Sensing and Measurement Problem Report

Differentiating between Ischaemic and Haemorrhagic Stroke

January 2019

THE UNIVERSITY *of* EDINBURGH

University *of* Glasgow

ISM

EPSRC
Engineering and Physical Sciences Research Council

Alix Bailie, Kaan Kesgin, Alberto Moreno, Gregory Myles

(5598 words)

Sensing and Measurement Problem Report

Differentiating between Ischaemic and Haemorrhagic Stroke

Alix Bailie, Kaan Kesgin, Alberto Moreno, Gregory Myles

Table of Contents

1. Abstract

In the course of this project, our team have endeavoured to explore new, fast and effective methods for the identification of stroke and differentiation between subtypes. By utilising our different backgrounds, we have been able to approach the problem from numerous angles to ensure our proposed solutions are ethical, practical and innovative.

2. Background

2.1 Introduction to Stroke

Worldwide, stroke is the second-leading cause of death and accounts for approximately 10% of all global mortality.[1] Those who survive the initial neurological insult are frequently left with permanent disability and loss of function, necessitating lifelong care, which may be expensive and obstructive to a person's independence and quality of life.

The term stroke, also referred to as a cerebrovascular accident (CVA), describes a neurological event in which the blood supply to a region of the brain or spinal cord is suddenly interrupted, leading to local oxygen deprivation and subsequent cell death.[2]

Despite weighing just 1.3kg on average, the high metabolic activity of the brain requires an estimated 20% of the total cardiac output, equating to a cerebral blood flow (CBF) of around 55ml/100g of brain tissue per minute. When this level falls below 23ml/100g/min, reversible intracellular changes occur with associated functional impairment. However, if the CBF drops below 12ml/100g/min, irreparable structural and functional damage ensues, resulting in neuronal and glial cell death.[3]

A typical stroke lesion consists of a central locus of dead cells surrounded by a region of hypo-perfused tissue known as the 'ischaemic penumbra'. Over time, the central core of dead tissue spreads to fill the outlying penumbra through multiple deleterious processes unless the stroke is resolved and normal blood flow restored.[4] Therefore, stroke is considered a medical emergency warranting speedy intervention to rescue as much of the brain as possible. However, in order to provide prompt treatment, it is first vital to differentiate between the two main stroke types.

2.2 Types of Stroke

Strokes may be broadly classified as either ischaemic or haemorrhagic based on their underlying aetiology. Approximately 87% of strokes are ischaemic in nature and are caused by an obstruction within one of the arteries supplying blood to the brain.[5] The remaining 13% are haemorrhagic and are the result of bleeding within the intracranial cavity.

Ischaemic strokes may be subdivided depending on whether they are the result of a thrombus, (a clot formed *in situ* within the artery, typically due to fatty deposits) or an embolus (a clot which forms elsewhere in the cardiovascular system before traveling to and obstructing the cerebral vasculature). Likewise, a haemorrhagic stroke may be further classified as either an intracerebral haemorrhage, which occurs within the brain tissue itself, or a subarachnoid haemorrhage, the result of bleeding between the surface of the brain and the surrounding meninges.[6] However, for the purpose of this report, only the two broad categories of ischaemic and haemorrhagic stroke will be considered since distinguishing between these is the most important diagnostic prerequisite for guiding treatment.

2.3 Treatment for Stroke

As aforementioned, the initial management for stroke depends entirely upon whether the stroke is identified to be ischaemic or haemorrhagic in nature. According to guidelines published by the National Institute for Health and Care Excellence (NICE), alteplase should be administered as soon as possible in the context of ischaemic stroke and is only considered clinically viable if given within 4.5 hours of symptom onset.[7] Alteplase is a tissue plasminogen activator which degrades fibrin and thereby helps to break up blood clots and restore normal blood flow.[8]

By contrast, in the event of a haemorrhagic stroke, surgical intervention may be required to remove the haematoma, prevent further bleeding, and relieve any increased intracranial pressure. If the patient is receiving any anticoagulant therapy, this ought to be immediately reversed via a combination of intravenous vitamin K and prothrombin.[7]

It is important to note that the treatments for these two stroke types are diametric opposites of one another and that incorrect classification and intervention may worsen the clinical outcome or indeed prove fatal. Moreover, the narrow window of opportunity that exists for certain interventions demands that rapid and highly-accurate diagnostic tools be in place, especially considering that the average time to hospital for a stroke victim in the UK was recently reported by the Royal College of Physicians to be nearly 3 hours.[9]

2.4 Current Stroke Diagnosis and Differentiation

Upon arriving at hospital, patients with suspected stroke must first undergo a rigorous clinical history and examination to help rule out other conditions which mimic stroke. Scoring questionnaires are frequently employed for this purpose and two of the most commonly utilised in the UK are the ROSIER and ABCD^2 questionnaires (Appendix 10.3). Although the history and clinical picture may provide some clues as to the origin and type of stroke, treatment should not be initiated until a definitive diagnosis can be made, which predominantly relies upon medical imaging.

X-ray Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are the two current diagnostic tools of choice for differentiating between ischaemic and haemorrhagic stroke.[2] CT scanners consist of an emitter which beams x-ray radiation through the body to multiple detectors arrayed opposite. The emitter and detectors move in an arc around the area of interest, producing numerous two-dimensional images which are combined digitally to yield a 3D computed image.[10] CT scanners have the advantage of being relatively fast and easy to use but impart a substantial dose of radiation in the region of 1-10mSv, the equivalent of over 100 plain film X-rays, and therefore do carry a small but detectable increase in the risk of cancer.[11]

An MRI scanner relies upon the principles of Nuclear Magnetic Resonance (NMR) and the property inherent to some subatomic particles known as “spin”. The human body is rich in hydrogen nuclei (protons), predominantly within fat tissue and internal fluids, and their spins become aligned in the strong magnetic field produced by the scanner which is in the order of 1-3 Tesla.[12] The scanner also pulses a radiofrequency current that creates a variable magnetic field and causes the protons to flip their spin. When this current is halted, the protons gradually return to their ordinary spin in a process known as precession.[12] This in turn produces a measurable radio signal and allows a 3D image to be constructed with exquisite soft-tissue detail since the rate of precession is different depending upon the tissue in which it occurs.

MRI has long been thought to be more accurate than CT imaging in the case of acute stroke and does not involve any harmful radiation, yet CT nonetheless remains the most common first-line investigation due to its wider availability, speed, ease of use and interpretation, and lower cost.[13]

An MRI scan typically lasts 30-60 minutes and is challenging for some patients who dislike the enclosed, claustrophobic nature of the scanner and the loud noises that it generates, particularly if the person is distressed or semi-conscious, which is frequently the case following a stroke.[2] Moreover, an MRI machine requires its own purpose-built room, devoid of all ferromagnetic materials, with a supply of liquid helium to cool the superconducting magnets within and it is prohibited to many

patients with metallic implants or tattoos.[2] A CT scanner is marginally more portable but remains a large and heavy machine that can only be wheeled around within a unit or potentially transported in the back of a specialised ambulance or mobile stroke unit.[14]

Both imaging tools are expensive, with quotes from LBN Medical placing a CT scanner at €35,000-€250,000 and an MRI scanner at €30,000-€3,000,000, not including the price of installation, warranty, staff training, and the cost of use.[15] As such, this precludes many individuals living in more deprived areas of the world as well as those living in remote locations far from the nearest specialist centre.

