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Computational Tool for the Prediction of Enantiomeric Solubility

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1 Abstract

Enantiomerically pure drugs are better than their racemate counterparts as they limit the side-effects caused by the medication. The mixtures from where these drugs are derived are complex, and require extensive experimentation to determine the solubility curves to crystallise enantio-pure products. Due to the private nature of pharmaceutical software, a free entry-level alternative needs to be offered. This research presents a developed software as a viable alternative, focused on enantiomeric solubility, that includes all the necessary functionality. A comparison based on reliability is performed on systems of mirroring and non-mirroring enantiomeric activity. Enantiomeric activity can be mirrored when using the activity coefficient NRTL model, but alternative models should be considered to reach better predictions. Parameterisation of interaction values of NRTL is investigated using an open source solver. The use of free solvers is approached but seen as less precise than proprietary choices.

2 Introduction

Stereoisomers have both the same molecular formula and connectivity but differ in their three-dimensional arrangement. Stereoisomers can be either diastereomers or enantiomers. Diastereomers have different arrangements of atoms that cannot be optically rearranged to form the counterpart. Enantiomers are mirrored non-superposable molecules that could be rearranged via a chiral shift to form the opposite (Figure 1A). The standard nomenclature is the Cahn–Ingold–Prelog (CIP) sequence rules, used to identify distinct enantiomers (Figure 1B). Enantiomeric molecules will share the same chemical and physical properties in solution which make them indistinguishable components. In biological systems the function of a protein is determined by its shape, and the shape of a protein can be defined by its amino acid components. 19 out of the 20 amino acids that naturally occur in nature are enantiomers, and only the S enantiomers are used for protein synthesis [1].

This chemical exclusivity extends to pharmaceuticals. Omeprazole (also known as Prilosec) has been used for years as a medication for gastrointestinal diseases. This drug is the crystal product of both enantiomers of omeprazole, commonly known as the racemate. In the treatment of gastrointestinal symptoms, only the S-enantiomer will have any medicinal properties. The R-enantiomer won't have the effect of its mirror molecule until it has produced a chiral shift in vivo. The more challenging example is that of salbutamol (also known as albuterol) which is an enantiomeric drug that is used to treat asthma. R-salbutamol causes the opening of airways in the lungs, but its mirror enantiomer produces a variety of unpleasant side-effects. This apparent limitation has pushed the industry to develop enantiopure drugs, or enantiomeric drugs of only one enantiomer. The benefits of these products in the private sector are undeniable. In the case of omeprazole, even though its pharmacological benefits are still debated, there is no doubt that it has been a financial success [2] [3].

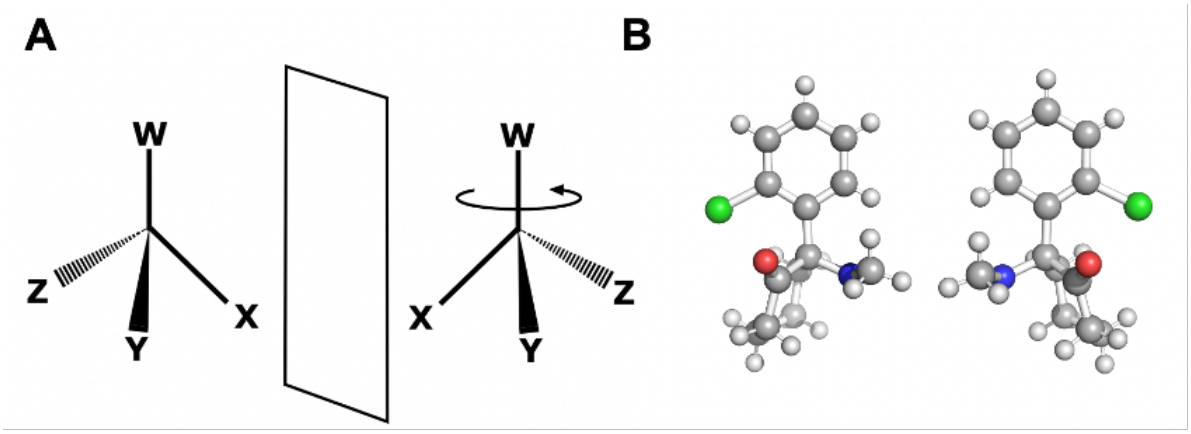

Figure 1: **A**: Enantiomers are non-superposable mirror images of each other. **B**: R-Ketamine (left) and S-Ketamine (right)

