

Millimetre-scale, bioresorbable optoelectronic systems for electrotherapy

Corresponding Author: Professor John Rogers

This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Referee #1

(Remarks to the Author)

The authors present millimetre scale bioresorbable devices for electrotherapy. The device structure is very simple - a phototransistor is used as the power source and power is delivered externally using IR light. A companion wearable detects changes in electrophysiology and closes the loop. It can also synchronise multiple implants. Finally, integration with catheters is demonstrated. These results represent a significant advancement in the state-of-the-art of the field of bioelectronics and fulfil an unmet clinical need. They also have significant implications for the development of treatments for conditions outside cardiology. The quality of the work is pioneering in concept and excellent in execution, therefore worthy of publication in Nature.

The manuscript would benefit from a discussion on the mechanism of operation of the Mg-MgO₃ element. Fig. 1f shows cations moving from the anode to the cathode. Would these be Mg cations? If yes, how would pacing affect biodegradation of the implant?

(Remarks on code availability)

Not an expert

Referee #2

(Remarks to the Author)

This article presents a bioresorbable optoelectronic system that is intended to provide minimally invasive electrotherapy, specifically for temporary cardiac pacing. The system addresses the risks and complexities associated with conventional temporary pacemakers, such as infections and the need for surgical removal, by using a wireless, optical control mechanism and an onboard power supply. This approach aims to reduce the invasiveness of cardiac support devices and associated patient recovery time.

This work stands out due to its focus on a fully bioresorbable form, with only a small amount (1.6% wt) of carbon black used in the cathodes unless replaced with Mo for complete bioresorption but slightly larger size for similar performance. Additionally, the use of optical mechanisms for device control and power represents a unique and innovative approach to managing and operating devices within the body. By eliminating the need for surgical intervention, this approach may also reduce the likelihood of long-term complications. However, it is essential to recognize that this research builds upon previous breakthroughs in bioresorbable electronics. Earlier works, such as those published in Science in 2002 and Science Advances in 2022 by the same PI, laid the groundwork in bioresorbable technology for medical applications. These seminal studies introduced pioneering concepts in bioresorbable materials and device designs that have significantly influenced subsequent technologies in this domain.

For all of that, the current study represents an incremental progression in the development of bioresorbable medical devices, building upon existing knowledge and techniques within the field of bioresorbable electronics. The integration of optical control and power mechanisms is innovative but does not represent a paradigm shift in the field. Instead, it reflects a natural evolution of the technology, marked by refinements and optimizations.

Besides this overall evaluation, several concerns have been raised during the review process about certain aspects of the work, which could be clarified and improved to enhance its value to the scientific community. One area that requires further elucidation is the extent to which the innovations presented represent a significant advance from previous research in the field. While the article highlights the incremental nature of the improvements, a comparative analysis with prior landmarks in bioresorbable electronics, including the authors' own previous work, could provide more context and insight into the novelty and impact of the current research. Another issue that requires attention is the lack of detail on the device's operational lifespan and degradation kinetics within the body. Greater clarity on these aspects would help to establish the practical implications of the device's bioresorbability. Furthermore, while the use of bioresorbable materials suggests improved safety and biocompatibility, specific data on these parameters are lacking. Studies or data on the biocompatibility of the materials used and any potential inflammatory responses would enhance the credibility of the device's application in clinical settings. The article could also benefit from more comprehensive technical specifications, including details on energy requirements, efficiency of the optical control mechanism, and the range of operable conditions, such as depth within tissue.

Referee #3

(Remarks to the Author)

Authors describe a possibly revolutionary resorbable temporary pacemaker system guided by transcutaneous illumination. The described device seems to be a working model in open chest and prepared heart models. Some data suggest that myocardial stimulation even in skinny animal models were possible, when the pacemaker nodule was within 3-4 cm below the skin surface. Further benefit of the system is that multi site pacing seems to be manageable with the utilisation of different wavelengths

The resorbable characteristics of the device seems to be promising, however clinical usability seems to be questionable.

I agree with the statement, that this concept will be best used in paediatric (small chest size) population.

• Remarks to the author

The device would be activated by a soft, skin-interfaced wireless device, which emits light in the NIR range. According to the given data the light absorption is quite significant, as in 4 cm depth- 0.001 of the light emitted over the skin could be simulated. On Fig 3b: Optical simulation does not take in account the ribs as in the current figure- is the absorption coefficient really so close to the soft tissue as in the model? I am really critical on this point. Furthermore, a greater number of patients will have the device deeper than 4cm with maximum depth up to 15 cm. Please add simulation until 10-15cm depth, with calculation of an effective light emission over the skin to reach adequate pacing output. Is this magnitude of light still reliably manageable for longer period of time?

Further clinical question arises when the pacemaker nodules are fixated onto the TAVI valve, with PM opposite to the septal surface. How much is the calculated distance to the skin surface in such a case, and how much emitted light needed for an effective stimulation? How was the illumination performed in the case of TAVI attached PM testing?

I miss the discharge characteristics of the PM battery based on standard values (e.g 100% 60 bpm, 500 Ohm)

Authors state: „These and additional experiments (Extended Data Fig. 3, Supplementary Note 1) demonstrate timescales for stable operation and complete bioresorption of ~16 days and ~1.2-2.5 years”

I could not find data on threshold changes over the maximum operation time of 16 days. It is generally expected to have a local inflammation leading to a significant threshold rise few days after PM lead implantation which is especially significant in the case of epicardial leads.

Authors state: „Collections of such integrated devices can deliver both rapid pacing during valve deployment and regular pacing during the post-operative period.”

It is important to highlight, that stable and reliable pacing is needed for an optimal TAVI implantation. The pacemaker will not be working before complete expansion of the TAVI valve. Furthermore, it is questionable whether adequate threshold can be reached in the TAVI valve position.

100% capture is not enough for a safe operation. A minimum of 2x safety window is needed to ensure a stable and reliable operation. Are there any simulations or direct measurements to reach this safety profile?

„The compatibility with MRI” : is the light emitting part MRI compatible/conditional? This is a crucial part of the pacemaker system.

Gabor Duray

Version 1:

Reviewer comments:

Referee #1

(Remarks to the Author)

The authors fully addressed my comment on the mechanism and I am now happy to support publication.

Referee #2

(Remarks to the Author)

The authors have addressed all the comments, and it is now clear that the main advance lies in the application of the technology, which is particularly strong. While the fundamental aspects may not present as significant a breakthrough, the clarity around the application is evident and will be an important factor in the evaluation

Referee #3

(Remarks to the Author)

The manuscript has improved significantly. The simulation including the light absorption effect of the ribs, and the modified device design for deeper level stimulation adds valuable information and gives hope for the clinical use of the device. My concerns regarding the pacing threshold over time have been resolved.

Altogether the additional simulations, testing and development of a modified design together with adequate remarks on the possible clinical usability of such a device makes the present manuscript acceptable from the clinician's perspective.

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Response to reviewers

Reviewer #1

Overall summary: The authors present millimetre scale bioresorbable devices for electrotherapy. The device structure is very simple - a phototransistor is used as the power source and power is delivered externally using IR light. A companion wearable detects changes in electrophysiology and closes the loop. It can also synchronise multiple implants. Finally, integration with catheters is demonstrated. These results represent a significant advancement in the state-of-the-art of the field of bioelectronics and fulfil an unmet clinical need. They also have significant implications for the development of treatments for conditions outside cardiology. The quality of the work is pioneering in concept and excellent in execution, therefore worthy of publication in Nature.

Our response: We thank the reviewer for these positive comments on the advances, impact, and quality of our work and for recommending its publication. Our responses to the reviewer's questions, accompanied by relevant changes to the manuscript, are detailed below.

Specific Comments: The manuscript would benefit from a discussion on the mechanism of operation of the Mg-MgO₃ element. Fig. 1f shows cations moving from the anode to the cathode. Would these be Mg cations? If yes, how would pacing affect biodegradation of the implant?

Our response: We thank the reviewer for this important comment. The Mg-MoO₃ electrode pairs serve as self-powered pacing electrodes. Specifically, the more electronegative Mg is the anode, and the more electropositive MoO₃ composite is the cathode. The cardiac tissue acts as the electrolyte for the Mg-MoO₃ galvanic cell. Fig. R1 shows the mechanism of operation. Upon illumination, the resistance of the phototransistor (PT) decreases by several orders of magnitude to $\sim 10^2 \Omega$, thereby closing the circuit and discharging the battery formed by the pacing electrodes and the adjacent cardiac tissue. During the discharge, the Mg anode undergoes an oxidation reaction ($Mg - 2e^- \rightarrow Mg^{2+}$), and the cathode undergoes a reduction reaction ($MoO_3 + ne^- \rightarrow MoO_3^{n-}$). The electrons move from the anode to the cathode. The current flows from the cathode to the anode. The Mg^{2+} ions and other cations like Na^+ and K^+ in the tissue move from the anode to the cathode, to complete the circuit.

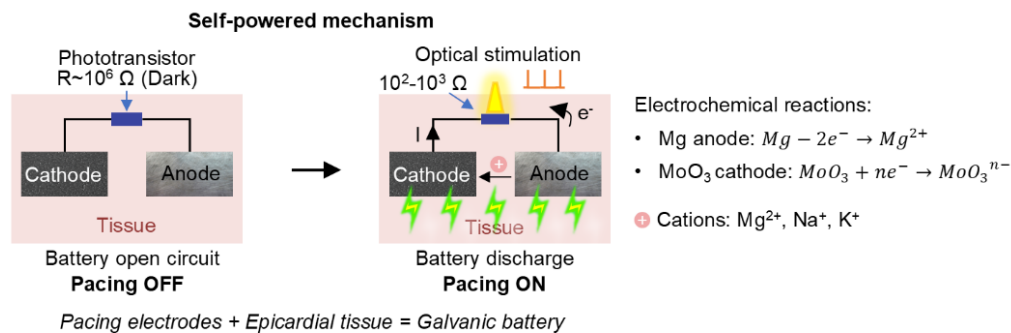


Fig. R1. Schematic diagram of light-controlled and self-powered pacing mechanism. Illuminating the phototransistor decreases its electrical resistance and thus discharges the electrochemical cell formed by the anode and cathode with surrounding tissue and biofluids as the electrolyte.

As mentioned above, Mg^{2+} ions transport from the anode to the cathode during discharge. The pacing process involves the electrochemical oxidation of the Mg anode and the reduction of the MoO_3 cathode. As a result, the pacing process increases the processes of biodegradation of these electrodes. Degradation reactions for the other components including the phototransistor, the conductive paste, and the polyanhydride (PA) encapsulation are relatively unaffected by the pacing process. Degradation of the Si phototransistor is the rate-determining step for the complete bioresorption, with a timescale of ~1.2-2.5 years.

Modifications to the draft: We added Fig. R1 as Supplementary Fig. 3.

On page 8 we added “During the discharge, the Mg anode undergoes an oxidation reaction ($Mg - 2e^- \rightarrow Mg^{2+}$), and the cathode undergoes a reduction reaction ($MoO_3 + ne^- \rightarrow MoO_3^{n-}$).”

In the Supporting Material on page 25 we added “During the discharge, the Mg anode undergoes an oxidation reaction ($Mg - 2e^- \rightarrow Mg^{2+}$), and the cathode undergoes a reduction reaction ($MoO_3 + ne^- \rightarrow MoO_3^{n-}$). The electrons move from the anode to the cathode. The current flows from the cathode to the anode. The Mg^{2+} ions and other cations like Na^+ and K^+ in the tissue move from the anode to the cathode, to complete the circuit.”

In the Supporting Material on page 11 we added “The pacing process involves the electrochemical oxidation of the Mg anode and the reduction of the MoO_3 cathode. As a result, this process increases the rate of bioresorption of these electrodes. Degradation reactions for the other components including the phototransistor, the conductive paste, and the polyanhydride (PA) encapsulation are relatively unaffected by the pacing process. Fig. 1i indicates that the dissolution of the ~10 μm thick Si-based phototransistor (PT) is the rate-limiting step of complete bioresorption.” and “which indicates timescales for complete bioresorption of ~1.2-2.5 years.”

Reviewer #2

General Comments: This article presents a bioresorbable optoelectronic system that is intended to provide minimally invasive electrotherapy, specifically for temporary cardiac pacing. The system addresses the risks and complexities associated with conventional temporary pacemakers, such as infections and the need for surgical removal, by using a wireless, optical control mechanism and an onboard power supply. This approach aims to reduce the invasiveness of cardiac support devices and associated patient recovery time.

