

FES or TES: How to start an industry?

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Thirty years of research on the electrical stimulation of muscles has yet to have major clinical impact. The original rationale for this effort was to reanimate paralyzed limbs, e.g. "to make paraplegics walk". Researchers now appreciate how difficult that will be to do successfully, but the field is just coming to grips with whether this is the only or even the best use of this technology. We have analyzed a broad range of potential clinical markets for a generic injectable stimulator that has been developed recently. The more promising reflect simpler but more widespread and debilitating problems that probably can be addressed more readily by therapeutic electrical stimulation (TES) or neuromodulatory stimulation (NMS) rather than functional electrical stimulation (FES).

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INTRODUCTION

In 1997 the U.S. Food and Drug Administration conducted a survey in which expert participants assessed 21 generic technologies and identified 36 specific examples of product-types expected to undergo significant development (Herman et al., 1998). Neuromuscular stimulation was rated lowest of all, with low probability of success and low numerical and qualitative impact on overall health. Does this reflect a technological approach that is futile, misdirected or undersold?

The field of FES may have much in common with commercial aviation. Both started with a primary interest in technology for its own sake, with little plan for developing useful applications. Commercial aviation was sustained for the first half of its 80 year existence by a mundane but lucrative and fault-tolerant business – delivering mail. We take for granted the prolonged refinement of technology, development of infrastructure and gradual consumer acceptance that reflect the more demanding requirements of the passenger business that now dominates the industry. FES technology and infrastructure are now where aviation was early this century – primitive but promising and desperately in need of a sustaining commercial application.

We are developing injectable microstimulators called BIONs™ (BIONic Neurons) which receive power and commands by wireless transmission and deliver precisely controlled stimulation pulses to paralyzed, weak or spastic muscles (Cameron et al., 1997; Loeb et al., 1998). The implants are "generic" (readily deployed in a variety of sites for a variety of functions), but external equipment, software, clinical trials, regulatory approval and reimbursement issues tend to be application-specific. In this paper, we provide a summary analysis of 20 different clinical applications that might be addressed by BIONs and other implantable stimulators. This analysis suggests that the primary reason for developing this technology in the first place – FES – may not be the place to start developing the clinical and industrial base needed to sustain this field of research.

TECHNOLOGY AND MARKET ANALYSIS

We have divided these applications into three types based on the nature of the interaction between the patient and the technology:

- TES (Therapeutic Electrical Stimulation) – electrically produced exercise in which the beneficial effect occurs primarily offline as a result of trophic effects on muscles and perhaps CNS.
- NMS (Neuromodulatory Stimulation) – preprogrammed stimulation that directly triggers or modulates a function without ongoing control or feedback from the patient.
- FES (Functional Electrical Stimulation) – precisely controlled muscle contractions that produce specific movements required by the patient to perform a task.

We have analyzed these applications by determining a benefit to cost ratio:

- BENEFIT was evaluated from the perspective of a commercial market analysis. Five items with a multiplicative relationship were each graded on a crude scale of 1-3:
 - Market size – the numbers of patients who would be candidates for the therapy based on medical criteria
 - Payers – the availability of reimbursement for invasive treatment based on available precedents or current trends
 - Probability – the likelihood of obtaining a clinically useful outcome in a given patient
 - Importance – the effect of a successful outcome on the quality of life of the patient
 - Competition (divisor rather than multiplier) – the availability of competing therapies
- COST was evaluated according to the amount of effort required to develop the clinical application and to deploy it in each patient. Five additive cost elements were evaluated according to a crude scale of 1-3 relative to the other applications:
 - Research – effort required to resolve outstanding scientific and medical questions.
 - Technology – added development effort required to build a therapeutic system for that specific application
 - Installation – effort required to implant the stimulators in the patient
 - Fitting – effort required to devise an appropriate stimulation program for each patient
 - Use – effort required from the patient to implement the treatment

RESULTS

Shoulder subluxation in stroke patients has been treated successfully by TES via percutaneous and surface electrodes (Faghri et al., 1994). It has a high probability of success in a moderately sized market but one with little reimbursement precedent for expensive rehabilitative treatment. We have selected it for the first clinical trial of the BION implants primarily because suitable technology is now available and simple to deploy and evaluate. Similar approaches to preventing atrophy and strengthening muscles via TES are under consideration for rehabilitation following **knee** and **hip** injury and arthroplastic surgery. These rate somewhat lower because they accelerate a largely inevitable recovery rather than addressing a chronic management problem.

Urinary urge incontinence presents a larger market in which more precedents exist for reimbursing treatment. Those precedents also present growing competition, however, both from existing sacral nerve stimulators and new autonomic drugs. Substantial research is still needed to identify the optimal stimulation sites to modulate bladder hyper-reflexia and to develop devices and implantation and fitting procedures appropriate for these sites. By contrast, **Urinary stress incontinence** is a much simpler and more certain application based on TES to strengthen pelvic floor muscles (similar to Kegel exercises), but this application has even more competing surgical and nonsurgical treatments.

Venous stasis and **decubitus ulcers** are two applications of NMS that seek to reduce the moderate incidence of severe and expensive complications in acutely and chronically

confined patients. Active contraction of calf muscles is particularly likely to be effective in preventing deep vein thrombosis (Faghri et al., 1997). However, a massive clinical trial will be needed to demonstrate a reduced incidence of pulmonary emboli (a more severe but rarer complication) in order to convince insurers to pay for an invasive preventive treatment.

