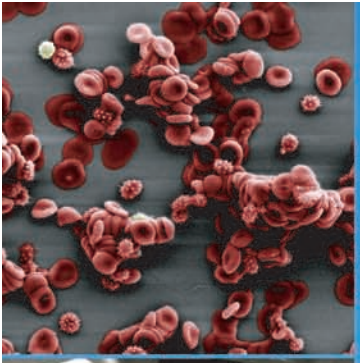

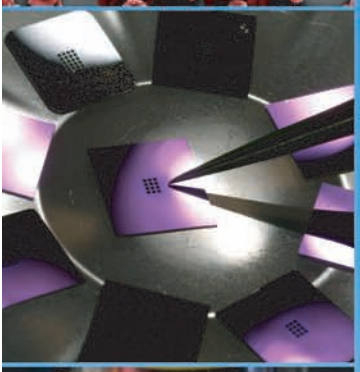

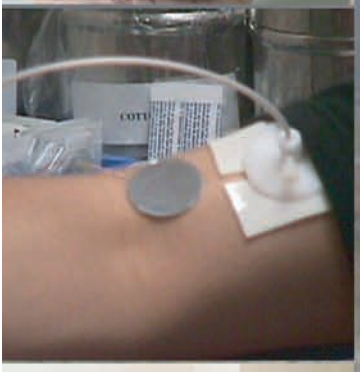

Improving Health Care Accessibility Through Point-of-Care Technologies

A Workshop Sponsored by
the National Institute of Biomedical Imaging and Bioengineering
the National Heart, Lung, and Blood Institute
and the National Science Foundation

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The organizers would like to thank Drs. John McDevitt (University of Texas at Austin), Rinat Esenaliev (University of Texas Medical Branch), Rebecca Richards-Kortum (Rice University), and Fei Wang (NIBIB) for submission of images used in the production of the workshop poster and cover art for the program booklet. Special thanks go to Dr. Wang for the design of the workshop poster.

National Institute of Biomedical Imaging and Bioengineering

Department of Health and Human Services
National Institutes of Health

Welcome to the workshop on "Improving Health Care Accessibility Through Point-of-Care Technologies." The meeting is jointly sponsored by the National Institutes of Health (National Institute of Biomedical Imaging and Bioengineering and National Heart, Lung, and Blood Institute) and the National Science Foundation. Each of these sponsoring agencies has an interest in evaluating the potential role that point-of-care testing can play in addressing many of the Nation's current health care challenges, including, among others, management of chronic illness, reduction of health care costs, improvements in accessibility and quality, and provision of care for an aging population.

As such, the goal of the workshop is to bring together technology developers, clinical researchers, and clinicians to assess the technological developments required for advances in point-of-care testing and to identify high-priority clinical problems that can benefit from a point-of-care approach. The workshop is structured around a "systems" perspective, both technology-based systems and the health care system as a whole, to reflect the belief that changing the way health care is delivered will lead to significant improvements in quality, accessibility, and cost of services.

The meeting will include oral and poster presentations on the state of the science in relevant technology areas, including sensors and lab-on-a-chip devices, noninvasive and minimally invasive patient monitoring, low-cost imaging, health informatics, and telehealth. In addition, leading clinicians and clinical researchers will provide insight into pressing clinical needs in health care settings with the potential for greatest impact on accessibility, specifically primary care, emergency medical services, home health care, and developing countries. Industry representatives will address broadly their perspectives on the barriers to commercialization of point-of-care technologies and the challenges and opportunities associated with working at the technology/clinical interface. The meeting will close with a discussion of the role of evidence in policy decisions and with a summary of community recommendations for advancing the field of point-of-care testing.

We are excited to be able to provide this comprehensive overview of the topic of point-of-care testing and hope you enjoy the meeting.

Brenda Korte, Ph.D.
On behalf of the Organizing Committee

Agenda

Speaker Abstracts

The Role of Point-of-Care Testing in Improving Health Outcomes

Christopher P. Price

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Point-of-care testing (POCT) can be defined as testing performed close to the patient, at the time care is required. The result should enable a clinical decision to be made, leading to some form of clinical action (e.g., treatment being given). For POCT to be effective, the combination of the test result, the decision, and the action should lead to an improved health outcome. POCT includes self-testing as well as testing being performed by a caregiver. The test may be used in screening for disease, ruling in or ruling out a diagnosis, identifying the appropriate treatment, optimizing and assessing compliance with treatment, and assessing prognosis. Most POCT today is performed either (1) as a clinical emergency (e.g., in a patient with chest pain), (2) to improve the efficiency of triage through the health care system (e.g., enabling day case surgery), or (3) to improve the effectiveness of the doctor/patient relationship (e.g., in long-term disease management, as in the case of assessing glycemic control at the annual review). The health outcome or benefit can be measured in terms of clinical, operational, and economic benefit, which can be viewed from the perspective of the patient, the physician, or other caregiver, the provider organization, or the purchaser organization. While the ultimate outcomes are measured in terms of morbidity, mortality, and the cost of health care, it is possible to assess the utility of POCT through a number of surrogate measures that reflect the disease status (e.g., improved glycemic control), reduced length of stay in hospital, reduced clinic visits, reduced pharmaceutical requirement, etc. All of these objectives are dependent on the quality of POCT being maintained. These considerations should be viewed in the context of the way in which health care is delivered and the societal goals of improving health and containing the cost of health care.

Technology for Point-of-Care Testing: Issues and Implementation

Larry J. Kricka

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Technology for point-of-care testing (POCT) (e.g., testing in the home, pharmacy, workplace, doctor's office, clinic, hospital) has evolved quickly from the early tablet tests to dipsticks to the current range of all-in-one tests. Samples for POCT include expired air (alcohol), saliva (HIV antibody test), urine (hCG), ocular fluid (glucose), and blood (glucose). Sampling methods include noninvasive (IR measurements), minimally invasive (access to interstitial fluid), and invasive (surgical implanted sensors). Eliminating the need for a sample and sampling is desirable and much effort is directed toward direct methods based on IR sensing. Most of the current POCT methods rely on enzymatic and immunochemical reactions to detect analytes. Qualitative tests utilize visual inspection of color formation, and quantitative tests employ a handheld meter to give a "number." Ensuring test reliability and removing operator dependence are key considerations. Most tests include controls, and end-of-test and invalid test indicators. Interpretation has been simplified by designing tests to give a simple "plus" or "minus" result or to give a direct message to the operator (i.e., "pregnant" or "not pregnant"). General requirements for a POCT are ease of use, self-calibrating, access can be restricted via lock-outs (prevent unauthorized use), and connectivity for data downloads. The latter is particularly important in the context of telehealth applications. The proliferation and types of POCT testing may pose ethical issues, as in the case of POCT genetic tests and tests for infectious agents (illicit testing and misuse of information).

Other issues for POCT include regulation and reimbursement for testing, and cost-effectiveness. Many technologies continue to emerge for POCT, but often the true potential of a new technology cannot be assessed because of inadequate validation with real samples in a clinically relevant environment.

Integrated Lab-on-a-Chip Devices for Point-of-Care Diagnostics

John T. McDevitt, Nicolaos Christodoulides, Pierre N. Floriano

Department of Chemistry and Biochemistry, Center for Nano and Molecular Science and Technology, Texas Materials Institute, The University of Texas at Austin, Austin, TX

Over the past five decades, the microelectronics industry has sustained tremendous growth and has become what is arguably the most dominant industrial sector for our society. However, recently it has become clear that this industry will face new challenges as component device feature sizes shrink into the nano-size regime. However, with the challenge comes the opportunity to develop a number of fascinating new sensors and devices. Accordingly, new nano-materials and nano-device concepts are combined in this program so as to develop a suite of customized diagnostic assays that can operate at the point of care with reduced cost. In spite of their ultra-small size and low cost, these now-proven micro-sensor systems exhibit excellent performance characteristics and compare favorably to their modern, expensive counterparts. Recent activities have led to the development of methods suitable for the creation of chemically tailored nano-pockets that are localized in the interior regions of bead “micro-reactors.” Tailored antibody and molecular reagents line these novel structures to create a series of miniaturized reaction vessels. These systems can be used to create integrated separation, collection, and detection ensembles that serve as the basis for eliminating their laboratory-confined counterparts. Micro-bead arrays bridge the nanometer to micrometer ranges and allow information to flow quickly and efficiently from the micro- to the macro-scale with the aid of digital video chips and associated transfer optics. The collected aggregated digitized data can be analyzed at remote central sites and then used to enable more effective health management as well as aid in the early identification of various global health syndromes. Methods traditionally used in the microelectronics industry to generate electronic devices have been adapted for the creation of these novel nano-bio-chip devices.

Acute Care Blood Testing at the Point of Care

Imants R. Lauks

Epocal Inc., Ottawa, Ontario, Canada

Foremost of the design considerations for a useful point-of-care device is the knowledge that the point-of-care user does not typically have laboratory training, and the patient-side blood testing environment is far more chaotic than the controlled laboratory environment. Accordingly the point-of-care product must be designed to achieve the laboratory's standard of analytical performance and be far more robust than a typical laboratory analyzer might have to be.

I will describe my experiences in the design of such products and their use at the point of care. The presentation will include information on work during the 1990s in development and deployment of the i-STAT System as well as new point-of-care products being developed at Epocal.

The focus of Epocal's activity has been to achieve the target performance in a product used at the patient bedside, but in a more cost-effective manner. For broad adoption of bedside blood testing in acute care, the product cost cannot be at a large premium relative to the cost of the laboratory alternative. The cost per test for a bedside device includes the cost of reagents and instrumentation and the labor costs associated with the point-of-care process.

Addressing reagent costs, I will compare and contrast devices based on chip technology to those based on flex (smart card like test cards). Addressing instrument cost, I will contrast traditional designs, which are based on a complete analyzer at each bedside, with a modular approach using de-featured card-reader peripherals. I will also discuss elements of system design that automate and reduce the cost of activities currently performed at the institution to support the point-of care activity.

Point-of-Care Testing for ACS, Heart Failure, and Drug Overdose in the Emergency Room

Kenneth F. Buechler, Joseph Anderberg, Steve Lesefko, Kevin Nakamura, Paul McPherson

Biosite, Inc., San Diego, CA

Patients who present to the emergency departments with life-threatening conditions require immediate attention to improve outcomes and save lives. We have developed a point-of-care (POC) immunoassay system, the Triage Meter system, which measures peptides, proteins, and small molecules in about 15 minutes. The Triage system comprises a portable battery-powered fluorometer, the Triage Meter, and a protein chip, the Triage device. The protein chip can measure single biomarkers or multiple biomarkers simultaneously. To perform the tests, the user adds several drops of EDTA anti-coagulated whole blood, plasma, or urine to the device and inserts it into the Triage Meter. The device incorporates novel concepts of capillarity and defined surface architectures to drive and control fluid flow during the immunoassay. The fluorescent label comprises two phthalocyanine derivatives incorporated into microparticles at concentrations that allow the dyes to exhibit fluorescence energy transfer. The donor dye is excited at 670 nm and the acceptor dye fluoresces at 760 nm. The concentrations of the biomarkers are read from the meter display or they can be printed. The markers comprising a panel are selected in a discovery phase to optimize the ROC curve area of a diagnostic or prognostic condition. The MultiMarker Index (MMX) will be described and is a single value calculated from an algorithm derived from clinical data. The MMX is the summation of the products of the marker concentration transfer functions, and weighting factors. The Triage CardioProfilER is a panel of markers comprising B-type natriuretic peptide, troponin I and complexes, CKMB and myoglobin. Data will be presented relating to the diagnostic and prognostic performance of the panel and on the performance of the panel utilizing MMX when myeloperoxidase and a new, undisclosed marker are added, and compared to troponin I.

The Founding of TheraSense

Adam Heller

Department of Chemical Engineering, The University of Texas at Austin, Austin, TX

TheraSense, Inc., was acquired in 2004 by Abbott Laboratories for $1.2 billion. TheraSense, now Abbott Diabetes Care, manufactures and sells worldwide a glucose monitor (*FreeStyle*™*)* for the management of diabetes. It uses only 300 nL of blood; a sample is small enough to be painlessly obtained. The core of *FreeStyle*™ is a microcoulometer in which glucose is electro-oxidized. It is the smallest mass-manufactured fluidic device. Because results of coulometry do not change with temperature, blood viscosity, or enzyme activity, *FreeStyle*™ is not only painless but also most accurate.

Abbott Diabetes Care is now planning to introduce a miniature, continuous, painlessly subcutaneously implanted, amperometric glucose monitor, replaced by the user about twice a week, also developed by TheraSense. The monitor is based on the electrical wiring of enzymes, a technology created at The University of Texas. TheraSense was originally founded on this technology in 1996 by my son, Ephraim Heller, who later conceived *FreeStyle*™. The enzyme wires are electron-conducting redox hydrogels. The flux of glucose is converted to the actually monitored electrical current in the wired glucose oxidase film of the implanted sensor.

