Fifty Years of Biomedical Engineering: From Origin to Smart Technologies

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Abstract In Italy, the Bioengineering Community was founded in 1980. The kick-off meeting was held in Montesicuro, a little village near Ancona and organized by Prof. Tommaso Leo from the then-named "Università degli Studi di Ancona" (now Università Politecnica delle Marche, UNIVPM) in cooperation with the nascent National Group of Bioengineering. This chapter aims to produce a brief review of the main results in Biomedical Engineering by UNIVPM during the first 50 years useful to understand the present and to track future contributions for the next 50 years. It is also an occasion to recall the pioneering work on the Bioengineering of the Neuromuscular, Cardiovascular and Metabolic systems performed by our leading colleagues Tommaso Leo, Paolo Mancini and Roberto Burattini, as well as to describe significant research achievements obtained by professors, researchers, post-doc fellows and Ph.D. students who worked and/or are currently working at the UNVPM. Though mainly focusing on research findings in the above cited physiological systems, it is also worth mentioning in this chapter that UNIVPM has also an educational mission, provided by the two Biomedical Engineering courses currently active at the Engineering Faculty: the three-year Bachelor and the two-year Master (in English) courses.

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1 Motion Analysis

The interest in Motion Analysis (MA) started by the very beginning of the research work at UNIVPM and is still lasting on the topics treated below.

1.1 Joint Kinematics

Since the beginning of 80's particular attention was devoted to 3D and in vivo analysis of human joints with advanced techniques. Initially, the attention was focused on the kinematics of the metacarpo-phalangeal joint (MCP).

This research started in collaboration with the Catholic University of Rome that put at disposal a photographic system constituted by two Polaroid cameras and an electronic chronophotographic apparatus based on LEDs emitting light in the visible band. Data were manually digitized on a commercial digitizer, 3D marker coordinates were computed by Direct Linear Transformation approach and joint angles computed with classical joint kinematic equations. Preliminary results were interesting but at the same time prone to errors that were successively minimized by the following innovations:

(a) use of an automatic optoelectronic stereometric system (firstly, a prototype version and successively a commercial system)
(b) use of Kalman filtering techniques for data processing and derivative estimation
(c) joint kinematic characterization by means of the Instantaneous Helical Axis (IHA) descriptor.

It has been shown that the determination of direction and position of axes of rotation at each time instant during motion can be improved if a continuous-time rigid body model is adopted. In this case, with respect to its finite counterpart (i.e. the Finite Helical Axis—FHA), IHA parameters are characterized by a more favorable signal-to-noise ratio but their estimate requires the knowledge of the first derivative of displacement data, i.e. of velocity of points). Unfortunately, numerical differentiation of noisy data as those derived by any measurement process, belongs to the class of ill-posed problems. Consequently, great attention was paid to the accuracy of data acquisition and processing in order to obtain reliable IHA estimates. In particular, an automatic stereophotogrammetric system (CoSTEL) very accurate and precise was used in order to record movements of point body landmarks and to interfere as little as possible with the subjects. Moreover, very accurate stereophotogrammetric and numerical differentiation algorithms based on Kalman filtering methodology were properly developed.

The idea at the basis of the filtering and differentiation algorithm based on Kalman filtering, or better on Kalman Smoothing, is that every band-limited signal (such as the trajectory of a marker placed in correspondence of a moving body segment) belongs to the class of C^{∞} function. Hence it is possible to define a state vector *X(t)* composed of the signal $x(t)$ and its derivative $x^{(i)}(t)$ up to *N*th order:

$$X(t) \triangleq \left[\frac{d^i x(t)}{dt^i}, i = 0, \ldots, N\right]^T, N = 0, 1, 2, \ldots \tag{1}$$

Differentiating *X(t)* with respect to *t*, the following equation results:

$$\dot{X}(t) = FX(t) + Gw(t) \tag{2}$$

where F is an $(N+1) \times (N+1)$ matrix with elements $f_{i,j} = \delta_{i+1,j}$ (δ is the Kronecker delta), G is an $(N + 1)$ vector given by $\begin{bmatrix} 0 \ldots 0 \ 1 \end{bmatrix}^T$ and $w(t) = x^{(N+1)}(t)$.

