Algorithm for the regulation of glucose infusion

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Executive Summary

Hyperinsulinemic clamp studies are used by endocrinologists, pharmacologists, and clinicians worldwide. The main purpose of these studies is to measure insulin sensitivity and thereby determine insulin resistance in patients. In these clamp studies, the plasma insulin concentration is acutely raised and maintained at 120 μU/ml by a continuous infusion of insulin. Simultaneously, the plasma glucose concentration is held constant at basal levels by a variable glucose infusion. When the steady-state is achieved, the glucose infusion rate equals the glucose uptake by all of the tissues in the body, and is therefore a measure of tissue insulin sensitivity. From this, the insulin resistance of the subject can be measured.

At Vanderbilt University Medical Center, Dr. James Luther conducts hyperinsulinemic clamp studies on human subjects to determine insulin resistance. Currently, he adjusts glucose infusion rate (GIR) on the fly based on his clinical judgment. However, this can lead to inaccurate adjustments which can affect subject safety and data validity. Some researchers claim that an algorithmic approach works, but no one Dr. Luther has talked to has been successful, and he has not had success with an algorithm either. Our goal is to develop on algorithm that predicts GIR in real time, allowing these studies to be performed in a more controlled manner.

Our solution will take place in the form of a MATLAB algorithm that communicates with a syringe pump. We have thoroughly considered the needs of the researcher, subject, and system in our design. For the researcher, we have developed a graphic user interface (GUI) in MATLAB that is simple to understand, can receive inputs for all possible variables (target glucose level, insulin clamp level, demographic data, date/time of study, etc.), and can simulate the glucose level in real time. The algorithm itself can calculate the amount of glucose uptake based on the constant insulin infusion rate specified by the researcher. Furthermore, each subsequent prediction is based on the actual GIR communicated to the pump, and the physician has the ability to override any predictions made by our algorithm. For the subject, safety is of course of utmost concern. Our algorithm ensures that the glucose levels do not exceed or drop below safe levels as determined by the researcher, and measurements are taken every five minutes to monitor glucose levels. The physician is alerted if the glucose levels are not within range. Finally, our solution will target the healthcare system by lowering future healthcare costs. Our algorithm will be open source, and should be applicable to different researchers and different institutions.

Competition with our solution could come in the form of different algorithmic approaches to predicting GIR. However, we are simultaneously developing an algorithm in Python that will rely on machine learning to improve our algorithm as future studies are conducted. We believe that this will be the primary reason our solution will be chosen over others. Not only is our GUI clean, simple, and intuitive to use, but the algorithm itself is constantly developing and will allow the greatest predictive power for GIRs in hyperinsulinemic clamp studies. Our solution is very feasible and is being presented at Vanderbilt University's School of Engineering Senior Design Day in April 2018.

No FDA approvals at this point are required, as the syringe pump is a proof of concept. However, if we were to move forward and utilize the algorithm and pump in human subjects, FDA regulation would be very stringent as we would now have a medical device. We would

likely follow the 510(k) premarket notification as syringe pumps are commonly used in studies. Our device would likely be Class II. No Medicare/Medicaid strategy is needed at this time.

Finally, the market for our device would consist of researchers and institutions that utilize hyperinsulinemic clamp studies. The patients that would be targeted are pre-diabetics, diabetics, and those with metabolic and endocrine disorders. All intellectual property belongs to Vanderbilt University, so all purchasing would go through them. Again, the algorithm itself would be open source but it would have to be licensed at a small price.

Description of the Problem to be Solved

In hyperinsulinemic clamp studies, many researchers including Dr. James Luther at Vanderbilt University Medical Center adjust glucose infusion rate (GIR) on the fly based on their own clinical judgment. However, this issue can lead to inaccurate adjustments that affect subject safety and data validity. While some people have claimed that an algorithmic approach works, no one that Dr. Luther has spoken to has had success with this method. We solved this problem by developing an algorithm and graphic user interface (GUI) in MATLAB that communicates with a syringe pump to predict and control GIR. Furthermore, it has an associated Python algorithm that allows for machine learning in order to improve our algorithm over time based on future studies. This will allow us to make available a unique product to a market that is currently utilizing obsolete methods.

Project Objective Statement

Our team has addressed the problem by designing an algorithm in MATLAB that accurately predicts glucose infusion rate. Initially, this is accomplished through a multiple regression analysis of demographic factors, including height, weight, body surface area, and age. From this initial prediction, the algorithm runs through iterations each time a new plasma glucose level is measured. Furthermore, the algorithm is simultaneously run in Python in order to implement machine learning mechanisms that continuously improve our predictions based on additional studies. We have also designed a graphic user interface in MATLAB that allows the researcher to monitor glucose levels and glucose infusion rate throughout the study. Finally, this algorithm/GUI can communicate serially with a syringe pump to literally control infusion. This final design solves the problem by more accurately predicting glucose infusion rates and transferring a greater power of validity to the studies.

