Research Article

Wirelessly triggered bioactive molecule delivery from degradable electroactive polymer films

Mark D. Ashton,[a] Isabel C. Appen,[a] Melike Firlak,[a,b] Naomi E. Stanhope,[a] Christine E. Schmidt,[c]* William R. Eisenstadt,[d]* Byul Hur[e]* and John G. Hardy[a,c,f]* (iD)

Abstract

The development of stimuli-responsive drug delivery systems offers significant opportunities for innovations in industry. It is possible to produce polymer-based drug delivery devices enabling spatiotemporal control of the release of the drug triggered by an electrical stimulus. Here we describe the development of a wireless controller for drug delivery from conductive/electroactive polymer-based biomaterials and demonstrate its function *in vitro*. The wireless polymer conduction controller device uses very low power, operating at 2.4 GHz, and has a supply voltage controller circuit which controls electrical stimulation voltage levels. The computer graphical user interface program communicates with the controller device, and it receives device information, device status and temperature data from the controller device. The prototype of the wireless controller system can trigger the delivery of a drug, dexamethasone phosphate, from a matrix of degradable electroactive polymers. Furthermore, we introduce the application of *in silico* toxicity screening as a potentially useful method to facilitate the design of non-toxic degradable electroactive polymers for a multitude of biotechnological applications, addressing one of the key commercial challenges to biomaterial development, in accordance with 'safe by design' principles.
© 2020 The Authors. *Polymer International* published by John Wiley & Sons Ltd on behalf of Society of Industrial Chemistry.

Supporting information may be found in the online version of this article.

Keywords: electroactive polymers; stimuli-responsive; *in silico*; Derek nexus; polymer design; smart materials; biomaterials; drug delivery; wireless control; bioelectronics

INTRODUCTION

Polymer-based bioactive molecule delivery systems are routinely employed to improve the biological efficacy of the bioactive molecules, wherein the polymers are key elements in the technology since they can control the release of bioactive molecules (e.g. agrochemical, drug etc.).[1–3] Although there are many clinical implementation hurdles, intelligent bioactive molecule delivery systems offer significant opportunities for innovations in industry.[4–7]

Devices capable of the precise control of levels of drugs in specific tissues or the bloodstream may enable maintenance of the drug within its therapeutic window (effective but not associated with undesirable side effects) and with their chronopharmacologies controlled in line with the chronobiology of the specific condition. Stimuli-responsive drug delivery systems potentially enable the treatment of such conditions because they have potential for spatiotemporally controlled drug delivery.[8] Indeed, materials responding to stimuli (such as enzymes, light, pH, temperature, ultrasound and electric/magnetic fields) have been developed for use as drug delivery devices,[9–24] with reviews

* Correspondence to: JG Hardy, Department of Chemistry, Lancaster University, Lancaster, Lancashire, LA1 4YB, UK, E-mail: j.g.hardy@lancaster.ac.uk; or CE Schmidt, J. Crayton Pruitt Family Department of Biomedical Engineering, University of Florida, Biomedical Sciences Building JG-53, PO Box 116131, Gainesville, Florida 32611, USA, E-mail: schmidt@bme.ufl.edu; or WR Eisenstadt, Department of Electrical and Computer Engineering, University of Florida, New Engineering Building, PO Box 116130, Gainesville, Florida 32611, USA, E-mail: wre@tec.ufl.edu; or Byul Hur, Department of Engineering Technology and Industrial Distribution, Texas A&M University, College Station, Texas 77843, USA. E-mail: byulmail@tamu.edu

a   Department of Chemistry, Lancaster University, Lancaster, UK

b   Department of Chemistry, Gebze Technical University, Kocaeli, Turkey

c   J. Crayton Pruitt Family Department of Biomedical Engineering, University of Florida, Biomedical Sciences Building JG-53, Gainesville, FL, USA

d   Department of Electrical and Computer Engineering, University of Florida, New Engineering Building, Gainesville, FL, USA

e   Department of Engineering Technology and Industrial Distribution, Texas A&M University, College Station, TX, USA

f   Materials Science Institute, Lancaster University, Lancaster, UK

specifically on the application of electroactive materials for drug delivery.[25–31]

A variety of electronic interfaces for the body have been clinically translated for long term applications, including electrodes for the central nervous system for deep brain stimulation, cochlear implants etc., that are designed to function for years; however, they are all metal-based, with mechanical mismatch-associated problems (e.g. inflammation and scar tissue formation around the metal–tissue interface) that motivates the development of softer non-degradable conductive coatings (e.g. conductive polymers),[32–39] potentially using microscale/nanoscale patterns to instruct cell behaviour,[40,41] or indeed capable of delivering bioactive substances from the electrode coating (e.g. anti-inflammatories such as dexamethasone phosphate (DMP) and antimicrobials).[42]

Wirelessly controlled electronic devices have been developed for a variety of applications, including (but not limited to) antennae,[43,44] drug delivery devices,[45–53] light emitting diodes (enabling optogenetic applications)[54–58] and sensors (perhaps the most popular application)[59–67] due to their potential integration in and control of other devices (e.g. wheel chairs,[68] drug delivery devices[55,69] etc.). Wirelessly controlled bioelectronics can be useful for recording cellular activity (particularly from muscle and nerve tissues)[70–79] or indeed for the stimulation of such tissues,[80–83] with examples of systems capable of both recording and stimulation.[84–86]

Transient electronics are an emerging field of technologies and have potential for fulfilling the market need for stimuli-responsive biomaterials used for shorter term applications (seconds to months).[87–91] Wireless control of such transient technologies has been a research goal for some time,[92,93] with a variety of elegant examples reported in the literature, including resorbable electronic patches for wirelessly controlled electrothermic drug delivery to the brain,[94] and wirelessly controlled sensing and delivery devices enabling control of genistein and metformin delivery.[95]

