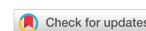


Review Article

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Liquid metal neuro-electrical interface

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Abstract

Liquid metal (LM), an emerging functional material, plays increasing roles in biomedical and healthcare areas. It has particular values in neural interfaces as it combines high conductivity, flowability, and biocompatibility properties. Neuro-electrical interfaces (NEIs) are effective tools to provide a bridge between the nervous system and the outside world. The main target of developing neural interfaces is to help disabled people repair damaged nerves and enhance human capacity above normal ability. This article systematically summarizes LM-based neural interface technologies, including neural electrodes for electrical signal acquisition and administration of electrical stimulation and nerve guidance conduits for neural connectivity and functional reconstruction. The discussion begins with an overview of the fundamental properties associated with LM materials involved in the field of neural interface applications. The fabrication methods of LM-based neuro-electrodes and conduits are then introduced, and the current development status of LM-based neuro-electrodes and conduits is elaborated. Finally, the prospects and possible challenges of LM-based neural interfaces are outlined.

Keywords: Liquid metal, neural interface, neural electrode, neural guidance conduit



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INTRODUCTION

Room temperature liquid metals (LMs) typically refer to gallium (Ga) metal and Ga-based low-melting point alloys^[1]. LMs are now extensively used in biomedical applications owing to their excellent electrical, thermal, mechanical, and biological properties^[2-4]. In the case of conventional biomaterials, such as rigid metals, ceramics, and silicon and their complexes, it is difficult to match their elastic moduli with those of human body tissues^[5]. Unlike this, LMs appear in fluid at room temperature and can, thus, easily be incorporated into various soft materials or even directly printed on the biological skin to work as the electronic tattoo (E-tattoo), which allows the quick fabrication of various bioelectronic devices^[6]. In recent years, fundamental discoveries and technological advances in this field have led to the establishment of novel therapeutic and diagnostic approaches, including the cutting-edge area of neural interfaces^[7-10]. Particularly, introduction of the LM as a connecting or functional recovery channel for the transected sciatic nerve^[10] significantly innovated the classical category of neurorepairing and interface reconstruction.

The neuro-electrical interface (NEI) serves as a bidirectional communication bridge between the nervous system and external electronic devices and typically includes the tissue and the sensing interfaces. The tissue interface converts biological signals from the nervous system into electrical signals (e.g., nerve conduits). The sensing interface realizes the acquisition and stimulation of signals (e.g., nerve electrodes). Conventional NEI mostly uses rigid materials. At present, NEI is developing in the direction of full flexibility, miniaturization, and high integration. One of the key roles of NEI is to transmit electrical signals quickly, efficiently and accurately. Therefore, it is extremely valuable to improve the conductivity of the electrodes and reduce the interfacial impedance between the electrodes and the neural tissue. The conductivity of Ga-based alloy is 3.4×10^6 S/m, which is in the same order of magnitude as that of platinum (Pt, 9.5×10^6 S/m), and it can be further enhanced by mixing a certain percentage of metal powders with high conductivity [e.g., silver (Ag) and copper]^[11-15]. In addition, micrometer-scale LM electrodes can be prepared using various processes, such as printing, injection, selective wetting, and deposition. Ga-based LM also possesses biocompatibility and has been applied to prepare epidermal electrodes and *in vivo* implantable electrodes. Therefore, considering the mechanical and electrical properties, preparation method, and biocompatibility, Ga-based LM is a suitable candidate for preparing flexible stretchable nerve electrodes.

The nervous system is classified into the central (CNS) and peripheral nervous systems (PNS). The CNS includes the brain and the spinal cord; in this case, the core hardware of the NEI is the electrodes used for recordings and stimulations [Figure 1A]. In the PNS case, the core hardware of the NEI consists of nerve electrodes and nerve conduits used to connect and repair nerves [Figure 1B]. Note that the nerve electrodes for CNS and PNS tend to differ in structures. The output of the nerve electrode is the external signal processor, while the nerve conduit acts on the autologous nerve. Thus, nerve electrodes used to be made as sheet-like arrays of electrodes that fit very snugly into the tissues. The nerve conduit tends to be a cylindrical conductor of electricity, similar to the morphology of the nerve.

Optimization strategies for nerve electrodes and nerve catheters are closely related to the development of electrode and catheter materials. The review of the development of electrode materials can be dated back as early as 1981. Hamill *et al.* adopted flint or borosilicate glass and metal wire to prepare the diaphragmic clamp^[16]. Subsequently, the neuro-electrodes composed of gold (Au), Pt, Ag, stainless steel, tungsten (W), doped polysilicon and other metals have been used^[17-23]. The schemes listed above have been mainly based on rigid materials, which may cause damage to soft human tissues. Long-term exposure to foreign bodies may also lead to progressive inflammatory and fibrotic reactions, further causing neuroglial scarring or loss of neurons^[24]. To enable better interaction between the CNS and external machines, it is becoming

