

A MATHEMATICAL ANALYSIS OF THE BJERRUM FUNCTION FOR THE STEPWISE EQUILIBRIUM MODEL

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Abstract

A mathematical analysis of the Bjerrum function is carried out. This function arises from the Stepwise Equilibrium Model, which is used to describe successive complex formation in systems consisting of free metal ion, free ligand, and all the ML_i complexes that can form in solution. The appropriate root of the Bjerrum polynomial allows the determination of the concentrations of all species present in solution, given the initial concentrations of metal and of ligand, and the equilibrium constants governing the system. It is proved that there is only one positive root of the Bjerrum polynomial, and thus that only a single equilibrium state can exist. It is also shown that the positive root of the Bjerrum polynomial can be reliably obtained by Newton's method, but only if the initialization point is properly chosen, and that the initial concentration L of ligand is the optimum such point. Finding this root is a calculation that typically must be carried out at each iteration in nonlinear least squares procedures for determining equilibrium constants. Finally, the necessary mathematical analysis is carried out to determine the optimum initial concentrations of metal and ligand which maximize the resulting concentration of a particular ML_i complex.

1. Introduction

The determination of equilibrium constants is a fundamentally important part of investigations into the interactions between molecules in solution or in the gas phase. A knowledge of the equilibrium constants governing a system permits the determination of the concentrations of all species in solution from the initial con-

centrations of reactants. Although the equations describing such interactions are well known, the determination of the set of equilibrium constants governing a chemical system is often an extremely difficult problem.

Methods for determining equilibrium constants have undergone extensive development. For reviews, the interested reader should consult Hartley et al. [1] and Gaizer [2]. The methods used for simple systems are either graphical or involve the solution of relatively simple equations. When the number of equilibria in a chemical system exceeds two, graphical procedures lose their precision, and procedures involving nonlinear least squares techniques become the rule. These techniques usually require considerable computing power, and there has been an enormous effort over the years to develop algorithms which will yield accurate and reliable values for equilibrium constants. However, very little attention has been paid to developing the mathematical properties of the system of equations which govern a particular equilibrium problem. Such properties can be extremely valuable in the computations that typically must be carried out. For example, it was shown by Macleod [3] that for a simple system consisting of a weak acid and its conjugate base, the cubic equation which must be solved in order to determine the hydronium ion (H_3O^+) concentration not only has a single positive root [4], but that all three roots must be real. The knowledge that there are also two negative roots is important in the development of an efficient and reliable algorithm for finding the positive solution of the cubic equation. A similar approach was used to develop an efficient and totally reliable method for calculating the amount of a given ligand bound to several proteins found in serum, as well as the free ligand concentration, based on a set of equilibrium constants determined using the Scatchard Model [5]. In that work, a mathematical examination of the equation that must be solved not only showed that there is only one meaningful root of that equation, but also showed exactly how one should proceed in finding that root by Newton's method. Both these examples, although relatively simple, amply illustrate the value of any knowledge of the mathematical properties of the equations under consideration.

The mathematical analyses briefly described below are based upon the classical consideration that a chemical system at equilibrium is determined by solving the system of equations arising from the mass balance equations and mass action laws. Alternatively, Gibbs has shown [6] that satisfying the mass action laws is equivalent to minimizing the free energy function, subject to the constraints that the composition variables be non-negative and also satisfy the mass balance relationships. Thus, a mathematical analysis of a particular equilibrium problem could proceed from either premise. Shapiro and Shapley [7] have addressed the question of the relationship between the classical solution of the mass action laws and the minimum in the Gibbs free energy function. In particular, they have demonstrated that in general there can only be a single minimum to the Gibbs free energy function, and hence a unique set of compositions at equilibrium for a chemical system at a defined temperature. Similar results were obtained by Hancock and Motzkin [8].

