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Materiomics for Oral Disease Diagnostics and Personal Health Monitoring: Designer Biomaterials for the Next Generation Biomarkers

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Abstract

We live in exciting times for a new generation of biomarkers being enabled by advances in the design and use of biomaterials for medical and clinical applications, from nano- to macro-materials, and protein to tissue. Key challenges arise, however, due to both scientific complexity and compatibility of the interface of biology and engineered materials. The linking of mechanisms across scales by using a materials science approach to provide structure–process–property relations characterizes the emerging field of 'materiomics,' which offers enormous promise to provide the hitherto missing tools for biomaterial development for clinical diagnostics and the next generation biomarker applications towards personal health monitoring. Put in other words, the emerging field of materiomics represents an essentially systematic approach to the investigation of biological material systems, integrating natural functions and processes with traditional materials science perspectives. Here we outline how materiomics provides a game-changing technology platform for disruptive innovation in biomaterial science to enable the design of tailored and functional biomaterials—particularly, the design and screening of DNA aptamers for targeting biomarkers related to oral diseases and oral health monitoring. Rigorous and complementary computational modeling and experimental techniques will provide an efficient means to develop new clinical technologies *in silico*, greatly accelerating the translation of materiomics-driven oral health diagnostics from concept to practice in the clinic.

Future(s) in the Making: Next Gen Biomarkers

When there is a change in your health, you want to find out as early as possible. Today, you can go to a local pharmacy and purchase highly advanced screening devices for chronic diseases such as diabetes (detecting glucose levels in the blood) and happier life events such as pregnancy (hormones in urine). One can envision a future pharmacy that has simple tests for a wide array of afflictions, including heart disease, cancers, tumors, Alzheimer's, Parkinson's, and other disorders. It is well known that regular screening tests (along with follow-up tests) reduce your chance of dying from many forms of cancer and other diseases. In theory, screening tests find early warning signs, when the chances of survival are highest. Some of these early warning signs are constantly emitted from your body *via* breathing, oral secretions, and other bodily emissions. Just as the gaseous components of an automobile's exhaust can be used to diagnose the ''health'' of the engine, some of components of your breath can be analyzed for oral health monitoring (Fig. 1).

At the forefront of such diagnosis capacity is the efficient identification and screening of oral biomarkers. Cholesterol, glucose, C-reactive protein (CRP), and human chorionic gonadotropin (hCG) are common examples, used to determine the likelihood of cardiovascular disease, diabetes, inflammation, or pregnancy, respectively. These biomarkers are typically simple molecules (cholesterol, for example, is simply $C_{27}H_{46}O$). Thus, the development of sensor and microsystem and low-cost screening technologies for point-of-care testing are turning towards nanotechnologies. Shrinking sensors to the nanoscale introduces novel selectivity mechanisms and enables the ultimate sensitivity limit: *single-molecule detection*.

In general, molecular selectivity can be achieved by engineering the interface of sensor material and biomarker. Understanding these sensors requires a range of modeling and simulation tools and presents a unique challenge to learn how

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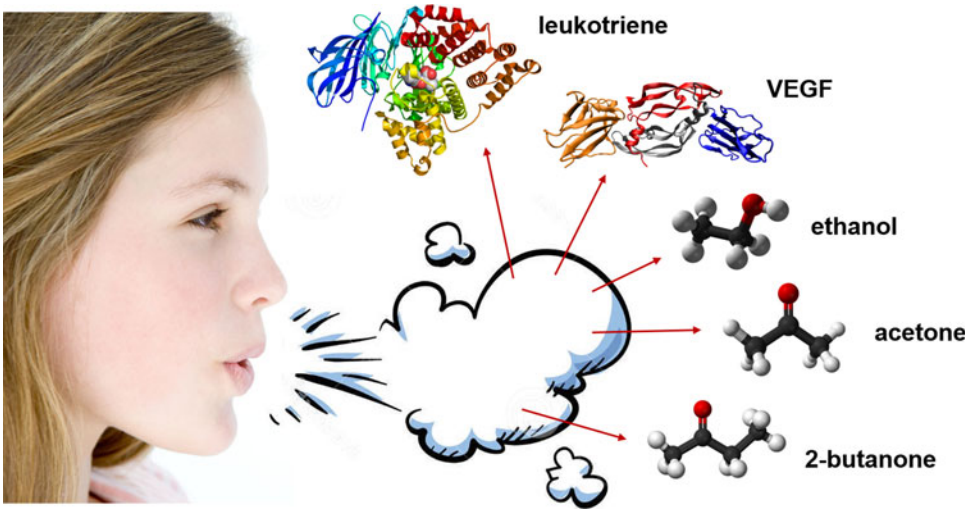

FIG. 1. The data in your breath: schematic of example biomarkers for potential health monitoring *via* breathe analysis. Example molecular structures include (*top to bottom*): leukotrienes (PDB: 1HS6), an inflammatory mediators linked to both asthma and COPD (Grob et al., 2008); vascular endothelial growth factor (VEGF, PDB: 1FLT), a cancer biomarker for breast cancer, lung cancer, and colorectal cancer, as well as rheumatoid arthritis (Rusling et al., 2010), and a trio of volatile organic compounds (VOCs)— ethanol, acetone, and 2-butanone—with concentrations correlated with both cancer and diseases such as diabetes (Garcia et al., 2014).

these potential materials interact with small molecules, to enable optimization of detection systems. Experimentally, noisy stochastic responses and limited spatiotemporal resolution are difficult to delineate precise atom-to-atom interactions. Computational approaches can enhance the characterization of molecular detection as an effective ''virtual microscope''.

The key challenge is thus developing sensing nanotechnologies that can extract the necessary data from a single breath. One potential solution is designer biomaterials that signal a targeted biomarker with specificity and reliability, similar to the catalytic systems applied to automobile exhaust (Goltl et al., 2013). The problem is thus no longer pathological, but becomes one of materials design.

Biomaterial Screening and Materiomics

Biomaterials have a huge impact on health care (Bell et al., 1979; Langer, 1998; 2001; Peppas and Langer 1994), and are being widely used in medical devices (Lendlein and Kelch, 2002; Lendlein and Langer, 2002; Stangel et al., 2001) and drug delivery systems (Lahann et al., 2003; Pun and Davis, 2002; Santini et al., 1999). Advancements have been made in the understanding of the natural functions of biological materials and systems, and more importantly, in designing and synthesizing new functional biomaterials useful in clinical applications (Hartgerink et al., 2002; Peppas, 1997; Vacanti and Langer, 1999; Zhang, 2002).

The necessary design space of materials and molecular compounds is clearly vast, with only a small percentage of possible materials being exploited in useful technologies. For complex interactions, high-throughput screening of molecular compounds has been the traditional *brute force* approach, and commonly applied in drug discovery (Broach and Thorner, 1996; Krstulovic, 1999). Recently, drug discovery has moved toward more rational strategies based on our increasing understanding of the fundamental principles of protein–drug or cellular–drug interactions.

With advancements of simulation and modeling, virtual approaches to screening have been successfully implemented with a goal of reducing large compound databases and to select a limited number of promising candidates for drug design (Jiang et al., 2003; Pozzan, 2006; Toledo-Sherman and Chen, 2002). Indeed, high-throughput computational materials design is an emerging area of materials science. By combining advanced thermodynamic and electronic-structure methods with intelligent data mining and database construction, and exploiting the power of current supercomputer architectures, materials scientists can generate, manage, and analyze enormous data repositories for the discovery of novel materials (Curtarolo et al., 2013; Yang and Tarascon, 2012).

