

A Novel Near Infrared Diffuse Optical Spectroscopy System for Stroke Prediction and Diagnosis on the Neck

By

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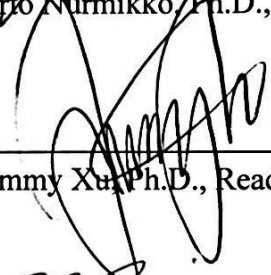
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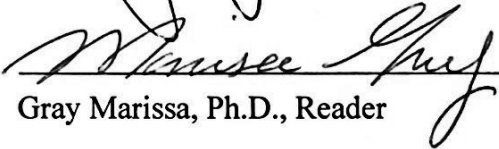
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Contents

1	Motivation and Objective	7
1.1	Motivation	8
1.2	Objective	10
2	Stroke, Stroke Diagnostics and State-of-Arts Review	12
2.1	Stroke and Importance of Stroke Diagnostics	13
2.1.1	What is a stroke?	13
2.1.2	What could cause a Stroke?	14
2.1.3	Why is stroke so important?	14
2.1.4	Why is stroke diagnosis so important?	15
2.1.5	What is the role of diagnostic technologies in clinical stroke management?	16
2.2	Technologies and Clinical Applications Review	17
2.2.1	Current state of technologies	17
2.2.2	Key Technologies Under Development	31
2.3	Market for Stroke Diagnostics	35
2.4	Key Challenges and Unique Opportunities	36
2.4.1	Challenges	36
2.4.2	Opportunities	38
2.5	References	39

3	Multi-layer Heterogeneous Tissue Mimicking Phantom Preparation With Optical and Mechanical Properties	42
3.1	Introduction	43
3.2	Materials and Methods	44
3.2.1	Materials	50
3.3	Results and Discussion	50
3.4	Reference	53
4	Non-invasive NIRS System Design for Stroke Prediction and Diagnostics	54
4.1	Introduction	55
4.2	System Design	59
4.2.1	System Concept	59
4.2.2	Noise and Error Sources	61
4.2.3	Lock-in Detection	63
4.2.4	Bench-top Design	63
4.2.5	Circuit Design	66
4.3	Results and Discussion	66
4.4	Reference	75

List of Figures

1.1	A. Several etiologies that cause an ischemic stroke; B and C. Anatomical structure of carotid arteries. [COPYRIGHT: McGraw-Hill Education. Harrison's Principles of Internal Medicine, 19th Edition]	9
1.2	An illustration of embolism ischemic stroke. [COPYRIGHT: NIH National Heart, Lung, and Blood Institute]	10
2.1	The work-flow for patients with suspected acute stroke in hospitals[7].	18
2.2	Basic blood and urine tests for stroke suspected patients[8].	20
2.3	(A) A CT scanner[11]. (B) The main structure of a CT system[11]. (C) The physical principle of CT[10]. (D) NCT image of a patient with a typical subarachnoid hemorrhage stroke (white arrow)[17].	23
2.4	(A) A NCT image of a patient with intracerebral hemorrhage in the basal ganglia (white arrow). (B) A NCT image of another patient with ischemic injury in the same area with (A)[17]. (C) A CTA image shows a large aneurysm arising from the vertebral artery on the left (white arrow)[2].	23
2.5	(A) CTP images for an ischemic stroke patient. Yellow circle indicates the abnormal region. (B) DWI confirms the lacunar infarction in right thalamus detected by CTP in (A)[28].	24

2.6	(A) A modern MRI scanner[10]. (B) The physical principle of MRI[14]. (C) The main structure of a MRI system[15]. (D) T2* MRI image of a patient with acute left thalamic intracerebral hemorrhage stroke[2]	26
2.7	MRI PWI-DWI mismatch. A, B are two PWI mean transit time (MTT) maps that show deficient blood flow through the right MCA territory (red region indicates prolonged MTT). C, D are DWI images showing a smaller area of infarction (white hyperdense). This PWI-DWI mismatch resulted in further reperfusion therapies, and good outcome was confirmed by a follow-up CT scan one day later (E). E only shows a subcortical infarct as a hypodense lesion (white arrows) [3].	27
2.8	T2-weighted MRI, DWI, contrast enhanced (CE) MRA and time of flight (ToF) MRA of one acute ischemic stroke. T2-weighted MRI didn't detect anything. DWI shows a hyperdense infarct region (white arrow). Both the two MRA images identified the position of occlusion in the right middle cerebral artery[21].	28
2.9	Advantages and disadvantages of CT and MRI for stroke diagnosis[8].	29
2.10	A. Catheter angiography performed by an interventional radiologist[19]; B. A whole cerebrovascular image by catheter angiography[20]; C. Internal carotid artery stenosis measured (white arrow) by catheter angiography[21]; D. A vertebrobasilar aneurysm measured (white arrow) by catheter angiography[21].	30
2.11	(A) An illustration of US working mechanism[13]. (B) An illustration of TCD operation[2]. (C) A new TCD product for stroke diagnosis invented by Neural Analytics, Inc[16]	32
2.12	Stroke diagnostic and prognostic POCT device summary table[29].	34
3.1	The anatomical structure of the human neck (transverse plane)	44

3.2	The ultrasound image of human neck	45
3.3	The structure of the multilayer phantom.	46
3.4	Thickness of each layer.	47
3.5	The basic materials for the multilayer neck phantom.	51
3.6	The basic materials for the homogeneous phantom.	52
3.7	The fabricated phantoms.	52
4.1	The proposed wearable NIRS system for stroke diagnostics.	57
4.2	The designed emboli detection system.	58
4.3	The designed emboli detection system.	59
4.4	The principle of CW NIRS[2].	60
4.5	The bench-top emboli detection system (with phantom).	63
4.6	The bench-top emboli detection system (with phantom).	64
4.7	Artificial emboli selection for experiments.	65
4.8	A close look at the artificial mental beads from 800 microns to 3 millimeters (diameter).	65
4.9	Watchdog: transmission optical module.	66
4.10	The circuit structure of the NIRS module.	67
4.11	A. Detected emboli signal on phantom (triple events); B. Detected single emboli event on phantom; C. The reference result from Solen et al.[13]; D. The measured blood flow waveform of carotid artery by the system.	67
4.12	Detected output for four different emboli on the phantom.	68
4.13	Upper: five emboli with different sizes; lower: four emboli with 800 μm diameter.	69
4.14	The emboli size dependent analysis.	69
4.15	Signal conditioning and drift removing by digital filters.	70

4.16	Left: Peak detection to differentiate embolic events; Right: Period calculation for circulation of the embolus	70
4.17	Asymmetric embolic waveform. Left: all the detected waveform in one plot; Right: 1 if left side valley is deeper.	71
4.18	Circuit schematic for NIRS module	72
4.19	Circuit schematic for power supply of the system.	72
4.20	An illustration of the PCB design in software	73
4.21	The fabricated PCB.	73
4.22	Published results comparison. Ref column 1 to 8: [5][6][7][8][9][10][11][12] . .	74

Chapter 1

Motivation and Objective

1.1 Motivation

Stroke is defined to describe brain injury caused by an abnormality of the blood supply to a part of the brain[2]. Once the blood does not carry enough sugar and oxygen or if the blood supply is inadequate to some parts of brain, the parts will stop working normally. If the time of this abnormal status exceeds some thresholds, it will lead to irreversible damage to the parts of brain, which we call it as a stroke event.

Stroke can not only kill people fast, but also permanently disable the people who survived. It is the third leading cause of death and the first leading cause of prolonged disability in most of the countries[2]. About 15 million people suffer a stroke each year worldwide. Five million of those die and five million are permanently disabled[4]. It is estimated the stroke mortality will be almost doubled because of the aging population and smoking population[5]. The situation is more serious in developing countries: by 2040 there will be a billion adults aged 65 years or older at risk for stroke[6]. Because Stroke is highly related to many chronic diseases such as hypertension, diabetes, arteriosclerosis and heart diseases. One family could be "destroyed" once one of the members got a stroke because of the resulting disability and long-term rehabilitation.

Time is the key factor for stroke management. The less time it takes to diagnose and treat a stroke, the less damage a stroke will bring to the brain. However, all the current diagnostic technologies in clinical can only be employed after the onset of a stroke: when patients experience suspected symptoms of strokes. A person could not feel any difference when he/she got a stroke. It usually takes some minutes, hours or even days, depending on the types, locations and severity of strokes, to perceive the stroke symptoms such as headache, muscle weakness, double vision and etc. When those symptoms happen, it means the brain tissues have already been damaged and neurons are dying. If there is a diagnostic technology

that could predict a stroke in advance or diagnose it at onset time by detecting the direct causes of a stroke, it will shorten the total time greatly thus save lives.

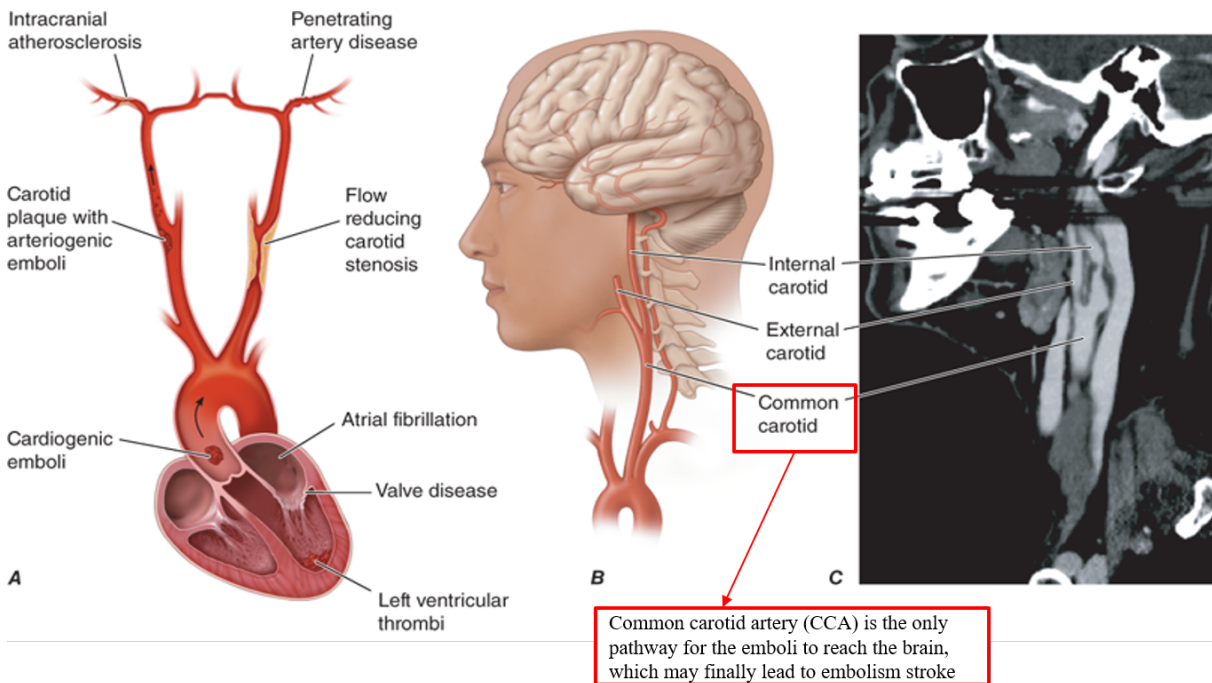


Figure 1.1: A. Several etiologies that cause an ischemic stroke; B and C. Anatomical structure of carotid arteries. [COPYRIGHT: McGraw-Hill Education. Harrison's Principles of Internal Medicine, 19th Edition]

Ischemic stroke is the most common type: it accounts for 80%-85% of total strokes in most parts of the world[3]. It is usually caused by an embolus or emboli that travel to occlude vessels of brain from proximal locations such as heart, aorta and carotid artery. Common carotid artery (CCA) is the only pathway for the emboli to reach the brain, which may finally lead to an ischemic stroke (Fig 1.1, Fig 1.2). It inspires us to place a "watchdog" above CCA to watch any "uninvited guests" (emboli) flow into cerebral vessels which will cause vessel blockages, thus, lead to an ischemic stroke.

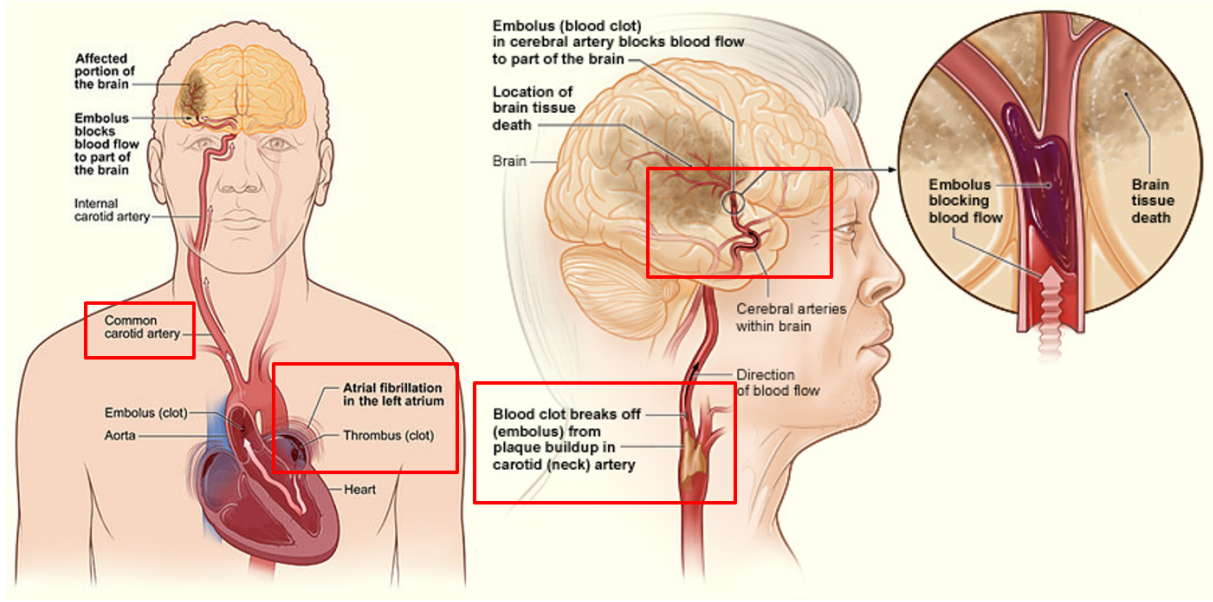


Figure 1.2: An illustration of embolism ischemic stroke. [COPYRIGHT: NIH National Heart, Lung, and Blood Institute]

1.2 Objective

The purpose of this research is to investigate the feasibility of developing a medical device to predict and diagnose an ischemic stroke by (1) counting the numbers of emboli which flow to cerebral vessels through CCA, (2) measuring the sizes of the emboli, (3) differentiating the types of the emboli, based on our diffuse optical method.

The final goal is to develop a wearable medical system to help predict and diagnose an ischemic stroke noninvasively in real-time, 24/7 with low cost. The system will be used in Step-down Units, Intensive Care Units, Emergency Rooms and Operation Rooms in hospitals (controlled environments) on high stroke risk patients such as patients who are having surgeries or have hypertension or had stroke before.

To achieve the final goal, in this pilot research investigation, we developed a near infrared (NIR) imaging system to detect artificial emboli on a tissue mimicking phantom, with cor-

related computed simulations. The objectives in this thesis includes:

1. A comprehensive review on state-of-arts stroke diagnostics technologies. By a detailed evaluation of all the current or under-development technologies, we can find a position (or role) for our technology in current stroke management process, and explain why our research is very necessary and promising in clinical use. The review is also unique and valuable since it is the first review that combines stroke diagnostic technologies, stroke management flow and stroke diagnostics market together to find the challenges and opportunities in stroke diagnostics. To our best knowledge, there is not any published review before like this.
2. Multi-layer heterogeneous tissue mimicking phantom design and preparation. The phantom is designed to mimic the optical and mechanical properties of neck tissues, CCA and arterial blood. Before testing the system on human subjects, all the experiments should be done on the phantom.
3. Non-invasive NIRS system design. The system is developed to detect emboli based on the NIR diffuse optical method. a complete benchtop system is designed and tested at first. Then an integrated system is developed on printed circuit board (PCB) to improve signal to noise ratio and reduce the system size.
4. Monte Carlo (MC) simulations on multi-layer heterogeneous tissue. MC simulations are developed and used to simulate the disturbance of detected photons caused by embolic events under the same conditions with real experiments. MC simulations are also used to guide the separation distance of sensors and sources.

Those four objectives can be regarded as the four necessary steps to the first milestone: proof of concept of the new stroke diagnostic technology.

Chapter 2

Stroke, Stroke Diagnostics and State-of-Arts Review

2.1 Stroke and Importance of Stroke Diagnostics

Stroke is a major cause of mortality and disability worldwide. In the US, stroke is the fourth leading cause of death and the first leading cause of long-term disability according to American Heart Association (AHA) [1]. It describes the abnormality of the blood supply to a part of the brain which could cause damage. Time is critical for stroke patients: once the stroke is onset, it should be treated as soon as possible to prevent irreversible brain injury. However, it is normally hard to become aware of stroke happening or distinguish the stroke with other stroke mimicking symptoms. Therefore, stroke diagnosis plays a key role in stroke treatments. This review will focus on stroke diagnostic technologies. Firstly, the background of stroke including the meaningful role of stroke diagnosis is explained. Then the current stroke diagnostic technologies which are widely applied in clinical settings are discussed. Following this, several key technologies which are not widely used and still under developing are introduced. Market for stroke diagnostics is briefly introduced. At last, key challenges and unique opportunities in stroke diagnostics area are discussed.

2.1.1 What is a stroke?

Stroke is defined to describe brain injury caused by an abnormality of the blood supply to a part of the brain[2]. Brain is one of the major energy consuming part in our bodies. It needs constant supply of sugar and oxygen to maintain its functionality. Both of them are carried by the blood: sugar in the serum and oxygen in the hemoglobin. Once the blood does not carry enough sugar and oxygen or if the blood supply is inadequate to some parts of brain, the parts will stop working normally. If the time of this abnormal status exceeds some thresholds, it will lead to irreversible damage to the parts of brain, which we call it as a stroke event.

2.1.2 What could cause a Stroke?

A stroke is caused by a disruption in the blood supply to the brain. It can be divided into two major types: ischemic stroke which is caused by occlusion of an artery in the neck or in the brain; hemorrhage stroke which is caused by rupture of a blood vessel in the brain.