In combination with an insulin pump, a processor, and an all important medical algorithm, the continuous monitor should provide in the future the artificial pancreas long sought by diabetic people. It would constitute one of the first examples of a drug-administering medical feedback loop, tailored to the individual user.

Important Clinical Targets for Noninvasive Monitoring

Donald S. Prough

Department of Anesthesiology, The University of Texas Medical Branch, Galveston, TX

A new noninvasive or minimally invasive monitor should have four important characteristics: (1) It should monitor a variable that strongly influences clinical outcome. (2) The variable must be subject to rapid change. (3) Appropriate interventions must be available to alter the variable. (4) A successful monitor must be user friendly. Several promising targets for noninvasive monitoring meet the first three characteristics; engineering must achieve the fourth characteristic.

Promising targets include total hemoglobin concentration (THb), concentration of hemoglobin derivatives such as carboxyhemoglobin (HbCO) and methemoglobin (HbMet), venous oxygenation (HbOxy), glucose concentration (glu), circulating blood volume (BV), cardiac output (CO) and index (CI), systemic oxygen delivery (DO_2), and hepatic perfusion and function. At present, these parameters require either blood sampling or insertion of invasive catheters.

Hematocrit and THb are the most frequently measured blood tests in both outpatients and inpatients. Chronically ill patients in whom THb is frequently measured include those with chronic renal failure and those undergoing chemotherapy for malignancy. THb is also closely monitored in acute medical and surgical illnesses that cause blood loss. The concentrations of hemoglobin derivatives such as HbCO and HbMet are important in emergency situations such as smoke inhalation and carbon monoxide poisoning.

Venous HbOxy reflects the ability of oxygen supply to meet oxygen demand in the body as a whole or in individual organs and has proven utility in several clinical situations, including sepsis and critical neurologic and neurologic illnesses.

The importance of glu monitoring in diabetics and nondiabetic patients is well recognized. In patients with diabetes, effective control of glu limits the complications of the disease. In 1,548 patients (87% of whom were nondiabetic) randomized to receive conventional management or intensive insulin therapy to tightly control glu between 80 and 110 mg/dL, intensive insulin therapy reduced mortality by more than 40% (from 8.0% to 4.6%) but carried a 5.0% risk of inducing severe hypoglycemia (glu < 40 mg/dL).

Quantification of indocyanine concentrations (ICG) can quantify BV, CO, CI (CO divided by body surface area), and hepatic clearance of ICG as an index of hepatic perfusion. Measurement of CI, THb, and HbOxy permits calculation of DO_2, which is a powerful prognostic indicator in critically ill patients.

Biomedical Monitoring Using Noninvasive and Minimally Invasive Approaches

Gerard L. Coté

Department of Biomedical Engineering, Texas A&M University, College Station, TX

The objective of this presentation is to provide an overview of some of the noninvasive and minimally invasive diagnostic imaging and sensing techniques being explored. Specifically discussed are ultrasound, parallel magnetic resonance imaging (MRI), and optical sensing and imaging methods. Emphasis will be placed on using these technologies toward point-of-care (POC) monitoring. Since the pulse oximeter, the optical approaches leading the way in terms of POC monitoring research have been those that focus on noninvasive and minimally invasive glucose monitoring. The approaches that will be mentioned here include infrared absorption spectroscopy and fluorescence spectroscopy for in vitro and in vivo monitoring of glucose and other analytes. In addition, surface-enhanced Raman spectroscopy for use as an in vitro platform for beta-amyloid detection in Alzheimer's disease will be presented. The vision put forward in this presentation for the MRI field with respect to POC monitoring is twofold: (1) The combination of low-cost MRI and the potential to image in inhomogeneous fields will be necessary to successfully diagnose patients at the bedside with this technology.
(2) Integrating MRI into lab-on-a-chip using new compact magnet technology could enhance point-of-care blood monitoring. In terms of ultrasound, several small, light-weight, and inexpensive POC echocardiography devices have recently become available. These devices could potentially make echocardiography available to many more physicians at the bedside. It has been reported that even medical house staff, with limited training in echocardiography, can use POC echocardiography for assessment of left ventricular function and pericardial effusion with moderate accuracy only slightly lower than that of standard echocardiography. Assessment of valvular disease and other diagnoses, however, would likely require more training and/or experience in echocardiography.

Noninvasive Monitoring With Novel, High-Resolution Optical Techniques

Rinat O. Esenaliev

Laboratory for Optical Sensing and Monitoring, Center for Biomedical Engineering, Department of Neuroscience and Cell Biology, Department of Anesthesiology, The University of Texas Medical Branch, Galveston, TX

Optoacoustics and optical coherence tomography (OCT) were recently proposed for high-resolution imaging in tissues. Optoacoustics is based on detection of ultrasound induced by short optical pulses and utilizes absorption contrast in tissues. It has a resolution of 0.2 mm and a probing depth of up to several centimeters. OCT is based on detection of backscattered low-coherent light and utilizes scattering contrast in tissues. It has a resolution of 1-15 μm and a probing depth of about 1 mm. Recently, we proposed to use these techniques for noninvasive, accurate, and continuous monitoring of a variety of physiological parameters including cerebral blood oxygenation and total hemoglobin concentration (optoacoustics) as well as blood glucose concentration (OCT). High resolution of these techniques allows for probing specific tissues: blood vessels (optoacoustics) and skin layers (OCT). This may provide noninvasive monitoring of the blood analytes with high accuracy, sensitivity, and specificity. We performed phantom, in vitro, animal, and clinical tests of these techniques. The results of the tests are encouraging. Optoacoustic and OCT signal parameters are linearly dependent on concentration of the blood analytes that may provide noninvasive monitoring with clinically acceptable accuracy. In this talk we will discuss the progress, achievements, and difficulties we faced during the development of these noninvasive techniques from idea to clinical tests. Moreover, we will discuss potential applications of these techniques for noninvasive monitoring of other physiological parameters including circulating blood volume, cardiac output and index, oxygen delivery, and concentration of hemoglobin derivatives such as carboxyhemoglobin and methemoglobin.

Overcoming Barriers in the Manufacture of Small Components and Devices

Kornel Ehmann

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The explosion of micro-scale products in markets including health care, communications, and electronics has the potential to significantly improve our quality of life. The health care field alone has seen major advances in diagnostic devices, cardiovascular system remediation, and noninvasive surgery. But for competitive product realization to keep pace with nano- and micro-scale science and technology, a new paradigm for manufacturing—micro-manufacturing—must emerge, rooted in the very technologies that it addresses. Micro-manufacturing in the context of this presentation is defined as the manufacture of high-precision components and products in the sub-millimeter to a few-millimeters range with micron-size feature characteristics in a wide range of materials by nonlithography-based processes. The presentation will address three topics: (1) The manufacturing technology needs imposed by product miniaturization are defined along with existing scientific, technological, and commercialization barriers. It will be shown that micro-manufacturing can become an enabler for a number of distributed manufacturing scenarios for producing devices at the point of use. (2) The findings of a worldwide study on micro-manufacturing, conducted by the World Technology Evaluation Center under the sponsorship of the National Science Foundation, National Institute of Standards and Technology, Office of Naval Research, and U.S. Department of Defense will be summarized. The summary is based on visits to over 50 industries, leading universities, and laboratories in Asia and Europe. The results of these visits are highlighted with an eye toward assessing both relative progress and needed directions in micro-manufacturing R&D here in the United States. (3) The potential impact of the evolving technological trend toward the miniaturization of manufacturing processes and equipment and their integration into autonomous desktop factories on point-of-care technologies will be discussed.

Cervical Screening in China by Automated Image Cytometry

Branko Palcic

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Screening for early cancer and precancerous lesions of the uterine cervix has been proven to save lives of women in their prime years. To achieve the best results, the screening must be implemented for the whole population, which requires building a very large infrastructure as well as training a sufficient number of highly skilled specialists.

Although in China today there are several excellent programs in large cities for screening of cervical cancer and precancerous lesions of the cervix, these programs cover only a very minute population of China. To achieve a significant reduction of the incidence of invasive cervical cancer with concomitant reduction in the death rate due to this malignancy, a population-based screening program would have to be instituted reaching all women at risk in this country of 1.5 billion inhabitants. It has been estimated that for a conventional approach, it would take at least two to three decades to build the required infrastructure and to train a sufficient number of the required technologists. It was thus decided to employ newly developed technology based on detecting cells with a very high level of DNA content by fully automated image cytometers that could be implemented in a much shorter period of time, allowing cervical screening for at least one-third of China in the shortest possible time.

At present, in a period of 1 year, over 10 laboratories have been set up in different regions of China with the capacity to process close to 500,000 samples per year. The up-to-date experience of this approach to population-based cervical screening will be discussed.

Multifunctional Optical Imaging Agents for Point-of-Care Diagnosis and Testing

Stephen A. Boppart

Departments of Electrical Engineering, Bioengineering, and Medicine, Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign, Urbana, IL

Advances in imaging technologies are enabling the detection and diagnosis of disease at earlier stages. Optical detection and imaging methods can offer molecular and cellular imaging capabilities in a potentially compact and portable instrument for point-of-care diagnosis and testing. Recent developments in novel optical molecular imaging contrast and therapeutic agents and methods have expanded the diagnostic capabilities of modalities such as optical coherence tomography, confocal microscopy, and spectroscopy.

Medical Information Bus Concepts for Collecting Clinical Patient Data From the Intensive Care Unit and Other Acutely Ill Patients

Reed M. Gardner, David K. Vawdrey

Department of Medical Informatics, University of Utah School of Medicine, Salt Lake City, UT

Gathering and recording patient data is a fundamental responsibility of all care providers, be they physicians, physician assistants, nurses, medical records clerks, geneticists, laboratory technologists, etc. In today's world of electronic health records (EHRs) and computer-assisted decision-support technologies, gathering and recording structured and coded data into a machine-understandable format is even more crucial. However, converting a medical care culture that has been trained with handwritten, paper-based record systems continues to be a challenge.

Gathering quantitative and structured data at times requires more time and effort for caregivers than just handwriting a shorthand note. Therefore, it is crucial that we optimize gathering at "point of care" from devices and instruments. Over two decades ago, the problem of having nurses "read" data from bedside patient monitors in intensive care units (ICUs) and "hand-keying" them into a computerized record was recognized. As a consequence, the Medical Information Bus (MIB) also known as IEEE 1073 was developed. Using the MIB standard, data from bedside monitors, IV pumps, ventilators, and bedside laboratory testing devices are now collected automatically. With the MIB, ICU patient data-gathering is more timely, accurate, and efficient.

As more data are collected from patients in the home, clinic, or other outpatient settings, technologies similar to the MIB should be developed to allow integration of a patient's data independent of where the patient is physically located. Today, many patients have blood pressure measurement instruments, blood glucose meters, and other devices at home. In the future, even more instruments will be developed that will allow much of the patient's data to be collected automatically. Using these automated "point-of-care" modalities to optimize patient benefit will require automated gathering of these data independent of where a patient is located. Lessons learned using the MIB in the ICU will be described.

Health Data Collection in Resource-Constrained Environments: Real-World Implementation Issues

Paul G. Biondich

Regenstrief Institute, Indianapolis, IN

One of the most challenging aspects of providing health care in resource-constrained environments is finding efficient, workflow-friendly mechanisms to collect clinical data. We will describe two clinical environments, a high-volume urban pediatric outpatient clinic and an HIV clinic in sub-Saharan Africa, and how successful data collection implementations were built by tailoring solutions to workflows. We will also discuss specific issues that both of these implementations now face as they scale up.

Communications for Rural Health Care

Eric Brewer

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We focus on communications options for rural areas of developing regions. We discuss cellular networks, intermittent networks, and long-distance video links. Intermittent networks move data in several steps, such as onto a bus and then later from the bus to a wireless access point. The connectivity is not interactive but can reach very remote places and is sufficient for e-mail and data collection. Finally, we present telemedicine results using low-cost long-distance links in India. These links connect an Aravind Eye Hospital to a set of rural health centers typically 20 km away.

