

Biomimetic Nerve Guidance Conduits for Peripheral Nerve Regeneration

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Injuries to the peripheral nervous system are a common clinical issue, causing dysfunctions of the motor and sensory systems. Surgical interventions such as nerve autografting are necessary to repair damaged nerves. Even with autografting, i.e., the gold standard, malfunctioning and mismatches between the injured and donor nerves often lead to unwanted failure. Thus, there is an urgent need for a new intervention in clinical practice to achieve full functional recovery. Nerve guidance conduits (NGCs), providing physicochemical cues to guide neural regeneration, have great potential for the clinical regeneration of peripheral nerves. Typically, NGCs are tubular structures with various configurations to create a microenvironment that induces the oriented and accelerated growth of axons and promotes neuron cell migration and tissue maturation within the injured tissue. Once the native neural environment is better understood, ideal NGCs should maximally recapitulate those key physiological attributes for better neural regeneration.

nerve guidance conduits

regenerative medicine

biomimetic

peripheral nerve regeneration

1. Introduction

The nervous system is a complex network that acts as the command center to relay information via electrical impulses to control the movement, thoughts, senses, and automatic reflexes of the body. It is organized into the central nervous system (CNS), comprising the brain and spinal cord, and the peripheral nervous system (PNS), containing all the nerves and ganglia that connect the CNS to the body ^[1].

Peripheral nerve injury (PNI) is characterized by disruption of the information relays between the CNS and the body caused by traumas leading to neural cell damage or death. These injuries commonly occur for 2–5% of patients worldwide who experience physically traumatic events such as car accidents, joint dislocation, or surgery ^[2]. PNIs can be categorized into three main types: neurapraxia, axonotmesis, and neurotmesis. Neurapraxia refers to a temporary loss of function without disruption in nerve continuity. Axonotmesis injuries completely sever the nerve axon and the surrounding myelin, leading to functional loss. Neurotmesis causes a complete loss of function due to the disconnection of a nerve. To functionally regenerate the damaged nerves, it is necessary for axons to regrow and to be remyelinated via Schwann cells (SCs) ^[3].

Various strategies have been exploited to assist in or facilitate the establishment of a connection in recognition of the limited regeneration capacity of neural cells. Surgical interventions are commonly utilized as the primary approach to treat PNIs. Specifically, the prevailing standard procedure for small nerve gaps of less than 1 cm

involves neuroorrhaphy, which can effectively restore sensation and motor function to the peripheral nerve [1][4]. Large nerve gaps between 1 and 3 cm can also be fully regenerated with interventions such as nerve grafting or commercial nerve guidance conduits (NGCs) [5]. However, substantial nerve gaps exceeding 3 cm, known as critical nerve injuries [6][7], necessitate grafts to bridge the gap. Conventional treatments typically rely on autologous grafts of sensory nerves or decellularized nerve allografts. Clearly, autologous nerve grafting is the gold standard [4]. However, it faces foreseeable challenges, such as an inadequate source of donor grafts, the loss of nerve function at the donor region, a mismatch between donor and damaged nerves, and the potential formation of painful neuroma [8]. On the other hand, allografts are also confronted with several noticeable limitations, such as mismatched size and geometry with the recipient, unreliable supply sources, and possible immune rejections [9].

To address the above-mentioned limitations, efforts have been made to inject cells and biomolecules directly into the injury site following PNIs in anticipation of functional regeneration [10]. As noted, this strategy has yielded some promising outcomes in animal models; however, its clinical translation would be limited considering the difficulties in choosing the optimal cell types for transplantation and achieving cell confinement and survival at the injury site without a supportive mechanism [11].

In the endeavor to substitute the need for grafts and alternatively provide a supporting structure for the delivery of cells and biomolecules, nerve guidance conduits (NGCs) represent a viable strategy to bridge the gap of severed nerve injuries while guiding axonal and nerve regeneration [12]. Typically, the first- and second-generation NGCs are simply designed as tubular structures serving solely to bridge the nerve injury gap and physically direct the growth of axons [13]. Unfortunately, clinical investigations have shown that such nerve conduits are ineffective for those lesions greater than or equal to 3 cm [11]. In response, third-generation NGCs that better mimic the natural nerve microenvironment have been developed and are currently under extensive investigation. Increasing evidence has highlighted that close imitation of the morphological and physicochemical properties of the native extracellular matrix (ECM) of nervous tissues can achieve better therapeutic efficacy [14]. To maximize the axonal regeneration capacity, it is recommended that NGCs should recapitulate the essential attributes of native nerve environments through the biomimetic design [15] of the composition, structure, and function of nervous tissue [8]. Furthermore, NGCs should be able to deliver the desirable biochemical and physical cues via neurotrophic factors, ECM proteins, anisotropic gradients, and diverse types of supporting cells [13].

