Table S1: Summary of Physiological Blood Glucose Prediction Model Approaches

| Author | Model Type | Additional Aspects | Sub-Systems | Prediction Horizon | Subjects used | | Inputs Used | | | | | Accuracy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Real Data | Simulated Data | CGM / BG | Simple carbohydrate | Mixed Meals | Insulin | Extra inputs | |
| Bergman, 1979 [50] | Glucose disappearance and insulin sensitivity | Three insulin-independent and four insulin-dependent models | Hepatic glucose balance and peripheral tissue uptake | | | | x | x | | x | | "Good precision" |
| Lehmann, 1992 [51] | First order Euler integration | Glucose–insulin interaction, insulin sensitivity | Hepatic and peripheral glucose handling. | 24 hr | 1 | | x | x | | x | Gastric emptying rate | 1 mmol/L |
| Andreassen et al., 1994 [52] | Carbohydrate and insulin absorption models | Renal loss of glucose, insulin-independent and -dependent glucose utilization | | 24 hr | 12 | | X | x | | x | | Average mean prediction error over day 2 for all patients 3.3mmol/L |
| Höfig et al.,1996 [53] | Extended mathematical models: 1. Exogenous glucose influx 2. Hepatic glucose production | | Gastric emptying and small intestine absorption using Michaelis–Menten kinetics | | 11 Non-DM; 5 T1DM | | X | x | | x | | |
| Arleth et al., 2000 [44] | Two-compartment carbohydrate absorption | DIAS | Gastric emptying rate. Factors affecting carbohydrate breakdown | | | | X | | Complex and GI ranking | | | |
| Dalla Man, 2007 [54] | Glucose–insulin control system | | Glucose and insulin sub-systems | | 204 | | X | | x | | | |
| Islam et al.,2007 [55] | Minimal and physiological models | | Hepatic glucose balance. Glucose appearance rate | | | | x | x | | x | | |
| Calm, 2011 [19] | Modal Interval Analysis (MIA) | | Insulin absorption, carbohydrate digestion, and absorption insulin PK/PD | 6 hr | | 1 | x | x | | x | | |

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| | | | glucose metabolism | | | | | | | | | |
| Elleri, 2013 [46] | Bayes model and two-compartment glucose kinetic model | Stable-label tracer dilution methodology | Stochastic modelling of glucose kinetics | | 8 | | x | Low GI v High GI | | x | | |
| Balakrishnan, 2014 [25] | Extended Bergman's minimal model absorption dynamics [48] | Roy and Parker exercise model | Meal absorption dynamics, insulin absorption kinetics, and exercise | | 34 | | x | x | | x | Exercise | $R^2$ fitness: > 0.7 overall, 0.8–0.96 (82% pts). $R^2$ validation 0.75–0.95 (88% pts) |
| Bock, 2015 [56] | Therapy parameter–based model (TPM) | | Bergman minimal model [48] and Hovorka, Prud'homme model [19,51] | 15–165 minutes | 12 | 10 | Finger pricks | | x | x | Exercise | MAD: TPM 6.91 LMM 4.94 MM 5.26 |
| Magdelaine et al., 2015 [57] | Glucose–Insulin and digestion models | | Glucose dynamics, insulin dynamics, digestion dynamics, insulin sensitivity | | Four hospitalized patients and one outpatient | | x | x | | x | | SD +/- 20mg/dL per patient |
| Contreras, 2017 [28] | Hovorka model [58] | Grammatical evolution | Glucose, insulin, glucagon dynamics | 6 hour (four segments) | | 100 UVA/ Padova T1D Simulator | x | x | | x | | 98.31% EGA zones A and B |
| Liu et al, 2018 [59] | Discretized version of composite model; Forward Euler's configuration | | Minimal model [48] and insulin/carbohydrate absorption model [51] | 30/60/90/120 minutes | 10 | 10 (UVa-Padova) | x | | x (amount and absorption type) | x (bolus) | Exercise | Simulated: 26.68+/-3.58mg/dL (fasting); 23.89+/-3.32 (meal/exercise). Real: 37.02+/-5.14mg/dL (fasting); 35.96+/-4.65mg/dL (meal/exercise) |
| Rozendaal, 2018 [60] | Physiology-based dynamic modeling (PBDM) [60] | Glucose–insulin dynamics, carbohydrate digestion | Insulin–glucose kinetics | | | 53 PPR datasets | X PPG | | | X | Gastric emptying (two terms: simple carbohydrate and | "Performs well for a variety of common foods and mixed meals" |

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| | | | | | | | | | | | complex carbohydrate) | |
| Gyuk et al.,2019 [61] | Arleth model with personalized mathematical model [43,62] | | Glucose and insulin absorption (differential equations) | 30–60 minutes | 26 T1 and insulin dep T2 | | x | | x | x | | RMSE (mmol/L): 3.00 (1 hr); 6.79(2 hr); 9.10(4 hr); 9.44(6 hr) \| EGA (A+B acceptable) 89% (1 hr); 67% (2 hr); 57% (4 hr); 57% (^ hr) |
| Liu et al., 2019 [62] | Bergman [48] and Hovorka models [51] | | Glucose–insulin dynamics | 30/60/90/120 minutes | 10 pts | UVa/Padova | x | x | | x | Optional input of meal absorption models | PMma RMSE (mg/dL) 17.67 +/- 2.12 (30m); 30.36+/-3.88 (60m); 38.14+/- 5.25; 40.46+/- 6.06 (120m) |
| Karim et al., 2020 [7] | Arleth model [43] | FNN quasi-newton method. FNN-ABS (absorption), FNN-NUT (raw nutrients quantity), and FNN-NUT-GI | Stomach and Intestinal compartments, glucose absorption | 60 minutes | 5 | | x | | x | x | Gastric emptying | 1.12 mmol/L |
| Munoz-Organero, 2020 [16] | Modified Lehmann and Deutsch model | Recurrent neural network using long short-term memory | | 30–60 minutes | 9 D1NAMO dataset | 40 AIDA simulator | x | x | | Fast and slow acting | BG history | RSME (30 minutes): <0.28 mmol/L (simulated), < 0.55 mmol/l (real). Clinically acceptable 90% (60 minutes), 99% (30 minutes) |

