United States Patent [19]

Peterson et al.

[11] **Patent Number: 5,964,860**

[45] **Date of Patent: Oct. 12, 1999**

[54] **SEQUENCE INFORMATION SIGNAL PROCESSOR**

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[73] Assignee: **California Institute of Technology**, Pasadena, Calif.

[21] Appl. No.: **08/831,798**

[22] Filed: **Apr. 8, 1997**

Related U.S. Application Data

[63] Continuation of application No. 08/154,633, Nov. 18, 1993, Pat. No. 5,632,041, which is a continuation of application No. 07/518,562, May 2, 1990.

[51] **Int. Cl.**^{6} **G06F 19/00**

[52] **U.S. Cl.** **712/19**; 712/898; 702/20

[58] **Field of Search** 702/20; 435/6, 435/132.1; 364/495, 496; 395/800.19, 898

[56] **References Cited**

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"Bio Scan: A VLSI–Based System for Bio Sequence Analysis", White et al. 1991.

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"Why Systolic Architecture" Kung 1982.

"The BioScan Project: An Interdisiplinary Approach to Biosequence Analysis" White et al, Oct. 1989.

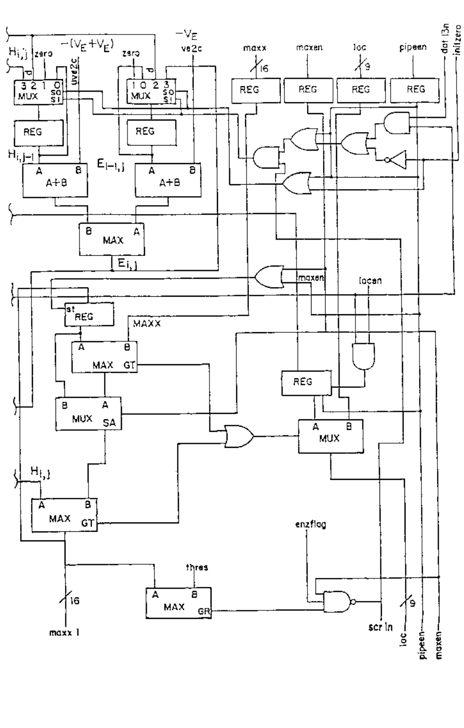
"A New Algorithm for Best Subsequence Alignment with Application to tRNA–rRNA Comparisons" Waterman et al. 1987.

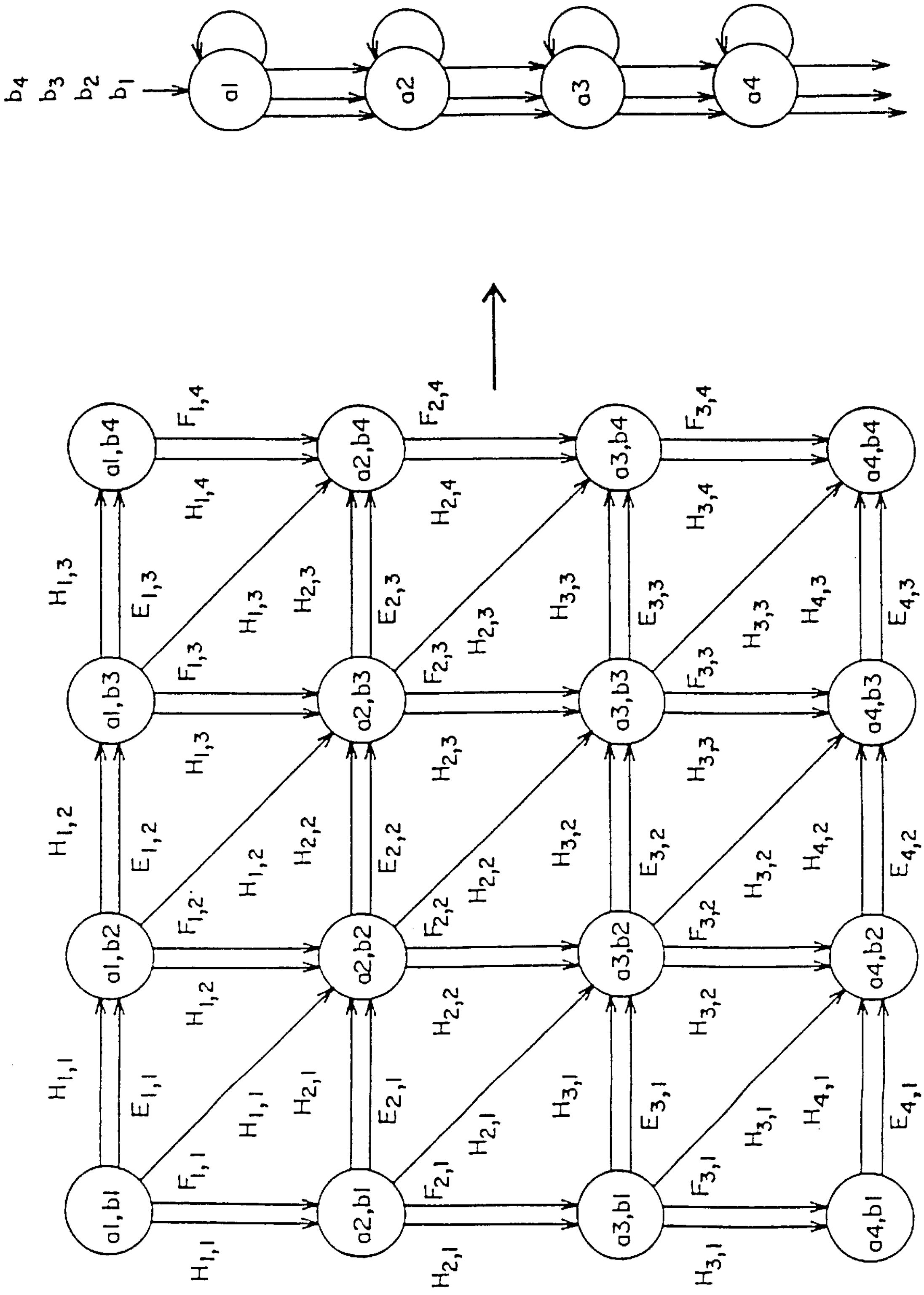
Primary Examiner—Larry D. Donaghue
Attorney, Agent, or Firm—Fish & Richardson P.C.

[57] **ABSTRACT**

An electronic circuit is used to compare two sequences, such as genetic sequences, to determine which alignment of the sequences produces the greatest similarity. The circuit includes a linear array of series-connected processors, each of which stores a single element from one of the sequences and compares that element with each successive element in the other sequence. For each comparison, the processor generates a scoring parameter that indicates which segment ending at those two elements produces the greatest degree of similarity between the sequences. The processor uses the scoring parameter to generate a similar scoring parameter for a comparison between the stored element and the next successive element from the other sequence. The processor also delivers the scoring parameter to the next processor in the array for use in generating a similar scoring parameter for another pair of elements. The electronic circuit determines which processor and alignment of the sequences produce the scoring parameter with the highest value.

14 Claims, 18 Drawing Sheets

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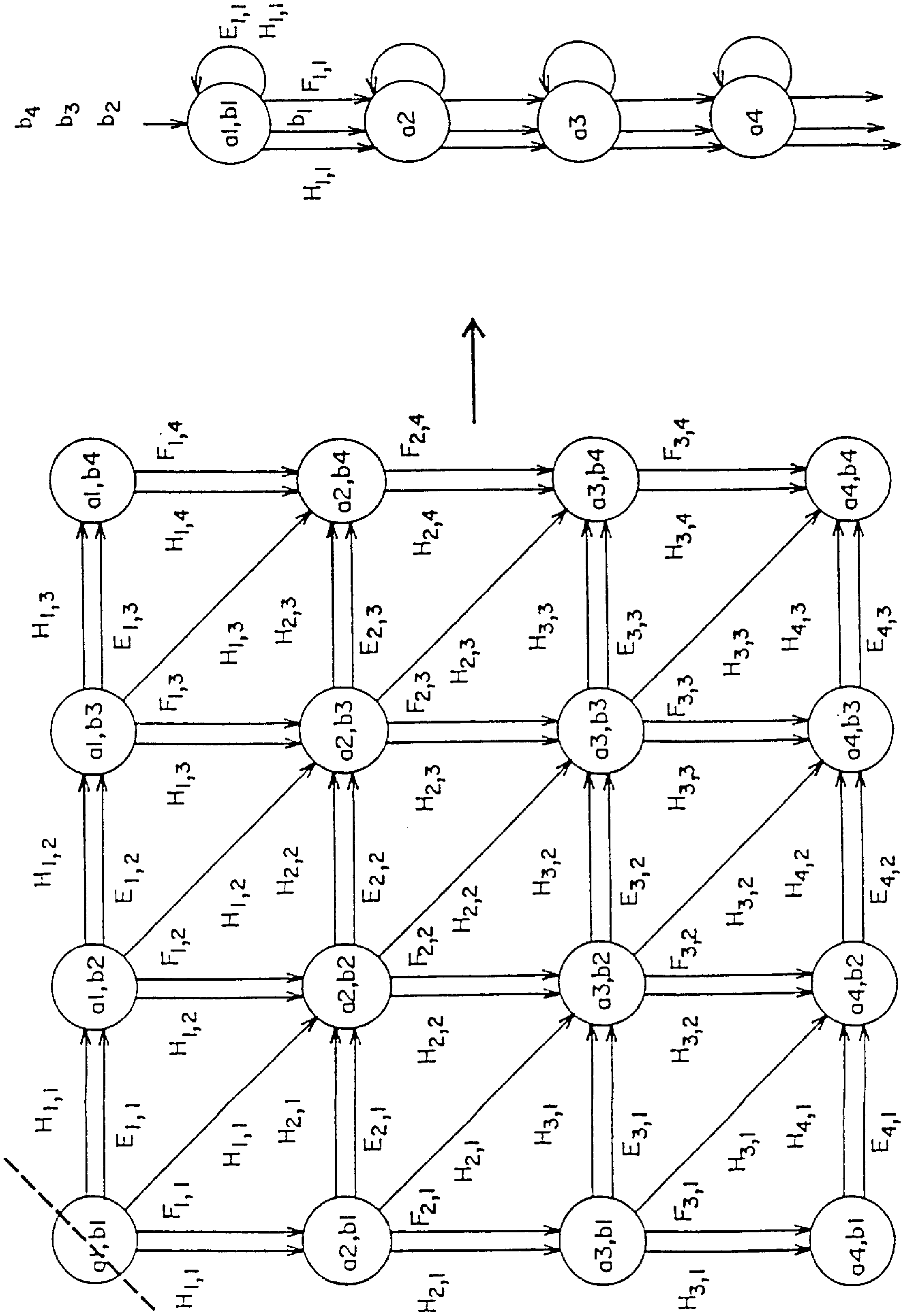
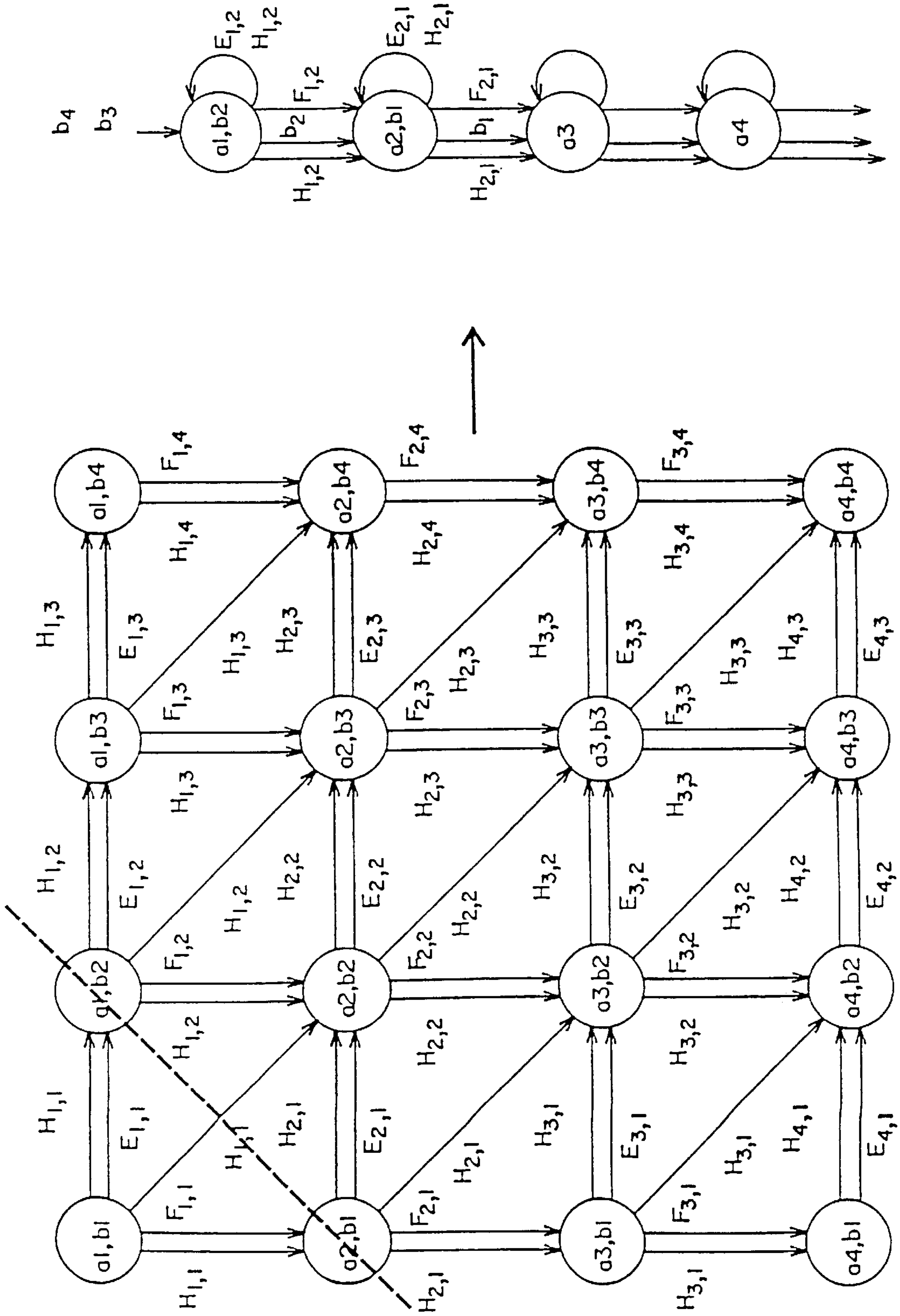
b3
b2
b1
a1
a2
a3
a4
a1,b1
a2,b1
a3,b1
a4,b1
a1,b2
a2,b2
a3,b2
a4,b2
a1,b3
a2,b3
a3,b3
a4,b3
a1,b4
a2,b4
a3,b4
a4,b4
H1,1
E1,1
F1,1
H1,1
H1,1
H2,1
E2,1
F2,1
H2,1
H2,1
H3,1
E3,1
F3,1
H3,1
H3,1
H4,1
E4,1
H1,2
E1,2
F1,2
H1,2
H1,2
H2,2
E2,2
F2,2
H2,2
H2,2
H3,2
E3,2
F3,2
H3,2
H3,2
H4,2
E4,2
H1,3
E1,3
F1,3
H1,3
H1,3
H2,3
E2,3
F2,3
H2,3
H2,3
H3,3
E3,3
F3,3
H3,3
H3,3
H4,3
E4,3
F1,4
H1,4
F2,4
H2,4
F3,4
H3,4

