Nanotechnology has recently been applied to study dynamic cellular processes, such as cell cycles and cell migration, providing rich spatial and temporal phenotype information. Tremendous opportunities and challenges exist in combining nanotechnology with signal processing techniques to develop faster, smaller, yet more accurate and sensitive biomedical devices for cancer genomics and proteomics to obtain a better understanding of the cellular and molecular mechanisms of different kinds of cancers. In this article, we present the applications of new nanoscale solutions that include nanoparticles and sensing devices for genomic signal processing (GSP) in cancer research.

GENETIC BASIS OF CANCER
Cancer, a major cause of death in the United States and throughout the world, accounts for nearly one-quarter of total human mortality. For example, colorectal cancer (CRC) affects approximately 135,000 people and results in 57,000 deaths annually in the United States [1, pp. 367–408]. Over the past decade, significant discoveries have been made that provide a better understanding of the genetic basis of cancers. In the case of CRC, we now know that progressive accumulation of genetic and epigenetic alterations would lead to the transformation of normal colonic epithelium to adenocarcinoma. In this process, the loss of genomic stability is a key molecular and pathophysiological step that creates a permissive environment for the occurrence of alterations in cancer-related genes. Tumor-suppressor genes and oncogenes like APC, K-RAS, and p53 appear to promote colon tumorigenesis by interfering with the function of signaling pathways or by affecting genes that regulate genomic stability. Changes in the genetic code of cells can result in RNA, protein, physiological, and pathological alterations, which subsequently can lead to diseases like cancer. In this context, we believe that the techniques of GSP can be used to process and interpret genomic signals to provide a better understanding of the underlying biological mechanisms of cancers and to assist in the development of optimal strategies for cancer therapy.

To get an idea of what may lie in the future, we quote an application scenario from a recent paper [2]: “With network models in hand that can predict disease dynamics, technology can make the application of scientific knowledge ever more productive: a device is embedded in the patient to monitor the relevant gene and protein expressions, this information is sent by wireless to a supercomputer that adjusts the network model to changing conditions in real time and applies control theory to obtain a therapeutic strategy, the details of the strategy are sent back to a nanodevice embedded in the patient, and the device dispenses the called-for..."
treatment in with the precise composition and timing called for by the control algorithm.” Nanotechnology plays a key role in this vision of the future.

Nanotechnology is defined as the creation of functional materials, devices and systems through the control of matter at the scale of 1–100 nm and the exploitation of novel properties and phenomena at the nanoscale [3]. It is a cross-disciplinary research field between medicine, engineering, and physical sciences, especially involving biochemistry and nanoelectronics. This research field is evolving and offers promising potential for cancer detection and treatment. For example, fluorescent tags are generally too big to enter cells, but the smaller sized nanoparticles (<10 nm) can. These nanoparticles, therefore, can be used to monitor subcellular activities via optical microscopy. Microelectromechanical systems (MEMS) devices are commonly used in GSP for cancer detection. Researchers are currently scaling down MEMS to nanoelectromechanical systems (NEMS), but many microfabrication techniques are re-deployed in NEMS fabrication.

A number of GSP algorithms, ranging from sequence analysis and statistic methodology in gene selection to modeling genetic regulatory networks and imaging, are presented in this special issue. Our article complements these articles by focusing on the GSP hardware design of the nanotools for cancer research. It provides a qualitative review of the nanotechnologies involved while the readers can refer to quantitative details from the reference material. In what follows, we introduce biomarker design for cancer labeling, GSP validation, and drug delivery. We then describe sensing devices for biomarker detection and DNA and protein sequencing. We also discuss the impact of nanotechnology on GSP and the associated challenges and opportunities. Our goal is to stimulate cross-disciplinary research in combining signal processing techniques with nanotechnology for optimal cancer diagnosis and personalized therapeutic intervention.

**ENGINEERING NANOSCALE PARTICLES**

Genetic mutations during the developmental process of cancer often produce distinctive molecular signatures. These signatures can be pinpointed by applying appropriate biomarkers. The recent development of biomarkers based on nanoscale designs coupled with cancer specific targeting agents, such as antibody probes, has the potential to provide sensitive and specific means to track tissue-specific targets, monitor the progression of cancers, and measure the effects of therapeutic treatments.

