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The application of machine perfusion for the testing of peripheral nerve and muscle interfacing for bionic prostheses: a systematic review

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Abstract

This systematic review evaluates the use of Normothermic Machine Perfusion (NMP) as a testbed for developing peripheral nerve and muscle interfaces for bionic prostheses. Our findings suggest that NMP offers a viable alternative to traditional models, with significant implications for future research and clinical applications. A literature search was performed using Ovid MEDLINE (1946 to October 2023), revealing 559 abstracts.

No studies using nerve and/or muscle electrodes for the testing or development of bionic interface technologies were identified, except for one conference abstract. NMP could serve as a test bed for future development of interface biocompatibility, selectivity, stability and data transfer, whilst complying with ethical practices and potentially offering greater relevance for human translation. Implemention of machine perfusion requires experienced personnel. Encompassing artificial intelligence alongside machine learning will provide a significant contribution to advancing interface technologies for multiple neurological disorders.

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Introduction

Limb amputation due to diabetes and vascular disease is projected to double by 2050, highlighting the urgent need for advanced prosthetic solutions (Ziegler-Graham et al. 2008). Many additional amputations result from trauma or military combat injuries. Current artificial prostheses often fail to replicate the sensory and motor functions of natural limbs, leading to high abandonment rates, with many individuals using them for cosmetic purposes only (Biddiss and Chau 2007).

We aimed to investigate the use of Normothermic Machine Perfusion (NMP) in the development of advanced neuroprostheses, specifically focusing on electrophysiological studies that evaluate muscle and nerve function. NMP mimics the in vivo physiological environment by delivering oxygenated blood and nutrients to preserve tissue viability. This technology may bridge the gap in preclinical testing of engineered interfaces.

Current state-of-the-art prostheses enabling real-time user control are based upon sensed muscle-controlled signals using surface electromyography as the communicating 'interface' between human and machine (Bergmeister et al. 2017). However, in complex injuries, muscle targets are absent or weak, and the quality of extracted signals is variable (Aszmann et al. 2015). The influence of neighbouring 'noise' from adjacent muscle contractions limits signal quality (Solomonow 1984). Furthermore, surface EMG electrodes are for prosthetic control only and are unable to provide meaningful information about sensory feedback. Restoring a sense of 'touch' into artificial prostheses is a priority area for researchers and users (Raspopovic et al. 2021). These are some of the reasons why thirty per cent of users abandon myoelectric prostheses resulting in emotional and psychological disturbance (Winslow et al. 2018). Collectively, current advanced prostheses offer variable degrees of fine motor control, limited sensory discrimination and lack realism, depriving embodiment (Biddiss and Chau 2007).

One attractive prospect would be to directly interface implantable bi-directional electrodes with the peripheral nervous system (Rapeaux et al. 2022). Peripheral nerves have efferent (motor) and afferent (sensation via cutaneous mechanoreceptors, proprioceptors, thermoreceptors and nociceptors) signals. Distinct subpopulations of axons convey tactile, proprioceptive, thermal or noxious stimuli (Johansson and Vallbo 1979). As far back as the 1970s attempts were made to reproduce sensation via cuff or needle electrodes and to apply direct electrical stimulation (Clippinger et al. 1974). With early attempts, subjects reported paraesthesia, vibrations, or a pulsing spread across their phantom hand, all deemed uncomfortable and unrealistic (Pylatiuk et al. 2006). As mentioned, sensory feedback is crucial for human interaction, and this for example, may give feedback on how tightly objects can be

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Table 1. Research targets for the development of desirable implantable nerve electrode

Selectivity	Selective stimulation refers to the minimal disturbance to surrounding tissues during the optimised communication with neural targets. Electrically stimulating large populations of afferents via single electrodes is unnatural and can evoke paraesthesia (15). With increasing invasivity, greater selectivity of individual nerve fibres is achieved, with lower stimulation intensities required, given the shorter distances between the electrode and individual axons. This potentially comes at the cost of permanent nerve injury (16). Cuff electrodes are easy to apply and commonly used, yet their selectivity and stability has been questioned (15). Bioelectronic interfaces must be highly accurate and reliable, and for this reason many electrode patterns, each with their advantages and disadvantages, have been described (17).
Biocompatibility	Biocompatibility is essential for the safety of the user, and suitable consideration is required for regulatory compliance. For the electrodes/implants themselves, electromagnetic interference can arise at the interface from tissue reaction and blood. Interaction of the body with implanted electrodes can lead to inflammation, matrix formation, granulation tissue, foreign body reaction and fibrosis, with additional concerns over hypersensitivity (18).
Stability	Long-term stability and reliability of an interface is crucial, especially if less invasive means to implant them remain underdeveloped. One concern yet to be verified is that neural stimulation can induce injury whilst depleting metabolic fuels within the nerve and build-up of toxic free radicals (19). This raises the possibility that long-term implants may require increasing stimulation thresholds and lose signal to noise ratio with time. Low stimulus frequencies for shorter durations have been proposed to mitigate this (15, 20). Lead migration and fracture occur in 24–50% of failures (21, 22), necessitating study of how electrodes move over time, particularly for limb with active movement.
Data transfer	Modern bionic prostheses limit data transfer across biological-mechanical interfaces, making them slow. However, there are substantial challenges in providing high bandwidth wireless chips, for example, and how such systems can be appropriately powered (21, 22). Moreover, there are data security issues given bioelectronic sensors can generate sensitive medical information that needs protecting from unauthorised access, hacking and data breaches.

held (Davis et al. 2016). Understanding and interpreting how biological neuromuscular signals are exchanged in a meaningful bidirectional manner has yet to be elucidated.

