From clinical data to the artificial pancreas system

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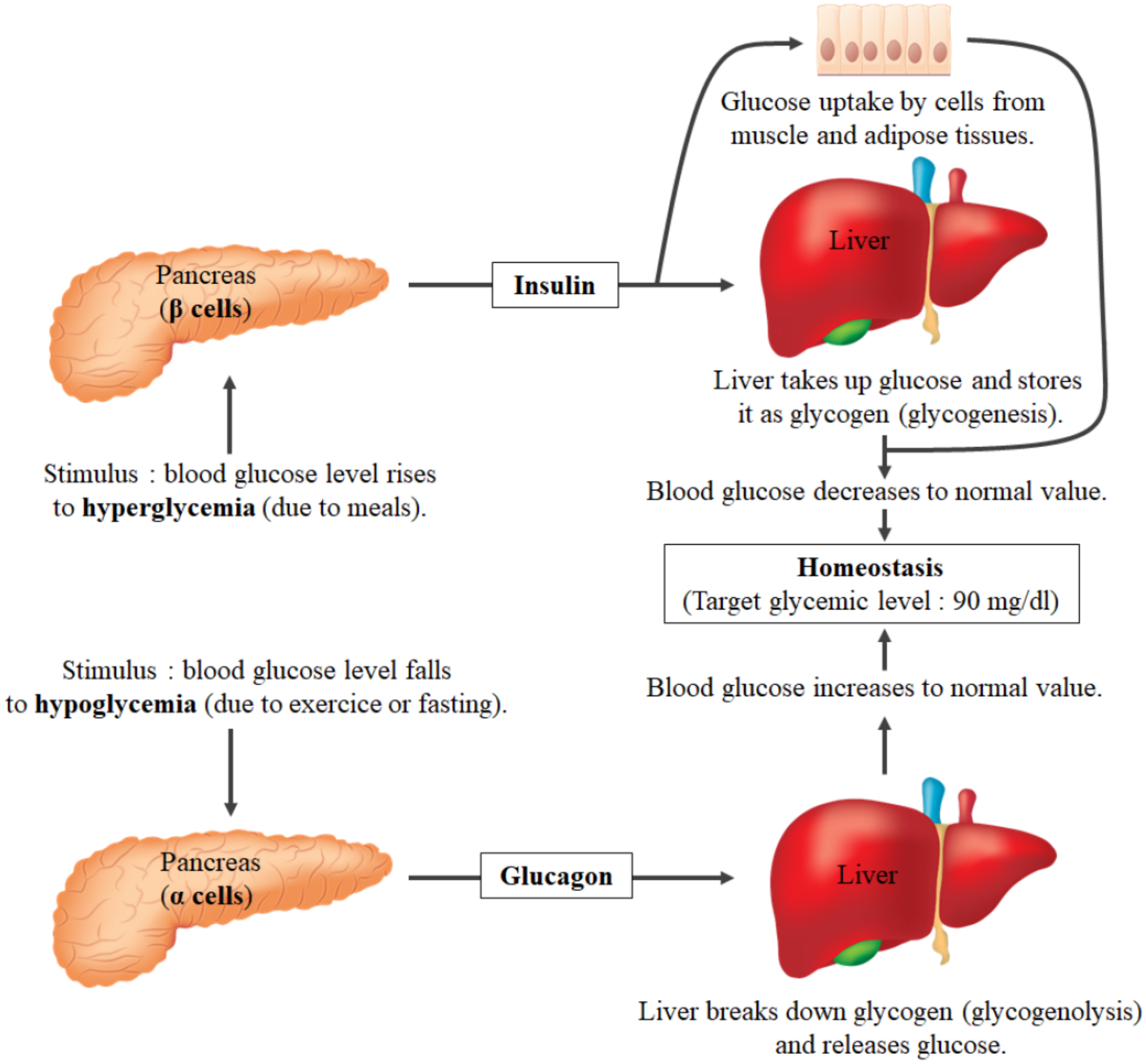
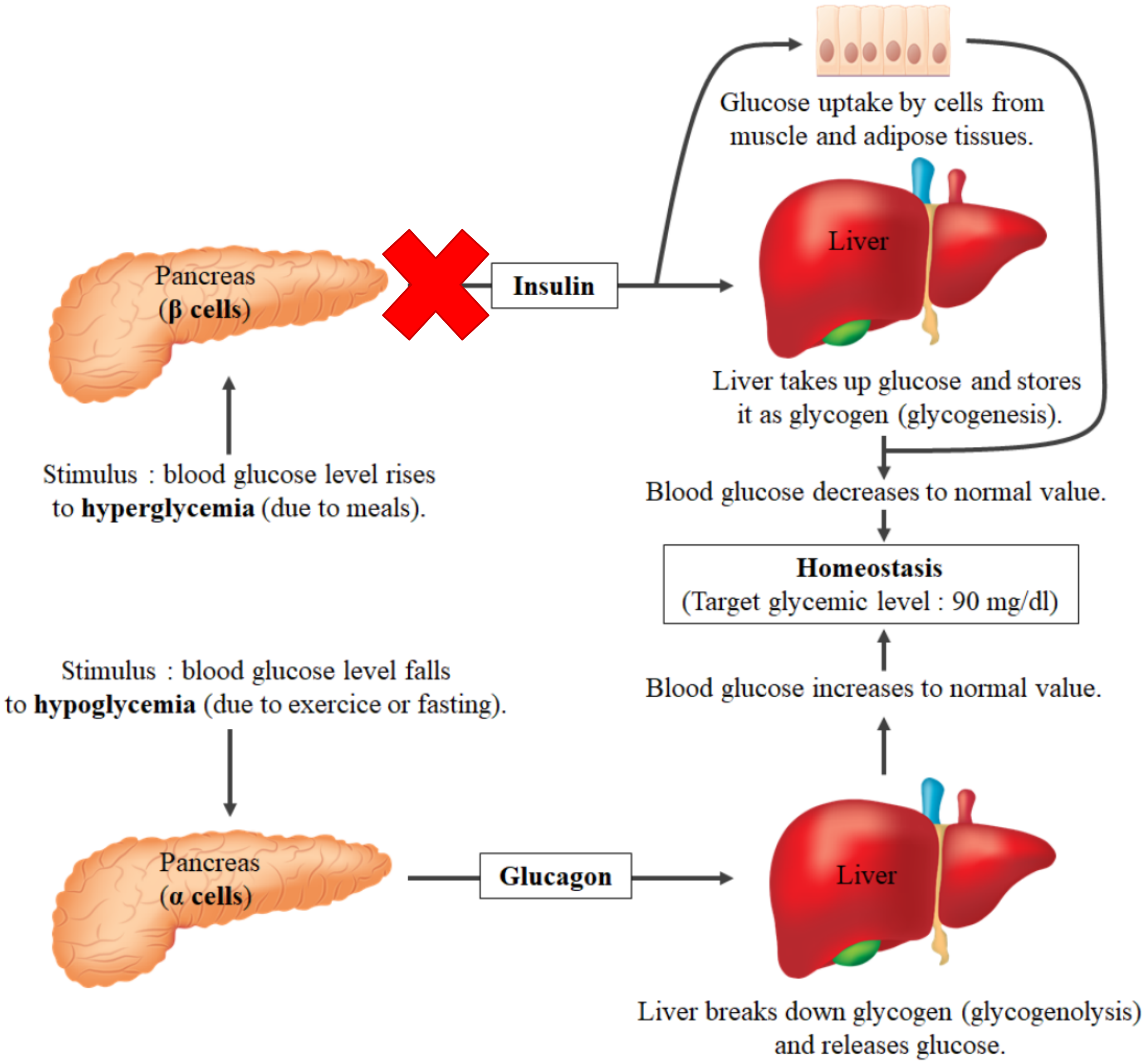
Master Thesis Presentation
August 21, 2020
ECN, Nantes

