International Journal of Engineering Sciences Paradigms and Researches (IJESPR)
(Vol. 32, Issue 01) and (Publishing Month: July 2016)
(An Indexed, Referred and Impact Factor Journal)
ISSN: 2319-6564
www.ijesonline.com

OPPORTUNITIES FOR IMPLANTABLE NEUROTECHNOLOGY

Ipsita Samal[1], Chandrakanta Nayak[2] and Subhashree Sahoo[3]

[1]Aryan Institute of Engineering & Technology, Bhubaneswar, Odisha

[2]NM Institute of Engineering and Technology, Bhubaneswar, Odisha

[3]Raajdhani Engineering College, Bhubaneswar, Odisha

Abstract

Neurotechnology incorporates fake gadgets coordinated with the neural tissue to relieve the weight of neurological and mental problems. This field has fundamentally extended its scope of utilizations on account of the improvement of adaptable, stretchable and injectable gadgets. Presently, the rise of green gadgets adds another resource for the neurotechnology tool compartment. Transient neurotechnology decreases the results of ongoing inserts and changes dormant gadgets into bio-dynamic and bio-responsive constructions. At last, it holds the capability of crossing over together innovative gadgets with current methodologies in regenerative medication. This survey centers around the rising capability of transient neurotechnology for human advantage, thoroughly sums up ongoing accomplishments and features highlight needs and difficulties.

Introduction

Green electronics is a fascinating strategy to preserve the environment by reducing waste production and establishing recycling processes for a sustainable future [1]. This idea is enabled by transient electronics: devices disappearing in the environment after a programmed time and leaving minimal and harmless traces after their disposal [2–7]. Transient electronic devices can be fabricated from natural food and foodstuffs, among other materials, introducing in this way the concept of edible electronics [8,9], which exploit disposable and harmless materials, easy to ingest and safe to digest.

Transient electronics becomes appealing also for medical applications like neurotechnology since transient, biodegradable and implantable devices eliminate the risks related to surgical retrieval [10•] and reduce the chronic foreign body reaction [11]. Permanent implants might be subjected to bacteria and biofilms development leading to infections and the consequent need for their removal [12,13,14•,15–17]. Since the first pioneering work [18], transient bioelectronics has grown fast, opening possibilities never thought of before. Among others, the portfolio of devices presented so far includes biodegradable sensors for monitoring neural activity, pressure, pH, biomarkers, temperature, motion and blood flow [19,20,21••,22, 23•,24,25••,26•], remotely controllable on-demand drug delivery systems [27••], smart stents [28], power supplies [29,30••,31–34] and neural stimulators [35–37].

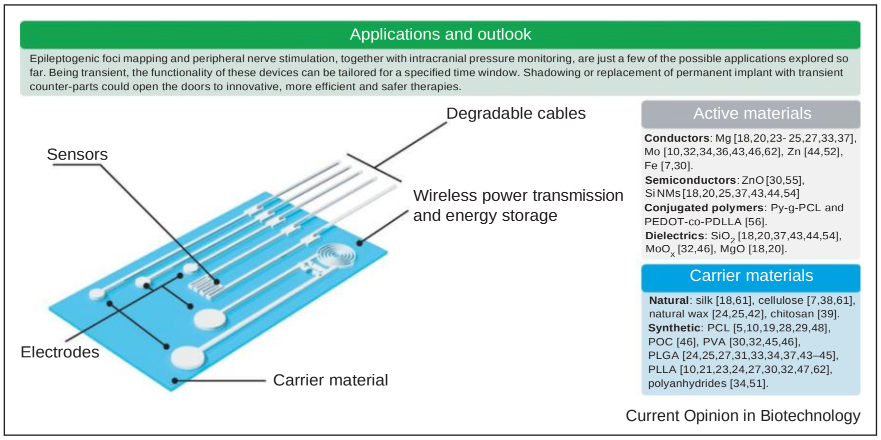
In neurotechnology, transient electronics is still in its infancy, but it represents an exciting direction towards innovative solutions to alleviate the burden of neurological and mental disorders. In this paper, we review recent research on transient implantable neurotechnology. We discuss current solutions, as well as future perspectives and exciting research opportunities. Finally, we present challenges towards clinical and industrial translation of transient neurotechnology.

