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A note on the quantitative properties of McGhee–von Hippel model

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Abstract

Exact closed-form expressions are presented for the properties of the McGhee–von Hippel model of non-specific binding of large ligands to one-dimensional homogeneous lattices. These properties include the midpoint location and the slope at the middle point of the binding isotherms ($\upsilon \sim \ln L$ plots), the location and magnitude of the maximum, as well as the location of the inflection point, in the Scatchard plots ($\upsilon/L \sim \upsilon$ plots).

Keywords: Cooperative ligand binding; McGhee–von Hippel model; Scatchard plot; Lattice model; Parking problem

Since its introduction, the McGhee–von Hippel model for non-specific binding of large ligands to one-dimensional homogeneous lattices (also known as multiple-contact binding, multi-valent binding, or parking problems) [1] has been widely used to analyze experimental data. It has also stimulated theoretical and computational investigations to further explore the quantitative properties of the model.

To model co-operative non-specific binding of large ligands to one-dimensional homogeneous lattices, the McGhee–von Hippel model uses three parameters: the intrinsic binding constant K; the unitless cooperative parameter w; and the number of lattice sites covered by one ligand n. Using the conditional probability method, McGhee and von Hippel obtained a closed-form expression for the Scatchard plots, $\upsilon/L \sim \upsilon$, where υ is the number of bound ligands per lattice site and takes a value from 0 to $1/n$, and L is the free ligand activity. The expression was validated by Tsuchiya and Szabo [2] through the manipulation of the secular equation of the transfer matrix, and by Di Cera and Kong [3] using site-specific thermodynamics. In general, the model deviates from the traditional linear Scatchard plots and results in curved plots. For some positively cooperative interactions (see below), the Scatchard plot shows a maximum.

In order to relate the experimental data to the three parameters that characterize the model, Ramanathan and Schmitz [4] used a numerical method on the secular equation of the transfer matrix to obtain empirical equations to express the midpoint location and slope at the middle point of the conventional binding isotherms ($\upsilon \sim \ln L$ plots) [Eqns. (12) and (16) of [4], respectively]. They also obtained an approximate equation to express the location of the maximum in the Scatchard plots

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($v/L \sim v$ plots) using the parameters w and n [Eq. (37) of [4]]. Their conclusions are only approximate, and only apply to a certain range of the parameters. In this paper, we give exact expressions for these three properties, as well as formulae for the magnitude of the maximum and the inflection point for those Scatchard plots which convex upward and have maxima.

1. The model

The McGhee–von Hippel model can be expressed in an alternative form as [3]:

$$\frac{v}{L} = Kw(1-nv)\frac{1+(2w-n-1)v+Q}{(2w-1)(1-nv)+v+Q} \times \left[\frac{2w(1-nv)}{(2w-1)(1-nv)+v+Q}\right]^{n-1} \quad (1)$$

where

$$Q = \sqrt{\left[1-(n+1)v\right]^2 + 4wv(1-nv)} \quad (2)$$

This expression, which is proven to be equivalent to the original equation [3], treats the non-cooperative ($w=1$) and co-operative ($w \neq 1$) situations uniformly, and its algebra can be manipulated more easily than the original formula [Eq. (15) of [1]].

Although the binding density v cannot be expressed explicitly as a function of L for general n and w, which is usually needed if the more conventional plot $v \sim \ln L$ is required, it should be pointed out that L can be expressed *explicitly* as a function of v:

$$L = f(v,w,n) = \frac{v}{Kw(1-nv)} \frac{(2w-1)(1-nv)+v+Q}{1+(2w-n-1)v+Q} \times \left[\frac{(2w-1)(1-nv)+v+Q}{2w(1-nv)}\right]^{n-1} \quad (3)$$

Using Eqs. (1) and (3), we can obtain the following exact expressions.

