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Determination of the Hansen solubility parameters from solubility data using an improved evaluation approach, the concentric spheroids method

Máté Mihalovits *

Department of Chemical and Environmental Process Engineering, Budapest University of Technology and Economics, Budapest, Hungary

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ABSTRACT

A new evaluation method for the determination of the Hansen solubility parameters of a considered substance is suggested in this paper. The earlier proposed gradient binary mixture method is to be conducted to obtain solubility data on a continuous scale (e.g. mg/ml) rather than the widely used soluble/insoluble dichotomous response. Using the continuous responses, Hansen spheroids can be fitted with any given radius, allowing the concentric spheroids model to be fitted to the experimental data. The common center of the spheroids is the estimate of the Hansen solubility parameters of the considered substance. The new suggested desirability function fits this mathematical problem and takes the continuous nature of the data into account. A simulation study was also carried out, which implies that the approach presented in this paper results in more precise estimates of the solubility parameters than the presently used method.

1. Introduction

The Hansen solubility parameters (HSP) are used in a wide range of scientific and industrial processes, such as cocrystal formulation [1], polymer chemistry [2], extraction [3], and semiconductor industry [4]. The HSP are physico-chemical indexes that use the intermolecular forces to describe the solubility character of different substances. They are derived from the cohesive energy density, which is the total amount of intermolecular energy in a unit volume [5]:

$$\delta = \sqrt{\frac{E}{V}} \tag{1}$$

where δ is the square root of the cohesive energy density or the so-called Hildebrand solubility parameter ($Mpa^{0.5}$), E is the amount of energy required to remove the intermolecular interactions between 1 mole molecules (kJ/mol), and V is the molar volume (dm^3/mol). When E is partitioned according to the type of the intermolecular forces, the HSP are obtained as [6]:

$$\delta_T = \sqrt{\delta_d^2 + \delta_p^2 + \delta_h^2} \tag{2}$$

where δ_T is the total Hansen parameter ($MPa^{0.5}$), and δ_d^2 (MPa) is the contribution of the dispersion intermolecular forces, δ_p^2 (MPa) is the contribution of the dipole intermolecular forces and δ_h^2 (MPa) is the contribution of the hydrogen-bonding intermolecular forces to the total Hansen parameter. The HSP define a single point in the three-dimensional Hansen space, where the axes are δ_d, δ_p and δ_h. The pair-wise differences between the HSP of two substances indicate the extent of the miscibility of the two substances. This difference can be described as:

$$Ra = \sqrt{4(\delta_{d1} - \delta_{d2})^2 + (\delta_{p1} - \delta_{p2})^2 + (\delta_{h1} - \delta_{h2})^2} \tag{3}$$

where the subscript of 1 or 2 refers to the two substances, and *Ra* is the Euclidean distance between the two points defined by the coordinates of (δ_{d1}, δ_{p1}, δ_{h1}) and (δ_{d2}, δ_{p2}, δ_{h2}) in the Hansen space. The smaller the *Ra* is, the better the solubility of the substances in each other. When δ_{d1}, δ_{p1} and δ_{h1} are fixed, Eq. (3) is an equation of a spheroid, which is a special ellipsoid with one of the radii ($\delta_{d1} - \delta_{d2}$) being half of the other two radii ($\delta_{p1} - \delta_{p2}$ and $\delta_{h1} - \delta_{h2}$). In this spheroid, the centrum with the fixed δ_{d1}, δ_{p1} and δ_{h1} values define a single substance, and a selected *Ra* defines points on the surface of the spheroid. Chemicals with HSP corresponding to this surface dissolve the substance in the centrum to the same extent. Increasing *Ra* results in increasing size of the spheroid and substances with reducing solubility potential on the surface. Fig. 1

* Address: Budapest University of Technology and Economics, Műegyetem rakpart 3, Budapest 1111, Hungary.
E-mail address: mihalovits.mate@vbk.bme.hu

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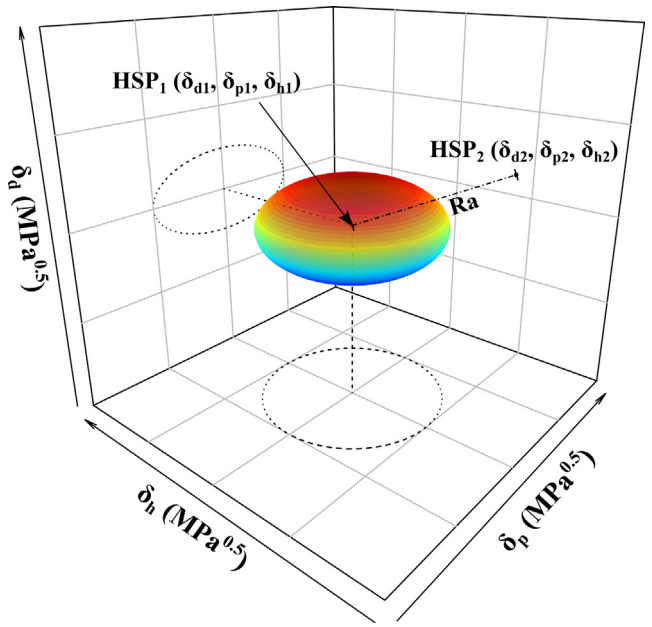

Fig. 1. Hansen spheroid with the center of HSP_1, and the distance Ra between HSP_1 and HSP_2.

depicts a spheroid (the coloring is only for visual purposes, and has no further meaning) around the centrum of (δ_{d1}, δ_{p1}, δ_{h1}), and a single *Ra* between the centrum and a point at (δ_{d2}, δ_{p2}, δ_{h2}).

To use the information from *Ra* the HSP of the considered chemicals are required. The values for some generally used organic solvents are readily available in the works of Barton [7] and Hansen [8]. However, they are unknown in most cases, and their determination is required. Three main approaches are generally used to obtain the HSP. The first method estimates the HSP values based on the calculation with the group contribution method. The most applied approaches are developed by Stefanis and Panayiotou [9], Hoftyzer and Krevelen [10], and K.C. Hoy [11]. While these methods have good or acceptable descriptive accuracy, their predictive accuracy might be questionable, and more precise estimates may be required in some cases. Besides the computational technique, two experimental approaches are followed. In the inverse gas-chromatographic (IGC) method, the HSP of the considered substance are determined based on the retention of the solute compared to those of the solvents with known HSP values [12]. The second experimental approach, which is the focus of this paper, uses solubility data of the considered chemical in solvents with known HSP. The solubility is typically measured in 30–40 solvents selected to cover the whole Hansen space [13]. The solvents in which no solubility can be detected are marked as bad solvents, while those with detectable solubility are marked as good solvents. The idea is that there exists a spheroid with the center as the HSP of the investigated substance and a specific *Ra*, that separates the good solvents and the bad solvents in the Hansen space. This specific *Ra* is defined as R_0. Good solvents fall inside the spheroid, bad solvents fall outside the spheroid, and the solvents that are on the border of being good or bad solvents (theoretically dissolve the investigated chemical exactly at the detectable level) can be found on the surface of such spheroid. The ratio of *Ra* and R_0 can be defined as:

$$RED = \frac{Ra}{R_0} \tag{4}$$

where *RED* is the relative energy difference, and $RED < 1$ for good solvents, $RED > 1$ for bad solvents, and $RED = 1$ for borderline solvents. The main objective is to find the center (therefore, the HSP of the investigated chemical) of the spheroid based on where the good and bad solvents fall in the Hansen space. Finding R_0 may also be of interest. Another approach was also suggested to conduct the solubility experiments [4]. Instead of selecting random solvents to cover the Hansen space, a more designed way is followed in this approach. One solvent, which dissolves the investigated substance very well, and at least four bad solvents are selected. The solubility experiments are conducted in the binary mixtures of the very good solvent and each of the bad solvents. The composition is systematically changed between 100 % and 0 % good solvent ratio in these mixtures. The HSP of binary mixtures may be calculated by the following approximation [8]:

$$\delta_x = \Phi_1 \delta_{x1} + \Phi_2 \delta_{x2} \tag{5}$$

where, Φ_1 and Φ_2 are the volume ratio of the two components, δ_{x1} and δ_{x2} are the HSP of the components (x is either d or p or h), and δ_x is the HSP of the mixture. Accordingly, the points of the binary mixtures in the Hansen space can be found between the points of the good solvent and the bad solvents. It should be noted that Eq. (5) assumes that the components form an ideal mixture. In ideal mixtures, the concentration of the components (solute included) is constant regardless of the location in the liquid, and the same intermolecular forces with the same strength rise between the different molecules. Solvents that possess both hydrophilic and hydrophobic characteristics or are strong acid or base may affect the orientation of the solute molecules to an extreme extent. In that case, the averaged characteristic of the mixture defined by Eq. (5) will no longer be valid for the immediate environment of the solute molecules. One should keep this limitation in mind when choosing the solvents for the binary mixture.