Although Shapiro and Shapley's work addressed the broad question of the uniqueness of the equilibrium state from the perspective of the Gibbs free energy function, their work does not give any insight into specific computational methods that will permit solution of a particular equilibrium problem. However, starting from the Gibbs free energy function, White et al. [9] have discussed the solution of complex equilibrium problems using standard numerical techniques as well as linear programming methods. Further discussion of this problem can be found in [10–13]. All of these methods, based on the free energy function, depend upon the availability of the appropriate thermodynamic parameters for the system of interest. However, our principal interests lie with systems in aqueous solution, and our work is motivated by problems arising in estimating equilibrium constants. Since the mass action laws are stated in terms of the equilibrium constants, our efforts are focused on the more classical approach using the mass balance equations and mass action laws.

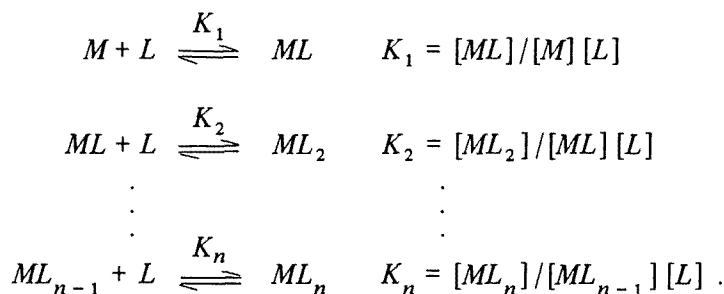
In our efforts to determine equilibrium constants in multi-component systems, our attention has been drawn to the mathematical properties of the general set of equations defining the stepwise equilibrium model. This model describes the interaction between chemical moieties L and M to form simple complexes of type ML_n for various n . The formation of simple inorganic complexes falls into this general case, as does the binding of a ligand to a protein, such as the interaction of palmitic acid with the protein serum albumin. Interestingly, the model used to describe the stepwise formation of polymers from monomers also fits this mathematical model [14]. In this paper, our efforts are focused on the calculation of the concentrations of all species present in solution from (assumed) values of the equilibrium constants of a system. This calculation is important not only because it yields the concentrations of all species present, but also because it is a calculation that typically must be made at each iteration in a nonlinear least squares procedure for estimating equilibrium constants from experimental data.

One result of these efforts is the proof of a theorem which validates some earlier approaches taken to determine equilibrium constants, and yields a rapid and reliable algorithm for the actual computation of the concentrations of the species present.

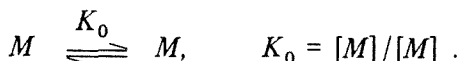
A second result of our investigation of the mathematical properties of the system of equations governing the stepwise equilibrium model is the determination of the total concentrations of the species M and L which maximize the concentration of a given complex ML_k for a given set of equilibrium constants. This is important for experimental design because it determines experimental conditions conducive to observing a particular complex in solution. Thus, if we want to observe this complex spectrophotometrically, we would choose the set of initial total concentrations which gives the greatest concentration of that complex in solution.

2. The stepwise equilibrium model

The use of the stepwise equilibrium model to describe the interaction of a metal ion or protein with a ligand is extremely common in both inorganic chemistry and in biochemistry. Interactions such as these can be described by the following equilibria expressions*:



The K_i are the equilibrium constants, and the quantities in brackets are the concentrations of the indicated species. For notational and mathematical reasons, it is convenient to introduce an additional equilibrium constant K_0 , always equal to 1, which can be thought of as arising from the trivial equilibrium expression



We make the convention that $[ML_0] = [M]$, and write a_i for the concentration $[ML_i]$. (Thus, a_0 is the free metal concentration.) Let c be the free ligand concentration $[L]$, let $x_i = K_0 K_1 \dots K_i$, and let L and M denote the *total* ligand and *total* metal concentrations, respectively. Expressing the concentrations a_i in terms of the x_i and the free concentrations, and writing the two mass balance equations of the system leads to the following system of equations, which is the mathematical formulation of the stepwise equilibrium model:

*Note that the activity coefficients of all species are assumed to be invariant with changes in concentration or to be unity, and that the charges on the various species present in solution have been omitted for clarity. If the activity coefficients are unity, the K 's are thermodynamic constants, and if the activity coefficients are constant as a function of concentration, the K 's are "apparent" equilibrium constants.

$$a_i = a_0 x_i c^i, \quad i = 1, 2, \dots, n,$$

$$L = \sum_{i=0}^n i a_i + c,$$

$$M = \sum_{i=0}^n a_i .$$

It is the mathematical properties of this system of equations that bear investigation.