It is now believed that computational methods can be exploited to better understand the use, selection, development, and discovery of materials, with a goal to achieve high-speed and robust acquisition, and dissemination of diverse materials data. Used as a screening tool, biomaterial systems can be designed, refined, and optimized prior to synthetic efforts, in an efficient manner. Moreover, computational approaches allow parametric exploration of parameters (e.g., interaction energies, and extreme temperatures or pressures) difficult to attain experimentally, and can thus be used to develop and confirm theoretical descriptions beyond a finite set of empirical data points.

This is one of the governing foundations of the recently proposed Materials Genome Project (Jain et al., 2013), removing guesswork from materials design and ''*accelerating materials discovery through advanced scientific computing and innovative design tools*.'' The concept that combinatorial computational screening can lead to material discovery and

property optimization has been recently demonstrated in applications such as solar energy generation (Castelli et al., 2012) and battery development (Mueller et al., 2011).

These successes, however, typically involved relatively exotic metal alloys and compounds. For biological and medical applications, physiological effects of the material such as toxicity must be considered, complicating matters. A more rational screening method must be applied, using known biocompatible materials as a platform, and considering system interactions beyond single property optimizations. This leads to the emerging field of materiomics.

'Materiomics' is defined as the systematic study of the complete material system. It examines links between physiochemical material properties and material characteristics and functions, particularly in biological roles—a paradigm similar to systems biology (Boer and Blitterswijk, 2013; Cranford and Buehler, 2010; 2012; Cranford et al., 2013). Simply put, materiomics rigorously attempts to map the possible interaction space of material combinations. Through materiomics, fundamental advances in our understanding of biological systems contribute to the mechanistic understanding of certain diseases and facilitate the development of novel biological, biologically inspired, and completely synthetic materials for applications in medicine (biomaterials), nanotechnology, and engineering. Inspired by genomics, many more 'omic disciplines' have been defined and studied (Table 1).

'Omic' is traditionally a general term for a broad discipline of science and engineering for analyzing the interactions of biological systems that can also be referred to as high-

Table 1. Some Common 'Omics' and their Focus and Scope Described Illustratively*

Omic	*Definition*	*Focus*	*Scope*	*Reference*
Omics	Informally referring to a field of study in biology ending in *-omics*	Analyzing the interactions of biological information in various 'omes'	Appling research paradigm to produce knowledge en masse from networks of information via holistic principles and methods	Horgan et al., 2011; Ward et al., 2002
Materiomics	The holistic study of material systems, examining links between physiochemical material properties and material characteristics and function	Material interaction space and characterization through components, structure, and function; *materiome*	Analysis of material systems through constitutive components, hierarchical and combinatorial SPP relations, cross-scale interactions, and effects on functionality	Cranford et al. 2010; 2013
Genomics	A discipline in genetics that applies recombinant DNA, RNA sequencing methods, and bioinformatics to sequence, assemble, and analyze the function and structure of genomes	An organism's entire hereditary information; *genome*	Determination of entire DNA sequences of organisms, fine-scale genetic mapping including genes, regulatory and noncoding sequences	Horgan et al., 2011; Schattner, 2009
Proteomics	The study of proteomes and their functions	Protein characterization, protein-coding regions of the genome; *proteome*	The entire complement of proteins produced by an organism or system, including protein structure, function, and expression	Horgan et al., 2011; Wilkins et al., 2006; 2009
Transcriptomics	The study of the transcriptome using high-throughput methods	RNA transcripts produced by the genome at any one time; *transcriptome*	Examining the expression level of RNA in a given cell population, which vary with external environmental conditions, including mRNA, rRNA, tRNA, and noncoding RNA	Horgan et al., 2011; Wang et al., 2009

*Citations provided are representative examples and not intended to be canonical works.

dimensional biology (Horgan and Kenny, 2011). Such fields are typically characterized by general systems (such as genomics for genes or proteomics for proteins) or processes (e.g., transcriptomics for genetic transcription or interactomics for cellular interactions). Omics technologies offer a system-wide approach to discover novel diagnostics and biomarkers for personal health monitoring (Arafah et al., 2014; Gu and Sivanandam, 2014; Pawar et al., 2014), while the new emerging field of materiomics forges innovative bridges between omics systems science and materials science (Cranford and Buehler, 2010; Cranford et al., 2013).

Materiomics can be conceptualized as the convergence of materials science, biological science, and technological advancements (encompassing computational methods and experimental tests) (Fig. 2). It provides a complete toolset required to describe the complexities introduced by multiscale relations, discrete hierarchical materials, cross-phase interactions, and structure–property dependencies across all scales that are critical to all biological materials. Moreover, materiomics can be applied in elucidating the biological role of materials, for example, in the diagnosis of diseases or even be exploited to predict diseases in the context of diagnostic tools by measuring material properties rather than focusing on symptomatic chemical readings alone, providing new strategies for treatment options. It can also be utilized to develop novel biomaterials which possess great diversity of potential in fields of bioengineering, biomedical devices and medicine. Inevitably, materiomics directs the advancement of nanoscience and nanotechnology, where materials science from biology will enable the bottom-up development of unique and effective biomaterials and devices.

Biomaterials Development

Biomaterials are defined here as materials composed of biologically derived components (e.g., amino acids or deoxyribonucleic acid (DNA)) irrespective of their applications. The field of biomaterials research has been very successful over the past 50 years, with a lot of innovations and developments affecting people's lives. It was witnessed by the introduction of a number of sensational devices that had relied on coordinated materials development, such as heart valves, hip implants, and contact lenses.

Another example can be the recent advancements in recombinant DNA techniques, bringing together genetic material from multiple sources and creating sequences and/or materials that would not otherwise be found in biological organisms [e.g., manipulating sequence replication in E. *coli* (Hannig and Makrides, 1998; Sorensen and Mortensen, 2005)]. There is now an ever-increasing interest in a variety of applications that require materials to be green, self-assembled, low-cost, biodegradable, energy efficient, self-healing, high