The approach is illustrated in Fig. 2, where four binary mixture systems are used. HSP_1 is the HSP of the solute to be determined, HSP_g is the HSP of the good solvent and HSP_{b1}-HSP_{b4} are the HSP of the bad solvents. The points between the bad solvents and the good solvent correspond to the HSP of these mixtures. The green

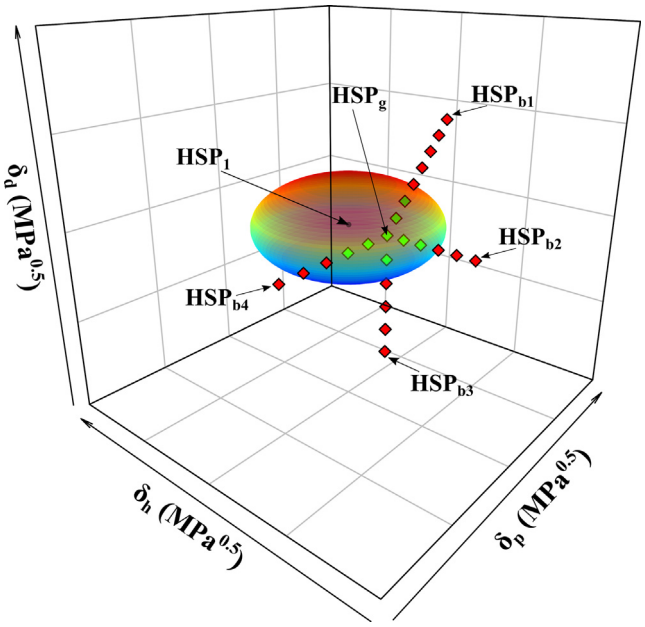

Fig. 2. Demonstration of the gradient binary mixtures method to determine the HSP_1 with four bad solvents with HSP of HSP_{b1}-HSP_{b4}; the green symbols correspond to the mixtures in which the substance is soluble, while the red symbols correspond to those in which the substance is insoluble. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

symbols correspond to the mixtures that dissolve the substance well, while the red ones correspond to the mixtures that dissolve the substance poorly.

It should be noted that none of the solubility measurement approaches consider the effect of the size of the molecules on the solubility. Nevertheless, the similar sizes of the typically used organic solvents in the experiments may justify the neglection of the effect.

In determining the HSP of an investigated substance, the common practice is to define a desirability function that is to be maximized. The originally suggested desirability function is the following:

$$d = \sqrt[n]{\prod_{i=1}^{n} A_i\left(\delta_{d1},\, \delta_{p1},\, \delta_{h1}, R_0\right)} \tag{6}$$

where d is the desirability, n is the number of solvents used during the experiments, and A_i which is a function of the variables of the fitted spheroid (δ_{d1}, δ_{p1}, δ_{h1} and R_0) is defined for the i th solvent as:

$$A_i = \begin{cases} 1 & \text{if } Ra_i < R_0 \text{ and the ith solvent is a good solvent} \\ 1 & \text{if } Ra_i > R_0 \text{ and the ith solvent is a bad solvent} \\ e^{-|Ra_i - R_0|} & \text{if outlier} \end{cases} \tag{7}$$

where R_0 is the radius of the fitted spheroid and Ra_i is the distance between the centrum of the fitted spheroid and the ith solvent in the Hansen space. 'Outlier' means that a point falls outside the fitted spheroid while it is a good solvent or inside the spheroid while it is a bad solvent. The aim is to find the spheroid that maximizes the A_i values, and thus maximize the desirability through the selection of the values of δ_{d1}, δ_{p1}, δ_{h1} and R_0. Two other desirability functions were also used [14,15], which are described by the following equations:

$$d' = \sqrt[n]{\prod_{i=1}^{n} A_i\left(\delta_{d1},\, \delta_{p1},\, \delta_{h1}, R_0\right)} * \frac{1}{\sqrt[m]{R_0}} \tag{8}$$

$$d'' = \sqrt[n]{\prod_{i=1}^{n} A_i\left(\delta_{d1},\, \delta_{p1},\, \delta_{h1}, R_0\right)} * \frac{1}{\sqrt[n]{R_0}} \tag{9}$$

where m is suggested to be set around 20. These functions were proposed in order to take the R_0 into account during the optimization and to force the algorithm to shrink R_0. It should be noted that it is not straightforward and was not shown why it is desired to restrict (minimize) R_0 and how the restriction affects the accuracy of the HSP determination. Also, no reason was given to set m to around 20 in Eq. (8). The use of R_0 in the desirability function seems to be a questionable adjustment for the original function.

The maximization of the desirability was suggested to be performed by different algorithms such as the Nelder-Mead algorithm [16] and the Genetic Algorithms [17]. The aim of the algorithms is to find the extremum of the function d, which depends on δ_{d1}, δ_{p1}, δ_{h1} and R_0 through the $A_i(\delta_{d1}, \delta_{p1}, \delta_{h1}, R_0)$ function. The output is the optimal HSP and the radius of the spheroid.

Martin et al. [18] suggested the extended Hansen solubility approach (EHSA or EHA) in which, contrary to the approach of the above-discussed methods, the solubility data is handled as a continuous variable. The method extends the regular solution approach of Hildebrand and Scatchard [5]. The following equation is used in practice [19,20]:

$$\log(x) = C_0 + C_1\delta_{1d} + C_2\delta_{1d}^2 + C_3\delta_{1p} + C_4\delta_{1p}^2 + C_5\delta_{1h} + C_6\delta_{1h}^2 \tag{10}$$

where the δ_1 values are the corresponding HSP of the solvents and x is the solubility (mole fraction) of the solute. The coefficients in the above equation are estimated by the regression fit of the logarithmic solubilities (x) on the HSP values of the solvents. From the coefficients, the estimated HSP of the solute are obtained as:

$$\delta_{2d} = -\left(\frac{C_1}{2C_2}\right) \tag{11}$$

$$\delta_{2p} = -\left(\frac{C_3}{2C_4}\right) \tag{12}$$

$$\delta_{2h} = -\left(\frac{C_5}{2C_6}\right) \tag{13}$$

Eq. (10) implies, that there is a linear connection between Ra (or similarly RED) and $\log(x)$. Hansen [21] discussed the correlation between Ra and $\log(x)$ in the case of fullerene, but based on the collected data, linearity is not evident. The assumption of linearity might be flawed when the data are collected in a wide range of Ra. This behavior can be observed in the case of fullerene in the work of Hansen [21]. Nevertheless, the assumption of linearity was used in the work of Sato et al. [22] to determine the HSP of oxygen. In this approach, the center of the HSP spheroid (the HSP of the solute in question) is chosen so that the best linear fit is obtained on the data of Ra and $\log(x)$.

Considering the solubility on the continuous scale instead of the dichotomous is advantageous and results in more precise estimates for the HSP of the solute. However, the assumption of linearity between Ra (or similarly RED) and $\log(x)$ may be questionable and may limit the effectiveness of the above methods.

In this paper, a new method is presented to evaluate solubility data considering it as a continuous variable. This method maximizes the information by considering the solubility on the continuous scale (e.g. mg/ml) instead of the dichotomus soluble/insoluble approach. Also, it is independent of the connection between Ra (or similarly RED) and $\log(x)$, and thus, it does not require the assumption of linearity. The approach allows estimating the centrum (the HSP of the solute in question) from numerous concentric spheroids with varying radii; hence the name of the approach: the concentric spheroids method.

