COGNITIVE BRAIN MRI ANALYSIS IN MS

GIORGOS PAPANASTASIOU

UNIVERSITY OF CYPRUS

DEPARTMENT OF COMPUTER SCIENCE

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Giorgos Papanastasiou

Research Consultant: Prof. Konstantinos S. Pattichis

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ABSTRACT

Multiple Sclerosis (MS) is chronic disease which affects mainly the brain and the spinal cord. Even with today's medical advancements it is very hard to diagnose and offer a specific treatment because on each individual patient MS strikes atypically, hence the numerous symptoms, both physical and mental.

In order to diagnose MS, a Magnetic Resonance Imaging (MRI) scan is necessary to identify the lesions created in the patient's brain. MRI is also vital for the treatment of MS where the patient's progress is monitored and the treatment is adjusted on each iteration.

Each individual MRI is almost unique in the way they are captured, not just their content. MRI is a 3D image which if you were to match with other images you'd have to first align them correctly and efficiently.

A tool that has a potential to do just that or even more is LONI PIPELINE. The user has to build workflows, from the most basic ones to the most complicated reflecting the problem he is trying to solve. Thru the usage of LONI Pipeline and the help of sample workflows that we run with datasets we might extract some results in order to analyze and reach certain conclusions to the MS progression.

TABLE OF CONTENTS

Chapter 1

Introduction

1.1 Motivation

The human brain, it’s a complicated as it is fascinating. It is much more than an organ, it is capable of producing enormous processing power, without us even noticing.

Never the less the brain is physical part of our body, an organ that as any other we have to take care so that it can take care us. Not just us individuals bus all of the human species, we must unlock its secrets for better healthier future

This thesis aims to study workflows for MRI analysis for the above reason. By using computing power from artificial ways we get to understand and improve our human processors.

How by taking “images” of our brain which is a fascinating idea by itself we can monitor diseases and functions of the brain we can study the effects of these diseases and provide hopefully someday treatment with the final goal to eradicate these diseases

1.2 Thesis Structure

This particular thesis will follow the structure below:

Chapter 2: Basic information and terminology about different parts, substances and functions of the human body.

- 2.1 Central Nervous System
- 2.2 The Brain
- 2.3 The Spinal Cord
- 2.4 The Spine
- 2.5 Brain Cells
- 2.6 Myelin sheath
- 2.7 Blood Brain Barrier
- 2.8 T Cell
- 2.9 B Cell

Chapter 3: in depth view of the Multiple Sclerosis disease

- 3.1 Multiple Sclerosis
- 3.2 Symptoms
- 3.3 Types of Multiple Sclerosis
- 3.4 Pathophysiology

Chapter 4: Magnetic Resonance Imaging

- 4.1 Magnetic Resonance Imaging
- 4.2 History of Magnetic Resonance Imaging
- 4.3 Magnetic Resonance Imaging Function

Chapter 6: Workflows of LONI Pipeline

- 6.1 Introduction
- 6.2 Basic Workflows

CHAPTER 2

Background and Terminology

For a better understanding of Multiple Sclerosis and the whole spectrum around this subject, we have to first and foremost understand some basic terminology around the body functions, the brain and neurology.

2.1 Central Nervous System

Therefore, it is important to explain about the most crucial organ of the body, the **Central Nervous System** or CNS. CNS is consisted by the brain which is a complex organ that defines each one of us individually, from our basic movement, our perception of our surroundings. Importantly, the brain is the organ that defines our character. With that in mind, the spinal cord is the other part of CNS which its main duty is to send messages from the brain to different parts of the body and to receive messages back.

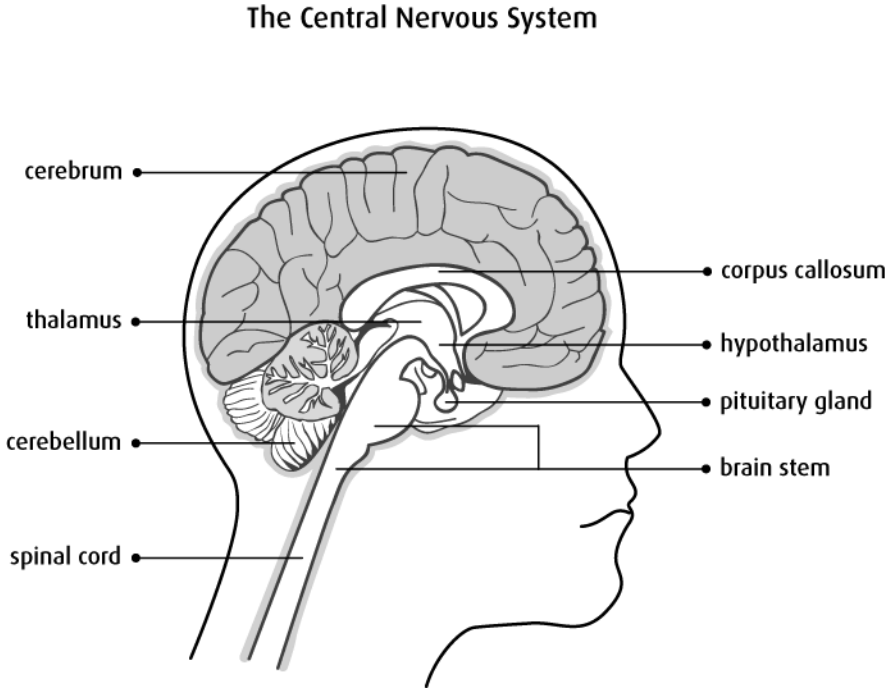

Fig 1 A side view of the brain and it's sections. [1]

2.2 The Brain

It is for the most part an unconditional fact that the brain is considered the "body's control center" since, "it constantly receives and interprets nerve signals from the body sensors and sends new signals based on this information" [1]. Moreover, different parts of the brain are focused on different functions such as; control movement, speech, emotions, consciousness and internal body functions, such as heart rate, breathing and body temperature.
The brain can be divided in three main parts, including **Cerebrum, Brain stem** and **Cerebellum.**

2.2.1 Cerebrum

That said, the **Cerebrum** is the largest part of the brain. It is divided into 2 hemispheres called the left and right cerebral hemispheres. Furthermore, the right half of the cerebrum or the right hemisphere, is the hemisphere which is responsible for controlling the left side of the body. In contrast, the left hemisphere is responsible for the right side of the body. In fact, these two hemisphere "are connected by a bridge of nerve fibers called the corpus callosum" [1]. Hence, the left and the right hemispheres are in charge of the whole body movement related functions. The cerebral cortex also referred to as the grey matter "is the outer, folded part of the brain" [1]. In order to understand the functionality of the cerebral cortex, it is important to explain another component of the brain, the cell bodies and dendrites of nerve cells (neurons). That is the case since, "cell bodies contain the nucleus and other main parts of the cell. Dendrites are the short branching fibers that receive signals from other nerve cells" [1]. The cerebrum also consists of white matter which is the inner part of the cerebrum. White matter "is mostly made up of the long fibers of a nerve cell (called axons) that send signals to and from the brain to the rest of the

body. The fatty coating that surrounds axons (called myelin) gives this part of the brain a whitish appearance" [1].

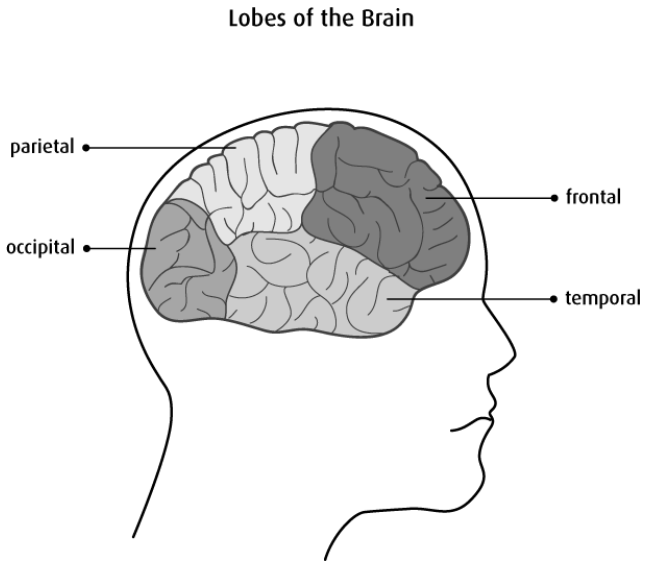

Fig 2 A side view of the brain and its lobes.[1]

Each brain hemisphere is divided into four sections called lobes. These lobes are the frontal, parietal, temporal and occipital lobes and each lobe has different functions:

- The frontal lobe: "controls movement, speech, behavior, memory, emotions and intellectual functions, such as thought processes, reasoning, problem solving, decision-making and planning" [1].
- The parietal lobe: "controls sensations, such as touch, pressure, pain and temperature. It also controls the understanding of size, shape and direction (called spatial orientation)" [1].
- The temporal lobe:" controls hearing, memory and emotions. The dominant (left side in most right-handed people) temporal lobe also controls speech" [1].
- The occipital lobe that controls vision.

2.2.2 Brain Stem

Brain stem is the accumulation of the nerve tissue which is located at the base of the brain. Importantly, the task of the brain stem is to connect the cerebrum and cerebellum to the spinal cord. Therefore, the brain stem sends information to and from the other parts of the brain to the rest of the body and thus, it controls breathing, body temperature, blood pressure, heart rate, hunger, thirst and digestion of food.
The brain stem also is consisted by three areas which are:

- midbrain (also called the mesencephalon)
- pons
- medulla oblongata

2.2.3 Cerebellum

Cerebellum is another part of the brain which is "located under the cerebrum at the back of the brain" [1]. likewise, as the other three main part of the brain. Cerebellum is divided yet again into two hemispheres and it also has grey and white matter.
The main responsible of the cerebellum is precisely to control functions such as:

- movement
- posture
- balance
- reflexes
- complex actions (like walking and talking)
- collecting sensory information from the body

2.3 Spinal Cord

Spinal Cord is the other main component of CNS and it is responsible for the fast transition of responses from and to the brain and the rest of the body. To be more precise, the spinal cord is "a thick column of nerves surrounded by vertebrae that runs from the brain stem to the lumbar region of the spine" [1]. Likewise, the spinal cord is similar to the brain since both of them have grey and white matter.
Along the spine, spinal nerves exit the vertebrae in pairs at the lumbar region, the spinal cord branches into a group of spinal nerves that exit the lumbar vertebrae and sacrum. The spinal nerves control body functions like movement, bladder and bowel control and breathing. The spinal nerves are numbered after nearby vertebrae.

2.4 The Spine

Having discussed about the spinal cord, it is crucial to discuss about the spine and its functions.

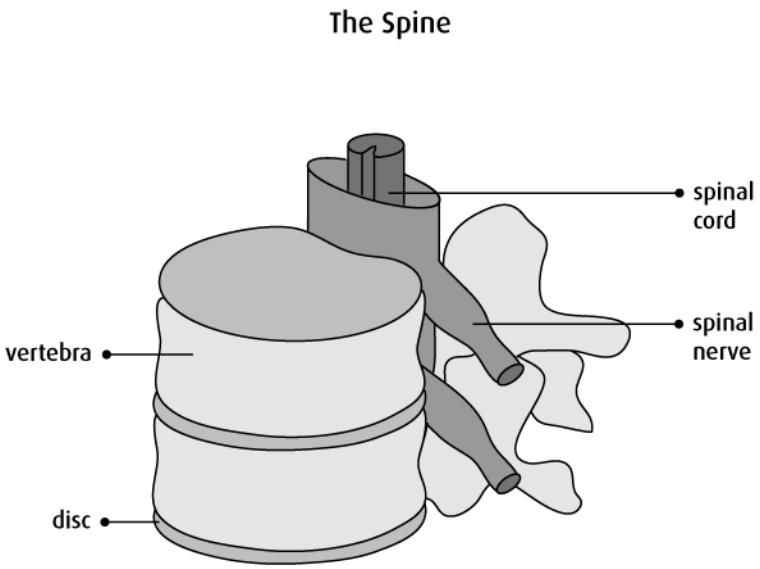

Fig 3 A cross section of the vertebrae. [1]

With that in mind, the spine is consisted of twenty-six bones that are responsible to surround and protect the spinal cord. Moreover, this collection of bones is divided into five sections which includes twenty-four vertebrae. To be more precise, the five sections are classified into cervical, thoracic and lumbar regions, the sacrum and the coccyx [1]. More precisely they are:

- Cervical region – These are 7 vertebrae at the top of the spine that run from the base of the skull to the lowest part of the neck.
- Thoracic region – These are 12 vertebrae that run from the shoulders to the middle of the back.
- Lumbar region – These are 5 vertebrae that run from the middle of the back to the hips.
- Sacrum – This is a large section of fused vertebrae at the base of the spine.
- Coccyx (tail bone) – This is a small, thin section of fused vertebrae at the end of the spine.
- Between the vertebrae are the discs (intervertebral discs). A layer of cartilage found between the vertebrae. Discs cushion and protect the vertebrae and spinal cord.

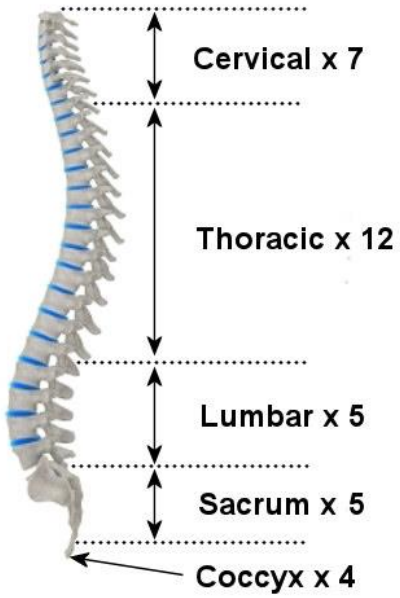

Fig 4 The spine and it's sections.[2]

2.5 Brain Cells

It is important to note that, the brain's two main types of cells are the Nerve cells and Glial cells.

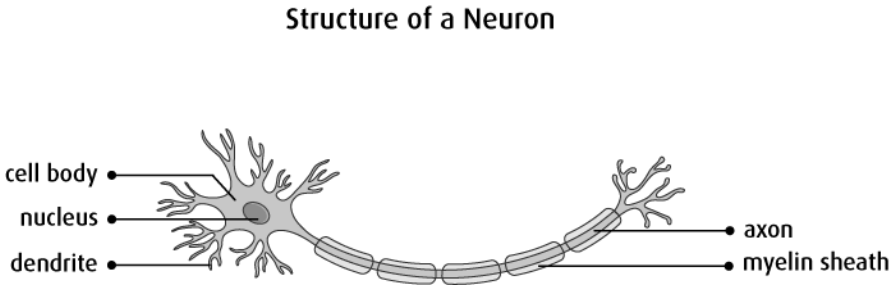

Fig 5 The structure of the Neuron. [1]

2.5.1 Nerve cells

Nerve cells (neurons): these are the cells that carry the electrical signals in order to make the nervous system work. In fact, the nerve cells are the longest cells in the body and in the event of any sort of damage they cannot be replaced or repaired.

2.5.2 Glial Cells

Glial cells (neuroglial cells): these are the cells that support, feed and protect the nerve cells. The different types of glial cells are:

- astrocytes

- oligodendrocytes
- ependymal cells
- microglial cells

2.6 Myelin sheath

Myelin is mainly a fatty material that covers, shields, and secures the axon of some nerve cells. Importantly, Myelin is enables the nerve cells to quickly conduct impulses between the brain and different parts of the body. Moreover, “Myelin coats the nerves of both the central nervous system and the peripheral nervous system” [2]. That said, Myelin encompasses proteins that the immune system takes advantage from. Therefore, a variety of symptoms of multiple sclerosis are being provoked through this corrosion of the Myelin in the central nervous system.

