In-vivo wireless bio-diagnosis system for long-term bioactivity monitoring network

Chun-Kuang Chen[a], Wen-Jong Wu[b], Shih-An Yu[d], Jhen-Gang Huang[e], Yun-Han Lin[f], Yih-Fan Chen[a], Ming-Hui Jin[c], Chih-Min Wen[a], Cheng-Yan Kao[c], Shi-Ming Lin[g], Shey-Shi Lu[d], Chii-Wann Lin[e], Jia-Yush Yen[h], Fu-Shan Jaw[i], Chi-An Chen[d], Fang-Jen Liao[d], Nan-Fu Chiu[e], Chia-Nan Chien[i], Chih-Kung Lee[*a]

[a]Inst. of Applied Mechanics, National Taiwan University, Taipei, Taiwan;
[b]Dept. of Eng. Science and Ocean Eng., National Taiwan University, Taipei, Taiwan;
[c]Dept. of Computer Science and Information Eng., National Taiwan University, Taipei, Taiwan;
[d]Dept. of Electrical Engineering, National Taiwan University, Taipei, Taiwan;
[e]Inst. of Biomedical Engineering, National Taiwan University, Taipei, Taiwan;
[f]Dept. of Chemistry, Tamkang University, Tamsui, Taipei, Taiwan;
[g]Centre for Optoelectronic Biomedicine, National Taiwan University of Medicine, Taipei, Taiwan;
[h]Dept. of Mechanical Engineering, National Taiwan University, Taipei, Taiwan;
[i]Inst. of Biomedical Engineering, National Taiwan University, Taipei, Taiwan

ABSTRACT

Attempts to develop a ***W***ireless ***H***ealth ***A***dvanced ***M***obile ***Bio***-diagnostic ***S***ystem (abbreviated as ***WHAM-BioS***) have arisen from the need to monitor the health status of patients under long-term care programs. The proposed ***WHAM-BioS*** as presented here was developed by integrating various technologies: nano/MEMS technology, biotechnology, network/communication technology, and information technology. The biochips proposed not only detect certain diseases but will also report any abnormal status readings on the patient to the medical personnel immediately through the network system. Since long-term home care is typically involved, the parameters monitored must be analyzed and traced continuously over a long period of time. To minimize the intrusion to the patients, a wireless sensor embedded within a wireless network is highly recommended. To facilitate the widest possible use of various biochips, a smart sensor node concept was implemented. More specifically, various technologies and components such as built-in micro power generators, energy storage devices, initialization processes, no-waste bio-detection methodologies, embedded controllers, wireless warning signal transmissions, and power/data management were merged and integrated to create this novel technology. The design methodologies and the implementation schemes are detailed. Potential expansions of this newly developed technology to other applications regimes will be presented as well.

Keywords: C-Reaction Protein, optomechatronics system, embedded system, micro power system, biomechanics, micro/nano bio-sampling probe array.

1. INTRODUCTION

Considering the cutting-edge technology and scientific development, biotech, information technology and communication technology are three mainstream industries in this century. The semiconductor giant, Motorola, announced it would invest 5 billion dollars in micro-electro-mechanical systems (MEMS) and wireless communication to keep its competitive advantage. The eSensor^{TM} DNA detection system and corresponding Reader is the representative result in its Life Science Department. In all these research topics, the system integration and nanotechnology breakthrough form the foundations. In other words, cross-disciplinary integration is must in all these efforts.

[*] .Corresponding Author: Professor C. K. Lee, National Taiwan University, Institute of Applied Mechanics, No. 1, Sec. 4, Roosevelt Road, Taipei, Taiwan; Tel/Fax: (+886) 2 2365-9436; e-mail: cklee@mems.iam.ntu.edu.tw

Health Monitoring and Smart Nondestructive Evaluation of Structural and Biological Systems III, edited by Tribikram Kundu, Proc. of SPIE Vol. 5394 (SPIE, Bellingham, WA, 2004) · 0277-786X/04/$15 · doi: 10.1117/12.539695

Following this new wave of industry revolution, Taiwan's Ministry of Economic Affaires supports National Taiwan University (NTU) Nano-BioMEMS Group to develop a "Wireless Health Advanced Monitoring Bio-Diagnosis System (WHAM-BioS)" that encompasses the integration of biotechnology, information technology, and network/communications, Nanotechnology/MEMS, etc. The proposed system includes three subsystems: Power & Data Distribution (PDD), Bio-Diagnosis Platform (BDP), and Lab Chip Platform (LCP).

