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Predicting Effects of Quality-Control Practices on the Cost-Effective Operation of a Stable, Multitest Analytical System

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The cost-effective operation of an analytical system depends on quality-control (QC) practices such as the QC procedure itself (control rules, number of control measurements); the batch size or the run length; and the use of bracketed, nonbracketed, or pre-control modes of operation. Predictive value models that predict the defect rate and test yield of each test, as well as of the system as a whole, have been used to study these practices and to develop strategies for improving the quality and productivity of a multitest analyzer. Quality was optimized for most tests by achieving high error detection and low false rejection by the QC procedures. For a few tests where ideal QC performance could not be achieved, predictive models indicate that high quality is achieved as long as the observed stabilities (low frequencies of errors) of the measurement procedures are maintained. In our laboratories, productivity gains of 2.9% ($17 400/year) were achieved by changing QC procedures. Predictive models indicate that further gains are possible by increasing batch size and changing from bracketed to nonbracketed control operation. In general, the common practice of bracketed control on stable analytical systems may need to be re-examined owing to its effect on the cost of operation.

Additional Keyphrases: *bracketed vs nonbracketed control procedures · data handling · statistics*

Koch et al. (*1*) recently described the selection of medically useful quality-control (QC) procedures for a multitest analytical system.[1] QC procedures were individualized for each test on the basis of the quality requirements and the analytical performance of each test. The control rules and the number of control measurements were selected to provide high error detection for runs having medically important errors and few false rejections for runs having only the inherent random error or stable imprecision of the measurement procedures. For 15 of 18 tests, the individualized QC procedures achieved nearly ideal performance, which improves both the quality and productivity of the multitest system.

Here we consider whether further improvements in quality and productivity are possible by additional changes in QC practices. Would quality be improved by use of multirule QC procedures for those few tests where single-rule QC procedures have less than ideal performance? What productivity gains are possible with changes in batch size or run length? Would productivity be improved if the practice of "bracketed" control was replaced by nonbracketed or pre-control procedures?

In assessing the potential effects of such changes, quantitative models are useful for studying the interactions of the many factors and variables involved. Predictive value theory (*2*) can be applied to QC testing (*3, 4*) to predict how quality and productivity depend on the performance characteristics of the measurement procedure (inaccuracy, imprecision, stability, or frequency of errors), the performance characteristics of the control procedure (probabilities for error detection and false rejection), and certain operational conditions (number of control samples, number of calibrators, number of patients' samples, and batch size). However, available models (*4, 5*) do not permit study of multitest systems in which different QC procedures are used for different tests. Here we describe multitest models that predict quality and productivity for each test, as well as for the multitest system as a whole. We have also considered instrument characteristics of the Hitachi 737 analyzer in developing specific models applicable to this complex multitest clinical chemistry analyzer. Using these models, we have studied how cost-effective operation depends on the individualized QC procedures; batch size or run length; and bracketed, nonbracketed, and pre-control modes of operation.

Materials and Methods

Application of Predictive Value Theory in Quality Control

Table 1 shows how analytical runs that are tested by a QC procedure can be grouped into four classes (true rejects, false rejects, false accepts, and true accepts) and how the number of runs in each class (n) can be expressed as a function of the frequency of medically important errors (f), probability for error detection (P_{ed}), and probability for false rejection (P_{fr}). Quality, in terms of "defect rate," is predicted from the ratio of false-accept runs to the total (n_t) of the true-reject, false-reject, false-accept, and true-accept runs. Productivity, in terms of "test yield," is predicted from the ratio of true-accept runs to the total number of runs. Substituting the expressions for the numbers of runs

Table 1. Quality and Productivity as Predictive Value Characteristics

	Control signal	
Analytical run	**Reject**	**Accept**
With error	$n_{tr} = n_t f P_{ed}$	$n_{fa} = n_t f(1 - P_{ed})$
Without error	$n_{fr} = n_t(1 - f)P_{fr}$	$n_{ta} = n_t(1 - f)(1 - P_{fr})$

Quality: defect rate = $n_{fa}/n_t = f(1 - P_{ed})$.
Productivity: test yield = $n_{ta}/n_t = (1 - f)(1 - P_{fr})$.

