Response Curves for Radioimmunoassay

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In quantitative estimates from radioimmunoassay, one of four types of response curves is usually used: a freehand curve, a spline function, an equation based upon mass-action considerations, or a logistic equation. This paper comments briefly on the subjectivity and labor of the first and on the overparameterization of the second. It is chiefly concerned to compare the single binding-site equation with a simple or modified logistic. Whatever the theoretical merits of the binding-site approach (these are not under discussion), estimation of parameters is difficult. The paper shows that under many but not all circumstances a four- or five-parameter logistic will fit data at least as well over a wide range of doses. This is particularly so when both the binding-site concentration and the equilibrium constant are small.

Many users of radioimmunoassay make no formal statistical analyses and rely on reading from freehand curves. Those who examine their data more critically include warm supporters of two very different formulations of the response curve. How important is this difference in practice? The multiple binding-site equation purports to represent the mass-action relations that determine the response. Without clear contrary evidence, a statistician should not challenge its merits, but its estimation from observed counts is often unsatisfactory because calculation of parameters converges slowly. The logistic equation has no theoretical pretensions but is simple to estimate; its similarity to equations used in various types of bioassay facilitates a uniform approach to problems of similar logical content.

For study directed at better understanding of radioimmunoassay technique, attention to the binding-site equation is needed. This paper is concerned solely with routine use of RIA, for which purpose any adequate calibration of unknown samples relative to the standard preparation will suffice. The equation must agree well with the data, but ease of handling can be balanced against theoretical correctness; whether or not the binding-site equation is "true" is not under discussion. The approach is to establish a simple rule for finding a logistic equation approximating to an arbitrary single binding-site equation, to assess the quality of this approximation, and to point out that this represents a lower limit to the agreement in an actual RIA. The results will not help the choice of an equation for an individual RIA, but may guide the application of experience with a particular type of assay.

The Two Equations

Whether expressed in terms of counts or of percent bound, the standard response curve represents the functional dependence of average or "expected" count upon dose. If \( u \) is a count (fixed time) for the bound portion of a sample at a dose \( z \), the expectation of \( u \),

\[
U = E(u|z)
\]

(1)
is determined by \( z \) and various parameters. Although the variance of \( u \) is important to the estimation, it is irrelevant to the choice of response function. The multiple binding-site equation (1, 2; symbols slightly altered to aid systematic presentation) is:

\[
R^{-1} = N + \sum_{i=1}^{s} \frac{Q_i}{z_0 + z + \frac{1}{K_i}}
\]

(2)

where

\[
R = (T - U)/U.
\]

(3)

Summation is over \( s \) binding-sites, \( T \) is the total count, \( N \) the nonspecific binding term, \( z_0 \) the concentration of labelled antigen, and \( Q_i \) and \( K_i \) the concentration and the equilibrium constant for binding site \( i \). The parameter \( T \) is easily and cheaply measured with high precision, and can usually be regarded as a known constant; \( N, z_0, \) and all \( Q_i, K_i \) must be estimated. Equation 2 displays the character of the system, but the following form

\[
\frac{U}{T - U} = N + \sum_{i=1}^{s} K_i Q_i T (z_0 + z)(T - U) + T
\]

(4)
is more compact. Only when \( s = 1 \) can equation 4 be solved to express \( U \) as an explicit function of \( z \) and the parameters, and even then estimation may converge slowly. Cox et al. (1), who state that many assays require \( s \geq 2 \), have developed computing procedures for estimating the parameters of equation 4. However, widespread use of an equation with so many parameters would require more standard doses to be included than is now customary.

The four-parameter logistic equation is (3, 4):

\[
U = C + \frac{D - C}{1 + (z/A)^D}
\]

(5)

All parameters are positive and \( D > C \); some authors write \( C, D, A \) for \( A, B, C \), and \( D \), respectively, but the notation here agrees closely with that introduced for quantal response bioassay in 1944 (5). Estimation is much easier for this explicit function of \( z \) and the parameters, but an equation with four parameters cannot have all the flexibility of fitting possessed by an alternative with \( 2s + 2 \) parameters. A modified logistic equation

\[
U = C + \frac{(D - C)(1 + (z/A)^P)^\gamma}{1 + (z/A)^P}
\]

(6)

has occasionally been found useful (6), the fifth parameter, \( \gamma \), introducing an asymmetry that better describes some data.

