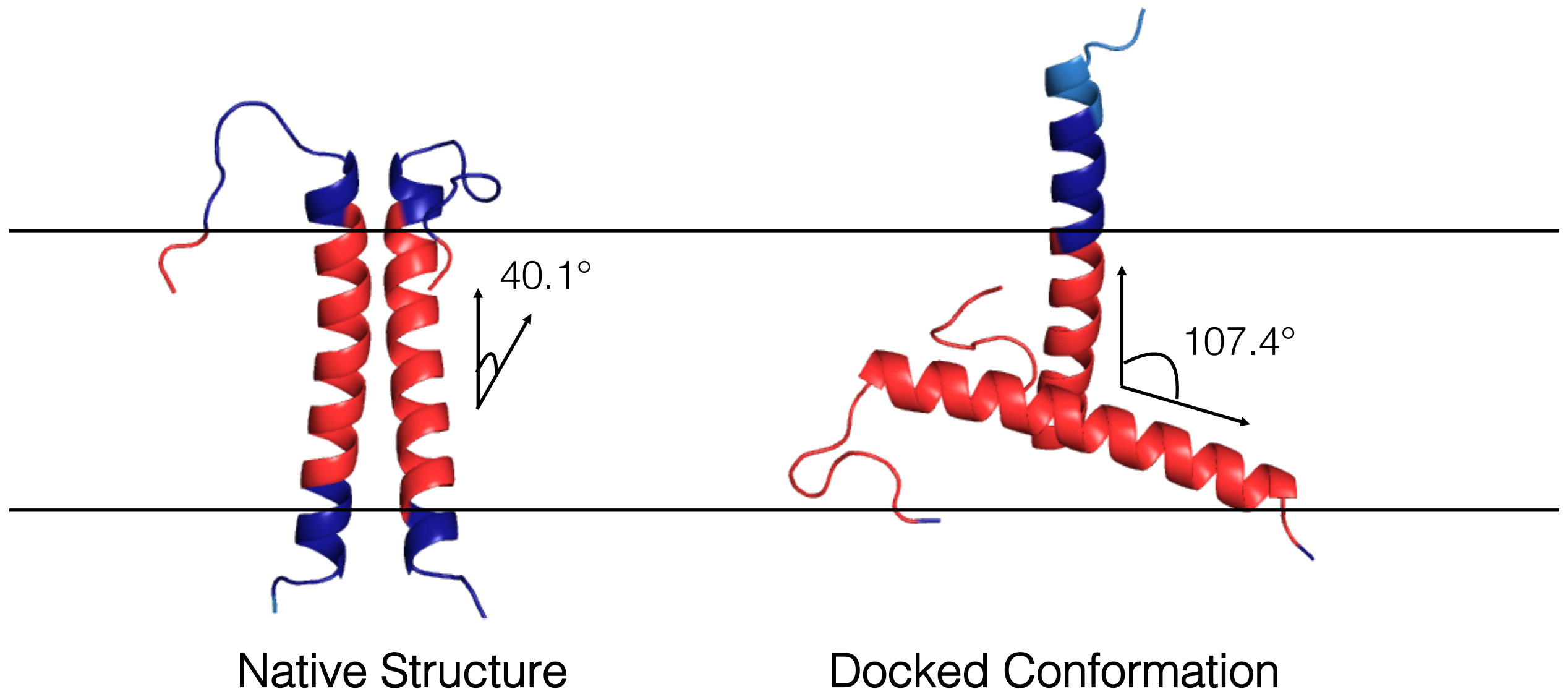
Current framework has deficiencies in docking proteins in the membrane bilayer



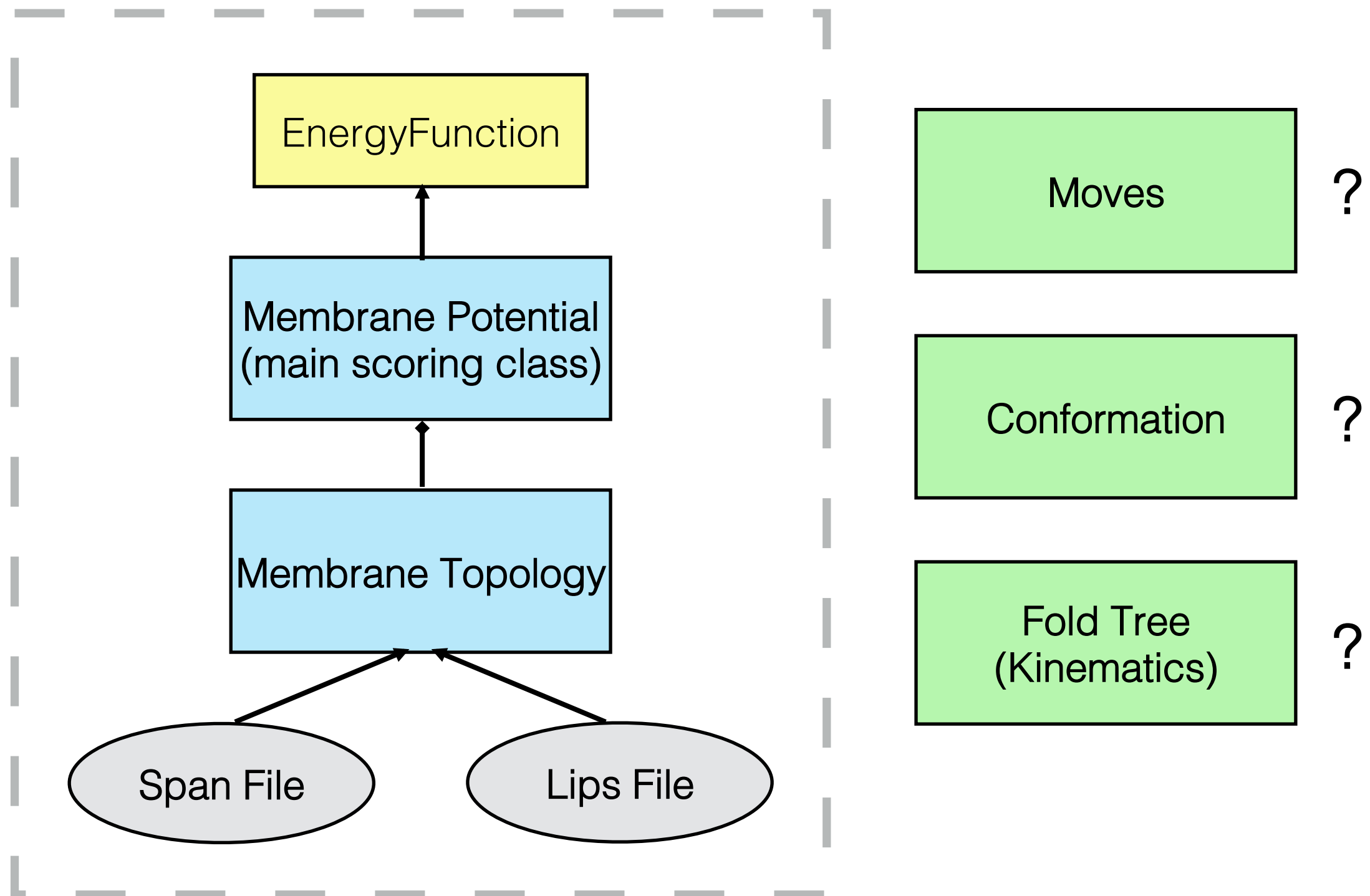
Current framework has deficiencies in docking proteins in the membrane bilayer



