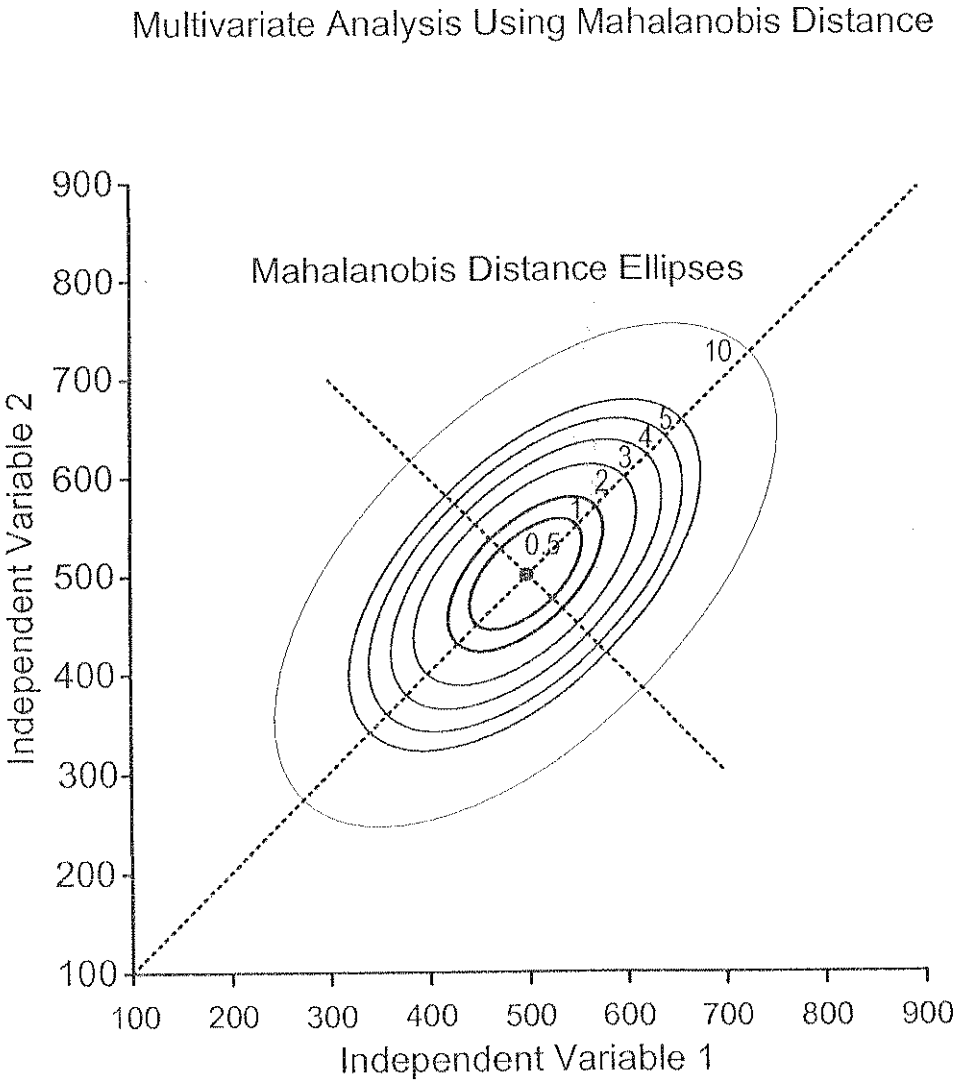


$$d(\vec{x}, \vec{y}) = \sqrt{(\vec{x} - \vec{y})^T \Sigma^{-1} (\vec{x} - \vec{y})}$$

FIG. 1

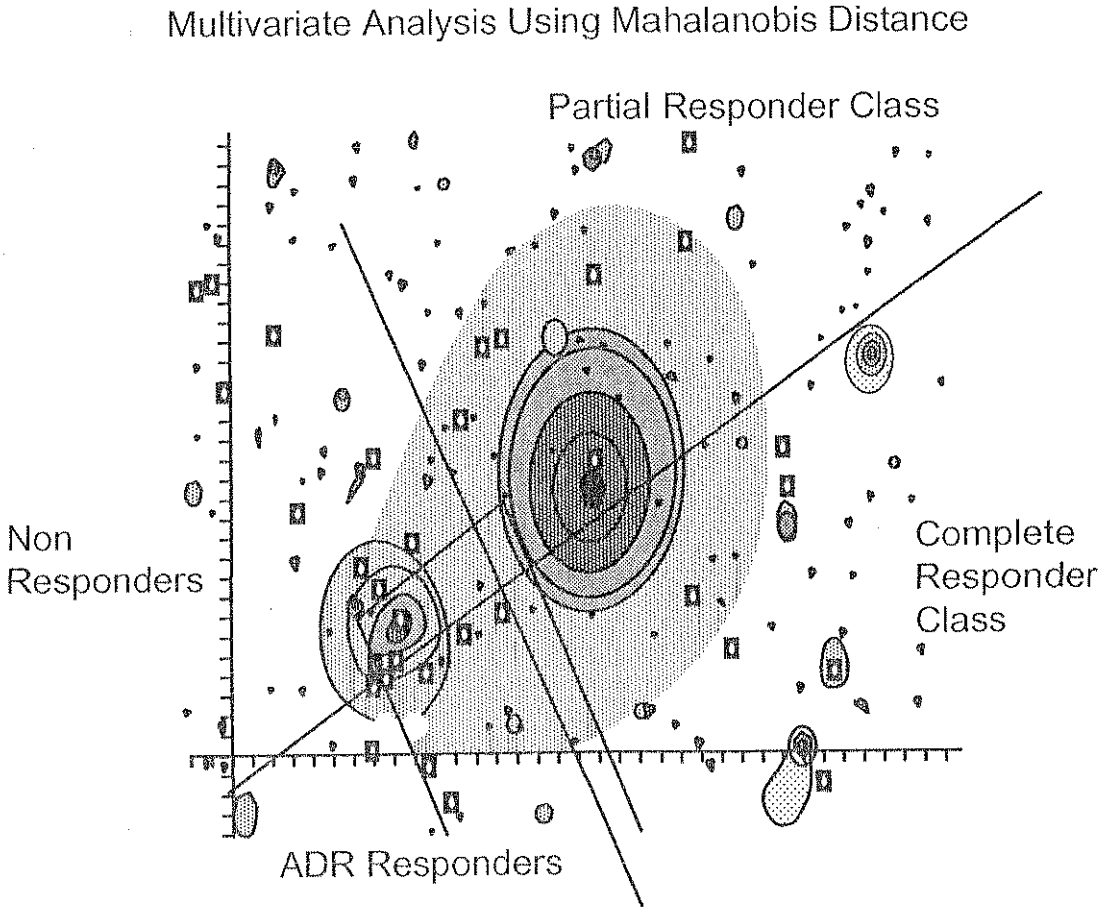

Multivariate Analysis Using Mahalanobis Distance
Partial Responder Class
Non
Responders
Complete
Responder
Class
ADR Responders

FIG. 2

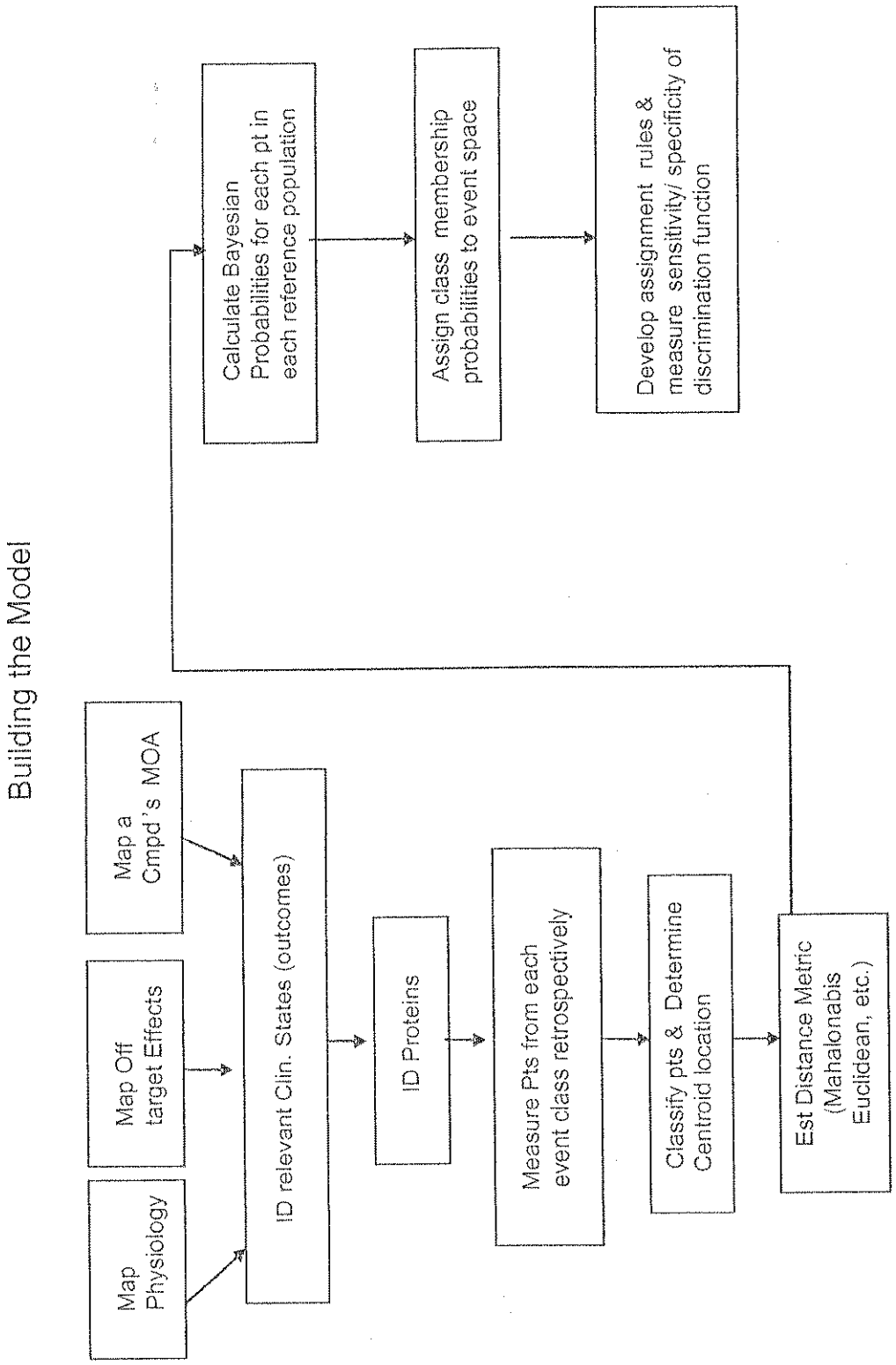

Building the Model
Map Physiology
Map Off target Effects
Map a Cmpd's MOA
ID relevant Clin. States (outcomes)
ID Proteins
Measure Pts from each event class retrospectively
Classify pts & Determine Centroid location
Est Distance Metric (Mahalonabis Euclidean, etc.)
Calculate Bayesian Probabilities for each pt in each reference population
Assign class membership probabilities to event space
Develop assignment rules & measure sensitivity/ specificity of discrimination function

FIG. 3

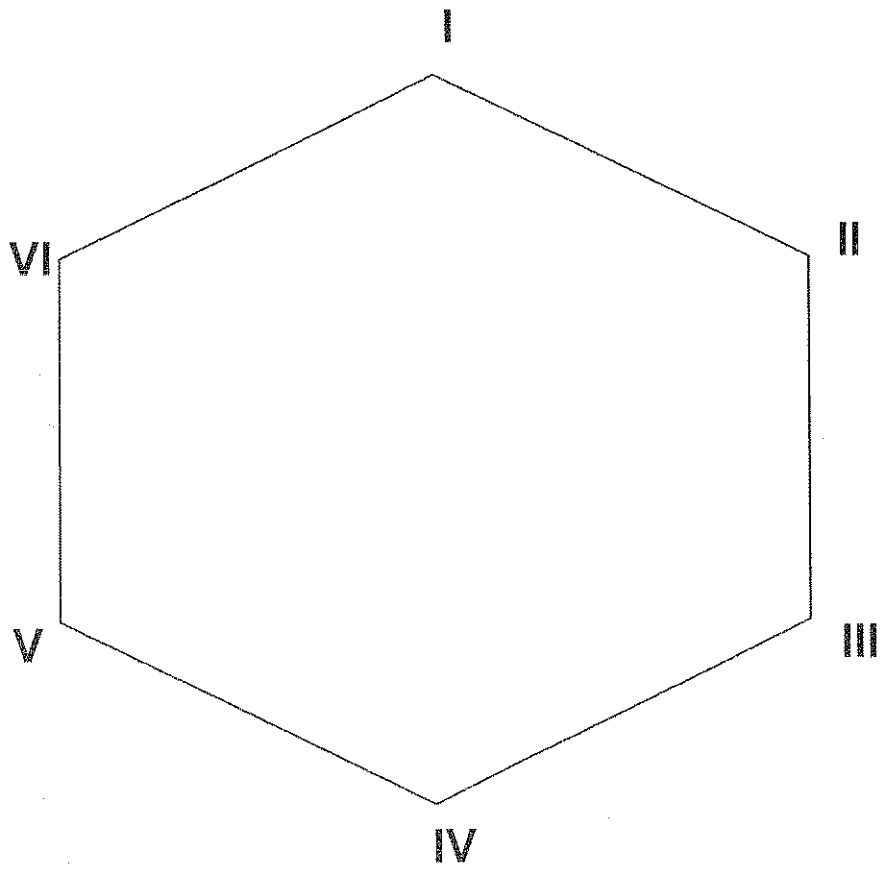

Establish the Patient Classes and Probability Space Boundaries
I
II
III
IV
V
VI

FIG. 4

Establish the Time
Dependent Trajectory in the Geometry of the Response Space

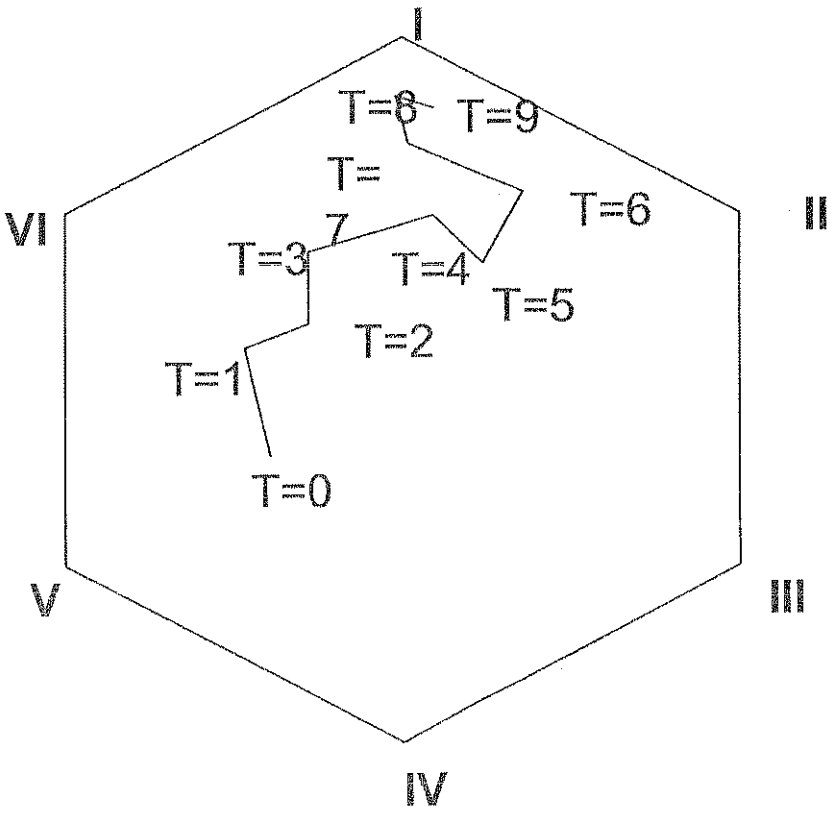


FIG. 5

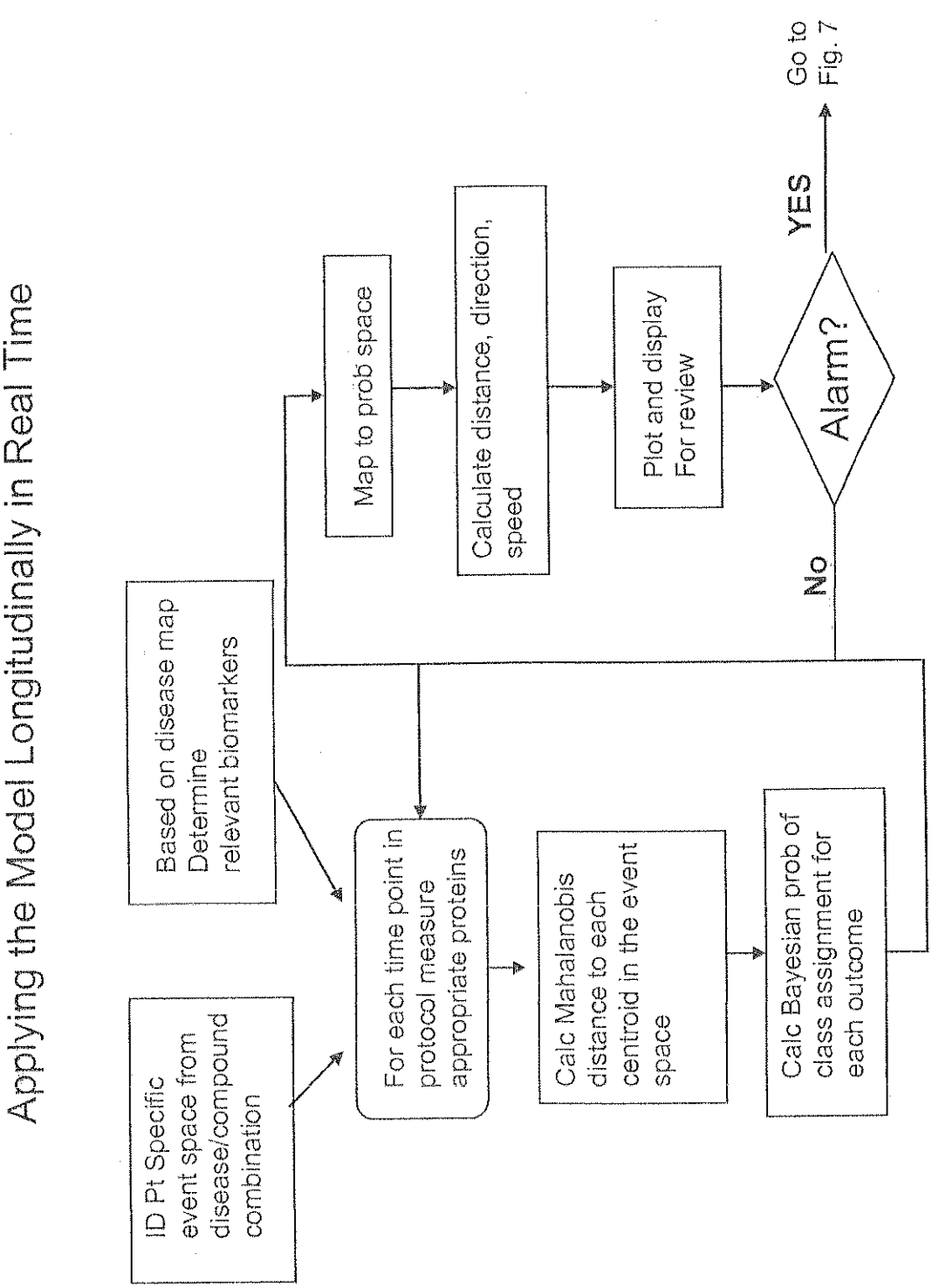

Applying the Model Longitudinally in Real Time
ID Pt Specific event space from disease/compound combination
Based on disease map Determine relevant biomarkers
For each time point in protocol measure appropriate proteins
Map to prob space
Calculate distance, direction, speed
Calc Mahalanobis distance to each centroid in the event space
Calc Bayesian prob of class assignment for each outcome
Plot and display For review
Alarm?
YES
No
Go to Fig. 7