If equations 5 and 6 can approximate well to the single-site case of equation 4, can they be generalized so as to be a good approximation when \( s = 2 \) while retaining an explicit expression for \( U \) in terms of \( z \) and so being easier to fit? Rodbard et al. suggested (7):

\[
U = C + (D - C) \sum_{i=1}^{s} P_i [1 + (z/A)^B_i]^{-1}
\]

(7)

where \( \Sigma P_i = 1 \), and alternatives with a comparable number
of parameters. Like any measuring or calibrating device, an assay technique for routine use should be simple and without possibility of ambiguities; if a many-parametered response curve is needed, perhaps a different technique ought to be sought.

The Meanings of Parameters

In equations 2 and 4, the parameters \( z_0, Q_i, \) and \( K_i^{-1} \) have the physical dimensions of a dose; both \( N \) and \( R \) are dimensionless quantities, and \( T \) is a count. Changes in \( T \) (with proportional changes in bound and free counts) do not alter the shape of the curve. The binding-site parameters \( z_0, N, Q_i, \) and \( K_i \) are meaningful in chemical terms but their effects on the response curve are not easily isolated. Equation 6 has five parameters but does not involve \( T \). Changes of \( C \) and \( D \) in the same proportion alter scale but do not affect shape, and \( A \) depends on the unit of dose. The remaining parameters have distinct roles in relation to the shape of the curve: \( C/D \) is the proportion of \( D \) attributable to nonspecific binding, \( B \) relates to the rate at which bound count decreases with increasing dose, and \( \gamma \) measures asymmetry or skewness when \( U \) is plotted vs log dose.

The main concern of this paper is the choice of parameters in equation 6 to make that equation approximate to equation 4 with \( s = 1 \). Insofar as this succeeds with one pair of equations, it will work equally well for other pairs for which the ratios \( D/T \) and \( A/z_0 \) keep the same values. There is no implication that the single binding-site equation is ideal. Those who normally find the logistic equation suitable for their data have no reason to change. But for circumstances where the binding-site equation is strongly advocated it is relevant to enquire whether the logistic, which lends itself more to statistical analysis, can do the job equally well.

Objectives

The aim of RIA is to construct a calibration curve that relates the expected count to dose for quantities of the standard ligand, and then to use the counts from an “unknown” sample to infer the concentration of the ligand in that unknown. If replicate counts at a dose of the unknown have a mean \( \bar{u} \), the concentration is estimated as the value of \( z \) in the calibration equation that has \( U = \bar{u} \). There are variants and complications if the time of counting is not constant, or if two or more different doses of an unknown have been used, but these do not affect the principle. Equations 5 and 6 have the convenience of being representable by a straight line in terms of the logit transform and the logarithm of dose (8). This assists appreciation of the parallelism requirement for a valid assay, a criterion equally important if equation 4 is used.

Estimation

The standard curve must be estimated from counts for the bound portions of samples containing known doses of the ligand. Estimation involves finding numerical values of parameters so as to optimize agreement between the data and corresponding values calculated from the fitted equation. The process should also produce estimates (at least asymptotically valid) of variances and covariances. These in turn can be used to assess the precision of potency estimates for the unknowns. For good data, choice of optimality criterion may be the least important consideration. The obvious choice is weighted least squares; when, as here, the weights also involve the parameters that are to be estimated, the quasi-likelihood modification (9) is useful. Whether the occasional occurrence of outliers is better handled by regular use of a “robust” estimation technique as an insurance policy or by detection and rejection is a question deserving more attention than it has received. Frequent occurrence of outliers is intolerable: it calls for improvement in laboratory practice, not the hiding of an avoidable imperfection by robust estimation.

