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Quad-Chamber Pump and Dual-Test Strip Artificial Extracorporeal Endocrine Pancreas

Ștefan-Radu Bâlă

Universitatea Petrol – Gaze din Ploieşti, Bd. Bucureşti 39, 100680, Ploieşti
e-mail: stefan.bala@upg-ploiesti.ro

Abstract

The incidence of patients with insulin-dependent diabetes is increasing and may lead to worsening of general health or even death. Current insulin pumps used in medicine offers no possibility of eliminating all major risks in terms of adjustment capabilities of blood glucose level. Based on the functioning of the human endocrine pancreas and including safety measures such as the use of two independent sensors and the possibility of compensation severe hypoglycemia with glucose intake, when glucagon infusion has not enough efficiency, it can effectively increase the level of safety in use of extracorporeal artificial endocrine pancreas. This paper addresses the principle of construction of such equipment from both systemically approach and recommendation of its practical realization. It will also be approached an automatic operation algorithm of such a device that may result in the elimination of major risks in use.

Key words: *automatic system; diabetes; pancreatic hormones; glucose; pump.*

Introduction

Insulin-dependent diabetes mellitus may lead to serious long-term complications if the blood glucose level is not being kept to a normal level [1]. In this case of serious metabolic disorder, human body’s self-maintaining blood glucose level abilities becomes impossible due to the loss of beta-cells located in the pancreas [2], being solely responsible for the production of insulin. The disease can be kept under control only with the intake of synthetic insulin [3].

The first method was the postprandial injection of insulin into the abdomen using medical recommendation due to metabolic dynamics and estimation of ingested carbohydrates quantity. When the blood glucose monitoring devices became less invasive and low cost, the patients monitored by themselves the blood glucose level and if a threshold was exceeded, they injected a certain amount of insulin recommended by the diabetes doctor.

Injection with insulin were replaced by insulin pumps with programmable continuous infusion and, when continuous blood glucose level monitoring became possible, the idea of an automated system that acts as an artificial pancreas was one step away.

First artificial pancreases contained a continuous blood glucose level monitor and an insulin pump triggered by a hyperglycemic threshold programmed in the controller. Synthetic amylin was added to the insulin pump for better postprandial glycemic control.

The next step was the dual hormone insulin pump that uses a second pump triggered by a hypoglycemic threshold.

The present paper goes further more in increasing the efficiency of the artificial endocrine pancreas and eliminating most major risks regarding the blood glucose level.

How Does the Artificial Endocrine Pancreas Work

Ideas that led to this device

First of all, the device is based on an automatic control system. The input variable is the blood glucose level (BGL) that is continuous monitored by the system. A controller analyses both the instant value and the dynamics of the BGL in order to apply a secure algorithm for pumps triggering.

Accent is being placed on extreme levels of BGL targeting prevention of severe cases of hypoglycemia and hyperglycemia.

Operating principles of the artificial pancreas

The input variable is being taken from two test strips placed on different places on the body in order to acquire BGL information with as much precision as possible (Fig. 1). If the values of the two test strips are close to each other, the system takes in consideration the mean of the two values. If the difference is too high, the system ignores the data sample and continues to acquire new data sample. If the high difference persists, a warning signal occurs and an alarm is sent to the user for test strip replacement or readjustment advice.

The sensor conditioner is responsible for the elaboration of the BGL accurate variable that will be sent to the controller. The information sent is the mean of the two variables or a warning signal for test strip replacement or readjustment.

The BGL level and dynamics analyzer is basically a sum of comparators and a variable change speed calculator. The comparators compare both the change speed and the instant value of variables with the reference values programmed by the medical personnel. The reference values can be set by the user with medical assistance and guidance.

The heart of the controller is a self-learning prediction algorithm processor based on user defined parameters (weight, age, etc.) and blood glucose level dynamics (estimation of carbohydrates consumed and metabolism rate by the diabetes doctor). The self-learning prediction is targeted on correct estimation of each pump amount of injectable fluid in time unit due the triggered duration. More details on the algorithm will be reveal while explaining the functional diagram.

A controller triggers the four pumps depending on the BGL conditions. There are four pumps:

- The insulin pump that has the role to reduce the level of BGL.
- The (synthetic) amylin pump that improves the BGL lowering efficiency due to inhibition of the natural pancreas glucagon release.
- The (stable) glucagon pump that increases the BGL.
- The glucose pump that intervenes when severe hypoglycemia occurs even though glucagon was injected. This might happen when the glucagon is ineffective due to metabolism dysfunctions, malnutrition or deficiency of external glucagon infusion into blood. This is a quick and extreme increase of BGL in case of severe hypoglycemia.