Under the hypothesis of a sampling frequency $f_c = 1/\Delta$, the integration of (1) between t and $t + \Delta$ results in:

$$X(t + \Delta) = AX(t) + W(t) \tag{3}$$

where:

$$A = e^{F\Delta} = \begin{bmatrix} 1 \ \Delta & \cdots & \Delta^N/N! \\ 0 \ 1 & & \Delta^{N-1}/(N-1)! \\ \vdots & \ddots & \vdots \\ 0 \ 0 & \cdots & 1 \end{bmatrix} \tag{4}$$

$$W(t) = \int_0^{\Delta} e^{F\theta} G w(t + \Delta - \theta) d\theta \tag{5}$$

Taking into account that the only observation is that of the signal (i.e. the point marker position), the following measurement equation can be associated with Eq. 3:

$$y(t) = CX(t) + v(t) \tag{6}$$

where C is a $(N + 1)$ row vector given by $\begin{bmatrix} 1 \ 0 \ldots 0 \end{bmatrix}$ and $v(t)$ is the white observation noise $\sim N\left(0, \sigma_v^2\right)$.

Equations 3 and 6 have a form suitable to the Kalman filter implementation provided that *W(t)* is modelled as white gaussian noise. Because Kalman filtering methodology gives at each time instant the best estimate of the state vector *X(t)*, it is evident from the definition of the state vector *X(t)* that by this approach one obtains contemporaneously the best estimate of the position and of its first *N*-order time derivatives that can be used to compute the IHA parameters characterizing the joint kinematics.

1.2 Standardization of Clinical Protocols Used in Movement Analysis for Rehabilitation

By the end of 80's, Movement Analysis obtained number of significant results used mainly in research contexts like kinesiology, ergonomics, sport medicine and obviously in rehabilitation. However, in this latter field, MA had received limited clinical acceptance, at least in Europe. The major causes which justify the transfer of laboratory based research findings into clinical practice can be summarized as follows:

(a) At that time, MA had limited diagnostic capability. It was mainly a tool for quantitative, functional movement assessment usually in already diagnosed diseases. Consequently, MA was mainly a useful tool in the clinical decision-making process and in monitoring the effects of conservative and surgical treatments. Today with the advent of artificial intelligence tools MA is becoming also a diagnostic tool.
(b) There was a lack of consensus on what motor ability is, and of the simplicity of the motor tasks required in the usual clinical protocols used as functional evaluation tools.
(c) There are many technical questions that gave rise to some doubts about the reliability of MA methods and techniques in managing relevant and intrinsic inaccuracies.
(d) The lack of standardization in the clinical and experimental protocols, hampered a coalescence of findings into coherent and agreed knowledge bases. Consequently, results obtained in individual laboratories were poorly or not at all communicable to others.

The above considerations have led a consortium of academic public-health and industrial european entities to the development of two main European Projects CAMARC and CAMARC-II leaded by Prof. T. Leo in order: to build-up a Europe-wide network to practice Movement Analysis; to define agreed clinical and experimental protocols; to integrate existing and new instrumentation; to define suitable User Interfaces driving the clinician in the tests; to define a comprehensive Knowledge Base (KB) of the MA experience; to build-up suitable databases (DB) of MA data accessible through the Network; to assess criteria for the definition of normative data for a conventional age-related classification of normality, impairment and disability for motor behavior. All these activities ran for a decade providing the basis for further EU projects and represented a recognized milestone in the development of MA in Europe.

