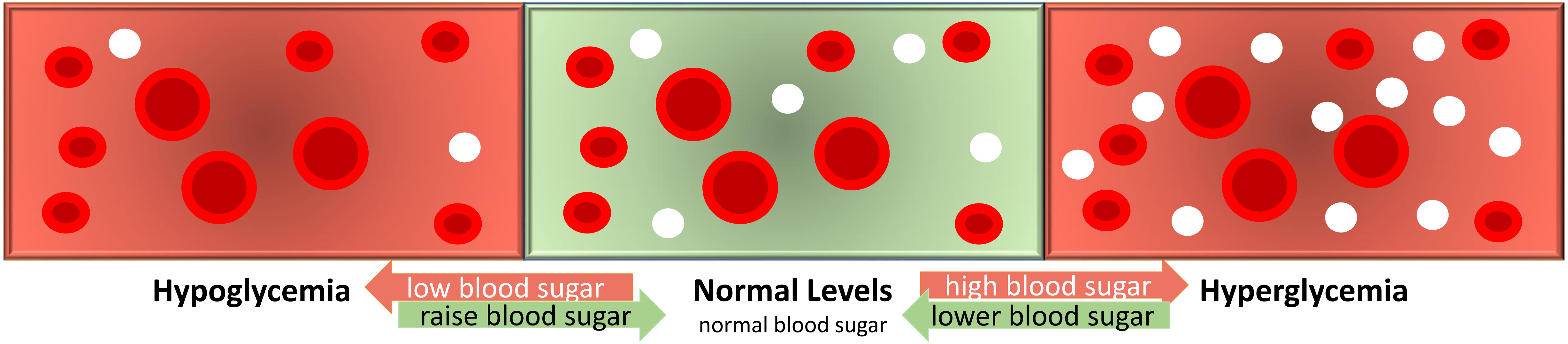
Exploring Non-invasive Features for Continuous Glucose Monitoring: Master’s Thesis Defense

By: Brian Bogue Jimenez

Advisor: Dr. Ana Doblas

What is Diabetes?

- Chronic condition that is characterized by abnormal levels of blood sugar [1].
- Diabetes has been estimated to effect 450 million worldwide [2]



- Management requires tracking glycemia

[1] CDC, 11-Jun-2020. [Online]. Available: https://www.cdc.gov/diabetes/basics/diabetes.html.
[2] W.V. Gonzalez et al., Sensors. 19(4), 1–45 (2019).

Types of Diabetes

- Type 1: Insulin dependent (Juvenile)
- Type 2: Non-insulin dependent (Adult On-set)
- Gestational diabetes
- Impaired Glucose Intolerance
  - Includes up to 30 other disorders including prediabetes [1]
- All of these can result in long term complications

[1] National Diabetes Data Group, Diabetes. 28, 1039-1057 (1979).

Complications caused by Diabetes

- Possible complications [1]
  - Ketosis
  - Cardiovascular Disease
  - Nerve Damage
  - Renal Failure
  - Skin Conditions

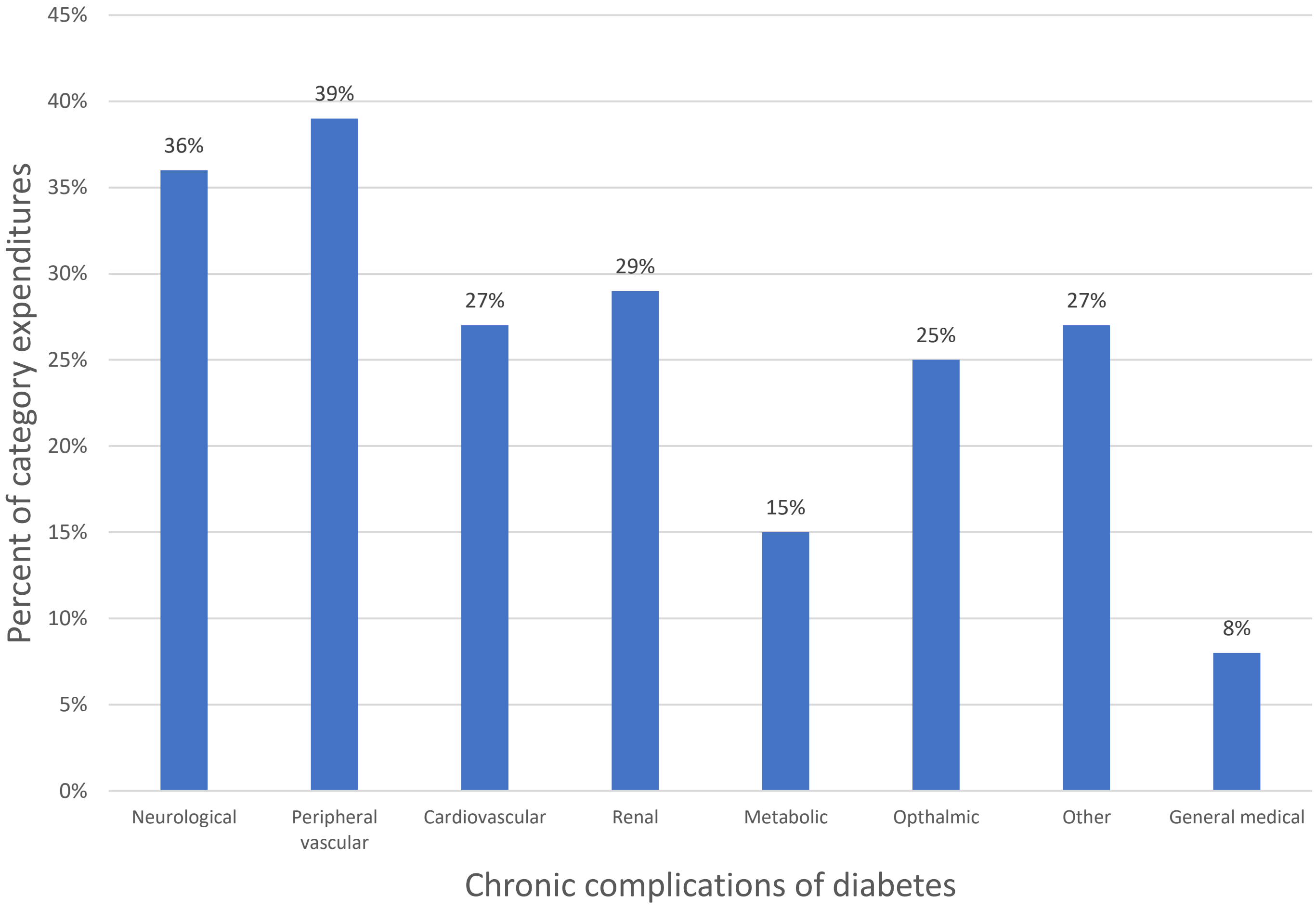


Figure: Cost of Complications [2]

[1] Diabetes Complications | ADA. Available: https://www.diabetes.org/diabetes/complications.
[2] W. Yang et al, Diabetes Care. 41(5), 917-928 (2017).

The Cost of Diabetes to the U.S. Economy

- Estimated ~24.7 million in the U.S. as of 2017 (**9.7**% of adults)
- $9,601 per year per patient
- Costs the economy ~$327 billion
  - $**237** billion from direct medical costs
  - $90 billion in lost productivity
  - Medical costs are 2.3 times for those with Diabetes
- 26% increase from 2012 to 2017

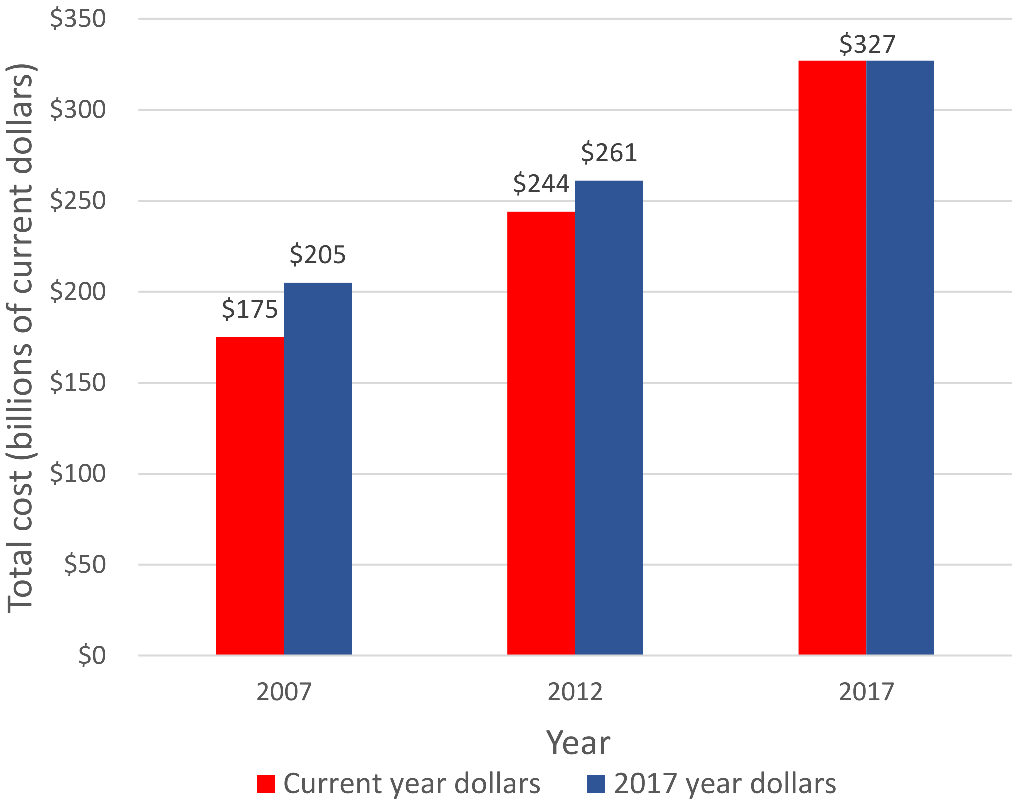
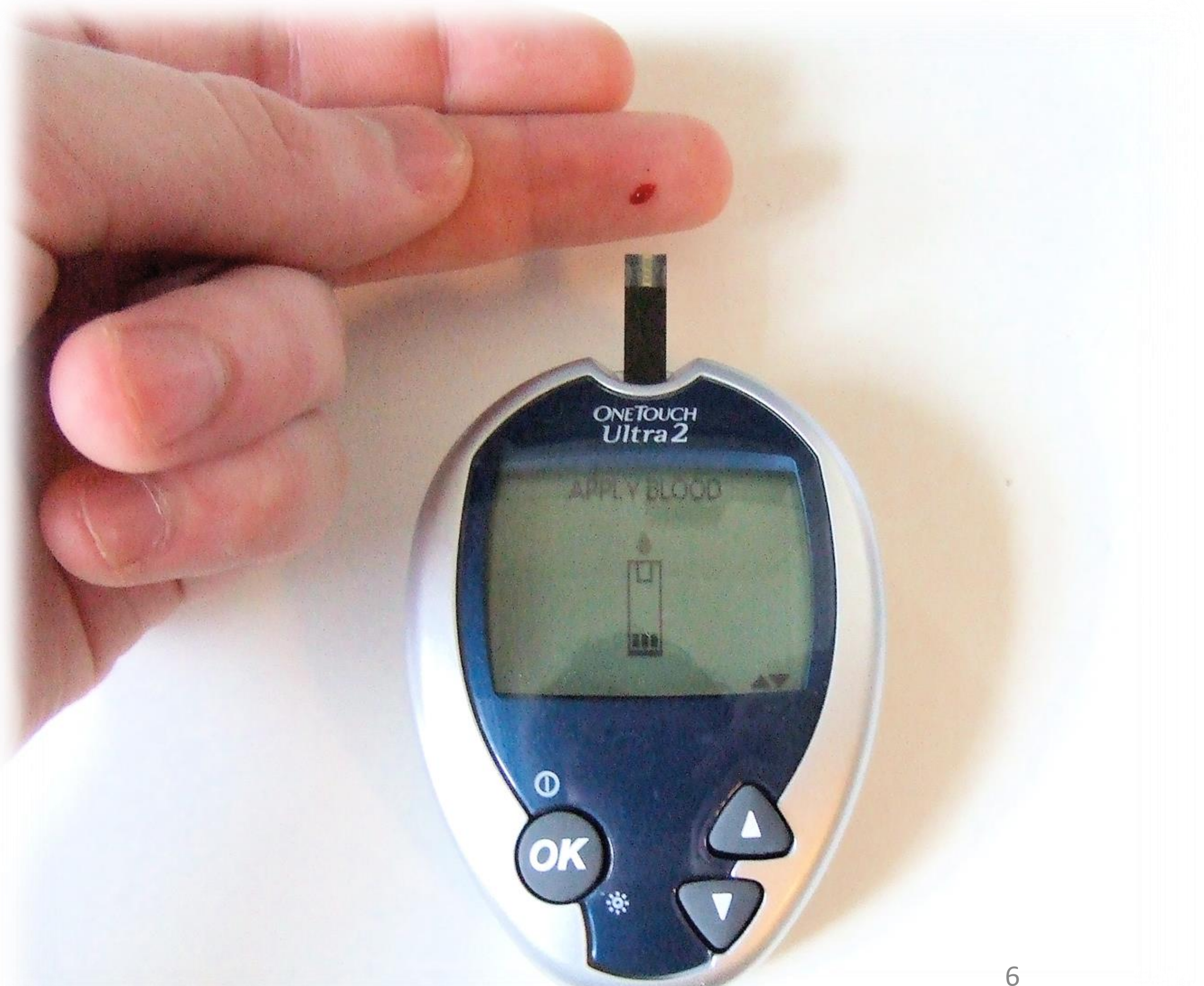


