Cyber-Medical Systems: Requirements, Components and Design Examples

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***Abstract*— Cyber-medical systems will produce a major revolution in health care, by both raising the quality of care and reducing its cost, thus reaching an important social and economic goal. The evolution of electronic devices and systems has already enabled societal changes. Inroads in the quantification of medicine, in the discovery and applications of biosensors in connection with integrated circuit technology, in the analysis of large-scale real-time biomedical data are strong indicators that cyber-medical systems will redesign health care in the years to come. To sustain this thesis, this paper presents three aspects of cyber-medical systems, describes their medical significance and potentials, and then delves in the detailed technology required to realize such systems. Specifically, this paper describes state of the art sensing devices and their integration into platforms, data processing for ultrasound medical imaging and system correctness approaches for drug administration support systems. The paper concludes with a brief outlook on the evolution of this emerging field in the years to come.**

***Index Terms*— cyber-medical systems, drug-administration support systems, e-health, remote monitoring.**

I. Introduction

THE relentless growth of computing, storage and communication technologies has enabled new services, living and working patterns. Along with the increase of performance of computers and servers, we have witnessed the ubiquitous presence of electronics systems for data acquisition, communication and control. The *Internet of Things* (IoT) is a general term to describe the interconnection of a very large number of nodes, corresponding to humans, objects and computing/storage server systems [40]. Within the IoT, functions can be initiated, executed and terminated by smart objects, whose simple structure is coupled to high intelligence due to the interconnection with other nodes. The potentials and growth of the IoT are unprecedented and huge and will affect the world population across different levels of wealth and geographic locations. *Cyber-physical systems* are integration of computation with physical processes [41]. They can be viewed as abstractions of complex mechanisms such as some of those supported by the IoT.

The new millennium has brought a renewed interest in the biomedical field, because the biological sciences have progressed and become more quantitative and because of the economic and societal need of improved and more affordable health care. The fusion of medical and engineering technologies has already lead to better care systems for therapy, surgery and monitoring. Still, the explosion of new applications on portable devices has touched the medical practice only in part. The expansion of the Internet of Things into the medical sector is still in its infancy, because of technical, regulatory and ethical reasons. Nevertheless, lifestyle applications and devices that involve non-invasive measurements of the human body and its performance have gained popularity, as shown by smart watches, belts and other wearable devices [55].

Precision medicine is a neologism that indicates medical practices based on quantitative and precise information and/or action. It is enabled by the use of new advanced electronic devices for sensing, data acquisition and elaboration as well as their connectivity to servers and databases. Some precision medicine problems involve big data issues, such as complex models and algorithms to deal with large scale data that can originate, for example, from comparative genomics or other "ohmics". The current interpretation of health includes the state of complex physical, mental and social well-being, and not merely the absence of infirmity [77]. Thus health management includes nutrition and habit control, an area where IoT-enabled devices can be very practical and useful.

Cyber-medical systems are specializations of cyber-physical systems to the medical domain to support health management in various dimensions and directions [41]. Their broad objective is to better medicine with engineering means as well as to rationalize health care, reduce costs and make it available to all. Essential elements of such systems are transducers, circuits, processing and communication means, where processing involves both hardware and software components. For cyber-medical systems, co-design of the various components is a key ingredient to their successful realization and application. Indeed, performance, power consumption, cost and dependability are related to the tight integration of the various parts in the realization of biomedical terminals and communication schemes that satisfy the constraint envelope. Whereas circuits and software for computing and communication is quite advanced – as exemplified by the services provided by mobile telephones – (bio) sensors and actuators are still often realized with *ad hoc* sizes, materials and operating parameters. Thus the harmonious integration of circuits and transduces, as well the exploitation of semiconductor fabrication technology for volume production of transducers at low cost is a clear and near-term objective. Within this perspective, many existing sensors have to be rethought and redesigned. As an example,

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a low-power data acquisition circuit cannot be achieved by coupling a low-power, low-voltage integrated circuit to a sensing element operating at much higher voltage.

Due to the variety, breadth and infancy of the cyber-medical system domain, this paper aims at showing some motivating examples to highlight the requirements from both the medical and engineering perspectives. Thereafter, the article will review some of the key underlying technologies, to show both the state of the art and the prospects for improvement. Because of the wide breadth of solutions, this article will focus on recent technologies that are relevant IoT realizations leveraging *integrated circuit* (IC) technology. The interested reader is referred to the literature for broad surveys, such as [21], [43], [44], and [52].

II. Telemedicine and E-Health

Telemedicine means broadly to provide health management at a distance. It is a wide concept, with many application domains. As an example, remote surgery has been available for a few years with impressive results [6]. Another example goes under the name of participative medicine, and consists of social media dedicated to patients and health providers who share data, experiences and therapies [56]. In this paper we consider telemedicine within the context of the IoT. *Electronic health* (or *E-health*) is the keyword denoting the use of connected electronic devices for health monitoring and care. Three examples of E-health will be described next along with their medical motivation and engineering constraints. Specific technologies to realize such systems will be described in Section III.

A. Remote Patient Monitoring

Remote patient monitoring provides a means to keep patients active or at home, while obviating hospital visits for tests. This is very important in the case of chronic and/or elderly patients, and it can reduce medical costs drastically. Moreover, remote tests are important also within a medical structure (e.g., hospital) as they can reduce human intervention as well as for emergency care, as test results are sometimes needed quickly on the field.

Remote monitoring can be achieved by wearable devices (*on- the-body*), by implanted devices (*in-the-body*) or by external devices (*off-the-body*). There exist today a myriad of *wireless non-invasive* devices that are good examples of IoT nodes. Examples include heart rate, oxygen saturation in blood (SpO_2), blood pressure monitors and are often housed in bands, watches, skin patches, etc. [7]. Many of these devices have been commercialized for paramedical applications, mostly without a thorough FDA approval. At present, there are two major challenges. The first one is to extend monitoring to molecular analyses of body fluids and tissues, by using *lab on chip* techniques [47] at various levels of miniaturization. The second one is to support invasive techniques of sample acquisition, especially in the case of implanted devices, while satisfying biocompatibility, size, shape, energy, communication and other constraints.

