Developing a Treatment Plan for Photodynamic Therapy

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Abstract

Photodynamic therapy (PDT) is a type of cancer treatment that utilizes the light-harvesting properties of certain molecules called photosensitizers to destroy tumor cells. A new linear programing model is developed whose solution gives an optimal light dosage plan for photodynamic therapy which is based on the flow of photosensitizer through blood and tissue within the treatment time interval.

1 Introduction

In order to successfully model a treatment plan for photodynamic therapy (PDT), it is critical to understand the basics of photochemical reactions. A large amount of information is available for PDT, and some sources [1,2] go in to extensive detail about photosensitizer's and their use in PDT. As discussed in [1], all light-harvesting molecules, including those used in photodynamic therapy, are called photosensitizers. The chemical structure of a photosensitizer is such that the molecule can absorb light of a specific wavelength depending on the chemical components of the molecule. When light is absorbed by a photosensitizer, a photochemical reaction has taken place. This photochemical reaction is the source of a product that ultimately destroys organic matter in tissue. Through PDT, this process can be directed toward the organic matter in tumorous tissue.

Photosensitizer's exist in a variety of molecular compositions and structures. Each respective composition and structure ultimately determines the wavelength of light that will initiate a photochemical reaction for a given photosensitizer (see [1] for details). The literature [2] shows that when a photosensitizer is activated by light, an electron of the photosensitizer is excited from a ground state to a much more reactive state. Once the electron has moved to a higher energy level, the molecule has been converted to a more energetic species. The significant fate of the photochemical reaction occurs when an excited electron converts oxygen to an extremely reactive species called singlet oxygen. It is this species of oxygen that destroys any organic matter in the cell with which it comes in contact. The reactive electron may also assist in the formation of super oxide, which can also play a role in destroying cancerous cells. Though the photochemical reaction may result in two destructive species, the formation of singlet oxygen is much more abundant and usually regarded as the key player in tumor cell destruction.

A photosensitizer requires specific properties to be a good candidate for PDT and these requirements are detailed in [2]. The photosensitizer is synthesized such that the molecule has a high affinity for cancerous cells. Cancerous cells tend to be more acidic that non-tumorous cells, and as a result the photosensitizer is made to accumulate in areas of lower pH. The photosensitizer is made to be water soluble so that flow of the photosensitizer through tissue is accomplished with ease. It is also easily degraded by the body in order to avoid cytotoxic response (an extensive exposure of tissue to foreign species that may result in cell death), or future photochemical activation from other light sources outside of the clinic. A photosensitizer with the above properties is an ideal candidate for PDT.

The Centre for Photobiology and Photodynamic Therapy has posted [3] details outlining the general procedure for PDT. In the clinical setting, a patient is injected with a photosensitizer. Once sufficient time has allowed for the drug to accumulate in tumorous cells, light administration commences. Depending on the structure of the photosensitizer, a light of specific wavelength is administered to the patient at the region of tumorous cells. This ultimately causes the photochemical reactions to occur where photosensitizer is present, producing singlet oxygen that then destroys targeted tissue. After treatment, the patient must avoid exposure to light for a period of time depending on the rate of elimination of the photosensitizer from the body. Photosensitizer elimination from the body may take up to three months. Hence strong light sources such as the sun may cause undesirable photochemical reactions to occur causing healthy and critical tissue to be destroyed.

Though a photosensitizer mostly accumulates in tumorous cells, it is still present in healthy tissue to some degree (see [2] for details). As discussed in [3], the goal of the physician is to destroy as much tumorous tissue as possible while minimizing the amount of non-tumorous tissue destroyed. A physician attempts to minimize the dosage of light over the treatment period to avoid as much healthy tissue destruction as possible while at the same time avoiding inconvenience and discomfort to the patient. The goal of this research project was to develop a new linear programming model for Photodynamic Therapy that takes into account the goals of the physician.

The light-dosage plan that we developed ultimately advises a physician as to how much light (including the direction of that light) a region of tumor should receive based on the concentration of photosensitizer in that region during any given time interval. Our new linear programming model develops this optimal dosage plan by maximizing tumor cell destruction while minimizing healthy cell destruction. Thus, in order to model PDT, it is essential to know the concentration of photosensitizer in tumorous and healthy tissue during the treatment interval. For this project a specific photosensitizer was chosen. Photofrin was chosen because it is the only approved photosensitizer for PDT by the Federal Drug Administration (FDA). Using parameters defined by FDA [4] for the drug Photofrin, the concentration of Photofrin in the blood over a treatment interval was evaluated using known blood flow equations [5]. For simplicity, instead of evaluating the arterial content of a real tumorous region (necessary to determine tissue concentration's of Photofrin), a matrix was generated with random arterial percentages such that each cell of the matrix would represent a region of a tumor. Once this matrix was generated and Photofrin blood concentration was determined for each cell, Photofrin tissue concentration (including arterial tissue) was then evaluated using known general tissue to blood and blood to tissue flow equations [6] over this random matrix. Based on the evaluated tissue and blood