Glycemic Regulation



Type-1 Diabetes Physiopathology



No endogenous Insulin production

=

Hyperglycaemia

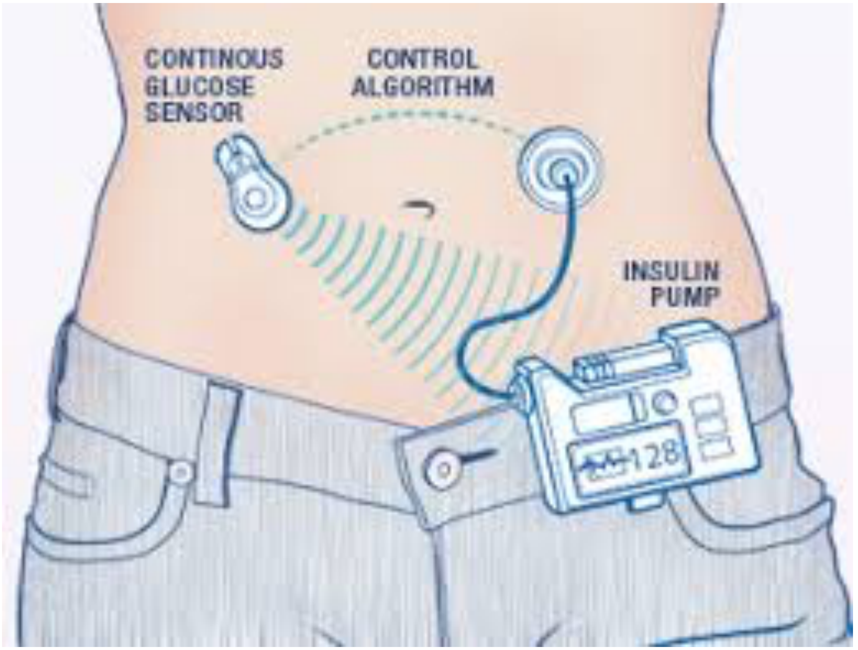
Insulin Injection

What is Type 1 Diabetes ?

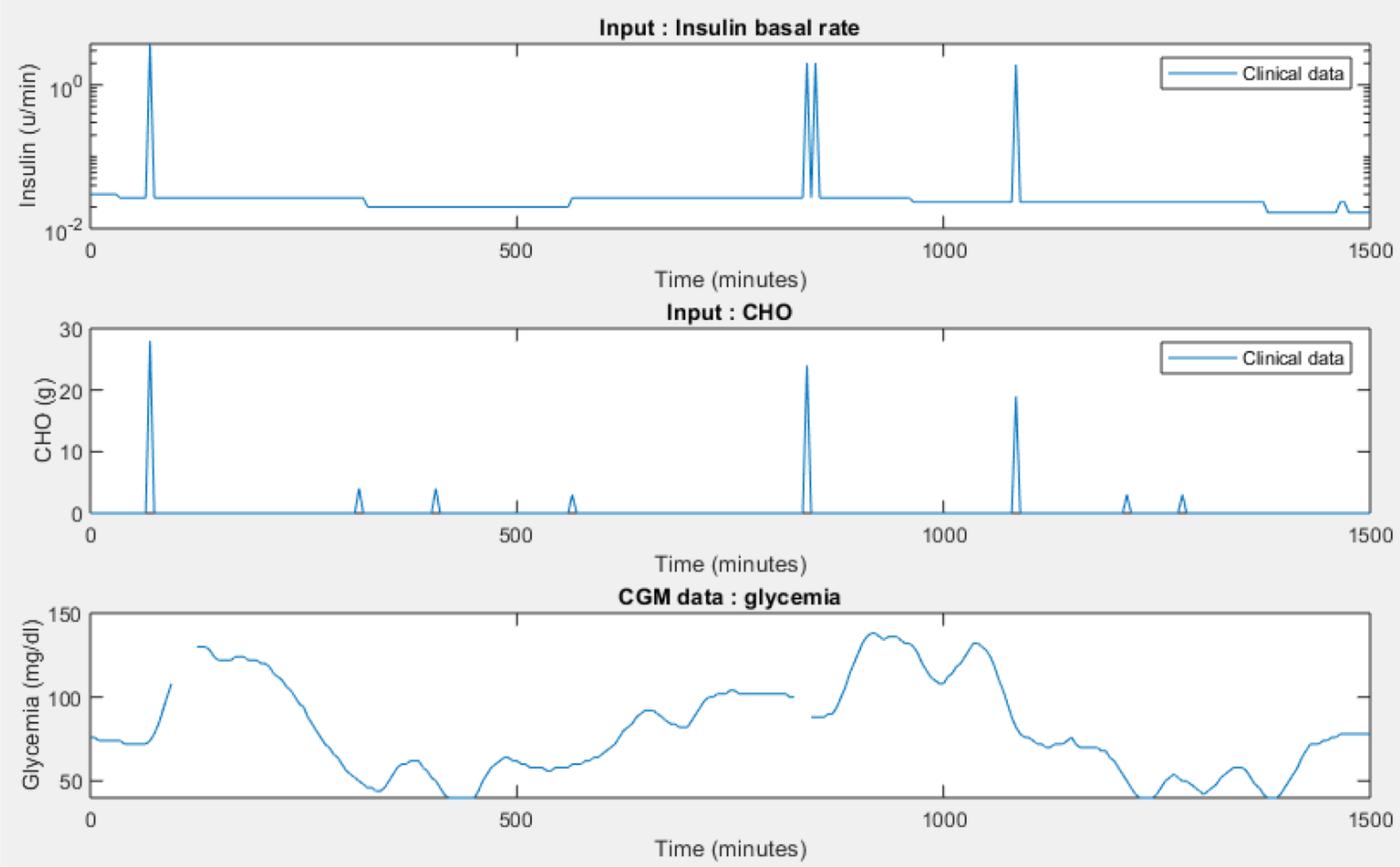
- Auto-immune disease
- Epidemiology
  - 40 millions T1D patients in the world
  - 350000 T1D in France
- Incurable disease
- Treatments :
  - Daily insulin injections
  - Insulin pump
- Treatment management : T1D self-care 78 to 305 minutes/day (Shubrook *et al.* 2018)

The Perfect Solution : Artificial Pancreatic Solution

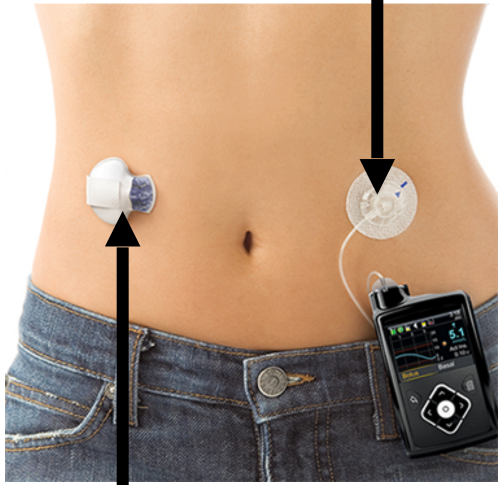
- Uncontrolled chronic blood glucose level lead to severe problems like kidney failure, blindness etc.
- Automatically adjust pump's insulin delivery to keep glucose in safe range.
- Improve and simplify the treatment.
- Reduce manual intervention to inject insulin boluses.



Continuous Glucose Monitoring



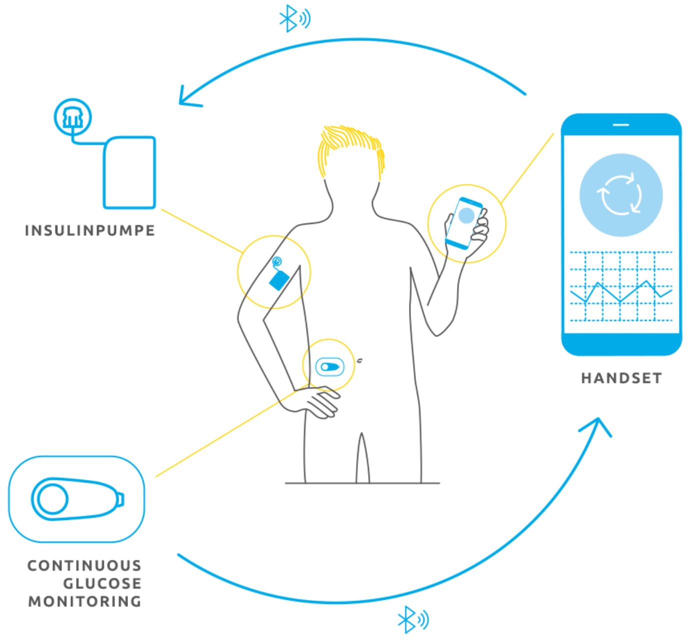
Insulin pump



CGM sensor

Existing Technologies

- Flexible Insulin Therapy (Daily Insulin Injections)
- openAPS
- Android Loopkit
- Diabeloop (MPC)
- Medtronic (PID+MPC)



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Objectives :

