

# MuMMI: Multiscale Machine-Learned Modeling Infrastructure

## AI-Driven Multiscale Investigation of RAS–RAF Activation Lifecycle (ADMIRRAL)

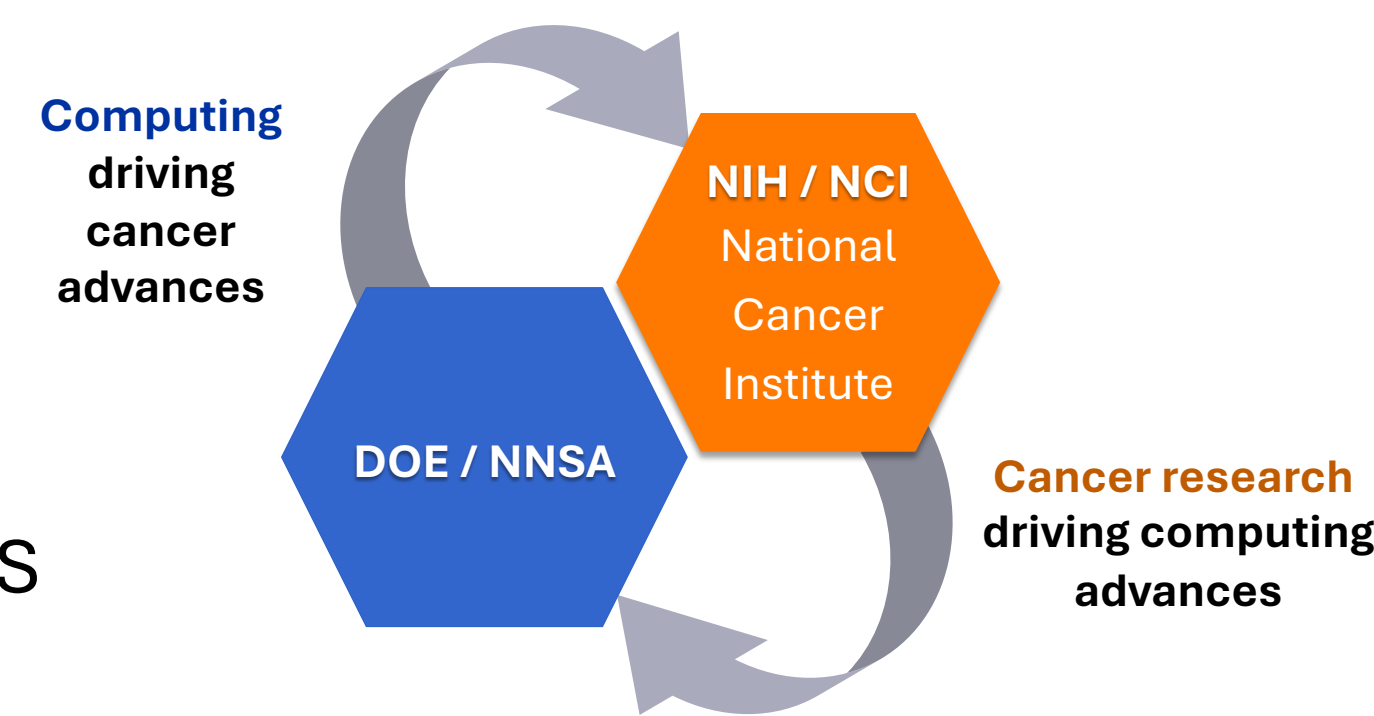
Loïc Pottier (LLNL/CASC) and H. I. Ingólfsson (LLNL/PLS)

Scientists rely on multiscale models to model biomolecular interactions involved in cancers. Multiscale simulations require massive amounts of computational power and a powerful workflow management system. We developed a software infrastructure called MuMMI that enables domain scientists to explore large-scale protein domain motion using HPC resources.

ADMIRRAL is a 4-year, \$13.25M project, funded by DOE/NNSA and NIH/NCI.

