MAR. 10TH, 2022

arvind ramanathan RESEARCH LAB

Argonne NATIONAL LABORATORY

DDMD: AI-ACCELERATED ENHANCE SAMPLING FOR MOLECULAR DYNAMICS SIMULATIONS

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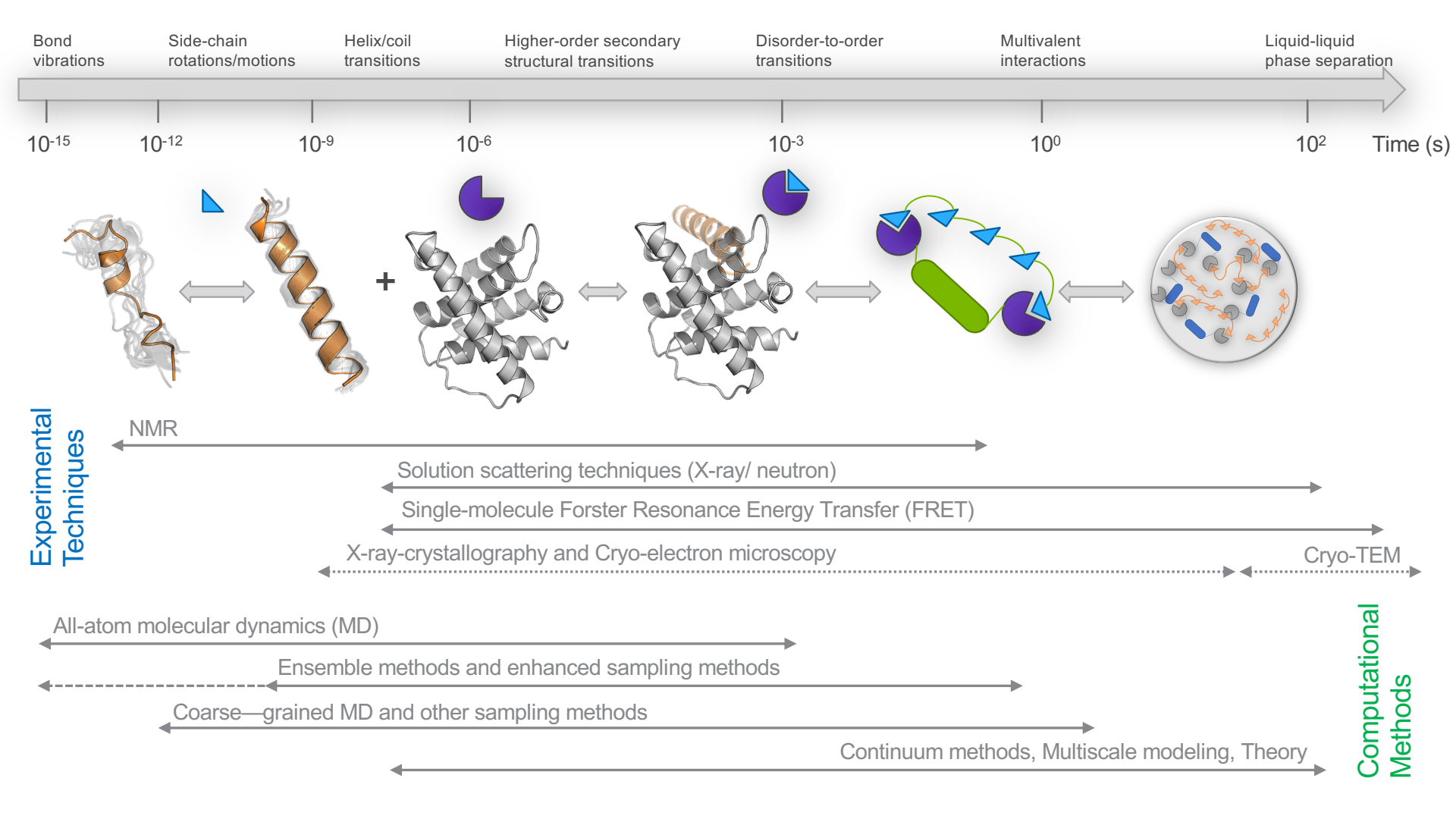
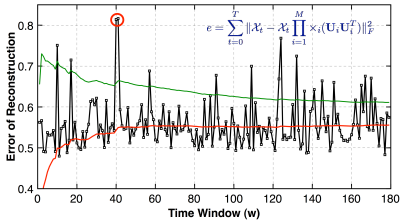
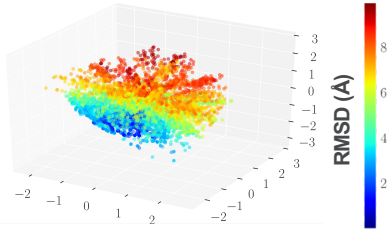

Bond vibrations
Side-chain rotations/motions
Helix/coil transitions
Higher-order secondary structural transitions
Disorder-to-order transitions
Multivalent interactions
Liquid-liquid phase separation
10-15
10-12
10-9
10-6
10-3
100
102
Time (s)
+
Experimental Techniques
NMR
Solution scattering techniques (X-ray/ neutron)
Single-molecule Forster Resonance Energy Transfer (FRET)
X-ray-crystallography and Cryo-electron microscopy
Cryo-TEM
All-atom molecular dynamics (MD)
Ensemble methods and enhanced sampling methods
Coarse—grained MD and other sampling methods
Continuum methods, Multiscale modeling, Theory
Computational Methods

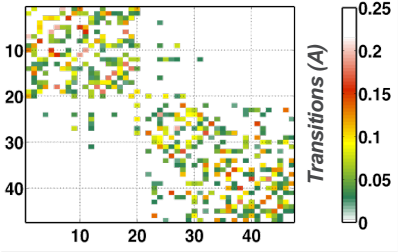
STATISTICAL INFERENCE: GLUE INFORMATION ACROSS SCALES



Event detection



Dimensionality reduction and clustering



Quantifying conformational transitions

ML and deep learning approaches

	Molecular & Macromolecular	Subcellular	Cellular
Spatial and Temporal Scales	Å	nm – μm	0.1mm - mm
	fs - μs	μs - ms	ms - s

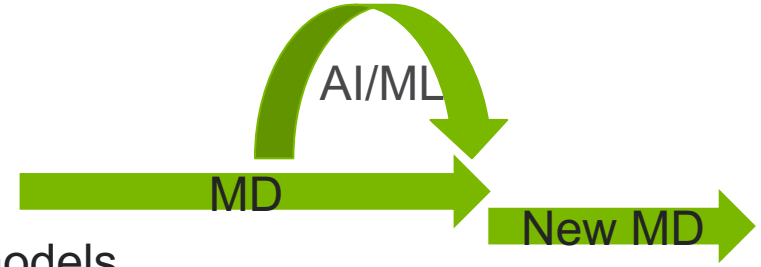
Standard simulations

Enhanced sampling workflows

AI/ML-driven workflows?

HOW CAN AI/ML HELP?

