

Multi-dimensional Quantile Regression Using Polynomial Function Fitting for Insulin Sensitivity Forecasting

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Abstract: A significant portion of patients in the intensive care unit experience hyperglycemia, meaning abnormally high blood sugar levels. Prolonged hyperglycemia poses numerous risks, leading to organ damage in the medium-term and potentially life-threatening conditions. Therefore, insulin dosing is essential to regulate the blood sugar levels of hyperglycemic patients. The STAR protocol is an insulin dosing support, a so-called tight glycemic control protocol that uses insulin sensitivity among the patient's physiological parameters to characterize their current state. Estimating the patient's future SI is crucial for determining optimal treatment. Various methods exist for this estimation, and different metrics are available for evaluating these methods. The challenge in the estimation task is to determine not the expected value of future SI but its 90% confidence interval, which is necessary for implementing clinical protocols. The research presented in the article developed SI estimation methods using quantile regression, polynomial fitting, and neural network-based approaches. Multiple previous insulin sensitivity values were used as input parameters to improve prediction accuracy.

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1. INTRODUCTION

Tight Glycaemic Control (Chase et al. (2010, 2011b)) (TGC) performed in intensive care units is essential during intensive therapy to prevent stress-induced hyperglycemia, with its application potentially reducing mortality by 25–40% (Chase et al. (2011a); Stewart et al. (2016)). One such tight glycemic control protocol is the Stochastic TARgeted glycemic control (STAR) protocol (Evans et al. (2012); Fisk et al. (2012)), which is utilized in clinical practice in various parts of the world, including New Zealand, Hungary, and Belgium (Preiser et al. (2009)).

The STAR protocol employs a model-based approach relying on the Intensive Control Insulin-Nutrition-Glucose (ICING) model (Lin et al. (2011)). This is a pharmacokinetic model describing the metabolic system of the human body. A simplified visualisation of this model can be seen in Figure 1. The patient's blood glucose response can be calculated with the ICING model for a given treatment configuration (nutrition and insulin dosage). This model is used in a special way in the STAR protocol. The parameters of this model are considered constant by the protocol, except for insulin sensitivity (SI) (Lin et al. (2008)), allowing changes in the patient's condition to be described by altering the SI parameter.

The STAR protocol performs SI estimation (Benyó et al. (2020, 2023)) based on measured physiological parameters for the next 1-2-3 hours, providing recommendations for patient care. A distinctive feature of this estimation is that, instead of providing a specific value, it estimates a 90% confidence interval.

This paper proposes a new SI prediction using quantile regression, aiming to enhance the efficiency of the STAR protocol. Multiple previous insulin sensitivity values were used as input parameters to improve prediction accuracy. The proposed methods were evaluated by clinically relevant metrics and with the de-facto in-silico validation (Viceconti et al. (2021)).

2. METHODS

2.1 Quantile regression

Quantile regression uses the pinball loss (Steinwart and Christmann (2011)) as its error function, a variant of absolute error. The quantile regression model directly approximates specific percentiles, regulated by a parameter of the error function. Using quantile regression, we can estimate the 5th and 95th percentiles of the future value of SI, providing the desired 90% confidence interval. The method implementing quantile regression was realised in

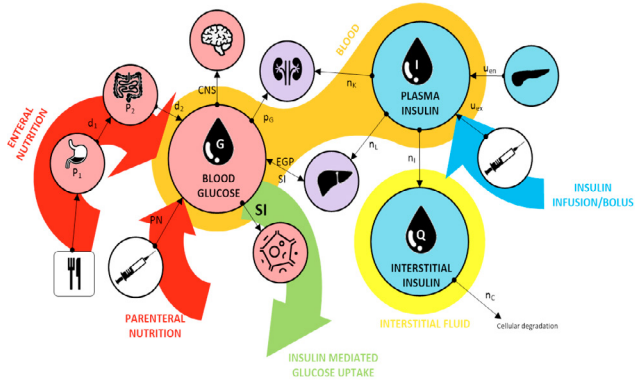


Fig. 1. Graphical representation of the ICING pharmacokinetic model. The different compartments are represented by different colours (Fisk (2014)).

two ways: one based on a neural network and the other on polynomial fitting.