concentrations of Photofrin over the matrix, we developed a set of *dose deposition* matrices that describe tissue destruction when light is administered to each cell from a number of directions in the treatment time interval. Next, a random image of tumorous and healthy tissue was generated using a program called Radiotherapy optimAl Design [7]. Finally, a new linear programming model was developed to combine this image with the *dose deposition* matrices to determine an optimal treatment plan. This treatment plan describes optimal directions and optimal times for light administration for the specific generated image.

2 Photofrin and Pharmacokinetics

The FDA has published a report [4] on the specifics of Photofrin use in PDT. As of 2003, the only FDA approved drug for Photodynamic Therapy is called porfimer sodium, or Photofrin. There are a few other photosensitizers being tested in clinical trials that may prove to be a more efficient drug for PDT, however accurate pharamacokinetic data for these drugs are not reported by the Federal Drug Administration and as a consequence only Photofrin was investigated for this model. Photofrin is injected at 2 mg/kg over a period of five minutes into the patient. This means that the amount of Photofrin (in milligrams) a patient would receive would be twice the patient's kilogram weight. Forty-eight hours after the intravenous injection, Photofrin should have mostly localized in the tumorous regions of the body as a result of the chemical properties of the compound, and light administration can begin. Laser light of wavelength 630 nm is delivered to the patient at the site of tumorous cells for a period not to exceed twenty-four hours. Finally the patient must avoid as much light exposure as possible for a period of six weeks after treatment. Because Photofrin requires time to be eliminated from the body, exposure to light sources up to about six weeks after treatment could cause activation of Photofrin in normal and healthy tissue (see [4] for details).

In order to determine the concentration of Photofrin in tumorous tissue,the amount of Photofrin in the plasma must first be calculated using pharmacokinetic methods. Pharmacokinetics is the mathematical analysis of drug absorption, drug distribution, and drug elimination in the human body [5]. This field of study is important for the model under investigation in that pharmacokinetics allow for an accurate measurement of drug concentration in the blood during the twenty-four hour treatment block. The flow of any drug through the body can be modeled by differential equations known in the literature. All of the following utilized blood flow equations and

integrated solutions in this section are found in [5]. The concentration of Photofrin in the body is measured by observing the infusion of the drug (injection time of the drug), the absorption of the drug, and finally the elimination of the drug. The change in drug plasma concentration during the injection is governed by an input and output process. According to the follwing equation found in [5], this change over time occurs as a result of a simultaneous infusion and elimination of the adminstered drug:

$$\frac{dC}{dt} = \frac{k_0}{V} - kC \tag{1}$$

The concentration of drug in the plasma, C, is calculated using the rate of elimination k from the body and the rate of infusion k_0. The volume of distribution, V, for a particular drug is defined by the volume of fluid that the drug administered would occupy if the total amount of drug in the body were at the same concentration as is present in the plasma. Equation 1 can integrated in [5] to yield the following:

$$C = \frac{k_0}{Vk}[1 - e^{-kt}] \tag{2}$$

This equation gives the concentration of a drug at any particular time during the injection alone. In order to calculate the concentration of drug at any time after the infusion, once solved, equation 2 is multiplied by the exponential term for drug elimination. The concentration of a drug in the body after the infusion follows a slow exponential decay, and as a result only elimination of the drug is necessary to evaluate the concentration of the drug. Drug elimination in the body is governed by the following differential equation found in [5]:

$$\frac{dC}{dt} = -kC \tag{3}$$

which can be solved by integration to yield the following:

$$C = C(0)e^{-kt} \tag{4}$$

Equation 4 describes the concentration of a drug in the body in the absence of injection. Hence, because the initial time for equation 4 in this case is the end of the injection process, $C(0)$ is replaced by the concentration of Photofrin obtained after the total injection time where the elimination of the drug immediately proceeds the total infusion time τ .

