Chapter

Frontiers of Brachial Plexus Injury: Future Revolutions in the Field

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Abstract

The field of brachial plexus surgery has undergone dramatic changes in the past 40 years. Most of these have been incremental in nature. We have seen increased use of nerve grafts and nerve transfers. We have seen the introduction of robotic limb replacements for the most severe flail limbs where surgical intervention has failed. In some cases, we have seen an increase in the use of computer simulation and virtual reality to train surgeons to plan and execute surgeries. More recently, we have seen the introduction of technologies derived from regenerative medicine research.

However, we expect to see a true revolution in the field of brachial plexus surgery in the next 40 years, specifically:

- We anticipate an increasing introduction of biotechnologies from regenerative medicine.
- We expect fundamental changes in our understanding of nerve repair and the introduction of Fusogens allowing us to couple nerve ends, establishing immediate functional connections, and avoiding distal Wallerian degeneration.
- We will be able to prevent atrophy of muscles distal to nerve injury and accelerate axonal regeneration.
- We will also see a comprehensive understanding in the mechanism of apoptosis of the distal peripheral segment, and brain and spinal cord neurons proximal to the injury, leading to pharmacological manipulation of the mitochondria and other organelles in the distal nerve from signaling cell death and therefore interrupting the normal cascade that leads to Wallerian degeneration.
- In chronic brachial plexus injuries where the limb musculature has irreversibly atrophied, we will have three choices – robotic replacements, limb transplantation and limb regeneration. However, the most likely solution will be robotics in the near future.
- We will see a revolution in both the design and control of robotic limbs through brain-machine interfaces. Computers will allow us through virtual reality to model the brachial plexus in extreme detail. These simulation models will enable the prediction of outcomes of our surgery. Detailed physically-based models of the injury obtained pre-operatively will allow us to better plan for surgery. Bringing

these models into the operating room (through augmented reality) creates a "performance machine" enabling us to better see and manipulate the brachial plexus as we operate by superimposing our living models on the patient's anatomy.

- In the more distant future, we will repair nerves by actually guiding axon connections, recreating normal neuro-muscular and neuro-sensory architecture.

All of these advances will revolutionize the practice of brachial plexus surgery and ultimately result in truly improved outcomes for our patients with the most devastating brachial plexus injuries.

"The dreams of yesterday are the hopes of today and the reality of tomorrow."[1] *— Robert H. Goddard — father of the US space program*

At the time of this quote, Robert Goddard was sitting in a tree in his backyard as a high school student — and a true visionary. He believed we would reach the moon and beyond, and he later created the original ideas that the space program was founded on for the next century.

Keywords: brachial plexus surgery, nerve grafts, robotic limbs, simulation, virtual reality, tissue engineering, regenerative medicine

1. Introduction

1.1 The last 40 years – Seeing further by standing on the shoulders of giants

Over the last 40 years, the field of brachial plexus surgery has greatly advanced. We have moved from a field with initial poor outcomes to one that is now able to provide hope to our patients. In many cases, our successes have changed a useless limb into a functional assistive limb. In occasional cases, we have restored almost-normal function to paralyzed limbs. However, in the most severe injuries, such as those resulting in a chronic flail arm, we continue to struggle with failure to improve outcomes. We have seen a wide adoption of new surgical techniques, first introduced in the latter half of the 20th century, which are now common practice in the daily treatment of patients with brachial plexus injuries. These techniques have been applied to patients in all stages of life, from birth defects to adult brachial plexus injuries. They include microsurgery, autologous and artificial nerve grafting, and tissue engineering to fabricate nerve conduits. Sophisticated surgical techniques including vascularized nerve grafts and functional muscle transfers have been developed and successfully applied. We have seen the use of nerve transfers, initially performed in selected cases, become the standard of care for some conditions, and in many clinical scenarios we have switched from an operative approach of repair of a very proximal injury to creating distal nerve transfers that more rapidly restore functional outcomes. Indeed, the rising popularity of nerve transfers has led to testing and validation of a variety of donor sites – including contralateral nerve roots and intercostals – with new ones being introduced and tested almost every year.

In the most severe chronic injuries when conventional surgery has failed, patients often accept amputation. In these cases, the distal limb muscles have atrophied and vthe limb has become a burdensome "parasite." For patients with a chronically denervated extremity, a robotic limb that can be controlled through myoelectric

[1] https://quotefancy.com/quote/1669979/Robert-H-Goddard-The-dreams-of-yesterday-are-the-hopes-of-today-and-the-reality-of

interfaces can be a dramatic improvement. Robotic technology has experienced a revolution in its capabilities to produce durable artificial hands with fully functional five-finger dexterity, and the materials and methodologies for their manufacture. We have seen the increasing clinical use of brain-machine interfaces to address neurological problems resulting in advances that can now be translated into use for artificial limbs. Many patients have received transplanted limbs; a technology that eventually could be applied to the most severe chronic brachial plexus injured limbs. The safety of whole-limb allotransplantation has improved with new immunosuppression protocols; however, donor limb supply still remains a major limitation. Although regenerative medicine has provided many solutions in multiple fields, the complete regeneration of a limb remains beyond the scope of this chapter. Even with the increased interest in total-limb regeneration in invertebrates and a few amphibians and the introduction of new tools of genetic engineering like CRISPR, it is unlikely that we will be able to manipulate our own genome to restore a limb in our Lifetime.

The realistic advances expected over the next 40 years will be driven largely by today's unanswered needs and questions. What is lacking today are the answers to clinical gaps that include:

- Lack of technologies that accurately assess the injured nerve roots and provide a detailed prognosis for recovery – we need sophisticated preoperative electrodiagnostic tools that map the injury and intraoperative imaging to guide the surgeon.

- Lack of nerve grafts – we need substitutes that are even better than autografts, that contain the right structural matrix and cells with already "up-regulated" genes.

- Slow pace of axonal growth – we need methods to speed axonal growth, or somehow obviate the need for axonal regeneration after nerve transection and repair or reconstruction.

- Nerve degeneration distal to the injury – we need protective molecules or technologies that either slow the pace of – or better, prevent – Wallerian degeneration of the axons distal to the site of injury.