- Incorporate FIT parameters in the Control Law
- Available solutions are hybrid and we need fully automated solution
- Account all the disturbances
- State feedback control over entire glucose-insulin dynamics
- Control Law which incorporates change in FIT parameters (e.g. CIR differs with day time)
- Reduced frequency of hypoglycaemia episodes almost to zero
- Increased percentage of time in target range (70-180 mg/dl)

Chapter - 2 : Glucose-Insulin Dynamics Model

Step-I

- 5 states model comprises of glucose-insulin and meal dynamics which quantify the following state variables :

x_1 = Glucose concentration in blood plasma
x_2 = Insulin Concentration in blood plasma
x_3 = Insulin Concentration in Subcutaneous compartment
x_4 = CHO content (Duodenum to plasma)
x_5 = CHO content (Stomach to duodenum)
u_i = Injected Insulin Rate
u_m = CHO from the meal
θ_1 = Glucose consumption by brain (const. value in mg/dl)
θ_2 = Insulin sensitivity
θ_3 = Response time for insulin dynamics
θ_4 = constant for glucose release from CHO digestion
θ_5 = Response time for CHO dynamics

$$\dot{x}_1 = \theta_1 - \theta_2 x_2 + \theta_4 x_4$$

$$\dot{x}_2 = \frac{-1}{\theta_3} x_2 + \frac{1}{\theta_3} x_3$$

$$\dot{x}_3 = \frac{-1}{\theta_3} x_3 + u_i$$

$$\dot{x}_4 = \frac{-1}{\theta_5} x_4 + \frac{1}{\theta_5} x_5$$

$$\dot{x}_5 = \frac{-1}{\theta_5} x_5 + u_m$$

Chapter - 3 : Implementation of Control Strategy

Step : II

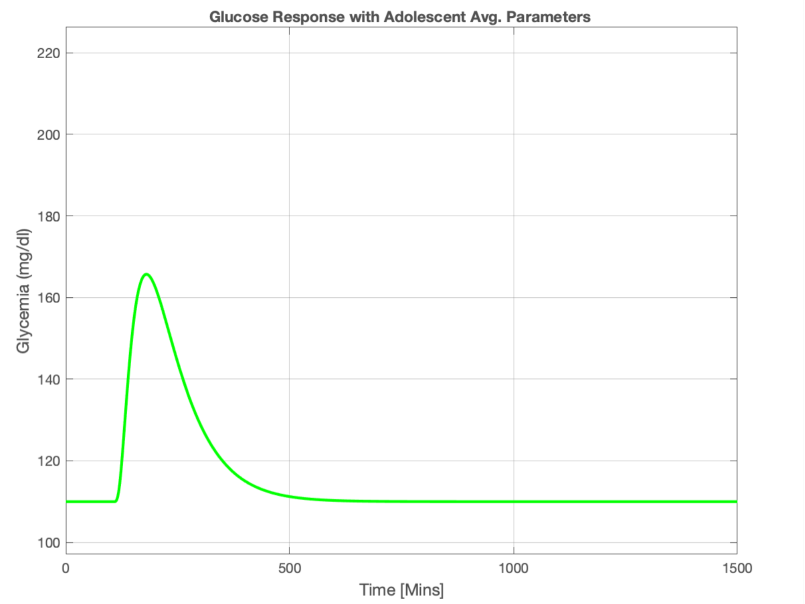
- State Feedback Control Strategy
- Control Output :

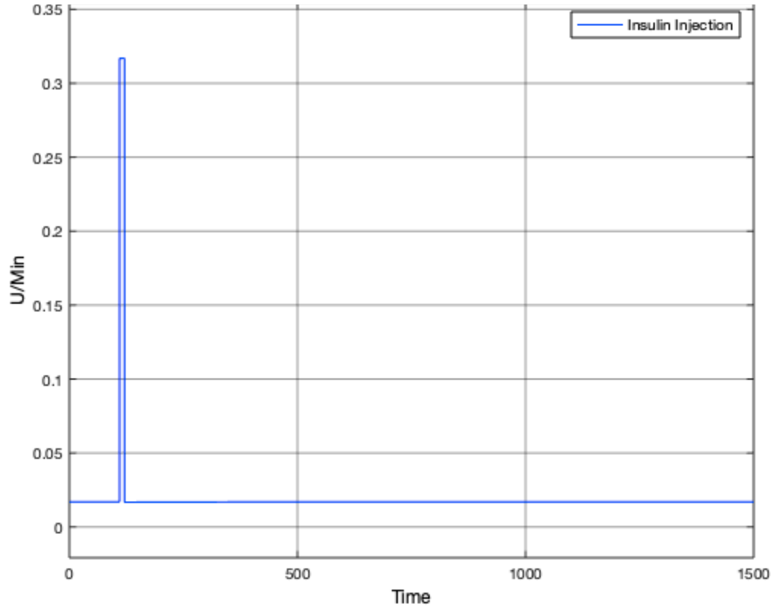
$$k[\frac{1}{\theta_2}(x_1 - x_{ref}) - \frac{1}{\theta_3}\tilde{x}_2 - \frac{1}{\theta_3}\tilde{x}_3 + \frac{\theta_4\theta_5}{\theta_4}x_4 + \frac{\theta_4\theta_5}{\theta_5}x_5$$

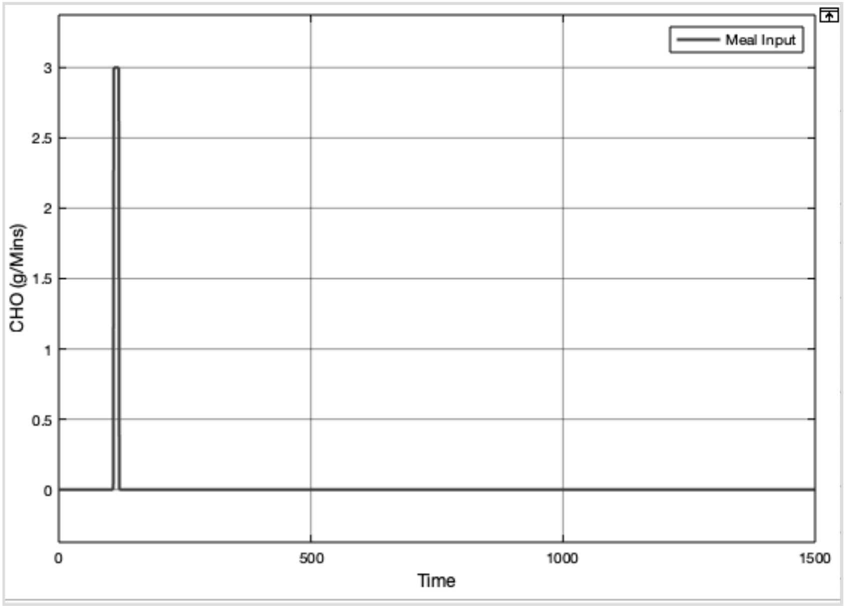
where k is a safety factor and $\tilde{x}_2 = x_2 - \frac{\theta_1}{\theta_2}$ and

$\tilde{x}_3 = x_3 - \frac{\theta_1}{\theta_2}$

State Feedback Control Response for 5 states glucose-insulin model







Meal (3 g/Min carbs) introduced at 110 mins for 10 mins.

