Institute for Design and Control of Mechatronical Systems

Prediction of hypoglycaemia of T1DM patients by means of the "Guaranteed Error Machine"

Presentation

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Motivation

- Type 1 Diabetes Mellitus (T1DM) patients can‘t regulate their blood sugar level due to a lack of capacity to produce insulin
- resulting high blood sugar level causes severe health issues like blindness, kidney disease, nerve damage, and heart and circulatory system problems
- common treatment is the administration of insulin via injection
- overdose of insulin or false injection-timing can cause a hypoglycaemia (low blood glucose level) which untreated can result in tiredness, lapse of concentration and in case of an extreme low blood glucose level even paralysis and brain damage

GEM

Problem:

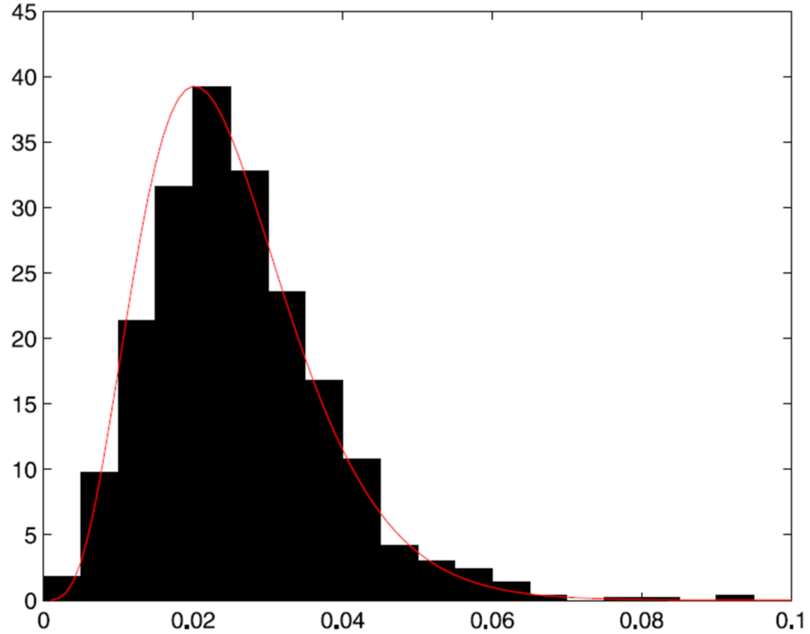
- An arbitrary and unknown mechanism generates instances x_i with corresponding binary outputs y_i
- x_i : input vectors (d-dimensional), N in total
- y_i: binary outputs, one y for each x

GEM

- Use geometrical shapes (ellipses, circles, ellipsoids, spheres) that connect points with one specific output (0 or 1) and that are enlarged until touching points of another output (shapes are found through the solution of a convex optimization problem)
- The points on the boundary of a shape are called 'active instances'
- The algorithm stops as soon as k 'active instances' are found, k in advanced fixed by user
- The sort of the shapes and the sequence in which they are constructed, depends on the dimension d and the value of k
- The probability for wrong predictions does not depend on the mechanism that generates instances x_i, nor on the function y(x), but only on the size of the training set N and the tuning parameter k

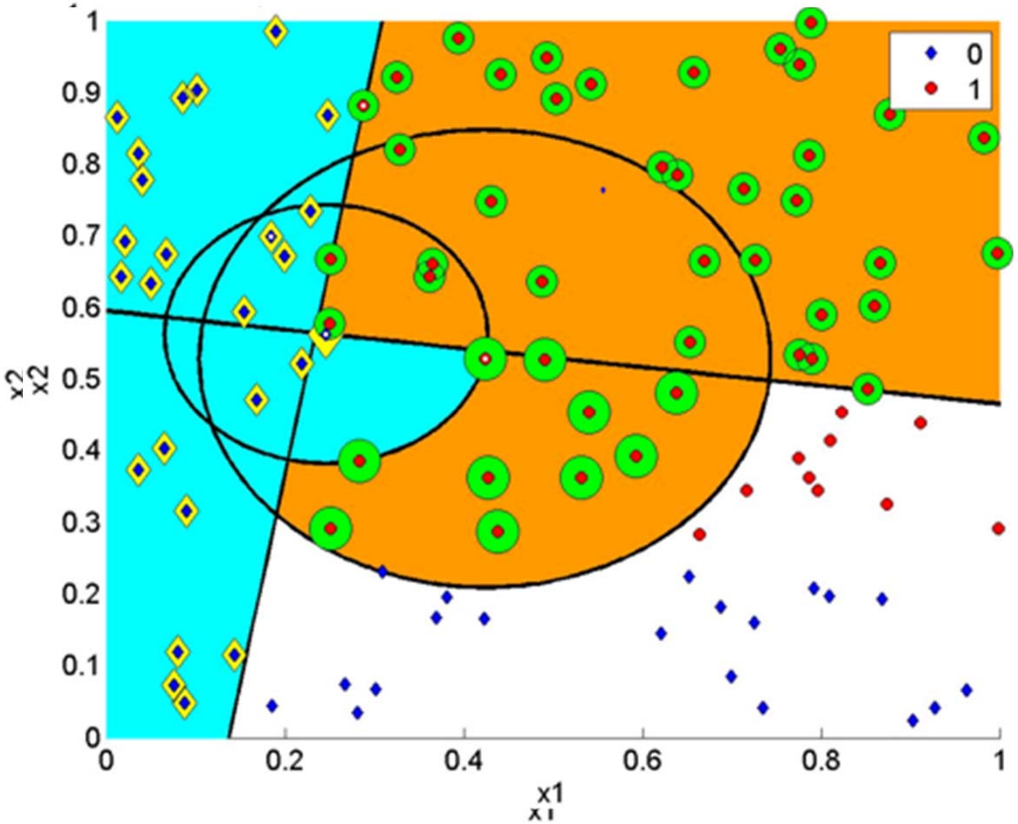
GEM

$$E[PE(y_N)] = E\left[\frac{wrong}{wrong + right + unclassified}\right] = \frac{k}{N}$$



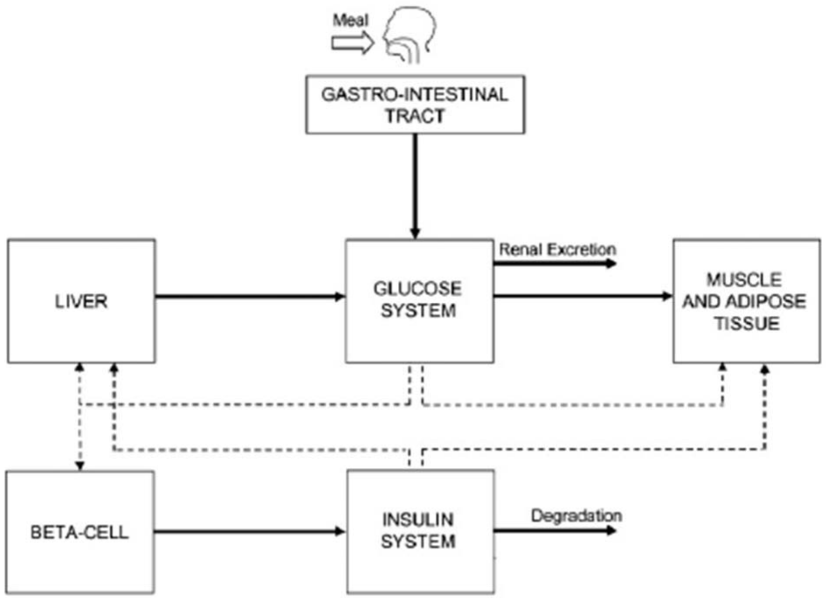
Probability-density function for PE 2%, Beta- Distribution

GEM



Example training GEM

The "Virtual Patients"