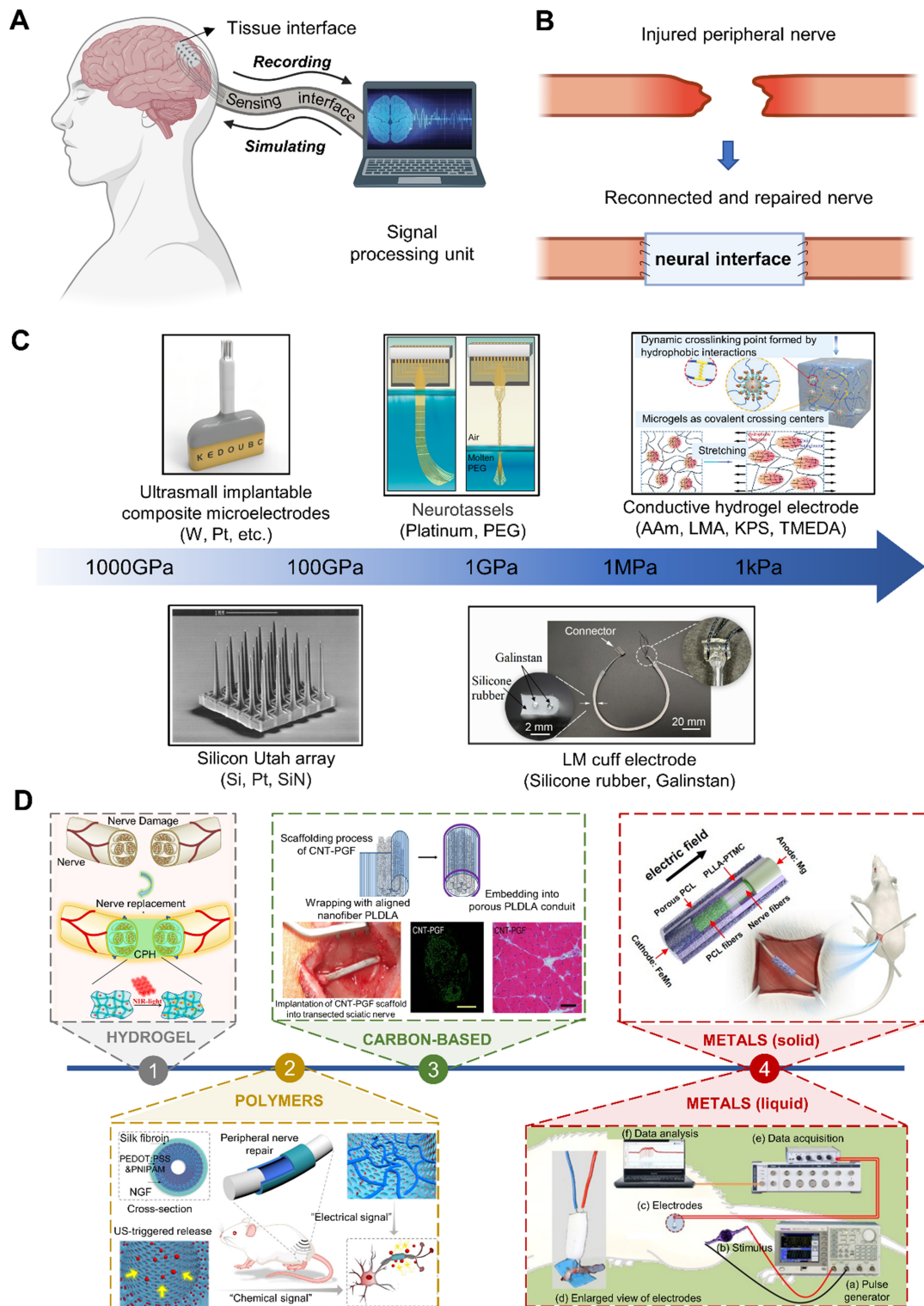


Figure 1. Functions of neural interfaces and the development and classification of conductive materials for neural interfaces. (A) Neuro-electrodes for acquiring nerve signals and electrically stimulating nerves; (B) Schematic diagram of connecting and repairing nerves; (C) The development of neuro electrodes over time [7,29-32]; (D) Conductive materials for neural connectivity and repair [8,44-47].

increasingly important to design electrodes with electrical and mechanical properties similar to those of neural tissue. The corresponding fabrication materials often need to be biocompatible, stable, and cause

minimal damage to neural tissue^[25]. Among the many developments of flexible neural interfaces, LMs have gained attention in recent years. As a class of materials with ease of preparation, they have been extensively tried in the fields of drug delivery, cancer therapy, and medical devices^[26-28]. Their high ductility, good biocompatibility, and excellent electrical conductivity make them outstanding candidates for fabricating flexible neural interfaces. A review of the development of neuro electrodes [Figure 1C] indicates that their transformation from rigid to flexible forms is a logical trend^[7,29-32]. While flexible electrodes develop to an end-point liquid form, which can be well adapted to the human body and applied in it.

In addition to their use for the preparation of nerve electrodes, LMs can also be adopted for preparing nerve conduits. Nerve conduits are used to connect and repair peripheral nerves. Peripheral nerve injury (PNI) is the most common cause of disability in the world^[33]. The medical target is to restore critical function and sensibility to the extremity by repairing the nerve directly under no-tension conditions while anticipating innate nerve regeneration^[34,35]. Autografting of the nerve defect is currently considered the gold standard procedure^[35,36] but causes donor site morbidity^[37]. Alternatives, such as commercial allograft nerves and nerve guidance conduits (NGCs), are available^[38,39], with allografts providing a scaffold for nerve regeneration. However, NGCs have limitations primarily in their ability to regenerate nerve function and prevent undesirable outcomes such as slow axonal growth or misdirection at the site of injury, atrophy of the target organ, and failure of re-innervation^[40,41]. Therefore, they currently only show acceptable outcomes for short, sensory nerve gaps^[42,43]. The ideal NGC could stimulate proximal nerve growth and allow bioelectricity to be conducted to emulate the natural environment in its distal part. There are four main categories of conductive materials currently used for nerve bridging: hydrogels, polymers, carbons, and metals [Figure 1D], in which the metals have the highest conductivity rate^[8,44-47] that may theoretically achieve instant bioelectricity. LMs are one of these materials that stand out for their modulus (similar to that of nerve tissue) and excellent flexibility^[7,10]. Their great potential as bridging materials provides an alternative for conventional NGCs in treating large nerve gaps.

This review first introduces the composition, classification, and development trend of NEI technology and summarizes how conductive LM materials can be utilized to realize the fabrication of flexible neuro-electrodes and stretchable nerve conduits. Subsequently, the electrical, mechanical, biological, and fluidic properties of LMs are systematically presented. These properties enable LMs to be fabricated into NEI using various preparation processes, including printing, injection, microfluidics, and deposition. Finally, this study summarizes the research progress and applications of LM-based NEI and provides an outlook on its future challenges.

LMS: BASIC PROPERTIES

The low-melting-point metal monomers in a liquid state near room temperature are mercury (Hg), cesium (Cs), and Ga. Among these, Hg is toxic, and Cs is too active chemically. Ga is more stable in air and has a lower melting point and higher boiling point, and has thus been extensively studied and applied. LMs used in NEI are dominated by Ga-based alloys. The elements of these alloys usually include Ga, lead, tin (Sn), and indium (In). Different compositions and proportional configurations may lead to varying properties of the alloys, and some typical properties are listed in Table 1. To explore the application of LMs in neural interfaces, focus should be placed on relevant properties when they function as tissue interfaces, i.e., in surface tension and double electro-layer models. Meanwhile, the electrical properties, biocompatibility, and mechanical properties should be considered when applied to organisms.

Table 1. Typical LMs and properties^[48-55]

Types	Ga	Ga _{75.5} In _{24.5}	Ga _{68.5} In _{21.5} Sn ₁₀	Ga ₆₁ In ₂₅ Sn ₁₃ Zn ₁
Melting point (°C)	29.8	15.5	10.5	7.6
Boiling point (°C)	2,204	2,000	> 1,300	> 900
Density (g/cm ³)	6.05	6.28	6.44	6.5
Surface tension (N/m)	0.72	0.624	0.718	0.5
Viscosity (10 ⁻⁶ m ² /S)	0.324	0.27	0.372	0.711
Electrical conductivity (10 ⁶ S/m)	3.7	3.4	3.46	2.8

Ga: Gallium; In: indium; Sn: tin; Zn: zinc.

Electrical properties

LMs have significant advantages when applied to NEI. The electrical conductivities of pure Ga, Ga_{75.5}In_{24.5}, Ga_{68.5}In₂₀Sn₁₂ are 3.7×10^6 S/m, 3.4×10^6 S/m, and 3.46×10^6 S/m, respectively^[56]. As shown in Figure 2A, the electrical conductivity of LMs is better than those of many carbon-based conductive materials (e.g., carbon nanotubes, 1-10 S/m) and organic conductive materials (e.g., polypyrrole, which has conductivity up to 10^{-5} S/m when doped)^[57-61]. Moreover, when LM electronic devices are subjected to deformations, such as stretching and bending, the change in resistance can be maintained at a low level (less than 5% change)^[62,63]. It should be noted that when the Ga-based metal is exposed to air, the Ga oxide layer generated on the surface will affect electrical conductivity. For example, for 40 g of GaIn₁₀, the resistivity increases rapidly and affects the signal transmission efficiency when the oxide content increases to 10 mg^[64]. Attention is also needed when using LM nanoparticles; in this case, the oxide layer on the surface needs to be removed before practical applications.

When a small area of LM is in contact with an electrolyte, the interface between the two media becomes electrically charged owing to a series of electrochemical activities; this interface is known as the electric double layer (EDL)^[65]. When the electrode surface potential changes, the EDL capacitor charges or discharges. When the cell and the electrode are coupled, the ionic current formed by the change of the membrane channel polarizes the electrode to form a voltage difference (i.e., the extracellular voltage). The basic principle of generating this difference is schematically represented in Figure 2B. Therefore, neural electrodes can record extracellular membrane action potentials and, thus, allow the transmission of electrical signals in cellular networks composed of electrically active cells. When a neural electrode is electrically stimulated, its equivalent circuit at the electrode/tissue interface is shown in Figure 2C. Similar to electrical signal acquisition, electrical stimulation is also enhanced by the lower impedance at the interface, thus allowing higher charge injection limitations; therefore, more effective and safer stimulation is achieved by using micrometer-sized electrodes^[66]. In future designs, it will also be possible to surface-modify LM-based electrodes so that the impedance at the interface is minimized.

