ICM 2010 Satellite Meeting on Application of
Control Theory and Optimization Techniques in Biomedical Pathways

Optimal Blood Glucose Regulation by Automatic Feedback Control

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Research Interests of Dr. R. Padhi

Theory

- Nonlinear Control
- State Estimation
- Adaptive Control
  - Neuro-Adaptive Design
- Optimal control
  - Adaptive Critic Design
  - MPSP Design

Applications

- **Aerospace Engineering**
  - Guidance and control of aerospace vehicles
  - Integrated guidance and control of vehicles
  - Engine control
  - UAV guidance and control
- **Biomedical Engineering**
  - Parturient Paresis
  - CML (Blood cancer)
  - Infectious diseases
  - Diabetes
- **Mechanical Engineering**
  - Vibration control
  - Temperature control

For further information, please visit www.aero.iisc.ernet.in/padhi

Reference:

Sk. Faruque Ali and Radhakant Padhi: **Optimal Blood Glucose Regulation of Diabetic Patients Using Single Network Adaptive Critics (SNAC),** *Optimal Control Applications and Methods*, In Press (already available online).

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MOTIVATION

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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!

Diabetes Type

- **<u>Type II</u>**

  - Dysfunctional endocrine pancreas which produces little insulin

  - Insulin receptor on the tissue cells respond abnormally to the circulating insulin (“insulin resistance”).

- **<u>Type I</u>**

  - Dysfunctional endocrine pancreas which produces *<u>no insulin</u>*

Blood Glucose Measurement & Control

- Traditional treatment:
  - Intermittent monitoring of blood glucose
  - Administering an appropriate dose of insulin
  - Three-four daily glucose measurements and an equivalent number of insulin injections
- Advanced diabetes research:
  - Improved blood glucose sensors
  - External and implantable insulin pumps (without any allergic reactions).

Note:

The discovery of Insulin at the University of Toronto in 1921-22 was one of the most important milestone in the history of medicine. The team was quickly awarded Nobel Prize in 1923.

Limitations of Traditional Approach

- Mostly relies on the patient's responsibility about diet, exercise and medication (and perhaps meditation too!)

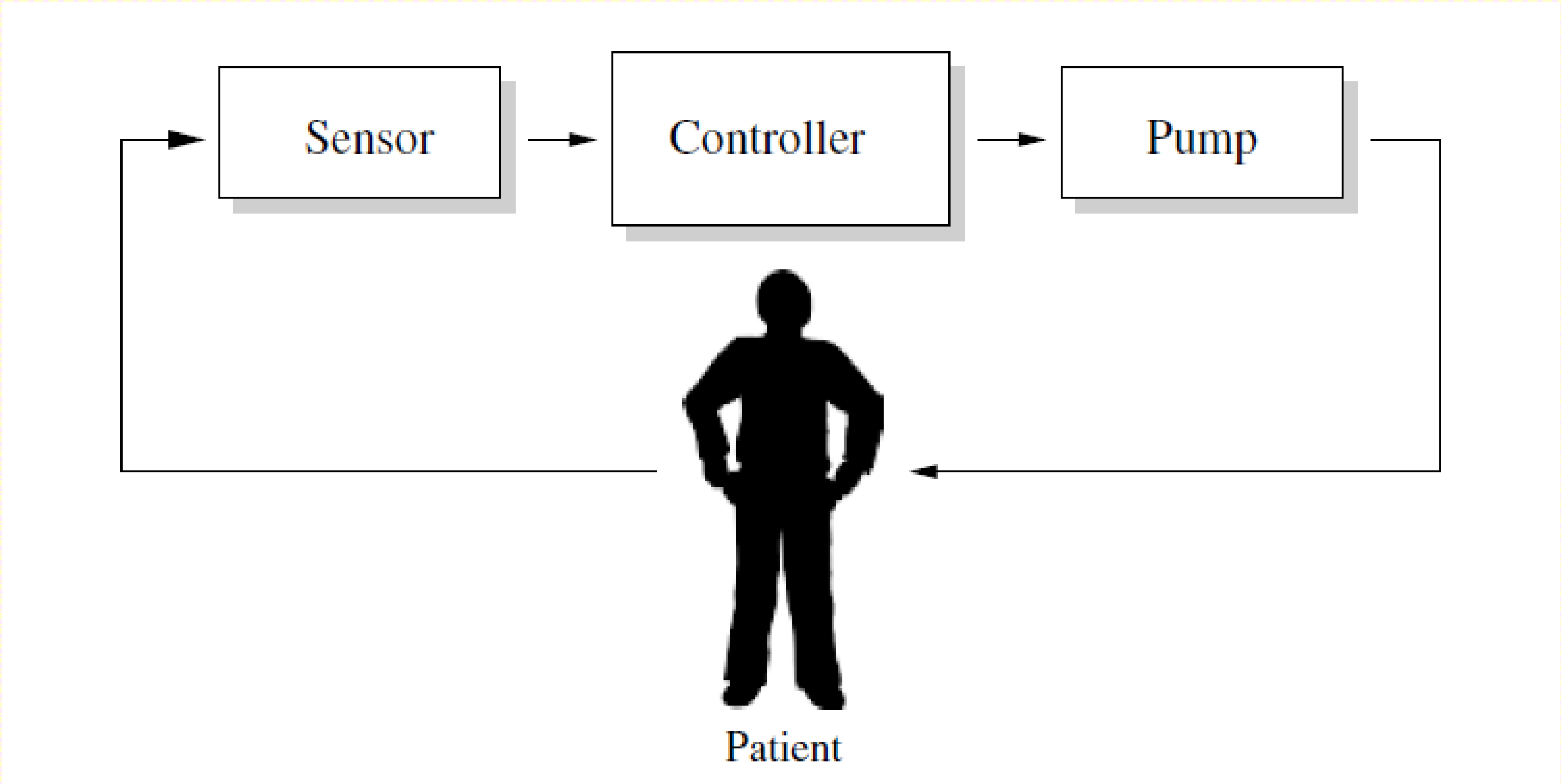
- **Medication is pre-defined (i.e. largely open loop)**

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

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

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

Blood Glucose Measurement Techniques

1. **Invasive** (via direct venous access)

2. **Minimally Invasive** (via subcutaneous glucose level)

   Continuous Glucose Monitoring System

3. **Non-invasive**

   Optical Spectroscopy and Dielectric Spectroscopy

   (Photoacoustic glucose measurement system)

Routes of Insulin Administration

1. Intraperitoneal
2. Subcutaneous
3. Intravenous
4. Intramascular
5. Alternate non-invasive routes: Oral, pulmonary etc.

