The Chicken-and-Egg Problem of Landmark-Driven Molecular Dynamics: Are Random Landmarks Useful?

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Metadynamics with PCV

Molecular dynamics of proteins can be guided to **explore wider range** of conformational space (folding paths in particular) with **biased potential** built on **path collective variables**.

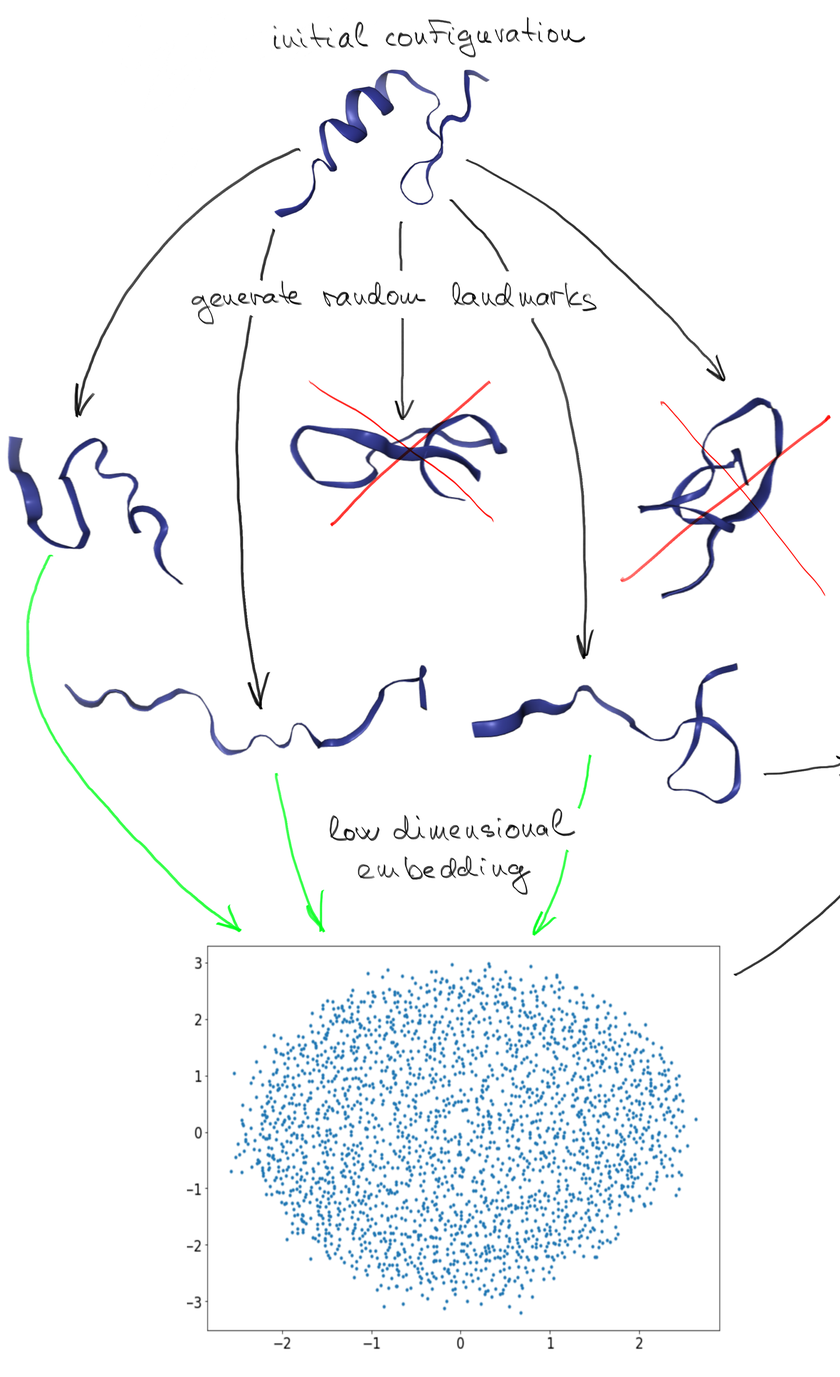
PCVs are derived from a **set of landmark structures** which approximate the desired trajectory [ ].

