

**Figure 2**—Results of simultaneous nonlinear least-squares fitting to Eq. 5 of terminal average capillary blood alcohol concentrations of eight subjects given four different doses. The solid line gives the model-predicted concentrations.

centration data obtained in six subjects given alcohol by constant-rate intravenous infusion) yields an estimate of 0.124 g of alcohol/kg/hr for the maximum elimination rate of alcohol in a normal male. For a 70-kg male, this is equivalent to 8.7 g of alcohol/hr.

In toxicology cases, where one wishes to estimate the future time course of blood alcohol concentrations, it is still valid to extrapolate an established pseudolinear decline in blood alcohol concentration down to about 0.2 mg/ml. However, this can only be done in individual patients who ingest a given dose of alcohol. It is invalid to predict the slope of the pseudolinear decline without a great deal of data and to compare slopes reported by two or more investigators who administer different doses of alcohol to different subjects. The slope of the pseudolinear decline is a function of  $C_0$ ,  $V_m$ , and  $K_m$ , as indicated by Wagner (11) and the data in this report.

This work conclusively demonstrates that zero-order kinetics are inappropriate for describing the elimination of alcohol in humans. The slope of the pseudolinear decline should not be utilized as a measure of metabolism rate of alcohol as it has been used in the past (1, 2, 4-7). The rate of metabolism of alcohol is described more accurately by the  $V_m$  and  $K_m$  values and Eq. 2.

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John G. Wagner<sup>x</sup>  
Paul K. Wilkinson  
Allen J. Sedman  
Donald R. Kay  
Donald J. Weidler

College of Pharmacy and  
Upjohn Center for Clinical Pharmacology  
University of Michigan  
Ann Arbor, MI 48104

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<sup>x</sup>To whom inquiries should be directed (at Upjohn Center for Clinical Pharmacology).

## Analysis of Diffusion through Concentric Right Circular Cylinders and Concentric Spheres

**Keyphrases** □ Diffusion—concentric right circular cylinders and concentric spheres, models for drug release from tubular devices, cylindrical systems, and vaginal or GI lumen □ Drug release—tubular devices, cylindrical systems, and vaginal or GI lumen, concentric right circular cylinders and concentric spheres as models

To the Editor:

We recently have been modeling several diffusional systems involving diffusion through a series (two or more) of concentric right circular cylinders. The modeling encompasses (a) drug release from tubular devices, particularly in the presence of fluid boundary layers; (b) drug release from cylindrical systems containing drugs suspended in polymeric matrixes (1); (c) absorption of drugs from the vaginal lumen (2) or the lumen of the intestine (3), each of which, to a first approximation, may be considered a cylindrical membrane; and (d) combinations of a, b, and c.

A general phenomenon associated with all geometrical systems of this type, when diffusion is from the

core of the cylinder to some external surface, is dilution along the radial vector as the concentration gradient develops because, for each unit incremental increase in radius,  $\Delta r$ , a larger and larger differential volume,  $\Delta V$ , is associated with the prescribed concentric tubular cylinder ( $\Delta V$  lying between the hollow cylinder prescribed by  $r_i$  and  $r_i + \Delta r$ ). In the steady state, the net flux through every concentric cylindrical plane is constant. However, since the incremental volume elements are growing to the third power of the radius as the radius is extended, the concentration gradient in the cylindrical case is nonlinear and effectively more severe than that generated in the planar case. Thus, the steady-state flux through a hollow tube of thickness  $\Delta r$  is greater than the steady-state flux of the same diffusant through a comparably thick planar slab of the same composition and area<sup>1</sup>.

Yet, often, cylindrical geometrical influences are ignored and cylindrical membranes are "flattened" in our treatments. For example, intestinal absorption is often treated as a planar process rather than as absorption through a cylindrical or "tubular" tissue barrier. Intuitively, this approach seems reasonable because the involved tissue "thickness" is small relative to the radius of the GI lumen. The purpose of this communication, in addition to providing general equations for steady-state diffusion through concentric cylindrical barriers in series, is to quantitate the conditions where planarization of the diffusional process is mathematically appropriate.