To summarise, stroke is a global health concern responsible for an extremely high level of mortality and morbidity worldwide. Rapid intervention is critical to limit the damage that occurs and rescue as much of the brain as possible, but treatment cannot begin until it is determined whether the stroke is ischaemic or haemorrhagic. Although the current imaging tools are capable of making this distinction, they suffer from a myriad of drawbacks related to cost, availability, safety, immobility, speed, and ease of interpretation. Therefore, this project seeks to identify ideas for a novel sensor in stroke identification which could mitigate some of these flaws and potentially find a place in clinical practice.

3. Identified Solutions

3.1 Initial Brainstorming

In the initial brainstorming session, the four project members pooled their knowledge and expertise in the fields of medicine, biology, chemistry, physics, and engineering in an effort to highlight avenues for further exploration. The aetiology of stroke and the differences between the types were discussed to identify potential targets for sensing systems and flaws in the current imaging techniques of CT and MRI were recognised.

Properties of a good sensor for this purpose were considered and included methods that were minimally invasive, inexpensive, sensitive, specific, portable, safe, fast, innovative, easy to operate, and non-damaging to tissues. Eight separate ideas were proposed for further discussion and investigation and are as follows:

- Specific biomarker detection
- Ultrasound imaging
- Microwave imaging
- Infrared imaging (with or without cold intra-arterial infusion)
- Impedance measurements
- Modified PET scan
- Modified intravascular 'lab on pill'
- Radioactively-tagged blood-specific proteins

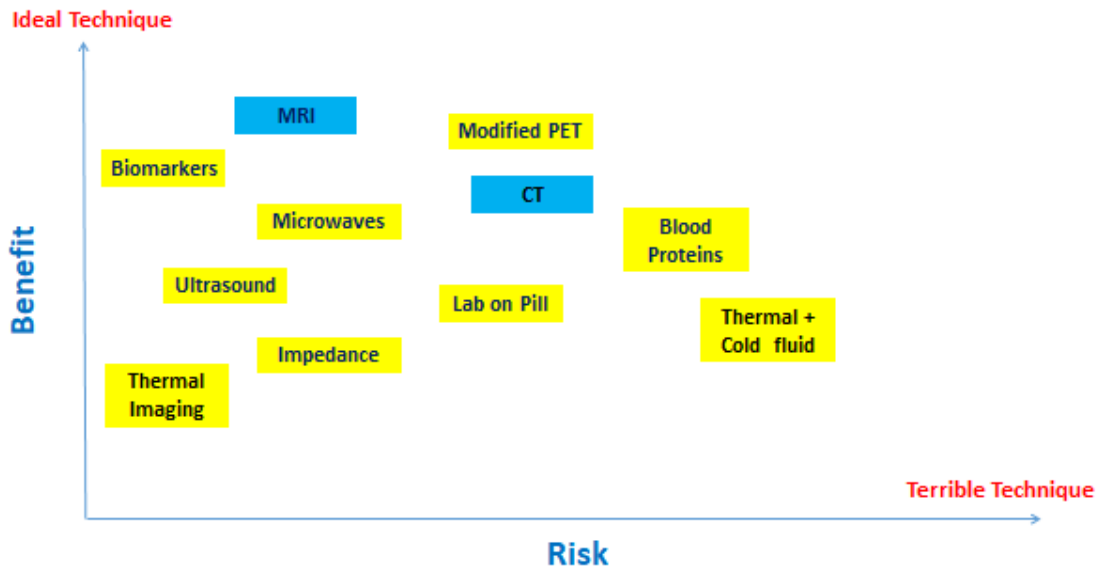

Figure 1 - Risk-Benefit Analysis Graph.

A cursory evaluation of these techniques took place in the form of a graphical risk-benefit analysis (*Figure 1).* Benefits included any of the ideal characteristics outlined above and risks entailed both hazard to the patient and threats to feasibility and success of the technique. All the suggested techniques were researched further following this first meeting, but priority was given to those that tended towards the top-left of the risk-benefit graph.

3.2 Second Brainstorming

The purpose of the second brainstorming session was to share preliminary findings on each of our ideas and to whittle them down to the few most promising. The idea of thermal imaging following injection of cold fluid was discarded due to multiple safety concerns and ultrasound was deemed to lack the resolution and innovation to warrant further speculation in this project. Little information could be found regarding the use of a lab on pill intravascularly and its potential feasibility and safety, so this was discounted also. Positron Emission Tomography (PET) scanning is already in use in stroke and suffers from many of the same drawbacks as CT and MRI including cost, duration, and specialist interpretation so this idea was not taken any further either.

This left five remaining techniques which were collectively scored for various criteria, weighted by importance, and then ranked accordingly. *Table 1* shows the results of this analysis with initial scores in brackets and final weighted scores in bold font. Initial scores are all out of 10, with higher scores being more desirable in all categories.

	Cost	**Minimally Invasive**	**Safety**	**Accuracy**	**Portability**	**Speed**	**Innovation**	**Ease of use**	**Total (/120)**
Weighting	*1.5x*	*1x*	*1.8x*	*2x*	*1.5x*	*2x*	*1x*	*1.2x*	-
Biomarkers	(7) **10.5**	(7) **7**	(8) **14.4**	(7) **14**	(10) **15**	(8) **16**	(7) **7**	(9) **10.8**	**94.7**
Microwaves	(8) **12**	(8) **8**	(9) **16.2**	(6) **12**	(8) **12**	(8) **16**	(8) **8**	(7) **8.4**	**92.6**
Thermal	(9) **13.5**	(9) **9**	(10) **18**	(2) **6**	(8) **12**	(8) **16**	(6) **6**	(7) **8.4**	**88.9**
Impedance	(8) **12**	(9) **9**	(10) **18**	(6) **12**	(7) **10.5**	(8) **16**	(8) **8**	(6) **7.2**	**92.7**
Blood Proteins	(6) **9**	(4) **4**	(6) **10.8**	(7) **14**	(6) **9**	(5) **10**	(9) **9**	(6) **7.2**	**73**

Table 1 – Weighted scoring analysis of various proposed techniques.

Accuracy and speed seemed to be the most critical characteristics of a good sensor in an emergent stroke, so these were weighted most highly. Any medical technology has stringent safety requirements so this was also considered to be of paramount importance and a device that is cheap and portable would be highly advantageous over the current state of the art giving these criteria greater significance too. The final scores from this exercise led to the following rankings for the remaining techniques:

1. Biomarker detection (94.7/120)
2. Impedance Tomography (92.7/120)
3. Microwave Imaging (92.6/120)
4. Thermal Imaging (88.9/120)
5. Radioactively-tagged blood proteins (73/120)

Notably, although the first three methods had similar overall results, they scored higher in different categories such that a combination of these methods would cover the problem from multiple angles and potentially have different scenario-specific applications. The three highest-scoring techniques were considered to be the most promising and feasible approaches to the problem of differentiating between ischaemic and haemorrhagic stroke and a deeper exploration of these formed the basis for the rest of this project.