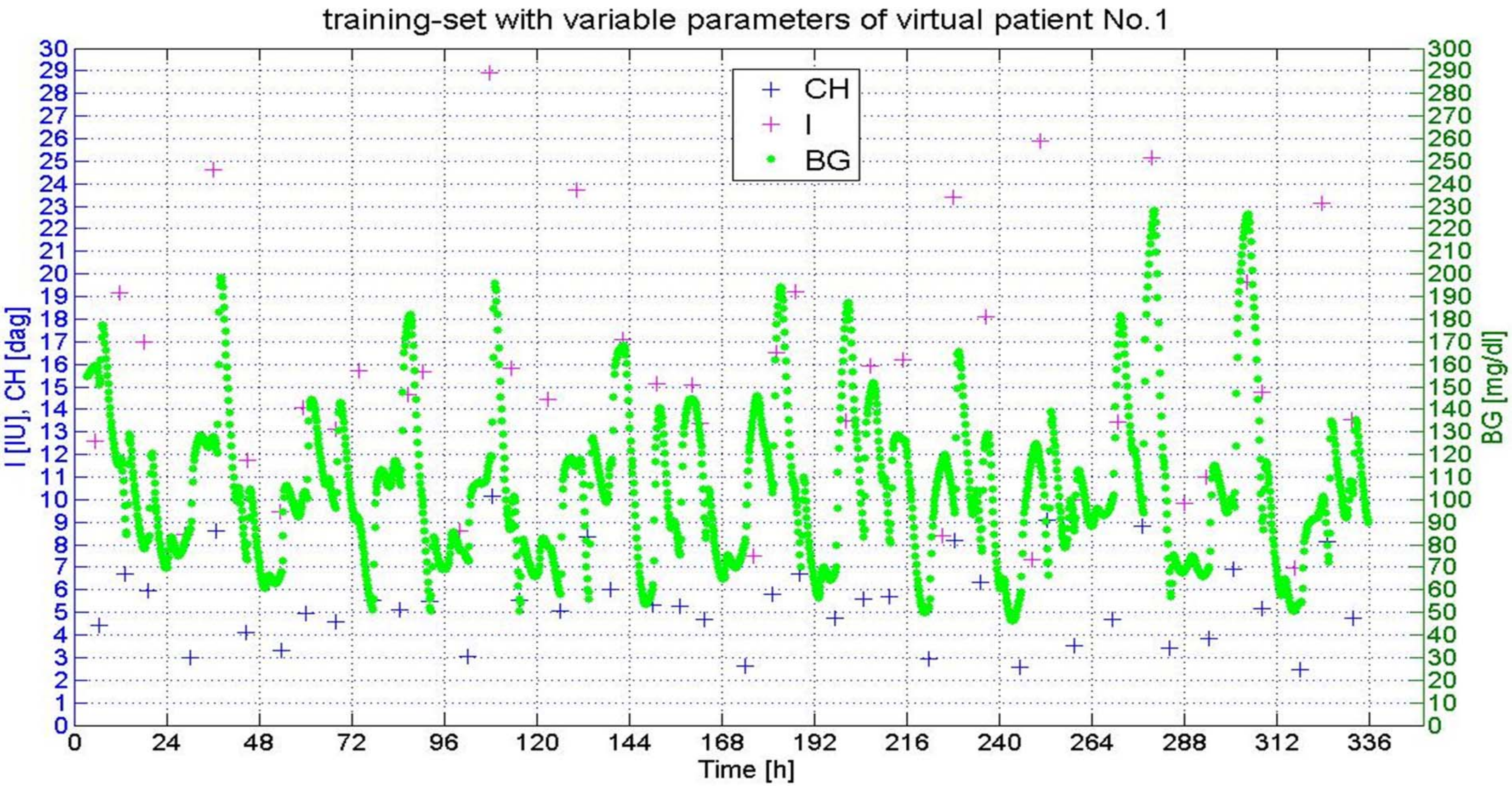
„Dalla Man and Cobelli" model

- database 204 subjects
- 10 artificial individuals, the so-called virtual patients
- T1DM, failing of the β-cells
- mainly made up of linear models
- UVA/Padova-Simulator in SIMULINK is based on this model

Generating datasets with UVA/Padova-Simulator

- This was done for two different types of „Virtual Patients“
  - constant patient parameters
  - variable patient parameters
    - glucose-intestinal-absorption rate
    - the insulin-absorption rate
    - steady-insulin-plasma state
- A training-set (14 days), a verification-set (14 days) and a test-set (7 days) for each patient were created
- To cause a large number of hypoglycaemia states, doses and timing of each meal as well as the insulin doses and timing were varied, even the possibility to throw up, after the insulin injection was implemented
- A sampling time of 10 minutes was chosen

Generating datasets with the UVA/Padova-Simuator

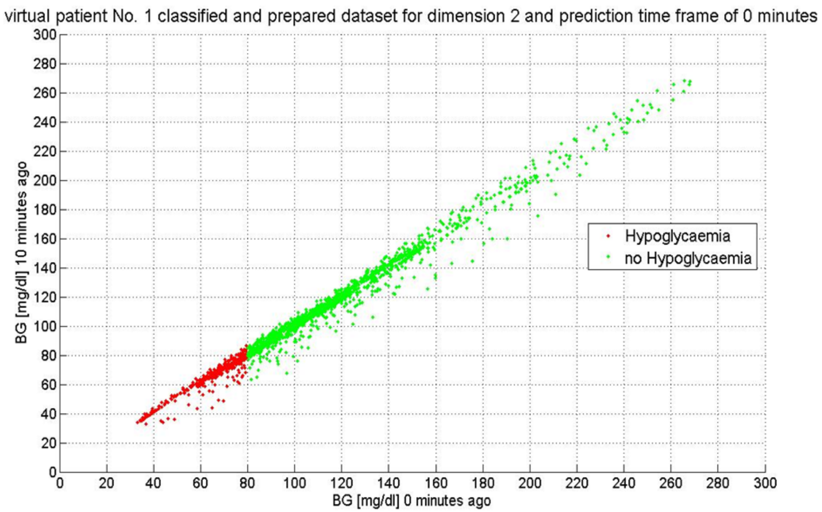


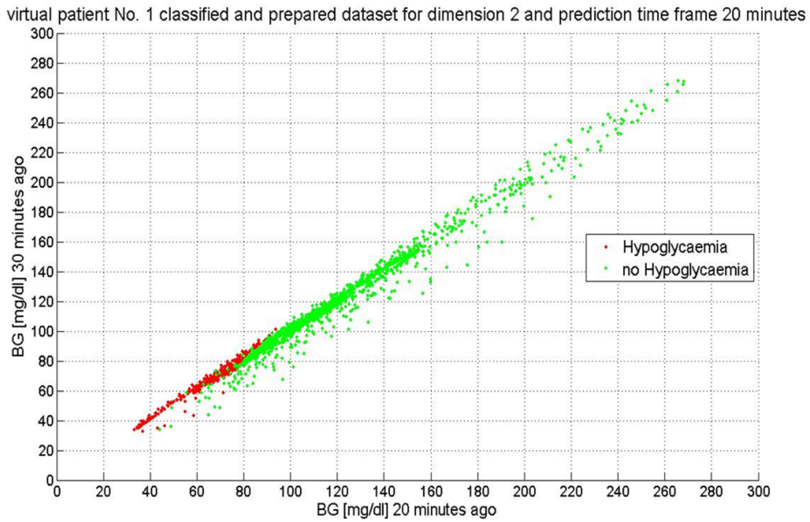
Training-set example „Virtual Patient“ No. 1, variable parameters

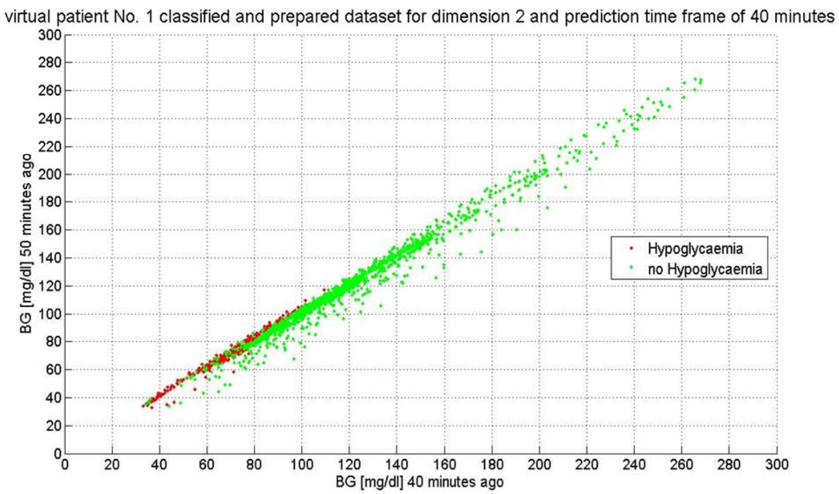
Real Patients

- Data for the two Real Patients were gathered in two different clinical studies
- Different Types of "Continuous Glucose Monitoring Sensor" were used.
- The training-set and the verification-set of each real patient were only half as long as the sets of the virtual patients (7 days)
- The datasets contained a significantly lower number of hypoglycaemic instances
- Data had to be prepared, due to sensor malfunctions and the resulting gaps in the datasets.

Prediction of hypoglycaemia of T1DM patients by means of the "Guaranteed Error Machine"







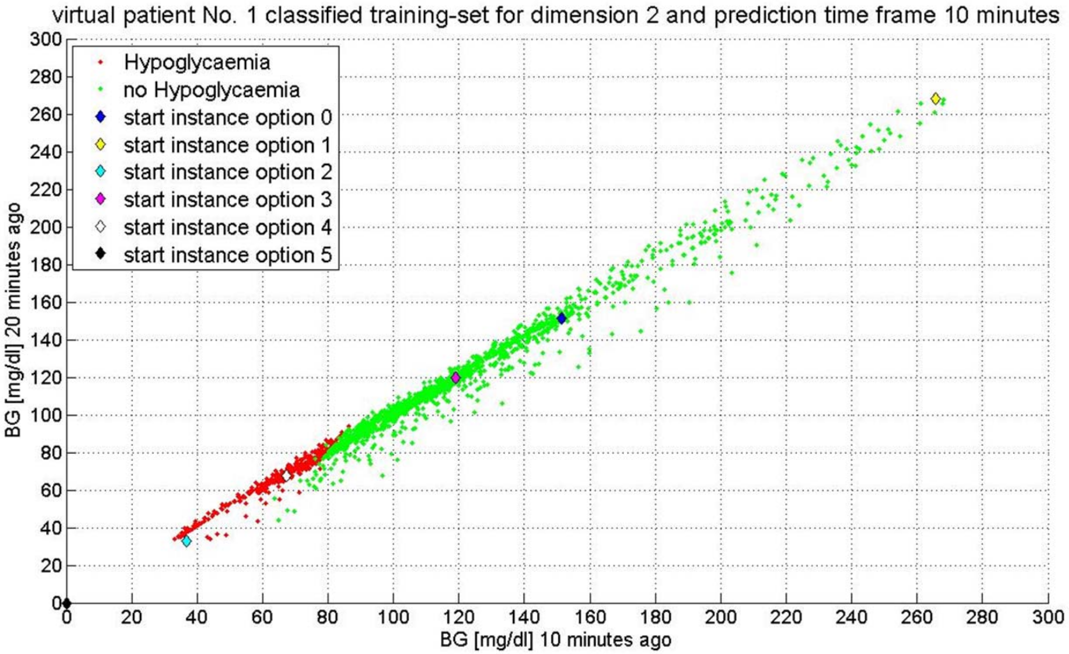
Training-set Vektor (point) plot, „Virtual Patient“ No. 1, constant, limit 80 mg/dl