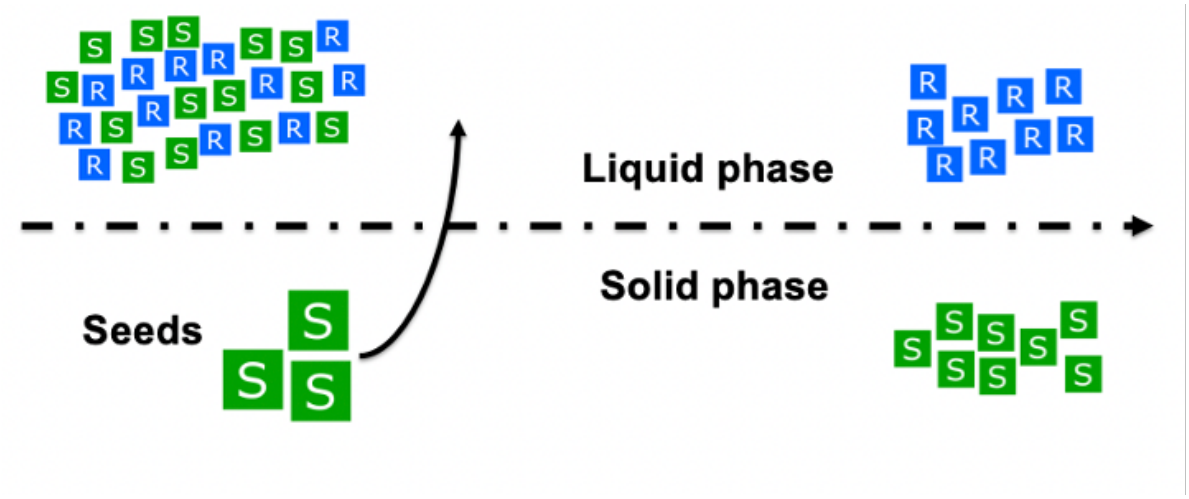

Figure 2: Direct crystallisation of one enantiomer.

The symmetrical properties of enantiomers in solution makes the separation of these components a challenge. To synthesize enantiopure medications, the product needs to be purely composed of the desired enantiomer crystal. In very few cases the process is very simple and chiral pooling, or a chiral catalyst can be used [4]. The most common procedure to separate enantiomeric molecules is to use the racemic method; in which you use chiral mobile phase additives to resolve a racemate into a pure enantiomer or you utilise a chiral derivatizing agent for enantioseparation. Either process is costly and time-consuming but have been consistently used in the pharmacological industry [5]. These methods have been successful in both small and batch processes but haven't been thoroughly researched in continuous processes.

There are some obvious economic benefits in transitioning to continuous methods. This lucrative opportunity interests pharmaceutical companies that want to maximise their production while keeping costs low. Therefore, one effective method is the direct crystallisation of one enantiomer in a racemic mixture (Figure 2) [6]. This process achieves enantiospecific crystallization by modulating the concentration of solutes. By saturating the solution of a mixture with one of the solutes, only the seeded component will crystallise, leaving only the opposite enantiomer in the solution. In a mixture of enantiomers, crystallisation can occur in two ways. In conglomerates, crystallisation occurs independently while racemic compounds produce a racemate crystal at certain compositions. 90% of enantiomeric mixtures will crystallise as racemic compounds and produce a racemate, which means solubilities are complex to determine [7].

Knowledge of the points of solubility, as a function of their temperature and composition, is essential to produce enantiopure products from a racemic compound. These experiments require extensive trial-and-error results that are both costly and time-consuming. The process is also solvent-solute specific, so the process needs to be repeated across any combination of components. To circumvent this requirement, we can develop a thermodynamic model in order to predict the possible solubility values. Solubility of a binary system can be predicted using the equations put forth by Schröder and van Laar (Equation 1) [8]. The ideal solubility of a compound (x_i^{sat}) in a solution can be calculated by knowing the compound's calorimetric properties ($\Delta_{fus}H_i$, T_m) and the activity coefficient (γ_i^L). This equation is simplified from the relationship between the activity coefficient and fugacity in the liquid phase (Appendix A). The calorimetric properties of a solute can be easily determined and used regardless of the solvent.

$$ln(x_i^{sat}\gamma_i^L) = \frac{\Delta_{fus}H_i}{R}(\frac{1}{T} - \frac{1}{T_m})$$

Schröder and van Laar equation of binary solubility (1)

The activity coefficient of a non-ideal mixture must be computed using thermodynamic models. Traditionally, empirical methods have been used to determine the activity coefficient. Empirical models such as Wilson, NRTL (Non-random two liquid), UNIQUAC (Universal Quasichemical), etc., have been successfully used in industry to model pharmaceutical solubility [9]. These equations are dependent on interaction parameters derived from experimental research. Once obtained, the unique solute-solvent parameters can

be used in any composition at a broad temperature range. Completely predictive models have also been used to determine the activity coefficient with limited success. The required information can be determined by either quantum calculations using COSMO-RS (Conductor like Screening Model for Real Solvents) or equations of state such as PC-SAFT (Perturbation-Chain Statistical Associating Fluid Theory). Both methods will yield an acceptable activity coefficient, but their use is considered less reliable compared to empirical models if the experimental data is available [10]. Recently, modifications to the empirical methods have yielded semi-empirical formulations that attempt to minimize error. Predominantly, this comes as the SAC modification (Segment Activity Coefficient), where the molecule's surface interactions are divided in segments and each type of solute-solvent interaction (hydrophobic, hydrophilic, and polar) has been predefined.