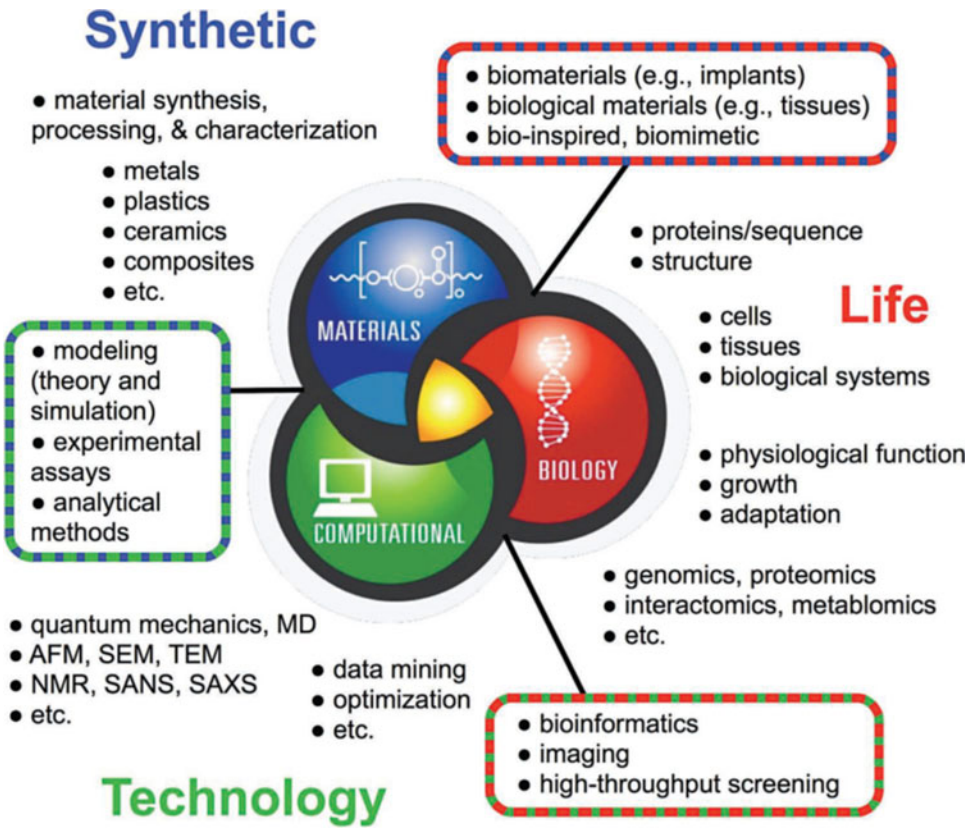

FIG. 2. Scope and effect of Materiomics. The interface of materials science (''synthetic'') and biology (''life'') has been successful in the development of new biomaterials, but recent technological advancements (''technology''—computational capabilities, experimental methods such as AFM, and imaging techniques such as NMR) allow for a truly integrated and holistic approach. Image reproduced with permission from Cranford et al. (2013).

sensitive, etc., such that biomaterials research encompasses all forms of biocompatible and biomedical materials, as well as biomimetic and bio-inspired systems (Meyers et al., 2008; 2011; Ruys, 2013; Sionkowska, 2011).

In the current age of technology, new materials for biomedical and clinical applications have undergone a modern Renaissance with a steady introduction of new ideas and productive branches (Burg et al., 2000; Eisen and Brown, 1999; Langer and Tirrell, 2004; Langer and Vacanti, 1993; Ma, 2008; Shin et al., 2003; Zhu and Snyder, 2003). The new generation of biomaterials includes surface-modified materials to overcome nonspecific protein adsorption *in vivo*, synthetic materials with controllable properties for drug delivery or as cell carriers, 3D architectures to produce well-defined patterns for disease diagnostics [e.g., biological microelectromechanical systems (BioMEMS)] and tissue engineering, just to name a few (Langer and Tirrell, 2004; Ratner and Bryant, 2004).

Materials that are sensitive to their surroundings, such as pH, temperature, and light, have been widely exploited as controllable tools in drug release, cell adhesiveness, mechanical properties, or permeability (Chilkoti et al., 2002; Jeong et al., 2002; Kim et al., 2003; Murthy et al., 2003; Shimoboji et al., 2002; 2003). Poly(N-isopropylacrylamide) (pNIPAAm), as one example, has been extensively investigated and applied in a number of different fields such as drug delivery (Sershen and West, 2002), cell patterning (Cheng et al., 2004), and tissue engineering (Stile et al., 1999).

BioMEMS devices functionalized with a variety of new biomaterials have demonstrated a great potential to be applied in disease diagnosis (Chin et al., 2012; Herr et al., 2007; Stangel et al., 2001; Zhang et al., 2015a; 2015b; Zhang and Wang, 2016) and drug delivery (Grayson et al., 2003; Santini et al., 1999; Yoshida et al., 2006). For example, silicon microchips were engineered to contain over 100 nm drug-containing wells covered with gold on a chip 1 cm $\times$1 cm. The drug in any of these wells can be released when applying approximately 1 V to the individually addressable wells (Santini et al., 1999). The systems can also perform multipulse drug delivery when they are made of resorbable polymeric materials (Grayson et al., 2003).

BioMEMS is one of the fastest growing areas that rely on biomaterials, and developing an integrated microanalysis system using lab-on-a-chip technology, in which multiple analyses can be performed in series and/or in parallel on one device, is of undeniable interest and importance (Figeys and Pinto, 2000; Service, 1998). Successful coalescence of clinical medicine, materials science, and engineering would tremendously revolutionize biological research and many biomedical applications such as drug design, medical implants development, disease diagnostics, and health surveillance (Andersson and van den Berg, 2004; ODonnell-Maloney and Little, 1996; Sanders and Manz, 2000; Weigl et al., 2003).

Molecular Targets and Biomarker Sensing

A biomarker has been defined by the NIH as ''*a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention*'' (Biomarkers Definitions Working Group, 2001; Strimbu and Tavel, 2010). Simply put, a biomarker refers to a measurable indicator of some biological state or condition—it is a small ''signal'' that your body generates that can be used to determine your physiological condition, whether good or bad.

In order to detect the molecules or biomarkers we are targeting, highly specific recognition is crucial for all molecular-based biosensors. It is essential that the biosensors provide a suitable platform that facilitates formation of the probe–target complex in such a way that the binding event triggers a corresponding signal for electronic readout. The basic elements for any biosensor include a molecular recognition layer and a signal transducer (can be optical, electrochemical, or mass/pressure sensitive) that can be coupled to an appropriate readout device. Growth in the field of biosensors has been phenomenal. They possess enormous potential in virtually every conceivable analytical area, ranging from food safety, process control, medical diagnostics, and drug design/delivery, to environmental monitoring, defense, and homeland security.

Enzymatic biosensor, introduced by Clark and Lyons when they built the first glucose biosensor in 1962 (Clark and Lyons, 1962), is a very popular field in bioanalytical applications witnessing tremendous work done over the past 50 years (Odaci et al., 2009; Stein et al., 2007; Wilson and Turner, 1992). Enzymes are the most used biocatalytic elements enabling the detection of analytes in various ways, such as measuring the consumed or produced species after the enzymatic reactions (Gough et al., 1985; Guilbault and Lubrano, 1973; Reach and Wilson, 1992) or tracking the electrons passed through the electrodes during reactions (Holland et al., 2011; Shan et al., 2009; Si et al., 2011; Wang, 2008).

Today's biosensor market is dominated by glucose biosensors where mass-produced enzyme electrodes are used for the rapid self-diagnosis of blood glucose levels. Nowadays, nanomaterials are more and more exploited to enhance sensing performances due to the possibility to immobilize more bioreceptor units at reduced volumes and even to act themselves as transduction elements. Nanoparticles, including metallic ones (Baioni et al., 2008; Hrapovic et al., 2004; Salimi et al., 2009; Su et al., 2003), polymer ones (Graham et al., 2013; Kumari et al., 2010; Pu et al., 2014; van Vlerken and Amiji, 2006), magnetic ones (Ito et al., 2005; McBain et al., 2008; Reiss and Hutten, 2005), have all found great usage in biomedical applications.

Gold nanoparticles in particular have been mostly used for bio-sensing applications among all metallic nanoparticles due to their good biocompatibility, great optical and electronic properties, and their relatively simple production and modification (Biju, 2014; Chen et al., 2011; Li et al., 2010; Mena et al., 2005; Reynolds et al., 2000; Zhang et al., 2015a; 2015b). Magnetic nanoparticles are very promising alternatives to fluorescent labels in biosensors because biological entities do not show any magnetic behaviors or susceptibilities, enabling no interferences or noise during signal capturing (Tamanaha et al., 2008). The examples can be the ultra-high sensitive detection of E. *coli* (Mujika et al., 2009) or Salmonella (Liebana et al., 2009). Furthermore, magnetic nanoparticles can be applied to carry the analytes to the transduction platform in microfluidic systems enabling simultaneous detection of different analytes (Konry et al., 2012) or to transport drugs or genes (Dobson, 2006; Kami et al., 2011), or for magnetic resonance imaging (Sun et al., 2008).

