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A Review of Emerging Technologies for the Management of Diabetes Mellitus

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Abstract

Objective—High prevalence of diabetes mellitus (DM) along with the poor health outcomes and the escalated costs of treatment and care poses the need to focus on prevention, early detection and improved management of the disease. The aim of this paper is to present and discuss the latest accomplishments in sensors for glucose and lifestyle monitoring along with clinical decision support systems (CDSSs) facilitating self-disease management and supporting healthcare professionals in decision making.

Methods—A critical literature review analysis is conducted focusing on advances in: 1) sensors for physiological and lifestyle monitoring, 2) models and molecular biomarkers for predicting the onset and assessing the progress of DM, and 3) modeling and control methods for regulating glucose levels.

Results—Glucose and lifestyle sensing technologies are continuously evolving with current research focusing on the development of noninvasive sensors for accurate glucose monitoring. A wide range of modeling, classification, clustering, and control approaches have been deployed for the development of the CDSS for diabetes management. Sophisticated multiscale, multilevel modeling frameworks taking into account information from behavioral down to molecular level are necessary to reveal correlations and patterns indicating the onset and evolution of DM.

Conclusion—Integration of data originating from sensor-based systems and electronic health records combined with smart data analytics methods and powerful user centered approaches enable the shift toward preventive, predictive, personalized, and participatory diabetes care.

Significance—The potential of sensing and predictive modeling approaches toward improving diabetes management is highlighted and related challenges are identified.

SECTION I INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic diseases that affect the body's ability to regulate blood glucose levels. In Type 1 DM (T1DM), the immune system attacks the insulin producing pancreatic cells resulting in absolute deficiency of insulin secretion, while Type 2 DM (T2DM) is characterized by increased resistance of the body cells to insulin, which frequently coexists with limited insulin secretion. T2DM is often progressed from prediabetes, which is classified into impaired fasting glucose (IFG) and impaired glucose

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tolerance (IGT). In the IFG condition, the fasting blood glucose is elevated above the normal levels, while IGT is a prediabetic stage of dysglycemia. Both IFG and IGT are associated with insulin resistance and increased risk of cardiovascular disease [1].

The prolonged elevated blood glucose levels, which is the main characteristic of diabetes, may cause damage to large and small blood vessels leading, in the long run, to mortality related complications such as cardiovascular disease (CVD), neuropathy, retinopathy, and nephropathy. Moreover, increased blood glucose levels may lead to several acute episodes such as ketoacidosis and hyperosmolar hyperglycemic state. DM complications can be delayed or even prevented through intensive glycemic control. The latter involves frequent glucose measurements and exogenous insulin administration in the case of T1DM, while insulin treatment overdoses may cause hypoglycemic episodes. The multitude of factors that influence glucose metabolism make optimal glucose regulation in patients with T1DM a very challenging task. In the case of T2DM, glycemic control can be achieved through appropriate medication treatment in combination with effective lifestyle changes in terms of diet and physical activity. However, due to the asymptomatic nature of the disease at the early stages, T2DM is usually diagnosed after the occurrence of complications. In particular, although general blood-test-based guidelines have been established for the diagnosis of T2DM and prediabetes, there is a large time delay between the onset and the diagnosis of the disease [2].

According to the International Diabetes Federation (IDF), in 2014, 387-million people worldwide suffered from DM, while it is estimated that by 2035 this number will rise to 592 million. The undiagnosed cases of DM reach up to 179 million. In 2014, 4.9-million deaths were attributed to DM, while the associated annual cost in health expenditure was estimated at USD 612 billion dollars, which corresponded to 11% of total spending in adults [3].

The high prevalence of DM, and the rapidly growing number of patients with DM, along with the rising costs of care, the predictable number of deaths and medical errors, poses the need to move from a reactive to a preventive approach in diabetes care and to shift the emphasis from the disease to wellness. Rapid advancements in wireless sensing combined with smart data analytics can be used to facilitate personalized, predictive, preventive, and participatory medicine approaches with the ultimate goal to optimize the management of DM through the following multifold focus:

identification of biomarkers which are strongly related with the onset and the progress of diabetes;

identification of individuals being at an increased risk of developing diabetes;

detection of diabetes at its early stages, in order to initiate appropriate treatment;

risk prediction of the incidence of long term diabetes complications enabling early intervention;

patients stratification facilitating the selection of optimal treatment;

tight glycemic control enabled through patient’s active participation.

Rapid advancements in wireless sensing and smart devices are creating a pervasive wireless environment that can address a wide range of major diabetes-related challenges through integration of different types of data acquired from heterogeneous sources. Sensor-based technologies for continuous glucose and lifestyle monitoring with the ability to operate with a resolution time up to 5 and 1 min, respectively, provide important information regarding the patient's glucose profile as a result of treatment and lifestyle. Moreover, data from patient's electronic health records (EHR), which include demographic, clinical, treatment, and medical history information, constitute the patient's health profile. Genetic information such as particular genes that are associated with the onset of T2DM gives additional insights about an individual's predisposition to T2DM development [4]. High-throughput omic technologies such as microarrays, next-generation sequencing (NGS), and mass spectrometry have led to the identification of molecular biomarkers associated with the onset and progress of T2DM and have created new opportunities in diagnosing, monitoring, and managing T2DM [5]. Common omic profiles include genomic, transcriptomic, epigenomic, proteomic, and metabolomic.

As more and more data are gathered, data processing and interpretation become more crucial in order to turn acquired data and information into knowledge toward supporting diabetes decision making and action and providing powerful tools for the patient and the clinician. Advanced modeling, control, classification, and clustering methodologies applied on different combinations of datasets, have led to the development of a range of clinical decision support systems (CDSSs). Glucose prediction models for patients with T1DM are able to forecast glucose profile, enabling early decision making in order to prevent the occurrence of large glucose excursions, while numerous studies have addressed the design, development, and evaluation of closed-loop glucose controllers able to provide estimations of appropriate insulin infusion rates and premeal boluses [6]. Moreover, several computer-based risk prediction models for the incidence of long-term diabetes complications have been proposed and their potential to support clinical decision making toward initiating appropriate treatment has been demonstrated [7] [8][9]. Models able to detect T2DM at its early stages and identify people at an increased risk of developing the disease have also been proposed. These are based on multilevel, multiscale approaches taking into consideration several mechanisms at the molecular, tissue, and organ levels that are known to contribute to the physiological processes leading to the development of T2DM. In addition, T2DM is highly heterogeneous in terms of clinical and molecular profiles, and it is well known that different patients respond differently to existing therapies [10]. Hence, the integration of clinical and molecular profiles can provide important information for selecting appropriate therapy and monitoring the progression of the disease toward personalized treatment.

The aforementioned CDSS constitute the key modules for the development of integrated systems and services for diabetes management, with the ultimate goal to empower patients toward the self-management of their disease and to support healthcare professionals in clinical decision making. Multiparametric monitoring systems combined with intelligent interoperable communication platforms have been developed within the framework of several EU-funded research projects, such as METABO [11], INCA [12], Reaction [13], AP@home [14] and SMARTDIAB [15]. These systems allow continuous glucose monitoring, context awareness, integrative risk assessment, as well as automated closed-loop

insulin delivery. In order to ensure safety, the systems are usually equipped with remote alarms facilitating expert's intervention upon cases of emergency [16] [17] –[18].

This paper focuses on describing and comparatively assessing state of the art and emerging technologies related to sensors and data analytics methodologies applied for personalized diabetes management. The latest advances in sensors for monitoring physiological and lifestyle-related parameters, which are relevant to DM, are discussed. Moreover, CDSSs with the ability to produce clinically meaningful outputs for the prevention, detection, and management of T2DM are presented, along with CDSS for the management of T1DM, including risk prediction models for the incidence of long-term complications, glucose prediction models and closed-loop glucose controllers. The potential of utilizing molecular data toward the development of multilevel predictive models for DM is discussed, while future research directions and challenges are highlighted.

SECTION IISENSORS FOR GLUCOSE AND LIFESTYLE MONITORING

Glucose measurements are particularly important for arranging meals and exercise and for adjusting insulin doses in insulin-treated patients. Moreover, the physician can utilize them in order to assess the patient's status and adjust therapy properly. The most widely used method for measuring blood glucose levels in patients with DM is the finger-stick procedure, which requires a small amount of capillary blood obtained by pricking one finger with a lancet. The main disadvantage of this method is that it provides the current capillary blood glucose concentration without giving information about the glucose trend, and thus, it can lead to wrong treatment decisions.

