How to balance computational accuracy and efficiency?

Balancing computational accuracy and efficiency in PBS involves considering various computational setups and parameters, such as MD sampling methods, time length, force fields, QM theories, and optimization approaches. Unlike traditional computational chemistry missions (e.g., thermochemistry predictions) with a well-established benchmark set, computational enzyme engineering deals with a moving target that hinges on experimental screening effort. The decision to adopt more sophisticated computational methods depends on whether they would improve the hit rate and function-enhancing speed compared to pure experimental screening. For example, in the *Ruegeria* sp. TM1040 amine transaminase-phenylethylamine system, 12 beneficial mutants were identified from experimentally screening 57 mutants in two rounds of site-saturation mutagenesis, leading to a screening hit rate of 21%.[76] With such a high hit rate from pure experimental screening, incorporating a higher level of QM theory, polarizable force field, and free energy perturbation for binding calculation into PBS will likely result in marginal to no improvement in hit rate but will undoubtedly require more computational time. For intrinsically difficult enzyme-engineering missions (i.e., having a low hit rate even though all mutations are screened or involving a complex mechanism), however, a combination of expensive molecular modeling methods can be critical to improve the number of hits from 0 to 1. The development of the critical assessment of computational enzyme-engineering tools will be necessary, considering the complexity of balancing computational accuracy and efficiency, and will be foundational for comparing computational enzyme-engineering approaches and achieving computational optimality.