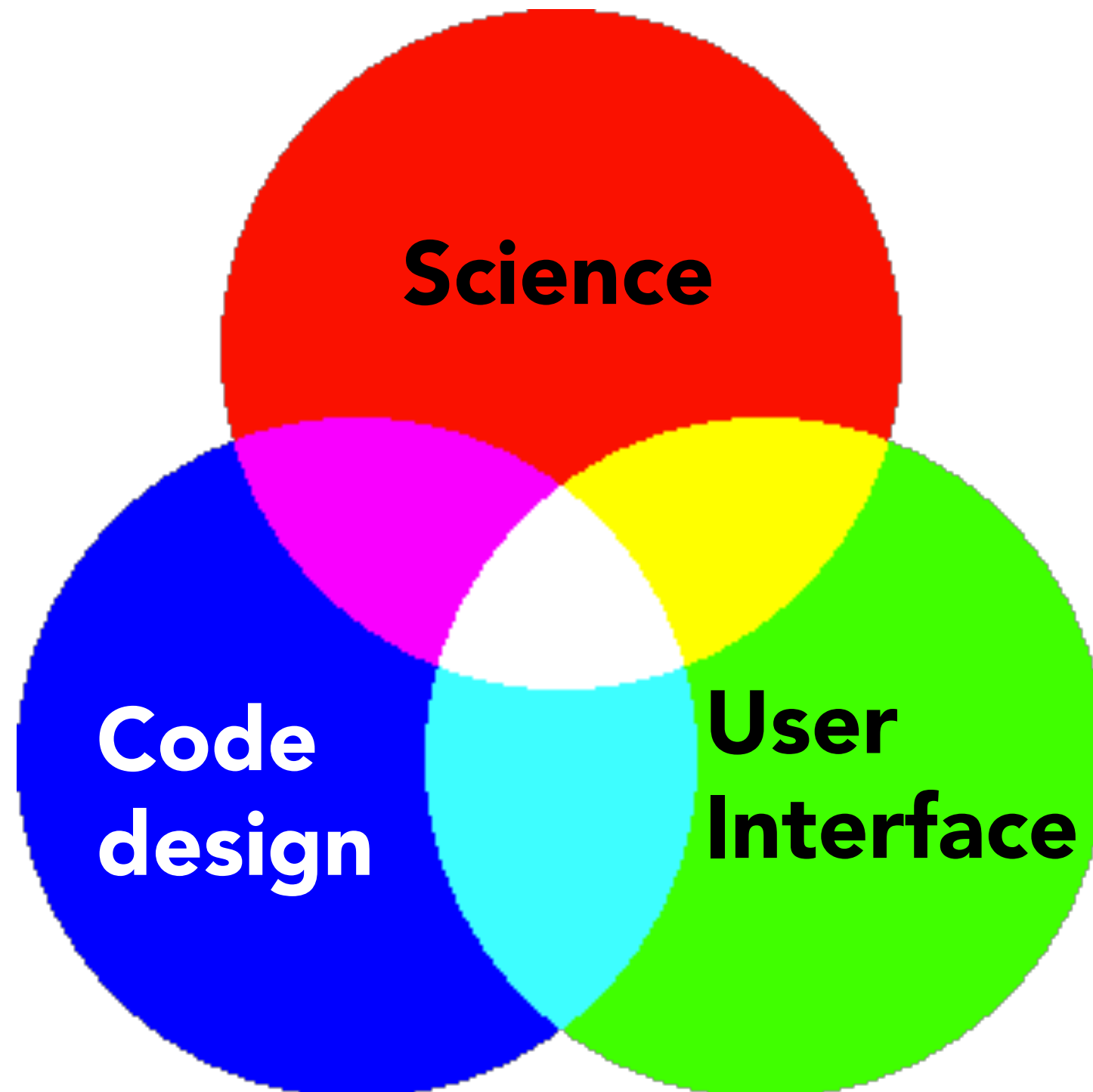
Current framework has deficiencies in docking proteins in the membrane bilayer



Why did docking fail? No connection between scoring, moves, and geometry



Development of new framework
needs to fulfill several requirements



New design should integrate well into Rosetta structure

1. Handle topology and embedding of multiple chains

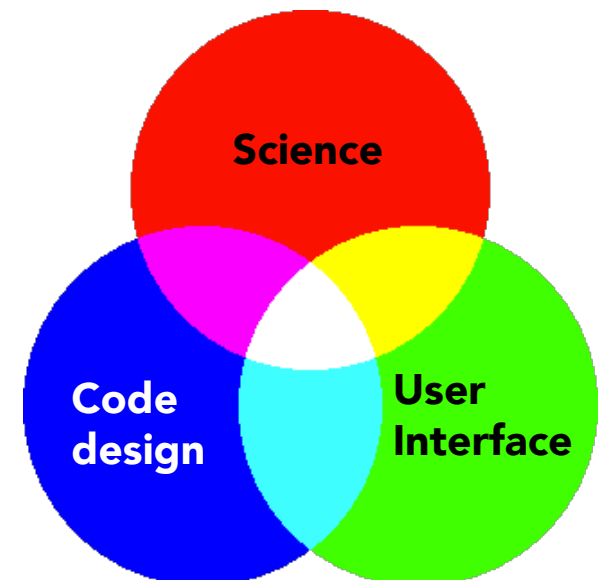
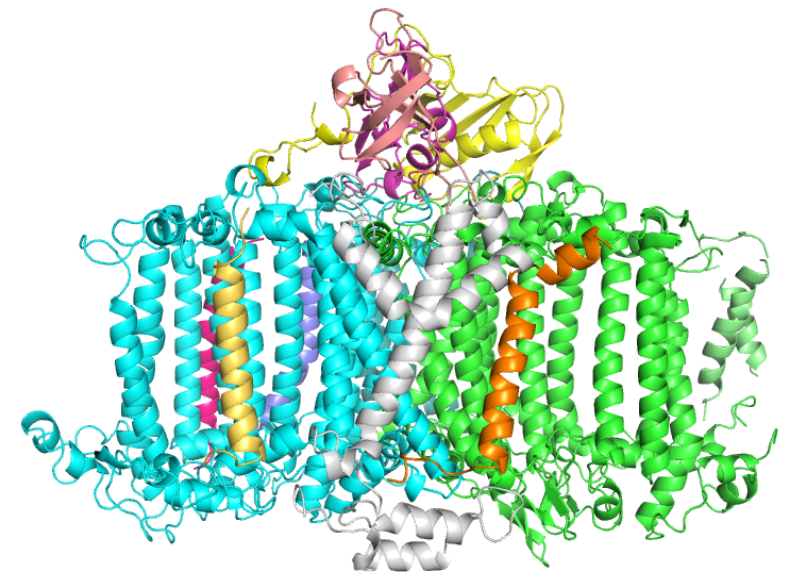
2. Model large membrane proteins

3. Build membrane Fold Tree

4. Accessible in-code interface to membrane framework

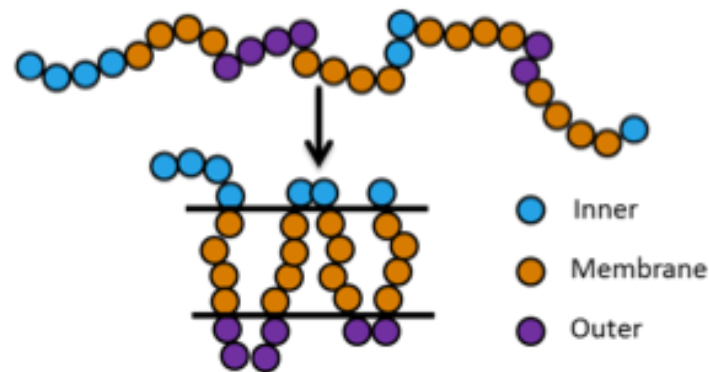
5. Allows easy development of new protocols

6. Improve input handling and user friendliness



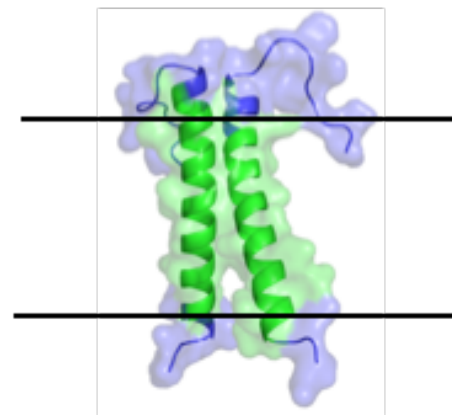
Definitions of basic objects in the code are reflected in the input