2. The binding isotherms ($v \sim \ln L$ plots)

2.1. Middle point location

Substituting $v = 1/(2n)$, which is the middle point in the normalized $v_n \sim \ln L$ plot ($v_n = nv$), into Eq. (3), we obtain:

$$KL_{1/2} = \frac{1}{2^{n-1}} \frac{1}{2w+n-1+P} \times \left[\frac{2wn-n+1+P}{wn}\right]^n \quad (4)$$

where

$$P = \sqrt{(n-1)^2 + 4wn} \quad (5)$$

When $n=1$, $KL_{1/2} = 1/w$; for general values of n, however, $wKL_{1/2}$ is not a constant. Expanding Eq. (4), we have:

$$KL_{1/2} \approx \frac{1}{w} - \frac{n-1}{2w^2} + \frac{n^2-1}{6n^{1/2}w^{5/2}} - \ldots \quad (6)$$

$wKL_{1/2}$ approaches 1 only when w is significantly larger than n.

When $w=1$, $KL_{1/2}$ has a simple form:

$$KL_{1/2}|_{w=1} = \frac{(n+1)^{n-1}}{n^n} \quad (7)$$

Fig. 1a shows $wKL_{1/2} \sim w$ for various values of n.

2.2. Slope at the middle point

The slope at the middle point of a normalized $v_n \sim \ln L$ plot is given by:

$$S_{1/2} = \left.\frac{\partial v_n}{\partial \ln L}\right|_{v_n = 1/2} = nL\left.\frac{\partial v}{\partial L}\right|_{v=1/(2n)} = \left.\frac{nf(v)}{f'(v)}\right|_{v=1/(2n)} \quad (8)$$

where $f(v)$ is defined in Eq. (3). Simplification of Eq. (8) yields:

$$S_{1/2} = \frac{1}{16} \frac{n(2w+n-1+P)(2wn-n+1+P)P}{(n^2+Pn+2wn+P+1)w} \quad (9)$$

which is true for any n and w. Ramanathan and Schmitz [4] used numerical calculation to obtain an empirical equation for this property over a small range of w [their Eq. (16)].

For $w=1$, we have:

$$S_{1/2} = \frac{n+1}{8n} \quad (10)$$

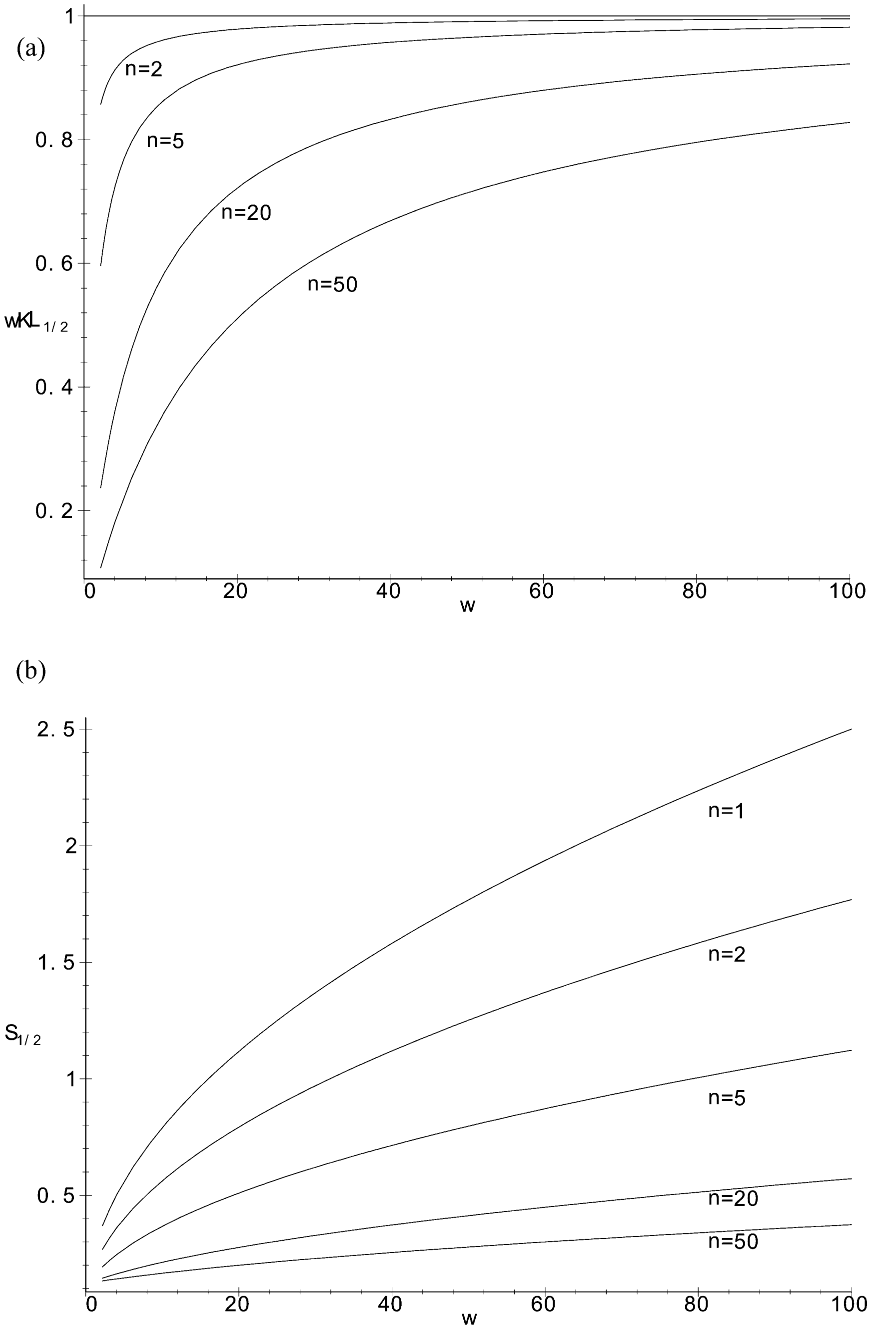

Fig. 1. (a) The midpoint location of the $\upsilon \sim \ln L$ plot times the cooperative parameter w as a function of w for $n=1$, 2, 5, 20 and 50. When $n=1$, $wKL_{1/2}=1$ for all values of w. For $n>1$, $wKL_{1/2}$ approaches 1 only when w is large enough. (b) The slope at the middle point of the normalized $\upsilon_n \sim \ln L$ plot as a function of the cooperative parameter w for $n=1$, 2, 5, 20 and 50.

The slopes at the middle point for various n are shown in Fig. 1b.

3. Scatchard plots ($v/L \sim v$)

3.1. Location of maximum in the Scatchard plots

As pointed out by McGhee and von Hippel [1], when $2w > 2n+1$, the Scatchard plot shows a maximum. Ramanathan and Schmitz [4] gave an approximate equation to relate the position of the maximum to w for the case of $n=1$ [their Eq. (1)] and tried to generalize this relation to any n [their Eq. (37)]. In this paper, we give the exact formula for the location of maximum in the Scatchard plot.

Differentiation of Eq. (1) yields a cubic equation of v for the position of the maximum v_m:

$$c_3 v^3 + c_2 v^2 + c_1 v + c_0 = 0 \tag{11}$$

where

$$c_3 = n^2\left[4wn - (n+1)^2\right] \tag{12a}$$

$$c_2 = -2n\left[6wn - (2n+1)(n+1)\right] \tag{12b}$$

$$c_1 = 12wn - 6n^2 - 6n - 1 \tag{12c}$$

$$c_0 = -2(2w - 2n - 1) \tag{12d}$$

Solving Eq. (11) for w, we obtain an express of w as a function of n and the location of the maximum v_m:

$$wpw = \frac{(n^2 v_m + n v_m - 2n - 1)(n^2 v_m^2 + n v_m^2 - 2n v_m - v_m + 2)}{4(n v_m - 1)^3} \tag{13}$$

When $n=1$, Eq. (13) reduces to:

$$w = \frac{(2v_m - 3)(2v_m^2 - 3v_m + 2)}{4(v_m - 1)^3} \tag{14}$$

Obviously Eqs. (13) and (14) differ from the approximate equations in Ramanathan and Schmitz [4].

