Docking with Design and Enzyme Design Tutorials

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Overview of Main Topics

- Small molecule flexible docking with RosettaLigand
  - Identify best interaction between ligand and protein
- Ligand docking with design
  - Identify best protein sequence to bind ligand
- Enzyme Design
  - Identify best protein sequence to bind reaction → substrate transition state

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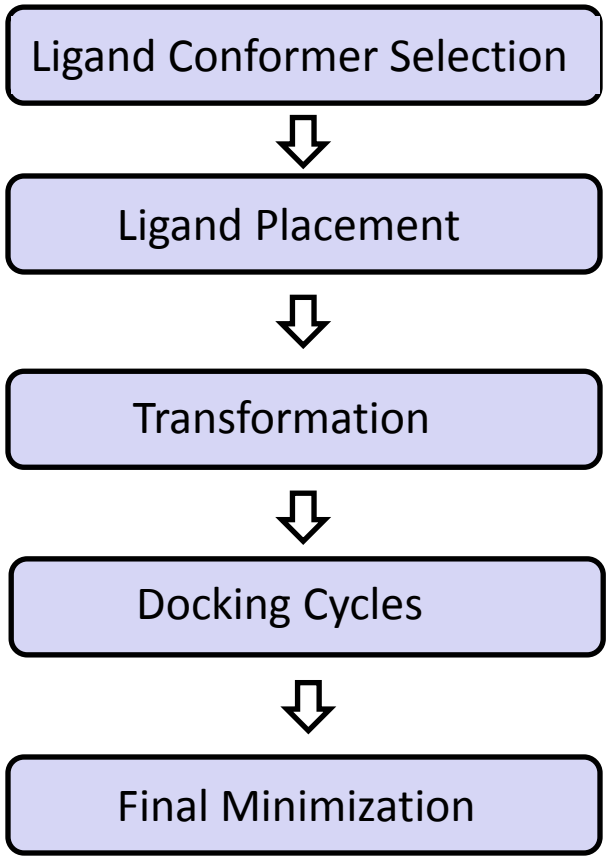
RosettaLigand

- Identify best interaction between ligand and protein

RosettaLigand Algorithm



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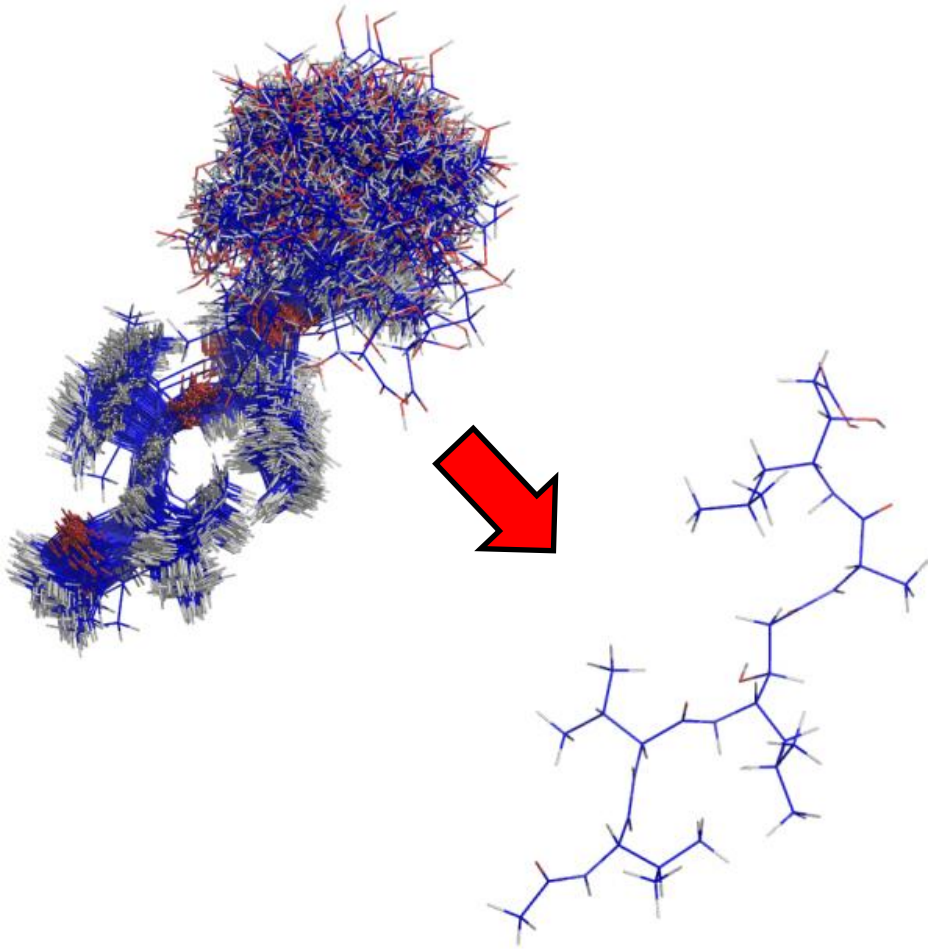
RosettaLigand Algorithm

- Ligand Conformer Selection
- Ligand Placement
- Transformation
- Docking Cycles
- Final Minimization



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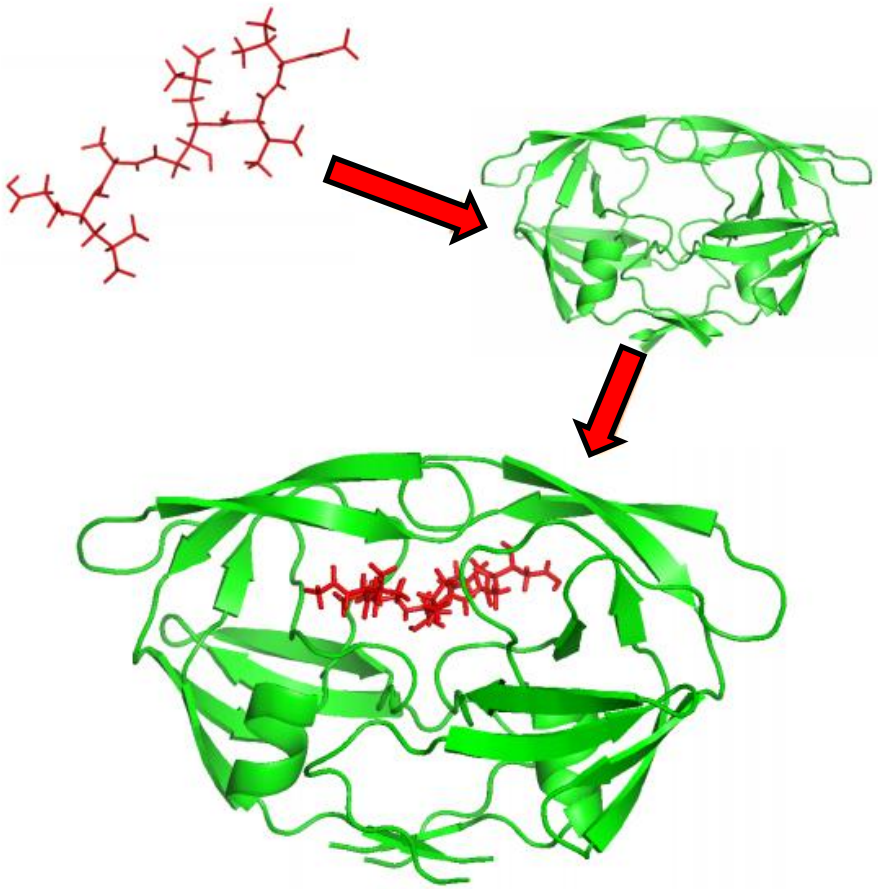
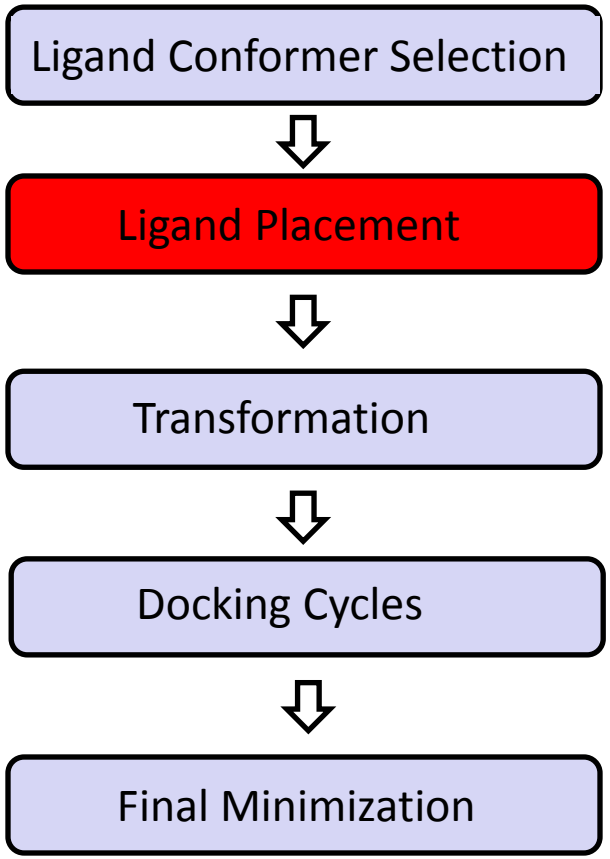
RosettaLigand Algorithm

