# Method for Diagnosis and Decision for Patients with Diabetes Mellitus

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**Abstract:** In this moment we have many diabetes patients with poor control of blood glucose. Some authors consider that the closed-loop system (artificial pancreas) is the best solution. An extra-corporeal blood glucose sensor is coupled to a pump, which controls the rate of infusion of insulin so as to maintain normoglycaemia. The continuous glucose monitoring system uses other sensors for the measuring of the blood glucose, placed under or on the skin. One of the most dangerous situations, having severe consequences on a patient's state is the introduction of incorrect values in the management system, responsible for all decisions and the control of the pump. For this reason it is necessary that each sample of blood glucose must be passed through a validation process. Therefore, it is very important that the transducers are in proper working condition. If one of the transducers provides inaccurate data, it must be quickly removed and replaced. The fault detection and isolation (FDI) problem is an inherently complex one. The author proposes an analytical method to detect and locate the presence of sensor failures using stochastic signal processing. The results of this study can also be applied to other physiological systems, offering important data for the medical practice and contributing to the introduction of computer assisted diagnosis, as a regular medical practice. These findings may have significant clinical implications in the diagnosis of diabetes mellitus, in blood glucose monitoring and in the management of diabetes therapy.

*Keywords:* Continuous glucose monitoring, blood glucose control, fault detection and isolation.

## 1. INTRODUCTION

The information about physiological blood glucose control and the physiopathology of diabetes mellitus could be subtracted with proper mathematical methods from acquired experimental data. The sources of blood glucose are: the gut in the digestive states, post absorptive of the meal and the liver in the inter-digestive states. The blood glucose is used in all cells under the absolute control of insulin (exceptions: red blood cells and neurons). Therefore, the medical concept in the diabetes management was focused on the insulin dynamics and insulin therapy. Physiologically, insulin stimulates glucose uptake by insulin sensitive tissue (mainly skeletal muscle and adipose tissue) and inhibits hepatic glucose production. Insulin secretion is an important oscillatory process and insulin oscillations are followed by plasma glucose oscillations. The normal pattern of insulin secretion rate displays (Iancu, 2003), (Troisi, 2000):

- Very rapid oscillations occurring at 10 second intervals, related to molecular intracellular processes;
- Rapid oscillations occurring from 8 to 15 minutes;
- Slow oscillations occurring at 90 to 120 minutes;
- Circadian oscillations related to cortisol circadian rhythm and growth hormone secretion after sleep;

Rapid and slow oscillations are still a controversial subject of experimental studies, but they are certainly related to the insulin glucose control system. All studies show the oscillatory feature of the long term blood glucose recordings (Makroglou, 2006). Also, in the blood glucose control, counter regulatory hormones intercede: glucagon, catecholamine, cortisol and growth hormones, which increase the concentration of blood glucose by stimulating the production of hepatic glucose and/or inhibiting tissue glucose uptake. The glucose values are registered in a discrete manner by intermitted measurements. The sample rate must be adapted for the specific dynamics of the biological parameters used for the experimental recordings. The actual protocols used in diagnosis and management of the diabetes mellitus include the classical clinical trials and the physicians' experience, but they do not account by the dynamics of the blood glucose and insulin. Therefore, it is having many diabetes patients with poor control of blood glucose values is a situation to be expected. The blood glucose dynamical pattern ascertained by mathematical methods for each patient could significantly improve the diabetes treatment in the future (Van Cauter, 1997).

## 2. METHOD FOR CONTINUOUS MONITORING

The continuous glucose monitoring system used a sensor for the measuring of the blood glucose, placed under or on the skin. The tested methods are of great diversity: the

oxidation reaction of glucose, reverse ionophorese, micro dialyse, spectroscopy, techniques based on laser and fluorescent lights. The sensors measure the glucose concentration at 5, 15 or 60 minute intervals. The systems used for continuous glucose monitoring offer the recordings of time series of blood glucose values for 72 hours. Basically, the system can realise the monitoring of the glycaemia with exceptional results, achieving:

- The continuous recording of the glycaemia values and their tendencies.
- The recording of all hypoglycaemia or hyperglycaemia episodes.