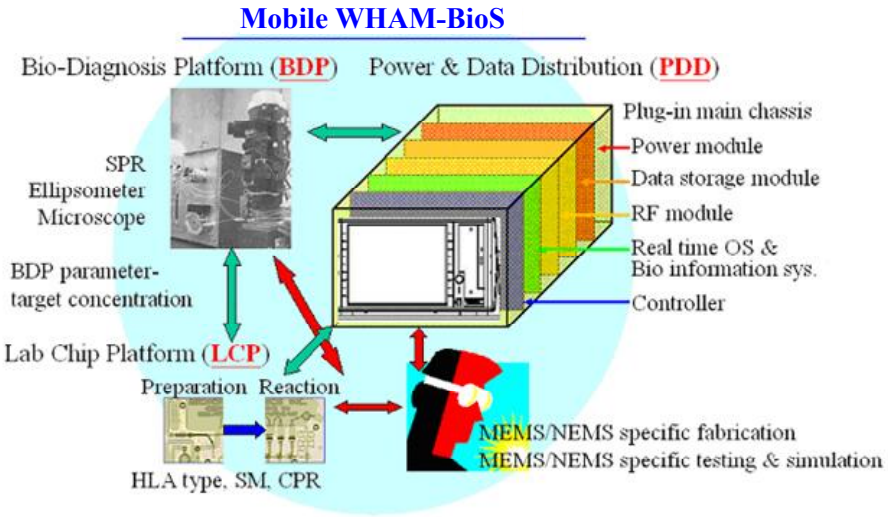


Fig 1: The Mobile WHAM-BioS System that includes three subsystems: PDD, BDP and LCP.

The PDD subsystem is set for specific data processing and control function for various types of biosensors by using a PC-based platform. It includes microprocessor, interface electronics, and embedded operating system. The BDP subsystem consists of several bio-specific measurement and optical imaging processing technologies, like ellipsometer, Surface Plamon Resonance (SPR), Optical Coherence Tomography (OCT), etc. This project first intended to downsize bulky components into 10cm×20cm×10cm volume and then to adopt MEMS technology to further miniaturize the overall system size. The LCP subsystem is to develop the mitogen-activated protein kinase (MAPK) biochip, and two lab-on-chips: Human Leukocyte Antigens (HLA) and Serratia Marcescens (SM), where MAPK chip will be used to measure the cell activated in response to a variety of extracellular stimuli in drug screening and HLA is usable in personal identification, SM is intended for real-time environmental monitoring. Modular design concept was adopted to establish the biochips starting from sample preparations to reaction detections.

There are well over 100 members within the team with a healthy mix of faculties, graduate students, and undergraduate students. The majority of the faculty members have been worked together for many important projects in Taiwan including more than 4 major National Science Council (NSC) University-Industry Collaboration projects for the last 9 years. Institutions ranging from NTU Hospital, N/MEMS group in Institute of Applied Mechanics, Department of Medical Engineering, College of Electrical Engineering and Computer Science, and College of Life Science worked together in this bold attempt. The NTU NEMS Center, which was grown out of the NSC Northern Regional MEMS Center, has established most of the facilities needed for the bio-chip fabrications.

The first milestone of this project is to complete a Mobile WHAM-BioS within 3 years, where the size of the whole measurement system is much less than 10cm×20cm×10cm. With long-term home care as the primary market, the full project proposes to perform real-time C-Reaction Protein (CRP) detection in blood serum. Using a miniature RF system, which can then be linked into the GSM/GPRS network for bio-informatics analysis, will then transmit the data obtained forward. All systems are based on PXI interface to pursue mechanical control and data processing. These systems are powered by a miniature power supply with biocompatible packaging that can harvest electric power from vibration appeared in patient's body movements.

2. SYSTEM AND WORK

2.1 Developing the RF transceiver

Communication systems for the sensor networks are developed rapidly for the last two decades[1, 2]. An RF micro-system was developed to construct the implantable portions in the sensor network. This micro-system is currently being fabricated by using the CMOS process in order to achieve a small-sized system-on-a-chip design, which contains an RF transceiver, a micro-control unit (MCU), an analog-to-digital converter (ADC), digital-to-analog converters (DAC), sensor preamplifiers, multiplexing buffer amplifiers (MUX), and an on-chip voltage regulator.

