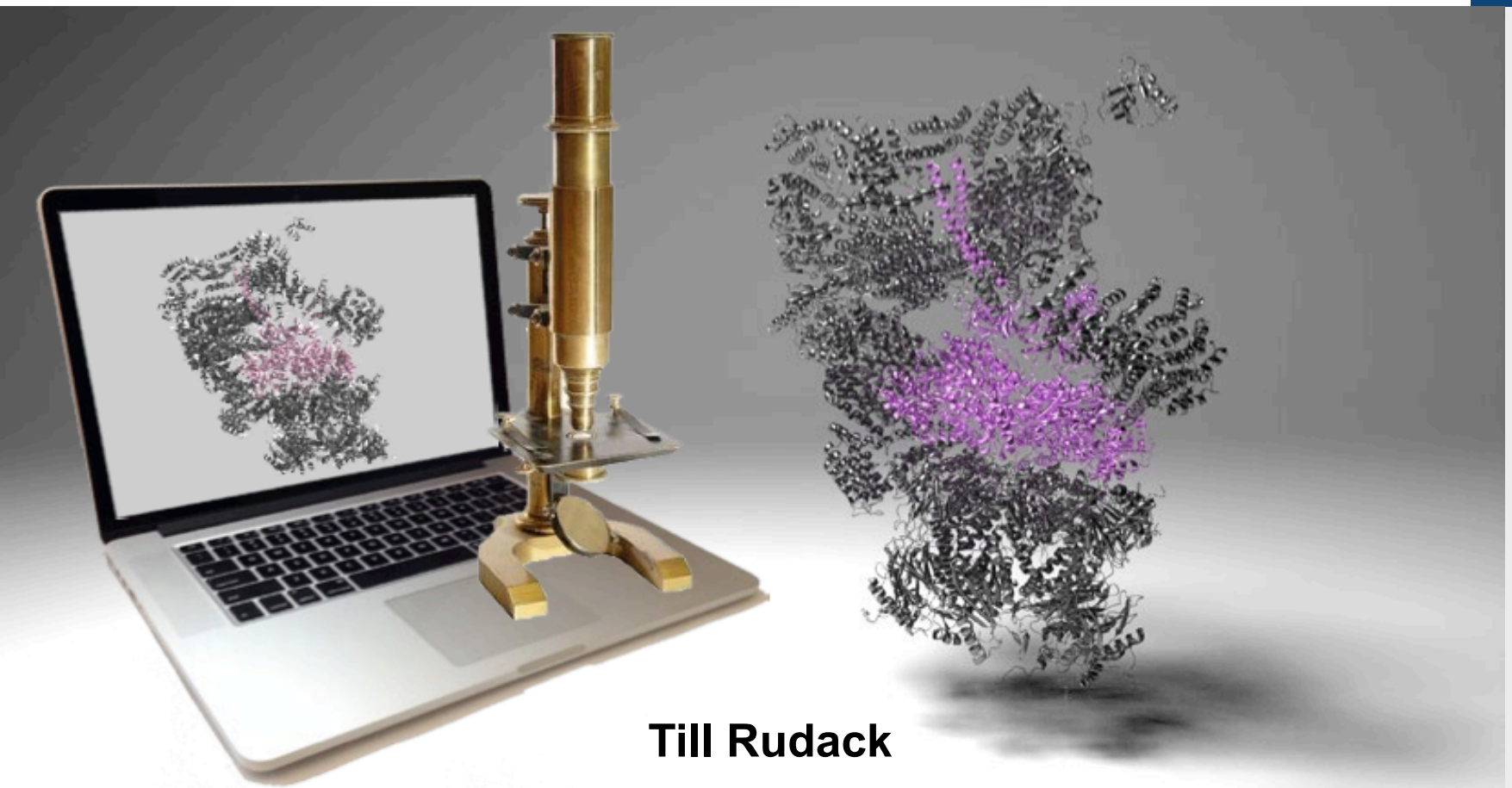
Integrative Modeling



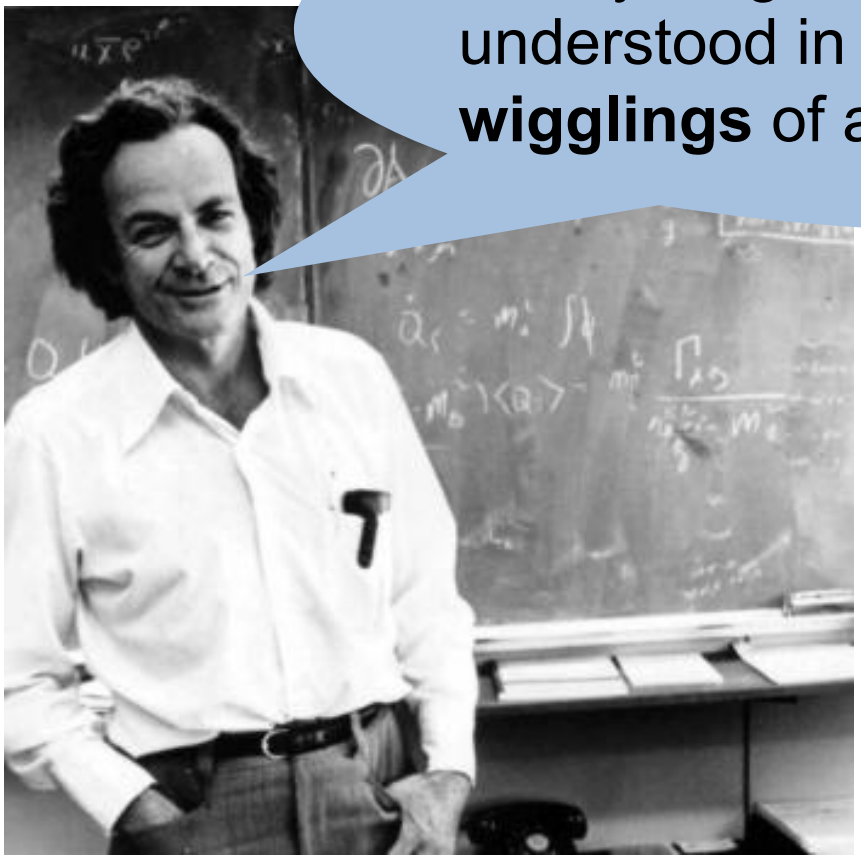
Till Rudack

Klaus Schulten Group - Theoretical and Computational Biophysics Group

NIH Center for Macromolecular Modeling and Bioinformatics

University of Illinois at Urbana-Champaign

The Key Principle

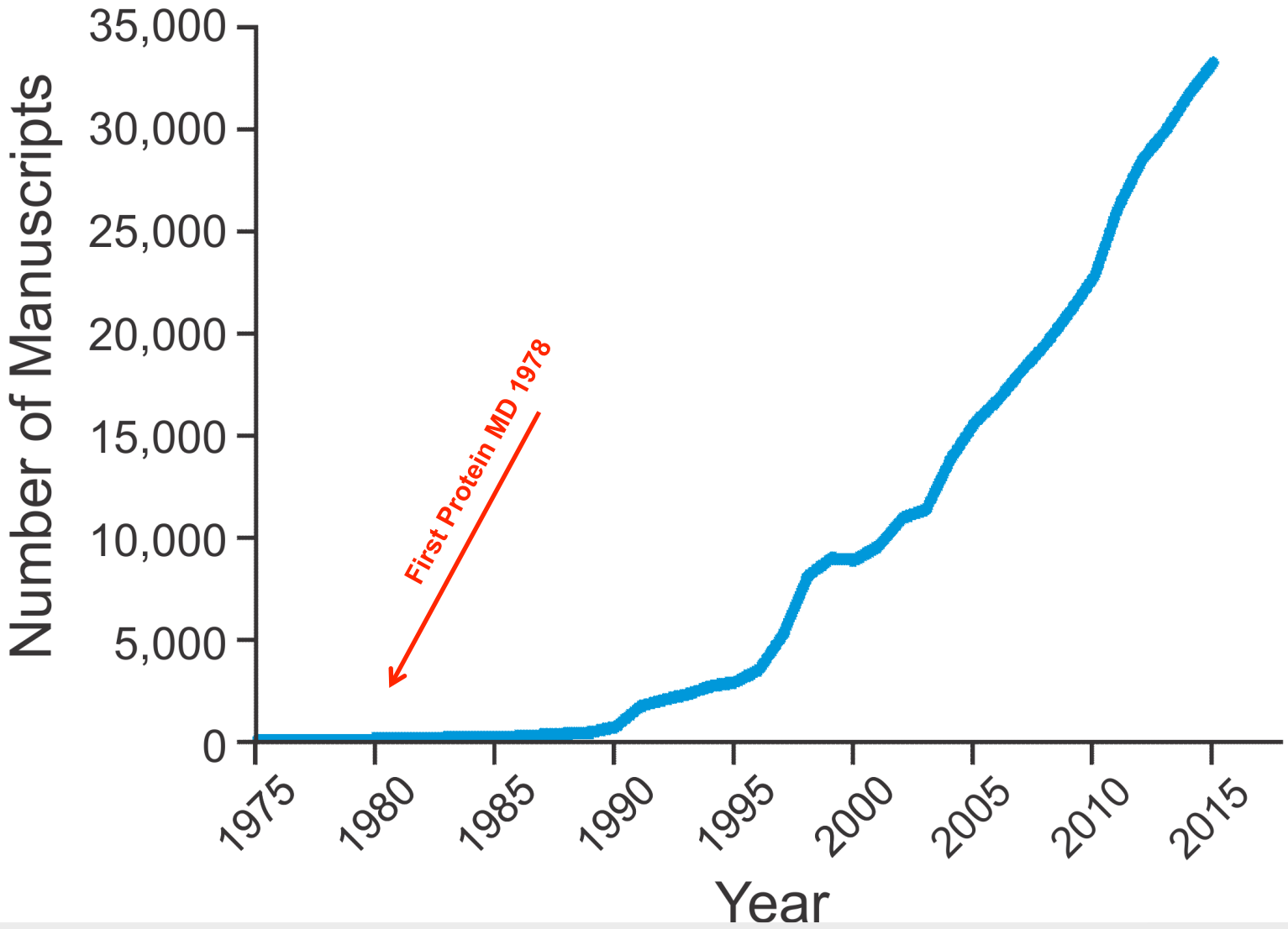


"Everything that living things do can be understood in terms of the **jigglings and wigglings** of atoms."

