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A FUZZY LOGIC CONTROLLER FOR HORMONE ADMINISTRATION USING AN IMPLANTABLE PUMP

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ABSTRACT

This paper describes the requirements for a Fuzzy Logic Controller for the physiologic administration of hormones by means of a FDA-approved surgically implantable infusion pump. Results of a LabVIEW computer simulation for the administration of insulin for diabetic adult patients as well as human growth hormone for pediatric patients are presented. A VHS video tape of the simulation in action has been prepared and is available for viewing.

INTRODUCTION

MiniMed Technologies, Inc. of Sylmar, California is currently conducting Phase II Clinical Trials for FDA approval on 335 patients of an open-loop implantable insulin pump for use by patents with insulin-dependent diabetes. This type of pump represents a significant advance over current practice, since it obviates the need for patients to self-administer insulin by Intra Muscular injections 2-3 times per day. On the other hand, this type of pump has the disadvantage that the patient must still anticipate their insulin requirements with each meal and dial in a specific dose level on a handheld calculator that in turn communicates with the implanted pump by means of a short-range digital radio-telemetry link. As a separate research and development activity, diabetes investigators are actively developing a variety of blood-glucose sensors. Anticipating the successful completion of such sensors at some future time, a physiologically-realistic algorithm for closed-loop control of blood-sugar levels would then provide the patient with the freedom to lead a relatively normal (more care-free) life, at least so far as eating is concerned. The final system, however, might fall short of the dream of a fully artificial pancreas, since the pump's reservoir must be periodically refilled with a concentrated form of insulin every few months, and this would be done by vacuum injection as an outpatient procedure.

A fuzzy control algorithm [1,2] was developed at JPL for the purpose of "closing the loop" based on the work of Prof. Richard Bergman at the USC Dept. of Physiology in the School of Medicine [3]. Refinements from Prof. Sam Bessman, M.D. of the Dept. of Pharmacology at the USC Medical School were added with respect to diabetic stress in a clinical setting [4]. Further refinements of complications secondary to pregnancy were added by Prof. Raul Artal, M.D. of USC Department of OB/GYN [5]. To verify the value of this sort of approach, a model for human growth hormone administration was developed based on the work of Prof. Johannes Veldhuis at the University of Virginia in Charlottesville [12-14]. Surprisingly, the time needed to construct the hGH administration model was just three hours.

Our models were implemented on an Apple Macintosh Quadra 950 using the LabVIEW software (v. 2.2.1) package, commercially available from National Instruments, Inc. of Austin, Texas. The CubiCalc Fuzzy Logic software development system from HyperLogic of Escondido, California will be considered in the next implementation on an IBM-PC. Later, the clinical importance and commercial potential of such implantable devices will be discussed.

RESULTS

Diabetes Model

Figure 1 shows the overall LabVIEW model of the pancreas, including the body's environment within which it operates, as developed by us at JPL over a four-day period. The high degree of model/developer interactivity, which is one of the major selling points of LabVIEW on a PC or MAC, is what permitted us to do the sort of "rapid prototyping" that allowed us to evolve of the model toward physiologically-correct behavior in such an accelerated time. In addition, the model included sub-models for patient-dependent parameters, food caloric values, stomach, liver, kidney, and body muscle/fat ratios. The patient model, shown in Figure 2, included age, gender, ethnic group, weight, family history of diabetes, and medication history. These were combined with temporal profiles for food consumption, physical exercise, and exposure to stress during the day, using rules of Fuzzy Logic to compute the relative sensitivity of the of body tissues to insulin for an individual patient.

Figure 3 illustrates a typical output of the model. The upper graph plots the change in blood glucose levels in mg/dl over a 24-hour period, while the lower graph plots the output of insulin from the artificial pump in micro liters over the same period. Breakfast at 7:00 AM, lunch at Noon, dinner at 6:00 PM, followed by a snack at 10:00 PM are conspicuous events. The "ringing" in blood sugar levels triggered by harp transitions in insulin levels at the onset of food consumption is likely to be an artifact of our computer implementation rather than representative of true physiological events in the body, since the tissues are likely to have a strong smoothing effect, and no effort was made to simulate this phenomenon in our model. Alarm conditions such as "excessive urination" or "headache," associated with hyper- and hypoglycemia respectively, are triggered in the model whenever certain blood glucose threshold values are exceeded or fall beyond normal limits, as specified by the investigator. This is manifested in the model by flashing error lights with alarm bells going off.

