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QUALITATIVE SIMULATION IN MEDICAL PHYSIOLOGY: A PROGRESS REPORT

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Qualitative Simulation in Medical Physiology: A Progress Report*

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June 17, 1985

Abstract

This progress report describes the current status of the application of the QSIM qualitative simulation representation and algorithm to mechanisms drawn from medical physiology. QSIM takes a qualitative description of the structure of a mechanism and produces a qualitative description of its behavior. Here we apply it to a set of different, medically realistic examples, to represent the following kinds of knowledge:

- **Physiology:** qualitative simulation handles the response of normally-functioning mechanisms for salt and water balance to a variety of different environmental perturbations.
- **Pathophysiology:** local changes to the structure describing a normal mechanism produces a structure that accurately describes the pathophysiology of a set of diseases.
- **Abstraction:** the knowledge of the complexity of human physiology can only be handled by organizing it hierarchically. A hierarchy according to the temporal scale of equilibrium processes appears to be promising.
- **Cardiology:** a complex structure describing maintenance of heart rate and blood pressure was adequately constructed during a short meeting with a set of computationally sophisticated physicians.
- **Future Directions:** we can outline some of the representational barriers in the way of capturing a broader range of medical knowledge.

Keywords: qualitative simulation, causal reasoning, medical expert systems.

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1 Introduction

Qualitative simulation predicts the behavior of a mechanism given a description of its structure. In exactly the same way, a differential equation describes the structure of a physical system in terms of a set of state variables and constraints, and the behavior of the system as a continuous function of time. Figure 1 shows how qualitative simulation is an abstraction of differential equations, which themselves are an abstract description of continuous change in the world.

The approach to qualitative simulation taken here was initially inspired by our protocol analysis studies of the explanations given by expert physicians when describing the mechanisms underlying disease [Kuipers and Kassirer, 1983, 1984]. The algorithms used have also evolved, from a relatively limited and slow algorithm using a decision tree to analyze changing qualitative state [Kuipers 1982, 1984], to a much faster constraint-filtering algorithm with sufficiently clear semantics to allow us to prove some useful theorems about its performance [Kuipers 1985a, 1985b]. The above references discuss in detail how this approach fits into the context of other research on qualitative simulation and causal reasoning.

In the medical domains of nephrology and cardiology, we are using qualitative simulation to

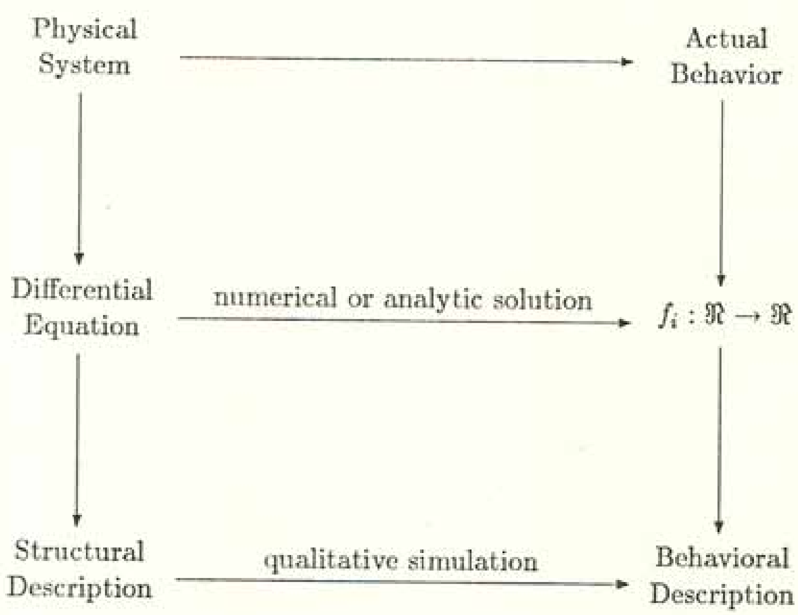


Figure 1: Qualitative simulation and differential equations are both abstractions of actual behavior.

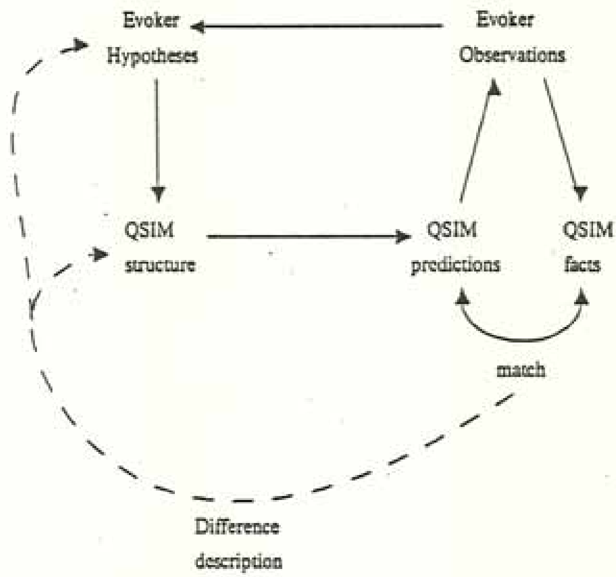


Figure 2: QSIM and the Evoker in a generate-and-test cycle

reason about the behavior of both intact and malfunctioning physiological mechanisms [Valtin, 1973, 1979]. The value of this approach will be tested in the context of a diagnostic expert system for nephrology. In this system, called RENAL, diagnostic hypothesis will refer to a set of mechanisms and the malfunctions and/or unusual environments in which they a believed to be operating. This structural description will be simulated to determine the behavioral consequences of the hypothesis. The behavioral description is then matched against the actual observed findings. Thus, predictions are used as part of the *test* portion of a *generate-and-test* diagnostic program. Hypotheses are generated by the Evoker, a modern implementation of a traditional hypothesis-directed diagnostic system based on weighted associations between findings and disease hypotheses. Figure 2 shows the overall problem-solving architecture of RENAL, consisting of the relation between the Evoker and the qualitative simulation program QSIM.

Our investigations have focused on the mechanisms in the kidney that maintain the body's sodium and water balances. This report summarizes our progress with those mechanism descriptions, and reports on a brief excursion into cardiology to test the broader applicability of our techniques. It must be emphasized that the medical knowledge embedded in these structures is tentative and incomplete. The discussion below of future directions describes certain known limitations of our approach.

Structural and behavioral descriptions are presented for each example.

- Graphical notation for the structure description, and in a few cases the corresponding Lisp code.

- Qualitative graphs for the behavioral descriptions.

The qualitative graph displays are very data-intensive, since each includes the behavior of every parameter used in the mechanism description. One research direction we will pursue in the immediate future is the development of techniques for focusing on the interesting or important parts of the behavior description. The more verbose ("graphose"?) format used here, however, clarifies the depth and extent of the information provided by QSIM to a program using it.

The medical content of these examples is intended to be accurate enough to demonstrate the power of the technique on realistic mechanisms. However, it is clear that significant revisions will be necessary, especially to include factors that are currently omitted entirely. The purpose of this paper is to present the current state of our work clearly enough to permit informed criticism and further debugging.

2 Normal Physiology

We have qualitative structural descriptions for the two equilibrium mechanisms that maintain balances of salt and water in the body. Each structural description is the qualitative version of a first-order differential equation. These structural descriptions, representing the correctly-functioning physiological mechanisms, can be simulated in a variety of environments and initial conditions to predict the resulting behavior.

2.1 Notation

The graphical form of the structural description shows the parameters or state variables of the mechanism, linked by constraints. The constraints must be satisfied by the values of its parameters at each point in time. This graphical form is helpful because the locality of information flow in the QSIM algorithm corresponds to locality in the structure graph. A parameter only knows about its own constraints, and vice versa.

In the Lisp code for the two mechanisms, the structural description (DEFINE-STRUCTURE) expresses the content of the graphical structure description, and a known normal state in which the mechanism is in equilibrium. The values of variables in the normal state are the ones ending in "*". The initialization form (DEFINE-INITIALIZATION) defines the initial state from which the mechanism is simulated.

The qualitative behavior plots describe the behavior predicted for the given structure and initialization. The small diagram in the upper right of the page gives the branching structure, if any, of the prediction. Ideally, it will be short and linear. The horizontal axis of each plot is time, although it may also include specially labeled reference points, such as "normal", to the left of the first time-point. The vertical axis is the set of landmark values of the parameter being plotted. On either axis, points may only be plotted at or midway between two landmarks or time-points. The points are plotted with small arrows to show direction of change, or circle for zero derivative.

2.2 ADH+WATER

Water balance is controlled by a system based around anti-diuretic hormone (ADH), which responds primarily to changes in the *concentration* of sodium in the plasma, and affects the net excretion of water through two pathways.

- The amount of water in the plasma ($amt(water, P)$, which is essentially the volume of the plasma) influences the glomerular filtration rate, which is the water taken out of the blood into the nephron.

- The concentration of sodium in the plasma ($c(Na, P)$) controls the secretion of ADH, which in turn influences reabsorption of water ($reabsorbed\ flow(water, U \rightarrow P)$) from the nephron back into the blood.

The structure assumes that three parameters are essentially constant, at least compared with the time-scale of this equilibrium (i.e. minutes).

- the amount of sodium in the plasma, $amt(Na, P)$,
- the rate of sodium excretion, $net\ flow(P \rightarrow U)$,
- the rate of water intake, $net\ flow(ingest \rightarrow P)$.

2.3 ALDO+SODIUM

Sodium balance is maintained by a system based around aldosterone, which responds primarily to changes in the *volume* of the plasma; i.e. to the amount of *water* in the plasma. Aldosterone controls the reabsorption of filtered sodium from the nephron back into the blood. This mechanism is based around the assumption that changes in plasma volume reflect changes in plasma sodium. Thus, its assumptions are:

- the rate of sodium intake, $flow(Na, ingest \rightarrow P)$ is constant.
- The monotonic function relation (M^+) between $amt(Na, P)$ and $amt(water, P)$, can be treated as essentially instantaneous.

The functional relation between $amt(Na, P)$ and $amt(water, P)$ represents one aspect of the behavior of the ADH+WATER system. The abstraction of the behavior of one system into an instantaneous relationship from the point of view of another system is justified by the fact that the ADH+WATER system (which equilibrates in minutes) is much faster than the ALDO+SODIUM system (equilibrates in hours to days).

2.4 Index to Examples

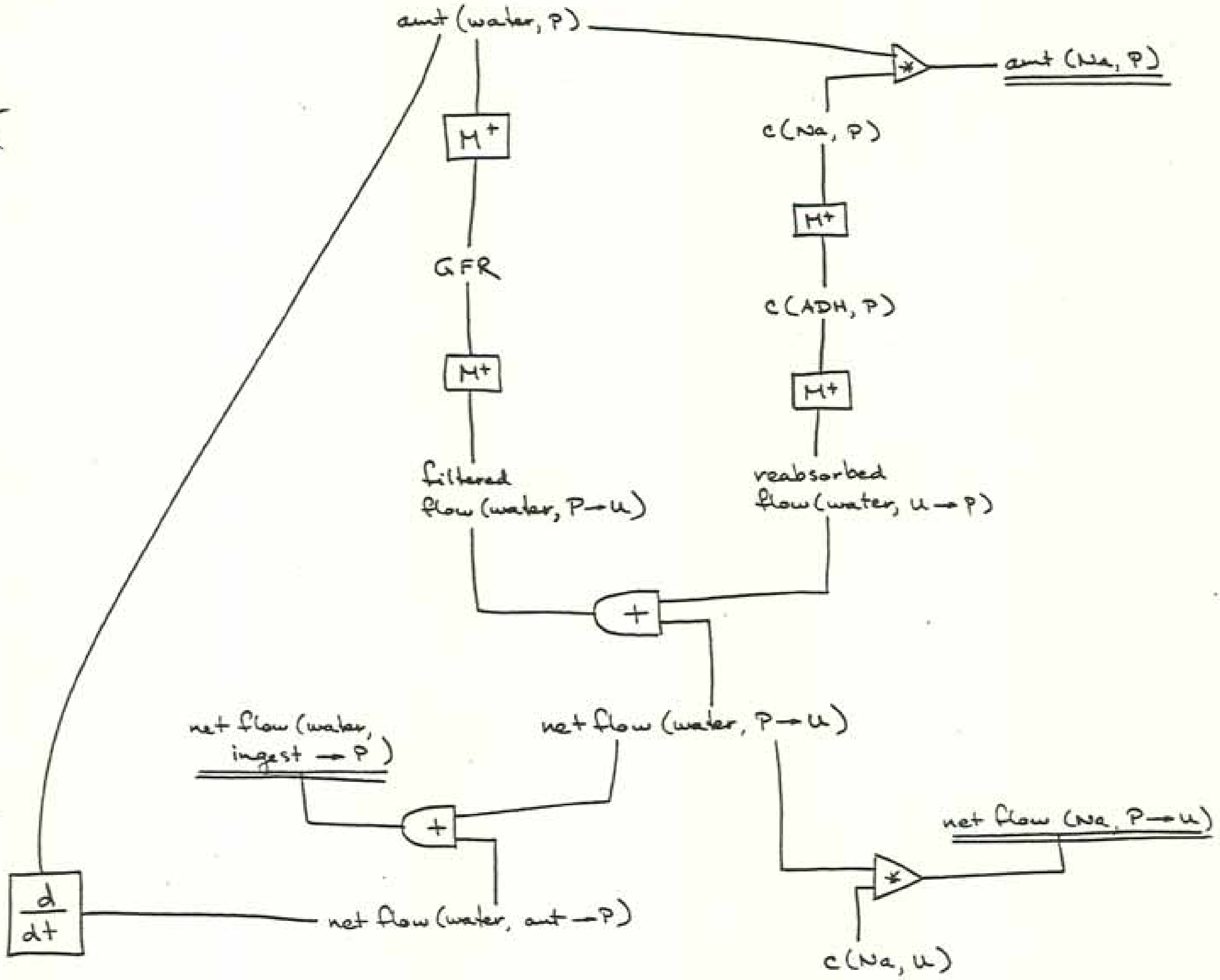
The normally functioning mechanisms are presented and simulated given a variety of different initial conditions.

1. ADH+WATER graphical structure.
2. ADH+WATER code.
3. ADH-WITH-HIGH-INTAKE behavior plot. Normal mechanism, but water intake is higher than normal and constant.
4. ADH-WITH-LOW-INTAKE behavior plot. Restricted water intake.
5. ALDO+SODIUM graphical structure.

6. ALDO+SODIUM code.

7. ALDO-WITH-HIGH-SODIUM-INTAKE behavior plot. High *rate* of sodium intake, but normal water intake.

8. POTATO-CHIP behavior plot. High plasma sodium (supposedly due to eating a single potato chip!) but normal rate of intake of both sodium and water.



Assumptions:

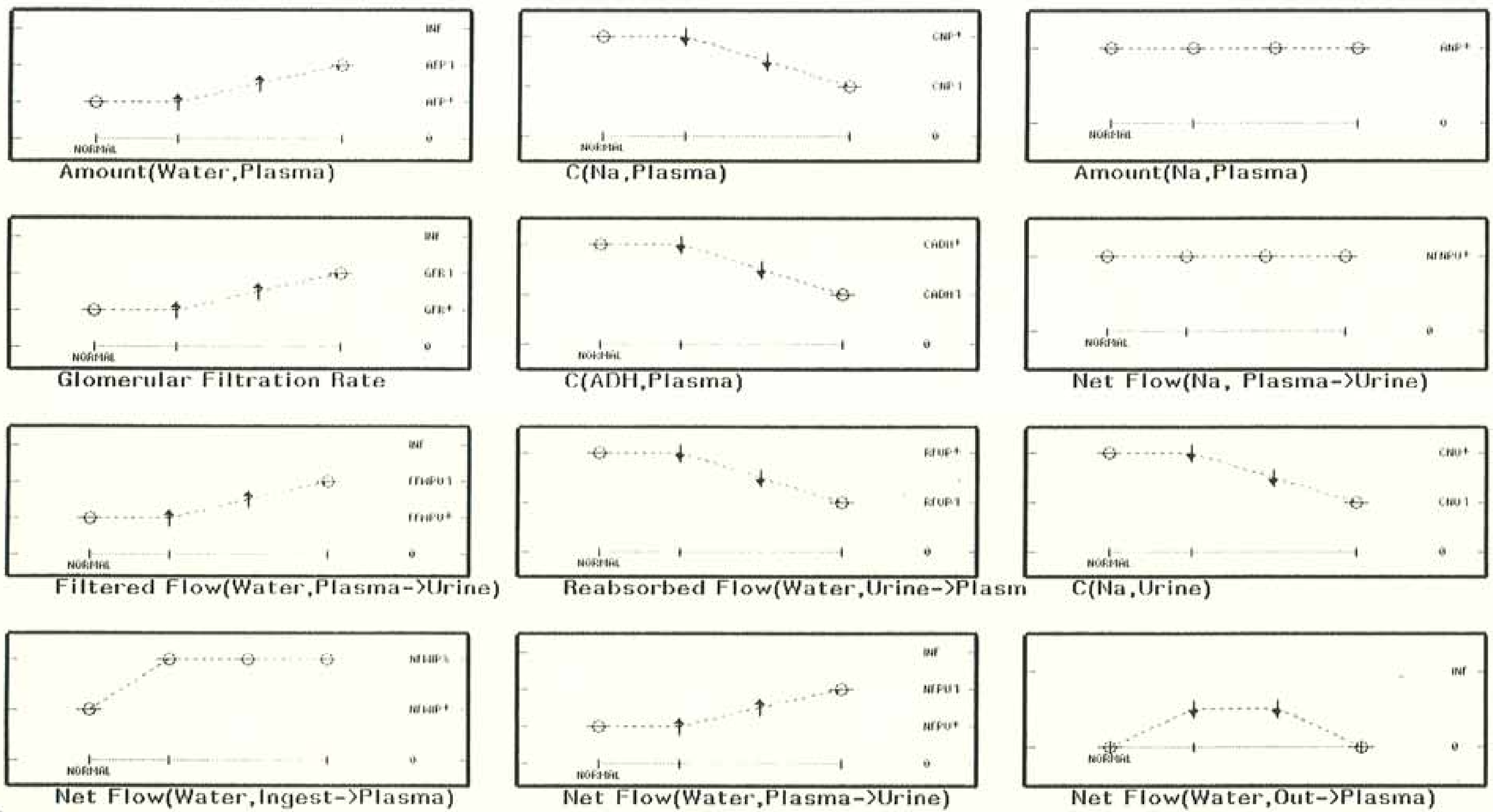
amt (Na, P)
net flow (Na, P→U)
net flow (water, ingest → P)

are all constant.