Figure 1 shows various kinds of biomarkers containing the necessary components, such as a targeting agent, so that the biomarkers can bind to the targeted tumor cells. For example, certain receptors, such as the epidermal growth factor receptor (EGFR), can be used to target the breast cancer cells. Because a receptor is expressed on the surface of a cancerous cell, the nanoscale design for the specific receptor can travel through the patient's circulation and bind specifically to those cancerous cells. Once the cancerous cell is labeled, an external device can be used to trace the activities of these cells in real time. The feedback information from these biomarkers can be used as the inputs to certain GSP algorithms for the feature selection or classification of cancer cells. Possible biomarker applications include: fluorescent tags on cell movement, drug and gene delivery, pathogen detection, protein movement tracking, DNA structure probing, tissue engineering, hyperthermia, separation and purification of biological molecules and cells, and magnetic resonance imaging (MRI) contrast enhancement. The development of tissue-specific biomarkers at different disease stages is important because tumors such as prostate cancer can have three to four stages, each exhibiting a distinct signature [4]. The multiple-variable information gained from the biomarkers can help improve the accuracy of prostate cancer related GSP algorithms. This, in turn, would allow the GSP algorithm to be deployed for an early detection of prostate-specific antigens like kallikrein 3. The knowledge gained would be important in the development of antibody-specific molecules that activate a patient’s immune system, thus suppressing the recurrence of cancer.

**NANOSCALE BIOMARKERS**

The knowledge gained from the Human Genome Project (http://doegenomes.org/) provides us with many new insights. One of these insights is that the human genome consists of only about 23,000 genes and is highly variable with approximately 60,000 functional polymorphisms. However, a major challenge is to identify novel genes and understand their...
functions and regulatory networks. Such information cannot be obtained from the study of structural genomics alone but will require other technologies. Newly designed biocompatible nanoparticles (<10 nm) can penetrate targeted cells for continual monitoring of intracellular events. The toxicity of nanomaterials can be further decreased by coating them with biocompatible materials. We can trace these nanoparticles to obtain high-resolution spatial and temporal information for GSP studies. Therapeutic nanomaterials, which are designed based on state-of-the-art biomarker technologies, are also expected to enable better targeting neoplastic cells in order to suppress the recurrence of tumors.

The size of a biomarker is important in determining whether it can penetrate through the porous structure of a cellular membrane. Nanoparticles can be made the same size as proteins or smaller. Size, however, is just one of the many sufficient conditions for utilizing nanoparticles as biotags. A nanoparticle should be coated with a biological layer, such as DNA, RNA, antibodies, collagen, or a small biocompatible monolayer for specific functions. Fluorescent, magnetic, paramagnetic, and metallic nanoparticles are widely used in nanobiomarker design. The core of these nanoparticles may have multiple layers and can be designed for multiple functions. For example, researchers can combine paramagnetic and luminescent layers so that these nanoparticles can be utilized for labeling and be manipulated remotely without interfering with the normal cell cycle. One of these techniques utilizes a superconducting quantum interference device (SQUID). Next, we will describe a number of biomarkers and discuss their potential for use in GSP and cancer genomics and proteomics. These techniques are still in the early stage of development and are subject to extensive evaluation in clinical trials.

METALLIC AND SEMICONDUCTOR NANOPARTICLES

Genomic and proteomic research generates enormous amounts of sequence data. High-throughput screening technologies are required to further advance research in these areas. Microarray technologies, however, are not cost effective for parallel analysis. A microarray, for example, easily reaches its limit when the number of array elements exceeds several millions. Optical biomarker or nanoparticle “bar coding” is an alternative technique. These markers can bind with specific DNA or RNA arrays to identify tissue-specific molecules. To identify and quantify protein-protein interactions for GSP study and cancer research, researchers can attach certain molecules with “tags” to different proteins on an array. The size distribution of the nanoparticle is critical when quantum effects are utilized to control material properties. To identify complex proteomes with large numbers of proteins, researchers developed a new technology using semiconductor nanoparticles, or quantum dots, as fluorescent tags. These nanoparticles can be broadly classified as metallic, semiconductor, paramagnetic, or magnetic nanoparticles.