1.3 Posturographic Analysis

Preliminarily, it is right to mention that all the studies cited in the present subsection that involved the presence of pathological subjects were conducted at INRCA Movement Analysis Laboratory in collaboration with the Rehabilitation, Diabetology and Neurology Departments of INRCA geriatric hospital.

Static posturography: A third topic that was studied both at the methodological and at the clinical application levels has been the study of equilibrium maintenance while subjects maintained a quiet orthostatic position.

Various methods to analyze healthy and pathological subjects were implemented and tested, starting from those usually applied in clinical contexts. Though the protocol is very simple to apply because it is required to maintain an upright posture for half a minute in open and closed eyes conditions while measuring by a force platform the trajectory of the point of application of the resultant ground reaction force vector, i.e. the center of pressure (CoP), results are prone to a great variability and to an unfavorable signal-to-noise ratio [52].

Traditional stabilometry techniques indicate just a descriptive way of characterizing body movement patterns, which mainly look at the geometrical-temporal and frequency characteristics of CoP.

Conversely, nonlinear analysis offers a way to characterize qualitative changes in the dynamics of this complex system and promises to be important for clinical practice because, unlike traditional (linear) models, it can extract hidden information related to the complexity, stability and variability of the human postural system. Because methods of nonlinear analysis and chaos theory may give effective quantitative descriptors of underlying system dynamics, the properties of neuromuscular control can be determined analyzing the CoP signal.

In [59] the largest Lyapunov exponent (LLE) was estimated to quantify the chaotic behaviour of postural sway. LLE is a parameter that nonlinear analysis methods allow to determine in a reliable manner. LLE values were found to be positive although close to zero, that suggested that postural sway derives from a process exhibiting weakly chaotic behavior. The same technique was also applied to parkinsonian patients (PARK) in order to study the stability of posture system, the role of visual input and the influence of an acute administration of levodopa. Results showed positive LLE values that, in the case of PARK, tend to be higher than LLE estimated for controls. This is particularly true before levodopa assumption thus showing a higher instability that is reduced after levodopa intake. This instability is not always evident looking at the classical posturographic parameters.

Static posturography was also applied to identify the presence of peripheral neuropathy in type-2 diabetic (T2D) subjects at an early stage [54] and to distinguish, retrospectively, non-fallers and frequent fallers in the elderly population [63]. In both cases, classification methods based on the principal component analysis were applied and a structural approach based on the sway-density plot resulted more indicative with respect to the classical, geometric, posturographic parameters.

Dynamic posturography: The stimulus to face this way to analyze equilibrium maintenance was the VAMA project financed by the ISS (Istituto Superiore di Sanità). Its aim was the functional evaluation of the motor ability of elderly people by means of simple but significant movement tests by the use of simple and low-cost instrumentation. The simplicity in the use of protocols and instrumentation was counterbalanced by the complexity of models used to pursue the Minimum Input Measured Model (MIMM) approach. The kinematics and dynamics of the functional reach (FR) test, usually used in rehabilitation to estimate the risk of fall of elderly people, was studied by the use of only one force-platform. The model and the optimization techniques used to obtain reliable results from the measurement of the ground reaction force data are shown in [53]. A more detailed study of the FR test by means of a complete set of classic movement analysis instrumentation has been applied on diabetic subjects in order to understand if there exist differences in the motor strategies employed to execute the FR test by patients with or without peripheral neuropathy. Results reported in [62] show that individuals adopt different motor strategies (both for kinematic and muscle behaviour) also when they exhibit the same clinical score.

