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Detection of Organ Dysfunction in Type II Diabetic Patients

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***Abstract*—Type II diabetes mellitus is characterized by several abnormalities in different body organs such as the pancreas, the liver, muscles and adipose tissues. We have developed a technique to detect the dysfunction of different organs in a group of type II diabetic patients. The detection of these abnormalities is performed through euglycemic insulin clamp and hyperglycemia clamp applied to a type II diabetes model developed in our previous work [1]. Since the peripheral insulin and glucose concentrations are the only common clinical measurements, we have used a particle filtering algorithm to estimate the insulin and glucose concentrations in different parts of the body. These concentrations reflect the pancreatic insulin secretion rate as well as the glucose metabolic rates in the liver, muscles and adipose tissues which represent the functional behavior of the corresponding organs. Our results show that the proposed technique is capable of detecting deficiencies in the pancreatic insulin production, the peripheral glucose uptake, endogenous glucose production and hepatic glucose uptake rates. The information provided by the algorithm can, therefore, be used to choose a suitable dietary program and/or prescribe an efficient medication for type II diabetic patients.**

I. Introduction

DIABETES mellitus is characterized by high blood glucose levels due to insulin production deficiencies in the islet beta cells of the pancreas and by the resistance of body cells against the insulin. Diabetes is one of the deadliest diseases and is the seventh leading cause of death in the United States [2]. Type II diabetes or non-insulin dependent diabetes mellitus (NIDDM) is the most common type of diabetes which has affected 90% of the diabetes population worldwide [3].

Multiple abnormalities in different organs lead to the deterioration of glucose homeostasis in type II diabetic patients [4]. Resistance of muscles and adipose tissues against the secreted insulin results in lower peripheral absorption of the blood glucose which in turn leads to accumulation of glucose in blood [5]-[12]. Augmented or delayed endogenous glucose production in diabetic patients due to impaired insulin-induced suppression of hepatic glucose production is well documented [10]-[18]. Impaired regulatory effect of the liver on the glucose concentration causes abnormal hepatic glucose uptake in type II diabetic patients [17]-[20]. Deficiency in pancreatic insulin production in response to a glucose stimulus leads to insufficient level of plasma insulin concentrations [21]-[26].

Unlike type I diabetic patients who need insulin injection to maintain glucose concentration at normal levels, elevated glucose concentrations in type II diabetes may be controlled at normal levels by regular exercise and suitable dietary program; however as the disease progresses, medication is required. Administration of a suitable and efficient medication for any individual patient needs accurate information from the patient. In our previous work [1], we developed a model for a group of type II diabetic patients. In the present work, we have applied different tests to the developed model to diagnose and evaluate the abnormal behavior of different organs in the same group. The information obtained from the tests may be helpful in choosing a suitable dietary program and in administering suitable medication for the respective patients.

Different detection tests are common in diabetes research. We have employed euglycemic insulin clamp technique *in silico* to evaluate the insulin mediated effect on glucose uptake in the liver and peripheral tissues as well as its suppression effect on hepatic glucose production. Also, hyperglycemia clamp is applied *in silico* to investigate the glucose suppression effect on hepatic glucose production. Early phase and overall insulin secretion rate in response to a glucose stimulus are also evaluated through hyperglycemia clamp.

The glucose metabolic rates in the liver, muscles and adipose tissues as well as the pancreatic insulin secretion rate represent the behavior of those organs. In order to measure these rates, measurements of glucose and insulin concentrations in different parts of the body are needed. However, these measurements require complex clinical facilities and in some cases may risk the life of the patient. Therefore, clinical measurements of all required concentrations are not possible. The commonly available clinical data include peripheral insulin and glucose concentrations only. Therefore, we propose using a Sequential Monte Carlo (SMC) filtering method called particle filters on a nonlinear model of a group of diabetic patients to estimate the glucose and insulin concentrations in different parts of the body. These estimates can then be used to measure the glucose metabolic rates in different organs and insulin secretion rate in the pancreas.

