BION microstimulators: A case study in the engineering of an electronic implantable medical device

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1. Introduction

The late 20th century has been marked by the proliferation of active implanted medical devices. Beginning with the earliest pacemakers of Elmqvist [1] and Greatbatch [2], a foundation of engineering knowledge was developed that has provided the basis for the advanced pacemakers, defibrillators, cochlear implants, neurostimulators, and drug pumps that followed. All these designs leveraged the earlier work, and the solutions created by this pattern of emulation and innovation have alleviated enormous human suffering. The BION (Bionic Neuron) is a single channel implantable neurostimulator that combines the current implanted device technology and microelectronics with a novel system design to yield a general-purpose single-channel neurostimulator that can be delivered by injection (Fig. 1).

As a natural outgrowth of medical device successes, corporations have been formed to design the increasingly complex active implanted devices used in contemporary medicine. In keeping with their commercial nature, most of the development knowledge associated with these devices has remained confidential. Companies are motivated to discuss the fruits of their successful designs as they bring them to market. However, they have no commercial or ethical imperative to discuss the inevitable mistakes that have occurred along the development path. Consequently, the design histories of successful active implantable medical devices and particularly the elucidation of development errors and traps are rarely discussed.

Unlike commercial devices, the BION has been developed in the public eye. The literature reveals the nuances of its design evolution in substantial detail. This record includes examples of biomedical engineering vision, successful innovations, and importantly, design errors and their remedies. As these occur in virtually all device design processes [3], and given the high quality of engineering applied to the BION, it is the view of the authors that its history is worthy of attention. This paper reviews the conception, early execution, and development of the BION, and recounts several of the process steps and decisions that drove its success. It also examines a few significant design revisions with a view towards other design teams that may benefit from the BION experience.

1.1. Origins of the BION devices

The need for an adaptable, compact, and wireless neural interface was becoming apparent to workers in the field in the late 1980s. Functional Electrical Stimulation (FES) had demonstrated great restorative potential. In pilot studies, paraplegic patients...
were able to stand, pedal bicycles, and walk short distances with support. Tetraplegics were able to gain enough limb control to perform simple, but essential tasks such as feeding themselves. But the transformative power of multi-channel control was constrained by hardware limitations. Surface electrode stimulation had shown insufficient spatial selectivity to enable complex, independent control of proximal muscles and nerves [4]. High thresholds and the concurrent activation of cutaneous pain fibers bounded the primary application space of surface electrode systems [5,6]. Internal electrodes offered the potential to overcome these limitations, driving the development of percutaneous and subcutaneous electrodes for sensing and stimulation. The acute properties of percutaneous electrodes were sufficient to establish the restorative potential of multi-channel FES systems [7–9]. However, the mechanical reliability and infection potential of multiple percutaneous lead systems inhibited their widespread adoption [10]. Fully implanted lead and stimulator systems reduced infection problems, but the surgical complexity was significant, as multiple subcutaneous leads had to be tunneled into disparate targets. While the percutaneous infection pathway was eliminated, the leads remained susceptible to mechanical fatigue and breakage. Redundant stimulation leads were impractical, and replacement leads required additional difficult surgery. Through the “Neural Prosthesis Project” of the National Institute of Neurological Disorders and Stroke USA, an initial specification for a wireless implantable stimulator system was proposed. This was refined by Loeb et al. and formed the conceptual nucleus of the injectable microstimulator [11]. Recognizing the broad potential of the microstimulator, the project vision was not limited to implementing a single therapeutic function. The designers conceived multiple applications and various levels of functionality that could eventually be achieved [12]. First though, a prototype had to be realized that demonstrated the primary technical challenges were surmountable. Foremost of those challenges were energy transfer, communications, and stimulus control, all within a remarkably small, biocompatible envelope.

