EC DENTAL SCIENCE
Mini Review

Introduction to Flexible Bioelectronics: Applications, Challenges and Perspective

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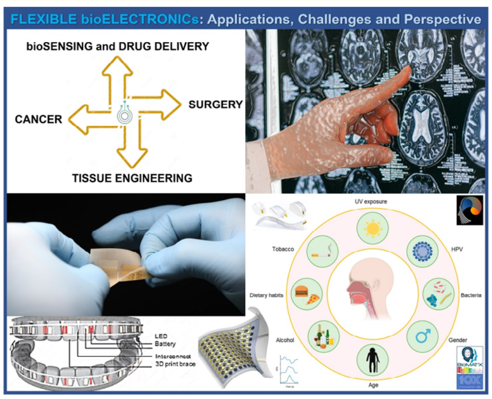
Abstract

In brief, flexible bioelectronics is an emerging field that combines the principles of biology and electronics to create flexible and stretchable electronic devices that can interface with biological systems. This field has gained significant attention in recent years due to its potential applications in a range of fields, including healthcare, biomedicine, bioengineering, surgery, and cancer research. This introductory piece provides a simplified overview of the current state of R&D&I in flexible bioelectronics, with a focus on its key concepts, applications, challenges, and perspective. With the lay reader in mind, the article aims to highlight the exciting potential of this cutting-edge biotechnology.

Keywords: *Flexible Bioelectronics; Cranio-Maxillofacial Surgery; 3D Printing; Regenerative Dentistry; Implantable/Wearable Sensors; Biosensing; Real-Time Monitoring; Bone Healing*

Graphical Abstract



Flexible bioelectronics: Applications thereof in bio-medicine/dentistry and beyond

Briefly, flexible bioelectronics are electronic devices or systems that are designed to integrate with biological tissues in a flexible and adaptable manner. These devices typically employ advanced materials that can bend, stretch, and conform to the shape of biological tissues without causing damage or discomfort. In biomedicine, flexible bioelectronics may also be designed to interface with biological signals, such as electrical or chemical signals, to monitor, modulate and/or restore the activity and function (enhancing the functionality) of the underlying, damaged, or diseased tissues; a rapidly growing R&D&I (research, development, and innovation) field with great promise for introducing new medical technologies [1]. Indeed, flexible bioelectronics has the potential to revolutionize a range of fields and subfields, including general healthcare, biomedicine, bioengineering, intra-/extra-oral surgery, and cancer research, amongst others. Some of the most promising applications of flexible bioelectronics, so far, include:

1. **Wearable health-monitoring devices:** Flexible bioelectronics can be used to create wearable health monitoring devices that can track vital signs, such as heart rate, blood pressure, and respiratory rate [2]. These devices can be worn on the skin like a patch (user-friendly) and can transmit real-time data to healthcare professionals, permitting for remote monitoring and early intervention.
2. **Prosthetics:** Flexible bioelectronics can also be used to create prosthetics that can better mimic the movements and sensations, of natural limbs, for example [3]. By integrating sensors and actuators into the prosthetic, it can offer more natural feedback and improve quality of life.
3. **Neural interfaces:** Flexible bioelectronics can be used to create neural interfaces that can interface with the brain or other parts of the nervous system. These interfaces can henceforth be used to treat serious conditions such as Parkinson's disease, epilepsy, as well as chronic pain [4].
4. **Cancer/oncology research:** Flexible bioelectronics has also shown promise in cancer or oncology research, particularly in the detection and treatment of brain cancer [5]. Brain cancer is a particularly challenging type of cancer to treat due to the blood-brain barrier, which prevents many drugs from reaching the tumor. Flexible bioelectronics can help overcome this challenge by enabling the development of new devices that can penetrate the blood-brain barrier and deliver drugs directly to the tumor site [6]. Flexible bioelectronics can also be used for the early detection and diagnosis of brain cancer. For example, researchers have developed flexible biosensors that can detect cancer biomarkers in the blood or cerebro-spinal fluid with high sensitivity and specificity [7]. These flexible electronic biosensors can be also integrated into wearable devices for real-time monitoring and early detection.

Challenges and Future Directions

Despite its promising applications, to date, flexible bioelectronics do face several challenges that must be addressed to realize the full potential. These challenges include:

- **Biocompatibility:** Many materials commonly used in electronics, such as silicon and metal, can cause inflammation or other adverse reactions when implanted in the body. Researchers are working to develop new materials (biomaterials) that are biocompatible and can integrate seamlessly with biological systems in application/implantation sites [8].
- **Durability:** Flexible bioelectronics must also be durable enough to withstand the harsh conditions of the body. Researchers are developing new materials and fabrication techniques to create novel and innovative devices that can overcome such limitations and withstand stretching, twisting, amongst other types of physical and mechanical stress [9].
- **Power supply:** Flexible bioelectronics require a reliable and long-lasting power supply. Henceforth, researchers today are exploring new methods for powering the produced flexible bioelectronics, including wireless power transfer as well as energy harvesting [10].

