ANALYSIS OF PHYSIOLOGICAL BEHAVIOR USING A CAUSAL MODEL BASED ON FIRST PRINCIPLES

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The objective of this research is to demonstrate a methodology for the design and use of a physiological model in a computer program that suggests medical decisions. The physiological model is based on first principles and facts of physiology and anatomy, and it includes inference rules for analysis of causal relations between physiological events. The model is used to analyze physiological behavior, identify the effects of abnormalities, suggest appropriate therapies, and predict the results of therapy. This methodology integrates heuristic knowledge traditionally used in artificial intelligence programs with mathematical knowledge traditionally used in mathematical modeling programs. In recognition of its origins in artificial intelligence and mathematical modeling, the system is named AI/MM. This paper briefly introduces the knowledge representation and examples of the system analysis of behavior in the domain of renal physiology.

I OVERVIEW

In AI/MM, analysis and explanation of physiological function are based ultimately on analysis of facts of anatomy and facts and principles of physiology. Physiological principles are expressed either as heuristic rules or as mathematical relationships describing physical laws. Causal relations are based on physiological principles, and they describe possible changes in the state of the modeled system. AI/MM distinguishes between two kinds of causal relations. "Type-1" causal relations are empirical and are based on definitions or on repeated observation. "Type-2" causal relations have a basis in physical law, represented mathematically. Inference rules are proposed for making valid qualitative causal arguments with both kinds of causal basis. Such analysis allows qualitative causal inferences to be based ultimately either on empirical observation or on physical laws. In both cases, causal effects are considered to propagate along an anatomical network through which physiological processes can function.

In its current domain, renal physiology, AI/MM analyzes physiological behavior and explains the rationale for its analyses. The program fits data to the model, decides whether the data are abnormal, and identifies the possible effects of any abnormalities. The physiological model is based on knowledge about anatomy, the behavior of the physiological system, and the mechanism of action of the system. The program analyzes many of the problems discussed in a physiology text.

Early expert systems have been built using large collections of rules that describe empirical associations. Some recent AI work is based on explicit representation of the structure and function of a system. Davis (Davis, 1982), Genesereth (Genesereth, 1982), and Patil (Patil, 1981) describe computer programs that are based on structure and function. AI/MM differs from these programs in its explicit representation of principles of physiology, its strategy for propagation of causal relations, and its explicit representation of the basis for causal relations.

II KNOWLEDGE REPRESENTATION

AI/MM represents anatomical objects, physiological processes, physiological substances, parameters, and mechanisms of action of processes. Figure 1 illustrates the way in which these generic kinds of concepts can refer to themselves and to related concepts. Knowledge of physical laws is represented as mechanisms of action, and the form of a law is represented as a mathematical formula. The system interprets mathematical relations both symbolically, to identify constraint relations in inferring causality, and quantitatively, to calculate the value of parameters.

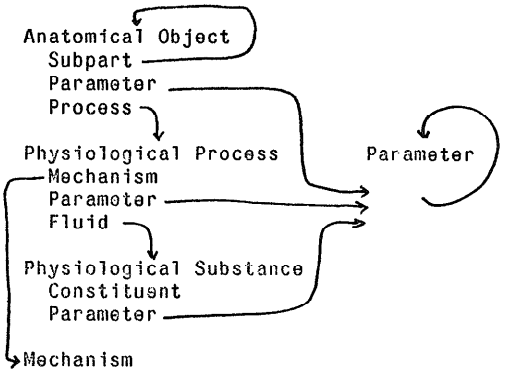

Figure 1:

The AI/MM vocabulary represents five main kinds of physiological concepts. Concepts can refer to other concepts as shown in the diagram.

The AI/MM knowledge base currently includes definitions of about 125 concepts. Concepts currently have between 5 and 65 individual features; 8 features per concept is typical. Concepts represent two kinds of physical objects: anatomical objects, such as the heart, and physiological substances, such as blood. Objects can have characteristic parameters: fluid volume, concentration, pressure, flow rate, etc. Additional concepts specify the features of each defined parameter. In addition, concepts define "physiological processes", or the rules by which parameters can change values. Finally, concepts describe "mechanisms", or the physical laws and causal relations that are the bases for explaining the operation of processes. The PCONCEPT function can be used to print the definition of any concept in the knowledge base, as shown in Figure 2.

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```
_PCONCEPT(Body)                          ; Typed by user.

; An excerpt of the AI/MM
; response is shown below.