- Ligand Conformer Selection
- ⇩
- Ligand Placement
- ⇩
- Transformation
- ⇩
- Docking Cycles
- ⇩
- Final Minimization



RosettaLigand Algorithm

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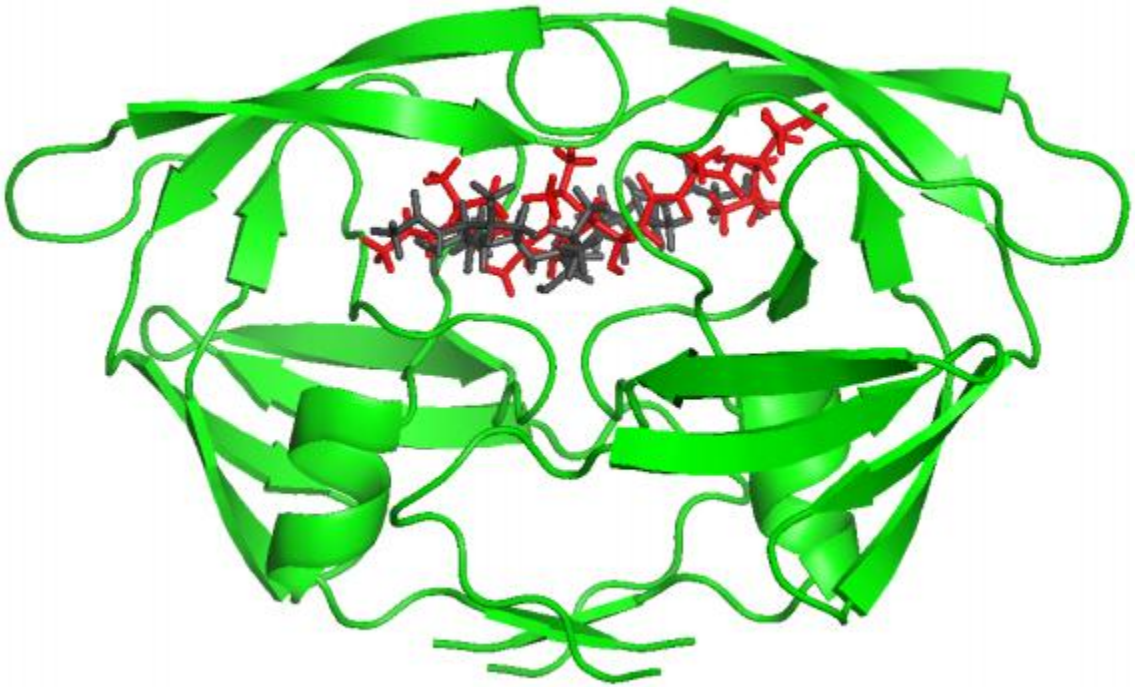
        </StartFrom>
</MOVERS>
```

RosettaLigand Algorithm

- Ligand Conformer Selection
- ⇩
- Ligand Placement
- ⇩
- **Transformation**
- ⇩
- Docking Cycles
- ⇩
- Final Minimization



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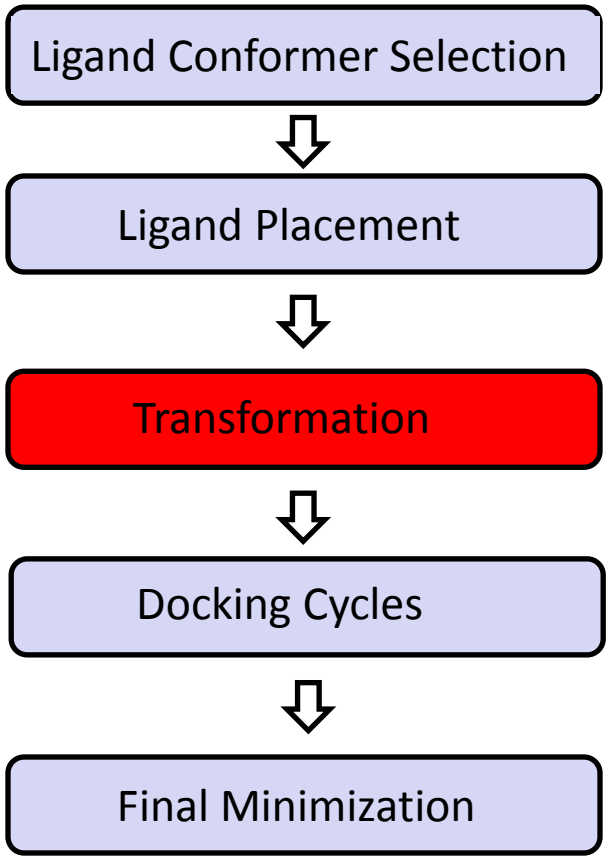
RosettaLigand Algorithm