Mechanical properties

The nervous system tissues in the human body are all soft, and their modulus of elasticity is at most in the order of MPa^[67]. If the materials used for the interface are too rigid, such as Pt (modulus of elasticity: 172 GPa) or silicon (modulus of elasticity: 190 GPa), there will be a huge difference between the mechanical properties of these materials and those of the nervous tissues that may lead to defects such as tissue damage.

As shown in Figure 2D, the elastic moduli of solid metals (Au, W, Pt, *etc.*), carbon-based materials, and conductive polymers (polyisoprene and polyamide) vary considerably from that of neural tissue. LMs with fluidity properties are well suited for applications as stretchable conductive materials. However, these Ga-based alloys need wrapping materials when combined with the human body in practical applications. LMs,

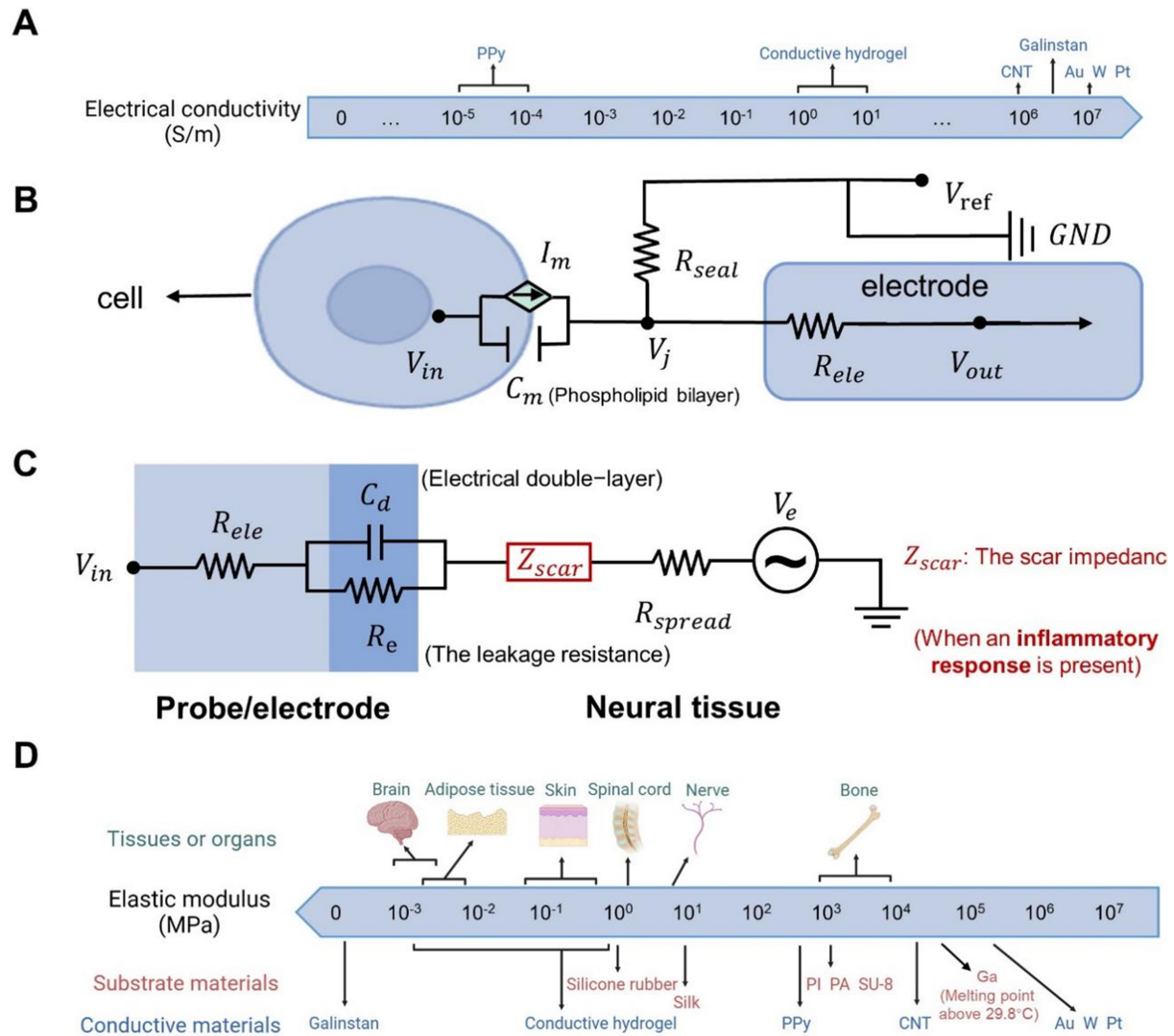


Figure 2. Electrical and mechanical properties of commonly used neural interface materials. (A) Electrical conductivity of commonly used neural interface materials; (B) Neuroelectric signal acquisition schematic; (C) Equivalent circuits at the electrode/tissue interface; (D) Elastic modulus of commonly used neural interface materials and biological tissues.

as pure liquid materials, have a lower modulus of elasticity than the wrapping material. Therefore, the elastic modulus of LM-based electrodes depends on the wrapping material. Furthermore, the common wrapping materials are Polydimethylsiloxane (PDMS), Styrene-Ethylene-Butylene-Styrene, Ecoflex, and others. When used as nerve conduits, the conduits and nerves need to be sutured. Therefore, in addition to focusing on the modulus of elasticity of various types of conductive materials, it is also necessary to focus on the mechanical and operational properties of diverse conduit materials during the suturing process. Currently, most of the commonly used commercial nerve conduits are designed as fibers. Therefore, in the future, the design of conductive nerve conduits can be performed by either designing the conductive materials in fibrous form or by designing the wrapping materials in fibrous form.

Wetting properties

The wettability of the LM plays a key role in its applications that mainly depend on the viscosity and surface

tension. Liquid Ga has low viscosity and high-surface tension, and both parameters decrease as a function of temperature^[55].

The oxidizing treatment reduces the surface tension of the LM, thus improving its wettability to the surface of the substrate material. The increased viscosity makes the LM printable. For example, the surface tension of pure eutectic gallium-indium (EGaIn) liquid drop is approximately 435 mN/m, while that of the EGaIn liquid drop-coated oxide films could be adjusted to 624 mN/m. Therefore, this method influences the wettability of the LM. It has been demonstrated that as the oxide content in the LM increases, the wettability of the LM gradually improves on different substrates, including paper, silica gel plates, and rubber sheets^[64]. Additionally, given the application of extra pressure, the wettability could also be improved^[68]. In the future, the flow capability of LM can be changed by controlling its oxidation level, resulting in the manufacturing of NEI devices that are stable over time and free of LM leakage. Appropriate treatment will promote LM to fill the entire flow channel during injection and thus better make flexible conducting wires.

Biological properties

As a class of materials directly applied to the human body, the biocompatibility of LM is an important factor to consider. As early as 70 years ago, researchers tested the toxicity of Ga lactate and chloride in rats and rabbits following inhalation, ingestion, and injection. The low toxicity of Ga ions was verified^[69]. In 2003, a pharmaceutical formulation of citrate-buffered Ga(NO₃)₃ was approved by the United States Food and Drug Administration (FDA) for treating malignancy-associated hypercalcemia^[70]. In 2014, Wang *et al.* performed an *in vitro* toxicity test (mouse embryonic fibroblasts) using the Cell Counting Kit-8 method and flow cytometry^[71]. Twenty-four hours later, the cell survival rate of the Ga dip was 100.6%. In 2019, Liu *et al.* injected 0.2 mL of Ga into the stomachs of female BALB/C mice (The mice used in the studies were approximately eight weeks of age with weight ranging around 20 ± 1 g)^[72]. Their experimental results showed that the mice were very healthy after injection and demonstrated good food consumption and normal defecation habits. These studies have laid the foundation for the extensive use of Ga-based alloys in biomedical applications. In 2017, Guo and Liu performed an *in vitro* cytotoxicity test (mouse 3T3 fibroblasts) on EGaIn and determined cell viability using the Methyl thiazolyl tetrazolium (MTT) assay^[73]. Their experimental results showed that the cell viability of mouse fibroblasts containing LM elements exceeded that of cells without LM elements. In 2019, Wang *et al.* conducted *in vitro* and *in vivo* cellular experiments (Cell Counting Kit-8 assay, human malignant C8161 cells, and normal HaCaT cells) and *in vivo* injection experiments (direct subcutaneous injection of 100 µL of LM, observed for four weeks) against EGaIn^[27]. Both experiments demonstrated the low toxicity of EGaIn.

