Journal of Diabetes Science and Technology
Volume 3, Issue 6, November 2009

ORIGINAL ARTICLES

A Benchtop Closed-Loop System Controlled by a Bio-Inspired Silicon Implementation of the Pancreatic β Cell

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Abstract

The normal pancreatic β-cell membrane depolarizes in response to increasing concentrations of glucose in a bursting pattern. At <7 m*M* (126 mg/dl), the cell is electrically silent. The bursting pulse width increases as glucose rises >7 m*M* (126 mg/dl) until a continuous train of bursting is seen at >25 m*M* (450 mg/dl). A bio-inspired silicon device has been developed using analogue electronics to implement membrane depolarization of the β cell. The device is ultralow powered, miniaturized (5 × 5 mm), and produces a bursting output identical to that characterized in electrophysiological studies.

Objective:

The goal of this study was to demonstrate the ability of silicon implementation of β-cell electrophysiology to respond to a simulated glucose input and to drive an infusion pump *in vitro*.

Method:

The silicon device response to a current source was recorded at varying simulated glucose concentrations. Subsequently, the bursting response to a changing analyte concentration measured by an amperometric enzyme electrode was converted to a voltage, driving a syringe pump loaded with a 50-ml syringe containing water.

Results:

Bursting responses are comparable to those recorded in electrophysiology. Silicon β-cell implementation bursts with a pulse width proportional to concentration and is able to drive an infusion pump.

Conclusion:

This is the first *in vitro* demonstration of closed loop insulin delivery utilizing miniaturized silicon implementation of β-cell physiology in analogue electronics.

J Diabetes Sci Technol 2009;3(6):1419-1424

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Abbreviations: (ATP) adenosine triphosphate, (CMOS) complementary metal oxide semiconductor

Keywords: β cell, closed loop, type 1 diabetes

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Introduction

Type 1 diabetes is a chronic metabolic disease characterized by T-cell-mediated autoimmune destruction of the insulin-secreting β cells of the endocrine pancreas. Absolute insulin deficiency occurs, leading to hyperglycemia. Current regimens for treating type 1 diabetes in clinical practice are mainly based on injections of subcutaneous insulin either continuously or several times daily in dosages determined by intermittent blood glucose measurements. The Diabetes Control and Complications Trial demonstrated that intensive management using this treatment algorithm reduced microvascular complications by 50–76%. However, this was at the expense of increased time spent in hypoglycemia, especially at hemoglobin A1c levels <7.5%.[1] In other studies, intensive management resulted in subjects spending 30% of the day with glucose values >10 m*M* (180 mg/dl) and >2 hours/day in hypoglycemia, often at night.[2] A closed-loop system provides the potential to improve hemoglobin A1c while avoiding hypoglycemia. It requires continuous glucose measurement, a control device, and a pump for insulin delivery.[3]

Intelligent control devices have been developed using the principles of feedback control or predictive modeling. These were initially cumbersome (e.g., the "biostator"[4]), but more recent systems have been miniaturized and are capable of achieving blood glucose control in the fasting state when provided with an input of interstitial glucose levels.[5]

Closed-loop control systems for diabetes have the potential to eradicate hypo- and hyperglycemic excursions, preventing the long-term, micro- and macrovascular complications of diabetes and, critically, improving quality of life. Implementation of these systems, however, poses a significant challenge as lags in interstitial glucose sensing and subcutaneous insulin absorption significantly delay the effective action of such devices. This problem may be minimized by exploring alternative sensing modalities and insulin administration routes.

This article presents an implementation of pancreatic β-cell electrophysiology in silicon electronics for use in future closed-loop systems. The approach of modeling physiology in silicon produces low-power, miniaturized chips well suited to implementation in medical devices and has been used in producing cochlear implant technology.[6] High volumes of silicon chips may be produced at low cost.

In addition to use in an ambulatory closed-loop insulin delivery device, there are other potential applications of a silicon device capable of mimicking voltage changes seen in depolarizing cells. These include use in critical care or surgical scenarios and in the laboratory, making use of the bursting output to explore effects on other cell types.

