INVESTIGATING [illegible] METERS ON THE PERFORMANCE OF MICROFLUIDICS ELECTROCHEMICAL BIOSENSOR

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ABSTRACT

The development of advanced technology for medical and biological diagnostician is significantly increased. Electrochemical biosensors become more desirable since it offered an attractive replacement for the bulky and expensive analytical instruments. The design and fabrication of a novel electrochemical biosensor using microfluidic chip are the aims of this research. Additionally, the effects of the design parameters including the microchannel size and electrode size are to be investigated. The designed biosensor is consisting of two chips; a microfluidic chip which was made of PMMA (polymethyl methacrylate) where the microchannel is created. The second chip is made of glass, where the three electrodes cell was fabricated. This design offered more flexible testing and multi diagnostician at the same chip. The performance of such biosensor is then examined using the electrokinetic and cyclic voltammetry techniques in order to ensure the quality of the biosensor. The effect of the microchannel size on the performance of the sensor was then investigated by conducting cyclic voltammetry testing for four different sizes of the fabricated channels at electrode size of 100μm. Likewise, similar channels sizes were investigated at 200μ electrode size. The fabricated chips morphology showed the smoothness on the surface in both the microchannel chip and the electrode chip. No defects on the fabricated chips were reported. The electrokinetic properties of the microchannel were found to be affected by the size of both the microchannel and the electrode. The highest sensitivity of the sensor was reported at microchannel size of 700 and electrode size of 200μm. High accuracy and fast responding electrochemical biosensor are expected to be produced through the optimization of the microchannel size and the electrode surface area.

ABSTRAK

Perkembangan teknologi maju untuk diagnostik perubatan dan biologi meningkat dengan ketara. Biosensor elektrokimia menjadi lebih wajar kerana ia ditawarkan pengganti yang menarik bagi instrumen analisis besar dan mahal. Reka bentuk dan fabrikasi yang biosensor elektrokimia novel menggunakan cip microfluidic adalah Tujuan kajian ini. Selain itu, kesan parameter reka bentuk termasuk saiz saluran mikro dan saiz elektrod yang akan disiasat. The biosensor direka adalah terdiri daripada dua cip; cip microfluidic yang diperbuat daripada PMMA (polymethyl metakrilat) di mana saluran mikro yang dicipta. Cip kedua diperbuat daripada kaca, di mana sel tiga elektrod telah dipalsukan. Reka bentuk ini ditawarkan ujian yang lebih fleksibel dan pelbagai diagnostik pada cip yang sama. Prestasi biosensor itu kemudiannya diperiksa menggunakan teknik voltammetri elektrokinetik dan kitaran untuk memastikan kualiti biosensor ini. Kesan saiz saluran mikro ke atas prestasi sensor kemudiannya disiasat dengan menjalankan ujian voltammetri berkitar selama empat saiz yang berbeza daripada saluran yang direka pada saiz elektrod 100μm. Begitu juga, saluran sama saiz telah disiasat pada saiz elektrod 200μ. Yang direka morfologi cip menunjukkan kelancaran di permukaan di kedua-dua cip saluran mikro dan cip elektrod. Tiada kecacatan pada cip direka dilaporkan. Sifat-sifat elektrokinetik daripada saluran mikro yang didapati dipengaruhi oleh saiz kedua-dua saluran mikro dan elektrod. Kepekaan tertinggi sensor dilaporkan pada saiz saluran mikro 700 dan saiz elektrod 200μm. Ketepatan yang tinggi dan cepat bertindak balas biosensor elektrokimia dijangka akan dihasilkan melalui pengoptimuman saiz saluran mikro dan kawasan permukaan elektrod.

REFERENCES

Abad, L., Javier del Campo, F., Muñoz, F. X., Fernández, L. J., Calavia, D., Colom, G., . . . Esteban-Fernández de Ávila, B. (2012). Design and fabrication of a COP-based microfluidic chip: Chronoamperometric detection of Troponin T. *Electrophoresis, 33*(21), 3187-3194.

Alfonta, L., Singh, A. K., and Willner, I. (2001). Liposomes labeled with biotin and horseradish peroxidase: A probe for the enhanced amplification of antigen-antibody or oligonucleotide-DNA sensing processes by the precipitation of an insoluble product on electrodes. *Analytical chemistry, 73*(1), 91-102.

Alivisatos, A. P., Johnsson, K. P., Peng, X., Wilson, T. E., Loweth, C. J., Bruchez, M. P., and Schultz, P. G. (1996). Organization of'nanocrystal molecules' using DNA. *Nature, 382*(6592), 609-611.

Alonso-Lomillo, M. A., Domínguez-Renedo, O., and Arcos-Martínez, M. J. (2010). Screen-printed biosensors in microbiology; a review. *Talanta, 82*(5), 1629-1636. doi:http://dx.doi.org/10.1016/j.talanta.2010.08.033

Anderson, J. R., Chiu, D. T., Jackman, R. J., Cherniavskaya, O., McDonald, J. C., Wu, H., . . . Whitesides, G. M. (2000). Fabrication of topologically complex three-dimensional microfluidic systems in PDMS by rapid prototyping. *Analytical chemistry, 72*(14), 3158-3164.

Armour, J. C., Gough, D. A., Lucisano, J. Y., and McKean, B. D. (1987). Complete glucose monitoring system with an implantable, telemetered sensor module: Google Patents.

Avramescu, A., Andreescu, S., Noguer, T., Bala, C., Andreescu, D., and Marty, J.-L. (2002). Biosensors designed for environmental and food quality control based on screen-printed graphite electrodes with different configurations. *Analytical and Bioanalytical Chemistry, 374*(1), 25-32.