A BRIEF OVERVIEW OF REAL-TIME OPTIMAL CONTROL DESIGN

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Optimal control formulation: Key components

An optimal control formulation consists of:

- Performance index that needs to be optimized
- Appropriate boundary (initial & final) conditions
  - Hard constraints
  - Soft constraints
- Path constraints
  - System dynamics constraint
  - State constraints
  - Control constraints

A Typical Optimal Control Problem

- Performance Index (to be optimized):

$$J = \varphi\left(t_f, X_f\right) + \int_{t_0}^{t_f} L\left(t, X, U\right) dt$$

- Path Constraint: $\dot{X} = f\left(t, X, U\right)$

- Boundary Conditions: $X\left(0\right) = X_0 : \text{Specified}$

$$t_f : \text{Fixed},\ X\left(t_f\right) : \text{Free}$$

Calculus of Variation Formulation: Necessary Conditions of Optimality

- State Equation $$\dot{X} = \frac{\partial H}{\partial \lambda} = f\left(t, X, U\right)$$
- Costate Equation $$\dot{\lambda} = -\left(\frac{\partial H}{\partial X}\right) \qquad \boxed{H \triangleq \left(L + \lambda^T f\right)}$$
- Optimal Control Equation $$\frac{\partial H}{\partial U} = 0$$
- Boundary Condition $$\lambda_f = \frac{\partial \varphi}{\partial X_f} \qquad X\left(t_0\right) = X_0 : Fixed$$

Summary of Variational Formulation

- State, Costate & Stationary equations
- Split Boundary Conditions: leads to Two-Point-Boundary-Value Problem (TPBVP)
- <u>Computationally very inefficient and results in a open-loop control design: Not possible to implement in real-time applications</u>
- Mainly been limited to trajectory optimization problems, where offline solutions are adequate

Dynamic Programming Formulation

- Define optimized cost function *V* as:

$$V(t, X) = \int_{t}^{t_f} L(t, X, U)\, dt$$

- Then *V*(*t*) must satisfy:

HJB equation

$$\frac{\partial V}{\partial t} + H_{opt} = 0$$

where,

$$H_{opt} = \underset{U \in \Omega}{Min}(H) = \underset{U \in \Omega}{Min}\left(L + \lambda^T f\right)$$

and $\lambda \triangleq \dfrac{\partial V(t, X)}{\partial X}$

Summary of Dynamic Programming Formulation

- Leads to Hamilton-Jacobi-Bellman (HJB) equation, which is a multi-dimensional coupled nonlinear partial differential equation.
- ***In most real-life problems, it is impossible to solve the HJB equation in closed form!***
- Attempts for numerical solutions get trapped in ***"Curse of Dimensionality"*** issue, i.e. they demand huge (infeasible) computations.
- Dynamic programming approach is also <u>not possible to implement in real-time applications</u>.

Real-time Optimal Control:
(Phenomenal development over last two decades)

- **Question:** Can the computational difficulty be avoided, so that optimal control design can be useful for real-time applications?
- **Answer:** ***Yes!***
  - Linear Quadratic Regulator (LQR) problems (classical)
  - Nonlinear quadratic regulator for control affine systems
    - SDRE Method
    - $\theta - D$ Method

    Infinite time problems
  - Pseudo-spectral methods
  - Model Predictive Static Programming (MPSP)
  - **Adaptive-Critic methods** (neural network based)

MATHEMATICAL MODEL FOR BLOOD GLUCOSE REGULATION

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Blood Glucose Regulation: Mathematical Model

Minimal Model for Insulin-Glucose Regulation

Glucose dynamics

$$\dot{G}(t) = -p_1[G(t) - G_b] - Z(t)G(t) + D(t)$$

$$\dot{Z}(t) = -p_2 Z(t) + p_3[I(t) - I_b]$$

Insulin kinetics

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

Meal disturbance

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

Model Variables and Units

Variable	Meaning	Unit
$G(t)$	the blood glucose concentration at time t (min)	mg/dl
$I(t)$	blood insulin concentration at time t (min)	$\mu U/ml$
$Z(t)$	represents insulin-excitable tissue glucose uptake activity	min^{-1}
$D(t)$	exogenous glucose infusion rate after meal	mg/dl/min
G_b	basal glucose level	mg/dl
I_b	basal insulin level	$\mu U/ml$
γ	the rate of pancreatic release of insulin after bolus	$\mu U/ml/(mg/dl)/min$
h	the pancreatic target glycemia [3]	mg/dl
n	the time constant for insulin disappearance	min^{-1}
$u(t)$	insulin injection rate (the control variable)	$\mu U/ml/min$
"U" indicates insulin strength. For example, U-100 reflects the number (100) of active insulin units in each ml of liquid.		

Blood Glucose control: State Space form

Nonlinear State Space form:

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

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

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: $\begin{bmatrix} x_{1o} & x_{2o} & x_{3o} & x_{4o} \end{bmatrix}^T \triangleq \begin{bmatrix} G_b & 0 & I_b & 0 \end{bmatrix}^T$

Deviation Dynamics: Normalized Deviation Dyn:

$$\begin{Bmatrix} \dot{x}_{1d} \\ \dot{x}_{2d} \\ \dot{x}_{3d} \\ \dot{x}_{4d} \end{Bmatrix} = \begin{Bmatrix} -p_1 x_{1d} - (x_{1d} + G_b) x_{2d} + x_{4d} \\ -p_2 x_{2d} + p_3 x_{3d} \\ -n x_{3d} + u(t) \\ -B x_{4d} \end{Bmatrix}$$

$$\begin{Bmatrix} \dot{\bar{x}}_1 \\ \dot{\bar{x}}_2 \\ \dot{\bar{x}}_3 \\ \dot{\bar{x}}_4 \end{Bmatrix} = \begin{Bmatrix} -p_1 \bar{x}_1 - \left(\bar{x}_1 + G_b / x_{1n}\right) \bar{x}_2 x_{2n} + \bar{x}_4 x_{4n} / x_{1n} \\ -p_2 \bar{x}_2 + p_3 \bar{x}_3 x_{3n} / x_{2n} \\ -n \bar{x}_3 + \bar{u}(t) \\ -B \bar{x}_4 \end{Bmatrix}$$

$[x_{1_n},\ x_{2_n},\ x_{3_n},\ x_{4_n}]^T$ are taken as $[150,\ 0.01,\ 100,\ 10]^T$

OPTIMAL BLOOD GLUCOSE REGULATION USING SINGLE NETWORK ADAPTIVE CRITICS

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Why Adaptive Critics…??