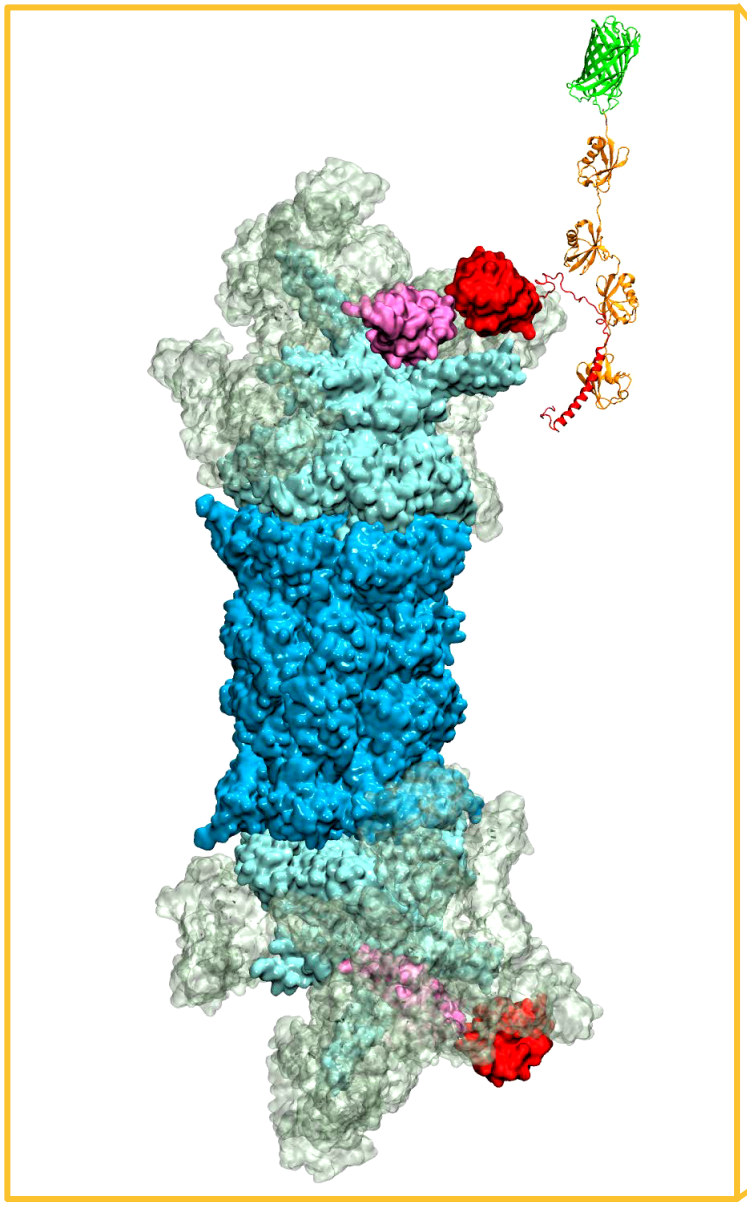
Richard Feynman
The Feynman Lectures on Physics: Mainly Mechanism, Radiation and Heat (1963)

Development of Molecular Dynamics Simulation

- Developed as a simple method in **the late 1950's**, MD algorithms evolved greatly.

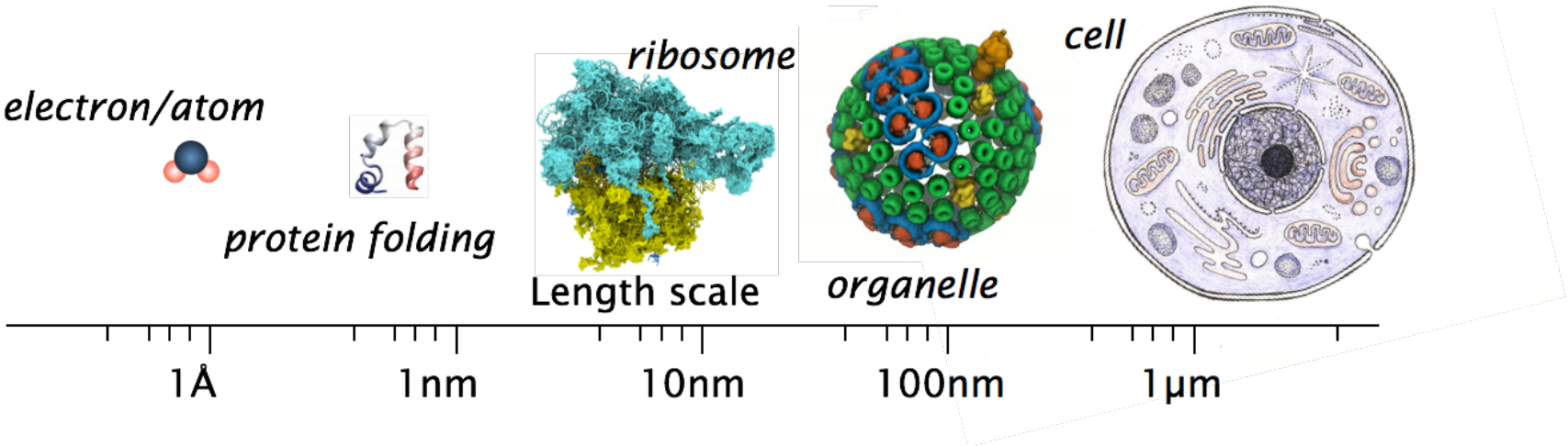


What can we discover with the Computational Microscope?

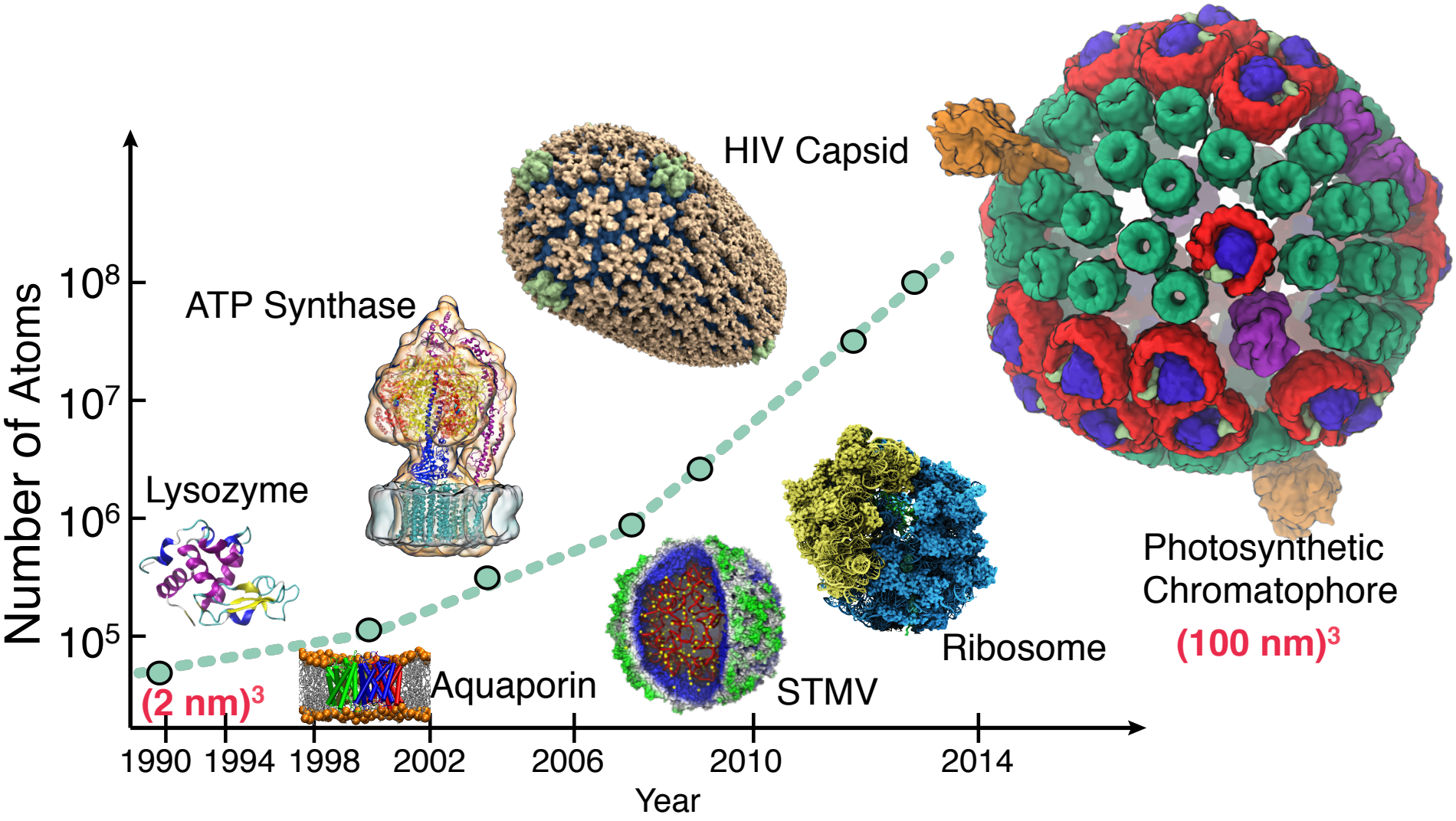


The range of the Computational Microscope

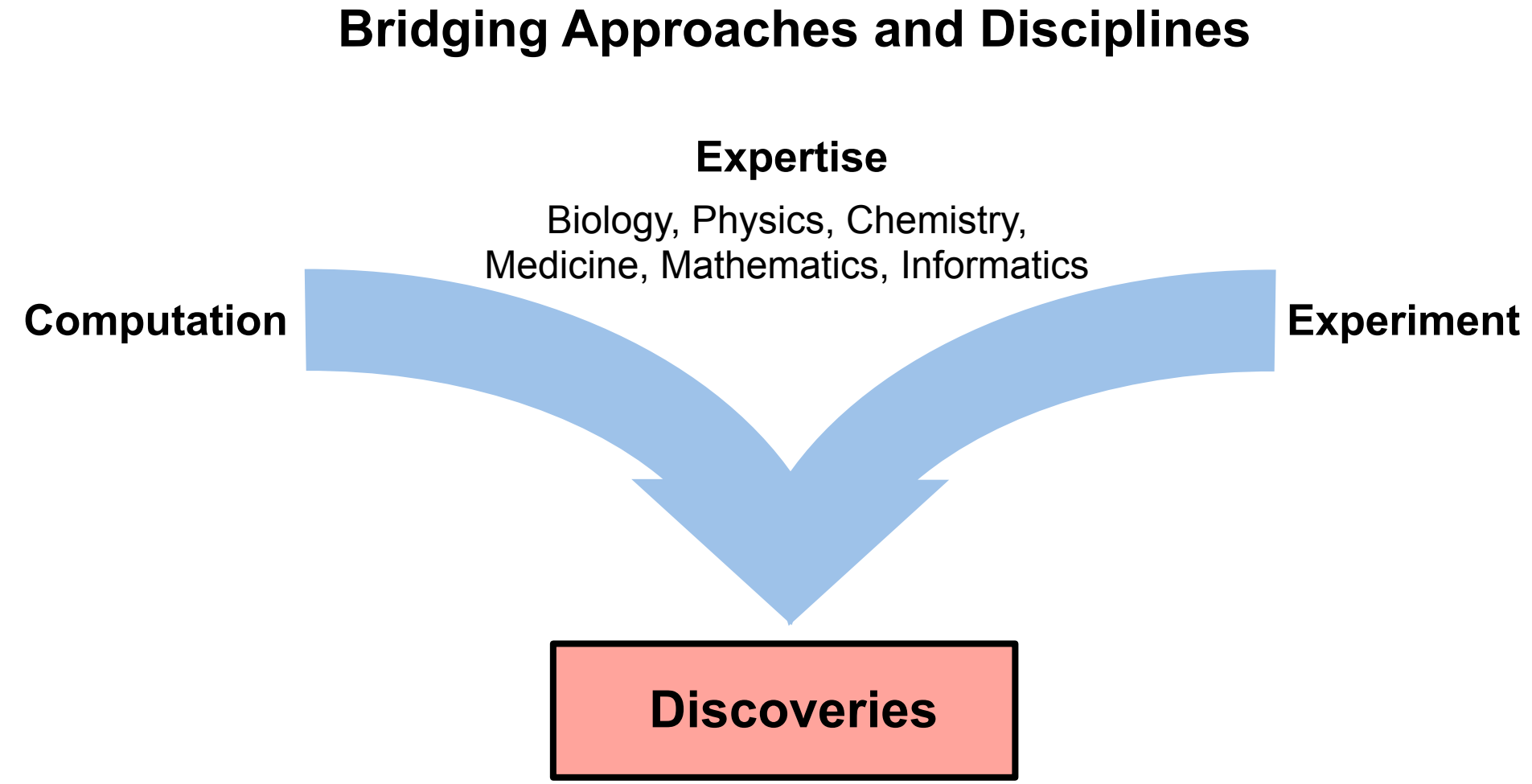
... Views Living Systems from Electron to Cell



Size Matters!