The Potential of Point-of-Care Testing To Revitalize Primary Care Office Practice

John M. Hickner

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There are three needs in primary care that will drive innovation in point-of-care testing in primary care venues. These are the need to improve quality of care, the need for improved financial viability of primary care practices, and the need to improve health outcomes of the population. The author's thesis is that improved point-of-care testing will expand the scope of practice of primary care providers, thereby improving quality and financial vitality. Point-of-care testing improves the efficiency of care and may improve the accuracy of diagnosis and safety as well. Specific examples will be presented that encompass care of acute illnesses, management of chronic diseases, and prevention. Following are some of the specifications that will be important in designing point-of-care testing instrumentation for primary care offices: Test results from the testing unit must transfer electronically and automatically to the patient's electronic medical record; equipment should have a small footprint, be easy to operate and maintain, and have easy-to-follow quality control checks; and results of testing performed in a patient's home or via home health care must transfer electronically and automatically to the patient's electronic medical record. Finally, there is great potential for low-cost imaging techniques for diagnosis and monitoring in primary care offices.

Emergency Medical Services: Needs and Opportunities in Point-of-Care Testing

Robert M. Domeier

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Emergency medical services (EMS) are performed in a wide variety of environmental, clinical, and geographic settings. Traditional EMS starts with a 911 call followed by ground ambulance dispatch, patient evaluation, treatment by EMS personnel, and transport to a hospital facility. EMS patients may be transported by ground or air.

Patient complaints and conditions vary widely, with a skew toward higher acuity of illness and injury than seen in an average emergency department. Time available for EMS patient evaluation and treatment (E&T) varies on the basis of geography and patient condition. Rural patients have longer transport times and more opportunity for E&T than do urban patients. Some conditions, e.g., asthma, allow for more in-home patient contact time than do conditions with time-limited treatments, e.g., acute myocardial infarction (AMI). Some conditions require immediate intervention without significant time for evaluation, e.g., cardiac arrest. Within this framework, many opportunities exist for new and improved point-of-care testing (POCT).

Monitoring patient vital signs and cardiac rhythms, including newer EMS AMI diagnostic techniques, is an important part of modern EMS. These POCT technologies have significantly less effectiveness in moving vehicles. There is also a need for specialty monitoring and diagnostic sensors. Sensors to detect abnormal hemoglobin could help in the diagnosis and treatment of certain life-threatening conditions. The measurement of other serum components and characteristics including lactate and coagulation properties could also be of benefit.

In this era of concern over terrorist threats, EMS has the need for radiological, chemical, and biologic sensors and technologies that can assist in identifying safe and contaminated areas, thoroughly decontaminating patients, and determining the need for various potential antidotes.

Within the world of EMS there exist many areas of need and opportunity for POCT. Efforts to develop these technologies could benefit a large number of patients.

The Many Faces of Home Point-of-Care Monitoring

Justin Starren

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When point-of-care testing in the home is discussed, it is often assumed that this is a homogeneous concept. In reality, health care in the home is a varied and diverse activity. There are several different health care scenarios that have relatively little in common, except that they all happen to occur in the home. First is the self-managed patient. In this scenario, the patient typically purchases the device and interprets the result. The most common example would be taking one's temperature when one feels ill. The second scenario involves traditional home nursing. In this scenario, a trained medical professional brings the device to the home. It may be used by the nurse during the visit or left behind for continued monitoring. The patient does virtually no interpretation of the data. The third scenario involves disease management. In this case, a third party (insurance or employer) contracts for disease monitoring with a centralized resource. This monitoring typically focuses on the sickest and most expensive patients with a chronic disease. Because the contracts are cost per member per year, the choice of inexpensive solutions is critical. Fourth is the chronic care scenario. In this case, the patient's primary provider is managing a chronic disease. The current use of glucose monitoring in diabetes is an example of this. The physician may suggest a specific device, but the patient typically purchases the actual device. Finally, there is growing interest in personal health records (PHRs). Home POC testing devices could be viewed as an extension of the PHR. The readings from the monitoring devices would be just one more data type in the PHR. Each of these scenarios has subtle but critical differences in the importance of cost, connectivity, data interpretation, usability, and accuracy. As a result, when designing POC testing for the home, it is necessary to design for a specific scenario, not just for "the home."

Use of Point-of-Care Testing in Home Health Care: Opportunities and Challenges

Carolyn R. Krause

Wisconsin Center for Nursing, Waukesha, WI

In the context of the home health care agency, point-of-care testing (POCT) technologies are multifaceted and used in a care system that supplements onsite nursing visits with the technology. Use of POCT, including telehealth monitoring, within an agency structure, has the potential to improve clinical decision-making and outcomes, increase patients' self-management of their disease, increase productivity of the home care nurse, reduce overall cost of care, improve patient satisfaction, and increase communication and collaboration between physicians and nurses. However, in order for successful implementation of POCT, the environment and culture of the home care agency must be adequately prepared to accept changes in traditional methods of practice. In addition, for some types of technology, a significant amount of capital and additional human resources are required and direct reimbursement is rare. Systems to manage and maintain the technology must be established, protocols and procedures for use must be developed, and understanding and incorporating the principles of behavior change are essential for successful implementation.

Disease Management: A Quantum Leap in Quality Improvement

Maureen A. Dailey

Dailey Solutions, Rockville Centre, NY

The four pillars of complex disease management (DM) include population stratification, evidence-based protocols, aggressive clinical management, and outcomes tracking and analysis. DM providers have implemented platforms that integrate data, patient point-of-care technology, and evidence-based clinician cueing to reduce errors of commission and omission. The results are timely interdisciplinary coordination to improve care processes and end outcomes. DM providers utilize risk-based, evidence-based protocols to effectively focus interventions to reduce avoidable adverse events (e.g., rehospitalization), empower patients in self-care, and reduce cost. The Disease Management Association of America (DMAA, 2005) has defined DM "as a system of coordinated healthcare interventions and communications for populations with conditions in which patient self-care efforts are significant." DMAA and accrediting agencies have illuminated DM terminology, essential program components, and rigorous evaluation methodologies. DM stakeholders have identified how DM programs contribute to meeting the full six Institute of Medicine aims for chronic DM and other complex management (e.g., wound care). The Medicare Health Support pilots (>100,000 clients enrolled) are facilitating systems development and interorganizational collaboration via incentives alignment. Payers, academic and community-based interdisciplinary providers, and DM providers are integrating point-of-care technologies and bridging interoperability, security, and cost barriers as feasible. Medicaid, Medicare, and commercial DM programs use telehealth, telenursing, and other disciplines to successfully:

- Overcome barriers to care management (i.e., geographic, emotional, physical disability, or caregiver shortage, etc.).
- Promote improved patient self-care and caregiver adherence via education, skill training, and support.
- Integrate use of devices for timely, efficient point-of-care monitoring, such as weight, peak flow, blood glucose, vital signs, etc.
- Provide timely patient-centered care, assisting patients to recognize early signs of exacerbation and take action to prevent avoidable adverse events.
- Reduce social isolation and anxiety, provide depression/anxiety screening, and identify and coordinate needed followup care.

Patient Portals: Connecting Clinicians and Patients at Home

James Ralston

Center for Health Studies, Group Health Cooperative, Seattle WA

Current health care systems, with their focus on the office visit, do not meet the needs of many patients. Patient Web portals with shared and interactive medical records can extend care from the office into the daily lives of patients. In this session, I will describe two patient Web portals that inform the emerging role of shared and interactive electronic medical records between patients and health care providers.

The "Self-Managed" Patient

Patricia Flatley Brennan

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Contemporary health care demands that lay people become active participants in health and health care. Active participation in health includes engagement in self- help and self-care activities, guided by personal awareness or health education and training. Active participation in health care includes the range of disease management activities, from medication adherence to self-monitoring, that occur in concert with the ministrations of health care providers. Self-management by individuals results from a complex interplay between personal health beliefs, recommendations from clinicians, and health knowledge gleaned from a variety of sources. Effective deployment of point-of-care technologies requires systematic integration of the findings from fields like psychology and nursing that provide guidance about how to engage individuals in healthy living.

Yet evidence suggests that in many households, health management is a responsibility shared by several individuals. Personal health and health information management requires a range of tasks, some familiar and some not so familiar, that are heavily shaped by the patient's health state, their personal care team strategies, and extent of engagement in the health care system. Findings from our group's study of Health@Home reveals important insights.

Lay people develop robust, rich strategies for managing health information in the home. Work by Brennan and colleagues (see reference) explored the personal health information management challenges faced by 49 community-dwelling adults. The study documented that most households handle 8-10 different types of health information, including treatment advice and instructions, insurance claim forms, appointments and clinical contact data, and general health resources and health promotion information. Although physicians and clinics were the most common sources of information, lay people also valued health information they received from family and friends, local news reports, and the public library. The family calendar served as a common health information management tool, as did binders, file drawers, and, occasionally, computerized files. Importantly, in more than two-thirds of the households, a single member, usually a woman, served as the primary health information manager. Thus, "self management" may be a shared task, and "patients" may include a broad range of individuals, sick or well, who can effectively use point-of-care technologies to achieve their health goals.

Reference

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Improving Health Care Accessibility Through Point-of-Care Technologies: Issues From the IVD Industry Perspective

Paul D'Orazio

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From the IVD industry perspective, there are several considerations when developing new technology/devices for point-of-care testing (POCT).

Technology Assessment. Collaboration between industry and academia is an attractive way to move promising new technologies from the research laboratory to commercialization. Beyond proof of concept, there are important requirements for a successful technology transfer from academia to industry. Primary among these is early demonstration that the technology/device is manufacturable in a desired format (e.g., unit use disposable, reusable device, etc.) in a cost-effective manner.

Regulatory Considerations. All testing sites performing POCT are subject to the CLIA 1988 requirements for quality control testing and are inspected to determine compliance. These can be burdensome requirements for POCT locations, whose primary function is patient care. In response to user needs, manufacturers have developed embedded quality control systems for POCT systems, to replace testing of external control materials. Although proven effective in mitigating risk, many of these alternative quality control schemes are not in compliance with current regulations, presenting an obstacle to implementation. Acceptance of manufacturer-recommended QC programs would require a collaborative effort between manufacturers, end users, and regulatory agencies, and a reassessment of the current regulations.

Understanding and Meeting User Requirements. Users have indicated that the most important factors in point-of-care instrument selection and implementation are (1) reliability, (2) ability to use whole blood as the sample (if whole blood is the applicable sample type), and (3) data transfer capability to the LIS/HIS (see reference). Reliability may include analytical performance of POC systems equivalent to traditional systems found in the core laboratory (for quantitative testing), fool-proof system performance in the hands of nonlaboratory personnel, and requirements for little or no instrument maintenance and downtime. POCT for in vitro diagnostics is an expanding delivery option because of increased pressure for faster test results. From the end-user perspective, POCT should not simply be used as a replacement for the central laboratory without evaluation of the effect of a faster result on patient care. To this end, the National Academy of Clinical Biochemistry has published guidelines that state, "The value of POCT really needs to be demonstrated through well-designed randomized control trials." The same guideline concludes that such studies, linking POCT to improved patient outcomes, are generally lacking in the clinical literature. Any support to the end-users from industry, funding agencies, etc. in developing this type of evidence would provide real impetus to the growth of point-of-care testing.

Reference

2004 US Hospitals Point-of-Care Survey, Enterprise Analysis Corp., Stamford, CT, November 2004.

Bedside Monitoring: An Industry Perspective

George M. Hutchinson[1], Pekka T. Merilainen[2]

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The point-of-care nature of patient monitors that obtain and display physiologic information at the bedside is self-evident. The direction it will take is less obvious. While noninvasive methods for obtaining physiologic information will continue to be pursued, the industry will likely acknowledge that many monitoring modalities will probably best be solved in a minimally invasive manner. Currently, traditional monitoring focuses on cardiovascular, respiratory, and, more recently, neurological systems. Advances in techniques of biochemical real-time or periodic analysis will open a new view into disease processes. Being mindful of parameter-level artifact rejection and data quality indices, the integration of traditional monitoring and biochemical analysis into information systems becomes realizable. These pieces all exist and can be brought together for meaningful improvements in patient care.

The genuine academic cross-disciplinary collaboration between researchers of industry, universities, and hospitals is an essential basis for all the success stories in this endeavor. How this works in practice varies country by country partly because of differences in regulatory and legal systems and partly because of cultural and health care system differences. In countries like Finland, government actively supports this kind of collaboration with financing schemes that can be either industry or university driven. Major companies have their internal research groups that talk the same language as academic groups. The only issues related to collaboration are around the intellectual property rights and ownership of results. Keeping these under control requires continuous involvement of well-informed and cooperative legal people for navigating between different interests of the teams: publish or perish versus patent or perish!

Telehealth Services to the Home: The Time Has Come

Dena S. Puskin

Office for the Advancement of Telehealth, Health Resources and Services Administration, U.S. Department of Health and Human Services, Rockville, MD

This session will discuss the recent expansion of telehealth services to individuals in residential settings and the experience of grantees funded by the Office for the Advancement of Telehealth. Emphasis will be placed on lessons learned and current challenges to the field.