In contrast with the unmyelinated fibers in which the impulses persistently move as waves, the myelin coated nerves propagate the impulses by the saltatory conduction. Furthermore, Myelin coated nerve cells have tiny spaces between the sections which are also known as nodes. During the event where the brain sends messages in the form of impulses through the nerves of the spinal cord then, these impulses jump from one node to another. Another function that needs to be mentioned is no other than the myelin sheath, which is responsible for preventing these impulses from breaking away from the nerve at the wrong point.
Myelin is composed by a diverse collection of chemical compositions and arrangements of different cell types. Having said that, the term *white matter* of the brain derives from myelinated axons which are white. Moreover, “Myelin insulates axons from electrically charged atoms and molecules” [8]. In addition, Myelin not only increases the speed of the nerve impulse but also it “helps in reducing energy expenditure over the axon membrane as a whole” [4]. That is the case since, “the amount of sodium and potassium ions that need to be pumped to bring the concentrations back to the resting state following each action potential is decreased” [4].

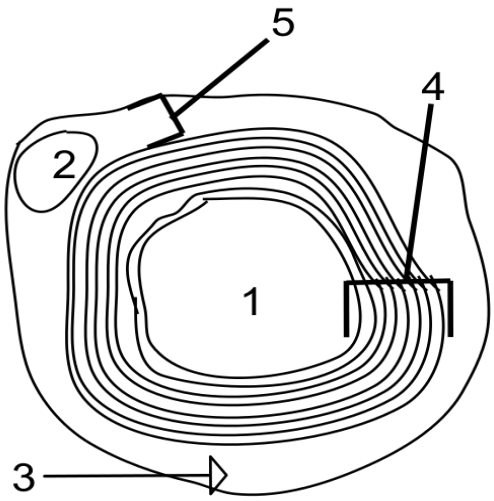

Fig 6 Cross section of a myelinated axon [3]
1. Axon,
2. Nucleus of Schwann Cell,
3. Schwann Cell,
4. Myelin Sheath,
5. Neurilemma

2.7 Blood-Brain Barrier

The blood-brain barrier (BBB) "is a highly selective semipermeable membrane barrier that separates the circulating blood from the brain and extracellular fluid in the central nervous system" [5]. Significantly, the BBB's main purpose is to limit the majority of substances, found in the blood, from slipping into the brain. BBB can also help sustain a steady environment in order for the nerve cells to function properly in the brain [1].

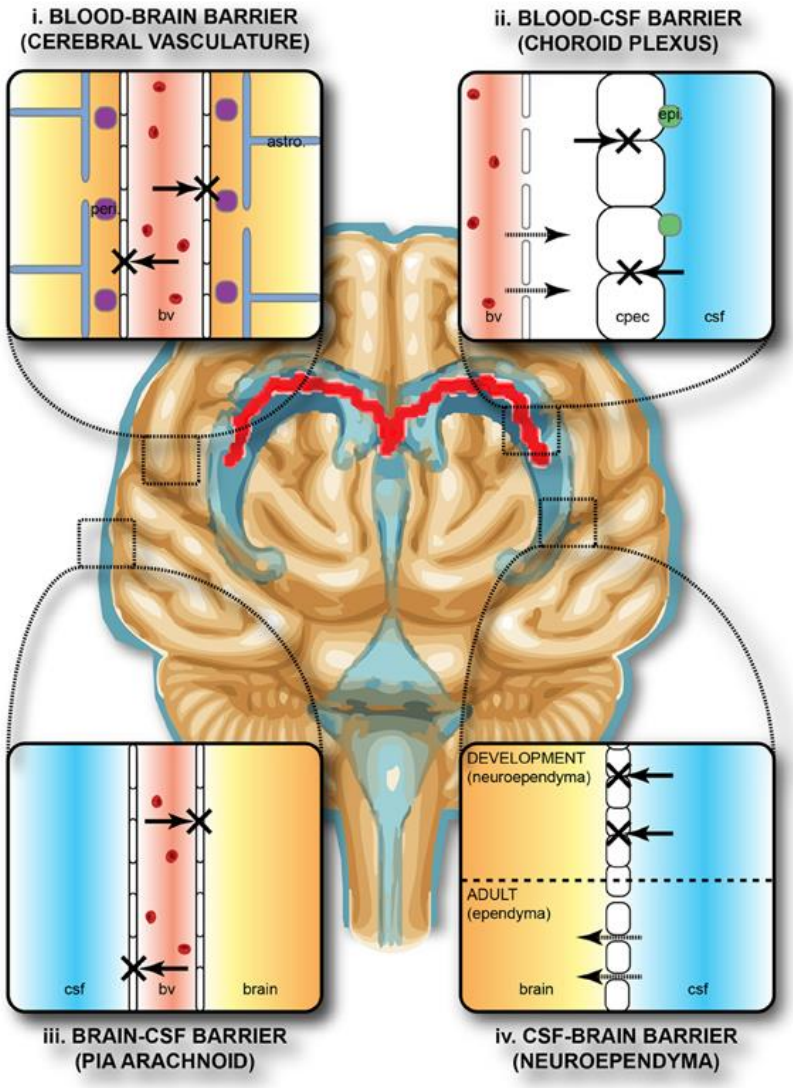

Fig 7 The Blood Brain Barrier, at different locations of the brain.[4[

In a more detailed analysis, "the BBB is made up of very small blood vessels that are lined with thin, flat endothelial cells" [1]. In contrast with other parts of the body the endothelial cells have narrow gaps between them in order to permit substances to travel in and out of the capillary. That said, it is through these narrow gaps that the blood can reach other cells and tissues. Nonetheless, the endothelial cells in the brain are tightly compressed together, so no substances can pass out from the bloodstream into the brain [1].

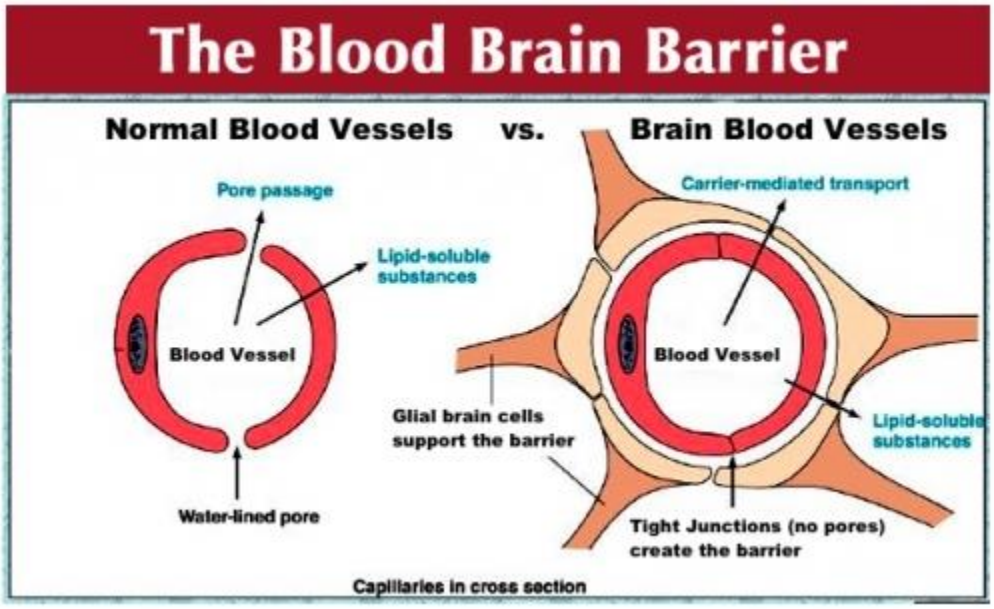

Fig 8 A cros section of a Normal Blood Vessels and the vessels at the Blood Brain Barrier.[5]

2.8 T Cell

T cell is a subtype of white blood cell, also known as lymphocyte, and it is crucially important for the immune system. More specifically, the T cell is the one responsible for adapting the body's immune system. Moreover, one of the main tasks of the T cells is to "search out and destroy the targeted invaders" [5].

Immature T cells drift to the thymus gland which is located in the neck area, where they eventually mature and transform into various types of T cells. Moreover, due to the effect of the hormone called thymosin and other factors these T cells are being activated in the immune system. Hence, normally during this maturational process the T-cells that are being potentially stimulated against the organism's own tissues are killed or modified. It is important to note that there are several different types of mature T cells. However, not all of the functions of those mature cells are known. To give an example, some T cells can "produce substances called cytokines such as the interleukins which further stimulate the immune response" [5]. All things considered, it is crucial to mention that the term T cell is also referred as T lymphocytes and the *T* stands for *thymus.* In comparison with the B cells in which the cells mature in the bone marrow, the T cell mature in the thymus.

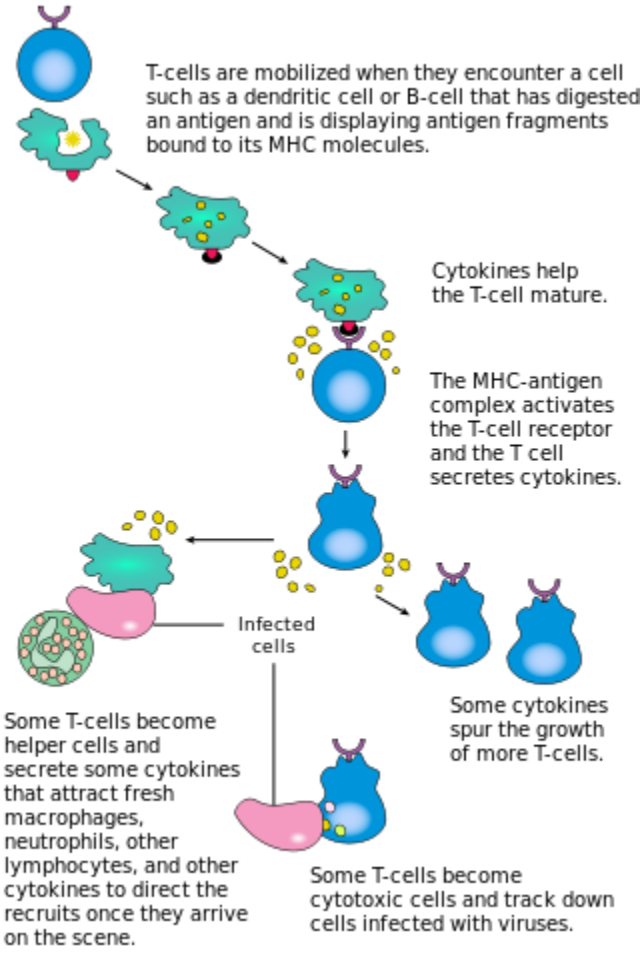

Fig 9 T Cell matuaring.

2.9 B Cell

B cell: B cells "are a type of white blood cell of the lymphocyte subtype" [7] that mature into plasma cells and memory cells. More specifically, B cells "produce antibodies (proteins) necessary to fight off infections while other B cells mature into memory B cells" [6].

All of the B cells that become plasma cells derive from a single B cell which produces the same antibody that is guided against the antigen that stimulated it to mature. Likewise, plasma cells function in the same way with memory B cells and thus, all of the plasma cells and memory cells learn the stimulus that prompt their formation. Hence, the B cells are important cells for the immune system. Last but not least, the B cells are in charge for the production of immunoglobulins and due to the fact that the B cells are not thymus-dependent, they have a narrower lifespan.

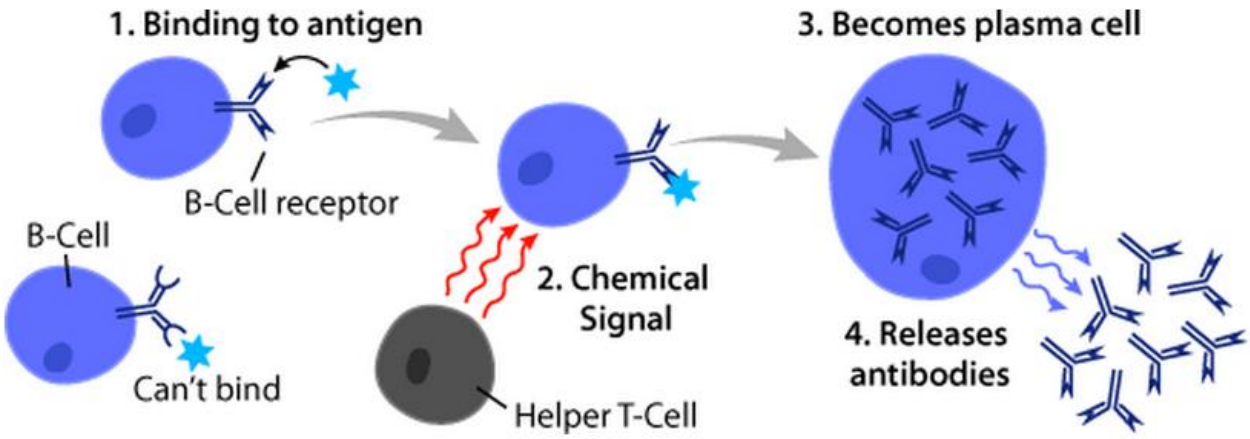

Fig 10 B Cells basic function.[7]

CHAPTER 3

Multiple Sclerosis

3.1 Multiple Sclerosis

Multiple sclerosis or as is often referred to as MS, is a chronic disease that the variety of individuals get diagnosed with. To be more precise, MS primarily affects the brain, spinal cord and the optic nerves of the patient's eyes and thus, it can cause extensive problems on the patient's muscle control, vision, balance and various other organs or function related with basic body functions. Therefore, in order to improve the treatments concerning MS, there is a great need to examine it thoroughly. With that in mind, "multiple sclerosis is a demyelinating disease in which the insulating covers of nerve cells in the brain and spinal cord are damaged" [9]. Having said that, the result damage of the brain and the spinal cord intervenes and disturbs the proper communication and function of the nervous system. Through this lack of communication of the nervous system a diverse mixture of symptoms and signs emerge indicating mental, physical and sometimes psychiatric issues.

"MS takes several forms, with new symptoms either occurring in isolated attacks (relapsing orms) or building up over time (progressive forms)" [11]. In other words, the disease's effects vary on different occasions of patients, from very mild symptoms that do not require any treatment to patients that find it really difficult to move around or do basic human body functions. Hence, most of the time MS patients require extensive help and monitoring. One may argue that, due to the fact that the symptoms of MS can vary depending on each individual, each patient with MS lives with a different illness. Thus, the complexity of this particular illness relies on the fact that the pattern is unique for everyone. However, nerve damage is always a part of the disease.

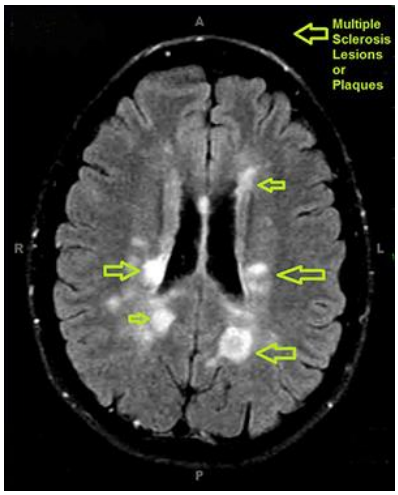

Fig 11 MRI of a brain with MS lesions.[8]

3.2 Symptoms

Due to the fact that the nerves do not work properly the patient may experience symptoms such as:

· Trouble walking
· Feeling tired
· Muscle weakness
· Muscle spasms
· Blurred vision
· Double vision
· Numbness and tingling
· Sexual problems
· Poor bladder
· Bowel control
· Pain

3.3 Types of Multiple Sclerosis

Importantly, the field of medicine managed to identify some primary types of MS. Moreover, the importance of these categories relies on the fact that they can contribute to a better understanding of how severe this disease can be and predict how well the treatment will work.

