Experiments/Users: Molecular Dynamics

Simulating Enzyme Catalysis, Conformational Change, and Ligand Binding/Release

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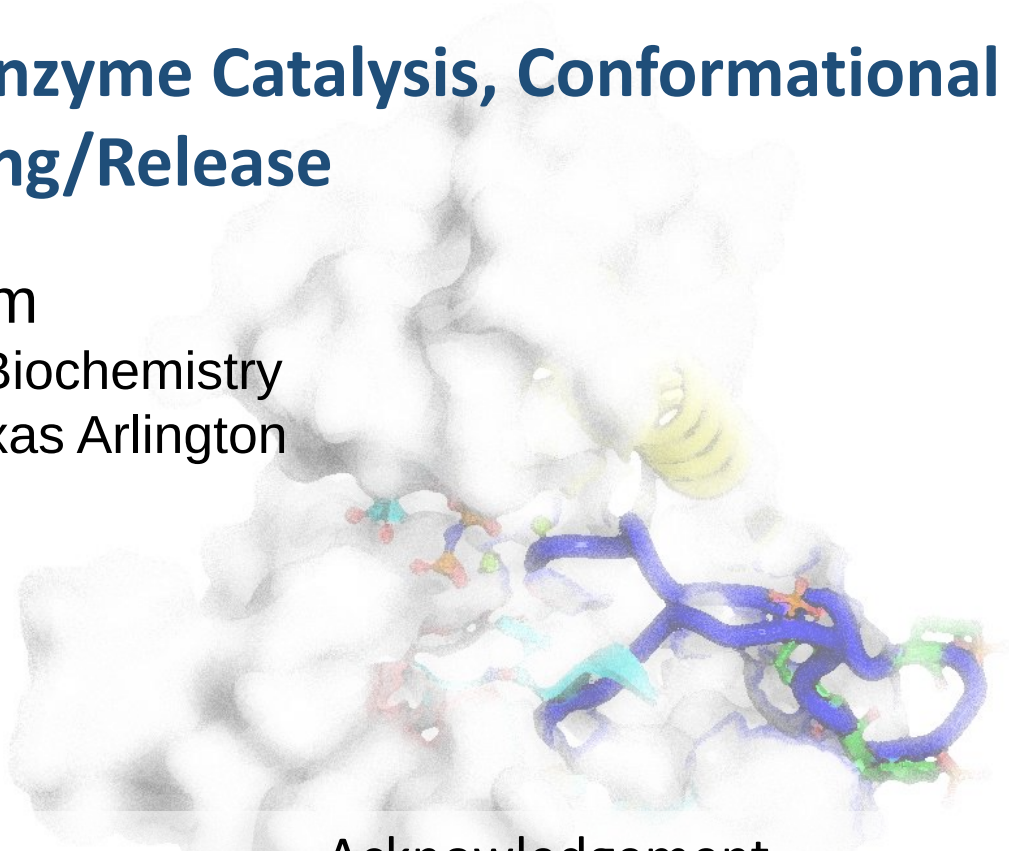