Engineering and scientific barriers

Engineering barriers exist to developing implantable interfaces including the powering of implants (Biddiss and Chau 2007), longevity, performance and interoperability (seamless data exchange and analysis). Other factors to consider are the regulatory components required for implant safety approval and the Research and Development costs required for testing prior to human implantation (Chakrabarty et al. 2023). The notable preclinical challenges for the safe implantation of a bionic interface are summarised below (Table 1).

Modelling barriers

Human implantation and interface design requires significant preclinical testing that conform with safety and efficacy laws (Pasquina et al. 2015). Many studies have attempted to use in vivo and in vitro testing of explanted nerves (Andreis et al. 2023). However, these have well known limitations, particularly around the use of laboratory animals. There is also limited translational relevance when using small animals (Aman et al. 2019). As a result, developing alternative approaches has become a 'grand challenge' for bioprosthetic research.

NMP serves to restore tissue viability by mimicking the in vivo environment via the delivery of a constant circulation to tissues. The core concept of perfusion technology is not novel and has been derived from clinical cardiopulmonary bypass circuits (CPB) and extracorporeal membrane oxygenation (ECMO), both of which have been used for decades. For example, a limb can be isolated from a food industry pig, connected to an advanced life support system and perfused with autologous blood and nutrients to simulate the biological environment more accurately (Amin et al. 2021). The approach is seen as being consistent with replacement, reduction and refinement efforts (Grimm et al. 2023) and offers greater translational relevance. Studies in both small and large animal models have primarily used this technology for the purposes of tissue preservation, for the interests of limb reconstruction, transplantation and pharmaceutical testing (Burlage et al. 2022).

Aims of this review

It has recently been acknowledged in a systematic review that there has been a significant upturn in the use of live animal models for interface development (Aman et al. 2019). However, our hypothesis was that despite increasing research activity, adoption of novel and advanced models has yet to occur. This is likely due to a lack of awareness of the approach in the bionic prostheses community. This is despite the fact that NMP offers a new tool for those developing bioelectronic devices to accelerate pre-clinical testing and ultimately shorten the routes to impact for patients impacted by amputation.

The aim of this article was to investigate the use of animal NMP models in advanced neuroprostheses development. This will consider electrophysiological studies targeted at muscle and peripheral nerves in both small and large animals for the development of implantable neuroprosthetic interfaces and discuss the barriers in their application when using NMP as a platform.

Methods

To investigate the use of animal NMP models in neuroprosthesis development, an electronic search was conducted in Ovid MEDLINE (1946 to October 2023) in accordance with PRISMA guidelines. The search targeted studies focusing on muscle and peripheral nerve interfacing with bionic prostheses using machine perfusion methods. This was followed by systematic screening of abstracts and full-text articles to identify relevant studies.

Search terms

An electronic search was conducted using Ovid MEDLINE (1946 to October 2023), following PRISMA guidelines (Liberati et al. 2009b). The research aimed to identify studies on animal limb machine perfusion specifically investigating muscle and peripheral

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Table 2. Review protocol outlining the predetermined inclusion criteria for article selection

	Inclusion criteria
Population	Original articles in English describing ex vivo machine perfusion of animal extremities for testing: (i) The nerve bionic interface (ii) Electrodes connected to peripheral nerves/muscles (iii) Muscle activity measured during ex vivo perfusion.
Intervention	Is EVMP as a technological platform being applied for use in animals testing of implantable nerve/muscle electrodes. Examples of these interventions include machine perfusion, at all temperatures (normothermic/subnormothermic/hypothermic), by any ex vivo perfusion technique including ECMO (extracorporeal membrane oxygenation) or cardiopulmonary bypass with any perfusion fluid including blood based or acellular fluids. This includes interest in various exposures including animal, all machine perfusion studies of relevance, and use of electrostimulatory and electrodiagnostic equipment: (i) Implantation of interfacing device or electrode that directly interacts with peripheral neuromuscular tissue (ii) Muscle led prostheses referred to as EMG included if this technology is evaluated using machine perfusion.
Comparison	None, unless a control group is present which may include contralateral limbs that undergo machine perfusion or preservation without the use of electromyographic and electroneurographic analyses.
Outcome	Evidence of electrophysiological activity recorded within the nerve or muscle (EMG or ENG) from any animal study that employs machine perfusion with the intention of testing for bionic prostheses.
Study design	Experimental study

nerve interfacing for bionic prostheses development. The search strategy, developed with librarian support from Manchester University Foundation Trust (MFT), included the following terms:

(i) Limb AND (implantable nerve OR Electrode OR Prostheses OR Peripheral nerve) AND (Ex-vivo OR machine perfusion OR Perfusion)
(ii) Limb AND (EMG OR ENG) AND (Ex-vivo OR machine perfusion OR Perfusion)
(iii) Limb AND electrode testing AND Ex-vivo OR machine perfusion (iv) Limb AND (Ex-vivo OR machine perfusion OR Perfusion)

An electronic search was performed on Ovid MEDLINE (1946 to October 2023) in accordance with PRISMA guidelines (Liberati et al. 2009b). The research question was designed to identify animal limb machine perfusion studies specifically investigating muscle and peripheral nerve interfacing for the development of bionic prostheses. Our search strategy was designed with librarian support from Manchester University Foundation Trust (MFT). The search terms used were:

(i) Limb AND (implantable nerve OR Electrode OR Protheses OR Peripheral nerve) AND (Ex-vivo OR machine perfusion OR Perfusion)
(ii) Limb AND (EMG OR ENG) AND (Ex-vivo OR machine perfusion OR Perfusion)
(iii) Limb AND electrode testing AND Ex-vivo OR machine perfusion
(iv) Limb AND (Ex-vivo OR machine perfusion OR Perfusion)

This combination of search terms was based upon the inclusion criteria (Table 2).

The protocol was registered with the PROSPERO international prospective register of systematic reviews, number CRD42022363528 available at (Page et al. 2018). All articles were stored and reviewed using Rayyan.ai software (Ouzzani et al. 2016). Two authors independently screened abstracts retrieved by all searches. After the initial assessment, full-text copies of all studies considered to be relevant were retrieved. Further screening of potentially relevant articles was performed via review of retrieved article reference lists.

Conclusions and perspectives

The initial search yielded 559 potential entries following deduplication (66 duplicates excluded). Full-text articles were sought for 44 studies. No studies using machine perfusion were identified directed solely towards the development of interfacing with muscle or peripheral nerves. Due to the paucity and heterogeneity of the included studies, a meta-analysis was not performed following the primary search. One single conference abstract was identified but contributed by our group as an abstract conference submission (Amin et al. 2023). Returned articles primarily comprised of interface imaging technologies and tracking of in vivo nerve health.

The initial search yielded 559 potential entries after deduplication (66 duplicates excluded). Full-text articles were sought for 44 studies. No studies using machine perfusion were identified that focused solely on the development of interfacing with muscle or peripheral nerves. Due to the paucity and heterogeneity of the included studies, a meta-analysis was not performed. One conference abstract, contributed by our group, was identified (Amin et al. 2023). The returned articles primarily involved interface imaging technologies and tracking in vivo nerve health.

The PRISMA flowchart summarises the selection process (Figure 1) (Liberati et al. 2009a). Our findings reveal that while several studies have explored electrical and muscle activity in NMP limb systems, none have employed this technology to advance bionic prostheses development. This underutilisation provides an opportunity, given the potential of NMP to enhance neuromuscular interfacing in bioelectronic devices. These findings align with prior research indicating limited application of NMP in neuroprosthetics (Aman et al. 2019). Future studies should explore ways to overcome barriers such as cost and technological complexity, which may explain this gap.

A systematic review by Aman et al. evaluated in vivo animal interface testing in rodents, cat, dog, pig and rabbits, comprising of direct muscle interfacing (23% of studies) and peripheral nerve interfacing (77% of studies). Studies were predominantly in rats. However, their rate of axonal regeneration is faster compared with humans, making them less comparable for clinical translation (Aman et al. 2019). Compared with large animals, small animals are cost-effective and allow for higher experimental turnover, but the acquisition of commercially available perfusion circuits is a