$$ln[4x_i^{sat}\gamma_i^L x_j^{sat}\gamma_j^L] = \frac{\Delta_{fus}H_{rac}}{R}(\frac{1}{T} - \frac{1}{T_m, rac}) \quad (2)$$

Prigogine and Defay equation for the racemate solubility using enantiomeric activity coefficient

The solubility data of enantiomeric mixtures is easily interpreted using a ternary phase diagram. In this three-variable chart, every point represents a composition of the R/S enantiomer and the solvent of the solution. The Schröder and van Laar equation allows for the solubility lines of the enantiomers to be calculated (Figure 3A). This is the case for conglomerates, but in most situations the mixture will behave as a racemic compound, where the racemate must be accounted for. Like single enantiomers, we require the activity coefficient of the racemate to model solubility. An expansion of the Schröder and van Laar equation leads to a modified Prigogine and Defay equation (Equation 2) (Appendix B) [11] [12]. This relationship can be used to determine the solubility point of the racemate with the activity coefficient of the constituent enantiomers. This allows for the calculation of the racemate solubility curve and determining the eutectic points (points of phase transition) of the solution. Knowing the eutectic points gives us enough information to design a process where we can produce one kind of crystal enantiomer.

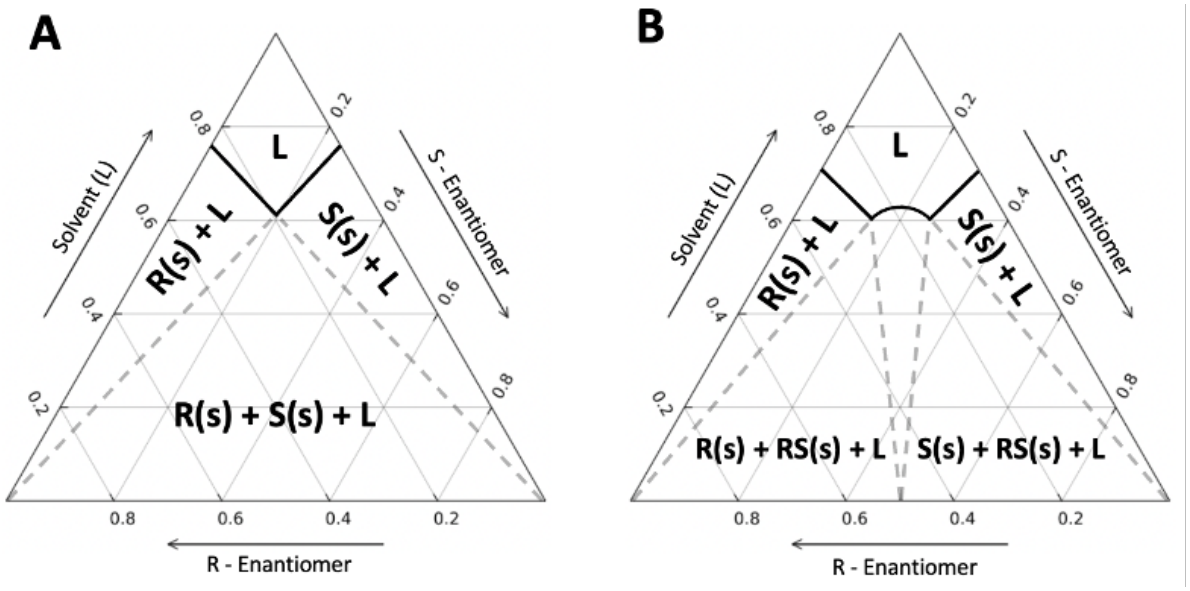

Figure 3: Ternary phase diagrams for a conglomerate (**A**) and for a racemic compound (**B**). Components in the solid phase are tagged with (s), while components in the liquid phase are group under L. RS refers to the racemate in the racemic compound.

3 Software Development

Pharmaceutical modelling is dominated by paid, closed-box software. Current methods to predict the solubility of pharmaceutical components is defaulted to software such as Mathworks' MATLAB and AspenTech's Aspen, which are commercial products that require paid licenses to operate. The objective of this research is to provide a free-of-charge framework for pharmaceutical modelling. In order to create a viable alternative, the software developed needs to meet all the demands required

to predict solubility. In order to predict pharmaceutical solubility, we require binary interaction parameters to predict the behaviour of components in a system. These interactions can be developed on a first principles approach, but the most reliable approaches require experimental data to infer these interactions. Parameters from experimental data can be approximated using non-linear optimization methods. Once these values are calculated, a thermodynamic model can be used to obtain the activity coefficient of the component at a specific composition and temperature. Using solubility equations we can confirm that the composition and temperature of interest is a point of solubility (Figure 4).

