REAL-TIME MULTIPROCESSING OF SLIT SCAN
CHROMOSOME PROFILES

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Abstract—The multiprocessor NERV and its application to slit scan flow cytometry is described. Up to 320 processors and 640 MBytes of RAM may be used in one VME crate, providing a computing power of \( \approx 1300 \text{ MIPS} \). The multiprocessor is controlled by a host computer that provides a friendly user interface and comfortable program development tools. All hardware and software has been tested on a prototype NERV system with 5 processors. For a real-time classification/detection of normal and aberrant chromosomes, the centromeric index or the number of centromeres are computed or specifically labeled DNA sequences are detected. The program is partitioned into 60 tasks that can be executed concurrently. A total analysis time of \(< 600 \mu \text{s} \) including system overhead will be achieved according to timing measurements which have been done for all individual tasks.

MIMD (multiple instruction stream multiple data stream) Computer architecture Parallel processing NERV Real-time chromosome classification Slit scan flow cytometry Biological dosimetry

INTRODUCTION

A fast classification of normal and aberrant (e.g. dicentric or translocation) chromosomes has become of practical importance in many fields of biology and medicine as for instance in biological dosimetry [1, 2]. For measurements of exposure rates a well established method is to determine the rate of dicentric chromosomes by investigating blood samples microscopically. This may be computationally very demanding especially in the low dose range. To measure, e.g. a radiation exposure of 10 rad with an accuracy of \( \pm 1 \text{ rad} \), up to \( 5 \times 10^6 \) chromosomes have to be classified. To realize this by conventional microscopy would be extremely time consuming so that at the moment only smaller samples (in the order of \( 10^4 \) chromosomes per case [2]) are scored by visual examination. Automation might overcome this disadvantage so that chromosome analysis can be completed within a reasonable time.

Slit scan flow cytometry offers an approach to a fast analysis of normal and aberrant chromosomes [3–6]. Particularly, this technique has been successfully applied to the detection of dicentric chromosomes and the quantification of genetic damage [6–8]. Recently, the detection of translocation chromosomes using two parameter slit scan flow cytometry has become possible [9, 10] by means of fluorescent labeling of specific DNA sequences of isolated chromosomes by \textit{in situ} hybridization in suspension [11].

In a slit scan flow cytometer, isolated metaphase chromosomes stained by fluorescence hybridization and/or a DNA specific fluorochrome (fluorescence intensity proportional to DNA content or DNA base pairs) are aligned in a flow cell by hydrodynamic focusing and pass one at a time through one or two strongly focused laser beams. For each chromosome the fluorescence emission of the fluorochromes is detected separately by photomultipliers during the few microseconds a particle takes to traverse the laser focus.
volume. Each signal is sampled and digitized at 256 instants. This results in time resolved profiles (in our case with a resolution of 100 ns/instant) of the distribution of the fluorescence along the chromosome axis [5, 9, 10, 12].

These chromosome profiles allow a classification according to centromeric index (DNA content of the long chromosome arm divided by total DNA content), number of centromeres (e.g. dicentrics), or specific DNA sequences (e.g. in the case of translocations). For the automatic determination of the centromeric index, different algorithms have been developed [4, 13–15]. To measure, e.g. radiation induced aberrations in the low dose range or to sort chromosomes according to their slit scan data, it is desired to increase the analysis speed of one and two parameter slit scan profiles to about 1000 chromosomes/s. In principle, there are several factors that limit the analysis rate in slit scan flow cytometry: the data acquisition rate allowed by the mechanical features of the apparatus, the morphological stability of the biological material, and the data analysis rate allowed by the on-line computer.

The latter limitation may be overcome by implementing the analysis algorithm on a multiprocessor system assembled of 60 high-end microprocessors as shown below.

In the following, a type of computation is outlined that has to be performed for a fast analysis of chromosomes. This is succeeded by a description of the NERV architecture. In the last section, the mapping of the problem onto the NERV architecture is described, i.e. the decomposition of the chromosome analysis program into a high number of independent tasks and the implementation on a 60 processor NERV system. It is shown that the real-time requirements of 1 ms analysis time can be met, so that on-line slit scan analysis and slit scan sorting might become feasible.

