Estimation of Glucose and Insulin Concentration Using Nonlinear Gaussian Filters

Prova Biswas
Institute of Pharmacy Jalpaigur
Jalpaiguri, West Bengal, India
e-mail:provaju@gmail.com

Shovan Bhaumik
Electrical Engineering Department
Indian Institute of Technology Patna
Patna, Bihar, India
e-mail:shovan.bhaumik@iitp.ac.in

Ishan Patiyat
Electrical Engineering Department
Indian Institute of Technology Patna
Patna, Bihar, India
e-mail:ishanpatiyat123@gmail.com

***Abstract*—In this ongoing work, three non-linear Gaussian filters *viz.* the unscented Kalman filter (UKF), the cubature qudrature Kalman filter (CQKF) and the Gauss-Hermite filter (GHF) are designed to track blood glucose and insulin concentrations, as well as interstitial insulin level with the help of the *'Bergman's minimal model of glucose-insulin homeostasis'*. All the filters successfully track the plasma glucose and insulin level, even without the declaration of meal intake. We evaluate the filters' performances in terms of root mean square error (RMSE) which shows all the three filters are equally capable of tracking plasma glucose and insulin from noisy blood glucose measurements.**

I. Introduction

Diabetes mellitus (DM) is a growing burden worldwide. It is reported (International Diabetes Federation, 2010) that more than 285 millions of populations are suffering from the disease worldwide. In a study, it is predicted that about 439 million of adults will be affected by diabetes mellitus in 2030 and the probability rate of growth of diabetes in developing and in developed countries are 69% and 20%, respectively [1]. Moreover, the chronic complications associated with the disease like diabetic retinopathy (DR), vision-threatening diabetic retinopathy (VTDR), diabetic neuropathy [2], diabetic foot ulcer [3], nycturia [4], microalbuminuria associated diabetic nephropathy and cardiovascular disease [5] as well as the progressive insulin resistance could not be avoided in long run.

Currently, the disease could be managed by oral hypoglycemic agents or by delivering insulin to patients in a calculated dose. But, the limitation of the current management is the death of a large no of patients by hypoglycaemic shock due to overdose of insulin as the dose is calculated manually. According to report [1] about 2-4% of patients with type I DM die due to hypoglycemic shock. The patients with type I DM have the blood glucose level in the range bellow 50 to 60 mg/dl 10% of the time [1]. The hypoglycemic condition of both type I and II diabetic patients can further leads to vasoconstriction, increased cytokine responses, and increases the posibility of arrhythmias and other vascular diseases [6],[7] and thus reduces the life expectancy of patients.

Therefore, an estimation of plasma and interstitial insulin levels are essential before the administration of insulin to prevent the mortality associated with hypoglycemia. In practice, glucometer provides noisy measurement of plasma glucose. But plasma and interstitial insulin levels are difficult to measure instantaneously. To overcome the problem, glucose measurement data is fused with previously existing glucose-insulin homeostasis model, popularly known as *Bergman's minimal model*, to obtain the accurate value of glucose and insulin concentrations. To combine the model and measurement data efficiently, nonlinear filtering algorithms available in engineering literature are used.

We define the blood glucose, blood insulin and interstitial insulin concentrations as the states of a system. *Bergman's minimal model*, a first order differential equation, is used to obtain the values of the states with time. Other hormones such as Glucagon, Adrenalin, Thyroid *etc.* which play an important role in optimal balancing of blood glucose concentration, are not considered here. Three different Gaussian filters namely the unscented Kalman filter (UKF), the Gauss-Hermite filter (GHF) and the cubature quadrature Kalman filter (CQKF) are used to combine the measurements with the process model. We compare the estimation accuracy of the above mentioned filters in terms of root mean square error (RMSE), obtained from Monte Carlo runs, calculated over ensembles.

It is worthy to mention here that similar study had been carried out in [8] where the authors calculated the RMSE over time horizon. The calculation of RMSE over time horizon is not justified as the noise sequence may change in every run leads to variation in results. The RMSE must be calculated over large ensemble for comparison. Further, the authors concluded that the UKF provides better results compared to particle filter (PF), which is difficult to justify as PF generates the actual probability density function (pdf) with large number of probabilistic weights and points.