ADH + WATER

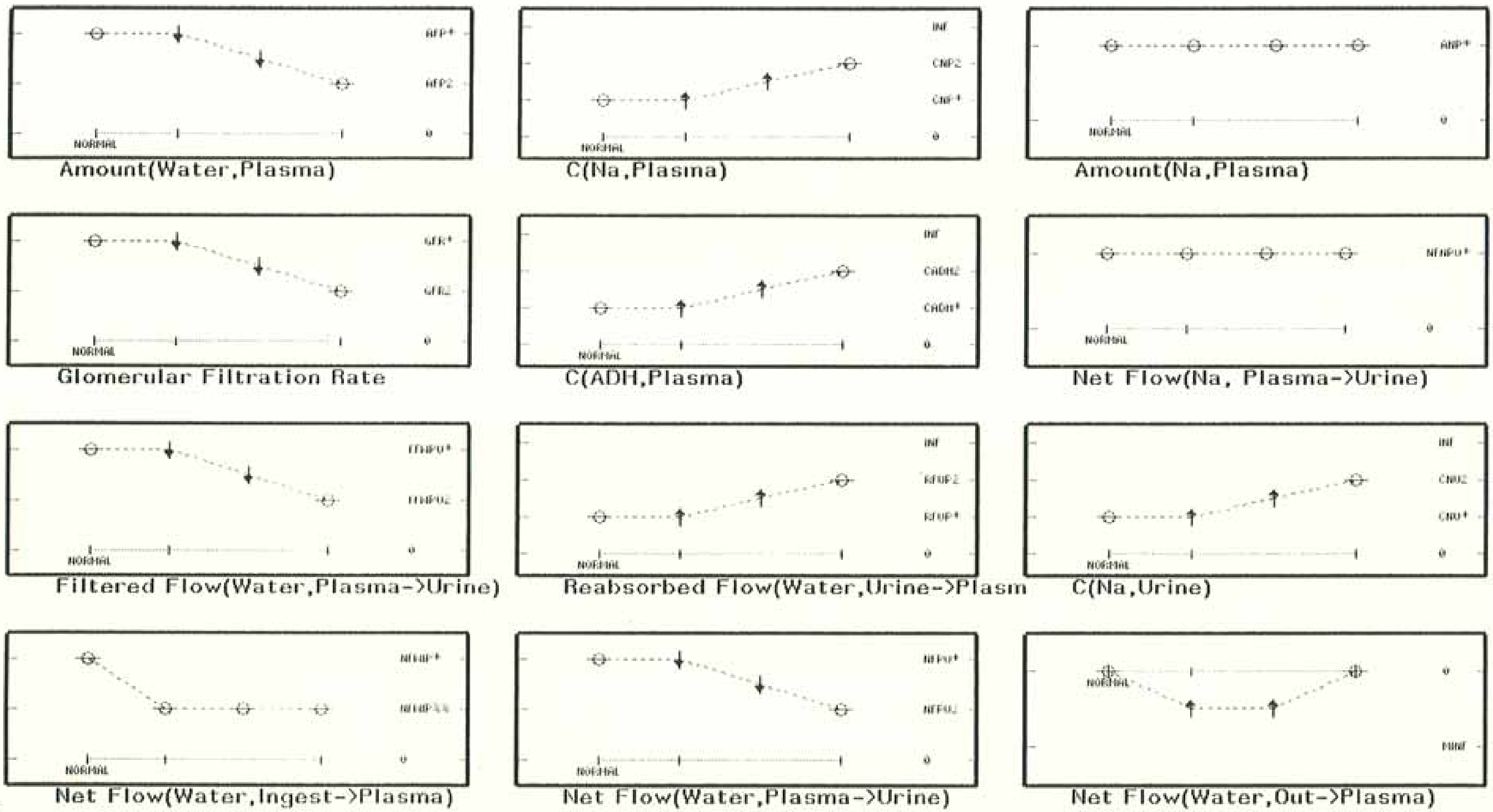
```
; STRUCTURES contains the structure definitions for the ADH and ALDO structures
; in their bare form.  The initialization objects, normal states, and
; corresponding values are to be created by other files.

; This structure is ADH+WATER without named states or correspondences.
; Behaviorally derived knowledge such as landmarks, correspondences, or named states
; are added by the programs creating the initializations.  The same structure will
; be sharable (eventually) by several incompatible initializations.

(defvar adh-structure nil)

(define-structure ADH+WATER
 (parameters AFP GFR FFWPU ANP CNP CADH RFUP NFPU NFWIP NFWOP CNU NFNPU)
 (landmarks (ANP (minf 0 ANP%% ANP* ANP% inf))
            (NFWIP (minf 0 NFWIP%% NFWIP* NFWIP% inf)))
 (invariants (GFR ((0 inf) nil))
             (CADH ((0 inf) nil))
             (RFUP ((0 inf) nil))
             (NFPU ((0 inf) nil))
             (ANP ((0 inf) nil))                    ; These "loose ends" are no longer
             (NFWIP ((0 inf) nil))                  ; constant in the structure:  the
             (NFNPU ((0 inf) nil)))                 ; initialization controls them.
 (constraints (M+ AFP GFR)
              (M+ GFR FFWPU)
              (mult AFP CNP ANP)
              (add RFUP NFPU FFWPU)
              (M+ CNP CADH)
              (M+ CADH RFUP)
              (d//dt AFP NFWOP)
              (add NFPU NFWOP NFWIP)
              (mult NFPU CNU NFNPU)))

(defun setup-adh-structure ()
  (setq adh-structure (adh+water))
  (send adh-structure
        :make-system-state 'normal
        '((NFWOP (0 STD)) (NFWIP (NFWIP* STD)) (NFPU (NFPU* STD))
          (RFUP (RFUP* STD)) (CADH (CADH* STD)) (CNP (CNP* STD))
          (ANP (ANP* STD)) (FFWPU (FFWPU* STD)) (GFR (GFR* STD))
          (AFP (AFP* STD)) (CNU (CNU* STD)) (NFNPU (NFNPU* STD)))))
```

Initialization HIGH WATER INTAKE, normal sodium
of structure ADH+WATER,
behavior 1 of 1.

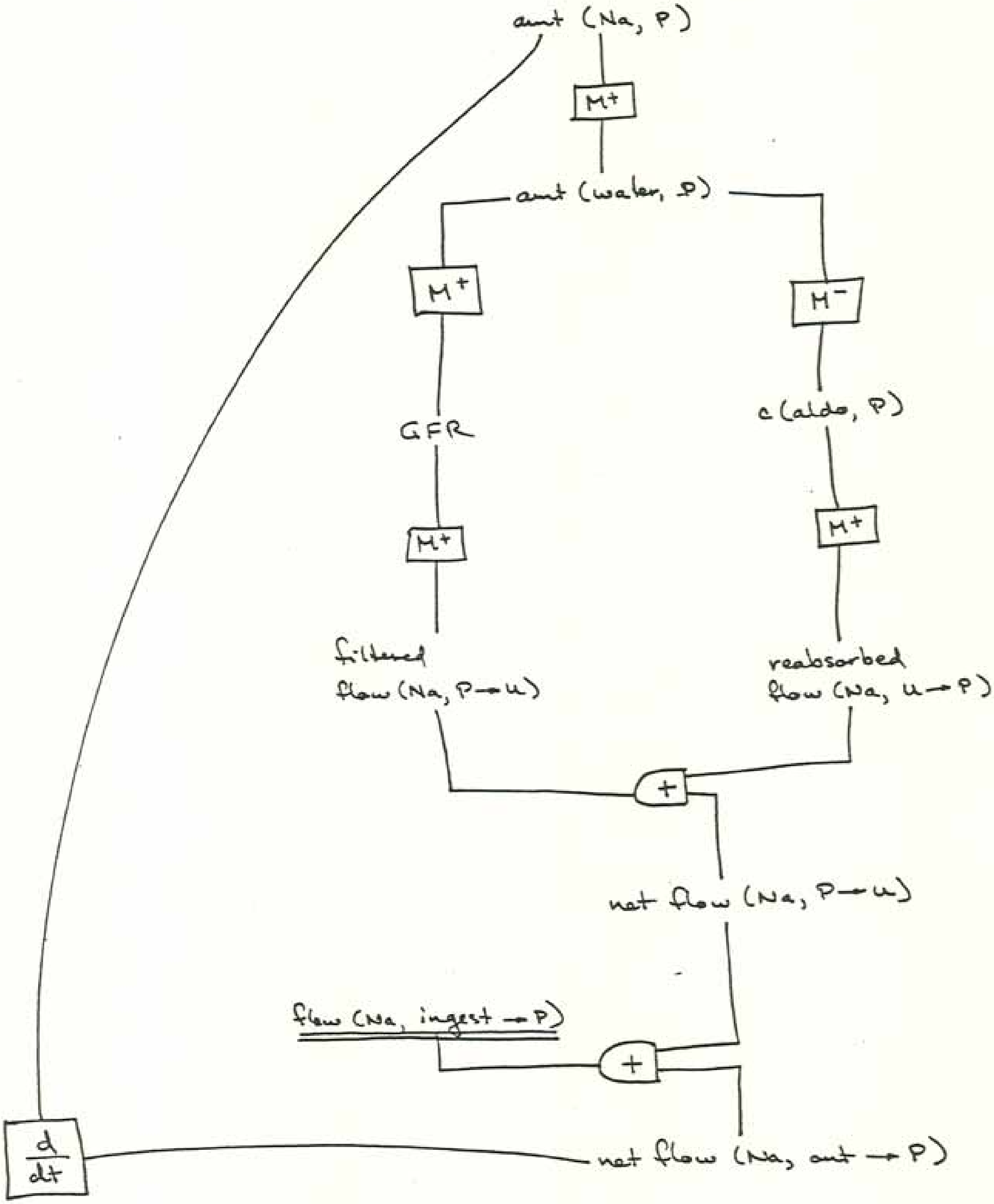


NIL

Initialization LOW WATER INTAKE, normal sodium
of structure ADH+WATER,
behavior 1 of 1.



NIL



Assumptions:

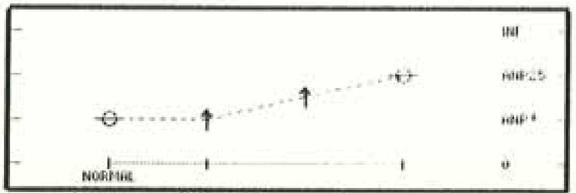
flow (Na, ingest → P) is constant

M+ (amp, afp) can be treated as a function
(i.e. water balance is faster than Na balance)

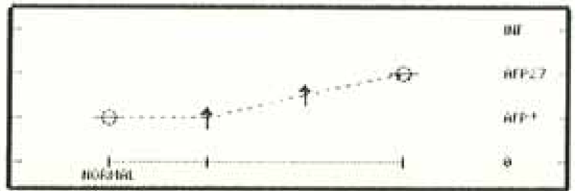
ALDO + SODIUM

```
; ALDO+SODIUM describes the sodium balance mechanism, as mediated by aldosterone.

(defvar aldo-structure nil)

(define-structure ALDO+SODIUM
                  (parameters ANP AFP GFR FFNPU CALDO RFNUP NFNPU NFNIP NFNP)
                  (landmarks (NFNIP (minf 0 NFNIP%% NFNIP* NFNIP% inf)))
                  (invariants (AFP ((0 inf) nil))
                              (ANP ((0 inf) nil))
                              (GFR ((0 inf) nil))
                              (CALDO ((0 inf) nil))
                              (FFNPU ((0 inf) nil))
                              (RFNUP ((0 inf) nil))
                              (NFNPU ((0 inf) nil))
                              (NFNIP ((minf inf) nil))) ; declared constant in initialization
                  (constraints (M+ ANP AFP)
                               (M+ AFP GFR)
                               (M+ GFR FFNPU)
                               (M- AFP CALDO)
                               (M+ CALDO RFNUP)
                               (add RFNUP NFNPU FFNPU)
                               (add NFNPU NFNP NFNIP)
                               (d//dt ANP NFNP)))

(defun setup-aldo-structure ()
  (setq aldo-structure (aldo+sodium))
  (send aldo-structure :make-system-state 'normal
        '((ANP (ANP* STD)) (AFP (AFP* STD))
          (GFR (GFR* STD)) (FFNPU (FFNPU* STD))
          (CALDO (CALDO* STD))
          (RFNUP (RFNUP* STD)) (NFNPU (NFNPU* STD))
          (NFNIP (NFNIP* STD)) (NFNP (0 STD)))))
```

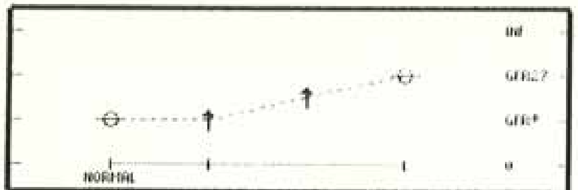
Initialization HIGH SODIUM INTAKE
of structure ALDO+SODIUM,
behavior 1 of 1.



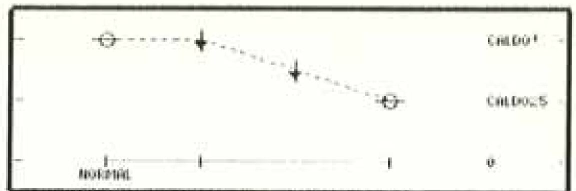
Amount(Na,Plasma)



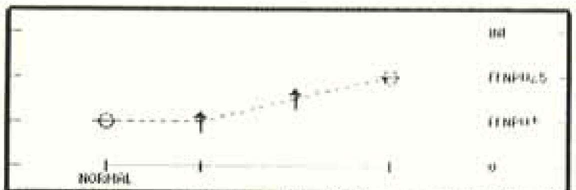
Amount(Water,Plasma)



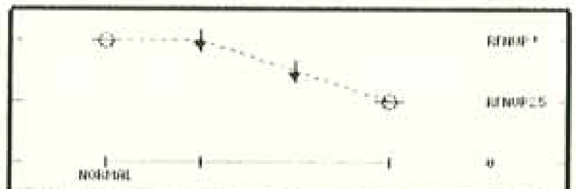
Glomerular Filtration Rate



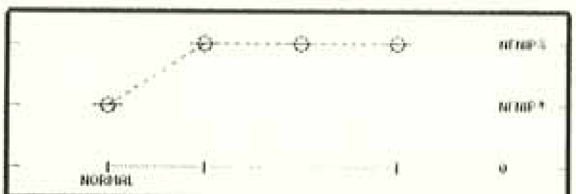
C(Aldosterone,Plasma)



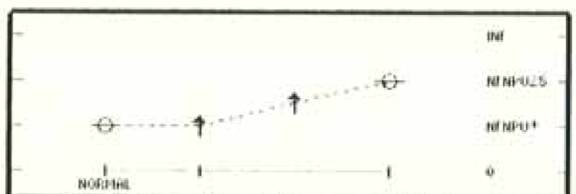
Filtered Flow(Na,Plasma->Urine)



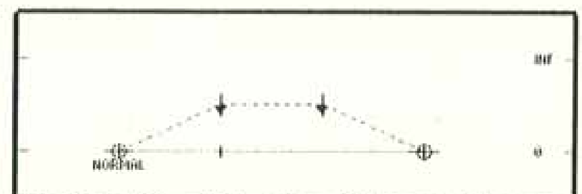
Reabsorbed Flow(Na,Urine->Plasma)



Net Flow(Na, Ingest->Plasma)



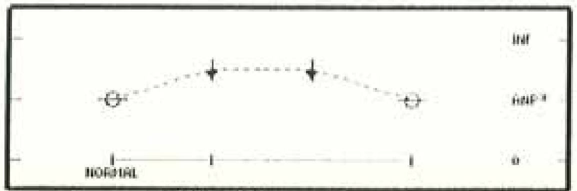
Net Flow(Na, Plasma->Urine)



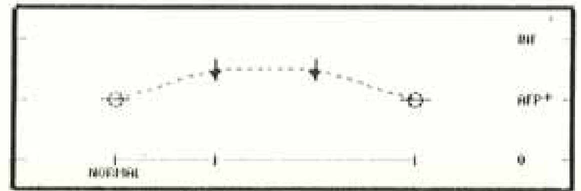
Net Flow(Na, Out->Plasma)

NIL

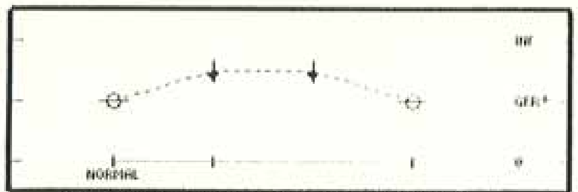
```
Initialization POTATO CHIP:  high sodium level, normal intake
   of structure ALDO+SODIUM,
   behavior 1 of 1.
```



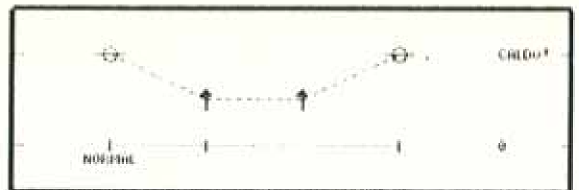
Amount(Na,Plasma)



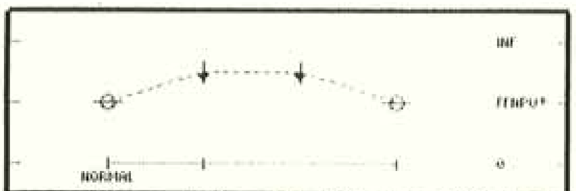
Amount(Water,Plasma)



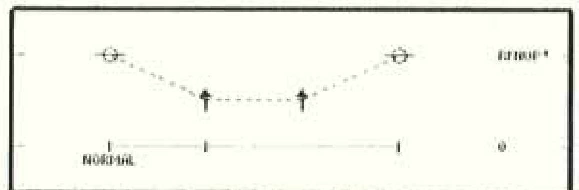
Glomerular Filtration Rate



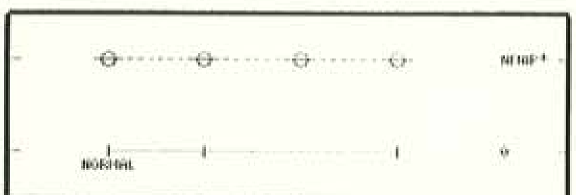
C(Aldosterone,Plasma)



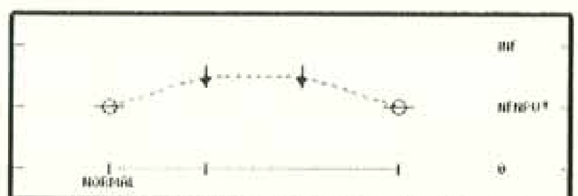
Filtered Flow(Na,Plasma->Urine)



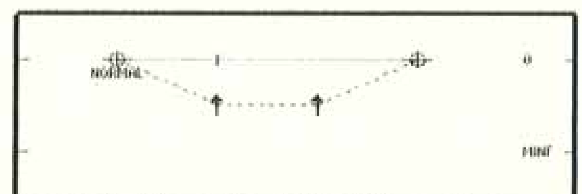
Reabsorbed Flow(Na,Urine->Plasma)



Net Flow(Na, Ingest->Plasma)



Net Flow(Na, Plasma->Urine)



Net Flow(Na, Out->Plasma)

NIL

15

3 Pathophysiology

A major advantage to this approach to the causal model is that pathophysiology is naturally derived from knowledge of the normal physiological mechanisms. Various disorders are simulated by simple modifications of the normal mechanism description.