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Vetenskapsrådet

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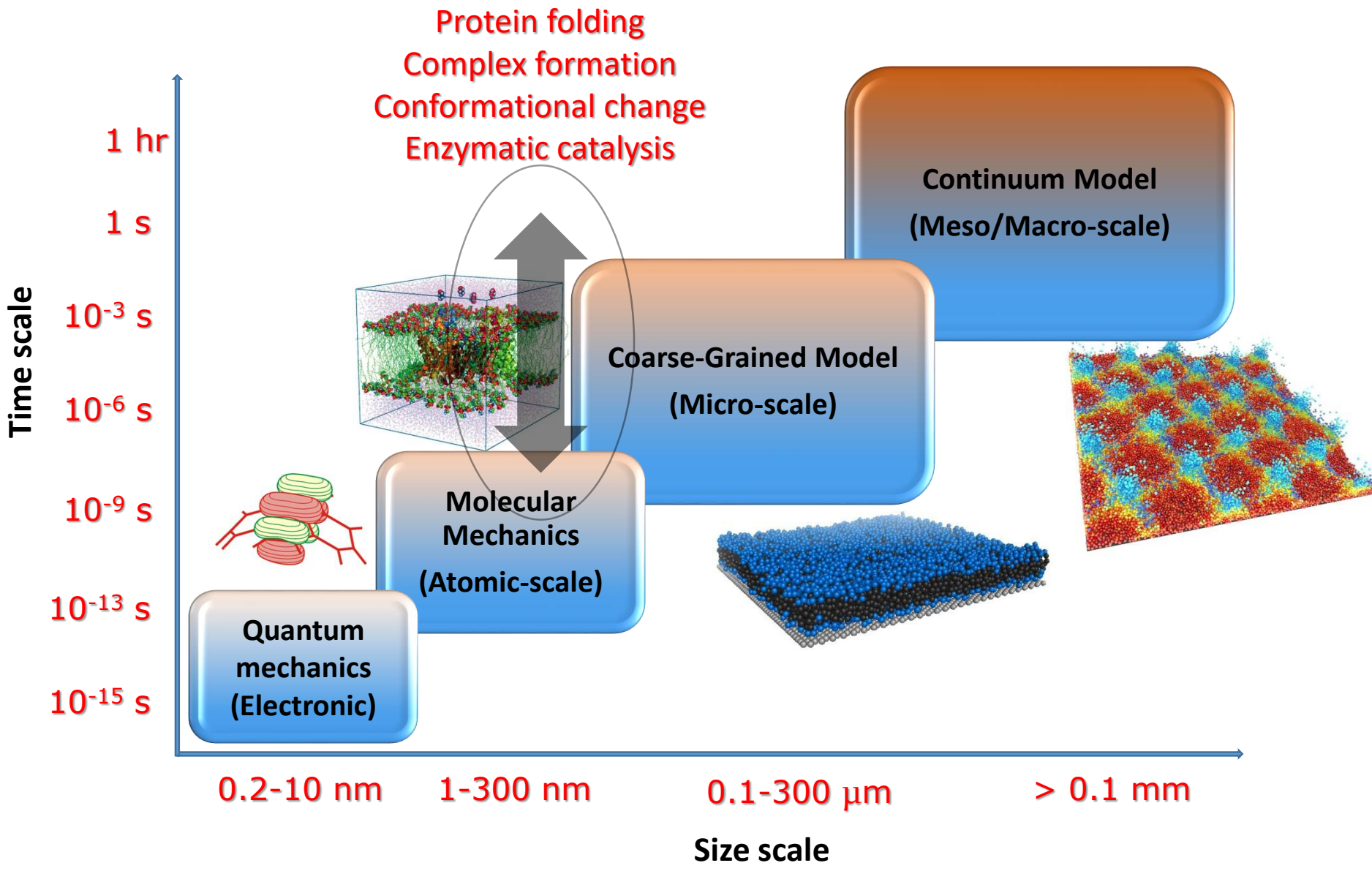
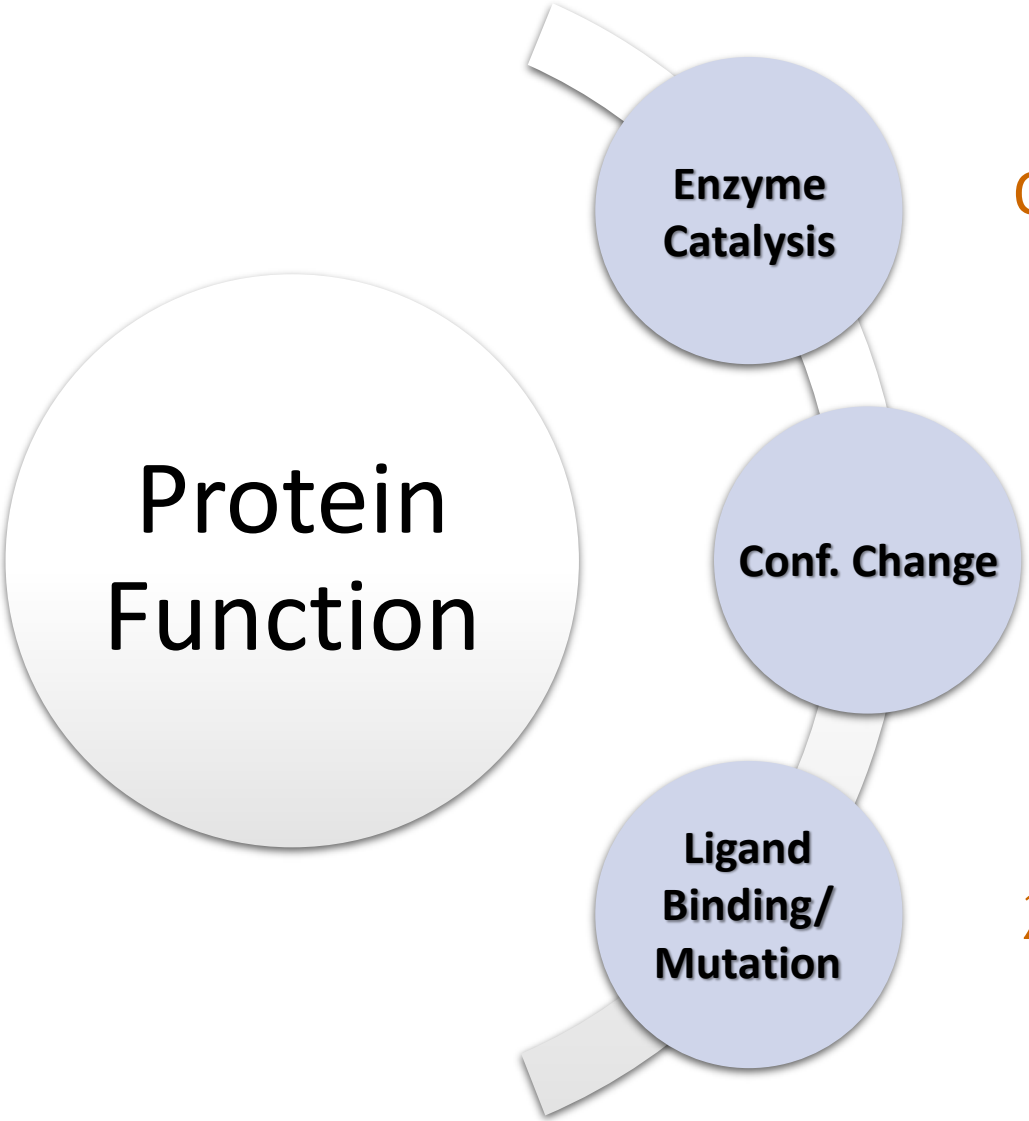
NERSC