Several misconceptions associated with [8] force us to re simulate the problem. In this paper, we report the execution of three Gaussian filters namely the unscented Kalman filter (UKF) [9], [10], the cubature quadrature Kalman filter (CQKF) [11] and the Gauss-Hermite filter (GHF) [12], [13] to estimate the accurate values of the state. We compare the filters based on estimation accuracy, (in terms of RMSE calculated over ensemble) and computation efficiency. It has been found that the three filters' estimation accuracy are same, however the CQKF uses lowest number of deterministic sample points (seven), hence computationally most efficient. We also showed that the declaration of meal intake is not required. Once the filters are initialized they can estimate the states even after the meal intake in which sudden jump of the state values are expected.

978-1-4799-1769-3/16/$31.00 ©2016 IEEE

II. GLUCOSE-INSULIN HOMEOSTASIS MODEL

To quantify the glucose and insulin concentrations, several models, namely, *Intravenous glucose tolerance tests (IVGTT) model* [14], emphMinimal modelinf technique [15], [16], [17], emphfirst order autoregressive model [18], emphadaptive first order model [19], emphoral glucose tolerance test (OGTT) model [20], [21], emphoffsel-free autoregressive model with exogenous input and moving average (ARMAX) model [22] and many more have been proposed in literature . Among all the available models, the *Bergmans minimal model for glucose-insulin homeostasis* [15] is most acceptable and popular for researchers.

The model describes the change in glucose and insulin concentrations with time using first order differential equations as follows:

$$dG(t)/dt = -(p_1 + X(t))G(t) + p_1 G_{basal} \tag{1}$$

$$dI(t)/dt = -nI(t) + max[0, \gamma t(G(t) - h)] \tag{2}$$

$$dX(t)/dt = -p_2 X(t) + p_3(I(t) - I_{basal}) \tag{3}$$

where G(t), I(t) and X(t) are plasma glucose, plasma insulin and interstitial insulin levels expressed in mg/dl, $\mu U/ml$ and min^{-1}, respectively. The values of the constant parameters are described in [16]. We summarized them in table 1. We consider the state vector of the system as $x = [G\ I\ X]^T$. So we can write the equations (1) - (3) as

$$\dot{x}(t) = f(x(t)). \tag{4}$$

However, there may be some error and the constant values of equation (1)-(3) may vary for individuals. To incorporate the uncertainties associated with the *Bergman's model* a noise parameter w known as process noise, is added with the equation (4),

$$\dot{x}(t) = f(x(t)) + w. \tag{5}$$

TABLE I. VALUES OF PARAMETERS USED IN BERGMAN'S MINIMAL MODEL

Parameters		Values
Basal values	G_{basal}	90 mg/dl
	I_{basal}	$7.3\mu U/ml$
Clearance	p_1	$0.03082min^{-1}$
	p_2	$0.02093min^{-1}$
	n	$0.3min^{-1}$
Input gain	p_3	$1.602 \times 10^{-5} ml/\mu U min^{-2}$
	γ	0.003349 $\mu U/mldl/mgmin^{-2}$
Threshold level	h	$89.5mg/dl$

We mentioned earlier that we measure the plasma glucose concentration at some fixed interval of time. So measurement at any time instant k is given by:

$$y_k = Hx_k + v_k. \tag{6}$$

The measurement matrix is given by $H = [1\ 0\ 0]$. v_k, the measurement noise, arises due to inaccuracy in plasma glucose measurements. Our objective is to determine the state values at every instant of time from the process dynamics and imperfect measurements.

III. GAUSSIAN FILTERS

The state estimation is done by three Gaussian filters namely, UKF, GHF and CQKF as mentioned earlier. The three filters approximate the posterior and prior pdf as Gaussian. The Gaussian pdf is characterized by few deterministically chosen quadrature points and their associated weights. The main advantage of Gaussian filters is their computational efficiency. The general algorithm, used for the estimation (described in appendix A), is same for all three filters. The points and associated weights are described here.