- Adaptive Critic (AC)
  - Avoids the “curse of dimensionality” issue and has feasible computational load
  - Gives a state feedback solution
  - Can be implemented online

- Single Network Adaptive Critic (SNAC)
  - Retains all good features of AC
  - Eliminates ‘Action Networks’ and hence computationally much simpler than AC
  - Leads to a significant amount of computational savings

Blood Glucose control: Discretized states

Discretized States $\begin{bmatrix} x_1 & x_2 & x_3 & x_4 \end{bmatrix}^T \triangleq \begin{bmatrix} \overline{x}_1 & \overline{x}_2 & \overline{x}_3 & \overline{x}_4 \end{bmatrix}^T$

$$X_{k+1} = X_k + \Delta t\, F_k(X_k, u_k)$$

Discretized Output

$$y_k = [1\ 0\ 0\ 0]\, X_k$$

Discretized Cost Function

$$J_k = \frac{1}{2}\sum_{k=1}^{\infty}\left[y_k^T Q_d y_k + u_k R_d u_k \right]$$

$$Q_d = Q\Delta t \geq 0, \qquad R_d = R\Delta t > 0$$

Necessary Conditions of Optimality

- State Equation

$$X_{k+1} = X_k + \Delta t\, F_k(X_k, u_k)$$

- Costate Equation

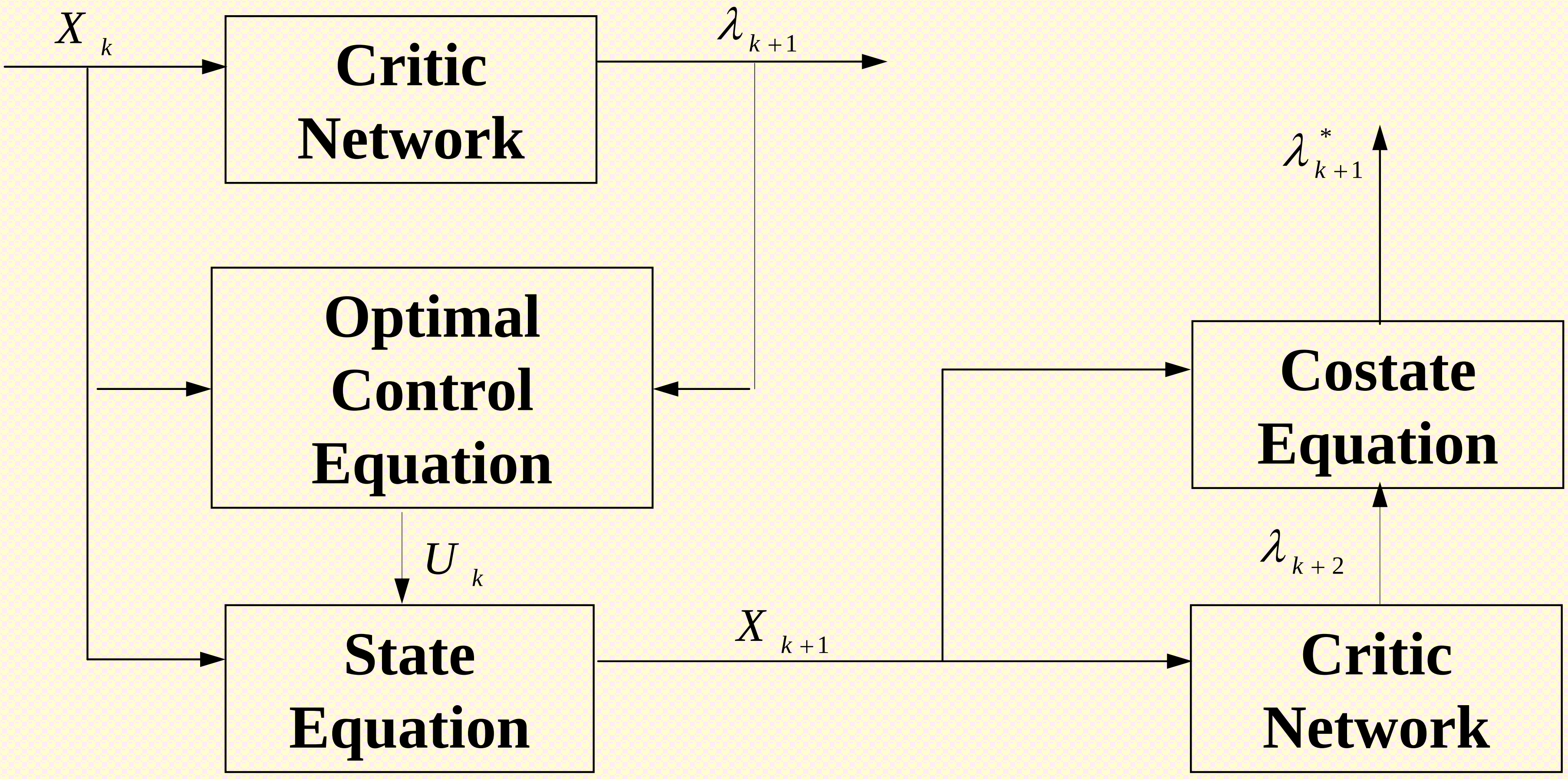
$$\lambda_k = \lambda_{k+1} + \Delta t \left[C^T Q C + \left(\frac{\partial F^k}{\partial X_k} \right)^T \right] \qquad C = [1\ 0\ 0\ 0]$$

- Optimal Control Equation

$$u_k = -R^{-1} \begin{bmatrix} 0 & 0 & 1 & 0 \end{bmatrix} \lambda_{k+1}$$

Single Network Adaptive Critic

Assumption: Critic Network is optimal at t_{k+1}



SNAC: Pre-training

- Linearize the Problem and Obtain LQR Solution

$\lambda_k = S_d X_k$	$U_k = -K_d X_k$

- Obtain the relationship between X_k and λ_{k+1}

$$
\begin{aligned}
\lambda_{k+1} &= S_d X_{k+1} = S_d \left(A_d X_k + B_d U_k \right) \\
&= S_d \left(A_d - B_d K_d \right) X_k \\
&= \tilde{S}_d X_k
\end{aligned}
$$

- Train the networks

Parameter Values and Range of State Variables

Parameter Values

Parameter	Value	Parameter	Value
p_1	0	p_2	0.0142
p_3	1.54×10^{-5}	B	0.05
n	0.2814	γ	0

Range of State Variables

state	Value	state	Value
$x_{1\ max}$	$220/x_{1_n}$	$x_{1\ min}$	$-80/x_{1_n}$
$x_{2\ max}$	$0.03/x_{2_n}$	$x_{2\ min}$	$-0.001/x_{2_n}$
$x_{3\ max}$	$200/x_{3_n}$	$x_{3\ min}$	$-10/x_{3_n}$
$x_{4\ max}$	$20/x_{4_n}$	$x_{4\ min}$	$0/x_{4_n}$

Design Parameters

G_b	$70\ {}^{mg}\!/_{dl}$
I_b	$7\ {}^{\mu U}\!/_{ml}$
Q	5×150^2
R	400×100^2
Δt	$10\,s$