- Inability to accurately connect proximal and distal axons at the site of nerve repair – we need to not only re-establish the nerve connections between the proximal and distal ends but also correctly connect proximal individual axons to the exactly corresponding distal axons. That would require nerve repair not at the epineural level, or at the fascicle level, but at the axon level – the true level that is needed for successful functional recovery [1].

2. Part I: Acute injuries and their treatment, now and in the future

2.1 Regenerative medicine: Augmenting the healing process

There has been a revolution in regenerative medicine in the past two decades (**Figure 1**). We have seen the ability to control human stem cells and transform them into almost every type of adult cell including the peripheral nervous system [2]. Today, regenerative medicine and tissue engineering allow us to grow human nerve grafts. Tissue-engineered nerve grafts (TENGs) have been developed and transplanted into large animal models to span large gaps [3, 4]. As allograft development has progressed, the scaffolds and materials available for nerve repair have provided functional outcomes for patients that are comparable to the existing gold-standard autograft [5]. Allografts also have the potential to exceed the ability of autografts to facilitate nerve regeneration, as they are capable of being modified

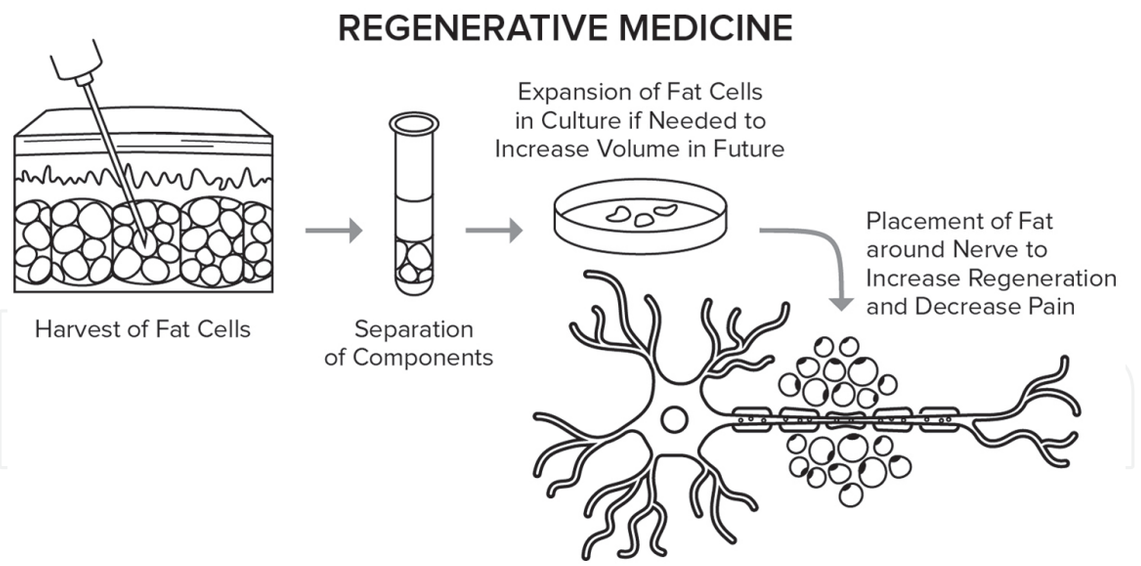

Figure 1.
Regenerative Medicine (Section 2.1). Cells (such as fat cells) are harvested and processed to concentrate the stem cells or grow them in culture. The cells are then injected around the nerve injury site, a process that has several roles: to assist in nerve regeneration and to decrease neuropathic pain. The cells act at the injury site and also at the proximal axon and cell body and further proximally in the spinal cord.

with pro-regenerative growth factors, impregnated with patient-derived stem-cells, and be structurally engineered to prevent axon misdirection [6–10].

We have seen the beginnings of a shift from autografts to allografts and can anticipate the common adoption of totally artificial, tissue-engineered substitutes. These will be a combination of scaffolds, key bioagents, and cell components. Widespread use of allografts that can improve on the functional outcomes of autografts is highly desirable as these biomaterials will reduce patient pain and disability from surgery to harvest autografts, increase the amount of graft material available to reconstruct long gaps in large nerves, and decrease operative time overall. Due to regulatory pathways of the Food and Drug Administration (FDA) and other agencies, there are many hurdles to overcome in the introduction of these stem-cell types, [11] whether derived from fetal cells or from the transformation of adult cells.

A second area of active interest in regenerative medicine is the use of stem cells to promote growth and speed healing. Mesenchymal stem cells are pluripotent cells that persist into adulthood, and can be found in bone marrow and adipose tissue. These cells can support nerve regeneration through multiple functions including secretion of growth factors such as vascular endothelial growth factor (VEGF), differentiate into progenitor cells, and modulate the inflammatory response [12–15]. At present, there is a growing use of adipose stem cells which are more abundant than bone-marrow stem cells and easily harvested in the operating room for peripheral nerve surgery [16] and several other orthopedic applications, including injection into joints and around tendons to encourage function and decrease pain. Fat cells are used to prevent scarred nerves that have been surgically freed from re-forming scars. Fat cells are also used to prevent neuropathic pain and encourage nerve regeneration [17]. They have been increasingly used in the past 10 years and we expect their use to expand in the next 40 years.

We can also expect to see regenerative medicine create nerve–muscle units. Much of this work is already being done successfully in many laboratories for small muscles such as the intrinsic muscles in the hand. In some cases, muscle is being grown to replace muscle that has been lost in limbs from blast injuries in wounded warriors. We expect these new biomaterials to become part of our armamentarium in brachial plexus injuries where distal muscle loss could be replaced with key nerve-muscle regenerated substitutes [18].

2.1.1 Tissue-engineered nerve grafts (TENGs) (additional reading)

These additional readings include an overview of peripheral nerve repair approaches used [19] and further delve into TENGs including their efficacy, [20] advances, [21] and interactions with native tissue [22].