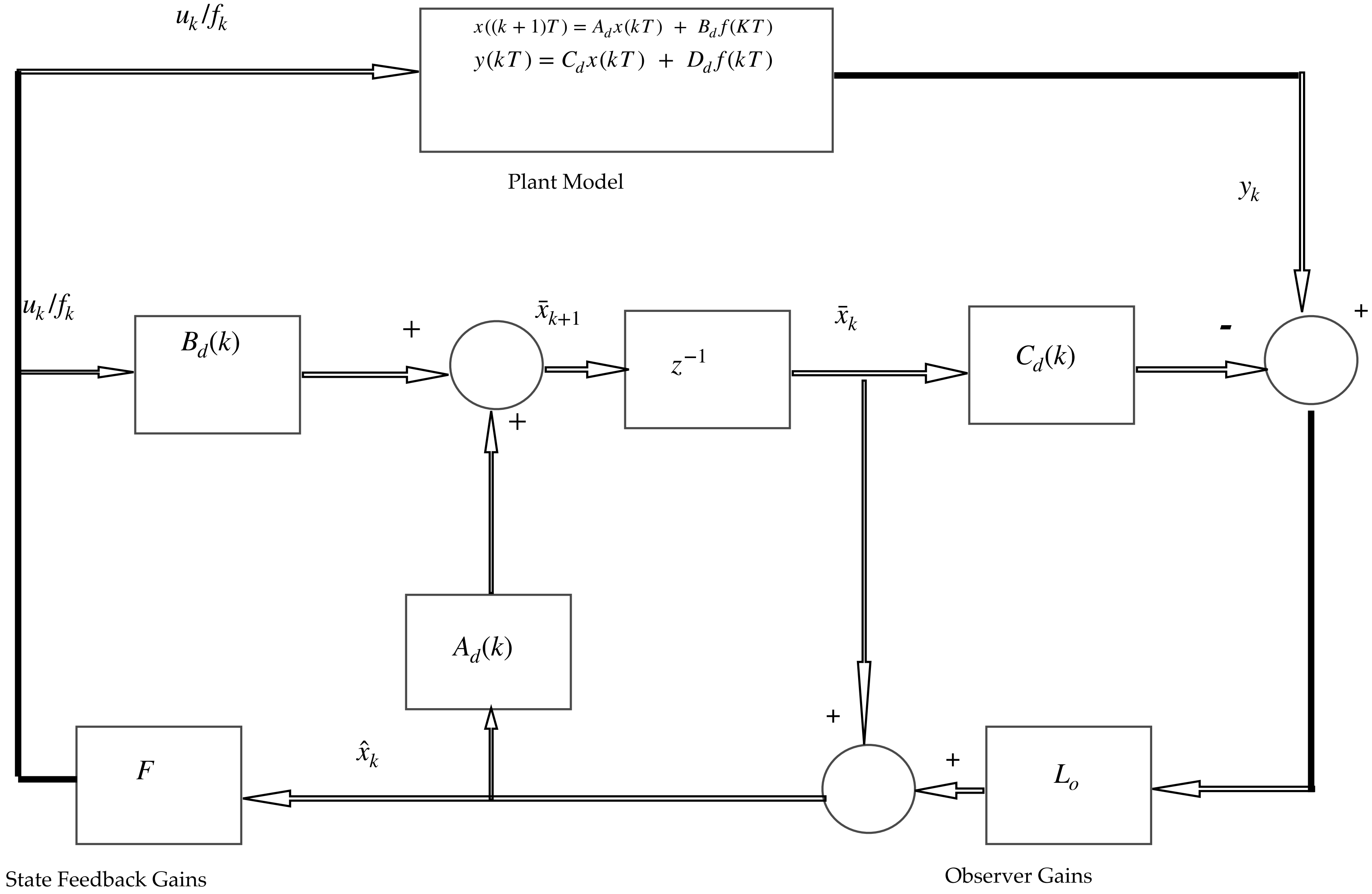
Target blood glucose is 110 mg/dl.

Time Scale is in Mins.

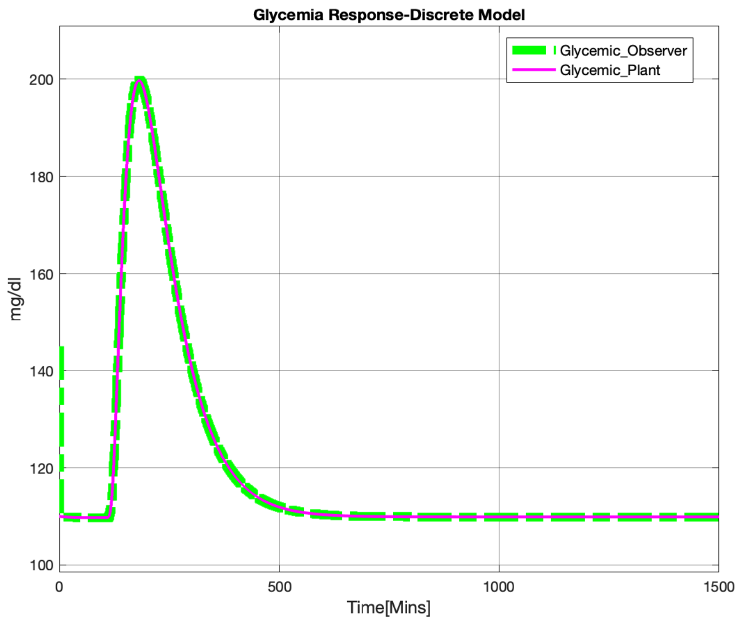
Step III : Implementation of the Luenberger Observer for Hybrid Control

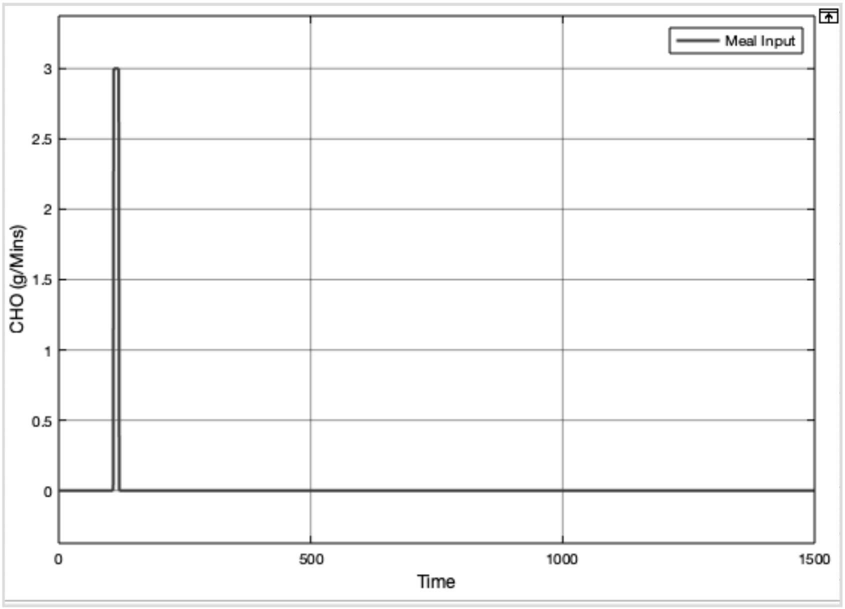
$$\begin{bmatrix} \dot{\hat{x}}_1 \\ \dot{\hat{x}}_2 \\ \dot{\hat{x}}_3 \\ \dot{\hat{x}}_4 \\ \dot{\hat{x}}_5 \end{bmatrix} = \begin{bmatrix} 0 & -\theta_2 & 0 & \theta_4 & 0 \\ 0 & \frac{-1}{\theta_3} & \frac{1}{\theta_3} & 0 & 0 \\ 0 & 0 & \frac{-1}{\theta_3} & 0 & 0 \\ 0 & 0 & 0 & \frac{-1}{\theta_5} & \frac{1}{\theta_5} \\ 0 & 0 & 0 & 0 & \frac{-1}{\theta_5} \end{bmatrix} \begin{bmatrix} \hat{x}_1 \\ \hat{x}_2 \\ \hat{x}_3 \\ \hat{x}_4 \\ \hat{x}_5 \end{bmatrix} + \begin{bmatrix} 0 & 0 \\ 0 & 0 \\ \frac{1}{\theta_3} & 0 \\ 0 & 0 \\ 0 & \frac{1}{\theta_5} \end{bmatrix} \begin{bmatrix} u_i \\ u_m \end{bmatrix} + \begin{bmatrix} \theta_1 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} + \begin{bmatrix} L_1 \\ L_2 \\ L_3 \\ L_4 \\ L_5 \end{bmatrix} (y - \hat{y})$$

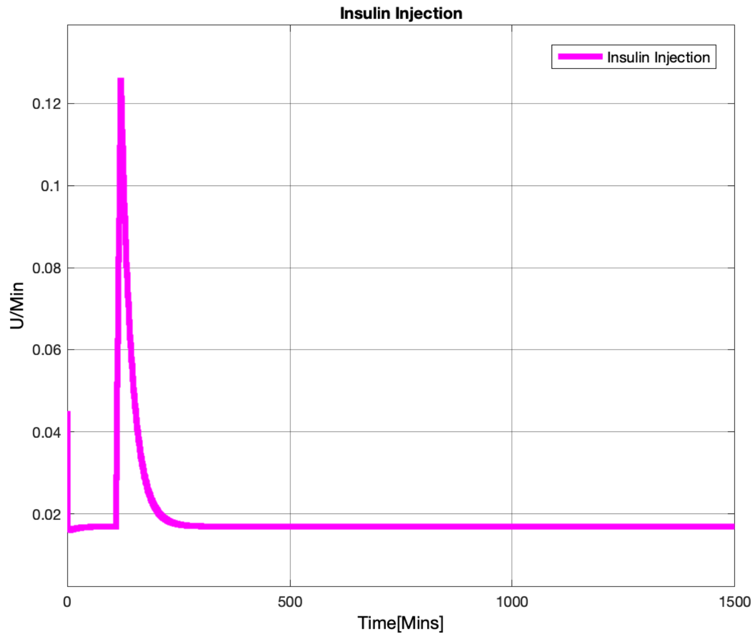
MATLAB implementation :



Responses of the Luenberger Observer with State Feedback Control







Meal (3 g/Min carbs) introduced at 110 mins for 10 mins.