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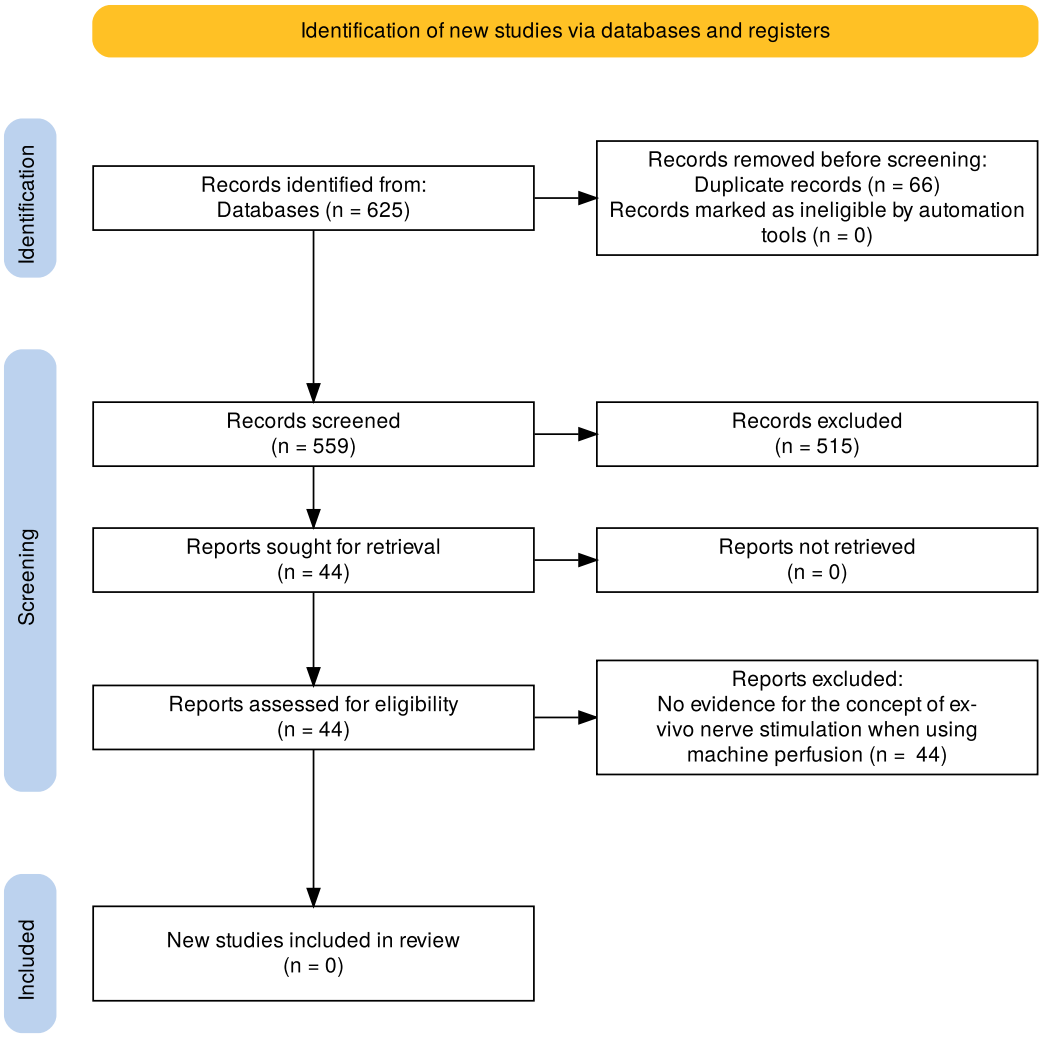

Figure 1. Selection process for systematic literature analyses as per PRISMA guidelines.

limitation, resorting to self-manufactured circuits and oxygenators that are not clinically translatable (Berner et al. 2012).

Though not within the main aim of this review, and not accounting for our own NMP conference abstract, 44 ex vivo limb perfusion studies were retrieved in this review from rodents (7%), pigs (86%) and horses (7%). The indications were primarily for tissue preservation in the field of transplantation. Of all the pig studies, nine used muscle stimulation/contraction as a surrogate marker of viability. Pig models are considered the most translational model and share anatomical (muscle mass, vessel diameter and nerve calibre) (Sauerbrey et al. 2014), and physiological characteristics that resemble humans (Dehoux and Gianello 2007; Kiermeir et al. 2013). Non-Human Primates (NHP) have preclinical relevance, but ethical concerns remain for in vivo testing, and they are prohibitively expensive. Therefore, an overview of how this technology can be applied to emerging bionic implant testing would be useful given the advantages non in vivo studies have on animal welfare (Prescott and Lidster 2017).

Use of NMP as a model

Despite the clear advantages of NMP in preserving tissue viability and neuromuscular function, our review identified a critical gap in its application for neuroprosthesis development. This underutilisation may stem from the complexity of NMP technology and the high costs of clinical-grade systems. However, integrating NMP into bioelectronic research could revolutionise preclinical testing by reducing reliance on live animal models, aligning with ethical guidelines, and potentially accelerating the development of advanced prosthetic technologies, ultimately improving patient outcomes.

Our lab has experience in developing physiological NMP protocols for pig limb perfusion (Amin et al. 2023; Amin et al. 2021). Two vital areas to control for using NMP as a model for bionic prosthetic development are ischaemia and maintenance of stable physiology. Critical ischaemia for muscle is 4 hours and nerve 8 hours, demonstrating the importance of limiting ischaemia (Muller et al. 2013). Studies by others have reported loss of nerve conduction and muscle contractility immediately after amputation, later restored following NMP, with no contractility observed in cold-stored controls (Constantinescu et al. 2011; Duraes et al. 2018; Fahradyan et al. 2020; Said et al. 2020). Recently, we have applied the application of this concept for the development of advanced prosthetic interface technologies (Amin et al. 2023). This study highlights the potential of NMP to serve as a valuable preclinical model for advancing bioelectronics. The ability of NMP to preserve neuromuscular function post-amputation, alongside real-time electrical stimulation, offers new avenues for testing implantable interfaces without the ethical and practical constraints

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of live animal models. Nevertheless, further formal comparisons with in vivo and in vitro data is required. Future studies should focus on overcoming barriers such as cost and technological complexity to fully realise the potential of NMP in advancing bionic prostheses.