Documentation of the Final Design

Our final design consists of a graphic user interface (GUI) that runs in MATLAB (Figure 1). This GUI is important because it allows for input of variables such as demographic indicators, syringe diameter, plasma glucose levels, and plasma insulin levels.

The algorithm itself is based primarily in MATLAB. We began with a multiple regression analysis of demographic factors in order to establish an initial prediction for glucose infusion rate. From this, the algorithm then relies on multiple iterations based on existing study data (Figure 2A). Our algorithm is also running in Python within several machine learning mechanisms so as to improve it as we collect more data and run more studies (Figure 2B). Finally, the algorithm actually functions within the GUI via serial communication between MATLAB and the syringe pump (Figure 2C).

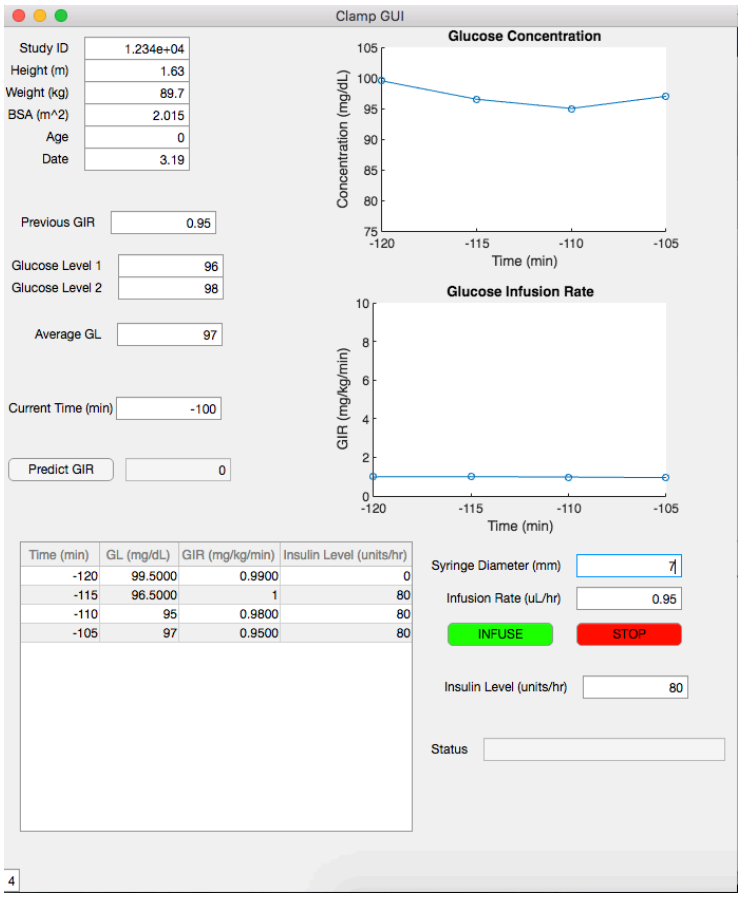


Figure 1: MATLAB graphic user interface. Inputs are on the left column, with real-time graphs of plasma glucose concentration and GIR. The predicted GIR is communicated to the syringe pump via the green "INFUSE" button.

A

```
% Button pushed function: Button
function ButtonButtonPushed(app, event)

    % Update number of button pushes
    app.buttonpush.Value = app.buttonpush.Value +1;
     butpush = app.buttonpush.Value;

     % initialize variables
    studyid = app.StudyID.Value;
    height = app.Height.Value;
    bsa = app.BSA.Value;
    weight = app.Weight.Value;
    age = app.Age.Value;
    prevgir = app.PrevGIR.Value;
    gl_one = app.GlucoseLevel1.Value;
    gl_two = app.GlucoseLevel2.Value;
    avg_gl = mean([app.GlucoseLevel1.Value, app.GlucoseLevel2.Value]);
    app.AverageGL.Value = avg_gl;
    curtime = app.CurrentTime.Value;
    LD = app.LowDose.Value;


    % Calculate the future GIR
    if prevgir==0 && curgl==0
        app.PredictGIR.Value = 1+ 15.35*height + .19485*weight - 20.895*bsa - age*.014226;
    else
        % This is where we will put in the algorithm
        app.PredictGIR.Value = 0;
    end
    % Update table
    app.UITable.Data{butpush,1} = curtime;
    app.UITable.Data{butpush,2} = avg_gl;
    app.UITable.Data{butpush,3} = prevgir;
    if LD == 1
        app.UITable.Data{butpush,4} = 'Low Dose';
    else
        app.UITable.Data{butpush,4} = 'High Dose';
    end
```

