Hybrid and customized approach in telemedicine systems: an unavoidable destination

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Abstract. Several important problems in the majority of industrialized countries have challenged the centralized and overburdened current model of healthcare. Telehealthcare systems are presented as a new paradigm, offering high expectations to provide effective solutions to this picture. With this paper we present a new methodological approach for telehealthcare systems that pursues the generation of clinical and physiological knowledge of the patient in a real time and personalized manner. This approach is based on a computational component, identified as patient physiological image (PPI), which is responsible for generating an image of the state of the patient and therapy devices. Three key issues of the proposed methodological approach are evaluated. With the objective to validate the capability of the PPI to determine the internal state of a patient, a digital simulation experiment over the mathematical model of a PPI is done. Numerical results are compared to those obtained by a validated mathematical model. Secondly, a laboratory prototype of a novel human physical activity monitor that follows the designed methodological approach will be tested, in order to evaluate the trade-off between processing capacity, portability, and cost-efficiency and power consumption, which are necessary to assure its compliance with the methodology. As a third key issue, the capability of our methodology to integrate physiological information belonging to different scales is analyzed. This is done by means of a case study related to the integration of the regulation of water function of AQP2 channels (genomic, proteomic and cellular levels) into a kidney collecting duct epithelium mathematical model of a PPI. The analysis and preliminary evaluation of the proposed telehealthcare methodological approach, featured by an advanced personalization of health assistance, have been satisfactory.

Keywords. Telehealthcare, Hybrid Signal Processing, Personalized Healthcare, Patient Physiological Image, Modelling and Simulation

Introduction

Several important problems in the majority of industrialized countries have challenged the centralized and overburdened current model of healthcare. The aging of population together with the growth of chronic pathologies such as diabetes mellitus, end stage renal disease, or cardiovascular disease [1-4], may be considered two of the reasons for this

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situation. Moreover the increase of quality of life and the change of social models and the structure of the families incorporate more social and healthcare requirements.

Telehealthcare systems are presented as a new paradigm, offering high expectations to provide effective solutions [5] to this picture. These systems pursue the decentralization of healthcare, allowing the geographical separation between patient and physician by means of modern multimedia services and communications networks. Telehealthcare systems may improve the supervision of the patient without a reduction in the quality of life associated to the hospital stays, reduce the waiting times, and facilitate the post-hospital follow-up, what can help to reduce the length of the hospital stays.

There is a trend towards the convergence and overlap of functions among the different types of telemedicine systems, what although complicates the classification process, is maximizing the possibilities that these systems offer to the healthcare model. A complete review of telemedical information systems from a technological perspective can be read in Horsch and Balbach [6]. A more clinical review about their capabilities and limitations was published recently by Wootton [7]. According to the cited evolution, modern telehealthcare systems are adding functions related to the management of patient’s clinical information [8], pushing the concept of knowledge-based telehealthcare.

Nevertheless, current telehealthcare systems still have many limitations, and many of them only offer an effective system of multimedia services based on wide-band communications [9]. Among the main areas of research in telehealthcare, the systems for the assistance to patients with diabetes mellitus can be cited. The UTOPIA (Utilities for Optimizing Insulin Adjustment) project is a representative example in this area [10]. This project was initially designed as a computer aided system for the insulin administration to the diabetic patient, although was subsequently extended to account for the telehealthcare concept [11]. UTOPIA generates therapeutic advices for the insulin dose from the solution of a linear equation system. This linear model is in turn obtained from the relationships between the insulin intakes and the glucose trend temporal patterns calculated from blood glucose measurements.

Regarding the application of telehealthcare to the elderly, between a 20 % and a 40 % of this population group report some inability to be alone and one third of them say that their quality of life is low or very low [12]. In addition, morbidity is also very high, as the mean of three diseases and ten different complaints reported by the study group of the aforementioned study [12], of which pain and impaired mobility were the most frequent. The fear of falling and the effect of these ones in morbidity and mortality is also an important issue in the elderly [4, 13, 14]. These problems are growing in industrialized countries due to the aging of the population, what is propelling the research and development in telehealthcare systems focused in elderly and people with mobility impairment [15], and in portable systems for falling detection. The latter have evolved towards portable monitors that enable movement analysis [16-19], facilitating the necessary research about the causes and conditions that produce instability and falling [20].

The number of telehealthcare systems devoted to the care of the chronic renal disease patients is still low, being a remarkable reference the HOMER-D (Home Rehabilitation Treatment - Dialysis) project, which started under the fourth framework program of the European union (EU), and which has surpassed different technical and clinical evaluations [21, 22]. The primary objective of HOMER-D is to provide an alarm management system based on a modern communication link that overcomes the lack of supervision in home hemodialysis (HD). Current research lines in telehealthcare for home HD assistance are mainly oriented to alarm telemonitoring [23, 24]. Stroetmann and colleagues published a similar system for telehealthcare of patients submitted to continuous automated peritoneal dialysis (CAPD) [25]. The latter allows videoconference facilities by means of an Integrated Services Digital Network (ISDN) channel (128 Kb/s). The outcomes of all these systems was positive, both in the response of the patient and in their integration into the clinical environment.

There is a explosion of new solutions and advances of non-invasive and portable biosensors for the measurement of different clinical variables, including hemodynamical variables as blood oxygen level, blood pressure, heart rate, or blood glucose level [26-28]. Continuous monitoring is a concept acquired by many of these new biosensors, allowing real time knowledge generation in a growing set of biosignals.

Discovery and extraction of knowledge from biosignals and clinical data is also a very important area [29], however it is mainly directed to the off-line processing of the data with the aim to detect and classify patterns. These tools use to be based on expert systems [30]. As a consequence, there is a lack of methodologies and technologies that allow the extraction of useful medical information in a real time mode from on-line biosignals, despite these knowledge could increase notably the capacity of supervision of telehealthcare systems, adding new values for this healthcare model that are not available in the classical centralized healthcare model.