---

4. Biomarker detection device

During either an ischaemic stroke (IS) or a haemorrhagic stroke (HS), neuronal and glial cells suffer an inadequate provision of oxygen and glucose. The ensuing energy failure triggers a complex biochemical process concluding eventually in the death of neurons and glial cells such as astrocytes.[16] Depending on the severity and duration of the stroke, these protective and detrimental pathways produce different molecules, some of them specific to each pathological mechanism.

A biomarker is a distinctive characteristic indicator that can be monitored to evaluate a physiological process quantitatively. It is usually a biochemical constituent or a biological substance that is, ideally, unambiguously associated with the evolution of a pathogenic condition.[17]

4.1 Panel composition

Our team found that numerous studies have reported distinct candidates to serve as biomarkers for the differentiation between IS and HS.[16–19] As specific proteins release into the bloodstream after brain cell damage, an initial approach was looking into biomarkers specific to neuronal and glial cells.

Glial Fibrillary Acidic protein (GFAP) has been extensively studied[20–23] as a specific marker of traumatic brain injuries, and comprehensive review reports[17,24,25] concluded that GFAP is the only marker capable of differentiating between IS and HS. Moreover, it is able to provide information on the damage extent and mortality outcome.

Recent reports[16,17] concluded that two proteins associated with neuronal cells, Heart Fatty Acid Binding Protein (H-FABP) and Myelin Basic Protein (MBP), have shown consistent performance as biomarkers for the early diagnosis of stroke.

As far as our group could explore, no previous studies have reported the simultaneous use of GFAP, MBP, and H-FABP for the differentiation between ischaemic and haemorrhagic stroke. After our interview with Dr Whitely, we found sufficient evidence to consider biomarkers as a feasible option for the purpose of this study.

4.2 Biomarker-based diagnosis proposal

We propose a panel of biomarkers, GFAP, MBP, H-FABP for the early diagnosis and identification of stroke type. Some considerations for this proposal are as follows:

- GFAP is the lead marker as this is the protein with the most reliable information supporting its role as bio-indicator.
- The dynamic range expected is $0 - 150\ ng \cdot ml^{-1}$
- The sensitivity must be a few $pg \cdot ml^{-1}$, at least five.
- The readings must be on intervals of 15-30 min to achieve sufficient resolution.
- MBP and H-FABP markers will enhance our cluster sensitivity allowing consistent and accurate monitoring of the level and its change over time of each protein.

4.3 Sensing method selection

Based on the above, our group consulted Professor Andy Mount for advice about protein detection. Professor Mount illustrated the antigen-antibody interaction mechanism and explained how antibodies evolve to bind with specific antigens.

After a brief review of biomarker sensing, we noticed that one reasonable prospect to accomplish the requirements is a FET-based device. Field Effect Transistors are one of the most matured technologies with proven capability of ultra-sensitivity and fast response.[26] FETs work either as a solid-state switch or as a continuous current modulator. A simplified operation mechanism is as follows. An electric field is regulated by an electric potential between the gate and a reference electrode. This, in turn, establishes a conductive region within the substrate enabling the electrical connection between the otherwise insulated source and drain electrodes (*Figure 2)*. The n-type minor carriers in the p-substrate are attracted to the gate by the effect of the electric field. The n-type conductive channel, i.e. the drain-source current, is proportional to the magnitude of the electric field. The original and detailed description of the FET working principle can be found in the publication by W. Shockley.[27]

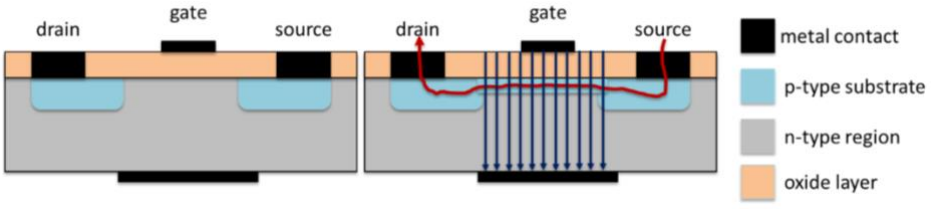

Figure 2 - Sectional view of an unbiased FET, left, and the established electric field (in blue) and current (in red) in a biased FET, right.

On the other hand, organic field effect transistors (OFETs) are a relatively emerging FET-based approach with distinctive advantages such as simple operation, large functional area (enhanced sensitivity), and biocompatibility. Furthermore, OFETs have proven the capability of real-time detection of numerous biological analytes.[21,23]

In an OFET, a receptor layer specially prepared to detect specific molecules carries out the detection mechanism[26] (*Figure 3)*. When target antigens combine with the immobilised antibodies, the reference potential at the receptor layer changes producing an alteration in the electric field between the receptor layer and the gate. An organic semiconductor (OSC) is used to generate the conductive channel as explained above.

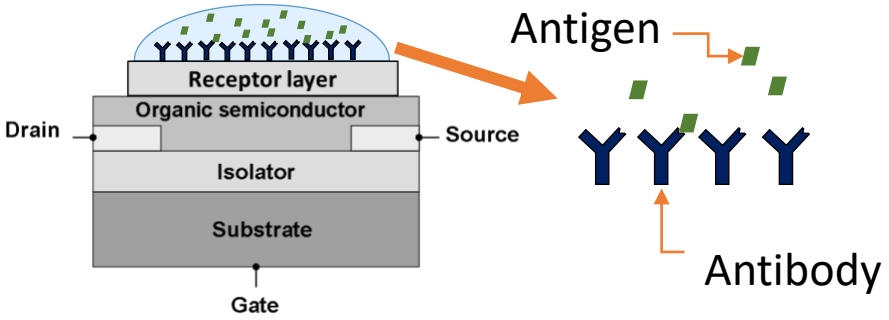

Figure 3 - Typical structure of an organic-semiconductor field effect transistor.

The idea of using a FET-based device for the detection of biomarkers is not new, including detecting GFAP[21,23]. However, these three molecules GFAP, MBP, and H-FABP have not been tested together in a panel, and therefore this approach can be regarded as novel.

Although our OFET-based panel detector features several advantages, some issues must be carefully addressed for the realisation of an optimised design.

- Challenges for real-time and continuous monitoring of proteins: to the best of our understanding, brain-injury-related proteins are currently measured *ex vivo*. Further research must be conducted to elucidate concerns associated with *in vivo* measurements.
- Carrier mobility: OSCs are mostly p-type and exhibit poor carrier mobility signifying low signal level. An innovative layer configuration or additional ancillary electronics should be developed to surmount this issue.

- Dielectric and receptor layers: appropriate selection of these layers is decisive for the stability (drift-free), accuracy of detection, sensitivity, and power consumption in the device.
- Electrostatic interaction: issues associated with cross-sensitivity must be analysed in an overall assessment. As most biomarkers and other biomolecules are charge carriers, they are likely to interfere with the sensor signal.
- Screening length: also known as Debye length, it is the minimum sensing distance in the device and therefore a central design parameter as it directly affects the sensitivity of the sensor.