These values are used for both Case-I and Case-II

SIMULATION RESULTS:

CASE – I: STUDIES WITH NOMINAL MODEL

$$\boxed{X_k^{inp} = X_k}$$

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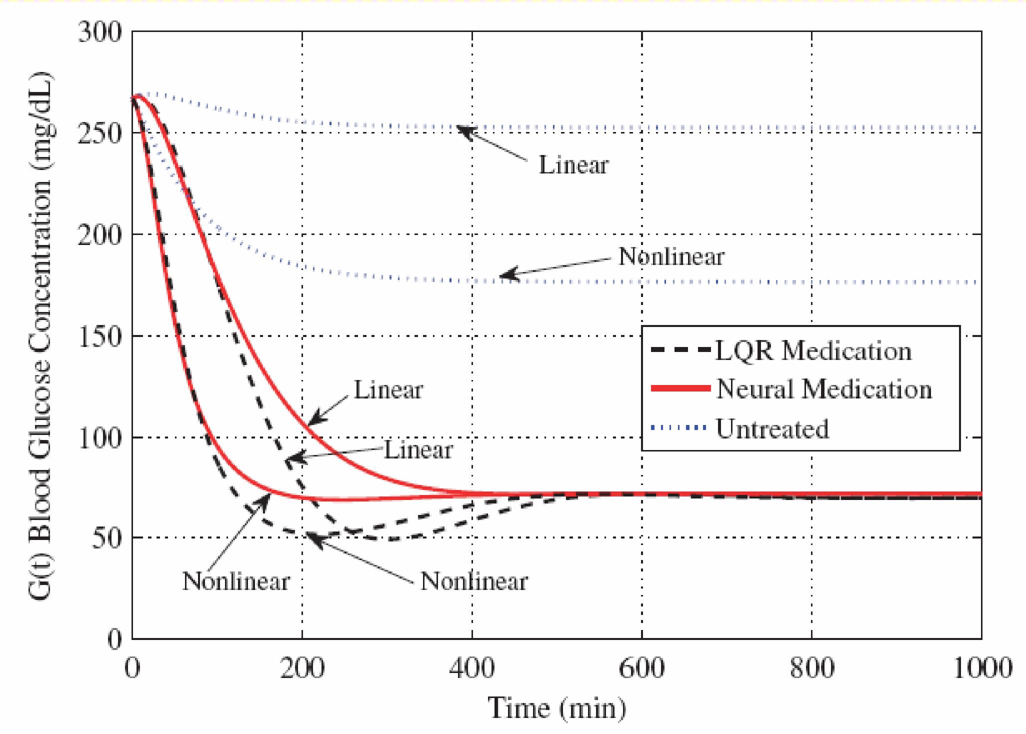
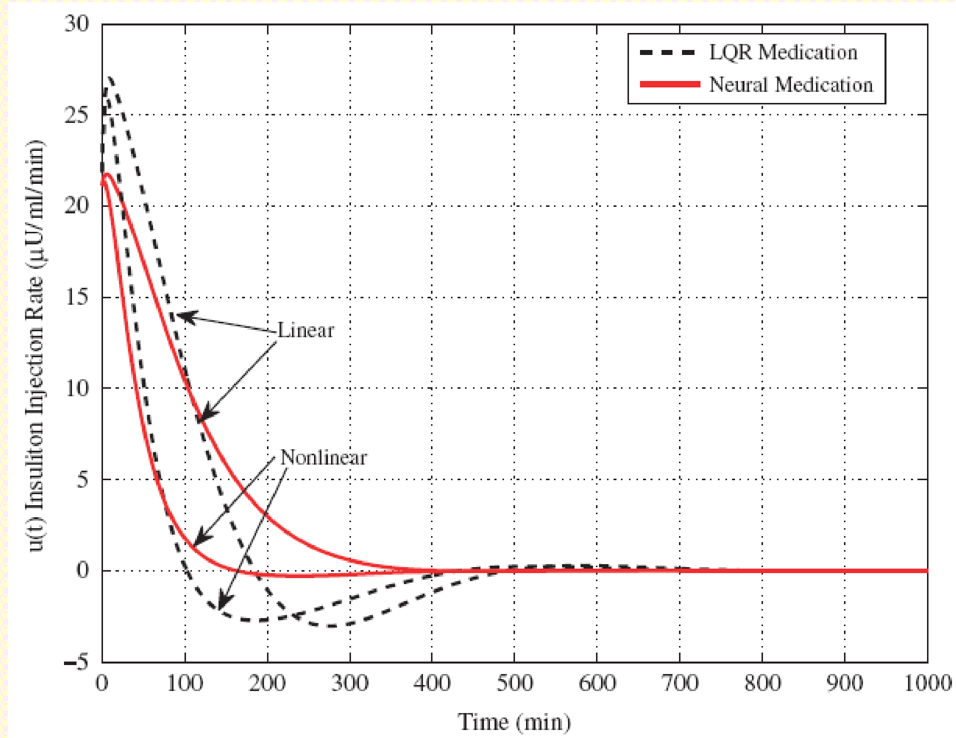
Results: State and Control Trajectories