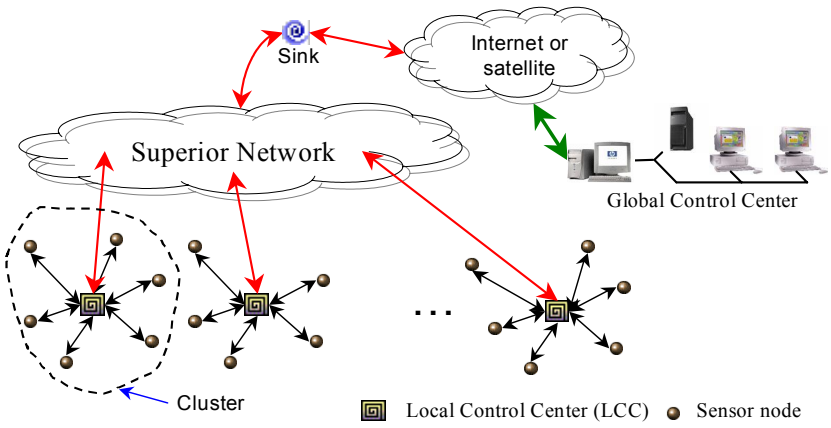


Fig.2 Network architecture

In the sensor network being developed, signals containing biochemical or physiological information are transmitted wirelessly from several clients. More specifically, the data can be accessed and processed more easily over the network. External local control centers will receive the data from several remote implanted micro-systems to form a cluster and then boost the over transmission efficiencies. These local control centers also have to monitor and control the subordinate micro-systems in their dominated clusters. Therefore, it is usually required to write-in versatile commands as well as to read-out various sensing signals in this implanted micro-system. Commands from local control centers are sent to define the status and the operation mode, in which the remote micro-system can be adjusted to control the sensors and process the signals properly. In other words, the RF micro-systems provide wireless interfaces between implanted bio-sensors and external network infrastructures.

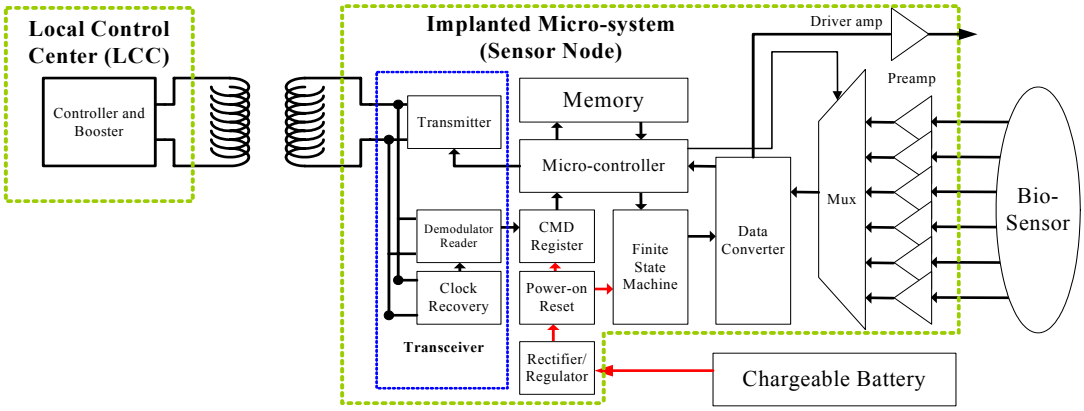


Fig.3 Schematic of an implantable sensor node and the local control center.

The selection of transceiver architecture limits both the performance and the practicability of the implantable micro-system. The complexity, sensitivity, power consumption, and chip area are main competing factors, which limits the application areas. To start the transceiver design, it is necessary to realize that the target system must possess low data rate, low noise, small bandwidth, low power consumption, and high sensitivity. In other words, a suitable communication system should be pre-determined. Since the analog communication system is susceptive to noise, especially when the transmission power is quite low, digital system was adopted. The versatile control schemes needed was also implemented within the digital communication system. In addition, modulation schemes affect the transceiver designs. It is known that amplitude modulation (AM) provides the simplest system with the least necessary components but the data rate is limited by its sensitivity. Frequency modulation (FM) can relax the sensitivity requirement with medium hardware complexity. Phase modulation (PM) or quadrature amplitude modulation (QAM) certainly can provide the best bandwidth efficiency but with the most complex hardware requirement. Attempt to balance the system performance and the component requirements, amplitude shift keying (ASK) and frequency shift keying (FSK) were chosen as the modulation schemes to be evaluated for the implantable system. To further counter the channel non-ideality, simple coding was also adopted to ensure the transmission quality.

Micro-control units served as the implanted control centers, which translate the commands from external local control centers, communicate with the subordinate sensors, and send the measured data back to the local control centers. Because the link between local control centers and micro-systems are asynchronous, the micro-system has to generate a clock signal to synchronize with the demodulated signal. The simple operating steps are described below. A local control center sends a measurement request to a designated implanted micro-system first, which was achieved by broadcasting a command with certain identity (ID) information encoded within the broadcast. Subordinate receivers demodulate the signals and synchronize it with the locally generated clock signal. Then the receivers check the (ID) coming with the command. If the ID does not match the firmware ID, the receiver ignores the command and returns back to listening mode. If the ID matches the firmware ID, the receiver will then send the command content into the command registers of the micro-control units according the address bits coded within the command. The controller then operates the peripherals such as ADC, DAC, or multiplexers with the aid of a built-in finite state machine. After the sensors output electrical signals, which contained the bio-chemical or physiological information of the patient, the multiplexing buffer amplifier defines the proper amplification factors needed to send the signal from the selected sensor to the ADC. The ADC converts the amplified analog signal to digital words and sends them to micro-control unit. The data will then finally be encoded, packaged, and transmitted back to the local control center.