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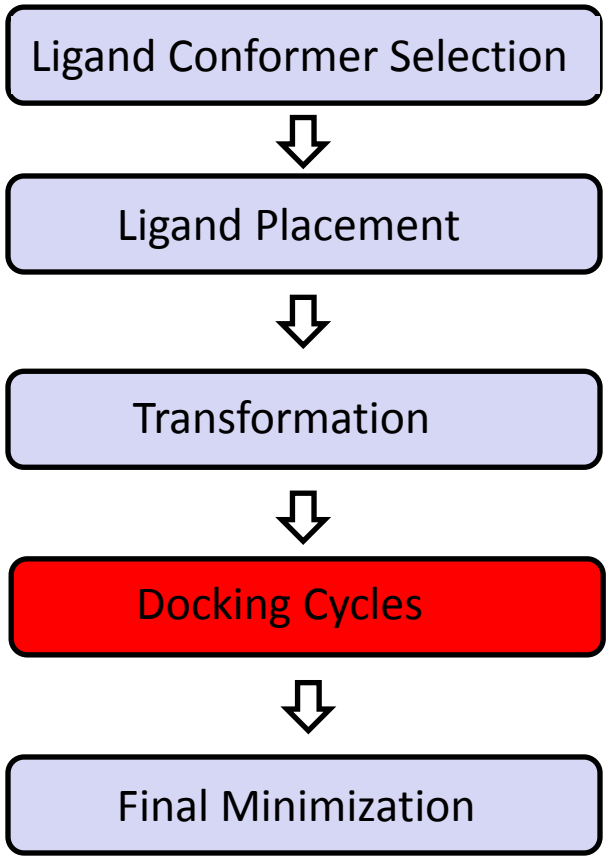
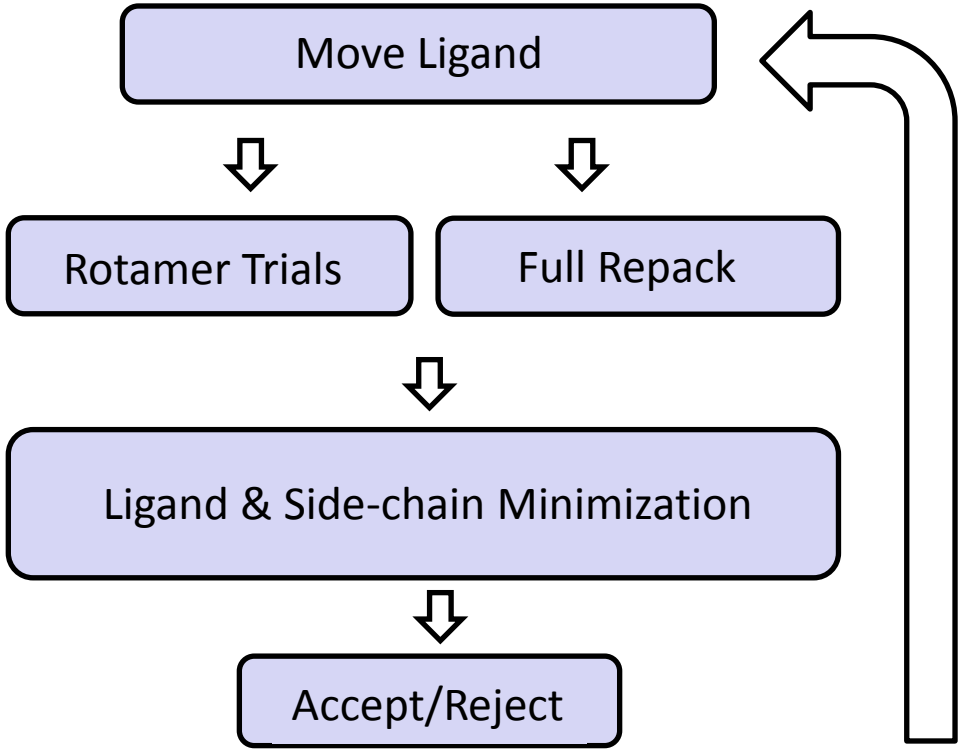
RosettaLigand Algorithm





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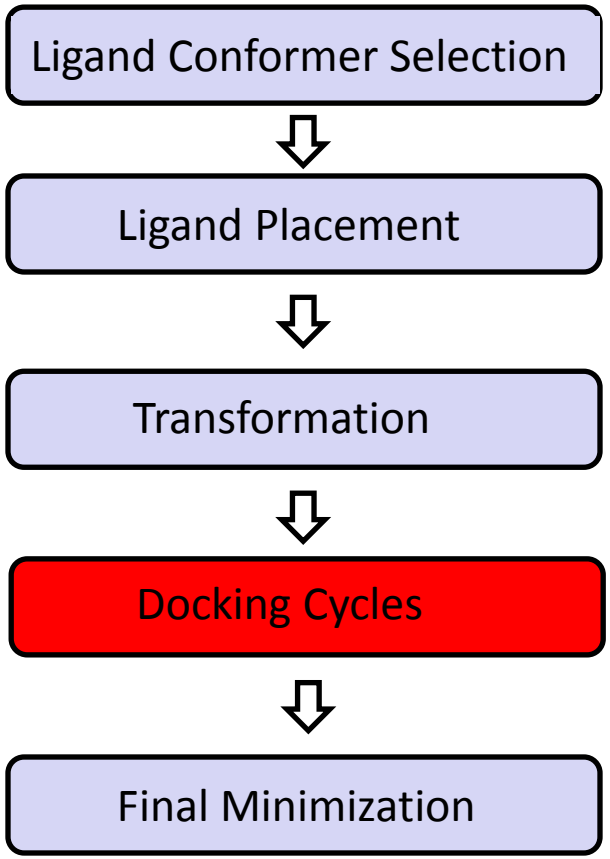
RosettaLigand Algorithm

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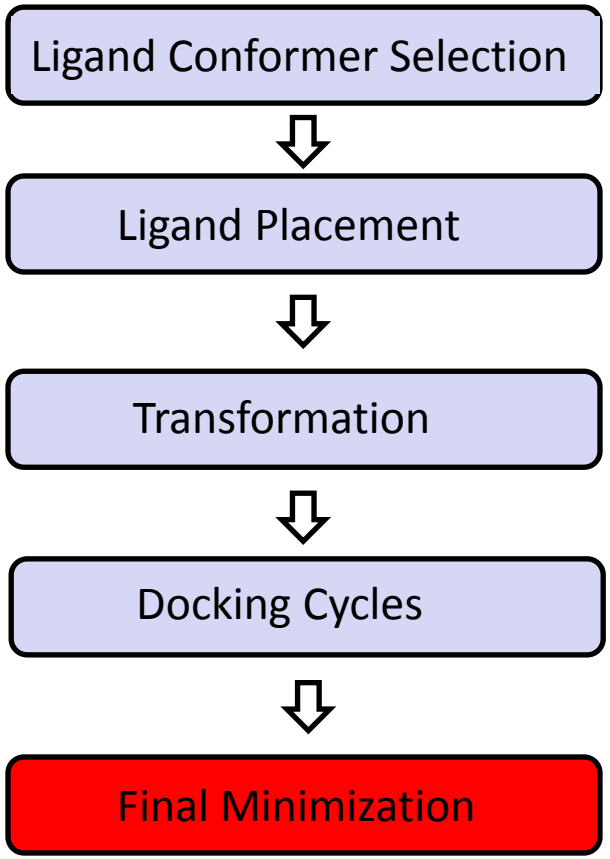
RosettaLigand Algorithm



Gradient-based Minimization
of Side-chains and
Backbone Angles

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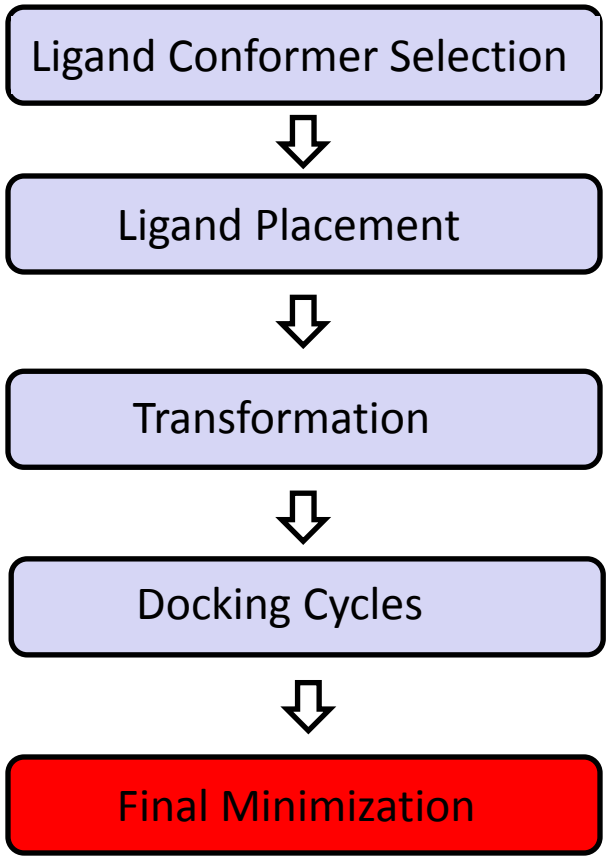
RosettaLigand Algorithm