The Strategy



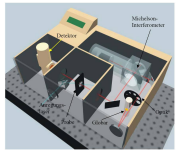
Computation needs Experiments and *vice versa*

Experimental Input

NMR

X-ray

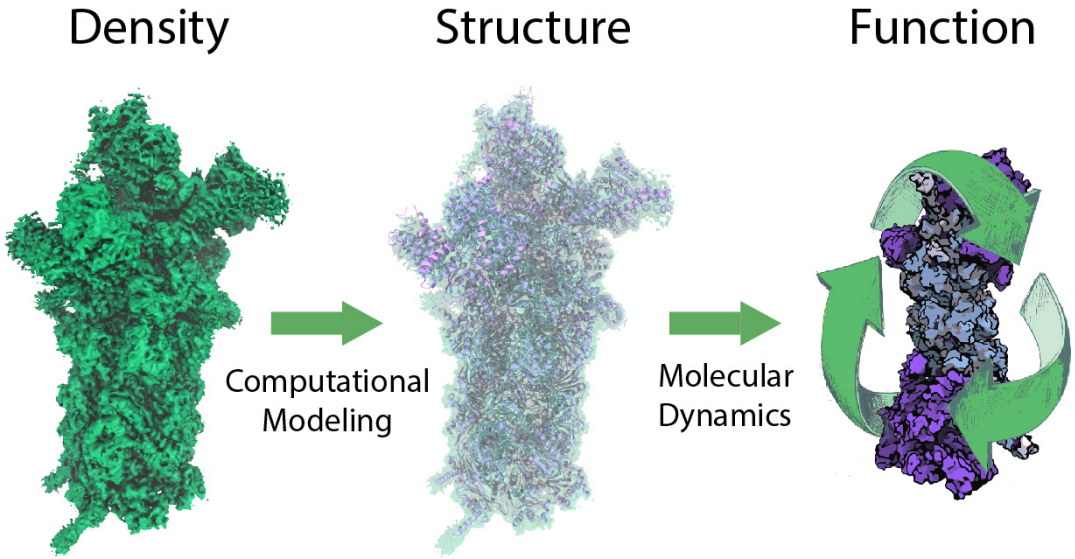
cryo-EM/ET



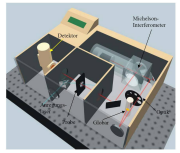
IR Spectroscopy

Computational Modeling and Molecular Dynamics Simulation

Structural Models
Analysis
Visualization
Hypothesis of Function
Suggestions for targeted Experiments



Experimental Validation



IR Spectroscopy

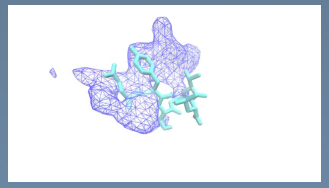
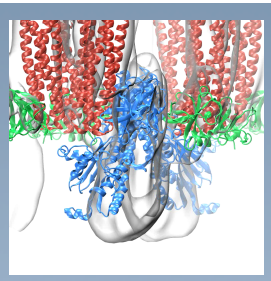
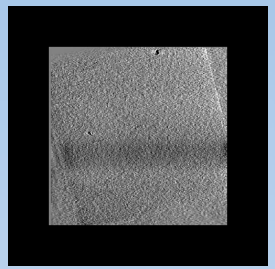
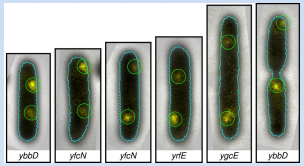
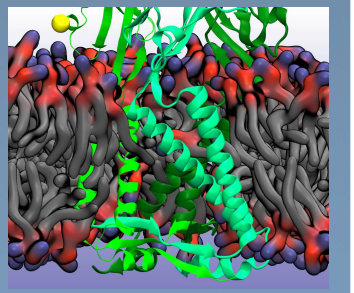
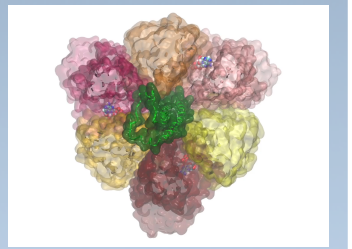
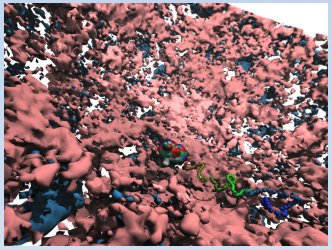
FRET

in vivo studies

clinical studies

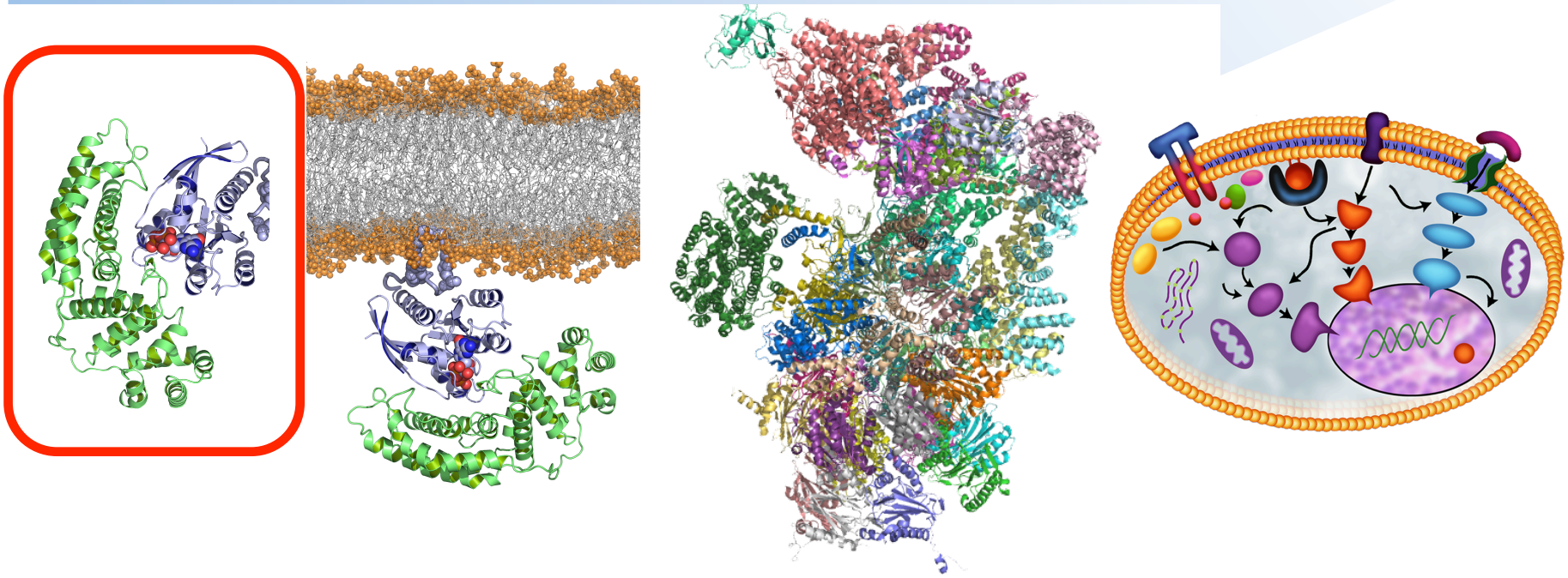
Range of the Computational Microscope

Proteins → **Multi-Protein Complex** → **Organelles** → **Cell**

Experimental Method	  NMR X-ray		 cryo-EM	 FRET
Data Types	 X-ray Density	 Cryo-EM Density	 Cryo-EM Tomogram	 Brightfield Illumination
Function	 Membrane Permeation	 Motor Action	 Molecular Movement	 Cell Division

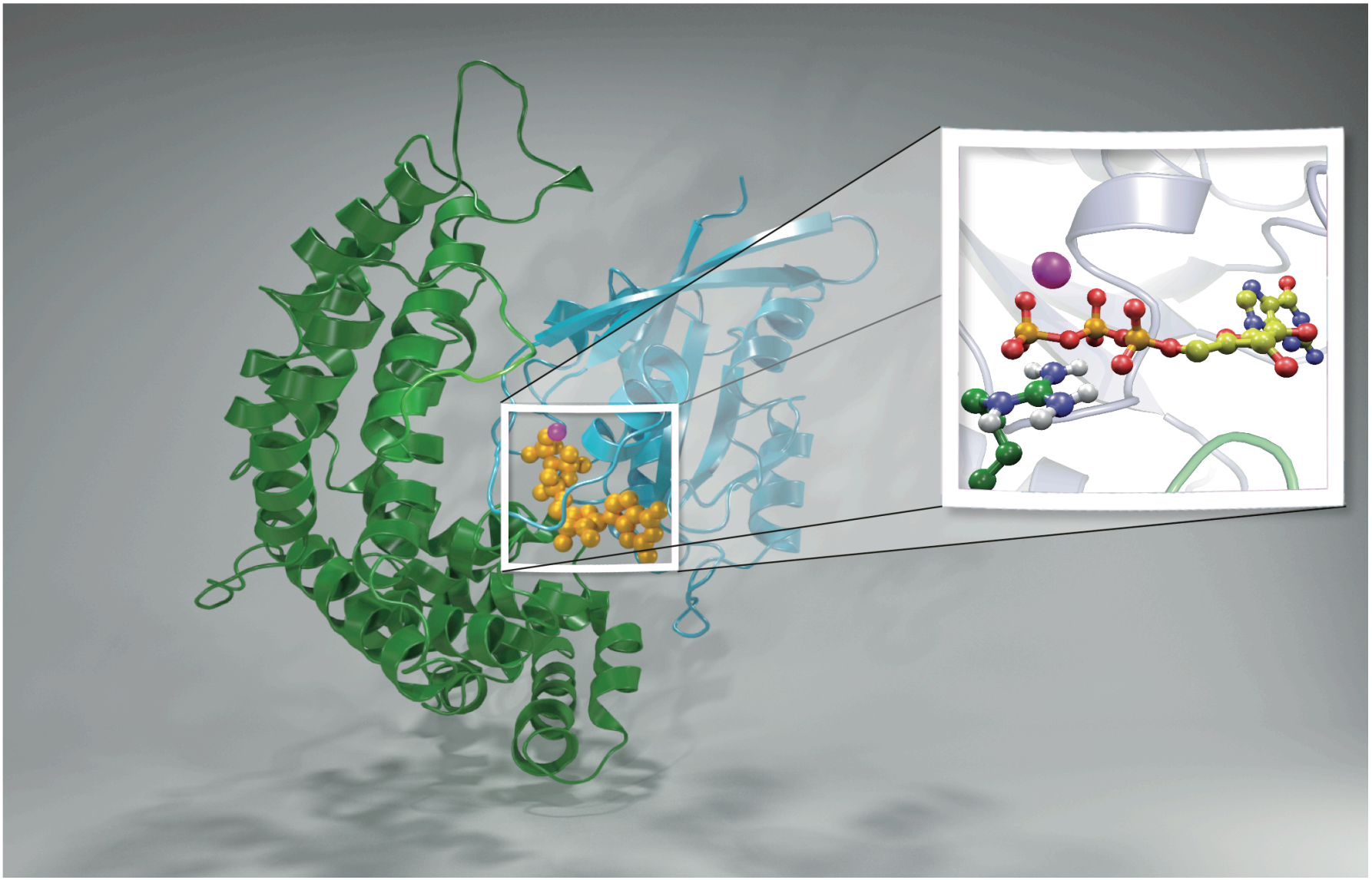
Application of MD simulations: from atom to cell