Sensor preamplifiers are utilized to amplify the measured current or voltage signals without introduce much additive noise. It is to be noted that such read-out amplifiers must amplify low-frequency bio-testing data, which typically with contaminated by flicker noise that is notoriously difficult to suppress in standard CMOS process. Besides, the offsets of basic IC amplifier will also tighten the requirement of linearity and dynamic range of these amplifiers. According to the characteristics of measured signals, the topologies of amplifiers are decided. A trans-impedance amplifier was chosen to convert the current signals, which often obtained from an electrochemical-based sensor such as the glucose detection chip, to voltage signals. On the other hand, voltage amplifiers are adopted to amplify the voltage signals, which are usually produced in physical-mechanism based biochips such as pulse sensing via electro-pressure devices[3, 4, 5, 6, 7, 8, 9, 10]. All bio-detection signals are basically converted into voltage signals after the amplifiers.

In order to avoid using many analog-to-digital converters, the dynamic range of the various preamplifiers were set to a proper range such that only one ADC is needed for various measurement conditions. All of the scaled/amplified signals are selected by the micro-control unit through a multiplexing buffer amplifier, which can multiplex the data conversion between numerous sensing branches in a time-division manner. Built-in analog-to-digital converters will convert the amplified analog signal to digital words. An 8-bit charge-redistributed ADC was designed for this purpose. In order to achieve higher accuracy and immunity from process variation, good physical design is required such as careful layout or noise reduction. In our charge re-distributed analog-to-digital converter, mismatch was reduced by choosing careful aspect ratio. However, the area of capacitors will become prohibiting larger if high resolution is required. In order to prevent the capacitor areas from becoming the limiting factor, resistor arrays are combined with the capacitor arrays ones [11, 12, 13, 14, 15].

Moreover, optional digital-to-analog converter can output controlled waveforms, which can be further amplified by a driver amplifier to inject stimulating signals to organs. The regulators will limit the sensitivity and noise immunity of the sensors while only extremely small current or voltage signals can be induced by the sensing mechanism[16]. These circuits provide the micro-system with maximum flexibility in various applications. With the aids of the interface functions, the detected signals can then be amplified properly to interface the overall sensor network.

2.2 Chip Design

Issues about nursing patients with chronic diseases or malfunctions have becomes very important problems in public health at developed nations. An ideal caring system for patients requires point-of-care, long-term monitoring and monitoring alarm when his or her health status deteriorated rapidly. In the first-version system currently being developed, we proposed a microchip with an IV catheter outside appearance, which was used to detect biomedical physical and electrochemical signal in subcutaneous environment. The sensor chip modules were shown in Fig.4, which included a silicon-based detection microneedle, a printed circuit board for signal connection and a plastic canula for sensing module protection. The detection microchips were fabricated by MEMS technology, as shown in Fig. 5, which consisted platinum sensing microelectrodes and parylene layers for signal insulation and ensured tissue biocompatibility. The signal detected was finally processed and connected to the RF communication modules for transmission to the local receiving server wirelessly.