Prediction of hypoglycaemia of T1DM patients by means of the "Guaranteed Error Machine"

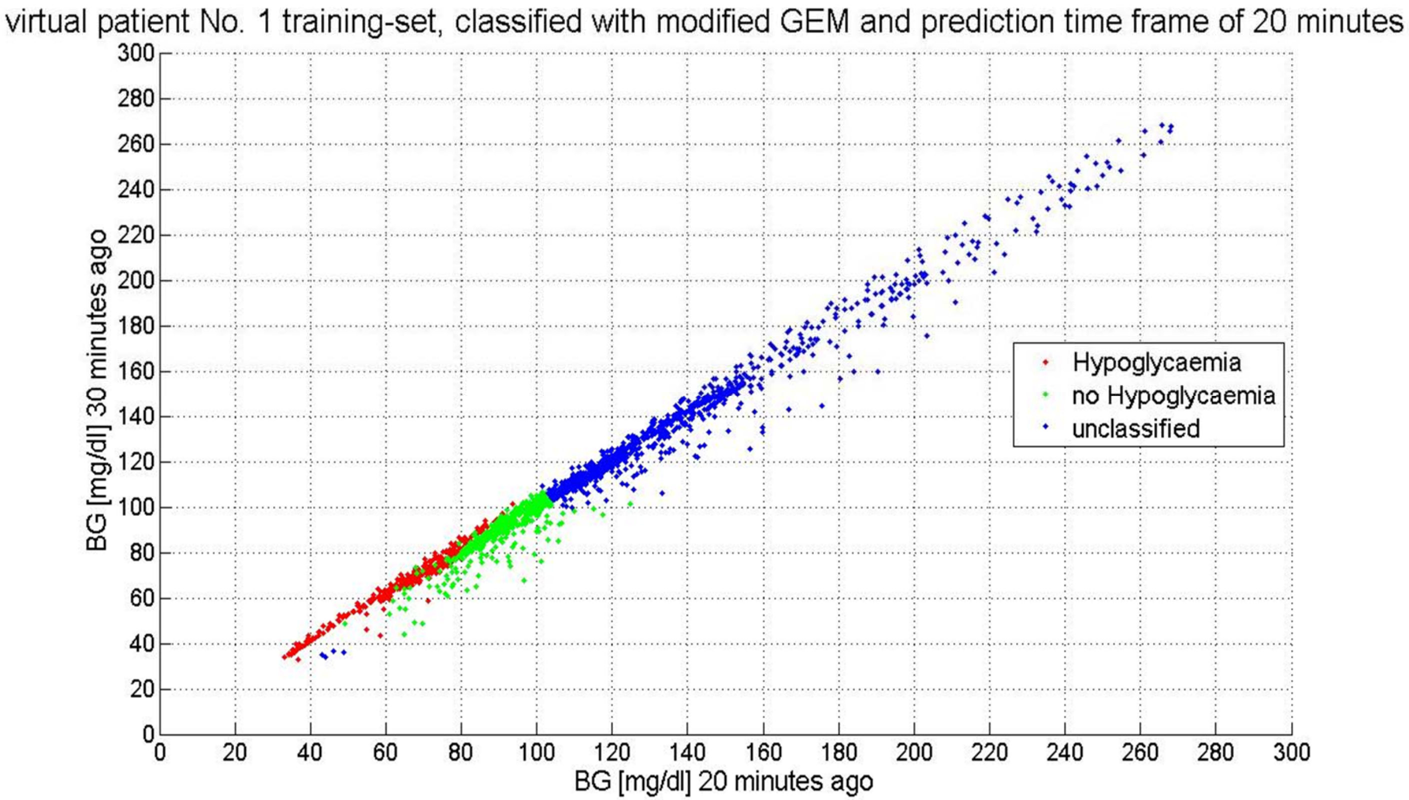
Problems / Modifications

- high number of unclassified instances, due to the concentration of instances
- high dependency from starting instance x_B

- forced the algorithm to create k shapes (one active instance per shape)
- a starting condition was implemented
- tested on simple geometric examples, PE slight deviation from the *Beta*-distribution



Prediction of hypoglycaemia of T1DM patients by means of the "Guaranteed Error Machine"



Training-set vector (point) plot, „Virtual Patient" No. 1, constant, limit 80 mg/dl
modified GEM trained

GEM applied on patients

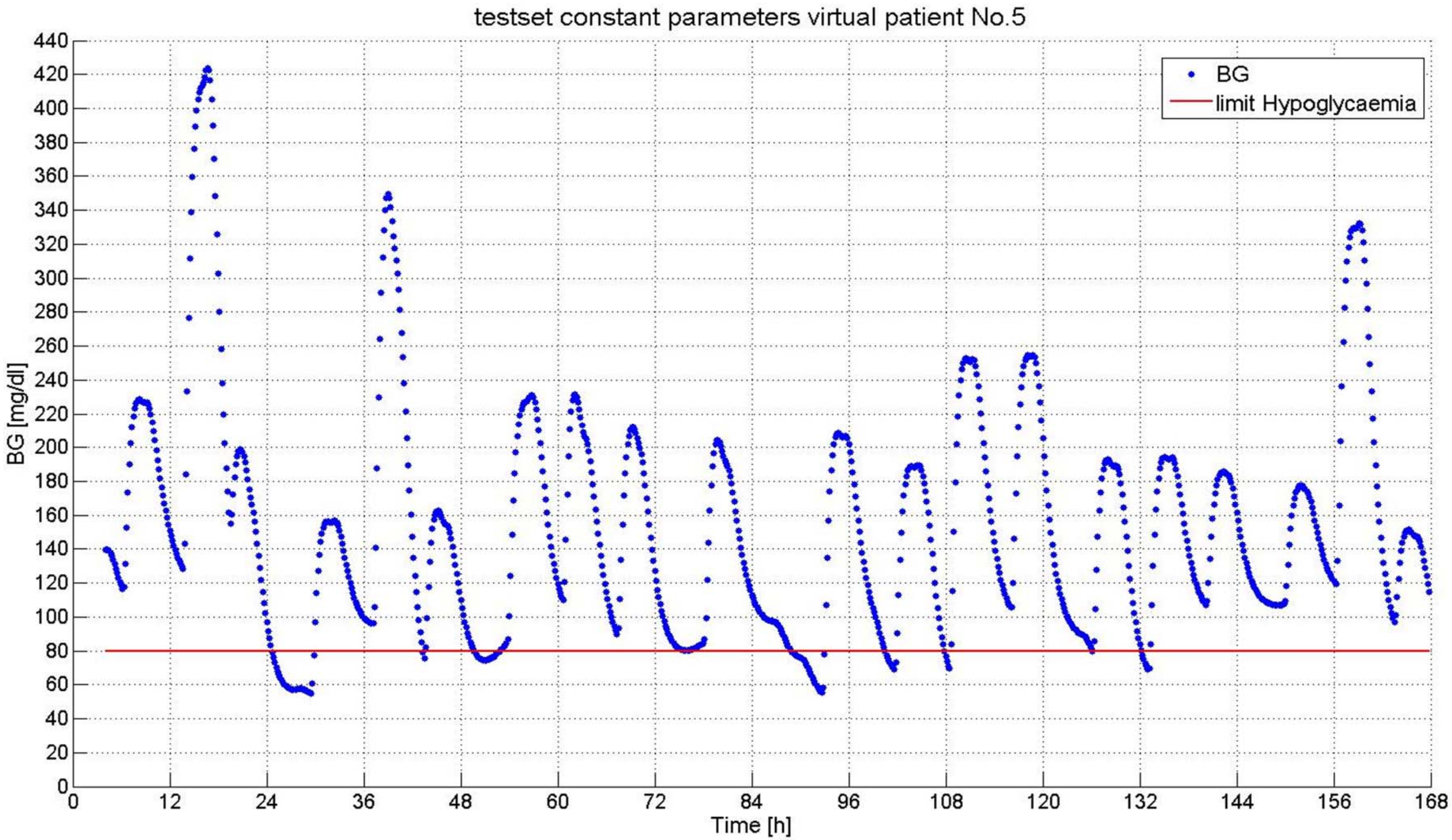
- For prediction time frames of 30 and 40 minutes two GEM with different dimensions were trained

$$d_1 = \frac{minutes - Ts}{Ts}, d_2 = \frac{minutes}{Ts}$$

- hypoglycaemia limits
  - Virtual Patients: 80 mg/dl
  - Real Patients: 70 mg/dl
- *k* was increased incremental for each case (different shapes)
- The verification-set was used two lower the computing time. For every increment of *k*, the GEM was tested on this set and if less than 10% percent of the hypoglycaemic states remained unclassified, the incrementation stopped.
- The criteria of the for ideal examples were used do determine *k*, $E\left[PE(\hat{y}_{N\ trining-set})\right]$ = 3%