Though out of the remit of our search criteria, an interesting study using NMP of human cadaver upper limbs (Rezaei et al. 2022) to preserve tissues for transplantation identified relevant findings. Contraction was preserved for approximately thirty hours. Neuromuscular function was significantly influenced by rising potassium (near limits expected to induce cardiac arrest in humans), decreasing calcium and acidosis. The cause of hyperkalaemia was unclear, but the authors suggested evaporative water loss, the absence of solid organs such as a kidney, intracellular loss from tissue injury and myocyte destruction (Rezaei et al. 2022). In the presence of acidosis, potassium can transit from the intracellular to extracellular space to buffer falling pH and could be one explanation, aside from cell death, for the higher concentrations observed at the start of perfusion (Oster et al. 1978). To address this, we have developed a multi-organ system incorporating autologous organs including spleen, liver and kidney (Stone et al. 2022).

To optimise perfusate physiology, perfusate exchange has been performed to account for electrolyte, red blood cell (RBC), lactate, creatine kinase (CK) and myoglobin derangements with time (Ozer et al. 2015). It is acknowledged that both CK and myoglobin increase with NMP, yet macroscopic contractility is observed for hours and therefore its significance is unknown (Duraes et al. 2018; Fahradyan et al. 2020). Unsurprisingly, increasing limb weight (a marker of oedema) correlates with muscle injury and reduced contraction in pigs (Meyers et al. 2022). Ozer *et al.* performed a perfusate exchange at two hourly intervals to overcome rising potassium concentrations, but their analysis used single fibre muscle biopsies (Werner et al. 2017). Kuecklehaus *et al.* found blood-potassium continued to rise, and this was unresponsive to boluses of glucose and insulin (Kueckelhaus et al. 2016), further demonstrating that the physiological environment is critical to neuromuscular function. This may explain why acellular solutions (Perfadex), frequently used clinically in solid organ perfusions demonstrates poor muscle contraction after 3 hours (Kueckelhaus et al. 2017).

In one pig study, the median nerve was stimulated directly by electrodes (Kruit et al. 2021). The lowest voltage of two repeated measurements needed to obtain a visible flexor muscle contraction was recorded. The mean nerve stimulation threshold to obtain visible muscle contraction was comparable between limbs that were cooled using the gold standard preservation approach of Static Cold Storage (SCS; 4 hours) and NMP (18 hours with University of Wisconsin). Limbs were then replanted and observed for 12 hours. In vivo contraction was better preserved after NMP than SCS. Histology did not correlate with muscle function at 12 hours post-replantation, further questioning the relevance of histology and neuromuscular function. Contralateral limbs had a stable muscle contraction threshold throughout the entire follow-up period with values between 4.3 and 4.9 mV (Kruit et al. 2021). The mean contraction threshold after replantation of SCS limbs ranged between 4.0 and 5.4 mV and showed a small increase at 2 h after replantation. NMP perfused limbs had contraction thresholds between 4.1 and 9.3 mV. When comparing the muscle contraction thresholds at the end of the experiment, there were no differences in strength of stimulation needed to reach visible muscle contraction between the three groups (Kruit et al. 2021).

Advanced prostheses will not only rely upon motor stimulation, but also acquisition of sensory function data. No animal model to our knowledge has been capable of peripheral nerve afferent sensory signals. Studies have used functional MRI in NHPs via stimulation of the somatosensory cortex, but this is not cost-effective or practical (Flesher et al. 2016). The adoption of NMP could revolutionise the preclinical testing landscape by reducing the reliance on live animal models, thus aligning with ethical guidelines and potentially accelerating the development of bionic prostheses.

Limitations and future directions of NMP as a model

(i) Several limitations exist in the current use of NMP. First, the reliance on clinically approved life-support systems and consumables can increase costs, limiting its widespread adoption in research. Future efforts should focus on developing more affordable, simplified NMP circuits that are accessible to research labs. Second, small animal models such as rodents have limited translational relevance due to differences in anatomy and nerve regeneration compared to humans. Larger animals, such as pigs, offer more accurate modelling but come with increased ethical and financial considerations. Developing NMP protocols for these larger models could overcome these challenges, while refining in vitro methods or utilising cadaveric human limbs might further reduce reliance on live animal testing. Finally, signal extraction from peripheral nerves remains variable, often due to 'noise' from neighbouring tissues. More sophisticated electrode designs and improved signal processing algorithms may offer a way to address this.

(ii) NMP requires clinically approved, advanced life-support systems and critical care consumables. Turbulent mechanical flow can damage intimal endothelium and provoke an inflammatory response (Matsuno and Kobayashi 2013), and NMP circuits cannot be constructed with uncoated surfaces made of foreign materials (plastic) that can activate the immune system and inflammatory cascades (Muller et al. 2013). NMP is highly complex, with expertise in surgery, advanced perfusion and critical care needed.

(iii) The optimisation of recirculating perfusate composition and experimental conditions requires further investigation.

(iv) There is time-dependent deterioration in the recirculating blood-perfusate.

(v) The pattern of nerve regeneration of the distal nerve after transection starts with that of peripheral nerve 'Wallerian degeneration', which results in phagocytosis of the axon and myelin remnants leaving a nerve scaffold. Macrophages stimulate Schwann cell proliferation in the proximal nerve attached to the cell body (NMP cannot account for this process in the amputated limb), later forming bands of Bungner that are essential for the regenerating axons to migrate towards the scaffold (Fu and Gordon 1997).