3.3.1 Relapsing-Remitting Multiple Sclerosis (RRMS)

One of the types of MS is Relapsing-Remitting Multiple Sclerosis. That said, it is important to note that the majority of people who are diagnosed with MS they often show symptoms of the disease in the range of the ages between twenty and forty. More specifically, usually the symptoms can be described as sporadic attacks, also known as relapses. With that in mind, most of the time these sporadic attacks are followed by a recovery period which is also referred to as

remissions. In other words, in this type of MS, when some of the sporadic attacks occur, they are being succeeded by weeks, months, or years of remissions." The nerves that are affected, how severe attacks are, the degree of recovery, and the time between relapses all vary widely from person to person and eventually, most people with relapsing-remitting MS will move on to a secondary progressive phase" [12].

3.3.2 Primary Progressive Multiple Sclerosis (PPMS)

PPMS depicts when the disease aggravates on a gradual level through time. "There are no well-defined attacks of symptoms, and there is little or no recovery" [12]. Significantly, the treatments of this kind of MS, PPMS, tend to not have the required results. Furthermore, this particular type of MS is much rarer since, "about 10% of people with MS have this type" [12].

The main differences between PPMS and the other kinds of MS include:

- "People with primary progressive MS are usually older when they're diagnosed - an average age of 40".
- "Roughly equal numbers of men and women get it. In other types of the disease, women outnumber men 3 to 1".
- "It usually leads to disability earlier than the most common type, relapsing-remitting MS" [12].

3.3.3 Secondary Progressive Multiple Sclerosis (SPMS)

Patients are frequently diagnosed with SPMS when they move from the RRMS phase and it often appears around ten to twenty years after RRMS is diagnosed. In fact, through the SPMS phase the symptoms tend to increase in a steady pace. However, in some instances the relapses and remissions tend to decrease. Thus, even though it's somewhat unclear why the disease makes this shift, some scientists claim to have understood some things about this particular process:

- "The older a person is when he's/she's first diagnosed, the shorter the time he/she has before the disease becomes secondary progressive".
- "People who don't fully recover from relapses generally move to secondary progressive MS sooner than those who do".
- "The process of ongoing nerve damage changes. After the transformation, there's less inflammation and more of a slow decline in how well the nerves work" [12].

SPMS is significantly harder to treat and patients are more likely to struggle with everyday tasks as they become harder to perform. More specifically, the symptoms in the SPMS phase tend to aggravate however, the degree of the symptom's intensity differs from one patient to another. Hence, even though the treatments work somewhat sufficiently, most of the patients will probably experience difficulties to utilize their body in the same way they used to.

3.3.4 Progressive Relapsing Multiple Sclerosis (PRMS)

Through the PRMS phase the relapses or attacks happen more frequently. However, the symptoms of MS do not cease to continue and in fact, in some cases the symptoms get worse. Furthermore, **"**this type is the rarest form of MS, it is so rare that doctors don't know much about it. Probably around 5% of people with multiple sclerosis have this form. In many ways, it seems similar to primary progressive MS" [12].

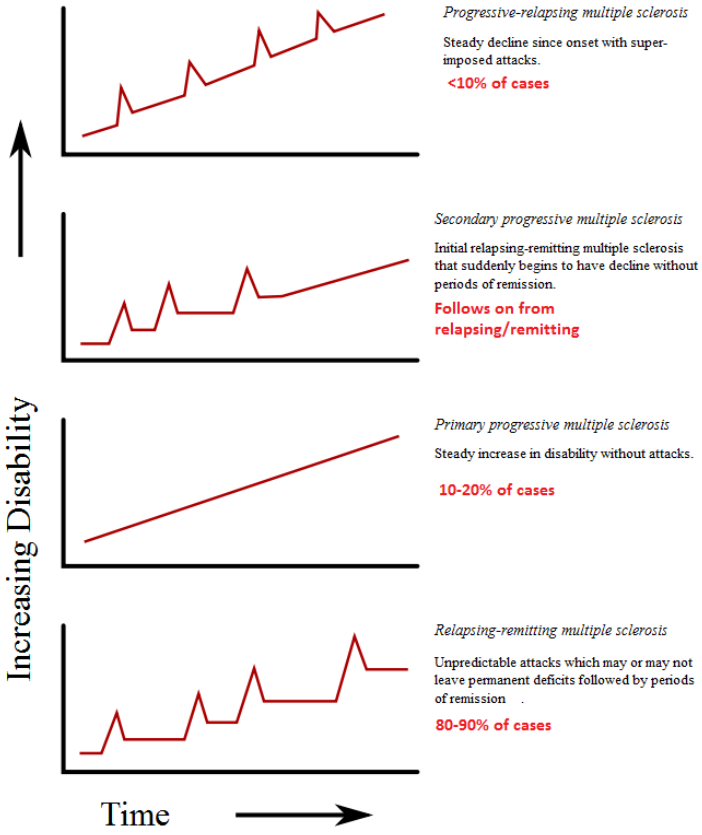

Fig 12 Chart of the types of MS disability according to time[9]

3.4 Pathophysiology

All things considered, MS occurs when the immune system attacks the myelin. To be more precise, the myelin protects and surrounds the neurons' axons since, the myelin allows the quick propagation of electrical impulses. With that in mind, myelin is produced by oligodendrocytes, which are a group of cells that support neurons. Furthermore, in MS, demyelination happens when the immune system inappropriately attacks and destroys the myelin, which makes communication between neurons break down. This ultimately leads to all sorts of sensory, motor, and cognitive problems resulting to the above mentioned symptoms.

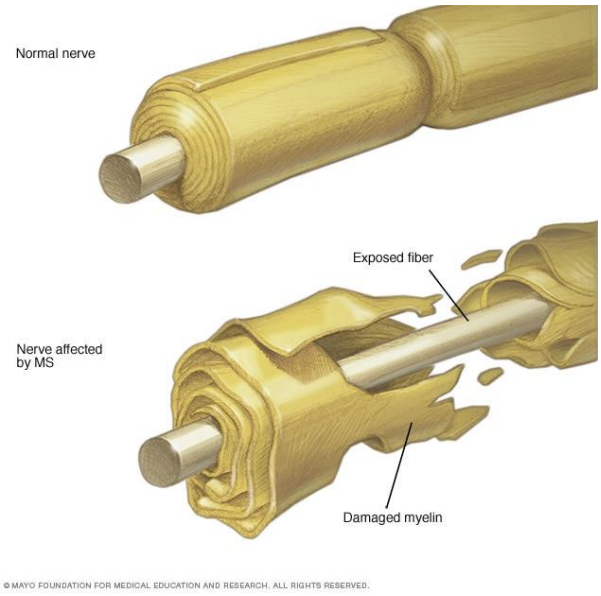

Fig 13 Healthy myelin vs damaged from MS.[10]

The neurons in the brain are protected by the blood brain barrier (BBB), which only lets certain molecules and cells through BBB and from the blood. Moreover, for immune cells like T and B cells this access means having the right surface molecule to get through the blood brain barrier. However, in the case of multiple sclerosis once a T cell makes its way in it can get activated by the myelin. Then, once the T-cell gets activated, it changes the blood brain barrier cells to express more receptors and thus, this allows the immune cells to bind and get in more easily.

Multiple sclerosis is a type IV hypersensitivity reaction, or cell-mediated hypersensitivity which means that those myelin specific T-cells release cytokines like IL-1, IL-6, TNF-alpha, and interferon-gamma. All these cytokines dilate the blood vessels which allow more immune cells to get in, as well as directly cause damage to the oligodendrocytes. Moreover, the cytokines also attract B-cells and macrophages as part of the inflammatory reaction. Those B-cells begin to make antibodies that mark the myelin sheath proteins and then, the macrophages use those antibody markers to absorb and destroy the oligodendrocytes.

Importantly, without oligodendrocytes there is no myelin to cover the neurons and this leaves behind areas of scar tissue, also called plaques or sclera. In multiple sclerosis, these immune attacks typically happen in sessions where an autoimmune attacks on the oligodendrocytes. In the event in which this happens the regulatory T cells will come in to inhibit or calm down the other immune cells, leading to a reduction in the inflammation. Early on in multiple sclerosis, the oligodendrocytes will heal and extend out new myelin to cover the neurons, which is a process called remyelination. Although over time as the oligodendrocytes die off the remyelination stops and the damage becomes irreversible with the loss of axons.

When the myelin is lost due to the T cell attack, it leaves a scar tissue at multiple areas. Therefore, when this scar tissue hardens is called sclerosis. Furthermore, the ability for the nerves to transmit messages, is due to the fact that the myelin sheath has been damaged. In other

words, these destroyed areas are also referred to as plaques. Thus, these plaques can be recognized through a magnetic resonance imaging (MRI). more specifically, the MRI is a technique that aids the doctors to observe and review thoroughly the progress of MS and hence, act accordingly.

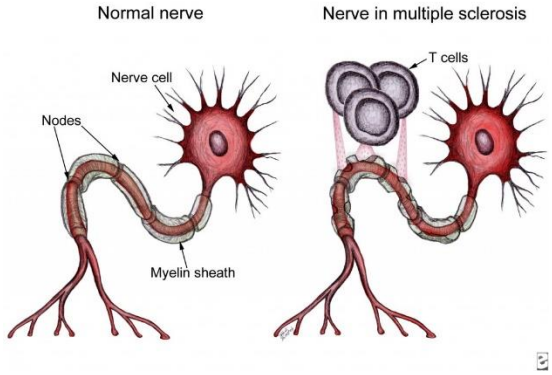

Fig 14 Healthy Nerve vs Nerve affected by MS.[11]

Other important symptoms of MS do not only concern physical problems but also, mental symptoms as well. In other words, it is quite often that the patient may encounter mental symptoms including mood symptoms and cognitive impairment. Moreover, people diagnosed with MS appear to have a higher number of psychiatric symptoms such as depression and anxiety due to functional status and way of life. In fact, the lives of MS patients can be affected by psychiatric disorders in a variety of ways.

The most notorious symptom and outcome of MS is depression. Significantly, the patients with depression often appear to have cognitive difficulties, including memory complaints. One may argue that, the patients experience high levels of stress or tough situations might have tendencies of depression. Therefore, it is quite apparent how the long-term physical symptoms of MS can result to changes in a patient's mood. Nonetheless, depression may be the result of MS on itself. That is the case since, MS distracts the protective coating surrounding the axon of the nerves which aids the brain to send signals that affect mood. Last but not least, "depression is also a side effect of some the drugs that are prescribed to treat MS, such as steroids and interferon." [13]

It is still somewhat of a mystery in the field of medicine what are the causes of MS however, it is considered by many to be linked to both genetic and environmental factors. Nonetheless, there are many things that seem to make the disease more likely. Moreover, some individuals who carry specific genes tend to have a higher risk on getting MS. The individuals with the higher chances of getting MS are primarily women and those having genes that contain a specific type of immune molecule called HLA-DR2. To be more precise, the immune molecule called HLA-DR2 is used to identify and bind to foreign molecules. Additionally, environmental risk factors might include infections as well as the lack of vitamin D. Thus, both the genetic and environmental factors may stimulate the body to not kill immune cells target myelin. Finally, another factor that may raise the risks of getting MS is smoking.

In some cases, some individuals might get MS as a result of getting a viral infection. That is the case since, when a viral infection occurs in the body the immune system fails to work properly. In addition, infections may generate or cause relapses. Even though, a variety of scientific studies have been made in order to find a link between MS and viruses, the answer still remains unclear.

Some scientific studies indicate that vitamin D, which is acquired through sun exposure, may lead to the strengthening and protection of the immune system. Furthermore, the individuals have lower chances of getting the disease who move to sunnier regions like the equator where there's a lot more sunlight compared to places with little or minimal sunlight like the northern and southern poles.

In regards with the treatment of MS, there is not a main cure. However, there are some specific medications which are effective for the relapsing-remitting type. That is the case since, these particular medications like corticosteroids, cyclophosphamide which is a cell cycle inhibitor, and intravenous immunoglobulin tend to help blunt the autoimmune process. Not only that, plasmapheresis can have similar effects since plasmapheresis is when the plasma is filtered to remove disease-causing autoantibodies.

The chronic treatment for MS contains immunosuppressants like recombinant beta-IFN which tend to reduce the level of inflammatory cytokines in the brain. Moreover, immunosuppressants are considered to raise the functionality of T regulatory cells. That said, some other immunosuppressants tend in actuality to stop T cells from passing into the brain. That is the case since, these immunosuppressants interfere with the T cell's surface molecules since, in the case of MS they used to gain passage through the blood brain barrier.

Unfortunately, though, a few treatment options are available for the development of MS. Instead, treatments are often provided to limit specific symptoms, ranging from depression to bladder dysfunction. Additionally, it is known that physical therapy and cognitive rehabilitation therapy may result to be particularly helpful with sensory, motor, and cognitive symptoms. All things considered, in regards with the treatment of MS there is an increasing interest in the role of vitamin D as an effective treatment.

CHAPTER 4

Magnetic Resonance Imaging

4.1 Magnetic Resonance Imaging

The Magnetic Resonance Imaging (MRI) was initially called 'NMRI' (nuclear magnetic resonance imaging). That said, MRI is common test or procedure in medical technology, where it is used daily for medical conditions diagnosis [18]. To be more precise, an MRI scanner utilizes radio waves and magnetism in order to generate a 3D image of the human or animal anatomy. Therefore, it is used for looking inside the body without using surgery, harmful dyes or x-rays, making it painless and harmless to the patient.

MRI "uses a very powerful magnetic field, radio frequency pulses and a computer to produce detailed pictures of organs, soft tissues, bone and virtually all other internal body structures of the person that is taking the test" [19]. Therefore, it is for the most part an unconditional fact that the detailed MR images are important in the process of determining the presence of a certain disease.

MRI of the body is used to evaluate:

- organs of the chest and abdomen such as the heart, liver, etc.
- pelvic organs such as the bladder and the reproductive organs.
- blood vessels.
- lymph nodes [19].

MRI is also being used to diagnose, examine or monitor treatments for a variety of conditions such as:

- tumors of the chest, abdomen or pelvis.
- diseases of the liver, such as cirrhosis, and abnormalities of the bile ducts and pancreas.

- inflammatory bowel disease such as Crohn's disease and ulcerative colitis.
- heart problems, such as congenital heart disease.
- malformations of the blood vessels and inflammation of the vessels.
- a fetus in the womb of a pregnant woman [19].

Fig 15. A modern MRI scanner. [12]

The base of an MRI is originated from a phenomenon called nuclear magnetic resonance (NMR). With that in mind, through this phenomenon specific magnetic fields and radio waves tend to cause atoms to emit tiny radio signals. Moreover, NMR spectroscopy was predominantly utilized as means to examine and study the composition of chemical compounds, was discovered around the 1930s by Felix Bloch, who was working at Stanford University at that time, and Edward Purcell, from Harvard University.

4.2 History of Magnetic Resonance Imaging

A medical doctor and a researcher by the name of Raymond Damadian, discovered the foundation of the usability of MRI as a medical diagnosis tool, around the 1970's [18]. More specifically, Raymond Damadian observed that "different kinds of animal tissue emit response signals that vary in length, and that cancerous tissue emits response signals that last much longer than non-cancerous tissue" [18].

In addition, two physicists called Peter Mansfield and Paul Lauterbur were able to develop MRI-related techniques in the late 1970's, earning themselves a Nobel Prize in Physiology or Medicine in 2003 [20].

From there on, the utilization of MRI was developed rapidly and the first MRI equipment was available at the beginning of the 1980s. Finally, “in 2002, approximately 22 000 MRI sensors were in use worldwide, and more than 60 million MRI examinations were performed” [18].

