FITTING DRUG CONCENTRATION DATA ACCORDING TO ITS CREDIBILITY: DETERMINING THE ASSAY ERROR PATTERN.

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Frequently, we need to consider the relative amount of information contained in a data point, to give more importance to one that is known with good precision and less to one known with less precision (greater measurement error). It would probably be ideal if all data had equal credibility, but almost always such is not the case.

Many methods have been used to fit a pharmacokinetic model to the serum level data. Unity weighting, weighting by the reciprocal of the measured concentration (or of its squared value), the use of a constant coefficient of variation, and others have been employed. Use of various weighting schemes has often been regarded as an art, in order to get the smallest sum of squares of the residuals, the "best" fit.

Let us consider the MAP Bayesian objective function (MAPBOF):

$$\text{MAPBOF} = \text{SUM}\ \frac{(\text{Cobs} - \text{C mod})^2}{\text{Var (Cobs)}} + \text{SUM}\ \frac{(\text{Ppop} - \text{Pmod})^2}{\text{Var(Ppop)}} \qquad (1)$$

Here Cobs represents the collection of all observed or measured concentrations, Cmod represents the collection of all predicted concentrations arrived at by some type of model, such as a pharmacokinetic/dynamic model having various parameters and parameter values, and Var(Cobs) represents the variances of the measured concentrations. In addition, Ppop represents the collection of the population mean parameter values in the model (volume of distribution, rate constants, clearance, etc.), Pmod represents the collection of the patient's individual values using Bayes' theorem to obtain the Bayesian posterior parameter estimates, and Var (Ppop) is the collection of the variances of the mean population parameter values.

Inspection of this objective function reveals that the important weighting factors are the reciprocals of the variances of each measured serum level, on the one hand, and on the other, the variances of each population parameter value in the pharmacokinetic/dynamic model used to describe the behavior of the drug. Putting the variances in the denominator (multiplying each data point by the reciprocal of its variance) is the factor that quantifies the relative credibility of each

measured serum level in the fitting procedure, and which correctly balances the credibility of the serum levels against that of the population parameter values. Thus the variances determine just how far the fitting procedure will move toward the measured serum levels or hold back toward the population model.

In general, the Fisher information of a data point (a good measure of its credibility) is the reciprocal of the variance with which that data point is measured [1]. Because of this, the optimal weight of a serum level, when used either in Bayesian fitting, as shown above, in weighted least squares fitting, or in population pharmacokinetic modeling, is the reciprocal of the variance by which each data point is measured. For such procedures, the objective function (OF) for the serum concentration data which is to be minimized is

$$OF = \text{SUM} \frac{(Cobs - C\ mod)^2}{Var\ (Cobs)} \qquad (2)$$

These considerations show that to be optimal in weighted least squares regression, in Bayesian fitting, and also in population modeling, we must know the variance with which each serum concentration (or other response) is measured, and therefore its standard deviation (SD). Data measured with more precision has a smaller SD and greater weight, and vice versa. The problem then becomes that of determining the assay SD over its working range in a practical way without having to measure each sample multiple times.

The Practical Determination of Serum Assay Error Patterns

At the suggestion of Gilman [2], the standard deviation of the EMIT gentamicin assay in use at the Los Angeles County - USC Medical Center was determined at several points over the working range of the assay. As shown in Figure 1, its error pattern was well represented by a second order polynomial.

That assay therefore had an SD of 0.57 ug/ml at 0.0 ug/ml (the blank), with variance 0.326 and weight (1/variance) of 3.07. The SD fell to 0.40 ug/ml at 3.0 ug/ml, with weight 6.25, double that of the blank. The SD then rose to 0.8 at 8.0 ug/ml and to 1.7 ug/ml at 12.0 ug/ml, when the variance was 2.89 and the weight was 0.346. The weights thus ranged over a factor of 18. Such polynomial equations and expressions can be used in appropriate software to provide a good estimate of the assay SD with which each subsequent single serum level is measured, to give a useful and practical estimate of its variance and proper weight in the fitting process.

In general, then, one can measure a blank sample, a low sample, a sample in the middle of the range, a high sample, and a very high one, each measured in at least quadruplicate. In this way one can determine the overall quantitative relationship between the concentration and the SD with which it is determined. One can then fit this relationship with a polynomial of up to 3rd order [3]. Thus, each subsequent serum level, when measured singly, can be provided with an easy and cost-effective estimate of the SD with which it is measured. The idea here is not simply to evaluate within-run or between-run errors to see if they are within acceptable limits, but rather to develop an overall view of the specific but average random assay errors which a sample will encounter as it progresses through the process of being assayed. Ideally, this might be done every day, but this is impractical. However, when the assay is redone with new reagents and/or new technicians, new data points can be obtained from time to time, and either added to the old data, or used to replace it.

The important point here is that each measured serum concentration (or any other measured response) can then be evaluated by its Fisher information, and can be given a weight (the reciprocal of the assay variance at its measured value) according to a good estimate of its credibility [1,3].

The SD is the Key, not the CV

It has been customary to describe an assay in terms of its coefficient of variation (CV), and it has been customary to think of a CV as being acceptable for an assay as long as it is within certain acceptable limits. After that, however, the actual error has usually been ignored, and not considered quantitatively in any specific way. An error of a certain percent CV appears at first glance to be logical, and is visually appealing.

However, a simple example will show that such a constant CV actually does not represent a constant assay error when it is desired to fit according to the Fisher information. Consider two concentrations, of 20 and 40 ug/ml respectively, each of which is measured with a 5 % coefficient of variation. The first concentration has an SD of ± 1.0 ug/ml, a variance of 1.0, and a weight (the reciprocal of the variance) also of 1.0. The second concentration also has the same percent error. Its SD is ± 2.0 ug/ml. Its variance, though, is 4.0, and its weight is therefore 1/4. This is the problem. It is not enough simply to characterize the assay CV and to keep it within some generally acceptable bounds. When doing therapeutic drug monitoring (TDM) and dosage individualization, or when doing population pharmacokinetic modeling, the actual assay SD must

be specifically estimated or determined. Since the variance is the square of the SD, a level measured with twice the SD has only 1/4 the weight, and so on.

