Risk-based Multi-Criteria Decision Analysis for Epilepsy Death Risk Reduction

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Sommario

L'epilessia é fra le malattie neurologiche piú frequenti: nel mondo colpisce circa 43 milioni di persone. Questo tesi tratta di un caso particolare di problema di analisi multicriterio. Il problema studiato proviene dal dominio medico ad di rilevanza pratica molto importante. Dato un paziente affetto da epilessia qual'é il modo migliore di diagnosticare e curare la malattia? Questa domanda contiene in sé lo scopo di questa tesi. Il modo piú comune per affrontare un problema di ottimizzazione multi-obiettivo é quello di applicare un'ottimizzazione paretiana tra le soluzioni. Viene qui proposto un modello basato sulla valutazione del rischio che utilizza strumenti sviluppati nel campo della analisi decisionale multicriteria (MCDA).

Summary

Epilepsy is among the most common neurological diseases: in the world affects about 43 million people. This thesis is a special case of multicriteria analysis problem. Studied the problem comes from the medical domain is of practical relevance to very important. Given a patient with epilepsy, what is the best way to diagnose and treat the disease? This question contains within itself the goal of this thesis. The most common way to deal with a problem of multi-objective optimization is to apply an optimization between the Pareto solutions. Here is proposed a model based on risk assessment using tools developed in the field of multicriteria decision analysis (MCDA).

Chapter 1

Introduction

As with any new technology or science developing a framework for selecting appropriate diagnosis and treatment and making medical decisions with uncertainly and incomplete information is the current challenge for the field of engineering. This requires mutiple set of information because of both the subjective illness and the often-limited database of relevant experimental studies. One of the tools widely used in risk assessment applications in similar situation is the Multiattribute utility theory in general Multiple-criteria decision-making.

Engineers are always making design decisions. Poor decisions could result in the loss of money, resources, and time. Therefore, it is important that engineers make logical and well reasoned decisions. However, the decision process can prove to be quite complicated, especially when trade offs need to be made, such as between efficacy and potential risk for patient treatment. Given the complexity of technology and systems, when there are dozens of attributes, there are can be hundreds of alternatives to choose from, which can lead to a seemingly infinite number of possible combinations. So, how does one choose the best combination? The purpose for using utility theory in decision making is to create a mathematical model to aid the process. It gives the decision maker the ability to quantify the desirability of certain alternatives. Utility theory is for design scenarios where uncertainty and risk are considered. The end result of using this

method is a function which represents the designer's preferences, given a certain set of design attributes. We believe that MCDA could be applied widely to support medical decision, diagnosis and treatment of epilepsy. The advantages of using MCDA techniques are numerous : MCDA provides a formal way for combining information from disparate sources. These qualities make decisions made through MCDA more thorough and defensible than decisions made through less structured methods. For example, MCDA could be used to support evaluation of some treatments and diagnosis. Our approach for making efficient decisions on appropriate for medical applications will allow joint consideration of the medical factors (patient criticity) and side effects with associated uncertainties relevant to selection of alternatives.

A generalized MCDA process will follow two basic steps: (1) generating alternatives about epilepsy diagnosis and treatment options, success criteria, and value judgments; and (2) ranking the alternatives by applying value weights. The first part of the process generates and defines choices, performance levels, and preferences. The latter section methodically prunes non-feasible alternatives by first applying screening mechanisms (e.g., significant potential risks, excessive cost) and then ranking in detail the remaining alternative by MCDA techniques.

Although it is reasonable to expect that the process may vary in specific details among patients applications , emphasis should be given to designing an management structure that uses learning as a means for incorporating changing decision priorities or new knowledge from epilepsy testing. The tools used within group decision making and scientific research are essential elements of the overall decision process. "Solving" can be interpreted in different ways. It could correspond to choosing the "best" alternative from a set of available alternatives (where "best" can be interpreted as "the most preferred alternative" of a decision maker). In our case, finding the best diagnosis and best treatment for epileptic patients. Another interpretation of "solving" could be choosing a small set of good alternatives, or grouping alternatives into different preference sets.

An extreme interpretation could be to find all "efficient" or "nondominated" alternatives (which we will define shortly). The difficulty of the problem originates from the presence of more than one criterion. There is no longer a unique optimal solution to an MCDM problem that can be obtained without incorporating preference information. Mathematically the multicriteria optimization problem can be regarded as solved when the Pareto optimal set has been determined.

The notion of Pareto efficiency is also useful in engineering. Given a set of choices and a way of valuing them, the Pareto frontier or Pareto set or Pareto front is the set of choices that are Pareto efficient.

Chapter 2

Epilepsy and Seizures

Epilepsy is a common chronic neurological disorder characterized by seizures. Epilepsy is among the most frequent neurological diseases: in the world affecting an estimated 43 million people. Thirty percent of epilepsy patients between the ages of 5 and 25 develop seizures related to illness or accidents involving an injury to the head. As many as 50 percent of epilepsies continue into adulthood. Epilepsy may be triggered in adulthood by head injuries, infectious diseases, slow-growing tumors, or from circulation problems. In approximately 70 percent of patients, there is no identifiable cause of seizures. Seizures are classified as *partial* or *generalized*. Partial seizures occur in one side, or hemisphere, of the brain. Generalized seizures involve abnormal activity on both sides of the brain.

It's important distinguish Epilepsy and Epileptic Seizures because the last one is a phenonmena instead the Epilepsy is a cronic patology that conistist in seiuzures. There are a different type of epilepsy with own definite symtomps.

A **Seizure** is a temporary loss of awareness of, and/or control over, certain body functions. It happens as a result of abnormal excessive or synchronous neuronal activity in the brain. A seizure may cause a sudden change in alertness, behavior, muscular movements, or feeling in the body. Twenty percent of all seizures occur in children from age 5 and under. Although scientists have not determined the exact cause of all seizures, some seizures can be related to brain

injuries, infections, birth defects, brain tumors, or circulation disorders such as strokes. Some seizures may have a mild warning sign called an *aura*. Examples of auras include a bad taste in the mouth, an unpleasant odor, spots in front of the eyes, or a feeling of anxiety or fear. Some patients describe a feeling of being cold or hot before a seizure.

TYPE	LEVEL OF CONSCIOUNESS	CHARACTERISTIC
	Partial	
Simple partial	No change in consciouness	Change in movement or behavior
Complex partial	Change in consciouness	Hallucinations, loss of awareness, deja vu, fear, confusion, wandering, change in movements such as lip smacking, picking at clothing
	Generalized	
Tonic clonic	Loss of consciouness	Two types of muscle movement First, muscles in the arms, legs and torso become stiff. These muscles then exhibit uncontrollable jerking movements.
Absence petit mal	Brief loss of consciouness less than 15 seconds	Response to environment impaired; less than 15 seconds staring off, non-responsive eye blinking
Myoclonic	No change in consciouness	Uncontrollable jerking of the muscles of the arms, legs or torso

Table1 : international classification of seizure -SHANDS- university of florida

Chapter 3

Multi-criteria decision analysis

Multiple-criteria decision-making or multiple-criteria decision analysis is a sub-discipline of operations research that explicitly considers multiple criteria in decision-making environments. Whether in our daily lives or in professional settings, there are typically multiple conflicting criteria that need to be evaluated in making decisions. Cost or price is usually one of the main criteria. Some measure of quality is typically another criterion that is in conflict with the cost. In purchasing a car, cost, comfort, safety, and fuel economy may be some of the main criteria we consider. It is unusual to have the cheapest car to be the most comfortable and the safest. In portfolio management, we are interested in getting high returns but at the same time reducing our risks. Again, the stocks that have the potential of bringing high returns typically also carry high risks of losing money. In service industry, customer satisfaction and the cost of providing service are two conflicting criteria that would be useful to consider.

In our daily lives, we usually weigh multiple criteria implicitly and we may be comfortable with the consequences of such decisions that are made based on only intuition. On the other hand, when stakes are high, it is important to properly structure the problem and explicitly evaluate multiple criteria. In making the decision of whether to be build a nuclear power plant or not, and where to build it, there are not only very complex issues involving multiple criteria, but there

are also multiple parties who are deeply affected from the consequences.

Structuring complex problems well and considering multiple criteria explicitly leads to more informed and better decisions. There have been important advances in this field since the start of the modern multiple criteria decision making discipline in the early 1960s.

3.1 Operation alternatives

Are usually thought of as given, in the sense that they are a priori and strictly defined. However, alternatives may result from the systematic exploration of the objectives pursued in the decision situation considered. Especially in problems of strategic nature, the challenge is to detect interesting alternatives not obvious or apparent at first sight- on the basis of the main concerns expressed during problem identification. In other occasions, where decision makers face a large number of a priori defined alternatives, a first crucial step is to identify a manageable set of 'good' or 'interesting' or 'representative' alternatives. Screening or sorting techniques can facilitate the search for preferred alternatives. Finally, alternatives may be implicitly defined as combinations of discrete actions. In such cases, decision makers seek to determine the most attractive combination (portfolio) of the available actions.

- *Acknowledging* uncertainty is another crucial element of MCDA problems. The main cause of uncertainty is limited knowledge about external parameters that may influence the performances of the considered actions. This type of uncertainty can be handled by constructing scenarios for various possible values of these uncertain parameters, as well as by the exploitation of probabilities in the treatment of stochastic events. In addition, decision makers have to handle internal uncertainty stemming from hesitations during the problem structuring process (which alternatives, how important are the criteria, etc.). The problems solution depends greatly upon the way

both external and internal uncertainties are taken into account and the techniques used to incorporate them into the analysis.

- *Decision makers* or other stakeholders involved in the decision situation are those identifying the nature of the problem and driving the solution procedure towards the preferred direction. Although the two terms are sometimes used interchangeably, for our purposes, decision makers are those assigned with the responsibility to take the final decision, whereas stakeholders is a much broader notion encompassing any single individual or group of people with an interest or concern in the examined problem. The decision makers are thus expected to take into account the stakeholders point of view depending on their overall managerial behaviour, the type of the problem considered and the ability of stakeholders to assist or to hamper the solutions implementation. However, the involvement of stakeholders in the MCDA procedure is useful in capturing several aspects of the problem and getting a better insight to its potential consequences.

- *Environment* refers to all those parameters defining the decision context. They may include fiscal, legislative or cultural aspects, which may broaden or restrict the scope of the analysis and impose constraints in the decision making procedure. Even if all other elements are the same, the problems solution might differ if the decision is taken in another location or time period.

