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# Glucose predictability, blood capillary permeability, and glucose utilization rate in subcutaneous, skeletal muscle, and visceral fat tissues

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ABSTRACT

This study suggests an approach for the comparison and evaluation of particular compartments with modest experimental setup costs. A glucose level prediction model was used to evaluate the compartment's glucose transport rate across the blood capillary membrane and the glucose utilization rate by the cells. The glucose levels of the blood, subcutaneous tissue, skeletal muscle tissue, and visceral fat were obtained in experiments conducted on hereditary hypertriglyceridemic rats. After the blood glucose level had undergone a rapid change, the experimenter attempted to reach a steady blood glucose level by manually correcting the glucose infusion rate and maintaining a constant insulin infusion rate. The interstitial fluid glucose levels of subcutaneous tissue, skeletal muscle tissue, and visceral fat were evaluated to determine the reaction delay compared with the change in the blood glucose level, the interstitial fluid glucose level predictability, the blood capillary permeability, the effect of the concentration gradient, and the glucose utilization rate. Based on these data, the glucose transport rate across the capillary membrane and the utilization rate in a particular tissue were determined. The rates obtained were successfully verified against positron emission tomography experiments. The subcutaneous tissue exhibits the lowest and the most predictable glucose utilization rate, whereas the skeletal muscle tissue has the greatest glucose utilization rate. In contrast, the visceral fat is the least predictable and has the shortest reaction delay compared with the change in the blood glucose level. The reaction delays obtained for the subcutaneous tissue and skeletal muscle tissue were found to be approximately equal using a metric based on the time required to reach half of the increase in the interstitial fluid glucose level.



## 1. Introduction

Glucose is distributed throughout the body primary through the blood vessels. The maintenance of a normal blood glucose level is accomplished by a network of hormones, neural signals, and substrate effects that regulate the endogenous glucose production and the glucose utilization by tissues other than the brain [1]. From the blood, glucose is transported through the blood capillary membrane to the interstitial fluid. The interstitial fluid, which is found in the intercellular spaces between tissue cells, supplies the cells with nutrients, including glucose. In the interstitial fluid, the glucose is either utilized or leaves the interstitial fluid to eventually return to the blood. The lymphatic system represents an accessory route through which the fluid can flow from the interstitial spaces into the blood [2].

The interstitial fluid glucose level then changes to reflect a change in the blood glucose level. However, the change in the interstitial fluid glucose level exhibits a delay and a different magnitude. Different compartments may have different glucose levels, and this difference is due to the fact that capillaries in different compartments have different permeabilities [2]. Subsequently, the cells of different tissues have different glucose utilization rates depending on the tissue's metabolic needs and the level of available glucose. These rates are of interest in the examination of possible links between obesity and insulin resistance and other adverse effects [3–6].

As blood passes through the blood capillaries, a continual exchange of extracellular fluid also occurs between the plasma portion of the blood and the interstitial fluid that fills the intercellular spaces [2]. Large amounts of fluid and its dissolved constituents diffuse back and forth between the blood and the tissue spaces [2]. The extracellular fluid throughout the body, including both that of the plasma and that of the interstitial fluid, is continually being mixed, which results in the maintenance of almost homogeneity in the extracellular fluid throughout the body [2].

Endothelial cells form the interior surface of blood capillaries. Although glucose is water-soluble, it cannot pass through the lipid membranes of the endothelial cells [2]. Glucose is transferred between the blood plasma and the interstitial fluid via diffusion

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through the cleft-pores of the capillary membrane. The transfer rate depends on the concentration gradient between the blood glucose level and the interstitial fluid glucose level. A greater difference between the concentrations of any given substance on the two sides of the capillary membrane results in a greater net movement of the substance in one direction through the membrane [2].

Blood capillaries are present in subcutaneous tissue, skeletal muscle tissue, and visceral fat. These compartments are the subject of the research presented. The glucose level in these compartments is measured in the corresponding interstitial fluid [7]. The muscle/fat cells utilize the glucose in these compartments. The glucose utilization rate is modulated with the insulin level.

Visceral fat refers to the adipose tissue surrounding the internal organs and is different from subcutaneous fat. This tissue is a loose connective tissue composed of adipocytes. Glucose transport into muscle and adipose cells occurs through facilitated diffusion that is mediated primarily by members of the glucose transporter (GLUT/SLC2A) family of proteins [8]. GLUT-4, which is the predominant glucose transporter [8], is regulated by insulin.

Not all fibers in skeletal muscle are exposed to the glucose in the medium, and the equilibration of the intercellular space is achieved only after the intercellular glucose level of the outermost fibers has equilibrated [9].