Imaging and Point-of-Care Technologies

Kai Erik Thomenius

GE Global Research, Niskayuna, NY

While the expression “point-of-care technologies” does not typically bring to mind medical imaging devices, the recent progress in that field has brought about miniaturization to the degree that this possibility must be considered. This discussion will review some of the developments in the area. Ultrasound imaging has advanced perhaps the farthest and possible applications will be discussed. The technical trends driving the modality to smaller sizes that are suitable for the bedside or a family practitioner’s office will be discussed along with those areas requiring additional research. Today’s scanners are already laptop sized and the potential for getting the sizes down even further is very real. Along with the size reduction, there is a commensurate cost reduction that enables spread to novel markets. In fact, there is the very real possibility of the use of such devices for patient monitoring.

Two other interesting medical imaging modalities with point-of-care potential are x-ray and optical imaging. While not as advanced as ultrasound, these also give indications of suitability to this application. The digitization of the x-ray image acquisition process is enabling further miniaturization and ease of use, allowing possible point-of-care applications. Optical imaging devices are inherently small in most cases; the need here is more along the lines of test development. The technology trends in these areas will be reviewed along with examples of devices developed for applications such as those in a mobile military hospital.

Point-of-Care Technologies, Telehealth, and Indian Health Care

Mark F. Carroll

Indian Health Service, Flagstaff, AZ

In partnership with Tribes and Tribal health programs, the Indian Health Service delivers health services to more than 1.9 million American Indian and Alaska Native people. These services are provided in more than 600 hospitals, clinics, and health stations located in the most remote regions of the United States. A diverse array of individual, community, and public health care programs support the Indian Health Service mission to raise the physical, mental, social, and spiritual health of American Indian and Alaska Native beneficiaries to the highest level.

Point-of-care services, telehealth, e-health, and related technologies offer new tools for service outreach to Native American communities. This presentation will highlight recent efforts in the Indian Health Service to implement these tools in diverse environments and situations. In particular, clinical needs, and efforts to address these needs using telehealth and point-of-care testing, will be overviewed. Focused activity on training, electronic information systems, and the use of telehealth and point-of-care monitoring in community and home settings will be highlighted. Perspectives on health care system change, business modeling, and collaboration will be briefly shared.

Evidence To Support Policy Decisions on Point-of-Care Testing

Christopher P. Price

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The introduction of point-of-care testing (POCT) should lead to an improved health outcome. Health outcomes are measured in terms of the objectives of maximizing benefit and minimizing risk for individual patients, at reasonable cost. This expresses the outcomes in clinical and economic terms and sets the agenda for the type of studies required to demonstrate the clinical utility of POCT, and the economic consequences. One of the first systematic reviews on POCT found that (1) there were very few publications of satisfactory quality, (2) most of the papers dealt solely with issues of technical quality, and (3) few focused on clinical outcomes. The design of studies on diagnostic procedures is not as well developed as in the case of interventions (e.g., new pharmaceutical interventions). Many studies focus on retrospective comparison between patient and control populations; critically the test result is not part of a decision-making process. Thus, while a randomized controlled study provides the best quality of evidence, and involves the test result in a decision-making process, it is not always possible to avoid bias in the results. Furthermore, when using an objective outcome measure, it may not be possible to ascribe the outcome solely to the use of the test result, i.e., by POCT. In addition, use of POCT invariably requires a change in clinical practice in order to deliver the benefit, e.g., perform the test as part of the consultation and thereby save a clinic visit. It may therefore be better to study a care process in which POCT is included. Policy decisions therefore are multifaceted, covering (1) proof of patient benefit, (2) ability to incorporate change in clinical practice, (3) economic consequences, and (4) ability to reallocate resources and leverage economic benefit.

Center for Devices and Radiological Health Review Practice for Point-of-Care Devices: A Diagnostic Perspective

Arleen F. Pinkos

Office of In Vitro Diagnostic Device Evaluation and Safety, Center for Devices and Radiological Health, U.S. Food and Drug Administration, U.S. Department of Health and Human Services, Rockville, MD

There are many things to think about when developing a product to be used for medical purposes, Federal regulations being just one of them. Most medical devices must be approved by the U.S. Food and Drug Administration (FDA) before they may be marketed. Although each device is unique, there are common elements considered by FDA while reviewing every type of product. Whether a device is simple in design or employs a more complex noninvasive or lab-on-a-chip technology, the types of studies and other requirements are similar. Understanding the Code of Federal Regulations, the processes employed, and the resources available will help innovative technologies reach the public faster. Topics that will be discussed include the driving force of a review, how to demonstrate that a device is safe and effective, how a point-of-care claim affects study requirements, the importance of human factors and risk mitigation, unique considerations, and the Clinical Laboratory Improvement Amendments (CLIA).

Regulation of Point-of-Care Medical Devices

Anthony D. Watson

General Hospital Devices Branch, Center for Devices and Radiological Health, U.S. Food and Drug Administration, U.S. Department of Health and Human Services, Rockville, MD

With technology becoming more and more user-friendly, caregivers and technology developers are preparing for a health care paradigm that is more patient-driven. As the paradigm shifts from hospital-centered patient care to home-based patient care, the U.S. Food and Drug Administration (FDA) is faced with challenging regulatory questions. The agency must develop a framework for regulating products produced by a diverse industry of software and hardware manufacturers. These products could be medical devices, but many manufacturers are unaware that they are manufacturing medical devices. In addition, the requirements for medical device development may require novel testing methods that are based not only on the technology but also on the intended use of the products as well, a somewhat different mindset for technology developers. Human factors considerations and rigorous quality software development processes are essential to ensuring safe and effective point-of-care technologies. Early communication with FDA can avoid costly pitfalls down the line.

The Medicare Coverage Process

Shamiram Feinglass

Coverage and Analysis Group, Office of Clinical Standards and Quality, Centers for Medicare & Medicaid Services, Baltimore, MD

This talk will discuss how the Centers for Medicare & Medicaid Services uses the evidence to make coverage decisions. The focus will be on how an issue comes to the national level, the differences between local and national coverage, the timeline of the coverage process, and how the coverage process works.

General Abstracts

Medical Applications of a Sensor Technology Using a Microarray of 50-µm Diameter Microcavity With Self-Contained Electrochemistry

Zoraida P. Aguilar

Vegrandis, LLC, Fayetteville, AR

We report our efforts toward the development of automated, rapid, sensitive, portable, low-cost, and reliable bioassays with electrochemical detection for medical applications that relies on our technology involving a chip that contains an array of 16-picoliter geometric volume microcavities with self-contained electrochemistry. The 50-µm diameter (with a depth of 8 µm) microcavity has embedded microelectrodes along its wall and bottom (with the bottom recessed microdisk electrode or RMD at 2 x 10^{-5} cm^2 and the wall tubular nanoband electrode or TNB at 8 x 10^{-8} cm^2) [1]. The microelectrodes in the cavity exhibit lower background signals and zeptomole detection limits. When the RMD is converted into a capture surface, the 4-µm distance to the TNB detecting electrode provides close proximity for a rapid response showing the first signal to be recorded within 30 seconds of enzyme substrate incubation in our mouse IgG studies [2]. The self-contained nature of the microcavity allows for a small volume of samples and reagents down to 200 nL in the unoptimized studies for mouse IgG. It is possible to use reagent volumes as low as the 16-picoliter geometric volume of the microcavity if evaporation can be eliminated.

Our goal is to develop the microcavities into self-contained microelectrochemical lab-on-a-chip (LOC) assay platforms that will integrate the high specificity of selected antibodies and DNA and the sensitivity of the microelectrodes in the microcavity. The self-contained microelectrochemical LOC assay can detect either in a single analyte or multiple analytes in an array assay format by using monoclonal antibodies or capture probes to different analytes for the detection of multiple analytes from a single sample.

Initial research on the application of our technology for the detection of antibody to protective antigen (anti-PA IgG) from *Bacillus anthracis* will be discussed. Using the TNB microelectrode inside the 50-µm diameter microcavity on a chip as the detecting electrode, we have detected as low as 50 ng/mL anti-PA IgG in an ~30-minute total assay time from capture to signal generation.

We will also present our preliminary results in the detection and quantitation of the pathogen *Plasmodium falciparum,* which is one of the causes of 300-500 million cases of malaria worldwide. Using the TNB microelectrode inside the 50-µm diameter microcavity on a chip as the detecting electrode, we have detected as low as 2 ng/mL CSP protein in an immunoassay and 1 ng/mL CSP DNA repeat sequence in a DNA-hybridization assay that were carried out in a streptavidin-coated 96-well plate [3]. We will include preliminary results on the solid phase-immunoassay capture of ovarian cancer biomarker TADG 14 on 1.44 cm^2 gold-coated silicon wafer chips detected electrochemically using our technology.

We will describe efforts toward portability and automation that will allow use in clinics, hospitals, and research laboratories. We will include advantages of our technology over existing techniques.

References

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2. Aguilar, Z.P., Vandaveer, W.R., Fritsch, I. (2002) Self-contained microelectrochemical immunoassay for small volumes using mouse IgG as a model system. *Anal Chem* 74:3321-3329.
3. Aguilar, Z.P. (2006) Small volume detection of *Plasmodium falciparum* CSP gene using a 50-µm diameter cavity with self-contained electrochemistry. *Anal Chem* Web Release Date:10-Jan-2006; (Article) DOI: 10.1021/ac051450i.

"Smart" Point-of-Care Diagnostic System for Patient Monitoring at Home or the Emergency Room

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Recently, the BioMEMS team of the University of Cincinnati has developed an innovative, fully integrated, "smart" point-of-care (POC) diagnostic system for the dual applications of a fully stand-alone diagnostic kit and a hand-held point-of-care diagnostic system. The smart point-of-care diagnostic system has sampling/identifying capabilities for the fast and reliable measurements of metabolic parameters or diagnostics of specific biomarkers from a human body with minimum invasion. The smart POC diagnostic system, which adopts the concept of a smart plastic lab-on-a-chip, is capable of multiparameter monitoring and also able to complete the whole sampling and analysis autonomously in less than 2 minutes.

The clinical tests are grouped into synergistic sets, where the collective information from all the tests will provide a comprehensive overview of the patient's condition. The core functions of the smart diagnostic system can be performed by an array of smart labs-on-chips (LOCs), with each "programmed" for diagnosing a specific clinically relevant target. The smart derives from the protocols where no patient intervention is required (after sampling) and the test protocol is completely autonomous.

This smart POC testing can provide a revolutionary leap in patient management – to move diagnostic clinical tests from a centralized laboratory to the home environment. This approach will dramatically enhance a physician's ability to provide immediate and appropriate care to patients using reliable, quantitative, clinically relevant data. This work envisions significant advances in public health due to the reduced turnaround time, fewer hospital visits, and regular convenient monitoring at home for the elderly and chronically ill.

In this presentation, an overview of the recent research achievements for the smart POC diagnostic system for blood analysis will be presented, discussing the relevant issues to the smart polymer lab-on-a-chip, protein assays, clinical diagnostics, and home care portals for the emergency care or patient monitoring at home.

Statistical Monitoring and Control of Patient-Level Data

James C. Benneyan

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This research focuses on statistical monitoring and bounded adjustment methods to detect and control changes in patient and physiologic data that exhibit nonhomogeneity, autocorrelation, or nonstationary behavior. Examples include surgical patients with acuity-adjusted infection risks and diabetic glucose levels that are desirable to control but where competing costs of frequent adjustments, deviations from target levels, and delayed detection need to be balanced.

In the first type of application, several SPC methods and sequential probability ratio tests have been developed based on a new mixed-risk probability model, including extension to the weighted case where outcomes receive unequal weights (such as based on complication severity). Monte Carlo and numeric analysis has shown these methods detect underlying changes faster than conventional methods. A second set of approaches have been investigated to monitor autoregressive physiologic data, such as blood pressure or respiration volumes. In particular, we developed and investigated dual monitoring schemes that combine the complementary properties of individual methods that tend to detect changes either slowly but eventually or quickly but not eventually because of their adaptive nature.

We also are investigating integrated SPC and bounded feedback adjustment algorithms to simultaneously minimize deviations from (for example) a patient's target warfarin anticoagulant level and also detect changes in their underlying physiology, but where periodic rather than continuous adjustments are preferable due to the cost and practicality of frequent interventions. The introduction of a deadband has implications on mathematical properties of the bounded adjustments (including center-truncated probability models), the best way to integrate SPC, and overall performance under different assumptions. Cost models therefore are being developed to determine optimal design and robustness. Other applications include glucose levels, blood counts, oxygen saturation levels, and hormone adjustment.