Solving the cubic equation [Eq. (11)] for v, we can obtain the exact location of the maximum expressed as a function of w and n. The exact closed-form solution can be approximated as:

$$v_m \approx \frac{1}{n} - \frac{1}{2}\frac{2^{1/3}}{n^{2/3}w^{1/3}} - \frac{1}{12}\frac{2^{2/3}}{n^{1/3}w^{2/3}} - \frac{1}{12}\frac{n^2-1}{n^2 w} - \frac{2^{1/3}(35n^2+54n+18)}{648 n^{5/3} w^{4/3}} + \ldots \tag{15}$$

It can be seen from Eq. (13) and Fig. 2a that when w approaches infinity, the location of the maximum approaches $1/n$ (1 in the figure for the normalized curves); As w decreases, the location of the maximum shifts to 0. When $2w-2n-1=0$, c_0 in Eq. (11) vanishes, the maximum is located at $v=0$. When $2w-2n-1<0$, Eq. (11) does not have a real root in the range $[0\ldots 1/n]$, so the Scatchard plot will not have a maximum.

3.2. Magnitude of maximum in the Scatchard plot

Substituting the exact solution of v_m, from above into Eq. (1), we can obtain the magnitude of the maximum. The exact formula can be expanded and approximated as:

$$\left(\frac{v}{L}\right)_m = K\left[\frac{w}{n} - 3\left(\frac{w}{2n}\right)^{2/3} + \frac{7}{2}\left(\frac{w}{2n}\right)^{1/3} - \frac{(3n+1)(9n-1)}{12n^2} + O\left(\left(\frac{w}{2n}\right)^{-1/3}\right)\right] \tag{16}$$

The antagonistic relation between n and w is clearly demonstrated in Eq. (16).

In the original paper, an inequality is set up for the magnitude of the maximum in the Scatchard plot without proof:

$$\frac{w}{2n} < \frac{1}{K}\left(\frac{v}{L}\right)_m < \frac{w}{n} \tag{17}$$

Here we give a brief proof.

Substituting w in Eq. (13) into Eq. (2), we have:

$$Q_m = \frac{1}{1 - n v_m} \tag{18}$$

Substituting Q_m into Eq. (1), we obtain the equation which relates the magnitude of the maximum to the location of the maximum:

$$\frac{1}{K}\left(\frac{v}{L}\right)_m = \frac{1}{4(1-nv_m)^3}\frac{\left[(1-nv_m)^2 - v_m(1-nv_m) + 1\right]^{n+1}}{\left[(1-nv_m)^2 + v_m(1-nv_m) + 1\right]^{n-1}} \tag{19}$$