Julia is a high-level, high-performance, dynamic programming language. Compared to other similar programming languages used in industry, it is both easy to read and fast. These benefits provide an excellent platform to develop software that requires calculations involving complex equations [13]. Solubility Modelling in Julia (SolMod.jl) has been developed as a package for the prediction of solubility, focused on creating ternary phase predictions for pharmaceutical solubility of enantiopure drugs. In order to achieve comparative utility, multiple functions relevant to pharmaceutical modelling have been included. In addition to subroutines that produce a curve of binary or ternary components, functions relevant to data management and analysis are also added (Figure 5). In accordance to the popular ideals of open-source software, the code is freely available through the hosting service GitHub (source code available at github.com/RGambarini/SolMod.jl). This allows for the software to be improved, fix, and shared as a community effort.

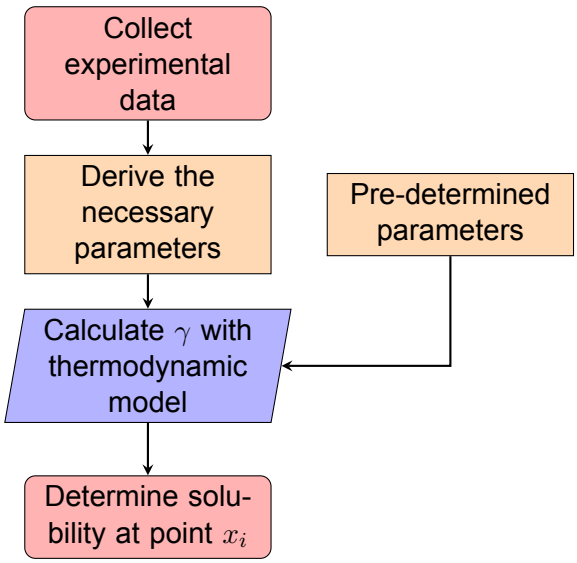

Figure 4: Process of solubility prediction

4 Model Testing

In order to test the effectiveness of the software, the solubility of a ternary system of enantiomers is predicted. Experimental data produced by Tulashie et al [12] (Appendix D) along with determined interaction parameters (Appendix C) is used as the basis in which the effectiveness of the package can be proven. This data-set represents the solubility of mandelic acid enantiomers in a solution of (2R,3R)-diethyl tartrate and predicted using the NRTL model. The Non-random two-liquid model (NRTL) is an activity coefficient model used to calculate the Gibbs free energy of a non-ideal system. It defines the activity coefficient γ_i as a function of the molar composition x_i. This model has been used in chemical engineering applications and has been used in a wide variety of mixtures calculating vapour-liquid and liquid-liquid equilibria [14]. The R is the universal gas constant, T is the temperature at equilibrium, G is a dimensionless interaction parameter that depends on a the specific component interaction energy parameter g, and a non-randomness factor α. The energy parameter $(g_{ij} - g_{jj})$ is the adjustable value obtained by the regression of experimental data. α_{ij} is the adjustable non-randomness parameter. Experimental data for a large number of systems show that the non-randomness parameter ranges from 0.20 to 0.47. It is sometimes chosen casually as it has no physical correlation [15].

$$ln\gamma_i = \frac{\sum_{j=1}^{C} \tau_{ji} G_{ji} x_j}{\sum_{j=1}^{C} G_{ji} x_j} + \sum_{j=1}^{C} \frac{x_j G_{ij}}{\sum_{k=1}^{C} x_k G_{kj}} (\tau_{ij} - \frac{\sum_{k=1}^{C} x_k \tau_{kj} G_{kj}}{\sum_{k=1}^{C} x_k G_{kj}})$$

$$G_{ij} = e^{-\alpha_{ij}\tau_{ij}}$$

$$\tau_{ij} = \frac{(g_{ij} - g_{jj})}{RT}$$

Multi-component NRTL equation (3)

To develop ternary phase predictions, every possible composition of the solution is tested. The software solves the activity coefficient of the solution at a targeted molar composition at constant temperature. It then uses the solubility equation to determine if solubility is possible at the target composition and is therefore recorded if true. The process is then repeated in a pre-determined step-size across every value that the molar composition might be possible (Figure 6). In a mandelic acid

enantiomer system, symmetry in the ternary solubility phase diagram is found with respect to the thermodynamic properties. This means that the solubility of one enantiomer can be mirrored across its vertical axis [16]. This effectively reduces the necessary computations and experimental data required. That being said, experimental data shows a deviation of the enantiomeric eutectic points. Consistently in the data-set, the apparent eutectic points happen at different enantiomeric fractions [12]. This implies that symmetry is an unnecessary approximation that reduces the quality of the model. In order to compare the extent of this error, the solubility prediction difference using equal enantiomer interactions and enantiomer-specific interactions is compared.