A. Unscented Kalman filter

In unsented transformed (UT) method [23], the mean x and covariance P_x of random vector x are evaluated with $2n + 1$ sigma points (n is the dimension of the system) and its corresponding weights are as follows: Assume $2n + 1$ sigma points are scattered around mean in accordance to square root of the covariance matrix as:

$$\chi_0 = \hat{x} \tag{7}$$

$$\chi_i = \hat{x} + (\sqrt{(n+\kappa)P_x})_i; i = 1, 2, ..., n \tag{8}$$

$$\chi_{i+n} = \hat{x} - (\sqrt{(n+\kappa)P_x})_i; i = 1, 2, ..., n \tag{9}$$

In $(\sqrt{(n+\kappa)P_x})_i$, the subscript i represents the i^{th} column or row of matrix $(\sqrt{(n+\kappa)P_x})$. The weights of the sample points are evaluated as,

$$W_0 = \kappa/(n+\kappa), \tag{10}$$

$$W_i = 1/2(n+\kappa); i = 1, 2, ..., 2n \tag{11}$$

where κ is scaling parameter and its recommended value is $\kappa = 3 - n$ for Gaussian distribution of x. Now, each sigma point is propagate through nonlinear function

$$\chi'_i = f(\chi_i); i = 0, 1, ..., 2n. \tag{12}$$

Using the transformed sigma points and its corresponding weights, the first two moments namely mean $\hat{x}$ and covariance P_x of vector x are computed as follows:

$$\hat{x} = \sum_{i=0}^{2n} W_i \chi'_i, \tag{13}$$

$$P_x = \sum_{i=0}^{2n} W_i(\chi'_i - \hat{x})(\chi'_i - \hat{x})^T. \tag{14}$$

B. Gauss Hermite Filter

The GHF [12] uses the Gauss-Hermite quadrature rule of integration. Here, the intractable integrals, encountered in nonlinear Bayesian filtering problem, are approximately evaluated. Generally, a quadrature rule approximately evaluates the complicated integral by rewriting it as the product of non-negative weights and a function of quadrature points. In the next equation the single dimensional Gauss-Hermite quadrature rule is mentioned:

$$\int_{-\infty}^{\infty} f(x) \frac{1}{(2\pi)^{1/2}} e^{-x^2} dx = \sum_{i=1}^{N} f(q_i) W_i \tag{15}$$

where q_i and W_i represent N number of quadrature points and weights associated with them.

To compute the quadrature points, let us consider a symmetric tridiagonal matrix M with zero diagonal elements and $M_{i,i+1} = \sqrt{i/2}; 1 \leq i \leq N-1$. The quadrature points are located at $\sqrt{2x_i}$, where x_i are the eigenvalues of M [13]. The weight W_i is the square of the first element of the i^{th} normalized vector. Product rule is used for the extension of quadrature rules to multi-dimension problem. The n dimensional integral,

$$I_N = \int_{R_n} f(s) \frac{1}{(2\pi)^{n/2}} e^{-(1/2)|s|^2} ds \tag{16}$$

could be approximately evaluated as,

$$I_N = \sum_{i_1=1}^{N} ... \sum_{i_n=1}^{N} f(q_{i_1}, q_{i_2}, ..., q_{i_n}) W_{i_1} W_{i_2} ... W_{i_n} \tag{17}$$

N^n number of quadrature points and weights are required to evaluate I_N for n^{th} order system. As an example for a three point GHF and second order system nine quadrature points and weights would be $\{(q_i, q_j)\}$ and $\{W_i W_j\}$ respectively for $i = 1, 2, 3$ and $j = 1, 2, 3$. The number of quadrature points increase exponentially with the increment of the dimension of the system.

C. Cubature quadrature Kalman filter

Similar to the UKF and GHF, the prior and posterior pdfs are approximated as Gaussian and realized with cubature quadrature (CQ) points and weights. The CQ points are generated from third order cubature and arbitrary order Gauss-Laguerre quadrature rule. The steps to generate CQ points and weights are provided here. For detailed formulation readers are requested to read [11]. The steps for calculating the support points and associated weights are as follows:

- Find the cubature points $[u_i]_{(i=1,2,...,n)}$, located at the intersection of the unit hyper-sphere and its axes.
- Solve the n' order Chebyshev-Laguerre polynomial for $\alpha = (n/2 - 1)$ to obtain the quadrature points $(\lambda_{i'})$.