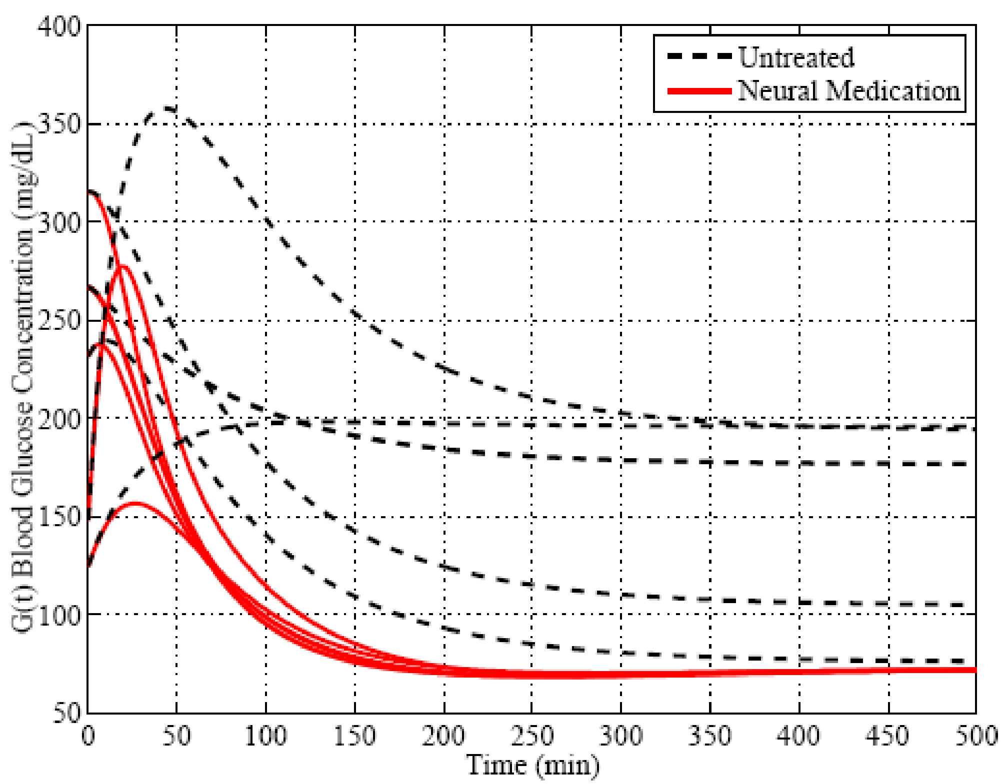


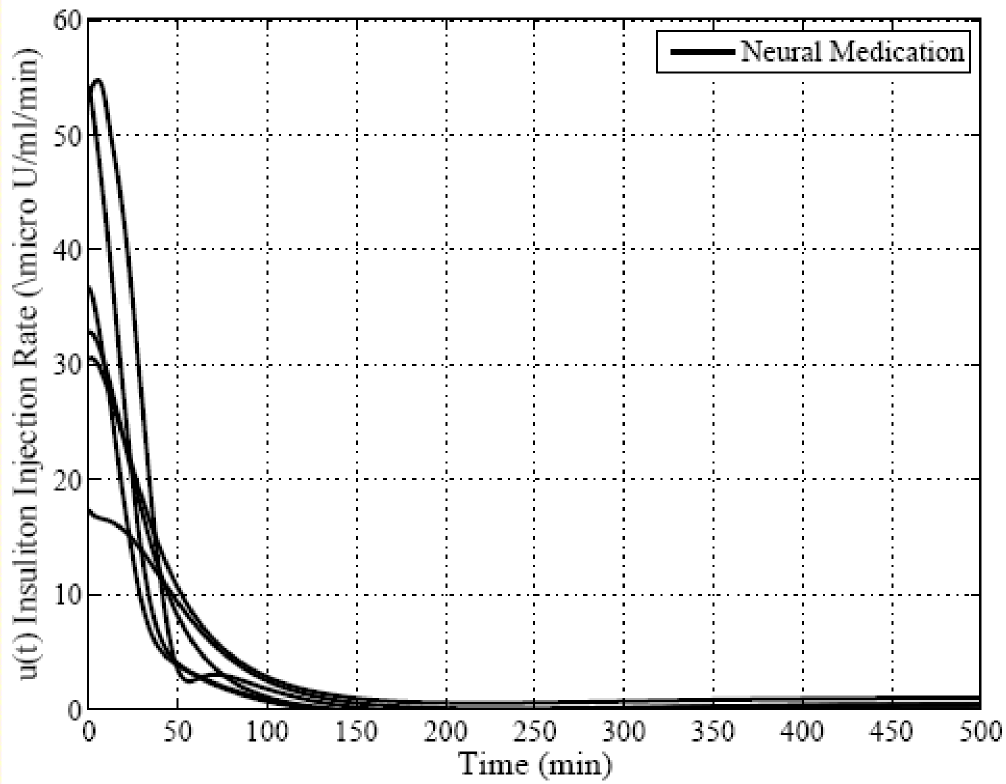
Blood glucose concentration

Insulin injection rate required

- LQR medication leads to overshooting during transient (hypoglycemia!)
- LQR medication demand is negative during transient (impossible to implement)
- SNAC medication leads to a faster closed-loop response

Results with Random Initial Conditions





Blood glucose trajectories

Insulin injection rates

- Even with initial BG more than 300 mg/dl, SNAC brings it to basal value.
- In cases where the patient without treatment can come to normal BG range, SNAC makes the convergence faster (within 2 hr)

SIMULATION RESULTS:

CASE – II: STUDIES WITH PERTURBED MODEL (KNOWN PARAMETERS)

$$\boxed{X_k^{inp} = \begin{bmatrix} X_k^T & P^T \end{bmatrix}^T}$$

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Range of Values

Range of parameter values for realistic model.

Parameter	Min value	Max value	Nominal value	Deviation (%)
p_2	$0.01/p_{2_n}$	$0.02/p_{2_n}$	0.015	± 33
p_3	$1 \times 10^{-6}/p_{3_n}$	$3 \times 10^{-6}/p_{3_n}$	2×10^{-6}	± 50
n	$0.12/n_n$	$0.30/n_n$	0.21	± 42
B	$0.01/B_n$	$0.10/B_n$	0.05	$+100, -80$

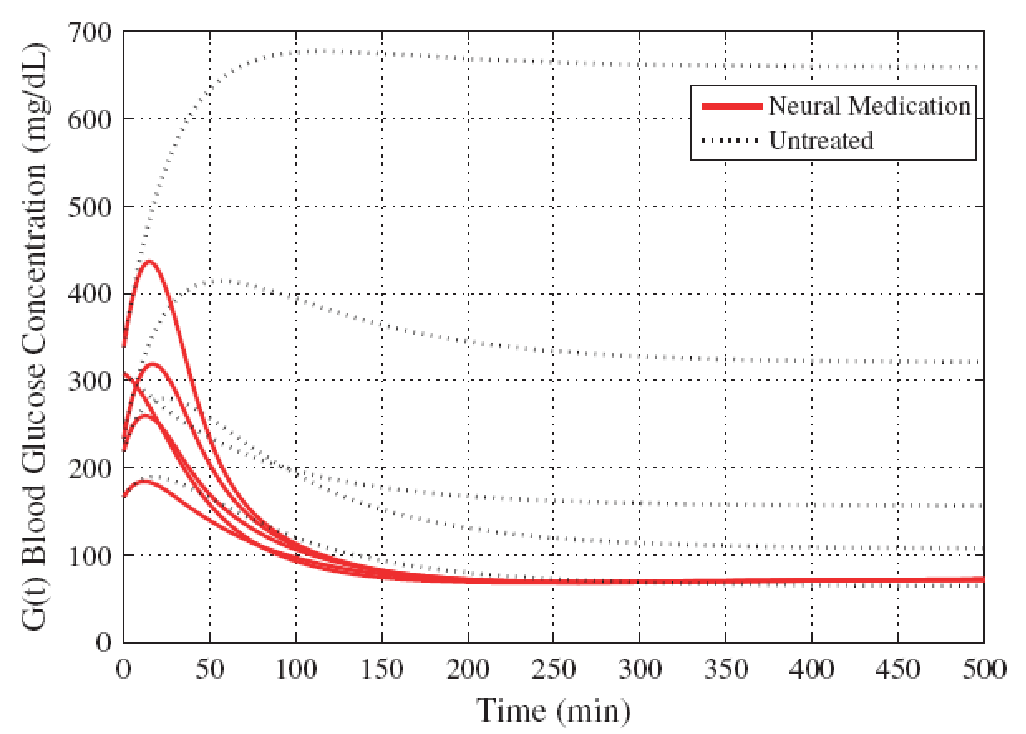
$[p_{2_n}, p_{3_n}, n_n, B_n]$: Nominal parameters.