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[1] Nonstandard abbreviations: QC, quality control; f, frequency of errors; P_{fr}, probability for false rejection; P_{ed}, probability for error detection; N, number of control measurements in a batch; C, number of calibrators in a batch; S_p, number of patients' samples in a batch; T, total number of samples in a batch; r_m, minimum repeat number for patients' samples in-process; s, standard deviation; GGT, γ-glutamyltransferase (EC 2.3.2.2); ALP, alkaline phosphatase (EC 3.1.3.1); AST, aspartate aminotransferase (EC 2.6.1.1); and LD, lactate dehydrogenase (EC 1.1.1.27).

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provides equations for predicting quality and productivity from f, P_{ed}, and P_{fr}, as shown at the bottom of Table 1.

Quality depends on f and P_{ed}. High quality, or a low defect rate, can be achieved by reducing f, which means selecting a stable measurement procedure and maintaining it properly so that the frequency of problems is zero. If problems do occur, then a low defect rate is assured by having a high P_{ed}, which requires selection of a QC procedure with high statistical power.

Productivity depends on f and P_{fr}. High productivity, or a high test yield, is achieved by having a low f, thereby obviating the need to reject and repeat analytical runs. High productivity also requires that P_{fr} be minimized; otherwise, runs are rejected and repeated even when no analytical problems are occurring.

Productivity is also affected by the relative numbers of samples, controls, and calibrators in a batch or run; policies for repeating analytical runs (rerun factors); and different control modes of operation (bracketed, nonbracketed, pre-control), as defined in the next section. Specific instrumental characteristics that must be considered include the type of analytical process (batch, simultaneous batch, random-access, hybrid) and additional repeats owing to samples in-process.

To consider these additional factors, we can expand the test yield equation in Table 1 by substituting $n_{ta} = n_t - n_{tr} - n_{fr} - n_{fa}$:

$$\text{Test yield} = 1 - n_{tr}/n_t - n_{fr}/n_t - n_{fa}/n_t \qquad (1)$$

Each ratio term represents a "loss" in yield from an ideal yield of 1. For example, n_{tr}/n_t is the loss from true-reject runs; n_{fr}/t_t, the loss from false-reject runs; and n_{fa}/n_t, the loss from repeat requests because of erroneous results reported in falsely accepted runs. "Loss factors" are added to allow each class of runs to be weighted appropriately, as follows:

$$\text{Test yield} = 1 - L_{tr}(n_{tr}/n_t) - L_{fr}(n_{fr}/n_t) - L_{fa}(n_{fa}/n_t) \qquad (2)$$

where L_{tr} is the loss factor for true-reject runs, L_{fr} for false-reject runs, and L_{fa} for false-accept runs.

Other losses in test output can be included by additional loss terms. Losses for calibration and control can be accounted for by including the term L_{cc}. Losses for repeat requests on true-accept runs can be included by the term $L_{ta}(n_{ta}/n_t)$, to account for tests re-ordered by physicians to confirm already correct results. With inclusion of these additional loss terms, the expanded form of the productivity model is as follows:

$$\text{Test yield} = 1 - L_{cc} - L_{tr}(n_{tr}/n_t) - L_{fr}(n_{fr}/n_t) - L_{fa}(n_{fa}/n_t) - L_{ta}(n_{ta}/n_t) \qquad (3)$$

This general model can be expressed in terms of the process variables by substituting the expressions (in terms of f, P_{ed}, and P_{fr}) from Table 1 for the number of runs in each of the classes. The loss factors can be defined in terms of numbers of control measurements (N), of calibration samples (C), and of patients' specimens (S_p); batch size ($T = N + C - S_p$); and rerun factors for different classes of runs (R_{tr}, R_{fr}, R_{fa}, and R_{ta}). Specific instrument characteristics (type of analytical process, samples in-process) and the control mode of operation require further modifications of these expressions and terms, as illustrated below for the Hitachi 737 analyzer.