Protein In Solvent → **Protein + Membrane** → **Multi-Protein Complex** → **Cell**

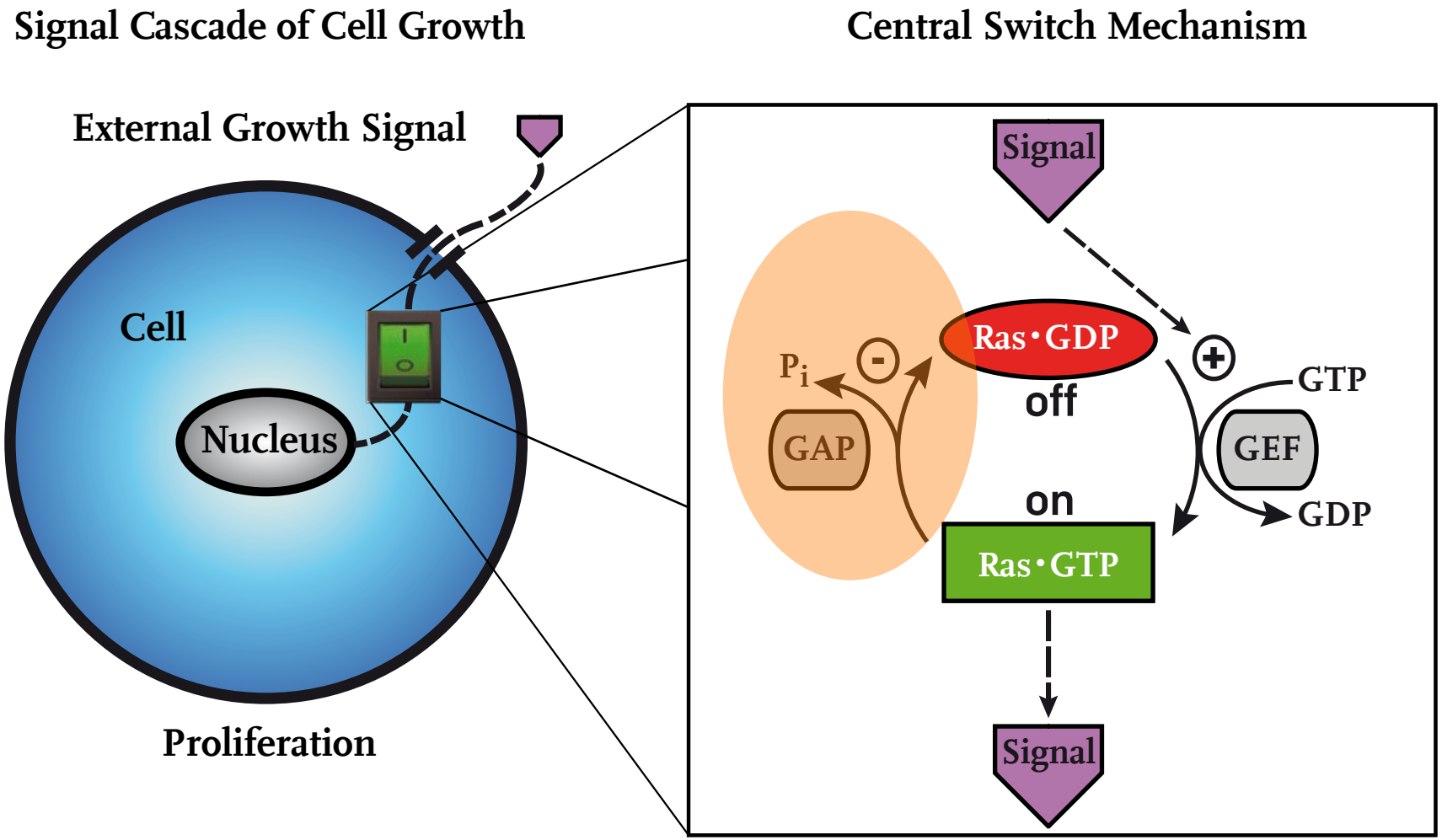


Molecular dynamics simulations connect **function** and **dynamics** to **structural data** from diverse **experimental sources** to investigate critical cellular processes occurring at the **sub-Ångstrom** level up to the **macromolecular** level.

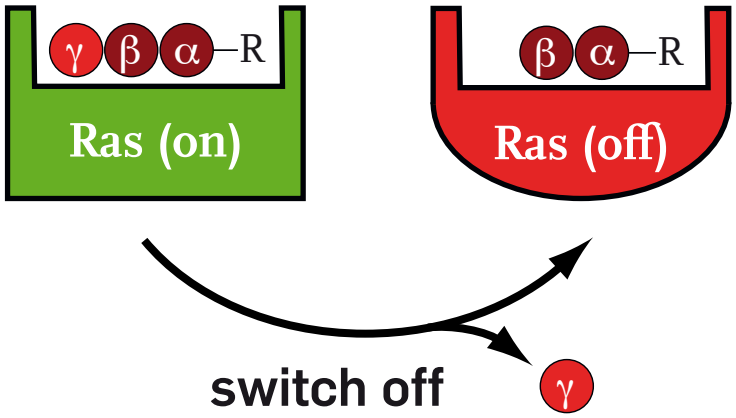
The sub-Ångstrom level for catalysis



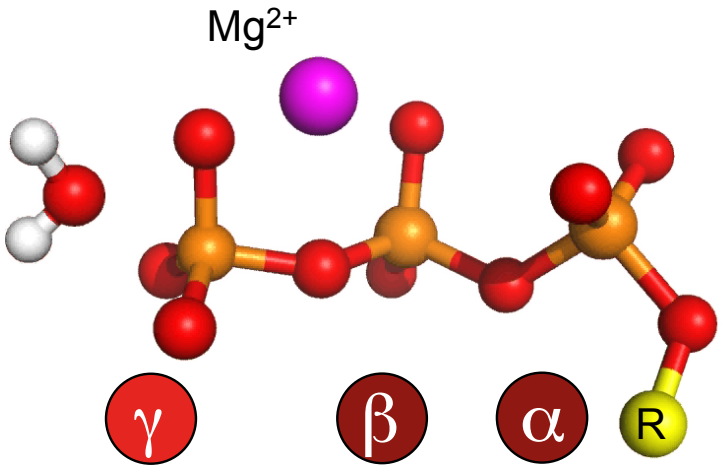
Ras: a Small GTPase



Ras: Switch Mechanism for Cell Growth



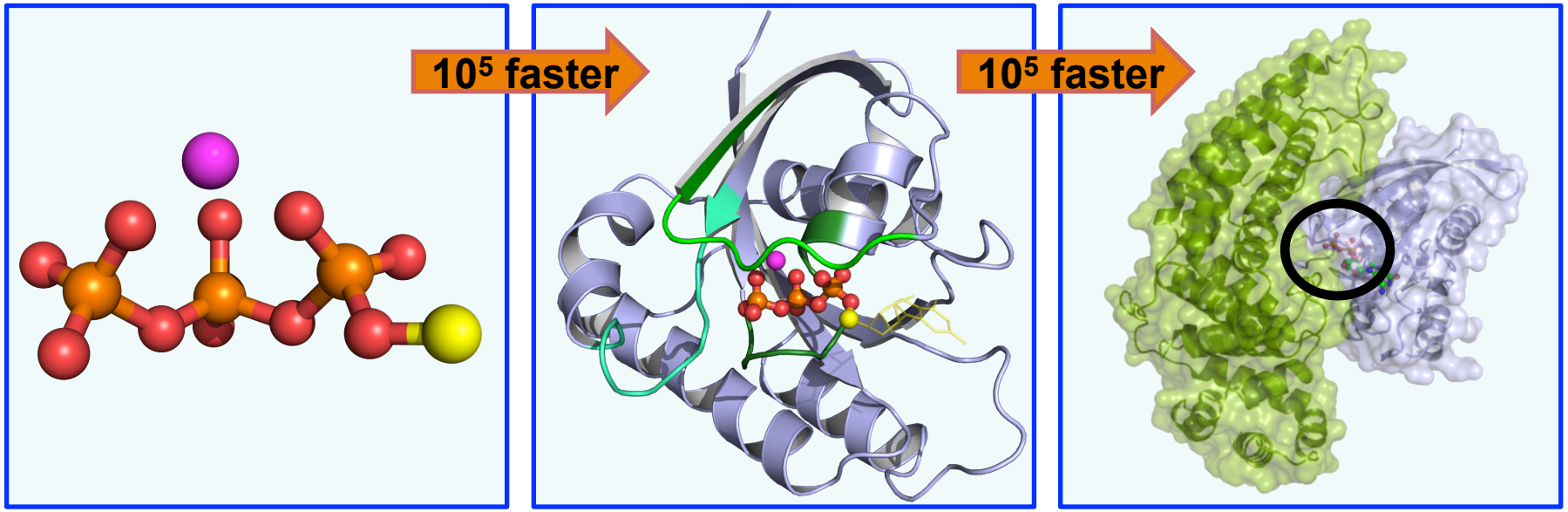
GTP Hydrolysis Model



GTP in H_2O

GTP + Ras in H_2O

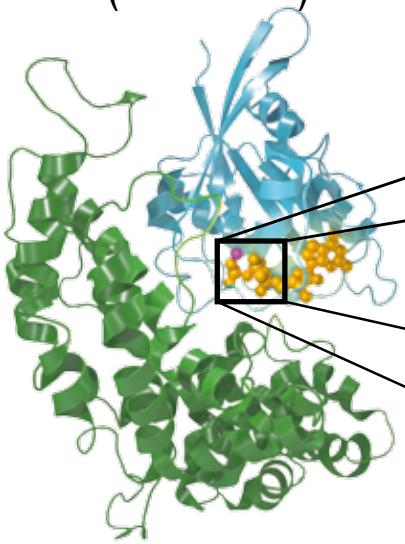
GTP + Ras + GAP in H_2O

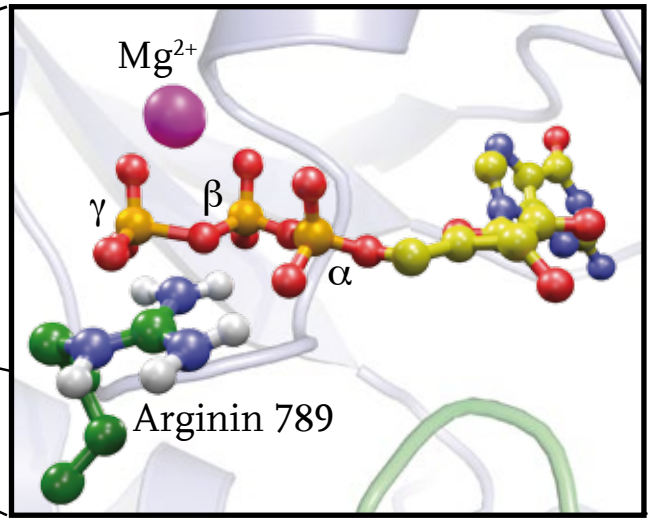


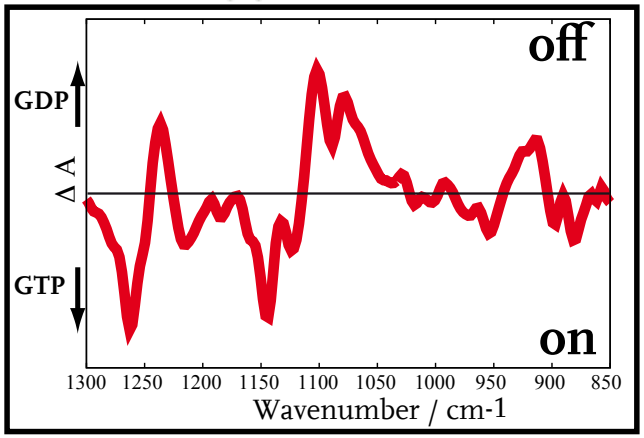
Combining spectroscopy, crystalography and MD

