

Computer Programs for Processing Radioassay Data from Raw Input To Output*

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Current techniques used to handle data generated in the radioassay laboratory are discussed. More specific details regarding a medium-sized configuration used in our laboratory are presented and an example of an approach to selecting the best method for determining the model of a standard curve is illustrated. On implementing our automated data system, we found that: (A) automated processing frees laboratory personnel from the tedious tasks of hand calculations and reporting; (B) large quantities of data may be entered into an automatic system and handled accurately; and (C) new tests may be added easily with a generalized radioassay program.

Various automated methods for handling radioimmunoassay and competitive protein binding assay data have been widely published. These reports are usually limited to a specific method. The purpose of this report is to review automated methods and discuss the design, development, and implementation of our automated system. Radioassay will be used as an inclusive term for the general groups of tests available.

System Design

The basic factors in the design of a radioassay automated system include the limitations of the assay, and the limitations of the data system.

Radioassay tests differ in their complexity but generally the limitations of a test are: (A) the range of the test standards; (B) the counting procedures required for adequate statistics; and (C) errors that result during preparation of the assay.

The limitations of the data system refer to the capabilities and requirements of the computation facility and are related to the choice of the computer (1-3). The rapid growth and wide variety of computers available make classification difficult. Evaluation of automated systems in a radioassay

laboratory can be placed in the following classifications: (A) large, (B) small-to-medium, and (C) desk-top instrumentation.

Large central computer facilities allow for multiple, simultaneous use. Data are entered and retrieved from computers (input and output) through peripheral devices including magnetic tape, punched card, paper tape, terminals, telephone line, printer, and plotter. Specialized computer personnel are usually required to implement and process the programs and often these large facilities have special room requirements, such as controlled temperature and raised flooring. In general they are remote from the hospital laboratory, which may be inconvenient if rapid test results are required.

The small-to-medium computers have lesser capabilities than the large computers and are less expensive. They have no special room requirements and are of immediate access to the user. The software and peripheral devices can efficiently handle laboratory data. This type of computer is compatible in a nuclear medicine facility that handles laboratory data and processes scintillation images. These computers allow ease of use by laboratory personnel due to their interactive nature. A computer consultant is recommended and is necessary if the facility plans to design its own assay programs or change any purchased packaged programs. They also handle technical problems that may occur.

The desk-top computer is the simplest and least expensive. Programming is usually easier but has strict capacity limitations. A desk-top computer may be the choice of a laboratory without access

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to a computer consultant. This computer can also alternate as a general purpose calculator. Many packaged programs are available for processing a variety of radioassay protocols (4, 5).

Our automated system uses a medium-sized computer, PDP 11/20 (Product Digital Equipment Corp., Maynard, Mass.) The processor contains a hard-wired multiplication and division unit which is necessary for efficient handling of complex mathematical equations. The capacity of our storage system includes 16,000 words of core and 1.2 million words of disk storage. This allows processing of complex programs. The input/output console includes a video terminal and a teletype. These are used for communication between the user and the computer. A high-speed tape reader is used to feed data from our automated gamma counters into the computer. Results are obtained from a high-speed line printer. The software includes an elaborate operating system that affords ease in editing, compiling, and executing programs. The radioassay programs are written in FORTRAN IV, a universal computer language.

System Development

Three basic components of the computer are utilized during data handling. They include (A) input, i.e., the type of data that are fed into the computer and the methods used for input; (B) process, i.e., the type of calculations required; and (C) output, i.e., the type of reports that are desired—summary report, individual reports, or inventory reports (5).

System Input

The modes of input may be on-line or off-line. On-line input affords the user the opportunity to become involved in the execution of the program whereas off-line does not. We use the on-line mode because it allows: (A) ease of operation, i.e., the computer is available to clinical personnel with little or no computer knowledge; (B) flexibility during input data stage; and (C) ease in using on-line programs.

The off-line mode is useful in large computer facilities with many users and types of programs. Although generally characterized by fast and efficient operation, the off-line mode requires a rigid program data structure and a computer-oriented operator or adviser.

