A Conceptual Review of Nanosensors

Teik-Cheng Lim[a] and Seeram Ramakrishna[a, b, c]

[a] Nanoscience and Nanotechnology Initiative, National University of Singapore, Singapore
[b] Division of Bioengineering, National University of Singapore, Singapore
[c] Department of Mechanical Engineering, National University of Singapore, Singapore

Reprint requests to Dr. T.-C. L.; E-mail: alan_tc_lim@yahoo.com

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Nanosensors are gaining increasing attention due to the need to detect and measure chemical and physical properties in difficult to reach biological and industrial systems that are in the nano-scale region. This conceptual review surveys various nanosensors, which are categorized into three broad types: optical, electromagnetic and mechanical nanosensors. The sensing concepts and their corresponding advantages are discussed with reference to their applications.

Key words: Nanosensor; Optical; Electromagnetic; Mechanical.

1. Introduction

Most reviews on nanosensors are focused on a particular type of sensors, such as nanobiosensors, optical nanosensors and magnetic nanosensors, with many technical details. Here we present an overview of all nanosensors, showing similarities and fundamental differences among the various categories. The aim of this review is to provide an overview, which is suitable for beginners to realize the growing importance of this field.

Nanosensors are sensing devices with at least one of their sensing dimensions being not greater than 100 nm. In the field of nanotechnology, nanosensors are instrumental for (a) monitoring physical and chemical phenomena in regions difficult to reach, (b) detecting biochemicals in cellular organelles, and (c) measuring nanoscopic particles in the industry and environment. A search on the terms "nanosensor(s)" and "nano-sensor(s)" appearing in titles of journal papers shows a growing trend in nanosensor research, as evident from the resulting publication record (see Fig. 1). Needless to say, a far greater number can be expected if a complete keyword search is performed to include all nanosensor publications. The advance in scientific understanding is naturally followed by technological development.

Although sensors have a long and illustrious history, the realm of nanosensors is relatively new. A milestone chart on the development of various nanosensors within 1994 and 2005 inclusive is summarized in Figure 2.

The various nanosensors can be loosely grouped into three broad categories of nanosensors:

(i) optical nanosensors,
(ii) electromagnetic nanosensors, and
(iii) mechanical and/or vibrational nanosensors,

bearing in mind other nanosensors that do not fall into the above-mentioned categories.

2. Optical Nanosensors

The first reported optical nanosensor was based on fluorescein which is trapped within a polyacrylamide nanoparticle, and was used for pH measurement [25]. In the most basic concept, fluorescent chemosensors are molecules composed of at least one substrate binding unit(s) and photoactive component(s) [26, 27]. The luminescence phenomenon is a process by which a fluorophore absorbs light of a certain wavelength, which is followed by emission of a quantum of light with an energy corresponding to the energetic difference between the ground and excited states [28, 29]. Figure 3 shows a conceptual schematics for a typical luminescent sensor, whereby the reflected light changes in color when the receptor binds with the analyte. The change in photo-vibrational properties underlies the sensing concept.

The most basic type of optical nanosensor is that of a molecular dye probe [30] inside a cell, which is essen-

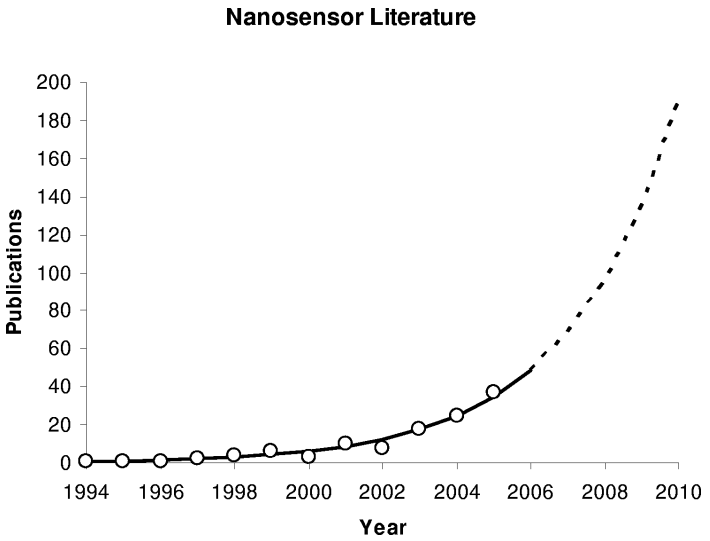

Fig. 1. Strict search count on the term "nanosensor" in the title of journal papers within a 12-year period (1994 – 2005 inclusive) with estimation up to 2010.

tially a direct cell loading of fluorescent dyes. An advantage of this basic approach is to minimize the physical perturbation of the cell, unlike that of the optical-fiber probe. However, a disadvantage of the free dye is the inherent dye-cell chemical interference as a result of protein binding, cell sequestration and toxicity.

A slightly different deviation from the free dye method is that known as the labelled nanoparticles that consist of a reporter molecule attached to the outside of the nanoparticles [31, 32]. The major difference between the labelled nanoparticles as compared to the free dye method is the solid state and fluid nature of the former and latter, respectively. Notwithstanding this difference, the labelled nanoparticles are freely flowing and the reporter molecules are in contact with the intracellular components – just like the free dye. These outer-labelled particles have been used for intracellular sensing, but retain similar drawbacks of using the free fluorescent dyes because the signal is derived from receptor molecules not insulated from the cellular environment.

2.1. Fiber Optic Nanosensors

Conventional methods for intracellular investigation need "fixing" of cell samples before performing the analysis. This fixing process usually destroys cellular viability and may, to a considerable extent, change the intracellular structure. Fiber optic nanosensors have the potential to analyze important cellular processes in vivo. Fundamental monitoring of biological processes at the cellular level is important to enhance further understanding of dynamic cellular functions. The interaction between the target molecule (A) and the receptor (R) is designed to produce a physicochemical perturbation that can be converted into an electrical signal or other measurable signal [33 – 37]:

$$\mathrm{R} + \mathrm{A} \rightarrow \mathrm{RA} + \text{measurable signal}. \qquad (1)$$

This measurable signal is then picked up by the optical probe and transmitted into the database.

The disadvantage associated with the dye-cell chemical interference prevalent in the free dye method is overcome by using the optical fiber probe due to the physical separation between the environment and the sensing tip. Another advantage of the optical nanosensor is the minimal invasiveness of this technique as compared to conventional wire-probe devices.