As reported earlier, the instrumental assessment of balance is nowadays considered fundamental in order to characterize the principles governing the optimization and deterioration of postural control. However, in some cases a subject can maintain the upright stance without showing abnormal oscillation of both center of pressure and center of mass and at the same time exhibit abnormal responses when his balance encounters perturbations, of environmental as well as of proprioceptive origins. In the last years, the analysis of balance responses to various type of external stimuli, such as translation, tilt, rotation or backward and forward shift of the base of support, has been applied to subjects suffering of different neuro-muscular diseases. In this context the research group of the Movement Analysis Laboratory, is involved in a series of experimental activities aimed at investigating the motor control strategies carried out after sudden translation of the base of support produced by a motor driven device. Dynamic posture tests characterized by different translation velocities, backward and forward shift of the base of support and by different conditions, i.e. with open- closed-eyes and in dual task, are performed to analyze subjects behavior. The habituation rate and the effect of the first trial have been examined through dynamic, kinematic and surface electromyography (sEMG) analysis in normal young adults [68, 69], when repeated perturbations are administered without providing any specific indication to the subject. Furthermore, the ability to maintain balance when the base of support translates with increasing velocity has been investigated and different perturbation-related responses at the ankle and hip joints have been recognized. Currently, the same analysis is carried out also in healthy children to assess postural and balance maintenance strategies when motor development is still poorly developed.

To completely characterize the analysis of the dynamic posture in the experimental conditions above described, the interest of the group is now focused on the development of complex motor control models able to reproduce, as faithfully as possible, the dynamic control of the central nervous system [71].

1.4 *Electromyographic Characterization of Walking*

In the wake of preliminary studies performed at the beginning of the new millennium, the processing of sEMG signal was introduced (Fig. 1). Besides acknowledged methodologies such as time filtering, muscular activity assessment, and frequency analysis [67], a novel technique, named Statistical gait analysis (SGA), was adopted and validated to characterize the walking task. SGA is able to provide a statistical characterization of gait, by averaging spatial-temporal and sEMG-based parameters over hundreds of strides during the same walking trial of each subject. This technique is based on the fact that muscle activates a number of times which is usually variable from stride to stride, so that averaging is performed only over features assessed in strides including the same number of activations. SGA requires a large amount of data to run. A population of nearly 50 healthy adults was analyzed in our Movement Analysis Lab, monitoring 10 muscles for each subject during 5 min walking. The aim was to provide reference and normative data for activation during adult walking of the main muscles involved in this motor task, such as thigh and ankle muscles [46, 47]. Further purpose was to study and assess the co-contraction activity of joint antagonist muscles, acknowledged as marker of pathophysiology of the neuromuscular system. Normative data were produced [72, 99] and novel techniques aimed at quantifying co-contraction in time-frequency domain were developed [100].

The effect of gender was also studied in the population. A more complex muscular recruitment was detected in female population, that seems to reflect a female need for a higher level of joint stabilization [73]. In collaboration with Politecnico di Torino, Italy, a population of more than 100 healthy school-age children was recruited at Santa Croce Hospital, Moncalieri, TO, Italy, with the aim of providing reference and normative data also for children walking and studying the maturation of gait. Findings support previous studies which indicate adolescence as the time-range where gait is completing its maturation path [45, 50, 51]. Further advancements will focus on developing new techniques in time-frequency domain, on evaluating of muscle

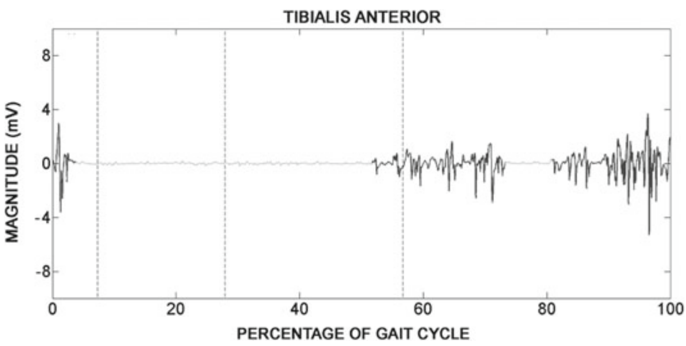

Fig. 1 sEMG signal acquired in the Movement analysis Lab during walking. Muscle activations detected by sEMG processing are highlighted in black

synergies by non-negative matrix factorization method, and on extracting significant features by data mining approach.