Bioerodible/biodegradable conductive/electroactive polymer-based materials may be useful for drug delivery, tissue engineering and regenerative medicine.[96–99] In response to the significant interest in using conductive/electroactive polymers for drug delivery, we reported the first application of degradable electroactive polymer-based materials (e.g. the polymer depicted in Fig. 1) for electrochemically triggered drug delivery either upon the application of a potential step or by potential cycling using a circuit with a computer-controlled potentiostat.[100,101] Here we report the further development of this novel research via a device that makes it possible to wirelessly trigger the delivery of a clinically relevant model drug DMP (Fig. 1) from the electroactive polymer-based materials *in vitro*.[102] The electroactive polymers used to prepare the polymer films in this report were copolymers of oligoanilines linked to polyethyleneglycol (PEG) via ester bonds

that were prepared and characterised as previously described,[101] and we extend our investigations here by reporting the application of *in silico* toxicity screening[103] as a potentially useful method to facilitate the development of non-toxic degradable electroactive polymers, thereby addressing some of the commercial challenges to biomaterial development,[104] in accordance with 'safe by design' principles.[105,106]
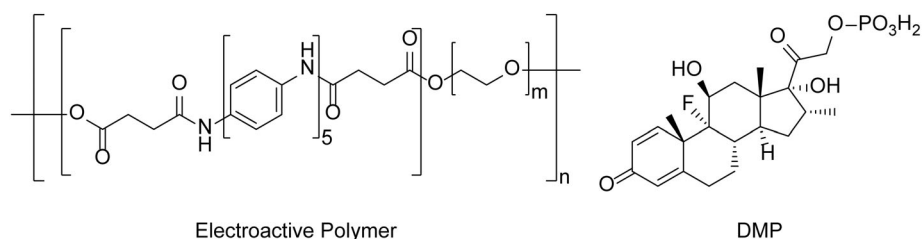
EXPERIMENTAL

Materials
Unless otherwise noted, chemicals were purchased from Sigma Aldrich (Gillingham, UK) and used as supplied. The electroactive polymers used to prepare the polymer films in this report were copolymers of oligoanilines linked to PEG (2 kDa) via ester bonds that were prepared and characterised as previously described (by techniques including FTIR, NMR, TGA, DSC, XRD, UV–visible, cyclic voltammetry, surface profilometry and conductivity).[101] A stock solution of the polymer and DMP (90 mg polymer, 10 mg DMP, 500 μL hexafluoroisopropanol) was prepared, and films of approximately 5 mg (as determined using a high precision balance) were cast on bioinert glassy carbon working electrodes (0.0314 cm², CH Instruments Inc., Austin, TX, USA) and dried under high vacuum for 72 h at 60 °C, after which they were cooled to room temperature and used for delivery experiments. Phosphate buffered saline (PBS) was prepared by the dissolution of one tablet (item P4417) in 200 mL of deionised water, yielding 0.01 mol L⁻¹ phosphate buffer, 0.0027 mol L⁻¹ potassium chloride and 0.137 mol L⁻¹ sodium chloride, pH 7.4, at 25 °C.

Wireless polymer conduction controller (WPCC) system
The wireless polymer conduction controller (WPCC) system for drug delivery includes an electrochemical cell, a remote wireless controller device and a wireless module that communicates with the controller device. The electrochemical cell used in the experiment is a three-electrode system composed of a working electrode (a carbon electrode that is coated with the drug loaded polymer films) and the reference electrode (a platinum wire) immersed in PBS (4 mL), housed in a glass beaker with a fitted lid. The WPCC is connected to the electrochemical cell, and it includes a low-power microcontroller unit (MCU), a low power 2.4-GHz wireless module, a bias controller, a temperature sensor and a boost converter. The bias controller is connected to the electrochemical cell and controls the release of the drug. A graphical user interface (GUI) control program manages the communication with the remote controller devices, and it receives device information, device status and temperature data. The prototype wireless controller device is designed to be compact. The width and length of the printed circuit board (PCB) are 30 mm × 52 mm (1.18 in. × 2.04 in.) The anode and cathode wires are attached to the bias controller block, and they are clipped to the polymer film

Figure 1. The structure of the degradable electroactive polymer and drug (dexamethasone phosphate, DMP) used in this experiment.
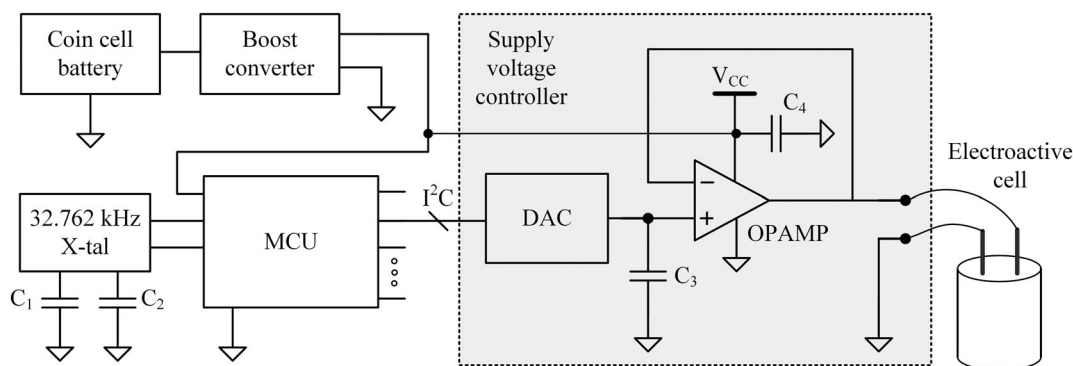
Figure 2. A circuit diagram of the supply voltage controller, booster converter and associated components.

coated glassy carbon working electrode and the platinum wire reference electrode. The hardware is designed to consume very low power. The MCU was programmed to control the components on the PCB including wireless module, the temperature sensor and digital-to-analogue converter (DAC) integrated circuit. It was designed to be operated in normal operation status for a couple of months without replacing the single coin cell battery.

WPCC hardware and firmware
The wireless device was designed using a low-power MCU. A Texas Instruments (TI) (Austin, TX, USA) MSP430x2 series MCU was used as it supports several layers of active and sleep modes. An external 32.768-kHz crystal oscillator was placed on the board for an auxiliary clock. An advanced and adaptive network technology (ANT) wireless module was mounted on the board, connected to the MCU through a universal asynchronous receiver/ transmitter interface. The ANT is an ultra-low power wireless protocol that can send wireless information from one device to another. The ANT supports many sensor network topologies such as peer-to-peer, star and practical mesh. The 2.4-GHz ANT module can use any RF frequency from 2.4 to 2.524 GHz other than 2.457 GHz which is reserved for ANT+. The MCU controls the ANT module during active or sleep modes. Effective use of the sleep mode of the ANT module minimises power consumption. These core hardware elements and the firmware structure were introduced previously and were applied to environmental sensor applications.[66,67]

A supply voltage controller block was implemented, the circuit diagram of which is shown in Fig. 2. The DAC integrated circuit communicates with the MCU using an I²C (inter-integrated circuit) interface. The bias controller block includes an operational amplifier. A TI OPA344 was used as a part of a buffer circuit. The voltage was generated to supply the voltage to the polymer films. When it is excited, the controller supplies a voltage of 0.6 V resulting in a 0.6 V difference between anode and cathode nodes of the electrochemical cell. If it needs to be cut off, the DAC is controlled to generate virtually zero voltage across the anode and cathode nodes.