4.3 Magnetic Resonance Imaging Function

As mentioned earlier, MRI bases its function on powerful magnetic field as well as radio frequency pulses and a computer to produce pictures of organs, soft tissues, bone and any other internals of the body. More specifically, MRI utilizes the radio signals produced by protons inside the nuclei of hydrogen atoms that are found in water and fat molecules in the body [18]. Generally speaking, during the MRI examination brief strong magnetic fields apply to the body and thus, changing the alignment of the poles of the hydrogen protons in the body’s tissues. Hence, causing the protons to emit radio signals that can be detected by the MRI machine and then, are being used for the 3D construction of the image.

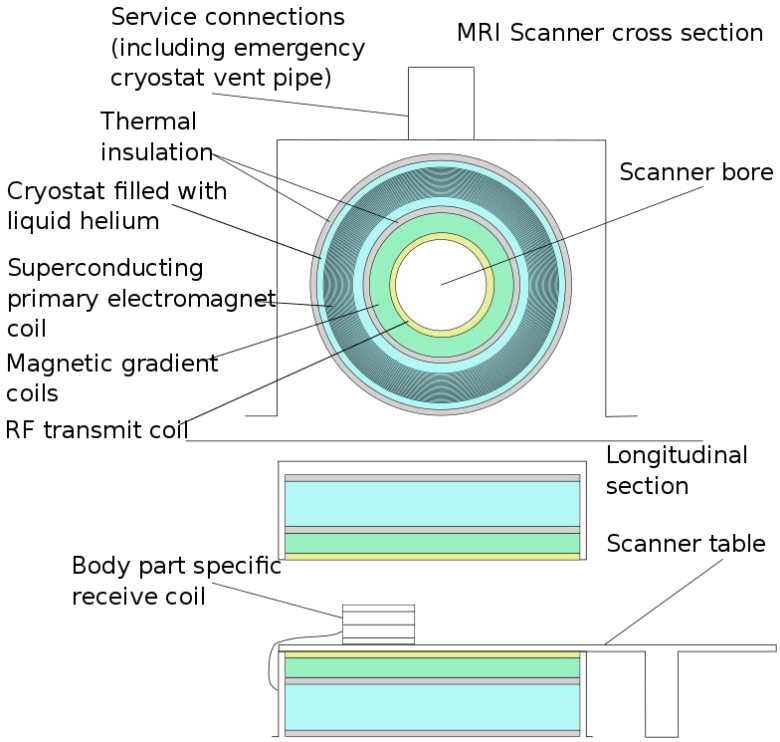

Fig 16. Detailed cross section of an MRI scanner.[13]

The human body is constituted up to 60% of water in which the hydrogen atoms primarily are there and hence, this explains why the MRI use has become so widely applicable in the field of medicine. In fact, it is crucial to mention that there is a difference in the water concentration at each organ or tissues. That is the case since, there is a variety of diseases that pathologically change the water content and therefore, there is a unique reflection in the MRI scanner.

At rest the magnetic poles of hydrogen protons are randomly oriented, so when an MRI scanner applies the strong magnetic field to them, the hydrogen protons will reorient themselves with the magnetic field. Additionally, a coil is utilized in order to transmit and receive radio frequency pulses. That is the case since, the coil is targeting the area of the body that is to be imaged. Importantly, this transmition and reception of radio frequency pulses knocks the protons out of alignment. The act of shutting down the pulse allows the protons to return to their previous alignment with the MRI machine's primary magnetic field. "As the protons return to their previous orientation, they emit their own radio signals that can be detected by the receiver coil" [21].

Through the help of advanced computer processing, it is fundamentally possible to build a three-dimensional image from 3D volumes of tissue. The MRI machine intercepts those signals emitted by the 3D volumes and then, they are being transformed into 2D matrices in grayscale. More specifically, these grayscale images derive from electromagnetic energy levels that are "assigned greyscale values and plotted on a 2D matrix" [21]. In fact, through this procedure is actually possible to build an image of a cross-sectional coronal, axial or sagittal slice of the body. Furthermore, electromagnetic energy is translated in to grayscale by depicting high levels of electromagnetic energy in white and the absence of electromagnetic energy with black. Normally, the greater the hydrogen content, the brighter the image. However, an MRI machines can be programmed in order to register only a certain direction of proton movement. Therefore, that is precisely the reason why teeth are not visible in MRI since, teeth do not contain hydrogen atoms and thus, they cannot be picked up by the sensor.

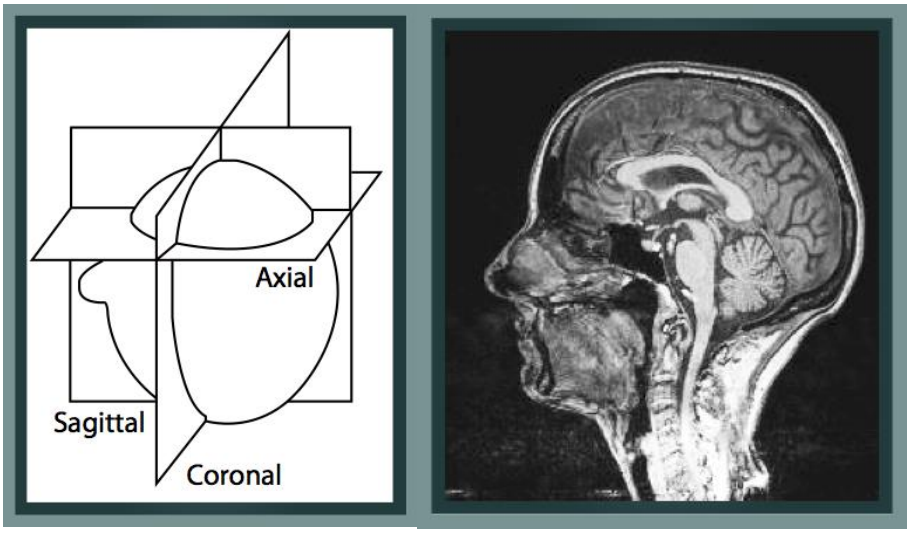

Fig 17. Coronal, sagittal and axial planes
Fig 18. side view cross-section image of the head.

In the recent years, the utilization of MRI in the field of medicine has become more wide. With that in mind, some of the MRI uses include: Neuroimaging, Cardiovascular, Musculoskeletal, Angiography and various more. Hence, all these have their own techniques and different types of specialized MRIs are being used for each diagnosis.

There are various types of MRI but the most notorious types are:

- T1 weighted MRI

- T2 weighted MRI
- FLAIR sequence MRI

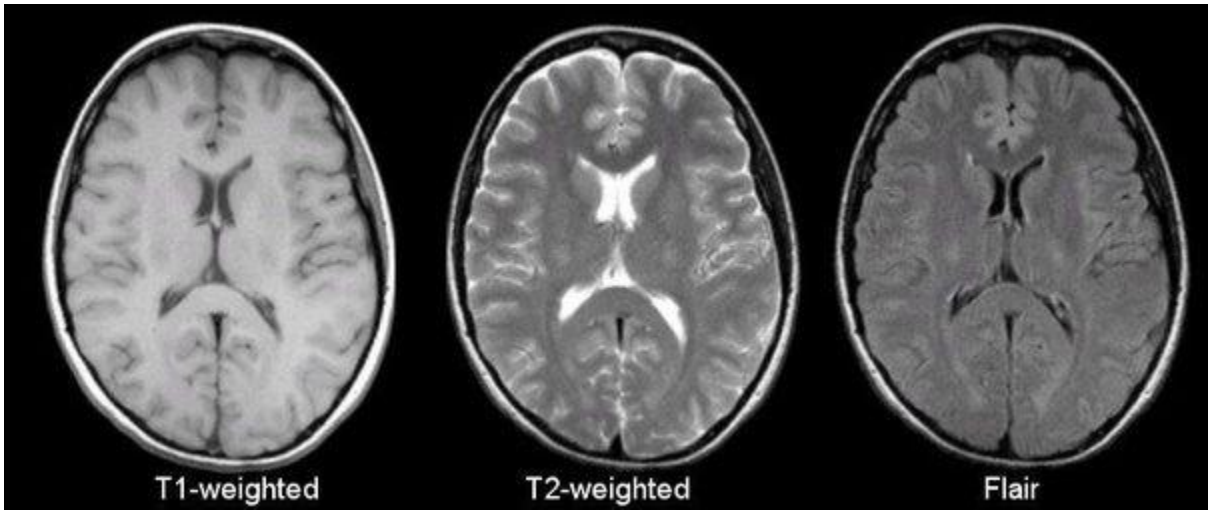

Fig 19. The same sample but deferent MR Images.[14]

The **echo time (TE)** depicts the time in milliseconds between the applied radiofrequency excitation pulse and the peak of the signal induced in the coil. Significantly, the TE controls the amount of T2 relaxation.

The **repetition time (TR)** represents the time in milliseconds from the applied radiofrequency excitation pulse to the application of the next pulse. More specifically, TR demonstrates precisely the amount of longitudinal magnetization that recovers between each pulse.

T1 is when the MRI machine is programmed by experts in order to only look at the longitudinal movement of protons. T1 images are usually used to look at normal anatomical details and "T1 weighting tends to have short TE and TR times" [22]. That said, T1 is the finest for looking at brain structure since, fat appears very bright and bone marrow contains a lot of fat.

T2 "is the transverse movement of protons and is usually used to look at pathology because most tissues involved in disease tend to have a higher water content than normal" [22]. In fact, T2 weighting requires long TE and TR times. Additionally, T2 is best for tissue edema since, the water and fluids are much brighter.

The main difference between T1 and T2 is that the "Cerebrospinal fluid (CSF) appears black in T1 while white in T2" [22]. Another key to remember is that in T1 the white matter appears a light grey where in T2 the white matter appears a dark grey.

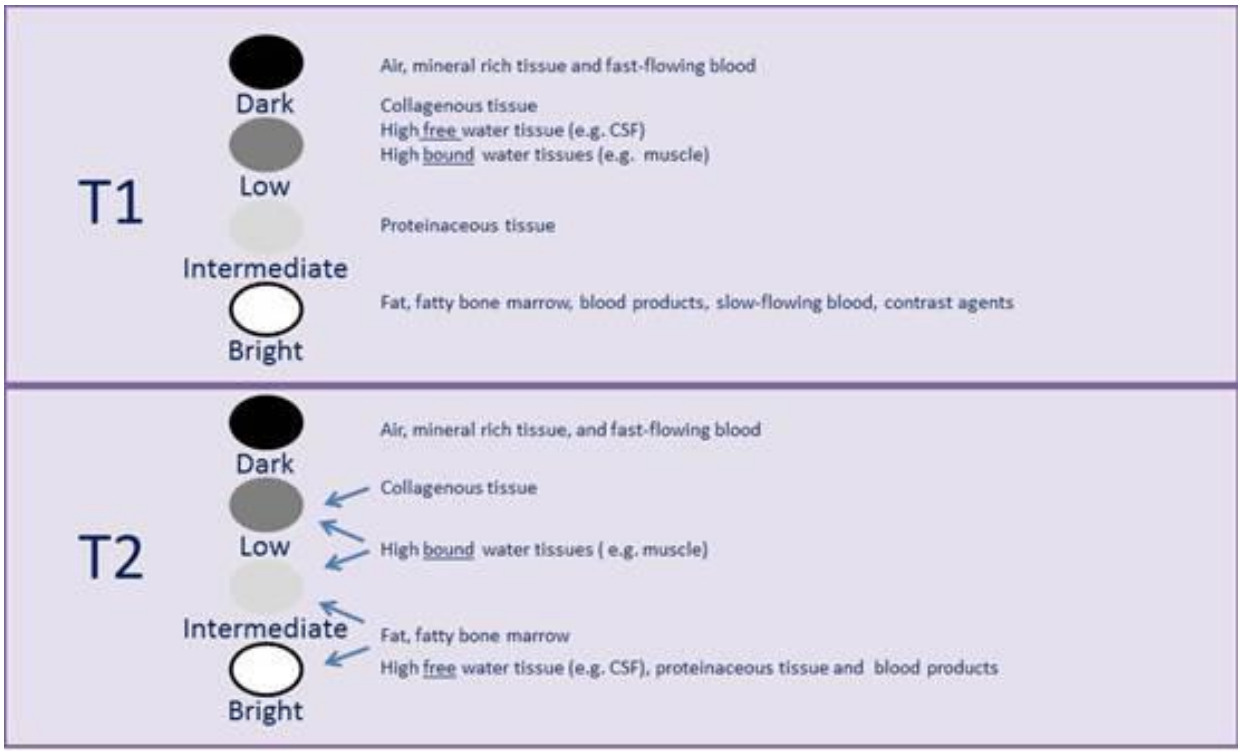

Fig 20. Major differences between T1 & T2 MR Images.[14]

FLAIR stands for Fluid Attenuation Inversion Recovery, and aims to suppress liquid signals. FLAIR can be used in brain imaging in order to suppress cerebrospinal fluid (CSF) which effects on the image. This is the case since, the absence of CSF exposes the periventricular hyperintense lesions.

MRI is the primary way to detect, monitor and evaluate Multiple sclerosis and more generally every **central nervous system** or CNS disease.

The MRI exam poses no existing threat to the patient or animal that takes the examination. Thus, if proper safety measures and guidelines are taken in to account and followed, MRI is harmless. These safety guidelines, are a collection of rules orbiting on one basic fact, that the MRI as it's name refers is magnetic. With this in mind, on an MRI exam all metal objects must be removed from the room in order to avoid potential injuries since, those objects will be flying fast towards the scanner when the MRI is activated.

It is important to mention that, some patients must first check with their doctors before the examination if they have any medical devises. Of course some of them are designed to be MRI compatible and pose no threat like:

- Artificial joints
- Staples
- Many cardiac valve replacements

- Disconnected medication pumps
- Vena cava filters
- Brain shunt tubes for hydrocephalus [14]

On the other hand, there are many medical devices that are out of the question because they will most probably end up in disaster, due to including metal in their design. Moreover, patients with some kind of discomfort or disease have to avoid MRI examination. Some of these conditions include:

- Heart pacemaker
- Cerebral aneurysm clip (metal clip on a blood vessel in the brain)
- Pregnancy
- Implanted insulin pump
- Metal in the eye or eye socket
- Cochlear (ear) implant for hearing impairment
- Implanted spine stabilization rods (except newer titanium rods and plates)
- Severe lung disease
- Heartburn
- Obesity (weighing more than 300 pounds may limit which machine can be used)
- Not able to lie on your back for 30 to 60 minutes
- Claustrophobia (which can be handled with sedation) [14]

CHAPTER 5

Workflows

5.1 Introduction

Workflows in LONI PIPELINE are complete structured data flows consisted from data processing in between input of these data and output of the processed result. They can vary in size, complexity and most importantly field of research.

With the modules and some of the already existed workflows provided with the LONI PIPELINE, a user can study existing workflows and learn from those. They can also build some out of the box workflows for a variety of subjects regarding neuroimaging, genomics, bioinformatics, etc.

5.2 Basic Workflows

As mentioned earlier LONI PIPELINE comes with some standard workflows with its installation, as well as some training workflows to help beginners to get to know better the platform. There are a sufficient number of workflows for new users to explore, as well as variety of those workflows for users who are looking for a workflow suiting their field of research. With that said, there are workflows that come with annotations to help even more the users to understand what they are seeing in each step of the workflow.

5.2.1 AIR-BrainSuite Heterogeneous Workflow

One of those workflows that was easy to understand and at the same time very important is the **AIR-BrainSuite Heterogeneous Workflow** located in the Workflow/Training subsection of the cranium.loni.usc.edu server library. According to this workflow's description "will showcase the potential for heterogeneity of image analysis tools within a Pipeline workflow. Also, it will present an often useful approach to putting together a workflow, in that we will take parts of already existing workflows and combine them in a meaningful way to perform a new type of analysis."