The first optical fiber submicron nanosensor is attributed to Tan et al. [38, 39]. Fiber optic nanosensors have so far been successful with their capability in the following applications:

(a) Measurement of benzopyrene tetrol (BPT) and benzo[*a*]pyrene (BaP) inside single cells [33 – 37]. These biochemicals are important for cancer studies.

(b) Monitoring apoptosis. Apoptosis, or programmed cell death, is a process in which cells degenerate (i) during normal development, (ii) due to aging, or (iii) as a result of disease. The fiber optic nanosensor has been used for monitoring of caspase-9, an apoptosis protein, in human mammary carcinoma cells (MCF-7) [40].

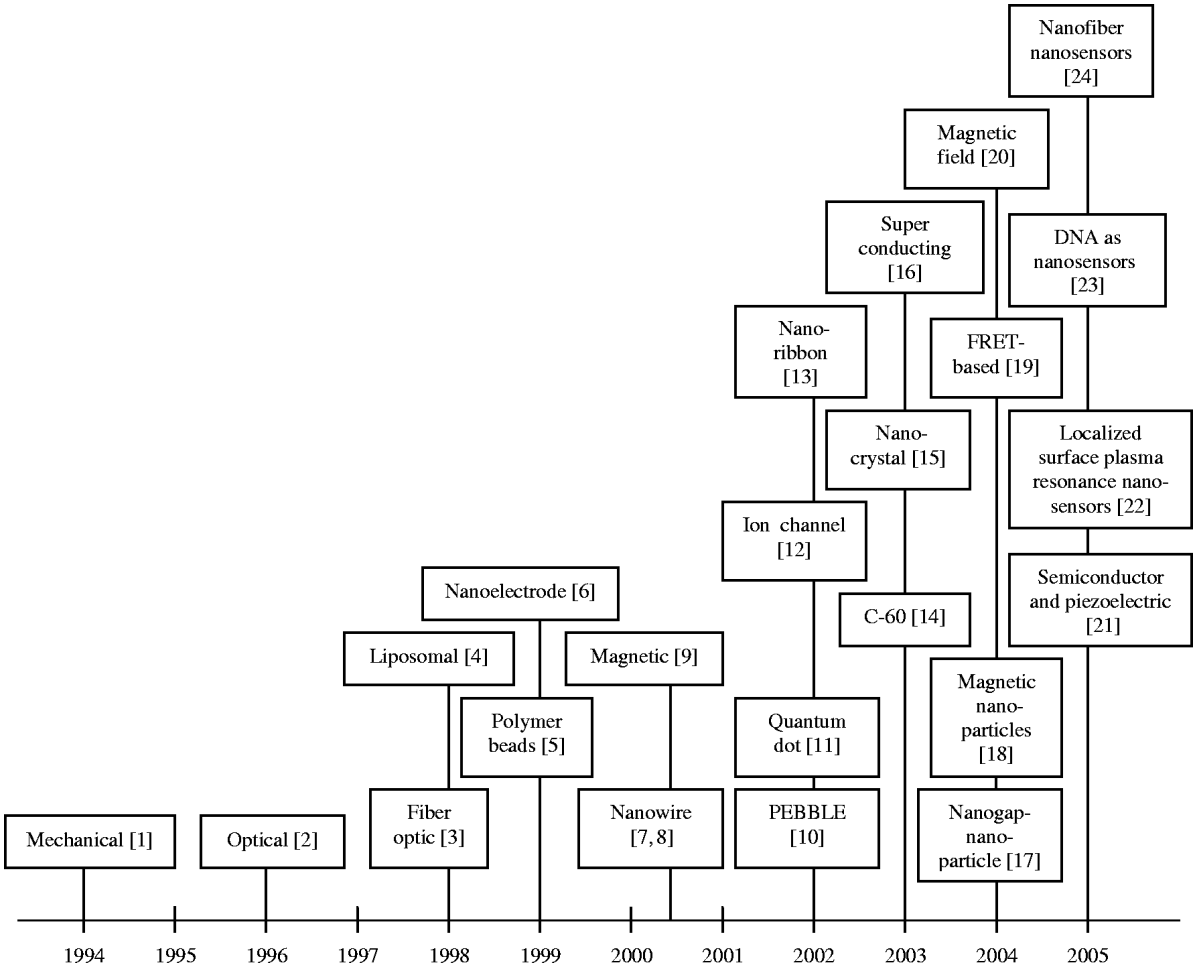

Fig. 2. Milestone chart of various types of nanosensors.

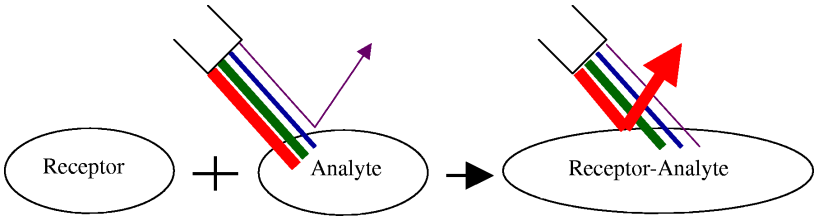

Fig. 3. Conceptual schematics of a luminescent dye for intracellular sensing.

(c) Measuring cytochrome c. Cytochrome c is an important protein involved in the production of cellular energy as well as in apoptosis. The release of cytochrome c from the mitochondria to the cytoplasm of individual MCF-7 cells is monitored by a fiber optic nanosensor inserted into a single cell, followed by an enzyme-linked immunosorbent assay (ELISA) outside the cell [41].

(d) Measuring caspase-9 [40]. One of the earliest biomarkers of apoptosis is the activation of cysteine aspartate-dependent proteases (caspases) due to the caspases' central role in the activation [42, 43].

(e) Fiber optic nanosensors have been developed and used for the detection of cellular pH value [44 – 46] as well as ions such as K^+ [47] and Ca^{2+} [48], NO [49], NO_2^- [50], Cl^- [50], Na^+ [51], Ca^{2+} fluctuation [3].

Due to the small sampling volume probed by the optical fiber nanosensor, the amount of target analyte in the excitation volume is small, hence making it a necessity to adopt a sensitive optical spectroscopic technique (such as fluorescence) for analysis. Another disadvantage is that in spite of the minimal invasiveness when compared with other wire-probe devices, some amount of physical damage on the cell may occur with the use of the optical fiber nanosensor.

