A Reference Model Based Patient Management System: Opportunities and Challenges

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Abstract— **Object oriented design (OOD) and hierarchical layered architecture are the dominant paradigms for building computer-based applications. The biological system deviates significantly from these paradigms, while adding self-adaptability as a paradigm that is worthy of emulation in the computer domain. Biological system components may be considered to be nearly decomposable, but not modular; further, the top-down command and control, the bottom-up information flow, and the fully submissive & reactive lower levels, as envisioned with a layered architecture, is replaced in biology with overlapping and self-aware/adaptive/intelligent layers. These differences pose challenges in integrating seamlessly computer and biological systems. A seamless system could help build personalized computer-based patient management systems for optimal management of chronic conditions such as Diabetes and Hypertension. The lower levels of sensing, data acquisition, data processing, and state detection would be based on the biological system while the higher levels of health assessment, prognostics, and advisory generation, generally the domain of medical personnel, could be substantially supplemented by a computer based expert system. With a better appreciation of the two domains, decisions made at the higher levels (in the computer domain) would be tempered with adaptive strategies that comprehend the adaptive and partially-reactive responses of the lower levels (of the biological system) for maximum benefit to the patient. This requires a seamless model that integrates the computer and biological domains. In this paper, we present our attempts at building such a seamless model for integration of computer and biological systems. We used OPD (object process diagrams) to build a systems biology OOD hierarchy at lower levels. The scope of this paper is limited to mapping glucose metabolism to an object oriented model, which is a prerequisite to building a viable multi-layer model.**

Keywords— **Object Oriented Design, Biological System Modeling, Object Process Diagrams, Cyber-Physical Systems, Hierarchical Layered Architecture.**

I. Introduction

CPS (Cyber-Physical Systems) is a recent NSF initiative that addresses the 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 an unifying 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 to be optimized to 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 worsens, better design of individual PMS systems, and better integration of such PMS systems into a holistic solution for the 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

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successful for the Internet, a fully digital implementation; however, ISO has also developed such a seven-layer model for machine condition monitoring (MCM) [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 sub-systems 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 more 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 buildup of a multi-layer 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 muti-layer model.

II. 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 multi-layer model for a PMS (patient management system) to track glucose metabolism and help manage diabetes or pre-diabetic 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].

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 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 well encapsulated with clearly defined boundaries and interfaces). One can at best call the biological system 'nearly decomposable' [7].

III. Model

As a first step towards that goal, we propose to use OPM (Object-Process Methodology) [8] 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 link 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 non-domain specific manner. This is very helpful in requirements capture and automatic translation to a specification document. Domain specific translation, via XML, becomes easy.

We present the model with the aid of OPM (object process methodology) due to Dr. Dori [8]. 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 [9]. 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 Patient Status 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 [10]. 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 is 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 more number of states, such as pre-symptomatic 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 interrelated: 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 robust program. Objects are represented by rectangles, while processes are depicted by ellipses.

We did not intentionally label the links in Figures 1 and 3, but the labeling will be evident in the lower levels. We have carried out the functional decomposition to several more levels below this. For one level below this see [11]. The concurrent processes in Figure 3 may seem inappropriate considering the fact that such object-oriented clear separation of activities does not occur in the human body. Certain objects and processes were duplicated to achieve this OO methodology at all levels. In the computing domain, such instantiation has the potential to cause coherency and concurrency issues, but can be addressed. 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 [12] and the current literature. We present below our work on two and more levels below that in Figure 3.

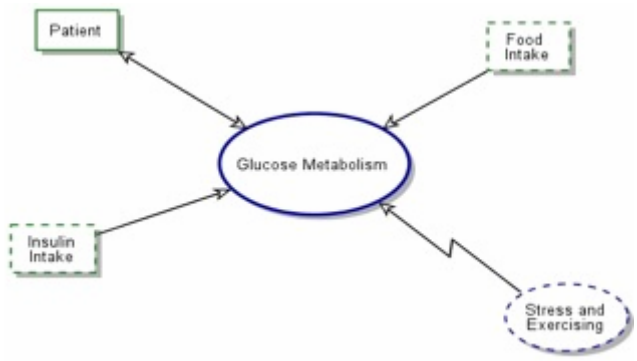

Fig. 1 OPD model for the top level of the glucose process

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.

Fig. 2 OPL model for the top level of the glucose process

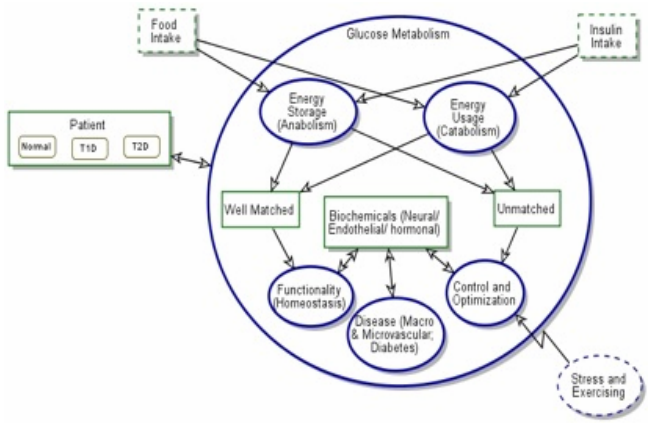

Fig. 3 OPD model depicting concurrencies of the glucose process

In type-2 diabetes, insulin secretion and insulin action are both impaired. Dysfunction of the beta cell is an important factor in the progression of the disease. Irregularities in insulin secretion occur before the onset of type-2 diabetes; this may exist even before the individual displays glucose intolerance. Insulin secretion is considerably decreased when the disease is diagnosed and it keeps on decreasing unavoidably during the time of the disease. At present, the literature indicates that insulin resistance causes diabetes only if there is a genetically determined tendency towards beta cell dysfunction. In these individuals, insulin resistance plays a key role in the progression of diabetes by placing a higher demand on the beta cell that the beta cell is unable to respond to [13].

