APPLICATIONS OF USING OPTICAL ENGINEERING SOFTWARE IN THE DESIGN OF OPTICAL IMAGING DEVICES FOR TISSUE-BASED APPLICATIONS

by

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STATEMENT BY AUTHOR

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ABSTRACT

FRED optical engineering software was used in device design and analysis of devices for separate applications in translational research. The photostress tester and falloposcope are designed to image the eye and fallopian tubes for early detection, monitoring, and prevention of respective blindness and ovarian cancer. Research was performed under Dr. Eniko Enikov and Dr. Gohlam Peyman for modeling of the photostress tester and under Dr. Jennifer Barton for modelling of the falloposcope. Simulations were performed for both applications that involve light-tissue interaction. Light levels and safety were modelled and evaluated with the photostress tester and stray light was modelled and determined for the falloposcope. I completed first author papers and presented posters for each of the research applications. An invention disclosure was completed for the photostress tester. This describes the translation of research into the public domain, where device end users could be lay people in rural communities or physicians operating out of clinics. In contrast, the falloposcope's use is limited to skilled surgeons in the clinic. The invention disclosure details the Photostress tester's use of FRED simulations for safety and illuminance values hitting the back of the eye. This analysis is essential information for the product if it is to be used to prevent and monitor blindness. In parallel, the falloposcope use FRED stray light runs and results as a diagnostic for device competence regarding field of view and signal to noise performance. These tested factors showed an aspect of the efficacy of the tool design as the device was prototyped. This again shows that FRED analysis played an important role in a device meant to help humans, i.e. imaging for early detection of ovarian cancer in women. An addition to the stray light analysis is a review on the advantages of using FRED for the stray light simulation work in comparison to some competing software's and a brief trouble-shooting section that will save future first time users a lot of time if they fun into similar issues that took me a while to resolve in order to obtain a correct simulation of the falloposcope. Light tissue interaction research is being performed here in multiple labs, and FRED is a unique and powerful diagnostic tool to use in the device design process.

In conclusion, I performed FRED optical engineering software simulations as part of the design and test of two optical engineering devices. I then completed a paper, an invention disclosure, and a proceedings paper. This master's thesis incorporates the aforementioned papers and invention disclosure in addition to creating a user review and trouble-shooting section for using FRED as a part of stray light simulations. This uniquely contributes to the optical sciences by detailing the use of illumination software in the development of two tools that can help save eye sight and life.

CHAPTER 1 –BACKGROUND ON BLINDNESS CAUSED BY AGE-RELATED MACULAR DEGENERATION (ARMD or MD)

Macular degeneration is the leading cause of vision loss among the elderly. Their growing demographic will soon propel Macular Degeneration afflictions to over two million in the United States. Unfortunately, by the time the most reliable current methods of diagnosing Macular Degeneration (MD) detect the condition, too much vision is already lost, or in the process of being permanently gone^[1].

Macular degeneration affects the macula, thus inhibiting the sharp, central vision. This disease occurs in two stages: dry MD and wet MD. In the more common dry MD, an accumulation of drusen - deposits of deteriorating tissue - occur in the macula. Deposits of drusen (yellow spots) indicate early signs of dry MD. Wet MD is much more advanced and severe. New blood vessels begin to grow under the retina and leak blood and fluid, which can cause irreversible damage to the light-sensitive cells in the retina. This results in blind spots. The damage to the macula in both cases of macular degeneration is the reason for delayed response times during the photobleaching test and will give much insight into whether the patient suffers from MD^[2, 3,4].

1.1 Risk Factors

Age, smoking, race, and family history are all major risk factors for getting ARMD. Caucasians over sixty years old who have a family history of ARMD are more likely to get the disease. Smoking additionally doubles the likelihood of contracting AMD. In order to decrease the risk of getting or worsening ARMD, people can quit smoking, exercise regularly, maintain a diet filled with green, leafy vegetables and omega three fatty acids that are found in fish, and keep blood pressure and cholesterol levels in check^[5].

1.2 Detection Methods

Due to the lack of symptoms presenting in the early and intermediate stages of AMD, people need to go to their eye doctor to get their eyes dilated and tested. The visual acuity test monitors how the person can resolve letters at a distance. The dilated eye exam enlarges the pupils and allows the doctor to look with a magnifier at the retina and optic nerve for signs of AMD. The Amsler grid test has a person look at a grid of some sort and ask how it appears; lines appearing distorted or missing indicate AMD. Fluorescein angiograms image leaking blood vessels in the eye that can indicate presence of AMD. Fluorescent dye lights up the blood vessels so that they can be imaged. Optical coherence tomography, the optical analogue to ultrasound, can be additionally used to obtain high-resolution images of the tissue. The eye doctor looks for larger than normal drusen deposits or decreased pigmentation occurring behind the retina as other indicators of AMD^[5].

1.3 AMD Stages

AMD is broken into three stages: early, intermediate, and late AMD. Drusen the size of a human hair indicates early AMD and no vision loss. Large drusen and/or decreasing pigmentation behind the retina indicates intermediate AMD and some vision

loss. Dry and wet AMD due to drusen present behind the retina and macular damage are considered late AMD; people experience gradual vision loss. Dry AMD indicates macular damage and vision loss. Wet AMD indicates new, abnormal blood vessels growing and leaking fluid, which causes macular swelling and rapid vision loss. Some people experience dry AMD, wet AMD, or both dry and wet AMD in one or both eyes. Symptoms may be mitigated if caught early on, and people may not be as affected if the AMD is only present in one eye. However, precaution should be taken as the other eye will be at higher risk of getting AMD. There is no known way to restore eye-sight once it is lost, which is why early detection is necessary to maintain vision^[5].

1.4 AMD Treatment

High dosages of certain vitamins have been proven to slow the progression of intermediate and late AMD. The Age-Related Eye Disease Studies (AREDS) studies showed that taking 500 mg of vitamin C, 400 IU of vitamin E, 25 or 80 mg zinc oxide (in AREDS studies 1 or 2), 2 mg of cupric oxide, and 15 mg beta-carotene or 10 mg lutein and 2 mg zeaxanthin decreased the risk of AMD by 25 percent. The vitamins are therefore sold and labeled with AREDS or AREDS2. People should consult their doctor for which formulation is best for them as smokers should avoid high dosages of beta-carotene. The vitamins reduce the likelihood that the disease may begin or worsen, but cannot reverse lost vision^[5].

Advanced neovascular AMD (advanced wet AMD) uses other therapies to try and prevent further vision lost. Injections, photodynamic therapy, and laser surgery are commonly used. Anti-VEGF eye injections work to slow the growth of new abnormal blood vessels. Once the drug reaches the new vasculature in the eyes, the eye doctor uses a laser to activate the drug, which closes off or slows the growth of new blood vessels. In laser surgery, the eye doctor uses a laser to burn the newly growing vasculature if it is far enough away from the retina. Although a small blind spot may be present, this preventative measure may save complete vision loss had the AMD worsened^[5].

CHAPTER 2 – BACKGROUND ON OVARIAN CANCER

Ovarian cancer is the leading cause of death due to a gynecological cancer in the United States. 70 percent of ovarian cancer is diagnosed at the advanced stage, which makes the survival rate only 30 percent at five years from the diagnosis. Early detection decreases chances of metastasis and increases chances of survival^[6].

The goal of building the falloposcope is to use it as a minimally invasive means for detecting and understanding the origin of ovarian cancer. Ovarian cancer is difficult to detect due to its lack of specific symptoms until it has progressed into stages III and IV and is therefore poor prognosis for those diagnosed with it^[7,8,9,10]. Research suggests that the cancer originates in the fallopian tubes^[11,12], thus requiring a scope that can access the fallopian tubes, about one-half meter in lengths and less than 1 mm in diameter. The scope can then fit inside the fallopian tubes and have access to the ovaries, while having the capability of imaging both.

2.1 About Ovarian Cancer

2.1.1 What Is Ovarian Cancer?

Today the origin of ovarian cancer is thought to be in the fallopian tubes and is still being studied^[13]. The American Cancer Society used to state that ovarian cancer originates in the ovaries, a female gland that releases the hormones estrogen and progesterone, and also releases eggs that travel down the fallopian tubes to the uterus where fertilization and subsequent implantation may occur for reproduction. The ovaries are made of epithelial cells that create the outer surface, germ cells that produce eggs, and stromal cells which provide structure and produce estrogen and progesterone. Each cell can potentially develop into epithelial, germ, or stromal tumors. Epithelial tumors are most common and can be classified as benign, low malignant potential (LMP), or malignant. Most epithelial tumors are benign and do not have a noticeable impact on women. Additionally, LMP epithelial tumors are rarely life threatening as they are selfcontained and slow-growing. In contrast, malignant epithelial tumors, or *carcinomas*, account for 85-90% of ovarian cancers, whose impact is determined by subtype, grade, and stage. The five subtypes include the following: serous (most common), mucinous, endometrioid, clear cell, and undifferentiated (most rapid growth and metastasis). The grade of the tissue is ranked as 1, 2, or 3: one being the most normal-looking tissue with the best prognosis for the patient and three being the most abnormal-looking tissue that leads to a more negative outlook for the patient. The tumor stage describes how far away the cancer has spread from the ovary, i.e. to nearby organs in and/or to the surface of the pelvis and abdominal cavity. It should be noted that aside from ovarian cancer, primary peritoneal carcinoma closely mimics the looks of the disease just found on the peritoneum of the abdomen or pelvis. Additionally, fallopian tube cancer is similar to epithelial ovarian cancer except that it originates in the fallopian tubes^[14].

Aside from epithelial ovarian tumors, under two percent of ovarian tumors are germ cell tumors. They include teratomas, dysgerminomas, endodermal sinus tumors, choriocarcinomas, or a combination of these. Although these may be deadly, 9 out of 10 women live five years after their diagnosis occurs^[14].

One percent of ovarian cancers are ovarian stromal tumors, with 75% of patients living long past their diagnosis due to ease of finding the malignant tumors at an early

stage. This stroma is the part of the ovary filled with blood vessels and some connective tissue^[15]. Symptomology includes vaginal bleeding even after menopause, as the tumors produce estrogen. Conversely, if the tumors produce testosterone, this causes normal menstrual periods to stop. Examples of malignant ovarian stromal tumors include granulosa cell tumors, granulosa-theca tumors, and Sertoli-Leydig cell tumors. Examples of benign ovarian stromal tumors include the comas and fibromas^[14].

The final type of ovarian cancer can be produced by is an ovarian cyst, or fluid built up inside an ovary. Cysts normally appear during ovulation in females and usually do not need to be treated. However, if the female has not started periods or is postmenopausal, cysts may be large or last longer than two months. This requires monitoring and possible surgery to remove the cyst. Surgery is the only way to tell for sure that the cyst is cancerous and to protect the patient if this is the case^[14].