Spanning Topology



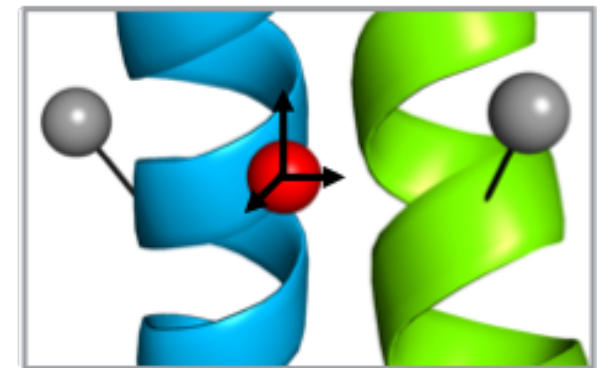
Sequence or structure based definition of membrane spanning regions

Lipid Accessibility



Sequence based residue exposure to lipids in the membrane

Embedding



Structure-based position of chain or individual helix in the membrane

TM helix: 15 – 29

TM helix: 36 – 52

center = (5, 12, 2)

normal = (1, 3, 10)

Input:

required

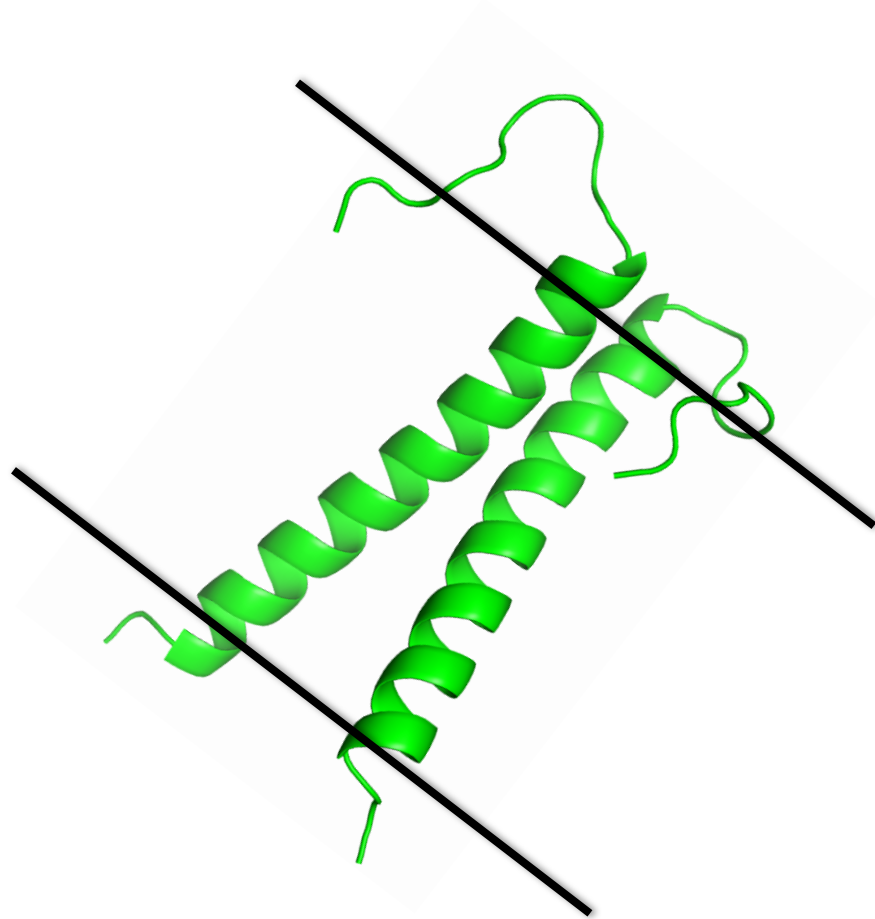
optional

optional

