Eleos Project
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Executive Summary

We are trying to determine whether a transplanted kidney is functional or if the kidney has failed during transplant utilizing a software analysis technique. It is interesting because we are creating a new technique that has never been used before. Additionally, this technique is significantly more accurate in that the entire kidney functionality can be tested instead of traditional methods which are only capable of testing isolated areas. We chose to utilize a software analysis approach because this method is non-invasive and can provide a fast, accurate and easy to use implementation for surgeons and technicians to use.

We will validate our design by testing it on both high and low quality images on a variety of pre-determined kidneys as the image quality posed a problem during very early tests. We will compare our results to traditional methods as well. We will also compare our results to actual pre-determined results to verify accuracy that traditional methods may have mis-determined.

Our work will continue so that we can make the software more accurate and more flexible for usage. We would also like the software to be capable of generating more viable and educated analysis of the kidney. We would also like it to be able to perform statistical analysis at various stages during kidney functionality in a future study.

Abstract

A great deal of background information was researched and compiled before beginning work on the project. Specifically, we were interested in kidney transplantation statistics as well as the anatomy and physiology of the kidney and this information would be a valuable resource for the development team, and for presentation of the product to the community.

In the transplantation statistics research, we determined the number of patients that our project would affect. We also gained some insight as to how our product changes the current regimen of post operative care. The statistical data was also used later on in economic analysis, determining the market size and potential growth.

We began the anatomy and physiology research to validate our method of kidney acceptance/rejection detection. A clear understanding of interrelated kidney structure and function were essential to using software to properly interact with the MRI kidney images.

This background information shows a large patient population and clear need for our project. Additionally, anatomical and physiological research shows that our detection theories are valid and implementable with MRI imaging capabilities

Introduction to Renal Transplantation

Renal (kidney) transplantation is a life saving technique for patients with a variety of end stage kidney diseases. 26 million Americans are affected by and 20 million more are at high risk for Chronic Kidney Disease (CKD), which includes any conditions that damage the kidneys and decrease their ability to perform essential tasks for the body. Early detection and treatment of CKD can stop or slow the progression of the disease. But, once it has progressed to end stage kidney failure, dialysis or transplant are the only options to maintain life[1].

The current waiting list for a kidney includes 77,698 patients, which make up 79% of all organ waiting lists. Each year over 30,000 patients are added to the waiting list for kidney transplants and over 16,000 procedures are performed. Almost 260,000 have been performed since The Organ Procurement and Transplant Network (OPTN) began keeping records in 1988, making the kidney the most commonly transplanted organ. The second most is the liver with about 6,000 transplants performed each year[2]. Similarly, in the UK, 1548 kidney transplants were performed each year and 368 were rejected and required removal[3]. Statistics for the European Union as a whole could not be found.

Unlike other transplantable organs, a kidney can be donated by a living donor with little or no effect on the donor's own excretory system function as long as the second kidney remains well and functional. This contributes to the relatively high numbers of kidney transplants, as living donors account annually for about 6,000 of the 16,000 procedures. Relatives or close genetic matches to the host can be selected, which increases the donor organ's compatibility with the host; transplants from living donors have a 9% higher survival rate than those from deceased donors[2].

Acute rejection occurs in 20% of kidney transplant patients and can result in injury to the organ or Chronic Allograft Neuropathy (CAN) if left untreated. It is characterized by an influx of cytotoxic cells to the area and is typically a humoral response. A regiment of high steroid pulses is used to treat acute rejection with an 85% success rate. Less than 5% of organ recipients end up losing their transplant due to acute rejection[4].

Chronic rejection, generally called Chronic Allograft Nephropathy, is the progressive decline of renal function over time and characterized by various histological features as well as hypertension and proteinuria. It is thought to be a primarily humoral mediated response to the transplant and may be detected 6 months post-transplant or later. Treatment is usually ineffective thus removal of the organ is required[4]. At this point, a second transplant or continued dialysis are the only options available to the patient. Of the transplant procedures performed each year, about 1,600 or 12% are repeat procedures to replace a rejected or failing donor kidney. These procedures have virtually the same survival rates as primary transplants at 1 (96%), 3 (91%), and 5 (85%) years[2]. This shows the efficacy of a repeat transplantation procedure if one is needed and the importance of monitoring renal function post-operation.

In a human being the kidneys are generally located in the lower portion of the abdominal cavity. Most humans have two kidneys. Both kidneys are situated slightly below the diaphragm[5]. The right kidney is positioned posterior to the liver while the left is posterior to the spleen. Due to the large size of the liver as compared to other abdominal organs, the right kidney is slightly lower and located in a more medial position then the left kidney[5]. Above each kidney is located a suprarenal gland.

