MODELING EXERCISE EFFECTS IN TYPE I DIABETIC PATIENTS

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Abstract: A model for glucose metabolism during exercise is developed for use in an automated insulin delivery device. Key changes that occur in the body during exercise are an increase and redistribution of blood flow, increased glucose uptake, and increased glucose production by the liver. A model of glucose and insulin metabolism for exercise intensity $\leq 60\%$ VO_2^{max} and duration ≤ 90 minutes has been constructed. The model-generated glucose profiles are consistent with physiological behavior over this time period based on comparisons with literature data.

Keywords: biomedical systems, dynamic modelling, nonlinear models, physiological models, time

1. INTRODUCTION

Type I diabetes mellitus is a disease characterized by elevated blood glucose concentration due to insufficient endogenous insulin production. Hence, exogenous insulin is necessary. The control of blood glucose level within the normoglycemic region (70–120 mg/dL) is essential to prevent major health complications. Prolonged hyperglycemia ($>$120 mg/dL) is the primary cause of the long–term health problems associated with the disease, such as retinopathy and poor circulation, often resulting in amputation (DCCT - The Diabetes Control and Complications Trial Research Group, 1993; DCCT - The Diabetes Control and Complications Trial Research Group, 1996). Hypoglycemia ($<$60 mg/dL) due to insulin shock is of short–term concern, and may lead to coma and death. Maintaining blood glucose in the normoglycemic regime often poses a problem for the diabetic patient.

A model for glucose metabolism representing a patient in the basal, or resting, state has been previously developed (Sorensen, 1985; Parker *et al.*, 2000). The advantage of using this model for glucose, insulin,

and glucagon metabolism is that the model structure is physiologically accurate, and parameters are identified from physiologic data. The human body is divided into compartments as shown in Figure 1, which represent key sites affecting glucose, insulin, and glucagon dynamics. The peripheral compartment
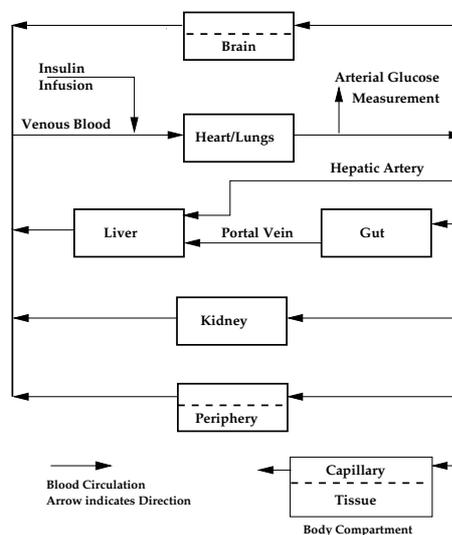
Fig. 1. Compartmental diagram of the human body.

contains both muscle and adipose tissue. However, the existing model does not account for the physiological changes in metabolism due to exercise.

Exercise causes changes such as altered blood tissue volumes and increased tissue blood flow (Chapman and Mitchell, 1965), increased glucose uptake by exercising muscle (Ahlborg *et al.*, 1974), and increased glucose production by the liver (Wahren *et al.*, 1971). Incorporating the effects of exercise into the existing model would provide improved predictions of glucose dynamics in a patient under a broader class of conditions. Presented herein is a model for short–term, mild or moderate exercise in a type I diabetic patient.

2. QUANTIFYING THE EXERCISE LEVEL

Exercise brings about changes in the body, including increased heart rate and oxygen consumption (Robergs and Roberts, 2000). The increase in oxygen utilization is necessary for increased metabolic breakdown of energy sources in the exercising tissue. The work associated with exercise correlates to a necessary oxygen consumption rate (Åstrand, 1960). When the exercise workload is expressed as a percentage of an individual's maximum oxygen consumption rate (PVO_2^{max}), exercise effects may be compared between individuals of the same sex and similar weight and conditioning state working at the same PVO_2^{max}. As an additional benefit, the value of PVO_2^{max} during exercise is more easily monitored than glucose uptake.