2. Physicochemical Properties and Regeneration Capacity of Peripheral Nerves

2.1. Structural, Compositional, and Physical Properties of Peripheral Nerves

Structurally, nerves within the PNS are organized in a hierarchal fashion to facilitate signal transduction from the CNS to peripheral tissues and organs. As the functional unit of the nervous system, neurons are specialized cells that transmit electrical and chemical signals to communicate with other cells at the synaptic junction [1]. They have three major components: (1) the cell body, where essential cell functions are performed, (2) the dendrites, which receive signals at the synapse, and (3) the axon, which acts as a cable to transmit electrical signals to the next

synapse. The axon is typically covered by a myelin sheath, comprising lipids and proteins, to protect the axon and conduct electrical signals [16]. The myelinated axons, also called nerve fibers, vary in diameter from 0.2 to 20 μm , depending on their function and location [17], and are surrounded by the basal lamina. The basal lamina is a highly specialized ECM secreted by myelinating SCs, and it is primarily composed of type IV collagen and laminin crosslinked with proteoglycans such as heparin sulfonate [18]. The space between individual nerve fibers is called the endoneurium, and it comprises highly aligned type III collagen fibers in the same direction as the axons [19]. Nerve fibers are bundled into fascicles via a connective tissue layer called the perineurium. The size of fascicles differs between nerves and within the same nerve at different locations [20]. Fascicles are, further, bundled with a connective tissue layer called the epineurium to form a larger nerve.

In addition to neurons, the PNS contains several glial cells, such as SCs, satellite glial cells (SGCs), and neural stem cells, that maintain the extracellular environment and support the neurons. SCs protect the peripheral axons, regardless of myelination. During the myelination of the peripheral axon, an SC envelops a segment of the axon within its cytoplasmic groove and wraps around the axon to form the myelin sheath [19]. Unmyelinated axons are protected and supported by SCs that envelop and surround multiple unmyelinated axons to form small, shallow grooves in the nerve bundle. However, it requires a series of SCs to enclose an entire axon. SGCs are another functional cell type found in the PNS that envelop the cell bodies of neurons in the peripheral ganglia [19]. While their functions are not fully understood, SGCs are believed to play a critical role in neural homeostasis and have been studied in relation to pain [21]. Throughout the connective tissue of the nerves, neural stem cells can be found in the ganglia. These stem cells are typically dormant but can be activated after injury to aid in the regeneration of damaged tissue [17].

Peripheral nerves experience various stresses during body movements such as stretching. As such, the PNS possesses specific mechanical properties crucial to its function and response to forces. Peripheral nerves are viscoelastic, enabling them to deform while dissipating energy. Typically, nerves can elongate 6% to 8% during normal body movement without damaging the tissue. However, straining the nerves by more than 11% but to an extent that is still within the toe region may trigger pain (See **Figure 1**). Upon exceeding 15%, the start of the elastic region, nerves begin to experience damage [17][18]. However, due to their viscoelastic nature, the maximal strain that nerves can withstand prior to injury depends on the strain rate [22].

