A Mathematical Model for the Determination of Total Area Under Glucose Tolerance and Other Metabolic Curves

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OBJECTIVE— To develop a mathematical model for the determination of total areas under curves from various metabolic studies.

RESEARCH DESIGN AND METHODS— In Tai's Model, the total area under a curve is computed by dividing the area under the curve between two designated values on the *X*-axis (abscissas) into small segments (rectangles and triangles) whose areas can be accurately calculated from their respective geometrical formulas. The total sum of these individual areas thus represents the total area under the curve. Validity of the model is established by comparing total areas obtained from this model to these same areas obtained from graphic method (less than ±0.4%). Other formulas widely applied by researchers under- or overestimated total area under a metabolic curve by a great margin.

RESULTS— Tai's model proves to be able to *1*) determine total area under a curve with precision; *2*) calculate area with varied shapes that may or may not intercept on one or both *X/Y* axes; *3*) estimate total area under a curve plotted against varied time intervals (abscissas), whereas other formulas only allow the same time interval; and *4*) compare total areas of metabolic curves produced by different studies.

CONCLUSIONS— The Tai model allows flexibility in experimental conditions, which means, in the case of the glucose-response curve, samples can be taken with differing time intervals and total area under the curve can still be determined with precision.

Estimation of total areas under curves of metabolic studies has become an increasingly popular tool for evaluating results from clinical trials as well as research investigations, such as total area under a glucose-tolerance or an energy-expenditure curve (1,2). Three formulas have been developed by Alder (3), Vecchio et al. (4), and Wolever et al. (5) to calculate the total area under a curve. However, except for Wolever et al.'s formula, other formulas tend to under- or overestimate the total area under a metabolic curve by a large margin.

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RESEARCH DESIGN AND METHODS

Tai's mathematical model

Tai's model was developed to correct the deficiency of under- or overestimation of the total area under a metabolic curve. This formula also allows calculating the area under a curve with unequal units on the *X*-axis. The strategy of this mathematical model is to divide the total area under a curve into individual small segments such as squares, rectangles, and triangles, whose areas can be precisely determined according to existing geometric formulas. The area of the individual segments are then added to obtain the total area under the curve. As shown in Fig. 1, the total area can be expressed as:

Total area = triangle a + rectangle b + triangle c + rectangle d + triangle e + rectangle f + triangle g + rectangle h + ...

If y = height, x = width

Area (square) = x^2 or y^2 ($x = y$);

Area (rectangle) = xy;

Area (triangle) = $xy/2$

Let: $X_1 = x_2 - x_1$; $X_2 = x_3 - x_2$

$X_3 = x_4 - x_3$; $X_4 = x_5 - x_4$;

$X_{n-1} = x_n - x_{n-1}$

$$\text{Total Area} = \tfrac{1}{2}X_1 (y_2 - y_1) + X_1y_1 + \tfrac{1}{2}X_2 (y_3 - y_2) + X_2y_2 + \tfrac{1}{2}X_3 (y_4 - y_3) + X_3y_3 + \tfrac{1}{2}X_4 (y_5 - y_4) + X_4y_4 + \ldots + \tfrac{1}{2}X_{n-1} (y_n - y_{n-1}) + X_{n-1}y_{n-1}$$

$$= \tfrac{1}{2}(X_1y_1 + X_1y_2 + X_2y_2 + X_2y_3 + X_3y_3 + X_3y_4 + X_4y_4 + X_4y_5 + \ldots + X_{n-1}y_{n-1} + X_{n-1}y_n) = \tfrac{1}{2}[X_1(y_1 + y_2) + X_2 (y_2 + y_3) + X_3 (y_3 + y_4) + X_4 (y_4 + y_5) + \ldots . X_{n-1} (Y_{n-1} + Y_n)]$$

If the curve passes the origin, $1/2[X_0y_1]$ should be added to above formula. If the curve intercepts at y_0 at the *Y*-axis, let $X_0 = x_1 - x_0$, $1/2[X_0(y_0 + y_1)]$ should be added to the above formula; Tai's formula applied to different conditions:

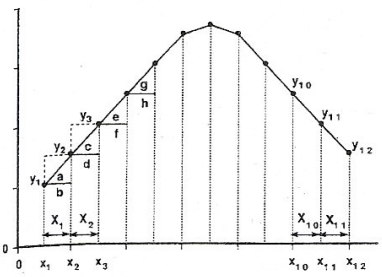

Figure 1—*Total area under the curve is the sum of individual areas of triangles a, c, e, and g and rectangles b, d, f, and h.*

$$\text{Area} = \frac{1}{2}\sum_{i=1}^{n} x_{i-1}\,(y_{i-1} + y_i)$$

(Tai's formula)

When the curve passes the origin: $x_0 = y_0 = 0$, $X_0 = x_1 - 0$;
When the curve intercepts *Y*-axis at y_0: $X_0 = x_1 - 0$
When the curve neither passes the origin nor intercepts at y-axis: $X_0 = y_0 = 0$

Example using Tai's model:
Blood glucose determined at six time periods: (6)

time (min)	0	30	60	90	120
Glucose (mg/dl)	95	147	124	111	101

$X_0 = x_1 - x_0 = 30 - 0 = 30$;
$X_1 = 60-30 = 30$; $X_2 = X_3 = 30$

$$\text{Area} = \frac{1}{2}[30(95 + 147) + (147 + 124) + (124 + 111) + (111 + 101)]$$
$$= 14400 \text{ mg/dl/120 min}$$

RESULTS

Comparison of Tai's formula to other formulas

Five sets of laboratory data from the previous experiments of the author are used here for calculating the total area under a curve using the four different formulas as indicated above. The validity of each model was verified through comparison of the total area obtained from the above formulas to a standard (true value), which is obtained by plotting the curve on graph paper and counting the number of small units under the curve. The sum of these units represents the actual total area under the curve. Results are presented in Table 1. From Table 1, it is evident that total area I can not be obtained from Alder's formula. Total area II has underestimated the total area under a metabolic curve by a large margin. Total area III corresponds well (− 6.1%) with the actual area estimated from the plot (total area V). However, this formula only permits a single *t* value, which means the time interval has to be the same.

CONCLUSIONS

Verification of Tai's mathematical model

From Table 1, it is clear that Tai's formula (total area IV) has the most accurate estimation of the total area under a curve. Total area IV agrees extremely well with actual total area obtained from the graph (+ 0.1%). Because no statistically significant differences were found between areas from these two methods, the validity of Tai's model can thus be established.

This formula also permits accurate determination of total area under the curve when the curve intercepts with *Y*-axis, as well as when the curve passes the origin. Furthermore, in this formula, values on *X*-axis do not have to be the same as the *t* in Wolever et al.'s formula. It allows flexibility in experimental conditions, which means, in the case of glucose-response curve, samples can be taken with differing time intervals and the total area under the curve can still be determined with precision. Thus, if different authors estimate the total area under a curve from

Table 1—*Summary of results: (% area: % of total area V)*

Total area	I	II	III	IV	V
Test					
Glucose	N.A.*	480 (3.3%)	13517 (94.3%)	14400 (100.4%)	14337
TEF (SM)	N.A.*	336 (3.2%)	9588 (92.6%)	10326 (99.8%)	10349
TEF (LM)	N.A.*	452 (3.2%)	13367 (94.7%)	14163 (100.3)	14115
RMR (L)	N.A.*	1157 (3.9%)	N.A.†	30040 (100.0%)	30047
RMR (O)	N.A.*	1636 (4.6%)	N.A.†	35733 (100.0%)	35725
Ave		(3.6%)	(93.9%)	(100.1%)	

t tests: II:V $P < 0.005$; III:V NS; IV:V NS

Area I: Alder (3)*; Area II: Vecchio et al. (4);
Area III: Wolever et al. (5); Area IV: Tai's Model
Area: V: Graphic Method;