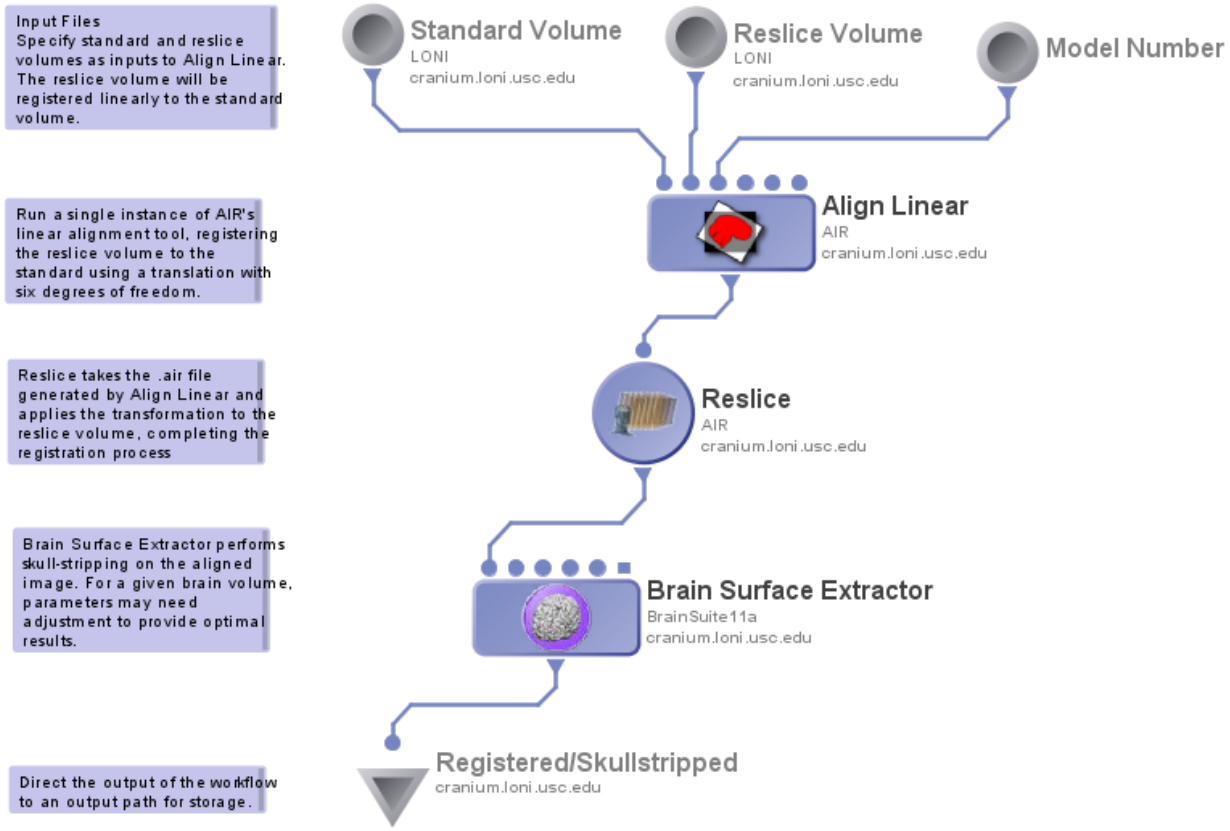

Fig 21. AIR-BrainSuite Heterogeneous Workflow

The AIR-BrainSuite Heterogeneous Workflow as any other workflow begins with its input sources. Those input sources are two different but almost identical MRI scans which in this case are in .img format that need to be aligned together.

In addition to those two 3D images, there is a third input source that provides the workflow with an integer number which translates to the amount of degrees of freedom. Degrees of freedom or DoF are the axis combined with rotation that a rigid body is free to move in three-dimensional space.

Moving away from the input sources, we find the heart of the workflow, the **Align Linear module** which is the first functional component of the workflow. This module is a general linear intramodality registration tool for 2D or 3D with a variety of options like:

- 3-D models:
  - 6. rigid body 6 parameter model
  - 7. global rescale 7 parameter model
  - 9. traditional 9 parameter model (must be on AC-PC line)
  - 12. affine 12 parameter model
  - 15. perspective 15 parameter model
- 2-D models (constrained to in-plane, no interpolation):
  - 23. 2-D rigid body 3 parameter model
  - 24. 2-D global rescale 4 parameter model
  - 25. 2-D affine/fixed determinant 5 parameter model
  - 26. 2-D affine 6 parameter model
  - 28. 2-D perspective 8 parameter model [23].

More specifically, Align Linear module in this specific workflow (Rigid Body 3D models) takes six inputs, the three input sources mentioned above and in addition to those, it takes three more inputs that are filled from the module itself. Those inputs are: threshold standard, threshold reslice and blur reslice.

Align Linear module uses a variety of strategies such as cost functions, different minimization methods, and various sampling, smoothing, and editing to generate and deliver the final result in a .air format that is passed on to the next module[23].

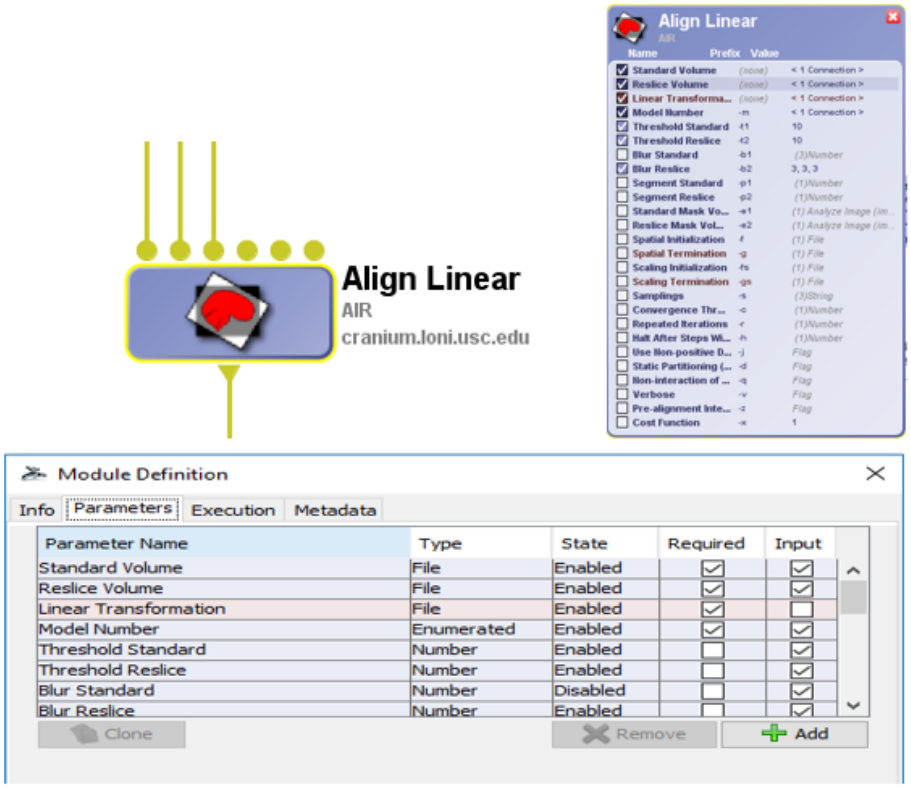

Figure 1. Align Linear as viewed from working surface and its parameters. Note that the three of the six inputs are already filled.

Moving downstream we find **Reslice module** where the .air file from Align Linear module ends. Here the .air file is analyzed and a linear transformation is applied to a Volume to bring it from the compatible source space to the target space specified within the transform [17]. Also according to its information the correct image file will be loaded. With that file and the .air file a new realigned file is created in an AIR package consisting of .hdr and .img files [25][26].

And with those two .hdr and .img files that Reslice module created, the **Brain Surface Extractor module** with five more inputs, removes non-brain tissue from the MRI [17]. A combination of anisotropic diffusion filtering, edge detection, and mathematical morphologies are used for this to work [17]. The final output is again passed in .hdr and .img format to the data sink and thus finalizing the workflow.

5.2.2 Skullstriping Workflow

A workflow as easy to understand as the previously mentioned is **Skullstriping Workflow** also located in the Workflow/Training subsection of the cranium.loni.usc.edu server library. This

workflow combines components from several packages in contrast to the previous one that was constructed from components only from AIR package.

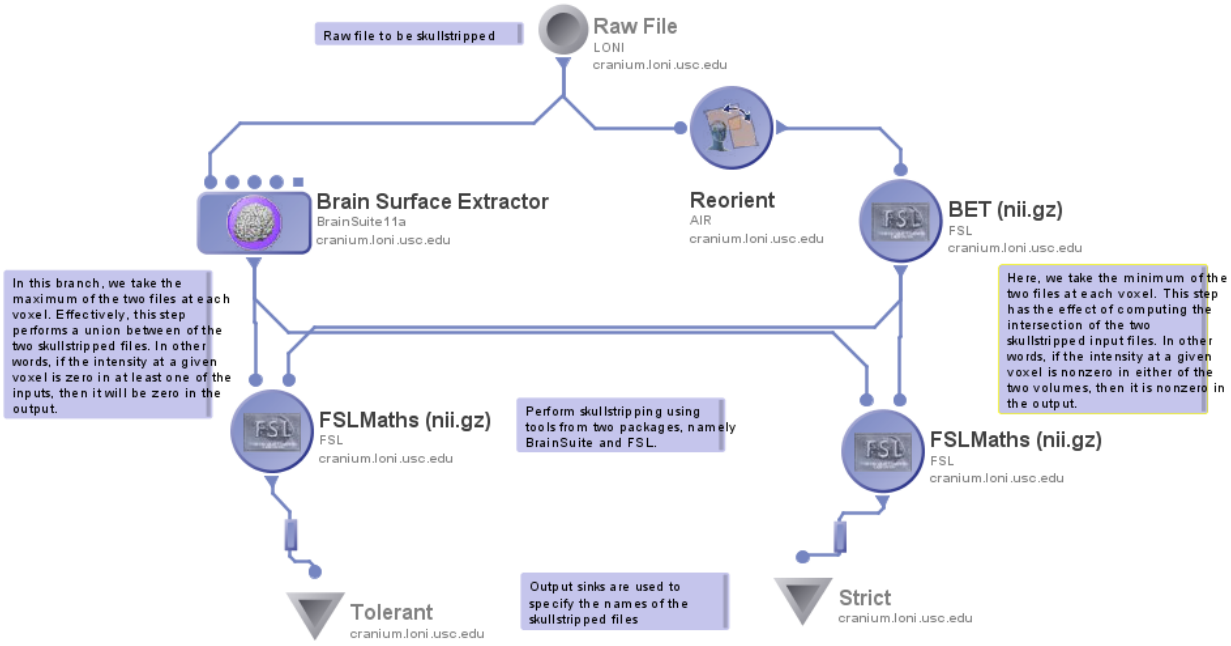

Fig 22 Skullstriping Workflow

As the name suggests, this Skullstriping Workflow removes the skull from the MRI. This is done by using two paths, each one using a different process and in the end comparing them with each other to determine which one is better for each instance.

More specifically Skullstriping Workflow takes off with its input source. Here an MRI is inserted by default in .img format and the workflow passes this image as .img and .hdr to both Brain Surface Extractor (BSE) and to a Reorient module that is needed for Brain Extraction Tool (BET). Both BSE and BET execute unique skullstripping algorithms and their output is channeled

In to two FSLMaths modules from FSL (Functional Structural Library) Package. The difference from one FSLMaths module to the other is that in the first one generates a tightly skullstripped result and the other more tolerant one. This is achieved by intersecting the whole-brain masks generated from the previous modules in the tight one and uniting the masks for the tolerant one.

Both of the FSLMaths modules that each one represents the tightly skullstripped and tolerant skullstripped end up in two data sinks named after each algorithm. There the user can view the results of each algorithm and choose the one that suits best for each instance or compare the one with the other.

5.3 Constructed Workflows

Based on the information gained by the already existing workflows and by browsing the modules in the libraries of LONI Pipeline, a workflow was constructed with the primary goal of MRI registration. This constructed workflow is based on **AIR-BrainSuite Heterogeneous workflow** due its primary function on image registration.

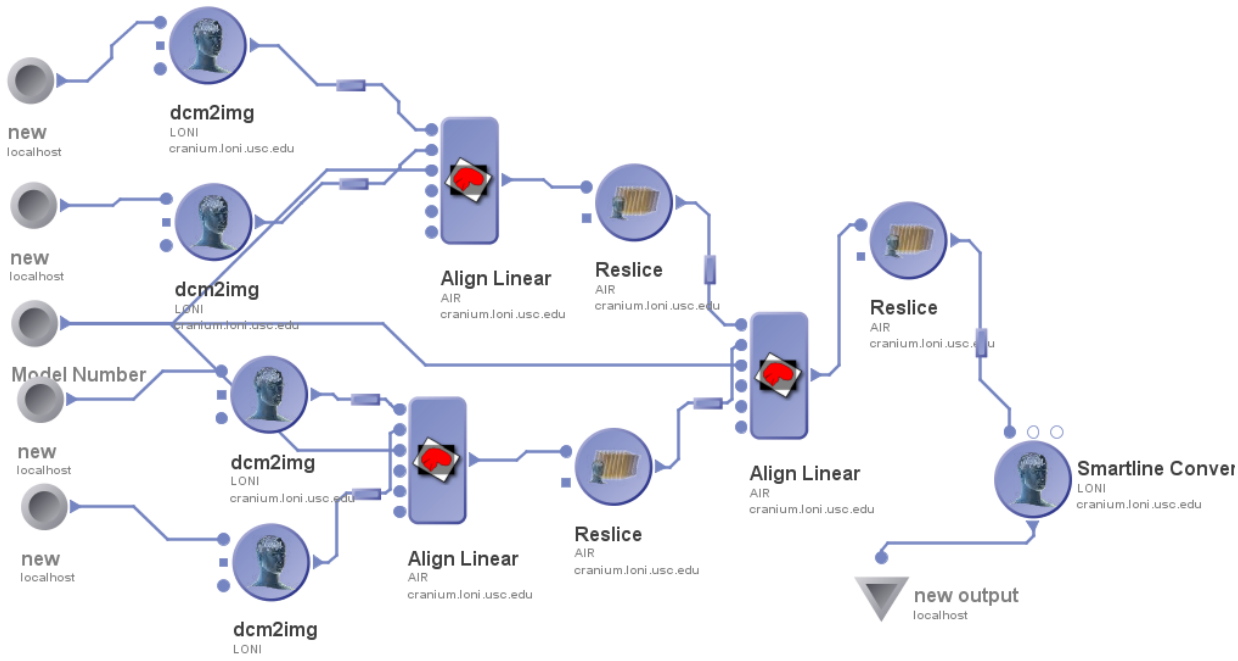

Fig 23 Constructed Workflow

This workflow as any other workflow begins with its input sources which in this particular one are five, the four instances of identical in format MRI scans and the input containing the Degrees of freedom or DoF.

Moving away from the input sources and where there should be **Align Linear module,** there is an extra module called **dcm2img** before **Align Linear module**. This is because in this particular workflow the data we are using are **dicom** format and the workflow is set up to accept .img data and a conversion is needed.

After the conversion there is the **Align Linear module** which functions the same as **AIR-BrainSuite Heterogeneous workflow** and so we move to **Reslice module** where the .air file from Align Linear module ends.

By the end of the **Reslice module** where we would expect a data sink instead we find again **Align Linear module** that takes this output as input as also the output of the another **Align Linear module** where other two MRI were registered.

This is the final registration in this workflow. The output of this **Align Linear module** goes thru a **Smartline Converter** and then ends un in a data sink.