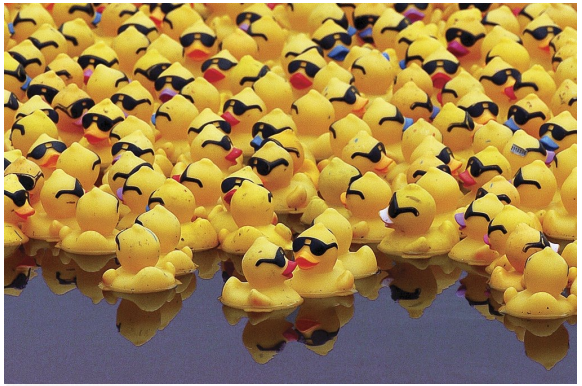
- Automatic AI/ML inferencing MD workflows
  - Learning the conformational states

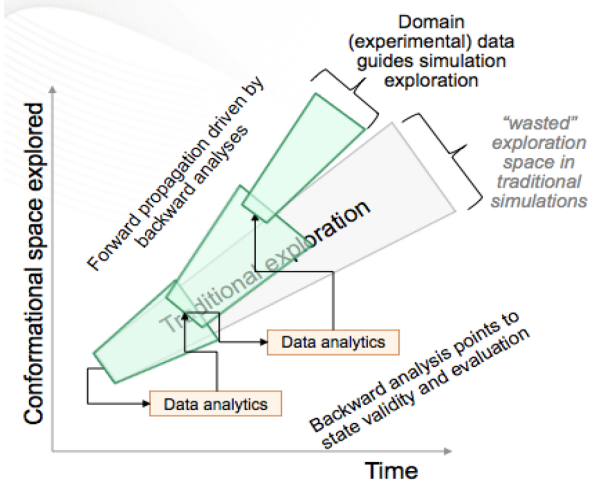


- AI/ML surrogate models
  - Learning the dynamics/propagation

ADAPTIVE SIMULATION: ON-THE-FLY ANALYSIS AND DECISION MAKING

- Generate ensemble of simulations in parallel as opposed to one realization of process
  - Strength in numbers
- Ensemble methods necessary, not sufficient!
  - Adaptive Ensembles: **Intermediate data, determines next stages**
- Adaptivity: How, What
  - Internal data: Simulation generated data used to determine “optimal” adaptation

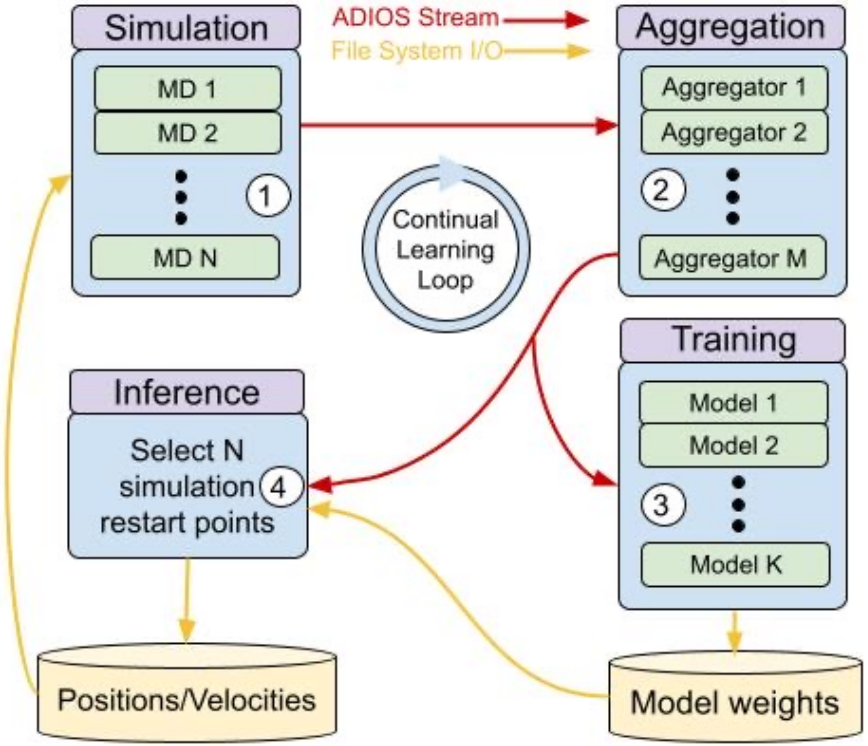




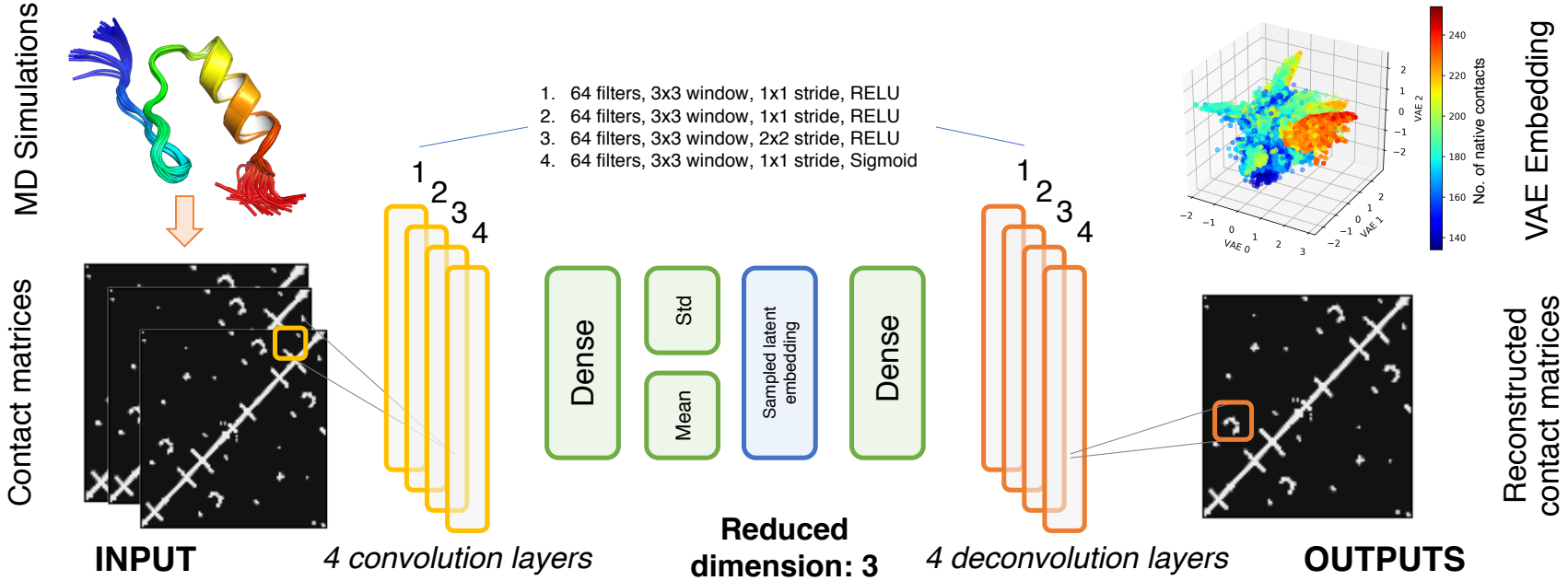
*Chodera, J.D., Noe, F., Curr. Opin. Struct. Biol. (2014)

DDMD - DeepDriveMD

- Simulation – Molecular Dynamics
  - OpenMM/NAMD on GPUs
  - Implicit/explicit solvent
- Aggregation
  - Adios Stream
- Training
  - Convolutional Variational AE
  - Keras/TensorFlow
- Inference
  - Outlier detection, sklearn
  - MDAnalysis