```
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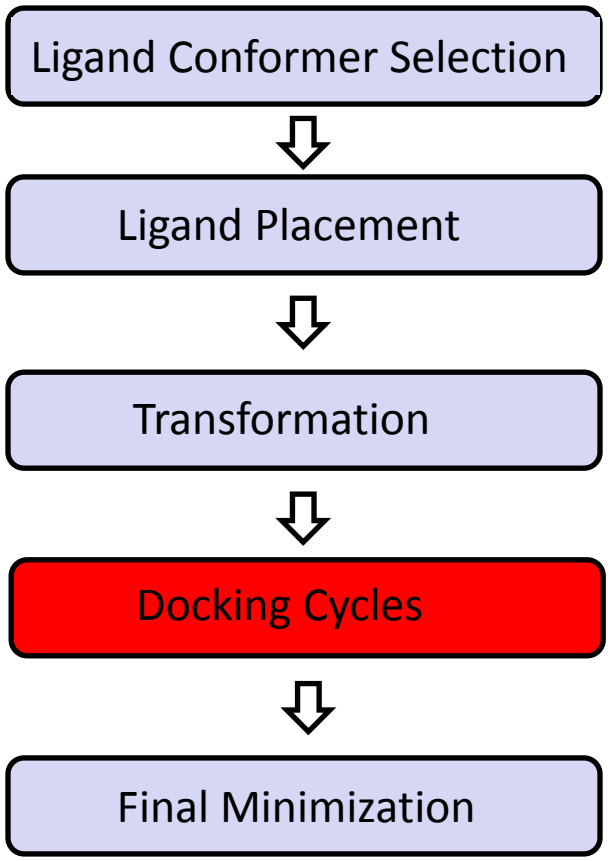
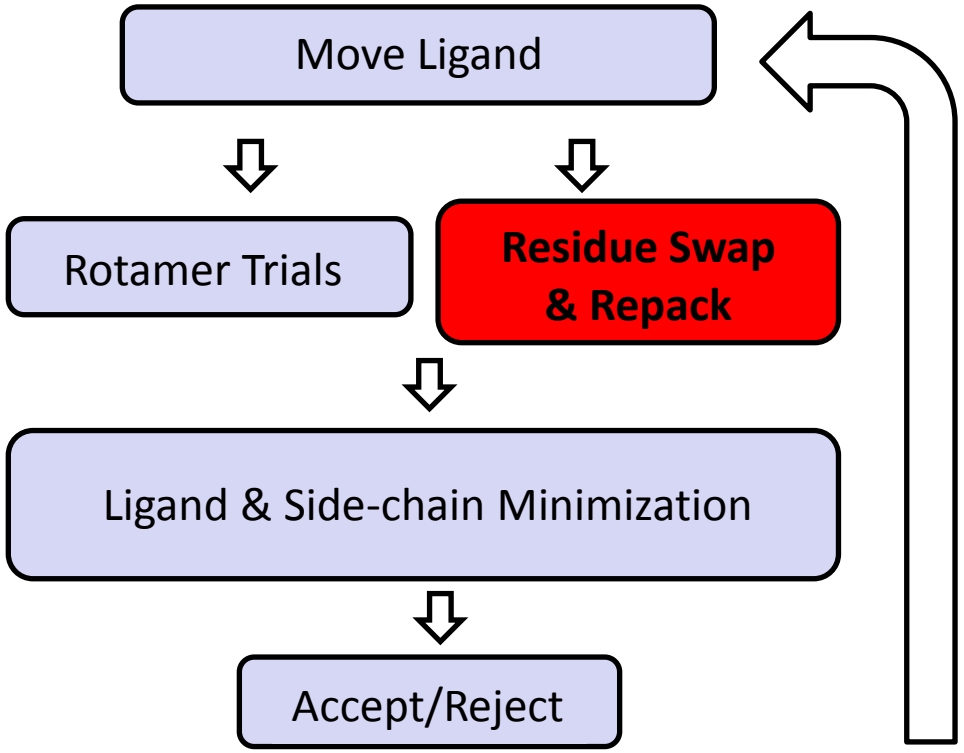
Dock and Design

- Identify best protein sequence to bind ligand

Dock with Design Algorithm





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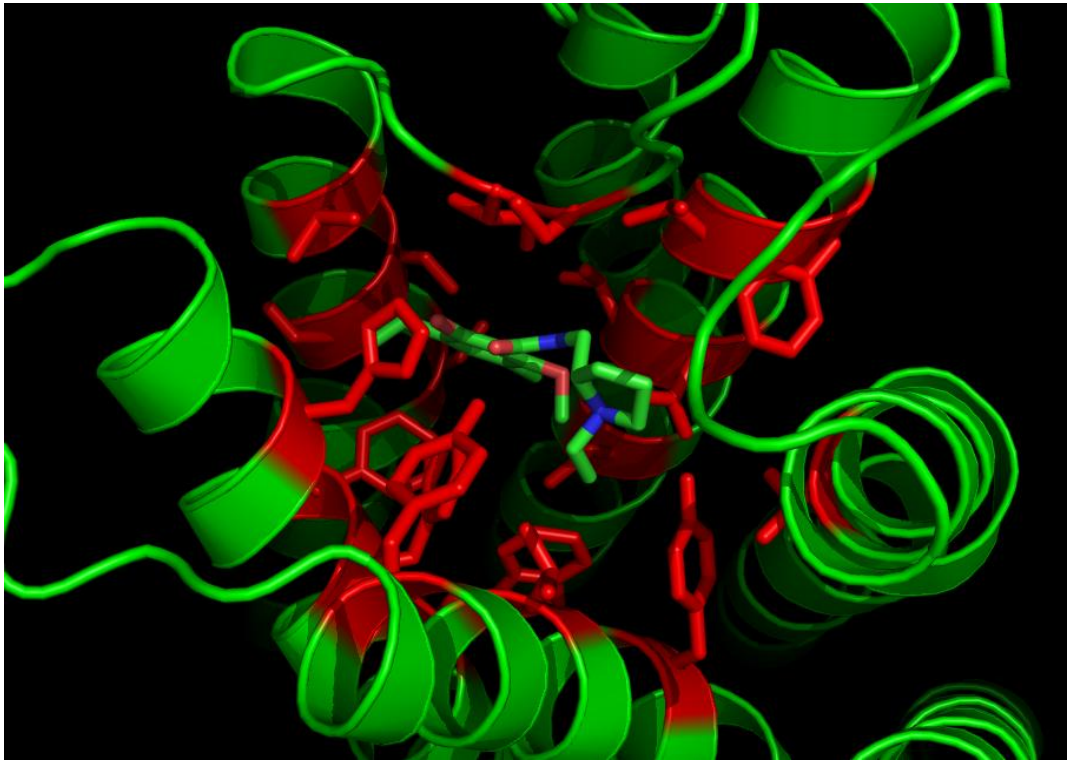
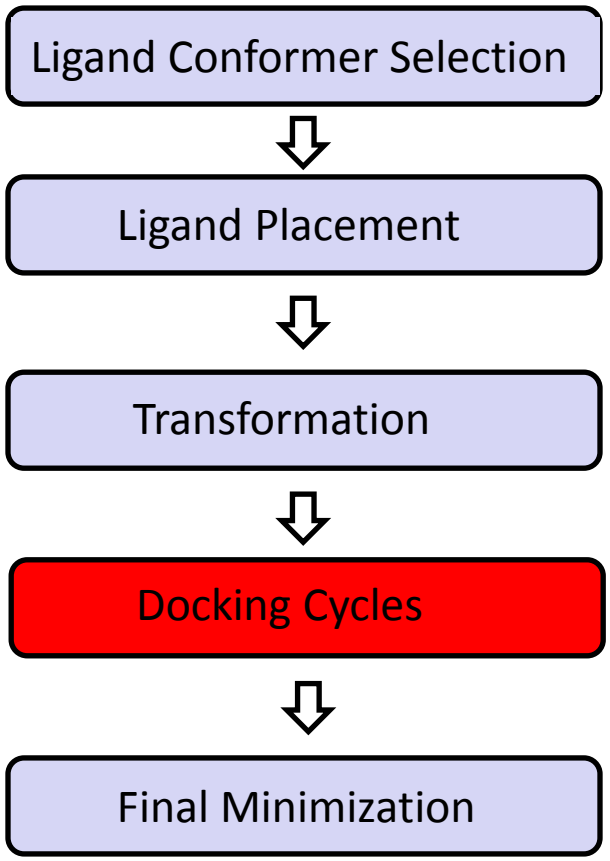
Dock with Design Algorithm

- Ligand Conformer Selection
- Ligand Placement
- Transformation
- **Docking Cycles**
- Final Minimization