This work stands out due to its focus on a fully bioresorbable form, with only a small amount (1.6% wt) of carbon black used in the cathodes unless replaced with Mo for complete bioresorption but slightly larger size for similar performance. Additionally, the use of optical mechanisms for device control and power represents a unique and innovative approach to managing and operating devices within the body. By eliminating the need for surgical intervention, this approach may also reduce the likelihood of long-term complications. However, it is essential to recognize that this research builds upon previous breakthroughs in bioresorbable electronics. Earlier works, such as those published in *Science* in 2002 and *Science Advances* in 2022 by the same PI, laid the groundwork in bioresorbable technology for medical applications. These seminal studies introduced pioneering concepts in bioresorbable materials and device designs that have significantly influenced subsequent technologies in this domain.

For all of that, the current study represents an incremental progression in the development of bioresorbable medical devices, building upon existing knowledge and techniques within the field of bioresorbable electronics. The integration of optical control and power mechanisms is innovative but does not represent a paradigm shift in the field. Instead, it reflects a natural evolution of the technology, marked by refinements and optimizations.

Our response: We thank the reviewer for these positive comments on the novelty of our mechanism and on the significance of our work. We want to declare that the current work is not a simple incremental progression on our prior works about bioresorbable electronics. This work represents significant key differences in the underlying concepts, in the engineering parameters and the clinical use cases. These differences allow for millimetre-scale pacemakers, suitable for implantation in a minimally invasive way and for unusual forms of integration within the body and/or on biomedical implants. These new platforms have particular value with paediatric patients. Currently, no pediatric pacemaker is available on the market, especially for newborns after open heart surgery for congenital heart defects. Unique opportunities are in integration with established medical implants, as demonstrated in the manuscript with first-of-a-kind pacemakers-integrated transcatheter aortic valve replacement (TAVR) systems, with additional opportunities across a wide range of applications in electrotherapy.

In the following, we further clarify and elucidate the significant advances that underpin our work and differentiate it from any previous research in the field of bioresorbable electronics including our own through a comparative analysis. The results appear in our response to the Reviewer's Specific Comment #1.

To address all of the reviewer’s concerns, we detailed our responses and associated modifications to our manuscript below.

Specific Comments: Besides this overall evaluation, several concerns have been raised during the review process about certain aspects of the work, which could be clarified and improved to enhance its value to the scientific community.

Our response: We thank the reviewer for the detailed comments and suggestions on our work. We believe that we can address the reviewer’s concerns and improve our manuscript, as outlined in our responses below and associated modifications to our manuscript.

Comment #1. One area that requires further elucidation is the extent to which the innovations presented represent a significant advance from previous research in the field. While the article highlights the incremental nature of the improvements, a comparative analysis with prior landmarks in bioresorbable electronics, including the authors' own previous work, could provide more context and insight into the novelty and impact of the current research.

Our response: We thank the reviewer for this constructive comment. To highlight the essential advances and key differentiating factors over previous research, we compared our devices with prior landmark achievements in bioresorbable electronics. Firstly, we compared our pacemaker with previously reported bioresorbable pacemakers (Table R1). With our newly introduced self-powered design, where asymmetric electrodes with different electrochemical potentials directly serve as the pacing electrodes, we are able to achieve millimetre-scale pacemakers, more than 21 times lighter by weight, 4.2 times shorter in length, and 5.5 times narrower in width than any previously reported bioresorbable pacemaker. These extreme, miniaturized dimensions allow implantation in a minimally invasive way, even via catheter delivery or, potentially, an injection. The small sizes, together with our unique optical methods for wireless activation and control, also create unusual opportunities for integration with established medical implants. Furthermore, through a wavelength-division multiplexed (WDM) technique, we are able to conduct multi-site pacing. None of these features are possible with previously reported concepts.

Table R1. Comparison between this work and previously reported bioresorbable pacemakers.

	This work	Bioresorbable pacemaker Nat Biotechnol 39, 1228–1238 (2021) Science376,1006-1012(2022)	Bioresorbable pacemaker Adv Healthc Mater 9, 1901342 (2020)
Design	Asymmetric pacing electrodes (with different electrochemical potentials)	RF receiver coil + symmetric pacing electrodes	Hydrogenated amorphous Si radial p–i–n junctions
Power supply	Self-powered	Wireless RF energy	Photovoltaic energy
Control method	Light	RF	Light
Implantation method	Injection – minimally invasive	Open-heart surgery	Open-heart surgery
Integration with other medical procedures	Integration with TAVR demonstrated	N/A	N/A
Programmability	Multi-site pacing demonstrated	N/A	N/A

Size	$\sim 1.8 \times 3.5 \times 1 \text{ mm}^3$	$\sim 40 \times 15 \times 0.25 \text{ mm}^3$	$\sim 15 \times 10 \times 0.015 \text{ mm}^3$
Weight	$\sim 13.8 \text{ mg}$	$\sim 300 \text{ mg}$	N/A
Operation	Skin-interfaced device with embedded LED for pulsed light stimulation	Skin-interfaced device with embedded RF transmission coil for pulsed energy transfer	Light source (not specified) + Optical fiber inserted into the body

RF: radio frequency; N/A: not available; LED: light emitting diodes.

We also compared our device to previously reported bioresorbable electrostimulators (Table R2). As before, the operating principles in our device are different, and thus allow for size scales that are orders of magnitude smaller than these alternatives, with similar consequent increases in options for implantation and clinical use.

Table R2. Comparison between this work and previously reported bioresorbable pacemakers.

	This work	Bioresorbable electronics – RF powered Sci. Adv.8,eabp9169(2022) Nat Med 24, 1830–1836 (2018)	Bioresorbable electronics – TENG/PENG powered Sci. Adv.2,e1501478(2016) PNAS 118 (28) e2100772118 (2021) Nano Energy 102, 107707 (2022)
Design	Asymmetric stimulating electrodes (with different electrochemical potentials)	RF receiver coil + symmetric stimulating electrodes	TENG/PENG + symmetric stimulating electrodes
Power supply	Self-powered	Wireless RF energy	Mechanical energy
Control method	Light	RF	Force/ultrasound
Implantation method	Injection – minimally invasive	Invasive surgery	Invasive surgery
Size	Millimetre-scale	Centimetre-scale	Centimetre-scale

Modifications to the draft: We added Tables R1 and R2 as Supplementary Tables 2 and 3.

On page 17, we added, “This system represents significant key differences in the underlying concepts, in the engineering parameters and the clinical use cases compared to previously reported bioresorbable electrostimulators (Supplementary Note 11 and Tables 2-3).”

In the Supporting Material on page 18 we added the following content.

Supplementary Note 11. Key conceptual differences and associated engineering advances of this platform compared to previously reported bioresorbable electrostimulators.

The millimetre-scale, bioresorbable optoelectronic system introduced here represents significant key differences in the underlying concepts, in the engineering parameters and the clinical use cases compared to previously reported bioresorbable electrostimulators. These differences allow for millimetre-scale pacemakers, suitable for implantation in a minimally invasive way and for unusual forms of integration. These platforms have particular value with paediatric patients. Unique opportunities are in integration with established medical implants, as demonstrated in the

main text with first-of-a-kind pacemakers-integrated transcatheter aortic valve replacement (TAVR) systems, with additional opportunities across a wide range of applications in electrotherapy.

Comparisons of our pacemaker with previously reported bioresorbable pacemakers (Supplementary Table 2) highlight key conceptual differences and associated engineering advances. The self-powered design, where asymmetric electrodes with different electrochemical potentials directly serve as the pacing electrodes, enables the realization of pacemakers with millimetre-scale dimensions, more than 21 times lighter by weight, 4.2 times shorter in length, and 5.5 times narrower in width than previously reported alternatives. This ultraminiaturized design allows for minimally invasive procedures for surgical implantation, including those based on transvenous catheters or injections. The technology also creates unique opportunities for integration with established medical implants. Furthermore, the optical control strategies support wavelength-division multiplexed (WDM) techniques for operation, to allow time-coordinated multi-site pacing, not achievable with other types of devices.

Additional comparisons involve previously reported bioresorbable electrostimulators (Supplementary Table 3). As before, the operating principles in devices reported here allow for size scales that are orders of magnitude smaller than these alternatives, with similar consequent increases in options for implantation and clinical use.

Newly added references in Supporting Material:

15. Choi, Y. S. *et al.* Fully implantable and bioresorbable cardiac pacemakers without leads or batteries. *Nat Biotechnol* **39**, 1228–1238 (2021).
16. Choi, Y. S. *et al.* A transient, closed-loop network of wireless, body-integrated devices for autonomous electrotherapy. *Science* (1979) **376**, 1006–1012 (2022).
17. Liu, Z. *et al.* Photoelectric Cardiac Pacing by Flexible and Degradable Amorphous Si Radial Junction Stimulators. *Adv Healthc Mater* **9**, 1901342 (2020).
18. Lee, G. *et al.* A bioresorbable peripheral nerve stimulator for electronic pain block. *Sci Adv* **8**, (2022).
19. Koo, J. *et al.* Wireless bioresorbable electronic system enables sustained nonpharmacological neuroregenerative therapy. *Nat Med* **24**, 1830–1836 (2018).
20. Yao, G. *et al.* A self-powered implantable and bioresorbable electrostimulation device for biofeedback bone fracture healing. *Proceedings of the National Academy of Sciences* **118**, (2021).
21. Wu, P. *et al.* Ultrasound-driven in vivo electrical stimulation based on biodegradable piezoelectric nanogenerators for enhancing and monitoring the nerve tissue repair. *Nano Energy* **102**, 107707 (2022).
22. Zheng, Q. *et al.* Biodegradable triboelectric nanogenerator as a life-time designed implantable power source. *Sci Adv* **2**, (2016).

Comment #2. Another issue that requires attention is the lack of detail on the device's operational lifespan and degradation kinetics within the body. Greater clarity on these aspects would help to establish the practical implications of the device's bioresorbability.

Our response: We thank the reviewer for mentioning this important point. We added below a discussion on the device's operational lifespan and degradation kinetics within the body.

Operational lifespan

We conducted additional benchtop and *in vivo* experiments to evaluate the operational lifespan of the device.

In benchtop experiments, we conducted electrochemistry impedance spectroscopy (EIS) measurements of devices on fresh chicken tissue and agarose gel (1 wt% agarose, 0.9 wt% NaCl and 0.5 wt% glycerol) to evaluate their impedance across a frequency range from 1 Hz to 10 kHz (Fig. R2a). The impedances of the agarose gel and chicken tissue are similar, ~ 500 Ohm at 1 kHz, corresponding to a ~ 1 ms pulse width during cardiac pacing. This result indicates that the agarose gel can serve as a phantom tissue to mimic the physiological impedance.

We then sandwiched the pacing electrodes in the agarose gel at 37 °C. The pacing electrodes, the phototransistor, and a current measurement module (PalmSens4) were electrically connected in series. A function generator (Rigol) powered the LEDs and generated pulsed illumination with a frequency of 1 Hz and a pulse width of 5 ms on the phototransistor. The output current of the pacemaker was measured every 6 h. As shown in Fig. R2b-c, the pacemaker can maintain a stable output for up to 16 days.

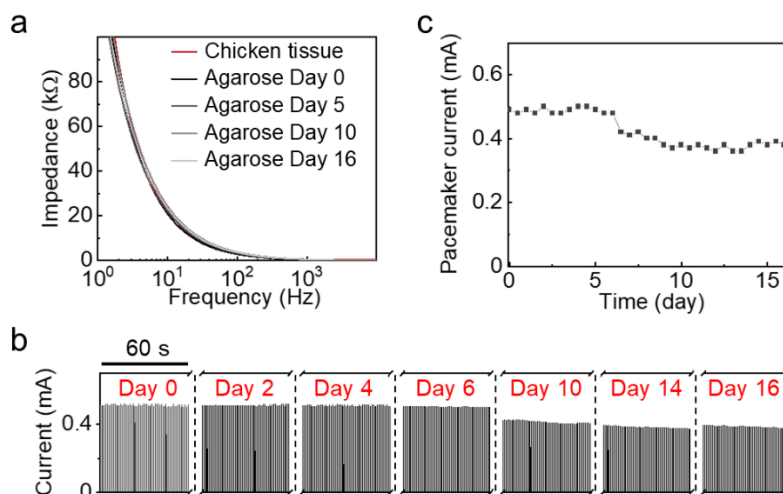


Fig. R2. Measurement of the operational lifespan of the device. (a) EIS of an agarose gel and chicken tissue at a frequency range from 1 Hz to 10 kHz. (b) The output currents of the pacemaker over days. (c) Output currents of the pacemaker over days under pulsed illumination.