4.4 SWOT analysis

After a careful SWOT analysis exercise (*Appendix 10.4)*, we concluded the sound advantage is that our proposed solution will enable enhanced selectivity, continuous monitoring, and portability.

Conversely, the main threats are costs associated with the sensitive layer and the respective antibodies for each analyte.

4.5 Additional comments on biomarker levels

The ascertaining of specific reference levels for each biomarker was not possible because there are no consistent numbers amongst authors. Review articles addressed this inconsistency and attributed this to several causes such as differences in study design, detection technique, clinical assessment, size sample, and non-heterogeneous patient groups. Nevertheless, the proteins selected in this study are the most promising biomarkers for the differential diagnosis of IS and HS.

5. Electrical Impedance Tomography

Electrical Impedance Tomography (EIT) is a sensing method that displays the changes in conductivity in a body, whether the change is in between the tissues or over time.[28] The basic principle is injecting known and small-volume AC currents through the body with electrodes attached to the surface and performing repeated measurements of the surface voltages through other attached electrodes.[29] As one may expect, this method would be remarkably cheaper and more portable compared to existing methods since a century of exponential advancement in the electronics industry has pushed the size and cost of very sophisticated electronic components down significantly.

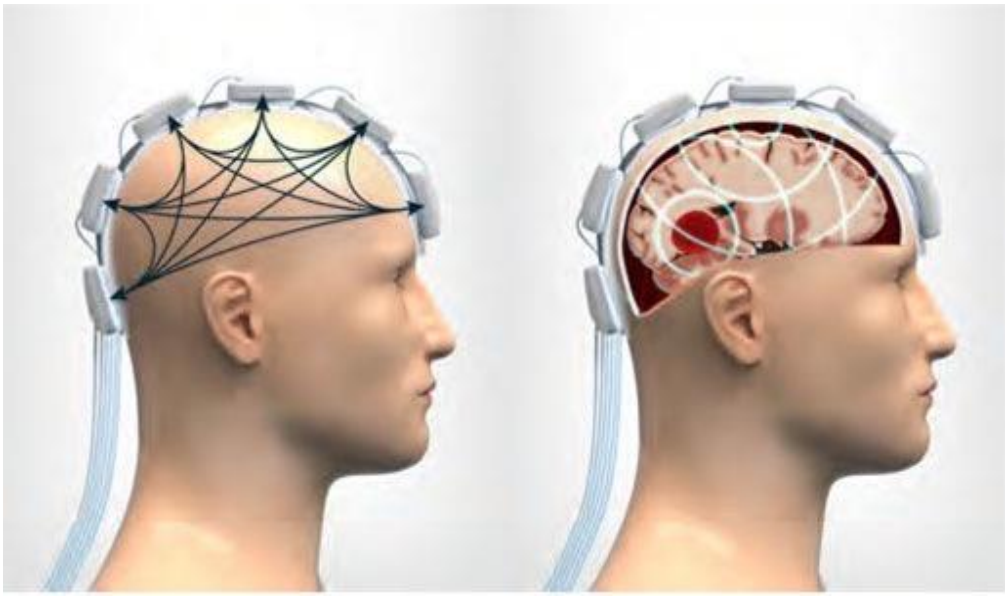

Figure 4 - Image showing what an EIT system would potentially look like.

The inspiration for this method came from body composition measurement systems present in gyms. Knowing that it injects a small amount of electricity into the body and relies on different impedance values between muscle, fat and bone tissues to display their spatial and mass distribution, we could be able to extract the location, size and specific impedance value of a stroke region when applied to a human head.

To be able to use EIT in differentiating between ischemic and haemorrhagic strokes, it is crucial to have a meaningful contrast in conductivity for each case. During one of the brainstorming sessions, it was proposed that a blood clot (and/or its associated O_2-deprived tissue) and a pool of blood (haemorrhage) would have different conductivity values compared to the healthy grey/white matter of the brain that shouldn't have these regions to begin with.

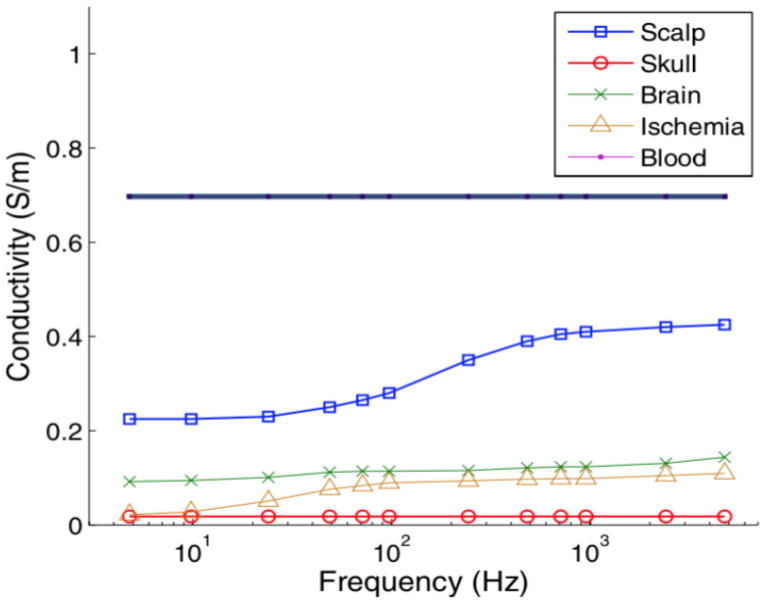

Figure 5 - Conductivity values of different tissues in the human head at different frequencies.

As it can be seen in *Figure 5*, there seems to be a measurable difference in conductivity values for such tissues.[30]

It is worth noting that one of the bigger challenges with EIT is getting the conductivity contrast with blood/ischaemia and brain tissue. *Figure 5* clearly shows that every measurable conductivity value lies above the conductivity value of the skull which significantly cripples our signal to noise ratio as higher impedance values tend to be more noticeable in the resulting signal spectrum. Unfortunately, this is not physically surmountable and needs to be dealt with via algorithms alone.

The main problem preventing wide spread adoption of EIT is the composition of the image from voltage measurements made on the skin surface. This happens because the resulting signal collected from the interaction of the tissues and electricity has to be used to identify the reverse of the path taken and reconstruct the image of the posterior state. This becomes a nonlinear and ill-defined problem due to errors in measurements and a wide range of variations between general distribution of electrical properties of the body and their susceptibility to internal current flows.[30]

Current applications of EIT that are in the trial stage involve mainly imaging the lung functions of the patient, detecting malignant tumours in breast area and diagnosis between ischemic and haemorrhagic stroke. However, in low contrast areas such as brain in skull, even state of the art phantom trials fail to identify tumour sizes smaller than 1 cm in diameter.[30]

6. Microwave Imaging

Microwave imaging is an imaging technique that is not so different than other diffraction-based imaging techniques that use interactions between electromagnetic waves and dielectric contrast in different biological tissues. It uses signals in the frequency range of hundreds of megahertz to a few gigahertz.[31] Equipment consists of a microwave source, a receiver-transmitter array and a switch.[31] For readers familiar with the costs of such electronic components, it will become clear that this method would be orders or magnitude cheaper than existing methods such as CT and MRI that not only have very high initial capital requirement but also have operating costs that would dwarf the operating costs of a microwave system. In addition, it is not unreasonable to expect component costs and sizes to go even further down as significantly larger telecommunications industry and IOT devices move towards microwave range for faster data transmission rates with 5G. Another major advantage of such a system would be safety as it uses non-ionising, low energy waves (100 times lower than what one would be exposed to using a mobile telephone).

