Continuous Glucose Monitoring Technology and a Workflow for its Data Analysis

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Abstract
Continuous glucose monitoring (CGM) system along with its data analysis is the new "cutting edge" technology for treating diabetes. Non-invasive CGM is the fine technology to capture data of glucose dynamics and thus is considered to be the "holy grail" for treating diabetes. The information from various CGM technology needed to be revealed in order to be used in diabetes management and treatment. Thus it is critical to analyze the data from CGM technologies. That is why prestigious companies like Apple, Samsung and Google not only are taking steps to push the invention of wearables for monitoring glucose levels but also have invested heavily in platforms with strong capacity in data analysis that offer consumers the ability to track data on their own health related to diabetes. Consequently, it is critical to know the development and characteristics of various CGM technologies and then to use a workflow for analyzing CGM data from various CGM technologies. Recently, we have developed a R package for analyzing CGM data. Therefore, in this presentation, we provide a map of milestones in the development of CGM technology and present a complete workflow for analyzing CGM data.

Key Words: Continuous glucose monitoring, Diabetes, Technologies, Data analysis, R package, Wearable

1. Introduction

Technology is changing the paradigm of healthcare and medicine on a global basis. In current paradigm, healthcare and medicine are confined to a doctor's office or a hospital. With the emerging plethora of wearable devices developed to track human body signals, the widespread wireless capabilities of instantly connecting people, the exponential increases in electronic data and the sprouting novel methods for analyzing big data information technology has introduced the age of digital health and medicine. In this upcoming age, digital information technology is revolutionizing the very nature of health care and medical practice from disease prevention and detection to treatment and monitoring, transforming the old "one size fits all" and treatment-centered approach to a much more precise, personalized and prevention-centered approach. One key development for digital health and medicine is the array of wearable devices and sensors, along with evolving analytic methods, that allows individuals to monitor their own health, to gather even continuous data of body signals in the real world and to derive more precise personalized decision for healthcare and medicine. For example, the continuous glucose monitoring (CGM) system is the new “cutting edge” technology for treating diabetes.

Diabetes is a metabolic disease characterized by the patients’ long-term blood glucose higher than the standard value. If not being treated, diabetes will lead to all kinds of complications which cause severe harm to the body's systems, especially the blood vessels and nerves. In 2016, 422 million people suffer from diabetes worldwide (organization 2016) [1], higher than 382 million people in 2013 [2] and 108 million people in 1980 [1]. Non-invasive CGM is considered to be the “holy grail” of treating diabetes. Prestigious companies like Apple, Samsung and Google are taking steps to push the invention of wearables for monitoring glucose levels and have invested heavily in platforms that offer consumers the ability to track and capture data on their own health. The CGM technology is under fast development especially in recent years. The information from various CGM technology needed to be revealed in order to use CGM for diabetes management and treatment. Thus it is critical to decipher the codes from CGM technologies. To do so, we need to know the development and characteristics of various CGM technologies and to understand and use the complete workflow for analyzing CGM data from various CGM technologies. Therefore, in this paper, we provide a map of milestones in the development of CGM technology and present a complete workflow for analyzing CGM data.

2. Historical overview of CGM system

The glucose measurement was started by urine testing in the 19th Century. However, urinary glucose measurement is not accurate with a number of limitations such as hysteresis, low sensitivity and so on. Until 1965，Ames research team lead by Clemens developed the first blood glucose test strip, Dextrostix, utilizing the glucose oxidase/peroxidise reaction to give a semiquantitative blood glucose value by assessing the color of the strip against a color chart. Obviously, this semiquantitative method cannot measure the glucose level accurately either. The first device for quantitative blood glucose value, Ames Reflectance Meter, became available in 1970. This apply reflectance photometry technology and the Dextrostix reagent test strips to measure glucose level. However, it was in large size, with expensive price and heavy weight. In 1980, Dextrometer, the first device with digital display and battery was developed. Consequently, a serious of this kind of devices using reflectance photometry was developed, such as Ames Glucometer（developed by Kyoto Daiichi）and Glucochek (produced by Lifescan). This kind of devices became more accurate, smaller and easier to use. Then the serial of biosensor blood glucose meters come. The first description of biosensor was conducted by Clarke and Lyons in 1962 with the application of amperometric enzyme method to monitor glucose. In mid-1970s, biosensor electrode became commercial available. The first biosensor blood glucose meter, the ExacTech, was launched in 1987 by MediSense. This system used the biosensor strip containing glucose oxidase and an electron transfer mediator [3] .

