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Accelerating Healing of Chronic Venous Leg Ulcers (CVLUs) through Electrostimulation and Adaptable Hydrogels

Introduction

Chronic Venous Leg Ulcers (CVLUs) are caused by sustained **venous hypertension**, its incidence increasing with age.

- An upwards of **two million people** are annually affected by CVLUs, and by traditional methods, around **40% fail to heal**, leading to **severely reduced mobility** or even **amputation**

Traditional methods like bed rest, debridement, compression, and silver-based dressings are **ineffective** due to lack of **customization** based on patient circumstances.

- Patients are unable to get their wound **evaluated** for advanced treatment options until after **four weeks** of **failed treatment**, increasing the risk of **amputation**
- Lots of **recurring** incidents of CVLUs (**78%** in **3 years**) because treatment does not target root cause

Introduction

We are able to **counter** these issues by…

Hydrogel Technology

Easy to **tailor** to patient **needs** with a wide range of applications

Electrostimulation

Various techniques depending on **treatment progress**

Compact Design

User friendly and cost effective, does not **restrict mobility**

Bluetooth

Allows patient to **wirelessly** monitor their wound in **real time**

Hydrogel Methodology

Objectives: biocompatibility, moisture retention, and material stability.

Biocompatibility	Calcium Alginate hydrogel chosen for its **non-toxic** properties, ease of **integration** with electrostimulation (ES) device, and **controlled release** capacity for drug delivery
	pH was tested and **adjusted to 7.0** after being submerged in phosphate-saline solution (PBS)
Moisture Retention	Hydrogel **readily absorbs** moisture, maintaining a **healthy moisture balance** to optimize wound-healing
	Immersed in **PBS** to test for the **swelling ratio** of hydrogels with different sodium alginate concentrations (1%, 2%, 3%, and 5%)
Material Stability	**Structurally similar** to the extracellular matrix, **ionic crosslinking** which promotes **flexible** mechanical strength without progressing to toxicity
	Exhibits **viscoelastic properties** which can be determined with **rheological testing***

*Unfortunately, there was limited access to a rheometer during this study, so extensive data was collected in reference to other sources.

Electrostimulation (ES)

	Principle	Application
Resistance	Most of the body's **resistance to current** is in the skin. Chronic wounds **disrupt** this, **hindering** the natural healing process	**Measure** resistance to inform healing progress and **modify current** accordingly
Frequency	**Lower** frequency ES increases **blood flow**, while **higher** frequency ES stimulates growth of new **connective tissue** (fibroblast growth)	**Modify** ES frequencies to meet the needs of each patient, **adjusting** frequency to target each stage of wound healing
Bioelectric Dressing	Using **embedded electrodes** to optimize a healing environment for the wound	Particularly suitable for **calcium alginate** hydrogels, easy for synthesis and embedding electrodes **directly within** gel

Methodology: **Electrical** Components

1	SEEED XIAO microcontroller **manages healing** based on electrical impedance
2	**Wireless** connection with external device to determine ES **current strength** & real time tracking
3	Microcontroller generates **low-level pulsed current**, passed through **embedded** electrodes
4	LM334 **current regulator** chip ensures current stays in a safe range (**<10mA**) when administered
5	Draws current at a rate of **~85mA**, will draw more based on feedback from **patient circumstances**
6	Small LiPo battery (3.7V, 1100mAh) ensures that device runs for **at least 11 hours**

Methodology: **Mechanical** Design

Objectives: lightweight, compact, and durable design.

Custom-printed Enclosure

Enclosure synthesized through **PLA plastic**, which is **durable** and easy to fabricate, adjustable to different size requirements.

Modular Requirements

Designed for **easy disassembly** for further customization, as connecting wires can be **hot-swapped**

Compact Design

Slotted for a SEEED XIAO microcontroller, small LiPo battery, and LM334 Current Regulator. Designed with an **ergonomic** footprint shape to ensure comfort, attached by adhesive or Velcro.

Front Panel

Power button, LED indicator to display **device status**, and two **electrode ports** for connection with conductive pad.

ES Data Collection Methodology

01 Electrical Impedance

XIAO outputs 10-100Hz **AC test signal**, generated by PWC outputs smoothed over a **low-pass filter** to approximate sine wave. Voltage divider measures **voltage drop** across the wound using the ESP32-C3's ADC pins.

02 Electrode Resistance

Before impedance test, small **DC current** measures **inherent resistance** (varies due to environmental factors) to ensure accurate **AC impedance measurements**. ES temporarily disabled during test to **prevent interference.**

03 Impedance/Resistance based Wound Monitoring

Changes reflect stages of wound healing. **Low impedance** (100Ω-1kΩ) indicates moist wounds in earlier healing stages, while **higher impedance** (1kΩ-10kΩ) suggests collagen formation and drier tissue.

Adjusted ES settings based on impedance:
Low impedance: 1-10Hz, **high-intensity pulses** to **boost blood flow** and cellular activity.
Medium impedance: **fibroblast** activity & **tissue formation** enhanced by 50-100Hz pulses
High impedance (>10kΩ): >1 kHz **microcurrents** for **cellular maintenance** and regeneration.