2.1.2 Key Statistics for Ovarian Cancer

In 2015, over 21,980 patients will be diagnosed with ovarian cancer, and 67 percent of the cases turn fatal. It is the fifth highest cancer killer of women overall, but the most deadly reproductive cancer. Females have a 1 in 75 chance of contracting the disease, half of whom are 63 or older when they are diagnosed^[16].

2.1.3 Signs and Symptoms of Ovarian Cancer

Symptoms of ovarian cancer are present in all of the stages, but get worse if the cancer has metastasized. The disease causes the following: bloating, constant and frequent urination, pain in the pelvis or abdomen, quickly feeling full after eating, and trouble eating. These symptoms are unique to ovarian cancer when they present persistently and abnormally from what the person usually experiences. It is suggested by the American Cancer Society that the person see a gynecologist if the symptoms persist more than twelve times in a month^[17].

2.1.4 Diagnosing Ovarian Cancer

A physical exam is required for patients who show the above-mentioned ovarian cancer symptoms. An enlarged ovary or presence of fluid in the abdomen known as *ascites* requires the patient to consult a gynecologic oncologist who performs necessary surgeries to remove the cancer. Imaging tests may be required to locate the presence of masses within the body and possibly indicate whether the masses have spread in the body if they are cancerous. The imaging modalities that specialists use include ultrasound, computed tomography (CT) scans, colonoscopy, magnetic resonance imaging (MRI) scans, chest x-rays, and positron emission tomography (PET) scans. Ultrasound is the first modality used to determine the size, location, and complexity of an ovarian tumor or cyst. CT scans are used to locate and determine the impact of larger tumors on organs near the ovaries if the tumor has spread. A CT-guided needle biopsy is then performed to biopsy potential metastasized tissue and give a patient a diagnosis. A colonoscopy is performed to see if the cancer has spread specifically to the colon. Similarly, MRIs are used to check the health of the brain and spinal cord. Ovarian cancer can cause tumors and fluid build-up in and around the lungs respectively, thus requiring a chest x-ray. PET scans are expensive but occasionally are covered by insurance; they are used to locate ovarian tumors and masses that have spread throughout the body^[18].

Optical techniques are emerging to detect ovarian cancer sooner including optical coherence tomography and second harmonic generation microscopy^[19]. Additional techniques include spectroscopy^[20,21], photoacoustic^[22], and confocal imaging modalities^[23]. Confocal microscopy has been used in an endoscope in past years, with novel uses with texture identification being researched to pinpoint and diagnose ovarian cancer^[24].

Additional tests include laparoscopy, colonoscopy, biopsy, and blood tests. Laparoscopy requires a small slit to be made to image areas of the pelvis and abdomen. Laparoscopy is used to biopsy tissue, confirm metastasis, and plan further treatments for the patient. The aforementioned colonoscopy checks for metastasis inside the intestines and biopsies are used to check whether spread masses or fluids are cancerous or not. Finally, blood tests account for blood count, liver and kidney function. They also are taken to look for a high CA-125 test (a cancer antigen that if elevated from a fiducial point can be indicative of ovarian cancer); high human chorionic gonadotropin (HCG), alpha-fetoprotein (AFP), or lactate dehydrogenase (LDH) ovarian germ cell tumor markers; and high levels of inhibin, estrogen, or testosterone more commonly occurring in women with ovarian stromal tumors^[18]. According to the National Ovarian Council Coalition, a Pap test does not detect ovarian cancer and elevated CA-125 protein occurs in women already diagnosed with advanced stage ovarian cancer. CA-125 levels are good for monitoring the disease but not reliable for early detection, especially when elevated levels may be due to pregnancy, endometriosis, fibroids, ovarian cysts, and liver disease^[25].

2.1.5 Staging Ovarian Cancer

Biopsies are taken of the pelvis and abdomen in order to determine how far tumors have spread from the ovaries. The International Federation of Gynecology and Obstetrics (FIGO) system stages ovarian and fallopian tube cancer based on when it is discovered, recurs, or spreads. T, N, and M describe the primary tumor, possible metastasis to nearby lymph nodes, and the possible metastasis beyond the lymph nodes. Stage grouping then determines the cancer stage from I to IV or from least to most advanced cancer. Stage I indicates that the cancer is only located in one or both of the ovaries or fallopian tubes. Stage IA-IC indicates T1a-T1c, N0, M0 respectively. These substages indicate cancer on one ovary or fallopian tube, both ovaries or fallopian tubes, or both ovaries or fallopian tubes plus cancer cells found in the abdomen or pelvis due to IC1-IC3: the tumor breaking during surgery, the tumor rupturing before surgery, or the presence of cells not due to either of these things. Stage II indicates the cancer has spread from one or both of the ovaries or fallopian tubes to nearby pelvic organs but not to lymph nodes. Stage IIA (T2a, N0, M0) and Stage IIB (T2b, N0, M0) occurs when the cancer has spread from the ovaries (or fallopian tubes) to the fallopian tubes (ovaries), uterus, or both and when the cancer spreads from the ovaries or fallopian tubes to other nearby organs in the pelvis such as the bladder, sigmoid colon, and the rectum. Stage III occurs when the cancer is present in the ovaries or fallopian tubes along with being spread to the abdominal lining or lymph nodes. Stage IIIA1 occurs when the cancer spread to the lymph nodes is less than (IIIA1i) or greater than (IIIA1ii) 10mm in diameter. Stage IIIA2 indicates that microscopic amounts of cancer have spread to the abdominal lining or rear lymph nodes of the pelvis. Stage IIIB and Stage IIIC show

present to the surgeon as less than or greater than 2cm masses in the abdomen or outer part of the spleen or liver. Stage IV is when the cancer has spread maximally to the areas outside the peritoneum including the inside of the liver and spleen, the lungs, the brain, the skin, and other organs. Stage IVA includes cancer metastasizing to only the fluid surrounding the lungs, while Stage IVB includes cancer spreading to all other organs in the body not already mentioned in the previous staging^[26].

Primary peritoneal carcinoma is staged II to IV. Stage II includes cancer present in the peritoneum, stage III also includes cancer on the outside of the liver and/or spleen, and stage IV further includes cancer metastasized to the inside of the liver and/or spleen, along with the lungs, brain, skin, and bones^[26].

2.1.6 Survival Rates for Ovarian Cancer by Stage

The five year survival rate is the percentage of people who survive five years after being diagnosed with ovarian cancer. The five year relative rate adjusts the percentage to take into account death due to other causes. Multiple factors such as overall health and personal response to treatment affect the survival rate. Currently, 45% of patients survive for five years post-diagnosis of ovarian cancer. The specific breakdowns of the rates vary by cancer type. Nine out of sixty people are diagnosed early in stages IA or IB and have a 92% survival rate. The survival rate drops as the stage of the cancer increases. Invasive epithelial ovarian cancer has a relative five-year survival rate of 90% if diagnosed in stage I and 17% if diagnosed in stage IV. This type of ovarian cancer has the lowest survival rates for those diagnosed with stage IV cancer. Ovarian stromal tumors, germ cell ovarian tumors, and fallopian tube carcinoma have relative 95%, 98%, and 87% for stage I and 35%, 69%, and 40% for stage IV diagnosis. This shows that germ cell tumors in the ovary are the least malignant cancer to be diagnosed with^[27].

2.2 Causes and Risk Factors

2.2.1 Risk Factors for Ovarian Cancer

There are numerous risk factors that potentially contribute the development of ovarian cancer. While ovarian cancer is rare in women under 40, postmenopausal women have a much higher risk of getting the disease. Risk increases if the woman has a body mass index of 30 or above. Women reaching full-term pregnancy before age 26 or who have completed multiple full-term pregnancies have lower risk; conversely, women who have their first full-term pregnancy after age 35 or never reproduce have a higher risk of getting diagnosed with ovarian cancer. A three to six month or longer use of oral contraceptives decreases risk along with use of depot medroxyprogesterone acetate injectable contraceptive. Tubal ligation and hysterectomy procedures each lower risk factor by two-thirds and one-third respectively. Low malignant potentials increase in women who have used fertility drugs such as clomiphene citrate, especially if they do not get pregnant while on the drugs; infertile women also carry the same increased risk. There is the possibility that male hormones called androgens, which are raised by taking drugs like Danazol, increase risk. Postmenopausal women taking estrogen without progesterone for five to ten years or more have a higher risk as well. The higher the family history of ovarian cancer on the maternal or paternal side increases the women's risk of getting the disease; the same increased risk is seen with colorectal and breast cancer due to gene mutations that are passed along within families. Five to ten percent of ovarian cancers are due to such mutations. BRCA1 and BRCA2 are two common cancer-prevention genes that can undergo mutations and cause higher incidences of ovarian, fallopian tube, breast, primary peritoneal, prostate, and pancreatic cancer. The malfunction of these tumor-suppressor genes leads to an ovarian cancer risk of 30 to 70 percent for those with the BRCA1 mutation and 10 to 30 percent for those with the BRCA2 mutation. Without these mutations, there is only a two percent chance of ovarian cancer diagnosis. Inherited PTEN gene mutations also cause increased risk, and is sometimes manifested concurrently with thyroid problems and breast cancer. Abnormal MLH1, MLH3, MSH2, MSH6, TGFBR2, PMS1, and PMS2 genes impede DNA's ability to repair itself and lead to hereditary nonpolyposis colon cancer and a 10 percent chance of developing ovarian cancer, along with possible endometrial cancer. Peutz-Jeghers syndrome from the STK11 gene mutation and MUTYH-associated polyposis from the MUTYH gene mutation develop polyps in the digestive tract, digestive tract cancers, and ovarian cancer^[28].

2.2.2 Ovarian Cancer Causes

The cause of ovarian cancer is unknown, but there are hypotheses made based on what research claims to reduce the risk of ovarian cancer. For instance, birth control and pregnancy lead to decreased likelihood of contracting the disease, which is why ovulation is speculated to be linked to ovarian cancer. Tubal ligation and hysterectomies additionally decrease the risk of contracting the disease, which led researchers to wonder whether the organs act as a conduit for cancerous agents to reach the ovaries. Male hormones are also thought to increase ovarian cancer risk. Additionally, mutated DNA that controls cell growth and division is known to cause cancer^[29].

2.2.3 Can Ovarian Cancer Be Found Early?

Research is currently being performed in order to find ways to detect ovarian cancer at early stages, where there is 94% chance of survival. This is due to the fact that pelvic exams only detect the most advanced stages of ovarian cancer. Although ovarian tumors are incapable of being felt by physicians during these checkups, other conditions and cancers may be discovered this way if the symptoms are similar for other related diseases^[30].