The limits of the system consist in the medical point of view: possible complications (infections, detachments or false readings) and the necessity of replacement at relative small periods of time. From the precision point of view, a high dispersion of measurements has been seen. For every administration way there is an absorption curve specific for insulin, time constants and action periods that impose the particularisation of the glycaemia control algorithms. For the current stage of development in the area of glucose monitoring, two systems that have recently entered use are suggestive:

- The Guardian RT Continuous Glucose Monitoring System (CGMS). It is a real-time monitoring and displaying system for glycaemia, determined every 5 minutes and its use in practice has been allowed by the US Food and Drugs Administration in September 2005.
- The MiniMed Paradigm REAL-Time Insulin Pump and Continuous Glucose Monitoring System. This is a device which has the insulin pump integrated with a monitoring system for blood glucose. Its use in practice has been allowed by the US Food and Drugs Administration in April 2006. The system contains an intelligent pump, equipped with a computer that estimates the necessary quantity of insulin starting from the active insulin existing in the organism with the purpose of avoiding hypoglycaemia episodes. The system is considered to be an important step up in the treating of the insulin-dependent diabetes in a closed loop, similar to the endocrine physiologic pancreas.

Measurements given by the CGMS are affected by perturbations (movement of the sensor, incomplete contact, etc.). Because of this, it is necessary to introduce a filter for the acquired data. The authors propose the algorithm described in the following, known as an optimal filtering method for stochastic signals. Blood glucose records (especially in patients with poor glycemic control) have the characteristics of a stochastic signal. But one of the most dangerous situations, having severe consequences on a patient's state is the introduction of incorrect values in the management system for diabetes patient. For this reason it is necessary that each amount of glucose to be subject to decision making. For this purpose we chose the criterion of Bayes.

## 3. OPTIMAL FILTERING

Let us consider the model represented in Fig. 1, intended to estimate the form of a continual signal. For the input

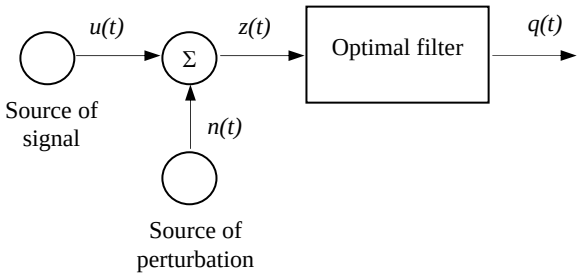


Fig. 1. The structure for optimal filtering

of optimal filter, we have the next relation:

$$z(t) = u(t) + n(t) \tag{1}$$

with $u(t)$ instrumental signal and $n(t)$ the noise. The filter has the purpose to generate a signal, which must be an optimal approximation of the signal $u(t)$:

$$q(t) = u(t) + \varepsilon(t) \tag{2}$$

where $\varepsilon(t)$ is a very small error of estimation process and

$$\lim_{t\to\infty} \varepsilon(t) = 0 \tag{3}$$

The quadratic average error of estimation process must be minimum, or equivalent:

$$E(\varepsilon^2) = E\left\{[u(t) - q(t)]^2\right\} \tag{4}$$

$$q(t) = \int_0^\infty h(t-\tau)z(\tau)d\tau \tag{5}$$

where $h(t)$ represents the response of the filter when the input is the Dirac impulse. The solution of this problem is represented by the Wienner-Hopf equation:

$$\int_0^\infty h(t-\tau)R_{zz}(\tau)d\tau = R_{uz}(t) \tag{6}$$

If the acquisition process generates the stochastic series:

$$u = \begin{bmatrix} u_0 \\ u_1 \\ \vdots \\ u_{N-1} \end{bmatrix},\ n = \begin{bmatrix} n_0 \\ n_1 \\ \vdots \\ n_{N-1} \end{bmatrix},\ z = \begin{bmatrix} z_0 \\ z_1 \\ \vdots \\ z_{N-1} \end{bmatrix} \tag{7}$$