2.2. PEBBLEs

In order to overcome the shortcomings associated with both the free fluorescent dyes method and the optical fiber method, the *P*hotonic *E*xplorers for *B*ioanalysis with *B*iologically *L*ocalized *E*mbedding (PEBBLE) was introduced. PEBBLEs are nano-scale sensing devices which encapsulate an analyte-specific dye and a reference dye inside a biologically inert matrix [52, 53]. Due to the absence of a long probe connecting the sensor in the cell to the outside of the cell, PEBBLEs are less physically disruptive to the cellular environment. Furthermore, the encapsulation of the dyes within an inert matrix ensures that the sensing phase is separated from the cell environment, thereby preventing chemical interference. PEBBLEs can be categorized into four types according to their distinct matrices, two categories on the basis of their working principles, and four methods of PEBBLE delivery into the cell. The four types of PEBBLE matrices are:

(a) Polyacrylamide [52, 53]: Polyacrylamide PEBBLEs are made by polymerizing a solution of monomer, sensing dye, reference dye and, to control the size, a surfactant. The dye molecules are simply incorporated in the matrix by being in the solution during polymerization.

(b) Polydecylmethacrylate (PDMA) [54 – 56]: PDMA PEBBLEs are polymerized within a hydrophobic environment without the presence of the dye molecules nor other sensing components. The hydrophobic sensing components, such as dyes, ionophores and ionic additives are then introduced by swelling the matrix of the nanospheres with a polar solution (tetrahydrofuran/water) in the presence of the relevant components [56].

(c) Sol-gel [57]: Sol-gel PEBBLEs are synthesized using “soft” techniques that allow the inclusion of delicate biological molecules. The sol-gel nanoparticle preparation is carried out in the presence of the sensing components. Sol-gel PEBBLEs are coated with poly(ethylene glycol) in order to enhance the biocompatibility [57].

(d) *Or*ganically *mo*dified *sil*icates (Ormosils) [58]: Ormosil PEBBLEs are prepared in two steps [58]. In the first stage, the core formation takes place by hydrolyzing phenyltrimethoxysilane within acidic environment, followed by silane condensation within alkaline environment. The nanoparticle cores are then coated with the ormosil layer. Finally, the sensing elements are incorporated into the ormosil PEBBLEs just before the second layer forms.

The two working mechanisms of PEBBLEs are (a) direct measurement PEBBLEs and (b) ion-correlation PEBBLEs. The direct measurement PEBBLEs apply for sensing both ions and small molecules. These allow the analyte to permeate the matrix and interact with the indicator dye directly and selectively, thereby causing stimulation or quenching of fluorescence. Direct measurement PEBBLEs have been used for sensing H^+ [52], Ca^{2+} [52], Mg^{2+} [59], Zn^{2+} [10] and glucose [60]. Sol-gel PEBBLEs are normally designed as dissolved gas sensors, and have been used for sensing dissolved molecular oxygen [57, 58]. However, some analytes lack highly selective fluorescent indicators. To overcome this setback, an ingenious method had been proposed. Ion-correlation, or ion-exchange, PEBBLEs have been developed to address this shortcoming.

The ion-correlation PEBBLE consists of a silent ionophore and a chromoionophore bound together as a pair working in a synergistic manner. As the name suggests, the silent ionophore has a high affinity towards the ion of interest but such bonds do not produce any fluorescent indication. Fluorescent indication is emitted through the chromoionophore by ion-exchange mechanism. Due to a change in the charge of the pair of silent ionophores and the chromoionophore, a proton (i.e. H^+) is released into, or absorbed from, the environment in order to maintain charge neutrality. Due to a change in pH of the chromophore as a result of the change in the H^+ concentration, the fluorescent behavior of the chromophore is expressed (see Fig. 4). The chromoionophore is usually a pH-dependent fluorophore. The phrase “ion-exhange” was coined due to the binding of a cation and the release of a proton. This principle has been initially reported in bulk level application [61 – 67], and was later adopted at a nanoscale fiber optic probe [68, 69]. The ion-

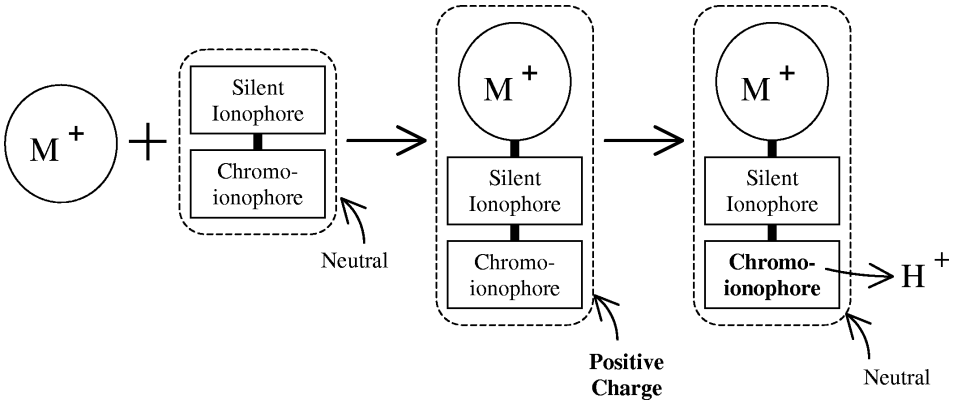

Fig. 4. Conceptual schematics of an ion-correlation PEBBLE.

correlation PEBBLEs have been tested for detection of K^+ [54], Na^+ [55], and Cl^- [56].

The four methods for PEBBLE delivery are [70]:

(a) Gene gun delivery: This is essentially a shotgun approach in which nanosensors are dried onto a plastic that is placed in front of a disc which, upon rupture at the preset helium pressure, shoots the nanosensors from the plastic disc into the cell culture. Gene delivery is the most effective technique, and hence the most commonly used method, for delivering PEBBLEs within a short time with ease and without compromising the cell viability.

(b) Picoinjection delivery: This technique maintains excellent cell viability but works well only for larger cells, such as oocytes and embryos, where more room is available for maneuvering. Apart from this limitation, the cell-by-cell injection is time-consuming.

(c) Liposomal delivery: The time-consuming disadvantage associated with the picoinjection approach is overcome by the liposomal delivery, which introduces numerous nanosensors to a number of cells simultaneously. The PEBBLE-carrying liposomes must be prepared before incubation with the cell culture in order to release the nanosensors into the cytosol upon interaction with the cell membrane. Although liposomal delivery maintains excellent cell viability, it is difficult to optimize.