A general approach to treating cylindrical barriers in series can be illustrated by considering the simplest such system, two concentric hollow cylindrical membranes. Figure 1 is an illustration of several such "membranes" in series. The situation specifically involves diffusion from a solution within the tubular lumen through the cylindrical membrane, determined by radii  $r_1$  and  $r_2$ , and then through the contiguous and concentric tubular region, determined by radii  $r_2$  and  $r_3$ . For the moment, we shall neglect diffusional resistance contributions of interfaces, although they could be treated as additional diffusional resistances in series.

For simplicity of treatment, it is assumed that there is a constant luminal concentration of the penetrant,  $C_0$ , at all times and that the diffusion is into an external sink (the outside concentration is zero at all times). Under these conditions, a true steady state develops in time and the flux is invariant through every concentric cylindrical plane. It also is assumed that the concentric cylinders are of length  $H$  and that there is no end diffusion.

Fick's first law states<sup>2</sup>:

$$J = -AD \left( \frac{dC}{dx} \right) \quad (\text{Eq. 1})$$

where  $J$  is the flux,  $A$  is the area,  $D$  is the diffusivity, and  $dC/dx$  is the concentration gradient. The lateral area of a right circular cylinder is given by:

$$A = 2\pi rH \quad (\text{Eq. 2})$$

where  $r$  is the radius, and  $H$  is the cylinder's length. Combining Eqs. 1 and 2 produces:

$$J = -2\pi rHD \left( \frac{dC}{dr} \right) \quad (\text{Eq. 3})$$

as the distance,  $x$ , is measured along a radial line. In the steady state,  $J$  is constant through every concentric cylindrical plane. In the first hollow cylindrical shell of a series of cylindrical shells:

$$J = -2\pi rHD_1 \left( \frac{dC}{dr} \right) \quad (\text{Eq. 4})$$

and:

$$\frac{dr}{r} = - \frac{2\pi HD_1}{J} dC \quad (\text{Eq. 5})$$

which may be integrated from  $C_1'$  to  $C_2$  and from  $r_1$  to  $r_2$  to yield<sup>3</sup>:

$$\ln \left( \frac{r_2}{r_1} \right) = \frac{2\pi HD_1}{J} (C_1' - C_2) \quad (\text{Eq. 6})$$

The second concentric cylindrical "membrane" may be similarly treated:

$$\ln \left( \frac{r_3}{r_2} \right) = \frac{2\pi HD_2}{J} (C_2' - C_3) \quad (\text{Eq. 7})$$

The assumption of a sink condition at the outer boundary leads to  $C_3 = 0$  at all times and:

$$\ln \left( \frac{r_3}{r_2} \right) = \frac{2\pi HD_2}{J} C_2' \quad (\text{Eq. 8})$$

To combine Eqs. 6 and 8, one has to adopt a uniform, continuous "concentration" (activity) scale. This is most conveniently done with respect to  $C_0$ , the core concentration, using partition coefficients. Let  $C_0/C_1' = K_I$  and  $C_2/C_2' = K_{II}$ . Then  $C_1' = C_0/K_I$  and  $C_2' = C_2/K_{II}$ . The latter relationship, when incorporated in Eq. 8, yields for  $C_2$ :

$$C_2 = \frac{K_{II}J}{2\pi HD_2} \ln \left( \frac{r_3}{r_2} \right) \quad (\text{Eq. 9})$$

which, when substituted into Eq. 6 along with the other partitioning relationship, yields for the flux:

$$J = \frac{2\pi HD_1 D_2 C_0}{D_2 K_I \ln \left( \frac{r_2}{r_1} \right) + D_1 K_I K_{II} \ln \left( \frac{r_3}{r_2} \right)} \quad (\text{Eq. 10})$$

The product  $K_I K_{II}$  is itself a distribution coefficient and is  $C_0 C_2 / C_1' C_2'$ . If the system proceeds to a true equilibrium, this quantity, being the product of two constants, remains constant (to the extent that partitioning is concentration insensitive) and, at true equilibrium,  $C_1' = C_2$  and  $K_I K_{II} = K_2 = (C_0 / C_2')$ . But this is simply the equilibrium distribution coefficient.