Ischemic stroke is the most common type: it accounts for 80%-85% of total strokes in most parts of the world[3]. Ischemic stroke can be divided into two categories: thrombosis and embolism. Embolism is caused by an embolus or emboli that travel to occlude vessels of brain from proximal locations such as heart, carotid artery and aorta. Thrombosis is caused by a local thrombus developing at the site of occlusion in arteries such as arteriosclerosis at carotid artery.

Hemorrhage stroke can be divided into intra-cerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) according to the bleeding sites in brain. ICH may be caused by hypertension, degenerative disease of vessels and structure abnormalities of intracranial arteries[3]. SAH can be caused by the rupture of aneurysm.

2.1.3 Why is stroke so important?

Stroke can not only kill people fast, but also permanently disable the people who survived. It is the third leading cause of death and the first leading cause of prolonged disability in most of the countries[2]. About 15 million people suffer a stroke each year worldwide. Five million of those die and five million are permanently disabled[4]. It is estimated the stroke mortality will be almost doubled because of the aging population and smoking population[5]. The situation is more serious in developing countries: by 2040 there will be a billion adults aged 65 years or older at risk for stroke[6]. Because Stroke is highly related to many chronic diseases such as hypertension, diabetes, arteriosclerosis and heart diseases. One family could

be "destroyed" once one of the members got a stroke because of the resulting disability and long-term rehabilitation.

2.1.4 Why is stroke diagnosis so important?

Because of the complex etiologies of stroke, stroke diagnosis is the key to a correct therapy for a stroke patient. Stroke diagnosis starts from the very beginning of stroke onset: from distinguish symptoms to basic laboratory testing to medical imaging (CT, MRI, etc). Appropriate and timely therapies only can be conducted after that the doctors have distinguished the type of the stroke and identify the location and size of the injured part of brain. The major goals for stroke diagnosis are listed below:

1. Tell the real stroke from stroke-mimic problems;
2. Distinguish the hemorrhage and ischemic stroke;
3. Assess the volume of the damaged brain tissue;
4. Locate the vascular lesions which cause the stroke.

The information above is crucial for doctors to treat stroke patients. Furthermore, for a better stroke management, it is suggested an individualized and eclectic program of diagnostic tests should be tailored to the individual patient's problems[2], which we could call it personalized medicine today.

2.1.5 What is the role of diagnostic technologies in clinical stroke management?

The role of diagnostic technologies is to help to achieve the above goals for stroke diagnosis. Specifically, a good stroke diagnostic technology can help the clinicians to

1. get high spatial resolution anatomical information to locate lesions, thrombosis, embolism sites in brain;
2. obtain high temporal resolution information to observe the dynamic changes of hemorrhage or ischemic area of the brain;
3. acquire the functional changes of the brain: neural activity, hemodynamics, metabolism and etc.

Moreover, time management is crucial after stroke onset. The less time it takes for stroke diagnosis, the more probability to recover the injured brain part. So the diagnostic technologies are being developed to shorten the diagnostic time of stroke. For example, recombinant tissue plasminogen activator (rtPA) has been proven effective for patients who suffer ischemic stroke which need urgent thrombolysis. It is FDA approved and only needs intravenous administration which is less complicated. However, the benefit of rtPA tends to decrease significantly as time goes by. According to the FDA protocol, it can only be used within 3 hours from onset of stroke symptoms. It means clinicians should get enough information (e.g. distinguish ischemic or hemorrhage stroke) in a limited time by the help of diagnostic technologies before proceeding to use rtPA.

2.2 Technologies and Clinical Applications Review

In current clinical settings, any one of the diagnostic technologies has its own advantages and disadvantages. Doctors can not rely on only one technology. Multiple combinations of diagnostic technologies are used according to different protocols in hospitals. On the one hand, there are some developed technologies that already have been commonly employed in hospitals. On the other hands, a few technologies are still under developing that could be applied in clinical soon. Both of them will be introduced in this section. Biomedical imaging technologies such as CT, MRI, ultrasound and near infrared optical imaging will be emphasized in this review as they are the core parts in stroke diagnosis.

2.2.1 Current state of technologies

There is not a technology that is solely designed for stroke diagnosis. All the current technologies are general used for different purposes besides stroke diagnosis. For a better introduction, this section is organized according to the protocol of stroke diagnosis in hospitals. Figure 1 lists an clinical protocol for patient with suspected acute stroke[7][8]. The example follows the guideline of AHA. All the protocols for initial diagnosis and treatment have the same standardized steps to process acute stroke:

1. General neurological evaluation, blood testing and vital signs monitoring;
2. Medical imaging diagnosis using CT, MRI and etc;
3. Therapeutic intervention based on the escalated diagnostic results above.

Step 1 and 2 are stroke diagnosis, and step 3 is stroke therapy which is based on step 1 and 2. This review focuses on step 1 and 2.

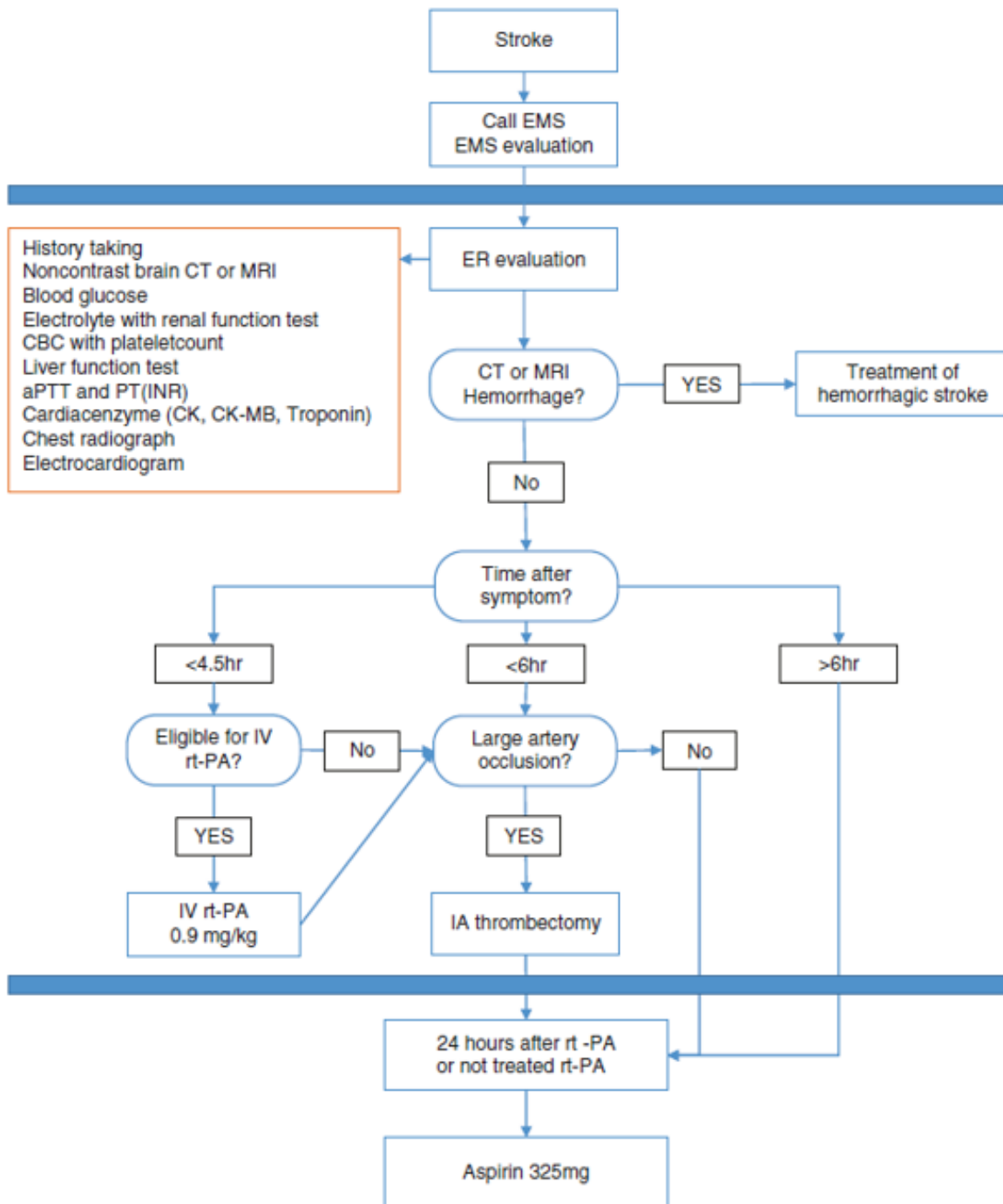


Figure 2.1: The work-flow for patients with suspected acute stroke in hospitals[7].

Basic Non-radiological Diagnostic Methods

After admission of stroke patients into hospital, the clinicians will score the patients according to the National Institute of Health Stroke Scale (NIHSS) to confirm the initial neurological status at the current stage. Meanwhile, all the stroke patients should have a check on several blood/urine tests and vital signs immediately. These non-radiological investigations are aimed to

1. distinguish possible stroke mimicking disorders which have similar symptoms with a real stroke. For example, the syncope can be caused by hypoglycemia instead of ischemic stroke.
2. find the possible causes of a stroke. For example, one type of embolus is lipid-core which is caused by hyperlipidemia.

Here the thesis review does not explain the detailed technologies used behind the blood testing and vital signs monitoring because they are widely utilized in hospitals.

Blood tests

The basic blood and urine tests for all the stroke suspected patients have been listed in figure 2. Through these tests, some treatable disorders may be revealed. **Full blood counts** including red, white blood cells and platelets are routinely performed, since abnormal amounts can cause strokes. **Erythrocyte sedimentation rate/C-reactive protein** are markers for inflammation. Inflammatory conditions and cancers may cause strokes. **Electrolytes, urea and urine analysis** may indicate the disorders of kidney which could cause complicate strokes. **Plasma lipids** test investigates the level of cholesterol, triglycerides and other lipoproteins. The high levels may lead to plaque formation and atherosclerosis which could generate thrombosis and embolism. **Hypoglycemia** could cause the stroke mimicking

symptoms. **Hyperglycemia** is known to worsen stroke outcome: it enlarges eventual stroke size and increases the risk of brain hemorrhage[9]. It is important to have a clotting screen: start from prothrombin time. If the blood coagulation time is abnormal, further tests will be ordered.

Investigation	Disorders detected
Full blood count	Anemia
	Polycythemia
	Leukemia
	Thrombocytopenia/thrombocytopenia
Erythrocyte sedimentation rate/C-reactive protein	Vasculitis
	Infective endocarditis
	Hyperviscosity
	Myxoma
Electrolytes	Hyponatremia
	Hypokalemia
Urea	Renal impairment
Plasma glucose	Diabetes
	Hypoglycemia
Plasma lipids	Hyperlipidemia
Urine analysis	Diabetes
	Renal disease
	Vasculitis

Figure 2.2: Basic blood and urine tests for stroke suspected patients[8].

Vital signs

- i. **Electrocardiogram (ECG):** ECG should be measured to check if there is atrial fibrillation or silent myocardial infarction which could be caused by a stroke. ECG Holter monitor which provides real time, long-term measurement will be used for a patient who has cardiac problems such as atrial fibrillation or other arrhythmia.
- ii. **Blood pressure (BP):** Hypertension is the single most important modifiable risk factor[9]. High BP can cause hemorrhage stroke because of the rupture of vulnerable vessels

or aneurysms in brain. Hypertension can also cause ischemic stroke because of the arterial blood flow may wash off the plaques and debris of thrombosis sites to generate embolus which can occlude the vessels in brain. Before treatment, BP control is very important to prevent complications: systolic BP should be less than 185 mmHg, diastolic BP should be less than 110 mmHg. BP can be monitored by a short-interval (15 mins) cuff-based oscillometric BP monitor noninvasively. If a real-time, accurate and long-term monitoring is needed in critical conditions, invasive catheter arterial line (A-line) method is necessary, which is, the gold standard of BP monitoring.

Basic non-radiological diagnosis is included in Step 1 in a standard clinical protocol described previously. Below is the step 2: medical imaging technologies are introduced for further stroke diagnosis.

Computed Tomography for Stroke Diagnosis

X-ray computed tomography (CT) revolutionized medical imaging since early 1970s. It provides the first noninvasive high resolution cross sectional images of the brain. CT technology has been continuously developed and widely deployed in most of hospitals since then. There are over 30000 CT scanners around the world and over 60 million CT scans are taken each year in the US[10]. Over the past decades, seven generations of CT technology have been developed. CT can be used for different imaging needs. For acute stroke diagnosis, three CT techniques, including non-enhanced CT, perfusion CT and CT angiography, could fulfill all the requirements for hyperacute stroke imaging[22].

Non-enhanced CT:

Imaging Principle: Non-enhanced CT (NCT), the fundamental one, use a CT scanner measure the X-ray attenuation through a finite thickness cross section plane of the body to

reconstruct an image of that slice. Through a large number of accurate measurements of slices (about 500000), the system can determine the complete image of the interested part of the body such as brain: we call this process as "tomography imaging". In detail, the CT system is consisted by three major parts: an X-ray tube with collimators, a linear array of detectors and an image reconstruction computer (figure 3). A fan beam of X-rays that are produced by an X-ray tube will attenuated by the body and measured by the array of detectors after transmission. The X-ray tube and detectors are mounted on a circular ring in a gantry. A complete image requires many projections at rotational angle intervals less than 1 degree for each cross section measurement. Based on the a large number of measurements, the actual attenuation (absorption coefficient) of each voxel can be reconstructed and displayed by the computer. The absorption coefficient of water is obtained as a calibrator. Materials which attenuate more than water have positive CT numbers while materials which attenuate less have negative CT numbers. For example, hemorrhagic parts in the brain absorb more X-rays, show hypertensive(white) than normal brain.

NCT is convenient and high sensitive to detect intracranial hemorrhage (ICH). So it has been used as the initial screening method for acute stroke patients to exclude ICH before further thrombolytic therapies such as rtPA. NCT can also diagnose the evolving infarction by showing the hyperdense sign at an artery, which indicates the thrombus at the artery. However, NCT only provides anatomical information with no physiological information. This limitation makes it very low sensitive for acute stroke detection[23].

Functional CT including perfusion CT (PCT) and CT Angiography (CTA), can measure physiological information to detect stroke. They can be performed immediately after NCT within the same CT examination to shorten the decision time. The total duration for one NCT, two series of PCT and a CTA is about 10 min[24].

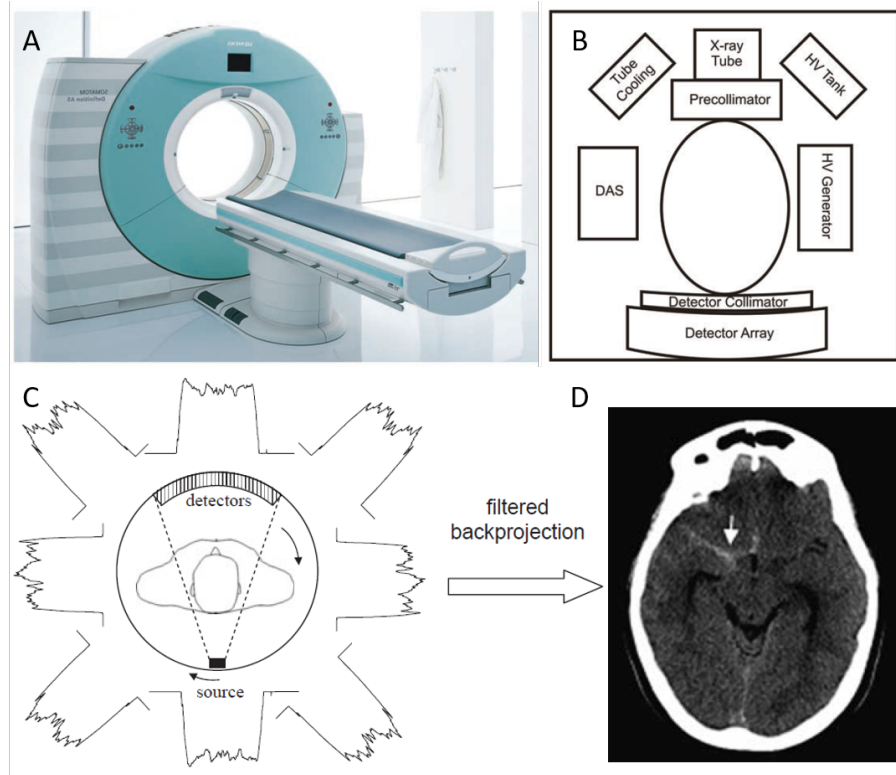


Figure 2.3: (A) A CT scanner[11]. (B) The main structure of a CT system[11]. (C) The physical principle of CT[10]. (D) NCT image of a patient with a typical subarachnoid hemorrhage stroke (white arrow)[17].

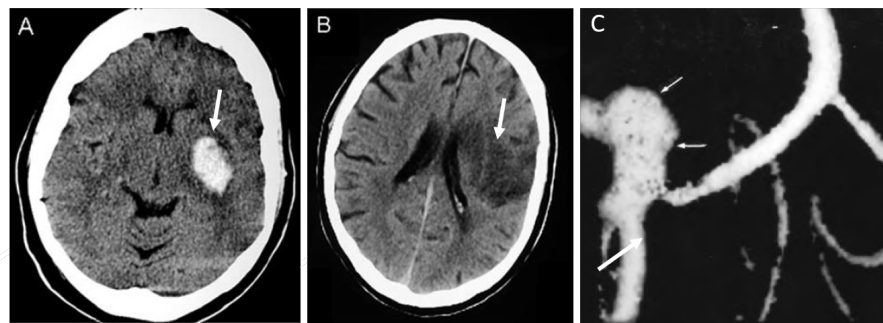


Figure 2.4: (A) A NCT image of a patient with intracerebral hemorrhage in the basal ganglia (white arrow). (B) A NCT image of another patient with ischemic injury in the same area with (A)[17]. (C) A CTA image shows a large aneurysm arising from the vertebral artery on the left (white arrow)[2].

Perfusion CT:

Imaging Principle: Based on the basic principles of CT, PCT imaging requires a helical CT scanner and an iodinated contrast. The scanner traces the entry and washout of a bolus of the dye injected into an arm vein through intravascular line[25]. PCT measures brain perfusion status by three types of parametric maps which relate to regional cerebral volume (rCBV), mean transit time (MTT), and regional cerebral blood flow (rCBF) respectively. Analysis of the perfusion measurement can help to reliably identify the irreversible infarct part and the reversible penumbra for ischemic stroke patients immediately.