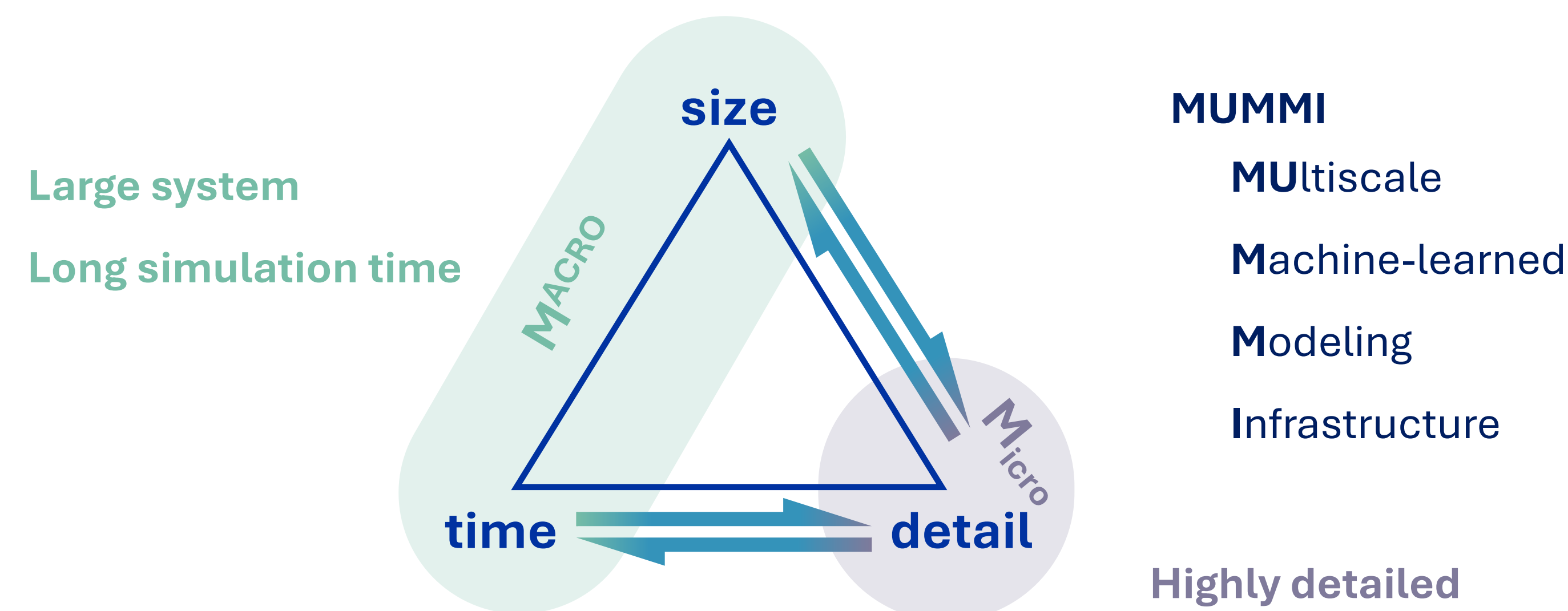
### NCI–DOE Collaboration to Bolster Cancer Research

- **ADMIRRAL:** AI-Driven Multiscale Investigation of RAS-RAF Activation Lifecycle
- 20+ team members, wide range of expertise from computer science to oncology
- **Pilot 2:** First iteration of the project, RAS Biology on Membranes
- Pilot projects initiated as part of the White House initiative *Cancer Moonshot*