Concept name:        Body
Concept type:        AnatomicalObject
Fluid Volume:        BodyWaterVolume
Major Fluid:         Water
Subparts:            (Arteries BodyWaterSpace
  Capillaries GI Heart Kidney Pituitary
  RestofBody Veins)
Fluid Flows into and out of the body:
   intake  WaterIntake
   loss    GIFluidLoss
   loss    BloodLoss
   loss    InsensibleLoss
   loss    UrineOutput
Parameters:
  BodyWaterVolume:  total body water volume
                Anatomical            Physiological
               connections:             process:
 output world    > intake GI         Water intake
 output Veins    > intake world      bleeding
 output Arteries > intake Kidney     Renal perfusion
...
```

Figure 2:

Excerpt of the definition of the concept of "Body" printed by AI/MM in response to a user query.

The knowledge base includes inference rules that are based on a definition of the causal relation between states. Using the causal relation and the knowledge of anatomy and physiology, the program makes inferences about normal physiological behavior and the causes and effects of abnormal physiological behavior.

Parameters may be related qualitatively or quantitatively. Causal relations are used to infer physiological behavior. For example, these relations are used to infer where fluids can flow within an anatomical network and to infer the effect of changes in pressures and concentrations on fluid flows and volumes.

An example of a causal relation is shown below in Figure 3. AI/MM uses the MRS knowledge representation system (Genesereth, 1980). This example of a rule is manually translated from its MRS syntax. The causal rule makes the causal relation between states explicit, such as the relation between a flow and a fluid capacity in this example. In addition, it explicitly describes the basis for the causal relation. I define the basis of a causal relation as its underlying principle. The basis of a causal relation is used in the explanation of its use. In AI/MM, the bases of causal relations include widely accepted empirical observations and laws of physics, described respectively as Type-1 and Type-2 causal relations. "Infectious disease causes fever, according to widely accepted clinical observation" is an example of a causal relation with a Type-1 basis in empirical observation of physiological behavior: The association between infectious disease and fever is widely known, yet the physiological mechanism for this association is not now widely understood. "Increasing resistance to flow in an artery causes reduced blood flow through that artery, according to Poiseuille's law" is an example of a causal relation with a Type-2 basis in physical law.

```
IF $AOBJECT is an anatomical object which has a
     fluid intake named $INTAKE, and
   $CAPACITY is the fluid volume of $AOBJECT, and
   $INTAKE is abnormally increased, and
   Change in fluid capacity of $AOBJECT equals
     the difference between its fluid intakes
     and its fluid losses
THEN the increased fluid intake of $INTAKE may
     cause increased fluid capacity of $AOBJECT,
     according to the law of conservation of mass
```

Figure 3:

An example of a causal rule. Variables prefixed by "$" are uninstantiated.

The distinction between Type-1 and Type-2 bases has several important uses. First, AI/MM explains physiological behavior by describing both the existence and the inferred basis of causal relations. The basis helps to elucidate the nature of the inferred relations. Second, Type-2 bases of causal relations are related to physiological principles, and thus they may have broad applicability in different domains and different contexts within a domain. In contrast, knowledge bases built solely with Type-1 causal relations will apply only in limited specific domains and contexts. AI/MM achieves some generality by applying laws of physics and fundamental principles of physiology in a useful and uniform way. Thus, the same principles may be useful for analyzing other domains to which these principles apply. Finally, the Type-1 / Type-2 distinction clearly identifies knowledge based on well-understood scientific principle from heuristic knowledge. This distinction helps to identify promising areas for further scientific research.

Type-1 bases for causal relations can have either qualitative or quantitative forms, while Type-2 bases for causal relations always have quantitative forms. Both the infectious disease and the resistance examples quoted above are expressed in qualitative form. The basis for the former relation is expressed qualitatively. The basis for the latter is inferred from a mathematical representation of a physical law: Flow = Pressure / Resistance (Poiseuille's law, which is a version of Ohm's law for fluids).

A single causal relation may be used to describe a particular behavior. Much more interesting than a single causal relation, however, is the inference of the description of a complex physiological behavior based on a sequence of causal relations. Causal relations can be propagated through an anatomical network, subject to the constraints imposed by the physiological function of that network. A propagated sequence of causal relations determines a "mechanism of action", which is a concept widely used in physiology and is often represented as a diagram with arrows connecting related physiological states. I define a mechanism of action in AI/MM as the sequence of causal relations by which an initial physiological state (the cause) propagates through an anatomical network to cause a resultant physiological state (the effect).

The mechanism of action provides a strong focus-of-attention heuristic for analyzing a physiological model to describe and predict behavior. Problems are analyzed in terms of the relatively small number of Type-1 and Type-2 relations that can affect physiological behavior at any point in an anatomical network. In addition, attention to mechanisms of action helps to focus the process of acquiring new knowledge about a problem. It is useful to include knowledge of a process in the knowledge base if the behavior of the process can be used for inferring the behavior of the modeled system. In addition, if a process is important, its parameters and its causal mechanisms are also important for inclusion in the knowledge base.

III EXAMPLE: ANALYSIS OF STATIC FACTS

In addition to its explicitly represented facts, the AI/MM knowledge base has rules for inferring facts of physiology and anatomy. Thus, the system can infer values that are not explicitly represented in its knowledge base. Within the tradition of applied AI systems, AI/MM is a rule-based system. For example, AI/MM has rules that allow the system to infer the identity of all the nested subparts of an anatomical object.

Both the user and the system can retrieve the quantitative value of a parameter. Depending on the situation, values can be looked up in the database, calculated from expected default values, and inferred. If the patient weight, for example, has been asserted in the database and the user types `(VALUE 'WEIGHT)`, the system looks up that value and prints it for the user. If the user types `(VALUE '(DEFAULTVALUE UrineOutput))`, the system attempts to infer a default value for the current qualitative state of the parameter. Quantitative parameter values can also often be calculated from quantitative relations.

The AI/MM knowledge base currently represents physiological concepts including the principle that the whole equals the sum of the parts, Ohm's law expressed as Poiseuille's law and the Starling hypothesis, and the law of conservation of mass expressed simply, as the Fick principle, and the principles of dilution volume and clearance. Figure 4 shows a simple example in which one of these methods is inferred by the system to be potentially applicable. This figure shows three ways that AI/MM had to calculate the value of a particular parameter. The first method is to make a specialized physiological measurement, and the second is to use a rule-of-thumb estimate based on the patient's sex and weight. These two methods are explicitly included in the knowledge base. The third method is inferred by the system from the anatomical facts of the situation and the general principle that the size of the whole equals the sum of the sizes of the parts.

When the user simply asks for the value of a parameter, as in the example of Figure 5, the system first identifies alternative calculation methods. Then it uses a precedence heuristic to choose the method in the current context that is likely to produce the most accurate value of the specified parameter, that is, depends least on default values. Finally, having chosen a method, the system calculates, reports and asserts the parameter value.