Cox et al. (1) worked with R, equation 3. They do not distinguish between observations and functions of parameters, so that it is not clear exactly how they perform their computations. They appear to take a metamer

\[
r = \frac{T - u}{u} = \frac{T}{u} - 1
\]

with variance

\[
\text{Var}(r) = (a_0 + a_1 R)^2
\]

and fit \( r \) to equation 2 by a weighted least squares procedure adapted to the implicit character of the equation. Estimation is better handled in terms of observations directly and independently recorded: \( u \) is more likely to be approximately normally distributed than is its reciprocal. A reasonable approximation (8) is that \( u \) is normally distributed about \( U \) with variance

\[
\text{Var}(u) = V(U)^2
\]

where \( V \) is a constant multiplier and \( J \) is usually in the range 1.0 to 1.5. To the first order,

\[
\text{Var}(r) = \text{Var}(u) \cdot \left( \frac{\partial R}{\partial u} \right)^2 = V(1 + R^4 - J T^2 - J)
\]

which is equivalent to equation 9 with \( a_0 = a_1 \) and \( J = 2 \). However, if \( J \geq 2 \), problems of convergence arise for weighted least squares estimation relative to \( U \). This will be reflected in similar difficulties for fitting relative to \( R \); a weight based on equation 9 may therefore be on the critical edge for convergence. The parametric formulation of \( U \) does not affect the manner in which the variance of \( u \) depends on \( U \). Variance derives from the departures of individual counts from their expectations: the variance of \( r \) must be the corresponding transform of \( \text{Var}(u) \).

Comparing the Equations

Feldman and Rodbard (10) illustrated extensively circumstances in which the single binding-site equation appears very similar to the logistic, not least under conditions said to be optimal for RIA. Rodbard (11) has compared qualitatively a wide assortment of suggested equations. As will be shown, for some combinations of parameter values the logistic equation 5 or 6 can be almost indistinguishable from the single binding-site equation. In such circumstances, a fitted logistic would certainly be as good a basis for calibration and might even be appreciably better. On the other hand, some combinations of binding-site parameters are not well mimicked by the logistic, discrepancies being large in parts of the range.

The Appendix summarizes simple algebraic formulas for obtaining a logistic equation that will approximate to the single binding-site equation. The logistic so obtained is not claimed to be “best,” and indeed there is no obvious criterion for optimality. It is, however, a simply and objectively determined lower limit to the quality of approximation. If this set of parameters is good enough for a set of data, the best logistic fit will be better. The important question is whether the response curves usually encountered in RIA have parameters that make the distinction between the two formulations numerically negligible, or whether curves are often such that one form of equation will fit noticeably better than the other.
Numerical Studies

Under what conditions is equation 6, or even equation 5, able to mimic equation A1 sufficiently well for any difference to be negligible? Relative deviation on the dose scale should be the criterion, because this is relevant to any bias in potency estimation. Consideration of scales indicates that, when a logistic equation is paired with a binding-site equation as described in the Appendix, the percentage difference between corresponding doses (i.e., doses for which expected counts are equal) depends solely on N, Kx0, and Q./x0. Study has been concentrated on N = 0.05 (or C/T = 0.048) but some computations were also made for N = 0.025, 0.1, and 0.2. No larger N seems likely to be of interest, for N = 0.2 corresponds with C/T = 0.17, or 17% binding for blanks. All deviations were calculated by using g = 50 in equation A10; slight differences occur for any other g.

Results were little affected by changes in N. The much greater influence of other parameters is most easily displayed in terms of Qx0 and KQ. Table 1 shows, for many combinations, the range of doses for which the corresponding dose for the five-parameter logistic differs by at most 10%. Dose is expressed as a multiple of that for the mid-response (C + D)/2, on which scale the upper limit always exceeds 500 and usually exceeds 10,000. Routine assays with more than 90% binding for blanks are unlikely to be important, and results with D > 0.9T have been excluded. If Qx0 and KQ are both small, 10% deviations of dose for the logistic curve do not occur except for very small or very large z. On the other hand, if Qx0 exceeds 2, unless KQ is still exceedingly small such deviations may occur for doses up to half that for the mid-response.

Table 2 is a similar table for 2% deviations. Where not otherwise noted, the range of small deviations extends almost to 100, and often to 10,000. Nevertheless, if 2% discrepancies are important, the distinction between equations 6 and A1 is evidently much more marked. Almost all deviations, small and large, were negative, suggesting that equations A8–A10 produce a consistently biased logistic approximation. Possibly some adjustment could improve the agreement, and better indicate the consequences of fitting both types of equation to the same experimental data. Though some may consider 10% to be too wide a tolerance, a reasonable choice should lie between that and 2%. Comparisons presented in Table 3 make clear that further attention to the value of N is unnecessary.