An abnormal mass or increase of fluid may cause swelling of the area and appear in the form of bloating to the patient. Atypical and more extreme symptoms of early satiety, change in urgency or frequency of urination, and pain or pressure in the abdomen also indicate ovarian cancer as the origin of the problem if occurring consistently on a daily basis. These symptoms may indicate later stages of the disease, but are important if found early enough to be linked to preferably early stages of ovarian cancer^[30].

Screening tests are currently being developed when no symptoms present themselves to the patient. Transvaginal ultrasound (TVUS) and the CA-125 blood test are the two screening tests currently used, with TVUS used for mass detection and the blood test used for monitoring the effectiveness of treatment once a person already has ovarian cancer. TVUS is non-specific on whether the mass is cancerous or benign and TVUS is more of a tracking method rather than early detection. Further, there are no screening tests used for detection of germ cell or stromal tumors. And, the previously mentioned epithelial tumor screening tests are not recommended for people who are asymptomatic to ovarian cancer, and only used when surgeries for investigative or tissue removal is required^[30]. *Thus, an effective screening test is still needed to effectively detect ovarian cancer at its earliest stages.*

2.3. Ovarian Cancer Treatment and Support

2.3.1 Treating Ovarian Cancer

A combination of surgery, chemotherapy, hormone therapy, targeted therapy, and radiation therapy are used for treating ovarian cancer.

Ovarian stromal tumors use hormones or hormone-blocking drugs as a therapy. These include the following: Luteinizing-hormone-releasing hormone (LHRH) agonists/ GnRH agonists, Tamoxifen, and Aromatase inhibitors. LHRH agonists lower estrogen levels released by the ovaries in pre-menopausal women. The draw-back is menopausal sypmtoms and onset of osteoporosis if the drugs with LHRH agonists are taken for years at a time. Tamoxifen also acts as a therapy for stromal ovarian tumors with anti-estrogen properties causing menopausal symptoms, and weak estrogen properties that avoid onset of osteoporosis but cause dangerous blood clots in the legs. Aromatase inhibitors block the enzyme aromatase from turning enzymes into estrogen in post-menopausal women; they act as a therapy against stromal tumors but may lead to osteoporosis and hot flashes. Note that Tamoxifen and Aromatase are commonly used in breast cancer treatment^[30].

Targeted therapy only attacks cancer cells, and the way they grow, divide, repair, and interact with other cells in the body. The therapy is unique in that it leaves noncancerous cells alone. Bevacizumab, an angiogenesis inhibitor, and Olaparib, a PARP (poly(ADP)-ribose polymerase) inhibitor, are two of the most common types of cancer therapies. Bevacizumab stops vascular growth that feeds tumors by binding to vascular endothelial growth factor (VEGF). Bevacizumab shrinks advanced epithelial ovarian tumors, but has many side effects such as bleeding and high blood pressure, yet does not prolong life. Olaparib helps block the PARP pathway and only works with mutated or blocked BRCA (tumor suppressor genes) pathways that no longer repair damaged DNA. In this specific, but uncommon case, the therapy can help slow or inhibit tumor growth in women with advanced ovarian cancer. However, there are symptoms like nausea and vomiting and no observed prolongment of life^[31].

Chemotherapy is a drug taken orally, intravenously (through an IV), or through a catheter in the abdomen to distribute to and kill metastasized cancer throughout the body. It is used to treat epithelial ovarian cancer, germ cell tumors, and stromal tumors. Epithelial ovarian cancer is treated with a combination of a platinum and taxane drug given intravenously every three to four weeks over the span of three to six cycles. There are thirteen well-known drugs used to treat epithelial ovarian cancer, which often shrinks and disappears, then possibly recurs later. The drugs also damage normal cells despite precautions taken by the doctor during treatment, and cause nausea and vomiting, loss of hair and appetite, rashes and mouth sores, and increased chances of fatigue, bruises, and infections due to low blood count. As a remedy, increased water is given to reduce the risks of kidney damage and anti-nausea medicine is provided. Neuropathy and ototoxicity are more permanent as there is no preventative medicine known to mitigate effects of the cancer drugs for the nerves in the body or to the ears. Both ovaries are typically removed before chemotherapy, so loss of fertility and menopause are already affected for preservation of life. Intraperitoneal (IP) chemotherapy involves injecting

concentrated cisplatin and paclitaxel into the abdomen through a catheter placed during surgery along with paclitaxel given through an IV. This is a highly beneficial treatment in order to get rid of the cancer sooner and prolonged life. This is only feasible if the increased severity of nausea, vomiting, and abdominal pain can be tolerated by the patient^[32].

Chemotherapy used for germ cell tumors includes the drugs cisplatin (Platinol), etoposide, and bleomycin, referred to as PEB. A more gentle combination of drugs includes carboplatin and etoposide. TIP, VeIP, and VIP drug combinations are used if the cancer does not respond the either of the abovementioned treatments. These drugs cause almost identical symptoms to those mentioned for epithelial ovarian cancer. These include nausea, vomiting, ototoxicity, neuropathy, fatigue, and potential kidney damage. In addition, the lung and bladder may be affected by some of the chemotherapy drugs. Although most side effects will go away, younger women with germ cell tumors may see early onset of menopause and inability to reproduce. As above, bone marrow may also be permanently damaged by the use of these drugs, which is rare, but serious^[32].

Stromal tumors are not commonly treated with chemotherapy. However, they are sometimes treated with PEB, the same drug combination used to treat germ cell tumors. It thus presents the same symptoms as listed for germ cell tumor chemotherapy^[32].

2.3.2 After Treatment for Ovarian Cancer

People may completely recover, recover and recur, or never completely recover from ovarian cancer. For those who do temporarily or completely recover, they need to make follow-up appointments with their doctor in order to monitor their symptoms and make sure side-effects are taken care of. It is also important in order to prevent recurrence in the future. For instance, CA-125 levels can be monitored and treatment started before the presentation of symptoms in order to avoid recurrence. However, this preventative treatment has its own symptoms that need to be discussed with the patient. The following markers are monitored for recurrence: CA-125, CA 19-9, CEA, and HE-4 for epithelial ovarian cancer; alpha-fetoprotein (AFP) and human chorionic gonadotropin (HCG) for germ cell tumors; and estrogen, testosterone, and inhibin for stromal cancers. These preventative tests will occur for years after the patient's cancer has terminated, with all documentation of their cancer transferred if they seek a new doctor for care^[33].

In summary, there are no effective screening tests for ovarian cancer that leads to prolonged life. This is why a minimally invasive scope for the fallopian tubes is being developed: in order to investigate the disease and prevent it in its early stages.

CHAPTER 3 – SUMMARY OF PHOTOSTRESS PAPER

I wrote the article "Photostress Testing Device for Diagnosing Retinal Disease" as continued independent research after completing the prototyped photostress tester with a team of multidisciplinary engineers. The goal was to analyze the safety and illumination levels at the back of the retina. This provides the user data to confirm accuracy of the test and safety of the device based on established research on both topics of what has been proven to be effective. I did the research and wrote the paper independently with acknowledgements listed at the end of the paper. This research adds to the field by contributing the simulation and lab tests required before tests can be performed on humans. This takes the research one step closer from the lab to market, and makes it effectively a step in the translational research process. This means the device was brought closer to its end goal of preventing and monitoring blindness a simple userfriendly tool.

CHAPTER 4 – SUMMARY OF PHOTOSTRESS TESTER INVENTION DISCLOSURE

I wrote an invention disclosure for the photosress tester because I wanted to set in motion a protection of my team's and my intellectual property rights to the prototype before I published a paper with research on the device. Additionally, I wanted to keep doors open for the device to get to market and be used by patients, so this was a necessary step in that process. All inventors are referenced in the disclosure and I got their critiques, inputs, and approval before I submitted the disclosure and got it accepted. A summary, overview, details, alternatives, and limitations were all detailed for the photostress tester as required for any invention disclosure.

The intent of the device is to be used at home as a simple test so that patients can monitor their eye health in between doctor visits. It is additionally a safe test. Shortcomings of the prior art included lack of proper eye focusing and alignment of the eye and lack of a test method or reading a vision chart before and after the test that fits all human's intellectual abilities. For instance one prior device required that the patient have the ability to be able to read in order to take the eye test. Additionally, the patient's refractive power was not corrected so even with the ability to read, they may not have accurate test results. The photostress tester's fixation ring provides a centration and alignment of the fovea and macula even for a dysfunctional retina. Also, the photostress tester takes into account the time in which a patient takes to recover their vision and see a low light flashing LED after being bleached by a bright light. Anything over a standard patient recovery time of 20 seconds recorded indicates macular damage. This test is thereby not subjective to the patient's reading abilities. Additionally, the refractive power of the patient's eye is adjusted before the test by a badal lens so that the patient's visual acuity does not prevent an accurate test from being taken. Overall, the photostress tester improves test accuracy for retinal health and can prevent macular degeneration as development continues.

CHAPTER 5 – SUMMARY OF STRAY LIGHT PAPER

I completed detailed stray light analysis on the group's designed falloposcope in order to determine the cause of stray light in the system, an accurate numerical aperture range over which the device would operate over as designed. These runs took up to 48 hours at a time even to make small adjustments in the setup of the simulations. I completed the simulations and wrote the paper individually and would like to acknowledge the other team members who designed the constraints of the system and gave input to the final simulation and critiques to the proceedings paper I completed. Such simulations identify the cover plate as the source of the stray light and show how such a simulation considered every surface in the system to reach that conclusion. As stray light is such a niche field, this thorough proceedings paper was valuable in identifying its location in analytical terms aside from just a guess about where the source of unwanted light emanated from. Further, the paper concludes that the designed system as is can have a 0.35 numerical aperture or 0.25 numerical aperture to have the signal be at the same level or a magnitude below the level of noise in the system. This is valuable information to have as a large numerical aperture is top priority in this and other such endoscope designs. Addressing the limiting factor of stray light gave the team a data to work from in order to mitigate stray light and optimize the device numerical aperture.

CHAPTER 6 – ADVANTAES OF USING FRED OPTICAL ENGINEERING SOFTWARE

Stray light is becoming a more worried about feature when aiming for high signal to noise ratio of medical devices. As a response, multiple optical software companies are writing code and incorporating this capability into their software package. There are several reasons why I chose to use FRED optical engineering software over more popular competing ZEMAX and ASAP programs.

ZEMAX is first and foremost a lens design software with only newly added stray light capabilities. ZEMAX advantageously has embedded lens modelling capabilities for any design completed in the program. Stray light analysis is immediately performed on the optical system without having to import lens geometry into the model. Fred requires the addition of certain lens specifications even when lens models are imported from ZEMAX or SolidWorks. All of the lens properties and materials are maintained in the ZEMAX program before stray light analysis is completed so that the user does not need to enter or define these parameters. While ZEMAX initially saves the user time in the lens modelling, the actual stray light tests are not nearly as thorough or complex as those that can be performed in illumination softwares like FRED and ASAP. The simulations performed in ZEMAX would only be performed for simple overview stray light work.

