

A differential approach to calculating osmotic equilibrium for multisolvent systems

Pedro de Alcântara Pessoa Filho*

Biochemical Engineering Laboratory, Chemical Engineering Department, Escola Politécnica, Universidade de São Paulo, Caixa Postal 61548, CEP 05424-970 São Paulo, SP, Brazil

Available online 11 July 2006

Abstract

A differential approach to the calculation of osmotic pressure of multisolvent systems within the Lewis–Randall framework is presented in this paper. Exact differential equations relating the osmotic pressure and the system composition along paths of constant solvent chemical potential are obtained and numerically solved. Although even for the simple case of an ideal solution no analytic expression for the osmotic pressure can be obtained, the system of differential equations does not pose numerical difficulties to be solved. Examples of the use of the proposed methodology are presented using the two-suffix Margules and Flory–Huggins equations, allowing an assessment of the influence of liquid-phase non-ideality on the performance of the method, and showing that it can be applied even for systems wherein liquid–liquid phase equilibrium occurs.

© 2006 Elsevier B.V. All rights reserved.

Keywords: Osmotic pressure; Differential approach; Gibbs energy

1. Introduction

There exists a large variety of systems wherein osmotic equilibrium takes place, not only in many fields of chemical industry, but also in apparently unrelated areas, being unnecessary to stress how significant the phenomenon itself is. However, specifically for thermodynamic modeling, the description of osmotic equilibrium is also important for it may appear as intermediate step in phase equilibrium calculations. For instance, the use of models based on the McMillan–Mayer [1] formalism for liquid–liquid calculations implies the equality of osmotic pressure in both equilibrium phases as a necessary condition [2].

Besides systems wherein osmosis actually occurs, for modeling reasons many kinds of mixtures can be described as a solute dissolved in a pure or mixed medium, e.g., an electrolyte in an aqueous solution, a protein in an aqueous saline solution. If there exists a process underlying the calculation, the role of a constituent substance (either solute or solvent) depends on the process itself. Just to cite a single example, for the osmotic processing of foods water is usually considered to be the only solvent, and all soluble substances are solutes [3]. However, for the sole purpose of describing the thermodynamic state of a system, there may be a certain degree of arbitrariness (since no real osmotic equilibrium takes place), and the choice of which compounds are solvents or solutes depends on which model is being used to describe the system. For instance, the electrolyte is considered to be the solute when dissolved in an aqueous alcoholic solution, and the medium properties necessary to calculate the long-range term of the excess Gibbs energy model may be considered an average of those of water and alcohol [4,5]; however, the electrolyte is considered to be a co-solvent when the studying the behavior of proteins in aqueous salt solutions [2].

Osmotic equilibrium calculations involving multisolvent systems often appear in the context of McMillan–Mayer descriptions of solution properties. This kind of approach has gained increasing attention recently due to the use of this framework to describe the phase behavior of protein solutions [6–9]: since it is very difficult to conduct Monte Carlo or molecular dynamic simulations accounting for every present species, all substances but the protein are considered to constitute the solvent, whose properties are calculated to be an average of theirs. Besides this one, another field wherein this approach is fundamental is the description of mixed-

* Tel.: +55 11 3091 1106; fax: +55 11 3091 2284.

E-mail address: pedro.pessoa@poli.usp.br.

solvent salt solutions. Following the pioneering work by Cardoso and O’Connell [4], some of the work conducted is concerned with the conversion between McMillan–Mayer and Lewis–Randall framework [5,10]; independently of any theoretical aspect, models for these systems within either framework are widely found in literature [11].

A methodology for calculating the osmotic equilibrium within the Lewis–Randall framework is presented in this paper. Differential equations relating pressure and composition are obtained and numerically solved for model systems. Using this approach, not only the osmotic equilibrium state can be calculated (which might be accomplished by solving the equilibrium conditions), but also the whole curve of osmotic pressure as a function of solute concentration can be recovered. The approach is completely general, and therefore can be used to describe osmotic equilibrium for any system within this framework.

2. Theoretical background

It is usual to distinguish two different categories of description in the thermodynamic modeling of solutions: the Lewis–Randall and the McMillan–Mayer frameworks. The Lewis–Randall framework corresponds to the classic description of mixtures: expressions for the excess Gibbs energy of mixtures are developed within it. The independent variables that define a thermodynamic state are temperature, pressure and composition, and the chemical potential of each species can be obtained as function of these independent variables through proper differentiation. On the other hand, in the McMillan–Mayer framework a solution is described as a collection of solute molecules in a continuum: therefore, the solvent (either pure or a mixture) is regarded simply as a medium wherein the interactions between solute molecules occur. Models within this framework are constituted by a Legendre transform of the Helmholtz energy, and have as independent variables temperature, volume, solute fractions and solvent chemical potential: the solute chemical potential and the osmotic pressure can be obtained by proper differentiation. One of the most important aspects to be stressed is that the Lewis–Randall framework establishes no *a priori* distinction between solutes and solvents (when asymmetric expressions for the Gibbs energy are used, this distinction is introduced at the level of the model), whereas the McMillan–Mayer framework entails an unambiguous dissimilarity between them. Although the subject of this paper – the calculation of the osmotic pressure – is often related to the McMillan–Mayer framework, the whole development is based on Gibbs energy models within the Lewis–Randall framework.

Let us consider a system with a composition ξ'_{S_i} , with $i = 1, \dots, n$ (S representing the solvents, and ξ representing any fraction, such as mass, volume or number fraction) and ξ'_R (R representing the solute), separated from other system containing only solvents by a semi-permeable membrane that allows the exchange of solvent molecules, but not of solute ones. A general scheme of this equilibrium is presented in Fig. 1; cell A is called “inside solution” and cell B is called “outside solution” [2]. Equilibrium can be established if there is a difference of pressure across the membrane; the equilibrium condition, besides the equality of temperatures in both phases, is

$$\mu'_{S_i}(T, p', \xi'_{S_i}, \xi'_R) = \mu''_{S_i}(T, p'', \xi''_{S_i}, \xi''_R = 0), \quad i = 1, \dots, n \quad (1)$$

wherein μ_i is the chemical potential of compound i . One possible method to solve the system of equations thus defined would be to simply modify existing liquid–liquid phase equilibrium algorithms. While the complexity introduced by considering the pressure to be a defining variable is not critical itself, convergence may be slow due to the relative insensitiveness of liquid phases (when far from critical conditions) with respect to changes in pressure.