These computations used the five-parameter logistic. Over most of the parameter combinations explored, γ was close to 1; this is always so for small Kx0, but for large Kx0 and large Q/x0 the Appendix procedure may give γ smaller than 0.5. The consequences of using equation 5 instead of equation 6 have therefore been examined. Table 4 is like Table 1 except for the constraint that γ = 1. When K and Q are small enough to ensure that the calculated γ exceeds 0.9, there is little to choose between the two. For larger K and Q, the overall advantage is with Table 1, as is to be expected, though in general γ = 1 gives better agreement at low doses. For example, with Qx0 = 2 and KQ = 2.56, the Appendix gives γ = 0.74; 10% agreement is achieved for all relative doses above 0.24, and 2% agreement between 0.48 and 236, but γ = 1 leads to 10% agreement between 0.08 and 4.1—a better lower limit but a much poorer upper limit.

Malan et al. (12) have found that at least 80% of assays can be fitted by equation A1. My experience is limited, but I have been unable to find data for which this equation fits better than equation 6. In a paper with objectives similar to those of the present paper but tackling them entirely differently, Raab (13) analyzed 40 assays for 10 different analytes and found few examples of superiority for equation A1. This is perhaps not surprising when one notes estimates of Qx0 and KQ reported for various assays (1, 12):

Table 3. Comparison of Values of Relative Dose in Tables 1, 2 with Corresponding Values for Different N

<table>
<thead>
<tr>
<th>Qx0</th>
<th>KQ</th>
<th>0.025</th>
<th>0.05</th>
<th>0.1</th>
<th>0.2</th>
<th>0.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% deviations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>0.16</td>
<td>0.0078</td>
<td>0.0075</td>
<td>0.0068</td>
<td>0.0057</td>
<td>0.0039</td>
</tr>
<tr>
<td>2</td>
<td>0.64</td>
<td>0.12</td>
<td>0.12</td>
<td>0.11</td>
<td>0.11</td>
<td>0.09</td>
</tr>
<tr>
<td>8</td>
<td>1.28</td>
<td>0.25</td>
<td>0.25</td>
<td>0.24</td>
<td>0.23</td>
<td>0.21</td>
</tr>
<tr>
<td>32</td>
<td>1.28</td>
<td>0.27</td>
<td>0.27</td>
<td>0.26</td>
<td>0.25</td>
<td>0.22</td>
</tr>
<tr>
<td>128</td>
<td>1.28</td>
<td>0.28</td>
<td>0.27</td>
<td>0.26</td>
<td>0.25</td>
<td>0.23</td>
</tr>
</tbody>
</table>

| 2% deviations |
| 0.5  | 0.16 | 0.14  | 0.14  | 0.13  | 0.12  |
| 2    | 0.64 | 0.37  | 0.36  | 0.36  | 0.35  |
| 8    | 1.28 | 0.51  | 0.51  | 0.50  | 0.49  |
| 32   | 1.28 | 0.53  | 0.53  | 0.52  | 0.51  |
| 128  | 1.28 | 0.53  | 0.53  | 0.52  | 0.51  | 0.49  |

*These are fitted with s = 2.

Elsewhere (14), Malan comments that equation A1 should perform well relative to equations 5 and 6 because it does not demand symmetry above and below the mid-response. This argument may mislead. Even the simplest curve has the four distinguishable characteristics describable as upper and lower limits (at extremes of z), position on the z-scale, and steepness. The four parameters of equation A1, with T known, must constrain choice if they are to represent all these four qualities and the amount of asymmetry. Equa-
tions 5 and 6 make explicit the role of each parameter, which does not ensure that they will fit better but does indicate the limitations on what can be done with only four parameters.