FIG. 6

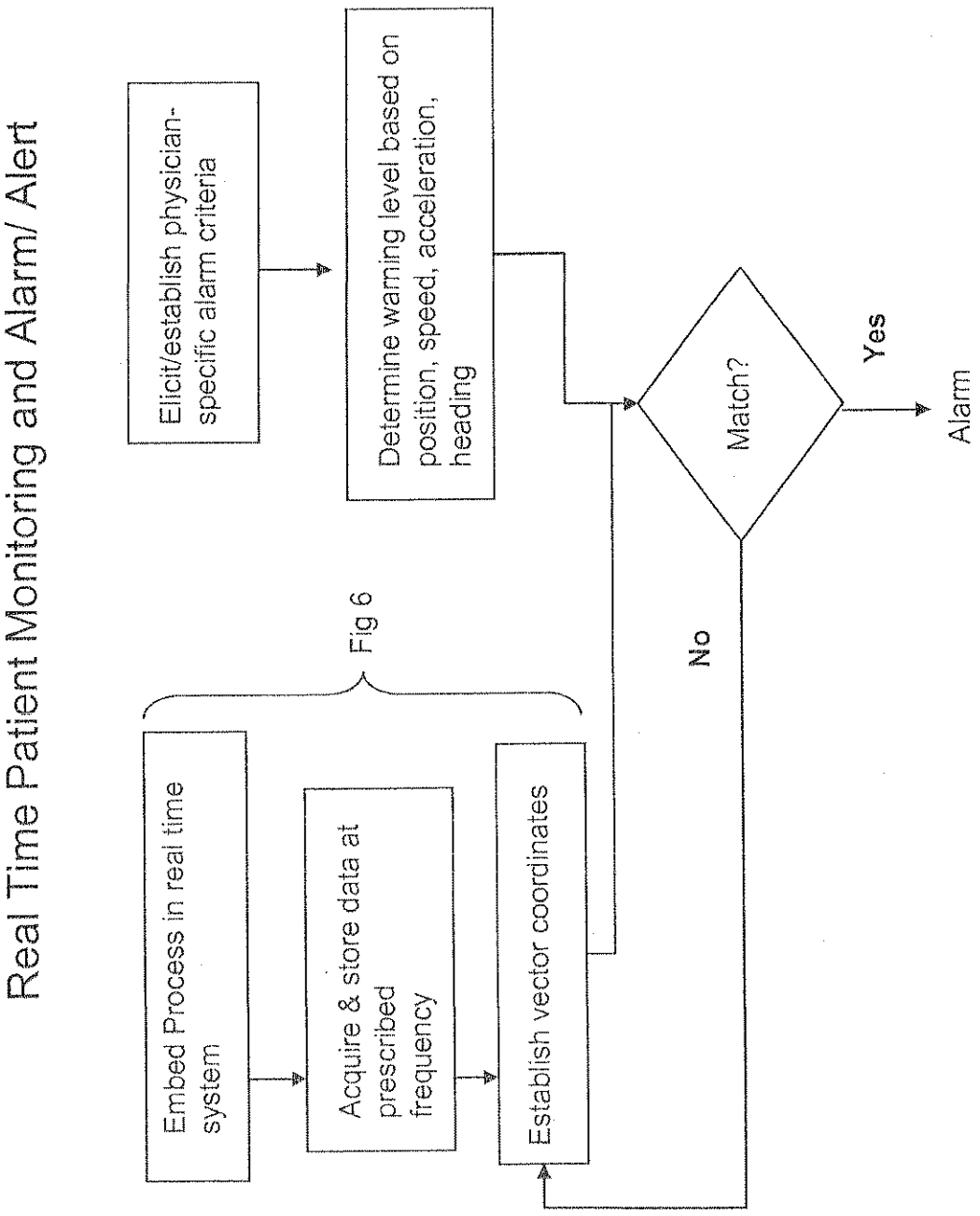

Real Time Patient Monitoring and Alarm/ Alert
Embed Process in real time system
Acquire & store data at prescribed frequency
Establish vector coordinates
Fig 6
Elicit/establish physician-specific alarm criteria
Determine warning level based on position, speed, acceleration, heading
Match?
Yes
Alarm
No

FIG. 7

Establish the Time Dependent Trajectory in the Geometry of the Response Space

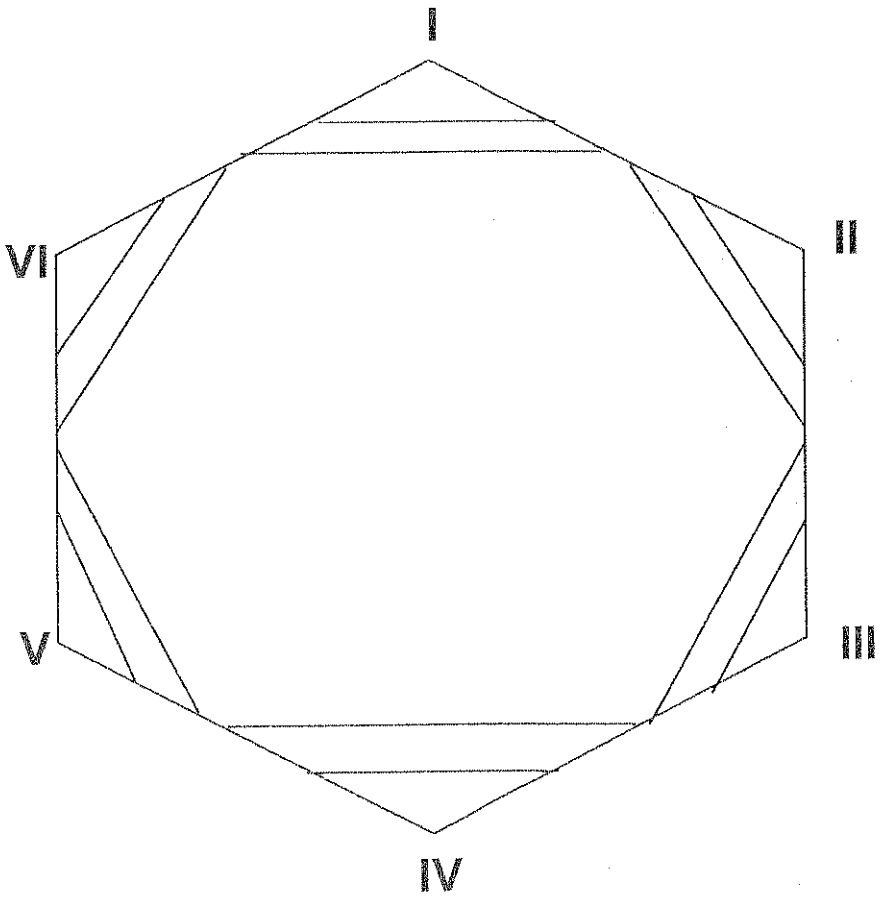


FIG. 8

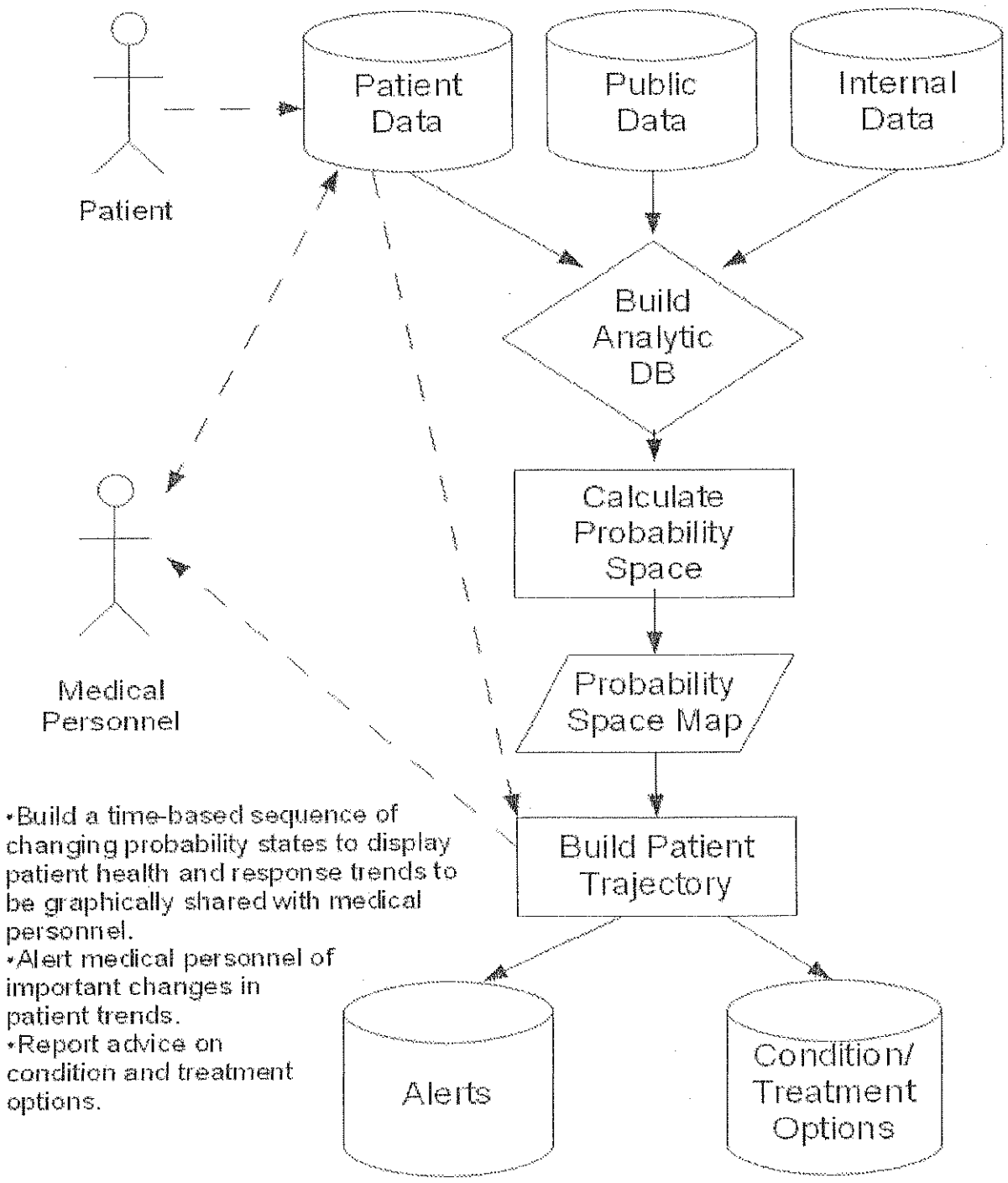

Patient
Patient Data
Public Data
Internal Data
Build Analytic DB
Calculate Probability Space
Probability Space Map
Medical Personnel
•Build a time-based sequence of changing probability states to display patient health and response trends to be graphically shared with medical personnel.
•Alert medical personnel of important changes in patient trends.
•Report advice on condition and treatment options.
Build Patient Trajectory
Alerts
Condition/ Treatment Options

FIG. 9

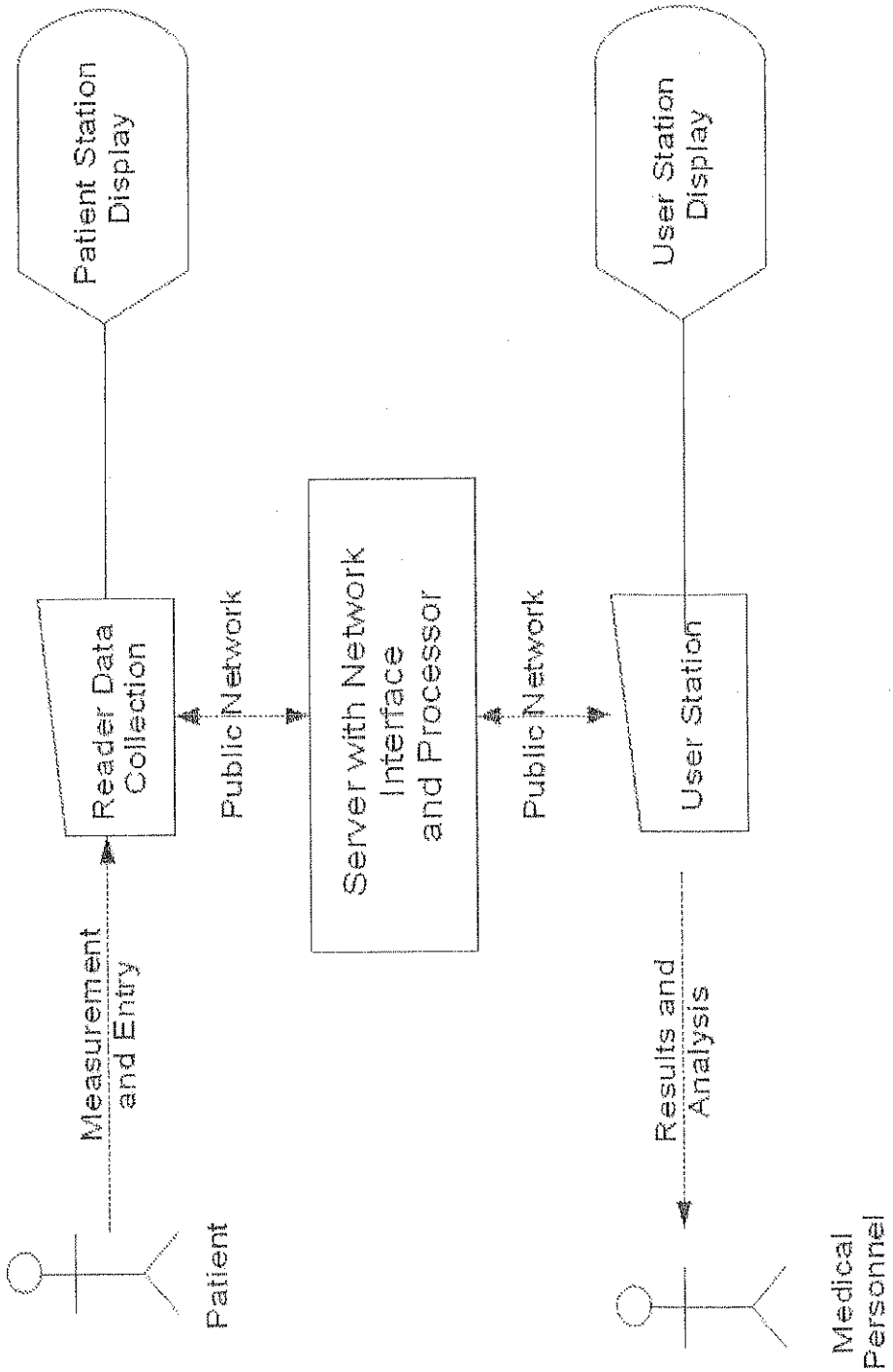

Patient Station Display
User Station Display
Reader Data Collection
Public Network
Server with Network Interface and Processor
Public Network
User Station
Measurement and Entry
Results and Analysis
Patient
Medical Personnel

FIG. 10

Turn disease-specific data into clinically relevant and actionable information.