The *in vivo* experiments were conducted in rat model. Pacemakers were sutured onto the surfaces of the hearts, and then the chest cavity was closed using surgical procedures described previously [Nat Protoc 18, 374–395 (2023)]. We triggered cardiac pacing through pulsed light illumination daily and recorded the ECG. The results (Fig. R3) show that the pacemakers made of the Mg-MoO₃ and Zn-MoO₃ pairs can function *in vivo* for up to 6 and 20 days post implantation, respectively. This timescale exceeds requirements in temporary pacing with an average duration of 4.2 days [Revista Española de Cardiología (English Edition) 57, 1045–1052 (2004)].

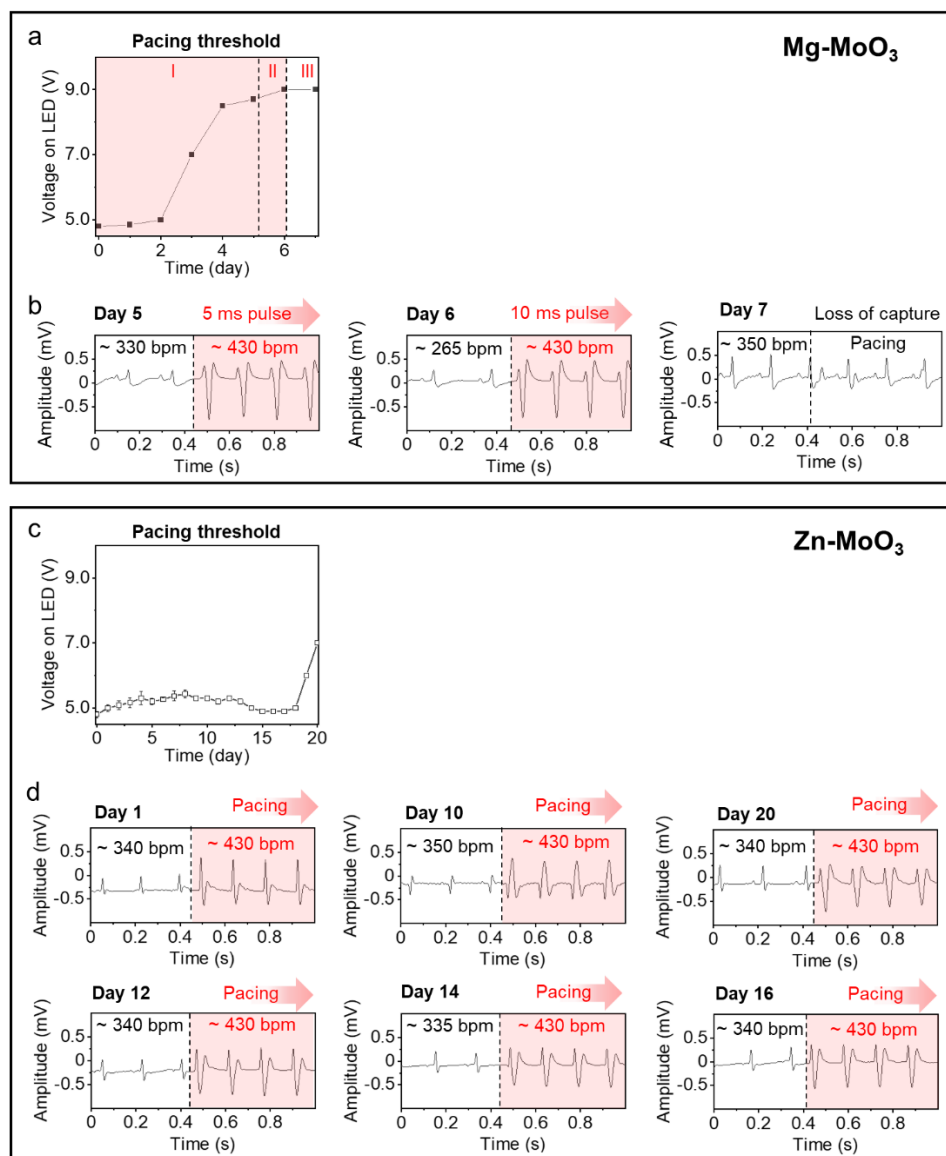


Fig. R3. Measurement of *in vivo* operational lifespan of the device. (a,c) Changes on the pacing threshold (minimum voltage applied on the NIR LED) after the implantation of pacemakers made of Mg-MoO₃ (a) and Zn-MoO₃ (c, pulse width: 5 ms) pairs. Phase I: capture under 5 ms pulse; Phase II: capture under 10 ms pulse; Phase III: loss of capture under 10 ms pulse. (b,d) ECG signal before and during pacing. Pacemakers utilize Mg-MoO₃ (b) and Zn-MoO₃ (d, pulse width: 5 ms) pairs. n = 4 biologically independent animals.

Degradation kinetics

The main components of the device are Mg/Zn, Mo, MoO₃, Si, and polyanhydride (PA). The biodegradation mechanisms and rates of these materials are summarized in Table R3. The products of degradation of Mg/Zn, Mo, MoO₃, Si, and PA are Mg(OH)₂/Zn(OH)₂, H₂MoO₄, H₂MoO₄, Si(OH)₄, and carboxylic acids, respectively. Each of these products is water soluble and can be harmlessly excreted in the urine [Adv. Funct. Mater. 24, 645–658 (2014); Proceedings of the National Academy of Sciences 120 (11) e2217734120 (2023); Corros. Sci. 49, 1696–1701 (2007); Small 14, 1800994 (2018); Microporous Mesoporous Mater. 131, 314–320 (2010); Adv. Funct.

Mater. 30, 2000941 (2020)]. H₂, as an additional degradation product of Mg/Zn and Si, dissolves into the adjacent tissues, diffuses through these tissues and blood vessels, and can pass through the skin [Acta Biomater. 9, 8714–8721 (2013)].

Table R3. The biodegradation mechanism, rates, and degraded products of device components in this work.

Bioresorption	Mechanism	Rate/solubility	Degraded products
Mg	$\text{Mg} + 2\text{H}_2\text{O} \rightarrow \text{Mg}(\text{OH})_2 + \text{H}_2$	$\sim 1 \mu\text{m/day}$ (PBS, pH 7.4, 37 °C)	$\text{Mg}(\text{OH})_2$, H ₂
Zn	$\text{Zn} + 2\text{H}_2\text{O} \rightarrow \text{Zn}(\text{OH})_2 + \text{H}_2$	$\sim 0.18 \mu\text{m/day}$ (PBS, pH 7.4, 37 °C)	$\text{Zn}(\text{OH})_2$, H ₂
Mo	$2\text{Mo} + 2\text{H}_2\text{O} + 3\text{O}_2 \rightarrow 2\text{H}_2\text{MoO}_4$	$\sim 0.025 \mu\text{m/day}$ (PBS, pH 7.4, 37 °C)	H ₂ MoO ₄
MoO ₃	$\text{MoO}_3 + \text{H}_2\text{O} \rightarrow \text{H}_2\text{MoO}_4$	Solubility ($\sim 1 \text{ g/L}$)	H ₂ MoO ₄
Si	$\text{Si} + 4\text{H}_2\text{O} \rightarrow \text{Si}(\text{OH})_4 + 2\text{H}_2$	$\sim 23 \text{ nm/day}$ (artificial cerebrospinal fluid, pH 7.4, 37 °C)	$\text{Si}(\text{OH})_4$, H ₂
PA	Hydrolysis of the anhydride bond, surface erosion	PA 1:1:2.5: $\sim 4 \mu\text{m/day}$; PA 1:4:7: $\sim 0.15 \mu\text{m/day}$ (PBS, pH 7.4, 37 °C)	Carboxylic acids

PA 1:1:2.5 or 1:4:7: the ratio of 4-pentenoic anhydride (4PA), 1,3,5-Triallyl-1,3,5-triazine-2,4,6-(1H,3H,5H)-trione (TTT), and 1,4-butanedithiol (BDT).

Modifications to the draft: We added Fig. R2 as Extended Data Fig. 3. We added Fig. R3 in Fig. 3i and Supplementary Fig. 18. We added Table R3 as Supplementary Table 1.

On page 7, we added, “The device exploits a self-powered mechanism, where the battery electrodes are the pacing electrodes. Specifically, an active, bioresorbable Mg alloy AZ31 (Mg₉₆Al₃Zn₁) foil or Zn composite (1.6 mm × 1.6 mm) serves as the anode, and a more electropositive bioresorbable molybdenum trioxide (MoO₃) composite (1.6 mm × 1.6 mm) serves as the cathode. The cardiac tissue and associated biofluids act as the electrolyte to form a galvanic cell/battery (Mg-MoO₃ or Zn-MoO₃). As a demonstration, the pacemaker utilizes the Mg-MoO₃ pair if not otherwise specified.”

On page 10, we added, “Discharge profiles of the Mg-MoO₃ pacing pairs (Extended Data Fig. 3) in agarose gel at 37 °C indicate an ability to operate continuously for ~ 16 days at currents, rates, and pulse widths of $\sim 0.4 - 0.5 \text{ mA}$, 60 bpm, and 5 ms, respectively.”

On page 29, we added, “Mixing 0.5 g Zn powder (Sigma Aldrich, size: 40 - 60 nm), 0.04 g carbon black, and 800 μL of 300 mg/mL PLGA in ethyl acetate formed a Zn slurry. Zn foil (50 μm thick, Goodfellow) served as current collectors for the Zn anode materials. The Zn slurry was applied on both sides of the Zn current collectors, followed by baking at 120 °C for 50 min. The Zn anodes were then sintered in 5 wt% acetic acid aqueous solution at room temperature for 30 min and dried in the air.”

On page 12, we added, “*In vivo* experiments in rat models define the operational lifespan. Pacemakers were sutured onto the surfaces of the hearts, and then the chest cavity was closed using surgical procedures described previously⁴⁰. Pulsed light illumination triggers cardiac pacing daily. The results (Fig. 3i, Supplementary Fig. 18) show that pacemakers made of Mg-MoO₃ and Zn-MoO₃ pairs can function *in vivo* for up to 6 and 20 days post implantation, respectively. This timescale exceeds requirements in temporary pacing with an average duration of 4.2 days³².”

In the Supporting Material on page 13 we added “**Supplementary Note 5. Discussion on the device's operational lifespan.**”

In benchtop experiments, we conducted electrochemistry impedance spectroscopy (EIS) measurements on fresh chicken tissue and agarose gel (1 wt% agarose, 0.9 wt% NaCl and 0.5 wt% glycerol) to evaluate their impedance across a frequency range from 1 Hz to 10 kHz. The impedances of the agarose gel and chicken tissue are similar, ~500 Ohm at 1 kHz, corresponding to a ~ 1 ms pulse width during cardiac pacing. This result indicates that the agarose gel can serve as a phantom tissue to mimic the physiological impedance. We then sandwiched the pacing electrodes in the agarose gel at 37 °C. The pacing electrodes, the phototransistor, and a current measurement module (PalmSens4) were electrically connected in series. A function generator (Rigol) powered the LEDs and generated pulsed illumination with a frequency of 1 Hz and a pulse width of 5 ms on the phototransistor. The output current of the pacemaker was measured every 6 h. As shown in Extended Data Fig. 3, the pacemaker can maintain a stable output for up to 16 days.”