Reference	Topic overview
[19]	A review of peripheral nerve repair approaches including hydrogel fillers, fibrous interluminal fillers, and interluminal scaffolds
[20]	A study investigating the efficacy of living vs. nonliving scaffolds in peripheral nerve repair
[21]	A review of the advances and efficacy of TENGs including recent modifications and enhancements to the scaffolds
[22]	A review paper examining the two-way interactions between native cellular tissues and electrospun matricies that serve as tissue scaffolds

2.2 Fusogens: Shifting the paradigm of nerve repair

Fusogens are a key innovation in peripheral nerve surgery. Fusogens are chemicals that allow cell membranes, which normally repel each other, to fuse together. In the context of nerve injury, they allow for fusion of the cell membranes enclosing the two severed ends of the axon, thus establishing continuity at the cellular level between the proximal and distal nerve. They are a paradigm shift in our thinking and approach to nerve injuries. Our surgical approaches have previously focused on fixing nerve discontinuity by suturing the epineurium of severed nerves together. This intervention fails to act on the underlying cellular structures that are affected by injury, namely the axon. By overcoming the inherent molecular barriers to axon continuity, fusogens offer a new therapeutic avenue for treating and rapidly healing acute nerve transections. This technology was not considered possible prior to the new millennium, but in the past two decades there has been an increasing accumulation of evidence that not only can invertebrates fuse proximal and distal divided axons, but we can also create the condition in vertebrates [23] to allow fusion to occur in both spinal cord [24] and peripheral nerve injuries [25]. Since 2000, there has been an explosion of different fusogen chemicals that would allow severed proximal axonal membranes to re-connect to distal axonal membranes [26] in the timeframe before Wallerian degeneration occurs [27]. Within the first 72 hours after a nerve transection, the axon membrane of the proximal axon and the axon membrane of the distal stump could be successfully fused in vertebrates (**Figure 2**). It was not clear what the mechanism for this fusion was, or what was the best pharmacological agent to encourage fusion. With this initial success in the peripheral nervous system of vertebrates, interest grew to move forward and at the present time fusogens are being used in clinical trials for digital nerve injuries [28, 29].

Fusogens are currently under investigation for clinical use in humans, using a digital nerve repair model. They have not yet been used for brachial plexus injuries, but their application to the brachial plexus would be very significant. The major limitation of brachial plexus injuries is the long distance from the injury site to the distal end organs, especially the motor units. By the time the regenerating axons reach the target muscles, significant muscle atrophy has transpired. A reconstructive alternative to nerve repair, nerve transfers, when possible, can significantly shorten regenerative times and re-establish myoneural junctions. This approach,

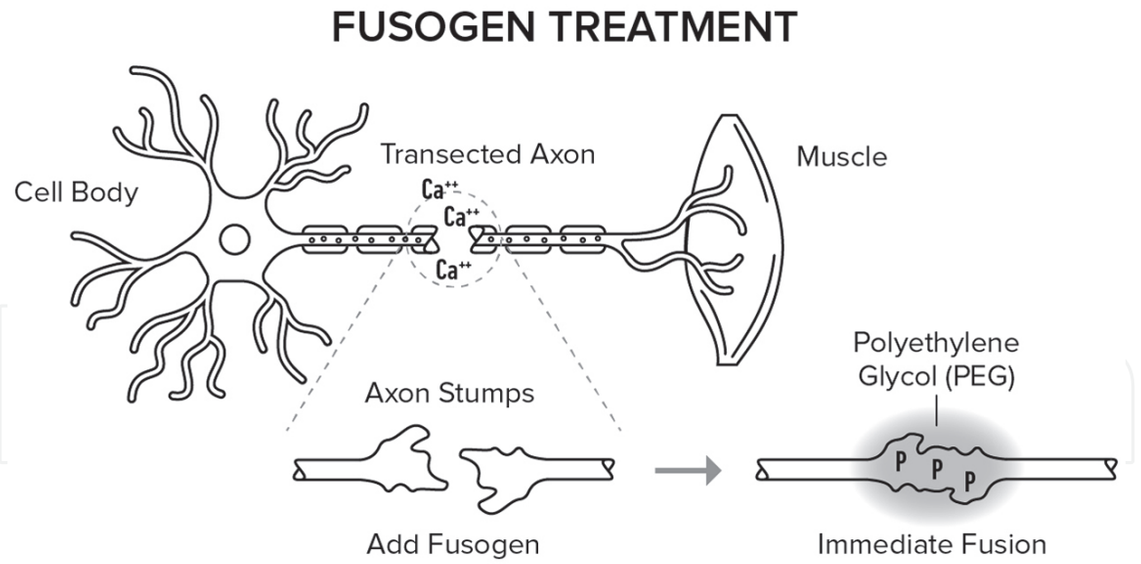

Figure 2.
Fusogen Treatment (Section 2.2). Fusogens act at the repair site to enable the cytoplasm of the proximal and distal axon to immediately fuse after being transected. The most commonly used fusogen at the present time is polyethylene glycol (PEG). The mechanism of action is not presently known but PEG is thought to act directly on the cytoplasmic membranes at the time of injury to enable them to fuse. PEG stabilizes the physical chemistry and properties of the membranes, enabling them to fuse through the biological-chemical interactions with the multiple layers of the cytoplasmic membranes and the influence of their surfactant properties.

when used in concert with a fusogen, could potentially provide immediate re-establishment of axon continuity and electrical conductivity. This would prevent the atrophy [30] seen in brachial plexus injuries. We are now at the beginning of clinical trials for digital nerves. This is the first test of this vast change in peripheral nerve surgery. We would then expect to see applications to larger mixed nerves such as the median and ulnar nerve at the wrist and then more proximal nerves. Eventually it could be applied to the most proximal brachial plexus injuries where it is clearly most needed.

In the next section, we discuss how to keep the distal nerve alive so that it would be available for a fusogen solution or just a conventional nerve repair. This would greatly increase the number of cases in which a fusogen could be used to instantaneously restore axon continuity and function.

2.2.1 "State-of-the-art nerve transfers" (additional reading)

In these additional readings, one can learn more information regarding nerve transfer including their uses, [31, 32] suggested adjunct procedures, [32] efficacy and outcomes, [33] and comparison to nerve grafts [34].