The BION device family is the result of the multi-institute collaboration that followed. Contributors included the US National Institutes of Health (NIH), Queens University of Ontario Canada, Illinois Institute of Technology and the Alfred Mann Foundation [13]. Public funding provided from the NIH, the Canadian Neuroscience Network of Excellence, and the Ontario Rehabilitation Technology Consortium combined with an alliance of strong academic partners ensured world-class research standards and broad publication. Four generations of BION devices have been developed in the ensuing years, and we are on the threshold of the first commercialization of BION microstimulator applications. Clinical and technical research continues at Alfred Mann Foundation, Boston Scientific, and research institutes worldwide.

2. Implantable stimulator architecture and attributes

The magnitude of the injectable microstimulator achievement is appreciated with a reflection on the operational requirements and functional blocks that are essential to the operation of any implantable stimulator, and also by observing some examples of how these blocks are realized in BIONs compared with contemporary implantable devices. A simplified stimulator architecture is shown in Fig. 2.

The energy source of an implantable stimulator is often the largest component of the assembly. While cardiac pacemakers typically use a lithium primary battery, commercial neurostimulator designs are divided between primary and secondary batteries [14–17]. The recharging afforded by secondary batteries accommodates larger energy demands for an equivalent device volume, but devices implemented with primary batteries require no user compliance to recharging intervals. In both cases, battery volume is optimized within the constraints of the clinical application, the acceptable frequency of recharging, and device replacement intervals. For a relevant comparison of energy sources, the devices closest in scale and scope to the BION are cardiac pacemakers. A very small pacemaker has a total volume of 12 ml; about 4 ml or 33% of that volume is occupied by the primary battery. Using the BION energy demands given by Schulman [18] and the typical training regimen suggested by Loeb [13], the size of a lithium primary battery suitable for 3 months of projected BION service would exceed the total allowed volume of the device. Yet BIONs were intended to have lifetimes of 10 years or longer. No existing battery technology was suitable, and the design strategy focused on externally powering the implant. This design decision required the partition of the implantable stimulator system into an external support module and an implantable stimulator module. The external module would deliver energy through inductive coupling to a coil wound

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Fig. 1. Three generations of BION microstimulators show the concept evolution and are the products of several distinct organizations. The glass capsule BION1-AMI was succeeded by the Ceramic BION1-AMF with integrated blocking capacitor. The BION3-ABC included a rechargeable battery (Alfred Mann Institute, Alfred Mann Foundation, Advanced Bionics Corporation). Reproduced with permission LGEB [13] Neurosurgical Focus.

Fig. 2. Simplified stimulator architecture depicts system blocks and functions common to most implantable stimulators. Usually only one type of stimulus regulation is employed (Vstim or Istim).
inside the housing of the implant, and the implant would deliver the desired stimulus to the patient.

The command port of a generic stimulator could be as simple as an on/off function achieved with a magnetic switch, but it is generally a unidirectional or bidirectional telemetry link that allows external control over multiple parameters. This typically requires an inductive communication coil or an RF transceiver circuit. While transceivers can be highly miniaturized, their energy demands increase the need for battery reserve capacity and subsequently increase battery volume. Given the intention for multiple BION implants in a single patient, a moderately sophisticated communication link was necessary for the command port to decode unique device addresses [12]. To fulfill the communication hardware requirement with minimal components, the energy coupling coil would concurrently serve as the receive coil of the telemetry circuit [19].

Voltage converters are required to match the supply voltage to the requirements of the electronic subsystems and to eliminate source fluctuations. This is typically achieved with inductive or switched-capacitor supplies and voltage regulation. But practical inductors tend to be large against the scale of the BION, and while capacitors for switched systems are slightly smaller, they are comparable to the inner diameter of the housing. Since the peak voltages available at the terminals of the inductive power coil were large enough, linear voltage regulation circuits could be implemented on the BION integrated circuit (IC). Once the discrete coil and capacitor requirements were eliminated, the space required for this function was negligible.

The pulse rate generator requires a stable clock circuit, often derived from a quartz crystal. The digital watch industry has created widely available micro-miniature low-frequency crystals useful for this application. Presently, the smallest of these are ~1.2 × 2 × 0.6 mm [20] and devices of a similar nature are commonly used in pacemakers. Though small enough to fit comfortably in a wristwatch, they would occupy a substantial volume within the context of the BION devices. Again the designers leveraged the external radio frequency (RF) magnetic field that coupled power and communications as a primary clock signal. This eliminated the need for an internal quartz crystal.

