The design of the optical touch pointer system for brain tumor resections

The electrical system design

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Abstract

Glioblastoma multiforme (GBM) is the most common and aggressive form of brain malignancy. The morphological similarities of the malignant and the surrounding tissue cause difficulties in distinguishing the tumors during surgery. Improved methods for precise tumor resection have long been investigated, with the aim to improve the results in resecting malignant brain tumors.

Real time diagnostics is obviously crucial for assisting neurosurgical tumor resection. An optical fiber based system is developed in this project. For this electronics is developed for amplifying the weak photocurrent from the photon detectors, modulating the light sources and supplying power for all the parts of the system. The electronics is controlled by LabView® (National Instruments) program. This Labview program also performs signal processing for extracting the diagnostic information from the detected light intensity signals.
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Chapter 1. Introduction

1 Background

In modern society, glioblastoma multiforme (GBM) is the most common brain tumors. GBM is aggressive and highly malignant. GBM is considered to be one of the most dangerous malignant tumors. Patients with GBM normally have very slim chances for long term survival and short survival periods even with the best available care.

Due to GBM’s infiltrative way of growing and the morphological similarities with surrounding tissue, the challenge in surgery of GBM is to resect the tumor in an optimal way. Accurate tumor resection will help to keep the proper function of the brain after surgery, and at the same time help getting the best surgical result [1].

Proper surgical resection appears to help extending the patients’ surviving time after surgery significantly. Although the least requirement for surgical resection of the tumor is 89%, over 98% resection of the tumor volume was proved further significantly better than less resection [2].

Many methods have been developed for assisting the tumor delineation during surgery. These methods are based on, for instance, intraoperative ultrasound, MR images, Raman spectroscopy, scattering spectroscopy (e.g. time-resolved spectroscopy) and autoflourence induced by UV-blue light (e.g. 366 nm and 405 nm) [3][4][5][6]. All the methods mentioned
above come with certain limitations. The most popular method nowadays is the fluorescence photodynamic diagnostics (PDD).

PDD uses the introduction of certain photoactive drugs used as contrast agents, e.g. HPD (hematoporphyrin derivative), ALA (5-aminolevulinic acid), Chlorins and Phtalocyanine [7][8]. Fluorescence spectroscopy technology can help to process fast, efficient and safe resections in various organs in vivo.
2 Purposes and objectives

The main purpose of this thesis project is to improve the performances of the OTP instrument created previously in a collaboration between Lund and Linköping Universities.

The OTP system has proved to serve well for tumor resection, while it cannot suppress the influences from the ambient light sources sufficiently in some cases. Some additional challenges also emerged with this instrument.

1. The size of the system is larger than preferable. The system is not sufficiently compact.
2. The system only provides slow data acquisition speed. Long integration time may, in addition, also lead to strong photobleaching of PpIX (protoporphyrin IX). This can slow down the surgery process and provide inaccurate results.
3. The data analysis of the spectrum results is not in real time.
4. In order to power the system and to run the spectrometer in the system, two computer programs have to be controlled simultaneously. Both of the programs have somewhat complicated control procedures.

In order to meet these challenges, we started to work on developing a new system. The new system should still be based on detecting the 5-ALA induced PpIX fluorescence. At the same time, it should be more compact, faster and easier to
handle. It should also be safe, accurate and insensitive to ambient light.

The purposes of this thesis project are:
1. Build a system in a box from all necessary optical components.
2. Build the electronics to operate the photonelectronic elements.
3. Test the possibility of detecting light signal under weak fluorescence light conditions with the new system.
4. Design a Labview Program for controlling the system and handling real time data processing.
5. Calibrate the system for future studies.
3 Fluorescence

The fluorescence signals considered in this project is tissue auto-fluorescence and PpIX fluorescence. Autofluorescence is generated from certain organic molecules existing in all tissue structures, while PpIX fluorescence is generated from concentrated PpIX fluorophores in tumor cells. The characteristic spectral emission peaks of these two types of fluorophores are located at different wavelengths, which makes it possible to distinguish the PpIX - rich tumor cells from normal tissue cells.

Autofluorescence

Autofluorescence is the phenomenon observable when UV/blue light illuminates the tissue surface, the tissue will then fluoresce in the blue - green spectral region. This tissue property is commonly used for tissue diagnostics in addition to the use of exogenous fluorophores [10].

The concentration of several endogenous fluorophores (including different structured proteins, flavins and porphyrins) vary a lot for different cells. Thus the fluorescence spectra from different tissues can be employed to characterize the tissue types [11]. Tumor vascularization leads to extra blood content in the tissue, reabsorbing large amounts of light and thus causing a decrease of detectable fluorescence light. This means the auto-fluorescence signal intensity variation can help distinguish tumor tissue as well [12].
**PpIX (protoporphyrin IX) fluorescence**

For fluorescence excitation of PpIX fluorescence 405 nm wavelength light is commonly used. Under 405 nm light, PpIX strongly fluoresce at 635 nm and 704 nm. The typical fluorescence spectrum of PpIX containing brain tissue following 405 nm light illumination is shown in Figure 1.

The technique of using fluorescent light to delineate malignant brain tumors gained clinical interest after a study performed by W Stummer. As shown in Figure 2, under violet-blue light the tumor color turns to hot pink, and the tumor margin becomes visible although blurry.

![Figure 1](image1.png)

**Figure 1** PpIX fluorescence spectrum introduced by 405 nm excitation light. The signal peak at around 510 nm is caused by brain auto fluorescence [13].

![Figure 2](image2.png)

**Figure 2** Intraoperative photographs demonstrating tumor cavity viewed under conventional white light (left) and violet-blue illumination (right). ALA induced fluorescence is proved to be able to mark the tumor margin briefly [14].