Reference	Topic overview
[31]	A review investigating the use of distal nerve transfers to the ulnar nerve in cubital tunnel syndrome
[32]	A review of nerve transfer use in peripheral nerve injury and suggestion of concomitant Schwann cell transplantation to aid in regeneration
[33]	A systematic review assessing the efficacy and outcome correlations of nerve transfer in patients with brachial plexus and axillary nerve injury
[34]	A systematic review evaluating nerve graft vs. nerve transfer regarding shoulder abduction recovery in patients with brachial plexus palsy

2.3 Apoptosis: The role of the mitochondria and other organelles in axonal death

Fusogens require a viable distal nerve to work. In most brachial plexus injuries, it is not possible to intervene before the distal nerve experiences Wallerian degeneration. Once the process of distal degeneration has begun, fusion of the membranes of the proximal and distal axons is no longer possible. However, in the past decade significant strides have been made in our understanding of the process of apoptosis – the cascade that initiates cell death and in the peripheral nerve, the process that initiates the loss of the distal axon. Through recent experimental work in vertebrate animal models, it is clear that organelles in the distal axon initiate apoptosis. In particular, the mitochondria play an overwhelming role in this process. Mitochondria were once a form or bacteria that invaded cells and then became a crucial part of the cell's metabolism responsible for energy production for the eukaryote cell. In the axon, there are several types of mitochondria – some that migrate and others that are relatively stationary [9, 35]. At the site of nerve injury, a calcium wave is propagated down the distal axon. The mitochondria are directly affected by this calcium wave. The mitochondria have an outside membrane wall and an inner membrane wall. The calcium wave causes a state of increased permeability of the outer membrane of the mitochondria [36]. The outer membrane of the mitochondria is contributed by the host cell and the inner mitochondrial membrane is a part of the original primordial mitochondria before it became a part of the cell or in this case the axon.

The state of increased permeability of the outer membrane is key to the initiation of the cascade that ultimately results in the signaling of cell death. The mitochondria release proteins in the form of enzymes that begins apoptosis. This then signals and engages the Schwann cells to transform into Bungner tubes. The Schwann cells then recruit monocytes, and the monocytes transform into macrophages that play a crucial role in engulfing the debris of the distal axon in the process of Wallerian degeneration.

What if we could interrupt the cascade of apoptosis initiated by the mitochondria? It has been shown through pharmacological means that molecules of certain dimensions [36] can block the permeability of the outer membrane caused by the calcium wave after nerve injury, whether by crush or transection. For example, molecules of polyethylene glycol (PEG) can be introduced and selectively block the pores in the outer membrane of the distal axon mitochondria and thus block apoptosis [27, 37]. This would provide a kind of immortality for the distal axon (**Figure 3**). If the distal axon remains viable, then this opens up key opportunities in the repair of nerves after a brachial plexus injury. Viable distal axons could be fused to proximal axons through the introduction of fusogens at the transection site, causing an immediate reconnection of the proximal and distal stumps and the immediate reestablishment of connectivity, and most importantly, conductivity of action potentials [38]. This would prevent the distal end organs from atrophying, [30] and allow the muscles to remain viable and functional through the connections with their distal axons across the myoneural junctions [39]. In addition, viable distal axons would allow nerve repair even without fusogens. The proximal nerve stump axons with their activated mitochondria will send out growth cones that will enter the distal axon and re-establish connectivity. There would be no distal Wallerian degeneration because the distal axons have remained viable [39]. In the case of a nerve injury with substantial nerve loss between the proximal and distal stump the gap would have to be bridged with a living nerve graft. This can be done with either a vascularized living nerve autograft or with a tissue-engineered nerve graft with living nerve axons grown in the laboratory [20, 40].

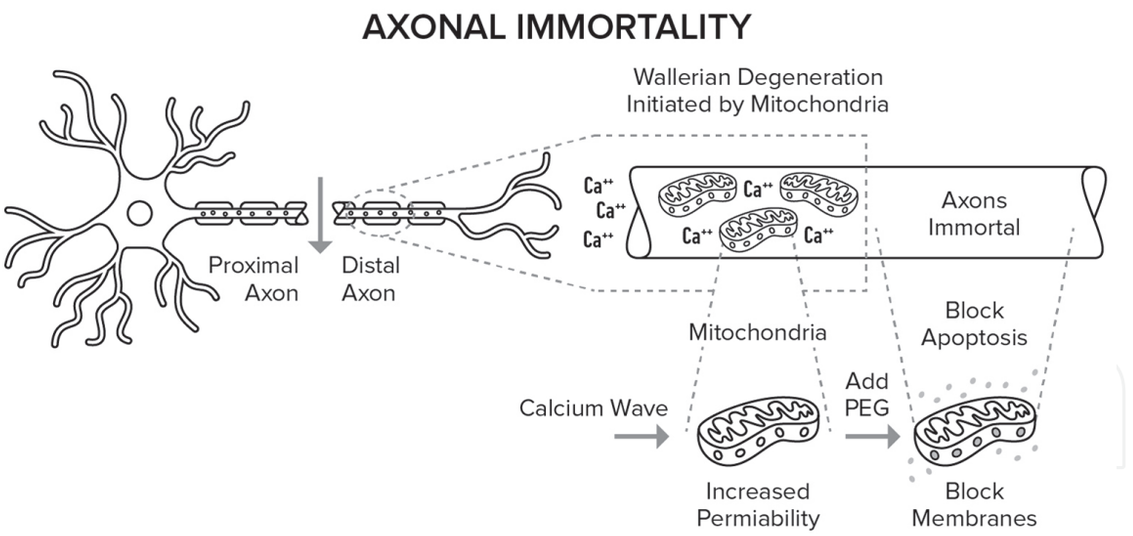

Figure 3.
Axonal Immortality (Section 2.3). Distal axons in the distal stump undergo Wallerian degeneration after the injury of the peripheral nerve, either by the mechanism of being cut or crushed. There is also proximal degeneration (retrograde degeneration), similar to Wallerian degeneration, which involves several nodes of Ranvier proximal to the injury site. It is believed that a calcium wave causes increased permeability in the outer membrane of mitochondria in the axon, and this increased permeability allows bioagents such as enzymes to be released by the mitochondria. The increased permeability then initiates Wallerian degeneration by signaling the cascade that causes the Schwann cells to begin the process, recruit monocytes, and transform them into macrophages to remove the debris in the distal axons. If polyethylene glycol is released at the injury site it plugs the pores in the mitochondria and therefore blocks this Wallerian degeneration cascade. This leads to the axons becoming "immortal".