Dock with Design Algorithm

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                design="1"
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</TASKOPERATIONS>
```


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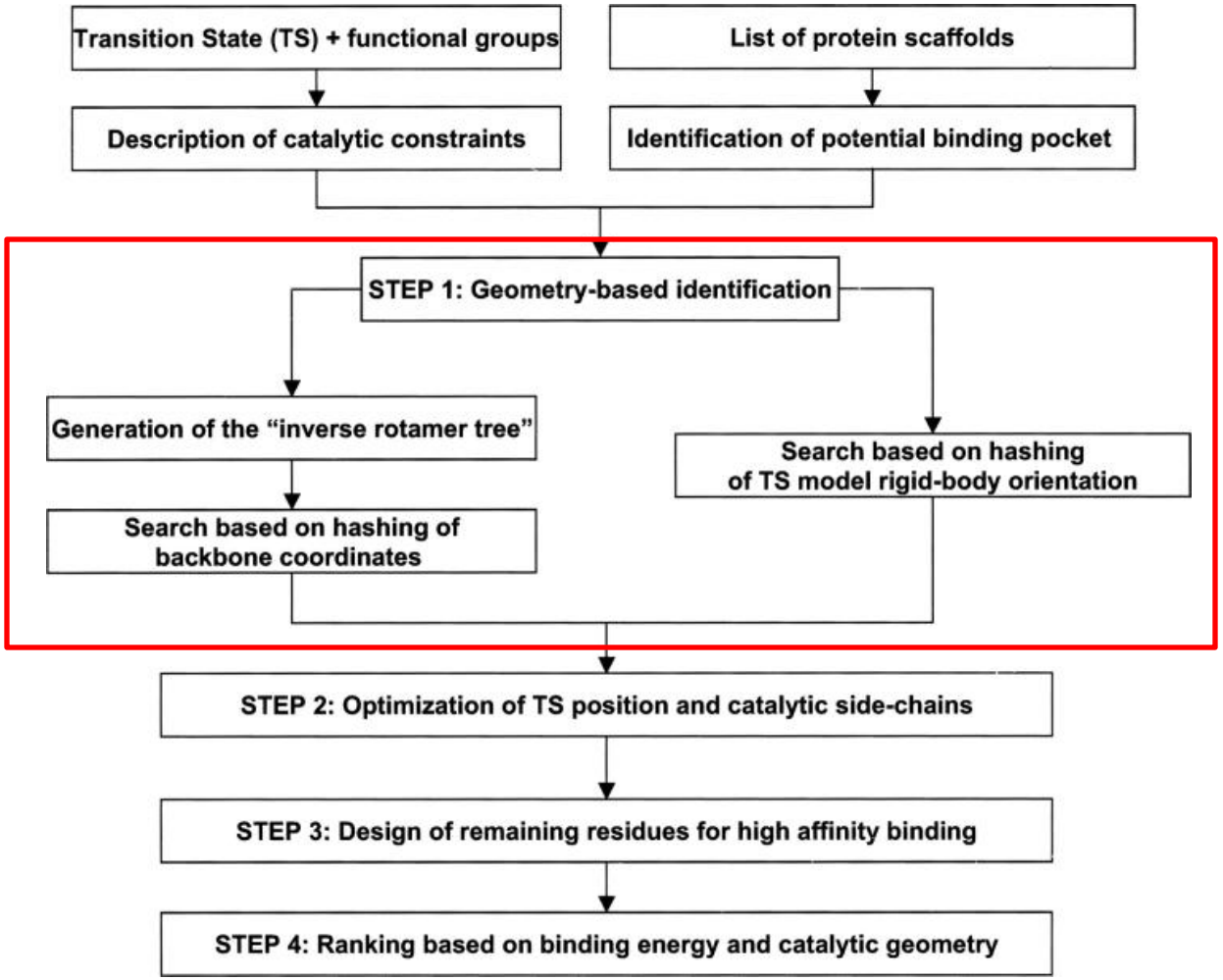
Enzyme Design

- Identify best protein sequence to bind reaction → substrate transition state

Enzyme Design Algorithm



Excluded for the purposes of this tutorial

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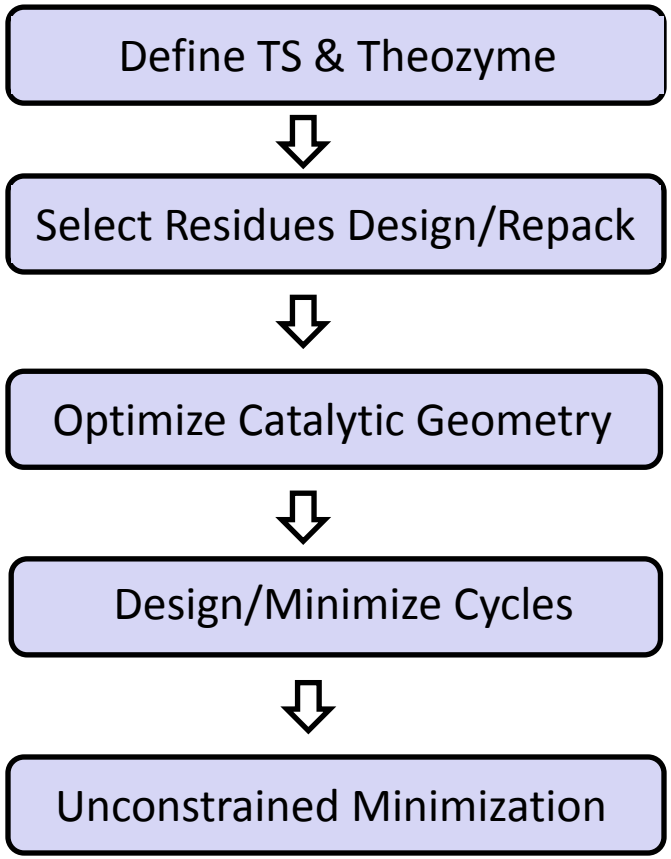
Enzyme Design Algorithm