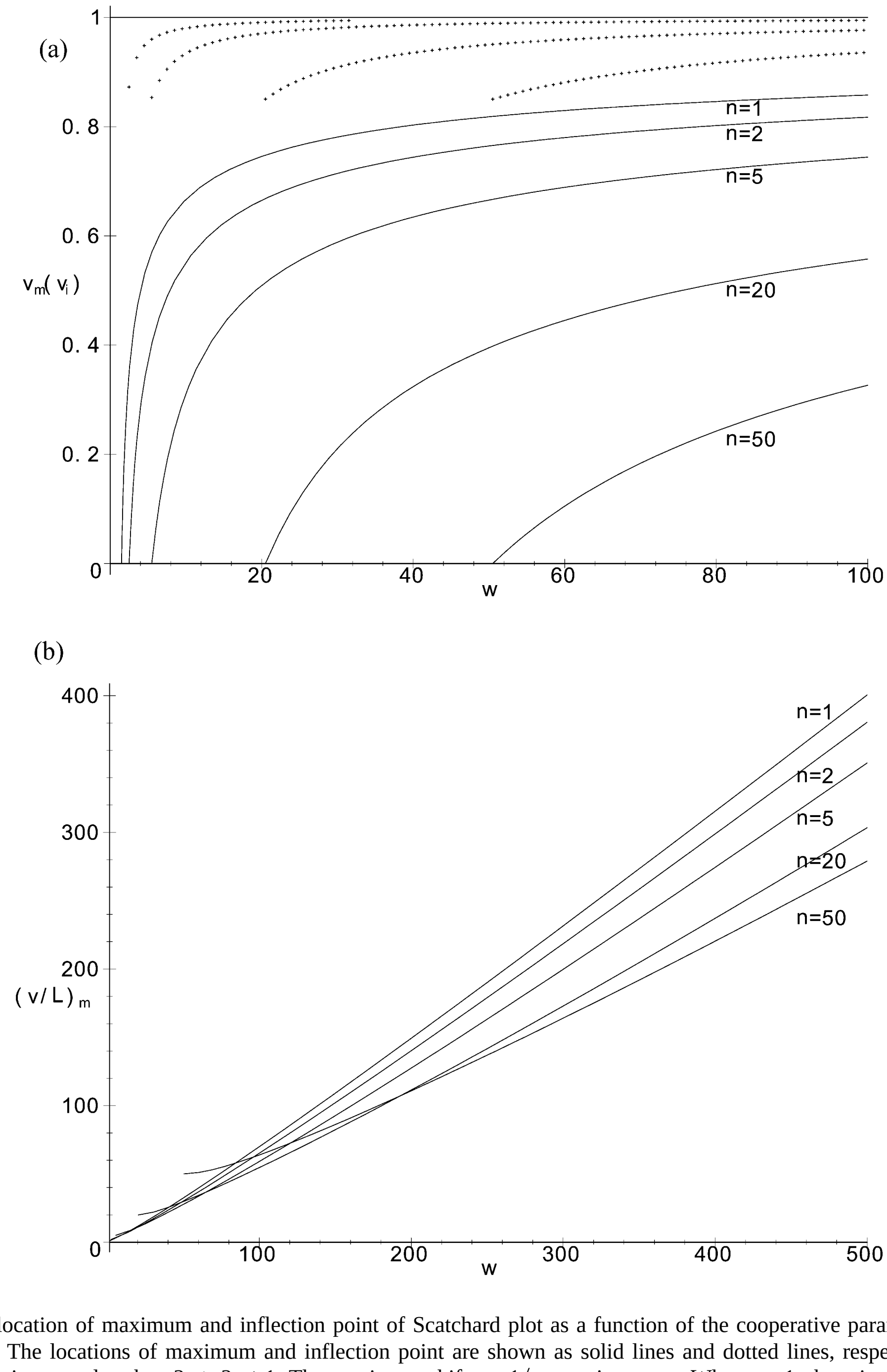

Fig. 2. (a) The location of maximum and inflection point of Scatchard plot as a function of the cooperative parameter w for $n=1$, 2, 5, 20 and 50. The locations of maximum and inflection point are shown as solid lines and dotted lines, respectively. Scatchard plot shows a maximum only when $2w>2n+1$. The maximum shifts to $1/n$ as w increases. When $n=1$, there is no inflection point for the Scatchard plot; when $n>1$, the inflection point lies between the maximum and $1/n$. The locations are normalized by n so that the plots of different n can be compared. The horizontal line at 1 only serves as a visual guide. (b) The magnitude of the maximum in Scatchard plot as a function of the cooperative parameter w for $n=1$, 2, 5, 20 and 50. $K=1$ is used for all the curves. The curves are normalized by n so that the plots of different n can be compared.