3. Determining the roots of the Bjerrum polynomial

We consider first the problem where the K_i 's, L , and M are known, and it is desired to solve for c and the a_i 's. This calculation yields the concentrations of all species present, and typically must be made at each iteration in a nonlinear least squares procedure for determining equilibrium constants.

Substituting for the a_i 's in the above equations for L and M yields

$$L = \sum_{i=0}^n i a_0 x_i c^i + c, \quad \text{and}$$

$$M = \sum_{i=0}^n a_0 x_i c^i .$$

Solving for a_0 in each of these equations yields

$$a_0 = (L - c) / \sum_{i=0}^n i x_i c^i \quad \text{and}$$

$$a_0 = M / \sum_{i=0}^n x_i c^i .$$

These two equations give

$$(L - c) \left(\sum_{i=0}^n x_i c^i \right) = M \sum_{i=0}^n i x_i c^i ,$$

which in turn gives the equation

$$\left(\sum_{i=0}^n x_i c^i \right) (c + iM - L) = 0.$$

The left-hand side is the well-known *Bjerrum function*, here viewed as a polynomial in c . A root c of this polynomial yields a value for a_0 via the equation

$$a_0 = (L - c) \left/ \sum_{i=0}^n i x_i c^i \right., \quad \text{or via}$$

$$a_0 = M \left/ \left(\sum_{i=0}^n x_i c^i \right) \right..$$

The other a_i 's can then be obtained from $a_i = a_0 x_i c^i$.

Thus, the real problem in finding the concentrations of the various complexes is to find the desired root of the Bjerrum polynomial. It is often implicitly assumed that there is only one root of chemical interest between 0 and L , and that the root found by some variant of Newton's method is the only correct and meaningful one. That there is at least one such root is mathematically trivial. However, we are not aware of any mathematical proof showing that the Bjerrum polynomial can have only one positive root. There is no a priori mathematical reason why there cannot be several roots between 0 and L . More than one root would suggest more than one possible equilibrium state of the chemical system being modeled. One of our principal results is that there is exactly one such root, and thus only one possible set of values for the equilibrium concentrations of the various species. Thus, the mathematical model allows only one equilibrium state. This result is part of the following theorem, which also gives information crucial in calculating the desired root of the Bjerrum polynomial.

It should be noted that our result for the stepwise model is consistent with the results of treatments based on the Gibbs free energy function, which also conclude that there must be a unique equilibrium state [7,8].

THEOREM

Let x_0, x_1, \dots, x_n, L , and M be positive real numbers with $n \geq 0$. Then the polynomial

$$p(c) = \sum_{i=0}^n x_i c^i (c + iM - L)$$

satisfies the following conditions:

- (1) $p(c)$ has exactly one positive root r .
- (2) $r \leq L$.
- (3) The derivatives of $p(c)$ of all orders are non-negative for all $c \geq r$.

Proof

The proof will be by induction on n or, equivalently, on the degree of $p(c)$, which is $n + 1$. If that degree is 1, then $p(c) = x_0(c - L)$, and (1), (2), and (3) are clearly satisfied. Now let the degree $n + 1$ of $p(c)$ be greater than 1, and suppose that all polynomials of the form indicated and of degree less than that of $p(c)$ satisfy (1), (2), and (3). We need this to imply that

$$p(c) = \sum_{i=0}^n x_i c^i (c + iM - L)$$

satisfies (1), (2), and (3). Since $p(0) = -x_0L$ is negative and

$$p(L) = \sum_{i=0}^n x_i L^i (iM)$$

is ≥ 0 , $p(c)$ has at least one positive root $\leq L$.

Now we need to distinguish two cases, $M \geq L$ and $M < L$. If $M \geq L$, then the derivative

$$p'(c) = \sum_{i=1}^n [x_i i c^{i-1} (c + iM - L)] + \sum_{i=0}^n x_i c^i$$

is positive for all $c \geq 0$, and hence $p(c)$ has exactly one positive root between 0 and L . It is clear that $p(c)$ satisfies requirement (3) as well.