A materials science driven research

Achievements in transient electronics came with the strategic employment of degradable and bioresorbable elements (Figure 1). There are different pools from which researchers can draw useful materials. Natural and synthetic polymers offer tuneable mechanical properties and good insulation capability. For this reason, they are typically employed for the substrate and the encapsulation of transient electronic devices ('Carrier materials' in Figure 1). Conversely, degradable and non-toxic conductors, semiconductors or dielectrics are typically used in the device functional elements ('Active materials' in Figure 1).

Natural polymers such as silk [18], cellulose [7,38] and chitosan [39] provide soft and flexible scaffolds for transient implants with a low inflammation response. Also, their processability has been improved, together with their compatibility with electronics. Current challenges for this class of materials lie in their porous structure, potentially leading to premature leakage [38], poor lot-to-lot reproducibility and critical immunogenicity of animal-derived samples. So far, silk represents the best trade-off in this category [39–41]. Finally, natural waxes could be exploited as an insulating material or, when mixed with

Figure 1



Transient neurotechnology.
The green box highlights current applications and future outlooks of transient neurotechnology. A set of representative devices is shown in the sketch, with identified components. Materials used and suggested for active components (sensors, electrodes, traces and connections) and insulating carriers are listed in the grey and light blue boxes, respectively.

conductive micro and nanoparticles, as electrical components [24,25••,42].

Synthetic polymers and their combinations offer highly tailorable degradation rates allowing transient devices to adapt to a wide range of applications requiring functionality for different periods. Common synthetic polymers in this field are: poly-L-lactide-co-glycolide (PLGA) [24,25••,27••,31,33,37,43–45], polyvinyl alcohol (PVA) [30••,32,45,46], poly-L-lactide (PLLA) [10•,21••,23•,24,27••,30••,32,47] and poly-e-caprolactone (PCL) [5,10•,19,28,29,48]. The interest in these materials is understandable as they all have Food and Drug Administration approval for certain medical applications [41,49,50]. Their main degradation route in the body is via hydrolysis, with their by-products becoming water-soluble and then excreted or entering the tricarboxylic acid cycle and being eventually cleared in the form of carbon dioxide and water [41]. As an alternative, polyanhydrides have also been proposed as encapsulation components of transient electronics, offering a hydrophobic barrier to biofluids [51]. For devices that need to sustain high strains, degradable and stretchable elastomers have been developed. Poly (1,8-octanediol-co-citrate) (POC) can endure strains as high as 50% while maintaining the electrochemical performances of stretchablesupercapacitors built on its surface [46]. PCL-derived polyurethanes with Young's modulus lower than 3.8 MPa can ensure efficient insulation for 30 days [36].

Conductive materials are crucial components of neurotechnology. Transient devices typically use metallic- based conductors, such as magnesium (Mg)

[18,20,23•,24,25••,27••,33,37], zinc (Zn) [44,52] and molybdenum (Mo) [10•,32,43,46], which are also conve- niently involved in biological functions [39]. One of the advantages of these metals is their complete solubility. However, it also represents their main weakness since their fast dissolution reduces the device lifetime to a few days or weeks, maximum.

Semiconductors is another relevant category of materials used in transient devices. A standard Si-based integrated circuit of a few hundred microns in thickness will require several hundred years to dissolve by hydrolysis. On the other hand, thin monocrystalline silicon nanomembranes (Si NMs) and nanoribbons of tens of nanometres in thickness can disappear in less than a few weeks, degrad- ing into $Si(OH)_4$ well below solubility limits and toxicity levels [18]. The degradation kinetics of Si NMs can vary mostly according to dimension, solution content and silicon doping [53]. Biologically friendly silicon opens the doors to more sophisticated electronics patterning on transient substrates [18,20,25••,37,43,44,54]. Zinc oxide (ZnO) is also used as a biodegradable semiconduc- tor in transient thin-film transistors [55] and energy stor- age units [30••].