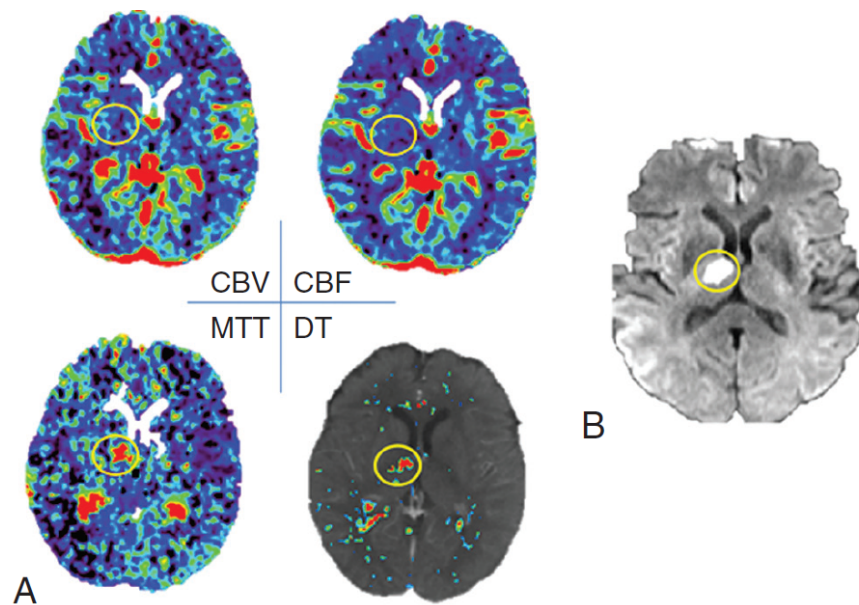


Figure 2.5: (A) CTP images for an ischemic stroke patient. Yellow circle indicates the abnormal region. (B) DWI confirms the lacunar infarction in right thalamus detected by CTP in (A)[28].

CT Angiography:

Arteries that supply the injured brain should be tested after the abnormal brain tissues being identified. CTA is one of the vascular imaging tools for stroke patients. **Imaging Principle:**

Similar to PCT, CTA also needs an intravenous administration of iodinated contrast. A CT scanner takes pictures rapidly when the dye goes through the arteries and vein in the brain, to diagnose occlusions, malformations, aneurysms and relative positions for extracranial and intracranial vessels.

Magnetic Resonance Imaging for Stroke Diagnosis

Magnetic Resonance Imaging (MRI) is relative new imaging modality based on the physical phenomenon of nuclear magnetic resonance (NMR). NMR has been known since the early 1940s and practically applied to get the first NMR medical image in 1973[12]. Atoms which have an odd number of protons or neutrons have a nonzero nuclear magnetic moment μ , which will precess after applying an external magnetic field B_0 with a frequency

$$\omega_0 = -\gamma B_0 \tag{2.1}$$

where γ is the gyromagnetic ratio. By applying a fixed high magnetic and variable radio frequency fields, the NMR properties of a target can be measured and reconstructed into an image. The major atom being scanned in MRI is hydrogen nuclei. Because it is common in water and fat molecules of the body. It makes MRI features high contrast sensitivity to soft tissues and thus is superior in neurological, musculoskeletal, cardiovascular and oncological imaging than other imaging methods[13]. Meanwhile, MRI is essentially safe to subjects comparing to other ionizing radiation technologies like CT. MRI has both the anatomical imaging capability and the functional imaging capability, provides high resolution and high contrast images with no risk. These features make it become one of the most powerful imaging technologies for diagnosis in hospitals.

Because the pulse sequences of these fields can be modified. MRI can generate multiple dif-

ferent images that have different emphases. Different combinations of pulse sequences enable MRI to distinguish different materials (water, fat, bone, etc), measure water diffusion and blood flow. A MRI stroke diagnosis protocol includes T2/T2* , perfusion, diffusion weighted MRI and MRI angiography.

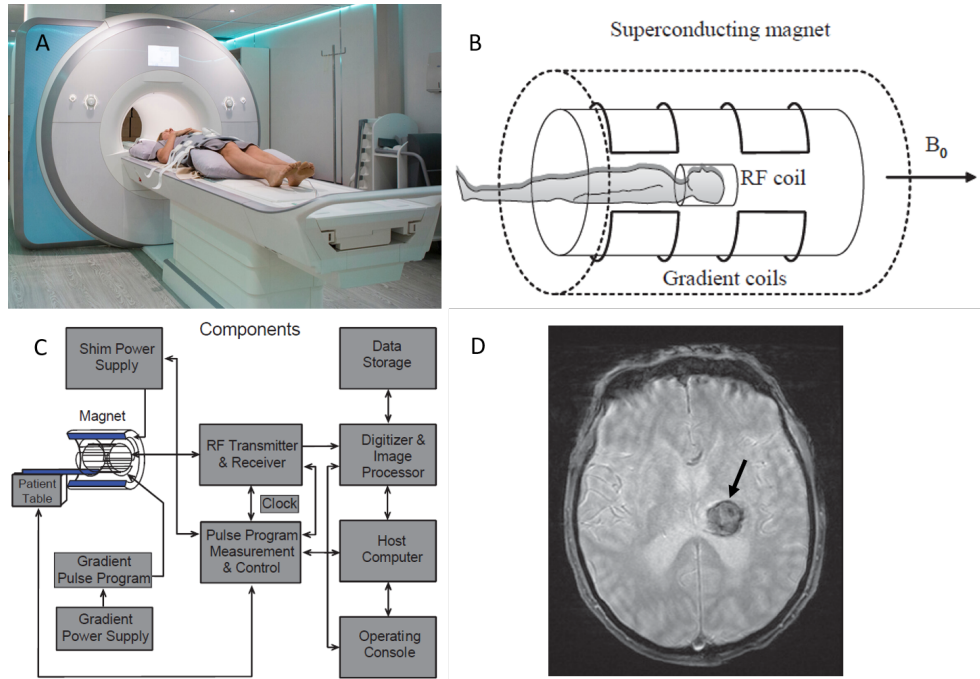


Figure 2.6: (A) A modern MRI scanner[10]. (B) The physical principle of MRI[14]. (C) The main structure of a MRI system[15]. (D) T2* MRI image of a patient with acute left thalamic intracerebral hemorrhage stroke[2]

T1/T2 Weighted MRI:

Imaging Principle: T1 and T2 means spin-lattice and spin-spin relaxation time respectively[26]. MRI images show the tomographic layers of proton distribution modified by T1 and T2. Because the water content of the ischemic regions are affected. T1 and T2 relaxation constants are prolonged. Generally, T1-weighted MRI is more spatial sensitive that used to evaluate structure and volume of brain; T2-weighted MRI is more pathology that used to evaluate stroke affected regions of brain.

Perfusion/Diffusion Weighted MRI

DWI Imaging Principle: If there is not enough blood supply to a region of brain tissue, it will lead to a shortage of necessary nutrients for metabolism which could cause failures of Na^+/K^+ channels in ischemic cells. Then a subsequent cytotoxic edema will happen which narrows the extracellular matrix so that the Brownian molecular motion within the extracellular space of a cell will reduce. Cytotoxic edema happens immediately after onset of an ischemic stroke (about 3-5 minutes). At the very beginning of an ischemic stroke, NCT does not show any differences in tissue images. However, this phenomenon could be detected with diffusion weighted MRI (DWI) and quantitatively measured by calculating the apparent diffusion coefficient (ADC). DWI is more sensitive to detect ischemic stroke than CT.

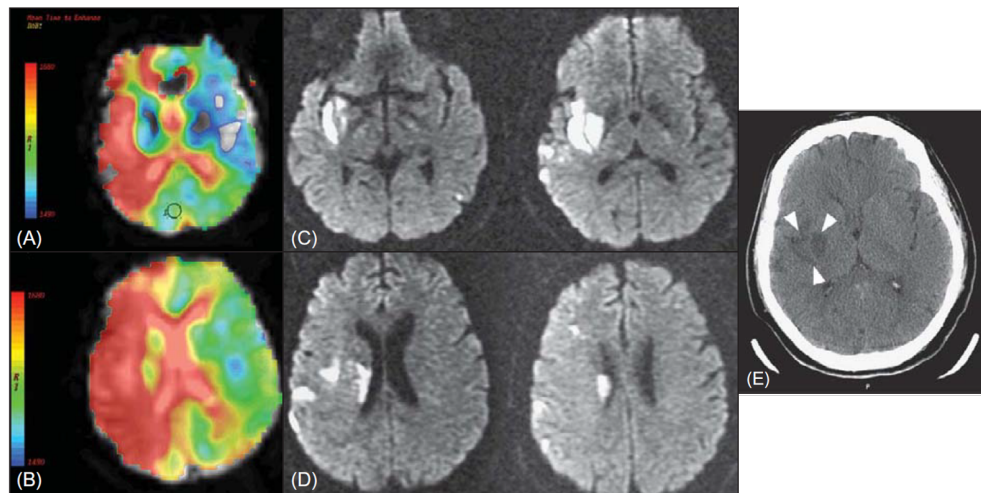


Figure 2.7: MRI PWI-DWI mismatch. A, B are two PWI mean transit time (MTT) maps that show deficient blood flow through the right MCA territory (red region indicates prolonged MTT). C, D are DWI images showing a smaller area of infarction (white hyperdense). This PWI-DWI mismatch resulted in further reperfusion therapies, and good outcome was confirmed by a follow-up CT scan one day later (E). E only shows a subcortical infarct as a hypodense lesion (white arrows) [3].

PWI Imaging Principle: Perfusion weighted MRI (PWI) measures any hypoperfused

brain tissue that is potentially at risk for infarction (be irreversibly damaged), which means still be salvageable. These tissues are named penumbra tissues. The region of penumbra is derived by a decreased cerebral blood flow (CBF), a decreased cerebral perfusion pressure (CPP) and an increased oxygen extration fraction (OEF). The cerebral blood volume (CBV) could be increased because of the compensated vasodilatation regulated by cerebral autoregulation.

To distinguish infarction from penumbra, both DWI and PWI are used. It is assumed that DWI can measure the irreversibly damaged infarct and PWI can measure the complete area of hypoperfusion[27]. The volume difference between the two results is called PWI/DWI mismatch (PWI minus DWI volume), which is, a very common and useful technique to see the ischemic penumbra. The penumbra is salvageable by further repurfusion therapies.

MRI Angiography:

Imaging Principle: Same with CT angiography, MRI angiography is a useful tool to image the extracranial and intracranial large vessel occlusions, malformations and stenoses. However it does not need an IV contrast dye essentially which enables MRI to be noninvasive and decrease any risks related to the dye administration such as allergic response.

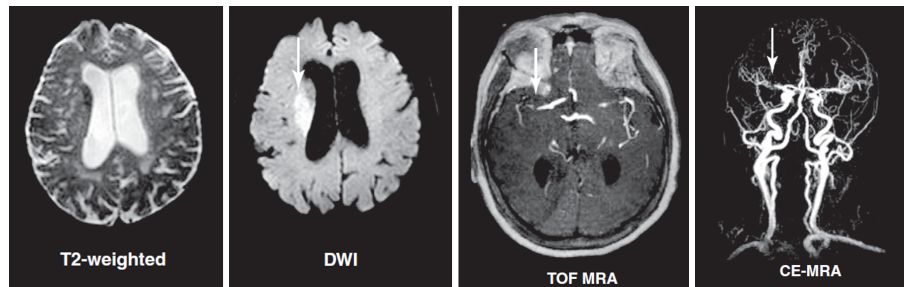


Figure 2.8: T2-weighted MRI, DWI, contrast enhanced (CE) MRA and time of flight (ToF) MRA of one acute ischemic stroke. T2-weighted MRI didn't detect anything. DWI shows a hyperdense infarct region (white arrow). Both the two MRA images identified the position of occlusion in the right middle cerebral artery[21].

In conclusion, CT and MRI are the two major methods that are widely used in clinical for stroke patients diagnosis. They have both advantages and drawbacks comparing to each other (listed in figure below). The stroke management team should decide which one to use based on the pre-evaluation results and availability of the diagnostic systems.

Modality	Advantages	Disadvantages
CT	Low cost and wide availability	Radiation exposure
	Safe for medically unstable patients	Poor image resolution for posterior structures
	Rapid acquisition of images	
	High sensitivity for hemorrhage in the acute phase	
MRI	High sensitivity for stroke mimics	Patient tolerability and contraindications
	High sensitivity for ischemia (with DWI) and cerebral perfusion	Low sensitivity for cerebral hemorrhage, but now much improved with GRE
	High resolution for imaging of vasculature	Slower image acquisition

Figure 2.9: Advantages and disadvantages of CT and MRI for stroke diagnosis[8].

Catheter Angiography for Stroke Diagnosis

Catheter angiography, together with MRI angiography and CT angiography, are the three vascular imaging techniques that could be ordered by clinicians for stroke patients. It is considered to be the gold standard (means the most accurate) for extracranial and intracranial vascular imaging in many situations. However, it is also the only invasive method introduced in this thesis review, which brings it obvious advantages and disadvantages comparing to other methods.

Imaging Principle: At first, the specialist chooses one artery to place an arterial sheath. The most common one is femoral artery (sometimes could be brachial or axillary artery). A catheter is then threaded from the sheath to the targeting arteries such as carotid artery under visual control. The contrast dye is then injected from the catheter. Meanwhile, a rapid series of X-ray images are taken to monitor the dye that is flowing through carotid artery



Figure 2.10: A. Catheter angiography performed by an interventional radiologist[19]; B. A whole cerebrovascular image by catheter angiography[20]; C. Internal carotid artery stenosis measured (white arrow) by catheter angiography[21]; D. A vertebrobasilar aneurysm measured (white arrow) by catheter angiography[21].

to arteries and veins in brain. These images can show if there are blockages, aneurysms, vascular malformations and narrowing paths.

Catheter angiography is an invasive procedure that requires well-trained specialists and long time (usually 30 to 60 minutes) to operate. It may cause injuries to the inserted arteries, or knock off plaques or clots from an artery that could then pass to the brain to cause an ischemic stroke. The injected dye may also cause allergic response. Nowadays, MRA and CTA have validated excellent performance in noninvasive cerebrovascular imaging. For acute stroke patients, catheter angiography is rarely used and displaced by MRA and CTA. But it still have the highest sensitivity and specificity than other less invasive methods. Moreover, it can be integrated with pharmacological and mechanical endovascular reperfusion procedures for treatment, which MRA and CTA can't[18].

2.2.2 Key Technologies Under Development

Ultrasound

Ultrasound (US) represents any sound waves that have frequencies above 20kHz, which is, above the range of human hearing. The imaging principle of ultrasound imaging starts from an US transducer.

A transducer that is consisted by an array of independent piezoelectric crystal elements can generate longitudinal sequences of mechanical waves (US waves). The crystal elements vibrate by applying oscillating electric current (electric to mechanic). Those piezoelectric crystal elements are also performing as detectors using reversed physical principle (mechanic to electric). A US wave is a form of an energy wave. A large number of the waves form a sound beam that is injected into the body to see how these waves interact with tissues.

The injected sound waves are attenuated by absorption, scattering, and reflection (back scattering) in tissue. People can get the information of the measured tissues by detecting the reflected sound waves. Because human tissues are heterogeneous, which means, a part of injected sound waves will be reflected at an interface between two tissues. The greater change in density and compressibility properties of the adjacent tissues, the greater amount of sound waves are reflected. Like a sonar, the penetration depth can be known by the time of flight (ToF) of the detected sound waves. The average speed of sound in tissue is about 1540 m/s (1460 m/s for fat, 1620 m/s for muscle).

By collecting the attenuation and ToF information of the detected reflection US waves, 2-D tomographic images can be reconstructed in real time. For clinical use, the frequency is between 1 MHz to 20 MHz. There is a trade-off: higher frequency leads to higher resolution imaging but lower penetration distance.

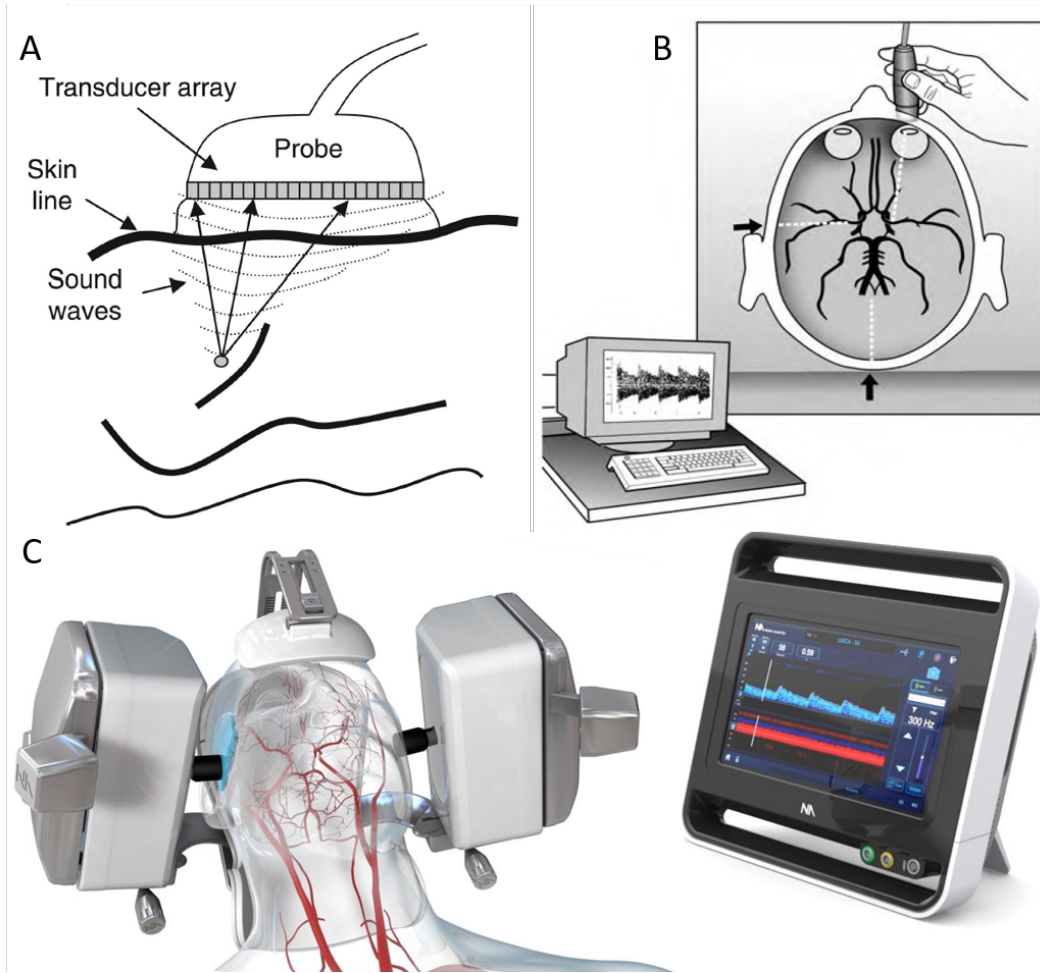


Figure 2.11: (A) An illustration of US working mechanism[13]. (B) An illustration of TCD operation[2]. (C) A new TCD product for stroke diagnosis invented by Neural Analytics, Inc[16]

Doppler ultrasound imaging uses Doppler effect to measure dynamic motions such as blood flow in the arteries. When there is a relative motion between the transducer and reflector, either toward or away to the transducer, the Doppler signal frequency is:

$$f_d = \frac{2f_0v}{c} \quad (2.2)$$

where f_0 is the frequency of the transmitted ultrasound, v is the relative speed of the reflector, c is the speed of sound in tissue.