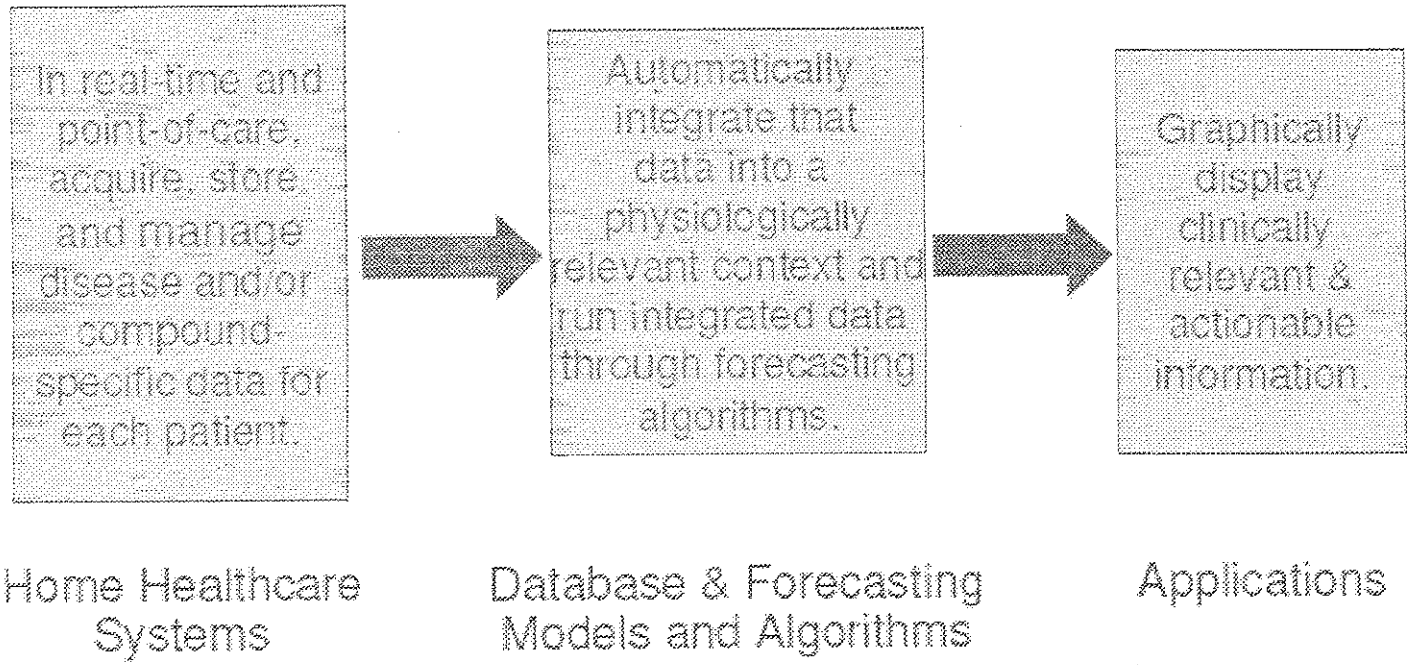


FIG. 11

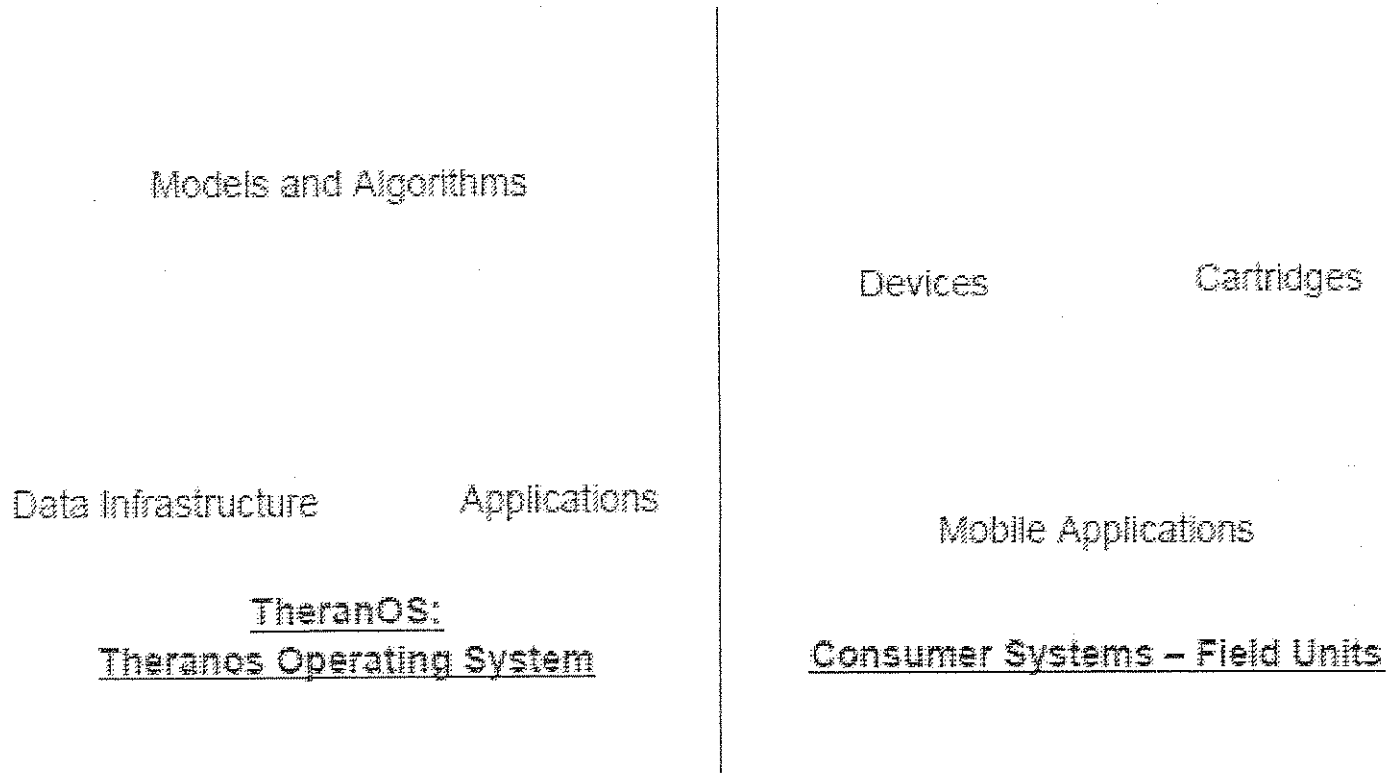

Models and Algorithms
Devices
Cartridges
Data Infrastructure
Applications
Mobile Applications
TheranOS:
Theranos Operating System
Consumer Systems – Field Units

FIG. 12

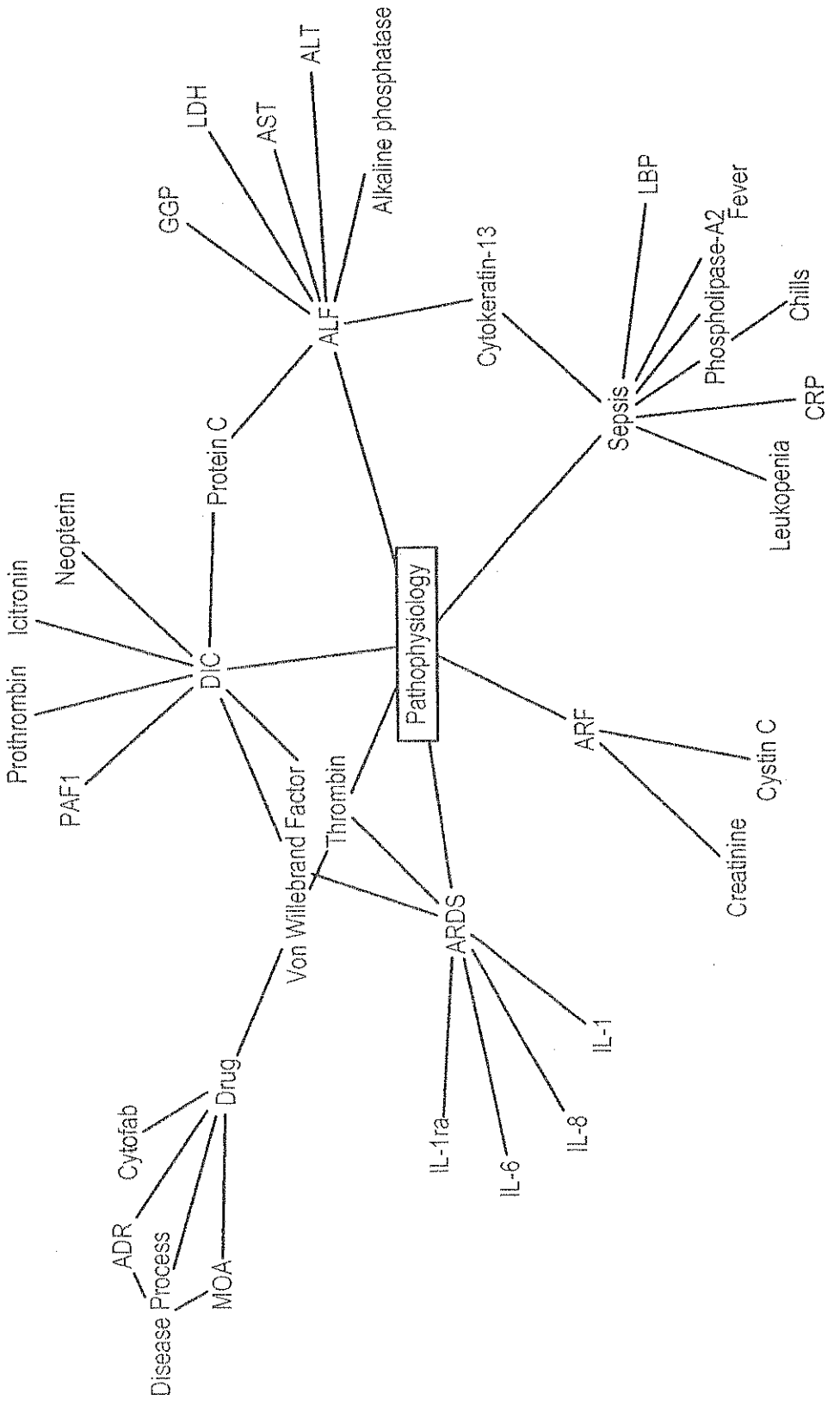

Pathophysiology
DIC
Prothrombin
Icitronin
Neopterin
PAF1
Protein C
ALF
GGP
LDH
AST
ALT
Alkaline phosphatase
Sepsis
Cytokeratin-13
LBP
Phospholipase-A2
Fever
Chills
CRP
Leukopenia
ARF
Cystin C
Creatinine
Thrombin
Von Willebrand Factor
ARDS
IL-1ra
IL-6
IL-8
IL-1
Drug
Cytofab
ADR
Process
MOA
Disease

FIG. 13

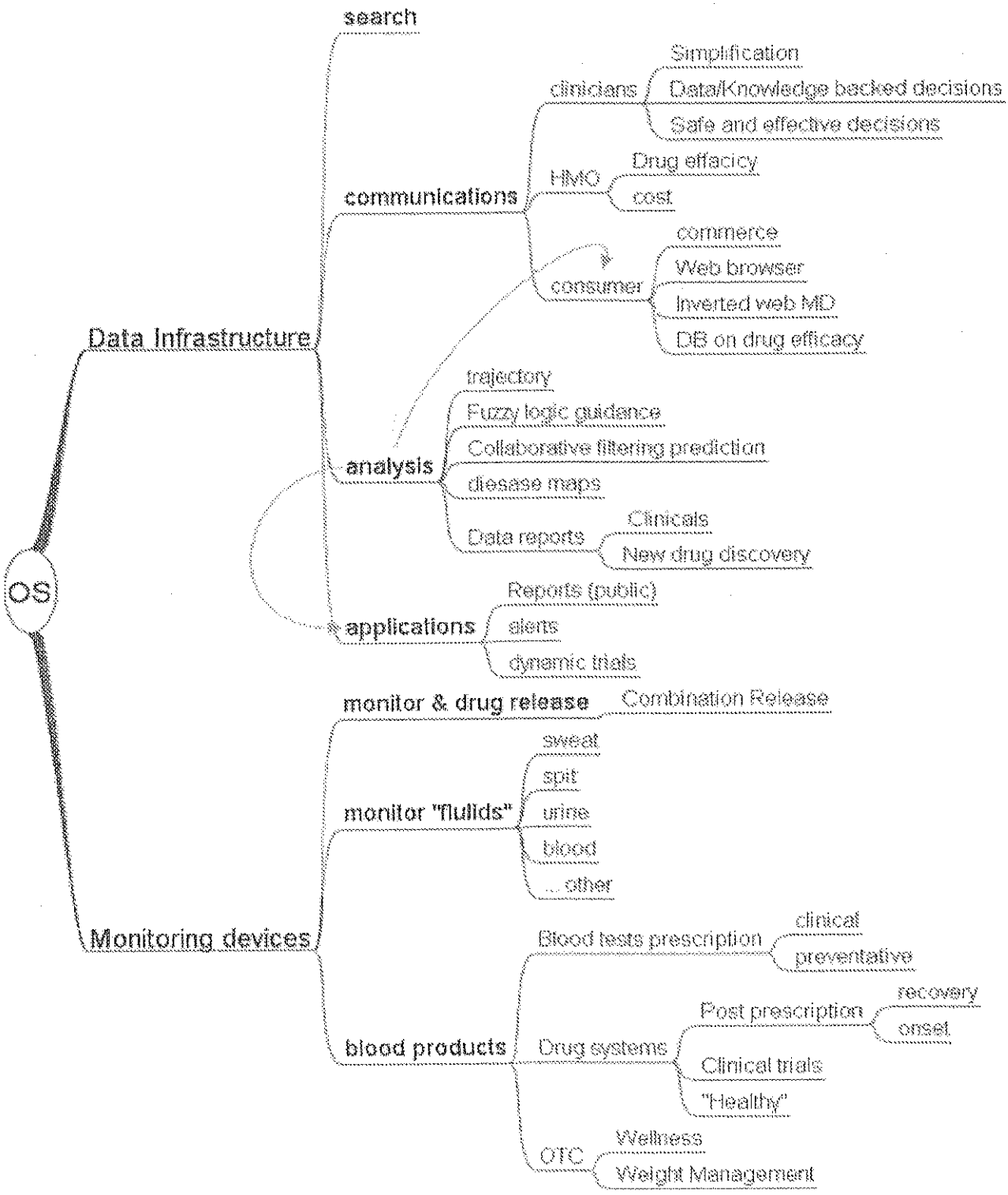

OS
Data Infrastructure
search
communications
clinicians
Simplification
Data/Knowledge backed decisions
Safe and effective decisions
HMO
Drug efficacy
cost
consumer
commerce
Web browser
Inverted web MD
DB on drug efficacy
analysis
trajectory
Fuzzy logic guidance
Collaborative filtering prediction
disease maps
Data reports
Clinicals
New drug discovery
applications
Reports (public)
alerts
dynamic trials
Monitoring devices
monitor & drug release
Combination Release
monitor "fluids"
sweat
spit
urine
blood
... other
blood products
Blood tests prescription
clinical
preventative
Drug systems
Post prescription
recovery
onset
Clinical trials
"Healthy"
OTC
Wellness
Weight Management

FIG. 14

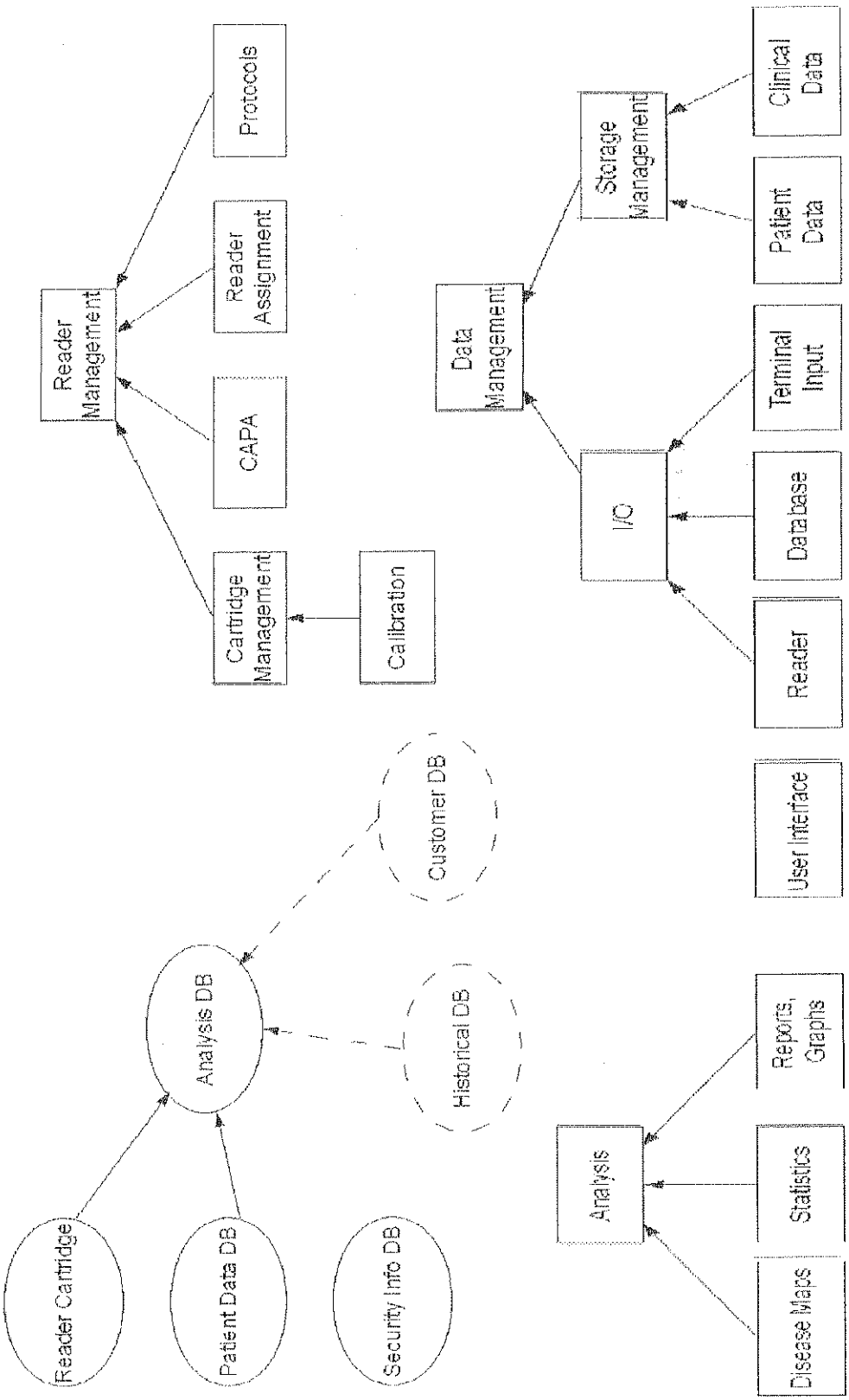

Reader Management
Protocols
Reader Assignment
CAPA
Cartridge Management
Calibration
Data Management
Storage Management
Clinical Data
Patient Data
I/O
Terminal Input
Database
Reader
User Interface
Customer DB
Analysis DB
Historical DB
Reader Cartridge
Patient Data DB
Security Info DB
Analysis
Reports, Graphs
Statistics
Disease Maps