Figure: Total direct cost of diabetes ‘07-’17 [1]

[1] W. Yang et al, Diabetes Care. 41(5), 917-928 (2017).

Diabetes Management via Glucometers

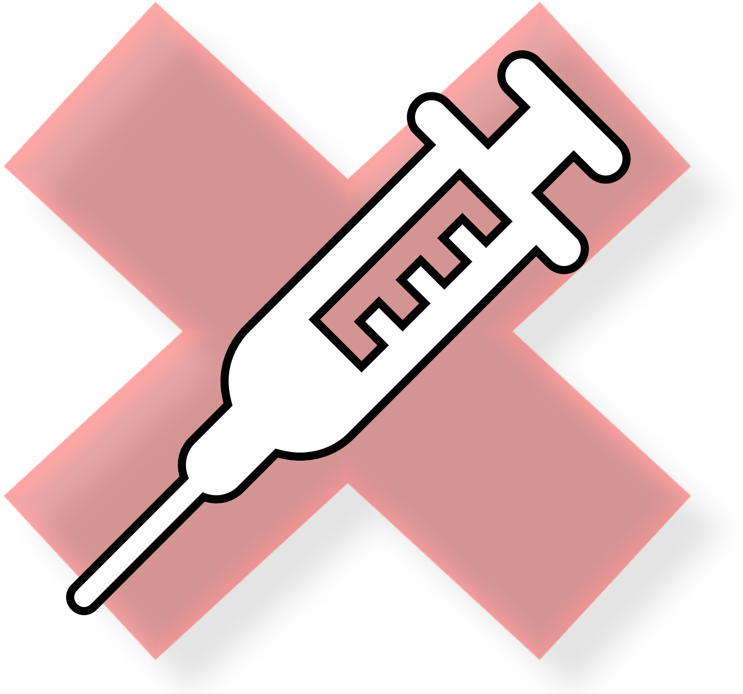
- Market Gold standard for accuracy
- Requires invasive samples
- Few measurements per day
- Single use disposable sensors



Images obtained from Wikipedia: https://en.wikipedia.org/wiki/Blood_glucose_monitoring

The Need for Non-invasive Continuous Glucose Monitoring (NICGM)?

- Current Methods are inconvenient [1]
  - Invasive
  - Painful
  - Costly
  - Discrete
- A Purpose:
  - The need for a NI-CGM System



[1] W.V. Gonzalez et al., Sensors. 19(4), 1–45 (2019).

Development of Continuous Glucose Monitoring through the last decade

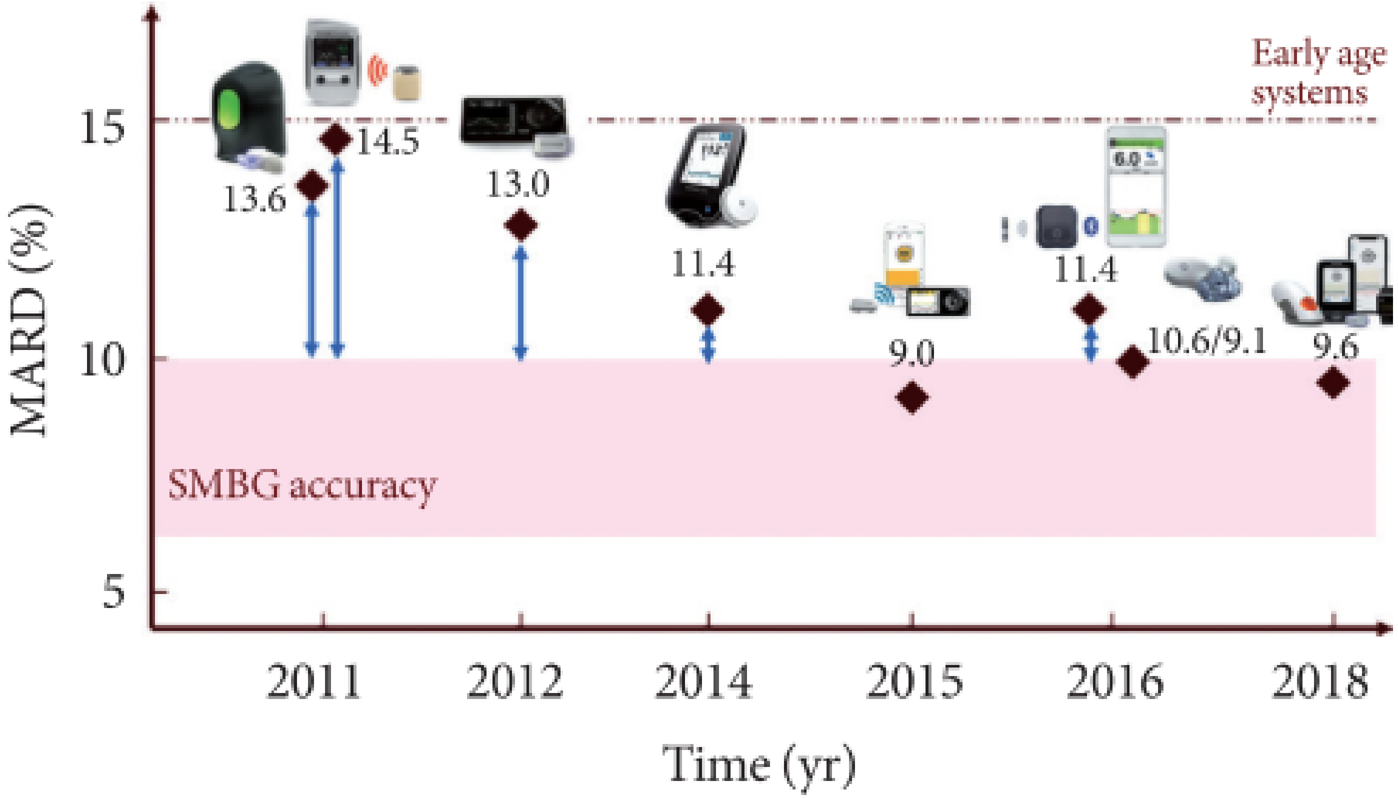


Figure: Accuracy evolution of CGM from [1]

- Principal based on: Glucose-oxidase-platinum-electrode needle
- Reads interstitial fluid
- Several commercial devices
- Minimally Invasive
- Sensor must be replaced

SMBG: Self monitoring Blood Glucose Devices
MARD: Mean Absolute Relative Difference

[1] G. Cappon et al., Diabetes Metab. J. 43(4), 383–397 (2019).

Leader in Market: Freestyle Libre II

- Can be used with data logger or app
- 14-day life cycle
- Rolling memory for up to 8 hours
- Sampling Frequency: 15/minute (or manual measurements up to every 1 minute)

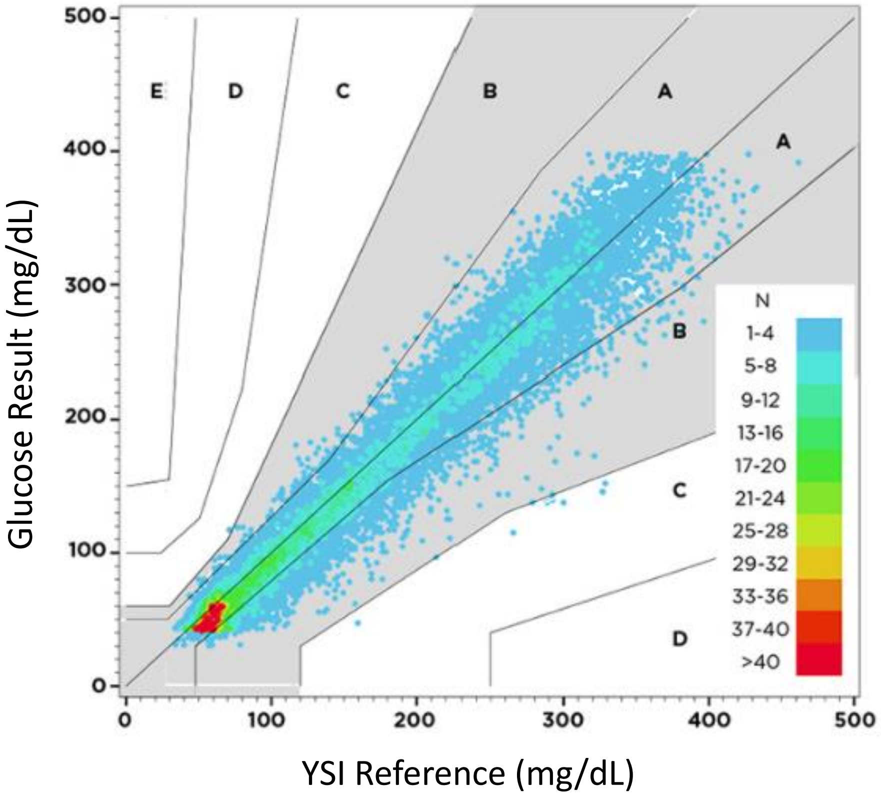


Figure: Consensus Error Grid of Freestyle Libre II [1]

[1] Images obtained from Abbott Freestyle Libre 2 website: https://www.freestyle.abbott/us-en/products/freestyle-libre-2.html

True NICGM based on Impedance Spectroscopy

- ☐Principle based on: bioimpedance at different depths to estimate BGL
- ☐Simple equivalent circuit based on Cole Model
- ☑Cost-effective
- ☑Completely Non-invasive and Continuous

