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Computer Aided Solvent Selection and Design framework

Igor Mitrofanov[1], Elisa Conte[1], Jens Abildskov[1], Gürkan Sin[1], Rafiqul Gani[1]

[1] CAPEC, Department of Chemical and Biochemical Engineering, DTU. Søfoldt Plads DK-2800 Lyngby Denmark

Solvents are widely used as a reaction medium, as a reactant or as carrier at some stages of the manufacturing chain in products from the chemical, fine chemical, pharmaceutical, food, and agrochemical industries. Solvent are either required for processing after which they are removed or they are part of the final product formulation. Therefore, solvents are playing an important role in product synthesis and formulation, product delivery, separation processes etc [1]. On the other hand, solvent selection and design is a complex problem, which requires decision making in several levels for indentifying the best candidates depending on different multi-objective criteria namely environment, health, safety, process feasibility and economics.

One of the criteria of solvent selection is the environmental impact because of the excessive consumption and utilization in a wide range of industries, millions of tons solvents have to be wasted every year [2]. Therefore, it becomes important to minimize and optimize the use of organic solvents as much as possible, to satisfy the "Green Chemistry Principles" [3]. Another challenge is that currently solvent selection relies very much on previous experiences, trial and error with different solvent candidates. Such heuristic approach while valuable on their own, however arguably are not fit to deal with a complex multi-criteria optimization and search problem, which is the case for solvent selection.

Therefore the purpose of this contribution is to develop a systematic framework and implement it as software for selection and design of solvents for many applications including organic synthesis, complex reaction systems and solvent-based separations. The solvent selection framework is based on a combination of knowledge from industrial practice and computer-aided tools and methods for property prediction and computer-aided molecular design (CAMD) principles. This framework is applicable for solvent selection and design in product design as well as process design.

The first module of the framework is dedicated to the solvent selection and design for organic synthesis. This part uses the solvent selection methodology of Gani et al. [4,5], which has been extended to handle multi-step chemical syntheses as well as solvent substitution for specific reaction steps in existing processes. The methodology for organic synthesis accordingly involves five steps for each reaction:

1. Problem identification. Finding an objective for given system, identifying actual functions of the solvent.
2. Search criteria definition. The solvent functions that satisfy the operational needs of the process are defined in terms of a set of search criteria (R-indices), defined in terms of: physical and chemical properties (solvent-pure properties); Environment, Health and Safety (EHS) characteristic (solvent-EHS properties); operational properties (solvent–solute properties).
3. Performing the search. The search step consists of two stages. The first is a generation and property identification of solvent candidates using special software ProCAMD and ProPred, which are the implementations of computer-aided molecular techniques. The second consists of assigning the RS-indices following the reaction–solvent and then consulting the known solvent database and identifying the set of solvents that satisfy search criteria.

4. Score table assignment. A list of feasible solvents needs to be created. The scores are assigned from the calculated values of RS indices. The scores give a weight to each of the calculated RS indices.
5. Matrix of solvents. After the scores table has been generated, a short list of feasible solvents is obtained for each reaction step.

This methodology has been evaluated with several practical application examples including a single reaction solvent screening problem, a solvent replacement problem and a solvent selection for a multi-stage system.

The second module of the framework is dedicated to solvent selection for separation processes. One of the important tasks in separation processes is an identification of a pure solvent or anti-solvent for a specific Active Pharmaceutical Ingredient, which is a problem of major concern for the pharmaceutical R&D departments. Solvents, lipids and other compounds are commonly employed in product formulation as well as in APIs processing. In addition, the design of solvent mixtures that sometimes show improved characteristics of solubility toward a particular API could bring several advantages.

The framework includes a model-based method for solvent screening and solvent mixtures design for pharmaceutical applications. The problems that can be solved with this method are the following: given the API, select a good solvent or a good antisolvent; design a solvent mixture that improves the solubility if the solubility target cannot be reached with a single solvent; identify the optimal antisolvent that added in mall amount to the mixture API-solvent gives the highest precipitation of API (for crystallization processes).

The method is based on the theory of the conceptual segments (hydrophobic, polar and hydrophilic) introduced by Chau-Chyun and Song (2004) with the NRTL-SAC method [6]. In order to make the method completely independent from the availability of experimental data, a Marrero and Gani (2001) Group Contribution model (M&G GC$^+$) [7] for the prediction of the conceptual segments is developed in this work. With the above model, the API molecule can be described in terms of conceptual segments (first step of the method) and, then, the solvent power of the pure solvents can be computed and ranked from the best to the worst (anti-solvent). Hence, the design of a solvent mixture that enhances the API solubility can be performed by identifying the conceptual segments combination that maximizes the excess properties. An anti-solvent that mixed with the best solvent gives a large decrease in the API solubility can be identified in the same way as before, but this time excess properties of mixing have to be minimized.

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