<sup>1</sup> Radial diffusion in the opposite direction, to the center of the cylinder, is accompanied by a "concentration" relative to a planar system. For the comparison, one can take the inner cylindrical area, associated with  $r_i$ , as the severest test of the statement (see Table I).

<sup>2</sup> The flux here is defined in terms of total surface area rather than on a per unit area basis. This form is useful in characterizing the mass current from nonplanar geometrical barriers.

<sup>3</sup> A convention has been adopted here in which subscript numbers for concentrations at interfacial boundaries are numbered with respect to the order of the radii, the inner radius being  $r_1$ , the next longer radius being  $r_2$ , etc. There are, of course, two surface concentrations at each interface, one on each side. The inner surface concentration is simply designated by the radius subscript, while the surface concentration in the material on the outer side of the interface is designated by a prime superscript in addition to the radius subscript. Thus,  $C_1'$  is the outer surface concentration associated with the interface found at radius  $r_1$ .

cient of the permeant between the core phase and the material comprising the outer cylindrical membrane. Extending the relationship to additional cylindrical shells in series shows that only a singular partition coefficient need be considered as the diffusant enters a new phase, and this coefficient is the equilibrium partition coefficient between the core and that particular phase.

It is easy to show, by repetitively using these mathematical operations, that diffusion through multiple concentric cylindrical barriers in series in the steady state mathematically conforms to<sup>4</sup>:

$$J = \frac{2\pi H(D_1 D_2 \cdots D_n) C_0}{\frac{(D_1 D_2 \cdots D_n)}{D_1} K_1 \ln\left(\frac{r_2}{r_1}\right) + \frac{(D_1 D_2 \cdots D_n)}{D_2} K_2 \ln\left(\frac{r_3}{r_2}\right) + \cdots + \frac{(D_1 D_2 \cdots D_n)}{D_n} K_n \ln\left(\frac{r_{n+1}}{r_n}\right)} \quad (\text{Eq. 11})$$

This form also can be applied to some quasi-steady-state problems upon substitution of  $\Delta C = [C_0 - C_{n+1}]$  for  $C_0$  (5).

We can now consider the conditions whereby a cylindrical system may be functionally planar. It can be seen from Eqs. 6 and 7 that, for any concentric tubular barrier, say the *i*th:

$$J = \frac{2\pi H D_i (C_i' - C_{i+1})}{\ln\left(\frac{r_{i+1}}{r_i}\right)} \quad (\text{Eq. 12})$$

Furthermore, any  $r_{i+1}$  may be put in terms of  $r_i$  and a differential radius:

$$r_{i+1} = r_i + \Delta r \quad (\text{Eq. 13})$$

and, thus:

$$J = \frac{2\pi H D_i (C_i' - C_{i+1})}{\ln\left(1 + \frac{\Delta r}{r_i}\right)} \quad (\text{Eq. 14})$$

The terms  $C_i'$  and  $C_{i+1}$  are the inner and outer "membrane" surface concentrations, respectively<sup>3</sup>.

