

Provide a summary (at least one page) of one concept in the paper that you found interesting?

High affinity of ligand for a receptor is used in biosensor devices. A biosensor consists of three elements, a bioreceptor, that could detect a specific ligand binding, a transducer converting the biological signal into an electrical signal, and an amplification and signal processing system [1]. The detection device needs to meet a variety of stringent requirements; it needs to be fast, reagentless, self-regenerating, ultrasensitive; it also needs to have high accuracy, to be stable, robust, tolerated by the patients and produced at low cost. Biosensors are classified either by their biological signaling mechanism or by the type of their transducer. There are five main biological recognition mechanisms:

- 1) **Enzymatic based sensor:** the highly specific interaction between ligand and their receptors provides these sensors with a higher detection limit compared to other types of biosensors.
- 2) **Immunosensors:** uses highly specific, and stable antigen-antibody binding properties. Optical and electrochemical detection methods are gaining momentum in early detection of cancers.
- 3) **DNA/nucleic acid sensors:** a single stranded DNA (**ssDNA**) is used as a probe which when exposed to a complementary ssDNA, results in hybridization and the formation of double stranded DNAs (**dsDNA**), the biochemical reaction is then amplified by the transducer into an electrical signal. The nucleic acid recognition layer is reusable after DNA denaturation.
- 4) **Cell-based sensor:** this type of sensors contains microorganisms such as bacteria or fungi and relies on the ability of the cell to detect intracellular or extracellular microenvironment changes. Limit of detection of these detectors is determined by cell selectivity, and the ability of the cell to survive various environmental conditions. However, cell-based biosensors, are less sensitive to inhibition by solutes, suboptimal pH, ionic composition, and temperature compared to catalytic sensors.
- 5) **Biomimetic sensors or Aptamers:** are synthetic strands of nucleic acid designed to recognize peptides, oligosaccharides, amino acids and proteins. Due to their components, they are limited in structural and chemical sensing properties and they have higher production cost.

Biosensors are also categorized according to the transduction method:

- 1) **Electrochemical:** characterized by the nature of the electrochemical changes detected. Electrochemical sensors are further divided by the technique used for detection:
 - **amperometric:** measurement of a current from oxidation of an electroactive species.
 - **potentiometric:** relies on the use of an ion-selective electrode and ion-sensitive field.
 - **conductometric:** measurement of electrolyte conductivity which varies with the changes in concentration of ionic species.
 - **electrical impedance spectroscopy (EIS):** consists of a 3-electrode system, a potentiostat and a frequency response analyser (FRA).
- 2) **Calorimetric:** based on heat exchange during the chemical or biological reactions.
- 3) **Piezoelectric:** a shift in signal frequency is correlated to the mass of the analyte to measure.

4) **Optical:** optical based sensors are popular and allow real-time monitoring, one major issue is sensitivity to ambient light. We can distinguish a variety of sensors:

- **Surface plasmon resonance (SPR)** biosensors use plasmon waves to detect changes in refractive index at the sensor surface. It is a label free technique which does not require radioactive or fluorescent tagging compounds. They can detect binding by molecules up to 2 kDa. Transducer surface is generally a thin gold film.
- **Chemiluminescence biosensors:** reaction between the target and the immobilized molecule which has been tagged with chemiluminescence species, generates light detected by a photo multiplier tube (PMT). The tool, due to its simple instrumentation and fast response time, is widely adopted in immuno-sensing and nucleic acid hybridization.
- **Fluorescence based sensors:** an external laser initiates a transition in fluorochrome molecules which produce light during the biological event, the light is then transduced to an optical signal; e.g., nucleic acid or antibodies are tagged with fluorochrome and hybridization between two sDNAs is converted to an optical signal.
- **Optrodes:** include a light source, a biorecognition component, an optical fiber. The light is transmitted through the biochemical reaction and its reflection is measured by a spectrophotometer. They are miniaturized high performance sensors, with high sensitivity and low detection limits.

Biosensors are used in many scientific domains like medicine, life-science, or for environment protection, in the food industry and in military applications. However, when real-time monitoring is not a requirement, simple buffer solutions are preferred due to their low complexity overhead and are cheaper to make. One promising research is the development of disposable, easy to use at-home biosensors for medical diagnostics saving on laboratory analyses.

Note how your knowledge of receptor-ligand interactions could help you in determining a new approach for a biomedical engineering application.

Oral microbiome includes up to 1000 microbial species comprising bacteria, fungi, viruses, archaea and protozoa. The vast majority of viruses in the oral cavity are bacteriophages; about 700 bacterial species live in the oral cavity making it the second largest bacterial community in the human body after the gut. Like many functions in the human body, oral microbiome in a healthy individual maintains interspecies relationships and host-microbial interactions in homeostasis (eubiosis). The human host immune response must balance between aggressive immune response for pathogen elimination and protection of beneficial oral microbes which prevent colonization of pathogens. Shift in eubiotic balance can lead to parasitic state promoting disease (dysbiosis). Dysbiosis is characterized by 1) loss of microbial diversity; 2) loss of beneficial microbes which are part of the nitrate-nitrite-nitric pathway exposing the host to carcinogenic metabolites and detrimental vascular changes [2][3][4][5][6], and 3) outgrowth of pathogens specifically *P.gingivalis*, *F.nucleatum* which have been associated to periodontal disease, various cancers (head, neck, colorectal), atherosclerosis, and Alzheimer's disease:

- *P.gingivalis*: a variety of studies have shown that *P.gingivalis*, led to a significant increase in α -defensin, boosting oral squamous cell carcinoma (OSCC) cell proliferation, induced β -

catenin destruction complex by gingipain-dependent proteolytic processing, contributing to cancer pathogenesis, and activated PI3K pathway, promoting proliferation of gingival epithelia cells.