In the case of the neural network-based method, a multi-layer neural network was trained. The mapping achieved by this network can be interpreted as a generic function whose behaviour can be controlled by real parameters.

The essence of training based on polynomial fitting is to attempt fitting tangents to the available data points, striving to map the rules within the data.

Two prediction models are developed using different lengths from the patient's SI history:

- the prediction called 2D prediction - predicting $SI(t+1)$ based on $(SI(t); SI(t-1))$:

$$SI(t+1) = F_{2D}((SI(t); SI(t-1))); \quad (1)$$

- the prediction called 3D prediction - predicting $SI(t+1)$ based on $(SI(t); SI(t-1); SI(t-2))$:

$$SI(t+1) = F_{3D}((SI(t); SI(t-1); SI(t-2))). \quad (2)$$

2.2 Dataset

The data of patients who spent at least 12 hours in the intensive care unit was selected from the patient cohort undergoing treatment using the STAR protocol. The patient records with obvious data processing errors (e.g. out of physiological range measurements) were also excluded.

After the exclusions, data from 2375 patients were included in the dataset: 2220 from Christchurch, 109 from Gyula, and 28 from Liege. The dataset comprises 92,646 blood glucose measurements, representing a total of 159,573 hours spent in the intensive care unit. The dataset was divided into two parts: data from 20% of the patients were withheld for in-silico validation, and these patients were not used during training.

The patient data selected for training various networks included 123,988 SI values. The distribution of these datapoints can be seen in Figure 2.

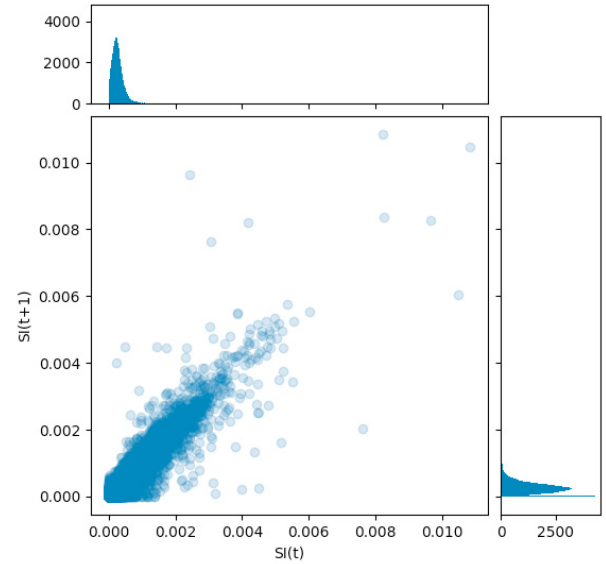


Fig. 2. The patient dataset shown in a $(SI(t); SI(t+1))$ space.

2.3 Metrics

Because of the uniqueness of the confidence interval prediction problem, multiple clinically relevant metrics were suggested.

The success rate (SR) indicates the percentage of data within the obtained 90% confidence interval. It calculates individually for each data point whether it truly falls above the 5th percentile and below the 95th percentile. The resulting value is a number between 0 and 1, with a higher value above 0.9, indicating a better result. The calculation of the success rate can be formalised as follows:

$$m_{SR} = \frac{N_{in}}{N} \quad (3)$$

where m_{SR} is the success rate, N_{in} is the number of datapoints that are in the predicted interval and N is the number of datapoints.

The interval ratio (IR) represents the ratio of areas between the originally applied STAR protocol and the new prediction's 5th and 95th percentiles. If the result is 1, it means the two areas are equal; a value less than 1 is favourable, indicating a successful narrowing of the predicted range. The calculation can be formalised as:

$$m_{IR} = \frac{1}{N} \sum_{i=0}^N \frac{h_i - l_i}{r_i}, \quad (4)$$

where m_{IR} is the interval ratio, N is the number of datapoints, l_i and h_i are the endpoints of the i -th confidence interval, and r_i is the width of the predicted interval calculated by the reference prediction method.

