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Energy Harvesting:

A Review of Novel Power Sources for Medical Devices

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Declaration of Authenticity and Author's Rights

This thesis is the result of the author's original research. It has been composed by the author and has not been previously submitted for examination which has led to the award of a degree.

Signed: Emily Button Date: 13/08/13

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Abstract

Energy-harvesting tactics are promising to be an autonomous energy source that could potentially replace the external and internal fuel cells currently used in implantable medical devices. Energy scavenging sources can be powered by physical or chemical energy generated by the body. Physical energy-dependent devices include those that feed off motion induced kinetic energy, respiratory air flow, thermal and pressure gradients. Chemical energy-dependent devices are split into those that have their own fuel source, for example a glucose fuel cell, and those that derive energy from endogenous substances, called micro-biofuel energy harvesters. There are many difficulties associated with implantable devices and their power sources, problems like compatibility with the surrounding tissues and sustainability of the source. This review summarises past advancements in the field, condenses current research and speculates about future applications. Different concepts, both biological and physical, are discussed and critically reviewed.

List of Key Terms

- **Cardiovascular Diseases**
- **Neural Diseases**
- **Sensory Impairment**
- **Autoimmune Diseases**
- **Battery**
- **Percutaneous Lines**
- **Sepsis**
- **Implantable Medical Devices**
- **Microelectrical Mechanical Systems**
- **Piezoelectric**
- **Electromagnetic**

- **Thermal**
- **Air Flow**
- **Cardiovascular**
- **Biofuel**
- **Nanowire**
- **Nanofiber**
- **BioMEMS**

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Table 5 – Adapted from Fei et al demonstrating the variety of compounds used in electromagnet commercialisation[62].

List of Abbreviations

- **IMDS:** implantable medical devices
- **MEMS:** microelectrical mechanical systems
- **NP:** nanoparticle
- **BFCs:** biofuel cells
- **EFCs:** enzymatic fuel cells
- **MFCs:** microbial fuel cells
- **CVDs:** cardiovascular diseases
- **VAD:** ventricular assist device
- **LVAD/RVAD:** left/right ventricular assist device
- **ICD:** implantable cardioverter-defibrillator
- **SCS:** spinal cord stimulation
- **VDRG**: velocity-damped resonant generator
- **CDRG**: coulomb-damped resonant generator
- **CFPG**: coulomb-force parametric generator
- **RF:** resonant frequency
- **PVDF:** polyvinylidene fluoride
- **PZT:** zirconate titanate
- **PEG:** piezoelectric energy generator
- **NFES:** near-field electrospinning
- **FFES:** far-field electrospinning
- **ZT**: figure of merit
- **MOCVD**: metal-organic chemical vapour deposition
- **PAMAM**: polyamidoamine
- **NADH**: nicotinamide adenine dinucleotide
- **ISFET**: ion-sensitive field-effect transistor
- **GFP**: green fluorescent protein
- **FRET**: fluorescent resonance energy transfer
- **ELISA**: enzyme-linked immunosorbant assay
- **iEEG**: implantable electroencephalograph

Chapter 1: Introduction

1.1. Layout of Thesis

This thesis consists of four chapters. In the first chapter, the general types of diseases that require implantable intervention for everyday use will be covered. Thereafter the chapter will demonstrate the History of Implantable Batteries. In chapter two, the methodology will be outlined and in chapter three the types of energy harvesting technology will be discussed individually: Piezoelectric, Electromagnetic, Thermoelectric, Air Flow and Biofuels. Each subsection will demonstrate the basic concepts behind this technology followed by an overview of research at the forefront. Their fundamental problems will also be discussed. In the final chapter, the general history of each field of therapeutic technology that could potentially be fully implantable upon modifications of current energy harvesting technology: cardiovascular, nervous system, sensory and autoimmune mediating therapeutics. These technologies include powering VAD technologies, drug-delivery pumps and biosensors for point-of-care/continual monitoring diagnostics. This is followed by a brief overview of the types of devices currently in production and the biggest problem pertaining to them, infection. This will be followed by an overview of pipeline devices and the future prospects of this technology are discussed in so far as how micro-generators could improve the quality of life for the patient.

1.2. Introduction

Today's modern medicine includes many stages of technological advancements present in many different fields. Currently, trends are emerging towards fully implantable devices which feature real-time data transmission/analysis which allows for diagnosis and/or automated treatment. In such patient cases as those in critical care or those with chronic conditions, these implantable medical devices (IMDs) are essential for continued survival and better quality of life. Such examples include: constant blood pressure monitoring in hypertensive patients, real-time ECG monitoring which allows the physician to remotely record and analyse a patient's condition and finally in diabetics, drug-eluting devices have been developed to react as a pancreatic replacement, administering glucagon or insulin as befits the patient's blood glucose level.

Perhaps the field this technology has brought forth the most advances are in cardiovascular medicine where defibrillators and pacemakers have undergone modifications. These allow them to be semi-/completely implantable and to fully assist patients for the remainder of their lives or until cardiac recovery occurs.

Typically an IMD must be lightweight, occupy a small volume (≤ $1cm^3$), possess a long life, low power consumption, not interfere with normal bodily function, demonstrate a high dependability and be cost-effective.

1.2.1. Conditions Requiring IMDs

Implantable medical devices (IMDs) are thought of as the up and coming technology in the medical field. Ideally these devices should be highly biocompatible, highly unobtrusive and greatly improve the patient's quality of life. IMDs are used in the treatment of diseases consistent with chronic symptoms such as cardiovascular conditions, diseases of the nervous system, sensory impairment and autoimmune diseases. As shown in figure 1, there are a great number of commercially available IMDs that benefit the patient greatly, but could be improved to be fully implantable.

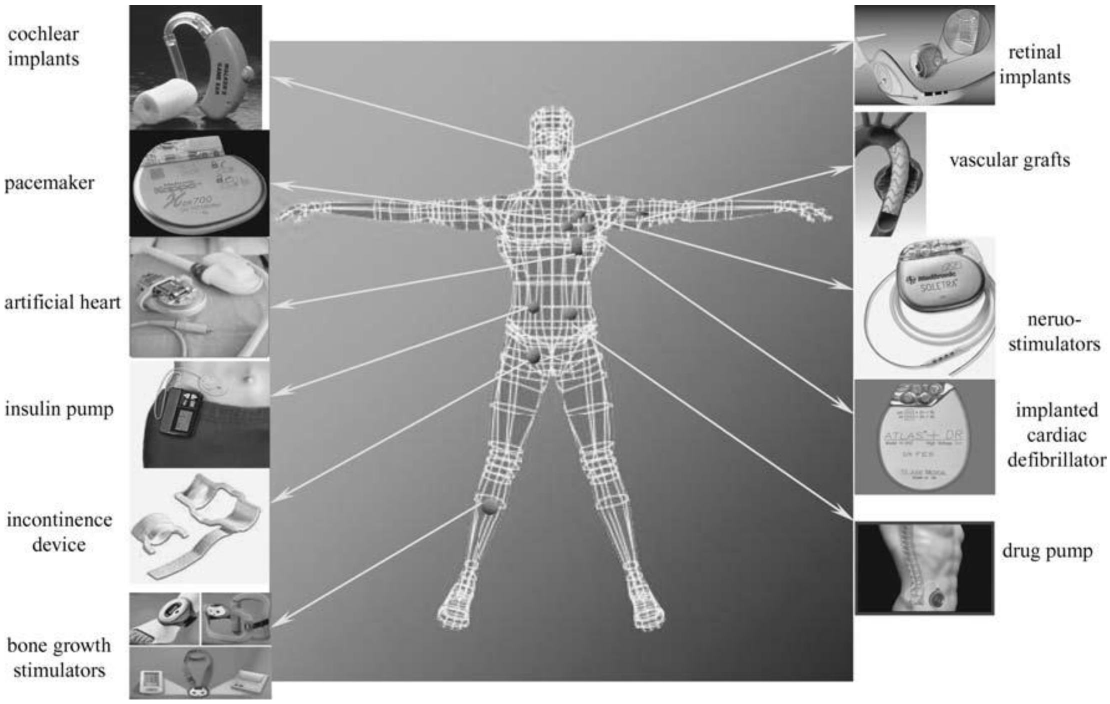

Figure 1 – listed map of IMDs adapted from Wei et al[4]. These different types of technology, specifically those with cardiovascular, drug-delivery and neural implants will be discussed.

1.2.1.1. Cardiovascular Diseases

Chronic cardiovascular diseases (CVDs) are debilitating to the patient and have a high mortality rate, accounting for over 17.3million deaths globally in 2008 alone, approximately 30% of deaths in America[1]. CVDs include angina, atherosclerosis, congestive heart failure, endocarditis, heart attack, hyperlipidemia, peripheral artery disease and stroke. Some of these conditions can cause or become a side effect of tachycardia and bradycardia which can be prevented following therapeutic options including prescription medication such as beta-blockers, key-hole surgery or surgery.

Many of these patients, having exhausted all other possible means of therapeutic aid, opt for an IMD. Implantable cardioverter-defibrillators (ICDs) can detect and respond to these kinds of arrhythmias before they cause heart failure

1.2.1.2. Nervous System Conditions

Chronic nervous conditions include headaches, chronic pain, epilepsy, Alzheimer's and Parkinson's. Epilepsy itself, affects over 60million people all over the world and approximately 40% of those 60million cannot control their condition through pharmaceutical means[2]. Most patients do not even realise they have had a seizure. Consequently intracranial EEGs are becoming popular areas of research, implanted devices which will carry out continuous EEG monitoring. A different area of research is being carried out for chronic pain sufferers: in the search for a cure to chronic pain there has been a recurrence of spinal cord stimulatory (SCS) devices which deliver a series of low powered shocks in order to subdue the pain sensors within the body[3].

1.2.1.3. Autoimmune Diseases

Chronic or genetic conditions including diabetes, Addison's, Grave's and thrombocytopenia are just some of the autoimmune diseases which could benefit from the development of fully implantable IMDs such as drug pumps. There is currently great number of diabetes combatant IMDs however this is not the case across the autoimmune spectrum.

1.2.2. Overview of Problems with Current Technology

Regretfully the portability of these therapeutic devices has not been followed by an increase in energy efficiency of the fuel sources, which are presently limited by the life of the battery and the performance of the IMD.

In IMDs batteries currently occupy a volume anywhere between 25-60% of the total device. This problem could be solved following an increase in the power density per volume occupied by the battery. In order to compare the power requirements of modern everyday devices to the current medical applications see tables: Table 1 shows the power consumption of some modern everyday devices, while Table 2 shows the power requirements of some implantable medical devices. As shown in tables overleaf, the power requirements of medical implants is anywhere between the order of microwatts to milliwatts.

	Device type	
	Power consumption	Energy autonomy
Smartphone	1 W	5 h
MP3 player	50 mW	15 h
Hearing aid	1 mW	5 days
Wireless sensor node	100 μW	Lifetime

Table 1 – adapted from Vullers et al. this table depicts the power consumption of everyday media devices and a couple of specialist devices[5]

implanted device	typical power requirement
pacemaker	30–100 μW
cardiac defibrillator	30–100 μW
neurological stimulator	30 μW to several mW
drug pump	100 μW to 2 mW
cochlear implants	10 mW

Table 2 – adapted from Wei et al. which depicts the power requirements of various medical devices (in the order of microwatts to milliwatts[4]

As such the body, according to Sue et al., of an average 68kg human with a 15% body fat should generate at least 380MJ of chemical energy at a given time[6]. According to Paulo et al, at rest the body expends 100W on organ/tissue/cellular function and about 25% is used by the skeleton/heart, 27% by the liver/spleen and 19% by the brain[7]. According to the same source the human body expends 81W while asleep and 1630W when walking. This appears to be an enormous store of energy to be potentially exploited. However, currently implantable medical devices are battery powered. These are heavy, expensive, need to be regularly replaced (every 3 to 5 years) or recharged. Some are radioactive and careful disposal is therefore required following environmental health and safety codes.

1.2.3. History of Implantable Batteries

Batteries today have many different uses across the commercial spectrum. A "battery" itself is defined as one or more power cells which are connected in order to achieve a higher energy density source. A cell is the building block of a battery[8].

Within batteries, the energy emitted is produced from electrochemical reactions which form products, often these are oxidation (loss of electrons) reactions. Typically these reactions would give off heat, however a battery will change the heat energy (kinetic energy since kinetic energy is proportional to change in temperature) to electricity[8]. Batteries however show no dramatic rise in temperature as the chemical reaction occurs under insulated conditions. This is consistent with the principle of energy conservation, since most of the energy produced by the chemical reaction is changed into electrical energy[12]. This is a highly efficient way of energy storage.

Figure 2 - insulin pump adapted from Accu-Chec[9] has been marketed as a portable diabetes monitor.

There are two kinds of battery power sources: primary and secondary. Primary sources have a single use and may be connected in series to produce a higher voltage source or in parallel to give a higher capacity or current capability. An example of a medical device which uses a primary source would be a portable blood glucose monitor such as Accu-Chek®, as seen in figure 2[9].

Secondary sources, or rechargeable power sources, can be discharged and connected to an external power source to rejuvenate the energy[10]. A recharge of a secondary source occurs when a current is forced to flow through the battery opposite to its normal direction which causes the chemical reaction within the battery to occur in the reverse direction; this eventually results in the battery reverting to its initial charged state[8]. The most prominent example today can be seen in rechargeable cardiac pacemaker batteries.

There are only three or four chemical reactions currently available for secondary batteries versus at least a dozen for primary batteries. The main reason for this is the need for secondary batteries to recharge very efficiently. For example, even a battery that can recharge with 95% efficiency will have lost half its capacity after only 13 cycles of discharge/recharge if it started with stoichiometric amounts of chemicals in the battery[11]. Changing the relative amounts of chemicals in the battery can compensate for inefficiencies of recharge, but this also lowers the amount of energy available in a given size of battery. This is a huge problem for implantable batteries as the size of the implant is then dictated by the size of the battery and therefore the lifetime of the battery.

In general, primary batteries have a higher energy density (same volume of device with greater energy storage capacity) than secondary batteries because they can be optimized for a single discharge whereas secondary batteries are designed foremost to produce a higher number of cycles[10].

Since batteries provide a portable source of power, it is inevitable they should be used to power packaged and sealed devices implanted within the body. In the last 40 years the major use of implantable batteries is within cardiac pacemakers[11].

During this time pacemakers have evolved from unsophisticated devices that emit electrical pulses to state-of-the-art devices that are extremely efficient and provide a multitude of special features. They have also been optimised to last up to a five times longer compared to the initial devices, which only lasted a year.

Implantable batteries use mainly lithium anodes and have done since the mid-1970s. The main reason for this was that batteries made with lithium anodes offer significant advantages over aqueous alkaline battery systems, primarily zinc-mercury oxide systems which were used initially. Lithium as a substance is electrically active and lightweight, and also forms many lithium-ion-conducting compounds. Moreover its ions are soluble in many non-aqueous solvents. Its low weight and high activity Lithium batteries exhibit high voltages, high capacities and high energy densities. They are also highly reliable and exhibit a long-lasting performance making them a very desirable option for high energy dense battery applications, such as IMD batteries.

1.2.3.1. Pacemaker Power Sources

By 1970, the average pacemaker used a Reuben-Mallory zinc-mercury battery developed in the 1940s which had a suggested life of five years, however almost 80% of these devices were explanted after the first year due to fuel exhaustion[11]. However, it met the need during war-time for a reliable, high-energy dense battery for military application. The battery usually was made with a zinc amalgam anode and a mercury-oxide mix with graphite as a cathode. Overall reaction shown below:

$Zn + HgO \rightarrow ZnO + Hg$ V = 1.35V

A concentrated solution of potassium or sodium hydroxide was used as an electrolyte. The most popular configuration for this type of cell was a “button” cell and as such the chemical anode and cathode are separated by a paper barrier or polymeric material see figure 3[10]. As shown overleaf in a typical button cell structure, Tyers et al postulated an expected life of 10-15yrs, the reality of which was much shorter[8].

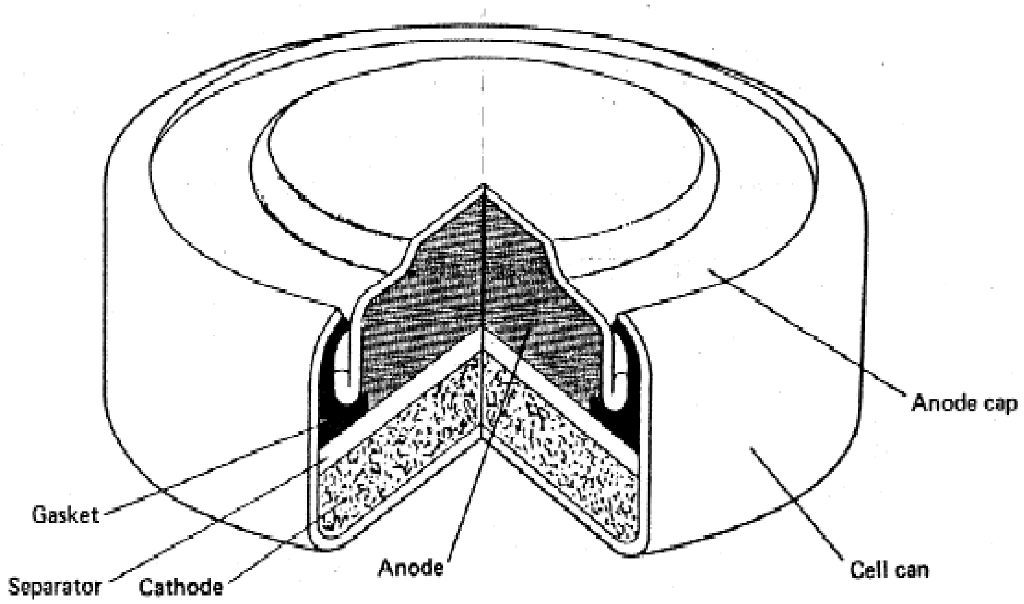

Figure 3 - example of button cell zinc silver oxide[10]. A mercuric oxide was mixed with 30% silver powder which increased conductivity whilst the zinc cathode was mixed with 10% silver. The two electrodes were separated from each other by a multilayer arrangement of ionically permeable, electronically nonconductive microporous separators.

These cells exhibit a high energy density and very stable discharge system, however there were some notable problems with this battery namely: a propensity to discharge gas, small amounts of hydrogen gas, during service life, which makes them difficult to hermetically seal (airtight). For this reason most cardiac pulse generators powered by Zn/HgO batteries were epoxy encapsulated, which permitted the hydrogen to escape through the casing. Secondly they had a tendency to form small dendrites of liquid mercury which caused the device to short circuit. In order to combat this, multiple wraps of separator material and additives were used to help minimise the problem. These were discontinued from commercial distribution on the IMD market.

1.2.3.2. *Bio Batteries*

Following the creation of the Zinc-Mercury battery it was postulated that the biological reactants within the body could be utilised for the production of electricity through similar electrochemical reactions as those that occur in batteries. During early source development, the principle investigators were Racin, Roy and Schaldach who all considered biogalvanic cells[11,13]. Their work was soon followed by Cywinski who managed to create a battery and implanted it within cats which lasted up to three years[11, 13].

Others such as Plumb et al considered using oxygen from arterial blood and hydrogen from proteins[140]. This research was dropped until recently where a sudden interest in using abundant biochemicals to create a near-perpetual device has been renewed these will discussed further in section 3.3.

1.2.3.3. *Rechargeable Batteries*

Batteries which need to be periodically refuelled from an external source were also highly popular areas of research. Before being considered commercially, these fuel sources needed to answer two important questions, namely: what is the average lifetime of the battery, supposing it was recharged, and is it longer than that of a primary cell?

Concerning IMD systems, Senning first implemented a battery system in 1958 in a medical context using a nickel-cadmium battery which was based on the oxidation of cadmium metal to cadmium hydroxide and the reduction of Ni (III) to Ni (II) as shown below[8]:

$$2NiOOH + 2H_2O + Cd \leftrightarrow 2Ni(OH)_2 + Cd(OH)_2 \qquad V = 1.2V$$

It was capable of producing high currents using potassium hydroxide as an electrolyte keeping the pH high enough to solubilize the metal of interest. These cells operated optimally at 10-25°C and at an elevated temperature of 37°C resulted in reduced charge acceptance, accelerated self-discharge, larger $Cd(OH)_2$ crystals, and gradual hydrolytic degradation of the nylon separators. This technology was then redesigned to counteract these problems.

The result was the rechargeable nickel oxide/cadmium cell successfully marketed by Pacesetter Systems, Inc. Maryland, USA, to power cardiac pacemakers in the 1960's[8,14}. It had been specifically designed and constructed for long-term service at 38°C. It is thought that the device experienced time-dependent changes, rather than cycle-number-dependent changes, which eventually lead to performance degradation. The battery was recharged *in vivo* via an alternating magnetic field of 25kHz through the skin. Without recharging, the cell could have operated a pacemaker for eight weeks before its energy was depleted. Unfortunately it failed to meet the first requirement above that of it having a longer service life than that of a primary cell.