Bandyopadhyay, K., Patil, V., Sastry, M., and Vijayamohanan, K. (1998). Effect of geometric constraints on the self-assembled monolayer formation of aromatic disulfides on polycrystalline gold. *Langmuir, 14*(14), 3808-3814.

Bandyopadhyay, K., and Vijayamohanan, K. (1998). Formation of a self-assembled monolayer of diphenyl diselenide on polycrystalline gold. *Langmuir, 14*(3), 625-629.

Bandyopadhyay, K., Vijayamohanan, K., Venkataramanan, M., and Pradeep, T. (1999). Self-assembled monolayers of small aromatic disulfide and diselenide molecules on polycrystalline gold films: A comparative study of the geometrical constraint using temperature-dependent surface-enhanced raman spectroscopy, X-ray photoelectron spectroscopy, and electrochemistry. *Langmuir, 15*(16), 5314-5322.

Bard, A. J., and Faulkner, L. R. (1980). *Electrochemical methods: fundamentals and applications* (Vol. 2): Wiley New York.

Basu, S., Kang, W., Davidson, J., Choi, B., Bonds, A., and Cliffel, D. (2006). Electrochemical sensing using nanodiamond microprobe. *Diamond and related materials, 15*(2), 269-274.

Beebe, D. J., Mensing, G. A., and Walker, G. M. (2002). Physics and applications of microfluidics in biology. *Annual review of biomedical engineering, 4*(1), 261-286.

Bennett, S. E. (2006). *Fabrication of water-soluble gold nanoparticle aggregates.* Massachusetts Institute of Technology.

Bozzola, J. J., and Russell, L. D. (1999). *Electron microscopy: principles and techniques for biologists*: Jones & Bartlett Learning.

Bridle, H., and Desmulliez, M. (2014). Chapter Seven - Biosensors for the Detection of Waterborne Pathogens. In H. Bridle (Ed.), *Waterborne Pathogens* (pp. 189-229). Amsterdam: Academic Press.

Brown, K. R., Fox, A. P., and Natan, M. J. (1996). Morphology-Dependent Electrochemistry of Cytochrome c at Au Colloid-Modified SnO2 Electrodes. *Journal of the American Chemical Society, 118*(5), 1154-1157. doi:10.1021/ja952951w

Brust, M., Bethell, D., Kiely, C. J., and Schiffrin, D. J. (1998). Self-assembled gold nanoparticle thin films with nonmetallic optical and electronic properties. *Langmuir, 14*(19), 5425-5429.

Bulgariu, L., and Bulgariu, D. (2008). Self-Assembled Monolayer of Thiols on Gold Electrodes Prepared by Gold Electro-chemical Deposition on Platinum Wire. *Chemical Bulletin" POLITEHNICA" Univ.(Timisoara), 53*(67), 163-167.

Cao, J., Sun, T., and Grattan, K. T. V. (2014). Gold nanorod-based localized surface plasmon resonance biosensors: A review. *Sensors and Actuators B: Chemical, 195*(0), 332-351. doi:http://dx.doi.org/10.1016/j.snb.2014.01.056

Cass, A. E., Davis, G., Francis, G. D., Hill, H. A. O., Aston, W. J., Higgins, I. J., . . . Turner, A. P. (1984). Ferrocene-mediated enzyme electrode for amperometric determination of glucose. *Analytical chemistry, 56*(4), 667-671.

Chen, I.-J., and White, I. M. (2011). High-sensitivity electrochemical enzyme-linked assay on a microfluidic interdigitated microelectrode. *Biosensors and Bioelectronics, 26*(11), 4375-4381.

Chen, L., Ren, J., Bi, R., and Chen, D. (2004). Ultraviolet sealing and poly (dimethylacrylamide) modification for poly (dimethylsiloxane)/glass microchips. *Electrophoresis, 25*(6), 914-921.

Chen, R., Guo, H., Shen, Y., Hu, Y., and Sun, Y. (2006). Determination of EOF of PMMA microfluidic chip by indirect laser-induced fluorescence detection. *Sensors and Actuators B: Chemical, 114*(2), 1100-1107.

Choi, S., and Chae, J. (2009). A regenerative biosensing surface in microfluidics using electrochemical desorption of short-chain self-assembled monolayer. *Microfluidics and nanofluidics, 7*(6), 819-827.

Choi, S., Goryll, M., Sin, L. Y. M., Wong, P. K., and Chae, J. (2011). Microfluidic-based biosensors toward point-of-care detection of nucleic acids and proteins. *Microfluidics and nanofluidics, 10*(2), 231-247.

Chowdhury, A. D., Gangopadhyay, R., and De, A. (2014). Highly sensitive electrochemical biosensor for glucose, DNA and protein using gold-polyaniline nanocomposites as a common matrix. *Sensors and Actuators, B: Chemical, 190*, 348-356.

Clark, L. C., and Lyons, C. (1962). Electrode systems for continuous monitoring in cardiovascular surgery. *Annals of the New York Academy of sciences, 102*(1), 29-45.

Conway, B., Ku, J., and Ho, F. (1980). The electrochemical surface reactivity of iron sulfide, FeS 2. *Journal of Colloid and Interface Science, 75*(2), 357-372.

Council, W. G. (2002). *Gold: The Magazine of the World Gold Council*: World Gold Council.