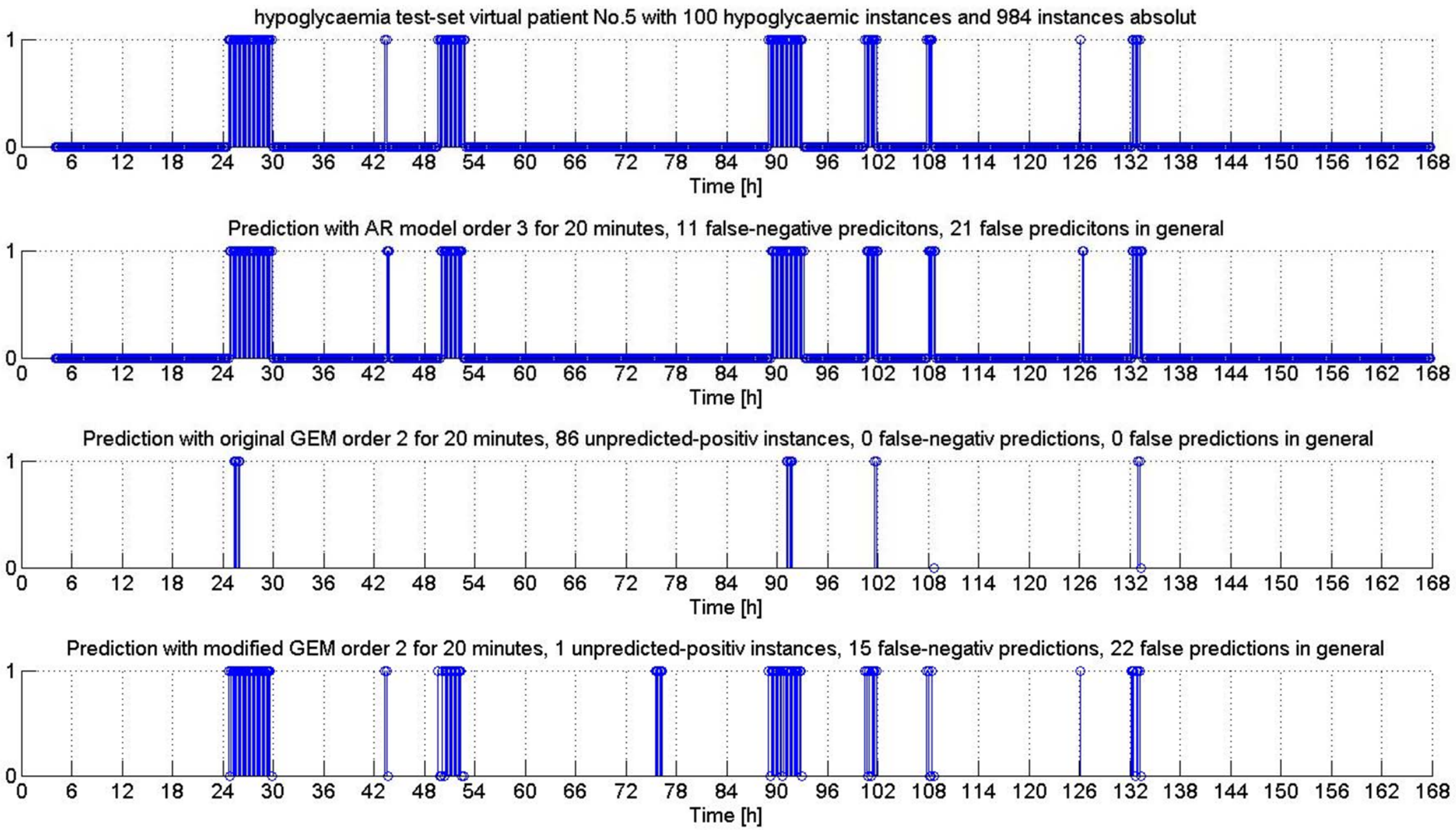
$$k_{max\ training-set} = \frac{E\left[PE(\hat{y}_{N\ trining-set})\right]\ N_{training-set}}{100}$$

Prediction of hypoglycaemia of T1DM patients by means of the “Guaranteed Error Machine”



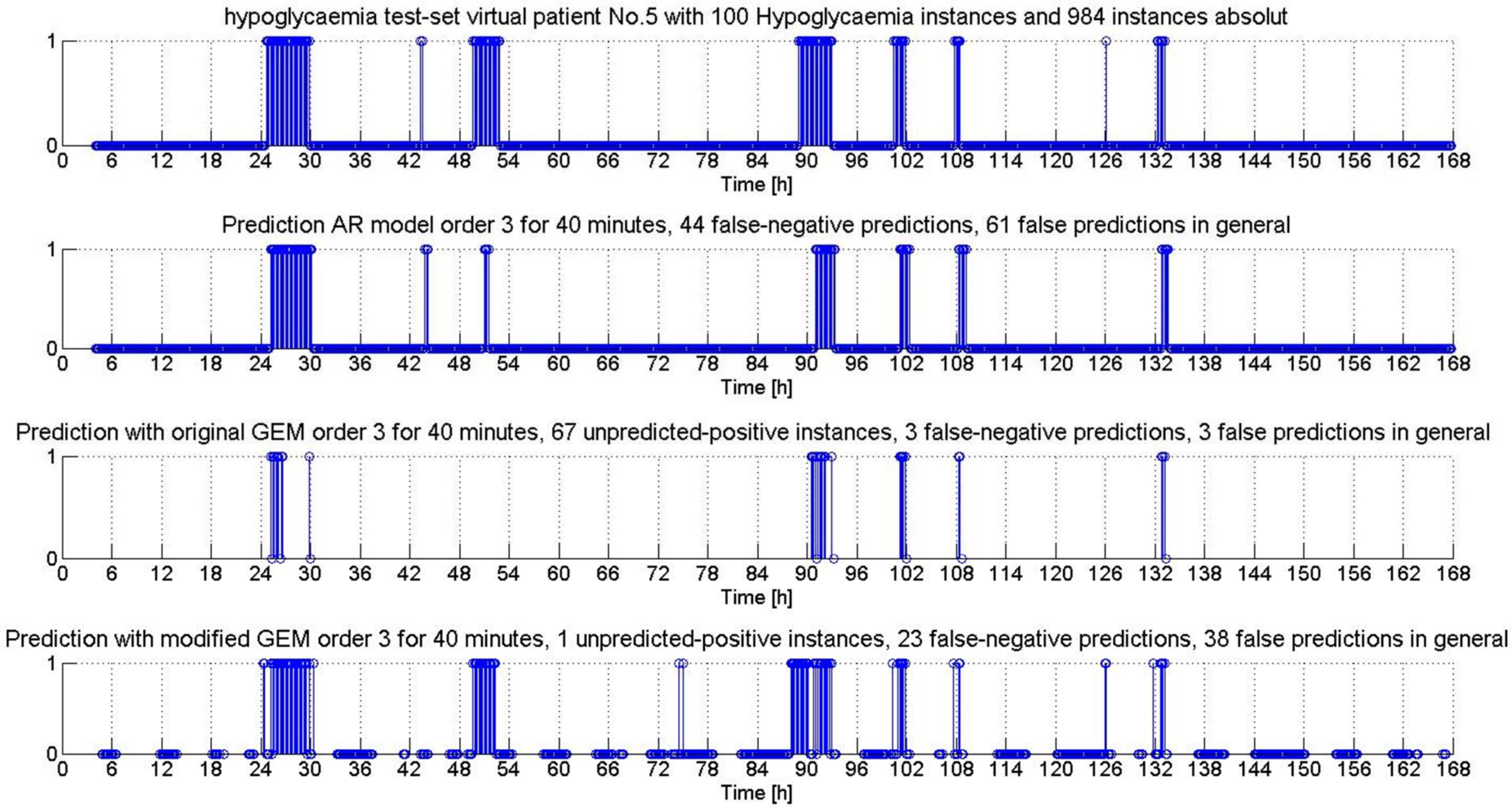
Test-set „Virtual Patient“ No.5, constant parameters, limit 80mg/dl

Prediction of hypoglycaemia of T1DM patients by means of the "Guaranteed Error Machine"