The exercise model developed in this work uses PVO_2^{max} as a method for quantifying the exercise level at which a person is working. The average PVO_2^{max} for a person in the basal state is 8% (Felig and Wahren, 1975; Kjaer *et al.*, 1991). At the onset of exercise, PVO_2^{max} increases, reaching its ultimate exercising value within 4–5 minutes and remains constant for the duration of exercise (Ahlborg *et al.*, 1974; Wahren *et al.*, 1971). In the model, the change in exercise level is governed by the following differential equation:

$$\frac{dPVO_2^{max}}{dt} = -\frac{5}{3}PVO_2^{max} + \frac{5}{3}ePVO_2^{max}. \quad (1)$$

Here PVO_2^{max} is the physiological exercise level experienced by the tissues, and $ePVO_2^{max}$ is the target exercise level of the patient at steady state.

3. BLOOD FLOW DISTRIBUTION

Exercise results in increased oxygen and glucose uptake by the exercising muscle to meet increased energy requirements. The increased uptake of these molecules necessitates a redistribution of blood throughout the body (Chapman and Mitchell, 1965). The blood flow to individual tissue groups is quantified in Table 1. Blood flow to the brain remains constant with respect to its basal value, as its energy needs remain

Table 1. Blood flowrates (dL/min) to tissues as a function of exercise

Tissue Group	PVO_2^{max}			
	8%	30%	60%	90%
Brain	5.9	5.9	5.9	5.9
Liver	12.6	9.8	6.1	2.3
Kidneys	10.1	8.1	5.3	2.5
Peripheral	15.1	50.6	99.1	147.5

fixed regardless of rest or exercise. It can be seen that as exercise intensity increases, blood flow increases to the peripheral compartment, while blood flow is decreased in the liver and kidney compartments. An increase in peripheral blood flow during exercise, primarily to the muscle, provides greater glucose availability to the exercising tissue. Blood flow to muscle is a linear function of work intensity (Andersen *et al.*, 1985). Retaining this functionality, total cardiac output and blood flow to individual tissue groups are modeled as linear functions of PVO_2^{max} using the data in Table 1. Therefore, the dynamics of blood flow, therefore, follow equation (1), mirroring the response in PVO_2^{max}.

4. PERIPHERAL GLUCOSE UPTAKE (PGU)

Peripheral tissue includes both muscle and fat (adipose tissue). During exercise, increased muscle contraction leads to greater glucose extraction to meet energy needs. Therefore, exercising tissue has a greater glucose uptake than non–exercising tissue. Muscle accounts for nearly all of the increased glucose uptake in exercising peripheral tissue (Kjaer *et al.*, 1991). For example, bouts of intense exercise ($PVO_2^{max}>80\%$) may increase glucose uptake by exercising muscle up to $20\times$ that of basal glucose uptake (Maynard, 1991). Therefore, the glucose uptake in adipose tissue is neglected as the mass of exercising muscle approaches the limit of 100%. The contributions of insulin, glucose, and exercise to total peripheral glucose uptake (PGU) is formulated as:

$$PGU = M^I \times M^G \times M^E \times 35. \quad (2)$$

Here M^I, M^G, and M^E are dimensionless multipliers representing the effect of insulin, glucose, and exercise respectively on peripheral glucose uptake. The basal peripheral glucose uptake rate is 35 mg/min. The form of M^I and M^G has been taken from Sorensen (1985). The quantity M^E is formulated as

$$M^E = 1 + \frac{PGU_A \times PAMM \times 28}{35} \quad (3)$$

where PGU_A is the active muscle peripheral glucose uptake rate (mg/(min·kg muscle)) and $PAMM$ is the percent of active muscle mass from 0 to 100. Skeletal muscle accounts for approximately 28 kg of the body mass in an average 70 kg man (Snyder *et al.*, 1975). The resting PGU rate (35 mg/min) is used to make

M^E dimensionless. The value for $PAMM$ is calculated using

$$PAMM = \frac{x \text{ kg active muscle mass}}{28 \text{ kg total muscle mass}} \qquad (4)$$

where x is the mass of muscle actively participating in exercise. In the basal state, $PAMM=0$ because there is no exercising muscle mass. The formulation of total peripheral glucose uptake in equation 3 is used so that the glucose uptake rate is equivalent to its non-exercising value when none of the muscle mass is exercising.