Evidently even equation 5 can approximate excellently to equation A1. The sole aim here is to support the view that an optimal logistic, with five or even only four parameters, will often lead to estimates of potencies of unknowns satisfactorily close to those from the optimal single binding-site equation. This will almost certainly be so over the range of values of z from which the standard curve is estimated, and equally surely will be less so far outside that range. For optimal sensitivity of the RIA system, Ekins et al. (15) recommend that \( Q/Q_0 = 0.75, KQ = 3 \), and from Tables 1 and 2 it can be seen that equation 6 will then approximate well (in fact with \( \gamma = 0.89 \)). The limitations on range of dose may seem important to assessors primarily intended for estimation or detection of very low concentrations of a hormone. A statistician hesitates to trust extrapolation far beyond the range of experimental data, unless great confidence attaches to the belief that the fitted equation is absolutely correct in mathematical form: the logistic equation might still be adequate for detection even though grossly wrong in estimation, but the present study throws little light on this.

Other Approaches

Many RIA users are content to plot counts against doses for the standard and to draw a freehand curve through the points. There are variants such as replacing \( u \) by the metamer value \( r \) (equation 8), or using log dose instead of dose. Potencies for unknowns can be estimated from the graph, as indicated at the start of the section on Objectives. Good data make this easy and without much dependence on subjective judgment. If the points are more scattered (even if there are no conspicuous outliers), serious subjectivity may enter. No quantitative assessment of precision for estimates is possible. Some users may be surprised to realize the further major objection, that of time. Plotting points, sketching a curve, and reading log potencies from that curve is not speedy as compared with well-organized computer. If the counter outputs to tape or other machine-readable medium, the time required for transfer to a good computer program is negligible, and good organization enables a printed listing of all desired results to be obtained very quickly. Even if counts must be read from a listing and keyed-in manually to a small computer or programmable calculator (16, 17), this will be much quicker than careful plotting, sketching, and counting of small squares; when allowance is made for adequate checking, reading from a graph may take 10 times as long.

Many variants of spline techniques are available, but the essential feature is that of fitting successive segments of the curve by smoothly joined polynomial equations. For example, successive sets of doses for the standard might be fitted by cubic polynomials constrained so that adjacent pairs of curves join and have the same slope at dose–response points specified as “knots.” Splines are well-adapted for smoothing very good data in order to secure internal consistency of interpolation, and may be valuable in early study of the qualitative characteristics of an unusual response curve. They are much less suited to estimation from points subject to appreciable experimental error, especially if the precision of that estimation is important to subsequent calculations. The process is objective, but is over-parametrized and uses implicitly a number of parameters comparable with the number of doses for the standard. Rodbard et al. (7) point out that splines will fit poor data almost as readily as good, so that no critical examination of the quality of fit or assessment of precision is possible; even serious outliers may be accommodated by a spline function of unusual shape. Yet splines (at any rate, polynomial splines) cannot well represent the approach of expected count to an asymptotic value.

Is the freehand or the spline method needed in order to handle antibody–antigen systems that lead to awkwardly shaped response curves? This also brings danger. Either method will work with any data, but uncritical use of a spline program may conceal the occurrence of grossly misleading counts. There might seem still to be a place for the adaptability of splines or freehand curves for those assay curves that are unquestionably less smooth. For research and exploratory studies this may indeed be so, though for such special tasks the fitting of a more complicated massage or other “realistic” formulation of the dose–response relation may be worth the effort. A routine assay that is to be used as a definitive method of hormone estimation for diagnostic or similar purposes, however, should have sufficient regularity for its standard curve to be representable with not more than five parameters. Any assay not conforming to this requirement perhaps should be regarded as a temporary and somewhat unstable estimation procedure, to be replaced as soon as better technology is available.

I am grateful to Mrs. Gillian M. Raab for comments on drafts of this paper that have led to substantial clarifications. To Dr. D. Rodbard I owe much gratitude for suggestions and advice over many years, and especially for a detailed critique of an earlier version of this paper.