CHROMOSOME CLASSIFICATION ALGORITHMS

Classification of normal chromosomes

The fluorescence profile of a chromosome stained with a DNA specific dye shows a typical dip in the centromeric region. For the evaluation of the centromeric index or the classification of dicentric chromosomes, minima and maxima of the profile have to be determined. By means of several profile characteristics, minima depending on instrumental noise or inhomogeneous staining can be discriminated from “real” centromeres. Figure 1, for example, shows the centromere finding procedure for a dicentric chromosome. From the original slit scan data $P(N)$ of the multichannel analyser, the maximum ($A_{MAX}$) and the channel of $A_{MAX}$ are determined. Since the first 24 channels represent background only, each third one of them is used to calculate a threshold ($THR$) for a background subtraction. The beginning $B$ of the chromosome profile is defined as the maximum channel number with $P(N) \leq THR$ below the position of $A_{MAX}$, while the end $E$ is defined as the minimum channel number with $P(N) \leq THR$ above the position of $A_{MAX}$. From the remaining data between $B$ and $E$, further profiles $DPA(N), P4(N), and D2P(N)$ corresponding to the first and second derivative are calculated for each second value:

$$DPA(N) = |P(N) - P(N + 1)|$$

$$P4(N) = \sum_{i=1}^{4} DPA(N - 2 + i)$$

$$D2P(N) = 16 \cdot P(N) - \sum_{i=1}^{8} P(N + 3 + 2i) - \sum_{i=1}^{8} P(N - 3 - 2i).$$
Slit scan chromosome profiles

$P(N) = \text{ORIGINAL PROFILE}$

$P_4(N) := \sum_{i=1}^{I-1} DPA(N-2+i)$

$DPA(N) = |P(N) - P(N+1)|$

$P_4_{\text{THR}} := 2 \cdot 4 \cdot (E \cdot B + I) \sum_{i=1}^{B} DPA(i)$

$DZP(N) := 16 \cdot P(N) - \sum_{i=1}^{B} P(N+3+2 \cdot I) - \sum_{i=1}^{I} P(N-3-2 \cdot I)$

If $P_4(N) > P_4_{\text{THR}}$:

$E(N) := 0$

Else:

If $DZP(N) > 0$:

$E(N) := 1$

If $DZP(N) = 0$:

$E(N) := 0$

If $D2P(N) < 0$:

$B(N) := -1$

P(N) - THRESHOLD

*: CENTROMERE

O: MAXIMUM

Fig. 1. Automatic classification of centromeres showed for the case of a dicentric chromosome. The first profile (fluorescence intensity vs time of flight in units of 100 ns) shows the original slit scan data from which two derivative profiles are calculated. The last profile shows the computed data after background subtraction and centromere finding procedure. The centromere positions are automatically marked by an asterisk (for details see text).

By means of an additional threshold $P_4 - \text{THR}$ (see Fig. 1) the extrema regions of the profile are determined analogous to a mathematical function. Therefore $EXT(N)$ is defined as follows:

$EXT(N) = 1$ if $D2P(N) > 0$

$EXT(N) = 0$ if $D2P(N) = 0$ or $P_4(N) > P_4 - \text{THR}$.

$EXT(N) = -1$ if $D2P(N) < 0$. 
Beginning ($EB$) and end ($EE$) of an extrema region is fixed to the channel where $\text{EXT}(N)$ changes from $-1$ to $1$ or vice versa. Within these extrema regions the position of a maximum or minimum is computed by

$$\frac{1}{4}(EB + EE + ML + MR + 2).$$

$ML$ (resp. $MR$) is the position of the extremum of $P(N)$ with odd (resp. even) channel numbers.

From the extrema all minima were excluded that do not fulfill the following criteria:

- There have to be directly neighboring maxima on both sides.
- The maxima on both sides must have a minimal distance to the minimum. In this case the distance was determined to more than 700 ns.

From these remaining minima the "real" centromeres are classified by calculating additional characteristics called $\text{TIEFE}$, $D3P$, and $\text{SYM}$. $\text{TIEFE}$ describes the depth of a minimum compared to the lower neighboring maximum while $D3P$ is an analogue to the third derivative of a mathematical function. $\text{SYM}$ participates from the calculation of $D3P$ and shows the degree of the symmetry around the minimum. For small values of $\text{SYM}$ corresponding to a big asymmetry, non-centromeres are overrepresented among the minima.

In a minimum histogram $\text{TIEFE}$ vs $D3P$, the classification value $\text{VAL}$ is determined.

$$\text{VAL} = \text{TIEFE} + D3P - X,$$

where $X$ depends on the value $\text{SYM}$. $\text{VAL}$ mathematically describes the projection of the histogram value of a minimum to an axis orthogonal to an experimentally determinable threshold $K$. This depends on the slit scan data used and on the rate of misclassifications being tolerated. If $\text{VAL}$ is greater than $K$ and lower than a fixed upper value, the minimum is classified as a "real" centromere.