Using Eq. (13) again, we can obtain:

$$\frac{1}{K}\left(\frac{v}{L}\right)_m = w\frac{1}{2n+1-nv_m^2-nv_m}\frac{\left[(1-nv_m)^2-v_m(1-nv_m)+1\right]^n}{\left[(1-nv_m)^2+v_m(1-nv_m)+1\right]^{n-1}} = wh(n,v_m) \tag{20}$$

Notice that the function $h(n,v)$ does not depend on w. In the region [0, $1/n$], where v_m takes its value, the function $h(n,v)$ obtains its maximum at $v=1/n$ as $h(n,1/n)=1/n$, and obtains its minimum at a value $v_0(n)$ where $v_0(n)$ is one of the roots of equation $n(n+1)v^2-(4n+1)v+2=0$, i.e. $v_0(n)=\dfrac{4n+1-\sqrt{8n^2+1}}{2n(n+1)}$. This is the only value in the region [0, $1/n$] where the derivative of the function $h(n,v)$ vanishes. At the value $v_0(n)$, the minimum of $h(n,v)$ multiplied by n increases monotonically as a function of n:

$$nh\big(n,v_0(n)\big)\big|_{n=1}=1/2 \qquad \text{and}$$

$$nh\big(n,v_0(n)\big)\big|_{n=\infty}=2\big(\sqrt{2}-1\big)e^{-(\sqrt{2}-1)}=0.5475.$$

From these results, we get:

$$\frac{w}{2n}\leq w\min\big(h(n,v_m)\big)<\frac{1}{K}\left(\frac{v}{L}\right)_m=wh(n,v_m) < w\max\big(h(n,v_m)\big)=\frac{w}{n} \tag{21}$$

The location and the magnitude of the maximum for various n as a function of w are given in Fig. 2a,b, respectively.

3.3. location of inflection point in the Scatchard plot

As co-operativity becomes more positive, the location of the maximum of the curved Scatchard plot becomes closer to $1/n$, and the plot becomes very steep. Counter-intuitively, as pointed out by Schwarz [5], the end slope of the Scatchard plot is zero, except for $n=1$, which is $-Kw^2$ (it was misprinted as $-Kw$ in [5]). The reason for this is that when $n>1$, it is not possible to bind any ligand to the lattice if only *one* empty site is left in the lattice. When $n>1$, the Scatchard plot will show an inflection point which lies between v_m and $1/n$, if the plot indeed has a maximum. Although it might be difficult to reach this portion of the curve experimentally, for completeness we give the equation of the inflection point here.

Differentiating Eq. (1) twice, we end up with a quartic equation for the location of this inflection point:

$$d_4v^4+d_3v^3+d_2v^2+d_1v+d_0=0 \tag{22}$$

where

$$d_4=n^2\big[4wn-(n+1)^2\big]^2 \tag{23a}$$

$$d_3=-2n^2\big[4wn-(n+1)^2\big][2w-n-1] \tag{23b}$$

$$d_2=-n\big[6wn-(n+1)(n+2)\big][2w-n-1] \tag{23c}$$

$$d_1=-4n\big[4wn-2w^2+2w-(n+1)^2\big] \tag{23d}$$

$$d_0=2(2wn+2w^2-2w-n^2-n) \tag{23e}$$

Although Eq. (22) has a closed-form solution, it is too complicated to write down. However, we can have a series expansion of the exact solution as:

$$v_i\approx\frac{1}{n}-\frac{1}{18n}\left[\frac{n^2-3}{n}+\sqrt{n^2+3}\right]\frac{1}{w}-\frac{1}{972n^2}\times\left[\frac{14n^4+27n^3-81n-36}{n}+\frac{14n^4+27n^3+81n+9}{n^2+3}\sqrt{n^2+3}\right]\frac{1}{w^2} \tag{24}$$

The exact locations of the inflection point for various n are shown in Fig. 2a. As can be seen from Fig. 2a, the location of the inflection point lies very close to $1/n$.

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