Conjugated polymers represent an attractive alternative as active materials for transient neurotechnology. Degrad- able conductive or semiconducting polymers are obtained generally by mixing pristine or doped conjugated poly- mers, such as polyaniline (PANI), polypyrrole (PPy) or poly(3,4-ethylenedioxythiophene) (PEDOT), with degradable polyesters, polyurethanes or natural polymers

[56]. The advantage of this solution is tailoring the degradation rate of the conductive components of transient devices, thus overcoming the fast dissolution rate of some metals. Nevertheless, this advantage comes at the cost of a substantial reduction in conductivity [56]. For this reason, their use in transient electronics has been delayed.

Last, films of silicon oxides (SiO_2) [18,20,37,43,44,54], magnesium oxides (MgO) [18,20] or molybdenum oxides (MoO_X) [32,46] can be used as degradable dielectrics.

Recent transient devices in neurotechnology

Multiple and multifunctional bioresorbable devices have been manufactured, addressing several medical needs, from transient monitoring of biological parameters to transient neurostimulation.

Continuous monitoring of the intracranial pressure (ICP) in patients that underwent a traumatic brain injury or invasive surgical procedure (e.g. decompressive craniectomy) is crucial to understand the clinical condition, improve the treatment and avoid possible adverse effects [57]. Kang *et al*. developed a wireless and fully degradable ICP sensor able to work for three days and degrade entirely within eight weeks *in vivo*. A temperature sensor, a pH sensor and accelerometers were added on the same degradable platform for a more comprehensive clinical status [20]. In another study, a temperature-sensitive capacitor, consisting of polyethylene glycol (PEG), monitored the rat's intracranial temperature for four days [24]. Yang *et al.* extended the device lifetime by adding natural wax to the encapsulation [25••]. Moreover, additional sensors were integrated to warn of leakage due to biofluids penetration. The device remained functional for three weeks *in vivo*. Lu *et al.* implemented an LC-resonance system coupled with a pressure-sensitive capacitor to bypass the percutaneous wires connected to the external device and eliminate the need for a battery [26•]. The device monitored the ICP and temperature in rats for four days before degradation.

Neural interfaces take advantage of transient neurotechnology by connecting the brain and nerves within a predetermined temporal window. The electrocorticography signal is typically used for foci mapping in drug-resistant epileptic patients before and after surgical sectioning of epileptogenic areas. Monitoring the neural activity depends on the surgery frequency and can last for several days [58]. Transient neural interfaces perfectly fit this application. Ferlauto *et al.* fabricated a fully polymeric transient neural interface based on a slowly degradable PCL-based backbone to detect acute epileptic activity and monitor visually evoked potentials together with local field potentials for twelve weeks in mice [19]. Fanelli *et al.* re-shaped the device to allow for a less invasive implantation procedure by targeting the neural tissue from blood vessels [48]. Yu *et al*. developed a transient neural interface able to capture interictal and seizure-like spiking activity in mice for a month before degrading, as well as smaller amplitude signals such as somatosensory evoked potential [43]. Xu *et al.* added a degradable pressure sensor on the same platform to monitor cortex swelling during neural recording [10•]. Neural signals monitoring was also demonstrated by Bai *et al.* using bioresorbable photonic devices able, as spectrometers, to sense the cerebral temperature and its oxygen saturation [44]. Similarly, Fu *et al*. fabricated a biodegradable fibre for optical neural interfaces capable of deep brain fluorescence sensing and optogenetic inter- rogation *in vivo* for up to three days [47].

