LOCATING CARBON DIOXIDE BINDING SITES IN PROTEINS USING A PHARMACOPHORE-BASED APPROACH

M. L. Drummond,* A. K. Wilson and T. R. Cundari

Department of Chemistry and Center for Advanced Scientific Computing and Modeling (CASCaM), University of North Texas, 1155 Union Circle, #305070
Denton,TX 76203-5070, USA
**Email: Michael.Drummond@unt.edu*

One of the greatest challenges facing humanity in the early 21st Century is the rise in atmospheric concentrations of greenhouse gases – particularly carbon dioxide – and its effect on global climate. One promising line of inquiry is to search the biosphere for ways to remove CO_2 from the atmosphere, as both the most abundant (Rubisco) and one of the most efficient (carbonic anhydrase) enzymes utilize this gas as a reactant. However, despite the importance of protein-CO_2 interactions, little fundamental research has been performed to understand how Nature binds this molecule. To this end, we have extracted binding patterns from roughly 20 crystallographically characterized protein-CO_2 complexes using a methodology analogous to the pharmacophore framework used in the drug discovery arena. In particular, some specific three-dimensional arrangements of simple functional groups found in known CO_2 binding sites are also identified within the active sites of enzymes that do not yet have a crystallographically located CO_2. For example, the functional group arrangement that binds CO_2 in 1KEK, an oxidoreductase (Enzyme Class 1), is commonly found in the active sites of a test set of phosphoenolpyruvate carboxykinase enzymes (Enzyme Class 4). Additionally, some simple methods to screen predicted CO_2 binding sites for likely false hits are discussed, as are efforts to develop a true scoring function using a semiempirical approach, tight-binding Density Functional Theory. With this approach, putative CO_2 binding sites can be suggested based solely on structure, even for enzymes of unknown function, such as those often produced through structural genomics initiatives. The findings of this work have potential ramifications in diverse areas such as biomimicry, bioengineering, CO_2 sequestration, and protein evolution.

* Corresponding author.