High-throughput Binding Affinity Calculations at Extreme Scales

In order to overcome the challenge of Resistance to chemotherapy and molecularly targeted therapies that are a major factor in limiting the effectiveness of cancer treatment that can be linked to genetic changes in target proteins, either pre-existing or evolutionarily selected during treatment, we should understand of the molecular determinants of drug binding. Using multi-stage pipelines of molecular simulations, we can gain insights into the binding free energy and the residence time of a ligand, which can inform both stratified and personal treatment regimens and drug development. The reading passage introduces a High-throughput Binding Affinity Calculator (HTBAC) in order to support the scalability, adaptability and automated calculation of the binding free energy on high-performance computing resources. HTBAC uses a building block approach in order to attain both workflow flexibility and performance.

The author demonstrates close to perfect weak scaling to hundreds of concurrent multi-stage binding affinity calculation pipelines. This permits a rapid time-to solution that is essentially invariant of the calculation protocol, size of candidate ligands, and the number of ensemble simulations. As such, HTBAC advances the state-of-the-art of binding affinity calculations and protocols. HTBAC provides the platform to enable scientists to study a wide range of cancer drugs and candidate ligands to support personalized clinical decision making based on genome sequencing and drug discovery. It is necessary to move beyond the prevailing paradigm of running individual MD simulations, which provide irreproducible results and cannot provide meaningful error bars. Further, the ability to flexibly scale and adapt ensemble-based protocols to the systems of interest is vital to produce reliable and accurate results on timescales which make it viable to influence real world decision making. To meet these goals, this research design and develop the high-throughput binding affinity calculator (HTBAC).

HTBAC employs the RADICAL-Cybertools to build ensemble-based applications for executing protocols like ESMACS at scale. The article implements the ESMACS protocol scales almost perfectly to hundreds of concurrent pipelines of binding affinity calculations on Blue Waters. This permits a time-to-solution that is essentially invariant of the size of candidate ligands, as well as the type and number of protocols concurrently employed.

The use of software implementing well-defined abstractions like that of “building blocks”, future proofs users of HTBAC to evolving hardware platforms, while providing immediate benefits of scale and support for a range of different application workflows. Thus, HTBAC represents an important advance towards the use of molecular dynamics based free energy calculations to the point where they can produce actionable results both in the clinic and industrial drug discovery.

In the short term, the development of HTBAC will allow a significant increase in the size of the study. Much of the literature on MD-based free energy calculations are limited to a few tens of systems, usually of similar drugs bound to the same protein target. By facilitating investigations of much larger datasets, HTBAC also provides ways of tackling grand challenges in drug design and precision medicine, where it is necessary to understand the influences on binding strength for hundreds or thousands of drug-protein variant combinations. In order to meet these ambitious

goals, we will be able to reveal the limits of existing simulation technology and the potentials used to approximate the chemistry of the real systems.