Stimulation pulses must be regulated for either voltage or current, and stimulator architecture may have one or both regulation functions. However, only one parameter can be controlled independently. The second depends on the interaction of the electrodes and the tissue impedance. For current controlled pulses, a fixed current is targeted for the duration of a pulse; however, the stimulator must have a voltage source sufficient to drive the current. If the tissue impedance is too high, the voltage compliance limit of the source will be reached, and the current value will fall below specification. Conversely, voltage controlled pulses into low impedance sources of unreliability [27–29]. Electrodes always occur in sets,

Leads and electrodes are the critical conduits and interfaces to tissue. Leads themselves can be a significant volume in relation to devices (Fig. 4), and in many applications are substantial sources of unreliability [27–29]. Electrodes always occur in sets, as even “unipolar” pacing systems use the device case or another indifferent electrode for a return current path. Electrode current density must be low enough to prevent irreversible electrochemical reactions, which implies large effective surface area [30,31].
Conversely, electrodes should produce sufficient local excitable tissue current density to efficiently recruit nerve or motor fibers [32]. The BION design eliminated the need for leads, as it was configured to be delivered directly to the stimulation target by virtue of its Lilliputian proportions. The integrated electrodes achieved high effective surface area through activated iridium oxide chemistry on the cathode and sintered tantalum pentoxide construction on the anode.

Connector systems (Headers) are required to establish mechanical and electrical union between the simulator and the leads. Depending on the complexity and the number of leads employed, the header may have a volume of 2–6 ml. As an electromechanical assembly outside of the hermetic chamber, headers operate within the hostile environment of the body. Though generally quite reliable, connector corrosion, current leakage, and shorting issues have occasionally been observed in commercial devices. The BION design eliminated the need for leads and in this eliminated the header and its potential failure modes.

The packaging challenge is clarified in Fig. 5 which shows the BION-1 package (Fig. 5A) between a commercial neurostimulator (Fig. 5B) and a cardiac pacemaker (Fig. 5C).

### 3. The BION specification

The initial RF Microstimulator specification set [26] was conceived to allow flexible, minimally invasive FES and neuromodulation functionality. Device dimensions were a top priority to enable delivery by hypodermic needles or cannulae. Stimulation capabilities were selected to enable effectiveness over the broad range of neuromuscular applications envisioned. The device concept was driven by the realization that a sufficiently small implant could leverage the relatively uniform stimulation thresholds across the neuromuscular system and be delivered to a broad range of end effectors [12]. Critical to the realization of a successful system was the inductive link and a multi-module addressing ability. Many performance criteria of specifications were stated briefly in the first draft of requirements, as they were implicit to the concept of a chronically implanted device, e.g. biocompatibility, mechanical fixation, reliability, benign failure modes, manufacturability, mechanical robustness, and hermeticity. Substantial effort was applied to fulfilling the last two criteria as performance in these areas was directly influenced by the injectable cylinder package.

To achieve a form factor that was injectable required innovation and component miniaturization, but the most substantial gains arose from assigning functions to the external electronics module. Table 1 lists some of the system design decisions used to shrink the stimulator along with their volume impact. The “Reference Volume” is the approximate required volume for each functional block if implemented using contemporary technology.

It is clear that design decisions to eliminate components and to integrate functions together created most of the miniaturization required for this form factor. By deploying the device at the point-of-use, leads and headers were eliminated. Of course the requirement to deploy to the broadest range of anatomical targets sharply bounded the allowable volume. Abandoning the primary battery and effectively coupling external power became a critical goal. Once realized, this approach meant that small size was combined with a nearly indefinite longevity. This is quite different from current technologies, where the battery, primary or secondary, usually defines the device’s service life.

