

Abstracts and Schedule

Arkansas Biomedical Engineering Forum
Shorey Building Ob/Gyn Conference Rm S5-25
University of Arkansas for Medical Sciences
Little Rock
Friday, June 8, 2007,
10:25 a.m. to 4 p.m.

10.25 am

Introduction and Welcome

Dr. Michael Jennings, Department of Physiology and Biophysics

Session 1: UAMS Presentations (Chair: Dr. Hari Eswaran, Department of Ob/Gyn)

10:30-10:50 am

Advances in *in vivo* Flow Cytometry Integrated with Nanotechnology

Dr. V. P Zharov

Phillips Classic Laser Laboratory

Departments of Otolaryngology–Head & Neck Surgery and Radiology

University of Arkansas for Medical Sciences

Flow cytometry is a well-established technique that revolutionized cell diagnostics *in vitro*. Despite its long history and many successful applications, conventional flow cytometry is limited by the invasive nature of cell extraction from a living organism, which may introduce artifacts and make it impossible to conduct long-term monitoring of the cells in their complex natural environment such as studies of metastasis, cancer recurrence, immune function, or cell death. We introduce a new technology called *in vivo* flow cytometry with photoacoustic and photothermal schematics for real-time detection of circulating metastatic cells, bacteria, nanoparticles, and conventional contrast dyes on animal models. Specifically, its capability was demonstrated by using a near-infrared tunable laser to label-free monitoring of individual metastatic melanoma cells, and bacteria such as *Staphylococcus aureus* and *Escherichia coli* labeled with carbon nanotubes. This technology demonstrated the unprecedented threshold sensitivity *in vivo* as one gold nanoparticle in the irradiated blood volume and as one cancer cells (or bacterium) in the background of 10^8 normal blood cells that is unachievable with existing technique including advanced PCR assays even *in vitro*. This technique can be considered as a new tool in the biological research with high potential of the quick translation to humans, providing ultrasensitive diagnostics of infections (e.g., bacteria and viruses) and metastatic cells, and pharmacokinetics of nanoparticles and contrast dyes among many other applications.

10:50-11:10 am

Ultrasound Augmentation Thrombolysis in an Angiographic Stroke Model in Rabbits

Aliza T. Brown, PhD¹, John Lowery, DVM², Leah Hennings, DVM³, William C. Culp, MD⁴

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Acute ischemic stroke affects 600,000 Americans each year and fewer than 3% get treatment with the therapy of choice, tissue plasminogen activator (tPA) in the first 3 hours. Many of these suffer a severe complication of this treatment, intracranial hemorrhage. A new and safer treatment is badly needed. Many rat and mouse models of neuroprotective therapies have not successfully translated into human applications. Therefore using a more clinically relevant angiographic rabbit internal carotid artery thrombus model of stroke we examined the safety and efficacy of three therapies including tPA with and without ultrasound and microbubbles plus ultrasound. Twenty-four New Zealand white rabbits (4-5 kg) had autologous 3 hour old blood clots 0.4X0.4X1.0 mm placed in the internal carotid artery (ICA) then treated with 1) no treatment (control), 2) tPA 0.9 mg/kg, 3) tPA 0.9 mg/kg plus ultrasound or 4) IV DEFINITY microbubbles plus ultrasound. IV tPA was administered at 3 min intervals and IV microbubbles at 5 min intervals for 30 min. Pulsed 1 MHz ultrasound at 0.8 W/cm² was applied for 60 minutes in appropriate animals. Endpoints include percentages of stroke volume (SV%) on histologic sections at 24 hours and neurological assessment scores (NAS). The control animals had significantly increased SV% at 1.073±0.41 vs. tPA 0.117±0.08, tPA+ultrasound 0.208±0.14 or

microbubbles+ultrasound 0.135 ± 1 , $P \leq 0.01$. There were no significant differences in SV% between therapies, $P = \text{NS}$. NAS was also significantly increased in controls vs. therapies, $P \leq 0.04$, with no significant differences between therapies, $P = \text{NS}$. Therapy treatment consisting of tPA, tPA+ultrasound or microbubbles were shown to be of similar benefit in reducing SV% and NAS in the acute rabbit ICA thrombus model.

11:10-11.30 am

Neonatal and Fetal Responses Decrement of Evoked Responses – A MEG Study

Ms. Carolin Sheridan

Department of Obstetrics and Gynecology, University of Arkansas for Medical Sciences

To investigate the response decrements of visual evoked responses (VER) in newborns and assess its applicability to fetuses in MEG recordings. Twelve newborns with no known risks or complications participated at chronological ages between nine and 22 days. They constituted the follow-up group to a prenatal study conducted on a sample of 25 fetuses. The fetal age at the recordings varied between 29 and 37 weeks gestational age. Trains of four light flashes with an interstimulus interval (ISI) of 2 s followed by 10 s without stimulation were delivered to record VER. Nine of the 12 newborns responded to the stimulation and showed a statistically significant response decrement in amplitude from the first to the last light flash. Furthermore, the response latency prolonged statistically significant with increasing number of stimuli. The remaining three recordings were discontinued early. Even though the prenatal visual evoked response rate was only 29%, the fetuses exhibited a response decrement after the first stimulus. The amplitude of VERs can be used to elicit a response decrement in newborns and with limitations even in fetuses. This paradigm might be a useful tool for a direct and non-invasive assessment of neonatal and prenatal brain development and CNS functioning.