The second rechargeable battery available for medical applications was based on mercuric oxide-zinc cells. Generally mercuric/zinc is thought of as a primary system (ie cannot be recharged) but altercations to the electrode structure meant that it could be used as a secondary source. Since recharging a secondary source is not without difficulty (particularly if they are used to power IMDs) it had to be closely controlled and therefore had limited commercial applications. It was invented by Fagan (1969) at Pennsylvania State University[8]. Despite promising trials in animals and encouraging characteristics such as reliability, this battery has never been introduced commercially as an implantable battery, probably because of the outstanding competitive simplicity and reliability of the primary lithium anode cells. The reaction of this cell is shown below:

$$HgO + H_2O + Zn \leftrightarrow Hg + Zn(OH)_2 \qquad E_0 = 1.343V$$

1.2.3.4. *Nuclear Batteries*

The third type of early implantable battery took a somewhat different method of energy provision. There are three types of nuclear batteries: fission, fusion and radioactive decay of nuclei. Radioactive decay is the only energy-producing process applicable to implantable devices. Both fission and fusion reactors require large amounts of nuclear material to sustain the reactions, and thus were declared unsuitable for small, nuclear batteries[11].

When the radioisotope's nucleus decays and emits particles, energy is released in the form of the kinetic energy at the particle level. This energy can be harnessed to create electrical power in two ways. The first method is to harness this energy via the beta voltaic effect where electrons emitted from the nucleus of a β-emitter are used to force a semiconductor to give off electrons. These are then converted to an electrical current which then provides electric power to drive the circuitry of an implantable device.

One such battery was manufactured by Donald W. Douglas Labs and termed the Betacel, which has since been used clinically to power implantable pacemakers[8]. The second way of harnessing this energy is to utilize the nuclear disintegration energy to allow the kinetic energy of the emitted particles to be converted into thermal energy and then to convert this thermal energy into electrical power by means of the Seebeck effect, or thermoelectric conversion. The Seebeck effect is when two dissimilar metals, or semiconductors, are joined together at two junctions and the two junctions are set at different temperatures[15]. A voltage is created that is proportional to the difference in temperature between the two junctions, the proportionality constant being individual for different materials and being much higher for semiconductors than for metals. The Seebeck voltage or potential voltage gradient will cause current to flow between the dissimilar materials; the value of current flowing is a function of the geometry of the materials and their electrical resistivity.

Several different nuclear batteries for implantable generators have been developed using the heat of decay of plutonium-238[11], a radioactive isotope, and the thermo-electric conversion of this thermal energy to electrical. The commercially available nuclear batteries each demonstrated their own different system of utilising thermal energy using different thermocouple materials and types. The battery developed by the Nuclear Materials and Equipment Corporation for the Atomic Energy

Commission utilized tophel cupron as its thermocouple material, a modified type K thermocouple chromel/alumel material, while batteries developed by Alcatel, Hittman and Coratomic utilized bismuth telluride as its thermoelectric material[8]. As shown below in figure 4 commercial nuclear batteries utilizing plutonium 238 were marketed as long-life pacemaker batteries[16].

Figure 4 – the Laurens-Alcatel battery for Medtronic devices used Plutonium 238 and converted thermal energy using a thermopile[16].

Through the years there have been six different models of pacemaker that utilized six different nuclear batteries from the time of the first human implantable battery in 1970 to 1982.

Leading up to the 1970 commercialisation of the nuclear battery, the 1960s pacemaker manufactured by Biotronik utilized promethium-147 isotope, a β-emitter. As beta particles are emitted they collide with atoms of the semiconductor, the electrons are released onto collector plates and used as a source of electrical current[8]. However, because of the short half-life of promethium-147, the anticipated life of this unit was approximately nine years and it was heavier compared with the plutonium-based devices introduced in the same time period[16]. In addition, the device required high-density shielding to reduce the high level of gamma energy produced and eventually it was realised that these problems could not be overcome and the battery was discontinued.

In the late 1960s, the AEC pacemaker with a Biotronik-Betacel was designed and implanted (1966)[16]. Initially it used plutonium metal but was later modified to plutonium oxide because of the cremation hazard associated with pure plutonium. This was the first pacemaker to utilize a vacuum insulated case and used tophel cupron thermocouples connected in series (as the thermopile) to obtain an output voltage of approximately 6V. The thermopile and insulation were integrated into a spiral wrap surrounding a cylindrical fuel capsule. This device used 500mg of plutonium oxide because of the relatively low efficiency of the tophel cupron compared with other semiconductor materials.

Later in 1970, the Medtronic Model 9000 was the first pacemaker to utilise a nuclear battery and be activley implanted in people [8]. This contained a G.I.P.S.I.E. 1 nuclear battery and continued to be commercially available until 1982.

The other pacemaker on the market was the Coratomic C- 101 which used a plutonium nuclear battery and was made commercially available in 1974, however it was removed from clinical use in 1986 when a product warning was issued.

Unfortunate disadvantages are associated with this type of technology: firstly the toxicity of the fuel source, a microgram of which is fatal, and secondly the excessively long half-life. As such, there are strict government regulations in place to control the manufacture and disposal of these devices.

More recent nuclear pacemakers use plutonium oxide which is a ceramic and represents far less of a hazard should the container be penetrated. However, with a half-life of 89yrs it is not an ideal fuel source; on the other hand the patient is exposed to less radiation than those living in high radiation risk places. It is thought that nuclear batteries should be used to power implantable drug-dispensing devices, such as insulin-dispensers, as these are needed by patients with chronic conditions for more than forty years from implantation.

1.2.3.5. *Lithium Batteries*

The final type of implantable battery utilised and currently marketed are lithium ion batteries. Lithium, as a material, can be easily handled and is the most reactive of all alkali metals. Almost all current pacemaker systems are powered by lithium ion systems of which there are three categories.

The first is an uncoated battery, where the lithium anode is placed in direct contact with an iodine-based cathode. The melted cathode depolariser is poured into contact with the lithium surface and forms an insulating layer of lithium iodide by direct chemical reaction. This layer is electronically insulated by lithium iodide ion conduction and serves as both an electrolyte and a separator. Batteries produced in this manner exhibit a linear decrease in power density at a given rate of use, which is due to the planar lithium iodide discharge between the anode and cathode[8].

The second type is similar to above, but before the depolarizer is poured onto the lithium anode, the anode surface is covered with a coating of pure poly2-vinylpyridine. When the cathode is then poured onto the poly2-vinylpyridine coating, a chemical reaction occurs that alters the performance of the battery dramatically. The batteries produced with this configuration do not exhibit a linear decrease in power density following discharge; they exhibit an exponential decay. The internal resistance of these coated batteries is usually a factor of 10 (or more) less than for an uncoated battery; this helps maintain a greater rate capability throughout discharge. This type of cell has been used in the majority of the lithium/iodide batteries implanted[8].

The third variation was also commercially available however in the previous two types the iodine and poly2-vinylpyridine are mixed and preheated for several days. However in this type, when the iodine and poly2-vinylpyridine are mixed, the mix is then pressed into a pellet and placed in the cell at the ambient temperature where the batteries are heated for a short period. This variation is called a pressed cathode battery and they exhibit very similar properties to the poured cathode batteries utilizing a poly2-vinylpyridine anode film however pressed cathode batteries do not exhibit exponential decay[8].

Present and past lithium ion batteries are listed in table 3, overleaf. This table details a brief overview of the history of implantable lithium-based batteries up until current day. As shown, some lithium ion batteries, such as lithium manganese dioxide and lithium sulphuryl chloride are still in use in everyday and medical devices. Others such as lithium copper sulphide and lithium lead iodide were discontinued due to unforeseen malfunction due to corrosion or an abundance of reaction products. Modifications to lithium power sources are being made to improve their performance and durability: the energy density is being increased and an efficient power management system is being developed. Progressively detailed modelling systems should aid in this research.

Lithium power sources and their use in IMDs must be treated with great care as all cathodes used are strong reducers which could interfere with the patient's health following a leak. In addition if the lithium within the battery melts, for example during cremation, the result can be catastrophic, with the possibility of an explosion equivalent to that of dynamite.

There are a number of concerns related to the use of lithium power sources, however as B.B. Owens stated "It can certainly be said the adventures offered by the lithium systems for implantable uses have been one of the major reasons implantable medical devices have progressed so far"[8].

Lithium Batteries	Inventor	Date of Commercialisation	Type of Cell (Name)	Fabricated by	Overall Equation(s)	OCV	Energy Density (Wh/cm^3)	Uses	Shelf-Life (providing nominal use)	Advantages over other designs	Disadvantages	Improvements throughout the years
Lithium Iodide	Moser	1971	Disc **(low-rate eg. 8426, medium-rate eg. 2282, high-rate eg. SVO cells)**	Wilson Greatbatch Ltd	$2Li + I_2 \rightarrow 2LiI$	2.8	0.3	Pacemaker battery	0-100 (≈ 50 years)	No separator, hermetically sealed (disallows effluents to escape casing), discharge is highly predictable	N/D	More concentrated materials, multiple coats of P2VP on anode surface, corrugating anode surface (increases anode SA)
Lithium Silver Chromate	W. Greatbatch	1973	Button **(Li 210)**	SAFT but implemented in Europe	$2Li + Ag_2CrO_4 \rightarrow Li_2CrO_4 + 2Ag$	3.35	N/D	Pacemaker battery	>800 days (≈ 2.2 years) to 8 years	When produced in parallel achieved a higher energy storage capacity	N/D	Increasing surface area of anode and using more concentrated materials
Lithium Copper Sulfide	N/D	1976	Button	Cordis Corporation	$Cu_2S + 2Li \rightarrow 2Cu + Li_2S$	2.1	N/D	Supported pacemaker circuitry when produced in series	Shorter but not long due to corrosive failures	Hermetically sealed	Required a separator, corrosion through casings resulted in serious device failures	Discontinued due to corrosion through casings
Lithium-Thionyl Chloride	W. Greatbatch	1975-1980	Cylinder	Mallory , Honeywell and Greatbatch: Electrochem (Excellbattery)	$4Li + 2SOCl_2 \rightarrow 4LiCl + S + SO_2$	3.65	0.97	Pacemaker battery	Low self-discharge which allows for long-life	Hermetically sealed, wide temperature range (-55-85 degrees celcius)	Only gave a few weeks warning before cell exhaustion, resulting in pacemakers ceasing to function between check-ups	Discontinued
Lithium Manganese Dioxide	N/D	N/D	Cylinder and button	Duracell (current)	$Li + MnO_2 \rightarrow Li.MnO_2$	3	0.8	Originally considered for pacemaker use however is currently the most popular battery for everyday use	5-10 years provided normal range of use	Inexpensive, relatively long-lived with a slow discharge rate, high energy density, wide temperature range (-20 to +60 degrees celcius)	N/D	N/D however batteries are tending towards smaller volumes and higher energy densities
Lithium Sulfuryl Chloride	N/D	N/D	Cylinder	Greatbatch: Electrochem (Excellbattery)	$2Li + SO_2Cl_2 \rightarrow SO_2 + 2LiCl$	3.96	0.7	Originally considered for pacemaker use	Shorter than most due to tendency of electrolyt to carrode lithium anode	Lower toxicity to humans, hermetically sealed, high temperature tolerance (>150 degrees celcius) and thus autoclavable	Tendency of electrolyted to carrode anode	Still in use today however longer shelf-life is needed, perhaps use of multiple P2VP coatings as in Lithium Iodide cells is needed to prevent carrosion at lithium anode
Lithium Vanadium Oxide	N/D	N/D	Button **(VL2320)** and cylinder	Panasonic	$LiV_3O_8 \rightarrow V_3O_8^- + Li^+$	3.2	0.3	Implantable heart defibrillators	5-10 years	Hermetically sealed	Large number of discharge products	N/D however batteries are tending towards smaller volumes and higher energy densities
Lithium Silver Vanadium Pentoxide	W. Greatbatch	1980	Button **(Model 8615)**	Wilson Greatbatch Ltd	$Li + AgV_2O_5 \rightarrow LiAgV_2O_5$	Dependent on remaining cell life but starts at 3.2	N/D	Pacemaker battery	N/D	Autoclavable as functions in >150 degrees celcius, discharge is almost linear, efficiency of reaction is very high	N/D	N/D however batteries are tending towards smaller volumes and higher energy densities
Lithium Lead Iodide	N/D	<1980	Button	Mallory	$2Li + PbI_2 \rightarrow 2LiI + Pb$	1.9	0.6	Low-rate applications such as pacemakers	Predicted: 0-100 (≈ 50 years)	Hermetically sealed	Very small self-discharge, contents split between solid and liquid	Discontinued due to cracking/separation of layers

Table 3 - Table detailing implantable lithium battery history up to present day. The technical details of each technology are described and their advantages and disadvantages following commercialisation. Current research into improvements and author's suggested reform are included.

1.3. Implantable Medical Device Requirements

Implantable devices require primarily low levels of power for long periods of time and because of this, an implantable battery has an interesting set of constraints and scope. Secondly they need to operate at 37°C with a safety range of ± 10°C. They must also be safe, reliable, have little to no thermal dissipation[17] and produce a sufficient energy density. Access can be a major problem therefore these batteries must be able to operate reliably and predictably for long periods of time. Thus, implantable battery systems must be chosen on the basis of consistency, predictability and be engineered to the highest quality standards. Their batteries must therefore be manufactured to exacting tolerances and undergo the scrutiny of very stringent quality-control procedures[12].

Because of the challenges faced in using finite battery solutions to power implantable devices, considerable research is currently focused on trying to replace them with alternative energy harvesting devices that present less significant safety and performance challenges. However, whatever energy producing solution is being considered, they face a common set of characteristic requirements. The overall life of the device will depend on: power consumption, usage pattern, device size and weight and the stresses which the device are subjected to.

1.4. Objectives

The objectives of this project were to

1. Summarise the current position in terms of the use of active implantable medical devices, their power requirement and their current sources of power
2. Carry out a critical review of the scientific literature in the area of energy harvesting, to identify potential alternative, sustainable sources of power for implantable medical devices, describe current technology levels and assess their suitability for medical applications
3. Speculate on future applications of energy harvesting technologies in implantable medical devices

Chapter 2: Methodology

Through the use of journal articles and library access I plan to produce a systematic review of energy harvesting technologies and their current and potential applications in medical research and clinical settings. The internet search engine Google was utilised to provide referenced journals unable to be found using journal search engines such as Science Direct and PubMed. Keyword searches and *Related Article* links were used throughout. Unfortunately due to constraints by the university on the number of journals subscribed to, all those referenced but published before 1980 were unable to be physically found. However, each of these was referenced multiple times by all subsequent works.

History of Implantable Batteries

Library search engine SUPrimo was used to discover the Encyclopaedia of medical devices and instrumentation (vol4). Edited by John G. Webster. 1988 © John Wiley & Sons, Inc. USA.

This was soon followed by: Batteries for implantable biomedical devices. Edited by Boone B. Owens. © 1986 Plenum Press, New York, USA. Each of these provided the basis for future research using Science Direct and PubMed which provided some more current ideas and advancements. However, not much had changed since 1986 as far as implantable batteries currently in surgical use.

MEMS

Searched keywords such as *MEMS, velocity-damped, coulomb-damped, coulomb-force, BioMEMS*. Following these in Science Direct, it was possible to refine the search to certain dates of publication or journals specific to clinical or sensor applications.

Electrostatic

Keyword search: *electrostatic, electrostatic energy harvest*, MEMS, MSEH*. Unfortunately this did not turn up much via SD or PM due to most MSEH research is being conducted in conjunction with thermal or respiratory research. The papers on MSEH were therefore found under keyword searches: *electromagnet* energy* *harvest*, MIEH, thermal energy harvest*, MTEH, air flow energy harvest*, respirat* energy harvest*, MAEH*.

Piezoelectric

Keyword search SD and PM: *MPEH, piezoelectric energy harvest*, PZT, PVDF, ZnO, nanowire, nanofiber, thin-film, thick-film, mechano*, piezo* batter**. Also came across piezoelectric in journals such as Biomechanics which shed light on the integral crystal structure needed for efficient energy conversion of piezoelectric materials.

Electromagnetic

Keyword search PM and SD: *electromagnet* energy harvest*, MIEH, micro-magnetic energy harvest*, magnet* batter**.

Thermal

Keyword search SD and PM: *thermal* energy harvest*, MTEH, micro thermal* energy harvest*, Thermo Life, thermocouple energy, seebeck energy, therm* batter**. Google keyword search: *Leonov pulse oximeter*.

Airflow

Keyword search SD and PM: *air flow energy harvest*, respirat* energy harvest*, MAEH, aero* energy harvest*, turbine, turbine batter*.*

Biofuel Sources

Keyword search SD and PM: *biomems, biofuel device, bio* energy harvest*, glucose monitor* advance*, bio sensor, biochemic* energy harvest*, biochemic* batter*.*

Applications of Energy Harvesting Generators

Keyword search SD, PM and Google: *pacemaker, drug delivery system, drug pump, active monitor device, implant neural, implant, cardio, implant sensor*.*

Devices in the Pipeline

Keyword search SD, PM and Google: *retinal implant, neural biomems, neurovista, valtronic, Seiko thermoelect*.*

Future Prospects

Keyword search SD, PM and Google: *thermoelectric pacemaker, diabetes pump, HeartMate II, Thoratec, Tomy: monitor, sudden infant death syndrome.*

Chapter 3: Review of Literature

3.1. Microelectro mechanical systems (MEMS) for energy harvesting applications

3.1.1. Introduction

The human body, as far as voluntary muscle movement is concerned, is an infrequent and random power source. Thus it is important for generators attached to any system of muscles to be able to store this energy to be used at a later time. The body possesses many abundant sources of energy only a few of which are discussed here, from heel strike to bacteria. Heel Strike itself has sparked a plethora of research into energy harvesting from voluntary and involuntary motion using devices set up in series with the muscle-tendon complex as shown below in a block diagram. On an as needed basis the generator would stimulate the muscles using the technology depicted to the left in figure 5. The muscle, the most prominent example of a need for this technology is in patients with a condition known as drop foot, brought on by stroke. The basic mechanism is the same for other devices: a generator stores electrical energy converted from a mechanical stimulus and is used at a later time to stimulate a response dictated by the gadget.

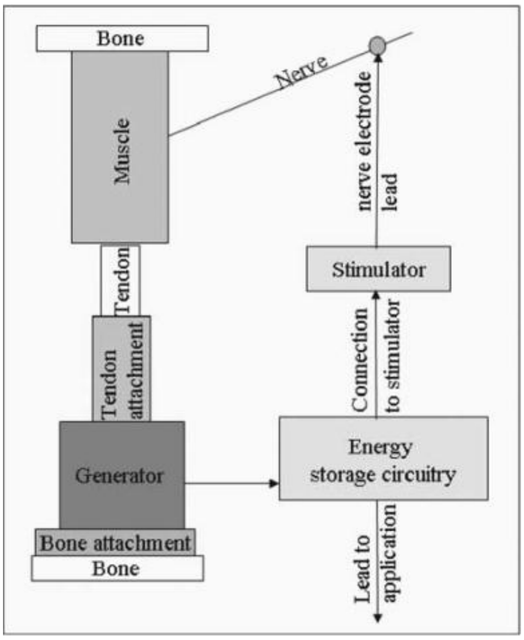

Figure 5 - block diagram of muscle-tendon-generator complex used to harvest energy from movement. Interpretation is that the generator sits on the tendon attachment and does not form an integral part of the complex. Adapted from Lewandowski et al[142].

3.1.1.1. *Voluntary Muscle Movement*

3.1.1.1. Heel Strike

Heel Strike is a stage of walking in which the most immediate force is applied from the foot onto the ground. It uses a system of muscle groups to create the largest mechanical force available for energy harvesting devices, converting mechanical motion to electrical energy. This theory was challenged when Howells et al built a proof-of-concept device which utilised the piezoelectric effect using a PZT (lead zirconate titanate) Bimorphic Crystal Stack to convert mechanical motion into electrical energy. In this case the generator was fabricated the form of an insert for the replacement heel of a shoe. Using the Heel Strike Generator Howell's system was less efficient than originally predicted which was attributed to the opposing forces within the PZT stack itself which cancelled outputs. It was suggested that the system could be improved if the PZT stack was made to be completely uniform throughout, allowing the device to store enough energy to power a low-powered bodily device. Howell's technology was not used to power a device in the study; however it could be used to power an external device such as a watch or an internal device such as a drug-delivery implant.

3.1.1.2. Small Muscle Movement

From large muscle group movement to small group movement; Yang et al have gone so far as to harvest energy from small muscle movement, namely finger tapping (human) and running (hamster) using the latest advancements in nanotechnology further explained in 3.2.1[141]. This technology is suggested as the future of pulse oximeter powering in via a finger covering piezoelectric impregnated fabric.

3.1.2. Involuntary Muscle Movement

3.1.2.1. Cardiac Muscle

A viable muscle-driven generator could harvest a near-constant source of motion from a beating heart. This type of generator would have to be a lasting device as the heart is said to beat over 1.8 billion cycles in a lifetime (≈ 70 years). Zurbuchen et al have developed a proof-of-concept mass imbalance oscillation generator from an original self-powering watch design[143]. First, Zurbuchen implanted this device (without modifications) onto a heart *in vivo*, then created a mathematical model which was then used to modify the final design. The final design produced enough energy to power a current pacemaker with a power consumption of less than 8µW.

3.1.2.2. Lungs

Respiration creates many different potential sources of mechanical energy. The motion of the lungs can create an estimated output of 1W per cycle (inhale and exhale). If this energy were used to power a pacemaker it would increase the time between battery replacements. At Princeton University, USA, Qi et al. has produced a rubber film imprinted with piezoelectric PZT combined in ribbon form[144]. This is thought to be a scalable technology that, when optimised, will prove a useful technology in implantable medical device advancements.