Membrane in new framework is fixed

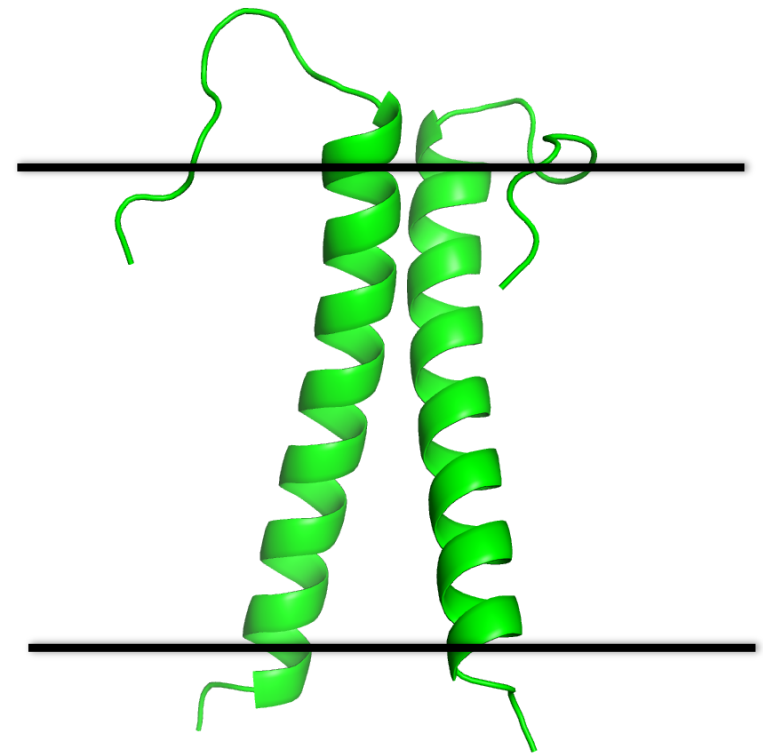
Current implementation

membrane is moved

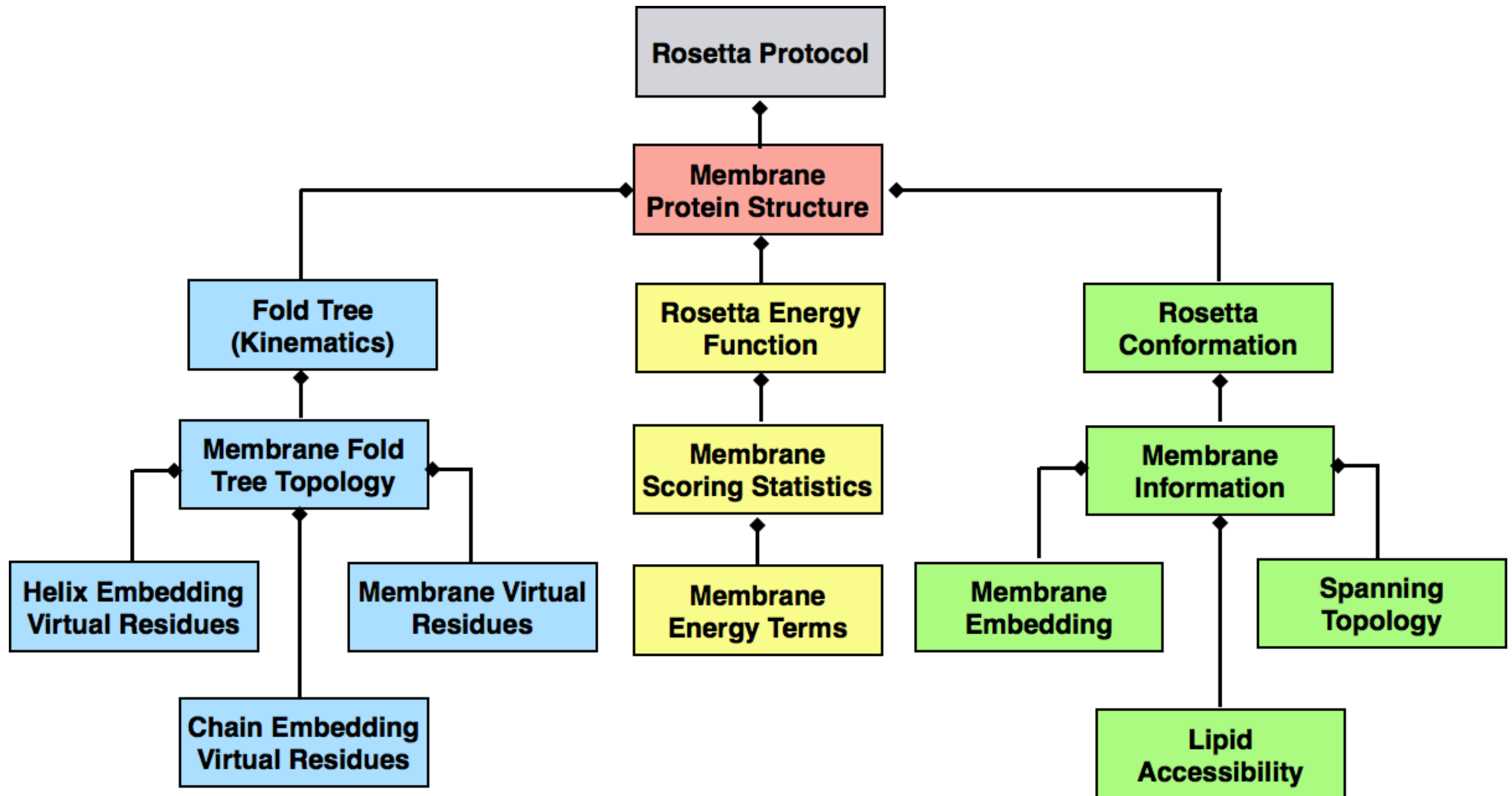


New implementation

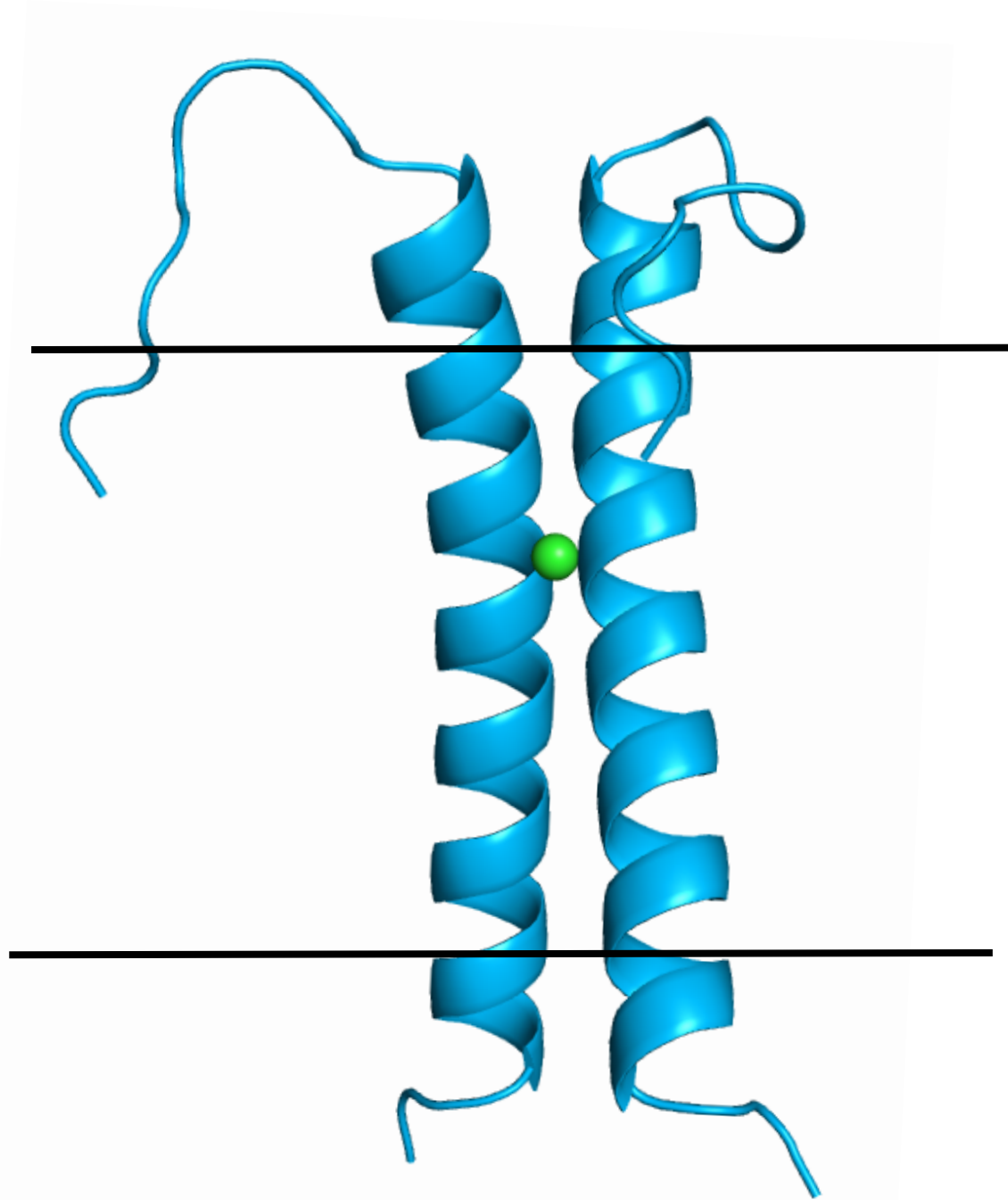
protein is moved



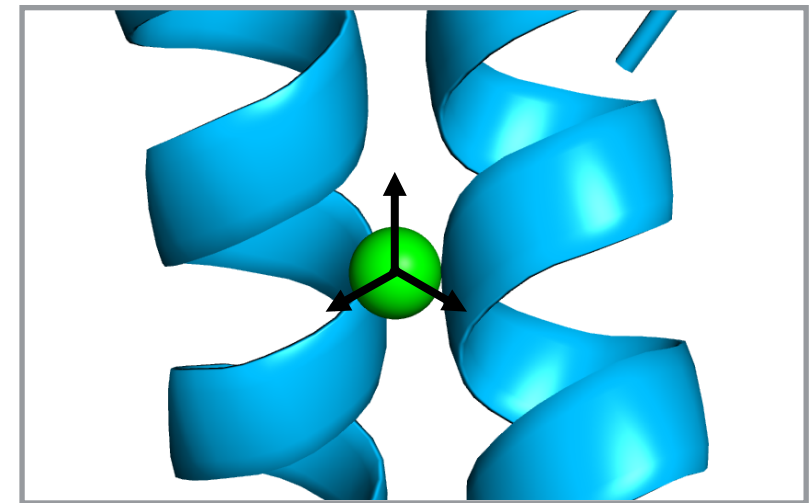
New framework incorporates conformation, kinematics, and energy function



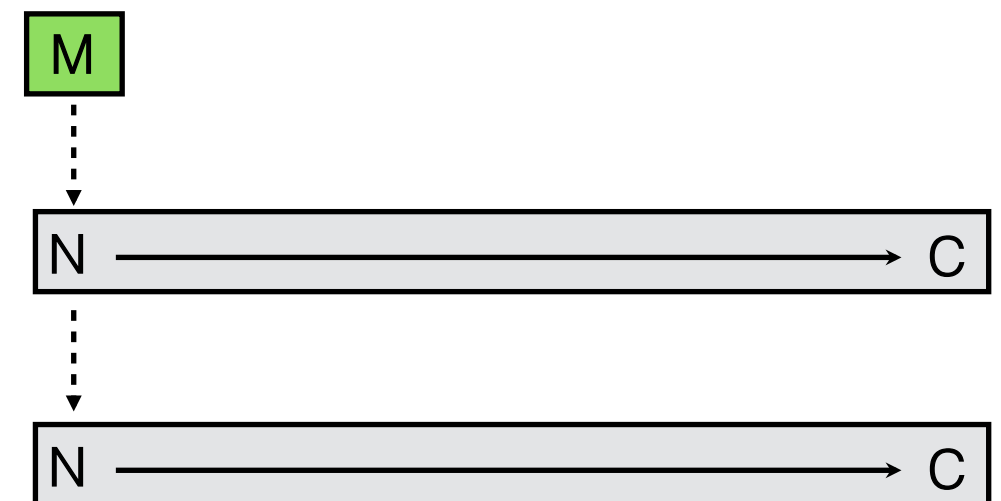
In current code MP only represented in scoring, not in conformation