(d) Cell-directed delivery: Cell-directed delivery mechanisms, such as phagocytosis and sequestration into macrophages, exhibit excellent cell viability [53] but are limited in controlling the nanosensor placement because the sensor location is determined by the cell.

3. Electromagnetic Nanosensors

Under the category of electromagnetic nanosensors, we have two types of sensors based on their physical mechanisms:

(a) detection by electrical current measurement;
(b) detection by magnetism measurement.

3.1. Electrical Current Measurement

We review the category of electrical current measurement for two cases: detection by current inhibition and detection by current enhancement. A salient advantage of this approach is the label-free methodology over the use of dyes.

In the category of current inhibition, Geng et al. [71] studied the interaction between hydrogen sulfide and gold nanoparticles, and found that the adsorption of hydrogen sulfide molecules onto the nanoparticles change the hopping behavior of the electrons through the particles – hence the suppressed hopping phenomenon. The hopping of electrons was measured by recording the current and voltage across chromium and gold electrodes in the presence of an applied electrical field (see Fig. 5).

Without exposure to hydrogen sulfide, the current increases with the applied voltage, but loss of current was observed with the exposure to hydrogen sulfide. It is known that the current loss is due to a change in surface properties of the gold nanoparticles following the adsorption of hydrogen sulfide molecules as a result of the strong chemical affinity between gold and sulfur atoms. Chemical adsorption of the hydrogen sulfide molecules onto the nanoparticles brings about partial substitution of the citrate layer, producing possi-

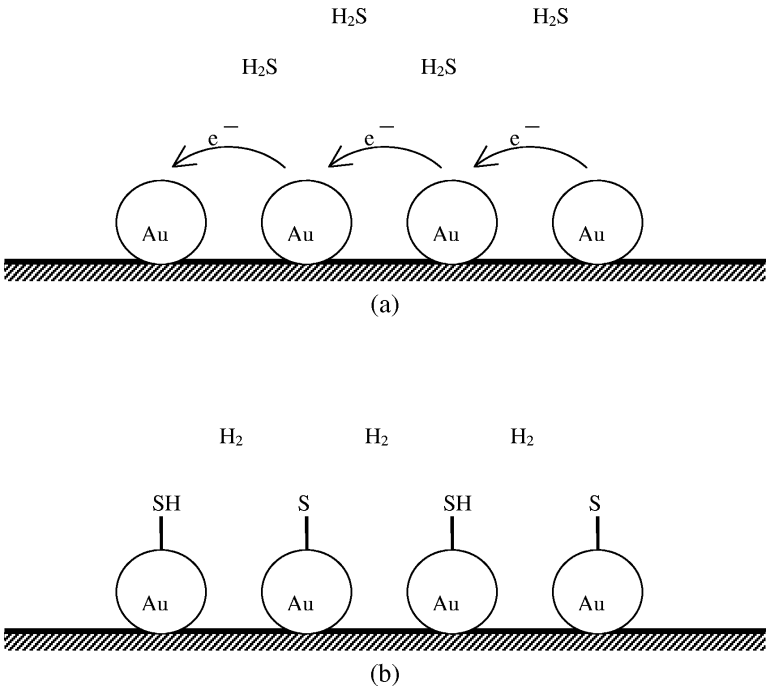

Fig. 5. Detection of analytes via inhibition of electron hopping (a) before bonding and (b) after bonding.

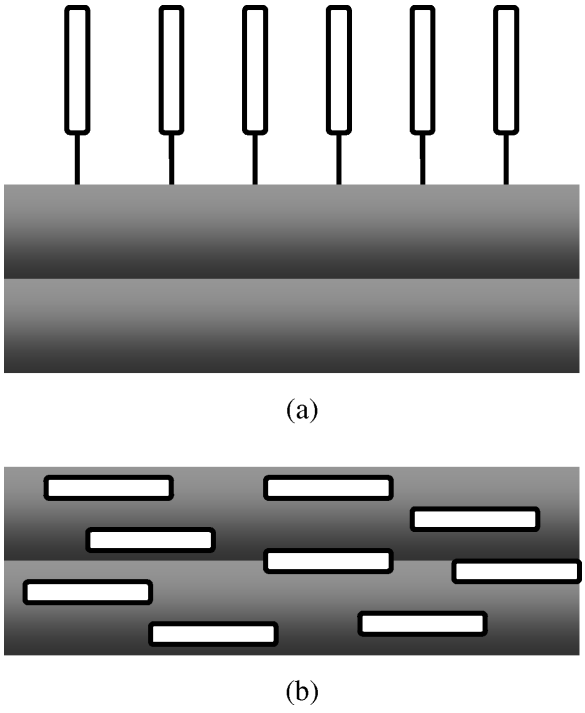

Fig 6. CNT-based nanoelectrode for electrical current-based nanosensor: (a) CNT-coating and (b) nanocomposite.

ble Au-S or Au-SH type species on the gold nanoparticle surface. Consequently, a sulfide shell is produced, thereby inhibiting the transfer of charge from one nanoparticle to the next. The byproduct is released into the gas phase as hydrogen molecules:

$$\mathrm{Au} + \mathrm{H_2S} \rightarrow \mathrm{AuS} + \mathrm{H_2}\uparrow, \tag{2}$$

$$2\mathrm{Au} + 2\mathrm{H_2S} \rightarrow 2\mathrm{AuSH} + \mathrm{H_2}\uparrow. \tag{3}$$

In the category of current enhancement, the critical components of the nanosensors are carbon nanotubes (CNTs) or conducting molecules. The incorporation of CNTs can be done either as vertically aligned arrays to form coating for electrode transducers [72 – 76] (see Fig. 6a) or by embedment to form nanocomposite electrodes [77 – 81] (see Fig. 6b).