2. Method

While the earlier suggested approach of maximizing the desirability function is sound, a more accurate and precise HSP determination algorithm may be achieved by improving the way the experiments are conducted and evaluated. There are two questionable aspects of the originally suggested random solvents method. First, it is not straightforward what insolubility means. The analytical detection limits vary from method to method, not to mention the uncertainty present when the solubility is determined by visual inspection. Varying results may be expected if the solubility is measured by different analytical methods. Secondly, due to the way the experiments are conducted, there is a lot of redundant information obtained in the experiment. The source of this is that the output of the experiments is handled only as dichotomous (soluble/insoluble), and the solvents are defined as bad or good solvents. The experiments provide information only on the whereabouts of the surface, which separates bad and good solvents. This approach results in redundant points.

Generally, the bad solvents that are far from the borderline ($RED \gg 1$) possess less information than the bad solvent close to the border ($RED \cong 1$), and similarly, the good solvents close to the centrum ($RED \ll 1$) possess less information than good solvents close to the borderline ($RED \cong 1$). A few examples are shown on a random dataset depicted in Fig. 3. Although points falling in circle A are close to the borderline and thus provide useful information, they are found in a cluster relatively close together, and each point offers practically the same information. Points in the ellipsoid B and circle E are redundant, as there are points closer to the border at that region and therefore provide practically zero

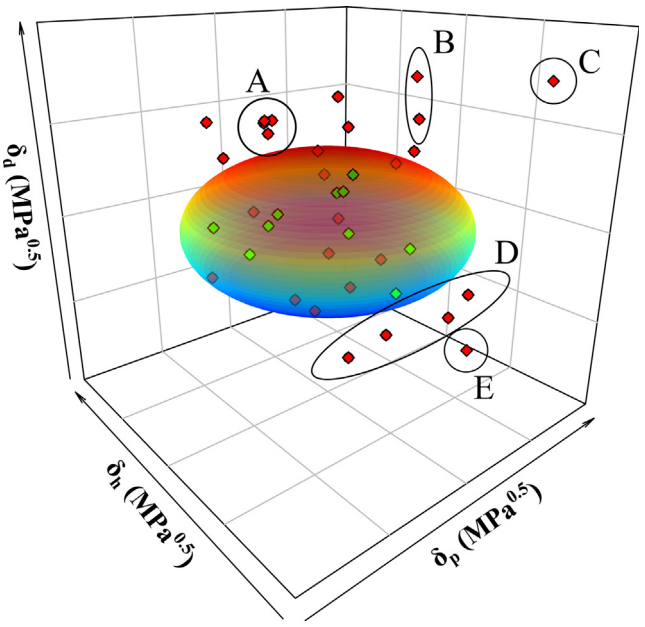

Fig. 3. Examples of redundant and important points in the random solvents method.

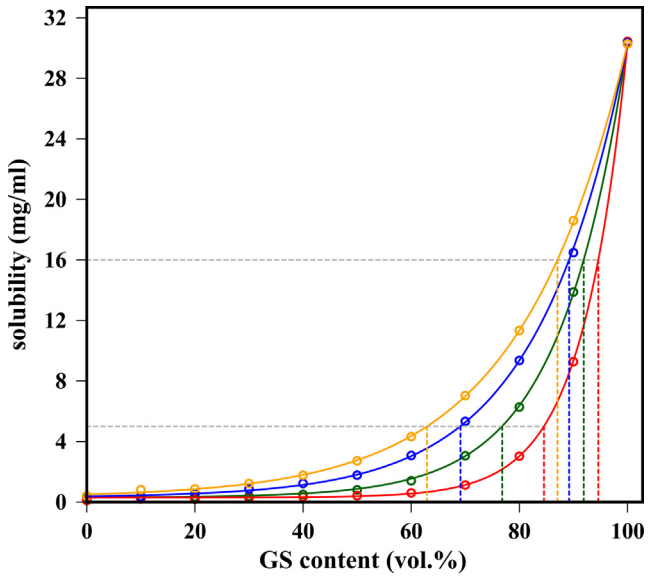

Fig. 4. Solubility of a solute in different binary mixtures of the same good solvent (GS), and four bad solvents (the coloring corresponds to the different binary mixtures).

extra information. Although the point in circle C is the only point in its direction from the centrum, it has no additional information compared to the other points falling closer to the borderline. That is because the orientation and the ratio of the radii of the spheroid are known (Eq. (3)), and based on the other points, it is straightforward that no good solvent can be found in the region of circle C. The points within ellipsoid D are useful as they are close to the borderline and help shape the fitted surface. Generally, those points are useful that help shape the surface by being as close to the border as possible ($RED \cong 1$).

The advantage of the gradient solvents approach used in [4], is that it can find points almost exactly on the surface of the true spheroid (see Fig. 2), resulting in those points providing close to maximum information. It was not recognized and used in the original paper, that the other points are just as useful and can provide the same amount of information. When the actual solubility is measured on a continuous scale (e.g. mg/ml), theoretically infinite number of radii and corresponding spheroids may be defined based on the solubility (e.g. mg/ml) of the investigated substance. Thus, it is not only the spheroid with the radius of R_0 that can be estimated, but other concentric spheroids with varying radii.

Fig. 4 shows a possible outcome of the results obtained in an experiment conducted with the gradient binary mixtures method. The differently colored points correspond to the binary solvent mixtures of the good solvent (GS) and the four bad solvents. With increasing bad solvent content (decreasing GS content), the HSP of the binary mixtures moves away from the HSP of the solute in the Hansen space (Fig. 2), and the solubility decreases. At any given solubility (y axis), a certain composition of each of the binary mixtures (x axis) can be found. These compositions can be estimated by a curve fitted to the measurements. The mixtures with the corresponding compositions dissolve the solute to the same extent. The HSP of the binary mixtures with the composition that dissolve the solute to the same extent are found on the surface of the same spheroid. In Fig. 4, two solubilities were selected at 16 mg/ml and 5 mg/ml (horizontal dashed lines), and each determine four HSP point in the Hansen space, which are defined by the composition of the mixtures that belongs to these solubilities using the fitted curves (vertical dashed lines). The objective, in this case, is to find the centrum of the two concentric spheroids using four-four points (at 16 mg/ml and 5 mg/ml) that estimate points on the true surfaces. Due to the random error of the measurement (and thus of the curve fitting), these points are estimates only of the points that fall on the true surface. Also, the approximation used in calculating the HSP of mixtures (Eq. (5))might increase the random error of the points.

Analogous to the least-squares method, the following function is suggested to be minimized to estimate the common center of the concentric spheroids:

$$F(\delta_{d1},\ \delta_{p1},\ \delta_{h1}, R_1, R_2, \cdots, R_m) = \sum_{j=1}^{m}\sum_{i=1}^{n}\left(R_j - Ra_{ji}\right)^2 \qquad (14)$$

where m is the number of the selected solubility values, and thus the number of concentric spheroids to be fit, R_j is the radius that belongs to the jth concentric spheroid, n is the number of binary systems and Ra_{ji} is the distance between the ith point of the jth binary system and the fitted centrum with the coordinates of δ_{d1}, δ_{p1}, and δ_{h1}. Accordingly, F is the sum of the sum of squares of the differences between the distance of each point from the center of the fitted spheroid and the corresponding radius of the fitted spheroid. The previously suggested Nelder-Mead algorithm and the Genetic Algorithms may be used to find the values of $\delta_{d1},\ \delta_{p1},\ \delta_{h1}, R_1, R_2, \cdots, R_m$ that minimize F.

2.1. Application on experimental data

The dataset in [23] is evaluated to determine the HSP of N(Ph-2T-DCN-Et)$_3$ using the concentric spheroids method. The data were obtained in an experiment conducted using the gradient binary mixtures method. The good solvent is chlorobenzene (CB), and the four bad solvents are propylene carbonate, acetone, 2-propanol, and cyclohexane. The solubility of N(Ph-2T-DCN-Et)$_3$ was measured in the binary solvents of CB, and each of the bad solvents with the composition of CB increased from 0 % to 100 %. Unfortunately, the data points are not given numerically in the original paper, and they are only depicted in a plot. The plot was reconstructed (Fig. 5) using graphics software, and the approximated values of the points were obtained, and they are given in Table 1.