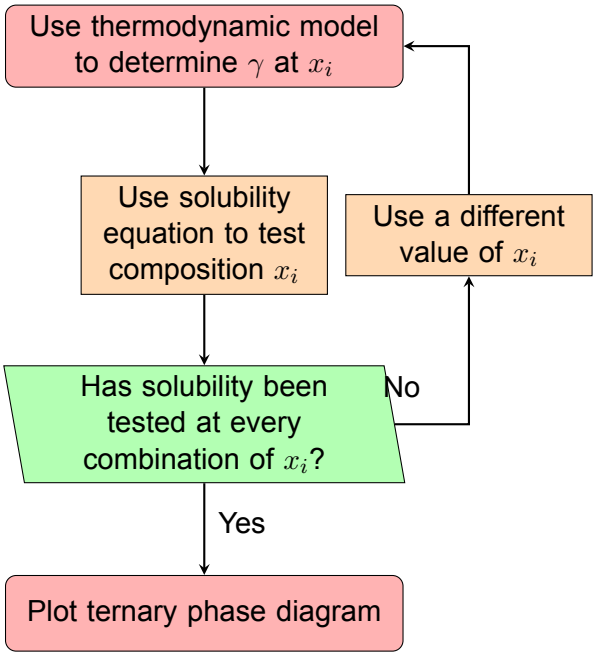

Figure 5: Routine for ternary phase behaviour prediction

5 Parameter Optimization

Prediction of solubility relies on the completeness in calculating activity coefficients. In the NRTL model, the reliability of the variable is dependent on binary interaction parameters. The literature interaction parameters for NRTL are derived by a Matlab routine using a Nelder-Mead optimiser with boundary conditions [12]. In order to provide an open-source alternative, an optimiser routine that doesn't use proprietary resources is used. MadNLP is a nonlinear programming (NLP) solver, purely implemented in Julia [17]. MadNLP implements a filter line-search algorithm, which is also used in Ipopt and is used as a viable solution to obtain interaction parameters from experimental data. The parameterisation for N number of experimental points is given by the objective function is shown as equation 4. Using boundary conditions, the difference in the composition-depending solution molar composition $x_{k,i}^{calc}$ and the corresponding $x_{k,i}^{exp}$ at constant temperature is minimised. The performance of the optimisation is tested by comparing the predictions produced compared to those from literature.

$$\text{OF} = \min \sum_{k=1}^{N} \left(\frac{x_{k,i}^{exp}(T) - x_{k,i}^{calc}(\alpha_{ij}, g_{ij}, g_{ji}, T)}{x_{k,i}^{exp}(T)} \right)^2$$

Objective function for NRTL parameters (4)

6 Results and Discussion

The objective in this research is to produce a useful alternative to many paid tools that are required to generate ternary phase diagrams on enantiomeric systems. In order to achieve this, example predictions are created from experimental data using the SolMod software. The symmetric properties of the enantiomers are tested by calculating the solubility using equal enantiomer interactions and specific enantiomer interactions. The prediction of a ternary phase diagram for a system of mandelic acid enantiomers in a (2R,3R)-diethyl tartrate solution is shown in figure 7. The figure shows a comparison of the predicted solubility of the components relative to the experimentally derived points shown as symbols. The isotherm-group A (dotted isotherm in figure 7) represents the solubility curves derived from literature parameters assuming a mirrored solubility with respect to (S)-mandelic acid. The isotherm-group B (solid isotherm in Figure 7) represents the solubility curves derived from literature parameters when the activity coefficient has been independently calculated for each mandelic acid enantiomer [12]. Isotherm group B shows a significant difference of enantiomeric excess (EE) at the eutectic points that replicates the behavior seen in experimental data. The asymmetry is seen from the difference in the EE values for the R-enantiomer in isotherm groups A to B. Although the independent activity coefficient prediction (group B) correctly mimics the behavior, the RMSD values show that the approximation from mirroring enantiomer activity leads to a smaller error at higher temperatures (Table 2).

Accuracy in solubility prediction is dictated by activity coefficient. For the NRTL model, this is based on the interaction parameters obtained from

experimental data regression. The method of obtaining the interaction parameters is tested using SolMod and comparing it to the parameters obtained from literature [12]. The calculated parameters obtained from the minimisation of the objective function using the MadNLP solver can be seen in table 1. The resulting prediction using these parameters are seen on figure 8 as isotherm-group C (solid isotherm) and is compared to isotherm-group A. There is no significant difference in the calculated values for the EE at the eutectic points. Isotherms with calculated parameters have a higher error compared to those produced using literature parameters. The accuracy found on the values of EE lead to the conclusion that the error must be in the heterochiral interactions parameters. Which implies a poorer description of the interactions between the R and S enantiomers of mandelic acid.