The glucose uptake by exercising muscle (PGU_A) in man has been measured via Fick's law using an arterial-venous concentration difference multiplied by a blood flowrate value (Ahlborg and Felig, 1982; Ahlborg et al., 1974; Ahlborg et al., 1986; Wahren, 1977). Glucose uptake rates in muscle for exercise at 30% and 60% VO_2^{max} are presented as a function of exercise duration in Figure 2. To facilitate comparison between the published exercising muscle glucose uptake values, PGU_A is expressed per kilogram of exercising muscle. It can be seen that the value for PGU_A increases for t<90 min, reaching a plateau value at 90 min. This is a result of the increased glucose extraction by exercising muscle. For t>90 min, PGU_A begins to decrease. This is due to a depletion of hepatic glycogen stores during prolonged exercise (Ahlborg et al., 1974). This will be discussed in greater detail in the **Hepatic Glucose Production** section, below. The dynamic change of PGU_A was implemented using the differential equation

$$\frac{dPGU_A}{dt} = -\frac{1}{30}PGU_A + \frac{1}{30}ePGU_A \qquad (5)$$

where $ePGU_A$ is the steady-state plateau value for PGU_A at a given exercise level. The value of $ePGU_A$ for 30% VO_2^{max} exercise is 32 mg/(min·kg muscle) and for 60% VO_2^{max} exercise is 85 mg/(min·kg muscle). The model responses, given by the solid lines in
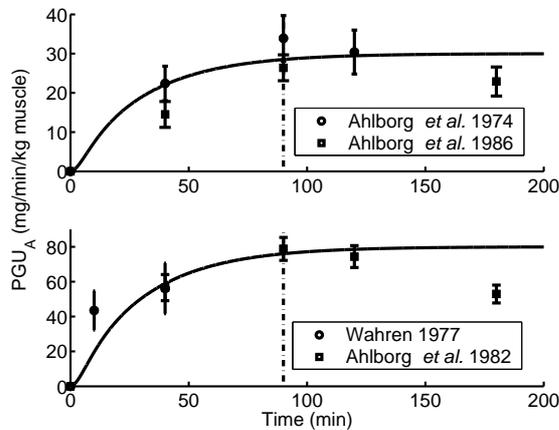
Fig. 2. Peripheral glucose uptake by exercising muscle over time, solid line – model prediction, dash-dot line – t=90 min. (a) 30% VO_2^{max}, (b) 60% VO_2^{max}.

Figure 2, are consistent with the published literature results up to time t=90 min.

5. HEPATIC GLUCOSE PRODUCTION (HGP)

The liver is the key site of glucose production in the body through the pathways for glycogenolysis and gluconeogenesis. Glycogenolysis, the breakdown of glycogen into glucose, is a major source of glucose for exercising tissue. Gluconeogenesis is the synthesis of glucose from gluconeogenic precursors such as alanine and lactate from the bloodstream (Ahlborg et al., 1974). Gluconeogensis, however, is a slower process, and cannot produce glucose release rates as high as glycogenolysis. The difference in these rates results in a decrease in glucose production capability in the liver when glycogen stores become depleted (Ahlborg et al., 1974).

At the onset of exercise, glycogenolysis from the 80–90 g glycogen store in the liver provides approximately 75% of the glucose released by the liver (Felig and Wahren, 1975). During short–term moderate exercise, hepatic glucose release is capable of increasing to maintain the blood glucose level at a nearly constant value (Wasserman and Cherrington, 1991). Prolonged exercise causes a decrease in hepatic glucose production, occurring when glycogen stores reach approximately 25% of their initial value (Ahlborg et al., 1974). At this point, the liver shifts its glucose release to the slower gluconeogenesis mechanism. A decrease in hepatic glucose production (HGP) results in a lowered blood glucose concentration, while peripheral glucose uptake (PGU) remains elevated. As the blood glucose level decreases, less glucose is available for uptake in exercising tissue. This causes PGU to decrease at prolonged times (t>90 min), as seen in Figure 2.