Recent advances have enabled the development of continuous glucose monitoring systems (CGMS), which can provide information regarding the glucose levels every 1 or 5 min. The CGMS are wearable devices consisting of a glucose sensor, a transmitter, and a receiver/wireless monitor that can be worn on the belt. The glucose readings are stored in a chip and can be subsequently downloaded and assessed by the physician or even the patient, while newer devices are equipped with a display to show in real time the glucose records, usually accompanied with a graph, and the glucose trend. The majority of the sensors embedded in the CGMS are invasive and mainly subcutaneous sensors. Thus, the glucose records derived from the subcutaneous space present a time lag, from 2 to 45 min with a mean time 6.7 min, compared to the blood glucose values. For this reason, the CGMS must be calibrated frequently using the finger-stick procedure. Aiming at improving the reliability of the CGMS, the concept of the smart CGM (sCGM) sensor has been recently proposed, which consists of a cascade of a commercial CGM sensor and three software modules for denoising, enhancement, and prediction of upcoming glucose excursions, able to work in real time [19]. In addition, subcutaneous sensors have limited life time and must be replaced after a few days of use. Table I presents commercial CGMS along with information related to the technology adopted, the sensors lifespan, the sensors warm up period, the calibration frequency, the records frequency, and the accuracy [20] assessed in terms of numerical and clinical evaluation criteria. Numerical criteria provide a measure of the difference between the measured and a reference glucose profile. These include mean absolute deviation

(MAD), mean absolute relative difference (MARD), and median absolute relative difference (MedARD), defined as

$$\begin{aligned} MAD &= \frac{1}{N} \cdot \sum_{i=1}^{N} \left| \hat{G}_i - G_i \right| \\ MARD &= \frac{1}{N} \cdot \sum_{i=1}^{N} \frac{\left| \hat{G}_i - G_i \right|}{G_i} \\ MedARD &= \text{median}_i \left\{ \frac{\left| \hat{G}_i - G_i \right|}{G_i} \right\} \end{aligned}$$

where N is the number of glucose measurements, $\hat{G}_i$ and G_I represent the measured and the reference glucose levels, respectively. The reference glucose levels are usually measured by means of Yellow Springs Instrument (YSI) blood glucose analyzers and blood glucose meters. Clinical evaluation criteria, such as the Clarke error grid analysis (EGA) [21], assess the clinical accuracy of the glucose measurements in terms of affecting decisions for regulating blood glucose levels. The EGA provides the scatter plot of a reference glucose meter and the glucose meter under evaluation, broken down into five zones (A–E) representing different levels of hazard. The clinically accepted zones are considered to be zones A and B.

The latest technological advances are focused on less invasive techniques (e.g., microneedles), noninvasive techniques based on optical methods (e.g., kromoscopy, Raman Spectroscopy, NIR Spectroscopy, and Photoacoustic Spectroscopy) and transdermal methods (e.g., reverse iontophoresis and sonophoresis) [22]. GlucoTrack by Integrity Applications utilizes an ear clip and measures glucose levels using ultrasonic, electromagnetic, and thermal technologies [23]. Abbott developed Freestyle Libre that can take glucose readings as many times a day as needed through a patch worn on the back of the upper arm and does not require finger-prick calibration [24]. MediWise's Glucowise is a pain free glucose sensor that squeezes the skin between the thumb and the forefinger and displays the reading in real time on the screen [25]. Symphony by Echo Therapeutics uses a transdermal sensor and a wireless transceiver in order to display real-time glucose data [26]. CNoga Medical has developed a device that uses skin color to diagnose high blood pressure and measure glucose levels without the need to puncture the skin [27]. Quick LLC introduced the iQuicklt Saliva Analyzer that can measure glucose levels and transfer the results wirelessly using saliva samples [28]. Google has announced the development of smart contact lenses able to constantly measure glucose levels in tears, a release date has not yet been announced [29]. The evolution over time of technologies applied for the development of sensors and devices for glucose monitoring is shown in Fig. 1.

Other approaches are directed to the implementation of fully implantable glucose sensors that are completely unobtrusive to the patient's daily life and can be implanted in the human body with a brief outpatient procedure. The majority of these approaches are based on the use of the glucose oxidase enzyme in order to calculate the glucose concentration. An important barrier in this technology is the decreased sensitivity of the sensors due to the degradation of the enzyme. To address this problem, a second enzyme has been added to eliminate one of the toxic byproducts of the reaction. Most preclinical results have shown a

lifetime of about 10–12 months. Preclinical studies with the GlySens' fully implantable sensor, an oxygen-based sensor with a dual-enzyme electrode technology, have shown accurate readings for a period up to 18 months. The system developed by Sensors for Medicine and Science, Inc., consists of a miniaturized sensor implanted into the subcutaneous space in the wrist and operates on induced fluorescence changes. A very important attribute of this device is that neither the indicator nor the analyte are consumed. The fluorescent indicator molecule and the analyte interact directly and reversibly. A human pilot study showed 77.6% in the A zone and 19.2% in the B zone of the EGA [21].

The CGMS are usually integrated with insulin infusion pumps. The latest technology insulin pumps come with the bolus wizard feature, which provides suggestions of the premeal insulin boluses taking into account the current blood glucose record, the carb-insulin ratio and other information such as insulin sensitivity [20].

Lifestyle behavior especially in terms of diet and physical activity strongly affects the glucose metabolism. On-body sensors such as pedometers (measure footsteps), accelerometers (measure acceleration along a given axis), and heart rate monitors are used to detect and quantify physical activity. These devices can compute indirectly the energy expenditure based on their records (number of steps, movements, heart rate) and their accuracy depends on the kind of the activity and the sensor type. Moreover, devices such as Garmin Vivofit 2, Jawbone Up 24, Fitbit Flex, Basis Peak, BodyMedia LINK Armband, and Withings Pulse O2 incorporate multiple sensors [30] [31] [32] [33] [34][35], which are worn on the arm and are able to track steps, movement, sleep, and calories burned. Misfit's Shine, on the other hand, can be worn anywhere on the body as it features a magnetic grip that can be attached on the clothes [36] and detect movement of body parts other than the arm.

SECTION IIICDSS FOR DIABETES MANAGEMENT

The onset and progress of DM are strongly affected by a multitude of data including lifestyle, clinical, molecular, and genetic data. Various modeling approaches along with different combinations of data acquired from heterogeneous sources can be used to provide clinically meaningful output. Taking into account that the onset of T2DM can be delayed or even prevented by applying effective lifestyle changes, risk prediction models for the incidence of T2DM can raise awareness in individuals at high risk. Models for the early diagnosis of T2DM are also of paramount importance since usually there is a large delay between the onset and the diagnosis of the disease. Prevention in T1DM is not feasible but glucose prediction models and closed-loop glucose controllers can be used to achieve optimal glycemic control and improve the participation of the patient in the care process. Risk prediction models for the incidence of long-term diabetes complications enable patients' stratification, thus provoking personalized treatment. Fig. 2 shows the various types of models that apply to healthy, prediabetic, and T2DM state. Models applied to T1DM management are also shown.

Heterogeneous data sources may be used to provide input to the aforementioned models and controllers (see Fig. 3). The input space consists of data related to the patient's EHR, lifestyle, glucose records, and molecular profile (e.g., genetic and omics data). Lifestyle data

usually include subjective dietary and smoking information reported by the patient, while physical activity is either recorded by a sensor or subjectively reported by the patient. Daily glucose profiles are recorded through CGMS or measured by finger sticks. Genetic data include a set of genes related with the onset of T2DM [4] , [37], [38]. An overview of the input data and the methodologies used toward the development of the aforementioned models and controllers, is presented in Fig. 3 and discussed in the following sections in more detail.

A. Models for T2DM Risk Prediction and Early Diagnosis

Primary prevention of T2DM aims at preventing the onset of the disease via reducing the risk of an individual to develop T2DM, while secondary prevention focuses on the early detection of the disease and optimization of diabetes treatment plan in order to control disease progression. Traditionally, the diagnosis of T2DM and prediabetes relies on clinical tests such as the glycosylated hemoglobin test, fasting plasma glucose test, and oral glucose tolerance test [39]. However, due to the asymptomatic nature of the disease in its early stages, there is a large delay between the onset and the diagnosis of T2DM (more than ten years), which usually occurs after the incidence of complications [40]. This poses a great need to develop computational tools and services with the ability to estimate the risk of the onset and to early detect T2DM by applying multifactorial analysis.

