NTNU

Innovation and Creativity

Automatic Blood Glucose Control for Diabetics

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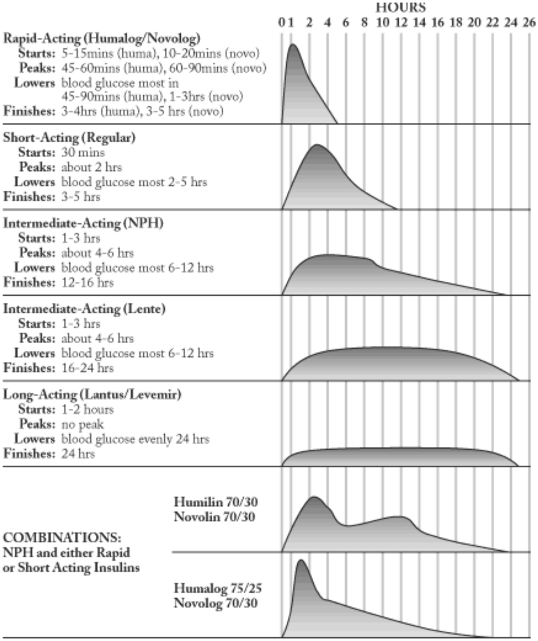
Outline

Diabetes Type I

- Autoimmune disease
- Deficiency or absence of insulin production
- Autoimmune attack and permanent destruction of the insulin-producing beta cells of pancreas
- Treatment with exogenous insulin via injections
- Hypoglycemia (plasma glucose level < 3.5 mmol/L)
- Hyperglycemia (> 7.5 mmol/L)
- Avoid short- and long-term complications due to hypoglycemia
- Avoid long-term complications due to hyperglycemia
- Control goal: Average plasma glucose ≈ 5 mmol/L and never hypoglycemia

Actuator: Insulin (I)

- Insulin analogs: Effect after 20 minutes, maximum after ≈ 1 hour, ends at $\approx 4-5$ hours
- Can be injected continuously, using an insulin pump
- Statement I: We have a slow actuator
- Statement II: Our actuator works only in one direction (down) for the plasma glucose level


HOURS
0 1 2 4 6 8 10 12 14 16 18 20 22 24 26
Rapid-Acting (Humalog/Novolog)
Starts: 5-15mins (huma), 10-20mins (novo)
Peaks: 45-60mins (huma), 60-90mins (novo)
Lowers blood glucose most in 45-90mins (huma), 1-3hrs (novo)
Finishes: 3-4hrs (huma), 3-5 hrs (novo)
Short-Acting (Regular)
Starts: 30 mins
Peaks: about 2 hrs
Lowers blood glucose most 2-5 hrs
Finishes: 3-5 hrs
Intermediate-Acting (NPH)
Starts: 1-3 hrs
Peaks: about 4-6 hrs
Lowers blood glucose most 6-12 hrs
Finishes: 12-16 hrs
Intermediate-Acting (Lente)
Starts: 1-3 hrs
Peaks: about 4-6 hrs
Lowers blood glucose most 6-12 hrs
Finishes: 16-24 hrs
Long-Acting (Lantus/Levemir)
Starts: 1-2 hours
Peaks: no peak
Lowers blood glucose evenly 24 hrs
Finishes: 24 hrs
COMBINATIONS:
NPH and either Rapid or Short Acting Insulins
Humilin 70/30
Novolin 70/30
Humalog 75/25
Novolog 70/30

Insulin Pump

- Insulin compartment (3 mL) lasts for $\approx 3 - 10$ days
- Soft cannula, must be moved every $3 - 5$ days
- Possible to disconnect tube from cannula
- Disconnect for swimming/showering

Disturbance 1: Food

— Effect starts after $10 - 40$ minutes, may last for $\frac{1}{2} - 10$ hours

— Forward-connection: Possible to predict with measurements in abdomen or in mouth?