Once we can keep the distal nerve stump alive along with its axons and Schwann cells, we will open up many possibilities for the future of brachial plexus surgery for acute injuries. What about chronic nerve injuries? We will address these in the next sections, for cases in which the upper limb has lost all of its function, the distal end organs of muscle have atrophied, the joints have become stiff and immobile, and even the distal nerve Schwann cells have undergone regression so there is no longer a distal nerve stump available for reconstruction to connect to the end-organs.

2.3.1 Preventing neuronal loss proximal to brachial plexus injuries

It has been known for many decades that even distal nerve injuries result in the death of at least sensory neurons in the dorsal horn cells, and that more proximal injuries result in a very notable loss of motor neurons as well. Many feel that this loss of both sensory and motor neurons is responsible to a major degree for the observed poor outcomes following brachial plexus reconstruction. A living neuron can generate a new axon, but neurons cannot replicate themselves to repopulate neurons lost following peripheral nerve injuries. Some studies have shown that almost 80 percent of motor neurons die following nerve root avulsion, a frequent component of brachial plexus injuries in babies and adults. Such studies have shown that early repair has a protective mechanism whose etiology is not yet clear [41].

Such early repair observations have led researchers (i) to study the potential mechanisms associated with proximal neuronal apoptosis and by understanding the mechanisms, (ii) to seek to discover therapies to prevent proximal neuronal apoptosis. Recently investigators have found that N-Acetylcysteine prevents retrograde motor neuron death after neonatal peripheral nerve injury [42].

Other investigators found that altering transmembrane proteins that are selectively expressed on neurons and oligodendrocytes facilitated neuron survival and

axonal regeneration, attenuated muscle atrophy and motor end-plate loss, enhanced neovascularization, and promoted functional recovery in a rat model [43].

As previously mentioned, mitochondrial dysfunction may play a role in neuronal apoptosis and mechanisms to reduce this role may be beneficial in preventing neuronal apoptosis. Over the coming years, we can easily anticipate the discovery of molecular solutions to proximal apoptosis along with novel delivery systems such as viral vectors.

3. Part II: Chronic injuries and treatment

3.1 Robotic limbs and brain-machine interfaces: Microelectronic axon processor

In the case of the most severe chronic brachial plexus injuries, the upper limb has become insensible and irreversibly paralyzed. The muscle end organs have atrophied. The neuromuscular junctions have resorbed. The distal nerve stump and its Schwann cells have regressed. There is no possibility to re-establish connectivity and conduction. In these most severe injuries, all of the roots of the brachial plexus have been avulsed. For these chronic patients, there is little to be gained by using nerve grafts from the contralateral seventh nerve root or other available donor nerve such as intercostals and the spinal accessory nerve to innervate the very few functional muscles that can be transferred from other parts of the body, such as the lower limbs. In these cases, the patient's surgical options for limb repair are severely limited. Often if they have one normal upper limb, they may opt not to proceed with a reconstruction of the functionless limb. One alternative is to consider amputation and replacement of the absent limb with an artificial prosthetic limb. There have been great strides made in robotic limbs in the past two decades [44]. Researchers have created endoskeletons; artificial or robotic prostheses that replace an entire amputated arm. There has also been significant progress in restoring function with an exoskeleton – a robotic device that is attached to the outside of the paralyzed limb, allowing it to move and in some cases have sensory function. For both the endoskeleton and exoskeleton prosthetics, phenomenal progress has been made in macrorobotics and microrobotics to enable the fabrication of limbs with dexterity that approaches the human upper limb.

New lightweight materials with increased strength have been used employing new fabrication techniques. These fabrication approaches include new computer-controlled milling machines and machines that extrude materials layer-by-layer at micrometer scale to build a full arm. These design and fabrication approaches allow us to now match the properties of a bird's wing skeleton with respect to both increased strength and decreased weight. Projects both in the US and globally have made huge strides in their production of robotic limbs. One project proposed a brain-machine interface (BMI) to control the new arms that would enable a direct coupling of signals from the brain to control the micromotors powering the new artificial limbs (**Figure 4**). This was pioneered by a number of universities. Even as the BMIs improved, many artificial arms continue to be controlled by more conventional myoelectric systems that use electrical impulses from surface electrodes placed over muscles not involved in the brachial plexus injury. In other cases, increased functional connections have been made in muscle units by dividing muscles into smaller segments and instrumenting these smaller units to control more degrees of freedom available in the robotic limbs.

BMIs have become ever more sophisticated with implants of specialized electrodes into the brain and in some cases, biological interfaces [20, 40, 45].

Work at Stanford by one of the authors envisioned a microelectonic axon processer (MAP) to interface with available peripheral nerves. The MAP would be coupled

