A new frontier for modeFRONTIER: an orchestrator for molecular simulation symphony

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The successful application of high throughput molecular simulations to determine biochemical properties would be of great importance to the biomedical community if such simulations could be turned around in a clinically relevant timescale. An important example is the determination of inhibitor efficacy against varying tyrosine kinase proteins in cancer target therapy through calculation of drug-protein binding affinities.
Here, we describe the Binding Affinity Calculator (BAC), i.e., a modeFRONTIER-integrated molecular simulation tool for the automated calculation of protein-ligand binding affinities (Figure 1). The tool employs fully atomistic molecular simulations alongside the well-established Molecular Mechanics Poisson-Boltzmann Solvent Accessible Surface Area (MMPBSA) free energy methodology to enable the calculation of the binding free energy of several ligand-protein complexes, including several mutant kinase proteins known to be both the etiological agents of different cancer types and the eventual cause of ultimate drug resistance and pathological resurgence.
This enables the efficacy of these inhibitors to be ranked towards the original aberrant protein as well as across several mutant clinical isolates.
BAC is a tool that utilizes the power provided by modeFRONTIER to automate all of the stages required to compute free energies of binding: model preparation, equilibration, simulation, post-processing, and data-marshaling, fully exploiting all compute resources utilized. Such automation enables the molecular dynamics methodology to be used in a high throughput manner not achievable by manual methods. This paper describes the architecture and workflow management of BAC and the function of each of its components. Given adequate compute resources, BAC can yield quantitative information regarding drug activity and resistance at the molecular level in a timescale of direct clinical relevance, and can assist in decision support for the assessment of patient-specific optimal drug treatment and the subsequent response to therapy for any given genotype.

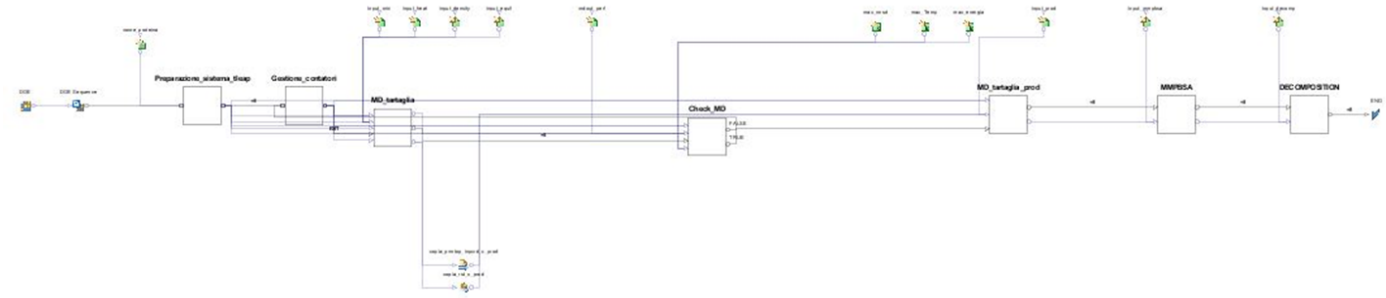

Figure 1. A prototypical example of a modeFRONTIER BAC workflow.

References

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