The microprocessor firmware program was developed in the C/C++ environment using Code Composer Studio (TI). First, the controller device performs the initialisation. After it finishes the initialisation, it goes into a normal loop state. In the normal loop state, the device executes essential operations such as controlling the wireless module and temperature sensor as fast as it can; then the controller device enters a sleep mode. The controller device wakes up every 2 s and resumes the normal loop state when triggered by the internal wake-up signal. When events occur, the program processes the relevant operations accordingly. For precisely controlled drug release, the time control of the supply voltage controller signal is localised using the clock of the MCU. For safety, if the stop button is pressed, the supply voltage controller attempts to stop generating the voltage immediately.

WPCC software
The WPCC GUI program was developed under Visual C++ environment. As described above, the ANT wireless protocol was used for
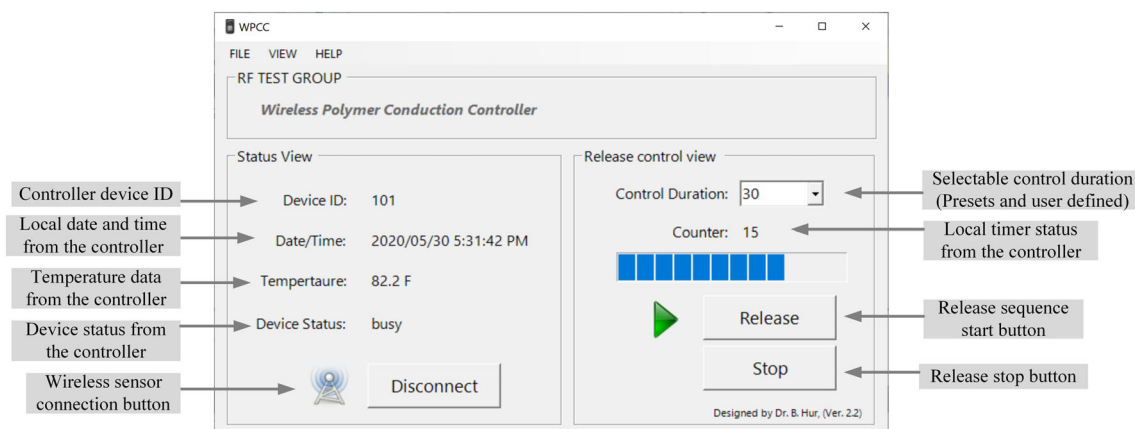
Figure 3. Example screen capture of the GUI.
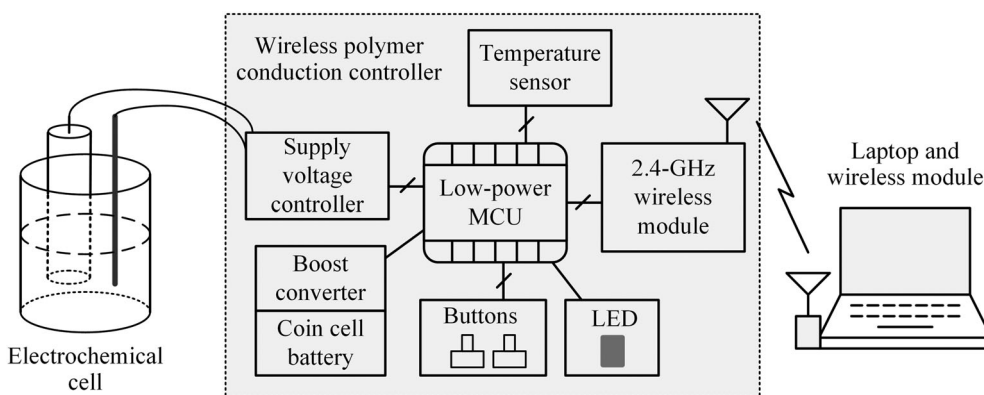
Figure 4. A simplified block diagram of the wireless controller system and electrochemical cell and a photograph inside the wireless polymer conduction controller device.

communication. In the normal state of operation, the WPCC sends a broadcast information packet every 2 s. The information packet includes temperature sensor data, the device ID, status information and a time stamp. The controller program receives the packet data, which is displayed on the computer screen (as shown in Fig. 3). There is a 'Release' button on the right side. There is a 'control duration' drop-down menu, which can select pre-determined durations in seconds (e.g. 10, 20, 30, 60 s), or a user can manually type in the duration in seconds. If/when the release button is pressed, the control program sends an event to the device. If the received event is valid, the wireless controller generates the supply voltage for the given period of time; then the voltage becomes virtually zero when the timer expires. There is a 'stop' button that attempts to stop the operation and to set the control signal inactive.

Drug delivery experiments

Electrically triggered release of DMP from the films deposited on glassy carbon substrates into PBS (4 mL) was controlled with the WPCC as outlined above. The films were allowed to rest for 10 s prior to stimulation at 0.6 V for 60 s to release DMP; the system was allowed to equilibrate for 10 min before a 10 μL aliquot was taken and frozen prior to analysis. The medium was unchanged between cycles, and the data are reported as cumulative release as a percentage of the total mass of drug in the film over the

period of the experiment. DMP release into PBS was quantified by UV–visible spectroscopy using a Thermo Scientific Nano-Drop2000c spectrophotometer (Thermo Fisher Scientific, Morecambe, UK) and compared to passive release samples (i.e. release of DMP from an equivalent setup without the application of a trigger). Experiments were carried out in triplicate ($n = 3$) with the mean average of the data presented with the standard deviation.

### *In silico* toxicity studies

In silico toxicity screening studies of the polymers were carried out using Derek Nexus (v.6.0.1, certified knowledge base 2018 1.1) in Nexus v.2.2.2 provided by Lhasa Ltd (Leeds, UK). The simplified molecular-input line-entry system (SMILES) notations for the oligomers screened are displayed in Table S1. The SMILES were entered into the integrated structure editor in Nexus and default prediction settings were used for Derek Nexus. Any compound activating an alert with a reasoning level of 'equivocal' or above was treated as a positive prediction from the system.