Such CNT electrodes have been used for monitoring of oxidase such as glucose [75, 78, 81 – 83]. Specifically, Davis et al. [84] and Besteman et al. [85] employed single-walled CNTs (SWCNT) whilst Ye et al. [86] adopted multi-walled CNTs (MWCNT) for the detection of glucose. Apart from glucose, another oxidase detection using CNTs is lactate oxidase [87]. In addition to oxidase, CNT-based nanosensors have been used for the detection of enzymes including dehydrogenase [88], peroxidase (such as horseradish-peroxidase [73], hydrogen peroxide [89, 90]) and cata-

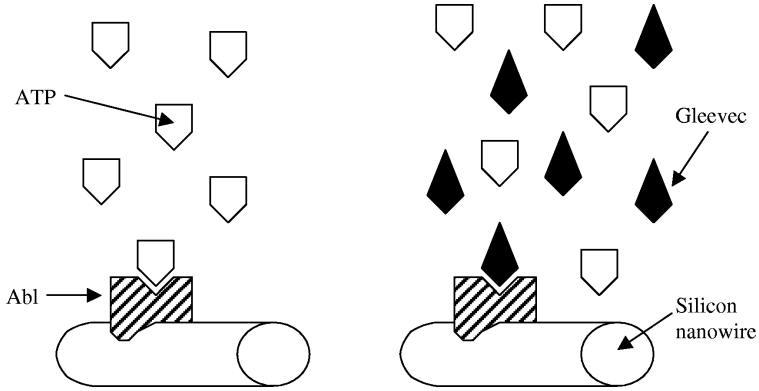

Fig. 7. Competitive binding of ATP and Gleevec on Abl attached to silicon nanowire.

lase [91]. Other enzymes detectable using this category of nanosensor include organophosphorous pesticides [92] and organophosphorous substrates of organophosphorous hydrolase [93]. In view of the significance of testing genetic and infectitious diseases, CNT-based nanosensors have been used for detection of DNA [94 – 100].

As an alternative to the vertically aligned array of CNT-coating, Wang et al. [101] replaced the CNTs by Abl, which is a protein tyrosine kinase whose constitutive activity is responsible for chronic myelogenous leukemia, whereby adenosine triphosphate (ATP) is bound with Abl. It is known in the medical community that the drug Gleevec, possessing certain extent of similarities with ATP, works well in inhibiting the disease. Hence the attachment of Abl on silicon nanowire as a detector ATP, and the use of Gleevec as the competitor binder was performed, see also Figure 7.

It was found that the conductance of the silicon nanowire increases linearly with the concentration of ATP without Gleevec. However, no significant change was observed in the presence of Gleevec. This result shows the viability of functionalized nanowire for the detection of small-molecule-mediated inhibition of protein-protein interactions with the potential impact in drug discovery and chemical genetics.

3.2. Magnetism Measurement

In nuclear magnetic resonance (NMR), the spin-spin relaxation time is defined as the time to reduce the transverse magnetism by a factor of e, i. e. 2.718281828. The spin-spin relaxation time is a biological parameter that is used in magnetic resonance imaging (MRIs) to distinguish between tissue types

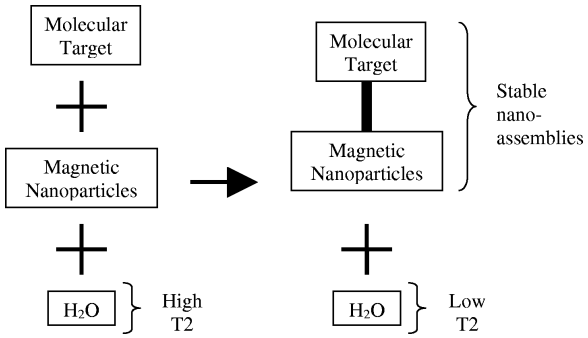

Fig. 8. Schematic of $T2$ measurement using magnetic nanoparticles as nanosensors.

and is called $T2$. Some examples of $T2$ readings are 40 ms, 90 ms, 180 ms and 2500 ms for muscle, fat, blood and water, respectively. It has been postulated that magnetic nanosensors composed of magnetic nanoparticles can be used for detecting molecular interactions by magnetic resonance techniques. When these magnetic nanoparticles bind to their intended molecular target, they form stable nanoassemblies, thereby leading to a corresponding decrease in $T2$ of the surrounding molecules [9], as schematically shown in Figure 8.

Perez et al. [18] hypothesized that when individual superparamagnetic nanoparticles assemble into clusters and the effective cross-sectional area becomes larger, the nanoassembly becomes more efficient at dephasing the spins of surrounding water protons, leading to an enhancement of the relaxation rates $(1/T2)$. This technique of measuring $T2$ has been performed in a number of experiments to detect oligonucleotide sequences [9, 102], enzymatic activity (such as proteases [102, 103] and endonucleases [104]), and viral particles in serum [105].

The unique sensing technique of magnetic nanoparticle sensor technology enables quick detection of targets without extensive purification of the sample or signal amplification. Since light is not used (as opposed to opto-chemical, optical, absorbance, etc.) it bears no influence on the outcome of the assay, and experimentation can be performed in turbid, light-impermeable media such as cell suspension, lipid emulsion, blood, culture media and even entire tissue [18]. Since the iron oxide nanoparticles used are non-toxic [106], this technology can be applied for in vivo sensing of molecular targets by MRI.

Apart from bioscience application, magnetic nanosensors – on the basis of magnetoresistance (MR) – have potential application for the electronics industry. MR is the phenomenon whereby the electrical resistance of a metal or semiconductor changes (either increases or decreases) as a result of the application of a magnetic field. A three orders higher variant of this phenomenon was termed colossal magnetoresistance or extraordinary magnetoresistance (EMR) [107 – 110]. EMR depends on the detailed shape of a device made from semiconductor and conductive metal, and could be applied for producing computer disc-drive read-heads that are faster and capable of storing higher densities of information than current read-heads, which rely on giant magnetoresistance (GMR) [111]. Since EMR read-heads do not have magnetic materials, they emit lesser noise than GMR read-heads, hence pointing towards an enhanced working performance. A number of possible applications have been suggested, such as position-sensing robot as well as speed and position sensors in industry [20].

4. Mechanical Nanosensors

The earliest mechanical nanosensor was proposed by Binh et al. [1] for measuring the vibrational and elastic characteristics of a nanosphere attached to a tapered cantilever. This work is important for application in nanodevices components and nano-scale subassemblies in microelectronic devices. Instead of measuring the vibrational and elastic properties of the subassemblies attached to a surface, Binh et al. [1] introduced the concept of producing replicas of these objects from heating of fine wires terminated with sharp tips. Experimental studies verify the possibility of a solid drop formation that is connected to the rest of the wire by a narrow neck [112 – 114]. It was shown that this technique is capable of producing a sphere of 10^2 nm diameter connected to the shank by a slender neck of 10^1 nm diameter and 10^2 nm length, which results in resonance frequency of $10^{2\pm1}$ MHz and spring constants between 10^{-2} and 10^1 Nm^{-1}.

Table 1. A summary on various types of nanosensors and their applications.