Application to the Hitachi 737 Multitest Analytical System

The Hitachi 737 analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN 46250) was used in routine operation at the University of Wisconsin hospitals and clinics. The initial QC procedure in use was a $1_{3s}/2_{2s}/R_{3.64s}$ multirule procedure with N = 2 for all tests. This was replaced by the following individualized QC procedures (*1*): single-rule with 3.5s control limits and two control measurements per run (N = 2) for sodium, potassium, glucose, urea nitrogen, creatinine, phosphorus, uric acid, cholesterol, total protein, total bilirubin, GGT, ALP, AST, and LD; single-rule with 2.5s and N = 2 for albumin, chloride, total CO_2, and calcium.

Type of analytical process. The Hitachi 737 is a random-access analyzer with a simultaneous batch feature available because of having four reaction cells per block. With this feature, all four reaction cells in a block are consumed when a single test is performed on a sample or when a repeat analysis must be performed because one test is out-of-control; i.e., when sample is added to only one reaction cell, the capacity for using the other three is lost. The probability for false rejection by the QC procedure is, therefore, critical because any repeat analysis of a single test causes a loss of output or capacity. To account for this "loss," the expression for n_{fr} (in Table 1) is modified by replacing P_{fr} with $[1 - (1 - P_{fr})^4]$, where the exponent 4 represents the number of simultaneous cells.

Control mode of operation. Bracketed control represents the operation in which control samples are assayed at the beginning and end of a batch of patients' samples. Control status is evaluated after the batch is completed; acceptability is judged from results for control samples at both the beginning and end of the batch. Nonbracketed control requires analyzing controls only at the beginning of the batch, evaluating control status as soon as possible, and judging acceptability from those controls only at the beginning of the batch. Pre-control occurs when control samples are tested and interpreted before analysis of patients' samples. These different control modes are accounted for in the productivity models by the numbers of samples that must be repeated for true- and false-reject runs.

Samples in process. When the analyzer is in continual operation with either bracketed or nonbracketed control, the number of patients' samples to be repeated when a run is out-of-control will increase by the number of patients' samples in process (already consumed by the instrument before the process can be stopped). We quantify these additional patients' samples by a term r_m (minimum repeat number), which depends on the ratio of the throughput time to the incremental time for sampling each additional patient's specimen (r_m = throughput time/incremental time). For our instrument configuration, r_m is 8 when 18 tests are analyzed per patient's specimen, 7 for 14 tests, 13 for six tests, and 40 for 1–4 tests. The effects of in-process samples are included by modifying the loss factor for true-reject and false-reject runs.

Loss factors. L_{cc} is the proportion of a run consumed by calibration and control samples [(C + N)/T]. L_{tr} and L_{fr} are products of the rerun factors (R_{tr} or R_{fr}) times the number of samples to be repeated, K_r, which changes with the control mode of operation. L_{fa} is the proportion of patients'

and control samples [(S_p + N)/T] times the rerun factor for false accepts (R_{fa}). To account for any repeat requests from physicians who are suspicious about the test results, L_{ta} is assumed to be proportional to the defect rate [f(1 − P_{ed})] times the samples to be repeated [(S_p + N)/T] times the rerun factor (R_{ta}). This considers only the loss in process output and does not account for additional costs in the treatment (or lack of treatment) of the patient (*5*).

The values assigned for rerun factors depend on laboratories' policies for repeat analyses and physicians' practices in re-ordering tests. R_{tr} and R_{fr} are generally assigned values of 1 because laboratory policy requires all out-of-control runs to be repeated. R_{fa} is often assigned a value of 2 because it is assumed that a physician who detects an erroneous result re-orders that test, gets a result different from the first one, and then re-orders the test again to determine which of the first two results is correct. R_{ta} is 1 because a re-order will result in a repeat analysis that agrees with the previous result, so that only one rerun is necessary.

Specific productivity models. Equation 4 shows the general expanded model.

$$\text{Test yield} = 1 - (C + N)/T$$

$$- K_r\{R_{tr}fP_{ed} + R_{fr}(1 - f)[1 - (1 - P_{fr})^4]\}$$

$$- \frac{S_p + N}{T}[R_{fa}f(1 - P_{ed}) + R_{ta}f(1 - P_{ed})(1 - f)(1 - P_{fr})] \quad (4)$$

Specific models differ only in the value of K_r, which depends on the number of samples to be repeated for true- and false-reject runs. K_r = (Sp + r_m + N)/T for bracketed control (Model I), K_r = (r_m + N)/T for nonbracketed control (Model II), and K_r = N/T for pre-control (Model III).