FIG. 1



b4
b3
b2
b1
a1,b1
a2
a3
a4
E1,1
H1,1
F1,1
H1,1
a1,b1
a2,b1
a3,b1
a4,b1
a1,b2
a2,b2
a3,b2
a4,b2
a1,b3
a2,b3
a3,b3
a4,b3
a1,b4
a2,b4
a3,b4
a4,b4
F1,1
H1,1
F2,1
H2,1
F3,1
H3,1
F1,2
H1,2
F2,2
H2,2
F3,2
H3,2
F1,3
H1,3
F2,3
H2,3
F3,3
H3,3
F1,4
H1,4
F2,4
H2,4
F3,4
H3,4
H1,1
E1,1
H1,2
E1,2
H1,3
E1,3
H2,1
E2,1
H2,2
E2,2
H2,3
E2,3
H3,1
E3,1
H3,2
E3,2
H3,3
E3,3
H4,1
E4,1
H4,2
E4,2
H4,3
E4,3
H1,1
H1,2
H1,3
H2,1
H2,2
H2,3
H3,1
H3,2
H3,3

FIG. 2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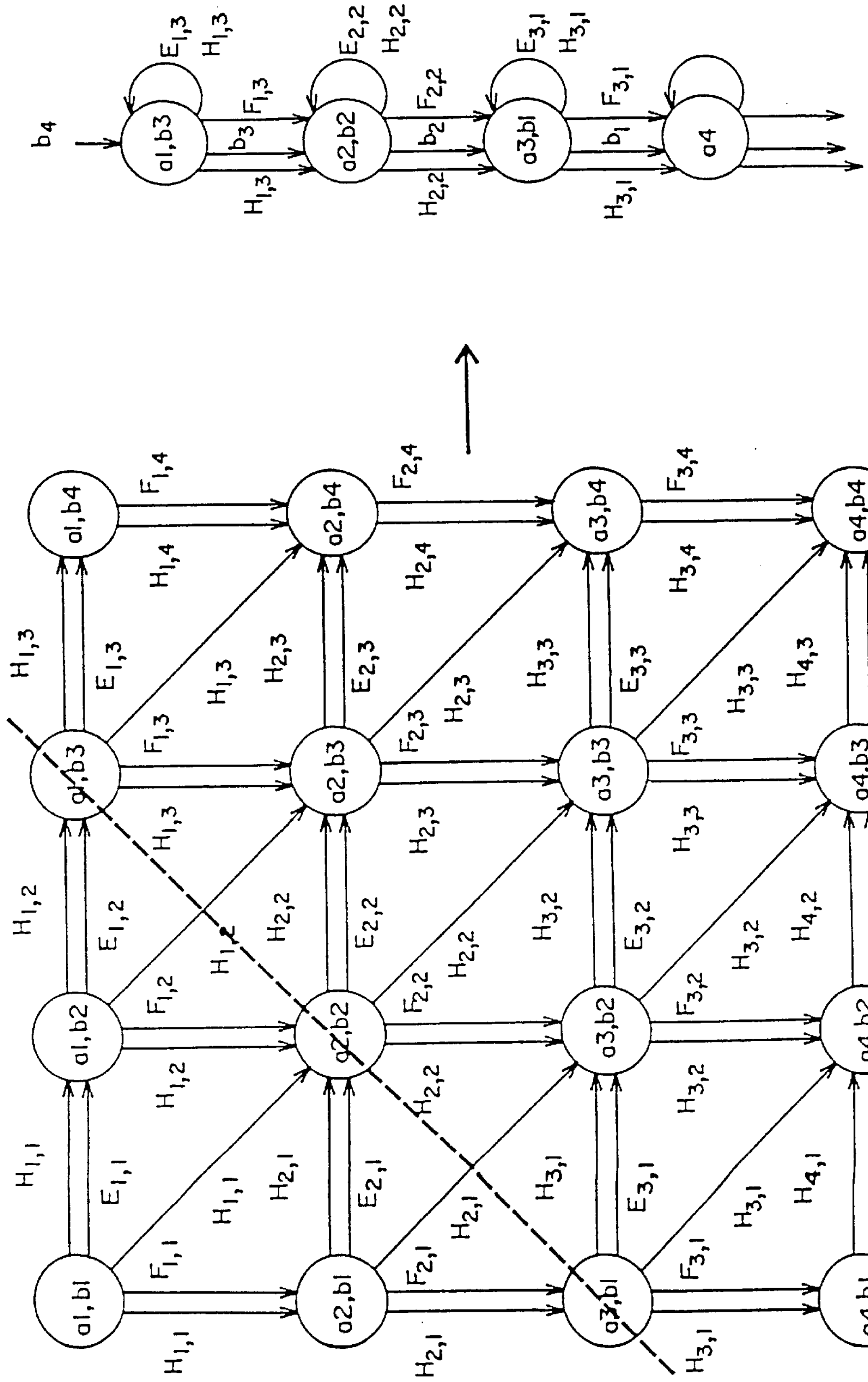
b3
a1,b2
a2,b1
a3
a4
E1,2
H1,2
F1,2
b2
H1,2
E2,1
H2,1
F2,1
b1
H2,1
a1,b1
a2,b1
a3,b1
a4,b1
a1,b2
a2,b2
a3,b2
a4,b2
a1,b3
a2,b3
a3,b3
a4,b3
a1,b4
a2,b4
a3,b4
a4,b4
F1,1
H1,1
F2,1
H2,1
F3,1
H3,1
H1,1
E1,1
H1,1
H2,1
E2,1
H2,1
H3,1
E3,1
H3,1
H4,1
E4,1
F1,2
H1,2
F2,2
H2,2
F3,2
H3,2
H1,2
E1,2
H1,2
H2,2
E2,2
H2,2
H3,2
E3,2
H3,2
H4,2
E4,2
F1,3
H1,3
F2,3
H2,3
F3,3
H3,3
H1,3
E1,3
H1,3
H2,3
E2,3
H2,3
H3,3
E3,3
H3,3
H4,3
E4,3
F1,4
H1,4
F2,4
H2,4
F3,4
H3,4

FIG. 3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a1,b3
a2,b2
a3,b1
a4
$E_{1,3}$
$H_{1,3}$
$E_{2,2}$
$H_{2,2}$
$E_{3,1}$
$H_{3,1}$
$F_{1,3}$
b_3
$H_{1,3}$
$F_{2,2}$
b_2
$H_{2,2}$
$F_{3,1}$
b_1
$H_{3,1}$
a1,b1
a2,b1
a3,b1
a4,b1
a1,b2
a2,b2
a3,b2
a4,b2
a1,b3
a2,b3
a3,b3
a4,b3
a1,b4
a2,b4
a3,b4
a4,b4
$F_{1,1}$
$H_{1,1}$
$F_{2,1}$
$H_{2,1}$
$F_{3,1}$
$H_{3,1}$
$H_{1,1}$
$E_{1,1}$
$H_{1,1}$
$H_{2,1}$
$E_{2,1}$
$H_{2,1}$
$H_{3,1}$
$E_{3,1}$
$H_{3,1}$
$H_{4,1}$
$E_{4,1}$
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$H_{1,2}$
$F_{2,2}$
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$F_{3,2}$
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$E_{1,2}$
$H_{1,2}$
$H_{2,2}$
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$H_{2,2}$
$H_{3,2}$
$E_{3,2}$
$H_{3,2}$
$H_{4,2}$
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$E_{2,3}$
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$E_{3,3}$
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$E_{4,3}$
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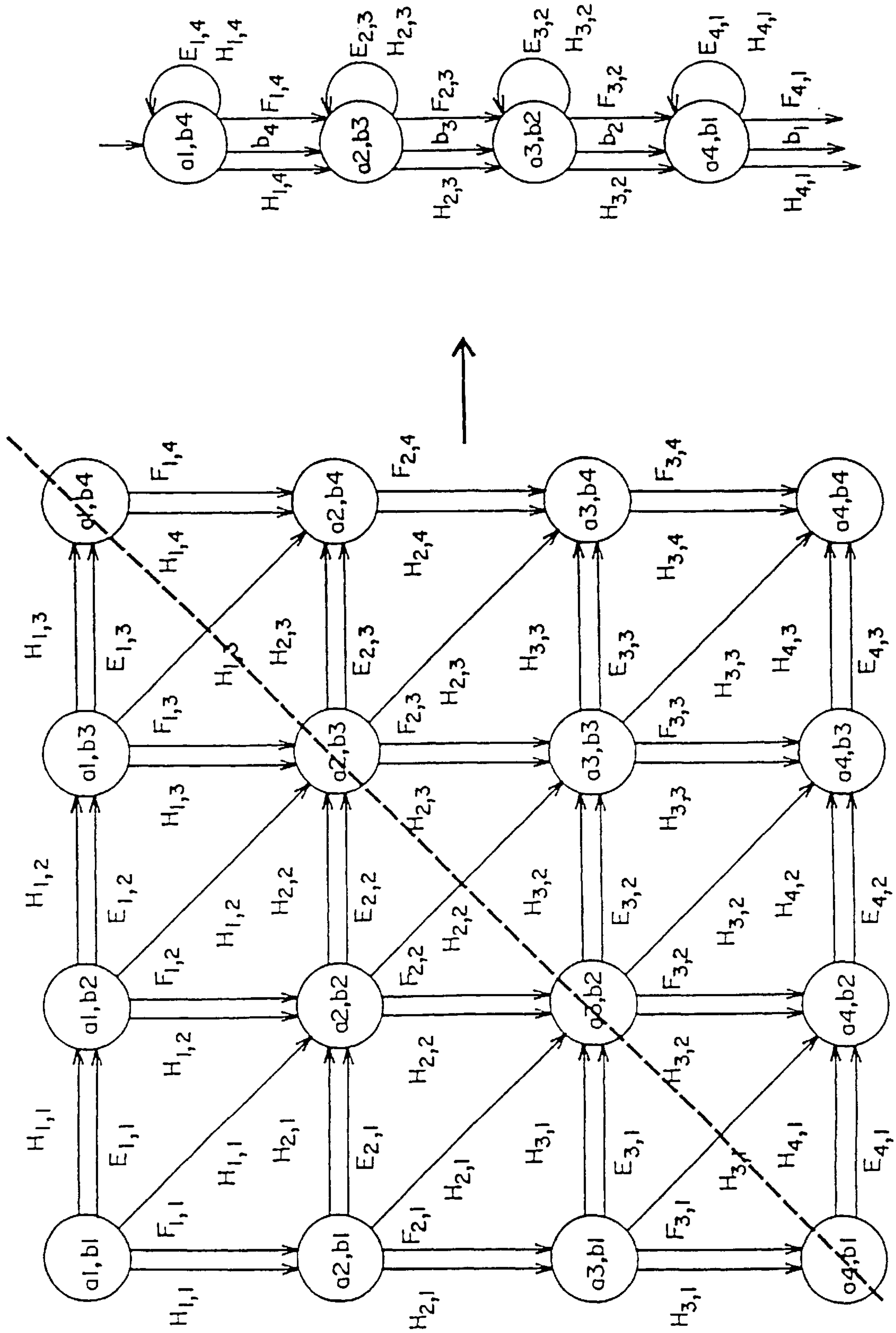
$F_{3,4}$
$H_{3,4}$

FIG. 4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a2,b3
a3,b2
a4,b1
$E_{1,4}$ $H_{1,4}$
$F_{1,4}$
b_4
$H_{1,4}$
$E_{2,3}$ $H_{2,3}$
$F_{2,3}$
b_3
$H_{2,3}$
$E_{3,2}$ $H_{3,2}$
$F_{3,2}$
b_2
$H_{3,2}$
$E_{4,1}$ $H_{4,1}$
$F_{4,1}$
b_1
$H_{4,1}$
a1,b1
a1,b2
a1,b3
a1,b4
a2,b1
a2,b2
a2,b3
a2,b4
a3,b1
a3,b2
a3,b3
a3,b4
a4,b1
a4,b2
a4,b3
a4,b4
$H_{1,1}$
$E_{1,1}$
$H_{1,2}$
$E_{1,2}$
$H_{1,3}$
$E_{1,3}$
$F_{1,1}$
$H_{1,1}$
$H_{1,1}$
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$F_{1,3}$
$H_{1,3}$
$H_{1,3}$
$F_{1,4}$
$H_{1,4}$
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$E_{2,2}$
$H_{2,3}$
$E_{2,3}$
$F_{2,1}$
$H_{2,1}$
$H_{2,1}$
$F_{2,2}$
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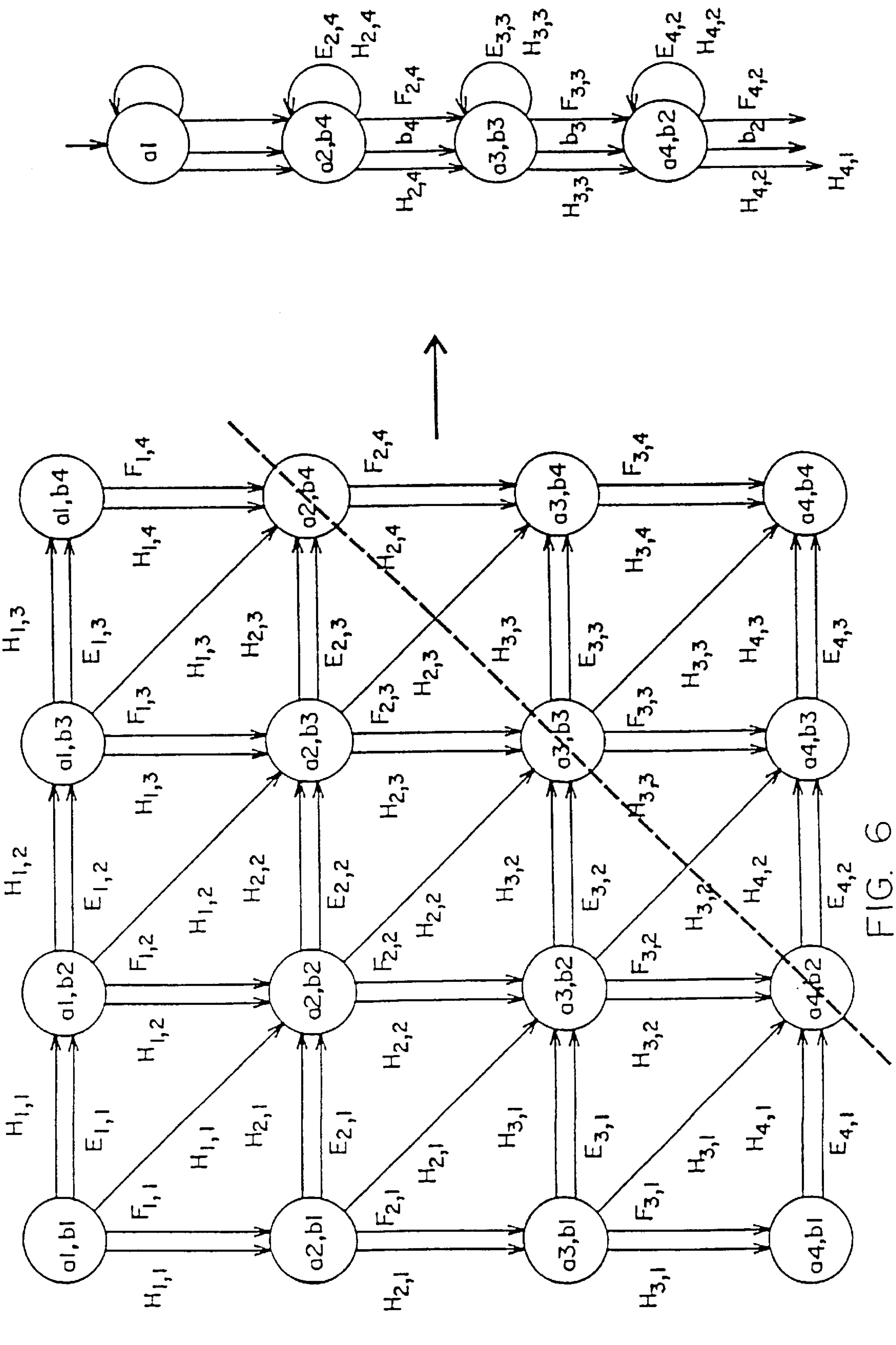
$H_{3,4}$
$H_{4,1}$
$E_{4,1}$
$H_{4,2}$
$E_{4,2}$
$H_{4,3}$
$E_{4,3}$