- Too much ADH. SIADH (the syndrome of inappropriate secretion of anti-diuretic hormone) can be simulated by eliminating one of the M^+ constraints in the ADH+WATER structure and declaring $c(ADH, P)$ to be high and constant.
- Not enough ADH. Diabetes Insipidus breaks either of two constraints in the structure, leaving water reabsorption abnormally low.
- Too much aldosterone. Primary hyperaldosteronism breaks the constraint between $amt(water, P)$ and $c(Aldo, P)$, and declares $c(Aldo, P)$ to be high and constant.
- Not enough aldosterone. Hypoaldosteronism works similarly.

3.1 SIADH Sequence

We can see the power of this approach by examining three closely related situations that might arise in the diagnosis and treatment of SIADH, in which the body retains excessive amounts of water in spite of normal intake.

- ADH-WITH-HIGH-INTAKE shows the normally-functioning mechanism coping with abnormally high water intake.
- SIADH-WITH-NORMAL-INTAKE shows that a patient with SIADH will retain large amounts of water, increasing $amt(water, P)$, even though intake is normal.
- STABLE-SIADH-WITH-WATER-RESTRICTION simulates the effect of the usual therapy, water restriction, starting with the stable state resulting from the previous example. There are three possible outcomes, depending on whether the water restriction is exactly sufficient to restore volume to normal, too much, or too little.

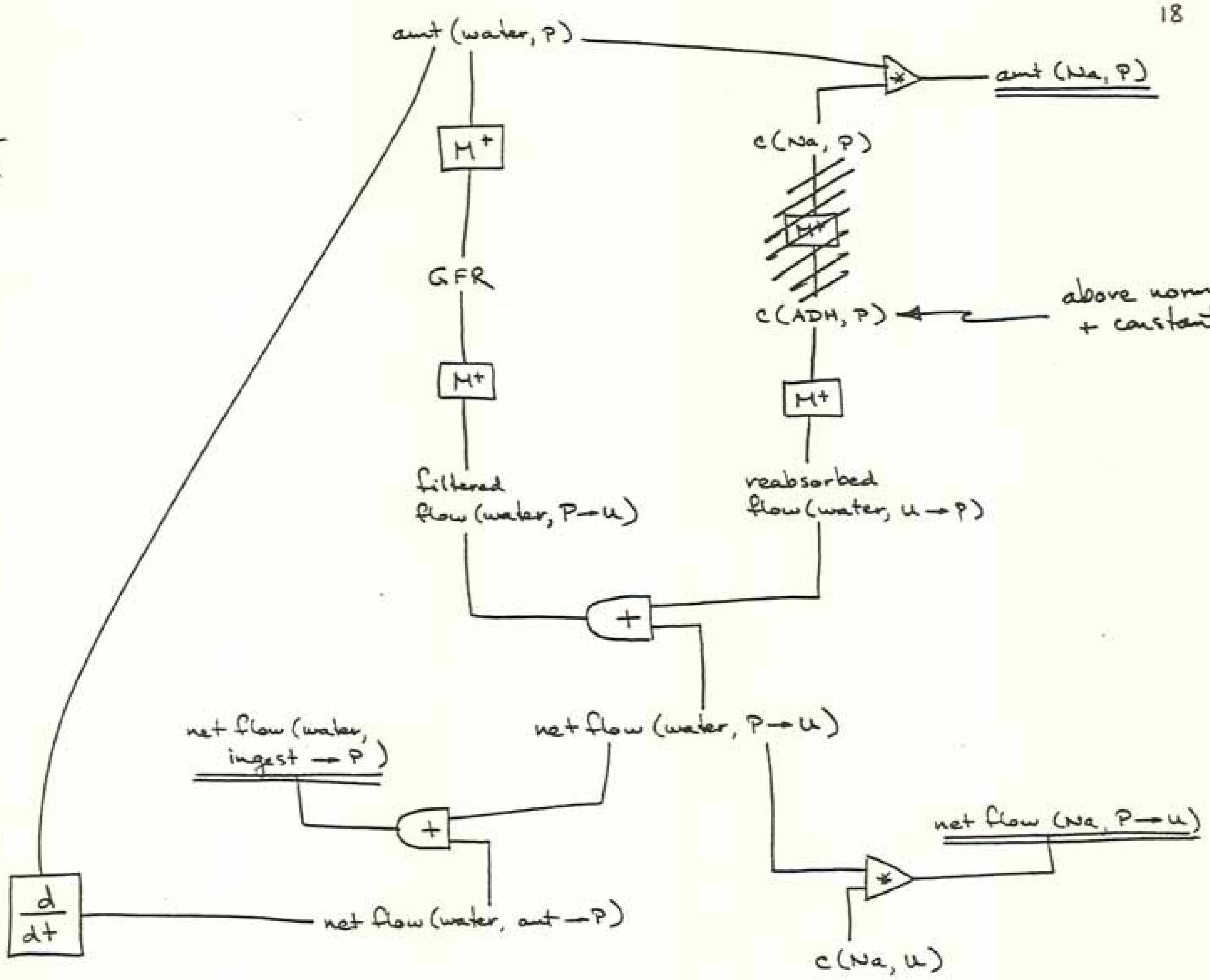
Although there are substantial similarities between the predicted observations under different circumstances, the predictions differ in certain key places, making it possible to select the observations needed to distinguish particular pairs of hypotheses. Automatic selection of the distinguishing predictions should not be difficult.

3.2 Other Disorders

Examples are presented of simulations of hyperaldosteronism, represented by a "broken" version of the ALDO+SODIUM mechanism, responding to several environmental conditions. Diabetes insipidus is also shown, with three different causes: pathologically high water intake, inappropriately low secretion of ADH, and insensitivity of the kidney to ADH.

3.3 Index to Examples

1. SIADH+WATER graphical structure. The M^+ link between $c(Na, P)$ and $c(ADH, P)$ has been eliminated.
2. SIADH-WITH-NORMAL-INTAKE behavior plot.
3. STABLE-SIADH-WITH-WATER-RESTRICTION behavior plot (1 of 3).
4. STABLE-SIADH-WITH-WATER-RESTRICTION behavior plot (2 of 3).
5. STABLE-SIADH-WITH-WATER-RESTRICTION behavior plot (3 of 3).
6. HYPERALDO+SODIUM graphical structure. The M^+ link between $amt(water, P)$ and $c(Aldo, P)$ has been eliminated.
7. HYPERALDO-WITH-NORMAL-SODIUM-INTAKE behavior plot.
8. HYPERALDO-WITH-HIGH-SODIUM-INTAKE behavior plot.
9. DIABETES-INSIPIDUS graphical structure. There are three types of Diabetes Insipidus, corresponding to:
   - excessive water intake, $net\ flow(water, ingest \rightarrow P)$,
   - broken M^+ link between $c(Na, P)$ and $c(ADH, P)$,
   - broken M^+ link between $c(ADH, P)$ and $reabsorbed\ flow(water, U \rightarrow P)$.
10. DI-FROM-HIGH-WATER-INTAKE behavior plot.
11. DI-W-DEC-ADH behavior plot.
12. DI-W-INSENSITIVITY behavior plot.



Assumptions:

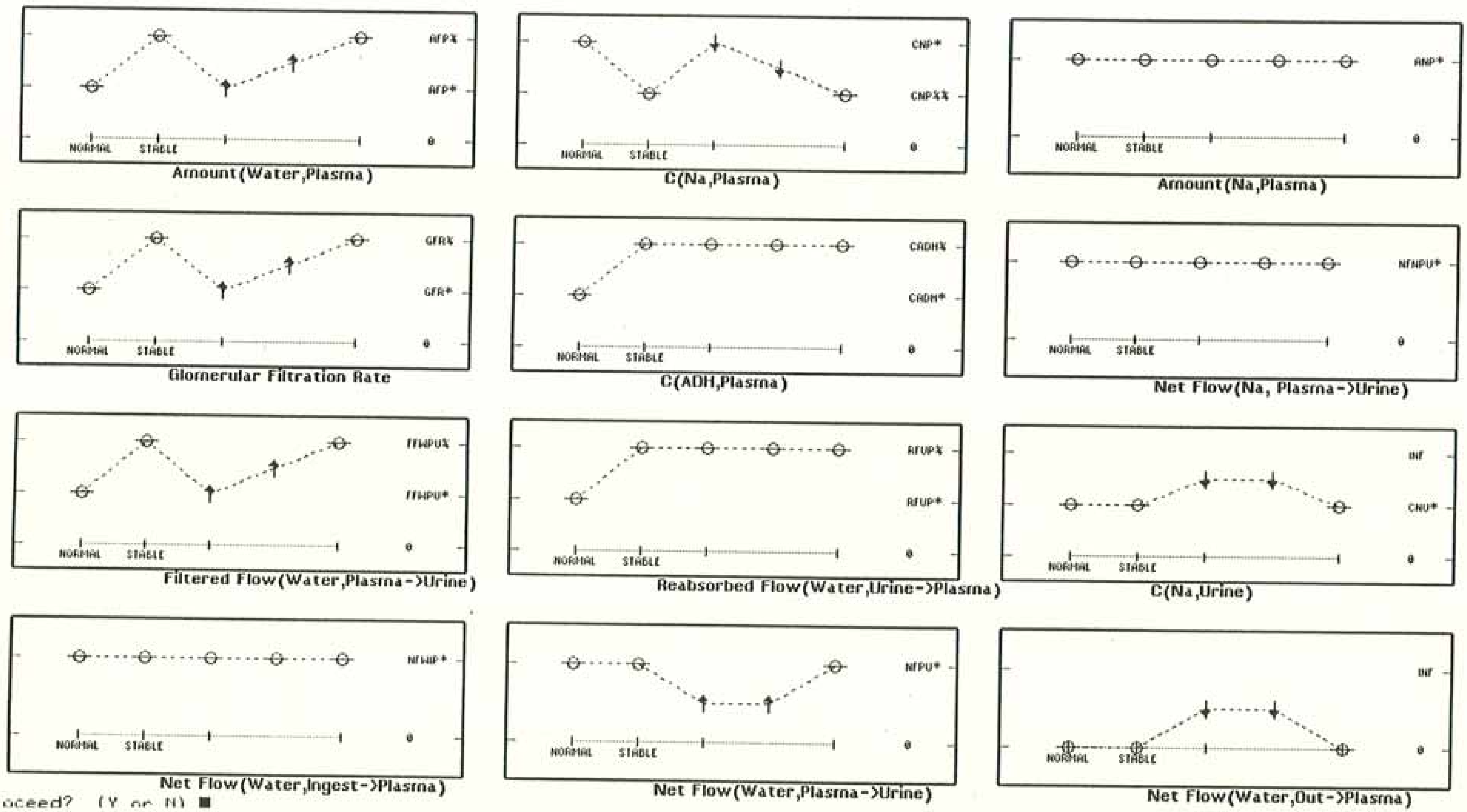
amt (Na, P)
net flow (Na, P→U)
net flow (water, ingest → P)

are all constant.

SIADH + WATER

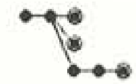
~~ADH~~ + WATER

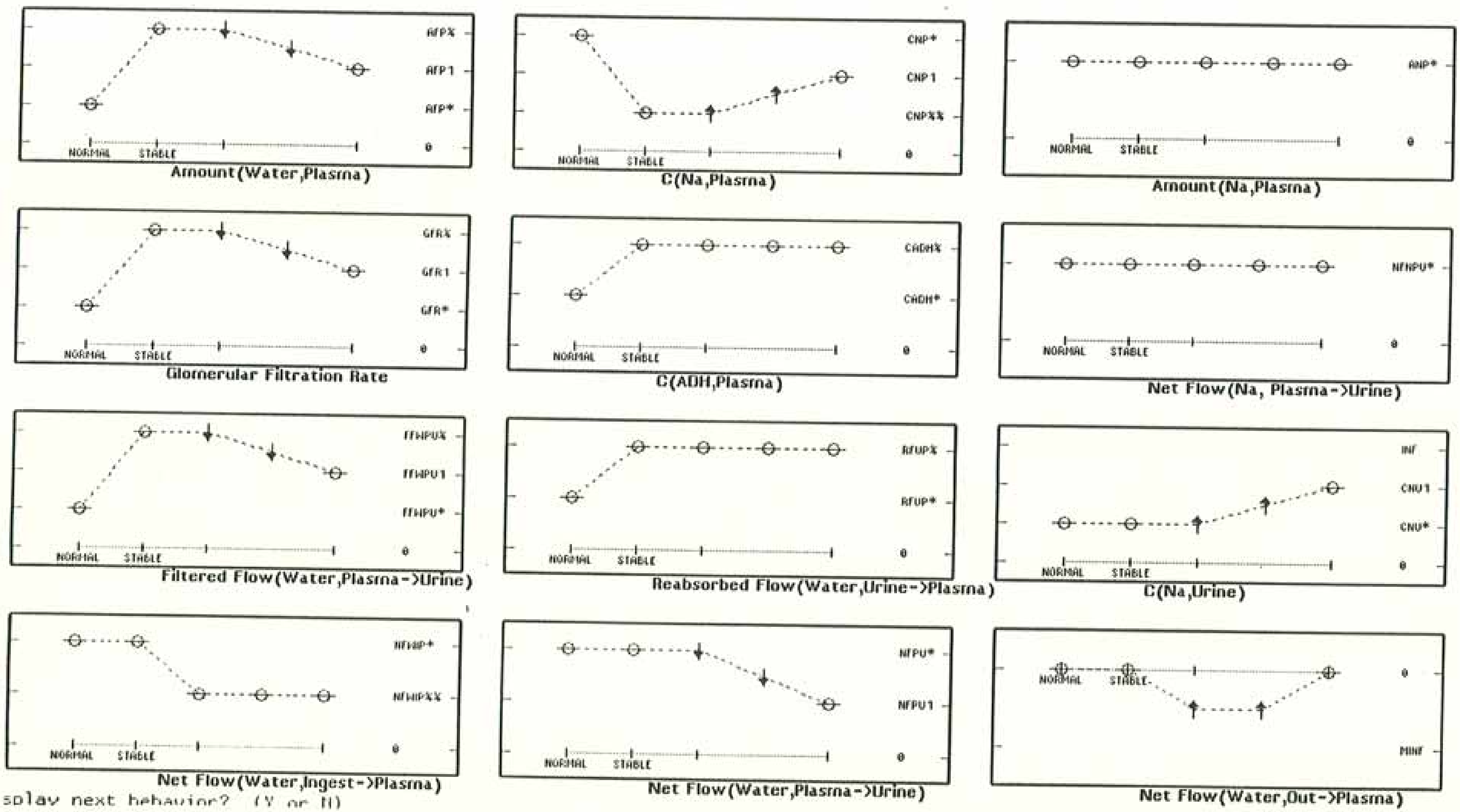
Initialization SIADH-WITH-NORMAL-INTAKE
of structure SIADH+WATER,
behavior 1 of 1.



Proceed? (Y or N)

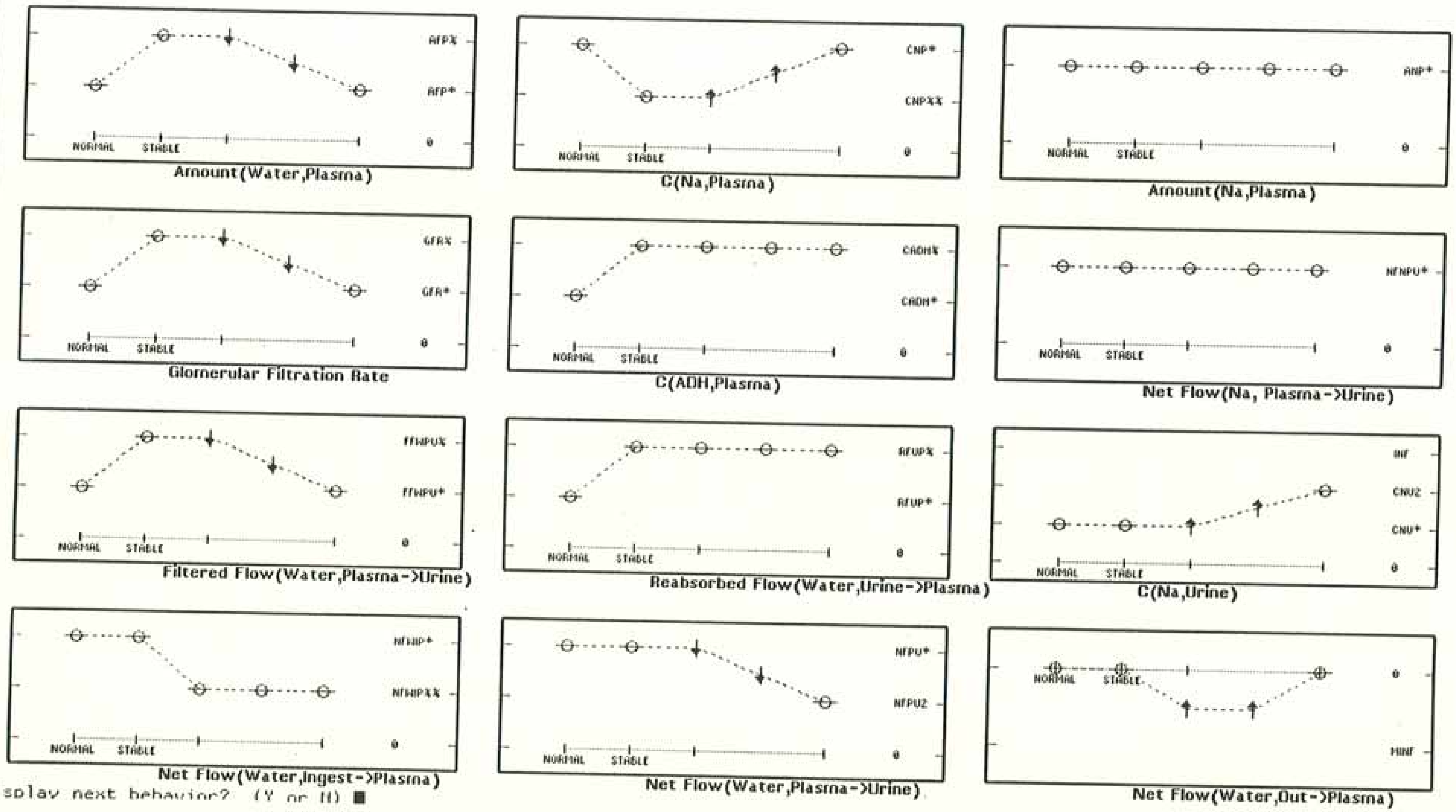
Initialization STABLE-SIADH-WITH-WATER-RESTRICTION
of structure SIADH+WATER,
behavior 1 of 3.





