Multiple on-line data collection and processing for radioimmunoassay using a micro-computer system

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SUMMARY A micro-computer system is described which has been designed to perform on-line data capture from up to seven radioisotope counters of different types in parallel with interactive results processing and subsequent transmission to a laboratory computer-based data management system.

With the purchase of a new radioactivity counter for use with radioimmunoassay (RIA), a Nuclear Enterprises 1600 (NE1600), resources were available to purchase a dedicated programmable calculator (Hewlett Packard). The data output from this would have to be entered into the laboratory's data management system based on a Modular One/8000 Computer (Computer Technology Ltd).^{1 2} The data from the existing counters have been output on paper tape produced by a teleprinter attached to each counter. This method has some drawbacks: long lengths of paper tape are liable to tear, and heavy use of the teleprinter's punches leads to wear and tape errors. Since, for a little extra expenditure, it was possible to develop a more flexible system which would handle the capture and processing of data not only from the new but from all the laboratory's counters, it was decided not to purchase the calculator. The choice lay between connecting the counters directly on-line to the main computer, like other instrumentation, or developing a self-contained system which would be on-line to the main computer. The latter is preferable because some of the counting is done over long periods such as overnight and at weekends. Furthermore, the stored data can be accepted by the main computer at low load times, and such a development is in keeping with the trend for most new analytical equipment to contain its own local primary processing capability.

Hardware

A micro-computer was assembled from the Intel SBC (single board computer) (Fig. 1) range of

modules housed in an Intel System 80/20 chassis which provides a card cage, bus, and power supply. A cabinet was used to package the chassis together with a Periflex twin double-density, floppy disc drive (Fig. 2). Total cost was about £6000.

Figure 3 shows the positions of each of the system modules:

- (a) an SBC 80/20/4 (Fig. 1) processor board with 4k bytes of RAM (random access memory), 4k bytes of EPROM (erasable programmable read only memory) timers, interrupt processors, V24 controller (CCITT recommendations V23 and V24) used to drive a 30 cps keyboard printer, etc.
- (b) two SBC boards which provide the floppy disc interface
- (c) one board (SBC 016) with 16k bytes of RAM
- (d) one board (SBC 310) to provide hardware floating point arithmetic
- (e) two boards (SBC 534), each providing four V24 interfaces (one for each counter and one for connection to the CTL Modular One).

The only local fabrication necessary was the provision of small configurable interface units (details available from authors) to connect to the existing counters, such as LKB Wallac, NE8000 series, etc., which use the 20 mA convention for driving their teletypes. The NE1600 is available with a V24 output option. These interface units also enable the teleprinter output to be retained if still desired.

Software

Available with the Intel processor was a simple software 'monitor' program which is plugged into two of the EPROM positions. Unfortunately, it is not designed to support the concept of interrupt-

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Fig. 1 *Intel SBC 80/20/4. A typical single board computer module.*

Fig. 2 *Complete RIA micro-computer system.*

Fig. 3 Hardware configuration — Intel 8080 based micro-computer

driven data input from the counters at the same time as interrupt-driven disc transfer necessary for this application. As a result, a more appropriate suite of code, 4k bytes in size, was written to act as a 'supervisor' and 'operating system' which could be loaded from disc. The supervisor provides system initialisation, multilevel disc transfer, input/output routines (mimicking the main computer's user interface), and other basic facilities, and the operating system controls the loading, cataloguing, and selective running of a suite of application programs also held on disc. Another 4k bytes are consumed by the code, parameter tables (which hold status and control bytes together with counter data output format for each counter), and data buffers used for the on-line data input. This section is loaded from disc at start-up and remains resident. The remaining 8k bytes accommodate one of the catalogued programs at a time as required.

The software was developed on a Modular One and 'down-line' loaded into the Intel micro-computer via the V24 communications line. Once established on a floppy disc the micro-system is self-contained and can be replicated using a disc-to-disc copy program. (A disc formatting program, which uses the random sector addressing option, provides a significant performance improvement over the sequential format used by the Intel monitor software.)

To simplify system start-up, a bootstrap loader (a short program entered from the Intel monitor) reads the systems software into store from disc and transfers control to the operating system con-

version. This loader is now fixed into an EPROM chip which fits into one of the remaining processor board positions. Table 1 summarises the store utilisation.