the filtered signal has the expression [Spataru,1987]:

$$q(t) = \mathbf{H}z(t) \tag{8}$$

where **H** it is a matrix with the form:

$$\mathbf{H} = \begin{bmatrix} h_{00} & h_{01} & \cdots & h_{0,N-1} \\ h_{10} & h_{11} & \cdots & h_{1,N-1} \\ \vdots & \vdots & \cdots & \vdots \\ h_{N-1,0} & h_{N-1,1} & \cdots & h_{N-1,N-1} \end{bmatrix} \tag{9}$$

In Spataru (1987) it is demonstrated for the matrix **H** the following expression:

$$\mathbf{H} = \mathbf{C}_u (\mathbf{C}_u + \mathbf{C}_n)^{-1} \tag{10}$$

where $\mathbf{C}_u$ - is the covariance matrix of input and $\mathbf{C}_n$ - is the covariance matrix of the perturbation.

## 4. PROCESSING OF STOCHASTIC SIGNALS

Let us consider the signal $x(t)$ and $y(t)$ as stationary random processes. The function of cross-correlation is a statistical quantity defined as:

$$R_{xy}(\tau) = E\{x(t)y(t+\tau)\} \tag{11}$$

Also, the cross-covariance is the mean-removed:

$$C_{xy}(\tau) = E\{(x(t) - \mu_x)(y(t+\tau) - \mu_y)\} \tag{12}$$

or, in terms of the cross-correlation

$$C_{xy}(\tau) = R_{xy}(\tau) - \mu_x \mu_y \tag{13}$$

where $\mu_x$ and $\mu_y$ are the mean values. For continuous stochastic process, the cross-correlation function is:

$$R_{xy}(\tau) = \lim_{T\to\infty} \frac{1}{2T} \int_{-T}^{T} x(t)y(t+\tau)dt \tag{14}$$

In practice, it is necessary to estimate this sequence, because it is possible to access only a finite segment of the infinite-random process. A common estimation, based on $N$ samples of $x(t)$ and $y(t)$ ($x_n$ and $y_n$) is the cross-correlation function also called the time-ambiguity function.

$$R_{xy}(m) = \sum_{n=0}^{N-m-1} x_n y_{n+m},\ m \geq 0 \tag{15}$$

We assume for this discussion that $x_n$ and $y_n$ are indexed from 0 to $N$-1. In the same conditions, the cross-covariance function and the mean values ($\mu_x$ and $\mu_y$) have the expressions (16), (17) and (18), (MathWorks, 1999).

$$C_{xy}(m) = \sum_{n=0}^{N-m-1} x_n y_{n+m} - \mu_x \mu_y,\ m \geq 0 \tag{16}$$

$$\mu_x = \lim_{N\to\infty} \frac{1}{2N+1} \sum_{n=-N}^{N} x_n \tag{17}$$

$$\mu_y = \lim_{N\to\infty} \frac{1}{2N+1} \sum_{n=-N}^{N} y_n \tag{18}$$

An important parameter, which characterized the correlated process, is the cross-correlation coefficient:

$$\rho(x_n, y_n) = \frac{C_{xy}}{\sigma_x \sigma_y} \tag{19}$$

Where $\sigma_x = \sqrt{D_x}$ and $\sigma_y = \sqrt{D_y}$ and $D_x$, $D_y$ represents the variances with the expressions:

$$D_x = \lim_{n\to\infty} \frac{1}{2N+1} \sum_{n=-N}^{N} (x_n - \mu_x)^2 \tag{20}$$

$$D_y = \lim_{n\to\infty} \frac{1}{2N+1} \sum_{n=-N}^{N} (y_n - \mu_y)^2 \tag{21}$$

The values of coefficient (19) are limited to the interval:

$$0 \leq |\rho(x_n, y_n)| \leq 1 \tag{22}$$

For $|\rho|$ =1 we have two stochastic processes fully correlated, during $\rho$ = 0, the processes are uncorrelated (it is very possible for them to be independent).