Pituitary Model

Figure 4 shows our proposed model of the hypothalamic/pituitary axis in the interface between the human brain and the endocrine system. The pulsatile diurnal output of human Growth Hormone (hGH) is subject to a "bang/bang" pair of antagonistic messenger molecules, Growth Hormone Inhibiting Hormone (GHIH) and Growth Hormone Releasing Hormone (GHRH), originating in the hypothalamus and connected to the pituitary by means of a specific portal vein network. GHRH secretion is essentially a series of pulses clocked at once a minute uniformly throughout the day, whereas GHIH secretion is the real "gate keeper" normally high and occasionally low, allowing pulses of hGH to flow out of the pituitary into the blood stream, where it has a constellation of effects in addition to growth in children.

Figure 5 shows the results of this model under conditions of significantly decreased GHIH at 2:30 AM and 5:30 AM (the top graph), normal uniform GHRH (middle graph), and resulting hGH output (bottom graph). This model accounts for the physiologically-observed major jagged-stairstep rises in hGH pulses several times during sleep with a few more randomly-distributed smaller pulses that occur during the waking hours. Figure 6 illustrates a different patient's parameters with greater bursts of hGH during the night. Figure 7 expands the resolution in the interval from Midnight to 6:00 AM for greater clarity of the cause-and-effect relationship between the two inputs (GHIH and GHRH) and the output (hGH).

DISCUSSION

The implications of such a control system running in LabVIEW for clinical and engineering applications is that, as pieces of the final hardware system are completed, they can be inserted into the model to replace their corresponding software component. In the case of the pituitary model, the existence of a physiologically-based secretion into the bloodstream of juvenile patients during the hours of sleep is much to be preferred over the bolus injections twice or three times a week, as they are administered now. Although the number of potentially affected children with shortness of height secondary to pituitary insufficiency (rather than receptor insensitivity) may be relatively small compared to the population as a whole, the potential to help the wider geriatric population with hGH supplementation in this manner could be enormous.