Table S2: Summary of Data-Driven Blood Glucose Prediction Model Approaches

| Author | Model Type | Additional Aspects | Prediction Horizon | Subjects Used | | Inputs Used | | | | | Accuracy |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Real Data | Simulated Data | CGM / BG | Simple Carbohydrate | Mixed Meals | Insulin | Extra Inputs | |
| Tresp and Briegel, 1997 [63] | Non-linear recurrent neural predictive model | Forward–backward Kalman filter | | | | x | x (times and amounts of Food—fast/int/slow CHO) | | x (basal and | Times and duration of exercise | |
| Sandham et al., 1998 [64] | Recurrent artificial neural network | | | 2 | | x | x | | x | Exercise, additional (stress/surgery/illness/pregnancy) | |
| Bremer and Gough, 1999 [15] | Autocorrelation function (ACF) | | 10/20/30 minutes | 22 datasets | | | | | | | RMSE 0.2mmol/L (10 minutes) |
| Ståhl, Johansson, and Renard, 2010 [65] | Black-box finite impulse response (FIR) | | 20 and 60 minutes | 18 | | x | x | | x | | CGA 94.2% Zone A |
| Cescon and Renard, 2011 [66] | Data-driven multi-step subspace-based patient-specific predictor models | | 30 minutes | | | x | x | | x | Exercise (heart rate) | |
| Pappada et al, 2011 [67] | Feed-forward neural network model | | 75 minutes | 10 | | x | | x | x | Lifestyle and emotional factors | RSME 43.9mg/dL +/- 6.5 and MAD 22.1; CEGA—zone A 62.3%, zone B 30.0% |
| Pappada, Cameron, and | Neural network model | | 50/75/100/120/ | 18 | | x | | x (nutrition | x | Sleep–wake cycles, | |

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| Rosman, 2008 [68] | | | 180 minutes | | | | | al intake) | | exercise | |

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| Robertson et al., 2011 [69] | Elman recurrent artificial neural network | AIDA, Levenberg–Marquardt algorithm | 60 minutes | | | x | | x | x | | RMSE (5 day)0.15+/-0.4SD mmol/L with error(max) 0.24mmol/L |
| Daskalaki et al., 2012 [70] | AR vs ARX vs ANN models | Tikhonov regularization | 30/ 45 minutes | | 30–10 adults, 10 adolescents, 10 children | x | x (meals with set CHO ranges at set times) | | x (basal / bolus regime based on ICR) | | RSME—AR: 14.0–21.6mg/dL (30m), 23.2–35.9mg/dL (45min) / ARX: 13.3–183.8mg/dl (30m), 22.8–29.4mg/dL (45m) / ANN: 2.8–6.3mg/dL (30 and 45 minutes) |
| Pappada and Cameron, 2012 [71] | Train developed time-lagged feed forward neural network model (TLFFNNM) | Proportional integral derivative (PID) | 75 minutes | | 10 (2 T1DM) | x | x | | x | Sleep–wake cycles and sleep quality, exercise, emotional states | CEGA: 92.3% zones A and B (clinically acceptable), 62.3% zone A |
| van Heusden et al., 2012 [72] | Zone model predictive control (ZMPC) | | | | | x (AP) | | | x (AP) | | |
| Steil, 2013 [73] | Proportional integrative derivative (PID) | | | | | | | | | | |
| Toffanin et al., 2013 [74] | Multiple-model predictor (MMP) | | 60 minutes | 18 | | x | x | | | Meal absorption / day period | |

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| Cameron et al., 2014 [75] | Multiple model probabilistic predictive controller (MMPPC) | Kalman filter | 5 hours | 4 pts/6 pts | | x | | x unannounced | | Exercise (walking <20 minutes between blood draws) | |

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| Del Favero et al., 2014 [76] | Model predictive control (MPC) | | | 6 | | x | x | | x | | Clinically acceptable: 94.5% (open loop); 88.3% (closed loop). TIR: 94.83% vs 68.2% (MPC vs open loop); hypo-events: 1.25 vs 11.9% (MPC vs open loop) |
| Efendic et al., 2014 [77] | Gaussian mixture models | Biometric and biological systems | 10/20/ 30 minutes | 12 | | x | x | | x | Days 2 and 5 fast-absorbing foods, 15% increased and 15 minutes delayed insulin bolus | 96.53% correct prediction rate |
| Kirchsteiger et al., 2014 [78] | CT identification algorithm | CHO and insulin sensitivity factor | | 28 | | x | x | | | Protein and fat intake | |
| Oveido et al., 2014 [79] | Personalized hybrid models using grammatical evolutions and physiological models | Gaussian distributions | 120 minutes | | 100 in silico | x | x | | x | | RSME 1am–7am 11.8; 7am–1pm 22.09; 1pm–7pm 21.43; 7pm–1am 29mg/dL |
| Plis et al.,2014 [80] | Support vector regression | Physiological features; Gaussian kernel | 30/60 minutes | | | x | x (meal absorption dynamics—CHO consumption; CHO digestion) | | x | Hypo prediction | SVR : 22.6 (30 minutes); 35.8 (60 minutes)/ ARIMA : 24.9 (30 minutes); 39.6 (60 minutes) |

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| Ståhl, Johansson, and Renard, 2014 [81] | Sliding window Bayesian model average predictor | Gaussian distribution | 40 minutes | | 12 pt datasets | x | | x (announced 30 minutes ahead) | x | | RSME 1.03 |
| Wang, 2014 [82] | Time-varying state space model | | 30 minutes | 1 | 30 | x | x | | x | | |
| Georga et al., 2015 [18] | Non-linear: on-line sequential extreme learning machine (OS-ELM) and online sequential extreme learning machine kernels (KOS-ELM) | 10-fold cross validation | 30 minutes | 15 | | x | x | | x | Physical activity | ELM: case 1 (15.7 +/- 3.0); case 2 (11.8 +/- 2.2); case 3 (9.3 +/- 1.9); K-ELM: case 1 (15.3 +/- 3.0); case 2 (8.6 +/- 2.2) ; case 3 (96.1 +/- 1.6); OS-ELM: case 1 (15.8 +/- 2.9); case 2 (13.9 +/- 2.3) ; case 3 (13.3 +/- 12.3); KOS-ELM: case 1 (16.6 +/- 2.69); case 2 (10.9 +/- 2.7); case 3 (8.5 +/- 2.7) |