In the Supporting Material on page 11 we added “The main components of the device are Mg/Zn, Mo, MoO₃, Si, and polyanhydride (PA). The biodegradation mechanisms and rates of these materials are summarized in Supplementary Table 1. The products of degradation of Mg/Zn, Mo, MoO₃, Si, and PA are Mg(OH)₂/Zn(OH)₂, H₂MoO₄, H₂MoO₄, Si(OH)₄, and carboxylic acids, respectively. Each of these products is water soluble and can be harmlessly excreted in the urine.^{1,4–8} H₂, as an additional degradation product of Mg/Zn and Si, dissolves into the adjacent tissues, diffuses through these tissues and blood vessels, and can pass through the skin.⁹

Newly added references in Supporting Material:

1. Choi, Y. S. *et al.* Biodegradable Polyanhydrides as Encapsulation Layers for Transient Electronics. *Adv Funct Mater* **30**, 2000941 (2020).
4. Yin, L. *et al.* Dissolvable Metals for Transient Electronics. *Adv Funct Mater* **24**, 645–658 (2014).
5. Song, G. Control of biodegradation of biocompatible magnesium alloys. *Corros Sci* **49**, 1696–1701 (2007).
6. Zhang, Y. *et al.* Self-powered, light-controlled, bioresorbable platforms for programmed drug delivery. *Proceedings of the National Academy of Sciences* **120**, (2023).
7. Huang, X. *et al.* A Fully Biodegradable Battery for Self-Powered Transient Implants. *Small* **14**, 1800994 (2018).
8. He, Q., Shi, J., Zhu, M., Chen, Y. & Chen, F. The three-stage in vitro degradation behavior of mesoporous silica in simulated body fluid. *Microporous and Mesoporous Materials* **131**, 314–320 (2010).
9. Kuhlmann, J. *et al.* Fast escape of hydrogen from gas cavities around corroding magnesium implants. *Acta Biomater* **9**, 8714–8721 (2013).

Comment #3. Furthermore, while the use of bioresorbable materials suggests improved safety and biocompatibility, specific data on these parameters are lacking. Studies or data on the biocompatibility of the materials used and any potential inflammatory responses would enhance the credibility of the device's application in clinical settings.

Our response: We thank the reviewer for this constructive suggestion. We conducted additional animal experiments to study the *in vivo* biocompatibility of our device in rat model. The device group (n = 3) and a control group of high-density polyethylene (HDPE, U.S. Food and Drug Administration–approved nontoxic material) (n = 3) were sutured onto the heart surfaces of rats. Rats were checked at regular time intervals. Blood and heart tissues adjacent to the implants were collected at 1- and 4-week endpoints. Heart tissues were fixed in 10% neutral-buffered formalin and embedded in paraffin. Cross-sectional samples were stained with hematoxylin and eosin (H&E) for histological analysis. Weights of animals and analysis of complete blood counts and blood chemistry tests (Fig. R4) show no statistically significant differences between the control and the device groups (significance level $P < 0.05$, One-Way ANOVA), suggesting the biocompatibility of the device. Fig. R5 shows representative images of the stained cross-sectional areas near the site of implantation. Animals euthanized and examined at the end of 1 and 4 weeks exhibited mild to moderate inflammatory cell infiltration, consisting of macrophages, lymphocytes, and plasma cells at the implantation site. The epicardial mixed-cell inflammation was comparable for control and device groups. At the end of 1 week, moderate inflammatory responses are observed in the device group with localized inflammatory exudate and noticeable proliferation of macrophages. At the end of 4 weeks, the device group shows alleviated inflammation, likely due to the natural healing process of the body and the attenuation of the initial inflammatory response. Control and device groups show comparable mild responses at the end of 4 weeks.

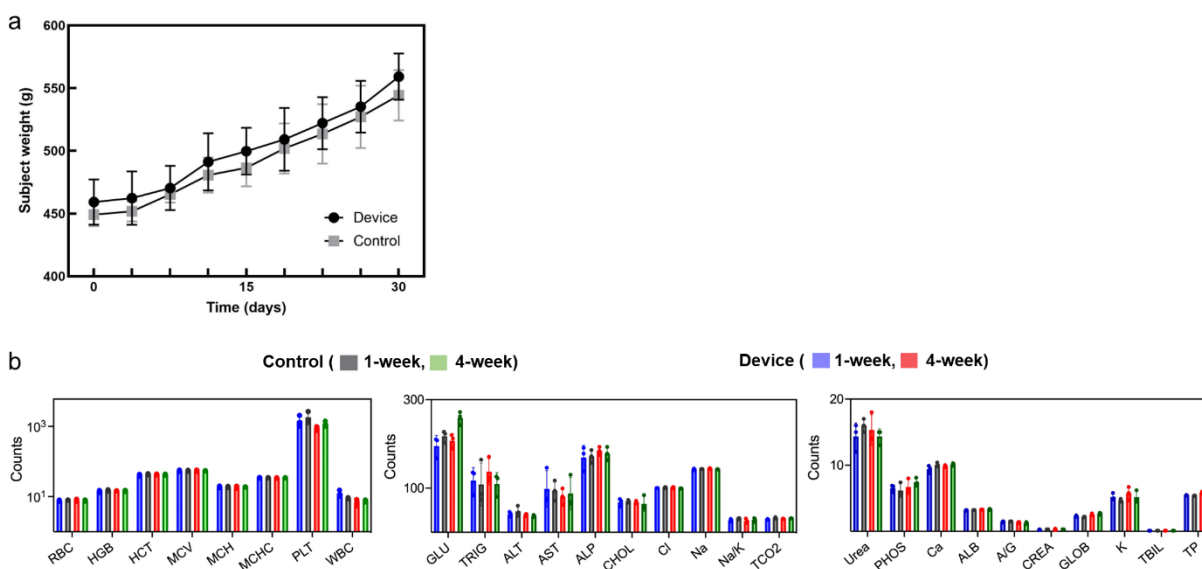


Fig. R4. (a) Weight changes of animals after the implantation of control and device groups. (b) Analysis of complete blood counts and blood chemistry after implantation of control and device groups at 1-week and 4-week endpoints. RBC, red blood cell ($\times 1,000,000 \mu\text{l}^{-1}$); HGB, blood haemoglobin level (g dl^{-1}); HCT, haematocrit level (%); MCV, mean corpuscular volume (fl); MCH, mean corpuscular haemoglobin (pg); MCHC, mean corpuscular hemoglobin concentration (g dl^{-1}); PLT, platelet count in blood ($\times 1,000 \mu\text{l}^{-1}$); WBC, white blood cell ($\times 1,000 \mu\text{l}^{-1}$); GLU, glucose (mg dl^{-1}); TRIG, triglycerides (mg dl^{-1}); ALT, alanine aminotransferase (U l^{-1}); AST, aspartate transaminase (U l^{-1}); ALP, alkaline phosphatase (U l^{-1}); CHOL, cholesterol (mg dl^{-1}); Cl, chloride (mmol l^{-1}); Na, sodium (mmol l^{-1}); Na/K, sodium/potassium ratio; TCO2, bicarbonate (mmol l^{-1}); Urea, blood urea nitrogen (mg dl^{-1}); PHOS, phosphorus (mg dl^{-1}); Ca, calcium (mg dl^{-1}); ALB, albumin (g dl^{-1}); A/G, albumin/globulin; CREA, creatinine (mg dl^{-1}); GLOB, globulin (g dl^{-1}); K, potassium (mmol l^{-1}); TBIL, total bilirubin (mg dl^{-1}); TP, total protein (g dl^{-1}). Data are presented with error bars as means $\pm$ s.d. n = 3 biologically independent animals.

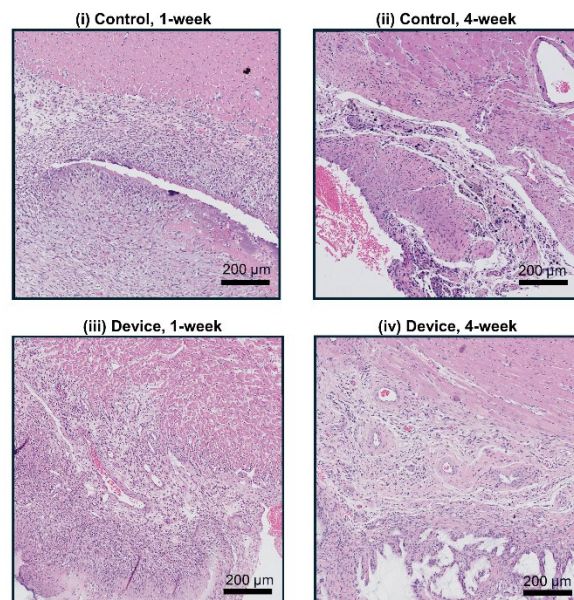


Fig. R5. Representative images of H&E-stained cross-sectional areas near the site of implantation of control and device groups at the 1-week and 4-week endpoints. $n = 3$ biologically independent animals. Scale bar: 200 μm . (i) Around the cavities of the implantation site, the infiltration of varying numbers of mononuclear macrophages, lymphocytes, and plasma cells are observed. Overall, there is a mild to moderate inflammatory response, accompanied by stromal fibrous tissue hyperplasia and myxoid degeneration. (ii) Fibrous tissue hyperplasia is observed around the implantation site, with localized aggregation of macrophages (mild inflammation), some of which show pigment deposition from phagocytosed red blood cells. The proliferation of small blood vessels is present in the surrounding area, with the scattered distribution of some atypical, deeply stained cells. (iii) Localized inflammatory exudate is observed adjacent to the implantation site, with significant proliferation of macrophages. In the stroma distant from the implant site, there is fibrous tissue hyperplasia accompanied by numerous macrophages, lymphocytes, and plasma cell infiltration. Lymphocyte and plasma cell infiltration can also be seen between adjacent myocardial tissues. Overall, a moderate inflammatory response is present, with exudation and necrosis resulting from acute inflammation. (iv) After the biosorption of the material, irregular cavity distribution is observed, seemingly with myxoid-like substances. There is a marked proliferation of mesothelial-like cells around the cavities, with scattered lymphocyte infiltration (mild inflammation) and proliferation of fibrous tissue and blood vessels in the stroma.

Modifications to the draft: We added Figs. R4 and R5 as Supplementary Fig. 10.

In the Method section on page 39, we added, “Studies involve a device group ($n = 3$) and a control group of high-density polyethylene (HDPE, U.S. Food and Drug Administration–approved nontoxic material) ($n = 3$), each sutured onto the surface of the heart. Animals were weighed every three days to monitor weight loss and health status post-surgery. Blood and heart tissues adjacent to the implants were collected at 1- and 4-week endpoints. Heart tissues were fixed in 10% neutral-buffered formalin and embedded in paraffin. Cross-sectional samples were stained with hematoxylin and eosin (H&E) for histological analysis.”

In the Supporting Material on page 10 we added “**Supplementary Note 2. Discussion on the device's biocompatibility.**”

Weights of animals and analysis of complete blood counts and blood chemistry tests (Supplementary Fig. 10a,b) show no statistically significant differences between the control and the device groups (significance level $P < 0.05$, One-Way ANOVA), suggesting the biocompatibility of the device. Fig. R5 shows representative images of the stained cross-sectional areas near the site of implantation. Animals euthanized and examined at the end of 1 and 4 weeks exhibited mild to moderate inflammatory cell infiltration, consisting of macrophages, lymphocytes, and plasma cells at the implantation site. The epicardial mixed-cell inflammation was comparable for control and device groups. At the end of 1 week, moderate inflammatory responses are observed in the device group with localized inflammatory exudate and noticeable proliferation of macrophages. At the end of 4 weeks, the device group shows alleviated inflammation, likely due to the natural healing process of the body and the attenuation of the initial inflammatory response. Control and device groups show comparable mild responses at the end of 4 weeks.”

Comment #4. The article could also benefit from more comprehensive technical specifications, including details on energy requirements, efficiency of the optical control mechanism, and the range of operable conditions, such as depth within tissue.

Our response: We thank the reviewer for this suggestion. We added the following discussions to provide more comprehensive technical specifications.

Energy requirements

Fig. R6a shows the relationship between the light intensity and the output current of the pacemaker. Fig. R6b plots the simulated normalized light intensity received by the phototransistor part of the device at various tissue depths beneath the skin. For adults, the average shortest distance between the surface of the skin and the surface of the heart is ~ 30 mm. For a device implanted at this depth, the light intensities required on the skin surface for different pacemaker outputs are plotted in Fig. R6c. These results suggest that the required light intensity increases with increasing pacemaker output. For example, a current of 0.64 mA from the pacemaker requires an intensity of ~ 10.6 mW mm $^{-2}$ at the surface of the skin, well within a safe range for human exposure [Nat Biotechnol 39, 161–164 (2021)].