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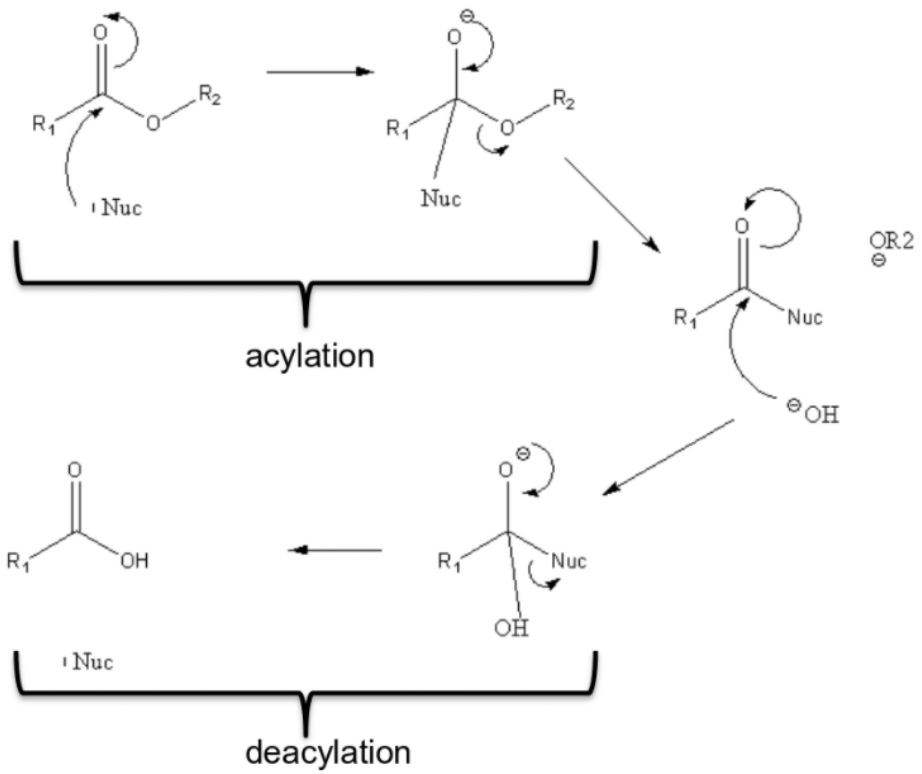
Enzyme Design Algorithm

- Define TS & Theozyme
- ⇩
- Select Residues Design/Repack
- ⇩
- Optimize Catalytic Geometry
- ⇩
- Design/Minimize Cycles
- ⇩
- Unconstrained Minimization



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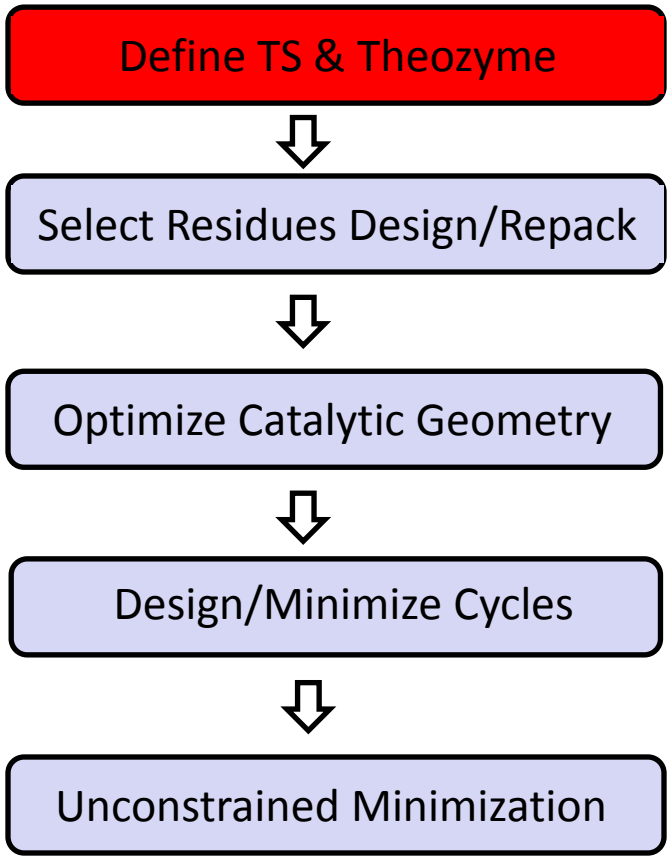
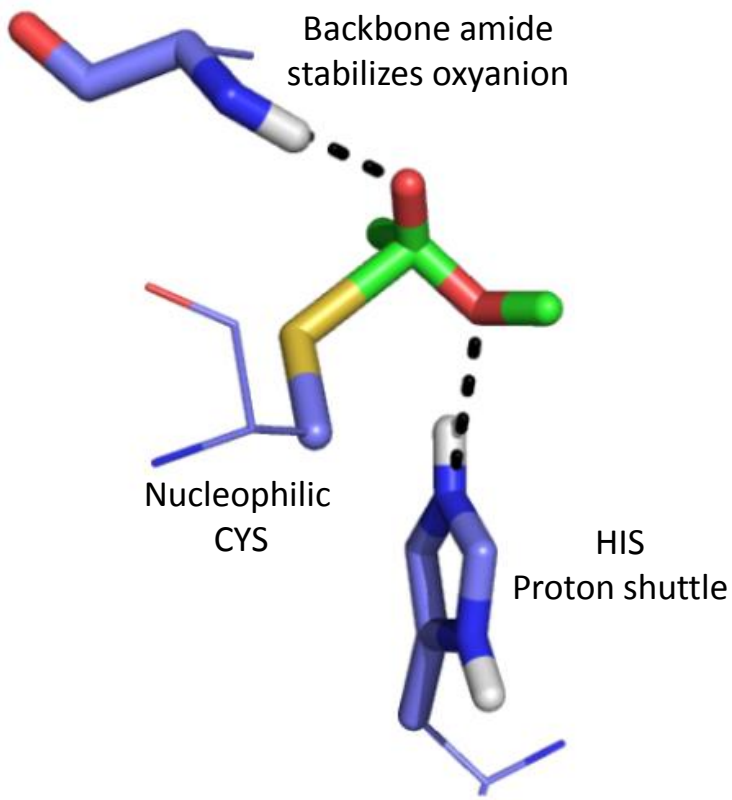
Enzyme Design Algorithm





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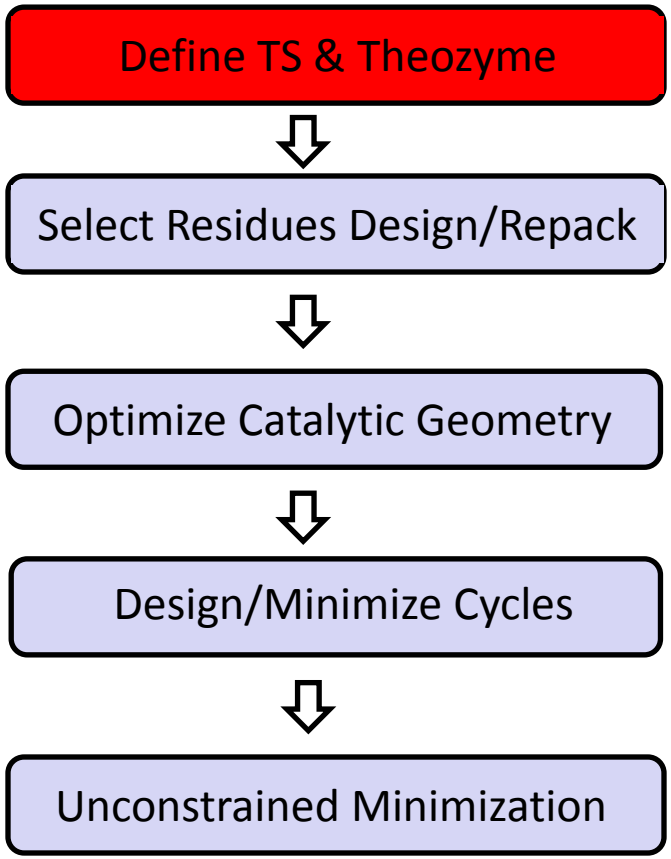
Enzyme Design Algorithm




