Investigation on Applicability and Suitability of Micro Cantilever Based Biosensors for DNA Detection

Suhaib Ahmed1*, Lubna Aslam2, Bisma Bilal1, Samiya Ali1 and Vipan Kakkar1

1Department of Electronics and Communication Engineering, Shri Mata Vaishno Devi University, India
2Department of Biotechnology, University of Jammu, India

Submission: February 13, 2017; Published: March 20, 2017

*Corresponding author: Suhaib Ahmed, Department of Electronics and Communication Engineering, Shri Mata Vaishno Devi University, India, Email: sabatt@outlook.com

Abstract
Highly sensitive and selective DNA detection has attracted extensive attention for its importance in clinical diagnostics, treatment, and various genome projects. Recently there has been a flurry of activities with the use of nano particle labels to detect DNA and proteins. These detection methodologies strongly depend on the availability of a mechanism that traduce and amplify specific DNA binding events to detectable signals. One such DNA detection technique is micro cantilever bio sensing. The micro cantilever biosensors are becoming popular due to their inherent ability to generate highly sensitive and quantitative measurements with low cost, portability, real time and label-free detection. The capability of the micro cantilever beams of detecting mechanical stress, mass additions and small forces offer encouraging prospects for physical and chemical sensing with high sensitivity and dynamic range. Keeping this in mind, in this paper a brief study on application and feasibility of micro cantilever based DNA detection has been presented.

Keywords: Micro cantilever; DNA detection; Biosensor; Deflection; Cantilever materials

Introduction
A micro cantilever is an extreme sensitive bio sensing transducer responding to detection of the target molecules in nano scale unit [1,2]. Generally, this device consists of a tiny horizontal beam which is fixed on the supporting material at one end of this beam. Another end is normally free for spatial movement according to the molecular interaction at biological recognition area on the beam surface. Micro cantilever-based biosensors have attracted much attention due to their small size, low cost, fast response, high sensitivity, and suitability for parallelization into arrays [3-5]. The biosensors are generally operated in two modes: static bending and dynamic resonance frequency shift [6]. The current methods for measuring micro cantilever bending involve optical, interferometer, piezo resistive, and capacitive detection technologies [7]. In the static case, label-free biosensors have provided common platforms for DNA hybridization [8], biotin-antibody binding [9], and BRAF mutation in RNA from melanoma cells [10]. Biological interaction between target molecules in analyzed samples and specific capture molecules immobilized on a surface of the beam induces structural bending. Deflection length of the micro cantilever beam can be measured by an optical device as found in Atomic Force Microscopy (AFM) application [11-15]. Optical-based detection offers very high sensitivity in determining a deflection length. However, this system requires great precision of the external readout device, laser source assembly, and position sensitive photo detector (PSD) which increases both cost and size of the whole device. A micro cantilever integrated with an embedded piezo resistive material serves as an inexpensive and portable micro cantilever biosensor platform [16,17]. Deflection length of this device is monitored by using the resistance change of piezo resistive material inside the beam [18,19]. Several previous studies developed piezo resistive micro cantilever-based DNA sensors to detect the short piece of synthetic DNA targets [8,20-22].

DNA Detection
The detection of DNA is considered to be a milestone in the advancement of microcantilever biosensors. Experiments have shown that deflections of the DNA micro cantilever can be induced by many factors such as length and sequence [23], grafting density and hybridization density of molecules [24], buffer salt solution concentration [25], moisture concentration [26], time, and temperature [27]. The detection of nucleic acid
hybridization is achieved using cantilever arrays where the micro cantilever surface is modified using oligonucleotide chain which reacts with the complementary single chain solution. The cantilever transduces this reaction process into the mechanical deflection. Compared to the commercial silicon nitride, the sub polymer fabricated cantilever shows enhanced sensitivity for single stranded DNA by a factor of 6 [28-34]. Micro cantilevers have also been investigated for studying the secondary structure of DNA. A comprehensive table of applications of micro cantilever sensor in DNA detection is provided in Table 1.