FIG. 5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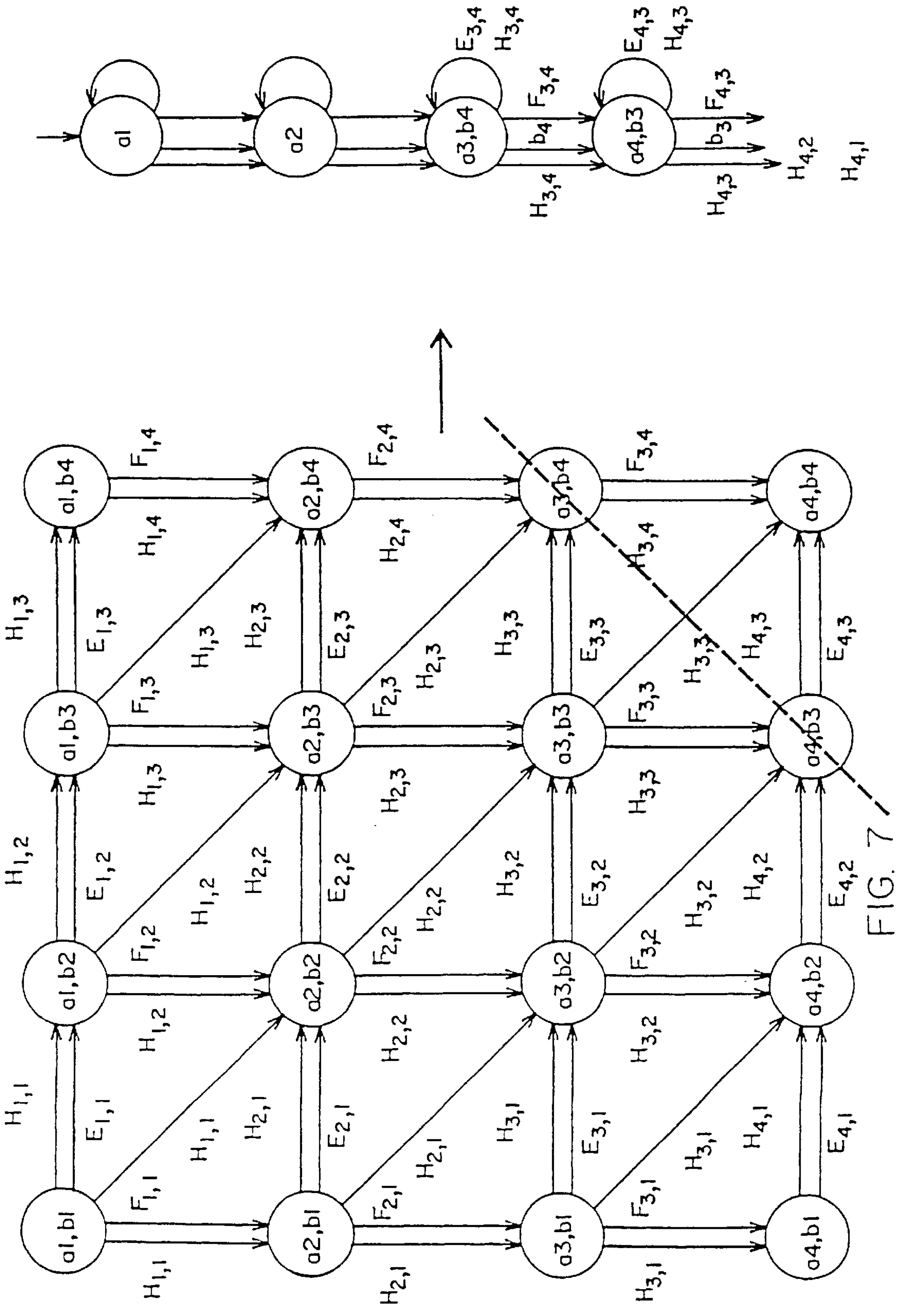
a2,b4
a3,b3
a4,b2
E2,4
H2,4
E3,3
H3,3
E4,2
H4,2
F2,4
b4
H2,4
F3,3
b3
H3,3
F4,2
b2
H4,2
H4,1
a1,b1
a1,b2
a1,b3
a1,b4
a2,b1
a2,b2
a2,b3
a2,b4
a3,b1
a3,b2
a3,b3
a3,b4
a4,b1
a4,b2
a4,b3
a4,b4
H1,1
E1,1
F1,1
H1,1
H1,2
E1,2
F1,2
H1,2
H1,3
E1,3
F1,3
H1,3
F1,4
H1,4
H2,1
E2,1
F2,1
H2,1
H2,2
E2,2
F2,2
H2,2
H2,3
E2,3
F2,3
H2,3
F2,4
H2,4
H3,1
E3,1
F3,1
H3,1
H3,2
E3,2
F3,2
H3,2
H3,3
E3,3
F3,3
H3,3
F3,4
H3,4
H4,1
E4,1
H4,2
E4,2
H4,3
E4,3

FIG. 6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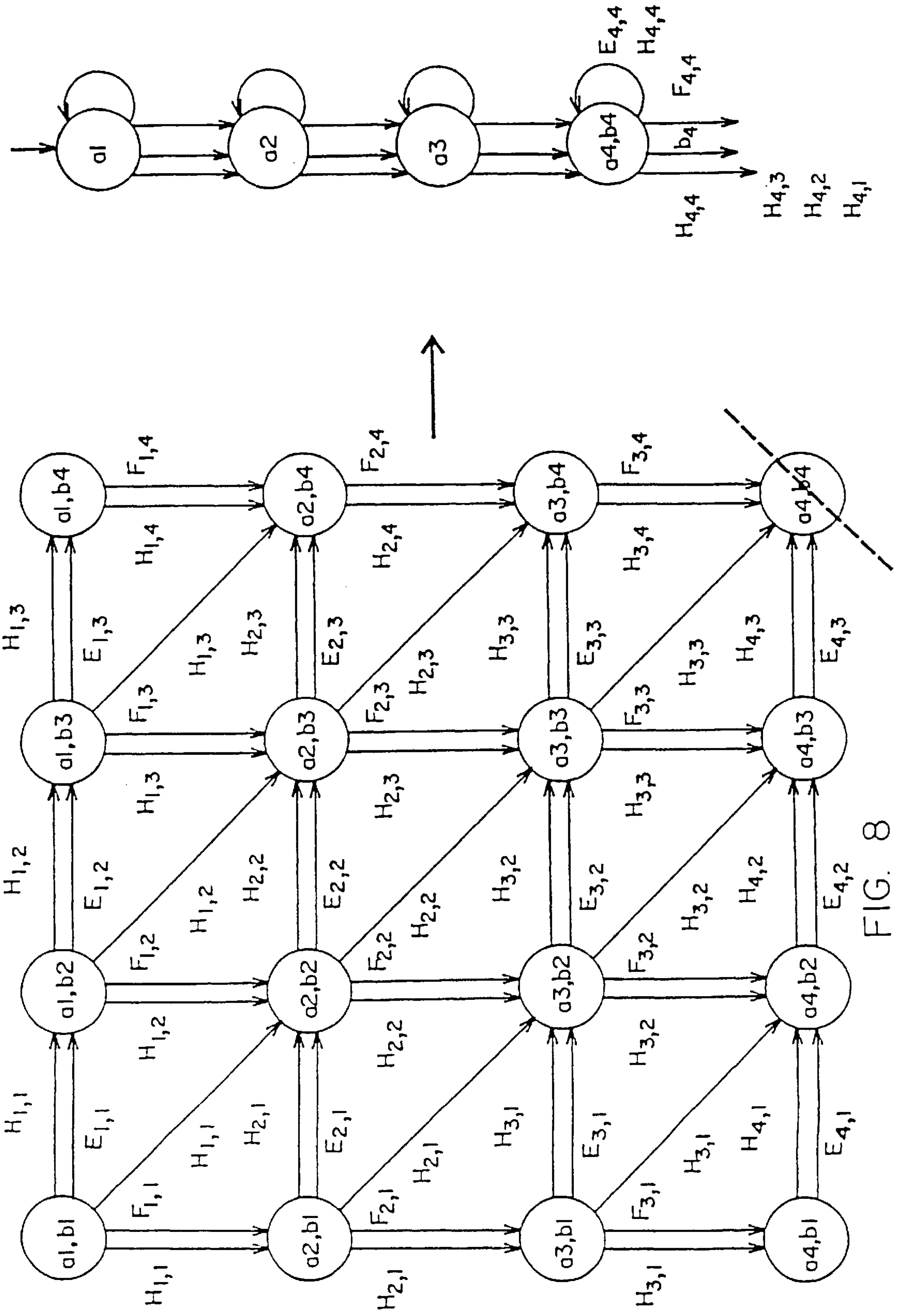
a2
a3,b4
a4,b3
E3,4
H3,4
E4,3
H4,3
F3,4
b4
F4,3
b3
H3,4
H4,3
H4,2
H4,1
a1,b1
a1,b2
a1,b3
a1,b4
a2,b1
a2,b2
a2,b3
a2,b4
a3,b1
a3,b2
a3,b3
a3,b4
a4,b1
a4,b2
a4,b3
a4,b4
H1,1
E1,1
F1,1
H1,2
E1,2
F1,2
H1,3
E1,3
F1,3
H1,4
F1,4
H2,1
E2,1
F2,1
H2,2
E2,2
F2,2
H2,3
E2,3
F2,3
H2,4
F2,4
H3,1
E3,1
F3,1
H3,2
E3,2
F3,2
H3,3
E3,3
F3,3
H3,4
F3,4
H4,1
E4,1
H4,2
E4,2
H4,3
E4,3

FIG. 7


a1
a2
a3
a4,b4
E4,4
H4,4
F4,4
b4
H4,4
H4,3
H4,2
H4,1
a1,b1
a2,b1
a3,b1
a4,b1
a1,b2
a2,b2
a3,b2
a4,b2
a1,b3
a2,b3
a3,b3
a4,b3
a1,b4
a2,b4
a3,b4
a4,b4
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F1,1
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F1,2
H1,2
H2,2
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F2,2
H2,2
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F3,2
H3,2
H4,2
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H1,3
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F1,3
H1,3
H2,3
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F2,3
H2,3
H3,3
E3,3
F3,3
H3,3
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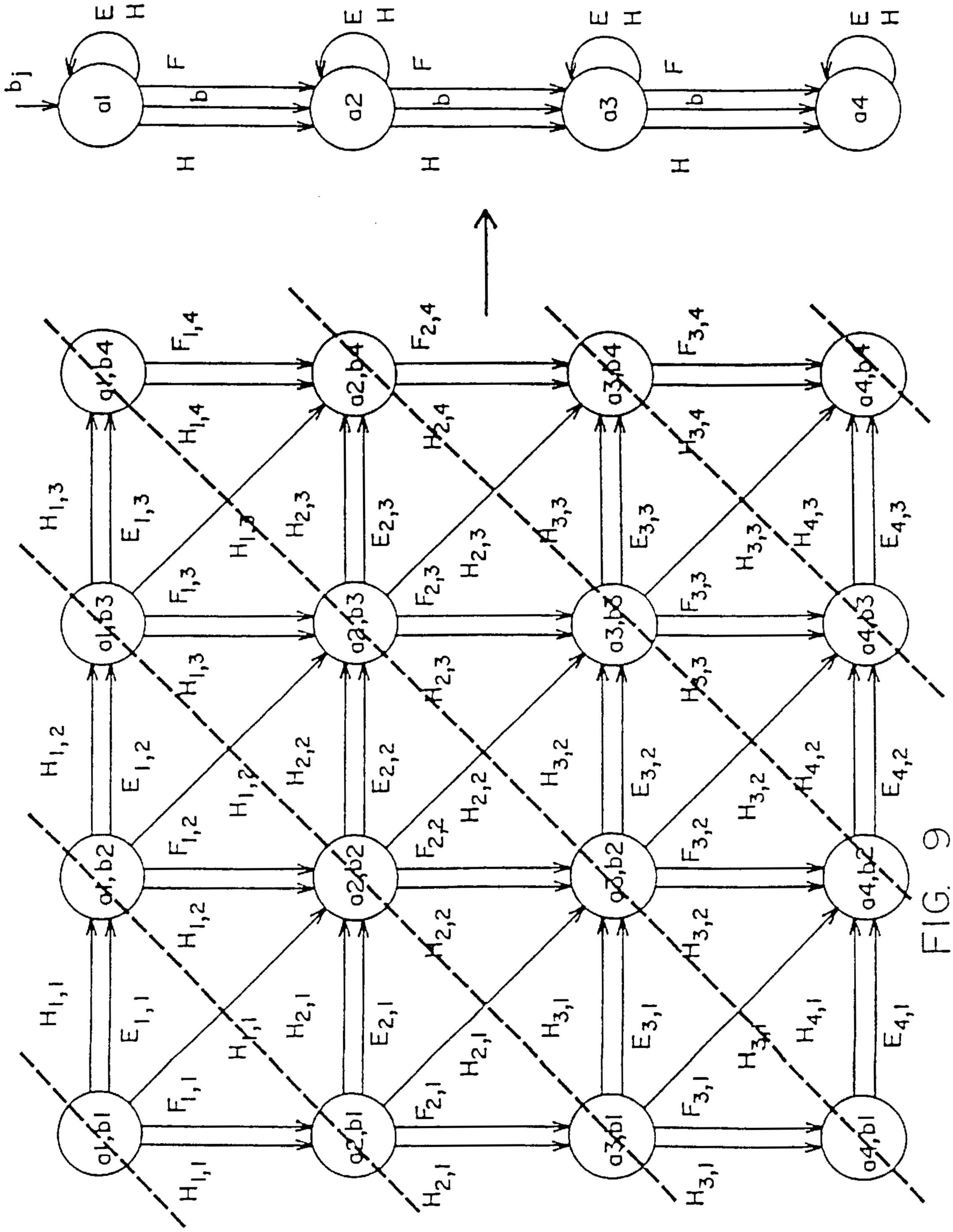
E4,3
F1,4
H1,4
F2,4
H2,4
F3,4
H3,4

FIG. 8


b_j
a1
a2
a3
a4
E
H
F
b
H
a1,b1
a2,b1
a3,b1
a4,b1
a1,b2
a2,b2
a3,b2
a4,b2
a1,b3
a2,b3
a3,b3
a4,b3
a1,b4
a2,b4
a3,b4
a4,b4
$F_{1,1}$
$F_{2,1}$
$F_{3,1}$
$F_{1,2}$
$F_{2,2}$
$F_{3,2}$
$F_{1,3}$
$F_{2,3}$
$F_{3,3}$
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$E_{3,3}$
$E_{4,3}$
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$H_{4,1}$
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$H_{2,2}$
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$H_{4,2}$
$H_{1,3}$
$H_{2,3}$
$H_{3,3}$
$H_{4,3}$
$H_{1,4}$
$H_{2,4}$
$H_{3,4}$