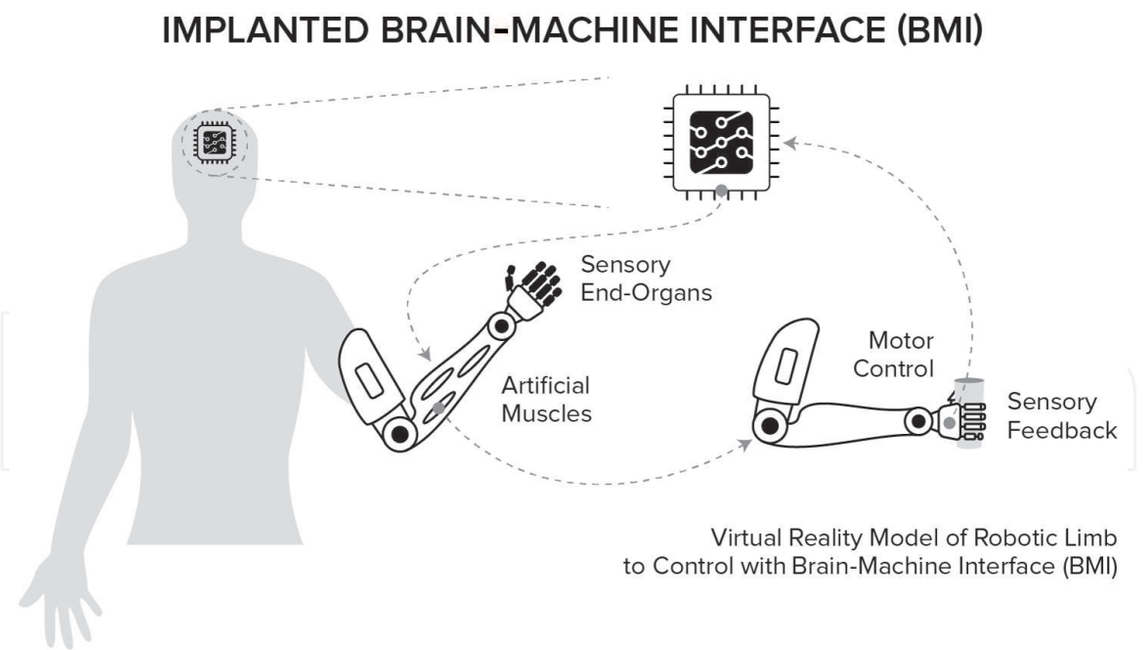

Figure 4.
Virtual Reality Model of a Robotic Limb Controlled by Brain-Machine Interfaces (BMIs) (Section 3.1). Robotic prostheses can serve as replacements for the missing limb, or as exoskeletons attached to the surface of the flail limb to replace the loss of limb function after a chronic severe avulsion injury of the pan brachial plexus. The robotic limb can be controlled with surface electrodes or be directly coupled to computer chips or deep brain electrodes placed in the brain or on the surface of the brain like an electroencephalogram (EEG). Deep brain stimulus is already widely used clinically. In this case, similar electrodes would be used to either (1) provide motor commands or inputs from the brain to the robotic limb or exoskeleton, or (2) provide sensory feedback from the limb to the brain.

to a peripheral nerve at a repair site and the proximal axons would connect to the distal axons through micrometer holes. Each hole would be instrumented with a recording and stimulator electrode as part of a dynamic random access memory (DRAM) microelectronic chip. The electrode sites would be made of iridium on iridium contacts that would improve the signal to noise ratio and would help to prevent the formation of scar tissue at the interface from causing decrements in the signal quality. Although this work was begun in the 1980s it was very much ahead of its time, as there is no present device with the same function.

Laboratory models of these chips were successfully tested in animal models. The thousands of electrode sites mounted on the chip could then be programmed using mirror technology programs taking advantage of artificial intelligence algorithms using neural networks. This would allow the nerves to communicate in a bidirectional manner with the robotic limbs at an axon level providing true detailed connections of the motor and sensory systems at the level of the full maximum set of degrees of freedom presently available in the human upper extremity.

First, we will see the introduction of simple BMIs but over time, we will see more and more complex BMIs to control the robotic limbs whether they are a full replacement of a limb or an exoskeleton fitted seamlessly around the non-functional human limb.

3.1.1 Robotic limbs and brain-machine interfaces (additional reading)

In these additional readings, one can learn more about upper limb prosthetics [46] including an advanced prosthetic called the DEKA arm [47, 48] and other advances funded by defense advanced research projects agency (DARPA), [49] interfaces involved in control of prosthetics, [50–54] exoskeletons, [55] and considerations for different levels of amputation [56].

Reference	Topic overview
[46]	A review including technological advances in prosthetics for upper limb amputees
[47]	A case series studying the DEKA arm– a prosthetic upper limb with active wrist control
[48]	An article exploring the various DEKA arm models created through funding from DARPA
[49]	A review discussing DARPA-funded peripheral nerve interfaces including a focus on provision of motor control and sensory feedback to prosthetic limbs
[50]	A review summarizing biosignal processing of BMIs that utilize EEG and EMG signals, as well as a discussion of sensors, features, and classifiers for upper limb prosthetics
[51]	A review investigating the impact of biomechatronic technology on amputee rehabilitation outcomes, including upper limb amputees
[52]	This book chapter discusses the way electromyography (EMG) is used to create pattern-based myoelectric movements of upper limb prosthetics
[53]	A clinical trial studying the use of Utah Slanted Electrode Arrays (USEAs) to provide more degrees of freedom in movement and increased proprioception for prosthetic hand users
[54]	A review of the state-of-the-art and the limitations of myoelectric signal control methods of upper limb prostheses
[55]	A systematic review of EEG used in BMIs for control of human limb exoskeletons, including background on upper limb exoskeletons
[56]	A review exploring exoprosthetic limb replacement considering different severities of amputation to the upper limb

3.2 Genetic engineering, growing new limbs, and transplantation of limbs

Many brachial plexus patients will refuse an amputation of their chronically denervated atrophied stiff limb. In these cases, it should be possible to take advantage of the advances in allotransplantation. The first kidney transplantation was performed 70 years ago and vital life-saving organ transplantation has become a major contribution to our surgical armamentarium for hearts, lungs, kidneys, livers, and other parts. We have seen a more recent increase in the allotransplantion of both faces and limbs. Hand transplants have become an everyday reality. They could also be used to replace non-functional limbs in combination with new approaches to keep the distal segment of the peripheral nerve functional to allow immediate reconnection of the nerves of the transplanted limb to the proximal stumps of the brachial plexus through the use of fusogens. However, two key limitations remain: the supply of donor-appropriate limbs and controlling the immune system [57]. Improvements in immune suppression have helped to overcome rejection and reduced the associated risks of immune suppression [58]. Research in modulating the immune system continues to result in major strides both for solid organs and allotransplantation of faces and limbs. However, the ultimate future solution for the limited supply of donor parts will be the ability to use either (i) regenerative medicine to grow a new limb or (ii) genetic engineering with new tools such as CRISPR to change our genetic code to let humans do what many other creatures can do – regenerate a totally new limb from an amputated stump. Limb regeneration will require breakthroughs that are beyond the timeframe of this chapter, and it will fall to others to speculate about the future beyond the next 40 years. For now, we are limited to transplanted limbs and the inherent limitations of immune suppression and supply of donor limbs.

3.2.1 Genetic engineering, limb growth, and transplantation (additional reading)

These additional readings further describe hand transplant background [59] and outcomes, [59, 60] immunosuppression needed for vascularized composite allotransplantation (VCA), [61, 62] complications in VCA, [63] and transplant waiting lists [64].