The outstanding properties of 5-ALA induced PpIX fluorescence makes it possible to develop fast, robust and non-invasive equipment. In the following chapters the equipment development details are introduced.
Chapter 2. Optoelectronics

Optoelectronics components are compact, robust and easy to fit in most electronic systems and can be easily modulated. These fabulous characteristics make it simple and fun to construct small and low weight electronic equipments.

In this project both semiconductor photon sources (Light emitting diodes and Laser diodes) and detectors (Photon detectors and Avalanche photon detectors) are used. In the design, one modulated 405 nm laser diode source is used to generate PpIX fluorescence signal. One PD is used to detect back scattered 405 nm light, and 4 other APDs are used to detect weak fluorescence signals at 4 different wavelengths.
1 Semiconductors

Semiconductors are materials in between electric materials and dielectric materials. Electric materials (conductors) like metals are great electrical conductors, but carry no light waves, and dielectric materials (insulators) like glass are good at guiding light but not electrons. Semiconductors can also carry current and light waves, and even allow the transformation between light and current [15].

1.1 Band structure

Electron flows give rise to an electrical current. This specific conducting behavior relies on how easily the electrons can move in-between electron occupied energy levels and empty energy levels. This difference in between energy levels is called the ‘band gap’ in solid state physics as in-between the bands no electron states can exist. The band gap presents the energy needed to free an outer shell electron from its orbit of the atom, and thus make it a mobile charge carrier [7][16].

As shown in Figure 3, there are two bands presented: the valance band and the conducting band. Between these two bands is the band gap mentioned in the previous paragraph.

The valence band and the conducting band are defined under the absolute zero temperature condition: the valence band presents the highest range of electron energies, in thermodynamic equilibrium and when T=0, this band is
totally filled. The conduction band is the range of electron energies which corresponds to mobile electrons. When T=0 this band is completely empty.

The energy levels in the valance band and the conducting band are not continuous. The round points dotted on these two bands in Figure 3 present these possible levels. The black dots show the level that is occupied by electrons, and vice versa, the white dots show the empty energy levels (holes).

The energy of an electron as a function of the wave momentum \( k \) is given as below

\[
E_c(k) = \frac{n^2 k^2}{2m_e} + E_g
\] (1)

\[
E_v(k) = \frac{n^2 k^2}{2m_v}
\] (2)

On the y-axis shown in Figure 3,

\[
E_v(0) = E_c(0) - E_g
\] (3)

In the formula, \( m_e \) and \( m_v \) are the effective masses of the electrons in the conduction band (the mass of holes) and valence band. The masses vary with the type of the semiconductor material. \( E_g \) is the bandgap energy, presenting the energy difference between the top of the valance band (highest energy level in the band) and the bottom of the conducting band (lowest possible energy in the band), which is shown in Figure 3 [17].
Equation 1 and Equation 2 are both formulas for parabola curves. This explains the shape of the bands shown in the figure.

The state density near the band edge in different bands can be obtained from the formulas below:

\[
D_c(E) = \frac{(2m_c)^{3/2}}{2\pi^2\hbar^3} \sqrt{E - E_c(0)} \quad (E > E_c(0)) \tag{4}
\]

\[
D_v(E) = \frac{(2m_v)^{3/2}}{2\pi^2\hbar^3} \sqrt{E - E_v(0)} \quad (E < E_v(0)) \tag{5}
\]

1.2 Occupancy probabilities

With the same k, an electron can either occupy \(E_{v(k1)}\) in the valence band or \(E_{c(k1)}\) in the conducting band. The distribution of the electrons in these two states is described by the Fermi function.

\[
f(E, T) = \frac{1}{e^{(E-E_F)/k_BT}+1} \tag{6}
\]

In Equation 6, \(T\) is the temperature, \(k_b\) is the Boltzmann constant and \(E_F\) is the Fermi-energy level. When \(T=0 K\), the Fermi level located at the gap midpoint and temperature increasing or dropping can both change the Fermi level. For example, under the thermal-equilibrium condition, a photon with frequency \(\omega\) is sent onto this semiconductor material, which ensures that one of the electrons in the valence band...
can absorb this photon and jump into one corresponding energy level in the conducting band, a process which meanwhile will leave a hole in the valence band.

According to the conservation of energy,

$$
\hbar \omega = E_v(k) + E_c(k) = \frac{\hbar^2 k^2}{2m_v} + \frac{\hbar^2 k^2}{2m_c} + E_g
$$

$$
= E_g + \frac{\hbar^2 k^2}{2} \left( \frac{1}{m_v} + \frac{1}{m_c} \right) = E_g + \frac{\hbar^2 k^2}{2m_r}
$$

(7)

Where $m_r$ is the reduced electron-hole mass defined by

$$
\frac{1}{m_r} = \frac{1}{m_v} + \frac{1}{m_c}
$$

(8)

On the other hand, Fermi function is also known as the Fermi-Dirac distribution. It is the function for presenting the probability of that an energy level E is occupied ($f(E, T)$) or empty ($1 - f(E, T)$), as shown in Figure 4, when the temperature rises, the Fermi function no longer remains as a step function. This is due to some electrons getting thermally excited to the conducting band leaving holes in the valence band. As a matter of fact $E_F$ is always located at the $f_{1/2}$, which is where $f(E, T) = 1/2$. 
The densities of electron/ holes at energy level $E_i$ can be obtained by multiplying the density states at this level and the probability of the holes’ occupancy.