Different weighting schemes lead to widely different parameter values being found in fitted pharmacokinetic models. This is well known, and has been explicitly shown in pharmacokinetic studies [4,5]. Weighting has in the past often been regarded as something of an art, to get the fit having the smallest residuals. However, one is never justified in using unrealistic weights simply to obtain fits that are pleasing to the eye. One is never justified in using unrealistic measures of credibility for data points. And yet this is commonly done when one uses an assumption of a constant assay CV, for example. A serum concentration of 0.1 unit, for example, has 100 times the weight of a concentration of 1.0 unit, and 10,000 times the weight of a concentration of 10.0 units when a constant assay CV is assumed! Even putting a small intercept on this relationship does not solve the problem. Different assumptions of assay error lead to widely different parameter values and distributions. Garbage in is truly garbage out. The safest thing to do is to trust nothing except the empirically determined error of the assay actually found, in each individual laboratory. Different laboratories will have different assay error patterns, especially when different assay methods are used. This can become a most important problem in doing Bayesian individualization of drug dosage regimens in different centers, and in doing multicenter population pharmacokinetic modeling. The data of each patient or subject must be correctly evaluated according to its Fisher information. It is easy to do, simply by developing the polynomials.

Analysis of Surveys by the American College of Pathologists

The College of American Pathologists (CAP) periodically sends laboratory specimens containing stated drug concentrations to many clinical laboratories, which then report their findings back to the CAP. The organization then publishes the mean values and the SD's of the various results, and the number of laboratories reporting.

We examined the results found in CAP data sets 1987 ZM-D, 1988 Z-D, 1989 Z-B, Z-C, and Z-D, and 1990 Z-A, Z-B, and Z-C, for Amikacin, Gentamicin, Digoxin, Lidocaine, Theophylline, and Vancomycin. We took the means and SD's of the results found for the various specimens and fitted them with a polynomial, usually of second order, to develop a library of assay error patterns for the assays mentioned above, which laboratories might consider using until they determine their own assay error polynomials. R^2, the square of the correlation coefficient between concentration and SD, represents the proportion of the overall variation explained by the

polynomial relationship [6]. A value near 1.0 indicates little scatter of the data, and a lower one reflects more scatter, and an assay which is less consistent in its errors over its working range.

Results of the CAP Analysis

Amikacin

Fifteen sample means, ranging from 1.1 to 30.0 ug/ml, and their SD's, obtained from 339 to 725 reporting laboratories, provided results for the Abbott TDx, The Dupont ACA, and the Syva Emit assays. The following polynomial equations for the error patterns were obtained.

Abbott TDx SD (ug/ml) = $0.30156 + 0.0053855C + 0.0011184 C^2$, $R^2 = 0.983$
Dupont ACA SD " = $0.46475 + 0.0281310C + 0.0026305C^2$, $R^2 = 0.939$
Syva Emit SD " = $0.23237 + 0.0470150C + 0.0016876C^2$, $R^2 = 0.965$
All Methods SD " = $0.32272 + 0.0183650C + 0.0012051C^2$, $R^2 = 0.983$

As shown in Figures 2A through C, the Abbott TDx assay was the most precise. The Dupont ACA and Syva Emit assays were less so. As was also the case with all subsequent results, the results found for all methods were heavily dominated by those found with the Abbott TDx assay, as so many laboratories used it.

Gentamicin

Seventeen sample means, ranging from 0.9 to 17.8 ug/ml, and their SD's, obtained from 2512 to 3600 reporting laboratories provided the data. The Abbott TDx, Dupont ACA, and the Syva Emit assays were evaluated. The Baxter Stratus assay was not evaluated as the number and range of data points was much less. The following polynomial equations for the error patterns were obtained, and are shown graphically in Figures 3A and B for the Abbott TDx and Syva Emit assays respectively.

Abbott TDx SD (ug/ml) = $0.02334 + 0.049741C + 0.0020206C^2$, $R^2 = 0.978$
Dupont ACA SD " = $0.25719 - 0.016215C + 0.0081998C^2$, $R^2 = 0.982$
Syva Emit SD " = $0.15859 - 0.007125C + 0.0186760C^2$, $R^2 = 0.995$
All Methods SD " = $0.09114 - 0.043524C + 0.0045964C^2$, $R^2 = 0.992$

It was noteworthy here that two samples were found by all laboratories to have concentrations significantly less than those labeled by the College. Except for this, all other samples had general good agreement between the target values stated by the College and the means found by the various laboratories. Again, the Abbott TDx assay was the most precise.

Digoxin

Seventeen sample means ranging from 0.2 to 3.0 ng/ml, and their SD's, obtained from 3160 to 4454 reporting laboratories provided the data. The Abbott TDx, Baxter Stratus, Clinical Assays, Dupont ACA, and Syva Emit assays were evaluated. The following polynomial equations were obtained.

Abbott TDx SD (ng/ml) = $0.09211 + 0.0088626C + 0.0099406C^2$, $R^2 = 0.948$
Baxter Stratus SD " = $0.142110 - 0.048708C + 0.022917C^2$, $R^2 = 0.911$
Clinical Assays SD " = $0.086719 + 0.017052C + 0.011857C^2$, $R^2 = 0.881$
Dupont ACA SD " = $0.15560 - 0.056293C + 0.035574C^2$, $R^2 = 0.562$
Syva Emit SD " = $0.16111 + 0.051579C$, $R^2 = 0.451$
All Methods SD " = $0.12312 - 0.0073104C + 0.020257C^2$, $R^2 = 0.951$

As shown in Figure 4A through E, the Abbott TDx assay was the most precise, and also had the highest R^2 (coefficient of the determination) of any single method. Because of this, the error pattern of that assay is best characterized by such a polynomial equation. When the Syva Emit assay findings were fitted with a second order polynomial, the curve reached a peak and then began to bend downward. This might yield dangerously low estimates of the SD when extrapolated beyond the range reported here (0.2 to 3.0 ng/ml). Because of this, and because the first order polynomial had essentially the same value of R^2, the first order polynomial was used here. The Syva Emit and Dupont ACA assays had the lowest values of R^2, showing that their error pattern had more scatter, while the Abbott TDx had a high value of R^2, showing that its error pattern has little scatter and was well captured by its equation. The Clinical Assays error pattern was intermediate. The Abbott TDx assay was the most precise.

Lidocaine

Fifteen sample means ranging from 0.3 to 6.0 ug/ml, and their SD's, obtained from 430 to 799 reporting laboratories, provided data. The Abbott TDx, Dupont ACA, and Syva Emit assays were evaluated. The following polynomial equations were obtained.