This paper is organized as follows. In Section II, a brief description of the mathematical model that we have used here is provided. In the following section, fundamentals of particle filtering algorithm are discussed. The proposed technique for detecting the organ dysfunction of a group of type II diabetic patients is explained in section IV.

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II. MATHEMATICAL MODEL

In the present work, we have used a detailed compartmental model representing the hormonal effects of insulin and glucagon on the plasma glucose concentration in a group of type II diabetic patients. This model was developed in our previous work [1]. Our model was based on an earlier model proposed by Guyton et al. [27] for a healthy human and modified by Sorensen [28]. The model contains three sub-models which represent blood glucose, insulin and glucagon concentrations in the body. Each sub-model is divided into individual compartments representing a specific part or organ in the human body. The number of compartments in each sub-model is different. The insulin sub-model is schematically depicted in Fig. 1. The glucose sub-model has the same compartments as those of the insulin sub-model except the pancreas compartment which is not included in the glucose sub-model. The glucagon sub-model treats the whole body as one compartment. Muscles and adipose tissues are lumped into the periphery compartment and gastrointestinal tract (including the stomach and the intestine) is represented by the gut compartment. Sub-compartments, such as those in the periphery compartment, are considered where significant transport resistance between the capillaries and interstitial fluid space exists [28].

Model equations comprise mass balance equations over individual sub-compartments in each sub-model except for the pancreas compartment, which has a separate mathematical model. Detailed model equations for a healthy human body are provided in [28]. Previously, we used a set of clinical data obtained from a group of type II diabetic patients to develop a model based on the Sorenson model. Based on our knowledge of type II diabetic patients, we chose relevant parameters of the Sorenson model and estimated them using the clinical data set from the patients. Complete details on the estimation of parameters in this model are provided in [1].

To investigate the behavior of different organs in type II diabetic patients and detect any abnormalities, we need to compare the behavior of each organ with the same organ in a normal subject. The insulin secretion rate from the pancreas and metabolic rates of glucose in different organs reflect the behavior of those organs in response to any glucose stimulus. Comparison of these rates in type II diabetic patients with those of a normal subject will allow us to detect any abnormal behavior of those organs. Since the peripheral glucose and insulin concentrations are commonly measured, we have used a particle filtering algorithm to estimate the glucose and insulin concentrations in different part of the body. The advantage of this method is that its accuracy can be improved by increasing the number of "particles used" and moreover, is independent of the degree of nonlinearity of the model – unlike extended Kalman filter. A brief description of this method is provided in the next session. In order to apply the particle filtering algorithm, the nonlinear model in [1] is rewritten in a discrete time stochastic nonlinear state space format as follows:

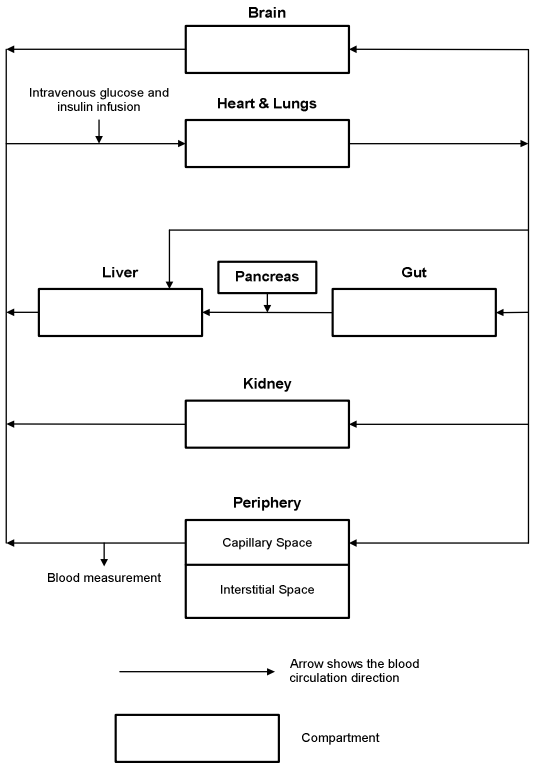

Fig. 1.Schematic diagram of insulin compartmental sub-model.