2 Cardiovascular Biomedical Engineering

Research studies on the cardiovascular system have always being performed at UNIVPM since 1977. Initially, the cardiovascular system was studied from a modellistic point of view to assess the cardiovascular hemodynamics, and in particular to quantitatively evaluate the physical properties of arterial systems through its input impedance, mathematically described by the windkessel models. In 1996 these studies allowed a critical comparison of linear and nonlinear formulations of the three-element windkessel model, from which it was concluded that the nonlinear three-element windkessel model cannot be preferred over its linear version. In 2007 Prof. R. Burattini proposed the four-element windkessel to study the development of systemic arterial mechanical properties from infancy to adulthood; the inductance and low-resistance terms of this model were finally physiologically interpreted in 2011.

Since 2006 the study of the cardiovascular system has been carried on mostly under the supervision of Prof. L. Burattini and focused on the computerized analysis of cardiovascular related signals, such as the electrocardiogram (ECG). Several filtering procedures have been developed in order to obtain signals of good quality from which to derive clinical information [4, 10, 55, 56, 91, 93, 94], and a great effort has been put in identifying noninvasive indexes of risk to develop malignant ventricular arrhythmias able to discriminate subjects to be treated before the occurrence of major cardiac events [24, 26, 57, 58, 61, 95].

Recently started research activities in the cardiovascular field still performed at the UNIVPM include, but are not limited to, the search for indexes of cardiovascular risk in athletes during sport activity [7, 84] and the automatic fetal monitoring [6, 9, 87, 89]. The automatic processing of the cardiovascular signals will surely remain a hot research topic for UNIVPM in the next years.

2.1 Automatic Identification of T-Wave Alternans

T-wave alternans (TWA) is an electrophysiologic phenomenon characterizing the ECG: it consists in beat-to-beat oscillations of T-wave morphology, concerning its amplitude, shape or polarity, unaccompanied by evident changes in the heart cycle length [17, 19, 32]. There are two types of TWA: the macroscopic one, first observed by Hering in 1908 and visible at naked eye, and microscopic one, first studied by Adam in 1984 and identifiable only through automatic methods [11]. Literature recognizes both macroscopic and microscopic TWA as useful markers of ventricular arrhythmias leading to sudden cardiac death [32, 33]. Given this clinical usefulness researchers have proposed many automatic methods for noninvasive detection and quantification of microscopic TWA and their performances can be tested and compared using TWA simulators [15, 19, 82]. Prof. L. Burattini first proposed the Correlation Method [17, 35, 39], implemented during her doctorate course in Rochester (USA) and later, at UNIVPM, the Heart-Rate Adaptive Match Filter (Fig. 2), an effective method the advantages of which are robustness against noises or interferences and suitability to identify both stationary and time-varying TWA episodes [12, 16, 18, 20, 22, 34, 37]. Both methods were applied in case of several particular conditions or real diseases to detect the tendency to develop this kind of electrocardiographic anomaly. In order to mention some of them: TWA was studied in ICD patients [25–28, 60, 61], in coronary-artery disease [21, 31], in acute myocardial infarction [14, 15, 36, 38], in epilepsy [64], in sleep apnea patients [23], but also during exercise [13] or during pregnancy [65, 66].

2.2 The Segmented Beat Modulation Method

The Segmented-Beat Modulation Method (SBMM) [10] was proposed in 2014 as a template-based filtering technique to clean noisy ECG (SBMM algorithm has also been patented in 2014). Template-based techniques usually do not reproduce beat-to-beat heart-rate variability. Instead SBMM, thanks to its modulation procedure that prolongs the template for short beats and shortens the template for long beats, is able to adjust for short-term as well as long-term heart-rate variability. SBMM has been tested for robustness and ability to extract clean ECG signal [10, 83, 88] from recordings affected by low, medium and high levels of noise of various kinds.