The most well known telemedicine problem is glycaemia control for diabetic patients. Due the increasing prevalence of diabetes and to the patients' need to be tested once or multiple times a day, a few invasive devices have been realized and marketed. Some rely on the extraction of body fluids via micro-needles and tubes (e.g., Menarini's GlucoMenDay), while some other are implanted under the skin and in direct contact with body fluids (e.g. Senseoniccs' Eversense implant). Despite the dominating presence on the market of glucose sensors (as compared to other endogenous metabolites like lactate, cholesterol, etc.), this technology is being ported to other bio-chemical compounds (e.g. endogenous metabolites like lactate and glutamate), thus opening new diagnostic means. Moreover this approach is applicable to measure exogenous compounds in the bloodstream, with direct application to the monitoring of infused drugs.

Whereas bio-chemical sensors can be achieved through electrical, optical and mechanical means, mainly the former approach is amenable of integration with the circuit data-acquisition chain. Thus the future of e-health is much related to the search for - and design of - electrical sensors compatible with microelectronic technology, because this is a scalable approach leading to low-cost IoT nodes [25], [82].

B. Remote Medical Image Analysis

Ultrasound (US) imaging is widely used because it is a non-invasive monitoring means that is preferable to ionizing-radiation imaging (because of potential side effects) and to nuclear magnetic resonance (because of capital and operational costs). The use of US imaging is progressing because of two mayor recent innovations: i) the design of real-time 3-Dimensional (3D) US scanners [27] and ii) the design of portable US imaging systems. The former are bulky and expensive hospital equipment while the latter are relatively inexpensive devices useful for points of care. Today most US equipment use 2D scanning and imaging.

The main disadvantage of ultrasound imaging is that is has to be performed by a trained radiologist or sonographer. Indeed, the rendering of the inside of the body in a two-dimensional image relies a lot on the positioning of the US probe and only an expert can move the probe in the search for the medical feature to be examined. Thus, the remote use of US imaging is very limited. A special case has been the use of a robot to position the probe remotely [50].

There is a real need of using US imaging on the field. Examples include emergency care, care in remote locations as well as care required after natural disasters or in the battlefields. It has been argued that the mere possibility of general practitioners using US imaging for screening would significantly simplify and better health care [48].

A recent research avenue, *telesonography*, has addressed the design of portable 3D US systems, capable of extracting a volume that can be transmitted and analyzed remotely. Indeed a remote radiologist/sonographer on call can analyze the volume by rotating and segmenting it, thus mimicking the positioning and movement of the probe. In such a case, even an untrained health provider (such as an ambulance care giver) could use the 3D probe to extract the volume, leaving the analysis to the remote center. Such telemedicine approach can be very effective for diagnosis and provide a new example

of an IoT node embodied by a US probe. Nevertheless the design of a portable 3D US probe is very challenging, not just due to the integration of the US transducer with the circuit, but because of the high data rate and processing requirements along with the power and thermal constraints. The engineering requirements and design of such a probe will be described in Section III.

C. Smart Drug Administration

Personalized medicine aims at providing each individual with the right amount of drug and at the right time. This field has developed in recent years, due to the understandings of the relations between "ohmics" and treatment. Nevertheless, standard medical procedures are based on prescribing medications in doses, thus neglecting in part the *pharmacokinetics* aspects related to absorption, distribution and metabolism of drugs that depend on the individuals. Indeed, a drug can be effective (or not) and toxic (or not) depending on the patient. Thus the drug concentration in the bloodstream is the final objective of a therapy based on a dosage.

Drug monitoring in the bloodstream can be achieved by sensors similar to those used for endogenous metabolites. The direct measurement is very important in specific cases, such as anesthesia, chemotherapy and transplant-rejection inhibitor drugs. Ideally, direct drug sensing in body fluids should control drug administration through a *policy* that determines *on line* the time and dose of the drug and adapts to the variation of other physical parameters [53]. In practice, complex pharmacological models are used to predict the drug concentration in the bloodstream (based on observing external parameters) and to determine the dose. In both cases, system-level observability is achieved through various sensing nodes.

From a cyber-medical system standpoint, design and operation of *drug administration support systems* (DASS) need to satisfy several engineering requirements, because of their life-critical nature [63]. Correctness must be insured under any external and internal conditions. The system has to be dependable, and provide a graceful degradation mode. Safety has to be guaranteed for the patient and the health care provider. Finally, the system has to be secure, to disallow any unauthorized access as well as to permit rapid access to any qualified practitioner in case of emergency [46]. These requirements map into specific models and constraints for the realization of a therapeutic protocol, as described in detail below.

III. Technologies

The design of cyber-medical systems requires a plurality of technologies and components. A coarse-grained classification of components would group them into sensors, circuits for data acquisition, computing and communication, fluidics and actuators. An important objective is to achieve seamless integration of these components. As a result, we highlight sensor structures that are compatible with silicon and can be possibly integrated with circuits and fluidics.

A. Sensors

Within the context of cyber-medical systems, sensors are the interface between living matter and electronic processing

Fig. 1. Portable terminal showing real-time measurements for endogenous glucose and lactate and exogenous acetaminophen. Reprinted from [66].

circuits. Biosensors are particular sensors with biological recognition elements. Sensors for biomedical applications target many analytes, ranging from small molecules (Na^+, K^+) to large molecules like proteins and nucleic acids, to growth factors and cells. Thus sensors vary a lot in terms of detection method, materials and size. We focus here on some sensor technologies for cyber-medical nodes, based on electrical transduction.