Transcranial doppler ultrasound (TCD) technique has been developed to examine cerebral blood flow status for stroke patients. By placing the transducer probe over the eyes, back of the neck and temples where the skull is absent or thin, blood flow velocities of different arteries in the skull can be check for narrowing, occlusion or other abnormal situations (figure 2.11).

In conclude, US imaging for stroke diagnosis cannot only provides anatomical imaging of brain, but also volume measurements and abnormal cerebrovascular blood flows monitoring noninvasively. It is becoming more and more popular because its advantages in low-cost, portability, real-time monitoring and risk-free (non-radiation) measurements.

Point of Care Testing Technology

As you can see in this thesis review, current clinical evaluation methods for stroke patients mainly rely on medical imaging technologies in hospitals. However, there is a strong demanding of new technologies who can provide personalized information on site to help to improve the time sensitive work flow for acute stroke patients. Point of care testing (POCT) technology has been under developing to meet the demand. POCT for stroke diagnosis uses platforms to detect the blood-derived biomarkers which are specific indicators for stroke.

The roles of POCT can be concluded as:

1. Aid clinical decision making process to shorten the time to treat;
2. Classify stroke subtypes to triage patients for optimal stroke therapies such as reperfusion therapy;
3. Improve the clinical outcome by understanding stroke mechanisms and improving stroke prognosis.

Here a POCT device summary for stroke diagnosis and prognosis is listed.

POCT Device	Description	Application	Clinical Value
Mobile Stroke Unit (MSU)	Imaging and a variety of Blood-tests. Integration of CT scanners and POCTs in ambulances, IV-tPA treatment can be started on-site	Consists of a registered nurse, paramedic, emergency medical technician, and a CT technologist, in addition, POCT are used, which includes coagulation profile, complete blood count, and blood chemistry	Pre-hospital: Improves stroke diagnosis and reduces time-to-IV-tPA admission
CoaguChek®(Roche)	Test strips with electro-chemical detection. Based on amperometric (electrochemical) determination of the PT time after activation of the coagulation with human recombinant thromboplastin, results are obtained within 1 min	Convenient, portable and user-friendly device for monitoring oral anticoagulation therapy which can determine the INR value from a drop of capillary whole blood	Pre/In-hospital: Improves stroke diagnosis and reduces time-to-IV-tPA admission
Hemochron®Junior (ITC)	Optical detection. Micro-coagulation system, results within minutes	POCTs monitoring of: (1) ACT-LR, (2) ACT, (3) PT, (4) Citrate PT, (5) APTT and (6) Citrate APTT	Pre/In-hospital: Improves stroke diagnosis and reduces time-to-IV-tPA admission
PocH-100i hematology analyzer (Sysmex)	Micro-fluidics. WBCs, RBCs and PLTs are counted using the direct current detection method with hydrodynamic focusing technology. Hemoglobin analysis is conducted using a non-cyanide method	Provides a full blood count and a 3-part differential leukocyte count	Pre/In-hospital: Improves stroke diagnosis and reduces time-to-IV-tPA admission
i-STAT (Abbott)	Micro-fluidics. Based on advanced microfluidic and deliver fast, reliable lab accurate results within 2 min	Bedside care tests such as blood gases, electrolytes, metabolites and coagulation	Pre/In-hospital: Improves stroke diagnosis and reduces time-to-IV-tPA admission
Reflotron®plus analyzer (Roche, Cobas series)	Test strips with optical detection (Reflectance photometry). Single-test clinical chemistry system which is able to measure whole blood, plasma or serum for: liver and pancreas enzymes, metabolites and blood lipids. Results within 2–3 mins	Used for blood clinical-chemistry parameters measurement, such as c-glutamyltransferase, p-amylase, and glucose	Pre/In-hospital: Improves stroke diagnosis and reduces time-to-IV-tPA admission
Abbott AxSYM®BNP/Alere Triage®BNP/i-STAT BNP	Optical Detection (AxSYM)/Fluorescent detection (Triage)/Electro-chemical sensor on a silicon chip (i-STAT). BNP POCT.	BNP elevated serum levels in stroke patients show (1) correlation with CEI stroke, (2) increased mortality and (3) indication on second stroke recurrence	In/Post-hospital: Improves stroke prognostic (correlation to CEI) and stroke recovery (indication on second stroke reoccurrence)
Cornell University, State University of New York and the New York Presbyterian Hospital	Luminescent detection. NSE POCT based on enzymes tethered to nanoparticles	NSE elevated serum levels in stroke patients assist in distinguishing stroke from mimics, an important first step in expediting the diagnostic process	In-hospital: Improves stroke diagnosis and reduces time-to-IV-tPA admission

Figure 2.12: Stroke diagnostic and prognostic POCT device summary table[29].

2.3 Market for Stroke Diagnostics

The total global management market which includes stroke diagnosis and stroke therapies is expected to have a size of USD 36.7 billion by 2023, growing at a CAGR of 7.4% from year 2017, according a new report published by KBV Research[31]. The North America and Europe stroke diagnostics market size is expected to reach USD 2.35 billion by 2025, growing at a CAGR of 6.2%[30].

The major factors that are responsible for the growth of the stroke diagnostics market are:

1. Fast growing population who have chronic diseases such as hypertension, diabetes, obesity and etc;
2. Rapid growing geriatric population;
3. Prevalence of unhealthy lifestyle: physical inactivity, too much pressure in life, tobacco and alcohol abuse and so on.

According to the Centers for Disease Control and Prevention (CDC), over 36% of US population is obese and geriatric population in US is going to be around 98 million by 2060. The stroke management costs US over \$34 billion USD each year.

Based on different stroke management market analysis reports[30][31][32], the stroke diagnostics market can be divided into six types:

- Computed tomography scan
- Magnetic resonance imaging
- Cerebral angiography
- Ultrasound (carotid and transcranial)
- Electrocardiography

- Other diagnostics

According to the market report published by Grand View Research[30], there are several key findings for stroke diagnostic market:

1. CT scan was the dominant method nowadays for its high usage rate for stroke evaluation and hemorrhage screening;
2. MRI earned significant revenue in 2016 due to innovations;
3. MRA and CTA is expected to continue growing in the next following five years because of the increased adoption of minimally invasive vascular imaging need;
4. North America is the leading market and will still be the first market in stroke diagnostics;
5. Carotid ultrasound is expected to continue growing because it is noninvasive and cost-effective.

The key manufactures for stroke diagnosis in the North America and Europe are Cordis Corporation, Siemens Healthineers, GE Healthcare, Toshiba Medical Systems Corporation, Boston Scientific Corporation, Hitachi Medical Systems, Neusoft Medical Systems, and Philips Healthcare[30].

2.4 Key Challenges and Unique Opportunities

2.4.1 Challenges

Stroke diagnostics is never a simple and direct thing. There are too many conditions and requirements that need to be meet to have a correct and timely diagnosis.

There are challenges for clinicians and hospitals, such as excellent first-aid teams, experienced stroke management teams, well-trained specialists, advanced but expensive stroke diagnostic devices. There are also challenges for the families who have potential stroke high-risk members. In this thesis review, we focus on the challenges for stroke diagnostic technologies.

1. Time. The time means diagnostic time for stroke. Time also means the duration from stroke onset to right therapies. Time is life, especially for acute stroke patients. A lot of people notice the stroke symptoms several hours after onset of stroke which leaves very limited time for stroke diagnosis. Among the major diagnostic technologies, CT is the fastest but still takes at least ten minutes. However, neuron cells start to die (cytotoxic edema) only several minutes (≤ 3 mins) after stroke onset. So developing new technologies or improve the current technologies by innovations to shorten the time for stroke diagnosis is extremely important.
2. Availability. Nowadays, accurate stroke diagnostic medical devices such as MRI are still only available in advanced and big hospitals.
3. Limitations. The work flow of Stroke diagnosis still relies on the combination of multiple diagnostic technologies. Because they all have their limitations. The diagnosis of intracranial hemorrhage is still only possible with CT. The need to perform both CT for exclusion of ICH and stroke MRI to guide therapeutic efforts is time-consuming, and medico-economically questionable[33].
4. Size and cost. The major stroke diagnostic technologies such as CT, MRI and catheter angiography use large size systems which are bulky and immobilized. Also, the testings and scans are expensive.
5. Prediction and prevention. Current diagnostic technologies only work after stroke onset. They may be able to do prognosis instead of prediction. However, if a stroke

could be predicted by a diagnostic technology before real happening, it will save lives.

2.4.2 Opportunities

The opportunities are like twin sisters of challenges. If you can see the challenges, you can also find the opportunities behind the difficulties.

1. Precision and personalized stroke diagnosis. The etiology of strokes is complicated. Each stroke patient has his/her own causes. Genetic analysis, precision diagnostic technology and personalized therapies are required for better outcomes in the future.
2. More cost effective, portable and continuous diagnostic technologies is urgently needed for long-term wearable monitoring. Near infrared optical method has a huge potential for its noninvasive and functional imaging advantages.
3. An accurate and fast hemorrhage stroke screening technology is urgently needed to replace NCT in hospitals. It even better to be portable and integrated into ambulances to distinguish hemorrhage stroke and ischemic stroke during transportation.
4. More stroke predictive technologies should be developed to monitor high-risk stroke potential population in their daily lives. People should be alerted before or at the stroke onset.

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Chapter 3

Multi-layer Heterogeneous Tissue Mimicking Phantom Preparation With Optical and Mechanical Properties

3.1 Introduction

A phantom is an artificial model synthesized by different materials to mimic certain properties. This chapter describes the design and fabrication of two types of phantoms for mimicking the optical and mechanical properties of human tissues. The first phantom is homogeneous, which includes one layer that can represent a single type of tissue or a mixed type of multiple tissues. The second phantom is heterogeneous, which includes multiple layers/tissues to mimic epidermis, dermis, hypodermis, blood vessels and blood. A homogeneous phantom is easier and faster to fabricate and a heterogeneous phantom is more accurate. They were designed for experimental validation for the designed emboli detection system.

The key parameters of optical properties includes absorption coefficient μ_a and scattering coefficient μ_s . The key parameters of mechanical properties includes Young's modulus E and shear modulus G . Those parameters of a phantom should be modified to be the same with the target tissues.

A good tissue phantom, according to Tuchin[1], should meet the requirements below:

1. It can mimic the geometry, optical properties of the tissue for the light transportation;
2. The related parameters must be reproducible and predictable according to the composition;
3. The materials in the phantom must be compatible with each other;
4. The phantom must be physically stable and independent (evaporation, aging, decomposition);
5. The phantom should be simple, quick and safe to fabricate.

3.2 Materials and Methods

The structure of the multi-layer heterogeneous phantom is designed according to the anatomical structure of the human neck (Fig 3.1). The average length of CCA is about 13cm[2].

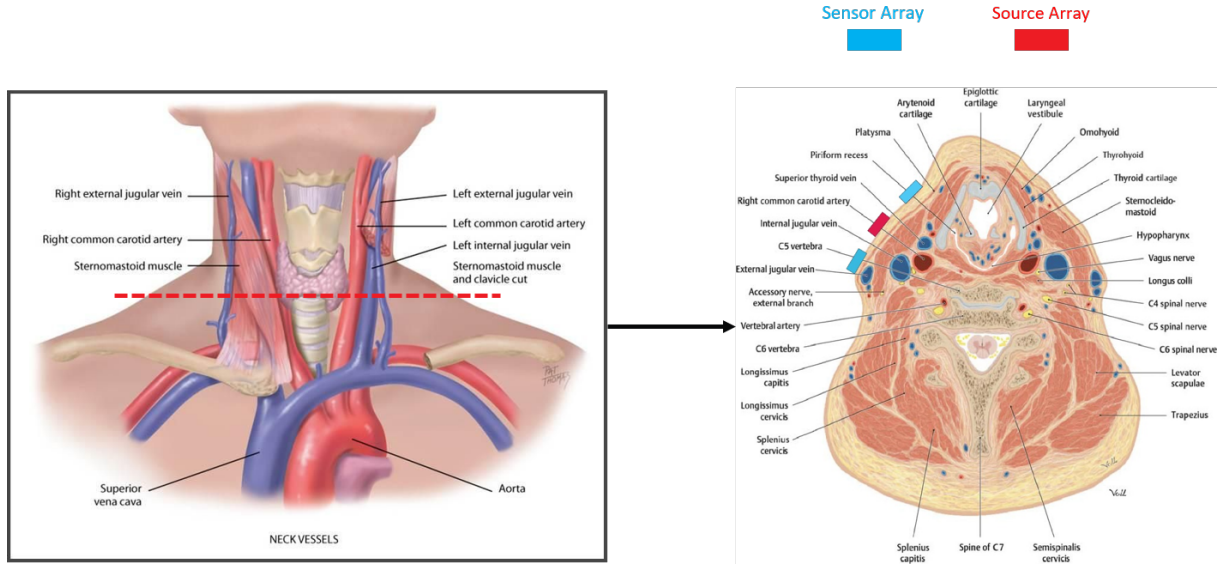


Figure 3.1: The anatomical structure of the human neck (transverse plane)

The average diameter of CCA is about 6mm[3]. The blood velocity in CCA: 28.6-178.4cm/s [4] (diastolic to systolic peak). A more detailed neck structure can be measured using ultrasound imaging (Fig 3.2). Based on the anatomical information above, the structure of the designed phantom is illustrated in Fig 3.3. The thickness of each tissue layer is described in Fig 3.4.

Materials and Apparatus Preparation

To fabricate the phantom, following apparatus are needed:

1. heater: heat the water and solution.
2. weighting instrument (electronic scale).

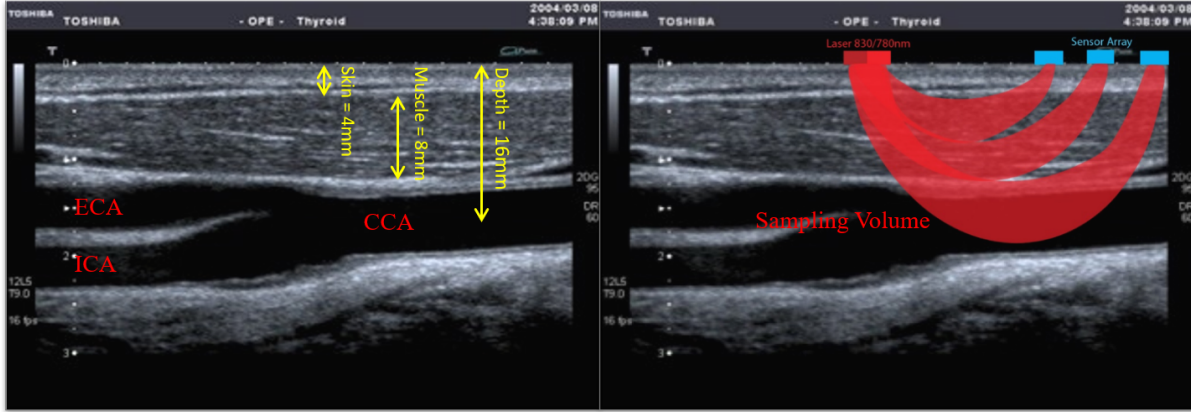


Figure 3.2: The ultrasound image of human neck

3. stirring machine(blender) with cover. (stirring(speed)+heating).
4. vacuum chamber at 21kPa to remove air.
5. syringes for minimize the air.
6. beakers and measuring cups.

Phantom Recipe

Multi-layer heterogeneous phantom recipe:

The recipe of the phantom is designed based on a published multilayer phantom designed by Chen et al[5].