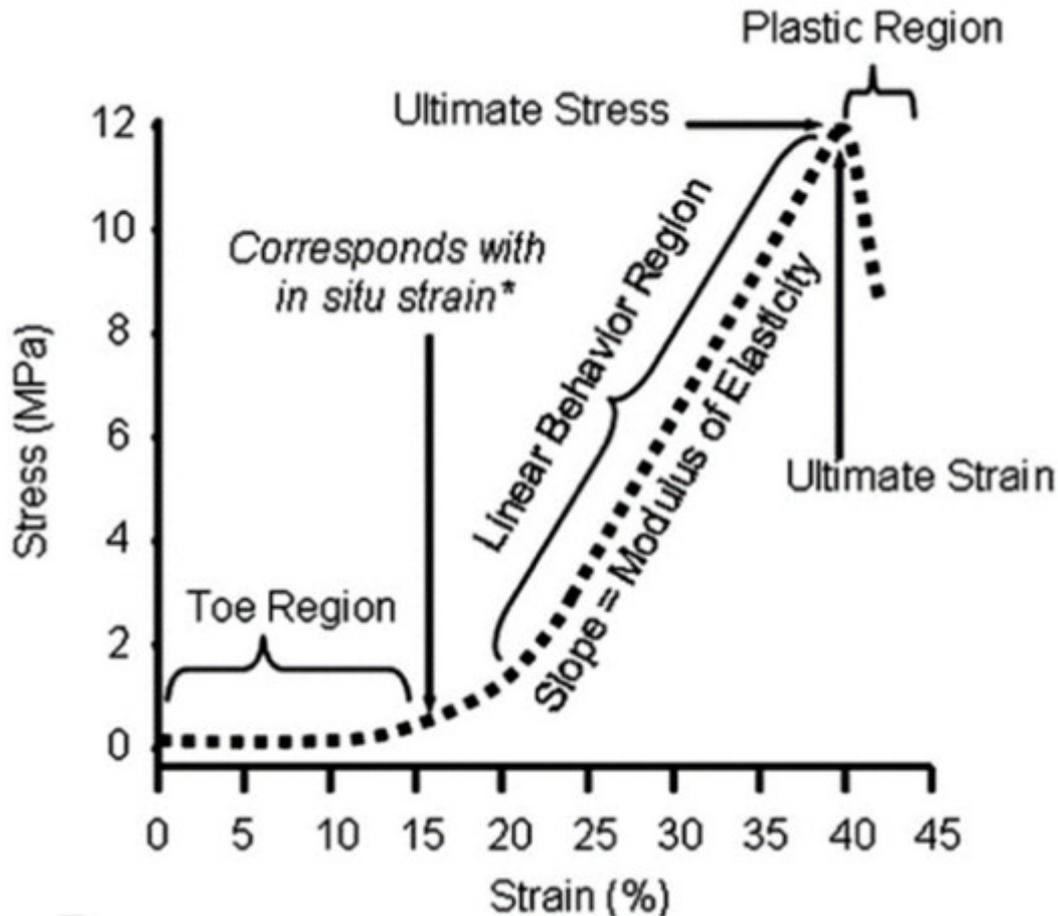


Figure 1. Stress–strain curve of a typical peripheral nerve, reproduced from [18]. This graph was generated based on the data collected in situ from rabbit tibial nerves using a strain rate of 0.5% per second [23].

2.2. Regeneration of Peripheral Nerve Injuries

Peripheral nerves can regenerate, but this capacity highly relies on the gap size of the injury. For gaps smaller than 1 cm, the nerve can heal with minimal assistance. For gaps larger than 1 cm, because of the complexity of coordinating different cells during the regeneration process, even a minor deviation can easily result in unsuccessful healing and loss of functions [1].

Following a PNI involving axonal disruption or nerve transaction, inflammation and degeneration occur at the proximal and distal ends to clear the damaged tissue. Nerve regeneration typically undergoes several stages and is highly orchestrated via cytokines and growth factors [20]. In the inflammatory and degenerative phase, tumor necrosis factor-alpha (TNF- α) and interleukin-1 β (IL-1 β) contribute to the recruitment of immune cells and start the inflammatory response. Interleukin-6 (IL-6) promotes the proliferation and activation of immune cells, facilitating debris clearance and initiating tissue repair [17].

During the proliferation stage, the second step toward nerve regeneration, SCs proliferate and align to form Büngner bands to guide the axonal sprouting from the severed proximal end to their distal target. In this stage, key

cytokines and growth factors such as transforming growth factor- β (TGF- β), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF) are involved in stimulating the migration and proliferation of neural fibroblasts, SCs, and endothelial cells [9].

At the last stage of nerve regeneration, i.e., the remodeling and maturation stage, axonal sprouts grow through the Büngner bands until they reach their target tissues. Once the connection is established, the regenerated axons undergo myelination, which is essential to functional recovery. In this stage, nerve growth factor (NGF), glial-derived neurotrophic factor (GDNF), and brain-derived neurotrophic factor (BDNF) support neuronal survival and axonal growth [9].