The cost-effectiveness of telemedicine systems has been addressed in many studies and application areas such as elderly, diabetes mellitus and renal chronic disease, obtaining good outcomes, although many of these studies do not include a sensibility study into the economical analysis and perhaps some methodological aspects of them must be improved, according to Whitten and colleagues [31]. Moreover, many studies indicate an improvement on clinical outcomes and patient satisfaction, although a larger analysis including both client and provider perspectives will be required to properly explore this issue [32].

In spite of all these advances, diffusion of telemedicine is still very scarce. The barriers to its diffusion have a technical, economical, organizational, and behavioural nature [33]. One of the factors that contribute to limit the diffusion of telehealthcare is the perception that this new model only offers a decentralization of the patient healthcare.

With the goal to change this perspective we have developed a new methodological approach for a telehealthcare system that pursues the generation of clinical and physiological knowledge of a patient in a real time manner. This methodology allows a very efficient customization of the supervision of a patient, using a distributed and hybrid computational architecture to process the information. This approach has been applied to the development of a prototype of a telehealthcare system for renal support, whose technological aspects and previous clinical review have been published recently [34, 35].

This paper presents an evaluation of three key issues of our proposed methodological approach. The first of them refers to the knowledge generation method. This is based on a computational component named PPI (Patient Physiological Image). The essential aspects of PPI will be summarized in the following Section. Its ability to compute personalized knowledge will be subsequently evaluated by a simulation experiment over a PPI’s prototype.

The processing of biosignals to generate a customized knowledge of the patient comprises also the sensor layer. According to this approach, and as a second issue, a novel human physical activity monitor that follows this concept will be presented and a laboratory prototype will be subsequently validated. This customizable monitor has important applications both in patients with chronic pathologies such as chronic renal disease and diabetes mellitus, and in persons with mobility impairment and falling risk, as the elderly.

The capability of the PPI to built knowledge from the dynamics mathematical models that represent the internal state of the patient is an essential property that can be exploited to allow the integration of physiological information pertaining to different scales, from genomic and proteomic level to organ and systemic level. This feature will be analyzed by means of a case study.

1. Methodological approach

Figure 1 shows a simplified block diagram with the processing stages followed by the monitored variables and the knowledge generated according to the developed methodology. A sensors layer gets relevant information from the patient and associated therapy devices and forwards the data through a remote access unit (RAU) to a service provider center, where all signals are processed. The upper layer performs a clinical decision support which can be implemented by an expert system, following a reasoning method based either on rules (RBR), cases (CBR), models (MBR) or multimodal strategies [30]. It also includes an algorithm-based mathematical module for the analysis of the state. This layer is not unusual in modern telemedicine, as for example the UTOPIA project aforementioned. However, unlike current state-of-the-art systems, in which this layer directly applies to patient’s recorded data and monitored variables, an additional processing layer has been included in this methodology. This layer is based on PPIs, which are responsible for generating an image of the state of the patient, and therapy devices. As shown in the same figure, each PPI is an autonomous simulator with real time execution capability, associated with only one patient.

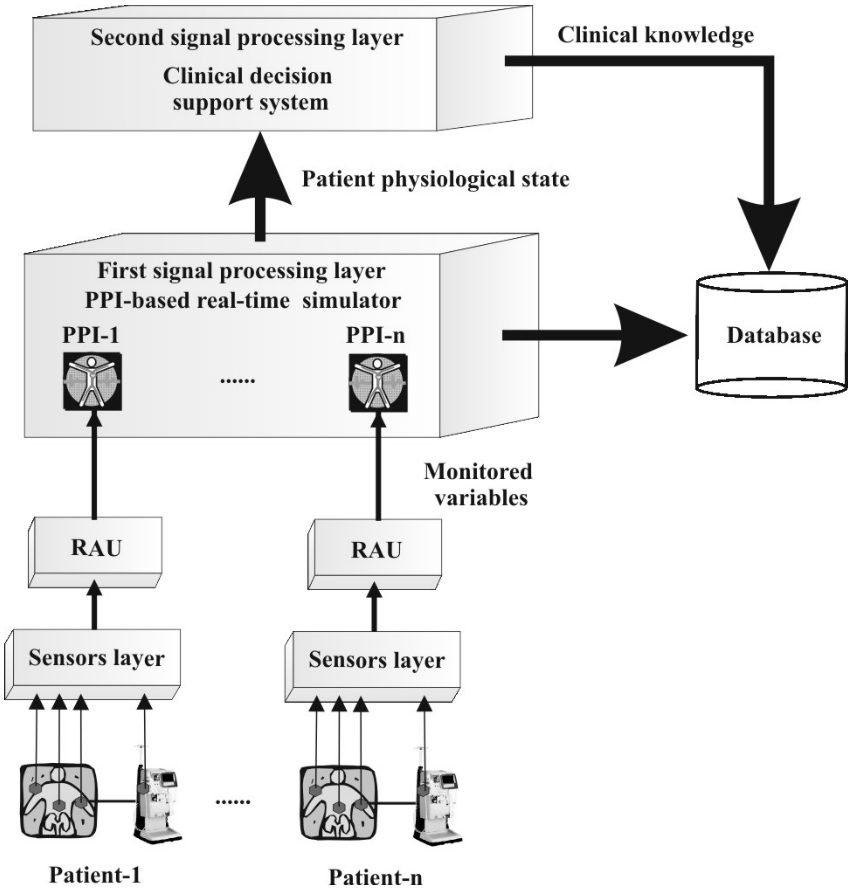

Figure 1. Signal processing according to the telehealthcare methodology presented. The first layer is a real-time simulator based on PPIs, which is able to build an integrated image of patients and their connected therapy devices. This knowledge is utilized in a second layer to generate warnings and alarms, and to feed the clinical decision support system.

Figure 2 outlines a block diagram of a PPI. As indicated this computational component is composed of a mathematical model together with two additional elements. The mathematical model is represented in that figure by a set of equations, related to a certain representation of the physical or physiological structure of the system. It is organized in a set of virtual components [36], a set of parameters customized to each patient and the values of the variables which define the state of the system in a particular instant (*snapshot*). The interfaces block (plug-in) provides the connection of the PPI to the outer world, i.e. databases and other computational objects, relying on different application protocols. Finally the execution control block is responsible for the simulation control of the PPI, based on the aforementioned model, and attends external commands.