The iscore (IS) metric combines the previous two. The improvement of SR has a negative effect on IR since a narrower interval may result in fewer or the same number of points falling within it, and vice versa. The IS metric provides ideal reference predictor intervals until it matches the SR of the examined predictor. Afterwards, it compares the ratio of interval widths, where the quotient becomes

the rate of the examined predictor's interval. If the IS is 1, there is a complete match, and a higher value indicates a better result. The i-score metric can be formalised as:

$$m_{IS} = \frac{\text{icdf}\left(0.5 + \frac{m_{SR}}{2}\right)}{\text{icdf}(0.95) \cdot m_{IR}} \quad (5)$$

where m_{SR} is the success rate, m_{IR} is the average interval ratio, and $\text{icdf}()$ is the inverse cumulative distribution function of the standard normal distribution.

3. RESULTS AND DISCUSSION

Figure 3 shows the resulted confidence intervals of the 2D polynomial fitting based quantile regression method visualised over the entire dataset. Blue dots represent the original ($SI(t); SI(t+1)$) datapoints, orange dots represent the 5th percentiles, and green dots represent the 95th percentiles over the entire physiologically relevant range of SI. The figure shows the projection of the results to a 2D space defined by $SI(t)$ and $SI(t+1)$. It can be seen that the majority of original data points corresponding to the treatment hours fall between the green and orange points.

A similar visualization of the 3D results is much more difficult in the 2D space as the prediction depends on multiple values. Figure 4 shows the projection of the results to a 2D space defined by $SI(t)$ and $SI(t+1)$. However, using the above-described notation, multiple green and orange points will belong to a single $SI(t)$ value in this figure. Thus, the visual interpretation of the results and the recognition of the 5th and 95th percentiles is not obvious.

K-fold cross-validation was used to assess the accuracy of the 2D and compare the accuracy of the 2D and 3D SI predictions. Table 2 presents the accuracy of 2D and Table 2 the accuracy of 3D Polynomial fitting-based method expressed by SR, IR, and IS.

Figures 6,7, and 5 present the SR, IR, and IS results of the five folds in the K-fold cross-validation of the 2D and 3D SI predictions in the form of boxplots. In terms of SR, the 3D slightly exceeds the 2D prediction. However, with a broader prediction range reflected by higher IR, IS worsens.

Table 3 shows the comparison of the prediction accuracy of the 2D and 3D predictions, and in addition to this, it compares the predictions with the one dimensional (1D) SI prediction, i.e. $SI(t+1) = F_1D(SI(t))$ (Pintér et al. (2024)). As can be seen, the accuracy of the prediction by SR metric is improved by the 3D prediction compared to the 2D version but worsened by the IR and IS. The improvement in SR was $0.908-0.900=0.008$, the deterioration in IR was $0.701-0.663=0.038$, and $1.477-1.517=0.040$ in IS. However, the prediction accuracy is improved by the 2D prediction compared to the 1D prediction according to IS metric $1.517-1.49=0.040$.

Table 1. KFold cross-validation: 2D Polynomial fitting-based method

Fold	0	1	2	3	4	Mean	Standard deviation
SR	0.915	0.901	0.900	0.869	0.917	0.900	0.017
IR	0.732	0.664	0.641	0.598	0.681	0.663	0.044
I-Score	1.431	1.509	1.563	1.535	1.545	1.517	0.046

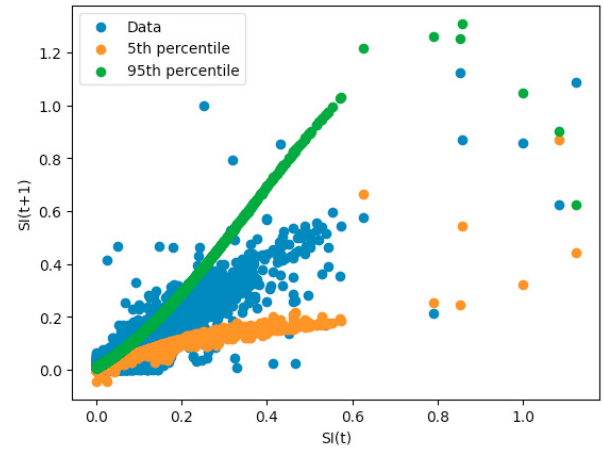


Fig. 3. The confidence intervals of the 2D polynomial fitting based quantile regression method visualised over the collected dataset. The figure shows the projection of the prediction results to a 2D space defined by $SI(t)$ and $SI(t+1)$. Blue dots represent the dataset, orange dots represent the 5th percentiles, and green dots represent the 95th percentiles.