At the end of this centromere finding procedure, non-chromosomes, normal, and dicentric chromosomes are classified according to their number of centromeres, and the positions of these centromeres are marked (Fig. 1).

For the evaluation of the centromeric index the background is subtracted and the content of the channels of the long ($a_l$) and the short ($a_s$) chromosome arm is summed up. The centromeric index is defined as

$$\text{CI} = \frac{\text{sum of content of the long chromosome arm}}{\text{sum of content of the entire chromosome}} = \frac{a_l}{a_l + a_s}.$$

Classification of translocation chromosomes

In the case of chromosomes labeled by fluorescence hybridization of specific DNA sequences, e.g. translocated sequences, and counterstaining with a normal DNA specific dye, two slit scan profiles can be analysed that are derived from the same object (Figs 2a and 2b). The first profile (fluorescence response of the DNA specific dye) discriminates non-chromosomes from chromosomes as described above.

For the evaluation of the second chromosome profile (fluorescence response of the hybridized chromosome region), the background is subtracted using a slightly modified procedure. The remaining fluorescence intensity and the maximum are determined. If these values are below certain limits or if the maximum of the second profile is not within the beginning and the end of the first profile, the value zero is assigned to the second profile. If not, the two profiles are normalized and smoothed. Then the difference of these two resulting profiles is calculated for each fourth channel and compared to an
Slit scan chromosome profiles

Fig. 2. Detection of a translocation chromosome by two parameter slit scan flow cytometry after fluorescence hybridization and counterstaining with a normal DNA specific fluorochrome (fluorescence intensity vs time of flight in units of 100 ns). (a) Fluorescence profile of the total DNA of the chromosome as used for the calculation of the centromeric index. (b) Fluorescence distribution of the hybridized DNA sequences (translocated chromosome part). (c) Difference of normalized profiles deriving from (a) and (b). If this profile fulfills several threshold conditions, the chromosome may be classified as a translocation (for details see text).

experimentally determined threshold (Fig. 2c). If more than two differences are above this threshold the chromosome may be classified as a translocation chromosome. Additionally, the corresponding values in the second profile have to be smaller than 50% of the maximum.

THE MULTIPROCESSOR SYSTEM

The system architecture

The NERV system is a parallel processing system that may consist of a high number (≤320) of 32 bit microprocessors with up to 640 MBytes of static memory in total. Logically, it is structured into a multiprocessor and a host computer. The multiprocessor has a master–slave structure, i.e. there is a single master processor that controls a high number of slave processors. All processors in the NERV system, i.e. in the host computer, the master processor, and the slave processors use the 32 bit microprocessor 68020. Figure 3 shows a block diagram of the NERV system.

The host computer is a Macintosh II which offers a friendly graphical user interface and comfortable program development tools. Among them are the Hypercard shell [16] that provides an extremely simple graphical user interface and the Macintosh Programmer's Workshop [17], an integrated system to edit, compile, and debug programs.

The multiprocessor is based on the VME bus standard. The master processor is a double-height PC-board (160×220 mm²) that occupies one slot of a standard VME crate. The other slots are filled with PC-boards carrying multiple slave processors. A
single VME crate may contain up to 20 multiprocessor boards and a single master processor. All communication and synchronization between master and slave processors, as well as between slave processors takes place on the VME crate backplane using the standard VME bus address, data, and control lines. However, a few additional bus lines have been defined and are used for hardware support of time critical operations as described below. The master processor is a commercial VME board [18] that is responsible for the communication between the host computer and the slave processors and for synchronizing them. Each multiprocessor board will contain up to 16 slave processors. For the running prototype system, it was not necessary to use a high density layout of the PC-board so that only two processors are used per VME board. The features of a slave processor are discussed below in detail. A single slave processor executes a task that is assigned to it by the master processor. When possible, as in the case of the analysis of chromosomes, a static assignment is used to keep the system overhead low. Else, a dynamic assignment of tasks to slave processors can be used.

The NERV system was originally designed to support the simulation of large neural networks [19, 20]. As with many other applications, such a simulation requires a very high computing power (in the order of 1000 MIPS) but only relatively simple operations [21]. Floating point computations, e.g. are not necessary. In order to get a maximum computing power per volume, the slave processors are equipped only with the absolute minimum of hardware. One consequence of this design principle is a special kind of communication and synchronization structure that is based on broadcast transfers via a bus system and a global compare logic [22] only. It turned out, however, that the NERV architecture is also well suited to support more general applications as long as only loose coupling is required, as shown below.