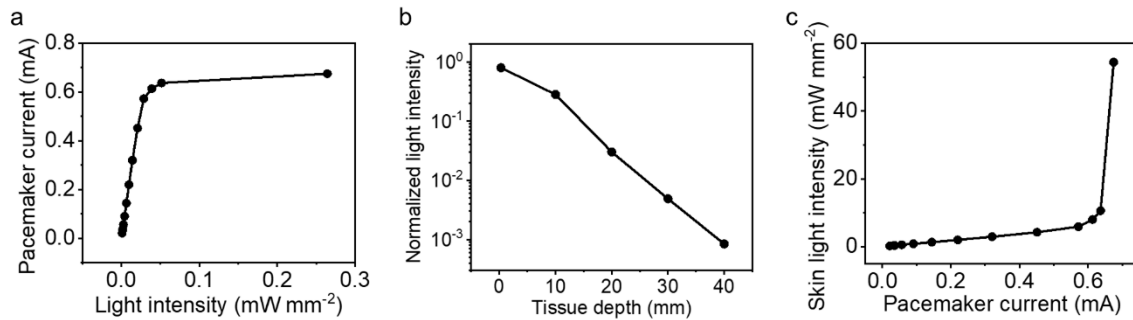


Fig. R6. Technical specifications of the device. (a) Output currents of a pacemaker as a function of light intensity. (b) Percentage of light received by the PT at various depths beneath the skin. (c) Light intensities required on the skin surface for different pacemaker outputs with the pacemaker implanted 30 mm deep beneath the skin.

Efficiency of the optical control mechanism

As shown above (Fig. R6b), the light intensity drops to 28%, 3.0%, 0.49%, and 0.08% at tissue depths of 10, 20, 30, and 40 mm, respectively.

Fig. R7 shows the temporal response of a pacemaker under pulsed light illumination. The rise and fall times are less than 25 μ s, far beyond the requirements for cardiac pacing.

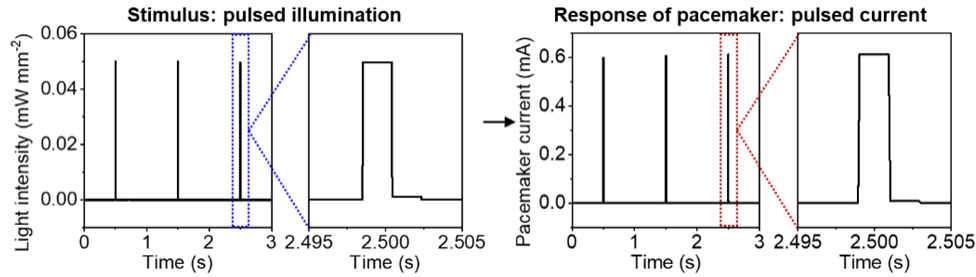


Fig. R7. Temporal response of a pacemaker under pulsed light illumination.

Range of operable conditions

To provide a comprehensive range of operable conditions, we plotted the required light intensities on the skin surface for different pacemaker outputs at tissue depths of 10, 20, 30, and 40 mm (Fig. R8). These results suggest that the required light intensity increases with increasing pacemaker output at a specific implantation depth. In addition, increasing the depth of implantation increases the required light input on the surface of the skin, for a given pacemaker output.

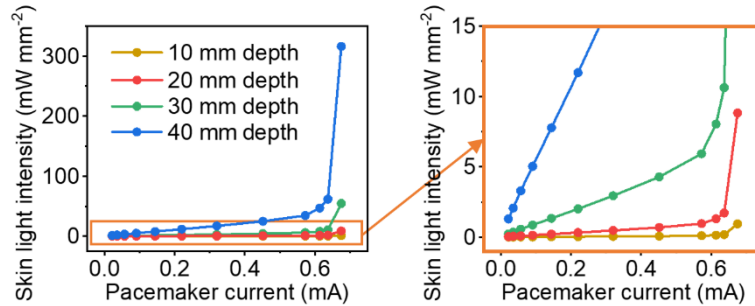


Fig. R8. Light intensities required on the skin surface for different pacemaker's outputs under tissue depths of 10, 20, 30, and 40 mm.

Calculations on the maximum permissible exposures for skin safety

According to the American National Standard for Safe Use of Lasers Guidelines ANSI Z136.1, we calculated the maximum permissible exposures (MPE) for skin safety for 850 nm light when pulsed at a frequency of 1 Hz with a duration of 2 ms. In this work, we utilized multiple-pulsed (repetitive-pulsed) light. Two rules apply for the case of the skin safety. The exposure is evaluated according to each rule to determine a set of possible MPEs, and the most restrictive MPE in the set is taken as the MPE for the exposure.

The wavelength correction factor C_A for 850 nm is

$$C_A = 10^{0.002(\lambda-700)} = 10^{0.002(850-700)} = 1.995$$

where λ is the wavelength of the light.

Rule 1: Single-Pulse MPE

The exposure from any single pulse in a train of pulses shall not exceed the MPE for the duration of the pulse. Rule 1 protects against injury from any single pulse having greater than average energy.

The MPE:H for a single 2 ms pulse is

$$\text{MPE: H} = 1.1 \times C_A \times t^{0.25} = 1.1 \times 1.995 \times 0.002^{0.25} = 0.464 \text{ J cm}^{-2}$$

where t is the duration of exposure, MPE:H is radiant exposure for a single pulse or exposure (J cm^{-2}).

In terms of peak irradiance,

$$\text{MPE: E} = \frac{\text{MPE: H}}{t_p} = \frac{0.464}{0.002} = 232 \text{ W cm}^{-2}$$

where t_p is the pulse duration, MPE:E is the maximum permissible irradiance (W cm^{-2}).

Rule 2: Average-Power MPE for Thermal and Photochemical Hazards

The exposure from any grouping of pulses within the train of pulses shall not exceed the MPE for the duration of the grouping. Rule 2 protects against cumulative injury from photochemical damage mechanisms and also against heat buildup.

Consider the MPE for a 10 s exposure,

$$\text{MPE: H}_{\text{Group}} = 1.1 \times C_A \times t^{0.25} = 1.1 \times 1.995 \times 10^{0.25} = 3.9 \text{ J cm}^{-2}$$

where MPE:H_{Group} is the radiant exposure for the summation of all the energy in a group of pulses (J cm^{-2}).

The MPE:H/pulse based on a 10 s exposure is

$$\text{MPE: H/pulse} = \frac{3.9 \text{ J cm}^{-2}}{10 \text{ pulses}} = 0.39 \text{ J cm}^{-2}$$

In terms of peak irradiance,

$$\text{MPE: E} = \frac{\text{MPE: H/pulse}}{t_p} = \frac{0.39}{0.002} = 195 \text{ W cm}^{-2}$$

The lower MPE value calculated from above two rules is taken as the MPE for the exposure. Therefore, the peak irradiance must be kept within 195 W cm^{-2} (1950 mW mm^{-2}). This result indicates that the device can reliably be implanted up to ~60 mm deep in the body, with the light magnitude manageable.

Modifications to the draft: We added Figs. R6 and R8 as Supplementary Figs. 11-12. Fig. R7 was shown as Fig. 2a.

In the Supporting Material on page 12 we added the following contents.

Supplementary Note 4. Discussion on the device's technical specifications.

Energy requirements

Supplementary Fig. 11a shows the relationship between the light intensity and the output current of the pacemaker. Supplementary Fig. 11b plots the simulated normalized light intensity received by the phototransistor part of the device at various tissue depths beneath the skin. For adults, the average shortest distance between the surface of the skin and the surface of the heart is ~30 mm. For device implanted at this depth, the light intensities required on the skin surface for different pacemaker outputs are plotted in Supplementary Fig. 11c. These results suggest that the required light intensity increases with increasing pacemaker output. For example, a current of 0.64 mA from the pacemaker requires an intensity of ~ 10.6 mW mm⁻² at the surface of the skin, well within a safe range for human exposure¹⁴.

Efficiency of the optical control mechanism

As shown in Supplementary Fig. 11b, the light intensity drops to 28%, 3.0%, 0.49%, and 0.08% at tissue depths of 10, 20, 30, and 40 mm, respectively.

Fig. 2a shows the temporal response of a pacemaker under pulsed light illumination. The rise and fall times are less than 25 μs, far beyond the requirements for cardiac pacing.

Range of operable conditions

To provide a comprehensive range of operable conditions, we plotted the required light intensities on the skin surface for different pacemaker outputs at tissue depths of 10, 20, 30, and 40 mm (Supplementary Fig. 12). These results suggest that the required light intensity increases with increasing pacemaker output at a specific implantation depth. In addition, increasing the depth of implantation increases the required light input on the surface of the skin, for a given pacemaker output.

Supplementary Note 6. Calculations on the maximum permissible exposures for skin safety.

According to the American National Standard for Safe Use of Lasers Guidelines ANSI Z136.1, we calculated the maximum permissible exposures (MPE) for skin safety for 850 nm light when pulsed at a frequency of 1 Hz with a duration of 2 ms. In this work, we utilized multiple-pulsed (repetitive-pulsed) light. Two rules apply for the case of the skin safety. The exposure is evaluated according to each rule to determine a set of possible MPEs, and the most restrictive MPE in the set is taken as the MPE for the exposure.

The wavelength correction factor C_A for 850 nm is

$$C_A = 10^{0.002(\lambda-700)} = 10^{0.002(850-700)} = 1.995$$

where λ is the wavelength of the light.

Rule 1: Single-Pulse MPE

The exposure from any single pulse in a train of pulses shall not exceed the MPE for the duration of the pulse. Rule 1 protects against injury from any single pulse having greater than average energy.

The MPE:H for a single 2 ms pulse is

$$\text{MPE:H} = 1.1 \times C_A \times t^{0.25} = 1.1 \times 1.995 \times 0.002^{0.25} = 0.464 \text{ J cm}^{-2}$$

where t is the duration of exposure, MPE:H is radiant exposure for a single pulse or exposure (J cm^{-2}).

In terms of peak irradiance,

$$\text{MPE:E} = \frac{\text{MPE:H}}{t_p} = \frac{0.464}{0.002} = 232 \text{ W cm}^{-2}$$

where t_p is the pulse duration, MPE:E is the maximum permissible irradiance (W cm^{-2}).

Rule 2: Average-Power MPE for Thermal and Photochemical Hazards

The exposure from any grouping of pulses within the train of pulses shall not exceed the MPE for the duration of the grouping. Rule 2 protects against cumulative injury from photochemical damage mechanisms and also against heat buildup.

Consider the MPE for a 10 s exposure,

$$\text{MPE:H}_{\text{Group}} = 1.1 \times C_A \times t^{0.25} = 1.1 \times 1.995 \times 10^{0.25} = 3.9 \text{ J cm}^{-2}$$

where $\text{MPE:H}_{\text{Group}}$ is the radiant exposure for the summation of all the energy in a group of pulses (J cm^{-2}).

The MPE:H/pulse based on a 10 s exposure is

$$\text{MPE:H/pulse} = \frac{3.9 \text{ J cm}^{-2}}{10 \text{ pulses}} = 0.39 \text{ J cm}^{-2}$$

In terms of peak irradiance,

$$\text{MPE:E} = \frac{\text{MPE:H/pulse}}{t_p} = \frac{0.39}{0.002} = 195 \text{ W cm}^{-2}$$

The lower MPE value calculated from above two rules is taken as the MPE for the exposure. Therefore, the peak irradiance must be kept within 195 W cm^{-2} (1950 mW mm^{-2}). This result indicates that the device can reliably be implanted up to ~60 mm deep in the body, with the light magnitude manageable.

Newly added references in Supporting Material:

14. Chen, R. *et al.* Deep brain optogenetics without intracranial surgery. *Nat Biotechnol* **39**, 161–164 (2021).

Reviewer #3

General Comments: Authors describe a possibly revolutionary resorbable temporary pacemaker system guided by transcutaneous illumination. The described device seems to be a working model in open chest and prepared heart models. Some data suggest that myocardial stimulation even in skinny animal models were possible, when the pacemaker nodule was within 3-4 cm below the skin surface. Further benefit of the system is that multi site pacing seems to be manageable with the utilisation of different wavelengths.

The resorbable characteristics of the device seems to be promising, however clinical usability seems to be questionable.

I agree with the statement, that this concept will be best used in paediatric (small chest size) population.

Our response: We thank the reviewer for considering that our work is “revolutionary” and for pointing out the benefit and the best use case of this system. We believe that we can address the reviewer’s concerns, including the clinical usability of the resorbable characteristics. Our responses and associated modifications to our manuscript are below.

Comment #1. The device would be activated by a soft, skin-interfaced wireless device, which emits light in the NIR range. According to the given data the light absorption is quite significant, as in 4 cm depth- 0.001 of the light emitted over the skin could be simulated. On Fig 3b: Optical simulation does not take in account the ribs as in the current figure- is the absorption coefficient really so close to the soft tissue as in the model? I am really critical on this point.