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| Georga et al., 2015 [83] | Random forest and RReliefF | Support vector regression or Gaussian process | 30/60 minutes | 15 | | x | | x (type of food, serving size, and time) | x (type, dosage, and time) | | Average RMSE (30 minutes): SVR/RF 21.4 +/- 7.5; SVR/RReliefF 24.9 +/- 5.9; GP/RF 22.9 +/- 9.7, GP/RRrelief 25.36 +/- 7.4 Average RMSE (60 minutes): SVR/RF 26.5 +/- 9.5, SVR/RReliefF 23.5 +/- 7.6; GP/RF 24.6 +/- 12.6 GP/RRelief26.4 +/- 11.6 |
| Bazaev and Pozhar, 2017 [84] | Sigma model | Bennett–Gourley model for NN training | | 52 (tracks) | | x | | Food intake | x | | RMSE: 15.7mg/dL, algorithm corrects 97.5% of errors |
| Hidalgo et al., 2017 [85] | 1) A variant of grammatical evolution that used optimized grammar. 2) A variant of tree-based genetic programming that used a three-compartment model for CHO and insulin | Genetic programming and grammatical evolution compared to KNN RF and two base line predictors | 30/ 60/ 90/ 120 minutes | 10 | | | | Food intake | x | | 90% zones A and B (Clarke Error Grid) |

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| Jankovic et al., 2016 [86] | Deep prediction model (DPM) | ARX, ANN used for prediction layer and ELM (correction layer) | 15/30/45 minutes | 6 | | x | x | | x | Physical activity | Model results (15 minutes):<br>ARX + ELM: 9.6 (2.15)<br>ARX without ELM: 9.9 (1.59)<br>cARX + ELM: 0.97 (0.01)<br>cARX without ELM: 12.5 (1.63)<br>ARXK + ELM: 9.4 (1.78)<br>ARXK without ELM: 10.0 (1.83)<br>ANN + ELM: 8.5 (1.49)<br>ANN without ELM: 9.6 (1.85)<br><br>Model results (30 minutes):<br>ARX + ELM: 19.9 (4.39)<br>ARX without ELM: 18.9 (3.61)<br>cARX + ELM: 19.9 (4.39)<br>cARX without ELM: 22.5 (4.19)<br>ARXK + ELM: 20.6 (5.82)<br>ARXK without ELM: 19.6 (4.31) |

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| | | | | | | | | | | | ANN + ELM: 17.8 (4.35)<br>ANN without ELM: 17.8 (4.36)<br><br>Model results (45 minutes):<br>ARX + ELM: 22.4 (4.69)<br>ARX without ELM: 26.5 (5.72)<br>cARX + ELM: 22.4 (4.69)<br>cARX without ELM: 29.8 (6.76)<br>ARXK + ELM: 23.1 (5.82)<br>ARXK without ELM: 27.5 (6.89)<br>ANN + ELM: 24.4 (6.11)<br>ANN without ELM: 24.5 (6.34) |
| Zecchin et al., 2016 [87] | Jump neural network | | 30 minutes | 10 | | x | | x | x | Physical activity, stress | RSME 17.6mg/dl JNN; RSME 22.9mg/dl Ref NN |
| Reiter, Reiterer anddel Re, 2017 [88] | Bayesian network | Markov chain model | | 37 | | x | x | | x | | |

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| Wang et al.,2017 [89] | L-MPC | | | 10 | | x | | | | Exercise day/alcohol intake day | |
| Acedo et al., 2018 [90] | Mathematical model | Swarm hybrid | | | | x | x | | | | |
| Buckingham et al., 2018 [91] | Model predictive control | | | 12 | | x | x / fat | High-fat meal (>30% TEl | x | Over-estimated bolus/extended bolus | 76.1% +/- 8% TIR |
| Li et al., 2018 | Convolutional recurrent neural network | Time series prediction using LSTM and a signalconverter | 30/60 minutes | 10 real cases | 10 (UVa/Padova) | x | x | | x (bolus) | | 30 minutes: 9.38 +/- 0.71mg/dL (simulated) 21.07+/- 2.35mg/dL (real) 60 minutes: 18.87+/- 2.25mg/dL (simulated) 33.27+/- 4.79mg/dL (real) |
| Vahedi et al., 2018 [92] | Random rorest regressor and MLP (neural networks regressor) | | 30 minutes | | | | | | | | |

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| Akbari and Chunara, 2019 [93] | Multi-signal Gaussain process | | | | | x | x | x | x | Sleep, work, exercise, heart rate, galvanic skin temp, skin temp, air temp, and step count | |
| Borle, Ryan,and Greiner, 2019 [94] | K-nearest neighbors, supportvector regression, ANN, wavelet neural network, ridge regression, random forest regression, Gaussian process regression | “Kok” features, 10-fold cross validation | | 47 | | x | x | | x | Physical activity (less than normal/normal/active/very active) | MAE: 2.91mmol/l; 7.1% relative improvement on baseline |
| Griva, Martínez, and Basualdo, 2019 [95] | Average long-term prediction model (ALTPM) | Kalman filter vs Wiener model | 60 minutes | 2 pts | | x | x | | x | | All data at 60 minutes—RMSE (Wiener model) 24mg/dL and 45.4 mg/dL; 37.6mg/dL and 48.9mg/dL (Kalman filter) |
| Georga, Príncipe, and Fotiadis, 2019 [96] | Non-linear, recursive, multivariant prediction model | Kernel Hilbert space (quantized kernel least mean square — QKLMS-FB; kernel recursive least squares—KRLS-ALD) | 15/60 minutes | 15 | | x | x | | x | physical activity | RSME of QKLMS-FM 13.1mg/dL (15 minutes); 37.7mg/dL (60 minutes) KRLS-ALD 10l.5mg/dL (15 minutes), |