3.2 Criteria

Criteria represent the decision maker or other stakeholders points of view along which it seems adequate to establish comparisons. There are two main approaches to determining the set of criteria, reflecting the two ways of building a MCDA problem. A top-down approach is compatible with "valuefocused thinking" where criteria are built in a hierarchical structure, known as "value tree",

leading from primary goals to main (fundamental) objectives, which in turn are further broken down to specific criteria. The bottom-up approach supports "alternative-focused thinking", where criteria are identified through a systematic elicitation process, and may subsequently grouped in broader categories. In both cases, a coherent set of criteria presents the following properties:

- *Value relevance*: Criteria are linked to fundamental goals of the stakeholders enabling them to specify preferences.
- *Understandability*: The concept behind each criterion is clear and there is a common view about the preferred direction of the alternatives performances.
- *Measurability*: The performance of alternatives can be expressed on either a quantitative or a qualitative measurement scale.
- *Completeness*: The set of criteria strives to cover all important aspects of the problem considered while still being concise and operational.

3.3 Pareto Optima

Pareto efficiency, or Pareto optimality, is a concept in economics with applications in engineering. The term is named after Vilfredo Pareto (1848?1923), an Italian economist who used the concept in his studies of economic efficiency and income distribution.

No part of a Pareto optimal solution can be improved without making some other part worse. Figure 1 shows four geometric examples of Pareto optimality. In these figures, the circles represent objectives that are satisfied best when the area of the circle is maximized. The constraints are that the circles may not overlap and must fit within the triangle.

We might further impose a global objective function in this case that is equal to the sum of the circle areas. Only one of these figures is globally optimal

whereas three of them are Pareto optimal. One figure is not Pareto optimal because the area of one circle may be enlarged without violating the constraints. This can occur in a distributed design project because one of the other circles has been moved or modified by one of the team members.

Pareto optimality is a predicate. While one may be able to assign a quantitative metric, such as the area of the circle, the answer as to whether the global solution is Pareto optimal is "yes" or "no". It does not matter initially how much a circle can be enlarged, only that it can be. How much is to be evaluated after the possibility is noted. A corollary is that Pareto optimality does not address local extrema with respect to any utility. Neither does Pareto optimality provide a method for choosing among preferences or alternatives.

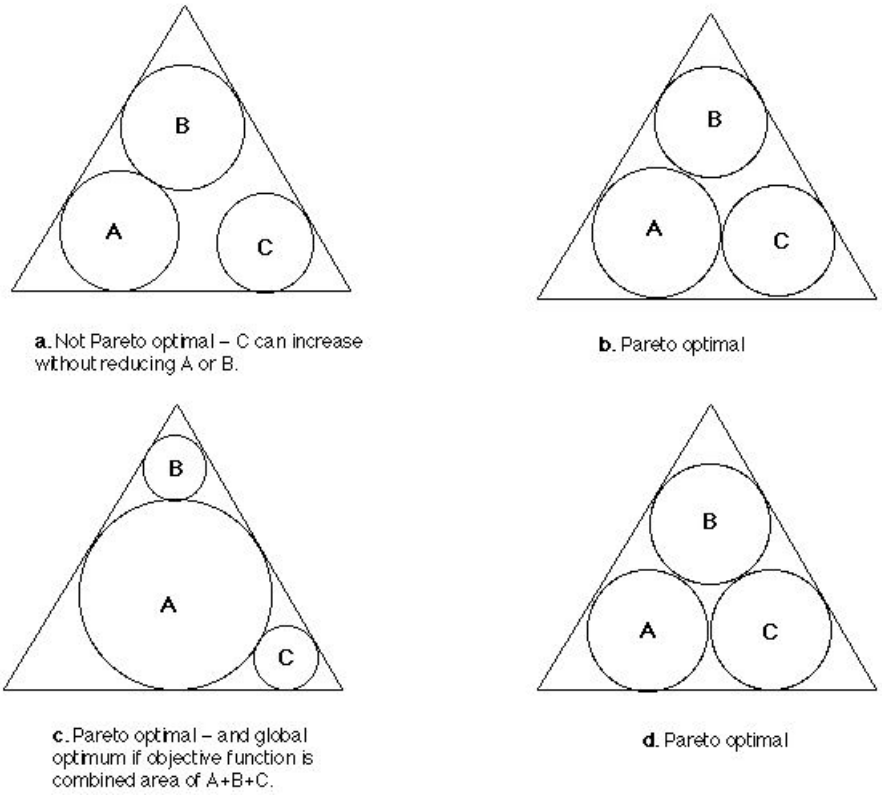


Figure 3.1:

Chapter 4

Diagnosis

4.1 Diagnosis Operation Alternatives

We considered six diagnosis management alternatives, that are defined independently of the epilepsy type. These management alternatives are defined following the current diagnosis methods uses , such as:

	Diagnosis
D_1	EEG test
D_2	CT test
D_3	PET test
D_4	MEG test
D_5	MRI test
D_6	Neuropsycological test

Table 2 - Diagnosis Alternatives for Epilepsy

Each operational alternative is characterized by a factor that increase the expected "probability of success" of the assets. Figures 10, 11 show the decision trees in which for each business line the operational alternatives are represented. For each operational alternative there is a binomial outcome for the assets: failure (F) and success (S). Failure corresponds to the probability of the assets to be no more functioning, while success corresponds to the probability of the assets to provide the desired function at the level guaranteed by each operational alternative. The probability of success is given by $1 - Pf\ qi$, where qi is inversely

proportional to the degree of functionality brought by each operational.

4.1.1 EEG test - D1

Apart from the patient history and the neurological exam, the EEG (electroencephalograph) is the most influential tool in the diagnosis of seizures and epilepsy. It provides a record of ongoing electrical activity in the brain.

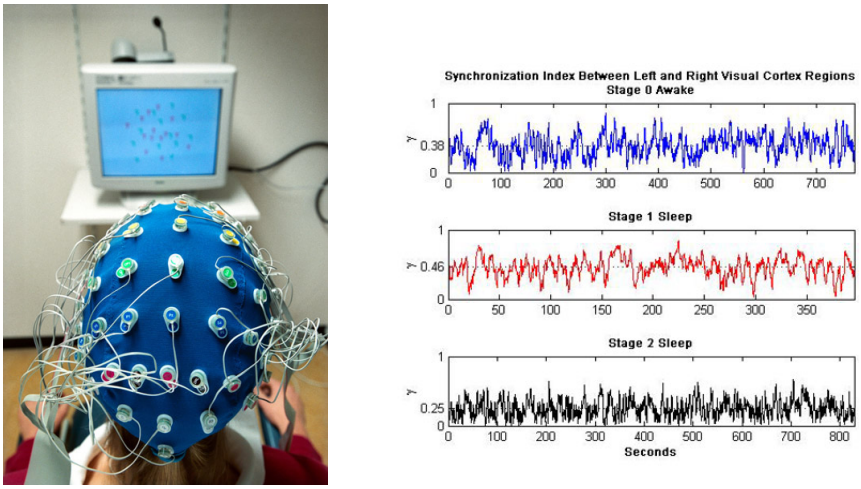
An EEG machine is a recording device connected by wires to electrodes pasted at key points on the patients head. The electrodes pick up signals produced by electrical discharge of neurons in the related areas of the brain; the amplified signal from each electrode causes pens writing on a moving belt of paper to jumpsimilar to the action of a seismograph when an earthquake occurs.

The resulting EEG tracing, with its record of electrical discharge, provides a record of activity in key areas of the brain during the period of the test. Excessive discharge (of the type that, if large enough, might cause a seizure) may show up as a sharp spike or series of spikes; some patterns (such as the 3-per-second spike and wave of absence seizures) are unique to particular forms of epilepsy.

EEG recordings of patients while awake are made with the eyes open and with the eyes closed. A flashing light is used to assess whether the patient is photosensitivethat is, if he or she will have a seizure in response to the stimulus of a flashing light.

Hyperventilation (rapid over breathing) is another common trigger for seizures and is also a feature of an EEG assessment. Almost all patients with typical absence seizures who are not receiving antiepilepsy medication will have the characteristic 3-per-second spike wave EEG pattern during hyperventilation. Patients may be asked to go to sleep during the test because EEG abnormalities are more likely to show up during sleep.

If standard recordings do not produce evidence of seizures, 24-hour EEGs, or portable home EEG monitoring devices may be used. Nasopharyngeal and sphenoidal electrodes (long wires inserted through the nose or inserted into the jaw



(a) (b)

Figure 4.1: eeg

muscle) may produce information unobtainable from regular recordings. Grid or depth electrodes may be implanted in the brain in a surgical procedure when patients are being evaluated for epilepsy surgery and it is vital to get precise information on where the seizure site is located.

If the type and cause of the seizures are unclear, a type of evaluation known as intensive monitoring may be undertaken. In this procedure, people are videotaped during an EEG recording session. The combined image of EEG tracings and visible behavior helps the physician diagnose the epilepsy and identify affected areas of the brain. Intensive closed circuit TV and EEG monitoring of this type also helps distinguish between true epileptic seizures caused by electrical discharge and non-epileptic seizures caused by psychological factors.

Various ictal (seizure) and interictal (between seizure) EEG patterns correspond to specific seizure types and types of epilepsy, although the correlation varies. While the EEG is almost always abnormal during a seizure, it may be normal between seizures. Thus, lack of interictal EEG abnormalities does not exclude a diagnosis of epilepsy. However, at some time, most epilepsy patients have abnormal EEG discharges. In contrast, some persons with EEGs that show epilepsy-like activity never have seizures. Thus physicians interpret EEG results within the context of other information they are gathering.

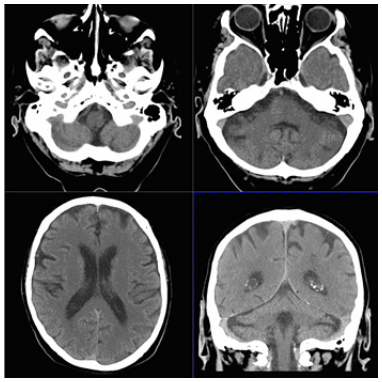
Despite some limitations, however, the EEG remains the most important clinical tool in evaluating patients with suspected seizures.

4.1.2 CT test - D2

Computed tomography (CT or CAT scan) was introduced in the United States in the early 1970s. It revolutionized the practice of neurology and neurosurgery by letting doctors see inside the brain without surgery for the first time. The CT scan is normal in most people with epilepsy. Abnormalities that might be seen are atrophy (shrinking of the brain), scar tissue, strokes, tumors, or abnormal blood vessels. Like ordinary x-rays, CT scans expose the patient to radiation. However, the amount is low and the procedure is safe even if it needs to be repeated several times. The scanner is a large machine, but less confining for patients than the machine used for MRI. The advantages of CT scanning include speed and easy availability in most places. It has lower resolution than MRI for showing brain structures, however, and it is not as good at discriminating between the brain's gray matter and white matter. Brain imaging is performed by special equipment. Typically, if you have a CT or MRI scan, you will lie on an examination table with your head resting on a curved support directly in front of the machine. The table will then be moved gently towards the machine so the head is inside its circular opening. A person having a CT scan may be given an injection of what's called a contrast medium. This is a fluid that goes up to the brain and makes the scan easier to read. After the injection, some people may feel flushed, have a metallic taste in the mouth, or feel a brief nausea.