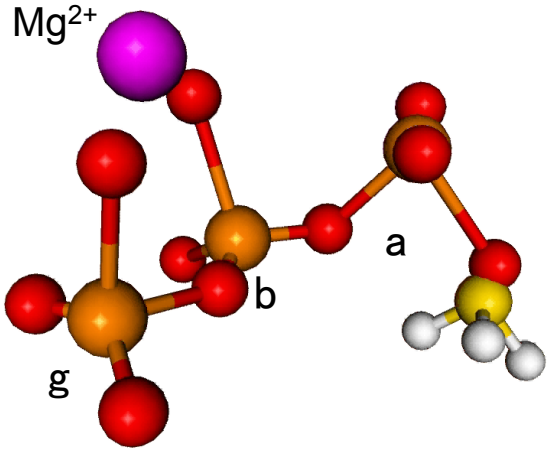
Experiment
X-ray Crystallography
(1.6-2.5 Å)

Theory
MD Simulations
(0,01 Å)









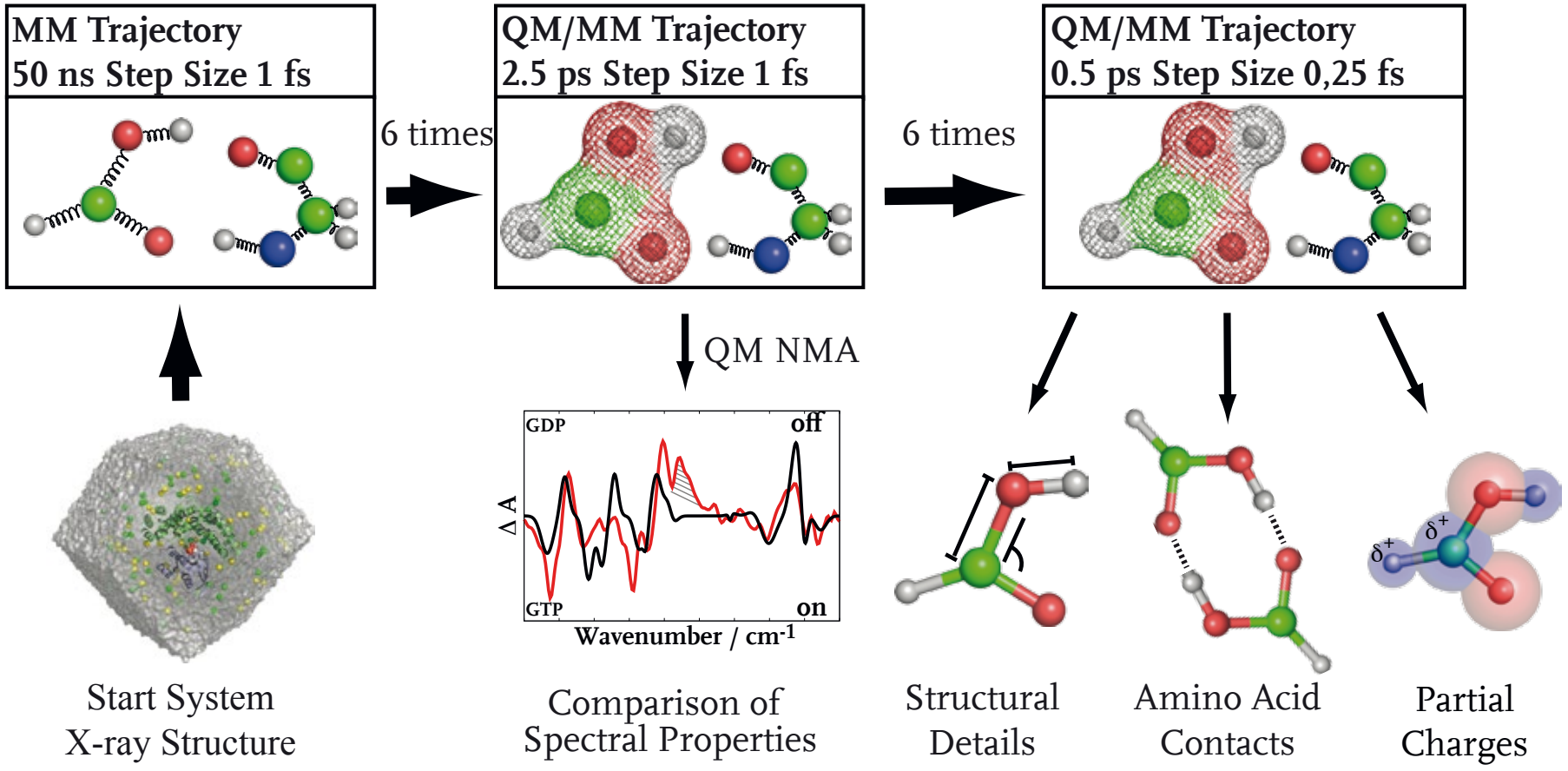
FTIR-Spectroskopy ($\Delta\nu$ = 1.0 cm^{-1}; 10^{-4} Å)

Workflow

MM: $\vec{F}_i\left(\vec{R}(t)\right) = -\vec{\nabla}_i V\left(\vec{R}(t)\right)$

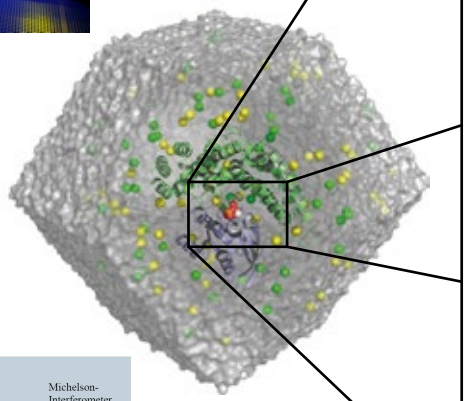
QM: $H\Psi(x_i, R_a) = E(R_a)\Psi(x_i, R_a)$