Within this context, several attempts have focused on the development and the evaluation of risk prediction models [41]. The most commonly identified risk predictors, which have been found as strongly correlated with the onset of T2DM and provide input to this type of models, are: age, family history of diabetes, body mass index, hypertension, waist circumference, sex, ethnicity, fasting glucose level, glycosylated hemoglobin, lipids, uric acid, or γ-glutamyltransferases, smoking status, and physical activity [41], [48]. Logistic regression [49], Cox proportional hazards model [50], recursive partitioning [51], and Weibull parametric survival model [52] are the most commonly used methodologies for building these models. The prediction horizon varies from 5 to 15 years, while the reported c-statistics range from approximately 71–86%, with the latter being achieved by applying the full Framingham seven-year risk calculator, which is based on regression models [53].

Since daily activity and health behavior are important factors to predict the development of T2DM, inclusion of such information acquired from a variety of sensors can improve the performance of T2DM risk prediction models. Temporal association rule mining is a new powerful methodology, which can generate predictive rule-based models using the patient trajectories created from applying the association rule mining (ARM) [54] [55][56]. In the prediction of T2DM-related symptoms, a rule indicates that, if a set of observed health-related events X has occurred in the past T_x time period, then another set of T2DM or indicators Y has a possibility p to occur in the following T_y time span.

Moreover, taking into account that T2DM has genetic predisposition, genotype risk scores, which are presented in Section IV, can provide powerful tools toward T2DM risk prediction.

In the area of models aiming at early diagnosis of T2DM, the Finnish Diabetes Risk Score [57] has gained wide acceptance. However, this method is sensitive to human errors since it

requires human intervention in deciding criteria and score. In order to overcome this problem, several attempts have been reported focusing on the application of statistic pattern recognition analysis and machine learning. Age, gender, body mass index, waist-to-hip ratio, waist circumference, random blood sugar test results, fasting blood sugar test results, postplasma blood, sugar tests, race/ethnicity, occupation, blood pressure medication, cholesterol medication, gestational diabetes, high blood pressure, high cholesterol, parental history of diabetes, and exercise, have been identified as risk factors for the incidence of T2DM [40], and subsets of these constitute the input space to various models. Recent efforts based on artificial intelligence (AI) have produced promising results.

In particular, clustering techniques that make use of k-means, mixture-of-Gaussians, self-organizing maps (SOM) and neural gas (NG) have been applied for the diagnosis of T2DM, while support vector machines (SVM) and several types of neural networks (NNs), such as multilayer, back-propagated, radial basis function (RBF), general regression NNs, and neurofuzzy inference systems have been used for classifying subjects in diabetics and nondiabetics [40]. Moreover, methods based on mixture of experts (ME), which combine the outputs of several classifiers for the calculation of the final decision, have been proposed in order to enhance the performance achieved by a single classifier. Modified ME (MME), which incorporate an assembly of expert networks and a gate-ban, have proven to further increase the classification performance [40]. Table II summarizes the classification performance of each of the aforementioned AI-based models.

B. Risk Engines for Long-Term T1DM and T2DM Complications

Severe long-term mortality-related complications of DM such as CVD, retinopathy, kidney disease, and neuropathy can be delayed or even prevented by early initiation of appropriate treatment. Risk score calculators have great potential to provide valuable support in clinical decision making by facilitating patients' stratification. Diabetes risk engines are fed with medical history data, clinical measurements, and environmental data and provide the probability of a patient to develop specific long-term diabetes complications. CVD and diabetic retinopathy constitute the most commonly target complications. Typical examples of risk engines for diabetes complications include the United Kingdom Prospective Diabetes Study (UKPDS) Risk Engine [7], the CDC/RTI Diabetes Cost Effective Model [8] and the Global Diabetes Model (GDM) [9]. The most widely used diabetes risk engines are those whose development is based on data collected within the framework of large clinical trials with minimum duration of 5 years, such as the Diabetes Control and Complications Trial (DCCT) [68], the Epidemiology of Diabetes Interventions and Complications (EDIC) study [69], the QRisk study [62], the UKPDS study [7], and the EuroDiab study [70]. Table III summarizes available risk engines, along with adopted methodologies and datasets used for their development, as well as the specific patient target group and complications. The diabetes complications risk prediction models are usually based on survival analysis, regression equations and Markov modeling [71]. A different methodological framework, which is based on AI techniques, has been utilized in [67] toward personalized risk prediction of diabetic retinopathy development in patients with T1DM. In particular, an FNN, a Classification and Regression Tree (CART), and a wavelet NN have been comparatively assessed using data from the medical records of 55 T1DM patients. The

performance achieved by each model has been evaluated in terms of sensitivity, False Positive Rate (FPR), accuracy, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV), and False Discovery Rate (FDR) (see Fig. 4).The increased discriminative ability of the wavelet NN along with its superiority over the FNN and CART, which are less parameterized, justifies the need to investigate the application of more sophisticated techniques in order to obtain reliable risk scores.

C. Glucose Prediction Models for Patients With T1DM

Glucose metabolism in T1DM patients is strongly affected by several exogenous and endogenous factors. In particular, environmental factors such as nutrition, physical activity, patient's psychological status, and overall lifestyle along with endogenous processes, such as circadian rhythms, play a crucial role in glucose metabolism. Furthermore, intra- and interpatient variability in response to therapy, makes the regulation of glucose levels a very challenging task. Computational models able to produce accurate and reliable estimations of future glucose profile in response to various stimuli can provide valuable tools within the context of achieving tight glycemic control. Predicted glucose profile is mainly used for producing early warnings of the upcoming hypoglycemic/hyperglycemic episodes or for adjusting insulin injections and insulin infusion rate in insulin-treated patients. Several efforts have been reported toward the development of glucose prediction models, which are usually based on either compartmental models (CMs) or data-driven approaches. CMs represent fundamental glucoregulatory processes, taking advantage of the knowledge of the physiological paths involved in the human metabolic process [72]. However, their acceptance has been limited because they take into account only a confined number of factors affecting glucose metabolism, while the identification of their parameters requires clinical measurements, which are not typically available in clinical settings. Moreover, the lack of personalization capabilities constitutes a major drawback [58].

In order to overcome the aforementioned limitations, the use of data-driven techniques that apply pattern recognition methods to capture the metabolic behavior of a patient with T1DM has been proposed. Several glucose prediction models have been developed based on Volterra series models, time-series analysis, and machine learning. Particularly, the application of Volterra models for the simulation of glucose–insulin dynamics has demonstrated good performance in the absence of noise [73], [74]. Moreover, Autoregressive (ARX) and Box–Jenkins models of various orders, identified based on data generated from a simulated physiological model, have achieved good prediction performance [75]. In addition, the potential of utilizing ARX models with time-varying parameters has been investigated [76]. Several types of Artificial NNs such as multilayer perceptron (MLP) [77], recurrent neural network (RNN) [78], radial basis function (RBF) [79], Wavelet NNs [80], and neurofuzzy techniques [81] have been successfully applied for the simulation of glucose metabolism. Furthermore, hybrid glucose prediction models based on the combined use of CM and data driven approaches such as RNN [78], support vector regression (SVR) [82], and SOM [83] have produced promising results. Table IV summarizes glucose prediction models of the literature, based on AI and autoregressive methods along with their input space, and reported accuracy. CGMS data, blood glucose

readings, insulin dosages, and lifestyle data in terms of ingested carbohydrates, physical activity and stress, are the most commonly used input factors.

Although a direct and fair comparison of models' predictive performance is not possible due to the different testing dataset, input space, and evaluation methodology used, several important conclusions can be drawn. In particular, as it is expected, the application of a more informative input space results in better predictive performance. In addition, as the prediction horizon (PH) increases, the models' predictive performance deteriorates. Moreover, the use of hybrid models for the simulation of glucose–insulin metabolism has achieved the lowest RMSE values justifying, thus, their superiority over other approaches. When only CGMS data are used to feed the models (shown in bold in Table IV), AI-based models achieve higher performance than autoregressive models (RMSE equal to 12.29 mg/dL-achieved by SOM- against 18.78 mg/dL), demonstrating thus, the need of applying more sophisticated techniques in order to capture the metabolic behavior of a patient with T1DM.