Application		Market size	Payers	Probability	Importance	Competition	TOTAL BENEFIT	Research	Technology	Installation	Fitting	Use	TOTAL COST	RATIO
TES	Shoulder subluxation	2	1	3	2	1	12	1	1	1	1	1	5	2.4
NMS	Urge incontinence	3	2	2	3	2	18	3	2	2	2	2	11	1.6
TES	Stress incontinence	2	1	3	3	3	6	1	1	1	1	1	5	1.2
NMS	Venous stasis	2	1	3	2	2	6	1	1	1	1	1	5	1.2
FES	Cough assist	1	1	3	2	1	6	1	1	1	2	1	6	1.0
TES	Knee rehabilitation	2	1	3	1	1	6	2	1	1	1	1	6	1.0
NMS	Decubitus ulcers	1	1	2	3	1	6	1	1	2	1	1	6	1.0
NMS	Sleep apnea	2	2	2	2	2	8	3	3	2	1	1	10	0.8
FES	Grasp assist	2	1	2	2	1	8	2	2	2	2	2	10	0.8
NMS	Pain control	3	3	1	2	3	6	2	1	2	2	1	8	0.8
NMS	Bowel emptying	1	1	2	3	1	6	2	1	2	2	1	8	0.8
FES	Footdrop	2	1	3	2	2	6	1	2	1	2	2	8	0.8
NMS	Gastric motility	1	2	2	2	1	8	3	2	3	2	1	11	0.7
NMS	Dysphagia	1	2	2	2	1	8	2	3	2	2	2	11	0.7
FES	Standing	1	2	3	2	2	6	1	2	2	2	2	9	0.7
FES	Vocalization	1	2	2	2	1	8	3	2	3	3	3	14	0.6
FES	Reaching	1	2	2	2	1	8	3	3	2	3	3	14	0.6
TES	Hip rehabilitation	2	1	2	1	1	4	2	1	2	1	1	7	0.6
TES	Cardioresp. exercise	1	1	3	1	2	1.5	1	2	2	2	3	10	0.2
FES	Walking	1	2	1	1	1	2	3	3	2	3	3	14	0.1
		$a \times b \times c \times d / e = TB$						$f + g + h + i + j = TC$						TB/TC

Table 1: Comparison of commercial attractiveness (descending order) of various clinical applications being considered for injectable electrical stimulators now under development.

Sleep apnea and **pain control** are NMS applications that address large markets with good precedents for reimbursement of treatment. Substantial clinical research will be needed to demonstrate whether implanted stimulators offer therapeutic advantages over competing therapies now available or under development.

The remaining NMS applications (**bowel emptying**, **gastric motility** and **dysphagia**) represent "orphan product markets" in which there are small numbers of patients with severe problems. The substantial effort required to apply the treatment to individual patients would probably be justified by substantial individual benefits, but clinical researchers will have to "borrow" the technology from other applications whose market size justifies the substantial development costs of the enabling technology. Fortunately, special government funding and regulatory policies are starting to be available to facilitate such university-industry research projects.

The three FES applications that seem most attractive commercially are those with relatively simple control systems, thereby reducing research and deployment costs: **cough assist**, **grasp assist**, and **footdrop**. Unfortunately, the spinal cord injury market is small and only a small percentage of stroke patients are likely to be candidates. The remaining FES applications

(standing, vocalization, reaching, and walking) address similarly small markets but require progressively more sophisticated command and control interfaces with the patient. These will require substantial advances in implantable sensors as well as highly expert biomedical teams to implant and program the stimulation and control systems.

DISCUSSION

Given the crude scale employed in this analysis, any given application could be shifted several places up or down in the table according to arguable changes in the values assigned to particular factors. Nevertheless, most of the applications at the top of the list involve TES and NMS rather than FES technology. FES involves a relatively large effort for generally small markets; assisted coughing ranks highly only because the level of effort to develop and use the technology is likely to be fairly low (Sorli et al., 1996). Of all types of applications that require substantial effort to develop, only urge incontinence and perhaps sleep apnea now offer the sorts of markets that might justify that effort to a commercial manufacturer.

The items at the very top of the list seem most likely to be transferable to private enterprise. A much larger number of items in the mid-range seem ripe for expanded government-sponsored R&D. This should be directed toward reducing the remaining development costs and demonstrating sufficiently high probability of highly beneficial outcomes to convince insurers to pay for them. Most of the FES applications toward the bottom will continue to generate excellent research projects with which to hone our technology and our understanding of sensorimotor control, but they will have little attraction for private enterprise for some time to come.

Experience to date in the implantable device business has shown that when technology platforms become available for one application (e.g. epidural stimulators for chronic pain), they commonly find use in surprisingly diverse "off-label" research (e.g. deep-brain and sacral root stimulation). Thus any commercial success in any application is likely to facilitate research well beyond its original scope. Furthermore, as companies mature and saturate profitable markets, they become both more confident and more motivated to tackle more difficult or marginal applications. The neural prosthetics research community needs to recognize and encourage the strategy of starting with simple applications that offer big payoffs rather than focusing exclusively on the "big research" challenges that have dominated the first 30 years of this field.

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