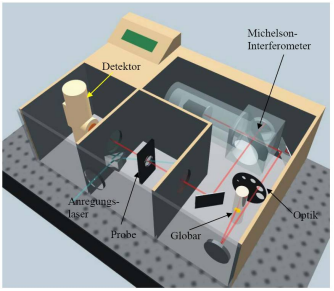
B3LYP/
6-31G*

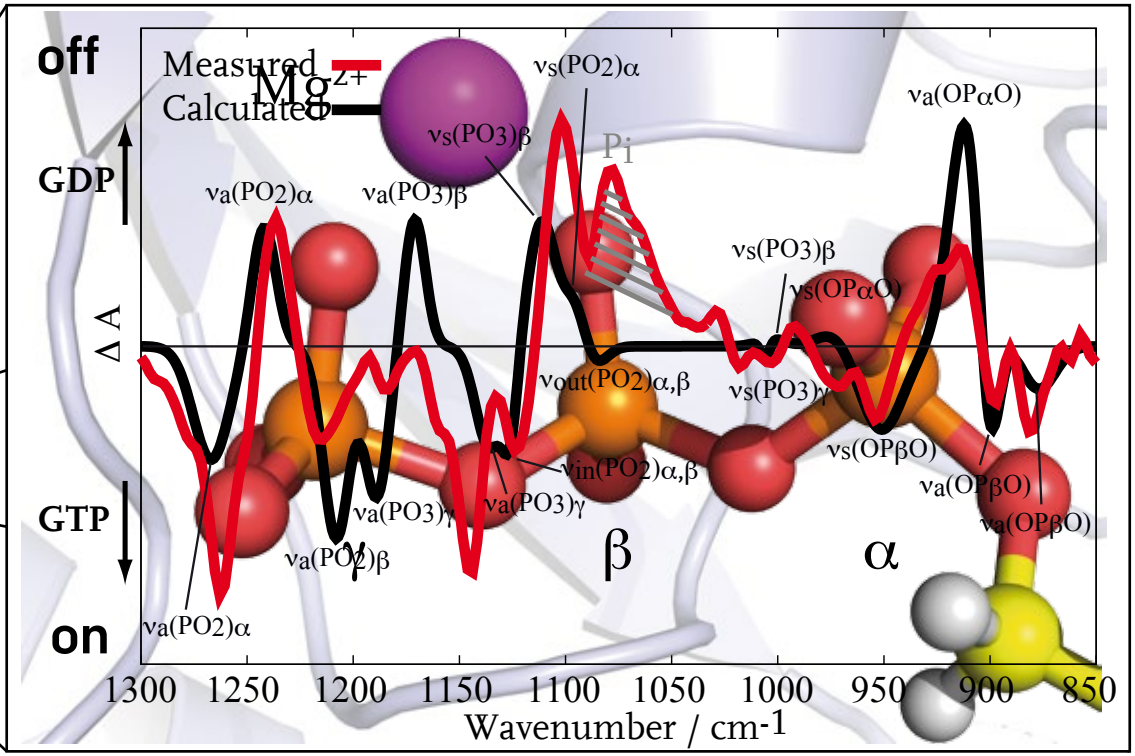


Rudack, Xia, Schlitter, Kötting, Gerwert, Biophys. J., 2012, 103:293

Validation of Computational Models

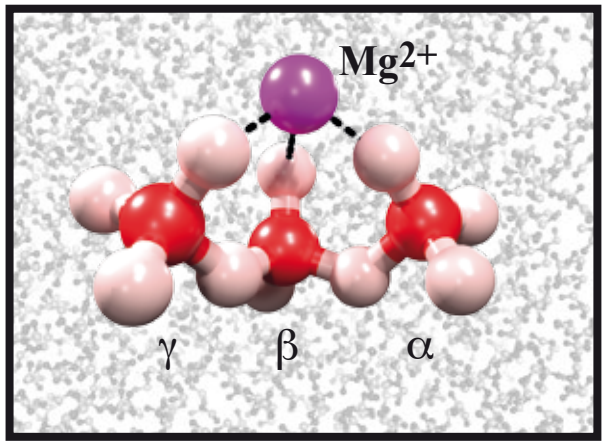


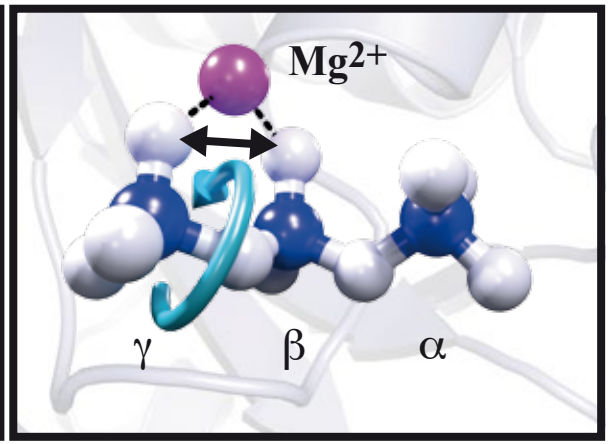


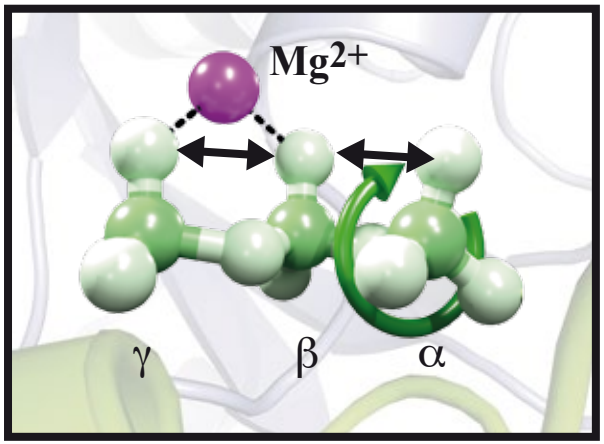


 Rudack, Xia, Schlitter, Kötting, Gerwert, PNAS, 2012, 109:15295

Charge distribution and geometry of GTP

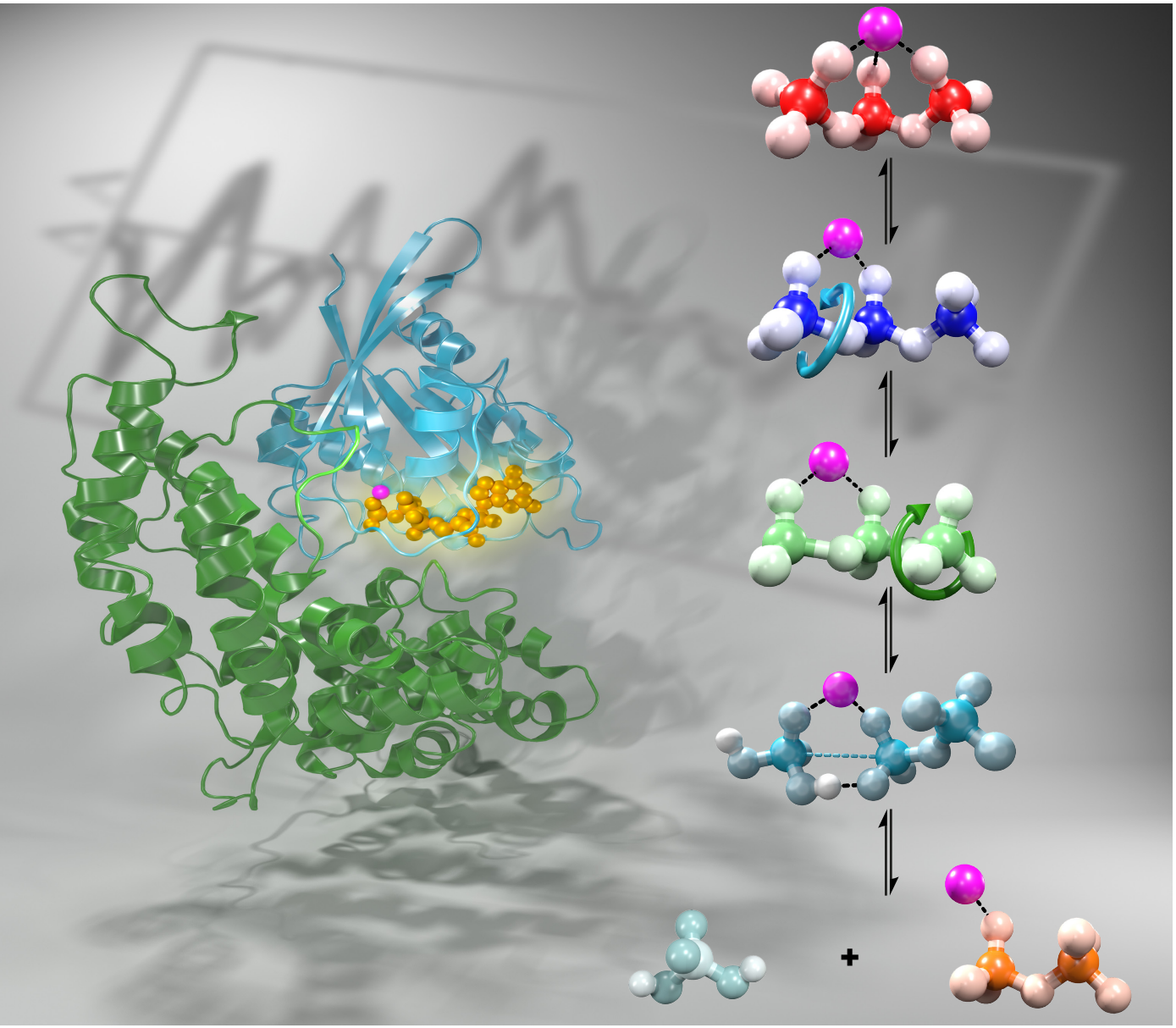






Rudack, Xia, Schlitter, Kötting, Gerwert, PNAS, 2012, 109:15295
Rudack, Xia, Schlitter, Kötting, Gerwert, Biophys. J., 2012, 103:293

Ras catalysis GTP hydrolysis



Rudack, Xia, Schlitter, Kötting, Gerwert, PNAS, 2012, 109:15295

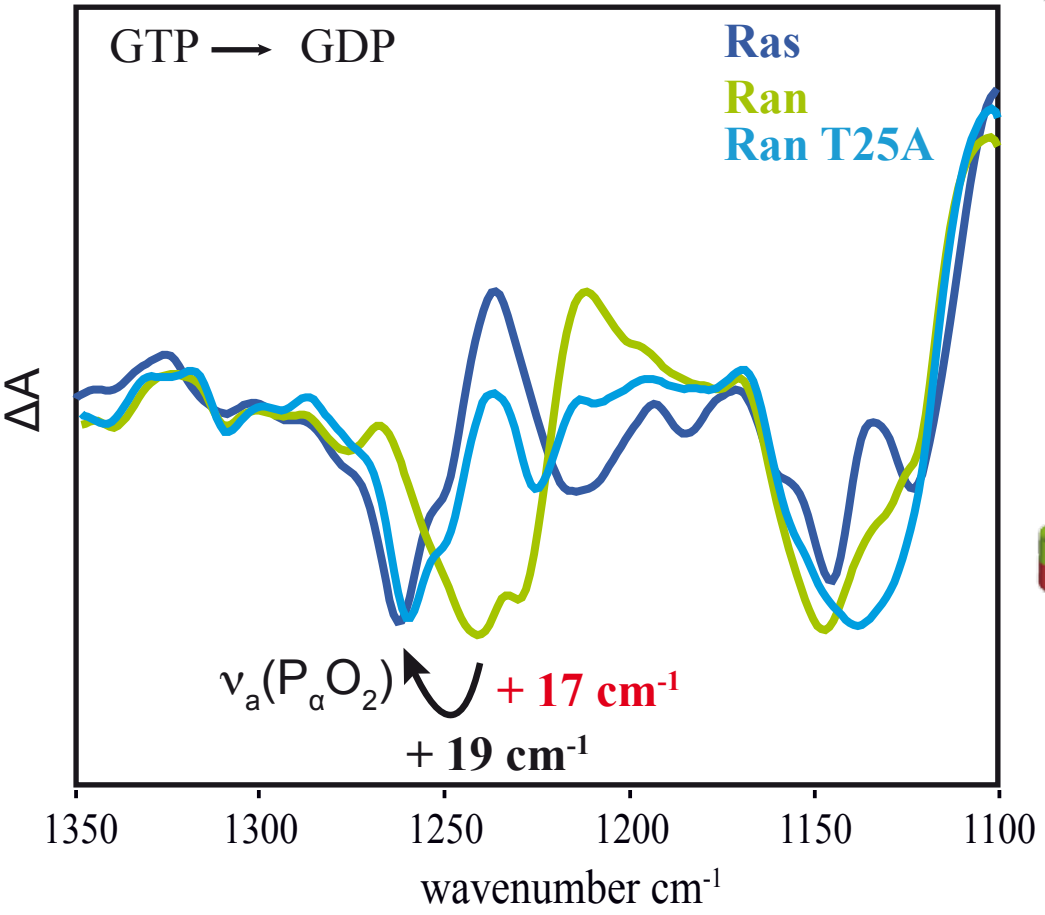
Rudack, Xia, Schlitter, Kötting, Gerwert, Biophys. J., 2012, 103:293

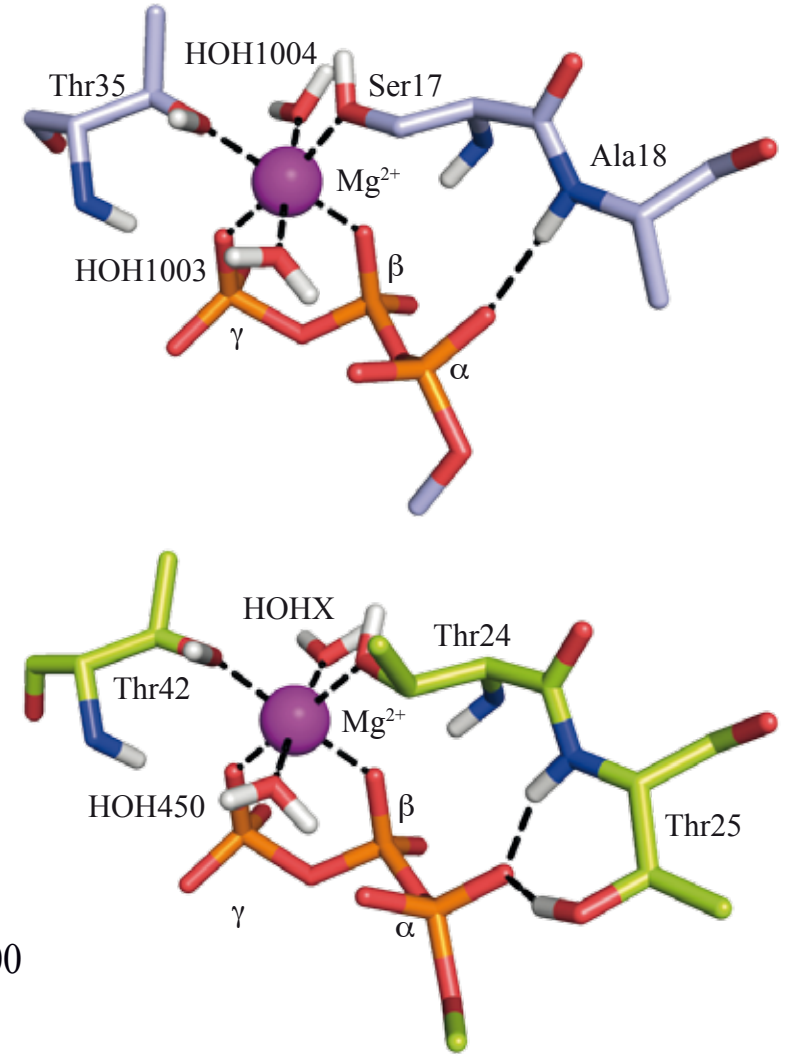
Rudack*, Jenrich*, Brucker, Vetter, Gerwert, Kötting, J. Biol Chem, 2015, 290,40: 24079