Indefinite longevity presented other issues for the BION, such as predicting the reliable life and scheduling replacements. This information is critical for life-sustaining devices such as cardiac pacemakers. However, to date, BIONs have not been targeted at similarly critical applications. Because the package is unobtrusively small, if it ceases to function, another can be placed with no need to explant the first. To enable this approach, the designers sought to establish lifetime biocompatibility of the package, and specified the durability of the housing to obviate the need for explanting devices [33]. With no leaded electrodes and no need to extract the primary device, replacement surgery is simplified.

Table 2 highlights selected BION specifications as they evolved over the early phase of the development cycle. In the first reported prototype, the initial specifications were achieved with general success. The length of the device had increased from 10 mm to 13 mm, but the most critical features were achieved: inductive power coupling, functional stimulation levels, clock transmission, addressing ability, and a 2 mm diameter package. The testing of this proof-of-concept device confirmed the significance of previously identified challenges and signaled the existence of others that became apparent though device evaluations. These results combined with the stability of recruitment thresholds and the ease of the implant procedures were critical milestones that allowed development to continue and drove subsequent refinements.
Table 1

<table>
<thead>
<tr>
<th>Function</th>
<th>Reference volume</th>
<th>BION approach</th>
<th>BION volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy source</td>
<td>150 μL LiCF battery&lt;sup&gt;a&lt;/sup&gt;</td>
<td>External source inductive coil</td>
<td>7 μL</td>
</tr>
<tr>
<td>Communications antenna</td>
<td>375 μL pacemaker coil</td>
<td>Integrated in energy collecting coil</td>
<td>0</td>
</tr>
<tr>
<td>DC blocking cap</td>
<td>80 μL SMT Cap&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Integrated with electrode</td>
<td>0</td>
</tr>
<tr>
<td>Leads</td>
<td>1500 μL Silicone helix wound or similar&lt;sup&gt;c&lt;/sup&gt;</td>
<td>None required</td>
<td>0</td>
</tr>
<tr>
<td>Electrodes</td>
<td>Integrated in leads</td>
<td>Fused to housing</td>
<td>4 μL</td>
</tr>
<tr>
<td>Clock-reference</td>
<td>1.5 μL crystal</td>
<td>None external field</td>
<td>0</td>
</tr>
<tr>
<td>Connector systems</td>
<td>1000 μL header</td>
<td>None integrated</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup> LiCF battery, 10 year nominal stimulation.
<sup>b</sup> Typical 6.8 μF 35V High Reliability Tantalum SMT.
<sup>c</sup> 0.5 m, 6-french bipolar lead volume.

Table 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Proposed value</th>
<th>First prototype</th>
<th>BION-1AMI</th>
<th>BION1-AMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter</td>
<td>2 mm</td>
<td>2 mm</td>
<td>2 mm</td>
<td>2.4 mm</td>
</tr>
<tr>
<td>Length</td>
<td>10 mm</td>
<td>13 mm</td>
<td>16 mm</td>
<td>16.7 mm</td>
</tr>
<tr>
<td>Power</td>
<td>Inductive</td>
<td>Inductive</td>
<td>Inductive</td>
<td>Inductive</td>
</tr>
<tr>
<td>Addressable devices</td>
<td>256</td>
<td>256</td>
<td>256</td>
<td>256</td>
</tr>
<tr>
<td>Current amplitude</td>
<td>0.1–15 mA</td>
<td>0.2–30 mA</td>
<td>0.2–30 mA</td>
<td>40 mA</td>
</tr>
<tr>
<td>Voltage compliance</td>
<td>8 V</td>
<td>8.5 V</td>
<td>17 V</td>
<td>(17V)</td>
</tr>
<tr>
<td>Repetition rate</td>
<td>50 pps</td>
<td>50 pps</td>
<td>50 pps</td>
<td>50 pps</td>
</tr>
<tr>
<td>Hermetic package</td>
<td>1 × 10&lt;sup&gt;−10&lt;/sup&gt; cm&lt;sup&gt;3&lt;/sup&gt; s&lt;sup&gt;−1&lt;/sup&gt;</td>
<td>Glass 40% yield</td>
<td>Improved glass</td>
<td>Ceramic</td>
</tr>
<tr>
<td>Electrodes</td>
<td>Ir/Ta</td>
<td>Ir/Ta</td>
<td>Ir/Ta</td>
<td>Ir/PtTi–6–4</td>
</tr>
<tr>
<td>Feed thru</td>
<td>Ir Ball/Ta Wire</td>
<td>Ir Ball/Ta Wire</td>
<td>Ir Ball/Ta Tube</td>
<td>Brazed ceramic</td>
</tr>
</tbody>
</table>