$$n(E_i) = D_c(E_i) \cdot f(E_i)$$  \hspace{1cm} (9)

$$p(E_i) = D_v(E_i) \cdot f(E_i)$$  \hspace{1cm} (10)

$$n = \int_{E_c}^{\infty} n(E_i) dE_i \approx N_c e^{\frac{E_p - E_c}{k_B T}}$$  \hspace{1cm} (11)

$$p = \int_{E_v}^{\infty} p(E_i) dE_i \approx N_v e^{\frac{E_p - E_F}{k_B T}}$$  \hspace{1cm} (12)

In the equations, $N_c$ and $N_v$ are the effective densities of states in the conduction band and the valence band respectively.

$$N_c = 2 \left(\frac{2\pi m_e k_B T}{\hbar^2}\right)^{\frac{3}{2}}$$  \hspace{1cm} (13)

$$N_v = 2 \left(\frac{2\pi m_v k_B T}{\hbar^2}\right)^{\frac{3}{2}}$$  \hspace{1cm} (14)
Here, $n$ is the electron concentration in the valence band, $p$ is the hole concentration in the conducting band. If the semiconductor is intrinsic, which means it is an extremely pure crystal, $n = p = n_i$ is always true, where $n_i$ refers to the intrinsic concentration. While at the thermal equilibrium condition,

$$n_i = \sqrt{N_e N_v} \cdot e^{\left(\frac{E_g}{k_BT}\right)}$$

(15)

1.3 Doping

Doping is a special way of increasing the concentration of electrons or holes in the semiconductor. The combination of different atoms in the crystal lattice can either bring extra mobile electrons or holes. Depending on the type of impurities that are added in the material, the doped semiconductors are either called n-type (with extra electrons) or p-type (with extra holes). The dopants in the n-type material are called donors, and the ones in the p-type material are called acceptors. The amount of these atoms is relatively small, normally only a very low proportion of the original atoms.

As shown in Figure 5, the energy levels of the acceptors are slightly higher than the valence band, and correspondingly, the donors have slightly lower energy levels than the conduction band. The acceptors can easily receive an extra electron from the valence band and thereby generate a hole in the valence band. Similarly, donors can easily be thermally
excited at room temperature, thus releasing electrons to the conducting band.
1.4 P-N junctions

![Diagram of P-N junctions](image)

**Figure 6** Energy levels sketch of n-type and p-type semiconductor under different condition (A) before two types of semiconductors contacting (B) p-n junction in thermal equilibrium at T>0 K (C) forward biased p-n junction (D) reverse biased p-n junction [17] [19].

The structure of a p-n junction is the base of any semiconductor diode [19]. Figure 6 (A) shows the energy conditions of two types of semiconductor materials. Before contact, the electron concentration in the n-type material, and the hole concentration in the p-type material would reach a static state when the thermal equilibrium is achieved. A simple p-n junction can be formed under high temperature, which allows p-type material to diffuse into the n-type material region. When these two materials are attached, electrons and holes begin to move towards the areas with lower concentration, i.e. electrons in the n-region will float into
the p-region, and correspondingly holes will move from the p-region to the n-region. As a result of these movements, the regions close to the junction on both sides become almost depleted of mobile charge carriers. This region is called the depletion layer. The depletion layer contains fixed charges, which form an inner electric field, and this field drives the rest of the electrons and holes across the p-n junction till the equilibrium is reached. As shown in Figure 6 (B), the equilibrium generates a potential voltage difference of $eV_c$ across the depletion region, which is why the energy band is bent down from the p-region to the n-region as seen in the sketch.

When the junction is biased, the outer electric field will break the equilibrium. If the junction is forward biased as shown in Figure 6 (C), the external voltage drives the carrier flow through the junction, and the electrons and holes begin to combine together and cause a recombination radiation (which leads to light emission). If the junction is reversed biased as shown in Figure 6 (D), the depletion region is enlarged.

A p-n junction acts like a diode, and possess a specific $I-V$ characteristic as shown in Figure 7.

$$i = i_s \left( e^{eV/\kappa T} - 1 \right)$$  \hspace{1cm} (16)
**Figure 7** The ideal p-n junction diode current-voltage character curve. $i_s$ is the reverse current in p-n diode [17].
2 Light emitting diodes and Laser diodes

A light-emitting diode (LED) is the simplest constructed optoelectronic component as it is only a forward-biased P-N junction. LEDs are widely used as indicator lights. Mobile and computer screens and televisions are all illuminated with visible LEDs. Due to the small size, low price but great durability, LED screens are gradually replacing all the older types of screens in the modern world. The remote controllers for TVs and some of the remote controlled toys are still using infrared LEDs as in the old days. As an illumination light source, white LEDs are taking the places of old fluorescent lamps and incandescent lamps as they are more stable and energy conserving.

Both lasers and LEDs are preferred in many applications due to their compact sizes, high luminescence power, high efficiency and good endurance. As a comparison, LEDs are widely used nowadays in all kinds of display screens (e.g. mobile phones’ screen, crystal display screen backlighting), as different high power lighting sources (e.g. high power flashlight, energy-saving light bulbs), remote controls and other wireless electronics. Laser diodes (LDs) are used in traditional DVD systems and higher definition optical systems like Blu-ray players. LDs are also used in optical communication signal sources, printing/scanning systems and so on. Due to the
narrow spectral and high power output, both LEDs and LDs are frequently used as monochromatic excitation light sources in fluorescence spectroscopy systems as well.

2.1 Light-emitting Diode and Laser diode luminescence

The light emission from a semiconductor is the result of electron-hole recombination. As mentioned previously, a forward-biased p-n junction can make the combining process more efficient. So the fundamental structure of LEDs and LDs are thus forward-biased p-n junctions.