An alternative solution can be obtained by considering that in the space of variables (ξ, P) both states belong to a subspace wherein:

$$\mu'_{S_i}(T, p', \xi'_{S_i}, \xi'_R) = \mu_{S_i}(T, p, \xi_{S_i}, \xi_R) \quad (2)$$

Each one of the cells is specified by $n + 2$ variables: temperature, pressure and n fractions (recalling that the total number of compounds is $n + 1$); hence, for both cells the total number of independent variables is thus $2n + 4$. The equilibrium conditions impose the equality of temperature and chemical potentials of each one of the solvents in both cells, with $n + 1$ restrictive equations. Therefore, the number of degrees of freedom is $n + 3$. The composition, temperature and pressure of cell A are usually defined beforehand, lowering the degrees of freedom to one: once the solute fraction in cell B is set ($\xi''_R = 0$), the problem is completely defined (by hypothesis, the

Cell A	Cell B
$\xi'_{S_i}, i = 1, \dots, n$	$\xi''_{S_i}, i = 1, \dots, n$
ξ'_R	$\xi''_R = 0$
p'	p''
T	T

Fig. 1. General scheme of an osmotic equilibrium cell for a multisolvent system.

pressure p' is high enough that pressure p'' is strictly positive). Although the osmotic pressure is calculated when the solute fraction in cell B vanishes, the problem is mathematically well posed also for any other value of ξ_R'' .

Therefore, using the solute fraction ξ_R as parameter, the previous Eq. (2) defines a subspace wherein:

$$\frac{d\mu_{S_i}}{d\xi_R} = 0 \quad (3)$$

As stated before, within the Lewis–Randall framework the chemical potential of any species (either solvent or solute) can be expressed as a function of temperature, pressure and composition. This previous equation can hence be written:

$$d\mu_{S_i} = \sum_{j=1}^n \left(\frac{\partial \mu_{S_i}}{\partial \xi_{S_j}} \right)_{T,p, [\xi]} d\xi_{S_j} + \left(\frac{\partial \mu_{S_i}}{\partial p} \right)_{T, [\xi]} dp = 0 \quad (4)$$

In order to avoid excessive lettering, the subscript $[\xi]$ is herein used to indicate that only the pertinent fractions are to be kept constant—for each derivative, all fractions used to define the state except the fraction with respect to which the derivative is calculated. One must also consider the restriction that:

$$\sum_{j=1}^n d\xi_{S_j} + d\xi_R = 0 \quad (5)$$

One can arbitrarily choose one of the solvents to be used as a reference, whose composition is to be eliminated by using this previous equation. Considering S_k as the reference solvent, the following set of equations is obtained:

$$\sum_{j=1, j \neq k}^n \left(\left(\frac{\partial \mu_{S_i}}{\partial \xi_{S_j}} \right)_{T,p, [\xi]} - \left(\frac{\partial \mu_{S_i}}{\partial \xi_{S_k}} \right)_{T,p, [\xi]} \right) d\xi_{S_j} - \left(\frac{\partial \mu_{S_i}}{\partial \xi_{S_k}} \right)_{T,p, [\xi]} d\xi_R + \bar{V}_{S_i} dp = 0 \quad (6)$$

Along the equilibrium curve:

$$\sum_{j=1, j \neq k}^n \left(\left(\frac{\partial \mu_{S_i}}{\partial \xi_{S_j}} \right)_{T,p, [\xi]} - \left(\frac{\partial \mu_{S_i}}{\partial \xi_{S_k}} \right)_{T,p, [\xi]} \right) \frac{d\xi_{S_j}}{d\xi_R} + \bar{V}_{S_i} \frac{dp}{d\xi_R} = \left(\frac{\partial \mu_{S_i}}{\partial \xi_{S_k}} \right)_{T,p, [\xi]} \quad (7)$$

This is a system of n differential equations with n functions. Eq. (7) actually describes a chain of osmotic cells with infinitesimal differences in solute concentration. Therefore, for a certain composition and pressure, it is possible to calculate how the composition and pressure shall vary in a path wherein the chemical potential of all solvent species is kept constant. The derivative of the fraction of compound S_k can be calculated through the following equation:

$$\frac{d\xi_{S_k}}{d\xi_R} = - \sum_{j=1, j \neq k}^n \frac{d\xi_{S_j}}{d\xi_R} - 1 \quad (8)$$

Thus, starting at the conditions of the inside solution, it is possible to calculate by numerical integration the composition of the outside solution and to obtain a function $\Pi(\xi_R)$. In a general sense this is a boundary-value problem, for the value of $\Pi(\xi_R')$ is unknown. However, if partial volumes can be considered to be pressure-independent – which is a reasonable assumption for most liquid solutions – the resulting set of equation is an initial-value problem. The methodology of defining differential equations that must be satisfied through an equilibrium path is known as *differential approach* [12].

2.1. Application to ternary systems

Further insight in the application of this methodology can be gained if one restricts the attention to a ternary system comprising a single solute and two solvents. In this case, one gets the set of equations:

$$d\mu_{S_1} = \left(\frac{\partial \mu_{S_1}}{\partial \xi_{S_1}} \right)_{T,p, \xi_{S_2}} d\xi_{S_1} + \left(\frac{\partial \mu_{S_1}}{\partial \xi_{S_2}} \right)_{T,p, \xi_{S_1}} d\xi_{S_2} + \left(\frac{\partial \mu_{S_1}}{\partial p} \right)_{T, \xi_{S_1}, \xi_{S_2}} dp = 0 \quad (9)$$

and

$$d\mu_{S_2} = \left(\frac{\partial \mu_{S_2}}{\partial \xi_{S_1}} \right)_{T,p, \xi_{S_2}} d\xi_{S_1} + \left(\frac{\partial \mu_{S_2}}{\partial \xi_{S_2}} \right)_{T,p, \xi_{S_1}} d\xi_{S_2} + \left(\frac{\partial \mu_{S_2}}{\partial p} \right)_{T, \xi_{S_1}, \xi_{S_2}} dp = 0 \quad (10)$$

Following the previous procedure, one can choose solvent S_1 as the reference compound. Therefore:

$$\left(\frac{\partial\mu_{S_1}}{\partial\xi_{S_2}}\right)_{T,p,\xi_{S_2}}(-d\xi_{S_2} - d\xi_R) + \left(\frac{\partial\mu_{S_1}}{\partial\xi_{S_2}}\right)_{T,p,\xi_{S_1}}d\xi_{S_2} + \left(\frac{\partial\mu_{S_1}}{\partial p}\right)_{T,\xi_{S_1},\xi_{S_2}}dp = 0 \quad (11)$$

and

$$\left(\frac{\partial\mu_{S_2}}{\partial\xi_{S_1}}\right)_{T,p,\xi_{S_2}}(-d\xi_{S_2} - d\xi_R) + \left(\frac{\partial\mu_{S_2}}{\partial\xi_{S_2}}\right)_{T,p,\xi_{S_1}}d\xi_{S_2} + \left(\frac{\partial\mu_{S_2}}{\partial p}\right)_{T,\xi_{S_1},\xi_{S_2}}dp = 0 \quad (12)$$