Implementation of models. An electronic spreadsheet (Lotus 1-2-3; Lotus Development Corp., Cambridge, MA 02142) was used to perform the calculations (Figure 1). The performance predicted for the multitest system as a whole is given by the average defect rate and average test yield at the bottom of the Figure. These unweighted averages are appropriate for the workload in our laboratory, but individual tests can be weighted differently to account for differences in workloads.

Results

To predict the productivity of the Hitachi 737 system, we selected input values for N, S_p, and T to describe the QC practices to be studied; C was set to 0 because the system was calibrated infrequently relative to the number of batches being analyzed. The rerun factors were assigned values of 1 (R_{tr}, R_{fr}, R_{ta}) or 2 (R_{fa}); r_m was set as 8 to represent our usual operation, in which 14–18 tests are performed per patient's sample. P_{fr} and P_{ed} were obtained from power function graphs (*6*) generated with a computer simulation program (*7*). We obtained estimates for f from laboratory QC records for a one-month period, during which the $1_{3s}/2_{2s}/R_{3.64s}$ multirule procedure (N = 2) was used to provide high detection of medically important errors. The tests with the highest frequencies of errors were AST (8.8%), ALP (4.1%), urea nitrogen (4.1%), total bilirubin (2.6%), and total protein (2.1%). For other tests, see Figure 1, column f, for the observed frequencies of errors.

Quality in terms of defect rate. The defect rates shown in Figure 1 are the rates expected for each test based on the QC rules and N that were selected (*1*) and the frequencies of errors observed. The average defect rate for the system is 0.0006 (0.06%), which suggests an error rate of only 1 in 1667 test results. The highest defect rate is 0.0051 (0.51%) for chloride. Use of a multirule QC procedure with P_{ed} = 0.90 would reduce the defect rate for chloride to 0.14% and for the system as a whole to 0.0003 (0.03%, 1 in 3333 tests). Use of a multirule procedure for total CO_2 would not provide any improvement because this test has been very stable in our laboratory (f is effectively zero). Tests having high values for f (AST, ALP, total bilirubin, total protein) will cause few defects because nearly all those errors will be detected by the QC procedures selected.

Bracketed-Control Hitachi 737 Model

Conditions: N = 2, C = 0, Sp = 18, T = 20, m = 4, Rtr = 1, Rfr = 1, Rfa = 2, Rta = 1, rm = 8

TEST	SEc	QC Rule	Pfr	Ped	f	Defect Rate	Test Yield
Sodium	4.32s	1:3.5s	0.000	0.00	0.015	0.0000	0.678
Potassium	6.92s	1:3.5s	0.000	1.00	0.005	0.0000	0.893
Chloride	2.19s	1:2.5s	0.028	0.00	0.016	0.0051	0.723
Total CO2	2.36s	1:2.5s	0.028	0.72	0.000	0.0000	0.760
Glucose	5.01s	1:3.5s	0.000	1.00	0.015	0.0000	0.879
Urea nitrogen	5.86s	1:3.5s	0.000	1.00	0.041	0.0000	0.843
Creatinine	8.36s	1:3.5s	0.000	1.00	0.000	0.0000	0.900
Calcium (1)	1.61s	1:2.5s	0.028	0.42	0.005	0.0029	0.740
Calcium (2)	1.61s	1:2.5s	0.028	0.40	0.000	0.0000	0.750
Phosphorus	6.19s	1:3.5s	0.000	1.00	0.000	0.0000	0.900
Uric acid	7.44s	1:3.5s	0.000	1.00	0.000	0.0000	0.900
Cholesterol	5.75s	1:3.5s	0.000	1.00	0.000	0.0000	0.900
Total protein	4.87s	1:3.5s	0.000	0.00	0.021	0.0000	0.870
Albumin	3.03s	1:2.5s	0.028	0.90	0.010	0.0010	0.738
Total bilirubin	7.44s	1:3.5s	0.000	1.00	0.026	0.0000	0.884
GGT	6.92s	1:3.5s	0.000	1.00	0.016	0.0000	0.879
ALP	6.92s	1:3.5s	0.000	1.00	0.041	0.0000	0.843
AST	5.01s	1:3.5s	0.000	0.00	0.088	0.0000	0.776
LD	5.01s	1:3.5s	0.000	1.00	0.000	0.0000	0.900
Multitest System Averages						0.0006	0.838

