Object-Process Modeling of Glucose Metabolism in Health and Disease

By

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ABSTRACT:

Object-oriented design and layered hierarchical architecture are the dominant paradigms for building computer-based applications. The biological system has significant nonoverlap with these paradigms. This poses challenges in integrating seamlessly computer and biological systems. A seamless system could help build personalized patient monitoring/management systems for chronic conditions such as Diabetes. We take the first step in that direction by depicting glucose metabolism using object-oriented design and hierarchy. It is shown that the hierarchy principle will require creation of virtual objects. Resulting data coherence and consistency issues are addressable, as with cache coherency algorithms in the computer domain.

INTRODUCTION:

NSF recently announced an initiative on CPS (Cyber-Physical Systems) to address the challenges in tight conjoining of and cooperation between computational and physical resources [1]. NSF envisions that the cyber-physical systems of tomorrow will far exceed those of today in terms of adaptability, autonomy, efficiency, functionality, reliability, safety, and usability. In CPS, physical and software components are deeply intertwined, each operating on different spatial and temporal scales, exhibiting multiple and distinct behavioral modalities, and interacting with each other in a myriad of ways that change with context. Most real-world systems and applications are of CPS-type. NSF identifies the following challenges with regard to CPS: (1) Time to develop such complex systems increases exponentially; (2) Overly conservative design decisions limit options and degrade overall performance and robustness; (3) Fears of unpredictable side-effects forestall even small software modifications and hardware upgrades; and (4) Current systems have limited ability to deal with uncertainty. It is imperative that we begin to develop the cross-cutting fundamental scientific and engineering principles and methodologies that will be required to create the future systems upon which our very lives will depend [1]. The CPS program at NSF aims to discover the missing core of fundamental knowledge to design CPS systems. A fundamental difference between the cyber and physical systems is that computer science builds upon discrete mathematics, whereas engineering is dominated by continuous mathematics. It is difficult to assess the impact of design decisions in CPS due to the lack of proper modeling abstractions for cross-cutting attributes. The lack of unifying or composable theory makes it impossible to guarantee safety and performance by design.

Chronic diseases such as diabetes and coronary artery disease require regular monitoring and optimal management to enhance the quality of life for the patient. Such a patient management system (PMS) is an example of CPS. It is further constrained by the need for personalization at the level of the individual patient, because of the biological variability and the underlying complex system. Dr. Rubin provides an interesting comparison of Cyber and Bio systems on a number of self-aware and self-adaptation attributes [2] with the intent to synergistically combine the cyber and physical systems for optimal performance and new application domains. As the American population grows older, and the cost of chronic disease management increases, better design of individual PMS systems, and better integration of such PMS systems into a holistic solution for the

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patient, will be necessary. To start with, one can base a PMS design on the seven layer ISO OSI model [3]. Such a model has been spectacularly successful for the Internet, a fully digital implementation; ISO has also developed such a seven-layer model for machine condition monitoring (MCM), a CPS [4]. As another example, HL7, an international community of healthcare subject matter experts and information scientists collaborating to create standards for the exchange, management and integration of electronic healthcare information, has adopted standards at the application layer level of the 7-layer OSI model [5]. The ISO 7 layer model developed for digital communications is built on fundamental principles of object-oriented design and clear separation of layers. Both MCM and PMS operate on continuous signals, show dependencies amongst their subsystems at any given layer, and may not be able to distinguish clearly the various layers. PMS in addition, to be truly customizable to a given patient, must incorporate a larger number of layers and account for large dynamic ranges in time and space dimensions. We take the example of Glucose Metabolism in this paper-draft to explore the construction of a multilayer MCM-type model, and investigate ways to extend the model to make it more realistic. NSF expects such a Cyber-Physical System (CPS) to enhance societal wellbeing (e.g., assistive technologies and ubiquitous health care monitoring and delivery).

The scope of this first report is limited to mapping glucose metabolism to an object-oriented model, which is a prerequisite to building a viable multilayer model. We will extend this model both above and below to achieve the equivalent of PMS. The critical consideration is that biological system is not object oriented, and that the hierarchy that exists does not hide the lower layers, as is the case with object-oriented 7-layer network design. The MCM standard recognizes this, but still the information flow is one way, from lower layers to higher layers. The biological system can have information flow in both directions. Further, the biological system also has self-aware and self-adaptive properties that need to be elucidated. Insight into such extensions might help one develop better CPS for nonbiological applications, such as MCM.

METHOD:

Chronic diseases such as diabetes and coronary artery disease require regular monitoring and optimal management to enhance the quality of life for the patient. Such management needs to be customized to the individual patient. One can base such a model on the seven layer ISO OSI model [1]. This pure-digital model has been adapted for machine condition monitoring by ISO [3]. We explore here the feasibility of such a 7-layer model for a PMS (patient management system) to track glucose metabolism and help manage diabetes or a prediabetic condition. Do, however, note that such designing and architecting is not without hidden risks: IEC (International Electrotechnical Commission) established the standard 61499 in 2005 for distributed control systems software engineering for factory automation. The standard has been shown to fail concurrency operation tests; the same code resulted in radically different behaviors on different vendor runtime environments; and more importantly, in nondeterministic behaviors on runtimes from any given vendor [6]. We expect to submit our model eventually to formal verification with model checking [7].