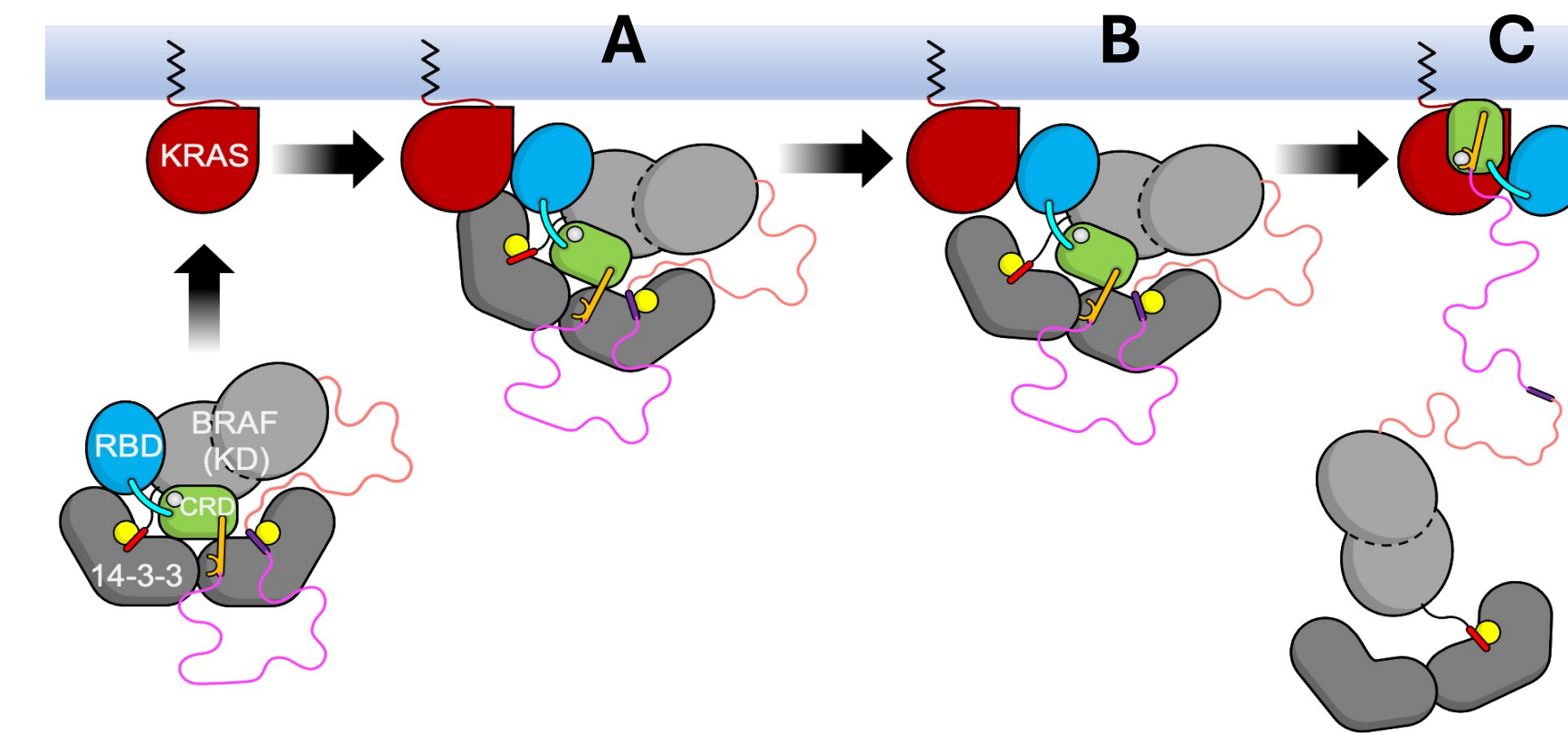
### Bridging the Gap Between Scales

Can you have your cake and eat it, too?