In order to obtain continuous glucose levels, the researchers started to develop CGMs. As early as 1974, the first CGMs prototypes, a glucose controlled insulin infusion system consisting of an automatic blood glucose determination apparatus, became available for research purpose [4] [5]. In 1977, Miles Laboratories developed the Biostator, which applied a cannula to withdraw venous blood continuously to monitor glucose levels ex vivo through redox reaction. However, this device didn’t become available in clinical [5] .

CGM first became available in 1999（approved by FDA）in the form of Minimed CGMS Physician-Use System. This device provided blinded retrospective glucose data to professors [6]. With a sensor inserted into the skin and measure the glucose levels through a chemical reaction applying glucose-oxidase-enzyme [7]. The Cygnus Glucowatch was the first real-time CGM which became commercially available in 2001. This device used Iontophoresis and electrochemical technology to measure glucose levels. But it was withdrawn since 2007 and was no longer available because of its inaccuracy, local skin reactions and short life [8] . In spite of its drawbacks, the Cygnus Glucowatch inspired other company to successfully develop new CGM devices. In 2001, A. Menarini Diagnostics made Glucoday, the first CGMs that applying microdialysis technology. The company developed a series of this kind CGMs, but they are mainly specifically for clinical use [9].

AS the technology develops rapidly, the CGM devices turn with more accuracy and sensitivity, which propels the production of alarm technology. The alarm technology first appears with the introduction of the Guardian by Medtronic in 2007 and the STSTM developed by DexCom in 2006 [8]. The alarm technology promotes the development of CGM devices with insulin pump. That is to say, some CGM devices can not only monitor glucose levels, but also pump insulin that can ameliorate hyperglycemia. Actually, FDA had approved First integrated wireless CGM and insulin pump in 2003 [10]. In 2009, Medtronic developed an insulin pump called Paradigm Veo. However the pump must match with a sensor before delivering insulin automatically. In order to overcome the inconvenience, Medtronic developed Minimed 530G which contains a sensor and a pump.

In 2008, Abbott launched a new system, FreeStyle Libre, with is a flash CGMs involving factory calibration. The system is commercially available in European but not in US. However, the company’s new device, Freestyle Libre Pro received FDA approval in 2017.

In 2011, a new device for CGM called OptiScanner received CE mark. With the measurement method of MIR absorption spectroscopy, this device was intended to be used in intensive care units (ICU) for critically ill patients [11]. Another device used in ICU, GlySure CGMs was launched in 2015 and utilized a fluorescence detection chemistry to measure glucose. Besides, Dexcom launched G4 in 2012, and FDA approved Dexcom G5 in 2016.

As most of the CGMs measure glucose continuously in a short period with 5 to 14 days, Senseonics, another company devoted to develop wearable medical devices, concentrates on developing a long time wearables. And in 2016, the Eversense system with the long-wear sensor of up to 90 days received CE mark and the Eversense XL system which can monitor glucose continuously for 180 days received CE mark in 2017. A simple milestone map about the history of CGM is demonstrated in figure 1.