After establishing that different tissues would have different conductivity values and that this can be exploited to differentiate the type of stroke with impedance measurements, another electrical property was also investigated which is the dielectric constant. Known electromagnetic waves would interact differently with different tissues based on their dielectric constant and, similar to EIT, an inverse image can be constructed through that interaction. Due to the fact that its non-ionising but might be able to penetrate through tissues with a sufficient amount of resolution, the microwave range is selected to exploit dielectric contrast.

As it is fundamental wave knowledge that some magnitude of waves gets reflected back when changing media with different impedance values (in our case, dielectric constant), the choice of matching medium between transmitter and patient head is extremely important to improve coupling between the probing wave and inspected tissues that maximises the amount of incident power that penetrates into brain tissue. *Figure 6* shows the transmission coefficient based on relative permittivity of matching medium with respect to wave frequency.[32]

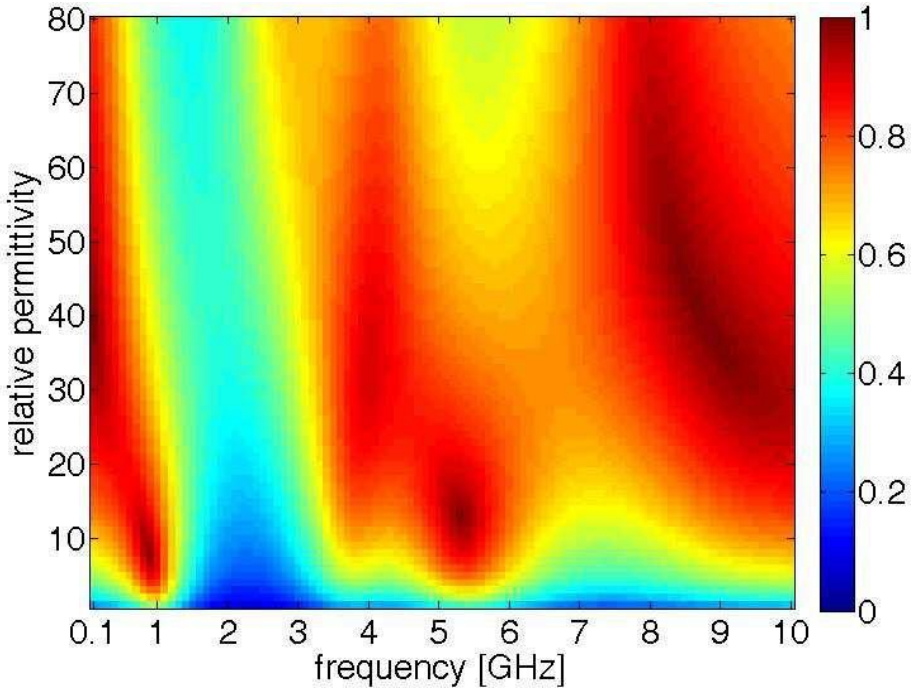

Figure 6 - Transmission coefficient based on relative permittivity of matching medium for different wave frequencies

It is also essential that waves passing through tissues should survive to be absorbed by receiver antennas in the end, in order for algorithms to be able to interpret the interaction and provide an image. That means penetration depth of different frequency waves becomes important as only the ones that can penetrate sufficiently can be used for this application, allowing us to fix one of the variables in such a design. *Figure 7* shows frequencies that can penetrate different types of brain tissues.[32]

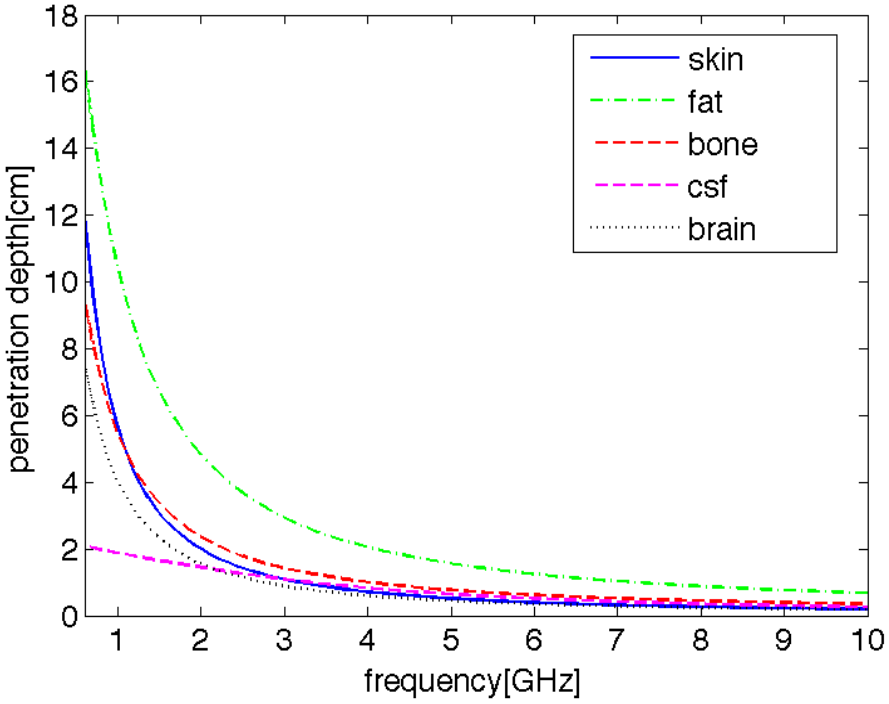

Figure 7 - Penetration depth of waves for different brain tissues.

Combining both graphs, we can see that using frequencies above 3.5 GHz would not be feasible as their penetration depth is very shallow and, regardless of the choice of matching medium, it looks like there is a forbidden band of frequencies between 1.2-3.5 GHz that does not penetrate well into the brain tissue. It is also worth noting that going below 600 MHz would also yield a very low spatial resolution leaving us with a narrow workable range between 0.6-1.2 GHz.

Microwave imaging in brain is widely investigated and there are simulations showing the feasibility of such application. However, they also show its limitations.