Increasing levels of glucose entering the pancreatic beta cells trigger the secretion of insulin. Glucose enters the beta cell with the help of type 2 glucose transporters (GLUT2). After entering, phosphorylation of glucose takes place to produce glucose-6-phosphate. The phosphorylation is catalyzed by glucokinase, which is the rate-limiting process in glycolysis, and it successfully keeps glucose inside the cell. While glucose metabolism continues, ATP is created in the mitochondria. The rise in the ATP:ADP ratio shuts ATP-gated potassium channels in the beta cell membrane. At this point, positively charged potassium ions (K^+) can no longer exit the beta cell. The increase in positive charge within the beta cell results in depolarization. Voltage-gated calcium channels unlock, letting calcium ions (Ca^{2+}) to flow into the cell. The rise in intracellular calcium concentration set off the secretion of insulin through exocytosis [14]. OPD for this will be included in the presentation.

Figure 4 shows how insulin performs its actions by binding to insulin receptors. The Insulin receptor is made up of a heterotetramer that has two α and two β glycoprotein subunits connected through disulphide bonds and found on the cell membrane. The gene that codes for insulin receptor is found on the short arm of chromosome 19. Insulin attaches to the extracellular α subunit, causes conformational alteration allowing ATP to attach to the intracellular component of the β subunit. ATP binding in return activates phosphorylation of the β subunit granting tyrosine kinase activity. This allows tyrosine phosphorylation of intracellular substrate proteins identified as insulin responsive substrates (IRS). The IRS can then attach to additional signaling molecules that perform further cellular actions of insulin. Insulin resistance usually understood to be evident at the cellular level through post-receptor defects in insulin signaling. A variety of insulin signaling defects have been identified in experimental animals. However, their relevance to human insulin resistance is uncertain at this time [15].

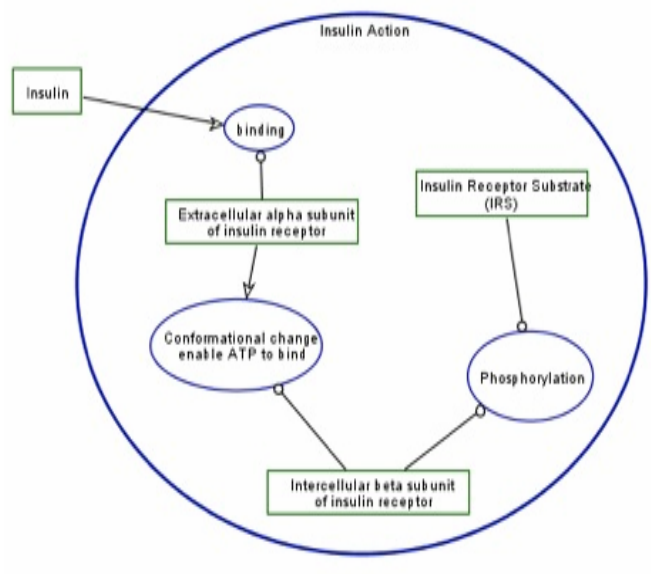

Fig. 4 OPD model for the insulin action sub-process

The extent of impact that multiple genes and the environment have on diabetes susceptibility and development is a continuing difficulty for the researchers, but they have numerous tools at their control. These consist of genome scans that utilize markers across the whole genome. They have been utilized in more than 50 family-based linkage studies on diverse populations. Association studies search for the connection amongst state of the disease and specific alleles, genotype or haplotype of a genetic marker or a group of markers. This type of research contrasts the occurrence of a disease indicator amongst affected and unaffected persons in a control study. A few genes and polymorphisms have been repeatedly associated with type-2 diabetes in numerous studies. Results from the genome scans have been incomplete, yet multiple possible localizations have been recommended but not each and every one has been confirmed by replication across many studies and using many diverse populations [16].

Association studies have had a notable outcome in discovering many key genes. The PPARγ gene (PPARG) and KCNJ11 signify the best candidate genes for human type-2 diabetes vulnerability to come out of association studies and are satisfactory repeated and confirmed. In addition, CAPN10 and HNF4A genes discovered initially using linkage studies have recently been verified utilizing the candidate gene association method. It is thought that polygenic type-2 diabetes is the outcome of inheritance of a group of vulnerability genes and that all put forth just a fractional effect adding to the progress of the disease in whole. Just in the case where the effect of these genes is combined in specific ways and in the occurrence of particular risk factors, like obesity, we will observe disease. Until recently precise examples of regular changes in genetic linked with insulin resistance and obesity were hard to find, but recent research has revealed that ENPP1 arbitrate both insulin resistance as well as concurrently participating in the progress of both obesity and type-2 diabetes. This finding adds value to the theory that a parallel molecular mechanism is behind both conditions [16]. OPD for this will be included in the presentation.

IV. 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 to ensure all factors are cross-checked. After that, the goal will be to update the model as new information is uncovered in the literature. Extending this effort to higher levels of patient management is also underway.

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.

V. 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).

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