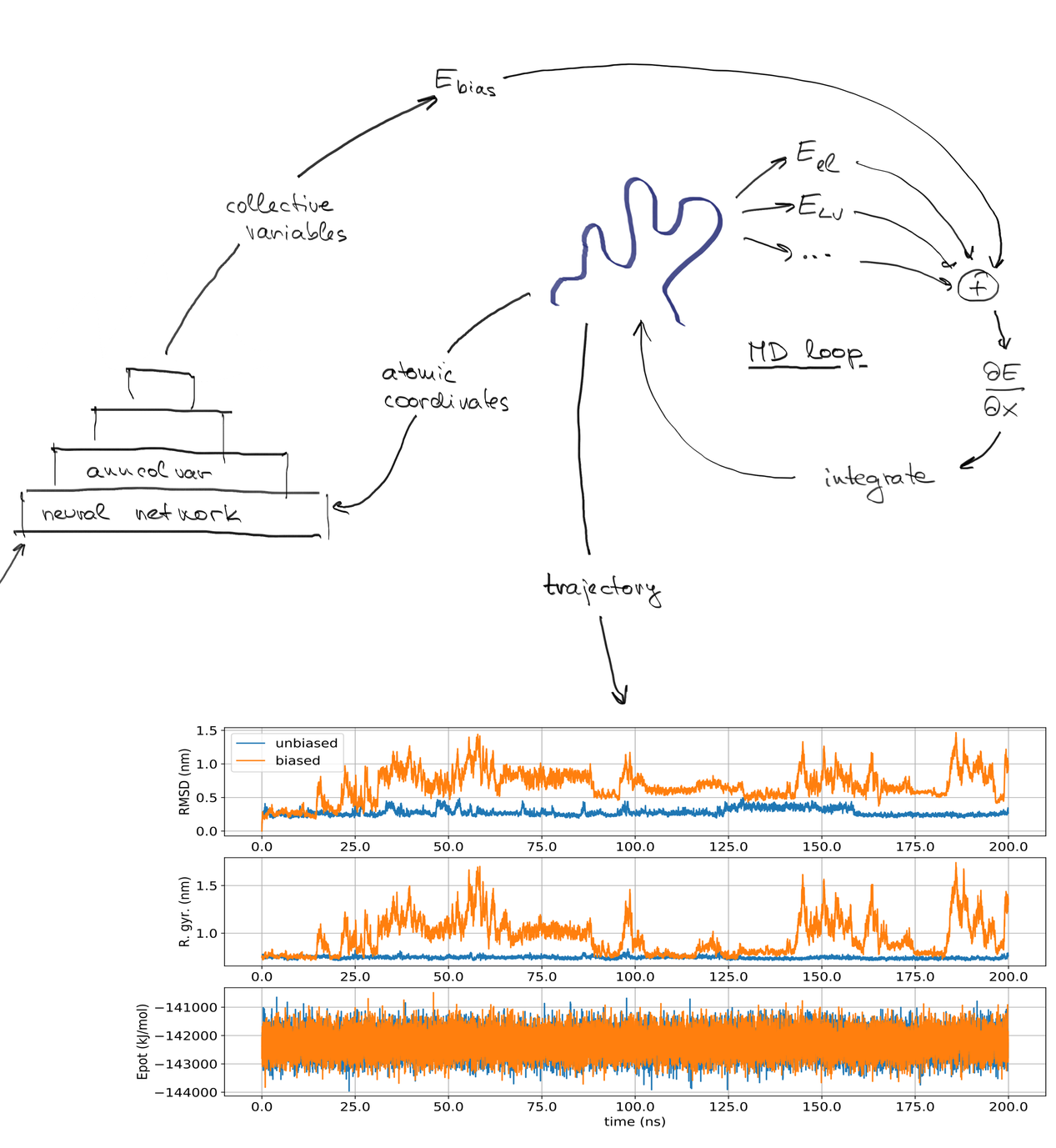
The technique can **reduce the time** of the MD simulation dramatically. On the other hand, the choice of landmarks is the core of the ***chicken and egg* problem** – if we know the landmarks along the trajectory, what would be the reason of recomputing the same trajectory?

Randomly Generated Landmarks

We aim at **computing the trajectories de novo**, without their prior knowledge. The essential steps are:

1. Generate a set of several hundreds to thousands of barely feasible landmarks by **random twisting of peptide bonds** in the subject protein
2. **Minimize by steepest descent** in vacuo, using simple force field (Amber99) to resolve unrealistic properties
3. Discard structures with **too high energy** or failed minimization
4. Compute low-dimensional embedding of 3N atomic coordinates to define **collective variables**
5. Train feed-forward **neural network** to estimate CVs from coordinates [ ]
6. Use the network outputs to **generate bias potential** in metadynamics simulation





Implementation

The whole workflow is implemented in Python as a **Jupyter notebook** using few standard biochemical packages.

The neural network training uses our **Anncolvar** package on top of Keras.

Core of the MD simulation is **Gromacs**.

Estimation of the CVs by neural network is done by our **optimized module in Plumed**.

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