D. Closed-Loop Glucose Controllers

Closing the loop between a CGMS and an insulin infusion pump through reliable, accurate, and effective glucose control algorithms, has become one of the most important research challenges in T1DM management. The problem of maintaining blood glucose levels within an acceptable range is particularly complex in patients with T1DM, since various exogenous parameters strongly affect the glucose metabolism, while the ever-changing and unpredictable nature of glucose metabolism leads to intra- and interpatient variability. Therefore, the glucose controller should be able to provide personalized and adaptive treatment recommendations. The majority of approaches applied toward the development of glucose controllers [6] are based on either proportional integral derivative (PID) control [84], [85] or model predictive control (MPC) [86] [87] [88] [89] [90] [91] [92] [93] [94] [95][96]. MPC-based glucose controllers have gained wider acceptance due to the MPC's ability to handle 1) high nonlinearities in glucose–insulin metabolism, caused by saturation and inhibition effects evidenced by chemical substrates and hormones involved in enzyme dynamics and hormonal control effects, 2) time delays in subcutaneous–subcutaneous (sc-sc) route due to the delayed effect of infused subcutaneous insulin and the glucose diffusion from the blood to the subcutaneous space, and 3) inaccuracies in subcutaneous glucose measurements. MPC incorporates glucose prediction models, described in Section III-C, which produce estimations of the future glucose profile. The estimated glucose profile is compared with the desired one and the obtained deviations are inserted into a cost function in order for the latter to be minimized toward producing advice on insulin infusion rates. The efficiency of the MPC controllers is strongly dependent upon the used glucose prediction model, the cost function and its tuning. Several attempts have been made toward the development of glucose controllers based on nonlinear model-predictive control (NMPC), and the effectiveness of the NMPC over the linear MPC has been studied and justified [92], [96], [98]. Moreover, the mathematical formulation of the cost function is of particular importance. Traditionally the cost function includes the sum of the squared differences of the glucose predictions from the desired glucose values and of the estimated insulin changes

$$J=\Gamma_e\sum_{i=1}^{N_p}(y\,(t+i)-r)^2+\Gamma_u\sum_{j=0}^{N_c}\Delta u^2\,(t+j)$$

where y and r represent the estimated and the desired glucose values, respectively, while u is the insulin infusion rate, N_p is the prediction horizon, N_c is the control horizon, and Γ_e and Γ_u are the prediction and control weighting coefficients, respectively. However, taking into account that the goal of a closed-loop glucose controller is to maintain glucose levels within an acceptable range, the addition of appropriate terms penalizing the cost function whenever future glucose predictions are outside a predefined range [98], [99], can improve control performance. Another important issue toward the implementation of MPC is its tuning. A set of parameters in the cost function influence the controller's performance and stability and their values are usually adjusted either via trial and error procedures or by following general tuning guidelines [72]. However, trial and error is a rather cumbersome task while systematic approaches cannot be implemented online because the glucose metabolism is subject to severe disturbances and changing operating conditions. In order to overcome this problem, online tuning has been proposed [98].

An exemplar adaptive glucose control algorithm (Insulin Infusion Advisory System—IIAS) addressing the aforementioned issues is presented in [98]. The system is able to adapt over time through continuously updating the parameters of both the glucose–insulin metabolism model and the cost function. In particular, the IIAS incorporates a hybrid personalized glucose–insulin metabolism model, which is based on the combined use of CMs for the simulation of glucose absorption from the gut and the subcutaneous insulin kinetics, respectively, and an RNN for the simulation of glucose kinetics. The ability of the RNN to be trained on line provides high personalization and adaptation capabilities. Moreover, online tuning of the cost function's parameters—prediction horizon (N_p), control horizon (N_c), and control weighting coefficient (Γ_u)—is achieved through a fuzzy-based logic strategy. The IIAS has been in silico evaluated using the UVa T1DM simulator [100] and its performance has been compared against both the adaptive basal therapy presented in [41] and the artificial pancreatic b-cell, which is based on zone-MPC and is adjusted automatically by linear difference personalized models [99]. The obtained results are presented in Tables V and VI . The IIAS has achieved the lowest risk associated with extreme glucose deviations (Risk Index) in the former case and the lowest percentage of glucose excursions in both cases. The superiority of the IIAS over the adaptive basal therapy and the linear MPC justifies the need of applying more sophisticated control strategies to regulate glucose levels in T1DM.

Several clinical studies have been conducted in recent years, in order to test and compare the performance of closed-loop glucose controllers against conventional therapies [101] [102] [103] [104][105]. Overnight closed-loop experiments using different MPC controllers have demonstrated the superiority of the closed-loop control over the conventional pump treatment [101], [104]. Similar conclusions have been drawn from closed-loop clinical studies lasting more than 24 hours [101], [107].

Recent technological advances have led to the development of systems supporting outpatient clinical trials over extended time periods in order to evaluate the performance of closed-loop glucose controllers under free living conditions. The Diabetes Assistant (DiAs), an experimental smartphone-based mobile system, is the first portable platform facilitating outpatient clinical trials [108]. In the same context, a three-layer modular architecture for closed-loop control of T1DM has been developed, consisting of a sensor/pump interface module, a continuous safety module, and a real-time control module [109].

Although great progress has been made toward the development of safe and accurate automated insulin delivery systems, the risk of hypoglycemia caused by overestimated insulin infusion rates is not completely eliminated. In order to prevent and treat hypoglycemia, latest research directions focus on the administration of both insulin and glucagon, the insulin-counteracting hormone. The feasibility of achieving safe and good glycemic control by applying bihormonal closed-loop glucose controllers has been investigated [106], and their superiority over insulin-only controllers has been proven [110]. The most common approach combines MPC for the estimation of insulin infusion rates in order to handle the time lags and delays imposed from the subcutaneous insulin delivery, and PID control for the calculation of glucagon infusion rates, since the subcutaneous glucagon absorption is rapid [106].

Although significant efforts have been reported toward the development of closed-loop glucose controllers, there are still severe limitations in terms of reliability, safety, and accuracy [111] . Considering the short duration (up to one week) of the inpatient and outpatient clinical trials along with the fact that closed-loop glucose controllers are intended for chronic use, there is a lack of clinical evidence for proving their effectiveness and safety. Moreover, the occasional inaccuracies in glucose records from the CGMS and the delays caused from the subcutaneous insulin administration makes the estimation of optimal insulin infusion rates a challenging task. Although the usage of more than one glucose sensors has been proposed, improvement of the existing or development of novel control strategies with various levels of safety is needed in order to enhance robustness. Bihormonal closed-loop systems seem to be very promising in achieving optimal glycemic control [106]. However, more stable glucagon preparations are needed in order for the glucagon to remain in a wearable pump for at least 3–7 days, and therefore, to enable long-lasting clinical trials for obtaining reliable evaluation results.

SECTION IVTOWARD T2DM PREDICTIVE MODELING USING MOLECULAR DATA

Although clinical data encompass phenotypic information, insulin secretion and resistance actually involve with multiscale biological processes affected by gene, protein, and metabolite factors [5], [112], [113]. A patient’s comprehensive biological state can be inferred by combining several omic data types, including genomic, transcriptomic, epigenomic, proteomic, and metabolomic. The omic profile is useful for investigating or predicting the underlying interactions, associations, and mechanisms in acquired samples. Recent advances in high-throughput technologies such as microarrays, NGS, and mass

spectrometry have enabled the identification of molecular biomarkers for T2DM. For example, the population-level genome-wide association study (GWAS) [4] helps discover novel genetic variants associated with T2DM that can be incorporated into T2DM risk prediction models. To be more specific, GWAS has identified putative causal genes for T2DM such as CDKAL1, CDKN2A, IGF2BP2, and MTNR1B, each of which corresponds to 15–20% increase in the T2DM risk. Because a tremendous amount of GWAS data has become publicly available, several studies have focused on the metaanalysis of these data and have resulted in the identification of 59 genetic loci that are associated with T2DM susceptibility [37], [38]. Moreover, multiple single nucleotide polymorphisms (SNPs) on CAPN10 have been found to collectively increase the risk of T2DM by 2.8 folds [114], while SNP on DACH1 gene is associated with familial young-onset diabetes, prediabetes, and CVD in the Chinese population [115]. Gene-expression patterns may also assist in predicting prediabetic states or uncovering underlying biological mechanisms of T2DM. Transcript expression levels among patients with T2DM, subjects with impaired glucose tolerance, and subjects with normal glucose tolerance have been studied. The authors have reported that TNF-alpha, TXNIP, and SOCS-3 genes are accurate indicators for various clinical conditions [116]. Furthermore, expression profiles of microRNA and their effects on regulating insulin sensitivity have been widely examined in recent years [117], [118].