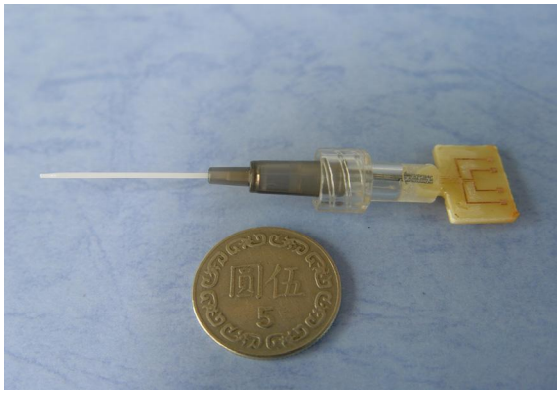


Fig. 4 the catheter-based sensing module

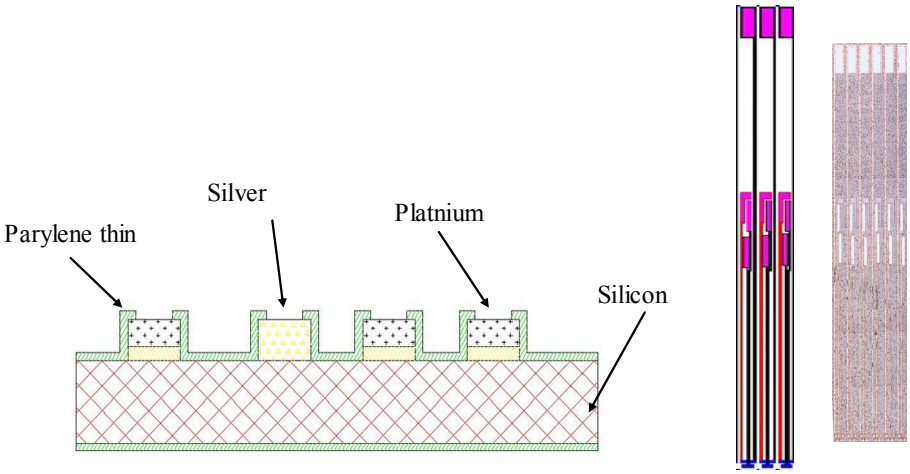
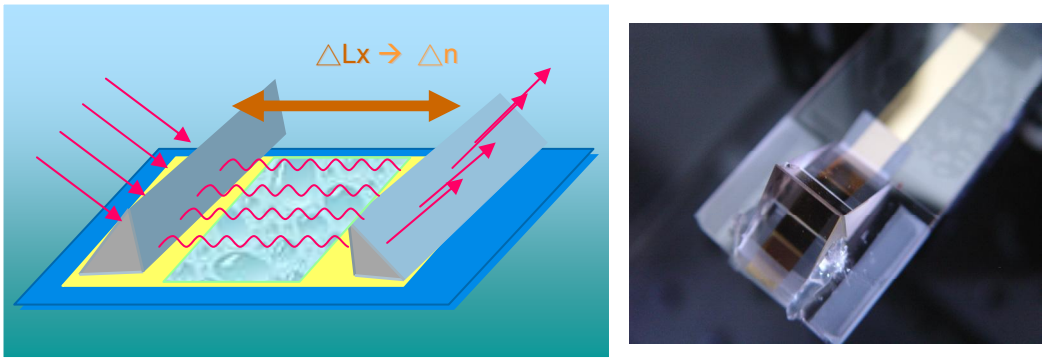


Fig. 5 The sensing microchips schematics (a) side view, (b) top view, and (c) top view of the fabricated microchips.

The polarized TM wave coupled with metal layer at the interface between metal and dielectric layer tends to excite surface plasmon in proper conditions, which translates to exponentially decayed intensity in horizontal and vertical direction. Surface plasmon resonance biosensors were thus used as our optical sensing device to detect the biomolecular conformation variation, blood contents concentration changes and constitution alternations by the shift of the SPR resonance angles. For the researchers concern with horizontal propagation in SPR, Schoenwald *et al*[17] developed a detection method based on two-prism coupling structure, in which two prisms were used to coupled exciting electromagnetic wave to be surface electromagnetic waves (SEW) and anti-coupled SEW to electromagnetic wave at a distant apart, respectively. However, Goubau[18], Barker[19], Bell *et al*[20], Alexander *et al*[21] and Ward *et al*[22] also discovered that SEW could propagation with a long distance when the metal surface plasmon was excited by infrared or low-frequency electromagnetic waves. It was found that the propagation length of SEW was determined by the metal surface characteristics, so it could be used to develop a high sensitivity biosensing device. In this research work, a SPR microsensor with horizontal propagation phenomena was constructed (see Fig. 6).



(a) (b)

Fig.6 (a) schematic and (b) photograph of horizontal propagation SPR biosensing device

2.3 The immobilization

The chip-based system for biological detection requires the immobilization of one binding partner. The requirement is to distinguish between specific bound compounds and non-specific adsorbed molecules. Self-assembled monlayers (SAMs) consists of 1~4 organothiols and disulfides on well-defined metal surfaces are well known in the surface science community. SAMs are especially attractive for the following reasons: 1) easy to prepare, 2) easy to be used as building blocks for more complex structures, 3) possible to form lateral structuring in the nanometer regime; and 4) can tailor for other applications.

Growth from solution is the traditional method for preparing SAMs. The alkanethiols on Au (1 1 1) surface typically used ethanol or hexane solution with concentrations in the micromolar to millimolar range. In our present study, we used the alkane chain molecules with thiol (-SH) groups on gold substrates to form uniform, densely packed and robust (covalent binding) monolayers spontaneously. The different chain lengths of alkanethiol provided each specific chemical property. The short-chain monolayers (butanethiol) usually have pronounced disorder. In contrast, SAMs with longer chains (dodecanethiol) form monolayers with a high degree of order. The drawback of long-chain alkanethiol on other hand lies on the fact that it is not easy to dissolve in water solution; therefore, we synthesized the new type organ-linker (Fig. 7) to counter this particular problem. The newly added amide group could increase the solubility of alkanethiol as described in Fig. 8.