1. Fabrication of phantom epidermis layers Epidermis mimicking films with thickness of 0.1 mm:
 - 1) Dissolve 5% w/v gelatin powder in distilled water.
 - 2) Add 0.01%–0.1% glutaraldehyde to the solutions, along with varying concentrations of synthetic melanin (described later).
 - (i. glutaraldehyde is for mechanical properties: the addition of 0.025% glutaraldehyde pro-

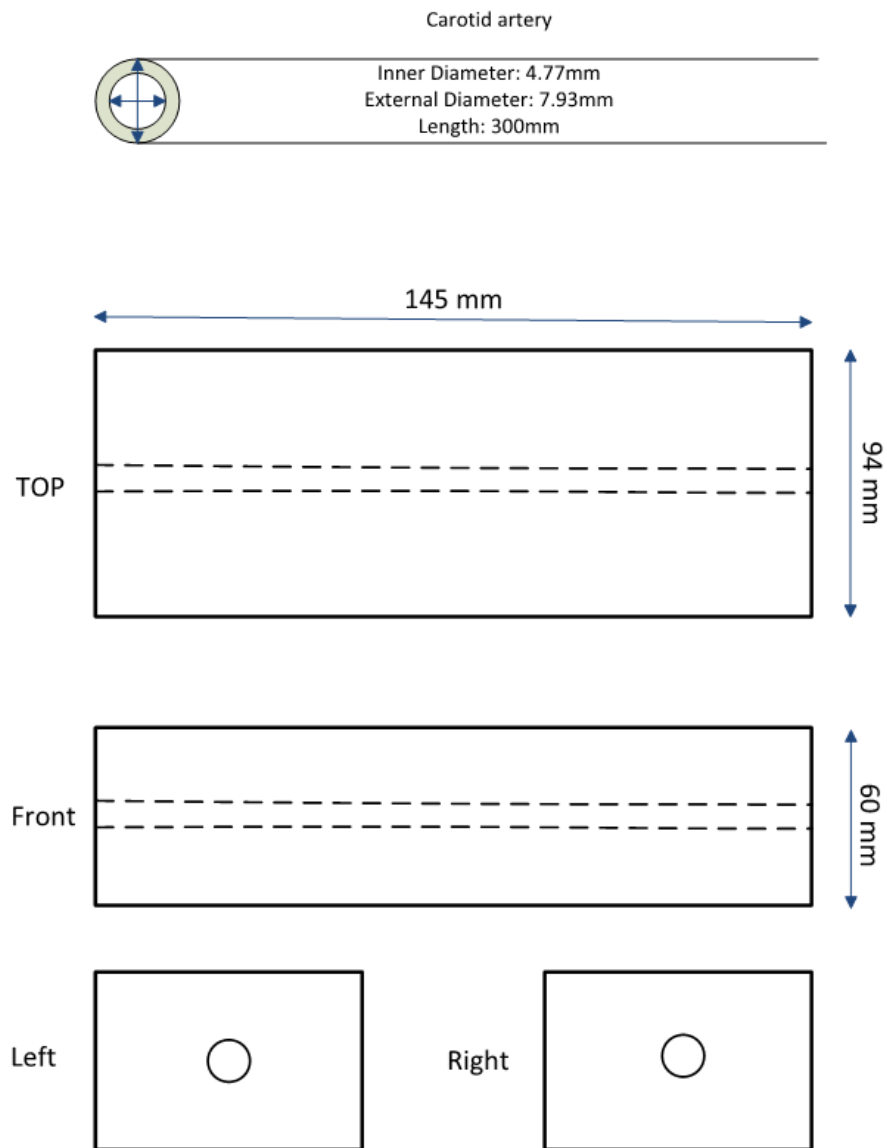


Figure 3.3: The structure of the multilayer phantom.

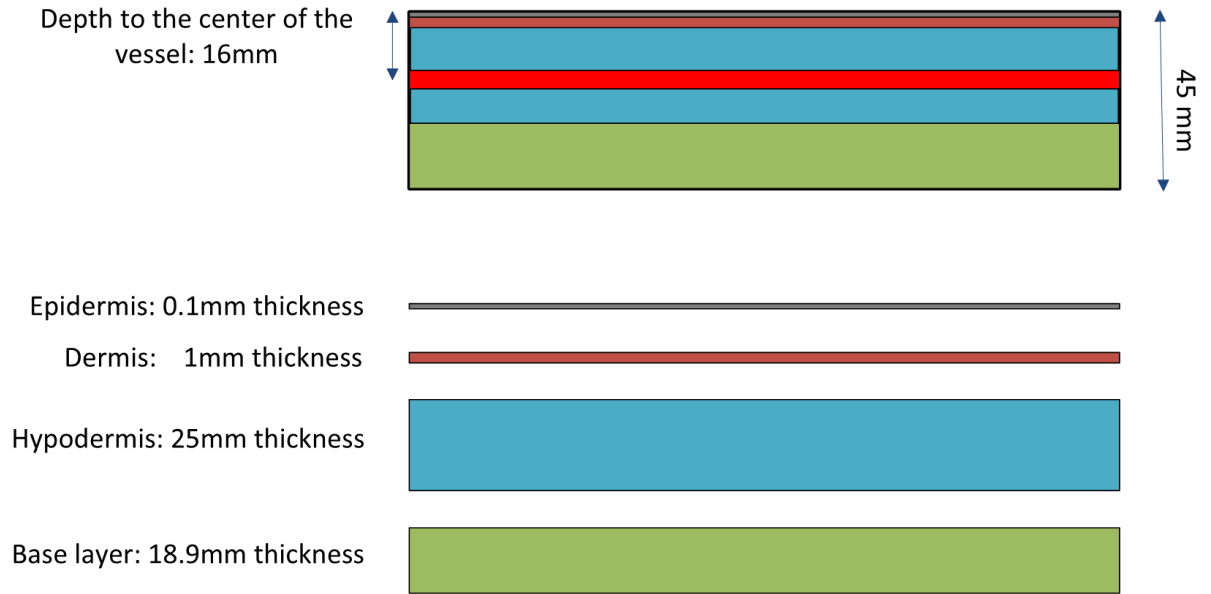


Figure 3.4: Thickness of each layer.

duced films with Young's modulus of 1 MPa[5]) 3) Pour the solutions onto a plate and dried for 48 hours to obtain the thin films.

Optical absorption and scattering: In the phantom epidermis layer, synthetic melanin powder was added at concentrations ranging from 0.0003% to 0.0216% w/v to simulate different skin tones.

2. Fabrication of phantom dermis and hypodermis layers:

The dermis mimicking layer: a mixture of 24% w/v gelatin and 1% w/v agar (A1296 powder, Sigma-Aldrich). The hypodermis mimicking layer: consisted of 2% w/v gelatin and 0.2% w/v agar. The base layer: 8% w/v gelatin.

1) Dissolved the above gelatin and agar in separate beakers according to the different concentration, and then combined.

2) Add optical modifiers along with 1.5% Germall-Plus which served as an antimicrobial agent.

- 3) Cool the final solutions to 40 Celsius degree under constant stirring and introduced into the phantom container sequentially.
- 4) Pouring 8% w/v gelatin solution through a 100 μm sieve until a 18.9mm viscous layer was formed the bottom of the container to form the base layer.
- 5) Wait the base layer to be fully gelled. Pour the hypodermis solution to a total height of 25 mm, allowing the vessels to be fully submerged.
- 6) Wait the hypodermis layer to be fully gelled. Pour the dermis solution to form a 1 mm layer.
- 7) Finally, pour the epidermis film above the dermis to form the top layer of the phantom, once the dermis layer was gelled.

Optical absorption:

0.0182% v/v of India ink and 0.058% w/v of 552 nm dye were added to the dermis.

0.0202% v/v of India ink, 0.047% w/v of 935 nm dye and 0.073% w/v of 552 nm dye were added to the hypodermis.

Molecular absorbing dyes (QCR Solutions Corp., FL, USA) are used to simulate local absorption peaks. The 552 and 935 nm dyes were added to simulate the increase in absorption due to hemoglobin and lipid, respectively. India ink (Higgins Waterproof Black, Sanford, USA) as the broad-spectrum absorber in the phantom dermis and hypodermis layers.

Optical scattering:

28.5% v/v Intralipid-20% were added as the optical scatterer in the dermis. 7.8% v/v Intralipid-20% were added as the optical scatterer in hypodermis.

3. Blood mimicking fluid Optical absorption (arterial blood): 552nm dye 26.09% w/v 935nm dye 0.374% w/v India ink 0.0301% v/v

4. Packaging and storage The addition of Germall-Plus further prolongs the shelf-life by

mitigating microbial or fungal infiltration.

Operating Logic:

1. Prepare ultrapure deionized water. The water was heated to 30° C and then combined with other materials.
2. Prepare type-A, 300-Bloom gelatin derived from acid-cured porcine skin (G2500, Sigma-Aldrich Corp., St. Louis, MO).
3. The gelatin powder was slowly added to mitigate aggregation of the powder in the water. The solution was continuously stirred, covered to minimize vapor loss, and slowly heated to 45° C over the course of 10 minutes. (stirring speed, gelatin concentration).
4. To remove the entrapped air that resulted from the stirring process, the samples were placed into a vacuum chamber at 21 kPa absolute for approximately 10 minutes.
5. The solution was then transferred into a mold with a syringe to further minimize the reintroduction of air.
6. Finally, the mold was placed into a 4° C refrigerator for one day to allow the solution to cross-link fully.

Homogeneous phantom recipe:

Need: TiO₂, SDS, 0.05% ink, agarose, water

Procedure:

1. Measure out 15g agarose. Use a electronic scale.
2. In the container you are going to use as your mold, combine 1000mL water and 15g of agarose. Use a stirring-heating plate to heat it to around 94° C while stirring. The high temperature will activate agar. It should be stirred into clear and less viscous.
3. Prepare 0.05% ink. Measure out 4ml. You can also use a syringe. (1cc = 1mL, 1mL = 20 drops)

4. Prepare 0.70g TiO₂ and a pinch of SDS in a container. Don't use too much SDS—this is just needed as a surfactant and you don't want to have too many bubbles.
5. Allow the water-agar mixture to cool to around 70 ° C.
6. When agar solution is ready, slowly add the TiO₂/SDS/ink and stir rapidly. Keep stirring for about X minutes. The new mixture needs to be stirred until it cooled sufficiently and the scatters (TiO₂) are suspended without sedimentation.
7. Cover the container (prefer to seal it) and place it in a refrigerator to solidify for a few hours.

Change amount of ink to vary the absorption. Notice: It is important for the sample to be allowed to cool sufficiently before stirring can cease. This usually takes around 2 hours after the heating has ended. Even a sample at around 35 ° C can be no viscous enough that the scattering TiO₂ particles tend to sink to the bottom of the beaker. Once the sample has cooled significantly the gel nature of the agar becomes more pronounced and the TiO₂ particles suspend in the solution to provide an even distribution of scatterers throughout the sample.

3.2.1 Materials

The materials for the two recipes above are described in Fig 3.5 and Fig 3.6.

3.3 Results and Discussion

The fabricated phantoms are showed in Fig 3.7.

Name	Description
G2500-500G	Type A porcine powder, 300 g Bloom, Sigma-Aldrich, Corp., MO, USA
49781-500ML	Glycerol (49781, $\geq 98\%$ purity, Sigma-Aldrich)
G5882-50ML	G5882, $\geq 99.5\%$ purity, Sigma-Aldrich
A1296-500G	A1296 powder, Sigma-Aldrich
Germall-Plus	International specialty products, Wayne, NJ, USA
CLS431752-50EA	100 μm sieve (BD Falcon™ Cell Strainer 100um)
Model 046	Blood Mimicking Fluid, CIRS, Inc., VA, USA
M0418-100MG	synthetic melanin powder, $\geq 97\%$ purity, Sigma-Aldrich Corporation, USA
India ink	Higgins Waterproof Black, Sanford, USA
VIS552A	Molecular absorbing dyes (QCR Solutions Corp., FL, USA)
NIR935A	Molecular absorbing dyes (QCR Solutions Corp., FL, USA)
I141-100	Intralipid-20% (IL-20, Fresenius Kaby AB, Sweden)
A7284-50	lyophilized BSA ($\geq 95\%$ purity, Roche Diagnostics, USA)
MIN-U-SIL-4	MIN-U-SIL-4, Sigma-Alrich
11-189-15M	PDMS. Sylgard 184 Silicone Elastomer Laboratory Tubing, Dow- Corning Corp., MI, USA
NIR757A	Molecular absorbing dyes (QCR Solutions Corp., FL, USA)

Figure 3.5: The basic materials for the multilayer neck phantom.

Material	Weight/Volume	Product
TiO ₂	0.7 g	<u>Acros Organic</u> AC277370010
Agarose	15 g	Sigma-Aldrich A1296-500G
Ink (0.05%)	4 ml	Higgins® Waterproof India Ink Black HIG44201
SDS	A pinch	<u>Fisher BioReagents</u> BP166-100
Water	1000 ml	Distilled water

Figure 3.6: The basic materials for the homogeneous phantom.



Figure 3.7: The fabricated phantoms.

3.4 Reference

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Chapter 4

Non-invasive NIRS System Design for Stroke Prediction and Diagnostics

4.1 Introduction

Basically, either hemorrhage or ischemic stroke is directly related with blood perfusion (supply) and blood oxygenation/deoxygenation. In an embolic stroke, a blood clot or plaque debris travels to cerebral vascular to block the blood supply that leads to an ischemic situation. It will cause slower blood flow, less blood volume, more deoxygenation hemoglobin and less oxygenation hemoglobin which all can be measured by near infrared spectroscopy (NIRS).

What can NIRS do?

With NIRS, we can measure the information: Optical properties: 1) Scattering parameter; 2) Absorption parameter. Tissue properties: 1) Oxyhemoglobin (HbO₂); 2) Deoxyhemoglobin (HHb); 3) Total hemoglobin (tHb); 4) Oxygenation saturation(Oxy/Total). Blood perfusion: 1) Blood volume; 2) Blood flow.

(To measure HbO₂, HHb, Blood volume. It needs at least two wavelengths near infrared light (e.g. 780nm, 830nm).

It's hard to monitor blood flow (which contains the blood velocity and kinetics). It usually can be realized by combining NIRS with dye (ICG).)

Continuous wave method of NIRS is used in this system. The penetration depth is about 1/3 to 1/2 of detection distance (from the laser to the sensor). .

What are the current NIRS applications for stroke?

There are several studies prove the invasive NIRS function during carotid endarterectomy. Because artery inflammation or carotid endarterectomy will cause plaque debris and blood clots that may cause an embolic stroke. It is the only existed relationship among NIRS, carotid and stroke. It was concluded that this continuous oxygenation monitoring is a promising method for detecting ischemic events in ICU settings. There are some studies

use spatial modulated NIRS on the head to detect reductions of the oxygen concentration on hemisphere with stroke and the contralateral side. For example, Marcel et al. assessed the results of peripheral arterial oxygenation by NIRS in the affected versus nonaffected hemisphere in 9 patients with acute stroke at stroke unit bedside. Significantly more NIRS drops were recorded in the affected compared with the nonaffected hemisphere (477 drops versus 184, $P=0.001$). In the affected hemispheres, nearly all peripheral arterial oxygenation drops ($n=128$; 96%) were detected by NIRS; in the nonaffected hemispheres only 23% ($n=30$; $P=0.17$).

There are some studies combine transcranial Doppler ultrasonographic (TCD) with transcranial cerebral oximetry (TCCO) by NIRS to monitor middle cerebral artery (MCA). TCD mainly tests subcortical changes in the middle MCA flow, while NIRS is exquisitely sensitive to cortical arterioles and capillary blood flow modifications. Ekelund et al. correlated TCCO with TCD values in 14 patients with Aneurysmal subarachnoid hemorrhage (aSAH). Their results supported the assumption that TCCO may enhance the reliability for detecting cerebral ischemia after aSAH.

In conclusion, all the research that uses NIRS/NIRF (NIR Fluorescence) for stroke research concentrates on onset or prognosis of stroke (ischemic stroke, hemorrhage stroke). There is no research about stroke prediction using wearable NIRS device to our best knowledge.

What are the proposed design in this thesis?

A noninvasive continuous NIRS laser/sensor system is designed to monitor the passing emboli in carotid artery blood flow. An illustration of a wearable version of the device is showed in Fig 4.1 below.

When blood clots or plaque debris travel to the brain via the common carotid artery, the regional blood flow and blood volume of carotid artery will change because of partially blocking. And the blood emboli have different density, composition and size from the normal

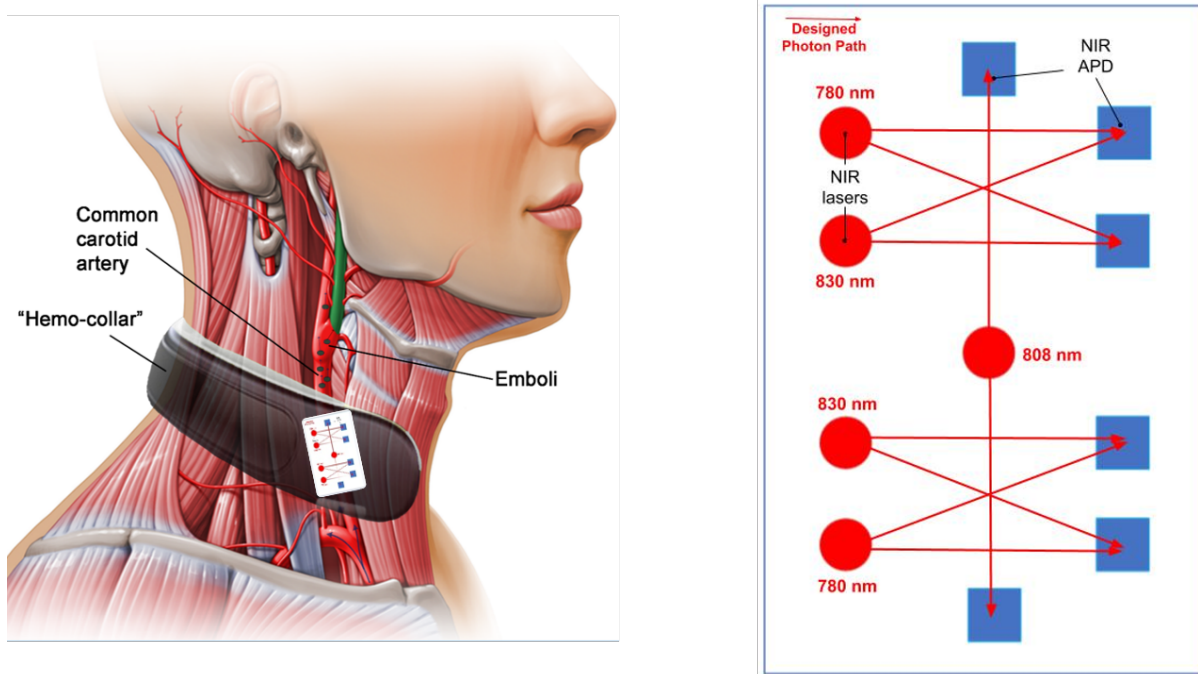


Figure 4.1: The proposed wearable NIRS system for stroke diagnostics.

composition in blood. The continuous NIRS method could capture those “drops” in real time (Fig 4.2). The carotid artery lies around 1.6 cm below the skin (Fig 4.2). The NIRS maximum penetration depth is about 4cm. But there is skin, subcutaneous fat, muscle (platysma, and sternocleidomastoid), some very thin connective tissue above the carotid artery (Fig 4.2, Fig 3.2). All those unrelated tissues would cause unrelated information and noise when we use NIRS. So it is necessary to use multiple lasers/sensors with the particular distance between them. Because increased distance between laser and sensor could have more penetration depth but the lower signal to noise ratio. We can remove the common noise by using multiple lasers/sensors (Fig 3.2).

To our best knowledge, no one has done noninvasive NIRS on carotid artery before. Current solution (imaging) on carotid imaging includes: 1) Carotid artery ultrasound; 2) Carotid artery angiography; 3) Computed tomography angiography; 4) MRI angiography.