Crumbliss, A., Stonehuerner, J., Henkens, R., Zhao, J., and O'Daly, J. (1993). A carrageenan hydrogel stabilized colloidal gold multi-enzyme biosensor electrode utilizing immobilized horseradish peroxidase and cholesterol oxidase/cholesterol esterase to detect cholesterol in serum and whole blood. *Biosensors and Bioelectronics, 8*(6), 331-337.

Csaki, A., Möller, R., Straube, W., Köhler, J., and Fritzsche, W. (2001). DNA monolayer on gold substrates characterized by nanoparticle labeling and scanning force microscopy. *Nucleic acids research, 29*(16), e81-e81.

Dalmia, A., Liu, C., and Savinell, R. (1997). Electrochemical behavior of gold electrodes modified with self-assembled monolayers with an acidic end group for selective detection of dopamine. *Journal of Electroanalytical Chemistry, 430*(1), 205-214.

Daniel, M.-C., and Astruc, D. (2004). Gold nanoparticles: assembly, supramolecular chemistry, quantum-size-related properties, and applications toward biology, catalysis, and nanotechnology. *Chemical reviews, 104*(1), 293-346.

Davis, F., and Higson, S. P. J. (2005). Structured thin films as functional components within biosensors. *Biosensors and Bioelectronics, 21*(1), 1-20. doi:http://dx.doi.org/10.1016/j.bios.2004.10.001

Delattre, C., Allier, C. P., Fouillet, Y., Jary, D., Bottausci, F., Bouvier, D., . . . Peponnet, C. (2012). Macro to microfluidics system for biological environmental monitoring. *Biosensors and Bioelectronics, 36*(1), 230-235. doi:http://dx.doi.org/10.1016/j.bios.2012.04.024

Diao, P., Jiang, D., Cui, X., Gu, D., Tong, R., and Zhong, B. (1999). Studies of structural disorder of self-assembled thiol monolayers on gold by cyclic voltammetry and ac impedance. *Journal of Electroanalytical Chemistry, 464*(1), 61-67.

Ding, L., Bond, A. M., Zhai, J., and Zhang, J. (2013). Utilization of nanoparticle labels for signal amplification in ultrasensitive electrochemical affinity biosensors: A review. *Analytica chimica acta, 797*(0), 1-12. doi:http://dx.doi.org/10.1016/j.aca.2013.07.035

Enright, R., Eason, C., Dalton, T., Hodes, M., Salamon, T., Kolodner, P., and Krupenkin, T. (2006). *Friction factors and Nusselt numbers in microchannels with superhydrophobic walls.* Paper presented at the ASME 4th International Conference on Nanochannels, Microchannels, and Minichannels.

Esplandiu, M., Hagenström, H., and Kolb, D. (2001). Functionalized self-assembled alkanethiol monolayers on Au (111) electrodes: 1. Surface structure and electrochemistry. *Langmuir, 17*(3), 828-838.

Evander, M., and Tenje, M. (2014). Microfluidic PMMA interfaces for rectangular glass capillaries. *Journal of Micromechanics and Microengineering, 24*(2), 027003.

Feng, X., Huang, H., Ye, Q., Zhu, J.-J., and Hou, W. (2007). Ag/Polypyrrole Core−Shell Nanostructures: Interface Polymerization, Characterization, and Modification by Gold Nanoparticles. *The Journal of Physical Chemistry C, 111*(24), 8463-8468. doi:10.1021/jp071140z

Finklea, H. O., Snider, D. A., Fedyk, J., Sabatani, E., Gafni, Y., and Rubinstein, I. (1993). Characterization of octadecanethiol-coated gold electrodes as microarray electrodes by cyclic voltammetry and ac impedance spectroscopy. *Langmuir, 9*(12), 3660-3667. doi:10.1021/la00036a050

Fiorito, P. A., and Torresi, S. I. (2001). Glucose amperometric biosensor based on the co-immobilization of glucose oxidase (Gox) and ferrocene in poly (pyrrole) generated from ethanol/water mixtures. *Journal of the Brazilian Chemical Society, 12*(6), 729-733.

Foulds, N. C., and Lowe, C. R. (1988). Immobilization of glucose oxidase in ferrocene-modified pyrrole polymers. *Analytical chemistry, 60*(22), 2473-2478.

French, M., and Creager, S. E. (1998). Enhanced barrier properties of alkanethiol-coated gold electrodes by 1-octanol in solution. *Langmuir, 14*(8), 2129-2133.

Frew, J. E., and Hill, H. A. O. (1987). Electrochemical biosensors. *Analytical chemistry, 59*(15), 933A-944A.

Goldschmidt, M. C. (2014). Biosensors – Scope in Microbiological Analysis. In C. A. Batt & M. L. Tortorello (Eds.), *Encyclopedia of Food Microbiology (Second Edition)* (pp. 274-287). Oxford: Academic Press.

Gomez, F. A. (2008). *Biological applications of microfluidics*: John Wiley & Sons.

Gorton, L., Lindgren, A., Larsson, T., Munteanu, F., Ruzgas, T., and Gazaryan, I. (1999). Direct electron transfer between heme-containing enzymes and electrodes as basis for third generation biosensors. *Analytica chimica acta, 400*(1), 91-108.

Goss, C. A., Charych, D. H., and Majda, M. (1991). Application of (3-mercaptopropyl)trimethoxysilane as a molecular adhesive in the fabrication of vapor-deposited gold electrodes on glass substrates. *Analytical chemistry, 63*(1), 85-88. doi:10.1021/ac00001a018

Gough, D. A., Lucisano, J. Y., and Tse, P. H. (1985). Two-dimensional enzyme electrode sensor for glucose. *Analytical chemistry, 57*(12), 2351-2357.