Xia*, **Rudack***, Cui, Kötting, Gerwert, JACS, 2012, 134:20041

Li, **Rudack**, Gerwert, Gräter, Schlitter, JCTC, 2012 8:3596

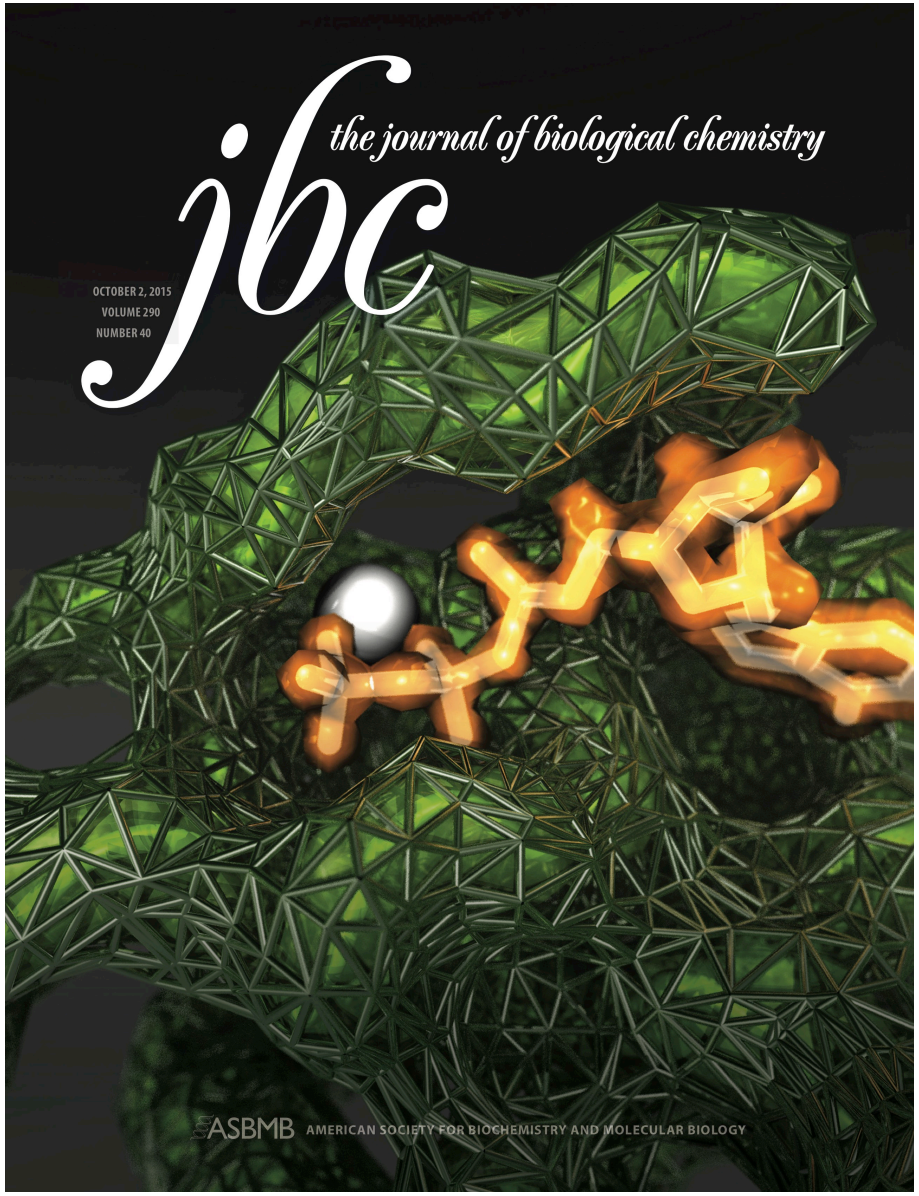
How Accurate is the Method?





Rudack*, Jenrich*, Brucker, Vetter, Gerwert, Kötting, J. Biol Chem, 2015, 290,40: 24079

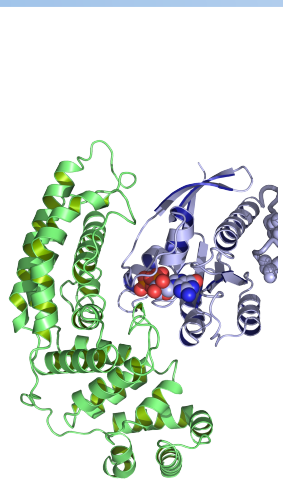
Bridging the divided

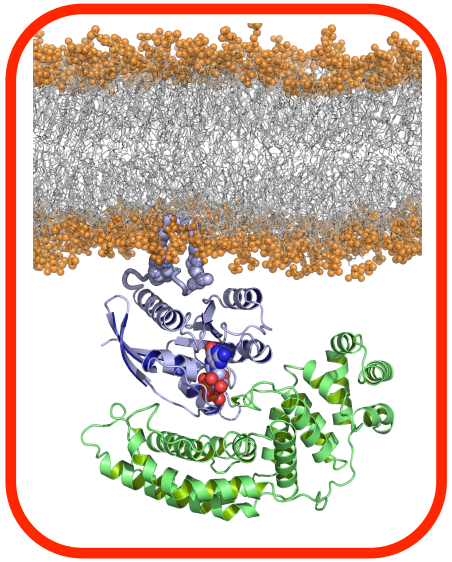


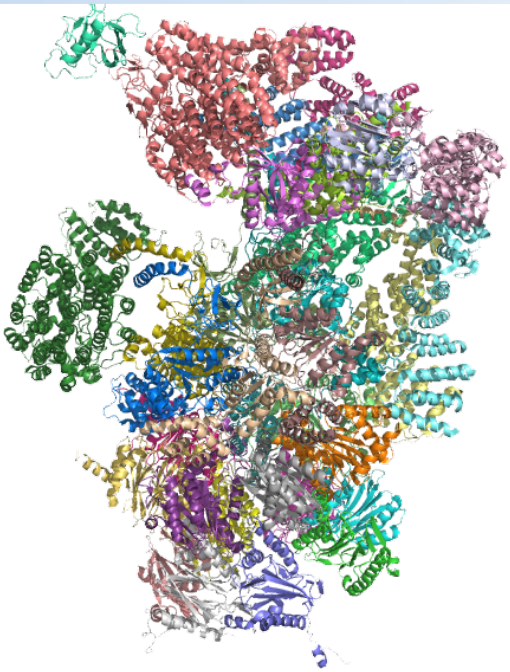
www.ks.uiuc.edu/~rudack*, Jenrich*, Brucker, Vetter, Gerwert, Kötting, J. Biol Chem, 2015, 290,40: 24079

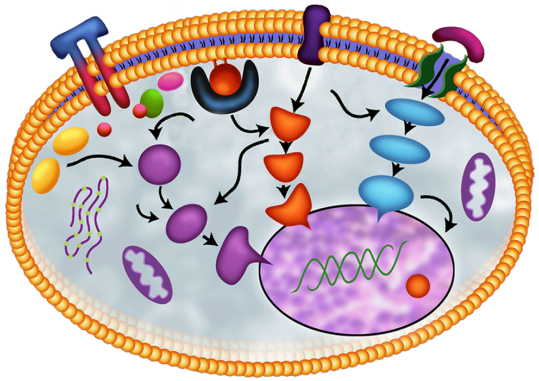
Application of MD simulations: Ras at Membrane

Protein In Solvent → **Protein + Membrane** → **Multi-Protein Complex** → **Cell**



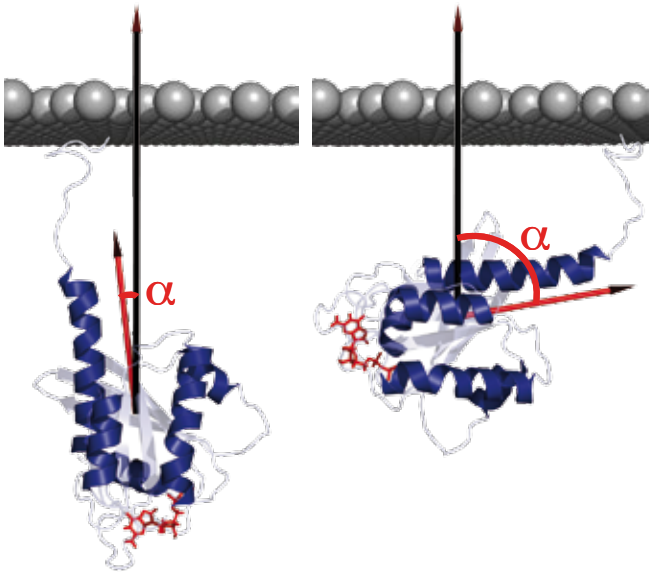




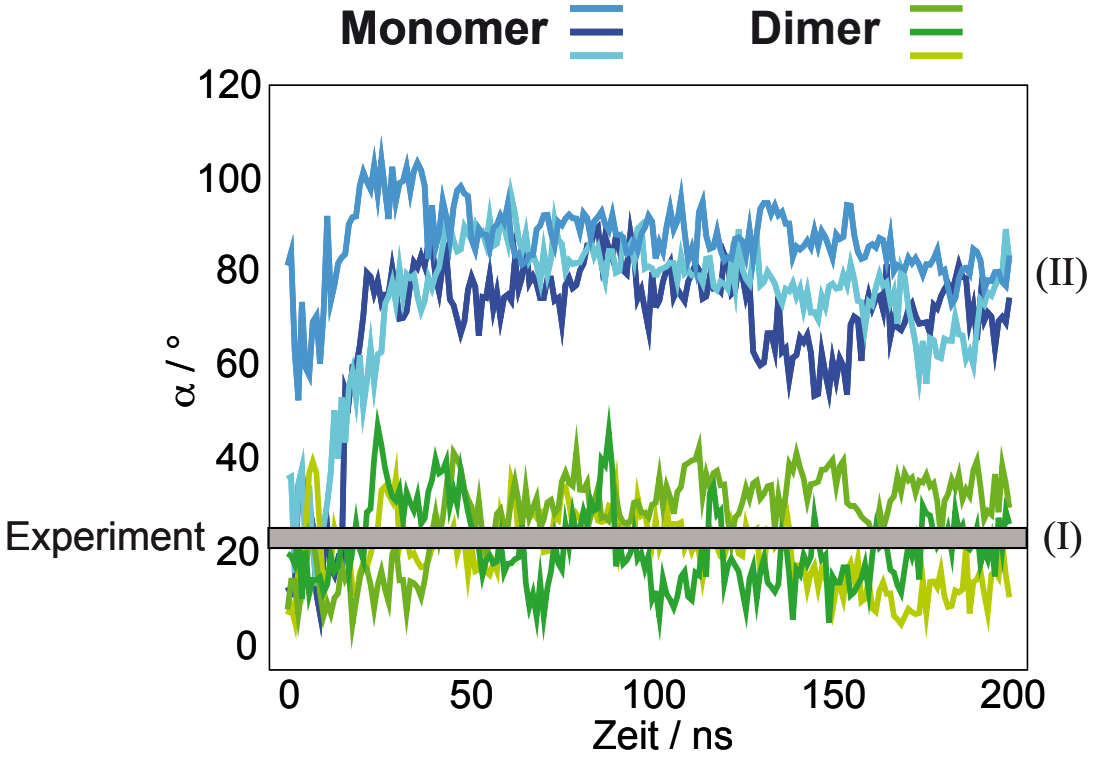


Molecular dynamics simulations connect **function** and **dynamics** to **structural data** from diverse **experimental sources** to investigate critical cellular processes occurring at the **sub-Ångstrom** level up to the **macromolecular** level.