$$C = \frac{k_0}{Vk}[1 - e^{-k\tau}]e^{-k(t-\tau)} \tag{5}$$

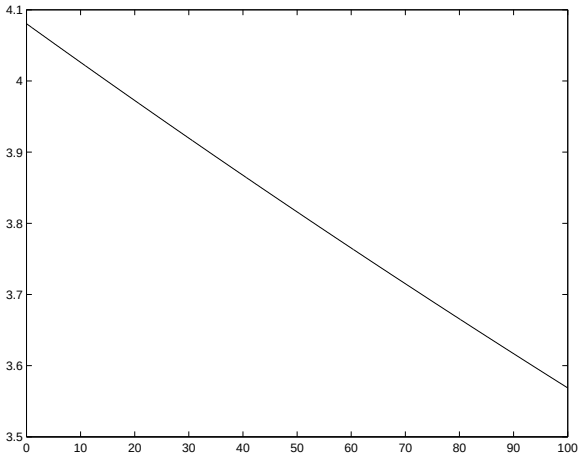

Figure 1: Concentration of Photofrin in the Blood (time(hrs.) versus concentration of Photorin(mg/L)

In order for us to solve the above differential equations for Photofrin, we obtained the constants k_0,k, and V from FDA approved clinical data in [4]. For Photofrin the infusion rate, k_0, is equivalent to the dosage at 2 mg/kg over a period of 5 minutes. Using an average 70 kg adult, 140 mg of Photofrin would be delivered over 5 minutes and thus $k_0 = 1680$mg/h. The mean volume of distribution, V,(ignoring standard deviation) for Photofrin is listed by the FDA as 0.49 L/kg or in the case of the 70 kg person, $V(70\text{kg}) = 34.3$L. The rate of elimination k was calculated using an elimination half-life equation found in [5].

$$t_{\frac{1}{2}} = \ln(2)/k \tag{6}$$

The elimination half-life, $t_{\frac{1}{2}}$, for Photofrin is 516 hours. Hence, $k = .00134$ h^{-1}. Using the above pharmacokinetic parameters for Photofrin over an infusion time of $\tau = .083$h, and a treatment interval from 48 - 72 hours after injection, Photofrin concentration in the blood was modeled.

$$C = 4.08e^{-.00134(t-.083)} \tag{7}$$

Figure 1 is a plot of equation 7.

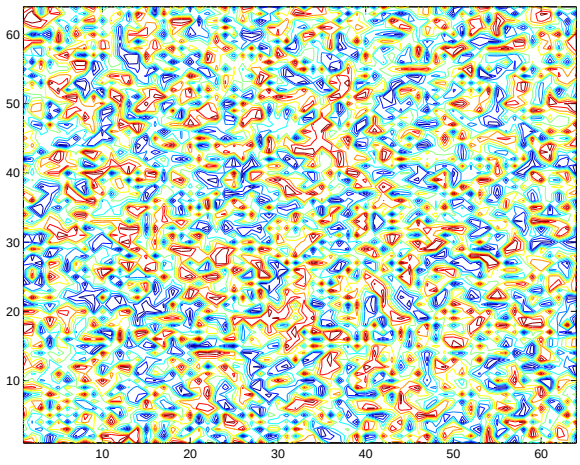

Figure 2: Randomly Generated Arterial Fractions

3 Photofrin Flow into Tissue

In order to calculate Photofrin tissue concentration a tumor region with known arterial concentrations was needed. For simplicity we generated a 64×64 matrix that contained random arterial fractions in each cell. Each cell or pixel of the matrix represents a region of a tumor with a particular amount of arterial concentration (see Figure 2).

Once we modeled the concentration of Photofrin in the plasma and generated the random arterial fractions, a model of Photofrin distribution into tissue was calculated using blood and tissue flow equations found in [6]. According to [6], a two-compartmental blood flow model is sufficient in order to evaluate the concentration of Photofrin in tissue in a particular time interval.

$$C_p(T) = k_1 \int_0^T C_A(t)dt - k_2 \int_0^T C_p(t)dt \tag{8}$$

$$C_{PET}(T) = V_A C_A(T) + C_p(T) \tag{9}$$

In the equations obtained from [6], blood and tissue flow was measured in terms of the concentration of radioactively labeled water. For our model all concentrations from [6] were evaluated by substituting Photofrin concentrations (see section 2) for labeled water concentrations. Hence, in equation 8 $C_p(t)$ represents the Photofrin concentration at time t in the tissue. Equation 8 showed us that in order to calculate

$C_p(T)$ the arterial Photofrin concentration $C_A(t)$ is needed to determine the amount of Photofrin flowing into the tissue. To do this $C_A(t)$ is multiplied by the tracer rate constant for tissue to blood flow, k_1. Secondly, the elimination of Photofrin from tissue to blood evaluated using the tracer rate constant for tissue to blood flow k_2 is needed. C_{PET} represents the Photofrin concentration in the tissue region including the arterial concentration of Photofrin. Because activation of the photosensitizer occurs in the arteries and in the tissue, C_{PET} is of great importance to this project. Equation 8 evaluates the concentration of Photofrin in the tissue and arteries depending on the arterial volume fraction V_A.