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| | | | | | | | | | | | 31.8mg/dL (60 minutes) |
| Litinskaia et al., 2019 [97] | Sigma model-based algorithm | | | DirecNet Database | | x | Food intake (un-announced) | | x | Physical activity | |
| Padmaprith a, 2019 [98] | Recurrent neural network–long short-term memory | Adam optimizer | | T2DM pop | | | | | | | RMSE 18.79mg/dL |
| Rodríguez-Rodríguez et al., 2019 [26] | Sequential input selection algorithm (SISAL) | | 30 minutes | 28 pts | | x | | x | x | Exercise, heart rate, sleep schedule, circadian rhythms | RMSE 17.83mg/dL |

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| Saiti et al., 2019 [99] | Support vector regression and an extreme learning machine | Autoregressive with exogenous inputs (ARX) | 30/45/60 minutes | | | x | | x | x | | RMSE training: ARX: 23.24 (30m), 29.54 (45m), 35.13(60m) SVR: 22.34(30m), 28.64 (45m), 34.3 (60m), ELM: 23.96 (30m), 32.07 (45m), 35.49 (60m), Comb: 20.18 (30m), 26.48 (45m), 33.33(60m)<br><br>RMSE testing: |

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| | | | | | | | | | | | ARX: 21.62 (30m), 27.02 (45m), 29.72(60m) SVR: 22.58(30m), 26.48 (45m), 31.17 (60m), ELM: 21.08 (30m), 27.20 (45m), 30.63 (60m); Comb: 20.36 (30m), 25.58 (45m), 26.48 (60m) |
| Alquah, Younes, and Aldudah, 2020 [100] | Neural network | One hidden layer NN; two hidden layer NN; Kalman filter | | 149 | | | | | x | Gender, age, BMI, disease history, total daily insulin dose, diabetes type, smoking factor, genetic factor, creatine clearance, and accumulative glucose | RSME: 2.3265mg/dL |
| Amar et al.,2020 [101] | Artificial neural network | Gradually connected network (3) | 30/60 minutes | | 30 | | | | | | |

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| Balasooriya and Nanayakkara, 2020 [102] | Long short-term memory | | 30 minutes | | | x | Food (CHO, prot, fat) | | x | Physical activity (light, sedentary, moderate, high); meal absorption; | 79.97% accuracy; RMSE 22.2mg/dL |

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| | | | | | | | | | | drug absorption | |
| Camerlingo et al., 2020 [103] | Support vector machine (SVM) classifier, univariant probability density parametric. Models; mathematical models | Radial basis function (RBF) kernel | | 32 | | | x (meal timing) | | x | Age, weight, last meal's CHO, mealtime, CHO sum (1 hr, 4 hr,6 hr), Mean CGM (1 hr, 4 hr, 6 hr), Initial CGM, CGM rate (1 hr), observation time, distinct hypo treatments | AUROC equal to 0.754 |
| Contador et al., 2020 [104] | Multi-objective grammatical evolution based on NSGA-II algorithm | | | | | x | x | | x | | |
| Hidalgo et al., 2020 [105] | Markov chains; grammatical evolution | Metropolis–Hastings algorithm; symbolic aggregate approximation (SAX); sampling importance resampling (SIR) | | 5 | | x | x | | x | Active IOB | |
| Kriventsov et al., 2020 [106] | Support vector machines for regression | Decision tree | 15/30/45/60 minutes | | | x | x | | x | Heart rate andphysical activity | |

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| Munoz-Organero, 2020 [16] | Recurrent neural network–long short-term memory | | 30/60 minutes | 9 pts - D1NAMO dataset | 40 - AIDA diabetes simulator | x | x | | x | Insulin absorption and utilization (dependent and independent), renal clearance, and endogenous production | RMSE (mg/dL) 10 memory cells 70% training and 30% validation—6.42(30m) and 11.35 (60m) |
| Pavan et al., 2020 [107] | Shallow neural network; ensemble trees | | 30/60 minutes | 6 - OhioT1DM dataset | | x | x | | x | Work and sleep routine | |
| Saiti et al.,2020 [99] | ARX and SVR models | Linear, bagging, and boost meta regressor | 30/45/60 minutes | 2 in hospital pts; 4 D1NAMO | | x | x | | x | | RMSE (mg/dL) pt 1 with BAGGING metaR 14.76+/-0.25 (30m); 22.32+/-0.41 (45m); 28.98+/-0.56 (60m) |
| Song et al.,2020 [108] | Learning type model predictive control | | | 29 | | x | x | | x | Physical activity, alcohol intake | 65.2% TIR |
| Sun et al.,2020 [109] | Latent variable (LV)-based Model | | 30/60 minutes | 6 - OhioT1DM dataset | | x | Meal | | IOB, basal, bolus | Exercise, work, illness | RMSE (mg/dL) 19.37+/-2.87 (30m); 32.50+/-5.35 (60m) |
| Zhu et al.,2020 [110] | Generative sdversarial network (GAN) | Recurrent neural network with convolutional neural network layers | 30/60 minutes | 12 | | x | x | | x | Physical activity, sleep, work, stress | RMSE 18.34 (30 minutes); 32.21 (60 minutes) |