ASAP has well-developed stray light capabilities that have been in use for longer than ZEMAX. However, for a novice in stray light or illumination, it is a large learning curve to use in comparison to FRED. This is because the user have to import or create the geometry that they want to use for the design, just like in FRED. However, for the user that does want the powerful stray light capabilities of FRED, this software may compete in that area, but lack the easy of the graphic user interface of FRED. Unlike FRED's ability to do stray light testing without any coding, ASAP requires much more data entry and coding capabilities that take much more training and expertise from the user. There is a lot more manual entry and from scratch building of geometries and light sources in ASAP in comparison to FRED.

FRED, on the other hand, does in depth stray light and advanced stray light runs and analysis allowing analysis planes to be set anywhere in the system by the user. Indepth illumination information is acquired. This includes the following: surface and raypath with the most stray power, illumination incident on forward or backward propagating rays, different definable light sources emanating anywhere in the system and being detected at any desired location, illumination and intensity from userdefined/catalogued/standard light sources with radiation specifications incorporated, and any light data captured from a user's experimental system setup to be imported into the program and run through the user's geometry set-up for analysis. FRED is a powerful, well-developed illumination software that has developed the most user-friendly in-depth analysis tools for stray light.

CHAPTER 7 – STRAY LIGHT TROUBLE-SHOOTING IN FRED

Multiple user hours can be saved when performing stray light analysis in FRED by following a few rules of thumb I learned along the way. First, I learned that FRED imports SolidWorks geometry using NERBS: non-rational B-Spline geometry that makes centering the object very difficult and referencing other objects to that geometry only possible with reading the coordinates provided by the curser tool. Using native FRED geometry and objects is very important to speed up ray tracing time and avoid difficulty in mating parts within the device. Additionally, I learned that for simulations lasting longer than 48 hours, it is wise to terminate rays from being traced that did not reach the surfaces being analyzed. For instance, a ray may bounce back and forth (due to factors like total internal reflection) within a specific geometry and never make it to the analysis plane, making the simulation last indefinitely. Furthermore, it is important to set the limits of the detectable power such that low light can still be detected. The trade-off is that ray-tracing time increases to unreasonable amounts if no cut-off is placed. Tracing too low light rays will keep the simulation running for a week, a very inefficient and unnecessary process to go through if the problem is tracing too many low light rays through the system.

CHAPTER 8 – FUTURE WORK

The photostress tester next steps include making sure that the current design upholds long term and is durable for the user. This means optimizing code for the microchip microcontroller and ensuring long battery life for the device. Additionally, further investigation regarding safe light levels on the eye would be performed in order to get the device FDA approved. Also, I would contact Janet Major, Associate Director of Facilities for Arizona Telemedicine Program. She has experience in taking devices such as the photostress tester and turning them into user-friendly tools for remote use. Further, about a year ago we were in contact and discussed our mutual interest in collaborating with each other. Our common ground was discovered at the 2014 AZTC/CCW Legislative Day. In order to turn the device into a fully functional tool for prevention of blindness, I would finish and polish up the technical ends on the prototype then collaborate with Janet Major to make the device ready for remote use. Then, sponsorship can be found for the manufacture of the device.

The falloposcope is still being actively prototyped in Dr. Jennifer Barton's lab and I have no doubt that it will be used translationally in research to one day contribute to determining the origin of ovarian cancer, working towards early detection, and saving women's lives.

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APPENDIX A – PHOTOSTRESS TESTER PAPER

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Article

Photostress Testing Device for Diagnosing Retinal Disease

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Abstract

Retinal diseases such as Age-Related Macular Degeneration (ARMD) affect nearly one in three elderly patients. ARMD damages the central vision photoreceptors in the fovea. The Photostress Test is a simple technique for testing for the early effects of ARMD. Here, the illumination sources in a novel self-administered Photostress Testing device were modeled for safety and distribution in illumination software. After satisfying the design constraints in the model, a prototype of the illumination system was fabricated and tested to confirm the modeling results. The resultant prototype can be used to aid in the diagnosis of retinal disease and is well within retinal safety levels. Keywords: photostress tester; Age-Related Macular Degeneration; Badal Lens

1. Introduction

Age-Related Macular Degeneration (ARMD) is a progressive disease where the photoreceptors of the retina are damaged, creating a localized blind spot in the field of vision. The disease typically affects the photoreceptors in the fovea, while leaving peripheral vision unaffected. Consequently people with ARMD tend to be able to navigate just fine, but have difficulty with tasks such as reading, watching television and identifying faces due to a central blind spot. Early diagnosis and treatment may help slow the progression of the disease. The Photostress Test is a simple means for screening for ARMD [1,2]. In the test, a bright spot of light is shone on the fovea to bleach the photoreceptors, effectively creating the spots people "see" following flash photography. In healthy retinas, the after image spots resolve fairly quickly, while in patients with early stage ARMD, the spots take much longer to disappear. We are developing a Photostress Testing device that can be self-administered. The Photostress Testing device was modeled and analyzed in FRED Optical Engineering Software (Photon Engineering, Tucson, AZ, USA). The purpose of the Photostress Testing device is to test the recovery time of a person's eye from being bleached by a central light source. The design calls for the patient to hold the device up to their eye and look through the center of a ring. This aligns the optical axis of the device with the visual axis of their eye. The person then presses a button that introduces a bright flash of light onto a small part of the retina called the fovea. This temporarily bleaches their retina so that their vision is impaired. The button, once pushed, triggers the light source to begin blinking at a much lower illuminance. Once the viewer sees this light, they re-push the button to stop the timer. The time elapsed from the initial bleach of their eye to the recovery of vision is called their recovery time. This time is compared to a standard value of recovery times that will be determined by test trials of many subjects using the device. If the viewer's recovery time is within a standard deviation of the accepted value, their fovea (the center of the retina) is healthy. However, if the recovery time is outside a standard deviation of the typical recovery time, the patient is diagnosed with diseases of the macula such as genetic disease affecting the macula, e.g., Retinitis Pigmentosa, Best disease, etc., Stargaurdt's disease, Diabetic Macular Edema (DME), Central Serous chorioretinopathy (CSCR) and Age-Related Macular Degeneration (ARMD): a degradation of the macula that causes a person to lose their central vision. The test also distinguishes optic neuropathy form macular diseases. Components of the Photostress Testing device are detailed in Section 2.1, a model of the in optical illumination software is shown in Section 2.2, analysis from that software shown in Section 3.1, a comparison between the software analysis and experimental results is made in Section 3.2, and a conclusion is made in Section 4.

2. Experimental Section

2.1. Components of the Photostress Testing Device

The Photostress Testing device consists of a target, a Badal Lens, and the eye. The target is the source of the system. It is composed of a center LED surrounded by six picoLEDsTM. The center LED (NSSW064, Nichia) is a 2.8 mm \times 3.2 mm LED with a circular emission region that is $2.4 \text{ mm} \times 2.4 \text{ mm}$. The target is placed at the front focal point of a Badal Lens, while the pupil of the eye sits at the rear focal point of the Badal Lens. In this configuration, the target can be axially shifted to compensate for refractive error in the eye, but the target size will remain constant on the retina. The purpose of the center LED is to "bleach," or temporarily blind the viewer by emitting 2000 Lx to 4000 Lx onto their retina [3,4]. The six picoLEDsTM, (SMLP12WBC7W1, Nichia), are 0.6 mm \times 0.6 mm LEDs that emit 11.5 μ W of light into the system [5]. Their function is for alignment; the viewer looks at the center of the ring of six picoLEDsTM, and by doing this, aligns the optical axis of the device to their visual axis. All seven sources emit white light. Figure 1 shows the layout of the LEDs. The Badal Lens, (NT49-664, Edmund Optics) is an aspherized achromatic lens with a 25 mm diameter and 40 mm focal length. Its purpose is to collimate the light from the source so that a clear image can form on the retina. For nearsighted and farsighted individuals, the target is moved towards or away from the Badal Lens by plus or minus 8.0 mm. This provides the eye with negative or positive corrective power within a range of plus or minus five diopters.



Figure 1. This is the source layout. Each grid line is 0.5 mm. The yellow rectangles represent where the LED and picoLEDsTM will be placed into. The rectangles are a little larger than the actual LED and picoLEDsTM. The gray represents the solder pads for the sources. The picoLED'sTM center coordinates are labeled.

2.2. Model of Photostress Testing Device in Optical Engineering Software

2.2.1. General Model

The center LED and picoLEDsTM were shown in separate ray traces for each model in order to more clearly show how each was traced through the system. Note that

the central LED at the bleaching setting is referred to the bleaching LED; at the blinking setting it is referred to as the blinking LED. Note also that the sources are kept at one position and not translated in the software for the illumination analysis.

2.2.2. Source Model

The sources in Figure 2A,B are modeled in optical engineering software as detailed optical sources. For the model of the picoLEDsTM (Figure 2a), rays are shown sitting on a 0.6 mm × 0.6 mm random grid plane that is rectangular. For the model of the bleaching LED (Figure 2b), rays are sitting on a 2.4 mm × 2.4 mm random grid plane that is circular. Once traced, the rays are set to emit into an angular range of 10 degrees in the X and Y directions from Z, the axis orthogonal to the source grids. This angle was chosen as to view only light that passes through the system. The source powers were set to 7.5×10^{-3} Lm, 0.8 lm and 5.8×10^{-3} Lm for the picoLEDsTM, bleaching LED, and blinking LED respectively, *i.e.*, the bleaching LED emits 144 times more power than the blinking LED and 112 times more power than the picoLEDsTM. Their spectrums were digitized into the optical engineering software from the data sheets. Ten million rays were traced from the center LED at each setting and 200,000 rays were traced from each of the six picoLEDsTM. This is more than is required by the Rose model to ensure an accurate ray trace; the Rose model required a minimum of 148,852 rays to be traced from the bleaching LED and 9716 rays to be traced from each of the six picoLEDsTM [6].





2.2.3. Lens Model

The lens model is number NT49-664 and was imported from Zemax (Radiant Zemax, Redmond, WA, USA). It is an aspherized achromat oriented for minimum spherical aberration (Figure 2). Its function is to collimate light from the source for viewers with perfect visual acuity (20–20 vision).