Grabar, K. C., Allison, K. J., Baker, B. E., Bright, R. M., Brown, K. R., Freeman, R. G., . . . Natan, M. J. (1996). Two-dimensional arrays of colloidal gold particles: a flexible approach to macroscopic metal surfaces. *Langmuir, 12*(10), 2353-2361.

Gravesen, P., Branebjerg, J., and Jensen, O. S. (1993). Microfluidics-a review. *Journal of Micromechanics and Microengineering, 3*(4), 168.

GÜLER, T., HİÇYILMAZ, C., GÖKAĞAÇ, G., and EKMEKÇİ, Z. (2009). Redox behavior of chalcopyrite. *International Journal of Natural and Engineering Sciences, 3*(1), 8.

Guo, S., and Dong, S. (2009). Biomolecule-nanoparticle hybrids for electrochemical biosensors. *TrAC Trends in Analytical Chemistry, 28*(1), 96-109. doi:http://dx.doi.org/10.1016/j.trac.2008.10.014

Hamidi-Asl, E., Palchetti, I., Hasheminejad, E., and Mascini, M. (2013). A review on the electrochemical biosensors for determination of microRNAs. *Talanta, 115*(0), 74-83. doi:http://dx.doi.org/10.1016/j.talanta.2013.03.061

Harper, A., and Anderson, M. R. (2010). Electrochemical glucose sensors—developments using electrostatic assembly and carbon nanotubes for biosensor construction. *Sensors, 10*(9), 8248-8274.

Hayat, A., and Marty, J. (2014). Disposable Screen Printed Electrochemical Sensors: Tools for Environmental Monitoring. *Sensors, 14*(6), 10432-10453.

Haynes, W. M. (2012). *CRC handbook of chemistry and physics*: CRC press.

Hees, J., Hoffmann, R., Kriele, A., Smirnov, W., Obloh, H., Glorer, K., . . . Williams, O. A. (2011). Nanocrystalline diamond nanoelectrode arrays and ensembles. *ACS nano, 5*(4), 3339-3346.

Heinze, J. (1993). Ultramicroelectrodes in electrochemistry. *Angewandte Chemie International Edition in English, 32*(9), 1268-1288.

Henares, T. G., Mizutani, F., and Hisamoto, H. (2008). Current development in microfluidic immunosensing chip. *Analytica chimica acta, 611*(1), 17-30.

Heo, J., and Crooks, R. M. (2005). Microfluidic biosensor based on an array of hydrogel-entrapped enzymes. *Analytical chemistry, 77*(21), 6843-6851.

Hong, T.-F., Ju, W.-J., Wu, M.-C., Tai, C.-H., Tsai, C.-H., and Fu, L.-M. (2010). Rapid prototyping of PMMA microfluidic chips utilizing a CO2 laser. *Microfluidics and nanofluidics, 9*(6), 1125-1133.

Hotchkiss, J. W., Lowe, A. B., and Boyes, S. G. (2007). Surface modification of gold nanorods with polymers synthesized by reversible addition-fragmentation chain transfer polymerization. *Chemistry of materials, 19*(1), 6-13.

Huang, Y., Shi, Y., Yang, H. Y., and Ai, Y. (2015). A novel single-layered MoS2 nanosheet based microfluidic biosensor for ultrasensitive detection of DNA. *Nanoscale, 7*(6), 2245-2249. doi:10.1039/C4NR07162J

Ikeda, T., and Kano, K. (2001). An electrochemical approach to the studies of biological redox reactions and their applications to biosensors, bioreactors, and biofuel cells. *Journal of Bioscience and Bioengineering, 92*(1), 9-18. doi:http://dx.doi.org/10.1016/S1389-1723(01)80191-2

Jager, E. W. H. (2015). Microfluidics in Detection Science – Lab-on-a-Chip Technologies, H.O. Fatoyinbo, F.H. Labeed (Eds.). Royal Society of Chemistry, Cambridge (2015). 281 pp., £145 GBP, ISBN 978-84973-638-1. *Biosensors and Bioelectronics, 71*, 483-484. doi:http://dx.doi.org/10.1016/j.bios.2015.03.075

Jena, B. K., and Raj, C. R. (2006). Electrochemical biosensor based on integrated assembly of dehydrogenase enzymes and gold nanoparticles. *Analytical chemistry, 78*(18), 6332-6339.

Jia, J., Wang, B., Wu, A., Cheng, G., Li, Z., and Dong, S. (2002). A Method to Construct a Third-Generation Horseradish Peroxidase Biosensor: Self-Assembling Gold Nanoparticles to Three-Dimensional Sol−Gel Network. *Analytical chemistry, 74*(9), 2217-2223. doi:10.1021/ac011116w

Jia, W.-Z., Wang, K., and Xia, X.-H. (2010). Elimination of electrochemical interferences in glucose biosensors. *TrAC Trends in Analytical Chemistry, 29*(4), 306-318. doi:http://dx.doi.org/10.1016/j.trac.2010.01.006

Kadilak, A. L., Liu, Y., Shrestha, S., Bernard, J. R., Mustain, W. E., and Shor, L. M. (2014). Selective deposition of chemically-bonded gold electrodes onto PDMS microchannel side walls. *Journal of Electroanalytical Chemistry, 727*(0), 141-147. doi:http://dx.doi.org/10.1016/j.jelechem.2014.06.006

Kafi, A. K. M., and Crossley, M. J. (2013). Synthesis of a conductive network of crosslinked carbon nanotube/hemoglobin on a thiol-modified Au Surface and its application to biosensing. *Biosensors and Bioelectronics, 42*(1), 273-279.