The natural logarithmic term in Eq. 14 is in the general form  $\ln(1 + X)$ , where  $X$  is obviously  $\Delta r/r_i$ . It can be shown that the function  $\ln(1 + X)$  expands to:

$$\ln(1 + X) = X - \frac{X^2}{2} + \int_0^X \left(\frac{X^2}{1 + X}\right) dx \quad (\text{Eq. 15})$$

which, as  $X$  takes a value less than one, is first well approximated by  $X - (X^2/2)$  and then, as  $X$  becomes sufficiently small, is simply approximated by  $X$  itself. Therefore, when using the simple but less exact approximation, in the limit that  $\Delta r/r_i \ll 1$ :

$$J = \frac{2\pi H D_i (C_i' - C_{i+1})}{\frac{\Delta r}{r_i}} \quad (\text{Eq. 16a})$$

or:

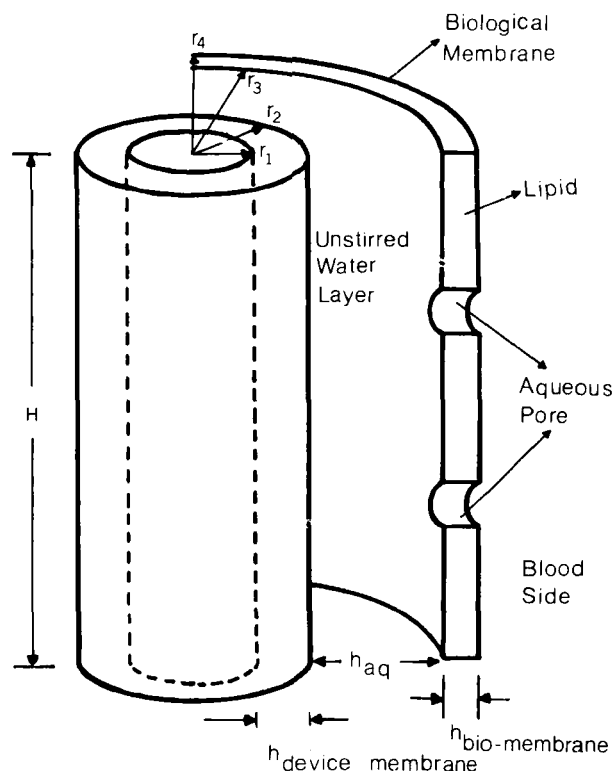
$$J = \frac{2\pi H r_i D_i (C_i' - C_{i+1})}{\Delta r} \quad (\text{Eq. 16b})$$

which is a planar form of the flux equation where the area,  $A$ , is  $2\pi r_i H$  and the laminate thickness is  $\Delta r$ .

The applicability of Eq. 16 now can be quantitated. The exact solutions of the function  $\ln(1 + X)$  along with solutions using both of the function approximations are listed in Table I for several ratios of  $r_{i+1}/r_i$ . The table also gives the percentage deviations from the exact solution. It can be seen that the "long approximation" gives very satisfactory results (<1% deviation) at a radial ratio of 1.1 or a  $\Delta r$  10% as large as  $r_i$ . The short approximation has an inherent 5% error at this ratio. When  $\Delta r$  is only 1% of  $r_i$ , the short approximation becomes quite satisfactory because the error is only 0.5%. In fact, the percentage error in

using the short approximation converges to half the percentage increase of  $r_{i+1}$  over  $r_i$ . Thus, the planar form gives a 0.5% error when  $\Delta r$  is 1% of  $r_i$ , a 0.05% error when  $\Delta r$  is 0.1% of  $r_i$ , and so on. The long approximation provides virtually exact solutions as the radial ratio approaches one.

In vaginal and intestinal absorption, one is dealing with reasonably cylindrical cavities which have radii measured in whole centimeters and membranes and boundary layer barriers of estimated thicknesses ranging from fractional to whole millimeters. The upper limit on the radial ratio experienced in these circumstances seems to be about 1:1 and should be considerably less in most cases. Thus, planarization of the absorption processes through these tissues is



**Figure 1**—Series of concentric cylinders as a drug delivery device in a biological setting. The "thicknesses" of the respective laminates are designated by *h* values. Each *h* can be described in terms of a differential radius,  $\Delta r$ .