Nanosensor type	Sub-category	Measured specimens or physical properties
Optical	Fiber optic	Benzopyrene tetrol, benzo[*a*]-pyrene, caspase-9 (an apoptosis protein), cytochrome c (a protein involved in producing cellular energy), pH, K^+, Ca^{2+}, NO, $NO_2{}^-$, Cl^-, Na^+
	PEBBLE (direct)	H^+, Ca^{2+}, Mg^{2+}, Zn^{2+}, glucose and dissolved O_2
	PEBBLE (ion-correlation)	K^+, Na^+, Cl^-
Electromagnetic	Current measurement	H_2S, GOx, lactase oxidase, dehydrogenase, peroxidase, hydrogen peroxide, catalase, organophosphorus pesticides, organophosphorus substrates of organophosphorus hydrolase, DNA, ATP
	Magnetism measurement	Molecular interactions, oligonucleotide sequences, enzymatic activity, viral particles, magnetic field, speed, position sensing
Mechanical	Vibrational	Resonance frequency, spring constant
	Inertial	Pressure, acceleration, yaw rate

Whilst the works of Binh et al. [1, 112 – 114] focus on the vibrational and elastic properties, Hierold [115] explored the possibility of down-scaling the mechanical inertia sensors from the micro-scale to nano-scale. The sensing force is measured as a result of pressure, acceleration and yaw rate that displaces the sensing electrode against the spring force. The change of distance with respect to the counter electrode is then measured by a change of the capacitance. Such micro-scale mechanical inertial sensors could be scaled down into nanosensors provided that self-assembly of nanostructures becomes a well controlled fabrication technology. Although development in mechano-vibrational nanosensors is not as remarkable as that of photo-chemical or electro-chemical nanosensors, one may expect an increasing progress in the former due to advances made in the nano-scale enabling technologies.

5. Conclusions

A wide range of nanosensors has been surveyed, categorized and discussed according to their working mechanism, which was then compared to their applications. One may note that, in general, optical nanosensors are highly useful for detection of chemicals inside a single cell, electromagnetic nanosensors are found to be applicable for both chemical sensing as well as electromagnetic-mechatronic measurements, whilst mechanical nanosensors are useful for determining the physico-mechanical properties and motion measurements. A brief summary of the various nanosensors with reference to their applications is furnished in Table 1.

In spite of the relatively short history of nanosensors, the advances made in this area have been remarkable. With the continuing progress in nanotechnology tools and increasing insight on the nano-scale phenomena, one may expect further advancement in the area of nanosensors through enhance performance of existing nanosensors and newer nanosensors based on novel mechanisms.

[1] V. T. Binh, N. Garcia, and A. L. Levanuyk, Surface Sci. **301**, L224 (1994).
[2] D. Uttamchandany and S. McCulloch, Adv. Drug Delivery Rev. **21**, 239 (1996).
[3] S. L. R. Barker, R. Kopelman, T. E. Meyer, and M. A. Cusanovich, Anal. Chem. **70**, 971 (1998).
[4] Z. Rosenweig and K. P. McNamara, Abstr. Pap. Am. Chem. Soc. **216**, 035-ANYL (1998).
[5] R. Meallet-Renault, P. Denjean, and R. B. Pansu, Sensors Actuators B Chem. **59**, 108 (1999).
[6] X. J. Zhang, J. Wang, B. Ogorevc, and U. E. Spichiger, Electroanalysis **11**, 945 (1999).
[7] H. X. He, C. Z. Li, and N. J. Tao, Abstr. Pap. Am. Chem. Soc. **220**, 239-COLL (2000).
[8] Y. Cui, Q. Q. Wei, H. K. Park, and C. M. Lieber, Science **293**, 1289 (2001).
[9] L. Josephson, J. M. Perez, and R. W. Weissleder, Angew. Chem. Int. Ed. **40**, 3204 (2001).
[10] J. P. Sumner, J. W. Aylott, E. Monson, and R. Kopelman, Analyst **127**, 11 (2002).
[11] P. T. Tran, E. R. Goldman, G. P. Anderson, J. M. Mauro, and H. Mattoussi, Phys. Status Solidi B **229**, 427 (2002).
[12] R. L. Maglathlin and B. A. Salvatore, Abstr. Pap. Am. Chem. Soc. **223**, 819-CHED (2002).
[13] M. Law, H. Kind, B. Messer, F. Kim, and P.D. Yang, Angew. Chem. Int. Ed. **41**, 2405 (2002).
[14] J. F. Maguire, M. S. Amer, and J. Busbee, Appl. Phys. Lett. **82**, 2592 (2003).
[15] A. Y. Nazzal, L. H. Qu, X. G. Peng, and M. Xiao, Nano Lett. **3**, 819 (2003).
[16] A. V. Sergeev, V. V. Mitin, B. S. Karasik, and M. E. Gershenson, Physica E **19**, 173 (2003).
[17] V. Haguet, D. Martin, L. Marcon, T. Heim, D. Stievenard, C. Oliver, O. El-Mahdi, and O. Melnyk, Appl. Phys. Lett. **84**, 1213 (2004).
[18] J. M. Perez, L. Josephson, and R. Weisleder, ChemBioChem **5**, 261 (2004).
[19] W. B. Frommer, M. Fehr, S. Lalonde, and I. Lager, Cytometry A **59**, 84 (2004).
[20] S. A. Solin, Sci. Am. **291**, 70 (2004).
[21] Z. L. Wang, Abstr. Pap. Am. Chem. Soc. **227**, U111-ANYL (2004).
[22] A. V. Whitney, J. W. Elam, S. L. Zou, A. V. Zinovev, P. C. Stair, G. C. Schatz, and R. P. V. Duyne, J. Phys. Chem. B **109**, 20552 (2005).
[23] R. Metzler and T. Ambjornsson, J. Comput. Theor. Nanosci. **2**, 389 (2005).
[24] N. L. Lala, R. Ramaseshan, and S. Ramakrishna, unpublished report.
[25] K. Sasaki, Z. Y. Shi, R. Kopelman, and H. Masuhara, Chem. Lett. **25**, 141 (1996).
[26] A. P. De Silva, H. Q. N. Gunaratne, T. Gunnlaugsson, A. J. M. Huxley, C. P. McCoy, J. T. Rademacher, and T. E. Rice, Chem. Rev. **97**, 1515 (1997).
[27] A. W. Czarnik, Fluorescent Chemosensors for Ion and Molecular Recognition, ACS Symposium Series 538, ACS, Washington, DC 1993.
[28] J. R. Lakowicz, Principles of Fluorescent Spectroscopy, Springer, Berlin 1999.
[29] S. Kulmala and J. Suomi, Anal. Chim. Acta **500**, 21 (2003).
[30] R. P. Haugland, Molecular Probes Handbook of Fluorescent Probes and Research Chemicals, Molecular Probes Inc., Oregon 1993.
[31] J. Ji, N. Rosenweig, I. Jones, and Z. Rosenweig, Anal. Chem. **73**, 3521 (2001).
[32] J. Ji, N. Rosenweig, C. Griffin, and Z. Rosenweig, Anal. Chem. **72**, 3497 (2000).
[33] B. Cullum, G. D. Griffin, G. H. Miller, and T. Vo-Dinh, Anal. Biochem. **277**, 25 (2000).
[34] P. M. Kasili, B. M. Cullum, G. D. Griffin, and T. Vo-Dinh, J. Nanosci. Nanotechnol. **2**, 653 (2002).
[35] T. Vo-Dinh, J. P. Alarie, B. M. Cullum, and G. D. Griffin, Nature Biotechnol. **18**, 764 (2000).
[36] T. Vo-Dinh, G. D. Griffin, J. P. Alarie, B. M. Cullum, B. Sumpter, and D. L. Noid, J. Nanoparticle Res. **2**, 17 (2000).
[37] T. Vo-Dinh and B. Cullum, Fresenius J. Anal. Chem. **366**, 540 (2000).