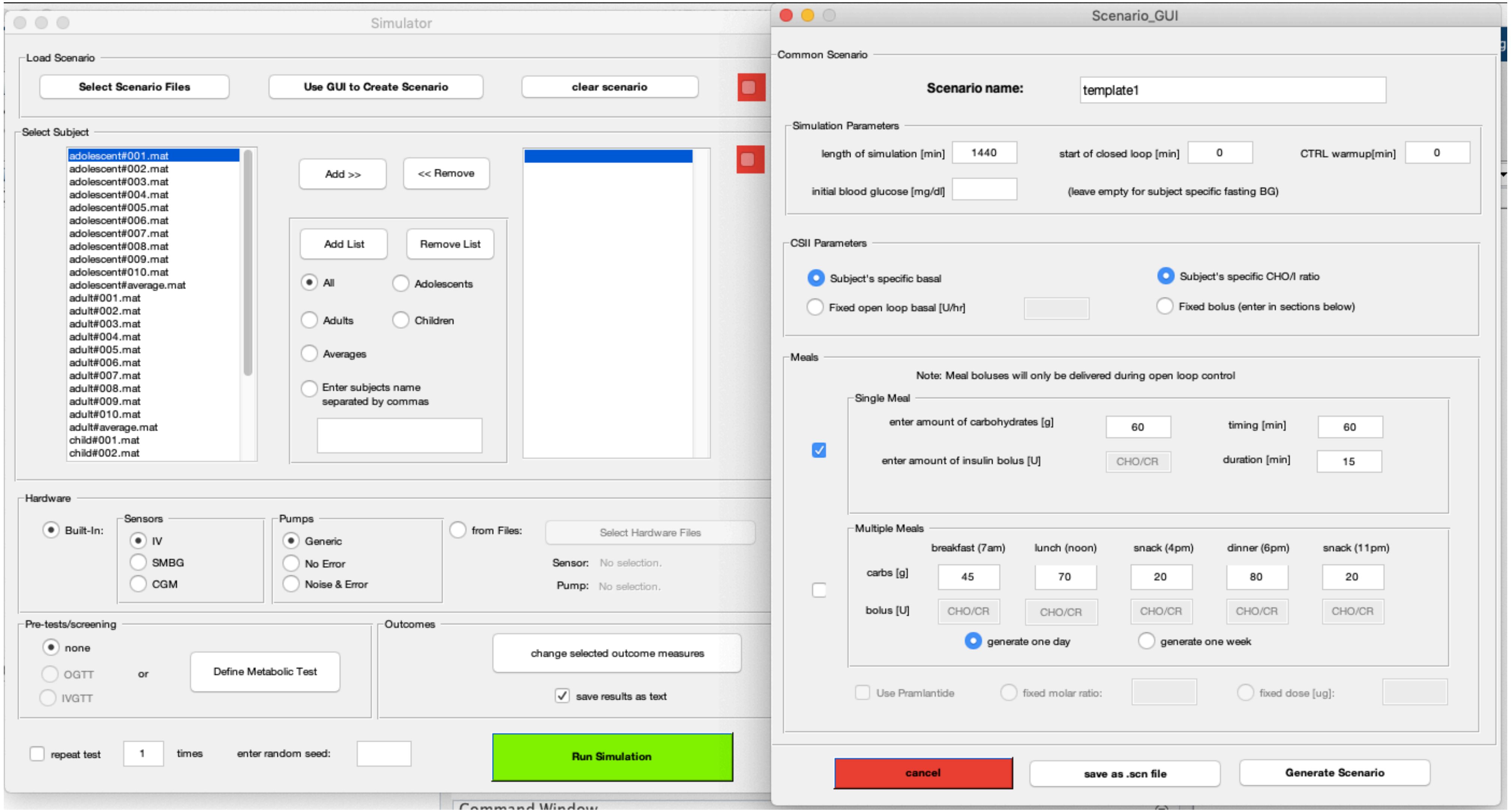
Target blood glucose is 110 mg/dl.

Time Scale is in Mins.

Chapter 5 : UVA Padova Simulator

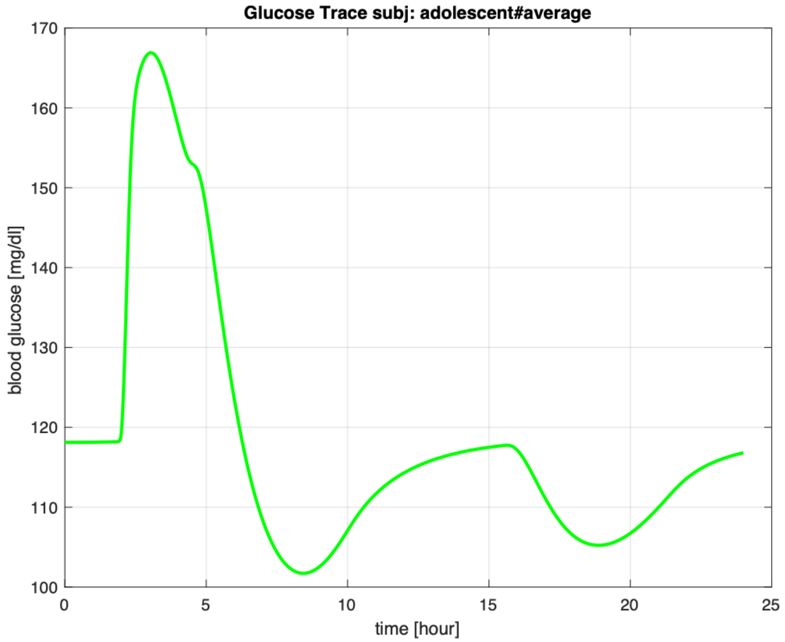
Step-IV

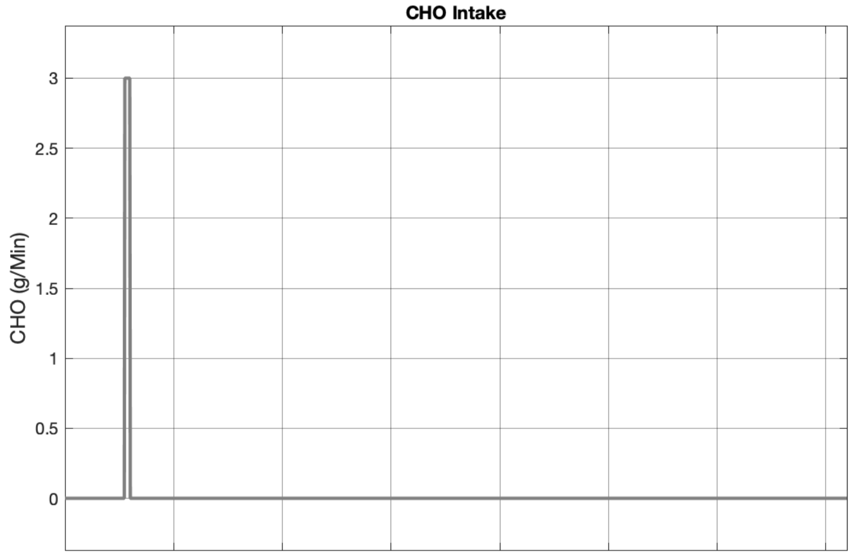
- First software model to be approved by FDA for pre-clinical trials of insulin treatments.
- The first model is introduced in 2008 which included 300 in-silico subjects (100 of each age group -adults, adolescents and children) for emulating model parameter database such as FIT parameters.
- The model is revised in 2013 which not only incorporates the non-linearities of insulin action during hypoglycaemia.
- One can modify the meal parameters, select the subjects and hardware based on the test requirements.