In general a sensor maps the concentration of an analyte to an electrical parameter, such as current, that then is converted to voltage and digitized. Important quality factors of a sensor are *sensitivity, linearity, limit of detection* and *selectivity* [18]. It is also of key importance that measurements can be effected within the pathological range of the analyte. Molecular sensors are also often coupled to temperature and pH sensors for calibration reasons.

An important sensor device, which is amenable of integration with circuits, is the *Ion Sensitive Field Effect Transistors* (ISFET) [14], [38], [42]. The ISFET is a MOSFET where the gate is replaced by a selective membrane, an electrolyte solution in contact with the gate oxide and a reference electrode immersed in the solution (Figure 2). The reference electrode (e.g., Ag/AgCl electrode) is used to apply a polarization and is also responsible for fixing the potential of the test solution (analyte). Ions, present in the analyte solution and selected by the membrane, change the ISFET threshold voltage, which can be measured by sweeping the reference electrode or by monitoring the drain current value at fixed value of the reference voltage.

ISFETs can be realized with silicon (and other) technologies and can be made compatible with CMOS

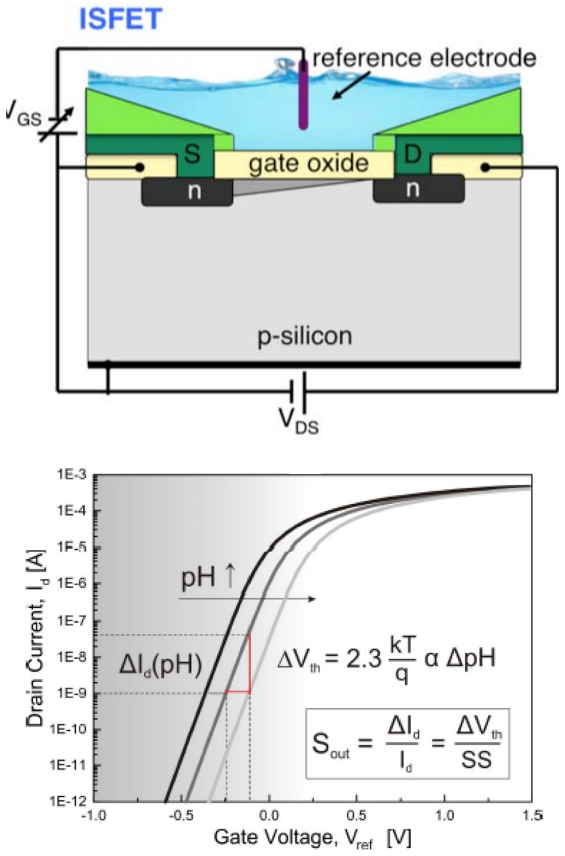

Fig. 2. ISFET transistor and electrical transfer curve as a function of pH.

fabrication. These transistors can be also made biologically sensitive (BioFETs) by coupling the ISFET gate oxide to specific biological recognition elements, i.e., the bio-receptors that are attached to the gate oxide via a chemical protocol. In these devices, the charge (or potential) effect is used to transduce the binding phenomena. According to the bio-recognition element, BioFETs have been classified into different classes: enzyme-modified FET (EnFET), Immuno Sensitive FET (ImmunoFET); DNA-modified FET (DNA-FET) and cell-based FET.

Current scaling trends in semiconductor technologies have ushered the way to 3-Dimensional (3D) transistors (as opposed to planar) such as *FinFETs* and *Silicon NanoWire* FETs (SiNW-FETs). The latter is a very effective structure to support sensing and is compatible with silicon circuit fabrication technology. Moreover, SiNW surfaces can be readily modified thanks to well-established silicon and silicon oxide functionalization protocols, thus making SiNW-FETs particularly attractive for label-free detection of biological species. As a result, SiNW FETs are better geared toward sensor support and integration than other nanomaterials.

Indeed SiNW FETs are particularly attractive for sensing for the following reasons. First, they have a high-surface-to-volume ratio. This provides a large interaction area and confines charge carriers to a very thin (almost one-dimensional) structure. Thus, whereas attachment of a biomolecule to a micro-scale planar device affects the surface characteristics,

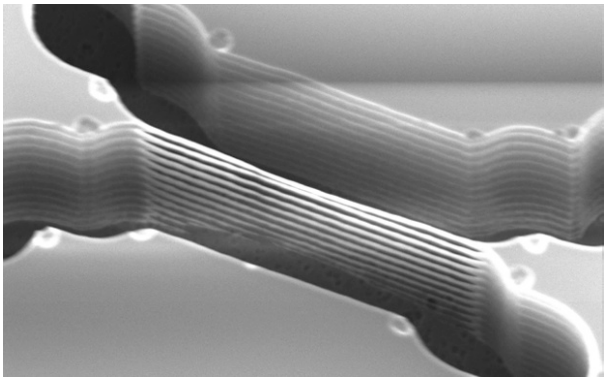

Fig. 3. Vertically-aligned SiNWs realized at EPFL.

attachment to a nanowire affects the bulk characteristics only. This offers ultra-high sensitivity detection possibilities for very low concentrations of a sample, which is not available in corresponding micro-scale sensing devices. Second, many biological molecules of interest in biomedical applications, such as proteins, cells and viruses, are known to have sizes on the micro- or nano-scale. Thus, a device with submicron or nano-scale dimensions represents an ideal candidate for interfacing to biological molecules. Finally, SiNWs can be realized in stacks of vertically-aligned wires, thus realizing a few devices in parallel with benefits to current levels and yield (Fig 3).

SINW transistors can be used for sensing in a way similar to ISFETs. Alternatively they can be used as nonlinear-resistors whose characteristics depend on their biofunctionalization and analyte concentration. Namely Puppo et al. [58] proposed a *voltage gap* (VoG)-biosensing principle that relates a gap measurement in the $I_{ds}-V_{ds}$ plots to analyte concentration. The physical model is complex and fully reported in [59]. In essence, when applying a full voltage swing to bare SiNWs, a memristive behavior [22] is detected (Fig. 4a) while the presence of an analyte causes a voltage gap, calculated as the voltage difference between the forward and backward current minima of the hysteretic $I_{ds}-V_{ds}$ plot. (Fig. 4b). The amplitude of the voltage gap is proportional to the analyte concentration.