Neurostimulation is crucial to address neurological and mental disorders. Transient neurotechnology offers excit- ing answers also in this direction. Koo *et al.* reported regeneration and functional recovery of injured nerves by electrical stimulation using a fully biodegradable cuff electrode wirelessly controlled through an Mg-based antenna [37]. Radiofrequency power transfer generates enough voltage from the electrodes for nerve activation at a depth of 80 mm. This transient neurostimulator over- comes the limits of intraoperative stimulation used to enhance neural recovery, allowing extra-operational and on-demand wireless stimulation for six days. The lifetime of this device was then extended by Choi *et al*. by using materials with slower degradation rates (i.e. PCL-derived polyurethane for encapsulation and Mo for electrodes) [36,53].

Implantable and biodegradable energy providers repre- sent an alternative to wireless power transfer. One of the first biodegradable batteries was developed by Yin *et al.*, who compared single-cell batteries with an Mg anode, phosphate-buffered saline as electrolyte and a cathode material varied among iron (Fe), tungsten and Mo, all encased in polyanhydride [59]. Huang *et al*. developed a fully biodegradable and self-electrified device for neuror- egenerative medicine with a battery composed of an Mg anode, a sodium alginate electrolyte and a Mo-MoO_3 cathode, all encapsulated by a PLGA-polyanhydride layer [34]. Similarly, Sheng *et al*. developed a fully biodegrad- able supercapacitor made out of *in situ* grown flakes of amorphous MoO_X electrodes and a sodium alginate elec- trolyte gel. Experiments in mice demonstrated device integrity for approximately a month before packaging rupture, followed by complete resorption in six months [32]. Another bioresorbable capacitor was introduced by Li *et al*. PLLA, ZnO, Fe and PVA/phosphate-buffered solution hydrogel were the main components of their device [30••]. The operational lifetime *in vivo* was fifty days, and complete degradation occurred within six months. In the future, it would be interesting to apply piezoelectric and triboelectric energy transducers in neu- rotechnology. Degradable materials with such properties have been recently tested for biomedical applications [31,45,60–63]. Jiang *et al*. reported several bioabsorbable triboelectric nanogenerators based on natural materials, reaching open-circuit voltages between 8 and 55 V [61]. Curry *et al*., instead, optimised the crystallinity and alignment of PLLA nanofibers to create a piezoelectric transducer, sandwiched between Mo electrodes, to convert electrical input into ultrasound waves for the transient opening of the blood-brain barrier in mice [62].

New research directions in transient neurotechnology

The possibilities introduced by transient electronics in the biomedical field are multiple. Advancement in chemistry, materials science and engineering allowed the definition of a new class of devices with a bright future in medicine. However, new research directions might be explored to widen even more the potential of these devices.

Transient devices can find application in several clinical cases like temporary brain mapping or preliminary trials of neurostimulators. By degrading harmlessly in time inside the body, no complicated removal surgery is required when the device is not needed anymore or whether it is malfunctioning. Also, transient neurotechnology reduces the waste of non-degradable disposable neural interfaces. Moreover, the absence of a permanent implant potentially allows the tissue to safely remodel around the site of implantation, decreasing the risk of chronic infections and inflammation. Biocompatible temporary implants could offer an invaluable instrument for research as well. Despite the invasiveness of the implantation procedure, transient neural interfaces might provide a more attractive alternative to standard devices for patients undergoing innovative treatments, which would greatly help neuroscience studies advance.

The few challenges in the field lie in the limited compatibility of standard microfabrication processes with biodegradable materials and the limited range in the degradation rate of the active components. In the past years, implantable neurotechnology has largely improved thanks to materials and fabrication strategies enabling soft [64], stretchable [65], conformable [66] and injectable [67] devices for compliant and minimally invasive neurotechnology. Some biodegradable polymers have appropriate mechanical properties, such as, among others, low elastic modulus, high strain at break and low hysteresis. However, their limitation often arises from the low compatibility with standard fabrication processes. Low temperature and solvent-free fabrication techniques are necessary for building biodegradable neurotechnology. However, the reproducibility and reliability of these manufacturing methods still need improvement com- pared to standard cleanroom processes.