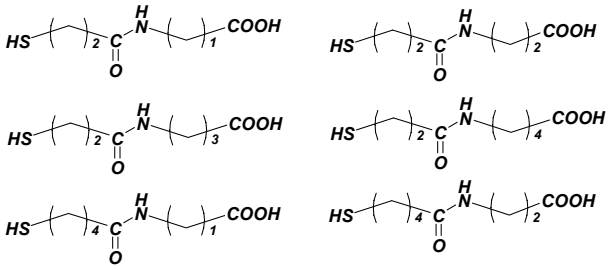


Fig. 7 The chemical composition of the newly developed organ-linker

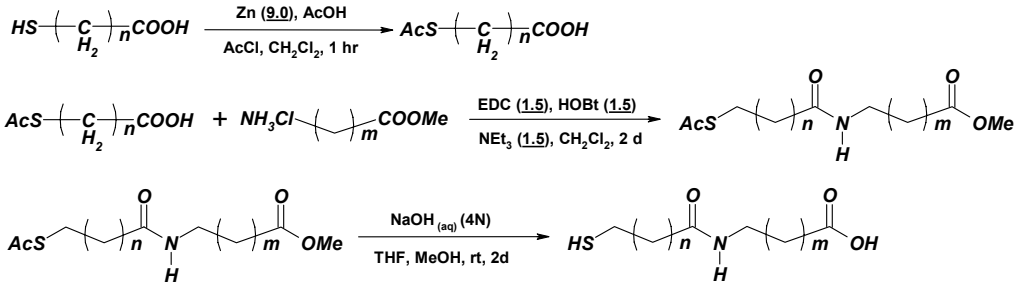


Fig.8. Mechanism of the new organ-linker synthesized.

Homogeneous self-assembled monolayers (SAMs) of alkanethiols on Au (111) surface were thus prepared by immersing fresh thermally evaporated gold film (~thickness is about 50 nm) into alkanethiol solutions for 30 min. Rinsed with DI water, and incubated for more than 30 min. The topography images (Fig. 9.) reveal the presence of nano-sized objects with a height of 2.5 ± 0.5 nm on the SAMs, which was imaged by using tapping mode atomic force microscopy (AFM) in air. This set of information could support the research on the interactions between the anti-body and antigen for future studies.

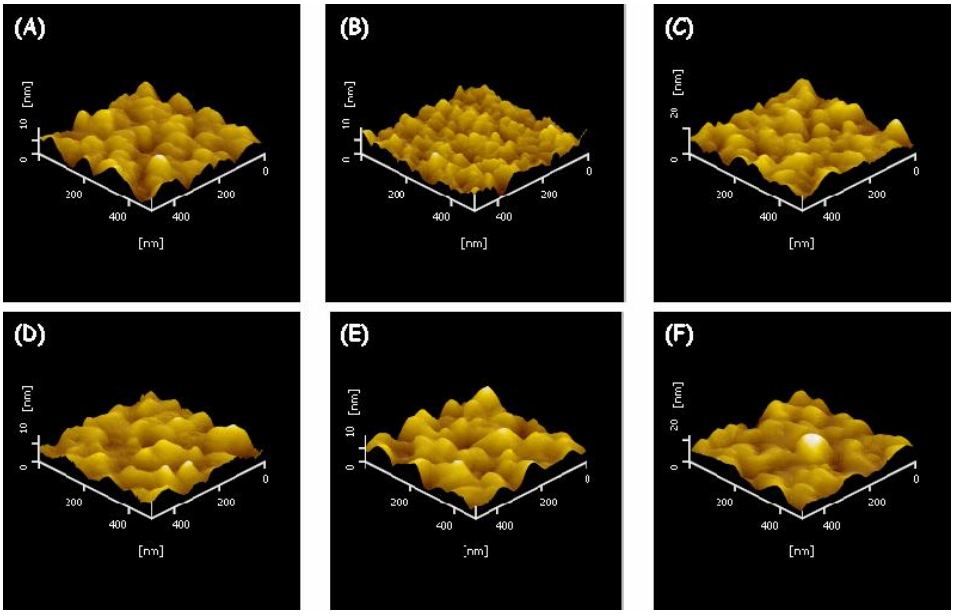


Fig. 9 The AFM topographic images of the SAM formed by using the new organ-linker.