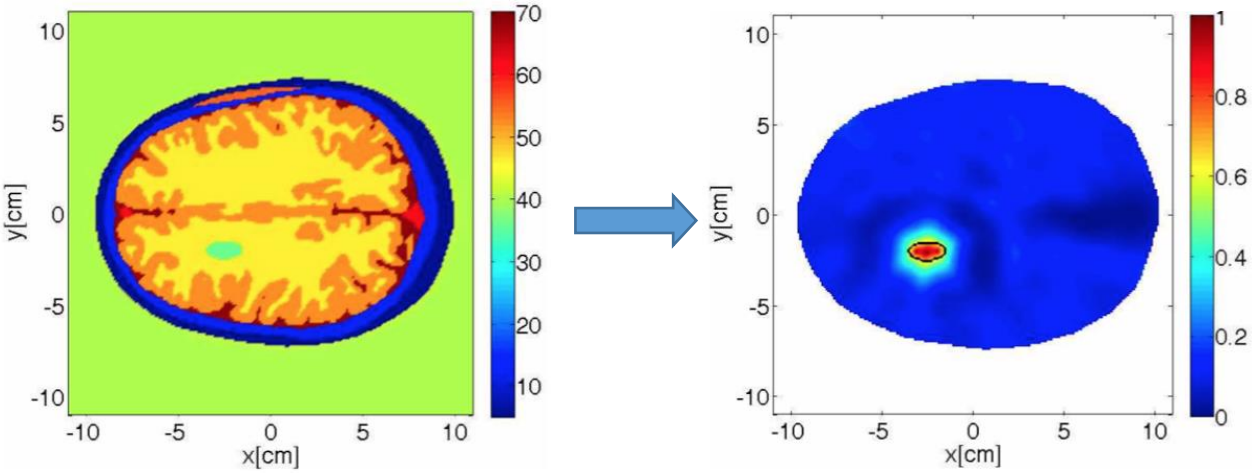

Figure 8 - Simulation for detecting a tumour with 2 cm diameter with microwave imaging.

Figure 8 shows how a tumour with a diameter of 2 cm shows up in microwave imaging[31]. Unfortunately, for practical applications, this paints a bitter picture similar to EIT since again the contrast we are interested in is shielded in another higher dielectric contrast between skull and brain tissue. Some studies clearly demonstrate that this becomes a problem with smaller sized anomalies.

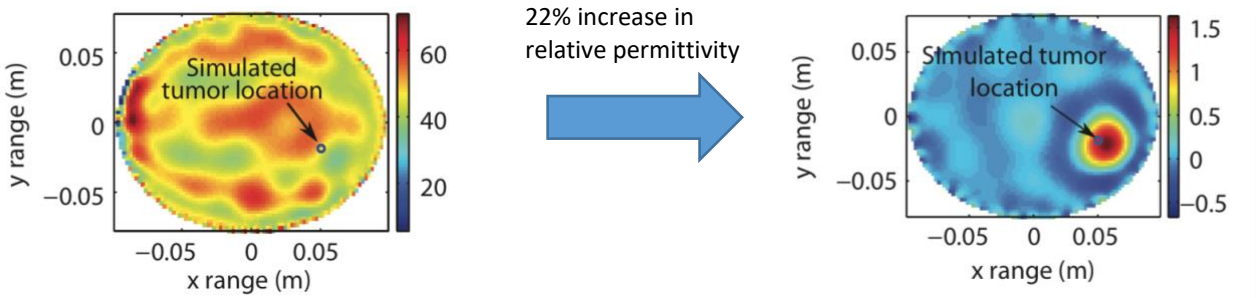

Figure 9 - Simulation for detecting a tumour with 5 mm diameter with microwave imaging aided by using contrasting agent

A tumour with 5 mm diameter does not give out sufficient amount of signal to be detected. However, by adding contrasting agent and taking a differential image, tumour location and size can be identified which can be translated to detect the size, shape and type of stroke since with haemorrhage local dielectric constant would increase whereas with ischaemia local dielectric constant would decrease.[31,33]

Similar to EIT, the main problem preventing widespread adoption of microwave imaging is the composition of the image from measurements made between transmitting and receiving antennas. This happens because the resulting signal collected from interaction of the tissues and electromagnetic waves has to be used to identify the reverse of the path taken and reconstruct the image of the posterior state. This becomes a nonlinear and ill-defined problem due to errors in measurements and the wide range of variations between general distribution of dielectric properties of the body and their susceptibility to internal current flows as well as the abundance of electromagnetic waves in almost any environment today. Coming up with robust algorithms that will perform well in identifying poorer signals would revolutionise microwave imaging and subsequently, the field of medicine as a whole.

---

7. Comparison of techniques

Our initial quantitative ranking of techniques led us to further investigate 3 methods for the differentiation between ischaemic and haemorrhagic stroke:

1. Biomarker detection (94.7/120)
2. Electrical Impedance Tomography (92.7/120)
3. Microwave Imaging (92.6/120)

A major complication in the diagnosis of stroke is that the possibility of a stroke mimic must also be excluded. This is compounded by the possibility of clots or bleeds being smaller than a centimetre in diameter, leading to the resolution requirements for any imaging-based technique to be extremely high. This was highlighted to us during our meeting with Dr Whitely, who impressed upon us that any new stroke diagnosis technique must improve upon what can currently be offered by CT and MRI scanners. Upon further analysis, it was clear that both EIT and microwave imaging suffer from similar difficulties with signal contrast which would require a huge investment of time to find algorithms capable of compensating for this fact.

This is not to say that biomarker detection is without possible fault, as further clinical testing is required to authenticate the viability of the panel. However, it has been shown that GFAP is effective at differentiating between ischaemic and haemorrhagic stroke, such that the inclusion of further biomarkers and creation of a fast-acting panel without the need for lab testing would give the effective and fast outcome required for objective success.

Another pivotal factor for our prospective solution to replace current technology is accessibility. The biomarker panel would require a blood sample, which would routinely be taken during a hospital admission, with the panel providing a clear indication of whether the required levels are present for the diagnosis of ischaemic/haemorrhagic stroke or a stroke mimic. This would, therefore, require very little extra training after implementation and bedside results.

For microwave and EIT techniques, while the core technology is closer to completion, specialist staff would be required to set-up and run the scan as well as read the results. This would make the technique less attractive to a hospital which must already employ staff and units dedicated to the operation of CT and MRI devices with their myriad uses.

8. Research Proposal

8.1 Research Proposal for stage 1 of panel creation

Problem Statement:

Thesis statement: Are GFAP, MBP and H-FABP suitable for the diagnosis of Ischemic and haemorrhagic stroke and recognition of a stroke mimic?

Main Points:

1. Measurement of protein levels
2. Consistency across a global population
3. Dangers of inconsistent results (not due to calculation error)

Purpose of study:

Research into the suitability of GFAP, MBP and H-FABP as a complete biomarker panel for the identification of ischaemic and haemorrhagic stroke and stroke mimic.