Abbott TDx SD (ug/ml) = $0.053404 + 0.020234C + 0.0036386C^2$, $R^2 = 0.971$
Dupont ACA SD " = $0.319570 - 0.132040C + 0.0265960C^2$, $R^2 = 0.407$
Syva Emit SD " = $0.158560 - 0.013422C + 0.0126140C^2$, $R^2 = 0.924$
All Methods SD " = $0.083569 + 0.008491C + 0.0068741C^2$, $R^2 = 0.985$

The Dupont ACA assay, as shown by its low value of R^2, had a widely varying and inconsistent SD, while the Abbott TDx and Syva Emit assay SD's were well characterized by their equations. The Abbott TDx assay was the most precise.

Theophylline

Seventeen sample means ranging from 3.0 to 30.0 ug/ml, and their SD's, obtained from 3682 to 4696 reporting laboratories, provided data. The Abbott TDx, Baxter Stratus, Dupont ACA, HPLC, and Syva Emit assays were evaluated. The following polynomial equations were obtained.

Abbott TDx SD (ug/ml) = $0.22605 + 0.023955C + 0.00056926C^2$, $R^2 = 0.978$
Baxter Stratus SD " = $0.04783 + 0.089087C - 0.00018739C^2$, $R^2 = 0.986$
Dupont ACA SD " = $0.29967 + 0.010201C + 0.0013798C^2$, $R^2 = 0.963$
HPLC assay SD " = $1.04060 - 0.120450C + 0.0093092C^2$, $R^2 = 0.707$
Syva Emit SD " = $0.21770 + 0.057018C + 0.00071318C^2$, $R^2 = 0.972$
All Methods SD " = $0.25463 + 0.039573C + 0.00088179C^2$, $R^2 = 0.976$

The Abbott TDx assay was the most precise, while the HPLC assay was the least. The Dupont ACA assay was next most precise, and the Baxter ACA and Syva Emit assays were intermediate and of about equal precision. The HPLC polynomial had the lowest value of R^2.

Vancomycin

Fifteen sample means ranging from 4.9 to 40.0 ug/ml, and their SD's, obtained from 645 to 862 reporting laboratories, provided data. The Abbott TDx and Syva Emit assays were evaluated. The following polynomial equations were obtained.

Abbott TDx SD (ug/ml) = $0.57694 + 0.012816C + 0.00058286C^2$, $R^2 = 0.971$
Syva Emit SD " = $0.93214 + 0.023689C + 0.00177600C^2$, $R^2 = 0.971$

All Methods SD " = 0.59421 + 0.012291C + 0.00071299C^2, R^2 = 0.979

Both error patterns were well characterized by their equations, with R^2 values over 0.97. The Abbott TDx assay was the more precise.

DISCUSSION

Sources of Error

The errors reported by the College survey are a mixture of within - run and between - run laboratory errors, as well as within - laboratory and between - laboratory errors. They provide useful guides for purposes of therapeutic drug monitoring and population pharmacokinetic modeling until a clinical laboratory determines its own assay error patterns for its own drugs and develops their own polynomial equations.

The Need for Models

Recently, a change is taking place in the process by therapeutic drug monitoring and the individualization of drug dosage regimens is performed. Less attention is being paid to the interpretation of the raw data of the individual serum concentration results, and more is being paid to the behavior of the patient's fitted pharmacokinetic or pharmacodynamic model which is made based on the data of the entire history of the doses given, the patient's renal function or other descriptor of elimination (which may change from dose to dose), the population parameter values and their SD's, and the serum concentrations and their SD's. Such individualized pharmacokinetic models can usefully cover a span of over a month in some cases, and can significantly reduce the frequency with which serum concentrations need to be obtained. Correlation of the patient's clinical behavior with the behavior of the patient's fitted model is most revealing, especially when the clinical effect of the drug correlates better with concentrations in the peripheral nonserum compartment. For example, an individual patient may exhibit sinus rhythm at one time and atrial fibrillation at another, with identical serum digoxin concentrations. It is not until the fitted model is made that one can see the good correlation between the patient's clinical behavior and that of the peripheral nonserum compartment. Use of models containing nonserum compartments is providing new views of the kinetic behavior of many drugs, including the aminoglycosides, lidocaine, digoxin, digitoxin, and vancomycin. Proper Bayesian fitting, using the correct assay error pattern, is essential. Inaccurate perceptions of the assay error patterns or simple assumptions of a certain coefficient of variation can lead to grossly inaccurate model parameter values, both in

individually fitted patient pharmacokinetic models and in population pharmacokinetic modeling. The SD should be empirically determined, in at least quadruplicate, for a blank, and for a low, medium, high, and a very high serum sample. The samples need not be laboratory standards, and the determination is probably best done on the actual patient samples themselves, after the assay is standardized.

The Need to Measure Blanks

It is interesting that none of the samples sent out by the College was a blank sample. Clinical laboratories, however, usually characterize the sensitivity of their assays (the "lower detectable limit") by choosing a value two SD's above a blank. When concentrations lower than those clearly detectable are encountered, they are often simply reported as being "less than X", where X is two SD's above the blank.

An Important Result - NO "Lower Detectable Limit" for TDM Assays

In toxicological studies, there is clearly a need for a lower detectable limit, usually about twice the SD of the blank determination. This is because in toxicology there is usually no other information than the sample itself as to whether or not the substance is actually present or not. However, in TDM or in any pharmacokinetic study, one clearly knows the time since the dose at which the sample was obtained, and one actually knows, therefore, that the drug is truly present. One clearly knows this from the history, the orders, and the nurses' notes, for example, or the statement from a reliable patient. Indeed, many clinical laboratories will not measure a serum drug concentration unless the time since the last dose is clearly stated on the request slip. The only question is just how much drug is present. Low trough aminoglycoside concentrations for example, below those clearly detectable, are not only useful but often necessary for therapeutic drug monitoring and Bayesian pharmacokinetic fitting and modeling. To withhold such results renders that measurement useless for Bayesian modeling, and should not be charged to the patient's bill when done for therapeutic drug monitoring rather than for toxicology. A vital data point is absent.

Lower detectable limits have been placed on assays and on many assay machines for purposes of toxicology, not for TDM. It is said that when the concentration gets low and approaches zero, that the CV becomes infinite. This has been used as another reason for setting a lower detectable limit. However, the SD is still clearly finite, as shown in any of the figures, for example, and so is the variance and the weight. Because of this, there is no need at all to report a gentamicin concentration as "less than 0.5 ug/ml", for example, when done for TDM or

population modeling. Instead of reporting a Gentamicin concentration as "less than 0.5 ug/ml" for example, the laboratory can easily report the actual value found, and can report it, for example, as "0.1 ug/ml, below the secure detectable limits of 0.5 ug/ml". This reporting procedure will answer both the needs of the toxicologists and the pharmacokineticists, and is therefore more generally useful. The SD of such a measurement can easily be found from the assay error polynomial, as shown in any of the figures.