These sensors have been applied to measure different concentrations of *Vascular Endothelial Growth Factor* (VEGF), a well-known cancer marker. Successful detection was achieved also in human specimens, such as unfiltered breast tumor extracts from patient biopsies at unprecedented low concentration levels (i.e., Femtomolar concentration) thus making these sensors attractive for early cancer detection. As another application, similar sensors were targeted to *prostate-specific antigen* (PSA) detection via a corresponding surface functionalization [81].

Many electrical sensors for (bio)-chemical compounds are based on the electrochemical three-terminal cell [8], [76]. The renewed interest in the three-terminal cell is related to its miniaturization, integration with silicon-based circuitry as well as the use of specific materials for the electrodes and their coating.

An electrochemical three-terminal cell has three electrodes are named *working, counter* and *reference* electrodes (WE, CE and RE respectively). Various configurations have been used, based on the principle that two electrodes keep a fixed

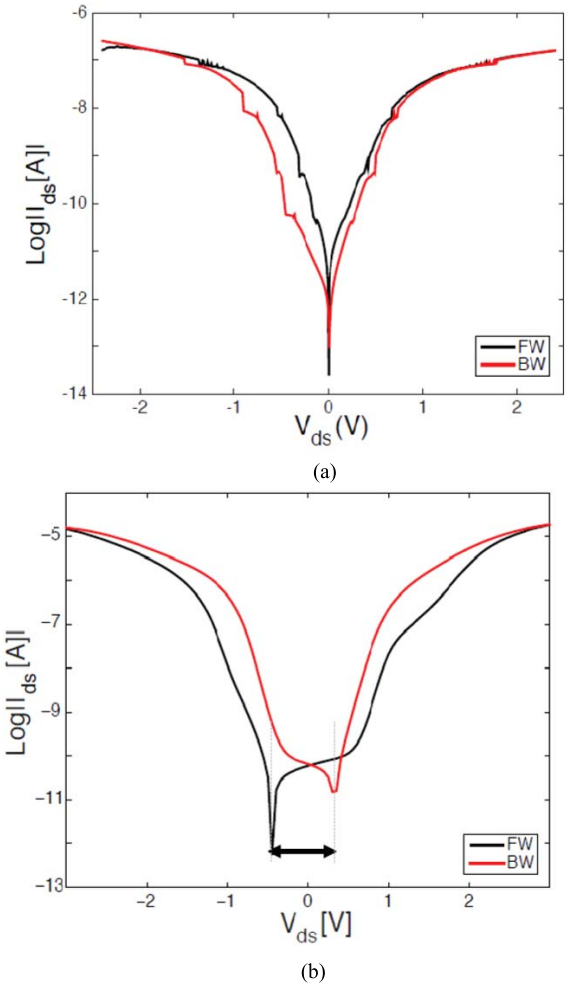

Fig. 4. a) Bare electrode; b) functionalized electrode in presence of target analyte.

(or varying) potential in the cell and the third sources or drains a current due to the electrochemical reaction (e.g., redox) happening in the cell at the given potential. Thus this current is a consequence of the reaction in the cell and depends on the analyte concentration and the applied voltage. Electrodes are covered by bio-recognition elements that capture the analyte. As an example, many glucose and lactate sensors use the corresponding oxidases as recognition elements: in presence of the analyte a reaction generates hydrogen peroxide whose redox releases/absorbs electrons and thus forms the current. The redox activity peaks at specific voltages that represent a signature of the reaction.

Standard screen-printed electrodes (in carbon) are available at low cost, but cannot be used as such. Beside the obvious issue of miniaturizing the electrodes and making them compatible with IC manufacturing technology, it is important that the electrodes are *nanostructured*, i.e., coated with a specific material to increase the surface at the fluid interface. Various materials, from *carbon nano-tubes* (CNT) to gold and platinum, have been used to this effect [11], [70]. The choice of material is very important and subject of recent research, because: i) an appropriate nanostructure increases sensitivity and decreases the limit of detection, thus bringing

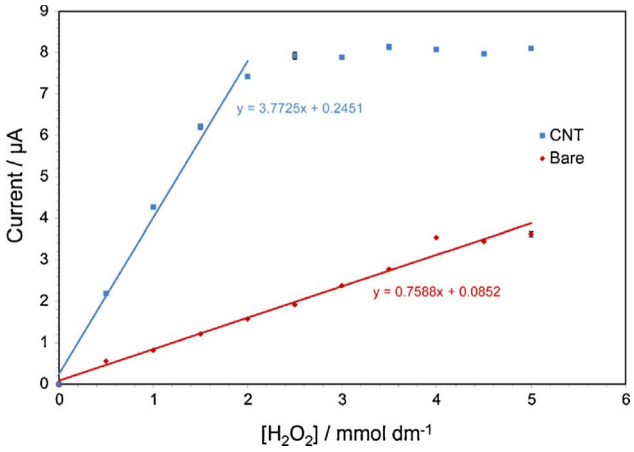

Fig. 5. Electrochemical detection by bare and CNT-nanostructured electrodes [20].

the sensor within the range of useful medical applications; ii) the coating of the electrode must either mediate the reaction for electrochemically-active analytes or support well the adhesion of an active layer that mediates the reaction (e.g., the enzyme cytochrome P450). Fig. 5 shows the sensitivity slope increase with CNT mediation [20] and Table 1 reports on comparisons of oxidase and CYP450-mediated biosensors [12]. A possible downside of enzyme-mediated sensors is the stability in time of the mediator molecule that can produce undesirable drifts of the sensed values. New synthesized mediators (enzymes) have shown stability in the range of months, about 5-10X better than wild types.