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| Alvarado et al., 2021 [111] | Takagi–Sugen–kang fuzzy rule-based system (TSK-FRBS) | What-if and agnostic scenarios | 30/60/90/120 minutes | 10 | | x | x | | x | | RMSE (mg/dL) 11.38 (training); 29.44 (testing) |
| Beauchamp et al., 2021 [112] | Two long short-term memory chain | Global average and ToD average | 30/45/ 60/75/ 90 minutes | 12 - OhioT1DM dataset | | x | x | | x | Physiological and lifestyle factors | N-BEATS.mean with pre-processed meals RMSE 8.84 (training); 6.16 (validation; N-BEATS.best RMSE 1.22 (with pre-processed meals) |
| Bhargav et al., 2021 [113] | MLP, LSTM, VAR, ensemble | | | | 40 | x | x | | x | Kidney functioning, liver insulin sensitivity, lower and upper glucose limit | RSME mmol/l test dataset MLP: 6.44/ LSTM: 5.67/ VAR: 7.16/ ensemble: 4.59 |
| Cui et al.,2021 [114] | Recurrent self attention-based deep network | Fully connected feed-forward network with ReLU activation (in hidden dimension) | 30/60 minutes | 12 - OhioT1DM dataset | | x | x | | x | | RMSE 17.82mg/dL (30m); 28.54mg/dL (60m) |
| De Bois et al., 2021 [115] | Fully convolutional neural networks (FCN) vs support vector regression | | | 6 - OhioT1DM dataset; 6 T2DM (IDIAB) | 10 T1DM dataset (simulated) | x | x | | x | | IDIAB RMSE 20.32+/-6.02 (SVR); OhioT1DM RMSE 20.10+/-2.34 (SVR) |

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| De Falco et al., 2021 [116] | Grammatical evolution | | 30 minutes | 12 - OhioT1DM dataset | | x | x | | x | | MAE (average) 13.48mg/dL |
| Rabby et al., 2021 [117] | Stacked long short-term memory (LSTM)-based deep recurrent neural network (RNN) | Kalman smoothing technique (correction of inaccurate BG readings) and feature extraction module (meal, insulin, step count) | 30/60 minutes | 6 - OhioT1DM dataset | | x | x | | x | Sleep quality, illness level, stress levels, hypo-events, work intensity, exercise duration, heart rate, skin temp, acceleration | Mean RMSE (mg/dL) smoothed CGM 5.89 (30m), 17.24 (60m); Single LSTM 18.96 (30m), 30.88 (60m); Stacked LSTM 18.57 (30m), 30.32 (60m) |
| Sahin and Aydin, 2021 | Artificial neural network | IOB, glucose absorption rate and activity on board models | 30/60 minutes | 6 - OhioT1DM dataset | | x | x | | x | Physical activity (steps) | RMSE (mg/dL): Primary model - 18.81 (30m), 30.89 (60m) |
| Shahid, Hussain, and Khan, 2021 [118] | Convolutional network (CNN) with modified recurrent network (RNN) using GRU (CGRU) | | 15/30/ 60 minutes | | | x | x | | x | HBGI and IBGI (as optional inputs) | RMSE (mg/dL) — 4.84+/1.83 (15m); 6.04+/-1.84 (30m); 8.12+/-1.46 (60m) |
| Wang, 2021 [119] | Comparison of machine learning algorithms | Support vector machines vs random forests vs linear regression vs K-nearest neighbors regression (KNN) vs XGBoosted trees | | | 10 Uva/Padova | x | x | | x | | LSTM RSME 7.55+/-0.19 |

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| Zaidi et al.,2021 [120] | Temporal convolution neural networks (TCNs) | | 30 minutes | 97 | | x | x | | x | | RMSE (mg/dL) 16.77 +/- 4.587 |
| Zhang, Flores, and Tran, 2021 [121] | Neural network architectures vs a reservoir computing model vs novel linear regression | | 30/60 minutes | 12 - OhioT1DM dataset | | x | x | | x | Sleep quality, illness level, stress levels, hypo-events, work intensity, exercise duration, heart rate, skin temp, acceleration | RMSE (mg/dL) 30 minutes: MLR 14.16 (train), 18.39 (test); BRC 10.82 (test), 24.49 (test); DCNN 21.41 (train), 29.96 (test); Seq-to-seq LSTM 10.02 (train), 17.52 (test) 60 minutes: MLR 221.39 (train), 24.58 (test); BRC 13.95 (test), 28.79 (test); DCNN 35.84 (train), 38.97 (test); Seq-to-seq LSTM 18.22 (train), 26.44 (test) |

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| Aashima et al., 2022 [122] | Combined ML models (LR, MLP, KNN, SVR, DCT, and EXT) with ensemble models (RF, EXT, bagging,Aboost, Gboost) | DCT expert used for predictions in: DCT-ABoost, DCT-EXT, DCT-Bagging, DCT-RF, DCT-GBoost | 24 hours (15-minute intervals) | | 40 - AIDA simulator | x | x | | x | Kidney functioning, liver insulin sensitivity, lower and upper glucose limit; pts weight; timestamp | Test/Train RMSE: Individual models: DCT: 0.202 / 2.027 EXT: 0.199 / 2.207 KNN: 0.667 / 2.374 MLP: 2.050 / 2.507 SVR: 2.160 / 2.642 LR: 2.908 / 2.777 TWO-STAGE models DCT-Aboost: 0.211 / 2.204 DCT-EXT: 0.199 / 2.207 DCT-Bagging: 0.200 / 2.208 DCT-RF: 0.199 / 2.208 DCT-GBoost: 0.203 / 2.208 |
| Daniels, Herrero, and Georgiou, 2022 [123] | End-to-end deep multitask learning approach (neural networks) | Single-task learning, transfer learning, multi-task learning, (glycemic variability) | 30/45/ 60/90/ 120 minutes | 12 - OhioT1DM dataset | | x | x | | x | Sleep quality, illness and stress levels, hypo-events, work intensity, exercise duration, heart rate, galvanic skin response (GSR), skin | RMSE (mg/dL): 18.8+/-2.3 (30m); 25.3+/-2.9 (45m); 31.8+/-3.9 (60m); 41.2+/-4.5 (90m); 47.2+/-4.6 (120m) |

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| | | | | | | | | | | temp, air temp, step count | CEG: 93% clinically acceptable |
| Simone et al., 2022 | ARX/ARMAX/ ARIMAX/BJ | PopOrd/CV/BIC/AIC | 30/60/ 90/120 minutes | 11 | | x | x | | x | Insulin-to-carb ratio and insulin sensitivity factor | Best prediction of those tested: non-parametric approaches 29.8mg/dL and median COD 57.4% (60m) |
| Yang et al.,2022 [124] | Autonomous channel deep learning framework (asynchronous temporal sequences) | Multi-lag structure embedded in autonomous channel network | 30/60 minutes | 12 - OhioT1DM dataset | | x | x | | x | Sleep quality, illness and stress levels, hypo-events, work intensity, exercise duration, heart rate, galvanic skin response (GSR), skin temp, air temp, step count | RMSE (mg/dL) 18.93+/-2.16 (30m); 31.79+/-3.43 (60m) |
| Mordvanyuk, Torrent-Fontbona, and López [125] | K-nearest neighbor (KNN) | Sequences of meals where each sequence contains all the ordered meals of a time window of d days | | | 11 | x | x | | x | | Overall performance TPRs up to 0.88; 83% accuray; FNR and FPR significantly lower, from 0.25 |