If $M < L$, then $L - M > 0$, and we write

$$p(c) = x_0(c - L) + c \sum_{i=1}^n x_i c^{i-1} [c + (i - 1)M - (L - M)] .$$

Let $y_i = x_{i+1}$ for $i = 0, 1, \dots, n - 1$. Then

$$p(c) = x_0(c-L) + c \sum_{i=0}^{n-1} y_i c^i [c + iM - (L-M)] .$$

Let

$$q(c) = \sum_{i=0}^{n-1} y_i c^i [c + iM - (L-M)] .$$

Using the fact that $L - M$ is positive, we see that $q(c)$ is a polynomial of the same form as $p(c)$. Since the degree of $q(c)$ is less than that of $p(c)$, the induction hypothesis implies that $q(c)$ satisfies the conditions of the theorem, which means that $q(c)$ has exactly one positive root r , $r \leq L - M$, and the derivatives of $q(c)$ of all orders are non-negative for all $c \geq r$. Note that

$$p(c) = x_0(c-L) + c q(c) .$$

Since the derivatives of $q(c)$ of all orders are non-negative for all $c \geq r$, it follows that the derivatives of $p(c)$ are non-negative for all c equal to or greater than the positive root r of $q(c)$. Since $q(c)$ is negative for $0 < c < r$, the polynomial $c q(c)$ is 0 at $c = 0$ and is negative for $0 < c < r$. Since $r \leq L$, adding $x_0(c - L)$ to $c q(c)$ yields a polynomial which is negative for $0 \leq c \leq r$, satisfies (3) for $c \geq r$, and is positive at L . Therefore, the resulting polynomial, which is $p(c)$, has exactly one root between r and L , and that root is greater than r . Thus, $p(c)$ satisfies (1) and (2). Since $p(c)$ satisfies (3) for $c \geq r$, it satisfies (3) for all c greater than or equal to its own positive root. This concludes the proof.

Since the first and second derivatives of $p(c)$ are non-negative for all c equal to or greater than the positive root of $p(c)$, Newton's method is ideal for finding that root numerically, *if the initialization point is taken to be L* (see fig. 1). If $M > L$, then the derivative $p'(c)$ of $p(c)$ is positive for c positive, but if $M < L$, then $p'(c)$ can attain negative values for positive c . In this case, taking the initialization point to be less than L may not lead to a solution at all. However, with a desktop computer and the initialization point L , Newton's method will produce in a very few seconds the positive root of a Bjerrum polynomial of degree six.

The degree of $p(c)$ is $n + 1$. For the degree no more than 4, there are formulae for the roots of $p(c)$, but for degree 4 especially, the formulae are cumbersome, and it is much easier, and no doubt just as fast and accurate, to find the positive root of $p(c)$ via Newton's method.

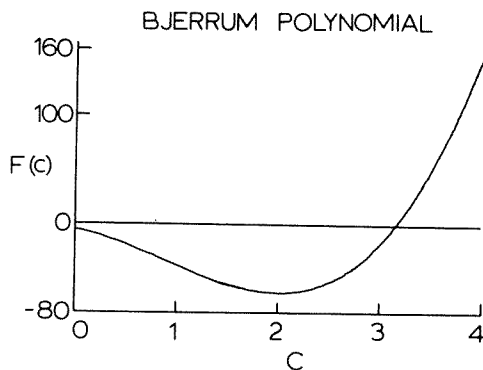


Fig. 1. A plot of the Bjerrum polynomial for $n = 2$, $M = L = 5$, $x_1 = 5$, and $x_2 = 10$. This cubic illustrates the important characteristics of the Bjerrum polynomial, in particular the single root between 0 and L , and the positive and increasing slope for $c > r$.

4. Maximizing the concentration of a complex

We now consider the problem of determining the total concentrations of the compounds M and L which maximize the concentration of a particular complex ML_k for a given set of equilibrium constants. Choosing such total concentrations gives conditions conducive to observing that particular complex in solution, and can be important in the design of an experiment.