References

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2. Benneyan, J. (2006) Statistical process control methods in health care: discussion. *Journal of Quality Technology* 38(2), in press.
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A Multiplexed Diagnostic Platform for Point-of-Care Pathogen Detection

James M. Birch[1], Ryan Mahnke[1], Sonia E. Letant[1], Robert W. Derlet[2], Stuart Cohen[2], Danielle Manning[2], Mary T. McBride[1]

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In public health laboratories and hospitals, there is an urgent need for convenient, accurate, and easy-to-use point-of-care diagnostic tools. Standard laboratory culture and analysis often require days for definitive results; thus, primary-care physicians who treat acutely ill patients must make "educated guesses" based on the clinical setting, the patient's signs, and reported symptoms. In collaboration with the University of California, Davis, Medical Center, Lawrence Livermore National Laboratory has developed, tested, evaluated, and piloted a point-of care diagnostic instrument (**FluID$_x$**) and multiplexed nucleic acid-based (PCR) assay for detection of influenza and other high-priority pathogens.

The **FluID$_x$** instrument consists of an automated reagent delivery system, a flow-through PCR module, and a Luminex flow cytometer for processing and identifying both respiratory pathogens and biothreat agents. The multiplexed assay panel currently screens for influenza A, influenza B, parainfluenza, respiratory syncytial virus, and adenovirus. Additional assays are under development and the panel is being continuously updated. No special sample preparation is necessary, and the current instrument accepts nasal swabs or nasal washes. Each sample requires ~2.5 hours to process. The system is easy to use, requiring no special skills or elaborate training to run the integrated software or interpret the results. The first version of the **FluID$_x$** instrument processes samples sequentially. This design will be modified in later versions to accommodate asynchronous sample preparation and processing.

The NanoCytometer: A New Method of Determining Cell Size and Performing Nanoscale Cell Separation at the Point of Care

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Introduction: We have developed a new method of determining cell size and of separating cells, named NanoCytometry. This system uses an artificial pore with an integrated microfluidic chip and nano-based electronics. Our system offers the opportunity to provide point-of-care service, because it permits label-free, direct signal detection, extreme rapidity, analysis using few cells, and ease of use.

Methods: The NanoCytometer is fabricated with well-established lithographic techniques and uses the resistive-pulse technique to size cells: a cell passing through the pore displaces media, leading to a transient decrease in current, or pulse. Pulse magnitude correlates with cell size, and pulse width corresponds to cell flow rate. To achieve molecular specificity, we functionalize the pore's inner walls with proteins, such as annexin V or an antibody, which interact with cells passing through the pore, thus performing an apoptosis assay or immunophenotyping, respectively.

Results: Unfunctionalized, our pore detects cell populations differing in diameter by 0.5 μm. Functionalized, the device distinguishes cells on the basis of surface marker expression. We have developed two apoptosis assays: (1) an indirect assay, in which apoptotic cells labeled with annexin V flow through a pore functionalized with an anti-annexin V antibody, and (2) a direct assay, in which unlabeled apoptotic cells flow through a pore functionalized with annexin V. In addition, we have functionalized the pore with antibodies to perform immunophenotyping of murine leukemia cells.

Conclusions: Our NanoCytometer determines cell size and detects cell surface marker expression very accurately and could be incorporated into a handheld instrument that could use a few drops of blood to (1) measure a complete blood count using an unfunctionalized pore and (2) perform immunophenotyping for acute leukemias using functionalized pores arranged in series. The NanoCytometer could be used at the point of care to improve patients' quality of life and disease assessment.

The iCare Worksheet in the Pocket PC

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Nurses in the paper-based system use self-designed paper-based worksheets to take reports of their patients during shift change. They write key patient information (e.g., name, diagnosis, problems, and test results) while listening to shift reports recorded in a tape recorder. With a workload of five to eight patients, each nurse can spend at least 30 minutes for shift reports before starting to care for assigned patients.

The iCare Worksheet was developed through a collaborative effort among the School of Nursing, the Department of Computer Technology, and a local hospital nursing staff to improve the efficiency of shift reports. The iCare Worksheet, loaded in the Pocket PC and desktop computer, simulates nurses' daily work processes and keeps track of patient condition and care activities. The iCare Worksheet has pull-down menus with text, voice, and handwriting note-taking features to reduce handwriting data entry. It has alarm features to remind nurses to perform certain tasks. The interface program can retrieve patient information from the mainframe (SMS) to a desktop computer at a specified regular interval. Whenever Pocket PCs are synchronized with the desktop computer, updated SMS patient information is transferred from desktop computer to the iCare Worksheet.

A pilot study was conducted for 1 month in August 2004. Nurses of one unit in a local hospital used the iCare Worksheet loaded in the Pocket PC for patient care and shift report. The presenters will show the functions of the iCare Worksheet in the Pocket PC, report nurses' perceptions of benefits and problems in using the iCare Worksheet, and make suggestions for future development.

Rapid Clinical and Molecular Diagnostic of Heart Disease Using Biosensor Technology

Douglas A. Christensen[2], Lyndon Tan[1], Jacob D. Durtschi[2], Samuel Tolley[2], Hsu-Kun Wang[1], Alan H. Terry[1], Mark E. Astill[3], Richard S. Smith[2], James N. Herron[1,2]

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The triage procedure for chest-pain patients in an emergency room often includes the measurement of plasma concentrations of cTnI, CK-MB, and myoglobin as indicators of acute myocardial infarction. Total internal reflection fluorescence (TIRF) is an ideal technology for such point-of-care (POC) testing because of its inherent high sensitivity and rapid assay speed. In TIRF assays, an optical substrate (such as a planar waveguide) immobilizes capture antibodies to specifically detect these analytes. The evanescent wave generated by the substrate will detect only those analytes (tagged with a fluorescently labeled second antibody) that bind to the capture antibodies, thereby eliminating a wash step.

Over the past 15 years, our laboratory has developed planar waveguide biosensors based on TIRF. The following attributes of these biosensors make them uniquely well suited for in vitro diagnostics in POC settings: (1) low picomolar assay sensitivity, (2) short assay times (5-10 minutes), (3) simple assay protocol, (4) multiple, simultaneous assays on a single patient sample, (5) no sample preparation, and 6) inexpensive disposable assay cartridge.

We report on the development of a system that uses 25x25x0.5-mm molded plastic planar waveguides as the binding substrate. Red light from a diode laser (635 nm) is formed into a sheet beam and coupled into the waveguide via an integrated lens. Fluorescence emission near 670 nm is collected and imaged by a cooled (-25 °C) CCD camera equipped with an f/2.8 lens and an optical bandpass filter. The rate of binding of the analytes is determined by a nonlinear least squares fit to the time-varying detected fluorescence intensity during the initial 5 minutes of binding. A small-scale clinical study (62, 27, and 175 subjects) demonstrated that the assay exhibited good linearity with analytical sensitivities of 1.41 ng/mL, 5.64 ng/mL, and 0.2 ng/mL for CK-MB, myoglobin, and cTnI, respectively.

A Compact System for Multiplex Immunoassay Using Bio-functionalized Optically Coded Nanorods

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[1]Lawrence Livermore National Laboratory, Livermore, CA; [2]Stanford University, Stanford, CA; [3]Nanoplex Technologies Inc., Menlo Park, CA

We demonstrate new enabling technology for multiplex biodetection systems that are flexible, miniaturizable, highly automated, low cost, and high performance. The work builds on prior successes at Lawrence Livermore National Laboratory with particle-based solution arrays, such as those used in the Autonomous Pathogen Detection System (APDS) successfully field deployed to multiple locations nationwide. We report the development of a multiplex solution array immunoassay based on engineered metallic nanorod particles. Nanobarcodes® particles are fabricated by sequential electro-deposition of dissimilar metals within porous alumina templates, yielding optically encoded striping patterns that can be read using standard laboratory microscope optics and PC-based image processing software. The addition of self-assembled monolayer (SAM) coatings and target-specific antibodies allows each encoded class of nanorod particles to be directed against a different antigen target. A prototype assay panel directed against bacterial, viral, and soluble protein targets demonstrates simultaneous detection at sensitivities comparable to state-of-the-art immunoassays, with minimal cross-reactivity. Studies have been performed to characterize the colloidal properties (zeta potential) of the suspended nanorod particles as a function of pH, the ionic strength of the suspending solution, and surface functionalization state. Additional studies have produced means for the non-contact manipulation of the particles, including the insertion of magnetic nickel stripes within the encoding pattern, and control via externally applied electromagnetic fields. Using the results of these studies, the novel Nanobarcodes®-based assay was implemented in a prototype automated system with the sample processing functions and optical readout performed on a microfluidic card. The unique physical properties of the nanorod particles enable the development of integrated microfluidic systems for biodefense, protein expression studies, and medical point-of-care applications.

Point-of-Care Microcytometer® Methodology for Cell Sorting and Counting

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Micronics is applying technology useful in the point-of-care detection of rare cancer cells to the direct separation of stem cells. By employing proven technologies in microfluidics, which enable fluid and cell manipulation at smaller volumes and greater speeds, we are devising a closed system, direct, in-line Microcytometer® for potential applications in cellular measurement of the output from an apheresis machine, with the additional capability of sorting cells of interest. The platform includes a disposable, credit card-sized lab-on-a-card device into which a sample of whole blood is placed. Using flow cytometric properties, red cell lysis, white blood cell enumeration, and antibody labeling of cells have been demonstrated within these plastic, microfluidics-enabled cards. Traditional laboratory-based flow cytometry produces a stream of individual cells in single file, which can be presented to light scatter, fluorescent detector, or image-based cell detection systems. This scheme suffers from the significant limitation that the detectors may only assess and detect one cell at a time. We have developed a method to achieve much higher throughput for the detection of stem cells or rare cells in a reasonable data accession time in a system to eventually be deployed in a doctor's office or hospital environment. The strategy is to utilize the formation of a thin ribbon monolayer of cells within a microfluidic structure. In this approach, multiple cells are viewed and sorted, not individually, but as a whole cell row or section of the ribbon at a time. As a model, we used the Microcytometer® to detect CD34 positive cells from normal blood and patients previously diagnosed with chronic myelogenous leukemia as compared to standard flow cytometry. The intended outcome is a near patient, portable device capable of benefiting both patient care and cellular yield, and that may enable a quantum advance in the therapeutic use of cells.

Toward Large-Scale Integration of Microsystems for Ultrasensitive Real-Time Detection of Biological Entities

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The Laboratory of Integrated Biomedical Micro/Nanotechnology and Applications (LIBNA) at Purdue University is currently engaged in diverse research projects, with the overall goal of large-scale integration of various biosensor modules onto a common microscale platform. This integration will involve microfluidic delivery of the reagents and analytes to the sensing elements, selective capture of the analytes using receptor molecules in conjunction with dielectrophoresis for active concentration to decrease the time of detection, as well as miniaturization of the overall system using nanosensors to make the microsystem portable, all key elements for point-of-care technologies. This abstract will focus on four current works being pursued to develop the biosensor elements: (1) Microsized cantilever beams have been demonstrated to be very sensitive resonant mass sensors, by scaling down the planar dimensions of the cantilever sensor to the microscale, with nanoscale thickness, and sensing the mass change due to a single, dry, vaccinia virus particle in air. (2) Electrical impedance-based biosensors for the measurement of the by-products of bacterial metabolism, in tandem with dielectrophoresis to concentrate and capture the bacteria into a volume chamber of size in the picoliter range, demonstrate an efficient and rapid method (as compared to the macroscale technique) for detecting the viability of a few bacterial cells. (3) Nanopore sensors (with the goal of sequencing DNA by means of translocating the molecule through the pore and obtaining an electrical signature corresponding to the base-pair sequence of the DNA) have reliably fabricated a silicon dioxide nanopore using transmission electron microscopy (TEM), and monitoring the passage of the DNA through the pore from ionic current fluctuations. (4) With the realization that nanowire sensors (label-free, ultrasensitive biomolecular sensors having already been demonstrated in literature) will prove to be invaluable for diagnostics, our group is currently investigating two novel device schemes: silicon nanowire devices (with sub-20 nm diameter devices fabricated using top-down techniques) and silicon nanoplate devices.