Rearranging:

$$\left(\left(\frac{\partial\mu_{S_1}}{\partial\xi_{S_2}}\right)_{T,p,\xi_{S_1}} - \left(\frac{\partial\mu_{S_1}}{\partial\xi_{S_2}}\right)_{T,p,\xi_{S_2}}\right)d\xi_{S_2} - \left(\frac{\partial\mu_{S_1}}{\partial\xi_{S_1}}\right)_{T,p,\xi_{S_2}}d\xi_R + \left(\frac{\partial\mu_{S_1}}{\partial p}\right)_{T,\xi_{S_1},\xi_{S_2}}dp = 0 \quad (13)$$

and

$$\left(\left(\frac{\partial\mu_{S_2}}{\partial\xi_{S_2}}\right)_{T,p,\xi_{S_1}} - \left(\frac{\partial\mu_{S_2}}{\partial\xi_{S_1}}\right)_{T,p,\xi_{S_2}}\right)d\xi_{S_2} - \left(\frac{\partial\mu_{S_2}}{\partial\xi_{S_1}}\right)_{T,p,\xi_{S_2}}d\xi_R + \left(\frac{\partial\mu_{S_2}}{\partial p}\right)_{T,\xi_{S_1},\xi_{S_2}}dp = 0 \quad (14)$$

From the above equations:

$$dp = -\frac{1}{\bar{V}_{S_1}}\left(\left(\frac{\partial\mu_{S_1}}{\partial\xi_{S_2}}\right)_{T,p,\xi_{S_1}} - \left(\frac{\partial\mu_{S_1}}{\partial\xi_{S_2}}\right)_{T,p,\xi_{S_2}}\right)d\xi_{S_2} + \frac{1}{\bar{V}_{S_1}}\left(\frac{\partial\mu_{S_1}}{\partial\xi_{S_1}}\right)_{T,p,\xi_{S_2}}d\xi_R \quad (15)$$

$$dp = -\frac{1}{\bar{V}_{S_2}}\left(\left(\frac{\partial\mu_{S_2}}{\partial\xi_{S_2}}\right)_{T,p,\xi_{S_1}} - \left(\frac{\partial\mu_{S_2}}{\partial\xi_{S_1}}\right)_{T,p,\xi_{S_2}}\right)d\xi_{S_2} + \frac{1}{\bar{V}_{S_2}}\left(\frac{\partial\mu_{S_2}}{\partial\xi_{S_1}}\right)_{T,p,\xi_{S_2}}d\xi_R \quad (16)$$

wherein \bar{V}_i is the partial volume of compound i . Therefore:

$$\frac{d\xi_{S_2}}{d\xi_R} = \frac{(1/\bar{V}_{S_2})(\partial\mu_{S_2}/\partial\xi_{S_1})_{T,p,\xi_{S_2}} - (1/\bar{V}_{S_1})(\partial\mu_{S_1}/\partial\xi_{S_1})_{T,p,\xi_{S_2}}}{(1/\bar{V}_{S_1})((\partial\mu_{S_1}/\partial\xi_{S_1})_{T,p,\xi_{S_2}} - (\partial\mu_{S_1}/\partial\xi_{S_2})_{T,p,\xi_{S_1}}) + (1/\bar{V}_{S_2})((\partial\mu_{S_2}/\partial\xi_{S_2})_{T,p,\xi_{S_1}} - (\partial\mu_{S_2}/\partial\xi_{S_1})_{T,p,\xi_{S_2}})} \quad (17)$$

It can be easily seen that:

$$\frac{d\xi_{S_1}}{d\xi_R} = \frac{(1/\bar{V}_{S_1})(\partial\mu_{S_1}/\partial\xi_{S_2})_{T,p,\xi_{S_1}} - (1/\bar{V}_{S_2})(\partial\mu_{S_2}/\partial\xi_{S_2})_{T,p,\xi_{S_1}}}{(1/\bar{V}_{S_1})((\partial\mu_{S_1}/\partial\xi_{S_1})_{T,p,\xi_{S_2}} - (\partial\mu_{S_1}/\partial\xi_{S_2})_{T,p,\xi_{S_1}}) + (1/\bar{V}_{S_2})((\partial\mu_{S_2}/\partial\xi_{S_2})_{T,p,\xi_{S_1}} - (\partial\mu_{S_2}/\partial\xi_{S_1})_{T,p,\xi_{S_2}})} \quad (18)$$

The derivative of the pressure can be calculated by either equation indistinctly:

$$\frac{dp}{d\xi_R} = -\frac{1}{\bar{V}_{S_1}}\left(\left(\frac{\partial\mu_{S_1}}{\partial\xi_{S_2}}\right)_{T,p,\xi_{S_1}} - \left(\frac{\partial\mu_{S_1}}{\partial\xi_{S_2}}\right)_{T,p,\xi_{S_2}}\right)\frac{d\xi_{S_2}}{d\xi_R} + \frac{1}{\bar{V}_{S_1}}\left(\frac{\partial\mu_{S_1}}{\partial\xi_{S_1}}\right)_{T,p,\xi_{S_2}} \quad (19)$$

which can be simplified as

$$\frac{dp}{d\xi_R} = \frac{(1/\bar{V}_{S_1}\bar{V}_{S_2})((\partial\mu_{S_2}/\partial\xi_{S_2})_{T,p,\xi_{S_1}}(\partial\mu_{S_1}/\partial\xi_{S_1})_{T,p,\xi_{S_2}} - (\partial\mu_{S_2}/\partial\xi_{S_1})_{T,p,\xi_{S_2}}(\partial\mu_{S_1}/\partial\xi_{S_2})_{T,p,\xi_{S_1}})}{(1/\bar{V}_{S_1})((\partial\mu_{S_1}/\partial\xi_{S_1})_{T,p,\xi_{S_2}} - (\partial\mu_{S_1}/\partial\xi_{S_2})_{T,p,\xi_{S_1}}) + (1/\bar{V}_{S_2})((\partial\mu_{S_2}/\partial\xi_{S_2})_{T,p,\xi_{S_1}} - (\partial\mu_{S_2}/\partial\xi_{S_1})_{T,p,\xi_{S_2}})} \quad (20)$$

As might be anticipated, this expression does not depend on the solvent chosen as reference.

2.2. Simplifying assumptions

Let us suppose that an expression for the chemical potential is known, such that:

$$\mu_i(T, p, \xi) = \mu_i^{\text{ref}}(T, p^{\text{ref}}, \xi^{\text{ref}}) + RT \ln a_i(T, p, \xi) \quad (21)$$

wherein a_i is the activity of compound i . It is a usual procedure to separate the activity into two parts:

$$a_i(T, p, \xi) = a_i^{\text{PI}}(T, \xi)a_i^{\text{PD}}(T, p, \xi) \quad (22)$$

The PI (pressure independent) part is that usually given by excess Gibbs energy models. The PD (pressure dependent) is given by

$$a_i^{\text{PD}}(T, p, \xi) = \exp\left(\int_{p^{\text{ref}}}^p \frac{\bar{V}_i}{RT} dp\right) \quad (23)$$

This part is usually ignored in low-pressure equilibrium calculations (either liquid–liquid or liquid–vapor), but must be retained in osmotic pressure calculations. Another usual simplifying assumption is that the partial volume is independent both of composition and pressure. Therefore, one gets for compound S_1 in a ternary system, for instance:

$$\left(\frac{\partial \mu_{S_1}}{\partial \xi_{S_1}}\right)_{\xi_{S_2}, p} = RT \left(\frac{\partial \ln a_{S_1}^{\text{PI}}}{\partial \xi_{S_1}}\right)_{\xi_{S_2}} \quad (24)$$

and

$$\left(\frac{\partial \mu_{S_1}}{\partial p}\right)_{\xi_{S_1}, \xi_{S_2}} = \bar{V}_{S_1} \quad (25)$$

and so on. As stated before, with these assumptions the boundary-value problem is changed into an initial-value problem, therefore, allowing a direct integration.