$$L_{n'}^{\alpha}(\lambda) = \lambda^{n'} - \frac{n'}{1!}(n' + \alpha)\lambda^{n'-1} + \frac{n'(n'-1)}{2!}(n' + \alpha)(n' + \alpha - 1)\lambda^{n'-2} - ... = 0 \tag{18}$$

- Find the cubature quadrature (CQ) points as $\xi_j = \sqrt{2\lambda_{i'}}[u_i]$ and their corresponding weights as

$$W_j = \frac{1}{2n\Gamma(n/2)}(A_{i'}) = \frac{1}{2n\Gamma(n/2)} \frac{n'!\Gamma(\alpha + n' + 1)}{\lambda_{i'}[\dot{L}_{n'}^{\alpha}(\lambda_{i'})]^2}$$

for $i = 1, 2, ..., 2n$, $i' = 1, 2, ..., n'$ and $j = 1, 2, ..., 2nn'$.

It should be noted that for all the three filters the sum of all weights are unity. Therefore, we can say that the sample points and associated weights represent the discrete pdf.

IV. Simulation results

The glucose, insulin concentrations have been estimated using the UKF, GHF, and CQKF. Here, we use three point GHF. So total 27 numbers support points are required. The CQKF has been implemented with 2^{nd} order Gauss Laguerre polynomial and hence 12 support points are required. We also tested the problem with two and four point GHF. However, no improvement in estimation accuracy is observed. The UKF uses 7 support points. The filters and truth model are realised with the initial values as described in table II.

The truth states are obtained from the solution of Bergman model. We use Rung Kutta method to solve the truth equations. To implement filters, process as well as measurement equations are considered in discrete domain with a sampling time $1min$.

TABLE II. Initialization of truths and filters

Parameters	Values
Initial states of filters ($\hat{x}_0$)	$[90\ 7.3\ 0]^T$
Initial states of truth (x_0)	$[287\ 403.4\ 0]^T$
Initial error cov (P_0)	$diag([400\ 200\ 0.1]^2)$
Process noise cov (Q)	$diag([1\ 1\ 0]^2)$
Measurement noise cov (R)	3^2

The truth and estimated values of plasma glucose, plasma insulin and interstitial insulin obtained from the UKF, GHF (two and three points), and CQKF (2^{nd} order Gauss Laguerre polynomial) have been plotted in fig 1- fig 3 respectively. It has been observed that estimated values obtained from different filters overlap with each other. To compare the estimation accuracy more rigorously, we calculate root mean square error (RMSE) over ensemble out of 500 MC runs. RMSE of plasma glucose, plasma insulin and interstitial insulin obtained from the filters are plotted in Fig 4- Fig. 6 respectively. From the figures we conclude all the filters perform with same estimation accuracy. This may be due to slowly varying process dynamics. It can also be observed that the filters can track the plasma insulin and interstitial insulin without measuring them. The developed method is also capable of tracking the glucose and insulin levels without any information about the meal intake. During our simulation, we assume meal intake happens on 181 seconds. The relative computational time of each filters are compared with respect to UKF as it took lowest time, shown in the table III.

TABLE III. Comparison of relative computational time of all filters

Filters	Relative compt time
UKF	1
GHF (N=2)	1.6154
CQKF (n'=2)	1.8077
GHF (N=3)	3.8846

V. Discussions and conclusion

In the recent article, we combined the glucose measurements with *Bergman's minimal model of glucose-insulin homeostasis* to estimate the plasma glucose, plasma insulin and interstitial insulin levels at every instant of time. As the system is observable, with the glucose only measurement, it is posible to estimate plasma insulin and interstitial insulin levels. We have implemented three advanced non linear Gaussian filters namely the unscented Kalman filter (UKF), the cubature