B

```
import sklearn
from sklearn.model_selection import train_test_split
from sklearn import svm

# Read Patient File
patientdata = pandas.read_excel('7832002.xlsx', sheet_name='DeltaData')
from sklearn.linear_model import LinearRegression

# Randomly Divide data into training and cross validation set
# (test_size is percentage of data used to evaluate)
X = patientdata.drop('delta glucose',axis = 1)
Y = patientdata.drop('delta gir',axis = 1)

X_train, X_test, Y_train, Y_test = train_test_split(X, Y, test_size = 0.33, random_state = 5)

# Build Linear Regression Model
lm = LinearRegression()
lm.fit(X_train,Y_train)
pred_train = lm.predict(X_train)
pred_test = lm.predict(X_test)

print('Estimated intercept coefficient:', lm.intercept_)
```

C

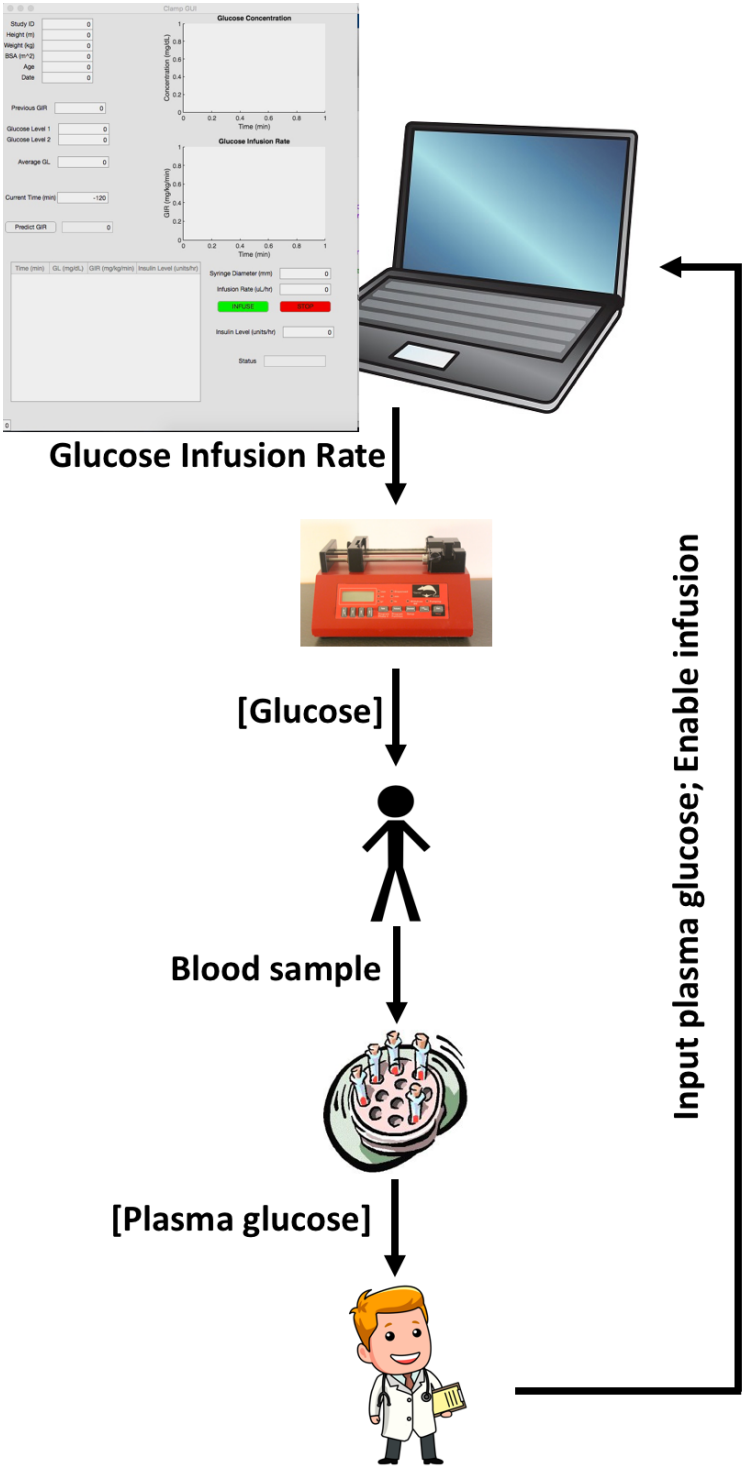
```
    % Value changed function: Infuse
    function InfuseValueChanged(app, event)
        % send command
        diam = app.dia.Value;
        rate = app.InfusionRate.Value;

        % Confirmation
       promptMessage = sprintf('Are you sure you would like to infuse?');
       button = questdlg(promptMessage, '!! Warning !!', 'Continue', 'Cancel', 'Continue');
       if strcmpi(button, 'Cancel')
                   return; % Or break or continue
       elseif strcmpi(button, 'Continue')
            fprintf(app.serialPump, 'DIA %5.3f\n',diam);
            fprintf(app.serialPump, 'DIA\n');
            pause(.5)
            fprintf(app.serialPump, 'RAT UH');
            pause(1);
            fprintf(app.serialPump, 'RAT %5.3d\n',rate);
       %             fprintf(app.serialPump, 'RAT\n');
            pause(.5);
            fprintf(app.serialPump, 'RUN');
            warning('off')
            app.Status.Value = fscanf(app.serialPump);        % Checks if command was received
```