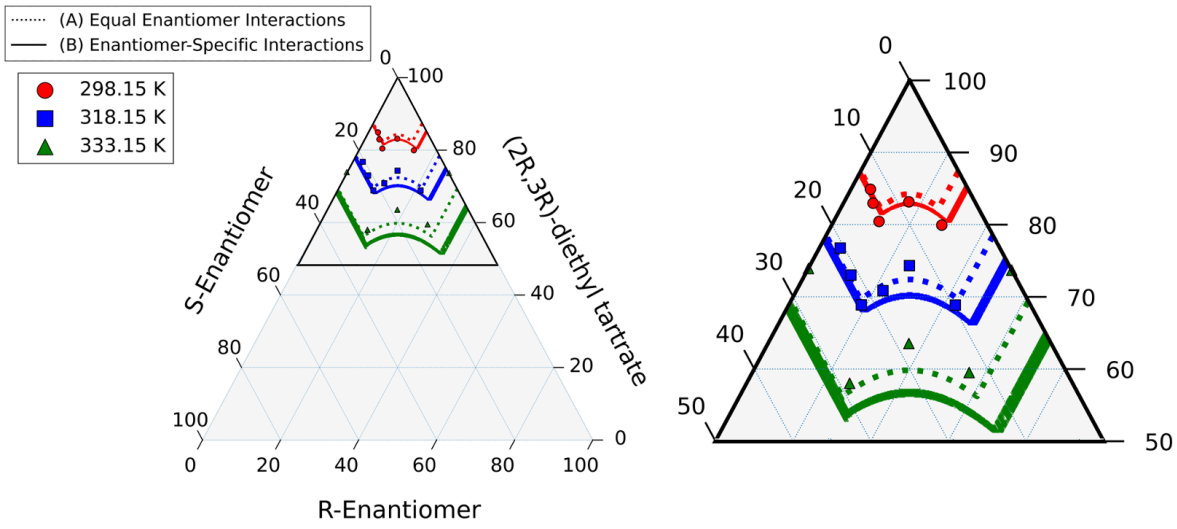

Figure 6: Predicted ternary phase diagram of the mandelic acid enantiomers in (2R,3R)-diethyl tartrate according to the NRTL model and measurement data for three solubility isotherms. Dotted isotherm represents solubility curve derived from literature parameters assuming a mirrored solubility with respect to (*R*)-mandelic acid. Solid represents solubility curve from literature parameters using enantiomerically independent activity coefficient for each enantiomer.

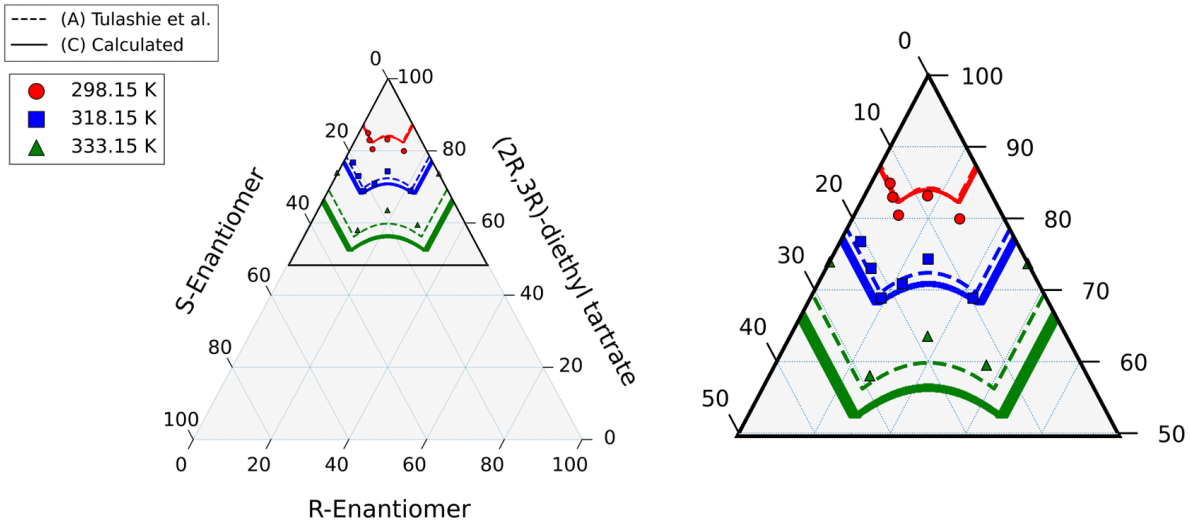

Figure 7: Predicted ternary phase diagram of the mandelic acid enantiomers in (2R,3R)-diethyl tartrate according to the NRTL model and measurement data for three solubility isotherms. Dotted isotherm represents solubility curve derived from literature parameters. Solid isotherm represents solubility curve from calculated parameters.

	α			g (kJ / mol)		
	S	*R*	*Solvent*	*S*	*R*	*Solvent*
S	0	0.979748	0.40104	0	22228	3755.37
R	0.979748	0	0.40104	142423	0	3755.37
Solvent	0.40104	0.40104	0	-3510.79	-3510.79	0

Table 1: Calculated binary NRTL parameters using the MadNLP solver for mandelic acid enantiomers in a (2R,3R)-diethyl tartrate system.