Other than genetic factors, the environmental modification of DNA sequences (e.g., DNA methylation and histone modification) substantially contributes to the risk of T2DM. Epigenetic mechanisms such as chromatin remodeling and oxidative stress, epigenetic regulation of gene expression, and histone modification in vascular epithelium exposed to hyperglycemia are related to T2DM [119], [120]. More specifically, the epigenetic regulation of the DLK1-MEG3 microRNA cluster by DNA methylation is associated with Type 2 diabetic islets [121]. Scaling up the biological scales, protein and metabolite markers, caused by genomic and transcriptomic variations, represent disease status with more directness and immediacy [122], [123]. Protein markers such as specific cytokines and chemokines are predictive for T2DM since inflammatory response is significant in the disease [124]. Five classes of protein markers in T2DM have been identified: hormones (e.g., amylin), protease inhibitors (e.g., cystatin), secretory vesicle proteins (e.g., chromogranin), cell adhesion (e.g., protocadherin), and secreted enzymes (e.g., phospholipase) [125]. Compared to other omic technologies, metabolomics is an emerging due to the complexity of the biochemical targets [122], which is caused by the variety of biological sample types being examined, the number of metabolites, and the large magnitude of variation in metabolite concentrations. Alterations in fatty acid, tryptophan, and lysophosphatidylcholine metabolism and in other metabolic pathways may constitute a metabolic signature for T2DM [126] [127] –[128]. In Fig. 5, the aforementioned molecular biomarkers associated with prediabetes and T2DM are summarized under the corresponding omic category.

To take advantage of emerging genomic knowledge and to translate it into clinically useful tools/services, genotype scores have been developed with the ability to assess the risk of T2DM incidence taking into account these genetic variations [129]. Within this context, several prospective cohort studies have been conducted aiming at assessing the impact of introducing the genetic profile into the T2DM risk prediction models. In particular, in these

studies, the models have been fed with different input space consisting of, either only the genetic factors, or only the conventional risk factors or both, and their predictive performance has been comparatively assessed. The models' discriminative ability has been evaluated in terms of the area under the receiver operating characteristic curve (AUC), which is created by plotting the true positive rate against the false positive rate at various threshold settings. In the case of the genetic input space, the AUC ranges from 55% to 68% with a median of 60% achieving lower performance than that achieved by applying only conventional risk factors (AUC range: 63%–90%, median: 78%) [129]. The highest performance has been achieved by taking into account both genetic and conventional risk factors (AUC range: 63%–91%, median: 79%). The inclusion of the genetic profile into the models' input space has resulted in slight improvement in their predictive performance, irrespectively of the study design, participants' race/ethnicity and number of genetic markers included. Although in theory, it could be speculated that the genetic profile can be useful in the case of the youngest population, because the phenotypic symptoms have not occurred, yet, there are no studies to justify this notion. The most important reason for not obtaining a significantly higher predictive performance by taking into account the genetic variants is the limited number of the identified genetic markers with the majority of them not strongly correlated with T2DM (odds ratios of heterozygous genotypes are less than 1.15) [129]. In order to achieve AUC up to 80% and even higher, based on the genetic profile, 400 genetic variants with minor allele frequencies of 10% and odds ratios of the heterozygous genotypes for each variant greater than 1.25 are needed [129], [130].

SECTION VFUTURE RESEARCH DIRECTIONS AND CHALLENGES

Although great progress has been made in the recent years toward the development of the CDSS for diabetes management, these systems have not yet been fully adopted in the clinical practice. This is mainly due to the biased data analysis and the lack of reliable and comprehensive evaluation studies, since the criteria for selecting patients and controls and the approaches for the treatment of controls vary greatly among published studies [131]. Moreover, although it is widely known that CDSS have great potential to provide with cost-effective solutions, substantial economic analysis for proving this has not been conducted.

Apart from the need for a systematic evaluation framework, current research challenges focus on the development of new CGMS and sensor networks able to monitor in an unobtrusive and seamless manner a wide range of physiological and lifestyle related parameters. Advanced data analytics and modeling approaches are needed to extract clinically meaningful knowledge from the multitude of collected raw data. User-centered approaches, taking advantage of the sensor networks and the personalized CDSS, can significantly contribute in reshaping and improving the clinical workflow for the management of DM.

A. Unobtrusive Sensing

The key challenges for the development of next-generation CGMS refer to decreasing the operational cost, reducing the number of calibrations and warm up periods, and improving accuracy. Furthermore, the current trends point to the development of noninvasive

techniques for accurate glucose monitoring. Although considerable efforts have been made in this direction, there are still issues related to precision, robustness, stability, long response time for glucose determination, which require considerable improvements [20].

Moreover, the development of sensors for automatically detecting meal consumption constitutes a major challenge in dietary monitoring. Within this context, the usage of wearable body sensors, for detecting intake gestures (e.g., intentional arm movements to bring food into mouth), chewing sounds during food intake, and swallowing have been recently investigated [132]. Intake gestures can be detected by inertial sensors integrated into clothing [133], chewing sounds can be recorded by ear microphones [134], and swallowing can be assessed using Electromyography at the hyoid or a textile capacitive sensor [135]. The signals from these sensors can be analyzed in order to recognize the time, type, and amount of a meal.

Taking into account that the DM pathophysiology is a continuing process, transient critical abnormalities should be early detected. Sensor networks able to provide with continuous physiological (e.g., glucose, blood pressure, pulse, cardiac rhythm) and lifestyle (e.g., diet, physical activity) monitoring data have great potential to detect such transitions and track the progress of the disease. The emerging technology of Internet of Things can significantly contribute toward this direction by providing global connectivity among sensors and devices that contain appropriate embedded technology, thus enabling seamless integration of more factors in clinical decision making related to diabetes management.

B. Emerging Methodologies for Modeling the Onset and the Progress of DM

Considering the multifactorial nature of DM, multilevel and multiscale modeling approaches should be applied in order to take into consideration all the different types of factors that are strongly associated with the disease onset and evolution. New powerful data analysis methods, such as undirected and directed networks, can be used to capture correlated and causal relationships among the variables. Undirected networks can represent correlations but no causal effects. For example, the weighted correlation network builds upon the pairwise correlation between features determining the significance of each link [136]. The regression-based network can use various regression models (e.g., linear regression, Poisson regression, and logistic regression) depending on the distribution of targeted response features [137], [138]. In directed networks, causal relationships may be inferred from the direction of each link. ARM-based and Bayesian are two examples of this kind of network. The Bayesian network applies Bayes rules to link features, wherein the occurrence of a feature depends on the occurrence of the other feature. The strength of each link depends on the posterior conditional probabilities [139], [140]. Such methods can be applied in order to identify novel biomarkers, which are strongly related with the onset of T2DM and the evolution of T1DM and T2DM.

An emerging methodology for discovering patterns in multiscale data is deep learning, which is applied for both unsupervised and supervised analysis [141], [142]. Deep learning methods are inspired by the hierarchical structure of the brain, and use multiple levels of abstraction in order to identify relevant patterns. Such methods have been, recently, applied in order to predict patient phenotypes from clinical data [143] and biomolecular properties

[144], [145]. In the case of DM, deep learning techniques can be used to search for patterns across clinical and multiple types of omic data.

C. User Centered Approaches

The development of user centered approaches, through body sensor networks, context awareness, and personalized modeling, can significantly contribute to empower citizens and patients toward the self-management of their own health and disease outside institutions, improving, thus, health outcomes in terms of both quality of life and health expenditures. A holistic user-centered approach, supported by computer-based predictive models, providing personalization capabilities and integrating heterogeneous sources of data (patient, clinical, biological, therapeutic, behavioral, physical training and performance, lifestyle and diet, environmental data, social data) has great potential to raise individual awareness, promote behavioral lifestyle changes, support treatment, and monitor the disease.

Increased emphasis should also be given on the development of the CDSS in order to improve interactions between patients and health professionals within the context of codecision making. Furthermore, the creation of ecosystems for DM management, involving multiple stakeholders such as patients, families, diabetologists, general practitioners, case managers, who undertake activities related to the coordination of services (assessment, planning, facilitation, evaluation, monitoring the patient’s progress, and promoting cost-effective care) on behalf of an individual patient, and health care policy makers is particularly challenging.

SECTION VICONCLUSION

Optimal management of DM requires redesigning the current system of healthcare delivery by shifting the focus from reactive to proactive care. Predictive and preventive medicine for DM must rely on the capacity to capitalize on information from a diverse range of data (lifestyle, social, clinical, treatment, and molecular) in order to early detect pathophysiological changes and to better tailor intervention and treatment. Recent advances in sensing technologies for monitoring physiological and lifestyle parameters coupled with advanced data analytics and modeling approaches for the prediction, diagnosis, and management of DM can play a key role. Enhanced integration of patient data through the development of multiscale and multilevel physiological models can generate new clinical knowledge and contribute to a more effective personalized diabetes care approach.