**Appendix. The Approximating Logistic**

The general single binding-site equation is

\[
\frac{U}{T - U} = N + \frac{KQT}{K(z_0 + z)(T - U) + T}
\]

(A1)

If C and D in equation (6) are chosen to satisfy

Table 4. Doses in Single Binding-Site Curve (\( N = 0.05 \)) between Which Corresponding Dose for Four-Parameter Logistic Deviates by \(<10\%^a\)

<table>
<thead>
<tr>
<th>(Q/Q_0)</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>8</th>
<th>128</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.16</td>
<td>–</td>
<td>–</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01-91</td>
</tr>
<tr>
<td>0.32</td>
<td>–</td>
<td>0.01-43</td>
<td>0.02-28</td>
<td>0.03-21</td>
<td>0.03-20</td>
</tr>
<tr>
<td>0.64</td>
<td>0.01-63</td>
<td>0.03-19</td>
<td>0.05-11</td>
<td>0.07- 8.5</td>
<td>0.07- 7.9</td>
</tr>
<tr>
<td>1.28</td>
<td>0.01-65</td>
<td>0.04-11</td>
<td>0.07- 6.3</td>
<td>0.10- 4.5</td>
<td>0.11- 4.2</td>
</tr>
<tr>
<td>2.56</td>
<td>–77</td>
<td>0.04-8.1</td>
<td>0.06- 4.1</td>
<td>0.11- 3.0</td>
<td>0.13- 2.8</td>
</tr>
<tr>
<td>5.12</td>
<td>–</td>
<td>0.03- 6.6</td>
<td>0.06- 3.1</td>
<td>0.10- 2.3</td>
<td>0.11- 2.1</td>
</tr>
<tr>
<td>10.24</td>
<td>–</td>
<td>0.02- 6.2</td>
<td>0.32- 2.5</td>
<td>b</td>
<td>b</td>
</tr>
</tbody>
</table>

\(^a\)Dose expressed as multiple of dose for mid-response. Unstated limits are less than 0.01 or greater than 100.

\(^b\)D exceeds 0.9T.
\[ C = \frac{TN}{1 + N}, \quad (A2) \]
\[ \frac{D}{T - D} = N + \frac{KQT}{Kz_0(T - D) + T}, \quad (A3) \]

the logistic will coincide at zero dose and in the limit at high doses. Equation A1 can be rewritten
\[ z = \frac{Q(T - C)}{U - C} - \frac{T}{K(T - U)} - z_0, \quad (A4) \]
whence
\[ U = C + [F_1 - (F_1^2 - F_2)^{1/2}] [2K(z_0 + z)], \quad (A5) \]
with
\[ F_1 = K(Q + z_0 + z)(T - C) + T, \quad (A6) \]
and
\[ F_2 = 4K^2Q(z_0 + z)(T - C)^2. \quad (A7) \]

When \( z = 0 \) in A5, \( U = D \). For any specified \( \gamma \), the further conditions
\[ A = 2^\gamma \left[ \frac{Q(T - C)}{D - C} - \frac{T}{K(2QT - C) - (D - C)} \right] - z_0 \quad (A8) \]
\[ A/B = 2^{\gamma - 1} \left[ \frac{Q(T - C)}{D - C} + \frac{T(D - C)}{K(2QT - C) - (D - C)^2} \right] \quad (A9) \]

make the curves identical in position and slope at the mid-response \((C + D)/2\). Finally, a value of \( \gamma \) can be obtained by evaluating \( U_1, U_2 \) for \( z = A/g, gA \) in A1 and taking
\[ \gamma = \left[ \ln(U_1 - C) - \ln(U_2 - C) \right]/\beta \ln g \quad (A10) \]
for any \( g > 1 \). In practice, the result is very stable over a wide range of \( g \), and \( g = 50 \) has been used in this paper. Iteration over A8, A9, and A10 rapidly converges.

Raab and McKenzie (6) drew attention to the inability of equation A1 to represent curves with relatively small slope. If \( \gamma = 1 \), division of A8 by A9, with substitution for \( z_0 \) from A4 with \( z = 0 \) and \( U = D \), leads easily to a demonstration that \( B > 1 \). Raab (personal communication) states that many data sets cause estimation of A1 to give \( K \to \infty \), which is essentially the same problem as \( \gamma = 1 \), whereas fitting of equation 5 gives \( B < 1 \). Unless the multiple-site equation can produce less-steep slopes, a serious practical inadequacy is exposed.

As an alternative to the "power logistic," equation 6, a "quadratic logistic," has been tried:
\[ U = C + (D - C)[1 + \exp(\alpha + \beta ln z + \chi(\ln z)^2)] \quad (A11) \]

This also may mimic equation A1 well, but is less successful than the power logistic, apparently because it can less well accommodate asymmetry.

References