FIG. 9

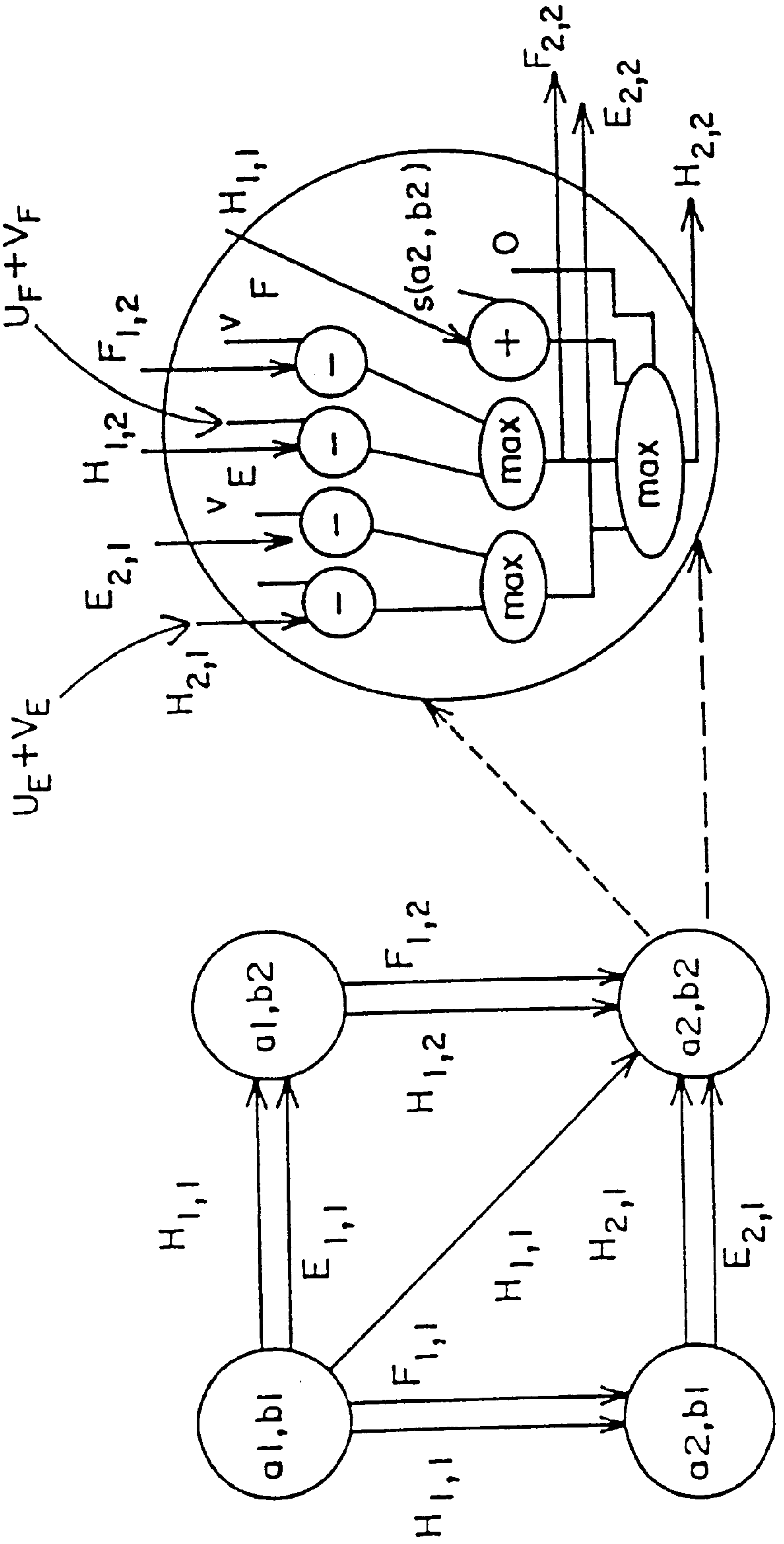
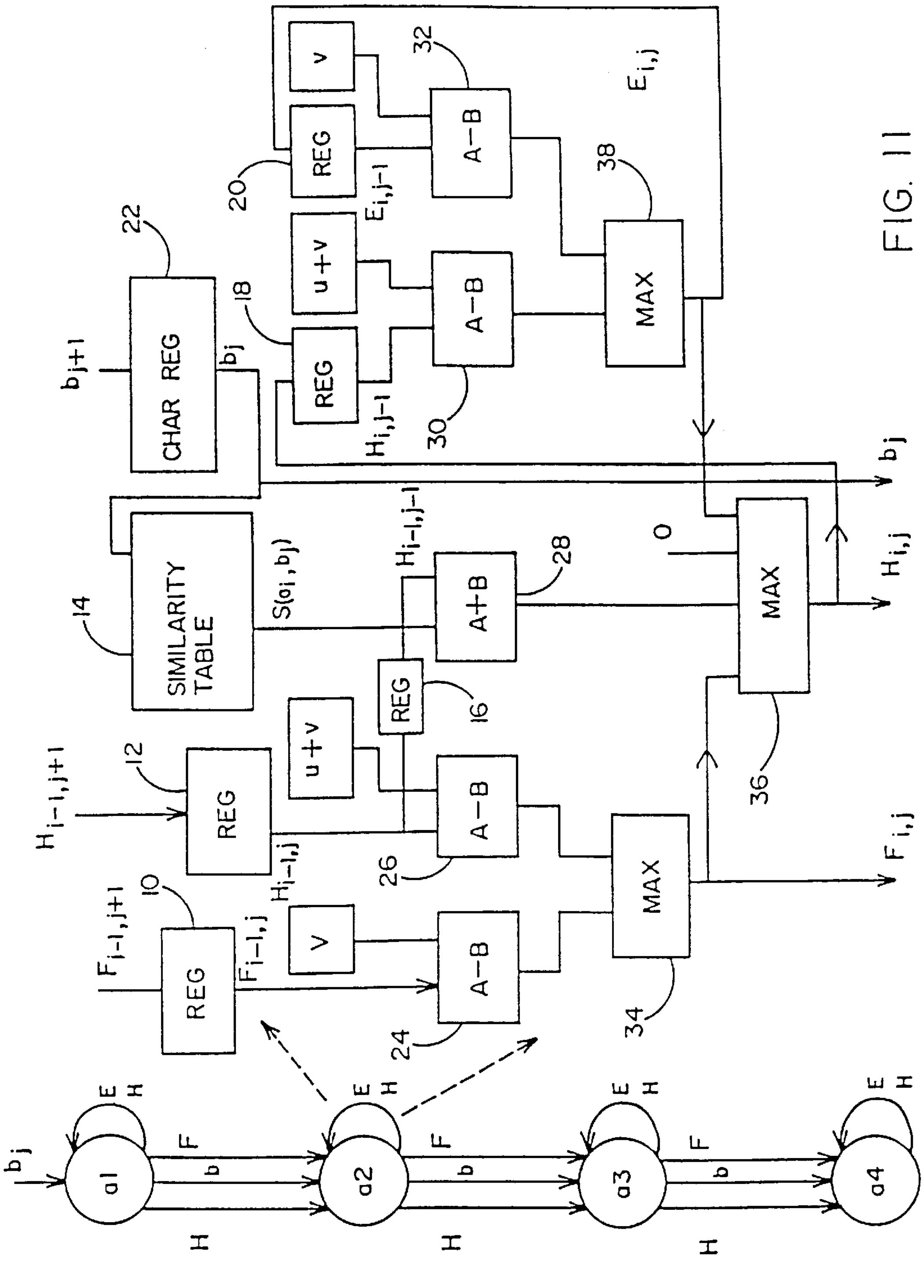

U_F+V_F
U_E+V_E
$F_{1,2}$
$H_{1,2}$
$E_{2,1}$
$H_{2,1}$
v_F
v_E
$H_{1,1}$
s(a2,b2)
0
−
−
−
−
+
max
max
max
$F_{2,2}$
$E_{2,2}$
$H_{2,2}$
a1,b1
a1,b2
a2,b1
a2,b2
$H_{1,1}$
$E_{1,1}$
$F_{1,1}$
$H_{1,1}$
$H_{1,1}$
$F_{1,2}$
$H_{1,2}$
$H_{2,1}$
$E_{2,1}$

FIG. 10



b_j
a1
a2
a3
a4
F
b
H
E
H
10
REG
$F_{i-1,j+1}$
$F_{i-1,j}$
V
24
A−B
$H_{i-1,j}$
12
REG
$H_{i-1,j+1}$
u+v
26
A−B
16
REG
MAX
34
$F_{i,j}$
14
SIMILARITY TABLE
$S(a_i,b_j)$
$H_{i-1,j-1}$
A+B
28
0
MAX
36
$H_{i,j}$
b_j
22
CHAR REG
b_{j+1}
b_j
18
REG
$H_{i,j-1}$
u+v
A−B
30
20
REG
$E_{i,j-1}$
V
A−B
32
MAX
38
$E_{i,j}$

FIG. 11

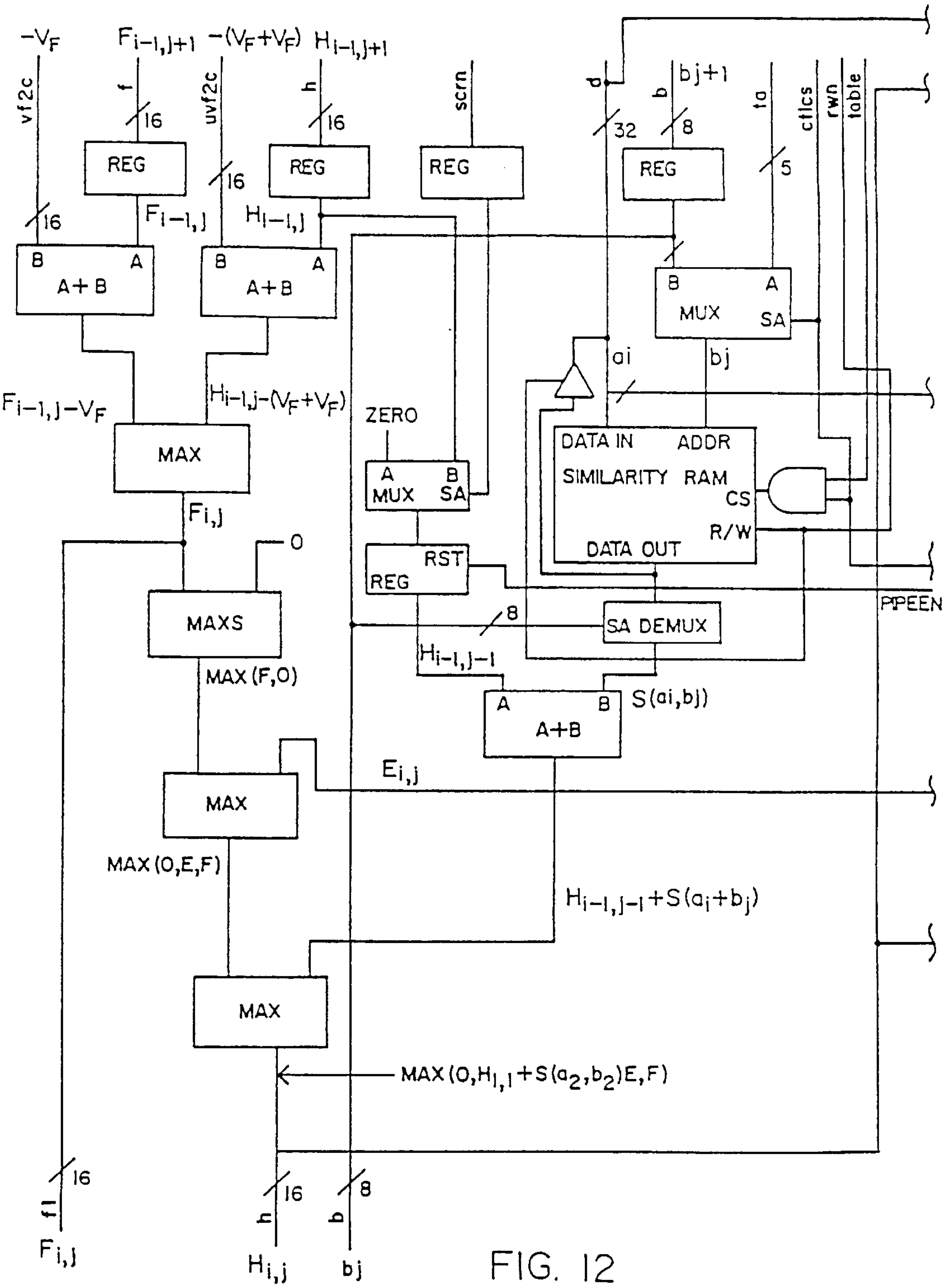

$-V_F$
$F_{i-1,j+1}$
$-(V_F+V_F)$
$H_{i-1,j+1}$
vf2c
f
16
uvf2c
h
scrn
d
b
bj+1
ta
ctlcs
rwn
table
REG
REG
REG
REG
32
8
5
16
16
16
$F_{i-1,j}$
$H_{i-1,j}$
B A
A+B
B A
A+B
B A
MUX SA
ai
bj
$F_{i-1,j}-V_F$
$H_{i-1,j}-(V_F+V_F)$
ZERO
MAX
A B
MUX SA
DATA IN ADDR
SIMILARITY RAM
CS
R/W
DATA OUT
$F_{i,j}$
0
RST
REG
PIPEEN
MAXS
8
SA DEMUX
MAX (F,0)
$H_{i-1,j-1}$
A B
A+B
S(ai,bj)
$E_{i,j}$
MAX
MAX (0,E,F)
$H_{i-1,j-1}+S(a_i+b_j)$
MAX
$MAX(0,H_{1,1}+S(a_2,b_2)E,F)$
16
f1
$F_{i,j}$
16
h
$H_{i,j}$
8
b
bj