11:30-12:00 noon

Guest Lecture

Overview of Biomedical Research at NCTR

Dr. Tucker A. Patterson

Division of Neurotoxicology

National Center for Toxicological Research U.S. Food & Drug Administration

12:00-1:00 pm

Lunch Break

Session 2: UALR Presentations (Chair: Dr. Kamran Iqbal, Department of Systems Engineering)

1:00-1.20 pm

A Fast and Accurate Approach to Extract and Visualize Hidden Information from Very Complex Biological Networks

Dr. Xiaowei Xu

Department of Information Science, University of Arkansas at Little Rock

Biological systems can be modeled as complex systems with many interactions between the components. These interactions give rise to the function and behavior of that system (for example, the enzymes and metabolites in a metabolic pathway). One of the important areas of research in the emerging systems biology is to systematically analyze very large complex biological networks such as

metabolic networks, protein-protein interaction networks and regulatory networks. Unfortunately, the existing methods are either not accurate or too slow for biological networks. We devised a new methodology that can efficiently extract and visualize hidden information contained in complex biological networks. More specifically, we demonstrate that we can find functional modules in complex networks and classify nodes into various roles based on their structure. Furthermore, the method can generate a "cartographic representation" of complex networks, which greatly improves our understanding and the interpretation of the mechanism of life and disease. Finally, we demonstrate the effectiveness of our methodology using metabolic network of twelve organisms from three different super-kingdoms.

1:20-1:40 pm

A Mathematical Model of the Human Uterine Myocyte

Dr. Pat Buford P.E.

Department of Applied Science, University of Arkansas at Little Rock and Department of Electrical Engineering, Arkansas Tech University

The focus of this presentation is an overview of a comprehensive electrochemical and chemomechanical model of a single uterine cell. This electrochemical model contains not only ionic channel currents but the additional effects of pumps, exchangers and the sarcoplasmic reticulum. The calcium-calmodulin complex of the electrochemical model is an input to the chemomechanical section of the model. The chemomechanical section develops force dependent on intracellular calcium concentrations of the electrochemical model. This force causes a stretch in the cell length which is then fed back to the electrochemical model in the stretch current component. Thus the two major sections of the model are integrated.

1:40-2:00 pm

Non-Linear Time Series Analysis Algorithms for Disease Detection

Mr. Umit Uluser

Department of Applied Science, University of Arkansas at Little Rock

Symptoms of diseases vary from disease to disease and people to people. Studies indicated that some modifications and adjustments are required in data analysis methods to analyze the physiologic data for particular diseases. For these kinds of situations, adaptive-learning techniques are developed. Unfortunately, the use of artificial intelligence and computer learning techniques in non-linear data analysis is almost none or very limited. Predicting the diseases to reduce the risk factor and improve the prevention may be crucial for some cases like heart diseases which are leading causes of death. Development of many diseases takes time and some of them can be detectable by experts by examining physiologic signals. However, the ability to accurately provide diagnosis with physiologic data can be difficult for many cases as the signs and symptoms of many diseases vary and they are not obvious. In recent years, we have seen many successful applications of non-linear data analysis techniques on physiologic data for prediction of diseases and discovering the hidden characteristics that can not be revealed by linear and statistical data analysis techniques. For many known diseases, diagnosis is usually an expensive, risky, and painful process, and sometimes requires invasive operations like a heart rejection test after heart transplantation. The improvements in non-linear data analysis based on non-invasive physiologic data such as electrocardiogram (ECG), electroencephalogram (EEG) and NIRS can improve the predictability of the diseases. In our study we are developing a non-linear data analysis system which will use non-invasive physiologic data for disease detection. There are various use of this kind of system. First, we are planning to develop a web page for the researchers who have physiologic data and want to analyze them with non linear techniques like Detrended Fluctuation Analysis (DFA), Hurst Exponent and Multiscale Entropy (MSE). Second, we are planning to improve the system by using real-time patient data and predict the disease as it develops and alert the doctor if the patients' health status changes. This presentation will cover the 2 studies we have conducted so far and their results.