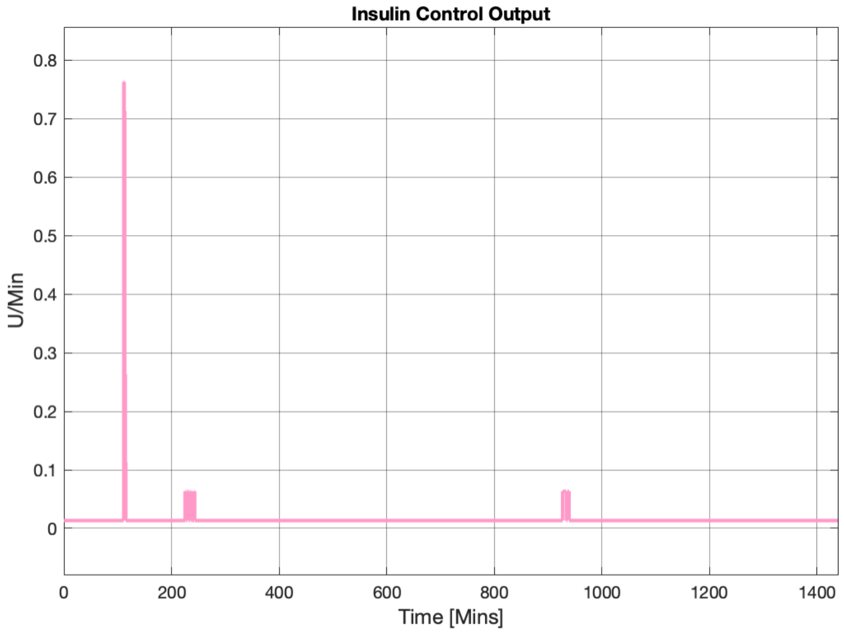


UVA Padova Simulator - Graphics User Interface

State Feedback Control Response on UVA Padova Simulator

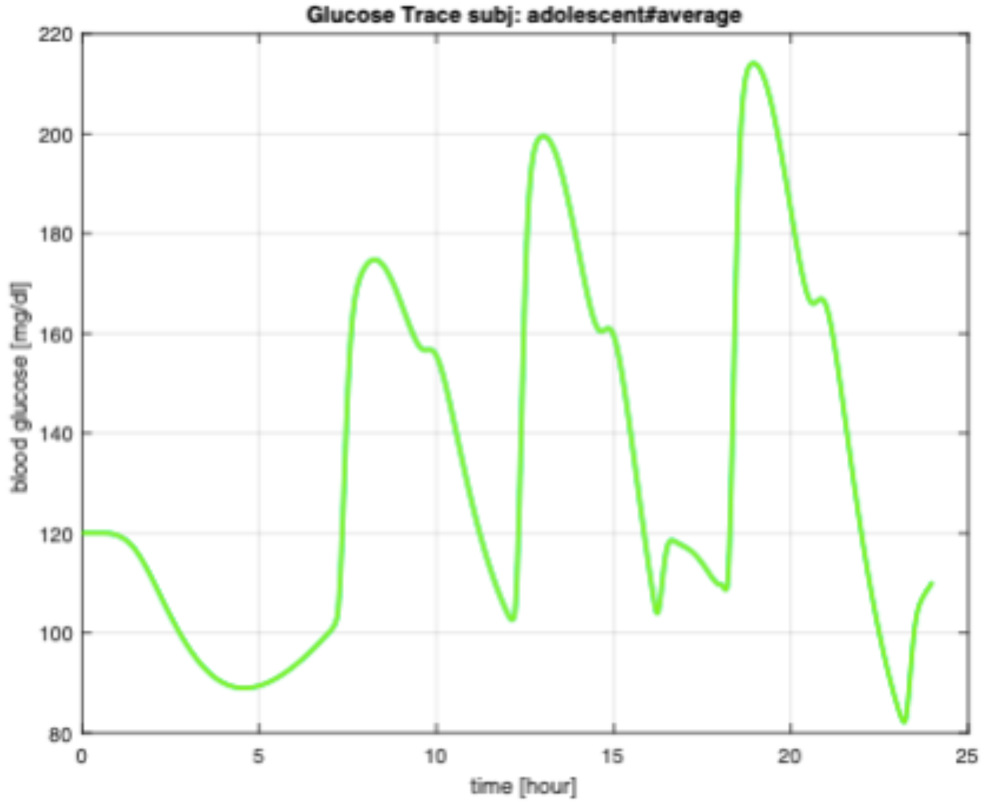


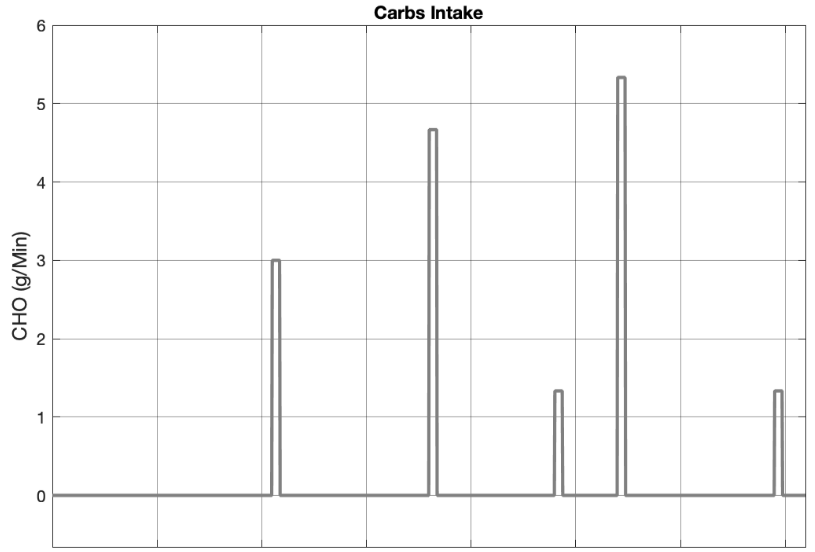


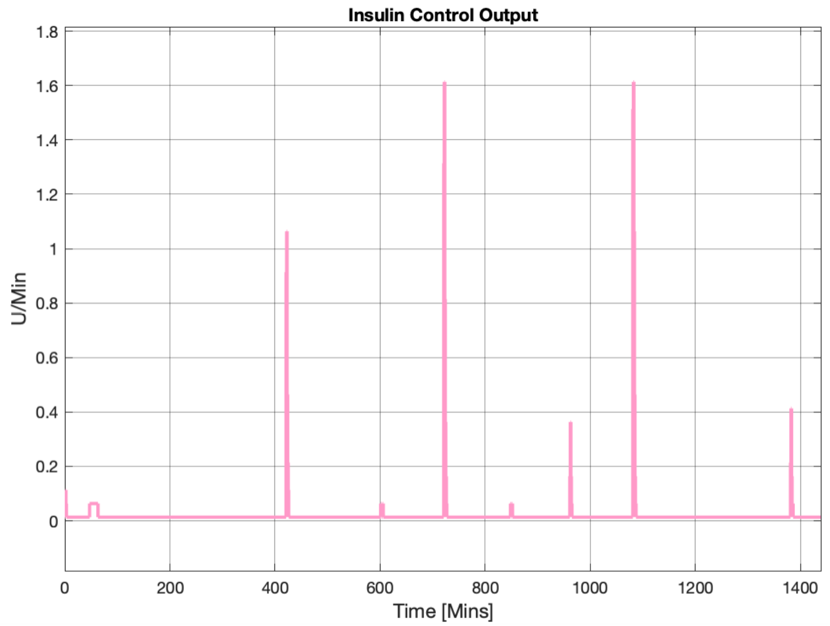


Meal (3 g/Min carbs) introduced at 110 mins for 10 mins.