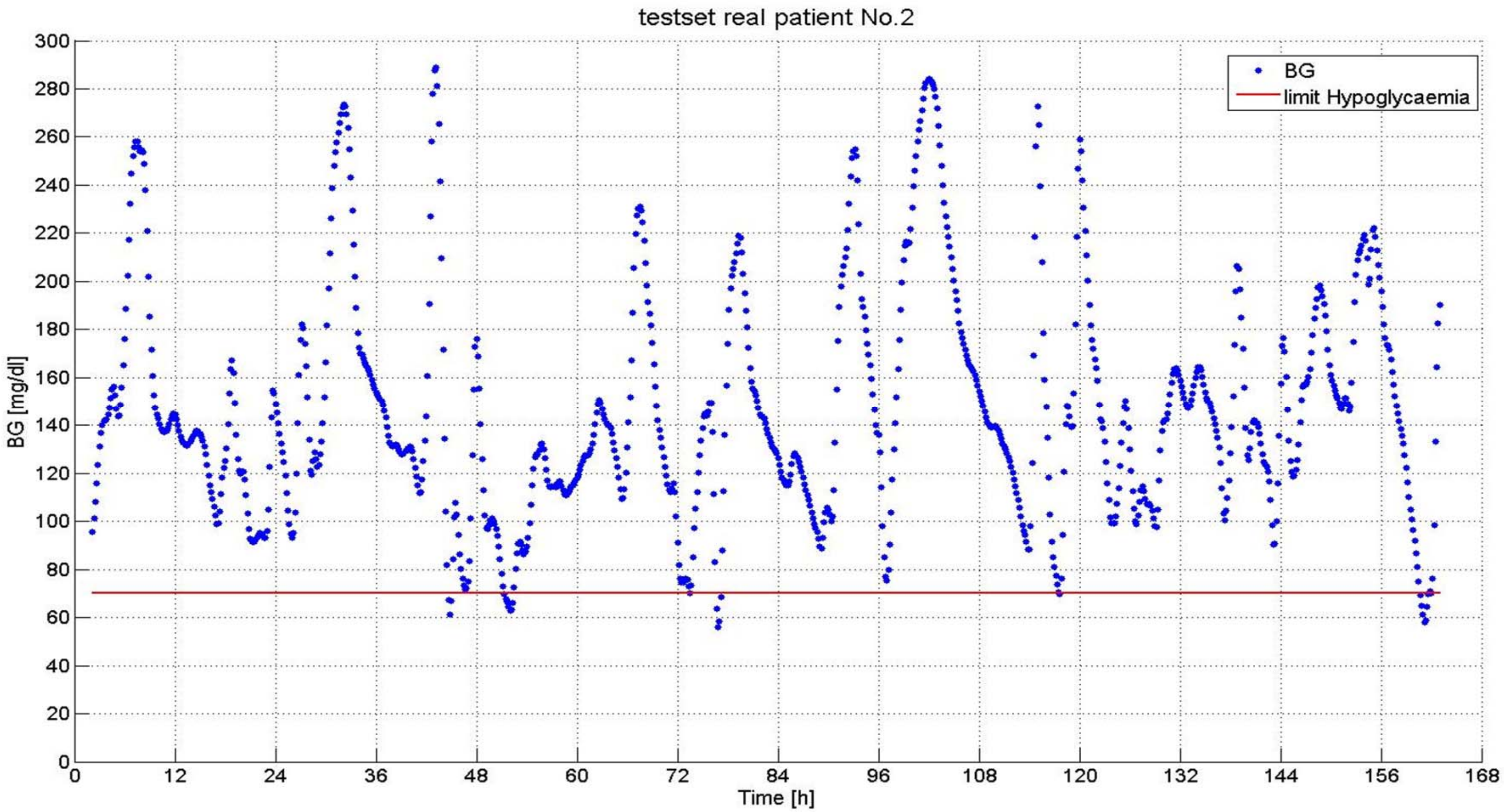
Results „Virtual Patient" No.5, constant parameters, predicted time frame 20 minutes

Prediction of hypoglycaemia of T1DM patients by means of the "Guaranteed Error Machine"



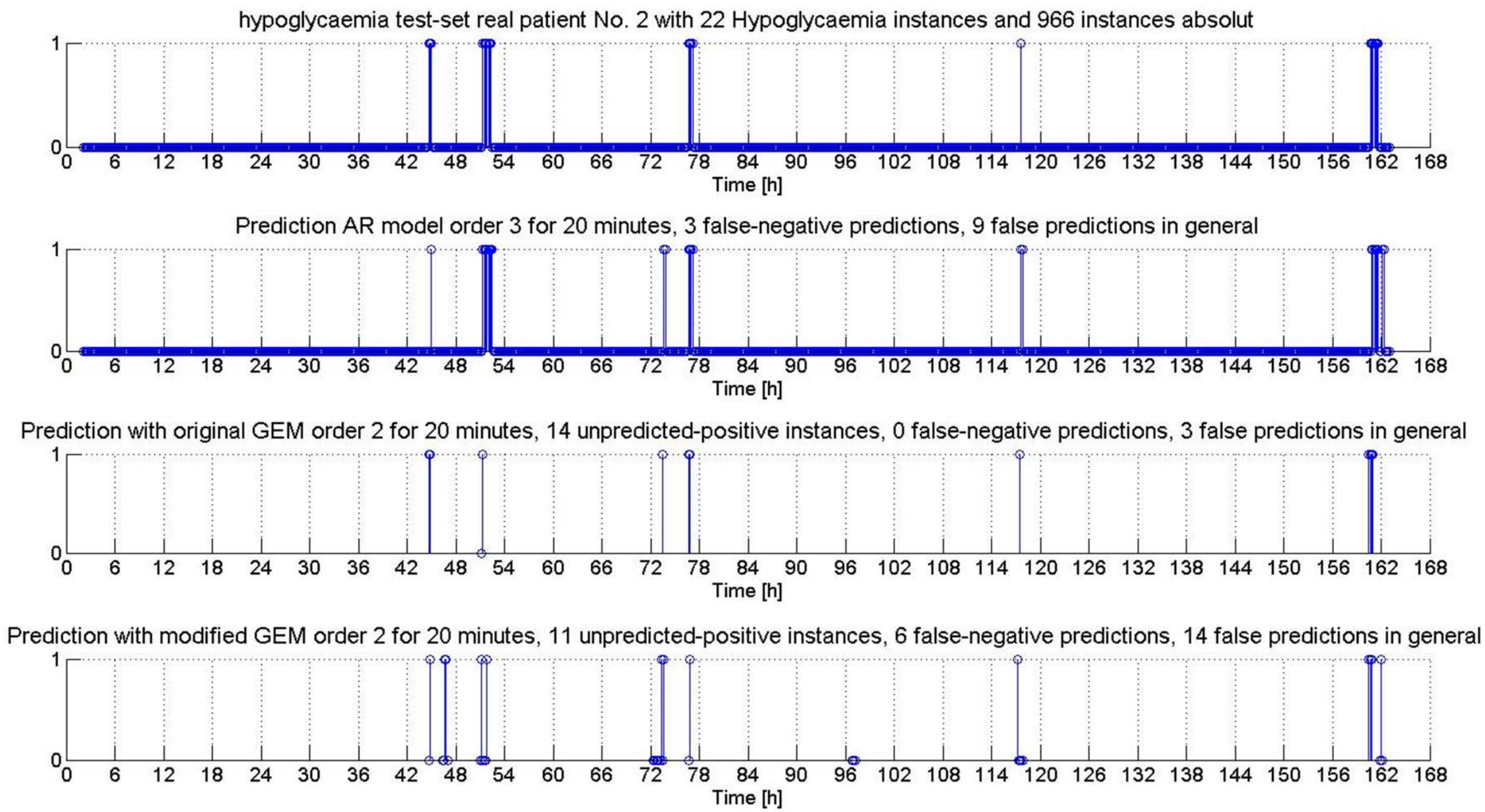
Results „Virtual Patient" No.5, constant parameters, predicted time frame 40 minutes

Prediction of hypoglycaemia of T1DM patients by means of the “Guaranteed Error Machine”



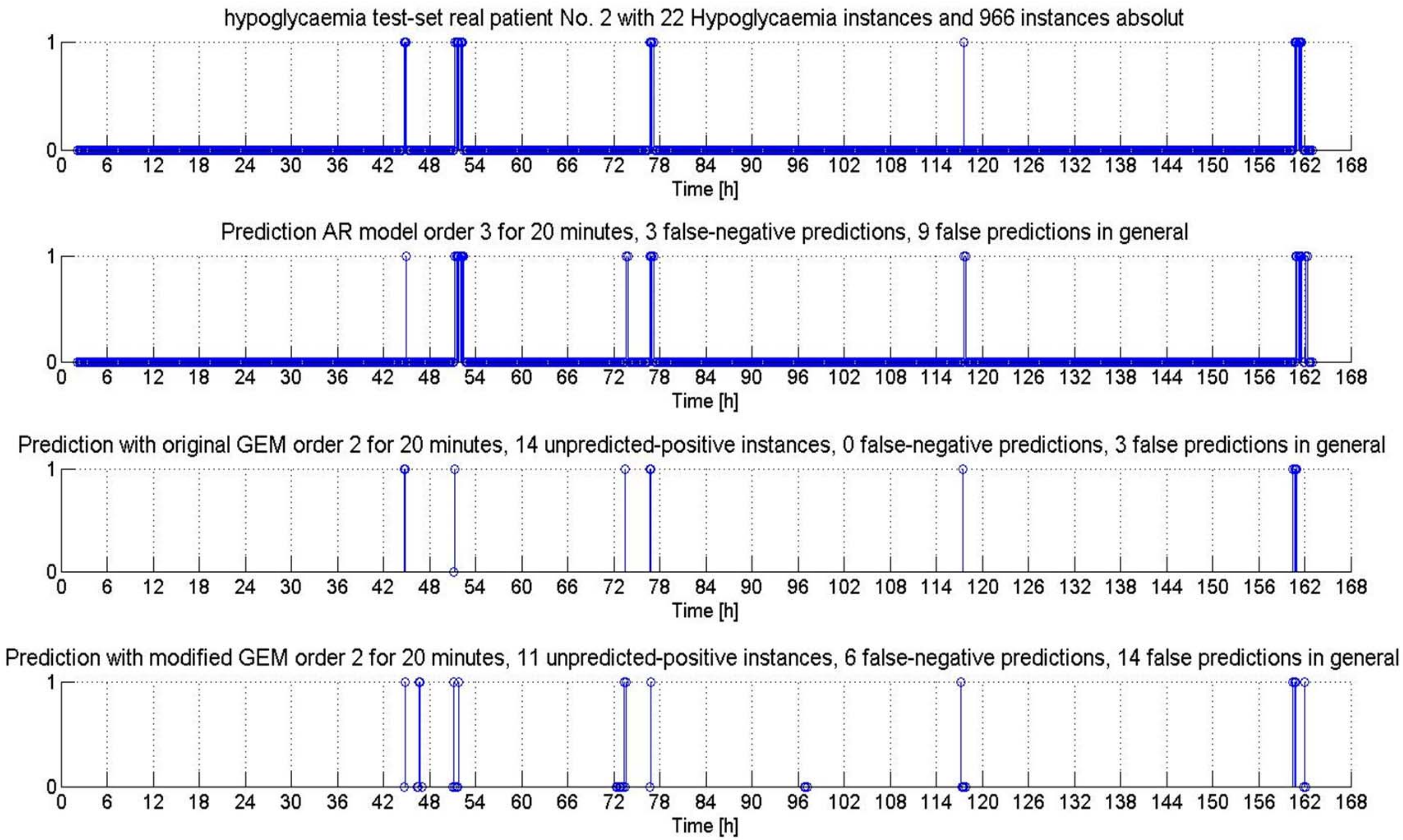
Test-set „Real Patient“ No.2, constant parameters, limit 70mg/dl