Metabolic studies:
Test I
Blood glucose at six time periods before and after a glucose load: (blood glucose: x, mg/dl; time interval between tests $t = 30$ min; obese women: $n = 6$) (6)
Test II and III
Thermic effect of food at ten time periods after one large meal (LM: 750 kcal) or six small meals (SM: 125 kcal)
(TEF: $\bar{x}$, 10^{-2} kcal · min^{-1} · kg^{-1} LBM; $t = 30$ min; lean women: $n = 7$) (2)
Test IV and V
Resting metabolic rate of lean (L) and obese (O) women.
(RMR: $\bar{x}$ 10^{-2} kg · min^{-1} · kg^{-1} LBM; L: $n = 7$, O: $n = 8$; $t_1 = t_2 = 20$ min; $t_3 = 25$ min; $t_4 = t_5 = t_6 = 30$ min) (6)

*Nonapplicable because of the irregular shape of the curve.
†Nonapplicable because of the uneven time intervals.

Tai's formula, comparisons can be made between areas under curves produced under different experimental conditions.

Acknowledgments— I would like to dedicate Tai's Model to my late parents Mr. and Mrs. T. C. Tai. I gratefully acknowledge Dr. F. X. Pi-Sunyer and Dr. H. Dowling from the Obesity Research Center for their support and encouragement, Dr. R. Kuc from Yale University for his expert review and Mrs. Y. Dam for her artwork.

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Determination of the Area Under a Curve

In a recent article, Tai (1) describes a method to determine total area under metabolic curves. However, what is exaggerately called "Tai's mathematical model" is nothing but a simple geometrical formula, well known for many years as the trapezoidal rule. This classical method, as well as a series of other approaches, was reviewed and investigated by Wagner and Ayres (2) 17 years ago. Moreover, the derivation of the trapezoidal rule is presented in a circumstantial way, the final equation called "Tai's formula" contains incorrect notations (e.g., 'x' must be 'X' with the author's definitions), and the division into different conditions of intercept and passing the origin is absolutely unnecessary.

The validation of the formula by means of comparison with a "true value" is useless and contains several fallacies. First, because of the geometrical interpretation of the trapezoidal rule, it is clear that the expression tends toward the true area under the curve (AUC) if the number of considered curve points increases. Hence, the adequacy of the trapezoidal rule is dependent on the number of curve points and cannot be investigated by a few examples. Second, the AUC value measured graphically by counting the numbers of small units under the curve is not the true AUC value. Like the trapezoidal rule, it is an approximation, which tends toward the true value if the units decrease. Thus, for comparison, not the [illegible] but another approximation was [illegible]. Third, Student's t tests were misused. Significance tests are generally inadequate tools for comparison of two methods of measurement (3). In addition, the sample size was only $n = 5$, resulting in low power, and multiple comparisons were made without adjustment. Even if the sample size had been [illegible] adjustment for multiple comparisons had been made, in principle, approaches adequate for method comparison should have been used (3).

Finally, the term *total area under a curve* is used in another sense than it is in the pharmacokinetic literature. The word *total* refers to AUC(0-∞), whereas AUC(0-T), where T is the investigator's last time point, is a partial area. Only the latter can be estimated by means of the trapezoidal rule; computation of the total AUC(0-∞) requires a mathematical or pharmacokinetic model (2). However, "Tai's mathematical model" is no model, it is an application of a simple geometrical rule.

In conclusion, Tai proposed a simple, well-known formula exaggerately as her own mathematical model and presented it in a circumstantial and faulty way.