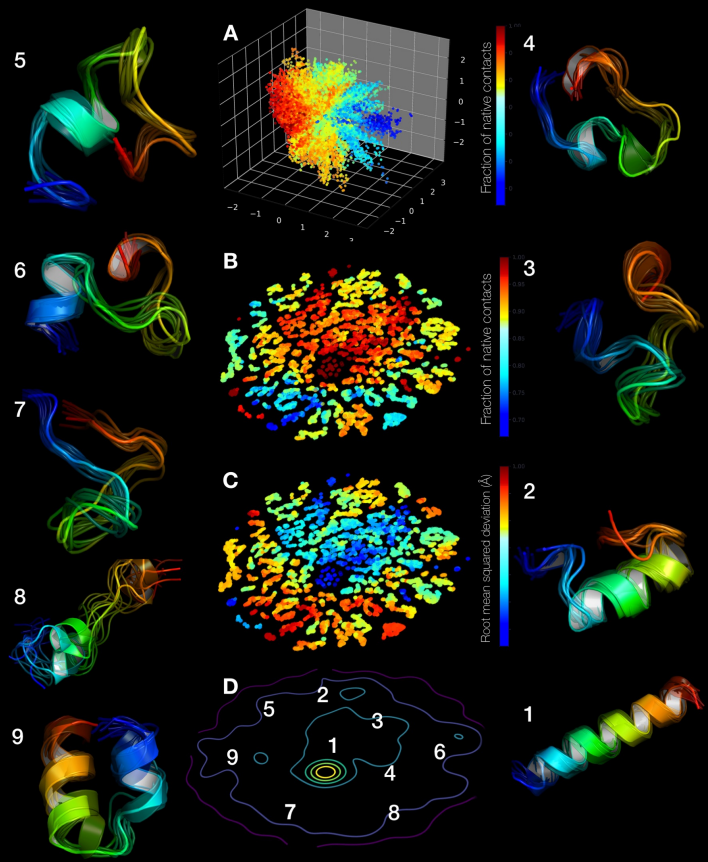
A VARIATIONAL APPROACH TO ENCODE PROTEIN FOLDING WITH CONVOLUTIONAL AUTO-ENCODERS



Related work:
Hernandez 17 arXiv,
Doerr 17 arXiv

DEEP CLUSTERING OF PROTEIN FOLDING SIMULATIONS

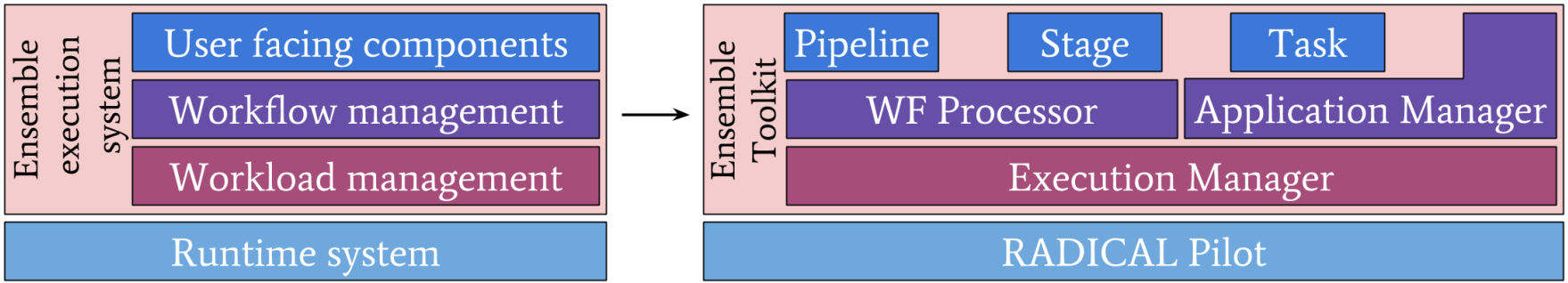
- Convolutional Variational Auto Encoders (CVAE)
  - Low dimensional representations of states from simulation trajectories.
  - CVAE can transfer learned features to reveal novel states across simulations
- On folding trajectories:
  - identify intermediate states in an unsupervised manner
- Applied across multiple protein systems can provide a general way to extract reaction coordinates



Deep clustering of protein folding simulations
D Bhowmik, S Gao, MT Young, A Ramanathan - BMC bioinformatics, 2018
Source code: http://ramanathanlab.org

RUN ENV

Radical EnTK



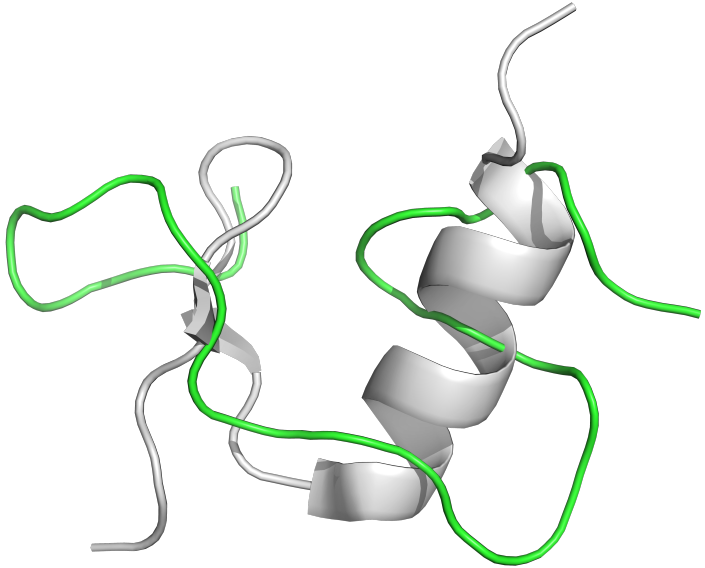
ADIOS 2 (Adaptable Input Output System)

- High performance I/O Framework
- Suitable for streaming workflow design
- Scalability

USER CASE 1: EXPLOITER

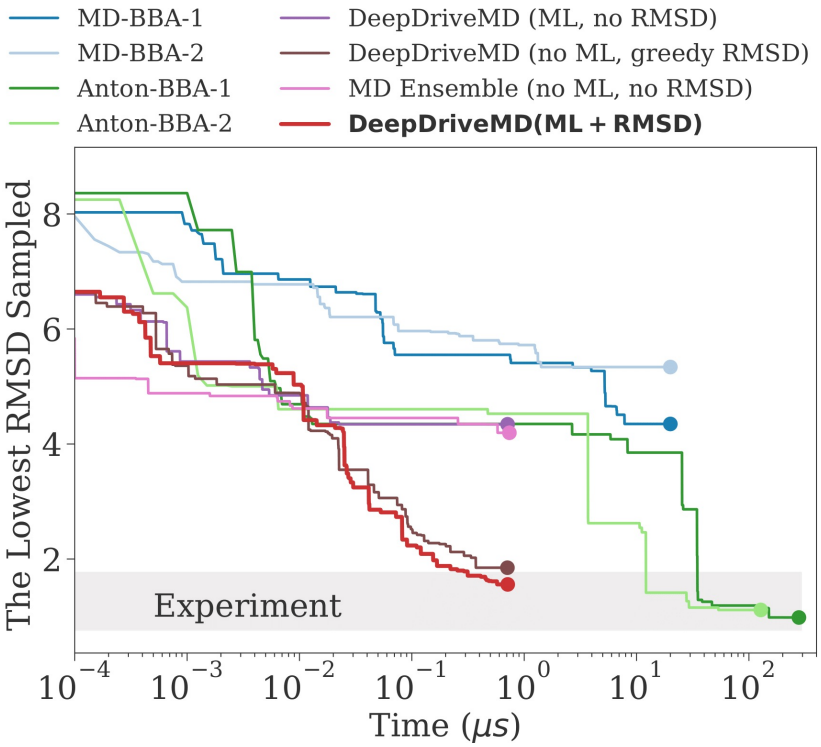
Protein Folding Pathway – BBA

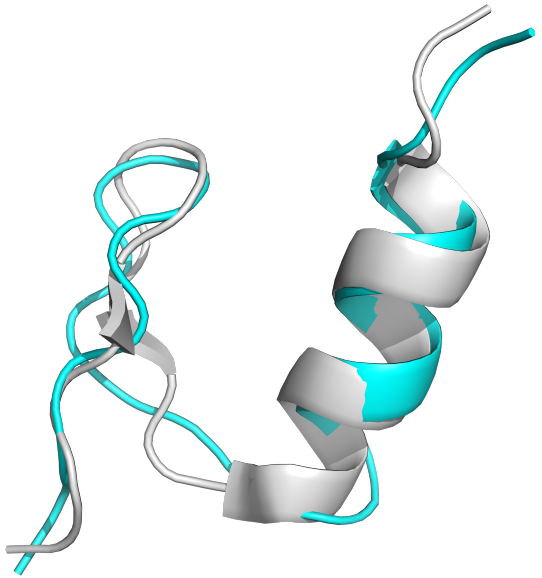
- OpenMM software package
- Amber99sb-ildn force field
- Amber99_obc implicit water model
- 300K Langevin integrator with 2 fs time-step
- 1.0 nm cut-off
- The same starting conf. as Anton runs
- 10-dimension latent space
- dbscan outlier search with RMSD rankings
- 120 simulation runs on CUDA
- 12-hr runs on Summit/Lassen