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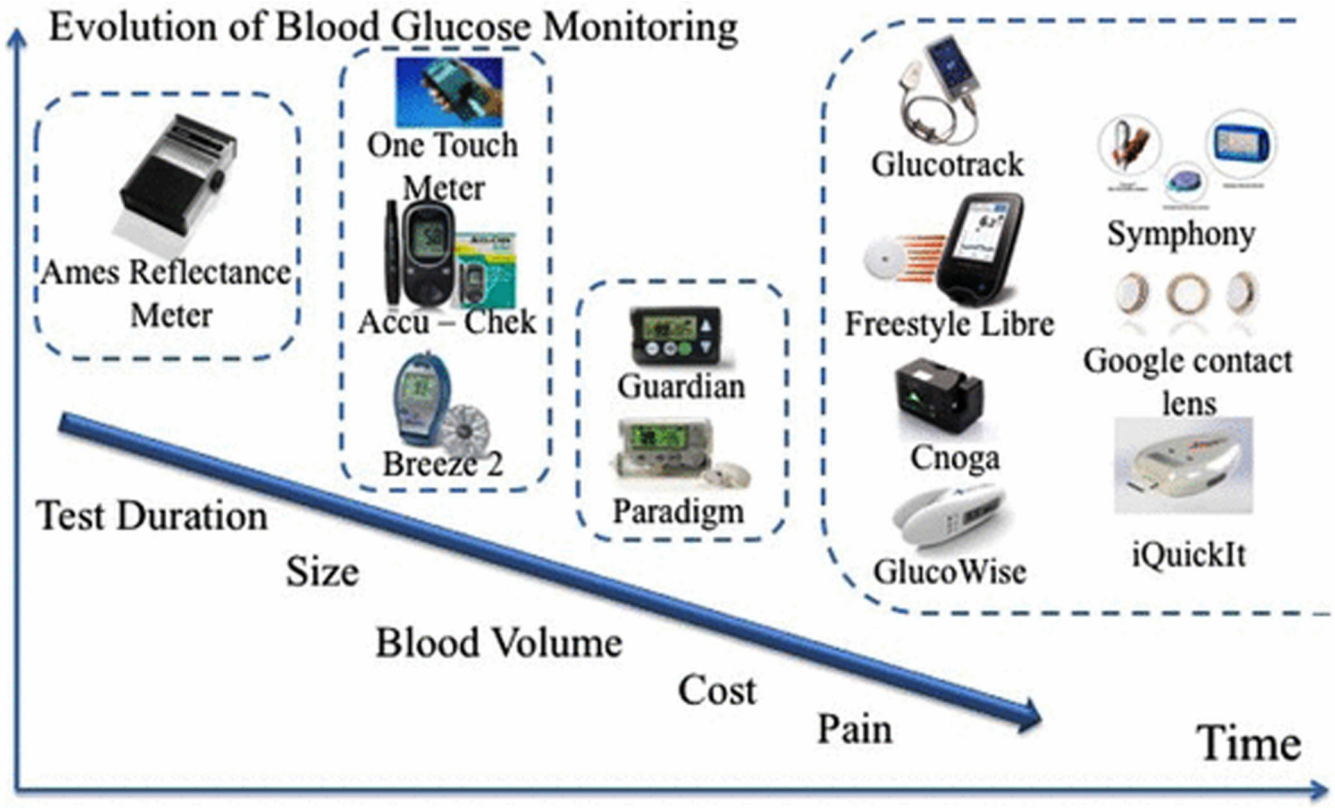

Fig. 1.
Evolution of devices for glucose monitoring.

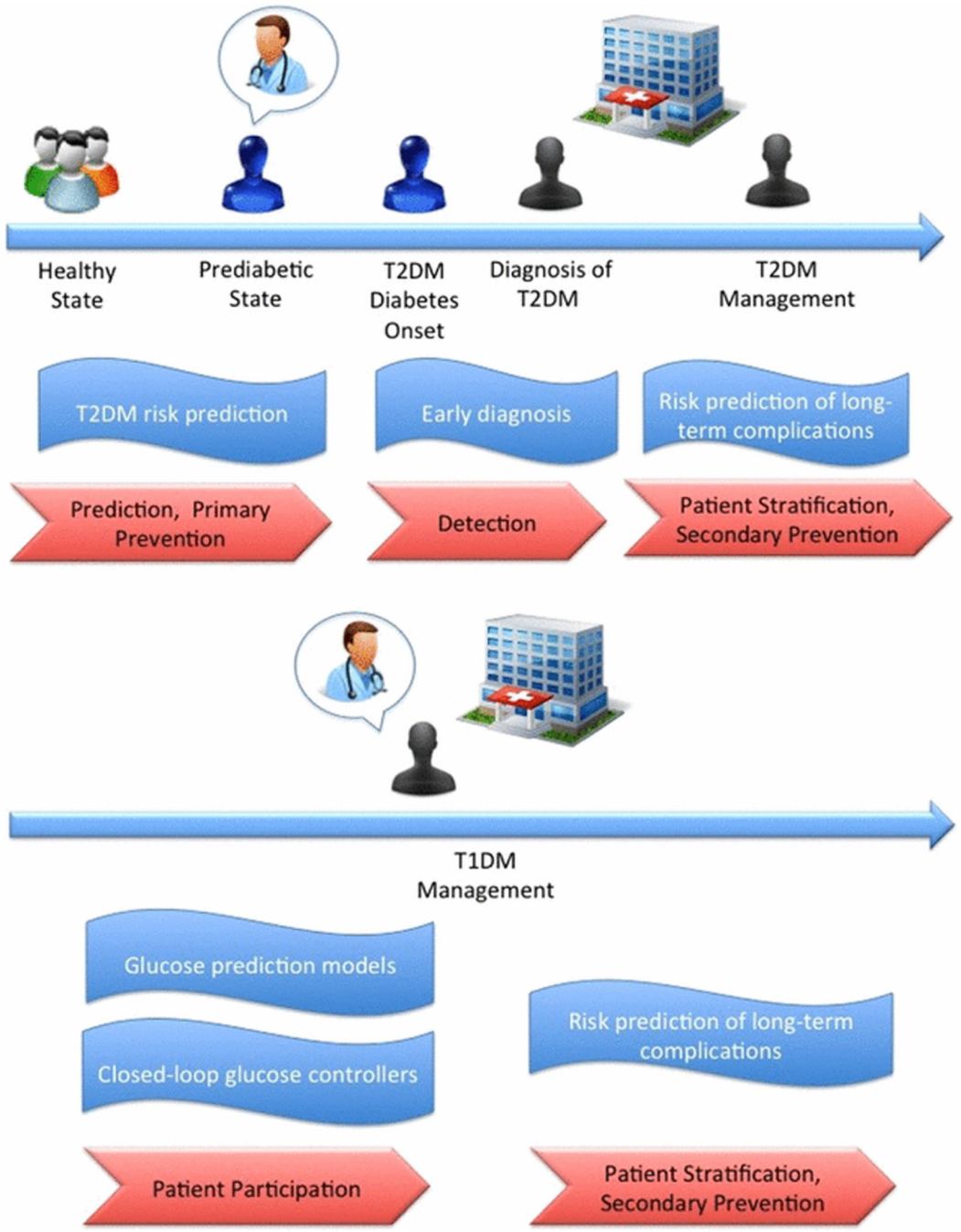

Fig. 2.

Upper panel: Progress from healthy state to prediabetic state and T2DM. Types of models that apply in each state. Lower panel: Types of models for the management of T1DM.

