Microprocessor-based insulin delivery device with amperometric glucose sensing

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Abstract

This paper details the design of a closed-loop insulin delivery device, consisting of a glucose sensing circuit, and a basic microprocessor-based syringe pump. The glucose sensing circuit contains the required components to interface with CGMS’s glucose sensor assembly, while the syringe pump design uses microprocessor to allow flexible control over the pump driver. Instrumentation developed in this paper provides a ready reference to other researchers on the construction of a closed-loop insulin delivery apparatus with amperometric glucose sensor.

1. Introduction

Pumps for delivering medication has been well-developed. These pumps are largely microprocessor-controlled, and pumps with pumping mechanisms such as syringe driver, peristaltic, and pressurized gas canister, are readily available. A basic pump contains switches on the panel for infusion rates to be entered. More advanced pumps feature the ability to pre-programme different infusion rates for delivery at different time, download infusion history, etc.

The combination of an infusion pump with amperometric glucose sensor has been attempted over the past decades (see e.g. [1, 3, 4, 10, 11, 12]), in an effort to automatically regulate blood sugar level (BSL) using insulin delivered in a closed-loop manner. The emergence of Medtronic MiniMed (Northridge, CA) Continuous Glucose Monitoring System (CGMS) in consumer markets made amperometric sensors more reachable to experts and non-experts in sensor manufacturing.

CGMS is a commercial product that can be purchased by physicians for monitoring patient’s glucose trend over 3 days. It is readily implantable in patient’s subcutaneous tissue, and it provides glucose reading every 5 minutes. The availability of CGMS facilitated the construction of closed-loop insulin delivery device.

This paper aims at providing a ready reference to the construction of a basic insulin delivery device with CGMS sensor assembly as its glucose sensor. It includes details on the design of the glucose sensing circuit (that interfaces with amperometric glucose sensor, such as CGMS sensor assembly), signal processing, and infusion pump mechanism.

2 Materials & Methods

2.1 Glucose sensing circuit

Amperometric sensors were one of the most simple and stable approaches in glucose measurement techniques [5], and has been widely studied. In general, amperometric glucose sensor used glucose oxidase as the active enzyme, which converts glucose into gluconic acid and hydrogen peroxide. A potential of -600 mV to -700 mV is applied (with reference to a working electrode) to oxidise the hydrogen peroxide ($H_2O_2$) into $O_2$ and $2H^+$ The resulting current is measured as an indicative of glucose concentration. Commonly used sensor configurations are

1. two electrodes system — a platinum (Pt) working-indicating electrode with a Ag/AgCl reference-counter electrode, such as those described in [4, 6, 2].

2. three electrodes system — a platinum (Pt) working electrode, an Ag/AgCl reference electrode, and a platinum (Pt) counter electrode such as those described in [6, 7, 8, 13].

Both of these configurations involve the application of a constant potential to the electrode and the measurement of the generated electrical current. Circuitry for two-electrode system was described in [2], and was presented for use with their in-house glucose sensor (see [9]).
This section presents a circuitry that can be used with three-electrode systems, particularly with CGMS sensor assembly. The circuit consists of three sections: (1) a constant potential application circuit, (2) a nano-ampere measuring circuit, (3) a supply potential splitting circuit.

2.1.1 Constant potential application circuit

![Figure 1. Glucose sensing circuit for integration with MiniMed CGMS glucose sensor assembly. Figure shows a constant potential application circuit (right), a nano-ampere measuring circuit (upper left) and a supply potential splitting circuit (bottom left). The resistances, \( R_{\text{body1}} \) and \( R_{\text{body2}} \) represent the flow of the current generated from the hydrolysis of \( H_2O_2 \) across the constant potential applied to the electrodes.](image)

The constant potential application circuit (formed by op-amps 2 and 3 in Fig 1) functions to impose a constant potential between two electrodes, for the hydrolysis of hydrogen peroxide. In this design, a negative potential is applied at the reference electrode, \( \text{REF} \), with respect to the working electrode, \( \text{WRK} \). The design used two op-amps (i.e. op-amps 2 and 3) arranged in voltage-follower configuration, and the variable resistor \( \text{VR1} \) tuned to provide the negative potential.

2.1.2 Nano-ampere measuring circuit

The generated current, due to its small magnitude (in nano-ampere range), is measured by a nano-ampere measuring circuit, which is formed around op-amp 1. The circuit employs a transimpedance topology, and converts the outflowing current (with respect to the op-amp’s “-” input) into a positive output voltage. The output voltage is proportional to the current, and is thus proportional to the amount of glucose present in the sensor insertion site. The two diodes that are connected back-to-back functions to limit excessive current from damaging the op-amp. The capacitor in series with the 5MΩ resistor forms a low-pass filter with a cut-off frequency of \( 1/\sqrt{2\pi \cdot (5M\Omega \times C1)} \) to eliminate noise in the measurement.

2.1.3 Supply potential splitting circuit

To permit the use of a single 5V battery, and yet simultaneously allowing the existence of a negative potential (for the reference electrode), and a positive voltage output (at the nano-ampere measuring circuit), a supply potential splitting circuit is used. Formed by op-amp 4, the supply splitting circuit selects a potential within the source potential range, and maps it for use as “ground” reference by the other circuits. This effectively splits the source potential into two separate potential sources, giving a positive and negative voltage reference. This eliminated the need for a separate generation of negative power supply.

The use of op-amps with very low power consumption...
minimised the effect of limited current sourcing/sinking ability of the op-amps configuration employed in the supply splitting circuit.