Figure 2(a) and (b) shows the gold and semiconductor nanoparticles (to avoid copyright dispute, all nanoparticle example pictures in this article are taken from our labs). The authors in [6] created efficient fluorescent probes, which emit narrow light in a very wide range of wavelengths by tightly controlling the average particle size and size distribution. The spectral emission peaks of these fluorescent probes are narrow, typically 10 nm or less in wavelength. This design helps create biomarkers with many well-distinguished colors, because nanoparticles of a single color glow at nearly the same wavelength while different nanoparticles can create a great variety of distinct labels for biological tests. Compared with typical fluorescent proteins, these probes do not undergo rapid photobleaching and therefore do not rapidly cease to function as labels.
Figure 3 shows examples of semiconductor nanoparticles. These tags fluoresce only after protein–protein interactions have been established, which is important for researchers to investigate regulatory networks and signal pathways. Ideally, each protein should get a tag with a unique color, like the bar code of a product, so that one can immediately determine which proteins participate in multiple interactions. These nanoparticles can produce multiple colors and thus allow researchers to simultaneously measure many samples for their signatures. The use of semiconductor nanocrystals (e.g., quantum dots) as fluorescent labels for multiphoton microscopy enables multicolor imaging for living tissues. One of the challenges to analyze fluorescent nanoparticles is in vivo imaging. In [7], the authors proposed to use water-soluble cadmium selenide–zinc sulfide quantum dots to help multiphoton imaging in live animals. These fluorescent probes have two-photon action cross sections as high as 47,000 Goeppert-Mayer units, which is by far the largest of any label used in multiphoton microscopy. They also visually inspect quantum dots dynamically through the skin of living mice, in capillaries hundreds of micrometers deep. The researchers found no evidence of blinking (fluorescence intermittency) in solution on nanosecond to millisecond time scales. Another challenge in analyzing fluorescent nanoparticles is the accuracy of labeling. Fluorescent nanoparticles or tags can be used to monitor the effectiveness of cancer treatment in animal studies; these fluorescent tags, however, remain fluorescent even if the targeted cells are destroyed. To circumvent this problem, there are efforts in developing programmable fluorescent nanoparticles, which work like programmable memory units. These tags fluoresce when the target cells are alive, but no longer to do so once the target cells are destroyed.

PARAMAGNETIC NANOPARTICLES
Living cells are typically 10 \( \mu \text{m} \) in diameter and contain many submicron-sized components such as mitochondrion, endoplasmic reticulum, and nucleus. Proteins are even smaller with a typical size of just 5 nm, which is comparable to the dimensions of the current smallest man-made nanoparticles. The comparable size of nanoparticles and biological building blocks suggests the possibility of using nanoparticles as probes to spy on the working of intracellular machinery without introducing much interference [8]. Figure 4 illustrates two examples of magnetic particles. The researchers in [9] successfully utilized magnetic nanoparticles for cell separation and probing and also developed a nanoparticle-based immunosensor. The idea is to attach magnetic beads to an anti-IgG antibody. Gold nanoparticle labels can then stick to these magnetic beads for labeling. Instead of using the enzyme label, this design offers a simple and sensitive detection mechanism. By quantifying the number of attached gold nanoparticles, one can determine the presence of target cells.
particles, the authors can indirectly measure the concentration of a targeted IgG antibody. The nanoparticle-based immunosensors can be used for detecting different kinds of proteins simultaneously and for validating GSP algorithms.

To reduce the toxicity, monolayers of an inert material, such as carbon paste or silica, are often utilized to protect the core nanoparticle. An additional linker molecule is also required. This linker molecule has two types of organic groups at each of its ends; one group is aimed at attaching the linker to the nanoparticle's surface, and the other is utilized to bind antibodies, dextrans, or fluorophores, depending on the applications [5]. The shape of a nanoparticle is often spherical, and this shape may limit the possibilities of using these nanoparticles as multifunctional biomarkers. For oncological or radiotherapeutic purposes, physicians would like to have nanoparticles of different sizes and shapes for different targeted treatments. Cylindrical, plate-like, and other shapes are possible as shown in Figure 4(b). The authors in [10] developed cylindrically shaped nanoparticles by employing metal electro-deposition in a nanoporous alumina template. The cylinder radii, which could be selected depending on the properties of the template, were in the range of 5–100 nm, while its length could be as large as 60 μm. The researchers demonstrated that, by sequentially depositing various thicknesses of different metals, the structure and the magnetic properties of individual cylinders could be tuned widely. Various ligands can be selectively attached to different segments of the nanocylinder. For example, porphyrins with thiol or carboxyl linkers can simultaneously attach to the gold or nickel segments, respectively. Thus, multifunctional magnetic nanobiomarkers can be made, and a weaker external magnetic field can be used to guide these magnetic-markers to desired locations. Nanoparticles can also be assembled in different fashions. Figure 5 shows paramagnetic nanoparticles in a chain. By assembling the nanoparticles in a chain fashion, we can prevent these particles from being uptaken by cytokines (the size of these nanoparticles is <10 nm). Due to their special shapes, these particles can be easily tracked and recovered.