FIG. 12

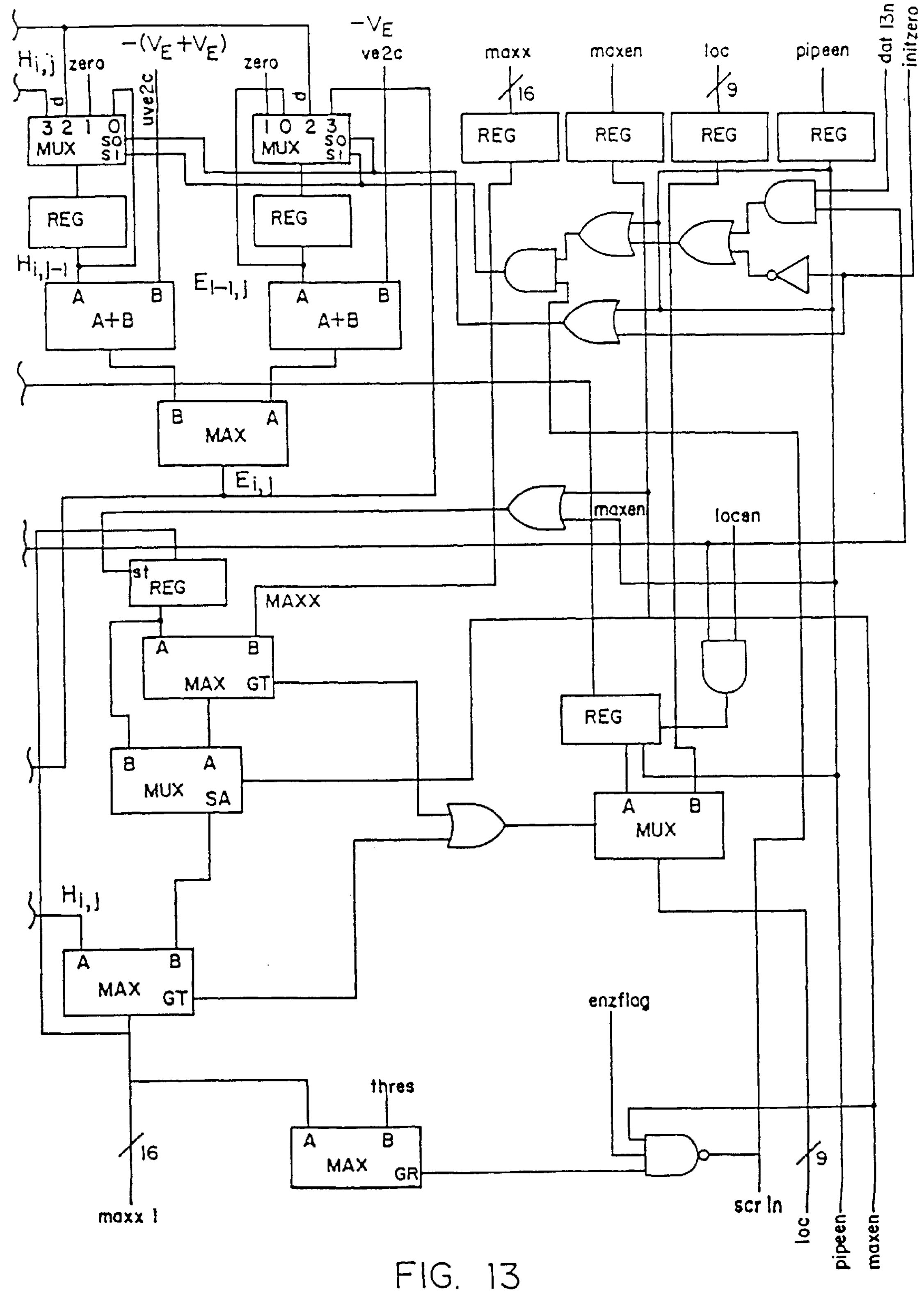

$H_{i,j}$
zero
$-(V_E+V_E)$
uve2c
3 2 1 0
MUX
S0
S1
d
REG
$H_{i,j-1}$
A B
A+B
$E_{i-1,j}$
zero
$-V_E$
ve2c
1 0 2 3
MUX
S0
S1
d
REG
A B
A+B
B MAX A
$E_{i,j}$
maxx
16
maxen
loc
9
pipeen
dat 13n
initzero
REG
REG
REG
REG
maxen
locen
st
REG
MAXX
A B
MAX GT
B A
MUX SA
REG
A B
MUX
$H_{i,j}$
A B
MAX GT
enzflag
thres
A B
MAX GR
16
maxx 1
scr In
9
loc
pipeen
maxen

FIG. 13

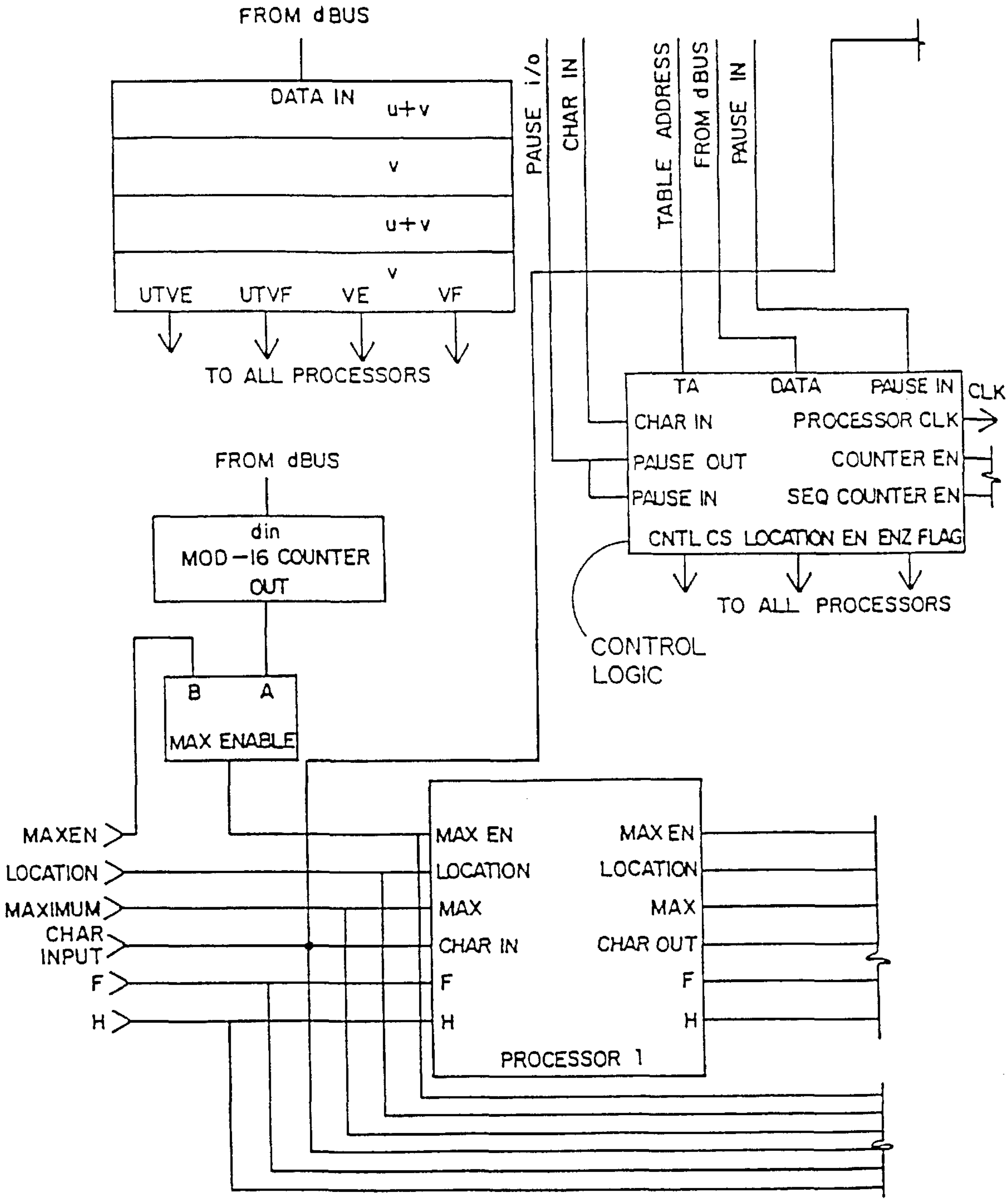

FROM dBUS
DATA IN
u+v
v
u+v
v
UTVE
UTVF
VE
VF
TO ALL PROCESSORS
PAUSE i/o
CHAR IN
TABLE ADDRESS
FROM dBUS
PAUSE IN
TA
DATA
PAUSE IN
CLK
CHAR IN
PROCESSOR CLK
PAUSE OUT
COUNTER EN
PAUSE IN
SEQ COUNTER EN
CNTL CS
LOCATION EN
ENZ FLAG
TO ALL PROCESSORS
CONTROL LOGIC
FROM dBUS
din
MOD-16 COUNTER
OUT
B
A
MAX ENABLE
MAXEN
LOCATION
MAXIMUM
CHAR INPUT
F
H
MAX EN
LOCATION
MAX
CHAR IN
F
H
MAX EN
LOCATION
MAX
CHAR OUT
F
H
PROCESSOR 1

FIG. 14

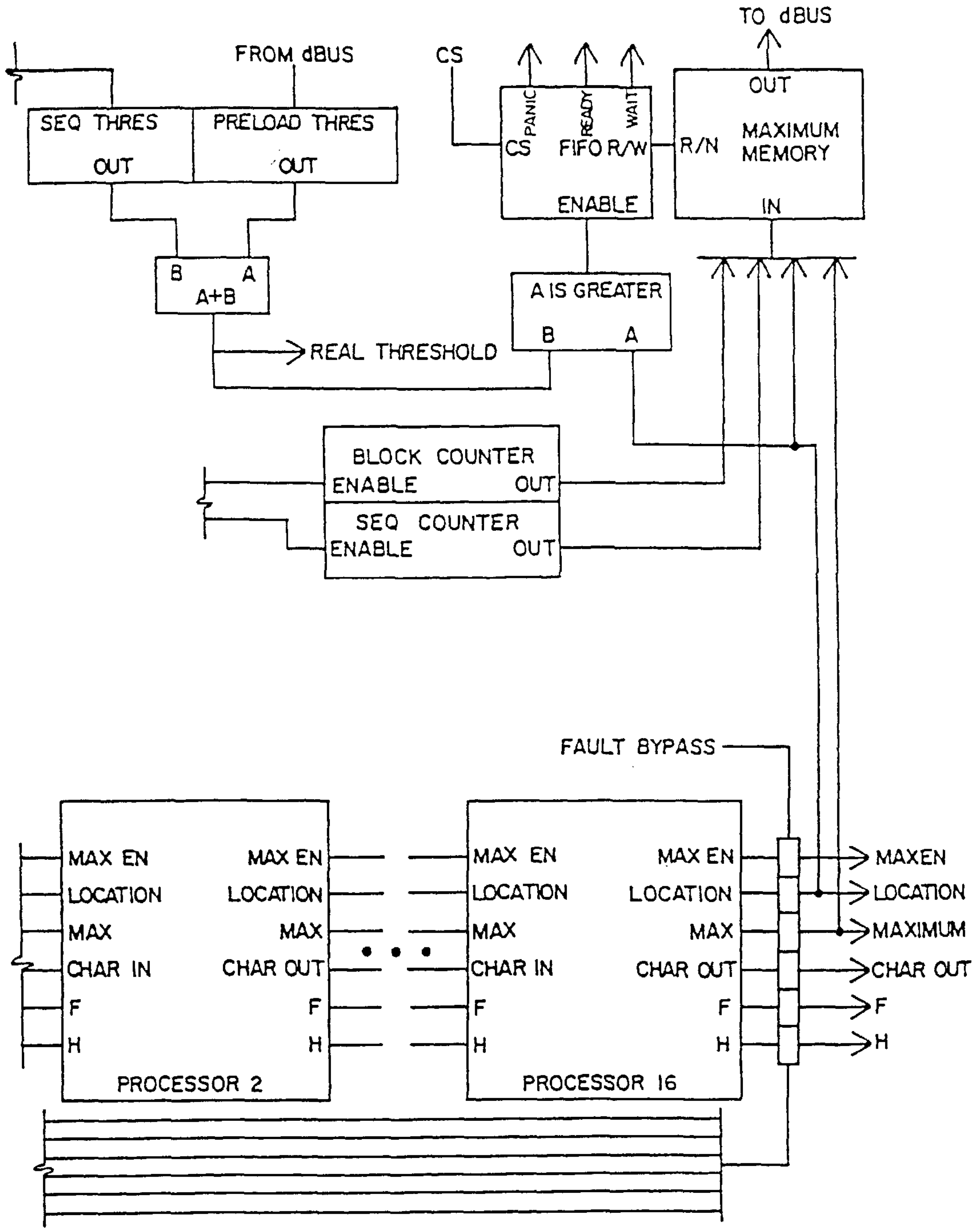

FROM dBUS
SEQ THRES
OUT
PRELOAD THRES
OUT
B
A
A+B
REAL THRESHOLD
CS
PANIC
READY
WAIT
CS
FIFO
R/W
ENABLE
TO dBUS
OUT
R/N
MAXIMUM
MEMORY
IN
A IS GREATER
B
A
BLOCK COUNTER
ENABLE
OUT
SEQ COUNTER
ENABLE
OUT
FAULT BYPASS
MAX EN
LOCATION
MAX
CHAR IN
F
H
MAX EN
LOCATION
MAX
CHAR OUT
F
H
PROCESSOR 2
MAX EN
LOCATION
MAX
CHAR IN
F
H
MAX EN
LOCATION
MAX
CHAR OUT
F
H
PROCESSOR 16
MAXEN
LOCATION
MAXIMUM
CHAR OUT
F
H