Reference	Topic overview
[59]	A review paper including hand transplant background and outcomes
[60]	A review of hand and upper extremity transplantation outcomes
[61]	A review of immunosuppression in VCA including approaches and future directions
[62]	A review discussing outcomes, resultant functionality, and immunosuppression in VCA procedures.
[63]	A review summarizing complications that have occurred in VCA
[64]	A review exploring the VCA waiting list in the US

3.3 Computers, virtual reality, augmented reality, and artificial intelligence

Computers were a product of World War II and there has been exponential progression over the past 75 years. The microprocessors powering computers have followed Moore's law, doubling their computational ability every two years for the past 40 years. This will eventually enable the development of a microelectronic axon processor as we have discussed above in Section 3.1. Computers and their computational power will let us design truly realistic models of the brachial plexus injuries facing us in the operating room. Mathematical models can mimic the behavior of the nervous tissue and other surgical tissues that we need to manipulate. These models will enable a future surgeon to visualize the brachial plexus and a specific injury in real time in a virtual reality environment. It can now be used to train surgeons and to prepare, plan, and practice surgeries prior to attempting to repair the most complex brachial plexus injuries. A virtual reality helmet or viewer such as the Oculus™ can link to a computer model of a specific injury, created using a physically-based finite element mathematical model of the brachial plexus and surrounding tissues of a patient, from data obtained from a detail-rich 3D MRI, CT scan, or ultrasound taken prior to surgery. Surgical simulation has now become an accepted tool in many of our fields since its inception in the 1980s. The original applications modeled gunshot ballistic injuries and congenital problems such as surgery on cerebral palsy. Once virtual reality established the use for these models for planning and practicing surgery, then it became possible to apply the same patient-specific models in the operating room by superimposing the models on the patient as we operated (on the patient – a technology known as augmented reality **Figure 5**). There exist several systems that enable the fusion of the computer-based mathematical model of the patient that was created prior to the surgery onto the actual patient during the procedure. The term coined for this by one of the authors is a "performance machine."

A performance machine allows the surgeon to conduct the surgery with the aid of the computer model and ultimately to predict the outcomes. The most advanced models with the aid of artificial intelligence will predict the outcomes of surgery. Outcome prediction has been done [65] in other fields such as musculoskeletal surgery and vascular surgery, and should eventually be possible for peripheral nerve surgery such as complex brachial plexus surgery. Although computationally intense, it is possible to accurately fuse the computer model on the actual patient in real time as we are performing the surgery. With the overlay of the computer model, we can "see through" the tissue that surrounds the brachial plexus, identify key landmarks, and avoid key structures. Surgeons also often use the surgical robot in performing brachial plexus surgery in areas that are difficult to reach, for example, beneath the clavicle in the area of the subclavian vessels. Our most challenging cases are in brachial plexus surgery or injuries where the subclavian vessels have been repaired or bypassed, and the normal surgical planes have become obliterated by scar.
In a similar manner where a tumor may encircle the brachial plexus, combining

computer simulation and robotic surgery technologies (**Figure 6**) may reduce some of the risks inherent in such cases. Each year we come closer to seeing virtual and augmented reality technologies introduced in brachial plexus surgery.

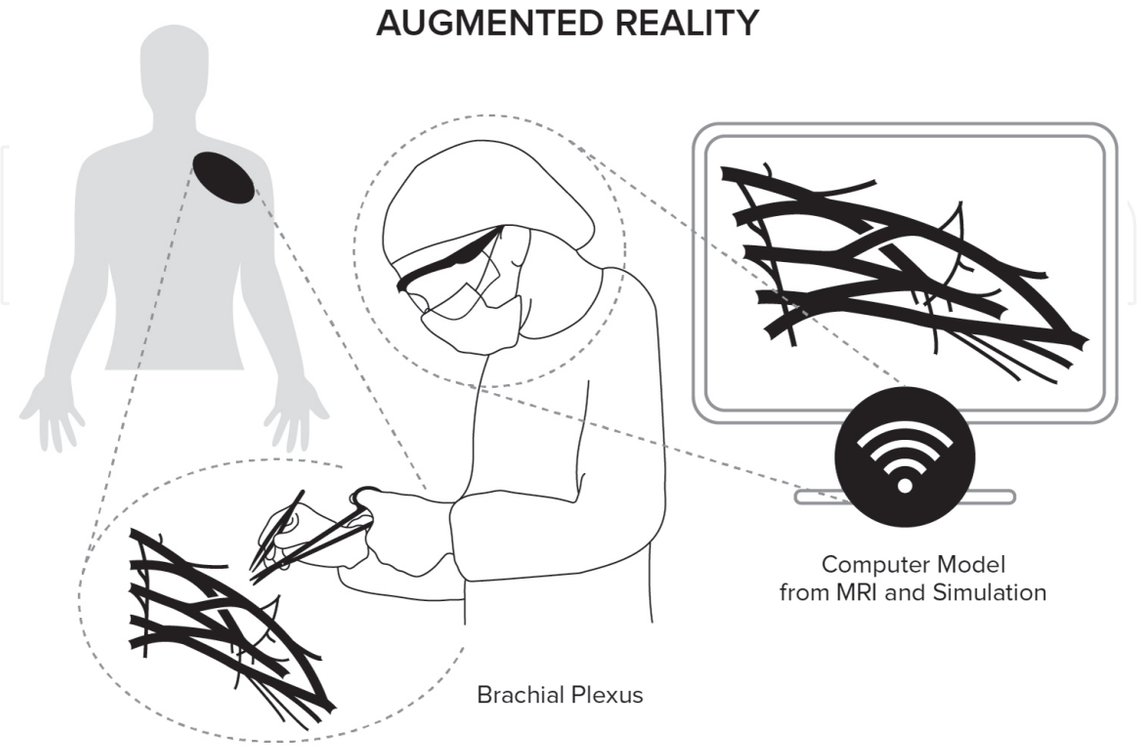

Figure 5.
Augmented Reality (Section 3.3). In augmented reality, we create 3D image models of the brachial plexus for a specific patient and then superimpose these images on the patient's body in real time during the surgical procedure. This superimposed 3D model allows the surgeon to "see into" the patient as the model displays transparent skin, soft tissue and bones to pinpoint the exact position of the nerves. The model can deform and change shape, adjust to the position of the patient and the brachial plexus with the patient location using fiducials or key markers that allow the computer the fuse the patient and the models together in the same space. These models can be combined with robotic surgery to allow the surgeon to use a minimally invasive approach to the brachial plexus, working around critical structures such as vessels and bones.