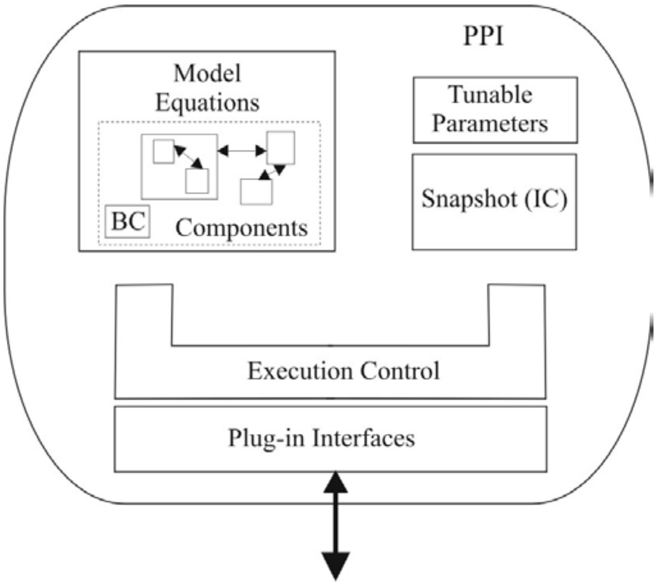

Figure 2. Simplified block diagram of a PPI

A PPI can be executed either in observation mode or in predictive mode. In addition, multiple instances of a PPI can be linked to a single patient in a particular instant. In this case at least one of them is always operating in the observation mode, obtaining in real time the evolution of the internal state of the patient and that of the associated therapy machines. This technique allows a very efficient knowledge generation from the monitored signals, providing at the same time an exhaustive supervision of the health state of the patient. The concept of mathematical observer is an essential part within the adaptive and optimum control theory [37], and has been widely applied to the control of industrial processes. During the last decade it has also been used in research applied to automatic diagnostic techniques and to the on-line evaluation of efficiency in energy plants, with successful results [38]. In predictive mode, instead of being synchronized with the real-time clock, the PPI allows the calculation of the short-time future evolution of the patient. For instance this technique can be applied to obtain the state of the physiological variables of a patient at the end of an HD session using the information available 15 minutes after the beginning of the HD. An experiment of digital simulation of this functionality has been reported by Prado and colleagues [34]. This operation mode can be started by explicit request of the physician or automatically every certain time period, allowing anticipation to the events together with the on-line trials of different therapeutic actuations over the computational image of the patient.

Knowledge representation in PPI is based on dynamic systemic mathematical models. This approach describes the structure of causal relationships of the physiological system under representation and therefore its methodology is completely different from that of data-driven approaches like linear regressive models, neural networks or rule-based systems. The last models are also known as functional models and they are frequently used within the clinical decision support module, providing a high precision in the therapeutic recommendations whenever the input variables take values that have been considered in the parameterization of the model or during its training phase. This kind of model is utilized in the UTOPIA system aforementioned. On the other hand, the kind of mathematical model selected for the PPI provides a higher predictive capability besides offering a more complete image of the dynamics of the represented physiological system.

PPIs offer other advantages associated with the applied technology, which are key issues to guarantee the feasibility of this methodology. These are described in detail in a recent paper of Prado and colleagues [34]. Among them we emphasize the modular architecture and the reusability of the mathematical models. The latter refers to the capability of reusing a mathematical model, or even a part of this one, in the representation of other system sharing some similarities. It also eases the incorporation of new knowledge to existing models.

In order to accomplish this capability we have applied modelling techniques based on virtual prototyping [36, 39], which guarantee the most perfect possible isomorphism between the virtual prototype (mathematical submodel) and the component or physical subsystem, removing the restrictions associated with the way how the variables are calculated. The last property defines the so-called non-causal modelling languages, where the causality concept refers to the flux of determination of the mathematical variables. We have taken advantage of this methodology together with the capability of the object-oriented hierarchical representation that these languages provide, to define a methodology of partition of the system to be modeled (space discretization) which distinguishes the physical processes in one or several lower layers, from the physical components where they are included, placed in the upper layers. This approach is a simple way to the integration of new physiological knowledge at different scales in the existing models.

The measurement of the physical activity and particularly certain kinetic parameters like walking speed, are related to the loss of independence in the elderly population, their admission to residences or even their mortality. On the other hand, the monitoring of postural and kinetic parameters together with measurements of vibration allows the detection of falls, which represent a valuable risk and challenging trauma for elderly people [4, 13, 14]. The risk of falls is emphasized when suffering from different chronic pathologies like end stage renal disease, due to secondary effects on the deterioration of mobility as a consequence of muscular loss and lack of D vitamin, as well as a higher incidence of arthropathy by β2-microglobulin [2]. In this sense a recent study [40] has proven the relationship of walking speed with Kt/V and the level of albumin in blood, which are two key parameters in End Stage Renal Disease (ESRD) patients subjected to periodic HD. In the case of individuals with diabetes mellitus, energy expenditure related to physical activity is also a relevant variable. Different researchers have demonstrated the possibility of measuring energy expenditure by physical activity, falling detection and obtain the postural and kinetic state of the individual by means of the monitoring of the corporal acceleration near the gravity center [16, 18] [41]. In agreement with our methodology for personalized knowledge generation, we have developed an intelligent monitor of the physical activity in humans, which overcomes some of the existing limitations in previous designs [42]. Its architecture is conceived as a wireless personal area network (WPAN) integrating a server device (PSE), and an intelligent sensor unit for the acquisition of corporal accelerations (IAU). The PSE is responsible for the access to the personal network, being in charge of the real-time processing of the signals measured by the IAUs, with which it communicates using a master-slave protocol over a low power wireless link. It also manages the communication with the RAU. In order to make available the permanent functioning and connection between the movement monitor and the service provider center of the telemedicine system, the architecture includes an additional client element, designated as router, which can be connected to a mobile phone by a serial port. This approach allows the separation of the accelerometric sensor from the elements that configure the interface with the patient, which are supported by the PSE. Indeed the IAU has been conceived to be attached to the body using an adhesive patch. The architecture is outlined in Figure 3.