We choose either the console or paper tape to enter data. The console is slow but dependable, while the paper tape is fast but not as dependable due to tearing or tangling of tape in paper punch or reader (6).

Radioassay Analysis Techniques

The basic radioassay processing calculations include simple ratio comparisons, i.e., positive and negative results for Ausria antigen and antibody, and standard curve evaluations, i.e., T_3 - T_4 , digoxin, IgE assay, etc.

The following discussion will concentrate on the IgE assay and competitive binding assays.

There are four basic types of standard curve representations. The first is the hand calculation method in which the technician plots the standard curve (i.e., percent bound versus concentration on linear or logarithmic graph paper). The concentration of unknowns is interpolated on the graph. A simple automated approach (piecewise linear approximation) consists of entering a set of standard counts and known concentrations, plotting the curve mathematically, and interpolating the unknowns by a line or curve between each set of standards. The success of this method depends on the counting data for each of the standard doses. Despite this limitation, this method is simplest and is appropriate for some tests.

Superior methods are the logit/linear model and nonlinear model. Both consider the statistical nature of the counting data. We have developed a general linear regression radioassay program called "RARAP." It is based on the logit/linear versus log model designed by Rodbard, et al, of the National Institutes of Health (7, 8). It is compared to the nonlinear model of the radioassay program of Dr. J. VanWyk's Pediatric Endocrinology group, which is run on an IBM-1130 in the Biomedical Computation Center at the University of North Carolina. The algorithms are based on work by Burger, et al, Prince Henry's Hospital, Melbourne, Australia (9).

In general, a linear versus log relationship has shown the best fit line to an exponential curve, while the logit versus log has shown the best fit line to a sigmoid-shaped curve. Our program selects the best fit transformation, either the linear (percent bound) versus log (concentration) interpreted as (7, 8):

$$Y = A + B \times \text{Log}(X) \quad (1)$$

where Y is defined as percent bound, A is the intercept, B is the slope, and X is the concentration, or the logit (percent bound) versus log (concentration) interpreted as:

$$\text{Logit}(Y) = A + B \times \text{Log}(X) \quad (2)$$

where logit refers to $\log[Y/(1-Y)]$. The nonlinear exponential model is interpreted as (9):

$$Y = \frac{A}{C + X^E} \quad (3)$$

TABLE 1. Comparison of Radioassay Processing Methods for IgE* Concentration Values

Known standard concentrations in U/ml	Linear regression model†			Nonlinear model 0-400 U/ml
	0-400 U/ml	4 points 5-200 U/ml‡	3 points 5-100 U/ml§	
0	1.38	0.	0.	0.
1.0	2.00	0.13	0.13	0.80
2.5	1.97**	0.10	0.09	0.77
5.0	7.55**	5.12**	5.09**	9.75**
25.0	17.55**	15.48**	15.68**	22.70**
100.0	98.13**	99.43**	103.80**	102.51**
200.0	182.56**	200.99**	212.22**	182.56**
400.0	403.87**	583.75**	627.09	438.32**

* Phadebas® IgE kit.

† Based on linear regression model by Rodbard (7, 8).

‡ Results based on 5-, 25-, 100-, and 200-U/ml model.

§ Results based on 5-, 25-, and 100-U/ml model.

|| Based on nonlinear model by Burger (9).

** Acceptable values.

where A, C, and E are constants determined by an interactive technique.

A comparison study is necessary to determine which processing methods are valid and best suited for determination of the concentration level of a particular assay. Table 1 compares the linear and nonlinear results for a set of known standards for a Phadebas® IgE kit. The approach consists of entering the known standard counts and concentrations, calculating a model by linear or nonlinear techniques, and then reapproximating the concentration by the model. For the Phadebas® IgE kit, below 50 U/ml is considered a normal concentration level. We can conclude then that results in the area surrounding the 50-U/ml standard are valid.