3.1.2.3. Diaphragm

The above-mentioned technology could be adapted to harvest energy from respiratory muscle expansion and contraction. Diaphragm movement is another potential source of energy scavenging as it is a large muscular system, which is almost constantly mobile. Minazara et al have produced a viable unimorph piezoelectric membrane transducer which produced a maximum power of 1.7mW which is sufficient to power low-powered devices[145].

3.1.3. Alternative Options

3.1.3.1. Air Flow

The movement of the respiratory muscles and organs offer potential sources, as does the actual airflow of respiration. Flutter devices use the force created by wind to mobilise a thin strip of material which vibrates to convert vibratory motion to electrical energy as seen in section 3.2.4[89]. Frayne et al created the Windbelt technology, which could be modified into an oesophageal diaphragm potentially driving a low-powered device from respiratory airflow.

3.1.3.2. Thermal Gradients

The thermal gradients between specific body parts (eg. Finger and hand) or areas of flesh (eg. Across dermal layers) are determined by the temperature differences. It has been hypothesised that the thermoelectric effect could also be utilised to power implantable devices that are situated within a patient's limbs such as drug delivery implants such as the contraceptive implant or an insulin secretor. At Wake Forrest University, Winston-Salem, NC, USA a team of researchers led by D. Carroll have fabricated thermoelectric felt which is currently being produced in aid of medical implant research[147].

3.1.3.3. Glucose Concentrations

Chemical sources within the body could also be utilised to create enough electrical energy to power a low-powered device. As such glucose would be an excellent potential source as it is a highly plentiful chemical compound found throughout the body. Using chemical sensors at the micro- and nano-scale it should be possible to power devices based on the abundance of glucose.

3.1.3.4. Bacteria

Microbes are an excellent source of power within the human body, particularly in areas of abundance such as the gut. Microbes could oxidise organic matter and excreted material (such as methane etc) could be used to power small-powered devices. As a proof-of-concept experiment, Lowy et al have developed a microbial-fuelled cell which uses microbial activity naturally found in oceanic sediment and seawater[146]. This basic design could be adapted to use E. coli or any microbes naturally found in the gut in order to power an implantable device, particularly those drug-delivery devices used to combat metabolic disorders.

3.1.4. Categories of Energy Harvesting Sources

In order to combat diseases of cardiovascular, neural, autoimmune and sensory systems this author believes energy harvesting generators will advance implantable medical technology in the coming years. There are currently several forms of energy harvesting being investigated: piezoelectric, electromagnetic, thermal, airflow and biochemical. Each of these will be described later in this chapter.

3.1.5. *Micro-fabrication of Inertial MEMS*

MEMS are primarily two-dimensional with some recent advancement into stacking fabricated materials for greater energy conversion efficiency but most of the 2D materials can be fabricated from the following fundamental techniques. Each of these is currently being investigated and modified to provide optimum power density and energy conversion efficiency in as far as micro-generators for implantable batteries is concerned. Several of these techniques will be mentioned later in this chapter.

3.1.5.1. Film Deposition

Film deposition is a fundamental category of technique in implantable MEMS fabrication, the most the necessary of these is called sputtering. This is defined as the process by which ionized atoms are accelerated onto a surface where they condense and form a thin film[148]. The most common method of commercial film deposition is chemical vapour deposition (CVD), a technique based on the reaction of a vapour species at the interface of a hot surface. Generally, it is used to deposit silicon and silicon compounds such as silicon nitride, silicon oxide and polysilicon. Other popular commercial techniques include plasma-enhanced CVD, atmospheric-pressure CVD and low-pressure CVD. Other techniques include physical and chemical vapour deposition, electrodeposition, sol-gel deposition, spin casting[26]. Park et al have used film deposition in the investigation of medical implantable micro-generators[149], however there are many more examples.

3.1.5.2. Pattern Transfer

Photolithography is one of the primary manufacturing techniques used to create MEMS and relies heavily on patterning. First a geometric pattern is created on a spin-coated resist to form a mask (a quartz plate patterned with an opaque layer) using electron-beam lithography. The spin-coated resist is then exposed to UV light in order to remove some of the patterned areas of the opaque mask, revealing an etched pattern. The desired pattern is then transferred to the target layer (like a stamp) and the remaining photoresist may be removed during a technique known as ashing[26]. Ashing simply removes any unwanted material in a chemically safe manner, usually by heating under various conditions. Overall photolithography is often employed to fabricate thin-films used in the manufacture of micro/nanogenerators, valves and membranes for drug delivery systems. Materials used are photo-definable polymers such as SU-8, PMMA and thin PDMS films[27]. However there is much investigation into different compounds as in Qi and McAlpine et al explained in greater detail later in this chapter[144].

Other pattern transfer techniques include optical proximity and projection step-and-repeat lithography, laser writing, direct electron-beam[26]. Utilising projection step-and-repeat lithography could allow for a greater control over the fabrication of implantable MEMS generators, allowing engineers to easily modify the technology.

3.1.5.3. Structural Change

Structural changing techniques involve the changing of the concentration of donor or acceptor electrons in substrates such as silicon. The fundamental changing of the internal structure allows for very fine modifications to the technology. This category of fabrication includes oxidation, doping, ion implantation, drive-in diffusion[26]. These methods are widely used in the fabrication of MEMS if moderate penetration depths are required, such as in the fabrication of piezoresistors, highly popular components of implantable micro-generators being investigated currently. For example, Egbert et al have developed a thermoelectric-based micro-generator using doping techniques to produce a viable implantable energy harvester[150].

3.1.5.4. Micromachining

Micromachining methods are widely used in the formation of movable structures on silicon wafers, all of which are chemical reactions between silicon and a gas/liquid etchant[26]. The etchant transforms the surface of the solid into soluble or volatile products which are then removed. The most popular of this class of technique includes vapour- and plasma-assisted dry etching, isotropic and anisotropic wet etching, planarization, deep reactive-ion etching, lift-off techniques, wafer cleaning, ashing, chemical-mechanical polishing[26]. These techniques use a micro-end mill to carve out channels and reservoirs in thermosetting polymers or thermoplastics[27]. This method is currently being investigated as an implantable micro-generator fabrication technique, as demonstrated in Zhu et al who investigated wet etching in the fabrication of an electrostatic micro-generator for implantation. Unfortunately this technique coupled with other factors, such as material selection, in the experiment produced a generator capable of a small output of only 0.1nW [151].

Overall most techniques are currently under investigation, however much research is still needed into the optimum fabrication technique for each type of micro-generator.

3.2. Physical Sources

In recent years the use of mechanical motion to generate energy has become the most popular area of research within the field of energy harvesting. Methods of mechanical power conversion include the use of electromagnetic, electrostatic or piezoelectric technologies. Physical source-based MEMS devices usually exhibit mass-spring damper systems which use a transducer to convert mechanical energy into electrical. These generators work most efficiently when an applied excitation has low amplitude, and a natural frequency close to the resonant frequency (RF) value as demonstrated in figure 6[21].

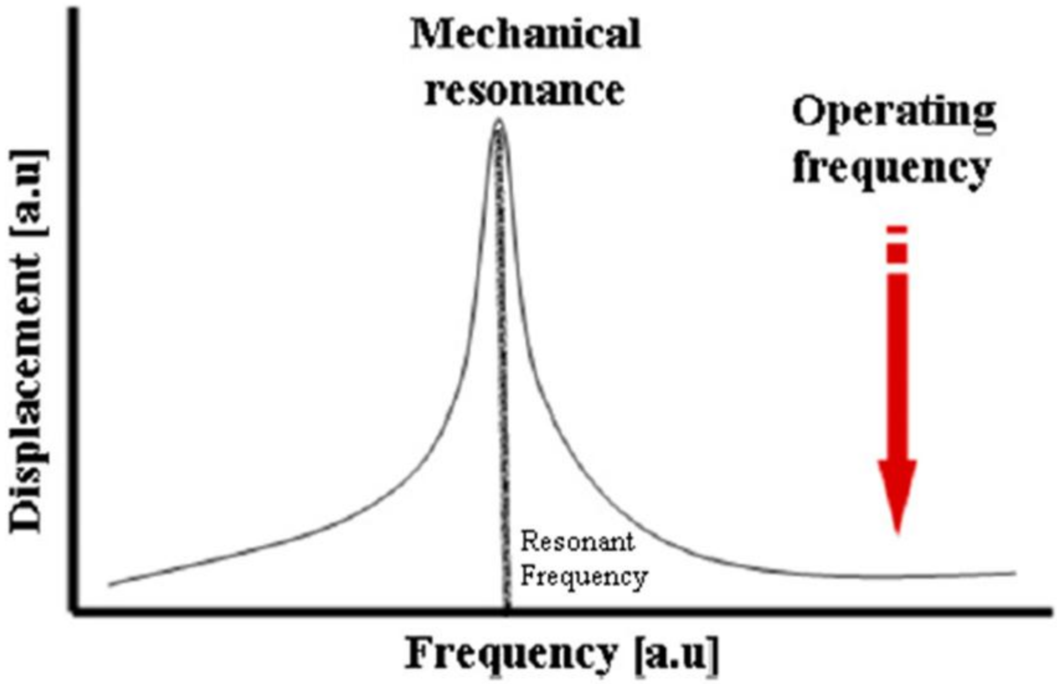

Figure 6 - The resonant frequency is the frequency at which a device can store energy between the conversion of two kinds of energy. In MEMS devices transducers are used as damper systems, which incur some losses between oscillating frequencies. When the damper system creates a small loss, the RF and the NF is approximately equal and the device will store energy at optimum efficiency[21].

3.2.1. *Piezoelectric Energy Harvesting*

In addition to electrostatic and electromagnetic harvesters described by the generators mentioned previously, there are also piezoelectric generators. These are generators based on the piezoelectric effect created by materials which deform over time and cause an energy conversion, materials such as zinc oxide (ZnO), polyvinylidene fluoride (PVDF) or lead zirconate titanate (PZT)[23]. The piezoelectric effect itself derives from the spontaneous dipole creation within the crystalline structure of the material as it is physically deformed under load. The resultant electrical energy is proportional to the stress created upon displacement between the poles. Unfortunately, although these generators have a high capacity to endure, the power created is limited to the amount of deformation that the material can undergo[6]. As such they would be highly useful in the current field of medical implants, if they were added as an emergency back-up source, in addition to a commercially available battery. This could lead to fewer replacement batteries expended overall and less time spent in a hospital environment for the patient.

The piezoelectric effect has been utilised for many years, most recently to harvest mechanical energy in novelty devices. The brothers Jacques and Pierre Currie first reported the piezoelectric effect in 1880, when they noticed the conversion of mechanical energy into electrical energy was possible through the deformation of crystalline structures through the compression or vibration of these structures[34].

The piezoelectric effect can be expressed in two equations:

$\delta = \left(\frac{\sigma}{E_Y}\right) + dE_e$ $\quad D = \varepsilon E_e + d\sigma$ Where δ and σ are stress and strain respectively, E_e is the electric field, E_Y is the Young's Modulus, d is the piezoelectric strain coefficient, D is the charge density and ε is the dielectric constant of the piezoelectric material[6]. So the strain of the material is directly proportional to the charge density (output).

The first medical device to run off scavenged mechanical energy was a pump used as a drug delivery system designed and built in 1978 by Spencer et al[35]. It was a simple system that allowed for an accurate, low flow rate that was controlled by a pressure-independent micropump. Following on from this was Williams et al. in 1995 who proposed a microgenerator which scavenged mechanical vibrational energy [36]. Then, in 2001, Glynne-Jones et al proposed the introduction of a thick-film capacitor into this technology[37] in order to increase the limit of energy stored.

Piezoelectric energy harvesters, also known as mechano-electrical converters[38] (types of linear mechanical resonators), can undergo three types of deformation of the piezoelectric capacitor[5]: lateral bending, vertical compression and lateral stretching. Each resulted in an output voltage directly proportional to the input mechanical energy[39]. When the piezoelectric material, usually highly organised, has mechanical stress applied to it, the dipoles within the structure are aligned, causing a net polarisation and thus an electric potential across the crystal. This creates the transducer effect between electrical and mechanical oscillations[40]. This type of energy harvester is the most studied in the literature, and a very popular area of research due to its high-energy output and low cost manufacturing process described earlier in 3.1.5. Currently mechanical potential energy harvesting capacitors are manufactured as thin-/thick-films, nanowires and nanofibers. The materials used in each of these constructions, from lead zirconate titanate (PZT), to quick pack, to microfiber composites[41], vary according to the mechanical strain they are expected to encounter.

3.2.1.1. Nanofiber PEGs

The nanofiber-based piezoelectric energy generator (PEG) is a technological advancement capable of applications in various medical devices and is highly scalable. It is often manufactured using a semi or fully modified electrospinning process with either lead zirconate titanate (PZT) or polyvinylidene fluoride (PVDF). PZT is a ceramic material which draws on excellent piezoelectric properties only recently pioneered by Chen et al and produces a nanogenerator capable of producing an output voltage of 1.6V and power of 0.03µW [42]. Most of the proposed PZT energy harvesters are film-based capacitors which exhibit the classic cantilever design. Unfortunately attempts to increase the energy conversion efficiency of designs based on PZT failed: as PZT has a high annealing temperature (>600°C)[42] , and during the electrospinning process PZT is mixed with a solvent that lowers the density and therefore the conversion efficiency. In a dense clump or as a thin-film, PZT can demonstrate a higher voltage output compared to other piezoelectric materials in sensing (immediately reacting to deformation), actuation (signal propagation) and, therefore, applications in medical device energy harvesting. PZT is being pioneered in the case of orthopaedic implants (usually leg joints) where activities such as walking provide sufficient power (see heel strike 3.1.1.1.), it is thought that at heel strike walking provides 67W of power, sufficient to support other implantable devices[43]. The potential medical applications, later described in chapter 4, of such suggest that PZT imbedded strips of material could be attached to the rib cage/diaphragm/lungs to power a cardiac pacemaker[44]. Platt et al demonstrated that it is possible using a PZT ceramic in a total knee replacement implant to produce enough power (4.8mW with a volume of 1.2cm^3) to support an active medical implant[45].

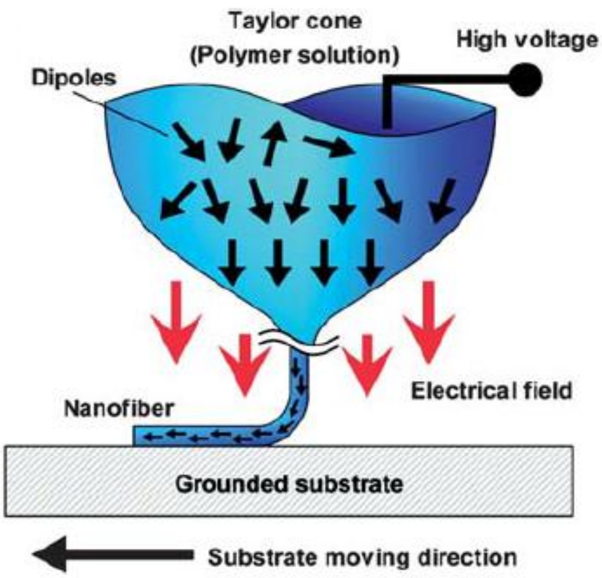

Figure 7 – near-field electrospinning (NFES) technique adapted from QI et al[139]. NFES is considered a more sensitive means of microfabrication the needle to collector distance was shortened to enhance the control of fiber deposition allowing for superior piezoelectric nanogenerators.

The alternative material, PVDF, is a polymeric material that demonstrates superior piezoelectric characteristics due to its highly organised crystalline structure, exhibiting two kinds of linkages: trans and gauche linkages. In comparing alpha phase and beta phase linkages within PVDF, alpha is more abundant throughout however beta-phase is thought to be responsible for the piezoelectric response to deformation. The polar nature of the beta-phase orientation (CH_2-CF_2) unit cells with a carbon backbone ensure maximum sharing of electrons between the units[144]. In order to ensure a greater number of beta-phase linkages, the manufacturing process has incorporated electrical poling and mechanical stretching in order to align the dipoles inherent to the structure. Unlike PZT, PVDF nanofibers are lightweight, biocompatible, flexible and available in custom-made lengths and thicknesses.

A copolymer known as poly(vinylidenefluoride-co-trifluoroethylene (VDF-TrFE) has recently attracted scientific researchers, Nunes-Pereira et al has recently pioneered this technology using VDF-TrFE copolymer inter-digitised with $BaTiO_3$, another piezoelectric semiconductor, in nanoparticle form. This embedded copolymeric fiber fabricated nanogenerator gave power outputs from 0.02μW to 25μW[46].

Each of these materials can be fabricated using techniques like drawing, template synthesis and phase separation self-assembly. However they can also be tailor made using electrospinning techniques, both near-field (NFES), as demonstrated in figure 7, and far-field (FFES). Conventional FFES involves forcing a spinneret through a viscous solution subjected to an electric field. The spinneret is crossed and the solution drips and forms an elongated cone shape. This shape is conducive for sufficient viscosity and surface tension that allows for a jet of solution to form from the cone that provides a stretching force as the jet travels to the collector where there is an electrical potential gradient. During NFES a single nanofiber can be deposited in a small area in a controlled manner whilst during FFES dense disorganised nanofiber networks are produced on large areas. NFES is a modified version of conventional FFES, where the needle to collector distance was shortened to enhance the control of fiber deposition allowing for superior piezoelectric nanogenerators which require densely packed highly organised parallel lines of fibers[47]. In addition to shorter needle to collector distance, researchers have also used electric fields to guide the deposition locations through the addition of two electrodes on the collector and one or more charged rings[48]. The fundamental principle which electrospinning relies on is the fact that fibers can be spun from solutions or melts. This technique can produce fibers up to 10nm in diameter and can be made from different materials including synthetic or natural polymers, polymer composites, polymer alloys, metals and ceramics[49]. Chen et al's proposed nanogenerator made of highly organised parallel PZT nanofibers which produced a high output voltage was fabricated using NFES[42]. The techniques are also extremely versatile and different parameters can be introduced to enhance the final piezoelectric properties of the product. In addition, the electrospinning process is a high throughput technique and can produce product in bulk for various applications including bio-scaffolds, wound dressings and medical implants[50].

There are various conditions and parameters which contribute to the piezoelectric properties not only in nanofibers but in thin-films as well. Many commercially available films are processed in unknown solvents and many papers where researchers have created their own piezoelectric material have missing parameters and details in their modifications. Thus there is such a difference between piezoelectric characteristics all of these could be due to solvent types, molecular weight, electrospinning methodologies, applied bias, and applied distance between the collector and the electrodes. Some researchers have modified the individual fibers further and embedded certain semiconducting nanoparticles in a bid to improve the energy storage capacity and therefore the piezoelectric property.

To conclude, nanofibers need to be produced in a cost-effective manner and as such electrospinning modifications are excellent candidates for commercial reproducibility. Current nanogenerators only produce a few microwatts of power; however some have advanced to higher power outputs using in vivo mechanical stimulation eg LED powered by a human heart. If power output could be increased from the current average, $1x10^{-11}$W to $1x10^{-6}$W, then nanofibers would become the leading nanogenerator technology in the energy scavenging race.

3.2.1.2. Nanowire PEGs

Nanowires on the other hand, were one of the earliest energy harvesting nanogenerator that utilised zinc oxide (ZnO)[51], a semiconducting material, which was later replaced with other semiconductors such as ZnS, GaN and CdS[52]. Each of these materials has consistently demonstrated their ability to store up electrical potential when put under mechanical strain and conveniently a large number (billions) may be integrated into nanogenerators. Recently Qin et al have used ZnO nanowires coated in microfibers to fabricate a more flexible nanogenerator capable of producing a higher output[53].

3.2.1.3. Thin-/Thick-Film

Piezoelectric individual nanostructures can be joined together to form bulk piezoelectric harvesting devices in the form of a film of varying degrees of thickness. Fang et al proposed a PZT film of 1.64µm, which produced an output voltage of 898V and 2.16µW upon a strength acceleration of 1g and suggest that to increase said output perhaps all that is needed is to increase the thickness of the film[54].

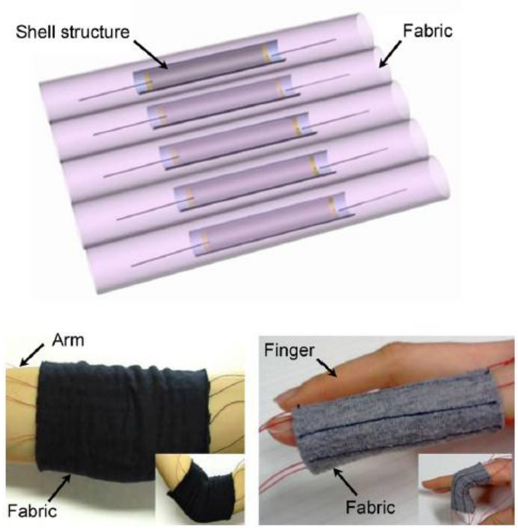

Figure 8 - Piezoelectric fabric with incorporated shell structure[28].

3.2.1.4. Piezoelectric Shells

Yang et al reported a novel integration of piezoelectric composite materials and polymers to form energy harvesting piezoelectric polymer in-shell structures. These could be worn as fabric straps around the wrist or finger see figure 8[55]. It is believed that this new advancement could lead to a revolutionary way of in-patient monitoring, incorporating BioMEMS technology and point-of-care devices to power each other. This will be explained later in 3.3.

In order to consider the most efficient way to harvest mechanical energy some issues must be considered: how the piezoelectric harvester units can all simultaneously be mechanically stimulated, how the energy can be harvested and applied and finally how the nanogenerators and microsystems may be packaged and assembled.