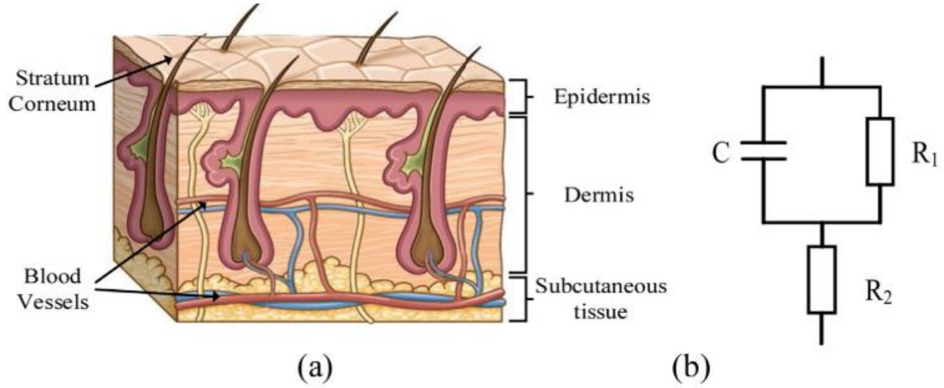


Figure 1: (a) Cross section of skin (b) Cole model of electrode-skin impedance. [1]

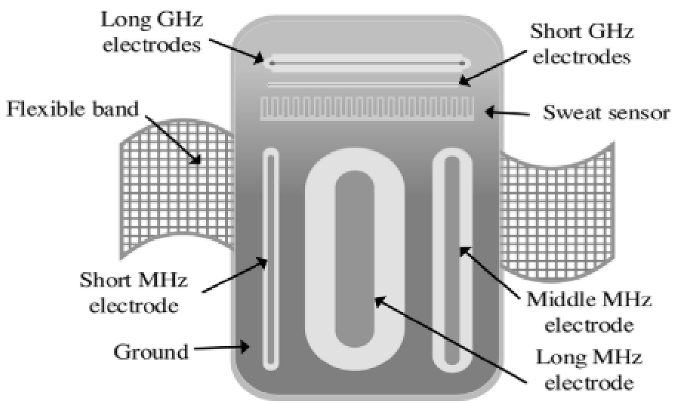


Figure 2: NI-CGM device proposed by Caduff, et al. from [1]

[1] J. Huang et al., Elsevier, 311, 1-9 (2020).

PENDRA Commercial Prototype of Impedance Spectroscopy

☐PENDRA (2003)

☑Completely Non-invasive and Continuous

☒Failed due to inaccuracy, and pulled off market [1]

☒Struggles due to interference of bad sensor to skin attachment

☒Currently no commercial devices implement this method

Figure: PENDRA device from [2]

[1] S. Weinzimer, Diabetes Technology and Therapeutics, 6(4), 442-444 (2004).
[2] J. Huang et al., Elsevier, 311, 1-9 (2020).

True NICGM based on Metabolic Heat Confirmation

- ☐Principal based on: multiwavelength spectroscopy to measure blood flow rate, hemoglobin and oxyhemoglobin
- ☐Array of electrical and optical sensors to measure ambient features and thermal properties of the skin
- ☐Applies regression methods to relate features to BGL
- ☒System was not continuous and limited to finger
- ☒Does not have commercial equivalent

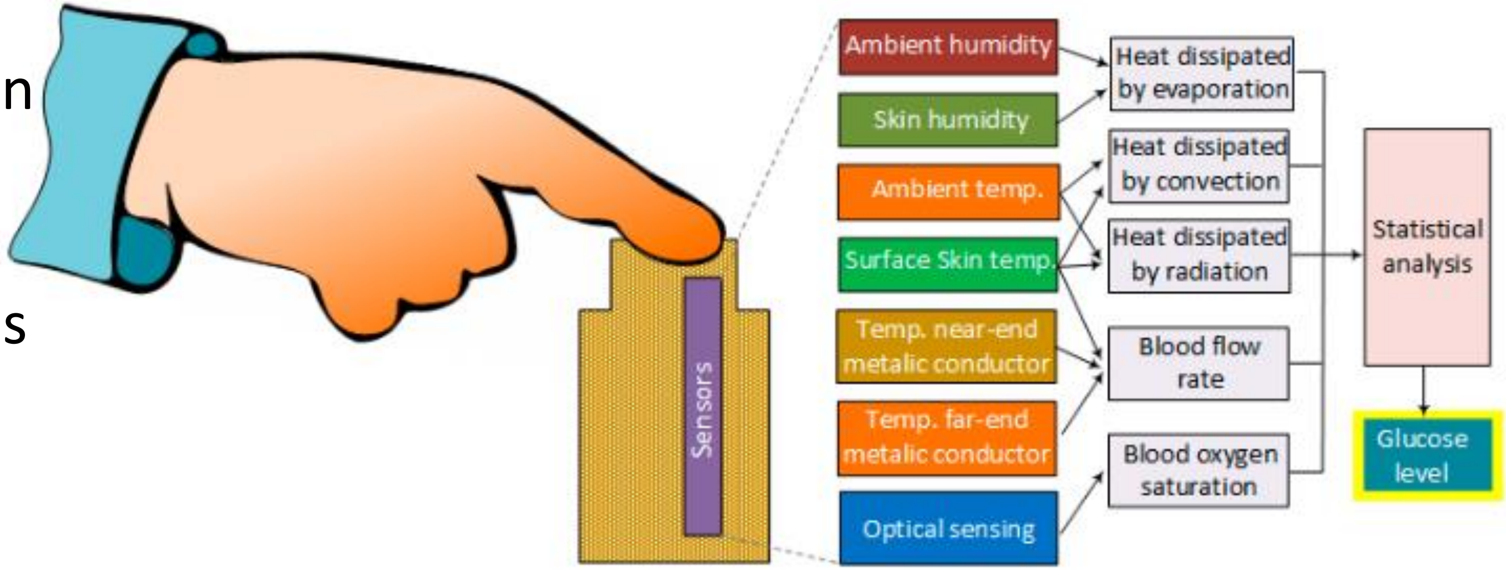


Figure: MHC flowchart [1]

[1] O. K. Cho, et al. Clin. Chem., 50(10) 1894–1898 (2004).

GlucoTrack Commercial Prototype of Combining Sensors

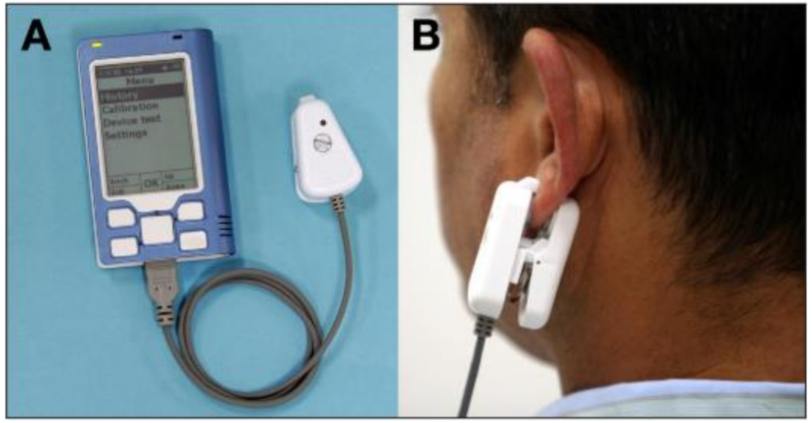


Figure 1: GlucoTrack device from [1].

☑Completely Non-Invasive (NI)

☐Combines 3 Different Methods

1. Electromagnetic (i.e. Impedance Spectroscopy)
2. Thermal (i.e. MHC)
3. Ultrasound

☒Spot Check device for Ear

☒Not Continuous

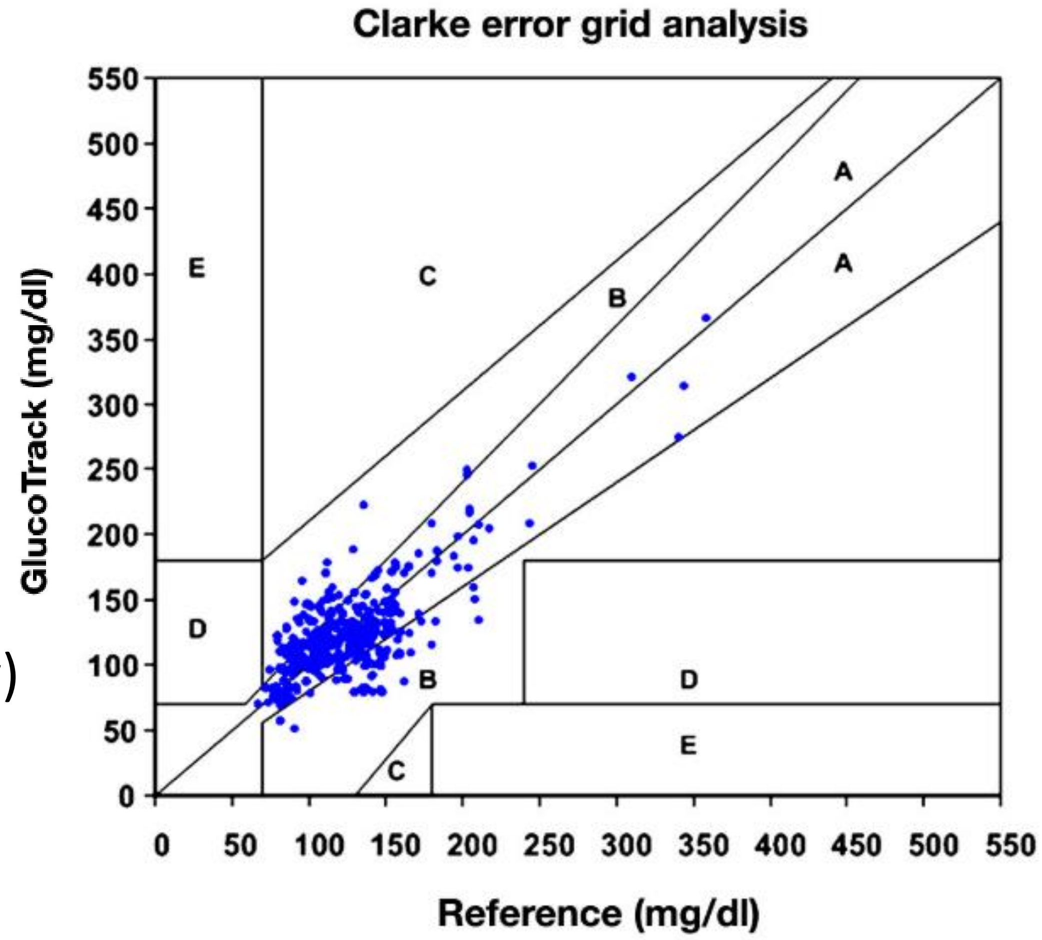


Figure 2: Clarke Error Grid of GlucoTrack[1].