2.2.4. Arizona Eye Model

The Arizona Eye Model was opened as a sample file in the software. It is composed of a cornea, lens, pupil, and eye ball. The light refracts at the cornea and a little at the gradient index lens. The pupil is the aperture stop of the system and limits how much light enters the eye. It is set to a diameter of 6 mm. At the back of the eye ball is the fovea, which is about the size of the image from the central LED source. The magnification m of the system changed the size of the source after it passed through the Badal Lens and through the eye by

$$m = \frac{f_{eye}}{f_{Badal \ Lens}} \tag{1}$$

where f_{eye} is the focal length of the eye (23 mm) and $f_{Badal Lens}$ is the focal length of the Badal Lens. In order to determine which focal length lens to use, the bleaching LED had to be chosen. Once an LED with the correct illuminance was found, the magnification was found to be

$$m = \frac{D_{fovea}}{D_{LED_{width}}}$$
(2)

where D_{fovea} is the diameter of the fovea (1.5 mm) and $D_{LED width}$ (2.8 mm) with the diameter of the shortest side of the LED. The magnification turned out to be m = 0.54. Using this magnification and the focal length of the eye, the desired focal length of the Badal Lens was calculated to be $f_{Badal Lens} = 42.9$ mm. The closest lens to that had a focal length of 40 mm and covered an image diameter of 1.6 mm, which is a little larger than the fovea.

2.2.5. Analysis Surface

The analysis surface was placed at the back of the retina, as shown as a green box in Figure 3. It is a 4 mm \times 4 mm grid that collects all of the rays. It has 51 \times 51 divisions.



Figure 3. Badal Lens. The Badal Lens reduces spherical aberration and collimates the light in its direction of propagation. (**a**) Note that for the whole system it is difficult to tell how the light is directed by the lens; (**b**) A bottom picoLEDTM gets refracted by the lens and focuses at the top of the retina. The light is well collimated at the angle it is propagating in; (**c**) The light is visibly collimated on the Z axis after the lens and before it enters the eye.

The analysis surface shows the source distribution on the retina in Figure 4.



Figure 4. Images formed by Photostress Tester. (**a**) The image of the source is a smaller image of the six picoLEDsTM; (**b**) The image of the source is a circle with the same shape, but with a smaller size.

3. Results and Discussion

3.1. Analysis of Photostress Tester in Illumination Software

Figure 5a shows a false color illuminance plot for the six picoLEDsTM. The maximum power detected was 1.20×10^{-5} lumens (Lm): 617 times less power than was emitted. The maximum illuminance detected was 4.1×10^{-5} Lm/mm^z. Figure 5b shows the illuminance data scaled by log (base 10) with the floor set to -2.4; the chart color levels were set to gray. The purpose of this was to model the image brightness perceived by the human eye, which is the log of the source's actual brightness [7]. Figure 5c shows the color image of the picoLEDsTM with a brightness setting of 2.2. This simulates what color the viewer will see when they look at the picoLEDsTM.



Figure 5. Illumination Analysis. (**a**,**b**,**c**) The illumination analysis windows show a false color illuminance plot; (**d**,**e**,**f**) perceived brightness plot; and (**g**,**h**,**i**) color plot for the picoLEDsTM, bleaching LED, and blinking LED.

Figure 5d shows a false color illuminance plot for the bleaching LED. There were 2.3×10^{-3} lumens covering the 1.76 mm² bleach area compared to the 0.8 lumens emitted from the LED. The maximum illuminance detected was 1.3×10^{-3} Lm/mm² or 1300 Lx. The diameter of the image is a 1.53 mm, showing that the fovea (with a diameter of 1.5 mm) will successfully be bleached. Figure 5e shows the illuminance data scaled by log(base 10) with a floor of -2.4. This models the illuminance perceived by the eye when the LED is at the bleach setting. Figure 5f shows the color plot of the bleaching LED with the brightness set to 2.2.

Figure 5g shows a false color illuminance plot for the blinking LED. There were 1.6×10^{-5} lumens covering the 1.76 mm² blinking area compared to the 5.8×10^{-3} lumens emitted from the LED. The maximum illuminance detected was 9.0×10^{-6} Lm/mm² or 9 Lx. This is two orders of magnitude lower than what was detected by the bleaching LED. The diameter of the image is 1.53 mm. Figure 5h shows the illuminance data scaled by log(base 10) with a floor of -2.4. This models the illuminance that the eye perceives when the LED is at blinking setting. Figure 5i shows the color plot of the blinking LED with the brightness set to 2.2.

3.2. Comparison of Software Analysis to Experimental Results

Data taken from the illumination analysis was compared with data taken in an experimental set up to test the safety of the device. Specifically, the illuminance of the bleaching LED was tested, as it was the primary safety concern for the device. The spot size was taken as well.

3.2.1. Setup

The experimental set up consisted of the source, Badal Lens, adjustable iris, and eye lens mounted with posts, post holders, translation stages, rail carriers, an optical rail, and an optical bread board (See Figure 6). The sources were fabricated after the model shown in Figure 1. The Badal Lens was the same lens modeled in the software (NT49-664, Edmund Optics). The adjustable iris had a diameter of 6 mm. The eye lens was a 12.5 mm diameter \times 17.5 mm focal length achromat (NT49-928, Edmund Optics). The focal length of the lens was a close match the eye's effective focal length in air: 17 mm [8]. This accounts for the lens being in air rather than surrounded by two disparate mediums, as it is in the eye.



Figure 6. Experimental setup of the Photostress Tester.

3.2.2. Experiment

The bleaching LED was turned on to emit 0.8 lumens of power. A handheld power meter from Edmund Scientific was held up to the focal point at the back of the eye lens and used to test to power there. The size of the image at the focal point was taken with calipers held up to a white imaging screen that captured the image. The area of the image was calculated and used to determine the illuminance at the image plane. The experiment was repeated at the two extremes of the source translation: -8 mm and +8 mm from the front focal length of the lens.

3.2.3. Results

Main Table 1 shows the illuminance values on the retina as 3106 Lx, 2622 Lx, and 2003 Lx. These values are all within the desired safe range of 2000 Lx to 4000 Lx. The illuminance from the software was 1300 Lx, which is lower than the targeted range. The variation is likely due to stray light entering the power meter from the room. The measured spot size at each location matches expected value of 1.5 mm.

Translation (mm)	Illuminance Ev (lux)	Spot size (mm)
-8	3106.7	1.5
0	2622.9	1.5
8	2003.2	1.5

Table 1. Illuminance on the retir

4. Conclusions

A Photostress Testing device was modeled and analyzed in optical engineering software. The illumination analysis showed that the image of the bleaching LED

successfully covered the entire 1.5 mm diameter fovea with a diameter of 1.53 mm. It also showed that 1300 Lx from the bleaching LED hit the retina, which is a safe value since it is under the initial target range of 2000 Lx to 5000 Lx. Experimental data confirmed that the Photostress Testing device produced an image 1.5 mm in diameter from the bleaching LED with illuminance values of 3106.7 Lx, 2622.9 Lx, and 2003.2 Lx at the -8 mm, 0 mm, and +8 mm translation distances of the source from the front focal length of the Badal lens. This showed that the bleaching LED produces illuminance on the retina within the safe illuminance range even when the target is translated. Discrepancies between data from the software and from the experiment are due to experimental error. In the experiment, light from the source did not fill the entire detector, thereby rendering higher values than expected. The apparent discrepancy between the experimental and theoretical prediction appears to be associated with the size limitations of the available detector. One possible improvement of the experimental design could include placing the detector closer to the source, so that its active area is overfilled. This will bring the measured illuminance values closer to those obtained via simulation.

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The work done in the paper was performed to enhance a senior design project consisting of an optical engineer (Elizabeth Swan), two mechanical engineers (Abraham Timler and Layne Castro) and an electrical engineer (Oscar Galvan) as part of the ATLANTIS student mobility grant at the University of Arizona. Oscar Galvan provided Figure 1 and the illuminance values required to bleach the retina. John Koshel provided FRED modeling and analysis insight. The project was sponsored by the US Department of Education (P116J080016) and the National Science Foundation (Grant #: 0856761, 1311851).

Author Contributions

Elizabeth Swan wrote the majority of the manuscript with edits done by Jim Schwiegerling. Jim Schwiegerling also suggested the use of a Badal Lens in the device. Eniko Enkov and Gholam Peyman were responsible for the funding of the project and main design and end objectives.

Conflicts of Interest

The authors declare no conflict of interest.

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APPENDIX B – PHOTOSTRESS TESTER INVENTION DISCLOSURE

OTT Use Only INV. DISC. NO.____

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Date Received:

OTT, Tech Launch Arizona The University of Arizona INVENTION DISCLOSURE FORM

1. Title & Summary of Invention

Title: A Photo-Bleach Test for Visually Impaired Patients

• Briefly describe the invention: The description should include enough detail so that a reasonably capable person could replicate your research results (manuscripts, theses and reports are examples of good starting points for technical descriptions). Please refer to the Guidelines section of the Appendix to help you think through each section more specifically.

Essence of the Invention: (A short Paragraph / Bullet Points)

• The Photostress Testing device detects visual changes in the retina before irreversible damage can occur. It works by temporarily blinding a small part of the retina called the fovea and testing the time it takes for full eyesight regeneration, a process known as photobleaching. Recovery times in healthy eyes are much shorter than in eyes with diseases such as macular degeneration.

Description of the Invention: (A short Paragraph / Bullet Points)

Guidance: The invention or development must be described in adequate detail so that a skilled scientist or engineer can fully understand the invention.

a. What was the problem(s) that you set out to solve and why did you decide to solve it?

Macular degeneration is a major cause of vision loss in the United States. It affects the macula, thus inhibiting the sharp, central vision. This disease occurs in two stages: dry MD and wet MD. In the more common dry MD, an accumulation of drusen - deposits of deteriorating tissue - occur in the macula. Figure 1 shows deposits of drusen (yellow spots) indicating early signs of dry MD. Wet MD is much more advanced and severe. New blood vessels begin to grow under the retina and leak blood and fluid, which can cause irreversible damage to the light-sensitive cells in the retina. This results in blind spots. The damage to the macula in both cases of macular degeneration is the reason for delayed response times during the photobleaching test and will give much insight into whether the patient suffers from MD[1.3,1.4].



Figure 1: Deposits of Drusen on Macula^[1.3]

The two additional diseases being tested with the retinal Photostress Tester are diabetic retinopathy and macular edema. Diabetic retinopathy occurs when increased glucose and fructose sugar levels in the blood begin hemorrhaging the retina's capillary system. The blood vessels in the retina are quite small making them quite vulnerable. This disease often occurs in people with long-term diabetes. Diabetic retinopathy often leads to macular edema in which the macula swells due to an accumulation of fluids and protein deposits. This affects cones in the macula and fovea causing problems with the central vision, namely with detail and color. Both diseases begin with small ruptures of the blood vessels in the retinal capillary system and affect the macula first before affecting the fovea or surrounding retina. This is because the density of the retinal capillary system is highest in the macula. For this reason, the LED ring will be used to target the macula and attempt to indicate where vision loss is present[1.5,1.6].