3.2.2. Electromagnetic and Electrostatic Energy Harvesting

Electromagnetism is described as the interaction between electrically charged particles within an uncharged magnetic field in the presence of electrical conductors, while electrostatic fields are described as the phenomena that

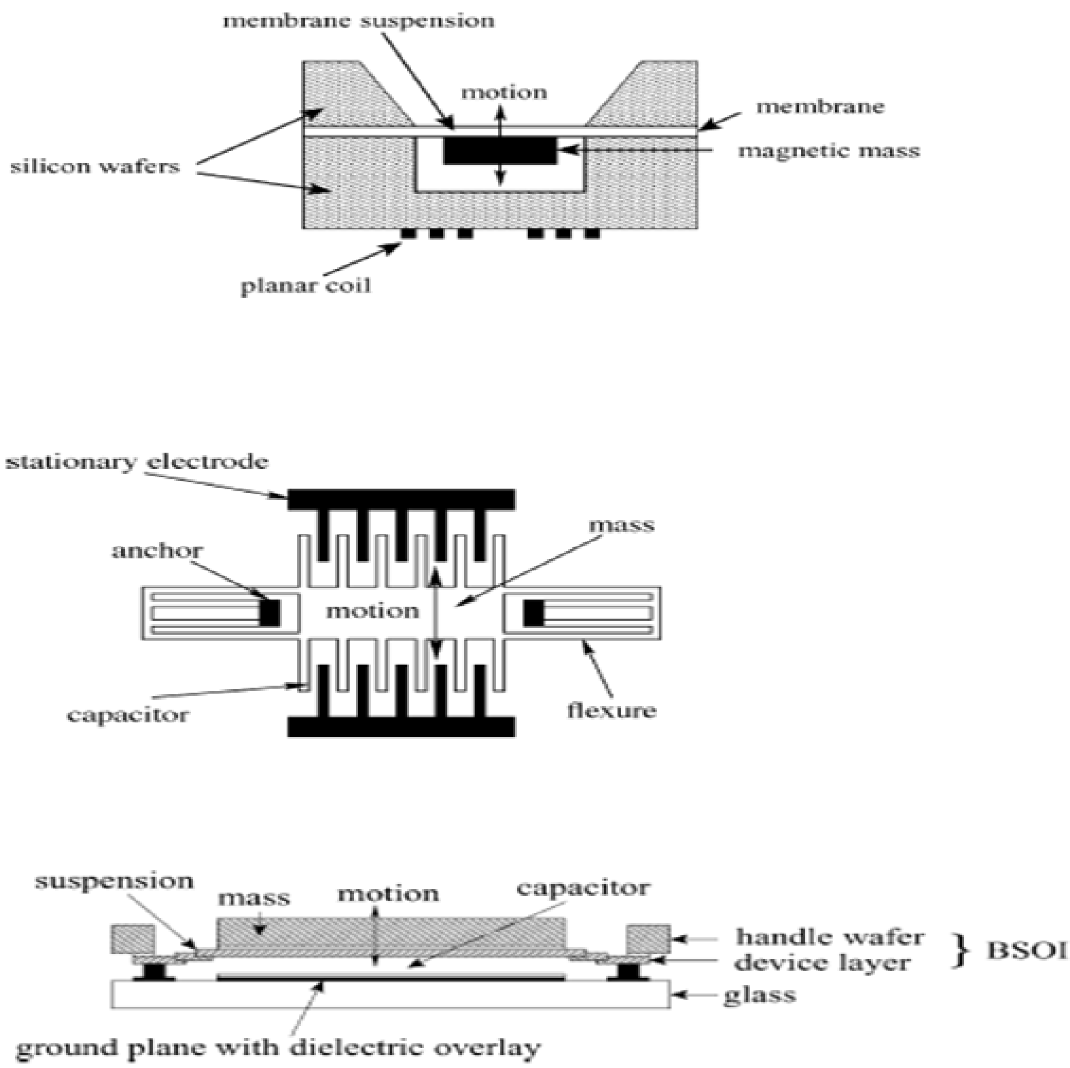

Figure 9 - From top to bottom: velocity-damped resonant generator (VDRG) which uses a magnet balanced on a membrane or cantilever to sense kinetic motion, coulomb-damped resonant generator (CDRG) and coulomb-force parametric generator (CFPG). Each of these is a type of generator using linear and nonlinear physical characteristics of electromagnetic and electrostatic sources. Figure adapted from Sue et al[6]

describes the properties of stationary or near-stationary electrically charged particles with no acceleration[20]. Electromagnetic and electrostatic energy harvesters use three types of generators: velocity-damped resonant generators

(VDRGs), coulomb-damped resonant generators (CDRGs) and coulomb-force parametric generators (CFPGs), schematics as seen in figure 7[20]. VDRGs are damped by a force that changes with velocity, CDRGs are damped by a constant force and CFPGs are nonlinear generators. Each of these generators can be implemented in different physical energy sources: VDRGs are used in electromagnetic (electromagnetism created from motion) harvesting devices and the other two are utilised in electrostatic harvesting devices[20]. Each of these power sources is examined in more detail in the sections that follow.

Electromagnetic harvesters operate under Faraday's principle in that the induced electromotive force (EMF) in a closed circuit is equal to the magnetic flux over a set period. An electromagnetic harvesters habitually consists of a rotor and an induction coil[6] and is used to harvest vibrational kinetic energy using, as seen in figure 9 the VDRG, a magnet balanced on a cantilever. This simple system is very sensitive to even the smallest of vibrations but it also has a complex manufacturing process which increases the cost of the overall device. Electromagnetism in its natural form (within an environment not as an exponent of kinetic energy) is defined the energy emitted from electrical devices which resembles a wave formation, like sound waves, but does not require a medium to travel. The most popular area of electromagnetic energy harvesting research is however based around mechanical vibrations such as those produced from muscle movement and is the area this paper will focus mainly on.

Electromagnetic energy harvesters are being used in implantable devices as a physical source of renewable energy, as seen in figure 9. These nanogenerators are VDRGs, usually these are linear generators, consisting of a resonant beam (an electromagnetic induction) which arises from the motion between one or more conductors (multi-turn coils) and the magnetic flux (permanent magnets)[21]. The conductors and the magnetic flux are spatially orientated according to the magnetic circuit structure ie the core. They start generating power when the resonant frequency is reached and is proportional to the input frequency. As with natural frequencies, such as those in found in the body, the ambient vibration sources are random[61], and therefore off-frequency situations occur thus decreasing the output. Hence there needs to be continuous or active tuning of the generator so the device can increase its energy conversion efficiency and be able to perpetually provide energy on a needed basis. This is particularly important in implantable device technology.

3.2.2.1. Electrostatic Energy Harvesting

The phenomena known as electrostatic is described as the properties used to describe stationary or near-stationary particles and is fully augmented in Coulomb's Law. C. Augustin de Coulomb first reported Coulomb's Law in 1785 while investigating the properties of amber in lightweight particle attraction[153]. It states that an electrostatic force between two charges is directly proportional to the charges multiplied and inversely proportional to the distances between them squared. It also describes the law of charged particles: opposite charges attract while same charged particles repel each other. Generators using this phenomenon to convert electrostatic energy to electrical energy are based on vibration-dependent capacitors depending on an oscillating capacitance within the circuit[20]. As seen in figure 9, CDRGs and CFPGs use the vibrations between separate plates of a charged variable capacitor to convert mechanical energy into electrical energy. Ideally this would be a low-cost technology with highly applicable functions within the field of medical implants, however ideally these generators require high voltage (in the order of 1×10^2 V) polarization source which in turn increases the number of components to contain this component and therefore the overall size of the generator[152]. In addition, the capacitors would need to be pre-charged before implantation[22]. These types of generators will not be further investigated as a result and this section will instead focus on electromagnetic generators and their applications.

3.2.2.2. Faraday in Electromagnetic Energy Harvesting

Electromagnetic energy harvesting is fundamentally based in Faraday's law of electromagnetic induction, where the voltage and electromotive force are proportional to the rate of change in magnetic flux linkage. $V = -\frac{d\varphi}{dt} = -\frac{dx}{dt}$ From this equation φ is the total flux linkage. However, the number of turns affects the voltage directly proportionally so when N is the number of turns. Furthermore in electromagnetic circuits the motion between the coils and the magnet are the same directionally and therefore voltage can be expressed as a product of velocity, number of coils and flux linkage: $V = -N\frac{d\varphi}{dx}.\frac{dx}{dt}$ The electromagnetic force can then be calculated from the induced current acting against the excitation force. $F_{em} = D_{em}\frac{dx}{dt}$ Where D_{em} is the damping coefficient and needs to be optimised in order to create maximum power harvested when dx/dt is limited. The power generated can then be calculated using: $P = F_{em}\frac{dx}{dt} = \frac{V^2}{R_L+R_C+j\omega L_C}$ Where R_L and R_C are load resistances, L_C is the coil inductance. The damping coefficient is therefore equal to $D_{em} = \frac{1}{R_L+R_C+j\omega L_C}\left(\frac{d\varphi}{dx}\right)^2$ where terms R_L, R_C, and L_C need to be reduced to increase the power output[62]. The lower the damping coefficient the greater the energy conversion efficiency.

3.2.2.3. System Comparisons

Suzuki et al. sought to design an electromagnetic harvesting IMD where a microgenerator (a high ratio gear) and a magnet were implanted while two-phase exciting coils were placed outside the body. By exciting the coils, an electromagnetic field was created thus driving the microgenerator to rotate. Using the high ratio gear, a higher speed of rotation is generated as well as a high output voltage and an output power of 11mW[63]. Later Suzuki et al. proposed an alternative system which employed a series of rotors external to the body which when coupled with each other accelerated the rotating speed of the generator to recharge a battery system, thus producing an output power of 1.9W. However the disadvantage of this system was the time taken to recharge the battery was in excess of 10 hours[64].

A linear system was proposed by Von Buren et al which harvested energy from a man below the knee as he walked, this generated an average power output of 35µW[65]. However, several authors suggested a nonlinear based system, the goal being to decrease the volume of the device and increase the power output. The authors demonstrated that the nonlinear system could improve the energy conversion and that the resultant range of frequency oscillations could improve the overall energy harvesting efficiency of the device[66].

One of the greatest problems faced by these devices is the unstable bandwidth and resonant frequency. The bandwidth is a particular problem because the conversion efficiency of a mechanical energy harvester is almost entirely dependent on whether it can sense the signal at a particular bandwidth. Research into modifications of the original design began when Sari et al. proposed using a cantilever design, replacing the coils as the moving component[67]. These generators also exhibited a low bandwidth and so were only efficient once they had reached the resonant frequency of the cantilevers. The fundamental idea behind this design was that the low-frequencies could be converted to high-frequencies through a *frequency up-conversion* technique. The distance between the components could be changed to suit the frequency, so the magnet could catch the cantilever at a certain point, tug it back up and release it. The cantilever upon release resonates at damped natural frequency (*frequency up*)[6]. Sari described how 35 cantilevers within the device generated a power output of 0.4 µW and an output voltage of 50mV, which is insufficient to power a low-powered IMD[67].

Continuing on from this research, Sardini et al, using a polymeric resonator system in order to decrease the Young's modulus of the materials, proposed a nonlinear and a linear system. The devices made of polymeric materials showed a ≈67% decrease in resonant frequency to about 30-40Hz, which in turn increased the power output of the linear system to 290µW and the output voltage to 182mV at a resonant frequency of >100Hz and the nonlinear system to 153 µW and 378mV at a resonant frequency of approximately 40Hz[68]. Much of the current additional research can be seen below in table 5.

Refs.	Frequency bandwidth (Hz)	Acceleration (g)	Volume (cm^3)	Max. power density ($\mu W\,cm^{-3}$)	Max. power density per g ($\mu W\,cm^{-3}\,g^{-1}$)
Sari	4200–5000	50	1.4	0.286	0.0057
Bin	35–75	0.2	2.703	0.148	0.74
Yang	369, 938, 1184	0.76	9.504	0.337	0.44
Nguyen	520–580	0.19	0.0271	5.609	29.52
Liu	30–47	1	0.016	33	33
Foisal	7-10	0.5	40.18	52.02	104.04

Table 4 – adapted from FOISAL demonstrating a comparison of power density and bandwidth research[138]. As clearly seen, those operating at a lower frequency demonstrate a higher maximum power density stored as a result.

Unfortunately lowering the resonant frequency (thereby increasing the frequency sensitivity), the overall dimensions of the generator need to be increased to make room for the larger resonant element. This presents a problem if the device was to be fabricated as an implantable mechanism where the goal is to have as unobtrusive a device as possible.

In addition to lowering the resonant frequency to increase overall efficiency, different materials can be used to fabricate the permanent magnets including ferrite, samarium-cobalt (Sm-Co) and neodymium (Nd-Fe-B)[62]. As seen in table 6, comparatively, Nd-Fe-B has the lowest cost and the highest flux density making it highly usable in commercial microgenerator production

Material type	Flux density (Br: mT)	Cercive force (Hc)	Density (kg/m^3)	Cost
Ferrite	300–500	High	~4980	Low
Nd–Fe–B	1100–1500	High	~8400	Normal
Sm–Co	1000–1200	High	~7470	High

Table 5 – Adapted from Fei et al demonstrating the variety of compounds used in electromagnet commercialisation. Nd-Fe-B is the most obvious choice for microgenerator commercialisation as the flux density is the greatest and costs the least, while the coercive force (resistive force of the magnet against demagnetisation) remains the same[62].

One of the main problems with electromagnetic energy harvesting is that in a lot of applications there are only at low frequencies, especially in medical applications. Secondly the electromagnetic field can have detrimental effects on the body and its environment[69] leading to costly medical procedures or repairs to everyday machines. Thirdly, the magnetic field may develop leaks during service which will reduce its efficiency[4] and lead to further replacement surgeries.

3.2.2.4. Recent Applications

Recently, a student in Germany, Denis Seigel, has fabricated a device which harvests redundant electromagnetic energy found in everyday devices[70]. This particular device has current applications in external applications ie mobile phone charger. However, the device could be modified to only harvest energy from watch for example, in a subcutaneous implant in the wrist, resulting in a charged battery to charge an IMD. Also, the technology could be adapted to allow for implantation anywhere within the body so long as it has access to natural magnetic fields such as those amplified by nerve conduction.

In addition, at the University of Hawaii, electromagnetic energy has been harvested via a nanogenerator from respiratory movement[71]. This technology uses vibrational energy created from muscle movement, presumably by an integrated VDRG, to convert into and store electrical energy. Shahhaidar et al[71[have fabricated a device which converts energy from respiration at a higher efficiency rate than piezoelectric material devices. The mean power generated from this device was estimated at 2mW. A possible energy harvester for IMDs, the technology would need to be modified to be as unobtrusive as possible and biocompatible.

1.2.3. Thermal

Thermal harvesters utilise thermoelectric cells fabricated using screen-printed PZT and PVDF films[24]. These cells convert temperature gradients into electrical energy via the Seebeck effect[15] and usually consist of two semiconductors: a p-type and an n-type in series with each other. This system produces an electrical field proportional to the temperature difference registered between these two junctions. Normal temperature for a human body is 36-37 °C but may vary depending on the individual's metabolism rate, therefore in considering these generators it is important to take into account differences between individuals.

Devices using thermocouples are dependent on the thermoelectric effect which in an IMD would harvest from ambient body temperature. Thermal energy harvesters utilise the Seebeck effect ie the thermoelectric effect first demonstrated in 1821 by T. Seebeck[72,73], to convert thermal energy to electrical energy. This effect relies on the second law of thermodynamics first demonstrated by S. Carnot in 1824[73]. Usually generators utilise pyroelectric cells consisting of PZT or PVDF films[74] with two semiconductors: a p-type and an n-type connected in series. This system produces a measurable voltage proportional to the temperature difference registered between these two junctions[6]. Notably, the thermoelectric effect is highly inefficient in most materials which led to discoveries in semiconductor doping combinations, eg with bismuth telluride or silicon germanium. Thermocouples have a second function, that of an actuator which can transport heat from one junction (cold) to another (one at ambient temperature) and as a result the cold junction is cooled in an effect known as the Peltier effect first demonstrated in 1834 by J. Peltier[73,75]. This particular function, could aid in the local cooling of an on-chip reference element or to reduce current leaks, as in a photodetector. Scaling down of this technology: vertical thermopiles fabricated via thick-film connected in series and parallely located between two substrates[76]. Multiple thermocouples connected in series or parallel form a thermopile and the former function of thermocouples could be utilised to drive generators to create enough electricity to power implantable electronic devices deep within the body where there are temperature differences between the colder and hotter areas.

The earliest research into micro-thermoelectric technology was conducted by Glosch et al. who proposed a thin-film fabricated silicon-based semiconductor thermopile on a chip the size of 16.5mm^2 [77]. This chip produced 1.5 µW from a temperature difference of 10K without a doped semiconductor.

The doping of semiconductors is common practice in commercial settings, particularly doping with polycrystalline silicon germanium (SiGe) alloys and polycrystalline silicon using BiCMOS technology (an integrated circuit made from a bipolar junction transistor and a complementary metal-oxide semiconductor), a technique developed by Infineon[76], however tellurium compounds feature a higher performance aptitude than conventional thermoelectric generators. Bismuth tellurium (BiTe) alloys are currently commercially available on the micro scale. As an example, Bottner et al. produced a thick-film fabricated device with 12 thermocouples on a chip size 1.12mm^2 and had an output power of 67μW utilising a temperature difference of 5K[78].

Following on from these groups, Huesgen et al. calculated the power factor of Glosch et al's thin-film silicon-based generator (9.1x10^{-4} μWmm^{-2}K^{-2}) and Bottner et al's thick-film device (2.4x10^{-2}μWmm^{-2}K^{-2}). Using these values they compared their own thin-film fabricated devices which used an aluminium/n-poly-silicon generator (3.63x10^{-3} μWmm^{-2}K^{-2}) and a bismuth antimony tellurium generator (8.14x10^{-3} μWmm^{-2}K^{-2})[76].

An alternative method used in miniature thermoelectric generators is membrane-based thin-film thermopiles, which is widely used commercially.

1.2.3.1. Power Conversion

In devices utilising the thermoelectric effect the induced voltage may be expressed as $V_{out} = (\alpha_n - \alpha_p)\delta T$ where α's are the Seebeck coefficients of the p- and n-type semiconductors[1]. The second part of this circuit is the thermopile, the thermal resistance of which can be calculated as $R_{tp} = \frac{R_{pp}R_{MTEH}}{R_{pp}-R_{MTEH}}$ where R_{pp} is the thermal resistance of air and the holding elements connecting the cold and hot plates of the elements in parallel with the thermopile (microthermal energy harvester - MTEH) and R_{MTEH} is the optimal thermal resistance of the MTEH to maximise power conversion. The optimal thermal resistance can be calculated using the following equation: $R_{MTEH} = \frac{(R_{body}+R_{si})R_{et}}{2(R_{body}+R_{si})+R_{et}}$ where the R_{body} is the thermal resistance of the individual human body, R_{et} is the resistance of the MTEH and R_{si} is the thermal resistance of the heat sink. The ratio N depends on the thickness of the MTEH and must be greater than one, $N = \frac{R_{et}}{(R_{body}+R_{si})}$ The smaller the value of N, the smaller the power conversion efficiency[6]. Therefore the power output is dependent upon the thickness of the thermopile and the difference between the two semiconductors.

The performance of thermoelectric devices depends on the figure of merit or ZT of a material where $ZT = \left(\frac{\alpha^2 T}{\rho K_T}\right)$ and α, ρ, K_T and T are the Seebeck coefficient, electrical resistance, total conductivity and absolute temperature respectively[79]. The ZT of a material demonstrates how the thermal difference can produce a power value sufficient to power a low-powered IMD, as demonstrated in [79] which shows that over 100 µW can be produced from 0.3-1.7 ° C temperature difference[79].

1.2.3.2. Fabrication

Thin-film technology has improved the ZT of materials[79] and also allows for very lightweight devices allowing generators to be integrated into very small volume devices[80]. Semiconductors are fabricated in several ways for the thin-film deposition of tellurium compounds, these include thermal co-evaporation, flash evaporation, co-sputtering, electrochemical deposition and metal-organic chemical vapour deposition (MOCVD)[75]. Co-evaporation and MOCVD are the procedures with the most uniform results. These techniques are currently implemented in fabricating experimental technology with the goal of placing them within an IMD[154].

1.2.3.3. Materials

Most commonly preferred is Bi_2Te_3, which has a ZT of 0.9 and is one of the materials NASA is investigating[1], and Poly-SiGe, ZT of 0.12. Bi_2Te_3 operates best as a thermocouple at room temperature, whilst Poly-SiGe is best suited to thermopiles due to be fabricated via micromachining[79].

1.2.3.4. Superlattices

Superlattice fabrication techniques are used to increase the semiconducting properties of certain compounds. Using MOCVD, it is possible to create superlattice structures of p-type and n-type semiconductor compounds. Venkatasabramanian et al. reported that using a p-type leg of $Bi_{0.5}Sb_{1.5}Te_3$ alloy and an n-type leg of $Bi_2Te_{2.85}Se_{0.15}$ alloy the best ZT values at 300K respectively were 1.0 and 0.9[81]. Using MOCVD to create superlattice compounds in thin-film form resulted in a maximum ZT of 2.0 for Bi_2Te_3/Sb_2Te_3 superlattices. In combining this technology the future of thermoelectric harvesting in IMDs holds great potential. Already a small temperature difference will produce a power output in the order of microWatts. Incorporating these recent fabricating processes and the use of superlattice structures could produce enough power to run a low-powered IMD or provide an emergency power source to be used between medical check-ups.