Katz, E., Riklin, A., Heleg-Shabtai, V., Willner, I., and Bückmann, A. (1999). Glucose oxidase electrodes via reconstitution of the apo-enzyme: tailoring of novel glucose biosensors. *Analytica chimica acta, 385*(1), 45-58.

Kermani, M. Z., Teodorczyk, M., and Guo, S. X. (2004). Determination of sample volume adequacy in biosensor devices: Google Patents.

Kimmel, D. W., LeBlanc, G., Meschievitz, M. E., and Cliffel, D. E. (2011). Electrochemical sensors and biosensors. *Analytical chemistry, 84*(2), 685-707.

Kissinger, P., and Heineman, W. R. (1996). *Laboratory Techniques in Electroanalytical Chemistry, revised and expanded*: CRC press.

Knudsen, M. (1909). The law of the molecular flow and viscosity of gases moving through tubes. *Ann. Phys, 28*, 75-130.

Konopka, S., and McDuffie, B. (1970). Diffusion coefficients of ferri-and ferrocyanide ions in aqueous media, using twin-electrode thin-layer electrochemistry. *Analytical chemistry, 42*(14), 1741-1746.

Kress-Rogers, E. (1996). *Handbook of biosensors and electronic noses: medicine, food, and the environment*: CRC Press.

Krysiński, P., and Brzostowska-Smolska, M. (1998). Capacitance characteristics of self-assembled monolayers on gold electrode. *Bioelectrochemistry and Bioenergetics, 44*(2), 163-168. doi:http://dx.doi.org/10.1016/S0302-4598(97)00089-5

Kulys, J. (1999). The carbon paste electrode encrusted with a microreactor as glucose biosensor. *Biosensors and Bioelectronics, 14*(5), 473-479. doi:http://dx.doi.org/10.1016/S0956-5663(99)00026-3

Kumar, A., and Whitesides, G. M. (1993). Features of gold having micrometer to centimeter dimensions can be formed through a combination of stamping with an elastomeric stamp and an alkanethiol ''ink''followed by chemical etching. *Applied Physics Letters, 63*(14), 2002-2004.

Lamberti, F., Luni, C., Zambon, A., Serra, P. A., Giomo, M., and Elvassore, N. (2012). Flow biosensing and sampling in indirect electrochemical detection. *Biomicrofluidics, 6*(2), 024114.

Lazcka, O., Campo, F. J. D., and Muñoz, F. X. (2007). Pathogen detection: A perspective of traditional methods and biosensors. *Biosensors and Bioelectronics, 22*(7), 1205-1217. doi:http://dx.doi.org/10.1016/j.bios.2006.06.036

Lei, K. F. (2012). Microfluidic Systems for Diagnostic Applications A Review. *Journal of laboratory automation, 17*(5), 330-347.

Li, Q. (2012). *Miniaturized Electrochemical Immunosensors for the Detection of Growth Hormone.*

Li, Y., Schluesener, H. J., and Xu, S. (2010). Gold nanoparticle-based biosensors. *Gold Bulletin, 43*(1), 29-41.

Liu, A., Wang, K., Weng, S., Lei, Y., Lin, L., Chen, W., . . . Chen, Y. (2012). Development of electrochemical DNA biosensors. *TrAC Trends in Analytical Chemistry, 37*(0), 101-111. doi:http://dx.doi.org/10.1016/j.trac.2012.03.008

Liu, F., Choi, K. S., Park, T. J., Lee, S. Y., and Seo, T. S. (2011). Graphene-based electrochemical biosensor for pathogenic virus detection. *BioChip Journal, 5*(2), 123-128.

Liu, P., Huang, H., Cao, T., Tang, Z., Liu, X., Qi, Z., . . . Wu, H. (2012). An optofluidics biosensor consisted of high-finesse Fabry-Pérot resonator and micro-fluidic channel. *Applied Physics Letters, 100*(23), 233705.

Liu, S., and Ju, H. (2003). Reagentless glucose biosensor based on direct electron transfer of glucose oxidase immobilized on colloidal gold modified carbon paste electrode. *Biosensors and Bioelectronics, 19*(3), 177-183. doi:http://dx.doi.org/10.1016/S0956-5663(03)00172-6

Lo, R. C. (2013). Application of microfluidics in chemical engineering. *Chem Eng Process Technol, 442*, 368-373.

Love, J. C., Anderson, J. R., and Whitesides, G. M. (2001). Fabrication of three-dimensional microfluidic systems by soft lithography. *Mrs Bulletin, 26*(07), 523-528.

Lowman, G. M., Nelson, S. L., Graves, S. M., Strouse, G. F., and Buratto, S. K. (2004). Polyelectrolyte-quantum dot multilayer films fabricated by combined layer-by-layer assembly and langmuir-schaefer deposition. *Langmuir, 20*(6), 2057-2059.

Lu, F., Wang, J., and Zhang, X. (2005). Microsensors for glucose and insulin monitoring: Google Patents.

Majumder, S., Bhattacharya, B., Singh, P. K., and Johari, S. (2013). Detection of banana bunchy top virus using impedance spectroscopy. *Sensor Letters, 11*(11), 2055-2059.

Manso, J., Mena, M., Yanez-Sedeno, P., and Pingarron, J. (2007). Electrochemical biosensors based on colloidal gold–carbon nanotubes composite electrodes. *Journal of Electroanalytical Chemistry, 603*(1), 1-7.

Manz, A., and Eijkel, J. C. (2001). Miniaturization and chip technology. What can we expect? *Pure and Applied Chemistry, 73*(10), 1555-1561.