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Rapid Molecular Identification of Uropathogens in Clinical Urine Specimens Using an Electrochemical DNA Biosensor

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We have achieved rapid, species-specific detection of bacterial pathogens in human clinical fluid samples using a microfabricated electrochemical sensor array. Each of the 16 sensors in the array consisted of three single-layer gold electrodes—working, reference, and auxiliary. Each of the working electrodes contained one representative from a library of capture probes with each specific for a clinically relevant bacterial urinary pathogen. The library included probes for *E. coli, P. mirabilis, P. aeruginosa, Enterococococcus* spp., and the *Klebsiella-Enterobacter* group. Bacterial 16S rRNA target derived from single-step bacterial lysis was hybridized to both the biotin-modified capture probe on the sensor surface, and a second, fluorescein-modified detector probe. Detection of the target-probe hybrids was achieved through binding of a horseradish peroxidase (HRP)-conjugated anti-fluorescein antibody to the detector probe. Amperometric measurement of the catalyzed HRP reaction was obtained at a fixed potential of –200 mV between the working and reference electrodes. 3′-Fluorescein modification of the detector probe combined with continuity between the detector and capture probe hybridization sites significantly enhanced signal intensity and increased detection sensitivity by 25-fold compared to use of a 5′-fluorescein-modified detector probe and a gap between the detector and capture probe hybridization sites. Species-specific detection of as few as 2,600 uropathogenic bacteria in culture, inoculated urine, and clinical urine samples was achieved within 30 minutes from the beginning of sample processing. In a feasibility study of this amperometric detection system using blinded clinical urine specimens, the sensor array had 100% sensitivity for direct detection of gram-negative bacteria without nucleic acid purification or amplification. Identification was demonstrated in 98% of gram-negative bacteria for which species-specific probes were available. When combined with a microfluidics-based sample preparation module, the integrated system would serve as a point-of-care device for rapid diagnosis of urinary tract infections.

Detection of Disease Biomarkers Using Electrophoresis Microchips

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Many diseases, including diabetes and cardiovascular disease, require routine monitoring of one or more biomarkers in a point-of-care setting for proper management. The best example of this is the measurement of glucose by diabetics. Existing methods for point-of-care measurements are generally limited by either the number of analytes that can be screened simultaneously or the portability of the instrumentation. These limitations necessitate the development of new chemistries capable of multi-analyte monitoring for specific disease biomarkers from complicated biological samples. The goal of our research is to demonstrate the use of electrophoretic microchips for rapid, multi-analyte monitoring of disease biomarkers relevant to diabetes, cardiovascular disease, and renal function as one potential solution to this problem. Microchip electrophoresis has shown recent promise for rapid separation and quantification of disease biomarkers ranging from DNA to small metabolites. Most systems, however, have used large optical detection instrumentation that makes point-of-care measurements unrealistic. Our group has designed an electrochemical detector that is readily adapted to point-of-care monitoring, inexpensive, and selective for metabolic markers of disease. In this presentation, examples of the use of this system to detect biomarkers of diabetes (glucose and glycated hemoglobin), cardiovascular disease (homocysteine and glutathione), and renal function (creatinine) will be presented. Progress in both sample handling and analysis will be presented along with existing hurdles that must be addressed prior to consideration of this type of technology for use in point-of-care monitoring. The development of this chemistry has promise for a better solution to existing point-of-care monitoring methods and ultimately better patient care in the long term.

The Case for Applying the Point-of-Care Testing Standard to Home Monitoring Devices

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Connectivity of home health care devices to clinical information systems remains an elusive target whose need is growing. At the core of the Point-of-Care Testing (POCT1-A) standard are three specifications describing the attributes of an Access Point (a unit to collect data from a testing device) and the communication protocol between the testing device and the access point; the Messaging Layer defining the protocol between the device and an Observation Reviewer (a data manager and analyzer); and the interface specification between the Observation Reviewer and clinical information systems. The vendor focus for compliance with POCT1-A has been on hospital POC devices like blood gas analyzers, but there is a clear need to extend the standard to home health care devices. Devices such as glucose meters, blood pressure cuffs, scales, etc. are currently available for home use by individuals with chronic diseases. As care of chronic diseases moves toward remote management, the need for standard device connectivity and integration with clinical information systems will only increase.

Daily POCT of one's blood sugar using a glucose meter plays an integral role in managing diabetes. By integrating these self-monitoring devices with a centralized information system, both patients and providers can review the blood sugar readings remotely. Applications that facilitate diabetes management and support among patients and providers are most valuable if they capture data from all available blood glucose meters and deliver those data using various communication infrastructures. However, in the current proprietary environment, it is difficult to create an application that extracts data from all blood glucose meters and transmits those data effortlessly. This poster details our experiences developing a collaborative diabetes management system that demonstrates the immediate need for standardization of connectivity to blood glucose meters so that patients and providers can use the readings to improve diabetes control.

Microfluidic Technologies for Point-of-Care Diagnostic

Daniel Irimia

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Separation and analysis of living cells from a patient's blood can generally provide a wealth of information for biological discovery and diagnostic, prognostic, and therapeutic applications. Although this is usually done in sophisticated and expensive laboratories, a promising alternative that allows access to the same information at the point of care is emerging through the use of microfluidic technologies. Lab-on-a-chip devices are being developed for sorting blood cells, for high-throughput biochemistry in small volumes, or for studying cellular behavior in controlled microenvironments, and in this trend the BioMEMS Resource Center has a leading position. Specifically, we are currently developing microfabricated devices for depleting red blood cells and platelet populations, for the sorting of homogeneous leukocyte phenotypes, and for the detection and isolation of circulating tumor cells, with direct applications in infectious diseases, trauma, cancer, and immuno-inflammatory processes. In addition, we are exploring strategies based on functional genomics tools that combine GFP reporter technology and microfabrication techniques for real-time monitoring and profiling of dynamic gene expression in living cell arrays. This new generation of point-of-care devices based on cell handling and analysis using microfluidics is prone to become key technology in 21st century medicine, enhancing the primary care resources for diagnostic and accessibility.

A Permanently Implantable Wireless Intracranial Pressure Monitor

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Existing neurosurgical intracranial pressure (ICP) monitors can be used only in a hospital setting and have a limited useful lifespan because of drift and infection. Our work aims to develop a reliable and mass-producible MEMS-based microwave ICP sensor and a portable microwave monitor allowing long-term noninvasive monitoring of ICP. The device will be small enough to be inserted through a burr hole of 12-mm diameter, stable with no significant drift, biocompatible over the life of the patient, compatible with modern imaging (CT, MRI, ultrasound), and low-power consuming (CMOS technology). The core of this active implantable sensor is an oscillator operating at the Industrial-Scientific-Medical (ISM) band of 2.4000-2.4835 GHz. The LC components of the tank oscillator are selected to confine the range of oscillation to 2.4-2.4835 GHz, for the pressure range of -25 to 200 torr, which corresponds to about S = 0.37 MHz/torr sensitivity. The total DC current and consumed power are 11.5 mA and 34 mW, respectively.

A prototype developed with a piezoresistive pressure sensor to monitor the signal transmission and biocompatibility was implanted in a pig. The results show predictable variation from in vitro studies in terms of pressure sensitivity. The device has a wireless range of 0.8 meter. The device is powered by a lithium rechargeable battery, 3V, 30mAh capacity. In a separate experiment, a laser of 830 nm wavelength, set at 140 mwatt illuminating an array of photodiodes generated a voltage of 5V across 500 ohms. With a phantom (slice of ham, 11 mm thick) between the laser and photodiodes, a transmission of 20% was observed. The laser-generated current can be used to recharge the battery.

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Sensitive Immunoassay of Biomarkers Based on Nanoparticle Labels

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An electrochemical immuno-biosensor based on poly(guanine)-functionalized silica nanoparticle labels and mediator-generated catalytic reaction is described. The functionalized silica NP conjugates were characterized by atomic force microscopy, x-ray photoelectron spectroscopy, and electrochemistry. The detection of mouse TNF-α via immunological reaction is based on a dual amplification: (1) a large amount of guanine residues introduced on the electrode surface through the silica nanoparticle and immunoreaction and (2) mediator-induced catalytic oxidation of guanine, which results in great enhancement of anodic current. The performance of the electrochemical immunosensor was evaluated and some experiment parameters (e.g., concentration of Ru(bpy)32+, incubation time of TNF-α, etc.) were optimized. The detection of limit for TNF-α is found to be 5.0×10^{-11} g/mL (2.0 pM), which corresponds to 60 attomoles TNF-α in 30 μL. This immunosensor based on the poly[G] functionalized silica NP label offers great promise for rapid, simple, cost-effective analysis of biological samples.

Digital Magnetofluidics

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We present a novel method to move and control drops of water on superhydrophobic surfaces through the use of magnetic fields. Small water drops (volume, 5-20 μL) that contain low-volume fractions of paramagnetic particles (less than 0.1%) can be moved on a superhydrophobic surface at relatively high speeds (7 cm/s) by displacing a permanent magnet. An aqueous drop pinned to a surface defect can be combined with another drop that contains paramagnetic particles, thus making it possible to move the newly formed drop. A drop can also be split using two magnetic fields. This new approach to microfluidics has the advantages of faster and more flexible control over drop movement and manipulation.

Remote Patient Monitoring via Object-Based Video Streaming

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Video monitoring of patients has been utilized as a major component in many health care systems, such as epilepsy monitoring and tele-rehabilitation. With the advancement of video compression technology and the increasing bandwidth of the Internet, performing the remote monitoring tasks anywhere and at any time is becoming a reality. We report a video streaming system specially designed for long-term video recording. We employ object-based coding strategy to improve the coding efficiency. In this approach, the video content is divided into three typical components, representing the background, stationary foreground, and moving foreground. Coding these components at different quality and rates shows a great reduction of the required bandwidth while maintaining the essential visual quality. At the same time, this system provides a function of content selection that may benefit data indexing and retrieval for offline applications. The real-world experiments on the preliminary system suggest a performance superior to that of the conventional video streaming systems.

Point Detection of Pathogens in Oral Samples via Up-Converting Phosphor Technology

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A major problem with current diagnostic paradigms is the time required between sample acquisition and informing the patient of the test results. If a sample could be analyzed on site with an immediate result, the individual could be counseled and/or appropriate therapy initiated. The goal of this study is to develop a rapid, accurate, and sensitive point-of-care diagnostic platform. Speed will be addressed by miniaturization, confirmatory by using simultaneous multiple testing strategies, and sensitivity by detection with unique up-converting phosphor technology (UPT) particles. Protocols for ELISA, and RT-PCR suitable for a microfluidic platform have been adapted to detect HIV and *B. cereus*, prototypical pathogens for proof of concept. The technology employs three interactive steps: (1) sample acquisition: collectors designed to pick up and release bacteria, soluble analytes, and virus from oral fluid, (2) microfluidic processing: the movement of microliter volumes of analyte using pneumatic or hydraulic forces, (3) detection of analytes utilizing UPT particles in an existing lateral-flow system, and (4) integrated software used for processing the results. The sensitive UPT technology is currently used to quantitate drugs of abuse, antibodies to pathogens, and nucleic acids. Monolithic polycarbonate chips have been constructed. We are developing an oral-based microscale diagnostic system that permits simultaneous analysis of HIV and *B. cereus* and/or other pathogen antigens and nucleic acids, as well as antibodies to these pathogens, thus enabling the diagnosis of multiple infectious diseases.

Integrating Data, Models, and Reasoning in Critical Care

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The objective of our research program is to develop and evaluate advanced intensive care unit (ICU) patient monitoring systems that will substantially improve the efficiency, accuracy, and timeliness of clinical decision-making in intensive care. Modern ICUs employ an impressive array of technologically sophisticated instrumentation to provide detailed measurements of the pathophysiological state of each patient. In the long term, we plan to build monitoring systems that not only report these measurements to human users but also form pathophysiological hypotheses that best explain the rich and complex volume of relevant data from clinical observations, bedside monitors, mechanical ventilators, and a wide variety of laboratory tests and imaging studies. Such systems should reduce the ever-growing problem of information overload and provide more accurate and timely alarms than do today's unintegrated limit alarms. By helping to focus attention on the most significant events and changes in the patient's state and by suggesting likely physiological interpretations of that state, such systems may facilitate early detection of evolving complex problems and provide useful guidance on therapeutic interventions and lead to improved patient outcomes. To achieve these long-term goals, we are creating a major new research database of data-rich ICU cases that we will de-identify and annotate. (To date we have collected 17,000 cases, of which 2,500 include waveforms of physiologic signals.) When complete, the database will be made available as a resource for the research community. We are developing an array of signal processing, model-based, and reasoning methods to analyze the data we collect and to create the technical means of abstracting from available data to pathophysiological hypotheses.

