Alchemical and Endpoint Free Energy Calculations at Scale

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***Abstract*—**

I. Introduction

The efficacy of drug treatments depends on how tightly small molecules bind to their target proteins. Quantifying the strength of these interactions (the so called 'binding affinity') is a grand challenge of computational chemistry, the surmounting of which could revolutionize drug design and provide the platform for patient specific medicine. Recently, improvements in computational power and algorithm design mean that reliably quantifying binding affinities from molecular simulation is now becoming a genuine possibility. Exploiting these advances and further refining the technologies involved requires the marshaling of huge simulation campaigns, and impacting clinical or industrial decision making means that computations must be turned around in timescales of hours or days.

II. Scientific Motivation

III. Binding Affinity Calculation Protocols

A. Alchemical Protocol (TIES)

B. Endpoint Protocol (ESMACS)

IV. Computational Challenges

V. Solution

VI. Impact of Solution

VII. Analysis of Solution

VIII. Demonstration