Most studies support the conclusion that Ga is associated with very low toxicity outcomes^[74]. However, the potential toxicity of LMs in specific environments remains to be confirmed, and the state of the material and the effects of long-term cumulative effects need to be considered. The biocompatibility studies of LMs acting on neurons and neural tissues are still relatively few and need further validation.

PREPARATION OF LM NEURO-ELECTRODE/CONDUIT

Currently, LMs can be easily fabricated into micrometer-sized neuro-electrodes through various preparation methods. When performing microfabrication, attention needs to be paid to the resolution and precision of the patterned structures based on two important criteria: the smallest size that can be fabricated and the roughness of the line edges^[75,76]. The following section describes the four main methods and the precision of each electrode.

Printing

Compared with other conductive materials, LMs are flowable and printable at room temperature. Therefore, the printing process can be applied to prepare NEI to obtain thinner LM-based NEI.

At the macroscopic scale, Guo and Liu printed an EGaIn-based, flexible neural microelectrode array system using a spray-based printing technique^[73]. A stainless-steel mask was first fabricated using metal chemical etching, and the mask was subsequently placed on a PDMS substrate. LM was atomized by a gas gun and gas pump. The LM stream was disrupted by a high-energy gas jet, which induced the formation of microdroplets and caused them to fall onto the PDMS substrate. The stainless steel mask was finally removed to obtain the LM electrode array attached to the PDMS substrate.

At the microscopic scale, the researchers sonicated Ga-based LM to obtain nanoscale LM particles. The preparation process is shown schematically in Figure 3. After obtaining the LM nanoparticles, LM ink for screen printing can be obtained by adding n-decanol to the nanometallic particles. LM ink was screen printed on a polyethylene terephthalate (PET) substrate using screen printing equipment. It was baked in an oven at 80 °C for 20 min to remove residual solvents from the LM ink. Subsequently, prepolymers of elastomers, such as PDMS or Ecoflex, were spin-coated on top of the LM patterns. After curing and peeling, the LM pattern was transferred from the PET film to the elastomeric substrate, thus resulting in a stretchable LM conductor^[77-79]. In addition, LM inks can be used to prepare electrodes using writing and laser printing processes^[80]. In contrast, the precision of the LM electrodes prepared by writing and laser printing is not as high as that of screen printing and will not be described in detail in this review. The precision obtained using the printing method depends on the precision of the mask plate. The minimum width and thickness of the electrodes are tens of micrometers. The LM electrodes produced by printing possess rough edges, which can be improved by increasing the uniformity of the LM particles in the ink.

Injection

The injection method tends to form the flow channel first and inject the LM later. Recently, Lim *et al.* explored the application of LM-based NEIs prepared using the injection method in the CNS by reducing the size of the LM flow channel^[81]. The team first injected liquefied Ga or EGaIn into polyether block amide (PEBAX) tubes. These tubes were heated to 170 °C to melt and then instantly stretched by 500% to form 60 and 20 µm LM/PEBAX core-shell structures. The LM-based nerve electrodes produced by this method could be bent and twisted at will, and the size could be controlled to a few tens of micrometers. However, the elastic modulus of PEBAX is at the level of tens of MPa, higher than the modulus of neural tissues, especially the brain. Therefore, Tang *et al.* proposed the encapsulation of LM with stretchable human silicone and prepared an LM-cuffed electrode with two channels with an elastic modulus of about 1 MPa^[7].

To increase the number of channels, Zhang *et al.* prepared an LM-based neural electrode array with 20 channels in combination with a soft broad engraving process^[9]. The preparation process is presented in Figure 3. First, SU-8 photoresist was coated on a silicon tray, and a SU-8 mold was then obtained on the silicon tray after the completion of the pre-baking, exposure, post-baking, and development steps. Then, PDMS was poured onto the mold and coated using a spin coater at 500 rpm for 2 min; it was then heated at 65 °C for 150 min. After that, the thin PDMS substrate was peeled off from the mold. After that, holes with a diameter of 0.5 mm were punched at both ends of the channel using a hole punch. Then, a plasma cleaner was used to attach the PDMS structure to another blank PDMS film by plasma bonding. Finally, EGaIn was injected directly into the channel using a syringe to obtain an electrode array with high throughput. The thickness of LM electrodes obtained by the injection method depends on the thickness of the photoresist, and the width of the LM electrode depends on the accuracy of the mask. The minimum width and thickness of the electrodes are tens of micrometers. Electrodes prepared by the injection method have smooth wire edges due to the constraints of the flow channel.

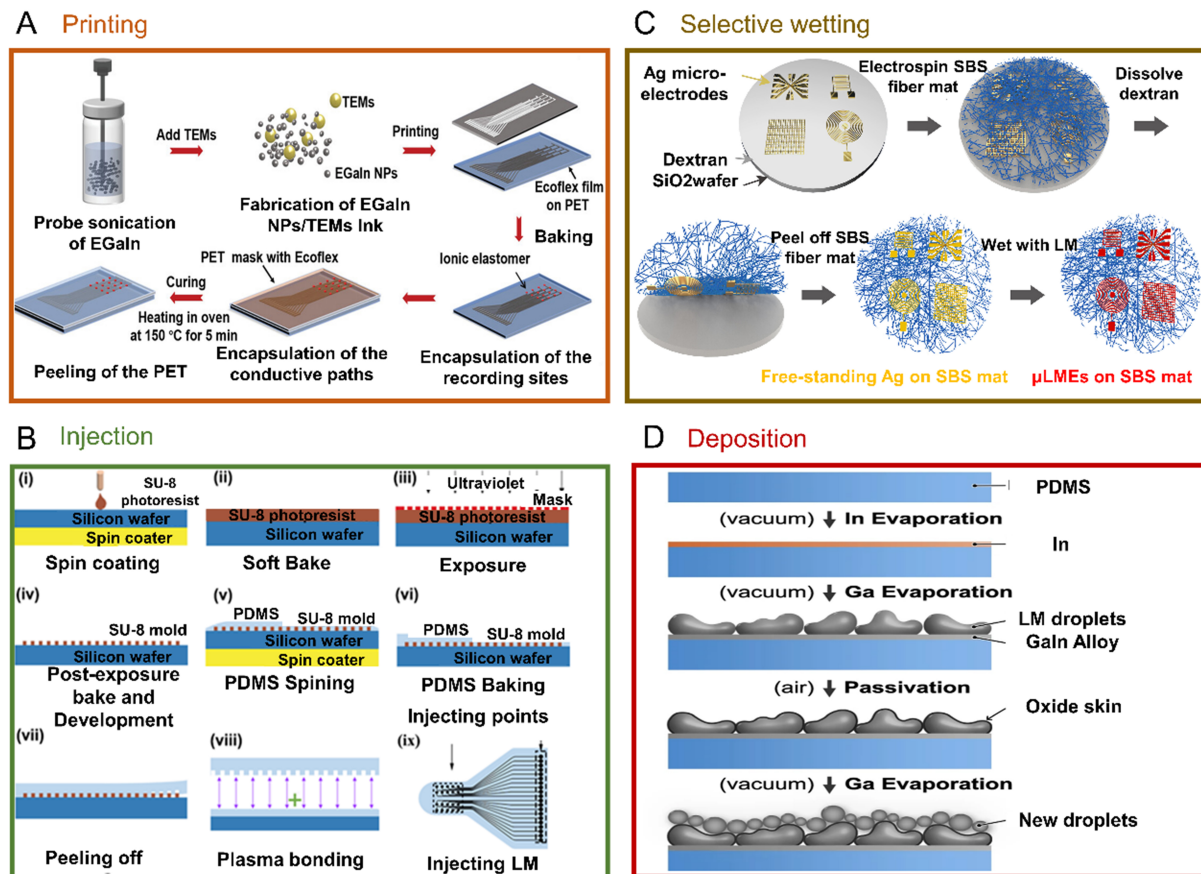


Figure 3. Process for the preparation of LM-based neural interfaces. (A) printing; (B) injection; (C) selective wetting; and (D) deposition^[9,78,87,88]. LM: Liquid metal.