3. SYSTEM SETUP AND INTEGRATION

Considering the complex perspective of the system integration, the RF transmitter was designed successfully and is now being taped out to ASIC fabrications. The topologies of wireless sensor network were also established, which used hierarchical sensor network architecture to establish the monitoring network. Both chemical self-assembly process and MEMS technology were integrated to fabricate the biochips. The immobilization of the biolinkers and the interactions between molecules were measured by using AFM.

To facilitate the integration of this project, all subsystems must be tested continuously so as to make sure the interface between each subsystem integrates smoothly. A prototype demonstration was schedule within half a year per current system development roadmaps. Currently, the experimental procedures and sub-systems verifications were performed on rat models. As it is shown in Fig. 10, ECG electrodes were penetrated into the rat's heart and the ECG information was transmitted to an FM receiver by using a miniaturized FM transmitter. The FM receiver was connected to a PC, which displayed real-time ECG signals on the local monitor as well as broadcasted over the internet. The successful measurement of the ECG signal demonstrates the feasibility of using our wireless technology for measuring physical parameters of rat's biological functions. To further extend the testing arena, the chemical parameters monitoring must be pursued. Since long-term home care was the primary development target, an implantable wireless bio-meter for real-time C-Reaction Protein (CRP) detection in blood serum is currently being studied.

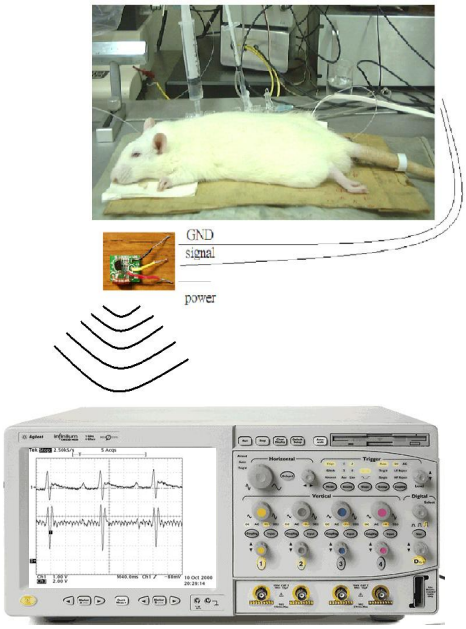


Fig. 10 Experimental setup for monitoring the rat ECG signal in real time.

4. CONCLUSIONS

Project scopes of a large-scale system intended for fully automatic patient diagnosis, which includes wireless network communication and miniature biochip design for real-time detection, was detailed. The difficulty and preliminary approaches adopted to circumvent the obstacles of using wireless technology embedded within the body for biological data transmissions were presented. Mixed signal processing ASIC was implemented to relay the biological information from the sensors embedded within the patient to an external receiver for further analysis. Cross-disciplinary interactions among fields such as nano/MEMS technology, biotechnology, network/communication technology, and information technology, etc. were found to be the most fundamental driving forces for system

performance advancements. Preliminary sub-system demonstrations were discussed to examine the underlying difficulty of this newly proposed research platform. With the need for long-term home care continues to expand swiftly, the pressure for a full and rapid system integration will mount quickly.

ACKNOWLEDGEMENTS

The financial and material support from Ministry of Economic Affairs, R.O.C through Grants TDPA (Technology Development Program for Academia) 91-EC-17-A-05-S1-0017 is greatly appreciated.