Figure 2
A) MATLAB pseudocode for algorithm, with initialization of variables and calculation of future GIR. B) Python pseudocode for machine learning. C) MATLAB pseudocode for serial communication to syringe pump

There are not any known risks as we will solely be using an algorithm with preexisting data for glucose and insulin levels. We have a high level of confidence that we will be able to optimize the algorithm using a database of over 100 studies that can be used to guide initial estimates. All subsequent studies will be performed by a trained researcher, Dr. James Luther.

Prototype of Final Design



Proof of Functionality
Preliminary results indicate high functionality of our algorithm. We ran a control study using the demographic info of a subject that Dr. Luther had already performed a hyperinsulinemic clamp study on. This accurately predicted glucose infusion rates in comparison to those that Dr. Luther used within a percent error of 10%. For the first iteration, we are very happy with this value as it is only relying on one study. Once we have completed the machine learning process and increased the power of the study, we are confident that our algorithm will be able to much more accurately predict glucose infusion rate. We aim to run our algorithm side by side Dr. Luther's upcoming clinical studies, without actually infusing any glucose to the subject. This will enable us to examine the functionality of our algorithm in a clinical setting without actually testing it and going through regulatory pathways. If this can accurately maintain the glucose level at 95 mg/dL within a narrow percent error, we have functionality, which can only increase with increased machine learning opportunities.

Patent Search
No existing patents were found. Of course, syringe pumps do exist, but the actual idea of an algorithm that predicts GIR and communicates with a syringe pump has not been patented and/or brought to market. This search was done through the United States Patent and Trademark Office, as well as by the Vanderbilt Center for Technology Transfer and Commercialization.

Anticipated Regulatory Pathway
Our design would likely require 510(k) premarket notification as syringe pumps are commonly used in studies. The FDA provides guidance on the premarket notification (510(k)) submissions for external infusion pumps. Therefore, it would primarily be proving the safety and efficacy of the algorithm and serial communication that would require regulatory pathways.

Reimbursement
We do not expect our device to be reimbursable by Medicare/Medicaid, as it will primarily be used in a research setting by individual researchers and institutions. The results of such hyperinsulinemic clamp studies will ideally drive down healthcare costs in the future, however, the actual use of our device will not be applicable to Medicare/Medicaid or other insurance options.

Estimated Manufacturing Costs
We actually will not have any manufacturing costs because our device consists of an open-source MATLAB algorithm, coupled with a syringe pump. Most institutions already have access to syringe pumps. If not, it would be up to the institution to purchase a pump that can be integrated with out algorithm. Therefore, we will have no manufacturing costs.

Potential Market

Our market would consist of researchers and institutions that perform hyperinsulinemic clamp studies. At Vanderbilt University Medical Center alone, our advisor Dr. James Luther has identified up to ten researchers that would be interested in this algorithm. If this were expanded to research institutions across the country, we could potentially have our algorithm being utilized in most major cities and major research institutions. These researchers would also be the end users of the product, and they would consist primarily of endocrinologists and pharmacologists. The specific subjects of these studies would consist of pre-diabetics, diabetics, and those with endocrine and metabolic disorders. The market size may consist of roughly 100 institutions. Pricing would consist primarily of a licensing fee, since MATLAB is open source. Distribution would be accomplished through Vanderbilt University, as all IP will be transferred to them.