FIG. 15

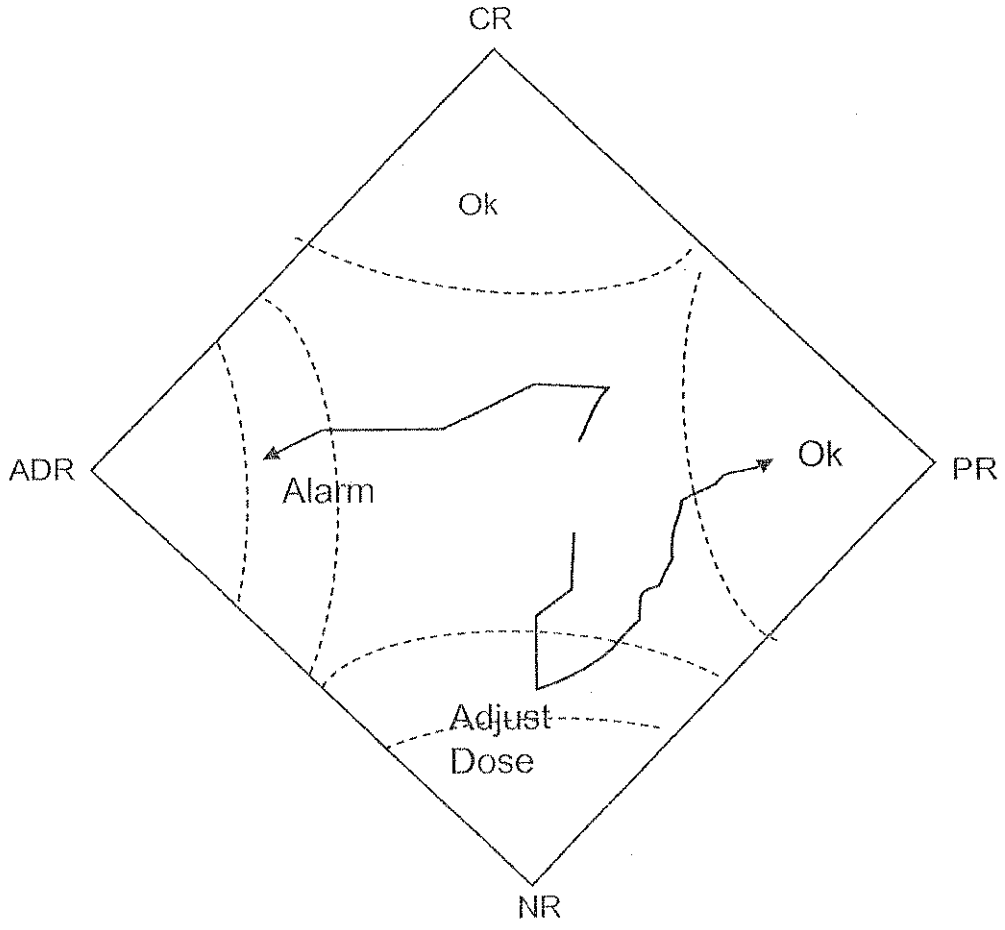

Probability Space Map Prostate Cancer and Anti-Angiogenesis
CR
Ok
ADR
Alarm
Ok
PR
Adjust
Dose
NR

FIG. 16

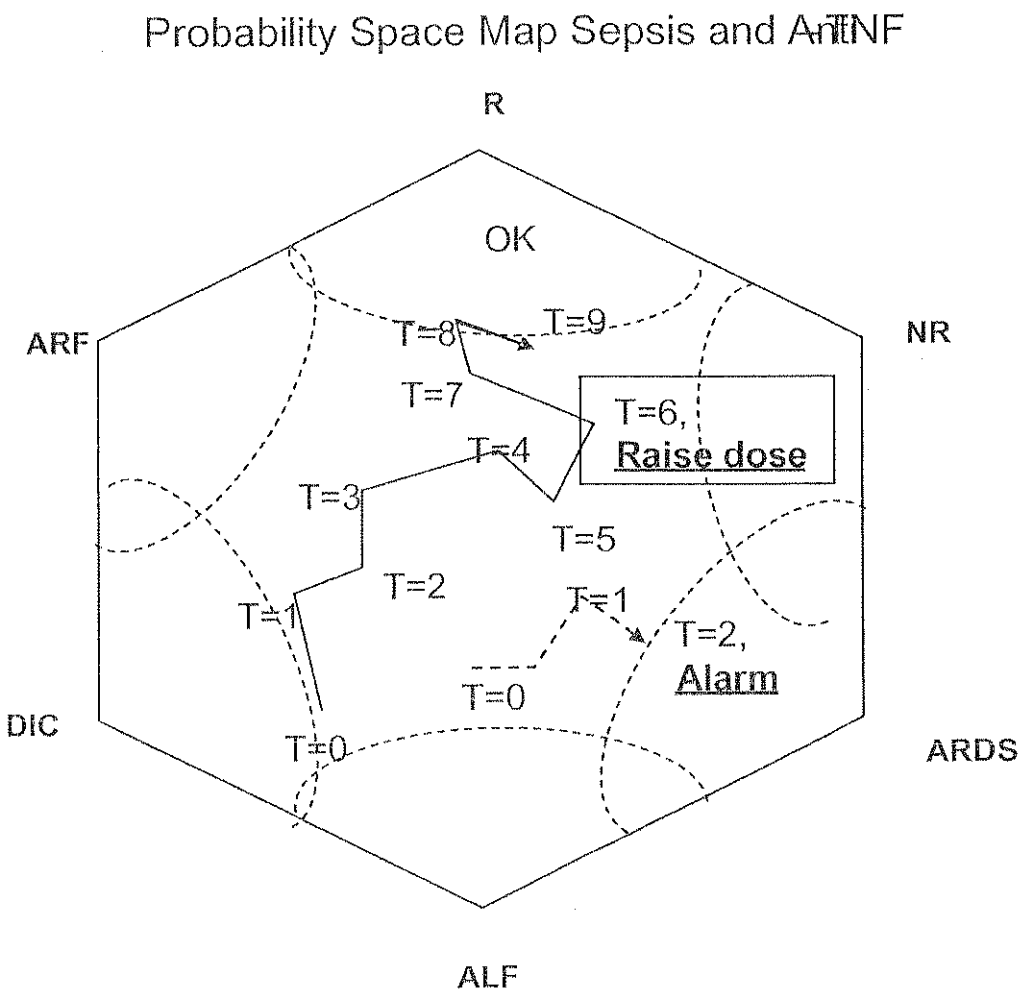

Probability Space Map Sepsis and Anti-TNF
R
OK
ARF
NR
T=8
T=9
T=7
T=6,
Raise dose
T=4
T=3
T=5
T=2
T=1
T=1
T=2,
Alarm
T=0
DIC
T=0
ARDS
ALF

FIG. 17

Probability Space Map Diabetes & Insulin Sensitization

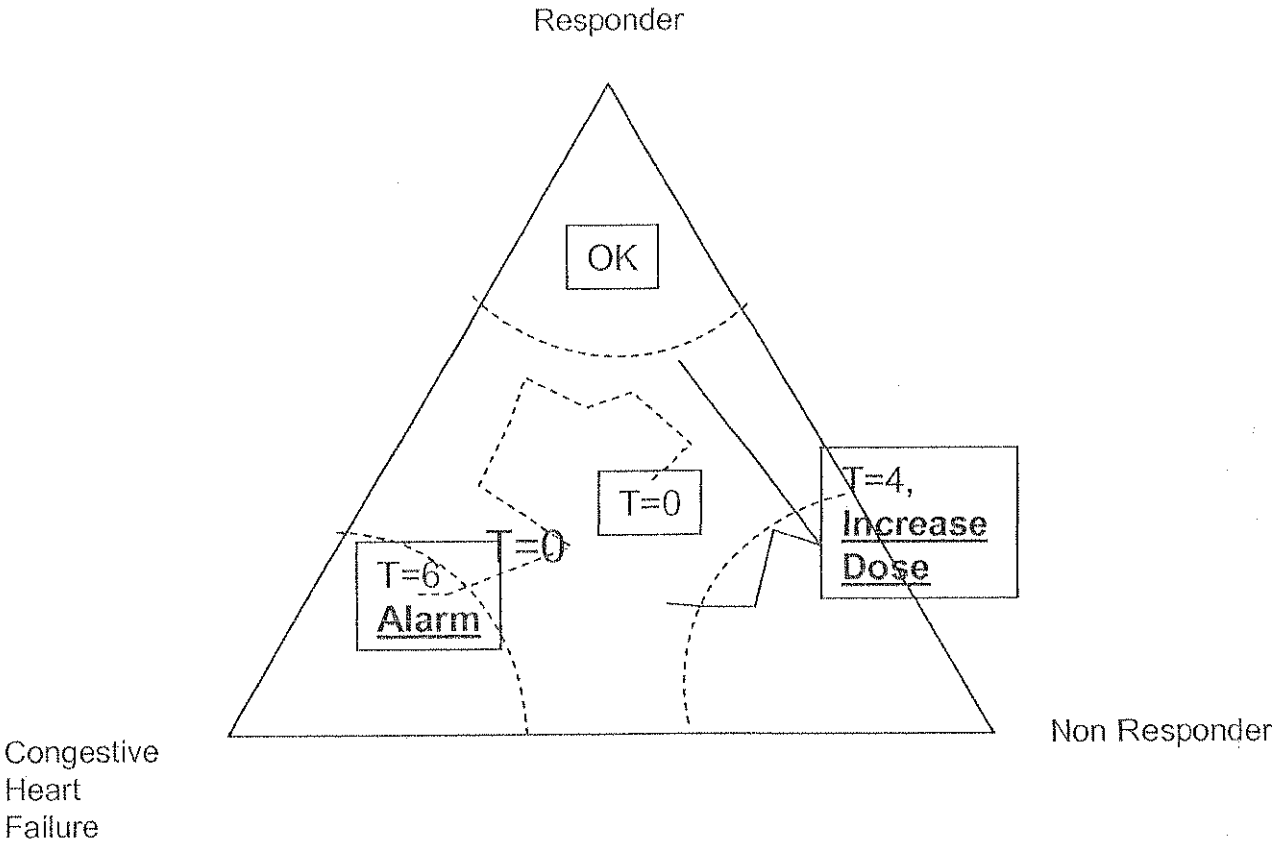


FIG. 18

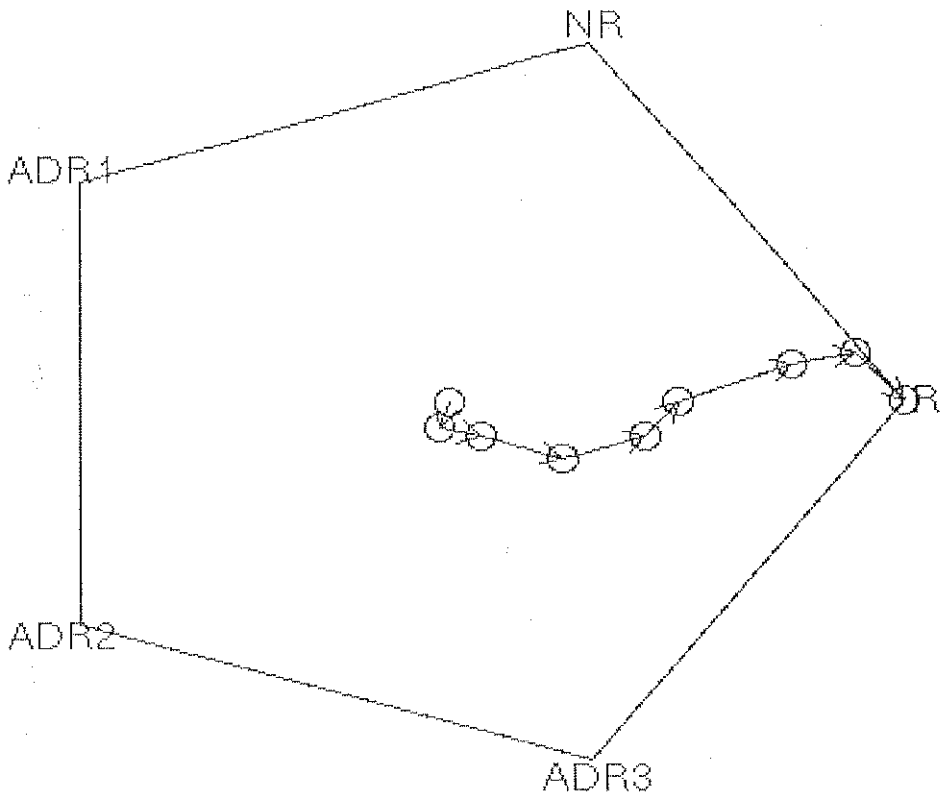


FIG. 19

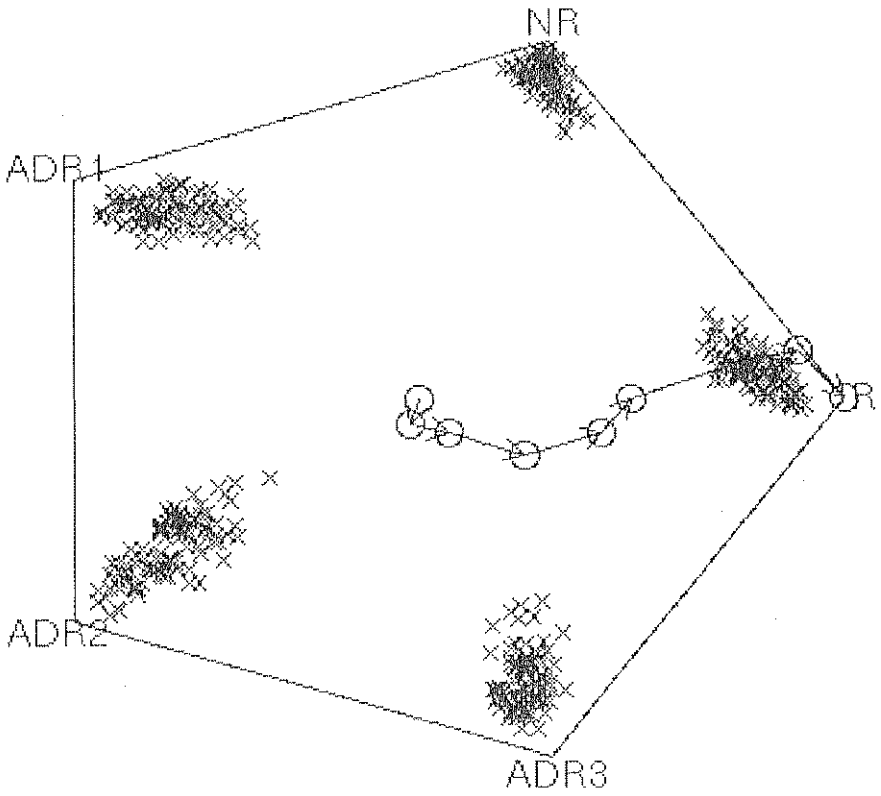
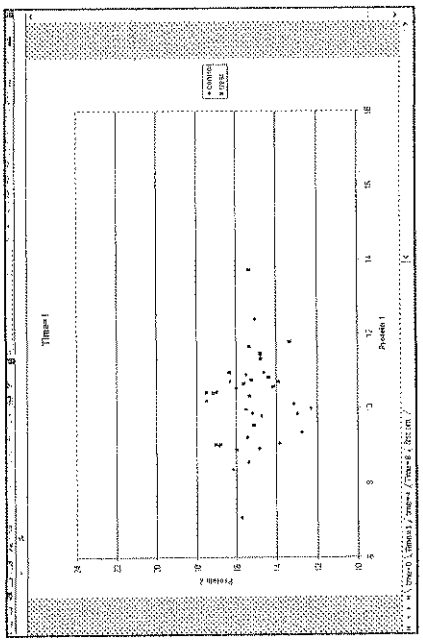
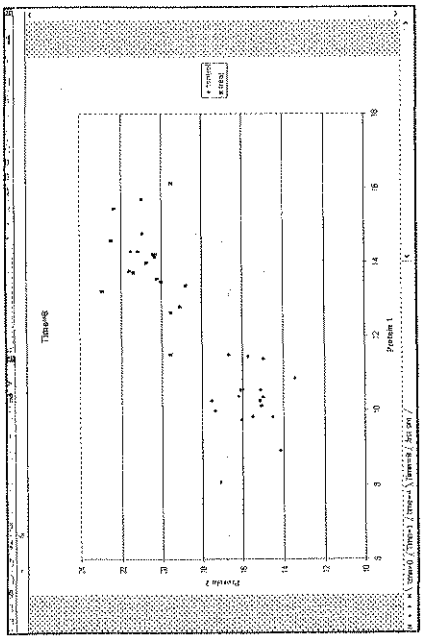
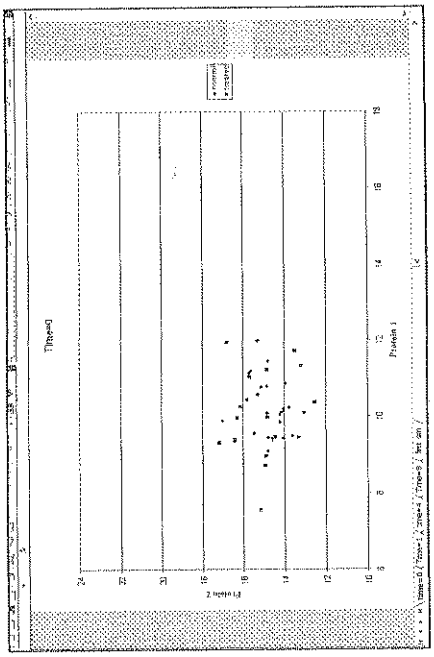