## 5. FAULT DETECTION AND ISOLATION SCHEME

Therapy with insulin pump is recommended worldwide as the most effective and physiological method of treatment in diabetes mellitus type I (insulin-dependent). Some authors consider that the closed-loop system, (artificial pancreas) is the best solution. An extra-corporeal blood glucose sensor is coupled to a programmable logic controller - PLC, which controls the rate of infusion of insulin into a subcutaneous site, so as to maintain normo-glycaemia. Although very successful in maintaining normoglycaemia in diabetic patients for up a few days, it has major disadvantages for long-term use. Prolonged infusions carry the risk of thrombosis and infection. The generalised structure of the control system for blood glucose is shown in the Figure 2.

The structure used for fault detection and isolation is represented in Fig. 3. In this case, the blood glucose is measured by two identical sensors. If $p$ < 1 is the probability to have one failed sensor, the probability to have two simultaneously failed sensors (considered two independent process) is:

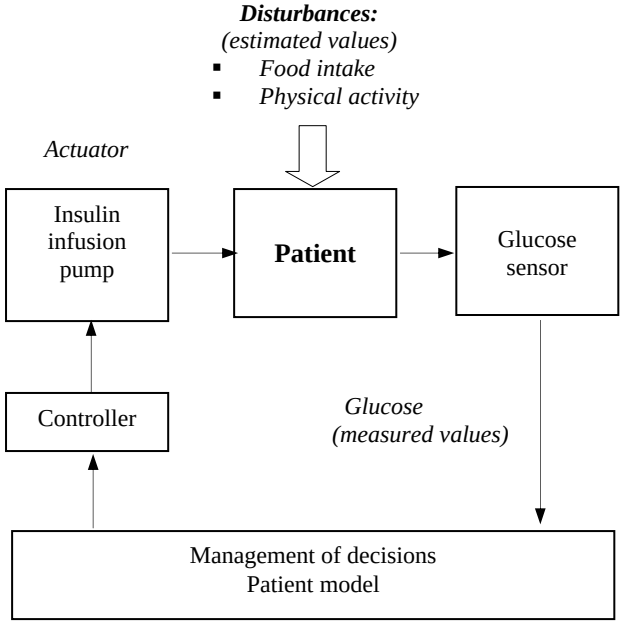


Fig. 2. The structure of the predictive system for blood glucose control

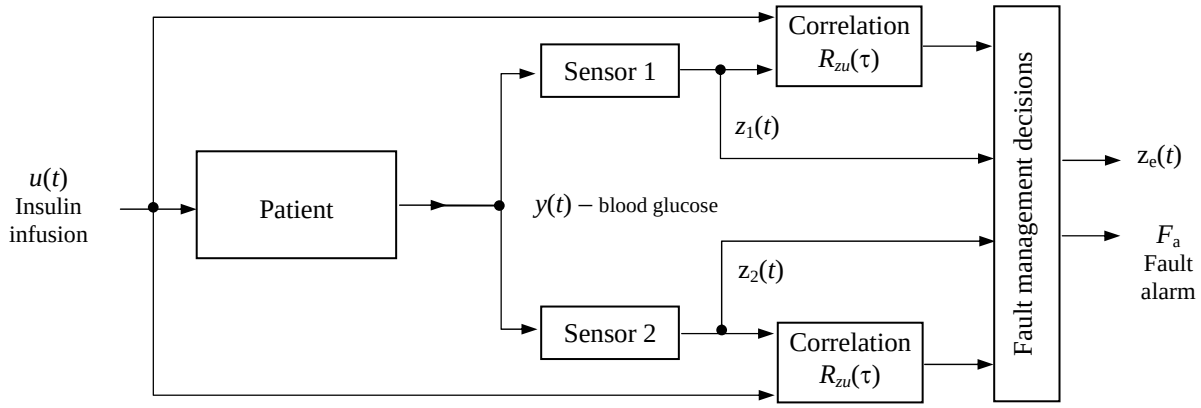


Fig 3. The structure with two sensors.