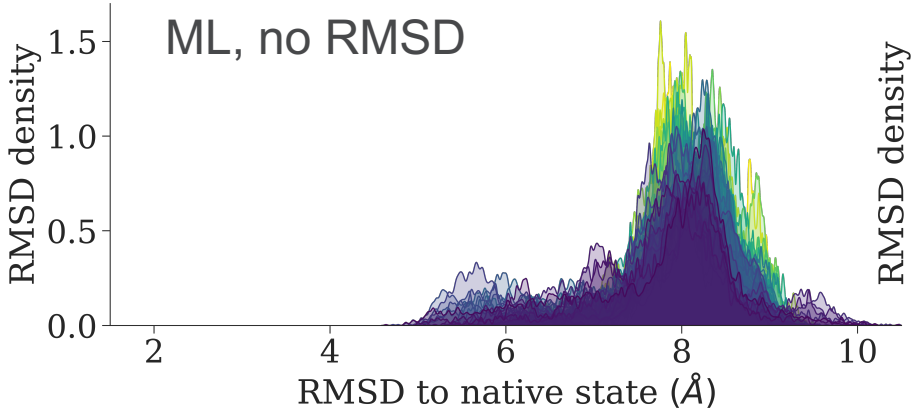
RESULTS - UC1

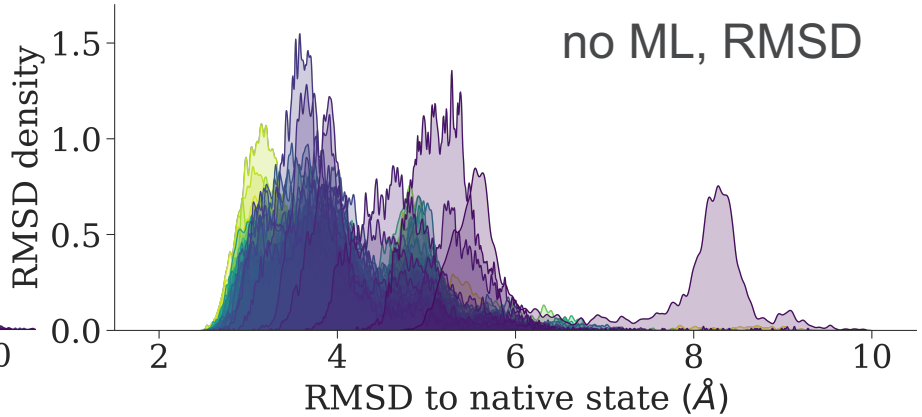
- Lowest RMSD: 1.56 Å

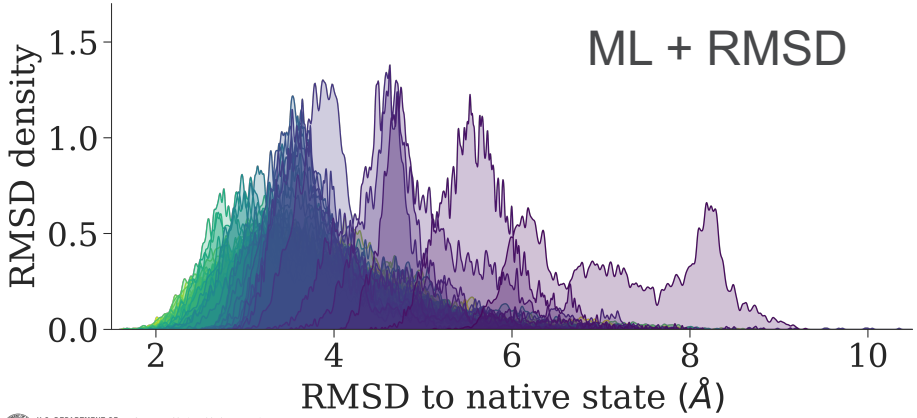




RESULTS - UC1





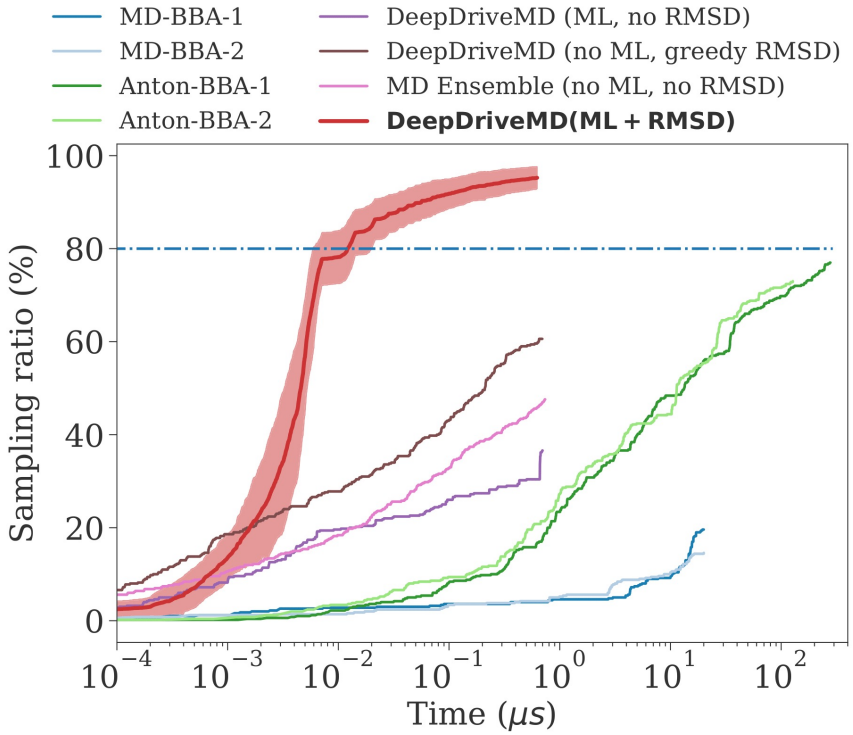


	RMSD only	RMSD + ML
mean	2.37 ± 0.30	1.81 ± 0.21
min	1.85	1.55
max	2.93	2.20

RESULTS - UC1

Sampling efficient
500 conformational states

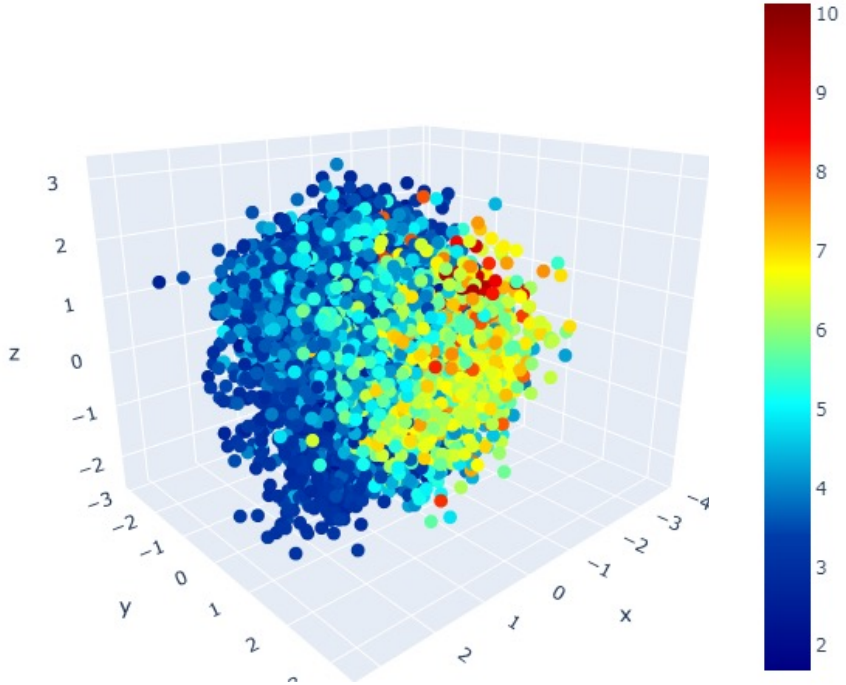
- DDMD (ML + RMSD) samples significantly more states
  - Faster sampling overall
- ML-only approach samples the near-by space, as there is no guide physical property
- MD is slow and steady with inferencing, and dependent on the simulation condition.