Fig. 1. Spreadsheet format for quality–productivity model for bracketed-control operation of the Hitachi 737 multitest analyzer

See footnote 1 and Table 1 for definition of terms. General study conditions are shown at the top; individual tests are listed in the column at the left side; other columns tabulate the size of the critical systematic error (SE_c), the control rule being applied (QC rule), the probability for false rejection (P_{fr}), the probability for detecting the critical systematic error (P_{ed}), the observed frequency of errors (f), and the predicted "defect rate" and "test yield" for that test

Productivity in terms of test yield. With the multirule procedure that was originally in operation, a test yield of 79.6% was predicted, which compares with an average of 77.8% observed in the laboratory for a five-month period. The observed yields were calculated from detailed workload records that identified patients' tests, QC samples, calibrators, and repeat analyses. No records of physicians' re-orders were available, so the observed yields may be somewhat high because these repeat analyses were not included. On the other hand, reanalyses of samples for which the concentrations exceeded the linear range of the assay means that the yields might be somewhat low because these repeats were not excluded. To improve the reliability of the estimates, we analyzed data from several months and averaged the monthly estimates.

With the change to the individualized medically useful QC procedures, the model predicts a yield of 83.8%, for a gain of 4.2%. In practice, we have observed an average yield of 80.7% over a five-month period, for a gain of 2.9%. The values for the predicted yields are high because of underestimating the loss from calibration. Workload data show that ~3% of the analyzer's output is actually consumed for calibration, compared with the 0% estimate included in the modeling studies. When the loss for calibration is taken into account, the predictions are in good agreement with the observed yields.

Table 2 summarizes the test yields that are predicted for changes in batch sizes and different control modes of operation. Test yield should increase by 6–8% by expanding the batch size from 20 to 60. The control mode chosen should affect test yield by an additional 4–6%. Changing from bracketed operation to nonbracketed operation would provide the biggest improvement; pre-control operation provides small additional gains over nonbracketed operation. Overall, productivity gains of 12 points appear possible when starting from bracketed operation with 20 samples and changing to nonbracketed operation with 60 samples per batch.

In the application of these models, the predictions of test yield are dependent on the false-rejection expression, which may be represented in various alternative ways, e.g., by using a linear term (number of simultaneous cells times the probability for false rejection). Table 3 compares the predicted yields for the original model for bracketed control (Model I) and this alternative model (Model *IA*). The differences are very small because of the low values for the probabilities for false rejection. Table 3 also shows the predicted test yields when there is no simultaneous batch characteristic (Model *IB*). For the false-rejection probabilities appropriate for the QC procedures used on our instrument, the predicted test yield would be ~3% higher if there were no simultaneous batch characteristic. For higher false rejections, the differences are much greater, which illustrates that (*a*) the productivity models are very sensitive to the false-rejection expression and the actual P_{fr} values and (*b*) the QC designs are especially critical for the cost-effective operation of simultaneous batch processes.

Discussion

Cost-effective operation, in our view, means maximizing both quality and productivity. Quality can be described in terms of defect rate, i.e., the portion of samples having medically important errors. Productivity can be described in terms of test yield, i.e., the portion of samples reported as correct patients' test results. Defect rate and test yield depend on many QC practices, such as the QC procedure itself and its control rules and number of control measurements, the batch size or run length, and the control mode of operation.

Based on modeling studies, only minor improvements in defect rate can be expected with further changes in QC procedures on our Hitachi 737. Our present QC procedures (*1*) do not limit cost-effectiveness because they achieve nearly ideal performance for most tests, detecting medically important errors whenever they occur and providing very few false rejections. For the few tests where QC performance is not ideal, the individual tests demonstrate low frequencies of errors under routine operation and very few errors that need to be detected. Quality, therefore, is well-optimized, and further efforts to improve cost-effective operation should be aimed at improving productivity.