All software, i.e. the operating system and the individual application software is usually written in Modula2 [23]. Only time-critical tasks are written in assembler as for instance the algorithms for chromosome classification that have been discussed above. By using native or cross development systems, the same programs can be run on the host for debugging purposes, or on the multiprocessor for high speed execution. Loading of programs into the parallel processor, their execution, and the readout and presentation of results is usually done via a Hypercard graphical user surface.
The slave processors

A multiprocessor board of the NERV system consists of a VME motherboard with the bus interface logic. In addition, the motherboard carries subboards with autonomous slave processors. As mentioned above, they have been designed to provide only the absolute minimum of functions in order to get a high package density. With a high density layout and surface mounted device technology, 16 slave processors fit onto a single motherboard in two layers of eight slave processors each (Fig. 4). Each one consists of a 68020 CPU operating at 25 MHz, 2 MBytes of no-wait-static RAM, and interface and control logic.

Each slave processor stores its program in its local memory, as well as all data required. The standard VME bus protocols have been extended to support broadcast transfers. Here, a write transfer into a certain part of the address space causes a simultaneous write operation to all local memories (Fig. 5). Here, the data transfer acknowledge signal of the VME bus cannot be used to signal a successfully terminated broadcast transfer, because the transfer has to be extended until all slave processors have acknowledged. This requires a logical AND of the individual acknowledge signals. For that purpose, a free bus line on the P2 connector was used as a broadcast acknowledge signal. It is an open collector line, whose HIGH level signals a successfully terminated broadcast write transfer. An extended version of this protocol is currently under consideration as a standard for the VME bus [24]. The typical broadcast time is about 1 μs. The slave processors use only broadcast transfers to communicate with each other and with the master processor.

Many applications require that all slave processors are synchronized during program execution and that the master processor is notified of that. For this, another free open collector line on the VME bus is used. This line can be set by each slave processor via a register. On the VME bus, this line becomes HIGH only after all slave processors had set their register to 1. In this case an interrupt is generated on the master processor. It can then do the required action, e.g. starting the next computation step or reading out results. The usual VME bus interrupt cannot be used for this purpose, because it does not allow the required synchronization of all slave processors.

An additional feature of the NERV system is a global compare logic that was implemented on the VME bus. Its operation is similar to the priority arbitration logic of the Futurebus system [25] or the OR-network of the Connection Machine [26]. Basically,
A binary coded value is asserted onto a set of open collector bus lines. Because all slave processors do so in parallel, the global OR of all values is built on the bus lines. A combinatorial logic on each slave processor compares this global value to the local value. This is done bit sequentially, starting with the most significant bit. If a difference is found, the slave processor does not have the highest priority and will negate its value. With unique values, this procedure ensures that all slave processors but one disconnect from the comparison bus. The remaining one is selected. In the NERV system, we use four lines for the comparison bus. A 4 bit value can be globally compared within ≈1 µs, but this operation can be cascaded.

The features of the NERV system are shown in Table 1.

**PARALLEL TASKS**

The chromosome analysis software as described above has been decomposed into 60 individual tasks. To achieve the goal of a real-time classification time of 1 ms, and to use the multiprocessor hardware most efficiently, these tasks have been programmed in assembler. It should be noted that the type of microprocessor used (68020) is particularly well suited for the analysis program. One example is the extensive usage of bit fields that is supported by machine instructions and allows a highly efficient code.

Figure 6 shows which tasks can be executed concurrently at which time by which processor. In this diagram, the x-axis represents a processor number and the y-axis the

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elapsed time. Each task is represented by a white box. Areas of the diagram that are not covered by boxes belong to time intervals where the corresponding processors are not running. Reasons for that might be communication and synchronization overhead or precedence constraints. In two cases, the diagram shows stair-like structures (the \textit{MIN-MAX} and \textit{CLASS} tasks). This is caused by the sequential operation of the master processor. In the first case, the master reads results from one task \textit{PROF-CR} and transmits new arguments to one template of the task \textit{MIN-MAX}. This is done sequentially until all results of the tasks \textit{PROF-CR} are read and all tasks \textit{MIN-MAX} are started. At this time, the first task \textit{MIN-MAX} is ready and the master can immediately evaluate its results. This interleaved operation reduces the communication overhead.