The whole process is completely automatic and has user access to reference values and informs the user about system malfunctions. There is only one syringe needle that collects the fluids from all the four pumps for blood infusion.

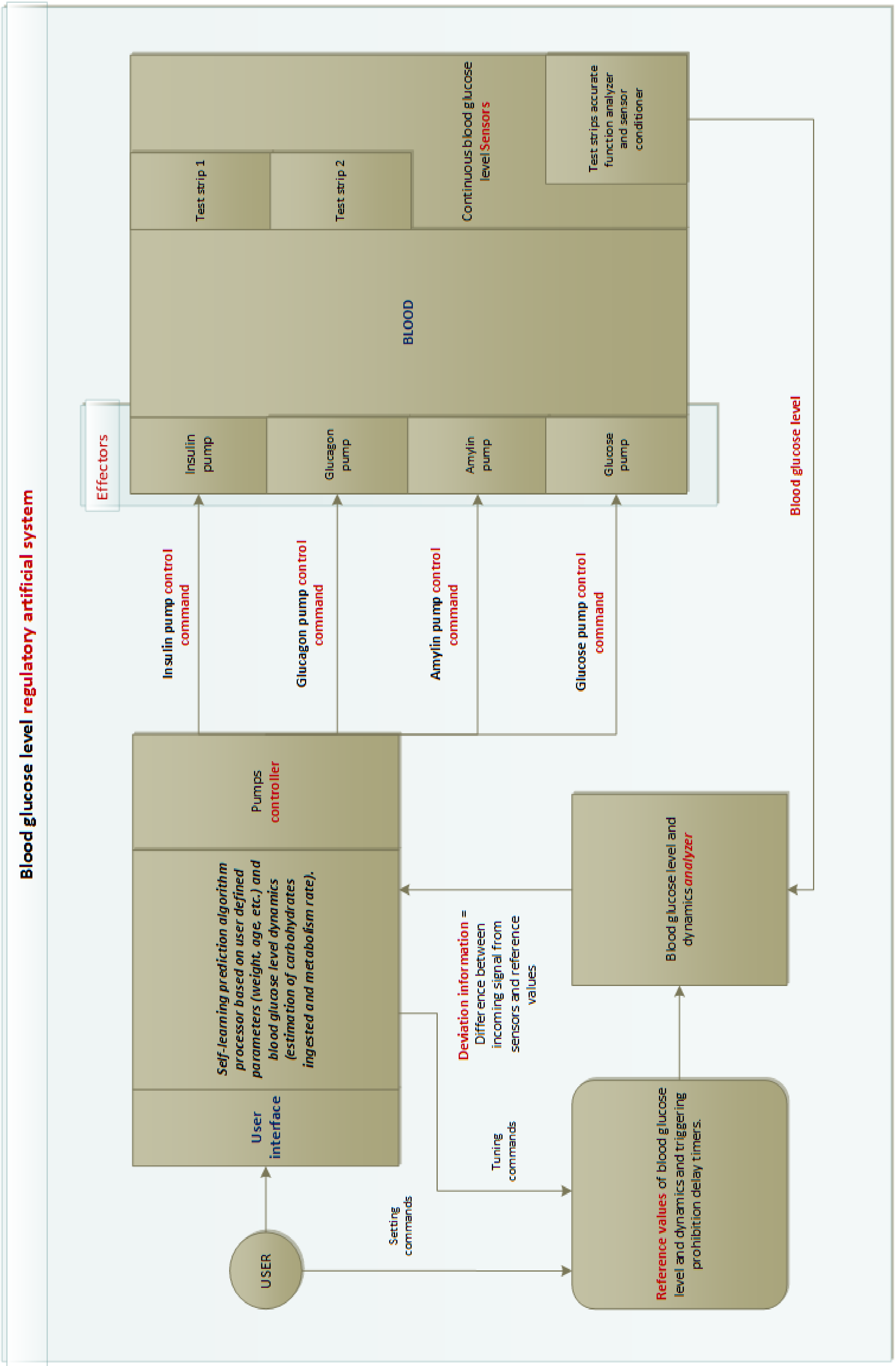

Fig. 1. Block diagram of the artificial extracorporeal endocrine pancreas.