State-of-art

Without doubt, flexible bioelectronics is an exciting and rapidly evolving field with promising applications in healthcare. Despite the present challenges, researchers are making significant progress in developing new materials, fabrication techniques, and power supplies that can enable the creation of truly flexible and biocompatible electronic devices with greater biocompatibility, durability, and functionality. Accordingly, as the field continues to advance, we can expect to see more innovative and impactful applications of flexible bioelectronics in the coming years. In particular, the application of flexible bioelectronics in cancer research, including brain cancer, holds great promise for improving diagnosis, treatment, and patient outcomes. By enabling the development of new devices and sensors that can penetrate the blood-brain barrier and detect cancer biomarkers with high sensitivity and specificity, flexible bioelectronics can help to revolutionize the way we diagnose and treat brain cancer, amongst others. In conclusion, flexible bioelectronics represents a significant advancement in the field of biomedicine and has the potential to transform a range of industries, including healthcare, dentistry, surgery, and cancer research. With ongoing R&D&I, we should expect to see even more innovative and impactful applications of flexible bioelectronics in the soon years to come.

Perspective

As mentioned above, flexible bioelectronics have potential applications in dentistry and oral and maxillofacial surgery and beyond. Some examples of these applications include:

1. **Oral health monitoring:** Flexible electronic sensors can be used to monitor oral health indicators such as pH levels and bacterial growth in the mouth. This information can help dentists as well as patients to better manage oral and dental health and prevent diseases such as tooth decay (caries) and gum (gingival and periodontal) disease [11].
2. **Oral cancer detection:** Flexible bioelectronics have the potential to improve the detection of oral cancer through the development of electronic biosensors that can detect cancer biomarkers (genetic biomolecules) in the saliva or other bodily fluids [12].
3. **Maxillofacial prostheses:** Flexible bioelectronics have the potential to enhance the functionality and comfort of oral, dental, and facial prosthetics, such as dentures, dental and facial implants. For instance, the integration of flexible bioelectronic sensors into dentures could provide patients with real-time feedback on their oral health status, including monitoring of temperature, pressure, and pH levels in the oral cavity. This would enable patients to take proactive steps to prevent oral health issues before they arise. Additionally, flexible bioelectronics could be used to develop smart facial prosthetics that are capable of sensing changes in facial expressions and movements, allowing for more natural and responsive prosthetic devices. Furthermore, the use of flexible bioelectronics in oral and maxillofacial prosthetics could improve the biocompatibility and durability of these devices. Flexible electronic materials are compatible with soft tissues and can conform to complex shapes, reducing the risk of irritation or discomfort for our patients. Additionally, these materials have the potential to be more durable and longer-lasting than traditional prosthetic materials (intra-/extra-orally), leading to reduced maintenance costs and enhanced patient satisfaction [13].
4. **Orthodontics:** Flexible bioelectronic sensors could be integrated into orthodontic appliances such as braces and aligners to monitor changes in tooth movement, jaw position, and bite force. This would provide orthodontists with real-time data on the progress of treatment, allowing for more personalized and efficient care. In addition, such sensors could be used to monitor patient compliance with the treatment protocol, ensuring that the braces are worn for the recommended amount of time each day [14].
5. **Cranio-maxillo-facial and orthognathic surgery:** Flexible bioelectronics have the potential to revolutionize the field of oral and maxillo-facial surgery (expanding to the craniofacial complex) through enabling the design and development of novel diagnostic tools and interventional treatment modalities. For example, flexible bioelectronic sensors could be integrated into surgical instruments and/or implantable devices to provide real-time data on tissue temperature, pressure, and pH levels during orthognathic surgery as well as information on the post-surgical status of the tissue and/or defect area, allowing for a much more personalized

and bio-efficient care. This could help us surgeons avoid un-necessary tissue damage and hence, improve surgical outcomes. Additionally, the use of flexible bioelectronics in implants could lead to the development of novel materials with improved mechanical and biocompatibility properties, reducing the risk of implant failure or rejection. Furthermore, such could be used in conjunction with the advancing 3D (three-dimensional) printing technology (including hybrids with electro-spinning) to create patient-specific surgical guides and implants (designed to match the unique anatomy of the jaw and dentition/teeth of each patient) to help improve more the accuracy and precision of surgical procedures, thus, reducing the risk of complications and thereby, enhancing patient outcomes also [15].