β-Cell Physiology

The pancreatic β cell displays similar electrophysiology to mammalian neurons with a steady-state voltage and depolarization activity. β-cell intracellular fluid contains multiple ions in various concentrations. Passage of these ions across the cell membrane is tightly regulated by transmembrane-gated ion channels, allowing the cell to create and maintain a potential difference across the membrane. In the resting state, this potential difference is around –70 mV. Glucose-dependent insulin secretion is dependent on potassium, K^+, and calcium, Ca^{2+}, ion movement. The principal β-cell ionic channels are represented in **Figure 1**.

As the glucose concentration rises in the extracellular space, glucose is transported into the β-cell cytoplasm by the transmembrane transporter protein glucose transporter 2.

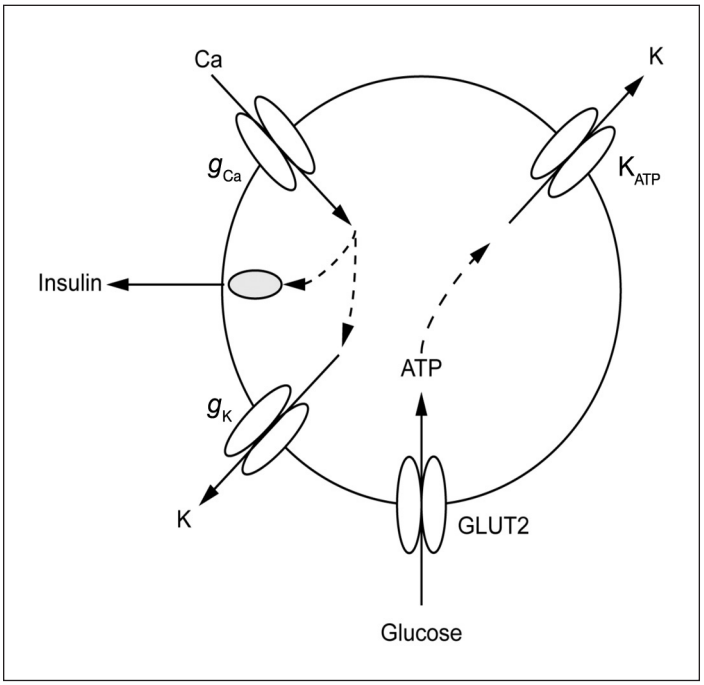

Figure 1. β-cell electrophysiology. GLUT2, glucose transporter 2; K_{ATP}, potassium ATP channel; K, potassium; Ca, calcium; g_{Ca}, voltage-gated calcium channel; g_K, voltage-gated potassium channel.

Intracellular glucose is metabolized to produce adenosine triphosphate (ATP), the common energy carrier. The consequent rise in ATP causes closure of ATP-sensitive K^+ channels, K_{ATP}.[7,8] This prevents active pumping of K^+ out of the cell, changing the ionic gradient and causing depolarization of the cell membrane from –70 mV.[9] When the transmembrane voltage reaches –40 mV, voltage-dependent Ca^{2+} channels open, allowing Ca^{2+} influx and initiating action potential behavior.[10] Prepackaged intracellular insulin granules are then released from the cell in response to the increased intracellular $[Ca^{2+}]$.[11] Simultaneously, calcium-sensitive K^+ channels open, bringing the cell membrane potential back to –70 mV, the resting state.

In contrast to neurons, the β cell depolarizes in a bursting pattern, which varies with glucose concentration.[12] At normal fasting glucose concentrations [5 m*M* (90 mg/dl) in subjects without diabetes], the cell remains electrically silent. An increase in glucose concentration above 7 m*M* (126 mg/dl) depolarizes the cell membrane and electrical activity is initiated, resulting in bursting behavior. As the glucose concentration rises, the pulse width of the bursts increases up to a concentration of 25 m*M* (450 mg/dl), at which the mechanism is saturated and a continuous train of action potentials remains (**Figure 2**). The bursting behavior of the β cell may be measured as the ratio of the duration of the active phase to the burst period. This is the plateau function, which determines the amount of insulin released from the cell.

Modeling

In 1952, Hodgkin and Huxley described the ionic movements that initiate and propagate action potentials in the squid giant axon.[13] The potential difference across an electrically active membrane may be expressed by the equation

$$C_{mem}\frac{dV_{mem}}{dt} = -I_{Ca(V)} - I_K - I_S$$

where C_{mem} is the membrane potential, I_{Ca} and I_K are the calcium and potassium ion channel currents, and I_S is a slow time varying current. The membrane potential is expressed as a function of the differential of voltage over time.

