OPTOGENETIC PACEMAKER

A NON-SURGICAL SOLUTION TO ARRHYTHMIA

OVERVIEW

A non-invasive, stick-on pacemaker. Lasers shine red light periodically onto cardiac sinus cells containing opsin, a protein which converts light into electricity. The action potentials generated form a regular heartbeat.

CONCORD COLLEGE

AMAE FUNG **Team leader.** Ideated optogenetics, researched delivery method

AN DUONG **Researcher.** Opsin and underlying cardiology

ELIANA DANG **Artist.** Poster design and original illustrations

SIMON CHU **Researcher.** Feasibility and affordability, insight into economics

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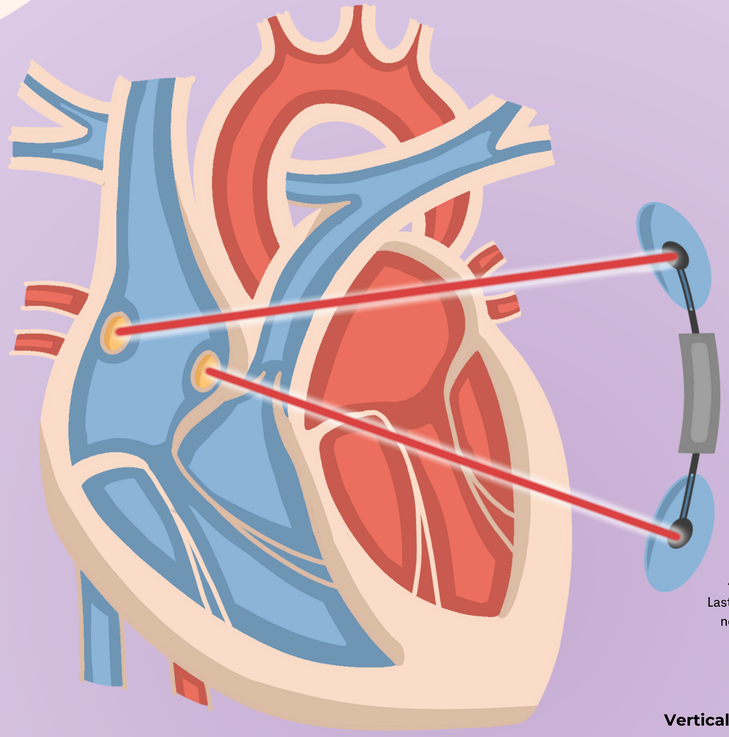
CITATIONS

THE PROBLEM

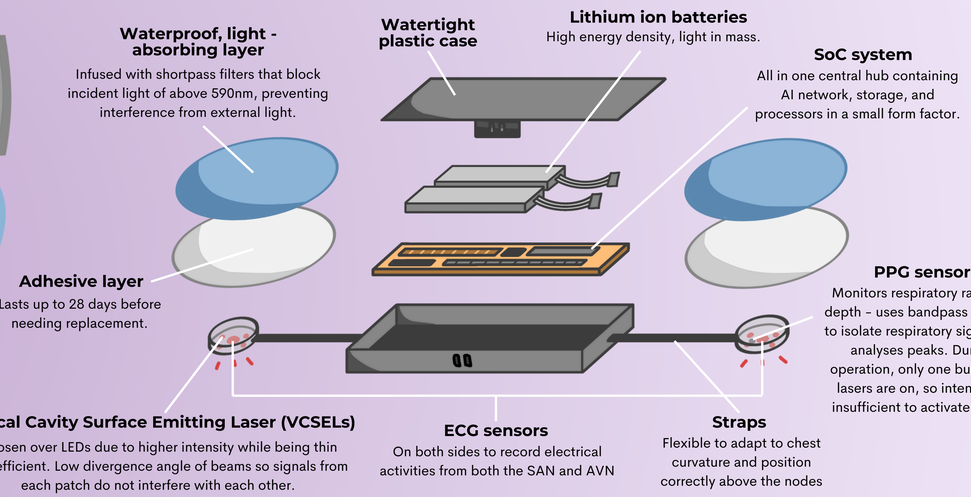
Arrhythmia is a condition where there is a **problem with heart rate or rhythm**. It affects over 2 million people in the UK. The current solution to arrhythmia is a **pacemaker**: a surgically implanted device which sends electrical pulses to cardiac cells to maintain a regular heartbeat. However, conventional pacemakers are invasive and can be problematic because:

- **Lead fractures** (damage to the pacemaker leads) can be life-threatening when not immediately fixed, because they require X-rays and ECGs to detect
- The **surgery** for replacing or implanting the pacemakers is **costly** and has unavoidable **risks**
- Follow-up appointments take **time** and put **stress** on **hospital personnel**



DEVICE MECHANISM

- The device is stuck onto the chest above the heart. It is completely external so no surgical wound is involved.
- Sensor receives electrical signals of the heart using an **ECG**, this signal is then converted to digital. ECG information is stored locally and replaced every 30 seconds.
- **AI** pattern recognition system identifies an irregular heartbeat.
- To correct heartbeat, lights on two patches directs red light to activate opsin at **sinoatrial node (SAN)** and **atrioventricular node (AVN)** at specific times:
  - For **irregular heart rates** (e.g. tachycardia, bradycardia), red light would be shone at the nodes at a regular intervals
  - For **synchronisation issues** between the nodes (e.g. heart-block, atrial fibrillation), red light is shone at regular intervals to both nodes separately, at a slight delay to each other to ensure the atria contract before the ventricles
- When an arrhythmia is detected, the ECG from continuous monitoring 30 seconds before and after the **recorded incident** will be sent to the NHS database
- PPG is used to detect changes in respiratory rate, in order to detect exercise and signal an increase to heart rate accordingly



PROS

- Likely to have **high social acceptability** and **medical endorsement** due to its non-invasive nature
- **Convenient replacement** of batteries and adhesives at home by the patient eliminates need for constant hospital visits
- **No infection risk** so increased safety for patients
- **Less demand** for **manpower, resources, and time** from the NHS because the procedure is non-surgical
- **Easily reparable** because any damage to the device would be external, unlike lead fractures in conventional pacemakers
- Built-in constant monitoring sends information to the NHS database, allowing better **connectivity** with the clinician

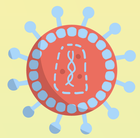
CONS

- **Regular maintenance** of components such as the adhesive layer and batteries is required
- The lifetime **cost** of the device and maintenance may still be substantial despite being potentially lower than conventional pacemakers
- Given that optogenetics is an emergent field, **prolonged observation periods** in clinical trials are needed to gather further knowledge on the opsin technology in a cardiac cell setting
- The novelty of the opsin technology could be a potential cause for social adversity

Despite certain limitations on technical, financial and social aspects, the benefits that our device brings still outweighs the drawbacks. The non-invasive nature of the device allows it to tackle the NHS's most urgent current issue: lack of resources. Though this technology still needs significantly more research, it has the potential to solve various medical, technical, and economic problems found in conventional pacemakers once it is fully developed.

DELIVERY METHOD

1. Assemble viral vector



We have chosen **lentivirus** as a vector to deliver the opsin gene to cardiac cells. Lentiviral gene delivery is suitable because:

- Attachment proteins can be added onto its lipid envelope, allowing it to enter the cell through **receptor-mediated endocytosis**
- The opsin gene is integrated into the host cell genome, so it is more **stable** and opsin can be **regularly produced** by protein synthesis
- It can carry **large genetic payloads** compared to other viral vectors
- It has negligible pathogenicity so there is a **low risk of immune response**

We designed an expression cassette to be packaged into the lentiviral vector.