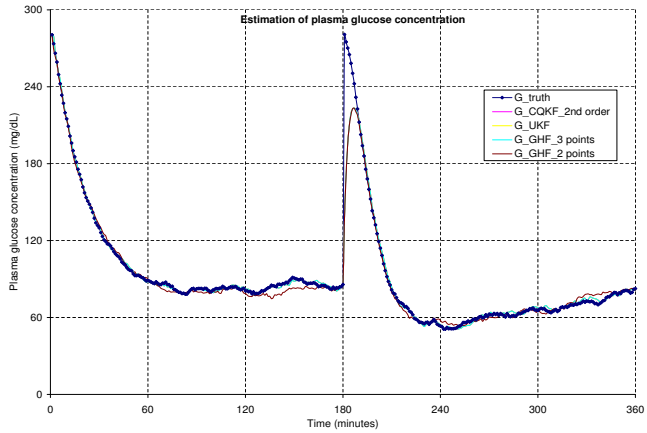

Fig. 1. Estimation of plasma glucose level

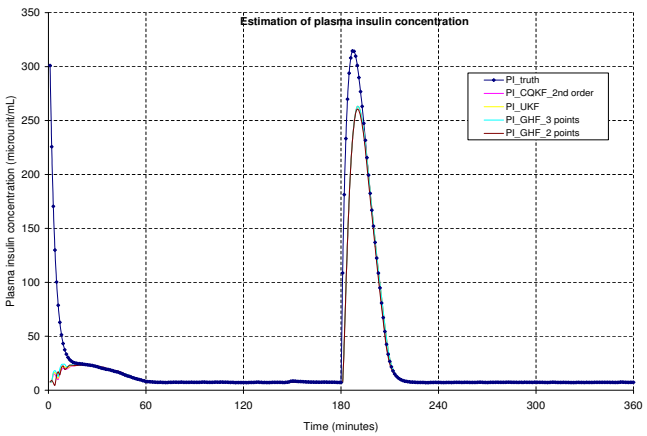

Fig. 2. Estimation of plasma insulin level

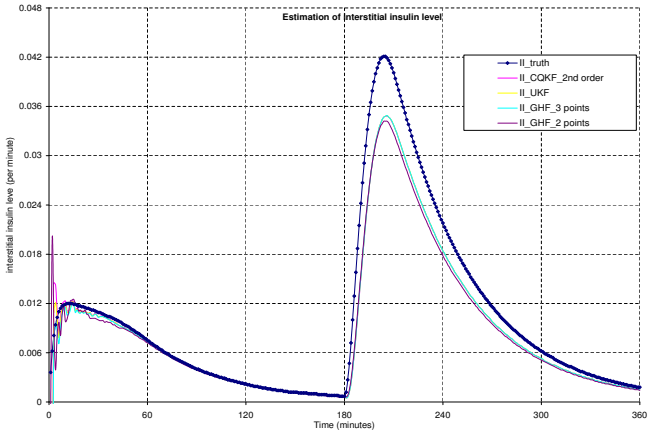

Fig. 3. Estimation of interstitial insulin level

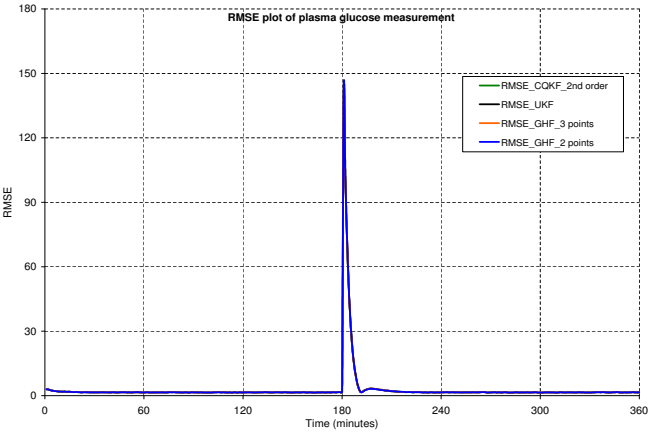

Fig. 4. RMSE plot of Plasma Glucose

qudrature Kalman filter (CQKF) and the Gauss-Hermite filter (GHF). Comparison of estimation accuracy in terms of RMSE shows that all three filters' performances are similar. The UKF takes lowest time to run. However, as the sampling time of measurement is quite high, the run time of the filters is less significant. We also showed that in our formulation the declaration of meal intake is not necessary to track the insulin and glucose levels. The estimated values of glucose and insulin at each time instant would help the meical practitioners to take appropriate measure to control the blood glucose of patients. The estimated data obtained from filters may be fed to control algorithms, which would be capable of calculating insulin dose at every instant of time and deliver the dose automatically through insulin pump.