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Comments on Tai's Mathematic Model

I commend Tai (1) for producing a correct method for calculating the total area under the curve. It uses the trapezoid rule, a basic geometrical concept, which is that the area of a trapezoid is the mean of the length of the two parallel sides times the width. This method has been used by those of us in the field for many years and, in my opinion, does not need a new name. I also have a number of other problems with her paper. Tai considers that the "true value" for the area under the curve is obtained by plotting the curve on graph paper and counting the squares under the curve. This method is subject to a number of errors arising from inaccuracies in plotting the points and lines and in estimating the area of the portions of squares that are bisected by lines whose width is large in relation to the size of the squares. The trapezoid rule is, in fact, the gold standard for calculating areas if the points are joined by straight lines.

The typographical error in the example calculation (which should read: area = 1/2[30(95 + 147) + 30(147 + 124) + 30(124 + 111) + 30(111 + 101)] = 14400) is a problem I cannot criticize. In one of my papers, there are a number of confusing errors in the section describing the effects of different ways of calculating the area under the curve that I was careless enough not to pick up in proof (2).

However, I will criticize her totally inappropriate use of "my" formula to calculate total area under the curve (3). As was clearly stated, my formula is for calculating the incremental area under the curve above the baseline and does not give the correct value for the total area. Therefore, her comparison of the accuracy of "her" method with "mine" is a completely meaningless exercise. In addition, to obtain the area she ascribes to my method (i.e., 13,517), she must have used the incorrect final term $tD^2/[2(D+|E|)]$, which, as explained, is only

substituted for $t(D+E)/2$ if increment D is positive and E negative (i.e., below the baseline) so as to ignore the area below the baseline. If $D<0$ and $E>0$, then the term becomes $tE^2/[2(E+|D|)]$. In her example, none of the postprandial points is less than fasting.

Finally, she says that my method only permits a single time interval. She is wrong, in that my method is based on the trapezoid rule and can be adapted for different time intervals, a point we made in an earlier and more complete description of the method (4). However, she is correct that the sample simplified formula in our 1991 paper (3) is only appropriate for equal time intervals. We made an error in assuming that readers would be able to modify it for different time intervals. Thus, the formula for the incremental area under the curve ignoring area below the baseline, where $x_1 \ldots x_n$ are the increments (i.e., the postprandial values minus the fasting value), and if all the increments are positive, is

$$\sum_{i=1}^{n} t_i(x_i + x_{i+1})/2$$

where t_i is the time interval between the ith and $i+1$th points. However, if either x_i or x_{i+1} is negative (i.e., below the baseline), then one of the terms described in the preceding paragraph is substituted (if both are negative, then the area between them is 0).

The lesson here is that calculating areas under the curve is deceptively difficult. I fear I may be responsible for contributing to the confusion.

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Tai's Formula Is the Trapezoidal Rule

We were disturbed to read the article by M. M. Tai titled "A Mathematical Model for the Determination of Total Area Under Glucose Tolerance and Other Metabolic Curves" (1). The author seems to claim "Tai's formula" as a new method of computing area under a curve. The formula given is simply the trapezoidal rule, published in many beginning calculus texts (for example, see Swokowski [2] or Faires and Faires [3]). Although we do not have a first reference, it is our understanding that the trapezoidal rule was known to Isaac Newton in the 17th century. Further, her article omitted any reference to the magnitude of error of the area approximation when the true curve is unknown, as is the case for measuring glucose tolerance.

The trapezoidal rule is used in undergraduate calculus courses to illustrate and develop the calculus of definite integrals. Calculus students begin estimating area under a known curve by dividing the x-axis into small intervals and totaling the area of the resulting trapezoids. The exercise demonstrates that the error in the area calculation decreases as the length of the x-axis intervals is decreased. Definite integrals are then defined by taking the limit of the trapezoid's summation as the x-axis intervals go to zero.

Shortcomings exist with the trapezoidal rule, even if the true curve is known, that are not mentioned in the article. Modeling a curve by a series of connected line segments will either over- or underestimate the actual area, depending on the direction of curvature in the true curve. In the case of the glucose tolerance response, the true curve is unknown; even so, the trapezoidal rule is the best possible approximation of the area based on linear segments given minimal assumptions about the true curve. Most statements of the trapezoidal rule include the upper bound of the possible error stated as $M(b-a)^3/12n^2$, where M is the maximum rate of curvature over the x segment, $[a, b]$, and n is the number of x-axis intervals.