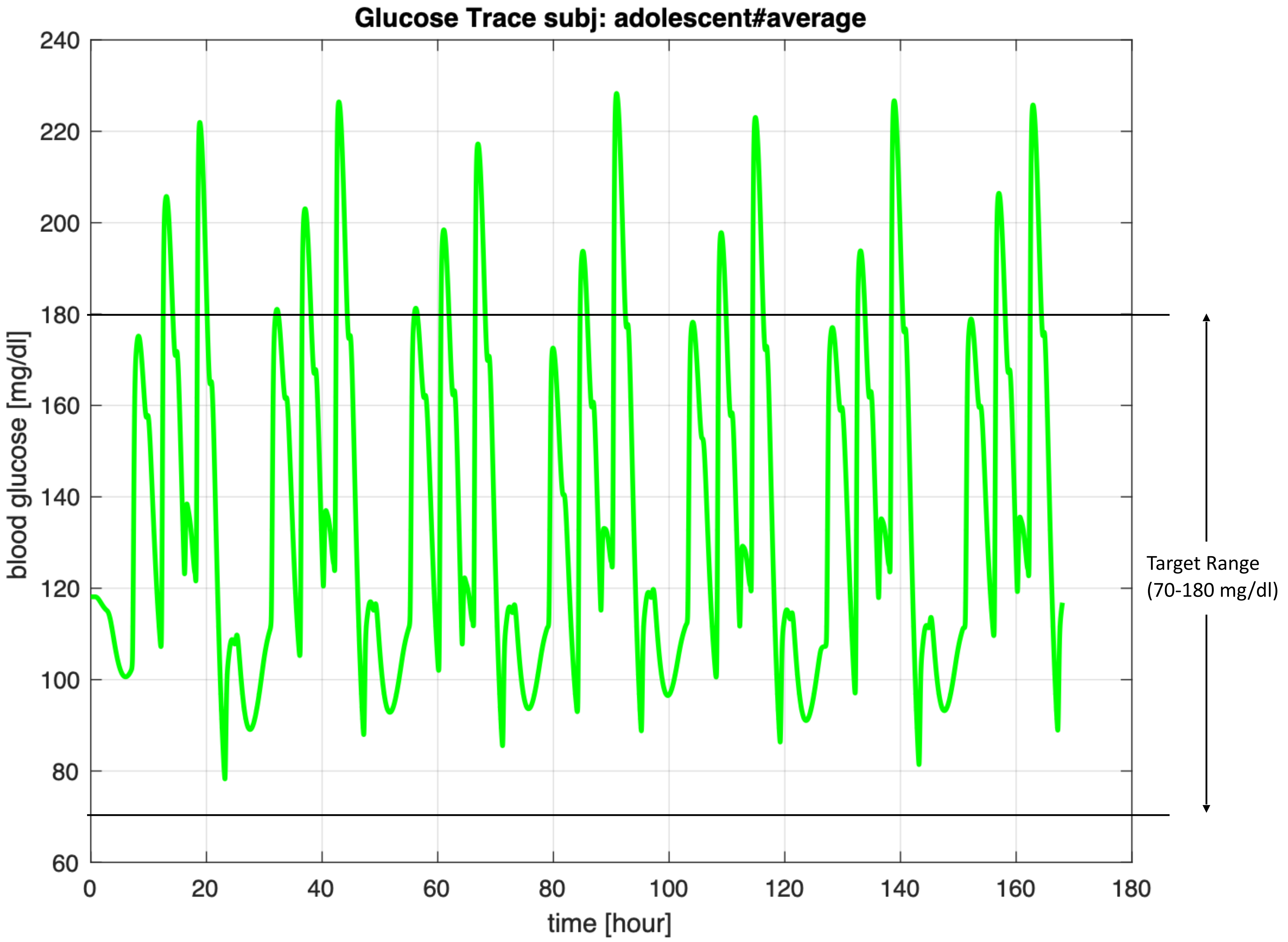
Target blood glucose is subject specific.







UVA Padova Simulator - Adolescent Avg.
State Feedback Control Response (using 5 states glucose-insulin observer)
24 hours scenario with multiple meals introduced at Breakfast(7 am), lunch (noon), snacks (4 pm), dinner (6 pm) and snacks (11 pm).


Glucose Trace subj: adolescent#average
blood glucose [mg/dl]
240
220
200
180
160
140
120
100
80
60
time [hour]
0
20
40
60
80
100
120
140
160
180
Target Range
(70-180 mg/dl)

UVA Padova Results for 1 Day 5 Meals Scenario

Population Group	ID Mean BG	% Time < TGT-low (70 mg/dl)	% Time in target (70-180 mg/dl)	% Time > TGT-high (180 mg/dl)	BG Risk Index
Adolescent	112.04	0.00	100.00	0.00	0.68
Adult	107.40	0.00	100.00	0.00	0.47
Children	124.87	0.00	97.43	2.57	0.73

Medical Time In Range for Clinical Practice :

- Time in Target (70-180 mg/dl) > 60%
- Time in target low (<70 mg/dl) < 5%

Medical Time In Range for Clinical Trial for Hybrid Artificial Pancreas for Adult :

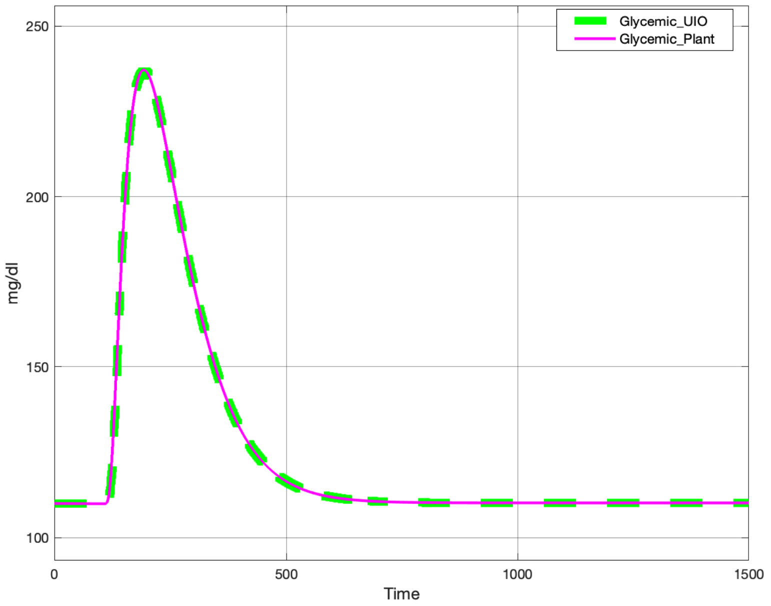
- Time in Target (70-180 mg/dl) > 82%
- Time in target low (<70 mg/dl) < 3%

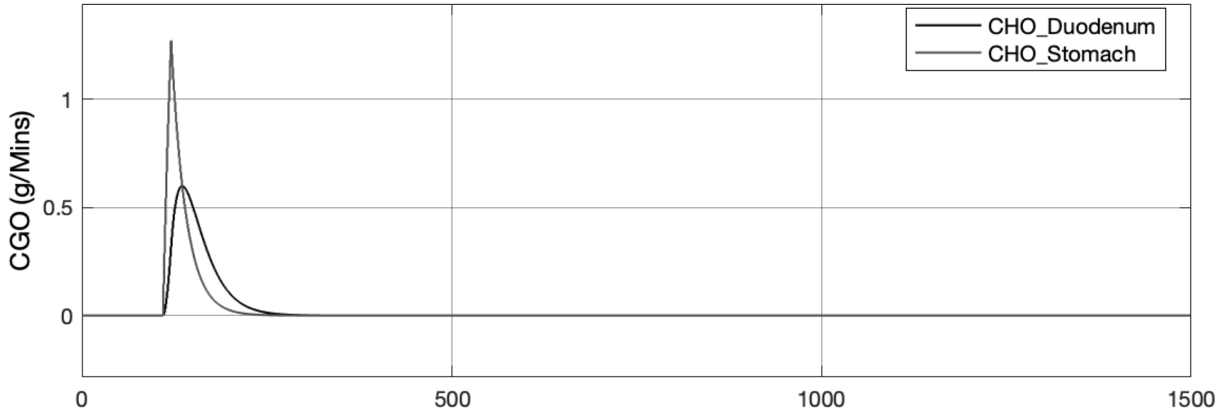
Extended Luenberger Observer with Unknown Input Observer (UIO) :

