

NCI-DOE Pilot 2
Ras Proteins in Membranes



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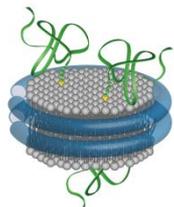
May 11, 2016

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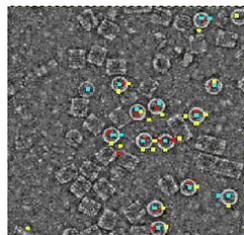


Pilot 2: RAS proteins in membranes

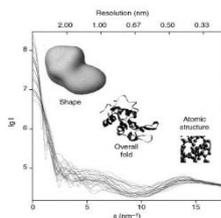
RAS activation experiments at NCI/FNL



Experiments on nanodisc



CryoEM imaging



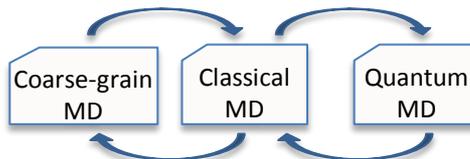
X-ray/neutron scattering

Multi-modal experimental data, image reconstruction, analytics

Protein structure databases

New adaptive sampling molecular dynamics simulation codes

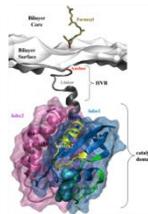
Adaptive time stepping



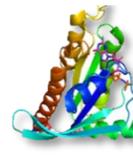
Adaptive spatial resolution

High-fidelity subgrid modeling

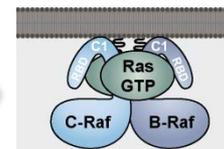
Predictive simulation and analysis of RAS activation



Granular RAS membrane interaction simulations

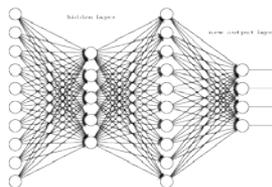


Atomic resolution sim of RAS-RAF interaction



Inhibitor target discovery

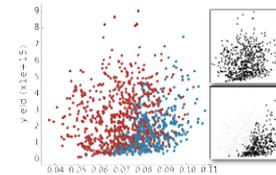
Machine learning guided dynamic validation



Unsupervised deep feature learning



Mechanistic network models



Uncertainty quantification

Pilot 2 Objectives

Goal is to develop a predictive molecular-scale model of RAS-driven cancer initiation and growth that can provide the needed insight to accelerate diagnostic and targeted therapy design.

Aims:

- Adaptive time and length scaling in dynamic multi-scale simulations.
- Extended RAS-complex interaction model
- Development of machine learning for dynamic validation of models

Methodology Overview: Molecular Dynamics (MD)

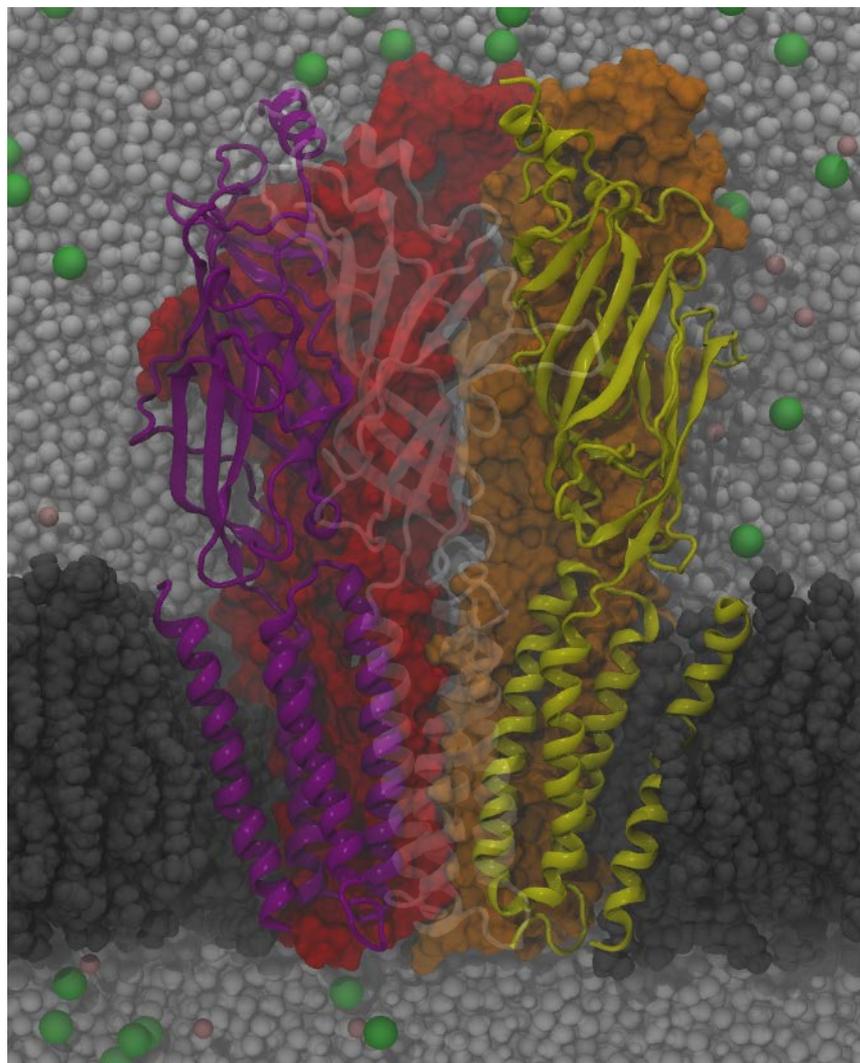
- Represent every atom in a system
- Describe the forces on all atoms:

$$\mathbf{F} = -\nabla U(\mathbf{r}) = m\mathbf{a} = m\ddot{\mathbf{r}}$$

- Integrate: $\mathbf{F} = m\mathbf{a}$ (millions of times)
- Result: position of every atom as a function of time
- Can compare with experimental structures/dynamics

Current limitations:

- 100,000's of atoms
- 10,000's of water molecules
- 1,000's of lipids
- $< 1 \mu\text{s}$



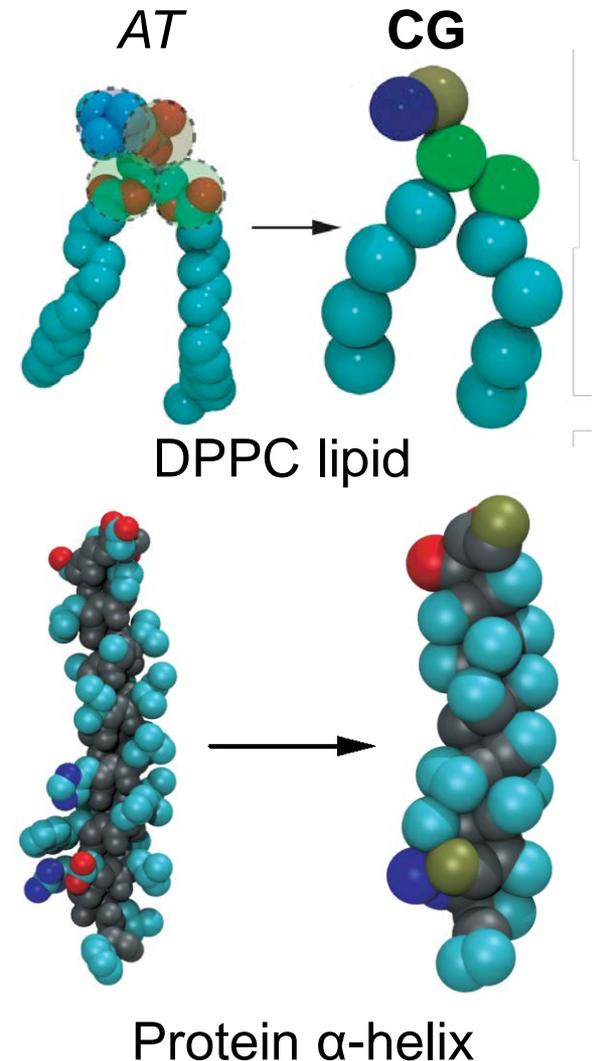
Coarse Grained Molecular Dynamics (CGMD)

- Merge several heavy atoms into a single “bead”
- Describe bead-bead interactions with averaged force field
 - Sacrifice atomistic structural and dynamic information
 - Much less computer and time intensive
 - Same computational scaling properties

6 orders of magnitude increase in sampling!