The Hodgkin–Huxley model was refined for the β cell by Chay and Keizer with addition of the calcium-gated potassium channel.[14] This addition resulted in a mathematical model of β-cell electrophysiology, which not only replicated depolarization but did so in a bursting fashion equivalent to experimental data.

Silicon Implementation

The glucose-dependent bursting behavior of the pancreatic β cell may be viewed as the control algorithm intrinsically linking glucose sensing and insulin secretion. In order to replicate this behavior in silicon, it is necessary to visualize the electrophysiology in terms of an electronic circuit. Ion channels are controlling ion flow and thus may be represented by nonlinear resistors (see **Figure 3**), electronic components that produce a voltage proportional to the electric current across them. In biology, ion channels create a voltage by regulating current across them.

By modeling ion channels as nonlinear voltage-dependent resistors (g_{Ca}, g_K, and g_S, where S is a slow time variable), it is possible to build an electronic circuit representative of a biological cell. These resistors are placed in a serial arrangement, with current inputs I_{Ca}, I_K, and I_S, and

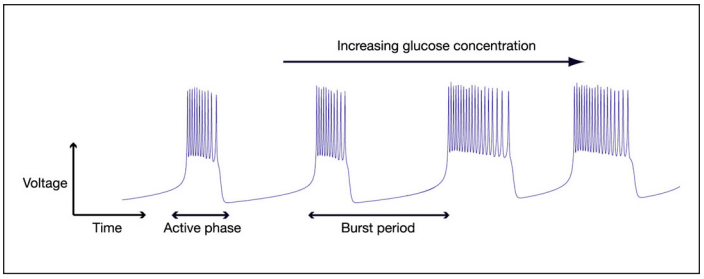

Figure 2. β-cell electrophysiology bursting behavior.

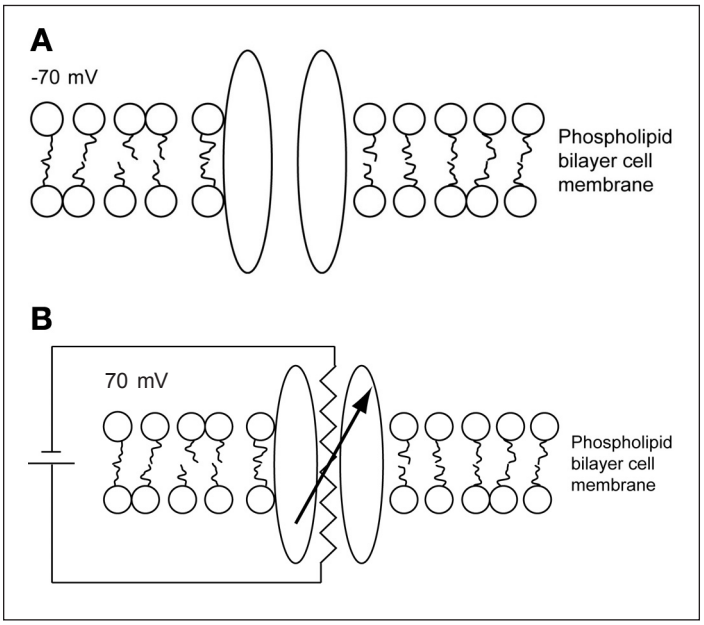

Figure 3. (A) Phospholipid bilayer with ion channel with **(B)** nonlinear resistor circuit overlaid.

the summation of their action (V_{Ca} + V_K + V_S) produces an overall membrane potential, C_m (see **Figure 4**). Further details of the electronics have been published previously.[15]

Silicon implementation of the β cell is manufactured using standard complementary metal oxide semiconductor (CMOS) processes to produce an analogue-integrated circuit using transistors that exploit the subthreshold region of operation. CMOS devices in this region operate in low power and can be used to create circuits with high noise immunity, making them ideally suited for use in biomedical applications. The device accepts a current in the nanoampere range, which may be fed directly from an electrochemical glucose sensor or from a benchtop current source. The output is a potential measurable in the millivolt range.