3. Design Considerations for Biomimetic Nerve Guidance Conduits

NGCs have undergone an evolution from simple, hollow-tube designs to multi-channeled structures and from nondegradable materials to bioactive, degradable materials. For example, first-generation conduits were solely meant to act as barriers against connective tissue infiltration while guiding directional nerve regrowth [24]. These conduits typically comprise decellularized allogenic or xenogeneic tissue or non-biodegradable materials such as silicone or polytetrafluorethylene (PTFE). However, decellularized grafts rely on scarce and costly sources, and non-biodegradable materials could cause complications, such as fibrotic encapsulation. Thus, the design of second-generation nerve conduits has focused on improving the biocompatibility of the implants via utilizing resorbable materials that are semi-permeable. Still, the simple, hollow tubular design of second-generation NGCs yields subpar functional regeneration compared to autologous nerve grafting. In recognition of the limitations of these designs and the growing body of evidence demonstrating the influence of extracellular features such as material stiffness, hydrophilicity, topography, and chemical properties on neural cell processes [25][26], emerging efforts are being made to formulate an encouraging microenvironment to improve functional recovery. As such, there is increased interest in designing NGCs that can recapitulate the key features of the native ECM of the PNS [6][24][27]. Diverse attempts have been made to fabricate NGCs that mimic various aspects, such as the composition, structure, and mechanics of nervous tissue.

3.1. Compositional Considerations

3.1.1. Material Choice

Nerve conduits can be made from various materials, including synthetic, natural, or hybrid biomaterials [28][29], and each type of material has its advantages and disadvantages. For example, nerve conduits made from collagen and poly (lactic-co-glycolic) acid (PLGA) have already received approval for the clinical treatment of peripheral nerve injuries because of their degradability and good biocompatibility. However, these grafts only partially meet clinical needs due to their limited effectiveness in promoting nerve repair, as well as the associated costs [28]. Compared to natural materials, synthetic polymers offer several benefits, such as ease of modification, minimal risk of pathogenic infection, low toxicity, and, presumably, fewer immune responses [30]. However, these materials often

fail to provide biological guidance, as they lack the functional motifs found in the native ECM of nervous tissue. Conversely, natural materials are appropriate for cell growth and adhesion but may cause uninvited immune responses and are less reproducible [31].

Biomimetic Synthetic Materials

Typically, synthetic materials are chosen for their ability to mimic the mechanical or conductive properties of native nerves [32]. To accommodate the mechanical complexity of native nerves, efforts have been made to combine various synthetic polymers, such as polylactic acid (PLA), polyglycolic acid (PGA), poly(lactic-co-glycolic acid) (PLGA), and polycaprolactone (PCL), to create multilayered NGCs with varying mechanical strength and degradation profiles [33].

Considering the conductive nature of nerves for electrical signals, synthetic conductive polymers have received particular attention for their use in fabricating NGCs. Emerging evidence has shown that incorporating conductive polymers into NGCs promotes axonal outgrowth [34][35], aids in establishing connections with neuronal circuits, and enhances nerve impulse conduction to encourage nerve regeneration [36]. Among several representative conductive synthetic materials, such as polypyrrole (PPy), polyaniline (PANI), poly(3,4-ethylenedioxythiophene) polystyrene sulfonate (PEDOT:PSS), and reduced graphene oxide (rGO), PPy has been demonstrated to be a popular choice for bioelectric applications such as electrode-cell interfaces in bionics [37]. The characteristics of PPy, such as its biocompatibility, conductivity, dynamic nature, and ease of polymerization, make it an ideal candidate for creating NGCs. PANI is another material that is commonly employed to create conductive NGCs. Studies have shown that PANI is beneficial in promoting cell attachment, proliferation, and differentiation [38], and PANI-coated intraluminal microtubes within NGCs favor nerve regeneration [39]. Lately, PEDOT:PSS has also gained substantial recognition and growing interest in biomedical applications for its unique properties [40]. As a polyelectrolyte complex, PEDOT:PSS has excellent conductivity and can disperse in an aqueous solution to form hydrogels, allowing for easy processing and application [41]. In an effort to further demonstrate the importance of conductivity, NGCs coated with carbon nanotubes (CNTs) or PEDOT:PSS were used to regenerate the recurrent laryngeal nerve defects in a rabbit model, and it was found that the conductive NGCs could help improve vocal cord mobility and reduce thyroarytenoid muscle atrophy [42].

Biomimetic Natural Materials

To take advantage of the inherent bioactivity of natural polymers, many materials, such as chitosan, collagen, silk fibroin, gelatin, HA, and fibrin, have been used to fabricate NGCs. These materials can create an environment that facilitates and promotes cellular activities and supports cell-material interactions that are favorable for nerve regeneration [43].

Among various natural polymers, ECM-derived biomaterials, such as collagen, gelatin (hydrolyzed collagen), and fibrin, are commonly used in particular consideration of their presence in native nerve ECM. As the primary component of nervous ECM, collagen has been extensively explored to fabricate NGCs. A recent study showed that NGCs comprising collagen and chondroitin-6-sulfate and incorporated with fibronectin and laminin

biomolecules enhanced the proliferation of SCs in vitro and regenerated the injured rat sciatic nerve in a similar capacity to autografts [44].