A kidney generally ranges in size from 9 to 13 cm in diameter and typically the left kidney is larger than the right[6]. On their upper portions, the kidneys are protected by the eleventh and twelfth ribs. Additionally each kidney is entirely surrounded by two layers of fat, the perirenal and pararenal layers and the renal fascia. The renal fascia is a fibrous tissue that additionally helps to cushion the kidney. A condition in which one or both kidneys are absent is known as renal agenesis[7].

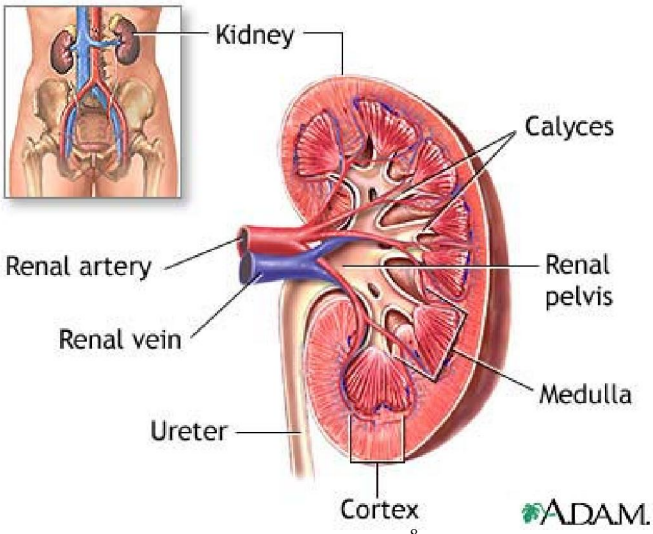


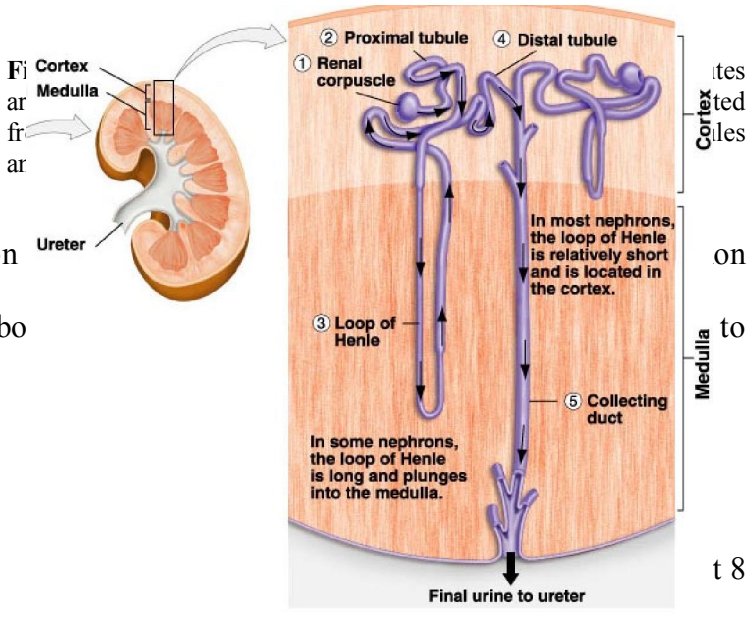
Figure 1: Anatomy of a human kidney[8].

A kidney, simplified, is divided into two functioning locations, the parenchyma and the renal pelvis[7]. The parenchyma, the solid body of the kidney, is the primary processing area for kidney filtration. The renal pelvis is responsible for the controlling the flow of waste and blood in and out of the kidney. The entire kidney is covered in a tough, dense, fibrous covering known as a capsule.

The parenchyma accounts for the solid functioning body of the kidney. This includes the cortex, medulla and calyx. The cortex is the outermost layer of the parenchyma and is primarily constructed of connective tissues[5]. The medulla is the largest portion of the parenchyma and contains the majority of the filtering structures. Henle's loops and pyramids of converging tubules can both be found within the medulla[6]. The calyx is the collecting duct for urine excretions in the parenchyma. This urine is then passed to the renal pelvis.

The renal pelvis is the central collection system for the kidney. The kidneys receive unfiltered blood through the abdominal aorta, which connects to the renal artery. The renal artery and vein connect to the pelvis of the kidney and are responsible for bringing allowing un-filtered blood into the kidney and removing filtered blood from the kidney, respectively. The filtered blood is then returned to the heart via the inferior vena cava. The junction where the renal pelvis, artery and vein all come together is referred to as the hilum. The ureter joins to the renal pelvis on the lower side to transfer waste urine from the kidney to the bladder. Renal blood flow can make up as much as one-third of the bodies entire blood supply[5,9].