Single Topology - One Pose

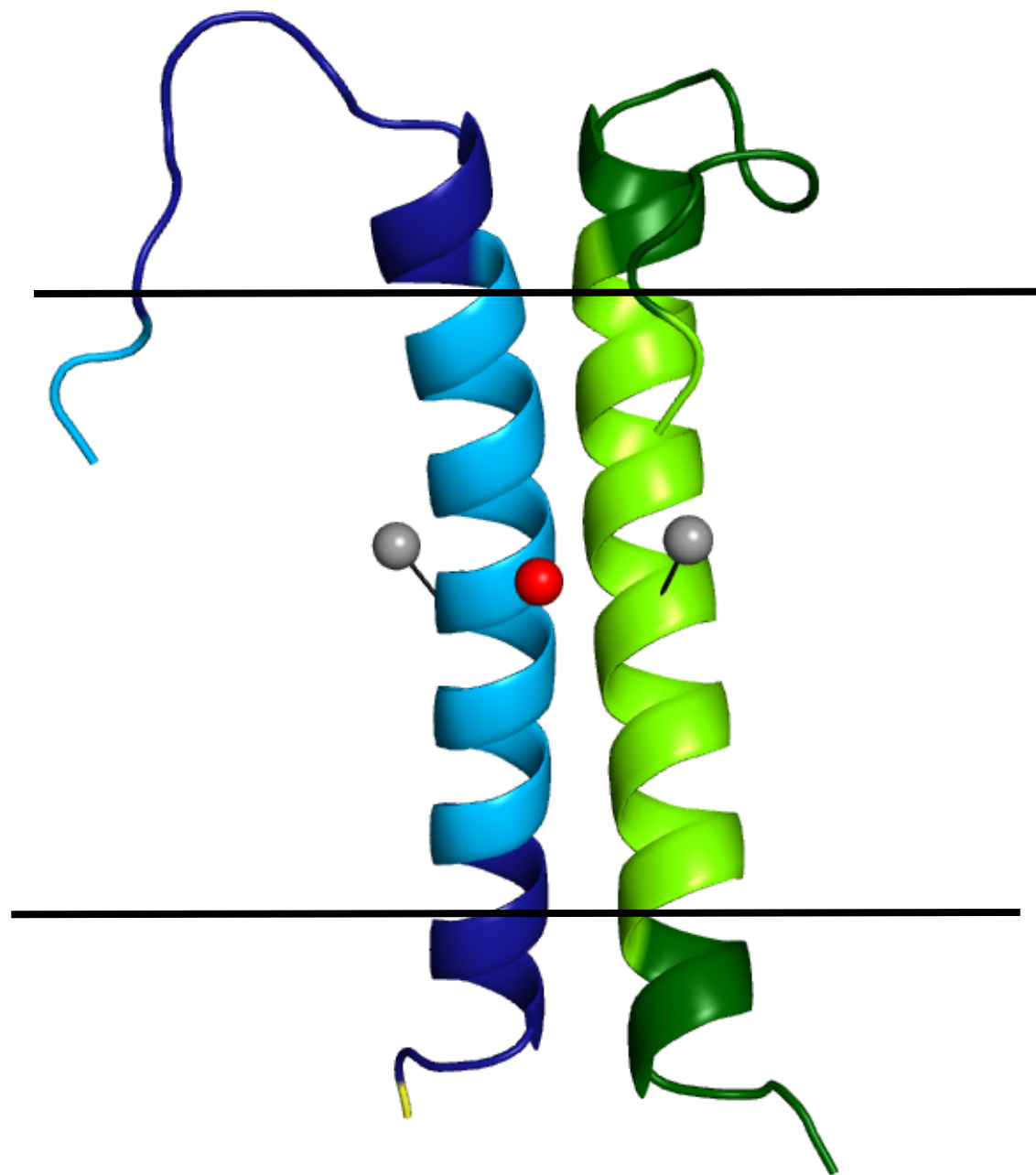


Single Embedding - One Pose

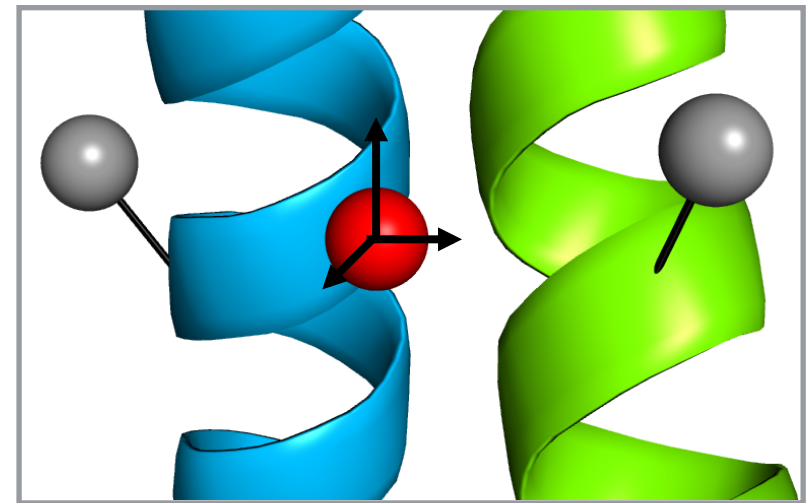


Old FoldTree

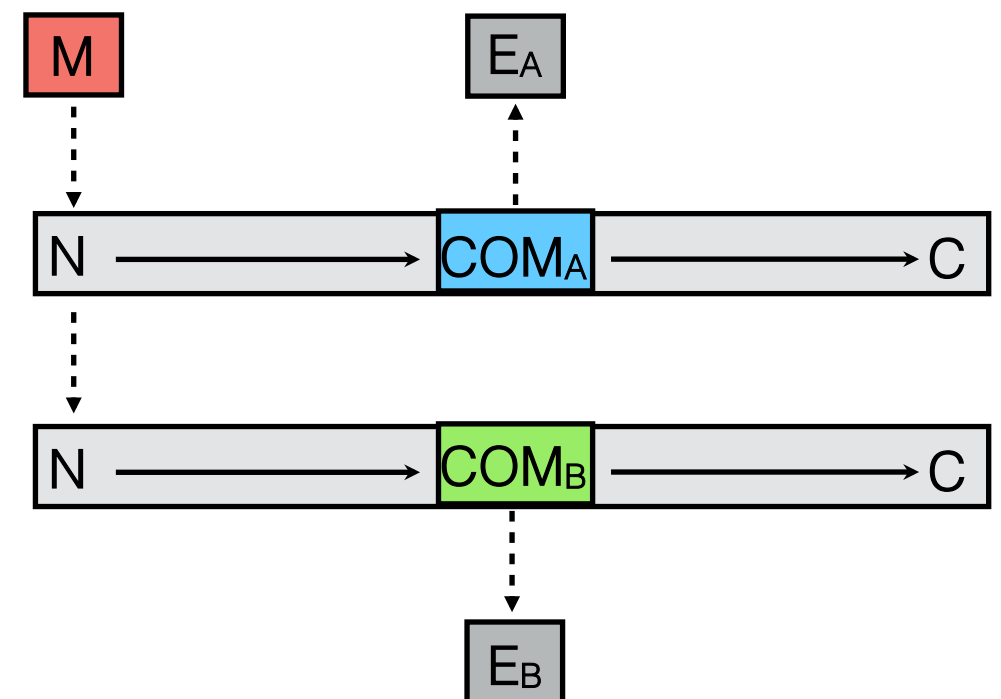
New code represents membrane topology and embedding by chain