[38] W. H. Tan, Z. Y. Shi, and R. Kopelman, Anal. Chem. **64**, 2985 (1992).
[39] W. H. Tan, Z. Y. Shi, S. Smith, D. Birnbaum, and R. Kopelman, Science **258**, 778 (1992).
[40] P. M. Kasili, J. M. Song, and T. Vo-Dinh, J. Am. Chem. Soc. **9**, 2799 (2004).
[41] J. M. Song, P. M. Kasili, G. D. Griffin, and T. Vo-Dinh, Anal. Chem. **76**, 2591 (2004).
[42] D. Nicholson and N. A. Thornberry, Trends Biochem. Sci. **8**, 299 (1997).
[43] G. M. Cohen, Biochem. J. **326**, 1 (1997).
[44] J. Samuel, A. Strinkovski, S. Shalom, K. Lieberman, M. Ottolenghi, D. Avnir, and A. Lewis, Mater. Lett. **21**, 431 (1994).
[45] W. H. Tan, Z. Y. Shi, and R. Kopelman, Sensors Actuators B Chem. **28**, 157 (1995).
[46] A. Song, S. Parus, and R. Kopelman, Anal. Chem. **69**, 863 (1997).
[47] I. Korinzi, J. Reichert, G. Heinzmann, and H. J. Ache, Sensors Actuators B Chem. **51**, 188 (1998).
[48] J. D. Bui, T. Zelles, J. H. Lou, V. L. Gallion, M. I. Philips, and W. H. Tan, J. Neurosci. Methods **89**, 9 (1999).
[49] S. L. R. Barker and R. Kopelman, Anal. Chem. **70**, 4902 (1998).
[50] S. L. R. Barker, B. A. Thorsrud, and R. Kopelman, Anal. Chem. **70**, 100 (1998).
[51] W. Tan, R. Kopelman, S. L. Barker, and M. T. Miller, Anal. Chem. **71**, 606A (1999).
[52] H. A. Clark, R. Kopelman, R. Tjalkens, and M. A. Philbert, Anal. Chem. **71**, 4837 (1999).
[53] H. A. Clark, M. Hoyer, M. A. Philbert, and R. Kopelman, Anal. Chem. **71**, 4831 (1999).
[54] M. Brasuel, R. Kopelman, T. J. Miller, R. Tjalkens, and M. A. Philbert, Anal. Chem. **73**, 2221 (2001).
[55] M. Brasuel, R. Kopelman, I. Kasman, T. J. Miller, and M. A. Philbert, Proc. IEEE Sensors **1**, 288 (2002).
[56] M. G. Brasuel, T. J. Miller, R. Kopelman, and M. A. Philbert, Analyst **128**, 1262 (2003).
[57] H. Xu, J. W. Aylott, R. Kopelman, T. J. Miller, and M. A. Philbert, Anal. Chem. **73**, 4124 (2001).
[58] Y. E. Koo, Y. Cao, R. Kopelman, S. M. Koo, M. G. Brasuel, and M. A. Philbert, Anal. Chem. **76**, 2498 (2004).
[59] E. J. Park, M. Brasuel, C. Behrend, M. A. Philbert, and R. Kopelman, Anal. Chem. **75**, 3784 (2003).
[60] H. Xu, J. W. Aylott, and R. Kopelman, Analyst **127**, 1471 (2002).
[61] E. Bakker and K. Simon, Anal. Chem. **64**, 1805 (1992).
[62] W. E. Morf, K. Seiler, B. Lehmann, C. Behringer, K. Hartman, and W. Simon, Pure Appl. Chem. **61**, 1613 (1989).
[63] P. Buhlmann, E. Pretsch, and E. Bakker, Chem. Rev. **98**, 1593 (1998).
[64] K. Suzuki, H. Ohzora, K. Tohda, K. Miyazaki, K. Watanabe, H. Inoue, and T. Shirai, Anal. Chim. Acta **237**, 155 (1990).
[65] K. Kurihara, M. Ohtsu, T. Yoshida, T. Abe, H. Hisamoto, and K. Suzuki, Anal. Chim. Acta **71**, 3558, 1999.
[66] G. J. Mohr, F. Lehmann, R. Ostereich, I. Murkovic, and O. S. Wolfbeis, Fresenius J. Appl. Chem. **357**, 284 (1997).
[67] G. J. Mohr, I. Murkovic, F. Lehmann, C. Haider, and O. S. Wolfbeis, Sensors Actuators B Chem. **39**, 239 (1997).
[68] M. Shortreed, E. Bakker, and R. Kopelman, Anal. Chem. **68**, 2656 (1996).
[69] M. R. Shortreed, S. Dourado, and R. Kopelman, Sensors Actuators B Chem. **38**, 8 (1997).
[70] M. Brasuel, J. W. Aylott, H. Clark, H. Xu, R. Kopelman, M. Hoyer, T. J. Millar, R. Tjalkens, and M. A. Philbert, Sensors Mater. **14**, 309 (2002).
[71] J. F. Geng, M. D. R. Thomas, D. S. Shephard, and B. F. G. Johnson, Chem. Commun. **2005**, 1895 (2005).
[72] J. J. Gooding, R. Wibowo, J. Q. Liu, W. Yang, S. Orbon, F. J. Mearns, J. G. Shapter, and D. B. Hibbert, J. Am. Chem. Soc. **125**, 9006 (2003).
[73] X. Yu, D. Chattopadhyay, I. Galeska, F. Papadimitrakopoulos, and J. F. Rusling, Electrochem. Commun. **5**, 408 (2003).
[74] S. Sotiropoulo and N. A. Chaniotakis, Anal. Bioanal. Chem. **375**, 103 (2003).
[75] Y. Lin, F. Lu, Y. Tu, and Z. Ren, Nano Lett. **2**, 191 (2004).
[76] J. Koehne, H. Chen, J. Li, A. Cassell, Q. Ye, H. Ng, and M. Meyyappan, Nanotechnology **14**, 1239 (2003).
[77] J. Wang and M. Musameh, Anal. Chem. **75**, 2075 (2003).
[78] M. D. Rubianes and G. A. Rivas, Electrochem. Commun. **5**, 689 (2003).
[79] F. Valentini, A. Amine, S. Orlanducci, M. Terranova, and G. Palleschi, Anal. Chem. **75**, 5413 (2003).
[80] P. J. Britto, K. S. V. Santhanam, and P. M. Ayajan, Bioelectrochem. Bioenerg. **41**, 121 (1996).
[81] J. Wang and M. Musameh, Analyst **128**, 1382 (2003).
[82] J. Wang, M. Musameh, and Y. Lin, J. Am. Chem. Soc. **125**, 2408 (2003).
[83] M. Gao, L. Dai, and G. G. Wallace, Electroanalysis **15**, 1089 (2003).
[84] J. J. Davis, K. Coleman, B. Azamian, C. Bagshaw, and M. L. Green, Chem. Eur. J. **9**, 3732 (2003).
[85] K. Besteman, J. Lee, F. Wiertz, H. Heering, and C. Dekker, Nano Lett. **3**, 727 (2003).
[86] J. Ye, Y. Wen, W. D. Zhang, L. M. Gan, G. Xu, and F. S. Sheu, Electrochem. Commun. **6**, 66 (2004).
[87] M. D. Rubianes and G. A. Rivas, Electroanalysis **17**, 73 (2005).
[88] J. Wang and M. Musameh, Anal. Lett. **36**, 2041 (2003).