$$p^2 << p \tag{23}$$

Installing two sensors for blood glucose is not a difficult issue to overcome, but in this case the voting method is inapplicable. The author proposes the *Fault management decision block* (Figure 3) the structure represented in Figure 4. The idea consists to processing the signal purchased from the patient, $u(t)$ and $z_i(t), i=1,2$ and to calculate an equivalent output signal $z_e(t)$ and to generate an alarm signal if the failures arise. The steps are as follows:

- To calculate the cross-correlations function and the cross-correlation coefficients for $u(t)$ and $z_i(t), i=1,2$.
- If

$$\rho(u_n, z_{1,n+m}) \geq \rho_0 \tag{24}$$

and

$$\rho(u_n, z_{2,n+m}) \geq \rho_0 \tag{25}$$

we can accept that the both sensors are in good conditions; $\rho_0$ is a decision threshold and $m$ is fixed in function by the time delay constant of the sensors.

- The value of equivalent output signal $z_e(t)$ is calculated with the formula:

$$z_e(t) = \begin{cases} \frac{1}{2}[r_1 z_1(t) + r_2 z_2(t)], \text{if } r_1 = r_2 = 1 \\ r_1 z_1(t), \quad \text{if } r_1 = 1 \text{ and } r_2 = 0 \\ r_2 z_2(t), \quad \text{if } r_1 = 0 \text{ and } r_2 = 1 \end{cases} \tag{26}$$

where $r_i$, i=1,2, are calculated as dependent to the two correlation coefficients: $\rho(u,z_1)$ and $\rho(u,z_2)$. If both sensors are fault free, $r_i$=1. If it is decided that one of the sensors has failed, $r_i$=0, in order to eliminate the influence of erroneous signals. So, we can say $r_i \in \{0,1\}$.

The Bayes decision block from Figure 4 has the internal law:

$$r_i = \begin{cases} 1, \text{if } \rho(u, z_i) \geq \rho_0 \\ 0, \text{if } \rho(u, z_i) < \rho_0 \end{cases}, i = 1,2 \tag{27}$$

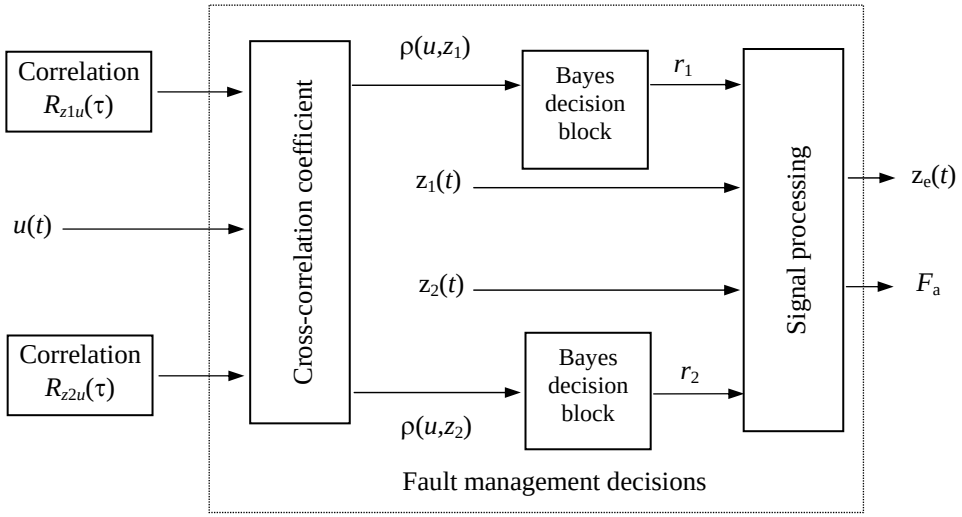


Fig. 4. Structure of the block for fault management.