RESULTS AND DISCUSSION

Polymer synthesis and film preparation

Here we report the development of a prototype device that is capable of wirelessly monitoring/sending temperature data and controlling the release of a clinically relevant drug (DMP) from
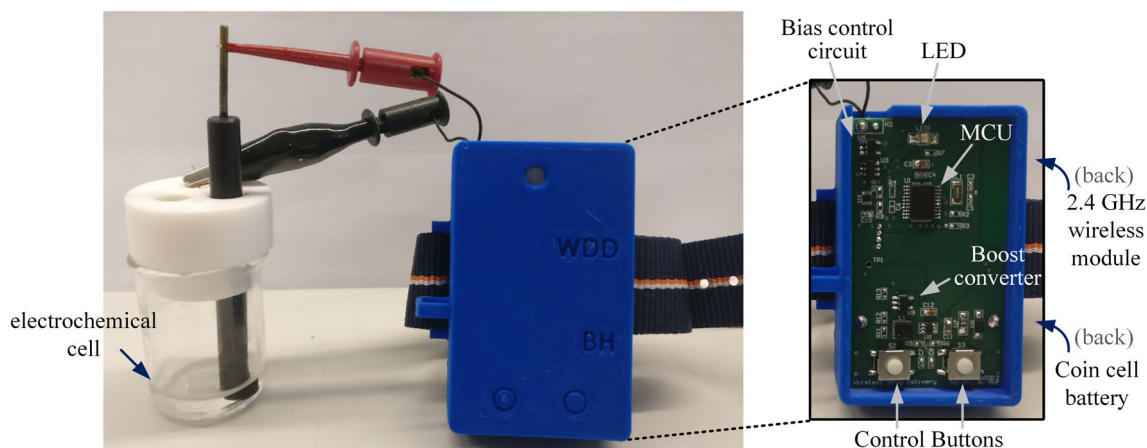
Figure 5. Photographs of the electrochemical cell, wireless controller device and the insides of the WPCC device.
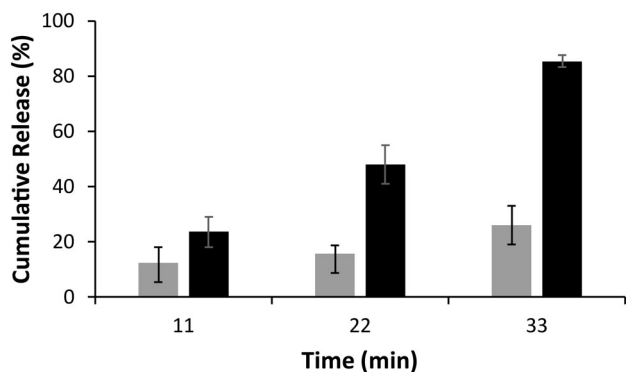
Figure 6. Delivery of DMP from degradable electroactive polymer films in PBS as determined by UV–visible spectroscopy. Cumulative release of DMP from electroactive polymer films (expressed as percentage of the total DMP content of the films (0.5 mg DMP + 4.5 mg polymer)): passive release (grey bars) and electrically stimulated release (black bars).

films of degradable electroactive polymers[101] *in vitro*. The electroactive polymers used to prepare the polymer films in this report were copolymers of oligoanilines linked to PEG (2 kDa) via ester bonds that were prepared and characterised as previously described (by techniques including FTIR, NMR, TGA, DSC, XRD, UV–visible, cyclic voltammetry, surface profilometry and conductivity),[101] and films of similar quality to those previously described were produced as described in the experimental section.

Wirelessly controlled drug delivery

The WPCC system is composed of an electrochemical cell (for *in vitro* validation studies), a remote wireless controller device
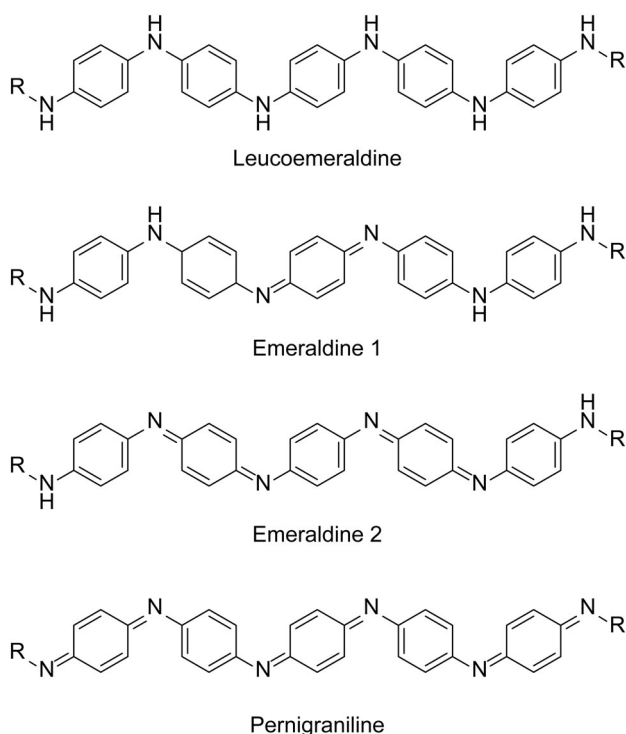
Figure 7. Electroactive oligoanilines in each of the different oxidation states (leucoemeraldine, emeraldine 1, emeraldine 2 and pernigraniline states) all of which were identified as potential causes of multiple toxicological endpoints including cancer, methaemoglobinaemia and skin sensitisation in mammals due to the presence of aniline derivatives.

and a wireless module that communicates with the controller device (a simplified block diagram of the wireless control system is depicted in Fig. 4). The core hardware elements and the firmware structure were previously reported for environmental sensor applications[66,67] and are further developed here for novel drug delivery applications.[102] The prototype wireless controller device was designed to be compact, consume very low power and operate in normal operation status for a couple of months without replacing the single coin cell battery. Photographs of the electrochemical cell, wireless controller device and the insides of the WPCC device are shown in Fig. 5.

The capability of the WPCC to control the delivery of DMP-doped films of the degradable electroactive polymer[101] into PBS (used in this work to mimic physiological conditions) was validated over a short period of time, where the electroactive polymer films were subjected to three rounds of electrical stimulation for 1 min and rest for 10 min for equilibration of the system. The experimental delivery paradigm was adapted from our previous report[101] using a wired setup designed to suit the use of a biodegradable battery capable of delivering 0.6 V described by Bettinger and coworkers.[107] We observed currents in the nanoamp to microamp regime as these polymers are not highly conductive, and such low currents are not likely to cause harm to tissues with which they are in contact. If using more conductive polymers it might be necessary to minimise contact of the conductive material with the tissue (to ensure low currents, below the milliamp regime) potentially by encapsulation of the device within a polymeric matrix (e.g. foam/hydrogel on the surface of the material), but that would clearly affect the rate of delivery from the materials.