In other words, four MRIs are divided in to two groups, where the first two are registered together into one. At the same time the other two registered together into other one and those two are registered together in the end.

CHAPTER 6

Conclusions and Future Work

6.1 Conclusions

LONI Pipeline is a diverse tool, aimed to help researchers, scholars, doctors, MRI specialists and all kinds of people focused or involved in the medical sector. But as diverse the tool aims to be, jack of all trades can be master of some.

The tool as helpful the GUI is in helping and welcoming a newcomer it is lacking some is some areas. As it is easy on first glance to navigate and find what you are looking in firsts tutorials and basic workflow, it is getting harder in each iteration that the user is looking for something more precise for his work.

As for the work intended to be produced by the analyzing and building of some workflows was very frustrating and at some point none existing due to the tools inconsistent provider of data translations to fit its modules that are some build for specific data types on input and output.

In addition to the previously mentioned issues, LONI Pipeline offers on download a tool called LONI viewer that as the name applies it views the outcome of the workflow as a whole 3D image. The issue with this is that if it is able to launch where the majority of times it does nothing it views a blurred image that little to none conclusion may have extracted from the workflow in review.

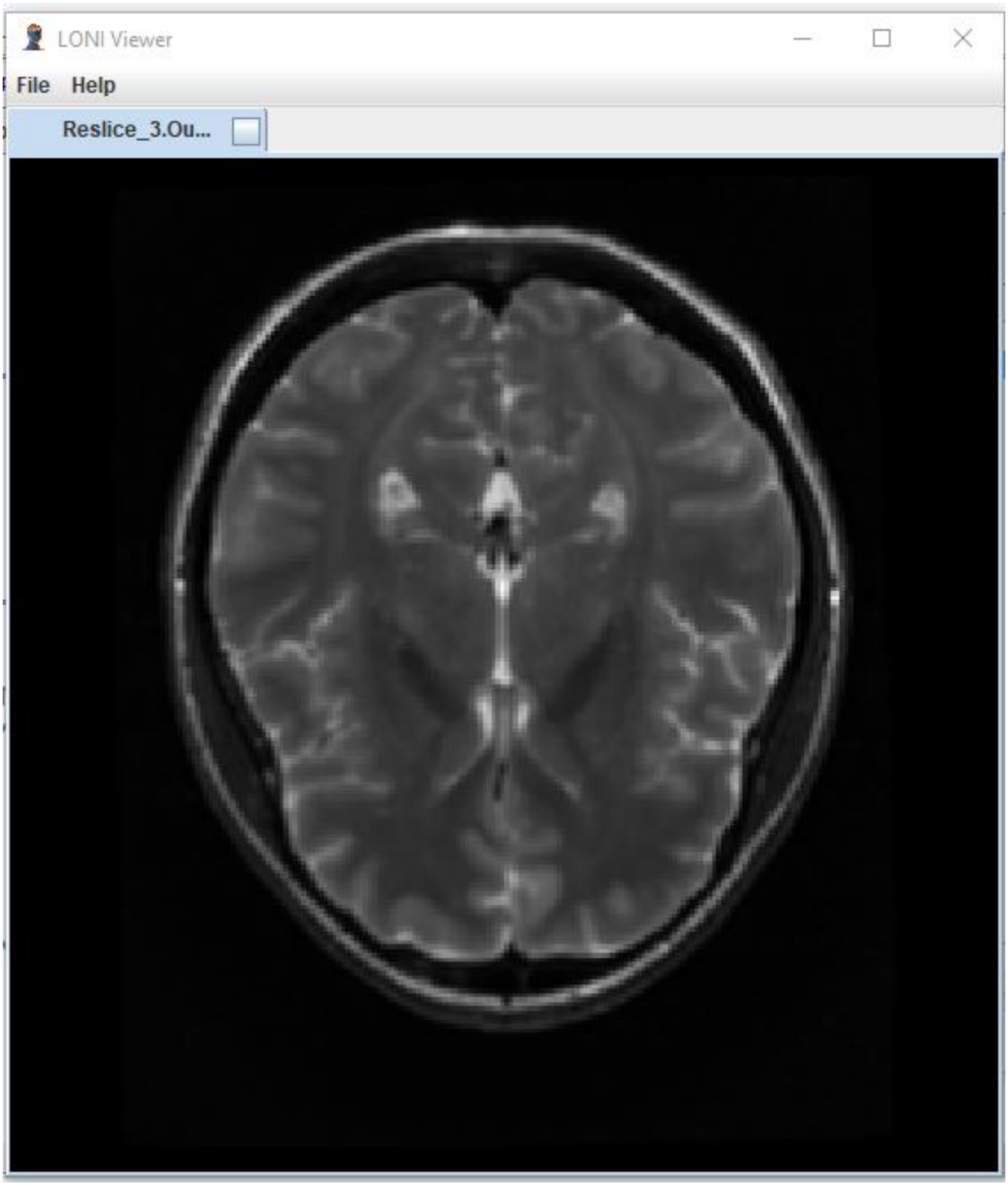

Fig 24 instance of a result as seen from LONI viewer.

To sum up the previously mentioned, in my point of view LONI Pipeline is not the ideal tool for the intended purpose of this thesis hence little can be extracted from the workflows and the data appointed to it. It may be extraordinary tool for other purposes and tasks as long as skilled and experienced people use this tool in an extend the itself allows it.

6.2 Future Work

As the result of the LONI Pipeline where not clear enough and the end result is still unclear, for future work might be in the form of tool shift. There are multiple tools in existence that can be swapped with LONI Pipeline as also am confident that even more are in process of been created
As per the task indeed to be done a fitting tool might be **KNIME Analytics Platform** that as it is also aimed for vast spectrum of purposes and not just MRI manipulation tool. Never the less it is used from specialists on almost similar tasks although it does not provide the eye candy GUI that LONI Pipeline provides it may me more appropriate for this type of tasks.
So in conclusion the way to go for future work has to exploring new tools for this task, with priority given to **KNIME Analytics Platform.** As also apply knowledge gained from the previous tools and trials for going thru better test that end up in clear results.

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5 https://www.quora.com/Do-red-blood-cells-pass-through-the-blood-brain-barrier-And-if-not-how-do-red-blood-cells-reach-the-brain

6 Public Domain

7 Arizona Science Center - https://askabiologist.asu.edu/b-cell

8 http://www.mslivingwell.org/learn-more-about-ms/diagnosing-multiple-sclerosis/

9 Jasper Jacobs

10 https://www.mayoclinic.org/diseases-conditions/guillain-barre-syndrome/symptoms-causes/syc-20362793

11 https://www.emedicinehealth.com/myelin_and_the_central_nervous_system/article_em.htm#how_is_the_myelin_sheath_destroyed_demyelination

12 https://sciencing.com/everyday-uses-magnets-5314850.html

13 http://www.wikiwand.com/en/Physics_of_magnetic_resonance_imaging

14 https://casemed.case.edu/clerkships/neurology/Web%20Neurorad/MRI%20Basics.htm

APPENDIX A

LONI PIPELINE

A.1 Introduction

"The LONI Pipeline is a free workflow application primarily aimed at computational scientists. With the LONI Pipeline, users can quickly create workflows that take advantage of all the greatest tools available in neuroimaging, genomics, bioinformatics, etc." [15]. Furthermore, with LONI Pipeline we can create, validate and execute a data analysis neuroimaging, as also we have the capability of automated data transformation, the net usage, ease of data input and a vast collection of computing tools.

In contrast with other graphical analysis architectures, LONI Pipeline offers two major advantages, the distributed Grid computing environment which allows of a more efficient jobs completion, jobs validation and it has permits efficient tool integration, protocol validation and broad resource distribution [16].

For the integration of existing data and computational tools within the LONI *Pipeline* environment there is no need for a modification of the resources themselves. The LONI Pipeline environment provides us with various types of process submissions based on the underlying server hardware infrastructure [16]. The only data stored within the LONI Pipelines environment are workflow instructions and references to data, executable scripts and binary instructions. Thus "making it portable, computationally efficient, distributed and independent of the individual binary processes involved in pipeline data-analysis workflows." [16].

In summary, LONI Pipeline is a workflow application allowing the execution of any executable for use in this environment. Does not require any change to our programs such as implementation of code or interfaces, for the usage of these programs inside of LONI Pipeline. We are ready to use LONI Pipeline with ease from the graphical interface or we must understand sufficiently the usage of the command line which is a somewhat more complicated.

A.2 Installation

A.2.1 Requirements

LONI Pipeline client requires an installation of JRE 1.6 or higher (https://www.java.com/en/download/) from Oracle. For Linux, java may be installed by default although it may not be Oracle's version. "To check which version of java you are running, under terminal, type `java -version`. If you did not see something like "Java HotSpot(TM)", then you need to download and install Java from Oracle" [17]. Furthermore, LONI Pipeline does not require large amounts of memory, so RAM is not an issue.

A.2.2 Downloading

Downloading LONI Pipeline is a strait forward procedure. You'll have to go to Pipeline website (http://pipeline.loni.usc.edu/) click on the Get Started -> Download link in the navigation bar at the top.

A.2.3 Setup and Launch

Setup and Launch varies from operational system(OS) to another, so we'll have to analyze them individually

For installing on Windows OS, you'll have to double-click the installer and follow the on-screen instruction. Once it finishes installing, you can close the installer and launch the program by going to the Start menu->Programs->LONI Pipeline and start the program.

For installing on OS X (MAC OS), you'll have to double click the disk image file you downloaded, and drag the LONI Pipeline application into the Applications folder. Once the program is done copying you can unmount (eject) the disk image and move it in the trash. To start the Pipeline, just go to your Applications folder and double-click on the LONI Pipeline application.

For installing on Linux/Unix), you'll have to extract the contents of the file to a file located on disk, and execute the PipelineGUI script. Note that you'll have to make sure to have the java binary in your path.

A.3 Interface Overview

A.3.1 Server library

On first launch of LONI Pipeline you'll notice the area to the left is empty. This is because here is the server library where you can see a list of all the modules available to you when you

connect to different servers and therefore because it's the first time, it is empty. When connected to a server here you will see the tools you have access to.

For gaining access to the tools LONI Pipeline, you'll have to log in with your username and password which you'll need to obtain from Pipeline server apply for an account. After receiving your credentials, you can connect to the server (cranium.loni.usc.edu) and be able to see the tools available on the server in the library. Server library supports workflows from multiple servers.

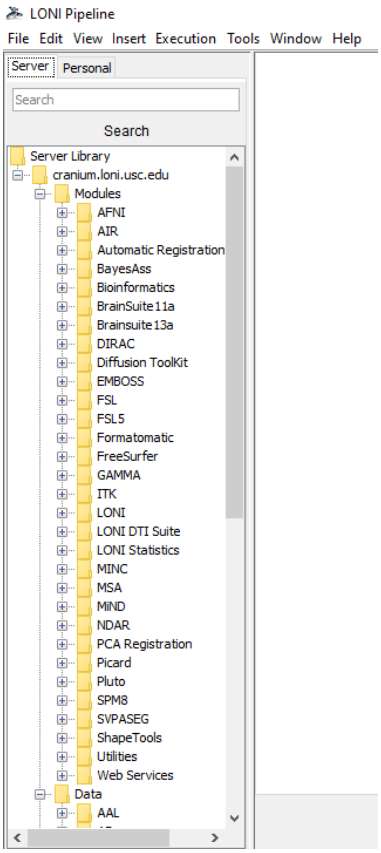


Fig 25. Server Library browser structure

Library items have some extra functionalities in the library. They can be sorted "by Module Type" or "by Server address", manually connect by right clicking and call Update library function which will automatically connect to servers included in your current server library and update the Server Library Content on your local computer. You can search the server library by keyword, and it will return matched result ranked by popularity [17]. If the library is empty due to removing library content and run Update library command, Pipeline will check for your current connections and will update only from servers you are connected to.

While you are not connected to a Pipeline server, server library will still display the list of tools as they are cashed to your computer, enabling you to build workflows even while offline.

A.3.2 Personal library

Personal library is located in ‘Window->Personal Library’ and it is here where your workflows and personal created modules are stored. Therefore, by selecting a directory or use the default directory from preferences you can save all the personal workflows and modules there. That said, you can visit your personal library whenever you want to see your modules and workflows or, you can drag a module in an open workflow with ease.

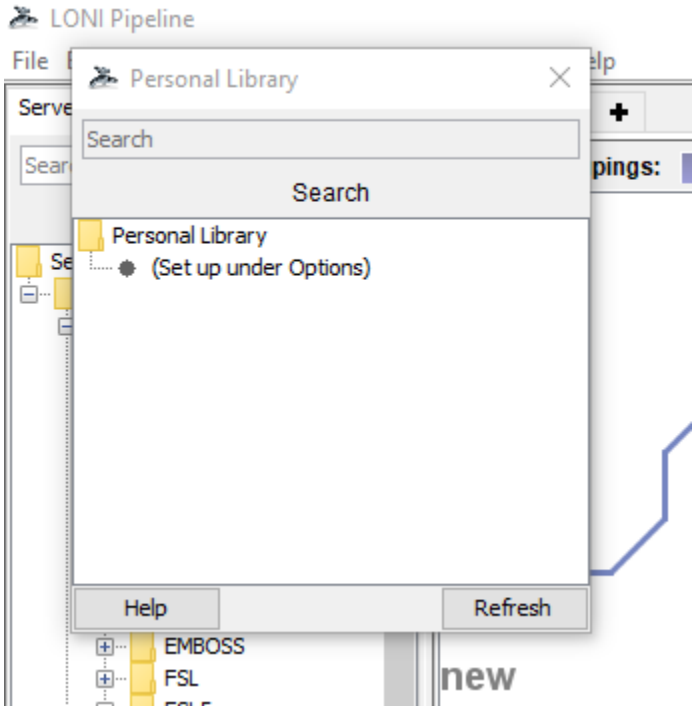


Fig 26.Personal Library with nothing saved in it.

LONI Pipeline also allows workflows to be opened or saved to or from to Personal library by the following path.