CyberInfrastructure Tools for Telehealth

Robert R. Meyer, University of Wisconsin-Madison, Madison, WI

CyberInfrastructure tools allow clinicians to access databases and diagnostic software not available to them within their local setting. Motivated by systems successfully employed at Argonne National Laboratories and the Computer Sciences Department of the University of Wisconsin-Madison, we are developing approaches that will allow clinicians to exploit large regional data repositories and sophisticated computational methods for diagnosis and treatment planning at no charge via the Web. The Network-Enabled Optimization System (NEOS) developed at Argonne is an outstanding example of the use of the Web to allow researchers (with difficult mathematical optimization problems) to electronically submit for solution (using the powerful solvers and computers at Argonne) their problems via a standardized Web interface. Very difficult or potentially time-consuming problems can be handled at the regional site by using systems similar to the Condor High-Throughput-Computing (HTC) environment (developed by a team at the University of Wisconsin) to parallelize the solution process (by applying a variety of alternative computational approaches simultaneously and then coordinating the results). This parallelized approach ensures both high-quality analyses of input data and fast turnaround.

The NEOS system was developed to assist in the solution of general mathematical optimization problems; our research has been focused on the development of an analogous system to aid clinicians in the utilization of sophisticated tools for radiation treatment planning based on submission via the Web of patient data files in the form of digitized and contoured CT scans. We believe that this telehealth approach also has considerable potential in dealing with other areas of medical treatment in which patient data can be sent via the Web to a regional computing site that can apply a variety of sophisticated database searches or computational tools to the data and quickly return one or several ranked treatment options or diagnoses.

Optical Integrated Microfluidic Tools

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Optical integration and manipulation is a powerful technique that possesses great potential utility within microfluidic point-of-care (POC) diagnostic technologies. Conventional optics, however, are far too bulky and cumbersome for adaptation to portable formats. Through the use of conventional optics, we have overcome these traditional limitations and have created a class of microfluidic tools that can be combined into a single, versatile platform for POC testing. This platform is facilitated by several complementary technologies, specifically, (1) new techniques for the visualization and creation of micromachined structures (using femtosecond lasers) within microfluidic channels, (2) new optical trapping methods that overcome previous scaling limitations in microfluidics, and (3) integration of machined structures (optical waveguides) and optical trapping for detection and manipulation of biological bodies as they flow through microfluidic devices. We have demonstrated the applicability of these tools to whole blood cytometry, coagulation analysis, and cell sorting, for instance.

Sandia MicroChemLab™ Technology for Handheld Analysis of Vapors

Thor Osborn

Sandia National Laboratories, Albuquerque, NM

Over the past decade, Sandia National Laboratories has invested heavily in the development of microsystem technologies for portable vapor-phase chemical analysis. MicroChemLab™ systems generally comprise a vapor preconcentrator, a micromachined gas chromatograph column, and a detector such as a polymer-coated SAW array. Each component may be imbued with selectivity in order to attain system performance in the sub-ppb range for the analytes of interest. Several versions of each component technology have been devised, providing substantial flexibility in application-specific system design. This approach has been very successful in the development of detection systems for explosives and chemical warfare agents. Recent data indicate that MicroChemLab™ systems can be developed to measure the light alcohols, ketones, alkanes, and glycols appropriate for breath analysis. With sparging or pyrolysis, liquid samples such as urine, blood, or interstitial fluid may also be addressed. MicroChemLab™ technologies show great promise for the development of high-fidelity handheld analysis systems for point-of-care diagnostic applications.

Development of a Handheld, Up-Converting Phosphor-Based Immunoassay System

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Cytokines are important early indicators of infection and immune response and therefore serve as excellent diagnostics for monitoring health. We are developing an easy-to-use handheld diagnostic sensor system for the rapid, noninvasive detection of multiple cytokine levels in saliva. Space travel may negatively impact immune function, and such a lightweight monitor for the routine measurement of cytokine levels could play an important role in astronaut health maintenance during long-duration space missions; it would be an asset to the medical community on Earth as well. The goal of this project is to develop an integrated immunosensor system to deliver results in minutes with appropriate sensitivity. Key features of our approach include adaptation of an affinity-based assay that utilizes up-converting phosphor (UCP) reporter technology developed at SRI International; comparison and optimization of assay performance on two lateral-flow platforms, a microfabricated polymer fluidic chip from Åmic, AB and a conventional nitrocellulose membrane; and development of a compact optical detection system for the UCP reporter assay. The immunoassay approach developed here should be extensible to a range of immunoassay analytes beyond the initial cytokine targets.

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Intensity-Modulated Radiation Therapy Treatment Plan Optimization

Edwin Romeijn

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When a cancer patient is treated with radiation therapy, the beams of radiation passing through the patient kill both cancerous and normal cells. Thus, the radiation treatment must be carefully planned so that a clinically prescribed dose is delivered to cancerous cells while sparing normal cells in nearby organs and tissues to the greatest extent possible. The preservation of healthy or functional tissues, and hence the quality of a patient's life, must be balanced against the probability of the eradication of the patient's disease. Recent technological advancements have lead to the rapid development and widespread clinical implementation of a delivery technique for radiation therapy to cancer patients that is known as intensity-modulated radiation therapy (IMRT). IMRT allows for the creation of highly conformal dose distributions that allow escalation of the radiation dose delivered to a clinical target while lowering or maintaining the side effects caused by radiation therapy. In this poster, we will describe our research on an integrated approach to finding high-quality IMRT treatment plans that can be delivered efficiently using currently available technology. In this approach, we find the best beam shapes (called apertures) from an astronomical number of potential apertures to use for treating a particular patient as well as the corresponding aperture intensities. We show how we can allow for four different types of delivery constraints often encountered in commercial radiation therapy delivery equipment and compare their efficiency. We also show how we can explicitly account for the fact that there is some transmission of radiation through the part of the radiation beam that is blocked by the aperture. Finally, our approach also enables quantifying the trade-off between treatment efficiency and treatment quality.

Transdermal, Noninvasive Monitoring of Medication Ingestion

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We are developing a noninvasive drug compliance monitor with the capability of detecting and recording the ingestion of any medication that would be of great utility in treatment regimens in which compliance is crucial to success of therapy. The technology under development consists of two parts: a fluorescent molecule that is incorporated into the medication as a traceable excipient, and a wristwatch-like device that can transdermally detect the presence of the excipient in the bloodstream. We selected a GRAS (generally regarded as safe) excipient for incorporation into the medication to be monitored and demonstrated that when orally ingested, the fluorescence from that excipient is detectable in the bloodstream. Additionally, we built a device with the capability of transdermally detecting fluorescence in an animal model.

Ultrathin and Flexible Catheterscopes for Minimally Invasive Imaging, Diagnosis, and Therapy Within Hospitals and Remote Clinics

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Minimally invasive medicine is well established in hospitals in the United States and is beginning to spread to more remote clinics. However, the poor performance and high cost of ultrathin flexible endoscopes prohibits the use of endoscopes less than 3 mm in diameter. The main problem with current endoscope technology using fiber bundles and small sensor arrays is that the image resolution is fundamentally limited because the resolution is proportional to the number of elements, thus requiring larger endoscope diameters for high-quality images. To make ultrathin, flexible endoscopes, this technology is pushed to its extreme with many sacrifices.

The problems with commercial, ultrathin flexible endoscopes based on coherent fiberoptic bundles are:

- Number of pixels within the field of view decreases with diameter,
- Honeycomb non-imaging area around central holes of imaging pixels,
- Not highly flexible shaft or semi-rigid,
- Expensive and fragile, and
- Degrades with cleaning.

We have developed a new type of ultrathin and flexible laser scanning endoscope that is called a catheterscope. Red, green, and blue (RGB) laser light is combined into a singlemode optical fiber at the base station and ends at a small tube piezoelectric actuator at the distal or in vivo end. The distal tip of the optical fiber is cantilevered a short distance and the tube piezo vibrates the cantilever at the mechanical resonance to achieve 15 Hz frame rate imaging. The scanned laser illumination is focused by a lens assembly that can be molded from plastic. The backscattered light, modulated by the tissue, is collected with a ring of 12 plastic optical fibers that return light to photodiodes at the base station. Full color, 500-line images are created similar to a laser scanning microscope, one pixel at a time. The in vivo part of the catheterscope is very small and the shaft is highly flexible (diameter, 1.6 mm with a rigid tip length of 13 mm); thus, catheterscope use on unsedated patients can be expected.

All four key components described for the distal end (singlemode optical fiber, tube piezo actuator, molded plastic lens assembly, and plastic signal collection fibers) are low in cost. Assembly of these components at high volume is possible so that the distal end may be disposed after a single use, eliminating the many requirements for cleaning endoscopes such as highly trained staff, costly equipment, and resulting chemical waste. The advantages of this catheterscope technology over current ultrathin and flexible endoscopes are listed below and compared side-by side in an upcoming publication (see reference). A caveat is that the two catheterscopes already developed (monochrome and full color) have the disadvantage of a longer rigid tip length for non-confocal geometry and the technology is not commercially available.

- 2x image resolution with no honeycomb non-imaging areas
- 10x minimum bend radius for the highly flexible shaft
- Low-cost components and able to be manufactured in high volumes
- Sterile single-use device with cleaning costs and chemical waste eliminated
- Requires less anesthetic or can be used with unsedated patients
- Can be battery powered in the future

Another major difference between the catheterscope technology and current flexible endoscopes is the use of directed or focused laser energy to image. This high-quality laser light can also be in the ultraviolet and infrared regions of the spectrum and at high power so many different types of optical diagnoses and therapies can be integrated with the imaging in situ. In the near future, the catheterscope will allow previously inaccessible regions of the body to be imaged at high resolution, and, while imaging, additional diagnostic and therapeutic procedures can be done efficiently using the same minimally invasive medical device that has all the advantages listed above.

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3D Cell Imaging for Early and Rapid Disease Diagnosis in Hospitals and Remote Clinics

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Currently, image-based disease diagnosis is made using conventional optical microscopes that produce 2D images of stained tissue, and fluorescence is rarely used. Greater sensitivity of the standard morphological analysis performed by cytologists can be achieved by imaging the cell nucleus in 3D instead of 2D [1]. There are additional features that indicate disease, such as cancers, which are clearly seen in 3D images having multiple perspectives, that are not easily seen in a 2D single perspective image [2]. Major reasons for the lack of image-based disease diagnosis in 3D is the prohibitive cost of 3D microscopes, their reliance on fluorescence imaging, and the lack of textbook training in 3D.

We have developed the Optical Projection Tomography Microscope (OPTM), a novel type of microscope, to image cells and nuclei in 3D that have been fixed and stained with the commonly used, absorption-based chromatin-associated dye, hematoxylin [3]. The stained cells are put in a microcapillary tube that is placed within a microfabricated rotational joint that has parallel optical surfaces to minimize any image distortion. As the capillary tube is rotated, 250 images are captured within 180 degrees of rotation within 1 minute. By using techniques developed for x-ray computed tomography (CT), volumetric 3D images are reconstructed with isometric and submicron resolution [3].

Applications of this technology in pulmonary and critical care medicine are envisioned to be close to the patient either within the hospital or in a remote clinic. In the hospital, a pulmonologist would like the specimen diagnosis for a patient with suspected respiratory disease while the patient is undergoing the medical procedure. Automated sample preparation techniques for the OPTM are being developed for sputum, fine needle aspirate (FNA), and bronchial alveolar lavage (BAL). In a remote clinic, an infectious respiratory disease may be suspected and a rapid image-based diagnosis will augment any DNA-based testing, thus reducing the chance of infection spreading across the local region.

Reducing the cost of 3D microscopes and automating the sample preparation are necessary steps for both the acceptance of more sensitive 3D image-based disease diagnosis and the localization of the 3D microscope closer to the patient for more rapid cytological analysis. The OPTM fills a need that is not being met by confocal laser scanning microscopes and wide-field deconvolution optical microscopes because the OPTM images absorption-based dyes used routinely in pathology. Furthermore, these commercially available 3D microscopes typically cost over $100,000 and acquire only a single perspective view of the 3D tissue structure, while the OPTM images and displays all (360°) perspectives and works in the more useful transmission mode, unlike commercial confocal microscopes. Thus, the OPTM is expected to provide much more diagnostic utility for less cost.