In these studies, the cumulative release of DMP into the PBS was quantified via UV–visible spectroscopy over the experiment lasting 33 min, and is compared to passive release from the films in an equivalent setup without application of the electrical stimulus. Approximately 25% of the DMP was released passively from the films over the course of the experiment, whereas approximately 85% of the DMP was released upon application of the electrical stimulus over the same duration, clearly validating the efficacy of the wireless control system.

In silico toxicity studies for electroactive oligomers employing 'safe by design' principles

The ethically sound development of new technologies involves self-critical assessment of the hazards that substances (used in the production of and/or comprising the final product) present to the environment and life. *In vitro* and *in vivo* tests have shown a variety of different reactions to electroactive/conductive polymers.[98,99] *In silico* toxicity screening methods have been developed primarily to aid the design of bioactive molecules (e.g. agrochemicals, drugs etc.) and help minimise the number of *in vivo* tests that need to be undertaken to understand/demonstrate their safety and to facilitate product development in line with 'safe by design' principles.[105,106] While the PEG component of the polymers[101] was chosen as PEGs are Food and Drug Administration (FDA) approved for a broad selection of medical applications, the electroactive oligomers[101] are not FDA approved, and their safety needs to be studied before contemplating their translation to environmental/medical applications.

Herein, we apply a bioinformatics approach to understand risks associated with the polymer employed in this study[101] using Derek Nexus (v.6.0.1) to assess the toxicity of the polymers. We assess the electroactive oligomers (flanked by short PEG chains,

shown in Table S1) in each of the different oxidation states (leucoemeraldine, emeraldine 1, emeraldine 2 and pernigraniline states, shown in Table S1), inspired by literature reporting subtle differences in the toxicity of graphene oxide in different oxidation states.[108,109] Derek Nexus identified that the electroactive oligomeric anilines in each of the different oxidation states (leucoemeraldine, emeraldine 1, emeraldine 2 and pernigraniline states, shown in Figs 6 and 7) within the electroactive oligomers (shown in Table S1) are potential causes of multiple toxicological endpoints including cancer, methaemoglobinaemia and skin sensitisation in mammals due to the presence of aniline derivatives. Derek Nexus also predicts leucoemeraldine to cause chromosome damage *in vitro*, due to the phenylenediamine, and the emeraldine 1, emeraldine 2 and pernigraniline states to be mutagenic *in vitro*, due to the phenylenediamine having been oxidised to the quinoneimine. Both endpoints provide predictions for potential genotoxicants and carcinogens. These observations are supported by data from *in vitro* toxicology studies of oligoanilines from Wei and coworkers, who report that the median lethal dose (LD50/LC50) for aniline dimers, trimers and tetramers was of the order of *ca* 70–300 µg mL^{-1} (dependent on the functionality displayed at their termini) with a short period of exposure (24 h).[110,111]

Systematic studies of the relationship between the synthesis and toxicity of conjugated oligomer derivatives (based on anilines, pyrroles, thiophenes etc.) are necessary to understand if such materials are safe for widespread use in technical and medical applications[104] employing 'safe by design' principles.[105,106] In the case of the polymer described herein incorporating aniline oligomers, it is possible to contemplate using them for short term application as minimally invasive (insertable) medical devices[112–114] that would be removed immediately after use and disposed of as hazardous medical waste by incineration. Clearly their toxicity limits their appeal as candidates for long term implantation (e.g. as tissue scaffolds)[98,115,116] where their potential to be carcinogenic, mutagenic and skin sensitisers could manifest itself (particularly when used in the quantities necessary for electrical stimulation of cells or the delivery of significant quantities of drugs).

CONCLUSIONS

In addition to the imperative need for fundamental research on environmental bioelectromagnetics,[117] we foresee significant development of electronic circuitry and systems to control/regulate the delivery of power (from various sources) to devices that are wearable or indeed implanted *in vivo*.[118–123] Here we describe the development of a wireless controller for drug delivery from degradable electroactive polymer-based biomaterials and validate its efficacy *in vitro*. The low power WPCC device operates at 2.4 GHz, receives device information, device status and temperature data from the controller device, and can trigger the delivery of a clinically relevant drug from a matrix of degradable electroactive polymers *in vitro*; such technology could be adapted for application for a variety of different bioelectronic applications. The use of more conductive polymers may necessitate minimisation of contact of the conductive polymers with tissue (to ensure low currents, below the microamp regime) potentially by encapsulation of the device within a polymeric matrix (e.g. foam/hydrogel on the surface of the material), but that would clearly affect the rate of delivery from the materials.

When designing other degradable conducting polymers for medical/technical applications it is important to contemplate their fate at the end of their useful lifetime. Here we demonstrate the utility of *in silico* toxicity screening as a potentially valuable method to facilitate the development of non-toxic electroactive oligomers for inclusion in degradable electroactive polymers for a multitude of biotechnological applications. This approach addresses key commercial challenges to electroactive biomaterial development,[104] in accordance with 'safe by design' principles,[105,106] and thereby advances the field, with potential long term benefits via improved patient compliance.

AUTHOR CONTRIBUTIONS

Conceptualisation, J.G.H., B.H., C.E.S. and W.R.E.; methodology, J.G.H., B.H.; software, B.H.; validation, all authors; formal analysis, J.G.H., B.H., M.D.A.; investigation, J.G.H., B.H., M.D.A., I.C.A, M.F., N.E.S.; data curation, J.G.H. and B.H.; writing – original draft preparation, J.G.H., B.H. and M.D.A.; writing – review and editing, all authors; supervision, J.G.H., C.E.S. and W.R.E.; project administration, J.G.H., B.H., C.E.S. and W.R.E.; funding acquisition, J.G.H., B.H., C.E.S. and W.R.E.

CONFLICT OF INTEREST

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

SUPPORTING INFORMATION

Supporting information may be found in the online version of this article.

REFERENCES

1 Allen TM and Cullis PR, *Science* **303**:1818–1822 (2004).
2 Liechty WB, Kryscio DR, Slaughter BV and Peppas NA, *Ann Rev Chem Biomol Eng* **1**:149–173 (2010).
3 Ashton MD and Hardy JG, *Johnson Matthey Technol* **63**:211–225 (2019).