<sup>4</sup> Barrer (4) presented a general derivation for concentric cylindrical barriers in series using a concise, alternative mathematical approach. The two forms, Barrer's and Eq. 11, appear different but can be shown to be interconvertible with proper manipulation and the use of a common set of symbols.

**Table I—Comparison of Exact and Approximate Solutions of the Function  $\ln\left(1 + \frac{\Delta r}{r_i}\right)$**

Radius <sup>a</sup> Ratio	Increase in $r_{i+1}$ over $r_i$ , %	$\ln\left(1 + \frac{\Delta r}{r_i}\right)$	Solution by First Approximation		Solution by Second Approximation	
			$\frac{\Delta r}{r_i} - \left(\frac{\Delta r}{r_i}\right)^2/2$	Deviation <sup>b</sup> , %	$\frac{\Delta r}{r_i}$	Deviation <sup>b</sup> , %
1.5	50	0.40547	0.375	-7.51	0.5	23.3
1.1	10	0.095310	0.095	-0.325	0.1	4.93
1.05	5	0.048790	0.04875	-0.082	0.05	2.48
1.01	1	0.0099503	0.00995	-0.0030	0.01	0.50
1.005	0.5	0.00498754	0.0049875	-0.008	0.005	0.25
1.001	0.1	0.000999500	0.0009995	0	0.001	0.050

<sup>a</sup> This is the same as  $1 + (\Delta r/r_i)$ . <sup>b</sup> Percent deviation of approximate solution with respect to exact solution.

accompanied by a small and, in most cases, a negligible error.

However, in release of drugs through tubular membranes (drug delivery devices) where radii are in fractional centimeters (a 0.5-cm diameter could be considered typical) and tubing wall thicknesses approach whole millimeters (a  $\Delta r$  of 1 mm might be typical), planarization of the treatment introduces large errors in estimating diffusional parameters or in characterizing flux as a function of tubing thickness from known diffusivities and partition coefficients, *etc.* In these situations, the geometrical factor has to be accounted for in the mass transport characterization. Because of the remarkably simple relationship between the error of approximation and the radial ratio, it is easy to determine if one can employ the simplified form.

A similar analysis can be applied to concentric spheres. Barrer (4) gave a general form for the permeability coefficient of multiple concentric spherical barriers. Alternatively, the procedure illustrated here can be employed to develop a mathematical model (6, 7). In any case, one obtains for the *i*th spherical lamina:

$$J = \frac{4\pi D_i(C_i' - C_{i+1})}{\frac{1}{r_i} - \frac{1}{r_i + \Delta r}} \quad (\text{Eq. 17})$$

**Table II—Comparison of Exact and Approximate Solutions for Concentric Spheres at a Constant Radial Ratio, 1.5**

$r_i$	$r_i + \Delta r$	$\Delta r$	$\frac{1}{r_i} - \frac{1}{r_i + \Delta r}$	$\frac{\Delta r}{r_i^2}$	Deviation, %
1	1.5	0.5	0.02083	0.5	50
2	3	1	0.1667	0.25	50
4	6	2	0.0833	0.125	50
8	12	4	0.04167	0.0625	50
16	24	8	0.02083	0.0313	50

**Table III—Comparison of Exact and Approximate Solutions for Concentric Spheres at Varying Radial Ratio for a Constant  $r_i$  Value of 1**

$r_i + \Delta r$	$\Delta r$	$\frac{1}{r_i} - \frac{1}{r_i + \Delta r}$	$\frac{\Delta r}{r_i^2}$	Radius Increase, %	Deviation, %
1.5	0.5	0.3333	0.5	50	50
1.1	0.1	0.090909	0.1	10	10
1.05	0.05	0.047619	0.05	5	5
1.01	0.01	0.009901	0.01	1	1
1.005	0.005	0.0049752	0.005	0.5	0.5

where  $r_i + \Delta r = r_{i+1}$ . The denominator can also be written:

$$\frac{1}{r_i} - \frac{1}{r_i + \Delta r} = \frac{\Delta r}{r_i(r_i + \Delta r)} \quad (\text{Eq. 18})$$

and it can be seen by inspection that when  $\Delta r$  becomes very small, the function approaches  $\Delta r/r_i^2$ . When substituted into Eq. 17, this approximation gives a planar form of the flux equation of area  $4\pi r_i^2$  and thickness  $\Delta r$ .