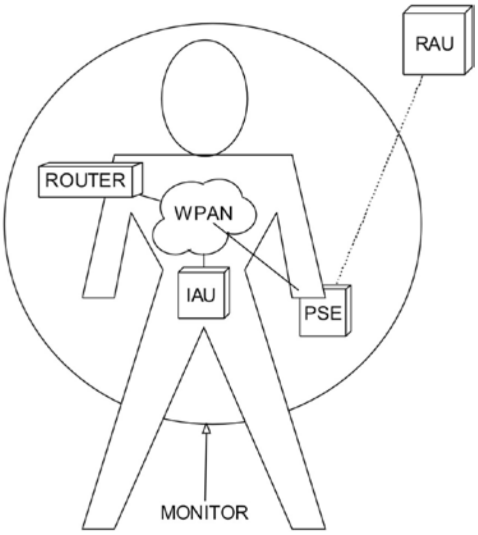

Figure 3. Diagram with the major components of the physical activity monitor

2. Materials and methods

2.1. Assessment of a customized supervision

We have accomplished an experiment by digital simulation over the mathematical model of a PPI, based on the aforementioned methodology. The objective of this experiment is the validation of the capability of the PPI to determine the internal state of an end stage renal disease patient during an HD session. To that aim we developed a pharmacokinetic library using the non-causal EcosimPro language (EL) [43]. The components of this library were applied to the definition of a three-pool urea kinetic model, with variable volumes, representing the vascular, interstitial and cellular compartments of the patient. Moreover this model can be connected to a dialyzer model, also developed with the components of the library, through the vascular compartment. Figure 4 shows an iconic diagram of the described model.

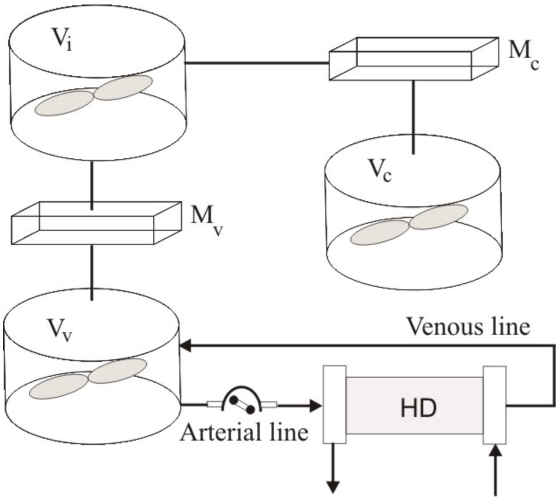

Figure 4. Iconic diagram of the tree-pool variable-volume urea kinetic model, representing vascular, interstitial and cellular human compartments, connected trough a vascular access to the hemodialyzer

Variables V_v, V_i and V_c represent the volume of the vascular, interstitial and cellular compartments, respectively, while M_v and M_c are the vascular and cellular membranes. The importance of urea kinetic in the quantization and adequacy of hemodialysis has been demonstrated in multiple studies [44], and therefore the election of this particular type of simplified physiological model as a base of PPI prototype in ESRD patients is justified in this experiment.

The experiment was performed off-line using data monitored from a patient submitted to periodic HD, randomly selected from a group of 30 patients with similar clinical conditions and number of sessions per week. The selected patient was a 50 years non-diabetic man, weight 95 kg and height 179 cm, reporting anuria. Access recirculation measured with the two-needle urea-based method [45] was below 10 %. We selected the Wednesday session for this study. Measurement data included blood urea concentration, BUC, plasma protein concentration, $Cp_{p,}$ and hematocrit, HTO, corresponding to blood samples extracted before the HD (point 1), at the end of the session (point 2), and thirty minutes before the end (point 3). Standard analyzers were utilized for all measurements. The postdialysis sample was taken approximately one minute after completion of the HD, keeping the flow in the arterial line at 50 ml/min. The values of BUC_1 BUC_2 and BUC_3 were 169, 59 and 67 mg/dl, being Cp_{p1}, Cp_{p2} and Cp_{p3} equal to 6.8, 8.6, 7.1 g/dl, and HTO_1, HTO_2 and HTO_3 values of 29.8, 35.8 y 33.5 %, respectively. The operating conditions remained constant during the whole session. The dialyzer flow rate was established at 500 ml/min and blood flow rate fixed at 300 ml/min.

A PPI was adjusted to the patient’s kinetic and subsequently executed to evaluate the evolution of urea concentrations in the corresponding compartments. Urea concentrations and related dKt/V were compared with those estimated by a classical two-pool kinetic model. Index dKt/V refers to the product of the dialyzer effective urea clearance by the total HD session time over the urea distribution volume. The accuracy of the urea concentration obtained by the reference model in the accessible compartment has been demonstrated in the study of Canaud and colleagues [46]. The methodology of adjustment of the parameters of the two-pool model applied in this experiment is similar to the methodology used in a previous study [47].

2.2. Wearable and customizable technology for physical activity monitoring

An important characteristic of the proposed activity monitor is its personalization capability for the user. This customization is a trade-off among processing capacity, portability, low cost and power consumption, which are necessary to assure its feasibility. In order to evaluate these key issues, together with precision, we have developed a prototype of monitor, which has been tested using the setup shown in Figure 5.