Integration Method

- Thin **carbon film electrodes** embedded into hydrogel for simultaneous treatment
  - Electrodes consist of **central circular portion** and **concentric ring** to ensure **radial current diffusion**
- Electrodes placed in mould with connecting wires to **MEU**
  - Sodium alginate solution poured into mould & **crosslinked** with calcium chloride solution to form **calcium alginate hydrogel**
- When current is applied, it flows through anode (ring) and cathode (center), generating an electric field & stimulating **cell electrotaxis**
  - **Macrophages** migrate toward anode
  - **Fibroblasts** migrate toward cathode
  - **Neutrophils** migrate to both electrodes

Hydrogel Results

PBS Swelling

- 1%: Very absorbent, requires **frequent replacement** (221%)
- 2%: Optimal for wounds which need **moisture retention** and some structural support (148%)
- 3%: Ideal for wounds which require **structural** support with less attention to moisture retention (97%)
- 5%: Very **rigid**, minimal wound interactions (57%)

PBS pH

- 1%, 2%, 3%, and 5% hydrogels adjusted to **around 7.0** with uncertainty of ±0.2, when taking an **average** of 5 trials
- Indicates that hydrogels can be adjusted to be **biocompatible**
- Next time, PBS will be **integrated** into the hydrogel **synthesis** process

Rheology

- 1%: Slower **crosslinks**, sensitive to environmental changes, fairly **viscous**
- 2%: Some development to overcome **shear strain**, effective for wounds with **complex** wound geography
- 3%: Stronger crosslinks, **mechanical stable** for structural support
- 5%: **Brittle** structure, could cause irritation or discomfort, very **elastic**

ES **Electrode Sensing** Results

Determine optimal frequency to alternate current for sensing the resistance of skin tissue.

5kΩ resistor connected anode & cathode electrodes to **simulate** dry skin tissue. Various AC frequencies were **pulsed** through the electrodes. Voltage measured by the ADC was **converted to resistance** using a peak AC voltage of **1.5V**.

Low Frequencies

- Measured resistance very **close to expected**
- Minimal error between values
    - Range of **<1% error**

Higher Frequencies

- **Apparent deviations** from expected resistance values
    - Likely due to **attenuation**
    - Increased frequency of AC decreases its **wavelength**, more **difficult** to pass through skin

ES **MPC Model** Results

Ability to adapt to differing values of skin resistance

1. Comparison of the **measured impedance values** and the corresponding ES parameters calculated by the **MPC algorithm** allows for the identification of **trends**
2. Using **changing** impedance to **optimize ES factors** for different conditions
3. Increased **resistance** correlates to increased **measured impedance**, leading to a **progressive shift** in stimulation frequency and intensity
4. **Confirmed** previous results (**lower impediance** → wounds with high moisture/early healing stage requires lower frequency, higher intensity ES)
5. **Higher impedance** → wounds with drier, more stable tissue benefits from higher frequency, lower intensity ES to **prevent overstimulation**

Conclusion

Portable

We offer a compact device, increasing **acessibility**

Tailored

Our solution is **adaptable** and **customizable** to patient needs

Consistent

24/7 monitoring with bluetooth, user-friendly & **easy to operate**

Cost-effective

Treatments can cost an upwards of **20K**, where our treatment costs **$20**

Next Steps

Area of Improvement	Changes
Rheological Testing	Use a rheometer or more patient data for further points of reference
Incorporating PBS	Adding PBS to different portions of the hydrogel synthesis to increase biocompatibility
Circuit Board	Custom printed circuit board and smaller, circular batteries similar to those found in smartwatches
MEU	MEU directly onto the hydrogel, reducing complexity and ridding requirement of wires
Multi-electrode Arrays	Multi-electrode arrays for targeted stimulation, making the treatment even more customizable

References

Abe, Y., & Nishizawa, M. (2021). Electrical aspects of skin as a pathway to engineering skin devices. *APL Bioengineering*, *5*(4). https://doi.org/10.1063/5.0064529

Bahadoran, M., Shamloo, A., & Nokoorani, Y. D. (2020). Development of a polyvinyl alcohol/sodium alginate hydrogel-based scaffold incorporating BFGF-encapsulated microspheres for accelerated wound healing. *Scientific Reports*, *10*(1). https://doi.org/10.1038/s41598-020-64480-9

Cuomo, F., Cofelice, M., & Lopez, F. (2019). Rheological characterization of hydrogels from alginate-based nanodispersion. *Polymers*, *11*(2), 259. https://doi.org/10.3390/polym11020259

Demidova-Rice, T. N., Hamblin, M. R., & Herman, I. M. (2012). Acute and impaired wound healing. *Advances in Skin & Wound Care*, *25*(7), 304–314. https://doi.org/10.1097/01.asw.0000416006.55218.d0

Farber, P. L., Isoldi, F. C., & Ferreira, L. M. (2021). Electric factors in wound healing. *Advances in Wound Care*, *10*(8), 461–476. https://doi.org/10.1089/wound.2019.1114