A diode laser and a LED can both fulfill the criterion of being compact as they are both semiconductor based light sources. But diode laser have better coherence and a higher power output and can be easily coupled into the fibers. As a conclusion, using LD instead of LED as light source in the system is a better choice.

LED luminescence property

A light emitting diode is a special type of forward biased heavily doped P-N junction. The luminescence properties of LEDs are mainly defined by their output power and the power conversion efficiency. The output wavelength and band the width of LEDS have to do with the semiconductor materials’ properties.
\[ P_0 = h \nu \varphi = h \nu \rho \frac{i}{e} \]  \hspace{1cm} (17)

Where \( \varphi = \rho \frac{i}{e} \) is called the output photon flux and \( \rho = \rho_i \rho_e \) is the external efficiency as a multiplex result of the internal efficiency \( \rho_i \) and the extraction efficiency \( \rho_e \). The typical external efficiency is lower than 50%.

The power conversion efficiency becomes

\[ \rho_c = \frac{P_o}{iV} = \rho \frac{h \nu}{eV} \]  \hspace{1cm} (18)

Here \( V \) denotes the voltage drop across the LED.

**LD luminescence property**

A Laser diode is a special version of a LED. There are several major differences between a LED and a LD. Firstly, a LD has narrower depletion layer compared with a LED, this structure that can get a high concentrate of the carriers. Secondly, in a LD the crystal plane normal to the p-n junction is either cleaved or highly polished, sometimes thin reflective layers are applied as mirrors. These methods are for forming a resonant optical cavity at the ends of the p-n junction. This cavity allows only very narrow band wavelengths lasing inside, which results in high power, narrow band and coherent radiation output.

In order to run a LD, a higher forward current level compared to LED is required.

Similarly to an LED, the LD output is given by
\[ P_0 = \rho_d (i - i_t) \frac{1.24}{\lambda} \quad (19) \]

In this equation, \( i_t \) is the threshold current. The external differential quantum efficiency is \( \rho_d = \rho_i \rho_e \). Here, \( \rho_e = \frac{\tau_1}{l} \) is the ratio between the transmission coefficient and the resonator loss.

The power conversion efficiency of an LD is given by,

\[ \rho_c = \rho_d \frac{(i - i_t) h \nu}{i e \nu} \quad (20) \]

LDs usually have more than 50% conversional efficiency, which is obviously higher than LEDs. At the same time, LDs suffer from a high heat radiation problem, so external cooling systems can sometimes be used to ensure the output power stability of the light sources.
3 Photodetectors

Photodetectors are for measuring the photon flux, which corresponds directly to the optical power. Photodetectors commonly transfer the photon energy into either current or heat. According to the generated signal types, the detectors are named photoelectric detectors and thermal detectors.

In this project, the electric output property is apparently more attractive, as the electric signal can be easily noted and analyzed.

3.1 p-n Photodiode

Semiconductor Photodiode detectors are either constructed from a p-n junction or a p-i-n junction. These two structures work in a similar way. In a p-i-n junction, the ‘i’ refers to the ‘intrinsic’ area, which is a really low doped semiconductor structure. As a result, a p-i-n junction structure offers a longer depletion layer so it can capture more photons. It has lower capacity and can process with higher speed.

In a p-n photodiode, light is mainly absorbed in the depletion region or regions that are really close to the depletion region. The absorption of photons allows electrons to jump to higher levels, which creates mobile carriers. If an external electric field is applied at the ends of this p-n junction, the mobile carriers can flow in a certain direction which leads to a photocurrent that is measurable.
**p-n Photodiode properties**

**A. Quantum efficiency**

The quantum efficiency tells the proportion of incident photons that can benefit the photon current output.

\[ \rho = (1 - r)\eta(1 - e^{-aL}) \quad (21) \]

\( r \) in the formula is the reflectance at the surface, \( \eta \) is the fraction of generated free carriers and the final output photon-electrons, \( (1 - e^{-aL}) \) is the material absorbed photon flux. \( L \) is the absorption depth.

**B. Responsivity**

Responsivity \( R = \frac{i_p}{P} \) is defined as the ratio of the output photon current over the input light power, \( i_p \) is the photon current and is proportional to the photon flux density \( \phi \)

\[ i_p = \rho e\phi = \frac{\rho eP}{h\nu} \quad (22) \]

So one can get

\[ R = \frac{i_p}{P} = \frac{\rho e}{h\nu} = \frac{\rho \lambda}{124} \quad (23) \]
C. i-V property

The i-V relation of the photodiode is quite similar to a simple p-n junction i-V relation

\[ i = i_s (e^{\frac{eV}{kT}} - 1) - i_p \]  \hspace{1cm} (24)

![i-V characteristic of p-n junction photodiode](image)

**Figure 8** Current-Voltage curve for short circuit operated photodiodes. Different photon current levels are caused by different photon flux densities \( \phi \) [17].

A photodiode is normally reverse-biased. This way of biasing improves the operating speed of the photodiode, at the same time increasing the area that is photosensitive.
3.2 Avalanche photodiodes (APDs)

Avalanche photodiodes (APDs) have almost the same properties as normal photodiodes, but APDs need a much higher voltage than normal PDs to be biased. The generated photon electrons in the semiconductor speed up dramatically with the higher external electric field, in the meantime these electrons have random collisions with other electrons. If the speed of the original electron is high enough, the electron after collision will acquire high enough energy which should be higher than $E_g$, and then an extra hole-electron pair can be successfully generated. This process is called ‘impact ionization’. High external electric field can accelerate the process and generate high output optical current.