Glucose production by the liver is modeled as:

$$HGP = M^G \times M^I \times M^\Gamma \times M^E \times 155. \qquad (6)$$

Here M^G, M^I, and M^Γ are dimensionless multipliers for the effect of glucose, insulin, and glucagon respectively on hepatic glucose production adopted from Sorensen (1985) and 155 mg/min is the basal hepatic glucose production rate. The effect of exercise on hepatic glucose production, M^E, is formulated as:

$$M^E = 1 + \frac{HGP_A \times PAMM}{155} \qquad (7)$$

where HGP_A is the augmented rate of glucose production (mg/min) balancing the increased glucose uptake in exercising tissue and $PAMM$ is the percent of active muscle mass. In the basal state, $PGU_A=0$ which results in $HGP_A=0$, and the basal HGP rate is maintained.

6. INSULIN UPTAKE

The removal of insulin from the bloodstream occurs in the liver, kidneys, and peripheral tissues (Duckworth *et al.*, 1998). In the basal state, insulin uptake by the liver and kidneys is formulated as a fractional extraction of the insulin presented to these organs (Sorensen, 1985). For example, the uptake of insulin by the kidneys (KIU) is:

$$\text{KIU} = F \times Q_K^I \times I_H \tag{8}$$

Here F is a fractional extraction term representing a percentage of insulin removed from the blood stream upon entering the compartment, Q_K^I is the kidney blood flowrate (L/min), and I_H is the arterial insulin concentration (mU/L). During exercise, there is a change in the tissue blood flowrates and the insulin concentrations in the body. To maintain a constant fractional uptake during exercise, the product $F \times Q_K^I$ is assigned a constant value based on basal values. This simplifies the insulin uptake term to be directly proportional to the amount of insulin presented to the compartment.

Insulin uptake by the peripheral tissue (PIU) was originally formulated using a steady-state mass balance between the peripheral capillary and tissue spaces (Sorensen, 1985) as

$$PIU = \frac{I_P^{muscle}}{\left[\frac{(1-F)}{F \times Q_P^I} - \frac{\tau_I}{6.3} \right]}. \tag{9}$$

Peripheral insulin uptake is found to be dependent on the peripheral insulin concentration in the muscle (I_P^{muscle}), a fractional extraction parameter ($F=0.15$), peripheral blood flowrate to the capillary space ($Q_P^I=1.05$ L/min) and a diffusion time constant from vascular to tissue space ($\tau_I=20$ min). Increased blood flow to the muscle during exercise leads to an opening of more capillaries throughout the tissue, resulting in a decrease in the diffusion path (Richter, 1996). This allows for more insulin to be transported from the vascular space to the tissue space, resulting in increased uptake. An increase in insulin uptake by exercising muscle to a level of $3.4\times$ the basal level has been observed (Kalant *et al.*, 1978). To account for this phenomenon, peripheral insulin uptake is formulated as

$$PIU = \frac{I_P^{muscle} \times (1 + 2.4 \times PAMM)}{\left[\frac{(0.85)}{0.15 \times 1.05} - \frac{\tau_I}{6.3} \right]}. \tag{10}$$

This expression shows that insulin uptake is directly proportional to insulin concentration. The peripheral insulin uptake is equivalent to its basal value when no muscle is exercising (*PAMM*=0). In the limit of 100% exercising muscle, the insulin uptake rate is 3.4 times its basal value, reflecting the literature observation (Kalant *et al.*, 1978).