SBMM has been successfully applied to several physiological signal processing applications such as (1) fetal ECG signal extraction from indirect ECG recording and (2) low-frequency component analysis and ECG noise removal in electromyography signals [88, 90, 96]. In these applications, some variations of the algorithm have been performed to adapt it to the specific problem [5, 83, 85].

The future work will include extending SBMM algorithm to detect cardiac arrhythmias (such as presence of premature ventricular beats) which could provide clinicians with valuable indications to specific diseases. An additional field of

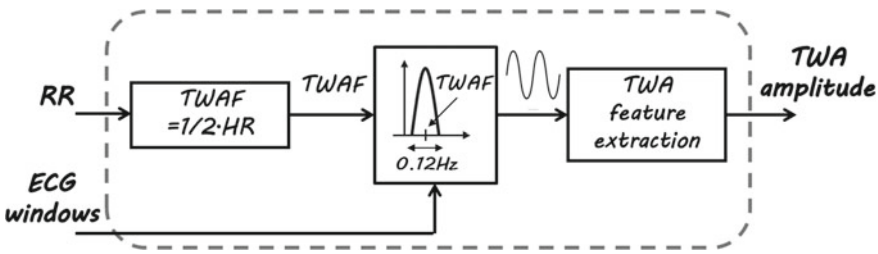

Fig. 2 Block diagram of Heart-Rate adaptive match filter

investigation will be using SBMM to extract ECG-derived respiratory signal from ECG recordings. Simultaneously directly acquired respiration signals will be used to evaluate SBMM performances. Eventually, another application for SBMM will be using SBMM for filtering ECG tracings obtained with wearable sensors, instead of conventional, in-clinic ECG systems. This will be a promising application for athletes requiring prolonged monitoring during exercise and sport activity, and for diseased patients who could be continuously monitored at home.

2.3 *Automatic Fetal Monitoring*

Fetal monitoring during pregnancy and labor is essential in clinics for establish fetal health status and thus to take prompt clinical decisions in critical cases. In the last four years, Prof. L. Burattini and her collaborators have developed several applications for fetal monitoring in order to support this sensitive practice. The focus was on standard fetal monitoring, like cardiotocography (CTG) [1, 2, 8, 87, 89, 92] as well as on challenging techniques, such as fetal electrocardiography [3, 6, 9, 65, 66] and phonocardiography [97, 98]. An example of these instruments is CTG Analyzer (Fig. 3), a graphical user interface for CTG feature extraction [87].

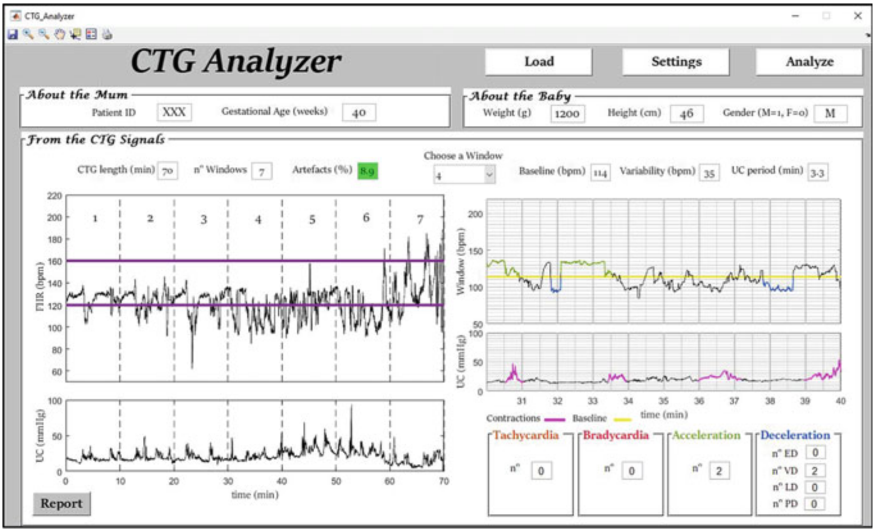

Fig. 3 CTG Analyzer, a graphical user interface for CTG features extraction

3 Metabolic Biomedical Engineering

Physiological processes regulating glucose tolerance can be described and quantified through a class of mathematical models called "compartmental models". The compartmental models defined as "minimal models" provides indexes that allow an indirect quantification of glucose-tolerance processes. Besides "minimal models", more complex integrated simulation models can be designed for a more detailed description of glucose-tolerance processes.