APD Properties

A. Gain coefficient of an APD

The gain coefficient of an APD is the average amount of generated electron pairs from one single free photon electron.

$$M = \frac{1-\delta}{e^{-\gamma w_\delta}} \equiv \frac{a}{e} \quad (25)$$

$w$ is the width of the multiplication layer, $\gamma$ represents the ionization coefficient for the electron’s ionizing ability, and $\delta$ is the ratio of the electron ionization coefficient and the hole ionization coefficient. $M$ is the bias voltage, which is really close to the breakdown voltage and it can reach a really high
value of $M = 100$ V or more. The gain coefficient is temperature sensitive, which means when the APD temperature rises, in order to get the same $M$-values, the bias voltage of the APD needs to increase as well. Unless the APD is constantly cooling down during the detection process, the output from the APD will always decrease during the detection period.

The photon current of an APD is given by

$$i_p = \rho q \phi = \frac{\rho e M \phi}{h v}$$  \hspace{1cm} (26)

B. Responsivity

$$R = \frac{i_p}{\rho} = \frac{\rho e M \phi}{h v} = \frac{\rho M \lambda}{1.24}$$  \hspace{1cm} (27)

APDs suffer from really high noise due to the avalanche multiplication processes. Thus the bias and the circuits for running the APDs should be carefully designed in order to maintain a high SNR level and a high processing speed.
Chapter 3. Method

1 Previous research in collaboration between Lund and Linköping Universities

The previous system made in a collaboration between Lund and Linköping Universities is called ‘optical touch pointer (OTP)’. This system has been tested in clinical surgeries and gives good results. The system sketch is shown in Figure 9.

![Figure 9](image)

*Figure 9* Sketch of the final version of first generation OTP system [20].

In this design, the light source is controlled by a computer interface created in LabView (National Instruments Inc., USA) through the signal in/out device DAQ card (National Instruments Inc., USA). The light source is pulsed with square wave. A spectrometer is used for detecting the light spectrums. With a short pulse duration, limited light power can be input into the tissue, this method can reduce the influence of the ambient lights and prevent high photon bleaching [20].
The transmission part of the system includes several optical fibers. Both the illumination light and the tissue emitted light are conducted through these fibers. The excitation fiber is relatively large with a core diameter of 600 μm and its numerical aperture is 0.37. The excitation fiber is surrounded by 9 other collection fibers. The collection fibers have 200 μm core diameter and numerical aperture is 0.22.

The detecting part of the system is based on the spectrometer (EPP 2000, Stellarnet), which uses a piece of 2048 element CCD operating in the wavelength range of 240 nm–850 nm. The resolution of the spectrometer is 3 nm. Though the theoretical resolution of the spectrometer is high, in order to get reliable results the spectrometer requires integration times of no less than 30 ms. The spectrometer is coupled to the system through the optical fiber to collect the optical signal. The ends of these optical fibers for conducting the light signal to the spectrometer are arranged in a line shape. This is for fitting the shape of the spectrometer light entrance slit. Before this slit, a long pass filter of 475 nm (Schott CG-GG-475-0.5C-3, CVI, USA) is setted for protecting the spectrometer from saturation of the reflected light [20][21].

To analyze the results from the spectrometer, two spectrum results are used. One of the spectra is taken with the light source set to off mode and the other with the light source on.

Compensated spec (i) = Light spec (i) − Dark spec (i)  \hspace{1cm} (28)
2 System design

2.1 Hardware design

Light spectroscopy methods employed by the instrument include diffuse light scattering, tissue auto-fluorescence and PpIX fluorescence. All these pieces of information can help with tumor region delineation and thus guide the surgeon during resection.

Optical filters can help to separate the characteristic wavelengths of the scattered light, the PpIX fluorescence light and the auto-fluorescence light. In the system, several channels which can detect the different characteristic wavelengths independently were designed.

1. Channel.1 is set for scattered light detection (405 nm).
2. Channel.2 (510 nm) and channel.3 (530 nm) together can detect the tissue auto-fluorescence levels.
3. Channel.4 (635 nm) is for PpIX fluorescence detection.
4. Channel.5 (660 nm) is for observing the photo-bleaching products formed from PpIX during light exposure.

An optical box was designed to support multi-channel light paths and to fix corresponding optical components in the system, as shown in Figure 10.

The details of the system designed in this thesis project are presented in Figure 11.
Figure 10 Ray tracing sketch (Fred®) for the optical system and optical box design. The ray tracing sketch proving the design is possible after properly selecting and placing the chosen optical components involved. The optical box is subsequently designed according to this sketch.
In this design, all the fiber connectors are of the SMA-type. Light exiting the fibres is automatically expanded, and made parallel with the first lens – the collimator.

The Collimator (64770, Edmund Optics) is used to expand the size of the incident light spot. Dichroic beam splitters 1-4 (DMPL425, 505, 567 and 638, Thorlabs) are for directing part of the incident light to fixed channels. The transmittance and reflectance of these splitters are depends on the wavelength, and which filter we study. The Long pass filter (GG-435, Edmund Optics) is set for lowering the reflected light from the tissue onto the detectors. Otherwise the reflected light will appear as a background in all other detected signal channels. The band-pass filters 1-5 (FB405-10, FB470-10, FB530-10, FB635-10, and FB660-10, respectively) are for selecting and the targeted wavelengths from the all the the collected light before detection. Corresponding to each band pass filter, a focal lens
(47884, Edmund Optics) is used for focusing the expanded light spot onto the small detection area of PD or APD.

### 2.1.1 Light source

The light emitting source used in the system is a pulsed violet diode laser with a 405 nm wavelength and 50 mW power output (Oxxius SA, France). High output power LD is selected to make sure that the illumination light can generate detectable fluorescence signal.

The light source is controlled by a computer interface created in LabView 2012 (National Instruments Inc., USA) through the signal in/out device DAQ card (USB-6351, National Instruments Inc., USA).