The integration of electrodes on top of silicon chips has been an area of active research for years. Schienle [62] fabricated DNA sensors on top of CMOS circuits, by connecting short (30 MER) segments of cDNA by using thiols on a gold plug. This was the first example of monolithic bio-3D integration. Other approaches to bio-3D integration included the study of a bio-layer that can be placed on top of a CMOS chip, where appropriate contact plugs provide top-down connectivity as well as possible replacement of the bio-layer itself [80]. It is important to mention that DNA sequencing integrated systems have shown the strength of electrical bio-sensing. This technology is not described here, as it is not related to IoT.

Electrodes fabricated on top layers of CMOS chips can be nanostructured with various nanocarbon-based layers (e.g. CNTs) that are deposited at, or grown upon, the surface and that can be very useful in improving the sensor characteristics [68]. When growing carbon nanostructures on silicon, the quality of CNTs decreases when lowering the temperature, which should go above the 450°C mark to avoid degradation of the CMOS IC. On the other hand, structures like carbon nanopetals can be deposited at low-temperature and provide for a relatively efficient nanostructure [68]. Figure 6 shows that as the nanocarbon yield increases with temperature (X axis) the desirable sensor parameters increase as well.

Nanostructuring can also be achieved by noble metals that are compatible with semiconductor processes and require relatively low temperature for deposition. Gold nanocorals have been used for enzyme-mediated glucose biosensing [69], while

TABLE I
COMPARISON OF SENSITIVITY, RANGE AND LOD OF VARIOUS SENSORS IN THE LITERATURE. ADAPTED FROM [12]

	Modification	Sensitivity	Linear Range	Limit of detection
GLUCOSE	CNT mat + GOD [61]	4.05 μA mM^{-1} cm^{-2}	0.2 - 2.18 mM	–
	MWCNT/Nafion + GOD [73]	4.7 μA mM^{-1} cm^{-2}	0.025 - 2 mM	4 μM
	MWCNT + GOD [83]	14.2 μA mM^{-1} cm^{-2}	0.05 - 13 mM	10 μM
	MWCNT-BA + GOD [32]	23.5 μA mM^{-1} cm^{-2}	0.01 - 2.5 mM 0 -	10 μM
	MWCNT/Nafion + GOD	55.5 μA mM^{-1} cm^{-2}	1 mM	2 μM
LACTATE	MWCNT/mineral oil + LOD [60] Titanate	0.204 μA mM^{-1} cm^{-2}	0 - 7 mM	300 μM
	NT + LOD [84]	0.24 μA mM^{-1} cm^{-2}	0.5 - 14 mM	200 μM
	MWCNT + sol-gel/LOD [33]	2.1 μA mM^{-1} cm^{-2}	0.3 - 1.5 mM	0.3 μM
	N-doped CNT/Nafion + LOD [29]	40.0 μA mM^{-1} cm^{-2}	0.014 - 0.325 mM	4 μM
	MWCNT/Nafion + LOD	25.0 μA mM^{-1} cm^{-2}	0 - 1 mM	11 μM
GLUTAMATE	Nafion + GlOD [54]	16.1 μA mM^{-1} cm^{-2}	0.001 - 0.013 mM	0.3 μM
	Chit + GlOD [85] PU/MWCNT + GlOD/PP [2]	85.0 μA mM^{-1} cm^{-2}	0 - 0.2 mM	0.1 μM
		384 μA mM^{-1} cm^{-2}	0 - 0.14 mM	0.3 μM
	MWCNT/Nafion + GlOD	0.9 μA mM^{-1} cm^{-2}	0 - 2 mM	78 μM
ARACHIDONIC ACID	MWCNT + CYP	1140.0 μA mM^{-1} cm^{-2}	0-0.04 mM	0.4 μM
CYCLOPHOSPHAMIDE	MWCNT + CYP	102.0 μA mM^{-1} cm^{-2}	0-0.07 mM	2 μM
IFOSFAMIDE	MWCNT + CYP	160.0 μA mM^{-1} cm^{-2}	0-0.14 mM	2 μM
FTORAFUR ®	MWCNT + CYP	883.0 μA mM^{-1} cm^{-2}	0-0.008 mM	0.7μM

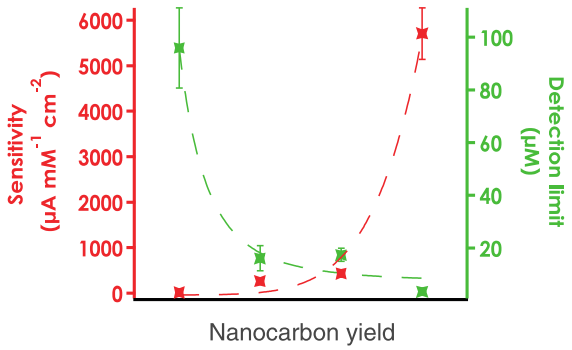

Fig. 6. Carbon nanostructuring effect on sensitivity and detection limit [68].

platinum nanopetals have been used to monitor potassium in acute cell-death monitoring [70]. Furthermore, bimetallic coatings (nanocoral gold on a gold substrate decorated by platinum nanospheres) have recently enabled the design of biosensors targeting glucose [78]. The significance of this result is that the current acquisition is achieved at a much lower voltage (as compared to state of the art), thus enabling a natively low-power sensing structure. Moreover, this structure can be personalized (for example by using oxidase mediators) to sense various relevant biological compounds.