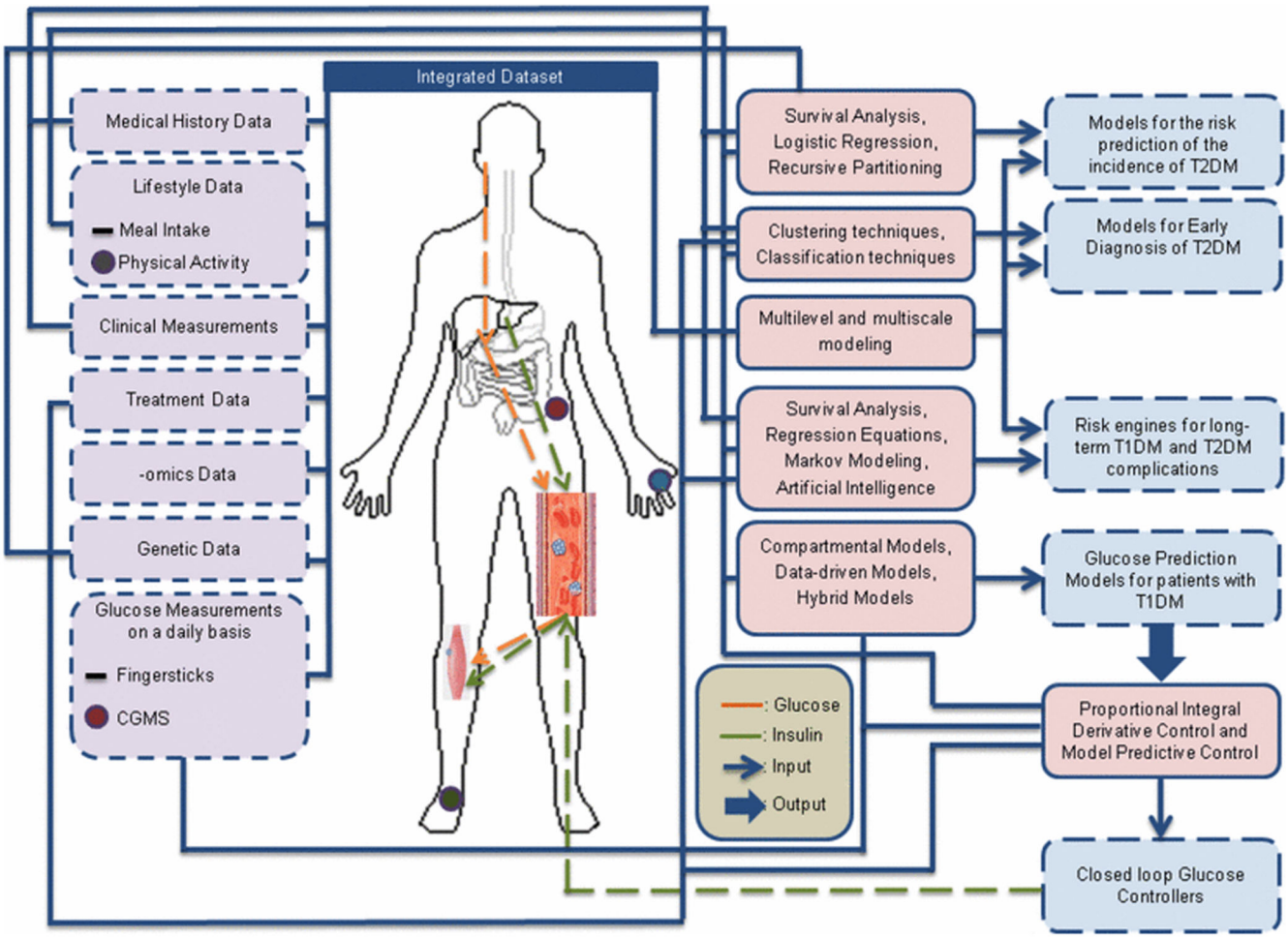

Fig. 3.
Overview of the DM data management flow.

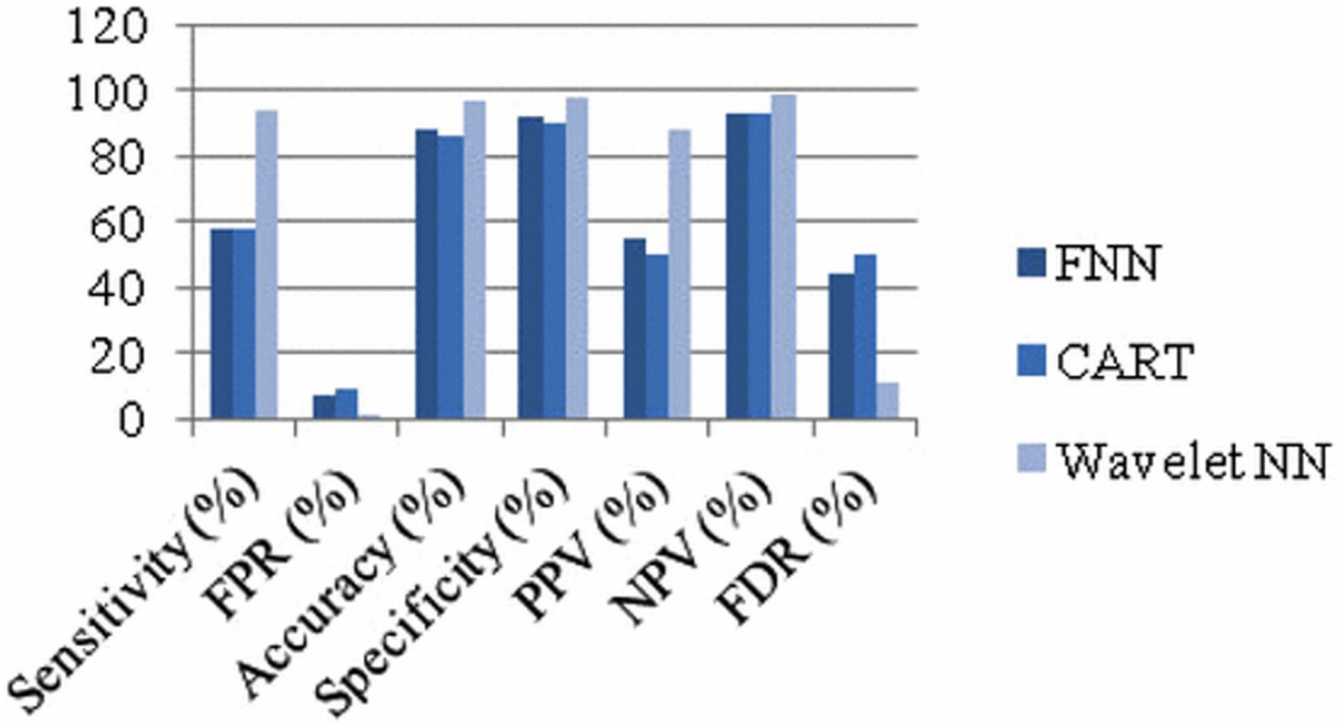

Fig. 4.
Performance evaluation of the FNN, CART, and wavelet NN-based risk prediction models for the incidence of diabetic retinopathy [67].

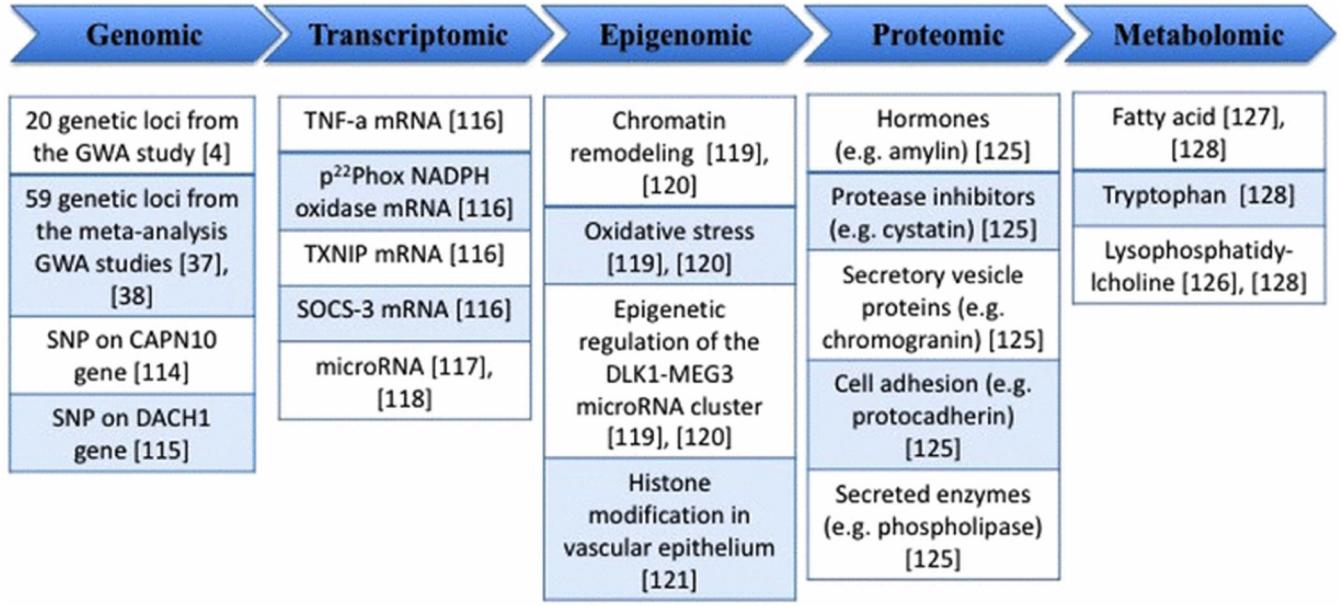

Fig. 5.
Molecular biomarkers for prediabetes and T2DM.

