DigitalHuman (DH): An Integrative Mathematical Model of Human Physiology

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Abstract. Mathematical models and simulation are important tools in discovering the key causal relationships governing physiological processes and improving medical intervention when physiological complexity is a central issue. We have developed a model of integrative human physiology called DigitalHuman (DH) consisting of ~5000 variables modeling human physiology describing cardiovascular, renal, respiratory, endocrine, neural and metabolic physiology. Users can view time-dependent solutions and interactively introduce perturbations by altering numerical parameters to investigate new hypotheses. The variables, parameters and quantitative relationships as well as all other model details are described in XML text files. All aspects of the model, including the mathematical equations describing the physiological processes are written in XML open source, text-readable files. Model structure is based upon empirical data of physiological responses documented within the peer-reviewed literature. The model can be used to understand proposed physiological mechanisms and physiological interactions that may not be otherwise intuitively evident. Some of the current uses of this model include the analyses of renal control of blood pressure, the central role of the liver in creating and maintaining insulin resistance, and the mechanisms causing orthostatic hypotension in astronauts. Additionally the open source aspect of the modeling environment allows any investigator to add detailed descriptions of human physiology to test new concepts. The model accurately predicts both qualitative and more importantly quantitative changes in clinically and experimentally observed responses. DigitalHuman provides scientists a modeling environment to understand the complex interactions of integrative physiology. This research was supported by NIH HL 51971, NSF EPSCoR, and NASA

1. 0 INTRODUCTION

Mathematical simulations of physiological processes have become an important tool in understanding normal and pathophysiological processes within the body. Beard and colleagues have presented a very detailed simulation of cardiac metabolism, in particular energy metabolism during cardiac ischemia (2). Secomb and colleagues have simulated microcirculatory hemodynamics in vascular networks (10). Oxygen delivery to tissue has been extensively modeled, (9) along with simulations of VEGF release demonstrating that hypoxia-induced VEGF release is important to direct angiogenesis towards hypoxic tissue (7). There are an extensive number of publications in the literature describing mathematical simulations of individual organ systems, but there are no comprehensive models demonstrating the integration across different organ systems. Olufsen et al. has described integrative models of the baroreflex/sympathetic nerve system interaction demonstrating blood pressure regulation during orthostasis (8), but these are also somewhat limited in the integration of the entire body responses. In this paper we describe a detailed integrative model of human physiology, designed such that the physiological descriptions can easily be changed by the user.

Starting with the Guyton cardiovascular model in the late 1960's and continuing to the present, Guyton and Coleman demonstrated the use of computer simulations for education purposes and to develop and test hypotheses concerning physiological systems (1; 5; 6). Perhaps one of the best known historical models of integrative physiology is the Coleman HUMAN model which contained a detailed description of circulatory function (4).

There are currently three available integrative models of the human body. All are based on the original model "Human" written by Drs. James Randall and Thomas Coleman between 1981 and 1987. The 1980 version of Human is

available at Skidmore College and is used as a web-based teaching tool. QCP2005.exe (Quantitative Circulatory Physiology) developed at the University of Mississippi Medical Center (UMC) incorporates the cardiovascular, renal, respiratory, endocrine, and nervous systems. A major limitation of this model is that the program is written in C++ and is compiled. Parameter values can be changed using slider bars and other active screen objects, but it is not possible to change or add underlying equations. Therefore we have developed DigitalHuman (DH), a simulation of human physiology where the underlying physiological relationships are written in XML. The model is completely specified in XML (which is both machine and human readable). This paper describes the basics of the current version of DH.

2.0 METHODS

The DigitalHuman simulation package is comprised of a series of files that describe the physiology (Structure files), a set of files that describe the display characteristics of the simulations (Display), and the executable DigitalHuman.exe file. To solve and display the XML based physiological descriptions the executable DigitalHuman.exe file is a compiled (C++) code which consists of a fast XML parser, numerical methods used in solving algebraic and differential equations, and the code that generates screen updates. No unusual libraries are used. The code is currently compiled for Windows using one of several Microsoft C++ compilers.

2.1 XML Structure Files For DH the XML files describing the physiological responses are located in a folder called "Structure". Within the "Structure" folder are a series of subfolders, each describing a particular organ or responses. Within these sub folders are simple text files having a .DES extension that contain the physiological descriptions. This organization is designed for ease of use in finding particular files. The individual XML files are simple text files and modifications can be made by anyone using a text editor.

The physiological variables and relationships are described using Extensible Markup Language (or XML). The extensible in XML's name identifies one of its major strengths as XML can be customized to meet specific needs. In the case of mathematical model documentation, we have developed an XML schema that is used to represent the details of mathematical models, including the structure of the model, the control of solutions and the display of results.