Tai stated that her "standard (true value). . . is obtained by plotting the curve on graph paper and counting the number of small units under the curve" (p. 153). By definition, the sum of the area of the small units, which she erroneously refers to as the "true value," should be exactly the area found by the trapezoidal rule. The formula should have been 100% accurate because she defined truth to be exactly the sum of the area of the graph paper trapezoids.

We hope that our comments as mathematics and statistics practitioners help to clarify the origin of the trapezoidal rule and its properties as an approximation of the area under the true curve.

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Modeling Metabolic Curves

While not denigrating the Tai model (1) for the total area under metabolic curves, nor denying its validity, we believe the Γ variate function also deserves to be better known. It cannot only be used to approximate the total area under the curve (AUC) but also describe these curves functionally with estimates of their characteristic parameters and to separate their secretion and clearance phases. The formula for this function is

$$y = y_0 + At^a e^{-bt}$$

for s (insulin, C-peptide, glucose concentrations), y_0 is a basal value, t is time, A, a, and b are found by simply fitting data to the straight line form of

$$(2) \quad \ln(y - y0) = \ln A + a\ln t - bt$$

in which $\ln(x)$ represents the natural logarithm. By differentiating y with respect to t, one can find the secretion and clearance rates as the first and second terms respectively of

$$(3) \quad dy/dt = Aat^{a-1}e^{-bt} - Abt^a e^{-bt}$$

The total above basal area under the relevant response curve, AUC, is then found by integrating (1) with respect to t between the limits of 0 and ∞ to obtain

$$(4) \quad AUC = A\Gamma(a + 1)/b^{a+1}$$

in which $\Gamma(x)$ represents the Γ function, values for which are in standard tables (2) (hence the name of the function).

An example of the use of the Γ variate function in this context may be found in Shannon et al. (3). The Γ variate model does not require seeding with initial values, nor does it require many sampling times to increase its accuracy.

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Reply From Mary Tai

I would like to thank all of the readers who have reviewed and responded to the publication of Tai's model. I am particularly grateful to those who have confidence in my intention of publishing and have considered Tai's model an effective tool in calculating total area under a metabolic curve. However, three of the readers expressed their concerns on the following issues. My replies are presented as follows.

To Dr. Bender

The originality of Tai's model. While a doctoral candidate working on my dissertation at Columbia University in 1981, I needed to calculate total area under a curve. During a session with my statistical advisor, and after examining several alternative methods, I worked out the model in front of him. The concept behind it is obviously common sense, and one does not have to consult the trapezoid rule to figure it out. The trapezoid rule is really not Nobel Prize material, such as the double helix or jumping genes. I also used the formulas to calculate the areas of a square or a triangle without knowing whose rules were being followed. Fortunately, I do not have to answer that for you.

Why I call it Tai's model. I never thought of publishing the model as a great discovery or accomplishment; it was not published until 14 years later, in 1994. Because of its accuracy and easy application, many colleagues at the Obesity Research Center of St Luke's-Roosevelt Hospital Center and Columbia University began using it and addressed it as "Tai's formula" to distinguish it from others. Later, because the investigators were unable to cite an unpublished work, I submitted it for publication at their requests. Therefore, my name was rubber-stamped on the model before its publication.

According to *Merriam Webster's Dictionary*, a model can be defined as "a

type of design of product;" "a description used to visualize something that cannot be directly observed;" or "a system of postulates, data, and inferences presented as a mathematical description of an entity. . . ." Even if Tai's model were based on the trapezoid rule concept, according to the definition of a model, I have worked out a "design" (mathematical expression) for the "structure units" (individual areas) on my own. In other words, I have presented the original concept into a functioning mathematical description that can be easily observed and applied. Following the above definition, I therefore carefully named the mathematical description as Tai's "model" rather than "formula" to indicate that I have used existing formulas for small area calculations.

