

JOHNSON SPACE CENTER, WYLE, UTMB

Implantable Medical Monitoring Devices

Tech Watch Report

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Background and Significance

NASA is planning missions of greater than one year in duration outside of low Earth orbit. To address the medical conditions that may arise during such a mission, a suite of on-board medical diagnostic equipment will be necessary. (1) In addition to physical findings and values such as blood pressure, physicians on the ground have an array of techniques available to them in order to diagnose and treat disease. The Molecular Diagnostics Survey Reports demonstrate that 70% of medical decision making in hospitals is based on molecular tests. (2) The majority of these techniques utilize blood tests in order to determine levels of serum glucose, calcium, blood urea nitrogen, creatinine, sodium, potassium, chloride, carbon dioxide, serum total protein, serum albumin, bilirubin, alkaline phosphatase, aspartate amino transferase and alanine amino transferase. Classically, to obtain these values, venous blood is drawn in the clinic which is then sent to a lab for analysis. The combination of physical exam and vital signs are used to guide lab testing in pursuit of a differential diagnosis and eventual treatment.

Space flight poses many challenges in obtaining laboratory values. Laboratory analysis devices often contain moving parts that may be fragile, heavy and numerous taking up valuable payload space. In the face of this issue, The Human Research Program at NASA has engaged itself in finding and fostering novel ways of ensuring laboratory analytes may be determined during long duration space flights as defined in ExMC GAP 4.05. As defined by the 4.05 report;

Instrumentation should include point-of-care devices that minimize: mass, volume, consumables, reagents and power. The instrumentation should be designed for ease of use by the local care provider and in consideration to the limited training available that the astronaut corps receives for medical equipment and procedures. Also, the analyzer(s) should be designed for minimal maintenance. In addition, the analyzers should be readily interfaced to an onboard medical system or data storage/relay hub, and provide wireless communications. As mission duration lengthens, an analyzer's capability should be readily expanded through software, reagents, dipsticks and/or microfluidic cartridges. Secondly, the instrumentation should be considered to serve a dual purpose that will address prospective research objectives and minimize redundancy with those efforts. The development effort is separate from, but will coordinate and integrate with developments for non-invasive diagnostic imaging capability, ultrasound, intravehicular physiological monitoring and pulmonary gas analysis. (3)

In recent years the advents of point of care (POC) devices have expedited lab analysis with accurate results that are available at the bedside. Point of care devices are compact, lightweight and often have very few moving parts. Additionally they typically require a small amount of blood which may be obtained via a finger stick as opposed to a large gauge needle. Thus, these systems have the potential to significantly reduce many of the issues present in the classical lab analysis hardware. POC devices are a huge step forward in lab analysis but they do pose issues for long duration flight. These systems often require reagents and consumables that have a prescribed shelf life that is problematic for long duration flights. Additionally these systems still contain moving parts which are apt to break. (2) POC devices

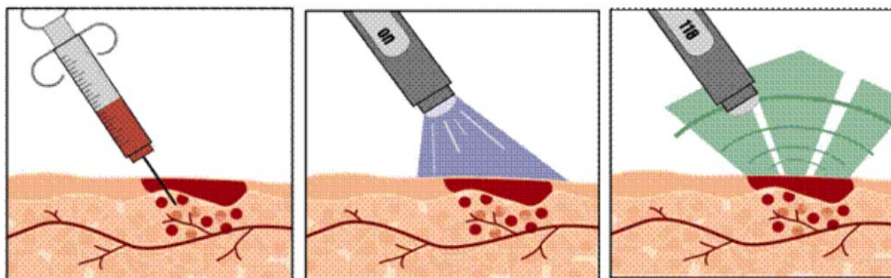
provide an enhanced capability for medical systems in space flight but further reduction in mass can be achieved.