In many ways CT scanning works very much like other x-ray examinations. X-rays are a form of radiation like light or radio waves that can be directed at the body. Different body parts absorb the x-rays in varying degrees.

In a conventional x-ray exam, a small amount of radiation is aimed at and passes through the body, recording an image on photographic film or a special image recording plate. Bones appear white on the x-ray; soft tissue, such as



(a)

Figure 4.2: ct scan

organs like the heart or liver, shows up in shades of gray and air appears black.

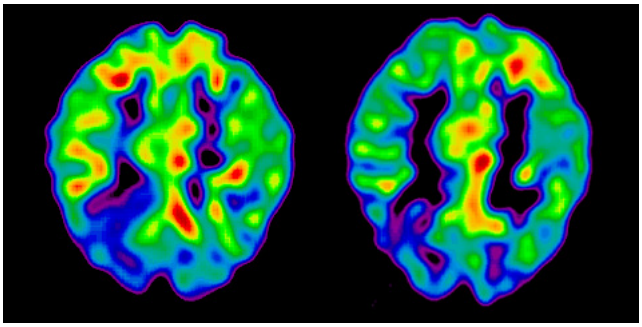
With CT scanning, numerous x-ray beams and a set of electronic x-ray detectors rotate around you, measuring the amount of radiation being absorbed throughout your body. At the same time, the examination table is moving through the scanner, so that the x-ray beam follows a spiral path. A special computer program processes this large volume of data to create two-dimensional cross-sectional images of your body, which are then displayed on a monitor. This technique is called helical or spiral CT.

4.1.3 PET test - D3

Another type of machine which produces images of the brain is the positron emission tomography (PET) scanner. It produces color-coded pictures of brain processes at work – including blood flow, use of glucose, and the presence of oxygen.

PET (positron emission tomography) shows the brain's use of oxygen or sugar (glucose). As with SPECT, a very low, safe dose of a radioactive substance is injected into your arm and the scanner records its circulation. Not all types of PET scans look alike, but often different colors are used to show areas of higher or lower use of oxygen or sugar.

This test can help to identify the area of the brain from which partial seizures



(a)

Figure 4.3: PET scan

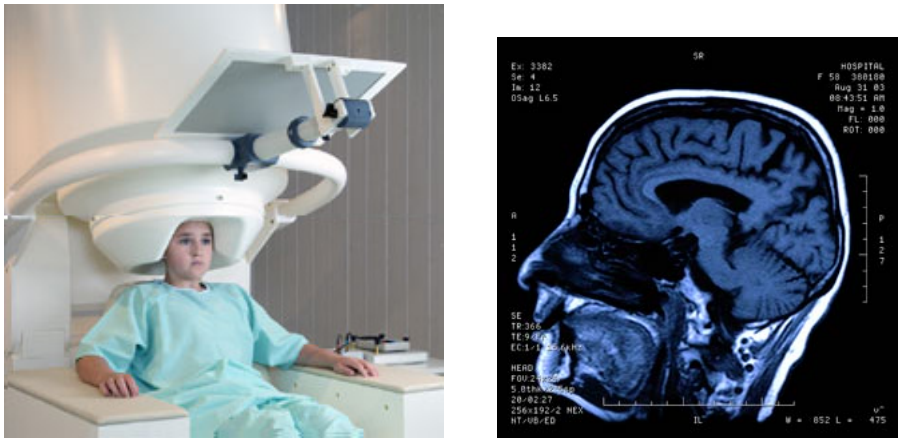
arise. It may be performed in the period between seizures, the interictal period. PET scans are expensive, and very few patients with epilepsy need them. Many insurance companies will pay for PET scans for patients who are being evaluated for epilepsy surgery.

4.1.4 MEG test - D4

Magnetoencephalography (MEG), also known as Magnetic Source Imaging (MSI), is a non-invasive scanning technique which provides information about the structure and function of the brain. It is a safe and painless procedure that detects small biomagnetic signals produced by the brain, recording magnetic fields over the surface of the head. These signals provide information about the location of active brain areas. This allows us to see how different areas of the brain interact with one another.

MEG can help to identify the areas of the brain that are emitting abnormal electric currents that are causing the seizures. Often patients perform cognitive tasks during the MEG, which helps to localize the learning and memory areas of the brain. The MEG produces a high resolution image of the brain that relates the functioning of the brain with behaviour.

One advantage that MEG has over PET and fMRI, which depend on changes in blood flow in the brain, is that it is fast enough to provide information about the millisecond by millisecond changes in neuronal firing, which PET and fMRI



(a) (b)

Figure 4.4: meg test

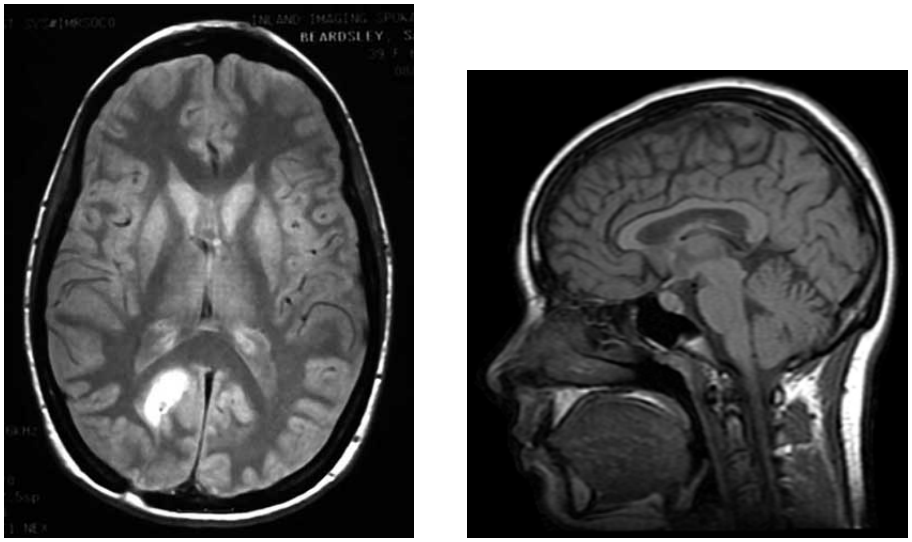
cannot. MEG records magnetic signals that are produced by the responding neurons, enabling us to see rapid brain potentials.

To some degree, MEG is similar to EEG (electroencephalography). An important difference is that the skull and the tissue surrounding the brain affect the magnetic fields measured by MEG much less than they affect the electrical impulses measured by EEG. The advantage of MEG over EEG is therefore greater accuracy owing to the minimal distortion of the signal. This allows for more usable and reliable localization of brain function. When MEG is added to magnetic resonance imaging (MRI), which shows brain structure, the combination of the images is extremely helpful for identifying areas of the brain that may be generating a potential for seizures, as well as for localizing the electrical activity in normal brain function.

In the evaluation of epilepsy, MEG is used to localize the source of epileptiform brain activity, which most likely is the source of seizures. It is usually performed with simultaneous EEG.

MEG may be helpful in the following situations:

It can improve the detection of potential sources of seizures by revealing the exact location of the abnormalities, which may then allow physicians to find the cause of the seizures. It can help when MRI scans show a lesion but the EEG findings are not entirely consistent with the MRI information. An MEG



(a) (b)

Figure 4.5: mri test

may be able to confirm that the epileptiform discharges (the brain waves typical of epilepsy) are indeed arising from the lesion. Then a decision can be made regarding surgery. In patients who have brain tumors or other lesions, the MEG may be able to map the exact location of the normally functioning areas near the lesion so that surgery can be planned to minimize postoperative weakness or loss of brain function. In patients who have had past brain surgery, the electrical field measured by EEG may be distorted by the changes in the scalp and brain anatomy. If further surgery is needed, MEG may be able to provide necessary information without invasive EEG studies.

4.1.5 MRI and fMRI - D5

Magnetic Resonance Imaging (MRI) is a safe and non-invasive scanning technique. Instead of using x rays, the MRI is based on nuclear magnetic resonance. In short, this means that all atoms have a nuclei that have their own resonant frequency. If you disturb them they sing like tuning forks. The different structural components of the brain have atoms with nuclei that have their own unique song. The MRI scan sends a high frequency alternating magnetic field through the brain, via electromagnets that surround the brain, thereby disturbing the

various nuclei. The magnetic sensors in the scanner pick up the activity of the nuclei.

A computer then generates a two or three dimensional image of the brain. This detailed picture of brain structures (not function) helps physicians locate possible causes of seizures and identify areas that may generate seizures. No x-rays or radioactive material are used, therefore this procedure is not known to be harmful.

An MRI offers doctors the best chance of finding the source of seizures. Because epilepsy can arise from scar tissue in the brain, an MRI can show scar tissue and allow doctors to determine the nature of it. The images produced from the MRI are extremely precise. The information provided by MRI is valuable in the diagnosis and treatment of individuals with epilepsy and to determine whether surgery would be beneficial.

Additional Types of MRIs

A Functional MRI (fMRI) is a non-invasive technique that provides both an anatomical and functional view of the brain. Similar to the MRI, fMRI uses magnetic fields instead of x-rays to produce detailed pictures of the brain. This technique allows us to localize specific areas of brain function by imaging patients while they perform specific tasks. Therefore, functional MRI can identify regions of the brain that are active during cognitive, sensory, and other tasks by detecting changes in blood flow to particular areas of the brain. This information is often very useful to the neurosurgeon; it helps physicians identify the exact location of the source of the seizures.

The advantage of using an fMRI is that it can measure blood flow without using radioactive tracers. Instead, fMRI takes advantage of the fact that haemoglobin, an oxygen carrying molecule in the blood, contains an iron molecule which has magnetic properties. When a magnetic field is presented to the brain, the haemoglobin molecules line up, like tiny magnets. fMRI indicates the presence of brain activity because the haemoglobin molecules in areas of

high brain activity lose some of the oxygen they are transporting. This makes the haemoglobin more magnetic, thereby responding more strongly to the magnetic field. The fMRI machine determines the relative activity of various areas of the brain by detecting changes in the magnetic response of haemoglobin.