Because $C_p(t)$ is unknown, linear interpolation of equations 8 and 9 was done in [6] to obtain an equation in terms of C_{PET} that is independent of $C_p(t)$. First $C_p(t)$ was solved from equation 9 and the resulting equation was integrated.

$$C_p(T) = C_{PET}(T) - V_A C_A(T) \tag{10}$$

$$\int_0^T C_p(t)dt = \int_0^T C_{PET}(t)dt - V_A \int_0^T C_A(t)dt \tag{11}$$

Equations 10 and 11 were then substituted in to equation 8 to give the following equation:

$$C_{PET}(T) = V_A C_A(T) + (k_1 + V_A k_2) \int_0^T C_A(t)dt - k_2 \int_0^T C_{PET}(t)dt \tag{12}$$

Finally by applying linear interpolation to to equation 12, C_{PET} was solved for independent of $C_p(t)$.

$$C_{PET}(T) = \frac{V_A C_A(T) + (k_1 + V_A k_2) \int_0^T C_A(t)dt - k_2[\int_0^{T-\Delta t} C_{PET}(t)dt + \frac{\Delta t}{2} C_{PET}(T - \Delta t)]}{1 + k_2 \frac{\Delta t}{2}} \tag{13}$$

We applied the equations obtained in [6] to our randomly generated matrix of arterial fractions V_A over a treatment time interval of 48-72 hours in increments of 10 minutes. In our case C_A is the calculated Photofrin cocnentrations in the 48-72 hour time interval (see section 2). We assume a 1:1 ratio of k_1/k_2. Using these values we were able to generate a set of matrices for the treatment time containing arterial and tissue concentration's of Photofrin by utilizing equation 13.

4 The Set of Dose Deposition Matrices

To reiterate, we define a pixel in a matrix to represent a region of tissue. This region of tissue can contain tumorous and healthy tissue. We calculated random

arterial and tissue concentration's for this tumor matrix in Section's 3 and 4 over a period of 48-72 hours in 10 minute time increments. In order to develop a light-dosage plan for this set of matrice's, we first needed to develop a set of *dose deposition* matrices. A *dose deposition* matrix $A_{p,a,t}$ is defined as a matrix that evaluates tissue destruction when light is directed from angle, a at a particular pixel,p, in a specific time frame t. The rows of A are indexed by p, and the columns of A are indexed by (a,t). Using the calculated arterial and tissue concentrations in an interval from 48-72 in 10 minute time increments,our goal was to develop a set of dose deposition matrices that would determine a value for destruction for each pixel when light was administered to these matrices. We then define $x_{(a,t)}$ to be the dosage plan over the entire treatment time that feasibly satisfies the desired constraints for treatment. Over a given tumorous region this vector tells us where and when to treat the tumor in the treatment period. By multiplying this vector by the set of *dose deposition* matrice's for the observed tumor, a physican can see the destruction of all tissue based on the dosage plan $x_{(a,t)}$. First, we developed our own set of *dose deposition* matrice's, and then built a linear programming model to determine the best dosage plan for a tumor image.

We show how to develop the set of dose deposition matrices. With Photofrin, we are working within a 48-72 hour block of time (post infusion). Thus we only looked at deposition matrices in this time frame were looked at. Suppose we have an $M \times N$ pixel image, and for simplification, the only angles available are perpendicular to the matrix such that an individual pixel can only be hit from at most two sides. As an example, a 4×4 matrix has a possibility of only 16 total shots (see Figure 3).

We define the angles a as $\theta_1, \theta_2, ..., \theta_n$. The distance from where the light enters the pixel image to where it reaches the pixel is $d_{(p,a,t)}$. Because the light, though aimed in one direction, is not concentrated in one direction as a result of attenuation of the light in the skin, we must consider the off-axis distance of the beam such that the off-axis distance where the light enters the pixel image is $\delta_{p,a,t}$. We then define the attenuation of the light in the skin as $C_{PET}(t)e^{-\mu_1 d_{(p,a,t)}} e^{\frac{-10\delta_{(p,a,t)}}{\delta_{i(p,a,t)}+1}}$, where μ_1 is the *attenuation coefficient* on-axis of the beam direction. In essence, this equation tells us how light is spread through the set of arterial and tissue concentration matrice's when the light is aimed in a certain direction at each pixel in any given time interval. The factor $e^{-\mu_1 d_{(p,a,t)}}$ measures how the beam of light attenuates as it passes through tissue in the body in the direction of the beam angle. The factor $e^{\frac{-10\delta_{(p,a,t)}}{\delta_{(p,a,t)}+1}}$ measures how the beam of light attenuates as it passes through tissue in the body off-axis of the beam angle. It should be noted that the equations for light attenuation may not be correct