Development and application of model-based methodologies to describe glucose-insulin regulatory system and pathological changes of glucose tolerance, has been a key research area at UNIVPM since late 1990s. Research activities in this field have been started by Prof. R. Burattini who gave substantial contribution especially in better understanding glucose tolerance deterioration in hypertension, both in man and in animal models. Over the years, important research collaborations in this field have been established and are still ongoing; it is worth recalling the collaborations with the Metabolic Disease and Diabetes Unit of INRCA (Ancona), the Department of Experimental Medicine of the University of Genova and the Metabolic Unit of the CNR (Padova).

3.1 *Glucose Tolerance Deterioration in Hypertension*

Insulin-dependent and insulin-independent processes deterioration in human hypertension have been extensively investigated at UNIVPM. Main results showed that hypertension significantly deteriorates insulin sensitivity but not glucose effectiveness, as assessed by glucose kinetics minimal model (GKMM) interpretation of frequently sampled intravenous glucose tolerance (FSIGT) test data (S_I and S_G indexes, respectively). Dynamics of insulin action in hypertension was also investigated by using the dynamic sensitivity index (S_I^D); results showed that hypertension deteriorates S_I^D index, similarly to S_I [30]. In normoglycemic hypertensive subjects, this reduction in insulin sensitivity was shown to be compensated by an increase in insulin secretion, as assessed by C-peptide minimal model (CPMM) [30]. Hepatic insulin degradation was not found deteriorated in hypertension and model-based techniques were also proposed to allow a reliable estimation of such process [48].

3.2 *The Role of Animal Models in the Study of Glucose Tolerance Deterioration*

Animal models have played an important role in the exploration and characterization of glucose tolerance deterioration. One of the most studied is the Zucker Fatty Rat (ZFR), in which a mutation of the leptin receptor-coding gene impairs the ability of leptin to suppress food intake. ZFR are characterized by a reduced insulin sensitivity (insulin resistance) and hyperinsulinemia. UNIVPM contributed to investigate in ZFR the existence of a relation between changes in sympathetic activity and alterations of glucose tolerance; results suggested that stronger sympathetic nervous reactivity in ZFR is associated with a severe insulin-resistant state before the onset of hypertension. UNIVPM contributed also to provide model-based [44], as well as empirical methods for the quantification of processes regulating glucose tolerance in ZFR [49, 76, 77, 79, 80].

3.3 Quantification of Insulin-Independent Processes

Insulin sensitivity is one of the insulin-dependent processes regulating glucose tolerance and is defined as the ability of dynamic insulin response to stimulate glucose uptake and reduce glucose production. At the same time, glucose tolerance is regulated also by insulin-independent processes. In fact, also glucose, per se, can stimulate its own uptake and suppress its own production even at basal insulin concentration; this property is called "glucose effectiveness". Recently, there has been a growing interest on the role of glucose effectiveness in the regulation of glucose tolerance, although it was underestimated for many years. It was demonstrated that glucose effectiveness is an independent strong predictor of T2D conversion and novel therapeutic agents acting on this process have been developed.