While the use of lower detectable limits is clearly needed in toxicological analysis to make a firm decision as to whether a substance is actually present in the body or not, it is a distinct obstacle to optimal therapeutic drug monitoring. In therapeutic drug monitoring there is no question that the drug has been given. Since the patient never excretes the last molecule of the drug, there is no question that the drug is still present in the body. The only question is its actual concentration - how much.

The Need to Collect High Serum Concentrations

The CAP Survey paid most attention to determining the laboratory errors for concentrations within the usual therapeutic ranges of the drugs under consideration. However, low trough concentrations, well below the usual detectable limits, are frequently encountered, especially since the vogue of "once-daily" aminoglycoside therapy. Because of this, one might suggest that more such low concentrations, and especially blank concentrations, might well be included in future surveys.

On the other hand, it is equally important to know the errors of concentrations found well into the very high range, again, especially since the vogue of "once-daily" aminoglycoside therapy. Because of this, when a high concentration is encountered, especially if extra dilutions are required, one might suggest that the laboratory run it again, and in at least quadruplicate if possible, to better characterize the error of the assay at its high end, and to extend the known SD pattern of that assay.

The Need to Improve Assay Precision at the High End

When doing Bayesian fitting or population modeling, one can only give equal weight to various serum concentrations when they actually have the same SD. An assay with a constant SD over its working range is said to be homoschedastic. Such an assay will actually have a coefficient of variation that decreases by half as the concentration doubles. None of the assays evaluated here

were homoschedastic. A homoschedastic assay is probably an unrealizable ideal. With such an assay, the fitting procedure would reach out equally well to fit both high and low levels. This would be an ideal state of affairs.

In contrast, a heteroschedastic assay error pattern is one in which the assay SD changes over its working range. An assay with a constant coefficient of variation is heteroschedastic. As the concentration doubles, the SD also doubles, the variance quadruples, and the weight given to the assay is reduced to one fourth. Because of this, when a constant coefficient of variation is assumed for an assay used in Bayesian fitting, high concentrations will be relatively ignored compared to lower ones, and the fitted model will not fit the high measured concentrations as closely as one might wish. This is also true for the polynomial equations described above. The difference here is that the polynomial equations are derived from empirically measured SD's over the working range of the assay, and should include blank concentrations as well. Because of this, they provide a more correct estimate of the assay error pattern over its working range. The fit, while often appearing to ignore the high concentrations, is actually being done correctly, according to the Fisher information of each data point.

One of two things needs to be improved. Either the current Bayesian fitting procedure based on the Fisher information of the data points is incorrect, or the assays need to have their precision improved at the high end to make them more homoschedastic. To discard the concept of Fisher information would be to overthrow several decades of carefully acquired and searchingly criticized mathematical and statistical knowledge. To try to improve the precision of assays at their high end is probably the most constructive thing to do. It may even be possible, for example, to alter the ratios of reagents so that the ratio of bound and unbound drug in the assay can be changed, with a resultant change in the error pattern toward the ideal of homoschedasticity.

Other Sources of Error - Process Noise

In making pharmacokinetic/dynamic models by any method, there are other sources of error and uncertainty in addition to that of the assay. Because of this, it has been common to model "intraindividual variability" as a separate parameter, either as part of, or in addition to, the assay error, and to include this parameter as a part or all of the overall measurement noise, separate from the "interindividual variability" within the pharmacokinetic parameter values, which is due to the diversity between the various subjects in the population.

Intraindividual variability is due, for example, to the fact that all drug doses are prepared with a certain error, and also are administered with a certain error in recording the time at which the dose was actually given. Further, there are similar errors in recording the times at which serum samples are drawn. In addition, there may be misspecification in the structural model made to describe the actual process being modeled, and model parameter values that are regarded as being fixed and constant during the study period may actually change. These factors all are important sources of environmental uncertainty and noise that surround each patient and his/her treatment, and which importantly affect the degree of precision with which it is possible to achieve a desired target goal in drug therapy [7,8].

These other environmental factors are frequently included as other sources of measurement noise. However, this is incorrect. Most of them are actually sources of noise in the differential equations that describe the behavior of the model. They represent process noise rather than measurement noise. The correct way to describe process noise in such stochastic dynamical systems is with stochastic rather than deterministic differential equations [9]. Such sources of process noise have been shown to be at least as important as the measurement noise resulting from the assay errors, in determining the degree of precision which it is possible to achieve with drug therapy [7,8]. Both simulation studies [7] and clinical studies [8] have shown their importance. It is for this reason that we advocate here the careful determination of the actual assay error pattern in each laboratory.

Since these other sources of noise, whether regarded as process or measurement noise, are as large as they are, and are often greater than the assay noise itself, they have often been regarded as dominating the determination of intraindividual variability when population modeling has been done, and the actual assay error itself has been neglected except for some general consideration of its form. However, the assay error is easy to determine, as described herein. Using the iterative two stage Bayesian population modeling in the USC*PACK collection, it is now possible to enter the assay error polynomial, correctly determined for the assay in question, and then to compute a parameter, gamma, which determines the overall intraindividual variability as a fraction of the assay error polynomial. When gamma is 1, there is no other source of variation than the assay. When gamma = 2, it is twice the assay error, and assay error is half the overall intraindividual variability. When gamma = 3, it is 3 times the assay error, and assay error is 1/3 of the overall intraindividual variability. Commonly, gamma often ranges between 1.5 and 3 in many population analyses, showing that assay error is a significant fraction of the overall intraindividual variability in a well-done clinical study.

In this way, it is easy to determine the actual error and the specific relationship between the drug concentration and the precision with which it is measured, so that the assay data can be weighted correctly, according to its Fisher information, in the fitting process or the population modeling process. The IT2B program now does this well. Then, once gamma is known and the assay error polynomial can be multiplied up by gamma, then that information can be used to make a nonparametric population model in an optimally informed manner.

Because the above environmental sources of error are not properly described without stochastic differential equations, as discussed above, it is felt that the most important and useful thing to do for the present is to carefully determine and establish the actual known error of each laboratory assay over its working range, as described here, then to determine the value of gamma in the population studied with software such as the IT2B program, and to make vigorous efforts to minimize the other environmental sources of error resulting from the errors in dosage preparation and administration [7,8]. It is not impossible that gamma may me used as an index of patient care, reflecting the precision of care in the therapeutic environment surrounding the patient in that center.