Functional Diagram of the Artificial Endocrine Pancreas

Blood glucose level variable conditioner output

The functional diagram is presented in Figure 2. As presented earlier we are dealing with an automatic control system that has input variables provided by a continuous blood glucose level (BGL) monitor. We are using two test strips for better accuracy and reliability, so we deal with two BGL primary values:

$$BGL_1 = first\ test\ strip\ BGL\ information \quad (1)$$

$$BGL_2 = second\ test\ strip\ BGL\ information \quad (2)$$

The output of the sensor conditioner is:

$$BGL_{out} = \frac{BGL_1 + BGL_2}{2} \quad (3)$$

If:

$$|BGL_1 - BGL_2| < BGL_{acc\Delta} \quad (4)$$

Where:

$$BGL_{acc\Delta} = \ acceptable\ difference\ between\ test\ strips\ info \quad (5)$$

Or:

$$BGL_{out} = ERR_{tsw} \quad (6)$$

Where:

$$ERR_{tsw} = error\ signal\ for\ test\ strip\ warning \quad (7)$$

If:

$$|BGL_1 - BGL_2| > BGL_{acc\Delta} \quad (8)$$

Now we have the input for the blood glucose level and dynamics analyzer (BGL_{out}).

Blood glucose level and dynamics analyzer

The analyzer is also presented in Figure 2. As presented before, the analyzer (fig. 1) outputs the difference between input values and reference values. Reference values are BGL thresholds and BGL variation speed thresholds.

BGL thresholds are:

$$threshold_{insulin} = insulin\ pump\ triggering\ threshold \quad (9)$$

$$threshold_{amylin} = amylin\ pump\ triggering\ threshold \quad (10)$$

$$threshold_{glucagon} = glucagon\ pump\ triggering\ threshold \quad (11)$$

$$threshold_{glucose} = glusose\ pump\ triggering\ threshold \quad (12)$$

$$threshold_{amylin} > threshold_{insulin} > threshold_{glucagon} > threshold_{glucose} \quad (13)$$

BGL variation speed thresholds are:

$$threshold_{hyperglycemia} = BGL\ increase\ speed\ after\ triggering\ insulin \quad (14)$$

$$threshold_{hypoglycemia} = BGL\ decrease\ speed\ after\ triggering\ glucagon \quad (15)$$

