Calculation of threshold and saturation points of sigmoidal baroreflex function curves

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McDowall, Lachlan M., and Roger A. L. Dampney. Calculation of threshold and saturation points of sigmoidal baroreflex function curves. Am J Physiol Heart Circ Physiol 291: H2003–H2007, 2006.—The logistic sigmoid function curve provides an accurate description of the baroreflex input-output relationship and is the most commonly used equation for this purpose. The threshold (Thr) and saturation (Sat) values for the baroreflex are commonly defined as the values of mean arterial pressure (MAP) at which the reflexly controlled variable (e.g., heart rate or sympathetic nerve activity) is within 5% of the upper or lower plateau, respectively, of the sigmoid function. These values are referred to here as Thr5% and Sat5%. In many studies, Thr and Sat are calculated with the equations Thr = A3−2.0/A2 and Sat = A3+2.0/A2, where A3 is the value of MAP at the point where the reflexly controlled variable is at the midpoint of its range and A2 is the gain coefficient. Although it is commonly stated that the values of Thr and Sat calculated with these equations represent Thr5% and Sat5%, we show here that instead they are significantly greater and less than Thr5% and Sat5%, respectively. Furthermore, the operating range (difference between Thr and Sat) calculated with these equations is 32% less than the difference between Thr5% and Sat5%. We further show that the equations that provide correct values of Thr5% and Sat5% are Thr5% = A3−2.944/A4 and Sat5% = A3+2.944/A4. We propose that these be used as the standard equations for calculating threshold and saturation values when a logistic sigmoid function is used to model the open-loop baroreflex function curve.

mathematical modeling; input-output relationship; baroreflex operating range; regression analysis

The baroreceptor reflex is the major feedback control system regulating arterial blood pressure in the short term (5, 14), and possibly also in the longer term (15, 27). Numerous studies in humans and animals have demonstrated that the baroreceptor reflex can be reset under physiological conditions such as exercise (6–8, 12, 17, 19–24, 26, 28), sleep (18), heat stress (3), or pregnancy (4) and also pathological conditions such as hypertension (9, 11) and cardiovascular deconditioning (10). To quantify the changes in baroreflex function that occur under different conditions, many investigators have used a mathematical equation to describe the relationship between input [e.g., mean arterial pressure (MAP)] and output (e.g., heart rate or sympathetic nerve activity). In some cases, where the carotid sinus pressure can be controlled independently of systemic arterial pressure, the input is carotid sinus pressure and the output is systemic arterial pressure.

Kent et al. (13) first proposed that a logistic sigmoid function curve be used to describe baroreflex function, according to the following equation:

\[ Y = A_1/[1 + \exp(A_2(X - A_3))] + A_4 \quad (1) \]

where \( Y \) is the output (dependent) variable (e.g., heart rate, sympathetic nerve activity, or systemic arterial pressure), \( X \) is the input (independent) variable (e.g., MAP or carotid sinus pressure), \( A_1 \) is the range (value of \( Y \) at the top plateau – value of \( Y \) at the bottom plateau), \( A_2 \) is the gain coefficient, \( A_3 \) is the value of \( X \) at the midpoint (which is also the point of maximum gain), and \( A_4 \) is the value of \( Y \) at the bottom plateau. Kent et al. (13) also showed that the maximal gain of the reflex, i.e., the maximum slope of the curve, can be derived directly from Eq. 1, as follows:

\[ \text{maximal gain} = -A_1A_2/A_4 \quad (2) \]

The logistic sigmoid function curve has been found to provide a very good fit of the baroreflex input-output relationship (1, 13) and has become the most commonly used equation for this purpose.

