DEVELOPMENT OF ARTIFICIAL PANCREAS FOR TYPE-1 DIABETIC PATIENTS

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Research Guides

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Motivation

**Diabetes** is a disease in which blood glucose concentration is elevated because of deficient insulin secretion.

**Diabetes can induce:**
- blindness
- gangrene and amputations
- kidney failure
- cardiovascular problems
- coronary heart disease
- stroke ....... etc

Associated complications can be reduced by injecting insulin to the blood of the diabetic patient.
Disturbing Facts...

WHO Report:

- More than **180 million people** world-wide have diabetes
- This number is likely to double by 2030
- **5%** of total deaths is associated with Diabetes
- This number is likely to rise to **50%** in next ten years

WHO also reports that in 2005, **1.1 million** people around the world died due to diabetes!
Limitations of Traditional Approach

- **Patient centric**: Mostly relies on the patient’s responsibility about diet, exercise and medication (and perhaps meditation too!)

- **Medication is pre-defined** (i.e. largely open loop)

- Insulin doses are based on *apriori* statistical data and therefore is not tailored made.

- Cannot ensure close regulation of blood sugar; ineffective for Type-I diabetes.
Diabetes Types

• **Type II** (pills, exercise etc. are OK)
  - Dysfunctional endocrine pancreas which produces very small amount of insulin
  - Insulin receptor on the tissue cells respond abnormally to the circulating insulin (“insulin resistance”).

• **Type I** (insulin should be infused externally)
  - Dysfunctional endocrine pancreas which produces no insulin
ARTIFICIAL PANCREAS:
CONTROL THEORETIC APPROACH

Sensor → Controller → ACTUATOR

PLANT
The Technology Timeline

1920s
- Insulin discovered by Frederick Banting

1960s
- Backpack insulin & glucagon pump

1970s
- First use of CSII
  - Pickup et al.; BMJ, 1978
- The Biostator®
- Second use of CSII
  - Tamborlane et al.; NEJM, 1979
- Subcutaneous Continuous Glucose Monitoring
  - Minimed CGMS, 1999

1980s
- Blood glucose meters becoming smaller and faster

1990s
- Insulin pumps becoming more reliable and portable
  - Diabetes Technology & Therapeutics Vol 1, 1999

2000s
- 2001: First U.S. Diabetes Technology Meeting

Courtesy: Dr. A. Basu, Mayo Clinic, USA
The JDRF Artificial Pancreas Consortium is launched (Kowalski)

First study of fully-automated vs. hybrid closed-loop control studies (Weinzimer & Tamborlane)

First human trials begin using a system designed entirely in silico (UVA, Padova, Montpellier)

The APS Introduced (Dassau, Doyle, Zisser)

First ATTD Meeting, Prague

The JDRF CGM trial reporting significant improvement in glycemic control, NEJM, 2008

Clinical trials completed showing 5-fold reduction in nocturnal hypoglycemia and increase time within target range overnight (UVA, Padova, Montpellier)

FDA accepts the UVA/Padova metabolic simulator as a substitute to animal trials (Cobelli & Kovatchev)

NIH launches artificial pancreas initiative

First studies of automated s.c. closed loop (Steil)

NIH launches High Impact DP3 2011

Implantable Insulin pumps (Renard)

JDRF announces strategic AP partnerships with J&J and BD

NIH launches artificial pancreas initiative

Mayo Physiology studies

EU launches the AP@Home artificial pancreas initiative (De Vries, Heinemann)

2006

2008

2009-10

2013 - 2015

JDRF multi-center trial of modular control-to-range (Zisser)

2000: the ADICOL Project (Hovorka)

First ATTD Meeting, Prague

NIH launches High Impact DP3 2011

First human trials begin using a system designed entirely in silico (UVA, Padova, Montpellier)

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**Blood Glucose Regulation: Control Theoretic Approach**

**Aim:** A smart device that can continuously measure blood sugar level, record it and infuse necessary amount of insulin into the patient body.

![Schematic of Diabetic Control System](image)

**Schematic of Diabetic Control System**

**Devices already available in the market**

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Continuous Glucose Monitoring System (CGMS)

- It is a medical device that measures and logs blood sugar readings frequently during the day and night. It then averages the blood sugar readings.

- It works in "real time" displaying blood sugar levels every five minutes on a monitor that can be worn on the belt.

- When blood sugars are too high or too low the user is alerted. This allows *the patient* to make adjustments in his/her insulin intake quickly.

Philosophy of Artificial Pancreas

**Objective**

**Question:** Can we design a ‘robust’ (possibly tailor made) automatic insulin delivery system that can infuse insulin to the patient in a continuous manner?

**Answer:** *YES!*

**Approach:** Continuous monitoring of blood glucose and continuous infusion of insulin

**Technique Followed:** Feedback optimal and adaptive control theory based drug delivery system
Blood Glucose Dynamics: Mathematical Model

Bergman’s Minimal Model

\[
\begin{align*}
\dot{G}(t) &= -p_1[G(t) - G_b] - Z(t)G(t) + D(t) \\
\dot{Z}(t) &= -p_2[Z(t)] + p_3[I(t) - I_b] \\
\dot{I}(t) &= -n[I(t) - I_b] + \gamma \left[ G(t) - h \right]^+ t \\
\dot{D}(t) &= -BD(t), \quad B > 0
\end{align*}
\]

Parameters:

- \(p_1\) - insulin-independent rate constant of glucose uptake in muscles and liver
- \(p_2\) - rate for decrease in tissue glucose uptake ability
- \(p_3\) - insulin-dependent increase in glucose uptake ability in tissue per unit of insulin concentration above the basal level

<table>
<thead>
<tr>
<th>Variable</th>
<th>Meaning</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>(G(t))</td>
<td>The blood glucose concentration at time (t) (min)</td>
<td>mg/dl</td>
</tr>
<tr>
<td>(I(t))</td>
<td>Blood insulin concentration at time (t) (min)</td>
<td>(\mu U/ml)</td>
</tr>
<tr>
<td>(Z(t))</td>
<td>Represents insulin-excitable tissue glucose uptake activity</td>
<td>(min^{-1})</td>
</tr>
<tr>
<td>(D(t))</td>
<td>Exogenous glucose infusion rate after meal</td>
<td>mg/dl/min</td>
</tr>
<tr>
<td>(G_b)</td>
<td>Basal glucose level</td>
<td>mg/dl</td>
</tr>
<tr>
<td>(I_b)</td>
<td>Basal Insulin level</td>
<td>(\mu U/ml)</td>
</tr>
<tr>
<td>(\gamma)</td>
<td>The rate of pancreatic release of insulin after bolus</td>
<td>(\mu U/ml/(mg/dl)/min)</td>
</tr>
<tr>
<td>(h)</td>
<td>The pancreatic target glycemia</td>
<td>mg/dl</td>
</tr>
<tr>
<td>(u(t))</td>
<td>Insulin injection rate (the control variable)</td>
<td>(\mu U/ml/min)</td>
</tr>
</tbody>
</table>
Blood Glucose Dynamics: Mathematical Model

Bergman’s Minimal Model (for Insulin-Glucose Regulation)

Glucose dynamics

\[ \dot{G}(t) = - p_1[G(t) - G_b] - Z(t)G(t) + D(t) \]
\[ \dot{Z}(t) = - p_2Z(t) + p_3[I(t) - I_b] \]

Insulin kinetics

\[ \dot{I}(t) = - n[I(t) - I_b] + u(t) \]

Meal disturbance

\[ \dot{D}(t) = - BD(t), \quad B > 0 \]

Nonlinear State Space form:

\[
\begin{align*}
\dot{x}_1(t) & = - p_1 [x_1(t) - G_b] - x_2(t)x_1(t) + x_4(t) \\
\dot{x}_2(t) & = - p_2 x_2(t) + p_3 [x_3(t) - I_b] \\
\dot{x}_3(t) & = - n [x_3(t) - I_b] + u(t) \\
\dot{x}_4(t) & = - Bx_4(t), \quad B > 0
\end{align*}
\]

\[
y = [1 \ 0 \ 0 \ 0] X
\]

Equilibrium point:

\[
X_0 = [G_b, 0, I_b, 0]^T
\]
Deviation Dynamics/ Normalized Deviation Dynamics

\[
\begin{bmatrix}
    x_1 & x_2 & x_3 & x_4
\end{bmatrix}^T = \begin{bmatrix}
    x_{1o} & x_{2o} & x_{3o} & x_{4o}
\end{bmatrix}^T + \begin{bmatrix}
    x_{1d} & x_{2d} & x_{3d} & x_{4d}
\end{bmatrix}^T
\]

Equilibrium Condition: \[
\begin{bmatrix}
    x_{1o} & x_{2o} & x_{3o} & x_{4o}
\end{bmatrix}^T \overset{\Delta}{=} \begin{bmatrix}
    G_b & 0 & I_b & 0
\end{bmatrix}^T
\]

Deviation Dynamics:

\[
\begin{align*}
\begin{cases}
    \dot{x}_{1d} = & -p_1 x_{1d} - (x_{1d} + G_b) x_{2d} + x_{4d} \\
    \dot{x}_{2d} = & -p_2 x_{2d} + p_3 x_{3d} \\
    \dot{x}_{3d} = & -n x_{3d} + u(t) \\
    \dot{x}_{4d} = & -B x_{4d}
\end{cases}
\end{align*}
\]

Objective: \[
\begin{bmatrix}
    x_{1d} & x_{2d} & x_{3d} & x_{4d}
\end{bmatrix}^T \rightarrow 0 \text{ as } t \rightarrow T_s \text{ (settling time)}
\]
Topics for Research

- System ID (parameter fit) for the extended minimal model based on patient/field trial.
- Control design methods to achieve the objective and validation through extensive simulation
- Observer / filter design (based on only blood glucose sensing) for state estimation
- Developing an artificial pancreas systems using sensor, pump and cell phone (with blue-tooth communication) and implementing the algorithm in it.
- Field trial with rats and humans (under doctor supervision)
Operational IMPRINT Project

- **Team:**
  - R. Padhi, K.V.S. Hari & M. Arora – Ind. Inst. of Science
  - M. Dharmalingam and P. Karla – MSR Medical College
  - A. Basu – Mayo Clinic, USA (consultant)
  - R. Sundaresan – Ind. Inst. of Science (consultant)

- **Title:**
  - Development of Artificial Pancreas for Closed Loop Blood Glucose Control of Type-1 Diabetic Patients in India

- **Funding Source:** IMPRINT (IMPacting Research Innovation and Technology)

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Thank you

1. The sensor continuously samples the glucose concentration under the skin and sends the data stream to be analyzed.

2. The computer algorithm applies to the data the rules it has derived from past behavior to determine the insulin dosage.

3. The pump administers the insulin via a pipette under the skin.