Abnormal glucose metabolism can lead to many large and small blood vessel diseases that can impact negatively one's health and cause chronic conditions such as diabetes, high blood pressure, heart disease, kidney disease, and eye disease. Medical researchers have uncovered many concurrent processes and feedback loops that are involved in the regulation of glucose. Any of these has the potential to deviate from the norm and cause a shift towards disease. Yet, the robustness of these loops and intricate relationships among these loops allow the body to adapt and adjust to significant shifts from the norm, and maintain normalcy. However, repeated episodes of such events and/or inattention to signs and symptoms exacerbate the balance and cause a shift towards various diseases. Advances continue to be made in understanding glucose metabolism and linking system level effects to genetic, molecular, and genomic (subsystem/system-wide) causes. Control of chronic conditions will require one to understand these various interactions and decide on a course of medical and/or life-style change interventions to control the long-term ill effects. For this, one needs to build a robust model that integrates the external interventions with the body's internal processes. This model should support large

dynamic ranges of time and size, and hierarchy that are inherent in the internal processes and should be customizable to the individual patient. One could build such a model based on the ISO standards on machine condition monitoring. Such a model consists of seven layers. From bottom-up, these layers are: sensing, data acquisition, data processing, state detection, health assessment, prognostics, and advisory generation. Application of such a model to biomedical applications such as chronic management of Diabetes is fraught with many challenges: (1) an obvious limitation is that there are many more layers in the hierarchy; and (2) a more subtle, but more important limitation, is that there are interdependencies among these layers, and the functionalities within a layer are not object oriented (that is, they are not well encapsulated with clearly defined boundaries and interfaces). One can at best call the biological system 'nearly decomposable' [8].

MODEL:

As a first step towards that goal, we propose to use OPM (Object-Process Methodology) [9] to model the interactions at the system level, and expand hierarchically to lower levels. OPM combines formal yet simple graphics with natural language sentences to express the function, structure, and behavior of systems in an integrated, single model. Objects and processes are the two main building blocks that OPM requires to construct models. OPM has been used by other investigators to describe complex systems with many concurrent processes.

Figure 1 shows the overall perspective. We will present the model here, without discussing how we arrived there. That will be deferred to the Discussion section. Figure 1 shows the 'Glucose Metabolism Process' interacting with several objects, by different types of links. The links from 'Food Intake' and 'Insulin Uptake' are called consumption links and are unidirectional. This high level diagram also shows a link with double arrows to the Patient entity. Glucose Metabolism process is occurring inside the patient and is both consuming the patient object and transforming it—perhaps to a different state (as stated earlier). The Stress and Exercising is a process that can trigger changes in the Glucose metabolism, as will be detailed in lower level diagrams. Figure 2 is included to show the corresponding representation in OPL (object process language). Note the careful manner in which the language depicts the relationships. It is well suited for automated manipulation in a very nondomain-specific manner. This is very helpful in requirements capture and automatic translation to a specification document. Domain specific translation, via XML, becomes easy.

This OPM (object process methodology) is due to Dr. Dori [9]. OPM is an easy to learn and use modeling methodology that can be used to describe modern complex systems in a hierarchical manner from abstract to more detailed levels. The tool, called OPCAT, may be freely downloaded for academic purposes from [10]. OPM combines, unlike UML, objects and processes into one common diagram. We use it for conceptualizing the overall system, the interaction and behaviors of concurrent & synergistic activities, and the mapping of the interventions (food intake, insulin uptake, stress and exercising) and status of the patient (normal, type-1 diabetes and type-2 diabetes) onto these activities, with the intent to seamlessly extract the needed patient information and data from this integrated picture. These interventions and the patient are objects represented as rectangles. Of course, such a model can be developed incrementally and any missing information can be incorporated in a later version. If some associations/connections are noted to be missing, then they become opportunities for further exploration to optimize PMS. Lack of validation techniques is a limitation of OPM; however, we have used another tool, in our study of other complex systems, to overcome this limitation [7]. OPM provides both a graphical and visual representation which makes it easy for brainstorming sessions, and a textual representation which is in a natural language. Both are semantically equivalent. They appeal to two different parts of the brain, the visual and the lingual. Typically, engineering and medical professionals would prefer a visual representation, while a textual representation will be useful to a computer professional to make the model executable. In our experience, the former is a good brainstorming tool, while the latter provides a good portable format which is amenable to computer manipulation for automatic code generation at least at the skeleton level (if appropriate). Objects and processes are the two main building blocks that OPM uses to build models with. It also uses a third type of entity, States. Objects exist, and processes transform the objects by

generating, consuming, or affecting them. States are used to describe objects, and are not stand-alone things. Thus, a patient (see Figure 3) can be in one of the three states: Normal, T1D (Type-1 Diabetes), and T2D (Type-2 Diabetes). Of course, one can define a larger number of states, such as presymptomatic diabetes and early and late diabetes for each of T1D and T2D. System objects for our example are various hormones and organs involved in disease processes (see the various figures).