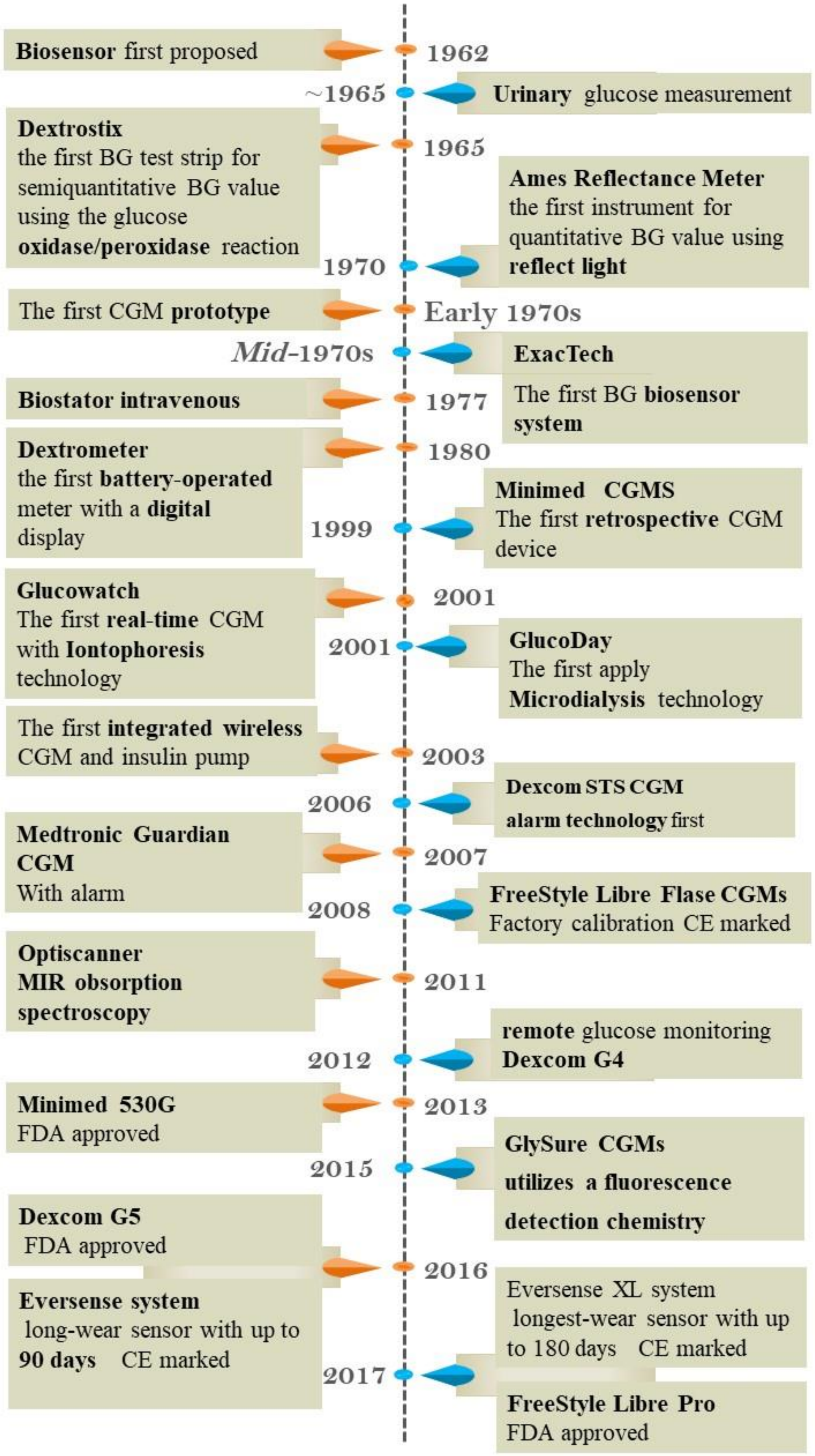


Figure 1. Historical map of CGM technology milestone

3. Sensor technologies

3.1 Classification of CGM based on glucose drawing technologies

A complete glucose measurement of the sensor involves the following steps: drawing glucose and detecting glucose level. The CGM devices measure glucose in blood, interstitial fluid or other body fluid such as tears, swear and saliva. The measurement of glucose in the blood frequently involves the sensor directly being inserted in the blood vessels (usually in vein). This method will cause reverse effects and patients' dissatisfaction. As the glucose concentration in interstitial fluid is similar to that in blood vessels, the majority of CGM devices measure glucose from interstitial fluid. These devices involve the senor to be putted outside the skin. Therefore, these devices contain fluid-drawing device to draw glucose. And it is obvious that measurement of glucose in blood veins can be conducted without blood-drawing devices because the senor can directly contact with blood. Hence, according to the placement of sensor, they can be classified into invasive and noninvasive (Figure 2).

Invasive technology involves placement of a sensor within a blood vessel for direct measurement of blood glucose. Currently available devices are minimally invasive. They involve transcutaneous measurement of interstitial glucose. Strictly speaking, because of the application of a fluid-drawing device, these devices are minimally invasive. Various methods to collect glucose are described in the following:

Microneedle technology applies a microneedle that is as thin as human hair to collect interstitial fluid through an about 1.4mm hole in the dermis [12]. When the needle penetrates the skin, glucose is drawn from the microneedle to the micropouch, in which the glucose concentration is measured. Both the microneedle and the pouch is disposable [13].

Iontophoresis technology utilizes a low current applied across the skin by a positive electrode and a negative electrode which can promote the movement of charged species across the dermis. The interstitial fluid that contains glucose is withdrawn to a collect device through this movement. The collect device contacts with sensors to detect glucose levels [14, 15].