7. RESULTS

The patient model response to 2–legged exercise (*PAMM* = 25%) as a step from 8% (resting) to 30% VO_2^{max} at t=30 min is shown in Figure 3. The patient undergoes constant insulin infusion at the basal rate of 24.0 mU/min throughout the simulation. In response to the step change in exercise level, there is an initial decrease in the arterial glucose concentration. This is due to the rapid dynamics of blood flow changes with respect to the other dynamic processes in the model. Blood flow changes occur during the first three minutes of exercise. After the blood flow stabilizes, the arterial glucose concentration rises, then decreases to a steady-state value of 76.1 mg/dL. This behavior is due to the competing dynamics of glucose production and consumption as seen in Figure 4. Between t=30 and t=55 min, the glucose production rate is larger than the consumption rate (difference in rates > 0). This results in the increased arterial glucose concen-
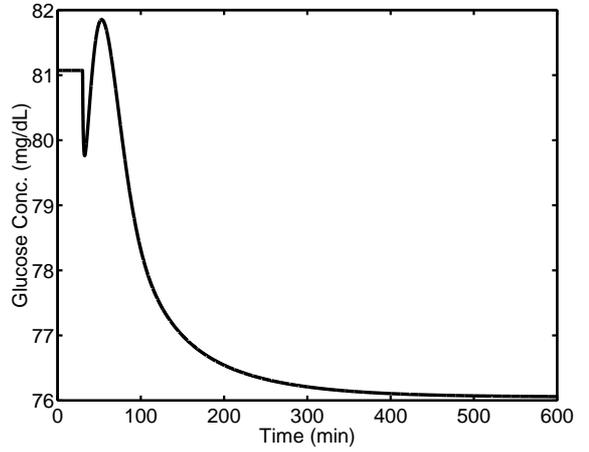
Fig. 3. Arterial glucose response to 2–legged exercise with a step from 8% to 30% VO_2^{max} at t=30 min and a constant insulin infusion rate of 24.0 mU/min.
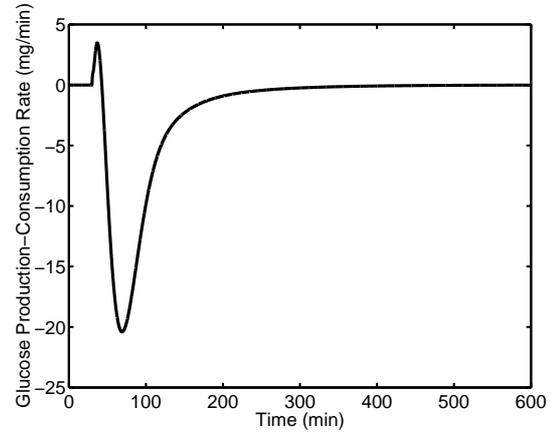
Fig. 4. Difference in rates of glucose production and consumption in response to 2–legged exercise with a step from 8% to 30% VO_2^{max} at t=30 min and a constant insulin infusion rate of 24.0 mU/min.

tration seen in Figure 3. After t=55 min, the glucose consumption rate is greater than the production rate (difference in rates < 0), resulting in a decrease in the arterial glucose concentration. At steady–state, the rates of glucose production and consumption are balanced, resulting in the 76.1 mg/dL concentration of glucose in the blood.

The arterial glucose concentration profile for a step change from rest to 2–legged exercise at 60% VO_2^{max} at t=30 min is shown in Figure 5. Once again, the rapid effect of blood flow dynamics results in the initial decrease in arterial glucose concentration. The rate of glucose uptake in the exercising muscle mass is almost $2.7\times$ greater at 60% VO_2^{max} than at 30% VO_2^{max}, which can be seen in Figure 2(b). As the rate of glucose uptake remains larger than the glucose production rate during the entire exercise duration, there is a constant decrease in the arterial glucose concentration unlike the result in Figure 3 This increased glucose uptake results in the drop in arterial glucose concentration of 15%, reaching a steady–state value of 68.8 mg/dL.