Topology for Each Chain

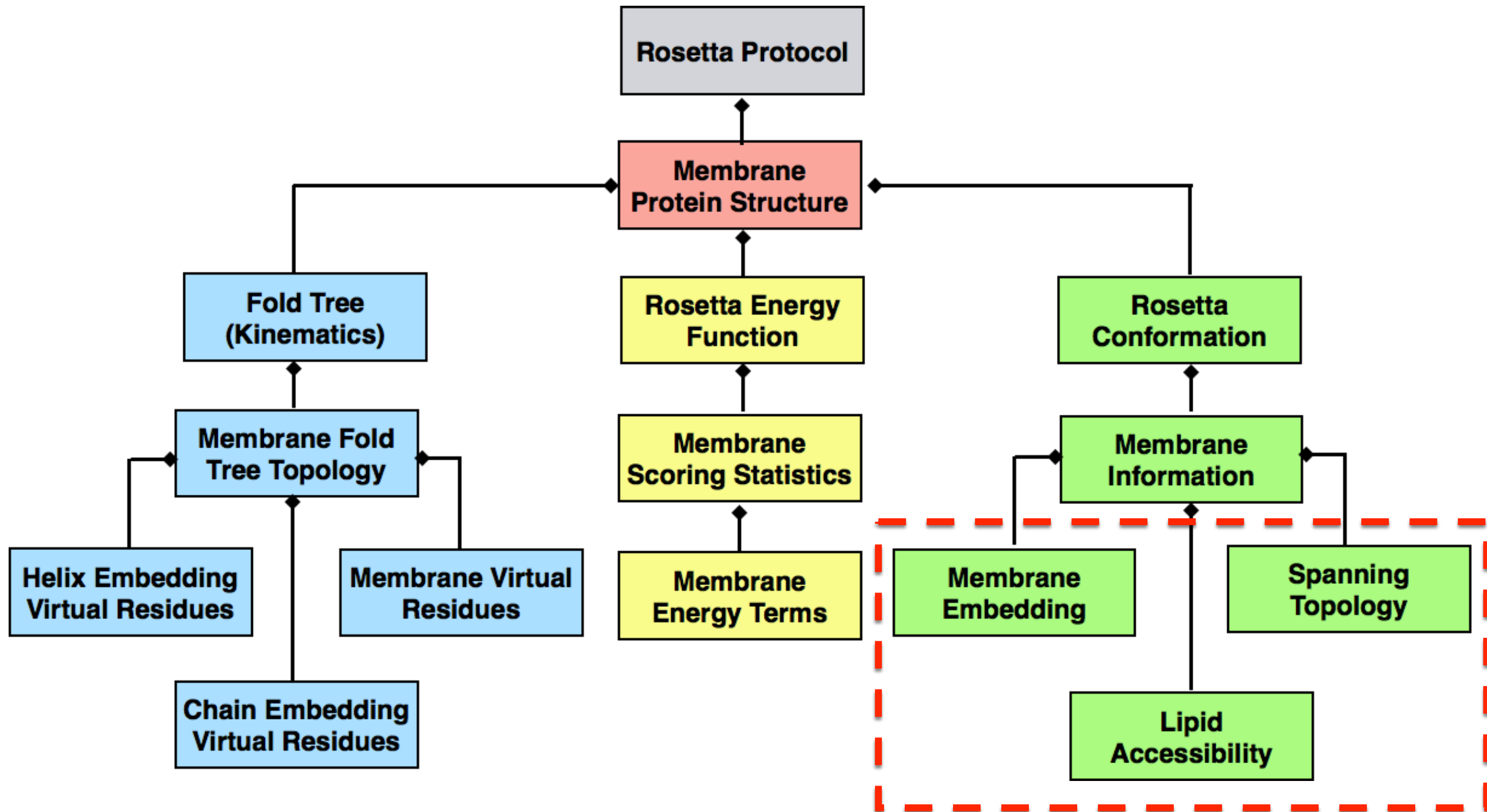


Embedding + Membrane Residues



Membrane FoldTree

New framework: user interface



New framework has simplified command line options

Previous Options File

```
-in:file:spanfile example.span  
-in:file:lipofile example.lips4  
-membrane:no_interpolateMpair  
-membrane:Menv_penalties  
-membrane:fixed_membrane  
-membrane:Membed_init  
-membrane:normal_cycles  
-membrane:normal_mag 15  
-membrane:center_mag 10  
-membrane:smooth_move_frac  
-membrane:center_search  
-membrane:normal_search  
-membrane:center_max_delta 10  
-membrane:normal_max_angle 10  
-membrane:normal_start_angle 10
```



Only specify one .span
and .lips file



Conflicting/undefined
option combinations

New framework has simplified command line options

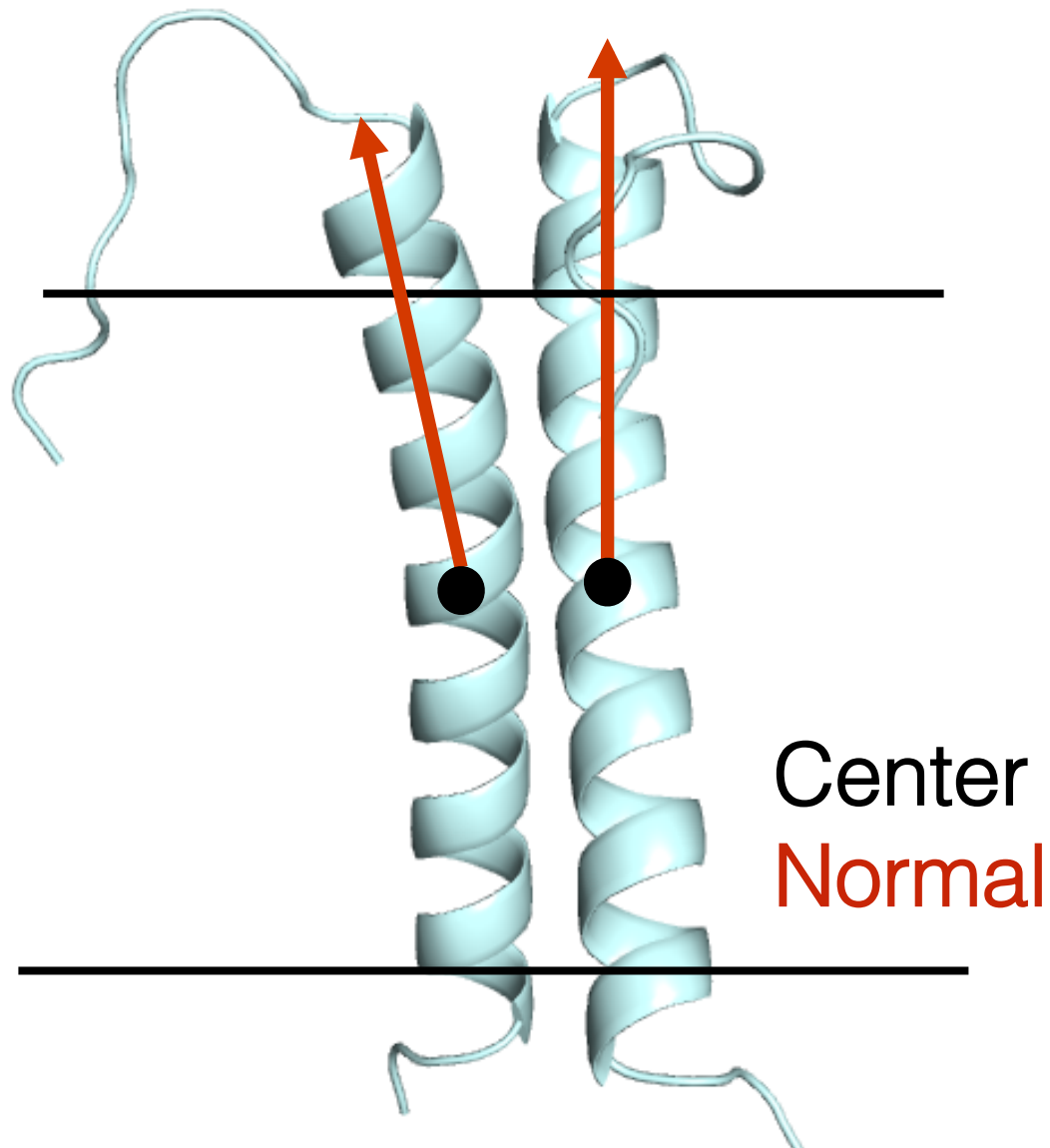
Previous Options File

```
-in:file:spanfile example.span  
-in:file:lipofile example.lips4  
-membrane:no_interpolateMpair  
-membrane:Menv_penalties  
-membrane:fixed_membrane  
-membrane:Membed_init  
-membrane:normal_cycles  
-membrane:normal_mag 15  
-membrane:center_mag 10  
-membrane:smooth_move_frac  
-membrane:center_search  
-membrane:normal_search  
-membrane:center_max_delta 10  
-membrane:normal_max_angle 10  
-membrane:normal_start_angle 10
```