Block Diagram

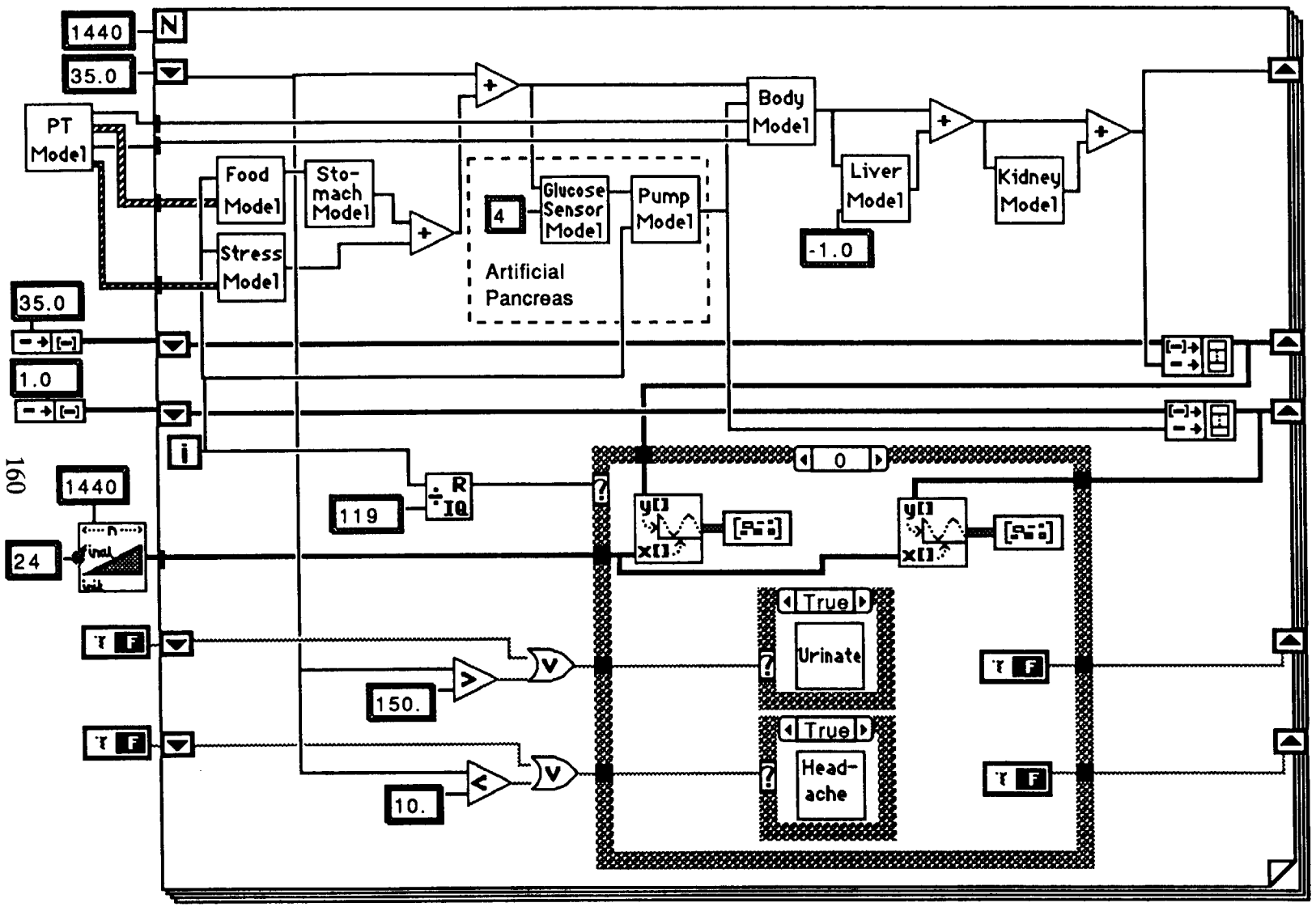
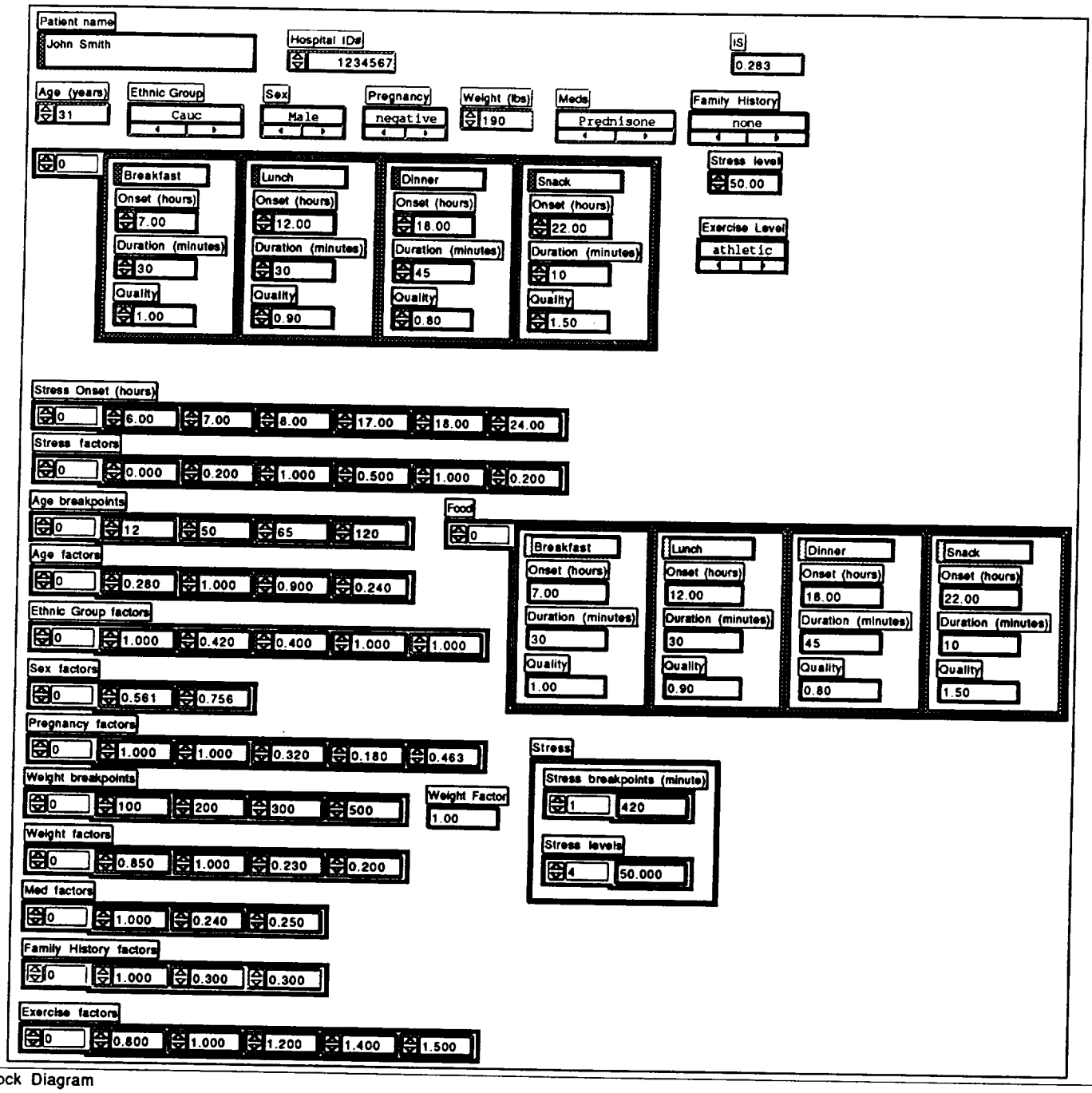


Figure 1: LabVIEW Block Diagram of the Artificial Pancreas System.