Another challenging research direction is the alignment of the materials degradation rate with the required device lifetime. Some applications might be short-term (e.g. a few days or a couple of weeks), and available transient neurotechnology can match this timeline already. For example, intraoperative brain mapping of epileptogenic areas lasts hours before resection, while two weeks are sufficient for intracranial pressure monitoring after sur- gery [68]. Other applications might require longer dura- tions, and the device degradation rate must be tailored accordingly. This material-related issue is currently faced by developers of bioresorbable stents, for which mechan- ical support is vital within the first 3–6 months after deployment [69]. In neurotechnology, a longer device lifetime (i.e. > two months) might be beneficial in neu- rostimulation for regeneration and functional recovery after nerve injury, surgery and stroke events [70,71]. Successful pain relief at 12 months has been obtained after a peripheral nerve stimulation therapy of 60 days [72]. A longer therapeutic application might further improve recovery. The short-termed functional life of devices is associated with the fast degradation of metals used in the active elements (e.g. Mg, Zn and Mo). Conductive or semiconductive materials with a slower degradation rate are necessary to extend the lifetime of transient devices. Degradable conductive polymers are advantageous for researchers to tailor the degradation rate. However, today this improvement is at the expense of their conductivity. The search for highly performant conductive and semiconductive biodegradable polymers is needed in transient neurotechnology.

Regardless of the device duration, the disposal of the implant within the body might require a different time- line. Slow degradation is an appealing feature for transient neurotechnology since it might also allow for better tissue remodelling and reduced chronic postsurgical wound complications [19,52,53]. On the other hand, trauma upon implantation is unavoidable; therefore, making transient neurotechnology combined with drug delivery and regen- erative medicine is an exciting pathway to lower acute reactions. While degrading, the transient neurotechnol- ogy might release compounds to mitigate the inflamma- tory response or embed cells to promote tissue remodel- ling and regeneration.

Achieving a slower degradation rate and longer lifetime might also enable transient neurotechnology for long- term applications. Whereas the transient electronics con- cept is intrinsically founded on temporary applications, chronic use of such devices could also be investigated. Permanent implants such as deep brain stimulators, car- diac defibrillators and pacemakers, are often subjected to infections [12,13,14•,15], loss of efficacy or appearance of adverse effects [16]. These problems can lead to com- plete or partial removal, substitution or repositioning of the device even within just the first year of implantation

[15,16]. Thus, transient devices able to sustain active functioning for longer periods before degrading offer the opportunity to mitigate these issues. Similarly, biodegradable power supplies with a slow degradation rate could substitute current non-degradable batteries, which need replacement every 2–5 years [17].

Challenges towards adoption of transient neurotechnology

Advances in materials science have been crucial to innovate in neurotechnology. However, scientific innovation is not necessarily adopted easily in the medical industry and clinics. So far, approved and widely adopted neurotechnology is still primarily based on extensively characterised material systems and electronic devices. The industrial and clinical translation of new materials or technological solutions is a long and costly journey requiring much more than just scientific or technical excellence. In medical devices, high technology performance is a necessary but not sufficient argument for the industry to decide whether it should accelerate the translation of novel technologies. Scientific innovation should meet regulatory compliance and industry standards to prove attractiveness for the medical industry. At the same time, because of the complex regulatory landscape, which usually turns into enormous costs for any innovation to reach the market, the medical industry might prefer to remain anchored to their established technologies.

Should the medical industry and clinics broadly adopt it, it is undoubtful that transient neurotechnology holds the potential to solve many of the current limits affecting implantable neural interfaces and can help in mitigating the burden of neurological and mental disorders for the benefit of humanity.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Li W, Liu Q, Zhang Y, Li C, He Z, Choy WCH, Low PJ, Sonar P, Kyaw AKK: Biodegradable materials and green processing for green electronics. *Adv Mater* 2020, 32:2001591.

2. Hu W, Yang B, Zhang Y, She Y: Recent progress in physically transient resistive switching memory. *J Mater Chem C* 2020, 8:14695-14710.