Magnetic and paramagnetic nanoparticles emit very weak magnetic fields \((10^{-14} \text{T})\). A SQUID is an extremely sensitive device for detecting magnetic flux. For example, this device is used to measure the heart's magnetic field \((10^{-10} \text{T})\) and the brain's magnetic field \((10^{-13} \text{T})\). The SQUID has the potential to be used for manipulating and tracking magnetic and paramagnetic nanoparticles in vivo. The device consists of two superconductors separated by thin insulating layers to form two parallel Josephson junctions. The flux-to-voltage characteristic has been used to detect small magnetic field, current, voltage, inductance, and magnetic susceptibility. When the SQUID is biased with a current greater than the critical current, the voltage across the SQUID is modulated with the flux. The sensitivity of the device is \(<10^{-6} \text{gauss/Hz}\), the spatial resolution is about 1 μm, and the signal-to-noise ratio is about \(10^4\) [11]. Magnetic particles labeled with molecular recognition elements can bind to the tissue-specific targets. A SQUID can then detect very small magnetic fields [12] because the majority of nanoparticles contain iron or other metal elements. A SQUID, therefore, provides quantitative and also spatial information about a cancer cell in vivo. SQUID sensors have been developed for traditional low-temperature superconductors. Researchers are now fabricating SQUIDs with new materials. In addition, for decades, SQUIDs have been used in noninvasive clinical imaging scanners such as magnetoencephalography (MEG) for epilepsy and mental health research and magnetocardiography (MCG) for detecting cardiac bioelectrical activity noninvasively. The incorporation of nanoparticles into cancer patients would have the potential to extend such noninvasive imaging techniques into oncological disease space.

The authors in [13] developed a technology called magnetism-based interaction capture (MAGIC). MAGIC can help deliver genes or drugs to target locations where conventional delivery methods cannot reach. It can also identify molecular targets due to the induced movement of superparamagnetic nanoparticles (coated with a small molecule of interest) inside living cells. The authors in [13] demonstrated that the efficient intracellular uptake of superparamagnetic nanoparticles was mediated by a transducible fusogenic peptide. These nanoprobes captured the small molecule's labeled target protein. A

CANCER CAN BE DESCRIBED AS A DEREGLATION OR HYPERACTIVITY IN A GENE REGULATORY NETWORK, WHICH CAN RESULT IN ABNORMAL INTRACELLULAR AND EXTRACELLULAR SIGNALING EVENTS.
MAGIC-based device was translocated in a direction guided by an external magnetic field. Researchers can utilize this MAGIC-based device in genomic expression screening and in identifying multiple drug-targeted proteins. MAGIC can also be utilized to monitor various signal-dependent modifications and signal pathways.

**NANOPARTICLES FOR DRUG DELIVERY**

Drug delivery is an important application of nanoparticles because some organelles are difficult to reach by conventional therapeutic treatment. Nanoparticle can help deliver genes or drugs to target locations where conventional delivery methods cannot reach. This design can also help GSP investigation. For example, we can use this technique to deliver siRNA to knock out specific genes for apoptosis study. Signal processing algorithms can then be developed to track and measure the apoptotic process. The hollow nanoparticle in Figure 6 is an example design that allows a gene or drug to be encapsulated inside the nanoparticle. The desirable feature of these nanoparticles is that we can control the release of the drug in an easy way: via controlling the surface area of these nanoparticles. Dendrimers are an early example for this type of design. Although they are not at the nanoscale level, researchers are emulating the dendrimer design in developing nanoparticles for controllable drug release. We introduce dendrimers below to give readers a good understanding of how programmable drug release works.

Dendrimers are highly branched spherical polymers that have a unique surface of primary amino groups with high solubility in water [15]. Figure 7 shows the schematic diagram. Because of the high number of positive charges on their surfaces, dendrimers form stable electrostatic complexes with negatively charged nucleic acids. Researchers utilized dendrimers to transfer genes to various cell lines with a higher efficiency and less cytotoxicity than polylysines [16]. Dendrimers are efficient at delivering oligonucleotides even in the presence of high concentrations of serum proteins because they protect the oligonucleotides from the degradation by exonuclease [17]. Dendrimers can also be utilized to deliver drugs for inducing programmed cell death.