Front Panel



Block Diagram

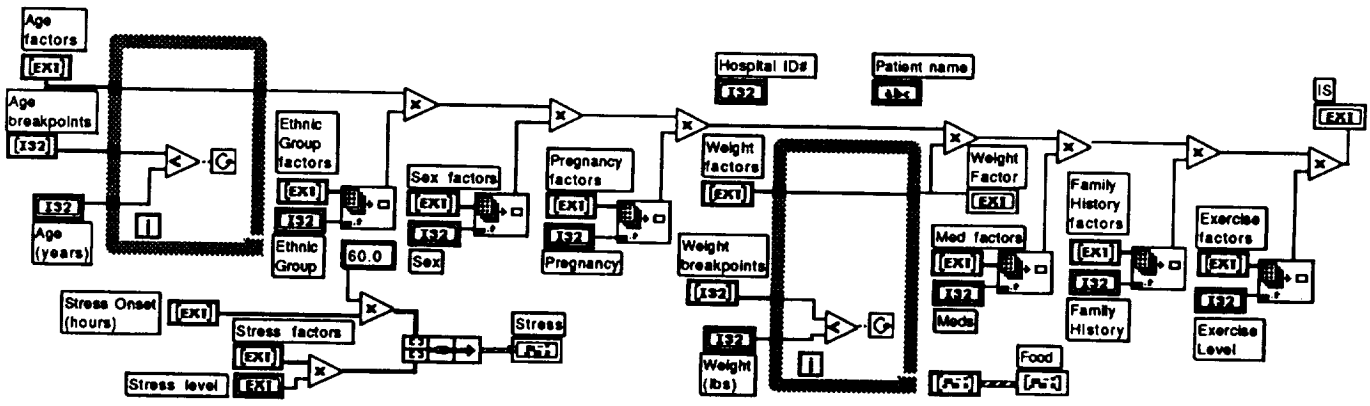
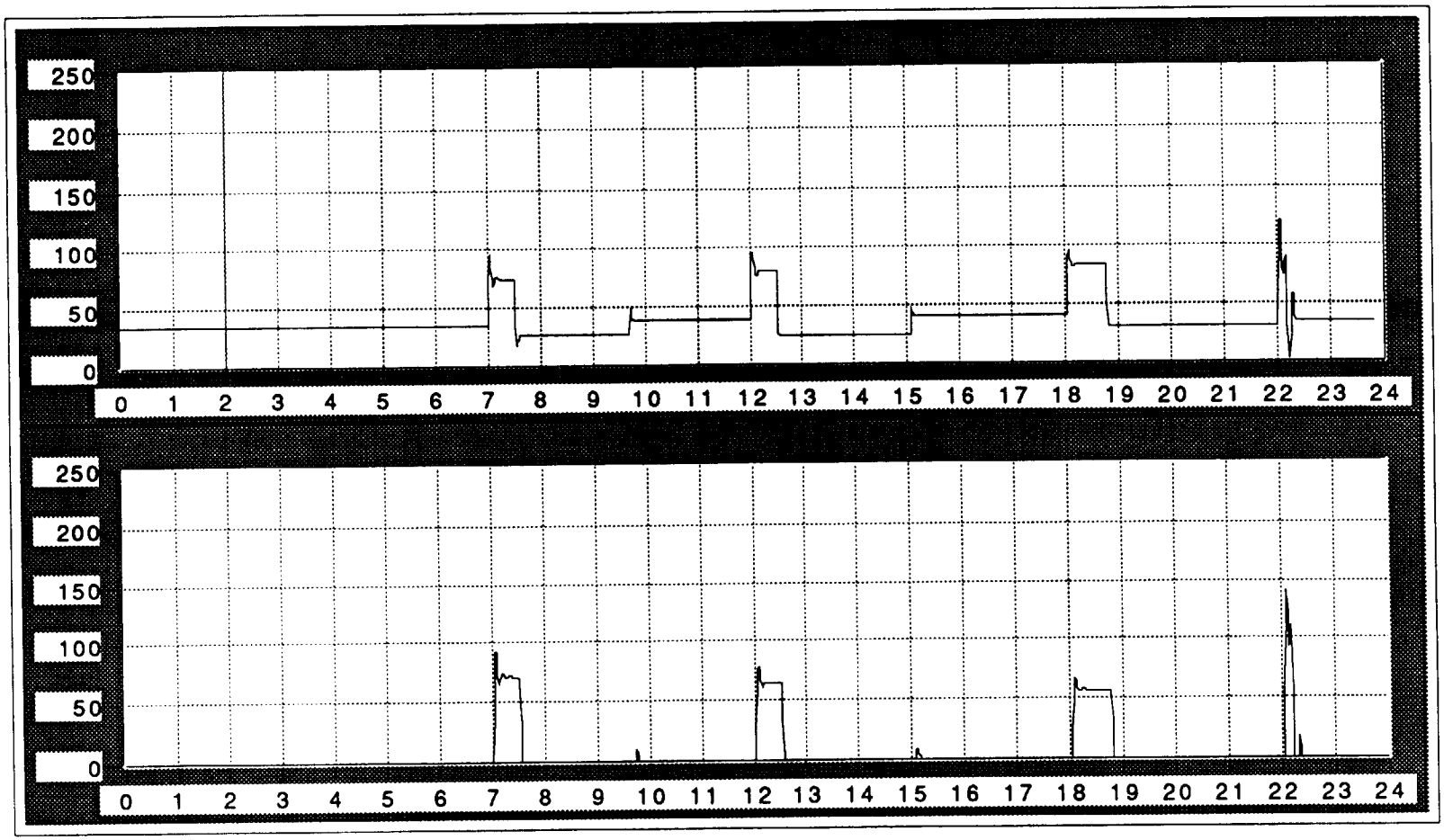