The complete silicon chip is 5 × 5 × 0.3 mm in size and has a mean power consumption of 4.4 μW at 2.5 volts (bursting phase 1.9 μA at 2.5 volts, silent phase 1.7 μA at 2.5 volts).

Results

Simulation

The β-cell electrophysiology algorithm was implemented in software using MATLAB (MathWorks, Natick, MA), and simulated glucose excursions were applied. The software simulator recorded glucose concentration and insulin secretion rate. A simulated glucose concentration of 16 mmol/liter (288 mg/dl) is shown (**Figure 5**). The silicon β-cell algorithm replicates physiology, producing first and second phase insulin responses. The first phase response lasts about 15 minutes, followed by a second phase of about 30 minutes. Simulated glucose concentrations fall to under 8 mmol/liter (144 mg/dl) over 45 minutes.

In Vitro

To demonstrate the behavior of the silicon chip *in vitro*, output from the silicon implementation of β-cell physiology was analyzed with varying input currents from a benchtop current source (Keithley 2602, Keithley Instruments, Cleveland, OH). The silicon cell is calibrated such that 1 nA is equivalent to 1 mmol/liter (18 mg/dl) glucose. Oscilloscope outputs for 7, 10, 12, and 14 nA are shown in **Figure 6**. The traces seen are equivalent to those noted in electrophysiological investigations.[16] With increasing simulated glucose concentrations, the bursting pulse width increases the plateau function.

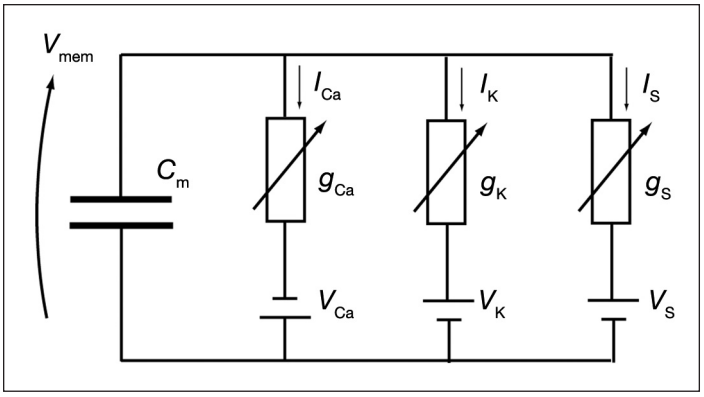

Figure 4. Ion channels as resistors in serial in a circuit provide a membrane potential in silicon implementation of the β cell. g_{Ca}, g_K, and g_S, where S is a slow time variable, are nonlinear resistors. I_{Ca}, I_K, and I_S are current inputs, and summation of their voltages, V_{Ca} + V_K + V_S, produces an overall membrane potential, C_m.

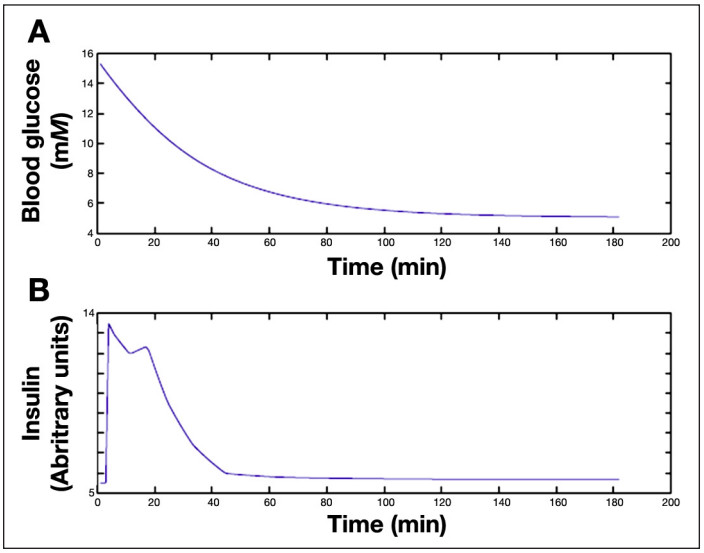

Figure 5. MATLAB simulation of glycemic excursion to 16 mmol/liter (288 mg/dl).