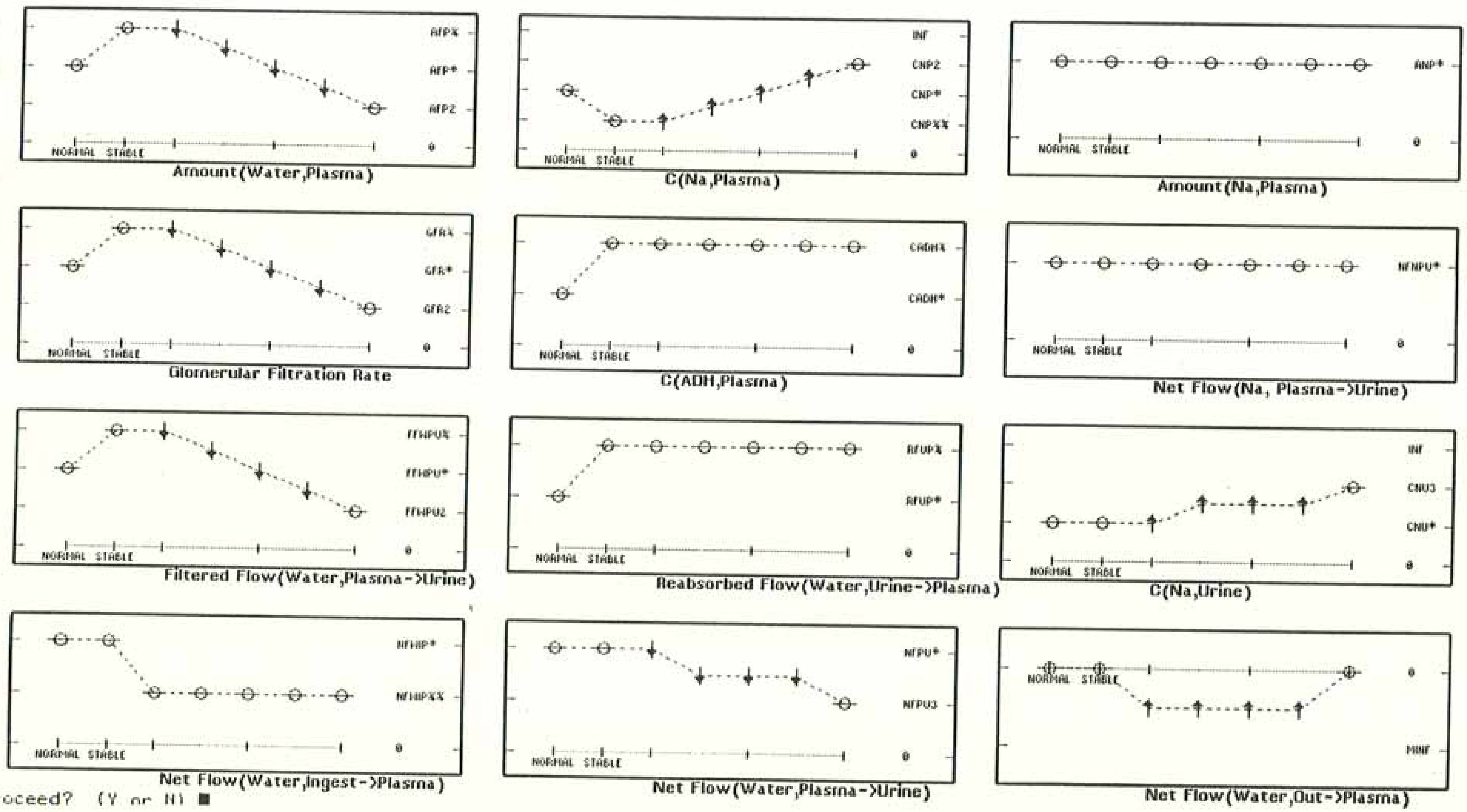
Display next behavior? (Y or N)

Initialization STABLE-SIADH-WITH-WATER-RESTRICTION
of structure SIADH+WATER,
behavior 2 of 3.

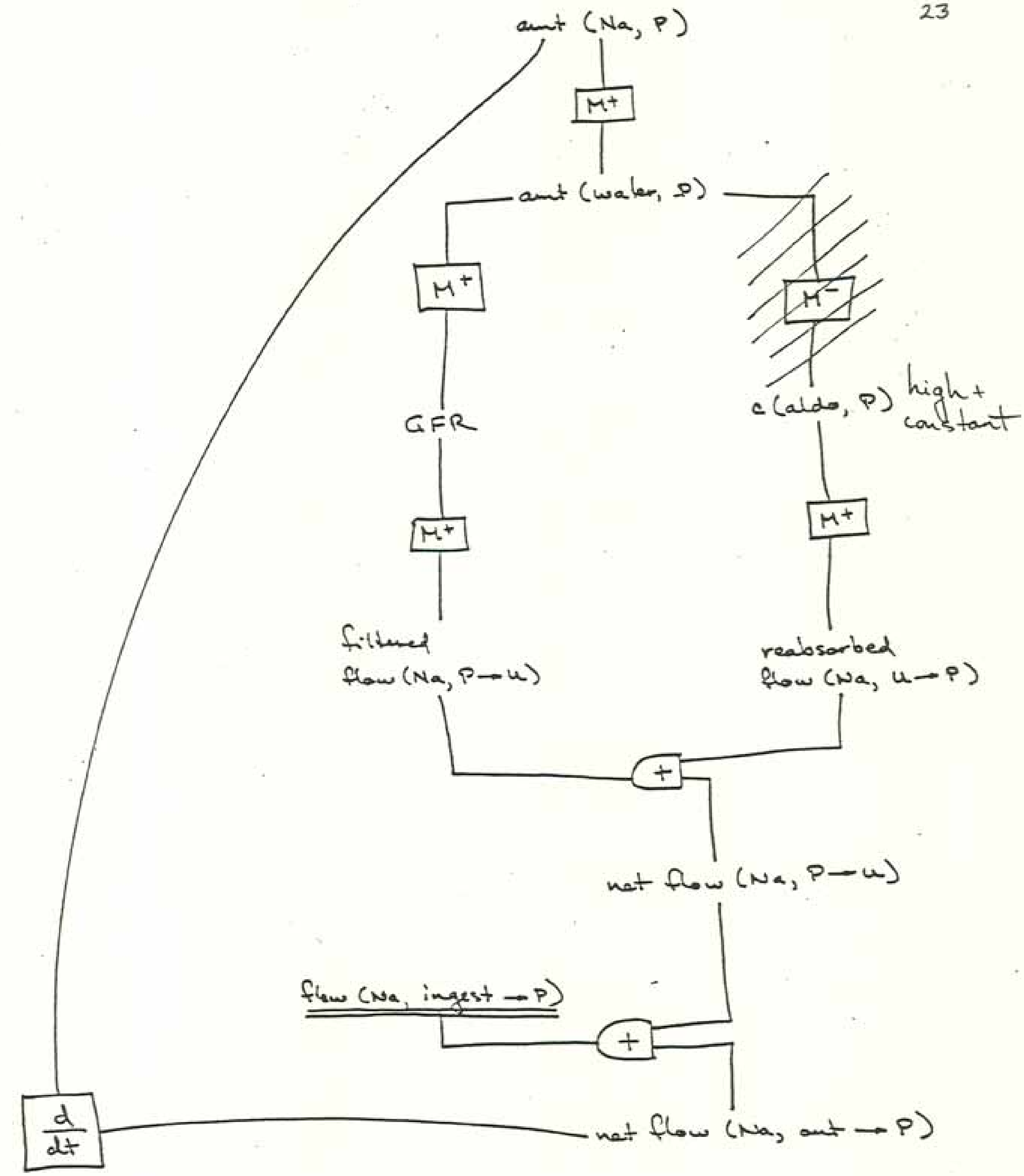


Display next behavior? (Y or N)

Initialization STABLE-SIADH-WITH-WATER-RESTRICTION
of structure SIADH+WATER,
behavior 3 of 3.



Proceed? (Y or N) ■

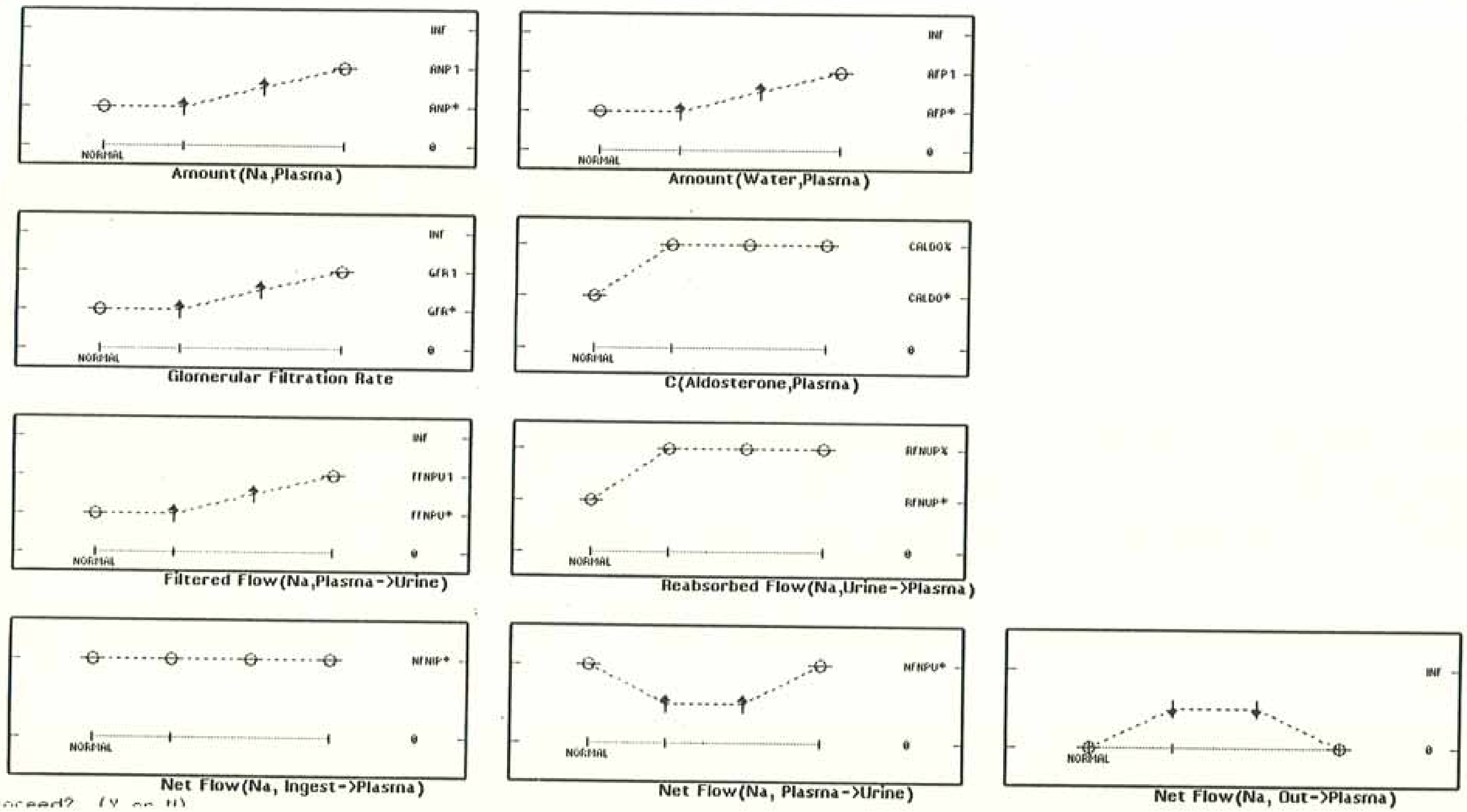


Assumptions:
flow (Na, ingest → P) is constant
M+ (amp, afp) can be treated as a function
(i.e. water balance is faster than Na balance)

HYPERALDO + SODIUM

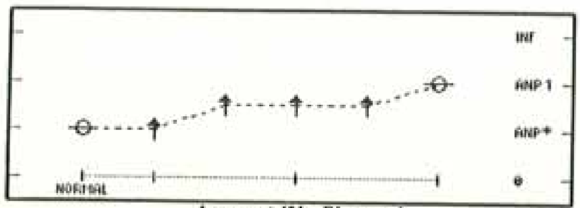
~~ALDO + SODIUM~~

Initialization HYPERALDO-WITH-NORMAL-SODIUM-INTAKE
of structure HYPERALDO+SODIUM,
behavior 1 of 1.

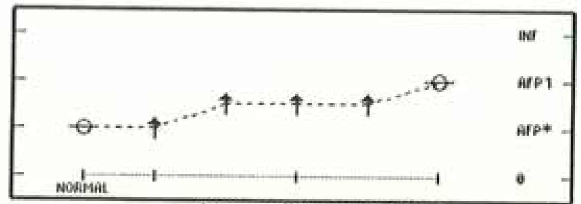


Proceed? (Y or N)

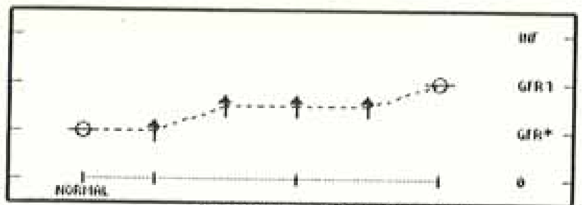
Initialization HYPERALDO-WITH-HIGH-SODIUM-INTAKE
of structure HYPERALDO+SODIUM,
behavior 1 of 1.



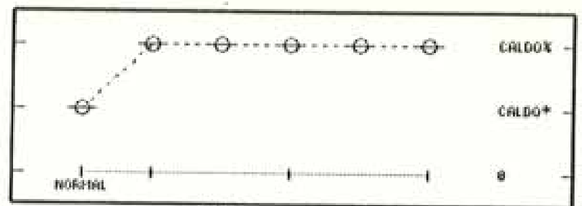
Amount(Na,Plasma)



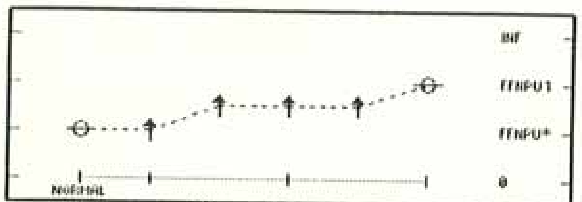
Amount(Water,Plasma)



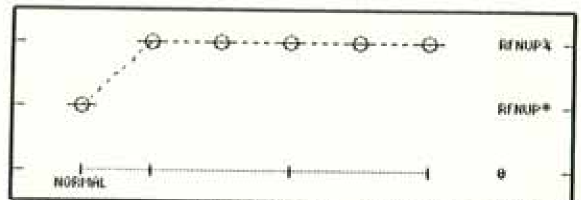
Glomerular Filtration Rate



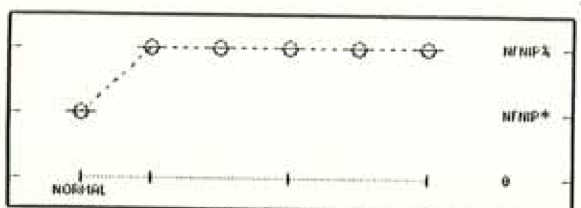
C(Aldosterone,Plasma)



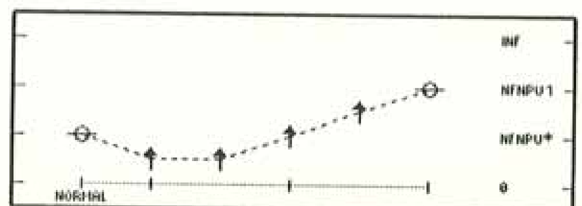
Filtered Flow(Na,Plasma->Urine)



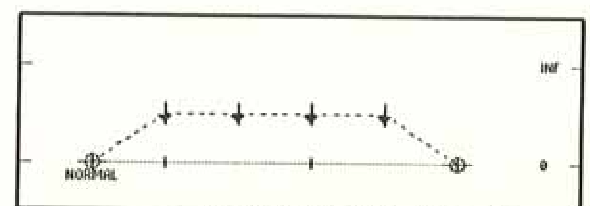
Reabsorbed Flow(Na,Urine->Plasma)



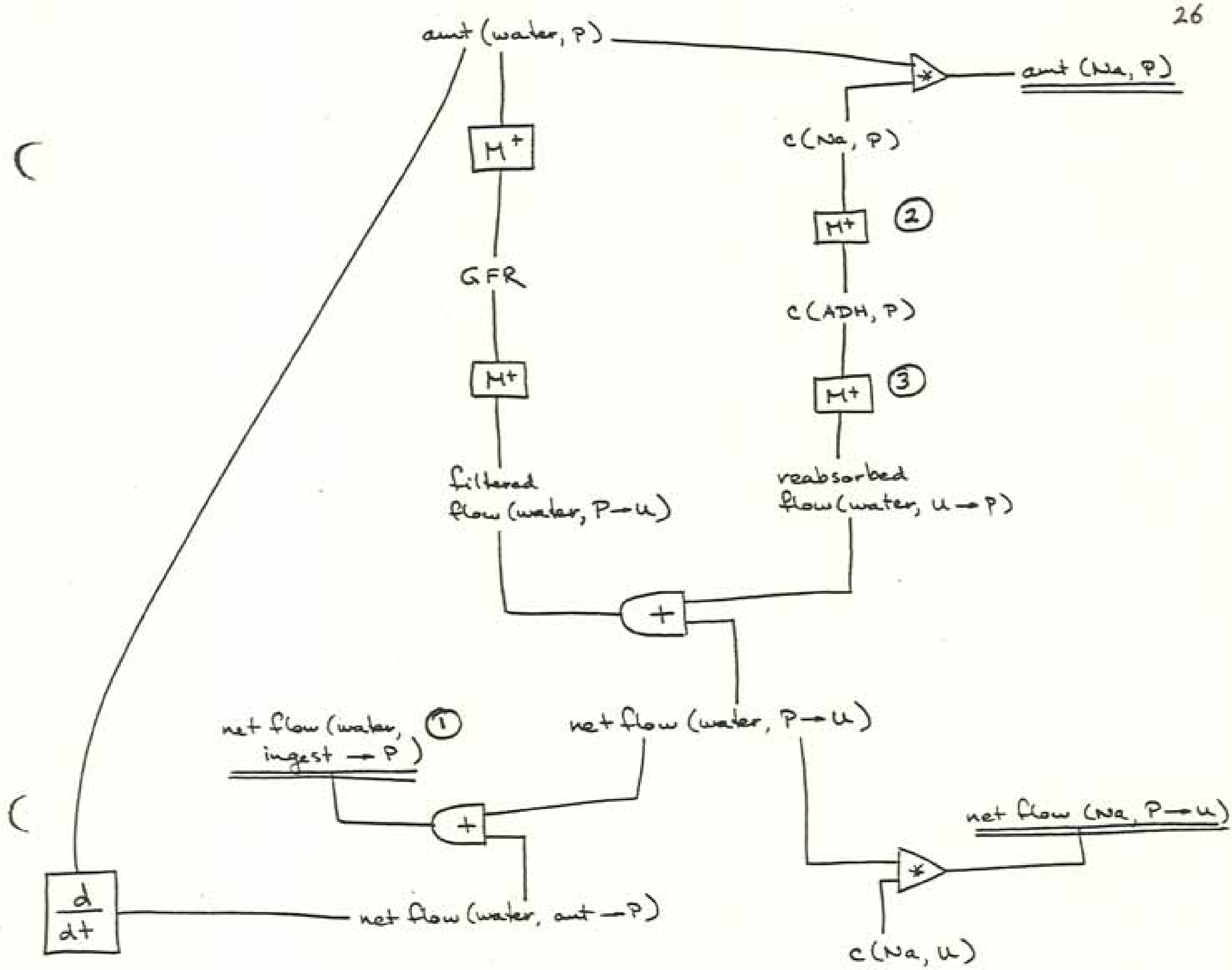
Net Flow(Na, Ingest->Plasma)



Net Flow(Na, Plasma->Urine)



Net Flow(Na, Out->Plasma)



Diabetes Insipidus:

① due to high water intake

② due to low ADH secretion.