### Understanding RAS–RAF Activation

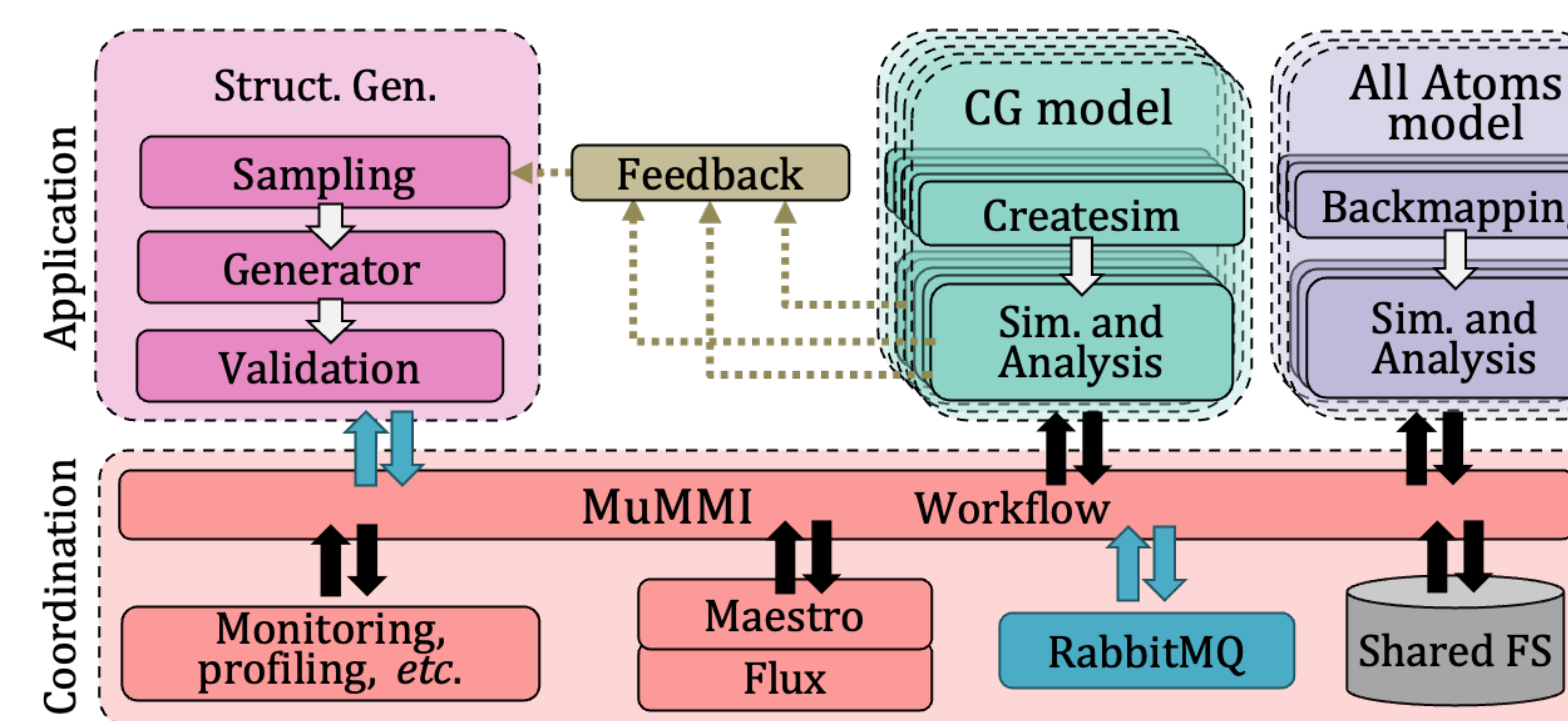
- RAS–RAF–MEK is the cell's main growth signaling pathway
- RAS proteins are involved in ~30% of cancer



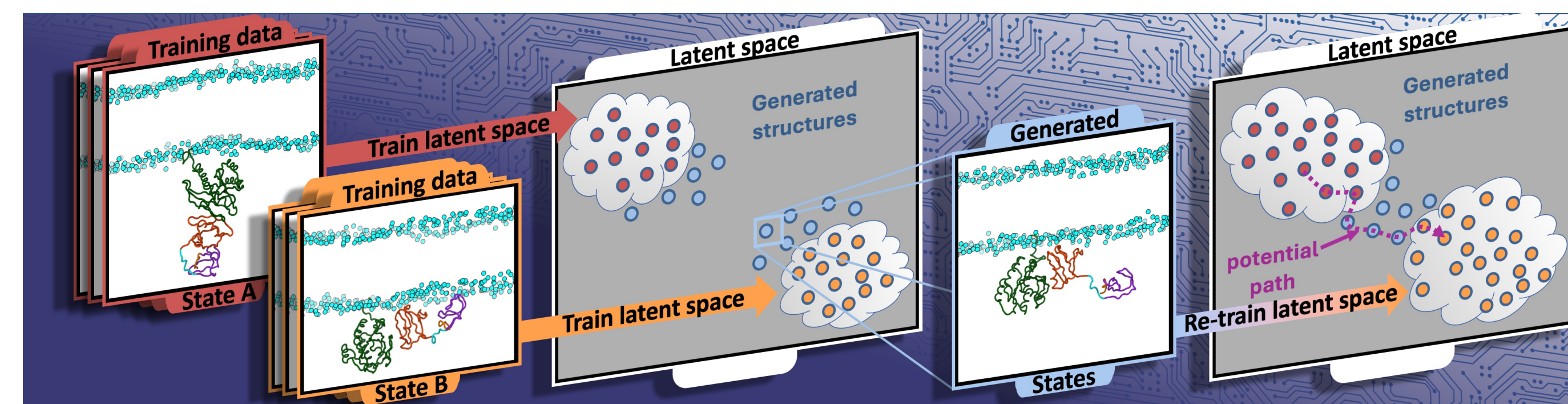
The goal of ADMIRRAL is to understand the RAS–RAF activation mechanisms. Here we depict three states of RAS–RAF interactions A, B, and C. We aim to find paths of valid conformational spaces going from A to C to better understand the underlying mechanisms of RAS–RAF activations.