Despite the noticeable advantages, ECM-derived materials often face challenges, such as high manufacturing costs and large source-dependent variabilities. In response, there is a continuous motivation to seek alternative ECM-like materials, such as silk fibroin (SF) and chitosan (CS). With a degradation rate close to the rate of nerve tissue ingrowth [45], SF-based NGCs displayed a lower risk of inflammation and rejection [46].

Biomimetic Hybrid Materials

Hybrid biomaterials, a subset of composites combining the biological properties of natural materials with the mechanical and functional properties of synthetic materials, offer a wide range of benefits, including tunable mechanical and degradation properties, scalable production, ease of processing, and biological activity [47]. There are many variations of hybrid materials, but recent interest in mimicking both the composition and function of nerves has led to the development of hybrid NGCs that contain two to three types of materials: (1) natural materials to improve cell adhesion and migration, (2) conductive synthetic materials to mimic the function of nerves, and (3) an optional synthetic material to provide mechanical strength.

In an effort to fabricate hybrid conductive conduits, PEDOT:PSS has often been included together with other materials, given that PEDOT:PSS can be made into various forms, is mechanically robust, and is highly elastic. For example, a recent publication demonstrated that a gelatin–PEDOT:PSS hydrogel was conductive and biocompatible, and was able to prolong astrocyte growth [48]. While this combination has not been used in NGCs, the encouraging results in supporting the cells of the CNS also imply its potential for PNI regeneration.

rGO is another popular choice for creating hybrid conductive NGCs due to its high conductivity, mechanical properties, and ability to be coated onto or dispersed into other materials. For example, NGCs fabricated via coating rGO on *M. Menelaus* butterfly wings effectively promoted the axonal regrowth and functional regeneration of nerve and muscle tissue compared to non-conductive controls [34].

To better tailor the mechanical properties, additional materials can also be included in the mixture. For example, in a recent study on the creation of a hollow NGC, PLCL with good strength and toughness was added to SF to improve the flexibility and strength of the electrospun nanofibers of a conduit, which was coated with PPy [42]. This hybrid conductive NGC improved the early proliferation of SCs post-surgery and enhanced myelin formation, and most importantly, it was demonstrated to be effective in restoring sciatic function, similar to autologous graft, 12 weeks post-surgery.

3.1.2. Cellular and Biomolecular Choices

Cellular Choices

In recognition of the roles of SCs and neural stem cells in supporting, promoting, and guiding axonal sprouting following PNIs, patient-derived cells have been incorporated into NGCs to minimize the risk of immune rejection

[49], promote axonal regrowth, and provide neurotrophic support [50]. For example, Liu et al. demonstrated that collagen-based conduits loaded with neural stem cells returned functional levels in the regeneration of 3-mm rat spinal cord injury models [51]. This is very promising, given that spinal cord injuries are more difficult to regenerate than PNIs. However, neural stem cell transplants alone cannot regenerate PNIs, as evidenced by the outperformance of neural stem-cell-seeded NGCs over the cell transplant-only group in a mouse sciatic injury model [52].

Despite the encouraging results from the encapsulation of SCs and neural stem cells in NGCs, it remains challenging to harvest and expand such autologous cells for clinical use. As such, Schwann-like cells derived from mesenchymal stem cells (MSCs) have been considered a promising alternative [11][53]. Results demonstrate that MSCs enhance the expression of neurotrophic and angiogenic factors that can better emulate the native environment for nerve regeneration [53].

Biomolecular Choices

Given that the primary purpose of encapsulating cells in NGCs is their ability to secrete growth factors and ECM proteins, oftentimes, reaching the desired therapeutic concentration is challenging. To this end, incorporating biomolecules directly into NGCs would allow for more control of the concentration needed, along with reductions in cost, time, and the risk of immune rejection associated with cellularized NGCs.

The typical biomolecules involved in nerve regeneration are neurotrophic factors (NTFs), such as NGF, BDNF, or glial-derived neurotrophic factor (GDNF), which promote neural cell survival and guide axonal growth [54]. Since NTFs are present at different stages and varying concentrations during nerve regeneration, the regeneration capacity and rate are closely regulated by the initial concentration, dosage, and release kinetics of NTFs [55].