RESULTS - UC1

Embeddings:

- The first 3 of 10 latent dimensions
- Clustering of conformers correlating to their RMSD
- The embedding space retains the configurational information of 3D protein models
- Similar conformations are packed as close neighbors
- Outlier detection picks out rare sampled conformations

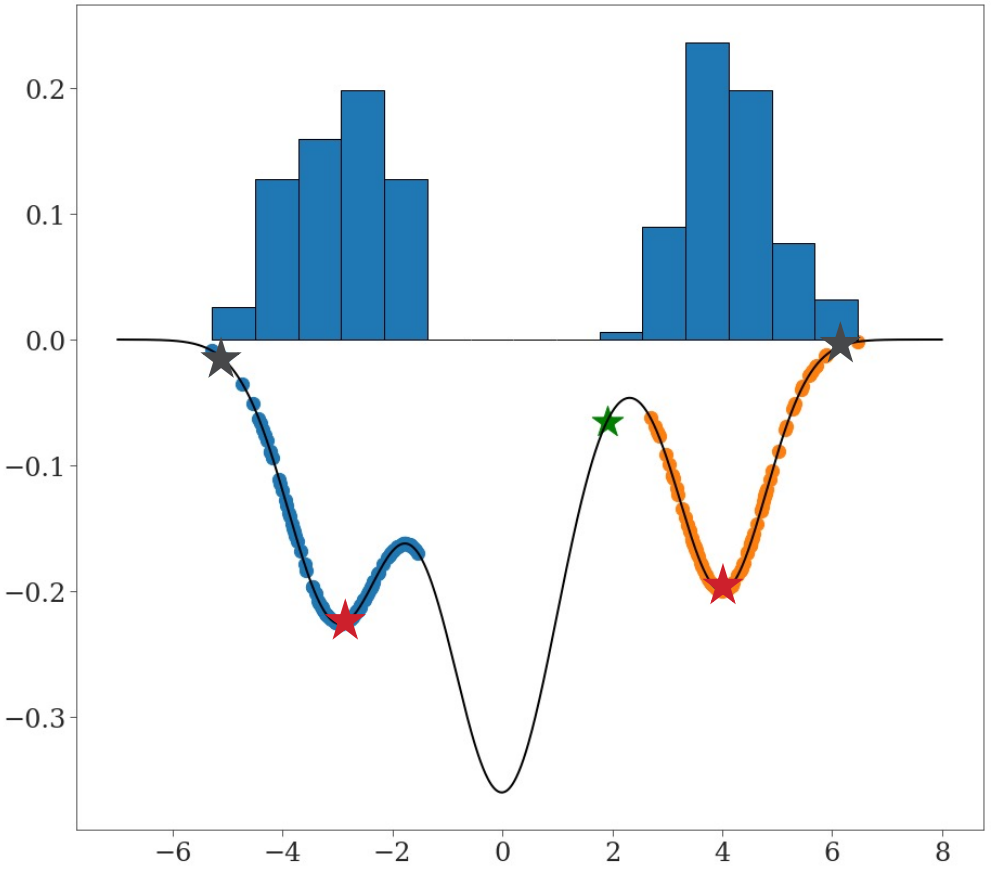


RESULTS - UC1

Why is it working?

- Restarting points
  - ML-only: black/green stars
  - greedy RMSD: red stars
  - ML+RMSD: green star
- Playout
  - ML-only: keep sampling low-sampled regions
  - greedy RMSD: might trapped in metastable/misfold
  - ML+RMSD: More prone to make good sampling decisions

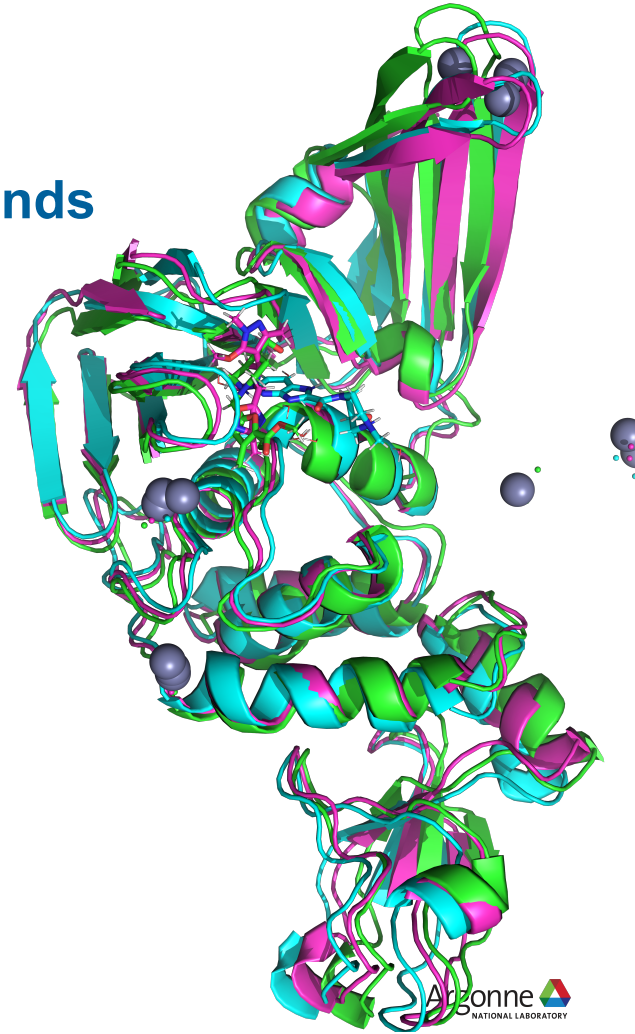
A pseudo 1D model



UC2

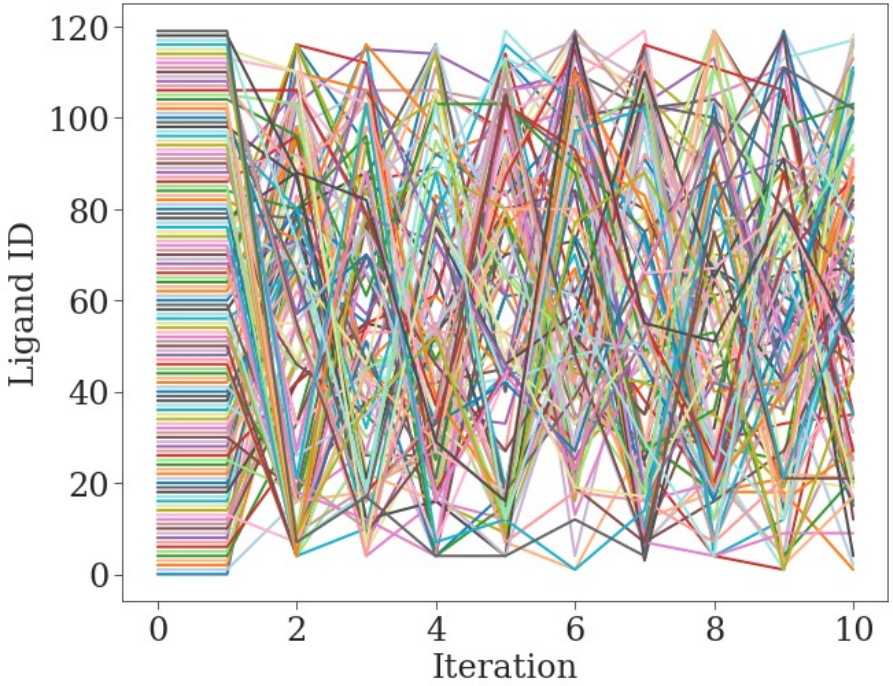
Explorer: 120 PLPro proteins with different ligands