2:00-2:10 pm

Coffee Break

Session 3: UAF Presentations (Chair: Dr. Lalit Verma, Dept. of Biological and Agricultural Engineering)

2:10-2:30 pm

Rapid Screening of Avian Influenza Virus H5N1 by Magnetic Nanobeads Based Microfluidic Immunosensor

Ronghui Wang¹, Yanbin Li^{1,2*}, Billy Hargis², Steve Tung³

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Avian influenza (AI) virus H5N1 has been reported in numerous countries, infecting not only a large number of poultry, but also an increasing number of humans with more than 50% fatality rate. Since current diagnostic methods are limited by long detection time, high cost or lack of specificity, there is an urgent need for a reliable technique for in-field rapid screening of AI virus H5N1. In this study, a novel biosensor technology based on the combination of a magnetic bio-nanobead separation/concentration procedure and a microfluidic chip with interdigitated array microelectrode was developed and demonstrated for sensitive, specific and rapid screening of AI virus H5N1 in swab samples. Magnetic nanobeads were coated with AI H5N1 antibodies, and mixed with the rinsing solution of a swab sample to capture the target virus. A magnetic field was applied to hold the nanobead-H5N1 virus complex and the rest of the sample was then washed away. This resulted in the separation and concentration of AI H5N1 virus from a swab sample. Following the magnetic nanobeads pretreatment of a sample, the resulted nanobead-H5N1 virus complex solution was injected into the impedance immunosensor in which a microfluidic chip was used as a flow-through device to deliver the sample to an interdigitated array microelectrode for impedance measurement. Changes in the impedance of the antibody coated nanobead-H5N1 virus complex was measured and correlated to the concentration of AI virus H5N1 in the swab sample. The magnetic nanobeads based microfluidic immunosensor was able to detect AI H5N1 as low as 1×10^3 EID₅₀/ml, and the total detection time from sampling to detection was only 35 min. The immunosensor showed its potential of being used for in-field rapid screening of AI H5N1 virus.

2:30-2:50 pm

Microwave Imaging and Detection of Breast Tumor Shape and Development of Tumorigenesis Model

Dr. Magda El-Shenawee

Department of Electrical Engineering, University of Arkansas, Fayetteville

Our goal is to develop an inversion algorithm for reconstructing the shape of 3D breast tumor using electromagnetic data. The method of moments forward solver is used to calculate the electric and magnetic equivalent surface currents at the tumor interface and consequently the scattered electromagnetic fields. The mismatch between calculated and synthetically measured fields at the receivers is used as new sources at all receiver locations and is back-propagated towards the tumor. The gradient is calculated as the product of the forward and *adjoint* fields at the best guess of the tumor interface in order to extract a new search direction. Using this technique, the forward solver is used only twice, regardless of the shape of the tumor; once for solving the forward problem and once for the *adjoint* problem. This process is repeated iteratively until the mismatch in the data is minimized according to some criterion. Numerical results in 3D are presented based on the proposed technique using multiple transmitting sources/receivers at multiple microwave frequencies. On the other hand, understanding the relationship between morphology and malignancy will be essential in diagnosing the images as malignant or benign even before invasive procedures are performed. This understanding can now be

visualized with the aid of mathematical biology modeling and simulation. It will be helpfully if one can forecast tumor shape in relation to relative malignancy. We propose some key factors to be considered such as: combining existing techniques with knowledge specific to Ductal Carcinoma of the breast, using reaction-diffusion spatiotemporal techniques for nutrient dependencies of tumor growth, incorporation of the hallmark mutations paradigm, consideration of constraints imposed by the local tissue environment, and cell-cell and cell-ECM adhesion. Initial results on modeling tumor growth of some cancerous tumors will be presented.

2:50-3:10 pm

Characterization of Differentiation of Embryonic Stem Cells into Insulin-producing Endocrines Cells in 3D Cultures

Xiuli Wang and Kaiming Ye*

Biomedical Engineering Program, College of Engineering
University of Arkansas, Fayetteville

Production of sufficient numbers of pancreatic endocrine cells that function similarly to primary islets is the premise of cell therapies for diabetes. To characterize the differentiation of embryonic stem (ES) cells into insulin-producing cell clusters (ILCCs) in three-dimensional (3D) environments, we cultured mouse ES Cells within collagen scaffolds and four-step differentiation protocol was developed and used to direct a pancreatic lineage-specific differentiation. The cell differentiation was determined by gene or protein-profiling the expression of a variety of islet-specific markers. Our data indicate that ES cells differentiated within 3D scaffolds and embryoid bodies (EBs) formed were similar to those in traditional two-dimensional (2D) cultures; however, unlike 2D differentiation, these EBs appeared embedded in a network of extracellular matrix and their sizes are more uniform. Most significantly, the differentiation of ES cells into IPCC on 3D collagen scaffolds gives rise to cells displaying morphological features, gene expression patterns and functional activities characteristic of islets, which may provide a potential source of differentiated cells for the diabetes treatment.

3:10-4:00 pm

Discussion of collaborations with NCTR and future meetings

4:00 pm

Adjournment