![Figure 12 Electrical circuit of the 405 nm diode laser. The output pulses from DAQ card if 0-5 V. With this circuit, the output power of LD can be changed manually.](image)

As shown in Figure 12, the output power of the LD can be adjusted. This design makes sure that the fluorescence light and the reflected light levels will not saturate the light detecting components.

The clock output signal from the DAQ card is used to pulse the light source. Analog output ports on the DAQ card
can also generate square pulses, but the pulse shape from the clock output port has a more favourable squared shape.

2.1.2 Transmission fiber

Figure 13 (A) shows the bundle ends of the Y-shaped fiber. It includes both the delivering fiber and the collection fiber. As this end of the fiber will be in contact with the tissue surface during the detection process, so it is covered with a 4 cm long stainless metal shed. The other two ends of the Y-shaped fiber both look the same, as shown in Figure 13 (B). They are both mounted into SMA connectors.

2.1.3 Light Detecting components

As shown in Figure 11, 4 APDs (S9075, Hamamatsu) and one PD (53378, Edmund Optics) are used for detecting the light signals. In order to achieve high speed detection, and at the same time maintaining a good amplification power for the fluorescence light, the proper electronic components for matching the impedance of this PD and the APDs should be carefully considered.

Figure 13 Both ends of the A Y-shaped fibre are illustrated. The two heads fiber is used for light transmission. (Fiber Patch Cord Bundle, Prizmatix Ltd.)
Figure 14 Electro optical system basic photodiode front end. C4 is the detector capacitor which is unavoidable and should always be considered in the design, $R_L$ is the load resistor and $i_d$ is the generated photocurrent. $i_{Nth}$ is the Johnson noise due to the load resistor and $i_{Ns}$ is the shot noise.

In the basic front end design, the detector capacitor is $C_d$, the full signal will swing across it. The output intensity rolls off at

$$f_{(RC)} = \frac{1}{2\pi R_L C_d}$$  \hspace{1cm} (29)

Meanwhile, the output voltage is related to the system load resistance,

$$V_o = \frac{R_L i_d(f)}{1+j2\pi R_L C_d f}$$  \hspace{1cm} (30)

In this design, the noise is mainly due to Johnson noise and shot noise, as shown in the right part of Figure 15. All noise sources are considered current sources.

$$\text{SNR} = \frac{i_d^2}{i_{Nth}^2 + i_{Ns}^2}$$  \hspace{1cm} (31)

Johnson noise is generated due to the external resistor
\[ i_{Nth} = \sqrt{\frac{4kT}{R}} \]  

(32)

\[ i_{Ns} \] is the shot noise

\[ i_{Ns} = \sqrt{2eTl_d} \]  

(33)

The \( C_d \) values of the PD and APDs chosen for the system are 300 pf and 30 pf, respectively, and if the data is inserted into Equation 29, a plot can be made according to the frequency response for different value of the applied load resistance.

![Figure 15](image)

**Figure 15** The bandwidth curve of the APD front-end and the PD front-end used in the design.

<table>
<thead>
<tr>
<th>( i_dR )</th>
<th>5.1</th>
<th>1.3</th>
<th>0.57</th>
<th>0.32</th>
<th>0.20</th>
<th>0.14</th>
<th>0.10</th>
<th>0.080</th>
<th>0.063</th>
</tr>
</thead>
<tbody>
<tr>
<td>( i_{Nth}/i_{Nshot} )</td>
<td>0.1</td>
<td>0.2</td>
<td>0.3</td>
<td>0.4</td>
<td>0.5</td>
<td>0.6</td>
<td>0.7</td>
<td>0.8</td>
<td>0.9</td>
</tr>
<tr>
<td>( \Delta SNR(\text{dB}) )</td>
<td>-0.04</td>
<td>-0.17</td>
<td>-0.4</td>
<td>-0.6</td>
<td>-1.0</td>
<td>-1.3</td>
<td>-1.7</td>
<td>-2.1</td>
<td>-2.6</td>
</tr>
</tbody>
</table>

Table. 1 Johnson noise caused noise [23].
From Table 1, one can tell the lost SNR results and \( \text{iR} \) results have no correlation to the component capacity or internal resistance. In the design, the signal from the PD channel is normally stronger than the signal from the other APD channels, assuming the expected current value is 1 \( \mu A \) from APD channels and 3 \( \mu A \) from the PD channel.

According to the suggestions of Philip C.D. Hobbs[REF], it is best to have the lost SNR to be less than 1dB, leading to a corresponding \( i_a R_f \) value of 0.20 if 3 \( \mu A \) is generated from the PD, which means \( R_f \) should be around 70 \( k\Omega \) according to the calculation. In order to reach the same lost SNR value for APDs, the load resistance can reach up to 200 \( k\Omega \) [24]. On the other hand, large \( R_f \) will waste the dynamic range and bandwidth of the system. If the load resistance for the APDs and the PD are both chosen to be 75 \( k\Omega \), the system bandwidth for both APD front-end and the PD front-end can be over 7000 Hz, which can be considered satisfying.

The system's inefficient bandwidth is due to the current swing across the \( C_a \). According to the method provided by Philip C.D. Hobbs, the feedback loop consisting of the \( R_f \) and the \( C_f \) can suppress the current swing and increase the possible bandwidth even more [24], \( R_f \) is set at 75 \( k\Omega \), and \( C_f \) is set to be 10 pf at last.
Figure 17 and Figure 18 shows the complete circuit designs of the APDs and the PD in the system. The operational amplifier LM324 was chosen for the following reasons.