Flexible bioelectronics in craniofacial and plastic/esthetic rehabilitative surgery: Herein, flexible bioelectronics have potential applications in craniofacial, aesthetic, plastic and rehabilitative or reconstructive surgery. Some examples of these applications include:

- **Tissue engineering and regeneration:** Flexible bioelectronics can be used in combination with tissue engineering approaches to promote the regeneration, repair, restoration, reconstruction, and replacement of defected craniofacial tissues such as bone, cartilage, and skin. For example, flexible electronic scaffolds can be used to provide critical physical and electrical cues that can enhance cell adhesion, proliferation, and differentiation [16].
- **Wound healing:** Flexible bioelectronics can be used to promote wound healing and prevent scar formation after complex or invasive craniofacial and esthetic surgeries. For example, electronic dressings can be used to deliver controlled electrical (neuromuscular) stimulation and controlled pharmaceutics (drug therapy) to the wound site [17].
- **Facial prostheses:** As mentioned earlier, flexible bioelectronics can be integrated in the design and creation of custom-fit facial prostheses that are more realistic and functional than traditional prostheses. Herein, electronic-incorporated prostheses can be used to mimic the movements of facial muscles and improve facial expression, for example [18].
- **Nerve regeneration:** Flexible bioelectronics can also be employed to promote nerve regeneration after craniofacial and esthetic surgeries, amongst other interventions or procedures. For instance, electronic nerve guides can be developed and used to provide electrical (neuro-muscular) stimulation and promote axonal growth and myelination [19].
- **Tumor detection and radiation therapy:** Herein, flexible bioelectronics can be used to detect tumors in the craniofacial region, as well. For example, flexible sensors can be utilized to detect any changes in the electrical properties of the tissue, *in situ*, which can indicate the presence of a tumor. Also, can be used to improve the delivery of irradiation therapy to craniofacial tumors where the electronic devices can be used to monitor the irradiation dose and ensure that the tumor receives the correct amount of irradiation [20].

Examples of flexible bioelectronics in dentistry literature: Demonstrative insights

Chen., *et al.* [21] in a 2020 study, demonstrated the feasibility of a wireless, tongue-controlled system for patients diagnosed with tetraplegia to perform oro-dental tasks, such as brushing teeth and eating. The system utilized flexible bioelectronics to detect the movements of the tongue and transmit the signals wirelessly to a computer (or other device). Results demonstrated the efficacy and ease-of-use of the system, highlighting the potential of flexible bioelectronics in improving the quality of life of tetraplegia patients.

The potential of flexible bioelectronics in monitoring the stability of dental implants was demonstrated in a 2019 study by Kim., *et al*. [22]. Herein, the researchers developed a flexible force sensor that could be attached to dental implants and detect changes in force, which can indicate implant loosening. Results of the study showed that the sensor was highly accurate and could detect changes in force in real-time, highlighting the potential of flexible bioelectronics in improving the monitoring and management of dental implants.

Cao., *et al.* [23] in a 2021 study, demonstrated the potential of flexible bioelectronics in improving the monitoring and management of orthodontic treatment. Smart orthodontic aligners were developed and included built-in force sensors to monitor the forces exerted on the dentition during therapy with demonstrated bio-efficacy of the aligners in monitoring treatment progress and detecting likely deviations from the therapeutic plan(s).

In a 2019 study, Kim., *et al*. [24] demonstrated the feasibility of using flexible bioelectronics to monitor sodium intake (in real-time) for patients suffering from chronic hypertension. The wireless, intra-oral hybrid electronic device can measure the amount of sodium in saliva and transmit the data wirelessly to a smartphone app, with accuracy and reliability.

Li., *et al*. [25] in 2018 reported on the feasibility of using a flexible, implantable sensor to measure bone strain *in vivo*. The developed sensor could be implanted into the bone and measure the stress and strain in response to mechanical loading, *in situ*, while precisely and consistently monitoring bone healing and success of cranio-maxillo-facial surgeries.

Concluding Remarks

As the design, development and optimization of flexible bioelectronics continues to progress, the potential to significantly transform dentistry and oral and cranio-maxillo-facial rehabilitative surgery is substantial. Such cutting-edge devices provide us with the ability to monitor oral and dental health in real-time, transmit data wirelessly, and even deliver targeted and personalized treatments directly to the affected area. Further, flexible bioelectronics can also be integrated with other medical technologies, such as implantable devices and wearables, to enhance capabilities (implant stability, early detection of potential complications, etc…) and improve patient outcomes. Herein, and to recap, the use of flexible bioelectronics in oral and cranio-maxillo-facial, orthognathic, rehabilitative, and reconstructive surgery has the potential to revolutionize our field via enabling precise and personalized surgical procedures. By incorporating sensors and other advanced technologies, surgeons can accurately map the surgical site, monitor tissue oxygenation levels, and track the progress of the healing process. This can result in faster recovery times, reduced risk of complications, and improved patient satisfaction (cost-effective too). In closing, while there is still much R&D&I to be invested, the promise of these innovative devices and technologies to improve our workflow, patient outcomes and overall quality of life is deemed truly exciting.