Comparisons between glucose concentration model predictions and data published in the literature for 30% VO_2^{max} (Ahlborg et al., 1974) and 60% VO_2^{max} (Ahlborg and Felig, 1982) are shown in Figures 6 and 7, respectively. It can be seen that the model predictions of arterial glucose concentration are consistent with the literature data for exercise durations of up to 90 minutes. After this time, when the model achieves steady-state, the literature reports a further drop in glucose concentration, resulting in overt hypoglycemia. As stated earlier, the formulation of the increase in glucose uptake by exercising muscle was only modeled for t≤90 min, where the active glucose uptake achieved its maximum rate, as shown in Figure 2. After this time, there is a depletion in the glycogen stores in the liver (Ahlborg et al., 1974), and hepatic glucose production decreases. Since glycogen dynamics and metabolism are not included in the current

model formulation, the accuracy of the current model is relevant only up to 90 minutes.
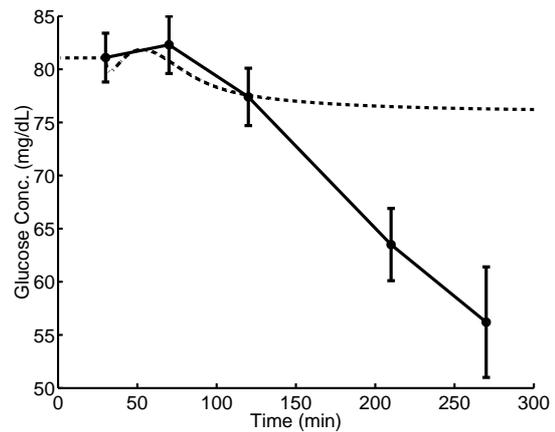
Fig. 6. Published and predicted arterial glucose profiles to 2–legged exercise with a step to 30% VO_2^{max} at t=30 min and a constant insulin infusion rate of 24.0 mU/min.
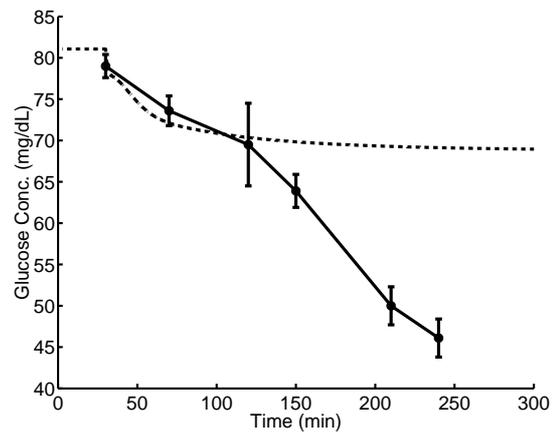
Fig. 7. Published and predicted arterial glucose profiles to 2–legged exercise with a step to 60% VO_2^{max} at t=30 min and a constant insulin infusion rate of 24.0 mU/min.

8. CONCLUSIONS

Mild and moderate intensity exercise have been incorporated into an existing diabetic patient model for glucose metabolism. The changes in blood flow dynamics associated with exercise have been captured by the current model. An increase in glucose uptake during exercise has been accounted for quantitatively for t<90 min. The predicted profiles for arterial glucose concentration are consistent with literature data within the sensitivity of the available glucose sensors.

A departure of the model response from literature values is observed for exercise durations greater than 90 minutes. In the current model formulation, the liver was assumed to possess an infinite reserve of glucose that can be supplied to the body. This is not physiologically accurate. The glucose release from the liver

Fig. 5. Arterial glucose response to 2–legged exercise in response to a step from 8% to 60% VO_2^{max} at t=30 min at a constant insulin infusion rate of 24.0 mU/min.

is predominantly derived from glycogen stores. As the glycogen becomes depleted, the rate of glucose production by the liver decreases. Since glucose uptake in the exercising muscle remains elevated, a further decrease in arterial glucose concentration will result. The extension of this exercise model to include glycogen effects is a topic of current research by the authors.

9. ACKNOWLEDGMENTS

10. REFERENCES

Ahlborg, G. and P. Felig (1982). Lactate and glucose exchange across the forearm, legs, and splanchnic bed during and after prolonged exercise. *J. Clin. Invest.* **69**, 45–54.