**Table 1:** Different applications of Micro cantilevers in DNA detection [28].

| Application                          | Mode of Operation | Research Outcome                                                                                                                                 |
|--------------------------------------|------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| DNA melting [29]                     | Static           | Changes in temperature and ionic strength are required for observation of melting process of DNA.                                                |
| DNA molecular motor [30]             | Static           | Different pH values of buffer result in DNA conformation change which drives repeatedly cantilever deflection, similar to working of motor.         |
| Hybridization [31]                   | Static           | A micro cantilever array is used for the detection of mismatch in the DNA hybridization.                                                        |
| Secondary structure of Oligonucleotides [32] | Static           | The effect on the surface properties of cantilever beam due to the secondary structure of nucleic acids is studied.                              |
| Detection [33]                       | Static           | Single stranded DNA attached to cantilever surface is used to detect DNA hybridization.                                                           |
| Detection                            | Dynamic          | Get an amplified detection signal with a Limit of detection 10−15 M                                                                              |
| Hybridization [34]                   | Dynamic          | A sensitivity of 2 x 10−18 mol is achieved in human serum.                                                                                     |

One such micro cantilever based mechanical resonance DNA detection using gold nano particle-modified probes has been demonstrated in [35]. The measurement of the mass change of a micro fabricated cantilever which is induced by DNA hybridization through the shift of the resonance frequency of the cantilever is the main focus. The attachment of gold nanoparticles on the cantilever reflects the hybridization which is then chemically amplified by gold nano particle-catalyzed nucleation of silver in a developing solution. The gold–thiol covalent bonding link the capture DNA strands on the cantilever as shown in Figure 1 & 2, following that the cantilever is dipped into the target DNA solution for hybridization. After that the DNA strands labelled with gold particles, are hybridized on the other end of target DNA through complementary interactions. When exposed to photographic developing solution the gold nano particles act as nucleating agent for the growth of silver. Detectable frequency shift is seen from the growth of silver particles by increasing the effective mass of the micro cantilever, which can be readily detected.

**Figure 1:** Illustration of (a) rectangular (b) triangular and (c) step cantilever designs.

**Figure 2:** Scheme of micro cantilever based DNA detection using nano particle probe and the sequences of capture DNA, target DNA, probe DNA, and single base pair mismatched DNA [35].

**Materials**

A wide range of materials have been investigated for micro cantilever sensors. Most popular materials include silicon and silicon based materials like silicon nitride and silicon dioxide because these materials resonate with high Q-values and have low energy dissipation. In addition to traditional silicon based materials the magneto elastic and piezoelectric materials exhibit unique properties of both actuation and sensing [36]. The piezoelectric materials occur in many forms such as single crystals (e.g. Quartz), piezo ceramic (PZT), thin film (e.g.,...
sputtered (ZnO) and polymer materials such as poly vinylene chloride (PVDF and SU8). A comprehensive table of commonly used materials for the sensing applications of materials is provided below Table 2 [37,38].

| Material       | Young’s Modulus (Gpa) | Poisson’s Ratio (V) | Density (Gm/Cc) |
|----------------|-----------------------|---------------------|-----------------|
| Silicon        | 170                   | 0.26                | 3.18            |
| SiO2           | 64                    | 0.25                | 106.8           |
| Al2O3          | 415                   | 0                   | 170             |
| Porous Silicon | 106.8                 | 0                   | 0.25            |
| Poly Silicon   | 160                   | 0.22                | 73              |
| Silica         | 73                    | 0.17                | 315             |
| Si3N4          | 315                   | 0.27                | 415             |
| Si3N4          | 315                   | 0.27                | 315             |

Conclusion

This paper investigated the application of micro cantilever biosensors for DNA detection and it was observed that the unique structural features of micro cantilever provides several advantages such as high sensitivity, high throughput, high mass detection accuracy, small volume, and low cost. Given the current advancements in the field of Micro-Electro-Mechanical Systems (MEMS), in future micro cantilevers with ability of parallel detection of multiple species at the same time by patterning different capture DNA strands can be designed.