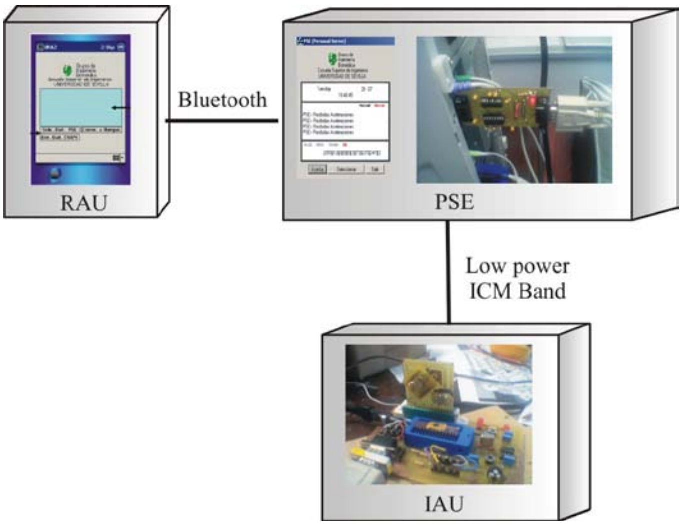

Figure 5. Set-up for the evaluation of the physical activity monitor

The developed IAU provides four-measurement axis, three of which form an orthogonal system, and can be fixed at the back of the individual, at the height of the sacrum, by means of a waterproof adhesive patch. This location is very near from the gravity center, and is recommended in several recent studies [16, 41]. This device consists of a low-cost, low-power microcontroller with embedded code (ROM) and RAM memory (PIC16LC66 from Microchip), two capacitive biaxial accelerometers (ADXL202E from Analog Devices), prepared to measure static and dynamic accelerations, a non volatile external memory (EEPROM), an integrated wireless transceiver, and other additional elements [42]. Sampling frequency for each of the four channels was adjusted at 40 S/s to optimize the capability to detect impacts [42]. The microcontroller provides the necessary processing capacity to the IAU for attending requests from the PSE, and for customizing a small signal analysis that is executed before signals will be sent to the PSE.

The set-up shown (Figure 5) has been applied to evaluate different strategies to read the accelerations, evaluating both precision and power consumption with each method.

The latter has been optimized keeping the microcontroller in the sleep mode and the sensors switched off for the largest possible time between successive sampling instants, but without affecting the evaluated measurement procedure. The images shown at the top of the blocks in the aforementioned figure refer to photographies of the devices or to captured screens of the software applications. This way, the picture representing the RAU refers to the main window of the RAU's application implemented in a Compaq iPAQ Pocket PC H3970 PDA, equiped with 64 MB of RAM and a PXA250 400 MHz processor. The PSE block shows a screen of the PSE simulated in a personal computer, and one of the electronic devices used to communicate the IAU with the simulated PSE. A detail of a laboratory prototype of the IAU is shown over the IAU's block.

2.3. Integrating different physiological scales by virtual prototyping

The hydraulic permeability, L_p, of the microvascular walls is not governed only by diffusion through channels (mainly intercellular) shared with low molecular weight compounds (urea, sodium, etc), but also there are specific channels for water, which are not shared with other low molecular weight solutes. These are responsible for an average percentage lower than 10 % of the overall value of L_p [48]. In certain tissues, like the renal one, these channels play a very important role and they can increase the value of L_p by a factor of four or even more, depending on the systemic and homeostatic conditions. Moreover recent studies have shown that vascular permeability is increased in renal and diabetic patients [49, 50].

Water specific channels are associated with proteins of the MIP class, with function of water channel, which are known as aquaporins (AQP). These proteins were discovered a decade ago and among them two groups may be distinguished, being represented by AQP2 and AQP3 respectively [51]. An important advance has been accomplished in the characterization of the structure, functions and mechanisms of regulation of the channels that these proteins form, specially of the AQP2, which plays a key role in the regulation of water absorption by the renal tubules under antidiuretic conditions (concentrated urea).

Diabetes mellitus is the first cause of ESRD in industrialized countries [52], and therefore mechanisms of regulation of AQP2 channels in the kidney collecting duct cells could be considered in PPIs linked to diabetic patients with functional kidneys, with the aim to study their clinical evolution. The methodology of integration of the genomic, proteomic and cellular mechanisms of regulation of AQP2 channels on the hydraulic permeability of the kidney collecting duct epithelium, will be analyzed using a diagram that shows a simplified hierarchical structure of this membrane, together with the associated EL source code. The component of the hydraulic permeability associated with AQP2 channels in the kidney collecting duct epithelium will be referenced as L_p*.

We do not pretend to present a complete mathematical model that describes the water flow through the kidney collecting duct epithelium, because this objective exceeds the scope of the present work, and moreover there are other proteins that regulate the hydraulic permeability of kidney collecting duct epithelium, as AQP3 and AQP4 in the basolateral membrane of the kidney collecting duct cells.

3. Results

The upper graph of Figure 6 shows the evolutions of the urea concentrations c, c_{int} and c_{cel} corresponding to the patient's vascular, interstitial and cellular compartments, respectively, calculated by the PPI. In the same graph we have also included the concentrations obtained with the two-pool model, c_{acc} y c_{nac}, corresponding to the accessible and non-accessible compartments, respectively. A value of 1.28 for dKt/V was calculated by the PPI, while the two-pool reference model yields 1.30. This small difference is due to the fact that the extracellular urea concentration depletion during HD calculated by PPI is slightly lower than that calculated by the reference model. In any case, urea dynamics computed by the three-pool model-based PPI accurately agrees with that of the reference model.

The lower graph of Figure 6 represents the variation of the volumes calculated by the PPI. It can be observed that the interstice behaves as a buffer, moderating the loss of vascular volume and therefore reducing the risk of hypotension events [53], especially under the conditions of the session, during which the cellular compartment did not contribute at all supplying ultrafiltrated liquid (4600 ml). This moderate reduction of V_v is in agreement with measurements reported in recent studies [54].