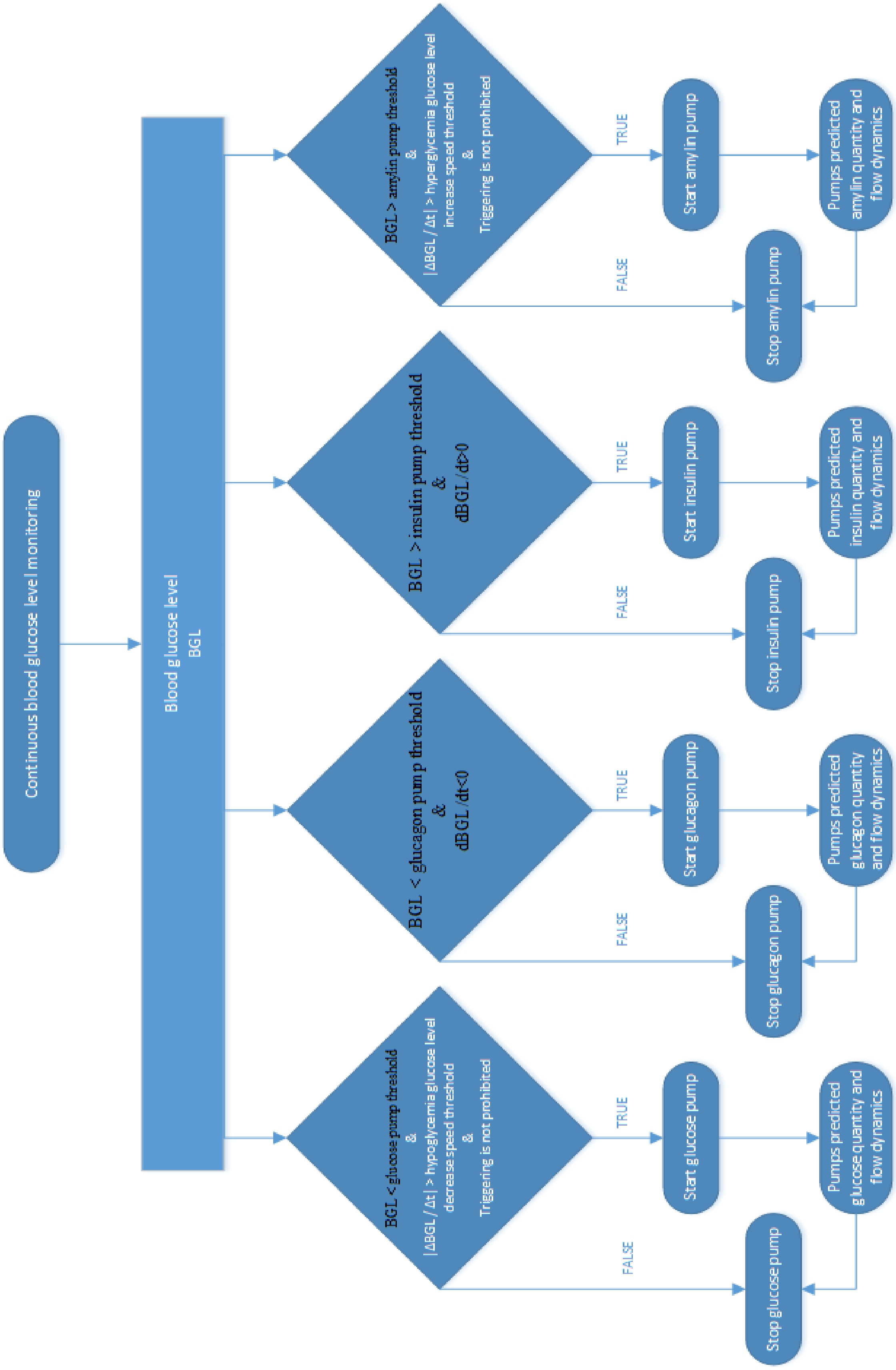

Fig. 2. Functional diagram of artificial extracorporeal endocrine pancreas.

The blood glucose level and dynamics analyzer follows this algorithm:

If:

$$BGL > threshold_{insulin} \quad (16)$$

And if BGL is increasing:

$$\frac{dBGL}{dt} > 0 \quad (17)$$

Then the insulin pump is triggered and injects a certain amount of insulin in a certain amount of time established by the diabetes doctor and tuned by the self-learning prediction algorithm processor.

If:

$$BGL > threshold_{amylin} \quad (18)$$

And if:

$$\frac{threshold_{amylin} - threshold_{insulin}}{t_{amylin} - t_{insulin}} > threshold_{hyperglycemia} \quad (19)$$

And if there is no triggering prohibition:

$$t_{amylin} - t_{insulin} > mintpd_{amylin} \quad (20)$$

Where:

$$t_{amylin} = the\ moment\ when\ threshold_{amylin}\ is\ reached \quad (21)$$

$$t_{insulin} = the\ moment\ when\ threshold_{insulin}\ is\ reached \quad (22)$$

$$mintpd_{amylin} = min\ triggering\ prohibition\ delay\ for\ amylin\ pump \quad (23)$$

Then the amylin pump is triggered and injects a certain amount of amylin in a certain amount of time established by the diabetes doctor and tuned by the self-learning prediction algorithm processor.

If:

$$BGL < threshold_{glucagon} \quad (24)$$

And if BGL is decreasing:

$$\frac{dBGL}{dt} < 0 \quad (25)$$

Then the glucagon pump is triggered and injects a certain amount of glucagon in a certain amount of time established by the diabetes doctor and tuned by the self-learning prediction algorithm processor.

If:

$$BGL < threshold_{glucose} \quad (26)$$

And if:

$$\frac{threshold_{glucagon} - threshold_{glucose}}{t_{glucose} - t_{glucagon}} > threshold_{hyperglycemia} \quad (27)$$

And if there is no triggering prohibition:

$$t_{glucose} - t_{glucagon} > mintpd_{glucose} \quad (28)$$

Where:

$$t_{glucose} = the\ moment\ when\ threshold_{glucose}\ is\ reached \quad (29)$$

$$t_{glucagon} = the\ moment\ when\ threshold_{glucagon}\ is\ reached \quad (30)$$

$$mintpd_{glucose} = min\ triggering\ prohibition\ delay\ for\ glucose\ pump \quad (31)$$

Then the insulin pump is triggered and injects a certain amount of insulin in a certain amount of time established by the diabetes doctor and tuned by the self-learning prediction algorithm processor.