References

1. Vashist SK (2007) A review of microcantilevers for sensing applications. J of nanotechnology 3: 1-18.
2. Lang HP, Gerber C. (2008) Micro cantilever sensors, in STM and AFM studies on (bio) molecular systems. unravelling the nanoworld Springer p. 1-27.
3. Shekhawat GS, Dravid VP (2015) Biosensors: microcantilevers to lift bio molecules. Nat nanotechnol 10(10):830-831.
4. Arlett JL, Myers E, Roukes M (2011) Comparative advantages of mechanical biosensors. Nat nanotechnol 6(4): 205-215.
5. Zhang N, Tan Z, Li J, Meng W, Xu L (2011) Interactions of single-stranded DNA on microcantilevers. Current opinion in colloid & interface science 16(6): 592-596.
6. Boisen A, Dohn S, Keller SS, Schmid S, Tenje M (2011) Cantilever-like micromechanical sensors. Rep Prog Phys 74(3): 036101.
7. Goeders KM, Colton JS, Bottomley LA (2008) Micro cantilevers: sensing chemical interactions via mechanical motion. Chem rev 108(2): 522-542.
8. Fritz J, Baller M, Lang H, Rothuizen H, Vettiger P, et al. (2000) Translating biomolecular recognition into nano mechanics. Science 288(5464): 316-318.
9. Shekhawat G, Tark SH, Dravid VP (2006) MOSFET-embedded microcantilevers for measuring deflection in biomolecular sensors. Science 311(5767): 1592-1595.
10. Huber E, Lang H, Backmann N, Rimoldi D, Gerber C (2013) Direct detection of a BRAF mutation in total RNA from melanoma cells using cantilever arrays. Nat nanotechnol 8(2): 125-129.
11. Berger R, Delamarche E, Lang H, Gerber C, Gimzewski J, et al. (1998) Surface stress in the self-assembly of alkanethiols on gold probed by a force microscopy technique. Applied Physics A: Materials Science & Processing 66: 555-559.
12. Fritz J, Baller M, Lang H, Strunz T, Meyer E, et al. (2000) Stress at the Solid- Liquid Interface of Self-Assembled Mono layers on Gold Investigated with a Nanomechanical Sensor. Langmuir 16(25): 9694-9696.
13. Wu G, Datar RH, Hansen KM, Thundat T, Cote RJ, et al. (2001) Bioassay of prostate-specific antigen (PSA) using microcantilevers. Nat biotechnol 19(9): 856-860.
14. Shu W, Lauw ED, Seshia AA (2007) Investigation of biotin-streptavidin binding interactions using micro cantilever sensors. Biosens bioelectron 22(9): 2003-2009.
15. Sungkanuk U, Sappat A, Wiritsoraram A, Promptsan C, Tuantranont A (2010) Ultrasensitive detection of Vibrio cholerae O1 using micro cantilever-based biosensor with dynamic force microscopy. Biosens Bioelectron 26(2): 784-789.
16. Porter TL, Eastman MP, Macomber C, Delinger WG, Zhine R (2003) An embedded polymer piezoresistive microcantilever sensor. SPRINGER p-1.
17. Na KH, Kim YS, Kang C (2005) Fabrication of piezoresistive microcantilever using surface micromaching technique for biosensors. Ultramicroscopy 105(1-4): 223-227.
18. Porter T, Eastman M, Pace D, Bradley M (2001) Sensor based on piezoresistive microcantilever technology. Sensors and Actuators A: Physical 88(1): 47-51.
19. Mutyala MSK, Bandhanadham D, Pan L, Pendyala VR, Ji HF (2009) Mechanical and electronic approaches to improve the sensitivity of micro cantilever sensors. Acta Mech Sin 25(1): 1-12.
20. McKendry R, Zhang J, Arntz Y, Strunz T, Hegner M, et al. (2002) Multiple label-free biodetection and quantitative DNA-binding assays on a nano mechanical cantilever array. Proc Natl Acad Sci U S A 99(15): 9783-9788.
21. Calleja M, Nordström M, Álvarez M, Tamayo J, Lechuga LM, et al. (2005) Highly sensitive polymer-based cantilever-sensors for DNA detection. Ultramicrscopcy 105(1-4): 21-222.
22. Mukhopadhyay R, Lorenzen M, Kjems J, Besenbacher F, et al. (2005) Nanomechanical sensing of DNA sequences using piezoresistive cantilevers. Langmuir 21(18): 8400-8408.
23. Nieradka K, Kapczyńska K, Rybka J, Lipiński M, Grabiec P, et al. (2014) Microcantilever array biosensors for detection and recognition of Gram-negative bacterial endotoxins. Sensors and Actuators B: Chemical 198: 114-124.
Advances in Biotechnology & Microbiology

24. Fu L, Zhang K, Li S, Wang Y, Huang TS, et al. (2010) In situ real-time detection of E. coli in water using antibody-coated magnetostrictive microcantilever. Sensors and Actuators B: Chemical 150(1): 220-225.