1.2.3.5. Commercially Available

Thermo Life ® is a relatively new device which is approximately 3cm^2, with a height of 3mm, and is thought to be able to power implantable devices for longer than the standard lithium ion battery currently in use[82]. Developed by Stark et al, this thin-film fabricated Bi_2Te_3 deposited on Kapton[5] device can produce anywhere between 10 and 100 µW with a temperature difference of 5K from its generator comprising of over 5000 thermocouples[83]. It uses a simple thermoelectric setup where both coupling plates are thermally connected via a heat source and sink. Heat then flows through the thermopile to generate an output, which is stored in a rechargeable battery or super capacitor. Depending on the situation, the storage device needs to be chosen on the basis of how frequent energy will be converted to allow for continuous running of the implantable device. Incorporating a Low Power Management system is therefore essential for the continuous running of the device. Reviewed by Vullers et al. the planar design is criticised for although planar has the advantage of large height of millimeters whilst the width can be as small as a few micrometers creating a large aspect ratio, the power leakages through the thermal resistance due to the Kapton and the maintenance of the temperature gradient between the hot and cold plates[5].

Nextreme have developed a second device, eTEG[84], the thermopiles consisting of superlattices of BiTe/SbTe, the dimension of which are 1.6mmx3.2mm. Under a temperature difference of 5K the device will generate a power of 450 µW[5].

The most important concepts to remember in the designing of a thermoelectric device are that a high thermal resistance is necessary to maintain a temperature gradient across a thermocouple and that the thermal resistance of the thermal heat coupling between the heat source, heat sink and the generator is to be kept to a minimum in order to maintain a maximum temperature difference. Incorporating these concepts into current investigations will no doubt prove useful in the field of implantable batteries.

1.2.4. Air Flow

Within a human body, respiration is an excellent potential source of energy as muscles are in perpetual motion and the air currents through the oesophagus and lungs. Current research utilises respiratory harvesters to convert electrical energy using aerodynamic principles including flutter motion sensors and piezoelectric methods[25]. This technology is more of a hybrid combination used to harvest energy from low speed winds[21]. An adult human will respire at a rate of 12 breaths per minute (0.2Hz), have a tidal volume is approximately 500-600cm^3 [6] and exhibit a wind speed of approximately 2m/s[85]. Assuming Fei et al's calculation is correct, then their device, if miniaturised, could produce a power output >4mW however Fei et al states that for a wind speed of 2m/s the device has a power output of only 2.5mW. This is still higher than that of most MEMS technological advanced devices and only used one type of harvesting method.

1.2.4.1. Methods of Air Flow Harvesting

Early air flow energy harvesters were fabricated upon different concepts including the axial-flux concept. Microturbines studied in depth at MIT, however, have been produced that feature a fully integrated wafer-stack combination of compressor, burner, turbine and electricity generator is being developed[86]. Other groups, such as Holmes et al. at the Imperial College of London have combined an axial-flow turbine (a turbine that can operate at very low pressure gradients) with an axial-flux electromagnetic generator which uses axial gas flows to drive a polymer rotor producing an output voltage in the planar coils[87]. Unfortunately, axial-flow turbines are difficult to fabricate with conventional techniques due to the curved rotor blades and guide vanes, therefore modified conventional means were necessary increasing the overall manufacturing cost[88]. Using excimer laser micromachining coupled with UV lithography solved this particular problem.

The power generated was in the form of milliWatts which is adequate for applications in remote sensing, but in order to generate higher outputs small modifications such as reducing the rotor-stator gap, increasing the number of coil turns at the stators or by increasing the power or number of magnets could be implemented. However, the device could produce around 1.1mW of power under a flow rate of 35 litres per min and a rotor speed of 30,000rpm which is a greater volume than the average human respires per min. Holmes et al. concluded by stating that if the device was optimised, the increase in output would be significant and the device would only be limited by the maximum operating speed of the ball bearings. Once these changes were made the device could be scaled down but at 0.5cm^3 it is already adequate for MEMS incorporation, but not as an alternative IMD fuel source.

1.2.4.1.1. Flutter Concept

Shawn Frayne and Co. fabricated the Windbelt™, a generator powered by wind energy, converted to mechanical and then to electrical, based on the aero-elastic flutter effect[89,90]. See fig 11 for the basic design concept in block diagram format. Using a membrane or string exposed to airflow will cause the aero-elastic material to oscillate at a flow-coupled resonant frequency which will then convert electromagnetic energy into electrical[90] as shown in figure 12. They are currently looking to market this as an alternative source of power to third world countries because this device claims to be 30 times more efficient than current commercially available wind turbines and is considerably cheaper in that the fabricating cost is approximately $10. However there are disadvantages: the magnets are fixed directly to the belt which causes a few problems in practice as the vibrating belt may collide with the coils at higher resonating amplitudes thereby disturbing the magnets from their fixed location. This means that the magnets must be systematically tested to ensure their correct placement. As far as medical implantation is concerned the technology still needs modifications to enhance the energy conversion efficiency. However, if this technology was down scaled and implanted as oesophageal diaphragm, which converted and stored energy it could be implanted with a thoracic IMD.

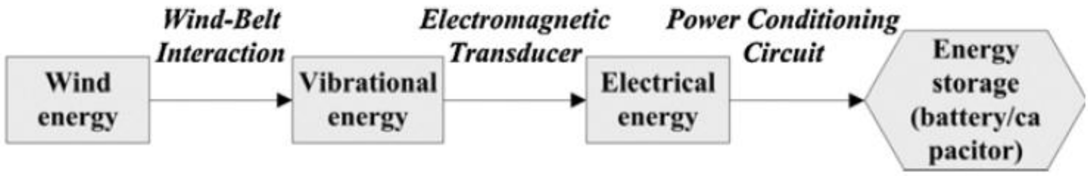

Figure 11 – Basic block diagram of Windbelt technology adapted from Frayne et al[89]. This is a kinetic energy – electromagnetic – electrical harvester.

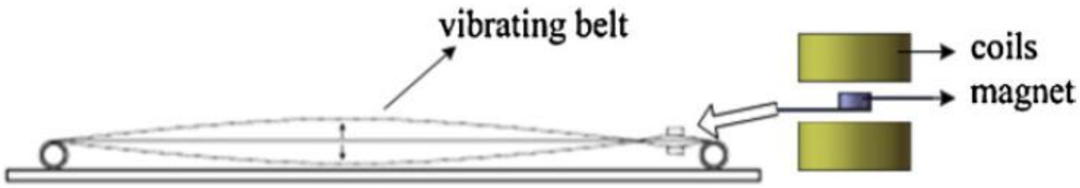

Figure 12 - Frayne et al's Windbelt design[62][89] which consisted of an aero-elastic material stretched between two points and connected in series to an electromagnet. The electromagnet was part of a MEMS electromagnetic generator which then stored the converted electrical energy.

Following this novel technology, other groups sought to improve on the original design shown in figures 13. Kim et al (2009)[90] and Fei et al (2011)[62] are just a couple of research groups investigating this area however there are many more.

Kim et al. proposed to verify Frayne's work at a much smaller scale than the original Windbelt design[90]. To do this they fabricated their own Windbelt and used a Helmholtz-resonator-based energy scavenger to compare the experimental results. Their proposed Windbelt was composed of polymer resonator embedded with permanent magnets, polymer housing and copper coils, whilst the Helmholtz-resonator is a simple gas-filled chamber with an open neck where spring and mass fluidic oscillation occurs. This creates a measurable acoustic wave which can be utilised for power generation post airflow via an electromagnetic set up. This device easily matched the mechanical and the Helmholtz resonant frequencies which are critical to mechanically driven MEMS, as stated previously: the lower the resonant frequency the higher the energy density stored. The results showed that the Windbelt-based energy harvester the voltage output is proportional to wind speed. The Helmholtz generator demonstrated this relationship also with an output of 4mV with a wind velocity of 5m/s[6], however at an invariant frequency, possibly due to the use of acoustic amplification before processing. This work proved Frayne's concept in that a large output could be gained from low wind speeds using the Windbelt[21].

Later, Fei et al. proposed a wind-belt specifically designed to convert low-speed wind into mechanical vibration (flutter) using an electromagnetic resonant device, with two coils within supports with a permanent magnet embedded inside a movable bolt. The device also has a power management circuit which stores energy in a super capacitor and supports a power output see figure 14[62]. Using the below equation, it was possible to calculate the power density proportional to wind speed.

$P = \frac{1}{2}\rho U^3$ Where U is the wind speed, ρ is the air density and P is the power density. This clearly shows that the Windbelt technology and subsequent potential respiratory energy harvesting technologies will demonstrate a power density proportional to the wind speed cubed. Already the problem is apparent: the wind speed (human respiration is approximately 2m/s) is a limiting factor in this technology for implant energy harvesting.

Fei et al. compared their technology with an existing product by Frayne and Co. which uses an spring-mass resonating (elastic) design as shown below[62,89].

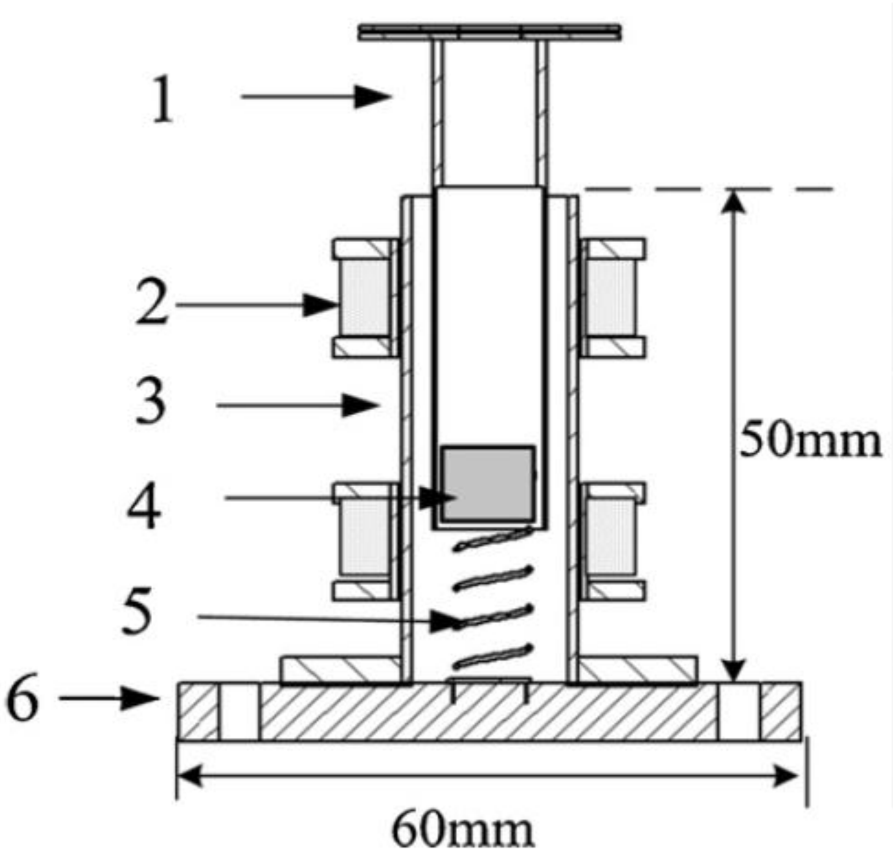

Figure 13 - Fei et al. proposed circuit. (1) bolt; (2) coils; (3) housing; (4) magnet; (5) spring; (6) base[62]. Not so different from Kim et al's technology however the power output is much greater due to the mobile magnet.

Following analysis, the design would exhibit an input frequency similar to the natural frequency a highly desirable MEMS feature to ensure the natural frequency equals the environment excitation frequencies in order to ensure stronger couplings and highest output. For electromagnetic equations, see section 3.2.2. The ambient mechanical-electromagnetic energy from the environment is only converted by about 1% which is normally too low to support an electronic device. Therefore a power management system was used to store the power in super capacitors or rechargeable batteries which allow for a greater output on a needed basis. Fei et al used a Seiko S-882Z charge pump to increase the input power enough to start-up the voltage and current for a DC-DC converter. This design enables very weak vibrations to be converted into usable electrical energy. Peak output is approximately 7mW with a wind speed of 3m/s. This demonstrates a lower rate of energy conversion efficiency when compared with other mechanical technologies, possibly due the use of copper coils, leakage of the super capacitor etc.

Following on from Windbelt technology, Sun et al demonstrated use of piezoelectric microbelts fabricated from thin-film PVDF which vibrated during low-wind speed at their resonant oscillation[90]; this lead to the conclusion that with the appropriate modifications such as power efficiency and amplification, it would be possible to harvest energy from respiratory flow within the body to power other implantable medical devices.

Despite the advances of mechanical to electromagnetic airflow energy harvesting microsystems, a sudden surge of piezoelectric-based airflow technologies is being developed. These technologies tend to utilise the vibration-based energy harvesting which is based in the same technology mentioned previously in this section. An aerodynamic material is induced to flutter via air currents, the fluttering effect causes the piezoelectric connections at the sides of the material to deform and subsequently a piezoelectric generator will store the electrical energy[156], as explained in section 3.2.1. Matova et al have used a Helmholtz resonator in conjunction with a piezoelectric harvester to create a generator with a power output of 42.2 μW[156]. Although this value is considerably less than the electromagnetic-based airflow energy harvesters, the technological advances in fabrication and design modifications mentioned in section 3.1.5. to currently commercialised piezoelectric technology could significantly increase the power output of such a device. Such technology could be used as an oesophageal implant to power various IMDs remotely from within the body.

1.3. Biofuels

So-called biofuel sources are abundant within the human body and are currently under investigation both as finite and continuous fuel cells. Fuel cells as an umbrella term include abiotic fuel cells, microbial and enzymatic. Microbial fuel cells, by utilising micro-biofuel energy harvesters, can generate electrical energy from chemical reactions instigated by microbial action. Abiotic fuel cells utilise acid and alkaline reactions to produce a power output and enzymatic fuel cells employ enzymatic activity to metabolise a given substrate in order to produce reaction products, which can then be used to create a power output.

Many researchers have studied biofuels, the first of which was M.C. Potter, a professor at Durham University, who investigated the decomposition of plant material and reported the biofuel phenomenon in 1911 using *E. coli* microbes[157].

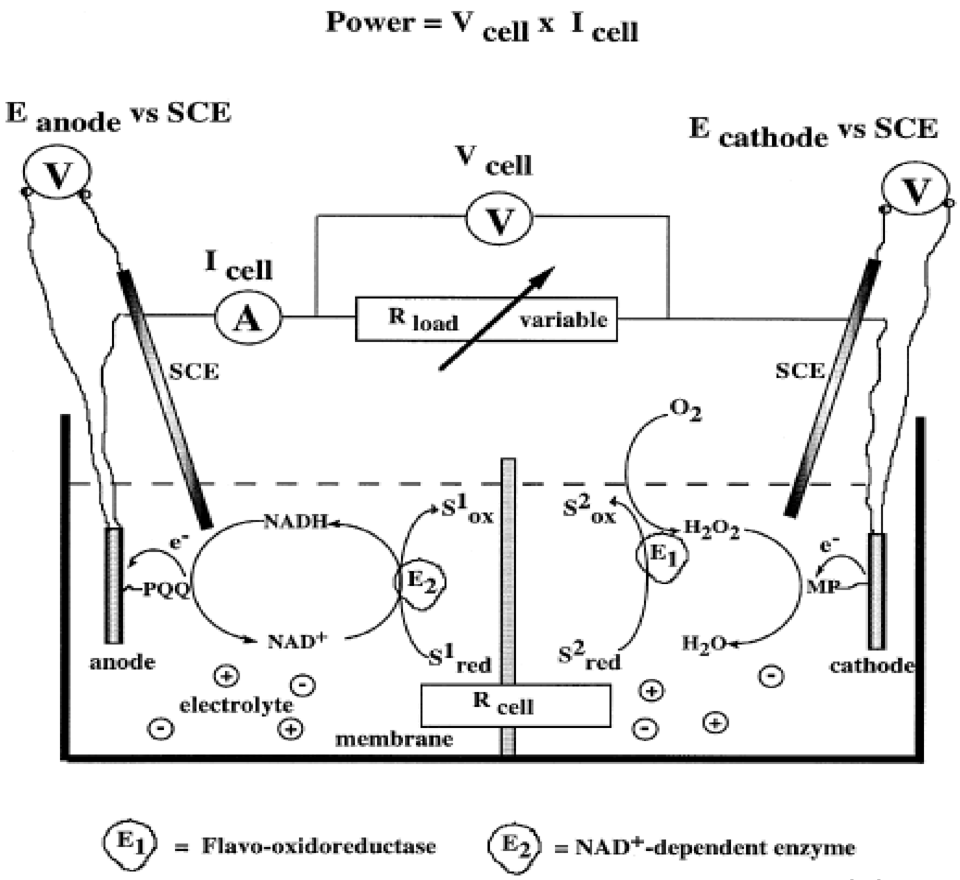

Figure 14 – Glucose biofuel cell described by Willner et al[92]. Across the membrane in the middle the two enzyme catalysts (E1 and E2) catalyse different substrates both of which are produced from reactions at the cathode and the anode. The electrical potential across the membrane causes an electrical current to flow.

The second, was B. Cohen who used microbial half-fuel cells to produce a voltage output of over 35 V[158]. From these researchers the foundations for biofuel technology was built.

The promising area of biofuel research is in enzymatic biofuel cells, an example of which is shown in figure 14. Figure shows the location of the electrodes in relation to the diffusion layer in the middle, across which electrons from the electro-oxidation of glucose flow from the anode to the cathode via an external load circuit, the driving force being the difference across the electrochemical gradient across the membrane. As such, there are a great variety of reactions to choose from; however within the human body the most plentiful biofuel supply is glucose. Though physically unproven, it should be possible to extract all 24 electrons from one molecule of glucose[28]. Thus far, in vitro experiments in replicated physiological conditions have demonstrated that tissue implanted with abiotic catalysed glucose cells deliver 18.6μWcm^{-2} for greater than 100 days[29]. In addition, in vivo operations with flow-through type fuel cells with a hydrophobic cathode membrane, intended for blood stream, demonstrated successful results with up to 50μWcm^{-2}[30].

3.3.1. Microbial Fuel Cells

Microbial fuel cells (MFCs) have the most applications in gut-related IMD technology as the microorganisms could be utilised directly for their electron transfer abilities, namely across a working cytochrome. Although some researchers believe that urine fuel cells will be able to power IMDs, the maximum output of which is 4.5mW[93], the most applications are within the intestines due to the higher microbe population density. In addition, the undigested cellulose found in the gut could be a potential fuel source in later research. Thirdly, the low oxygen pressure inside the large intestine does not disrupt the generation of electrical energy and finally the continuous flow system through the intestine would ensure a plentiful supply of fuel. Du et al 2010 found that microbes extracted from faeces solution could be fabricated into an MFC with a maximum output power of 240mWm^{-2}[94]. Following on from Du et al, Han et al implanted a transverse MFC into in vitro replica conditions. This resulted in a maximum power density of 73.3mWm^{-2} with a hypothesised 7-10mW generation following an increase in intestinal surface area. Subsequently, Dong et al proposed a membrane-less large intestine IMD[95]. However this study was unsuccessful due to a significant drop in pH and the MFC configuration needs to be redesigned with particular attention to the biocompatibility of the electrode material. However, the technology looks promising in so far as specific thoracic IMD technology is concerned.

3.3.2. Enzymatic Cells

Enzymatic fuel cells (EFCs) can be full or hybrid cells. Full EFCs have purified enzyme catalysts at both the anode and the cathode while hybrid-EFCs have only one.

Three types of redox enzymes are used: enzymes with NADH or NADPH redox centres weakly connected to the protein (eg. glucose dehydrogenase), those which have the redox centre near the protein shell (eg peroxidase) and those strongly bound with the protein of the enzyme (eg glucose oxidase).

$C_6H_{12}O_6 + 6H_2O \rightarrow 6CO_2 + 24H^+ + 24e^-$ Example anode reaction

$24H^+ + 24e^- + 6O_2 \rightarrow 12H_2O$ Example cathode reaction

Glucose fuel cells can be divided into two categories: abiotically catalysed (non-biological catalysts such as metals) and enzymatically catalysed (enzymes such as glucose oxidase)[96].