Based on the progress that has been achieved in glucose-homeostasis research, mathematical models have been established to simulate glucose homeostasis. Although these were mainly developed for diabetes, a number of the available glucose-prediction models were developed using several different strategies: control models for insulin pump therapy and an artificial pancreas [10–12], regression data-driven models [13,14], and artificial neural-network models [15,16]. However, the parameters of a model cannot always be interpreted as physiological markers, as is the case when the model is based on statistical analyses rather than physiology.

Compartment models, which are based on physiological knowledge, attempt to model the glucose kinetics. For example, a previously developed model [17] targeted the GLUT-4 glucose transporter. These types of models differ in both their design and their purpose. Although compartment models started as simple models [18], these models continued to evolve and gain complexity as quantitative assessments of the individual steps of the glucose metabolism have been needed to understand mechanism of action of insulin in normal and physiopathological states, such as diabetes [19]. Because direct *in vivo* measurements are not possible in humans, indirect approaches have been devised. For example, a previously referenced study [3] used an approach based on fluorodeoxyglucose and positron emission tomography. Similarly, another previous study [19] also utilized an approach based on the use of fluorodeoxyglucose and positron emission tomography. The corresponding compartment model relates the fluorodeoxyglucose concentrations in four different compartments using a set of equations with five constants.

Using positron emission tomography, a glucose solution was used as a metabolic tracer to identify areas with an increased glucose utilization rate, e.g., malignant cells. Despite a number of advantages, there is a considerable limiting factor associated with the use of this technique: a radioactive component (the tracer) is required to perform a position emission tomography scan, and this is a risk factor for pregnant and breastfeeding women. Another limiting factor is the price of the scan and the actual availability of the equipment and materials in a particular hospital. Although it cannot be as precise as positron emission tomography, the analysis of blood samples through a continuous glucose monitoring system (CGMS) is markedly more inexpensive and requires no radioactive component. Therefore, this study suggests a potential approach for the comparison and evaluation of particular compartments using a less demanding setup. Using an experiment setup with a constant insulin infusion rate, a two-compartment glucose-level prediction model was used to evaluate the compartment′s glucose transport rate across the blood capillary membrane and the glucose utilization rate by the cells.

First, this study extends an existing interstitial-fluid glucose-level prediction model through the use of boundary conditions for its parameters, which enables the interpretation of the parameters as physiological markers. Then, the glucose levels in different compartments were measured. Using these levels, the model′s parameters were calculated to verify the boundary conditions. The results obtained were compared against the results of studies based on positron emission tomography.

## 2. Materials and methods

Using a constant insulin infusion rate, the glucose levels of subcutaneous tissue, skeletal muscle tissue, and visceral fat were experimentally examined during a rapid change in the blood glucose level. As the blood glucose level changes, the glucose levels of these compartments change to reach equilibrium with the blood glucose level; however, these changes exhibit different reaction delays. The reaction delay depends on the glucose transfer rate through the blood capillary membrane and the glucose utilization rate. We considered the possibility that multiple transfer and utilization rates could achieve the same reaction delay. Therefore, we compared the effects of blood capillary permeability, concentration gradient, and glucose utilization on the reaction delay.

The effects were calculated using a prediction model of the interstitial fluid glucose level that was based on research on glucose transporters [20,21]. The model requires the measurement of only two compartments and the estimation of only three parameters. This paper proposes boundary conditions for these parameters such that the parameters could be considered valid physiological markers. The parameters quantify the examined effects on the reaction delay.

### 2.1. Experiment setup

Based on the similarity in sugar and insulin physiologies between humans and rats, experimenters are able to conduct the required experiments on rats. The work presented was tested on hereditary hypertriglyceridemic rats. The rats were provided by the Diabetology Center, University Hospital in Pilsen, Charles University in Prague, and the experiments were conducted by researchers from this institution.

First, the experimenter administered a combination of xylazine and ketamine as an anesthetic. The specific chemicals used were xylazine (active ingredient, xylazine hydrochloride) and Narkamon (active ingredient, ketamine hydrochloride), which are drugs that are manufactured by Bioveta a.s.

The experimenter then catheterized the internal jugular vein and the carotid artery of the anesthetized rats. The blood glucose level was measured in the arterial blood. Sensors associated with CGMS were placed in the subcutaneous tissue, skeletal muscle tissue, and abdominal subcutaneous tissue, i.e., the visceral fat. After the sensors were calibrated, insulin infusion was started. The insulin infusion rate was constant at 50 mUI/kg/min. A variable 20% glucose infusion was also started using a manual correction to maintain the desired blood glucose level of 6 mmol/l. The rats were administered the insulin and glucose infusions through their jugular vein.