Sonophoresis technology employs low-frequency ultrasound to make gaseous materials in the skin expanse and contract, resulting skin permeability increase. This encourages the collection of glucose outside the skin to be tested by the sensor.

Micropore technology uses laser ablation to produce microscopic holes in the outermost part of the skin and employs a local vacuum to facilitate the collection of glucose. The glucose then is assayed by the sensor outside the skin.

Skin suction blister technology uses a vacuum device outside the skin to form small blisters at the adjunction of dermal and epidermal. The glucose to be quantified can collected from these blisters.

Microdialysis technology applies a catheter whose tip is equipped with semipermeable membrane inserted within the skin. The catheter is filled with glucose-free perfusion fluid of which the osmotic pressure is as high as the interstitial fluid within the skin. When arriving at the semipermeable membrane, the perfusion fluid will pick up glucose to be assayed by the sensor externally [16].

The sonophoresis, micropore and skin suction blister technologies involve number of safety and practicality issues to be resolved. Hence these three approaches have no applications [17].

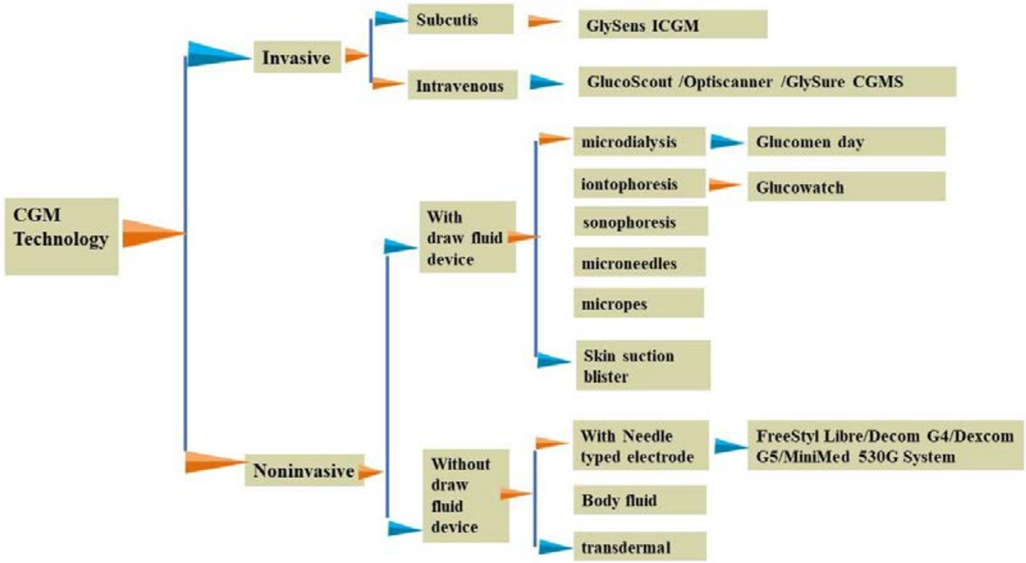


Figure 2: Classification of glucose technology according to the placement of the sensors