In recent years much research has been focused on the development of implantable devices that are capable of measuring a multitude of values ranging from glucose to blood pressure. (5) These devices provide continuous monitoring of analytes within the body and utilize novel power supplies and data acquisition methods. Additionally, many devices have been tested in animal models for up to one year. (6) An ideal implantable device fulfills the criteria of having a high-degree of integration, minimal invasive surgery, long-term biocompatibility, security and privacy in data transmission, high reliability, high reproducibility, high specificity, low detection limit and high sensitivity. (7) These devices are also incredibly small, measuring only a few millimeters, in comparison to the bulky handheld point of care devices. These devices are of particular interest because; they vastly reduce the amount of weight to be carried into space, reduce or eliminate the need for spare parts and allow continuous monitoring of astronauts while in space.

This report will describe implantable technologies that are coming to market or in development. These technologies utilize various methods for evaluating analyte and blood pressure values as well as various methods for maintaining power. For further reading on the engineering principles of many of these implantable devices refer to an article by Carrara S et al (<http://www.ncbi.nlm.nih.gov/pubmed/23112644>)

Devices

Dermally Implanted Smart Tattoo for Blood Chemistry Monitoring



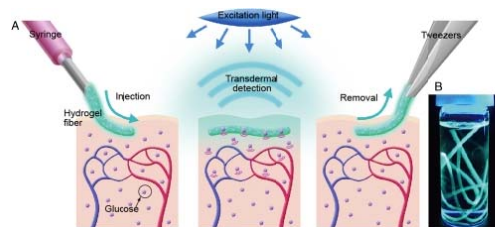
Summary: Texas A&M is developing color changing particles that are to be injected directly into the dermis where they will change color based on binding affinity or enzymatic properties. In contrast to normal tattoo ink, these particles provide no visible pigmentation but may be interrogated non-invasively using light to monitor for color changes indicating blood analyte levels. (8)

Implantable Hydrogel Based Glucose Monitoring System



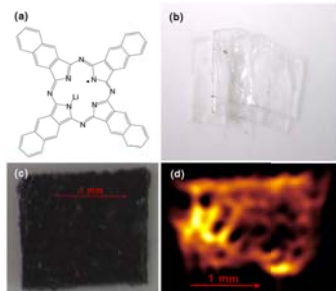
Tokyo University has developed an implantable system that may be utilized to continuously monitor glucose. The system utilizes hydrogels with affinity to Glucose. As the blood glucose level raises the fluorescent gel changes its luminescence. The light emitted from the hydrogel is monitored every five minutes by a camera on the outside of the skin and analyzed by computer software. The system was found to be accurate during the three day trial on a rat. Longer terms studies in humans are planned for the future. (9)

Florescent Hydrogel Fibers



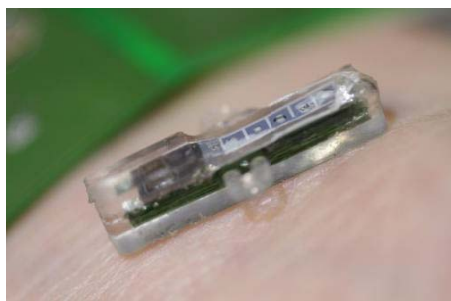
Dr. Heo and his team have developed a new type of hydrogel which was fabricated in a fibrous structure which allows for longer duration implantation as well easy removal. The hydrogel fibers are composed of a glucose sensitive fluorescent hydrogel coated in a polyethylene glycol- bonded polyacrylamide which reduces inflammation. The gels have been demonstrated to continuously respond to glucose concentrations lagging by about 5 minutes in comparison to values found with blood tests. The fibers have demonstrated effectiveness for upwards of 100 days in mouse models. Fluorescence is measured with a camera and analyzed by computer software. (10)

Implantable Teflon chip holding lithium naphthalocyanine microcrystals for measurements of pO₂ in tissues