Dendrimer disassembly is a new nanotechnology technique [18]. As mentioned previously, dendrimers are commercially available in different molecular weights and sizes. They have recently emerged as one of the most suitable drug carriers because of their biocompatible properties and their nanometer size and dimension. Dendrimers can be tailored to mimic certain biomolecules, and scientists are also working on designing biocompatible dendrimer materials. The operating principle is that dendrimers can be constructed to fall apart in response to a single triggering event, such as an enzymatic reaction of a signaling event. As the dendrimers fall apart, they release the molecules that they are carrying [18]. The mechanism of the dendrimer disassembly is as follows. Dendrimers are the covalent assemblages of active species. The disassembly is an opposite process that enables the release of these species into a system. This design is useful in drug delivery; a drug can be encapsulated in the dendrimers and released by chemical means to disassemble the dendrimers. As a result, this method would provide a more targeted or localized drug delivery than current methods while reducing the drug’s side effects. Dendrimer disassembly is a powerful mechanism, in which dendrimers and dendritic structures can be made up of a wide variety of subunits. Dendrimer materials with disassembly capabilities can be used as biosensors for cancer detection.


[FIG7] Dendrimers are highly branched spherical polymers (adapted from [6]).
SENSING DEVICES FOR CANCER GENOMICS AND PROTEOMICS

GSP for cancer research involves an array of biotechniques, such as microarray, two-dimensional-gel electrophoresis, and mass spectroscopy. Researchers are attempting to develop more accurate and sensitive techniques to monitor cellular changes of cancer cells in both temporal and spatial domains. The research so far has been focused on the development of MEMS devices. Signal disturbance due to background noise, however, remains as a major challenge for accurate measurement in MEMS devices. The sizes of MEMS devices are also too large to be used for cellular studies. These problems motivate the development of new schemes incorporating nanotechnology to monitor intracellular activities since a nanoscale device can be made hundreds of times smaller than a cell. Nanoscale sensors can assist in checking cellular behaviors, examining proteins, and detecting RNA splicing at the cellular level. A number of examples of nanoscale sensors for GSP are provided as follows.

ELECTROCHEMICAL METHODS TO DETECT GENOMIC INSTABILITY

A biochip is a tiny portable device for analyzing cellular behavior. The device is also called a lab-on-a-chip because all chemical reactions occur inside the biochip’s proprietary buried channels or on its surface. MEMS are used to study or manipulate small objects, such as living cells. MEMS devices are small instruments that can handle microdynamics and microfluidics in living organisms. A biochip can perform nucleic-acid amplification and detection on one chip, as shown in Figure 8 [20].

A lab-on-a-chip includes a section for detecting and another for amplifying DNA samples by precisely controlled heating. A biochip’s layout and manufacturing process rely heavily on microfluidic MEMS technology, which includes inkjet printer technology and well-established IC-fabrication techniques. Biochips can be used to monitor cellular behaviors, such as cell metabolism, cell morphology change, intracellular fluid flows, and even cellular signal pathways [21]. By monitoring these cellular behaviors, researchers can accurately separate normal cells from cancerous cells, which are useful for GSP in terms of feature selection and classification. Most importantly, these devices can deliver DNA analysis results in minutes rather than in hours. MEMS devices can be broadly classified into invasive and noninvasive devices. For instance, invasive or implantable MEMS devices can deliver drugs, coddle graft tissue, and protect transplanted cells [22], whereas noninvasive devices are used in studying molecular cell biology including single-molecule, single-cell, and cell population studies [23].

Although MEMS devices do not use nanotechnology, researchers are now working to miniaturize these MEMS devices to the nanoscale. These nanoscale devices are called NEMS devices. Many microfabrication techniques used in MEMS are still deployed in NEMS fabrication. MEMS components can now be reliably made with the feature sizes below 100 nm. Therefore, there is no clear boundary between NEMS and MEMS. Nanoelectromechanical systems use fewer reagents and less power than conventional MEMS systems and enhance device sensitivity and reduce noise interference. Nanoscale electrochemical methods can be utilized to detect DNA hybridization. They include i) monitoring a change in the oxidation/reduction peak current of a label that selectively binds with DNA, ii) monitoring the electrochemical signals of the substrate after hybridization with an enzyme-tagged probe, and iii) monitoring the electrochemical signals of a metal nanoparticle probe attached after hybridization. Researchers have developed several nanoscale monitoring techniques by combining NEMS designs, including the use of metal nanoparticles as labels for the detection of DNA hybridization and carbon nanotubes for the electrochemical detection of DNA hybridization [40].