Significance of Research:

- Data can be used to safely show the utility of a biomarker panel in stroke diagnosis
- Additional objective of using research conclusions to inform the design of the physical panel for use in hospitals and ambulances globally

Methodology:

Research biomarker levels across different human populations

1. At normal levels
2. During a stroke and stroke mimic event
3. With a positive outcome being reliant on a lack of discrepancy between populations

Research design:

- Literature Review
- Study of healthy individuals from a diverse genetic pool
- Study of hospitalized individuals presenting with symptoms of stroke from a diverse genetic pool

Instrumentation:

Need to authorise, collect and test blood samples

- Needles, syringes, hazardous materials containment
- Medical biology lab

Data collection and analysis procedures:

Blood samples

- Individuals opt-in to study, provide personal details
- Collected from hospitals and GPs surgeries around the world
- Shipped to central testing lab to ensure consistency in testing
- Measure levels of GFAP, MBP and H-FABP

Budget:

	Time (years)	Expenditure (£)	Total (£)
PhD student (normal levels)	3	14,500	43,500
PhD student (stroke levels)	3	14,500	43,500
Lab tech	3	22,000	66,000
Supervisor	6	50,000	300,000
Hospital incentive (35 hospitals)	~	140,000-200,000	200,000
Lab	3	100,000	300,000
Expenses	6		+10%
		TOTAL (£)	**1,050,000**

(£10 per test, ~400 per hospital, 14,000 sample (7,000 each type))

8.2 Further Work

After validation of the biomarker panel, further research would be commissioned to produce a working prototype of the panel device. This would be reliant on a positive outcome from stage one of the research. As listed in section 4.3, the viability of FET and OFET would need to be tested for viability as part of a portable device capable of reliable and fast GFAP, MBP and H-FABP detection.

It would be at this stage that targeting of the device to the market will need to be examined.

While it is the case that the completion of the biomarker panel would signal a marked improvement in detection times in developed regions of the world, this device could also present a giant leap forward in the developing world where CT and MRI scanners are frequently inaccessible. It is true that this project would require huge investments of time and money to present a successful outcome. However, as stroke the second leading cause of death globally, it also presents a huge opportunity to these untapped markets.

To conclude, we have successfully produced a research proposal to develop a novel method for the diagnosis of ischemic and haemorrhagic stroke from stroke mimics. By examining different methods of sensing and utilising the backgrounds within the group, we have ensured any ideas have been investigated for validity, safety and effectiveness. *(5598 words)*

9. References

1. World Health Organisation Top 10 Causes of Death, https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death, (accessed December 2018).
2. B. R. Walker, N. R. Colledge, S. H. Ralston and I.D. Penman, *Davidson's Principles and Practice of Medicine,* Churchill Livingstone Elsevier, Edinburgh, 22nd edn, 2014.
3. E. Auriel, in *Stroke,* ed. N. M. Bornstein, Karger, Basel, 2009, Anatomy and Pathophysiology of Stroke, pp. 1-8.
4. P. Ramos-Cabrer, F. Campos, T. Sobrino and J. Castillo, *Stroke,* 2010, **42**, S7-S11.
5. American Stroke Association, https://www.strokeassociation.org/STROKEORG/AboutStroke/TypesofStroke/IschemicClots/Ischemic-Strokes-Clots_UCM_310939_Article.jsp, (accessed December 2018).
6. Etiology, Classification, and epidemiology of stroke, https://www.uptodate.com/contents/etiology-classification-and-epidemiology-of-stroke?topicRef=1134&source=see_link, (accessed December 2018).
7. Clinical Guideline [CG68] Stroke and transient ischaemic attack in over 16s: diagnosis and initial management, https://www.nice.org.uk/guidance/cg68/chapter/1-Guidance#pharmacological-treatments-for-people-with-acute-stroke, (accessed December 2018).
8. British National Formulary Alteplase, https://bnf.nice.org.uk/drug/alteplase.html, (accessed December 2018).
9. Royal College of Physicians Latest Quarterly Sentinel Stroke National Audit Programme (SSNAP) Results, https://www.rcplondon.ac.uk/news/world-class-stroke-care-achievable-latest-quarterly-sentinel-stroke-national-audit-programme-0, (accessed December 2018).
10. J. Hsieh, *Computed Tomography: Principles, Design, Artifacts, and Recent Advances*, SPIE, 3rd edn, 2015.
11. D. J. Brenner and E.J. Hall, *N Engl J Med,* 2007, **357,** 2277-2284.
12. D. B. Plewes and W. Kucharczyk, *JMRI,* 2012, **35(5),** 1038-1054.
13. A. Ciccone, R Sterzi and L. Munari, *The Lancet,* 2007, **369,** 1342-1343.
14. UCLA Trials Ambulance Equipped with CT Scanner for Rapid Stroke Treatment, https://www.medgadget.com/2017/10/ucla-trials-ambulance-equipped-ct-scanner-rapid-stroke-treatment.html, (accessed December 2018).
15. LBN Medical Products, https://lbnmedical.com/, (accessed December 2018).
16. K. Makris, A. Haliassos, M. Chondrogianni and G. Tsivgoulis, *Crit. Rev. Clin. Lab. Sci.,* 2018, **55**, 294–328.
17. M. Katan and M. S. Elkind, *Clin. Transl. Neurosci.*, 2018, 2, DOI: 10.1177/2514183X18768050.

18. N. Hasan, P. McColgan, P. Bentley, R. J. Edwards and P. Sharma, *Br. J. Clin. Pharmacol.*, 2012, **74**, 230–240.

19. J. Y. Lee, C. Y. Lee, H. R. Kim, C.-H. Lee, H. W. Kim and J. H. Kim, *J. Korean Neurosurg. Soc.*, 2015, **58**, 93.

20. U. Missler, M. Wiesmann, G. Wittmann, O. Magerkurth and H. Hagenström, *Clin. Chem.*, 1999, **45**, 138–141.

21. W. Huang, K. Besar, R. LeCover, P. Dulloor, J. Sinha, J. F. Martínez Hardigree, C. Pick, J. Swavola, A. D. Everett, J. Frechette, M. Bevan and H. E. Katz, *Chem Sci*, 2014, **5**, 416–426.

22. Department of Neurosurgery, The Central Hospital of Xian, Shanxi Province, Xian, 710004, China and T. Wang, *Int. J. Electrochem. Sci.*, 2017, 7341–7350.

23. J. Song, J. Dailey, H. Li, H.-J. Jang, P. Zhang, J. T.-H. Wang, A. D. Everett and H. E. Katz, *Adv. Funct. Mater.,* DOI:10.1002/adfm.201606506.

24. L. Schiff, N. Hadker, S. Weiser and C. Rausch, *Mol. Diagn. Ther.,* 2012, **16**, 79–92.

25. M. Rozanski and H. J. Audebert, *AME Med. J.,* 2018, **3**, 14.

26. Y.-C. Syu, W.-E. Hsu and C.-T. Lin, *ECS J. Solid State Sci. Technol.,* 2018, **7**, Q3196–Q3207.

27. W. Shockley, *Proc. IRE*, 1952, **40**, 1365–1376.

28. D. S. Helder, *NeuroImage*, 2003, **20**, 752-764.

29. I. R. Cohen, A. Lajtha, J. D. Lambris, R. Paoletti and N. Rezaej, *Advances in Experimental Medicine and Biology,* Springer, Corfu, 2016, vol. 989, ch. 9, pp. 109-117.

30. E. Malone, M. Jehl, S. Arridge, T. Betcke and D. Holder, *Physiological Measurement,* 2014, **35,** 6.

31. R. Chandra, I. Balasingham, H. Zhou and R. M. Narayanan, in *Medical Image Analysis and Informatics: Computer-Aided Diagnosis and Therapy,* ed. P.M. de Azevedo-Marques, A. Mencattini, M. Salmeri, R.M. Rangayyan, CRC Press, 2018, ch. 19, pp. 451-466.