B. Circuits and Platforms

The slow progress and penetration of sensor-intensive cyber-medical system is also related to the high *non-recurring engineering* (NRE) costs for their development. It can be strongly argued that a regular and structured co-design methodology can significantly reduce design time and cost of the devices. Whereas not all analytes fit in one "size", most relevant analytes can be grouped in classes for which scalable and customizable structures can be used. *Grosso modo*, sensing structures can be seen as standard cells similar to I/O pads that connect both to circuitry and to the external environment. The design of libraries of sensing structures can greatly simplify the overall design and bring benefits reminiscent of the introduction of semicustom design in the eighties [39]. Similarly, design methods and tools can help designing, sizing and personalizing such structures. The realization of a *platform* for integrated multi-sensing is a required enabler for achieving effective low-cost nodes for cyber-medical systems [24], [39].

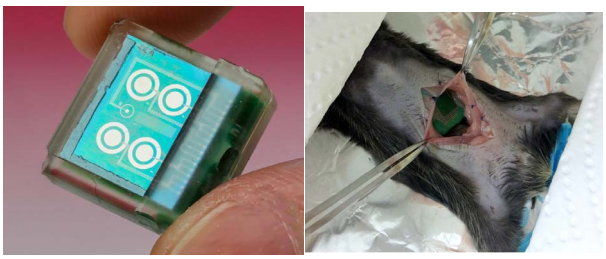

Fig. 7. a) 3D-integrated multi-sensor b) Surgical implant in animal model.

Let us consider first commonalities and constraints of electro-sensing. Most measurements are achieved by using the following techniques: i) *chronoamperometry*, i.e., the recording of a current $I(t)$ in response to an analyte at a fixed potential; ii) *cyclic voltammetry*, i.e., the recording of $I(t)$ as function of a cyclically-varying potential, iii) *impedance measurement* (often achieved as a frequency response $I(f)$, iv) *open circuit voltage measurement*. The reader is referred to Li et al. [44] for a recent review of circuits for bio-sensing. Even though the electrical analog front-end employs standard components such as operational amplifiers, the design of such circuits is very challenging [45]. Bio-chemical processes are slow, and thus frequencies of operation may be low for voltammetry and therefore noise and drift considerations are important in design. Moreover, low-power operation is required for both mobility and interface temperature reasons. A comprehensive study of noise limits for CMOS biosensor interface [34] shows that the noise of a transconductance amplifier would benefit from having either active feedback (in place of feedback resistor) or a capacitive feedback (with cyclic charge resetting). The former approach is advantageous at higher operational frequencies (as in the case of DNA sequencing through nanopores) while the latter is better applicable to protein/ion sensing devices where variations are low and where power consumption reduction is important.

Sensor programmability relates to the selection of a given compound. In the case of ions, such as Na+ and K+, membranes can do the appropriate selective filtering. In the case of proteins, electroactive species (e.g. uric acid) can be detected by the voltammetry peaks, i.e., by the voltages typical of specific redoxes. In the case of mediated sensing, a specific layering is required for each compound. For example, oxidases, like glucose and lactate oxidases are efficient mediators for glucose and lactate sensing [13], [17]. Thus, programmability relates to an additional fabrication step per compound.

Sensor miniaturization and integration open the door to the realization of multiple sensing sites on the surface of the same chip (e.g. Fig 7). Thus, multiple measures can be supported locally, with analytes distributed via standard microfluidic channels. The possibility of achieving multiple independent measures can be used as a way to enhance the reliability of the measure itself. Each analyte can be sensed at different nodes and the values averaged. Alternatively, tests resulting in the presence/absence of an analyte above a given threshold can be screened through majority evaluators.

A prototype exemplifying multiple integrated testing has been realized as an implant for animals and shown in Fig. 7.

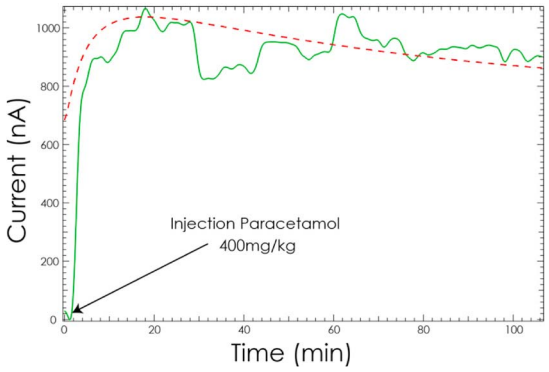

Fig. 8. Concentration impulse response in animal interstitial tissue.

The implant is realized on three layers, a sensing layer (visible on the top) with four sensing sites in addition to a local temperature and pH sensor, an IC processing layer and an antenna to capture RF operational energy as well as to transmit data bi-directionally. The device has been tested *in vivo* in laboratory animal models for drug concentration measurement [3]–[5]. The impulse response of blood concentration – in a moving mouse - due to a Paracetamol (Acetominophen) injection is shown in Fig. 8.

Field-programmable sensing arrays (FPSAs) are the extensions of *field-programmable gate arrays* (FPGAs) to sensing. Modular sensing sites are encapsulated in programmable circuits that provide for polarization, signal amplification and signal routing. Sites can be programmed by either a last fabrication step defining the target (membrane or mediator) or by activating the designed number of sites within the array, thus choosing the measures to be performed. Thus, specific sensing sites can be activated "on the field" and tuned to the desired sensing range. FPSAs achieve the following goals: i) a "multi-purpose" sensing fabric that can be customized to specific applications thus reducing overall NRE costs and market entrance barriers; ii) more reliable measurements because of locality and redundancy in the array, as well as response averaging; iii) higher sensitivity due to local nano-structuring of the electrodes and local signal amplification, leading to lower detection limits; iv) overall benefits of scale of semiconductor processing technologies. Regular integrated multi-sensor platforms are the emerging technology for cyber medical nodes.

C. Ultrasound Data Acquisition and Circuitry

An ultrasound system consists of a transducer probe (i.e., piezoelectric or capacitive-CMUT), a *beamforming platform* and an image analysis system [34]. Telesonography involves also image compression and transmission beyond the beamformer. Specific research progress has been achieved in probe and beamforming design as well as in their effective coupling, while image transmission and analysis exploit standard techniques used in other fields. Thus the beamforming platform requirements and new design inroads will be the focus of this section.