Our response: We appreciate the reviewer's attention to this crucial point. The reviewer is correct that the light attenuation in the tissue is quite significant, with only 0.08% of the light penetrating through a 4 cm thick tissue. However, our device requires only a minimal amount of light to trigger because light does not contribute to the energy of stimulation; it only triggers it. The device is self-powered by asymmetric electrodes with different electrochemical potentials directly as the pacing electrodes. These electrodes and the cardiac tissue form a battery that provides power for the pacing process. The light-sensitive component (phototransistor) acts only as a light-controlled passive switch. A small amount of light (0.05 mW mm^{-2}) is sufficient to open the switch. For a pacemaker implanted at tissue depths of 10, 20, 30, and 40 mm, an output current of 0.64 mA from the pacemaker requires light intensities of ~ 0.18 , ~ 1.72 , ~ 10.6 , and $\sim 61.7 \text{ mW mm}^{-2}$ at the surface of the skin, respectively. These values are all well within a safe range for human exposure [Nat Biotechnol 39, 161–164 (2021)].

We also appreciate your critical comment regarding the inclusion of ribs in the optical simulation. We conducted additional simulations to re-calculate the light transport within the human body, with ribs and soft tissue. In our optical model, the absorption coefficient of ribs is approximately five times that of soft tissue (as detailed in the Methods - Optical Simulation section). We re-plotted Fig. 3b. Fig. R9a shows the normalized light intensity in the body when illuminating the skin of the chest with NIR light. We also plotted the normalized light intensity in the body as a function of tissue depth (Fig. R9b) along two parallel trajectories in the direction of the incident

light: one passing through the ribs and the other penetrating only soft tissue. These results reveal that the ribs block more light than the soft tissue, as expected. However, due to strong light scattering within the body, the differences between areas underneath the ribs and soft tissues become less pronounced at deeper body locations.

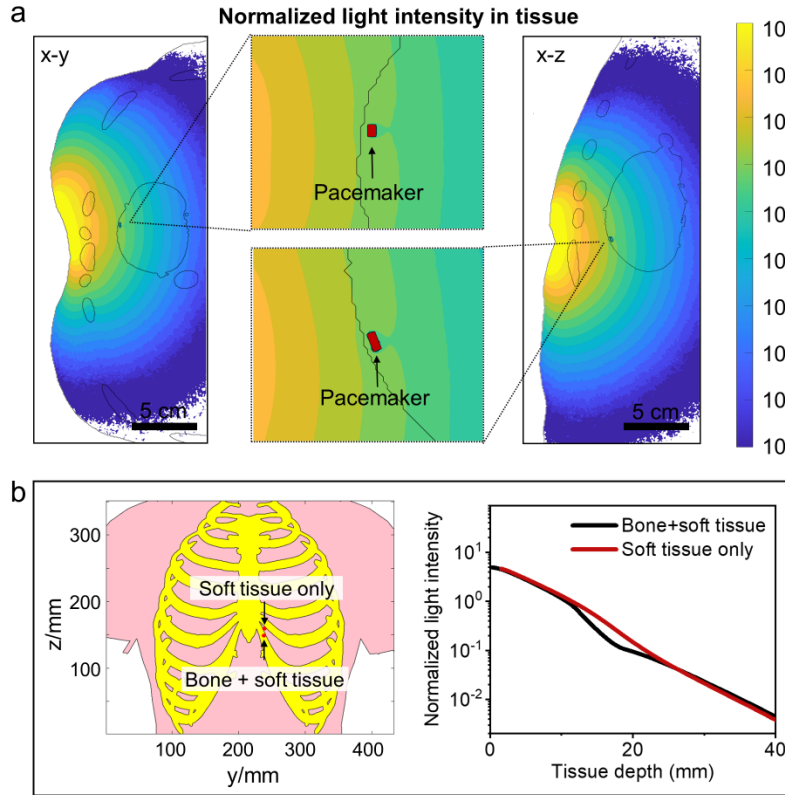


Fig. R9. (a) Optical simulation showing the normalized light intensity in the body when illuminating the skin of the chest with NIR light (850 nm). (b) Normalized light intensity in the body as a function of tissue depth along two parallel trajectories in the direction of the incident light: one passing through the ribs and the other penetrating only soft tissue.

Modifications to the draft: We replaced Fig. 3b with Fig. R9a. We added Fig. R9b as Supplementary Fig. 15a.

On page 9, we added, “As discussed earlier, the pacing electrodes and the cardiac tissue form a battery that provides power for the pacing process. The phototransistor acts only as a passive switch that can be activated at low intensities.”

On page 11, we added, “For a pacemaker implanted at tissue depths of 10, 20, 30, and 40 mm, an output current of 0.64 mA can be achieved with light intensities of ~ 0.18 , ~ 1.72 , ~ 10.6 , and ~ 61.7 mW mm $^{-2}$ at the surface of the skin. These values are all well within a safe range for human exposure¹⁴.”

On page 11, we added, “Fig. 3b reveals that the ribs block more light than the soft tissue. Due to strong light scattering within the body, differences between areas underneath the ribs and soft tissues become less pronounced with increased depth.”

Newly added references in Supporting Material:

14. Chen, R. *et al.* Deep brain optogenetics without intracranial surgery. *Nat Biotechnol* **39**, 161–164 (2021).

Comment #2. Furthermore, a greater number of patients will have the device deeper than 4cm with maximum depth up to 15 cm. Please add simulation until 10-15cm depth, with calculation of an effective light emission over the skin to reach adequate pacing output. Is this magnitude of light still reliably manageable for longer period of time?

Our response: We thank the reviewer for this comment. We extended the simulation to include tissue thicknesses up to 15 cm. Fig. R10a displays the normalized light intensity at various depths beneath the skin. The required light intensities on the skin necessary to achieve an adequate pacing output of 0.64 mA are plotted in Fig. R10b.

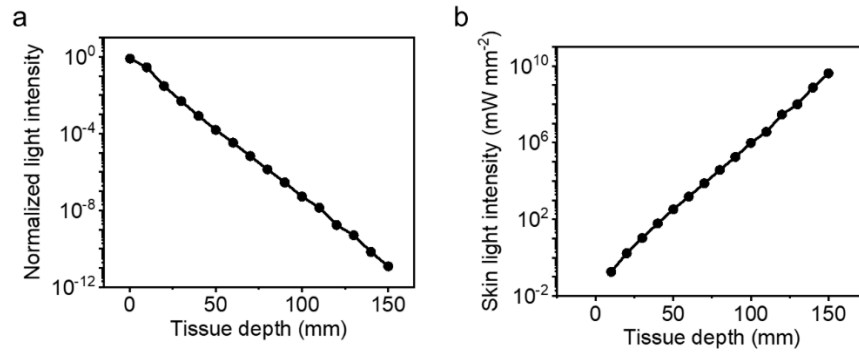


Fig. R10. Optical simulation results. (a) Percentage of light received by the PT at various depths beneath the skin. (b) Light intensities required on the skin surface to achieve an adequate pacing output of 0.64 mA for various implantation depths beneath the skin.

According to the American National Standard for Safe Use of Lasers Guidelines ANSI Z136.1, we calculated the maximum permissible exposures (MPE) for skin safety for 850 nm light when pulsed at a frequency of 1 Hz with a duration of 2 ms. In this work, we utilized multiple-pulsed (repetitive-pulsed) light. Two rules apply for the case of the skin safety. The exposure is evaluated according to each rule to determine a set of possible MPEs, and the most restrictive MPE in the set is taken as the MPE for the exposure.

The wavelength correction factor C_A for 850 nm is

$$C_A = 10^{0.002(\lambda-700)} = 10^{0.002(850-700)} = 1.995$$

where λ is the wavelength of the light.

Rule 1: Single-Pulse MPE

The exposure from any single pulse in a train of pulses shall not exceed the MPE for the duration of the pulse. Rule 1 protects against injury from any single pulse having greater than average energy.

The MPE:H for a single 2 ms pulse is

$$\text{MPE: H} = 1.1 \times C_A \times t^{0.25} = 1.1 \times 1.995 \times 0.002^{0.25} = 0.464 \text{ J cm}^{-2}$$

where t is the duration of exposure, MPE:H is radiant exposure for a single pulse or exposure (J cm^{-2}).

In terms of peak irradiance,

$$\text{MPE: E} = \frac{\text{MPE: H}}{t_p} = \frac{0.464}{0.002} = 232 \text{ W cm}^{-2}$$

where t_p is the pulse duration, MPE:E is the maximum permissible irradiance (W cm^{-2}).

Rule 2: Average-Power MPE for Thermal and Photochemical Hazards

The exposure from any grouping of pulses within the train of pulses shall not exceed the MPE for the duration of the grouping. Rule 2 protects against cumulative injury from photochemical damage mechanisms and also against heat buildup.

Consider the MPE for a 10 s exposure,

$$\text{MPE: } H_{\text{Group}} = 1.1 \times C_A \times t^{0.25} = 1.1 \times 1.995 \times 10^{0.25} = 3.9 \text{ J cm}^{-2}$$

where MPE: H_{Group} is the radiant exposure for the summation of all the energy in a group of pulses (J cm^{-2}).

The MPE:H/pulse based on a 10 s exposure is

$$\text{MPE: H/pulse} = \frac{3.9 \text{ J cm}^{-2}}{10 \text{ pulses}} = 0.39 \text{ J cm}^{-2}$$

In terms of peak irradiance,

$$\text{MPE: E} = \frac{\text{MPE: H/pulse}}{t_p} = \frac{0.39}{0.002} = 195 \text{ W cm}^{-2}$$

The lower MPE value calculated from above two rules is taken as the MPE for the exposure. Therefore, the peak irradiance must be kept within 195 W cm^{-2} (1950 mW mm^{-2}). This result indicates that the device can reliably be implanted up to ~60 mm deep in the body, with the light magnitude manageable.

For patients requiring device implantation deeper than 60 mm, we performed additional experimental work to modify our device design (Fig. R11) in a way that ensures reliable light management. Here, we configured the phototransistor (light-sensing component) to extend closer to the skin, while the pacing electrodes remain inserted into the heart. The pacing electrodes and phototransistor are electrically connected through serpentine interconnects.

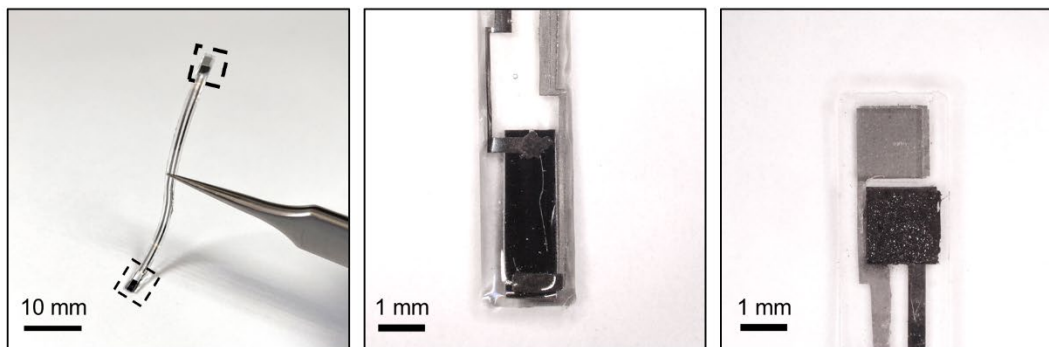


Fig. R11. Photographs of pacemakers with the extended phototransistor.

Modifications to the draft: We added Figs. R10-R11 as Supplementary Figs. 15b,c and 16.

On page 11 we added “Additional simulation results on tissue thicknesses up to 15 cm (Supplementary Fig. 15) and calculations on the maximum permissible exposures for skin safety (Supplementary Note 6) indicate that the device can reliably be implanted up to ~60 mm deep in the body. Modified device, with the phototransistor extended closer to the skin and pacing electrodes remained inserted into the heart, allows for pacing on deeper heart (Supplementary Fig. 16).”

In the Supporting Material on page 40 we added “This modified design is for patients requiring device implantation deeper than 60 mm, in a way that ensures reliable light management. Here, the phototransistor (light-sensing component) lies close to the surface of the skin, while the pacing electrodes remain inserted into the heart. The pacing electrodes and phototransistor electrically connect through serpentine interconnects.”

In the Supporting Material on page 14 we added the following contents.

Supplementary Note 6. Calculations on the maximum permissible exposures for skin safety.