The advantages of this solution is 1) simple structure; 2) easy to integrate with ultrasound

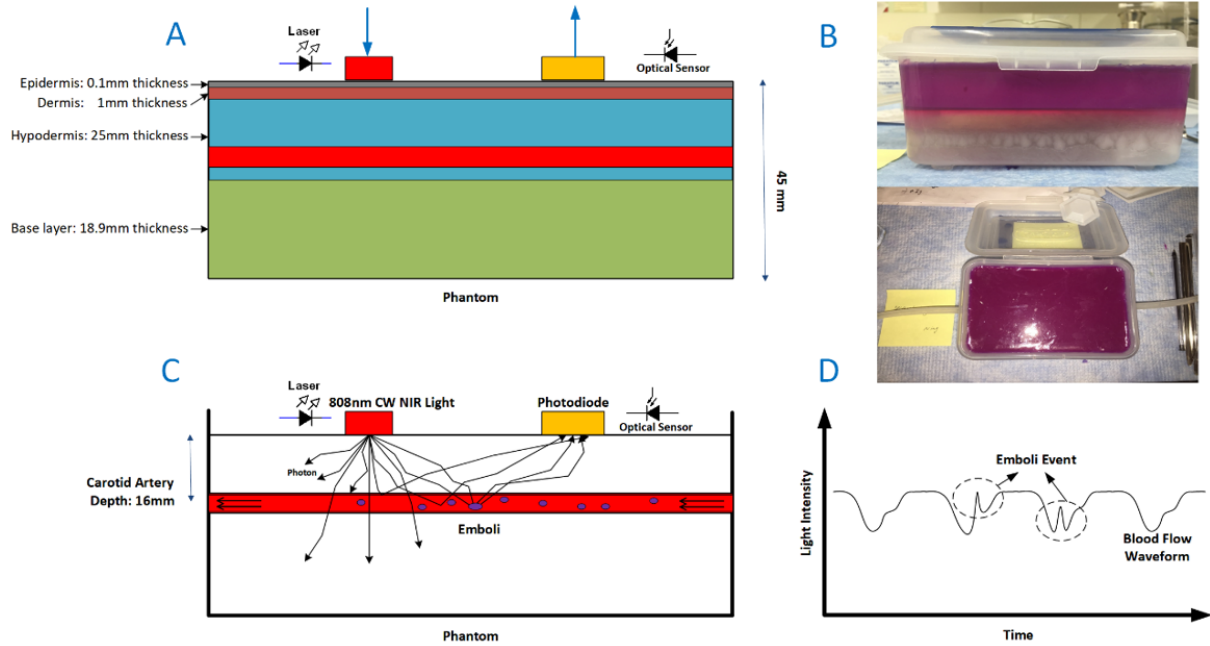


Figure 4.2: The designed emboli detection system.

method on neck; 3) less obtrusive to use. The disadvantages: 1) position problem (big challenge, will be discussed below); 2) low sensitivity.

What are the potential challenges?

Sensor position is definitely a significant problem for the NIRS system on the neck. The mechanical structure needs to ensure the absolute stability. Any tiny change will result in a false measurement that leads to a wrong prediction. The NIR is diffusion imaging method. The result reflects the region information (not specifically the artery). And the optical methods have limited penetration depth.

4.2 System Design

4.2.1 System Concept

The designed system concept is described in Fig 4.3 below. The system are consisted by three parts: The first part is the front-end including NIRS optical module and anxillary sensors. The second part is the main board including digitalization (ADC), embedded control unit, storage, power management and data analysis. The third part is the wireless communication. Because of the proof-of-concept stage, this thesis focuses on developing the front-end and main board to detect the emboli as small as possible on tissue mimicking phantoms.

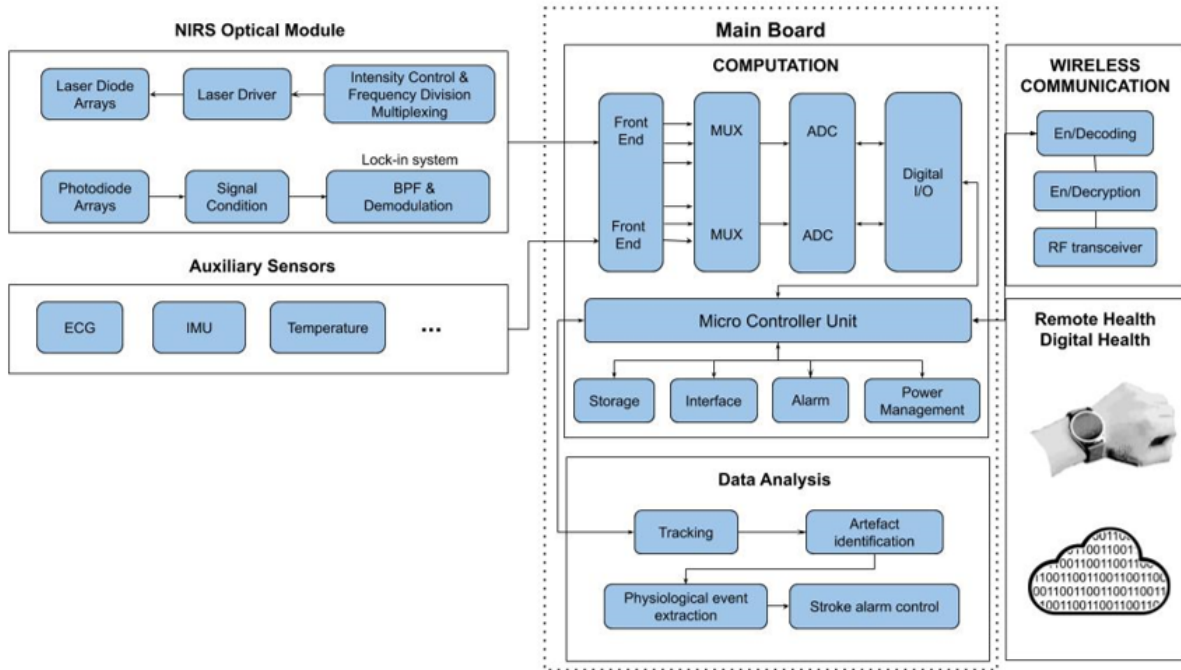


Figure 4.3: The designed emboli detection system.

There are three types of NIRS techniques including: 1) Continuous wave (CW) NIRS; (2) Frequency domain (FD) NIRS and (3) Time domain (TD) NIRS. Comparing to the other two techniques, CW NIRS is low cost, easy to be miniaturized and lightweight so that it can

be used for wearable medical applications.

CW NIRS method uses continuous or low frequency modulated near infrared light at a constant intensity I_0 to illuminate the tissues. The reflected or transmitted light is then measured over time to calculate relative changes. Both absorption and scattering events happen and couldn't be resolved and differentiated from the detected output in CW method (Fig 4.4).

As illustrated in Fig 4.2, when the emboli flow through CCA, the optical properties (absorp-

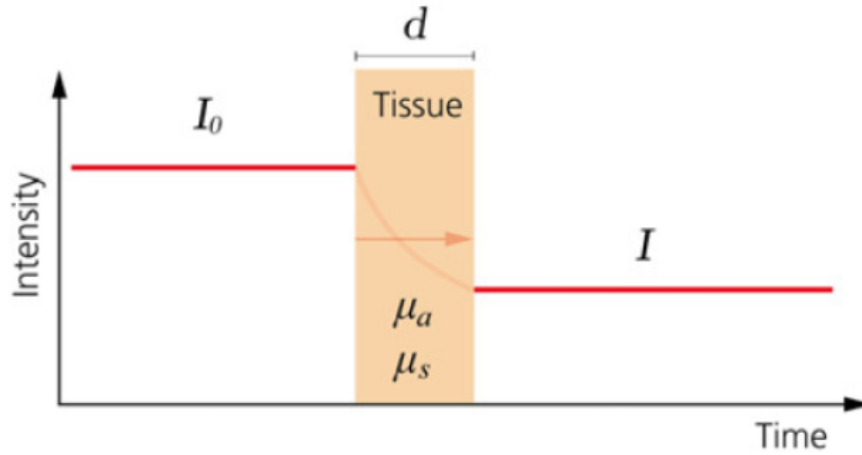


Figure 4.4: The principle of CW NIRS[2].

tion, scattering) of that region will change. It brings disturbance of the photon propagation pathway between the source (NIR laser) and the sensor (NIR avalanche photodiode). In principle, as the injected photons propagation pathway cover the target CCA, all the micro emboli (diameter from hundreds of microns to millimeters) can be detected by CW method if the system is sensitive enough (with high SNR). The total detected reflected photons are much less than detected transmitted photons because most of the scattering events in the tissues are forward scattering (with anisotropy parameter larger than 0.8). The reflected photons which interacted with emboli previously are buried in the total reflected photons. So improve the SNR of the system is the number one important thing to be considered.

4.2.2 Noise and Error Sources

Describe the noise and error sources in the system and how they are reduced by design. There are multiple noise and error sources that could limit the sensitivity and accuracy of the system.

Noise in Photodetector

The noise in photodetector mainly consisted by three types: shot noise, dark current and thermal noise.

Shot noise is caused by the random fluctuations in photon-to-electron conversion process of the detector. Because the photons arrive at the detector independently and randomly. Shot noise is an intrinsic and fundamental noise that exists in all optical detection system and could not be avoid. It is proportional to the number of incident photons (square root of incident light power).

Dark current is caused by spontaneous generation of electron-hole pairs in the depletion region of the PN junction[3]. It is a small DC current in the detector when there is no optical signal.

Thermal noise (Johnson noise) is caused by Brownian motion of charge carriers in resistors. It is usually the largest single noise component in photodetector.

The overall SNR of the detector can be described by this equation[4]:

$$SNR_{detector} = \frac{\eta N_p \tau}{\sqrt{\eta N_p \tau + N_d \tau}} \quad (4.1)$$

where η is the quantum efficiency of the detector, τ is a time interval, N_p and N_d are the average photon arrival rate and the average electrons generated because of dark noise,

respectively.

According to the equation, to get a high SNR:

- quantum efficiency of the detector should be as high as possible;
- the photon arrival rate or the incident light intensity should be as high as possible;
- the dark noise should be minimized;

The dark current and thermal noise can be reduced by cooling the detection system. The shot noise could be reduced by preventing measuring other irrelevant photons from background radiation.

Crosstalk

The crosstalk of the system can be electrical crosstalk and optical crosstalk. Electrical crosstalk can be minimized by good PCB design (e.g. large ground planes). Optical crosstalk is caused because a detector might measure optical signals from multiple sources of the system.

System drift

The system drift is an error source for long-term measurement. It represents the stability of the system. The drift should be tested in the experiments.

Stray radiation

The ambient light is an error source that affects the detected signal. It can be avoided by applying lock-in technique.

4.2.3 Lock-in Detection

The lock-in technique is used to extract the weak vital signal from many larger noises. The lock-in technique works like a great bandpass filter at a designed frequency. It can not only enable the system to be used regardless of ambient light but also enable simultaneous measurements of multiple source-detector pairs without interference.

4.2.4 Bench-top Design

The bench top system is developed for experiments (Fig 4.5).

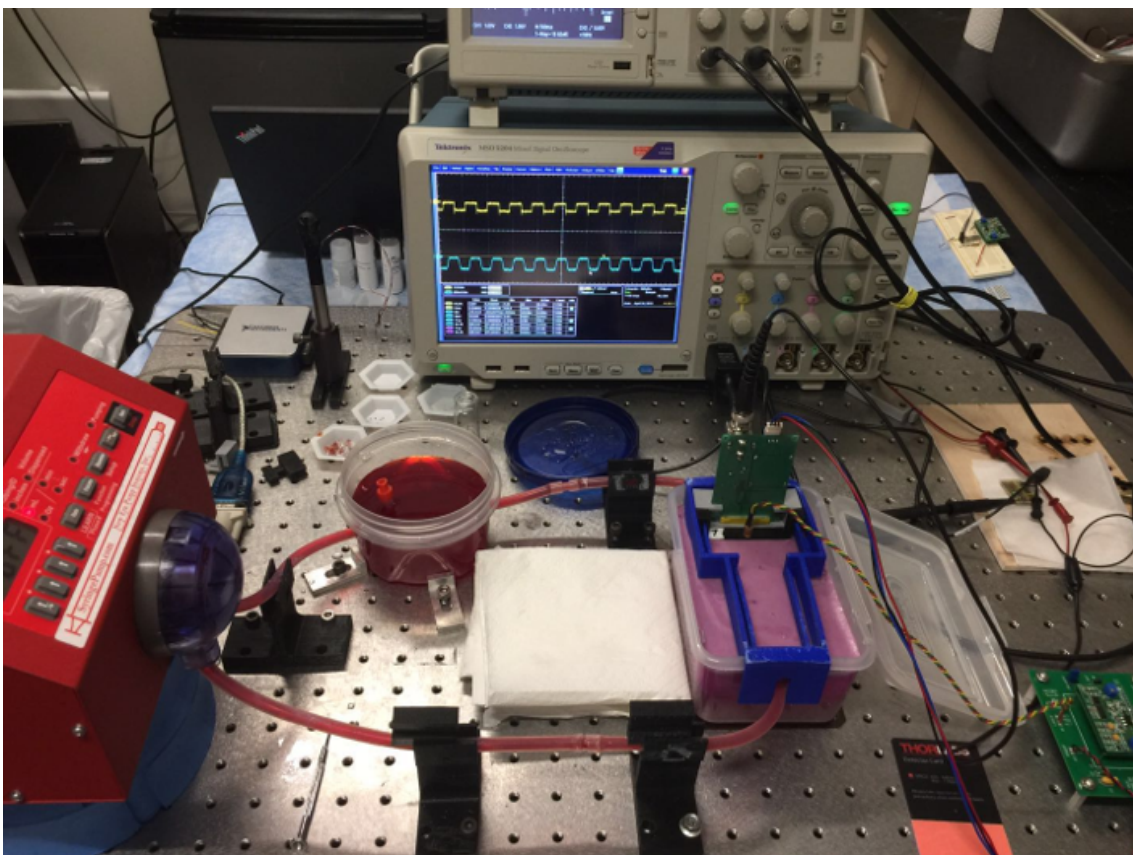


Figure 4.5: The bench-top emboli detection system (with phantom).

The system is consisted mainly by the following instruments(Fig 4.6): Flow pump; Phantom; Laser and APD sensor; Laser board; Blood reservoir; Carotid artery tube; Conditioning circuit; AD Converter; Monitors; Lock-in System.

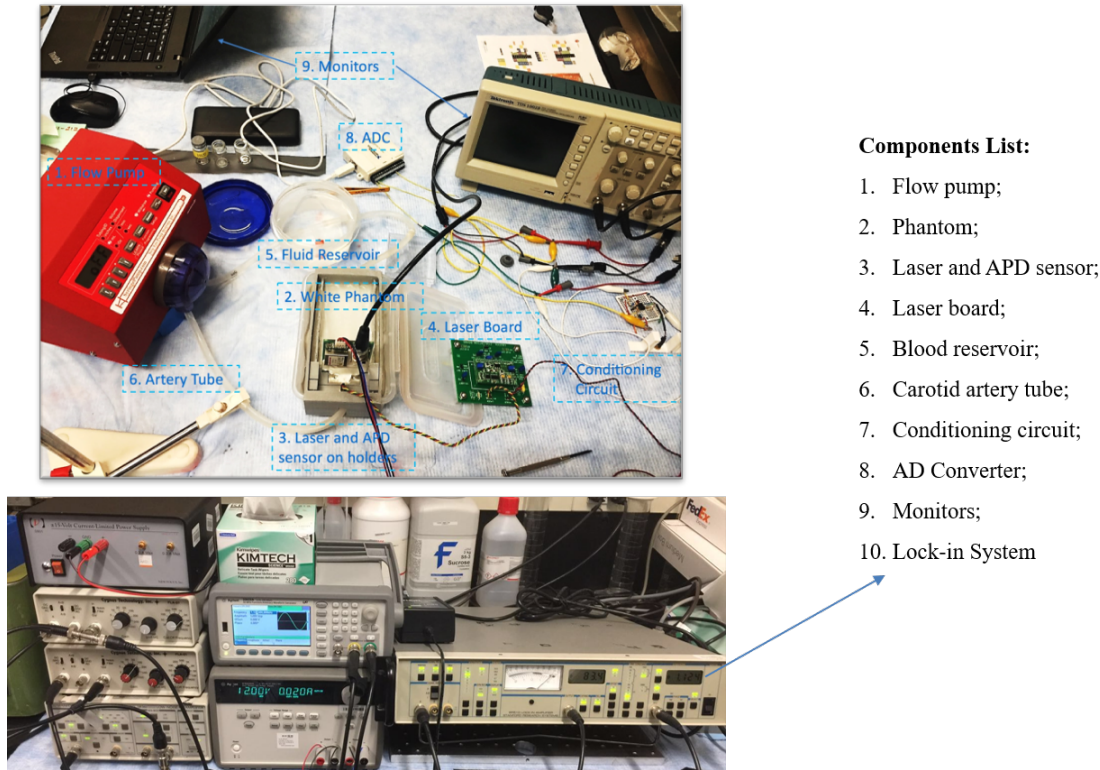


Figure 4.6: The bench-top emboli detection system (with phantom).

Emboli selection: Different artificial sphere beads are chosen to mimicking different types of emboli as described in the Fig 4.7 and Fig 4.8.

Watchdog design: A direct transmission optical module is designed as a trigger and double-checker for the emboli detection system(Fig 4.9). Because the emboli detection system measures reflected photons which are few.

Optical property:

High absorption at the target (808) wavelength (black, polyethylene)

No absorption (transparent, air bubbles)

High reflection (white, polyethylene)

Sizes: different size in the range of 200um to 2000um

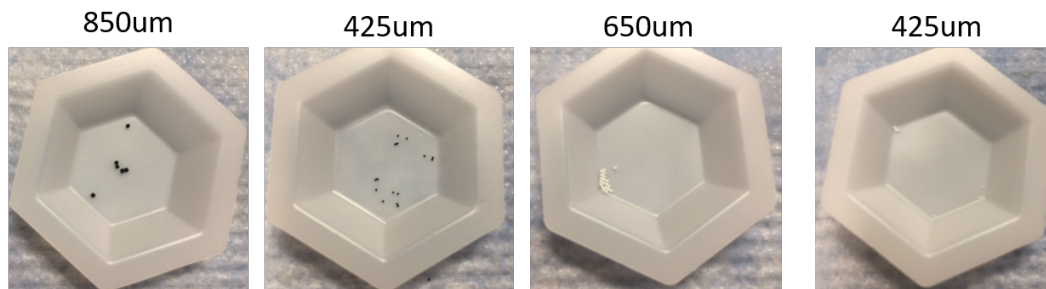


Figure 4.7: Artificial emboli selection for experiments.