T (K)	EE (%) [*S* / *R*]			RMSD		
	A	B	C	A	B	C
298.15	72.88 / 73.18	75.63 / 70.43	73.18 / 73.18	0.9998	0.5798	0.9398
308.15	72.46 / 72.57	75.10 / 69.92	72.73 / 72.84	0.7766	0.6791	0.6785
318.15	72.08 / 72.17	74.63 / 69.47	71.96 / 72.14	1.375	2.292	2.125
323.15	72.00 / 72.08	74.55 / 69.32	72.09 / 72.09	1.980	4.149	3.891
328.15	71.65 / 71.79	74.19 / 69.17	71.73 / 71.80	3.624	5.923	6.138
333.15	71.46 / 71.52	73.98 / 68.9	71.61 / 71.61	4.221	6.833	7.481

Table 2: Isotherm group A is derived from literature parameters assuming a mirrored solubility. Isotherm-group B is derived from literature parameters for independent activity coefficient. Isotherm-group C is derived from calculated interaction parameters assuming mirrored solubility. (1) Enantiomeric excess of the eutectic point in respect of the S enantiomer and the R enantiomer $EE = (x_1 - x_2)/(x_1 + x_2) \times 100.$ (2) Error analysis as the root mean squared deviation $RMSD = \sqrt{\sum_{k=1}^{C} (x_k^{exp} - x_k^{calc})^2 / C}$.

7 Conclusion

SolMod, a competitive software for solubility modelling, serves as a successful groundwork for the future of open-source pharmaceutical software. The tool works as a comprehensive tool to support experimental research. The analysis performed of a mandelic acid enantiomer system shows a realistic proof-of-work that can be replicated to different applications. The study of enantiomer interactions leads to an agreement with the assumption that mirroring the activity of the enantiomers leads to a good approximation of solubility. The failure to get a better prediction using specific enantiomer interactions might be attributed to a deficiency in the NRTL model. A different model, that is able to produce a more complete activity coefficient, might be necessary to have a prediction closer to experimental data.

The optimization of parameters from experimental data led to a prediction, that although replicated the shape of the desired curve, contained a shift from the experimental data that became more pronounced as temperature increased. The assumption that the shift is caused by an error in the heterochiral interactions suggests that the parametrization of these interactions is not attained properly. It could be addressed by increasing the number of experimental points to have a better correlation between the R and S enantiomer. This would be counterproductive to the goal of this research, since pharmaceutical modelling should cause less experimental dependence. Considering that good parameters are achieved using the Nelder-Mead optimiser, it should be considered to use other non-linear solvers that could parameterise solubility calculations while adhering to open-source ideals.

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Appendix

A. Schröder and van Laar Equation [12].

$$ln(\frac{f^S(Tm,P)}{f^S(T,P)}) = -\int_T^{T_m}(\frac{H^S - H^{ig}}{RT^2})dT$$

$$f^S(T_m,P) = f^L(T_m,P)$$

$$ln(\frac{f^L(T,P)}{f^L(T_m,P)}) = -\int_T^{T_m}(\frac{H^L - H^{ig}}{RT^2})dT$$

$$ln(\frac{f^L(T,P)}{f^S(T,P)}) = -\int_T^{T_m}\frac{\Delta H_{melt}(T_m) + (T-T_m)\Delta C_p}{RT^2}dT$$

$$\Delta H_{melt} = H^L(T_m) - H^S(T_m)$$

$$H^L = H^L(T_m) + C_p^L(T - T_m)$$

$$ln(\frac{f^L(T,P)}{f^S(T,P)}) = \frac{\Delta H_{melt}}{R}(\frac{1}{T} - \frac{1}{T_m}) - \frac{T_m}{R}\Delta C_p(\frac{1}{T} - \frac{1}{T_m} - \frac{\Delta C_p}{R}ln(\frac{T}{T_m})$$

$$ln(x_i^{sat}\gamma_i^L) = \frac{\Delta H_{melt}}{R}(\frac{1}{T} - \frac{1}{T_m}) - \frac{T_m}{R}\Delta C_p(\frac{1}{T} - \frac{1}{T_m} - \frac{\Delta C_p}{R}ln(\frac{T}{T_m})$$

$$f_i^S = f_i^L(T,P,x_i)$$

$$f_i^S = x_i^{sat}\gamma_i^L f_i^L(T,P)$$

$$ln(x_i^{sat}\gamma_i^L) = \frac{\Delta_{fus}H_i}{R}(\frac{1}{T} - \frac{1}{T_m})$$

A pure solid can be heated until melting temperature has been achieved during constant pressure. At melting temperature the solid will enter the solid-liquid transition phase. The species can then be cooled carefully as a meta-stable fluid down to its original temperature. Under the assumption that the chemical potential of any species in all phases can be assumed to be identical. This requires the assumption that the fugacity of a dissolved solute equals the fugacity of the undissolved species in the solid state. During ideal interactions, the mutual solubility of the liquid and solid phase is ignored. The heat capacity below the melting point cannot be experimentally calculated. Its shape is not clearly defined either, which means the value cannot be extrapolated [18]. Approximations between the solid and liquid heat capacities have been developed, such as making the value equal at the temperature of fusion under the assumption of being temperature insensitive [19]. In most cases, good results can be produced when neglecting the heat capacity contribution which leads to the simplified binary solubility equation.