Save: Click File -> Save To -> Personal library

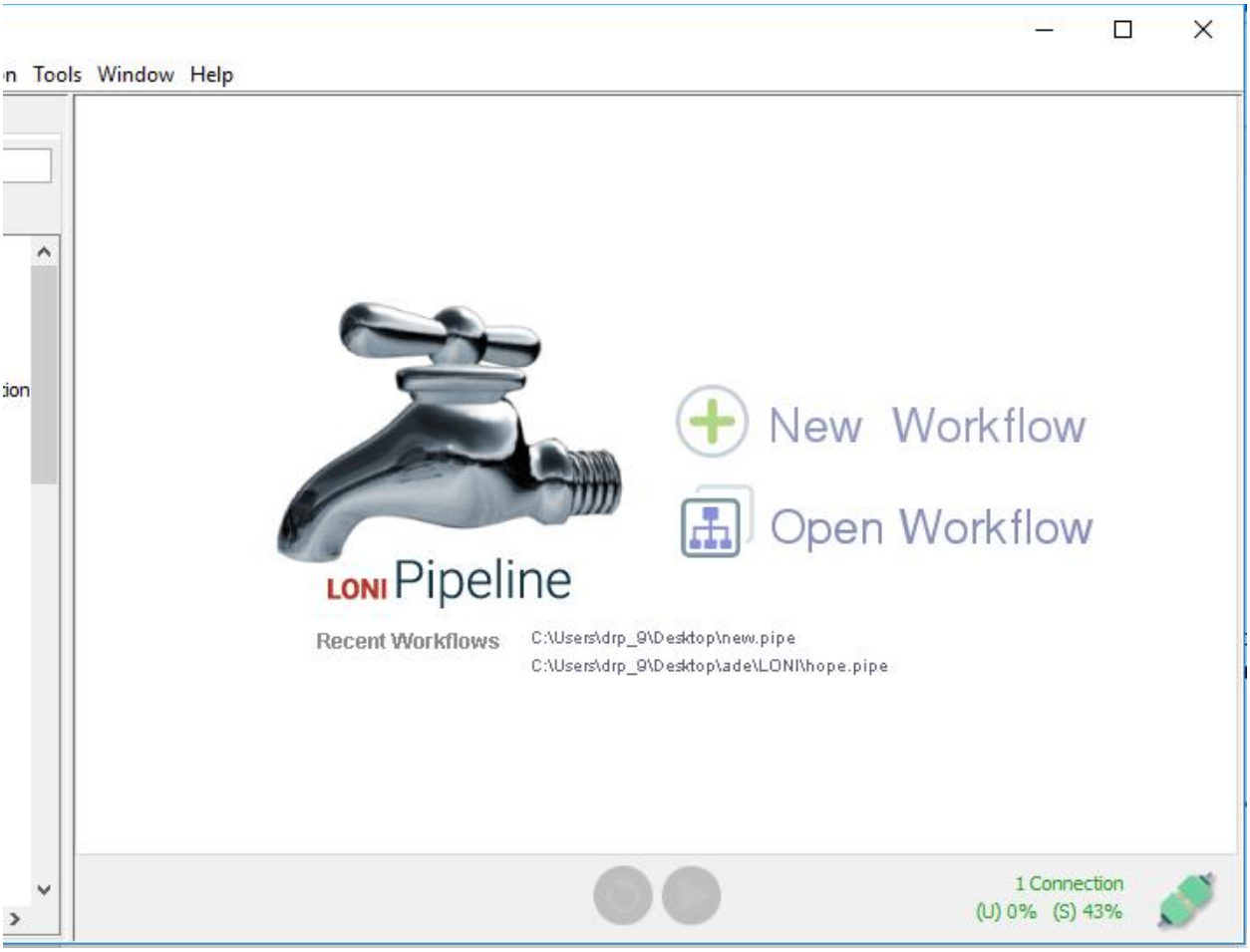
Open: File -> Open From -> Personal library

Personal library is very similar to server library as it can be used with the same way to construct workflows. “If you have defined lots of modules that describe executables on your local

computer or even module groups, you can drag in copies of them to create even more sophisticated workflows." [17]

A.3.3 Workflow Area

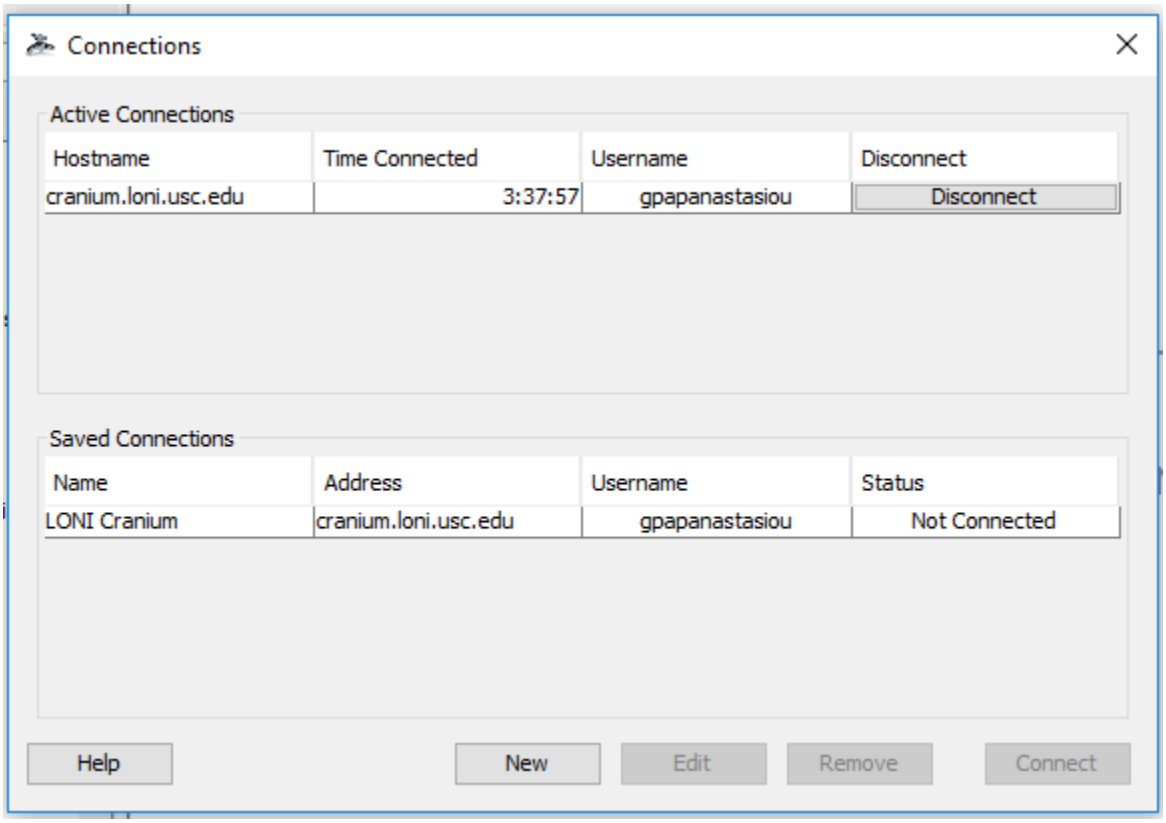
The largest area of the interface of LONI Pipeline is the workflow area where you can open or start a workflow by selecting either of the two buttons at the center. In addition, there is a list of the recently opened workflows if there is any for ease of access.



On the workflow area you can open multiple workflows at the same time by utilizing tabs or windows. Just like browser tabs, these tabs can be dragged and dropped to generate a new window, rearranged by the user or closed by clicking the cross icon for the tab. "You can also move over the tab that is not in current view, it will show you a small overview of the workflow" [17].

A.3.4 Connection Manager

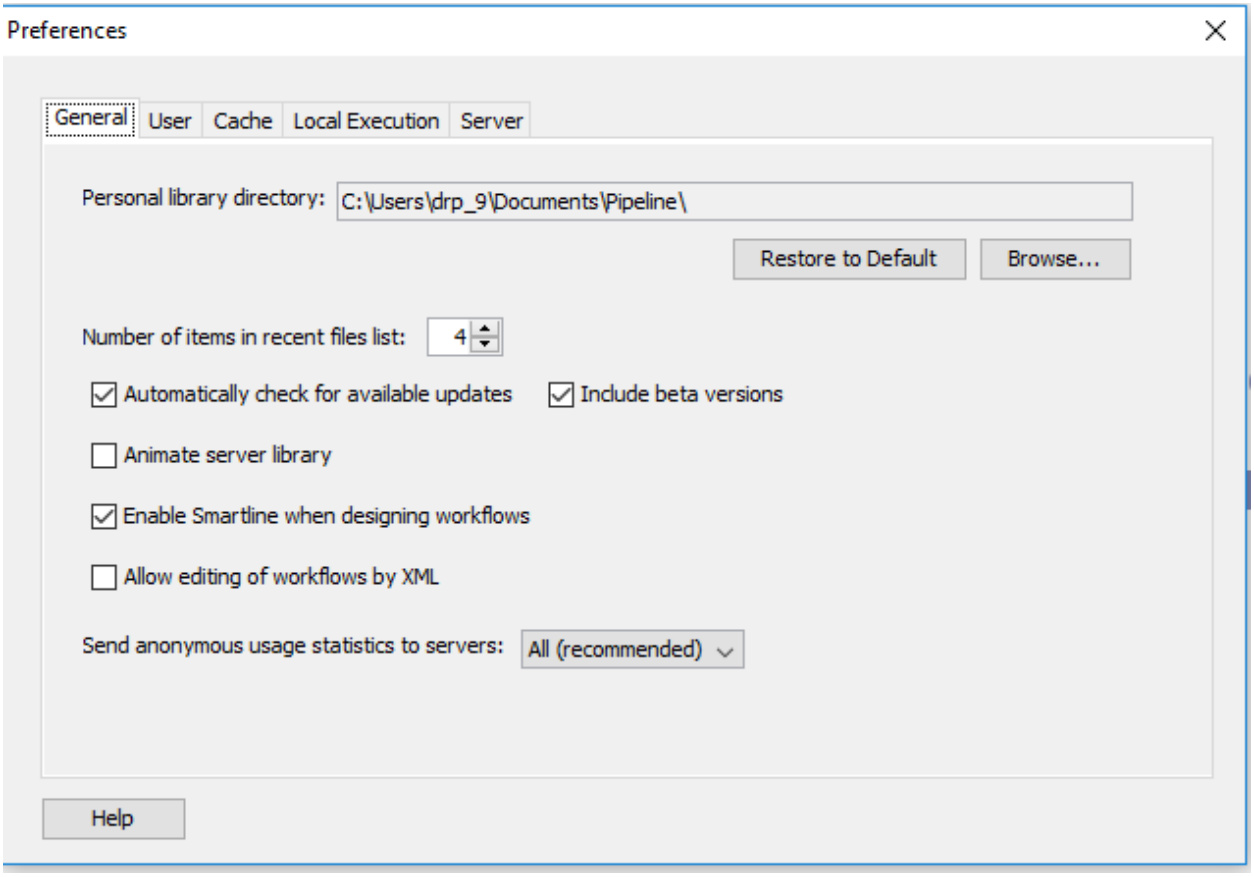
By default, LONI Pipeline has the cranium.loni.usc.edu server as saved connections, but nevertheless you might want to connect to deferent servers to get access to their tools. Therefore, to view the list of connections, you'll have to go to 'Window -> Connections' or click on the disconnected circles at the bottom right of the window and a menu will pop up which you'll have to click on connections.



As mention earlier Pipeline has LONI server as a default but you'll have to apply for an account to connect with it and use it." You can click Edit and put your LONI username, and then click Save. Once you've entered the connection, go ahead and click 'Connect'. After 30 seconds or so you'll notice that your server library has been populated with tools from the server." [17] Moreover, you can add a new connection to any pipeline server by clicking New.

A.3.5 Preferences

Preferences are partitioned in to various tabs like General Tab, User Tab, etc. which each one has its corresponding preferences settings. However, for OS to OS varies in to the procedure of bringing up the preference menu:

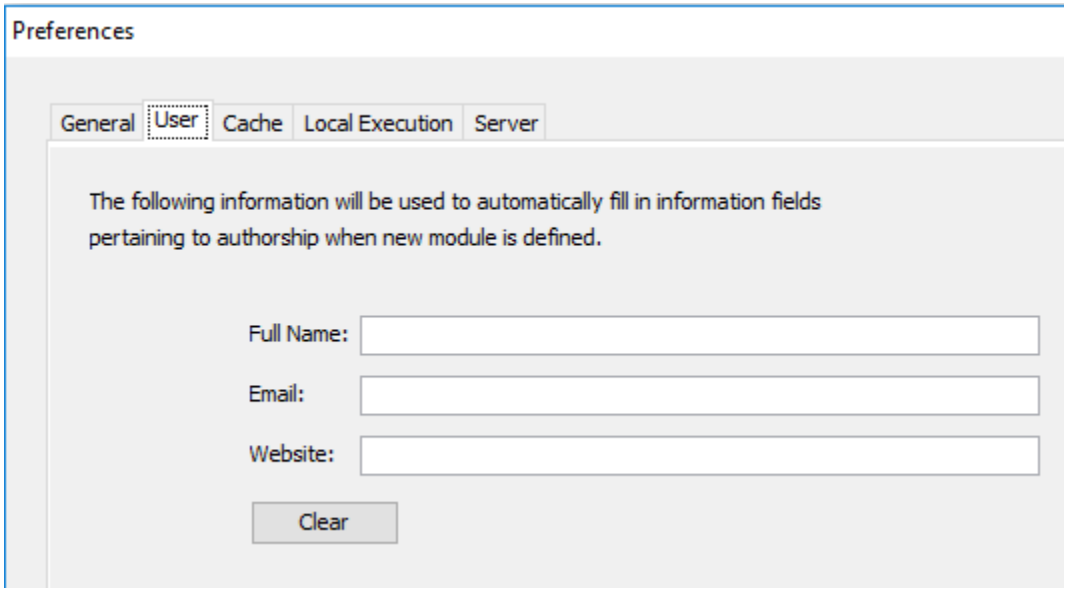


OS X: Go to the 'LONI Pipeline' menu and select 'Preferences.'
Windows: Go to 'Tools'->'Options'
Linux/Unix: Go to 'Edit'->'Preferences' [17]

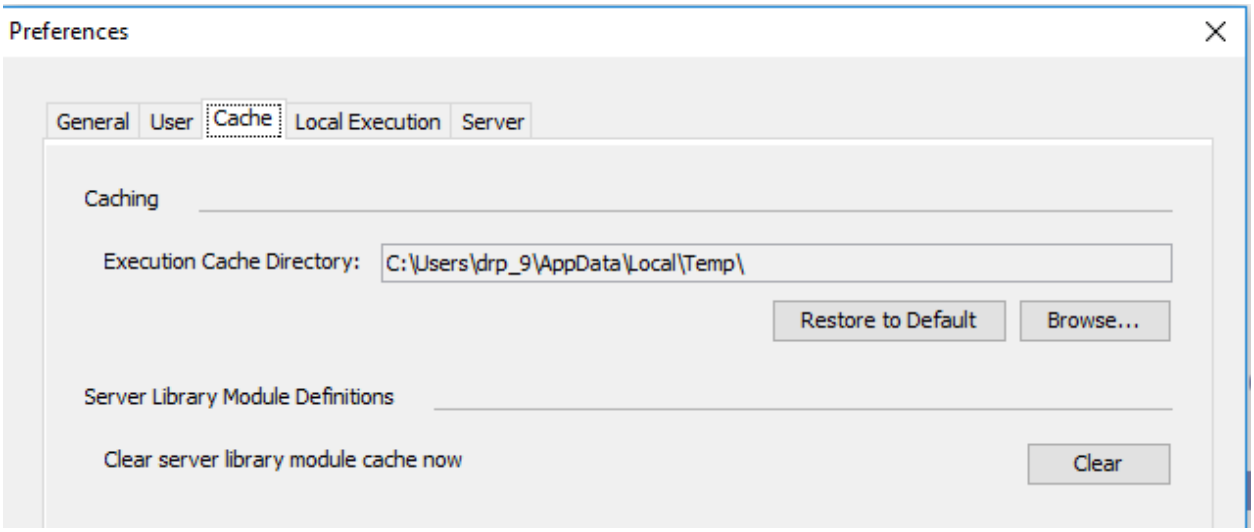
In **General Tab** we can view and change:

- Personal Library (where your library of workflows and personally created modules are stored).
- Automatically check for available updates (if checked, Pipeline will check for update every time it starts).
- Animate Server Library (if selected, server library will hide automatically when workflow is executing, and will show up automatically when workflow is stopped).
- Enable Smartline when designing workflows (If enabled, Pipeline will create translation module between image files automatically when making connections) [17].