An analysis of the cylindrical case appears in Tables II and III. In Table II, the function  $\Delta r/r_i^2$  is compared with the exact function  $(1/r_i) - 1/(r_i + \Delta r)$  for varying  $r$  values but for a constant 50% increase in  $r_{i+1}$  over  $r_i$ . Unlike the cylindrical case, the absolute magnitude of  $r_i$  in addition to the ratio  $r_{i+1}/r_i$  is a determinant of the quantitative value of the function. However, the percentage error at a given ratio remains constant. Moreover, the percentage error is the same as the percentage increase of  $\Delta r$  over  $r_i$  (inspection of Eqs. 17 and 18 indicates that this is to be expected). The relationships are further illustrated in Table III, where the radial ratio has been varied but  $r_i$  has been held constant at 1.

These equations and their analysis indicate where one can simplify the characterization of absorption of drugs and nutrients by cultured cells and microorganisms, of uptake and release mechanisms of emulsion droplets in the presence of diffusion layers and interfacial barriers, and of release of drugs from spherical capsules and other spherical devices.

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Gordon L. Flynn \*  
Norman F. H. Ho  
William I. Higuchi  
College of Pharmacy  
University of Michigan  
Ann Arbor, MI 48104

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\* To whom inquiries should be directed.

## Consistency Relations in Solid Solution Melting-Point Diagrams

**Keyphrases** □ Solid solution systems—melting-point diagrams, consistency relations, thermodynamic analysis □ Melting-point diagrams—solid solution systems, consistency relations

To the Editor:

Solid solution systems have been of pharmaceutical interest in recent years (1-7). The thermodynamic basis for solid solution systems is given in standard texts on solid-state physics or chemistry; *e.g.*, Zhdanov (8) listed the expression for the free energy,  $F$ , at temperature  $T$  °K of a system containing  $x$  mole fraction  $A$  and  $(1-x)$  mole fraction  $B$  as:

$$F(x, T) = K(T) + 0.5NZ[x^2V_{AA} + (1-x)^2V_{BB} + 2x(1-x)V_{AB}] + RT[x \ln x + (1-x) \ln(1-x)] \quad (\text{Eq. 1})$$

where:

$N$  = Avogadro's number

$Z$  = coordination number

$V_{AA}$  = interaction energy between two  $A$  molecules

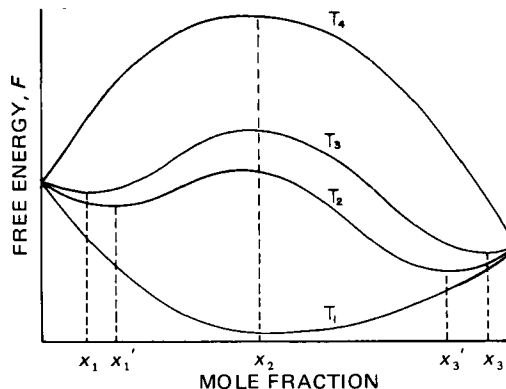
$V_{BB}$  = interaction energy between two  $B$  molecules

$V_{AB}$  = interaction energy between an  $A$  and a  $B$  molecule

$$K(T) = \int_0^T c \, dT - T \int_0^T \frac{c}{T} \, dT, \text{ where } c = \text{heat capacity}$$

The assumptions made here are that: (a) only nearest neighbor interactions are considered, (b) Stirling's formula is applicable, and (c) the heat capacities for the two solids and for the solid solutions are identical. This last assumption is made in all published treatments [*e.g.*, Zhdanov (8) and Ashbee (9)] and is implicit in the use of the terminology  $K(T)$  rather than  $K(T, x)$ . This assumption may not necessarily be a good one (as evidenced by a great deal of thermoanalytical work) but is, nevertheless, made here.