③ due to insensitivity of the tubules to ADH

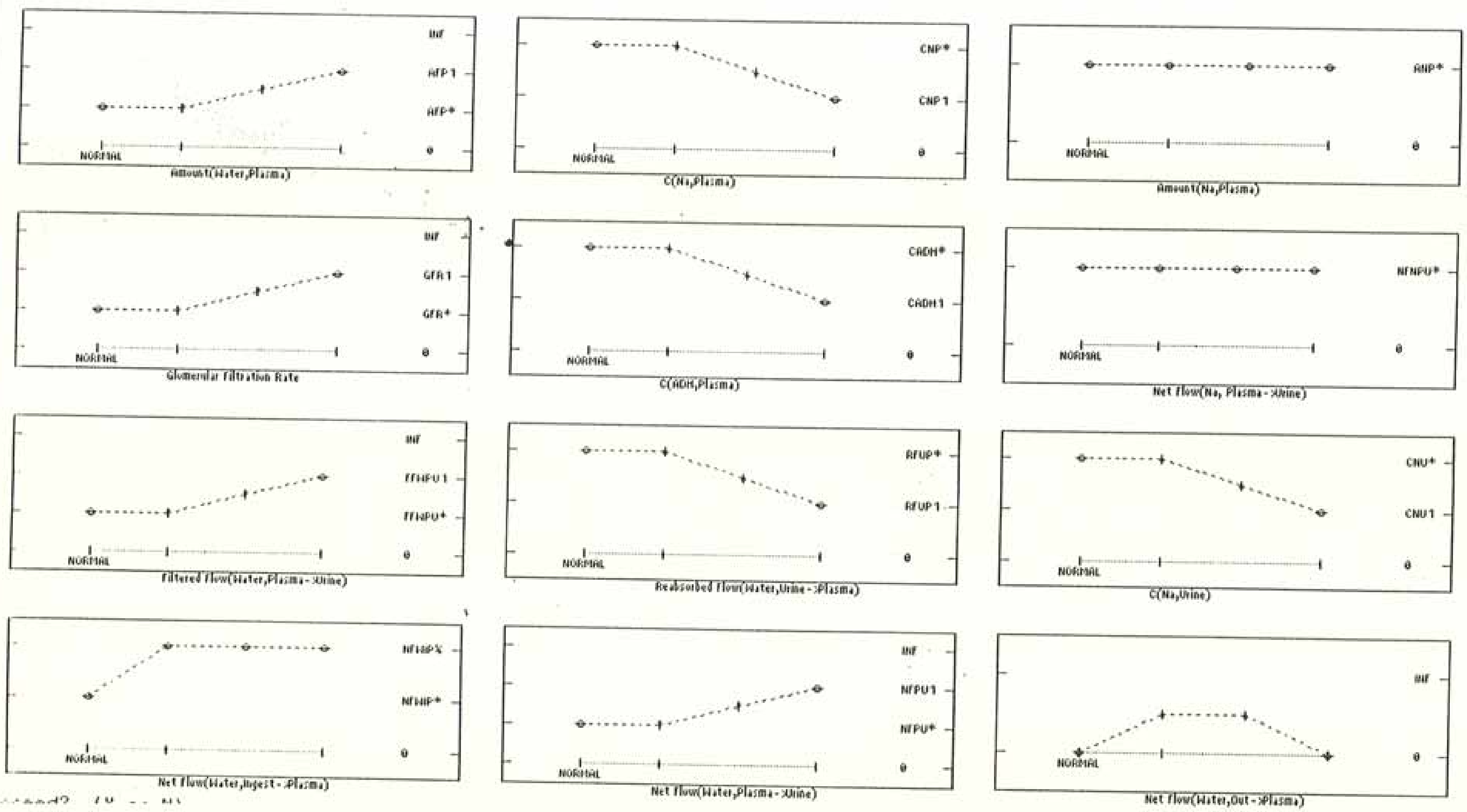
Assumptions:

amt (Na, P)
net flow (Na, P→U)
net flow (water, ingest →P)

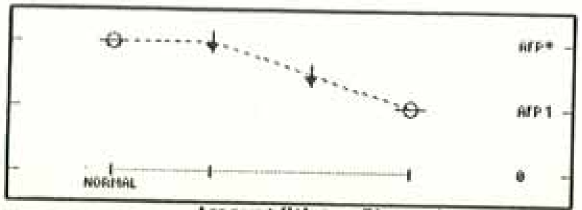
are all constant.

ADH + WATER

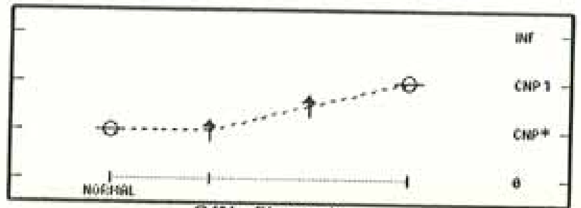
Initialization DI-FROM-HIGH-WATER-INTAKE
of structure DIABETES-INSIPIDUS,
behavior 1 of 1.



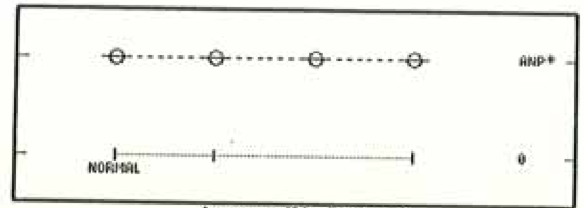
Initialization DI-W-DEC-ADH-INIT
of structure DI-W-DEC-ADH,
behavior 1 of 1.



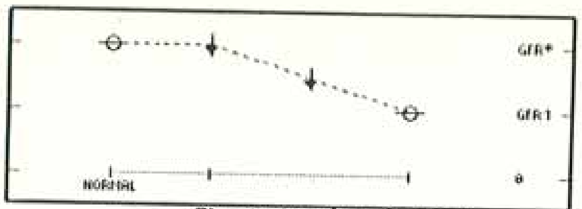
Amount(Water,Plasma)



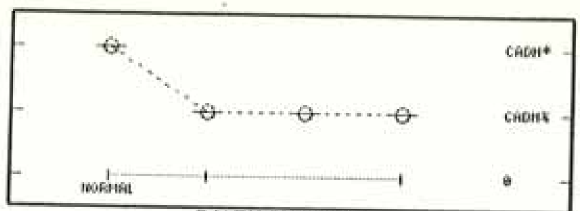
C(Na,Plasma)



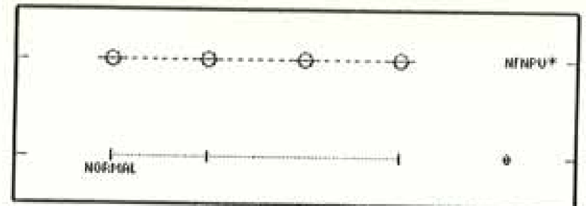
Amount(Na,Plasma)



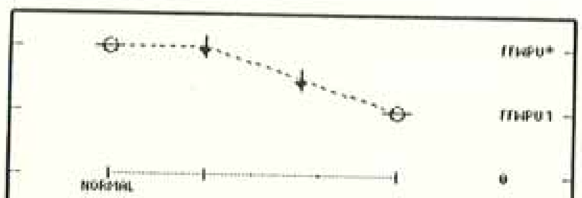
Glomerular Filtration Rate



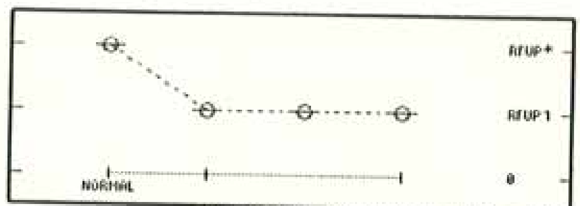
C(ADH,Plasma)



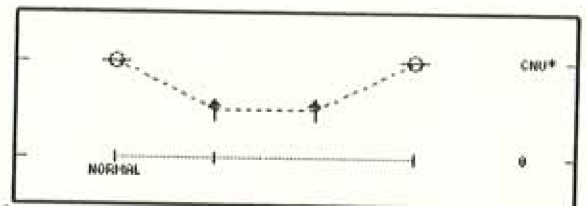
Net Flow(Na, Plasma->Urine)



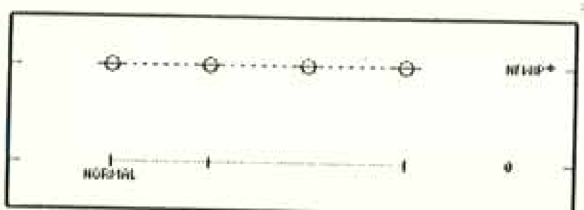
Filtered Flow(Water,Plasma->Urine)



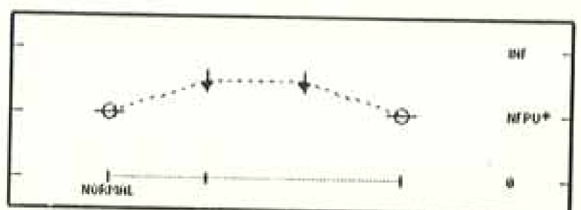
Reabsorbed Flow(Water,Urine->Plasma)



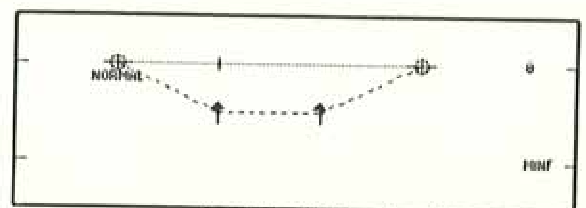
C(Na,Urine)



Net Flow(Water,Ingest->Plasma)



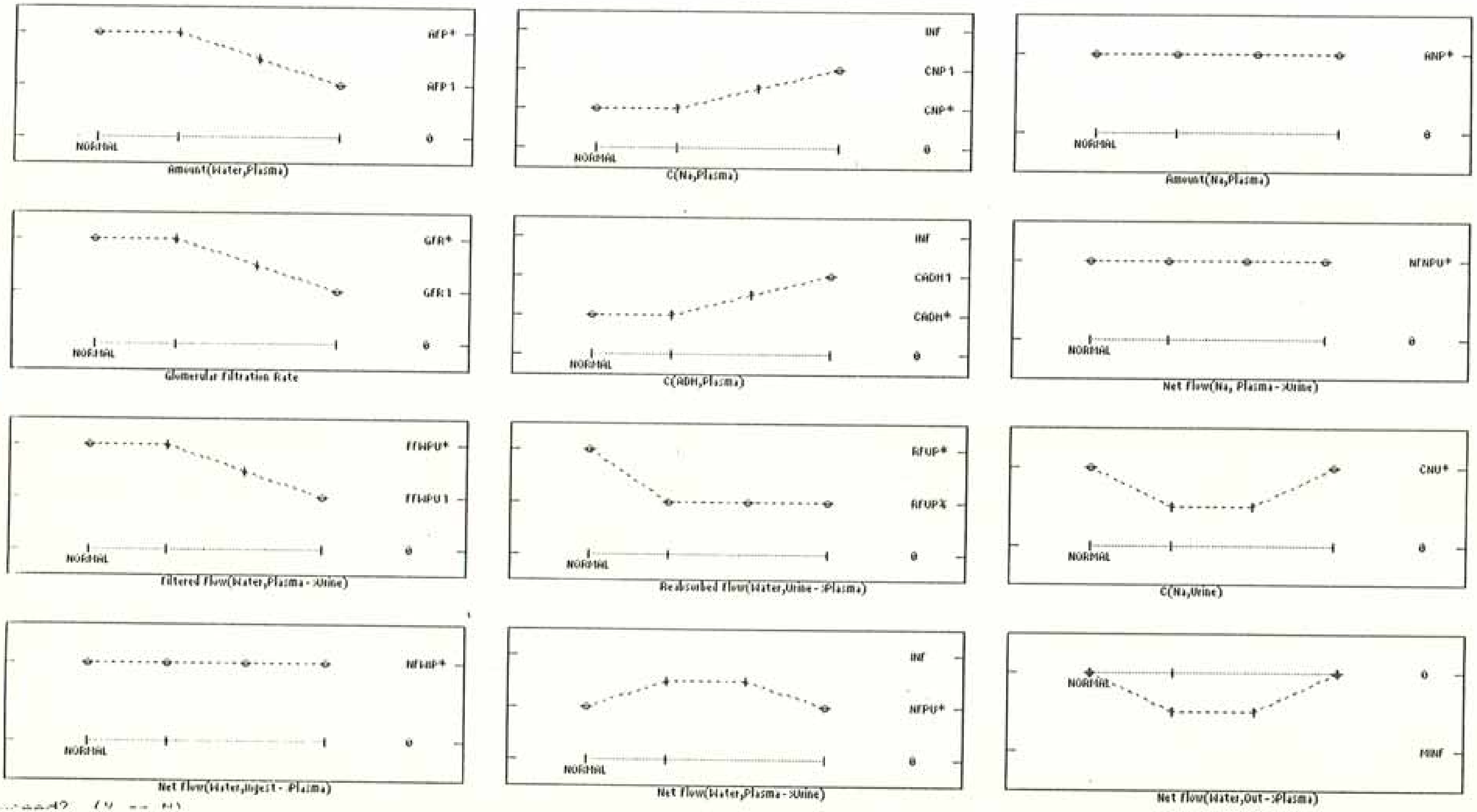
Net Flow(Water,Plasma->Urine)



Net Flow(Water,Out->Plasma)

Proceed? (Y or N)

Initialization DI-W-INSENSITIVITY-INIT
of structure DI-W-INSENSITIVITY,
behavior 1 of 1.



4 An Abstraction Hierarchy

In order to cope with the complexity of the overall physiological mechanism of the body, its description must be divided into simpler structures organized into a hierarchy. Each structural description is a qualitative version of a first-order differential equation, and constitutes one local view of the overall mechanism. Ideally, any given problem will require attention to only a few structures.

The hierarchical relations between different structures are based on the fact that equilibrium processes operate at very different time-scales. For example, the ADH+WATER mechanism responds to perturbations in a matter of minutes, while the ALDO+SODIUM mechanism may require hours to days to restore equilibrium. Without excessive distortion (we hope) one mechanism can treat the changes produced by a much faster process as being instantaneous, and the parameters controlled by much slower processes as being constants. In the ALDO+SODIUM structural description, the M^+ constraint between $amt(Na, P)$ and $amt(water, P)$ summarizes the behavior of the ADH+WATER mechanism given changes to $amt(Na, P)$. The two parameters, $amt(Na, P)$ and $amt(water, P)$, are thus treated as changing together according to the M^+ functional relation, when in fact there is a time-delay as the faster process responds to a change in one parameter to produce a change in the other parameter.

We can illustrate the use of this abstraction relation to represent the process by which long-term *water* balance is maintained by changing the retention or excretion of *sodium*.

1. Decreased water intake increases the concentration of sodium in the plasma and decreases plasma volume (ADH+WATER). The amount of plasma sodium, $amt(Na, P)$, is treated as constant.

2. The reduced volume ($amt(water, P)$) triggers the ALDO+SODIUM mechanism into retaining sodium, terminating when volume returns to normal, which results in higher than normal $amt(Na, P)$.

3. The ADH+WATER mechanism responds to increased $amt(Na, P)$ by increasing $amt(water, P)$ from its low value. The qualitative description of the ADH+WATER mechanism does not allow us to deduce whether the increase takes $amt(water, P)$ back to its normal value, so the simulation branches three ways. However, the ALDO+SODIUM simulation determined that $amt(water, P)$ returns to normal, allowing us to select the correct behavior.

The first two steps of the simulation actually predict the subsequent behavior of the system from given information, first over a short time-scale, then over a longer one. The third step elaborates on the final equilibrium state found by the ALDO+SODIUM system, demonstrating the process by which $amt(Na, P)$ and $amt(water, P)$ achieved their values, not just the constraint between them.