FIG. 20







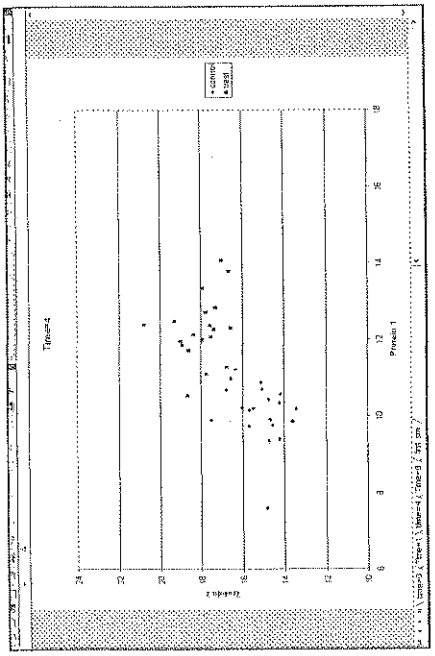


FIG. 21

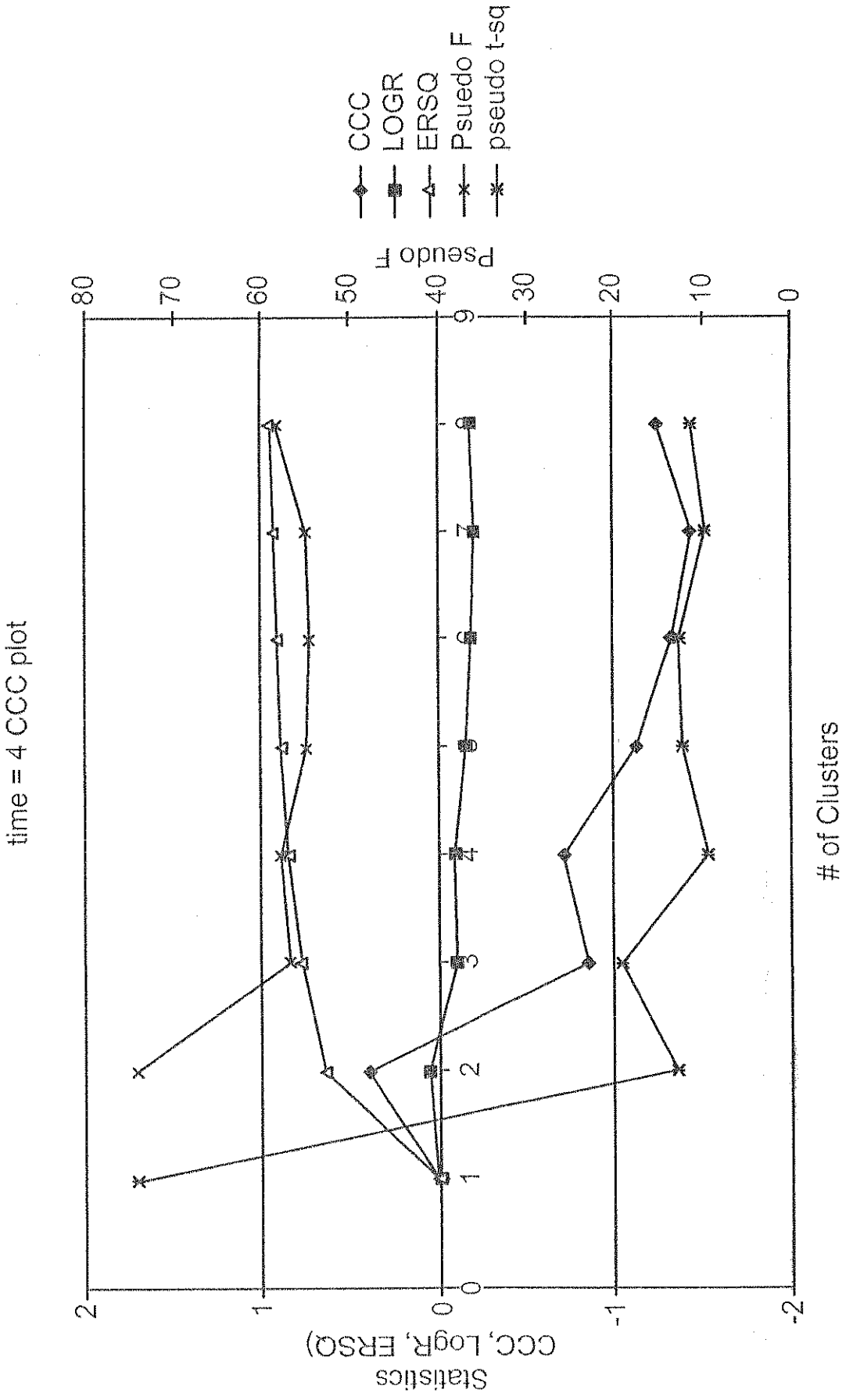

time = 4 CCC plot
CCC
LOGR
ERSQ
Psuedo F
pseudo t-sq
Pseudo F
80
70
60
50
40
30
20
10
0
9
7
6
4
3
2
1
0
2
1
0
-1
-2
Statistics
CCC, LogR, ERSQ)
# of Clusters

FIG. 22

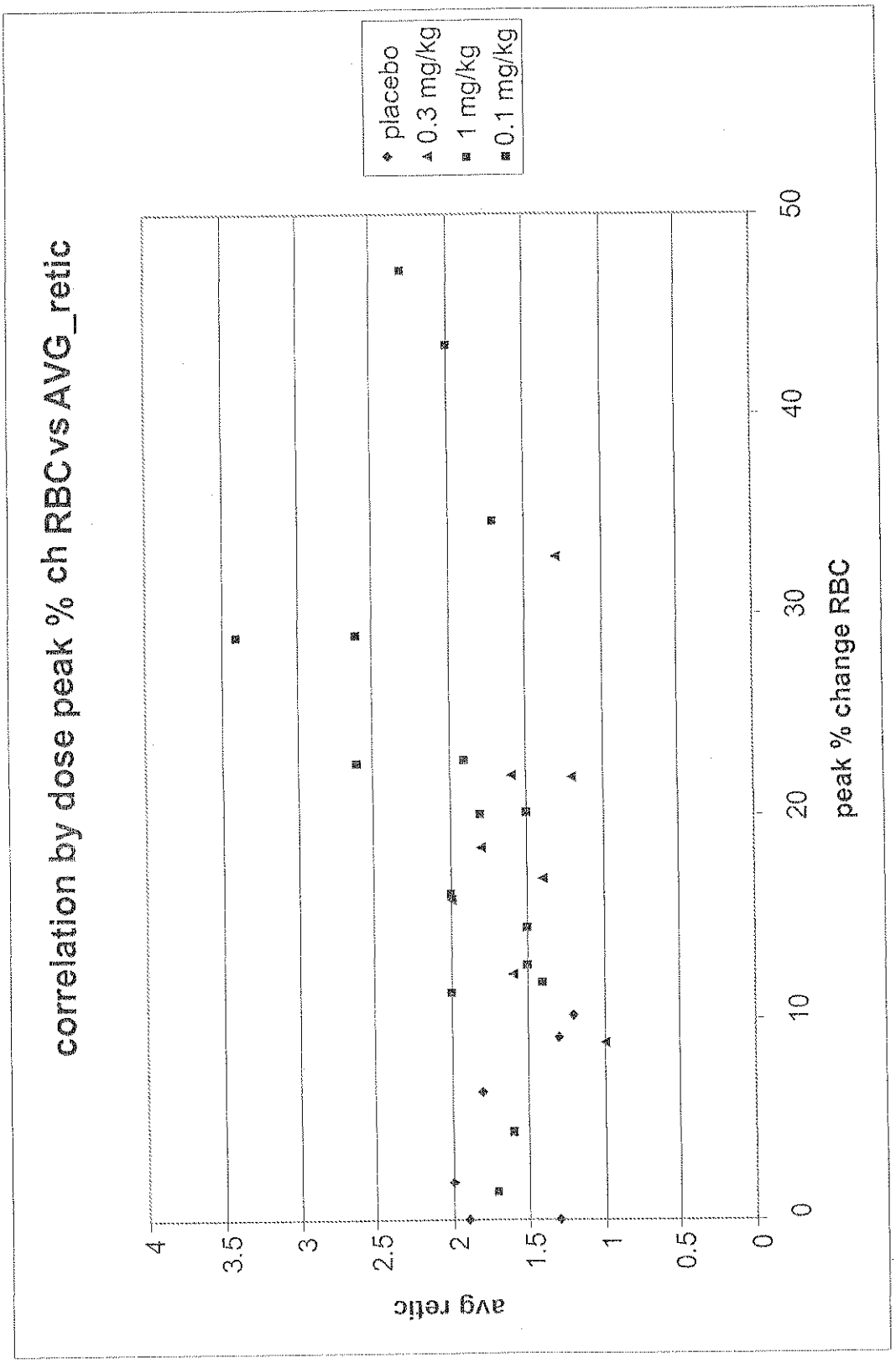

correlation by dose peak % ch RBC vs AVG_retic
placebo
0.3 mg/kg
1 mg/kg
0.1 mg/kg
avg retic
peak % change RBC
0
0.5
1
1.5
2
2.5
3
3.5
4
0
10
20
30
40
50

FIG. 23

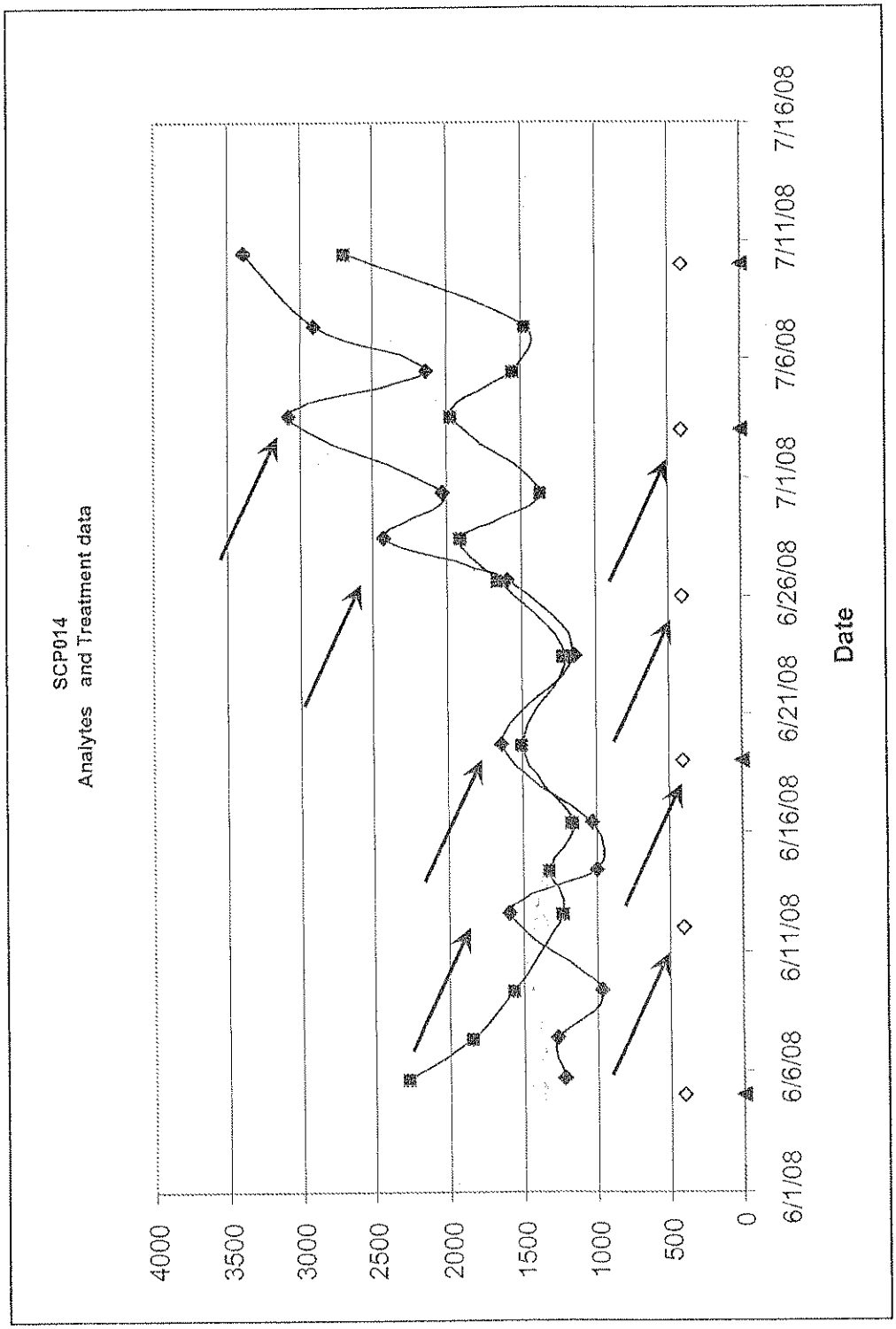

SCP014
Analytes and Treatment data
4000
3500
3000
2500
2000
1500
1000
500
0
6/1/08
6/6/08
6/11/08
6/16/08
6/21/08
6/26/08
7/1/08
7/6/08
7/11/08
7/16/08
Date

FIG. 24

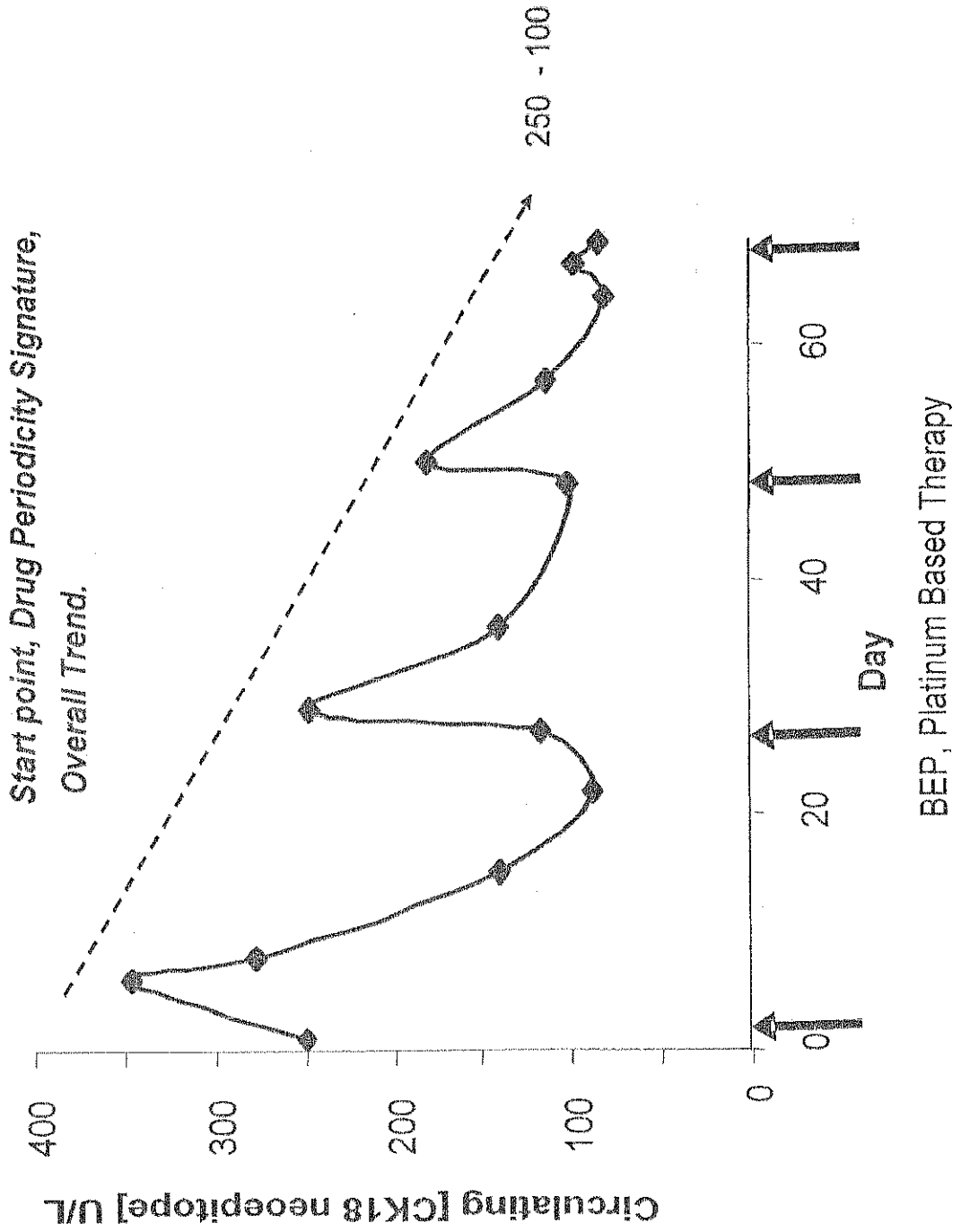

Start point, Drug Periodicity Signature,
Overall Trend.
250 - 100
Circulating [CK18 neoepitope] U/L
400
300
200
100
0
0
20
40
60
Day
BEP, Platinum Based Therapy