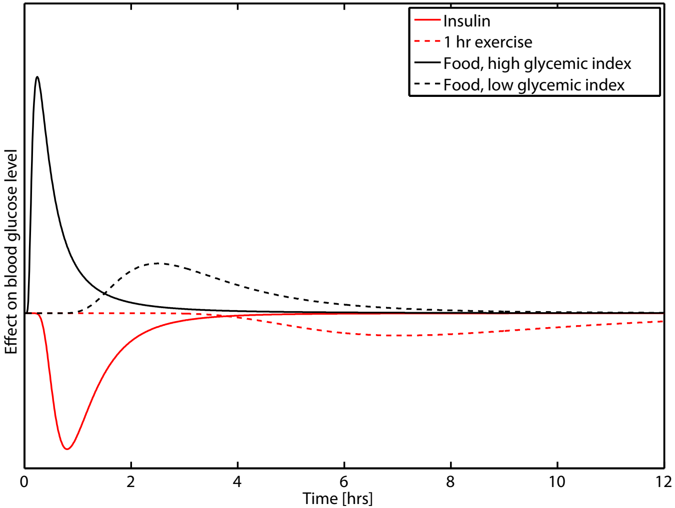
— Statement I: This disturbance is often faster than the actuator

— Statement II: This disturbance may vary a lot (depending on the type and amount of food/drink)

Disturbance 2: Activity

— Effect starts after $30 - 60$ minutes, may last for $1 - 72$ hours
— Forward-connection: Possible to predict, using a pulse watch
— Statement I: This disturbance is slow, and slower than the actuator

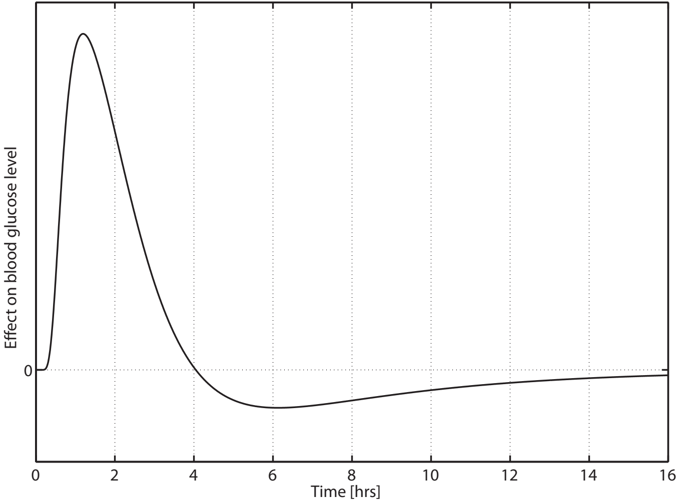
Actuator and Disturbance Effects



Special Case: Alcohol

- Effect of the sugar contained in some alcohol drinks (beer): Fast effect (after $10 - 40$ minutes), raising the blood sugar
- Effect of alcohol: Slow effect ($5 - 10$ hours), lowering the blood sugar. Dangerous!

Alcohol: Effect on Plasma Glucose Level

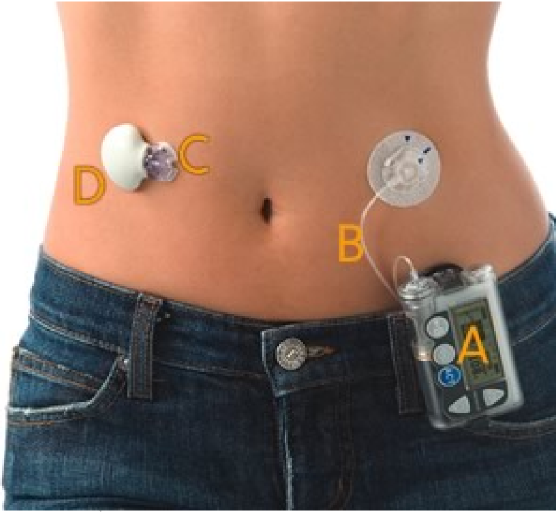


Measurements: Plasma Glucose

- Unit: mmol/L in Europe [US: mg/dL]
- Difficult to measure continuously, but it is possible with new technology (although the price is high, ≈ 200 NOK/day)
- Not accurate
- Needs calibration (at least two times every day)
- In Norway: Available for testing, from december 2007