The behavioral abstraction of beamforming is the computation of the surfaces that backscatter an acoustic signal produced and received by the probe. In standard (2D) US systems

the probe is a linear array of transducers, while in 3D US systems the probe is bidimensional. Thus, beamforming requires acquiring the echoes from all scattering points and from all transducers and combining them to generate the surface through the different time of flights. Some US systems [79] perform analog pre-computation before beamforming, some others use either multiplexing [16] or compressed sensing to deal with the trillions of echoes per sample [10]. It is obvious that the use of 3D imaging requires more processing power; still size, energy dissipated and cabling have to be strongly reduced for telesonography. Thus new engineering solutions tend to either integrate the probe with the beamformer or do some preprocessing on the probe itself to enable a lightweight optical cable to connect to the beamformer platform [30].

Whereas a beamforming platform has to be general enough to be programmed to achieve a variety of US modalities, the beamforming kernel is the common problem of identifying the relevant echoes that should be combined in real time to determine each point of the reflecting surface. In medical applications, one can assume a constant propagation speed through soft tissues and reflections due to strong discontinuities (e.g., void, bone). Three challenges have to be addressed by the beamforming kernel; i) the accuracy of delay computation is essential for achieving high resolution; ii) the size of the delay table (storage) to buffer the echoes; iii) the access bandwidth to the delay tables themselves.

A review of various approaches to beamforming is presented in [34] as well as two novel solutions; the former avoids the use of delay tables at the expense of more circuitry and the latter keeps a small delay table in memory and derives the delays with an approximate computation thus requiring limited hardware. The latter solution enables the realization of a 1024-channel beamformer extracting 2.5 Megavoxels in a volume of $73^\circ \times 73^\circ \times 10$cm, performing at 133MHZ with a peak throughput of 53 frame/second and consuming less than 5W on a Xilinx Kintex FPGA. These results show the real possibility of realizing US nodes for cyber-medical systems enabling US image acquisition for telesonography. It is important to stress that US techniques are applicable beyond the medical field, e.g., to assess the health of mechanical structures, possibly in remote locations. Thus, such nodes are important elements of broader IoT systems.

D. Safe Drug Administration

Therapeutic drug monitoring and administration are important services that can be rendered by cyber-medical systems. In this section we highlight the systems aspects for design and operation. The underlying assumption is that a medical doctor is in charge of choosing the therapy and the system supports care by realizing drug delivery, that may be fully automated, remotely-monitored and/or controlled [57]. A system-level abstraction calls for a high-level specification of a cure that can be embodied by a *medical protocol*. A realization of a drug administration support system consists of both a hardware platform and a control scheme, that can be abstracted as a hybrid real-time system with observable (e.g., analyte concentration) and controllable (e.g., drugs) variables. Such reactive *safety-critical systems* [1], [9], [31] have to be conceived and designed accordingly to guarantee correctness. Thus, from a system standpoint we can distinguish two problems: 1) verification of the medical protocol specification and 2) verification that the cyber-medical system behavior is contained within the protocol behavior. The latter point is crucial for the realization and operation of DASS, because it guarantees that a machine behaves at least as well as a human medical operator under doctors' supervision.

Therapeutic protocol specification and validation requires the use of specialized languages and environments. Some of them were developed in the past years in order to assist medical doctors. Many, such as PRODIGY [37], EON [74], GLIF3 [15], PROforma [67], SAGE [75], represent a class of tools used to assemble complex decision-support systems. They adopt flowcharts as a core formalism to represent a sequence of actions that are supported by ontology-based medical terminology interpretation modules. Most of these tools also provide links to patients' databases. They enable validation of medical *guideline* (GL) structures only by means of their formal representation and have no support for the automatic verification of their formal properties. There exist frameworks such as GLARE [71] and Asbru [26] that provide translation links to model checking environments such as SPIN [64] and SMV [65]. Nevertheless, if a verified property fails, it is difficult to trace back the result needed to change the initial protocol model. Moreover, these formalisms provide the notion of time only in terms of partial orders of actions and association of time periods with respect to the patient condition evaluation, which enables us only to validate the GLs structure. While this has merit, it is also important to be able to map medical actions into the time scale in order to verify timing properties of a GL and thus close the gap between medical software and hardware interoperability, including data acquisition via biosensing.

Modeling and verification of cyber-medical systems can be achieved through the use of *Timed Automaton extended with Tasks* (TAT) [28] and the TIMES toolbox [72], originally designed for general real-time systems. TIMES includes not only a *Graphical User Interface* (GUI) for system modeling but also a model-checker engine that supports system verification where properties are described by means of *Computational Tree Logic* (CTL).

This methodology as been applied to the formal model of the *Imatinib* therapeutic protocol and algorithms for dose adjustment for adult patients with newly diagnosed Ph+ *Chronic Myeloid Leukemia* (CML) [63]. An example is shown in Fig. 11 in terms of a finite-state system. Each state is annotated with a given drug dose (initiated at 400). Clinical event cause state transitions leading possibly to higher or lower dose. Formal analysis of the diagram can lead to the discovery of over-specified or undefined clinical states, where obviously "correct doses" have still to be administered. Moreover, the formal model of therapeutic protocols can be combined with real-time data acquisition, to make accurate and predictable models of drug dispensing. Thus, the model can be viewed as the starting point to derive the control portion of a related drug-dispensing system. Eventually, a state-based model of drug dispensing systems (in hardware or software)