[1] I. Harman-Boehm et al, J. Diabetes Sci. Technol., 3(2), 253–260 (2009)

Our Proposal for a multiarray sensor NICGM

- This thesis will explore multiple off-the-shelf wearable sensors that could be implemented in smartwatches and create a feature set sufficient for prediction.
- Hypothesis:
  - The following sensors will provide sufficient features to accurately predict blood glucose levels within healthy individuals
- Non-invasive Sensors combined with Machine Learning:
  - G-Skin Heat Flux, Empatica E4 wristband (EDA and Skin Temp.), Delfin MoistureMeterD, Viatom Checkme O2, Adafruit DHT11, Omron 3 Series Upper Arm Blood Pressure Monitor

Comparison of Management Methodology

Traditional Glucometers

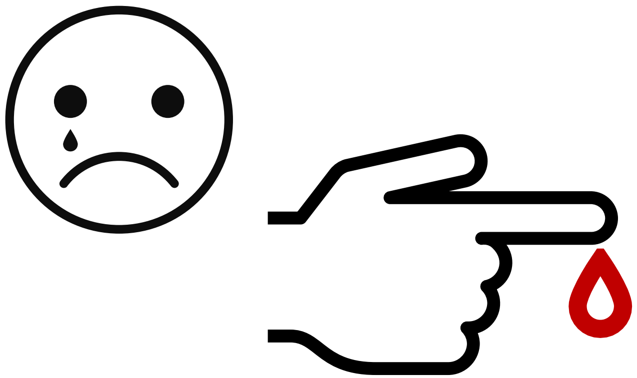
☑Accurate

☒Painful and inconvenient

☒Poor monitoring habits

☒“Snapshot”

☒Disposable sensors



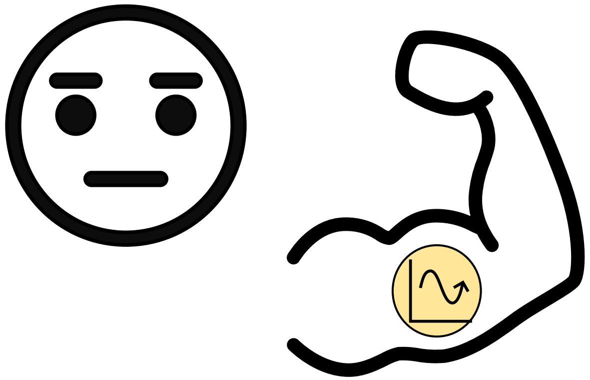
Glucose Oxidase Needle

☑Continuous

☑“full picture”

☒Disposable sensors

☒Minimally Invasive



Proposed

☑Non-invasive

☑More frequent measurements

☑“full picture”

☑No additional cost

Flowchart for our proposal

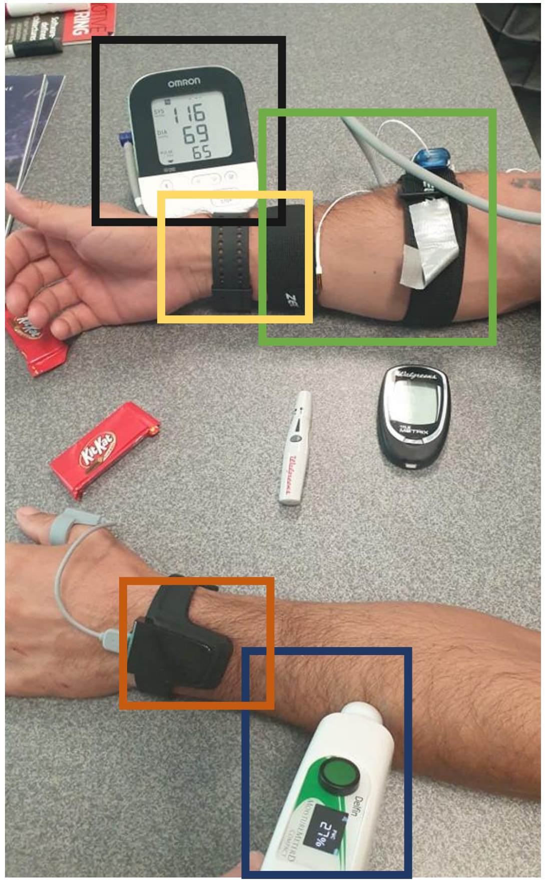
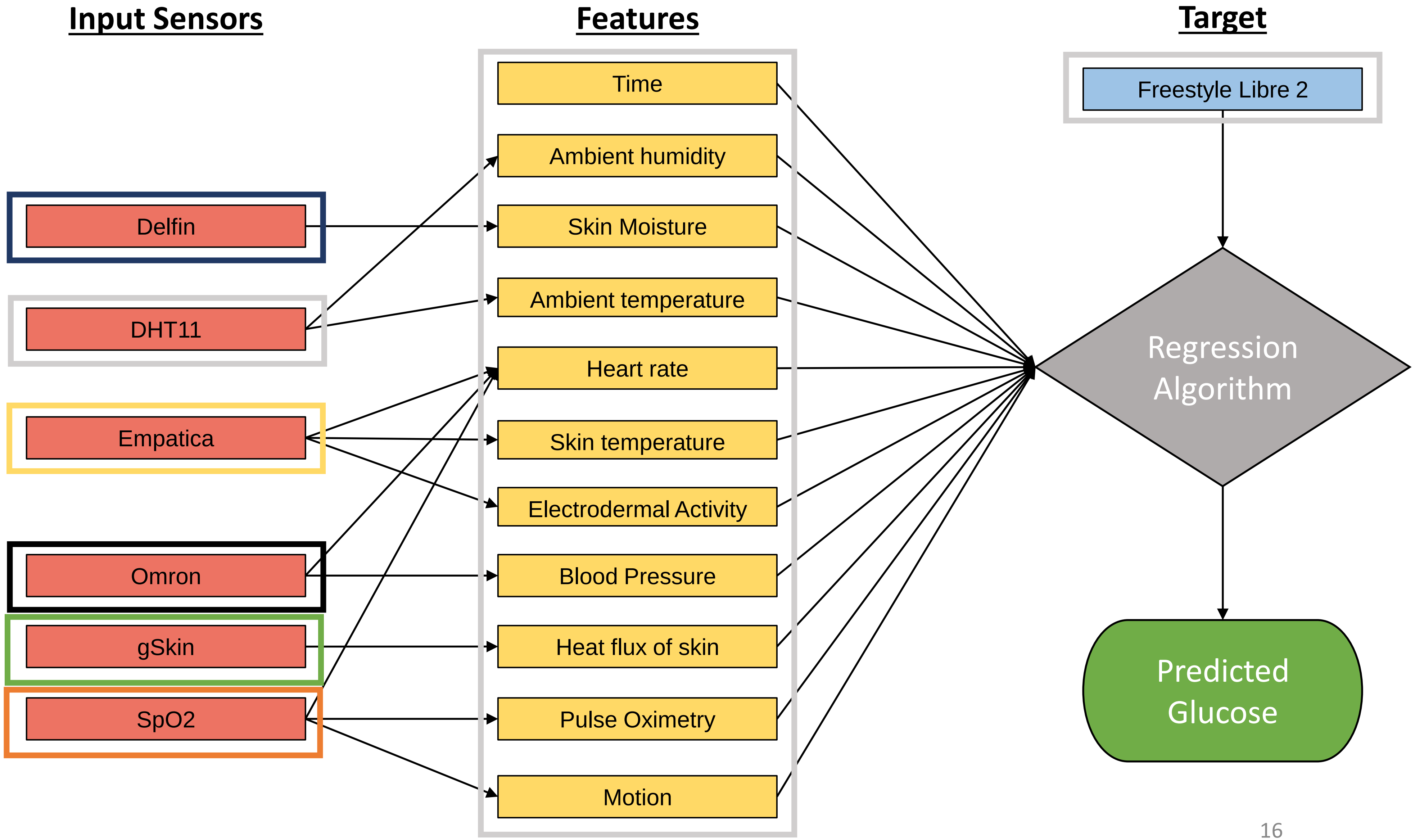


Figure: Sensors used
UofM dataset



Preliminary investigation into non-invasive sensors to track BGL in Diabetics Patients

- OhioT1DM Dataset
- 2 Subjects selected based on variance of target variable: 559 (70.35 mg/dL) and 563 (50.50 mg/dL)
- Original features
- Relevant features: Blood Glucose, Ambient Temperature, Galvanic Skin Response (GSR), Heartrate, Skin Temperature

Original Features

Glucose Level

Basal

Bolus

Meals

Sleep

Self Reported Stressors

Illness

Heart rate

GSR

Skin Temperature

Ambient Temperature

Step count

	Time	test_glucose	test_ambTemp	test_gsr	test_heartrate	test_skinTemp
0	07-Dec-2021 12:55:00	240	81.68	0.000087	103	84.92
1	07-Dec-2021 13:00:00	229	84.38	0.000101	68	87.98
2	07-Dec-2021 13:05:00	223	85.46	0.000147	68	88.88
3	07-Dec-2021 13:10:00	214	[illegible]	0.000643	70	89.24
4	07-Dec-2021 13:15:00	210	86.18	0.000133	71	89.78
...	...	...	...	...	...	...
12427	27-Jan-2022 17:10:00	125	[illegible]	[illegible]	77	83.30
12428	27-Jan-2022 17:15:00	125	83.53	0.000073	60	84.88
12429	27-Jan-2022 17:40:00	144	84.92	0.000074	75	85.82
12430	27-Jan-2022 17:45:00	146	83.48	0.000075	80	86.36
12431	27-Jan-2022 17:50:00	151	79.70	0.000071	118	80.96

12432 rows × 6 columns

Figure: Example of the Ohio dataset

Subject 559 - Description of Dataset

Value	Glucose	Ambient Temp	GSR	Heart Rate	Skin Temp	log(GSR)
Mean	167.23	84.28	0.40	73.89	87.66	-3.31
Std. Dev.	70.36	4.38	2.04	15.94	3.44	1.37
Min.	40.00	63.86	0.00	46.00	72.32	-4.17
25%	110.00	81.32	0.00	62.00	85.10	-4.11
50%	158.00	83.66	0.00	69.00	87.44	-3.99
75%	210.00	87.62	0.00	83.00	90.50	-3.25
Max	400.00	96.98	23.02	189.00	95.90	1.36
Count	12,432	12,432	12,432	12,432	12,432	12,432

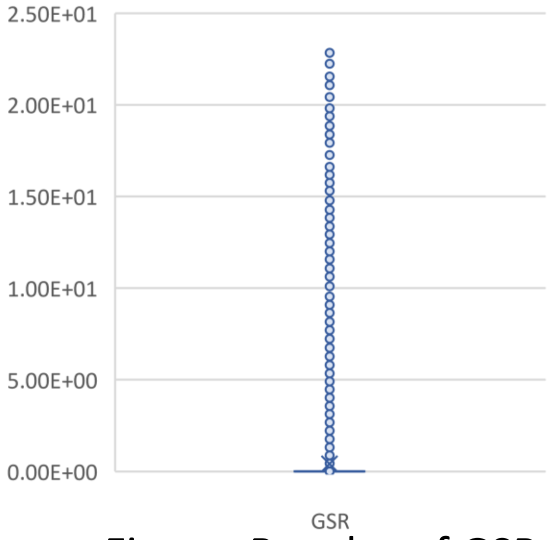


Figure: Boxplot of GSR

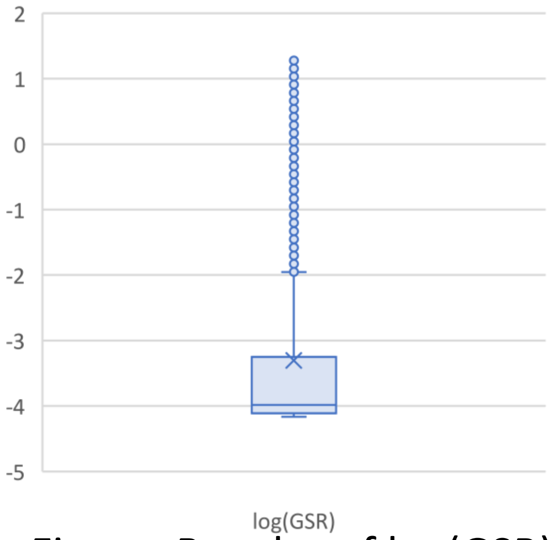
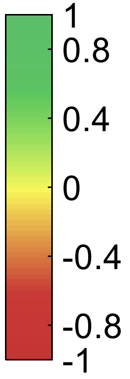


Figure: Boxplot of log(GSR)

No linear relationship between these features and glucose in Ohio Dataset

a)