To advance this field, future research should focus on optimising the perfusate composition to enhance nerve preservation. Additionally, exploring the integration of real-time monitoring systems coupled with artificial intelligence and machine learning algorithms could provide deeper insights into tissue responses during NMP. This should be cost-effective and a simplified system that can be readily adopted for prosthetic

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development for not only interfacing but other aspects of research such as aiding signal transduction research. Interdisciplinary collaboration is essential to fully utilise the capabilities of NMP as a promising technology. This systematic review reports that studies have investigated the electrical and muscle activity present in NMP limb systems, but not utilised this technology to evaluate bionic technology. It may offer a new preclinical tool for those developing bioelectronic devices and ultimately accelerate the routes to impact for bioelectronics in medicine and healthcare.

Data availability statement. Data sharing not applicable, no new data generated.

Author contribution. KA, AC, JF conceptualised the review.

KA and EA were responsible for Data curation, formal analysis after agreeing a methodology with AC and JF.

All authors were responsible for writing the original draft as well as agreeing to the final publication.

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Connections references

Chakrabarty S, Chew D, Güemes A, Shivdasani M and Yin H (2024) How can innovative design strategies in biotechnology address biocompatibility and signal processing challenges in next-generation bioelectronic interfaces? *Research Directions: Biotechnology Design*. **2**, e16. https://doi.org/10.1017/btd.2024.22

References

Aman M, Bergmeister KD, Festin C, Sporer ME, Russold MF, Gstoettner C, Podesser BK, Gail A, Farina D, Cederna P and Aszmann OC (2019) Experimental testing of bionic peripheral nerve and muscle interfaces: animal model considerations. *Frontiers in Neuroscience* **13**, 1442. https://doi.org/10.3389/fnins.2019.01442.

Amin K, Stone J, Cowey W, Bowers C, Smith S, Entwistle T, Casson A and Fildes J (2023) Developing a porcine ex-vivo living limb system to investigate the bidirectional control of advanced prostheses. *Tissue Engineering - Part A* **29**, 13–14. https://doi.org/10.1089/ten.tea.2023.29043.abstracts.

Amin KR, Stone JP, Kerr J, Geraghty A, Joseph L, Montero-Fernandez A, Wong JK and Fildes JE (2021) Randomized preclinical study of machine perfusion in vascularized composite allografts. *Br J Surg* **108**, 574–582. https://doi.org/10.1002/bjs.11921.

Andreis FR, Metcalfe B, Janjua TAM, Fazan VPS, Jensen W, Meijs S and Nielsen T (2023) Morphology and morphometry of the ulnar nerve in the forelimb of pigs. *Anat Histol Embryol* **53**, e12972. https://doi.org/10.1111/ahe.12972.

Aszmann OC, Roche AD, Salminger S, Paternostro-Sluga T, Herceg M, Sturma A, Hofer C and Farina D (2015) Bionic reconstruction to restore hand function after brachial plexus injury: a case series of three patients. *Lancet* **385**, 2183–2189. https://doi.org/10.1016/S0140-6736(14)61776-1.

Bergmeister KD, Vujaklija I, Muceli S, Sturma A, Hruby LA, Prahm C, Riedl O, Salminger S, Manzano-Szalai K, Aman M, Russold MF, Hofer C, Principe J, Farina D and Aszmann OC (2017) Broadband prosthetic interfaces: combining nerve transfers and implantable multichannel EMG technology to decode spinal motor neuron activity. *Frontiers in Neuroscience* **11**, 421. https://doi.org/10.3389/fnins.2017.00421.

Berner M, Clement D, Stadelmann M, Kistler M, Boone Y, Carrel TP, Tevaearai HT and Longnus SL (2012) Development of an ultra mini-oxygenator for use in low-volume, buffer-perfused preparations. *International Journal of Artificial Organs* **35**, 308–315. https://doi.org/10.5301/ijao.5000075.

Biddiss EA and Chau TT (2007) Upper limb prosthesis use and abandonment: a survey of the last 25 years. *Prosthetics and Orthotics International* **31**, 236–257. https://doi.org/10.1080/03093640600994581.

Burlage LC, Lellouch AG, Taveau CB, Tratnig-Frankl P, Pendexter CA, Randolph MA, Porte RJ, Lantieri LA, Tessier SN, Cetrulo CL, Jr. and Uygun K (2022) Optimization of ex vivo machine perfusion and transplantation of vascularized composite allografts. *Journal of Surgical Research* **270**, 151–161. https://doi.org/10.1016/j.jss.2021.09.005.

Chakrabarty S, Chew D, Güemes A, Loeb G, Sharma R, Shivdasani M, Sridhar A and Yin H (2023) How do we overcome the current limitations of bioelectronic sensors used in healthcare and medicine? *Research Directions: Bioelectronics* **1**, e2. https://doi.org/10.1017/bel.2023.4.

Clippinger FW, Avery R and Titus BR (1974) A sensory feedback system for an upper-limb amputation prosthesis. *Bull Prosthet Res* **10–22**, 247–258.

Constantinescu MA, Knall E, Xu X, Kiermeir DM, Jenni H, Gygax E, Rieben R, Banic A and Vogelin E (2011) Preservation of amputated extremities by extracorporeal blood perfusion; a feasibility study in a porcine model. *Journal of Surgical Research* **171**, 291–299. https://doi.org/10.1016/j.jss.2010.01.040.