Our model at the next lower level (Figure 3) shows five concurrent processes (depicted as ellipses) that are inter-related: Energy Storage (Anabolism), Energy Usage (Catabolism), Functionality (Homeostasis), Control and Optimization (with neural/hormonal/endothelial biochemicals), and Disease progression (both macro- and microvascular diseases and concurrent diabetes). An explicit model helps all to undertake a holistic approach towards building a realistic model. As indicated earlier, objects are represented by rectangles, while processes are depicted by ellipses. Figure 4 shows the OPL language text that corresponds to Figure 3.

We did not intentionally label the links in Figures 1 and 3, but the labeling will be evident in the lower level diagrams. The concurrent processes in Figure 3 may seem inappropriate considering the fact that such object-oriented (OO) clear separation of activities does not occur in the human body. As will be seen in lower level figures, certain objects and processes will have to be duplicated to achieve this OO methodology. In the computing domain, such instantiation has the potential to cause coherency and concurrency issues, but that can be addressed. The intent here is to explore avenues to use OO methodology, even though the human body may be ill-suited for this type of modeling. The reason for this is obvious: a significant amount of expertise and information exists to translate such an OOD system to a practical implementation. Further, this will provide a way to infuse real world CPS applications with autonomic computing behavior.

Figures 5 to 9 show the details of the 5 underlying processes (at one level below the highest level depicted in Figure 3). Note how the links in Figure 6 are now directly connected to the underlying processes. This process has not been completed for other diagrams, primarily because concepts involved in OOD representation of biological systems with OPD are still evolving. We do not show some of the labels to reduce the clutter and to enhance legibility. All the information in these diagrams was extracted from Salway [11].

DISCUSSION:

The OOD methodology, even with OPD modeling, does not allow easy integration of the information and generate a systemic perspective. However, once they are documented with OPDs, it does become easy to go across the diagrams and evolve different perspectives. Here is our attempt at that. We do acknowledge that much about Glucose Metabolism was known to us a priori and it is debatable whether OPDs could have provided such clear perspectives without such a priori information. Much work is still needed to complete these diagrams and also to extend this effort to lower levels of system biology and upper levels of patient management.

Our goal is to relate these OPD diagrams to known acute and chronic systemic effects of Diabetes. The intent is to find ways to translate OPD diagrams using concurrency modeling tools such as FSP and LTSA [7] to yield cause-and-effect type of outputs, specifically for Diabetes in our example. This is a work in progress.

CONCLUSION:

Human biology has features of hierarchy and near-decomposability that may, with certain modifications, allow one to exploit object-oriented modeling techniques. This representation will allow practical reference models to be built that are amenable to computer implementation; this in turn will help build patient specific models that are reasonably accurate, fast, and have small memory footprints. The mismatches will help us understand the

limitations of object oriented design in building self-adaptive systems. Narrowing of the mismatches will help us move towards incorporating biological robustness into man-made cyber physical systems (CPS).

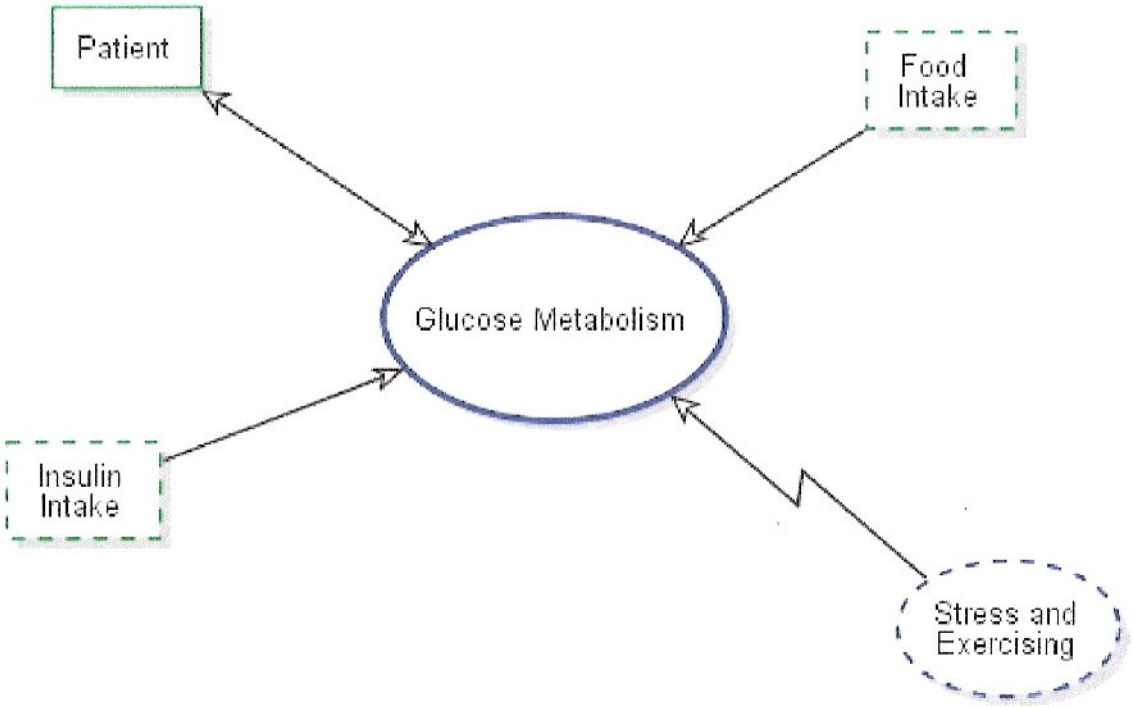

FIGURE 1: OPD MODEL FOR THE TOP LEVEL OF THE GLUCOSE PROCESS

Patient is physical.
Insulin Intake is environmental and physical.
Food Intake is environmental and physical.
Glucose Metabolism is physical.
Glucose Metabolism affects Patient.
Glucose Metabolism consumes Food Intake and Insulin Intake.
Stress and Exercising is environmental and physical.
Stress and Exercising invokes Glucose Metabolism.