The vertical box size, i.e. the execution time of the corresponding routine, follows from measured values obtained by running the task on a slave processor which has been operated with a 12 MHz clock. For that, the profile shown in Fig. 1 has been used, e.g. for analysis. If executed sequentially, the whole analysis takes 4.6 ms. As can be seen from Fig. 6, a parallel analysis on a 49 processor system (including the master processor) requires about 400 \mu s without the profile read-in time of 250 \mu s. Of course, the analysis time depends on the actual profile. The worst case analysis time can, however, be estimated from the known possible variations of the profiles and from the structure of the analysis routines. In our case, the worst-case time amounts to 600 \mu s. Compared to the algorithm for the analysis of the first profile, which was decomposed as displayed in Fig. 6 and gives a rather complicated dependency graph, the parallelization of the algorithm for the analysis of the second profile is rather simple. A parallel execution is possible on 11 additional processors. Thus, the total analysis time is not increased.

It should be noted that the actual NERV system is operated with a clock frequency of 25 MHz, so that these times will be reduced roughly by a factor of two. This would allow a real-time chromosome analysis at a rate of 1800 chromosomes/s.

Since the multiprocessor system is not yet available with 60 slave processors, the parallel software has been developed on a smaller system. The execution of the parallel tasks has been simulated by a main program that calls the tasks of the slave processors as subroutines.

![Fig. 6. Parallelization of the chromosome analysis algorithm. For each task the number of the employed processor is shown vs the processing time in \mu s (measured with a system with a 12 MHz clock—the actual clock rate will be 25 MHz).](image)
CURRENT STATUS AND OUTLOOK

The NERV system was developed as a prototype with a small number (five) of slave processors. Its hardware has been tested completely. The basic operating software and the parallel analysis program are also tested. Currently, a compressed layout of the printed circuit board of the slave processor is in hand. We expect to have a prototype VME board with 16 slave processors at the end of 1990. To provide a certain degree of compatibility with commercial computer systems, the NERV system is currently adapted to host computers that run under UNIX and a X-Window graphical user interface [27].

The application of the NERV system to the real-time classification of chromosomes as described above will be tested as soon as a system with $\geq 59$ slave processors is available. This would require only four multiprocessor boards and should be possible in the near future. Since the execution time of all time critical routines has been measured, we expect that the estimated performance will be achieved without major problems. However, for a routine application there are still a number of technical problems that have to be solved.

If required, the system performance could be increased by another factor of 10 beyond the values given above. This could be done by interconnecting multiple VME crates via bus repeaters. The Heidelberg Polyp multiprocessor [28, 29] demonstrates that a system of this size is feasible. Using a comparable setup, the NERV system might use up to 3360 slave processors. The NERV architecture, therefore, is capable to be extended to provide the extremely high computing power of over 13,000 MIPS.

Whereas this is important for other applications, the real-time chromosome analysis cannot exploit these possibilities since the algorithm is already decomposed into parallel tasks nearly as far as possible. Since the computational speed of the NERV system is determined by the slave processors (Fig. 6), only an increase in the processing speed of the slave processors would allow a higher analysis rate. Today, the data taking speed of a commercial flow cytometer can usually be increased up to 4000 particles/s. The processing speed of a slave processor can probably be increased by the same factor of $\approx 2.2$ by using software compatible successors of the microprocessor 68020, e.g. 68030 or 68040. Besides architectural enhancements like larger cache memories, faster memory access, and optimized instructions, these processors can be operated at 33 MHz or even higher clock rates. If, however, this speed increase cannot be attained, it would be possible to use instead new RISC processors that are already available with speeds of up to 100 MIPS.

SUMMARY

The architecture of the multiprocessor system NERV and its application to slit scan flow cytometry is described. Up to 320 32 bit processors 68020 (25 MHz), each one equipped with up to 2 MBytes no-wait-state static RAM, may be used in a single VME crate. They are controlled by a master CPU that assigns tasks to processors, provides input data, and collects results. Whereas the master has full read/write access to all local memories, the slave processors can only execute broadcast writes to all other processors including the master. The master processor is connected to a Macintosh II host computer. This set-up provides a computing power of 1300 MIPS as well as a friendly user interface and comfortable program development tools. As an application example, the real-time classification of normal and the detection of aberrant chromosomes in slit scan flow cytometry is described. This is done by computing the centromeric index or the number of centromeres, or by detection of specifically labeled DNA sequences. This program is parallelized into independent tasks that can be executed on a 60 processor system. Taking into account the time needed to distribute data and to assemble all results, and all synchronization delays, an analysis time of $< 600 \mu s$ can be achieved with a processor clock of 25 MHz.

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REFERENCES


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