Prediction of hypoglycaemia of T1DM patients by means of the "Guaranteed Error Machine"



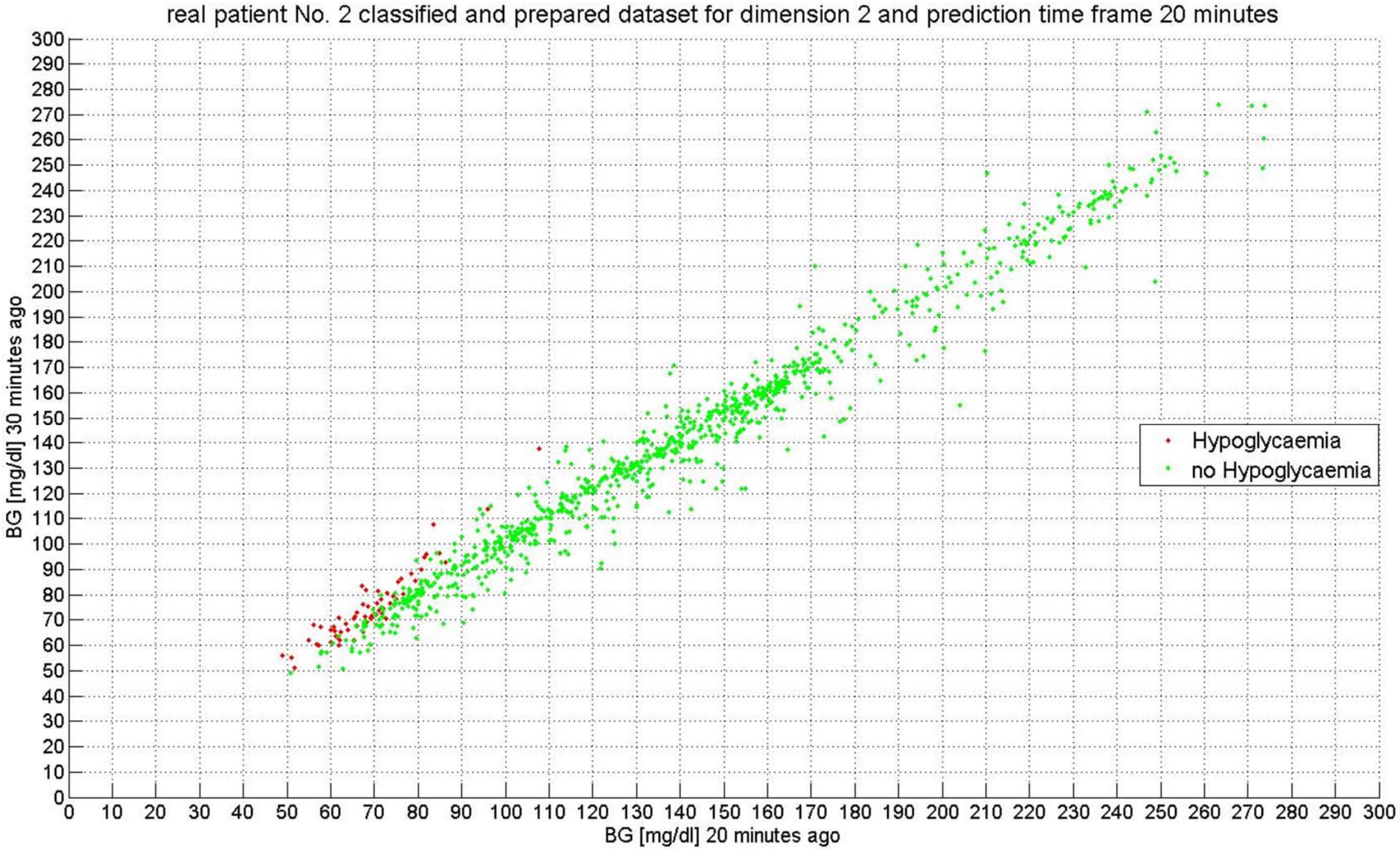
Results „Real Patient“ No.2 predicted time frame 20 minutes

Prediction of hypoglycaemia of T1DM patients by means of the "Guaranteed Error Machine"



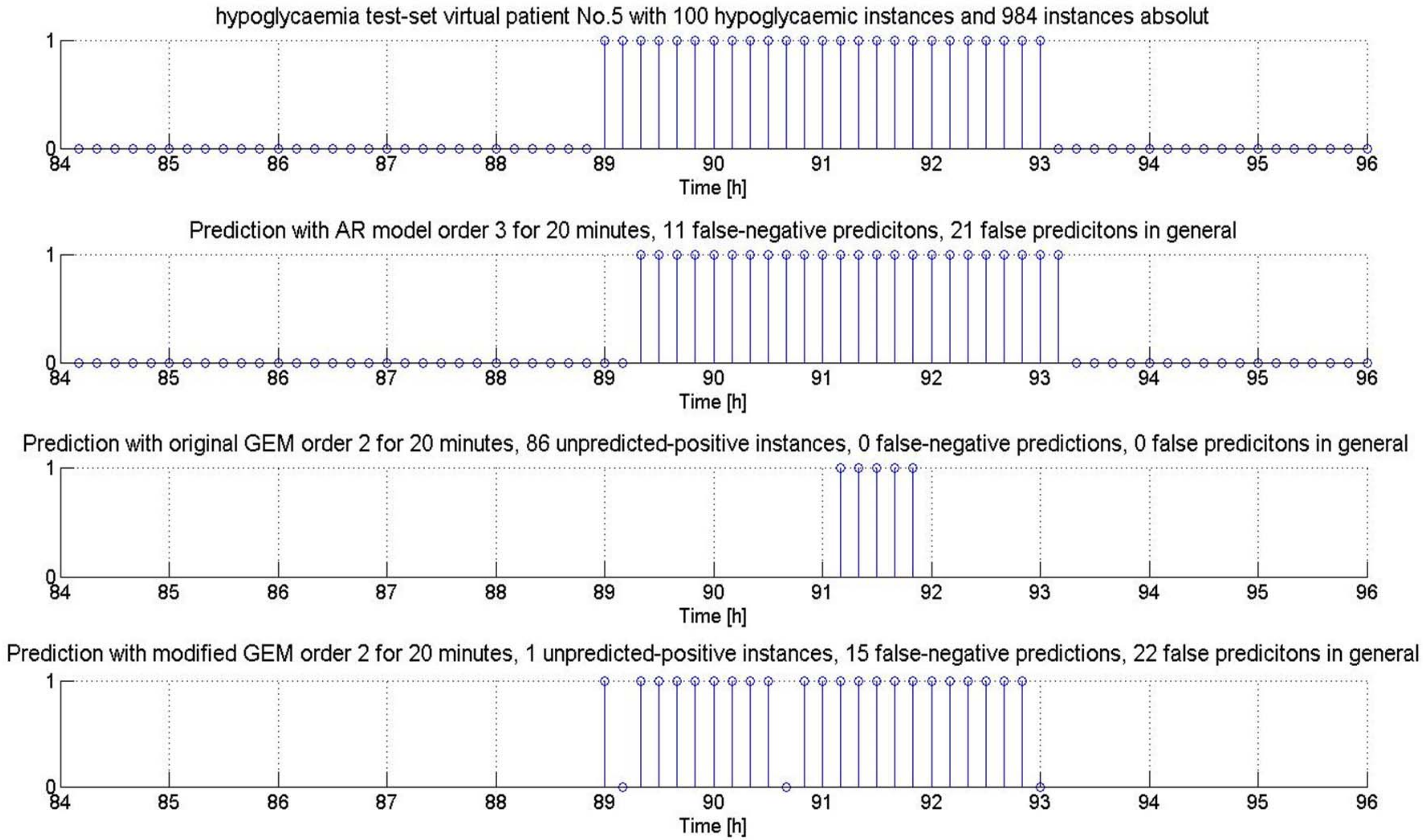
Results „Real Patient“ No.2, predicted time frame 40 minutes

Prediction of hypoglycaemia of T1DM patients by means of the “Guaranteed Error Machine”