HPC2N

Multiscale simulation



Protein function, issues and simulation tools



QM/MM method

Nam, JCTC 2005, 2013, 2014;
Ojeda-May, JCTC 2017

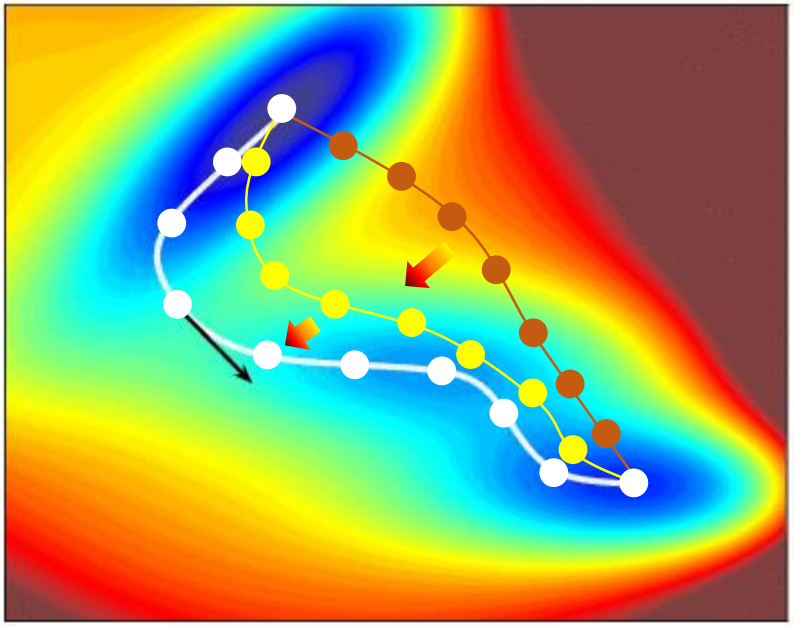
String FE, Metadynamics, MSM builder, & GPU