$$x_k = f(x_{k-1}, u_{k-1}, \theta) + \nu_k \quad (1)$$

$$y_k = g(x_k, u_k, \theta) + \omega_k \quad (2)$$

where f and g are the state and measurement dynamic functions, respectively; k denotes a time step; x_k is the vector of states, u_k is the vector of inputs and y_k is the vector of measurements; θ denotes a vector of model parameters which are constant values; ν_k and ω_k are state and measurement noise sequences with known probability density functions (PDF) with zero mean. We assume that the state and measurement noises affect the model in a linear manner. The states of the model correspond to the insulin and glucose concentrations in different organs of the body. Our mathematical model contains 22 states and two measurements. Therefore, sizes of x_k and y_k are respectively 22 and 2. The model inputs are the glucose and insulin infusion rates to the body and therefore, the size of u_k is 2.

III. PARTICLE FILTERS – A SEQUENTIAL MONTE CARLO METHOD

The Sequential Monte Carlo (SMC) approach is a recursive Bayesian estimation method for nonlinear and non-Gaussian filtering problems. The basic framework of the SMC approach is presented below.

A. *Recursive Bayesian Estimation*

The SMC approach in filtering problems is based on calculation of the probability density function of the model states at the current time step k (i.e. x_k), given a sequence of the measurements up to time k (i.e. $y_{1:k}=\{y_1, y_2, ..., y_k\}$). The

Bayesian solution to this filtering problem is to calculate the probability density function (PDF) of x_k given $y_{1:k}$, $p(x_k|y_{1:k})$, for each iteration. The density $p(x_k|y_{1:k})$ is calculated recursively into two steps - prediction and update. In the prediction step, the PDF of x_k is calculated given the sequence of the measurements up to time $k-1$ through the following equation:

$$p(x_k|y_{1:k-1}) = \int p(x_k|x_{k-1})\, p(x_{k-1}|y_{1:k-1})\, d\, x_{k-1} \quad (3)$$

In the update step, the density $p(x_k|y_{1:k})$ is calculated via the following equation:

$$p(x_k|y_{1:k}) = \frac{p(y_k|x_k)\, p(x_k|y_{1:k-1})}{p(y_k|y_{1:k-1})} \quad (4)$$

It is assumed that the PDF of the initial time step, $p(x_0|y_0)$, is known. Equations (3) and (4) do not have analytical solutions except for linear processes with Gaussian noise. In most cases the integrals in equation (3) are complex and intractable. For general non-linear, non-Gaussian systems described by equations (1) and (2), there is no simple way to proceed. The sequential Monte Carlo algorithms make these complex integrals tractable through the use of efficient sampling strategies [29], [30].

B. Sequential Monte Carlo

Salmond et al. [31] introduced Sequential Monte Carlo methods for the first time in 1993 and later on the SMC algorithm has been further developed and adapted to many different applications [30]. It has appeared in the literature in different names such as bootstrap filtering [31], particle filtering [32] and interacting particle approximations [33]. The basic idea of SMC follows the framework of Bayesian recursive estimation described above. In this approach the recursive computation of relevant probability distributions is accomplished using the concepts of importance sampling and approximation of probability distributions by a set of random samples with associated weights.