The Ohio State University has developed and evaluated an oxygen-sensing implant, the Lithium naphthalocyanine: Teflon AF 2400 (LiNc:TAF) chip. The chip detects pO₂ via electron paramagnetic resonance (EPR). The chip was fabricated by encapsulating LiNc particulates in TAF 2400 using solvent-evaporation techniques. The chips were stable in tissues more than 2 months *in vivo*, and were capable of repeated real time measurements via band (1.32 GHz) spectrometer and a topical (surface loop) resonator. The LiNc:TAF chip was repeatedly a highly sensitive sensor of local oxygen concentration in tissues with high resolution even at low oxygen concentrations.(11)

Lab on Chip Portable Blood Testing



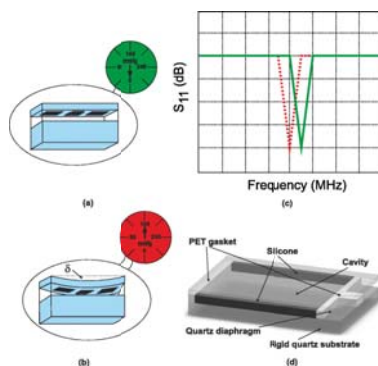
The Federal Institutes of Technology in Lausanne has developed an implantable device that utilizes enzymatic processes to detect targeted substances such as lactate, glucose or ATP. The scientists say that they device's five sensors could potentially be used to detect any substance in the body allowing for impressive customizability. The device requires 1/10 of a watt which it receives transcutaneously via an external patch on the arm which also receives communications from a radio transmitter in the implant. Data is then transferred to a mobile device to be viewed by the physician. The scientists claim the device can be left in a patient for up to 1.5 months at this point. (12)

PSM BioChip



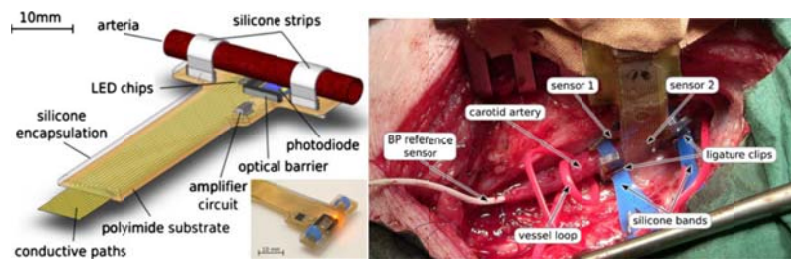
Dr. Anthony Guiseppi-Elie and his team at Clemson have developed an implantable device that is specifically developed to be inserted intramuscularly after trauma. This particular form of the device monitors both lactate and glucose levels via enzymatic reactions. The system is capable of monitoring Glucose, Lactate, potassium, VO_2 , pH and temperature. The device was shown to show minimal cytotoxicity and demonstrated 80% operational stability at 5 days. The device receives power and transmits data transcutaneously via an external IronIC Patch which has been developed by a separate institution. (13)

Continuous in vivo blood pressure measurements using a Fully implantable wireless SAW sensor



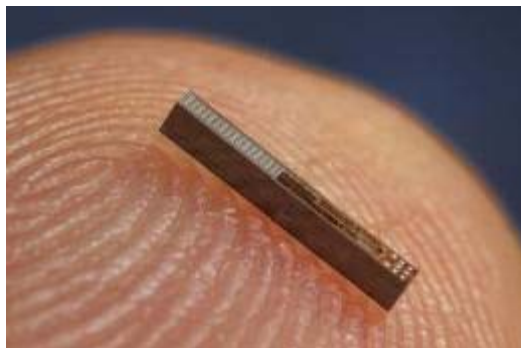
Olive Murphy and her team at Imperial College London describe a fully implantable pressure sensor system based on precise Surface Acoustic Wave (SAW) resonators, which has the capability of providing continuous real-time wireless and therefore ambulatory blood pressure monitoring. Blood pressure data is acquired via an external interrogator that powers the implantable passive sensor using electromagnetic radiation. The external device then receives data and interprets and calculates a pressure reading. The results show that such a system compares very well with commercially available catheter-tip transducers however this iteration was only a proof of concept design and was not implanted for a significant amount of time. Future iterations of this system will address the current limitations of the sensor as well as a reduction in size of the sensor, antenna and interrogator with a view to assessing pressures in other cavities and vessels and leading to a fully certifiable system with a range of uses. (14)