The XML data files have several important elements. With respect to the XML schema used by DH, these are:

<variables> which is used to declare (and sometimes define) variables. There are a variety of variable types including ordinary, parameters, constants, timer variables and random variables.

<equations> Declare and parameterize differential and implicit algebraic equations.

<functions> Define curvilinear functions.

<definitions> Create the blocks of math that calculate the derivative values and do additional ancillary math.

One element that is important is the XML element **<curve>**. Sometimes, the precise underlying physiological description is not known, but can be described as a curvilinear function. To accomplish this we have developed the element **<curve>** which is described by the following text demonstrating the relationship between PO_2 and erythropoietin section.

```
<curve>
    <name>PO2Effect</name>
        <point><x>  0.0 </x><y>  4.0
        </y><slope> 0 </slope></point>
        <point><x> 35.0 </x><y>  0.0
        </y><slope> -0.14
        </slope></point>
        <point><x> 60.0 </x><y> -1.0
        </y><slope> 0 </slope></point>
</curve>
```

The parser reads the text and fits the data to a cubic spline. Since most data sets are small we have determined that the model builder must specify the slope of the curve at each data point to provide a better fit That is the approach used in DH and the curve for the above equation is shown in Figure 1. The benefit of this method of describing a curve is that the researcher does not have to do any mathematical analysis.
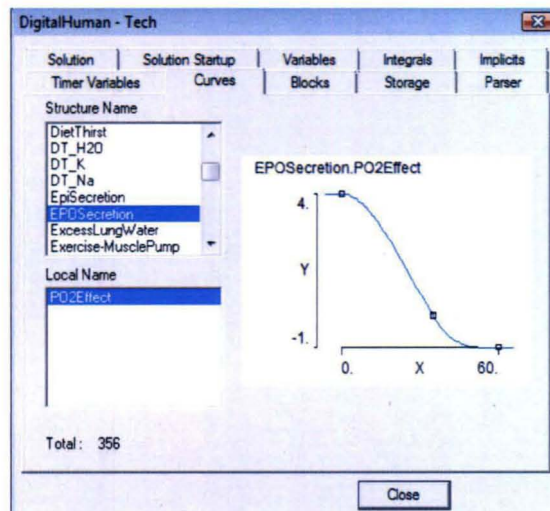
130

Figure 1: Curve fitting capability of DH

The examples of the code and Figure 1 describing erythropoietin secretion demonstrate the ease of writing code to describe physiological responses. The "curve" function allows the investigator to describe a physiological relationship with an arbitrary number of points (the minimum is two), along with the slope at each point. The numerical methods then fit a cubic spline curve to the data and use this fitted equation in DH. The investigator can view the curve and determine if the curve accurately demonstrates the physiological responses.

2.2 Parser and Solver

DH parses mathematical expressions directly and evaluates them in its own math engine. There are some important rules for writing the XML code. A common source of error is the failure to comply with these rules, however the parser will inform the user of any rules that are broken so the code can be corrected. The XML parser makes the following tests:

1. Is the document well-formed? This means does it conform to the general rules of XML. For example, is each opening tag paired further down with a corresponding closing tag?

2. Is the document valid? Does it conform to its XML defined document structure? Are all the element names recognized?

3. Is the data acceptable? Is text interpretable? Is the literal a valid number? Is the number within range?

DH uses a serial access (SAX) parser that completes all three tests in one pass. The parser stops if an error is detected and the exact spot in the document is logged and reported when the error is detected.

Parsing of DH requires <4 seconds on Dell desktop (2.8 GHz, 3 GB, XP). Subsequent parses require less time since Windows memory maps recently read files. The quick re-parse response is convenient during model development when lots of parses are needed.

3.0 RESULTS

3.1 Physiological responses

DH allows the user to adjust many characteristics of the patient's physical environment, from global conditions such as altitude to local qualifiers such as temperature, humidity, and barometric pressure. Other external parameters that can be adjusted include partial pressures of the individual gases in inspired air and nutritional composition and amount of ingested food and fluids. Control of the patient's daily routine schedule allows the user to adjust basic functions such as sleeping, working, and feeding on an hour-to-hour basis, whereas the Exercise Panel facilitates studying the effects of differing types of exercise on both a short and long-term scale.

Various panels such as the Organ Details and Basic Physiology button groups allow the user to investigate and adjust physiological parameters on a more in-depth basis. Panel features include graphical data displays, information buttons, and adjustable variables. In some instances, pathophysiological states can be mimicked through the use of radio and slider buttons that allow hormone levels to be clamped or fixed at a given level.