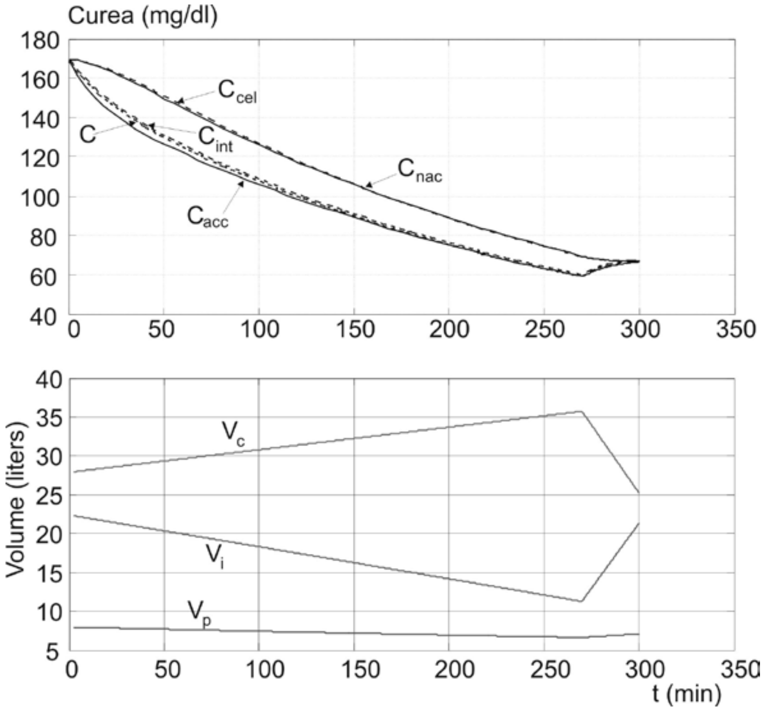

Figure 6. Evolution of the urea concentrations calculated by the two-pool model (solid lines in the upper graph) and with a PPI based on a three-pool model (dashed lines in the upper graph), during the HD session and the period of subsequent rebound for the selected patient. The lower graph depicts the evolution of the compartmental volumes.

With regard to the evaluation of the physical activity monitor, when samples were acquired in parallel for the four channels, in order to reduce the power consumption at the minimum level, the dispersion of the measurements was much higher than the 5 % target value specified during the design. The high value of this error is associated with the delay in the process of management of interruptions in the microcontroller and the high requirements that the concurrent reading of all the channels impose. However, dispersion dropped below 4 % once the channels were attended sequentially following a polling scheme. This solution is still compatible with low power consumption. The IAU presents autonomy above 2 months using a non-rechargeable Lithium button battery (CR2450, 500 mAh, 6 grams), without considering the integrated transceiver. This autonomy can be doubled if particular energy-saving strategies are accounted for, like switching the IAU off during the night, with a command from the PSE. Power consumption in the integrated transceiver depends on the transmission level and is currently under optimization in order to keep high values of autonomy in the monitor.

Figure 7 shows the value of gravitational acceleration in static conditions, expressed in units of g, as a function of the angle θ formed between one of the IAU measurement axis and the horizontal reference. The dispersion referred above has been removed averaging the samples at the point of measurement, every 15 degrees, in order to validate the precision of both the calibration and the measurement algorithm in static conditions. Deviations between each point (measurement) and the theoretical value (circle with unit radius) are practically negligible.

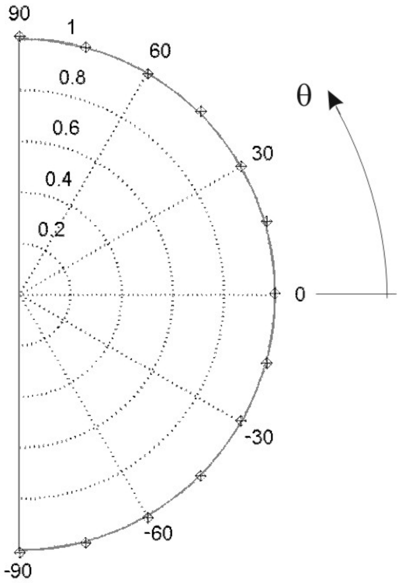

Figure 7. Gravitational acceleration measured in one axis of the IAU as a function of the angle with the horizontal reference

Finally, and in agreement with the method previously stated, Figure 8 shows the hierarchical structure associated to a virtual component representing kidney collecting duct epithelium. This diagram is focused on the hydraulic permeability of the membrane. A virtual component is a mathematical submodel that can be linked to other submodels by means of its connection ports. Components and ports are the main elements of a non-causal modelling language-based library, as EcosimPro. As described in that figure, the kidney collecting duct epithelium can connect both of its faces with two compartments through the ports represented as rectangles with solid border lines. This membrane is asymmetric, in such a way that AQP2 channels are in epithelium cell apical membrane (duct side), while epithelium cell basolateral membrane, at interstice side has AQP3 and AQP4 channels. This asymmetry can be associated to mi and mo ports. The inside of the component includes the two major physical processes related to the hydraulic permeability of the component: L_p, which refers to the hydraulic permeability associated with the normal diffusive channels, usually paracellular paths, not controlled by AQP, and L_p*, which is the component of the hydraulic permeability associated with AQP channels. According to this methodology, physical processes are also represented by non-causal components and ports. This is another advantage since it is possible to increase the complexity or modify the behaviour of a virtual component adding or changing the physical processes of the lower layers. As can be seen in the aforementioned hierarchical diagram (Figure 8), the physical processes are connected in parallel through their ports.

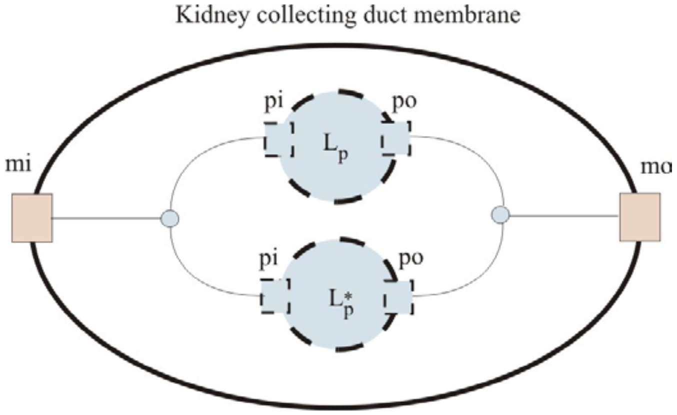

Figure 8. Hierarchical structure of a kidney collecting duct membrane component

The EL source code of L_p process (box 1) is formed basically by the declaration of two port variables corresponding to pi and po ports (PORT block), together with the equations that describe the physics. The latter are represented here by the law of mass conservation and the law of transfer mass (CONTINUOUS block). The last law has been simplified in this example to consider only static pressure difference, given by pi.ptotal-po.ptotal. The other blocks are mainly related to variables and parameters definitions.