2.3. Gibbs–Duhem equation

For a non-isobaric change, the Gibbs–Duhem equation can be written as

$$x_R d\mu_R + \sum_{i=1}^n x_{S_i} d\mu_{S_i} = V dp \quad (26)$$

wherein x_i is the number fraction of compound i and V is the volume per amount of substance of the mixture. Along a path defined by Eq. (7), there will be no change in the solvent chemical potential. Therefore:

$$x_R d\mu_R = V dp \quad (27)$$

Since μ_R , V and p are ultimately functions of x_R , Eq. (27) can in principle be integrated. Considering the general expression for the chemical potential, Eq. (21), one gets:

$$\int_{\mu_R(x_R \rightarrow 0)}^{\mu_R(x_R)} x_R d\mu_R = \int_0^{x_R} V \frac{dp}{dx_R} dx_R \quad (28)$$

The right side of the above equation can be calculated using the results from Eq. (7), while the left term can be calculated by

$$\int_{\mu_R(x_R \rightarrow 0)}^{\mu_R(x_R)} x_R d\mu_R = x_R \mu_R \Big|_{x_R \rightarrow 0}^{x_R} - \int_0^{x_R} \mu_R dx_R = x_R RT \ln a_R - RT \int_0^{x_R} \ln a_R dx_R \quad (29)$$

This equation shall be verified not only for the cell composition, but also for any intermediate composition. Although it is tantalizing to simplify them, these equations are to be numerically calculated, since the integration path is not known *a priori*. Moreover, one cannot forget that the activity in this previous equation contains the pressure-dependent term according to Eq. (22). Eq. (29) can thus be used to verify whether the path calculated through Eq. (7) does define a path of constant solvent chemical potential.

2.4. Implementation

The set of differential equations defined by Eq. (7) was solved using the Runge–Kutta fourth order method, using Maple™ programming language. Final results were checked both by using the osmotic equilibrium criterion defined by Eq. (1) and by applying the Gibbs–Duhem equation for the whole integration path. All calculations were carried out with the standard precision of the software, although only four digits are herein presented for the sake of readability.

3. Results and discussion

The presented methodology was applied with similar efficacy to calculating the osmotic equilibrium of systems whose liquid phase non-ideality is described by various G^{EX} models (Margules, Flory–Huggins, Wilson, NRTL). As the objective of this work is to establish the methodology itself, assessing the influence of the non-ideality on the performance of the method, results for model systems are presented firstly; results for a real system (a protein in a polymer solution, described by the Flory–Huggins equation) are shown afterwards.

3.1. Ternary ideal solution

For a liquid phase constituted by an ideal solution the previous equations can be greatly simplified, though no analytical solution for the composition of the outside solution can be achieved. Let the fraction ξ be the number fraction, and let V_i represent the volume of the pure species i . Therefore:

$$\frac{dx_{S_1}}{dx_R} = -\frac{x_{S_1}V_{S_1}}{x_{S_1}V_{S_1} + x_{S_2}V_{S_2}} \quad (30)$$

and, symmetrically:

$$\frac{dx_{S_2}}{dx_R} = -\frac{x_{S_2}V_{S_2}}{x_{S_1}V_{S_1} + x_{S_2}V_{S_2}} \quad (31)$$

For the pressure, one gets:

$$\frac{dp}{dx_R} = \frac{RT}{x_{S_1}V_{S_1} + x_{S_2}V_{S_2}} \quad (32)$$

It can be seen that no general analytical solution can be found even in this simple case. However, the same statement is true for the integral formulation given by Eq. (1). Numerical results for calculations involving ternary ideal solutions are presented in next section as trivial cases of the Margules equation.

3.2. Ternary non-ideal mixtures—Margules equation

In order to assess how the non-ideality of the liquid mixture can affect the efficiency of this methodology, a system whose non-ideality is given by the two-suffix Margules equation is considered. Although this model is not widely used for phase equilibrium calculations, it is the simplest expression for excess Gibbs energy allowing for liquid-phase non-ideality. Since the aim of this work is to investigate the methodology itself, general conclusions shall apply independently of this choice. If one considers that there is no excess volume upon mixing, the model is self-consistent.

The expression for the excess Gibbs energy (G^{EX}) for a mixture of solvents S_1 and S_2 and a solute R is given by

$$\frac{G^{\text{EX}}}{RT} = A_{S_1R}x_{S_1}x_R + A_{S_2R}x_{S_2}x_R + A_{S_1S_2}x_{S_1}x_{S_2} \quad (33)$$

wherein A_{ij} is a adjustable parameter related to compounds i and j . Pertinent derivatives are presented in Appendix A.

In order to better characterize the mixture of solvents, a solute-free fraction y_{S_1} is defined:

$$y_{S_1} = \frac{x_{S_1}}{x_{S_1} + x_{S_2}} \quad (34)$$

Some examples of osmotic equilibrium calculations are presented in Table 1, considering $V_{S_1} = 18.0 \text{ cm}^3 \text{ mol}^{-1}$ and $V_{S_2} = 200.0 \text{ cm}^3 \text{ mol}^{-1}$. These results allow a direct analysis of the influence of the parameters (and hence of the non-ideality) on the calculated osmotic pressure and outside cell composition. For instance, considering systems 1–4 in Table 1, it can be seen that positive deviations from the ideal behavior between the solvents, related to higher values of parameter $A_{S_1S_2}$ in Eq. (33), lead to lower values of the concentration of the solvent with smaller volume (S_1) in the equilibrium cell, while negative deviations lead to higher concentrations. From systems 5–8, it can be inferred that positive deviations from the ideal behavior between a solute and

Table 1
Results for osmotic pressure calculations for systems described by the Margules equation at 298.15 K

System	$A_{S_1S_2}$	A_{S_1R}	A_{S_2R}	x'_R	y'_{S_1}	x''_{S_1}	Π (bar)
1	0.0	0.0	0.0	0.02	0.5	0.4916	4.563
2	0.5	0.0	0.0	0.02	0.5	0.4888	4.563
3	1.0	0.0	0.0	0.02	0.5	0.4833	4.554
4	-1.0	0.0	0.0	0.02	0.5	0.4944	4.551
5	0.0	1.0	0.0	0.02	0.5	0.4966	4.544
6	0.0	-1.0	0.0	0.02	0.5	0.4866	4.559
7	0.0	0.0	1.0	0.02	0.5	0.4868	4.470
8	0.0	0.0	-1.0	0.02	0.5	0.4964	4.635
9	1.9	0.0	0.0	0.02	0.5	0.3865	4.188
10	0.0	0.0	0.0	0.1	0.5	0.4576	23.14
11	1.0	0.0	0.0	0.1	0.5	0.4173	22.93