Three runs of the linear model include: (A) the standard curve over the full range of values (0-400 U/ml); and (B) 4 points (5-200 U/ml); and (C) 3 points (5-100 U/ml). These were compared against a run using the full-range curve in the nonlinear model. Values followed by asterisks in Table 1 show the predicted range acceptable for the determination of the concentration levels of IgE.

Comparison of the relative errors for IgE concentration values as in Table 2 gives the acceptable methods. Error is defined as:

$$/ \text{Error} / = \frac{/ x_p - x_k /}{/ x_p /} \quad (4)$$

where x_k is the known concentration at time of preparation and x_p is the concentration resulting from the model.

The asterisked values in Table 2 indicate an area where the relative errors are less than 0.5. This agrees with the accepted range predicted in Table 1.

TABLE 2. Relative Errors for IgE Concentration Values*

Known standard concentration in U/ml	Linear regression model			Nonlinear model
	0-400 U/ml	4 points	3 points	
0.	1.			
1.0	2.	6.69	6.69	0.25
2.5	0.21**	24.00	26.78	2.25
5.0	0.34**	0.02**	0.02**	0.487**
25.0	0.30**	0.38**	0.37**	0.10**
100.0	0.02**	0.01**	0.04**	0.02**
200.0	0.10**	0.01**	0.06**	0.10**
400.0	0.00**	0.32**	0.57	0.09**
x_k^*	x_{p2}^*	x_{p2}^*	x_{p3}^*	x_{p4}^*

* Relative error = $1x_{pi} - x_k / 1x_{pi}$, where x_{pi} is concentration results from the models for $i = 1, 2, 3, 4$ and x_k is the known standard concentration.

** Acceptable values resulting from each model. Allowable relative errors are defined as less than 0.5.

TABLE 3. Summary Report Sample

Date: 01/13/75	Lot No. BA-6789		
AUSRIA-125	In vitro		
Mean negative control: 239 count/min			
Mean positive control: 2,215 count/min			
Ratio: (Mean positive to mean negative) 9.3			
Negative range: 120 to 502			
Questionably positive range: 359 to 502			
Sample should be repeated.			
Positive range—Greater than 502			
Blood unit No.	Count/min	Ratio	Result
1. B31311.	175	0.73	Nonreactive
2. B31343.	176	0.74	Nonreactive
3. B31346.	178	0.74	Nonreactive
4. B31347.	109	0.46	Nonreactive
5. B31348.	13,528	56.60	Positive
6. B31349.	145	0.61	Nonreactive
7. B31350.	364	1.52	Questionably Positive
8. B31351.	179	0.75	Nonreactive
9. C. M. 1/10/75	146	0.61	Nonreactive
10. C. J. 1/10/75	134	0.56	Nonreactive
11. L. B. 1/10/75	210	0.88	Nonreactive
Physician: Dr. No.			
Technician: _____, R. T.			

TABLE 4. Individual Report Sample

5	B31348	13,528
Date: 01/13/75		
AUSRIA-125		In vitro
Result: Positive		
Physician: Dr. No		
Technician: _____, R. T.		

We observed that the full linear regression model has the smallest error with the nonlinear model a close second, and that the 4-point and 3-point models have less overall error in the 5–200-U/ml range.

The preliminary results of the IgE comparison indicate the following: (A) The linear and nonlinear models are the most acceptable for determining the IgE concentration. (B) Choice of method may be highly dependent on the nature of the assay and computational capabilities. Statistical variation of the assay data, limits of the computer system in handling complex mathematical algorithms, as well as the speed of the processor in executing instructions are primary considerations. Transformations as log require the definition of the function in the system, and iterative methods require that fast processing be available. (C) Further studies are indicated to validate the above and to make further conclusions about the choice of a processing technique.

Output Results

Automated systems produce summary and individual results with the same accuracy and efficiency each and every time. The summary results are the compilation reports of patients with corresponding values for a particular test. Nuclear medicine physicians and technologists may review these quickly to determine abnormal patient results.

Individual results are given to the patient's physician and are filed in the patient's chart. The

summary report is shown in Table 3. The individual report in Table 4 shows identification values and patient results.

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