Nanowires, with the characteristics of low weight with extraordinary mechanical, electrical, thermal, and multifunctional properties, have also been widely used in numerous bio-sensing applications (Curreli et al., 2005; Laocharoensuk et al., 2007; Roberts and Kelley, 2007; Shi et al., 2005; Wanekaya et al., 2006; Zhu et al., 2006). For example, some metal nanowires can be adopted in the detection of glucose (Cusma et al., 2007; Lu et al., 2007; Qu et al., 2007), cholesterol (Aravamudhan et al., 2007a; 2007b), or DNA (Gao et al., 2007; Yi et al., 2010). Other types of nanowires have been exploited to detect inosine (Liu et al., 2006), bacterial (Basu et al., 2004; Garcia-Aljaro et al., 2010; Mishra et al., 2008), or cancer biomarkers (Choi et al., 2010; Ramgir et al., 2007; Zheng et al., 2005).

Another prominent example of nanomaterials used for bioapplications are luminescent semiconducting nanocrystals called quantum dots (QDs). The fluorescence quenching properties of QDs have permitted their applications in optical DNA and oligonucleotide sensors (Freeman et al., 2013; Zhang et al., 2005) or as optical transducers (Algar et al., 2010; Frasco and Chaniotakis, 2009). This technology has been introduced to breast-cancer surgery for helping better and more accurately identify tumor tissue margins during mastectomy. Previously, prior to the technology's introduction, the positive margin rates have been quoted as 15%–60% intraoperatively (Fang et al., 2012).

A great example in advancements of bio-sensing is glucose sensing. Noninvasive glucose sensing is the ultimate goal of glucose monitoring. This approach has been directed toward glucose measurements in saliva (Zhang et al., 2015), tears (Hennig et al., 2014; Yao et al., 2011), or sweat (Potts and Moyer, 2010). Compared to the normal blood glucose concentration range of 80–120 mg/dL (4.4–6.6 mM), the glucose content in saliva, tears, or sweat is much lower, thus, highly sensitive, accurate, and convenient glucose determination technology is essential. Tremendous work has been done to push the detection limit of glucose sensors by tuning the sensor's building blocks/biomaterials [e.g., electrochemical glucose biosensors in Table 2, also seen in Chen et al.'s review (2013)].

DNA as a Biomarker Binding Platform

With a focus on biomarkers, it would be prudent to take advantage of Nature's own materials as detection platforms. Recent developments in bio-sensing and device-level integration with nanomaterials have taken such an approach, exploiting DNA, RNA, and protein-based materials. Indeed, electronic bio-sensing and detection represents the most developed area of bio-nanoelectronics. One reason is due to the potential to control the molecular sequence of the structure (e.g., via peptide or nucleobase). DNA, for example, has a limited set of four building blocks (four nucleobases). Yet even with such a simple base set, sequencing of DNA leads to the genetic diversity we see across Nature.

Rather than screen thousands of potential material candidates, it would be pragmatic to optimize variations of well-known materials. DNA (through nucleobases) have their own ''programming language'' to explore, with a finite number of sequence combinations. Exploration of synthetic DNA sequences has enabled the development of DNA-origami as well as bio-imaging and functional scaffolds (Linko and Dietz, 2013; Pinheiro et al., 2011). The flexibility of DNA sequencing allows for the incorporation of multiple ligands, labels for bio-imaging, antibodies, hormones, and so forth that might be used for efficient and site-specific drug delivery and release (Noy et al., 2009; Pinheiro et al., 2011).

The AFIRMA chip is such an example in management of thyroid malignancies. Here, we discuss the variation of sequence with oral biomarker interaction. Ultimately, a library

Table 2. Performance of Various Electrochemical Glucose Sensors Using Biomaterials

Glucose Biosensor	*Linear range/mM*	*Sensitivity/ $\mu A\ mM^{-1}\ cm^{-2}$*	*LOD/μM*	*Reference*
GCE/GCNT/GOx/GAD	6.3–20.09	2.47	–	Periasamy et al., 2011
GCE/CNT/gold colloid/PDDA-GOx	0.5–5	3.96	–	Yao et al., 2008
Au/GNp/MWNTs/GOx	up to 9	7.3	128	Liu et al., 2007
$[GOx/PDDA]_3$/[SDS-MWCNT/PDDA]$_3$/MPS/Au/Ti/PET	0.02–2.2	5.6	10	Yan et al., 2007
GCE/CNT/PTBO-GOx	1.0–7	14.5	–	Yao et al., 2007
ITO/PEDOT/GOx/Nafion	0.1–1	14.06	10	Jung et al., 2011
Au/dithiol/au/cystamine/GOx	0.02–5.7	8.8	8.2	Zhang et al., 2005
ITO/(PEDOT/PSS+PVA)/GOx/PDA	up to 18	9.33	0.25	Lee et al., 2008
$Au/(GOx/GNPs)_n$	0.01–13	5.72	–	Yang et al., 2006
$Au/MPS/TH/(SCGNPs/TH)_n$	up to 3	3.8	35	Sun et al., 2007
GCE/CS/MWNTs-Fc/GOx	0.012–3.8	25	3	Qiu et al., 2009
Pt/PAA/GNps/GOx/CS/GNPs/GOx	0.5–16	–	7	Wu et al., 2007
GCE/CS-PB@MWNTs/HPtCo/GOD/Nafion	0.003–3.6	21	0.85	Che et al., 2010
Pt/PAA/SWNT/$(CS/GNp/GOx)_3$	0.017–0.81	61.43	5.6	Zhang et al., 2015
Platinized Au/(PDA-GOx-PtNP)	0.0005–5.5	129	0.07	Fu et al., 2009

CS, chitosan; CS-PB, chitosan-Prussian blue; GAD, glutaraldehyde; GCE, glassy carbon electrode; GCNT, gelatin-multi-walled carbon nanotube; GOD, glucose oxidase; GOx, glucose oxidase; LOD, limit of detection; GNp, gold nanoparticle; HPtCo, hollow PtCo; ITO, indium tin oxide; MPS, sodium salt; MWNTs-Fc, ferrocene-modified multi-walled carbon nanotubes; PAA, poly (allylamine); PDA, 1,3-phenylenediamine; PDDA, poly(diallyldimethylammonium chloride); PEDOT, poly (3,4-ethylenedioxythiophene); PET, poly (ethylene terephthalate); PSS, poly (4-styrenesulfonic acid); PTBO, poly (toluidine blue O); PtNP, Pt nanoparticle; PVA, polyvinyl alcohol; SCGNP, sulfonate-capped gold nanoparticles; SDS, sodium dodecyl sulfate; TH, thionine.

of DNA sequences can be developed, to encompass all of the nucleobase sequence combinations within the ''sight'' of the biomarker (a function of molecular size and atomistic interaction distance). While great, the number of sequences is finite in size. The key challenge will be the development of a robust computational protocol to assess the biomarker interaction of a suite of target molecule and DNA chemistries. Minimal effort is required to successfully model the materials, enabling the potential to automate the approach. Atomistic interactions can then be used to interpret and guide experimental efforts, which reciprocally feed computational models. This feedback loop provides unprecedented insight into the behavior of complex material systems.

