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A novel strategy for long-term implantable artificial pancreas

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***Abstract*—Technology has recently changed type 1 diabetes treatment by introducing several advancements able to improve patients' quality of life. However, despite of several decades of research efforts, the dream of a fully-automated implanted artificial pancreas is quite far from its realization. The need for periodically restoring the implanted battery charge and refilling the implanted insulin reservoir are the main issues, for which invasive surgery, transcutaneous catheters or external portable devices are presently the only solutions. In this paper we propose a novel approach to these issues, describing a totally implanted closed-loop artificial pancreas with a wireless battery charger and a non-invasive strategy for insulin refilling, based on sensorized swallowable "insulin carrier" capsules. Such system has the potential to represent a final solution for diabetes treatment, by fully restoring patients' quality of life.**

I. Introduction

TYPE 1 diabetes (T1D) is one of the most spread illnesses of recent times [1], mainly related with the lost of functionality of pancreatic β cells, and resulting in a lack of insulin production. The traditional therapy for T1D relies on multiple daily insulin injections, with the aim to lower blood glucose levels, but this approach has several drawbacks. The physiological insulin profiles are not well mimicked with this technique, and dosing errors can be made [2]. Furthermore, T1D patients are constantly slave of their pathology, without the opportunity to restore a full quality of life, as the adherence to therapy is crucial 24 hours a day, 365 days a year [3].

The dream of the development of an artificial pancreas, able to fully restore the lost pancreatic functionality in an automated way, has been a goal for more than 30 years [4]. To accomplish this aim, three main elements are required: a continuous insulin delivery device, a continuous glucose monitoring system, and a control algorithm linking insulin delivery to glucose measurements [5].

Insulin pump therapy allows a continuous delivery of insulin. This approach has been used both in type 1 and type 2 diabetes, thus allowing a good control of glycemic values [6], [7]. The two possible strategies for a continuous insulin delivery are the continuous subcutaneous insulin infusion (CSII) and the continuous intraperitoneal insulin infusion (CIII). The subcutaneous infusion is the simplest approach, but it has some limiting factors, related to delays in the modulation of insulin action and to the need of portable external devices [8]. CIII shows many benefits, among which a fast insulin action, low basal plasma insulin levels, a tight control of glycaemia, and a low incidence of hypoglycemic events [9], but it also implies a surgical operation, needed to implant the insulin pump, and the need of periodical replacement of the device battery and refilling of the insulin reservoir, by quite invasive procedures.

The efficacy and safety of continuous glucose monitoring (CGM) in T1D has been recently supported by several randomized controlled trials [10]-[12], and the integration of CGM with insulin pumps offers additional benefits [13]. The basic strategy is to use subcutaneous glucose sensors, able to detect glucose levels in the interstitial compartment (thus implying a certain delay respect to the real blood glycaemia), but also intravenous glucose sensors have been tested *in vivo* [14], [15].

Regarding control algorithms, their development and application in diabetes treatment marked the beginning of a new era, with the introduction of semi-closed-loop systems, able to prevent or minimize nocturnal hypoglycaemia, hybrid systems to manage blood glucose levels with minimal user intervention, and even fully automated systems that would take the user out of the loop [16]. Advanced control algorithms have been recently proposed for diabetes management, like bi-hormonal closed-loop [17], model predictive control [18], and model predictive iterative learning control algorithms [19].

The idea of an algorithmic/technological way to control glycaemia is not new, but recent improvements in both glucose-sensing technologies and insulin delivery, as well as in control and system engineering, allowed to think that the replacement of the endocrine pancreatic function by means of an artificial pancreas is achievable. Many efforts have been made in order to build external, internal or hybrid devices, but research recently focused on closed-loop fully automated systems based on subcutaneous glucose monitoring and subcutaneous or intraperitoneal insulin delivery [20]-[22]. The systems based on subcutaneous insulin infusion are characterized by external portable devices. The patients are obliged to wear such devices and to constantly take care of them, thus affecting many activities of daily life (sports, showers, etc). Furthermore, the catheters

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needed for insulin delivery can cause infections or similar problems. In the present paper we propose a novel idea [23] for a long-term implantable fully-automated artificial pancreas, based on continuous glucose monitoring, intraperitoneal insulin delivery and closed-loop control, and provided with a wireless battery charging system and an insulin refilling device placed in the duodenum, able to recognize and dock to insulin carrier capsules that can be swallowed by the patients. The overall system architecture is described, as well as its components, highlighting the possibility to use such approach to build a novel artificial pancreas for fully restoring T1D patients' quality of life.

II. The Concept for Long-Term Implantable Artificial Pancreas

A. Overall system architecture

The system architecture of our artificial pancreas is depicted in Fig. 1.