[1.3] Bianco, Carl. "How Vision Works." HowStuffWorks. HowStuffWorks, Inc. Web. 24 Sept. 2011. <science.howstuffworks.com/environmental/life/human-biology/eye2.htm>.

[1.4] Haddrill, Marilyn. "Age-Related Macular Degeneration." All About Vision. Access Media Group LLC, 13 Oct. 2011. Web. 24 Sept. 2011. <www.allaboutvision.com/conditions/amd.htm>.

[1.5] Bek, Toke. "Clinical Presentations and Pathological Correlates of Retinopathy." Karger Publishers 20:1 (2010): 1-19. Web. 5 Oct. 2011. http://content.karger.com/

ProdukteDB/Katalogteile/isbn3_8055/_92/_75/FDIAB20_02.pdf>.

[1.6] Cessna, Christopher T., and David G. Telander. "Macular Edema, Pseudophakic (Irvine-

Gass)." Medscape. WebMD LLC, 21 Apr. 2010. Web. 5 Oct. 2011. http://emedicine.medscape.com/article/1224224-overview>.

b. Describe the new process, method, or composition with enough information so that someone knowledgeable in the area could understand its key elements.

Include all essential elements, an explanation of how they relate to one another, and how they solve the problem.

The retinal Photostress Tester device detects visual changes in the central vision before irreversible damage can occur by timing the sight recovery response of a temporarily blinded central vision. A light source originating from a pattern of LEDs within the handheld Photostress Tester is focused via a single lens directing the light source into the eye's fovea, inducing photobleaching, a subtle blindness similar to the harmless blinding of night vision. The lens is adjustable to accommodate for the natural range of visual acuities. A timer, programmed and wired through a self-contained circuit, displays to an onboard LCD screen the time interval for full eyesight regeneration. Proper medical supervision will interpret the time interval for any delayed eyesight regeneration, which indicates the possibility of the early stages of macular degeneration. If an increased response time is observed, the lens can be switched out for a different lens that creates a smaller spot size on the macula. This allows for the specific area of the macula that is damaged to be located in order to better pinpoint the most severely damaged areas of the eye. Similarly, a circular pattern of white LEDs surrounding the central LED is focused over a wider area of the fovea for the purpose of testing visual sensitivities of off-center vision. A patient unable to detect the full LED arrangement due to blurs or shadows spotted throughout their visual field will be prompted to a likely loss in vision caused by diabetic retinopathy or macular edema.

The retinal Photostress Tester underwent three simultaneous areas of design based on the requirements of the optical, electrical, and mechanical fields. The optics of the Photostress Tester consisted of a specific lens capable of directing the light source into the eye's fovea and moving along the visual axis to account for a range of various visual acuities, such as nearsightedness and farsightedness, under different light wavelengths and intensities. Electrical design included the coding of a circuit that powers the light source and controls subsequent light intensity and the onboard timer, which allows user-inputted start and stop times via a start-stop button. Mechanical design consisted of coalescing the optical and circuitry components into a physical, fully operating handheld device capable of adjusting the distance between lens and eye as well as housing the circuit board, timer, and light sources. Structural design began with SolidWorks 3-D modeling software and was completed with the machining of an exterior casing and other necessary components.

Basic Requirements			
Table 1: Basic Requirements			
Requirement	Description		
Spot size	A safe spot size that will not damage any		
	part of the eye		
Illuminance	A safe intensity of light that will		
	photobleach the eye without causing it damage		
Bleaching LED,	A central LED to photobleach the eye and		

System Requirements

Blinking LED,	a ring of LED lights used to align the central LED
Alignment LED Ring	with the visual axis of the eye; i.e. the radius of
	the LED ring must be the right size to properly
	align this visual axis
Badal Lens	Single lens to (a) collimate/provide
	vergence so that light from the LEDs forms a
	clear image on the retina and (b) provide de-
	magnification of the source to form a smaller
	specified spot size on the retina
Recording Devices	A button, timer, and display to record
	how long it takes the patient to recover from their
	eye being photobleached
System Size	A small enough system size to be
-	considered a hand-held, portable device

Functional Description				
Table 2: Functional Decomposition				
Function	Description			
Circuit	Circuit to wire batteries to both ring LEDs			
	and central LED so that light can propagate			
	through the system			
Two Varying Lenses	Two stationary lenses to create two			
	different spot sizes on the macula in a movable			
	casing to account for varying visual acuities			
Mechanics	User-friendly mechanics to slide the lens			
	along the length of the Photostress Tester in the			
	specified range to adjust the patients' myopia or			
	hyperopia			
Button	Button for the patient to push once their			
	vision has recovered from being photobleached			
Timer	A timer that is powered to record the			
	patients' recovery time from their eye being			
	photobleached			
Photostress Tester Housing	Photostress tester housing to enclose and			
	lock down all electronic and optical parts and			
	hold the system together			

Novelty and major advantages: (A short Paragraph / Bullet Points)

• Discuss the uniqueness novel or unusual features of the invention and explain how it differs from or improves upon existing technologies.

The Photostress Tester utilizes a ring device that was previously patented by Dr. Peyman.

This Photostress Tester uses an LED for a bleaching source at a much lower illuminance than the previously patented arc lamp. This allows for a much lower and

safer light level that is incident on the eye.

Using the ring device uniquely allows this Photostress Tester to target a smaller and more specific area of the eye: the fovea, where ARMD originates, such that degeneration may be caught earlier, before it spreads to the outer regions of the retina. Further, the location of the degeneration can be more specifically than before.

\rightarrow Please attach additional supporting material \leftarrow









3. Internal Funding

Identify the source of the internal (UA) funding used to make this invention

4. List State/Federal Funding

Source

Sponsor Name, Grant/Contract Number and (%) contribution by Grant to your invention

Sponsor Name, Grant/Contract Number and (%) contribution by Grant to your invention

Sponsor Name, Grant/Contract Number and (%) contribution by Grant to your invention

5. External Funding

Industry Sponsor Name, Grant/Contract Number and (%) contribution by Grant to your invention

6. Fellowship money to post-

Identify non-government sponsors

(If none, please state "NONE")

1. US Dept. of Education # P116J080016 (FRS **3097700) 90%**

2. National Science Foundation (FRS 314110/1) 10%

3.

7. Materials		
Were any materials (e.g., plasmids or cell		
lines) used in making the invention received	Yes 🗌	No 🗌 🗴
from a third party?		
If yes, please identify the organization and		
whether there was a material transfer		
agreement (MTA)		
	(Name, Phone Nu	mber and e-mail, if
8. Principal Investigator	different from abo	ove)
Identify the Lead Inventor (the primary	Dr. Eniko	T Enikov
contact):	DI. LIIIKO	I. LIIKOV
Has a publication (abstract, website, ppt) submitted/presented in the past month or planned within Yes Pla	n to a paper	No 🗌
Has a publication (abstract, website, ppt) submitted/presented in the past month or planned within the next month? Yes Pla submit ASAP [10. Signatures	an to a paper	No 🗌
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Has a publication (abstract, website, ppt) submitted/presented in the past month or planned within the next month? 10. Signatures Inventor 1 Signature Inventor 2 Signature Inventor 3 Signature	n to a paper	No Date Signed Date Signed 6/9/2014 6/10/22

Appendix A

Please replicate this page to include additional inventors:

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	Ban Delor		Oscar Galvar	-Lopez	6/12/2014	
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Appendix B

Guidelines for Processing a New Invention Disclosure

1. Overview

• Describe the process of how you arrived at your invention.

Age Related Macular Degeneration (ARMD) is one of the major causes of loss of central vision of 1/3 of the people over the age of 70 Y. Aside from an early detection, there is a need for the chronic follow up of these patients. With the advent of anti-Vascular Endothelial Growth Factor (VEGF) in the last decade, we can now treat the wet or the neovascular type of this disease and halt its progress. However, the treatment requires monthly follow up of the patients and if needed, intraocular injection of the

medication. The repeated office visits present a burden to a number of the patients who may not need to be treated as often to prevent their disease deterioration before the patient's scheduled appointment. Therefore we felt that there is a need for a simple test that can be administered by the patient at home, to eliminate guessing of the patient, if his or her vision is getting worse which is an important sign of persistence or worsening of the disorder.

Shortcomings of the existing tests are:

1) Proper eye focusing and alignment of the eye and 2) The tests method or reading a vision chart before and after the test.

The previous tests suffer from the fact that proper focusing or alignment of the patient's eye during the test was not recognized as an important component of the test.

The center of the retina (Fovea) is the area with which the eye normally focuses an external light source, for fine vision and alignment of the eye accordingly. In the presence of the ARMD this area (Fovea) is damaged and the eye automatically chooses an eccentric adjacent area of the retina for fixation with their variable sensitivity for reading. This produces a variable focusing (misalignment) of the retina and the eye each time the eye is examined and an unreliable stress test result when the patient has to read the vision chart before and after the test. The patient does not notice this misalignment, which is recognized only by a doctor by examining the back of the eye. The misalignment affects also when the central retina is bleached by the administration a strong flash light.

Another shortcoming of the previous systems is the use of the subjective "reading of a visual chart" by the patient for evaluation of the "recovery time" after the flash light has stressed (blinded) the retina. This test is subjective and requires precise correction of the refractive power of the eye prior to the stressing the retina. Otherwise the patient cannot read properly to start with.

Finally, since the reading is a higher function of the brain than the simple recognition of a standard low level of light as in our system, the result is affected by the mental ability of the patients to read the visual chart and process what has been read. This function is not precise and is affected by the degree of patients' attention. In addition the presence of a small cloudiness (cataract) in the crystalline lens, reduction of the function of the optic N. or brain influences the results.

Elimination of the above shortcoming in our system.

The fixation ring in our unit provides a centration and alignment of the eye without the need of a functioning retina; since it is a two dimensional area. When presented to the patient, the retina automatically positions itself so that the image of the ring is always located or falls around the center of the retina (Fovea) with or without a functioning fovea. After fixation (alignment with the ring light) the strong but non-toxic

single light pulse of our system bleaches the center of the retina. The subsequent low level pulses of our system are standardized and have the same amount of low level light energy for all the subjects examined. Our results are evaluated by the recognition of low level pulsing light and not by reading a vision chart. These light pulses are recognized by the subjects only after recovery of the visual pigment or the function of the bleached central area of the retina. This recovery time for the healthy retina is within a standard of limitation of less than 20 seconds. However, any disease process affecting the fovea, increases this recovery time beyond what is measured in all normal subjects or "normal recovery time."

The patient can record their recovery time easily as soon as they recognize the low level light pulse by pressing a knob on the instrument. This recovery time (number) indicates precisely if the eye has improved, is stable, or worsened compared to a previous examination or compared to a normal eye.