A benchtop closed-loop system was developed utilizing an electrochemical sensor, the silicon device, and a syringe pump system (see **Figure 7**). A platinum disc electrode with immobilized glucose oxidase (EC 1.1.3.4) was used as an amperometric sensor driven by a potentiostat (which maintains the potential of the working electrode at a constant 700 mV with respect to the reference electrode). The current produced by the sensor was used as input to the silicon implementation of the β cell, and the bursting output of the β cell fed through a spike converter to a stepper motor. The spike converter converts the physiological voltages, which are in the order of millivolts (70-mV spike amplitude) to a 3.3-volt spike amplitude, which is required to drive commercially available motorized pumps.

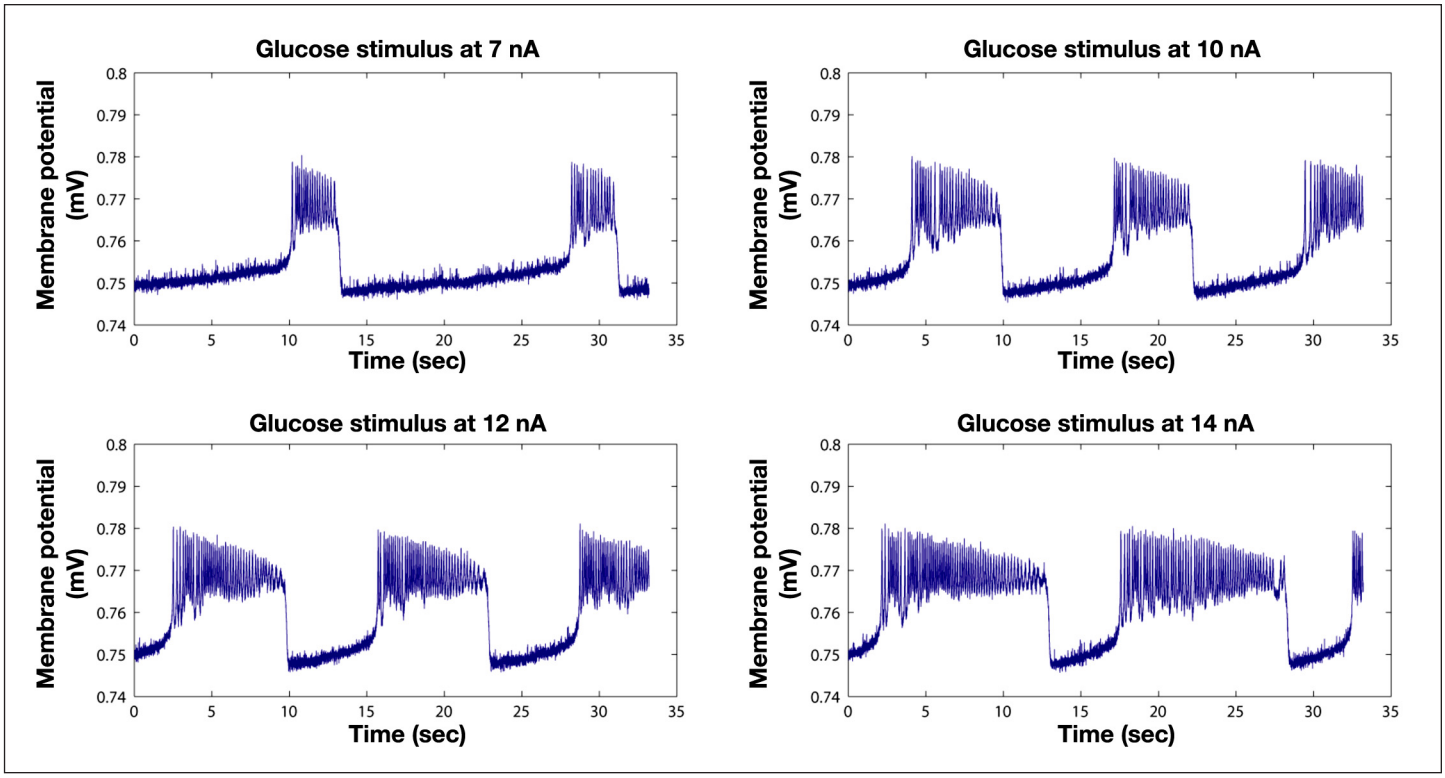

Figure 6. Experimental results from silicon implementation of the β cell showing increasing burst pulse width with increasing current (simulated glucose concentration input).