In addition to manipulating physiological parameters, DH allows the user to administer pharmacological agents to treat a simulated patient. Currently, several drugs are available for interventional treatment: chlorothiazide, digoxin, furosemide, midodrine, insulin and epinephrine.. Additional drugs can be added as the quantitatively relationships regarding their effect upon physiological functions are determined. Several additional treatment options are available in the DH model, including placing the patient on a ventilator, administering fluids via an IV drip, and performing a blood transfusion.

The "Chart" panel provides graphical description of blood pressure, body temperature, heart rate, and ventilatory rate. The full drop-down menu provides additional windows with organ and

physiological responses. Panel features include graphical data displays, information buttons, and adjustable variables. Pathophysiological states can be mimicked through the use of radio buttons and slider bars that allow values to be changed or fixed at a given level.

Currently DH has ~5000 variables describing a variety of physiological responses. The following demonstrates the physiological response to exercise, both at a global and at a tissue level. To run a simulation, DH is started and there is approximately a 5-10 second period (depending on the speed of the computer) while the program parses all of the XML code. The simulation is initiated once the user activates the dropdown menu under "Go", and "brings the person to life" for a period of time, from 1 second to 1 month, depending on the desire to observe acute or chronic physiological changes.

Figure 2 demonstrates the cardiovascular responses upon standing, followed by a period of exercise. The simulation is run for 10 minutes while the subject is lying down, followed by another 10 minutes of standing, followed by 20 minutes of exercise. Each 10 minutes of simulation take approximately 2 seconds of computation time. Note that the increase in heart rate (Figure 2 upon standing). For exercise we can make the subject exercise for 20 minutes on an exercise bicycle at an level of 200 watts. Note the rapid increase in blood pressure, heart rate, and respiratory rate. In Figures 3-5 we provide examples of the detail of DH, demonstrating acid-base balance, liver metabolism, and neural activity.

DH saves the values of all variables along with the state of the timer variables. Saving complete solutions is also supported. A solution can subsequently be reloaded for viewing and can even be continued. File sizes may be large, with the file size for the experiment in Figure 2 requiring ~ 10 MB of disk space.

Gender Specific DH model

We have added detail and scaling to DH to simulate certain aspects of female physiology. In DH the parsing of the XML document is conditional depending on the criteria set in a simple text file.

Figure 6 shows the initial screen for the DH female version (note the female morphology). Figure 7 shows the simulation results for ovarian secretion of estradiol, under cyclic LH control for

one month. We are working to add additional content to DH to fully simulate female physiology.

4.0 CONCLUSION

We have developed an integrative model of human physiology. The physiological equations, variables, parameters and quantitative relationships as well as all other model details are described in XML text files. The advantage of using XML is that it is a universally used format; it can be rapidly parsed by computers but also be read and edited by humans as a text-based document. Additional detail can be added by simply writing a XML file with the appropriate description and including it into the structure folder. The use of scaling allows DigitalHuman to simulate male and female physiological responses and many other traits. DH provides a rich environment for understanding human physiology and provides researchers with an environment to easily make changes in the model.
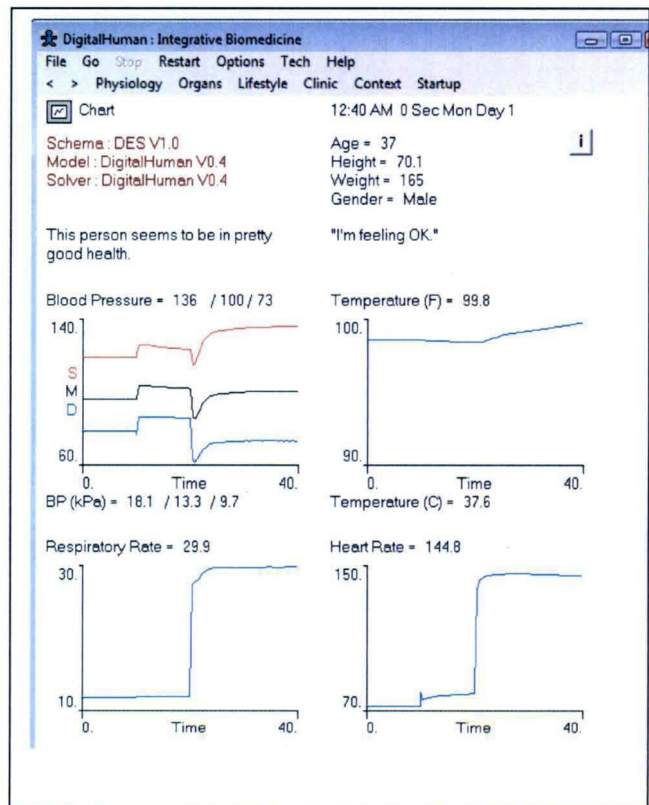