DNA is the genetic material of all living organisms. DNA consists two long polynucleotide chains that run in opposite directions and are twisted around each other right-handedly (Watson and Crick, 1953). Each strand of the double helix is a linear chain with a backbone made of sugars and phosphate groups joined by ester bonds. Attached to each sugar is one of the four types of bases, including the purines: adenine (A) and guanine (G), and the pyrimidines: cytosine (C) and thymine (T). DNA is well suited for bio-sensing applications because of their specific and robust base-pairing interactions between complementary sequences (Hvastkovs and Buttry, 2010; Vanness et al., 1991).

Exploiting DNA's ''code'' to bind to a particular molecule inevitably led to the field of aptamers (Iliuk et al., 2011; Xiao and Farokhzad, 2012). The term aptamer is derived from the Latin 'aptus' meaning ''to fit'' and is based on the strong binding of nucleobase sequences to specific targets based on structural conformation (Ellington and Szostak, 1990; Robertson and Joyce, 1990; Tuerk and Gold, 1990). Aptamers can be both single-stranded RNA or DNA oligonucleotides, typically 15 to 60 bases in length that fold into secondary and tertiary structures and bind with high affinity to specific molecular targets.

In addition to the genetic information encoded by nucleic acids, aptamers also function as highly specific affinity ligands by molecular interaction based on the three-dimensional folding pattern. The three-dimensional complex shape of a single-stranded oligonucleotide is primarily due to the base composition-led intra-molecular hybridization that initiates folding to a particular molecular shape. This molecular shape assists in binding through shape-specific recognition to its targets, leading to considerable three-dimensional structure stability and thus the high degree of affinity. The dual consideration of both *sequence* and *shape* (Fig. 3) is difficult to assess *a priori*—as such, aptamer discovery has been driven primarily by a high-throughput screening process. Aptamers are commonly engineered through repeated rounds of *in vitro* selection or equivalently, SELEX [Systematic Evolution of Ligands by EXponential enrichment (Tuerk and Gold, 1990)] to bind to various molecular targets such as small molecules, proteins, nucleic acids, and even cells, tissues, and organisms.

High affinity RNA aptamers have been obtained by selection against tobramycin, neomycin, and streptomycin (see Arnaud et al., 2013, and references therein). Like inter-strand attraction, binding is based on strong electrostatic complementarity as well as a hydrogen bonding network that involves the carbohydrate rings of the ligands. As an application, RNA aptamers may be useful in clinically-based assays to detect antibiotics in blood serum (Rowe et al., 2010). While promising, derived aptamers are typically one-off molecules, with high affinity to a particular ligand. Missing is the mechanistic and physiochemical understanding of why sequence ''A'' binds with sequence ''B'', preventing optimization and engineered design.

Be that as it may, the results of *in vitro* selection and the SELEX process enable reverse engineering of RNA and DNA complexes bound with small molecules, peptides, proteins, nanoparticles, and drugs, as well as viruses and bacteria, increasing our understanding of such interactions (Chen et al., 2011; Tan et al., 2011; Xing et al., 2012; Yang L et al., 2011; Yang C et al., 2012). With such knowledge, we can hope to customize DNA on a sensor-like device.

DNA sensors have been used to detect DNA (Rogers et al., 2001; Wang et al., 1998), proteins (Ban et al., 2004; Leung et al., 2012), and even small molecules/ions (Li and Lu, 2000; Zhang et al., 2014) in the form of optical (Chen et al., 2007; Rogers et al., 2001; Vo-Dinh et al., 2001), electrochemical (Kinsella and Ivanisevic, 2007; Odenthal and Gooding, 2007; Wang, 2006), or mass-sensitive (Garcia-Martinez et al., 2011; Mannelli et al., 2005) for a variety of biological applications. One particular example can be using DNA probes to differentiate healthy, gingivitis, and periodontitis subjects using DNA–DNA hybridization techniques (Palys et al., 1998).

Most recently, DNA microarray technology has emerged, offering remarkable high-throughput screening properties and reliable biomedical diagnostics applications (Cooper, 2001; Grouse et al., 2001; Triche et al., 2001). It provides a discovery platform of functional genomics (Schena, 1996; Schena et al., 1998) and a revolutionizing way of drug design and disease diagnostics (Barry et al., 2000; Service, 1998). DNA sensors are envisioned to be valuable, easy, inexpensive, fast, and specific techniques in many applications such as medical diagnostics, genetic screening, drug design, food and agricultural analysis, environmental monitoring, and health surveillance. In addition, DNA is compatible with other emerging nanomaterials such as carbon nanotubes (Dwyer et al., 2002; Kang et al., 2014; Staii and Johnson, 2005), enabling the potential exploitation of the benefits of both materials on simple devices.

One example of a DNA sensing system used in diagnostics is the Afirma chip technology used to help further identify benign versus malignant thyroid disease using tissue obtained from fine-needle aspiration biopsy samples. This technology, first introduced in 2012, was designed to reassess indeterminate fine-needle aspiration biopsies of thyroid nodules to help further identify those indeterminate biopsies that were actually benign (approximately 75%) (Duick et al., 2012). Since its introduction, endocrinologists and surgeons have been able to avoid unnecessary surgeries and treatments for benign thyroid disease.

DNA Functionalized CNT Sensors

Carbon nanotubes (CNTs), first discovered in 1991 (Iijima, 1991), have been widely used as nanomaterials utilized in various applications, such as chemical and biological sensors (Britto et al., 1996; 1999; Collins et al., 2000; Davis et al., 1997; Kong et al., 2000; 2001), field emission materials (Tans et al., 1998), electronic devices (Saito, 1997), and actuators (Park et al., 2004). Particularly, single-walled carbon nanotubes (SWCNTs or SWNTs) are more favored due to their