FIG. 25

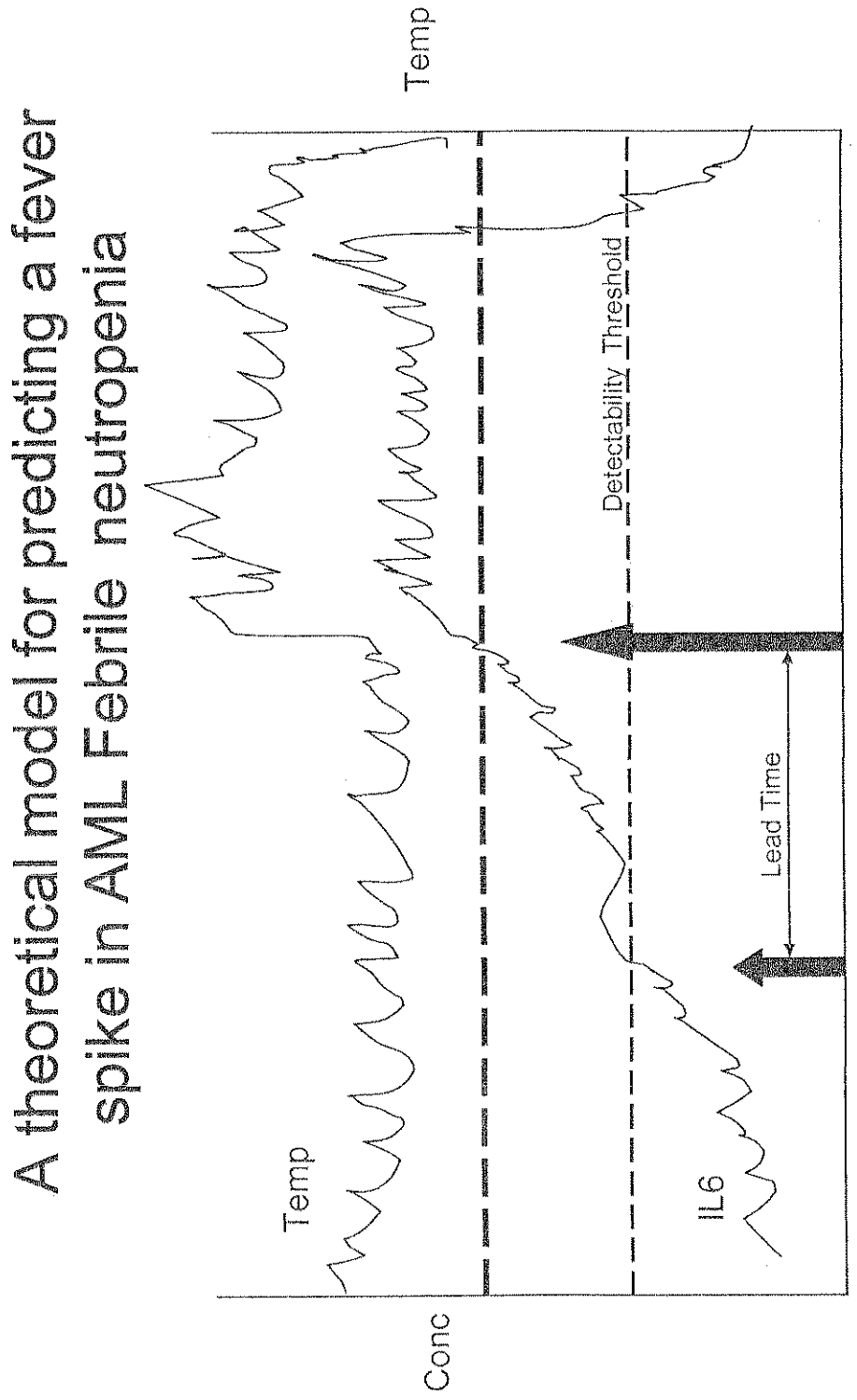

A theoretical model for predicting a fever spike in AML Febrile neutropenia
Temp
Temp
Detectability Threshold
Lead Time
IL6
Conc
Time

FIG. 26

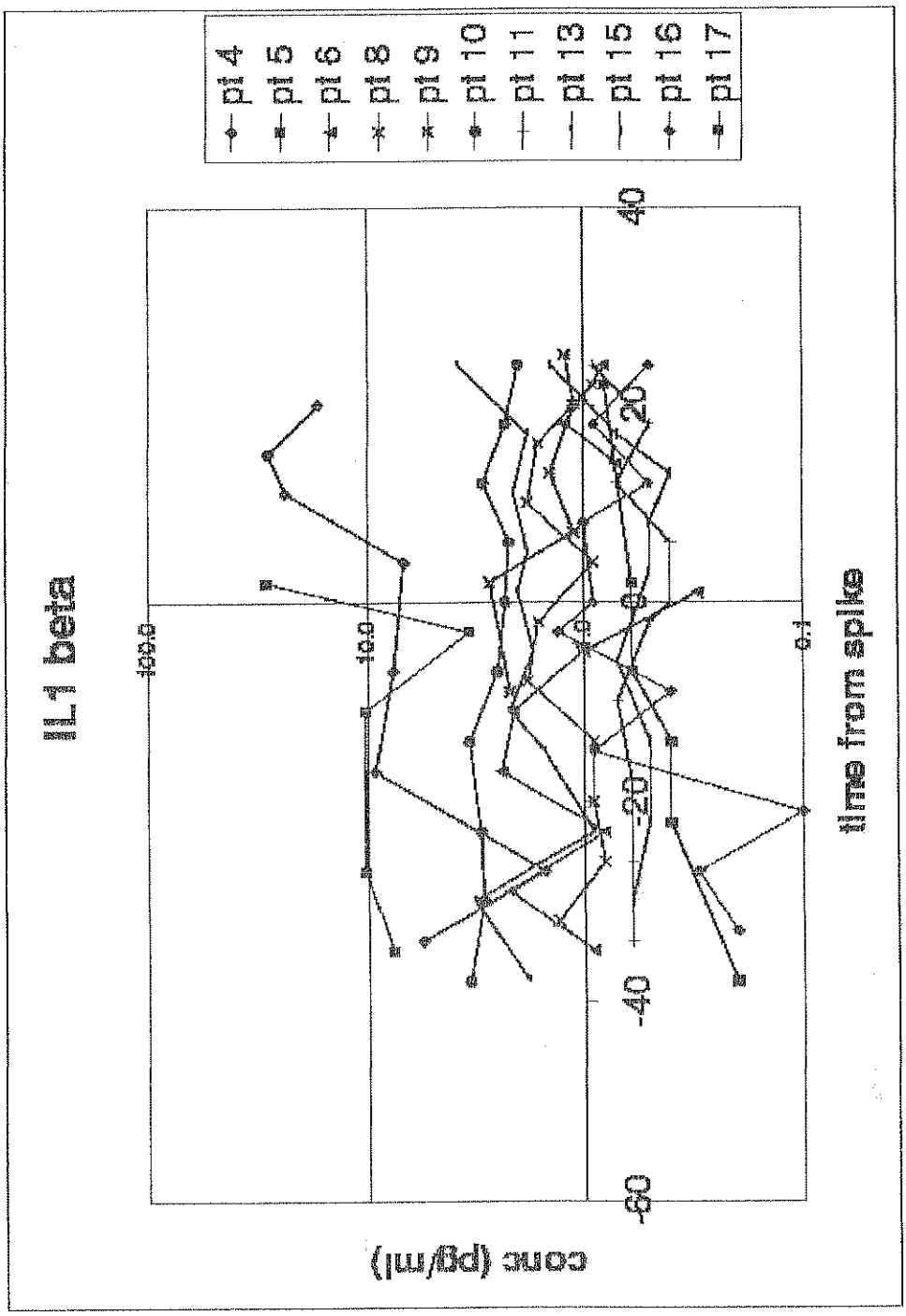

IL1 beta
conc (pg/ml)
100.0
10.0
1.0
0.1
40
20
0
-20
-40
-60
time from spike
pt 4
pt 5
pt 6
pt 8
pt 9
pt 10
pt 11
pt 13
pt 15
pt 16
pt 17

FIG. 27

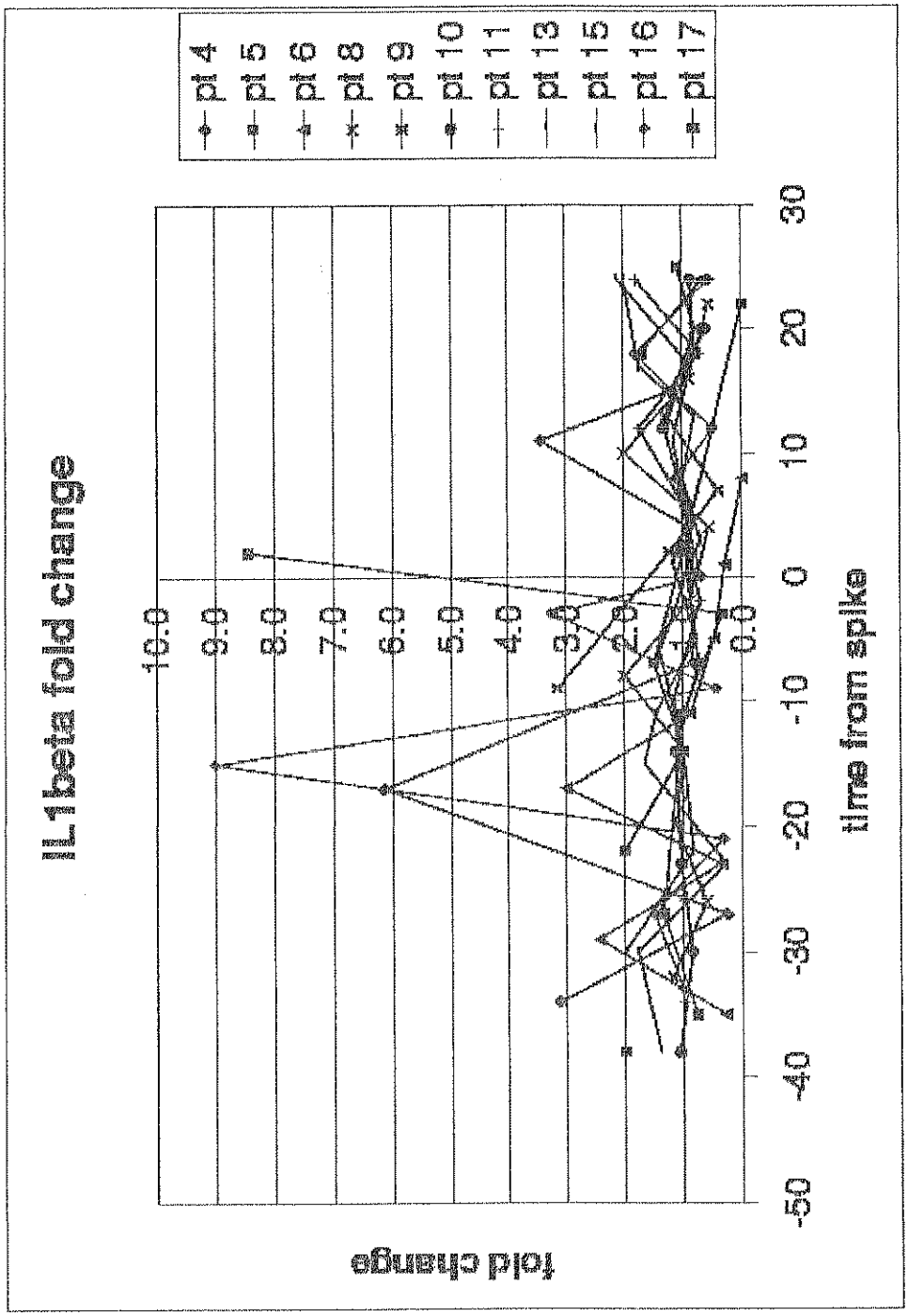

IL1beta fold change
pt 4
pt 5
pt 6
pt 8
pt 9
pt 10
pt 11
pt 13
pt 15
pt 16
pt 17
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
fold change
30
20
10
0
-10
-20
-30
-40
-50
time from spike

FIG. 28

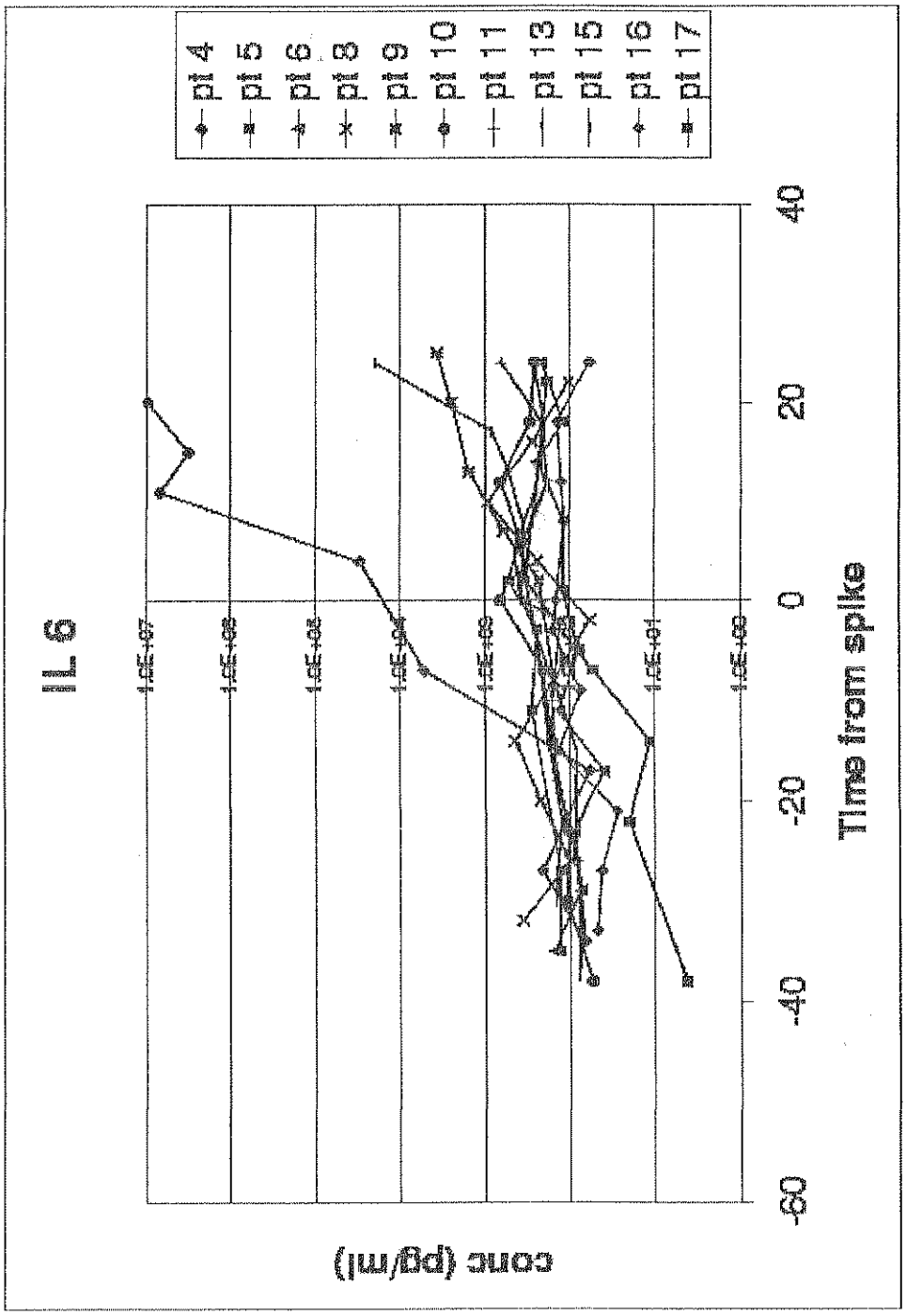

IL 6
conc (pg/ml)
1.0E+07
1.0E+06
1.0E+05
1.0E+04
1.0E+03
1.0E+02
1.0E+01
1.0E+00
-60
-40
-20
0
20
40
Time from spike
pt 4
pt 5
pt 6
pt 8
pt 9
pt 10
pt 11
pt 13
pt 15
pt 16
pt 17

FIG. 29

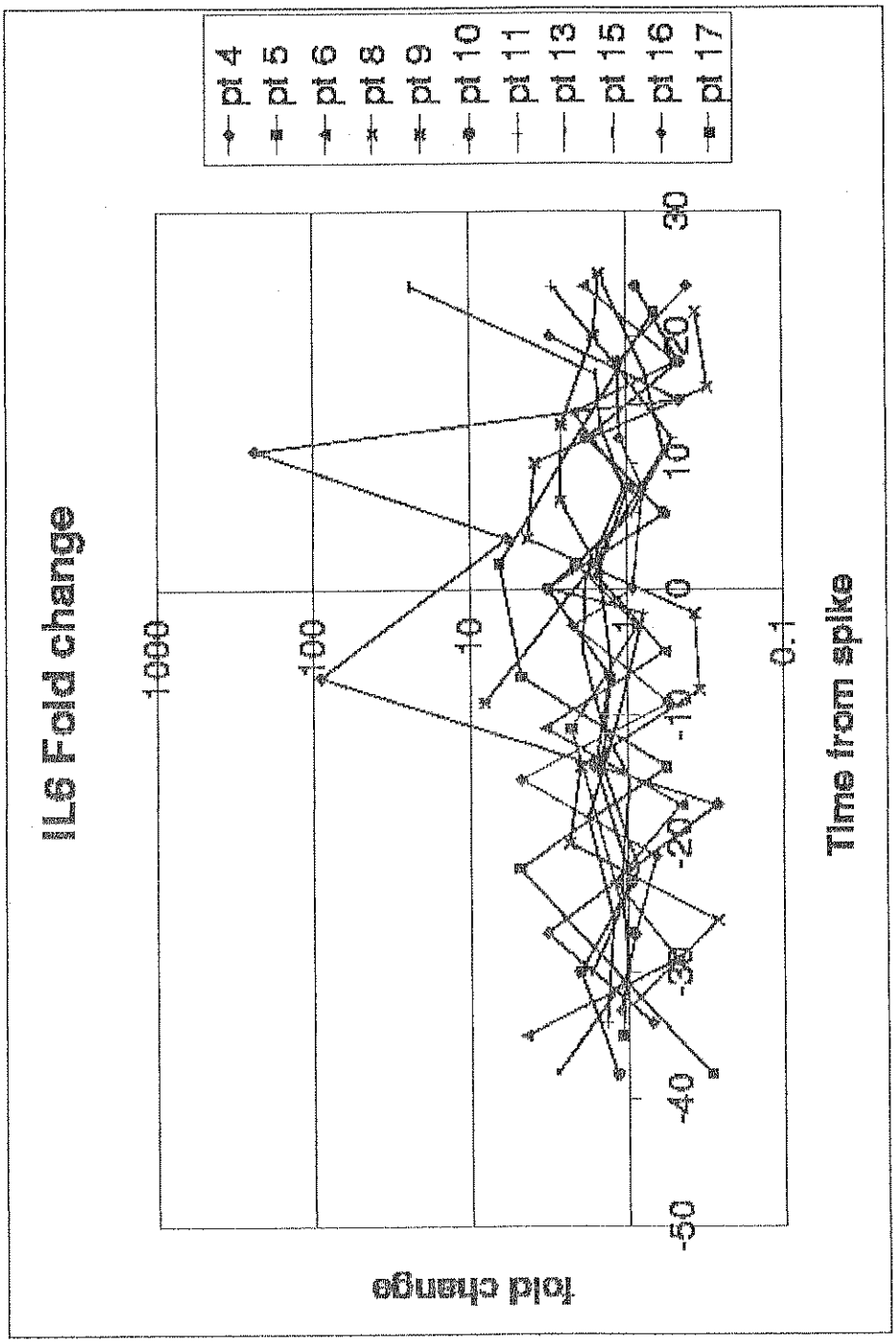

pt 4
pt 5
pt 6
pt 8
pt 9
pt 10
pt 11
pt 13
pt 15
pt 16
pt 17
Ls Fold change
1000
100
10
1
0.1
fold change
30
20
10
0
-10
-20
-30
-40
-50
Time from spike

