Implantable device for wirelessly controlled drug delivery

Image credit: Arek Socha, Pixabay

By Andy Tay

Drug delivery is a key pillar in modern medicine. Most drugs are still being delivered orally or intravenously. While medically convenient, drugs administered through such routes often result in systemic effects where non-target cells and tissues are also affected.

In the last two decades, there has been tremendous interest in the design of programmable, intelligent materials including nanoparticles to enhance localized and controllable drug delivery and release. Such methods can significantly reduce the dose needed, thus reducing adverse side effects, and improving therapeutic efficacy. However, it is challenging to control *in vivo* pharmacokinetics and site specificity of nanomaterials because they are typically injected intravenously.

Wireless implantable devices loaded with drugs are showing promise for localized and on-demand pharmaceutical delivery. For instance, they can be used to alleviate conditions that benefit from targeted drug delivery such as severe diabetic hypoglycemia and joint inflammation. Compared to chemicals like nanoparticles, the manufacturing process of implantable devices is simpler and can more easily comply with good manufacturing practices. Nevertheless, implantable drug delivery devices are bulky (especially when compared to nanoparticles), battery powered which limits their implantation depth, and require invasive surgeries.

Ultrasound-powered device for drug delivery

In a paper authored by Professor Amin Arbabian, Max Wang and colleagues in the Department of Electrical Engineering at Stanford University, and supported by Professor Richard Zare at the Department of Chemistry and Professor Justin Annes at the Stanford School of Medicine, the team developed an implantable potentiostat integrated with nanoparticles for electrochemically-controlled drug release (Wang et al., 2021). Wang's device integrated the benefits of both

nanoparticles and implantable devices for targeted *in vivo* drug delivery by creating a potentiostat that measures current flow between working and reference electrode due to detection of target analyte (**Fig. 1**).

"Drug delivery implants can enable controlled, targeted drug release which can maximize efficacy while minimizing side effects and avoiding compliance issues. Current implants are usually battery-powered, which limits their lifetime and where they can be easily implanted. By pairing drug-loaded electroresponsive nanoparticles developed by the Zare lab with ultrasonically powered custom electronics, we can develop implants that can be placed anywhere in the body and precisely release drugs on-demand. In addition, because the release is dictated by an electrochemical reaction, the electronics can track the release rate by measuring the redox current. The implant can then wirelessly send back the digitized data and receive commands to tune the release profile in real-time," says Wang.