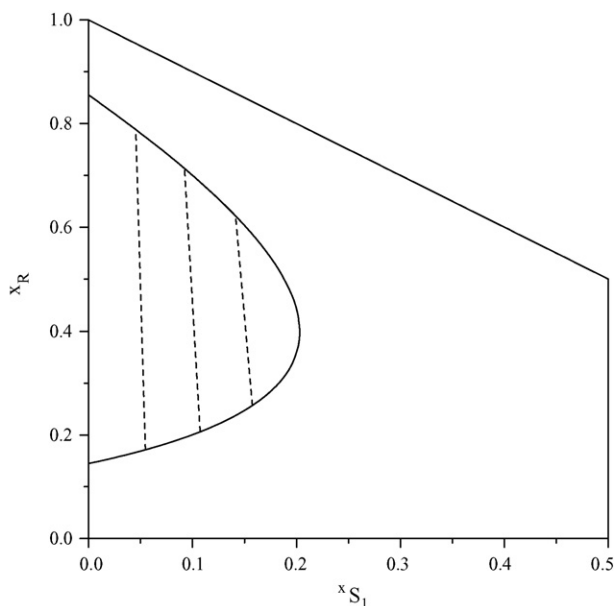


Fig. 2. Phase equilibrium diagram of a hypothetical system formed by a solute partially miscible in a solvent. Continuous line: binodal curve; dashed lines: tie lines.

one of the solvents increase the concentration of this solvent in the equilibrium cell, while negative deviations lead to a decrease. Although the results seem at first to indicate no expressive difference in the composition when the outside cell is calculated, the situation changes significantly when highly positive deviations from the ideal behavior are present: system 9, wherein the solvents are close to partial miscibility, presents strong deviations on the calculated composition of the equilibrium cell and on the calculated osmotic pressure. High differences from the ideal behavior also can be noticed for higher solute fractions, as inferred from systems 10 and 11; even for the ideal behavior shown in system 10, the hypothesis that the proportion between the solvents is constant in both cells is a very poor assumption. Concerning the methodology itself, besides the fact that these equilibria could be straightforwardly calculated, another significant feature of the presented procedure is that the computation time is insensitive to the non-ideality of the mixture.

In order to verify whether the present approach applies also for situations wherein phase equilibrium takes place, a hypothetical system with the phase behavior presented in Fig. 2 is considered—parameters for this system are $A_{S_1R} = 0.5$, $A_{S_2R} = 2.5$ and $A_{S_1S_2} = 0.20$, and volumes of pure compounds are the same as before. Results for osmotic equilibrium calculations for the three equilibrium compositions depicted in this figure are presented in Table 2. In all cases, calculated osmotic pressure and equilibrium cell compositions are equal within the limit of the numeric precision. Since partial volumes were not considered to depend on composition, this result could have been anticipated directly from Eq. (1). Concerning the methodology, one can see that it can be applied for situations wherein phase separation occurs—since no restriction was made on the stability along the integration path, unstable systems may exist therein. In this case, the analogy with the curve generated by a volumetric equation of state follows straightforwardly: in Fig. 3, the osmotic pressure for systems at constant solvent chemical potential is presented, each curve containing one of the systems presented in Table 2.

However, different results are obtained when the solvents themselves present partial miscibility—an example is given by the Margules equation with parameters $A_{S_1R} = 0.1$, $A_{S_2R} = 0.5$ and $A_{S_1S_2} = 3.0$, whose equilibrium curve is presented in Fig. 4; results for osmotic equilibrium calculations for the presented equilibrium compositions are shown in Table 3. It can be seen that neither the calculated osmotic pressure nor the composition of the outside cells are the same. In fact, they do not even correspond

Table 2
Results for osmotic pressure calculations for systems presenting liquid–liquid separation at 298.15 K, solute partially miscible in one of the solvents

System	Phase	x'_R	x'_{S_1}	x''_{S_1}	Π (bar)
12	I	0.1712	0.05452	0.04289	58.48
	II	0.7885	0.04533	0.04289	58.48
13	I	0.2060	0.1072	0.08319	66.09
	II	0.7132	0.09219	0.08319	66.09
14	I	0.2567	0.1575	0.1210	74.41
	II	0.6216	0.1413	0.1210	74.41

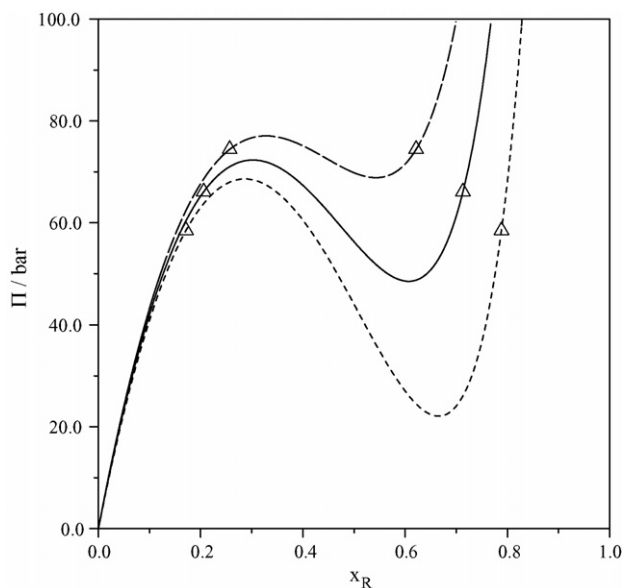


Fig. 3. Osmotic pressure for systems at constant solvent chemical potential. Dashed line: curve for system 12 (referred to Table 2); continuous line: curve for system 13; dotted line: curve for system 14; symbols (triangles): equilibrium points.

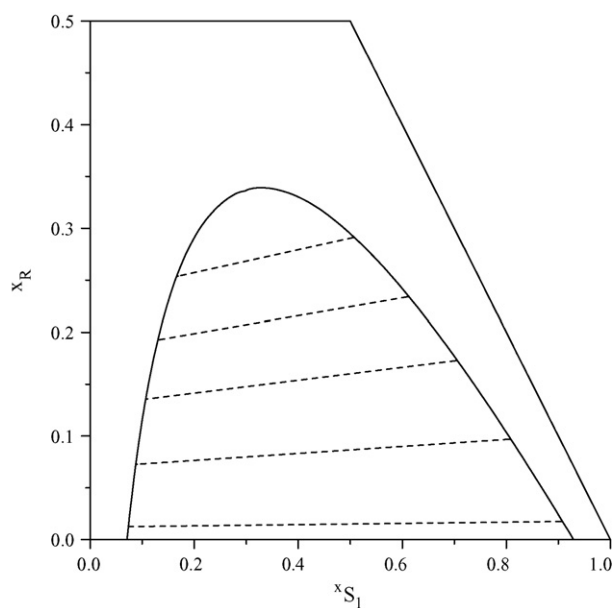


Fig. 4. Phase equilibrium diagram of a hypothetical system formed by two solvents partially miscible. Continuous line: binodal curve; dashed lines: tie lines.