FIG. 30

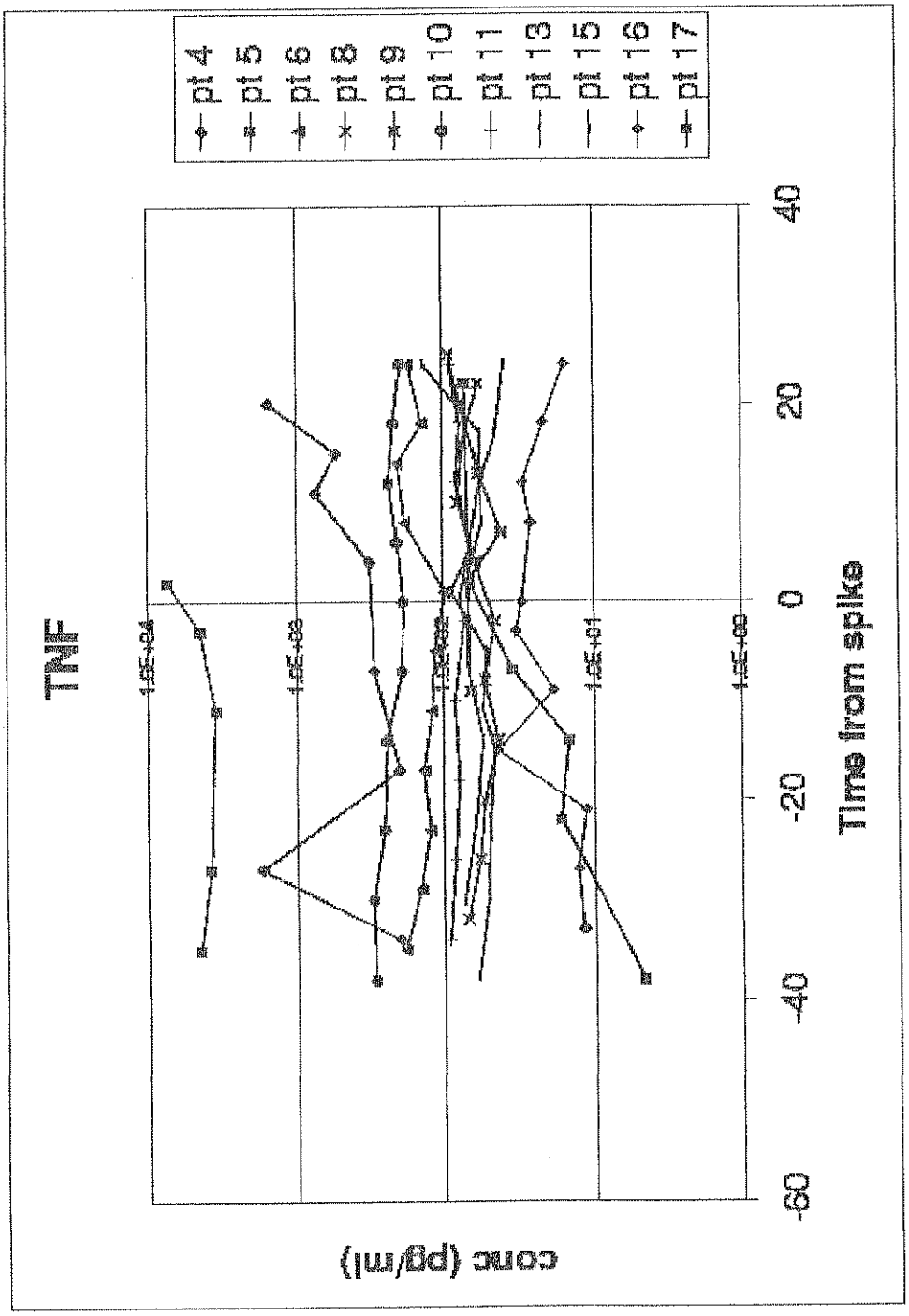

TNF
conc (pg/ml)
1.E+04
1.E+03
1.E+02
1.E+01
1.E+00
-60
-40
-20
0
20
40
Time from spike
pt 4
pt 5
pt 6
pt 8
pt 9
pt 10
pt 11
pt 13
pt 15
pt 16
pt 17

FIG. 31

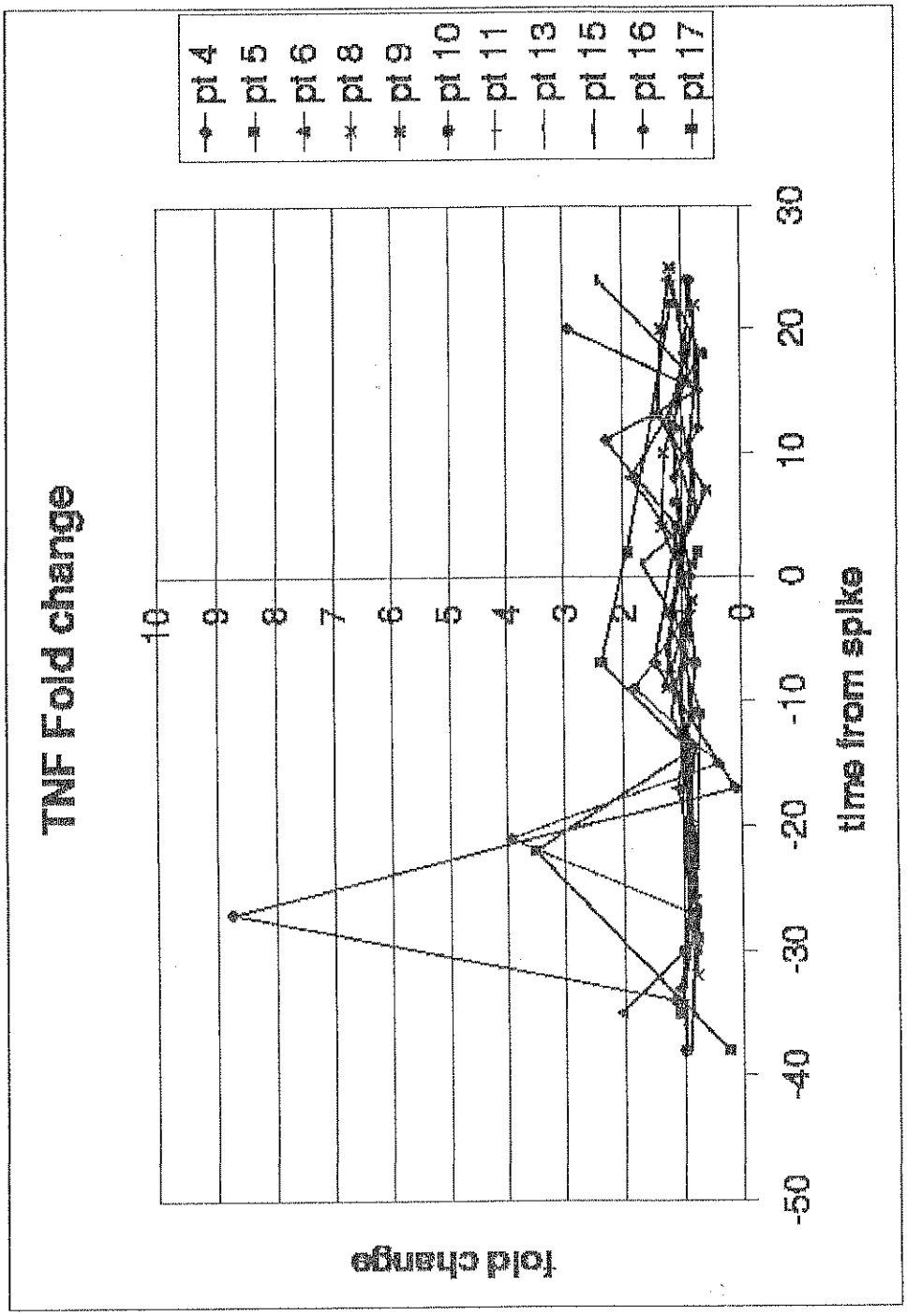

TNF Fold change
fold change
time from spike
pt 4
pt 5
pt 6
pt 8
pt 9
pt 10
pt 11
pt 13
pt 15
pt 16
pt 17
10
9
8
7
6
5
4
3
2
1
0
-50
-40
-30
-20
-10
0
10
20
30

FIG. 32

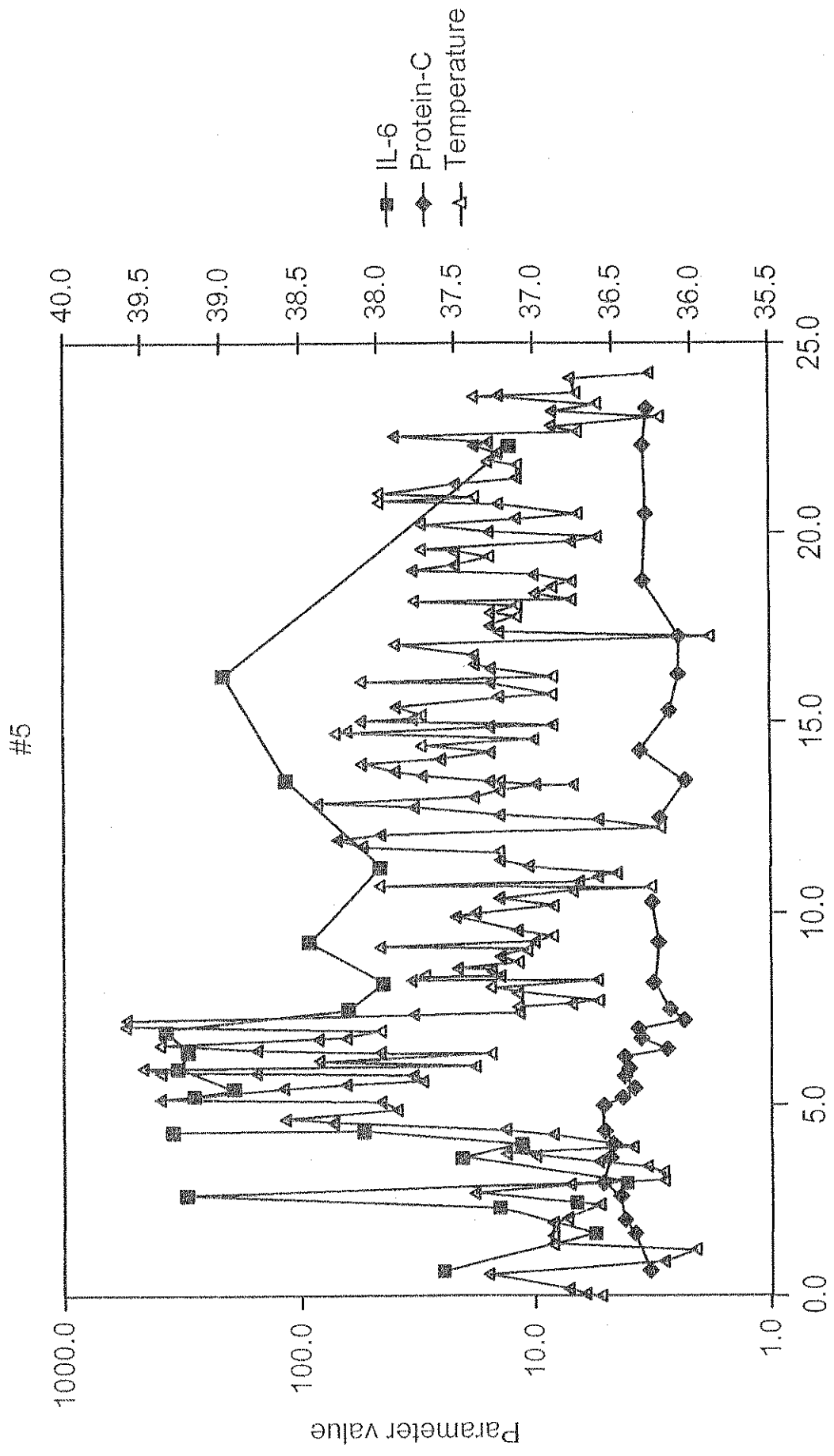

#5
IL-6
Protein-C
Temperature
Parameter value
1000.0
100.0
10.0
1.0
40.0
39.5
39.0
38.5
38.0
37.5
37.0
36.5
36.0
35.5
0.0
5.0
10.0
15.0
20.0
25.0
Time, days

FIG. 33

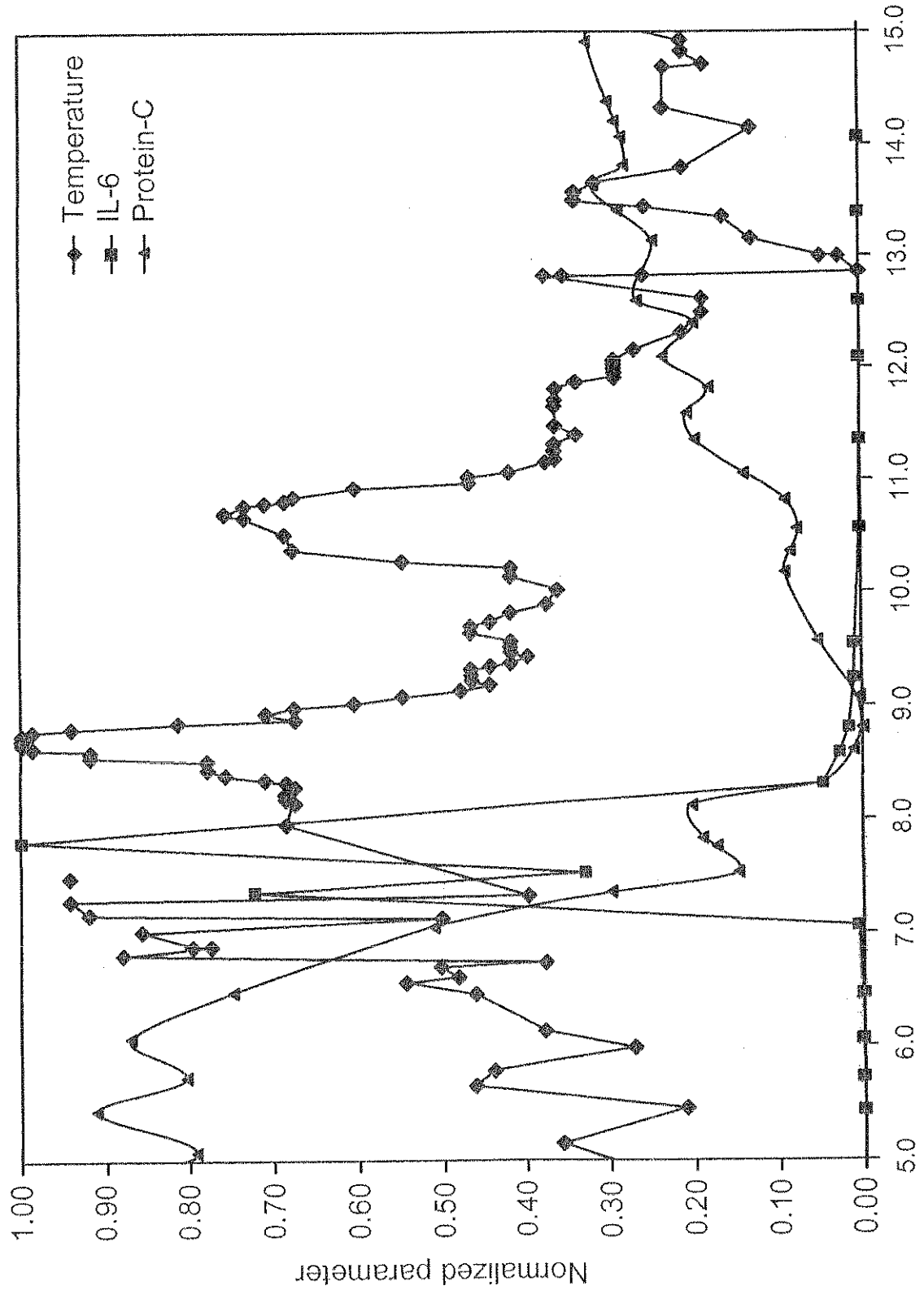

Temperature
IL-6
Protein-C
Normalized parameter
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
14.0
15.0
Time, days

