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Predicting interactions between small molecules and RNA

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Recently the interaction of small molecules with RNA structures has moved back into the focus of interest. The emergence of multi resistant bacterial strains, on the one hand and the question of the relevance of riboswitches and ribozymes and non coding RNA sequences in general, has renewed interest in understanding and predicting the interaction between RNA and small molecules.

Methods for receptor ligand docking and virtual screening are however still dominated by applications for protein-based receptors. In this contribution we discuss the particularities of RNA based systems and discuss our approach for developing a general method applicable to the different realms of chemistry in biologically relevant interactions.

We discuss a number of relevant points in this context and attempt to improve the situation by:

1) Compiling the largest currently relevant benchmark of RNA based receptors, including aptamers, riboswitches and ribosomes as receptors. Depending on the benchmark subset used, we obtain accuracies between 35 and 58% for structure prediction. As these numbers are based on relatively small sets it is both possible and more reasonable to perform a detailed analysis of the results in order to identify factors contributing to success or failure of the prediction. Thus for example, poor quality of experimental data, is certainly not the only reason, but often enough a significant factor contributing to poor results.

2) Removing redundancy from the data in the discussion of the methods' accuracy. A number of methods have been published with apparently good overall results, which however owe the apparent high accuracy to the misleading redundancy of particular types of ligands.

3) Assessment of the particular difficulties of using NMR structures for benchmarking

4) Taking particular chemistry of the receptors into account in devising measures of accuracy

5) Assessing the effect of necessary adaptations of the scoring function and the sampling protocol on general systems and protein ligands systems in particular.

Finally we discuss the relevance of our results for designing ligands and modulators of RNA structures. In particular we discuss the "dockability" of different antibiotic sites on the ribosome, and suggest schemes for improving specificity of designed ligands. If time permits we will discuss our current combined experimental/theoretical chemical biology approach for understanding the function of the ribosome.