REFERENCES

[1] J. C. Lacherade, S. Jacqueminet, J. C. Preiser,"An Overview of Hypoglycemia in critically ill", Jour. of Diab. Sci. and Tech., vol. 3, no. 6, pp. 1242-1249, 2009.

[2] S. Tesfaye, D. Selvarajah, "Advances in the epidemiology, pathogenesis and management of diabetic peripheral neuropathy", Diab. Metab. Res. Rev., vol. 28, no. 11, pp. 8-15, 2012.

[3] N. Djahmi, N. Messad, S. Nedjai, A. Moussaoui, D. Mazouz, J. L. Richard, A. Sotto, J. P. Lavigne,"Molecular epidemiology of Staphylococcus aureus strains isolated from inpatients with infected diabetic foot ulcers in an Algerian University", Clin. Microbiol. Infect., vol. 19, no. 9, pp. E398-E404, 2013.

[4] I. A. Harsch, "Acute and chronic complications of diabetes mellitus affecting sleep", Human Health Handbooks, vol. 3, pp. 256-269, 2013.

[5] Y.Vergouwe, S.S. Soedamah-Muthu, J. Zgibor, N. Chaturvedi, C. Forsblom, J.K. Snell-Bergeon, D.M. Maahs, P.H. Groop, M. Rewers, T.J.

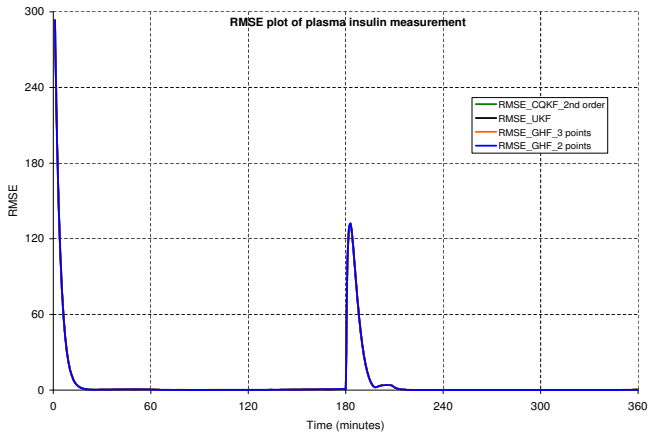

Fig. 5. RMSE plot of Plasma Insulin

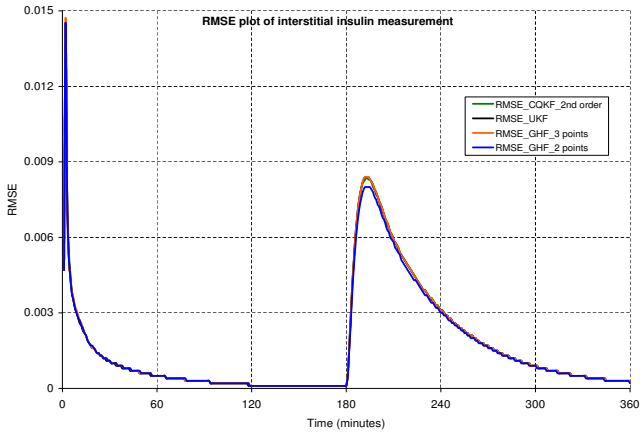

Fig. 6. RMSE plot of Interstitial Insulin

Orchard, J.H. Fuller, K.G.M. Moons, "Progressiontomicroalbuminuriaintype1diabetes: development and validation of a prediction rule", Diabetologia, vol. 53, pp. 254262, 2010.

[6] K. Fagher, M. Lndahl, "The impact of metabolic control and QTc prolongation on all-cause mortality in patients with type 2 diabetes and foot ulcers", Diabetologia, vol. 56, pp.11401147, 2013.

[7] A. K. Gitt, P. Bramlage, C. Binz, M. Krekler, T. Plate, E. Deeg, D. Tschpe, "Hypoglycaemia is more frequent in type 2 diabetic patients with co-morbid vascular disease: an analysis of the DiaRegis registry", Euro. Jour. of Prev. Cardio., vol. 19, pp. 765-772, 2012.