Box 1: EL code of a virtual component that represents the physics process Lp.

```
COMPONENT LpProcess
PORTS
    IN physics pi                 "Input port"
    OUT physics po                "output port"
DATA
    REAL Lp   "Hydraulic permeability (m3/s/Pa)"
DECLS
    REAL atrans    "Transfer area (m2)"
TOPOLOGY
    PATH pi TO po
CONTINUOUS
    -- Law of conservation of mass
    pi.wbulk=po.wbulk
    -- Law of mass transfer
    pi.wbulk=Lp*(pi.ptotal-po.ptotal) – water flow
END COMPONENT
```

The virtual component associated to the kidney collecting duct membrane is denoted as KidneyCollectorMembrane, and can be formed by simply aggregating simulation components representing physical processes, as is shown in the following EL code (box 2). This task can be done declaring and connecting components. The resulting virtual component will pertain to an upper hierarchically layer, as indicated in Figure 8.

Box 2: EL code (simplified) of a virtual component that represents the kidney collecting duct membrane

```
COMPONENT KidneyCollectorMembrane
PORTS
    IN physics mi  "Input side"
    OUT physics mo  "output side"
TOPOLOGY
    LpProcess LpPromedio (atransfer=200)
    LpStarProcess LpAQP
    CONNECT LpPromedio.pi TO LpAQP.pi
    CONNECT LpPromedio.po TO LpAQP.po
    ...
END COMPONENT
```

Virtual component representing the physical process L_p* has been denoted as LpStarProcess, and it has been instanced once under the name LpAQP. Two fundamental strategies are defined to incorporate the behaviour of the AQP channels into the component LpStarProcess. The first one, called functional strategy, defines this physical process using phenomenological equations that describe the variation of L_p* without considering the feedback relationships related to regulation mechanisms. This is a simple approach to include new knowledge in the model. The second procedure, called structural strategy, accounts for the feedback relationships that define the regulation mechanisms affecting the value of L_p* at different scales.

Figure 9 describes in a simple way the main regulation mechanisms known for L_p*. The type of line used in the arrows is used to distinguish the level of regulation. According to this diagram, the mechanism at the genomic level shows that an increase of vasopressin (VP) stimulates the formation of intracellular cyclic adenosine monophosphate (cAMP) through membrane receptors, which stimulates the transcription of the AQP2 gene, increasing thus the concentration of its associated mRNA, and therefore the total of AQP2 (TAPQ2), which in turn has been demonstrated that increases the value of L_p*, possibly increasing the number of AQP2 channels. At the proteomic level, it has been proven that VP stimulates phosphorylation of AQP2, through the kinase cAMP-dependent protein (PKA). Phosphorylated AQP2 protein increases the permeability of the channel to water. Finally, at the cellular level, it has been demonstrated the existence of a traffic of AQP2 in vesicles, which formation and fusion by endocytosis and exocytosis with apical membrane, increase or decrease the number of available AQP2 channels. The mechanisms are not completely known and therefore they have been included as a box in the referred figure.

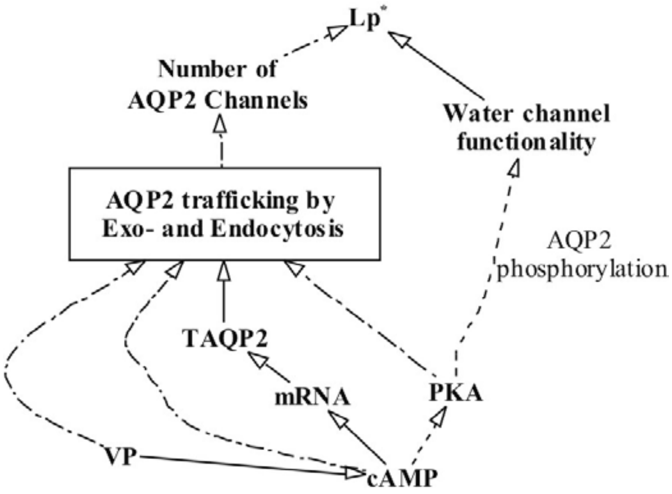

Figure 9. Diagram showing in a simple way the major regulation mechanisms of L_p* related at genomic level (solid arrows), proteomic (dotted arrows) and cellular level (dashed-dot arrows)

These mechanisms are implemented into LpStarProcess component, using a structural modelling technique, as bond graph [55, 56]. This structural component can be used instead of the functional component by means of a simple aggregation. This technique can be extended to account for more anatomical details in physiological models.

4. Discussion

The simulation experiment presented was designed to show the capability of PPI as mathematical observer and predictor of the internal dynamics state of the patient. The selection of a compartmental urea kinetic model is justified by the proved ability of these models to improve clinical outcomes of renal replacement therapies [44, 57]. Moreover we selected an ESRD patient submitted to periodic HD, given the increasing importance of this disease and the new advances of telemedicine in nephrology, propelled by daily and nocturnal HD therapies [58-60], among other reasons.

According to our outcomes, extracellular and intracellular urea dynamics calculated by PPI agrees accurately with the reference two-pool model. Urea concentration shows an abrupt depletion in the extracellular compartment, during HD, followed by a rebound during the subsequent 30 minutes after the HD end. This is due to the non-uniform distribution of urea between the different compartments and also to the low blood perfusion in some tissues. The last mechanism can be observed from the three-pool model that forms the PPI (Figure 4), formulating vascular and cellular membranes by means of their characteristic geometries, and solving an equivalent average cellular diameter. The comparison between computed cellular diameter and the human average cellular diameter gives a measure of the influence of blood regional mechanism. A preliminary advance of this model has been presented in Prado and colleagues [61].