3.3.2.1. Glucose-fueled cells

The first glucose fuel cells were implanted in canine subjects but only showed a 2 μWcm^{-2} for a period up to 150 days. Despite the decreased power output, there did not appear to be any adverse effects on the animals. Unfortunately these studies failed to describe the materials and fabrication processes of these devices. The performance of this type of cell relies on several factors though: the location of the electrodes and the thickness of the diffusion layer determine the power output. In addition to these variables, these cells employ enzymes such as deactivated glucose oxidase and laccase (ie their precursors)[28], unlike the microbial fuel cells which rely entirely upon an electroactive microorganism to convert chemical to electrical energy. It is unlikely that this particular type of micro-biofuel energy harvester will solve the IMD energy harvesting challenge however, due to the highly infectious nature of the micro-organisms. This technology contrasts with abiotically catalysed fuel cells which use noble metals or activated carbon (non-biological) to carry out the energy conversion. These do not carry the same disadvantages as biologically catalysed fuel cells especially in regards to sterilizability, long-term stability and biocompatibility. Unfortunately since 1972 and the advancement in the use of the lithium iodine battery as a power source for pacemakers, abiotic fuel sources have not developed further[28]. Currently experimental data from new research into self-sufficient biofuel-dependent implants has revived interest in stable long-term IMDs containing glucose fuel sources, using abiotic catalysts as a road map. It appears that a glucose-fuelled generator is capable of generating 26µW/cm^2 and as such is under continuous development. Unfortunately, these generators rely entirely upon the catalytic ability of enzymes which have limited stability and so the lifespan of such fuel sources are very low[28]. As biofuel is a renewable energy source and it is biocompatible, micro-biofuel energy harvester technological improvements are highly sought after[6]. In the 1780s, Galvani realised that biological pathways within the body can be simplified to electrical current transduction pathways when he saw a frog's leg twitch after applying a current[4]. Ever since then, research into the relationship between the body and electricity has advanced to understand that bodily mechanisms can be manipulated through the application of current eg. Heart defibrillators. Fuel cells convert chemical reactions into electricity through the oxidisation of a fuel source and a reduction of an oxidant at the cathode using noble metal catalysts. Biofuel cells (BFCs) are fuel cells which harness the biological catalytic reactions, see figure 17 for example, that occur at low temperature to generate electricity from electrolysis[2].

Yahiro et al reported the earliest glucose-based biofuel cell in 1964, which operated at neutral pH [97]. In the 1980s, biofuel cells mainly focused on glucose oxidation reactions where the enzymes and electrodes were separate entities within the fuel cell. This system produced a low power output of 8µW and it was quickly shown to obsolete in comparison to the lithium iodide cells, both in longevity and power output. Research has shown that such a system can be improved with the modification of electrodes so that electron transport occurs directly between enzymes and electrodes. Willner et al. fabricated one of the first reported biofuel cells with modified electrodes in 1998. A membrane biofuel cell with a pyrroloquinoline quinone, a cofactor of glucose-oxidising enzymes, monolayer-functionalised gold anode and a microperoxidase-11 modified gold as the cathode[92]. This eliminated the need for oxygen reactions at either electrodes and thus rendered the membrane useless. Consequently, in 1999 Katz et al. reported a membrane-less biofuel cell with modified electrodes[98]. However with such a small power output and power consumption it was not prudent to miniaturise such a device.

Following from Katz et al, Jimbo et al used gastric fluid as an electrolyte with platinum and zinc electrodes to create a biofuel cell that had a maximum power output of 1.0mW, suggesting that this cell could, theoretically, be applicable in the case of swallow able medical devices for treatment and diagnostic purposes[99].

Subsequent research has shown that enzymes entrapped in a gel matrix covering the electrodes or enzymes adsorbed into a metal complex on the electrode surface, demonstrate increased electrical conductance due to direct electron transport. It has been suggested that this technology could be incorporated to increase the energy efficiency of these cells.

3.3.2.2. Current EFCs

Relatively recently, Mano et al developed a glucose fuel cell which demonstrated a power density of 280μWcm^{-2} at low glucose concentrations[110] by using glucose oxidase from *Penicillium pinophilum* and not from the conventionally used *Aspergillus niger*[100].

Recent research has sought to incorporate different areas of electrochemistry into one fuel cell. For example, Zhang et al have fabricated a hybrid system of carbon nanotubes (known for their ability to increase the conductivity of an enzyme membrane)[101] with the biocompatible dendrimer PAMAM (polyamidoamine)[102] encapsulating platinum NPs[103] (their unique quantum tunnelling effect greatly increasing electron conductivity)[104] in order to increase the power output of a glucose oxidase fuel cell – termed a $(GOx/Pt\text{-}DENS)_3/CNTs$ modification[105]. The subsequent results from this 2012 study showed a 17µW output.

Cinquin et al have followed on from Mano et al's work and have created a biofuel cell which is powered by both glucose and urea via a quinhydrone compound[106]. This cell produced a maximum power output of 24.4μWmL^{-1} within a rat subject, proving the viability of pH-based biofuel cells as suitable batteries for IMDs.

The advantages of biofuel cells are as follows: the fuel sources are naturally found in the body such as glucose, NADH etc and could therefore be theoretically replaced continuously by the body. Secondly the reactions themselves are fairly environmentally inert: they operate at ambient temperature, pH and pressure. Thirdly they are biocompatible with the human body and therefore suitable replacements for current finite batteries found in IMDs. However, the disadvantages are that first the biofuel cells of today are still only capable of operating for a short period and this technology has yet to overcome the problem of irreparable bio-fouling within the device.

1.3.3. BioMEMS

MEMS technology can also be used in biosensory systems, analytical devices used to detect biological or chemical changes within the body at a sensitive level in real-time[107]. These sensory mechanisms could be incorporated into the original MEMS technology to enhance the sensitivity or form additional energy harvesting methods to an original generator. These devices have three sensory mechanisms: mechanical, electrical and optical as shown in figure 18[91].

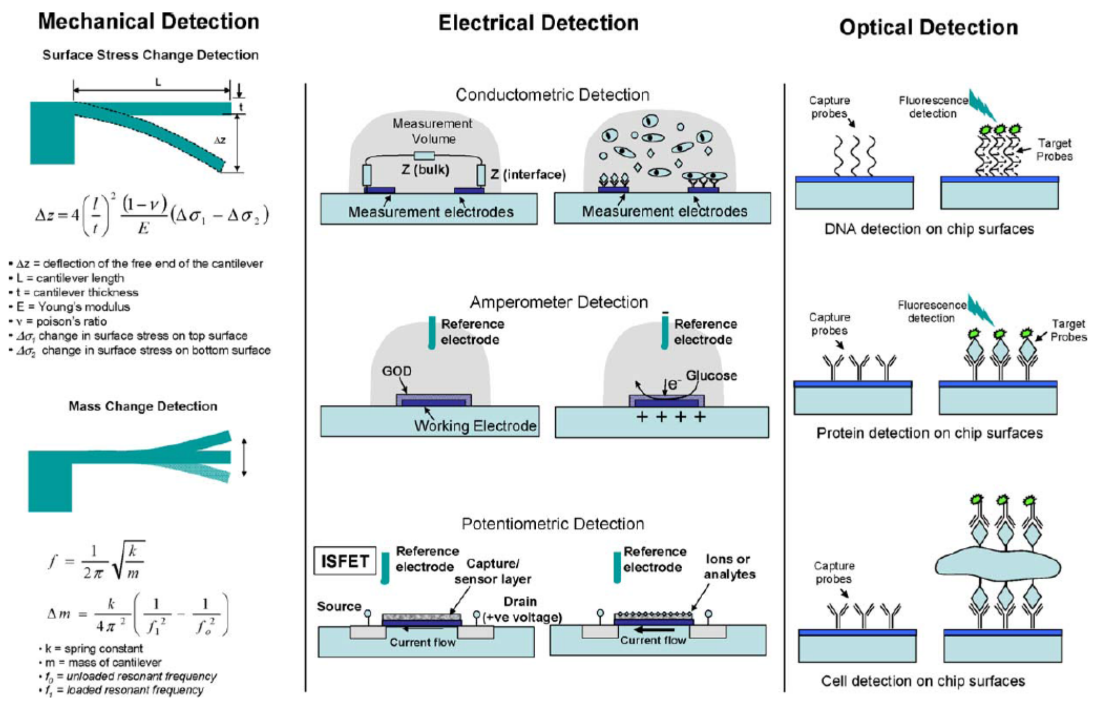

Figure 15 - BioMEMS detection methods: mechanical, electrical and optical adapted from BASHIR et al[18]. Mechanical detection relies on the change in surface stress or a change in mass. Electrical detection relies on three different methods: conductometric (the change in charge across a surface which impairs or assists conductance of a sensor), amperometric (the change in surface charge due to reactants which affect the overall current across a working electrode) and potentiometric (the ability to detect a difference in potential across a surface due to additional chemicals). Optical detection relies on visually stimulating antibodies or proteins which are sensed using spectral methods.

1.3.3.1. Mechanical

Mechanical detection for biochemical compounds or reactions have been more recently utilised through the use of micro-/nano-scale cantilever sensors on lab-on-chip devices. Cantilevers have two modes: stress sensing and mass sensing. In the case of biochemical detection, stress sensing involves the biochemical reaction taking place at one end of the cantilever, where the free energy change due to the reaction causes a change in surface stress and thus a bend in the cantilever. Due to this phenomenon, label-free detection can be performed and the bend in the cantilever can be sensed using optical methods (using a laser to reflect the cantilever surface) or electrical means (embedding a piezoelectric resistor at the fixed edge of the cantilever). Alternatively, the cantilever could be mass sensing which involves the cantilever being mechanically stressed so that it vibrates at a resonant frequency but then compared to when a biochemical unit is captured. The resonant frequency is measured using electrical or optical means as with stress sensing. The mass difference is proportional to the resonant frequency shift[18]. Using either mass difference or stress sensing techniques piezoelectric sensor technology could be incorporated to run off the original mechanical movement. So this technology would not only sense mechanical occurrences but also the device would store energy via the piezoelectric effect to power an IMD, for instance a cardiovascular device such as a defibrillator.

1.3.3.2. Electrical

Electrochemical detection of BioMEMS can be split into three categories: amperometric, potentiometric and conductometric. Amperometric biosensors can sense the electric current which is associated with the electrons involved in the redox process. Potentiometric biosensors can measure a change in potential at the electrodes due to changes in ionic concentration, similar to ion-sensitive field-effect transistor (ISFET) analysis. Conductometric biosensors however, measure the change in conductance associated with overall ionic medium changes between two electrodes. This particular biosensor is more practical in its use as it can sense more transient reactions such as those between DNA molecules, the import/export of metabolic products as well as the semi-permanent reactions such as antigen-antibody reactions. Conductance sensors also can provide information about the presence of toxins, nucleic acids as well as the ionic concentration of glucose and urea. There is currently on-going research into the coupling of these devices with enzymes to increase the specificity of the overall design. Recent research using modified conductance sensors has shown that electrically hybridised DNA demonstrated that the binding of oligonucleotides embedded with gold nanoparticles caused a subsequent deposition of silver on the gold nanoparticles which allowed the conductance sensor to readily measure the deposition. Using cell-based biosensors are a very attractive area of research presently because they appear to be the ultimate in biochemical specificity, inherently equipped with highly selective ion channels, receptors and enzymes. Cellular signals may be sensed following the transduction pathway in order to measure the transmembrane and cellular potentials, changes in impedance, metabolic activity, genetic reporter molecules and optically active fluorescence or luminescence[108]. It is hypothesised that this technology could be incorporated into implantable biosensors such as those used in diabetics. Ideally these would run off an abundant substrate, such as glucose, and sense the predominance of this molecule in the circulatory system.

1.3.3.3. Optical

Optical detection is the most prevalent in biochemistry analysis techniques. These are mainly based on the naturally occurring phenomena of fluorescence or chemiluminescence using commercially available synthetic genetic or protein elements, such as green fluorescent protein (GFP) principally found in the jellyfish *Aequorea victoria* and the sea pansy *Renilla reniformis*. Fluorescence detection techniques are based on fluorescent markers which emit light at certain wavelengths and the increase or decrease in the signal using fluorescent resonance energy transfer (FRET) analysis will indicate a binding or synthesis reaction. The biological units must first be attached to the chip surface in order to efficiently capture the target species. Techniques such as these frequently use antibodies in an enzyme-linked immunosorbant assay (ELISA) detection method. Chemiluminescence, as a phenomenon, is the generation of light by the release of free energy resulting from a chemical reaction, for example using synthetic compounds and highly oxidised species. Point-of-care diagnostic researchers have made bioluminescent-based devices a highly popular area of research. Unfortunately, optical detection devices are often bulky which is where current research into BioMEMS will play a significant part in the advancement of these techniques within clinical practice and continuous patient monitoring[18]. However, if they were scaled down, these technologies may discover a niche within IMD technology such as in continuous monitoring devices. Ideally these devices would run off their sensory molecules.

Continuous and portable monitoring is becoming increasingly popular within clinical practice, where highly sensitive devices that use integrated technology will allow for the early detection of relevant proteins directly from urea or blood, such as cancer markers which will have a huge impact on the population[107].

The main goal of biosensor research has been to incorporate BioMEMS and biofuel systems into implantable drug delivery systems such as an implantable synthetic pancreas which would ideally run perpetually off of an abundant source such as glucose. Currently technology is focused on powering recreational media devices, for example Sony has developed a biofuel device which charges a Walkman (2007)[109]. This device senses the glucose oxidation reaction and harvests electrical energy from this reaction, however in order to do this it uses electrical sensing BioMEMS and a finite biofuel source. Advancements are being made in this potentially highly efficient area of research, however future modifications to the technology must be made in order for it to function as a cohesive circuit with other MEMS technologies.

However in utilising biofuel cells, without other technologies, for IMD co-implantation there is still a significant amount of modification is needed to scale-up the energy density available and to increase the energy harvesting efficiency of the device.

1.4. Problems with Micro-generator Technology in Implantable Applications

Micro-generator research experienced expected set-backs during in-depth investigation including net power output, frequency tuning and bandwidth, biocompatibility of devices and environmental setbacks when attempting to prepare this technology for implantation in humans. Each of these problems was prompted by different factors.

The power output of the micro-generator experienced problems such as parasitic damping, which reduced the overall power output. They also experienced charge leakage, a phenomenon found particularly in electrostatic generators which will leak charge between the moving plates during a generation cycle due to the infinite impedance between them. This then reduced the Coulomb force and therefore the power generated. In addition, the operational overhead in which power is consumed by the electronic system within the actual device was greater than the power supplied by the generator and finally the devices experienced electrical losses from conduction[23].

As far as the tuning frequency and bandwidth of the generator is concerned: in general the maximum power output can only be achieved if the frequency of the measurable quantity (eg vibration) is approximately the same as the natural frequency of the energy harvester. Therefore different materials and different fabrication techniques need to be analysed in order to gain the optimum resonance frequency (ie an RF value that is low and close to the natural frequency).

The micro-generators must also be compatible with the *in vivo* environment, preferably all materials within the device would be biocompatible however at a minimum the coating surrounding the primary material must be biocompatible in order to prevent full and immediate rejection by the body[31]. Engineers and scientists use a measure of biocompatibility known as the foreign body giant cell (FBGC) density index when testing a new material for a device[32]. Ideally this value would be low as possible for the entire device, including its components.

Environmental setbacks like stress exerted on the device, especially one that harvests mechanical energy, can have detrimental effects on the energy conversion efficiency. This problem is predominant in piezoelectric energy harvesters.

1.5. Summary

MEMS technologies have many applications within the field of possible energy harvesting technologies to be utilised in medical implants. There are many different possible energy sources including physical and biological sources.

Physical sources include mechanical sources harvested by various means such as piezoelectric harvesters which use piezoelectric materials which deform under stress and create a viable electric current from the alignment of the dipoles at the atomic level. Other means of harvesting mechanical energy include using electromagnetism to harvest, using Faraday's principle, the mechanical motion of charged particles within an uncharged magnetic field in the presence of conductors. Electromagnetism is also a natural occurring phenomenon which can be harvested within the human body, specifically around the localisation of nerve centres. In addition to these harvesting techniques, they can be combined to harvest more complex phenomenon such as airflow during respiration. Another physical source of energy is in thermal energy harvested using thermal gradients and the Seebeck effect to convert and store electrical energy.

Biological sources include the use of biofuel cells in energy harvesting both from abundant chemicals found in the human body. There are three types of biofuel cells: enzymatic, microbial and abiotic. Enzymatic fuel cells use the action of enzymes to metabolise substrates to produce products used to produce an electrical potential and hence an electrical output. Microbial fuel cells utilise the electron transport chain of microbial cytochromes to create an electrical potential upon the metabolism of a substrate. Abiotic fuel cells utilise acid/alkaline reactions to create an electrical potential and hence electrical energy.

On balance, piezoelectric energy harvesters appear to be the most popular and the most advanced technology poised for commercialisation into the field of medical implants. It also appears the technology with the most applications and versatile amalgams as far as structure and imbedding options are considered. However, it appears that any successful technology produced from this field of research will be a hybrid of several technologies, such as a BioMEMS sensor combined with a piezoelectric micro-generator connected to a device which will produce an effect. For example, if a glucose sensor was used (BioMEMS component) and it produced a mechanical output, the piezoelectric generator could create the electrical energy needed to be stored for use by a drug-delivery implant (perhaps a device that controlled insulin release); creating a very neat negative-feedback system.

Chapter 4: Discussion

4.1. Current Potential Applications

In researching energy harvesting generators for implantable applications there are many different possible applications of for use in combination or separately depending on the location of the implant. Physical sources of energy generation may be optimally placed in muscle-based implants, such as in the respiratory or cardiovascular systems, and biofuel sources may be more aptly placed in areas of metabolic importance, such as the gut or the circulatory system. Throughout the IMD spectrum there are various devices aimed at improving patient quality of life all of which are engineered to the highest standard and exhibit functional characteristics tailored to their purpose. Current popular IMDs are found in the fields of cardiovascular repair, neural stimulation, autoimmune drug-combatants and active implantable monitoring devices. Each of these technologies is heading towards becoming fully implantable devices, requiring minimum maintenance throughout the patient's lifetime.

4.1.1. Cardiovascular Devices

The first pacemaker was implanted in Buffalo, New York, USA designed by Greatbatch in 1960[111]. Powered by an original mercury zinc battery with an output voltage of 1.35V and transcutaneous leads, the first pacemaker extended a 77 year-old patient's life by 18 months[112]. By 1980 the original pacemaker design had undergone many modifications and advancements in the field tending to higher energy dense batteries that were rechargeable, or self-sustaining, and miniaturizing the device overall. In the case of implantable cardio-defibrillators, specifically, present state-of-the-art systems are required to demonstrate: a single endocardial lead system, have a small volume of 70cm^3, a bradycardia pacing aid, be able to give non-invasive electrical stimulation, possess the ability to deliver rate-adaptive therapy and be able to create a tiered therapy following miss-step. In addition, cardio-defibrillators must exhibit an optimized biphasic waveform, increase the patient's life by an average of >6 years and be able to accurately record tachycardia events[113,114].

4.1.1.1. Defibrillators

Implantable cardioverter-defibrillators (ICDs) are capable of the detection and defibrillation of tachyarrhythmatic hearts in a life-threatening situation. The eventual self-powering of these devices would enable a more durable implant with lower maintenance or a device with an additional emergency back-up power supply. This approach would be more convenient for the patient as overall the device would require fewer to no visits to hospital visits presently required to replace finite batteries. This would reduce the overall clinical cost of the device in terms of clinician's time.

4.1.1.2. Stimulators

Pacemakers or devices responsible for cardiac resynchronisation (CRT) are also heading towards the goal full implantability. The novel technology would exhibit similar benefits to those associated with self-powered ICDs.

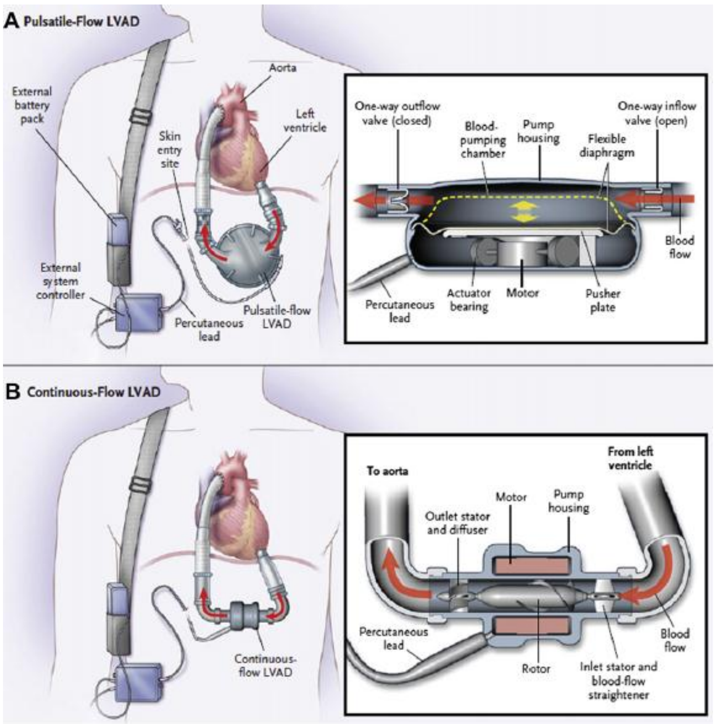

Figure 16 - VADs pulsatile- and continuous-flow[115,116]. Pulsatile-flow VADs use a one-way outflow valve to provide a stop-start circulatory flow, while continuous-flow VADs use a stator diffuser to provide a nonstop circulatory flow.

4.1.1.2.1. VADs

Ventricular assist devices (VADs) are utilised to propel blood through the circulatory system following the failure of one of the cardiac ventricles. Left-VADs in particular are important to end-stage heart failure and are used as a destination therapy, a bridge to transplantation, a bridge to recovery or a bridge to decision device in those patients suffering from acute cardiovascular failure. There are two types of VADs: pulsatile flow and continuous flow, as shown in figure 16[115,116]. Each demonstrates the use of percutaneous leads to an external system control and battery pack attached to the patient. Current practice indicates that the leads are encouraged to move between the implant and the battery to an extent through the use of a clip, however percutaneous leads are a present and severe source of sepsis in patients with active implants.