An implantable optical blood pressure sensor based on pulse transit time



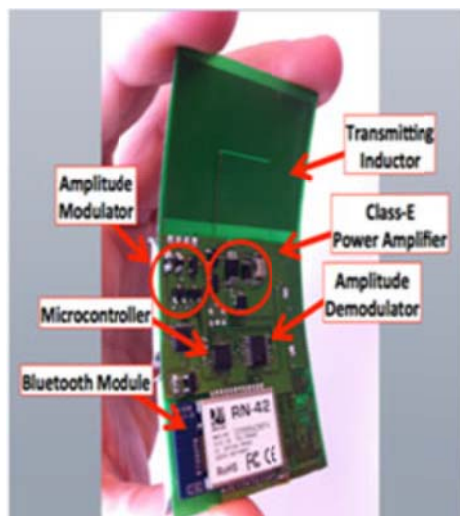
The Micro-Optics Laboratory at the University of Freiburg has developed an implantable sensor system for continuous long-term blood pressure measurement which is measured via pulse transit time. The device is mounted on an artery while not constricting blood flow and employs eight LED lights with varied wave lengths to determine oxygen saturation, deoxyhemoglobin concentration, caboxyhemoglobin concentration, methomoglobin concentration and hemoglobin concentration. The device was able to accurately evaluate all parameters in a sedated and awake pig but was not left implanted for an extended period of time. Long term testing is planned for the future. (15)

Blood Pressure monitoring device placed in the femoral Artery



Researchers at Fraunhofer Institute for Microelectric Circuits and Systems have developed an implantable 1 mm in diameter blood pressure monitoring device that is placed in the femoral artery. The devices is connected to a transponder unit placed under the skin in the groin that transmits data to an external reading device that is worn like a cellphone on the hip. The device measures blood pressure 30 time per secon and the device can receives power trancutaneously. Clinical trials are currently in progress. (16)

IronIC Patch: A Wearable Device for Powering and Monitoring Implantable devices



The IronIC Patch while not specific to any particular analyte is a device that is used to provide both power and receiver capabilities for implanted medical devices. This device has been paired up with various implantable devices and can provide up to 1.17 mW of power, 100 kbps of downlink communication via amplitude modulation and 66.6 kbps of Uplink communication via load modulation. The device has been paired up with the PSM BioChip in some trials. **(17)**

Discussion

The implantable devices described above demonstrate a remarkable step forward lab analysis capability. If a suite of devices could be deployed in astronauts on long duration flights, the medical team would have access to an unprecedented level of laboratory data.

It is clear from even the most advanced implantable lab analysis technologies that the complete metabolic panel is still not ready for implementation in space medicine. Many of the technologies are focused on a signal analyte of interest, whether that is glucose, lactate or blood pressure. However examining these prototypes from a global view demonstrates the start of what will be integral technologies in closing GAP 4.05. Devices in the vein of the Lab on Chip of the EPFL demonstrate promise in providing targeted monitoring of desired blood components which may be forwarded to a smart phone device for analysis. The IRONFC patch is a tangible demonstration of the ability to use a small package to provide power and data retrieval that can potentially be used with a variety of devices. Fluorescent Hydrogel technologies, while currently focused on glucose monitoring,, allow for simple modification of the gel affinity for other analytes, opening the possibility for a number of these hydrogels to be utilized for an on demand basic metabolic panel that can be read by a smart phone. Integration of the data by all of these different sources into a

single device such as a smart phone can potentially lead to an extraordinary medical capability for long duration space flight in a small package.