Two other very important parameters that describe baroreflex function are the threshold and saturation values for the input \( X \) (i.e., Thr and Sat). For the baroreceptor reflex, Thr is generally defined as the value of \( X \) at which no further increases in the output variable occur despite further reductions in \( X \), whereas Sat is the value of \( X \) at which no further decreases in the output variable occurs despite further increases in \( X \). Defined in this way, Thr and Sat cannot be determined from the logistic sigmoid function curve because \( Y \) changes continuously as \( X \) increases or decreases, approaching the lower and upper plateau values, respectively. To avoid this problem, Thr and Sat have been defined as the values of \( X \) at which \( Y \) is below or above the upper and lower plateau values of \( Y \), respectively, by some arbitrary small value. Very commonly (see, e.g., Refs. 6–8, 12, 17–23, 28), this arbitrary value is taken as 5% of the response range for \( Y \), and we shall follow this convention here.

Many authors have used an equation derived by Chen and Chang (2) to calculate Thr and Sat, as follows:

\[ \text{Thr} = A_3 - 2.0/A_2 \quad (3) \]
\[ \text{Sat} = A_3 + 2.0/A_2 \quad (4) \]

It is commonly stated (see, e.g., Refs. 6–8, 12, 17–23, 28) that the values of Thr and Sat calculated according to Eqs. 3 and 4 are the values of \( X \) at which the corresponding \( Y \) values are 5% (of the response range) below and above the upper and lower plateau values of \( Y \), respectively. We refer to these values here as Thr5% and Sat5%. In their original paper, however, Chen and Chang (2) did not claim that Thr5% and Sat5% could be
Fig. 1. Baroreflex logistic sigmoid function curve showing the threshold and saturation points as defined by Chen and Chang (2). They defined the threshold value (ThrC) as the X value at the point where the straight line passing through the midpoint (where \( X = A_3 \)) and with a slope equal to the slope of the curve at that point (i.e., \(-A_4/A_2/4\)) intersects with the asymptote of the upper plateau portion of the curve, i.e., the line \( Y = A_4 + A_1 \). Similarly, Chan and Cheng (2) defined the saturation value (SatC) as the X value at the point where this straight line intersects with the asymptote of the lower plateau portion of the curve, i.e., the line \( Y = A_4 \). The operating range (ORC) is the difference between ThrC and SatC.

As defined above, \( \text{Sat}_{5\%} \) is the value of \( X \) when the value of \( Y \) is 5% of the \( Y \) range above the upper plateau, i.e., when

\[
Y = A_4 + 0.05 \times A_1
\]

Substituting Eq. 5 into Eq. 1 gives:

\[
A_4 + 0.05 \times A_1 = A_4/(1 + \exp[A_4(\text{Sat}_{5\%} - A_3)]) + A_4
\]

Subtracting \( A_4 \) from both sides and then dividing both sides by \( A_1 \),

\[
0.05 = 1/(1 + \exp[A_4(\text{Sat}_{5\%} - A_3)])
\]

Dividing both sides by 0.05 and then multiplying both sides by \( 1 + \exp[A_4(\text{Sat}_{5\%} - A_3)] \),

\[
1 + \exp[A_4(\text{Sat}_{5\%} - A_3)] = 1/0.05 = 20
\]

Therefore,

\[
\exp[A_4(\text{Sat}_{5\%} - A_3)] = 19
\]

Taking the logarithm (to the base e) of both sides:

\[
A_4(\text{Sat}_{5\%} - A_3) = \log_{e}19
\]

Rearranging to make \( \text{Sat}_{5\%} \) the subject:

\[
\text{Sat}_{5\%} = A_3 + \log_{e}19/A_4
\]

Similarly, determination of the threshold by the same process (using \( Y = A_4 + 0.95 \times A_1 \)) yields the equation

\[
\text{Thr}_{5\%} = A_3 - 2.944/A_2
\]

With the use of a similar process in reverse, the values of \( Y \) that correspond to the values of \( \text{Sat} \) and \( \text{Thr} \) according to the equations derived by Chen and Chang (2) (Eqs. 3 and 4) can also be determined as follows. Starting with Eq. 1, i.e.,

\[
Y = A_4/(1 + \exp[A_4(X - A_3)]) + A_4
\]