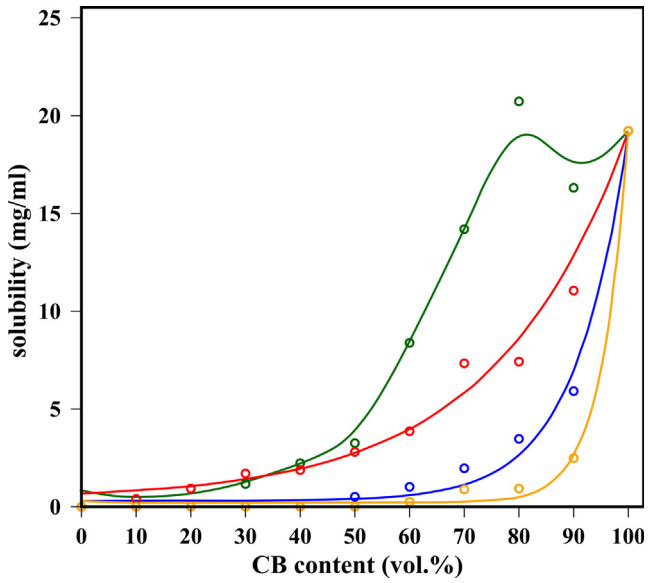

Fig. 5. Solubility of N(Ph-2T-DCN-Et)$_3$ in the binary mixtures of chlorobenzene (CB) and propylene carbonate (green), acetone (red), 2-propanol (blue) and cyclohexane (yellow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

It should be noted that the local minimum in the solubility curve of the mixture of CB/2-propylene carbonate at around 90 % CB content should not be possible. The points in the Hansen space cannot first moves away from the centrum with increasing propylene carbonate content (decreasing solubility), then starts to move closer again (increasing solubility). Therefore, the points at 100 %, 90 %, and 80 % CB content are rather inconsistent in that case. On a side note, it would be possible that the solubility increases with decreasing good solvent ratio, and then decreases, resulting in the global maximum shifted from the 100 % good solvent. The appropriateness of the fitted curves is questionable in Fig. 5, but it was not the intention of the original authors to use the fitted curves for interpolation only to show the trend of the data. However, more appropriate regression curves would presumably not result in a more accurate estimate in this case due to the seemingly questionable appropriateness of the data. Accordingly, for the demonstration, the curves are accepted as appropriate fits and are used to obtain compositions of the mixtures for the selected solubility values. The intervals of the solubility where local minimum or local maximum are present (above 15 mg/ml due to the CB/propylene carbonate mixture and between 4 mg/ml and 8 mg/ml due to the CB/acetone mixture) are not considered for the selection of the solubility values for which the concentric spheroids are fitted. The semi-randomly selected solubility values are 2.9 mg/ml, 9.1 mg/ml, 12.6 mg/ml and 15 mg/ml.

The compositions of the mixtures that corresponds to these solubility values are obtained from the fitted curves with the help of the graphics software. The values are given in Table 2.

The Hansen parameters of the mixtures are calculated by Eq. (5) using the reference values of the pure solvents given in Table 3. The calculated values for the mixtures with the CB contents defined in Table 2 are shown in Table 4.

The four HSP at each solubility estimates the surfaces of four concentric spheroids. The centrum of these spheroids is the HSP of the investigated substance. To obtain the center, the F function given in Eq. (14) is to be minimized. One adjustment may be used in F, so its value is comparable across different datasets. The mean square error of the residual distances may be used for this purpose:

$$MSE = \frac{F}{\sum_{j=1}^{m} n_j - m} = \frac{\sum_{j=1}^{m}\sum_{i=1}^{n}\left(R_j - Ra_{ji}\right)^2}{\sum_{j=1}^{m} n_j - m} \tag{15}$$

where the denominator is the degrees of freedom (df), obtained as the difference between the number of data used in the fitting ($\sum_{j=1}^{m} n_j$) and the number of parameters to be estimated (m).

First, the spheroids may be estimated one-by-one without the constrain of a common centrum, using only the four corresponding HSP points. The results of this approach are shown in Table 5.

This approach is useful for obtaining insight regarding the appropriateness of the concentric spheroids method and the uncertainty of the estimates. The MSE are all zero, because all the points fall exactly on the fitted surface. That is because four points are used in each fit, while four parameters are estimated, namely R, δ_d, δ_p and δ_h and the degrees of freedom is zero. Regardless, these estimates are still statistically appropriate. As can be seen in Table 5, the estimates at the solubility of 2.9 mg/ml noticeably differ from the estimates of the other solubility levels, especially in the case of δ_d and δ_p. The source of this deviation might be the questionable precision of the data.

When two concentric spheroids are fit, the number of points is eight, while the number of the parameters to be estimated is only five: R_1, R_2, δ_d, δ_p and δ_h. The more concentric spheroids are fit, the greater the degrees of freedom is, and the more precise the estimates are. Table 6 shows the estimated parameters for situations in which a different number of concentric spheroids are fitted. While the fit of two and three spheroids results in MSE with an insignificant difference, the inclusion of the outermost points to fit all four spheroids significantly increased MSE. This information and the outlier nature observed in the one-by-one fitting method imply that the outermost points are less precise or not accurate estimates of the corresponding spheroid. Accordingly, based on the results obtained from fitting the three inmost concentric spheroids, the HSP of N(Ph-2T-DCN-Et)$_3$, (δ_d, δ_p, δ_h) is found to be (20.2, 6.1, 2.6). In the original paper [23], the values were found to be 19.09–19.20 for δ_d, 6.33–8.96 for δ_p and 2.28–3.47 for δ_h. It should be noted that the use of the unit mg/ml for the solubility might not be the most appropriate choice to compare over mixtures with different bad solvents, and one may consider the use of mg/mol instead for example.

Table 1
Solubility values (mg/ml) in Fig. 5.

Mixture	CB content (vol%)										
	0	**10**	**20**	**30**	**40**	**50**	**60**	**70**	**80**	**90**	**100**
CB/propylene carbonate	0.0	0.0	0.9	1.2	2.2	3.3	8.4	14.2	20.7	16.3	19.2
CB/acetone	0.0	0.4	0.9	1.7	1.9	2.8	3.9	7.3	7.4	11.1	19.2
CB/2-propanol	0.0	0.0	0.0	0.0	0.0	0.5	1.0	2.0	3.5	5.9	19.2
CB/cyclohexane	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.9	0.9	2.5	19.2

Table 2
CB content (vol%) in the mixtures at the selected solubilities.

Solubility (mg/ml)	CB/propylene carbonate	CB/ acetone	CB/2-propanol	CB/ cyclohexane
2.9	45	51	80	90
9.1	60	81	92	96
12.6	66	89	95	97
15	70	94	97	98

Table 3
HSP of the solvents at 298.15 K and 0.101 MPa.

Solvent	δ_{dref} (MPa$^{0.5}$)	δ_{pref} (MPa$^{0.5}$)	δ_{href} (MPa$^{0.5}$)
CB	19	4.3	2
propylene carbonate	20	18	4.1
acetone	15.5	10.4	7
2-propanol	15.8	6.1	16.4
cyclohexane	16.8	0	0.2

3. Simulation study

The comparison of the different techniques would require an extensive simulation study, which is beyond the aim of this paper. However, to justify the application of the methods and to obtain some insight into their effectiveness, an investigation should always be carried out. Unfortunately, the literature lacks any simulation study regarding the determination of the HSP of a given solute. A brief study is presented here. Three main scenarios are considered, the random solvents method, the extended Hansen solubility approach (EHA), and the gradient binary mixtures method. In the gradient binary mixtures method and EHA, the solubility is considered on the continuous scale, while in the random solvents method, the response is soluble/insoluble. The two desirability functions suggested in the literature are used in the random solvents method. The desirability function suggested in this paper is used in the gradient binary mixtures method. Also, two different allocations of the points of the solvents in the Hansen space (A and B) are considered in the random solvents method. The EHA is investigated only in the more advantageous scenario of the allocation A. The six situations are summarized in Table 7.