FIG. 15

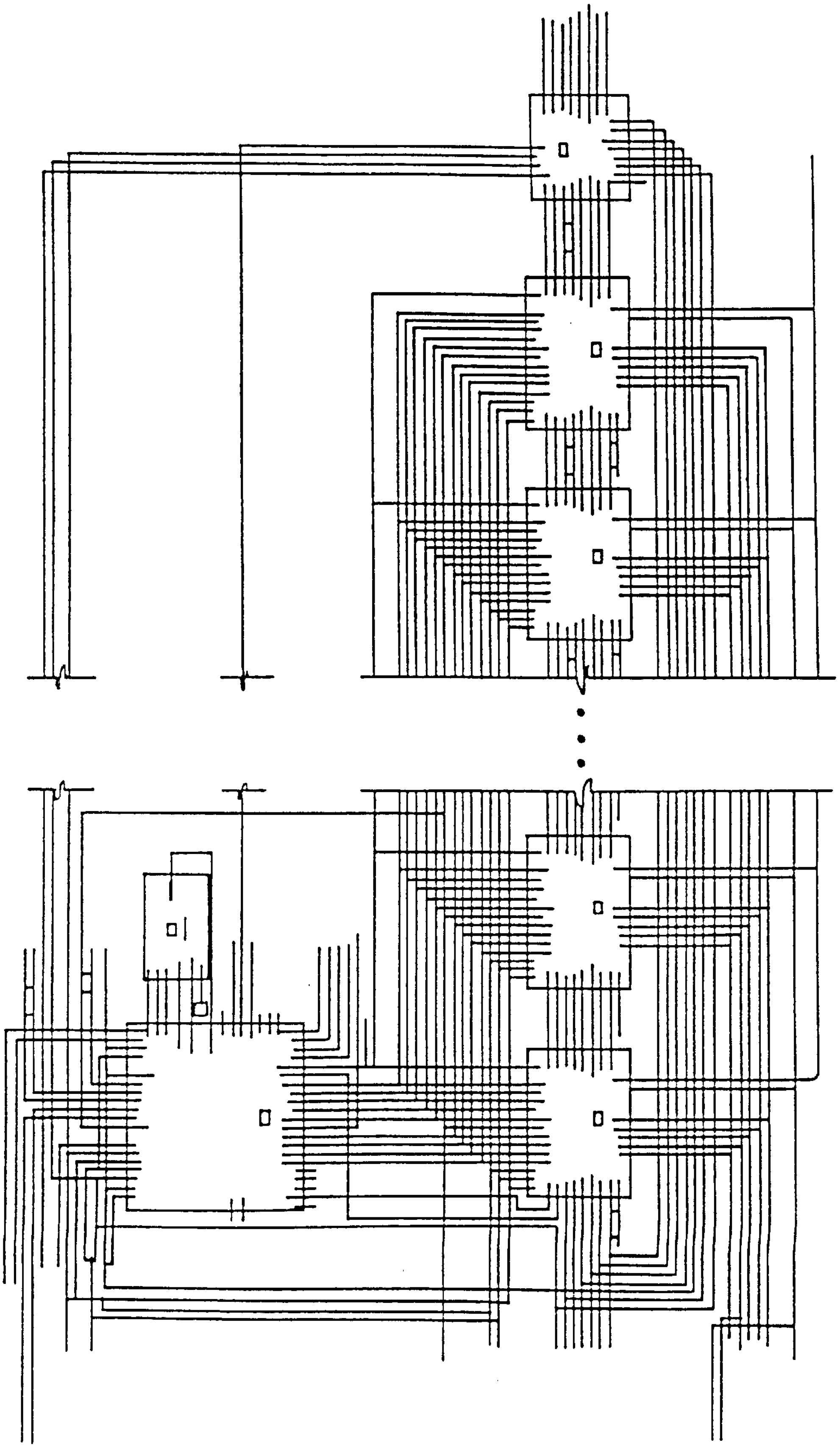


FIG. 16

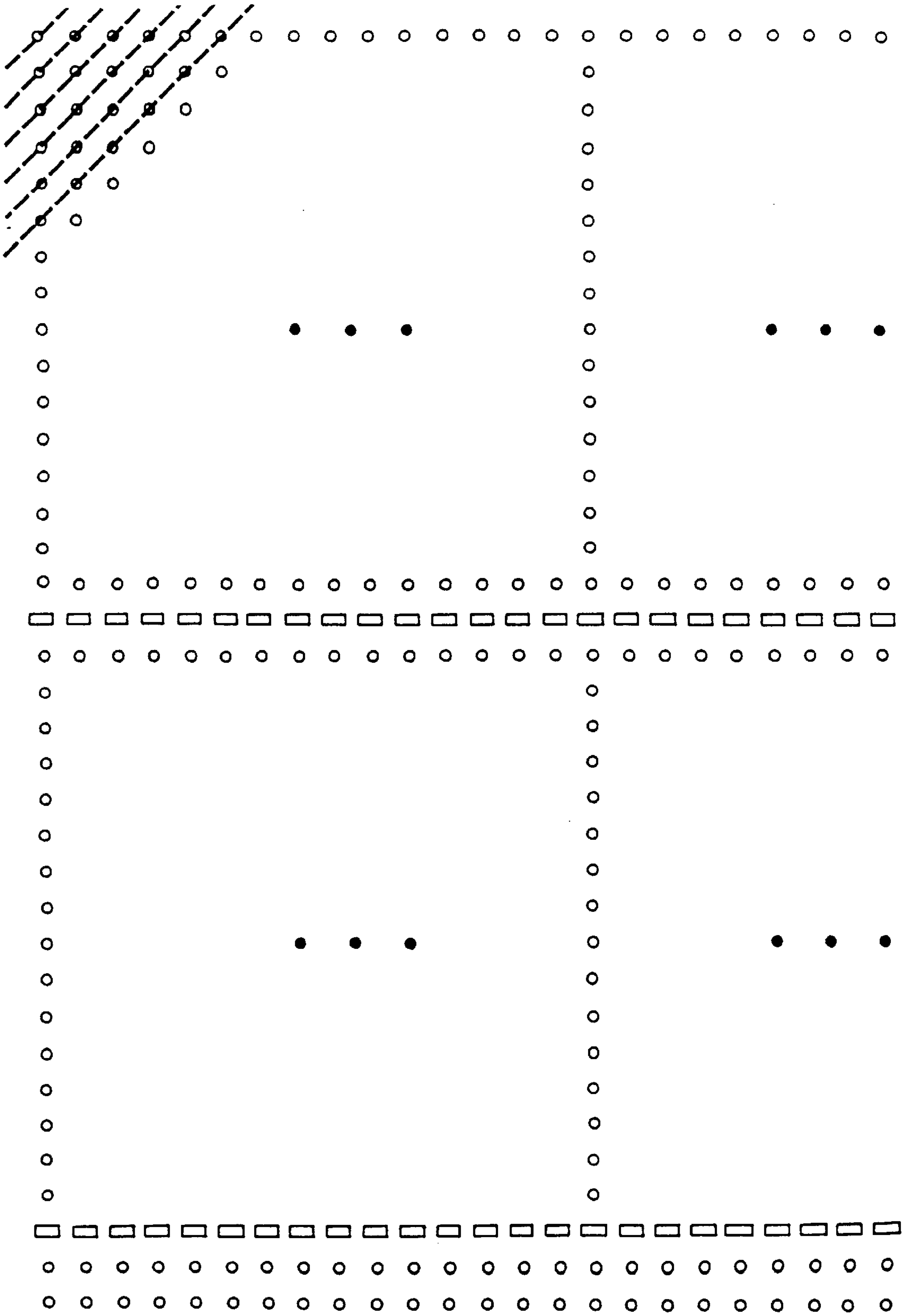


FIG. 17

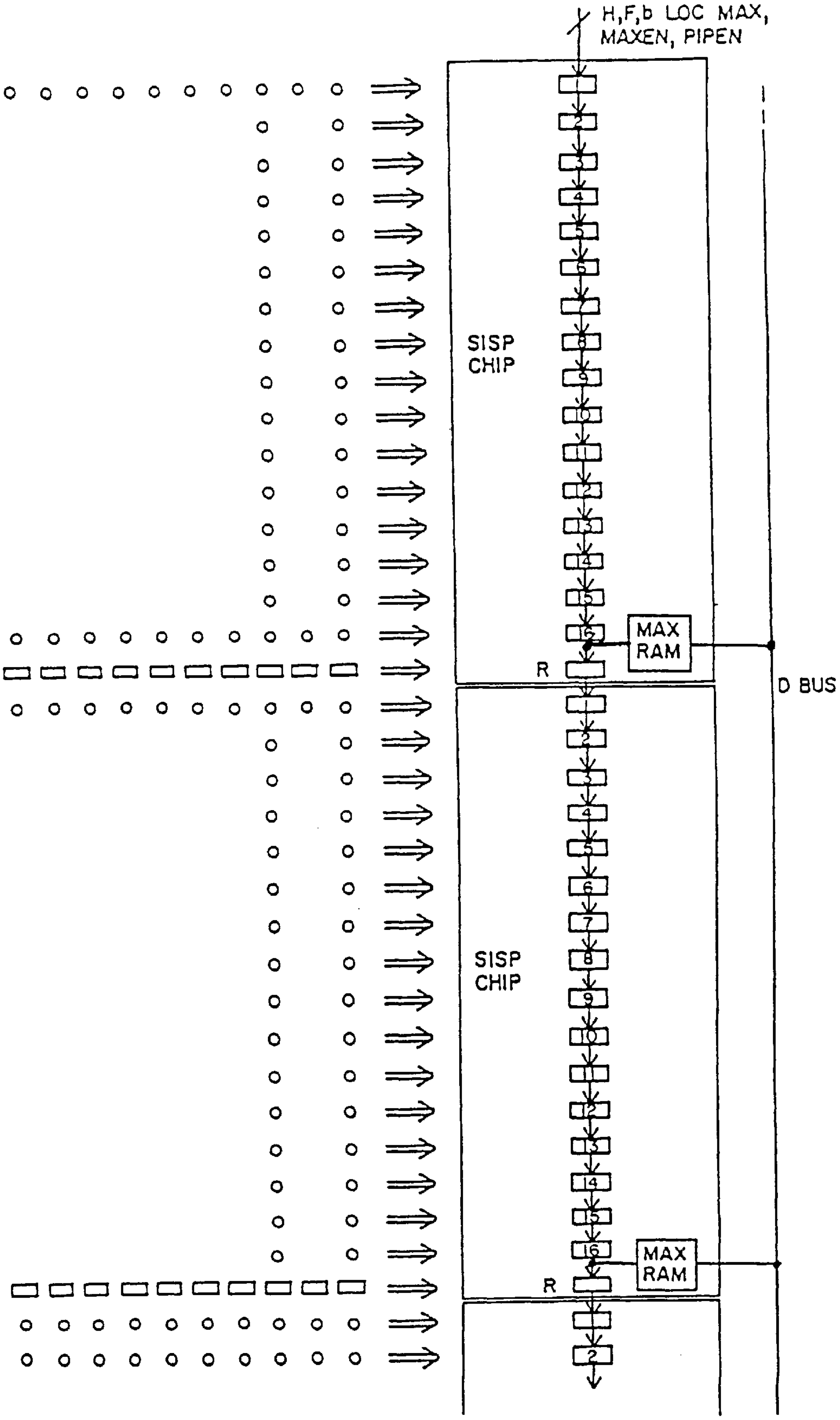

H,F,b LOC MAX,
MAXEN, PIPEN
SISP
CHIP
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
MAX
RAM
R
D BUS
SISP
CHIP
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
MAX
RAM
R
1
2

FIG. 18

SEQUENCE INFORMATION SIGNAL PROCESSOR

This is a continuation of application Ser. No. 08/154,633, filed Nov. 18, 1993, now U.S. Pat. No. 5,632,041 which is a continuation of Ser. No. 07,518,562, filed May 2, 1990.

The invention described herein was made in the performance of work under the following contracts: NASA contract NAS7-918; DOE contract DEFG03-88er60683; NSF contracts DIR-8809710 and DMS-8815106; and NIH contract GM 36230, and is subject to the provisions of Public. Law 96-517 (35 USC 202) in which the Contractors have elected to retain title.

ORIGIN OF INVENTION

1. Technical Field

The present invention relates generally to an integrated circuit developed primarily in support of the human genome effort which is a molecular genetic analysis for mapping and sequencing the human genome. The present invention relates more specifically to an integrated circuit co-processor which may be used for carrying out an algorithm for identifying maximally similar sequences or subsequences and for locating highly similar segments of such sequences or subsequences.

2. Background Art

Release 63.0 of the national nucleic acid data base, Genbank, contains over forty million nucleotides representing about thirty-three thousand separate entries. Similarly, the current protein information resource (PIR) has close to six thousand entries with over one and one-half million amino acids. These data reflect primarily the efforts of the molecular biology community over the last decade. The rate at which new data are being added to this total demonstrates that the available computing resources are already inadequate for thorough and timely analysis of the data. Recently, an international commitment has been made to map and sequence the entire human genome in the next 10 to 20 years. Such a program will generate at least 3.4 billion nucleotides of final data and maybe ten times that amount of raw sequencing data. This constitutes about three orders of magnitude more data than has been collected to date. In addition, the sequences from other animal and plant genomes will also accumulate. In the near term, the 40 million nucleotides currently available and already proving burdensome, will become trivial by comparison to the total. Novel computer resources must be developed if these data are to be adequately understood and their unique potential for enhancing our understanding of human genetics and diseases are to be realized.

A required adjunct to any program designed to characterize the human genome is the development of computer hardware and software systems capable of maintaining and analyzing the vast amounts of information that will be generated. This information will consist of both nucleotide and amino acid sequence data as well as extensive annotation necessary to provide a biological context for these data. It is critical for the complete and timely analysis of new sequence data, that they be thoroughly compared to the published data contained in the national data libraries. This analysis is important for determining and defining the functional and evolutionary relationships between sequences. Significantly, such sequence comparison is also critical to the task of constructing the complete genome sequence from millions of partially overlapping fragments, the so-called melding process. The computational load of this melding process will grow not only at the national level of coordinating the efforts of many researchers, but also at the level of individual laboratories that must deal with the increasing load of raw data generated by the development of automated sequencing technologies.

The ability of individual investigators to analyze their own data is limited by the power of the computers they have available, as well as the limited software tools capable of dealing with the entire sequence library. The amount of total sequence data generated to date is still less than 50 million character equivalents. However, this amount of data already taxes the ability of currently available algorithms and general use computers to conduct the needed comparative analysis of new data to the collected total. The data libraries have been doubling in size every year. The program that is envisioned to characterize complete genomes, will soon cause the data libraries to increase exponentially. Such programs will also change the basic nature of the collected data and consequently the requirements for effective tools for its analysis.

In the latest Genbank release, the average length of an individual entry can span over one million bases. Many of the current methods of analyzing this data are based on the notion that each entry represents a discrete genetic element. However, this scenario does not adequately represent the more diffuse and complex organization of a eukaryotic genome, where the coding and regulatory elements of a simple gene can span more than one million bases. More complex loci, such as those coding for the rearranging receptors of the immune system, can span over one million bases and include hundreds or thousands of identifiably related elements. As more and larger sequencing efforts are undertaken, the complexity of information contained in single entries will require a novel set of maintenance and analytical tools.

The human beta globin locus is a good example. Its entry in Genbank is over 73 thousand bases long and has been constructed from over 70 overlapping contributions. This single entry contains the coding and regulatory information for at least 4 genes and 1 pseudogene. The repetitive nature of much of the genome will also severely complicate the alignment and melding problems. With megabase sequencing projects, the current concept of data entry will become obsolete. Not only will faster algorithms to compare sequences be needed as the amount of data increases, but these new tools will also have to be designed to better deal with longer strings of data that more directly reflect true genomic organization. Accordingly, novel schemes to handle and define these data and the biological information associated with them must be developed if this resource is to be useful to the scientific community.

Of the many pressing and analytical needs concerning the current sequence data libraries, as well as the genome project, initially the most significant is the ability to survey the existing collection of data for sequences related to the new data. In its simplest form, this need is illustrated by searching the collection of gene or protein sequences for any that are "similar" to a discrete piece of new data. The comparative analyses possible between related sequences are critical for completely understanding the structural, functional and evolutionary characteristics of any sequence. Furthermore, in the case where large portions of the human genome are known, it will also be necessary to have the ability to find the precise genetic location of physiological markers in those cases where there may be only limited CDNA or protein sequence data available.

Such searches are complicated by the fact that related sequences may be quite divergent. This means that it is essential to define some measure of similarity between pairs of sequences that can then be tested statistically. The explicit series of minimal evolutionary events (substitutions, deletions, insertions) between two sequences must be determined; i.e., the sequences must be aligned. Traditionally, the most common method of alignment has been by eye, relying on the researcher's ability to recognize conserved patterns. This method can be rapid and effective when the sequence distance is relatively small and/or the researcher has a priori information about the probable nature of the alignment. For example, many new members of the immunoglobulin gene superfamily have been identified and aligned to other members on the basis of a very limited, but well-defined set of conserved features. However, it is certainly no longer possible for any investigator to reliably compare a novel sequence against a significant portion of the existent data base.

It is possible in theory to generate every possible combination of genetic events between two sequences, score each one and discover the most similar. This is in practice, impossible for all but the shortest sequences however, as the combinations increase exponentially with the length of the sequences. Some investigators have implemented rule-based methods by which, given a reasonable starting alignment point, gaps and insertions are included according to a very restricted set of possibilities. These methods can be relatively rapid, but, like manual alignment, are non-rigorous methods as they cannot predictably guarantee that the results represent the optimal minimum distance, that is, the minimum evolutionary distance between two sequences or the series of events that provides the smallest weighted sum required to transform one sequence into the other.

When the assumption is that two sequences are generally similar along their entire length, the alignment process is considered to be global in nature. However, an alignment proceeding from this premise can fail to recognize more limited regions of similarity between two otherwise unrelated sequences. What is required then is the ability to find all regions of local alignment. For example, if an investigator has a new sequence related to a human beta globin gene, such as one from another species, the need is to be able to find the local alignment of that, more limited sequence to some particular portion of the 73 thousand base of the known beta globin locus. The same concerns are manifest in the melding problem. By definition, most overlapping sequences will only share a limited region of identity, illustrating a local alignment problem.

In 1970, S. B. Needleman and C. D. Wunsch authored a paper entitled "A General Method Applicable To The Search For Similarities In The Amino Acid Sequence Of Two Proteins", which was published in the Journal of Molecular Biology, Volume 48, Page 444. Their paper has had a great deal of influence in biological sequence alignment. Its particular advantage is that an explicit criterion for optimality of alignment is stated and an efficient method of solution is given. Insertions, deletions and mismatches were allowed in the alignments. The method of Needleman and Wunsch fit into a broad class of algorithms, commonly referred to as dynamic programming. The general category of dynamic programming alignment of two sequences is discussed at length in a text entitled "Mathematical Methods for DNA Sequences" and particularly Chapter 3 thereof, entitled "Sequence Alignments" written by Michael S. Waterman, of the University of Southern California, a co-inventor of the, present invention.

In 1980, Dr. Waterman, then with the Los Alamos Scientific Laboratory, collaborated with T. F. Smith, then a Professor at Northern Michigan University, in publishing a letter entitled "Identification of Common Molecular Subsequences" which appeared in the Journal of Molecular Biology, Volume 147, pages 195–197, 1981. In this letter, Waterman and Smith defined a new algorithm, the intention of which was to find a pair of segments, one from each of two long sequences, such that there was no other pair of segments with greater similarity (or "homology"). The algorithm produced a similarity measure which allowed for arbitrary length, deletions and insertions.