```
; Typed by the user.
_(MEASURE '(VOLUME BodyWaterSpace))
; The response typed by the
; system is shown below.

To measure (VOLUME BodyWaterSpace)
     = BodyWaterVolume, measure one of
  VDISTRIBUTION D20
  Fraction of total body weight assumed to
    be water TIMES patient weight
  Sum of (volume of intra-cellular fluid space,
    volume of the extra-cellular fluid space)
```

Figure 4:

Description of the methods inferred by the system for determining the value of a particular parameter.

IV EXAMPLE: CAUSAL ANALYSIS OF EFFECT OF CHANGE

Consider the case of a patient who is observed to drink 10 liters of fluid in a day ("Normal" is 1.5 - 2.5 liters/day). The user reports this value to the program and asks the program to interpret the significance of the observation. Figure 6 below shows the input by the user and the top-level summary provided by AI/MM of the effects of the specified observation. Subsequent subsections in turn show the detailed analysis by the program of the expected physiological behavior of the modeled system.

As mentioned, Figure 6 shows the top-level system response to the request to interpret a value of water intake (named WaterIntake in the knowledge base) that is abnormal. The summary of effects describes the effects of this abnormal flow on the body; additional effects for subparts of the body are discussed below at a greater level of detail. The top-level summary is prepared by AI/MM by summarizing detailed analyses. Figure 7 shows an intermediate level of detail prepared by the system in identifying the effects of increased water intake. The top-level summary of effects is prepared from this

---

```
; Typed by the user.
_(VALUE '(VOLUME BodyWaterSpace))
; The response typed by the
; system is shown below.

Value of (VOLUME BodyWaterSpace)
      = BodyWaterVolume
      = SEX-F TIMES WEIGHT
      = Fraction of total body weight assumed to
         be water TIMES patient weight
       = .6 TIMES 70.0
        [according to a Type-1 relation
         represented as a regression equation]
      = 42.00 [Liters]
```

Figure 5:

Computation of a quantitative value of a parameter. The system infers alternative ways to calculate a value, chooses a method, and returns the result with a summary of the equation used in the computation.

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intermediate-level summary; the heuristic used in preparing the top-level summary is to summarize effects at the highest appropriate level of anatomical detail. More detailed analysis of cause and effects is presented at a finer level of anatomical detail.

Validation of hypothesized relations is an important issue in causal analysis. This issue is complicated in biological systems when each case is different and the analysis of a model can have only limited accuracy in predicting the behavior of a modeled system. The AI/MM approach to the issue is to be as careful as possible in hypothesizing causal relations and then to help the user to validate hypothesized relations by identifying effects of the given cause that can be tested in the modeled system. In the second example [Figure 6], the system hypothesizes increased urine output as one result of the initial change to the system. An elevated urine output would support the hypothesis that the cause and effect are related in the specified way in an individual case.

The reasoning shown in this example is typical of AI/MM. The system reasons forward from observed cause to hypothesized effect. In the presence of evidence for a hypothesized effect, the system assumes that the effect is present for the patient. The system then searches for further effects of the newly hypothesized cause. Propagation of effects continues until no further effects are found or until a negative feedback loop is recognized. The validity of the inferred sequences of events can be tested in the modeled system, namely, the patient. AI/MM can propose tests to confirm the presence of hypothesized states. for example, it could suggest that urine output should be measured. AI/MM also reports normal therapy goals for each abnormal state in a cascade of effects; in the example, none was found.

; Typed by the user.
`_(INTERPRETVALUE 'WaterIntake 10)`

; The response typed by
; AI/MM is shown below.