[89] K. Yamamoto, G. Shi, T. S. Zhou, F. Xu, J. M. Xu, T. Kato, J. Y. Jin, and L. Jin, Analyst **128**, 249 (2003).
[90] J. Z. Xu, J. J. Zhu, Q. Wu, Z. Hu, and H. Y. Chen, Electroanalysis **15**, 219 (2003).
[91] L. Zhou, J. Wang, and F. Zhou, Electroanalysis **16**, 672 (2004).
[92] Y. Lin, F. Lu, and J. Wang, Electroanalysis **16**, 145 (2004).
[93] R. P. Deo, J. Wang, I. Block, A. Mulchandani, K. A. Joshi, M. Trojanowicz, F. Scholz, W. Chen, and Y. H. Lin, Anal. Chim. Acta **530**, 185 (2005).
[94] J. J. Gooding, Electroanalysis **14**, 1149 (2002).
[95] M. Pedano and G. A. Rivas, Electrochem. Commun. **6**, 10 (2004).
[96] J. Wang, M. Li, Z. Shi, N. Li, and Z. Gu, Electroanalysis **16**, 140 (2004).
[97] J. Li, H. T. Ng, A. Cassell, W. Fan, H. Chen, Q. Ye, J. Koehne, and M. Meyyappan, Nano Lett. **3**, 597 (2003).
[98] H. Cai, X. Cao, Y. Jiang, P. He, and Y. Fang, Anal. Bioanal. Chem. **375**, 287 (2003).
[99] J. Wang, G. Liu, and M. Jan, J. Am. Chem. Soc. **126**, 3010 (2004).
[100] H. Cai, Y. Xu, P. He, and Y. Z. Fang, Electroanalysis **15**, 1864 (2003).
[101] W. U. Wang, C. Chen, K. H. Lin, Y. Fang, and C. M. Lieber, Proc. Natl. Acad. Sci. USA **102**, 3208 (2005).
[102] J. M. Perez, L. Josephson, T. O'Loughlin, D. Hogemann, and R. Weissleder, Nat. Biotechnol. **20**, 816 (2002).
[103] M. Zhao, L. Josephson, Y. Tang, and R. Weissleder, Angew. Chem. Int. Ed. **42**, 1375 (2003).
[104] J. M. Perez, T. O'Loughlin, F. J. Simeone, R. Weissleder, and L. Josephson, J. Am. Chem. Soc. **124**, 2856 (2002).
[105] J. M. Perez, F. J. Simeone, Y. Saeki, L. Josephson, and R. Weissleder, J. Am. Chem. Soc. **125**, 10192 (2003).
[106] M. G. Harisinghani, J. Barentsz, P. F. Hahn, W. M. Deserno, S. Tabatabaei, C. H. van de Kaa, J. de la Rosette, and R. Weissleder, N. England J. Med. **348**, 2491 (2003).
[107] J. Fontcuberta, Physics World **12**, 33 (1999).
[108] S. A. Solin, T. Thio, D. R. Hines, and J. J. Heremans, Science **289**, 1530 (2000).
[109] P. Grunberg, Physics Today **54**, 31 (2001).
[110] S. A. Solin, Physics World **14**, 29 (2001).
[111] S. A. Solin, D. R. Hines, A. C. H. Rowe, J. S. Tsai, Y. A. Pashkin, S. J. Chung, N. Goel, and M. B. Santos, Appl. Phys. Lett. **80**, 4012 (2002).
[112] V. T. Binh and R. Uzan, Surface Sci. **179**, 540 (1987).
[113] V. T. Binh, A. Piquet, H. Roux, R. Uzan, and M. Drechsler, J. Phys. E **9**, 377 (1976).
[114] N. Garcia and V. T. Binh, Phys. Rev. B **46**, 7946 (1992).
[115] C. Hierold, J. Micromech. Microeng. **14**, S1 (2004).