Advantages of fMRI: It can look at discrete areas of brain activation The final image depicts more detail than CT scans It can measure fast-changing physiology better then the PET scan.

4.1.6 Neuropsycological tests - D6

Neuropsychological testing (also known as neuropsychometric testing) are designed to assess a variety of brain functions, including memory, reading, comprehension, judgment, motor abilities, spatial perception and ability to process and interpret information. The tests quantitatively measure these functions, thereby demonstrating possible abnormalities of the brain.

Individuals with epilepsy occasionally report difficulties with memory, concentration, or other cognitive areas. Neuropsychological tests assess these abilities and provide information about a person's strengths and weaknesses. This offers doctors some insight into the cause and severity of seizures. These tests may help to identify the type of epilepsy an individual has, and locate the origin within the brain of the patient's seizures by determining which parts of the brain are functioning abnormally. They may be used in evaluation for surgical treatment.

Examples of commonly used tests: Wechsler Intelligence Scale for Children (WISC) Bender Visual-Motor Gestalt Test: The visual test involves copying a bunch of abstract designs. This test is good at identifying organic brain damage. The motor test may involve sorting cards into different categories that the patient needs to determine, based on the feedback of the clinician. Wechsler Adult Intelligence Scale (WAIS): used to help test memory, and retention Minnesota Multiphasic Personality Inventory Rorschach Ink Blot Test Thematic

Apperception Test (TAT) Sentence completion Goodenough draw-a-person test Stanford-Binet intelligence Scale

4.2 Diagnosis Criteria

In order to mark out the effects and results of these diagnosis four evalutation criteria were considered (*Table3*)

	Criterion
C_1	efficacy
C_2	potential riscks
C_3	execution time
C_4	results time

Table 3 - Criteria considered for Diagnosis evalutation

Indicative values have been used for test purpose.

	C_1	C_2	C_3	C_4
D_1	9	1	3	3
D_2	8	4	2	2
D_3	6	4	1	8
D_4	8	5	2	3
D_5	8	1	3	7
D_6	7	1	8	2

Table 4 - Criteria values considered as Diagnosis matrix input

Chapter 5

Treatment

5.1 Operation Alternatives

The problem is to rank treatments illustrated in Table 1 subject to multicriteria. For the treatment of Epilepsy many methods can be applied. The evalutation of the treatment methods from multiple points of view is difficult and has a high degree of subjectivity. The complex and the original study with many patients, over the usual number from related studies, can contribute greatly to the evolution of this domain. We made a clinical study of the following treatment methods of epilepsy.

	Treatment
T_1	Ketogenic Diet
T_2	Lesionectomy
T_3	Corpus Callosotomy
T_4	Functional Hemispherectomy
T_5	Multiple Subpial Transection
T_6	Vagus Nerve Stimulation
T_7	Drug therapy

Table 5 - Treatments Alternatives for Epilepsy

5.1.1 Ketogenic Diet - T1

The ketogenic diet is one of the oldest treatments for epilepsy. It is intended to maintain the starvation or fastingmetabolism over a long period of time. When the body is in a fasting state, it creates ketones, a by-product of fat-burning metabolism. It has long been recognized that seizures often lessen or disappear during periods of fasting in some individuals with epilepsy.

The diet is very high in fat and low in carbohydrates. When fat is the primary source of calories, ketones are formed. The diet must be followed very strictly and requires a significant commitment to work effectively. Children on the diet often will not gain weight or grow much during the time the diet is in use. After that, however, growth is expected and should be carefully monitored.

The diet has been used mostly in children with difficult-to-control, generalized epilepsies – such as those with the Lennox-Gastaut syndrome. Lennox-Gastaut is a generalized epilepsy which is characterized by drop attacks or tonic-clonic attacks (with violent, rhythmic convulsions) and often occurs in children with other neurological conditions such as paralysis and mental retardation. It's often very resistant to treatment. In this group of individuals, the diet can be as successful as medications. Thus, it is most often recommended for children ages 2 through 10 or 12 years old who have been diagnosed with a generalized type of epilepsy, and who have failed to respond to a variety of drugs. Recent studies have shown that the diet may also be effective in those with partial seizures.

The diet is typically started with a period of fasting lasting until the body produces a moderate to large amount of ketones. This initiation period usually takes place in the hospital, so that the individual can be monitored for potential side effects such as vomiting, low blood sugar, dehydration, and seizures. Medications may also be adjusted during this period to prevent sedation (the tranquilizing effect of medications), another common side effect.

A two-month trial period is suggested for deciding whether the diet is effective. If effective, it is typically continued for two years. During this time, indi-

viduals are often able to lessen the amount of medication they take for seizures. Many children seem happier and more alert on the diet, even before medication is significantly lessened.

People on a ketogenic diet should be monitored by a dietician, nurse and doctor – particularly a neurologist – familiar with its use. Specialized epilepsy clinics are available to monitor a person on this diet.

Side effects of the ketogenic diet The ketogenic diet can have a variety of side effects, including:

Dehydration this needs to be monitored very carefully as a certain degree of dehydration is necessary to make the diet effective, but excessive dehydration can have serious consequences. Constipation this is due to the lack of dietary fibre in the diet caused by omitting fruit, vegetables, grains and cereals. The epilepsy specialist will have to prescribe a suitable, gentle laxative. Kidney or gallstones may develop because of the high fat content of the diet. Children need to be monitored regularly to check if they're developing kidney or gallstones. Vitamin deficiencies induced by omitting fruits, vegetables and grains. As mentioned before, the child needs to take a vitamin and mineral supplement. Increased blood cholesterol levels, particularly in children with an inborn defect in terms of cholesterol metabolism. This can have serious consequences and the medical team will monitor your child throughout her use of the diet. Refusal by the child to follow such a diet. The ketogenic diet is unpalatable and may make children feel marginalised because they cannot eat 'normal' foods. Behavioural counselling may be necessary to help the child manage her diet.

Difficulty in applying the diet. Foods for each meal have to be carefully weighed and the volume of liquid the child drinks each day must be carefully controlled. Some parents may find it impossible to adhere to such a strict regimen, particularly if they work or are away from home often. Short duration. The ketogenic diet can generally not be applied for longer than two years.

5.1.2 Lesionectomy - T2

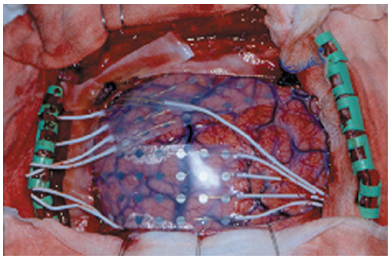
A lesionectomy is an operation to remove a lesion – a damaged or abnormally functioning area – in the brain. Brain lesions include tumors, scars from a head injury or infection, abnormal blood vessels, and hematomas (a swollen area filled with blood).

A lesion causes seizures – also called the seizure focus – in about 20 per centoo to 30 per centoo of people with epilepsy that do not improve after taking medication (intractable or refractory epilepsy). It is not known for certain if the lesion itself triggers the seizures, or if the seizures result from irritation to the brain tissue surrounding the lesion. For this reason, surgery may also include the removal of a small rim of brain tissue around the lesion, called lesionectomy plus corticectomy.

Lesionectomy may be an option for people whose epilepsy is linked to a defined lesion and whose seizures are not controlled by medication. In addition, it must be possible to remove the lesion and surrounding brain tissue without causing damage to areas of the brain responsible for vital functions, such as movement, sensation, language, and memory. There also must be a reasonable chance that the person will benefit from surgery.

Candidates for lesionectomy undergo an extensive pre-surgery evaluation-including seizure monitoring, electroencephalography (EEG) and magnetic resonance imaging (MRI). These tests help to pinpoint the location of the lesion and confirm that the lesion is the source of the seizures. Another test to assess electrical activity in the brain is EEG-video monitoring, in which video cameras are used to record seizures while the EEG monitors the brain's activity. In some cases, invasive monitoring – in which electrodes are placed inside the skull over a specific area of the brain – is also used to further identify the tissue responsible for seizures.

A lesionectomy requires exposing an area of the brain using a procedure called a craniotomy. ("Crani" refers to the skull and "otomy" means "to cut into.")



(a)

Figure 5.1: lesionectomy

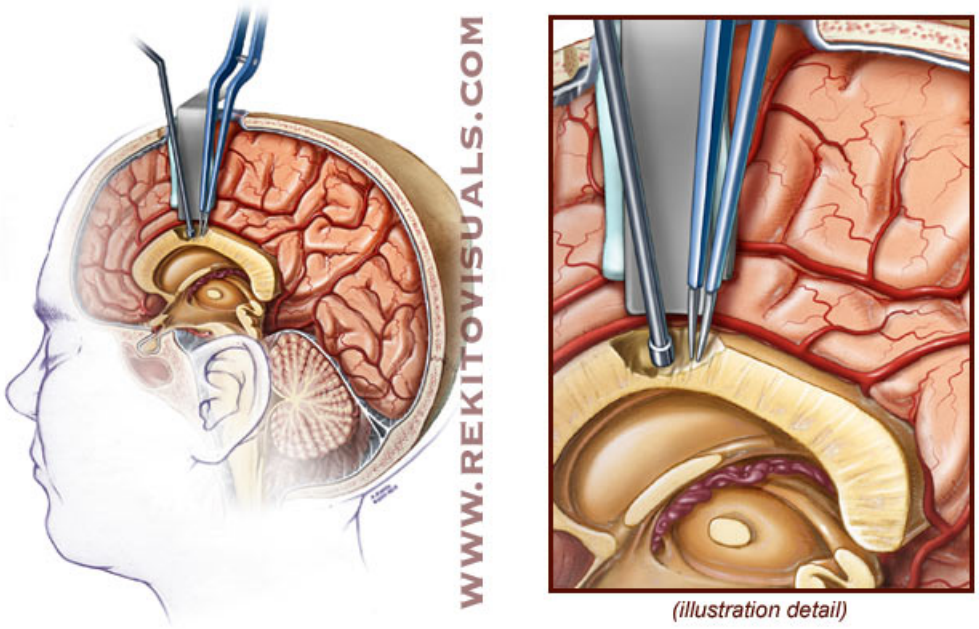
After the patient is put to sleep with general anesthesia, the surgeon makes an incision (cut) in the scalp, removes a piece of bone and pulls back a section of the dura, the tough membrane that covers the brain. This creates a "window" in which the surgeon inserts special instruments for removing the brain tissue. Surgical microscopes are used to give the surgeon a magnified view of the lesion and surrounding brain tissue. The surgeon utilizes information gathered during pre-surgical brain imaging to help identify abnormal brain tissue and avoid areas of the brain responsible for vital functions.