New Options File

```
-in:membrane  
-in:file:membrane_input setup.txt  
-in:file:fullatom
```

Single setup file allows for flexibility in user input



setup.txt:

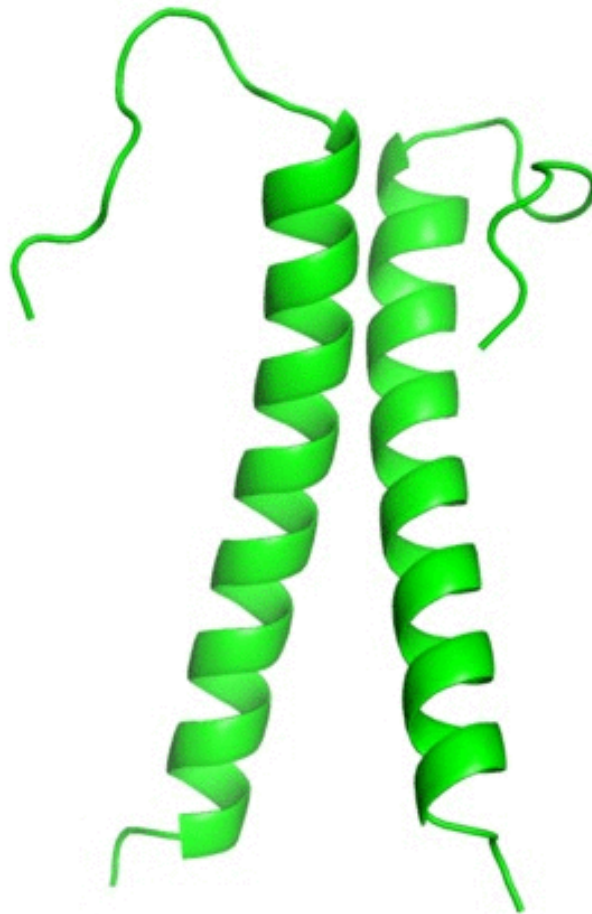
```
1afo_A spanfile  
1afo_B search
```

spanfile
search

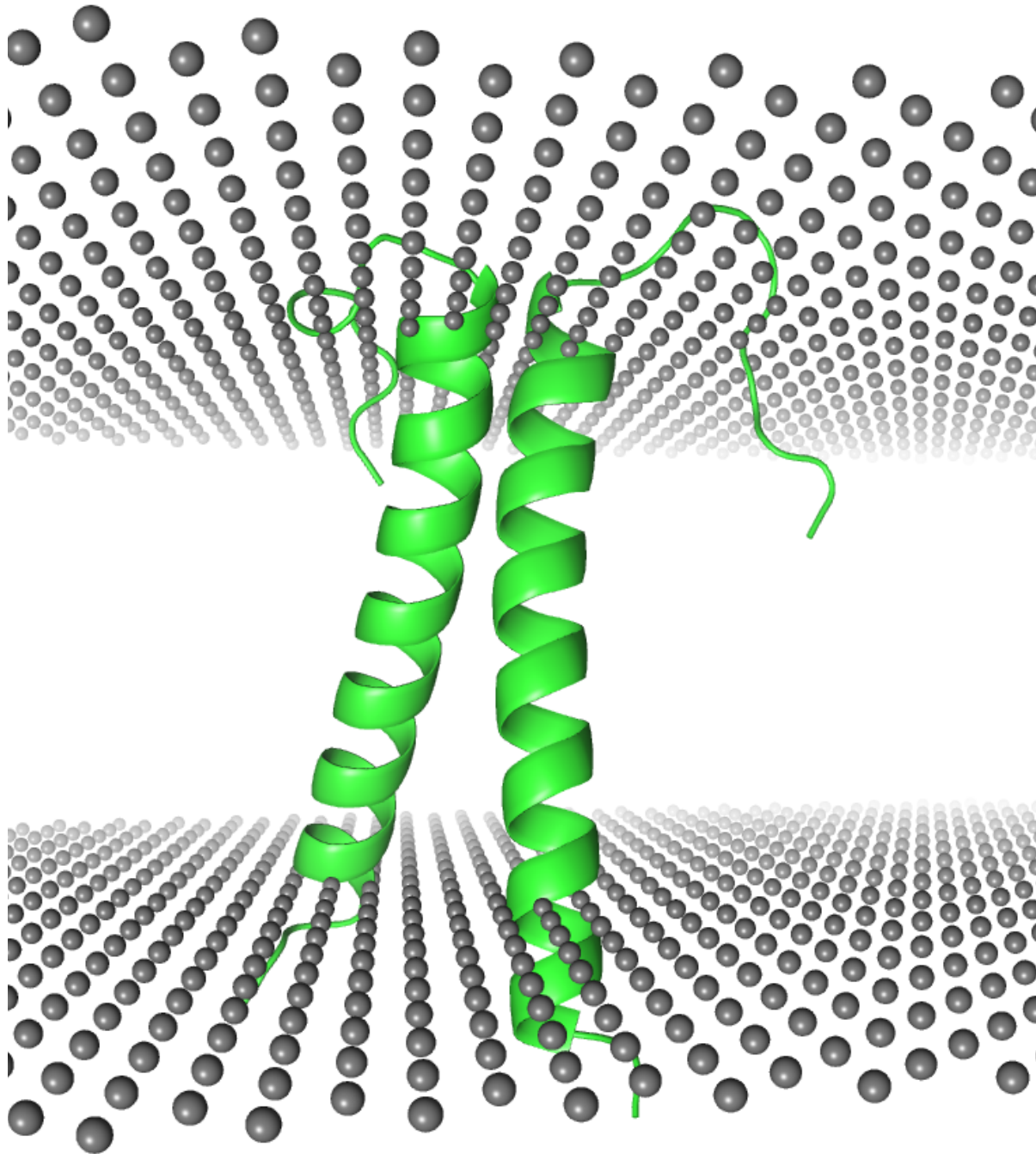
user normal 0 0 1 center 1 1 1

- Rosetta looks automatically for input files
- Rosetta warns the user when input is not supplied and certain defaults are used

MoveSet can move objects (helices, chains, or proteins) for folding, docking, etc