In a more recent publication, entitled "A New Algorithm for Best Subsequence Alignments With Application to tRNA-rRNA Comparisons", Waterman and Mark Eggert, in the Journal of Molecular Biology, Volume 197, pages 723–728, (1987), describe the efficiency of the algorithm of Smith and Waterman for identification of maximally similar subsequences. The article describes the use of the algorithm in which alignments of interest are produced first for the best alignment and then making small modifications to the matrix for producing non-intersecting subsequent alignments. The algorithm is applied to comparisons of tRNA-rRNA sequences from *Escherichia coli.* A statistical analysis therein shows results which differ substantially from the results of an earlier analysis by others and furthermore, that the algorithm is much simpler and more efficient than those previously in use.

The need for low cost, high speed data sequence comparisons cannot be met even with current supercomputers because of existing data base size. There is therefore an existing need to provide an electronic circuit device for carrying out subsequence alignments of molecular sequences or global alignment thereof and more specifically for a sequence information signal processor designed to carry out a dynamic programming algorithm which is both effective and efficient in identifying subsequence or global alignments of molecular information.

SUMMARY OF THE INVENTION

The present invention comprises a sequence information signal processing integrated circuit chip designed to perform high speed calculation of a dynamic programming algorithm based upon Waterman and Smith. The signal processing chip of the present invention is designed to be a building block of a linear systolic array, the performance-of which can be increased by connecting additional sequence information signal processing chips to the array. The chip provides a high speed, low cost linear array processor that can locate highly similar segments or contiguous subsequences from any two data character streams (sequences) such as different DNA or protein sequences. The chip is implemented in a preferred embodiment using CMOS VLSI technology to provide the equivalent of about 400,000 transistors or 100,000 gates. Each chip provides 16 processing elements, operating at a 12.5 MHz clock frequency. The chip is designed to provide 16 bit, two's compliment operation for maximum score precision of between −32,768 and +32,767. It is designed to provide a comparison between sequences as long as 4,194, 304 elements without external software and between sequences of unlimited numbers of elements with the aid of external software.

The sequence information signal processor chip of the present invention permits local and global similarity searches, that is subsequence and full sequence alignment. It provides user definable gaps/insertion penalties; user definable similarity table contents; user definable threshold values for score reporting; user definable character set of up to

128 characters; user definable sequence control characters for streamline data base processing; variable block size for low or high resolution similarity searches; makes possible unlimited sequence length and numbers of blocks; on-chip block maximum score calculation; and on-chip maximum score buffer to relieve control processor data collection. It provides linear speedup by being configured for cascading more such chips and it provides threshold control with boundary score reset. The chip also provides for programmable data base operation support; block maximum value and location calculation and buffering; user-definable query threshold and preload threshold and built-in self test and fault bypass.

It will be seen hereinafter that each of sixteen processor elements on a sequence information signal processing integrated circuit chip of the present invention, provides the circuitry to compare the sequence characters of a matrix H, based upon a novel modification of the Smith and Waterman Algorithm for two sequences. Circuitry is also provided for defining the degrees of similarity of two sequences so that different linear deletion functions can be defined for each of the two sequences and different similarity weights can be defined for each character of the query sequence.

In its preferred embodiment, the chip of the present invention is configured as a 208 pin, CMOS VLSI integrated circuit device.

OBJECTS OF THE INVENTION

It is therefore a principal object of the present invention to provide a sequence information signal processing system on a single integrated circuit chip for performing a best subsequence and global alignments algorithm at high speed, at low cost and with optimum parameter control.

It is an additional object of the present invention to provide an integrated circuit chip having highly integrated VLSI technology for ascertaining the similarity between two segments of two different DNA or protein sequences by performing a best subsequence alignment algorithm.

It is still an additional object of the present invention to provide an integrated circuit chip having a plurality of processors thereon, each such processor being designed to carry out an algorithm for providing scoring of the relative alignments of sequence segments for such uses as biological information signal processing, speech recognition, cryptology, geological strata analysis, handwriting recognition, large text database searches and other applications which require the comparison of multiple sequences of data.

BRIEF DESCRIPTION OF THE DRAWINGS

The aforementioned objects and advantages, as well as additional objects and advantages thereof, will be more fully understood hereinafter as a result of a detailed description of a preferred embodiment when taken in conjunction with the following drawings in which:

FIG. **1** is a graphical illustration of the matrix elements of the algorithm of the present invention and illustrating a projection technique for reducing the number of real time processors for carrying out the algorithm;

FIGS. **2–9** illustrate sequential snapshot representations of the algorithm steps of the present invention in a four-by-four exemplary matrix;

FIG. **10** is a graphical schematic illustration of the manner in which the architecture of a processor of the present invention performs the algorithmic steps for a particular matrix element;

FIG. **11** is a generalized, functional block diagram of a processor of the present invention;

FIGS. **12** and **13**, when taken together, represent a block diagram of an actual processor of the present invention;

FIGS. **14** and **15**, when taken together, constitute a schematic block diagram of the chip circuit of the present invention;

FIG. **16** is a layout schematic illustrating the physical configuration of the signal processing chip of the invention; and

FIGS. **17** and **18** taken together provide a dependence graph mapping for multiple chips representing a total of 34 processors of the present invention.

DETAILED DESCRIPTION OF A PREFERRED EMBODIMENT

The information signal processor integrated circuit chip of the present invention is designed to compare two sequences, such as two molecular sequences, and to determine their similarity by ascertaining the best score of any alignment between such sequences. A preferred embodiment of the invention illustrated herein is designed to perform this sequence comparison by carrying out the previously identified Smith and Waterman algorithm. Accordingly, the method and apparatus of the present invention may be best understood by first understanding the algorithm on which it is based and which comprises the following:

For two sequences A=$a_1a_2 \ldots a_n$ and B=$b_1b_2 \ldots b_m$, the best (largest) score from aligning A and B is S(A,B). $H_{i,j}$ is defined as the best score of any alignment ending at a_i and b_j or 0. So,

$$H_{i,j}=\max\{0;\ S(a_xa_x+1 \ldots a_i,\ b_yb_y+1 \ldots b_j);\ 1<=x<=i,\ 1<=y<=j\}.$$

The similarity measure between sequence letters a and b is s(a,b) where,

s(a,b)>0 if a=b

s(a,b)<0 for at least some cases of a not equal to b. The similarity algorithm is started with:

$$H_{i,0}=H_{0,j}=0,\ 1<=i<=n,\ 1<=j<=m.$$

Then:

$$H_{i,j}=\max\{0,\ H_{i-1,j-1}+s(a_i,b_j),\ E_{i,j},\ F_{i,j}\}$$

where:

$$E_{i,j}=\max\{H_{i,j-1}-(u_E+v_E),\ E_{i,j-1}-v_E\}$$

$$F_{i,j}=\max\{H_{i-1,j}-(u_F+v_F),\ F_{i-1,j}-v_F\}$$

From the above, it will be seen that each processor for determining the best score $H_{i,j}$ of an alignment ending at a_i and b_j must provide parameters for the calculation of $H_{i+1,j}$; $H_{i,j+1}$; and $H_{i+1,j+1}$. This requirement for generating parameters for subsequent best score calculation processes may be better understood by reference to FIG. **1**, which for purposes of example, illustrates a four-by-four matrix of calculations for n=4 and m=4. It will be seen in FIG. **1** that each alignment comparison process is represented by a circle having within it elements of the two sequences, A and B, at which the respective alignments are being scored. It will also be seen in FIG. **1**, that parameters are passed either from left to right or from top to bottom or diagonally from upper left to lower right from each alignment process circle to the others in the matrix in order to carry out the algorithm of the present invention. Thus for example, it will be seen in FIG. **1**, that the best score for the alignment ending at a_2 and b_2, receives the parameter $H_{1,1}$ from the a_1,b_1 comparison process; receives $H_{1,2}$ and $F_{1,2}$ from the a_1,b_2 comparison process; and receives the $H_{2,1}$ and $E_{2,1}$ parameters from the a_2,b_1 process. All of these parameters are, in accordance with the Waterman and Smith algorithm, required to generate $H_{2,2}$ which is defined as the best score of the alignment of the A and B sequences ending at a_2 and b_2.

It will also be seen in FIG. **1**, that as a result of the computation carried out by the process at a_2,b_2 parameters $H_{2,2}$, $E_{2,2}$ and $F_{2,2}$, all resulting from the best score alignment computation at a_2,b_2 are transferred as required to each of the three subsequent comparisons a_2,b_3,a_3,b_2 and a_3,b_3. Based upon the need for the generation of parameters for best score alignment comparisons for previous values of a_i and b_j in the sequences of A and B, it will be seen that not all of the best score alignment computation processes can be carried out simultaneously. Thus for example, best score computation for a_1,b_2 and a_2,b_1 must await the results of the computation process for a_2,b_2. Similarly, the computation process for a_1, b_1 must await the results of the computation processes for a_1,b_1 a_2,b_1 and a_1,b_2. Consequently, it would be entirely inefficient to perform the algorithm depicted in FIG. **1** for an exemplary four-by-four matrix with a separate processor for each combination of a_i and b_j. On the contrary, it would be most efficient to use only that number of processors which equals to the maximum number of processors being used at any one time, based upon the sequence of parameter generation required, as shown in FIG. **1**. Accordingly, as seen in the right most portion of FIG. **1**, the Smith and Waterman algorithm for a four-by-four matrix, that is for $A=a_1,a_2,a_3,a_4$ and $B=b_1,b_2,b_3$ and b_4; may be carried out by four computation processors with appropriate interconnections to assure the transfer of necessary parameters from processor to processor.

In the language of VLSI array processor design, the left-most portion of FIG. **1** is referred to as a systolic parallel processor array and the right-most portion of FIG. **1** is referred to as a signal flow graph. The technique for mapping algorithms into systolic parallel processor arrays and the technique for projecting such graphs into signal flow graphs may be understood best by referring to the text entitled VLSI Array Processors by S. Y. Kung, published by the Signal and Image Processing Institute of the University of Southern California, Copyright 1986.

The signal flow graph of the right side of FIG. **1**, illustrates that the systolic processor array graph on the left side may be horizontally projected into a signal flow configuration which requires only four processor elements to carry out the four-by-four matrix algorithm. For the example, as shown in FIG. **1**, each such processor on the right-most portion of FIG. **1** is permanently associated with an element of the A sequence, namely a_1,a_2,a_3, and a_4, respectively. On the other hand, the B sequence elements, namely, b_1,b_2,b_3 and b_4 $_1$ respectively, are sequentially applied in a serial manner through the elements so that the first alignment best score computation occurs at a_1,b_1.

The lines with arrow heads associated with each of the elements in the right-most portion of FIG. **1**, represent parameter values that are either transferred from element to element in series or are fed back and used in the same element for the next computation. More specifically, FIG. **2** represents a combined systolic array graph and horizontal projection graph at a "snapshot" in time at which the a_1,b_1 alignment computation is taking place as represented by the dashed line through the a_1,b_1 processor in the left portion of FIG. **2**. The b_1 signal has been applied to the first processor to permit the computation of the score ending at a_1,b_1. The parameter values emanating from this first sequence computation are represented by the arrow head lines emanating from the first processor element shown therein at the right most portion of FIG. **2**. As seen therein, $E_{1,1}$ and $H_{1,1}$ are both fed back into the a element for the subsequent computation. In addition, the $H_{1,1}$ the $F_{1,1}$ and the b_1 signals are transferred to the next processor element with which a is permanently associated.

The next subsequent snapshot of sequence operation is shown in FIG. **3**, and as illustrated by the dashed line in the left most portion of FIG. **3**, this snapshot finds the top-most sequence processor in the right-most portion of FIG. **3**, operating on the a_1,b_2 computation and the processor below the first operates on the a_2,b_1 computation. Each of these first two element processors generates appropriate parameter signals required by computations in the next snapshot period which is shown in FIG. **4**, each element with a new value of b_j entering the top-most element and the value of b_j processed by the top most element being transferred to the next element along with the other required parameters for the algorithm.

This process continues, snapshot after snapshot, as represented by FIGS. **5**, **6**, **7** and **8**. This example illustrates that the four-by-four matrix of processors for calculating the best score of any alignment between sequences A and B in the Smith and Waterman algorithm can be achieved with only four actual processors operating in an appropriate sequence. It, of course, requires the appropriate signals representing parameters required by the algorithm to be transferred from processor to processor as illustrated in snapshot to snapshot sequence of FIGS. **2** to **8**.

The signal flow through four processors represented by the right-most portion or signal flow graph portion of FIG. **9**, may be used to carry out all the required steps of the algorithm for a four-by-four matrix in seven snapshots or clock periods represented by the seven dashed lines of the left-most portion or systolic processor array portion of FIG. **9**. It will be understood however, that the four-by-four matrix of processors of FIGS. **2**–**9**, are presented herein by way of illustration only. It would be highly preferable to provide many more than four processors in order to be able to compare sequences having a great deal more than just four elements. In fact, it will be seen hereinafter that the integrated circuit (IC) of the present invention provides sixteen such processors. In addition, the architecture of each such IC permits the serial interconnection of the sixteen processors on one chip with the sixteen processors on another chip, so that a large number of such processors can be tied together from chip to chip to provide a long sequence of interconnected processors. In the present invention, up to 512 such processors can be tied together to form a block and up to 8,192 such blocks or 4,194,304 such processors can be effectively interconnected without external software. The IC chip of the present invention, when operating in conjunction with other such chips, can compare sequences as long as 4,194,304 elements without the aid of external software.

The logical operations actually carried out by each element of the systolic processor array of FIGS. **2**–**9** may be better understood by reference to FIG. **10**. In FIG. **10** the computations and parameter generation that occur within the a_2,b_2 processor **11** are shown by way of example. As seen in FIG. **10**, in each such processor there are four subtractors, an adder and three calculators of maximums. The relevant equations are:

$$H_{1,1} = \max\{0, H_{0,0} + s(a_1, b_1), E_{1,1}, F_{1,1}\} \quad H_{1,2} = \max\{0, H_{0,1} + s(a_1, b_2), E_{1,2}, F_{1,2}\}$$
$$E_{1,1} = \max\{H_{1,0} - (u_E + v_E), E_{1,0} - v_E\} \quad E_{1,2} = \max\{H_{1,1} - (u_E + v_E), E_{1,1} - v_E\}$$
$$F_{1,1} = \max\{H_{0,1} - (u_F + v_F), F_{0,1} - v_E\} \quad F_{1,2} = \max\{H_{0,2} - (u_F + v_F), F_{0,2} - v_F\}$$

$$H_{2,1} = \max\{0, H_{1,0} + s(a_2, b_1), E_{2,1}, F_{2,1}\} \quad H_{2,2} = \max\{0, H_{1,1} + s(a_2, b_2), E_{2,2}, F_{2,2}\}$$
$$E_{2,1} = \max\{H_{0,2} - (u_E + v_E), E_{2,0} - v_E\} \quad E_{2,2} = \max\{H_{2,1} - (u_E + v_E), E_{2,1} - v_E\}$$
$$F_{2,1} = \max\{H_{1,1} - (u_F + v_F), F_{1,1} - v_F\} \quad F_{2,2} = \max\{H_{1,2} - (u_F + v_F), F_{1,2} - v_F\}$$

In accordance with these equations, the input parameters for the a_2,b_2 processor comprise: $H_{2,1}$, $E_{2,1}$, $H_{1,2}$, $F_{1,2}$ and $H_{1,1}$. The $H_{2,1}$ parameter is applied to a subtractor to which is also applied the value U_E+V_E, a constant which may be stored within the processor. The parameter $E_{2,1}$ is applied to a subtractor to which is also applied the constant value V_E. $H_{1,2}$ is applied to a subtractor to which is also applied the constant U_F+V_F and the parameter $F_{1,2}$ is applied to a subtractor to which is also provided the value V_F. The parameter $H_{1,1}$ is applied to an adder to which is also supplied a similarity function of a and b_2 which, as previously indicated, is a constant greater than zero if a_2 is equal to b_2 and a constant less than zero for a_2 not equal to b_2.