Manz, A., Harrison, D. J., Verpoorte, E. M., Fettinger, J. C., Paulus, A., Lüdi, H., and Widmer, H. M. (1992). Planar chips technology for miniaturization and integration of separation techniques into monitoring systems: capillary electrophoresis on a chip. *Journal of Chromatography A, 593*(1), 253-258.

McDonald, W. I., Compston, A., Edan, G., Goodkin, D., Hartung, H. P., Lublin, F. D., . . . Reingold, S. C. (2001). Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Annals of neurology, 50*(1), 121-127.

Mena, M., Yanez-Sedeno, P., and Pingarrón, J. (2005). A comparison of different strategies for the construction of amperometric enzyme biosensors using gold nanoparticle-modified electrodes. *Analytical biochemistry, 336*(1), 20-27.

Metters, J. P., Kadara, R. O., and Banks, C. E. (2012). Electroanalytical sensing of chromium (III) and (VI) utilising gold screen printed macro electrodes. *Analyst, 137*(4), 896-902.

Metzger, B. E. (1991). Summary and recommendations of the third international workshop-conference on gestational diabetes mellitus. *Diabetes, 40*(Supplement 2), 197-201.

Meyerhoff, M., and Opdycke, W. (1986). Ion-selective electrodes. *Adv. Clin. Chem, 25*, 1-47.

Mirkin, C. A., Letsinger, R. L., Mucic, R. C., and Storhoff, J. J. (1996). A DNA-based method for rationally assembling nanoparticles into macroscopic materials. *Nature, 382*(6592), 607-609.

Muck, A., Wang, J., Jacobs, M., Chen, G., Chatrathi, M. P., Jurka, V., . . . Schöning, M. J. (2004). Fabrication of poly (methyl methacrylate) microfluidic chips by atmospheric molding. *Analytical chemistry, 76*(8), 2290-2297.

Murphy, C. J., Sau, T. K., Gole, A. M., Orendorff, C. J., Gao, J., Gou, L., . . . Li, T. (2005). Anisotropic metal nanoparticles: synthesis, assembly, and optical applications. *The Journal of Physical Chemistry B, 109*(29), 13857-13870.

Nakamachi, E., Hwang, H., Okamoto, N., and Morita, Y. (2011). Development of a micropump for Bio-MEMS using a new biocompatible piezoelectric material MgSiO3. *Journal of Micro/Nanolithography, MEMS, and MOEMS, 10*(3), 033013-033013-033017.

Ng, S., Tjeung, R., Wang, Z., Lu, A., Rodriguez, I., and de Rooij, N. F. (2008). Thermally activated solvent bonding of polymers. *Microsystem Technologies, 14*(6), 753-759.

Niemeyer, C. M., and Blohm, D. (1999). DNA microarrays. *Angewandte Chemie International Edition, 38*(19), 2865-2869.

Noh, H.-S., Lee, H., Kim, B.-K., Lee, H.-W., Lee, J.-H., and Son, J.-W. (2011). Microstructural factors of electrodes affecting the performance of anode-supported thin film yttria-stabilized zirconia electrolyte (~1 μm) solid oxide fuel cells. *Journal of Power Sources, 196*(17), 7169-7174. doi:http://dx.doi.org/10.1016/j.jpowsour.2010.09.038

Okawa, Y., Nagano, M., Hirota, S., Kobayashi, H., Ohno, T., and Watanabe, M. (1999). Tethered mediator biosensor. Mediated electron transfer between redox enzyme and electrode via ferrocene anchored to electrode surface with long poly (oxyethylene) chain. *Biosensors and Bioelectronics, 14*(2), 229-235.

Ottova, A. L., and Ti Tien, H. (1997). Self-assembled bilayer lipid membranes: from mimicking biomembranes to practical applications. *Bioelectrochemistry and Bioenergetics, 42*(2), 141-152.

Oyama, N., and Anson, F. C. (1980). Factors Affecting the Electrochemical Responses of Metal Complexes at Pyrolytic Graphite Electrodes Coated with Films of Poly (4-Vinylpyridine). *Journal of The Electrochemical Society, 127*(3), 640-647.

Park, S.-J., Taton, T. A., and Mirkin, C. A. (2002). Array-based electrical detection of DNA with nanoparticle probes. *Science, 295*(5559), 1503-1506.

Park, W., Han, S., and Kwon, S. (2010). Fabrication of membrane-type microvalves in rectangular microfluidic channels via seal photopolymerization. *Lab on a Chip, 10*(20), 2814-2817.

Pingarrón, J. M., Yáñez-Sedeño, P., and González-Cortés, A. (2008). Gold nanoparticle-based electrochemical biosensors. *Electrochimica Acta, 53*(19), 5848-5866. doi:http://dx.doi.org/10.1016/j.electacta.2008.03.005

Plant, A. L. (1993). Self-assembled phospholipid/alkanethiol biomimetic bilayers on gold. *Langmuir, 9*(11), 2764-2767.

Prakash, S., Chakrabarty, T., Singh, A. K., and Shahi, V. K. (2013). Polymer thin films embedded with metal nanoparticles for electrochemical biosensors applications. *Biosensors and Bioelectronics, 41*(0), 43-53. doi:http://dx.doi.org/10.1016/j.bios.2012.09.031

Prathish, K. P., Barsan, M. M., Geng, D., Sun, X., and Brett, C. M. A. (2013). Chemically modified graphene and nitrogen-doped graphene: Electrochemical characterisation and sensing applications. *Electrochimica Acta, 114*, 533-542.