An important consideration for space flight, however, is that these technologies could potentially fail, yielding inaccurate results. These failures could be caused by fibrosis around the devices or even immunological/biochemical modification of the detection medium. Additionally, there has been no evaluation of these systems in microgravity. All of these issues may necessitate secondary measures to ensure medical decisions are made with accurate data. The possibility of errors such as these may be prevented through redundancy in the system through multiple implants or back up systems. In addition to space flight considerations, few long term studies have been done on these devices and even the few long term studies have only been performed on animals. In spite of these limitations there is huge economic incentive in producing these devices for monitoring of diabetes and hypertension so the field will likely progress rapidly.

Many issues will need to be evaluated when these technologies become available. The exploration medical team will need to consider the frequency with which these devices are interrogated. Additionally, although there is the potential for continuous monitoring of analytes, the operational need for such monitoring must be determined.

One thing is clear, implantable medical devices will become part of the medical arsenal used in the care of our astronauts. These devices are proving to be light weight, safe, accurate and easily incorporated into existing systems such as mobile devices.

Future direction

The following points outline some areas of further research that are likely to be of benefit for the use of the above mentioned technologies in space flight:

- Determination of the scope of medical treatment available on long duration flights to drive focus of specific molecular targets.
- Evaluation of the longevity of implantable devices
- Evaluation of these technologies in microgravity to examine if function is altered in space.
- Evaluation of immunological effects of long term implantable devices in humans
- Evaluation of the necessity of the full scope of laboratory analysis in consideration of limited treatment options

References

1. Exploration Medical Capabilities Element and Behavioural Health and Performance Element. *TechWatch Gaps Summary*. Johnson Space Centre, National Aeronautics and Space Administration. 2012
2. Murg, S.; Moore, B.; Lovell, M.; Wolf, R.; Bejjany, B.A.; Wu, A.H.B.; Kelles, S. *Business Strategy for Molecular Diagnostics in the Lab, Report Summary*, 2nd ed.; Washington G-2 Reports; Kennedy Information: Peterborough, NH, USA, 2009.

3. Laboratory Analysis Requirements for Exploration Missions. GAP 4.05 Report, Michael Krihak, Susana Zenllo
4. Kotanen C et al, *Monitoring systems and quatitive measurement of biomolecules for management of Trauma*, 77058. Biomedical devices 2013, 15:561-577
5. Murg, S.; Moore, B.; Lovell, M.; Wolf, R.; Bejjany, B.A.; Wu, A.H.B.; Kelles, S. *Business Strategy for Molecular Diagnostics in the Lab, Report Summary*, 2nd ed.; Washington G-2 Reports; Kennedy Information: Peterborough, NH, USA, 2009.
6. Gough, D.A.; Kumosa, L.S.; Routh, T.L.; Lin, J.T.; Lucisano, J.Y. Function of an implanted tissue glucose sensor for more than 1 year in animals. *Sci. Trans. Med.* **2010**, *2*, 1–8.
7. Carrara S, et al, *Fully integrated biochip platforms for advanced healthcare*, *Sensor* 2012;12(8):11013-60
8. http://biomed.tamu.edu/BioSyM/dermal_implants.html
9. Portable Continuous Glucose Monitoring Systems with Implantable Fluorescent Hydrogel Microfiber MEMS 2013, Taipei, Taiwan, January 20 – 24, 2013
10. Proc Natl Acad Sci U S A. 2011 August 16; 108(33): 13399-13403.
11. Biomedical Microdevices 12.3 (Jun 2010): 381-7.
12. <http://phys.org/news/2013-03-scientists-tiny-portable-personal-blood.html>
13. Guiseppi-Elie, An implantable biochip to influence patient outcomes following trauma-induced hemorrhage. *Anal. Bioanal. Chem.* 399(1), 403–419 (2011)
14. Biomedical Microdevices 15.5 (Oct 2013): 737-49
15. Biomedical Microdevices 15.1 (Feb 2013): 73-81
16. <http://phys.org/news150393796.html>
17. : J. Olivo, S. Carrara, G. De Micheli (eds.), IronIC Patch: A Wearable Device for the Remote Powering and Connectivity of Implantable Systems. Instrumentation and Measurement Technology Conference (I2MTC), 2012 IEEE International. 13–16 (2012)