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| Jaloli and Cescon, 2023 [126] | CNN-LSTM based deep neural etwork | Windowed samples of past data with length three times the PH (3× PH), which was the optimal length of input for all PHs, are input to a stack of 1D convolutional and pooling layers, followed by an LSTM block containing two layers of LSTM, each containing 100 LSTM units, followed by two fully connected layers | 30/60/ 90 minutes | Replace-BG and DIAdvisor datasets | Replace-BG dataset: 168<br><br>DIAdvisor data set: 59 | X | X | | X | | 90-minute PH: 17.30 ± 2.07 and 18.23 ± 2.97 mg/dL |
| Sun, Rashid, Askari, and Cinar, 2023 [127] | MPC (AP system) | Glucose–insulin metabolism dynamic; unscented Kalman filter | | | | X | | | | | |
| Cui, Nolan, Daskalaki, and Suominen, 2023 [128] | LSTM backbone with hidden dimension D followed by a rectified linear unit (ReLU) | Hyper and hypo prediction<br><br>Matthew's co-efficient | 30 minutes | OhioT1DM dataset | 12 | X | X | | X | | RMSE 18.23 ± 0.35 (hyperglycemia)<br>13.25 ± 0.17 (hypo) |

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| Langarica, Rodrigues-Fernandez, Doyle, and Núñez, 2023 [129] | Input and state recurrent Kalman network (ISRKN) | | 30/60 minutes | UVA/ Padova simulator | 10 virtual patients<br><br>6 Ambulatory individuals | X | | X | X | | RMSE in silico—9.38mg/dL (30minutes), 18.87mg/dL (60 minutes).<br>Real—8.88mg/dL (30 minutes), 19.90mg/dL (60 minutes) |
| Langarica, de la Vega, Cariman, Miranda, Andrade, Núñez, and Rodriguez-Fernandez, 2024 [130] | LSTM<br><br>Encoder–decoder (Enc-Dec)<br><br>Bidirectional encoder–decoder (Bi Enc-Dec)<br><br>Encoder–decoder with double attention (Enc-Dec DAttn) | | 30 minutes | UCHTT1 DM dataset | 20 | X | X | | X | | Clarke error 80.4% Zone A, 18.1% Zone B |
| Aiello, Jaloli, and Cescon, 2024 [131] | LSTM-MPC<br><br>ARX-MPC | Stochastic meal generator<br>Scenario-I: Insulin therapy based only on the administration of the basal insulin throughout the day.<br>Scenario-II: Insulin therapy based on the administration of basal insulin together with insulin boluses at mealtimes. | 120 minutes | In silico | 10 subjects | x | | x | x | | TIR: 74.99 ± 7.09 vs. 54.15 ± 14.89;<br>TITR: 47.78 ± 8.55 vs. 34.62 ± 9.04;<br>Time in severe hypo: 1.00 ± 3.18 vs. 9.45 ± 11.71 |

Table S3: Summary of Hybrid Blood Glucose Prediction Model Approaches

| Author | Model Type | Additional Aspects | Sub-Systems | Prediction Horizon | Subjects Used | | Inputs Used | | | | | Accuracy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Real Data | Simulated Data | CGM / BG | Simple Carbohydrate | Mixed Meals | Insulin | Additional Aspects | |
| Hutten, 1990 [132] | Black-box model | Multi-compartment physiological model | Glucose–insulin compartment | | | | x | | x | x | Gender, age, weight, height, body type, physical activity | |
| Parker et al., 1999 [133] | Linear step-response model | Kalman filter | Glucose–insulin systems | | | x | | x | | | Glucose uptake from the gut (Lehmann and Deutsch model) | 15mg/dL |
| Hovorka et al., 2004 [58] | Non-linear model predictive control | Bayesian parameter estimation | Glucose–insulin kinetics; glucose sub-system; insulin sub-system; insulin action sub-system | 15–240 minutes | 5 x 2 | | x | x | | x | | Clarke error grid 95% zone A and 5% zone B (60 minutes); 66% zone A, 33% zone B, 1% zone C, and 0.1% zone E (240 minutes) |
| Mougiakakou, Prountzo, and Nikita, 2005 [134] | Combination: compartmental models and artificial neural networks | Feed-forward NN; recurrent NN; free-run RNN-FR, and teaching-force RNN-TF | Compartmental model: glucose absorption from the gu/insulin kinetics | | 275 glucose measurements | | | x | | x | | RMSE RTRL-FR 41, RTRL-RF 45 |
| Roy and Parker, 2006 [135] | Model predictive control | Extended minimal model linearized using first- | Bergman minimal model | 350 minutes | | | x | | x | | Gut absorption of glucose, protein, and fat | |