```
<MOVERS>
        <AddOrRemoveMatchCsts
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</MOVERS>
```

Enzyme Design Algorithm

Define TS & Theozyme

⇩

Select Residues Design/Repack

⇩

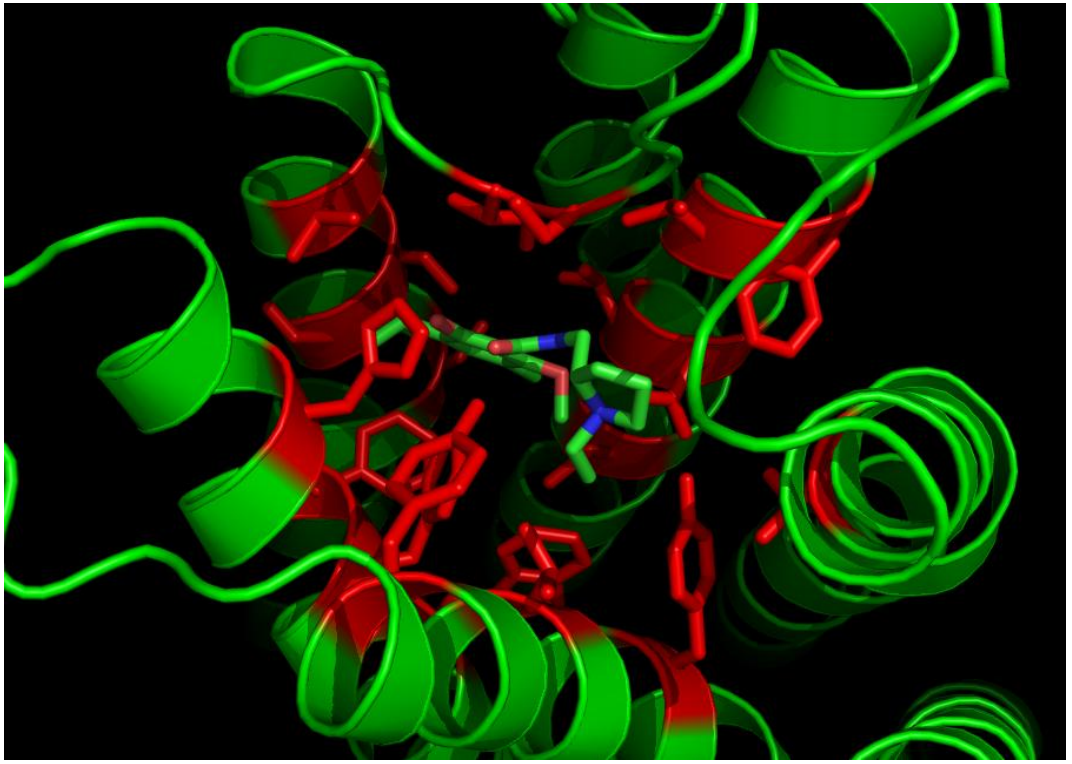
Optimize Catalytic Geometry

⇩

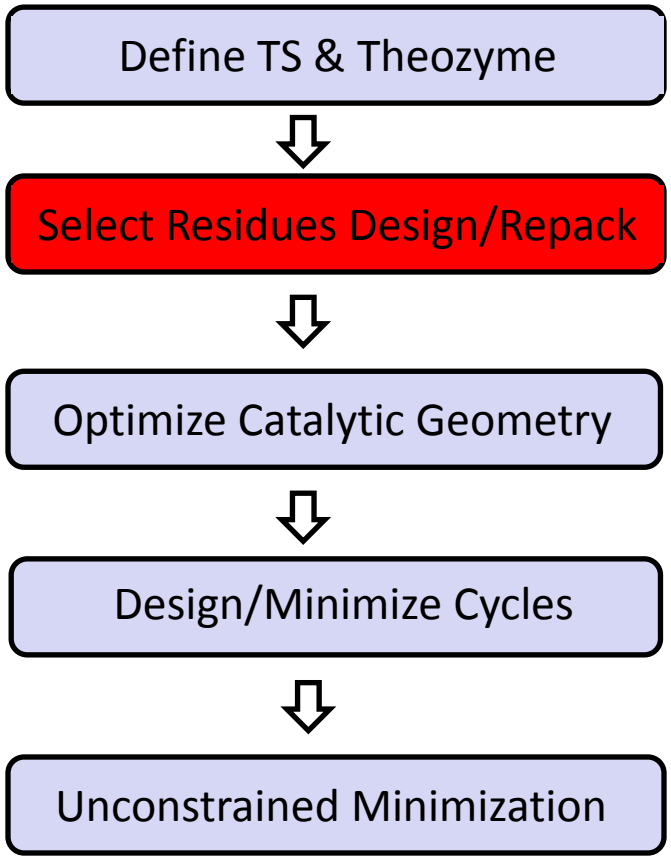
Design/Minimize Cycles

⇩

Unconstrained Minimization



Enzyme Design Algorithm



Rosetta resfile and/or
-detect_design_interface flag

Follows same rules as Dock and Design

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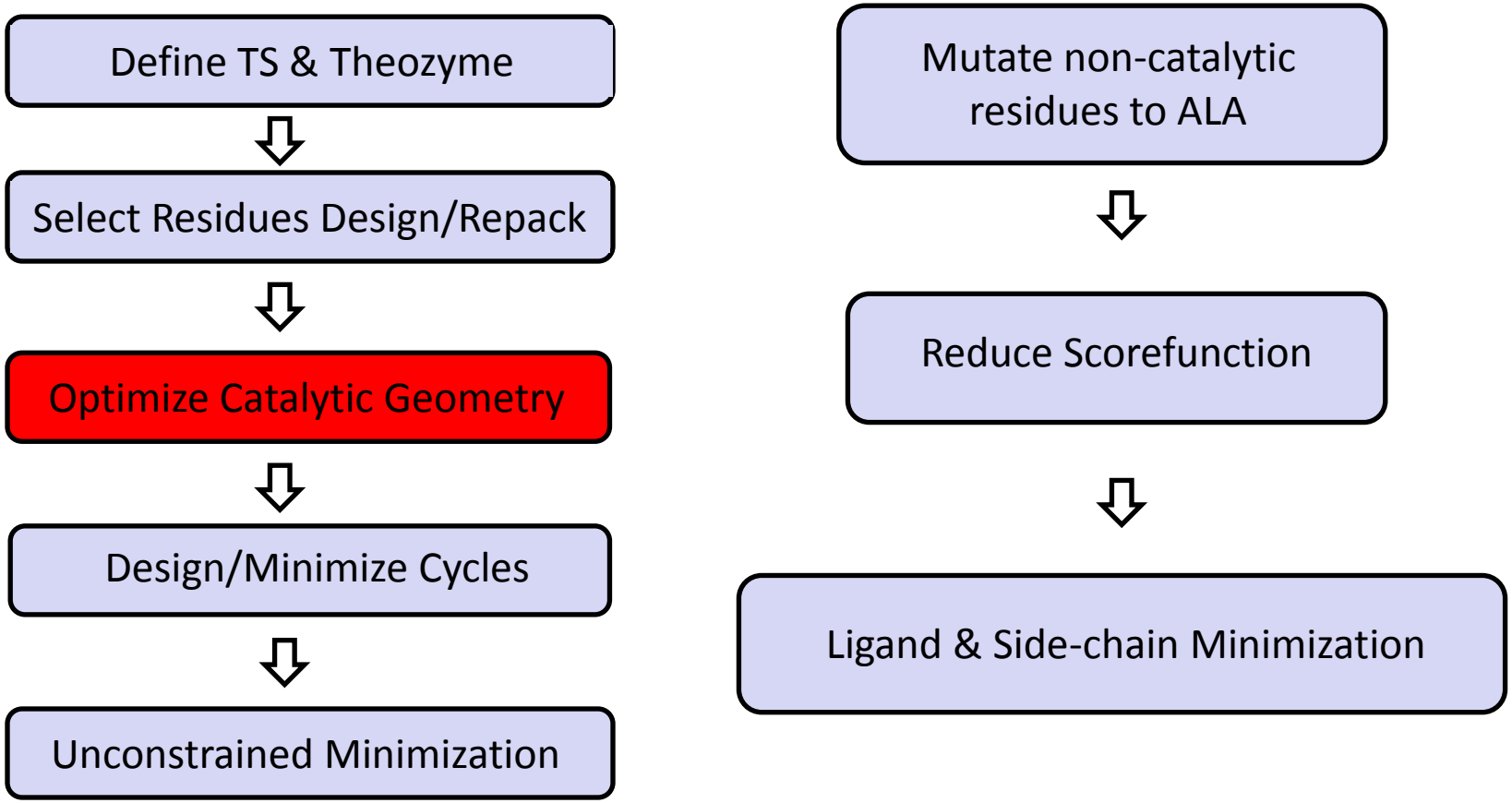
Enzyme Design Algorithm



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Define TS & Theozyme

⇩

Select Residues Design/Repack

⇩

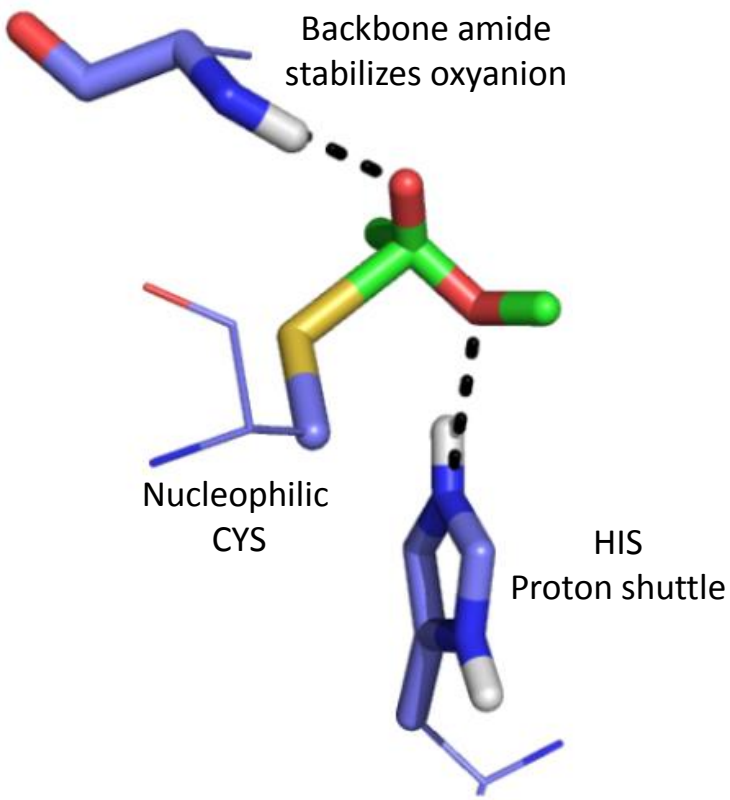
Optimize Catalytic Geometry

⇩

Design/Minimize Cycles

⇩

Unconstrained Minimization



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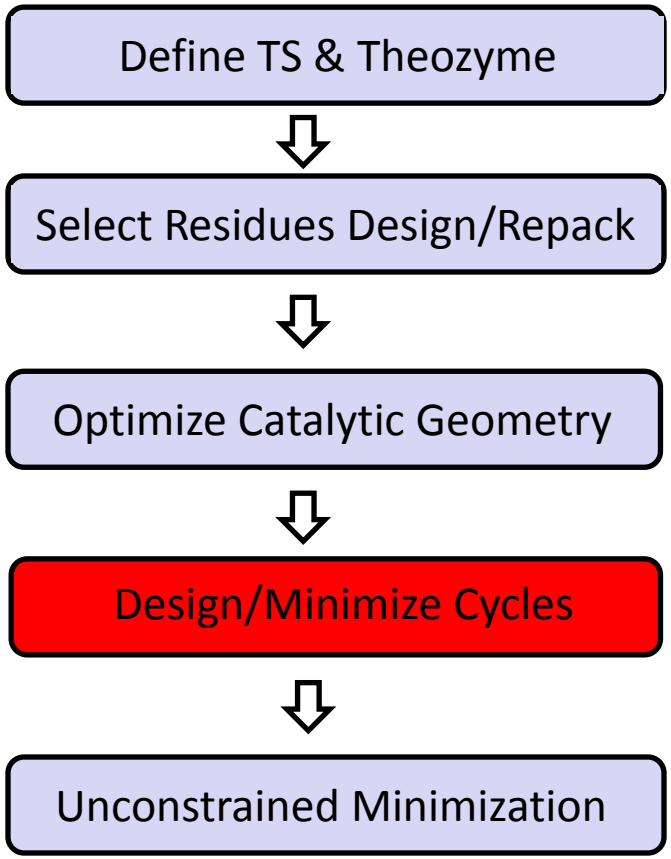
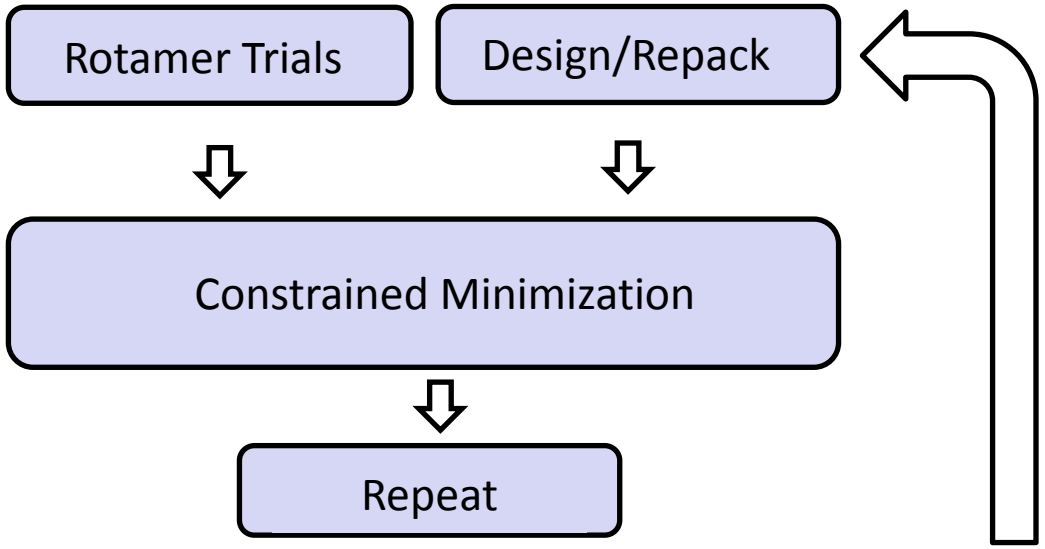
Enzyme Design Algorithm





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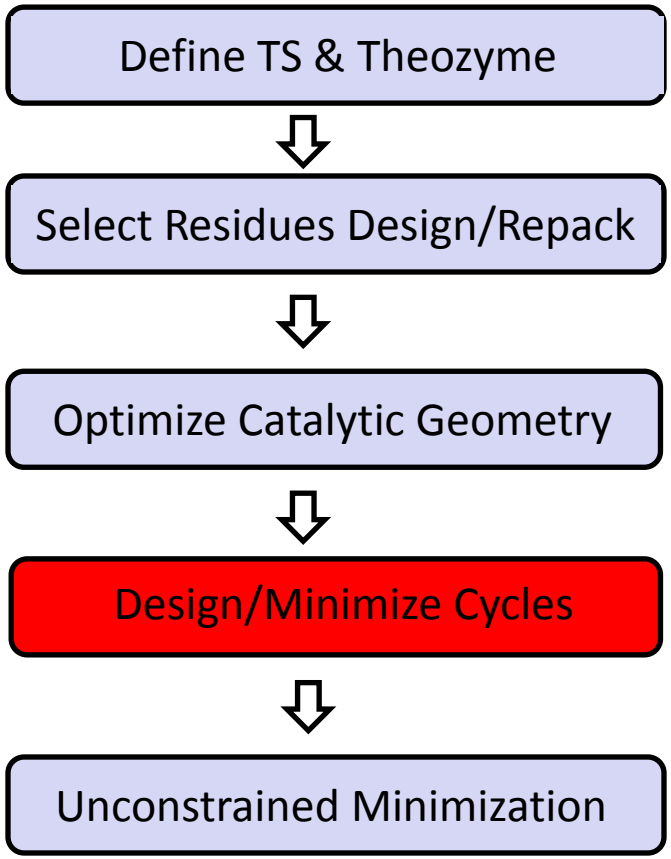
Enzyme Design Algorithm

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```