3.1. Packaging development

Compared to external medical systems, packaging for implantable medical electronics has a much greater impact to the overall success of a therapy. The geometry, construction, and material set of the package interact with the implant environment and set the foundations of device reliability. Whilst from a reliability perspective, the thermal environment of the body is extremely stable and benign; all other conditions present additional risk. The electrolyte-laden interstitial fluid threatens to penetrate any sealing failure, causing leakage currents, forming dendrites, and inducing a host of subsequent malfunctions. The fibrous encapsulation tissue that inevitably surrounds an implant impedes the electrical interface to excitable tissue. It must stabilize the device quickly to inhibit migration and to facilitate predictable stimulation thresholds. Surface morphology and materials affect the course and extent of this encapsulation [34,35]. Excessive encapsulation can yield unstable or increasing stimulation thresholds [36]. Trace contamination and compromised sterility present immediate threats to wound health and healing. The overall device morphology controls patient comfort, deployment and retrieval ease, and physical stability. Depending on the ultimate location of a device in the body, repetitive mechanical stress can fatigue housings, feedthroughs and interconnects, causing failures or patient injury. Since even minor surgery engenders infection risk and recovery discomfort, a pattern of packaging failures can threaten the acceptance of a substantially beneficial technology.

The hermetic packaging of the BION devices was an initial difficulty [37]. While glass to metal sealing was a well-established technology, the miniscule interior volume of the implants (approximately 25 μL) made evaluating the hermetic performance of the devices problematic. Leak rates slightly below the detectable threshold were capable of inducing moisture related failures within the span of several months [12]. This testing difficulty was anticipated, and a long-term proposal for the use of a desiccant was considered, but not implemented on early builds. The initial yield of the hermetic packaging was quite low. Gross leak failure rates approached 60%, and some devices were found to fail later in life with trace moisture levels [33]. The latter observation was identified not as a hermetic failure, but the consequence of two sources: moisture trapped within the organic materials of the assembly and the residual moisture from the flame sealing method [33]. A desiccant impregnated silicone getter was incorporated into subsequent device generations, an approach currently practiced in commercial pacemakers and neurostimulators. The desiccant was capable of absorbing all of the out-gassed moisture and a lifetime quantity of feed-through leakage at rates below the detection threshold.

While the human body presents a stable thermal environment, the thermal life of implantable devices begins at manufacturing and includes multiple temperature excursions. Curing epoxies, forming glass-to-metal seals, moisture bake-out cycles, welding, anode formation, and sterilization processes each induce thermal stress. Eventually devices stabilize at ambient storage temperatures, but even these may fluctuate repeatedly before implantation. While most or perhaps all of these thermal events were known to the designers, the initial prototypes did not have a stress relief mechanism between the circuit assembly and the glass envelope (see Fig. 6). A tiny spring was incorporated shortly after the first proof of concept prototypes [25]. This spring provided a thermally stable, electro-mechanical union between the circuit module and the feed-through contacts (Fig. 7). This compensating mechanism for thermal expansion mismatch improved yield and reliability. Its exclusion from the earliest prototypes could have been oversight or simply a choice made to focus resources on more important challenges early in the development effort.