Selective wetting

Over the past few decades, scientists have made remarkable achievements in developing highly stretchable electronics by patterning devices and circuits on polymeric film substrates [e.g., polyimide (PI)] and elastomers (e.g., PDMS and Ecoflex)^[82–85]. However, LM cannot be patterned directly on elastic substrate materials owing to its large surface tension^[86]. To solve this problem, Zhuang *et al.* designed a wafer-level patternable strategy to achieve the high-resolution fabrication of ultrasoft, stretchable, and permeable LM microelectrodes (μLME)^[87]. The preparation process is presented in Figure 3. Ag lithography was first performed on a silica wafer and premodified with a thin layer of water-soluble dextran. Subsequently, a polyfiber mat [styrene–butadiene–styrene (SBS)] was electrospun on the Ag micropattern after the dextran layer was dissolved. Finally, the Ag micropatterns on the silica wafer were transferred onto the SBS fiber mats, and the LM on the Ag-covered area was selectively wetted to generate μLME with an approximate thickness of 2 μm. Patterning here mainly takes advantage of differences in the wettability of the substrate material. The part modified by Ag has excellent wettability to LM, while the other parts have poor wettability to LM. The thickness and width of the LM electrodes can be a few micrometers, which is adjusted by the thickness and width of Ag/Cu. The resolution of the LM electrode depends on the wire edge roughness of the patterned Ag/Cu.

Deposition

To maintain the original mobility of LM and avoid the generation of other intermetallic compounds (e.g., AgGa₂), Park *et al.* prepared an LM microscale network film using the deposition method^[88]. The preparation process is presented in Figure 3. First, a PI shadow mask was placed on a PDMS substrate. After cleaning the surface of the prepared PDMS substrate with isopropyl alcohol and air plasma, the substrate was placed in the vacuum chamber of a thermal evaporator. In was deposited once to form a solid metal layer followed by the deposition of Ga on a layer-by-layer basis. After setting the vacuum level and deposition rate, LM microdroplets were introduced into the chamber by introducing ambient air into the chamber for 60 s with air pressures > 1.0 kPa. By applying tensile strain to the resulting LM microstructures, LM microscale network (LMMN) films were obtained with a thickness of a few micrometers. The thickness of the LM electrodes can be adjusted by varying the deposition time and deposition rate. The width and thickness of the electrodes can be a few micrometers. The resolution of the electrodes prepared by this method depends on the precision of the pattern structure in the mask.

Neuro-electrodes have a wider range of applications than neural conduits and are currently used in brain-computer interfaces, precision medicine and neuroscience. There are more methods for preparing LM neuro-electrodes than those for LM nerve conduits. Currently, all studies on the LM nerve conduit used the injection method. In 2014, Zhang *et al.* proposed the fundamental strategy of using LM conduct to bridge the disconnected nerves and, thus, reconstruct their signal transmission functions for the first time^[10]. Subsequently, Liu *et al.* investigated the injection of LMs as feasible agents to repair the function of peripheral nerves, using stainless steel wire to plug the stumps of the fragments^[8]. The LM-based NEI prepared using this method was demonstrated to connect the injured sciatic nerve in mice. In contrast, LM nerve electrodes can be prepared using processes such as printing, injection, selective wetting and deposition. Actually, these methods are not limited to the fabrication of electrodes but also can be used to prepare nerve conduits. Future attempts should be made to prepare LM nerve conduits using different preparation processes.

APPLICATIONS OF LM NEIS

LM-based neural electrodes

Throughout the development of the LM nerve electrodes, the researchers first conducted a series of *in vitro* testing experiments, including electrical stimulation and electrical signal acquisition of isolated cells, tissues, and organs. These experiments laid the foundation for conducting *in vivo* implantation experiments. Currently, the animals commonly used for *in vivo* implantation experiments are mice, rats, and nonhuman primates.

Hallfors *et al.* conducted electrical stimulation tests on isolated neuronal cells^[89]. They combined pure Ga and EGaIn with their previously developed microfluidic culture platform to obtain a neurostimulation platform that achieved stimulation of neurons with subcellular precision. As shown in Figure 4A, Jin *et al.* prepared implantable bioelectrodes (cylinders with diameters of 1 mm) by constructing electrode molds in gelatin followed by LM injection^[90]. The *in vivo* animal experiments showed that LM-based electrodes can be used for the acquisition of electrical signals and the administration of electrical stimulation. Subsequently, in 2017, the present group designed an LM-based neural electrode capable of being used in the PNS [Figure 4B]. The mechanical and electrical properties of the electrodes were tested in detail and included tensile, fatigue resistance, and electrochemical tests. The experimental results showed that the LM-based electrodes were suitable for recording electrical signals and for electrical stimulations during prolonged periods^[73]. The conductive material in direct contact with tissues in the studies listed above was LM. However, LM exposed to physiological aqueous environments may undergo oxidative behavior that affects the electrical performance of the electrodes. To address this issue, Lim *et al.* electrochemically