Features	Glucose	Amb. Temp.	Heart Rate	Skin Temp.	log(GSR)
Glucose	1.00				
Amb. Temp.	-0.16	1.00			
GSR	-0.02	-0.15			
Heart Rate	0.20	-0.49	1.00		
Skin Temp.	-0.15	0.97	-0.49	1.00	
log(GSR)	-0.04	0.05	0.17	0.07	1.00



b)

Feature	Glucose	Amb. Temp.	Heart Rate	Skin Temp.	log(GSR)
Glucose	1.00				
Amb. Temp.	0.07	1.00			
Heart Rate	0.04	-0.09	1.00		
Skin Temp.	0.09	0.95	-0.07	1.00	
log(GSR)	-0.04	-0.01	0.25	0.01	1.00

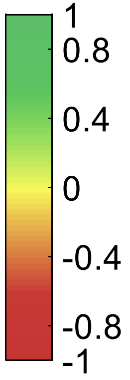
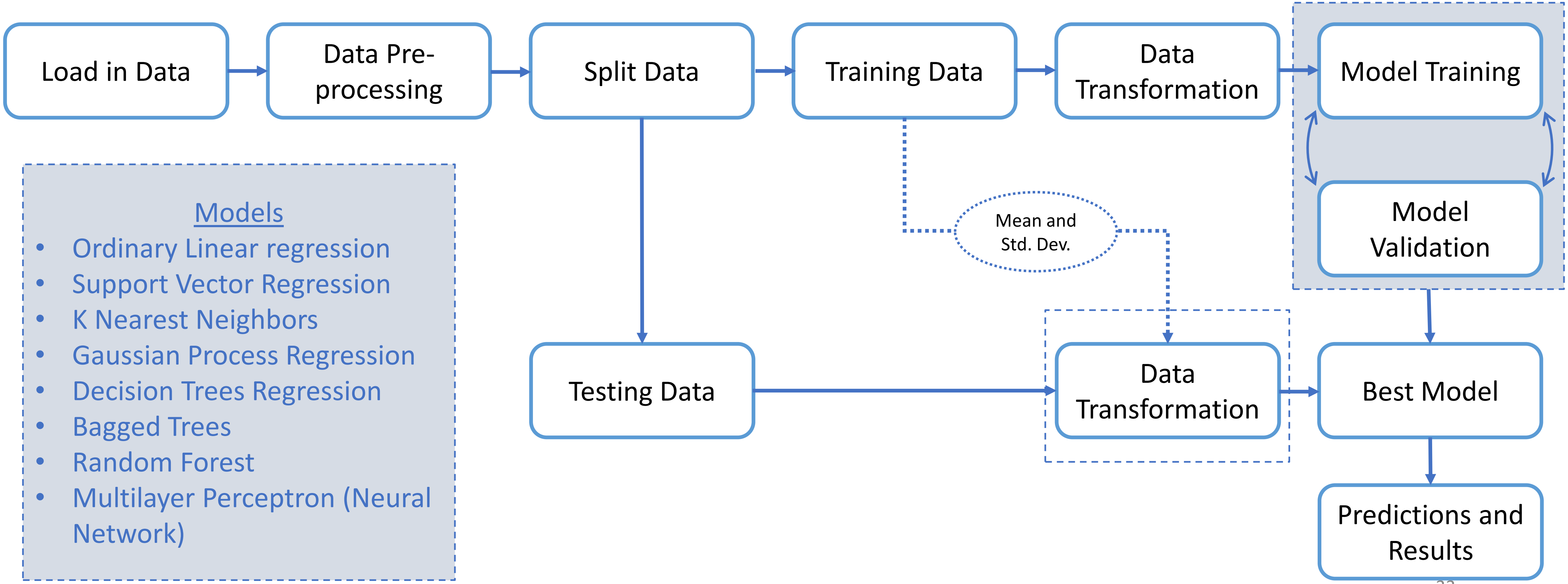
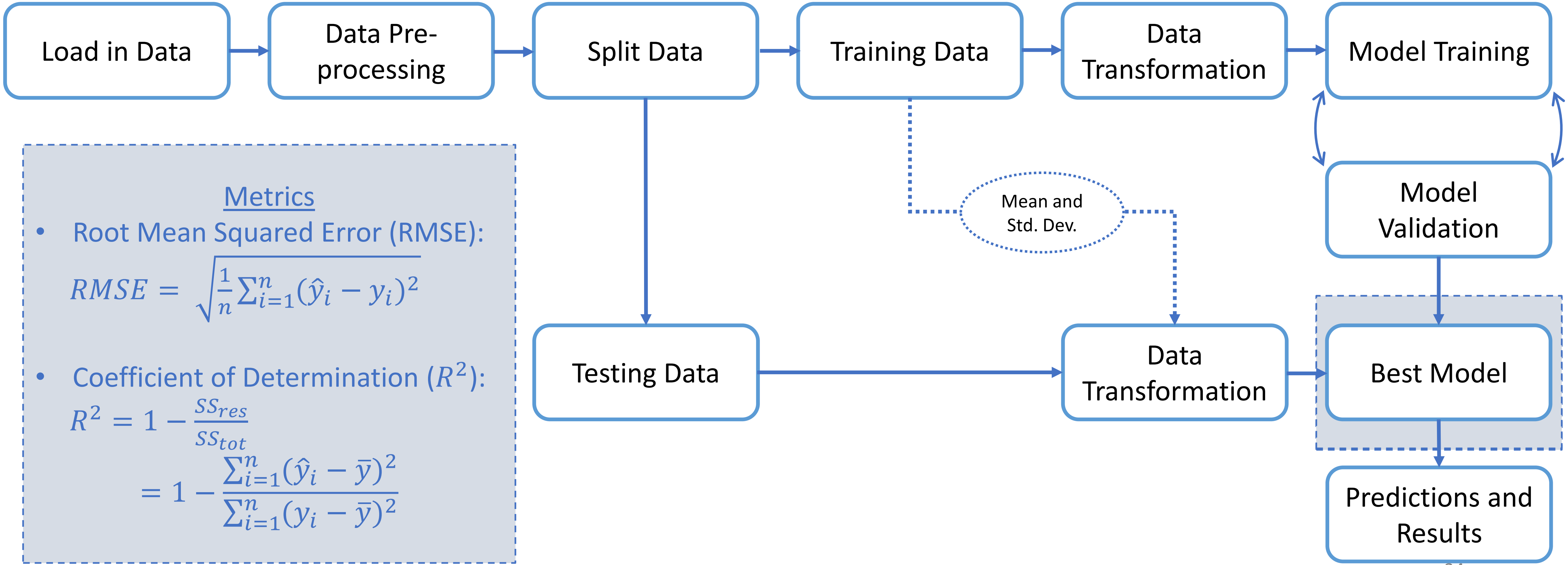


Table: Correlation Coefficient Matrix for (a) Subject 559 and (b) Subject 563

Machine Learning Pipeline Diagram



Machine Learning Pipeline Diagram



Metrics

- Root Mean Squared Error (RMSE):

$$RMSE = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(\hat{y}_i - y_i)^2}$$

- Coefficient of Determination (R^2):

$$R^2 = 1 - \frac{SS_{res}}{SS_{tot}}$$

$$= 1 - \frac{\sum_{i=1}^{n}(\hat{y}_i - \bar{y})^2}{\sum_{i=1}^{n}(y_i - \bar{y})^2}$$

Poor performance tracking glucose using Ohio dataset features

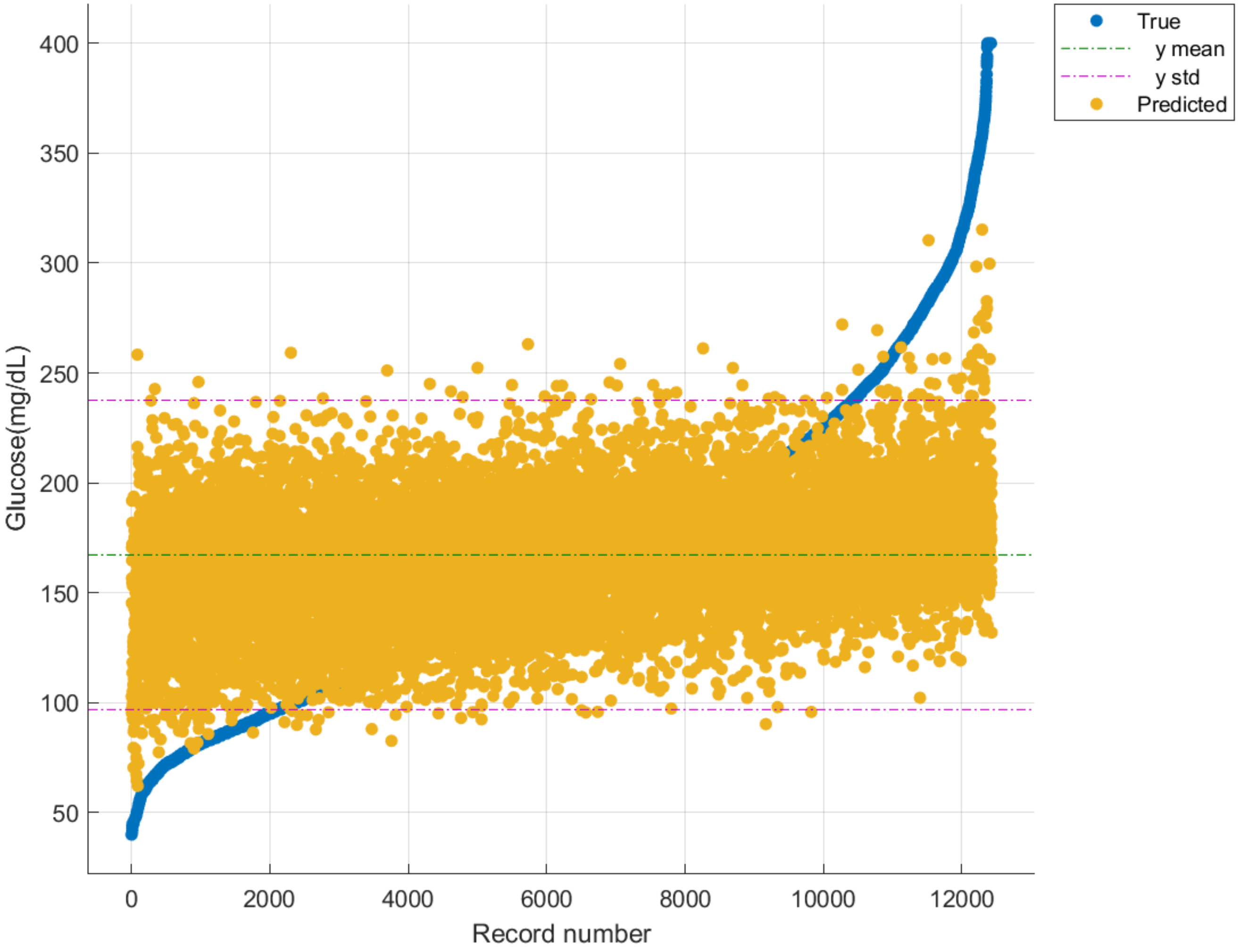


Figure: Predictions and True values vs the sample index

- Very poor performance
- Centers around mean and rarely predicts outside the one standard deviation of the true target data
- Features have no predictive power
- Best model: Bagged trees

Metrics	Subject 559
RMSE	66.321
R^2	0.11
Mean of true	167.23
Std. Dev. of true	70.36

Clarke Error Grid Analysis (CEGA)

- Scatterplot of the reference values plotted against the true values to determine the accuracy of the prediction
- 5 regions denoted A, B, C, D, E:
  A. Values fall within 20% of reference
  B. Falls outside 20%, but would not lead to inappropriate action
  C. Could cause the patient to make inappropriate actions.
  D. Could lead to harmful action due to lack of detection of hyper- and hypo-glycemia
  E. Confuses hyperglycemic for hypoglycemia and vice-versa