Continuous Glucose Measuring Unit

Overall System

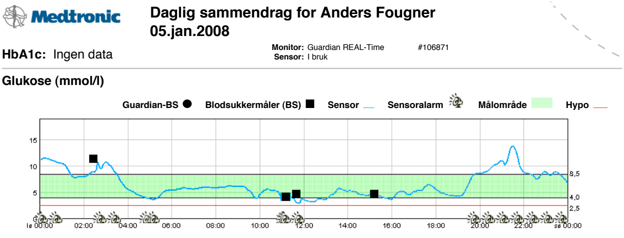


A: Insulin pump
B: Cannula (soft tube)
C: Glucose sensor
D: RF transmitter

Blood Glucose Sensor: Experiences

- Sensor lifetime ≈ 3 days, but sometimes up to 6 days
- Sometimes the sensor does not work at all (gives constant values) and needs to be changed
- Absolute accuracy is quite bad
- Good at showing trends (increasing/decreasing level)
- Alarms (low/high/increasing/decreasing), very useful!
- Simple feedback (turn insulin pump on/off) would be a simple improvement
- Not very user-friendly yet

5–6 jan 2008


Medtronic
Daglig sammendrag for Anders Fougner
05.jan.2008
HbA1c: Ingen data
Monitor: Guardian REAL-Time #106871
Sensor: I bruk
Glukose (mmol/l)
Guardian-BS
Blodsukkermåler (BS)
Sensor
Sensoralarm
Målområde
Hypo
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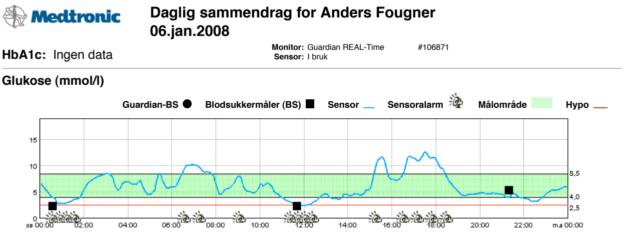
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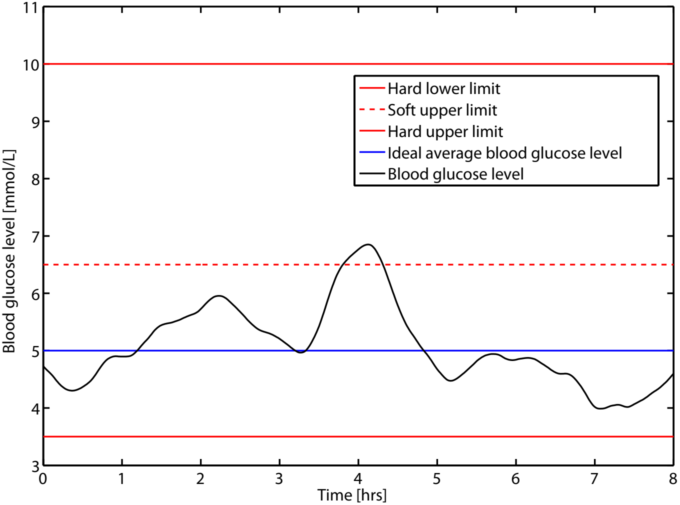
Previous Work on Automatic Control

- Bergman's (1991) "minimal model" ($3-5$ differential equations)
- The first insulin pumps (1985)
- Fisher (1991) uses the Bergman model for simple open-loop controllers
- Lynch et al. (2002) describes MPC, though based on not-reliable sensors and only simulations
- First reliable sensors (2006)

Constraints



Bergman's "Minimal Model"

$$\dot{G} = -p_1 G - X(G + G_B) + D(t) \quad (1)$$

$$\dot{I} = -n(I + I_B) + \frac{u(t)}{V_I} \quad (2)$$

$$\dot{X} = -p_2 X + p_3 I \quad (3)$$

$G(t)$ - Deviation of plasma glucose concentration [mmol/L] from its basal value G_B