The parameters of the simulations in the random solvents method are the following:

- the HSP of the solute to be determined is defined as (15, 10, 13.5)
- the borderline radius R_0 equals four
- in the case of allocation A, 40 random points are generated in a single loop using uniform distribution in the range of 11–19 for δ_d, 5–15 for δ_p and 8–19 for δ_h
- in the case of allocation B, 40 random points are generated in a single loop using uniform distribution in the range of 13–19 for δ_d, 8–18 for δ_p and 12–19 for δ_h
- 10,000 loops are simulated

In each loop, 40 points are generated in the given region, and good solvent/bad solvent responses are assigned to them based on their position compared to the borderline spheroid with the center of (15, 10, 13.5) and radius of $R_0 = 4$. In the case of allocation A, the HSP to be determined is in the middle of the space of the generated points. Thus, the spheroid can be shaped in all directions by the generated 40 points. In the case of allocation B, the HSP is shifted toward the edge of the space of the generated data and cannot be shaped in all directions. In each loop, based on the assignment of the points, the desirability function is minimized, and the estimates of the HSP of the solute are obtained.

The parameters of the simulations in the EHA are the following:

- the HSP of the solute to be determined is defined as (15, 10, 13.5)
- random points are generated in a single loop using uniform distribution in the range of 11–19 for δ_d, 5–15 for δ_p and 8–19 for δ_h (allocation A)
- 10,000 loops are simulated
- the following theoretical function is used: $\log(x) = -0.5\mathrm{Ra}$
- solubility ($\log(x)$) is generated with the standard deviation of 0.2 and the expected value of -0.5Ra, where Ra is obtained from the known HSP of the solute and the HSP of the generated points

The used theoretical function was chosen to resemble the results of the studies of the oxygen and fullerene solubility in the literature [21,22]. Using the standard deviation of 0.2, the relative

Table 4
Calculated HSP of the mixtures with the composition corresponding to the solubility values.

Solubility (mg/ml)	Mixture	δ_{dmix} (MPa$^{0.5}$)	δ_{pmix} (MPa$^{0.5}$)	δ_{hmix} (MPa$^{0.5}$)
2.9	CB/propylene carbonate	19.6	11.8	3.2
2.9	CB/acetone	17.3	7.3	4.5
2.9	CB/2-propanol	18.4	4.7	4.9
2.9	CB/cyclohexane	18.8	3.9	1.8
9.1	CB/propylene carbonate	19.4	9.8	2.8
9.1	CB/acetone	18.3	5.5	3.0
9.1	CB/2-propanol	18.7	4.4	3.2
9.1	CB/cyclohexane	18.9	4.1	1.9
12.6	CB/propylene carbonate	19.3	9.0	2.7
12.6	CB/acetone	18.6	5.0	2.6
12.6	CB/2-propanol	18.8	4.4	2.7
12.6	CB/cyclohexane	18.9	4.2	1.9
15	CB/propylene carbonate	19.3	8.4	2.6
15	CB/acetone	18.8	4.7	2.3
15	CB/2-propanol	18.9	4.4	2.5
15	CB/cyclohexane	19	4.2	2

Table 5
MSE and the estimated parameters of the spheroids fitted independently at each solubility.

	15 mg/ml	12.6 mg/ml	9.1 mg/ml	2.9 mg/ml
MSE	0	0	0	0
R	2.7	3	3.2	4.1
δ_d (MPa$^{0.5}$)	20	19.9	19.8	19.1
δ_p (MPa$^{0.5}$)	6.1	6.3	6.7	7.8
δ_h (MPa$^{0.5}$)	2.4	2.3	2.6	2.7

Table 6
MSE, df, and the estimated parameters of the concentric spheroids using different sets of data.

	Two innermost concentric spheroids	Three innermost concentric spheroids	All four concentric spheroids
df	3	6	9
MSE	0.014	0.05	0.33
$R_{15mg/ml}$	3.1	3.3	3.3
$R_{12.6mg/ml}$	3.3	3.5	3.4
$R_{9.1mg/ml}$	–	3.8	3.7
$R_{2.9mg/ml}$	–	–	4.7
δ_d (MPa$^{0.5}$)	20.2	20.3	20
δ_p (MPa$^{0.5}$)	6.1	6.2	6.5
δ_h (MPa$^{0.5}$)	2.6	3	3.7

standard deviation of the solubility (x) in 90 % of the cases is between ± 30 %, while the median of R^2 is 0.94. Both statistics resemble those obtained in the work of Beerbower et al. [19] and thus may be accepted as justified. An example obtained in a random loop can be seen in Fig. 6. The estimates of the HSP of the solute are obtained by the regression fit of $\log(x)$ on the HSP of the solvents in the form of Eq. (10) and the use of Eq. (11) - (13).

The parameters of the simulations in the gradient binary mixtures method are the following:

- the HSP of the solute to be determined is defined as (15, 10, 13.5) (black point in Fig. 7)
- in each loop, the point of the good solvent is generated within a spheroid that has a radius of 2, and the center of the HSP of the solute in question (15, 10, 13.5) (the red point in Fig. 7 is an example of the generated point of the good solvent)
- The radii of the concentric spheroids around which points are generated are 3, 3.3, 3.6, 3.9, 4.2 (R_1-R_5 in Fig. 7)
- in each loop, points are generated in four directions (n = 4) from the good solvent onto the surface of the innermost three, four, and five concentric spheroids (m = 3, 4, 5) and errors from the normal distribution with an expected value of zero and variance of 0.1 are added to them – for example, when a point is generated on the surface of a spheroid (it defines a given HSP), an error that has an expected value of zero and variance of 0.1 is generated and added to each Hansen component (green and blue points in Fig. 7 represent the points before the errors are added to them)
- three of the directions of the generated points are parallel with the main axes; in each direction, the corresponding Hansen component is increased compared to the good solvent (blue points and the green points on the right in Fig. 7, the points parallel with the δ_h axis are not visible)
- the fourth direction of the generated points is parallel with the δ_p axis, but δ_p is decreased compared to the good solvent (the green points on the left in Fig. 7)
- 10,000 loops are simulated

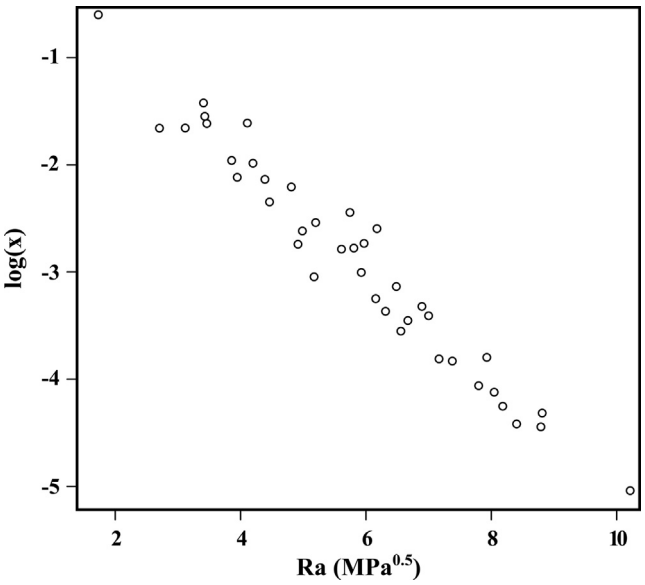

Fig. 6. Randomly generated points in a single loop.

The error added to the points represents the error of the curve fitting and the error from using the approximated Eq. (5). It is shown in the discussion of the study results that the error variance of 0.1 is justified. In each loop, the concentric spheroids are fitted

Table 7
Scenarios in the simulation study.