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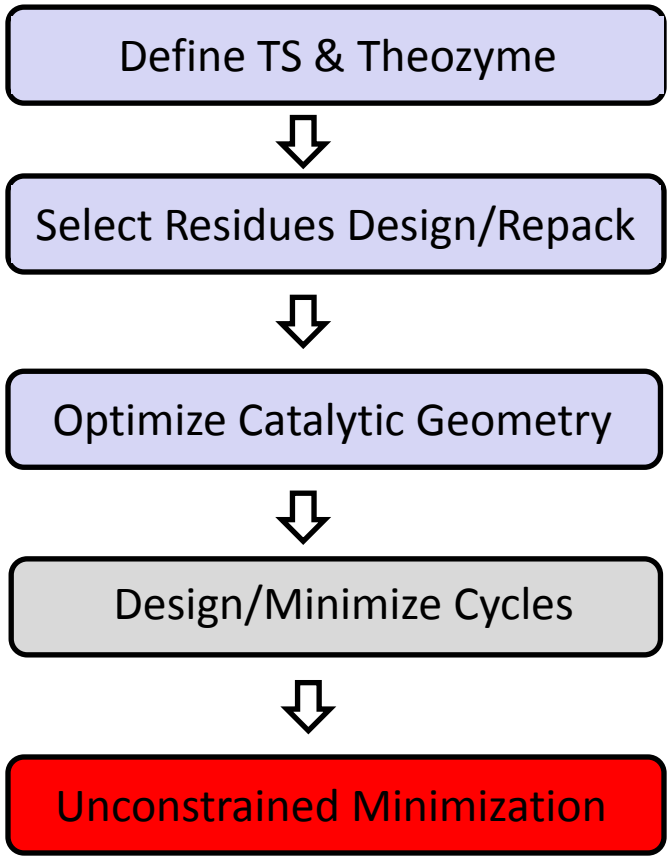
Enzyme Design Algorithm



Unconstrained Gradient-based Minimization of Backbone, Side-chains, and Substrate Position

References

- J. Meiler, D. Baker, ROSETTALIGAND: Protein – Small Molecule Docking with Full Side-Chain Flexibility, Proteins 548, 538–548 (2006).
- S. Combs et al., Small-molecule ligand docking into comparative models with Rosetta, Nature Protocols 8, 1277–1298 (2013).
- B. Allison et al., Computational Design of Protein-Small Molecule Interfaces. Journal of Structural Biology 185(2):193-202 (2014).
- F. Richter et al., De Novo Enzyme Design Using Rosetta3. PLoS ONE 6(5): e19230 (2011).

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Today's Tutorial

- Dock an ester ligand to a haloacid dehalogenase-like hydrolase (HAD)
- Sequence optimize the protein-ligand binding interface between HAD and the ester ligand
- Convert the HAD protein into an ester hydrolase

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Let’s get started

- ~/RosettaWorkshop2018/enzdes_dockdesign
- Follow the instructions provided in the enzdes_dockdesign_tutorial.pdf