My intention in publishing the model is therefore to share, rather than to gain honor or glory with its publication, because there is none. Many other investigators probably thought about the same thing, but maybe they did not bother to follow up or produce a model (or the same model). You indicated that I probably did work this out on my own and I am grateful for your "probability," because I did indeed do so with a witness present. Maybe I can address the model as my creation based on fact rather than your doubtful "probability." Besides, if I do not address the model as "Tai's," other investigators who wish to cite it will.

The precision of Tai's model. Because Tai's model is based on the calculations of individual squares and triangles, its precision is obviously absolute. You are correct in saying that I have verified the validity of the formula by comparison with its approximation, meaning counting squares.

The size of *n*. Following the statistical principle that you consider elementary, it is correct that n does represent numbers of data sets. However, in this case, elemental principle simply does not apply. The hypothesis here is the validity of the formula. The acceptance or rejection of the hypothesis is not based on the findings of each individual data set, as is a general rule in an experimental study. It should not be difficult to see that each data set here represents the findings from its respective research protocol and answers its individual research questions rather than answering the validity of Tai's model. Furthermore, because the same formula was used for each data set, the degree of accuracy on the resultant total area obtained will be exactly the same for each set. Therefore, increasing n of the data set does not increase statistical power as you suggested.

I introduced other formulas simply for the purpose of comparison. Because the formula cannot be compared with its approximation and there are limited formulas available, I decided to count, because every published curve has been based on counting squares. I also believe, if one increases the N I am talking about, meaning the number of methods, one can better verify the validity of Tai's model.

To Dr. Wolever

After receiving your recent graphic representation of your formula, I began to realize that I have indeed misunderstood your formula as some other readers did. Your incremental area is the area above the baseline rather than the total area under the curve including the baseline area. I apologize for the misapplication of your unique formula, which I do fully support. I also acknowledge that you, too, have indeed used the concept of adding triangles and rectangles in your mathematical model for the total increment. I also appreciate your idea of weighing, because I did weigh the total area under an arc and, as you know, that might be the only way.

To Dr. Anderson and Ms. Monaco

Tai's model is designed to calculate total area under a metabolic curve that is plotted by connecting experimental points x_i, y_i with straight lines as shown in Fig. 1 in my article. Because the metabolic curve is not an arc, the exact area can be calculated without assumption and approximation. If a smooth arc represents the true curve, it is obtainable only if $x_i \to \infty$ and $\Delta x \to 0$, as presented in the trapezoid rule or calculus, and it is theoretically impossible in an experimental condition.

Finally, I would like to correct some typographical errors in my article.

On p. 153, the correct formula should be

$$\text{Area} = \frac{1}{2}\sum_{i=1}^{n} X_{i-1}\,(y_{i-1} + y_i)$$

and in example 1:

$$\text{Area} = \frac{1}{2}\,30\,[(95 + 147) + (147 + 124) + \ldots]$$

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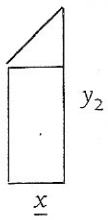
Addendum to Monaco's and Anderson's Letter

Tai responds that her formula is based on the sum of the areas of small triangles and rectangles and is not based on the sum of the areas of trapezoids (the trapezoidal rule). As is evident in the following figure and algebra, the small triangle and the contiguous rectangle form a trapezoid. The sum of the area

of the triangle and the rectangle is the area of the trapezoid. Using her notation,

$$\begin{aligned}&\text{triangle area} + \text{rectangle area}\\ &= \tfrac{1}{2}\underline{x}(y_2 - y_1) + \underline{x}y_1\\ &= \tfrac{1}{2}\underline{x}(y_2 - y_1 + 2y_1)\\ &= \tfrac{1}{2}\underline{x}(y_2 + y_1)\\ &= \underline{x}\bar{y}\\ &= \text{trapezoid area.}\end{aligned}$$



The trapezoid area is the mean of the length of the parallel sides, $\bar{y}$, times the width. Summing over all trapezoids under the curve yields the trapezoidal rule, the expression listed as Tai's formula in Tai's article.