Ovchinnikov, JPCB 2016

Alchemical FE & λ-dynamics simulation methods

Li, in preparation

String FE simulation method



E, JPCB (2002); Ovchinnikov, JCP (2011)

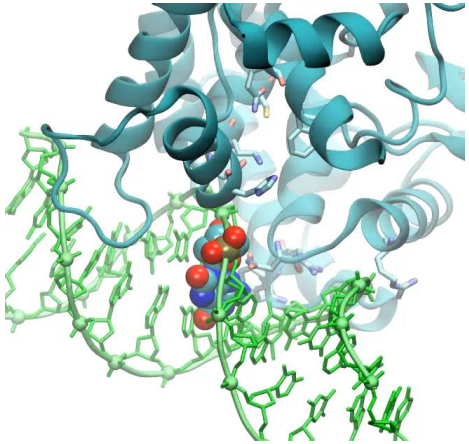
•Path is optimized using $-M(\boldsymbol{\theta})\nabla F(\boldsymbol{\theta})$ as a force while enforcing even arc-length distance along the path, where

$$M_{i,j}(\boldsymbol{\theta}) = \sum_k \frac{1}{m_k} \left\langle \frac{\partial \hat{\theta}_i(\boldsymbol{x})}{\partial x_k} \frac{\partial \hat{\theta}_j(\boldsymbol{x})}{\partial x_k} \right\rangle_{\hat{\boldsymbol{\theta}}(\boldsymbol{x})=\boldsymbol{\theta}}$$

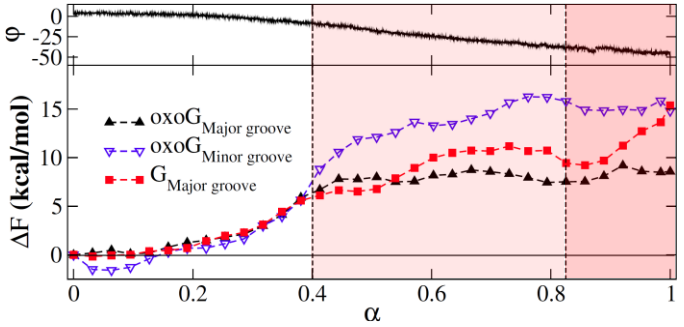
$$F_{\alpha^*} - F_0 = \int_0^{\alpha^*} \sum_{j=1}^{N} \frac{\partial F}{\partial \theta_j^*} \frac{d\theta_j^*}{d\alpha} d\alpha$$

•Slow in achieving convergence (path optimization/FE evaluation).

hOGG1:
oxoG extrusion
(Cori on NERSC)