Conflict of Interest

None.

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Bibliography

1. Kim DH., *et al*. "Materials for multifunctional balloon catheters with capabilities in cardiac electrophysiological mapping and ablation therapy". *Nature Materials* 10.4 (2012): 316-323.
2. Liang X., *et al*. "Wearable and flexible electronics for continuous molecular monitoring". *Chemical Society Reviews* 47.15 (2018): 5866-5887.

3. Lipomi DJ., *et al*. "Skin-like pressure and strain sensors based on transparent elastic films of carbon nanotubes". *Nature Nanotechnology* 6.12 (2011): 788-792.
4. Piret G and Bao Z. "Soft Electronic Interfaces for In Vivo Neural Recording". *Advanced Healthcare Materials* 10.5 (2021): 2001303.
5. Son D., *et al*. "Multifunctional wearable devices for diagnosis and therapy of movement disorders". *Nature Nanotechnology* 9.5 (2014): 397-404.
6. Kim Y and Lee S. "Recent advances in flexible and stretchable bio-electronics: materials, devices, and applications". *Advanced Materials* 31.42 (2019): 1903634.
7. Hou X., *et al*. "Recent Progress on Flexible Electronics for Wearable Sensors and Devices". *Journal of Materials Chemistry C* 8.38 (2020): 13207-13225.
8. Huang X., *et al*. "Stretchable and flexible electronic devices using two-dimensional materials". *Nano Today* 24 (2019): 91-109.
9. Xu L., *et al*. "3D multifunctional integumentary membranes for spatiotemporal cardiac measurements and stimulation across the entire epicardium". *Nature Communications* 5.1 (2014): 1-11.
10. Chen Y., *et al*. "Bioinspired and Biomimetic Nanomedicines". *Accounts of Chemical Research* 52.5 (2019): 1255-1264.
11. Mannoor MS., *et al*. "Flexible sensors for disease monitoring in the oral cavity". *Advanced Healthcare Materials* 5.6 (2016): 711-721.
12. Lee H., *et al*. "A graphene-based electrochemical device with thermoresponsive microneedles for diabetes monitoring and therapy". *Nature Nanotechnology* 11.6 (2016): 566-572.
13. Mannoor MS., *et al*. "3D printed bionic ears". *Nano Letters* 13.6 (2013): 2634-2639.
14. Popat KC., *et al*. "Elastomeric free-standing polyimide thin films for microsystem applications: fabrication and characterization". *Journal of Microelectromechanical Systems* 15.6 (2006): 1620-1628.
15. Choi J., *et al*. "Electronic skin: recent progress in flexible sensors for wearable and implantable devices". *Advanced Materials* 32.27 (2020): 2001975.
16. Kim DH., *et al*. "Electronic sensor and actuator webs for large-area complex geometry cardiac mapping and therapy". *Proceedings of the National Academy of Sciences* 109.49 (2012): 19910-19915.
17. Li Y., *et al*. "Electroactive hydrogel dressings for wound healing". *Acta Biomaterialia* 111 (2020): 1-19.
18. Ladd C., *et al*. "3D printing of free standing liquid metal microstructures". *Advanced Materials* 25.36 (2013): 5081-5085.
19. Tyler DJ. "Neural interfaces for somatosensory feedback: bringing life to a prosthesis". *Current Opinion in Neurology* 28.6 (2015): 574-581.
20. Gao L., *et al*. "Flexible and wearable sensors for personalized cancer detection and diagnosis". *Advanced Materials* 31.45 (2019): e1904339.
21. Chen C., *et al*. "Wireless intraoral tongue-controlled system for people with tetraplegia: A feasibility study". *IEEE Transactions on Biomedical Engineering* 67.5 (2020): 1309-1318.

22. Kim J., *et al*. "Real-time detection of dental implant loosening using a flexible force sensor". *Scientific Reports* 9.1 (2019): 1-10.

23. Cao L., *et al*. "Smart orthodontic aligners with built-in force sensors for improved treatment monitoring". *Sensors and Actuators A: Physical* 326 (2021): 112790.

24. Kim J., *et al*. "Wireless, intraoral hybrid electronics for real-time quantification of sodium intake toward hypertension management". *Proceedings of the National Academy of Sciences* 116.38 (2019): 18888-18892.

25. Li T., *et al*. "Flexible and implantable sensor for *in vivo* measurement of bone strain". *Biosensors and Bioelectronics* 107 (2018): 110-116.

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