Range of values for state variables.

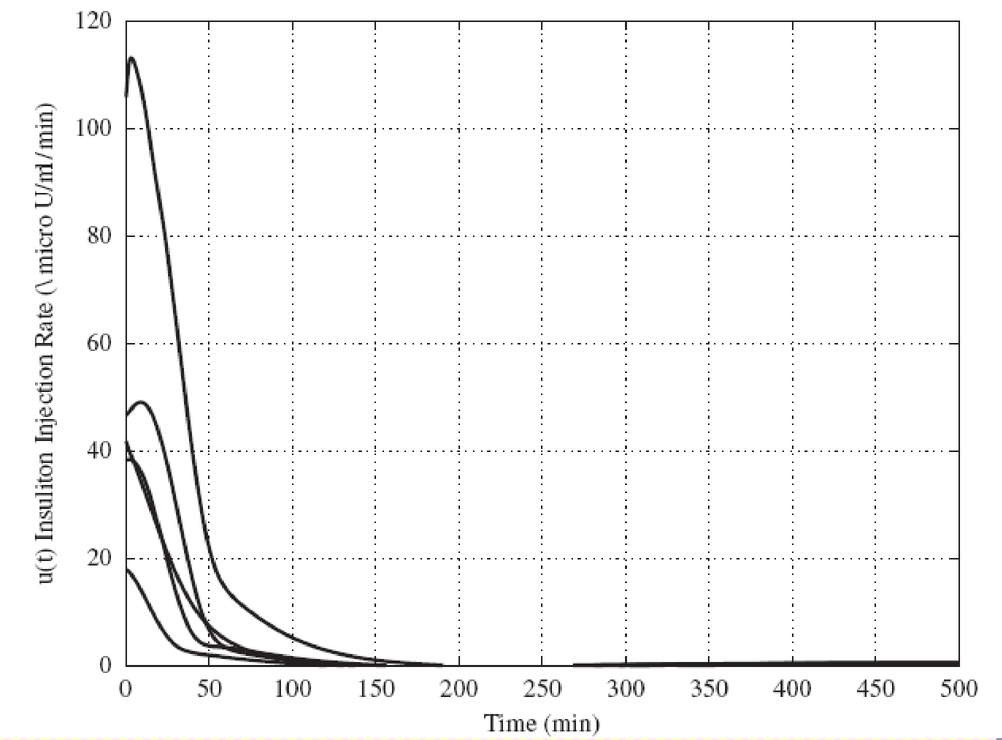
State	Value	State	Value
$x_{1\,\max}$	$220/x_{1_n}$	$x_{1\,\min}$	$-80/x_{1_n}$
$x_{2\,\max}$	$0.03/x_{2_n}$	$x_{2\,\min}$	$-0.001/x_{2_n}$
$x_{3\,\max}$	$200/x_{3_n}$	$x_{3\,\min}$	$-10/x_{3_n}$
$x_{4\,\max}$	$20/x_{4_n}$	$x_{4\,\min}$	$0/x_{4_n}$

Note: The range of values considered is high and can represent a wide variety of patient parameters and initial state deviations