In some cases, a portion of the surgery is performed while the patient is awake, using medication to keep the person relaxed and pain-free. This is done so that the patient can help the surgeon find and avoid vital areas of the brain. While the patient is awake, the doctor uses special probes to stimulate different areas of the brain. At the same time, the patient is asked to count, identify pictures, or perform other tasks. The surgeon can then identify the area of the brain associated with each task. After the brain tissue is removed, the dura and bone are fixed back into place, and the scalp is closed using stitches or staples.

Lesionectomy results are excellent in patients whose seizures are clearly associated with a defined lesion. Seizures usually stop once the lesion is removed.

5.1.3 Corpus Callosotomy - T3

The corpus callosum is a band of nerve fibers located deep in the brain that connects the two halves (hemispheres) of the brain. It helps the hemispheres share



(a)

Figure 5.2: corpus callosotomy

information, but it also contributes to the spread of seizure impulses from one side of the brain to the other. A corpus callosotomy is an operation that severs (cuts) the corpus callosum, interrupting the spread of seizures from hemisphere to hemisphere. Seizures generally do not completely stop after this procedure (they continue on the side of the brain in which they originate). However, the seizures usually become less severe, as they cannot spread to the opposite side of the brain.

A corpus callosotomy, sometimes called split-brain surgery, may be performed in patients with the most extreme and uncontrollable forms of epilepsy, when frequent seizures affect both sides of the brain. A serious type of seizure – called a drop attack – often results in the person having sudden falls with a high risk of injury. In addition, people considered for corpus callosotomy do not experience improvement after receiving treatment with anti-seizure medications.

A corpus callosotomy requires exposing the brain using a procedure called a craniotomy. After the patient is put to sleep with anesthesia, the surgeon makes an incision (cut) in the scalp, removes a piece of bone and pulls back a section of

the dura, the tough membrane that covers the brain. This creates a "window" in which the surgeon inserts special instruments for disconnecting the corpus callosum. The surgeon gently separates the hemispheres to access the corpus callosum. Surgical microscopes are used to give the surgeon a magnified view of the brain structures.

In some cases, a corpus callosotomy is done in two stages. In the first operation, the front two-thirds of the structure is cut, but the back section is preserved. This allows the hemispheres to continue sharing visual information. If this does not control the serious seizures, the remainder of the corpus callosum can be cut in a second operation. After the corpus callosum is cut, the dura and bone are fixed back into place, and the scalp is closed using stitches or staples. The person will continue taking anti-seizure drugs.

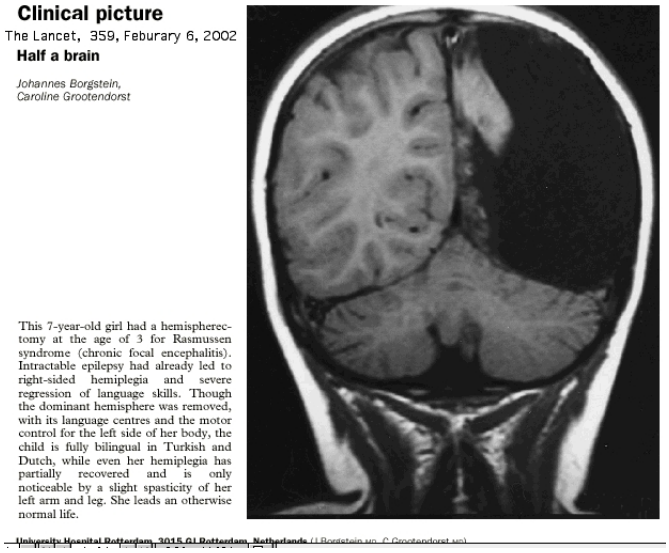
Corpus callosotomy is successful in stopping drop attacks in about 50 % to 75 % of cases. This can decrease the risk of injury and improve the person's quality of life.

5.1.4 Functional Hemispherectomy - T4

The largest part of the brain, the cerebrum, can be divided down the middle lengthwise into two halves, called hemispheres. A deep groove splits the left and right hemispheres, which communicate through a thick band of nerve fibers called the corpus callosum. Each hemisphere is further divided into four paired sections, called lobes – the frontal, parietal, occipital, and temporal lobes.

The two different sides or hemispheres are responsible for different types of thinking. Most individuals have a distinct preference for one of these styles of thinking and tend to have one side of the brain function much more than others. For example, left hemisphere thinkers are logical, analytical, objective, while right hemisphere thinkers are intuitive, creative, subjective, holistic thinkers.

A functional hemispherectomy is a procedure in which portions of one hemisphere – which is used the least – are removed, and the corpus callosum is cut.



Clinical picture

The Lancet, 359, Feburary 6, 2002

Half a brain

Johannes Borgstein, Caroline Grootendorst

This 7-year-old girl had a hemispherectomy at the age of 3 for Rasmussen syndrome (chronic focal encephalitis). Intractable epilepsy had already led to right-sided hemiplegia and severe regression of language skills. Though the dominant hemisphere was removed, with its language centres and the motor control for the left side of her body, the child is fully bilingual in Turkish and Dutch, while even her hemiplegia has partially recovered and is only noticeable by a slight spasticity of her left arm and leg. She leads an otherwise normal life.

(a)

Figure 5.3: functional hemispherectomy

This disconnects communication between the two hemispheres, preventing the spread of seizures to the functional side of the brain.

This procedure generally is used only for people with epilepsy who do not experience improvement in their condition after taking medication and who have severe, uncontrollable seizures beginning in a non-functioning hemisphere. This type of epilepsy often occurs in young children who have an underlying disease, such as Rasmussen's encephalitis or Sturge-Weber syndrome, which has damaged the hemisphere.

Candidates for functional hemispherectomy undergo an extensive pre-surgery evaluation – including seizure monitoring, electroencephalography (EEG), and magnetic resonance imaging (MRI). These tests help the doctor identify the damaged hemisphere and confirm it as the source of the seizures. An intracarotid amobarbital test, also called a WADA test, is done to determine which hemisphere is dominant for critical functions such as speech and memory. During this test, each hemisphere is alternately injected with a medication to put it to sleep. While one side is asleep, the awake side is tested for memory, speech, and ability to understanding speech.

A functional hemispherectomy requires exposing the brain using a procedure

called a craniotomy. "Crani" refers to the skull and "otomy" means "to cut into." After the patient is put to sleep (general anesthesia), the surgeon makes an incision (cut) in the scalp, removes a piece of bone and pulls back a section of the dura, the tough membrane that covers the brain. This creates a "window" in which the surgeon inserts special instruments for removing brain tissue. Surgical microscopes are utilized to give the surgeon a magnified view of the brain structures. During the procedure, the surgeon removes portions of the affected hemisphere, often taking all of the temporal lobe but leaving the frontal and parietal lobes. The surgeon also gently separates the hemispheres to access and cut the corpus callosum. After the tissue is removed, the dura and bone are fixed back into place, and the scalp is closed using stitches or staples.

Most patients will need to continue taking anti-seizure medication, although some may eventually be able to stop taking medication or have their dosages reduced.

About 85 % of people who have a functional hemispherectomy will experience significant improvement in their seizures, and about 60 % will become seizure-free. In many cases, especially in children, the remaining side of the brain takes over the tasks that were controlled by the section that was removed. This often improves a child's functioning and quality of life, as well as reduces or eliminates the seizures.

5.1.5 Multiple Subpial Transection - T5

Sometimes brain seizures begin in a vital area of the brain – for example, in areas that control movement, feeling, language, or memory. When this is the case, a relatively new epilepsy treatment called multiple subpial transection (MST) may be an option. MST stops the seizure impulses by cutting nerve fibers in the outer layers of the brain (gray matter), sparing the vital functions concentrated in the deeper layers of brain tissue (white matter).

Most people with epilepsy can control their seizures with medication. How-

ever, about 20 % of people with epilepsy do not improve with drugs. In some cases, surgery to remove the part of the brain causing the seizures may be recommended.

MST may be an option for people who do not respond to medication and whose seizures begin in areas of the brain that cannot be safely removed. In addition, there must be a reasonable chance that the person will benefit from surgery. MST may be done alone or with the removal of a section of brain tissue (resection). MST also may be used as a treatment for children with Landau-Kleffner syndrome (LKS), a rare childhood brain disorder which causes seizures and affects the parts of the brain that control speech and comprehension.

Candidates for MST undergo an extensive pre-surgery evaluation – including seizure monitoring, electroencephalography (EEG), magnetic resonance imaging (MRI), and positron emission tomography (PET). These tests help to pinpoint the area in the brain where the seizures occur and determine if surgery is feasible.

Another test to assess electrical activity in the brain is EEG-video monitoring, in which video cameras are used to record seizures as they occur, while the EEG monitors the brain's activity. In some cases, invasive monitoring – in which electrodes are placed inside the skull over a specific area of the brain – is also used to further identify the tissue responsible for seizures. What Happens During Multiple Subpial Transection?

MST requires exposing an area of the brain using a procedure called a craniotomy. ("Crani" refers to the skull and "otomy" means "to cut into.") After the patient is put to sleep with anesthesia, the surgeon makes an incision (cut) in the scalp, removes a piece of bone and pulls back a section of the dura, the tough membrane that covers the brain. This creates a "window" in which the surgeon inserts his or her surgical instruments. The surgeon utilizes information gathered during pre-surgical brain imaging to help identify the area of abnormal brain tissue and avoid areas of the brain responsible for vital functions.

Using a surgical microscope to produce a magnified view of the brain, the

surgeon makes a series of parallel, shallow cuts (transections) in gray matter, just below the pia mater (subpial), the delicate membrane that surrounds the brain (it lies beneath the dura). The cuts are made over the entire area identified as the source of the seizures. After the transactions are made, the dura and bone are fixed back into place, and the scalp is closed using stitches or staples.