4 Timko BP, Dvir T and Kohane DS, *Adv Mater* **22**:4925–4943 (2010).

5 Chertok B, Webber MJ, Succi MD and Langer R, *Mol Pharm* **10**: 3531–3543 (2013).

6 Kowalski PS, Bhattacharya C, Afewerki S and Langer R, *ACS Biomater Sci Eng* **4**:3809–3817 (2018).

7 Li J, Liang JY, Laken SJ, Langer R and Traverso G, *Trends Chem* **2**: 319–340 (2020).

8 Neumann K, Lilienkampf A and Bradley M, *Polym Int* **66**:1756–1764 (2017).

9 Hajiaghajani A and Abdolali A, *Bioelectromagnetics* **39**:325–338 (2018).

10 Jayaneththi VR, Aw K, Sharma M, Wen J, Svirskis D and McDaid AJ, *Sens Actuators B Chem* **297**:126708 (2019).

11 McConville A, Atchison J, Roddy A and Davis J, *Sens Actuators B Chem* **294**:24–31 (2019).

12 Chen XZ, Liu JH, Dong M, Muller L, Chatzipirpiridis G, Hu CZ *et al.*, *Mater Horiz* **6**:1512–1516 (2019).

13 Majumdar S, Kargupta K, Ganguly S and Ray P, *Polym Eng Sci* **51**: 2001–2012 (2011).

14 Hathout RM, Metwally AA, El-Ahmady SH, Metwally ES, Ghonim NA, Bayoumy SA *et al.*, *J Drug Delivery Sci Technol* **47**:176–180 (2018).

15 Puiggali-Jou A, del Valle LJ and Aleman C, *Materials* **12**:2633 (2019).

16 Puiggali-Jou A, del Valle LJ and Aleman C, *ACS Biomater Sci Eng* **6**: 2135–2145 (2020).

17 Xiao YH, Ye XX, He L and Che JF, *Polym Int* **61**:190–196 (2012).

18 Mousavi ST, Harper GR, Municoy S, Ashton MD, Townsend D, Alsharif GHK *et al.*, *Macromol Mater Eng* **305**:2000130 (2020).

19 Hu JM, Zhang GQ and Liu SY, *Chem Soc Rev* **41**:5933–5949 (2012).

20 Mu J, Lin J, Huang P and Chen XY, *Chem Soc Rev* **47**:5554–5573 (2018).

21 Ganesh VA, Baji A and Ramakrishna S, *RSC Adv* **4**:53352–53364 (2014).

22 Ulijn RV, *J Mater Chem* **16**:2217–2225 (2006).

23 Manouras T and Vamvakaki M, *Polym Chem* **8**:74–96 (2017).

24 Municoy S, Álvarez Echazú MI, Antezana PE, Galdopórpora JM, Olivetti C, Mebert AM *et al.*, *Int J Mol Sci* **21**:4724 (2020).

25 Svirskis D, Travas-Sejdic J, Rodgers A and Garg S, *J Control Release* **146**: 6–15 (2010).

26 Pillay V, Tsai TS, Choonara YE, du Toit LC, Kumar P, Modi G *et al.*, *J Biomed Mater Res A* **102**:2039–2054 (2014).

27 Zhao Y, Tavares AC and Gauthier MA, *J Mater Chem B* **4**:3019–3030 (2016).

28 Puiggali-Jou A, del Valle LJ and Aleman C, *J Control Release* **309**: 244–264 (2019).

29 Clancy KFA and Hardy JG, *Curr Pharm Des* **23**:3614–3625 (2017).

30 Hardy JG and Schmidt CE, Toward organic electronic materials for electrically stimulated gene delivery. JD Ramsey, ML Forrest, in *Nanoparticles for Biotherapeutic Delivery*. 1, London: Future Medicine; **2**:58–70 (2015). https://www.futuremedicine.com/doi/book/10.4155/9781910420430.

31 Hardy JG, Chapter 4 - organic electronic materials for gene delivery, in *Engineering of Nanobiomaterials*, ed. by Grumezescu AM, 1, **2** Waltham, MA, USA: William Andrew Publishing, pp. 119–144 (2016). https://www.elsevier.com/books/engineering-of-nano biomaterials/grumezescu/978-0-323-41532-3.

32 Nezakati T, Seifalian A, Tan A and Seifalian AM, *Chem Rev* **118**: 6766–6843 (2018).

33 Woeppel KM, Zheng XS, Schulte ZM, Rosi NL and Cui XYT, *Adv Healthc Mater* **8**:1900622 (2019).

34 Evans D, *Polym Int* **67**:351–355 (2018).

35 Talikowska M, Fu XX and Lisak G, *Biosens Bioelectron* **135**:50–63 (2019).

36 Green RA, Lovell NH, Wallace GG and Poole-Warren LA, *Biomaterials* **29**:3393–3399 (2008).

37 Liu Y, Yin PF, Chen JR, Cui B, Zhang C and Wu F, *Int J Polym Sci* **2020**: 5659682 (2020).

38 Harris AR, Morgan SJ, Chen J, Kapsa RMI, Wallace GG and Paolini AG, *J Neur Eng* **10**:016004 (2013).

39 Bayer CL, Trenchard IJ and Peppas NA, *J Biomater Sci Polym Ed* **21**: 623–634 (2010).

40 Li P, Dou XQ and Schonherr H, *Polym Int* **68**:1015–1032 (2019).

41 Hardy JG, Khaing ZZ, Xin SJ, Tien LW, Ghezzi CE, Mouser DJ *et al.*, *J Biomater Sci Polym Ed* **26**:1327–1342 (2015).

42 Shah SAA, Firlak M, Berrow SR, Halcovitch NR, Baldock SJ, Yousafzai BM *et al.*, *Materials* **11**:1123 (2018). https://www.mdpi.com/1996-1944/11/7/1123.

43 Yang FY, Lee PM, Dong ZY, Tian X and Ho JS, *Phys Rev Appl* **12**: 054020 (2019). https://journals.aps.org/prapplied/abstract/10.1103/PhysRevApplied.12.054020.

44 Kong YL, Zou XY, McCandler CA, Kirtane AR, Ning S, Zhou JL *et al.*, *Adv Mater Technol* **4**:1800490 (2019). https://onlinelibrary.wiley.com/doi/full/10.1002/admt.201800490.