ACKNOWLEDGMENTS

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References.

1. DeGroot M: Probability and Statistics, 2nd ed., Addison-Wesley Publishing Company, 1989, p.423.

2. Gilman T: Personal communication.

3. Jelliffe R: Explicit Determination of Laboratory Assay Error Patterns - A Useful Aid in Therapeutic Drug Monitoring. American Society of Clinical Pathologists Check Sample Continuing Education Program. Drug Monitoring and Toxicology 10: 1-6, 1990.

4. Dodge W, Jelliffe R, Zwischenberger J, Bellanger R, Hokanson J, and Snodgrass W: Population Pharmacokinetic Models: Effect of Explicit versus Assumed Constant Serum

Concentration Assay Error Patterns upon Parameter Values of Gentamicin in Infants on and off Extracorporeal Membrane Oxygenation. Ther. Drug Monit., 16: 752-559, 1994.

5. Jelliffe R: Effect of assumptions concerning assay error patterns upon pharmacokinetic parameter values and model behavior. J. Vet. Pharmacol. Ther. 17: 105-109, 1994.

6. DeGroot M: Probability and Statistics, 2nd ed., Addison-Wesley Publishing Company, 1989, p. 640.

7. Jelliffe R, Schumitzky A, and Van Guilder M: Nonpharmacokinetic Clinical Factors Affecting Aminoglycoside Therapeutic Precision: A Simulation Study. Drug Invest. 4: 20-29, 1992.

8. Charpiat B, Breant V, Pivot-Dumarest C, Maire P, and Jelliffe R: Prediction of Future Serum Concentrations with Bayesian Fitted Pharmacokinetic Models: Results with Data Collected by Nurses Versus Trained Pharmacy Residents. Ther. Drug Monit., 16: 166-173, 1994.

9. Jazwinski A: Stochastic Processes and Filtering Theory. Academic Press, New York, 1970.

Figures and Legends

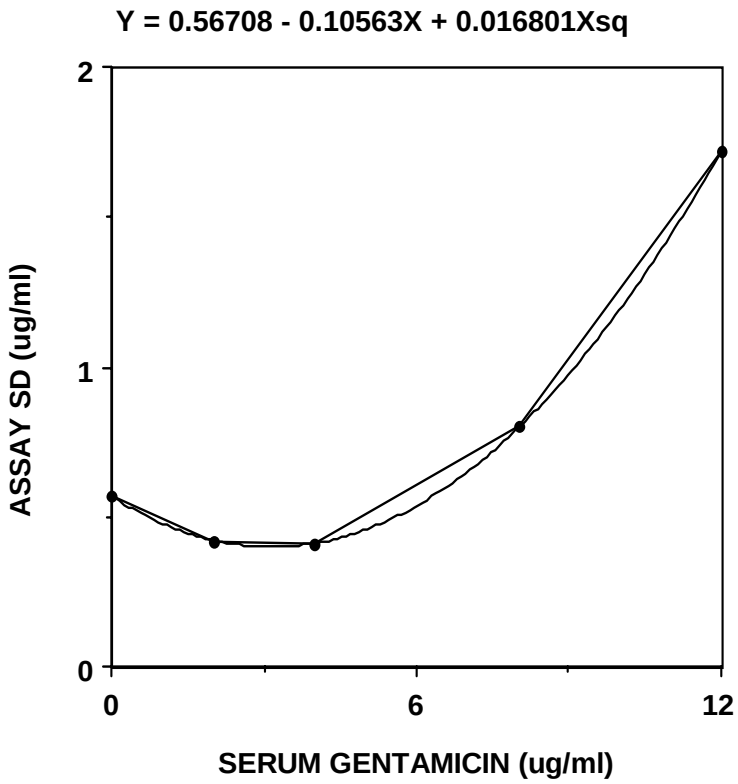

Figure 1. Plot of our hospital's Emit Gentamicin assay and its associated Standard Deviation (SD).

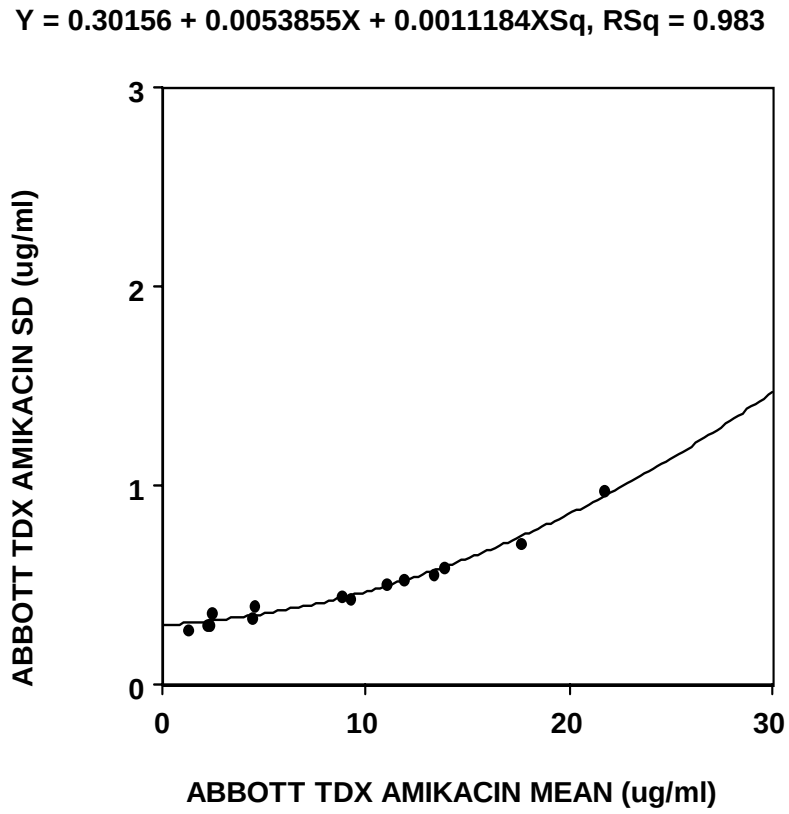

Figure 2A. Plot of the Abbott TDx Amikacin assay and its associated Standard Deviation (SD).