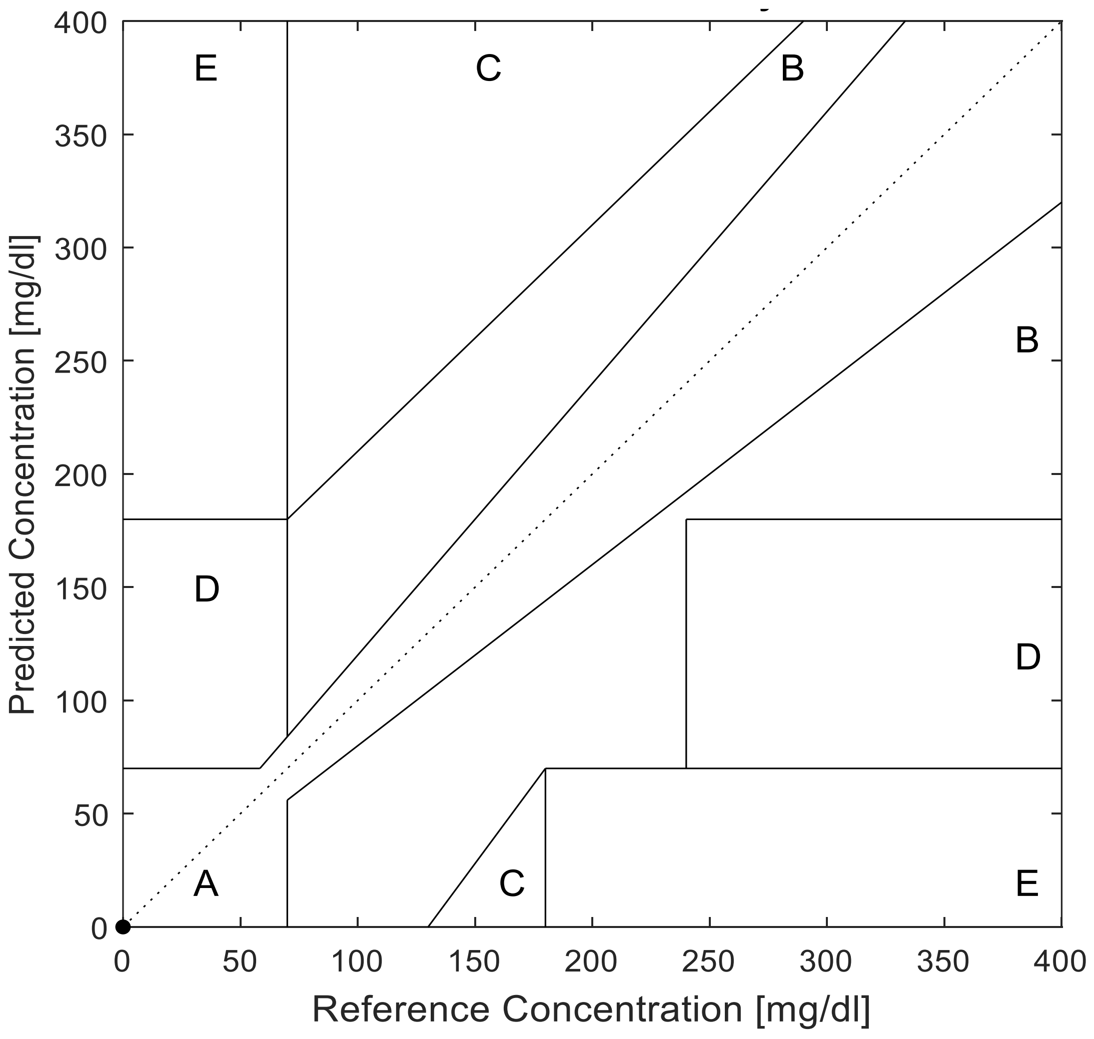


Figure: Example Error Clarke Grid

Aim 1: Ohio Data – Subject 559 – Results

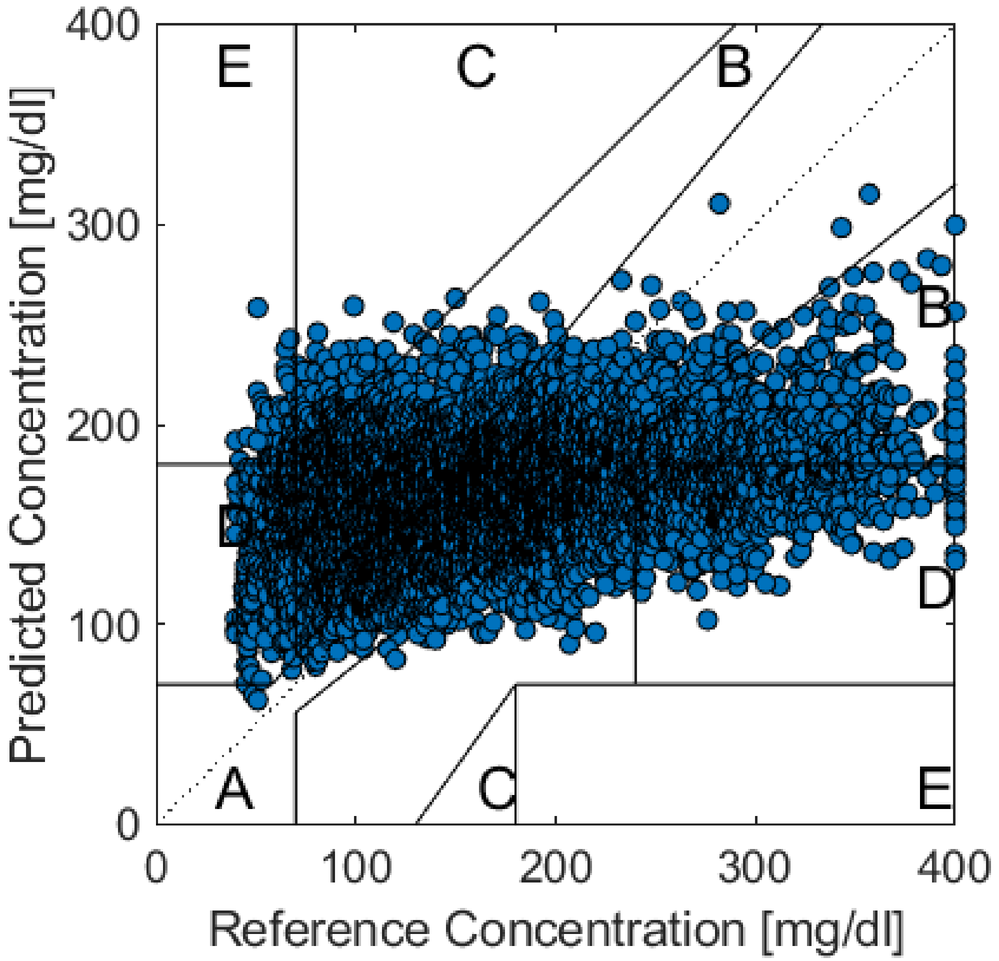


Figure: Error Clarke Grid for Subject 559

- Far too many predictions result in dangerous treatment
- R^2 value is to low to say the prediction represent the data

Metric	Subject 559
A	37.89%
B	49.02%
C	1.67%
D	10.80%
E	0.62%
Total	12432
RMSE	66.32
R^2	0.11

Aim 1: Ohio Data – Subject 563 –MATLAB APP Results

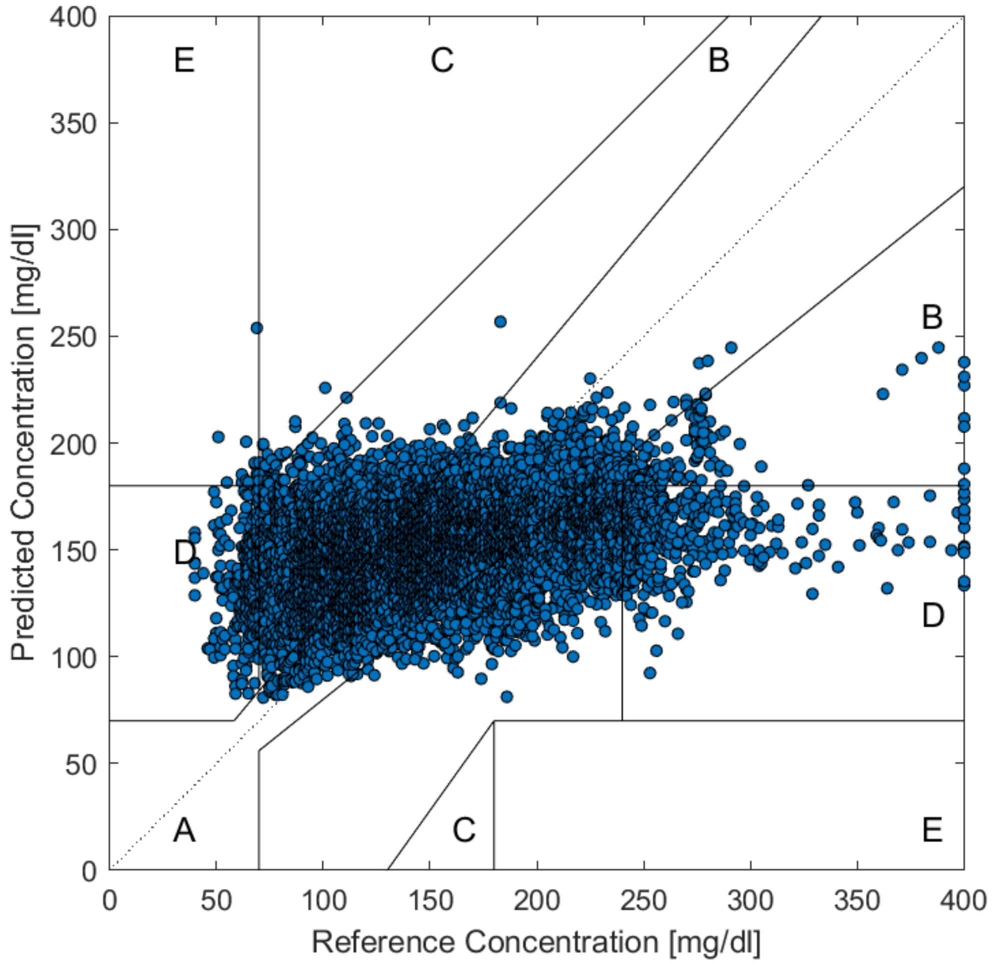


Figure: Error Clarke Grid for Subject 563

- Not surprisingly we see the same happen for Subject 563
- Lower RMSE resulting from lower variance

Metric	Subject 563
A	49.91%
B	43.83%
C	0.12%
D	6.03%
E	0.12%
Total	13008
RMSE	46.38
R^2	0.16

Can we monitor glucose in the healthy range?