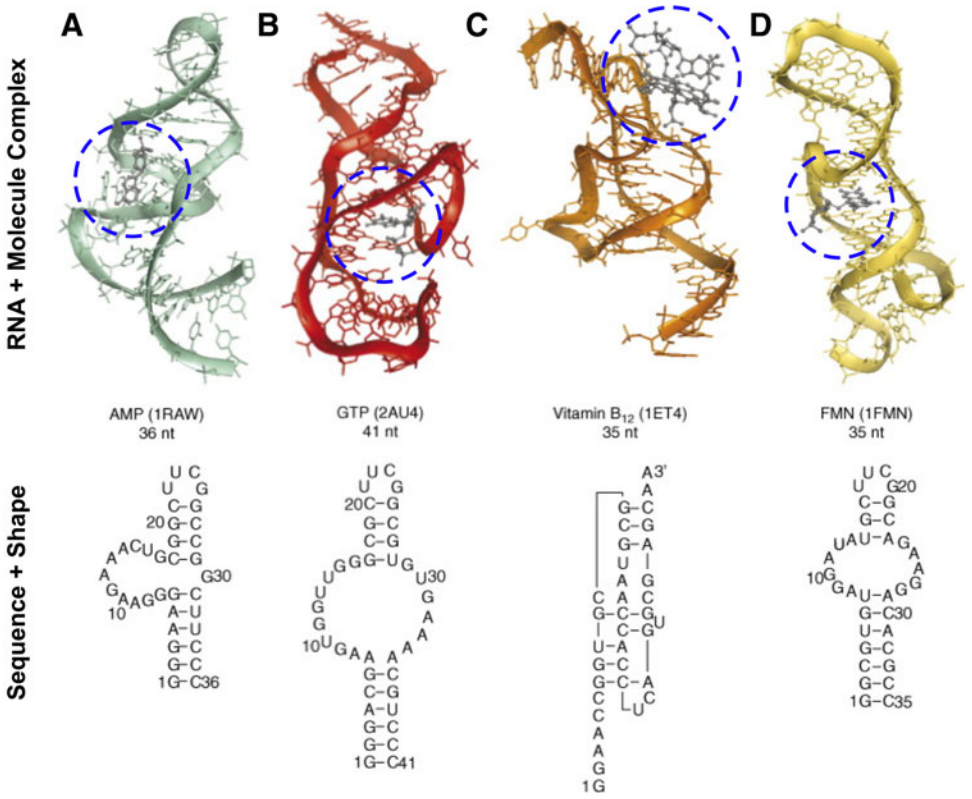

FIG. 3. Examples of ligand binding to RNA aptamers evolved *in vitro* as a function of sequence and shape. Non-natural RNA aptamer structures are shown in *stick representation with a ribbon* drawn through the riboses of the RNA (*top*). The bound ligands are *circled* and listed with the PDB accession codes in *parentheses* and the number of nucleotides. Ligands are shown in *gray ball-and-stick* representation. Sequence and molecular shape depicted, indicating predominate binding pockets (*bottom*). **(A)** The ATP-binding aptamer, bound to AMP. **(B)** The recently determined GTP aptamer shows the ligand is largely buried in its binding pocket. **(C)** The vitamin B12 aptamer, wherein the molecule is bound peripherally to the surface of the aptamer. **(D)** The FMN aptamer. Adapted with permission from Wakeman et al. (2007), Copyright © 2007 Elsevier.

specific electrical, mechanical, optical, chemical, and thermal properties. Diverse applications of SWCNTs have been explored, including chemical/biological sensors (Kim et al., 2007), electrical interconnects (Close et al., 2008), agents for drug delivery (Liu et al., 2007; Prato et al., 2008), low voltage, cold-cathode field-emission display (Choi et al., 1999) and nanoscale circuits for beyond silicon based complementary metal-oxide-semiconductor (CMOS) electronics (Avouris et al., 2007; Thompson and Parthasarathy, 2006; Wong, 2002).

The electronic properties of CNTs, correlated with their optical, mechanical, chemical, and thermal properties, have enabled carbon nanotubes to be a novel material for diverse sensing applications (Appenzeller et al., 2002; Roberts et al., 2009). Changes caused by external stimuli can easily be electrically evaluated in resistor, transistor, or capacitor (Abraham et al., 2004; Izadi-Najafabadi et al., 2010; Roberts et al., 2009). Thus, it is possible to exploit SWNTs as sensing sites for various interested molecular targets and biomarkers, from toxic chemical vapors to bio-macromolecules (Besteman et al., 2003; Mahar et al., 2007; Pengfei et al., 2003).

That being said, a major disadvantage of SWNT sensors is the lack of specificity. To solve this problem, an effective scheme to functionalize the SWNT sensors is required, which can enable the SWNTs to respond specifically to a wide spectrum of molecular targets. Modification of SWNTs with polymers (Bradley et al., 2003; Novak et al., 2003; Snow et al., 2005) and biomolecular complexes (Staii and Johnson, 2005; Wong et al., 1998; Zhang et al., 2007) has shown great enhancement in the specificity and sensitivity of the SWNT-based sensors (Fig. 4a). Among these molecules, DNA can bind nonspecifically to the sidewalls of SWNTs through hydrophobic interactions, π–π bonding (Zheng et al., 2003), and possibly amino-affinity. SEM images of assembled single-stranded DNA (ssDNA)-SWNT bundles reveal small white dot-like structures, which were believed to be individual ssDNA molecules, were randomly dispersed in the SWNT bundles (Fig. 4b). The aromatic structures in oligomers' bases on DNA bind to the aromatic structures on SWNTs *via* the π–π stacking interactions.

A system that consists of SWNTs coated with a self-assembled monolayer of ssDNA has integrated the selective odorant interactions of ssDNA (White et al., 2008) with the sensitivity of SWNTs to the changes in its surface electronic environment when exposed to targets (Johnson et al., 2008). Moreover, the response of these devices to a particular molecule of interest can always be optimized by changing the

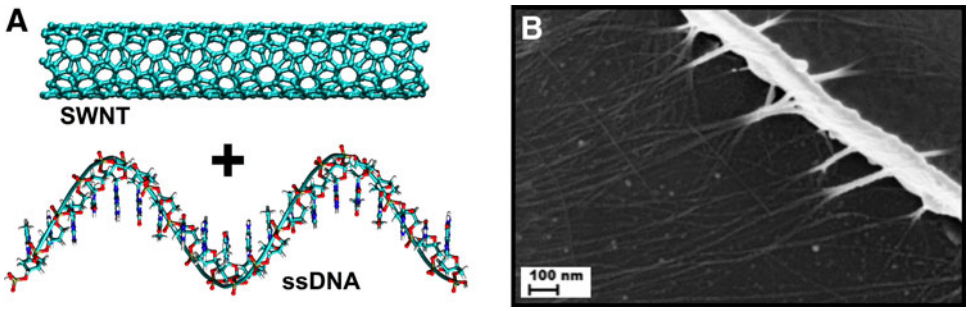

FIG. 4. **(A)** Full atomistic molecular model representations of SWNT and ssDNA. **(B)** SEM photograph of ssDNA-decorated SWNTs assembled between the microelectrodes. Adapted from Zhang et al. (2013).

base sequence of the ssDNA. The system can be considered flexible, allowing the CNT base to be outfitted with designer DNA sequences, without fundamentally changing the device operation.

As a result, functionalization of SWNTs with DNA has demonstrated attractive prospects in various fields, including the detection of molecular targets, solubilization in aqueous media, the nucleic acid sensing, and probing biomolecular interactions (Daniel et al., 2007; Meng et al., 2007; Staii and Johnson, 2005; Yang et al., 2008). For example, Aravind et al. have successfully fabricated ssDNA immobilized, platinum nanoparticles decorated CNT composites to selectively detect dopamine, which is a vitally important neurotransmitter that affects brain function (Aravind and Ramaprabhu, 2011). Moreover, their biosensors have achieved much better results with nafion coating, leading to good stability, short response time, and selective detection of dopamine even with presence of ascorbic acid and uric acid.

Furthermore, a number of different ssDNA-functionalized SWNT sensors can be integrated into a wireless sensor array on one micro device to detect/distinguish different targets or biomarkers simultaneously (Liu et al., 2013; Zhang et al., 2013; Zhang and Wang, 2016). An array-based sensing approach is enormously efficient in real-time, highly sensitive, and capable of fast detection because of its high selectivity, good sensitivity, great repeatability, and excellent precision.

Different biomaterials are more and more often integrated to build various biosensors enabling advanced sensing mechanism and results (Chen et al., 2003; Patolsky et al., 2004; Xiao et al., 2003; Zhu et al., 2007). However, the field has largely been characterized by trial-and-error experimentation and low throughput research (Barradas et al., 2011; Zhang et al., 2015). A systematic approach convergent of methods from experimental to computational and across all scales for material design is highly needed. In effect, a protocol is necessary to discriminate or objectively rank a good sequence from a bad sequence, in terms of biomarker interaction.