- *F.nucleatum*: was found to contribute to colorectal cancer growth via TLR4, myeloid differentiation primary response 88 (MyD88) protein activation, and upregulation of microRNA 81a and 4802. When bacterial lipopolysaccharides (LPS)-mediated activation of TLR4 are overproduced, they can damage small blood vessels, can cause disseminated intravascular coagulation and multiple organ failures.
- *S100A8/A9 in saliva*: are two inflammatory calcium-binding S100 proteins, and were associated with rheumatic diseases. S100A9 has also been reported to increase IL-6 production and RANKL expressions in osteolysis [7].

Periodontal disease (**PerioD**) affects more than 50% of elderly people. Amyloid- β ($A\beta$) plaques are hallmarks of Alzheimer's disease (AD). In a recent NYU study, 48 patients were divided into two groups: one with CSF $A\beta_{42}$ levels < 600 pg/mL and \geq 600 pg/mL. Researchers showed a strong correlation between PerioD bacterial species and greater brain $A\beta$ levels, but not with tau, another Alzheimer's biomarker. AD slowly develops over the years, a biosensor to monitor levels of PerioD bacteria could help to understand its progression, and create prevention therapies [8].

Over the years, most of the studies have been focused on the detection of *E.coli* using either SPR, quartz crystal microbalance (QCM), microcantilever or impedimetric based sensors [9][10]. *E. coli* is a gram-negative bacteria likewise *P.gingivalis* and *F.nucleatum*, thus some of the crafting which went into these devices could be to some extent reused; still the devices will need to be recalibrated to have a high affinity to the cells of the targeted microorganism. The "lab-on-chip" device will need to be cost-effective, reagentless, miniature to fit on a tooth, not a discomfort to their host, and be able to survive the challenging oral cavity environment. Regarding the detection of S100A8/A9 proteins, we will investigate the recent "lucCage" system that includes two major components: 1) the "lucCage" itself which includes a cage and a latch domain, and a split luciferase fragment 2) a "luckKey" that contains a key peptide that binds to the open state of lucCage upon activation of luciferase and the target protein. Compared to existing protein-based biosensors, the "lucCage" sensor is based on binding thermodynamic properties but not on the geometry of a specific coupling, allowing the component to detect a variety of analytes with different binding energies [11].

References

- [1] V. Perumal and U. Hashim, "Advances in biosensors: Principle, architecture and applications," *J Appl Biomed*, vol. 12, no. 1, pp. 1–15, Jan. 2014, doi: 10.1016/j.jab.2013.02.001.
- [2] C. Petersen and J. L. Round, "Defining dysbiosis and its influence on host immunity and disease," *Cellular Microbiology*, vol. 16, no. 7, pp. 1024–1033, 2014, doi: 10.1111/cmi.12308.

- [3] L. Gao, T. Xu, G. Huang, S. Jiang, Y. Gu, and F. Chen, "Oral microbiomes: more and more importance in oral cavity and whole body," *Protein Cell*, vol. 9, no. 5, pp. 488–500, May 2018, doi: 10.1007/s13238-018-0548-1.
- [4] A. Cekici, A. Kantarci, H. Hasturk, and T. E. Van Dyke, "Inflammatory and immune pathways in the pathogenesis of periodontal disease," *Periodontol 2000*, vol. 64, no. 1, pp. 57–80, Feb. 2014, doi: 10.1111/prd.12002.
- [5] L. J. Suárez, H. Garzón, S. Arboleda, and A. Rodríguez, "Oral Dysbiosis and Autoimmunity: From Local Periodontal Responses to an Imbalanced Systemic Immunity. A Review," *Front. Immunol.*, vol. 11, p. 591255, Dec. 2020, doi: 10.3389/fimmu.2020.591255.
- [6] A. Radaic and Y. L. Kapila, "The oralome and its dysbiosis: New insights into oral microbiome-host interactions," *Computational and Structural Biotechnology Journal*, vol. 19, pp. 1335–1360, 2021, doi: 10.1016/j.csbj.2021.02.010.
- [7] G. Hajishengallis and J. D. Lambris, "Complement and dysbiosis in periodontal disease," *Immunobiology*, vol. 217, no. 11, pp. 1111–1116, Nov. 2012, doi: 10.1016/j.imbio.2012.07.007.
- [8] A. R. Kamer *et al.*, "Periodontal dysbiosis associates with reduced CSF A β 42 in cognitively normal elderly," *Alz & Dem Diag Ass & Dis Mo*, vol. 13, no. 1, Jan. 2021, doi: 10.1002/dad2.12172.
- [9] L. Steigmann, S. Maekawa, C. Sima, S. Travan, C.-W. Wang, and W. V. Giannobile, "Biosensor and Lab-on-a-chip Biomarker-identifying Technologies for Oral and Periodontal Diseases," *Front Pharmacol*, vol. 11, p. 588480, Nov. 2020, doi: 10.3389/fphar.2020.588480.
- [10] A. Ahmed, J. V. Rushworth, N. A. Hirst, and P. A. Millner, "Biosensors for Whole-Cell Bacterial Detection," *Clin Microbiol Rev*, vol. 27, no. 3, pp. 631–646, Jul. 2014, doi: 10.1128/CMR.00120-13.
- [11] A. Quijano-Rubio *et al.*, "De novo design of modular and tunable protein biosensors," *Nature*, vol. 591, no. 7850, pp. 482–487, Mar. 2021, doi: 10.1038/s41586-021-03258-z.