3. Seck M, Mohammadian N, Diallo AK, Faraji S, Erouel M, Bouguila N, Ndiaye D, Khirouni K, Majewski LA: Organic FETs using biodegradable almond gum as gate dielectric: a promising way towards green electronics. *Org Electron* 2020, 83:105735.

4. Xu J, Zhao X, Wang Z, Xu H, Hu J, Ma J, Liu Y: Biodegradable natural pectin-based flexible multilevel resistive switching memory for transient electronics. *Small* 2019, 15:1803970.

5. Tran H, Feig VR, Liu K, Wu H-C, Chen R, Xu J, Deisseroth K, Bao Z: Stretchable and fully degradable semiconductors for transient electronics. *ACS Cent Sci* 2019, 5:1884-1891.

6. Jiang T, Meng X, Zhou Z, Wu Y, Tian Z, Liu Z, Lu G, Eginlidil M, Yu H-D, Liu J *et al.*: Highly flexible and degradable memory electronics comprised of all-biocompatible materials. *Nanoscale* 2021, 13:724-729.

7. Lee MH, Lee J, Jung S, Kang D, Park MS, Cha GD, Cho KW, Song J, Moon S, Yun YS *et al.*: A biodegradable secondary battery and its biodegradation mechanism for eco-friendly energy-storage systems. *Adv Mater* 2021, 33:2004902.

8. Sharova AS, Melloni F, Lanzani G, Bettinger CJ, Caironi M: Edible electronics: the vision and the challenge. *Adv Mater Technol* 2021, 6:2000757.

9. Wu Y, Ye D, Shan Y, He S, Su Z, Liang J, Zheng J, Yang Z, Yang H, Xu W *et al.*: Edible and nutritive electronics: materials, fabrications, components, and applications. *Adv Mater Technol* 2020, 5:2000100.

10. • Xu K, Li S, Dong S, Zhang S, Pan G, Wang G, Shi L, Guo W, Yu C, Luo J: Bioresorbable electrode array for electrophysiological and pressure signal recording in the brain. *Adv. Healthc Mater* 2019, 8:1801649 http://dx.doi.org/10.1002/adhm.201801649

Implants that vanish. *Nat Biomed Eng* 2019, 3:585.

11. Bernstein JE, Kashyap S, Ray K, Ananda A: Infections in deep brain stimulator surgery. *Cureus* 2019, 11:e5440 http://dx.doi.org/10.7759/cureus.5440.

12. Conen A, Raabe A, Schaller K, Fux CA, Vajkoczy P, Trampuz A: Management of neurosurgical implant-associated infections. *Swiss Med Wkly* 2020, 150:w20208 http://dx.doi.org/10.4414/smw.2020.20208.

15. Abode-Iyamah KO, Chiang H-Y, Woodroffe RW, Park B, Jareczek FJ, Nagahama Y, Winslow N, Herwaldt LA, Greenlee JDW: Deep brain stimulation hardware–related infections: 10-year experience at a single institution. *J Neurosurg* 2019, 130:629-638.

16. Frizon LA, Nagel SJ, May FJ, Shao J, Maldonado-Naranjo AL, Fernandez HH, Machado AG: Outcomes following deep brain stimulation lead revision or reimplantation for Parkinson's disease. *J Neurosurg* 2019, 130:1841-1846.

17. Israeli-Korn SD, Fay-Karmon T, Tessler S, Yahalom G, Benizri S, Strauss H, Zibly Z, Spiegelmann R, Hassin-Baer S: Decreasing battery life in subthalamic deep brain stimulation for Parkinson's disease with repeated replacements: just a matter of energy delivered? *Brain Stimulat* 2019, 12:845-850.

18. Hwang S-WW, Tao H, Kim D-HH, Cheng H, Song J-KK, Rill E, Brenckle MA, Panilaitis B, Won SM, Kim Y-SS *et al.*: A physically transient form of silicon electronics. *Science* 2012, 337:1640-1644.