A typical plot of  $F$  as a function of composition  $x$  at temperatures  $T_1 > T_2 > T_3 > T_4$ , where  $T_2$  is the eutectic temperature, is shown in Fig. 1. The curves in Fig. 1 are based on  $2V_{AB} > V_{AA} + V_{BB}$  (9). The corresponding binary melting-point diagram is shown in Fig. 2.



**Figure 1**—Free energy versus mole fraction of a binary mixture forming a random solid solution. The indicated temperatures are of the rank  $T_1 > T_2 > T_3 > T_4$ . The minima correspond to solid solution compositions at the indicated temperatures (at which the mixture is solid). In this example,  $T_2$  could be the eutectic temperature and  $T_3$  could be room temperature.

There are three extrema (at compositions  $x_1$ ,  $x_2$ , and  $x_3$ ) when solid solutions exist, the two minima ( $x_1$  and  $x_3$ ) being at the compositions of the solid solutions at the eutectic temperature,  $T_2$ . That the maximum coincides with the eutectic composition is, however, not thermodynamically obvious. The values for  $x_1$ ,  $x_2$ , and  $x_3$  satisfy the first derivative equation of Eq. 1 when equated to zero, *i.e.*:

$$\left. \frac{\partial F}{\partial x} \right|_T = NZ \{ xV_{AA} - (1-x)V_{BB} + (1-2x)V_{AB} \} + NkT \ln \{ x/(1-x) \} = 0 \quad (\text{Eq. 2})$$

where  $k$  is Boltzmann's constant. Inserting  $x = x_1$ ,  $x_2$ , and  $x_3$  then yields three equations with three unknowns:

$$x_1V_{AA} + (x_1 - 1)V_{BB} + (1 - 2x_1)V_{AB} = -\frac{kT}{Z} \ln [x_1/(1-x_1)] \quad (\text{Eq. 3a})$$

$$x_2V_{AA} + (x_2 - 1)V_{BB} + (1 - 2x_2)V_{AB} = -\frac{kT}{Z} \ln [x_2/(1-x_2)] \quad (\text{Eq. 3b})$$

$$x_3V_{AA} + (x_3 - 1)V_{BB} + (1 - 2x_3)V_{AB} = -\frac{kT}{Z} \ln [x_3/(1-x_3)] \quad (\text{Eq. 3c})$$

where  $V_{AA}$ ,  $V_{BB}$ , and  $V_{AB}$  are the unknowns. There is no unique solution to these three equations, because the determinant  $D = |x_i, (x_i - 1), (1 - 2x_i)|$  equals zero for all values of  $x_i$ ; *i.e.*, there is a linear dependence among  $x_1$ ,  $x_2$ , and  $x_3$ . If the coefficients of dependence are denoted  $\alpha_1$  and  $\alpha_2$ , it follows from Eqs. 3a-3c that:

$$\alpha_1 x_1 + \alpha_2 x_2 = x_3 \quad (\text{Eq. 4a})$$

$$\alpha_1 (x_1 - 1) + \alpha_2 (x_2 - 1) = (x_3 - 1) \quad (\text{Eq. 4b})$$

$$\alpha_1 (1 - 2x_1) + \alpha_2 (1 - 2x_2) = 1 - 2x_3 \quad (\text{Eq. 4c})$$

The solutions to Eqs. 4a-4c are:

$$\alpha_1 = (x_2 - x_3)/(x_2 - x_1) \quad (\text{Eq. 5})$$

$$\alpha_2 = (x_3 - x_1)/(x_2 - x_1) \quad (\text{Eq. 6})$$