B. Prigogine and Defay Equation [12].

$$
\begin{aligned}
dG &= (\frac{\partial G}{\partial T})_{p,n} dT + \frac{\partial G}{\partial p})_{T,n} dp + \sum \mu_i dn_i \\
-(\frac{\partial G}{\partial \zeta})_{T,p} &= A \\
A &= \mu^S_{rac} - v_i \mu^L_i + v_j \mu^L_j \\
d(\frac{A}{T}) &= \frac{H}{T^L} dT - \frac{V}{T} dp + \frac{1}{T} (\frac{\partial A}{\partial x})_{T,p} dx \\
d(A) &= \frac{A+H}{T} dt + (\frac{\partial A}{\partial x^L_j}_{T,P} dx^L_j \\
\frac{\partial A}{\partial x^L_j} &= v_i \cdot (\frac{x^L_j}{x^L_i} - \frac{v_j}{v_i}) \cdot \frac{\partial \mu^L_j}{\partial x^L_j} \\
\frac{\partial T}{\partial x^L_j} &= - \frac{v_i T \cdot (\frac{x^L_j}{x^L_i} - \frac{v_j}{v_i}) \cdot \frac{\partial \mu^L_j}{\partial x^L_j}}{H} \\
\mu &= \mu \circ (p, T) + RT ln(x) \\
(\frac{\partial \mu^L_j}{\partial x^L_j})_{T,p} &= \frac{RT}{x^L_j} \\
(\frac{v_j}{x_j} - \frac{v_i}{x_i}) \partial x_j &= \frac{H}{RT^2} \partial T \\
-ln \frac{x_i x_j}{0.25} &= \frac{\Delta_{fus} H_{rac}}{R} (\frac{1}{T} - \frac{1}{T_{m,rac}}) \\
ln 4 x_i x_j &= \frac{\Delta_{fus} H_{rac}}{R} (\frac{1}{T_{m,rac}} - \frac{1}{T}) \\
ln[4 x^{sat}_i \gamma^L_i x^{sat}_j \gamma^L_j] &= \frac{\Delta_{fus} H_{rac}}{R} (\frac{1}{T_{m,rac}} - \frac{1}{T})
\end{aligned}
$$

To obtain the solubility equation of a racemate defined by Prigogine and Defay we start from the total differential of the Gibbs free energy to the chemical potential to affinity. The reaction progress variable ζ at constant pressure and temperature links this relationship. During isothermal/isobaric conditions the equilibrium in racemic solubility and the enantiomeric solubility is defined. In this state, Gibbs free energy can be set to zero and the chemical potential of the solid racemate is equal to the sum of the chemical potentials of the enantiomers during the liquid phase. A racemate composition of 0.5 is chosen as the lower integration boundary, and the calorimetric properties of the racemate are applied.

C. Literature Parameters

	α			g (kJ / mol)		
	S	*R*	*Solvent*	*S*	*R*	*Solvent*
S	0	0.979748	0.40104	0	216631	25269
R	0.979748	0	0.40104	141879	0	25269
Solvent	0.40104	0.40104	0	-3235.6	-3235.6	0

Table 3: NRTL interaction parameters for a mandelic acid enantiomer mixture in a (2R,3R)-diethyl tartrate solution [12].

D. Experimental Data

x1	x2	x3
t = 298.15		
13.34	0.0	86.66
12.58	2.5	84.92
13.22	3.81	82.97
13.71	5.83	80.46
8.53	8.31	83.16
5.88	14.17	79.95
0.0	13.24	86.76
t = 308.15		
17.03	0.0	82.97
16.37	2.89	80.74
16.67	4.91	78.42
17.22	7.71	75.07
13.98	9.73	76.29
7.85	17.08	75.07
10.7	10.66	78.64
0.0	17.01	82.99
t = 318.15		
20.0	0.0	80.0
20.56	2.69	76.75
21.05	5.94	73.01
21.77	9.35	68.88
18.0	11.15	70.85
9.69	21.46	68.85
12.887	12.81	74.32
0.0	19.11	80.89
t = 323.15		
22.87	0.0	77.13
22.21	10.28	67.51
10.04	22.26	67.7
14.8	14.64	70.56
0.0	22.28	77.72
t = 328.15		
24.15	0.0	75.85
25.28	11.36	63.36
10.96	24.99	64.05
15.86	15.8	68.34
0.0	24.1	75.9
t = 333.15		
26.07	0.0	73.93
28.72	13.26	58.02
12.58	27.92	59.5
18.32	18.13	63.55
0.0	26.31	73.69

Table 4: Experimental data [12].