45 Forouzandeh F, Zhu XX, Alfadhel A, Ding B, Walton JP, Cormier D *et al.*, *J Control Release* **298**:27–37 (2019).

46 Reddy MA, Pradhan BK, Qureshi D, Pal SK and Pal K, *J Med Dev Trans ASME* **14**:011104 (2020). https://doi.org/10.1115/1.4045933.

47 Li PY, Givrad TK, Sheybani R, Holschneider DP, Maarek JMI and Meng E, *Lab Chip* **10**:101–110 (2010).

48 Jo WJ, Baek SK and Park JH, *J Micromech Microeng* **25**:045014 (2015).

49 Yan B, An D, Wang X, DeLong BJ, Kiourti A, Dungan K *et al.*, *Med Dev Sens* **2**:e10055 (2019).

50 Khan AN, Ermakov A, Sukhorukov G and Hao Y, *Appl Phys Rev* **6**: 041301 (2019).

51 Yi Y and Kosel J, *Sens Actuators A Phys* **261**:177–183 (2017).

52 Gao W, Li JM, Cirillo J, Borgens R and Cho Y, *Langmuir* **30**:7778–7788 (2014).

53 Gao W and Borgens RB, *J Control Release* **211**:22–27 (2015).

54 Tian X, Lee PM and Ho JS, *AIP Adv* **8**:095308 (2018).

55 Zhang Y, Castro DC, Han Y, Wu YX, Guo HX, Weng ZY *et al.*, *Proc Natl Acad Sci U S A* **116**:21427–21437 (2019).

56 Noh KN, Park SI, Qazi R, Zou ZN, Mickle AD, Grajales-Reyes JG *et al.*, *Small* **14**:1702479 (2018).

57 McCall JG, Qazi R, Shin G, Li S, Ikram MH, Jang KI *et al.*, *Nat Protoc* **12**: 219–237 (2017).

58 Jeong JW, McCall JG, Shin G, Zhang YH, Al-Hasani R, Kim M *et al.*, *Cell* **162**:662–674 (2015).

59 Boutry CM, Chandrahalim H, Streit P, Schinhammer M, Hanzi AC and Hierold C, *Sens Actuators A Phys* **189**:344–355 (2013).

60 Cui Y, *Sensors* **17**:2289 (2017).

61 Lee Y, Kim J, Joo H, Raj MS, Ghaffari R and Kim DH, *Adv Mater Technol* **2**:1700053 (2017).

62 Banerjee A, Bhattacharyya TK and Nag S, *IEEE Sensors*:1–4 (2018) 2018. https://ieeexplore.ieee.org/document/8589651.

63 Strakosas X, Selberg J, Pansodtee P, Yonas N, Manapongpun P, Teodorescu M *et al.*, *Sci Rep* **9**:10844 (2019).

64 Sempionatto JR, Brazaca LC, Garcia-Carmona L, Bolat G, Campbell AS, Martin A *et al.*, *Biosens Bioelectron* **137**:161–170 (2019).

65 Kwon YT, Lee Y, Berkmen GK, Lim HR, Scorr L, Jinnah RA *et al.*, *Adv Mater Technol* **4**:1900458 (2019).

66 Hur B and Eisenstadt WR, Progress in development of the low-power wireless multiple temperature sensor pole for pesticide, agriculture, and mosquito research, in *SoutheastCon*, Fort Lauderdale, FL, pp. 1–6 (2015). https://doi.org/10.1109/SECON.2015.7132963.

67 B. Hur and W. R. Eisenstadt, Low-Power Wireless Climate Monitoring System with RFID Security Access Feature for Mosquito and Pathogen Research, in 2015 First Conference on Mobile and Secure Services (MOBISECSERV), Gainesville, IEEE, FL, USA, pp. 1–5 (2015). https://doi.org/10.1109/MOBISECSERV.2015.7072871.

68 Mishra S, Norton JJS, Lee Y, Lee DS, Agee N, Chen Y *et al.*, *Biosens Bioelectron* **91**:796–803 (2017).

69 Sheybani R, Cobo A and Meng E, *Biomed Microdevices* **17**:74 (2015).

70 Lee S, Wang H, Wang JH, Shi QF, Yen SC, Thakor NV *et al.*, *Nano Energy* **50**:148–158 (2018).

71 S. Lee, W. Y. X. Peh, J. S. Ho, N. V. Thakor, S. Yen and C. Lee, Batteryless pelvic nerve direct modulation for bladder Voding using an active neural clip, in 2018 IEEE 13th Annual International Conference on Nano-/Micro Engineered and Molecular Systems (NEMS), pp. 452–455 (2018).

72 Tanabe Y, Ho JS, Liu JY, Liao SY, Zhen Z, Hsu S *et al.*, *PLoS One* **12**: e0186698 (2017).

73 Wein AJ, *J Urol* **203**:40–41 (2020).

74 Mickle AD, Won SM, Noh KN, Yoon J, Meacham KW, Xue YG *et al.*, *Nature* **565**:361–365 (2019).

75 Hernandez-Reynoso AG, Nandam S, O'Brien JM, Kanneganti A, Cogan SF, Freeman DK *et al.*, *J Neur Eng* **16**:046002 (2019). https://iopscience.iop.org/article/10.1088/1741-2552/ab1c36.

76 Lee S, Peh WYX, Wang J, Yang F, Ho JS, Thakor NV *et al.*, *Adv Sci* **4**: 1700149 (2017).

77 Seo D, Neely RM, Shen K, Singhal U, Alon E, Rabaey JM *et al.*, *Neuron* **91**:529–539 (2016).

78 Kanchwala MA, McCallum GA and Durand DM, A Miniature Wireless Neural Recording System for Chronic Implantation in Freely Moving

7

Animals. *IEEE Biomedical Circuits and Systems Conference (BioCAS)*, Cleveland, OH, pp. 1–4 (2018). https://doi.org/10.1109/BIOCAS.2018.8584701.

79 Rush AD and Troyk PR, *IEEE Trans Biomed Eng* **59**:3255–3262 (2012).

80 Hsiao YS, Liao YH, Chen HL, Chen PL and Chen FC, *ACS Appl Mater Int* **8**:9275–9284 (2016).

81 Sun HJ, Yu DQ, Guan YJ, Du Z, Ren JS and Qu XG, *Chem Commun* **55**:9833–9836 (2019).

82 Agrawal DR, Tanabe Y, Weng DS, Ma A, Hsu S, Liao SY et al., *Nat Biomed Eng* **1**:0043 (2017).

83 Abiri P, Abiri A, Packard RRS, Ding YC, Yousefi A, Ma JG et al., *Sci Rep* **7**:6180 (2017).

84 P. Schönle, F. Michoud, N. Brun, A. Guex, S. P. Lacour, Q. Wang and Q. Huang, A Wireless System with Stimulation and Recording Capabilities for Interfacing Peripheral Nerves in Rodents, in 2016 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), pp. 4439–4442 (2016).