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| | | order Taylor series | | | | | | | | | | |
| Schlotthauer et al., 2006 [136] | Non-linear model predictive control | Lavenberg – Marquardt algorithm | Physiological patient model | | | | x | x | | x | Carbohydrate absorption | |
| Kildegaard et al., 2007 [137] | AI model | Gaussain-shaped weighting | AIDA - physiological model simulating BG, plasma insulin, and carbohydrate absorption | | 12 | | x | | x | x | | |
| Markakis et a, 2008 [138] | Model predictive control | Non-parametric / principle dynamic modes model | Augmented minimal model. Glucose regulation (Sorensen's model) | | | | x | | x | x | | |
| Ståhl and Johansson, 2009 [139] | ARMAX model | GTFM - Wiener model | Glucose, glucose–insulin, and glucose–insulininteraction sub-model | 120 minutes | 56 datasets | | | x | | x | | 95% <1mmol/L |
| Estrada, Del Re, and Renard,2010 [140] | Linear model with physiologically derived inputs | Normalized least mean squares (NLMS) | Glucose–insulin sub-system, plasma insulin model | 45 minutes | 15 | | x | | x (meal model) | x | | CG-EGA 97.35% clinically accurate |
| Estrada et al., 2010 [137] | Autoregressive model with exogenous input ARX | Normalized least mean square method with constant and adaptive gain | Glucose–insulin sub-system, mealmodel, plasma insulin, Aspart model, plasma insulin, Determir model | 45 minutes | 4 | | x | x | | x | | 92.99% zone A (hypoglycemic) 91.99% zone A (Euglycemic), 96.34% zone A hyperglycemic |
| Calm et al.,2011 [19] | Monte Carlo simulation (MCS) with modal interval analysis (MIA) | | Insulin absorption and appearance rate, intestinal glucose absorption, glucose appearance rate, insulin–glucose sub-system | | | 4 | x | x | | x | Variation in carbohydrate (%), variation insulin sensitivity (%) | |
| Georga, Protopappas , | Support vector machines for regression | Physiological processes-related | | 15/30/60/ 120 minutes | | | x | | x (glucose appearance | x | Exercise | RSME pt 1 - 12.57 (15m), 21.36 (30m), |

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| and Fotiadis, 2011 [141] | | compartmental models (s/c insulin, absorption of glucose from the gut, effects of plasma glucose and insulin dynamics) | | | | | | | nce after meal) | | | 33.06 (60m),62.29 (120m). Pt2 - 9.69 (15m), 16.32 (30m), 34.52 (60m), 31.10 (120m). CEGA - Zone A 73.84%, zone B 24.66% |
| Percival et al.,2011 [142] | Multi-parametric model predictive control | Gaussian white noise, second order plus time delay transfer function | Hovorka model/ Wilinska insulin absorption model | 3 hours | | 10 x 2 | x | x | | x | Carb-to-insulin ratio, carbohydrate, CF | RMSE 26mg/dL |
| de Pereda et al., 2012 [143] | Ordinary differential equations | | Hovorka glucose–insulinmodel | 30 minutes | | x | | x (digestion and absorption) | | x | | |
| Bunescu, 2013 [27] | Modified Lehman and Deutsch glucose absorption model and support vector regression | Meal absorption dynamics; insulin dynamics and glucose dynamics | | 30–60 minutes | 10 | x | x | | x | Exercise and sleep data | RSME 18mg/dl (30 minutes )and 30.9mg/dl (60 minutes ) | |
| Toffanin et al.,2013 [74] | Model predictive control | Kalman filter | Glucose–insulin state | | | UVa/Padova | | x | | | Carb-to-insulin ratio and correction factor | |
| Georga *et al.*,2013 [24] | Multivariant regression using support vector regression | Gaussian radial basis function optimized with differential evolution algorithm, 10-fold | Insulin model (absorption kinetics), meal model (Lehmann and Deutsch) | 15/30/60/ 120 minutes | | 27 pts datasets | x | x | | x | Energy expenditure, food diary (portion size, mealtime, etc.) | Average errors 5.21 (15m), 6.03 (30m), 7.14 (60m), and 7.62 (120m) |

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| | | cross validation | | | | | | | | | | |
| Gondhalekar et al., 2013 [144] | Periodic zone model predictive control (PZMPC) | | Insulin–glucose model (van Heusden et al.) | | | 100 (in silico UVa/Padova) | x | x (unann ounced) | | x | | |
| Toffanin *et al.,* 2013 | Linear model predictive control (LMPC) | Kalman filter | Insulin–glucose dynamics | | | 47 | x | x | | x | | |
| Bock, François, and Gillet, 2015 [56] | Stochasti cmodel | Extended Kalman filter; therapy parameter-based model | Gut glucose absorption | | | 10 (Uva/ Padova) | | x | | x | | |
| Cescon, Johannson, Renard, 2015 [145] | Subspace-based linear multi-step predictors; discrete time-linear time-invariant system | Hankel matrices; Kalman filters | Glucose model/ insulin model/ glucose–insulin interaction (Dalla Man model) | 30/60/90/ 120 minutes | | | x | x | | x | | |
| Zecchin et al.,2016 [87] | Feed-forward neural network | | Dalla Man absorption model | 15/30/45/ 60 minutes | 15 | | x | x | | x | Compar es CGM vs CGM + Insulin vs CGM + carbohyd rate vs CGM + Insulin + carbohyd rate | |
| Contreras et al., 2017 [28] | Hybrid approach | Grammatica l Evolution/ physiologica l modeling (Hovorka)/ | 01:00 - 06:59/ 07:00 - 12:59/ 13:00 - 18:59/ 19:00 - 00:59 | 6 hours | 20 | 100 virtual (Uva/Padova ) | x | x | | x | Glucag on dynamic s | 98.31% zones Aand B (Clarke error grid)/ RMSE: Breakfast (testing) - 24.60mg/dL; Lunch (testing) - 23.20mg/dL; Dinner (testing) - 33.00mg/dL; 24 (testing) - 23.25mg/dL |