Considering the model equations represented by equations (1) and (2), the Bayesian recursive estimation is applied via a SMC algorithm instead of analytically solving the equations (3) and (4). At each time step k, two pieces of information are required for estimating the PDF: the samples x^i_k and their associated weights w^i_k. Samples x^i_k are assumed to be generated from a known PDF called importance density function, $q(x_k|y_{1:k})$. Then, the corresponding weights of the samples are calculated from the following equation:

$$w^i_k = \frac{p(x^i_k|y_{1:k})}{q(x^i_k|y_{1:k})} \quad (5)$$

and the weights after normalization are:

$$w^i_k = \frac{w^i_k}{\sum_{i=1}^{N} w^i_k} \quad (6)$$

where N is the number of particles used. If the importance density function is chosen to be factorized such that:

$$q(x_k|y_{1:k}) = q(x_k|x_{k-1}, y_{1:k})\, q(x_{k-1}|y_{1:k-1}) \quad (7)$$

then the samples at time step k, $x^i_k \sim q(x_k|y_{1:k})$, are computed by multiplying the existing samples, $x^i_{k-1} \sim q(x_{k-1}|y_{1:k-1})$, and the new state, $x^i_k \sim q(x_k|x_{k-1},y_{1:k})$. The corresponding weights are updated using the following equation:

$$w^i_k \propto w^i_{k-1} \frac{p(y_k|x^i_k)\, p(x^i_k|x^i_{k-1})}{q(x^i_k|x^i_{k-1}, y_{1:k})} \quad (8)$$

In common cases when only a filtered estimate of $p(x_k|y_{1:k})$ is required, it is useful to assume that $q(x_k|x_{k-1},y_{1:k}) = q(x_k|x_{k-1},y_k)$ and then, the importance density only depends on x_{k-1} and y_k. Under this assumption, equation (8) can be rewritten as:

$$w^i_k \propto w^i_{k-1} \frac{p(y_k|x^i_k)\, p(x^i_k|x^i_{k-1})}{q(x^i_k|x^i_{k-1}, y_k)} \quad (9)$$

and the filtered density $p(x_k|y_{1:k})$ can be approximated by the following equation:

$$p(x_k|y_{1:k}) \approx \sum_{i=1}^{N} w^i_k \delta(x_k - x^i_k) \quad (10)$$

where δ is the Dirac delta function, x^i_k is the ith sample that approximates the distribution, and the coefficient w^i_k is the corresponding weight. As $N \to \infty$, the above density approximation approaches the true filtered density $p(x_k|y_{1:k})$.

IV. Detection of Organ Dysfunction

There are some techniques that are commonly used in diabetes research to evaluate how well an individual metabolizes glucose, how well an individual's body responds to glucose, and how resistant an individual is against insulin. Glucose clamp is a commonly used technique proposed by Defronzo et al. [34] in 1979. They proposed two types of clamps called hyperglycemia clamp and euglycemic insulin clamp which have been widely used in diabetes research. We have applied these two tests *in silico* to detect and evaluate the deficiencies (if they exist) in different organs of a group of type II diabetic patients using the model of type II diabetes developed for these patients. The same tests have also been applied to the Sorensen model to obtain similar information on a healthy subject. Comparing the glucose and insulin concentrations in different organs of diabetic patients with those obtained from healthy individuals will provide insight into any organ deficiencies in the patients. The filtering algorithm was implemented with 25 particles in all tests.

A. Euglycemic insulin clamp

This technique was developed by Defronzo et al. [34] in 1979. In this technique, the plasma insulin concentration is raised and clamped at around 100 mU/l by a continuous infusion of insulin. At the same time, the plasma glucose concentration is held constant at basal levels by glucose injection via a negative feedback principle. At steady state conditions, since the endogenous glucose production is decreased to a negligible level, the rate of glucose infusion is approximately equal to rate of glucose uptake by all body tissues and is therefore a measure of tissue insulin sensitivity. The information obtained from particle filtering