Table 3
Results for osmotic pressure calculations for systems presenting liquid–liquid separation at 298.15 K, partially miscible solvents

System	Phase	x'_R	x'_{S1}	x''_{S1}	Π (bar)
15	I	0.001170	0.9279	0.9291	1.311
	II	0.0008302	0.07089	0.07062	0.4297
16	I	0.002339	0.9265	0.9288	2.622
	II	0.001661	0.07105	0.07052	0.8595
17	I	0.01050	0.9166	0.9273	11.79
	II	0.007490	0.07224	0.06983	3.869

to the equilibrium compositions of a solute-free system: calculated equilibrium compositions for the solute-free system would be $x_{S_1}^I = 0.9293$ and $x_{S_1}^{II} = 0.07072$.

A careful analysis shows that the calculated equilibrium phase that is rich in solvent S_1 lies in the two-phase region, and would naturally split into two liquid phases. This may not be a problem when describing real systems, since the pair S_1 and S_2 would not be *a priori* considered to be a composite solvent. However, it shows that care must be exercised when modeling systems wherein the role that the constituent compounds play in their description is arbitrary—it should be stressed that in principle all hypotheses underlying the whole development are fulfilled. These results do not mean that it is impossible to establish an osmotic equilibrium with a system with this composition, since the equality of chemical potentials shows that the osmotic equilibrium calculated for the other phase fulfills equilibrium conditions, Eq. (1).

3.3. Ternary non-ideal mixtures—Flory–Huggins equation

A more severe test for the presented methodology would be a situation wherein there is a large deviation from the ideal behavior due not only to specific interactions between the compounds, but also to differences in their volumes per amount of substance. Therefore, the Flory–Huggins equation, which accounts for these differences, is considered:

$$\frac{G^{\text{EX}}}{RT} = x_{S_1} \ln \frac{\phi_{S_1}}{x_{S_1}} + x_{S_2} \ln \frac{\phi_{S_2}}{x_{S_2}} + x_R \ln \frac{\phi_R}{x_R} + \frac{(x_{S_1} V_{S_1} + x_{S_2} V_{S_2} + x_R V_R)}{V_{\text{ref}}} (\chi_{S_1 S_2} \phi_{S_1} \phi_{S_2} + \chi_{S_1 R} \phi_{S_1} \phi_R + \chi_{S_2 R} \phi_{S_2} \phi_R) \quad (35)$$

wherein ϕ_i is the volume fraction of compound i and χ_{ij} is the interaction fraction between compounds i and j . Pertinent derivatives for the Flory–Huggins equation are presented in Appendix A; they are written in terms of volume fractions, since these are easier calculated in this case.

Values of equation parameters were chosen so that the model is able qualitatively reproduce the behavior of bovine serum albumin (BSA) in an aqueous solution of polyethylene glycol (PEG) of chain size 6000. Considering S_1 to be the polymer ($V_{S_1} = 5000.0 \text{ cm}^3 \text{ mol}^{-1}$), S_2 to be water ($V_{S_2} = 18.0 \text{ cm}^3 \text{ mol}^{-1}$) and R to be the protein ($V_R = 60,000 \text{ cm}^3 \text{ mol}^{-1}$), the following parameters were used: $\chi_{S_2 R} = 0.44$, as suggested by Guo et al. [13], $\chi_{S_1 S_2} = 0.37$, obtained through fitting water activity data from Großmann et al. [14], and $\chi_{S_1 R} = 0.00$, since it is expected to be small, but there is no reliable information on this value; water was chosen as reference compound.

The Gibbs–Duhem equation can be changed in order to eliminate the need to calculate number fractions. Eq. (27) can be rewritten as

$$\phi_R d\mu_R = V_R dp \quad (36)$$

which leads to an alternative form of Eq. (29):

$$\phi_R \ln a_R - \int_0^{\phi_R} \ln a_R d\phi_R = \frac{V_R \Pi(\phi_R)}{RT} \quad (37)$$

The phase equilibrium that occurs when a protein in solution is precipitated by the addition of polymers is often modeled through describing dense and light phases separately by appropriate equations. Phase equilibrium is subsequently calculated by obtaining the composition wherein the osmotic pressure and solute chemical potential are equal [15]; as a necessary condition, outside solution composition must be the same [2]. The above development can be useful to describe the osmotic pressure of the light phase. In this case, the procedure is to be applied in inverse order—starting from the outside solution and obtaining osmotic pressure as a function of solute volume fraction.

Figs. 5 and 6 present, respectively, the osmotic pressure and the polymer volume fraction as a function of protein fraction, using the composition of the outside solution as a parameter. It can be seen that both curves are straightforwardly reconstructed, therefore allowing in principle this kind of phase equilibrium to be calculated using excess Gibbs energy models. It must be stressed that the decrease in polymer concentration observed in Fig. 6 does not correspond to the sole effect of adding a new component—otherwise the proportion between ϕ_{S_1} and ϕ_{S_2} would be constant along the curves.

The behavior of the Gibbs–Duhem equation can be seen in Fig. 7. It can be noticed that the terms in the left side of this equation are very close one to another, and the value of the right side is considerably smaller than the absolute value of any of them. Nevertheless, absolute differences between both sides of Eq. (37), when independently calculated, were always less than 10^{-5} .

If one restricts the attention to the curves of constant solvent chemical potential (Figs. 3 and 5), it is tempting to consider that the presented methodology might replace usual algorithms for liquid–liquid equilibrium calculations, since the equilibrium state corresponds to the osmotic pressure for which the solute chemical potential is equal in both phases—which may lower the number of iterations to calculate phase equilibrium. Moreover, as can be seen in Appendix B, the procedure can be easily extended to calculations involving any number of solutes. However, one must recall that the number of numerical operations that must be carried out to solve Eq. (7) increases when the number of solvents increases. It is certainly possible to extend the above methodology for flash-type liquid–liquid equilibrium calculations, but the approach may not be feasible: the absence of information on which is the

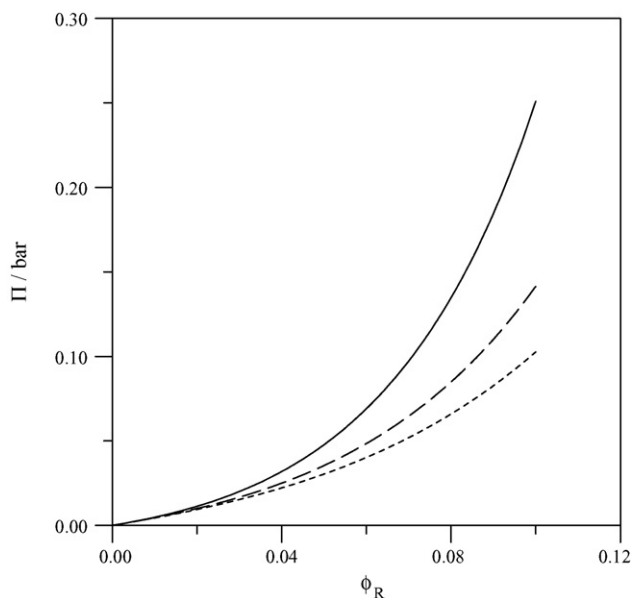


Fig. 5. Osmotic pressure as function of solute fraction and outside cell composition. Continuous line: $\phi''_{S_1} = 0.10$; dashed line: $\phi''_{S_1} = 0.15$; dotted line: $\phi''_{S_1} = 0.20$.

composition of the outside solution at the beginning of the procedure is equivalent to not knowing the temperature in usual flash-type calculation. While this difficulty can be overcome through introducing another iteration loop, it may lower the overall efficiency of the whole algorithm.