### Automatic Framework for Coupling Scales

- Exploring all possible protein configurations to find paths from A to C would be intractable
- A workflow to orchestrate the sampling of a vast conformational space and launch only the most interesting simulations
- MuMMI leverages ML to better sample the space and bridge gap between scales



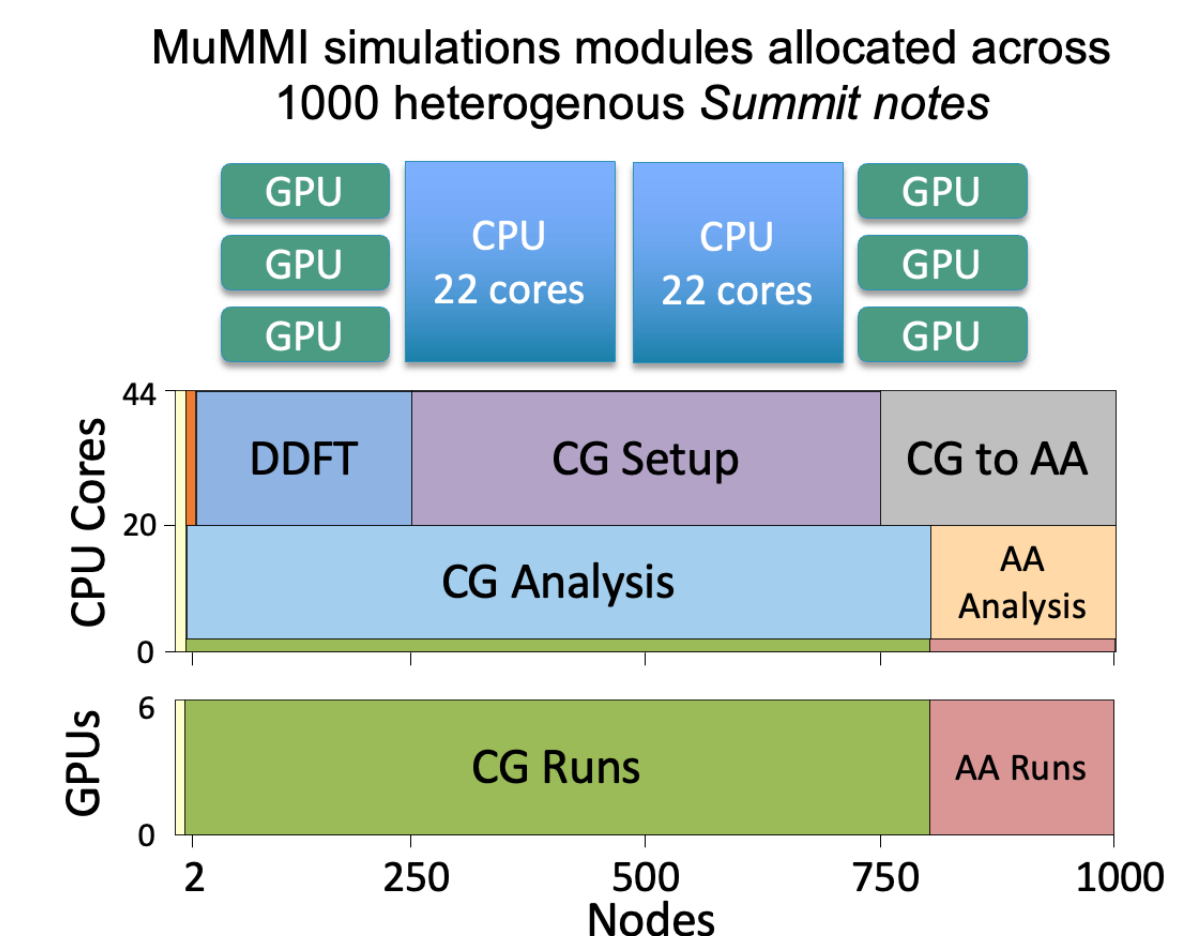
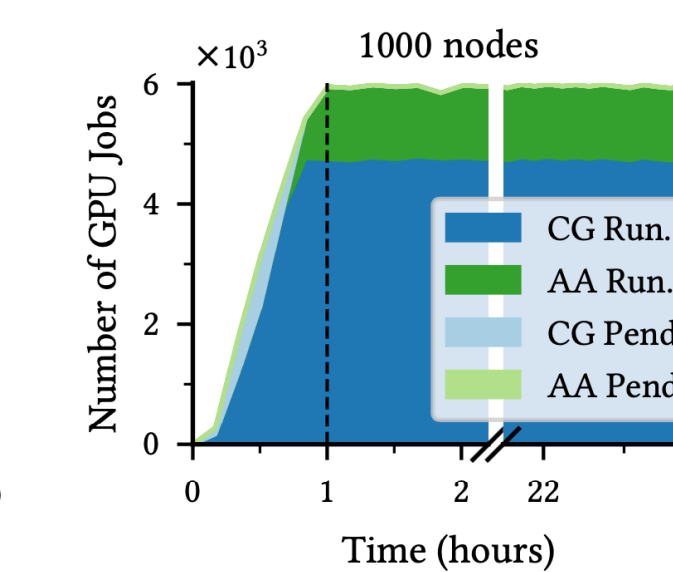
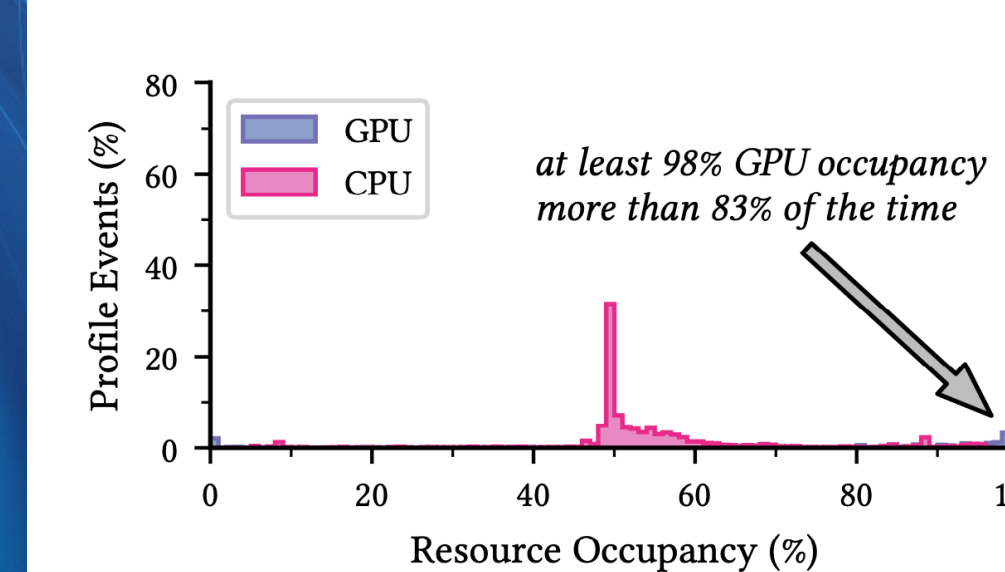
The MuMMI workflow: data flow from left to right. The workflow orchestrates the generation of interesting structures using ML, which are then turned into CG simulations. The most promising CG simulations are turned into AA simulations.