According to the American National Standard for Safe Use of Lasers Guidelines ANSI Z136.1, we calculated the maximum permissible exposures (MPE) for skin safety for 850 nm light when pulsed at a frequency of 1 Hz with a duration of 2 ms. In this work, we utilized multiple-pulsed (repetitive-pulsed) light. Two rules apply for the case of the skin safety. The exposure is evaluated according to each rule to determine a set of possible MPEs, and the most restrictive MPE in the set is taken as the MPE for the exposure.

The wavelength correction factor C_A for 850 nm is

$$C_A = 10^{0.002(\lambda-700)} = 10^{0.002(850-700)} = 1.995$$

where λ is the wavelength of the light.

Rule 1: Single-Pulse MPE

The exposure from any single pulse in a train of pulses shall not exceed the MPE for the duration of the pulse. Rule 1 protects against injury from any single pulse having greater than average energy.

The MPE:H for a single 2 ms pulse is

$$\text{MPE: H} = 1.1 \times C_A \times t^{0.25} = 1.1 \times 1.995 \times 0.002^{0.25} = 0.464 \text{ J cm}^{-2}$$

where t is the duration of exposure, MPE:H is radiant exposure for a single pulse or exposure (J cm^{-2}).

In terms of peak irradiance,

$$\text{MPE: E} = \frac{\text{MPE: H}}{t_p} = \frac{0.464}{0.002} = 232 \text{ W cm}^{-2}$$

where t_p is the pulse duration, MPE:E is the maximum permissible irradiance (W cm^{-2}).

Rule 2: Average-Power MPE for Thermal and Photochemical Hazards

The exposure from any grouping of pulses within the train of pulses shall not exceed the MPE for the duration of the grouping. Rule 2 protects against cumulative injury from photochemical damage mechanisms and also against heat buildup.

Consider the MPE for a 10 s exposure,

$$\text{MPE: } H_{\text{Group}} = 1.1 \times C_A \times t^{0.25} = 1.1 \times 1.995 \times 10^{0.25} = 3.9 \text{ J cm}^{-2}$$

where MPE: H_{Group} is the radiant exposure for the summation of all the energy in a group of pulses (J cm^{-2}).

The MPE:H/pulse based on a 10 s exposure is

$$\text{MPE: H/pulse} = \frac{3.9 \text{ J cm}^{-2}}{10 \text{ pulses}} = 0.39 \text{ J cm}^{-2}$$

In terms of peak irradiance,

$$\text{MPE: E} = \frac{\text{MPE: H/pulse}}{t_p} = \frac{0.39}{0.002} = 195 \text{ W cm}^{-2}$$

The lower MPE value calculated from above two rules is taken as the MPE for the exposure. Therefore, the peak irradiance must be kept within 195 W cm^{-2} (1950 mW mm^{-2}). This result indicates that the device can reliably be implanted up to ~60 mm deep in the body, with the light magnitude manageable.

Comment #3. Further clinical question arises when the pacemaker nodules are fixated onto the TAVI valve, with PT opposite to the septal surface. How much is the calculated distance to the skin surface in such a case, and how much emitted light needed for an effective stimulation? How was the illumination performed in the case of TAVI attached PM testing?

Our response: We thank the reviewer for this clinical question. Our clinical collaborator measured the distance between the skin surface and the aortic root/LVOT junction (where the TAVR sits) of

6 adult patients on the CT or MRI. Combining this with the literature [Translational Research in Anatomy, 22, 100083 (2021)], the distance ranges from 5 to 10 cm.

For effective stimulation at the distances between 5 to 10 cm, the intensity of light on the surface of the skin is $1.54 - 980 \text{ W mm}^{-2}$. For skin safety, the peak irradiance must be below 1950 mW mm^{-2} at 0.2% duty cycle (2 ms pulse, 60 bpm). Thus, for distance larger than 60 mm, the modified design (Fig. R11) needs to be used. Another illumination strategy using optical fibres to deliver light directly on the phototransistor at low and safe intensity levels can also help.

Feasibility tests described in the manuscript used fiber-coupled LEDs (Thorlabs, M660FP1) to independently activate each pacemaker by illuminating the corresponding phototransistor.

Modifications to the draft: On page 15 we added “Supplementary Note 10 discusses the illumination strategy. Feasibility tests use fibre-coupled LEDs to activate each pacemaker separately.”

In the Supporting Material on page 17 we added the following contents.

The distances between the skin surface and the aortic root/LVOT junction (where the TAVR sits) for six patients evaluated by CT or MRI are between 5 to 10 cm. For effective stimulation at these distances, the required emitted light on the surface of the skin is $1.54 - 980 \text{ W mm}^{-2}$. For skin safety, the peak irradiance needs to be kept within 1950 mW mm^{-2} at 0.2% duty cycle (2 ms pulse, 60 bpm). Thus, for distance larger than 60 mm, the modified design (Supplementary Fig. 16) needs to be used. Another illumination strategy using optical fibres to deliver light directly on the phototransistor at low and safe intensity levels can also help.

Comment #4. I miss the discharge characteristics of the PM battery based on standard values (e.g 100% 60 bpm, 500 Ohm)

Our response: We thank the reviewer for this comment. We conducted additional experiments to assess the discharge characteristics of the battery.

In benchtop experiments, we conducted electrochemistry impedance spectroscopy (EIS) measurements on fresh chicken tissue and an agarose gel (1 wt% agarose, 0.9 wt% NaCl and 0.5 wt% glycerol) to evaluate their impedance across a frequency range from 1 Hz to 10 kHz (Fig. R2a). The impedances of the agarose gel and chicken tissue are similar, $\sim 500 \text{ Ohm}$ at 1 kHz, corresponding to a $\sim 1 \text{ ms}$ pulse width during cardiac pacing. This result indicates that the agarose gel can serve as a phantom tissue to mimic the physiological impedance.

We then sandwiched the pacing electrodes in the agarose gel at 37°C , which formed a battery. The pacing electrodes, the phototransistor, and a current measurement module (PalmSens4) were electrically connected in series. A function generator (Rigol) powered the LEDs and generated pulsed illumination with a frequency of 1 Hz (60 bpm) and a pulse width of 5 ms on the phototransistor. The discharge characteristics of the battery were measured every 6 h. As shown in Fig. R12b-c, the battery can maintain a stable output for up to 16 days.

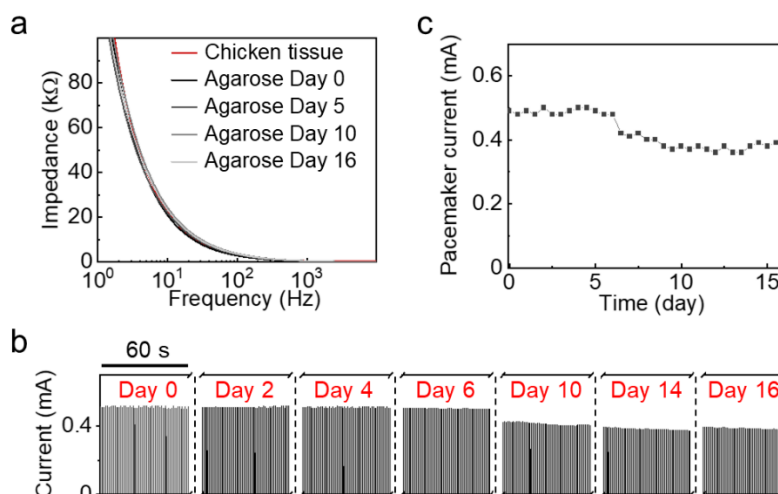


Fig. R12. Measurement of the discharge characteristics of the battery. (a) EIS of an agarose gel and chicken tissue at a frequency range from 1 Hz to 10 kHz. (b) Discharge characteristics of the battery over days. (c) Output currents of the pacemaker over days under pulsed illumination.

Modifications to the draft: We added Fig. R12 as Extended Data Fig. 3.

On page 10 we added “Discharge profiles of the Mg-MoO₃ pacing pairs (Extended Data Fig. 3) in the agarose gel at 37 °C indicate an ability to operate continuously for ~ 16 days at currents, rates, and pulse widths of ~ 0.4 - 0.5 mA, 60 bpm, and 5 ms, respectively.”

In the Supporting Material on page 13 we added “In benchtop experiments, we conducted electrochemistry impedance spectroscopy (EIS) measurements on fresh chicken tissue and an agarose gel (1 wt% agarose, 0.9 wt% NaCl and 0.5 wt% glycerol) to evaluate their impedance across a frequency range from 1 Hz to 10 kHz. The impedances of the agarose gel and chicken tissue are similar, ~500 Ohm at 1 kHz, corresponding to a ~ 1 ms pulse width during cardiac pacing. This result indicates that the agarose gel can serve as a phantom tissue to mimic the physiological impedance. We then sandwiched the pacing electrodes in the agarose gel at 37 °C. The pacing electrodes, the phototransistor, and a current measurement module (PalmSens4) were electrically connected in series. A function generator (Rigol) powered the LEDs and generated pulsed illumination with a frequency of 1 Hz and a pulse width of 5 ms on the phototransistor. The output current of the pacemaker was measured every 6 h. As shown in Extended Data Fig. 3, the pacemaker can maintain a stable output for up to 16 days.”

Comment #5. Authors state: “These and additional experiments (Extended Data Fig. 3, Supplementary Note 1) demonstrate timescales for stable operation and complete bioresorption of ~16 days and ~1.2-2.5 years”.

I could not find data on threshold changes over the maximum operation time of 16 days. It is generally expected to have a local inflammation leading to a significant threshold rise few days after PM lead implantation which is especially significant in the case of epicardial leads.

Our response: We appreciate this critical comment from the reviewer. We conducted additional benchtop and *in vivo* experiments to evaluate the operational lifespan of the device. As shown in Fig. R12b-c, the pacemaker can maintain a stable output for up to 16 days in the benchtop experiments.

We agree with the reviewer that local inflammation can lead to a significant increase in the threshold following the implantation of the pacemaker lead *in vivo*. Therefore, maintaining a safety margin of at least two times the sensing threshold is necessary to ensure stable and reliable operation, a standard practice in clinical settings to counteract post-implantation threshold increases.

Fig. R13 displays the strength-duration curve measured while pacing the porcine heart. The results confirm that the pacemaker can achieve more than twice the threshold, ensuring reliable operation post-implantation despite increase in the threshold.

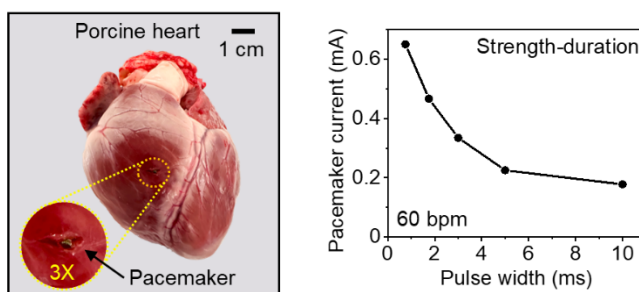


Fig. R13. Photograph and strength-duration curve of *ex vivo* porcine heart pacing.

In addition, we conducted *in vivo* experiments in the rat model to monitor the performance and threshold changes of devices over a period of time after implantation. Pacemakers were sutured onto the surfaces of the hearts. The incisions were then closed. We triggered the cardiac pacing through pulsed light illumination every day and recorded the ECG. The results (Fig. R14) show that the pacemakers made of the Mg-MoO₃ and Zn-MoO₃ pairs can function *in vivo* for up to 6 and 20 days post implantation, respectively. This timescale exceeds requirements in temporary pacing with an average duration of 4.2 days [Revista Española de Cardiología (English Edition) 57, 1045–1052 (2004)]. Pacing thresholds rise significantly from day 2 for the Mg-MoO₃ and from day 19 for the Zn-MoO₃ pair, possibly due to the synergistic effect of local inflammation and electrode degradation. Zn anodes exhibit better electrochemical stability than Mg anodes.