FIGURE 2: OPL MODEL FOR THE TOP LEVEL OF THE GLUCOSE PROCESS

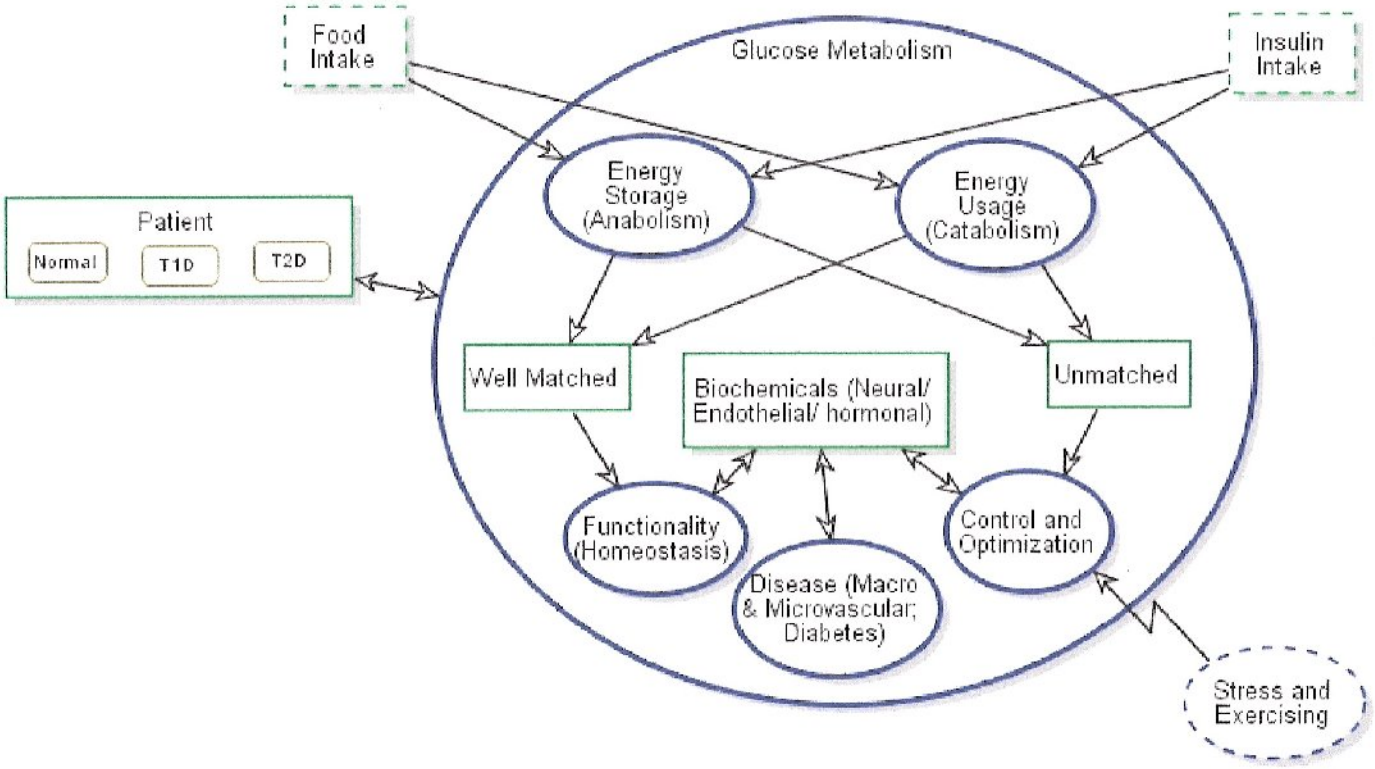

FIGURE 3: OPD MODEL DEPICTING CONCURRENCIES OF THE GLUCOSE PROCESS

Patient is physical.
Patient can be Normal, T1D, or T2D.
Insulin Intake is environmental and physical.
Food Intake is environmental and physical.
Stress and Exercising is environmental and physical.
Stress and Exercising invokes Control and Optimization.
Glucose Metabolism is physical.
Glucose Metabolism exhibits Well Matched, Unmatched, and Biochemicals (Neural/Endothelial/hormonal).
Glucose Metabolism consists of Energy Storage (Anabolism), Energy Usage (Catabolism), Functionality (Homeostasis), Control and Optimization, and Disease (Macro & Microvascular; Diabetes).
Glucose Metabolism affects Patient.
Glucose Metabolism zooms into Energy Storage (Anabolism), Energy Usage (Catabolism), Control and Optimization, Functionality (Homeostasis), and Disease (Macro & Microvascular; Diabetes), as well as Biochemicals (Neural/Endothelial/hormonal), Unmatched, and Well Matched.
Biochemicals (Neural/ Endothelial/ hormonal) is physical.
Energy Storage (Anabolism) is physical.
Energy Storage (Anabolism) consumes Food Intake and Insulin Intake.
Energy Storage (Anabolism) yields Well Matched and Unmatched.
Energy Usage (Catabolism) is physical.
Energy Usage (Catabolism) consumes Insulin Intake and Food Intake.
Energy Usage (Catabolism) yields Well Matched and Unmatched.
Control and Optimization is physical.
Control and Optimization affects Biochemicals (Neural/Endothelial/hormonal).
Control and Optimization consumes Unmatched.
Functionality (Homeostasis) is physical.
Functionality (Homeostasis) affects Biochemicals (Neural/Endothelial/hormonal).
Functionality (Homeostasis) consumes Well Matched.
Disease (Macro & Microvascular; Diabetes) is physical.
Disease (Macro & Microvascular; Diabetes) affects Biochemicals (Neural/Endothelial/hormonal).