Results: State and Control Trajectories



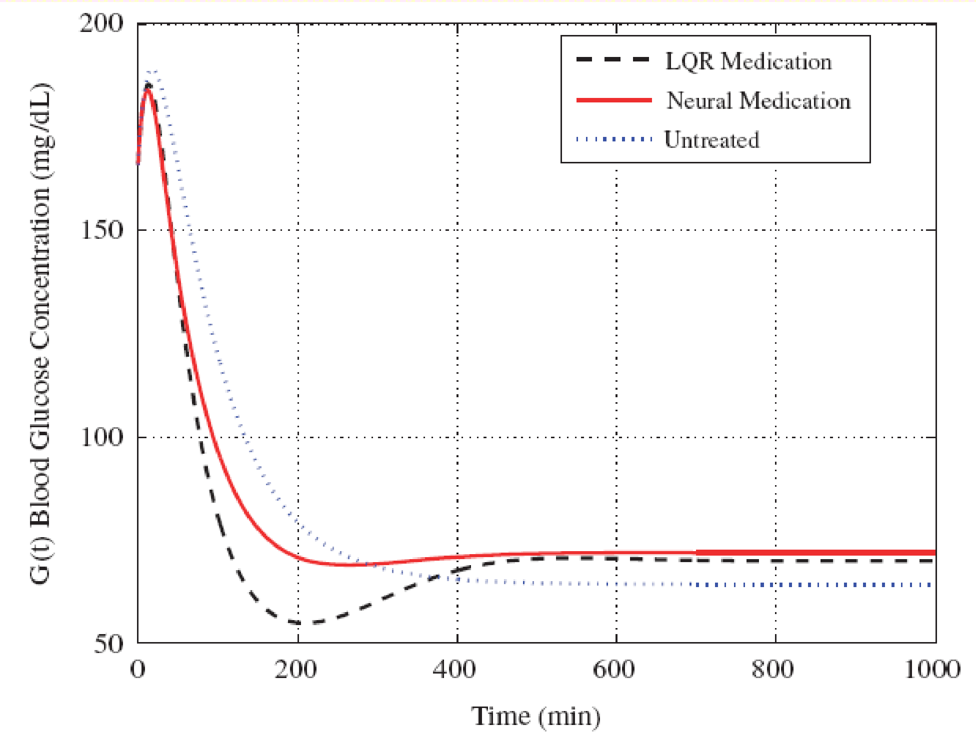
Blood glucose trajectories



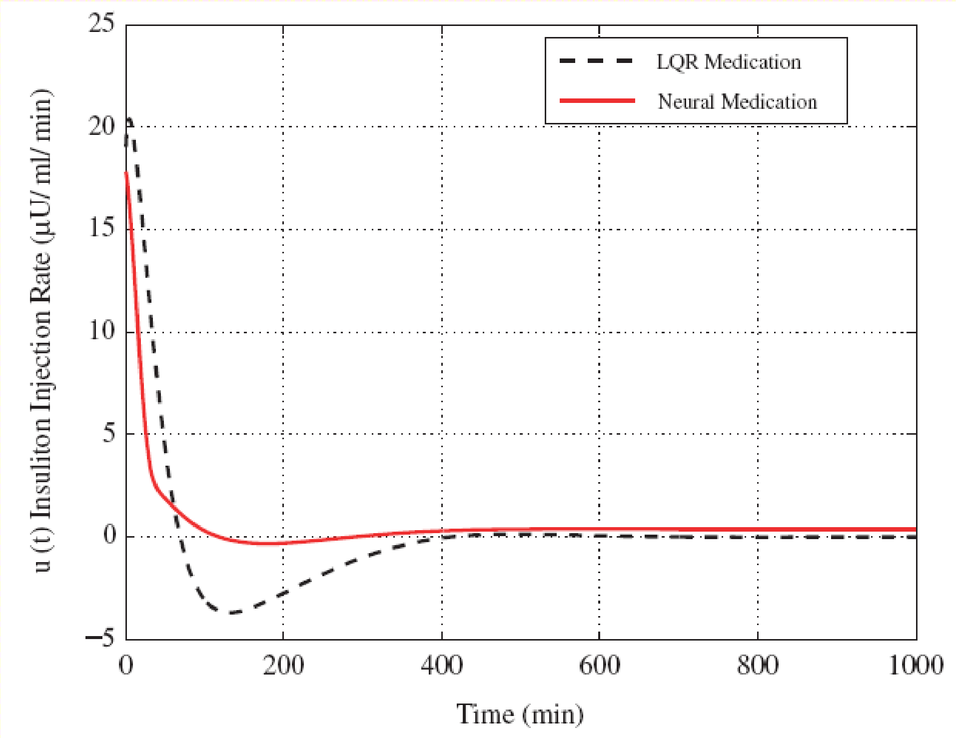
Insulin injection rates

Same benefits as earlier…!

Results: Comparison with LQR controller



Blood glucose trajectories



Insulin injection rates

Same benefits as earlier…!

SIMULATION RESULTS:

CASE – III: STUDIES WITH PERTURBED MODEL (UNKNOWN PARAMETERS)

$$\boxed{X_k^{inp} = X_k}$$

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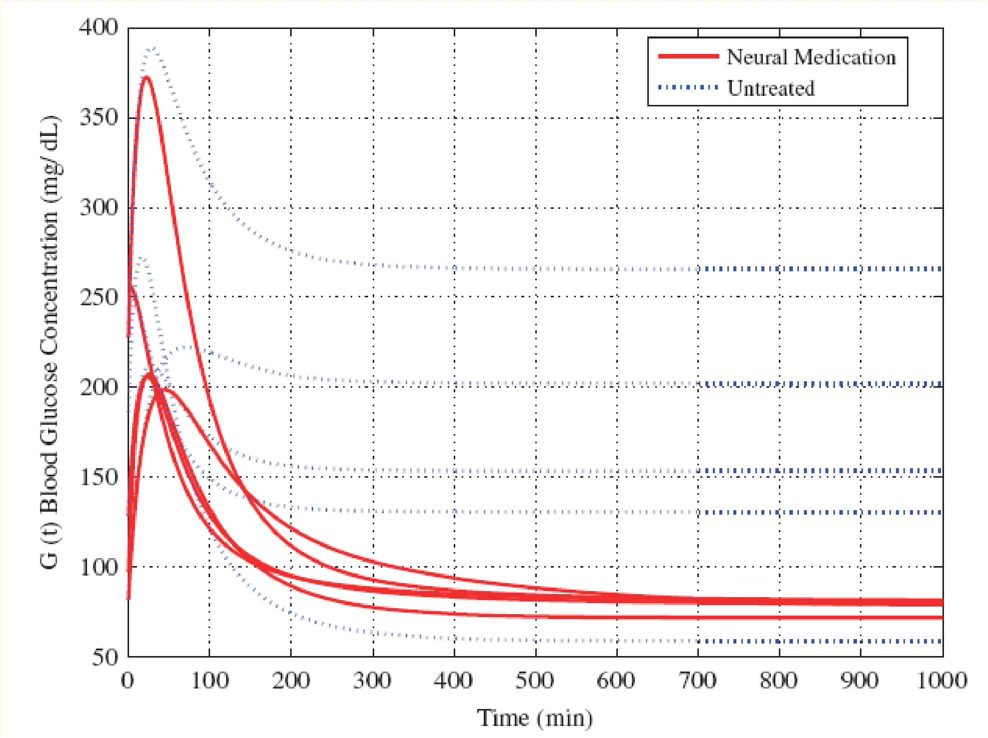
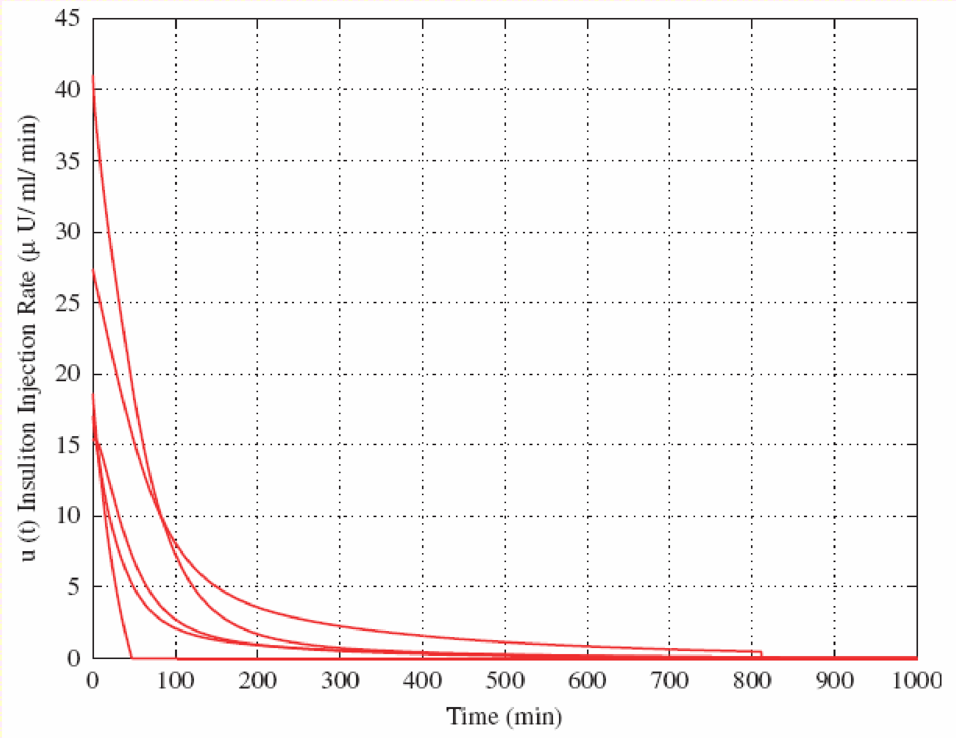
Results: State and Control Trajectories (G_b = 80 mg/dl)