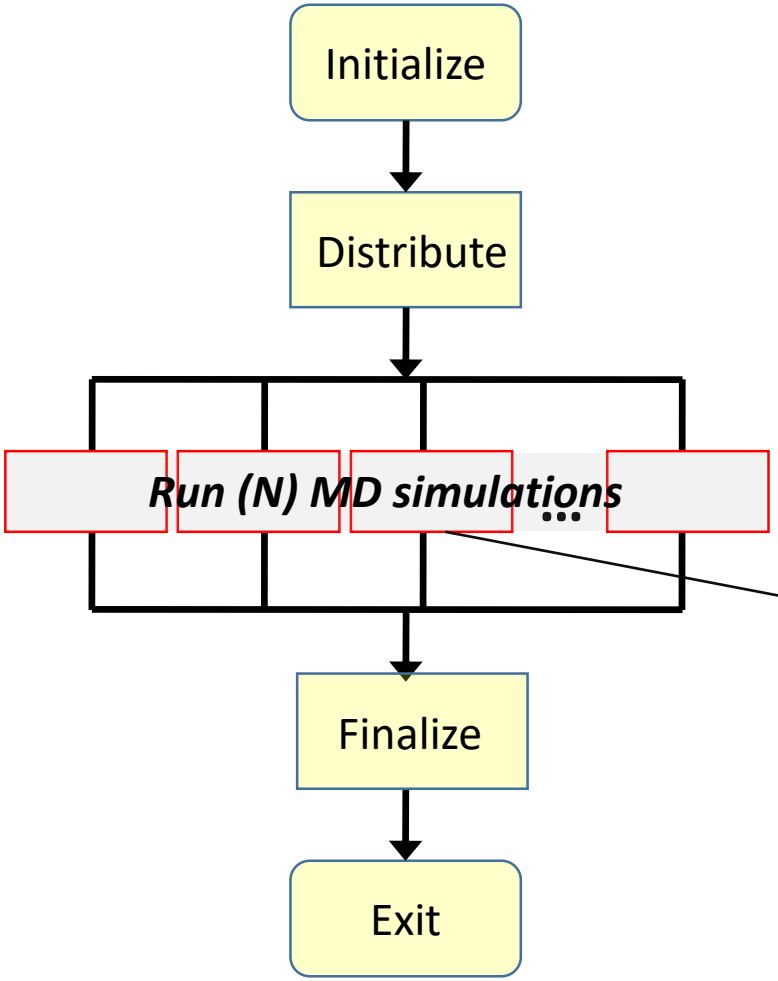


Total cost: ~2.4 μs

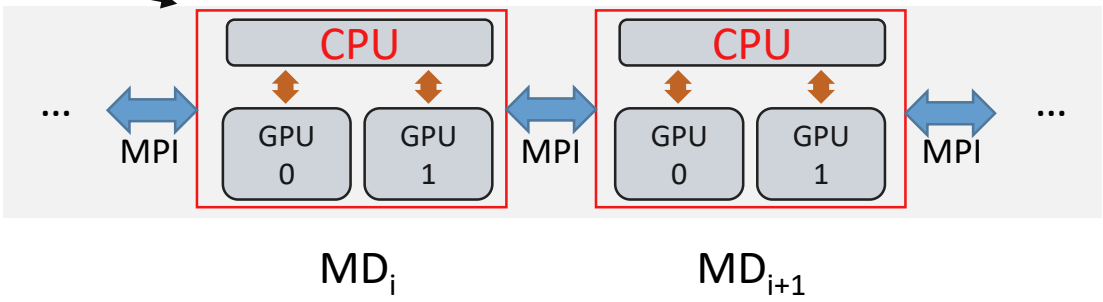


Shigdel et al., in preparation

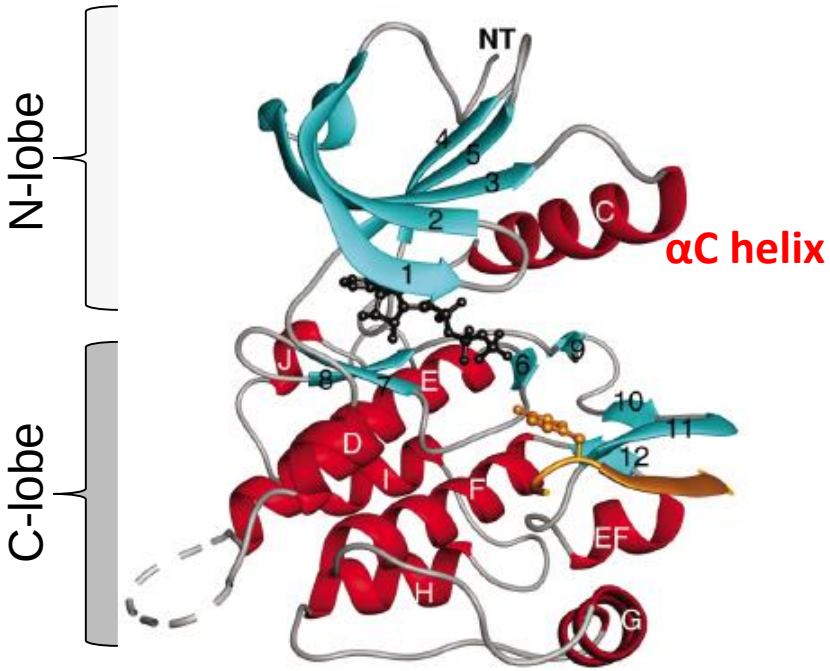
CHARMM design for hybrid MPI/OpenMP/GPU computing