NANOPORES FOR READING OUT GENOMICS AND PROTEOMICS INFORMATION

Many GSP studies depend heavily on genomics and proteomics sequencing. Modern DNA sequencing techniques require about 10^{10} copies of template DNA for sequencing devices that utilize gel electrophoresis. DNA sequencing requires two working days using gel electrophoresis and one day using capillary electrophoresis. Current techniques for examining a base-pair cost about US$0.50–$1. Examining the genotype of over 10,000 to 1 million base pairs using the conventional approach would be costly. To reduce sequencing error, processing time, and the cost involved with such a process, researchers proposed a better idea for sequencing DNA: using nanopores to analyze a single strand of DNA [24]. The nanopore design began around 1991. Nanopores are holes as small as 30 atoms across, which exist in all living organisms in such forms as “breathing holes,” through which molecules can pass [25].
A nanopore is essentially a protein channel in a lipid bilayer or an extremely small hole in a thin, solid-state membrane. Its diameter is comparable to the diameter of DNA molecules [26]. An applied voltage across this membrane generates a potential, thereby pulling the DNA molecule through the nanopore. The passing of different nucleotides through the nanopore causes ionic current fluctuations that can be detected by using sensitive electronic devices. The pulling of the DNA molecule is achieved electrophoretically through an applied electric potential [27]. A DNA molecule can be pulled through a nanopore and analyzed in microseconds. This new design is much faster than the conventional DNA sequencing method.

The basic idea behind nanopore design is that the amount of ionic current blockage will differ for each of the nucleotides on the DNA when the DNA passes through the pore. The technical challenge lies in making the nanopore. Researchers used alpha-hemolysin as the nanopore [29]. Alpha-hemolysin is a 293-amino acid protein toxin, which is derived from the common bacterium Staphylococcus aureus and can self-assemble into a protein channel on cell membranes. Testing results show that a high 100 pA ionic current passes through the alpha-hemolysin nanopore when a potential of 100 mV is applied. However, according to the report from NASA [30], it is difficult to achieve sufficient accuracy from alpha-hemolysin. As is the case with many biological molecules, alpha-hemolysin has limited lifetime (5 min to 24 h) as well as lumen irregularities and lipid bilayer fragility. Furthermore, the interactions of DNA with the inner cavity of alpha-hemolysin are frequent and unpredictable. All these properties make alpha-hemolysin unsuitable for commercial applications.

Hence, research focus has been shifted to the use of solid-state nanopores for sequencing DNA. Currently, a well-characterized nanopore is the Si3Ni4 or the SiO2 membrane nanopore that replaces the lipid bilayer in the nanopores of alpha-hemolysin [31]. This semiconductor nanopore will ensure more conformity in shape and finer control of DNA entry into the nanopore. The nanopore is difficult to make as is controlling the size of the nanopore diameter to within several nanometers. The speed at which DNA translocates through the nanopore is another significant problem facing researchers. Nonetheless, the alpha-hemolysin structure is still useful as a reference for solid-state nanopores, as it has been tested extensively and has enjoyed moderate success. Another approach is to use a carbon nanotube (CNT)-based nanopore for DNA sequencing. In this design, a single-wall carbon nanotube serves as a nanochannel connecting two containers charged with positive and negative voltage. The diameter of the CNT-based nanochannel is so tiny (around 1.5 nm) that it allows only single-strand DNA to pass through. The translocation of each nucleotide on a DNA strand is monitored by recording the ionic current modulation or “blockade” that occurs whenever a translating polymer occupies the nanopore. Based on the difference between recorded current values, we can distinguish individual nucleotides and thus sequence the DNA strands. The translocation process of a polymer chain from a source container to a drain container through a nanochannel is reported in [28]. The conductance change when DNA molecules attached to the side-contact CNT probe is simulated in [32].

These nanopore devices sequence a single-strand of DNA at the speed of $10^4$ bases/s. The device requires 15 min to complete a sequencing protocol in average. This is about 30–40 times faster than the most efficient conventional protocols (e.g., capillary sequencing with an ABI3100). The device can sequence DNA strands that are tens of thousands of base pairs in length, possibly as long as an entire gene, in one pass through the nanopore. These devices can sequence DNA without amplification, thus significantly reducing noise when compared with the conventional microarray approach. The nanopore device has significantly fewer errors than the present Sanger method, and the error rate should be less than $10^{-6}$ [33]. It is expected that these devices will revolutionize DNA sequencing. With the advances in DNA-sequencing techniques, the nucleotides (A, T, C and G) on the DNA can be digitized, such as “00, 01, 10, and 11.” Biology would then become “digital biology,” and a broad spectrum of digital-processing techniques could be deployed to decipher cancer mechanisms. The ultimate design goal is to build digital circuits that emulate cancer cell mutation and simulate biological process, e.g., gene regulatory networks.