- 100s of μs^* (+3 orders of magnitude)
- 100,000s of lipids (+2 order of magnitude)

*Actual “physiological” timescale is even longer as there is also about a 10-fold increase in dynamics



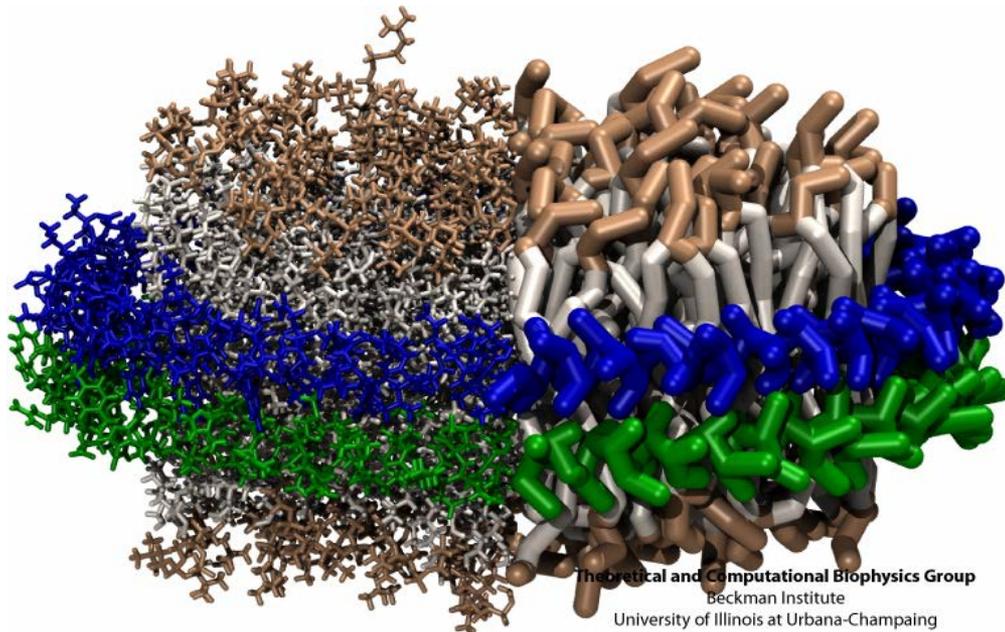
Atomistic MD vs CGMD

Atomistic (MD)

- Use for smaller systems where greater detail is required
- Can obtain quantitative results
- Ideal for local conformational changes or calculations of energetics

Coarse Grained (CGMD)

- Use for larger systems that require a longer timescale
- Good for obtaining general properties
- Ideal for self-assembly and protein-protein interactions



Aim 1

We will create a new capability: Adaptive resolution MD that switches methodology as needed