REFERENCES

1 H. Yu, and K. Najafi, "*Low-power interface circuits for bio-implantable Microsystems*," ISSCC 2003.
2 Z. Tang, B. Smith, J.H. Schild, and P.H. Peckham, "Data transmission from an implantable biotelmeter by Load-Shift Keying using circuit configuration modulator," *IEEE Trans. Biomed. Eng.* vol. 42, pp. 524-528, May 1995.
3 C.C. Enz, and G.C. Temes, "Circuit techniques for reducing the effects of op-amp imperfections: auto-zeroing, correlated double sampling and chopper stabilization," *Proc. of the IEEE*, vol. 84, no. 11, pp. 1584-1614, Nov. 1996.
4 C.C. Enz *et al.*, "A CMOS chopper amplifier," *IEEE JSSC*, vol.22, pp.335-342, June 1987.
5 C. Menolfi, and Q.Huang, "A fully integrated CMOS instrumentation amplifier with submicrovolt offset," *IEEE JSSC,* vol. 34, pp.415-420, March 1999.
6 A. Bakker et al., "A CMOS nested chopper instrumentation amplifier with 100nV offset," *IEEE JSSC*, vol. 35, no. 12, pp. 1877-1883, 2000.
7 K.A.A. Makinwa, and J.H. Huijsing, "A wind sensor with an integrated low-offset instrumentation amplifier," *Proc. of ICECS 2001*, vol. 3, pp. 1505-1508.
8 C. Menolfi, and Q. Huang, "A low-noise CMOS instrumentation amplifier for thermoelectric infrared detectors," *IEEE JSSC*, vol. 32, no. 7, pp.968 -976, July 1997.
9 C. Menolfi, and Q. Huang, "A 200nV 6.5 nV/√ Hz noise PSD 5.6kHz chopper instrumentation amplifier," *Digest of ISSCC 2001*, pp.362-363.
10 A. Thomsen, "DC measurement IC with 130nVpp noise in 10Hz," *Digest of ISSCC 2000*, p.334-335.
11 W. Kester, "*Mixed signal and DSP design techniques,*" Analog Device Inc.
12 A. Hastings, "*The Art of Analog Layout,*" Prentice Hall, 2001.
13 J.L. McCreary, and P. R. Gray, "All-MOS charge redistribution analog-to-digital conversion techniques," *Solid-State Circuits, IEEE Journal of*, vol. 10, Issue: 6, pp.371-379, Dec 1975.
14 H. Russell, Jr, "An improved successive-approximation register design for use in A/D converters," *Circuits and Systems, IEEE Transactions on*, vol. 25, no. 7, pp.550-554, July 1978.
15 J. Park, H.-J. Park, J.-W. Kim, S. Seo, and P. Chung, "A 1 mW 10-bit 500KSPS SAR A/D converter," *Circuits and Systems, 2000. Proceedings*, ISCAS 2000 Geneva. The 2000 IEEE International Symposium on, vol. 5, May 2000, pp.581-584
16 G.A. Rincon-Mora, *Voltage references,* IEEE Press, 2002.
17 J. Schoenwald, E. Burstein, M. Elson, "Propagation of surface polaritons over macroscopic distances at optical frequencies,"*Solid State Commu.* vol. 12, pp.185-189, 1973.
18 G. Goubau, "surface waves and their application to transmission lines," *J. Appl. Phys.* vol. 21, 1950.
19 A.S. Barker, "Optical Measurements of Surface Plasmons in Gold," *Phys. Rev.* vol. B8, pp.5418-5426, 1973.
20 R.J. Bell, R.W. Alexander, Jr., W.F. Parks, G. Kovener, I.L. Tyler, "Surface excitations in absorbing media," *Opt. Commun*. vol. 8, pp.147-150, 1973.
21 R. W. Alexander, Jr., R. J. Bell, C. A. Ward, J. H. Weaver, I. L. Tyler, and B. Fischer, "Possible applications of surface electromagnetic waves to measure absorption coefficients," *J. Chem. Phys.* vol. 59, 1973, pp.3492-3494.
22 C.A. Ward, R.J. Bell, R.W. Alexander, G. Kovener, "Surface electromagnetic waves on metals and polar insulators some comments," *Appl. Opt.* vol. 13, pp.2378-2381, 1974.
23 R.J. Bell, R.W. Alexander, Jr., C.A. Ward, I.L. Tyler, "Introductory theory for surface electromagnetic wave spectroscopy," *Surface Science*, vol. 48, pp.253-287, 1975.

24 M. Olivier, N. Rochat, A. Chabli, G. Lefeuvre, F. Conne, “Infrared Study of Hydrogen in Ultra-Thin Silicon Nitride Films Using Multiple Internal Reflection Spectroscopy (MIR) in 200 mm Silicon Wafers,” P*hys. Stat. Sol. (a)* vol. 175, pp.137-143, 1999.
25 N. Rochat, Michel Olivier, Amal Chabli, Francis Conne, and Georges Lefeuvre, “Multiple internal reflection infrared spectroscopy using two-prism coupling geometry: A convenient way for quantitative study of organic contamination on silicon wafers,” *Appl. Phys. Lett.* vol. 77(14), pp.2249-2251, 2000.
26 N. Rochat, A. Troussier, A. Hoang, F. Vinet, “Multiple internal reflection spectroscopy for quantitative infrared analysis of thin-film surface coating for biological environment,” *Materials Science and Engineering C*, vol. 23, pp.99–103, 2003.
27 Ulman, A. “Formation and Structure of Self-Assembled Monolayers,” *Chem. Rev.*, vol. 96, pp. 1533-1554, 1996.
28 Poirier, G. E. “Characterization of Organosulfur Molecular Monolayers on Au(111) using Scanning Tunneling Microscopy,” *Chem. Rev.*, vol. 97, pp.1117-1128, 1997.
29 T. Yasuda, T. Okuno, and H. Yasuda. “ Contact Angle of Water on Polymer Surfaces,” *Langmuir*, vol. 10, pp. 2435-2439, 1994.