85 Deshmukh A, Brown L, Barbe MF, Braverman AS, Tiwari E, Hobson L et al., *J Neurosci Methods* **333**:108562 (2020).

86 Zhang B, Zhuang LJ, Qin Z, Wei XW, Yuan QC, Qin CL et al., *J Neurosci Methods* **307**:221–229 (2018).

87 Zhang YJ, Zhou ZT, Fan Z, Zhang SQ, Zheng FM, Liu KY et al., *Small* **14**:1802050 (2018).

88 Phan HP, Zhong YS, Nguyen TK, Park Y, Dinh T, Song EM et al., *ACS Nano* **13**:11572–11581 (2019).

89 Tian BZ, Xu S, Rogers JA, Cestellos-Blanco S, Yang PD, Carvalho-de-Souza JL et al., *Phys Biol* **15**:031002 (2018).

90 Kang SK, Murphy RKJ, Hwang SW, Lee SM, Harburg DV, Krueger NA et al., *Nature* **530**:71–76 (2016).

91 Cha GD, Kang D, Lee J and Kim DH, *Adv Healthc Mater* **8**:1801660 (2019).

92 Boutry CM, Chandrahalim H, Streit P, Schinhammer M, Hanzi AC and Hierold C, *Phil Trans R Soc A Math Phys Eng Sci* **370**:2418–2432 (2012).

93 Kim J, Ghaffari R and Kim DH, *Nature Biomed Eng* **1**:0049 (2017).

94 Lee J, Cho HR, Cha GD, Seo H, Lee S, Park CK et al., *Nat Commun* **10**:5205 (2019).

95 Keum D, Kim SK, Koo J, Lee GH, Jeon C, Mok JW et al., *Sci Adv* **6**:eaba3252 (2020).

96 Zelikin AN, Lynn DM, Farhadi J, Martin I, Shastri V and Langer R, *Angew Chem Int Ed* **41**:141–144 (2002).

97 Mawad D, Gilmore K, Molino P, Wagner K, Wagner P, Officer DL et al., *J Mater Chem* **21**:5555–5560 (2011).

98 Guo BL, Glavas L and Albertsson AC, *Prog Polym Sci* **38**:1263–1286 (2013).

99 Hardy JG, Lee JY and Schmidt CE, *Curr Opin Biotechnol* **24**:847–854 (2013).

100 Hardy JG, Amend MN, Geissler S, Lynch VM and Schmidt CE, *J Mater Chem B* **3**:5005–5009 (2015).

101 Hardy JG, Mouser DJ, Arroyo-Curras N, Geissler S, Chow JK, Nguy L et al., *J Mater Chem B* **2**:6809–6822 (2014).

102 B. Hur, J. G. Hardy, W. R. Eisenstadt and C. E. Schmidt, Drug delivery integrated circuit (IC) and system. WO/2017/143200 (2017). http://www.freepatentsonline.com/y2020/0215317.html.

103 Hasselgren C, Ahlberg E, Akahori Y, Amberg A, Anger LT, Atienzar F et al., *Regul Toxicol Pharmacol* **107**:104403 (2019).

104 Harris JJ, Lu S and Gabriele P, *Polym Int* **67**:969–974 (2018).

105 Yan L, Zhao F, Wang J, Zu Y, Gu ZJ and Zhao YL, *Adv Mater* **31**:1970325 (2019).

106 van de Poel I and Robaey Z, *Nanoethics* **11**:297–306 (2017).

107 Kim YJ, Chun SE, Whitacre J and Bettinger CJ, *J Mater Chem B* **1**:3781–3788 (2013).

108 Wu W, Yan L, Chen SY, Li QY, Gu ZJ, Xu HW et al., *Nanotoxicology* **12**:819–835 (2018).

109 Ou L, Song B, Liang H, Liu J, Feng X, Deng B et al., *Part Fibre Toxicol* **13**:57 (2016).

110 Zhang XY, Qi HX, Wang SQ, Feng L, Ji Y, Tao L et al., *Toxicol Res* **1**:201–205 (2012).

111 Qi HX, Liu MY, Xu LX, Feng L, Tao L, Ji Y et al., *Toxicol Res* **2**:427–433 (2013).

112 Barbone AS, Meftah K, Markiewicz K and Dellimore K, *Biomed Phys Eng Express* **5**:062002 (2019).

113 Tsai RJ, Aldaoud A, Redoute JM, Garrett DJ, Prawer S and Grayden DB, *Biomed Microdev* **22**:14 (2020).

114 Nguyen KT, Hoang MC, Choi E, Kang B, Park JO and Kim CS, *Int J Control Automat Syst* **18**:65–75 (2020).

115 Zarrintaj P, Bakhshandeh B, Saeb MR, Sefat F, Rezaeian I, Ganjali MR et al., *Acta Biomater* **72**:16–34 (2018).

116 Saberi A, Jabbari F, Zarrintaj P, Saeb MR and Mozafari M, *Biomolecules* **9**:448 (2019).

117 McKee L, *Environ Res* **164**:100–108 (2018).

118 Wey TA, Southcott M, Jemison WD, MacVittie K and Katz E, *Proc IEEE* **102**:1795–1810 (2014).

119 P. M. Raj, R. G. Spurney, S. Dwarakanath, K. Mohanalingam and R. Tummala, Nanostructures for Enabling Implantable Bioelectronic Systems, in 2018 IEEE 13th Nanotechnology Materials and Devices Conference (NMDC), pp. 1–5 (2018).

120 Reddy S, He L and Ramakrishana S, *Biomed Signal Proc Control* **41**:255–263 (2018).

121 Wu CY, Tseng CK and Cheng CH, *Jpn J Appl Phys* **57**:064202 (2018).

122 Liu F, Cheng X, Zhang F, Chen Y, Song HL, Huang YG et al., *Adv Electron Mater* **5**:1900256 (2019).

123 Jang KI, Li K, Chung HU, Xu S, Jung HN, Yang YY et al., *Nature Commun* **8**:15894 (2017).