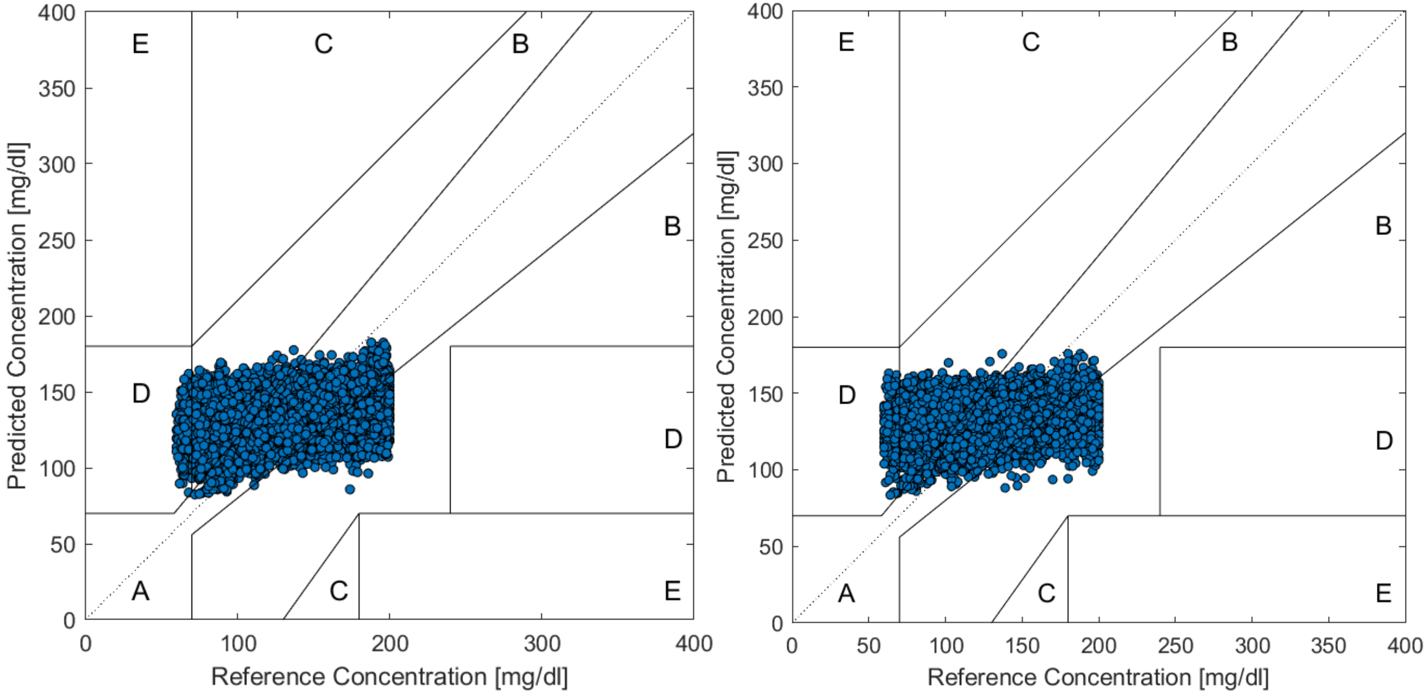


Figure: Error Clarke Grid for Reduced range (a) Subject 559 and (b) Subject 563

- Features are not sufficient even for those with a healthy range of blood glucose levels
- Further highlights why predictions don't have value

Metrics	Subject 559	Subject 563
RMSE	37.168	32.756
R^2	0.06	0.13

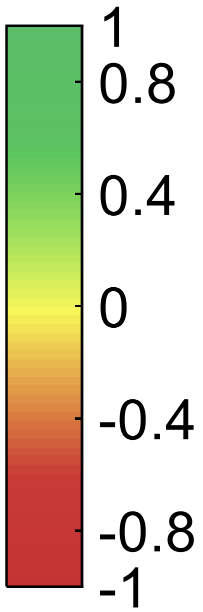
Aim 2: UofM Dataset

- Significantly more features than Ohio dataset
- 3 Subjects
  - Subject ID: 1,2,3
- Up to 15 vs 4 features

Value	Target	Predictors													
	Glucose	SpO2(%)	Heart rate	Motion	Amb. Humidity	Amb. Temp.	Moisture(%): Ventral	Moisture(%): Dorsal	Heat Flux (W/m)	Empatica: BVP	Empatica: IBI	Empatica: TEMP	Empatica: EDA	Systolic	Diastolic
Mean	87.30	96.72	75.05	2.32	49.40	21.52	41.56	40.93	622.63	-1.42	0.44	28.76	9.78	125.24	81.07
Std. Dev.	12.96	1.04	14.15	1.57	9.83	5.20	9.57	9.36	375.18	10.51	0.32	4.48	18.77	11.67	5.33
Min.	68.00	92.00	56.00	0.33	0.00	0.00	0.00	19.30	-438.21	-33.30	0.00	0.00	0.00	106.00	65.00
25%	78.00	96.31	64.67	1.27	48.35	20.63	39.20	35.80	325.07	-1.38	0.21	27.95	0.18	117.00	78.00
50%	83.00	96.97	71.43	1.97	50.10	21.00	43.20	39.70	615.68	-0.20	0.45	28.49	0.44	121.00	80.00
75%	96.00	97.28	83.32	2.83	52.75	21.70	46.55	46.35	819.54	0.69	0.65	29.36	6.97	130.25	83.63
Max	119.00	98.30	112.63	8.13	65.30	34.20	55.40	56.60	1248.14	57.16	1.33	39.34	80.99	163.00	94.00
Count	80.00	80.00	80.00	80.00	80.00	80.00	80.00	80.00	80.00	80.00	80.00	80.00	80.00	80.00	80.00

Subject 1 - Description of Dataset

Features	*Glucose*	*SpO2(%)*	*Heart rate*	*Motion*	*Amb. Humidity*	*Amb. Temp.*	*Moisture(%): Ventral*	*Moisture(%): Dorsal*	*Heat Flux (W/m)*	*BVP*	*IBI*	*Skin Temp*	*EDA*	*Systolic*	*Diastolic*
Glucose	1.00														
SpO2(%)	-0.02	1.00													
Heart rate	-0.32	-0.07	1.00												
Motion	-0.24	0.06	0.48	1.00											
Ambient Humidity	-0.08	0.18	0.02	-0.17	1.00										
Ambient Temp.	-0.10	0.13	-0.05	-0.18	0.86	1.00									
Moisture(%): Ventral	-0.24	0.05	0.22	-0.04	0.79	0.62	1.00								
Moisture(%): Dorsal	-0.19	-0.19	0.42	0.14	-0.10	-0.21	0.16	1.00							
Heat Flux (W/m)	-0.45	0.08	0.35	0.44	-0.10	-0.30	0.03	0.09	1.00						
Empatica: BVP	-0.04	-0.12	0.15	-0.02	-0.07	-0.05	-0.03	0.09	-0.02	1.00					
Empatica: IBI	0.05	-0.04	0.06	-0.07	-0.08	-0.23	0.06	0.27	0.06	0.09	1.00				
Empatica: TEMP	-0.05	0.23	-0.10	-0.30	0.16	0.25	0.10	0.04	-0.43	-0.01	-0.04	1.00			
Empatica: EDA	-0.45	-0.10	0.71	0.47	-0.04	-0.17	0.30	0.57	0.49	0.10	0.21	-0.05	1.00		
Systolic	-0.09	-0.02	0.71	0.46	-0.17	-0.38	0.12	0.49	0.32	0.10	0.24	-0.15	0.61	1.00	
Diastolic	-0.08	-0.09	0.39	0.14	-0.07	-0.27	0.10	0.42	0.30	-0.01	0.29	-0.12	0.48	0.47	1.00



Results of Trained Model on Unseen data (Subject 1)

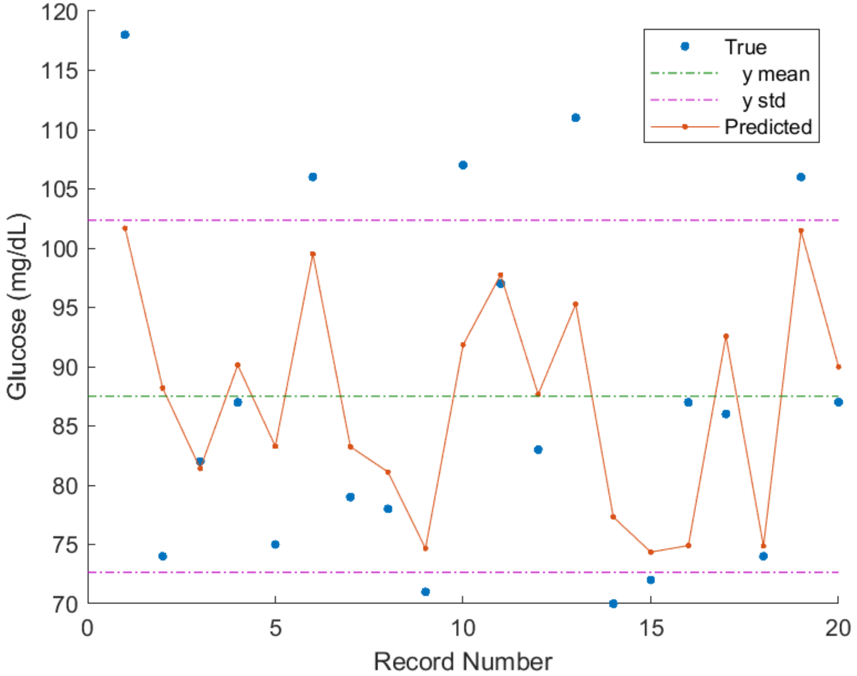


Figure: Plot of predictions for Subject 1

Metric	Subject 1
A	100.00%
B	0.00%
C	0.00%
D	0.00%
E	0.00%
Total	20
RMSE	8.39
R^2	0.71

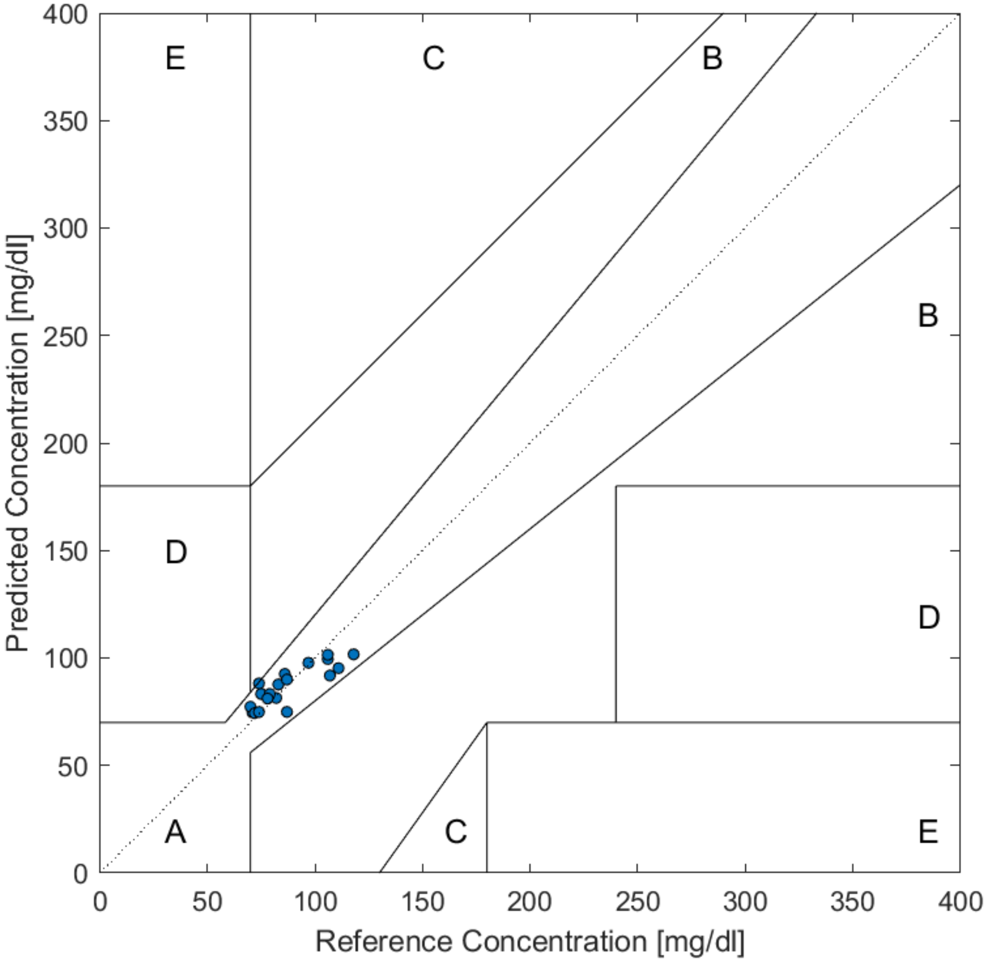


Figure: CEGA for Subject 1

- Model: Bagged Trees
- Split data into testing and training sets
- Performance on completely unseen data
- All values fall with the A
- Only 20 samples