Vector (point) plot „Real Patient“ No. 2, predicted time frame 20 minutes

Prediction of hypoglycaemia of T1DM patients by means of the “Guaranteed Error Machine”



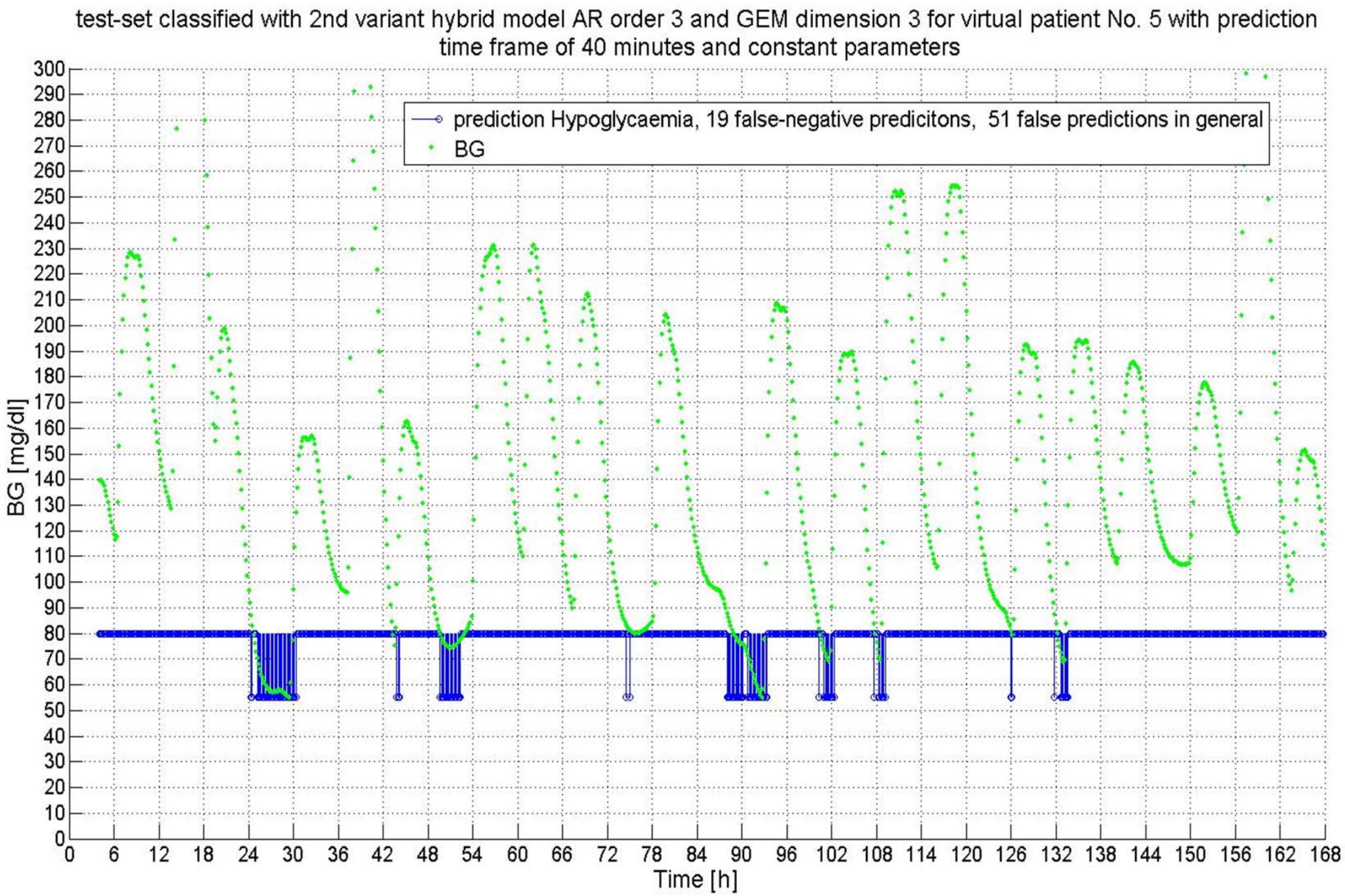
Results „Virtual Patient“ No.5, variable parameters, predicted time frame 20 minutes

Hybrid model

- AR model and GEM combined
  - variant 1:
    - prediction values GEM inside range 65 to 140 mg/dl
    - Outside this range AR-model prediction values
    - all unclassified instances replaced with AR-model predictions
  - variant 2:
    - prediction values AR-model were used in general
    - If the GEM predicted hypoglycaemia and the AR-model no hypoglcaemia, the prediction value was changed into hypoglycaemia
  - dimension criterion

$$d_{GEM_{opt}} = \arg \min_{d_{GEM} \in \mathbb{N}^+ \mid d_{GEM} \geq 1} \left(FNP(d_{GEM}) + UPI(d_{GEM}) \right)$$

Prediction of hypoglycaemia of T1DM patients by means of the "Guaranteed Error Machine"



pure AR-model, FNP 44, FPG 61 / Hybrid model, FNP 19, FPG 51

Binary Diagnositc Test

		DISEASE	
DIAGNOSIS		**present**	**not present**
	positive test result	true positive prediction	false positive prediction
	negative test result	false negative prediction	true negative prediction

Confusion matrix of binary classifier

$$Sensitivity = \frac{TPP}{(TPP + FNP)}$$

$$Specificity = \frac{TNP}{(FPP + TNP)}$$

Prediction of hypoglycaemia of T1DM patients by means of the "Guaranteed Error Machine"

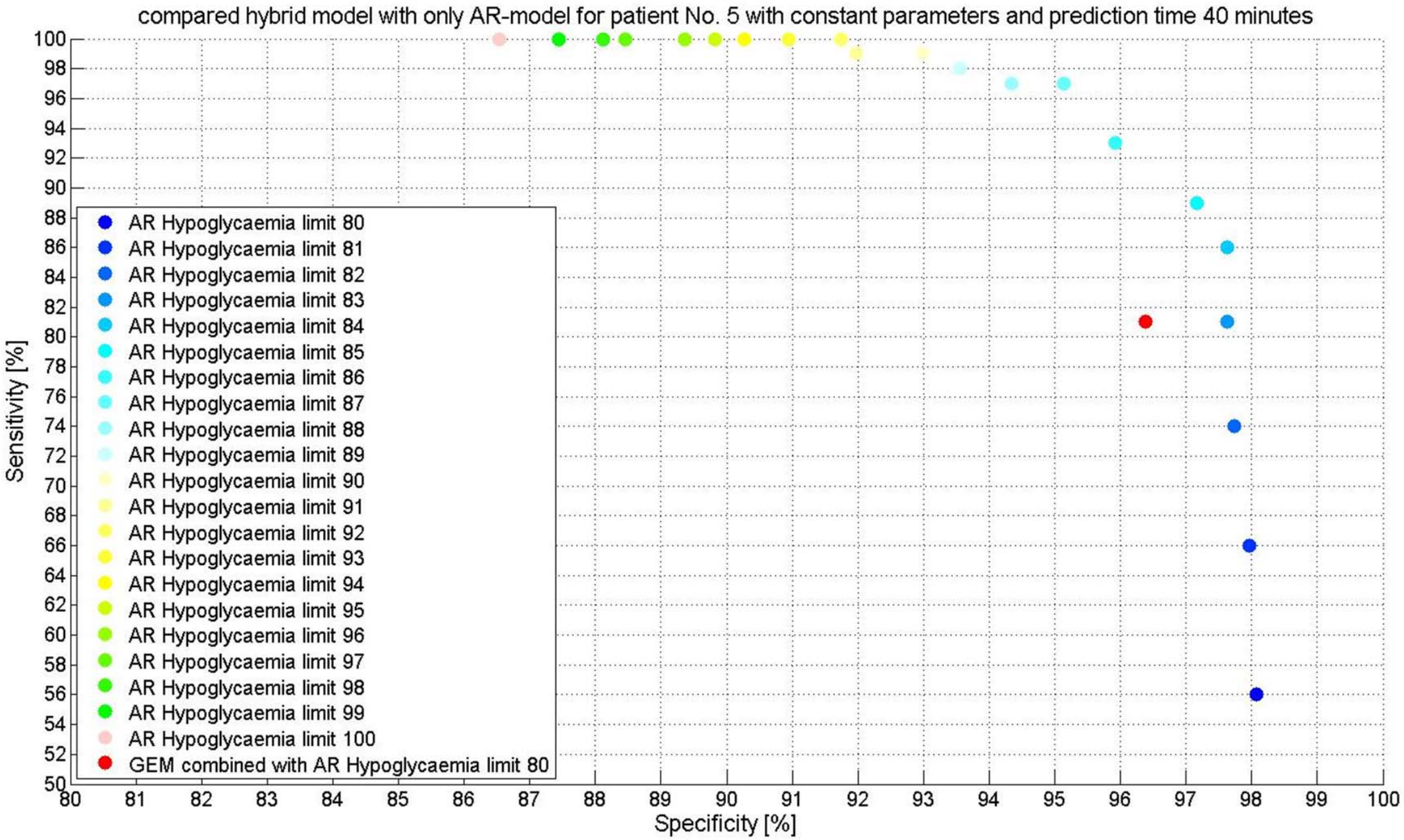
Virtual Patient const.	5			
prediction time frame	40			
model type	AR order 3		Hybrid	
test result	hypoglycaemia	no hypoglycaemia	hypoglycaemia	no hypoglycaemia
positive	56	17	81	32
negative	44	867	19	852