**NANOMECHANICS FOR GENOMICS AND PROTEOMICS**

Microfabricated cantilevers are developed to detect the changes of surface stress when DNAs bind to targeted receptor-ligands. A variety of nanoscale techniques, such as atomic force microscopy (AFM), have been quantifying and characterizing biomolecular interactions, such as cell adhesion or receptor-ligand interactions. An illustration of the nanomechanical detection of biomolecules is shown in Figure 9. The red and blue curves represent different oligonucleotide-based
sequences attached to the nanoscale beams. When the oligonucleotides are hybridized with their complementary ones, the beam starts to bend. Based on the bending angle, the researchers can estimate the amount of targeted oligonucleotides. The differential deflection of the cantilevers was found to provide a true molecular recognition signal despite the large nonspecific responses of individual cantilevers. By putting cantilevers in an array, the authors in [34] could select various biomolecules. For instance, the hybridization of complementary oligonucleotides showed that a single base mismatch between two 12-mer oligonucleotides was clearly detectable. Similar experiments on protein immunoglobulin interactions demonstrated the wide-ranging applicability of nanomechanical transduction to detect biomolecular recognition [34]. Such an approach has been used to study DNA hybridization reactions with single base pair mismatch, antigen-antibody binding of cancer-related proteins at clinically relevant concentrations, and phosphorylation reactions by kinases.

To reduce the noise induced by the cantilever, researchers are working on improving the accuracy of nanoscale cantilevers. Electrospray ionization mass spectrometry (EIMS) is a promising technology. The technique is sensitive and can filter out the noise caused by cantilever so that it usually can be carried out on small amount of sample. Typically, 10 µl of a 1–10 µM protein solution is needed for an analysis. The use of this mass spectrometry is an alternative technique that is based on nanomechanical design and can weigh as low as 10–100 Dalton [35]. EIMS provides exact mass and stability to fragmentation information by analyzing the mass or the charge ratio of ions in the gas phase. While mass spectrometry is largely used in biological and polymeric tools, significant advances in the development of EIMS techniques have shown soft-ionization methods, such as electrospray. These techniques are ideal for studies of solution phase species in the gas phase without perturbation of the solution structures. For this reason, these techniques are particularly useful in biological study.

**NANOTOOLS FOR ANALYZING AND MANIPULATING MOLECULAR PROCESSES**

Cancer can be described as a deregulation or hyperactivity in a gene regulatory network, which can result in abnormal intracellular and extracellular signaling events. Because gene microarray analysis cannot provide the information needed for post-translational phosphorylation, the researchers in [36] proposed a “reverse phase protein microarray” technique to measure and profile these intracellular and extracellular signaling events. The information can benefit GSP in terms of understanding signal pathway and communications between cells. In this study, the researchers used the ovarian epithelial carcinoma as an application example. The treatment of ovarian cancer, unfortunately, always takes place during metastasis since this disease is often not detected until late stages. This reverse phase protein microarray technique has been used to study the molecular network within a tumor specimen and to investigate signaling changes occurring upon metastasis and common pathway elements arising in the metastatic microenvironment [37]. Various nanotechnology tools for understanding cellular behavior, the difference between normal and abnormal cells, and communications between cells have also been discussed in [38]. These tools can measure energy metabolism, internal fluid flow, transportation of components, and the signaling pathways of cells. Remotely controlling the functions of nanotools is desirable. For example, magnetic nanodevices can be delivered to a tumor site and then be either made to release the drug load or just heated to destroy the cancerous cells. The trend in developing nanotools is to make them multifunctional and controllable by external signals or by a local environment, thus essentially turning them into nanodevices.

**CHALLENGES IN COMBINING NANOTECHNOLOGY AND GSP**

Current cancer genomics and proteomics research heavily relies on microarray techniques. Many articles in this special issue address the software design and development of signal processing methods in genomics and proteomics. With the emergence of new nanotools and nanoscale biomarkers, we expect significant advancements to be achieved by coupling both research areas, specifically in reverse genetics, data collection for genomics and proteomics, hypothesis validation for systems biology, construction of biological networks, sequence analysis, and molecular and subcellular imaging [1]. For instance, by designing genetic-specific biomarkers using nanotechnology, multiple in vivo biopsies would become possible. Signal processing methods can then be utilized to analyze these multiple-variable problems in parallel and can be integrated with nanotechnology tools for creating effective cancer diagnosis solutions. Many challenges, however, remain. In what follows, we list the major challenges for applying nanotechnology in GSP and in cancer diagnosis and treatment (please also refer to [39] for more details).