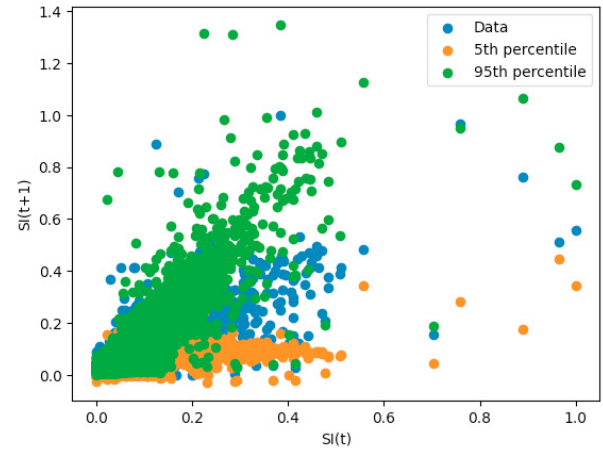


Fig. 4. The confidence intervals of the 3D polynomial fitting based quantile regression method visualised over the collected dataset. The figure shows the projection of the prediction results to a 2D space defined by $SI(t)$ and $SI(t+1)$. Blue dots represent the dataset, orange dots represent the 5th percentiles, and green dots represent the 95th percentiles.

Table 2. KFold cross-validation: 3D Polynomial fitting-based model

Fold	0	1	2	3	4	Mean	Standard deviation
SR	0.880	0.884	0.939	0.916	0.922	0.908	0.023
IR	0.627	0.634	0.809	0.742	0.694	0.701	0.069
I-Score	1.508	1.508	1.410	1.415	1.545	1.477	0.055

4. CONCLUSIONS

This paper presented two quantile regression-based SI prediction methods using two and three previous-hour values of the SI—both methods combined polynomial fitting with quantile regression. The prediction accuracy of the proposed methods was compared with each other and with a method using just the current IS value for the

Table 3. Comparison table of the 1D/2D/3D polynomial fitting-based prediction metrics

Method	1D	2D	3D	2D vs. 1D	3D vs. 1D	3D vs. 2D
SR	0.88 - 0.90	0.900	0.908	0	0.008	0.008
IR	0.67 - 0.69	0.663	0.701	-0.007	-0.007	-0.038
I-Score	1.43 - 1.49	1.517	1.477	0.018	-0.002	-0.040

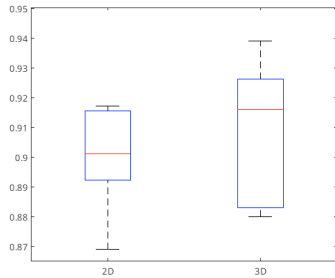


Fig. 5. Boxplot presenting the Success Rate results of the five folds in the K-fold cross-validation of the 2D and 3D SI predictions.

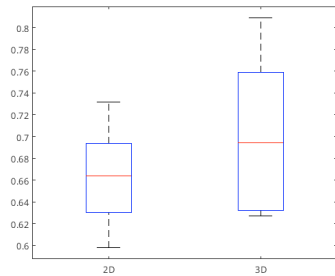


Fig. 6. Boxplot presenting the Interval Ratio results of the five folds in the K-fold cross-validation of the 2D and 3D SI predictions.

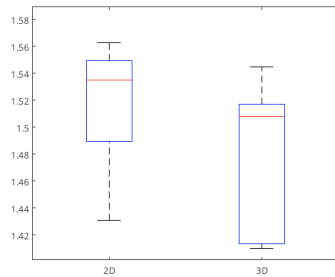


Fig. 7. Boxplot presenting the iscore results of the five folds in the K-fold cross-validation of the 2D and 3D SI predictions.

prediction. Even though slight improvements were seen in some of the methods assessing the prediction accuracy, the improvement of applying a longer patient history was not as apparent as was expected based on similar works (Uyttendaele et al. (2019)). A potential reason for this observation is that the quantile regression method is not efficient when used with multiparameter models, resulting in sophisticated decision surfaces as prediction borders. This shortcoming of the quantile regression method will be investigated with benchmark problems.

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