Figure 2: Front Panel for a Human Adult Patient with Diabetes Mellitus.

Front Panel



Block Diagram

Figure 3: Output from the Model
Upper Graph: Blood Glucose (mg/dl) vs. Time (hours)
Lower Graph: Blood Insulin (units secreted) vs. Time

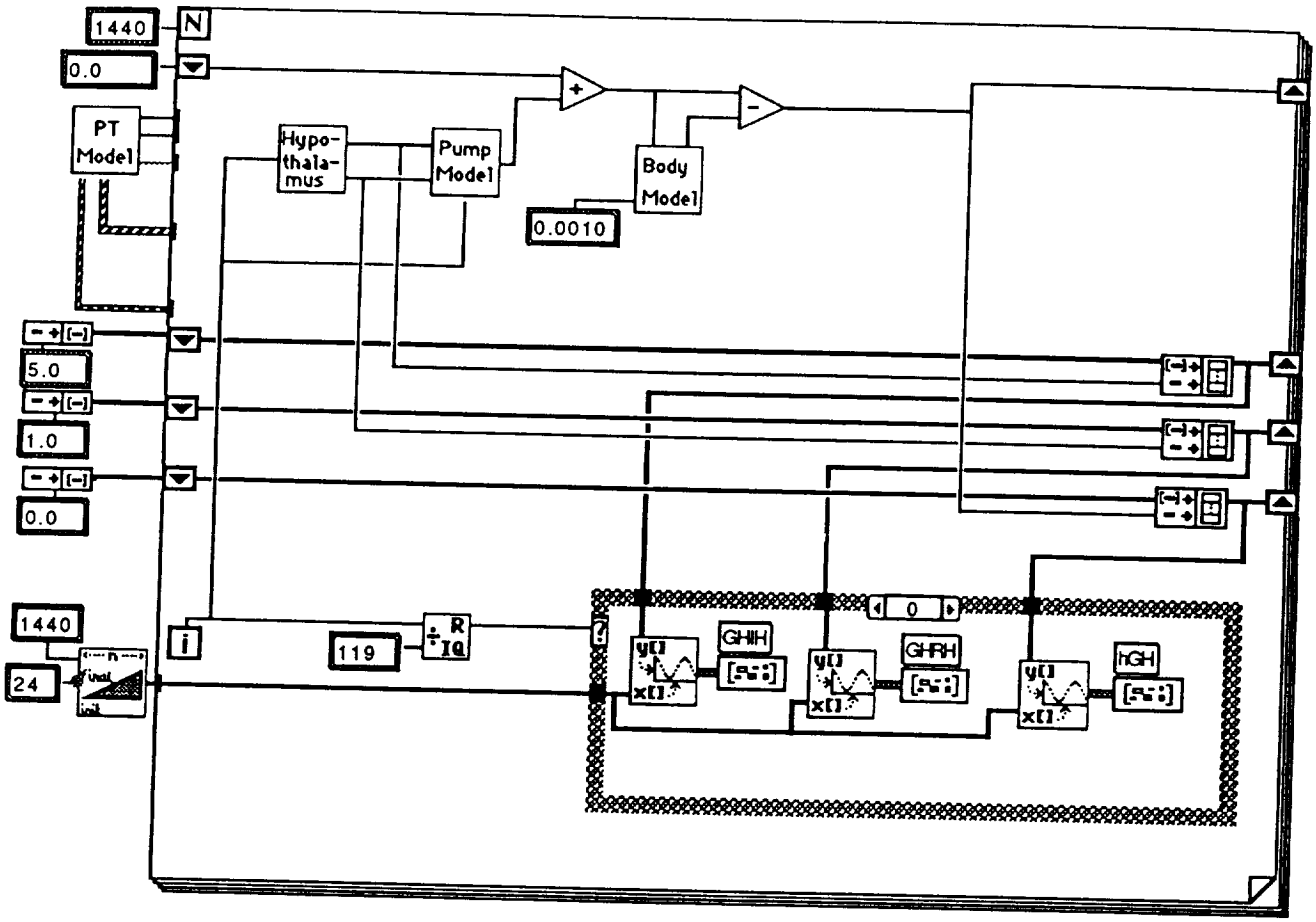
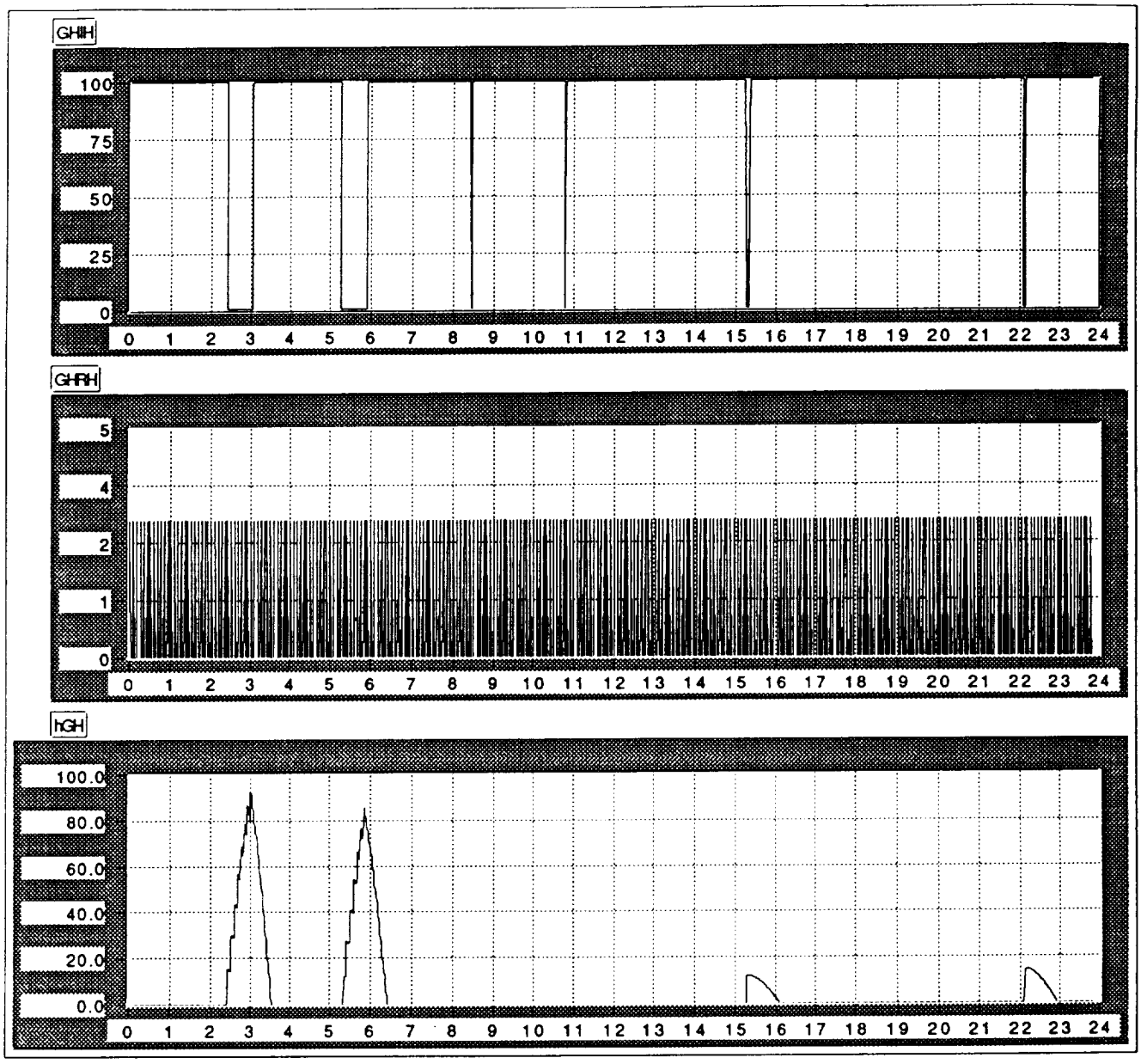