```
Water Intake of 10 Liters/day is in the
range 5 Liters/day < Water intake <= 20
Liters/day, which is moderately elevated.
Normally, increased water intake causes
increased body water volume. Increased body
water volume causes decreased water intake.
In addition, increased body water volume
causes increased urine output. Increased
urine output causes reduced body water
volume. Increased urine output normally
will continue until body water volume returns
to normal. Moderately increased water intake
does not normally require therapy.
```

Figure 6: Initial top-level summary by AI/MM of the expected effects of a given measurement.

A. Sequence of Causal Events

Figure 7 summarizes the cascade of causal inferences made by AI/MM as it infers that increased water intake can cause increased urine output (named UrineOutput in the knowledge base). This summary was prepared by the system by describing each element in the inferred cascade of causal relations. Each causal relation in this cascade is inferred because there is a lawful basis for the relation and because there is an anatomical network through which physiological functions can propagate and allow the cause to produce the effect. Thus, the individual relations in this cascade are intermediate in detail level between the top level, shown in Figure 6, and the most detailed analysis performed by the system. The first relation in the cascade shown in Figure 7, for example, describes the fluid flow from the outside to the gastrointestinal tract (GI), through the GI, from the GI to the veins, and so on. The second relation in the cascade describes the effect of Antidiuretic hormone.

The AI/MM causal rules will infer that a physiological event, such as an increase in water intake, is a possible cause of a second event, such as increased urine output, if a hypothesized causal relation has a legitimate basis and is plausible. The basis of a causal relation is either a Type-1 basis in empirical observation or a Type-2 basis in physical law. A causal relation is plausible if it is not known to be impossible in a context and if there is an anatomical link by which normal physiological function can cause change in the first parameter to propagate and cause change in the second parameter. A nonphysiological example of an anatomical link that supports a function is the overflow drain in a bathroom sink. When the regular drain is closed, the overflow drain will keep the sink from overflowing if there is a structural connection between the overflow-drain entry and the regular drain pipe and if the function of that overflow pipe is normal -- for example, free of potatoes.

```
Normally, increased water intake causes
increased body water volume, according to
the effect of the law of conservation of
mass.

Increased body water volume causes
reduced renal tubule water permeability,
according to an empirical Type-1 causal
relation.

Decreased renal tubule water
permeability causes reduced renal tubule
reabsorption, according to the effect of
Poiseuille's Law.

Decreased renal tubule reabsorption
causes increased urine output, according to
the effect of the law of conservation of
mass.

Increased urine output causes reduced
body water volume, according to the effect
of the law of conservation of mass.
Increased urine output will continue until
body water volume returns to normal.
```

Figure 7:

Intermediate-level summary of the sequence of effects of high water intake. This summary was prepared by AI/MM. Each of these conclusions is described at a level of anatomical detail that is intermediate between the top-level summary and the detailed cascade of effects.

V CONCLUSION

AI/MM includes modest but nontrivial structural complexity in its representation of the domain anatomy. It represents behavior that is partially understood in terms of laws of physics and basic definitions. Use of AI/MM shows that it is possible to analyze the behavior of a physiological system based on knowledge of anatomy, physiological processes, and first principles of physiology. In this application, integrated use of symbolic and quantitative analysis is more powerful than either one alone. Symbolic knowledge is used to infer both the qualitative relations and the mathematical constraints that relate the parameters of the modeled system. Thus, symbolic analysis is useful for structuring problems to be solved in particular cases. Quantitative analysis is needed to actually analyze the quantitative behavior of a modeled system. Quantitative analysis can resolve qualitative ambiguities, and it can provide quantitative estimates of values for parameters that are not or cannot be measured.

The model contains knowledge of anatomy, function, and mechanism. It may be possible to use such models to analyze behavior of a broad class of systems similar to that of this project. The AI techniques allow an integrated representation of all the knowledge included in the model, including its definitions, anatomy, behavior, and mechanisms. Knowledge may be represented and used in a qualitative or quantitative form, as appropriate. The same inference procedure is used to infer both normal and abnormal behavior. Because the basic inference method is to propagate effects through an anatomical network, the inference procedure will exploit the available information that is relevant, and it ignores irrelevant information.