The output of the first two subtractors, that is the subtractors to which the parameters $H_{2,1}$ and $E_{2,1}$ are applied, respectively, are applied to a maximum value calculator. The output of this maximum value calculator is, by definition, $E_{2,2}$ and the outputs of the other subtractors are applied to a separate maximum value calculator, the output of which is by definition, the parameter $F_{2,2}$. $E_{2,2}$ and $F_{2,2}$ are applied to a third maximum value calculator to which is also applied the output of the adder and a zero signal. The output of this third maximum calculator is by definition $H_{2,2}$ which is the score of the alignment ending at a_2,b_2.

The functional block diagram of a processor of the present invention for performing the subtractions, additions and maximum calculator functions illustrated in FIG. **10**, is shown in FIG. **11**. As seen in FIG. **11** at the upper left hand corner thereof, the input parameters are $F_{i-1,j+1}$, $H_{i,1,J+1}$ and the sequence element b_{j+1}. As also seen in FIG. **11**, there are a plurality of registers, namely a register into which the input parameters are stored for one clock cycle, as well as registers into which parameters generated within the processor of FIG. **11** are stored for one clock cycle. The purpose of these registers, as will be seen hereinafter, is to provide the necessary delays in signal transfer to the adder, subtractors and maximum calculators so that the processor carries out its algorithmic steps in the proper sequence and at the appropriate time and furthermore, so that the various algorithm parameters are available at the appropriate adder, subtractors and maximum calculators when the addition, subtractions and maximum calculations actually occur. More specifically, it will be seen hereinafter that each register of FIG. **11** imparts the appropriate amount of time delay in signal flow through the processor so that the input of any j parameter occurs simultaneously with the output of a j−1 parameter. Thus for example the $F_{i-1,j+1}$ parameter is input to a register **10** which, because of its predetermined delay, outputs simultaneously therewith, the parameter $F_{i-l,j}$. Similarly, the input to register **12**, which is $H_{i-1,j+1}$ occurs substantially simultaneously with the output which is $H_{i-1,j}$. The output of registers **10** and **12** are applied to subtractors **24** and **26**, respectively, to which are also supplied the constants, V and U+V, respectively. The output of register **12** is also applied to a register **16**, the output of which is $H_{i-l,j-l}$, which is applied to an adder **28**. Also applied to adder **28** is a signal indicative of the similarity of lack thereof between a_i and b_j, referred to previously in the algorithm as the function s(a_i,b_j). This similarity value is generated by a similarity table **14**, based upon the a_i stored therein and the b_j input therein, from a character register **22**, the input to which is b_{j+l}.

The output of subtractors **24** and **26** are both applied to a maximum calculator **34**, the output of which by definition is $F_{i,j}$ which is an output signal of the processor of FIG. **11** for use in subsequent processor. The output of maximum calculator **34** is also applied to a maximum calculator **36**. Other inputs to maximum calculator **36**, include the output of the adder **28** and a zero signal. The output of maximum calculator **36** is by definition, the score value signal $H_{i,j}$ which constitutes the principal information desired from the comparison of two sequences ending at $a_i b_j$. The output of maximum calculator **36** is also applied to register **18**, the output of which is thus $H_{i,j+l}$ which is, in turn, applied to the subtractor **30**. Subtractor **30** also receives input U+V. The output of subtractor **30** is applied to maximum calculator **38**, the output of which it will be seen hereinafter is $E_{i,j}$. Parameter $E_{i,j}$ is applied both to the maximum calculator **36** as an input thereto and also to register **20** in the right-most portion of FIG. **11**, as an input to that register. The output of register **20** is thus $E_{i,j+l}$ which is applied to subtractor **32** to which a second input is the constant V. The output of subtractor **32** is also applied to maximum calculator **38** to produce the $E_{i,j}$ parameter.

Thus it will be seen that the architecture depicted in FIG. **11** carries out the various computations of a single processor for comparing two elements of the sequence A and B in accordance with Waterman and Smith Algorithm, including providing the necessary time delay registers, subtractors, adder and maximum calculators to receive the appropriate parameters and to generate the parameters for the subsequent processor which, in turn, computes the same type of information for two sequence characters. It will be understood that the block diagram of FIG. **11** is of a functional nature only, to indicate the treatment of parameters that occur within one processor. However, the actual implementation of a processor is illustrated in FIGS. **12** and **13** taken in combination. Reference will now be made to FIGS. **12** and **13** for a more detailed understanding of the actual architecture of a processor of the present invention.

The principal differences between the functional block diagram of FIG. **11** and the actual block diagram of FIGS. **12** and **13** are the following: Subtractors of FIG. **11** are actually adders with one of the inputs inverted prior to application to the adder, so that the equivalent operation is a subtraction. Another distinction is that maximum calculators only accept two values, consequently, there are more maximum calculators in the actual implementation of FIGS. **12** and **13** than there are in the functional block diagram of FIG. **11**. Still another distinction between the functional block diagram and the actual block diagram of the processor of the present invention, is the fact that the latter must incorporate signals, which in addition to the parameter signal previously discussed in conjunction with FIG. **11**, must be input and output to permit proper interface from processor to processor, as well as to facilitate appropriate timing of operation. In addition, there are at least two additional capabilities in the actual block diagram of FIGS. **12** and **13** as compared to the functional block diagram of FIG. **11**. Specifically, in the actual block diagram, an additional maximum calculator is provided which compares the value of $H_{i,j}$ to a preselected threshold value permitting the logic of the actual process or to ignore any scores which fall below the preset threshold value. In addition, the actual architecture of the processor of the present invention; provides an additional signal path through all processors in a block, as well as an additional maximum calculator in each processor of a block, for comparing the maximum value of each processor with a maximum value of every other processor and propagating a signal which indicates when the maximum value of this particular processor is in fact the highest $H_{i,j}$ of all of the processors in the block.

Furthermore, it will be seen that in the block diagram of the actual processor of the present invention, the similarity table of the functional block diagram of FIG. **11**, comprises a random access memory in which the data bus of the chip brings the character data into the similarity RAM, where it can be either written into the RAM or read out of the RAM and b_j is applied to the addressed terminal of the RAM. In addition, the similarity RAM is provided with a chip select signal and a read/write signal as well as a data output which provides the similarity function output from a look-up table in the similarity RAM. A table address signal (TA) is also applied to the address terminal of the similarity RAM through a multiplexer as a high order five byte address for the similarity RAM table.

Other signals shown used in the block diagram of FIGS. **12** and **13** include location input an d location output, which provide an indication of the location of the current maximum value in the block of processors. Maximum enable input and maximum enable output signals enable the comparison of the locally generated maximum value with the input maximum value in each processor. A pipeline enable signal is used and its state indicates when the $F_{i,j}$ and $H_{i,j}$ values are valid data so that these values can be saved. Synchronous clear signals are also input and output to each processor. The synchronous clear input resets the $H_{i,j}$ value so that the maximum value does not exceed the threshold value and the synchronous clear output, under certain conditions, namely when the maximum value generated is greater than the threshold value, sets the H value of the next processor to zero. However, it will be understood that except for the timing control and logic control, the use of threshold and maximum value transfer from processor to processor, the functional effect of the actual architecture depicted in FIGS. **12** and **13** is identical to that explained previously in conjunction with FIG. **11**.

The manner in which the processors are integrated in a chip of the present invention and the other electronics associated with each circuit chip of the present invention will now be discussed in conjunction with FIGS. **14** and **15** which together comprise a functional block diagram of the biological information signal processor. Referring therefore now to FIGS. **14** and **15**, it will be seen that each integrated circuit chip of the present invention comprises sixteen of the aforementioned processors connected in a serial array configuration in which a plurality of the aforementioned signals used within each processor, may be transferred from processor to processor on this particular chip, as well as to processors on other chips to which the present chip is connected. As previously indicated, without the aid of external software, up to 512 processors may be interconnected to form what is called a block and up to 8,192 such blocks may be interconnected without external software to handle one sequence.

All of the other elements of a signal processor of the present invention are designed to provide the requisite information, timing and signal flow input to and generated by the processors. Thus for example in the upper left-hand corner of FIG. **14**, there is shown a plurality of registers which are loaded from a data bus to provide the U+V and V constants which are needed in all of the processors and which represent various values of a linear function, representing scoring penalties for insertions and deletions in the Smith and Waterman Algorithm.

Also provided in the integrated circuit chip of the present invention is a control logic device which controls the application of timing and logic signals to the processors, as well as signals which enable block and sequence counters, the outputs of which are stored in a maximum memory device shown in the upper right-hand corner of FIG. **15**. The control logic also controls pause input and output signals which are used under certain conditions for temporarily halting the operation of the processors, such as when maximum memory is filled. The processor of the present invention also provides means for loading a threshold into the chip and for utilizing this threshold for enabling storage of maximums into memory only when the threshold is exceeded. The threshold registers are shown in the upper left-hand corner of FIG. **15**. There is a preload threshold register which receives its input from the data bus and a sequence threshold register which receives its input from the character port when the chip is to be loaded with a query sequence threshold. Also provided is an adder which adds the sequence threshold and the preload threshold to provide what is referred to as a real threshold against which the scores of the respective processors are compared in a threshold comparator. A pair of counters is also provided, namely a block counter and a sequence counter. These counters enable the maximum memory to correlate the maximum score value with the sequence and the user defined block. A physical representation of the layout of the integrated circuit chip of the present invention is shown in FIG. **16**.

The sixteen processors are arranged in a serial array terminating in a pipeline register. The device in the upper left-hand corner of FIG. **16** is a control block which comprises the control logic, counters and registers previously described in conjunction with FIGS. **14** and **15**.

The interface between integrated circuit chips of the present invention may be best understood by referring to FIGS. **17** and **18** which provide an exemplary dependence graph for 34 processors on three separate chips, the latter being shown on the right side of FIG. **18**. Each chip provides 16 processors and a pipeline register. In the dependence graph the pipeline registers are shown as rectangles which merely delay the operation between the last processor of one chip and the first processor of the next chip.

The dependence graph of FIGS. **17** and **18** is generally a larger matrix version of the graphs of FIGS. **1**–**9**, except that it includes a sufficient number of processors to demonstrate the “block edge” behavior based upon a minimum block size of 16 elements. This “block edge” behavior is designed to prevent maximum score buffer overflow by resetting “H” values in the a_{16}, b_{16} processor, the a_{32}, b_{32} processor, etc. Only the “H” values which exceed the previously noted threshold and which are output in the horizontal and diagonal directions to the adjacent processors are reset.

This "block edge" resetting procedure constitutes a modification to the Smith and Waterman algorithm which is unique to the present invention. It is implemented in each chip by means of a boundary set zero enable signal (ENZ flag) in the control logic of FIG. **14**. If this bit is set and the output H value is greater than the threshold value, then the SISP chip will reset the internally fedback E value and the $H_{i-l,j-l}$ value of the next SISP chip.

It will now be understood that what has been disclosed herein comprises a sequence information signal processing integrated circuit chip designed to perform high speed calculation based upon the dynamic programming algorithm defined by Waterman and Smith. This chip is designed to be a building block of a linear systolic array. The performance of the systolic array can be increased by connecting additional such chips to the array. Each such chip provides sixteen processor elements, a 128 word similarity table in each processor element, user definable query threshold and preload threshold and block maximum value and location calculation and buffering. The chip provides the equivalent of about 400,000 transistors or 100,000 gates. All numerical data are input in 16 bit, two's compliment format, and result in comparison scores ranging from +32,767 to −32,768. A control logic device in the chip performs the control and sequencing of the processor elements. It contains threshold logic for sequence and timing, as well as enabling counters for sequence and block counts.

Those having ordinary skill in the arts relevant to the present invention will now, as a result of applicants' teaching herein, perceive various modifications and additions which may be made to the invention. By way of example, the particular algorithm as well as the architecture designed to perform the algorithm processes, may be altered while still providing a useful and accurate measure of the homology of two or more data sequences or subsequences thereof. Accordingly, all such modifications or additions are deemed to be within the scope of the invention which is to be limited only by the claims appended hereto.

We claim:

1. An electronic circuit for use in comparing two sequences of elements to determine which alignment of the sequences produces the greatest similarity between the sequences, the circuit comprising:

multiple processors connected in series and individually configured to:

compare an element in one of the sequences with successive elements in the other sequence,

for each pair of elements compared, generate a scoring parameter indicating which of a plurality of segments ending at those elements produces the greatest degree of similarity between the sequences,

use the scoring parameter to generate another scoring parameter for the next pair of elements compared, and

deliver the scoring parameter to another processor in the series for use in generating another scoring parameter for another pair of elements,

threshold circuitry configured to determine which processor produces the scoring parameter with the highest value, and

alignment circuitry configured to determine which alignment of the sequences is associated with the scoring parameter having the highest value.

2. The electronic circuit of claim **1**, wherein each processor is configured to deliver the scoring parameter to the next processor in the series.

3. The electronic circuit of claim **1**, wherein all of the processors, except a final processor in the series, are configured to deliver the scoring parameter to another processor.

4. The electronic circuit of claim **1**, further comprising adjustment circuitry configured to adjust the scoring parameters when two segments differ because one or more deletions appear in one of the segments.

5. The electronic circuit of claim **4**, wherein the adjustment circuitry is configured to adjust the scoring parameters by a value that depends on which of the segments contains the deletion.

6. The electronic circuit of claim **1**, further comprising adjustment circuitry configured to adjust the scoring parameters when two segments differ because one or more insertions appear in one of the segments.

7. The electronic circuit of claim **6**, wherein the adjustment circuitry is configured to adjust the scoring parameters by a value that depends on which of the segments contains the insertions.

8. The electronic circuit of claim **1**, wherein the processors are configured to generate scoring parameters concurrently and each concurrently generated scoring parameter represents a comparison of segments ending at different elements in the sequences.

9. The electronic circuit of claim **1**, wherein the sequences are represented as $A=a_1, a_2, \ldots, a_n$, and $B=b_1, b_2, \ldots, b_m$, and wherein each processor is configured to generate the scoring parameter associated with any two elements a_i and b_j, respectively, according to the following equations:

$$H_{i,j}=\max\{0, H_{i-1,j-1}+s(a_i,b_j), E_{i,j},F_{i,j}\}$$

$$\text{where } E_{i,j}=\max\{H_{i,j-1}-(U_E,+V_E), E_{i,j-1}-V_E\}$$

$$F_{i,1}=\max\{H_{i-1,j}-(U_F+V_F), F_{i-1,j}-V_F\}$$

$$H_{i,0}=H_{0,j}=0$$

$$s(a_i,b_j)>0 \text{ if } a_i\neq b_j$$

$$s(a_i,b_j)<0 \text{ if } a_ib_j$$

and U_E, V_E, U_F and V_F are selected constants.

10. The electronic circuit of claim **9**, wherein each processor is configured to generate all three values $H_{i,j}$, $E_{i,j}$, and $F_{i,j}$ for two elements a_i, b_j.

11. The electronic circuit of claim **9**, wherein each processor is configured to receive the values $H_{i-l,j}$ and $F_{i-l,j}$ from a preceding processor in the series.

12. The electronic circuit of claim **9**, further comprising a memory device that stores a table from which the values for $s(a_i,b_j)$ are derived.

13. The electronic circuit of claim **1**, wherein each processor stores a single element from one of the sequences and compares this element to all other elements in the other sequence.

14. The electronic circuit of claim **13**, wherein each processor generates a scoring parameter for each comparison of the stored element with another element.

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