As microstimulators demonstrated their feasibility and practical potential, additional packaging and manufacturing improvements were pursued to increase the overall reliability. Thermal cycling

![Fig. 6. Early microstimulator realization 13 mm with spherical electrode and rigid connections to the hybrid circuit. Reproduced with permission Cameron [33] ©1997 IEEE.](image-url)
tests were used to screen devices for electro-mechanical faults. High-pressure saline baths of 160 bar rapidly fractured compromised hermetic seals at the tantalum-glass feedthrough interfaces [26]. Micro-torch sealing was eschewed for the benefits of CO\textsubscript{2} and YAG laser assembly [37]. Specialized assembly fixtures were created that minimized the number and complexity of manual assembly operations required for completing a device, and lot acceptance testing was introduced to establish the suitability of a build-population for use in human trials. The consequence of these design and process improvements was the ability to demonstrate the reliability levels necessary to support clinical trials.

3.2. Electronic challenges

The primary electronic design challenges were energy transfer, telemetry, clock crystal elimination, stimulus generation, and DC current protection. Overshadowing these requirements was the necessity of keeping the component count to an absolute minimum. Heetderks had calculated that the energy transfer characteristics for millimeter sized solenoidal coils were comparable to the calculated demand for BIONS [38]. Voltage regulation would be required to compensate for coupling variations, and ferrite cores would improve the power transfer. The receive coils were wound to have self-resonance at 2 MHz. This eliminated a tuning capacitor at the cost of complexity in the transmitter design [39]. While not a component of the implant, external power and telemetry electronics were required to accommodate the implants. Class-E transmission circuitry and an auto-tuning feature were created to address the weak coupling between the implant and the external driver and to compensate for external coil inductance shifts [40].

By the same decision that had eliminated an internal battery, the presence of a continuous external driving field became a fixed requirement. This enabled real-time control over devices by amplitude modulating the charging field and incorporating a Manchester encoded command structure [33]. The continuous presence of the charging field was then leveraged to create the on-chip clock signal. The “0” bit amplitude of the field was 80% of the “1” bit amplitude, allowing continuous clock detection independent of the telemetry data. This eliminated the need for a crystal clock circuit, contributing to miniaturization and assembly ease.

As Table 2 shows, the electronic design did not escape evolutionary changes. The pulse-width range and step-sizes evolved, as did the compliance voltage limit and the recharge circuit implementation. Though the BION was not designed to employ leads, experiments using lead extensions inadvertently exposed a current stability issue in the electrode recharge and charge-recovery circuit (see Fig. 2) that was not apparent during bench and in vitro testing. [18] These changes are within the scope of expectation for prototype silicon, and their occurrences reflect the reality that even highly competent device design for medical electronics remains an iterative process. Performance and requirements differences that may be acceptable in non-medical applications require correction in medical devices, and fully refined requirements for implantable devices cannot always be realized in advance of pre-clinical and clinical testing.

3.3. Pre-clinical testing

Testing was conducted to establish the functionality and stability of the microstimulators using in vivo models [33,41]. In functional evaluations, the allowable distance to the target and the ability to predictably transition between partial and complete recruitment of motor units in muscle were primary characteristics of interest. Testing established that placing the BIONs proximal to the nerve entry zone optimized contractile forces. Alignment of the anode was not critical if the cathode was appropriately close to the motor point. Contractile forces of up to 80% of the maximum recruitment were compared to stimulus pulse duration and amplitude, and slopes were deemed acceptable. However, some step changes interrupted the generally sigmoidal response curves (Fig. 8). These were hypothesized as the result of far-field recruitment of adjacent motor nerves combined with the well-known reverse recruitment effect.

These early prototypes were not able to fully recruit all the motor units in the target muscle. This limitation was identified as the result of a compliance voltage inadequate to support the 30 mA stimulus current requirement [41]. The importance of careful place-
ment combined with the stepwise changes in recruitment caused Cameron et al. [41] to suggest that two or more BIONs with different levels of coupling to the same target muscle could be employed to achieve control through the full range of contractile force for large or complex muscles.

