We pursue a multi-dimensional approach towards deciphering and quantifying weak intermolecular interactions in chemical and biological systems. Experimental study in this research involves the investigation of protein-ligand interactions, synthetic host-guest complexation, and dynamic processes in designed unimolecular model systems, such as molecular torsional balances.

It is complemented by computational analysis and exhaustive data base mining in the Cambridge Crystallographic Database (CSD) and the Protein Data Bank (PDB). Examples of intermolecular interactions quantified by this approach are orthogonal dipolar interactions, organofluorine interactions, stacking on peptide bonds, and halogen bonding. We also investigate the energetics of the replacement of conserved water molecules in protein co-crystal structures by ligand parts. This multi-dimensional approach is illustrated in examples taken from a variety of structure-based drug design projects. Lessons learned are directly applicable to ligand design and optimization in drug discovery and crop protection research, but equally to the assembly of synthetic supramolecular systems.

Specific examples will include the replacement of water clusters in protein-ligand complexes of tRNA-guanine transglycosylase (TGT), a target against bacterial shigellosis dysenteriae. Ligand development against novel targets for antimalarials is illustrated by the inhibition of the enzyme IspD from the non-mevalonate pathway of isoprenoid biosynthesis, which is used by plasmodium and other parasites but not by humans, and of serine hydroxymethyl transferase (SHMT), a key enzyme from the folate cycle for which ligands had surprisingly not been reported previously.