Prieto-Simón, B., Cortina, M., Campàs, M., and Calas-Blanchard, C. (2008). Electrochemical biosensors as a tool for antioxidant capacity assessment. *Sensors and Actuators B: Chemical, 129*(1), 459-466. doi:http://dx.doi.org/10.1016/j.snb.2007.08.004

Randviir, E. P., Brownson, D. A., Metters, J. P., Kadara, R. O., and Banks, C. E. (2014). The fabrication, characterisation and electrochemical investigation of screen-printed graphene electrodes. *Physical Chemistry Chemical Physics, 16*(10), 4598-4611.

Reichert, J., Csáki, A., Köhler, J. M., and Fritzsche, W. (2000). Chip-based optical detection of DNA hybridization by means of nanobead labeling. *Analytical chemistry, 72*(24), 6025-6029.

Rossier, J., Roberts, M., Ferrigno, R., and Girault, H. (1999). Electrochemical detection in polymer microchannels. *Analytical chemistry, 71*(19), 4294-4299.

Rubinstein, I. (1995). *Physical Electrochemistry: Science and Technology* (Vol. 7): CRC Press.

Sadana, A. (1998). Analyte-receptor binding kinetics for biosensor applications. *Applied Biochemistry and Biotechnology, 73*(2-3), 89-112. doi:10.1007/BF02785648

Saen-Oon, S., Lucas, M. F., and Guallar, V. (2013). Electron transfer in proteins: Theory, applications and future perspectives. *Physical Chemistry Chemical Physics, 15*(37), 15271-15285.

Schena, M., Heller, R. A., Theriault, T. P., Konrad, K., Lachenmeier, E., and Davis, R. W. (1998). Microarrays: biotechnology's discovery platform for functional genomics. *Trends in biotechnology, 16*(7), 301-306.

Schuhmann, W. (1995). Electron-transfer pathways in amperometric biosensors. Ferrocene-modified enzymes entrapped in conducting-polymer layers. *Biosensors and Bioelectronics, 10*(1), 181-193.

Schuhmann, W., Kranz, C., Wohlschläger, H., and Strohmeier, J. (1997). Pulse technique for the electrochemical deposition of polymer films on electrode surfaces. *Biosensors and Bioelectronics, 12*(12), 1157-1167.

Serra, B., Jiménez, S., Mena, M. L., Reviejo, A. J., and Pingarrón, J. M. (2002). Composite electrochemical biosensors: a comparison of three different electrode matrices for the construction of amperometric tyrosinase biosensors. *Biosensors and Bioelectronics, 17*(3), 217-226. doi:http://dx.doi.org/10.1016/S0956-5663(01)00269-X

Shoorideh, K., and Chui, C. O. (2014). On the origin of enhanced sensitivity in nanoscale FET-based biosensors. *Proceedings of the National Academy of Sciences, 111*(14), 5111-5116.

Su, H., Yuan, R., Chai, Y., Zhuo, Y., Hong, C., Liu, Z., and Yang, X. (2009). Multilayer structured amperometric immunosensor built by self-assembly of a redox multi-wall carbon nanotube composite. *Electrochimica Acta, 54*(17), 4149-4154.

Sumerlin, B. S., Lowe, A. B., Stroud, P. A., Zhang, P., Urban, M. W., and McCormick, C. L. (2003). Modification of Gold Surfaces with Water-Soluble (Co)polymers Prepared via Aqueous Reversible Addition−Fragmentation Chain Transfer (RAFT) Polymerization†. *Langmuir, 19*(14), 5559-5562. doi:10.1021/la034459t

Taton, T. A., Mirkin, C. A., and Letsinger, R. L. (2000). Scanometric DNA array detection with nanoparticle probes. *Science, 289*(5485), 1757-1760.

Tavares, M. F., and McGuffin, V. L. (1995). Theoretical model of electroosmotic flow for capillary zone electrophoresis. *Analytical chemistry, 67*(20), 3687-3696.

Tertis, M., Florea, A., Sandulescu, R., and Cristea, C. (2013). Carbon based electrodes modified with horseradish peroxidase immobilized in conducting polymers for acetaminophen analysis. *Sensors (Switzerland), 13*(4), 4841-4854.

Tien, H. T. (1974). *Bilayer lipid membranes (BLM): theory and practice*: M. Dekker.

Tien, H. T., and Ottova, A. L. (1999). From self-assembled bilayer lipid membranes (BLMs) to supported BLMs on metal and gel substrates to practical applications. *Colloids and Surfaces A: Physicochemical and Engineering Aspects, 149*(1), 217-233.

Tsao, C., Hromada, L., Liu, J., Kumar, P., and DeVoe, D. (2007). Low temperature bonding of PMMA and COC microfluidic substrates using UV/ozone surface treatment. *Lab on a Chip, 7*(4), 499-505.

Ueno, K., Hayashida, M., Ye, J.-Y., and Misawa, H. (2005). Fabrication and electrochemical characterization of interdigitated nanoelectrode arrays. *Electrochemistry communications, 7*(2), 161-165.

Uosaki, K., Sato, Y., and Kita, H. (1991). Electrochemical characteristics of a gold electrode modified with a self-assembled monolayer of ferrocenylalkanethiols. *Langmuir, 7*(7), 1510-1514. doi:10.1021/la00055a038

Updike, S., and Hicks, G. (1967). The enzyme electrode. *Nature, 214*, 986-988.