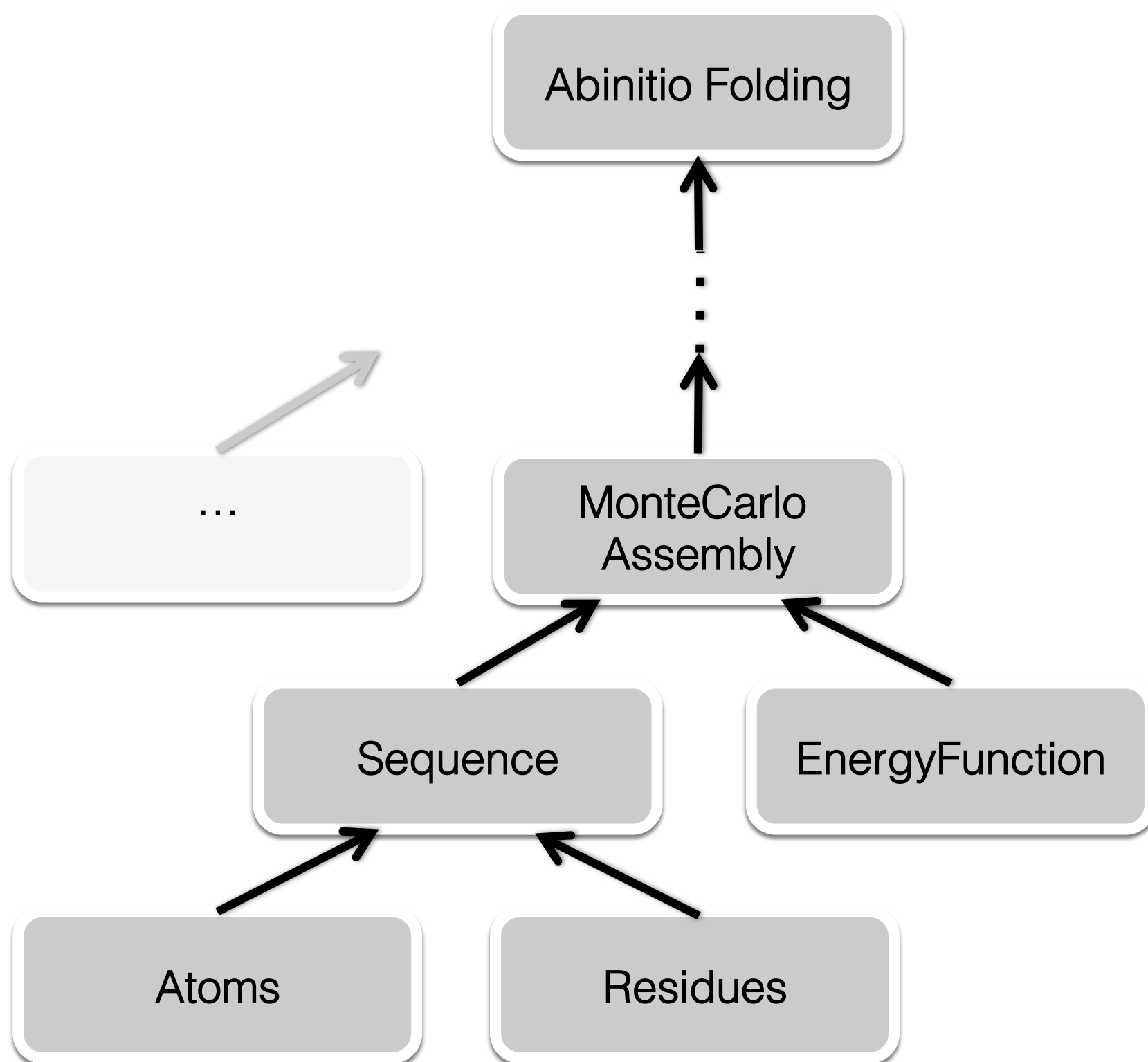


Visualize membrane application



- shows membrane for PDB file
- user can define thickness
- also shows MEM and EMB residues (not shown here)

Timeline for development



Protocol layer
= to do next
= fall 2014

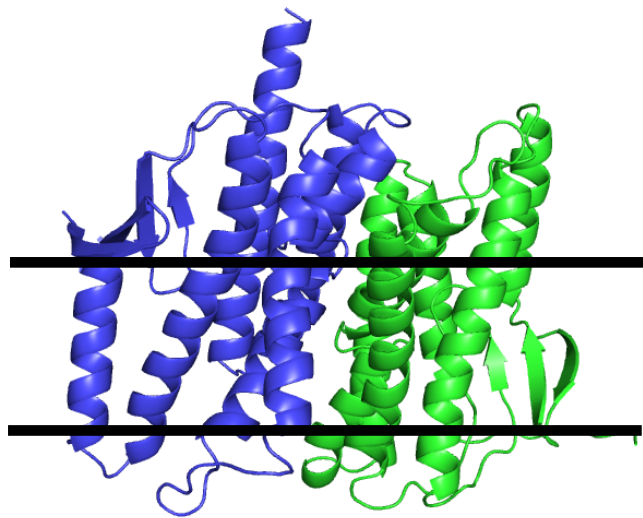
2

Core layer
= membrane
framework currently
being developed
= summer 2014

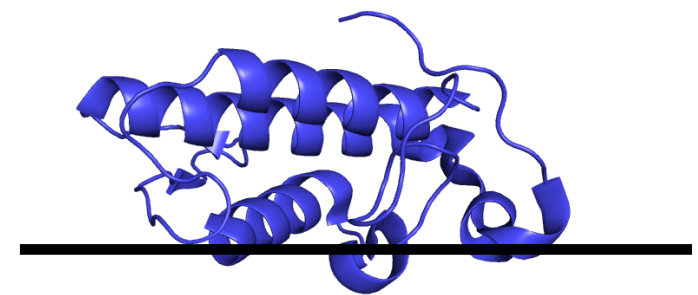
1

Next Steps: Docking and Modeling Membrane Proteins

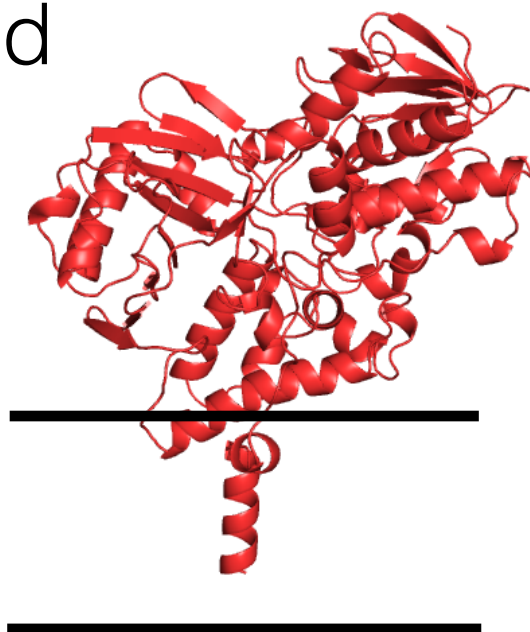
Protein-Protein Docking



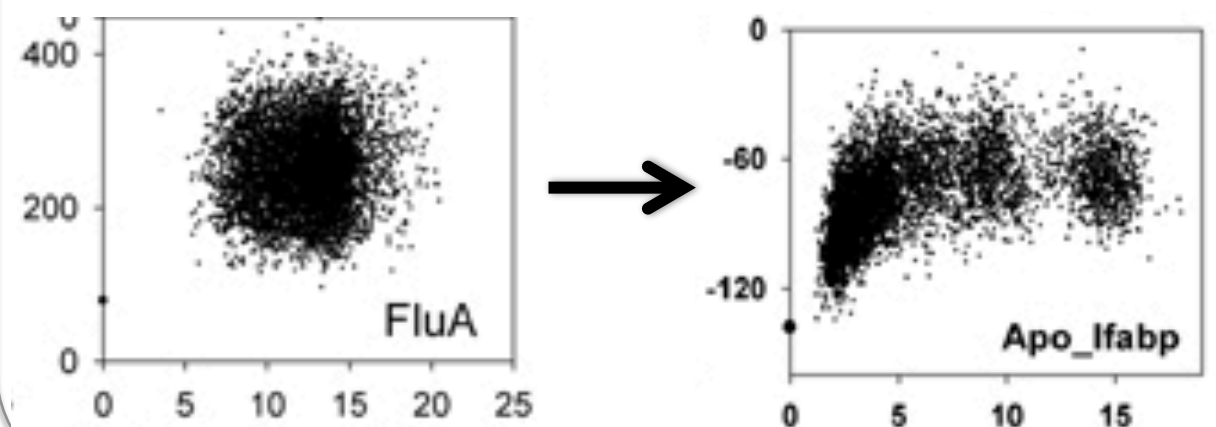
Peripheral Membrane Proteins



Half-Inserted Helices



Updating scoring function



Acknowledgments

- Rebecca Alford
- Brian Weitzner
- Jeff Gray
- Andrew Leaver-Fay
- Vladimir Yarov-Yarovoy
- Sarel Fleishman