The specific mathematical problem is to find the relation between L and M , purely in terms of the equilibrium constants, that maximizes a_k . Then from a value of L or of M , one can choose the values of the other that maximizes a_k . We choose to express L as a function of M . So, given the quantities x_1, x_2, \dots, x_n and M , we must find L so as to maximize a_k for a given k . Thus, a_k is a function of L , and we need to know which positive L makes a_k biggest. From the equations describing the stepwise equilibrium model, it is clear that a_0 is maximum when $L = 0$. For $k > 0$, we will determine when $\partial a_k / \partial L = 0$. This will be done as follows. First we will show that for $c > 0$, $\partial L / \partial c > 0$. That is the difficult part, although it just corresponds to the chemically apparent fact that increasing the total concentration of L increases the free concentration of L . The fact that $\partial L / \partial c > 0$ and the relation $\partial a_k / \partial c = (\partial a_k / \partial L)(\partial L / \partial c)$ then shows that $\partial a_k / \partial L = 0$ exactly when $\partial a_k / \partial c = 0$. Thus, we can find the L that maximizes a_k by finding the c that maximizes a_k . The required L is the one corresponding to that c .

Of course, it is not clear that there is an L that maximizes a_k . Indeed, for $k = n$ there is no such L , as is intuitively clear from the fact that if L is increased indefinitely, the only species present would be ML_n and free L . However, for $k < n$, the quantity a_k does attain a maximum with respect to L .

The relationship between L and c is given by

$$\sum_{i=0}^n x_i c^i (c + iM - L) = 0,$$

from which we get

$$L = c + (M \sum_{i=0}^n x_i i c^i) / \sum_{i=0}^n x_i c^i.$$

LEMMA

For $c > 0$, $\partial L / \partial c > 0$. That is, L is a strictly increasing function of c when $c > 0$.

Proof

Let $D = \sum_{i=0}^n x_i c^i$, and D' be its derivative with respect to c . From

$$\begin{aligned} L &= c + (M \sum_{i=0}^n x_i i c^i) / \sum_{i=0}^n x_i c^i \\ &= c + (M \sum_{i=0}^n x_i i c^i) / D, \end{aligned}$$

we get

$$\partial L / \partial c = 1 + (DM \sum_{i=0}^n x_i i^2 c^{i-1} - M \sum_{i=0}^n x_i i c^i D') / D^2.$$

Therefore, $\partial L / \partial c$ is positive if

$$\begin{aligned} &D \sum_{i=0}^n x_i i^2 c^{i-1} - \sum_{i=0}^n x_i i c^i D' \\ &= \left(\sum_{i=0}^n x_i c^i \right) \left(\sum_{i=0}^n x_i i^2 c^{i-1} \right) - \left(\sum_{i=0}^n x_i i c^i \right) \left(\sum_{i=0}^n x_i i c^{i-1} \right) \end{aligned}$$

is positive. But this expression is

$$\begin{aligned} & \sum_{i,j} x_i x_j c^{i+j-1} c^{j-1} - \sum_{i,j} x_i x_j i j c^i c^{j-1} \\ &= \sum_{i,j} x_i x_j c^{i+j-1} j(j-i) = \sum_{i,j} x_i x_j c^{i+j-1} i(i-j), \end{aligned}$$

so

$$2 \sum_{i,j} x_i x_j c^{i+j-1} j(j-i) = \sum_{i,j} x_i x_j c^{i+j-1} (j-i)^2,$$

which is positive when $c > 0$. Therefore, $\partial L/\partial c$ is positive whenever $c > 0$. This completes the proof.