Veloso, A. J., Cheng, X. R., and Kerman, K. (2012). 1 - Electrochemical biosensors for medical applications. In S. Higson (Ed.), *Biosensors for Medical Applications* (pp. 3-40): Woodhead Publishing.

Vidal, J. C., Bonel, L., Ezquerra, A., Hernández, S., Bertolín, J. R., Cubel, C., and Castillo, J. R. (2013). Electrochemical affinity biosensors for detection of mycotoxins: A review. *Biosensors and Bioelectronics, 49*(0), 146-158. doi:http://dx.doi.org/10.1016/j.bios.2013.05.008

Walcarius, A., Gondran, C., and Cosnier, S. (2013). Amperometric Sensors *Chemical and Biological Microsensors: Applications in Liquid Media* (pp. 115-171).

Wang, F., Liu, X., and Willner, I. (2013). Integration of photoswitchable proteins, photosynthetic reaction centers and semiconductor/biomolecule hybrids with electrode supports for optobioelectronic applications. *Advanced Materials, 25*(3), 349-377.

Wang, J. (2006). Electrochemical biosensors: Towards point-of-care cancer diagnostics. *Biosensors and Bioelectronics, 21*(10), 1887-1892. doi:http://dx.doi.org/10.1016/j.bios.2005.10.027

Wang, J. (2008). Electrochemical glucose biosensors. *Chemical reviews, 108*(2), 814-825.

Wang, J., Zhao, H., Du, L., Cai, H., and Wang, P. (2013). An enzyme-metal-insulator-silicon structured sensor using surface photovoltage technology for potentiometric glucose detection. *Sensors and Actuators, B: Chemical, 187*, 147-152.

Wisitsoraat, A., Karuwan, C., Wong-ek, K., Phokharatkul, D., Sritongkham, P., and Tuantranont, A. (2009). High sensitivity electrochemical cholesterol sensor utilizing a vertically aligned carbon nanotube electrode with electropolymerized enzyme immobilization. *Sensors, 9*(11), 8658-8668.

Woolley, A. T., Sensabaugh, G. F., and Mathies, R. A. (1997). High-speed DNA genotyping using microfabricated capillary array electrophoresis chips. *Analytical chemistry, 69*(11), 2181-2186.

Wopschall, R. H., and Shain, I. (1967). Effects of adsorption of electroactive species in stationary electrode polarography. *Analytical chemistry, 39*(13), 1514-1527.

Wu, C., Du, L., Zou, L., Zhao, L., Huang, L., and Wang, P. (2014). Recent advances in taste cell- and receptor-based biosensors. *Sensors and Actuators B: Chemical, 201*(0), 75-85. doi:http://dx.doi.org/10.1016/j.snb.2014.04.021

Wu, J., Suls, J., and Sansen, W. (2001). The glucose sensor integratable in the microchannel. *Sensors and Actuators B: Chemical, 78*(1), 221-227.

Xia, Y., Si, J., and Li, Z. (2016). Fabrication techniques for microfluidic paper-based analytical devices and their applications for biological testing: A review. *Biosensors and Bioelectronics, 77*, 774-789. doi:http://dx.doi.org/10.1016/j.bios.2015.10.032

Xia, Y., and Whitesides, G. M. (1998). Soft lithography. *Annual review of materials science, 28*(1), 153-184.

Xu, H., Ling, X. Y., van Bennekom, J., Duan, X., Ludden, M. J., Reinhoudt, D. N., . . . Huskens, J. (2008). Microcontact printing of dendrimers, proteins, and nanoparticles by porous stamps. *Journal of the American Chemical Society, 131*(2), 797-803.

Xu, Y., and Wang, E. (2012). Electrochemical biosensors based on magnetic micro/nano particles. *Electrochimica Acta, 84*(0), 62-73. doi:http://dx.doi.org/10.1016/j.electacta.2012.03.147

Yang, Y.-L., Chuang, M.-C., Lou, S.-L., and Wang, J. (2010). Thick-film textile-based amperometric sensors and biosensors. *Analyst, 135*(6), 1230-1234.

Yeom, S.-H., Kang, B.-H., Kim, K.-J., and Kang, S.-W. (2010). Nanostructures in biosensor--a review. *Frontiers in bioscience (Landmark edition), 16*, 997-1023.

Yoo, E.-H., and Lee, S.-Y. (2010). Glucose biosensors: an overview of use in clinical practice. *Sensors, 10*(5), 4558-4576.

Zhang, C., Gao, Q., and Aizawa, M. (2001). Flow injection analytical system for glucose with screen-printed enzyme biosensor incorporating Os-complex mediator. *Analytica chimica acta, 426*(1), 33-41.

Zhang, S., Wang, N., Yu, H., Niu, Y., and Sun, C. (2005). Covalent attachment of glucose oxidase to an Au electrode modified with gold nanoparticles for use as glucose biosensor. *Bioelectrochemistry, 67*(1), 15-22.

Zhang, X., Jones, P., and Haswell, S. J. (2008). Attachment and detachment of living cells on modified microchannel surfaces in a microfluidic-based lab-on-a-chip system. *Chemical Engineering Journal, 135*, S82-S88.

Zhao, F., Rahunen, N., Varcoe, J. R., Roberts, A. J., Avignone-Rossa, C., Thumser, A. E., and Slade, R. C. (2009). Factors affecting the performance of microbial fuel cells for sulfur pollutants removal. *Biosensors and Bioelectronics, 24*(7), 1931-1936.

Zviman, M., and Ti Tien, H. (1991). Formation of a bilayer lipid membrane on rigid supports: an approach to BLM-based biosensors. *Biosensors and Bioelectronics, 6*(1), 37-42.