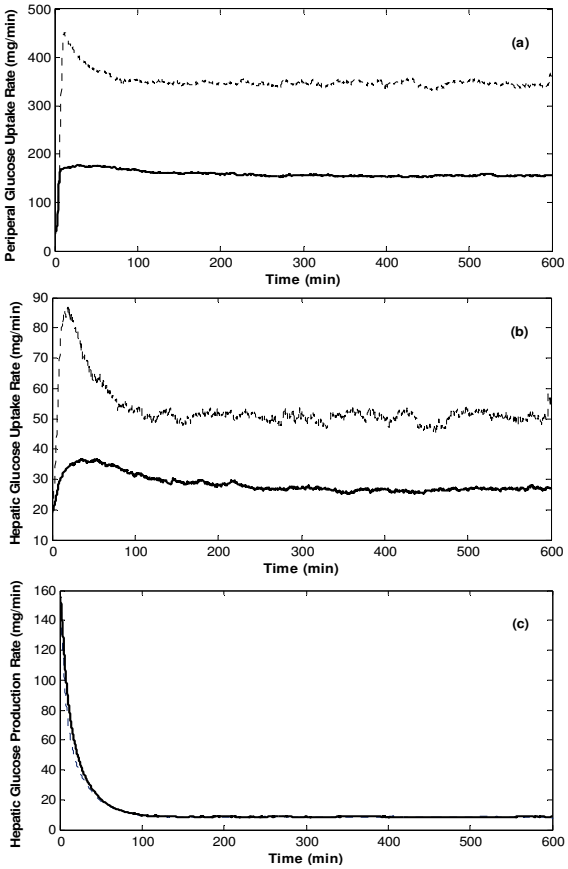

Fig. 2. Variations of different glucose metabolic rates during the euglycemic insulin clamp, NIDDM (—) and normal subjects (--)

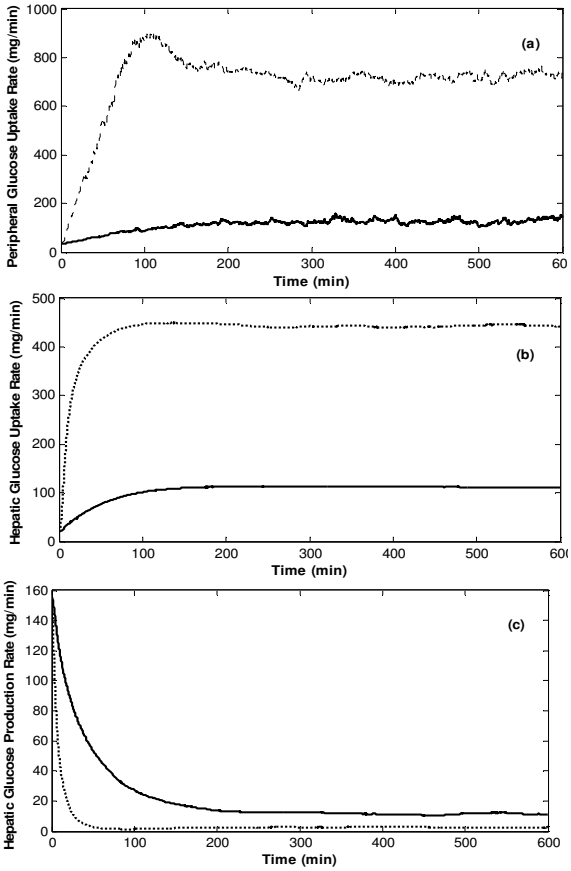

Fig. 3. Variations of different glucose metabolic rates during the hyperglycemic clamp, NIDDM (—) and normal subjects (--)

helps in measuring the uptake rate of glucose in different organs which in turn will allow us to determine the sensitivity of that organ to insulin.

In our previous work, we used the data provided by Nagasaka et al. [35] to develop our model. The same basal conditions for both control subjects and diabetic patients are used here. The peripheral insulin and glucose concentrations at the basal condition for the diabetic group were reported to be 4.5 ± 0.4 mU/l and 117 ± 7 mg/dl, respectively. The corresponding values reported for control subjects were 5.1 ± 0.3 mU/l and 91 ± 8 mg/dl for the peripheral insulin and glucose concentrations, respectively. To perform euglycemic insulin clamp, the rate of insulin infusion is set to 76.88 mU/min and 72.72 mU/min, and the glucose infusion rate is set to 270.8 mg/min and 489.1 mg/min for the diabetic patients and control subjects, respectively. These values are obtained by trial and error to maintain the insulin concentrations at 100 mU/l and the glucose concentrations at its basal value. Considering the decreased rate of endogenous glucose production due to hyperinsulinemia, the overall glucose infusion rate shows that the overall sensitivity of the body to insulin is decreased by approximately 63% in diabetic patients. It reflects sever insulin resistance in their body tissues.