Aim 2: Understanding activation of extended Ras complex

Size study of realistic membranes

Membrane structure/morphology

Internally consistent and validated force fields

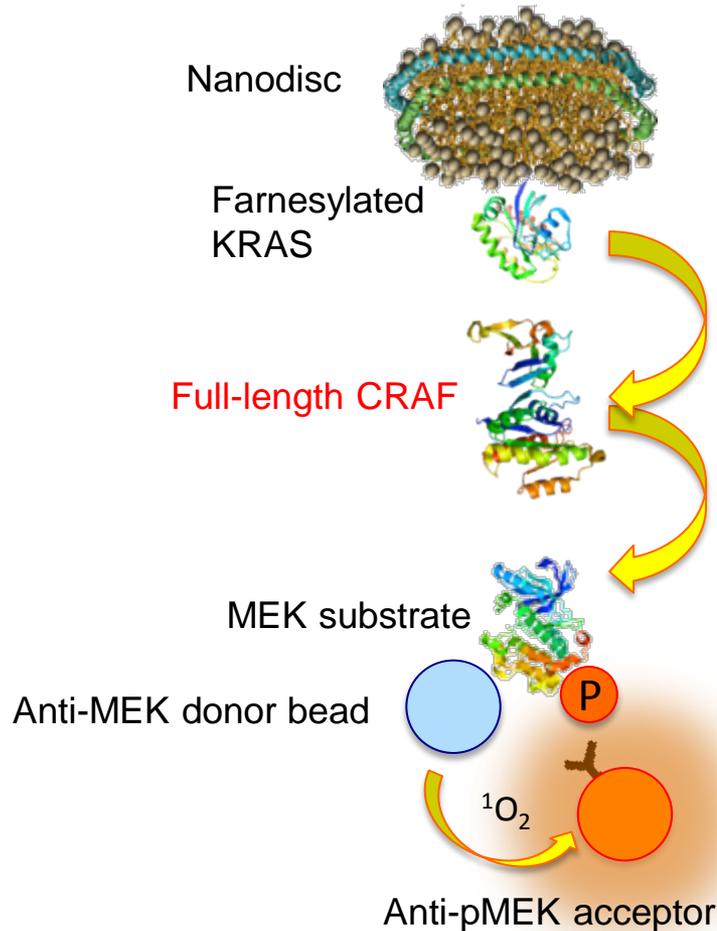
Ras dimerization/clustering

Resolution switching algorithm

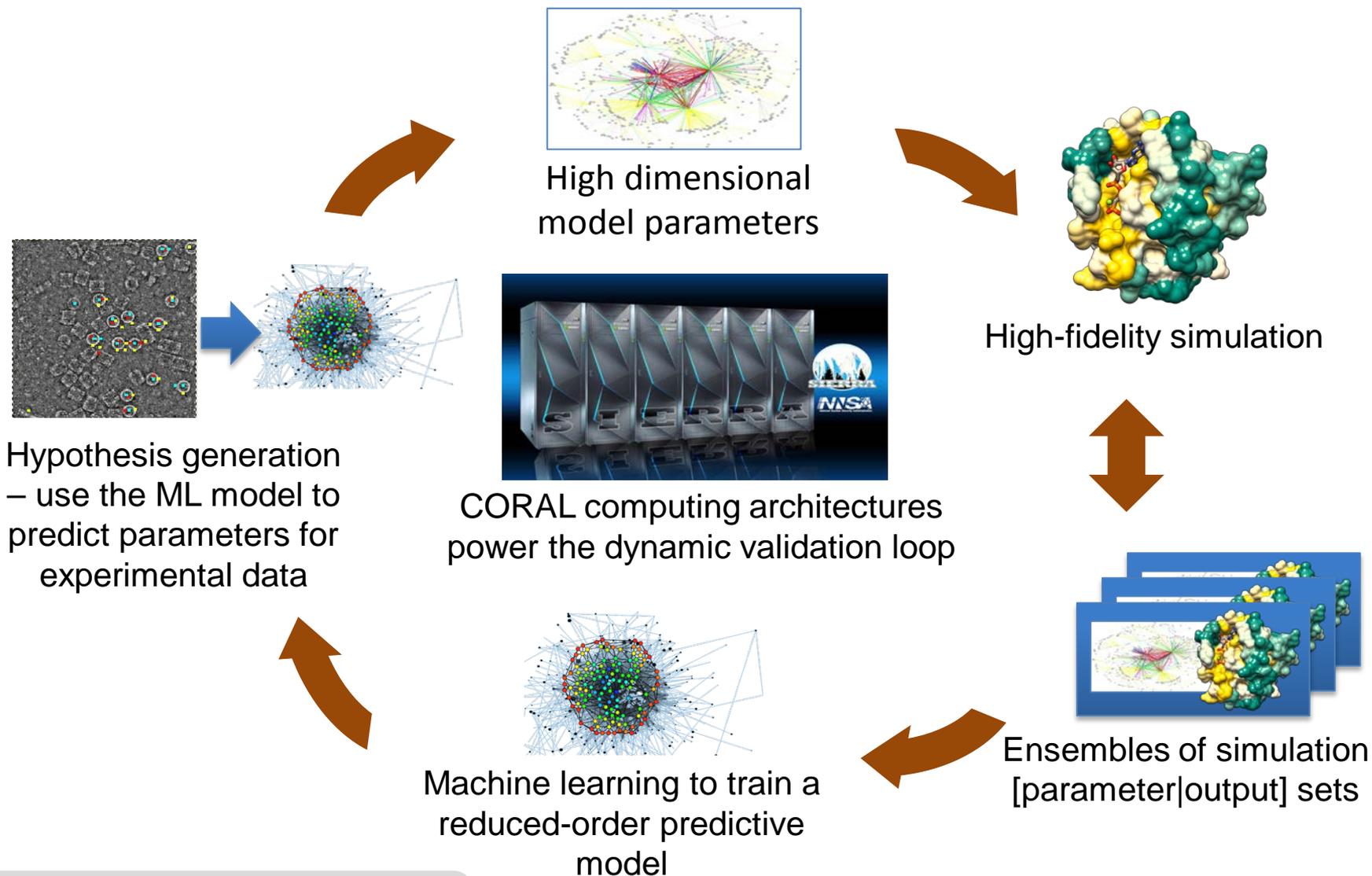
Ras-Raf binding/activation

Machine-learning algorithms to optimize resolution

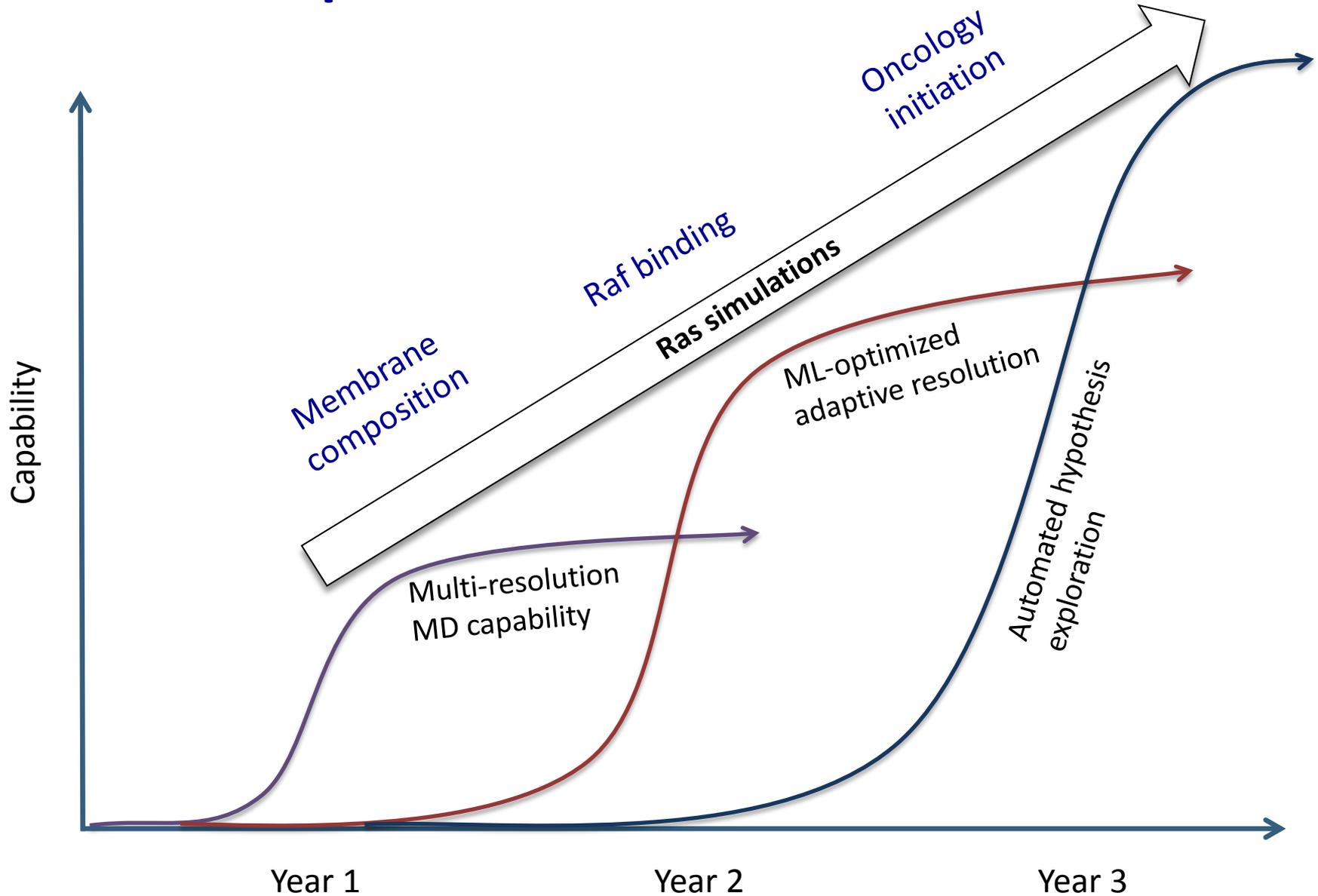
Activation of extended Ras complex



Aim 3: Automated hypothesis generation and dynamic validation



Build on computational advances



Current Status

- Focused team of NIH and DOE laboratory members have been meeting bi-weekly since March
 - 20+ scientists spanning skills from biology and oncology to computer science and physics
 - More frequent discussions for subgroups: Algorithms, Workflow/Analysis, Molecular Simulation
- Created Confluence website, plan quarterly site visits
 - Establishing touch-points across organizations to ease data/information flow
- Defined Technical Goals and project approach
 - Established milestones and schedule
- Already working!
 - Beginning to explore test cases and evaluate strategies