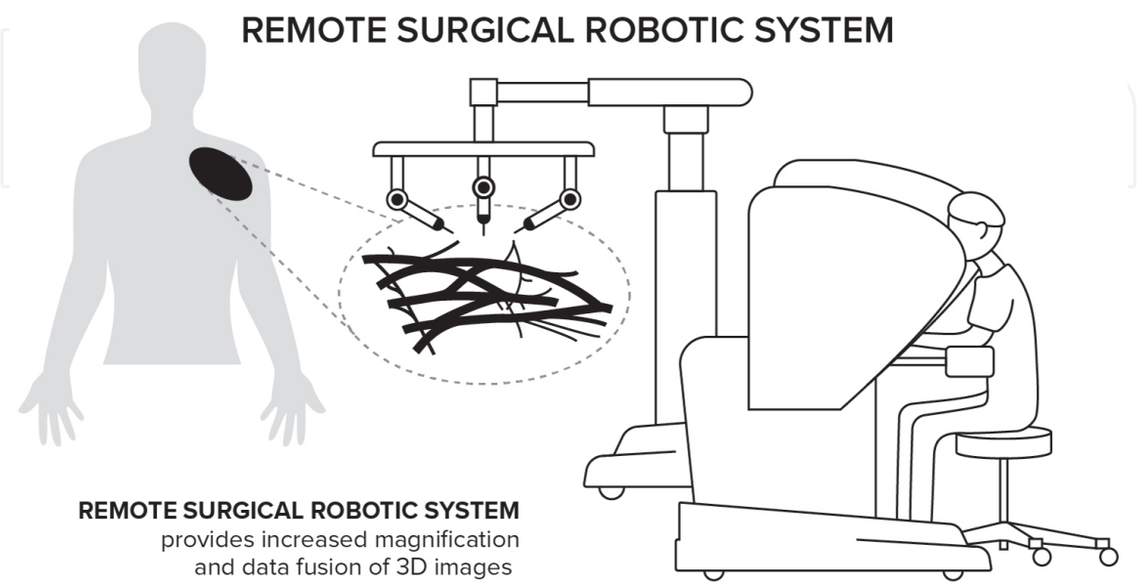

Figure 6.
Robotics (Section 3.3). This remote surgical robotic system uses a surgical robot to assist the surgeon in operating on the brachial plexus. This system provides increased magnification, removes the surgeon's tremor, and provides the ability for data fusion of pre-acquired 3D images.

Another promising development in computers is the use of artificial intelligence (AI) in decision-making. We have done research in modeling surgical cases to improve the communication between the patient, the physicians, and surgeons [66]. These models have used the AI discipline of Bayesian algorithms to model the behavior of the patient and the physician during complicated procedures [67]. Lack of communication or miscommunication can lead to poor outcomes where the needs of the patient and the decisions made by the surgeon are misaligned. It is possible to develop models based on AI that can help to reduce these errors [68]. Brachial plexus surgery is an especially rich area for this type of decision-making because of the complexity of the decision-making and the many choices available to the surgical team in deciding which is the best course of action for the patient [66, 69, 70].

3.3.1 Virtual reality, augmented reality, and artificial intelligence (additional reading)

One can learn about virtual reality, augmented reality and artificial intelligence by reading about models that capture decision-making processes, [71] Bayesian 2-test cases in medicine, [72] and VR and AR use in medical imaging [73] and procedures [74].

Reference	Topic overview
[71]	A proceeding that utilized a cognitive model to capture decision-making processes
[72]	An article exploring the use of visual aids to better demonstrate results of Bayesian 2-test cases in the medical field
[73]	A review investigating the use of VR and AR in medical image viewing/manipulation, including background on VR and AR development
[74]	A review exploring the documented uses of VR and AR in medicine, including in diagnostic and surgical procedures

4. Conclusion: brave new world of brachial plexus surgery

In looking forward, as Sir Isaac Newton was quoted as saying in 1695, "If I have seen further than others, it is by standing on the shoulders of giants."[2] Many scientists and clinicians have provided the foundation that we presently stand upon. The authors have contributed to many of these fields, but many others have led these fields and created the technologies that we discussed in this chapter that can, one day, further advance the field of brachial plexus surgery. This chapter cannot possibly give credit to all of those scientists and clinicians that have preceded us. However, our goal has been to look at possible scenarios for the future of brachial plexus surgery and provide an optimistic view of the future.

This optimistic view sees a future in which a patient with a severe brachial plexus injury can dream of, hope for and ultimately experience the reality of a fully functional limb, whether biological or artificial, following their treatment. The solutions in the future will stem from many of the present technologies and methodologies that we have presented in this chapter. But these are only our vision for

[2] "If I have seen further," Isaac Newton wrote in a 1675 letter to fellow scientist Robert Hooke, "it is by standing on the shoulders of giants." https://fs.blog/2020/04/shoulders-of-giants/. This was a saying that was well known in Newton's time and he was paraphraing it: (https://www.quora.com/When-Newton-said-If-I-have-seen-further-it-is-because-I-have-stood-on-the-shoulders-of-giants-to-whom-was-he-referring-Who-were-his-giants).

the future. We are sure that there are other technologies that we have not discussed, and ones that we have not foreseen, that will impact this field.

During our careers our most severe challenges have been seeing our unfortunate patients with brachial plexus injuries that do not turn out well, whether a child with a birth defect, or an adult with a traumatic injury. They have been among our most courageous and most thankful patients. It is important that we dedicate ourselves through our careers to help them in any way that we can. We will participate in many successes and failures as we introduce new technologies and surgical techniques to address the many challenges presented by this field. It is through our patients and our camaraderie to share our knowledge, our successes and our failures, that we will move this field forward. This book is an important milestone in our field and we feel fortunate to have contributed this chapter to the success of this book. Its publication is very timely to mark the past progress in this field, the present state of the field, and in some small part, to look at the future ahead of us as practitioners of the field of brachial plexus surgery.

Acknowledgements

The authors wish to acknowledge Robyn Mosher, MS, for manuscript editing, literature searches, and reference management; and Linnea Spelman, BA, for image design and production, editing, and proofreading.

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