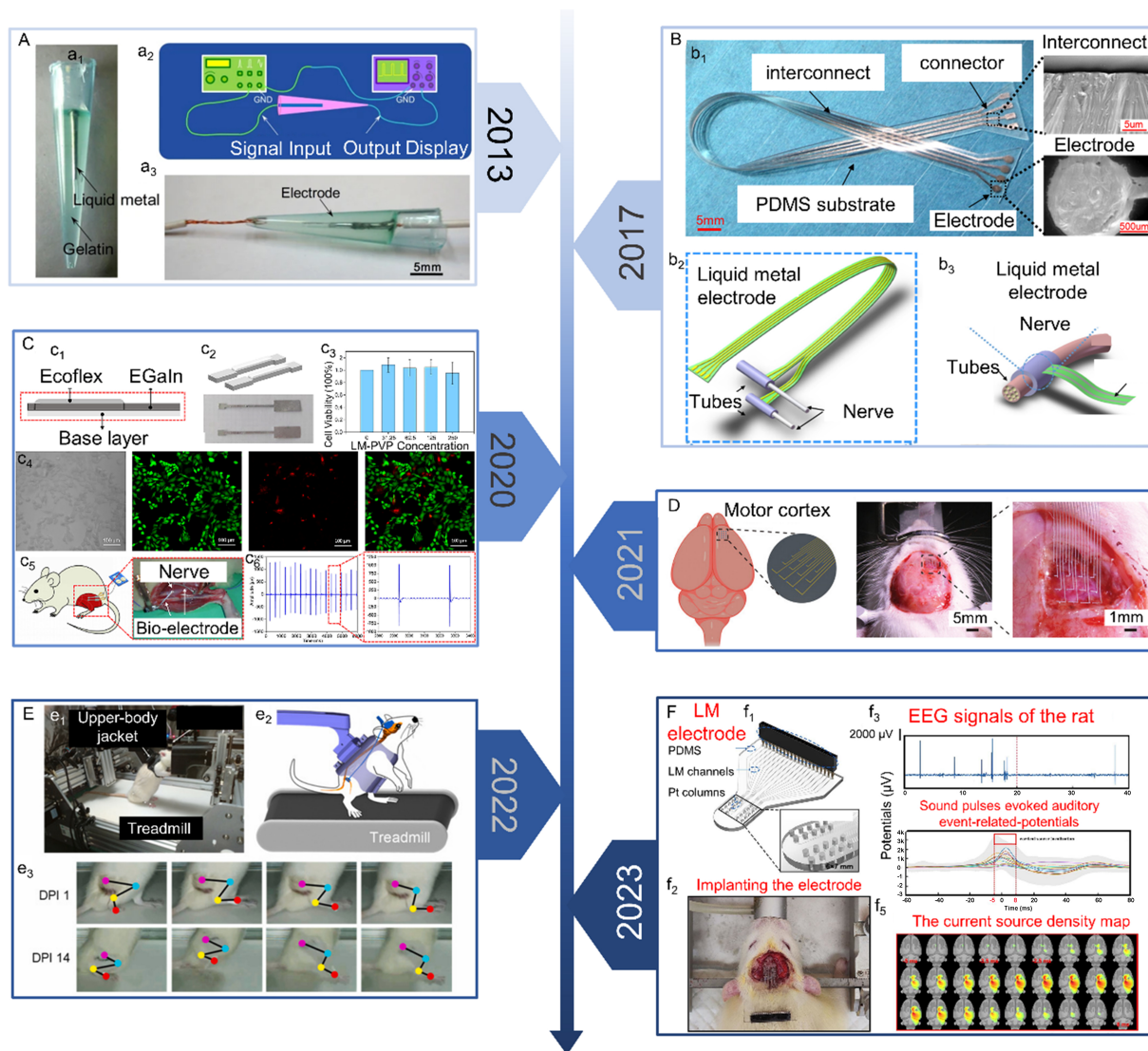


Figure 4. The evolution of LM-based neuro-electrodes. (A) Fabrication of 3-D medical electronic devices directly in living organisms by continuous injection of biocompatible packaging materials and LM inks^[90]; (B) The LM nerve electrodes and the machining process^[73]; (C) LM nano-ink based bioelectrode^[92]; (D) LM neuro-electrodes that can be used to record EEG signals and ECG signals^[77]; (E) LM cuff electrodes that can be adapted to the movement process^[7]; (F) LM-based nerve electrode arrays that fit very well into the skull^[9]. LM: Liquid metal.

deposited a conducting polymer onto the surface of Ga-based LM and implanted LM-based electrodes into animals to record action potentials^[81]. Results showed that the performance of the modified electrodes was superior to those of the bare and Pt electrodes. This was also the first demonstration of LM-based bioelectronic devices for single-neuron signal recordings in conscious nonhuman primates.

LM nanoparticles have received considerable attention in recent years^[91]. However, they require the design of sintering processes or mechanical forces to remove the oxide film from the surface of the nanoparticles to restore electrical conductivity. In 2020, Zhang *et al.* accomplished the preparation of LM-based electrodes by writing EGaIn nano-inks directly and laser-printing EGaIn nano-inks^[92]. As shown in Figure 4C, these two types of electrodes could receive nerve signals from mice and electrically stimulate nerves *in vivo*. In 2021, Dong *et al.* obtained LM circuits based on the screen-printing technique with sputter-deposited Pt as

the recording electrode^[79]. The cell experiments showed that the electrochemical performance of this electrode was similar to that of conventional titanium nitride electrode arrays. Furthermore, the electrode has mechanical properties of stretchability and fatigue resistance while maintaining good electrical conductivity. Subsequently, the team also designed an LM-based neural electrode capable of ECoG signal acquisitions in rats [Figure 4D]^[77]. The electrode allows real-time monitoring of epileptic activity in different seizure states and provides a new avenue for neural diagnosis and monitoring. However, it is important to note that nanoparticles require the removal of the oxide film on their surfaces to restore their conductivities.

In 2022, our team implanted the dual-channel LM cuff electrode in rats [Figure 4E]; the electrodes can adapt to postural changes, such as repeated stretching or twisting, and still maintain stable and effective bidirectional transmission of high signal-to-noise ratio neural signals. The LM electrodes could also transmit neural stimuli to peripheral nerves over a long period by triggering the cortical potentials and the sciatic nerve signals with a clear event-related potential. Experimental results showed that the LM electrode meets the requirements for long-term implantable peripheral nerve signal recordings and stimulations. This suggests that the LM peripheral nerve electrode has the potential to be used as an artificial peripheral nerve prosthesis and to repair peripheral nerve tissue in the future^[7]. In 2023, the present research team developed an LM-based brain electrode array [Figure 4F], which exhibits excellent bending, twisting, and stretching deformability and can form conformal contact with the skull surface of rats. The electrodes can record electroencephalographic signals in rats at different anesthetic doses and the potentials evoked in the rat cerebral cortex associated with auditory events (the rats were stimulated with acoustic pulses by snapping their fingers)^[9]. Analysis of the above studies reveals that the development of recording neural interfaces focuses on capturing neural activity with high sensitivity, spatial resolution and minimal invasiveness. High sensitivity is often achieved by coatings, such as IrOx, PEDOT, TiNx, platinum black, *etc.*, to reduce the interfacial impedance. To provide high spatial resolution recording, micro or even nano level fabrication techniques were utilized to fabricate high density neural interfaces array. For concern of minimal invasiveness, the recording interface should be biocompatible and mechanically compliant to match the softness of neural tissue, reducing the risk of immune responses and tissue damage from mechanical mismatch. Therefore, low interfacial impedance is preferred when selecting conductive encapsulation materials. Stimulation Interfaces also need biocompatibility and minimal invasiveness but with an emphasis on delivering electrical stimuli to modulate or therapeutic purposes. For these purposes, Charge injection capacity (CIC) is crucial for delivering sufficient charge to elicit neural response. In addition, the stability of interface material is also very important to withstand the repeated oxidative/reductive processes and minimize the risk of electrode degradation during the stimulation cycles. These studies demonstrate the advantages of using LMs as neural electrode materials. In the future, LM-based neural electrodes have the potential to become a new generation of neural interface devices to interface, supplement, and even enhance and replace actual nerves.

LM-based neural connecting agent and functional repair

Since nerves are located throughout the body, they are very susceptible to damage in accidents (e.g., traffic accidents, fires, *etc.*). However, all the instructions from the brain need to be transmitted by the nerves. Repairing different degrees of damaged nerves is a hot topic in the clinical field. Around 2005-2007, the present team developed a group of methods to reduce the damage to the nerves and maintain their functions when subject to clinical surgery or accidents by controlling the ambient conditions^[93,94]. The microfluidic technology was also introduced to realize the switch on or off the entry and exit of ions, which, in turn, affects the transmission of electrical signals^[95]. All these studies have stimulated subsequent research trials on the neural functional connections.

For most cells in the human body, potassium ions (K^+) predominantly exist within the cell, and sodium ions (Na^+) predominantly exist outside the cell in the resting state. As the cell membrane is more permeable to K^+ than to Na^+ , the resting state is dominated by the efflux of K^+ (from the cytoplasm to the extracellular space). However, as the number of K^+ leaving the cell increases, the electric field force on both sides of the membrane that prevents K^+ from being transported extracellularly will also increase. Finally, the concentration gradient difference and the electric potential difference on both sides of the membrane are opposite in direction but equal in magnitude, and the net movement of K^+ becomes zero. The potential difference at this state, which defines the extramembrane potential as zero, is called the equilibrium potential of K^+ or the resting potential (-70 mV)^[96]. The process of action potential generation is shown in [Figure 5A](#), and the threshold for a nerve cell to generate an action potential is -55 mV (intracellular potential). An action potential is triggered when a stimulus can depolarize the cell membrane from the resting potential to the threshold potential. Therefore, one of the keys to neural connectivity and nerve repair is to realize the transmission of action potentials. When LM is used for nerve connection and repair, a double electric layer is formed on the surface of the LM connecting the two ends of the nerve [[Figure 5B](#)]. When the right side of the nerve is stimulated to generate an action potential, Na^+ flows from the outside to the inside of the cell, decreasing the potential on the right surface of the LM, resulting in a potential difference between the left and right ends of the LM. As shown in [Figure 5C](#), the movement of electrons within the LM will affect the intracellular potential of the cell in the left portion. The action potential can be triggered when the intracellular potential of the left cell part increases to -55 mV . At this state, the LM then realizes the action potential transmission effect.