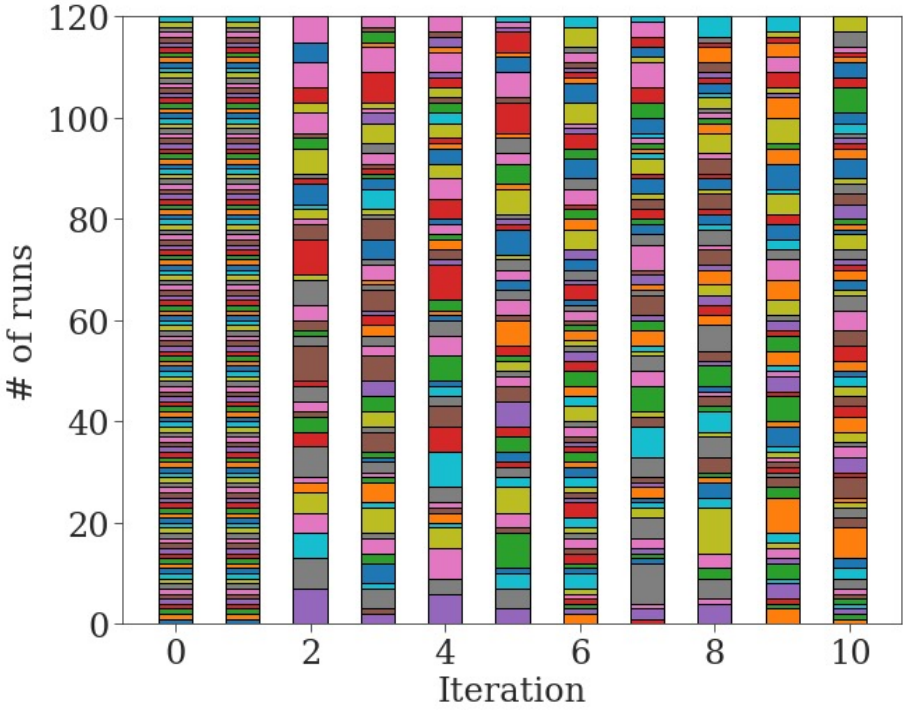
- OpenMM software package
- Amberff14sb force field with tip3p explicit water model
- 300K Langevin integrator with 2 fs time-step
- 1.0 nm cut-off
- 10-dimension latent space
- DBScan and LOF outlier search
- 120 simulation runs on CUDA platform
- 12-hr runs on Summit/Lassen



RESULTS - UC2

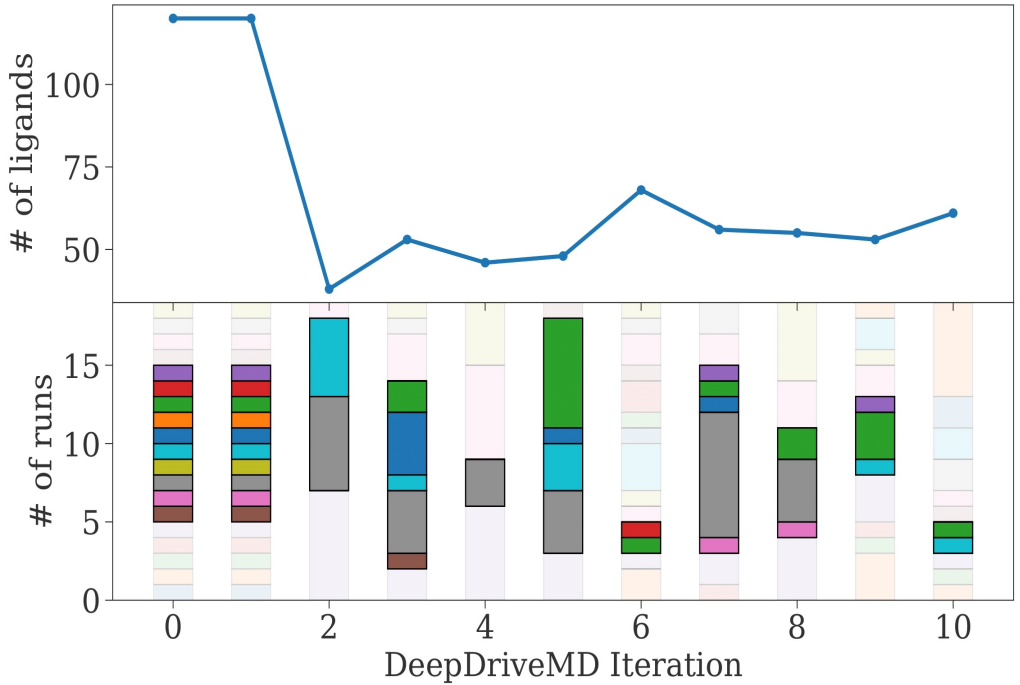
Sampling behavior





RESULTS - UC2

Sampling behavior



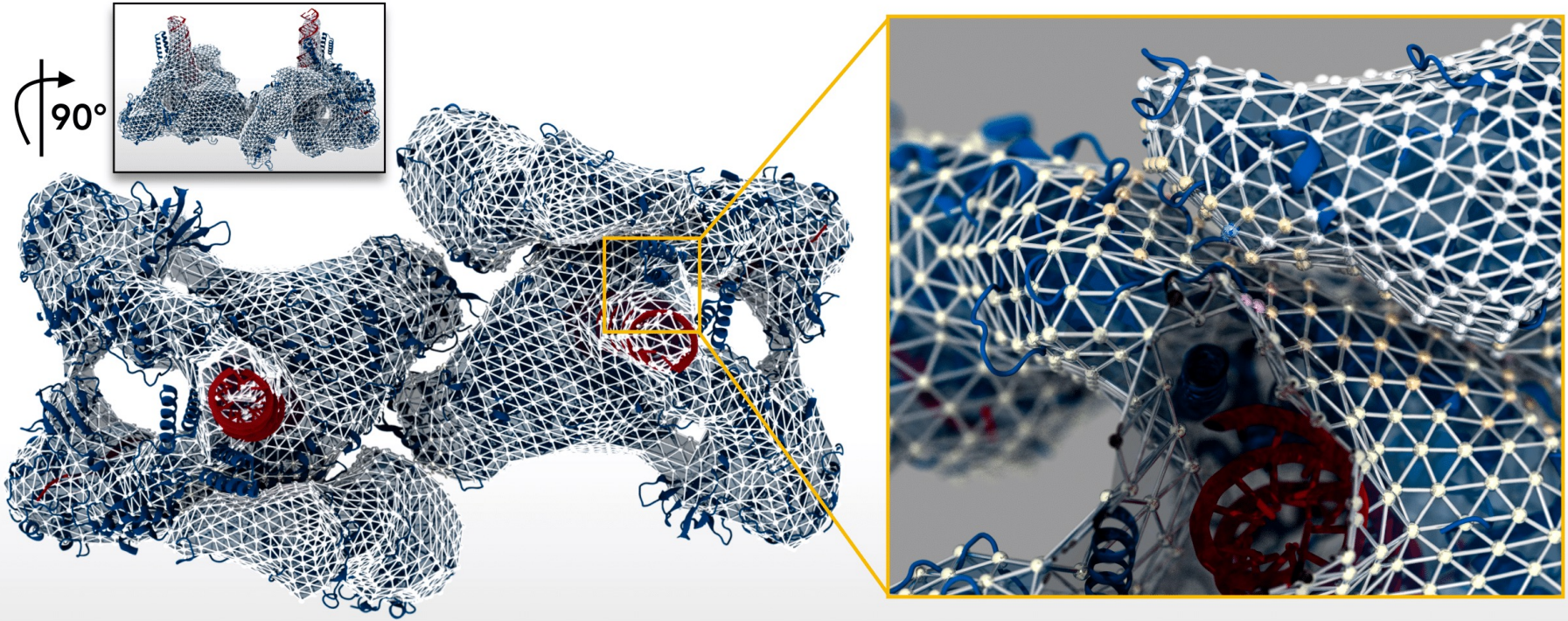
- DDMD automatically picks the ”interesting” conformer/ligand to simulation
- It reverts to previous ligands when the current runs are sufficiently modelled