32. R. Scapaticci, L. Di Donato, I. Catapano, and L. Crocco, *Progress in Electromagnetics Research B,* 2012, **40**, 305-324.

33. M. Persson et al., *IEEE Transactions on Biomedical Engineering,* 2014, **61(11)**, pp. 2806-2817.

10. Appendix

10.1 Notes from Technical Meeting with Dr Will Whitely

Dr Whitely: Outlined stroke types, treatments and how those treatments and their outcomes are strongly linked with time to diagnosis.

Alberto**:** Proposed our blood biomarker panel.

Dr Whitely: Be aware that people have different normal levels, so a larger panel may create false negatives. Ensure a high level of understanding in the pathological processes when selecting biomarkers.

Kaan: Proposed microwaves method.

Dr Whitely: Approved of the idea. Clots can be very small, so equipment must have a high level of resolution.

Gregory: Proposed thermal imaging technique.

Dr Whitely: Other factors could affect blood flow. Detection would be highly reduced within the skull. Areas seem to paradoxically get hotter, not colder during stroke.

Alix: Asked where does he see the future of stroke diagnosis.

Dr Whitely: Miniaturisation of current technologies - smaller and cheaper CT scanners. Recommended improvement over innovation.

10.2 Notes from Technical Meeting with Prof Andrew Mount

Our group interviewed Professor Mount after one of his lectures in the James Watt Building. We introduced the subject and explained to Professor Mount the reason we asked him for some advice.

Group: Where should we start to look when it comes to protein detection?

Prof Mount: Explained in-depth the way antibodies evolve to bind to specific analytes and addressed the topic of field effect transistors.

Group: Could we use a kind of electronic device to detect this type of proteins?

Prof Mount: This is the way that some proteins have been detected for a while. Also suggested looking into ISFETS (Ion-sensitive FET) for a better understanding of these devices and perhaps a possible answer to our question.

After our brief talk with Professor Mount, our team was encouraged to continue considering the biomarkers avenue for further assessment.

10.3 Clinical Assessment Questionnaires

ROSIER Scale
Stroke Assessment

The aim of this assessment tool is to enable medical and nursing staff to differentiate patients with stroke and stroke mimics.

Assessment Date ☐☐☐☐☐☐ Time ☐☐☐☐

Symptom onset Date ☐☐☐☐☐☐ Time ☐☐☐☐

GGS E=☐ M=☐ V=☐ **BP** ☐☐☐ ***BM** ☐☐☐

**** If BM < 3.5 mmol/l treat urgently and reassess once blood glucose normal***

Has there been loss of consciousness or syncope?

Y (-1) ☐ N (0) ☐

Has there been seizure activity?

Y (-1) ☐ N (0) ☐

Is there a NEW ACUTE onset (or on awakening from sleep)?

I.	Asymmetric facial weakness	Y (+1) ☐	N (0) ☐
II.	Asymmetric arm weakness	Y (+1) ☐	N (0) ☐
III.	Asymmetric leg weakness	Y (+1) ☐	N (0) ☐
IV.	Speech disturbance	Y (+1) ☐	N (0) ☐
V.	Visual field defect	Y (+1) ☐	N (0) ☐

*Total Score _____ (-2 to +5)

Provisional diagnosis: ☐ Stroke ☐ Non-stroke (specify) _____

* Stroke is likely if total scores are > 0. Scores of </= 0 have a low possibility of stroke but not completely excluded.

A&E / EAU Stroke Instrument Guidelines

1. If total score > 0 (1 to 6) a diagnosis of acute stroke is likely. If total scores 0, -1 or -2 stroke unlikely but is not excluded and patient should be discussed with the stroke team. DECT phone 21616 – Stroke Specialist Nurse 9-5. Medical SpR – Out of hours.
2. All patients admitted with a suspected stroke, irrespective of score should be admitted to the Emergency Admissions Unit (EAU) at the RVI. Patients with a score of 0, -1 or -2 should be admitted to the EAU at the RVI.
3. If symptom onset within 3 hours and score >0 contact acute stroke team IMMEDIATELY for potential thrombolysis treatment and arrange urgent CT scan. Monday to Friday discuss with Stroke SpR or Consultant. Out of hours contact on call Stroke Consultant.

PTO

ABCD^2 Scale
TIA Assessment

The ROSIER scale is not suitable for patients with suspected TIA with no neurological signs when seen. **Please use the ABCD^2 assessment for patients with suspected TIA. This assessment assists in the identification of patients with a high or low risk of early disabling stroke.**

Please circle the appropriate point on the ABCD^2 assessment:

Age is 60 years or older	1 point	
Blood pressure >140/90mmHg	1 point	
Clinical features:		
▪ Unilateral weakness	2 points	Note, maximum score of 2 points
▪ Speech disturbance without weakness	1 point	
▪ Other	0 points	
Duration:		
▪ > 60 mins	2 points	
▪ 10 – 60 mins	1 point	
▪ < 10 mins	0 points	
Diabetes	1 point	
ABCD^2 Score _____ points	(Total score 0-7)	

Note: High risk patients (six to seven points) have an 8.1% two-day recurrent stroke risk.

High risk TIA patients (scoring 5 or more on ABCD^2 score) should be:-

- Seen within 24 hours of the event at the TIA clinic (patients referred to the TIA clinic at the RVI need a TIA clinic referral form completed)

or

- Out of hours (e.g. at weekends), contact the on-call Stroke Consultant and admit for review, urgent investigation and initiation of secondary prevention.

Any patient with more than one episode in the last week is at a greater than 30% risk of stroke within a week and should be admitted to EAU for investigation and review by a Consultant Stroke Physician.

This ABCD^2 scale is not a substitute for a full medical assessment.

10.4 SWOT Analyses

1 - Biomarkers

	Helpful	Harmful
Internal	**Strengths** • High selectivity • Continuous monitoring • Portability	**Weaknesses** • Minimally invasive • Specificity

External	**Opportunities**
	• Conclusive data for stroke type diagnostic and prognostic.
		Threats
		• Cost dependent of sensitive layer
		• Other techniques
		  • Electrochemiluminescence
		  • Spectrophotometry, etc.

2 – Microwave Imaging

	Helpful	Harmful
Internal	**Strengths** • Non-Ionizing • Continuous monitoring • Portability	**Weaknesses** • Low spatial resolution • Lack of suitable inverse imaging algorithms
External	**Opportunities** • Advancements in telecom industry drive component costs down	**Threats** • Low participation in clinical trials (time sensitive treatment)

3 – Electrical Impedance Tomography

	Helpful	Harmful
Internal	**Strengths** • Non-Ionizing • Continuous monitoring • Portability	**Weaknesses** • Low image quality • Lack of suitable inverse imaging algorithms
External	**Opportunities** • Advancements in electronics industry drive component costs down	**Threats** • Low participation in clinical trials (time sensitive treatment)

[End of Report]