4.1.2. Nerve Stimulators

Nerve stimulators are becoming a widespread area of engineering research, especially stimulators which will help combat predominant neural diseases, such as epilepsy. Epileptic fit sensors are an implantable novel way of warning a patient about the near-onset of a fit. One such sensor, developed by NeuroVista, Melbourne, Australia in 2010 and lead by Cook et al have implanted this device within a patient resistant to epileptic drugs[159]. The sensor within the implant uses EEG signal monitoring to detect the epileptic-pattern of electrical signals within the brain. The sensor then triggers a response to a second implant in the chest which will remotely alert a third handheld device. This ensures the patients have time to make themselves safe before the onset of a fit. However, with only an estimated 65% prediction accuracy there are still improvements to be made within the technology.

Figure 17 – The Nevro Corp. HF10 ™ Device from left to right: patient controller, charger and implantable pulse generator[113]. Combined, this SCS device has been marketed effectively as a chronic pain relief therapy.

In addition to epileptic patients, chronic pain sufferers have seen an increase in marketed spinal cord stimulation (SCS) devices. Chronic pain, as a widespread and costly condition for employers, has seen an increase in opioid-related deaths even exceeding those caused by heroin and cocaine combined. As such there is very little recommended pharmaceutical help commercialised for these patients. Consequently, SCS implants have become a popular area of research and through advances now deliver charges in a range of 50-60kHz which is lower than most deep-brain stimulants[113]. A new system has been developed by Nevro Corp. Menlo Park, California, USA which delivers a small charge (up to 10kHz) as seen in figure17[113]. This system is currently being marketed in the Europe and Australia with patients seeing a remarkable increase in quality of life. Again, however, this device requires the active powering of batteries external to the body and linked to the implant via percutaneous leads.

4.1.3. Drug Delivery Devices

These devices can be classified into three categories: biodegradable and non-biodegradable, implantable pump systems and atypical implantable systems[117]. In this review only the non-biodegradable pump system will be discussed as biodegradable systems do not require a fuel source.

4.1.3.1. Drug Delivery Pumps

Piezoelectric applications have extended to implantable drug-delivery devices which can deliver a dosage without transcutaneous injection. Advancements in this field will improve the quality of life to those with chronic conditions such as diabetes where injections form a part of daily life. Implantable pumps for clinical use either rely on a fluorocarbon propellant or a battery operated stepper motor (available from Medtronic, Inc. and Codman and Shurtleff)[117]. The former, allows for a continuous flow of drug into the patient's system regardless of the patient's own needs. The latter, is controlled by a programmed system that releases the drug on a needed basis. These second systems are very popular currently due to their comparative longevity of 4-7 years. Regretfully, both of these types can only be refilled by percutaneous injection given by a medical practitioner. Those with chronic conditions requiring regular injections are heavily invested in this technology becoming a reality. Those companies ahead of the game have developed implants for the blood-glucose responsive insulin pumps for the continuous treatment of diabetics[118]. The need for an implantable solution to diabetes has become very popular in recent years with advancements in regenerative medicine as demonstrated in Hiscox et al where an Islet of Langerhans transplant was carried out to treat Type 1 diabetes[160].

4.1.4. Active Monitoring Devices

Biochemical monitoring devices using BioMEMS are increasingly popular in implantable medical technology as point-of-care and continuous monitoring devices are the current trend in diagnostic medicine. Those with chronic conditions find this a very patient friendly option. As previously mentioned diabetics and epileptics will benefit greatly from developments in this area of medical diagnostics however patients less at risk will also benefit. Example of less at risk patients include those suffering from hypertension, others suffering from slow-healing wounds and those entering Accident & Emergency being tested with a diagnostic point-of-care device (eg MRSA).

4.1.5. Problems

Current devices fulfil a hitherto unmet need in patient care: constant aid in chronic conditions. However these devices are either powered by external sources that require percutaneous wiring or by internal finite sources that require maintenance and/or replacement several times within a patient's lifetime.

The main problem with implantable devices is the threat of infection and sepsis. Miller et al. reported that 14% of all patient-related infections implanted with VADs were thought to be infected through the percutaneous lead. In addition, 20% of those patients infected continued to develop sepsis[112]. Similarly, Loor et al reported an infection rate of approximately 50% in patients with Left-VADs implanted at the Washington University School of Medicine[112]. In short, 22% of all Left-VAD fitted patients reported infection and of that percentage the infection was three times more likely to have originated from the driveline[116]. Fully implantable devices however, such as contraceptive implants, also demonstrate a significant risk of infection due to bacterial adhesion to outer biofilm coatings used in manufacturing processes to make implantable devices more biocompatible[119]. To combat this, coatings have been fabricated with a direct antibacterial activity resulting in reduced bacterial infection rates across IMD implantation[120], but not eradicating the problem.

The second problem with current IMD technology is the need to replace finite fuel sources at the end of the service life. In lithium ion batteries this is between 5 and 10 years, which to a patient with an average lifespan of 70 years requires on average four or five minor surgical operations following IMD issue. Surgical operations not only put the patient's life at immediate risk but also increase the chance of infection with the number of surgeries.

4.2. Future Applications

From this investigative overview, physically-sourced MEMS-based technology seems to produce generators with the most potential for commercial application in IMD technology. As such, there has been great investment in MEMS-based energy harvesting across the spectrum of IMDs, specifically in micro-drug dosing systems[33] and cardiovascular IMDs.

Novel materials and fabrication techniques are a popular source of interest in today's commercial market, particularly in regards to nanotechnology: nanofibers, carbon nanotubes, nanoparticles embedding and electrically conducive polymers[28]. This technology has already been applied to other markets and can be found in biosensors and ordinary fuel cells. Nano-patterned catalytic technology could have a high potential efficiency when applied to the development of glucose/biofuel based energy harvesters, especially considering that the need for reactant separation would be rendered unnecessary and so engineers could be given a higher degree of freedom in the design of the device[28].

Research into future micro-generator applications in the field of IMDs are on-going and can now be considered feasible, however it is clear there are many different applications yet to be explored and realised. Key to achieving the promise of these technologies is the development of more suitable power sources that require little to no maintenance and do not threaten the patient's health further with hospital stays. In short, sources need to remove the need for percutaneous leads and demonstrate a perpetual ability to provide energy.

4.2.1. Implantable Medical Devices

There are many devices being developed for the current IMD market; only a few are mentioned covering cardiovascular, autoimmune and neural degenerative aids. Included are some possible applications of current technology in implantable devices for medical use and possible features micro-generators could improve upon.

4.2.1.1. Cardiovascular Applications

As far as cardiovascular devices are concerned, the future applications of this technology are certain. The viability of a fully-implantable self-charging pacemaker, such as the one shown below in figure 18, for example is looking promising and research into this branch is widely held. However, there are some issues with this technology, the main issues being the high safety standards required by the FDA and the overall durability of the IMDs. In general terms, a self-charging cardiovascular aid the heart would pump blood and the IMD would charge through a mechanical energy harvesting generator.

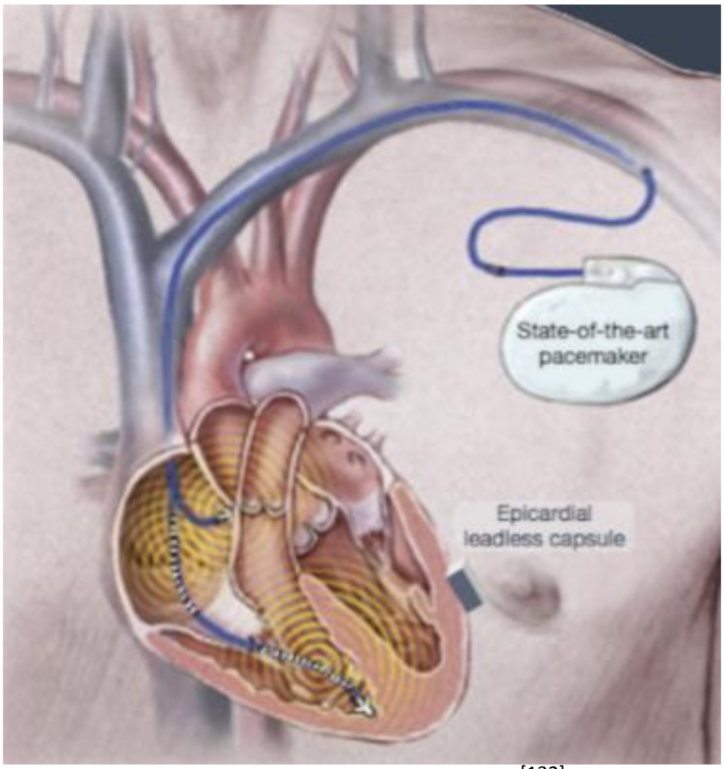

Figure 18 - fully implantable pacemaker[132]. Self-perpetuating and state-of-the-art.

For example, the cardiac muscle induces an electric current in a wire running from the heart via an electromagnetic generator which transforms mechanical energy to electrical. Unfortunately implanted pacemaker piezoelectric devices currently only charge up to 160µW of power from pulsating myocardium/pericardium[6][23]. In order to increase the energy harvesting capabilities of this technology it may be a case of simply scaling up ie increasing the number of piezoelectric nanofibers, adjusting the fabrication process or modifying the original manufacture material.

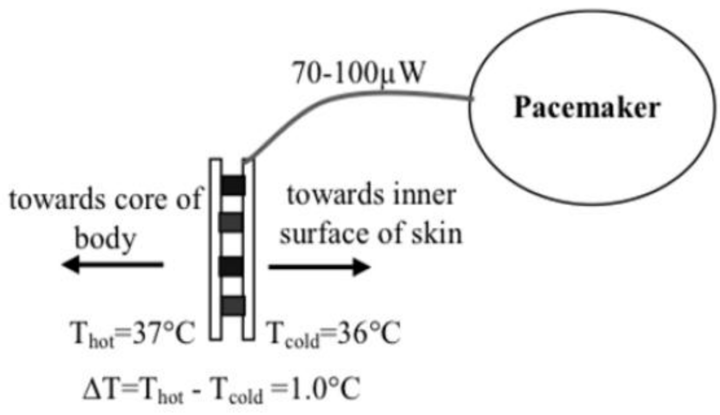

Figure 19 - pacemaker powered by the thermoelectric effect generated from the temperature difference across the skin[7,133]

Advances in state-of-the-art pacemaker systems are occurring worldwide. The realistic goal is to design and commercialise fully implantable pacemakers, as see in figure 18[132], where the device is powered by and environmental power source. There are many different areas of energy harvesting generators which have this goal in mind; however in Berkeley, CA scientists are further along the road to success. Venkatasubramanian et al[133] has reported a thermoelectric nanogenerator with a power density equal to 1100µWcm^{-2} at a temperature difference of 2K[28] see left figure 19. Trials have not yet been reported however this is a promising type of energy harvesting generator for alternative pacemaker technology.

Following from Yang et al’s work on piezoelectric shell-based fabrics[55], a possible application of this technology could be in a piezoelectric jacket for a side of the heart to power VADs. The left of the heart with an LVAD implant will cease to function and therefore it would be a very simple solution to utilise the still mobile right side of the heart. Figure 20, overleaf, represents the basic system modelled with the HeartMateII commercialised by Thoratec[135].

4.2.1.2. Neural BioMEMS

Neural diseases are not as prevalent as cardiovascular disease is in the Western world however more than 60 million people worldwide would benefit from novel epileptic treatments[124]. With greater advances occurring around the world those patients who do not benefit from modern pharmaceutical aid will soon gain a better quality of life if fitted with advanced EEG sensors or other aids. Epileptic patients will soon have access to a BioMEMS based devices which will predict the onset of a seizure. NeuroVista, Australia has developed a device that can predict seizures. The iEEG (implantable electroencephalograph) has shown great promise in trials with canine subjects[125] and currently human clinical trials are underway[126].

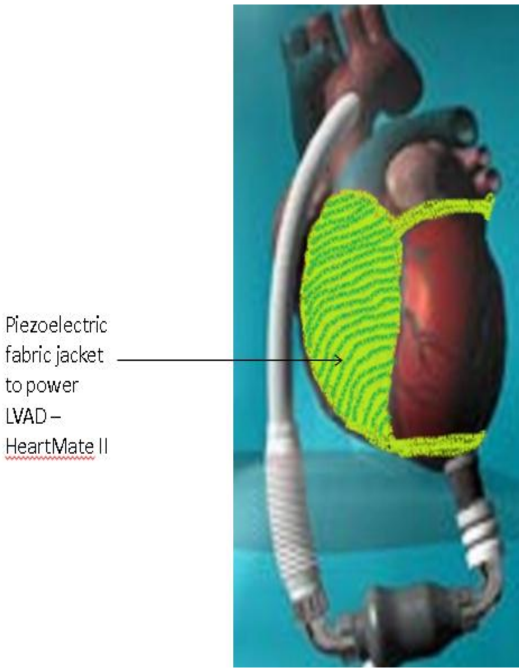

Figure 20 - HeartMate II for left ventricle failure with theoretical piezoelectric fabric jacket[134]

4.2.1.3. Drug Delivery Systems: Insulin Infusion Pumps

In the future, insulin delivery systems for diabetics will ideally power themselves through any of the energy harvesting nanogenerators mentioned previously. However a simple system of blood glucose uptake and subsequent oxidation by an inbuilt biofuel cell would solve the problem neatly. The device itself would create the energy needed to pump insulin into the circulatory system on a simple BioMEMS driven sense and response system, much like a negative feedback system; a synthetic pancreas.

In addition there is thought to be a great opportunity to utilise micro-generators in chemo and radiotherapies. In drug-delivery implant clinical trials, reported by Yoo et al. (2011)[33], a MEMS-based chemotherapeutic biodegradable eluting device was implanted in rat subjects with tumour growths. No power generator was needed as the device consisted of eluting agent reservoirs carved into silicon substrates, which were released upon the electrochemical dissolution of the reservoir-covering gold membranes. This technology is showing promise however it may be noted that a delivery device with a power source may be more economical as it may be designed to deliver chemotherapeutic drugs on demand.

4.2.2. Microbial Fuel Cells to Power Medical Devices

Although physically sourced energy harvesters are thought to be the future of medical technology, biofuel-based micro-generators are being investigated also. However there is more of an interest in media applications and large companies such as Panasonic are developing novelty devices. Yet smaller teams are also developing similar technologies, such as a research team at the University of Bristol[131]. They have demonstrated a novel way of charging mobile phones using MFCs. This technology uses anaerobic respiring microbes situated in a stacking formation to produce electrical power. However this biofuel powered device has a low power output which in the future could be connected to a super capacitor to further develop this technology[131]. It is believed that this technology could be adapted for bladder implants, specifically in the case of commercially available bladder stimulators.

4.3. Conclusion

Understanding the diseases and general methods of energy harvesting has led to much advancement in today's applied field of MEMS. Consequently we are now able to conceivably harvest energy using the body's own sources from biochemical sources (glucose) to movement (of organs or tissues). The variety of energy harvesting types: piezoelectric, electromagnetic, thermoelectric, air flow and biofuels are all currently capable of harvesting enough energy to power specific devices such as a neural stimulatory device. However in order to power those devices which are increasingly power demanding, such as pacemakers and drug pumps, this technology need to be scaled up. Within the next ten years the advances made in the field of medical technology will be significant in the powering of fully implantable devices and will eventually prove to become a rapidly expanding commercial development. Presently, the medical device market is producing more compact, versatile implants able to provide the patient with a much improved quality of life. Already devices are tending towards removal of the current lithium ion sources which are finite and often require maintenance/replacement over the patient's lifetime. There is still an overwhelming problem: sepsis often caused by percutaneous leads established across therapies from neural stimulants to cardiovascular aids. Thus, by utilising optimised energy harvesting micro-generators (as far as materials, fabrication techniques etc are concerned) researchers hope to manufacture lasting medical implants. Overall, as shown in chapter 3 and table 2 chapter 1, piezoelectric micro-generators have proved to be the most advanced in the field, already able to power some pacemaker technology, however thermoelectric power is not far behind and may only require up-scaling to achieve similar level of power conversion efficiency. Perhaps in combination micro-generators could power existing medium-powered implant technology such as drug pumps. There are a great many of unexplored applications of this technology in both external medical devices and implantable technolgoy as demonstrated earlier in this chapter. Continuing research into these individual, yet interlinking, fields will be significant to the commercialisation of much needed therapeutic aids to those suffering from chronic conditions.

References

1. Global status report on noncommunicable diseases 2010 Geneva, World Health Organisation, 2011
2. Kwan, P; Brodie, M.J. (2000). Epilepsy after the first drug fails: substitution or add-on? Seizure 9(7): 464-468
3. Davis, K; Sturges, B.K; Vite, C.H. (2011). A novel implanted device to wirelessly record and analyse continuous intracranial canine EEG. Epilepsy Research 96: 116-122
4. Wei, X; Liu, J. (2008). Power sources and electrical recharging strategies for implantable medical devices. Front. Energy Power Eng. 2(1): 1-13
5. Vullers, R.J.M; van Schaijk, R. Doms, I; et al. (2009). Micropower energy harvesting. Solid-State Electronics 53: 684-693
6. Sue, C-Y; Tsai, N-C. (2012). Human powered MEMS-based energy harvest devices. Applied Energy 93: 390-403
7. Paulo, J; Gaspar, P.D. (2010). Proceeding so the World Congress on Engineering Vol II WCE 2010, June 30-July 2, 2010, London, UK.
8. Batteries for implantable biomedical devices. Edited by Boone B. Owens. © 1986 Plenum Press, New York, USA.
9. Figure of glucose pump. Accu-Chec. https://www.accu-chek.com/us/glucose-meters/aviva.html
10. Dell, R.M. (2000). Batteries: fifty years of materials development. Solid State Ionics 134: 139-158
11. Encyclopaedia of medical devices and instrumentation (vol4). Edited by John G. Webster. 1988 © John Wiley & Sons, Inc. USA
12. Wenzl, H; Baring-Gould, I; Kaiser, R; et al. (2005). Life prediction of batteries for selecting the technically most suitable and cost effective battery. Journal of Power Sources 144: 373-384
13. Davis, F; Higson, S.P.J. (2007). Biofuel cells-Recent advances and applications. Biosensors and Bioelectronics 22: 1224-1235

14. Schmidt, C.L; Skarstad, P.M. (2001). The future of lithium and lithium-ion batteries in implantable medical devices. Journal of Power Source 97-98: 742-746.
15. Boniche, I; Masilamani, S; Durscher, R.J; Morgan, B.C; Arnold D.P. (2009). Design of a miniaturized thermoelectric generator using micromachined silicon substrates. *Journal of Electronic Materials* 38(7): 1293-1302
16. Prutchi, D. (2005). Nuclear batteries published on www.prutchi.com. Visited 17/06/13
17. Lazzi, G. "Thermal effects of bioimplants" IEEE English Medical Biology Magazine 24(5): 75-81
18. Bashir, R. (2004). BioMEMS: state-of-the-art in detection, opportunities and prospects. Advanced Drug Delivery Reviews 56: 1565-1586
19. Jha, A.R. MEMS and nanotechnology- based sensors and devices for communications, medical and aerospace applications.
20. Mitcheson, P.D; Green, T.C; Yeatman, E.M. (2004). Architectures for vibration-driven micropower generators. Journal of Microelectromechanical Systems 13(3): 429-440
21. Kim, S-H; Ji, C-H; Galle, P; et al. (2009). An electromagnetic energy scavenger from direct airflow. Journal of Micromechanics and Microengineering 19: 1-8
22. El-hami, M; Glynne-Jones, P; White, N.M; et al. (2001). Design and fabrication of a new vibration-based electromechanical power generator. *Sensors and Actuators* 92: 335-342
23. Harb, A. (2011). Energy harvesting: State-of-the-art. Renewable Energy 36:2641-2654
24. Cuadras, A; Gasulla, M; Ferrari, V. (2010).Thermal energy harvesting through pyroelectricity. *Sensors and Actuators* 158: 132-139
25. Visited 04/08/13. Frayne et al. http://www.humdingerwind.com/
26. Kempe, V. (2013). Inertial MEMS – Principles and Practice. Chapter 4 – MEMS technologies. Cambridge University Press pp. 152-204
27. Ochoa, M; Mousoulis, C; Ziaie, B. (2012). Polymeric microdevices for transdermal and subcutaneous drug delivery. Advanced Drug Delivery Reviews 64: 1603-1616

28. Kerzenmacher, S; Ducree, J; Zengerle, R; von Stetten, F. (2008). Energy harvesting by implantable abiotically catalysed glucose fuel cells. *Journal of Power Sources* 182: 1-17
29. Rao, J.R; Richter, G. (1974). Naturwissenschaften 61: 200-206
30. Malachesky, G; Holleck, G; McGovern, F; Devarakonda, R. (1972). Proceedings of the seventh intersociety energy conversion engineering conference pg 727-732
31. Anderson, J.M; Langone, J.J. (1999). Issues and perspectives on the biocompatibility and immunotoxicity evaluation of implanted controlled release systems. *Journal of Controlled Release* 57: 107-113
32. Xia, Z; Triffitt, J.T. (2006). A review on macrophage response to biomaterials. *Biomedical Materials* 1: R1-R9
33. Yoo, J-W; Doshi, N; Mitragotri, S. (2011). Adaptive micro and nanoparticles: temporal control over carrier properties to facilitate drug delivery. *Advanced Drug Delivery Reviews* 63: 1247-1256
34. George W. Taylor. Piezoelectricity. Gordon and Breach Science Publishers 1st Jan 1985. (Vol IV of Ferroelectricity and Related Phenomena).
35. Spencer, W.J; Corbett, W.T; Dominguez, L.R et al. (1978). An electronically controlled piezoelectric insulin pump and valves. IEEE Transactions on Sonics and Ultrasonic 25:153-156
36. Williams, C.B; Yates, R.B. (1995). Analysis of a micro-electric generator for microsystems. The 8th International Conference on Solid-State Sensors and Actuators 1:369-372
37. Glynne, P.J; Beeby, S.P; White, N.M. (2001). Towards a piezoelectric vibration-powered microgenerator. IEE Proceedings on Science Measurement and Technology 148:68-72
38. Ferrari, M; Ferrari, V; Guizzettia, M; et al. (2009). Improved energy harvesting from wideband vibrations by nonlinear piezoelectric converters. Procedia Chemistry 1:1203-1206
39. Falconi, C; Mantini, G; D'Amico, A; et al. (2009). Studying piezoelectric nanonwires and nanowalls for energy harvesting. Sensors and Actuators 139:511-519