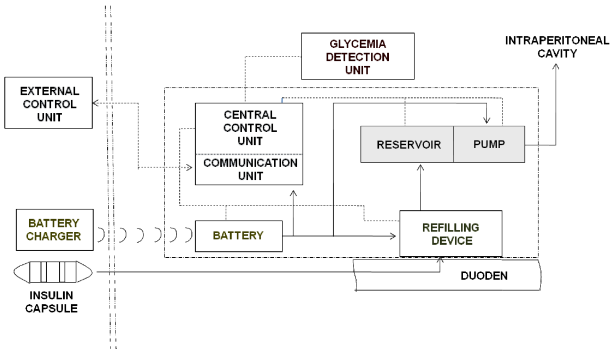

Fig. 1. The implanted core of the artificial pancreas is constituted by the insulin pump, connected with an insulin reservoir, a central control system and a battery. Close to the implanted core there is the refilling device, facing the duodenum and able to dock insulin capsules swallowed by the patient. An implanted glucose sensor provides glycemic values to the central control unit, that communicates with an external unit, managed by the patient. A wireless battery charger allows to charge the implanted battery in a non-invasive way.

The artificial pancreas is thought to be implanted in an anatomical region close to the pancreatic one, and in proximity of the first duodenum loop. The implanted pump allows insulin infusion in the intraperitoneal cavity, and it is connected to a dedicated insulin reservoir. Glycaemia is detected by an implanted sensor (e.g. the Dexcom™ continuous glucose monitoring system, or the SMSI® glucose sensor), that furnishes in real-time and in a wireless mode glycemic data to the central control unit, which continuously adjusts the amount of insulin to deliver in the peritoneum. The implanted battery is crucial for allowing the system functionality, and it is periodically charged in a wireless mode, by means of a belt, that the patient can wear overnight, based on solenoids, able to restore the full battery charge [24]. The refilling device is based on a docking system, surgically fixed on the duodenum wall and able to activate, when required, a switchable permanent magnet, and on a aspiration device (a needle able to enter into the duodenum lumen, when actuated, and to take liquid by means of an embedded vacuum system). The insulin capsules are small sensorized polymeric pills filled with insulin. An integrated RFID tag allows the precise position recognition of the capsule once arrived in the duodenum lumen, and two small ferromagnetic rings allow the docking with the implanted docking system at the duodenum wall. After a patient swallows a capsule, it arrives in proximity of the duodenum, and the RFID tag communicates its position to the implanted central control unit, that activates the switchable magnet. The capsule is thus attracted and docks with the refilling device. The aspirating device (the implanted needle) enters into the duodenum lumen, punches the capsule and sucks the insulin contained in the carrier. By means of a sterile connection tube, the aspirated insulin is brought to the implanted insulin reservoir, that can be therefore refilled in a non-invasive way. At the end of the procedure, the switchable magnet is automatically de-activated and the capsule is released and finally expulsed by the patient. An implanted communication unit continuously sends data to an external control unit portable by the patient (e.g. a clock), informing him/her about the system parameters (insulin and battery level, glycaemia, docking procedure, foreseen date for insulin and battery charge needed, etc.).

B. Insuline capsules

The insulin refilling strategy is the crucial aspect of this system. Fig. 2 shows the insulin capsule structure.

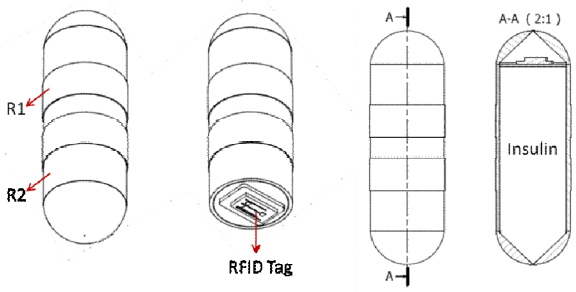

Fig. 2. Insulin capsule outer and inner structure. An RFID tag is embedded in the carrier, allowing its real-time position recognition. The internal cavity hosts the insulin load. The two ferromagnetic rings (R1 and R2) allow the docking with the implanted refilling system in the duodenum lumen.

The capsule is made of polymeric biocompatible material, and it is provided with two ferromagnetic rings allowing the docking to a complementary structure implanted in the duodenum. A position sensor (RFID) is embedded in the polymeric structure, and constantly sends information about the capsule position to the central control system of the artificial organ, in order to detect the arrival of the capsule in the duodenum. The dimensions of the capsule

should not exceed 11 mm in diameter and 26 mm in length, recognized as the "maximum swallowable size" [25, 26]. A capsule of 10 mm x 15 mm could be used, filling its internal cavity with insulin (for a total volume of about 650 mm^3). Using concentrated insulin, one capsule could provide enough hormone for several days.