Davis TS, Wark HA, Hutchinson DT, Warren DJ, O'Neill K, Scheinblum T, Clark GA, Normann RA and Greger B (2016) Restoring motor control and sensory feedback in people with upper extremity amputations using arrays of 96 microelectrodes implanted in the median and ulnar nerves. *Journal of Neural Engineering* **13**, 036001. https://doi.org/10.1088/1741-2560/13/3/036001.

Dehoux JP and Gianello P (2007) The importance of large animal models in transplantation. *Front Biosci* **12**, 4864–4880.

Duraes EFR, Madajka M, Frautschi R, Soliman B, Cakmakoglu C, Barnett A, Tadisina K, Liu Q, Grady P, Quintini C, Okamoto T, Papay F, Rampazzo A and Bassiri Gharb B (2018) Developing a protocol for normothermic ex-situ limb perfusion. *Microsurgery* **38**, 185–194. https://doi.org/10.1002/micr.30252.

Fahradyan V, Said SA, Ordenana C, Dalla Pozza E, Frautschi R, Duraes EFR, Madajka-Niemeyer M, Papay FA, Rampazzo A and Bassiri Gharb B (2020) Extended ex vivo normothermic perfusion for preservation of vascularized composite allografts. *Artificial Organs* **44**, 846–855. https://doi.org/10.1111/aor.13678.

Flesher SN, Collinger JL, Foldes ST, Weiss JM, Downey JE, Tyler-Kabara EC, Bensmaia SJ, Schwartz AB, Boninger ML and Gaunt RA (2016) Intracortical microstimulation of human somatosensory cortex. *Science Translational Medicine* **8**, 361ra141. https://doi.org/10.1126/scitranslmed.aaf8083.

Fu SY and Gordon T (1997) The cellular and molecular basis of peripheral nerve regeneration. *Molecular Neurobiology* **14**, 67–116. https://doi.org/10.1007/BF02740621.

Grimm H, Biller-Andorno N, Buch T, Dahlhoff M, Davies G, Cederroth CR, Maissen O, Lukas W, Passini E, Tornqvist E, Olsson IAS and Sandstrom J (2023) Advancing the 3Rs: innovation, implementation, ethics and society. *Frontiers in Veterinary Science* **10**, 1185706. https://doi.org/10.3389/fvets.2023.1185706.

Johansson RS and Vallbo AB (1979) Tactile sensibility in the human hand: relative and absolute densities of four types of mechanoreceptive units in glabrous skin. *The Journal of Physiology* **286**, 283–300. https://doi.org/10.1113/jphysiol.1979.sp012619.

Kiermeir DM, Meoli M, Muller S, Abderhalden S, Vogelin E and Constantinescu MA (2013) Evaluation of a porcine whole-limb heterotopic autotransplantation model. *Microsurgery* **33**, 141–147. https://doi.org/10.1002/micr.22038.

Kruit AS, Brouwers K, van Midden D, Zegers H, Koers E, van Alfen N, Hummelink S and Ulrich DJO (2021) Successful 18-h acellular extracorporeal perfusion and replantation of porcine limbs - histology versus nerve stimulation. *Transpl Int* **34**, 365–375. https://doi.org/10.1111/tri.13802.

Kueckelhaus M, Dermietzel A, Alhefzi M, Aycart MA, Fischer S, Krezdorn N, Wo L, Maarouf OH, Riella LV, Abdi R, Bueno EM and Pomahac B (2017) Acellular hypothermic extracorporeal perfusion extends allowable ischemia time in a porcine whole limb replantation model. *Plast Reconstr Surg* **139**, 922e–932e. https://doi.org/10.1097/PRS.0000000000003208.

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Kueckelhaus M, Fischer S, Sisk G, Kiwanuka H, Bueno EM, Dermietzel A, Alhefzi M, Aycart M, Diehm Y and Pomahac B (2016) A mobile extracorporeal extremity salvage system for replantation and transplantation. *Ann Plast Surg* **76**, 355–360. https://doi.org/10.1097/SAP.0000000000000681.

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J and Moher D (2009a) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Medicine* **6**, e1000100. https://doi.org/10.1371/journal.pmed.1000100.

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J and Moher D (2009b) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *The BMJ* **339**, b2700. https://doi.org/10.1136/bmj.b2700.

Matsuno N and Kobayashi E (2013) Challenges in machine perfusion preservation for liver grafts from donation after circulatory death. *Transplantation Research* **2**, 19. https://doi.org/10.1186/2047-1440-2-19.

Meyers A, Pandey S, Kopparthy V, Sadeghi P, Clark RC, Figueroa B, Dasarathy S, Brunengraber H, Papay F, Rampazzo A and Bassiri Gharb B (2022) Weight gain is an early indicator of injury in ex vivo normothermic limb perfusion (EVNLP). *Artificial Organs* **47**, 290–301. https://doi.org/10.1111/aor.14442.