- The translation of nanotechnology-based biomarkers from cellular GSP studies to animal and human applications is nontrivial. The challenge is to design reliable engineering and manufacturing processes to make devices that evaluate nanoscale biomarkers efficiently.
Nanotechnology for GSP in cancer treatment requires joint efforts from biologists, clinicians, computer scientists, and engineers. Biologists and clinicians tend to use nonquantitative (e.g., a patient has cancer or not) and hypothesis-driven approaches, whereas engineers are inclined to use mathematical (e.g., what percentage of cells are cancerous cells) and technology-driven approaches. To cultivate cross-disciplinary research and communication, we believe that the next generation of biologists will need a more extensive background in quantitative mathematics and systems engineering while future students of engineering and computer science will have to acquire sufficient knowledge in particular areas of biology.

To enable close coupling between signal processing and nanotechnology for cancer genomics and proteomics, open and sharable databases are needed. These databases will serve as repositories of searchable information, such as the cytological profiling of small molecular compounds, and the modeling platform connecting measurements at different spatiotemporal scales from cancers.

GSP models for cancer genome and proteome can vary from patient to patient. The challenge of integrating GSP with nanotechnology includes i) designing personalized cancer treatments and ii) further advancing from treatment methods to prevention.

Researchers are trying to use GSP methods to find tissue-specific cell surface molecules and then to use these molecules to develop antibodies for cancer-cell detection. The challenge is to apply nanotechnology coupled with GSP that can activate the innate immune system for cancer treatments.

To help researchers address the aforementioned challenges, the U.S. government sponsors many programs to support nanotechnology research for cancer genomics and proteomics:

- The National Cancer Institute (NCI) created the “Unconventional Innovations Program” (UIP). The UIP has taken a new management approach to the development of technologies that target either quantum improvements in existing technologies or entirely new approaches, rather than incremental improvements. The UIP program actively funds researchers from different disciplines that have not traditionally received supports from NCI. The details of the program are available on the NCI Web site http://otir.nci.nih.gov/tech/uirp.html. The innovative molecular analysis technologies (http://otir.nci.nih.gov/tech/imat.html) is another program supporting technology development for detecting the alterations and instabilities of genomic DNA, and for analyzing and detecting genes or cellular products, including the post-translational modification and function of proteins.

- NASA and the National Cancer Institute (NCI) are collaborating on the development of innovative minimally invasive sensing technologies and disease-intervention strategies for biomolecular sensors (http://nasa-nci.arc.nasa.gov).

- The division of Early Detection Research Network (EDRN) in the NCI sponsors research in the areas of: i) developing and testing biomarkers and nanoscale detection technologies, ii) molecular genetics and clinical oncology, and iii) public health and clinical applications for early cancer prevention and detection (http://www3.cancer.gov/prevention/cbpg/edrn).

- Other agents including the Advanced Technology Program (ATP) in NIST (http://www.atp.nist.gov) are also interested in supporting nanotechnology research for cancer genomics and proteomics. The grants support benchmark development for evaluating the performance of nanodevices.

The goal of these government-funded programs is to develop integrated platforms for cancer diagnosis, prognosis and treatment platforms.

CONCLUSIONS

Biology research today is data intensive and is becoming an information science endeavor. GSP has been an active research area over the past decade and aims to integrate signal processing theories and methods with a global and systematic understanding of functional genomics and proteomics. New development in nanotechnology has the potential to make significant contributions to the understanding of cancer biology and the disease management of cancer. Nanotechnology also provides an effective means to facilitate communications between genes and proteins within the living cells and the outside world, thus allowing the detection and treatment of cancers early on. Scientists and clinicians expect that cancer diagnosis, prognosis, and treatment can be fully integrated into the delivery of personalized medical care. This timely article reports the exciting nanotechnology for GSP beyond microarray technology and the challenges and opportunities that we are facing. Much nanotechnology research for genomics and proteomics involves chemistry, material science, and device engineering. We hope that this article will motivate researchers and scientists from these different disciplines to work together in designing the new generation of nanotools and corresponding GSP solutions for combating cancer.

ACKNOWLEDGMENTS

The authors would like to thank Jie Zeng and Xiaoping Wang for valuable discussions about creating nanoparticles and nanoparticle pictures. The authors would also like to thank Dr. James Xing for valuable discussion about cancer biology. Andrew Burke and David Cao drew the schematics for this article. Woon Tiong Ang, James Bell, and Thomas McIntyre assisted with the
finalization of this article. The funding support of Jie Chen is from the NSERC discovery grant and the Idea to Innovation Program. The funding support of Stephen Wong is from a Research Center Grant from the Harvard Center of Neurodegeneration and Repair, Harvard Medical School.

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