Used in conjunction with CGMS sensor assembly, this glucose sensing circuit allows minute-by-minute measurement of subcutaneous glucose concentration, to be used by a control algorithm in the insulin delivery device.

It must be emphasized that this circuit is designed mainly for application that requires shorter measuring interval than those of CGMS monitor (i.e. minute-by-minute measurement versus CGMS’s 5-minute interval), and is not a replacement of CGMS monitor.

2.2 Microprocessor-based syringe pump design

The construction of the basic insulin infusion device is based on a syringe-driver pumping mechanism. The syringe pump hardware design consists of: (1) a motor driving circuit, (2) a motor rotation detector circuit, (3) a liquid crystal display and hardware buttons, and (4) a microprocessor.

2.2.1 Motor driving circuit

The motor driving circuit consists of a voltage source with current limiter. The motor is turned on by a logic high placed on the I/O pins of the microprocessor that connects to transistor TR1 (i.e. PA3 in Fig 2). When the motor drew more than a pre-defined current determined by the value of resistor R2 (e.g. when there is a flow resistance in the delivery catheter), TR2 would turn on, drawing currents away from the base of TR1, and thus reducing the current to the motor, and protecting the motor windings from overcurrent.

2.2.2 Motor rotation detector circuit

The motor rotation detector circuit consists of a light emitting diode, and a phototransistor, which can also be replaced by a slotted optical switch assembly. A slotted wheel, which is mounted on the motor shaft, is located between the slot of the optical switch assembly. Feedback on the degree of motor rotation was provided by the motion of the wheel interrupting the light beam between the slot (see Fig 2 and Fig 4).

As the optical switch is mainly used to detect the degree of rotation made by the motor, the microprocessor can be programmed to save power by switching on the optical switch only when the motor is turned on. The motor and the optical switch can then be switched off when the motor has rotated a pre-selected amount, or when a time-out has occurred. The values of resistor R1 to R4 varies with different types of motor and optical switch desired.

2.2.3 LCD and hardware buttons

The LCD and hardware button are provided for sensor value readout and infusion rate programming or viewing. The designer can also choose to provide dials in place of the LCD and hardware buttons.

2.2.4 Microprocessor

A microprocessor was used to coordinate the on-off sequence of the syringe pump motor mechanism, to provide the signal processings of the sensor readings, and to allow user to change infusion rates via the LCD and hardware buttons. Sensor signal are fed into the microprocessor through the Analog-To-Digital (ATD) channel.

To achieve automatic infusion of insulin based on sensor glucose readings, a closed-loop control algorithm can also be programmed into the microprocessor. The choice of the control algorithm is open to the designer.

2.3 Signal processing

Noise was inevitable when sensor signals are in nanocurrent magnitude, and hence filtering of noise was required. Since the sensor signal is fed into the microprocessor, the designer can implement the digital filter of their choice.

In our design, a simple moving average filtering was employed to obtain a relatively stable current readout on the microprocessor. A fast filtering mechanism was required to permit real-time reporting of sensor readings. The algorithm used a first-in-first-out buffer, with 1000 taps set aside for the averaging.

3 Result

To examine the performance of the nano-ampere measuring circuit, used in conjunction with the fast moving averaging algorithm, the linearity of the measuring circuit was tested by injecting test input currents into the circuit and
measuring the output of the circuit. Test currents in the nano-ampere (nA) range were generated, by means of using different resistor values for $R_{\text{body 1}}$ and $R_{\text{body 2}}$ (to effect different current values). Since $R_{\text{body 1}}$ and $R_{\text{body 2}}$ reflect the generation of current from hydrogen peroxide and its flow across a constant potential, one can simulate this current generation by using different resistors (as described above).

For the purpose of the test, $R_{\text{body 2}}$ was set equal to $R_{\text{body 1}}$, and the glucose sensing circuit was constructed using National Semiconductors LM6464. This micro-power quad CMOS operational amplifier features 20 μA/Amplifier supply current, >10kΩ input resistance, 150nA input current, and +5V DC single supply operation. A comparison of the output measured by the nano-ampere measuring circuit (i.e. $V_{\text{out}}/R$ in Fig 1) with the test currents applied at the input of the circuit (i.e. at WRK electrode) over the tested range of 10 nA to 400 nA showed that the output measurement is linear with respect to the input current.

To examine the performance of the moving averaging filter in combination with the ATD, the output of the nano-ampere measuring circuit was compared to the those sampled by a 10-bit ATD channel and subsequently filtered by the moving average algorithm. The comparison showed that $V_{\text{out}}$ is linear with respect to the ATD’s output measurement.

4 Discussion

The design of the microprocessor-based syringe pump and the associated glucose measuring circuit in this paper focused on presenting a basic “working” framework for the construction of closed-loop insulin delivery apparatus, which can be extended by other researchers. The bulk functionality of the syringe pump are software oriented (e.g. the off-on sequencing of the motor, signal processing of the sensor readings, closed-loop control algorithm for insulin infusion, etc.), and is open to designer’s preferences, giving flexibility for designer to tailor aspects of the pump according to research needs. Fig 2 provides a suggestion to the circuitry design while Fig 4 shows a possible layout of the device when packaged.

Tests on the performance of the nano-ampere measuring circuit, used in conjunction with the fast moving average filter, showed good linearity from the current input at the working electrode to the ATD output.

5 Conclusion

The design of a basic microprocessor-based syringe pump with a glucose sensing circuit was presented. The design gives a basic “working” framework for the construction of a closed-loop insulin delivery apparatus, allowing aspects of the apparatus to be tailored according to research needs (including the closed-loop control algorithm). This paper provides a ready reference to other researchers in the construction of a closed-loop insulin delivery system.

References