Figure 4: LabView Block Diagram of the Hypothalamic/Pituitary Model.

Front Panel



Block Diagram

Figure 5. Typical Diurnal Pulsatile Output from the Model
Upper Graph: Growth Hormone Inhibiting Hormone (GHIH)
Middle Graph: Growth Hormone Releasing Hormone (GHRH)
Lower Graph: Human Growth Hormone (hGH)

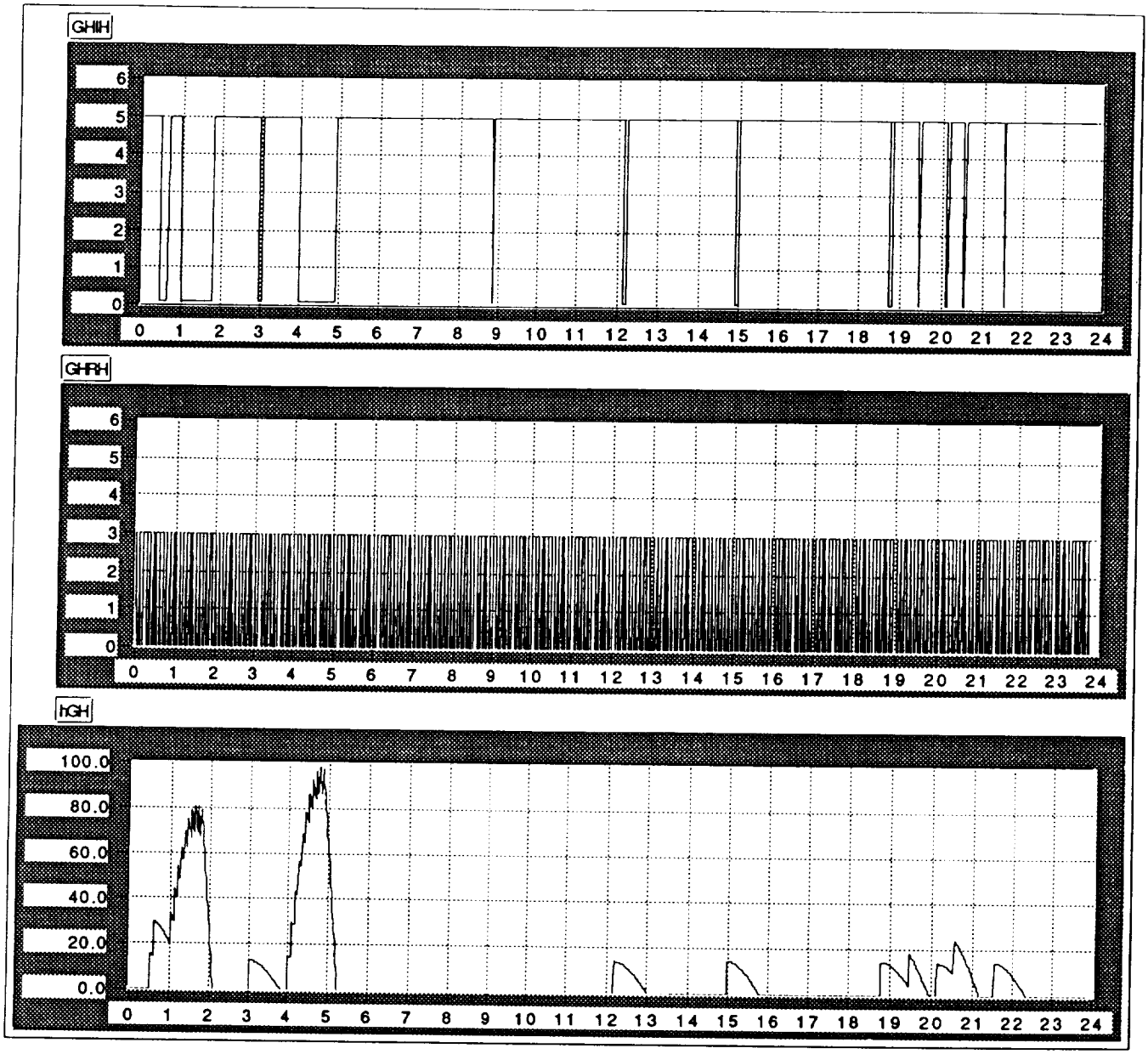


Figure 6: Another Model Output with Stronger hGH Secretion.