FIGURE 4: OPL MODEL FOR THE SECOND LEVEL DEPICTING CONCURRENT PROCESSES

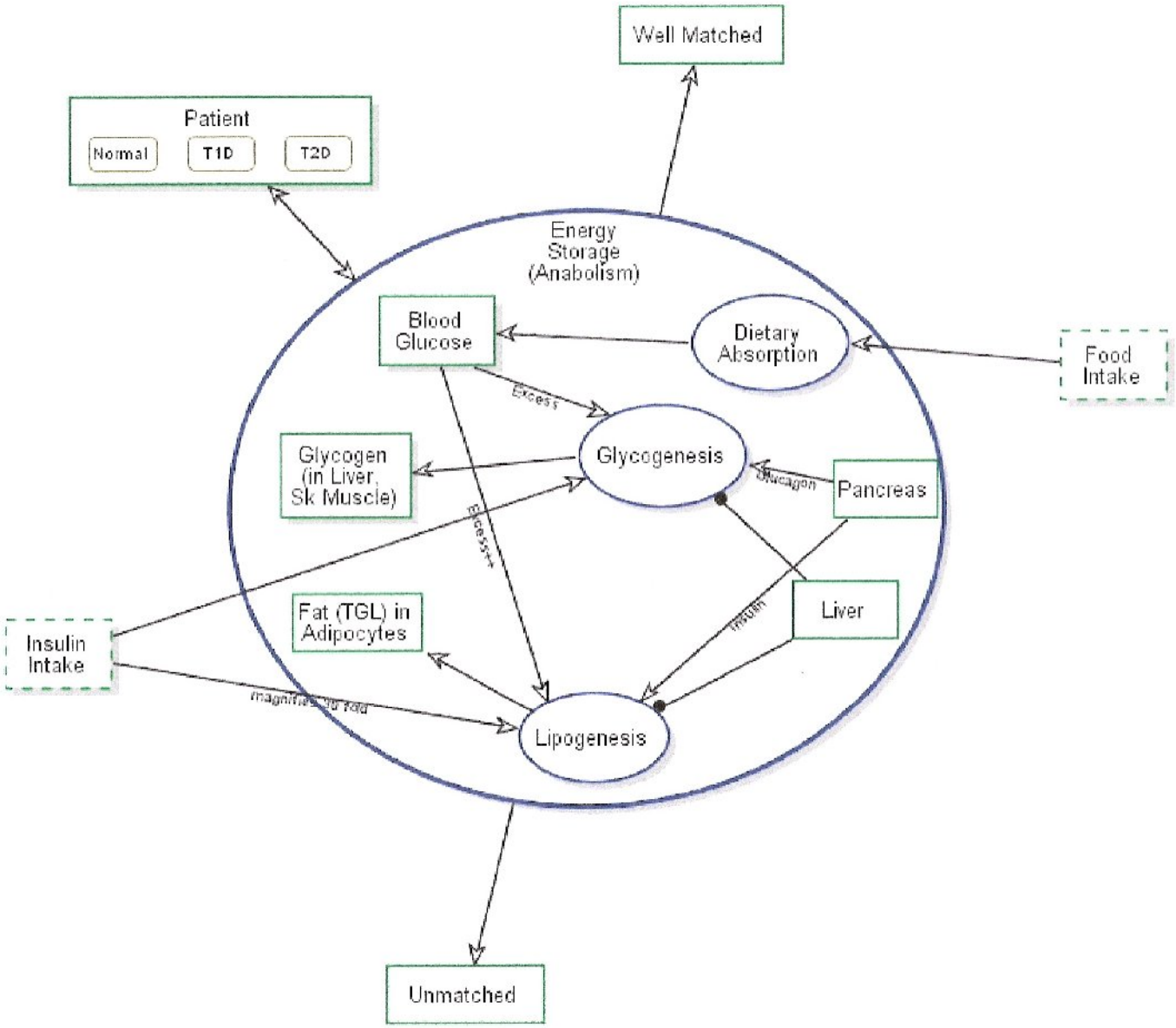

FIGURE 5: OPD MODEL FOR THE ANABOLISM SUBPROCESS