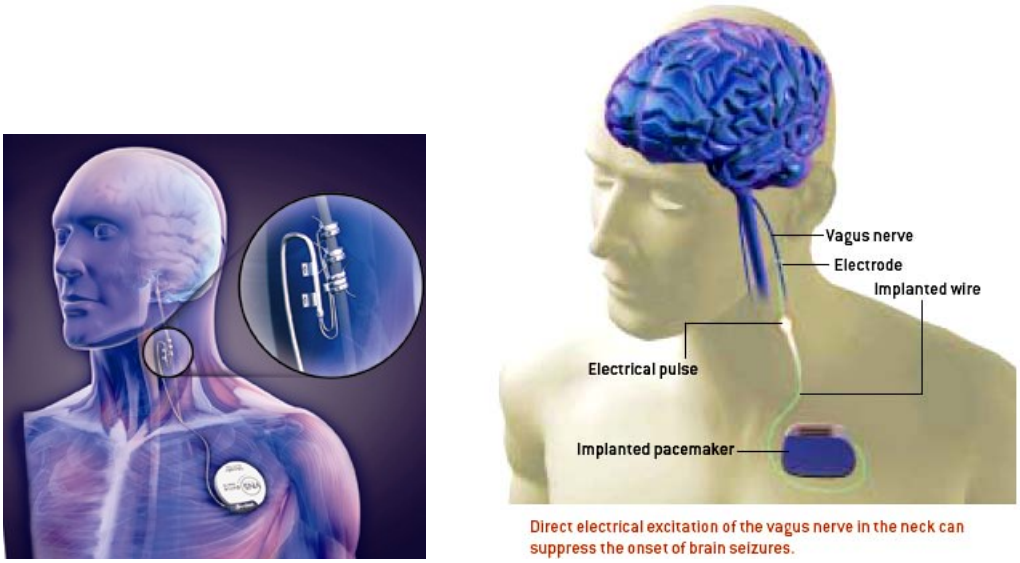
After MST, the patient generally stays in an intensive care unit for 24 to 48 hours and in a regular hospital room for three to four days. Most people who have MST will be able to return to their normal activities, including work or school, in six to eight weeks after surgery. Most patients will continue to take anti-seizure medication. Once seizure control is established, medications may be reduced or eliminated.

MST results in satisfactory improvement in seizure control in about 70% of patients, although the procedure is still relatively new, and no long-term outcome data are available. Children with LKS or other forms of epilepsy not controlled by medication may have improved intellectual and psychosocial functioning following MST.

5.1.6 Vagus Nerve Stimulation (VNS) - T6

Vagus nerve stimulation (VNS) is a technique used to treat epilepsy. It involves implanting a pacemaker-like device that generates pulses of electricity to stimulate the vagus nerve. The vagus nerve is one of the 12 cranial nerves, the paired nerves that attach to the undersurface of the brain and relay information to and from the brain. Cranial nerve fibers conduct impulses between the brain and other parts of the brain and various body structures, mostly in the head and neck. The vagus nerve - the longest of the cranial nerves - also extends to organs in the chest and abdomen. (The word vagus comes from a Latin word for "wandering.')

Some cranial nerves bring information from the senses (like touch or sight) to the brain (sensory) and some control muscles (motor). Other cranial nerves,



(a) (b)

Figure 5.4: vsn

like the vagus, have both motor and sensory functions. The vagus nerve serves many organs and structures, including the larynx (voice box), lungs, heart and gastrointestinal tract.

While the patient is asleep (general anesthesia), the stimulator device - which is about the size of a silver dollar - is surgically placed under the skin in the upper part of the chest. A connecting wire is run under the skin from the stimulator to an electrode that is attached to the vagus nerve, which is accessible through a small incision (cut) in the neck.

After it is implanted, the stimulator is programmed using a computer to generate pulses of electricity at regular intervals, depending on the patient's tolerance. For example, the device may be programmed to stimulate the nerve for 30 seconds every five minutes. The settings on the device are adjustable, and the electrical current is gradually increased as the patient's tolerance increases. Re-programming the stimulator can be done in the doctor's office. The patient also is given a hand-held magnet, which when brought near the stimulator, can generate an immediate current of electricity to stop a seizure in progress or reduce the severity of the seizure.

VNS is an add-on therapy, which means it is used in addition to another

type of treatment. Patients who undergo VNS continue to take their seizure medications. In some cases, however, it may be possible to reduce the dosage of medication.

Brain cells communicate by sending electrical signals in an orderly pattern. In people with epilepsy, this pattern is sometimes disrupted due either to an injury or the person's genetic make-up, causing brain cells to emit signals in an uncontrolled fashion. This creates over-excitement, somewhat like an electrical overload in the brain, leading to seizures. Seizures can be produced by electrical impulses from throughout the brain, called generalized seizures, or from a small area of the brain, called partial seizures.

Most people with epilepsy can control their seizures with medications called anti-convulsant or anti-seizure drugs. About 20 % of people with epilepsy do not respond to anti-seizure medications. In some cases, surgery to remove the part of the brain causing the seizures may be used. VNS may be a treatment option for people whose seizures are not controlled by anti-seizure medications and who are not considered good candidates for surgery; for example, if their seizures are produced throughout the brain (generalized).

It is not known exactly how VNS works. It is known, however, that the vagus nerve is an important pathway to the brain. It is thought that by stimulating the vagus nerve, electrical energy is discharged upward into a wide area of the brain, disrupting the abnormal brain activity responsible for seizures. Another theory suggests that stimulating the vagus nerve causes the release of special brain chemicals that decrease seizure activity.

The risks of VNS include injury to the vagus nerve or nearby blood vessels, including the carotid artery and jugular vein. In addition, there are risks associated with any surgical procedure, such as infection, bleeding and an allergic reaction to the anesthesia.

VNS is not a cure, and the total elimination of seizures is rare. However, many people who undergo VNS experience a significant (more than 50 %) reduction

in the frequency of seizures, as well as a decrease in seizure severity. This can greatly improve the quality of life for people with epilepsy.

5.1.7 Drug Theraphy

The majority of epileptic seizures are controlled through drug therapy, particularly anticonvulsant drugs. The type of treatment prescribed will depend on several factors including the frequency and severity of the seizures as well as the person's age, overall health, and medical history. An accurate diagnosis of the type of epilepsy is also critical to choosing the best treatment.

In general, for a given type of epilepsy there are only minor differences among appropriate drugs. The choice is most often based on other factors specific to each patient, such as which side effects can be tolerated by the patient, other illnesses they may have, and which delivery method is acceptable.

Although the different types of epilepsy vary greatly, in general, medications can control seizures in about 70% of patients.

As is true of all drugs, the drugs used to treat epilepsy have side effects. The occurrence of side effects depends on the dose, type of medication, and length of treatment. The side effects are usually more common with higher doses but tend to be less severe with time as the body adjusts to the medication. Anti-epileptic drugs are usually started at lower doses and increased gradually to make this adjustment easier.

5.2 Treatment Criteria

In order to mark out the effects and results of these treatments seven evalutation criteria were considered (*Table 6*)

	Criterion
C_1	efficacy
C_2	invasiviness
C_3	potential risks
C_4	side effects
C_5	hospitalization period
C_6	costs
C_7	remission period
C_8	decrease in medication
C_9	decrease in the number of seizures

Table 6 - Criteria considered for treatments evalutation

Indicative values have been used for test purpose.

	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9
T_1	7	2	2	4	2	2	?	5	6
T_2	6	8	8	7	6	10	8	5	5
T_3	5	7	8	7	6	10	7	5	6
T_4	7	9	9	9	6	10	8	5	5
T_5	6	6	7	7	6	10	8	5	5
T_6	6	5	6	5	4	6	5	5	4
T_7	5	3	3	6	3	5	?	10	6

Table 7 - Criteria values considered as Treatments matrix input

Chapter 6

Proposed approach for Risk-based MCDA for Epilepsy Death Risk Reduction

6.1 Methods

A *set of business line* is defined as $B = \{b_i\}_{i=1}^{K}$, where K is the number of business lines. In this case study we considered only treatments and diagnosis of the epilepsy, however an infinite number of business lines may be defined and considered at the same time.

A *set of resource types* is defined as $RT = \{rt_i\}_{i=1}^{H}$ where H is the number of resource types. In this case study we considered only cost and efficacy of treatments and diagnosis.

The *budget* can be written as $B = \{b_i\}_{i=1}^{H}$, where r_i is the quantity of resource type rt_i .

A *set of assets of business line* is defined as $A_i = \{a_{i,j}\}_{i=1,K;j=1,N_i}$, where N_i is the number of assets of business line i.

A *set of operational alternatives* for each asset j of business line i is defined as $O_{i,j,k} = \{O_{i,j,k}\}_{i=1,K;j=1,N_i;k=1,M_{i,j}}$ where $M_{i,j}$ is the number of operational

alternatives for each asset i of business line j.

The *cost* of each operational alternative k of asset j of business line i is the vector of resources required to implement each operation alternative.

The *cost* is defined as $C_{i,j,k,l} = \{C_{i,j,k,l}\}_{i=1,K;j=1,N_i;k=1,M_{i,j};l=1,H}$.

The *probability of failure of asset* (that represents the condition where epilepsy is not recognised or it is not treated with success) is the value from 0 to 1 which represents the risk associated with the status quo of each asset.

The *set of probabilities of failure of assets of business line* i is defined as $P_{i,j} = \{p_{i,j}\}_{i=1,K;j=1,N_i}$.

The *operational alternative coefficient* represents the influence of each operation alternative on the asset condition. Values of coefficient are from 0 to 1.

The *set of coefficient* is defined as $Q_{i,j,k} = \{q_{i,j,k}\}_{i=1,K;j=1,N_i;k=1,M_{i,j}}$.

The *operational alternative coefficient* is greater than or equal to zero and the probability of failure of each asset after applying the operation alternative is calculated based on initial condition of asset and on the operational alternative coefficient.

However, in the case of the operation alternatives disposition, the probability of failure of an asset after applying the operation alternative cannot be based on the initial condition of an asset. In that case the probability of failure is calculated considering a negative value of the operational alternative coefficient which means the complete loss of benefits.