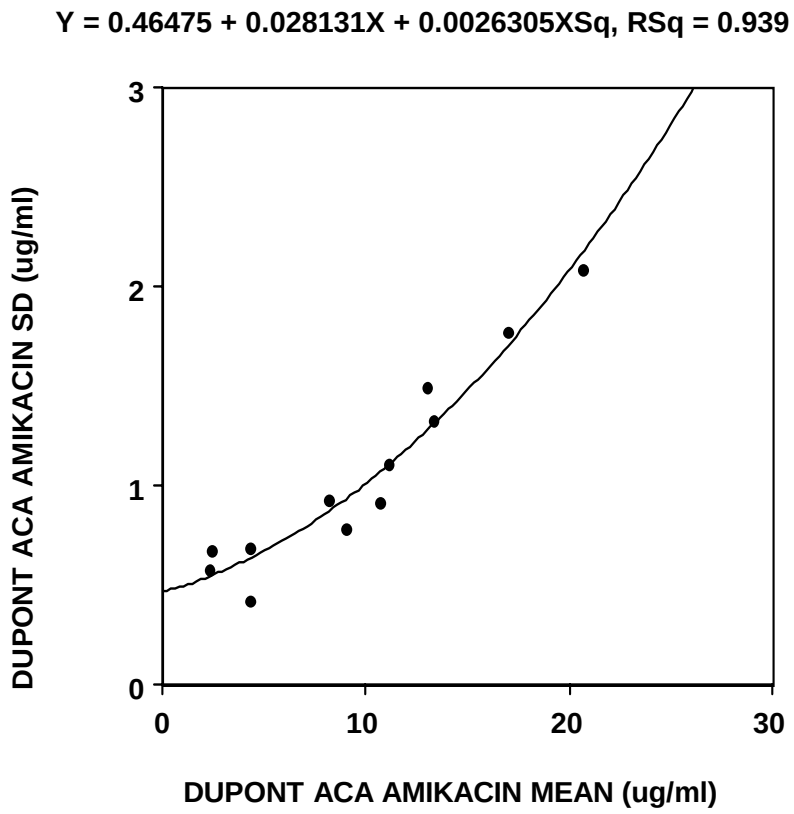

Figure 2B. Plot of the Dupont ACA Amikacin assay and its associated Standard Deviation (SD).

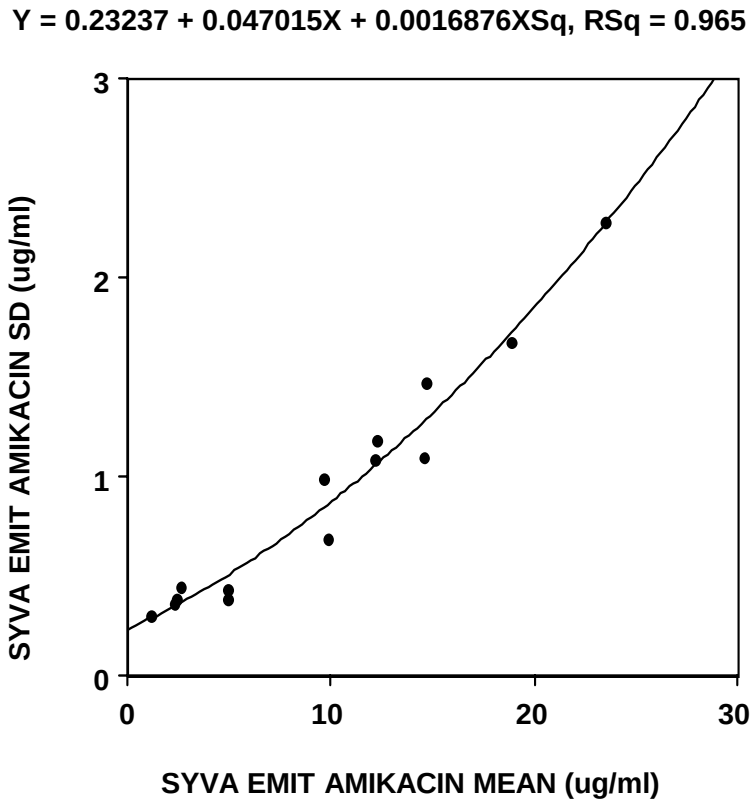

Figure 2C. Plot of the Syva Emit Amikacin assay and its associated Standard Deviation (SD).

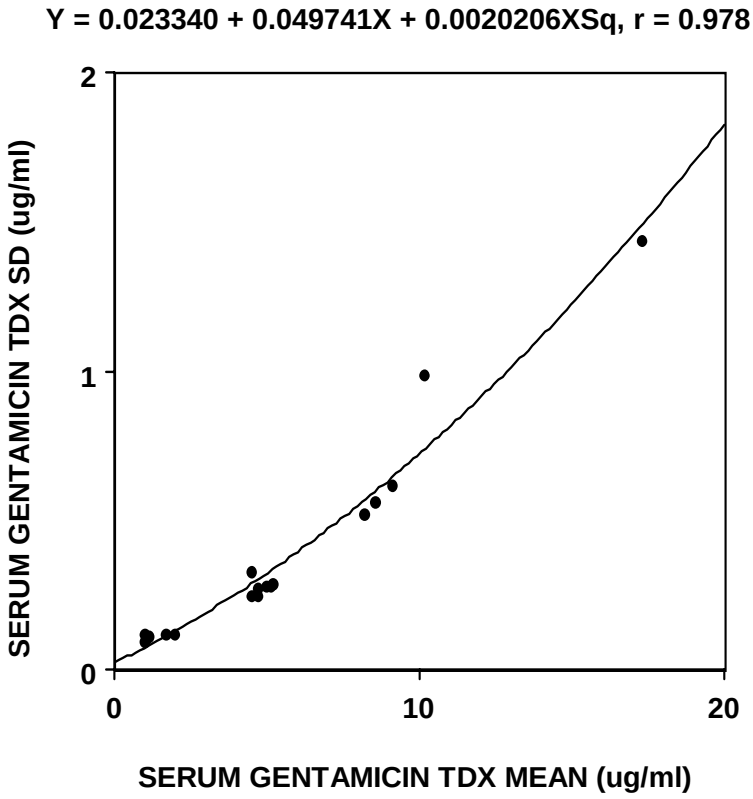

Figure 3A. Plot of the Abbott TDx Gentamicin assay and its associated Standard Deviation (SD).