In addition, the evolution of compartmental volumes shows the importance of interstice to moderate the blood volume reduction due to ultrafiltration during HD, reducing this way the risk of a hypovolemia event. The hypotension complication appears in 30 % of all HD treatments, and although the genesis of this problem is multifactorial, hypovolemia is the major responsible mechanism [53]. Several studies indicate that blood pressure can be controlled by a proper management of the extracellular volume (ECV) [62, 63]. This fact suggests that the ability of a PPI to predict excessive plasma volume depletion can be used to avoid the occurrence of hypotension events.

Blood volume can be monitored by means of the HTO value [64], which in turn can be measured by optic reflection, allowing a non-invasive and on-line monitoring of blood volume [65]. However, HTO measurements could be better utilized as input variables by a customized PPI, providing an integral and correlated image of the three compartmental volumes and even other state variables of the patient. This greater knowledge can help to know the causes that originate a more abrupt depletion in plasma volume for some patients, and provides a better control of ultrafiltration velocity, avoiding for example, the occurrence of backfiltration due to low transmembrane pressure [66].

Several research works support the ability of dynamics mathematical models to predict hypotension events in patients submitted to intermittent dialysis therapy, being a remarkable reference the study from Cavalcanti and Marco [67]. Regarding other important chronic pathologies in telemedicine, as diabetes mellitus, glucose and insulin kinetic models have been successfully applied in support systems for therapy of insulin [68]. Mathematical dynamics models are also utilized to analyze the falling risk in subjects with motor control impairment by means of the study of the relationships between postural and kinematic states [69].

Signal monitoring is a key issue in any telehealthcare system. We have presented a laboratory evaluation of a novel physical activity monitor for humans. This device is mainly featured by its ability to customization and distributed process based on intelligent sensors, performing a monitoring non limited to local environments, neither to the corporal position of the sensors nor to particular clothing. This way it overcomes several limitations of other monitors [16-19]. The design has been based on modern microelectromechanical-system (MEMS) technologies and wireless communication. Vibratory artefacts related to bouncing and jolting are removed because of its permanent contact with the subject skin.

The first results of the laboratory prototype were satisfactory. The accuracy of dynamic measurements was greater than 4 % of *g* for the algorithm selected to read and calibrate the sensors. The remaining processing capacity of the IAU’s microcontroller is available for customizing it to the client, satisfying this way the requirements of the telehealthcare methodological approach. We have evaluated the different noise sources proving the possibility to improve the previous accuracy using the CCP (Capture/Compare/PWM) module in the microcontroller. The communication links indicated in Figure 5 were also validated. Power consumption of IAU, without the integrated transceiver, and according to the selected algorithm for measurement, provides more than two months of autonomy for IAU for a Lithium non-rechargeable battery type CR2450. We are optimizing the power consumption of the transceiver taking profit of the very low range necessary for the WPAN, by hardware and software techniques. These outcomes suggest that the physical activity monitor will accomplish the whole economical and functional specifications needed to be applied under the novel telehealthcare methodology presented.

The capability to measure energy expenditure and extract postural and kinematic information from accelerations measured at waist and chest has been demonstrated in several studies [41, 70, 71]. The relationship between the corporal position of the accelerometric sensor axis and suitable postural and activity classifications has also been analyzed by Foerster and Fahrenberg [72] with successful conclusions. Finally, the monitor has been designed with the aim to process acceleration signals captured by the IAU in a real time manner. This objective is achieved by a modern digital signal processor (DSP TMS 320 C6713 from Texas Instrument) that joins high power process together with low cost and low power consumption. Moreover we have distributed the signal processing between the IAU and the PSE [42]. This device is currently under international patent process.

This telehealthcare methodology provides an opportunity to give new technological and scientific solutions to human physiology simulation environments, as the one represented by the Physiome project [73]. These simulation environments are emerging as a trend that is also known as System Biology [74, 75]. Modelling and simulation tools are essential in this new area, because they assist us forward integrating and connecting information from several domains and scales [75, 76].

Multiscale integration in virtual prototyping is a very powerful capability that has been analyzed in the framework of our telehealthcare methodology. Some preliminary aspects of the modelling and simulation methodology developed to the PPI were presented in Prado and colleagues [77]. In this work we have briefly studied the compatibility of the PPI methodology with multiscale knowledge integration approaches by means of a virtual component that describes the hydraulic permeability of the kidney collecting duct epithelial membrane. We have presented two types of strategies to integrate the hydraulic permeability associated to AQP2 channels. The concepts have been clarified by means of the simplified EL source code of the kidney collecting duct epithelial membrane virtual component. The EL codification of the connection ports is not shown here because it exceeds the scope of the paper.

5. Conclusions

We have presented a new methodological approach in telehealthcare systems based on the on-line, customized, and dynamics generation of knowledge about the physiological and internal state of patients or clients of the system and the associated therapy devices. This approach modifies the current focus in telemedicine and telehealthcare systems, which is directed to optimize remote monitoring, process biosignals to generate alarms and warnings, and speed up the clinical information management, by means of advances on information and communication technologies.

The study has been based on three key aspects of the methodology that have been previously and briefly described. Firstly, we have evaluated the capability of the PPI for building an image of the internal state of its associated patient. With that aim we have performed a simulation experiment over a urea kinetic model-based PPI associated to a patient during an HD session. The outcomes were in agreement with those obtained by a validated reference mathematical model.

The processing of biosignals to generate customized knowledge of the patient comprises also the sensor layer. A novel physical activity monitor that follows this concept has been presented and a laboratory prototype has been validated.

Finally, we have analyzed the manner to integrate multiscale knowledge into the mathematical models that form the PPI, using a simplistic virtual component of the kidney collecting duct membrane, together with the genomic, proteomic and cell regulation mechanisms of AQP2 channels.

As a major conclusion the study presents a new telehealthcare model in which the goal is not the decentralization but the personalization of the health assistance by means of modern technologies both in communications and in mathematical modelling and simulation.

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