C. Docking system

Fig. 3 shows the main component of the docking system, and its working principle.

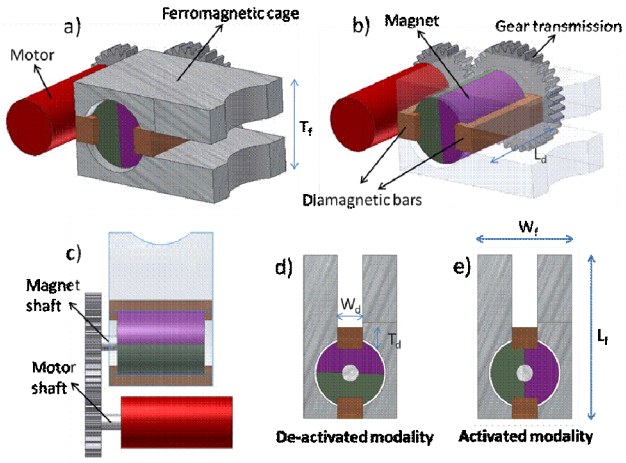

Fig. 3. a) and b) 3D view of the docking device and its components; c) top view of the system, highlighting the mechanical connection between the motor and the magnet, by means of a gear transmission; d) and e) lateral view, showing two different magnet configurations, corresponding to de-activated and activated docking modality, respectively. L_f, W_f, and T_f are the length, width and height of the ferromagnetic cage, respectively, L_d, W_d, and T_d are the dimensions of the diamagnetic bars (see Table I).

A cylindrical, diametrically magnetized permanent magnet is lodged in a structure made of a ferromagnetic cage which is interrupted by two diamagnetic bars. The magnet is free to rotate around its axis, and it is provided with a shaft that mechanically connects it to a rotary electrical motor, by means of a gear transmission. The actuator must have some special characteristics (it must be able to work near a permanent magnet, its energy consumption should be limited, etc.). The system is implanted in proximity of the first duodenal loop, and the two ferromagnetic expansions pass through the duodenal wall, facing into the internal duodenal lumen. They thus represent the interface that the swallowable capsule finds during its route. When the magnet is in the configuration of Fig. 3 d), the magnetic field lines can find a short path to close themselves from the north to the south pole, and the ferromagnetic expansions are not polarized. In the configuration of Fig. 3 e), magnetic field lines find the only possible path to close themselves through the ferromagnetic expansions, polarizing them and activating the docking mechanism able to attract the ferromagnetic rings placed on the insulin capsule. Fig. 4 further explains this effect, with the support of some simulations.

As confirmed by the simulations, a 90° rotation of the magnet allows the activation or the de-activation of the docking mechanism, and therefore of the capsule capture in the duodenum lumen. The simulation has been performed by means of the software COMSOL and using the parameters

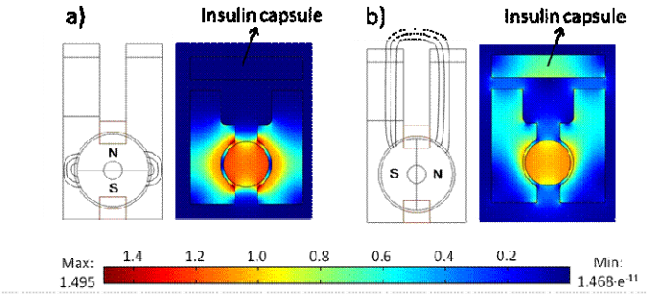

Fig. 4. a) System with the magnet in the de-activated modality. Magnetic field lines are schematically represented closing themselves in a limited space in proximity of the magnet. The corresponding simulation confirms that the magnetic field intensity is almost null in proximity of the insulin capsule; b) system with the magnet in the activated modality. Magnetic field lines are forced to close themselves passing through the ferromagnetic expansions. The corresponding simulation shows that such expansions are polarized, and that the insulin capsule feels a considerable magnetic field. Scale values are expressed in Tesla.

resumed in Table I.

With this approach, the permanent magnet remains de-activated during patient's daily life, avoiding undesired effects (attraction of metallic objects, etc.), being activated only for few seconds during the insulin refilling procedure.