Though the initial strategy proposed intramuscular stimulation for its shallower and more predictable recruitment characteristics [42], work was conducted later to evaluate stimulating peripheral nerves. This approach can stimulate multiple muscle groups served by the nerve, increasing the resulting force at the cost of steeper recruitment curves. An effective working distance for recruitment was within 10–15 mm from motor nerves [43], and muscle recruitment characteristics were mapped against the effects of orientation and across the range of available stimulus parameters. It was shown that the proximity of the cathode to the stimulation site was important for recruitment threshold, whilst the axial orientation of the devices had little effect [43]. Other factors may influence the placement such as comfort or stability, but these were not in the scope of this study. The importance of precise device placement drove the development of a specialized surgical instrument kit (see Fig. 9). This simplified the implant technique, enabling a minimally invasive approach [44,45]. Biocompatibility was extensively evaluated and proven using established methods that are not elaborated here but can be found in substantial detail elsewhere [36].

The series of in vitro and pre-clinical evaluations of BIONs had driven improvements to the physical and electronic design. The devices were now 16 mm long and substantially more robust than the first prototypes. The revised devices were demonstrating in vitro and in vivo performance within all of the major design goals.

3.4. Clinical tests

Human trials were the next milestone and two initial applications were selected: post-stroke shoulder subluxation and knee osteoarthritis. Ten patients participated in the initial subluxation study, and five in the osteoarthritis study [46]. These studies targeted large or deep muscles, well suited to accepting the BION assembly. The knee osteoarthritis study stimulated the femoral nerve, and the shoulder subluxation study stimulated motor points of the supraspinatus muscle and the middle deltoid muscle fibers. Therapy in both studies was stimulated contraction intervals of up to 30 min duration repeated 3 x daily with pulses administered for 10 s followed by 5 s rest [46]. The external software was configured to track patient compliance, and yielded objective use data. These automated data varied from patient reported data that were slightly overstated by subjects. Both subjective and objective data demonstrated significant improvements in shoulder subluxation and knee function for the respective studies.

Though the sample sizes were small, these trials demonstrated positive therapeutic effects from BION stimulation. Their execution also provided observations that prompted further technical and clinical refinement. Relevant to the surgical technique and placement, two instances of mild discomfort were associated with implants near the crease in the groin in the osteoarthritis study. One device was explanted for this, and it was deemed to be in an orientation unsuited to hip flexure [46]. In the shoulder subluxation study, a device was not deployed fully into its anatomical target, though it proved effective nonetheless.

The implantable hardware and external software were adequate for the studies, but a number of refinements were indicated in the course of real-world applications. Interference from certain computers’ serial ports disrupted the use of the pre-implant test functions, and external hardware was reworked for ease of handling and improved durability. In two subluxation patients, BIONs were difficult to align to the transmitting coil for simultaneous coupling to the external unit. These patients’ data were pooled into non-compliant group that included patients unable to self-administer therapy because of stroke related cognitive changes [46]. The communication issue was traced to the telemetry circuits of the BION’s ASIC, and manufacturing tests were revised to screen out this failure mode. These external interference and deployment observations exemplify what is difficult either to anticipate in design or to discover in the lab prior to clinical use. However, given that the BIONs had been specified for multiple, concurrent activation, the communications failure might have been discovered with a sufficiently comprehensive electrical performance evaluation prior to the clinical study.

A subsequent pair of studies evaluated the BION against surface stimulation for both shoulder subluxation and hand spasticity therapies. The two methods were substantially equivalent in subjective improvement scores: BIONs were rated 70% and 85% compared to surface stimulation at 70% and 90% for shoulder subluxation and spasticity improvements, respectively. However, patients reported 100% overall satisfaction with both surface stimulation therapies, compared to the BION with 88% satisfaction in the shoulder study and 99% in the spasticity studies [47]. The comfort of the BION approach was rated substantially higher in each study, 85% vs. 45% and 70% vs. 50%. The comfort results reflect the advantage of intramuscular stimulation over surface stimulation from the minimization of cutaneous pain fiber recruitment. However, the lower overall patient satisfaction in the subluxation study can be seen a consequence of the decision to locate the BION control and energy delivery functions in an external assembly. In these comparative studies, the freedom provided by the battery powered surface stimulators was cited as a significant advantage over the mains powered BION equipment. This has preceded with...
A ceramic body, integrated capacitor, increased length and diameters and received Investigational Device Exemption status from the US Food and Drug Administration.