Therefore our unit is independent of the subjective reading ability of a patient and is more accurate and quantifiable.

• Describe how the invention resolves the problem(s) (continued)

The Photostress Tester targets a small area of the back of the retina to test for degeneration for the prevention and early detection of many retinal diseases such as age related macular degeneration. It also can slow the progression of the degeneration if caught early.

• List any *additional* advantages and features of the invention.

Low bleaching levels are achievable and safe for the user. A small area is also bleached (instead of the whole retina), causing the degeneration to be found localized to a specific location, i.e. a slower user recovery time indicates degeneration in specifically the fovea in this device. The prior art suggests that there is degeneration at some point on the retina, but does not specify which region. As the degeneration is initiated in the fovea (center of retina) and spreads outward, this device is particularly suited to early detection of age related macular degeneration.

2. Details of the Invention

• Describe the individual components of the invention. Drawings, flow diagrams, and pseudo-code listings are always helpful, so feel free to attach as many as you like. If you use an unusual term or an ordinary term in an unusual way, please define or describe the term.



Figure 2. Photostress Tester Device

Letter	Component
А	LCD/Digital Timer Screen
В	End Casing
С	Timer Button
D	"Bleaching" / "Blinking" LED
E	Six PicoLEDs TM (Fixation Ring)
F	Outer Scope
G	Interchangeable Scopes (to create
	different retinal spot sizes)
Н	Eye Guard



Figures 3a and 3b. Suppressed and Rear View of End Casing Showing Inside Components

Letter	Component
Н	Battery Slot
I	Battery

J	Button Chip
Κ	LED Circuit Board



Figure 4a and 4b. Assembly of the Photostress Tester Device Interchangeable Scope

Letter	Component
L	Lens
Μ	Lens Holder



Figure 5: Cross Sectional View of Entire Photostress Testing Device

• Are any of these component parts new? If so, which ones?

The barrel was custom made out of ABS plastic via 3D printing for the Photostress Testing device prototype. Delrin (Acetal Homopolymer) is the proposed production material of the Photostress Testing device. Most other things were off the shelf components used in the Photostress Testing device according to the design.

• How are the components connected? How do they make the invention work?

The barrel screws in and out of the device to adjust for the near and far sighted vision of viewers without changing the magnification of the LED and therefore the size of the image of light that bleaches the back of the retina.

• Indicate the parts or connections that you believe are ESSENTIAL to the invention – that is, for each part, ask, "If this part were left out, or changed, would the remaining device still be my invention?" Or, "If this part were changed or left out, would the invention still work?"

The ring of picoLEDsTM and the relatively low bleaching intensity (in comparison to an arc lamp) of the center LED make the design novel and must be implemented for the device to work. In the prototype, the center LED "bleaches," or temporarily blind the viewer by emitting 2,000lx to 4,000lx onto their retina^{[1], [2]}. The six picoLEDsTM emit 11.5 μ W of light into the system^[3]. For the device to work, the lower power "blinking" light that follows the flash light must have considerably less power than the "flash" or "bleaching" light level; both the "bleaching" and "blinking" illumination settings are from light emitted from the central LED. This means that for the device to work, the blinking light should fall at the same area of the retina as the flash light; otherwise the peripheral photoreceptors of the retina will see that creates a false recovery time. In fact, the "blinking" light setting should be barely visible in comparison to the light emitted at the "bleach" setting. For instance, in the initial modeling of the Photostress Tester in optical engineering software, the source powers were set such that the bleaching setting of the central LED emits approximately 144 times more power than the blinking setting of the central LED and approximately 112 times more power than the picoLEDsTM (The exact source emittance values are in the paper I will submit if you think them necessary to include).

Please note that the fixation ring light is outside the central LED. The central light is a flash light that is converted to a very low power blinking light.

References:

- 1. Jacobs, Robert J., Lacey, Andrew. "The Macular Photostress Test" The Australian Journal of Optometry 66.4 (1983): 147-150. Print.
- Sykes, S.M., Robinson, W.G., Waxler, M., Kuwabara, T. "Damage to the Monkey Retina by Broad-Spectrum fluorescenet Light" Investigative Ophthalmology & Visual Science 20.4 (1981): Web.
- 3. Dhalla M.S., Fantin, Blinder KJ, et al. "The photostress test as a guide to etiology" Journal of the American Optometric Association 78.11 (2007): 570-571. Print.
 - Which parts took longest to develop? Why?

Choosing the correct source size and intensity too the longest to develop because it had to meet the electrical, mechanical, and optical requirements.

• Which features of your invention will competitors want to copy?

Low bleaching illuminances on the eye will want to be copied due to easily attainable safety ranges. This is most easily achieved using LEDs as light sources.

3. Alternatives

• Could any parts or processes be omitted changed or substituted with similar parts without changing the overall invention? How?

A different LED could achieve a different bleaching size and illuminance on the retina and a recovery time would be found. The time for recovery for a healthy eye and therefore relative recovery times would change in the diagnosis of the retinal degeneration. The Photostress Tester housing could be made with a different material or manufactured via a different process. The lens could be interchanged to create different spot sizes on the retina, along with changing the range of visual acuities that could be corrected for. Different lengths of the Photostress Tester interchangeable scopes would have similar effects on image size and range of correctable visual acuities (to make sure the viewer has 20/20 vision for the test).

• Is there a generic description for any of the parts or processes you listed (i.e., "interface" instead of liquid crystal display," or "switch" instead of "triac")?

-"Display" could be "liquid crystal display," "digital screen," or "LCD screen."

-The Photostress Testing device or Photostress Tester has been referred to as a type of "device" or retinal "photometer."

-The "central" LED has two functions and is referenced as the "bleaching" LED or flash light (which is set to the higher illuminance and bleaches the retina) and as the "blinking" LED (is set to the lower illuminance and is detected once the retina is recovered).

-"Barrel" and "scope" are interchangeable.

-"Badal lens" could be interchanged with "lens."

-"Illuminance" may also be seen interchanged with terminology such as "irradiance," "intensity," "luminous intensity," "luminous irradiance," "radiant energy," "radiant flux," or "flux."

- -"fixation" ring or "fixation" light or ring of picoLEDsTM
- Could the functions of any of the parts be changed? How about combined into a single component? Or eliminated altogether?

The scope currently twists and rotates to make the scope longer and shorter. A sliding mechanism could have also worked to shift the lenses closer/further from the source. Additionally, different length scopes result when used in combination with different focal length lenses to bleach a larger or smaller area of the back of the retina. Two scopes holding two different lenses were prototyped to test for 1.6mm and 512 micron spots on the back of the retina. Addition scopes could be fabricated and used with different lenses to allow for a range of testing diameters on the back of the retina. Blocking and then showing any part of the image that hits the retina would further increase specificity on where the retinal degeneration/disease was occurring in the eye.

• Can your invention be used for anything other than its intended application or environment?

No. However, patients using the Photostress Tester can be diagnosed with multiple diseases of the macula such as genetic disease affecting the macula (not just ARMD), e.g. Retinitis Pigmentosa, Best disease etc., Stargaurdt's disease, Diabetic Macular Edema (DME), Central Serous chorioretinopathy (CSCR) and Age-Related Macular Degeneration (ARMD): a degradation of the macula that causes a person to lose their central vision.

4. Limitations: When will the invention not work?

- Are there any critical characteristics or ranges of size, weight, pressure, etc. for any of the parts of your invention?
 - -The eyepiece must fit snuggly against the users and not let in stray light.

-The weight must not exceed the user's ability to hold the Photostress Testing device level and therefore aligned with their eye that is being tested for degeneration. This is different for each individual based on the user's strength.

-The size must be small enough to remain a hand-held device.

• Must some parts be made of particular materials to make the invention work? Name the materials and why they are necessary.

The lenses must be made of glass or the images will not focus and may not even be transparent and have high throughput of light in the visible range of wavelengths.

- What other products or services compete with or work like the invention? Visual Examination Apparatus was patented in 1985, but uses a high power xenon flash source that bleaches the entire retina. No rotary potentiometer was used in the proposed Photostress Testing device; i.e. the previously patented device tested for degeneration for red, green, and blue photoreceptors individually.
- What other products or services serve the same purpose? MDD2 is a commercialized hand-held product that uses a diffused xenon flash lamp to illuminate the entire back of the retina (the Photostress Testing device only bleaches the area of the retina being tested for degeneration). The purpose of MDD2 is to test for the health of the macula via a recovery time by the Photostress Tester; i.e. the overall purpose is the same as the proposed Photostress Testing device.

5. Invention Process

• When did you first begin to work on the invention? When did you come up with the idea for the invention?

The project was suggested by Dr. Peyman as part of collaborative work on tactile tonometer between Enikov and Peyman. Subsequently Enikov recruited and hired Logan Rivas as NSF REU intern who developed a generation 0 prototype. The following year Enikov recruited the Swan, Timler, Galvan and Castro, to participate in a group capstone design project abroad. The student team traveled to EU and upon return developed the current prototype.

Has the invention been built? If so, when?

Yes, the invention had a prototype built in May 2012.

• Has a description of the invention ever been published, by you or anyone else? If so, when and where?

Senior Design Report, May 2013 – posted on campus repository website:

http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0 CCYQFjAA&url=http%3A%2F%2Farizona.openrepository.com%2Farizona%2Fbitstrea

m%2F10150%2F297519%2F1%2Fazu_etd_mr_2013_0032_sip1_m.pdf&ei=uRGJU7izF 42xyASg14KwAw&usg=AFQjCNEsSnB-

aKawgKlxwUmgWHz709HTiA&bvm=bv.67720277,d.aWw&cad=rja

• Has the invention ever been shown or used in public, or presented at a trade show, seminar, or in a technical presentation?

Yes, Pitch McGuire presentation (no details of the work were given) and Industrial Affiliates poster (no optical analysis was given, just higher level pictures and overview of the device).

- If so, where and when? Both general overviews occurred around October of 2012.
- Has the invention ever been offered to a possible customer, for sale, testing, or evaluation? If so where and when? No.
- Has the invention ever been used experimentally or evaluated by a third party? If so, describe when and where? No.

Stray light mitigation in a novel endoscope for fallopian tubes

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ABSTRACT

Stray light in an endoscope largely contributes to whether a signal can be detected or not. This FRED analysis used a novel endoscope designed for the fallopian tubes to show how common endoscope elements cause stray light contamination, and to offer suggestions on how to mitigate it. Standard and advanced optical raytracing was performed. Raytrace reports determined which ray paths caused the highest power and irradiance distributions after reflecting one or more times from an element in the system. The analysis revealed that the cover plate introduced significantly more stray light into the system than other endoscope components. The imaging lenses and variable stop reflectivity had a negligible impact on the signal. To obtain acceptable signal-to- noise ratio, the source numerical aperture (NA) was lowered to 0.35 and 0.25 to keep the stray light within the same order of magnitude and an order of magnitude lower, respectively than the desired signal. There was a single specular reflection off of the cover plate distal surface. This illumination reflected back into the imaging fiber without first scattering off the tissue, which resulted in high stray power at the back of the imaging lenses. The specular light appeared brighter at higher source NAs and saturated the desired signal at the edge of the imaging fiber. An NA between 0.25 and 0.35 provides maximum illumination to image the tissue, with minimal stray light degrading the desired signal.