First of all, LM324 contains 4 independent amplifiers, thus simplify the electrical circuit. It can also provide high bandwidth and a wide range of operational input voltages. This makes it possible to share other components power supply.

The reference voltage applied in the design does not influence the amplification power of the amplifiers, it only multiply the reference voltage value and the detected signal voltage value. The reference voltage is chosen to be 2 V in the final design. In this way, the real time signal variation can be presented more clearly in the Labview graph panel.

A simple PCB board was made according to the design as shown in Figure 19. It was made for deacreasing the noise and simplifying the wiring.

Figure 16 Transimpedance amplifier sketch [24].

Figure 17 The concept sketch for porting PD in the circuit [24].

Figure 18 The concept sketch for porting APDs in the circuit [24].
Unfortunately, the test board was just made on a simple layer bronze covered plastic board. This old fashioned homemade board picks up unknown noise signals from surrounding space. Compared with the signal strength generated by the fluorescence light, the noise signal level is too high. On the other hand, as the TTL pulses are used to power the light source, low pass filters cannot be used as they will distort the signal shape. So we didn’t bother to go on with the home made PCB board but used a piece of normal bread board for now.

2.1.4 System Input/Output ports

In the previous design as shown in Figure 11, all the electronic components needed to be controlled and powered by the system. In order to classify all the input and output ports in the system, all the ports are listed in Table 2.
**Table. 2** Input and output ports summary for the OTP system design.

<table>
<thead>
<tr>
<th>Input</th>
<th>Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>APD 1-4</td>
<td>DAQ A1-A4</td>
</tr>
<tr>
<td>PD</td>
<td>DAQ A0</td>
</tr>
<tr>
<td>Clock pulses</td>
<td>Clock pulses for diode laser</td>
</tr>
<tr>
<td>for diode</td>
<td>Diode laser</td>
</tr>
<tr>
<td>laser</td>
<td>LM324 amplifier (3 pieces)</td>
</tr>
<tr>
<td></td>
<td>LM324 reference voltage</td>
</tr>
<tr>
<td></td>
<td>APD bias voltage power supply</td>
</tr>
<tr>
<td></td>
<td>(M6017) supply voltage</td>
</tr>
<tr>
<td></td>
<td>M6017 gain control voltage</td>
</tr>
<tr>
<td></td>
<td>APD bias voltage(from m6017)</td>
</tr>
<tr>
<td></td>
<td>PD bias voltage</td>
</tr>
<tr>
<td></td>
<td>DAQ clock(0-5 V)</td>
</tr>
<tr>
<td></td>
<td>220 V</td>
</tr>
<tr>
<td></td>
<td>12 V</td>
</tr>
<tr>
<td></td>
<td>2 V</td>
</tr>
<tr>
<td></td>
<td>5 V</td>
</tr>
<tr>
<td></td>
<td>0-3 V</td>
</tr>
<tr>
<td></td>
<td>-5 V—-200 V</td>
</tr>
<tr>
<td></td>
<td>12 V</td>
</tr>
</tbody>
</table>
2.2 Signal processing method

As shown in Figure 20, fast modulation is the solution for suppressing the ambient light influence.

Figure 20 (A1) shows the DAQ card generated high frequency light pulses.

Figure 20 (A2) shows the waveform of the ambient light (50 Hz).

Figure 20 (A) shows the detected waveform from the APDs/PD. It is a combined signal result caused by the scattered light and the ambient light.

Figure 20 (B) gives a detailed view of Figure 20 (A). One can tell if the light source is modulated with a high frequency, the intensity shift on of the output signal on y axis will be rather small.

Figure 20 (C) shows that the light intensity data points over each half cycle are averaged. This way of processing data can efficiently suppress the high frequency noises like the white noise.

Figure 20 (D) shows the signal compensation process. The compensated signal results are obtained by subtracting the signal under dark conditions from the signal under light conditions. After this process, the real signal can be recovered from the noisy signal from the detectors.

Figure 20 (E) shows the recovered signal after all processes. The optimal final result is supposed to be noise free and ambient light influence free.
Figure 20 The signal processing method. The ambient light suppression is based on the fast modulation of the illuminating light.
2.3 Software design

As mentioned above, the system is controlled by Labview. In this part of the thesis, only the system front panels are shown. The full back panel design can be found in the Appendix A.

![Real time signal graph: all channels plotting and individual channel plotting](image1)

![Data can be saved when signal gets stable](image2)

![Integrated average signal strength results for each channel](image3)

![Modulation frequency can be tuned here](image4)

**Figure 21** LabView program front panel of the OTP system The different colors that appear in the plotting show the corresponding wavelengths. (e.g. 405 nm channel wave form is plotted with blue lines)

In this picture, the light source is modulated by 777 Hz pulses. All detected signals are plotted in real time in the front panel graph. Every 200 cycles’ results after signal processing are averaged for giving more accurate and stable results. This result is also shown in time on the front panel. All the data points presented on the front panel are saved to a text file for further use.
3 System overview

The final system set up is shown in Figure 22.

![System overview image]

**Figure 22** This group of pictures shows the whole system set up and the detailed view of the electrical circuit board. (A) gives the set-up overview, behind the diode laser in the image locating the DAQ card. (B) shows that the electrical board is closely fixed on the side of the optical box, the APDs and the PD are inserted in the corresponding holes. On the very left part on the optical box in this picture is the APD for the 660 nm channel and it is linked by a group of wires. (C) shows the detailed view of the electrical board. Almost all components are portable on the board. (D) shows the back side of the board [24].