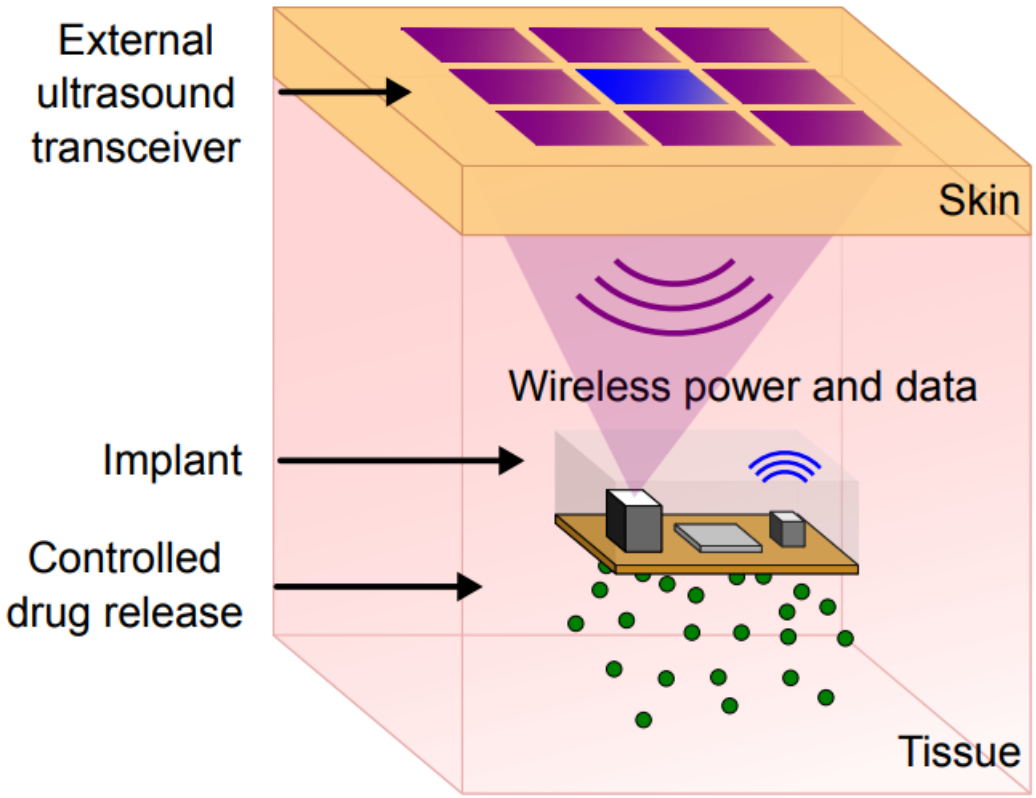

Figure 1 showing the system concept where ultrasound is used to power device, and the potentiostat makes use of electrochemical sensing for controlled drug release. Credit: Max Wang

The implantable device consists of three main components: transducers, an integrated circuit, and a drug delivery module. There are two piezoelectric transducers, one receives ultrasound power and the other uplinks sensor data. Ultrasound was chosen as a way to power the device as it has low propagation loss in tissue, high safety limits and millimeter wavelength which allows it to penetrate deep tissues. The ultrasound functions as a source of power and is converted by the piezoelectric transducer into electrical signals. The received signals are used to power the integrated circuit to control the drug delivery module. The drug delivery module contains drug-loaded polypyrrole nanoparticles (placed in a working electrode), a reference electrode and counter electrode. Polypyrrole is used as it is an electro-responsive material and can be electrochemically activated for controlled drug release via an oxidation/reduction reaction while offering higher drug loading capacity than polymer films.

When ultrasound power is received by the piezoelectric transducer, the implant is ready to receive commands to program drug release. At the same time, the potentiostat also starts current sensing at a programmable sampling rate to control the timing and dose of drug release.

The authors also designed their device such that it can handle both positive and negative potential differences between the working and reference electrodes to enhance versatility of the device through a broad working dynamic range. This corresponds to a working voltage range of -1.5 to 1.5 V.

As a proof-of-concept, the authors loaded a fluorescence molecule, fluorescein, into their nanoparticles to act as 'drugs'. The authors found minimal leakage of fluorescein at body temperature (37^{o} C). The fluorescein release rate was then analyzed using a fluorometer at 1 minute intervals for 10 minutes. Throughout the process of fluorescein release, the current readout was well within the device's dynamic current sensing range of -100 to 100 µA.

Wang adds that the main limitation of their device, as with other drug delivery implants, is the drug loading capacity. More research needs to be done to maximize the implant drug capacity without affecting the release rate or leading to undesired drug leakage.

"We are also investigating new drug release mechanisms as well as closed-loop drug delivery techniques for precise and personalized release control. We are currently working on packaging the electronics and drug-loaded nanoparticles in a mm-sized implant form factor so that it can potentially be tested in an animal model. In this work, we used fluorescein, a fluorescent molecule, as a model drug. In collaboration with the Zare and Annes labs, we are working on testing the implant with real drugs to combat severe diabetic hypoglycemia," says Wang.

"We hope that these ultrasonically powered devices can serve as a platform for future wireless implantable drug delivery systems."

Drug discovery is an expensive process with high failure rates. Through innovations in implantable devices, patients can expect to benefit from targeted drug delivery with greater clinical efficacy and minimal adverse side effects.

Source article

Wang, M. L., Yeon, P., Chamberlayne, C. F., Mofidfar, M., Xu, H., Annes, J. P., Zare, R. N., & Arbabian, A. (2021). A Wireless Implantable Potentiostat for Programmable Electrochemical Drug Delivery. *BioCAS 2021 - IEEE Biomedical Circuits and Systems Conference, Proceedings*. https://doi.org/10.1109/BioCAS49922.2021.9644991

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