UC3

Large multimer system

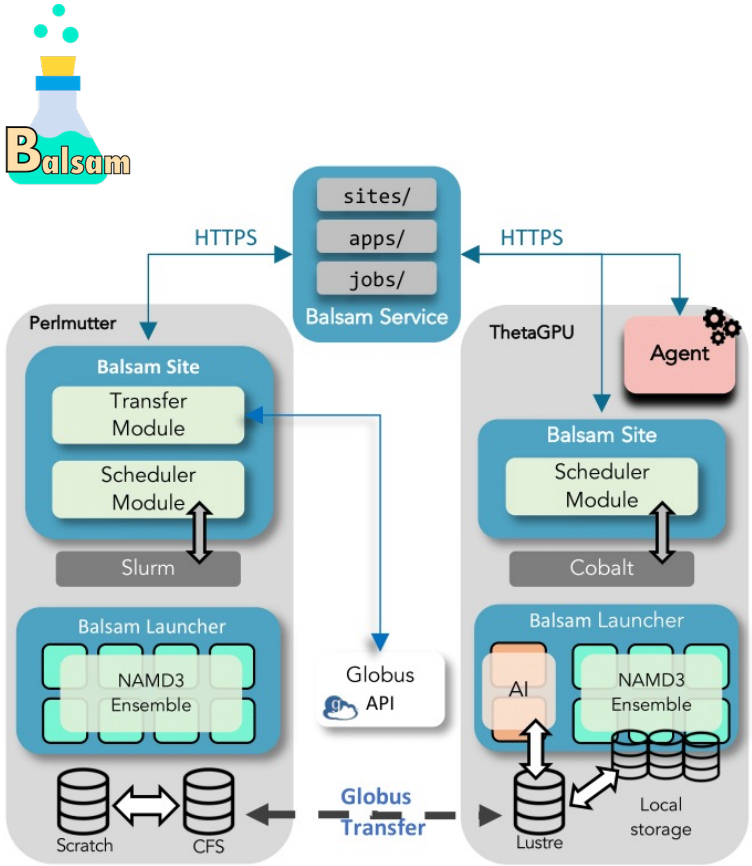
A. Trifan, …, A. Ramanatha, SC21, GB covid-19 finalist

- Covid-19 nsp RNA system (7egq), 6760 residues, 1.09M atoms



UC3
New env

- Balsam
  - Job launching on multiple HPC platfrom
  - From your own laptop
- Globus
  - Data transfer platform
- NAMD3
  - Parallel multiple-GPU MD engine
- (Fluctuating Finite Element Analysis) FFEA
  - Blob simulation
- (Graph Neural Operator) GNO
  - ML PDE solver learning MD/FFEA trajs