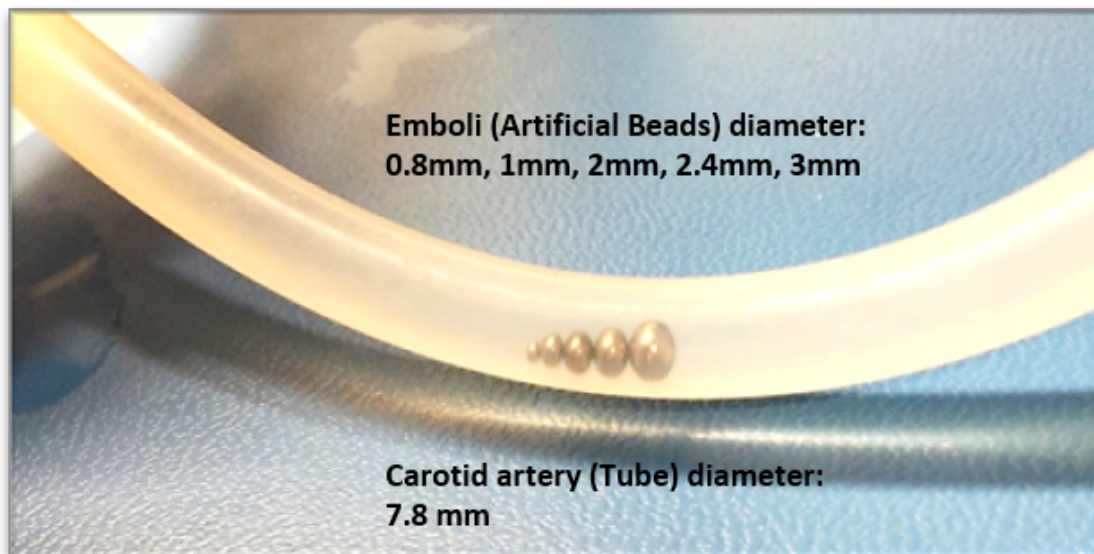


Figure 4.8: A close look at the artificial mental beads from 800 microns to 3 millimeters (diameter).

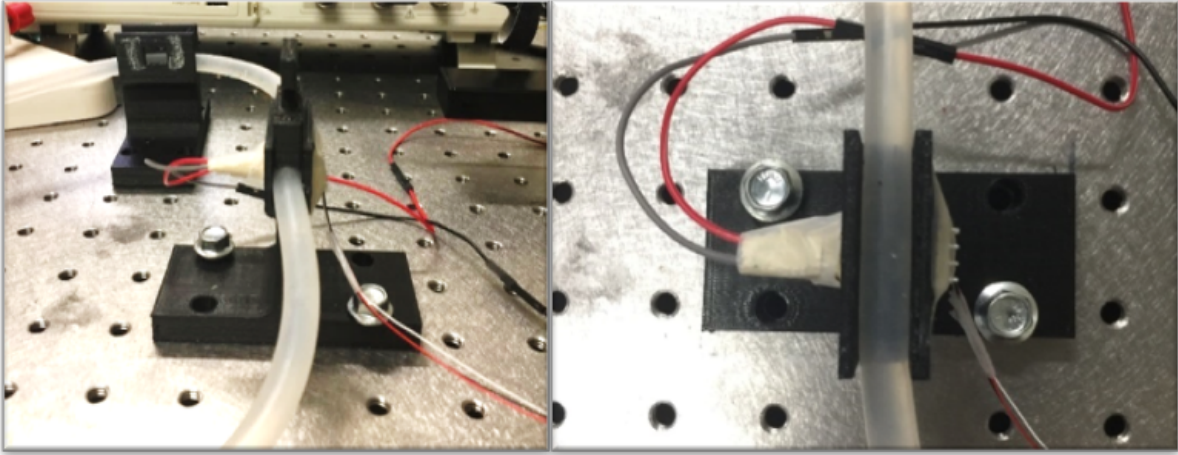


Figure 4.9: Watchdog: transmission optical module.

4.2.5 Circuit Design

To minimize the system and improve the signal to noise ratio, an integrated circuit for NIRS module is designed and fabricated on a PCB (printed circuit board). The basic structure of the NIRS module is designed based on an open-source design[1]. The structure of the circuit is showed in figure below:

4.3 Results and Discussion

The figure below shows the detected signal of emboli on oscilloscope directly. The flow pump ran at a fixed rate to pump the circulated flow at 40cm/s. Repetitive high intensity transient (HIT) optical signals were detected at periodically (Fig 4.11 A). The CW measurement remained stable at the baseline (Fig 4.11 B, C) when no embolus detected. A HIT signal is an index for a detected embolus.

In Fig 4.12, four emboli with different sizes were detected on the phantom. They can be differentiated by the signal's amplitude. The embolus existing will decrease the light intensity

NIRS Module 1.0

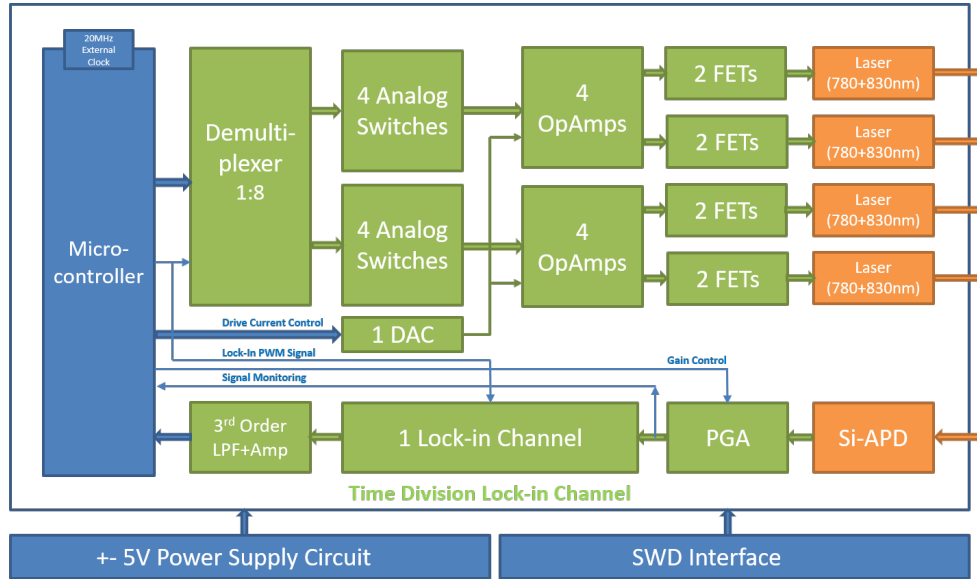


Figure 4.10: The circuit structure of the NIRS module.

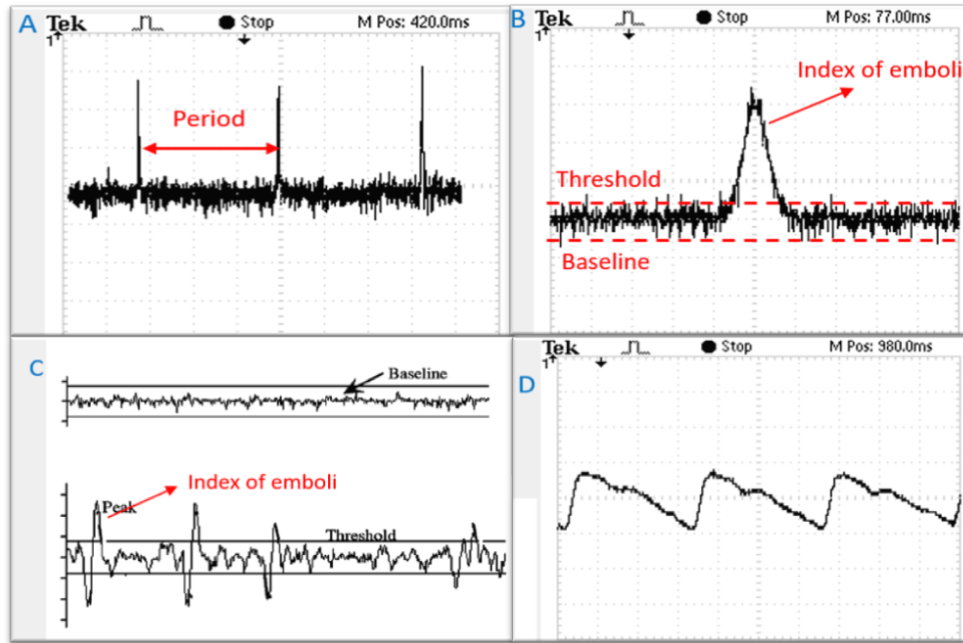


Figure 4.11: A. Detected emboli signal on phantom (triple events); B. Detected single emboli event on phantom; C. The reference result from Solen et al.[13]; D. The measured blood flow waveform of carotid artery by the system.

(the larger size, the more decrease).

Emboli signals from oscilloscope from diameter = 0.8, 1, 1.2, 2mm

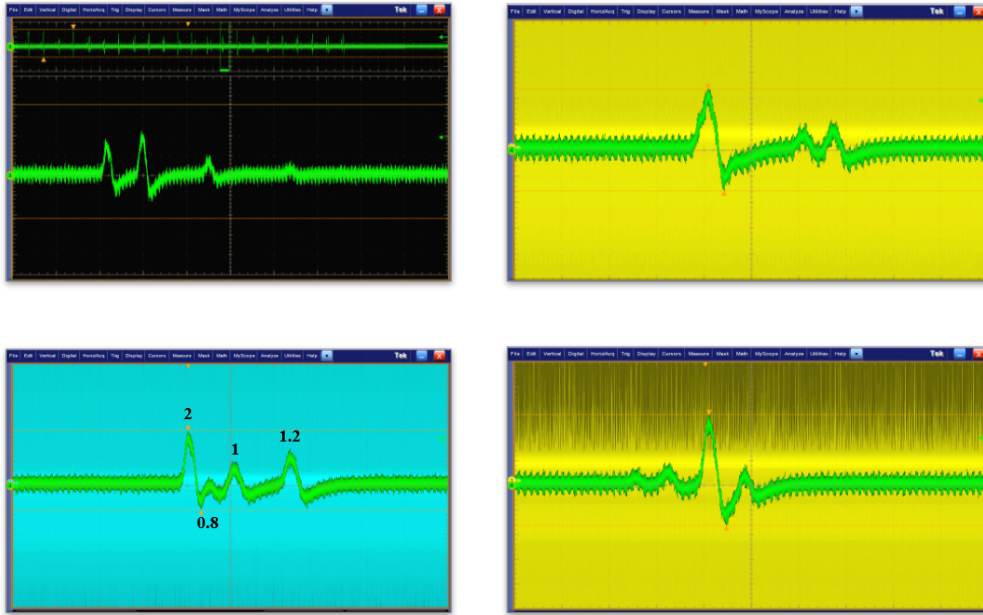


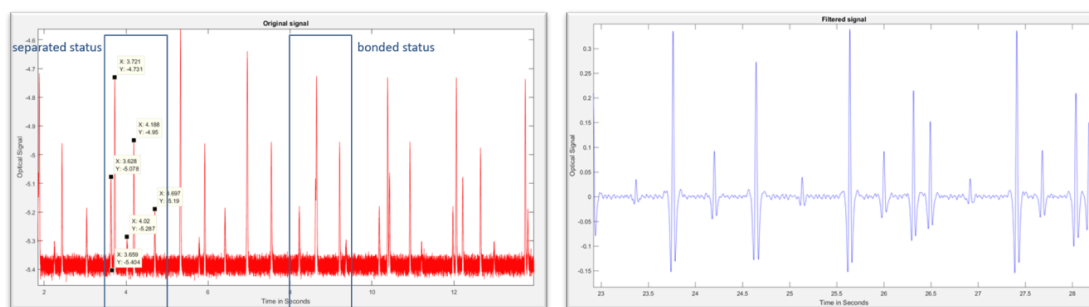
Figure 4.12: Detected output for four different emboli on the phantom.

The analog output of measurement was digitalized by AD converter for further signal processing and analysis to extract more information. The results of five different emboli is showed in Fig 4.13. The HIT signals are more clear and obvious after filtered. During the repetitive circulation, those microbeads could become separated or bonded together as showed in Fig 13. The same four embolus with 800 micron diameter could be measured accurately and stably which validates the performance of the system.

Fig 4.15 shows a relationship of the peak of the detected signal of an embolus and the diameter of it.

A series of signal analysis methods have been employed for experiments with a 1mm embolus. The flow speed was controlled at 40cm/s. The measurement time was set to be 90 seconds. The circulation stopped at 45 seconds after beginning, to compare measurements with flowing

5 emboli ($d = 800\mu\text{m}$, 1mm, 2mm, 2.4mm, 3mm) at flow rate: 700ml/min (Left: Raw Data Right: Filtered Data)



4 emboli ($d = 800\mu\text{m}$) at flow rate: 700ml/min

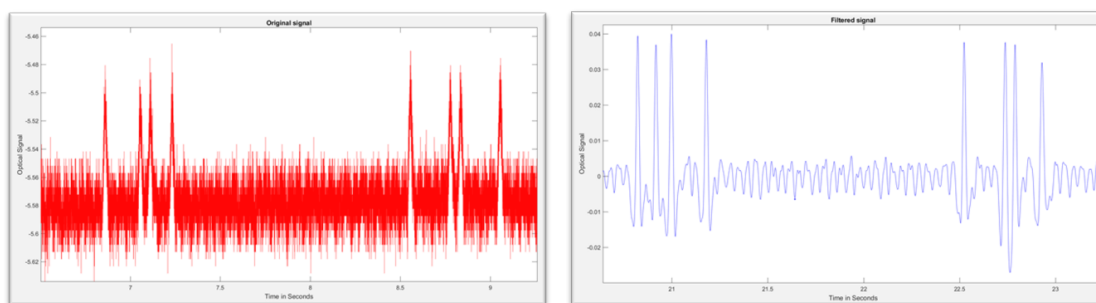


Figure 4.13: Upper: five emboli with different sizes; lower: four emboli with $800\mu\text{m}$ diameter.

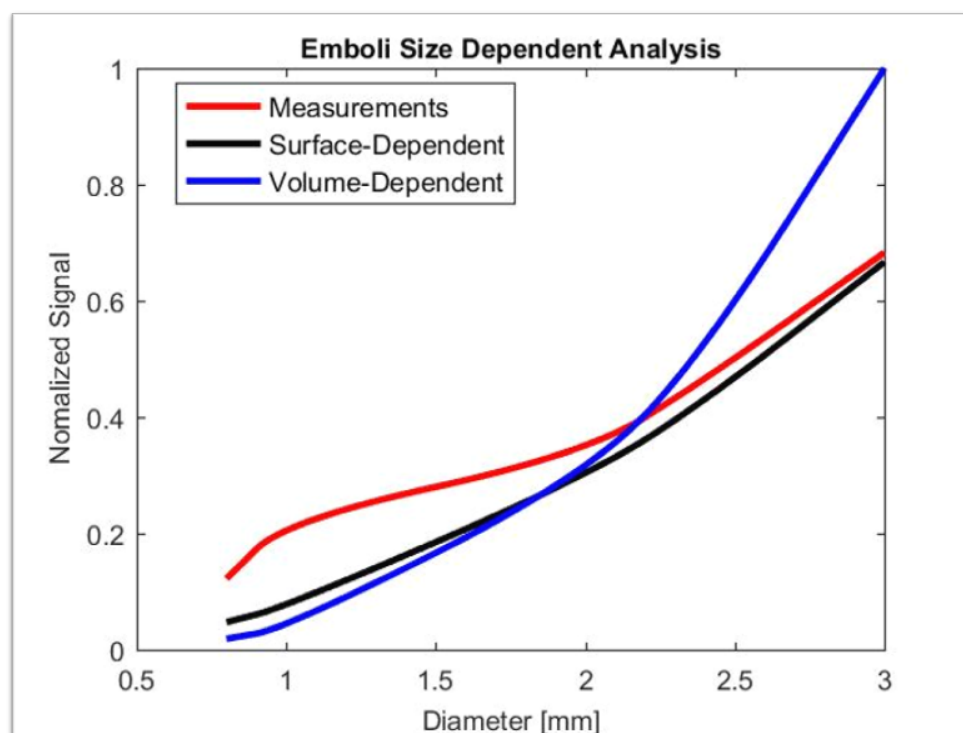


Figure 4.14: The emboli size dependent analysis.

emboli and measurements with nothing. In Fig 4.16, the system drift and noises in the original detected signal can be removed with digital filters.

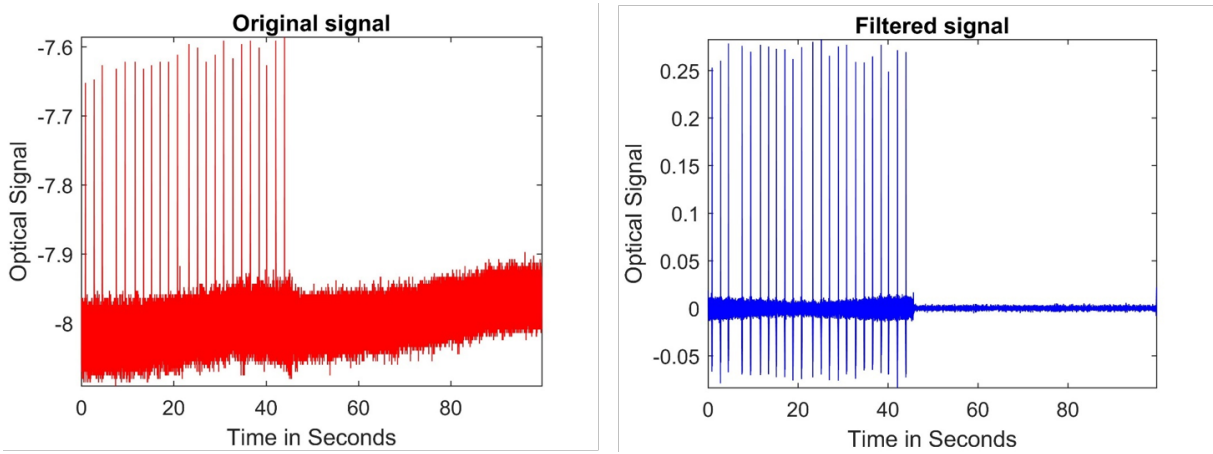


Figure 4.15: Signal conditioning and drift removing by digital filters.