40. Howells, C.A. (2009). Piezoelectric energy harvesting. Energy Conversion and Management 50:1847-1850
41. Korla, S; Leon, R.A.; Tansel, I.N; et al. (2011). Design and testing of an efficient and compact piezoelectric energy harvester. Microelectronics Journal 42:265-270
42. Chen, X. Xu, S, Yao, N; et al. (2009). Applied Physics Letters 94: 253113
43. Kymissis, j; Kendall, C; Paradiso, J; et al. (1998). Parasitic power harvesting in shoes. Presented at the 2nd IEEE International Conference on Wearable Computing.
44. Enger, C.C; Kennedy, J.H. (Nov. 1963). "Piezoelectric power sources utilizing the mechanical energy of the human heart." Presented at the Annual Conference of Engineering in Medicine and Biology, Baltimore, MD.
45. Platt, S.R; Farritor, S; Garvin, K; et al. (2005). The use of piezoelectric ceramics for electric power generation within orthopaedic implants. Transactions on Mechatronics 10(4): 455-460
46. Nunes-Pereira, J; Sencadas, V; Correia, V; et al. (2013). Energy harvesting performance of piezoelectric electrospun polymer fibers and polymer/ceramic composites. Sensors and Actuators A: Physical 196:55-62
47. Chang, J; Lin, L. (2011) Large array electrospun PVDF nanogenerators on a flexible substrate, in: Proceedings of the 16th International Solid-State Sensors, Actuators and Microsystems Conference, IEEE pp. 747-750.
48. Li, D; Wang, Y; Xia, Y. (2003). Nano Letters 3:1167-1171
49. Huang, Z. (2003). Composites Science and Technology 63:2223-2252
50. Boland, E; Wnek, G; Simpson, D et al. (2001). Journal of Macromolecular Science, Part A 38:1231-1243
51. Wang, Z.L; Song, J. (2006). Piezoelectric nanogenerators based on zinc oxide nanowire arrays. Science 312:242-246
52. Chang, J; Dommer, M; Chang, C; et al. (2012). Piezoelectric nanofibers for energy scavenging applications. Nano Energy 1:356-371
53. Qin, Y; Wang, X; Wang, Z.L. (2009). Nature 451:809-813

54. Fang, H-B; Liu, J-Q; Xu, Z-Y; et al. (2006). Fabrication and performance of MEMS-based piezoelectric power generator for vibration energy harvesting. Microelectronics Journal 37:1280-1284
55. Yang, B; Yun, K-S. (2012). Piezoelectric shell structures as wearable energy harvesters for effective power generation at low-frequency movement. Sensors and Actuators 188: 427-433
56. Li, Z; Zhu, G; Yang, R; et al. (2010). Muscle-driven in vivo nanogenerator. Advanced Materials 22: 2534-2537
57. Junwu, K; Zhigang, Y; Taijiang, P; et al. (2005). Design and test of a high-performance piezoelectric micropump for drug delivery. Sensors and Actuators 121:156-161
58. Wilkins, E; Atanasov, P. (1996) Glucose monitoring: state-of-the-art and future possibilities. Med. Eng. Phys. 18(4):273-288
59. Wang, X; Hu, Y; Wang, Z; et al. (2011). Finite element analysis of the coupling between ossicular chain and mass loading for evaluation of implantable hearing device. Hearing Research 280:48-57
60. Wang, Z.G; Abel, E.W; Mills, R.P; et al. (2002). Assessment of multi-layer piezoelectric actuator technology for middle-ear implants. Mechatronics 12:3-17
61. Tang, L; Yang, Y; Soh, C.K. (2010). Toward broadband vibration-based energy harvesting. Journal of Intelligent Material Systems and Structures 21:1867-1897
62. Fei, F; Mai, J.D; Li, W.J. (2012). A wind-flutter energy converter for powering wireless sensors. Sensors and Actuators A 172:163-171
63. Suzuki, S; Katane, T; Saotome, H; et al. (1999). A proposal of electric power generating system for implanted medical devices. IEEE Transactions on Magnetics 35:3586-3589
64. Suzuki, S; Katane, T; Saotome, H; et al. (2002). Electric power-generating system using magnetic coupling for deeply implanted medical. IEEE Transactions on Magnetics 38:3006-3008
65. Von Büren, T; Tröster, G. (2007). Design and optimization of a linear vibration-drive electromagnetic micro-power generator. Sensors and Actuators 135:765-775

66. Mann, B.P; Sims, N.D. (2009). Energy harvesting from the nonlinear oscillations of magnetic levitation. Journal of Sound and Vibration 319:515-530
67. Sari, I; Balkan, T; Kulah, H. (2008). An electromagnetic micropower generator for wideband environmental vibrations. Sensors and Actuators A 145-146:405-413
68. Sardini, E; Serpelloni, M. (2011). An efficient electromagnetic power harvesting device for low-frequency applications. Sensors and Actuators A 172:475-482
69. Bahl, A; Chongtham, D.S; Kumar, R.M; et al. (2007). Inappropriate shock delivery by implantable cardioverter defibrillator due to electrical interference with washing machine. International Journal of Cardiology 118:e44-e45
70. Siegel, D. Visited 08/08/13. http://dennissiegel.de/electromagnetic-harvester/
71. Shahhaidar, E; Boric-Lubecke, O; Ghorbani, R; et al. (unknown). Electromagnetic generator as respiratory effort energy harvester. U.S. Government, University of Hawaii.
72. Boniche, I; Masilamani, S; Durscher, R.J; Morgan, B.C; Arnold D.P. (2009). Design of a miniaturized thermoelectric generator using micromachined silicon substrates. *Journal of Electronic Materials* 38(7): 1293-1302
73. Paulo, J; Gaspar, P.D. (2010). Proceeding so the World Congress on Engineering Vol II WCE 2010, June 30-July 2, 2010, London, UK.
74. Cuadras, A; Gasulla, M; Ferrari, V. (2010).Thermal energy harvesting through pyroelectricity. *Sensors and Actuators* 158: 132-139
75. Carmo, J.P; Goncalves, L.M; Wolffenbuttel, R.F; et al. (2010). A planar thermoelectric power generator for integration in wearable microsystems. Sensors and Actuators A 161:199-204.
76. Huesgen, T; Woias, P; Kockmann, N. (2008). Design and fabrication of MEMS thermoelectric generators with high temperature efficiency. Sensors and Actuators A 145-146:423-429
77. Glosch, H; Ashauer, M; Pfeiffer, U; et al. (1999). A thermoelectric converter for energy supply. Sensors and Actuators 74:246-250

78. Böttner, H; Nurnus, J; Gavrikov, A; et al. (2004). Thermoelectric components using microsystem technologies. Journal of Microelectromechanical Systems 13(3): 414-420
79. Venkatasubramanian, R; Siivola, E; Copitts, T; et al. (2001). Thin-film thermoelectric devices with high room-temperature figures of merit. Nature 413:597-602
80. Watkins, C; Shen, B; Venkatasubramanian, R. (2005). Low-grade-heat energy harvesting using superlattice thermoelectrics for applications in implantable medical devices and sensors. IEEE International Conference on Thermoelectrics
81. Venkatasabramanian, R; Colpitts, T; Watko, E; et al. (1997). MOCVD of Bi_2Te_3, Sb_2Te_3 and their superlattice structures for thin-film thermoelectric applications. Journal of Crystal Growth 170:817-821
82. Visited 03/07/13. Thermo Life. http://www.poweredbythermolife.com/
83. Stark, I. (2006). Thermal energy harvesting with Thermo Life®. IEEE Proceedings of the International Workshop on Wearable and Implantable Body Sensor Networks.
84. Visited 20/07/13. Nextreme. http://www.nextreme.com/pages/power_gen/power_gen.shtml
85. Lin, H-I; Horng, R-H; Wuu, D-S. (2013). ZnO nanogenerator as a wind speed sensor for human respiration detector. The Electromechanical Society Abstract 1492
86. Epstein, A.H. (2003). Millimeter-scale, MEMS gas turbine engines. Proceedings of ASME Turbo Expo. Georgia, USA
87. Holmes, A.S; Hong, G; Pullen, K.R; et al. (2004). Axial-flow microturbine with electromagnetic generator: design, CFD simulation, and prototype demonstration. IEEE 568-571
88. Holmes, A.S; Hong, G; Pullen, K.R. (2005). Axial-flux permanent magnet machines for micropower generation. Journal of Microelectromechanical Systems 14(1):54-62
89. Visited 01/07/13. Humdingerwind.com. http://www.humdingerwind.com/
90. Sun, C; Shi, J; Bayerl, D.J. (2011). PVDF microbelts for harvesting energy from respiration. Energy & Environmental Science.
91. Leech, D; Kavanagh, P; Schuhmann, W. (2012). Enzymatic fuel cells: Recent progress. Electrochimica Acta 84:223-234

92. Willner, I; Arad, G; Katz, E. (1998). A biofuel cell based on pyrroloquinoline quinone and microperoxidase-11 monolayer-functionalized electrodes. Bioelectrochemistry and Bioenergetics 44:209-214
93. Lee, K.B. (2005). Urine-activated paper batteries for biosystems. Journal of Micromechanics and Microengineering 15: 210-214
94. Han, Y; Yu, C; Liu, H. (2010). A microbial fuel cell as power supply for implantable medical devices. Biosensors and Bioelectronics 25: 2156-2160
95. Dong, K; Jia, B; Yu, C; et al. (2013). Microbial fuel cell as power supply for implantable medical devices: A novel configuration design for simulating colonic environment. Biosensors and Bioelectronics 41: 916-919
96. Olivo, J; Carrara, S; De Micheli, G. (2011). Energy harvesting and remote powering for implantable biosensors. Sensors Journal 11(7): 1573-1586
97. Yahiro, A.T; Lee, S.M; Kimble, D.O. (1964). Biochim. Biophys. Acta 88:375-383
98. Katz, E; Willner, I; Kotlyar, A.B. (1999). Journal of Electronanalytical Chemistry 479:64-68
99. Jimbo, H; Miki, N. (2008). Gastric-fluid-utilizing micro battery for micro medical devices. Sensors and Actuators 134: 219-224
100. Mano, N. (2008). A 280µWcm^{-2} biofuel cell operating at low glucose concentration. Chem. Commun. Pg. 2221-2223.
101. Grohn, F; Bauer, B; Akpalu, Y. A; et al. (2000). Dendrimer templates for the formation of gold nanoclusters. Macromolecules 33:6042-6050
102. Caminade, A. M; Majoral, J.P. (2010). Dendrimers and nanotubes: a fruitful association. Chemical Society Reviews 39:2034-2047
103. Tang, L.H; Zhu, Y.H; Xu, L.H; et al. (2007). Amperometric glutamate biosensor based on self-assembling glutamate dehydrogenase and dendrimer-encapsulated platinum nanoparticles onto carbon nanotubes. Talanta 73:438-443
104. Carbonera, C; Luis, F; Campo, J. et al. (2010). Effect of crystalline disorder on quantum tunnelling in the single-molecule magnet Mn_{12} benzoate. Physical Review B81, 014427

105. Zhang, J; Zhu, Y; Chen, C; et al. (2012). Carbon nanotubes coated with platinum nanoparticles as anode of biofuel cell. Particuology 10: 450-455

106. Cinquin, P; Gondra, C; Giroud, F; et al. (2010). A glucose biofuel cell implanted in rats. PlosOne 5(5): e10476

107. Vo-Dinh, T; Cullum, B. (2000). Biosensors and biochips: advances in biological and medical diagnostics. Fresenius' Journal of Analytical Chemistry 366(6): 540-551

108. Wereley, S. BioMEMS and Biomedical Nanotechnology: Biomolecular sensing, processing and analysis. (2006). Edited by Ferrari, M; Bashir, R; Springer.

109. Visited 03/08/2013. http://news.mongabay.com/bioenergy/2007/08/bioeconomy-at-work-sony-develops-most.html

110. Soukharev, V; Mano, N; Heller, A. (2004). A four-electron O-electron reduction biocatalyst superior to platinum and biofuel cell operating at 0.88V. J. Am. Chem. Soc. 126(27): 8368-8369

111. Chardack, W.0; Gage, A.A; Greatbatch, W. (1960). A transistorized, self-contained, implantable pacemaker for the long-term correction of complete heart block. Surgery 48:643-654

112. Topkara, V.K; Kondareddy, S; Malik, F; et al. (2010). Infections and complications in patients with LVAD:etiology and outcomes in the continuous flow era. Ann. Thorac. Surg. 90(40): 1270-1277. Via LOOR et al.

113. Vallejo, R. (2012). High-frequency spinal cord stimulation: An emerging treatment option for patients with chronic pain. Techniques in Regional Anesthesia and Pain Management 16: 106-112

114. Kenknight, B.H; Jones, B.R; Thomas, A.C. (1996). Technological advances in implantable cardioverter-defibrillators before the year 2000 and beyond. Excerpta Medica, Inc.

115. Loor, G; Gonzalez-Stawinski, G. (2012). Pulsatile vs. continuous flow in ventricular assist device therapy. Best Practice & Research Clinical Anaesthesiology 26:105-115

116. Miller, L.W; Pagani, F.D; Russell, S.D; et al. (2007). Use of continuous flow device in patients awaiting heart transplant. New England Journal of Medicine 357(9): 885-896

117. Meng, E; Hoang, T. (2012). MEMS-enabled implantable drug infusion pumps for laboratory animal research, preclinical and clinical applications. Advanced Drug Delivery Reviews 64: 1628-1638.

118. Wilkins, E; Atanasov, P. (1996). Glucose monitoring: state-of-the-art and future possibilities. Medical Engineering Physics 18(4): 273-288.

119. An, Y.H; Friedman, R.J. (2000). Handbook of Bacterial Adhesion: principles, methods and applications. Published by Humana Press.

120. Hetrick, E.M; Schoenfisch, M.H. (2006). Reducing implant-related infections: active release strategies. Chemistry Society Reviews © Royal Society of Chemistry 2006.

121. Sharma, P; Sample, P.A; Zangwill, L.M; et al. (2008). Diagnostic tools for glaucoma detection and management. Survey of Opthalmology 53: 17-32.

122. Visited 06/07/13. Valtronic. http://www.valtronic.com/

123. Figure modified. Visited 07/07/13. http://www.b2match.eu/ssbbs2012/system/files/S0203%20Valtronic_Group_Presentaion%20Scandenavian%20summary.pdf

124. Kwan, P; Brodie, M.J. (2000). Epilepsy after the first drug fails: substitution or add-on? Seizure 9(7): 464-468

125. Davis, K; Sturges, B.K; Vite, C.H. (2011). A novel implanted device to wirelessly record and analyse continuous intracranial canine EEG. Epilepsy Research 96: 116-122

126. Visited 04/08/13. http://www.bbc.co.uk/news/health-22342448

127. Hayakaw, M. (1989). “Electronic wristwatch with generator” U.S. Patent 5 001 685

128. Hayakawa, M. (1988). A study of the new energy system for quartz watches (ii) – the effective circuit for the system. Congr. Eur. Chronométrie.

129. Snyder, G.J. (2008). Small thermoelectric generators. The Electrochemical Society Interface pp.54-56

130. Goto, H; Sugiura, T; Harada, Y; et al. (1999). Feasibility of using the automatic generating system for quartz watches as a leadless pacemaker power source. Medical & Biological Engineering & Computing 37: 377-380

131. Ieropoulos, I.A; Ledezma, P; Stinchcombe, A; et al. (Accepted recently to the RSC, but was published in the Bristol News on 16/07/13). Waste to real energy: the first MFC powered mobile phone. Royal Society of Chemistry Publishing.

132. Visited 05/08/13. E-brains. http://www.e-brains.org/applications/activemedicalimplant/

133. Venkatasubramanian, R; Watkins, C; Caylor, C; et al. (2006). Microscale thermoelectric devices for energy harvesting and thermal management. The 6th International Workshop on micro and nanotechnology for power generation and energy conversion applications pp. 1-4

134. Heart figure with jacket: visited 06/08/13 and modified. Medgadget. http://cdn.medgadget.com/img/he3sfe.jpg

135. Visited 06/08/13. Thoratec. http://www.thoratec.com/

136. Visited 16/08/13. Tomy. http://www.tomy.co.uk/CGI-BIN/lansaweb?webapp=WKWSEARCH+webrtn=search+ml=LANSA:XHTML+partition=PRD+language=ENG

137. Visited 07/08/13. http://www.nhs.uk/Conditions/Sudden-infant-death-syndrome/Pages/Introduction.aspx

138. Foisal, A.R; Hond, C; Chung, G-S. (2012). Multi-frequency electromagnetic energy harvester using a magnetic spring cantilever. Sensors and Actuators A: Physical 182:106-113

139. Qi, Y; McAlpine, M.C. (2010). Nanotechnology-enabled flexible and biocompatible energy harvesting. Energy Environmental Science 3:1275-1285

140. Plumb, R.C; Hobey, W.D. (1972). Biogalvanic cells. Journal of Chemical Education 49(6): pp.413

141. Yang, R; Qin, Y; Li, C; et al. (2009). Converting biomechanical energy into electricity by a muscle-movement-driven nanogenerator. Nano Letters 9(3):1201-1205

142. Lewandowski, B.E; et al. (2008). Chpt. 15: Feasibility of an implantable, stimulated muscle-powered piezoelectric generator. Energy Harvesting Technologies. Edited by Priya, S; Inman, D.J. pg. 392-393

143. Zurbuchen, A; Pfenniger, A; Stahell, A; et al. (2012). Energy harvesting from the beating heart by a mass imbalance oscillation generator. Annals of Biomedical Energy 41(1):131-141

144. Qi, Y; McAlpine, M.C. (2010). Nanotechnology-enabled flexible and biocompatible energy harvesting. Energy Environment 3:1275-1285

145. Minazara, E; Vasic, D; Costa, F; et al. (2006). Piezoelectric diaphragm for vibration energy harvesting. Ultrasonic 44:e699-e703

146. Lowy, D.A; Tender, L.M; Zeikus, J.G; et al. (2006). Harvesting energy from the marine sediment-water interface II kinetic activity of anode materials. Biosensors and Bioelectronics 21:2058-2063

147. MDDI website. Author H. Thompson (2012). Visited 06/08/13. http://www.mddionline.com/article/thermoelectric-felt-has-medical-device-power-all-wrapped

148. Simon, A.H. Chapter 4 – Sputter processing. Seshan, K. (2012). Handbook of Thin Film Deposition. William Andrew pg. 55-56

149. Park, K.I; Xu, S; Liu, Y; et al. (2010). Piezoelectric $BaTiO_3$ thin film nanogenerator on plastic substrates. Nano Letters pg. A-E

150. Egbert, R.G; Harvey, M.R; Otis, B.P. (2007). Microscale silicon thermoelectric generator with low impedance for energy harvesting. Relation 2(10): 10

151. Zhu, Y; Moheimani, S.O.R; Yuce, M.R. (2009). A 2-DOF wideband and electrostatic transducer for energy harvesting and implantable applications. IEEE Sensors pp. 1542-1545

152. Suzuki, Y; Miki, D; Edanoto, M; et al. A MEMS electret generator with electrostatic levitation for vibration-driven energy-harvesting applications. (2010). Journal of Micromech. And Microeng 20:e1-e8

153. Stewart, J.V. Intermediate Electromagnetic Theory. © 2001 World Scientific pp. 51-52

154. Thermoelectric IMD energy harvesters - NASA website. Updated 29/03/08. http://www.nasa.gov/centers/ames/research/technology-onepagers/human_devices.html. Visited 05/08/13.

155. Piezoelectric energy harvesting. Erturk, A; Inman, D.J. (2011) John Wiley & Sons.

156. Matova, S.P; Elfrink, R; Vullers, R.J.M; et al. (2011). Harvesting from airflow with a micromachined piezoelectric harvester inside a Helmholtz resonator. Journal of Micromechanics and Microengineering 20(10):

157. Potter, M.C. (1911). Electrical effects accompanying the decomposition of organic compounds. Proceedings of the Royal Society of London 84(571):260-276

158. Cohen, B. (1931). The bacterial culture as an electrical half-cell. Journal of Bacteriology 21:18-19

159. Cook, M.J; O'Brien, T.J; Berkovic, S.F; et al. (2013). Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: first-in-man study. The Lancet Neurology 12(6):563-571

160. Hiscox, A.M; Stone, A.L; Hoying, J.B; et al. (2008). An islet-stabilizing implant constructed using a performed vasculature. Tissue Engineering Part A 14(3):433-440