COSMO-RS:
From quantum chemistry to cheminformatics

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The COSMO-RS method [1,2], an efficient combination of dielectric continuum quantum chemistry and statistical thermodynamics, and its program implementation COSMO*therm* meanwhile are widely accepted as a most fundamental and most predictive access to many fluid phase equilibrium properties as activity coefficients, partition coefficients and solubilities. This was further underlined by winning the First Industrial Fluid Phase Simulation Challenge organized by NIST in 2002.

While COSMO-RS initially was mainly used for chemical engineering thermodynamics, it has been extended to drug and agrochemical applications in the last years. A straight forward application area is the drug development process, where often solubilities of drugs in a variety of solvents, solvent mixtures, and even more complex phases are required. Since available substance amounts typically are small and measurements often are difficult and time consuming, a solvent screening with a predictive method as COSMO-RS is very useful to efficiently find good solvent candidates.

In the drug design area predictions for ADME properties like water solubility and physiological partitioning are routinely required. COSMO-RS can deliver reliable predictions of water solubility, blood-brain partitioning, and intestinal absorption, and other models are easy to develop. While in this area the existing more empirical and highly parameterized QSAR models often are much faster and approximately as accurate as COSMO-RS, the sound quantum chemical and thermodynamic fundament makes COSMO-RS more robust for extensions to novel chemical situations and it provides a more insight than empirical models, which can be helpful in resolving specific property problems.

A new program COSMO*frag* [4], a combination of COSMO*therm* with a huge database of about 40000 pre-calculated drug-like compounds, meanwhile allows for very fast, but slightly more approximate calculation of these ADME parameters and makes the COSMO-RS approach applicable to high-throughput projects.

Considering the fundamental importance of COSMO-RS σ-profiles for all kinds of physiological portioning and interactions, another straightforward extension of COSMO-RS is the use σ-profiles as basis for drug similarity searches. Based the fast COSMO*frag* tool, we now have a highly efficient drug similarity screening tool COSMO*sim* [5], which generates a lot of meaningful an promising similarity proposals for drugs, which often are not accessible with more conventional, structure based similarity tools.

Thus the suit of COSMO*therm*, COSMO*frag*, and COSMO*sim* now provides a bridge from quantum Chemistry to Cheminformatics.

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