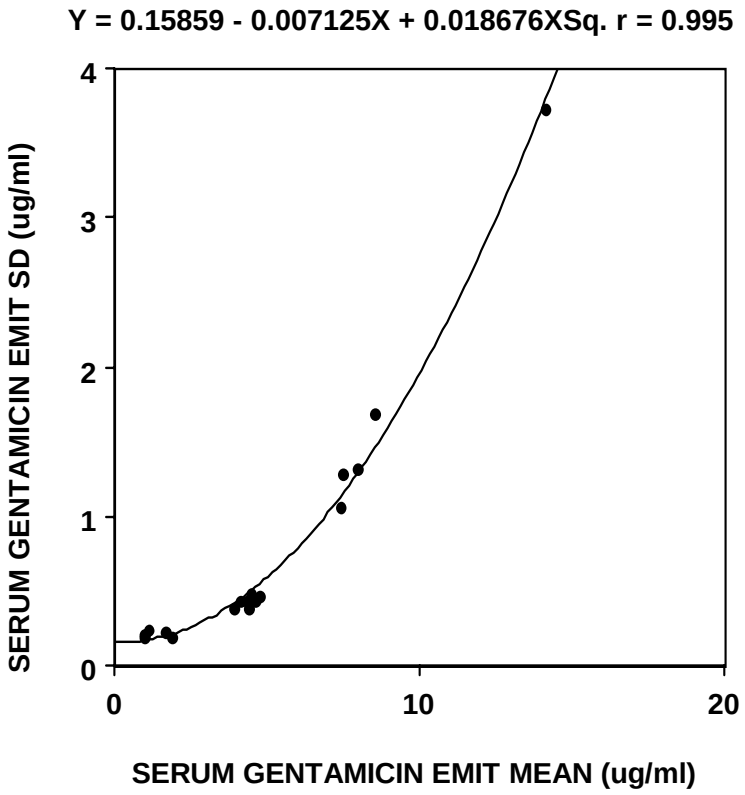

Figure 3B. Plot of the Syva Emit Gentamicin assay and its associated Standard Deviation (SD).

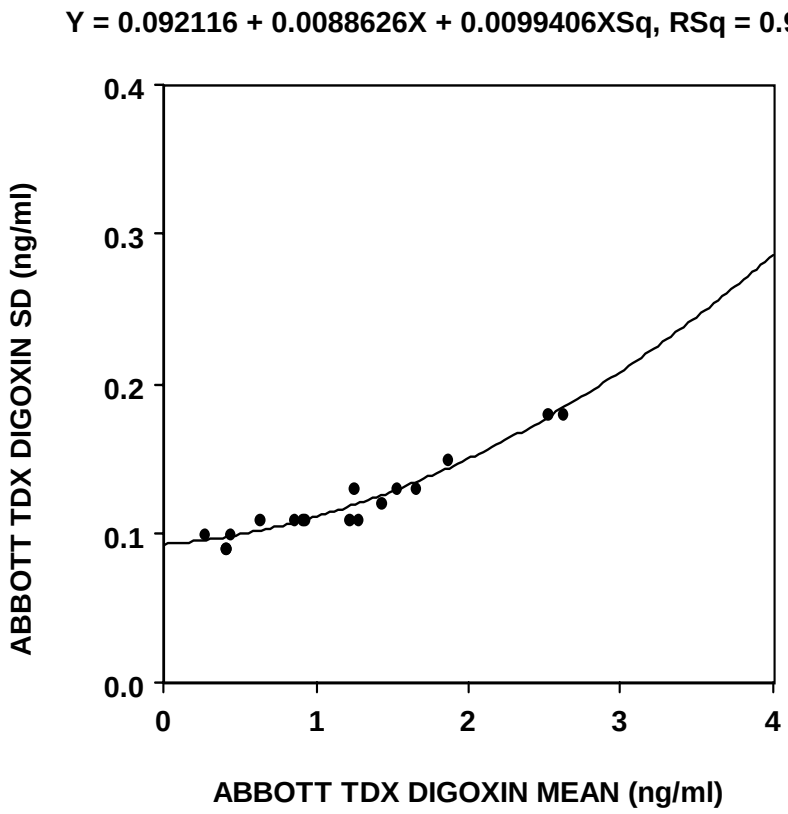

Figure 4A. Plot of the Abbott TDx Digoxin assay and its associated Standard Deviation (SD).

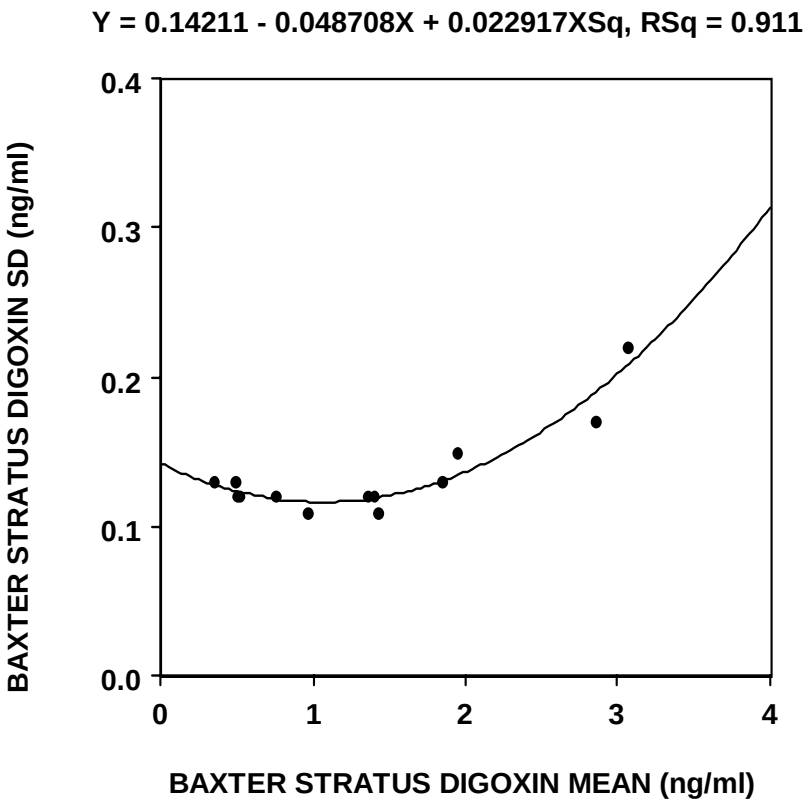

Figure 4B. Plot of the Baxter Stratus Digoxin assay and its associated Standard Deviation (SD).