As a concluding remark, a possible use of this methodology includes the relationship between McMillan–Mayer and Lewis–Randall frameworks. There is substantial controversy about this subject, concerning not only the way a conversion between both frameworks can be carried out, but also the very possibility of modeling multisolvent systems within the McMillan–Mayer framework when solvents are dissimilar. Although it is not the objective of this work to resolve this controversy, it can be considered that the presented approach facilitates the use of Lewis–Randall expressions for interpreting results obtained from experiments and simulations usually associated with the McMillan–Mayer framework, as it allows the osmotic pressure to be straightforwardly calculated. Although with a different reasoning, this remark is in agreement with the general conclusion of the work by Breil and Mollerup [16], according to whom any solution theory – and hence any experimental or simulation result – can be interpreted within the Lewis–Randall framework.

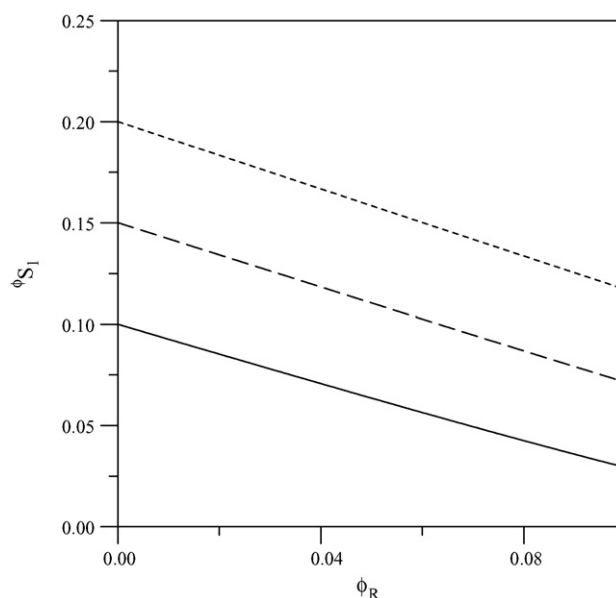


Fig. 6. Solvent (S_1) fraction as function of solute fraction and outside cell composition. Continuous line: $\phi''_{S_1} = 0.10$; dashed line: $\phi''_{S_1} = 0.15$; dotted line: $\phi''_{S_1} = 0.20$.

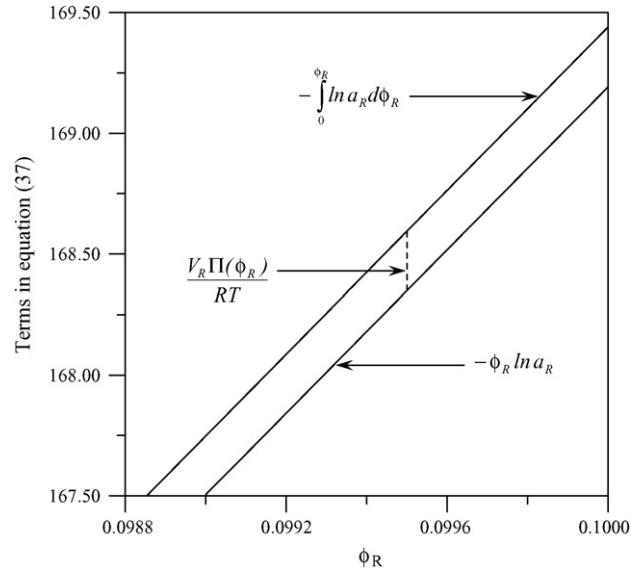


Fig. 7. Terms in Gibbs–Duhem equation.

4. Conclusions

In this work a differential approach for the calculation of osmotic equilibrium for multisolvent systems is presented. This methodology avoids the use of iterative algorithms to calculate osmotic equilibrium through the definition of a set of differential equations, which could be readily integrated for liquid phases whose volume can be considered independent of the system pressure. Examples were presented using the Margules and Flory–Huggins equation, but the approach is completely general and independent of the equation used to describe liquid phase non-idealities. The methodology also allows the calculation of the osmotic pressure curve as a function of the solute fraction, and is numerically stable even when applied for situations wherein liquid–liquid equilibrium takes place.

Appendix A. Auxiliary expressions

For the Margules equation, one gets the following expressions:

$$\ln a_{S_1}^{\text{PI}} = \ln x_{S_1} + A_{S_1 S_2} x_{S_2}^2 + A_{S_1 R} x_R^2 + (A_{S_1 S_2} + A_{S_1 R} - A_{S_2 R}) x_{S_2} x_R \quad (\text{A.1})$$

and

$$\left(\frac{\partial \ln a_{S_1}^{\text{PI}}}{\partial x_{S_1}} \right)_{x_{S_2}} = \frac{1}{x_{S_1}} - 2A_{S_1 R} x_R - (A_{S_1 S_2} + A_{S_1 R} - A_{S_2 R}) x_{S_2} \quad (\text{A.2})$$

$$\left(\frac{\partial \ln a_{S_1}^{\text{PI}}}{\partial x_{S_2}} \right)_{x_{S_1}} = 2A_{S_1 S_2} x_{S_2} - 2A_{S_1 R} x_R + (A_{S_1 S_2} + A_{S_1 R} - A_{S_2 R})(x_R - x_{S_2}) \quad (\text{A.3})$$

For the Flory–Huggins equation, pertinent expressions are

$$\ln a_{S_1}^{\text{PI}} = 1 + \ln \phi_{S_1} - V_{S_1} \left(\frac{\phi_{S_1}}{V_{S_1}} + \frac{\phi_{S_2}}{V_{S_2}} + \frac{\phi_R}{V_R} \right) + \frac{V_{S_1}}{V_{\text{ref}}} (\chi_{S_1 S_2} \phi_{S_2} + \chi_{S_1 R} \phi_R - (\chi_{S_1 S_2} \phi_{S_1} \phi_{S_2} + \chi_{S_1 R} \phi_{S_1} \phi_R + \chi_{S_2 R} \phi_{S_2} \phi_R)) \quad (\text{A.4})$$

and

$$\left(\frac{\partial \ln a_{S_1}^{\text{PI}}}{\partial \phi_{S_1}} \right)_{\phi_{S_2}} = \frac{1}{\phi_{S_1}} - 1 + \frac{V_{S_1}}{V_R} + \frac{V_{S_1}}{V_{\text{ref}}} ((\chi_{S_2 R} - \chi_{S_1 R} - \chi_{S_1 S_2}) \phi_{S_2} + \chi_{S_1 R} \phi_R) \quad (\text{A.5})$$

$$\left(\frac{\partial \ln a_{S_1}^{\text{PI}}}{\partial \phi_{S_2}} \right)_{\phi_{S_1}} = -V_{S_1} \left(\frac{1}{V_{S_2}} - \frac{1}{V_R} \right) + \frac{V_{S_1}}{V_{\text{ref}}} ((\chi_{S_1 S_2} - \chi_{S_1 R})(1 - \phi_{S_1}) - \chi_{S_2 R}(\phi_R - \phi_{S_2})) \quad (\text{A.6})$$

For the other compounds analogous expressions can be obtained by merely changing the subscripts, since these expressions are symmetrical.