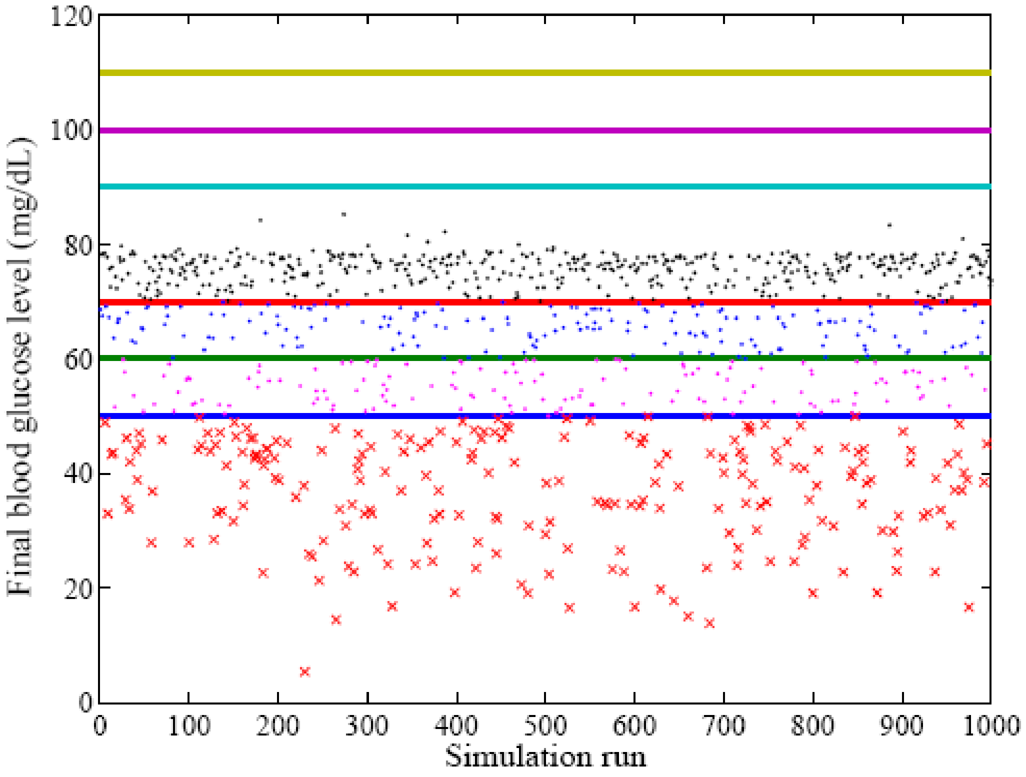
Blood glucose trajectories

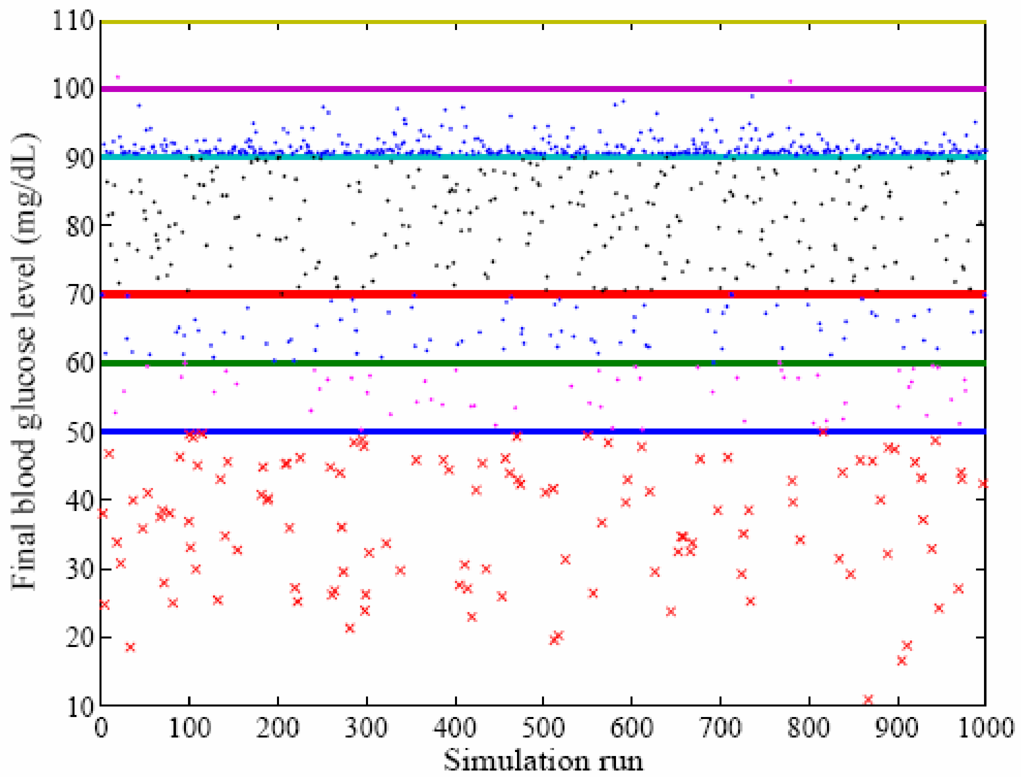


Insulin injection rates

Same benefits as earlier…!

Steady State Blood Glucose with Parameter Perturbation





Simulation results with
$G_b = 70$ mg/dl

Simulation results with
$G_b = 90$ mg/dl

Robustness Study with 1000 Random Cases

Basal Value	Ranges of blood glucose concentration			
G_b	$70-90$ **mg/dl**	$60-100$ **mg/dl**	$50-110$ **mg/dl**	>110 *and* <50 **mg/dl**
70	447	634	777	223
80	598	713	809	191
90	280	817	879	121

Conclusion: Fairly good robustness (about 80% success) for a wide deviation in parameter values

Conclusions

- A feedback control theoretic approach is presented for close regulation of blood glucose
- Nonlinear optimal control approach is followed using SNAC
  - State feedback design
  - Feasible computational load (can be implemented in real time)
  - Fairly good robustness
- Advantage of the SNAC approach over the LQR approach is shown (no overshooting in transient)
- Robustness study shows 80% success for a wide deviation in parameter values

Ongoing and Future Works

- Drug infusion synthesis using "dynamic inversion" in a hierarchical formulation
- Robustness enhancement using "neuro-adaptive design"
- "Dynamic re-optimization" with online incremental system identification (customized medicine)
- Experimental trials (in search of a collaborator…)

Thanks for the Attention…!

<u>Reference:</u> Sk. Faruque Ali and Radhakant Padhi: **Optimal Blood Glucose Regulation of Diabetic Patients Using Single Network Adaptive Critics (SNAC)**, *<u>Optimal Control Applications and Methods</u>*, In Press (already available online).

Questions … ??