The MuMMI approach: by coupling scale we can quickly explore a vast space of solutions.

### Efficiently Utilizes Heterogenous Resources Across the Largest HPC

- Manage O(10–100k) MD simulations
- Scheduling done by **Flux**
- MuMMI is a thrust in LDRD FRACTALE (Flux)
- Co-scheduling at scale with in-situ analysis
- Large software stack (250+ packages) managed by **Spack**



MuMMI efficiently uses CPUs and GPUs on Summit (ORNL). MuMMI fully leverages heterogeneous nodes with GPUs. Thanks to Flux, MuMMI is also able to leverage Rabbit I/O nodes (El Capitan).

### Future Work

- MuMMI is fully automated but still requires expert users; further improvements will reduce human in the loop and allow for fully autonomous workflows
- Several LDRDs in PLS rely on MuMMI technology to study other proteins
- Extend MuMMI to other domains (e.g., material science)

### Conclusions

- MuMMI enables ML-driven ensemble-based coupled multiscale simulations
- Developed an award-winning (SC) workflow running multiscale MD simulations at unprecedented scales using state-of-the-art HPC machines at LLNL and ORNL (Sierra, El Capitan, Summit, Frontier)
- MuMMI allows scientists at NCI to explore new scenarios that can be then validated in a wet lab environment

### Collaborators



Accelerating cancer research using ML-driven workflows and HPC resources