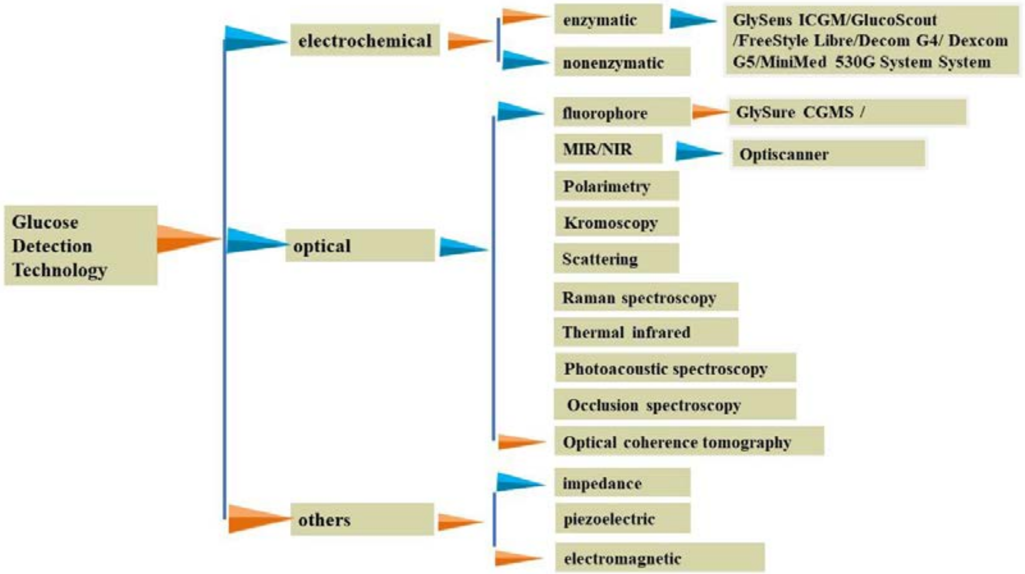


Figure 3: Classification of glucose technology according to the transduction mechanism of the sensors

3.2 Classification of CGM based on glucose detection technologies

According to transduction mechanism of the sensor, they can be classified into electrochemical, optical and other (Figure 3). These glucose detection methods are described as follows.

Electrochemical methods are the mostly widely used technology. Electrochemical approaches include enzymatic and non-enzymatic methods. The enzymatic approach involves a series of chemical reactions which begin with the process of glucose been catalyzed by glucose-specific enzyme [13] and end up with the creation of electrons. The movement of the electrons then produce a current or voltage that will measured by electrodes [18]. The glucose concentration can be correlated to the current or voltage. However, non-enzymatic approach does not involve the oxidation of glucose by enzyme. This method involves direct electro-oxidation of glucose. The electric signal produced at the sensor can be sent to the transmitter. The transmitter then transfers information wirelessly to the receiver via wifi or bluetooth. The receiver can be a smart phone, digital watch or insulin pump.

Optical technology is completely noninvasive. This technology use light with variable frequencies to assay glucose through evaluating light properties after interacting with glucose.These properties include absorbance, transmission, fluorescence intensity, refractive index, polarization, and reflectivity [19].The optical technologies include fluorophore technology, mid-infrared technology and near infrared technology which are described as follows.

Fluorophore technology mainly uses an affinity sensor principle in which glucose compete against a fluorescein-labelled bind for a receptor that is site specific to both ligands. The glucose concentration is measured based on fluorescence intensity, forster resonance energy transfer and the lifetime of the labelled ligand [13]. Mid-infrared (MIR) technology is based on the measurement of intensity for MIR light before and after interaction with matter [20]. Near infrared (NIR) technology is based on the principle that light with wavelengths in the NIR range can pass through the stratum corneum of human skin where the glucose concentration varies. The concentration change results in instability of optical properties. Therefore, we can register glucose concentration according to the changes in the absorbance, inflection and refraction of NIR radiation [13].

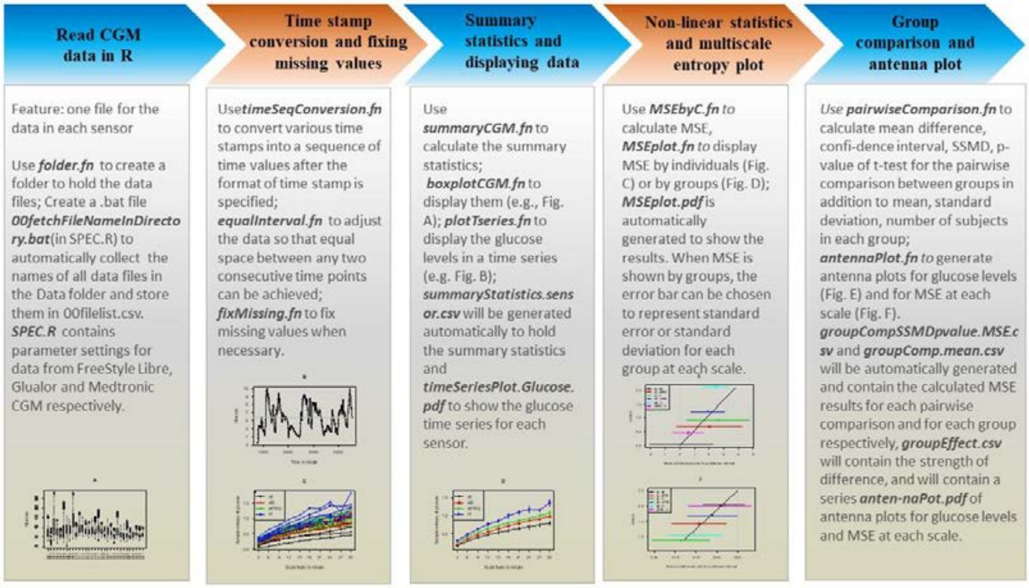
Others optical technologies are Kromoscopy, Thermal infrared, Raman spectroscopy, Polarimetry, Scattering, Optical coherence tomography, Occlusion spectroscopy, Photoacoustic spectroscopy.