As shown below, qualitative simulation of the structures we have developed is able to express this behavior. The sequence of mechanisms and initial states selected for simulation is not constructed automatically. However, we must remember that human experts also learn this type of knowledge through explicit instruction, rather than deducing it from the physiology.

4.1 Index to Examples

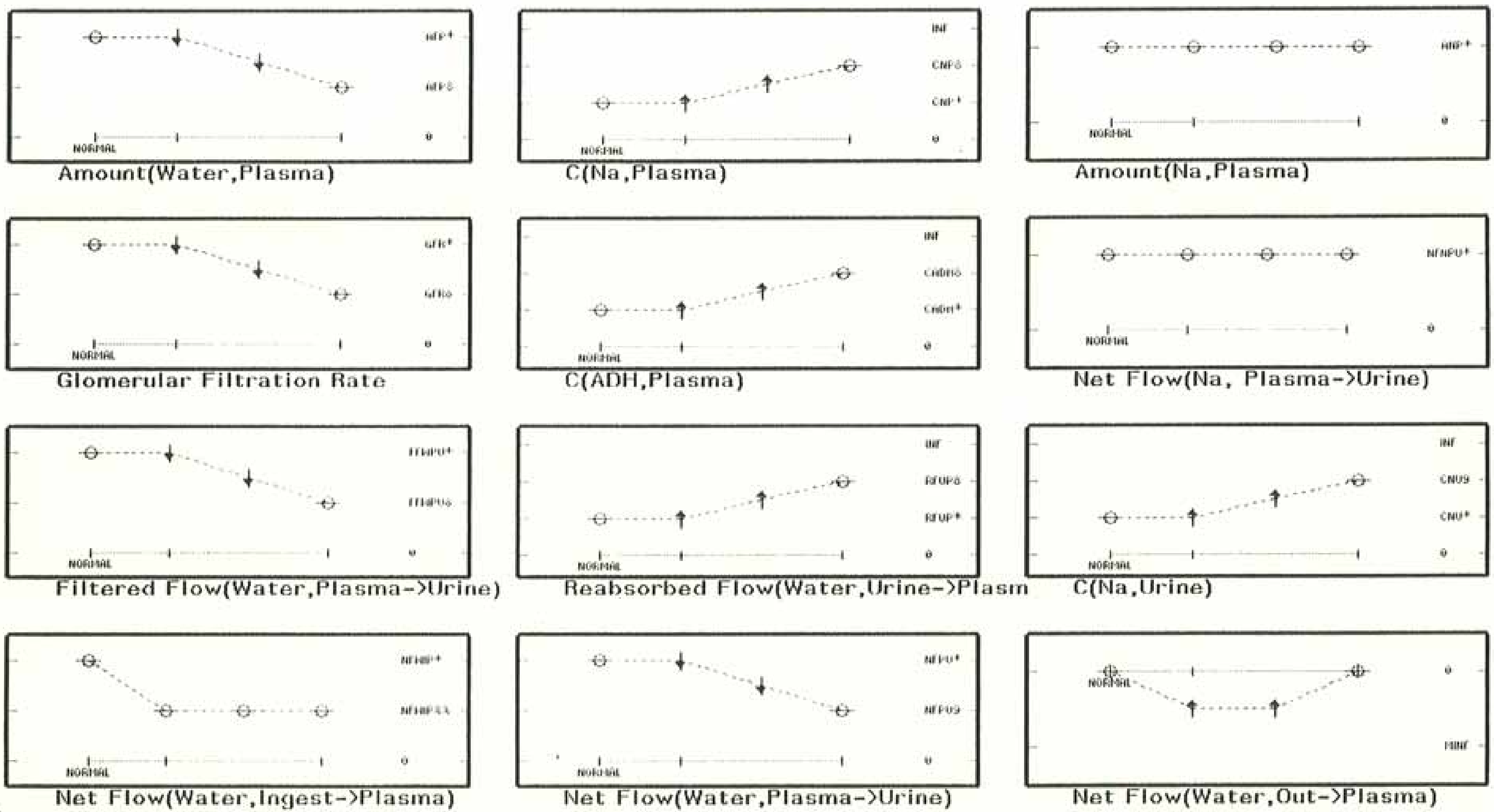
1. Abstraction example code.
2. "(1) ADH+WATER given low intake" behavior plot. The first step takes the normal ADH+WATER mechanism and simulates the consequences of low water intake.
3. "(2) ALDO+SODIUM given low fluid volume" behavior plot. The second step. After ADH+WATER has reached equilibrium, the relationship $M^+(amt(Na,P),\ amt(water,P))$ is shifted below its normal position, and the value of $amt(water,P)$ is low while $amt(Na,P)$ is normal. ALDO+SODIUM responds to decreased volume by retaining sodium until volume returns to normal.
4. "(3) ADH+WATER; first low intake, then increased amt(Na,P)" behavior plot (1 of 3). The third step produces the state of the ADH+WATER system after the ALDO+SODIUM mechanism has reached its final equilibrium state.
5. "(3) ADH+WATER; first low intake, then increased amt(Na,P)" behavior plot (2 of 3). This behavior is selected as the correct one because $amt(water,P)$ returns to its normal value, as predicted in step 2.
6. "(3) ADH+WATER; first low intake, then increased amt(Na,P)" behavior plot (3 of 3).

```
; ABSTRACTION sets up and runs the abstraction examples with the ADH and ALDO systems.
; It assumes that the file STRUCTURES has been loaded.

; The intuition is that a structure should be runnable from a variety of initializations,
; then the knowledge gained accumulated in the form of landmarks, correspondences, and
; known states, and new situations run in the resulting context.

; The abstraction method demonstrated here consists of:
;  - running the faster mechanism to equilibrium (adh+water)
;  - running the slower mechanism from its final state (aldo+sodium)
;  - filling in the description of the mechanism by taking the faster mechanism
;    from the state resulting from (1), perturbing according to the "input" information
;    supplied to the M+ in the slower mechanism (i.e. the state of ANP high),
;    and getting several possible results.  We then select the outcome we believe in
;    by looking at what the slower mechanism said happened.

(defun setup-adh-abstraction ()
  (setq adh-structure (adh+water))
  (send adh-structure :make-system-state 'normal
        '((NFWOP (O STD)) (NFWIP (NFWIP* STD)) (NFPU (NFPU* STD))
          (RFUP (RFUP* STD)) (CADH (CADH* STD)) (CNP (CNP* STD))
          (ANP (ANP* STD)) (FFWPU (FFWPU* STD)) (GFR (GFR* STD))
          (AFP (AFP* STD)) (CNU (CNU* STD)) (NFNPU (NFNPU* STD))))
  )

; The abstraction scenario
; takes normal ADH+WATER, and simulates with the assumption of low water intake,
; leading to low plasma volume.  The ALDO+SODIUM mechanism will respond by retaining
; sodium.  In turn, the ADH+WATER system will respond to increased sodium by retaining
; more water to keep volume up (though not as high as previously?).

; The first step takes the normal ADH+WATER system, and predicts the response to
; restricted water intake:  net flow(water,I->P)  =  NFWIP%% < NFWIP*.

(defun first-step ()
  (setq b (make-initialization adh-structure (generate-time-point)
                               '((NFWIP (NFWIP%% std))
                                 (anp (anp* std))
                                 (nfnpu (nfnpu* std))
                                 (afp (afp* nil)))
                               '((anp (anp* std))         ; normal sodium
                                 (nfwip (nfwip%% std))  ; constant low intake
                                 (nfnpu (nfnpu* std)))  ; normal sodium excretion
                               "(1) ADH+WATER given low intake"
                               ))
  (qsim b)
  (setq c (send b :get-behaviors))
  (qsim-display b adh-layout)
  )
```

```
; The second step simulates the effect of the ALDO+SODIUM system, starting with
; low volume produced by low intake, considered by ADH+WATER.
; The "normal" time-point is eliminated, since it creates the now-incorrect
; correspondence between ANP* and AFP*.  No new correspondence needs to be
; inserted, since the initial state contains enough information to lead the
; simulation in the correct direction.

(defun second-step ()
  (setq a2 (aldo+sodium))
  (loop for (con corr) in '(((M+ AFP GFR)       (afp* gfr*))
                            ((M+ GFR FFNPU)     (gfr* ffnpu*))
                            ((M- AFP CALDO)     (afp* caldo*))
                            ((M+ CALDO RFNUP)  (caldo* rfnup*))
                            ((add RFNUP NFNPU FFNPU)  (rfnup* nfnpu* ffnpu*))
                            ((add NFNPU NFNP NFNIP)   (nfnpu* 0 nfnip*)))
        for con2 = (find-constraint con a2)
        do (send a2 :add-extra-correspondence con2 corr))

  (setq b2 (make-initialization a2 (generate-time-point)
                                '((afp ((0 afp*) nil))
                                  (anp (anp* nil))
                                  (nfnip (nfnip* std)))
                                '((nfnip (nfnip* std)))
                                "(2) ALDO+SODIUM given low fluid volume"
                                ))
  (qsim b2)
  (setq c2 (send b2 :get-behaviors))
  (qsim-display b2 aldo-layout)
  )
```

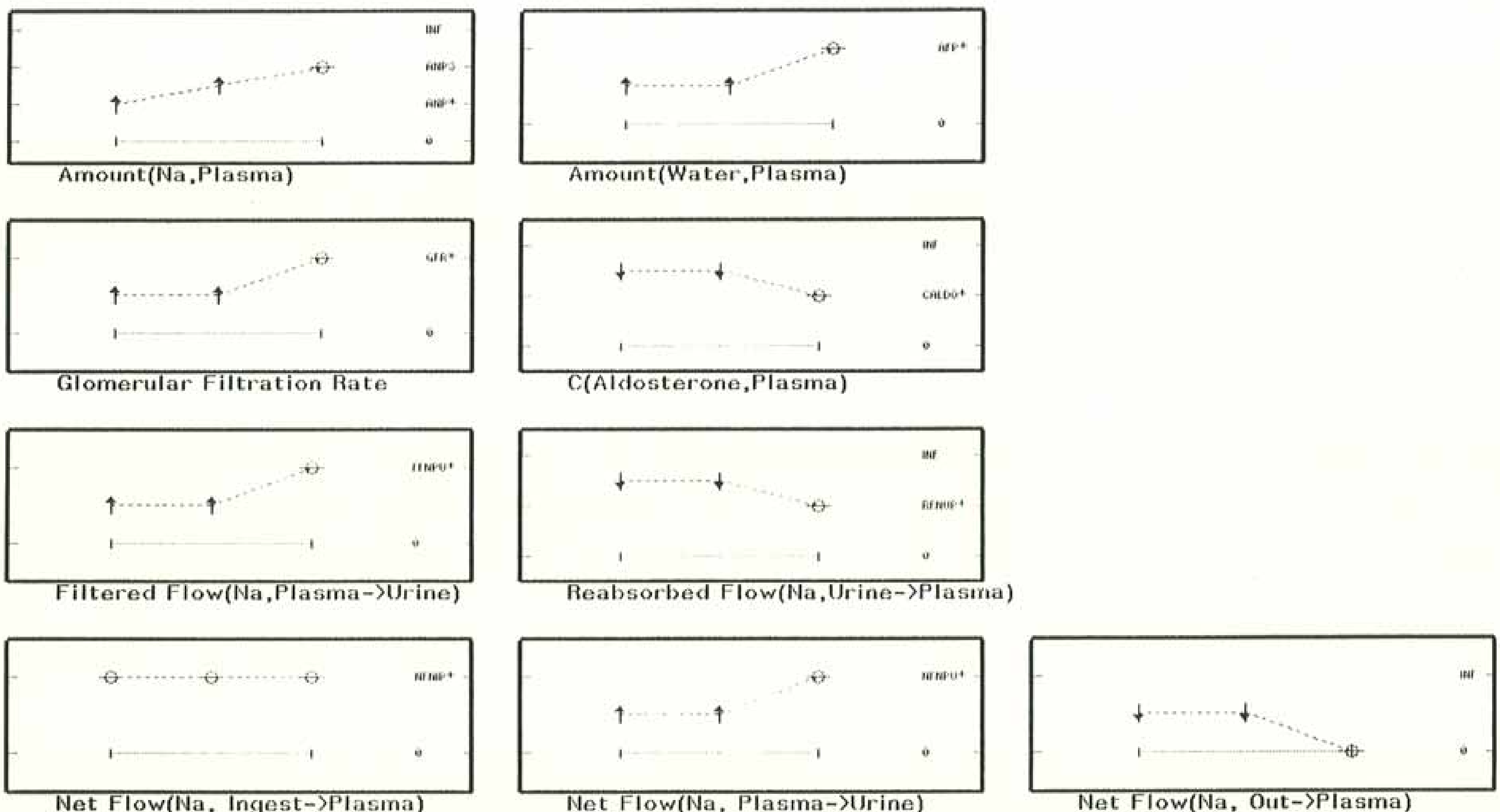
```
; The third step starts with amt(Na,P) = ANP%, whose significance is
; "some value higher than normal", rather than being a particular high value.
; Amt(water,P) is less than normal but increasing, as we know from step two
; with ALDO+SODIUM.

(defun third-step ()
  (setq b4 (make-initialization adh-structure (generate-time-point)
                                 '((NFWIP (NFWIP%% std))
                                   (anp (anp% std))
                                   (nfnpu (nfnpu* std))
                                   (afp ((0 afp*) inc)))
                                 '((anp (anp% std))        ; high sodium
                                   (nfwip (nfwip%% std))  ; constant low intake
                                   (nfnpu (nfnpu* std)))  ; normal sodium excretion
                                 "(3) ADH+WATER; first low intake, then increased amt(Na,P)"
                                 ))
  (qsim b4)
  (setq c4 (send b4 :get-behaviors))
  (qsim-display b4 adh-layout)
  )
```

Initialization (1) ADH+WATER given low intake
of structure ADH+WATER,
behavior 1 of 1.



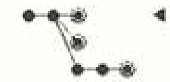
NIL

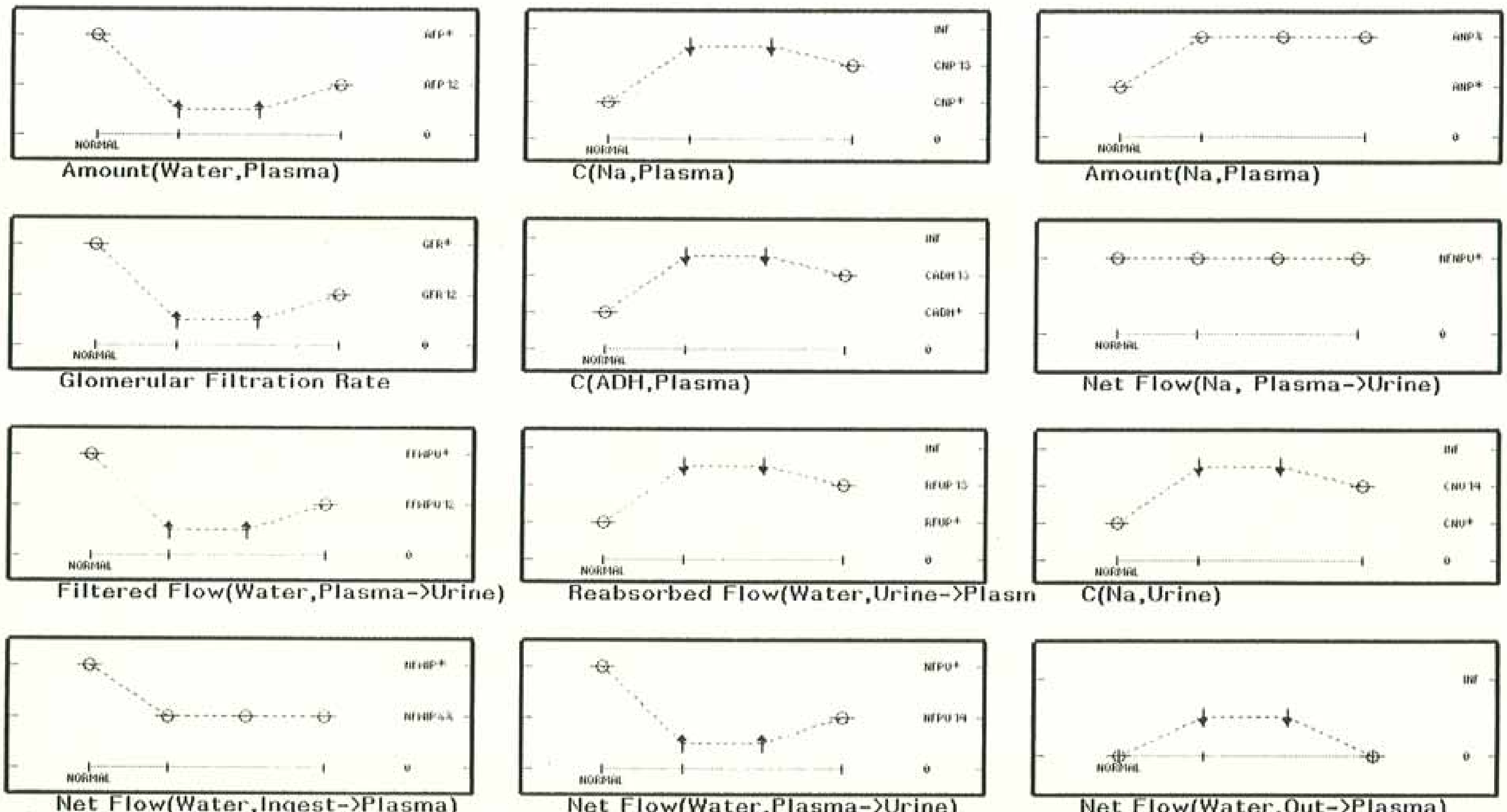
Initialization (2) ALDO+SODIUM given low fluid volume
of structure ALDO+SODIUM,
behavior 1 of 1.