Ranking Interaction with Targeted DNA Nucleobases

The stated challenge is to develop a systematic computational design methodology to tailor the behavior of a material system driven by molecular interaction metrics (Fig. 5). Specifically, (1) computational screening, and (2) novel sequence exchange approaches can be developed to exploit DNA as a tunable material to be applied in building medical devices for oral disease diagnosis and point-of-care screening. The interactions between DNA and small molecules have been largely applied to build biochemical sensors for disease diagnosis (Aravind and Ramaprabhu, 2011; Babkina et al., 2004; Drummond et al., 2003; Evtugyn et al., 2005; Johnson et al., 2010) and detection of explosives (Liu et al., 2011; Staii and Johnson, 2005).

The first step is to rank DNA sequences with specific biomarkers to demonstrate potential specificity. According to our knowledge, no other group has reported how to design DNA sequences to achieve the best detection results for particular molecules. It has opened up a tremendous possibility to map an array of DNA sequences for reliable detection of several particular biomarkers of one specific disease, and provides a new paradigm of design, development, and application of advanced engineering material systems, combining computational approaches, optimization methods, and DNA informatics.

Clearly, there is a multitude of potential diseases and biomarkers to explore. Focus here is given to a single affliction: *diabetes*. Diabetes has known biomarkers throughout the body. The most common of which is glucose levels in the blood (which defines the disease) requires blood screening as definitive diagnosis. Indeed, in order to use a biomarker for diagnostics, the sample material must be as easy to obtain as possible. Current state-of-the-art sensor technologies enable the rapid analysis of blood samples for several critical care assays, including blood chemistry, electrolytes, blood gases, and hematology, toxicology, and drug screens, bedside diagnosis of heart disease through detection of cardiac markers in the blood, and glucose self-testing.

However, blood sampling, by definition, requires breaking the epidermis (i.e., a needle prick) which is adversarial to many patients, especially to children or the elderly. Thus, our hope is to develop sensing and screening technologies that can noninvasively detect diabetic oral biomarkers from breath or saliva (Zhang et al., 2015; Zhang and Wang, 2016), among which we will focus on the detection of diabetic 'signature' VOC (Volatile Organic Compounds) components from breath using DNA sensors.

A recent preliminary investigation explored the variation of DNA sequence with diabetes biomarker interaction to demonstrate proof-of-concept screening approaches (Fig. 6). A short sequences of both ssDNA and double-stranded DNA (dsDNA) were modeled interacting with a particular diabetes biomarker molecule using full atomistic molecular dynamics

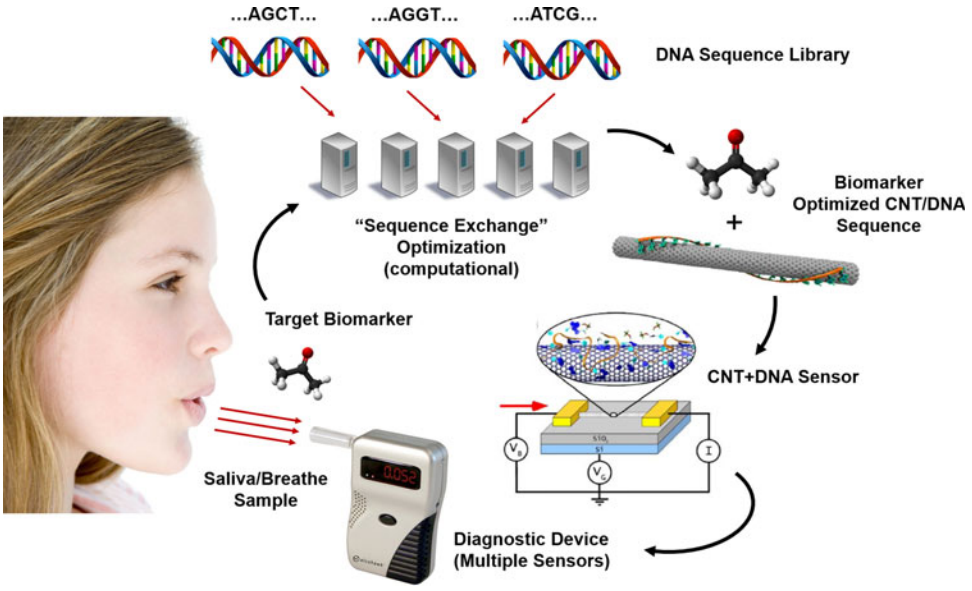

FIG. 5. Engineering materials design for point-of-care diagnostics using an automated sequence optimization approach for DNA/CNT sensing disease specific biomarkers in saliva/breath.

(MD) simulation. This approach can therefore bypass experimental assessment until the top sequences are isolated, thereby reducing both synthetic effort and experimental cost (*e.g.*, computational materials design).

The breath biomarkers of diabetes selected for the study were acetone (Greiter et al., 2010; Miekisch et al., 2004; Minh et al., 2011) and ethanol (Galassetti et al., 2005; Minh et al., 2011). Acetone, for example, is reported to be less than a few hundred ppb (by volume) in the breath of healthy individuals (Henderson et al., 1952), while for diabetic patients, acetone concentration can reach 560 ppm or even >1000 ppm (Sulway and Malins, 1970). The interaction between four single DNA nucleotides (A, G, C, and T) on both ssDNA and dsDNA with acetone and ethanol was studied via Steered Molecular Dynamics (SMD) (Zhang et al., 2015) applying the well-utilized CHARMM and CVFF potentials. Large-scale Atomic/Molecular Massively Parallel Simulator (LAMMPS; http://lammps.sandia.gov/), an open-source molecular dynamics software package is used to perform all MD simulations (Laboratories, 2010; Plimpton 1995).

SMD is a novel approach to study the dynamics of binding or unbinding events in biomolecular systems (Deuflhard et al., 1999), revealing the details of molecular interactions in the course of unbinding (Izrailev et al., 1997; Molnar et al., 2000) and providing important insights of the binding mechanisms underlying these processes. The primary advantage of non-equilibrium SMD over conventional equilibrium MD methods is the possibility of inducing relatively large conformational changes in molecules within the nanoscale time scales accessible to computation.