2. Inject intravenously

Solution should be isotonic and pH buffered

3. Opsin is produced

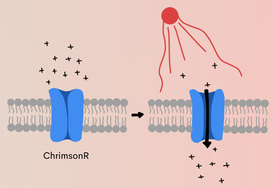
Takes up to 72 hours (circulation and infection period)

HOW OPSIN WORKS

- **Opsin** is a protein that converts light into electrical signals
- **Channel rhodopsins** are intrinsic membrane ion channel proteins that open and close based on exposure to certain wavelengths of light. They are made of a **retinal** light receptor and **7 proteins**
- We chose to use **ChrimsonR**, a modified form of the channel rhodopsin receptive to light of wavelength 590 to 630 nm because:
  - Red light penetrates deep into tissue so can reach the heart easily
  - ChrimsonR is the fastest responding red light opsin
  - It is showing success in clinical trials for other applications of gene therapy, such as managing the symptoms of Parkinson's Disease and Epilepsy, and restoring vision in patients with Retinal Degenerative Diseases

How would ChrimsonR affect heart rate?

- When stimulated with red light, ChrimsonR opens its cation channels
- This causes an influx of **Na+** and **Ca2+** ions into the cell, causing it to **depolarise**
- When the red light is turned off, the potassium channels open, causing an outflux of **K+** ions and **repolarisation** of the cell
- This action potential triggers the contraction of atria and ventricles at a steady rhythm



FEASIBILITY

Optogenetics is a relatively new and developing area of science.That being said, opsin is already in use in many different fields with promising results:

- Optogenetic toolkits are becoming the standard in areas of **neuroscience** for neural pathway stimulation
- **Vision** was restored in a patient with Retinitis pigmentosa using opsin and light emission goggles
- Lentiviral vectors have shown success in clinical trials for treating various **genetic disorders, cancers, and infectious diseases**

AI INTEGRATION

In the **machine learning** process before clinical trials, the AI will be fed different parts of ECGs from large databeses and be able to recognise resting heart rate and arrhythmia events. It will then go through a **feature extraction** practice process, where it will encounter false positives and improve its algorithm. The other function of the AI is to analyse PPG information about **respiratory rate**. A high respiratory rate will be used as an indication for physical activity and heart rate will be adjusted accordingly by the AI.

AFFORDABILITY

The current cost for pacemaker implantation, which includes the pacemaker, leads, the surgical procedure, hospital stay, and follow-up care, typically ranges from £6,000.
However due to the need to **change the battery** of the pacemaker every 6 years, the typical cost of a lifetime treatment using a pacemaker is about **£18,000**

Total cost of our solution:

- Clinical-grade lentivirus per dose: £7,000
- Two 12 - red-light VCSELs bundles: £1,000
- Low-Power Processor: £50
- Medical-grade adhesives with thin film optical filters for a lifetime supply: £3,000
- Rechargeable batteries: £200

So in total, each treatment costs **£11,250** with **minimal man-power** needed to install and maintain the device for a lifelong treatment. **Saving the NHS around £7,000 per device**.

CLINICAL TRIALS

1. Pre-clinical testing

Toxicology studies and action potential generation efficiency assessed using cardiomyocyte tissue culture and rodent models. Also includes the training of AI model using publicly available ECG data.

2. Safety and dosing

Enrol patients with arrhythmias unresponsive to conventional therapies, and a control group. Evaluate the safety, tolerability, and optimal dosage of opsin and light stimulation.

3. Efficacy and Outcome assessment

Researchers periodically check up on volunteers to assess the efficacy of the opsin-based pacemaker in maintaining regular heart rhythms and improving patient outcomes.

4. AI efficacy and comfort study

Give time for the AI model to get used to the interpretation of arrhythmias and the recognition of abnormalities in ECGs as well as ensuring accurate actions taken by the model. Survey quality of life of all volunteers.

5. Accessibility

Finally, the opsin based pace-maker is sent for regulatory approval to the MHRA, and made available over-the-counter and through GP recommendations to ensure accessibility for those eligible for free prescriptions.