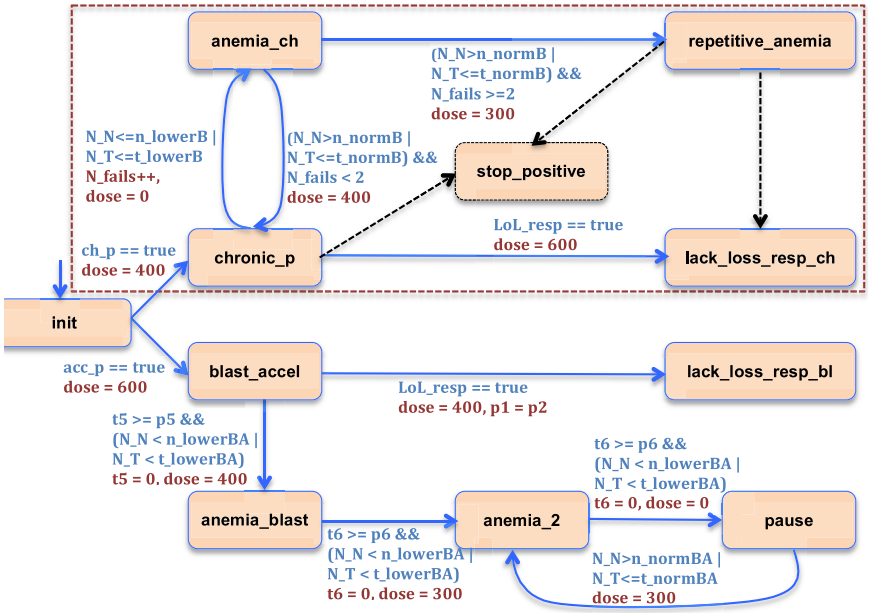

Fig. 9. Imatinib dose adjustment protocol with TAT [63].

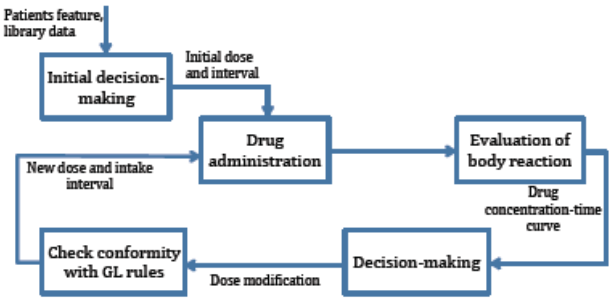

Fig. 10. Essential elements of a drug monitoring and administration system.

can be formally verified against the original protocol model.

Cyber medical systems for drug dispensing can be abstracted as closed loop systems (Fig.10), where drug administration is followed by an evaluation of the body reaction, conformity check and decision about time and dose of the next drug administration.

A conceptually simple but effective tool for drug quantification is the *EzeCHieL* environment [36], which provides data analysis to answer questions as: i) Is the observed concentration normal (w.r.t. standard population data); ii) What is the trend in concentration profile?; iii) What posology adjustment is required to attain the appropriate target range? Answering these questions in real/short time is very useful to pharmacologists and doctors even with standard drug administration means.

Whereas DASS and even simpler therapeutic computer aids are still in their infancy, their importance is widely recognized for applications to humans and laboratory animals for drug discovery and development. In both cases, automatic data acquisition and informative decisions can both improve the practice and reduce costs.

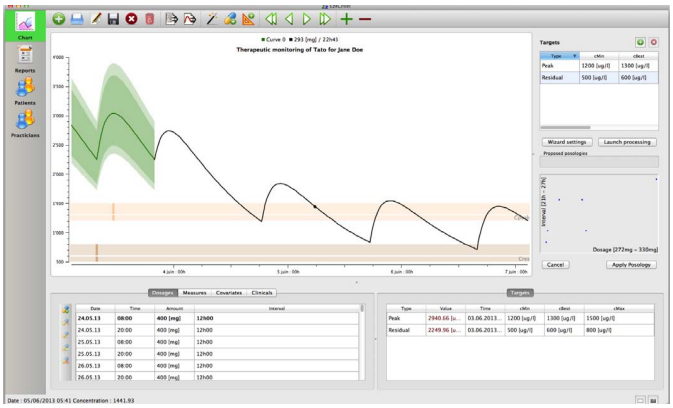

Fig. 11. An EzeCHiel screen shot showing drug concentration trends.

IV. Outlook

Cyber medical systems represent the rational engineering response to the emergency situation created by ever growing medical needs and costs. The quest for better diagnosis and therapy cannot be stopped, as well as the right of all sectors of the world population – including the weak (e.g., indigent, elderly, remotely-located people) - to access medical care. The medical community is well aware and supportive of engineering advances in healthcare and enlightened politicians understand that cyber medical systems will enable better and broader services and help curbing costs.

Still the road ahead toward rational and universal care is long. Whereas computational platforms are available at reasonable costs, (bio) sensors and their integration into platforms are still both expensive and far from the desired level of accuracy and reliability in realistic application environments.

Comprehensive software systems for health management are also still mainly proprietary and thus not flexible enough to support innovation toward newer practices and cost reduction.

The design of cyber-medical systems requires the collaboration of various scientific partners to understand the essential nature of the service to be provided and its implications. Several universities, research centers and consortia have addressed fundamental and application-oriented issues in cyber-medical systems. Notably, the Nano-Tera.ch initiative in Switzerland has fostered many multi-disciplinary multi-institutional projects in this domain addressing important research issues and achieving relevant and demonstrable prototypes [51]. Nano-Tera.ch is a government-funded consortium to support medium-term research at the intersection between the engineering and the biomedical world. The rate of progress and potentials in this domain, as well as potential economic, social and ethical implications, show the importance and need of "no strings attached" funding instruments. The involvement of the industrial sector is important, as the market size is potentially large, but priorities and directions should not be driven by financial greed in this domain.

V. Conclusions

The evolution of science, technology and medicine, the ubiquitous connectedness and the realization of bio-electrical interfaces are enabling the design of cyber medical systems to address health management in its various aspects. This field is extremely articulated, as problems and solutions are diverse. Nevertheless, scientific approaches that foster problem analysis, taxonomy and structured solutions have the possibility of achieving valid and affordable applications in front of potentially large development costs.

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