The initial BION design demonstrated a 20N 3-point bend force tolerance, a 7-times improvement. It also removed the external electrode/capacitor from the risk of surgical procedure damage at the cost of a slightly increased volume. A small eyelet was included in the anode to permit acute retrieval. Finally, the glass to metal seal feedthroughs at each end were eliminated in favor of a stronger perimeter brazed joint that distributed stress.

4. Concluding remarks

The BION project has demonstrated success in many aspects, and most of the applications for which it has been evaluated have demonstrated substantial potential. Conversely, its revision history reveals some limitations in the initial design and implementation.

Successes of the BION resulted in part from the initial expansive view of its potential applications, and the specification set which ensured substantial clinical utility. These specifications were largely achieved in early builds. The early development process drove changes to mechanical dimensions, improved manufacturing approaches, and revised internal and external electronics. But the key design objectives of injectability and system partitioning were met.

The completion of relevant pre-clinical studies and the accumulation of evidence linking the theoretical performance of the system to the observed performance of the devices established a credible foundation for subsequent human trials. Each successive phase of the BION development was preceded by sufficient design and evaluation rigor to enable success. This rigor required time, and the project duration was substantial: Nearly two decades elapsed from initial specification to the realization of the revised glass BION, an interval that appears commensurate to the challenge.

The shortcomings and device failures in development, even with the benefit of hindsight, do not appear obvious or easily avoidable. The mechanical packaging was significantly revised twice to enhance strength, yet the initial design was conceived with break forces well exceeding that expected in muscle tissue. The discrepancy between performance and expectation was not due to misestimating muscle forces, but from the eventuality that devices were implanted across muscle bodies and between muscles and connective tissues where shear forces significantly exceeded those of homogenous muscle. This is similar to the evolution of implantable defibrillator requirements. They are generally placed subcutaneously. Occasionally however, they are placed subpectorally. This technique results in much greater repetitive mechanical loading of the devices between the muscle sheet and the ribs. Defibrillator designers have had to create specifications and evaluation techniques for these implant approaches that simply did not exist in the early days when devices were implanted abdominally. The BION designers faced this problem very early in their development. Similarly, designers of novel devices should strive to foresee potential “misplacements” and alternative uses of their devices when they evaluate the design margin in their performance specifications.

The electrical performance of the system at the implant level was remarkably successful, perhaps because of the ease or rigor of bench testing. Some minor revisions to stimulation parameters, compliance voltage, and fixes for inductive coupling and stimulation stability are noted in the literature [18,41]. Of these, the coupling and stability issues are ASIC implementation consequences. The voltage compliance and parameter levels met the initial design specifications. However, these specifications were revised in response to subsequent study data, and their evolution is within character for early device development.
In clinical trials, the acceptance of these devices by initial patients was generally positive. However, independent of the technical merit of the design, what mattered to patients was how the overall experience fit their clinical needs within their lifestyle. The BION has demonstrated great progress in realizing the original goals of distributed implantable stimulation, and the technology shows continued evolution and maturation. But the final success of each application may rely as much on the convenience and cosmetics of externals as it does on the technology of the implant.

The BION project team created a unique design with an active legacy of therapies and therapeutic devices directly following from their core innovations. The challenge was formidable. However, the task was sorted into important, manageable increments that upon achievement propelled the overall project forward. Optimal partitioning of the system functions was critical to the technical success. Equally important was the effective coordination of resources from across industry and academia. Some device integrity issues had been foreseen, though they were underestimated. But the compelling evidence of the therapeutic potential had been established sufficiently and motivated the resources required for resolution. The legacy of the BION design team is a project that has met many of its ambitious objectives and a concept that continues to evolve new therapeutic applications.

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Conflict of interest

No conflicts of interest are known to the authors.

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