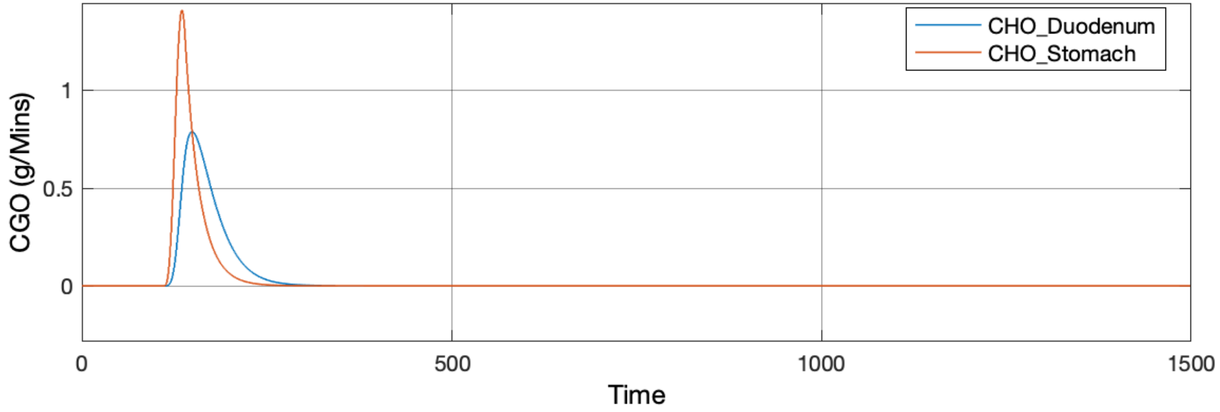
Step-V

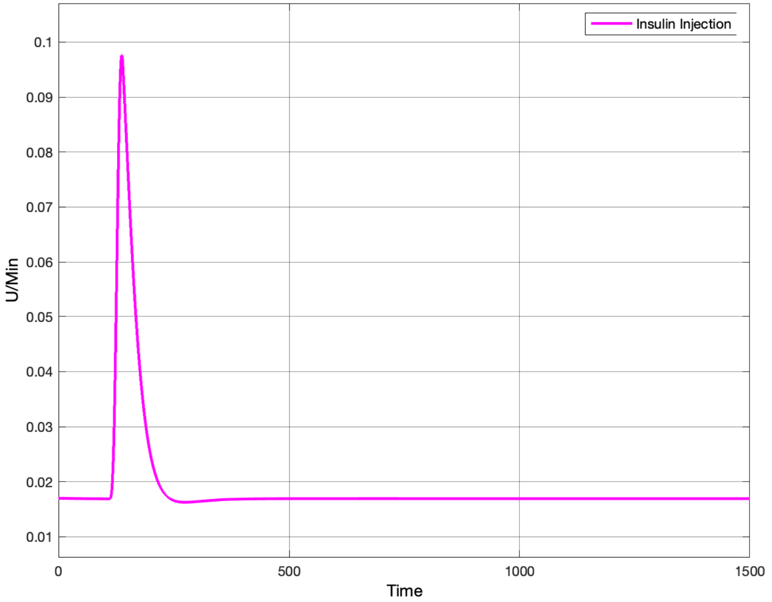
- $\dot{\hat{x}} = A\hat{x} + Bu + L(y - \hat{y}) + G\hat{d}$
- $\hat{d} = \rho K(y - \hat{y})$
- Conditions :
  - rank(CG) = rank(G) = r
  - rank $\begin{bmatrix} A - LC & G \\ C & 0 \end{bmatrix}$ = n+r, n is a rank of A-LC
- Finding Value of K & P:
  - $P(A - LC) + (A - LC)^T P = -Q$ where Q is known and, P & Q are symmetric positive definite matrix
  - $G^T P = KC$
- *Reference : Corless, M., & Tu, J. (1998). State and input estimation for a class of uncertain systems. Automatica, 34, 757–764.*

Responses of the UIO with State Feedback Control









Meal (3 g/Min carbs) introduced at 110 mins for 10 mins.

Target blood glucose is 110 mg/dl.

Time Scale is in Mins.

Step - V : Prototype Development

Concept & Idea

- Better Control Law
- Integration of engineering and medical parameters
- Fully automated device

R&D

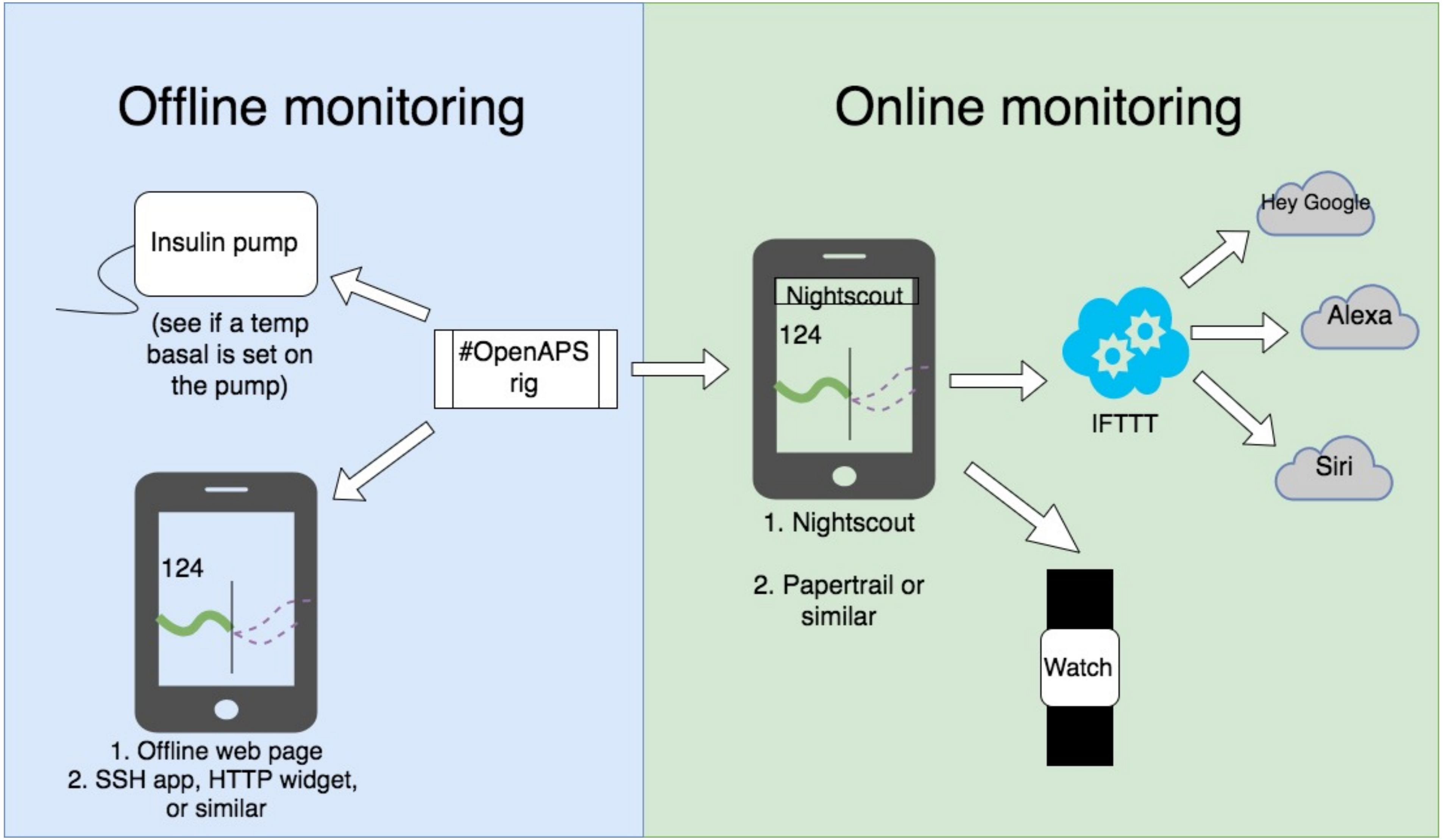
- Glucose - Insulin dynamics model design and development
- Estimator
- State feedback control design

Test & Validation

- Testing and validation on UVA Padova Simulator
- Implementation on MATLAB

APS Technology

- Hardware Selection
- Control algorithm
  - Programming


Offline monitoring
Online monitoring
Insulin pump
(see if a temp basal is set on the pump)
#OpenAPS rig
124
1. Offline web page
2. SSH app, HTTP widget, or similar
Nightscout
124
1. Nightscout
2. Papertrail or similar
IFTTT
Hey Google
Alexa
Siri
Watch

OpenAPS

Diagnosis of OpenAPS

- Automated glucose monitoring system along with database management and analysis over web protocol.
- Open software development - https://github.com/openaps/openaps
- Toolkit comprises of automation program, pump, glucose monitoring system, database (cloud service) and communication devices (including bluetooth, wifi etc.)

Conclusion and Perspectives

- An observer & state feedback control strategy is implemented and tested with FIT parameters on UVA Padova Simulator for Hybrid Control
- Achieved desired results for fully automatic control with unknown estimation on 5 state model as Simulator.
- Prototype Implementation - functional check of control algorithm is complete, full fledged development of state feedback control with UIO and integration with openAPS is in progress.

Thank you for your attention!

LS2N

cnrs

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l'institut du thorax