The main functions of the kidneys are to filter waste from the blood and to regulate water supply. They remove the waste and excess water by producing urine, which is passed to the bladder and released when urinating[10]. Roughly 50 gallons of blood are filtered each day, removing a half gallon



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communicate with other organs of the body to maintain homeostasis through the regulation of acid-base balances, electrolytes, blood pressure, and plasma volume[8].

Waste removal and water regulation are performed through three mechanisms: filtration, reabsorption, and secretion. The mechanisms are all performed in the nephrons. There are roughly one million nephrons in each kidney[10]. The nephron is divided into three components: the renal corpuscle, the loop of Henle, and collecting ducts[12,13].

Blood enters the kidneys through the renal artery. The artery branches into smaller vessels called arterioles. These vessels carry the blood through the renal corpuscle, which is located in the cortex of the kidney[13,14,15]. The renal corpuscle is comprised of a glomerulus and a Bowman's capsule. The blood enters the glomerulus capillaries and the filtrates are collected in the Bowman's capsule in a high-pressure gradient process known as ultrafiltration. The contaminants collected during ultrafiltration are processed further along the nephron to form urine[12,13].

After filtration, the urine created is passed through the loop of Henle[14]. It is here that water, sodium, potassium, and other chemicals are reabsorbed from the urine back into the blood[12,13]. What is left in the urine is passed through a series of collecting ducts in the medulla and passed through the ureters to the bladder. At the same time as reabsorption is occurring, smaller particles are secreted from the blood into the tubules by active transport. Very few substances are secreted from the blood, but the concentrations of these are too large and must be lowered[13].

Through these mechanical methods, the kidneys regulate which chemicals and substances, and the concentrations of them, that should be present in the blood and

remove the excess in order to maintain a healthy body and degree of homeostasis. The "dirty" blood enters through the renal artery and the "clean" blood, with the proper levels of key chemicals and water, is returned to the body through the inferior vena cava. It is because of the importance to clean the blood that these mechanisms are so vital to a healthy body. Kidney failure is a major concern that should desperately be addressed through the advancement of medical technology to increase the quality of life for those suffering from it.

Design Strategy

We opted to approach a solution by breaking the task into smaller parts and having the program accomplish a series of phases in a linear order. Each phase is broken down into sub-phases that each has its own unique set of functions. Note that some of the more generic functions are used by multiple phases to compact code.

The first phase of the approach is the kidney isolation phase. This phase can be broken into three sub-phases, the region-of-interest sub-phase, the active contour sub-phase and the layer isolation sub-phase.

Once the software receives an image (this is a component of the GUI and is not accounted for as being a function of the main processing phases) it enters the region-of-interest sub-phase. In this sub-phase the user is prompted to click a "box" of infinite points around the general kidney location. This serves two purposes. It allows a vague area of the kidney to be removed from an overall MRI image making the processing matrix (size of the image) significantly smaller. It also greatly increases the possibility of the program correctly isolating the kidney. Upon receiving user confirmation of a region-of-interest being selected the program will send the sub-image (the smaller extracted image with the kidney inside) to the active contour sub-phase.

The active contour sub-phase works in two steps and within the final build is actually coupled with the layer isolation sub-phase although they are in fact fully separate functions. The active contour sub-phase begins by determining the overall energy of the image. It then performs an active contour using only "outer" energy to move the boundaries in on the kidney. An outer energy active contour functions by comparing the energy of the current pixel to the energy of the surrounding pixels. If a surrounding pixel

has a higher energy then the boundary "steps" inward. The program utilizes this to extract all images in the shape with a comparative energy to the kidney itself. While this method will reliably extract the kidney it will also extract small regions that are similar to the kidney. Once all regions are extracted the regions are passed to the layer isolation sub-phase.

In the layer isolation sub-phase the kidney is extracted from the total regions that are determined by the active contour sub-phase. To accomplish this task the layers are highlighted as being white and non layers are deemed black. The software then begins to locate white pixels. Once a white pixel is found the software extracts all contiguous white pixels to the point of origin. It writes these as a new image layer. The software proceeds to step through the image until all regions have been accounted for. Based on sub-phase one, the region-of-interest sub-phase, it is safe to assume that the largest extracted region will always be the kidney. The code proceeds by determining which layer is the largest and returning this layer as the "kidney mask". Following phases will be able to utilize this mask to extract the actual kidney energy.

The second phase is the energy calculation phase and can be broken down into two main sub-phases, the energy extraction sub-phase and the energy analysis sub-phase. This phase is significantly less intensive than the first phase. The energy extraction sub-phase functions by removing the original kidney from an MRI image utilizing the kidney mask created in phase one. This extracted kidney is then sent to the energy analysis sub-phase. In this sub-phase the overall energy of the kidney is determined and average over a time interval (specified in the GUI). The phase continues to map a curve to the energy values so that the activity of the kidney can be plotted on a graph.