From the relation $\partial a_k/\partial c = (\partial a_k/\partial L)(\partial L/\partial c)$ and the fact that $\partial L/\partial c$ is positive whenever $c > 0$, we get that $\partial a_k/\partial L$ is zero exactly when $\partial a_k/\partial c$ is zero. Thus, the L that maximizes a_k is the one corresponding to the c that maximizes a_k . Now, for those $k \geq 1$,

$$f(c) = a_k = a_0 x_k c^k = M x_k c^k / \sum_{j=0}^n x_j c^j, \quad \text{and}$$

$$\partial a_k/\partial c = \left[\left(\sum_{j=0}^n x_j c^j \right) M k x_k c^{k-1} - M x_k c^k \sum_{j=0}^n j x_j c^{j-1} \right] / \left(\sum_{j=0}^n x_j c^j \right)^2.$$

Thus, we need the positive roots of

$$\left(\sum_{j=0}^n x_j c^j \right) k - c \sum_{j=0}^n j x_j c^{j-1},$$

or of

$$g(c) = \sum_{j=0}^n (k-j) x_j c^j.$$

If $k = n$, then $g(c)$ has no positive roots, and indeed it is easily seen that a_n converges to M as c goes to ∞ . If $0 < k < n$, then the coefficients of $g(c)$ have exactly one sign change, from positive to negative, namely at that term where $j = k + 1$. By Descartes' rule of signs, such a polynomial $g(c)$ has exactly one positive root. Thus, there is only one flat spot on $f(c)$. Since $f(0) = 0$, $f(c) > 0$ for $c > 0$, and $f(c)$ converges to 0 as c goes to ∞ , there is exactly one maximum of $f(c)$ for $c > 0$. This

can be found by finding the unique positive root r of $g(c)$. The L that maximizes a_k is then

$$L = r + (M \sum_{i=0}^n x_i i r^i) / \sum_{i=0}^n x_i r^i.$$

We sum up in the following theorem.

THEOREM

Let $K_i, i = 0, 1, \dots, n$, be the equilibrium constants and let $x_i = K_0 K_1 \dots K_i$. Then for $0 < k < n$, the relation between the total concentrations M and L which maximizes the concentration of the species ML_k is given by

$$L = c + (M \sum_{i=0}^n x_i i c^i) / \sum_{i=0}^n x_i c^i,$$

where c is the unique positive number satisfying

$$\sum_{j=0}^n (k-j) x_j c^j = 0.$$

To carry out computations to find the L maximizing a_k requires finding the unique positive root r of

$$g(c) = \sum_{j=0}^n (k-j) x_j c^j$$

and evaluating the expression

$$r + (M \sum_{i=0}^n x_i i r^i) / \sum_{i=0}^n x_i r^i.$$

To find the positive root of $g(c)$ using Newton's method requires care in choosing the initialization point. If $k > 1$, then the derivative

$$g'(c) = \sum_{j=1}^n j(k-j) x_j c^{j-1}$$

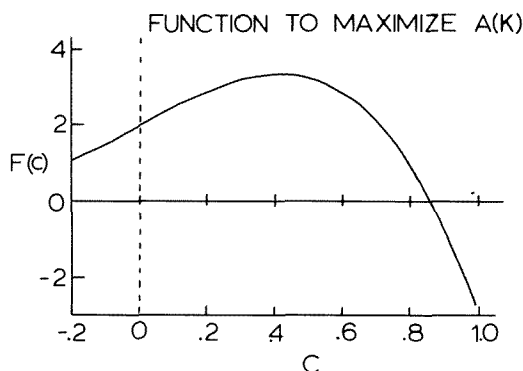


Fig. 2. A representative example of the function used to find the maximum concentrations of a complex ML_k . Values of $k = 2$, $n = 3$, $x_1 = 5$, and $x_2 = 10$ were chosen to illustrate the important characteristics of this function, namely the single maximum and the single root for positive c .

of $g(c)$ has exactly one sign change in its coefficients. Therefore, it has exactly one positive root by Descartes' rule of signs. Since $g'(0) = (k - 1)x_1$ is positive (still assuming that $k > 1$), the polynomial $g(c)$ has the shape shown in fig. 2. Thus, the initialization point for Newton's method must be at a positive number x for which $g'(x)$ is negative. Alternately, one could simply initialize at a positive number x for which $g(x)$ is negative.

When $k = 1$, $g'(c)$ is negative for all positive c , so that one can initialize at any positive number.

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