Results of Subject 2

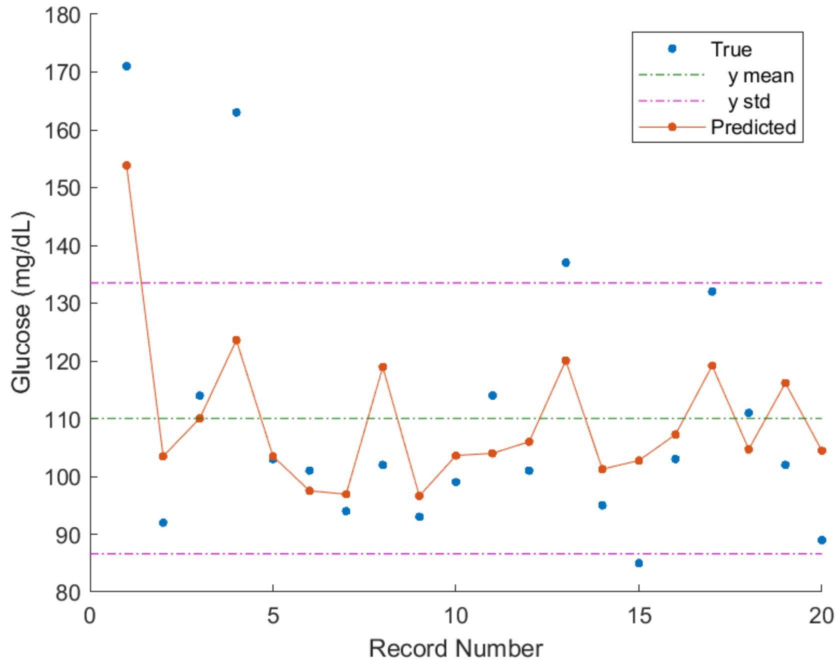


Figure: Plot of predictions, Subject 2

Metric	Subject 2
A	90.00%
B	10.00%
C	0.00%
D	0.00%
E	0.00%
Total	20
RMSE	13.72
R^2	0.72

- Model: Gaussian process regression (Rational Quadratic)
- Performance on completely unseen data
- All within A and B

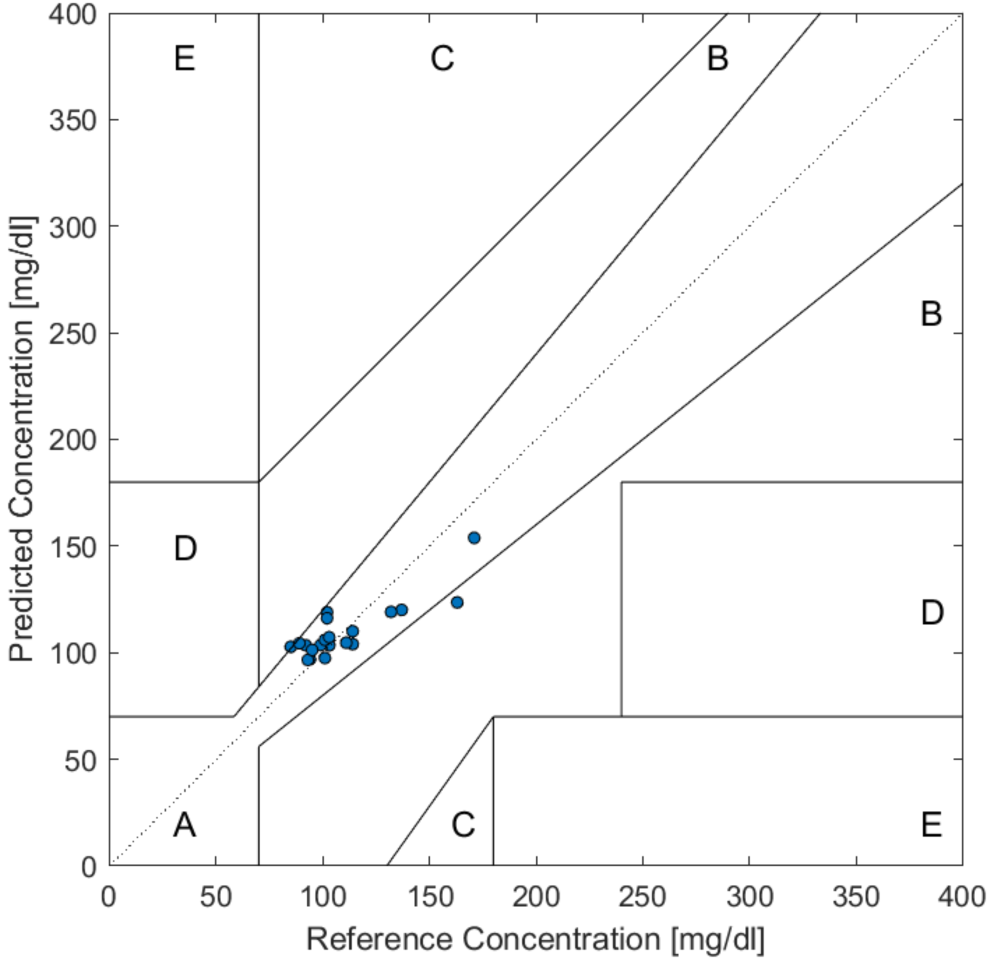


Figure: CEGA for Subject 2

Results from an Automated data collection

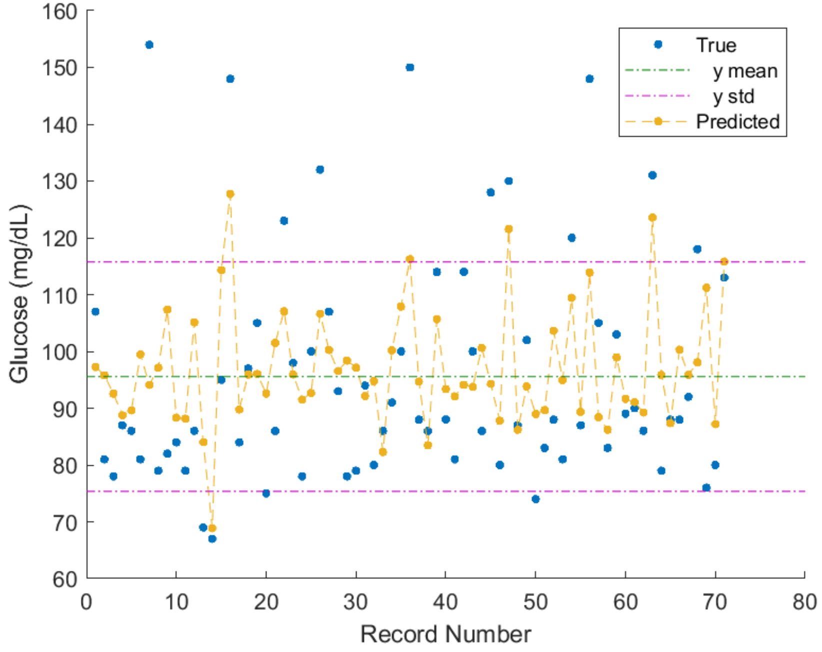


Figure: Plot of predictions, Subject 3

Metric	Subject 3
A	77.46%
B	21.13%
C	0.00%
D	1.41%
E	0.00%
Total	71
RMSE	15.84
R^2	0.40

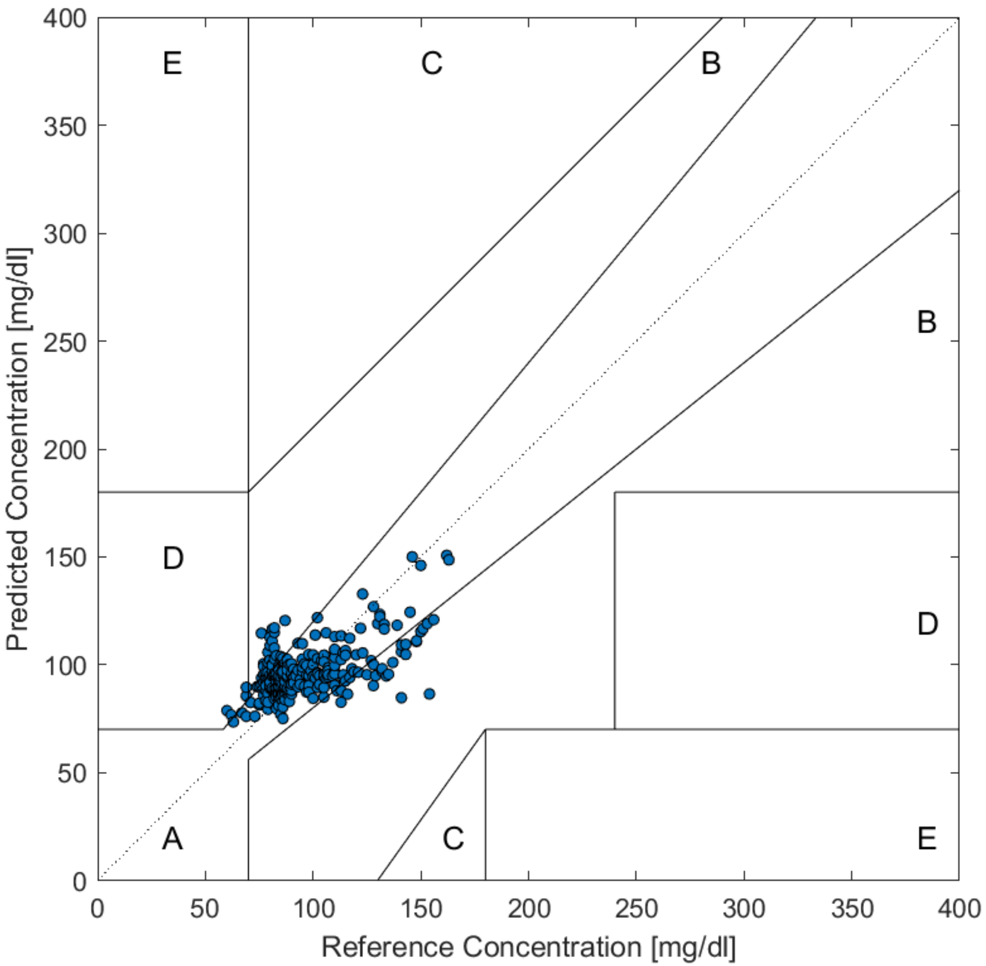


Figure: CEGA for Subject 3

- Model: Gaussian process regression (Matern 5/2)
- Some features were removed
- More relaxed data collection procedure
- Scalability of the features chosen

Conclusions

- Tested this hypothesis on 2 datasets
- Ohio had many samples but only 4 features
    - Not good enough for BGL predictions
    - Regardless of range
- Our dataset contains up to 15 features
- Features appear to increase predictive power when compared to the OhioT1DM dataset features
- Insufficient data to make any hard conclusions

Potential Pitfalls and Future Works

- Scalability of features
- Dataset is too small
- Curse of Dimensionality
- Variance of target data is too low
- Feature Extraction and Engineering
  - Heart Rate Variability and GSR
- Hyperparameter tuning
- More continuous target variable
- Add more output variables (e.g., blood pressure, blood iron)
- Explore generalization of Personal to Global Models (USAID)

Q & A