3.2. Structural Considerations

3.2.1. Biomimetic Architectures

To better guide axonal growth and support nerve regeneration, it would be desirable for NGCs to capture the microstructural features of native nerves [56]. In recognition of the drawbacks of non-porous, hollow NGCs, such as the limited capacity of bridging nerve gaps over 1 cm and poor permeability to nutrients and growth factors [57], secondary structures such as grooves, pores, channels, and fillers have been added to NGCs [58]. The creation of aligned grooves or channels in NGCs could effectively mimic the fibrin network and Büngner bands for axonal regeneration, while the presence of fillers and pores supports cell infiltration, neovascularization, and nutrient diffusion to the regenerating nerves [59] (see **Figure 2**).

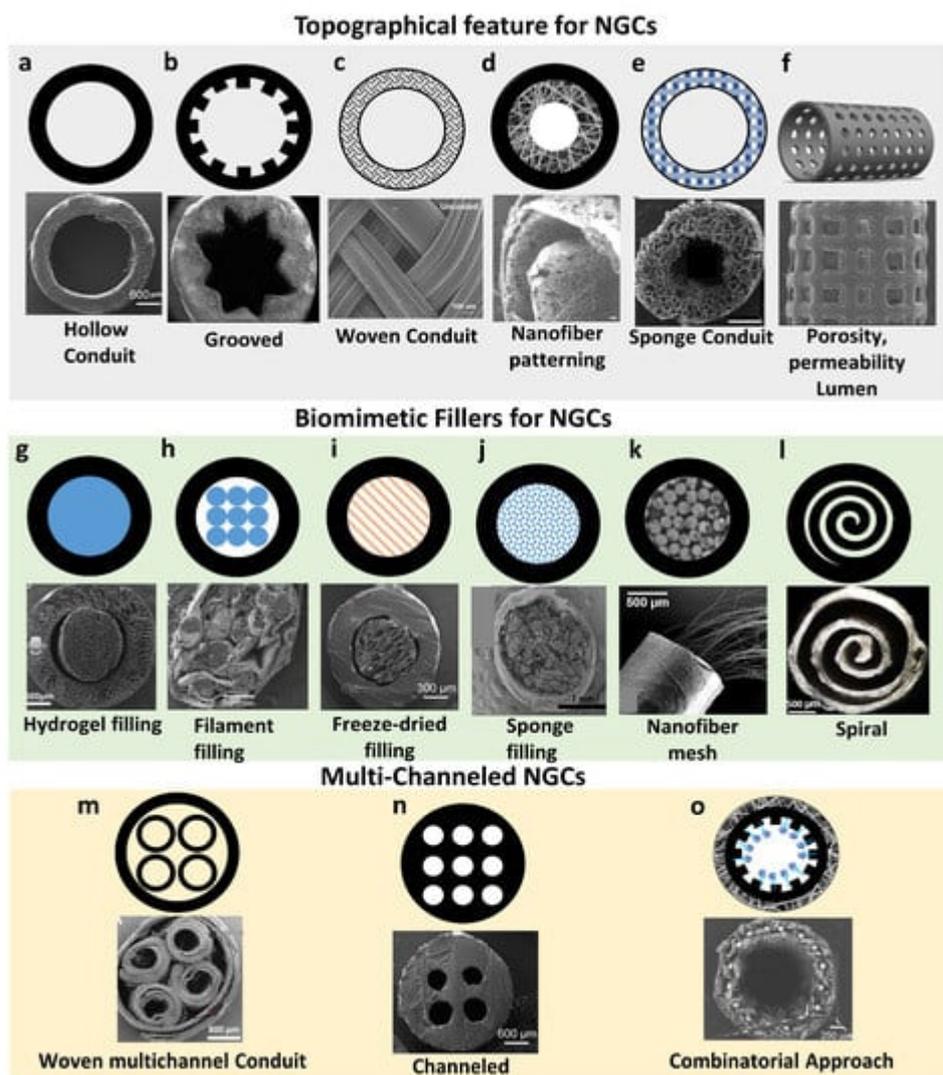


Figure 2. Different NGC architectures. (a) Simple hollow conduit of first-generation NGCs [60]. (b–f) Grooved and porous hollow NGCs [35][58][61][62][63]. (g–l) Biomimetic fillers for NGCs [62][64][65][66][67][68]. (m,n) multichannel conduits [58][65]. (o) NGC containing multiple biomimetic features [69].

Biomimetic Topographical Features of NGCs

The inclusion of additional features in the luminal wall of NGCs, such as pores to increase permeability and microgrooves to provide alignment cues, would significantly improve the efficiency of hollow NGCs in nerve regeneration. For example, a 3,4-dihydroxy-L-phenylalanine (DOPA)-coated PLGA NGC with the presence of porous microgrooves on the luminal wall enhanced the permeability of nutrient exchange and promoted axonal outgrowth [70]. Notably, such aligned porous microgrooves could modulate neurite orientation and the length of neural mouse stem cells in vitro compared to porous flat NGCs.