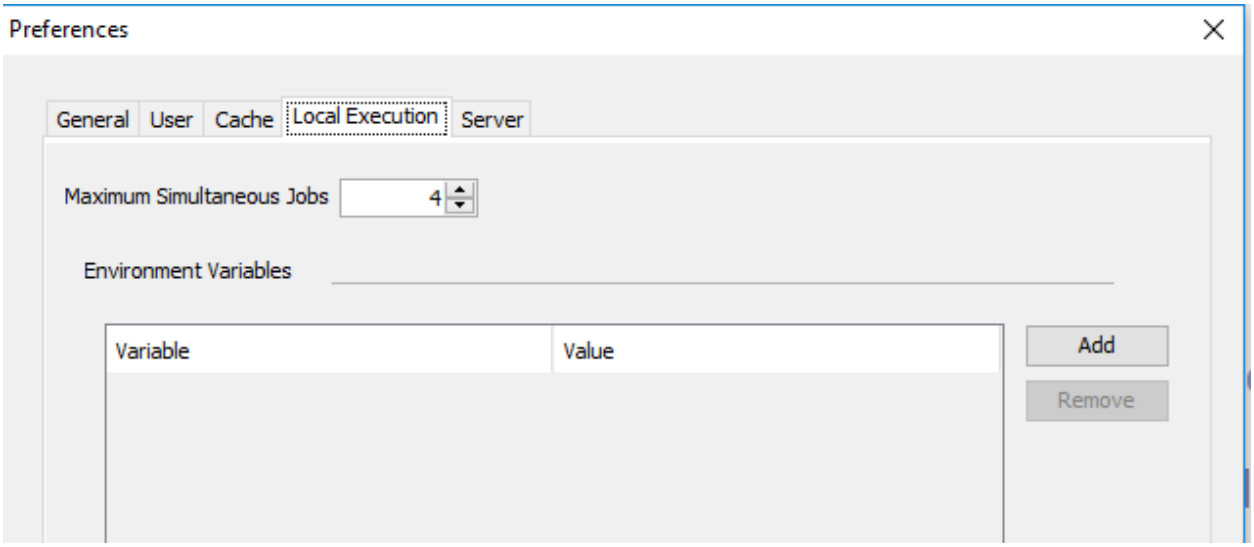
In **User Tab** we can view and change authors information, in other words it will automatically apply to the "Module Described by" field for the module you created [17].



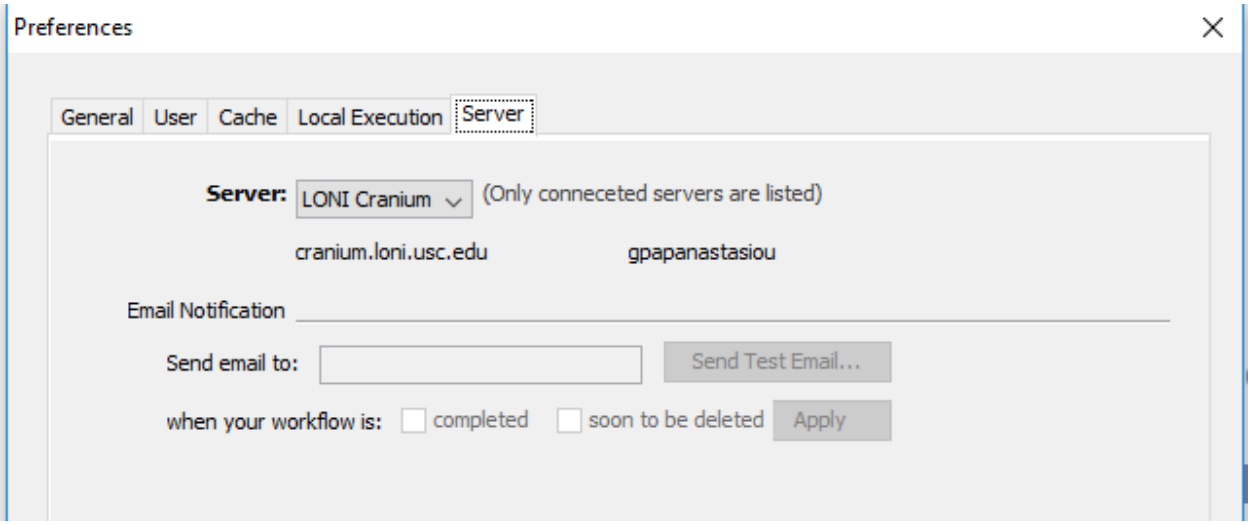
In **Cache Tab** we can view and change the execution cache directory and library module cache. "The execution cache directory is where all intermediate data is written to while executing a workflow and the library module cache can be cleared here" [17].



In **Local Execution Tab** we can view and change the Maximum simultaneous jobs, Use Grid Plugin and Environment Variables for your local execution. Maximum simultaneous jobs are the upper limit of the jobs running in parallel that are ready to submit at once, when this number is reached, the other jobs will be queued up until other ones complete. Use Grid Plugin, "if you have a grid manager locally, checking this will enable your local workflows sent to the grid manager" [17]. a specification has to be made for grid plugin jar file path and the class name.



In **Server Tab** you can set up specific preferences to a Pipeline server such as, email notification about various workflow states. To view or edit this you'll have to connect to the server since, this setting is synchronized to the Pipeline server. "Once you clicked Apply, the changes will take effect to all your workflows on that server" [17].



A.3.6 Search Feature

The Search feature allows the user to query for modules in Library and Personal Library panels and it will return "results drawn from the module's name, author list, citations, tags, description, and parameter fields" [17].

A.3.7 Checking for latest updates

Although Pipeline will inform you if there is a newer version available, you can check if you have the latest version of the LONI Pipeline client in the Help Menu by clicking on 'Check for Updates'. From there on you can download and install it if there is any newer version by simply following the instructions.

A.4 Workflow Building

A.4.1 Dragging in modules

Modules located either in personal or server collection can be dragged and dropped on to the workflow area. Furthermore, all modules that are used in a workflow have to be from the same server or local libraries or a pair of a remote server and your local machine. "For example, you can mix modules from the LONI Pipeline server and your local machine, but you cannot mix modules from the LONI Pipeline server and modules from the Acme Pipeline server" [17].

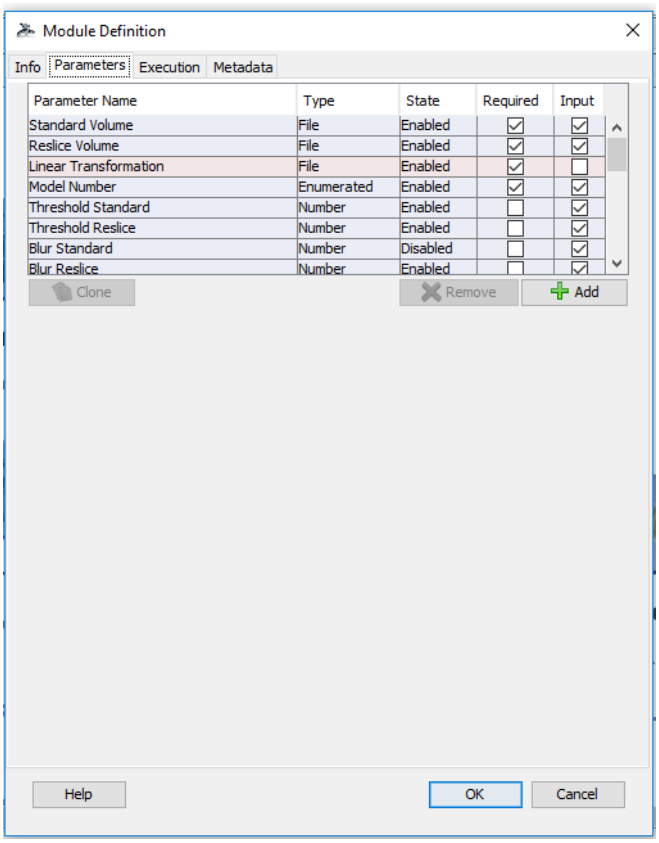
A.4.2 Connecting modules

Modules in a workflow can have more than one inputs and outputs and they need to be connected with other modules. However, when an attempt is made to connect two modules Pipeline does some initial checking to make sure the connection is valid. Connections that are not valid such as a file type parameter to a number type parameter, or connecting an output to another output and more. Pipeline also "supports the connection of a single output parameter to multiple input parameters, as well as the connection of multiple output parameters to a single input parameter " [17].

When connecting two module Smartline may be appear. "Smartline is an automatic file conversion tool which based on information about input and output, a Smartline will take care of any file translation needed" [17].

A.4.3 Setting parameter values

A module in a workflow as mentioned above has inputs and outputs. Modules can be inputs for other modules as well as input parameters and data inputs which we will see later. Parameters can be enabled or disabled depending on the scope of the workflow and the module itself. Modules come with their default parameters found in a list like interface by Right click-> Parameters tab. Here also you can change the Parameters setting as well as add more parameters to the module as seen below



Data for these parameters can be mixed from local (located on your personal computer) and remote (from server), and Pipeline will manage the data accordingly for the user. As LONI's website describes an example "the input to the 'Align Linear' could be located on your local drive, but you could set the output of the 'Reslice AIR' to be written to some location on the Pipeline server or vice versa" [17].

A.4.4 Data sources and data sinks

Every workflow needs some sort of input of data and an output repository, this is where you can take advantage of sources and sinks. Therefore, by right-click on any blank space in the workflow area and select New > Data source a new window will appear and a data course icon will be placed on the workflow area. This window has two tabs the 'Inputs' and 'Browse' tab. In inputs tab you can enter some information about the data source and on brows tab you can browse and select multiple files into the list, or you can just type in the path to a file manually. In addition, in brows tab there "an option for a server in case you want the data source to represent data on another computer" [17].

With that in mind, data sinks work pretty much the same way only in reverse. Therefore, by right-click on any blank space in the workflow area and select New > Data sink a new window will appear and a data sink icon will be placed on the workflow area. Here, you can specify the output filenames and location in a data sink and connect to the output of the module, the file will be generated specifically on that destination. Files in data sinks are not copied over from temporary directories, but rather generated directly on execution time." If no data sink is specified, output files will be in the temporary directory, with system generated filenames" [17].

Data sinks also enables you to specify a target directory without point out each file individually by selecting Directory Source and specify desired directory. Moreover, you can insert filters so that only filenames inside the directory that meet the filter will be included, the same can be done with file types, which filter based on file extensions.

A.4.6 Adding Metadata

Inside any regular data source there is an option to 'Add metadata' and enhances the data source functionality, allowing the fusion of imaging data and non-imaging meta-data together, enable queries groupings, and construct study-designs based on user-specified criteria. Moreover, two new tabs will appear next to the Input Tab. Metadata can be inspected for any module's output under the module output files panel.

Metadata as well as image data are propagated to subsequent modules all over the pipeline workflow in data-metadata pairs generated by the application. That said, metadata can be read and fed to any module (Data Extraction), and values produced by any module can be added back to the metadata (Metadata Augmentation). "The metadata information may be represented as an XML file, as long as it's schema is valid (well-formed) and consistent (uniform for every subject in the study), or as a tabular spreadsheet (CVS)" [17].

A.5 Execution

A.5.1 Validation

When successfully building a workflow and proceed to execute it by pressing the button on the screen under the workflow area. LONI Pipeline firstly goes thru validation of the whole workflow to check for errors and warnings while showing 'Validating' status to the user. Moreover, LONI Pipeline can validate a workflow without executing it by going to Execution->Validate, and validation will automatically begin. For validation as well as execution a connection with a Pipeline server is essential, so if a user is not connected Pipeline will prompt you for a username and password. Finally, if any warnings or errors are found during validation a dialog will pop up listing all the errors found in the workflow [17].

A.5.2 Executing a workflow

For executing the workflow, it's the same procedure as the validation phase, after all a validation must be done prequel to the execution as mentioned earlier. That said, by pressing the 'Play' button located on the bottom of the screen, beneath the workflow area. The program will initiate the execution (validation first) except if the user is not connected to a server where Pipeline will prompt for a username and password." Once all necessary connections have been made and validation has completed the workflow will begin to execute." [17].

LONI Pipeline has various types of statuses for each module indicated next to each one, depending on traffic the Pipeline handles at the moment and the result of the execution. These statuses show detailed information about each module. Note that more than one may be indicated. These statuses are:

- Initializing – Appears when instance is preparing for submission
- Queued – Appears when instance already submitted the job and it is on the queue
- Running – Appears when job starts execution
- Complete – Appears when this module finishes executing successfully
- Error – Appears when this module has error(s). Since version 4.2, Pipeline will continue to run whole workflow execution for succeeded instances after marking failed instances.
- Backlogged – Appears when maximum job count has been reached for current server and the server temporary blocked the instance until new slots available
- Staging – Appears when transferring files to/from server from/to localhost
- Incomplete – Appears when module has finished its execution and some instances failed
- Cancelled – Appears when parents of current module failed and continuation of current module became pointless
- Paused – Appears when user pauses a running workflow. All running modules and their successor will be paused [17].

By hovering the mouse above the module, a popup box will appear and more detailed status information about each job for that module are also shown. Moreover, this information can be found in the execution logs, which can be opened by clicking a module and clicking on 'View Execution Info'.

LONI Pipeline estimates the runtime of each individual job on the grid depending on the modules and workflow by comparing them with similar jobs that ran in the past. By calculating the runtime for each module, it can conclude to an estimated runtime for the whole workflow. Moreover, it takes in to consideration instances, currently available grid resources, and other factors. To view this information, the user hat to move the mouse above the module for the modules instance estimate and move the mouse above lower left corner where workflow runtime is displayed.

A.5.3 Client disconnect/reconnect

When the workflow successfully passes from the validation to execution, due to it is running on a Pipeline server therefore, it is independent from the user's computer. The user can shut down their computer or quit LONI Pipeline no matter what the workflow will be still running on the server until it's completion or in the event the user presses Stop. Therefore, to view executed workflows start up the Pipeline client and use the Connection Manager to connect to the server where the workflow was running on. Moreover, at "Window -> Active Sessions on the top menu, a dialog with a list of all active workflows will pop up and there the file name of the workflow, start time, finish time is visible (if it's still running, it will show "Running")" [17]. By selecting and reconnecting on any of the workflows, the workflow will open with the latest status on the workflow area.

Workflows can be removed from Active Sessions list manually or after the past of fifteen days.

A.5.4 Server Status

When the workflows are initiated then, the workflow is submitted to the Pipeline server and queued up and therefore, the Pipeline server responses the information about the status of the server. More specifically, this information includes the total slots of the server, the traffic on the server, jobs that are queued up, and jobs executed on the server. In fact, the above information is displayed at the bottom right corner of Pipeline window.

A.5.5 Pausing a workflow

When pausing the workflow while it is working by pressing the ‘Pause’ button, it will stop all running jobs/instances and all their output files will be deleted. However, output from completed jobs will be kept. The workflow can resume by pressing the ‘Play’ button.

A.5.6 Restart a module

Each completed or erroneous module can be restarted by pressing on the completed module and select ‘Restart Module’. Another way to do so is by opening the Execution Logs on the module and press the ‘Restart Module’ under the Info tab. More specifically, for the restarting module and its successor modules, all instances and jobs will be resubmitted to run. Finally, their output files will be deleted in order to avoid any possible conflict on subsequent run.

A.5.7 Viewing output

As the workflow proceeds and executes modules, the user can view the output and error streams of any completed module. By going to ‘Window->Log Viewer’ or by pressing on the module and click on ‘Execution Logs ’to bring up the log viewer and view information about it. Furthermore, in the left column of the log viewer the user can select the instance of the module that wants to view their output.

The execution info window, not only displays status information but also a variety of additional job information such as the server that it runs on, its running time, job and session ID’s, and command string. More specifically, session ID is a unique ID to all active workflows and its used with your workflow’s name for ease of access and reconnection to a specific workflow.

The output and error logs are very helpful in in debugging failed jobs and they are located in synonymous tabs that contain data that are captured by the application’s output and the error streams, respectively. That said, information from the error stream and output can be viewed through a variety of tools that determine the reason why the job lead to failure.

The output files tab is consisted by a list of all files that are created by that instance of the module. Here you can view them by pressing ‘View data’ or download them by pressing ‘Download’ to your system.

A.5.8 Debugging execution

Subsequently, in some of the instances the module will end up failing and they there will be a red ring around it. Therefore, by using the log viewer and view the failed incenses or jobs of the module highlighted in red and with help from the output and error stream all problems should be diagnosed.