In order to make the system neat and organized, many aspects were considered when the electrical board was made and different scratch versions were produced. This final version electrical board can be attached to the side of the
optical box properly. Most of the electrical components shown in the design are portable, so that they can easily be replaced.
Chapter 4. System calibration

Several aspects can influence the final signal strength accuracy detected by the system. For example, the long pass filter causes high power loss, the band pass filters’ transparency efficiencies are different for different channels, the sensitivity of the APDs and the PD and the amplification power of the electrical circuits for each APD or the PD varies. The system was calibrated to make it more accurate.

A high power broadband calibration lamp (63355, Driel) was used to calibrate the system. This lamp has a standard spectrum intensity document attached. The lamp is powered by a current power supply (68830, Driel). When the input current reaches 6.5 A, the lamp spectrum should be the same as the spectrum recorded in the attached document.

The system calibration is made by comparing the standard intensity at corresponding wavelengths, to the power strength results from the OTP system built in the project.
Figure 23 plotting of calibration lamp real spectrum and experimental spectrum from the spectrometer.

The light intensity at the target wavelengths are all normalized to the 405 nm light intensity. Suppose that this group’s results is called $\alpha$. The read out signal intensity results from the Labview system are normalized to the readout of the 405 nm signal intensity and this group of results is called $\beta$.

$$c_{510} = \frac{\alpha_{510}}{\beta_{510}}$$  \hspace{1cm} (34)

Factor $c_{510}$ is the calibration coefficient of 510 nm. Do the same calculation for the rest of the channels. These results are used in the Labview program in order to show the real light intensity value.
The calibration coefficients of each channel are listed in Table 3.

**Table. 3** OTP system calibration results

<table>
<thead>
<tr>
<th>Wavelengths</th>
<th>Normalized factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>405</td>
<td>1</td>
</tr>
<tr>
<td>510</td>
<td>5.2652</td>
</tr>
<tr>
<td>530</td>
<td>6.2252</td>
</tr>
<tr>
<td>635</td>
<td>9.8197</td>
</tr>
<tr>
<td>660</td>
<td>10.1885</td>
</tr>
</tbody>
</table>
Chapter 5. Results and analysis

Results

- Skin autofluorescence detection

![Figure 23](image) Front panel of the Labview program for experiments on skin. The figure on the left side is the real time waveform from the multi-channels, the figure on the right side shows the 530 nm autofluorescence waveform.

Human skin fluoresces mostly in the blue - green region due to tissue auto fluorescent. But in the red light region, skin fluorescence very weakly. Meantime, finger skin is quite smooth, so one can expect a high reflected light intensity from this part of the skin.

Figure 23 shows that the 530 nm channel has the highest fluorescence intensity and the 510 nm channel has the second highest intensity while the light intensity from the 635 nm and 660 nm channels are much lower.
Figure 24 System test with a red fluorescence marker pen on wood surface.

The rough surface of wood board causes strong diffuse light reflection, so the amount of reflected light that can be detected should be dramatically decreased. The test was done on the wood surface with red fluorescence pen marks. Theoretically, the detected signal should have the intensity in the red spectrum region.

Figure 24 shows low signal intensity in the green regions (510 nm to 530 nm) and very high signal intensity in the red region (635 nm to 660 nm). The reflected light intensity in this test is also lower compared to the results shown in Figure 23.

Comparing these two groups of test results, the intensity variance for the same wavelength is obvious. All results
correspond well with the theory. These all shows that the system works as designed.

In both tests, a bright lamp was shining right on the testing samples. The stability of the signal plots shows the ambient light influence is successfully eliminated.

During the experiments, the system runs smoothly and swiftly, no delay of the figure plotting. At the same time, most of the noise signal is removed and the output data appears to be stable. The system can also detect much weaker fluorescence signal than expected, this shows that the system has good sensitivity.

The performances of the system are satisfying. The system noise and ambient light eliminating abilities are even better than expected. As a conclusion, the thesis project is successful.
Chapter 6. Discussion and conclusions

The idea in this project is to distinguish the tissue types by combining information from tissue autofluorescence, fluorescence from the contrast agent ALA-induced PpIX, as well as diffuse reflected light. Malignant glioma cells will take up ALA as a consequence of a damaged blood-brain-barrier in tumor tissue, and be converted into strongly fluorescent protoporphyrin IX (PpIX). The PpIX concentration in the tumor can reach 50 times the concentration in the surrounding brain. With 405 nm excitation light, the PpIX would fluoresce intensively around 635 nm.

The system built in the thesis project is insensitive to ambient light. In the system a 405 nm LD is square-wave modulated at a high frequency. This allows lock-in detection to suppress any influence of 50 Hz ambient room light. The LD is coupled to an optical fiber. The distal ends of the fiber are beside a detection fiber in an optical probe. The detection fiber guides the light back to a compact detection unit. This is constructed for directing light of different wavelengths to independent light detectors. After efficient amplification electronics, the signals are directed to a data acquisition board (NI-DAQ card) for data acquisition and further signal processing. In the signal processing, the influence of noise is first reduced by signal filtering, and the signals are then
multiplied by a calibration factor to provide a true signal level. The calibration considers optical losses in the signal path as well as detector efficiency. The average signal strengths of each channel for a certain time period are calculated. The system is now available for further tests.

This thesis project proved the possibility of an optical touch system based on electronic signal processing methods. In the project, the author was working with a PhD student. This two members team was tutored by Professor Stefan Andersson Engles. During the period, the author managed to

1. Develop this signal processing method
2. Design and produce the main electric board
3. Programmed the Labview program and Matlab program
4. Process system calibration tests

From the final testing results, one can see the system works properly under all planned functions and it can give reasonable results. The future plans are to improve the stability of the system, and process sensitivity tests of the system to low intensity fluorescence light.
References


Appendix

1 Labview back panel

2 Labview sub-vi back panel