TABLE I
SIMULATION PARAMETERS

ELEMENT	Dimensions L, W, T (mm)	Relative magnetic permeability
FERROMAGNETIC ELEMENTS	10 x 4 x 5	1980
DIAMAGNETIC ELEMENTS	2 x 2 x 5	0.75
INSULINE CAPSULE (assumed homogeneously ferromagnetic)	2 (diameter) x 10 (length)	1800
ELEMENT	**Dimensions (mm)**	**Residual induction (T)**
MAGNET (N48, diametrically polarized)	4 (diameter) x 5 (length)	1.36

D. Refilling device

The insulin refilling procedure is described in Fig. 5. During the first phase (approaching, Fig. 5a), the RFID tag embedded in the capsule sends position data to the implanted

control system, that activates the rotary motor, causing a rotation of the permanent magnet, and therefore the activation of the docking mechanism. During this phase (docking and insulin transfer, Fig. 5b), the capsule is stably maintained in position by the ferromagnetic expansions, while a needle is actuated by a linear motor, allowing it to pass through a unidirectional valve placed on the duodenal wall and to penetrate into the capsule. A remote vacuum system is activated and the insulin in the capsule is aspirated by the needle and transferred, by means of a sterile connection tube, to the implanted insulin reservoir. An alternative approach could be based on a overpressured capsule, allowing the automatic transfer of the insulin, without the need of a vacuum system and reducing the number of actuators. Once the transfer phase is finished, the

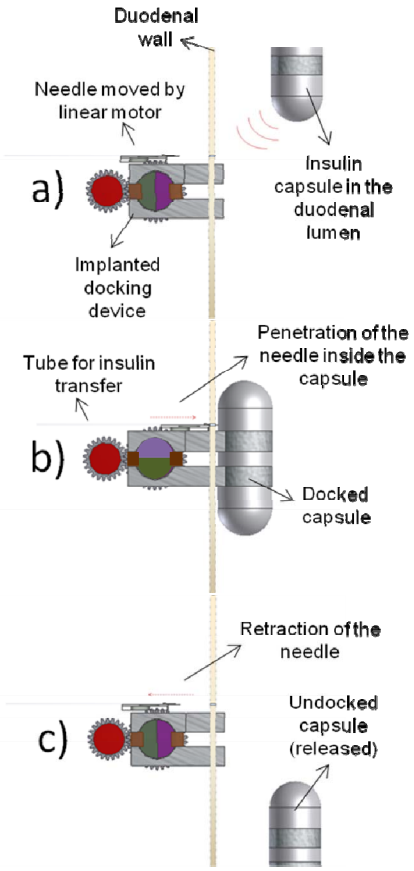

Fig. 5. Insulin refilling procedure. a) approaching phase; b) docking and insulin transfer phase; c) undocking phase. The yellow line represents the intestinal wall; on the right there is the duodenal lumen, on the left the outside region, with the implanted system.

needle retracts and the magnet is rotated again, thus deactivating the docking (undocking phase, Fig. 5c) and releasing the empty capsule, that will be then expelled by the patient.

E. Wireless battery charger

The possibility of charging a battery in a wireless mode has recently emerged in electronic systems, opening new opportunities, above all concerning medical devices. A wireless power supply module includes a first resonator, used to receive electrical energy, that works at a first resonance frequency. The wireless receiving module (connected to the battery) has a second resonator and a charging circuit. The second resonance frequency of such device is substantially the same of the first one, allowing a coupling and a non-radiative energy transfer. The received electrical energy is then used to charge the battery [24, 27]. In our system, a portable belt with an embedded resonator, as described, can be used. When needed, the patient can wear the belt (for example overnight), in order to restore a full battery charge.

F. Glucose sensor, insulin pump and control system

In our system, existing commercial elements for glycaemia detection, for intraperitoneal insulin infusion and for predictive advanced control can be employed. In particular, our aim is to use an implanted glucose sensor with a wireless communication module (like the SMSI® glucose sensor), able to transmit information about glycemic levels in real-time to the control system. Regarding the pump, there are some suitable commercial intraperitoneal implantable pumps (like the MiniMed Medtronic implantable insulin pump). The main issue concerns the sterility of the insulin aspirated from the capsules. A system of filters in the implanted device could prevent the contamination of the infused insuline. As described in the introduction, many control algorithms are presently available in literature; predictive algorithms could be a good options for our system.

G. External portable control unit

An external portable device (like a clock) has the double function of keeping aware the patient of the situation of the implanted device, and of warning him/her when battery charging or insulin refilling are needed. On the clock display many parameters can be shown, such as real-time glycemic values, insulin reservoir level, residual battery charge, estimated time for capsule or belt need, etc. Such data could be furthermore sent to a medical doctor or to the hospital, in order to plan capsule supply to the patient.

III. CONCLUSION

It has been broadly demonstrated that psychological issues are of primary importance in the management of T1D [28]-[30]. The dream of a fully-implanted and fully-automated lifelong artificial pancreas represents the possibility for many patients to live a normal life, without minding about their pathology, and almost forgetting it. The system proposed in this paper is based on a completely implantable device able to regulate insulin infusion in the peritoneum according to real-time-provided glycemic data. A wireless battery charging system and a non-invasive insulin refilling strategy configures such system as a promising solution for the achievement of a lifelong artificial pancreas, able to fully restore T1D patients' quality of life.

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