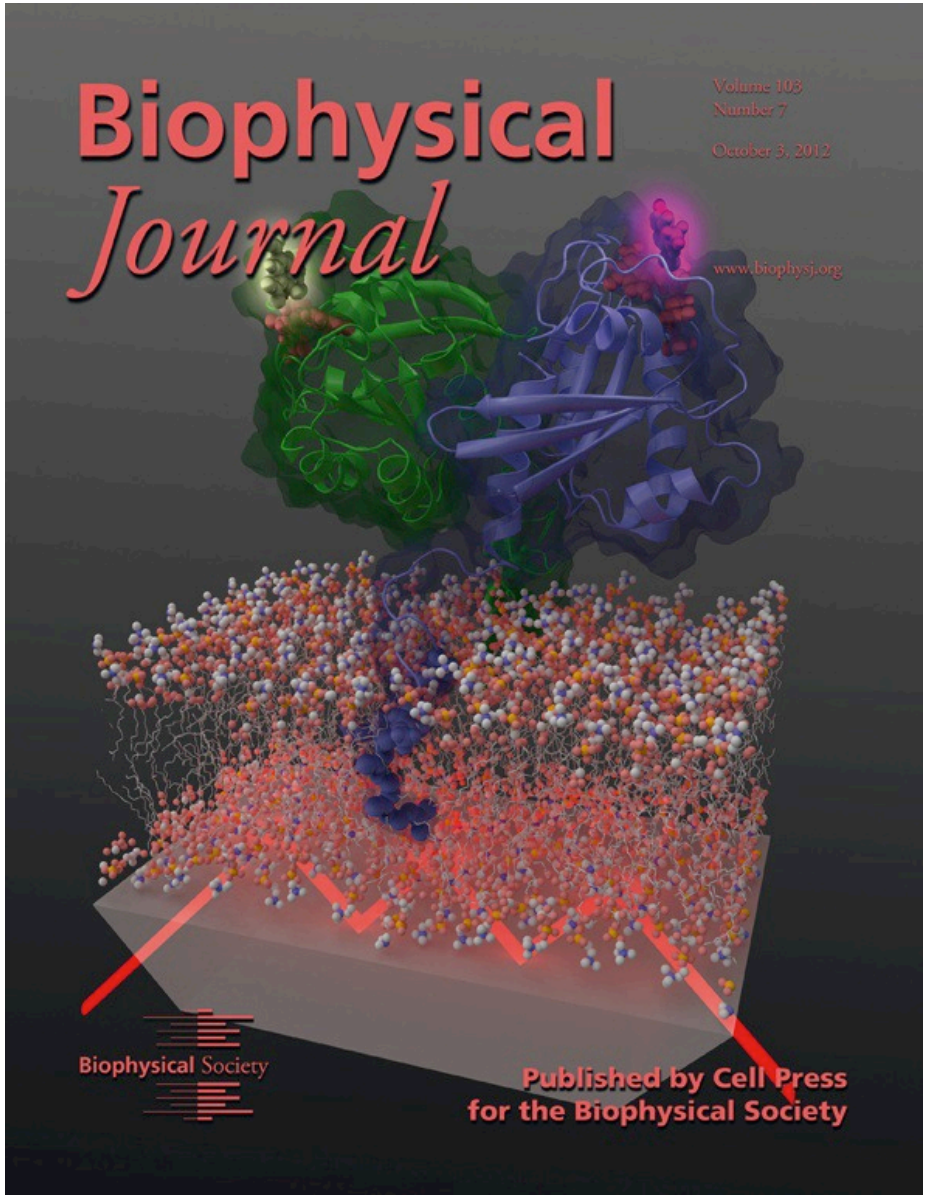
MD simulations of N-Ras at a Membrane



(I) (II)



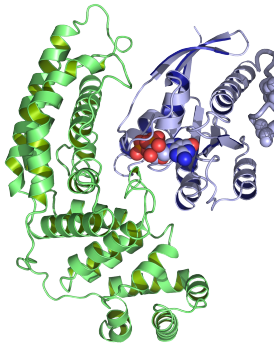
N-Ras forms dimers attached to a membrane

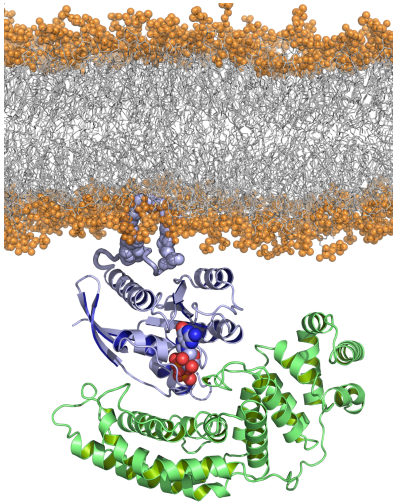


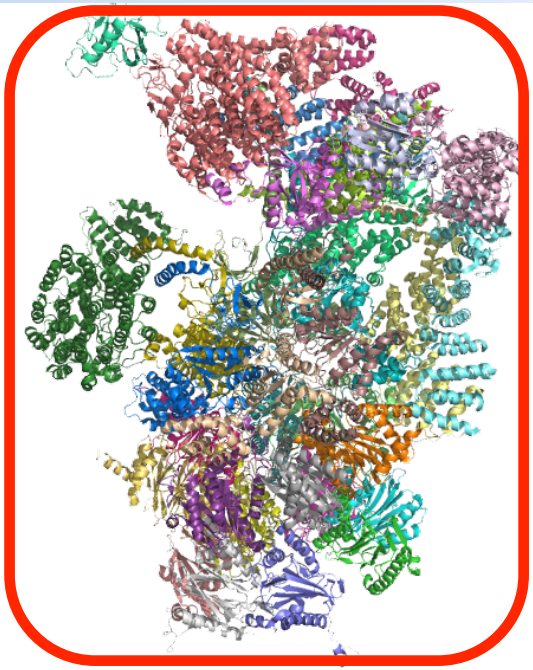
Güldenhaupt, Rudack, Bachler, Mann, Triola, Waldmann,, Kötting, Gerwert,
Biophys. J., 2012, 103:1585

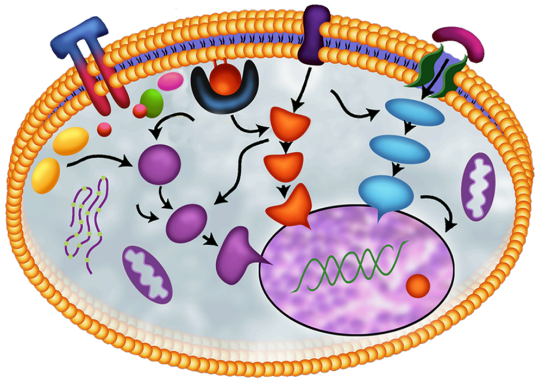
Application of MD simulations: 26S Proteasome

Protein In Solvent → **Protein + Membrane** → **Multi-Protein Complex** → **Cell**









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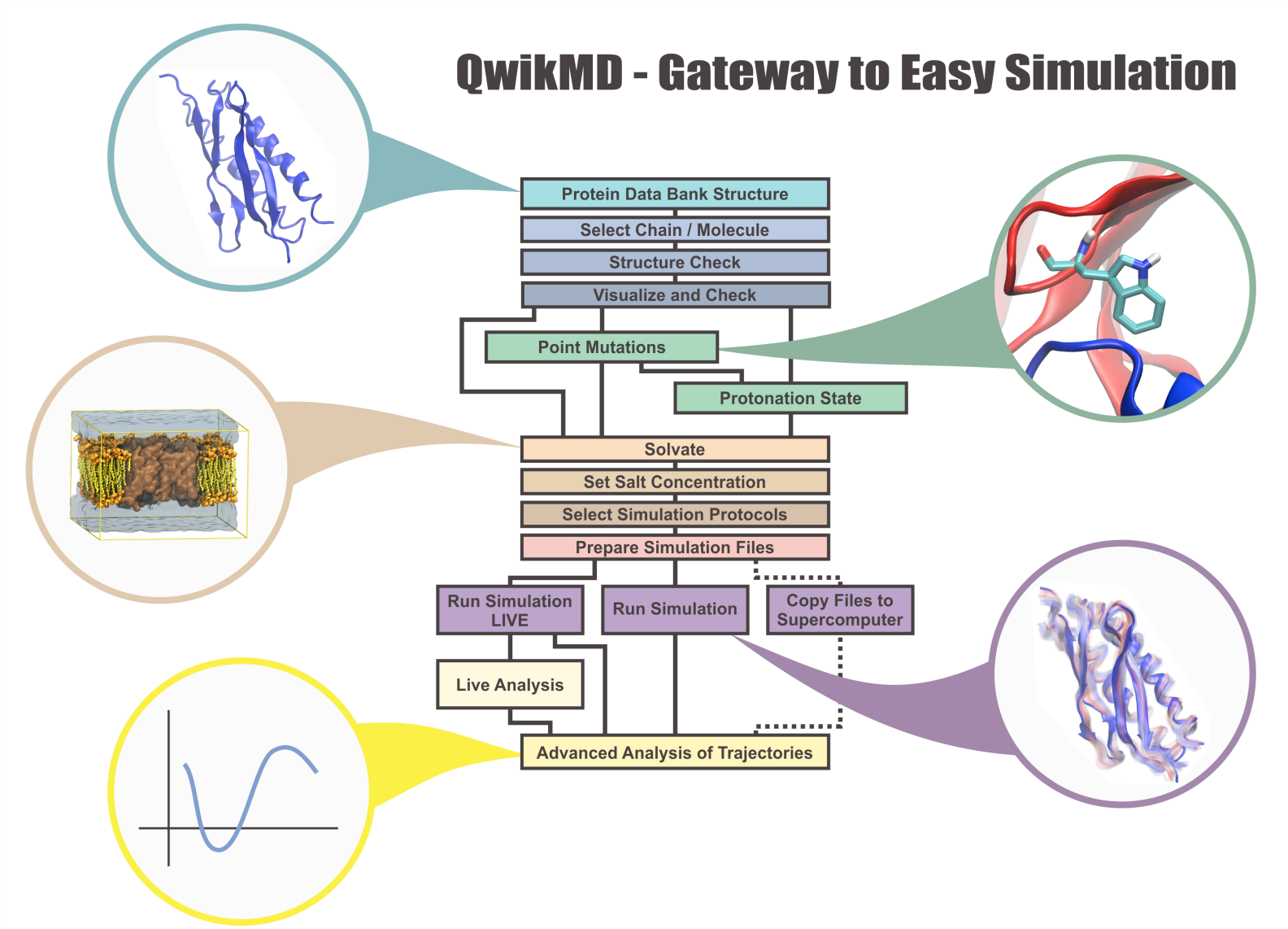
QwikMD


QwikMD - Gateway to Easy Simulation
Protein Data Bank Structure
Select Chain / Molecule
Structure Check
Visualize and Check
Point Mutations
Protonation State
Solvate
Set Salt Concentration
Select Simulation Protocols
Prepare Simulation Files
Run Simulation LIVE
Run Simulation
Copy Files to Supercomputer
Live Analysis
Advanced Analysis of Trajectories