TABLE I

Technical Specifications and Accuracy of Commercially Available CGMS [20]

Device	Technology	Sensor Lifespan	Sensor Warm-Up	Calibration	Records Frequency	Accuracy	Reference
Dexcom Seven Plus (Dexcom)	Invasive	168 h	2 h	every 12 h	5 min	MARD: 16% MAD in hypoglycemia: 16 mg/dL	YSI blood glucose analyzer
Dexcom G4 Platinum (Dexcom)	Invasive	168 h	2 h	every 12 h	5 min	MARD: 13% MAD in hypoglycemia: 11 mg/dL	YSI blood glucose analyzer
Guardian Real-Time (Medtronic)	Invasive	72 h	2 h	every 12 h	5 min	MARD: 17.6% EGA (A+B): 99.6%	Arterial samples
FreeStyle Navigator (Abbott)	Invasive	120 h	10 h	calibration at 10 h, 12 h, 24 h and 72 h.	1 min	MARD: 12.8% MedARD: 9.3% EGA (A+B): 98.4%	YSI blood glucose analyzer
FreeStyle Navigator II (Abbott)	Invasive	120 h	10 h	calibration at 10 h, 12 h, 24 h and 72 h.	1 min		
HG1-c (C8 Medisensors)	Non Invasive(Raman spectroscopy)	–	–		5 min	MARD: 38 mg/dL MedARD: 30 mg/dL EGA (A+B): 92%	Blood glucose reference values
GlucoTrack (Integrity Applications Ltd.)	Non Invasive (thermal ultrasound and electromagnetic)	6 months (ear clip lifespan)	–	Every 6 months (for a new ear clip)		MARD: 29.9% MedARD : 19.9% EGA (A+B): 92%	Commercial glucose meter and glucose analyzer
Symphony (Echo Therapeutics Inc)	Prelude SkinPrep System	–	–		1 min	EGA (A+B): 96.9%	YSI 2300 STAT Plus glucose analyzer and commercial glucose meters

TABLE II

Classification Performance of AI-Based Models for T2DM Diagnosis [42]

Model	Accuracy (%)	Sensitivity (%)	Specificity (%)	Reference
Modified FNN	80.07	84.38	74.00	[43]
Adaptive neurofuzzy inference system	98.14	98.58	96.97	[44]
SVM	94.00	94.00	93.00	[45]
Linear discriminant analysis and adaptive network-based fuzzy inference system	84.61	85.18	83.33	[46]
Multilayer FNN	91.53	91.19	92.42	[47]
ME	97.93	98.01	97.73	[47]
MME	99.17	99.43	98.48	[47]

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TABLE III

Risk Prediction Models for Long-Term Diabetes Complications [58]

Risk Assessment Model	Data from Reference Study	Number of Patients and Type of Diabetes	Target Complications	Reference
Cox regression model	DCCT/EDIC	1441 T1DM patients	CVD	[59]
Cox regression model	DCCT/EDIC	1441 T1DM patients	Atherosclerotic occlusion in peripheral vascular disease	[60]
Tobit survival regression model	DCCT/EDIC	1441 T1DM patients	CAC	[61]
Cox proportional hazard model and fractional polynomials	QRisk	1280000 T2DM patients	CVD	[62]
Multivariate logistic regression	UKPDS	5102 T2DM patients	Fatal and nonfatal MI and stroke	[63]
Survival analysis	UKPDS	5.102 T2DM patients	Stroke	[64]
Weibull proportional hazard regression model	UKPDS	5102 T2DM patients	Death, MI, stroke, heart failure, amputation, renal failure, diabetic eye disease	[65]
Markov modeling	UKPDS	5102 T2DM patients	Nephropathy, neuropathy, retinopathy, CHD, and stroke	[8]
Logistic regression	EuroDiab	1115 T1DM patients	Microalbuminuria	[66]
CART, FNN, wavelet NN	EuroDiab	55 T1DM patients	Retinopathy	[67]

TABLE IV

Glucose Prediction Models Based on AI and Autoregressive Models With Time Varying Parameters [97]

Model	Input Space	No. of T1DM Patients (Monitoring Period)	Evaluation Results
Multilayer FNN [77]	CGMS data, blood glucose readings, insulin dosage, carbohydrate intake, hyperglycemic and hypoglycemic symptoms, lifestyle (activities and events), emotional states	18 (3–9 days)	PH (*min*)/ MAD (%): 50/6.7, 120/14.5, 180/18.9
FNN with two hidden layers [98]	**CGMS data**	9 (12 days) 6 (2 days)	PH (*min*)/RMSE(*mg/dl*): 15/10, 30/18,45/27
RBF NN [79]	Blood glucose readings, insulin dosage, food intake, stress, level of exercise	1 (77 days)	Interval/RMSE (*mg/dl*): morning/1.49, afternoon/0.92, evening/0.67, night/0.21
Wavelet NN [80]	Blood glucose readings, insulin dosage, food intake, stress, level of exercise	1 (77 days)	Interval / RMSE (*mg/dl*): morning/0.81 afternoon/0.63, evening/0.60, night/0.30
Neurofuzzy (applying wavelets as activation functions) [81]	CGMS data, physical activity data from sensor	6 (7–15 days)	PH (*min*)/ RMSE (*mg/dl*): 15/14.42, 30/20.20, 45/24.79, 60/28.49
SOM [83]	CGMS data, physical activity data from sensor	10 (6 days)	PH (*min*)/ RMSE(*mg/dl*):30/11.42, 60/19.58 120/31.00
SOM [83]	**CGMS data**	10 (6 days)	PH (*min*)/ RMSE (*mg/dl*):30/12.29, 60/21.06 120/33.68
SVR [82]	**CGMS data**	15 (5–22 days)	PH (*min*)/ RMSE(*mg/dl*):30/15.29, 60/24.19, 120/33.04
Hybrid model based on the combined use of CMs and RNN [78]	CGMS data, insulin infusion rates, carbohydrates ingested	9 (10 days)	PH (*min*)/ RMSE (*mg/dl*): 30/18.34
Hybrid model based on the combined use of CMs and SVR [82]	CGMS data, insulin dosages, carbohydrates ingested, physical activity data from sensor, time	15 (5–22 days)	PH (*min*)/ RMSE (*mg/dl*): 15/5.21, 30/6.03, 60/7.14, 120/7.62
Hybrid model based on the combined use of CMs and SOM [83]	CGMS data, insulin infusion rates, carbohydrates ingested	12 (10 days)	PH (*min*)/ RMSE (*mg/dl*): 30/14.10, 60/23.19
Autoregressive models with time varying parameters [76]	**CGMS data**	28 (2 days)	PH (*min*)/ RMSE (*mg/dl*): 30/18.78

TABLE V

Comparison of a Glucose Controller (IIAS) Based on Nonlinear Model-Predictive Control With the Adaptive Basal Therapy [42]

Controller	Hypoglycemia Percentage	Hyperglycemia Percentage	Safe Percentage	Risk Index
IIAS	0.00 ± 0.00	0.60 ± 1.52	99.40 ± 1.52	0.99 ± 0.43
Adaptive Basal Therapy	0.50 ± 0.01	1.3 ± 0.03	98.20 ± 0.03	1.7 ± 0.59

TABLE VI

Comparison of a Glucose Controller (IIAS) Based on Nonlinear Model-Predictive Control With the Artificial Pancreatic B-Cell [42]

Controller	Average Glucose Value	Percentage of Hyperglycemic Episodes
IIAS	117.61 ± 7.11	0.81 ± 2.05
Zone-MPC (bounds: 80–140 mg/dl) (Experiment 5 in study [99])	152.00 ± 28.00	27.99 ± 20.51
Zone-MPC (bounds: 100–120 mg/dl) (Experiment 6 in study [99])	141.00 ± 29.00	20.75 ± 19.45
MPC (set-point 110 mg/dl) (Experiment 7 in study [99])	136.00 ± 29.00	17.54 ± 18.58