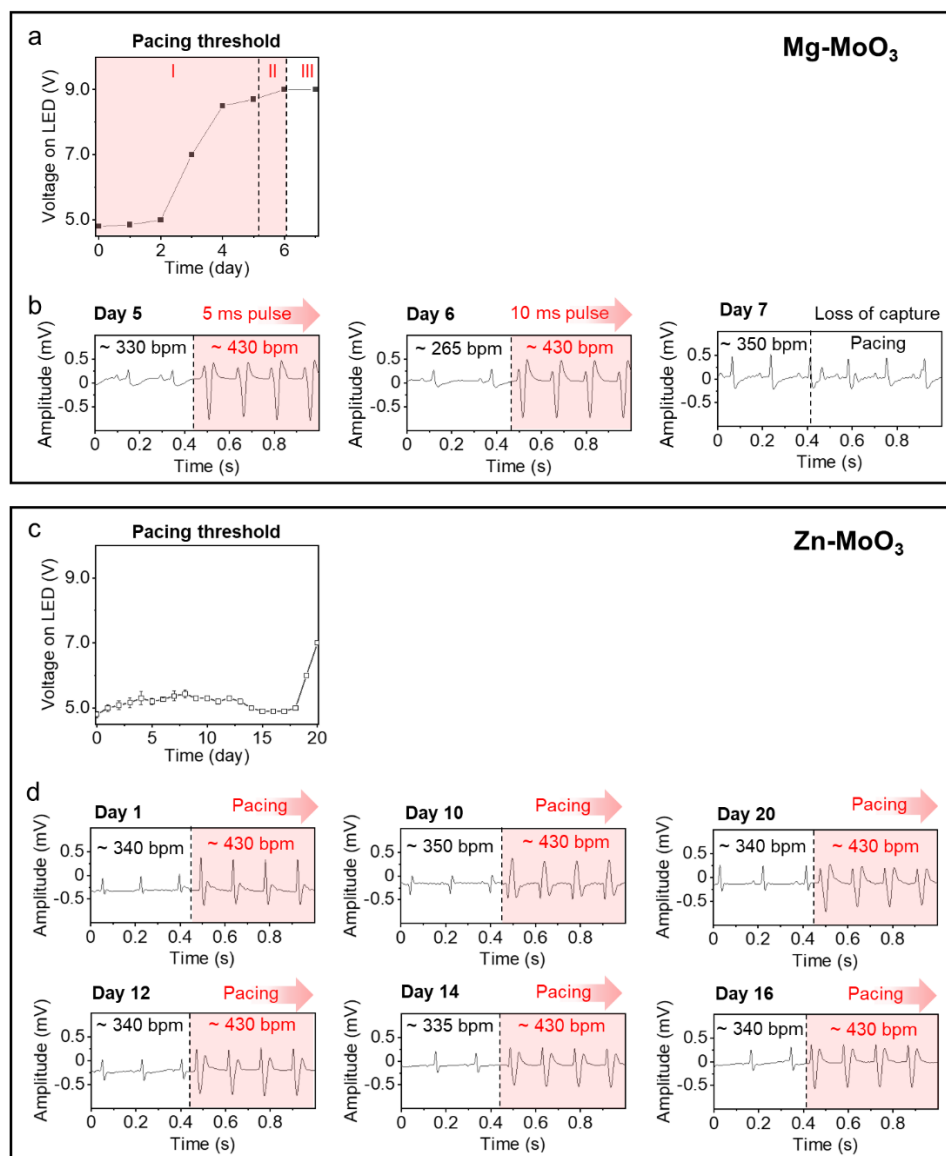


Fig. R14. Measurement of *in vivo* operational lifespan of the device. (a,c) Changes on the pacing threshold (minimum voltage applied on the NIR LED) after the implantation of pacemakers made of Mg-MoO₃ (a) and Zn-MoO₃ (c, pulse width: 5 ms) pairs. Phase I: capture under 5 ms pulse; Phase II: capture under 10 ms pulse; Phase III: loss of capture under 10 ms pulse. (b,d) ECG signal before and during pacing. Pacemakers utilize Mg-MoO₃ (b) and Zn-MoO₃ (d, pulse width: 5 ms) pairs. n = 4 biologically independent animals.

Modifications to the draft: Fig. R13 was shown as Fig. 2c-d. We added Fig. R14 in Fig. 3i and Supplementary Fig. 18.

On page 7 we added “The device exploits a self-powered mechanism, where the battery electrodes are the pacing electrodes. Specifically, an active, bioresorbable Mg alloy AZ31 (Mg₉₆Al₃Zn₁) foil or Zn composite (1.6 mm × 1.6 mm) serves as the anode, and a more electropositive bioresorbable molybdenum trioxide (MoO₃) composite (1.6 mm × 1.6 mm) serves as the cathode. The cardiac tissue and associated biofluids act as the electrolyte to form a galvanic cell/battery (Mg-MoO₃ or

Zn-MoO₃). As a demonstration, the pacemaker utilizes the Mg-MoO₃ pair here if not otherwise specified.”

On page 29 we added “Mixing 0.5 g Zn powder (Sigma Aldrich, size: 40 - 60 nm), 0.04 g carbon black, and 800 μ L of 300 mg/mL PLGA in ethyl acetate formed Zn slurry. Zn foil (50 μ m thick, Goodfellow) served as current collectors for the Zn anode materials. The Zn slurry was applied on both sides of the Zn current collectors followed by baking at 120 °C for 50 min. The Zn anodes were then sintered in 5 wt% acetic acid aqueous solution at room temperature for 30 min and dried out in the air.”

On page 10 we added “This curve confirms that the pacemaker can achieve more than twice the threshold, ensuring reliable operation post-implantation.”

On page 36 we added “Local inflammation can lead to a significant increase in the threshold following the implantation of the pacemaker. Therefore, maintaining a safety margin of at least two times the sensing threshold is necessary to ensure stable and reliable operation, a standard practice in clinical settings to counteract post-implantation threshold increases.”

On page 12 we added “*In vivo* experiments in rat models define the operational lifespan. Pacemakers were sutured onto the surfaces of the hearts and then the chest cavity was closed, using surgical procedures described previously⁴⁰. Pulsed light illumination triggers cardiac pacing every day. The results (Fig. 3i, Supplementary Fig. 18) show that pacemakers made of Mg-MoO₃ and Zn-MoO₃ pairs can function in vivo for up to 6 and 20 days post implantation, respectively. This timescale exceeds requirements in temporary pacing with an average duration of 4.2 days³². Pacing thresholds rise significantly from day 2 for the Mg-MoO₃ and from day 19 for the Zn-MoO₃ pair, possibly due to the synergistic effect of local inflammation and electrode degradation.”

In the Supporting Material on page 42 we added “Zn anodes exhibit better electrochemical stability than Mg anodes.”

Comment #6. Authors state: “Collections of such integrated devices can deliver both rapid pacing during valve deployment and regular pacing during the post-operative period.”

Is important to highlight, that stable and reliable pacing is needed for an optimal TAVI implantation. The pacemaker will not be working before complete expansion of the TAVI valve. Furthermore, it is questionable whether adequate threshold can be reached in the TAVI valve position.

100% capture is not enough for a safe operation. A minimum of 2x safety window is needed to ensure a stable and reliable operation. Are there any simulations or direct measurements to reach this safety profile?

Our response: We appreciate the reviewer for highlighting this crucial aspect. We agree that the pacemaker will not function until it is fully expanded. We revised our manuscript accordingly. To ensure stable and reliable pacing during TAVI implantation, a conventional commercial cardiac pacemaker may be used temporarily. After the procedure, this temporary pacing lead can be

removed, as tissue will not have grown around the lead in such a short period. Our device can take over pacing duties during the post-operative period, which allows safe and early patient discharge.

We conducted additional *ex vivo* human heart experiments to understand whether adequate threshold can be reached in the TAVI valve position. Fig. R15a displays the strength-duration curve. Fig. R15b plots the ECG results at two pacing conditions (72 bpm, 0.4 ms pulse, 1.14 mA; and 72 bpm, 8 ms pulse, 0.23 mA). These results indicate that an adequate threshold can be achieved.

We agree with the reviewer that a minimum of 2x safety window is needed to ensure a stable and reliable operation. The strength-duration curve (Fig. R15a) demonstrates that the pacemaker can achieve more than twice the threshold, to ensure a stable and reliable operation.

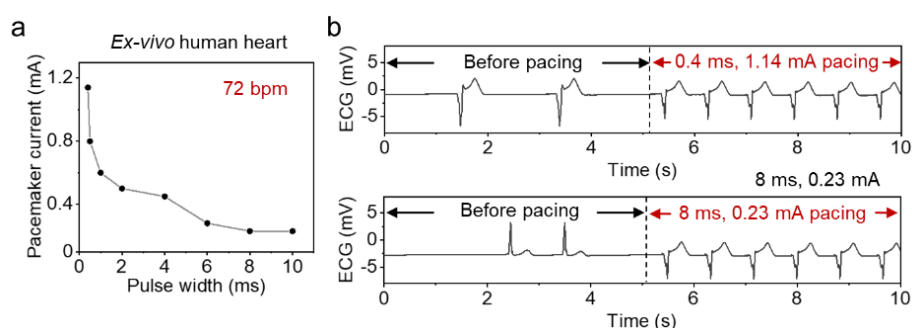


Fig. R15. Strength-duration curve (a) and ECG results (b) of *ex vivo* human heart pacing with pacemakers located in the TAVI valve position.

Modifications to the draft: We added Fig. R15 as Supplementary Fig. 25.

On page 15 we added “Collections of such integrated devices can deliver regular pacing during the post-operative period. Supplementary Note 9 describes the pacing technique during TAVR implantation. This function reduces patient risks and exposures to potential complications, simplifies the procedure, refines the post-operative care process, and allows safe and early patient discharge.”

In the Supporting Material on page 17 we added “**Supplementary Note 9. Pacing technique during TAVR implantation.** To ensure stable and reliable pacing during TAVI implantation, a conventional commercial cardiac pacemaker may be used temporarily. After the procedure, this temporary pacing lead can be removed, as tissue will not have grown around the lead in such a short period. Our device can then take over pacing duties during the post-operative period, which allows safe and early patient discharge.”

On page 15 we added “Experiments show that this integrated device placed in the area of the aortic annulus can effectively capture the ventricular myocardium in the *ex vivo* Langendorff perfused human heart model (Supplementary Fig. 25).”

In the Supporting Material on page 50 we added “The ECG were collected at two pacing conditions (1.2 Hz, 0.4 ms pulse, 1.14 mA; and 1.2 Hz, 8 ms pulse, 0.23 mA). The above results indicate that

an adequate threshold can be achieved in the TAVI valve position. The strength-duration curve reveals that the pacemaker can achieve more than twice the threshold, to ensure a stable and reliable operation.”

Comment #7. “The compatibility with MRI”: is the light emitting part MRI compatible/conditional? This is a crucial part of the pacemaker system.

Our response: We thank the reviewer for this question. The current version of the skin-interfaced patch (light emitting part) is not MRI-compatible. However, a significant advantage of our self-powered and light-controlled system is that the pacemaker operates on light. In this design, the skin-interfaced patch does not contain coils, previously used for wireless inductive power transfer in other studies, thereby avoiding interference with MRI systems. Although Bluetooth communication may be disrupted in an MRI environment, the LED used for pacemaker illumination remains functional, allowing the pacemaker to be activated as needed. To develop an MRI-compatible patch, one solution is to use the MRI-compatible LED, controlled by MRI-compatible electronic components, and powered by the MRI-compatible battery.

Modifications to the draft: In the Supporting Material on page 10 we added “The skin-interfaced patch is an essential part of the pacing system. It does not contain coils, previously used for wireless power transfer in other studies, thereby avoiding interference with MRI systems. Although Bluetooth communication may be disrupted in an MRI environment, the LED used for pacemaker illumination remains functional, allowing the pacemaker to be activated as needed. To develop an MRI-compatible patch, one solution is to use the MRI-compatible LED, controlled by MRI-compatible electronic components, and powered by the MRI-compatible battery.”

Response to reviewers

Reviewer #1

Comment: The authors fully addressed my comment on the mechanism and I am now happy to support publication.

Our response: We thank the reviewer for supporting its publication.

Reviewer #2

Comment: The authors have addressed all the comments, and it is now clear that the main advance lies in the application of the technology, which is particularly strong. While the fundamental aspects may not present as significant a breakthrough, the clarity around the application is evident and will be an important factor in the evaluation.

Our response: We thank the reviewer for these positive comments.

Reviewer #3

Comment: The manuscript has improved significantly. The simulation including the light absorption effect of the ribs, and the modified device design for deeper level stimulation adds valuable information and gives hope for the clinical use of the device. My concerns regarding the pacing threshold over time have been resolved.

Altogether the additional simulations, testing and development of a modified design together with adequate remarks on the possible clinical usability of such a device makes the present manuscript acceptable from the clinician's perspective.

Our response: We appreciate these positive comments from the reviewer.