1. ***N*** MD simulations are mapped on to the ***N*** nodes of the conformational change path.
2. MPI communication b/w MD simulations
3. Within each MD system, split workloads.
   -OpenMP for CPU (MPI in near future)
   -Cuda for GPU



Protein kinases



- Key enzymes in a broad range of signal transduction pathways regulating cell metabolism and growth.
- Share essentially identical kinase domain structure: catalysis and allostery.
- Carry out the same catalytic function: a transfer of a phosphoryl group from ATP to a target residue.

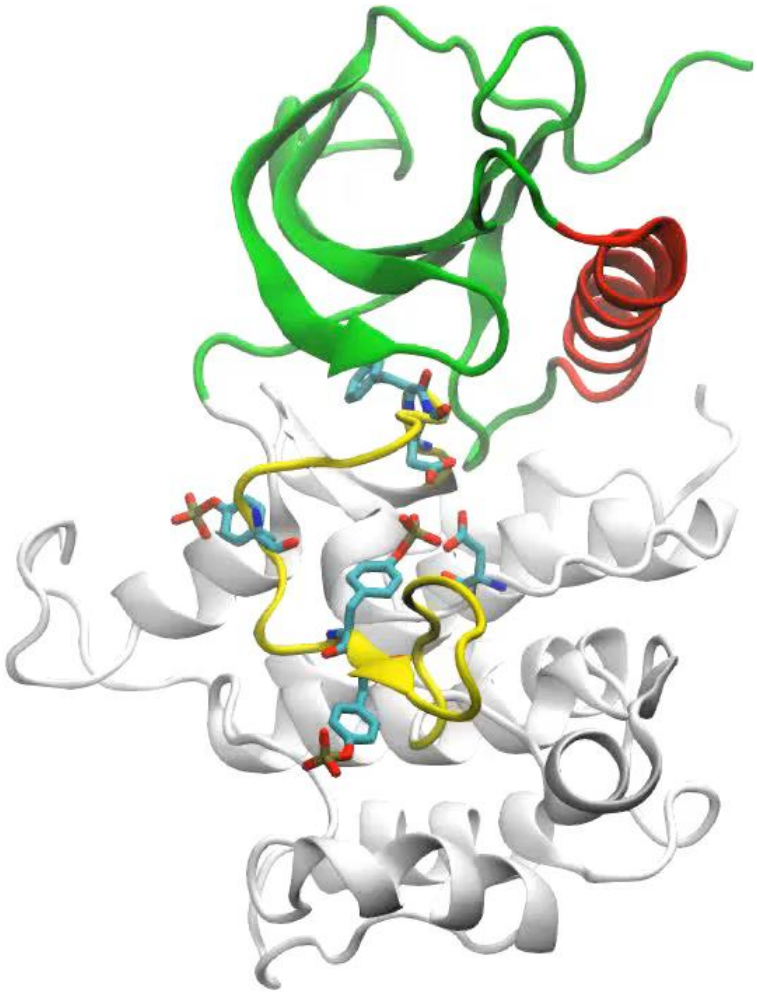
$$\text{ATP + Sub} \xrightarrow{\text{PK}} \text{ADP + P-Sub}$$

Our interests: Protein Tyrosine Kinase (PTK)

- Families: 30
- Subfamilies: 30
- In human: 90 (ratio: 90/518~17%)

Figure adopted from Favelyukis, NSMB (2001).

Current status



- 124 nodes for each conf. change simulation: study multiple paths
- Each titan job: 248 nodes (3968 Cores); typically < 1 hr.
- Since Nov. 2017, 2.5 M core hours used.