It is obvious that the state of normality is reached when:

$$threshold_{glucagon} < BGL < threshold_{insulin} \quad (32)$$

In this particular case no pump is triggered.

Self-learning prediction algorithm

The self-learning prediction algorithm is used to improve the quantities and flow rate infusion of fluids in the four pumps. This are reflected both in the speed of normal BGL restauration but also in the frequency of pump triggering. The normal BGL restauration has to be fast enough to avoid prolonged hyperglycemia or hypoglycemia that affects different organs and the anatomic systems [4], but slow enough to avoid fast increase or decrease of BGL. Fast decrease of BGL leads to increase secretion of adrenaline with negative effect on the body and creates false hypoglycemic reactions [5]. Rapid changes in BGL lead to short times between pumps triggering altering both the human body functions and the usefulness of the artificial endocrine pancreas. That is why there are triggering prohibition delay timers for the amylin pump and the glucose pump as a safety measure.

This being said, the processor analyzes time intervals between insulin pump trigger and glucagon pump trigger as long as the other two pumps do not trigger. This is the period of normal BGL that has to be as long as possible. A balanced diet correlated to the amount of physical and psychical effort can significantly increase the period of normal BGL, avoiding the need of insulin to manage the BGL surplus.

Basically, the self-learning prediction algorithm is a conditional maximizing function:

$$f_{slpa} = \text{maximize } (|t_{insulin} - t_{glucagon}|) \quad (33)$$

If:

$$threshold_{glucose} < BGL < threshold_{amylin} \quad (34)$$

Where:

$$f_{slpa} = self - learning\ prediction\ algorithm\ function \quad (35)$$

And:

$$f_{slpa} = \text{maximize}(|t_{amylin} - t_{insulin}|) \quad (36)$$

If:

$$BGL > threshold_{amylin} \quad (37)$$

And:

$$f_{slpa} = \text{maximize}(|t_{insulin} - t_{glucagon}|) \quad (38)$$

If:

$$BGL < threshold_{gucose} \quad (39)$$

The maximizing process is realized by tuning the reference values of blood glucose level and dynamics and triggering prohibition delay timers. The tuning process is semi-automatically, allowing the user to accept reference tuning confirming the system request for tuning. After the tuning process took place, manual tuning is also possible.

Conclusion

The artificial endocrine (the digestive component isn't approached) pancreas presented in this paper tries to offer a solution to major risks unsolved in the current marketed devices. It can be built with existent components (al parts are commercially available) following instructions on white papers that are generously available from device component manufacturers. Both the architecture and the algorithm can be further developed and perfected. Even though this paper contains only a theoretical approach, creating a device based on it is very easy due to existing hardware devices, the algorithm is only a controller firmware programming.

Even though the beta cells transplantation [6] is the favorite future method of insulin-dependent diabetes mellitus, there are cases when the implant method is not possible or reliable [7], the alternative of using an artificial endocrine pancreas being the only automatic way to control the diabetes.

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Pancreas endocrin artificial extracorporal ce utilizează patru pompe de infuzie și două bandelete de testare

Rezumat

Incidența de pacienți cu diabet zaharat insulino-dependent este în creștere și poate duce la agravarea stării generale de sănătate sau chiar la moarte. Pompele actuale de insulină utilizate în medicina nu oferă posibilitatea de a elimina toate riscuri majore în ceea ce privește capacitățile de reglare ale nivelului de glucoza din sânge. Bazat pe funcționarea pancreasului endocrin uman și adoptând măsuri de siguranță cum ar fi utilizarea de doi senzori independenți și posibilitatea de compensare a hipoglicemiei severe prin aport de glucoză, când infuzia de glucagon nu este eficientă, pancreasul endocrin artificial extracorporal propus în acest articol poate crește în mod eficient nivelul de siguranță în utilizare. Această lucrare abordează principiul de construcție a acestor echipamente, propune o abordare sistemică și oferă recomandări pentru construcția acestuia. Este propus, de asemenea, un algoritm al funcționării automate a unui astfel de dispozitiv care poate duce la eliminarea riscurilor majore în utilizare.