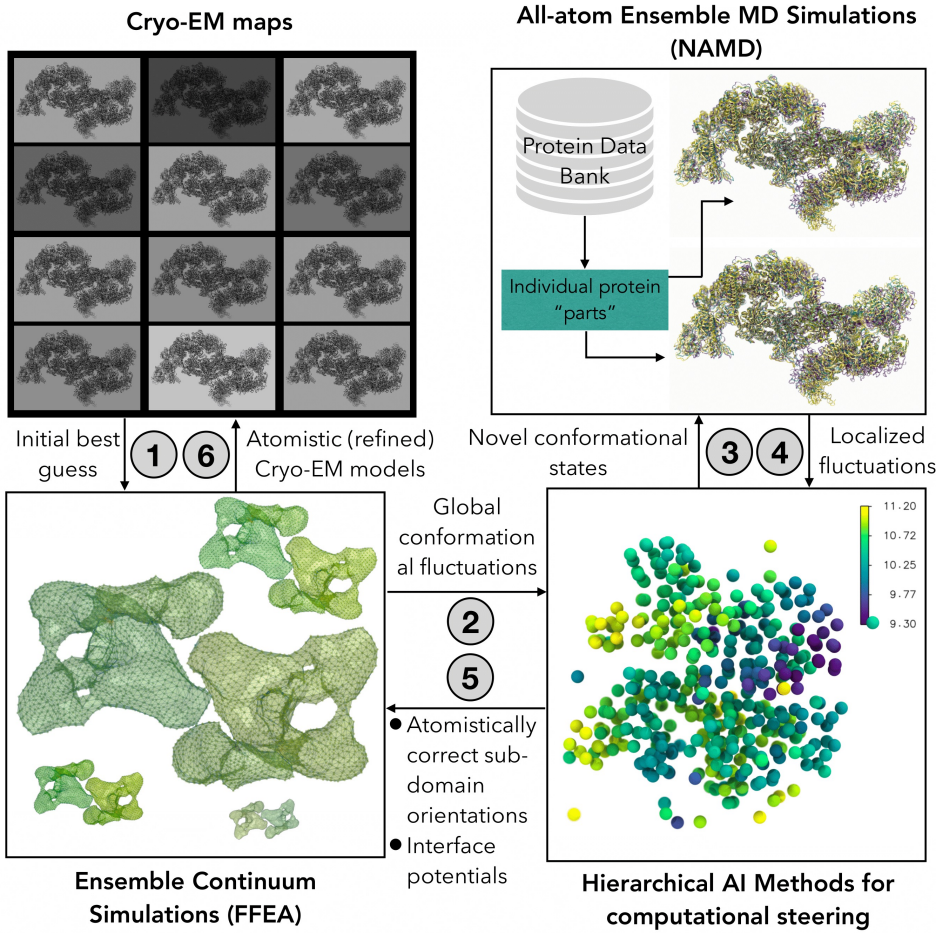


UC3

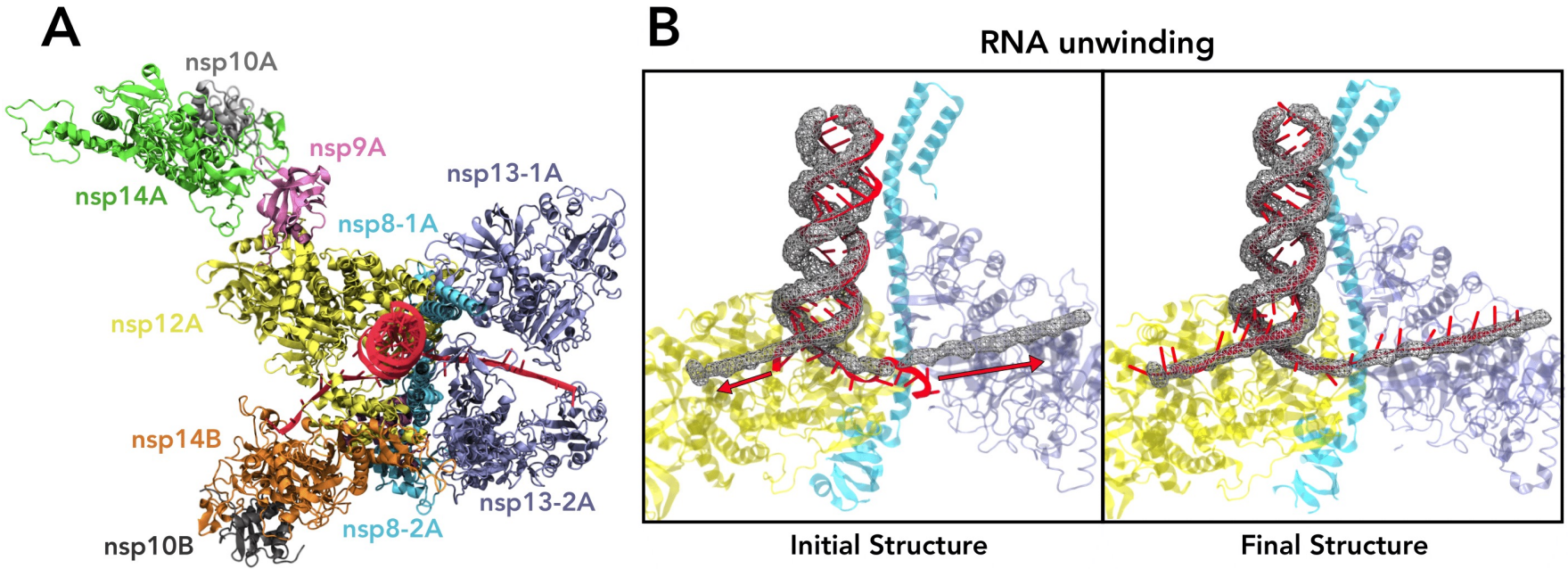
Multi-scale models

Making the tools do what they're good at

- FFEA
  - Directly from cryo-EM blobs
  - Global fluctuation info for ML
- All-atom MD
  - Local interactions info for ML
- Hierarchical AI models
  - Record the input info from simulations
  - Generate/identify novel states for MD simulations
  - Update FFEA interfacial interactions or blob rotation



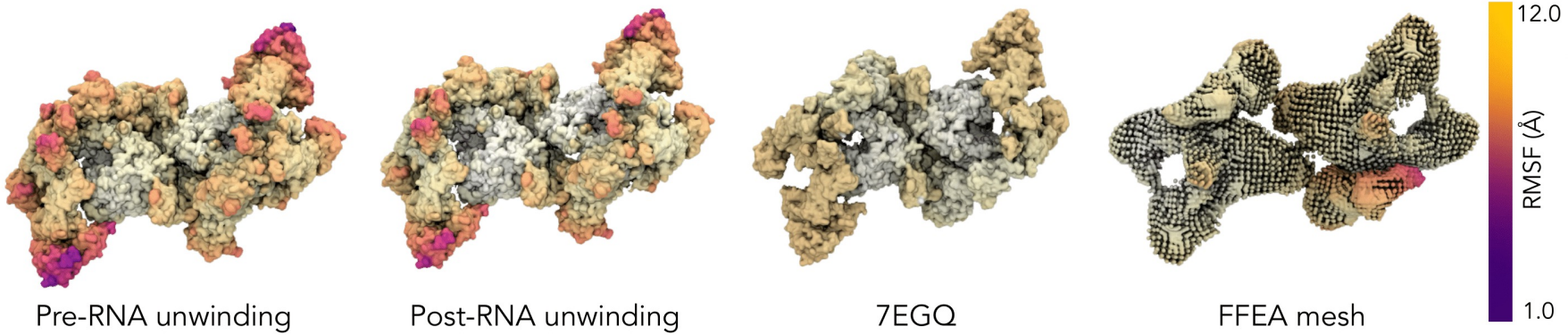
RESULTS - UC3 – MD



UC3

Molecular fluctuation of different approaches

This bar is wrong

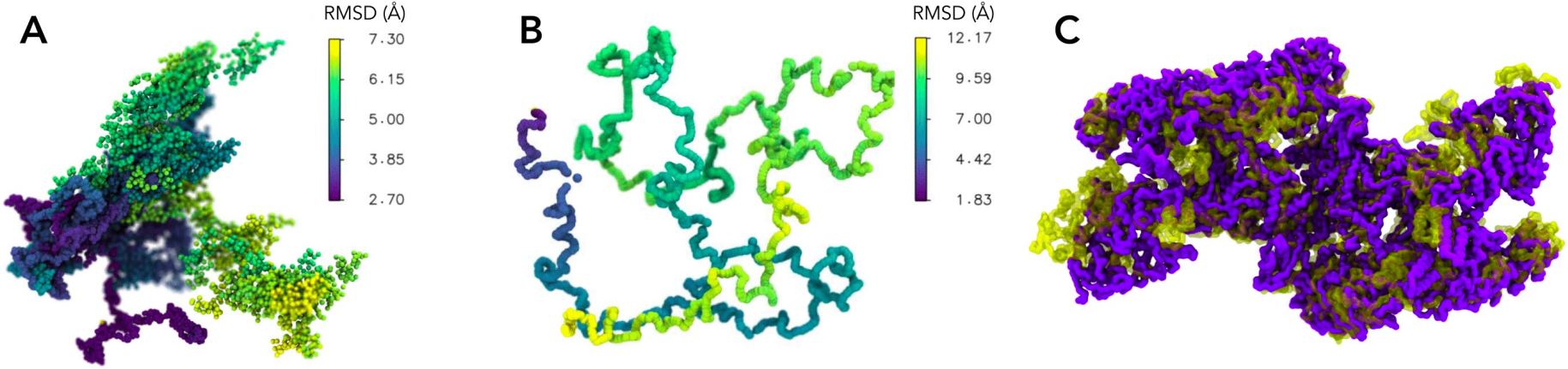


- The MD and FFEA results corresponds to the CryoEM results
- Fluctuations at the nsp13
- FFEA mesh interaction needs improvement, at the nsp10-nsp14 blob

Simulation	Non-equillibrium Sampling Methods	GFLOPs/step	Total sampling (μs)
Equilibration (pre-unwinding)	None	24.9	2.107
RNA unwinding	Extrabonds, Distance colvar, MDFF grid	25.9	0.004
RNA post-unwinding	Atom restraint, MDFF	11.04	1.904
RNA post-unwinding	None	11.04	3.916

UC3

MD surrogate models



- (A) FFEA latent embeddings separates various states
- (B) GNO perturbation in latent space from low-RMSD to high-RMSD
- (C) Overlay of high- and low- RMSD states from GNO

Z. Li, …, A. Anandkumar, arXiv:2003.03485v1

CONCLUSIONS AND FUTURE WORK

- DeepDriveMD utilizes AI/ML to pivot MD simulation runs to speed up BBA folding
- Modes: Exploiter, Explorer, …
- It is flexible to incorporate different frameworks and implement multiple sampling strategies.
  - Better ML models?

- It needs more validations to understand the underlying mechanism
- Possible MD surrogate models from AI/ML, GNO or other sequence models

ACKNOWLEDGEMENT

- The teams:
  - Arvind Ramanathan, Rick Stevens, Alex Brace (CELS, UChicago)
  - Ian Foster, Igor Yakushin (DSL)
  - Anda Trifan, Defne Ozgulbas, John Stone (UIUC)
  - Venkatram Vishwanath (ALCF)
  - Shantenu Jha (Rutgers/BNL)
  - Sarah Harris (Leeds), Geoffrey Wells (UCL)
  - Lillian Chong, Anthony Bogetti (UPitt)
  - Anima Anandkumar, Zongyi Li (Caltech)
  - And many more
- Computing support:
  - ALCF, OLCF, LLNL computing
  - XSEDE: TACC, NERSC, SDSC,
- Funding:
  - DOE NVBL, Exascale Computing Project
  - ANL LDRD

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THANK YOU

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