Then the developed program can detect the peak of the HIT signals to indicate the embolic events. The amplitude of each peak can be measured and analyzed to tell the size. The period of this repetitive circulation can also be calculated to show the motion of the embolus in the flow.

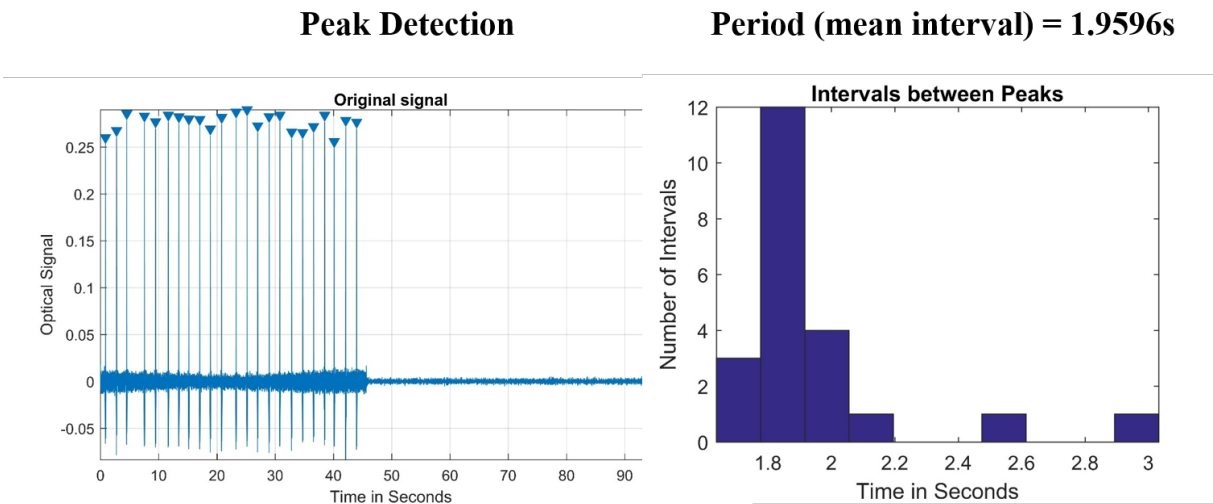


Figure 4.16: Left: Peak detection to differentiate embolic events; Right: Period calculation for circulation of the embolus

The emboli flowing in the artery can be regarded as a fluid dynamic mechanic situation. There exists emboli-flow interactions by 1) one-way coupling and 2) two-way coupling. The presence of particle disturbs the blood flow and will leads to an exchange momentum back to the fluid. To explore the phenomenon, all the measured embolic signals were plotted in a same plot as showed in Fig 4.18. As showed in the Fig 4.18, the waveform was asymmetric: left side (valley) is deeper than the right side. It might be the influence of turbulence introduced by the embolus. More investigations are needed on this topic in the future since the turbulence is related to the embolus' composition and physical properties. Thus, we could get more information about the embolus through the asymmetry.

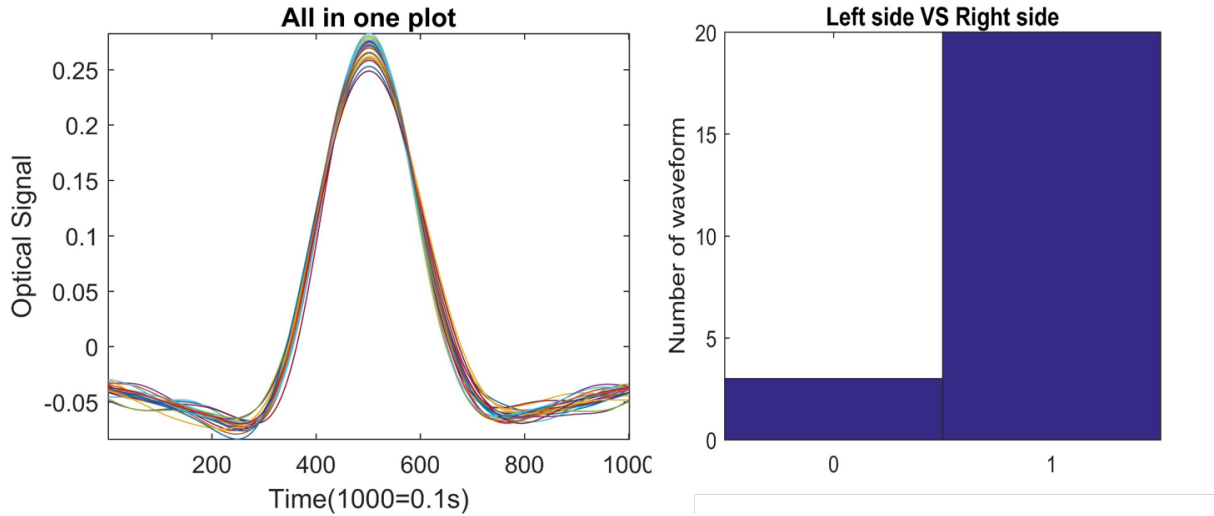


Figure 4.17: Asymmetric embolic waveform. Left: all the detected waveform in one plot; Right: 1 if left side valley is deeper.

The circuits for the NIRS module are designed according to the structure in Fig. 4.10.

A small PCB is designed and fabricated for system integration and SNR improvement.

The artificial emboli can be detected as small as 800 microns by current bench-top system(Fig 4.8). More experiments will be done to detect as small as about 400 microns diameter emboli. Comparing to the other previous investigations (Fig 4.9), the results are impressive and

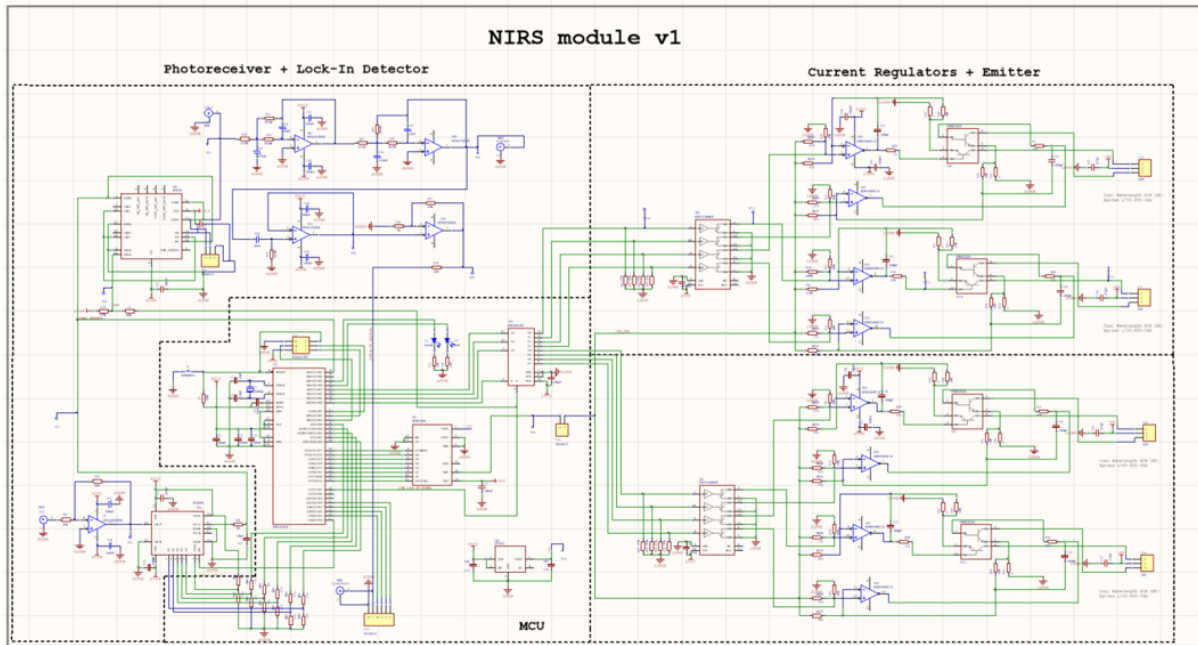


Figure 4.18: Circuit schematic for NIRS module

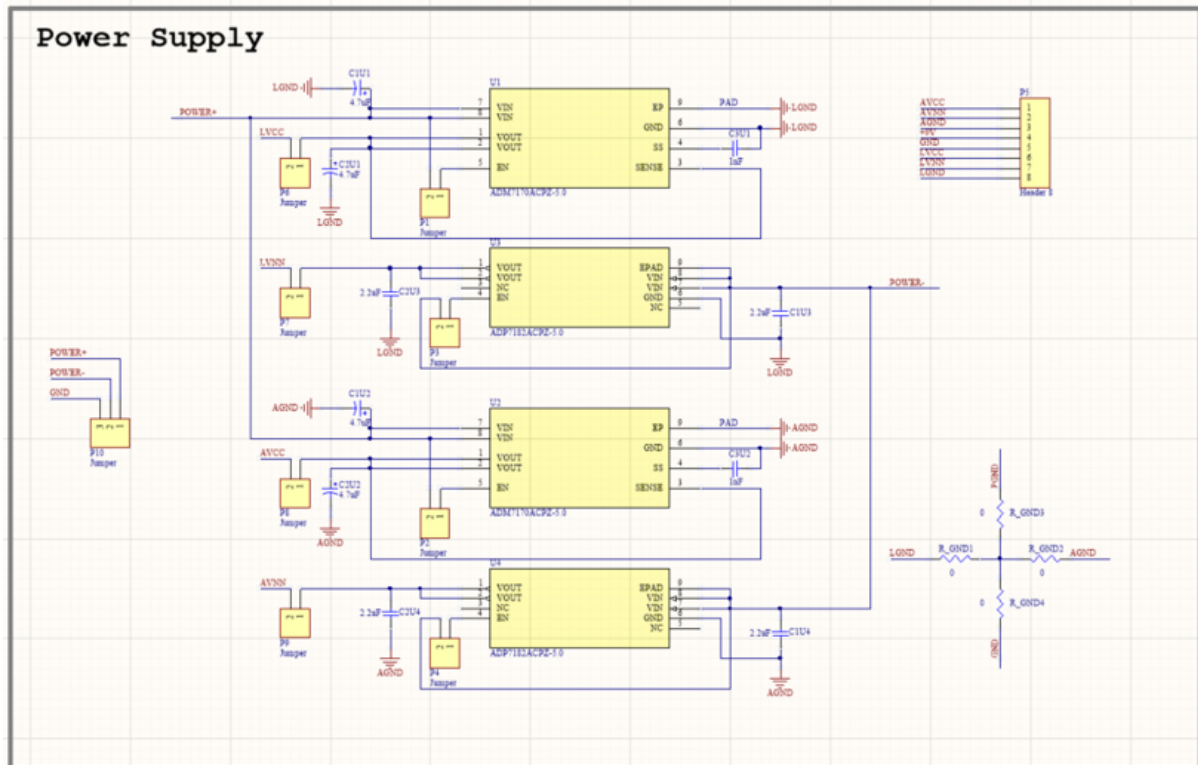


Figure 4.19: Circuit schematic for power supply of the system.

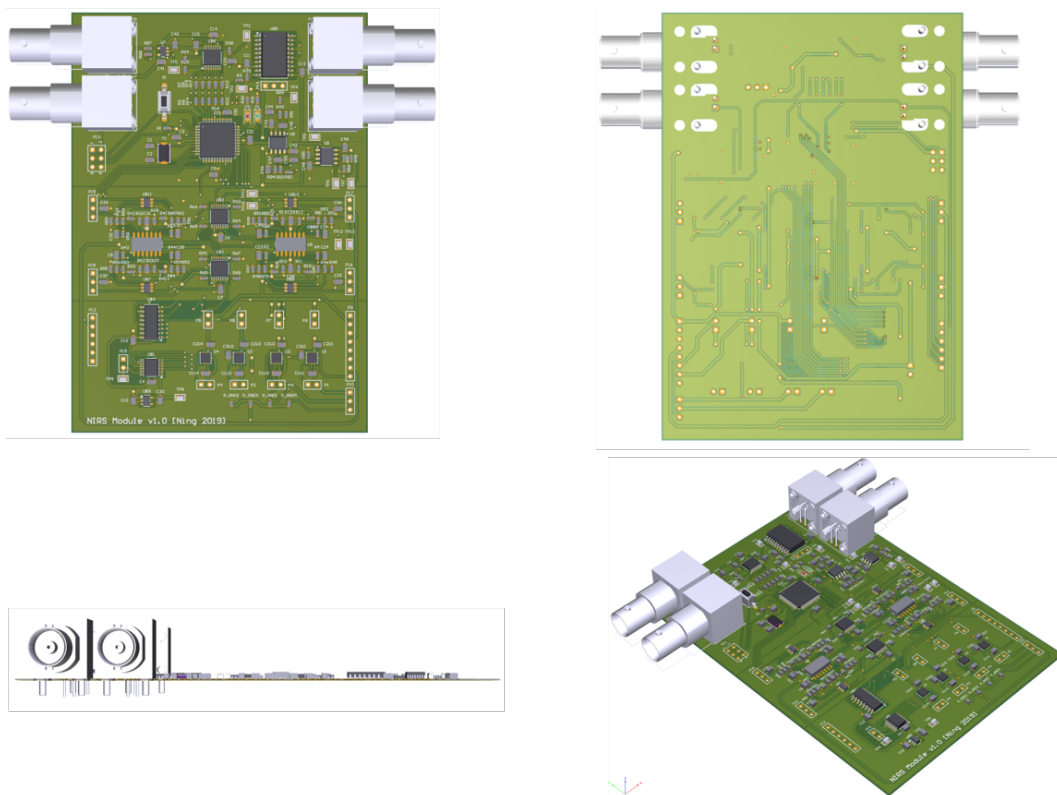


Figure 4.20: An illustration of the PCB design in software

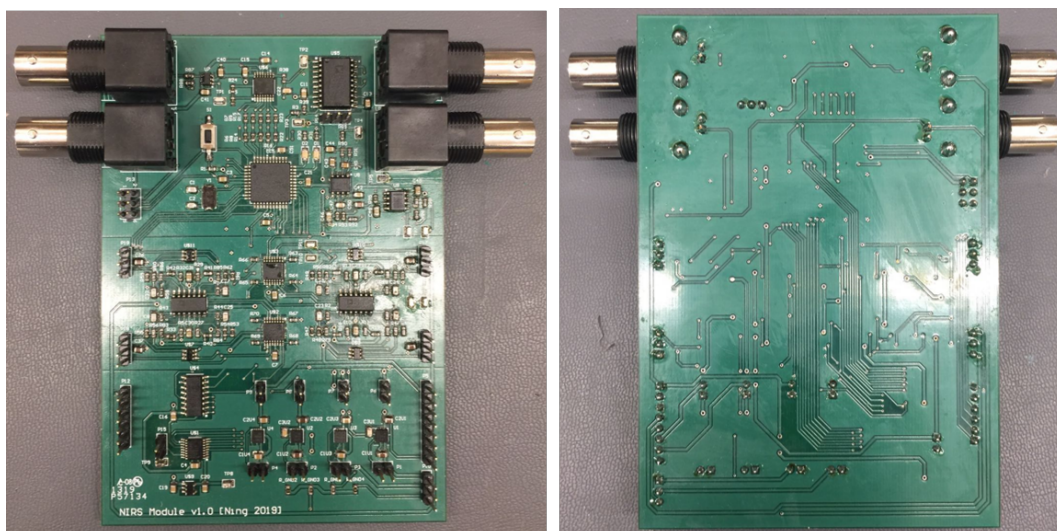


Figure 4.21: The fabricated PCB.

promising, which indicates that the system has potential to be continuously developed and translated to a realistic medical device in clinic. (the) In this design, a pair of sensor and

Ref	Optical Units			Pump		Vessel		Blood		Emboli	
	Source	Detector	Mode	Pulsation	Rate (ml/min)	Type	Diameter	Source	Agent	Type	Diameter (um)
1	BLAZER T-1 semiconductor laser 805nm, 2mW (optical fiber)	BLAZER T-4 photon detector (optical fiber)	Reflectance D= 15 mm	No	N.A.	N.A.	N.A.	Blood	N.A.	Celite powder; Plastic bead (black)	100 x 20; 200
2	Chip type LED (EPIGAP, Berlin, Germany), 810nm, 1mm^2	SMD photodiode (KODENSHI, Tokyo, Japan), 1mm^2	Reflectance and Transmission D= 3 mm	Yes, Small pulse	100-290	Transparent tube	4 mm	Bovine blood	Sodium citrate (anticoagulation), Calcium chloride (neutralization)	Polystyrene beads	450, 2500
3 5	He-Ne laser, 632.9nm, (optical fiber)	PMT, 3, (optical fiber)	Transmission D= N.A.	No	60	N.A.	2.216m m(outer), 1.016m m(inner)	Bovine blood	N.A.	Polystyrene beads Air bubbles; Natural blood clots	43.8, 90, 200; 1ml of air
4	Array of eight large LEDs	1M30CCD (DALSA, Waterloo ON)	Transmission D= N.A.	Yes, 40/min	120cm/s	N.A.	5.12mm	Water	N.A.	EmboGold	100 to 300
6 7	He-Ne laser, 632.9nm, (optical fiber), 1	Dual Dec 1123 computer based multichannel analyzer (optical fiber), 5	Transmission D= N.A.	Yes	3100-3500 first calf; 4100-4900 second calf	I.D. Tygon tubing	9mm	Bovine blood	Heparin (5000U)	Carbon particles; Polystyrene beads	20-1000 for both
8	Laser (Melles Griot, Boulder, CO), 830nm, 30mW, (optical fiber d= 600um)	Photodiodes (Melles Griot, Boulder, CO), 2, (optical fiber d= 200um)	90 degree angle	Yes, 10-12/min	50	ID polyurethane tubing	3.175mm	Bovine blood	Heparin (5000U)	Natural emboli	N.A.

Figure 4.22: Published results comparison. Ref column 1 to 8: [5][6][7][8][9][10][11][12]

source were used. Multiple pairs or arrays of sensors and sources should designed in future research. It will introduce a question about the source-detector (SD) pattern design (such as illustrated in Fig 4.1). The patterns for source and detectors depend on the applications and are specially designed. The pattern design is related to multiple questions: How deep you want to measure? How much the noise your device can tolerate? What are the compositions of the tissue region you want to measure? How good is your laser and source? More investigations are needed for sensor and detector geometry and pattern design.

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