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Single-Molecule Detection as an Approach for Near Real-Time DNA Mutational Analyses

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Several cancer-related diseases have been determined to be highly associated with point mutations in genomic DNA that can be used as biomarkers for diagnosis, prognosis, or monitoring disease recurrence. One such cancer is colorectal cancer (CRC); it has been shown that point mutations in the *KRAS* gene occur early in tumorigenesis and therefore show promise as biomarkers for diagnostic screening. There are 19 different point mutations in the *KRAS* gene, all of which must be tested for securing reliable diagnoses and prognoses. This represents a challenge due to the low abundance (minority) of these mutations found in most clinical samples, with the majority of DNA present as the wild type. Previous work in our laboratory has focused on the development of the ligase detection reaction with single-pair fluorescence resonance energy transfer (LDR-spFRET) using molecular beacons as the reporter system and single molecule photon burst analysis to detect point mutations in DNA rapidly and efficiently (see reference). This presentation will discuss two new technologies emanating from our laboratory using this assay format: (1) design and fabrication of a field-portable single molecule detection system for rapidly screening low-abundant point mutations in genomic DNA and (2) multiplexing the LDR-spFRET assay using a multi-channel chip to increase throughput and provide complete molecular profiles by screening the entire panel of *KRAS* mutations associated with CRC. (1) A polymer fluidic chip containing dual optical fibers, which were interfaced to a diode laser and single photon avalanche diode, was assembled into a small package. Insertion of genomic DNA into the device and using a flow-through processing format generated molecular beacons that underwent spFRET, indicating the presence of the mutation. (2) A microfluidic chip was designed to test for all 19-point mutations simultaneously by imaging detection zones of the multiple channels onto an array of pixels of a CCD camera. The fluorophores in the channel array were illuminated using a photodiode laser launched into the side of the device, which possessed an integrated waveguide. The waveguiding was supported by an SU-8 core embedded into a poly(methylmethacrylate), PMMA, microfluidic chip. The SU-8 waveguide irradiated a series of fluidic channels with the coupling from waveguide to waveguide accomplished using microlenses formed at the terminus of each waveguide (see reference).

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Lessons Learned From Applying Interoperability and Information Exchange Standards to a Wearable Point-of-Care System

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Interoperability at the device and system levels has the potential to improve ease of use for point-of-care systems while lowering the cost of these systems. To this end, we developed a prototype wearable monitoring system based on interoperability standards that demonstrates plug-and-play wireless connectivity between the system components. The system utilizes both device-level (IEEE 11073, Bluetooth) and system-level (Health Level [HL7], CORBA) standards. The wearable monitoring system stores data in a local database, and these data are then sent to a remote database via HL7 messages. The remote data can be viewed and processed with a graphical user interface created in Java that employs the CORBAmed PIDS and COAS services as implemented by OpenEMed. Lessons learned from this endeavor are summarized.

Progress Toward Developing Polymer Microfluidic Systems for Point-of-Care Diagnostics

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Miniaturized chemical analysis systems offer excellent potential to facilitate inexpensive point-of-care testing. We have focused on developing polymeric microdevices for the rapid analysis of biological molecules. We have demonstrated a facile method for covalently derivatizing poly(methyl methacrylate) microchip surfaces by using atom transfer radical polymerization (ATRP) [1]. We have now generalized this ATRP approach to other polymer substrates, such as thermoset polyester; we have characterized ATRP-modified polymer surfaces and have carried out capillary electrophoresis (CE) in microchips made from these functionalized polymers. We have also developed a straightforward technique for solvent bonding polymer microfluidic devices for CE using a phase-changing sacrificial layer method [2]. These CE microchips are robust, withstanding high internal pressures (>2,200 psi) and the application of high electric fields (>1.5 kV/cm). Importantly, phase-changing sacrificial materials offer a general route for making microfluidic arrays in various polymer substrates. We are also applying phase-changing sacrificial layers in constructing polymeric microdevices that have ion-permeable membranes interfaced with microchannels [3]. These microchips can integrate analyte preconcentration with microchip CE, and provide >10,000-fold enrichment of protein samples. Advances in surface modification, device fabrication, and sample preconcentration make polymer microfluidic systems appealing candidates for low-cost and rapid point-of-care testing.

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MEMS-Based Endoscopic Optical Confocal Imaging

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Optical coherence microscopy (OCM) is a combination of low-coherence interferometry and confocal imaging, and can provide cellular or even subcellular resolution that is sufficient for early cancer detection, but the size and imaging speed prevent them from in vivo imaging of internal organs. We report a MEMS-based OCM imaging probe that is only 5 mm in diameter. The key feature of this miniature imaging probe is the utilization of a vertically scanning MEMS microlens. Based on a novel large-vertical-displacement (LVD) microactuator technique, the microlens has a large axial scanning range (~0.7 mm) and fast scanning speed (~0.4 kHz). Photoresist reflow technique is used to form microlenses on lens holders that are integrated with LVD microactuators. The lens holders are fabricated using a post-CMOS micromachining process which can provide additional thermal isolation to the polymer microlens and form a transparent oxide mesh within the hollow lens-holders to enable formation of larger polymer microlenses. Microlenses with a diameter of 0.6 mm have been fabricated and a lateral resolution of 1 μm has been demonstrated. The size of this endoscopic OCM imaging probe can be further reduced by improving the packaging design.

Integrated Nanotube- and Nanowire-Based Wireless Sensors for Point-of-Care Diagnostics

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For point-of-care (POC) diagnostics, it is very attractive to develop devices that can monitor the health condition of patients outside the hospital environment via a wireless communication network. To this end, we have developed (1) aligned nanotube and nanowire array sensors on silicon substrate integrated with multichip module (MCM) and wireless communication module and (2) aligned nanowire array on flexible polymeric substrate with organic thin film transistor for wireless communication. Aligned nanotube and nanowire arrays have been grown by chemical vapor deposition and electrochemical deposition using nanoporous templates with their electrical connections constructed by a thin film process through lithography. The radius of nanotubes and nanowires and the spacing between the nanoelectrodes on electrochemical sensing array have been controlled to realize ultrasensitivity, spatial resolution, and fast response for a small quantity of target biomolecules. Nanoscale electrodes on a sensing platform are functionalized with, for instance, antibody against biomarkers. For the integration of nanoscale sensors with signal processing and wireless communication modules, multichip module technology including the low-temperature cofired ceramic (LTCC) process has been applied for compact and reliable operation in POC use. Potential applications to cardiovascular diseases and neurodegenerative disorders will be presented.

Detection of Cytochrome P450 CYP1B1 Using Recombinant Antibody (scFv) Piezoimmunosensors

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Cytochrome P450 CYP1B1, a recently identified CYP1 gene family member, was reported to be overexpressed in multiple types of cancer. As a potential tumor biomarker, the enzyme becomes an immediate target for research, focused on cancer diagnostics, monitoring, and treatment. The intensive and systematic studies of P450 expression, regulation, and function in tumor cells required the new sensor systems development. Traditional methods, however, are time consuming and have a high cross-reactivity rate between P450 subfamilies.

In this work, we successfully developed a CYP1B1 biosensor using phage displayed recombinant antibodies (scFvs) and QCM-transducer. The smaller size of scFvs compared to commonly used monoclonal antibodies increased the surface density, which greatly improved sensor sensitivity. Cross-reactivity of the traditional immunoassay was addressed by using four distinct scFvs, which bind to different epitopes of CYP1B1. All scFvs were biotinylated and coupled to the Au QCM surfaces using pre-immobilized neutravidin layer. Our scFv-QCM biosensors showed excellent sensitivity (detection limit, 9 nM) and specificity (confirmed by utilizing different negative control antigens). The kinetics of binding events was also fully studied. The scFv-QCM biosensors were successfully used to measure CYP1B1 concentration in several cancer and normal cell lysates. The results show that the expression of the CYP1B1 is higher in the cancer cell lines than in those normal ones tested. Our system demonstrates the outstanding attribute of scFvs for improving sensitivity and specificity in sensing application. It will enable us to further analyze and characterize different P450 subfamilies and clarify some questions addressed in cancer diagnostic, monitoring, and treatment.

Miniaturized Silicon Instruments for Cellular Manipulation, In Vivo Imaging, and Nanoscale Sensing

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Nano-Micro, Info, and Bio are integrative components of our research, in which engineering expertise in photonics, microelectronics, microfabrication, and nanotechnologies is synergized to facilitate biomedical studies and to obtain a better understanding of the fundamental problems in life science. This in turn benefits the advancement of engineering research. Actively pursued areas are the following:

- Miniaturized silicon instruments for in vivo cell and embryo manipulation and culturing, in particular, microinjections, ultrasonic cellular-scale surgical tools, self-assembly and high-speed particle sorting for studying cell mechanics, cellular interactions, and embryo development network.
- Nano-micro fabricated photonic sensors and scanners for in vivo imaging and microscopy toward miniaturized endoscopic precancer detection and diagnosis.
- Multiscale simulation of fundamental fields, forces, flows, and energy processes involved in cell-cell interactions, cell-material interactions, and subcellular interactions.

Our recent work on development of silicon MEMS-based RNA interference (RNAi) instruments has demonstrated important benefits to genetics and developmental biology studies. The microinstruments enable high-throughput investigation of how gene activities control embryonic development and how errors in gene action lead to birth defects and cancer. Our invention and development of a MEMS-based microinjector with on-chip optical force sensor is capable of high-speed injection of precise amounts of regulatory molecules into fruit fly embryos. The impact is likely to be significant not only for developmental biology studies but also for a range of other biomedical applications such as drug delivery, diagnostic screening, and genetic testing. We also made contributions to self-assembly MEMS technology by experimentally characterizing the positioning forces during self-assembly. Our measurements, combined with numerical modeling, enable researchers to quantify the role of the shape of the part-to-be-assembled in self-assembly processes. Our recent findings in this area are likely to have a profound impact on the design and optimization of microfluidic self-assembly technologies, in both biology and MEMS fabrication technology.

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Diabetes Technology: Continuous Glucose Monitoring

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An individual with Type 1 diabetes has lost the ability to produce insulin and must receive daily injections, or continuous infusions, of insulin. Diabetics must closely monitor their blood glucose levels by pricking their fingers several times each day to obtain blood glucose values from glucose test meters. *Intensive insulin therapy*, with frequent (painful) blood glucose measurements and insulin adjustments, leads to better blood glucose regulation and reduced long-term complications that are due to *hyperglycemia* (high blood glucose). The primary negative aspect to intensive insulin therapy has been an increased risk of *hypoglycemia* (low blood glucose); this can be quite dangerous if an individual is driving a car, for example. In this presentation, we demonstrate how continuous glucose sensor signals combined with *estimation* algorithms can be used to warn an individual that he or she is at risk of violating hypo- or hyperglycemic thresholds, allowing corrective action (consume glucose or give a bolus of insulin) to avoid the dangerous condition. A long-term goal of this project is to combine a continuous glucose *sensor* with an insulin infusion pump (*actuator*) to form a closed-loop *artificial pancreas*.

Systems Engineering and Health Care

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Health care delivery in the United States is in a crisis of inconsistent and sometimes dismal quality, safety and efficiency, and rapidly growing cost. As recognized by a recent joint study of the National Academy of Engineering (NAE) and the Institute of Medicine (IOM), a major reason for these shortfalls is the absence of involvement in health care by the systems engineers and researchers who have done so much to improve the effectiveness of manufacturing and distribution operations. Paradoxically, engineering has been central to many of the miraculous advances in modern medical diagnostics and interventions, but health care processes and operations to utilize those technologies remain largely unimproved in half a century. One major reason is that health care is massively under-invested in information technology, whether patient medical records, point of care and communication technologies, information sharing among providers, or telehealth.

Building on the NAE/IOM report, growing interest from the National Science Foundation and National Institutes of Health, and emergence of interdisciplinary collaborations like Purdue's Regenstrief Center for Healthcare Engineering, systems engineering researchers are beginning to confront the challenge. Improvements in medical technology, especially IT and communication, provide the building blocks. But the systems task is to develop replicable predictive models and other tools for engineering integrated systems of personnel, information and communication technologies, facilities, and planning and control regimes that can together transform the safety, cost, quality, and efficiency of health care delivery.

Building a Better Delivery System: A New Engineering/Health Care Partnership, A Joint National Academy of Engineering/Institute of Medicine Study

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Research Objectives. To identify engineering applications with the potential for significantly improving the quality and productivity of health care delivery, factors that affect the deployment of these applications, and research priorities in engineering and other fields to advance performance in health care delivery.

Approach. A committee of 14 experts from engineering and health care fields, supported by National Academies' staff and National Academy of Engineering postdoctoral fellows, reviewed the relevant research literature, conducted site visits, took expert testimony, and convened two fact-finding workshops involving 68 researchers and practitioners from engineering, health care, and management to examine challenges and opportunities for application of systems engineering tools, information/communication technologies, and various fields of engineering research. The committee prepared a consensus report, including findings and recommendations and 38 individually authored papers of workshop presenters.

Significant Results. Specific systems engineering tools for design, analysis, and control and information and communication technologies with potential to improve care delivery processes and outcomes at all levels of the health care system are identified. Important opportunities and challenges for research in engineering and related fields are identified as are opportunities for cross-disciplinary education in health care, engineering, and management.

Broader Impact. Public- and private-sector action on the report's recommendations to (1) advance development, adaptation, and widespread application of identified systems engineering tools and information technologies to health care delivery, (2) expand engineering and related multidisciplinary research in areas identified, and (3) implement changes in the education of engineers, health care professionals, and managers has the potential to radically improve the quality and productivity of health care delivery in America.