To evaluate the insulin sensitivity in different parts of the body, the glucose metabolic rates in peripheral tissues and the liver are provided in Fig. 2. According to Fig. 2 (a), the peripheral glucose uptake rate is decreased by approximately 63% due to low insulin sensitivity in peripheral tissues. The same approximate amount of decrease in glucose uptake rate is observed in the liver (see Fig. 2 (b)). It shows that the insulin sensitivity of peripheral tissues and the liver is impaired at the same level in the group of diabetic patients. Fig. 2 (c) indicates that the insulin-induced suppression of hepatic glucose production at hyperinsulinemia condition is not impaired in the group of diabetic patients. Our results are in agreement with the discussion by Defronzo [4] which indicates normal suppression of hepatic glucose production due to hyperinsulinemia over physiological range (~100 mU/l). Nevertheless, Defronzo [4] has argued that the dose-response curve showing the relationship between hepatic glucose production and the plasma insulin concentration is shifted to the right which indicates relative resistance to the suppression effect of the insulin on hepatic glucose production at physiological concentrations

B. Hyperglycemic clamp

This technique was also proposed by Defronzo et al. [34] in 1979. In this technique, the plasma glucose concentration is raised and maintained at 125 mg/dl above basal levels by a

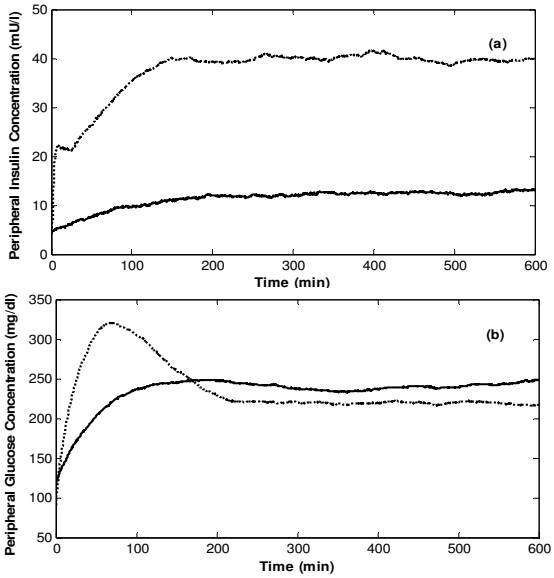

Fig. 4 Peripheral insulin and glucose concentrations during hyperglycemia clamp, NIDDM (—) and healthy body (--)

continuous infusion of glucose. Since the plasma glucose concentration is clamped at hyperglycemia level, the glucose infusion rate is an index of insulin secretion capacity and also shows how the glucose is metabolized. More detailed information about the pancreatic insulin secretion rate and its acuteness in response to a glucose stimulus can be obtained from the filtering results.

Here, the peripheral insulin and concentrations at basal condition are the same as previous section. Hyperglycemia clamp is performed for both groups of diabetic patients and control subjects at a glucose infusion rate of 330.8 mg/min for diabetic patients and 1229 mg/min for control subjects. The values for glucose infusion rates are obtained by trial and error to maintain the peripheral glucose concentrations at 125 mg/dl above the basal level for both groups.