$I(t)$ - Deviation of free plasma insulin concentration [mU/L] from its basal value I_B

$X(t)$ - Insulin concentration in the remote compartment

Bergman's "Minimal Model"

$$\dot{G} = -p_1 G - X(G + G_B) + D(t) \quad (1)$$

$$\dot{I} = -n(I + I_B) + \frac{u(t)}{V_I} \quad (2)$$

$$\dot{X} = -p_2 X + p_3 I \quad (3)$$

p_j	-	Parameters describing the dynamics of plasma glucose and insulin interaction
$D(t)$	-	Rate of exogenous infusion of glucose
$u(t)$	-	Rate of exogenous infusion of insulin
V_I	-	Insulin distribution volume [L]
n	-	Fractional disappearance rate of insulin [/min]

Bergman's Extended Model (I)

Models a first-order lag of 5 minutes from plasma glucose concentration to subcutaneous glucose.

$$\dot{G}_{sc} = \frac{G - G_{sc}}{5} - R_{ut} \quad (4)$$

$G(t)$	-	Deviation of plasma glucose concentration [mmol/L] from its basal value G_B
$G_{sc}(t)$	-	glucose concentration in subcutaneous/peripherous layer [mmol/L]
R_{ut}	-	tissue rate of utilization [mmol/L/min]

Bergman's Extended Model (II)

Meal glucose disturbance function (very simplified!)

$$\dot{D}_m = -\alpha D_m(t) \tag{5}$$

$D_m(t)$	-	Meal glucose disturbance [mmol/L/min]
α	-	Parameter depending on type of food (typically $0.001 - 0.5$)

Parameters (I)

$$
\begin{aligned}
V_I &= 20 && \text{[L]} \\
n &= \tfrac{5}{54} && \text{[/min]} \\
G_B &= 4.5 && \text{[mmol/L]} \\
I_B &= 15 && \text{[mU/L]}
\end{aligned}
$$

Parameters (II)

For normal persons:

$$\begin{aligned} p_1 &= 0.028 \\ p_2 &= 0.025 \\ p_3 &= 0.000013 \end{aligned}$$

For a diabetic:

$$\begin{aligned} p_1 &= 0 \\ p_2 &= 0.025 \\ p_3 &= 0.000013 \end{aligned}$$

Model Predictive Control

- Difficulty: The actuator works only in one direction (lowering the plasma glucose level)
- Estimate plasma glucose concentration based on subcutaneous glucose measurements (Kalman filter)
- Performance might be improved with a feed-forward connection (input from the user; food/exercise/etc)
- Simulate before implementing/testing
- Verify the model (now possible)
- Large margins on the first tests

Constraints (Lynch et al. (2002))

Input

$0 \leq u \leq 10$ [U/h, where U $= \frac{1}{100}$ mL]

Predicted plasma glucose concentration

$3.5 \leq \hat{y} \leq 10$ [mmol/L]

Input increments

$-1.0 \leq \Delta u \leq 1.0$ [U/h]

Future

— Improve the sensors
— Improve and verify the models
— Measure/observe disturbances (feed-forward)?
— Simulate with MPC
— Test MPC on insulin pumps for real diabetics
— Build sensor into cannula
— Lower price for sensors and insulin pumps

References

Fisher, M. E. *A Semiclosed-Loop Algorithm for the Control of Blood Glucose Levels in Diabetics.* IEEE Trans. Biomed. Eng., **38**:57–61, 1991.

Ibbini, M. S., Masadeh, M. A. and Amer, M. M. B. *A Semiclosed-Loop Optimal Control System for Blood Glucose Levels in Diabetics.* J Med. Eng. & Tech., **28:5**:189–196, 2004.

Lynch, S. M. and Bequette, B. W. *Model Predictive Control of Blood Glucose in Type-I Diabetics Using Subcutaneous Glucose Measurements* Proc. Am. Contr. Conf., pp. 4039–4043, 2002.