NIL

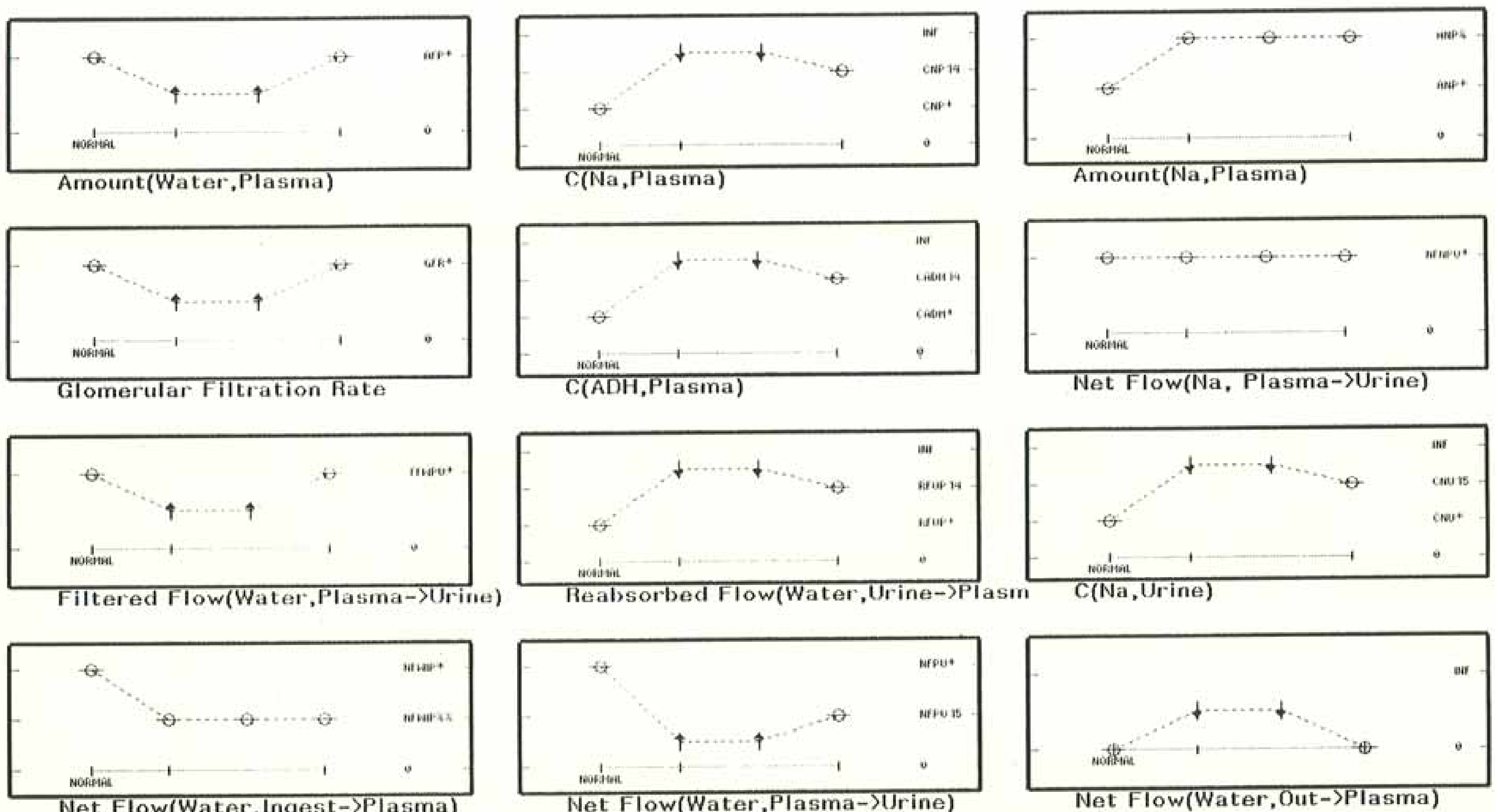
```
Initialization (3) ADH+WATER; first low intake, then increased amt(Na,P)
   of structure ADH+WATER,
   behavior 1 of 3.
```





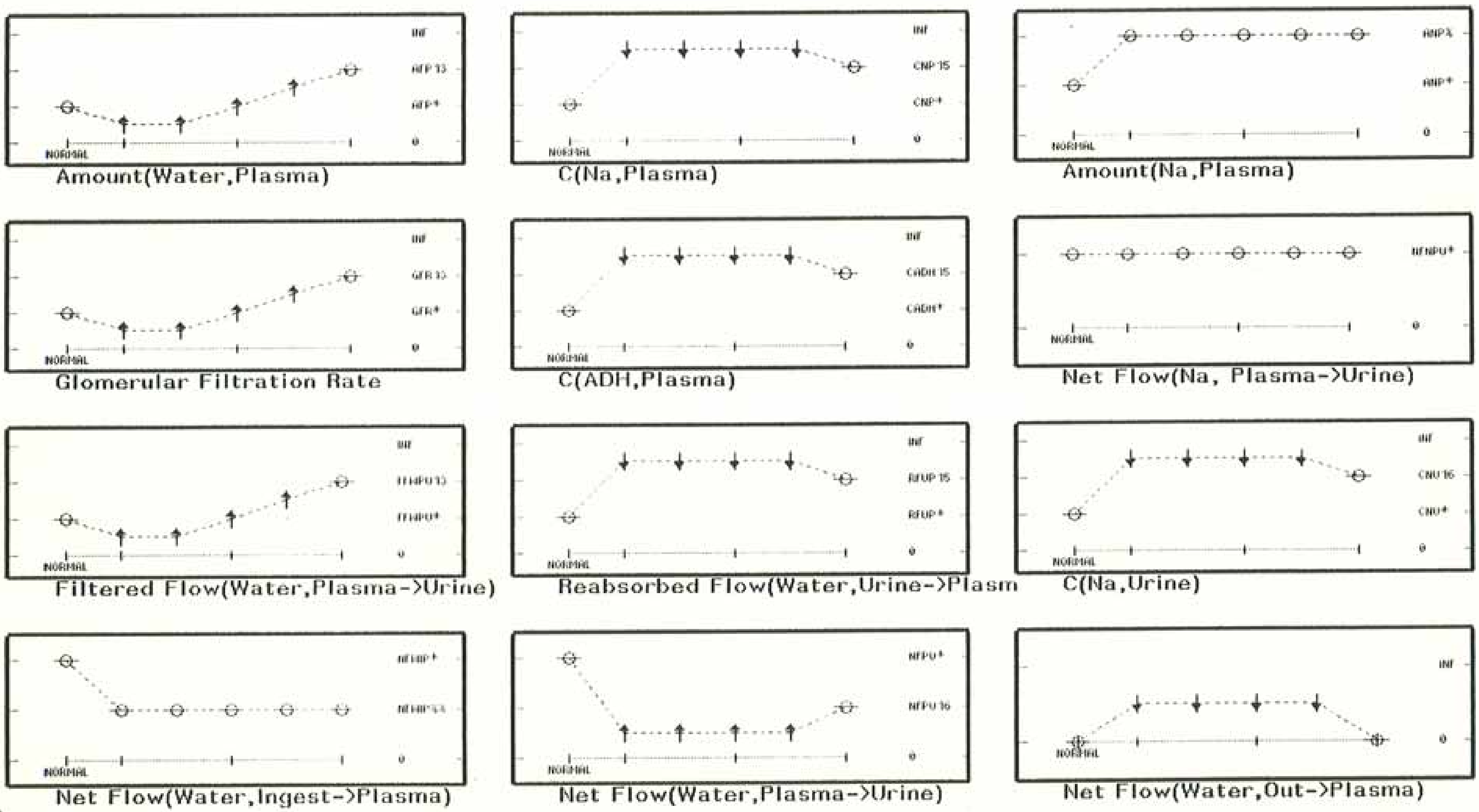

```
Display next behavior?  (Y or N)
```

Initialization (3) ADH+WATER; first low intake, then increased amt(Na,P)
of structure ADH+WATER,
behavior 2 of 3.



Display next behavior? (Y or N)

Initialization (3) ADH+WATER; first low intake, then increased amt(Na,P)
of structure ADH+WATER,
behavior 3 of 3.



NIL

5 Regulation of Blood Pressure

Considering the generality of qualitative simulation as an abstraction of differential equations, it should be applicable to other medical domains where physiological knowledge can be expressed as differential equations. In order to test this hypothesis, I enlisted the aid of a group of physicians to construct a description of an important mechanism in cardiology, starting from scratch.

In a guest lecture at Peter Szolovits' seminar, Artificial Intelligence in Medicine, a varied group consisting of decision analysis fellows (MDs), computer science graduate students, and myself (BK, non-MD), constructed a structural description for the regulatory system for blood pressure via sympathetic stimulation. After a lecture on the goals and methods of the representation, they were presented with a naive first draft of the structural description. We spent about two hours rearranging, expanding, consolidating, and debugging the original description, ending up with a slightly simpler version of the structure presented below. After typing it in and correcting typos, the QSIM simulation ran successfully on the first try, with the results reported below.

The structural description consists of 27 parameters linked by 21 constraints. Of those 27 parameters, six are "loose ends" which are considered constant, and provide a way to express an input condition. They are:

AB	alpha stimulation, base component
BB	beta stimulation, base component
INx	inotropic state, additional factors
HRx	heart rate, additional factors
PVRx	peripheral vascular resistance, other factors
BV	blood volume

5.1 Example: Response to Beta Blocker

In the example below, the system is initialized in a state where all parameters are normal except for beta-base (BB), which is lower than normal. Thus, it corresponds to the cardiac response to a beta blocker. Given this initial state, QSIM finds five distinct behaviors which are described in the table below. They differ primarily in the behavior of Stroke Volume, Ejection Fraction, and Inotropic State. The first behavior represents the normal behavior of the system, and the other four represent various cases where the compensating increase in alpha stimulation dominates the decreased beta stimulation. These may not represent real possibilities, but rather indicate deficiencies in the structural description, as discussed below.

	Stroke Volume	Ejection Fraction	Inotropic State
1.	low	low	low
2.	normal	low	low
3.	high	low	low
4.	high	normal	normal
5.	high	high	high

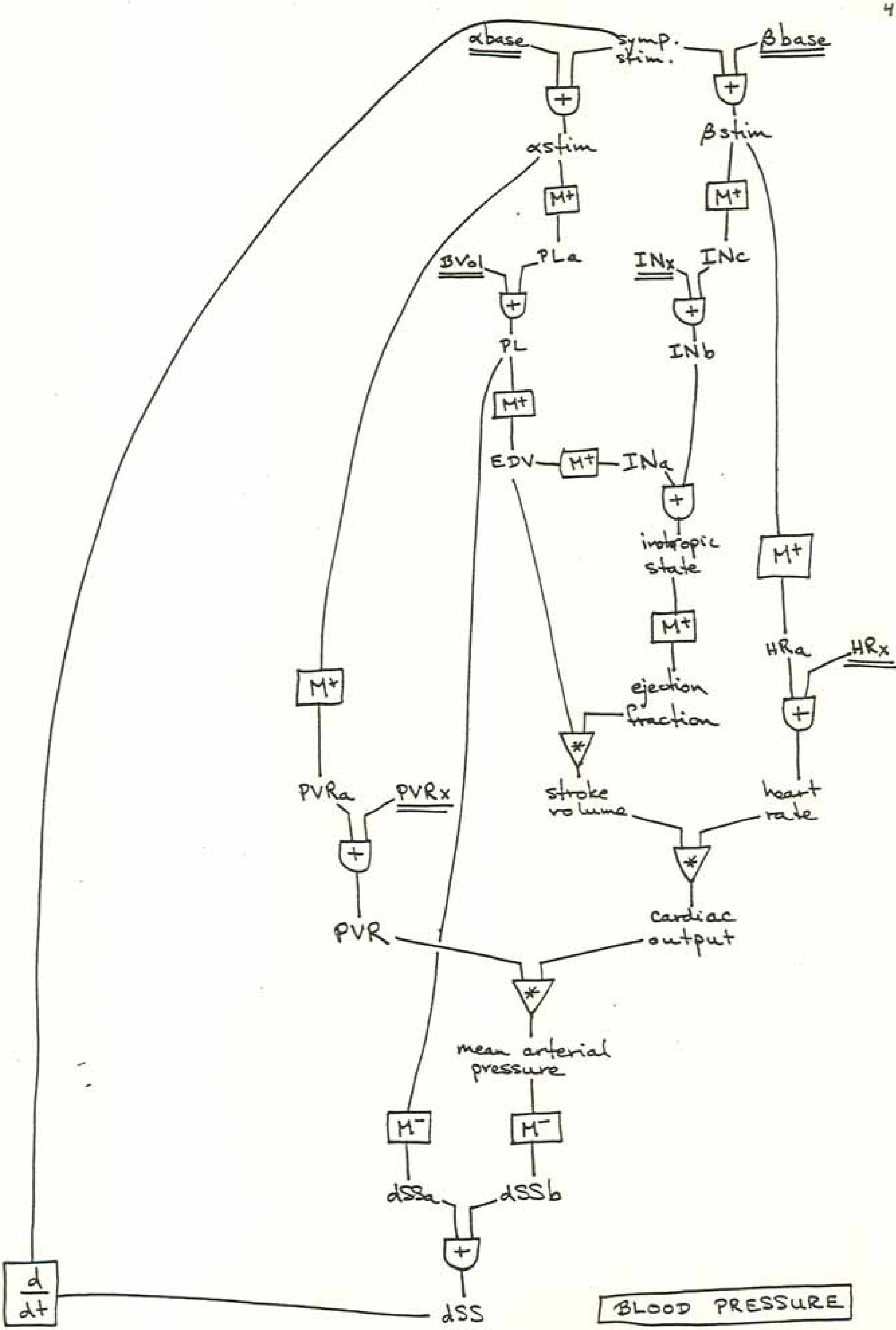
5.2 Problems with the Structure

While this structure yields reasonable predictions considering that it was essentially completely constructed in a short seminar meeting, there are significant inadequacies in the medical content. Creation of a genuinely adequate structural description for this mechanism will require extensive consulation with an expert cardiologist.

- The connection between alpha-stimulation and preload ($M^+(AS, PLa)$) is much more complex than the structure captures, and needs expansion.
- Increased end diastolic volume can increase inotropic state, as shown in the structure, but it cannot result in increased ejection fraction. The M^+ relation between inotropic state and ejection fraction assumes constant volume.
- Decreased alpha stimulation decreases afterload, which for a given inotropic state results in increased ejection fraction.
- Increased heart rate decreases stroke volume through decreased filling time and thus end diastolic volume.

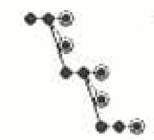
5.3 Index to Examples

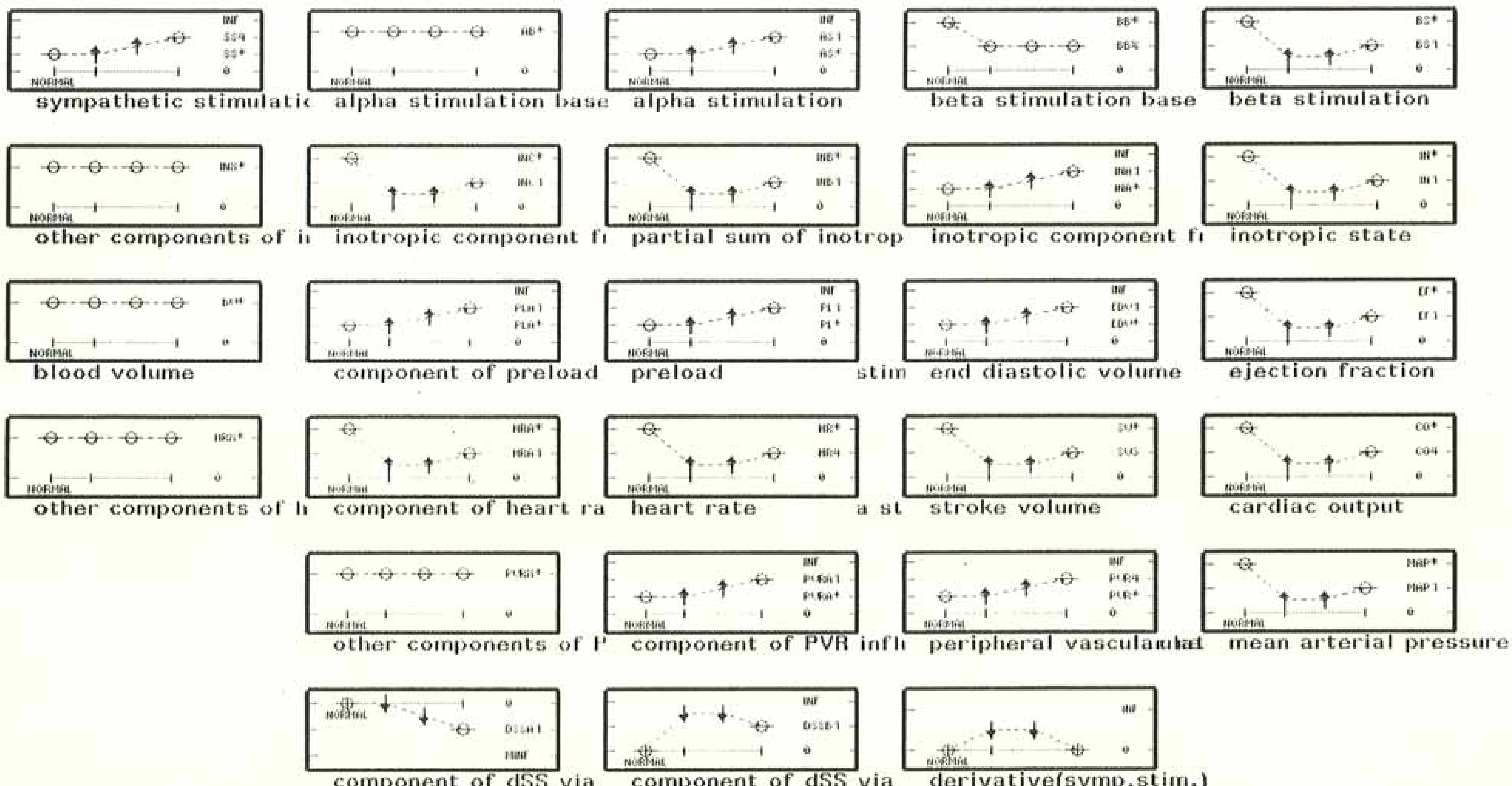
1. BLOOD-PRESSURE graphical structure.
2. "Blood Pressure given beta blocker" behavior plot (1 of 5)
3. "Blood Pressure given beta blocker" behavior plot (2 of 5)
4. "Blood Pressure given beta blocker" behavior plot (3 of 5)
5. "Blood Pressure given beta blocker" behavior plot (4 of 5)
6. "Blood Pressure given beta blocker" behavior plot (5 of 5)



BLOOD PRESSURE

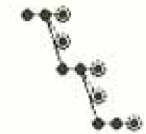
Initialization Blood Pressure given beta blocker
of structure BLOOD-PRESSURE,
behavior 1 of 5.