Keywords: endoscope, stray light, optic, fallopian tube, FRED, raytracing

1. INTRODUCTION

A novel falloposcope design was used as a model to test and minimize stray light. The falloposcope has a light source fiber, collecting fiber with lenses, and cover plate that are commonly found in many different endoscopes. Stray light is prevalent in many of these endoscopes and is a limiting factor for image formation and data collection. In the past, unwanted illumination has been mitigated through optic and cover plate design, especially when the illumination source and imager occur under the same cover plate or dome¹. It has also been dealt with by painting metallic surfaces with enamel². The optics, cover plate, and mechanical housing are all possible sources of stray light in the designed endoscope as well.

In this endoscope, the stop was one of the most-studied components for its effects on stray light. The falloposcope's three lens imaging objective (Figure 1) has a stop that limits the amount of light that can propagate through the system. This stop is created by coating the curved surface of the lens (at the stop location) with a chrome-oxide layer (Cr_2O_3) . This material has a reflectivity of 12% instead of the ideal 0% reflectivity (i.e. 100% absorptivity). This stop is therefore analyzed for its contribution of stray light in the system.



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Figure 1. FRED Optical Engineering Software falloposcope model close-up.

2. METHODOLOGY

To analyze the effect of the reflectivity introduced into the system by the stop, a signal-to-noise ratio (SNR) was calculated. The FRED software [Photon Engineering] traced rays at an arbitrarily specified 1,000 units of power from the 0.57 NA fiber source, as specified by the system design. Note that the units are unspecified as source power values will be compared to power values on the analysis plane and only relative quantities are of interest. The rays traveled from the source and through the modeled falloposcope to a user-defined analysis plane located at the back of the three lens imaging objective. Then, an advanced ray trace was completed to generate a ray path summary. This summary (Table 2A, 2B) consists of power values and the number of specular reflections for each ray path traced. The purposed of the ray paths was to show which elements yielded the most stray light at the analysis plane. SNR was then computed at the analysis plane. Equations 1 and 2 show the two SNR ratios calculated:

$$SNR = 20 \log_{10} \left(\frac{Power (0 Specular Reflections)}{Power (2 Specular Reflections)} \right)$$
(1)

and

$$SNR = 20 \log_{10} \left(\frac{Power (0 Specular Reflections)}{Power (1 + Specular Reflections)} \right).$$
(2)

The first is the ratio of the power hitting the analysis plane with zero specular reflections divided by the summed power hitting the analysis plane with two specular (or "ghost")

reflections from optical system components. The second SNR calculation is the power ratio at the analysis plane for zero specular reflections divided by the summed power hitting the analysis plane with one or more specular reflections. The ray traces and two SNR calculations were completed for each stop reflectivity, which was originally thought to have strong impact on SNR. Finally, irradiance distributions were analyzed at the back of the imaging lenses. This analysis was performed in order to determine how to mitigate stray light in the image.

3. DATA AND RESULTS

The details of the ray path show that for two specular reflections, the illumination trajectories with the most stray light power are path 1285 and 771 (Table 1) for the system with the 12% and 0% reflective stops respectively. The illumination first reflects off the distal end of the cover plate that faces the tissue (Event 1), then reflects off of the inner shell (Event 3) which holds the lenses and illumination fiber, and finally reflects off of the distal end of the cover plate (Event 5) before it transmits to the analysis plane. The illumination never hits the tissue that is supposed to be imaged, and goes directly to the detector. This shows the importance of a low stray light level in order to achieve an optimal SNR. Additionally, other stray light generated by reflections off of the stop, lenses, or lens housing always reach the tissue before reaching the analysis plane. This shows why reducing field of view is an option to block wide angle light from back reflecting into the system is an option to mitigate low SNR and washed out data collected. This test is shown later in figures 1 through 3.

Event	Transmit/Reflect	Component
0	Transmit	Source
1	Reflect	Cover Plate Distal End
2	Transmit	Cover Plate Proximal End
3	Reflect	Inner Shell
4	Transmit	Cover Plate Proximal End
5	Reflect	Cover Plate Distal End
6	Transmit	Cover Plate Proximal End
7	Transmit	Through Imaging Lenses to Analysis
		Plane

Table 1. Stray light ray path for 0% and 12% reflective stop.

Major sources of stray light contamination are shown in Table 2. The cover plate distal surface, which faces the tissue, by far contributes the most stray light, 41.35382 units, to the image. The outer wall and proximal end of the cover plate have the next two highest power values of 15.87156 units and 9.955094 units respectively. The next highest power contribution is the edge and surface one of lens one with 2.636501 units and 2.088398 units of respective power. All other components are fractions of power units and do not contribute greatly to stray light power at back of the imaging lenses.

Endoscope Component	Power (units)
Cover Plate Distal End (Faces the Tissue)	41.35382
Cover Plate Proximal End	9.955094
Cover Plate Outer Wall	15.87156
	i
Lens 1 Edge	2.636501
Lens 1 Surface 1	2.088398
Lens 1 Surface 2	0.000478
Lens 1 Stop	0.038006
Lens 2 Edge	0.011857
Lens 2 Surface 1	0.011656
Lens 2 Surface 2	0.021496
Lens 2 Edge	0.000311
Lens 3 Surface 1	0.007366
Lens 3 Surface 2	0.119299
Fallopian Tube Inner Wall	0.000207
Inner Shell	0.046266
Outer Ferrule Inner Wall	0.031269
Outer Ferrule Outer Wall	0.000175
Tissue Surface	0.000275

Table 2. Power from each endoscope component on analysis plane for a 0.65 source NA.

The maximum stray power that hits the analysis plane is only negligibly lower with the 12% reflective stop than the falloposcope with the 0% stop. Those values are 2.79E-05 units and 2.81E-05 units of power respectively (Table 3). Table 2 shows that there is a slightly higher SNR for the 0% reflective stop. The percent difference of the SNR (0 Spec/2Spec) for the 12% and 0% reflective stop is 4.7%. The percent difference of the SNR (0 Spec/1+ Spec) for the 12% and 0% reflective stop is 7.5%. This shows that the 12% reflective stop minimally decreases the SNR, which makes it a promising option for the falloposcope.

Table 3. SNR and maximum ghost power for a 0.25 source NA.

12% Reflective Stop			
Calculation/Measurement	Value		
SNR (0 Spec/2 Spec)	2.19E+01		

SNR (0 Spec/1+ Spec)	2.13E+01		
Max Power (units) from 2 Specular Reflections:	2.79E-05		
Ray Path 1285			
0% Reflective Stop			
Calculation/Measurement	Value		
SNR (0 Spec/2 Spec)	2.29E+01		
SNR (0 Spec/1+ Spec)	2.29E+01		
Max Power (units) from 2 Specular Reflections:	2.81E-05		
Ray Path 771			

According to Table 4 below, for the system with the 12% reflective stop, the maximum stray light power hitting the analysis plane is 2.81E-05 units; this is one magnitude lower than the path power with zero specular reflections at 7.66258E-04 units. For the system with the 0% reflective stop, the maximum stray light power hitting the analysis plane is 2.81E-05 units; this is also one magnitude lower than the path power with zero specular reflections at 7.66258E-04 units. These values show that the increase in stop reflectivity negligibly impacts the peak power hitting the analysis plane.

12% Reflective Stop				
# Specular Reflections	Power (units)			
0	7.66258E-04			
1	9.33E-08			
2	2.79E-05			
0% Reflective Stop				
# Specular Reflections	Power (units)			
0	7.66258E-04			
1	9.33E-08			
2	2.81E-05			

Table 4. Number of specular reflections and accompanying maximum power on analysis plane for a 0.25 source NA.

Once stop reflectivity was determined to have negligible impact on stray light, changing the numerical aperture was then tested in order to mitigate unwanted power in the image plane. The irradiance pattern at the analysis plane of the designed falloposcope was taken for numerical aperture values of 0.65, 0.35, and 0.25 respectively (Figure 2A, 2B, and 2C). The irradiance is the power per area incident on the analysis plane. The scale in the figures goes from red to blue, showing ranges of irradiance values from high to low. The peak irradiance values for each consecutive NA are 145 units/mm², 0.0594 units/mm², and 0.149 units/mm². Figure 2A shows that for a source NA of 0.65, stray power dominates the image plane, washing out the desired data to be collected.



Figure 2. Irradiance plot on analysis planes for source NAs of (A) 0.65, (B) 0.35, (C) 0.25, and (D) 0.25. Figures 2 A-C have 100% absorptive stops and figure 2D has a 12% reflective stop.

The smaller NA blocked the light reflecting off of the cover plate and into the imaging lenses without hitting the tissue (Figure 2B). This stray light no longer reached the image plane to get collected as data. However, a small amount of stray light can still be seen in Figure 2B, so the numerical aperture was decreased further in order to obtain a cleaner image (Figure 2C).

Higher peak irradiance was seen with minimal stray light in the system. This is due to FRED consistently sending 1,000 units of power through the system regardless of the decrease in field of view. The image shows negligible stray light at the 0.25 source NA (Figure 2C).

The peak irradiance at the analysis plane at the back of the three lens objective is 0.168 units/mm² for the system with a 12% stop reflectivity (Figure 2D). As shown above, the peak irradiance does not change and the irradiance patterns look very similar for the system, regardless of the stop reflectivity. The 12% reflective stop thereby does not greatly contribute to stray light.

4. CONCLUSIONS

It can be concluded that the distal cover plate/inner shell reflections are the primary contributors for the majority of the stray light in the system. Decreasing the illumination fiber's numerical aperture to 0.25 decreases the field of view of the falloposcope but also removes the unwanted stray light in the system without changing the lens design. The power of the stray light is an order of magnitude lower than the desired signal level hitting the analysis plane. Contrary to what was predicted, stop reflectivity only minimally introduced stray light into the system and does not need to be compensated for. Other endoscope components such as the mechanical housing and imaging lenses provide negligible stray light in comparison to the cover plate and its mechanical housing. The reflection off of the cover plate makes light back reflect into the system without first imaging the tissue. It is understandable, then, that the primary contributor to stray light is the cover plate. Adjusting the numerical aperture of the source reduced the induced stray light from the cover plate and increased the system SNR without changing the original falloposcope design.

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