Firlar, I., Altunbek, M., McCarthy, C., Ramalingam, M., & Camci-Unal, G. (2022). Functional hydrogels for treatment of chronic wounds. *Gels*, *8*(2), 127. https://doi.org/10.3390/gels8020127

Fish, R. M., & Geddes, L. A. (2009). Conduction of electrical current to and through the human body: a review. *Eplasty*, *9*, e44. https://pmc.ncbi.nlm.nih.gov/articles/PMC2763825/

References

Gupta, S., & Bit, A. (2018). Rapid prototyping for polymeric gels. *Polymeric Gels*, 397–439. https://doi.org/10.1016/b978-0-08-102179-8.00016-8

Hao, Q., Hamson, A., & Horton, J. (2023, July). *Electrostimulation devices for wounds*. CADTH Health Technology Review. https://www.ncbi.nlm.nih.gov/books/NBK595136/

He, B., Shi, J., Li, L., Ma, Y., Zhao, H., Qin, P., & Ma, P. (2024). Prevention strategies for the recurrence of venous leg ulcers: A scoping review. *International Wound Journal*, *21*(3). https://doi.org/10.1111/iwj.14759

Hossain, M. T., & Ewoldt, R. H. (2022). Do-it-yourself rheometry. *Physics of Fluids*, *34*(5). https://doi.org/10.1063/5.0085361

Kelechi, T. J., Muise-Helmericks, R. C., Theeke, L. A., Cole, S. W., Madisetti, M., Mueller, M., & Prentice, M. A. (2021). An observational study protocol to explore loneliness and systemic inflammation in an older adult population with chronic venous leg ulcers. *BMC Geriatrics*, *21*(1). https://doi.org/10.1186/s12877-021-02060-w

Larsen, B. E., Bjørnstad, J., Pettersen, E. O., Tønnesen, H. H., & Melvik, J. E. (2015). Rheological characterization of an injectable alginate gel system. *BMC Biotechnology*, *15*(1). https://doi.org/10.1186/s12896-015-0147-7

Li, J., & Mooney, D. J. (2016, October 18). *Designing hydrogels for controlled drug delivery*. Nature Reviews. https://www.nature.com/articles/natrevmats201671

References

Liu, X., Qian, L., Shu, T., & Tong, Z. (2002). Rheology characterization of sol–gel transition in aqueous alginate solutions induced by calcium cations through in situ release. *Polymer*, *44*(2), 407–412. https://doi.org/10.1016/s0032-3861(02)00771-1

Matyash, M., Despang, F., Ikonomidou, C., & Gelinsky, M. (2013, November 6). *Swelling and mechanical properties of alginate hydrogels with respect to promotion of neural growth*. Tissue engineering. Part C, Methods. https://pubmed.ncbi.nlm.nih.gov/24044417/

McDaniel, J. C., Roy, S., & Wilgus, T. A. (2013). Neutrophil activity in chronic venous leg ulcers—a target for therapy? *Wound Repair and Regeneration*, *21*(3), 339–351. https://doi.org/10.1111/wrr.12036

Rajendran, S. B., Challen, K., Wright, K. L., & Hardy, J. G. (2021). Electrical stimulation to enhance wound healing. *Journal of Functional Biomaterials*, *12*(2), 40. https://doi.org/10.3390/jfb12020040

Ren, S.-Y., Liu, Y.-S., Zhu, G.-J., Liu, M., Shi, S.-H., Ren, X.-D., Hao, Y.-G., & Gao, R.-D. (2020). Strategies and challenges in the treatment of chronic venous leg ulcers. *World Journal of Clinical Cases*, *8*(21), 5070–5085. https://doi.org/10.12998/wjcc.v8.i21.5070

Saco, M., Howe, N., Nathoo, R., & Cherpelis, B. (2016). Comparing the efficacies of alginate, foam, hydrocolloid, hydrofiber, and hydrogel dressings in the management of diabetic foot ulcers and venous leg ulcers: A systematic review and meta-analysis examining how to dress for success. *Dermatology Online Journal*, *22*(8). https://doi.org/10.5070/d3228032089

Senin-Camargo, F., Martínez-Rodríguez, A., Chouza-Insua, M., Raposo-Vidal, I., & Jácome, M. A. (2022). Effects on venous flow of transcutaneous electrical stimulation, neuromuscular stimulation, and sham stimulation on soleus muscle: A randomized crossover study in healthy subjects. *Medicine*, *101*(35). https://doi.org/10.1097/md.0000000000030121

References

Spectric Precision Instrumentation and Controls Company. (2016). *A Basic Introduction to Rheology*. Rheology and Viscosity. https://cdn.technologynetworks.com/TN/Resources/PDF/WP160620BasicIntroRheology.pdf

Stojkov, G., Niyazov, Z., Picchioni, F., & Bose, R. K. (2021). Relationship between structure and rheology of hydrogels for various applications. *Gels*, *7*(4), 255. https://doi.org/10.3390/gels7040255

Venous ulcers. Johns Hopkins Medicine. (2020, July 20). https://www.hopkinsmedicine.org/health/conditions-and-diseases/venous-ulcers