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| Mirshekarian et al., 2017 [146] | Recursive neural network (RNN) | Long short-term memory (LSTM)/ support vector regression (SVR)/ extended Kalman filter (EKF) | Meal absorption dynamics; insulin dynamics; glucose compartment; glucose–insulin concentrations | 30/60 minutes | 5 | | x | x (mealtime and carbohydrate content) | x | x (bolus - time, type, and amount AND basal rate) | | RMSE: vanilla RNN 225 (30 minutes) and 40.5 (60 minutes)/ LSTM 21.4 (30 minutes) and 38.0 (60 minutes) |
| Reitter, Reitrer, and delRe 2017 [87] | Markov chain model | Bayesian network | Carbohydrate absorption in the gut, absorption, and action of insulin | 30/60 minutes | 37 | | x | x | | x | | |
| Bertachi et al.,2018 [147] | Regression model (ANN) | Physiological models (insulin on board, CHO on board, and activity on board) | Carb on board (Hovorka model), IOB (Wilinska et al.) | | | | x | x | | x | Activity (step count) | RMSE (ave) 19.33 (30m), 31.72 (60m) |
| Contreras et al., 2018 [148] | Grammatical evolution | | Insulin on board model; activity on board model; carb absorption model | 30/60/90 minutes | | | x | x | | x | Activity | RSME (average) 21.19 (30 minutes); 31.34 (60 minutes); 36.26 (90 minutes) |
| Hajizadeh et al., 2018 [149] | Predictor-based subspace identification | Unscented Kalman filter | Insulin sub-system (Hovorka model) | 30 minutes | 10 pts | | x | x | | x | Exercise (two sessions 20–30 minutes before and after lunch) | RMSE 22.50mg/dL (30 minutes) |
| De Falco et al., 2019 [150] | Neuroevolution of augmenting topologies (NEAT) | Padding pre-processing for glucose values, Bergman model for pre-processing of insulin | Gut glucose absorption | 30/60 minutes | 6 - OhioT1DM dataset | | x | x | | x | | RMSE (mg/dL) 20.636 (average); 20.494 (best) |

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| Hajizadeh et al., 2019 [151] | Model predictive control (MPC) | Recursive predictor-based sub-space identification (PBSID; linear time varying glycemic models | Glucose–insulin dynamics (Hovorka); plasma–insulin risk index; plasma–insulin concentration bounds | 20 minutes | | | x | x | | x | Exercise | |
| Knopp et al., 2019 [152] | Two-compartment gut model | NICING glucose–insulin model for very premature infants | Glucose in the stomach and in the intestine | | 4 (Budapest) and 10 (SUGAR-BABIES) | | x | x | | | | |
| Dias, Kamath, Vidyasagar, 2020 [153] | Model predictive control (MPC) | Self-organizing map (SoM) | Glucose, insulin, glucagon model in ODE form | | | | x | x | | x | | 4.4mg/dL average tracking error |
| Goyal et al., 2020 [154] | Discrete event simulator in an object-oriented manner (SIMulation ConTroLler object and HumanBody Object) | | Food, exercise; insulin production; glucose transport; gluconeogenesis; glycolysis; liver glycogen synthesis and breakdown | | | | x | x | | x | GI, Protein, and fat per serving; exercise | |
| Karim, Vassányi, and Kósa, 2020 [7] | Feed-forward artificial neural network | | Arleth absorption model | 60/90/120/180 minutes | | | x | x | | x | Absorption profiles | RMSE 1.49mmol/L (60m); 1.62mmol/L (90m); 1.72mmol/L (120m); 1.95mol/L (180m) |
| Montaser et al., 2020 [155] | SARIMAX; Fuzzy C-means clustering algorithm | Unscented Kalman filter | Modified Bergman's minimal model | 15/30/45/60/90 minutes | | | x | x | | x | Physical activity, multivariant adaptive artificial pancreas system (MAAP) | ED: 5.26 (15 minutes); 7.4 (30 minutes); 9.31 (45 minutes); 11.10 (60 minutes); 12.92(90 minutes) |

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| Pereira et al.,2020 [30] | Hybrid model (ODEs; agent-based models (ABMs)) | Runge–Kutta fourth order method | Human glucose–insulin regulation (HGIRS); computational models | | | | x | Carbohydrate and fat | | x | Physical activity | |
| Adelberger et al., 2021 [156] | Kirchsteiger model | Process model combined with Kalman filter (KF-PM); hybrid process and autoregressive model (AR-PM) | | 45/60/90 minutes | 175 | | x | x | | x | Carb-to-insulin ratio and insulin sensitivity factor | ZOH breakfast 4.3 (45m), 25.7 (60m), 25.0 (90m); Lunch 33.3 (45m), 27.3 (60m), 21.4 (90m); Dinner 48.1 (45m), 33.3 (60m), 25.0 (90m) |
| Cervigón, Velasco, and Burgos-Simón, 2021 [157] | Real-coded genetic algorithm | Data augmented by Gaussian white noise; daily samples divided into 12 equally sized slots; genetic algorithm to adjust minimal model; time series outcome from previous stage adjusted using probabilistic fitting; averaging the individual predictions of the ensemble's model | Prud'homme et al. adapted Bergman minimal model | 24 hours | 4 (in patient) | | x | x | | x | Physical activity, time of day | Parker error grid: Pt 1 all results in zones A and B bare one exception; Pt 2mainly zones Aand B high percentage in zone c; Pt 3 most points in zone B small percentage in zone C; Pt 4 high percentage points in zone C |

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| Karim, Vassányi, and Kósa, 2021 [10] | Feed-forward artificial neural network | Quasi-Newton (training) | Meal absorption (Arleth method); AUC whole absorption curve, time lapsed from basal injection | 120–180 minutes | 5 (1TD, 4 T2D) | | x | | x | x | Meal absorption, time since basal injection | RSME 1.72mmol/l (120min) and 1.95mmol/L (180 minutes) |
| Martínez-Delgado, Munoz-Organero, and Quiepo-Alvarez, 2021 [42] | Recurrent neural network (LSTM) | Insulin pre-processing and food data pre-processing | Carbohydrate absorption curves and Haiya et al. insulin absorption model | 60 minutes | D1NAMO dataset - 6 T1DM | | x | x | | x | Glycemic index | RMSE (mmol/L) 0.510 (best case scenario: 1 pt mean) |
| Muñoz-Organeron et al., 2021 [42] | Recurrent neural network based on LSTM | Unscented Kalman filter, mutGaussain parameter | Horvorka's glucose–insulinmodel | 30/60 minutes | | 40 | x | x (meal intake) | | x | Physical activity, stress, hormones | Two-layer RNN: average mean error 0.077; single layer RNN: average mean error 0.088 |
| Tavarez et al.,2022 [158] | Stochasticmodel | Kalman filter | First order dynamics are added to physiological model for BG meter, absorption of glucose in gut | 1/15 minutes | | 1 | x | x | | x | | Kalman filter with CHO and EI delivery achieved improvements > 50% |