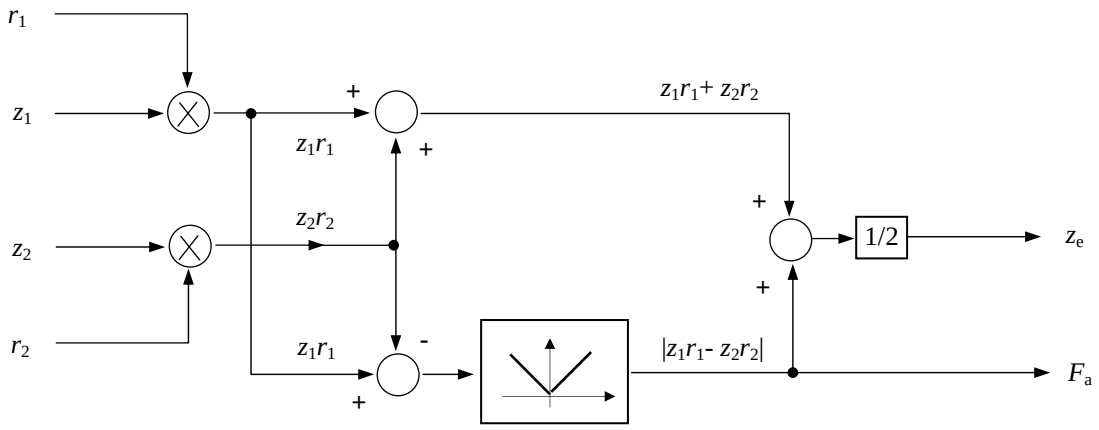


Fig. 5. Structure of the block for signal processing.

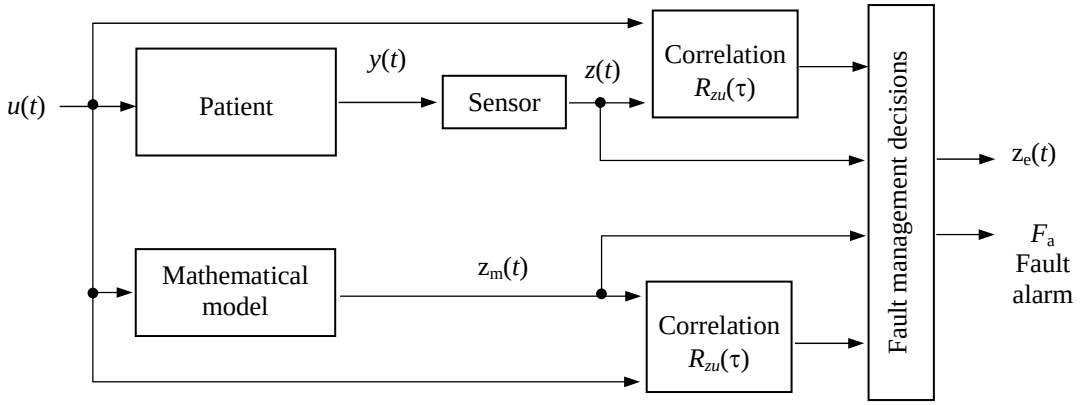


Fig. 6. The structure with one sensor and mathematical model.

The structure of the signal processing block (Figure 4) is a complex one and is represented in Figure 5.

The intermediary signal $|z_1r_1 - z_2r_2|$ can be used like fault alarm signal $F_a$. If the both sensors are in good conditions (fault free), than

$$\left|z_1(t)r_1 - z_2(t)r_2\right| \approx 0 \tag{28}$$

If a failures arise, then

$$\left|z_1(t)r_1 - z_2(t)r_2\right| \neq 0 \tag{29}$$

Another application is represented by the case when we use a single sensor. A possibility to detect a failure, at the sensor level, consists in the utilization of a similar scheme (Figure 6). This time, the role of the second sensor is assumed by the mathematical model, which represents the entire process (input-output). The structures of the blocks for fault management and for signal processing are the same.

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