The pores within the luminal walls of NGCs can also be used to load biomolecules for local release to induce the preferred cellular response. A hollow NGC comprising 3D-printed gelatin-hydrogel-based microgrooves wrapped with electrospun PLCL membrane successfully guided axonal regeneration while releasing a neurogenic drug from

the gelatin hydrogel [14]. Testing in rat sciatic models showed that such conduits were able to guide axon outgrowth and achieve remyelination, which was essential for functional recovery.

Biomimetic Fillers for NGCs

Hollow NGCs, regardless of their added topographical features, still fail to capture the key structural attributes of native nerves, that is, containing multiple fascicles that each house numerous axons. In this regard, a growing interest has shifted to filling the luminal space of NGCs with various fillers, especially the aligned anisotropic ones, closely mimicking the conditions of the endoneurium surrounding individual axons to improve the regenerative capacity of nerves.

There is growing interest in utilizing natural polymers as NGC fillers in the forms of hydrogels, filaments, or porous sponges. Due to their soft properties and biocompatibility, these materials can serve effectively as regenerative guides for repairing PNIs and supporting the functionality of nerve conduits during the repair process [71].

Compared to hydrogels, anisotropic aligned fillers are believed to better induce axonal organization than random fillers by encouraging axons to extend through the conduit while facilitating nutrient exchange. For instance, CS fibers or chitin-containing composite fibers are employed as fillers. These fibers guide axonal growth through their oriented structure to establish electrical connectivity between injured nerve terminals [72].

Fillers can also be functionalized with biomolecules or conductive polymers to achieve high biomimicry. The introduction of pores can aid in nerve regeneration and nutrient exchange; however, pores larger than 30 μm may lead to the infiltration of fibrous tissue, thereby blocking axonal regeneration. To this end, coating the fillers with fibrin and HA can help alleviate this issue [61].

Multi-Channeled NGCs

While filled NGCs are able to facilitate neuronal cell adhesion, promote cell differentiation, and guide neurite outgrowth [73][74][75], fillers, occupying the luminal space, would limit the number and size of axons growing through the conduit [76]. As such, multi-channeled NGCs have been proposed to enhance nerve regeneration within large nerve defects, as they can provide better guidance for axonal ingrowth than the pores of anisotropic fillers [76][77]. These channels also partially mimic the unique morphology and structure of peripheral nerve fascicles, where myelinated and unmyelinated axons are surrounded by a collagen-based endoneurium, to promote neurogenesis and nerve regeneration [78].

The primary difficulty in mimicking fascicles is the large variation in fascicle size and axon number, which are closely related to the location and function of the peripheral nerve [79]. Typically, the diameter of axons ranges between 4 and 16 μm [80], and fascicles can contain a few to several hundred axons [81]; thus, it remains highly challenging to identify an ideal channel size that effectively mimics the fascicle anatomy. Through experimentation, researchers have noticed that the channel diameter of ~ 125 μm seemed more favorable to encouraging functional regeneration [82].

Apart from the channel diameter, the number of channels in an NGC also impacts nerve regeneration. As expected, a higher density of channels could effectively reduce the dispersion of axons, therefore promoting more directed and organized axonal growth [2].

3.2.2. Fabrication of Biomimetic Features

Many fabrication technologies, such as electrospinning, 3D printing, molding, casting, freeze-drying, and micropatterning, are available to deliver some of the biomimetic features to the above-discussed NGCs [2][83]. Depending on the fabrication method, there is a good possibility of controlling the porosity, channel size, density, and alignment, but each method has its limitations.

Inkjet printing and micropatterning are less utilized to create NGCs than electrospinning, but both techniques enable control over the local topography. Inkjet printing, a subtype of 3D printing, uses heat or piezoelectric pulses to jet bio-inks in a drop-by-drop fashion. This method can create spatial and concentration gradients of various biomolecules, print conductive patterns, and localize cells onto NGC surfaces [15]. Due to the ready incorporation of growth factors, cells, or conductive nanoparticles into inks for inkjet printing, it is very likely to achieve the bioactive topographical modifications of NGCs and specifically promote neurite outgrowth [14][84][85]. On the other hand, micropatterning is a template-based method that uses photolithography, microcontact, or microfluidic stamping to create a variety of micropatterns, including lines, dots, and grids, to guide axonal alignment and promote neurite outgrowth [86][87][88]. However, similar to electrospinning, inkjet printing and micropatterning are also done on 2D surfaces, which generally require the rolling step to create conduit structures.