In addition, the LM material has a broad liquid-phase temperature range, which makes its use easier for fabrication, encapsulation, and surgical manipulation. Not only is the stiffness of LM close to zero, but its electrical conductivity is several orders of magnitude higher than those of nonmetallic materials. LM can be directly printed on a broad range of materials, including polymers, textiles, and hydrogels^[97,98]. These properties make it suitable for applications such as reconnecting transected nerves.

In 2014, Zhang *et al.* clarified that LM (EGaInSn) could be used as a connecting or functional restoration channel to repair PNI [[Figure 5D](#)]^[10]. *In vitro* experiments showed that LM effectively reconnected the transected sciatic nerves and allowed the conduction of electrical signals. In addition, the visualization of the LM under flat X-ray films showed its convenient use in performing secondary surgery. It was revealed that the electrical nerve signals (including amplitude and frequency) recorded after the electrical stimulation of the bullfrog sciatic nerve reconnected by the LM were close to those of the intact sciatic nerve. Control experiments using conventional Rigel solutions in place of EGaInSn showed that the performance of Rigel solutions as functional recovery channels could not be compared with that of LM. In addition, by evaluating the basic electrical properties, the EGaInSn material appears more suitable for conducting weak electrical nerve signals because its impedance was several orders of magnitude lower than that of the well-known Rieger's solution. Using more test animals, Liu *et al.* demonstrated the adoption of liquid Ga to reconnect the transected sciatic nerve in mice [[Figure 5E](#)]^[8]. Their experiments showed that the electrical signals detected in the sciatic nerve after the LM connection were almost identical to those of the intact nerve. Moreover, there was no negative burst firing caused by PNI on the nerve discharge curve after surgery. According to the pathological examination, the tendency of atrophy of the gastrocnemius muscle was delayed considerably, and the fibrillatory potentials appeared immediately in the PNI mice; by contrast, the mice that underwent nerve connection surgery did not generate fibrillatory potentials until the third month. The findings of this study confirm the stability of Ga and its potential for use in future clinical applications. It is expected that this technique will work well in treating nerve injuries (including CNS injuries) in future clinical procedures. In 2024, Chung *et al.* prepared a three-dimensional LM-based microelectrode array^[99].

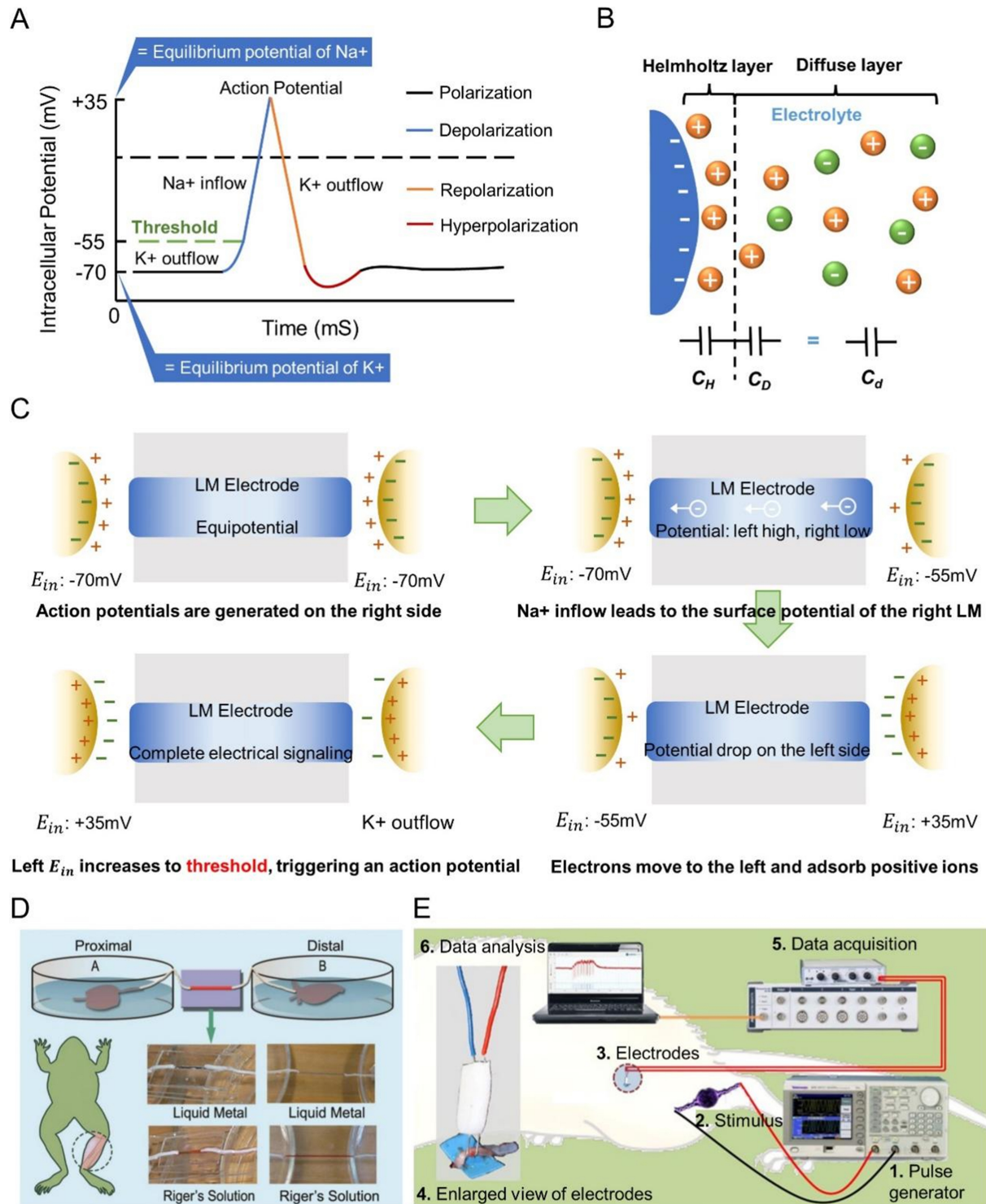


Figure 5. Mechanism of action of LM-based nerve guidance conduits and related studies. (A) Schematic diagram of action potentials; (B) Schematic diagram of the bilayer; (C) Process of electrical signaling by LM; (D) The schematic diagram of the transected sciatic nerve reconnected by LM and Riger's Solution, respectively; (E) The experimental setup for neurological electrophysiology study on sciatic nerve^[8,10]. LM: Liquid metal.

These microelectrodes can enhance proximity to target retinal ganglion cells and provide effective charge

injection ($72.84 \text{ mC}\cdot\text{cm}^{-2}$) to trigger neural responses in the retina, thereby facilitating vision recovery. These results have prognostic implications for repairing and connecting various types of nerves.

FUTURE OUTLOOK

LM possesses a series of unique and excellent properties and can be leveraged to create various LM-based neuro-electrode interface devices using innovative processing methods.

These devices can serve as neural signal sensors for monitoring neurological disease, nerve stimulators for intervening in disease, and nerve information transfer media for brain-computer interface devices. They are even expected to be used as artificial peripheral nerve prostheses for repairing, replacing, or enhancing damaged peripheral nerve tissues. However, further exploration of LM neuro-electrodes and the specialized neural interfacing systems are needed to meet the requirements of brain-computer interfaces for long-term implantation and reliable functioning of neuro-electrodes within the body.