Financial data from our laboratory indicate that a 1.0-point gain in test yield should provide a savings of over $6000 per year in direct labor and supply costs. The 2.9-point gain we achieved by changing QC procedures provides a savings of $17 400 per year, or $87 000 over an expected five-year lifetime of the analytical system. Although this savings is difficult to achieve directly in the financial bottom line of the laboratory, some resources should be freed for other activities. Alternatively, the gain in test yield can be viewed as increasing the analytical capacity of the laboratory, allowing additional testing to be performed without addition of more resources. In any case, laboratories cannot afford to ignore opportunities for increasing the productivity and cost effectiveness of operations. Describing the potential gains in terms of cost savings or increased capacity should help motivate these efforts.

Modeling studies indicate that we should be able to achieve further significant gains in productivity and corresponding cost savings in our laboratory. The strategies for improving productivity are to increase the batch size and to change from bracketed to nonbracketed control. Pre-control operation offers little additional gain in test yield and potentially would slow the reporting of patients' results; thus such a change is not a viable strategy.

In retrospect, the changes implemented and additional ones in progress clearly provide the best strategies for improving the cost-effective operation of the analyzer. However, the modeling studies were useful for illustrating the magnitude of the possible gains and for developing stepwise strategies. For example, when starting from bracketed control with a batch size of 20, changes in the batch size may take priority over changes in the control mode of operation; comparable gains are possible, but a change in batch size will generally be easier to implement than a change in the control mode.

In general, the practice of using bracketed control on

Table 2. Predicted Average Test Yields for Different Control Modes of Operation and Different Batch Sizes

	Batch size			
Productivity model	20	30	40	60
Bracketed control	0.838	0.877	0.897	0.916
Nonbracketed control	0.877	0.917	0.938	0.958
Pre-control	0.894	0.929	0.946	0.964

Table 3. Predicted Test Yields as a Function of the False-Rejection Expression of the Model for the Example Illustrated in Fig. 1[a]

	Test yield as predicted by		
P_{fr} per test	Model I: m = 4, R_{fr} = 1	Model *IA*: m = 1, R_{fr} = 4	Model *IB*: m = 1, R_{fr} = 1
Actual[b]	0.8370	0.8354	0.8661
All 0.000	0.8763	0.8763	0.8763
All 0.010	0.8221	0.8212	0.8626
All 0.020	0.7694	0.7661	0.8488
All 0.030	0.7183	0.7110	0.8350

[a] Bracketed control operation with N = 2, C = 0, S_p = 18, T = 20, R_{fr} = 1, R_{fa} = 2, R_{ta} = 1, r_m = 8, and other input parameters as shown.
[b] P_{fr} values from Fig. 1.

stable analytical systems may need to be re-examined. The practice of bracketing probably originated on single-channel continuous-flow analyzers, which were subject to drift owing to instrument and reagent instabilities. This QC practice was naturally carried over to multichannel continuous-flow analyzers and was then passed on to the instruments that replaced them, including those stable, random-access analyzers that have little in common with the earlier systems. Regulations and accreditation guidelines tend to further establish past practices as the requirements for the future. Maintaining these old practices, without carefully assessing their suitability for new analytical systems with improved imprecision and stability, contributes to inefficient operations and increases the cost of health care.

Such QC practices live on because their effects are very difficult to evaluate in the laboratory. We need to be able to study these practices and proposed changes off-line to predict their effects and to judge whether potential improvements are possible. Predictive models for quality and productivity provide an off-line tool for doing this. Better planning of QC practices is possible and more cost-effective operation of analytical systems may be achieved.

Arguments for the careful planning of QC practices for analytical tests parallel those for careful optimization of diagnostic tests (*2, 8*). If evaluating diagnostic sensitivity and specificity is important, then it should also be important to know the probabilities for error detection and false rejection. If it is useful to assess the effect of the prevalence of disease by calculating the predictive value and efficiency of test results, then it should also be useful to assess the effects of frequency of errors by calculating the quality and productivity of the testing process. We have illustrated that the careful planning of QC procedure can be accomplished for a complex multitest analytical system such as a Hitachi 737.

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