The glucose infusion rate of the diabetic group shows that the whole body absorption of glucose is significantly low with respect to normal subjects. Euglycemic insulin clamp technique indicated that this group of patients had high resistance against insulin. In the current experiment, low insulin sensitivity of the patients is supplemented by the low plasma insulin concentration due to the deficiencies in the pancreatic insulin secretion. These two factors together have

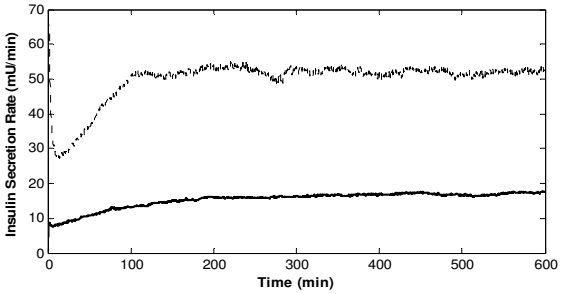

Fig. 5. Pancreatic insulin secretion rate during hyperglycemic clamp, NIDDM (—) and healthy body (--)

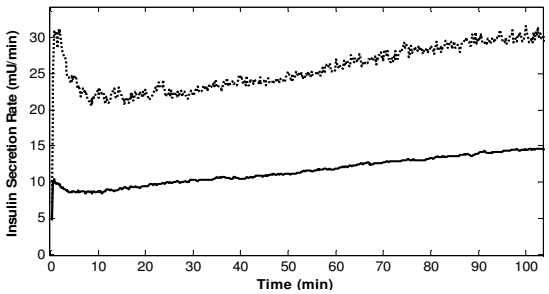

Fig. 6. Early phase of pancreatic insulin secretion rate due to glucose infusion for 500 mg/min, NIDDM (—) and healthy body (--)

resulted in significantly lower overall body glucose uptake in the diabetic group. As Fig. 3 (a) and (b) show, the peripheral glucose uptake rate and the hepatic glucose uptake rate of the diabetic group are approximately 80% lower than the corresponding values for the normal group. Again, it suggests the same insulin resistance in peripheral tissues and the liver of the diabetic group.

According to Fig. 3 (c), the hepatic glucose production in both groups of diabetic patients and normal subjects is suppressed significantly due to the increase in plasma glucose concentrations. It suggests normal glucose-induced suppression of hepatic glucose production in the diabetic group which agrees with the investigations by Del Prato et al. [36] and Nielsen et al. [37]. Since the plasma glucose concentration has risen faster in the normal group than that of diabetic patients (Fig. 4 (b)), suppression of hepatic glucose production is faster in the normal group. As Fig. 3 (c) shows, the final amount of suppression is higher in the normal group than that of the diabetic group due to lower plasma insulin concentrations (Fig 4 (a)) and due to the insulin resistance at low insulin concentrations. It is consistent with the results discussed in the previous section.

The hyperglycemia clamp results also indicate defected pancreatic insulin secretion in the diabetic group. As Fig. 5 shows, the pancreatic insulin secretion rate is reduced by approximately 60% in this diabetic group which in turn resulted in low plasma insulin concentrations (see Fig 4 (a)).

Since the magnitude of exogenous glucose stimulus during the hyperglycemia clamp is not the same for both diabetic and normal groups, the profile of pancreatic insulin secretion rate (Fig 5) will not reflect the actual deficiency in the early phase of insulin secretion. Therefore, another glycemic clamp is performed to compare the early phase insulin secretion rate for both groups. Fig. 6 shows the first 100 min of the pancreatic insulin secretion rate due to 500 mg/min glucose infusion for both diabetic and normal subjects. As expected, the early phase pancreatic insulin secretion rate is reduced by about 65% in the diabetic group with respect to the normal group.

V. CONCLUSION

In this study, we used a model of a group of type II diabetic patients developed in our previous work to diagnose the deficiencies in their bodies. We employed particle

filtering method to estimate the model states as well as the glucose metabolic rates in different organs and pancreatic insulin secretion rate. Abnormal behavior of different organs is detected via euglycemic insulin clamp and hyperglycemia clamp *in silico*. Implementation of these techniques together with a mathematical model and a nonlinear filtering method is efficient in detecting the abnormalities in the liver, the pancreas and peripheral tissues of type II diabetic patients.

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