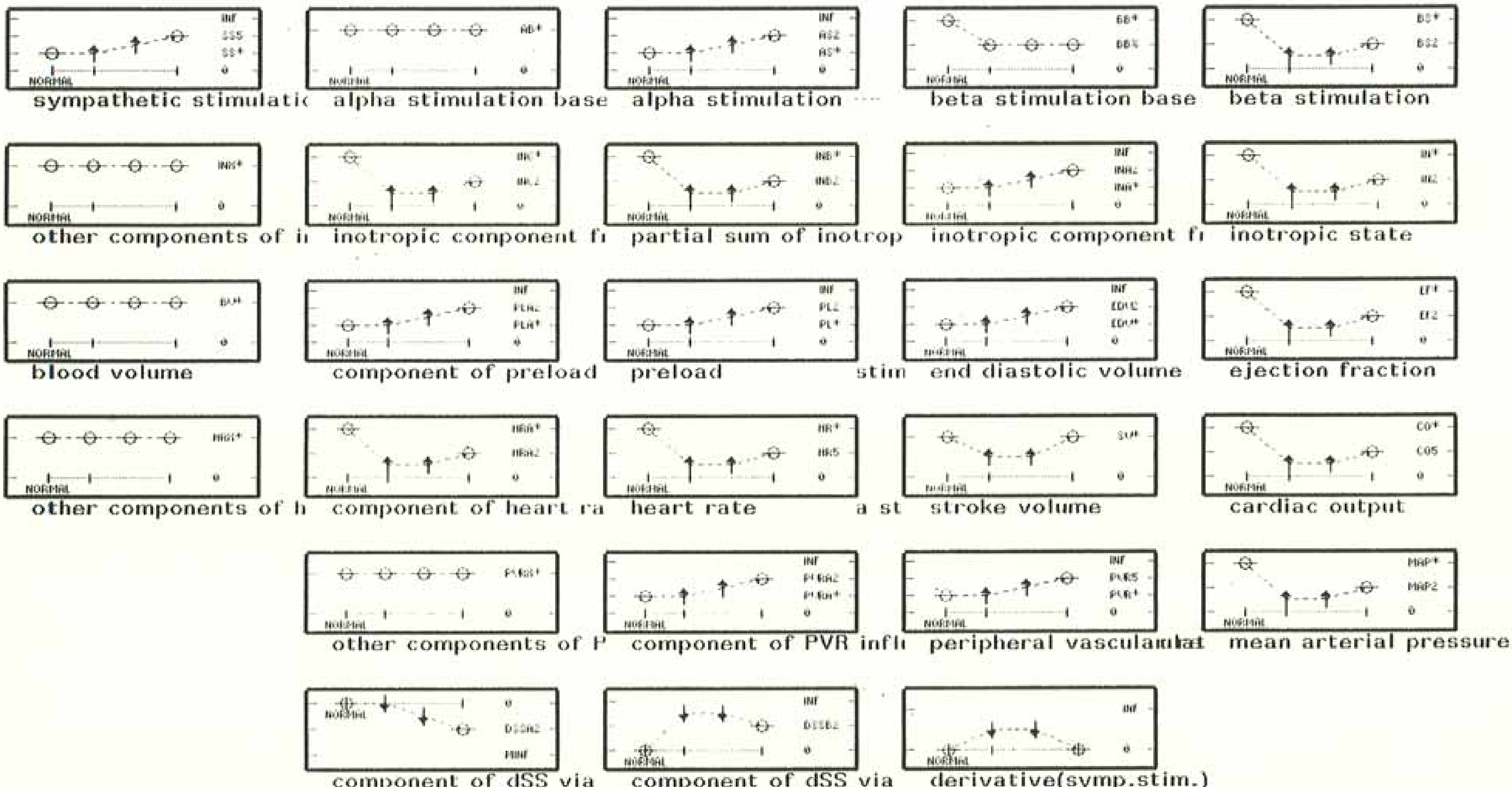




Display next behavior? (Y or N) █

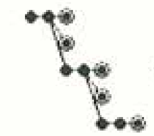
Initialization Blood Pressure given beta blocker
of structure BLOOD-PRESSURE,
behavior 2 of 5.

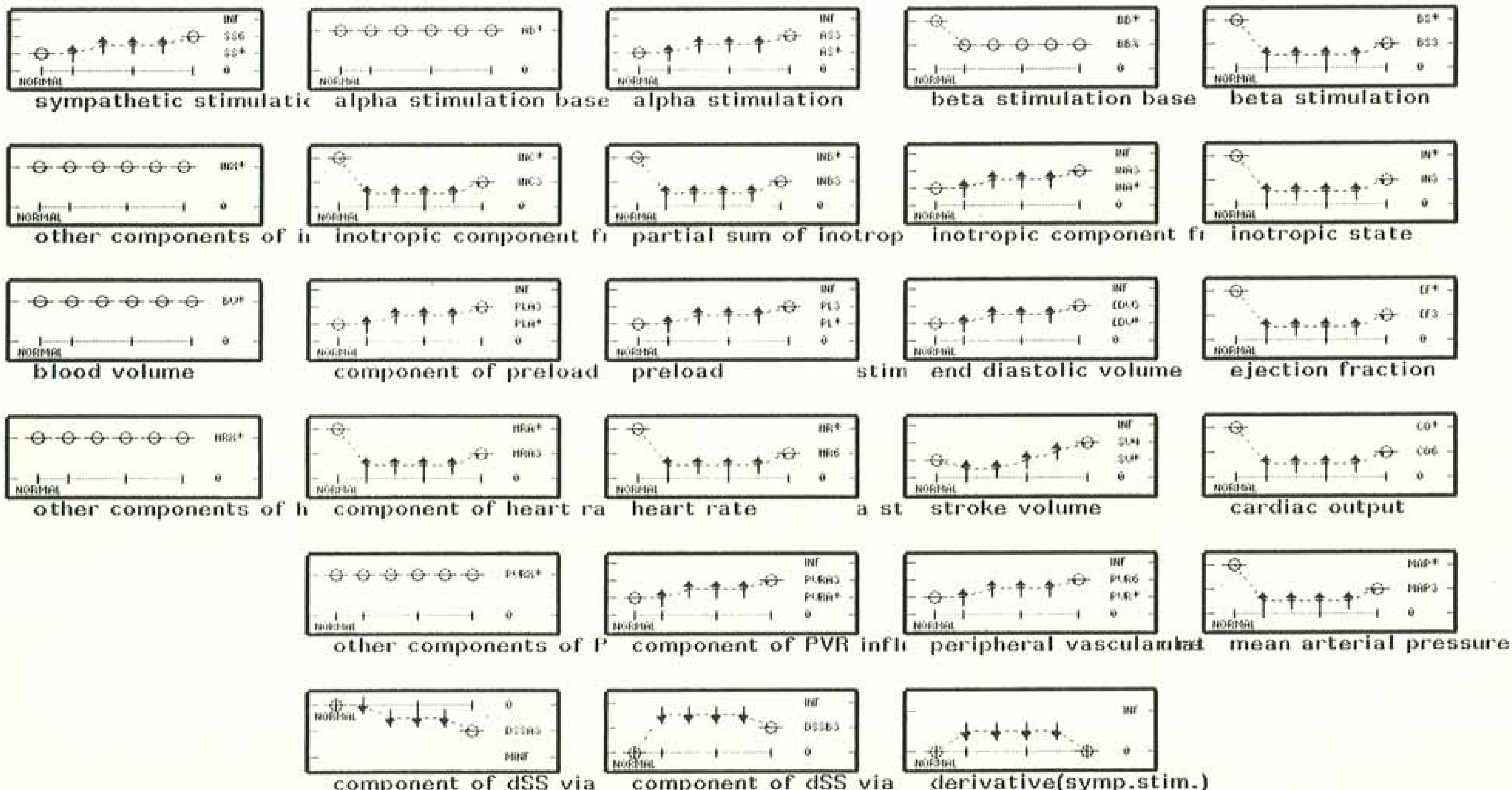




Display next behavior? (Y or N)

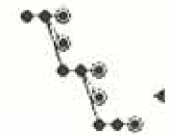
Initialization Blood Pressure given beta blocker
of structure BLOOD-PRESSURE,
behavior 3 of 5.

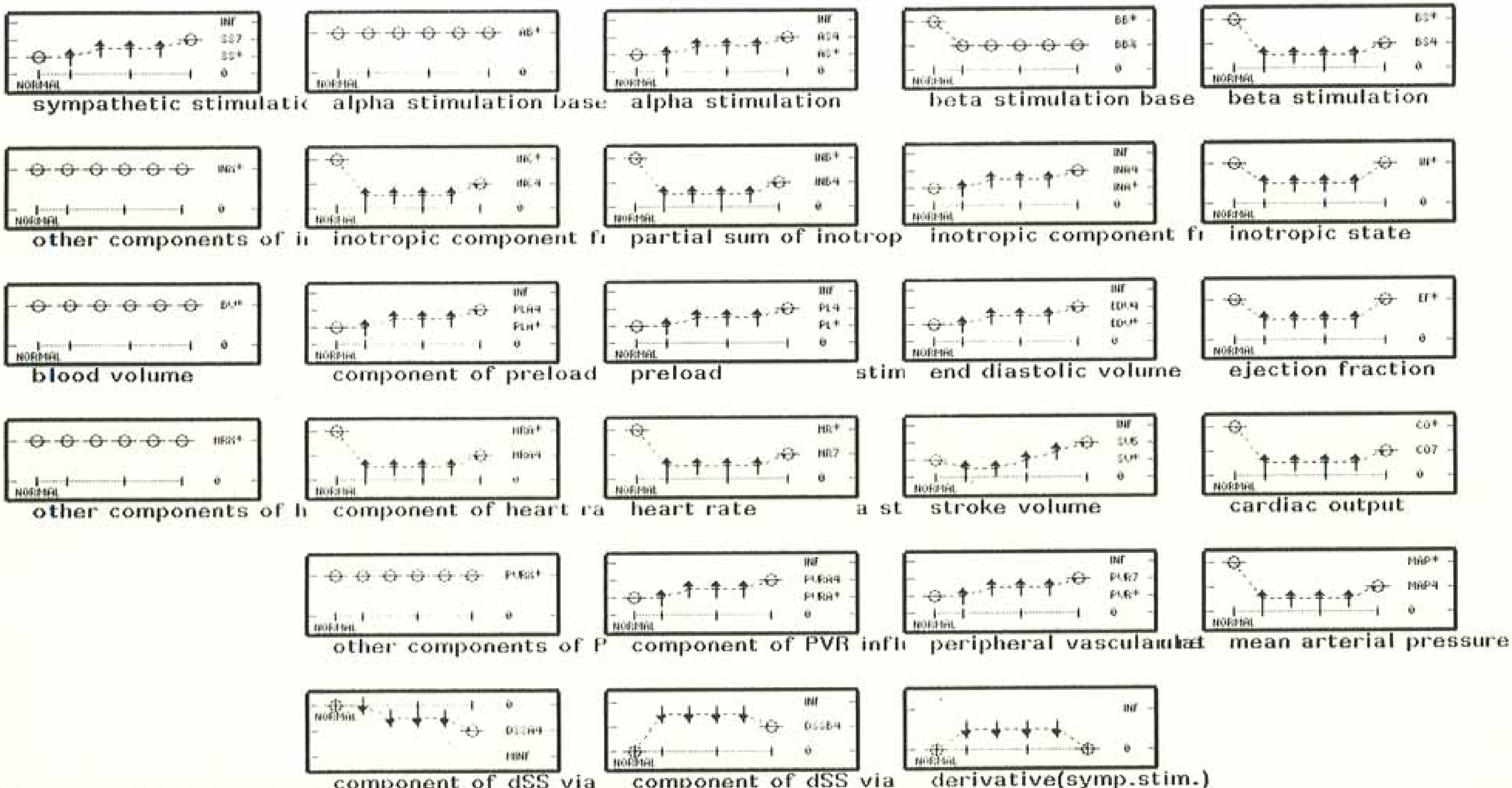




Display next behavior? (Y or N)

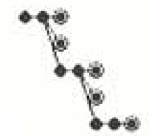
Initialization Blood Pressure given beta blocker
of structure BLOOD-PRESSURE,
behavior 4 of 5.

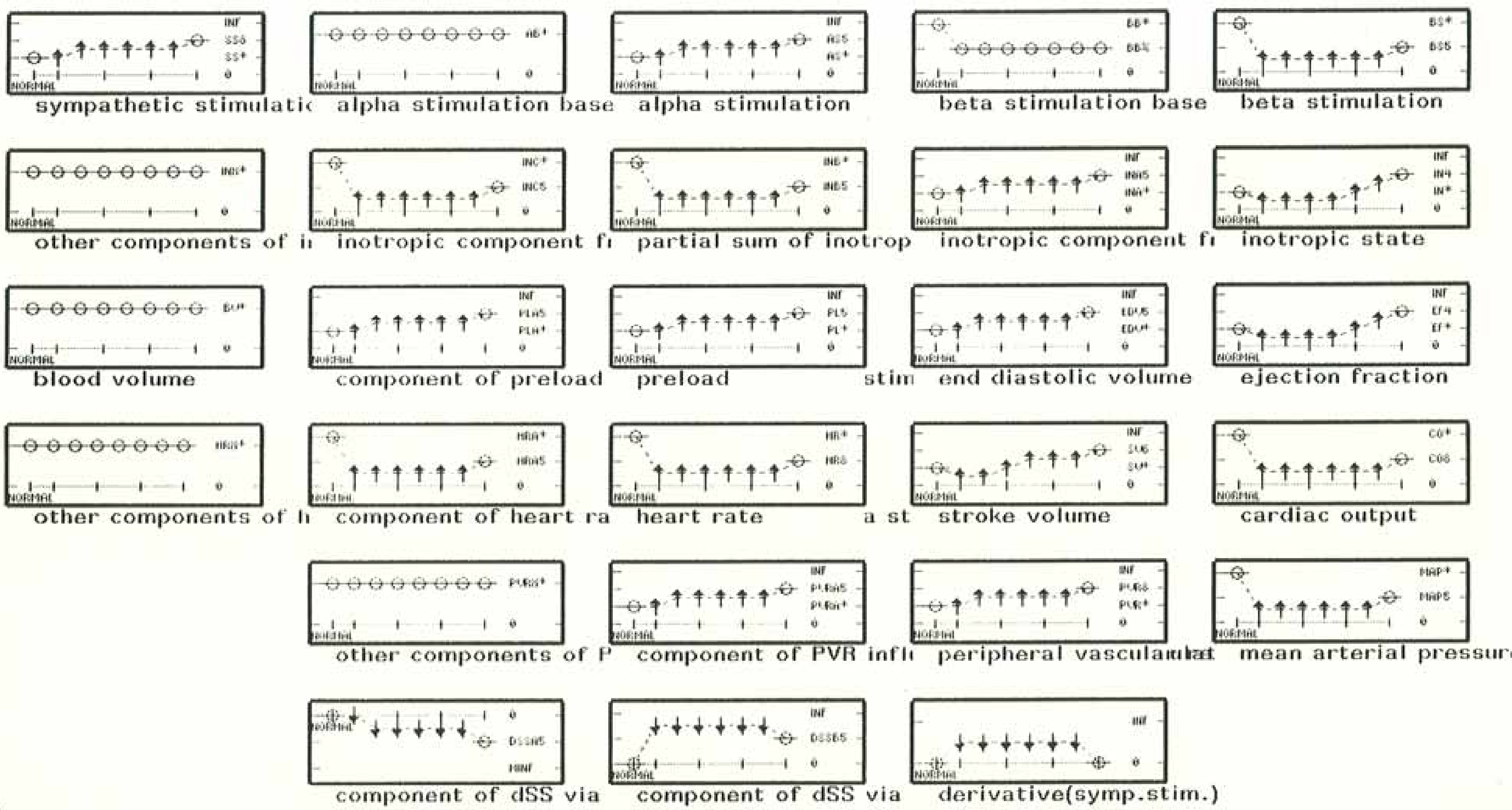




Display next behavior? (Y or N)

Initialization Blood Pressure given beta blocker
of structure BLOOD-PRESSURE,
behavior 5 of 5.





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6 Future Directions

6.1 Representational Issues

There are a few representational problems to consider.

- Consider the validity of the assumptions made by each mechanism descriptions, particularly the relation between the sodium and water balance mechanisms. Can the rates of the different equilibrium mechanisms be legitimately treated as being so different? The Guyton-Coleman model apparently makes a similar assumption: time-constants are allowed to fall into three classes: seconds, hours, and months. All of the faster ones are allowed to reach equilibrium before simulating the next slower set.

- Guyton's (1981) explanation of water balance implies that volume is so well controlled that it remains essentially "flat" with respect to changes in water intake. This qualitative behavior is not derivable by QSIM because an input change may be damped, but must be reflected to *some* extent in the output. In his more detailed explanation, however, Guyton explains this "infinite" response to input as the product of several curves of high slope.

- All structure descriptions are first-order systems. Similar attempts to simulate clinically interesting second-order systems, for example one combining the salt and water balances, have yielded intractibly branching behavior. It is not clear whether we need second-order systems for anything in nephrology, but consider naturally cycling systems, like those in endocrinology [cf. Lein, 1979].

6.2 Domain Extensions

There are several types of medical knowledge about sodium and water balance that are not captured by these two mechanism descriptions. They will be added as the representation problems posed by this first interaction are are solved.

- Sweating, vomiting, diarrhea, and IV fluids as actions affecting fluid balance.

- Thirst.

- Fluid balance between intra-cellular and extra-cellular spaces.

- The renin-angiotensin system and the effect of vasoconstriction on *effective* circulating volume.

6.3 Diagnosis and Matching

In order to evaluate a diagnostic hypothesis, a behavioral description must be matched against the clinical observations of the patient. There are a number of methods for mapping between the Evoker's language of clinical observations and the QSIM language of ordinal relations between values and landmarks. There are also representational problems with this mapping and matching problem that have not yet been worked out.

- A laboratory finding that is clearly a low value may be mapped into an ordinal relation with the landmark for the "normal" value of that parameter. However, there may be a range of different lab values that would be considered normal, and thus should be mapped onto the "normal". landmark value.
- Conversely, some of the variation predicted by QSIM in response to changes affecting a mechanism can be clinically imperceptible: i.e. they take place entirely within the "normal" range of a parameter as observed clinically. Thus a parameter which is clinically constant may have to be matched against what QSIM considers a change. [Bill Long, personal communication]
- Some QSIM parameters can be estimated as the result of diagnosis from clinical parameters. For example, dizziness suggests postural hypotension, which suggests dehydration. If confirmed, dehydration provides a qualitative value for $amt(water, P)$.

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