A reliable estimation of glucose effectiveness can be achieved by GKMM interpretation of FSIGT test data (S_G index). S_G index allows also to separately quantify the contribution of insulin-sensitive and non-insulin-sensitive tissues to the insulin-independent glucose disappearance; S_G components are called BIE (Basal Insulin Effect) and GEZI (Glucose Effectiveness at Zero Insulin). Studies performed at UNIVPM using GKMM-based methodology showed that S_G deteriorates with age but not with impairment of insulin sensitivity, if a normal glucose tolerance is maintained. In this latter condition, an increased proportional contribution of GEZI, when BIE declines, may allow the maintenance of normal S_G [78].

However, GKMM-based methodology suffers from two main limitations: it requires expertise to run GKMM and requires at least a 3 h-test. Studies performed at UNIVPM aimed to provide a simple predictor of S_G applicable to short tests (1 h) [75], thus allowing a simple but reliable quantitative estimation of insulin-independent processes.

3.4 Glucose Absorption and Incretin Effect Modeling

The modelling of glucose transit through the gastro-intestinal tract and its absorption represents a key issue in the modeling of glucose-insulin regulatory system. This issue became increasingly important after the finding that an augmented glucose-dependent insulin secretion (insulin potentiation) exists in response to glucose transit through the gastro-intestinal tract. This phenomenon is the so called "incretin effect", mostly due to the gut-derived incretin hormones.

Incretin-based treatment for T2D have been proposed over recent years and simulation models contribute to improving knowledge of T2D pathophysiology and to assess the efficacy of hypoglycemic agents in clinical drug development. An integrated simulation model, intended to illustrate the importance of incretin effect, has been proposed by UNIVPM [29, 81].

4 Conclusion and Future Remark

4.1 Smart Technologies for Movement Analysis: Where Are We Going?

All the above cited MA applications are mainly based on classic MA instrumentation as stereophotogrammetric systems synchronized with force platforms and sEMG apparatus, and have been performed in a structured environment like a Movement Analysis Laboratory. The level of accuracy obtainable in such condition is very high but the type of instrumentation used avoids to perform analyses of daily living activities in non-structured environments like at home, or during working or just walking along a street. In recent years, new systems have been introduced in the consumer grade market based on very cheap sensors like 3D-accelerometers, 3D-gyroscopes, 3D-magnetometers that can be found integrated in smartphones or in light, cheap and wearable systems like IMU (Inertial Measurement Units). Very cheap gaming devices like the Microsoft Kinect (RGB-D camera) or force plates like the Nintendo Wii-balance board or webcams can be thought to be used in different scenarios like in ambulatory or in home environments. Attention has been given in the last years to this kind of devices as reported in [40–43, 70, 74, 86]. The low level of accuracy obtainable for example by wearable IMU devices can be counterbalanced by more complex digital signal processing techniques based on Kalman filtering that allows data fusion by redundant and different measurement sensors. In future we think that great attention has to be given by Machine Learning applications in order to extract from data, hidden features that characterize different motor tasks and behaviors.

4.2 Wearable Sensors and Smart Technology: The Future of Cardiovascular Monitoring

The future of cardiovascular monitoring will rely on the extensive use of wearable sensors and smart technologies. Indeed, wearable sensors are much more comfortable than traditional clinical devises and can be used routinely also at home allowing a continuous monitoring of the patient. Patients' data will be sent real-time to cloud databases and computational center thanks to telemedicine techniques, where they will be analyzed by using deep learning and big data approaches. Self-monitoring will also become popular thanks to software applications running on smartphone that will be able to read the data recorded by wearable sensors and to provide alarms when the cardiovascular risk increases.

4.3 Toward Simple Quantification of Glucose Tolerance

Although the previously described modelling methodologies provide an easier assessment of processes mediating glucose tolerance, application to clinical settings is still prevented. In fact, tests required for the applications of model-based methodologies are usually time-consuming and expensive. In this context, the development of simpler but reliable methodologies is encouraged. Such simple indexes could be applied also in epidemiological studies, especially to understand the role of glucose effectiveness, on which new therapeutic agents are based, in the regulation of glucose tolerance.

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