The multicriteria decision analysis (MCDA) is the model adopted for the calculation of the Value to the Patient (VTP) of each asset. The criteria are built for each business line separately because each business line has its own benefits, in general, for the whole patients. In the MCDA a linear utility function is defined:

$$F_{utility}(x)\{1, x > x_{xmax};$$
$$\frac{x - x_{min}}{x_{max} - x_{min}}, x_{min} < x < x_{max};$$
$$0, x \leqslant x_{min}\}$$

(1)

where, x is the value of each criteria,and x_{min} and x_{max} are the lower and upper limits of each criteria respectively. The selection of lower and upper limits of the criteria scale requires a separate definition for each criterion. The value out the MCDA model for each operation alternatives of asset j of business line i is given by:

$$V_{i,j,k} = \{v_{i,j,k}\}_{i=1,K;j=1,N_i;k=1,M_{i,j}}, \omega_c$$

(2)

where $\omega_c = \omega_1, ..., \omega_Q$ are a set of weights that express the stakeHolders preferences for each benefit e of the business of the line.Thus, the value is the typical weighted sum out of multicriteria decision models. The Value to The Patien (VTP) is given by the expected value of the utility of each operation alternative for each asset. Thus, VTP is given by :

$$VTP_{i,j,k}\{(1 - v_{i,j,k})p_{i,j}, q_{i,j,k} \geq 0;$$
$$(1 - v_{i,j,k})q_{i,j,k} < 0\}$$

(3)

The above calculation of the VTP is based on the assumption of equivalence of the business line at the enterprise scale. Nonetheless the problem of management is a decision making problem ultimately. In fact, even with a quantitative model to asses the social, economical, and environmental benefits of assets it is impossible to asses importance of a business line vs the others on the same scale. It is case by case that stakeholders need to balance preferences and priorities. The case for $VTP_{i,j,k} < 0$ corresponds to the asset disposition in which

there is the complete loss of benefits. Therefore in order to consider different stakeholder's preferences, VTP can be calculated as

$$VTP^{\omega}_{i,j,k} = VTP_{i,j,k}\omega_i \tag{4}$$

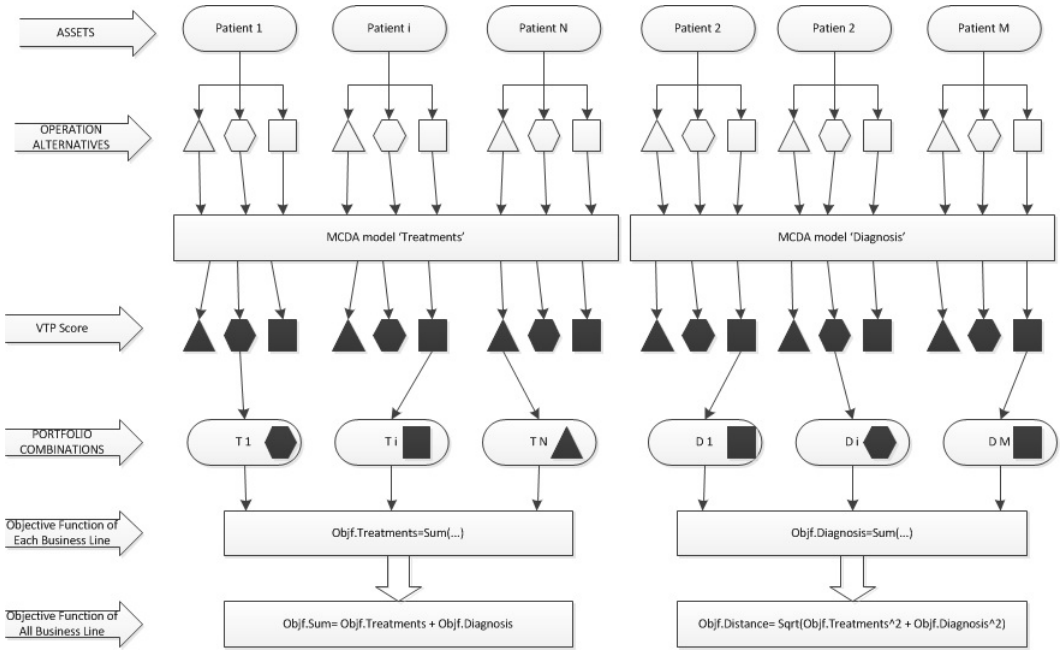


Figure 6: Risk-based Multi-Criteria Decision Analysis for Epilepsy Death Risk Reduction. The management model is universally applicable to any number of patients and illness types.

6.2 Portofolio Decision Model

A portfolio model was developed to select candidate sets of operational alternatives of which belong to multiple business lines that are "efficient" (also called "noninferior", "nondominated" or "Pareto optimal") in the sense that no other single portfolio of operational alternatives could yield an improvement in one objective without causing a degradation in at least one other objective. The objective is the maximization of the medical quality, which implicity includes multiple objectives that are the maximisation of the social, economical benefits,

and the minization of the probability of faliure. The number of portfolio cambinations is a product of the number of operation alternatives for all assets of busines lines:

$$T = \Pi_{i=1}^{K} \Pi_{j=1}^{N_i} M_{i,j} \tag{5}$$

for the set of possible cambination of operational alternatives $X = \{x_1, ..., x_T\}$ The portfolio cambinationis a vector which selects operation alternatives for all assets of all business lines, i.e. $X_t = \{x_{t,i,j}\}_{t=1,T;i=1,K;j=1,N_i}$.

The portfolio combination X_t constrained by the aviable resources is:

$$\Sigma_{i=1}^{K} \Sigma_{j=1}^{N_i} c_{i,j,x_{t,i,j,h}} \leq r_h \forall h \epsilon RT \tag{6}$$

where h represents the resource type. The objective function for multiple business lines according the "distance formulation" is

$$VTP(X_t) = \sqrt{\Sigma_{i=1}^{K} VTP(X_t, i)^2}$$

In the case of Pareto optimization unconstrained to the resources for maximization of $VTP(X_{t,i})$: if $VTP(X_{1,i}) \geq VTP(X_{2,i}), \forall i \epsilon \{1, K\}$ and $j \epsilon \{1, N_i\}$ if if $VTP(X_{1,j}) \geq VTP(X_{2,j})$ then the portfolio combination X_1 dominates X_2.

The Pareto optimization may also be performed conditional to two constraints: $VTP(X_t)$ at the enterprise level and $Cost(X_t, h)$ of resurce type h. Cost is defined as $Cost(X_t, h) = \Sigma_{i=1}^{K} \Sigma_{j=1}^{N_i} c_{i,j,x_{t,i,j,h}}$. In this case , if $VTP(X_1) \geq VTP(X_2)$ and $Cost(X_1, h) < Cost(X_2, h)$, then the portfolio combination X_1 dominates X_2.

Indicatively we chose to take into account three types of patient in different disease states

Assets		
Name	Probability of Failure	Description
Patience 1	0,95	
Patience 2	0,5	
Patience 3	0,1	

Operation Alternatives		
Name	Coefficient of Probability of Failure	Description
Eeg - Veeg	1	
MRI	1	
CT	1	
PET	1	
MEG	1	
Neuropsicological test	1	

Table 9: Three types of patient in different disease states and alternative diagnosis considered. We have chosen to give approximately the same probability of failure for each alternative.

Assets		
Name	Probability of Failure	Description
Patience 1	0,95	
Patience 2	0,5	
Patience 3	0,1	

Operation Alternatives		
Name	Coefficient of Probability of Failure	Description
ketogenic diet	1	
lesionectomy	1	
corpus callosotomy	1	
functional hemisphere	1	
multiple subpial transe	1	
vagus nerve stimulatio	1	
drug therapy	1	

Table 10: Three types of patient in different disease states and alternative treatments considered. We have chosen to give approximately the same probability of failure for each alternative.

Criteria			Sub-Criteria						
Name	Weight	Weight (Norm.)	Name	Maximize(1) / Minimize(0)	Weight	Weight (Norm.)	Lower Limit	Upper Limit	Unit
efficacy	10	0,357	efficacy	1	10	1,000	0	10	
potential risk	5	0,179	potential risk	0	5	1,000	0	10	
execution time	5	0,179	execution time	0	5	1,000	0	10	
diagnosis result time	8	0,286	diagnosis result time	1	8	1,000	0	10	

Table 11: Model for Diagnosis. The criteria represent the benefits of each business line. We assigned an approximate weight of each criterion according to importance.

Criteria			Sub-Criteria						
Name	Weight	Weight (Norm.)	Name	Maximize(1) / Minimize(0)	Weight	Weight (Norm.)	Lower Limit	Upper Limit	Unit
efficacy	10	0,185	efficacy	1	10	1,000	0	10	
invasiveness	7	0,130	invasiveness	1	7	1,000	0	10	
potential risk	9	0,167	potential risk	0	9	1,000	0	10	
side effects	2	0,037	side effects	0	2	1,000	0	10	
hospitalization period	6	0,111	hospitalization period	0	6	1,000	0	10	
remission period	5	0,093	remission period	0	5	1,000	0	10	
medication degree	7	0,130	medication degree	0	7	1,000	0	10	
number of seizures	8	0,148	number of seizures	0	8	1,000	0	10	

Table 12: Model for Treatments. The criteria represent the benefits of each business line. We assigned an approximate weight of each criterion according to importance.

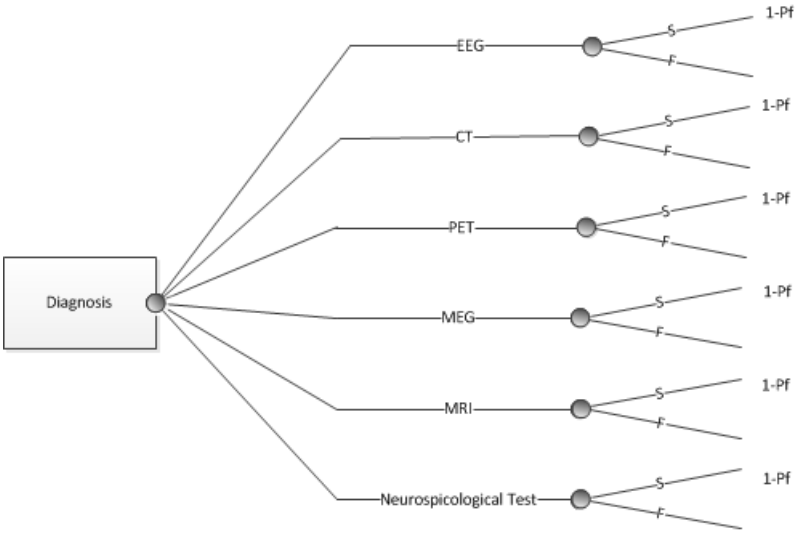


Figure 6.1: *Decision trees for the diagnosis management problem. The decision is represented by the node. The expected value to the patient (VTP) is calculated for each "success" branch after the chance node . The coefficient of criticality of each management alternative (that multiplies the probability of failure) is proportional to the ability of each alternative to increase the functionality of an asset.*

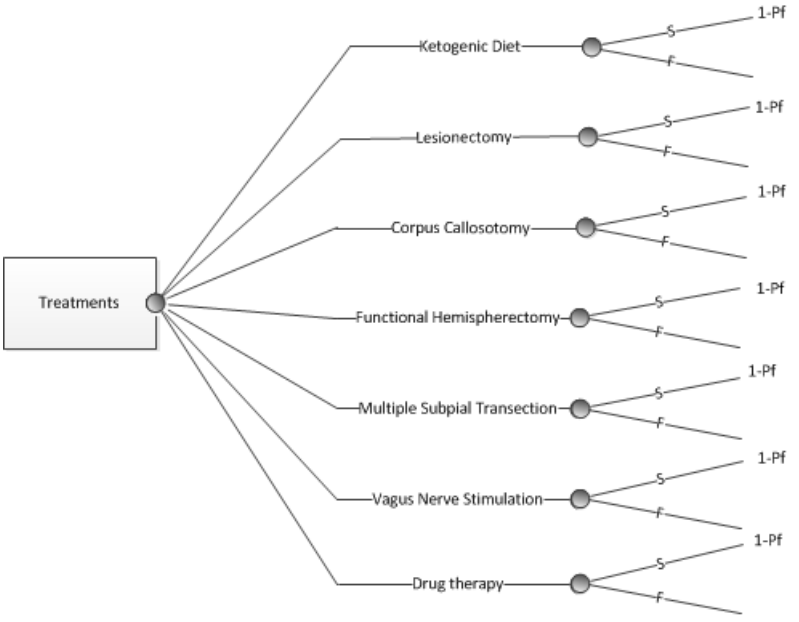


Figure 6.2: *Decision trees for the Treatments management problem. The decision is represented by the node. The expected value to the patient (VTP) is calculated for each "success" branch after the chance node . the coefficient of criticality of each management alternative (that multiplies the probability of failure) is proportional to the ability of each alternative to increase the functionality of an asset.*

Chapter 7

Results

Graph 1,2 reports the outputs of the portfolio decision model that is schematically represented in Figure 6. The model is composed by a multicriteria decision model out of which values of benefits of each assets are determined. The benefits are weighted by the stakeholders preferences (Eq. 2). The expected Value to The Patient is then obtained as the product of the MCDA value and the complementary of the expected probability of failure (Eq. 3). It is important to emphasize the concept of expected value and of expected probability since the estimated quantity are not the true values that are observed in reality but just best estimation of the assets' value and criticality. In this paper we provide a case study with the test data, however a real estimation would be required.