Besides electrochemical and optical technologies, there comes impedance, piezoelectric, electromagnetic approaches. Most of these devices provide alerts when specified high and low limits are reached, when the glucose is predicted to cross a high or low threshold in the near future, and when glucose levels are rising/falling beyond a specified rate [6]. Most of the CGM devices need calibration according to finger-prick blood glucose level before or after usage.

4. CGM data analysis

Recently, we have developed a R package for analyzing CGM data [21] . The R package CGManalyzer contains functions for analyzing data from a CGM study. It covers a wide and comprehensive range of data analysis methods. This package was developed to directly analyzing data from various CGM devices such as the FreeStyle Libre, Glutalor, Dexcom, and Medtronic CGM. This package should greatly facilitate the analysis of various CGM studies. This package can be used to analyze a CGM study from the very beginning to the end. The workflow for analyzing the CGM data are shown in Figure 4.

We do the five steps to analyze the CGM data: read CGM data in R, convert time stamps and fix missing values, calculate summary statistics and display data, calculate non-linear statistics and generate multiscale entropy plot, do group comparison and generate antenna plot. The five steps are described in detail in our published paper[21] . for fixing the missing values, please refer to our another published paper [22].



Read CGM data in R

Feature: one file for the data in each sensor

Use ***folder.fn*** to create a folder to hold the data files; Create a .bat file ***00fetchFileNameInDirectory.bat***(in SPEC.R) to automatically collect the names of all data files in the Data folder and store them in 00filelist.csv. ***SPEC.R*** contains parameter settings for data from FreeStyle Libre, Glualor and Medtronic CGM respectively.

Time stamp conversion and fixing missing values

Use***timeSeqConversion.fn*** to convert various time stamps into a sequence of time values after the format of time stamp is specified; ***equalInterval.fn*** to adjust the data so that equal space between any two consecutive time points can be achieved; ***fixMissing.fn*** to fix missing values when necessary.

Summary statistics and displaying data

Use ***summaryCGM.fn*** to calculate the summary statistics; ***boxplotCGM.fn*** to display them (e.g., Fig. A); ***plotTseries.fn*** to display the glucose levels in a time series (e.g. Fig. B); ***summaryStatistics.sensor.csv*** will be generated automatically to hold the summary statistics and ***timeSeriesPlot.Glucose.pdf*** to show the glucose time series for each sensor.

Non-linear statistics and multiscale entropy plot

Use ***MSEbyC.fn*** *to* calculate MSE, ***MSEplot.fn*** *to* display MSE by individuals (Fig. C) or by groups (Fig. D); ***MSEplot.pdf*** is automatically generated to show the results. When MSE is shown by groups, the error bar can be chosen to represent standard error or standard deviation for each group at each scale.

Group comparison and antenna plot

Use ***pairwiseComparison.fn*** to calculate mean difference, confi-dence interval, SSMD, p-value of t-test for the pairwise comparison between groups in addition to mean, standard deviation, number of subjects in each group; ***antennaPlot.fn*** *to* generate antenna plots for glucose levels (Fig. E) and for MSE at each scale (Fig. F). ***groupCompSSMDpvalue.MSE.csv*** and ***groupComp.mean.csv*** will be automatically generated and contain the calculated MSE results for each pairwise comparison and for each group respectively, ***groupEffect.csv*** will contain the strength of difference, and will contain a series ***anten-naPot.pdf*** of antenna plots for glucose levels and MSE at each scale.

Figure 4: Workflow for CGM data analysis

5. Discussion

In this paper, we provide a map of milestones in the development of CGM technology and present a complete workflow for analyzing CGM data. Researchers can get specified knowledge of CGMs about the development history and the sensor technologies. By using the R package CGManalyzer, researchers can analyze the CGM data from the beginning to the end.

Acknowledgements

This work was supported by University of Macau through Research Grant FHS-CRDA-029-002-2017 and EF005/FHS-ZXH/2018/GSTIC.

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