Function Design

The following pages discuss the individual functions used by the Eleos System divided into the appropriate phases. Note that some phases may utilize functions that have been pre-defined in a previous phase. Functions are listed in the phase where they are primarily used.

Phase One

Region-of-interest Sub-phase

regionParseGUI.m – *Region-of-interest selection utility for use in GUI based environment.*

regionParseROI.m - *Region-of-interest selection utility for use in non-GUI based environment.*

Active Contour Sub-phase

regionGrowing.m – *Active contour function based on external energy active contours originating from four points of origin.*

regionFilter.m – *Multiple pass simple filter for 2D images.*

regionAverage.m – *Averaging function that excludes black pixels and only averages pixels with energy above a specified value.*

Layer Isolation Sub-phase

regionIsolate.m – *Layer isolation function that is responsible for determining layer locations in an image and sorting them into appropriate layers; also responsible for determining the largest layer in the image.*

regionGrowingSeed.m – *Active contour function based on internal energy active contours originating from one point of origin. Used by regionIsolate.m.*

Phase Two

Energy Extraction Sub-phase

regionParse.m – *Utilizes a kidney mask to extract a kidney containing energy from an MRI image.*

regionParseBatch.m – *Code to repeatedly call regionParse based on pre-specified static parameters.*

regionParseBatchArray.m - *Code to repeatedly call regionParse based on pre-specified dynamic parameters.*

Energy Analysis Sub-phase

regionAverageBatch.m - *Code to repeatedly call regionAverage based on pre-specified static parameters.*

extrapolateArray.m – *Code to expand a 1D matrix across a specified time intervals.*

extrapolateArrayFilter.m - *Code to expand a 1D matrix across a specified time intervals and apply a simple filter to the data for visual smoothing purposes.*

**Files related to the GUI or auxiliary visual files are not listed in these functions as these are extraneous to the actual methodology behind the processing and do not directly impact the processing methods.

Economic Analysis

Introduction

Our software will analyze data from MRI images to determine the functionality of a transplanted kidney, thus replacing the current biopsy and blood test techniques. In determining the economic impact of our product, we first compared the cost of an MRI to biopsy and blood tests. Then we took into account the decrease in suffering and quicker recovery time of the patient into consideration. Finally, we estimated the market size for our product.

Cost Comparison

Credible sources for biopsy and blood work pricing were hard to find, best estimates place the total cost of a kidney biopsy from $200-$1000, and blood work somewhere in that range as well. Prices depend greatly on the facility, and what tests are being done (determined by doctor opinion and patient condition). MRI scans cost from $400-$2000+[1]. Our software fees would be incorporated into this cost as described below in "market size". Assuming these ranges are consistent and less MRI scans would be needed than biopsy and blood testing, we believe patients will break even on the cost of the diagnostic procedure with our product as opposed to current methods.

Kidney transplantation costs vary widely, depending somewhat on the facility that performs the procedure but mostly on complications that the patient encounters and how well the new kidney is integrated into the host.

Kidney transplant costs	
Surgical Procedure and Hospital Stay	$25,000 - $150,000[2]
Anti-rejection medications	$700 - $2,000 per month[2]

Average one year cost (procedure, medications, tests)	$116,100[3]
Estimated Average Annual Medication cost	$16,000 per year[2]

This is obviously a large spectrum. Complications requiring extended hospitalization are responsible for driving the initial cost from $25,000 up to $100,000 and beyond. Also, the more smoothly the new kidney integrates into the host, the less medication will be required. We expect that our product will be able to significantly lower the average costs of kidney transplantation by giving the doctors more accurate and quickly obtainable information on the condition of the implant without further injury to the patient. Thus the doctors will be able to quickly and more effectively treat any problems that arise, resulting in shorter hospital stays and fewer medications needed long term.

Market Size

Today, over 16,000 kidney transplants are performed each year[4] at 245 transplant centers registered with the United Network for Organ Sharing (UNOS)[5]. If our product can decrease the average cost of the procedure by just 10%, almost $200 million would be saved each year.

Also of note, kidney dialysis (the only alternative to transplant) costs about $44,000/year[6]. This quickly becomes more expensive than a transplant procedure plus medications. By increasing the efficiency of the transplant procedure, our product could make more transplants possible, thus improving quality of life for more patients and saving them money.

Of the 245 transplant centers, we expect to be able to sell our product to all of them. Some may need multiple licenses. Price would have to be determined by the cost of getting the product approved, which is probably the most significant cost that our project faces.

Conclusions

Our economic analysis has determined that our product will cost approximately the same as current methods but will the benefits of more accurate information, and no harm to the recovering patient. Our costs include the product development, testing and approval as well as licensing and distribution. These can easily be recovered with the $200 million plus market that exists in this field.

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