Substituting for \( X = A_3 + 2.0/A_2 \) [according to Chen and Chang (2)]

\[
Y = A_4(1 + \exp[A_4(3.0/A_2 - A_3)]) + A_4
\]

Canceling out and rearranging:

\[
Y = A_4(1 + \exp(2.0)) + A_4
\]

Therefore,

\[
Y = A_4 + 0.119 \times A_1
\]
correspond to these values of Sat and Thr are \( Y = A_4 + 0.211 \times A_1 \) and \( Y = A_4 + 0.789 \times A_1 \), respectively. Thus the \( Y \) values corresponding to Sat and Thr as defined by Kent et al. (13) are \( >21\% \) (of the \( Y \) range) above and below the lower and upper plateaus, respectively (Fig. 2).

It is clear that Eqs. 6 and 7, as well as the equations derived by Chen and Chang (2) (Eqs. 3 and 4) and Kent et al. (13) (Eqs. 9 and 10) all depend only on the value of the midpoint \( A_3 \) and gain coefficient \( A_2 \) and are thus independent of the \( Y \) value at the lower plateau (\( A_2 \)) or the \( Y \) range (\( A_1 \)). The difference in the values of Thr and Sat calculated with the three different methods depends only, however, on the value of \( A_2 \). When the value of \( A_2 \) is decreased, the absolute magnitude of these differences increases.

For example, Fig. 2 shows two sigmoidal baroreflex function curves with different values for the parameters \( A_1, A_2, A_3, \) and \( A_4 \), and Table 1 shows, for each of these two curves, the numerical values for Thr and Sat as calculated with the equations of Chen and Chang (2) and those of Kent et al. (13), as well as the values of Thr5% and Sat5% as determined with Eqs. 6 and 7. When the value of \( A_2 \) is 0.1 (Fig. 2A), the difference between the value of Thr from the equation of Chen and Chang (2) and the value of Thr5% is 9.4 mmHg (100.0 – 90.6; Table 1). When the value of \( A_2 \) is 0.06 (Fig. 2B), however, the difference is 15.8 mmHg (91.7 – 75.9; Table 1).

The operating range of the baroreflex is defined as the difference between Thr and Sat, which (from Eqs. 6 and 7) is equal to 5.888/\( A_2 \). When the equations of Chen and Chang (2) (Eqs. 3 and 4) are used, the operating range is 4.0/\( A_2 \), and when the equations derived by Kent et al. (13) (Eqs. 9 and 10) are used, it is 2.634/\( A_2 \). Thus the operating range derived from the equations of Chen and Chang (2) is 32% less than that derived from Eqs. 6 and 7 (i.e., the difference between Thr5% and Sat5%), whereas that derived from the equations of Kent et al. (13) is 55% less than that derived from Eqs. 6 and 7. Therefore, although the value of \( A_2 \) affects the absolute magnitude of the differences between the values of the operating range calculated according to the three different methods (Table 1, Fig. 2), it does not affect the relative percentage differences in these values.

**DISCUSSION**

It is commonly believed (see, e.g., Refs. 6–8, 12, 17–23, 28) that the equations derived by Chen and Chang (2) produce values of Thr and Sat that are equal to Thr5% and Sat5%. The above analysis, however, shows that the values of Thr and Sat as calculated from the equations of Chen and Chang (2) are significantly greater and less than Thr5% and Sat5%, respectively, and that the correct values of Thr5% and Sat5% are those calculated according to Eqs. 6 and 7.