Given that a pore size between 10 and 40 μm and a porosity of roughly 80% are typically needed to recapitulate the native nerve environment and encourage PNI regeneration [89], efforts have been geared toward the creation of NGCs using freeze-drying or solvent casting/salt leaching. Freeze-drying is often employed to create porous conduits by sublimating the solidified solvent (e.g., ice) between polymer molecules and leaving the interstitial space empty [61]. The porosity of the NGC can be easily customized by adjusting the polymer concentration, and the pore morphology can be tailored by varying the freezing speed and methods. Although its ability to create interconnected anisotropic pores within NGCs has been recognized [44], the freeze-drying method has limited control over the size and uniformity of pores.

Three-dimensional printing and molding have been exploited to create multichannel NGCs. Three-dimensional printing, particularly stereolithography (SLA) and fused deposition modeling (FDM), offers a platform to fabricate complex structures with the opportunity to encapsulate living cells and biomolecules [90][91]. For example, the SLA-enabled fabrication of NGCs from gelatin–methacrylate (GelMA) demonstrated the possibility of creating multi-channeled NGCs with varying diameters and densities [92]. However, constrained by the printing resolution and time consumption, molding becomes a primary choice for fabricating multichanneled NGCs.

To overcome the limitations of individual fabrication methods, it would preferably combine various methods or use hybrid technologies to fabricate biomimetic NGCs. For example, Liu et al. used near-field electrowriting, dip-

coating, and electrospinning to create a tri-layer conduit with structural characteristics resembling the human nerve [93].

3.2.3. Mechanical Properties of Biomimetic NGCs

In addition to composition and design, the mechanical properties of the NGCs should, preferably, match the stiffness, flexibility, and elongation of native nerves. Evidently, the NGCs that closely resemble the morphological, physical, and mechanical properties of native nervous ECM tend to achieve more effective therapeutic outcomes [87]. Since the elastic modulus of human peripheral nerves is approximately 0.5–13 MPa [94], NGCs made from soft polymers with an elastic modulus in this range or slightly higher have immense potential to heal PNIs. During normal body movement, the nerves can be stretched as much as 6 to 8%; thus, NGCs should be able to tolerate such a stretch under repetitive stresses [18].

4. Conclusions

While peripheral nerves can regenerate, large gaps (>1 cm) typically result in unsuccessful healing and a loss of function. In view of the shortage of, and comorbidities associated with, autografting, NGCs serve as a promising alternative to bridge the gap of the severely damaged nerve and guide axonal growth.

To maximize the regenerative capacity of NGCs and restore lost nerve function following severe PNIs, it is preferred for these conduits to deliver a native PNS-like environment via the optimal selection of composition, structural configurations, and functionality close to the native nerves. With respect to composition, hybrid biomaterials combining both the biological attributes of natural materials and the mechanical/conductive properties of synthetic materials are the most attractive ones to achieve the desirable physical performance (e.g., flexibility, degradation, and conductivity) while inducing the required cellular responses (e.g., the recruitment of neuronal cells, the migration of SCs, and improved myelination). NGCs can further benefit from the incorporation of cells such as SC or neural stem cells and biomolecules, such as fibronectin, laminin, NGFs, and/or SC-secreted exosomes, to better mimic the composition of native nerves and promote cell adhesion, SC migration, vascular infiltration, axonal growth, and consequent functional recovery. To mimic the structural hierarchy of PNS, where each nerve houses the fascicles and each fascicle holds the nerve fibers to facilitate signal transduction from the CNS to peripheral tissues, biomimetic NGCs are also designed to include additional features, such as grooves, pores, channels, and fillers. Parallel grooves and channels should present nano- and micro-scale topographical cues similar to the fibrin network. Additionally, NGCs should contain fillers and pores (10–40 μm in size with 80% porosity) to support cell infiltration, neovascularization, and nutrient diffusion to facilitate nerve regeneration. Finally, conduits should have multiple channels whose size and density maximally mimic the fascicles at the injury site.

To implement the structural complexity of biomimetic NGCs, various fabrication technologies, such as electrospinning, 3D printing, molding, casting, freeze-drying, and micropatterning, can be adopted as either single fabrication platforms or combined ones to create those biomimetic features. Advances in high-resolution

fabrication, such as e-beam lithography, would further enhance the capability of creating NGCs with delicate structures.

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