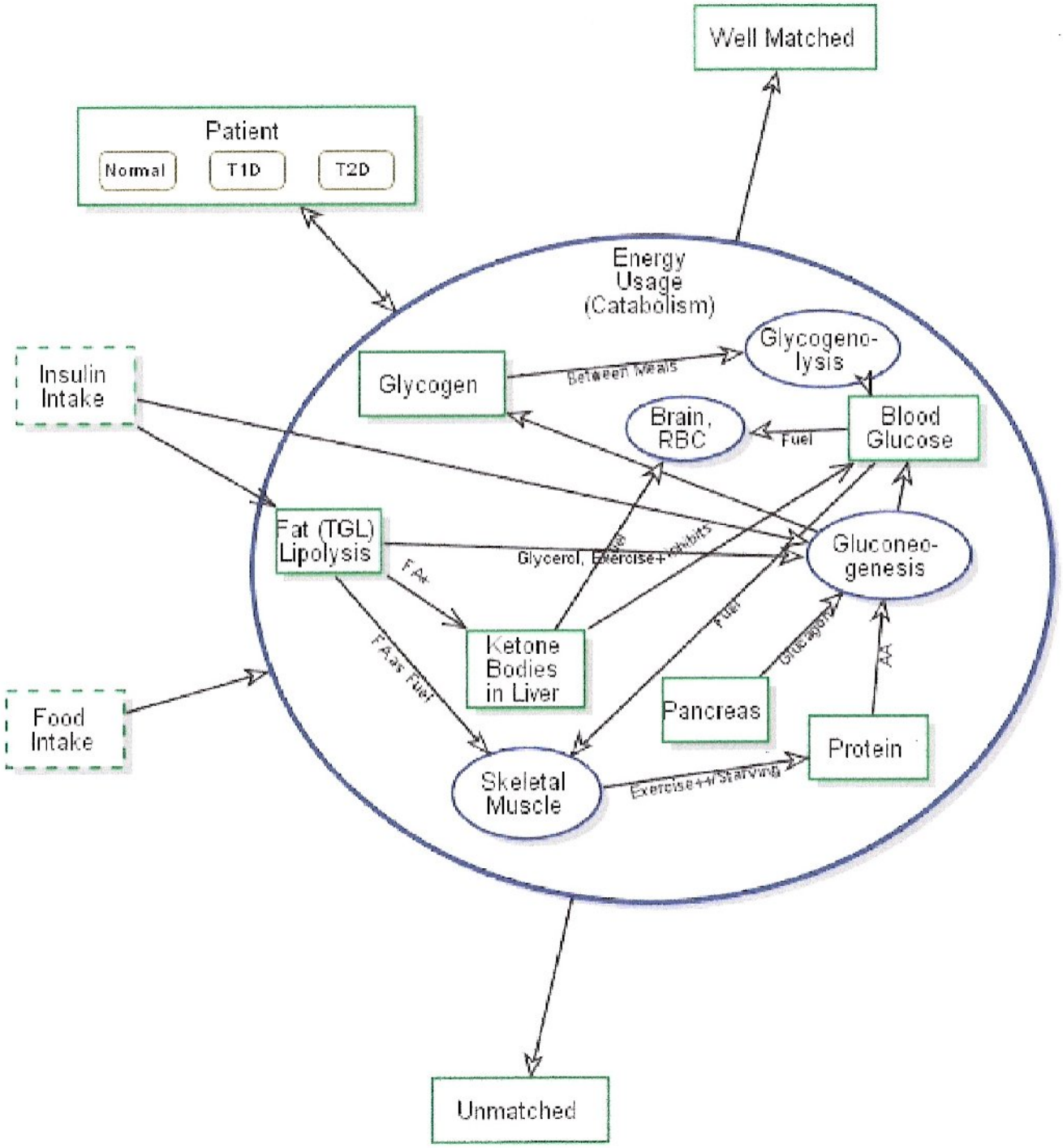

FIGURE 6: OPD MODEL FOR THE CATABOLISM SUBPROCESS

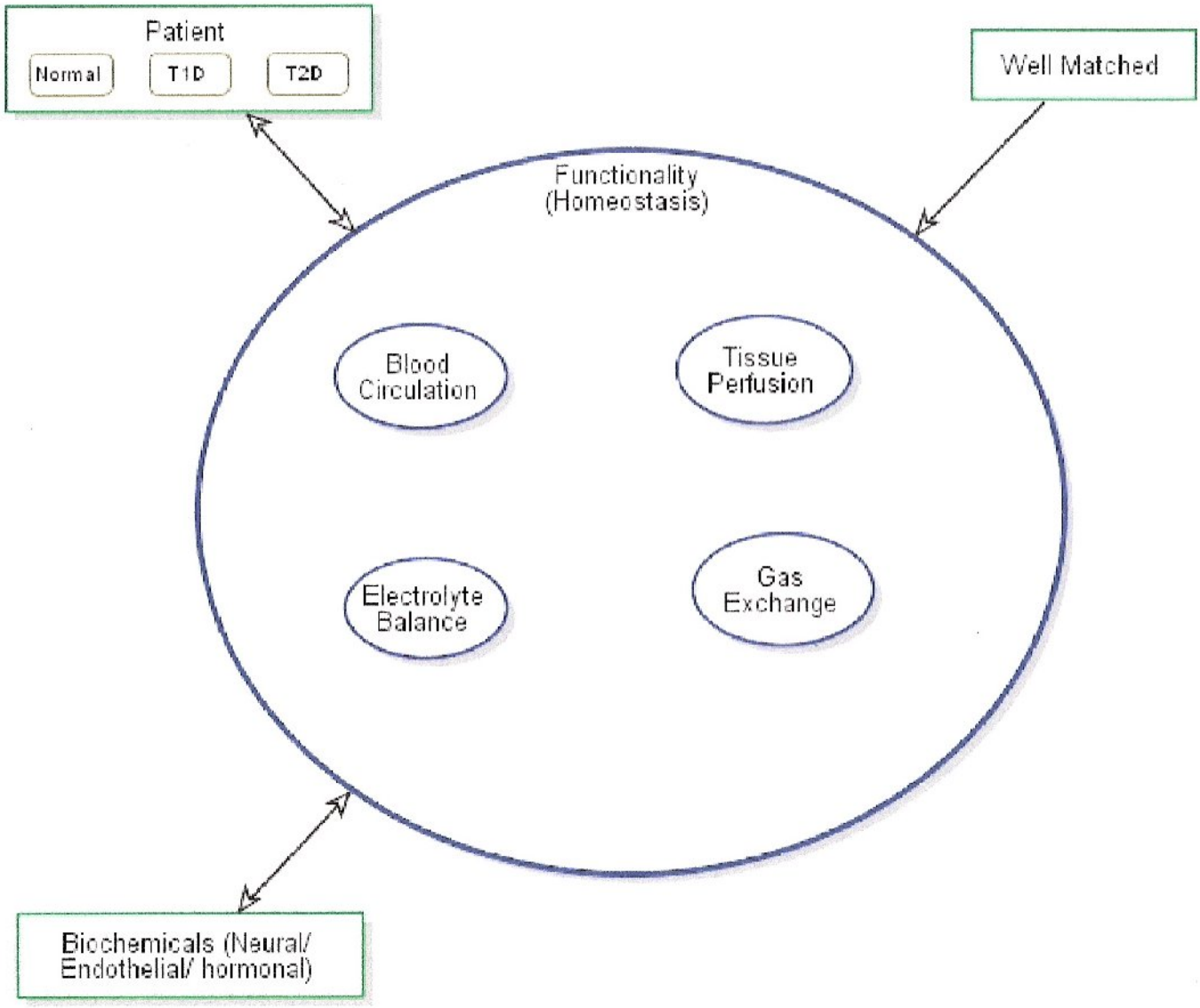