In most studies of baroreflex function in which Thr and Sat are calculated, comparisons are made between groups within the same study. In these cases, when the same equations are used to calculate Thr and Sat, such comparisons are likely to be valid, even though the absolute calculated values are different from Thr5% and Sat5%. The problem becomes much more

**Table 1. Baroreflex parameters determined for theoretical curves in Figure 2 with equations from present and previous studies**

<table>
<thead>
<tr>
<th>Method</th>
<th>Threshold Point, mmHg</th>
<th>Saturation Point, mmHg</th>
<th>Operating Range, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Curve in Fig. 2A</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(( A_1 = 200, A_2 = 0.1, A_3 = 120, A_4 = 300 ))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kent et al. (13)</td>
<td>106.8</td>
<td>133.2</td>
<td>26.4</td>
</tr>
<tr>
<td>Chen and Chang (2)</td>
<td>100.0</td>
<td>140.0</td>
<td>40.0</td>
</tr>
<tr>
<td>Present study</td>
<td>90.6</td>
<td>149.4</td>
<td>58.8</td>
</tr>
<tr>
<td><strong>Curve in Fig. 2B</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(( A_1 = 100, A_2 = 0.06, A_3 = 125, A_4 = 350 ))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kent et al. (13)</td>
<td>103.1</td>
<td>147.0</td>
<td>43.9</td>
</tr>
<tr>
<td>Chen and Chang (2)</td>
<td>91.7</td>
<td>158.3</td>
<td>66.6</td>
</tr>
<tr>
<td>Present study</td>
<td>75.9</td>
<td>174.1</td>
<td>98.2</td>
</tr>
</tbody>
</table>

\( A_1 \), \( Y \) range; \( A_2 \), gain coefficient; \( A_3 \), midpoint; \( A_4 \), lower plateau; \( \text{Thr} \), threshold; \( \text{Sat} \), saturation. Operating range is defined as the difference between Thr and Sat values. Equations used in calculations: Kent et al. (13): Thr = \( A_3 - 1.317/\text{A}_2 \); Sat = \( A_3 + 1.317/\text{A}_2 \); Chen and Chang (2): Thr = \( A_3 - 2.00/\text{A}_2 \); Sat = \( A_3 + 2.00/\text{A}_2 \); present study: Thr5% = \( A_3 - 2.944/\text{A}_2 \); Sat5% = \( A_3 + 2.944/\text{A}_2 \).
significant, however, when comparisons are made between studies, and it is therefore important to have a standardized and accurate method of calculating these important parameters of the logistic sigmoid function curve.

As an illustration of this point, we have compared the Thr and Sat values of MAP for the baroreflex control of renal sympathetic nerve activity (RSNA) as determined in anesthetized rats in a recent study from our laboratory (16) with those derived by Ricketts and Head (25) is used, however, the equation of this straight line is

\[
Y = a + bX
\]

At this point, the slope \( b = -A_1A_2/4 \) (see Eq. 2). As shown in Fig. 1, when \( X = A_3, Y = A_4 + A_1/2. \) Therefore,

\[
a = A_4 + A_1/2 + A_1A_2/4
\]

Thus the equation of this straight line is

\[
Y = A_4 + A_1/2 + A_1A_2/4 - A_1X/4
\]

At the point where this line intersects with the lower asymptote, \( Y = A_4 \) and (by definition) \( X = Sat_C \) (Fig. 1). Therefore, at this point,

\[
A_4 = A_1 + A_1/2 + A_1A_2/4 - A_1 \times Sat_C
\]

Subtracting \( A_4 \) from both sides and rearranging,

\[
A_1A_2 \times Sat_C/4 = A_1/2 + A_1A_2/4
\]

Dividing both sides by \( A_1A_2/4, \)

\[
Sat_C = A_1 + 2.0/A_3
\]

Similarly, the threshold value \( Thr_C \) is defined as the point where the straight line intersects with the upper asymptote, i.e., where \( Y = A_4 + A_1 \) and (by definition) \( X = Thr_C \) (Fig. 1).

By a derivation similar to that shown above for the Sat\(_C\) value,

\[
Thr_C = A_1 - 2.0/A_3
\]

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GRANTS

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REFERENCES