Tai invites readers to "do a small problem using any existing geometric concept(s) you prefer and without using the geometric concept behind Tai's formula." We prefer no other method to the trapezoidal rule; rather, our goal is to point out that Tai's formula is the trapezoidal rule, as shown above.

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Revision of Improved Mean Glycemia From HbA_{1c}

Nathan's formula (1) for average glycemia, 33.3 A_{1c} − 86 mg/dl, requires modification to include normal average glycemic estimates from normal HbA_{1c}s. This formula misleads physicians into diagnosing chronic hypoglycemia for diabetes patients who have normal HbA_{1c}. Furthermore, new data from the Diabetes Control and Complications Trial (DCCT) (2), with more subjects, 1,441 compared with 21, should be used to refine this average. For these reasons, the following derivation is proposed to extend the Nathan equation into the range of normal HbA_{1c} assays. This letter describes the mathematical basis for an improved estimate of mean capillary blood glucose concentration from the high-performance liquid chromatography–assayed HbA_{1c}.

The solution for HbA_{1c} from mean glycemia is assumed to be the Hill equation (3) from enzyme kinetics. A theoretical saturation of 100% is assumed for the maximum HbA_{1c} (note that a lower saturation will estimate a higher mean glycemia for the normal). The Hill equation parameters can be determined using data points from Santiago (4) of 210 mg/dl at 9% (DCCT baseline [2]), 150 mg/dl at 7% (DCCT intensive therapy [2]), and 90 mg/dl at 5% (5). Linear regression applied to a Hill plot of this data has a correlation coefficient near one and gives the following solution:

$$A_{1c} = \frac{100(\bar{G})^{0.741}}{536 + \bar{G}^{0.741}}$$

$$= \frac{100(\bar{G}_{SI})^{0.741}}{62.9 + \bar{G}_{SI}^{0.741}}\ \%;\ G_{SI} \text{ in mmol/l}$$

Rewriting the equation for mean glycemia yields

$$\bar{G} = \frac{4{,}827}{\left(\frac{100}{A_{1c}} - 1\right)^{1.35}}\ \frac{\text{mg}}{\text{dl}} \text{ or } \bar{G}_{SI}$$

$$= \frac{267.9}{\left(\frac{100}{A_{1c}} - 1\right)^{1.35}}\ \text{mmol/l}$$

Note that these equations are mathematically correct over the ranges of A_{1c} and glycemia. Moreover, the parameters have been optimized for the low and middle range of A_{1c} values typically found in insulin-dependent diabetes mellitus (IDDM). For example, a 7% A_{1c} gives an average glycemia of 147 mg/dl, a 9% A_{1c} has a value of 212 mg/dl, and an 11% A_{1c} has the mean glycemia of 287 mg/dl. Finally, the normal of 5.05% (2) gives a 91.9 mg/dl compared with Nathan's 82.2 mg/dl.

Figure 1 compares Nathan's equation with the Hill solution for average glycemia over the normal and typical IDDM range of A_{1c}.

In reviewing the DCCT (2) results for mean glycemia, the seven-point average used in this report may generate an erroneous estimate of average glycemia. An example of a hypothetical normal mean glycemia may clarify this concern. The glycemic response of this normal will be 70 mg/dl for 8 h of fasting, a waking floor of 85 mg/dl for 16 h, and postprandial peaks of 135 mg/dl for three meals lasting 3 h each (from the start of the meal until euglycemic, 1.5 h peak from the start). The prandial excursion is assumed to be half-sinusoidal, with a mean given by

$$\frac{1}{\pi}\int_0^{\pi} \Delta \sin x\, dx = \frac{2}{\pi}\Delta;\ \Delta = 135$$

$$- 85\ \frac{\text{mg}}{\text{dl}}$$