Ahlborg, G., J. Wahren and P. Felig (1986). Splanchnic and peripheral glucose and lactate metabolism during and after prolonged arm exercise. *J. Clin. Invest.* **77**, 690–699.

Ahlborg, G., P. Felig, L. Hagenfeldt, R. Hendler and J. Wahren (1974). Substrate turnover during prolonged exercise in man. Splanchnic and leg metabolism of glucose, free fatty acids, and amino acids. *J. Clin. Invest.* **53**, 1080–1090.

Andersen, P., R.P. Adams, G. Sjogaard, A. Thorboe and B. Saltin (1985). Dynamic knee extension as model for study of isolated exercising muscle in humans. *J. Appl. Physiol.* **59**, 1647–1653.

Åstrand, I. (1960). Aerobic work capacity in men and women with special reference to age. *Acta. Physiol. Scan.* **49**, 1–92.

Chapman, C.B. and J.H. Mitchell (1965). The physiology of exercise. *Sci. Am.* **212**, 88–96.

DCCT - The Diabetes Control and Complications Trial Research Group (1993). The effect of intensive treatment of diabetes on the development and progression of long–term complications in insulin–dependent diabetes mellitus. *N. Engl. J. Med.* **329**, 977–986.

DCCT - The Diabetes Control and Complications Trial Research Group (1996). The absence of a glycemic threshold for the development of long–term complications: The perspective of the diabetes control and complications trial. *Diabetes* **45**, 1289–1298.

Duckworth, W.C., R.G. Bennett and F.G. Hamel (1998). Insulin degradation: Progress and potential. *Endocr. Rev.* **19**, 608–624.

Felig, P. and J. Wahren (1975). Fuel homeostasis in exercise. *N. Engl. J. Med.* **293**, 1078–1084.

Kalant, N., T. Leibovici, I. Rohan and K. McNeill (1978). Effect of exercise on glucose and insulin utilization in the forearm. *Metabolism* **27**, 333–340.

Kjaer, M., B. Kiens, M. Hargreaves and E.A. Richter (1991). Influence of active muscle mass on glucose homeostasis during exercise in humans. *J. Appl. Physiol.* **71**(2), 552–557.

Maynard, T. (1991). Exercise: Part I. Physiological response to exercise in diabetes mellitus. *Diabetes Educ.* **17**, 196–206.

Parker, R. S., J. H. Ward, N. A. Peppas and F. J. Doyle III (2000). Robust H_∞ glucose control in diabetes using a physiological model. *AIChE Journal* **46**, 2537–2549.

Richter, E.A. (1996). *Exercise: Regulation and Integration of Multiple Systems*. Handbook of Physiology; Section 12. Oxford University Press. New York.

Robergs, R.A. and S.O. Roberts (2000). *Fundamental Principles of Exercise Physiology for Fitness, Performance, and Health*. McGraw-Hill Companies, Inc.. Boston.

Snyder, W.S., M.J. Cook, E.S. Nasset, L.R. Karhausen, G.P. Howells and I.H. Tipton (1975). *Report of the Task Group on Reference Man: A Report Prepared by a Task Group of Committee 2 of the International Commission on Radiological Protection*. Pergamon Press. Oxford.

Sorensen, J.T. (1985). A Physiologic Model of Glucose Metabolism in Man and its Use to Design and Assess Improved Insulin Therapies for Diabetes. PhD thesis. Department of Chemical Engineering, MIT.

Wahren, J. (1977). Glucose turnover during exercise in man. *Ann. N. Y. Acad. Sci.* **301**, 45–55.

Wahren, J., P. Felig, G. Ahlborg and L. Jorfeldt (1971). Glucose metabolism during leg exercise in man. *J. Clin. Invest.* **50**, 2715–2725.

Wasserman, D.H. and A.D. Cherrington (1991). Hepatic fuel metabolism during muscular work: Role and regulation. *Am. J. Physiol.* **260 (Endocrinol. Metab. 23)**, E811–E824.