For ease of use, the whole system operates using only one of the floppy disc drives, reserving the other for copying and fall-back in the event of one failing. Each floppy disc provides 512k bytes of data storage and, apart from the sections used for systems and logging software and program catalogue mentioned above, a further area is used as a catalogue of parameter tables, one for each type of radioimmunoassay method used. A user-driven catalogued program 'ESTC' permits a conversational establishment of these tables. Table 2 shows one of these estimation tables.

The remaining disc area is used for data buffers. Both the sharing of counter runs by different estimations and the need for each sample to be run in duplicate, or higher replication frequencies, prohibit a one-to-one relationship between 'raw-data' input and the subsequent processed results. To provide the greatest flexibility, the disc area is divided into 'raw' and 'processed' batch buffers, and these are interleaved to minimise head movement, which, inevitably, is slow with the simple worm-driven mechanism that is employed. Figure 4 summarises the disc utilisation.

Catalogued programs are available to initiate counting runs into raw data batches (labelled A, B, C, etc), to list and edit both raw and processed batches (the latter labelled 11, 12, 13, etc. to avoid confusion with the main computer system batch

Table 1 *Store utilisation for radioimmunoassay*

		HEX Address
INTEL MONITOR in 'EPROM'	1K bytes	0000H
		07FFH
BOOTSTRAP in 'EPROM'	1K bytes	0800H
		11FFH
Unused 'EPROM' position	1K bytes	1200H
		15FFH
Address Gap		
SBC 80/20/4 'RAM' (Stack etc.)	4K bytes	3000H
		3FFFH
OPERATING SYSTEM	4K bytes	4000H
		4FFFH
Store-resident COUNTER SCANNER : TABLES	4K bytes	5000H
		5FFFH
RE- SABLE AREA FOR ONE BACKGROUND PROGRAM AT A TIME	8K bytes	6000H
		7FFFH

Fig. 4 *Floppy disc utilization for radioimmunoassay*

Table 2 An estimation parameter table

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JOB?RUN Y?Y
ESTC;PGM NAME?
Y;ESTIMATION CATALOG Y/N?
L;(M)AKE/(D)ELETE/(L)IST/(R)ESET/E(X)IT?
S;(C)ATALOG/(S)INGLE/(A)LL?
ECOR;ESTIMATION NAME?
TECOR
    2N BACKGROUND COUNTS?
    2N TOTAL COUNTS?
    2N STD'S?
    1N UNKNOWN'S?

    .000000
    5.000000
    10.000000
    20.000000
    30.000000
    40.000000
    50.000000
    60.000000
    80.000000
    99.999900

MOD I SCALE FACTOR?      2

CONC
MINIMUM VALUE             .000
VALUE OF INCREMENT        2.500
NO. OF PLACES AFTER DEC. POINT      3

CO/CB-1
MINIMUM VALUE             .000
VALUE OF INCREMENT        .100
NO. OF PLACES AFTER DEC. POINT      3

COUNTS/TIME
MINIMUM VALUE             15.000
VALUE OF INCREMENT        1.250
NO. OF PLACES AFTER DEC. POINT      3

% BOUND
MINIMUM VALUE             10.000
VALUE OF INCREMENT        1.000
NO. OF PLACES AFTER DEC. POINT      3

X;(M)AKE/(D)ELETE/(L)IST/(R)ESET/E(X)IT?
JOB?

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buffer numbers), and also to load and edit laboratory accession numbers and quality control identifiers in the processed batches. The catalogued program 'PROC', which is called in to perform the processing

function, places its results into a nominated processed batch, although source data can be taken from selected sections of the raw counter batches to permit mixed counting. After the total, background, and standard counts have been processed, three calibration graphs can be plotted on the printer (C0/CB-1, COUNTS, and PER CENT. BOUND versus CONCENTRATION) and the most appropriate chosen for calibration. Processing can be repeated after editing of raw data if required. The results for the subsequent patient samples are then computed by linear interpolation between adjacent standards, with measures of precision, and placed in the chosen processed batch on disc. The appropriate estimation parameter table specifies the batch format, such as replication frequencies, for each of total and background counts, standards and samples, as well as the number of and assigned values for the standards. The graph dimensions are also specified using 'ESTC'. Table 3 illustrates a selection of printouts and Fig. 5 a typical graph.