Virtual Patient const.	5	
prediction time frame	40	
model type	AR order 3	Hybrid
sensitivity [%]	56,00	81,00
specificity[%]	98,08	96,38
positive prediciton value [%]	76,71	71,68
negative prediciton value [%]	95,17	97,82

Real Patient	2			
prediction time frame	40			
model type	AR order 3		Hybrid	
test result	hypoglycaemia	no hypoglycaemia	hypoglycaemia	no hypoglycaemia
positive	7	12	8	23
negative	15	932	14	921

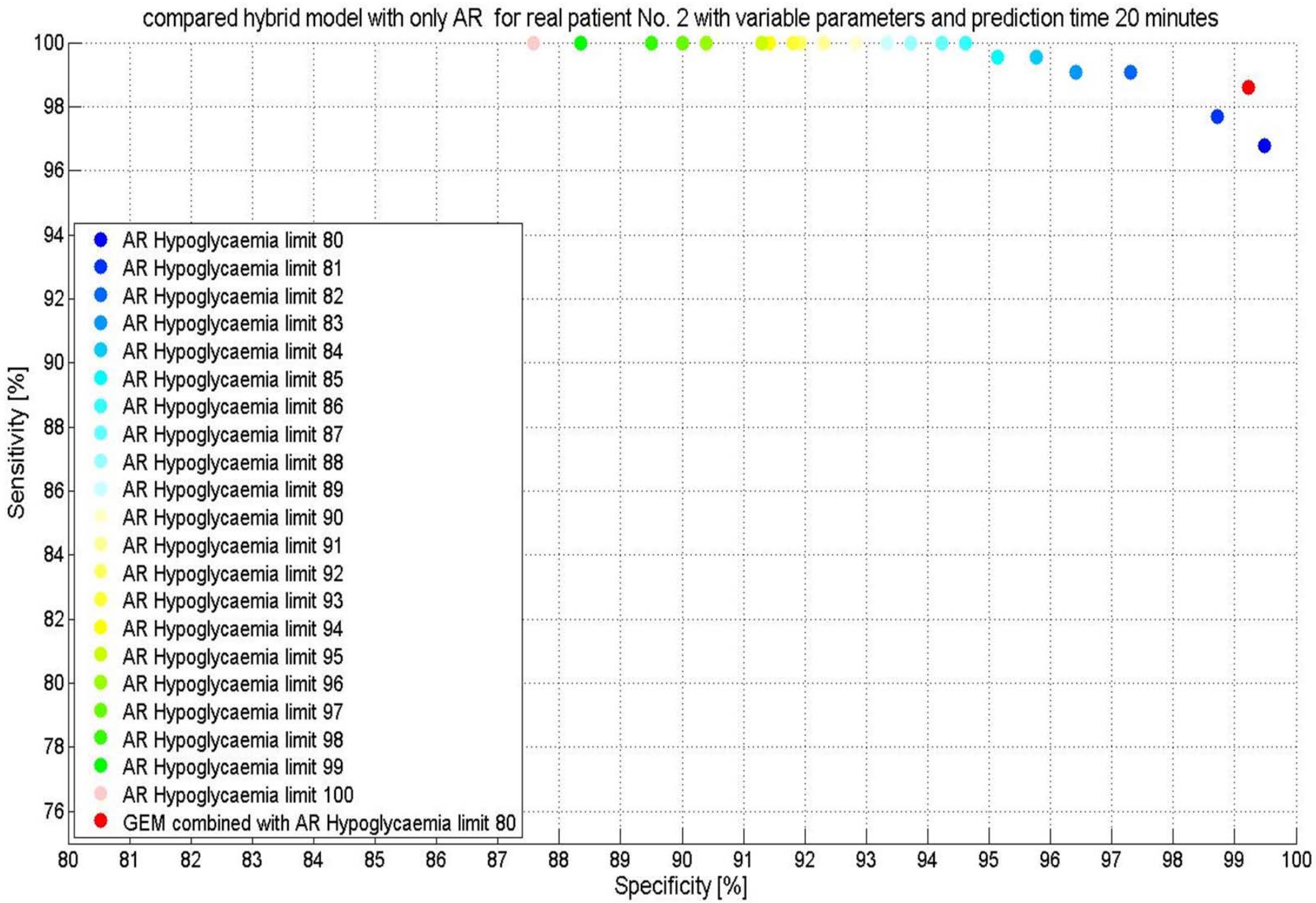
Real Patient	2	
prediction time frame	40	
model type	AR order 3	Hybrid
sensitivity [%]	31,82	36,36
specificity [%]	98,73	97,56
positiv prediciton value [%]	36,84	25,81
negativ prediciton value [%]	98,42	98,50

Prediction of hypoglycaemia of T1DM patients by means of the "Guaranteed Error Machine"



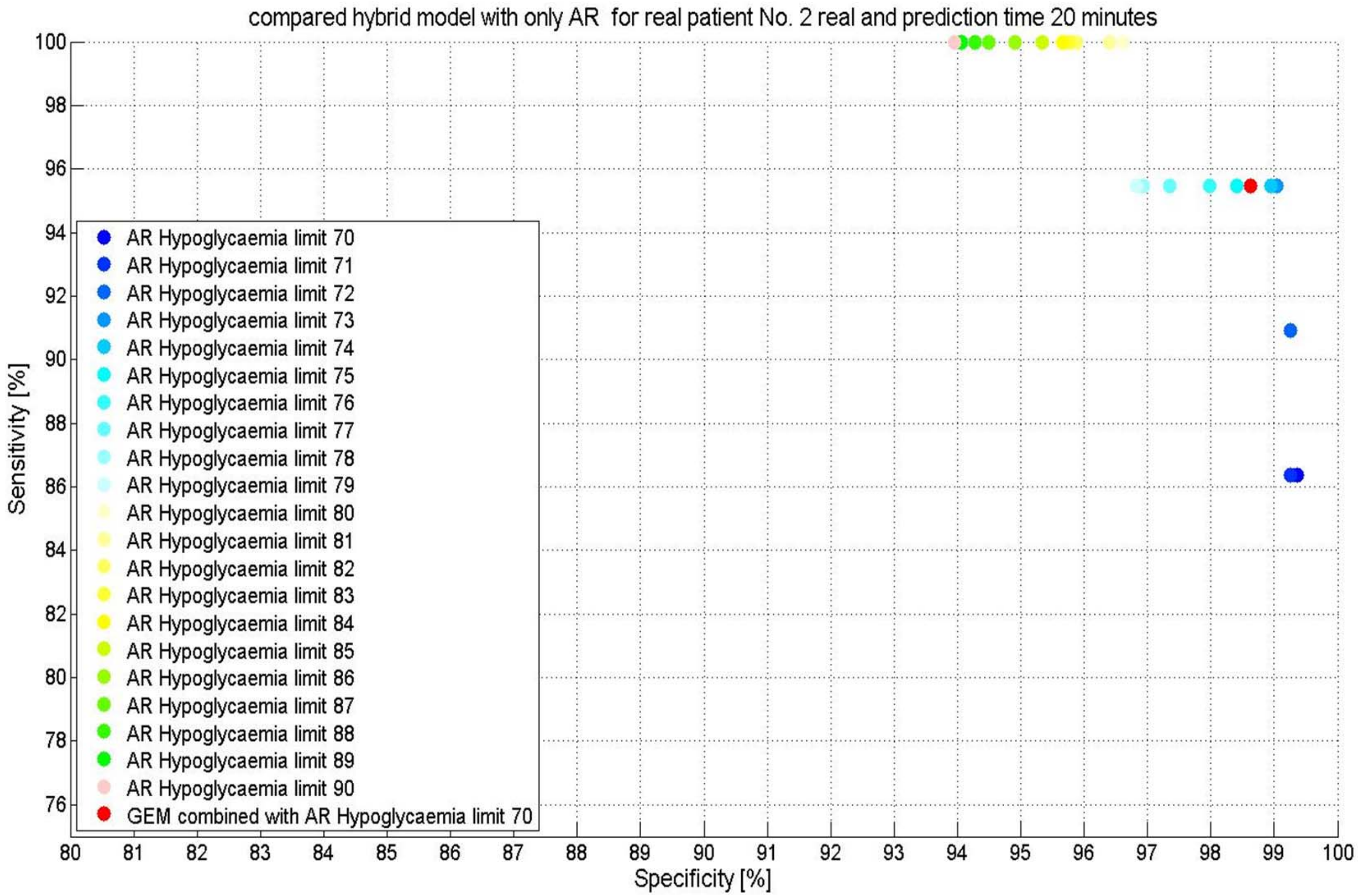
Comparison, AR – Hybrid, Sensitivity/Specificity, Virtual Patient No. 5 constant parameters, 40 minutes

Prediction of hypoglycaemia of T1DM patients by means of the "Guaranteed Error Machine"



Comparison, AR – Hybrid, Sensitivity/Specificity, Virtual Patient No. 5 variable parameters, 20 minutes

Prediction of hypoglycaemia of T1DM patients by means of the "Guaranteed Error Machine"



Comparison, AR – Hybrid, Sensitivity/Specificity, Real Patient No. 2, 20 minutes

Conclusions

- high number of unclassified instances
- high calculation time compared to an AR-model
- difficult to find the optimal settings for *d* and *k*
- practical application of the GEM only possible in combination with other models, due to the unclassified instances

Using the **GEM** for **prediction of hypoglycaemia** is **not advisable**