Method	Allocation	Response	Desirability functions and theoretical function of EHA
Random solvents method	A	dichotomous	$d = \sqrt[n]{\prod_{i=1}^{n} A_i(\delta_{d1}, \delta_{p1}, \delta_{h1}, R_0)}$
		dichotomous	$d' = \sqrt[n]{\prod_{i=1}^{n} A_i(\delta_{d1}, \delta_{p1}, \delta_{h1}, R_0)} * \frac{1}{\sqrt[m]{R_0}}$
	B	dichotomous	$d = \sqrt[n]{\prod_{i=1}^{n} A_i(\delta_{d1}, \delta_{p1}, \delta_{h1}, R_0)}$
		dichotomous	$d' = \sqrt[n]{\prod_{i=1}^{n} A_i(\delta_{d1}, \delta_{p1}, \delta_{h1}, R_0)} * \frac{1}{\sqrt[m]{R_0}}$
EHA	A	continuous	$\log(x) = C_0 + C_1\delta_{1d} + C_2\delta_{1d}^2 + C_3\delta_{1p} + C_4\delta_{1p}^2 + C_5\delta_{1h} + C_6\delta_{1h}^2$
Gradient binary mixtures method	–	continuous	$F = \sum_{j=1}^{m}\sum_{i=1}^{n}(R_j - Ra_{ji})^2$

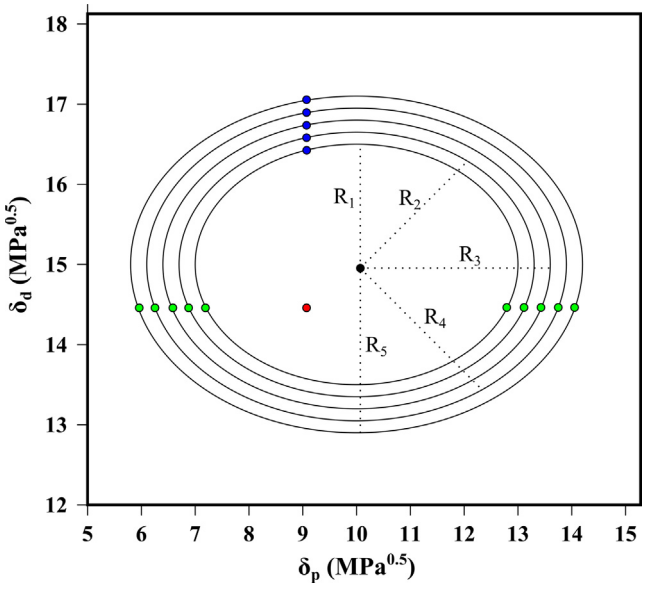

Fig. 7. Demonstration of a simulation loop: defined point of the solute (black point), random good solvent (red point), points parallel with the main axes generated on the surface of the spheroids with radii of Ra_1-Ra_5. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

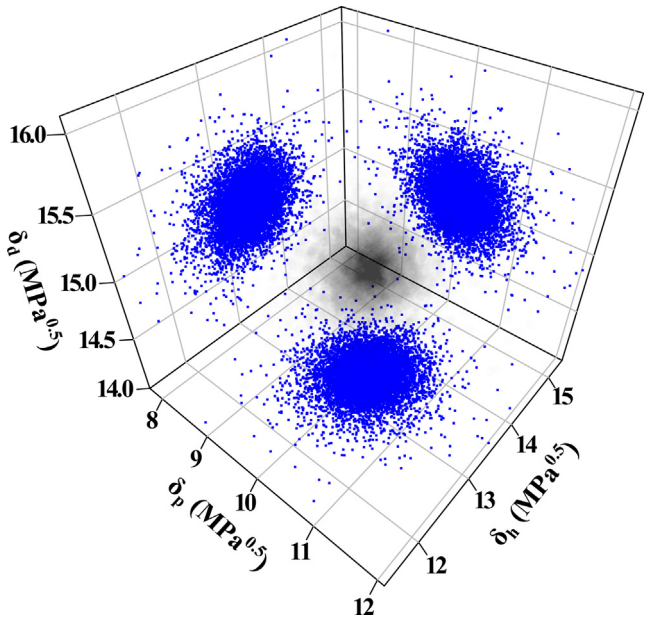

Fig. 8. Estimates of the HSP of the solute with HSP of (15, 10, 13.5) obtained with the random solvents method and use of the desirability function *d*.

by the maximization of the desirability function, and the HSP of the solute in question is estimated.

R programming language (4.1.2) in RStudio (build 372) was used to perform the calculations. The 'GA' package (3.2.2) [24] was used to minimize the desirability function. The desirability function in the cases of the random solvents method was minimized by the 'ga()' function, which uses the Genetic Algorithm. In contrast, in the case of the concentric spheroids method, the 'de()' function was more effective and therefore was used. The 'de()' uses the Differential Evolution [25] which is similar to the Genetic Algorithm, but more effective for continuous parameter space.

3.1. Results of the simulation

3.1.1. Random solvents method allocation A

When the desirability function $d = \sqrt[n]{\prod_{i=1}^{n} A_i(\delta_{d1},\ \delta_{p1},\ \delta_{h1}, R_0)}$ is to be maximized, the algorithm finds multiple solutions, especially when the maximum value (one) is found. However, the variance of the solutions is neglectable (the estimated center points are so close to each other in the Hansen space). Thus the mean of the multiple solutions can be used. Fig. 8 shows the points obtained in the 10,000 loops. The quantiles of the estimates are shown in Table 8. It can be seen that the mean (50 %) is close to the defined HSP of the solute, which implies that the method is unbiased. Also, it can be stated that with 95 % probability, the Hansen components are found in the range of 14.63–15.36 for δ_d, 9.23–10.73 for δ_p and 12.74–14.17 for δ_h.

When the desirability function $d' = \sqrt[n]{\prod_{i=1}^{n} A_i(\delta_{d1},\ \delta_{p1},\ \delta_{h1}, R_0)} * \frac{1}{\sqrt[m]{R_0}}$ is used, the uncertainty of the estimates becomes larger, as can be seen in Fig. 9 for δ_d. The same observation can be made for δ_p and δ_h. The cause of this behavior can be seen in Fig. 10. By constraining R_0 during the maximization of the desirability function d', the estimates of R_0 becomes distorted and tends to be much smaller than the expected value of four. It should be noted that the'ga()' function requires setting an interval for each variable within which it searches for the optimal values. The minimum of the searching interval for R_0 was set to two, and the solutions that would have been smaller than two are accumulated there. Due to its uncertainty increasing effect, the modified desirability function d' should not be used when the solute is expected to have HSP around the centrum of the HSP space.

3.1.2. Random solvents method allocation B

In this case, the uncertainty of the estimates is increased, and their distribution is slightly left-skewed. This is the effect of the HSP of the solute shifted towards the (left) edge of the space where generated points are available, so the spheroid is not shaped in every direction. Thus, the estimates have greater uncertainty than in the case of allocation A. The quantiles of the estimates are summarized in Table 9.

In this situation, the use of R_0 in the desirability function results in approximately the same uncertainty in the estimation. Fig. 11 shows the histograms of the estimated δ_d values, while Fig. 12 shows the distribution of the estimated R_0 values in both cases of the desirability function. The skewed distribution of R_0 in the case of *d* is the result of the spheroid not being properly shaped from every direction.

3.1.3. Extended Hansen solubility approach (EHA)

The obtained HSP of the solute in the simulated datasets are plotted in Fig. 13 and given in Table 10. With 95 % probability, the EHA estimates the HSP to be in the range of 14.88–15.12 for δ_d, 9.65–10.36 for δ_p and 13.17–13.81 for δ_h. The mean of the HSP agrees with the known HSP of the solute used in the simulation, and thus, the EHA method is proven to be mathematically accurate when the relationship between $\log(x)$ and Ra is linear. However, it should be kept in mind that if linearity is not fulfilled (which is a potential phenomenon), the EHA will result in distorted estimates of the HSP, limiting the precision of the approach.

Table 8
Quantiles of the estimates obtained in the case of allocation A.