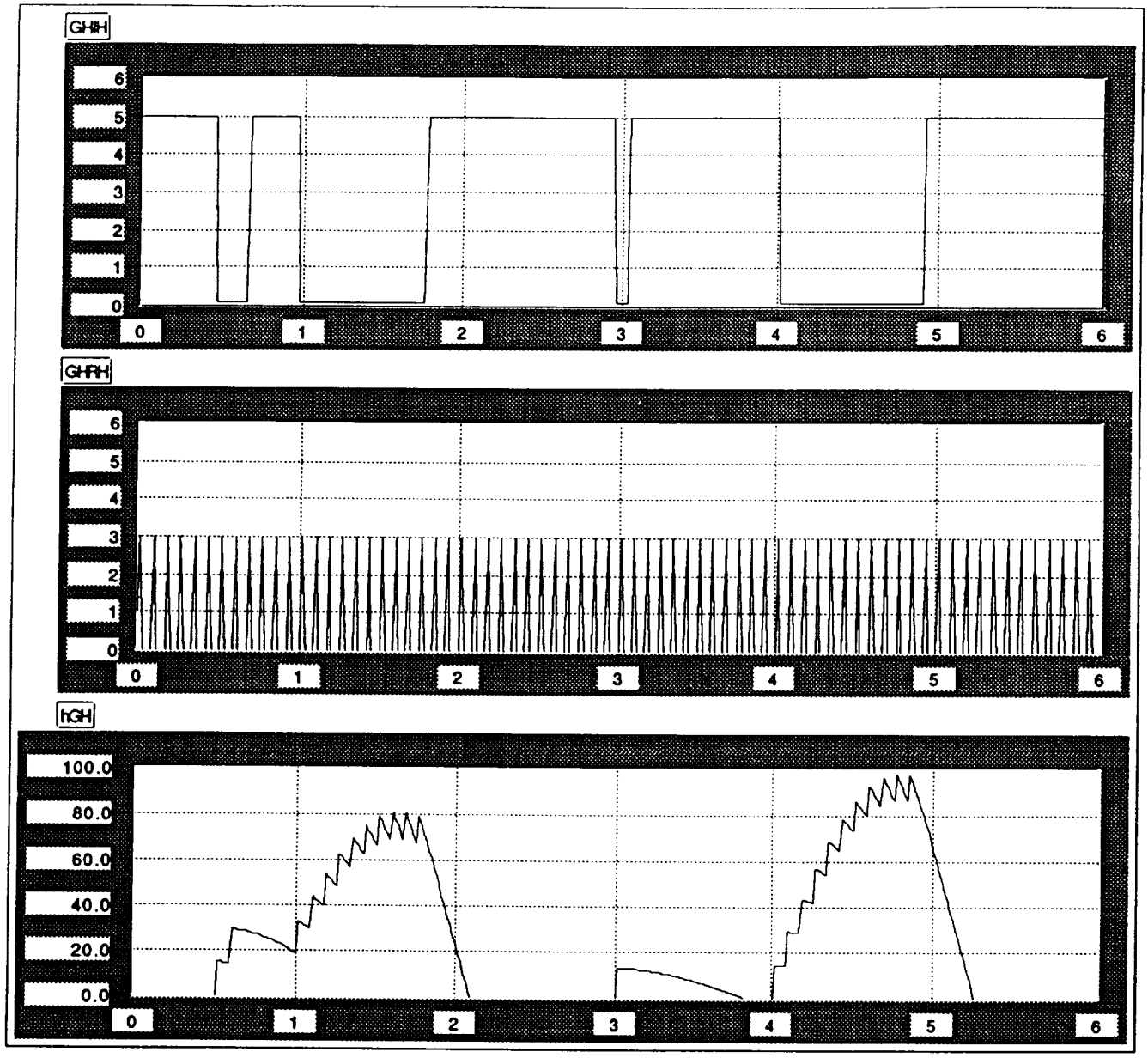


Figure 7: Higher Resolution from Midnight to 6:00 AM when hGH Secretion is most active.

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