On addition of analyte to the system, the current from the amperometric sensor increases, causing an increase in bursting pulse width from the silicon β-cell device. This in turn drives the stepper motor to depress the plunger of the syringe. Depolarization activity is monitored by an oscilloscope.

In benchtop trials of this system, a rudimentary closed loop is demonstrated, diluting a solution by the addition of water. It should be noted that this system is not calibrated to demonstrate insulin delivery in type 1 diabetes or to show a dynamic response to a glucose load *in vivo*. It does, however, demonstrate the electronic feasibility of the device in accepting an amperometric glucose sensor input and converting this to a voltage capable of driving a syringe pump. This is the first step in the ongoing development of a bio-inspired closed-loop insulin delivery system based on silicon implementation of the pancreatic β cell.

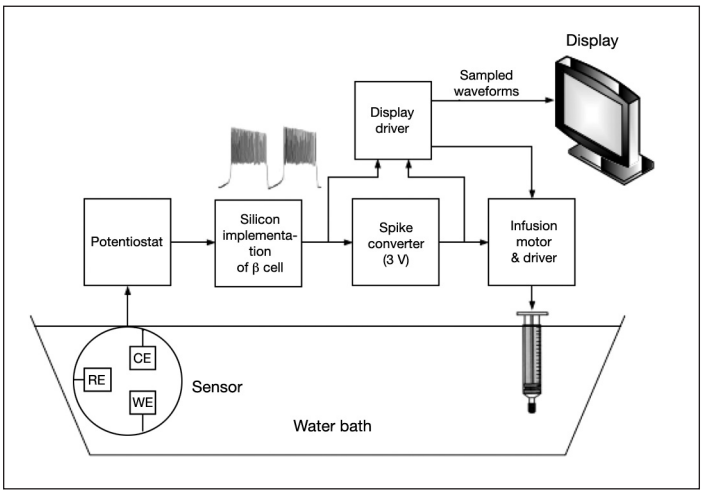

Figure 7. Benchtop closed loop schematic. CE, counter electrode; WE, working electrode; RE, reference electrode.

Discussion

This article described a novel implementation of pancreatic β-cell electrophysiology in low-power analogue electronics. Preliminary studies demonstrated the ability of the device to provide a bursting output equivalent to that seen in the biological cell and to convert an electrochemical sensor signal into a voltage to drive an infusion pump.

The development of closed-loop systems for the management of type 1 diabetes is a competitive domain and it is important to recognize the barriers to success. This has been reviewed extensively elsewhere.[3] Implementation of such systems is hampered by a lag in glucose sensors and in insulin delivery, which is likely

to mean that real-time β-cell electrophysiology is not required for a subcutaneous–subcutaneous closed-loop control system. However, future closed-loop systems are likely to incorporate novel glucose sensors and improved insulin administration technology that may enable, and indeed make desirable, a physiological control system.

Other control algorithms, such as model predictive control, include a predictive component to partially compensate for technical and pharmacological lags in the system. The silicon device described here does not have this but may be integrated with predictive or forecasting algorithms.

The potential advantages of using silicon implementation of β-cell behavior are that it is low power, miniaturized, and thus may be incorporated into the other components of a closed-loop system. The manufacturing process for this device is rapid and simple, leading to a low-cost solution.

β-cell bursting behavior may be utilized for *in vitro* experimentation, and there is also potential to use the platform technique of implementing transmembrane ion channel behavior in silicon to model other electrically active cell types, such as neurons, pancreatic α cells, and secretory anterior pituitary cells.

Conclusion

We presented a silicon implementation of the electrophysiology of the pancreatic β cell using low-power analogue electronics to produce a miniaturized device capable of acting in a closed-loop insulin delivery system. Further work is required to optimize the β-cell algorithm *in silico*, and potential exists to expand the behavior of the cell to include more complex electrophysiological models, such as phantom bursting and slow wave oscillation.

Acknowledgment:

Thanks to Dr. Mel Ho and Dr. Suket Singhal.

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