	Quantiles of the estimates								
Hansen components	**2.5 %**	**5 %**	**10 %**	**25 %**	**50 %**	**75 %**	**90 %**	**95 %**	**97.5 %**
δ_d	14.63	14.7	14.78	14.89	15.00	15.10	15.22	15.29	15.36
δ_p	9.23	9.39	9.56	9.79	9.99	10.21	10.43	10.59	10.73
δ_h	12.74	12.89	13.03	13.25	13.47	13.68	13.88	14.03	14.17

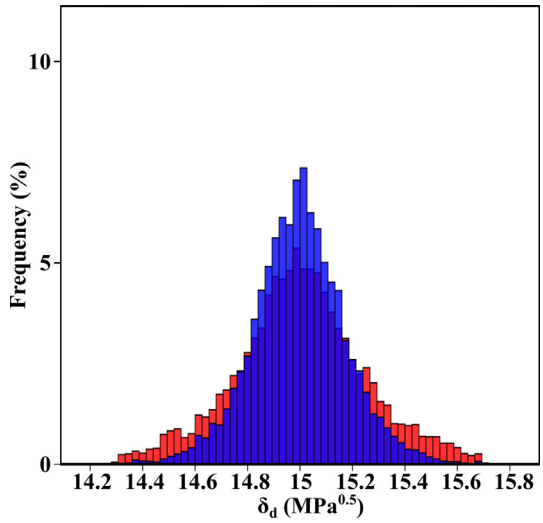

Fig. 9. Estimated δ_d values obtained using the desirability function d (blue) and d' (red); the real δ_d equals 15. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

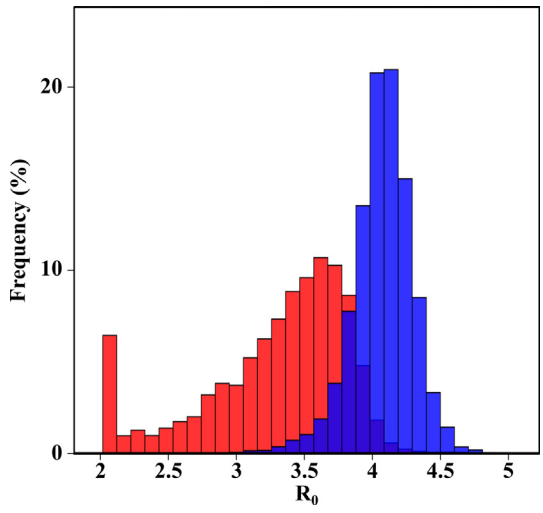

Fig. 10. Estimated R_0 values obtained using the desirability function d (blue) and d′ (red); the real R_0 equals four. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

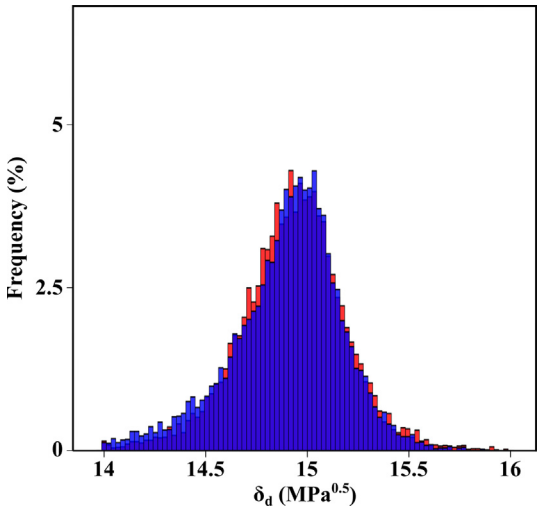

Fig. 11. Estimated δ_d values obtained using the desirability function d (blue) and d′ (red); the real δ_d equals 15. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.1.4. Gradient binary solvents method using the concentric spheroids method

The results of the simulations are depicted in Fig. 14 and given in Table 11 for the case of five fitted concentric spheroids. The coloring corresponds to the different number of fitted concentric spheroids (m = 3, 4, 5). With 95 % probability, the concentric spheroids method estimates the HSP to be in the range of 14.88–15.12 for δ_d, 9.92–10.08 for δ_p and 13.35–13.65 for δ_h when $m = 5$ (Table 11).

The uncertainty of the estimates depends on:

- the number of points available around each spheroid (fixed in the study, $n = 4$)
- the uncertainty of the points, which is the uncertainty of the solubility curve fitting and the error from the approximation of the use of Eq. (5) to define the HSP of a mixture
- the directions of the generated points (fixed in the study, parallel with the main axes)
- the number of the fitted concentric spheroids.

The more points available around each spheroid (the more bad solvents are used), the smaller the uncertainty is. The uncertainty of the solubility curve (see Fig. 4) can be decreased by increasing the number of solubility experiments with varying compositions

Table 9
Quantiles of the estimates obtained in the case of allocation B.

	Quantiles of the estimates								
Hansen components	**2.5 %**	**5 %**	**10 %**	**25 %**	**50 %**	**75 %**	**90 %**	**95 %**	**97.5 %**
δ_d	14.13	14.32	14.51	14.75	14.94	15.08	15.22	15.31	15.39
δ_p	8.05	8.4	8.79	9.3	9.72	10.05	10.33	10.51	10.68
δ_h	12.07	12.37	12.7	13.1	13.42	13.69	13.96	14.14	14.3

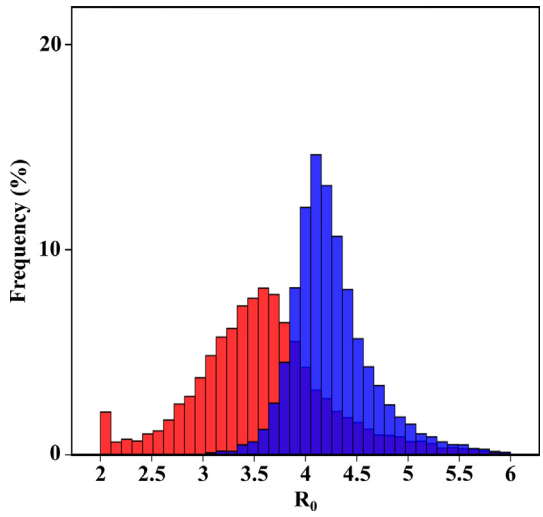

Fig. 12. Estimated R_0 values obtained using the desirability function d (blue) and d′ (red) in the case of allocation B; the real R_0 equals four. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

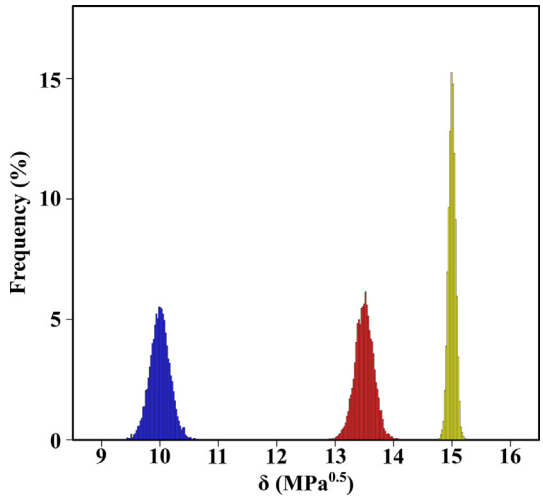

Fig. 13. HSP estimates obtained in the EHA: δ_d (yellow), δ_p (blue), δ_h (red). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of the mixtures. The directions of the points in the Hansen space should point as far from each other as possible. It can be achieved by using well-selected bad solvents. The situation used in the simulation, where the directions are perpendicular, is a close-to best-case scenario. The number of the fitted spheroids is theoretically infinity. The increment of the selected solubility levels (using the solubility curves) at which the spheroids are fitted makes the uncertainty of this component approach zero. Therefore, the more spheroids are used, the more precise the estimates are (Fig. 14). It should be noted that this is the only component of the total uncertainty that can be reduced mathematically, and the uncertainty of the other elements is always present due to the uncertainty of the measurement. Accordingly, at some point, the further increment of the spheroids will not decrease the uncertainty anymore. Based on the results of this study, the maximum number of spheroids to be fit might be around six-eight, but all in all, it depends on the magnitude of the uncertainty of the other components.

The MSE defined in Eq. (15) can be used to compare the precision of the estimation in different datasets. The MSE values obtained in the example used in Section 2.1 are in the range of 0.01–0.05 (in the cases which were accepted as appropriate). In this study, the mean of the MSE values obtained in each loop is around 0.02, the same magnitude as in the example. Thus, the magnitude of the errors (with the variance of 0.1) added to the points generated onto the spheroids (blue and green points in Fig. 7) results in an uncertainty of the HSP determination that resembles the practice.