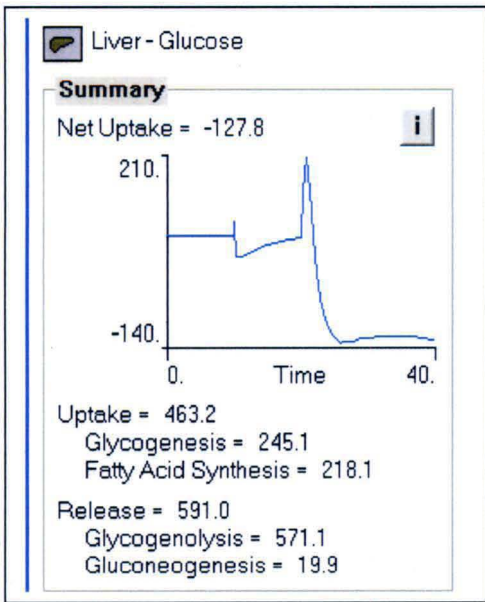Figure 2: Physiological responses during 20 minutes of exercise

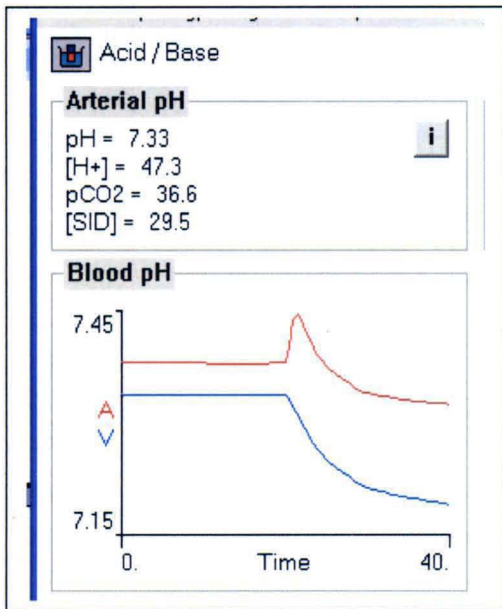**Figure 3:** Liver glucose metabolism during exercise
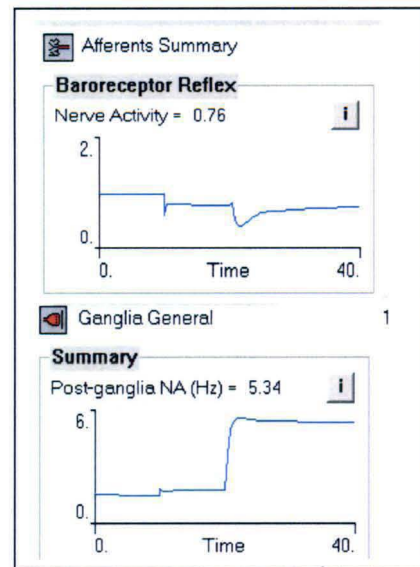

Figure 4: Blood pH changes during exercise
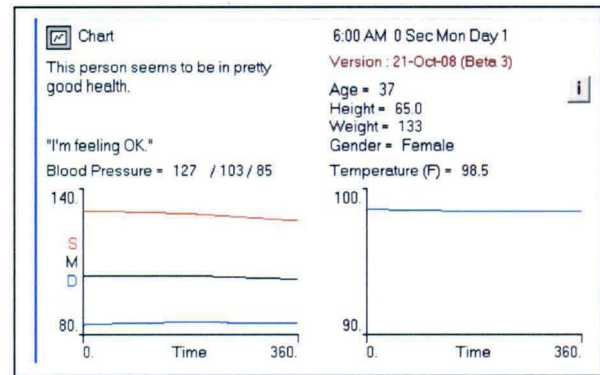

Figure 5: Neural activity during exercise

Figure 6: Female version of DH
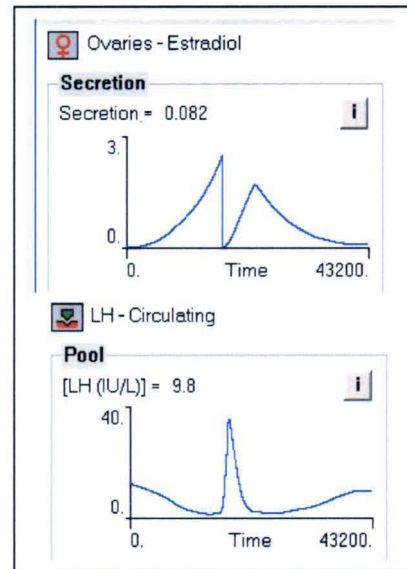
Figure 7: Estradiol responses in the female versions of DH

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