

## Selectivity and Specificity Of Methionyl-tRNA Synthetase

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The *in vivo* incorporation of non-natural amino acids into proteins is controlled in large measure by the specificity of aminoacyl-tRNA synthetases (aaRS), the class of enzymes that safeguards the fidelity of amino acid incorporation into proteins. Search for amino acids analogs that bind to the active site becomes challenging where there is no crystallographic data on the amino acid binding site in the protein. In such a situation analogs are designed based on speculation and limited information gained from mutation analysis of the synthetase. Methionyl tRNA synthetase (MetRS) is such a system for which the crystal structure MetRS-methionine complex has only recently been published (Serre, Verdon et al. 2001).

We have used Heir-Dock protocol to 1) predict the binding region of L-met in MetRS, 2) to compare specificity of MetRS for methionine compared to other 19 natural amino acids, and 3) calculate the binding energies of L-met and various analogs of methionine to MetRS and compare the calculated binding energies with biochemical data. We have demonstrated that our predicted binding region for methionine in MetRS is highly specific for L-met from the pool of 20 natural amino acids. We find an excellent correlation between the calculated binding energies for L-met and its analogs and the experimental binding energies. Thus, we find that the computational methods described here are an excellent complement to experimental investigations of aaRS, or in general, for ligand design application for cases where the ligand binding site is unknown. This protocol is an exciting start for the development of a high throughput ligand screening. We have also identified a recognition site for methionine in MetRS, that undergoes conformational changes on methionine binding. We predict that this recognition site is specific for the recognition of methionine and its analogs.