25. Detzel AJ, Campbell GA, Mutharasan R (2006) Rapid assessment of Escherichia coli by growth rate on piezoelectric-excited millimeter-sized cantilever (PEMC) sensors. Sensors and Actuators B: Chemical 117(1): 58-64.

26. Cha BH, Lee SM, Park JC, Hwang KS, Kim SK, et al. (2009) Detection of Hepatitis B Virus (HBV) DNA at femtomolar concentrations using a silica nanoparticle-enhanced microcantilever sensor. Biosens Bioelectron 25(1): 130-135.

27. Kim HH, Jeon HJ, Cho HK, Cheong JH, Moon HS, et al. (2015) Highly sensitive microcantilever biosensors with enhanced sensitivity for detection of human papilloma virus infection. Sensors and Actuators B: Chemical 221: 1372-1383.

28. ZHANG HY, Hong Qing P, ZHANG BL, Ji Lin T (2012) Microcantilever Sensors for Chemical and Biological Applications in Liquid. Chinese Journal of Analytical Chemistry 40(5): 801-808.

29. Biswal SL, Raorane D, Chaiken A, Birecki H, Majumdar A (2006) Nanomechanical detection of DNA melting on microcantilever surfaces. Anal Chem 78(20): 7104-7109.

30. Shu W, Liu D, Watari M, Riener CK, Strunz T, et al. (2005) DNA molecular motor driven micromechanical cantilever arrays. J Am Chem Soc 127(48): 17054-17060.

31. Hansen KM, HF Ji T, Wu G, Datar R, Gote R, et al. (2001) Cantilever-based optical deflection assay for discrimination of DNA single-nucleotide mismatches. Anal Chem 73(7): 1567-1571.

32. Zheng S, Choi JH, Lee SM, Hwang KS, Kim SK, et al. (2011) Analysis of DNA hybridization regarding the conformation of molecular layer with piezoelectric micro cantilevers. Lab Chip 11(1): 63-69.

33. Álvarez M, Carrascosa LG, Moreno M, Calle A, Zaballos Á, et al. (2004) Nanomechanics of the formation of DNA self-assembled mono layers and hybridization on micro cantilevers. Langmuir 20(22): 9663-9668.

34. Rijal K, Mutharasan R (2007) PEMC-based method of measuring DNA hybridization at femtomolar concentration directly in human serum and in the presence of copious noncomplementary strands. Anal Chem 79(19): 7392-7400.

35. Khemthongcharoen N, Wonghumsom W, Suppat A, Jaruwongrungshee K, Tuantranont A, et al. (2015) Piezoresistive micro cantilever-based DNA sensor for sensitive detection of pathogenic Vibrio cholerae 01 in food sample. Biosens Bioelectron 63: 347-353.

36. Johnson BN, Mutharasan R (2012) Bio sensing using dynamic-mode cantilever sensors: A review. Biosens bioelectron 32(1): 1-18.

37. Lim YC, Kouzani AZ, Duan W, Kaynak A (2010) Effects of design parameters on sensitivity of micro cantilever biosensors. In Complex Medical Engineering (CME), 2010 IEEE/ICME International Conference on IEEE.

38. Nallathambi A, Shanmuganantham T (2014) Performance analysis of cantilever based MEMS sensor for environmental applications. In Smart Structures and Systems (ICSSS), 2014 International Conference on IEEE.

Your next submission with Juniper Publishers will reach you the below assets

- Quality Editorial service
- Swift Peer Review
- Reprints availability
- E-prints Service
- Manuscript Podcast for convenient understanding
- Global attainment for your research
- Manuscript accessibility in different formats (Pdf, E-pub, Full Text, Audio)
- Unceasing customer service

Track the below URL for one-step submission

https://juniperpublishers.com/online-submission.php

This work is licensed under Creative Commons Attribution 4.0 License
DOI: 10.19080/AIBM.2017.02.555593