Muller S, Constantinescu MA, Kiermeir DM, Gajanayake T, Bongoni AK, Vollbach FH, Meoli M, Plock J, Jenni H, Banic A, Rieben R and Vogelin E (2013) Ischemia/reperfusion injury of porcine limbs after extracorporeal perfusion. *Journal of Surgical Research* **181**, 170–182. https://doi.org/10.1016/j.jss.2012.05.088.

Oster JR, Perez GO and Vaamonde CA (1978) Relationship between blood pH and potassium and phosphorus during acute metabolic acidosis. *Am J Physiol* **235**, F345–351. https://doi.org/10.1152/ajprenal.1978.235.4.F345.

Ouzzani M, Hammady H, Fedorowicz Z and Elmagarmid A (2016) Rayyan-a web and mobile app for systematic reviews. *Systematic Reviews* **5**, 210. https://doi.org/10.1186/s13643-016-0384-4.

Ozer K, Rojas-Pena A, Mendias CL, Bryner B, Toomasian C and Bartlett RH (2015) Ex situ limb perfusion system to extend vascularized composite tissue allograft survival in swine. *Transplantation* **99**, 2095–2101. https://doi.org/10.1097/TP.0000000000000756.

Page MJ, Shamseer L and Tricco AC (2018) Registration of systematic reviews in PROSPERO: 30,000 records and counting. *Systematic Reviews* **7**, 32. https://doi.org/10.1186/s13643-018-0699-4.

Pasquina CP, Carvalho AJ and Sheehan TP (2015) Ethics in rehabilitation: access to prosthetics and quality care following amputation. *AMA J Ethics* **17**, 535–546. https://doi.org/10.1001/journalofethics.2015.17.6.stas1-1506.

Prescott MJ and Lidster K (2017) Improving quality of science through better animal welfare: the NC3Rs strategy. *Lab Anim (NY)* **46**, 152–156. https://doi.org/10.1038/laban.1217.

Pylatiuk C, Kargov A and Schulz S (2006) Design and evaluation of a low-cost force feedback system for myoelectric prosthetic hands. *JPO Journal of Prosthetics and Orthotics* **18**, 57–61.

Rapeaux A, Syed O, Cuttaz E, Chapman CAR, Green RA and Constandinou TG (2022) Preparation of rat sciatic nerve for ex vivo neurophysiology. *Journal of Visualized Experiments : JoVE* **185**, e63838. https://doi.org/10.3791/63838.

Raspopovic S, Valle G and Petrini FM (2021) Sensory feedback for limb prostheses in amputees. *Nature Materials* **20**, 925–939. https://doi.org/10.1038/s41563-021-00966-9.

Rezaei M, Ordenana C, Figueroa BA, Said SA, Fahradyan V, Dalla Pozza E, Orfahli LM, Annunziata MJ, Rohde E, Madajka M, Papay F, Rampazzo A and Bassiri Gharb B (2022) Ex vivo normothermic perfusion of human upper limbs. *Transplantation* **106**, 1638–1646. https://doi.org/10.1097/TP.0000000000004045.

Said SA, Ordenana CX, Rezaei M, Figueroa BA, Dasarathy S, Brunengraber H, Rampazzo A and Gharb BB (2020) Ex-vivo normothermic limb perfusion with a hemoglobin-based oxygen carrier perfusate. *Military Medicine* **185**, 110–120. https://doi.org/10.1093/milmed/usz314.

Sauerbrey A, Hindel S, Maass M, Kruger C, Wissmann A, Kramer M, Nafz B and Ludemann L (2014) Establishment of a swine model for validation of perfusion measurement by dynamic contrast-enhanced magnetic resonance imaging. *BioMed Research International* **2014**, 390506. https://doi.org/10.1155/2014/390506.

Solomonow M (1984) External control of the neuromuscular system. *IEEE Transactions on Biomedical Engineering* **31**, 752–763. https://doi.org/10.1109/TBME.1984.325235.

Stone JP, Amin KR, Geraghty A, Kerr J, Shaw M, Dabare D, Wong JK, Brough D, Entwistle TR, Montero-Fernandez A and Fildes JE (2022) Renal hemofiltration prevents metabolic acidosis and reduces inflammation during normothermic machine perfusion of the vascularized composite allograft: a preclinical study. *Artificial Organs* **46**, 259–272. https://doi.org/10.1111/aor.14089.

Werner NL, Alghanem F, Rakestraw SL, Sarver DC, Nicely B, Pietroski RE, Lange P, Rudich SM, Mendias CL, Rojas-Pena A, Magee JC, Bartlett RH and Ozer K (2017) Ex situ perfusion of human limb allografts for 24 hours. *Transplantation* **101**, e68–e74. https://doi.org/10.1097/TP.0000000000001500.

Winslow BD, Ruble M and Huber Z (2018) Mobile, game-based training for myoelectric prosthesis control. *Frontiers in Bioengineering and Biotechnology* **6**, 94. https://doi.org/10.3389/fbioe.2018.00094.

Ziegler-Graham K, MacKenzie EJ, Ephraim PL, Travison TG and Brookmeyer R (2008) Estimating the prevalence of limb loss in the United States: 2005 to 2050. *Arch Phys Med Rehabil* **89**, 422–429. https://doi.org/10.1016/j.apmr.2007.11.005.

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