FIGURE 7: OPD MODEL FOR THE FUNCTIONALITY SUBPROCESS

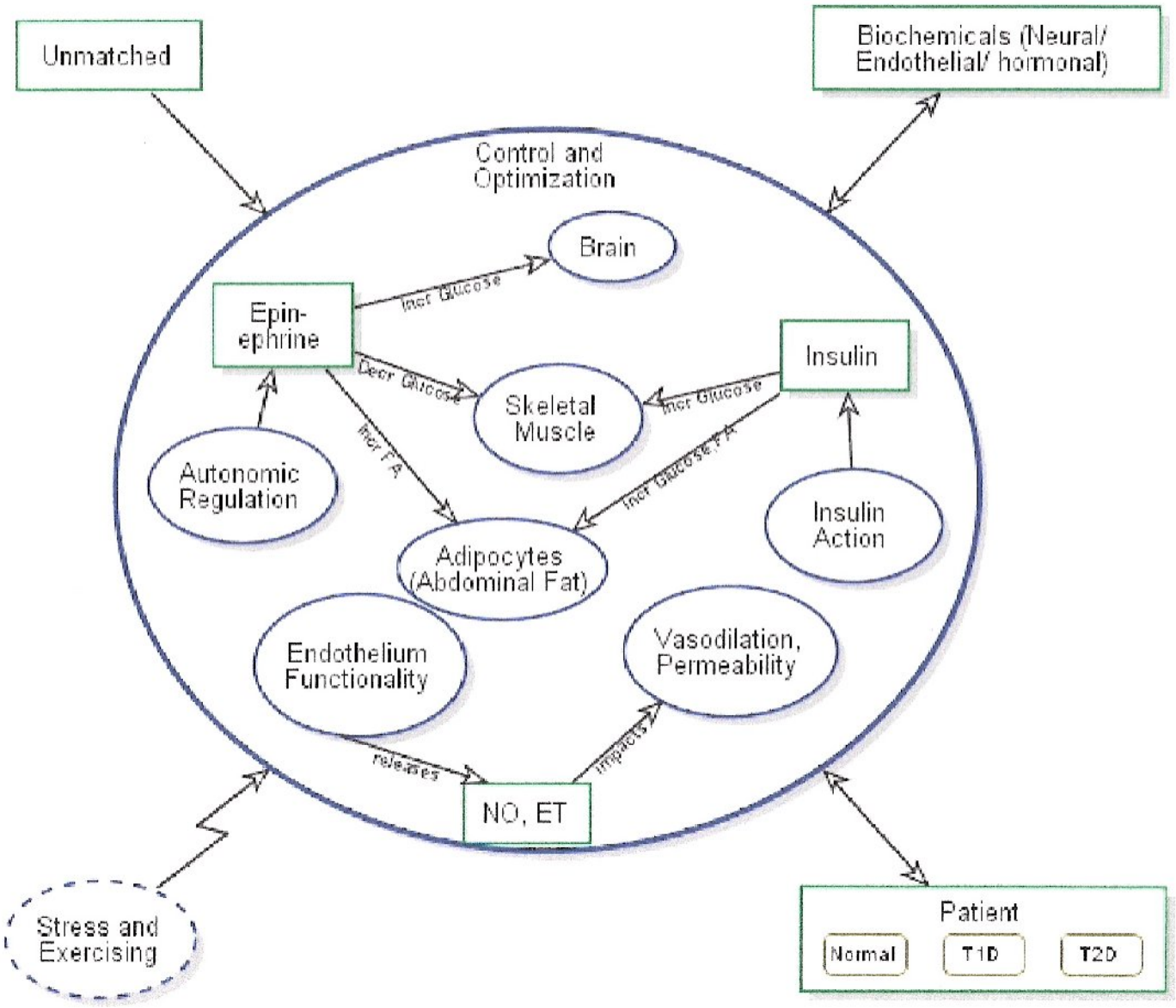

FIGURE 8: OPD MODEL FOR THE CONTROL AND OPTIMIZATION SUBPROCESS