[8] C. Eberlea and C. Amentb, "The Unscented Kalman Filter estimates the plasma insulin from glucose measurement" BioSystems, vol. 103, pp. 67-72, 2011.

[9] S. J. Julier, J. K. Uhlmann, H. F. Durrant-Whyte, "A new extension for filtering non linear system", In Proc. of the Amer. Contr.l Conf., Washington, pp. 1627-1632, 1995.

[10] S. J. Julier, J. K. Uhlmann, "A new wxtension of the Kalman filter to non linear system", In proc. of Aerosci.: The 11th International Symp. on Aerospace Defence Sensing, Simumation and Controls, 1997.

[11] S, Bhaumik and Swati, "Cubature Quadrature Kalman Filters", IET Signal Process., vol. 7, no. 7, pp. 375-382, 2013.

[12] K. Ito, K. Xiong, "Gaussian filter for non linear filtering problems", IEEE Trans. Autom. Control, vol. 45, no. 5, pp. 910-927, 2000.

[13] G. Chalasani and S. Bhaumik, "Bearing onlu tracking using Gauss-Hermite filters", Proc. 7th IEE Conf. on Indust. Electronics and Applications, Singapore, pp. 1549-1554, 2012.

[14] R. N. Bergman, Y. Z. Ider, C. R. Bowden, C. Coblli, "Quantitative estimation of insulin sensitivity", Amer. Jour. of Physiol., vol. 236, no. 6, pp. E667-E677, 1979.

[15] R. N. Bergman, L. S. Phillips, C. Cobelli, "Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and nbeta cell glucose sensitivity from the response to intravenous glucose", Jour. of Clin. Inves., vol. 68, no. 6, pp. 1456-1467, 1981.

[16] G. Pacini, R. N. Bergman, "'MINIMOD': A computer programme to calculate insulin sensitivity and pancreatic responsively from the frequently sampled intravenous glucose tolerance test", Comput. Math. Programs Biomed., vol. 23, no. 2, pp. 113-122, 1986.

[17] C. Cobelli, C. Dalla Man, G. Sparacino, L. Magni, G. De Nicolao, B. P. Kovatchev, "Diabeted: Models, signals and control, methodological review", IEEE Rev. Biomed. Engg. vol. 2, pp. 54-96, 2009.

[18] T. Bremer, D. A. Gough, "Is blood glucose predictable from previous values? A solicitation for data", Diabetes, vol. 48, no. 3, pp. 445-451, 1999.

[19] G. Sparacino, F. Zandarigo, S. Corazz, A Maran, A. Facchinetti, C. Cobeli, "Glucose concentration can be predicted ahead in time from continuous glucose monitoring sensor tiem series", IEEE Trans. Biomed. Engg., vol. 54, no. 5, pp. 931-937, 2007.

[20] A. Cretti, M. Lehtovirta, E. Bonora, B. Brunato, M.G. Zenti, F. Tosi, M. Caputo, B. Caruso, L.C. Groop, M. Muggeo, R.C. Bonadonna, "Assessment of betacell function during the oral glucose tolerance test by aminimal model of insulin secretion", Eur. Journ. Clin. Invest, vol. 31, no. 5, pp. 405416, 2001.

[21] P. M. Jauslin, H.E. Silber, N. Frey, R. Gieschke, U.S. Simonsson, K. Jorga, M.O. Karlsson, "An integrated glucose-insulin model to describe oral glucose tolerance test data in type 2 diabetics", Jour. Clin. Pharmacol., vol. 47, no. 10, pp. 12441255, 2007.

[22] D. Boiroux, S. Schmidt, A.K. Duun-Henriksen, L. Frossing, K. Norgaard, S. Madsbad, O. Skyggebjerg, N.K. Poulsen, H. Madsen, J.B. Jorgensen, "Control of Blood Glucose for People with Type 1 Diabetes: an in Vivo Study", Proc. of the 17th Nordic Process Control Workshop, Technical University of Denmark, Kgs Lyngby, Denmark, pp. 133-140, 2012.

[23] S. L. Julier, "The scaled unscented transformation", Amer. Contr. Conf., pp. 4555-4559, 2002.