Finally, when it is convenient, the catalogued program 'XMIT' is used to transfer a processed batch into the Modular One. The input software in the Modular One uses a small module specific to this device but shares with other on-line instruments the remaining data acquisition software.

It may be valuable also to note some of the data

Fig. 5 One of the possible calibration graphs

Table 3 A selection of printouts (a) Raw data batch buffer; (b) Part of the output from 'PROC'; (c) A processed batch ready for transmission to the Modular One

(a)				
CUP	TRAY	TUBE	TIME	COUNT
1	J	1	60	9
2	J	2	60	6
3	J	3	60	10618
4	J	4	60	9981
5	J	5	60	5204
6	J	6	60	5270
7	J	7	60	4231
8	J	8	60	4390
9	J	9	60	3730
10	J	10	60	3873
11	J	11	60	2829
12	J	12	60	2996
13	J	13	60	2306
14	J	14	60	2382
15	J	15	60	1984
16	J	16	60	1975

(b)							
RCUP	TIME	COUNT	CT/TIME	PCBND	C0/CB-1	RESULT	QUALITY
1	60	9	BKG				
2	60	6	.125	QC	.775		
3	60	10618	TCN				
4	60	9981	171.658	QC	4.438		
5	60	5204	STD				
6	60	5270	87.203	50.811	.000	.000	QC .645
7	60	4231	STD				
8	60	4390	71.842	41.809	.215	5.000	QC 1.712
9	60	3730	STD				
10	60	3873	63.358	36.064	.378	10.000	QC 1.640
11	60	2829	STD				
12	60	2996	40.542	20.226	.000	20.000	QC 2.108

(c)		
CUP	LABNO	RESULT
1	00033G	65.000
2	00034H	.000
3	00035J	2.886
4	00036K	2.086
5	00037H	22.324
6	00038N	22.755
7	00039Q	12.892
8	00040R	12.290
9	00041S	20.581
10	00042U	21.995
11	00043V	19.129
12	00044W	19.701

storage and processing constraints. 'Raw' data is stored in the form:

TIME—16 bit integer, COUNT—16 bit integer.

Processing is performed using the hardware floating point unit which has an 8 bit exponent and a 23 bit mantissa, and all derived values are stored in this form as four bytes.

The quality monitor is based on removing replicate counts which are more than 3.6 SD, from the mean, and repeating this process until too few remain or an acceptable dispersion is found.

The final results are therefore constrained only by the initial data. Much has been written discussing

various curve-fitting techniques, but there is considerable agreement³ that the greater flexibility to accommodate differing curve shapes offered by linear interpolation makes it the preferred choice for a general-purpose facility. Careful attention to positioning and frequency of calibration standards across the working range can be used to minimise calculation error. It was also felt that the display of the various calibration options in graphical form, before processing, would offer a visual judgement of suitability to be made³ and if it is considered appropriate, the editing facilities can be used to adjust the raw data values. Indeed, this entire cycle of operation can be repeated as often as necessary with no loss of source data, which helps to reduce the

number of occasions on which a complete re-assay of a batch of specimens is necessary.

Discussion

The micro-computer was assembled to meet the exact requirements of the task. No hardware expertise was necessary, and a convenient commercially available SBC micro-technology packaging system was used. The initial investment of approximately four person-months in providing development aids and systems software will serve also for other future applications. The programs specific to this particular application have taken only three person-months to produce and are very simple in nature. Their division into separate catalogued modules will permit modifications to be made readily and extra functions to be developed as the need arises. The day-to-day operation and configuration necessary to add extra estimations and modify existing ones can be performed by laboratory technical staff. This development is consistent with the desirable concept of distributing the immediate data processing from analytical instrumentation and has become financially possible with the advent of micro-technology. Indeed the system described has been designed to operate either in a free standing mode or on-line to any laboratory data processing system which supports V24 devices such as VDUs.

Since the hardware is available in off-the-shelf form from a number of suppliers, and the entire software package can be transported on a standard floppy disc, it could easily be installed in other laboratories. Full documentation which covers support and operation has been prepared.

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