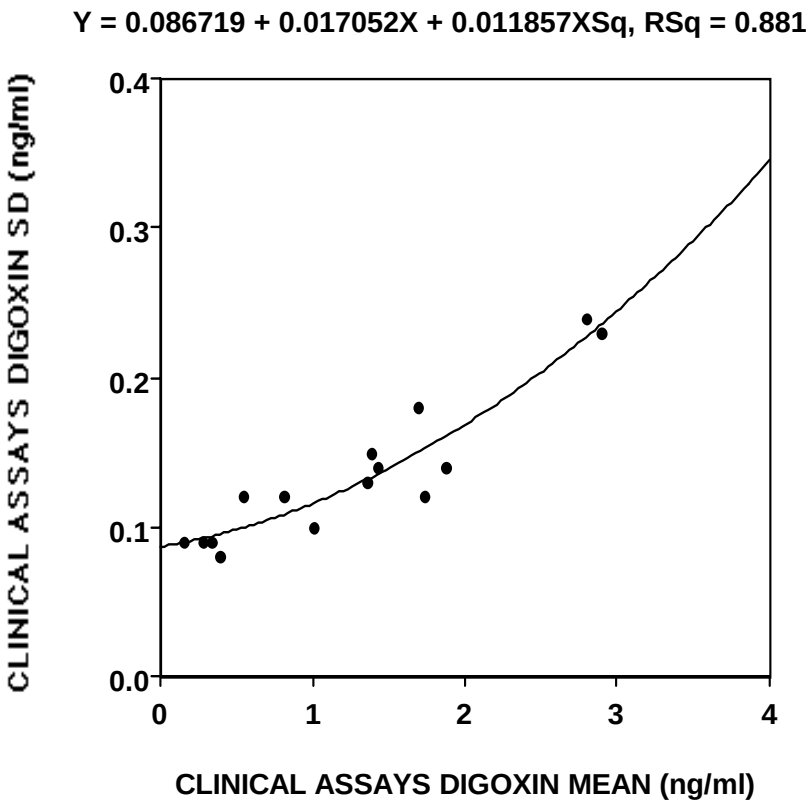

Figure 4C. Plot of the Clinical Assays Digoxin assay and its associated Standard Deviation (SD).

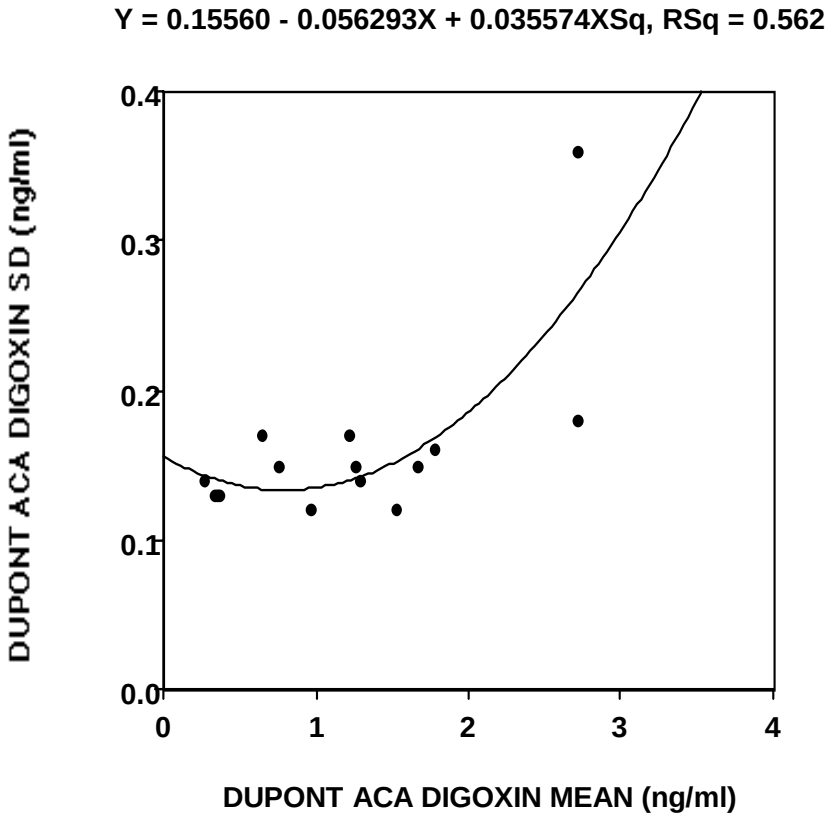

Figure 4D. Plot of the Dupont ACA Digoxin assay and its associated Standard Deviation (SD).

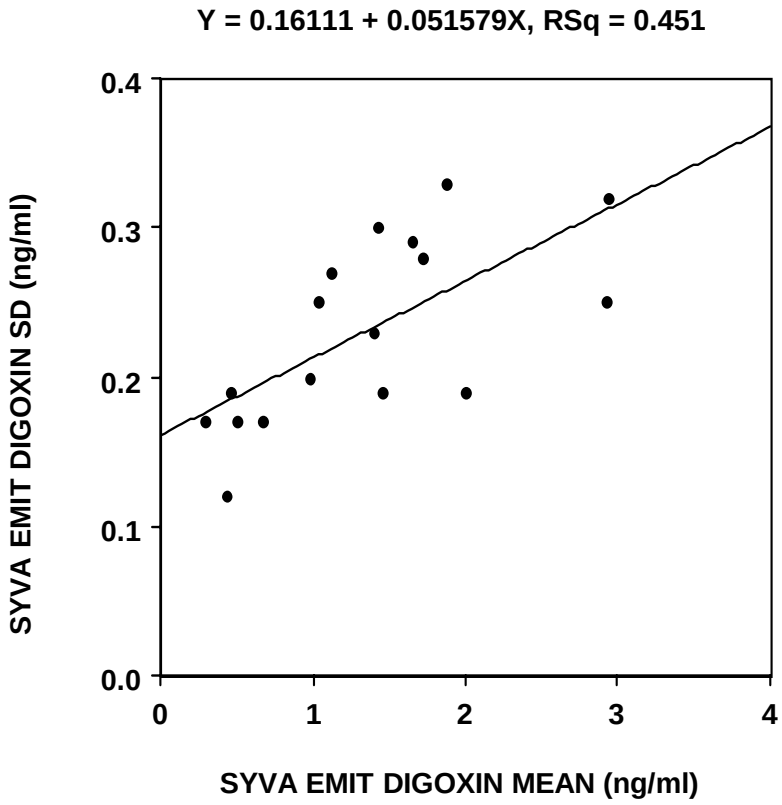

Figure 4E. Plot of the Syva Emit Digoxin assay and its associated Standard Deviation (SD).