Run Portfolio (Logs)	Maximize(1)/Minimize(0)	Resource name	Cost
Run Portfolio (Charts & Logs)	Objective Function	Available	20
	1		
Asset	**Operation Alternative**	**Score**	
Patience 1	Eeg - Veeg	0,65821	2
Patience 1	MRI	0,59036	7
Patience 1	CT	0,53946	6
Patience 1	PET	0,57339	8
Patience 1	MEG	0,73286	5
Patience 1	Neuropsicological test	0,47839	3
Patience 2	Eeg - Veeg	0,34643	2
Patience 2	MRI	0,31071	7
Patience 2	CT	0,28393	6
Patience 2	PET	0,30179	8
Patience 2	MEG	0,385714286	5
Patience 2	Neuropsicological test	0,251785714	3
Patience 3	Eeg - Veeg	0,069285714	2
Patience 3	MRI	0,062142857	7
Patience 3	CT	0,056785714	6
Patience 3	PET	0,060357143	8
Patience 3	MEG	0,077142857	5
Patience 3	Neuropsicological test	0,050357143	3

Table 13: Diagnosis VTP scores set on the Pareto frontier constrained to the

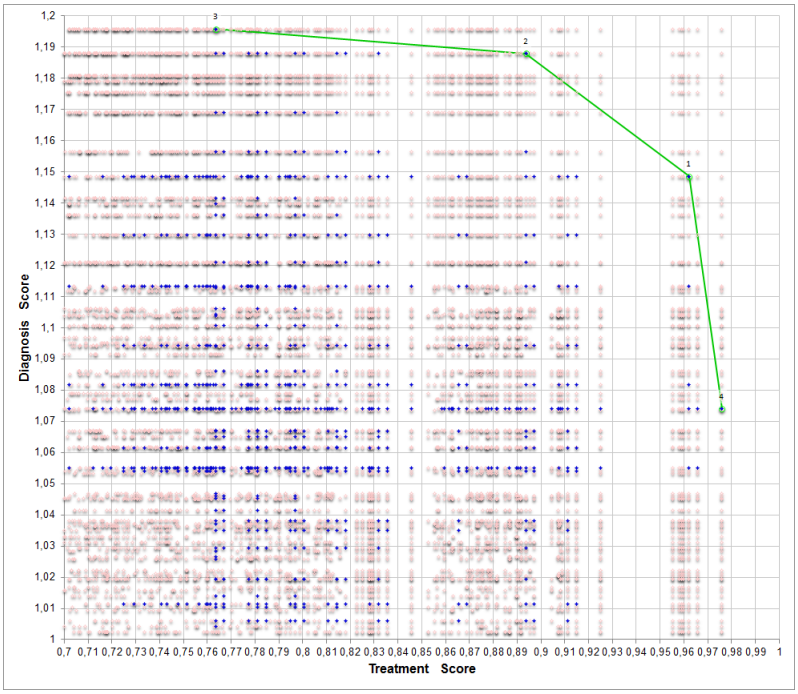
resource available (cost=20).

Run Portfolio (Logs)	Maximize(1)/Minimize(0)	Resource name	Cost
Run Portfolio (Charts & Logs)	Objective Function	Available	20
	1		
Asset	**Operation Alternative**	**Score**	
Patience 1	ketogenic diet	0,59815	8
Patience 1	lesionectomy	0,43806	10
Patience 1	corpus callosotomy	0,40287	10
Patience 1	functional hemispherectomy	0,44509	10
Patience 1	multiple subpial transection	0,42926	10
Patience 1	vagus nerve stimulation	0,50139	6
Patience 1	drug therapy	0,46796	5
Patience 2	ketogenic diet	0,31481	8
Patience 2	lesionectomy	0,23056	10
Patience 2	corpus callosotomy	0,21204	10
Patience 2	functional hemispherectomy	0,234259259	10
Patience 2	multiple subpial transection	0,225925926	10
Patience 2	vagus nerve stimulation	0,263888889	6
Patience 2	drug therapy	0,246296296	5
Patience 3	ketogenic diet	0,062962963	8
Patience 3	lesionectomy	0,046111111	10
Patience 3	corpus callosotomy	0,042407407	10
Patience 3	functional hemispherectomy	0,046851852	10
Patience 3	multiple subpial transection	0,045185185	10
Patience 3	vagus nerve stimulation	0,052777778	6
Patience 3	drug therapy	0,049259259	5

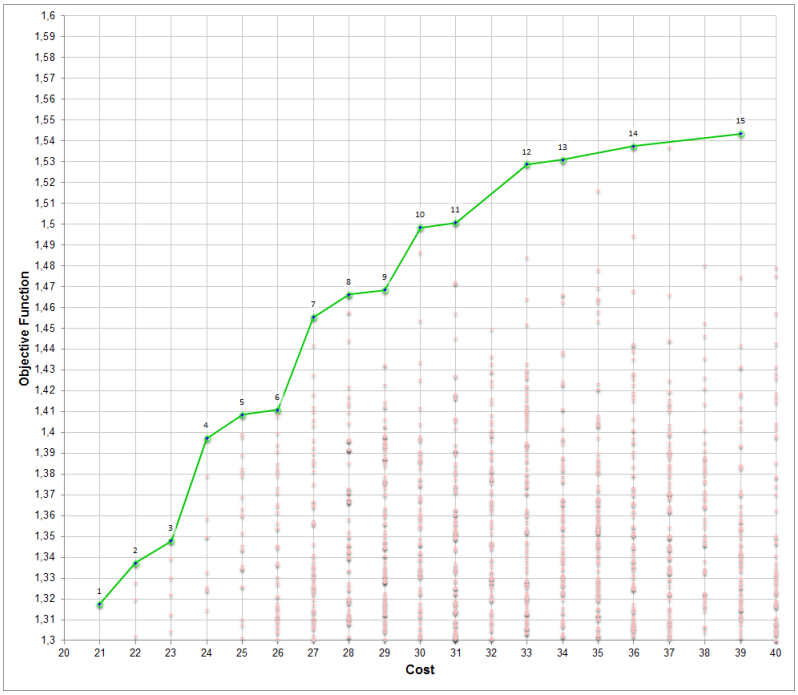
Table 14: Treatments VTP scores set on the Pareto frontier constrained to the resource available (cost=20).

		Maximize	Resource name	Cost
		Objective Function	Available	30
	Log ID: 1665	***1,49836***	***Needs***	***30***
data update	**Asset**	**Operation Alternative**	**Score**	
Treatment	Patience 1	ketogenic diet	0,598148148	8
Treatment	Patience 2	ketogenic diet	0,314814815	8
Treatment	Patience 3	drug therapy	0,049259259	5
Diagnosis	Patience 1	MEG	0,732857143	5
Diagnosis	Patience 2	Eeg - Veeg	0,346428571	2
Diagnosis	Patience 3	Eeg - Veeg	0,069285714	2

Table 15: Final Results VTP scores



Graphic 1: Output of the management model. (a) Pareto frontier (green curve), the blue and red dots represent affordable and unaffordable combinations of management alternative of assets.



Graphic 2:Outputs of the management model.Objective function proportional to the expected value to the patient, and unconstrained to the resources available. The green curve is the Pareto frontier unconstrained to the resources.

Chapter 8

Conclusions

A portfolio model was developed to create an optimal budget allocation framework for operation alternatives of assets of multiple business lines as a function of assets criticality and social, economical and environmental benefits. The model is composed by a multicriteria decision model and by a Pareto optimization component. Due to the many uncertainties in the parameters of the model, the presented model can be used only in a indicative mode, and further development is needed to finalize criteria and weights. Nonetheless we envision that the formulation of criteria and weights is a more subjective calibration step to be evaluated case by case. The inclusion of asset interdependencies, the adoption of a probabilistic framework for criteria and weights, the representation of better failure probabilities, the inclusion of patients stressors, and the adoption of better utility functions are more important ingredients of the portfolio model that will be addressed in the future. It is worth pointing out:

- The portfolio decision model allows to optimally prioritize a criteria such as efficacy and cost, considering their benefits ("triple bottom line" framework), their criticality, and the future alternatives development. The Value of The Patient is defined as an integrated measure for characterizing each asset in an "integrated top-down" purview that. All the assets are considered together according their VTP and a Pareto efficient frontier is found

to detect the optimal sets that maximize VTP for a given cost;

- The model can be an optimal tool for expenditures management for hospitals, patients and financial companies with the possibility of prioritizes at some criteria than others. The Portfolio solution can be applied in different medical environment and can be associated with a hospitals patients database with the final goal to eliminate the waste and optimize the sanitary system. The model is also flexible to consider stakeholder preferences variations of criteria or of business lines.

- The portfolio model potentially solves any diseases management problem considering every asset together at the patient criticity.

- The model may be easily extended outside the boundaries of a epilepsy diagnosis and treatments and it can constitute a tool for the prioritization of multiple heterogenous business lines of an ecosystem.

- The portfolio model combines toghether several type of dignosi and treatments, with patient state and budget available, maximizing benefits and minimizing risks in a sustainable perspective of illness.

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a coloro che ancora mi sono vicini