FIG. 34

Th1-Th2 switching

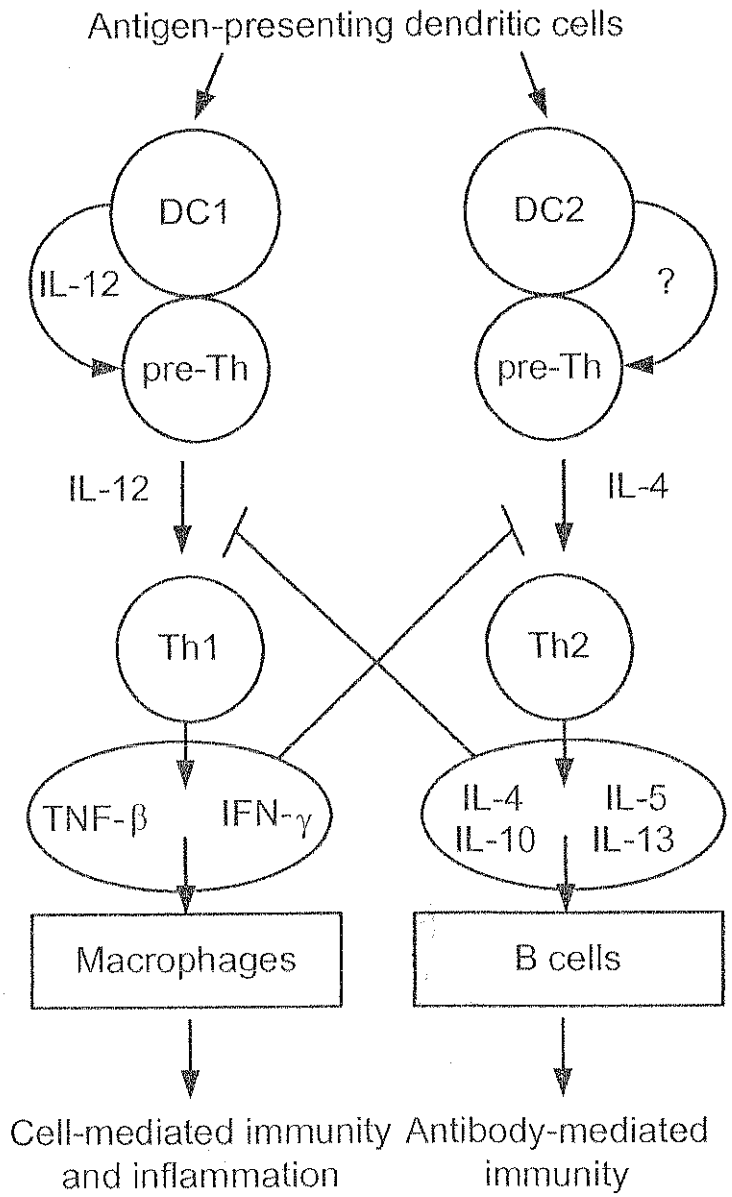


FIG. 35

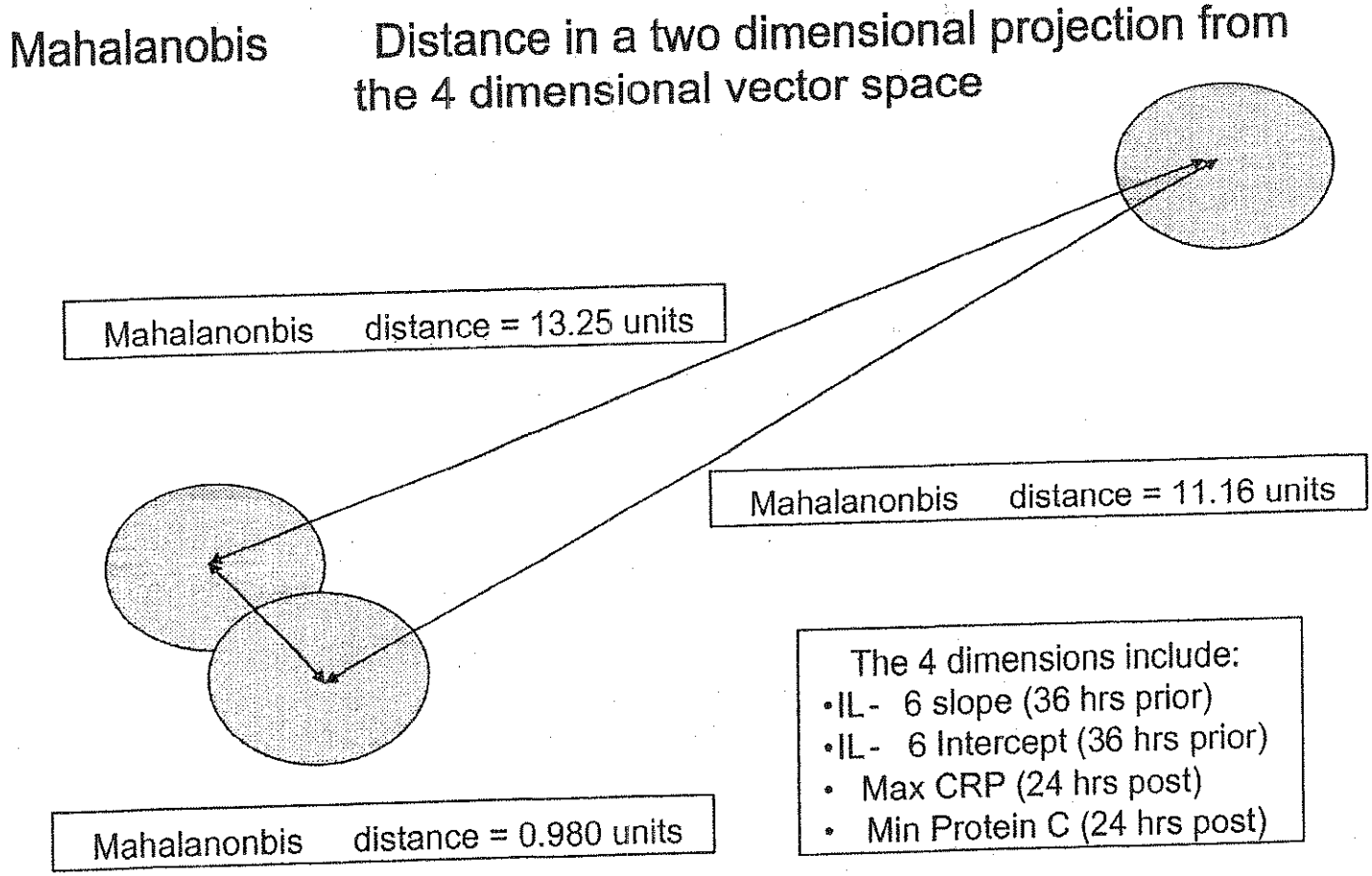

Mahalanobis Distance in a two dimensional projection from the 4 dimensional vector space
Mahalanonbis distance = 13.25 units
Mahalanonbis distance = 11.16 units
Mahalanonbis distance = 0.980 units
The 4 dimensions include:
•IL- 6 slope (36 hrs prior)
•IL- 6 Intercept (36 hrs prior)
• Max CRP (24 hrs post)
• Min Protein C (24 hrs post)

FIG. 36

Probability Landscape derived from 3 patient outcomes

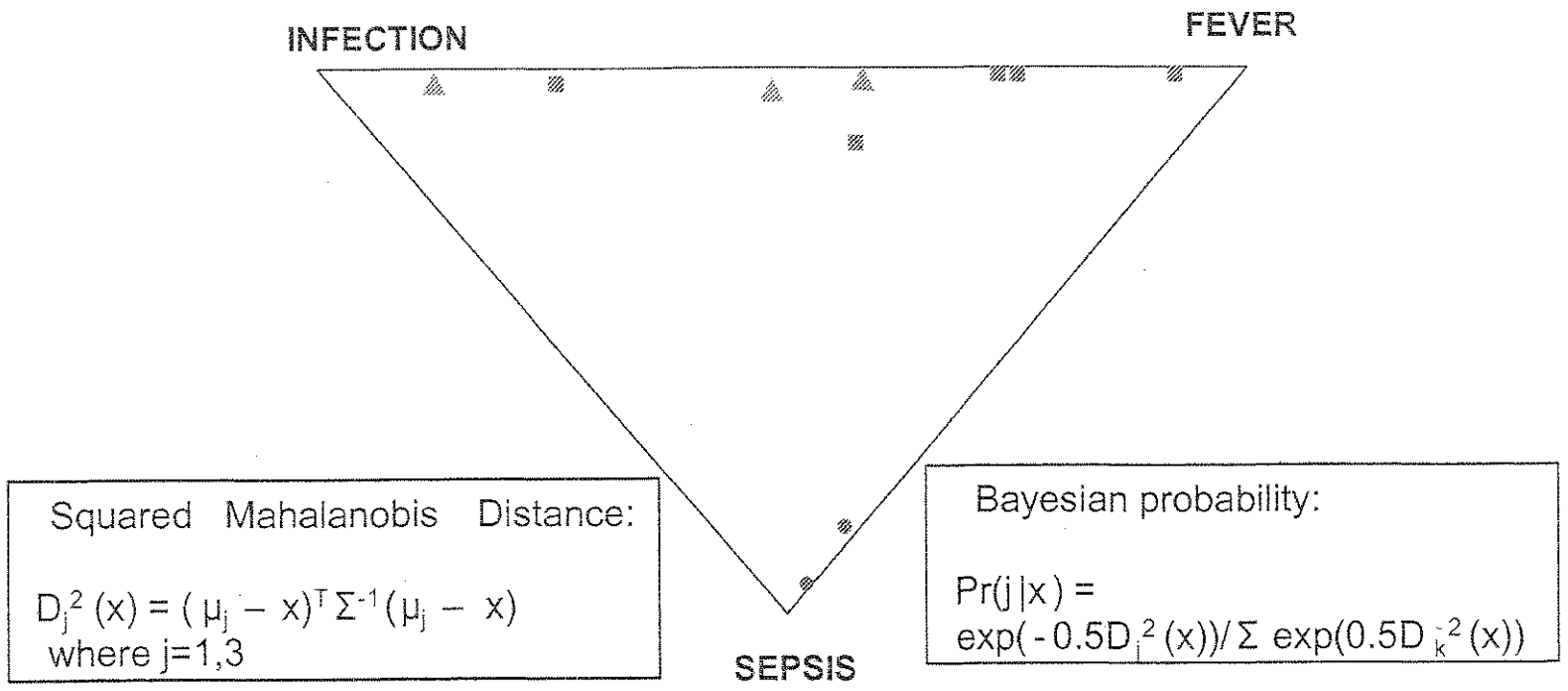


FIG. 37

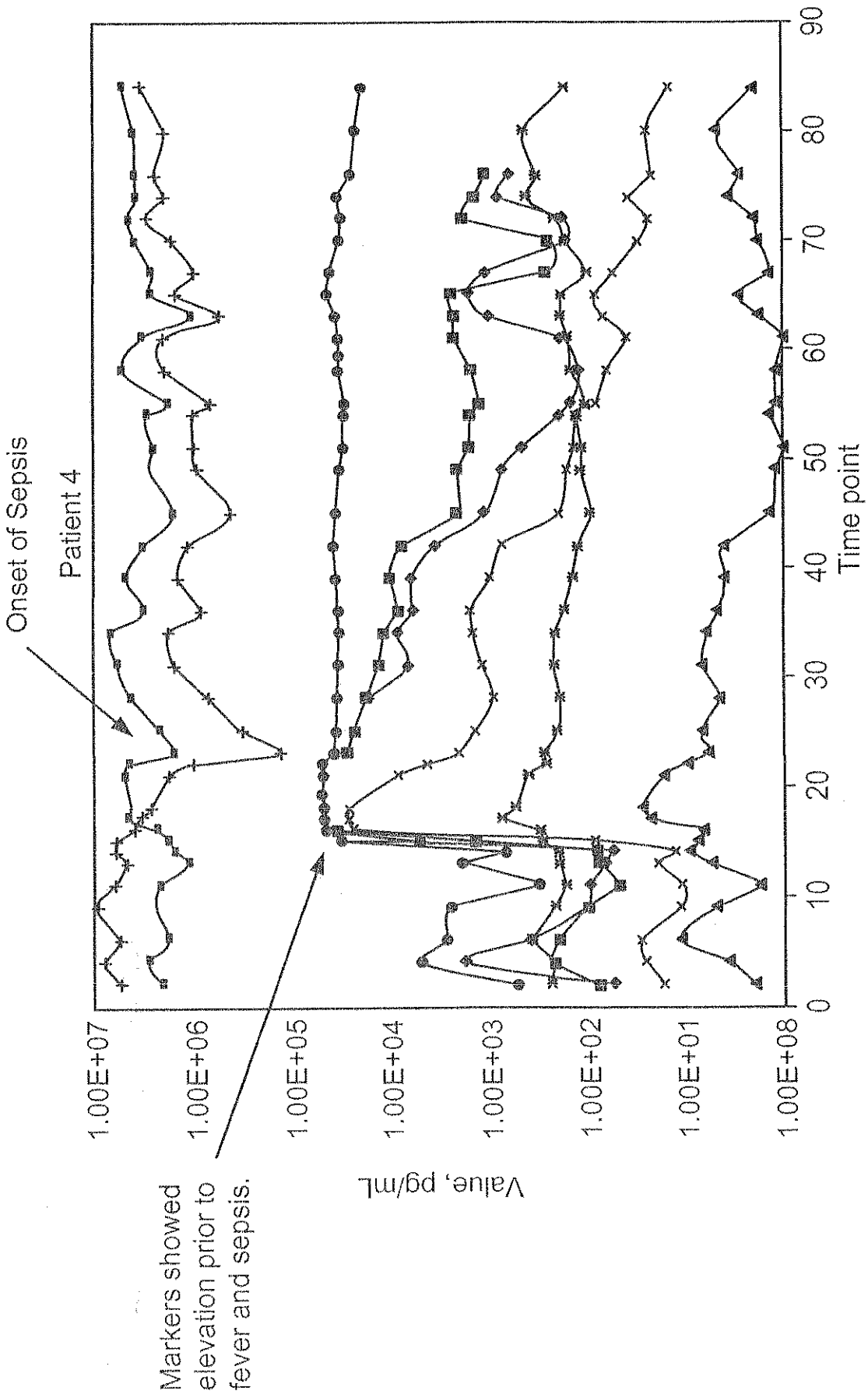

Onset of Sepsis
Patient 4
Markers showed elevation prior to fever and sepsis.
Value, pg/mL
1.00E+07
1.00E+06
1.00E+05
1.00E+04
1.00E+03
1.00E+02
1.00E+01
1.00E+08
0
10
20
30
40
50
60
70
80
90
Time point

FIG. 38

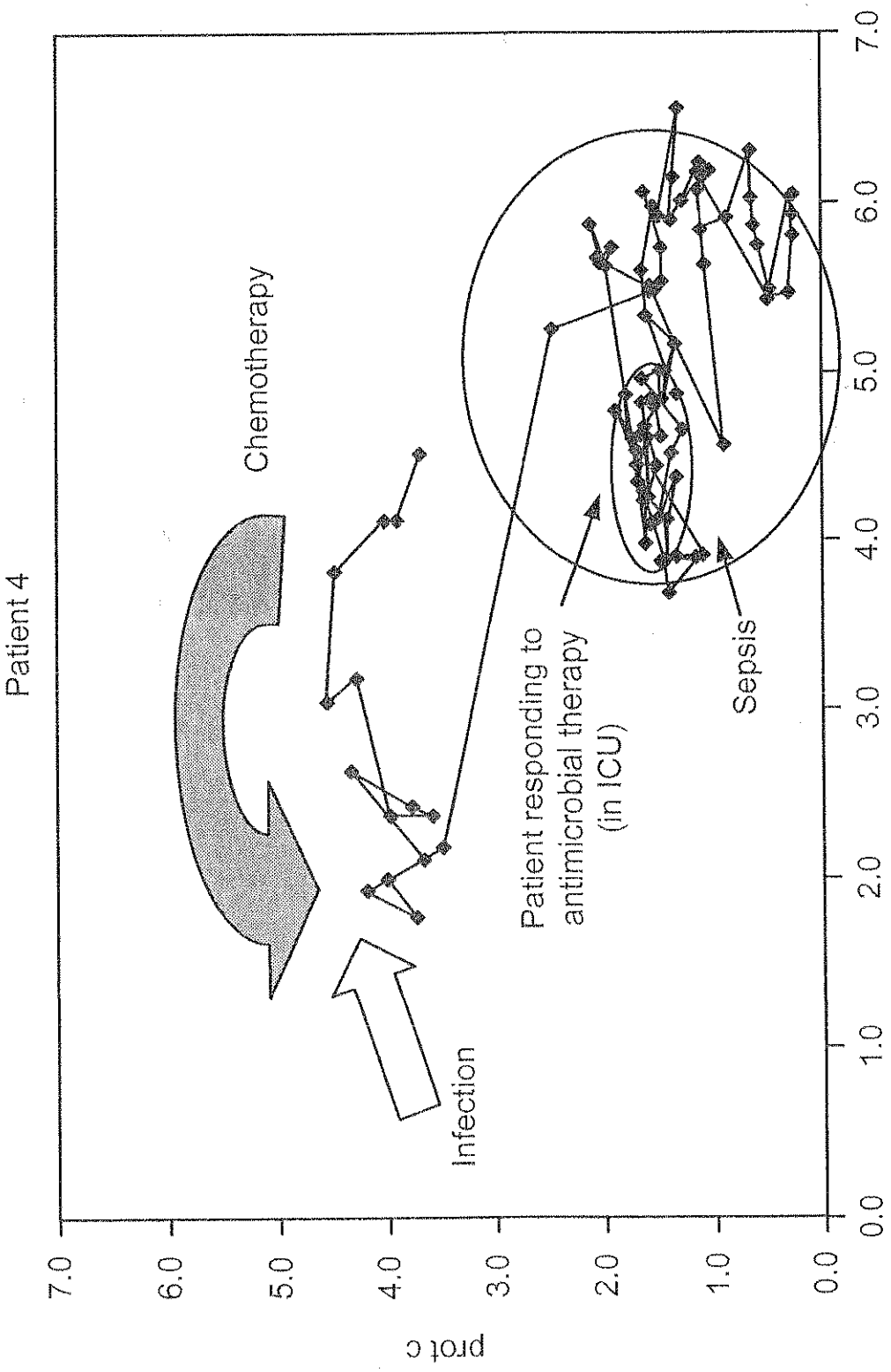

Patient 4
Chemotherapy
Infection
Patient responding to antimicrobial therapy (in ICU)
Sepsis
prot c
Ln crp
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0

FIG. 39