Both of the six simulated scenarios are somewhat ideal. It is hard to find 40 uniformly distributed solvents in the Hansen space. Thus there will be a lot of redundant points, which increases the uncertainty of the estimation compared to the results of the study. Also, in the gradient binary mixtures case, it is hard to find bad solvents close to the best-case scenario (perpendicular directions). This will increase the uncertainty compared to the results of the study as well. Nevertheless, the obtained information from the simulation study is rather useful, and further studies may help improve the suggested or the earlier used methods further.

4. Discussion

While the presently used methods (except the EHA) to determine the Hansen solubility parameters of a solute categorizes the responses of the solubility measurements, the concentric spheroids method maximizes the information that can be obtained from the measurement by evaluating the responses on the continuous scale. To use the concentric spheroids method, the experiments are to be conducted according to the previously suggested gradient binary mixtures method, instead of the more widely applied random solvents method. The good solvent is to be selected so that it dissolves the solute in question as well as possible. To obtain insight regarding the location of the solute in the Hansen space (for which the determination is the ultimate goal) group contribution method might be used, or a few screening solubility tests may be conducted, and the best solvent may be chosen. The minimum number of bad solvents to be used is four, but the more solvent is used, the more the uncertainty of the HSP determination decreases. To increase the number of solubility tests using mixtures of each bad solvent and the good solvent with varying compositions is also advantageous. If a resource for 40 measurements is available, in the lack of further knowledge, it is reasonable to use five bad solvents and eight solubility tests with each instead of using four bad solvents and ten tests with each. The maximization of the information from the gradient binary mixtures method is achievable when the new proposed desirability function is used. Based on the simulation study, which seems to resemble the practice, it

Table 10
Quantiles of the estimates obtained in the EHA.

	Quantiles of the estimates								
Hansen components	**2.5 %**	**5 %**	**10 %**	**25 %**	**50 %**	**75 %**	**90 %**	**95 %**	**97.5 %**
δ_d	14.88	14.9	14.92	14.96	15.00	15.04	15.08	15.1	15.12
δ_p	9.65	9.71	9.78	9.86	10.00	10.11	10.22	10.29	10.36
δ_h	13.17	13.23	13.30	13.39	13.50	13.61	13.70	13.76	13.81

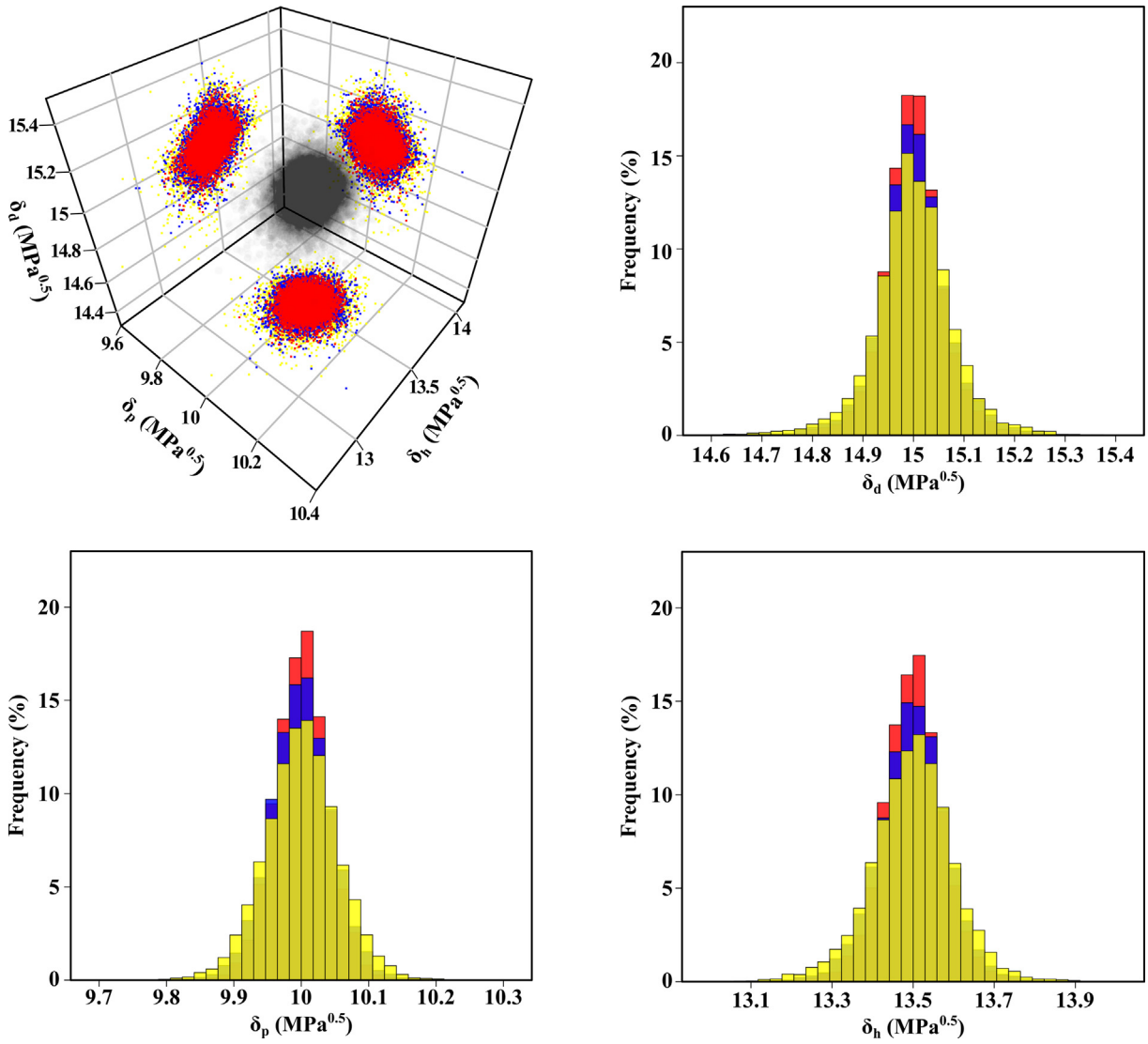

Fig. 14. Estimates obtained with the gradient binary mixtures method using a different number of concentric spheroids: $m = 3$ (yellow), $m = 4$ (blue), $m = 5$ (red). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

was found that the random solvents method estimates the HSP of the solute (15, 10, 13.5) to be in the range of 14.63–15.36 for δ_d, 9.23–10.73 for δ_p and 12.74–14.17 for δ_h with 95 % probability. The concentric spheroids method estimates the HSP to be in the range of 14.88–15.12 for δ_d, 9.92–10.08 for δ_p and 13.35–13.65 for δ_h with 95 % probability. The EHA results in similar estimates for δ_d, but its precision is slightly decreased for δ_p (9.65–10.36) and δ_h (13.17–13.81). The superior precision of the methods where the solubility is handled as a continuous variable is evident. The comparison of EHA and the newly proposed method requires further investigation using real datasets. Also, the appropriateness of the assumption regarding the linear connection between $\log(x)$ and Ra in the EHA is to be studied more deeply. If linearity is not fulfilled, the HSP estimates become distorted, and their precision decreases. The simulation study also showed that the desirability function, which restricts the radius R_0 in the random solvents method, is not justified and may not be used due to its uncertainty-increasing effect in certain cases.

CRediT authorship contribution statement

Máté Mihalovits: Conceptualization, Methodology, Software, Formal analysis, Writing - original draft, Writing - review & editing.

Table 11
Quantiles of the estimates obtained in the concentric spheroids method when $m = 5$.

	Quantiles of the estimates								
Hansen components	**2.5 %**	**5 %**	**10 %**	**25 %**	**50 %**	**75 %**	**90 %**	**95 %**	**97.5 %**
δ_d	14.88	14.9	14.93	14.96	15.00	15.03	15.07	15.1	15.12
δ_p	9.92	9.94	9.95	9.97	10.00	10.03	10.05	10.06	10.08
δ_h	13.35	13.38	13.41	13.45	13.50	13.54	13.59	13.62	13.65

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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