Increase the number of flow paths

First, in the design and fabrication of LM-based neuro-electrodes, the number of channels needs to increase (first approach). A greater number of channels can provide a larger bandwidth of neural information and more stimulation sites, thus resulting in more comprehensive neural behaviors and more precise neuromodulation effects. High throughput devices can be obtained by reducing the size of LM electrode arrays. For example, an electrical tube (PDMS, $40 \mu\text{m}$ in diameter) with stretchable and biocompatible fibers is introduced, and LMs are printed or injected into it^[100].

Anti-leakage

Ga-based LMs are liquid at room temperature so they may be pressed out of the package under excessive force, resulting in electrode failure. The present group previously used the Pt pillar to encapsulate Ga-based LMs^[36]. However, the mechanical properties of Pt are far more different from those of the soft organism. For quick and simple packaging, a bismuth (Bi)-based alloy [a eutectic alloy of Bi, In, and Sn (EBiInSn)] with a melting point down to 60°C is a good choice^[101]. The liquid Bi-based alloys can be dropped directly onto exposed Ga-based LMs. When the temperature drops to room temperature, the Bi-based alloy undergoes a phase change to a solid state and acts as an encapsulant. In addition to the solid metal encapsulation, adhesive sealing has also been used, whereby a flexible kraft adhesive is used to secure the connection of LM and external equipment^[7]. Besides the direct encapsulation methods, the leakage of LM in nerve electrodes can be prevented by inhibiting the fluidity of LM. Lu *et al.* verified that mixing rubidium-iron-boron@Ag powder into LM can inhibit the fluidity of LM by magnetic attraction, thus providing a dynamic leakage-free state^[102]. In addition, LM has excellent wettability to Ag and Cu, and doping Ag or Cu powder into LM can generate intermetallic compounds (such as Ag_2Ga , CuGa_2) to reduce fluidity; this method can also play a certain role in preventing leakage.

Minimally invasive insertion

Agno *et al.* designed an intravenous needle that is stiff enough to be inserted into soft tissue^[103]. However, it becomes irreversibly pliable after insertion, adapting to the shape of the blood vessel and reducing the risk of needle stick injuries during removal. Based on this idea, if an inserted phase change nerve electrode can be designed, then the risk of implantation can be avoided and there is no tissue modulus mismatch after insertion. The melting points of Ga-based LMs range from 7.6 to 29.8°C . This temperature range is common in our daily life, and the temperature of the human body (37°C) is higher than the melting point of all Ga-based LMs. Therefore, needle-like Ga-based LM phase-change neuro-electrodes are expected to be implanted in a minimally invasive insertion manner.

Signal acquisition processing integration

In terms of designing the specialized neural interfacing system and integrating the LM electrodes with the system, there is a need to develop a small, wireless, specialized neural interfacing circuit system compatible with the LM-based neural electrodes. The major challenge is transmitting and processing considerable neural information obtained by the LM electrodes. Conventional methods require a cable-connected interface to transmit the neural signals to a large neural information processing device at the back end. This inevitably creates open wounds that increase the risk of infection, while the requirement for large equipment restricts the range of applications for neural interfacing. The key to solving this problem lies in the miniaturization, wireless connectivity, and implantation of the neural signal transmission and processing system. A fully implantable and wireless approach not only avoids the presence of open wounds but also minimizes the risk of infection and neurological damage. Additionally, it allows the animal to move freely without the constraints of the transmission wires, further enhancing its mobility. The ideal neural signal transmission and processing system should be able to be implanted in the body as a whole after encapsulation with LM electrodes, transmit neural signals wirelessly, and provide online processing capability for these signals. This necessitates using a fully implantable NEI system to address challenges related to size, biocompatibility, and electrolyte-isolated encapsulation. In addition, the system must be able to acquire weak neural signals in the presence of the body's electrophysiological background noise, overcome the shielding effect of biological tissues, establish wireless communication with electronic devices, and acquire electrical energy.

Regarding PNI, particularly for large defects, all clinical treatments have drawbacks, and the demand for improvement never ceases. LMs have shown potential for peripheral nerve connection or repair, attributed to their achievements in signal recording and stimulation functions.

Electrical connection and electrical stimulation

The most straightforward method for treating PNIs with LMs involves reconnecting nerve pathways. It can directly reconfigure the basic functions of the pathway through bioelectrical signal connections, preventing secondary hazards of functional decline, such as atrophy of the target organ of muscle tissue that cannot be protected by other NGCs. This advantage distinguishes LMs from NGCs, positioning them as highly appealing innovative materials. Another advantage is that retrograde electrical stimulation from LMs to proximal neurons may facilitate nerve growth, a technique widely used in specific neuropathy treatments^[104]. It is the ability of *in vivo* nerve regeneration that matters in the outcome after graft. And this electrical stimulation seems to accelerate the progress.

Regenerating bed

As LMs could be manufactured as a film or a conduit, there is no limitation regarding wall permeability and bioactivity, which could be adjusted using the basal membrane materials. So, the fluid surrounding the nerve can communicate with the enclosed room by LMs, which let nutrients in and waste metabolites out. The hollow conduit of LMs connects two stumps of nerve, and offers the space and regeneration beds for nerve, rather than the barriers, which may be encountered in other metal materials.

Easy application

The film form of LMs is flexible, and could be used as a wrapper, assisting in nerve regeneration when applied on the outer layer of the injured nerve. The mechanical strength of the conduit could be adjusted by the base and can match that of the native nerve. So, the LM wall could be strong enough to allow for suturing and prevent collapsing. Also, because of the softness of LMs, these two forms can be easily trimmed with microsurgical scissors in clinical applications to accommodate various nerve lengths and diameters. In addition, LMs have similar modules as nerve tissue and can be tolerant to extensive

movements within the body and be prevented from fatigue failure.

Drawbacks

Side effect or potential toxicity is the major concern. Previous tests were conducted in rats and demonstrated minimal side effects^[74]. However, the long-term outcome on humans remains unclear. Biodegradability remains another unsolved issue, potentially hindering their clinical applications. LMs had ever been compared with a biodegradable nerve conduit for nerve regeneration^[10]. Although the experiments succeeded in aspirating the LM using a microinjector with X-rays, this acknowledged the need for a secondary procedure to remove the LM after nerve regrowth. However, such inconvenience may be neglected if LMs display excellent performance in other aspects, such as preventing the atrophy of target organ muscle.

In summary, the versatile properties of LMs, including their biocompatibility, electrical conductivity, and flexibility, make them promising materials for use in NEIs and nerve repair. Future research should focus on exploring these behaviors and developing methods to harness the potential of LMs in these applications.

CONCLUSION

The potential of Ga-based LMs (that possess fluidity, high conductivity, and biocompatibility) for applications in neural interfaces is enormous. Regarding the neuro-electrodes, a flexible LM-based neuro-electrode is expected to be available in the near future, a system that can be implanted in a living body for a long period of time, wirelessly transmitting neural information and stably acquiring neural signals. Regarding nerve conduits, the true realization of artificial LM neural interfaces for repairing, replacing, and enhancing biological nervous systems is a core target. Tremendous fundamental and practical opportunities are emerging in this direction. Given the increasing investment in research and development, the growing maturity of the technology, and the continuous verification of products, it is expected that the future will usher in more innovative practices of LMs in neuroscience.

DECLARATIONS

Authors' contributions

Proposed original conceptualization: Liu J, Li L

Investigated the related work: Zhang X

Prepared the figures and wrote the article: Zhang X, Liu C, Gao J, Tang R, Feng W, Wu B, Deng Z

Revised and corrected article: Zhang X, Liu C

Supervised the manuscript: Liu J, Li L

Availability of data and materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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