Appendix B. Extension to multiple solutes

The difficulty of applying the presented procedure increases only slightly in the situation wherein there are n solvents and m solutes. In this case:

$$d\mu_{S_i} = \sum_{j=1}^n \left(\frac{\partial \mu_{S_i}}{\partial \xi_{S_j}} \right)_{T,p,[\xi]} d\xi_{S_j} + \sum_{j=1}^{m-1} \left(\frac{\partial \mu_{S_i}}{\partial \xi_{R_j}} \right)_{T,p,[\xi]} d\xi_{R_j} + \left(\frac{\partial \mu_{S_i}}{\partial p} \right)_{T,[\xi]} dp \quad (\text{B.1})$$

In this case, an integration path must be defined beforehand. Once one wants to integrate this system from an initial composition $(\xi_{S_j}^0, \xi_{R_j}^0)$ to a final composition in which solute concentrations are null, the following parameter is defined:

$$\lambda = 1 - \frac{\xi_{R_j}}{\xi_{R_j}^0} \quad (\text{B.2})$$

so that $\lambda = 0.0$ corresponds to the inside solution composition, and $\lambda = 1.0$ corresponds to the outside solution composition. The integration is to be conducted following a path wherein this proportion is constant. Therefore:

$$d\xi_{R_j} = -\xi_{R_j}^0 d\lambda \quad (\text{B.3})$$

Thus, one gets:

$$d\mu_{S_i} = \sum_{j=1}^n \left(\frac{\partial \mu_{S_i}}{\partial \xi_{S_j}} \right)_{T,p,[\xi]} d\xi_{S_j} - \left(\sum_{j=1}^{m-1} \left(\frac{\partial \mu_{S_i}}{\partial \xi_{R_j}} \right)_{T,p,[\xi]} \xi_{R_j}^0 \right) d\lambda + \left(\frac{\partial \mu_{S_i}}{\partial p} \right)_{T,[\xi]} dp \quad (\text{B.4})$$

Considering the restriction that:

$$\sum_{j=1}^n d\xi_{S_j} + \sum_{j=1}^m d\xi_{R_j} = 0 \Rightarrow \sum_{j=1}^n d\xi_{S_j} + \left(\sum_{j=1}^m \xi_{R_j}^0 \right) d\lambda = 0 \quad (\text{B.5})$$

Choosing S_k as the key solvent compound:

$$\sum_{j=1, j \neq k}^n \left(\left(\frac{\partial \mu_{S_i}}{\partial \xi_{S_j}} \right)_{T,p,[\xi]} - \left(\frac{\partial \mu_{S_i}}{\partial \xi_{S_k}} \right)_{T,p,[\xi]} \right) d\xi_{S_j} - \left(\sum_{j=1}^{m-1} \left(\frac{\partial \mu_{S_i}}{\partial \xi_{R_j}} \right)_{T,p,[\xi]} \xi_{R_j}^0 \right) d\lambda + \bar{V}_i dp = 0 \quad (\text{B.6})$$

Therefore:

$$\sum_{j=1, j \neq k}^n \left(\left(\frac{\partial \mu_{S_i}}{\partial \xi_{S_j}} \right)_{T,p,[\xi]} - \left(\frac{\partial \mu_{S_i}}{\partial \xi_{S_k}} \right)_{T,p,[\xi]} \right) \frac{d\xi_{S_j}}{d\lambda} - \left(\sum_{j=1}^{m-1} \left(\frac{\partial \mu_{S_i}}{\partial \xi_{R_j}} \right)_{T,p,[\xi]} \xi_{R_j}^0 \right) + \bar{V}_i \frac{dp}{d\lambda} = 0 \quad (\text{B.7})$$

Also considering that:

$$\frac{d\xi_{S_k}}{d\lambda} = - \sum_{j=1, j \neq k}^n \frac{d\xi_{S_j}}{d\lambda} - \sum_{j=1}^m \xi_{R_j}^0 \quad (\text{B.8})$$

For a single solute, these equations have the same form as derived before.

References

- [1] W.G. McMillan Jr., J.E. Mayer, *J. Chem. Phys.* 13 (1945) 276–304.
- [2] R.A. Curtis, J. Newman, H.W. Blanch, J.M. Prausnitz, *Fluid Phase Equilibria* 192 (2001) 131–153.
- [3] A.M. Sereno, M.D. Hubinger, J.F. Comesaña, A. Correa, *J. Food Eng.* 49 (2001) 103–114.
- [4] M.J.E.M. Cardoso, J.P. O'Connell, *Fluid Phase Equilibria* 33 (1987) 315–326.
- [5] R.-S. Wu, L.L. Lee, *Fluid Phase Equilibria* 78 (1992) 1–24.
- [6] R. Guo, M. Guo, G. Narsimhan, *Ind. Eng. Chem. Res.* 35 (1996) 3015–3026.
- [7] J. Jiang, J.M. Prausnitz, *J. Phys. Chem. B* 103 (1999) 5560–5569.
- [8] S.G. Kim, Y.C. Bae, *Macromol. Res.* 11 (2003) 53–61.
- [9] N. von Solms, C.O. Anderson, H.W. Blanch, J.M. Prausnitz, *AIChE J.* 48 (2002) 1292–1300.

- [10] L.L. Lee, *J. Mol. Liq.* 87 (2000) 129–147.
- [11] A. Anderko, P. Wang, M. Rafal, *Fluid Phase Equilibria* 194–197 (2002) 123–142.
- [12] J.W. Tester, M. Modell, *Thermodynamics and its Applications*, 3rd ed., Prentice Hall, Upper Saddle River, 1997.
- [13] R. Guo, M. Guo, G. Narsimhan, *Ind. Eng. Chem. Res.* 35 (1996) 3015–3026.
- [14] C. Großmann, R. Tintinger, J. Zhu, G. Maurer, *Fluid Phase Equilibria* 106 (1995) 111–138.
- [15] F. Fornasiero, J. Ulrich, J.M. Prausnitz, *Chem. Eng. Proc.* 38 (1999) 463–475.
- [16] M.P. Breil, J.M. Mollerup, *Fluid Phase Equilibria* 242 (2006) 129–135.