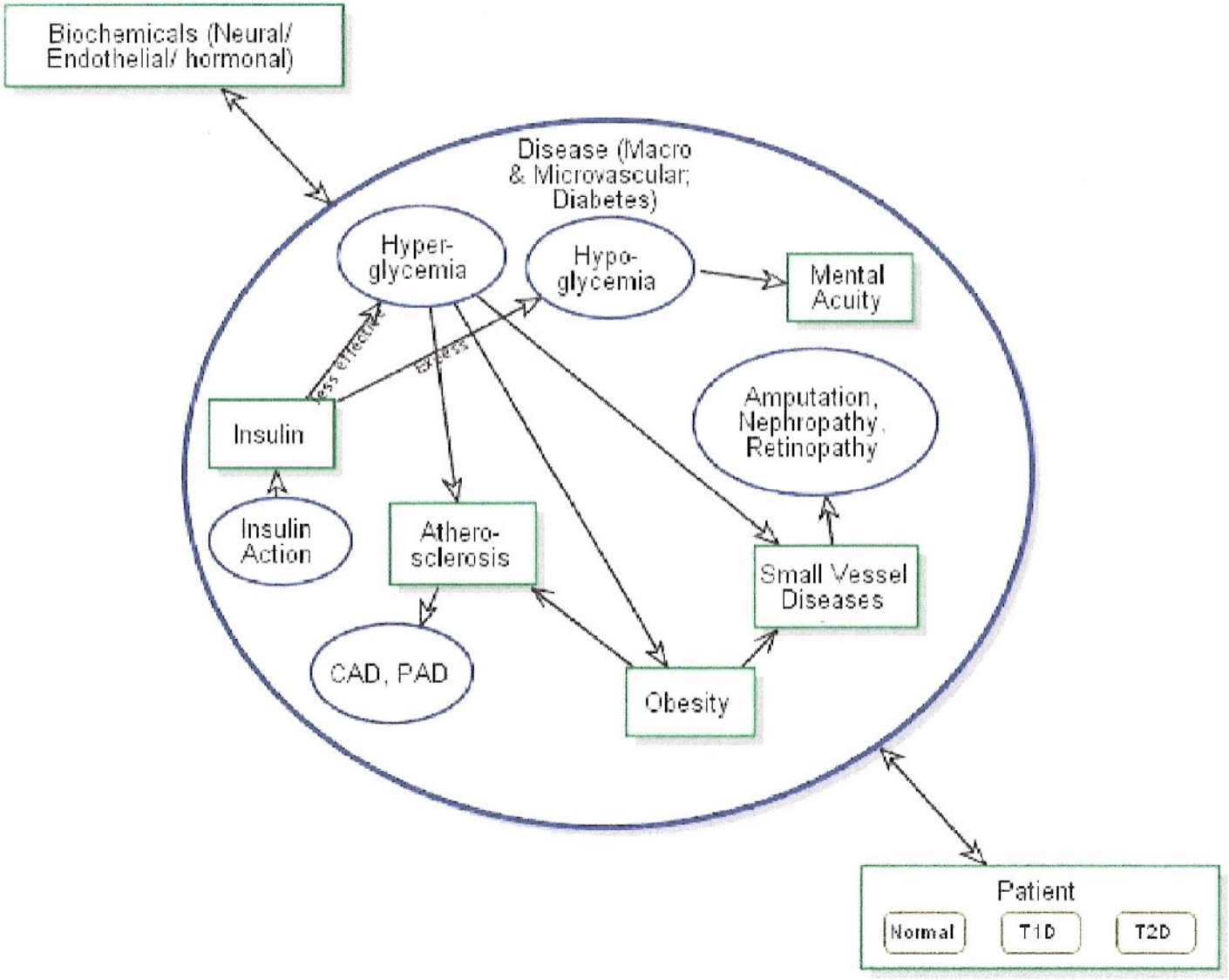

FIGURE 9: OPD MODEL FOR THE DISEASE SUBPROCESS

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