Computationally, the SMD method applies a moving spring force so that the molecule can behave in a manner not obtained by either force or displacement loading alone, allowing induced conformational changes in a system along a

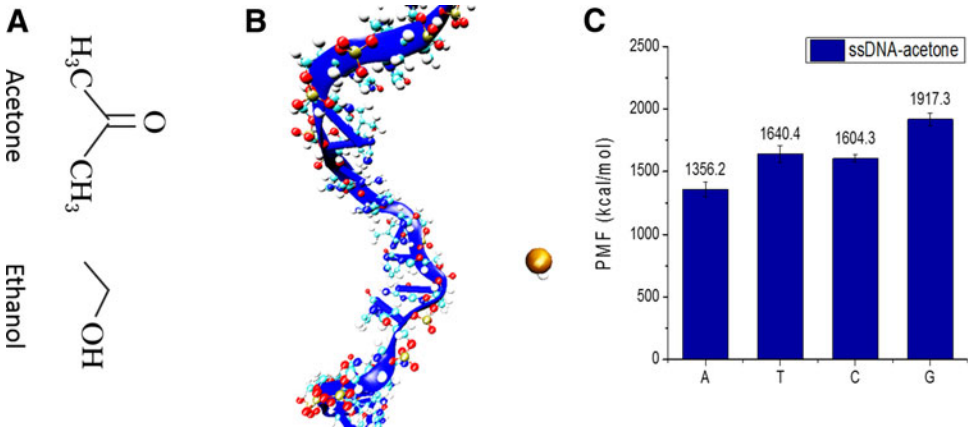

FIG. 6. Ranking of base/biomarker interaction via simulation. **(A)** Chemical structures of breath biomarkers of diabetes. **(B)** MD simulation snapshot. **(C)** Ranking of acetone interaction with DNA nucleobases. From Zhang et al. 2015, in press.

prescribed reaction vector. The DNA molecule, either single-stranded or double-stranded, was set at one end of the solvation box, and the SMD force is applied at the geographical center atom of the biomarker. The small molecules were pulled towards the middle of one particular nucleotide each simulation. Total force and the potential mean force (PMF) during the SMD simulations can then be plotted against the distance between the biomarker and DNA, enabling analysis and comparison of the interaction pathways.

Despite plentiful modeling methods for the interactions between a biomarker and DNA (Hornak et al., 1999), little is known *a priori* about processes of binding and unbinding, limiting any predictive (or design) power. An SMD simulation is a non-equilibrium process, which accepts irreversibility, ceding for the present time accurate evaluation of binding affinities and PMFs, but gaining access to biologically relevant information related to non-covalent bonding. PMF can be equated to the free energy profile along the reaction path. To properly capture the free energy describing the conformational space of the binding event, the SMD simulations would need to include a very large statistical sample of both multiple initial conditions and multiple directions of the binding vector. For *ranking* purposes, however, this degree of accuracy is unnecessary. Only one approach/trajectory per biomarker/nucleobase pairing is necessary for a preliminary assessment.

The interaction between four single DNA nucleotides (A, G, C, and T) on both ssDNA and dsDNA with acetone and ethanol was studied. The mechanical work of pulling it forwards (forward pulling path) and backwards (reverse pulling path) at a number of points was measured during this process. By sampling these forward and reverse paths, the free-energy profiles of the eight aforesaid systems for each targeted molecule could be assessed. Four DNA nucleotides on dsDNA were found to react differently to the targeted molecules than on ssDNA, requiring significant higher energy to move the molecule close to DNA than the latter. Comparing the PMF values of the different systems, we obtained the optimal DNA nucleotide for the detection of each molecule: Adenine for acetone, and Thymine for ethanol, which are in good agreement with experimental sensing results using DNA sensors.

Beyond single nucleotides, the simulation process can be automated to assess a whole library of possible DNA sequences to select the optimal arrangement in order to optimize the **entire** DNA sequence for one specific biomarker interaction. This necessitates modifying the MD code to swap sequences on-the-fly based on the determined critical metrics.

Conclusions and Future Outlook

DNA nanotechnology has already become an interdisciplinary research field, with researchers from chemistry, materials science, computer science, biology, physics, and medicine coming together to tackle important problems. As the field is progressing rapidly, we believe that exciting new directions will emerge well beyond the limited set described here. Such bottom-up computational approaches, capable of understanding atomistic-scale interactions in biomaterials, provide an outstanding platform to screen/design high-performance biomaterials for cheap and efficient medical diagnosis, drug design, or point-of-care assessment.

The ideal of *in silico* materials design requires new approaches in computational evaluation. Automation of the screening process by sequence-exchange using a finite library and selected metrics provides a self-optimizing procedure to produce nanotechnological systems from the bottom-up. Combined with similar efforts linked to the Materials Genome Initiative creating material property libraries, *in silico* screening and assessment, combined with automated sequencing techniques, will pave the way to the next generation of materials development, prior to any (necessary) laboratory validation.

It is stressed that the umbrella term ''materiomics'' is not an attempt to introduce a new field of science. Rather, it is a unifying proposition motivated by the convergence of many fields towards a fundamental integrated description of materials and their functional roles. Materiomics takes a materials science perspective towards complex biological systems, explicitly accounting for feedback loops that link functional requirements (and changes thereof) to altered material components and structures, at different scales in both time and length. It overcomes the barrier that currently separates the understanding at different length and time-scales, through the development of new experimental synthesis and characterization methods, novel model systems, and an enhanced appreciation for a multi-scale view of materials in general, in order to fully understand multi-scale or cross-scale interactions of the materiome (Cranford and Buehler, 2012).

To fully explore the potential of materiomics, systematic development of general methodologies is needed that are applicable to a number of material systems, living and synthetic. This asks for development of new tools and insights in the design of (evolutionary) search algorithms, performance metrics, and universal characteristics across systems. The ultimate goal of materiomics is to reduce the complexity of biosystems and to enable effective engineering solutions to shape tomorrow's technology and innovation.

A clear application at the interface of biology and materials lies in oral health monitoring. One's breath, for example, has a vast amount of data that can be extracted with the right diagnostic tool. Similar to an automobile's catalytic system for exhaust, one can potential design a material platform to screen a patient's breath for a tangible breadth of biomarkers. Beyond general health monitoring, determination of infectious oral diseases, caries, gingivitis, and periodontitis using bioinformatics has also attracted a great amount of attention (Gursoy et al., 2014; Keskin et al., 2015).

For example, Gürsoy and their group used an *in silico* gene/protein interaction network model to define inflammatory proteins in saliva, induced or inhibited by estradiol, as early diagnostic biomarkers or target proteins related to pregnancy-associated gingivitis (Gursoy et al., 2014). Keskin et al. (2015) have concluded that human beta defensing (hBD)-2 can be employed as a diagnostic and therapeutic tool to improve the quality of life of susceptible individuals and minimize the economic costs of the two major global public health problems—Crohn's disease and periodontitis. They also proposed that a unique angle pertinent for both diagnostic and therapeutic sciences involves rethinking clinically distinct diseases with a view to their shared molecular targets, interactions, and pathophysiologies.

Materiomics plays a major role in assessing the interactions between biomaterials and targeted biomarkers. While we focus on a specific application (i.e., DNA-based detection), the design methodology—namely optimizing molecular building blocks based on known performance metrics—can be easily

adapted for other platforms, pathologies, and diagnosis. Again, building on concepts from the Materials Genome, it is the ultimate goal to develop a contained computational ''black box'' approach to integrated materials system design, optimizing materials properties and behavior *in silico*, and enabling rapid development of clinical applications.

Executive Point-by-Point Summary

- Biomarkers in one's breath can indicate an array of oral disease and health conditions.
- Single-molecule detection is necessary to efficiently screen molecules and biomarkers in a nanotechnology-based device, driven by fundamental material interactions.
- *Materiomics* refers to the holistic study of materials, considering function and interactions alongside multiscale properties and structure. Due to the intrinsic complexity, materiomics provides a platform for biomaterial development and screening.
- Biomaterial/biomarker interactions have previously been screened for one-to-one enzymatic and chemical reactions.
- DNA-based sensors provide a programmable platform for aptamer or sequence design and enhance molecular interaction affinity and specificity.
- Computational approaches can enhance the characterization of molecular detection as an effective ''virtual microscope.''
- Process can be automated, potentially self-optimizing a DNA sequence from a known library given an arbitrary biomarker/molecule.

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Author Disclosure Statement

The authors declare they have no competing financial interests.

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