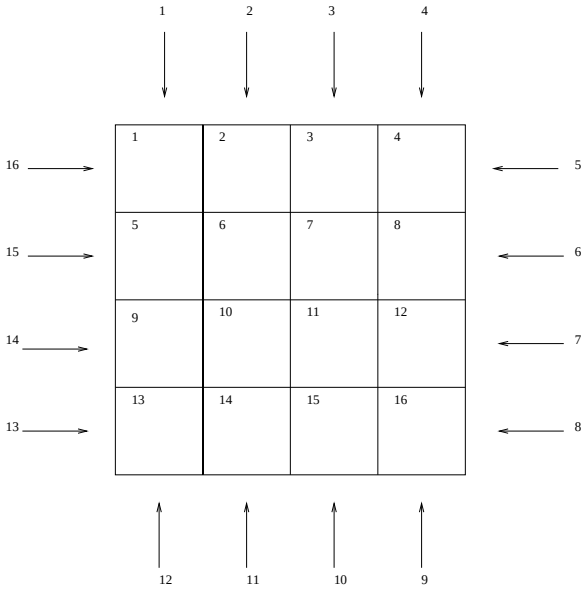

Figure 3: Shot Matrix for a 4×4 Image

for the laser light at 630 nm. This was however a good estimate for light attenuation and is subject to change in the future. A set of dose deposition matrices for the interval from 48-72 hours in increments of 10 minutes over a randomly generated 64×64 pixel image was calculated using the obtained Photofrin concentrations in the blood and tissue. In order to obtain a sensible value for tissue destruction it was critical to generate values that gave a percentage of tissue destroyed. Hence, in the set of *dose deposition* matrice's, all values were divided by $2 \times \max C_{PET}$. Thus, at most only 50% of a tissue region could be destroyed in one time increment of 10 minutes. This value is subject to change since we did not know that actual value for Photofrin activation to rate of tissue destruction. We then successfully generated the set of dose deposition matrices over the desired time interval.

5 Our Model

Each pixel of the set of *dose deposition* matrices is assumed to contain either tumorous or non-tumorous tissue. A physician desires a prescription that is comprised of a complete tumor dosage, and upper bounds for the non-tumorous tissue dosage. The prescription is the 4-tuple (TUB, TLB, CUB, NUB). TUB is a vector of upper

bounds for the tumor. TLB is a vector of lower bounds for the tumor. CUB is a vector of upper bounds for the critical structures, and NUB is a vector of upper bounds for the normal structures. Critical structures are those that are of extreme delicacy in the human body and hence light dosage must be avoided as much as possible in these areas. Normal structures are tissue of less importance than crticial tissue, however light exposure to this tissue is avoided as well so as not to destroy any healthy tissue. We assume that a uniform tumoricidal dose is to be delivered to the patient, and so lower and upper bounds for the tissue types are fixed percentages by the physician.

The rows of the *dose deposition* matrices were reordered into rows corresponding to the three tissue types: tumorous, critical, and normal. This reordering is indicated by the submatrices A_T, A_C, and A_N for tumorous, critical, and normal tissue dosage, respectively. Then,

$$A = \begin{bmatrix} A_T \\ A_C \\ A_N \end{bmatrix} \tag{14}$$

We next applied constraints to the dosage plans such that the physicians goals to minimize the amount of dosage that critical and normal structures receive, and to maximize the amount of dosage that tumorous tissue receives were met. Given the vectors α, β, and $\gamma \in R$, the desired constraints are elastic because the upper and lower bounds are allowed to vary with these vectors. We also let e be the vector of one's. Thus, for any positive scalar, ω, we have that

$$\begin{gathered} \min \omega\alpha + (\beta + \gamma) \\ \text{such that} \\ (1-\alpha)e \leq A_T x_{(a,t)} \leq e \\ A_C x_{(a,t)} \leq CUB + \beta e \\ A_N x_{(a,t)} \leq NUB + \gamma e \\ 0 \leq \alpha \leq 1 \\ -\min CUB_i \leq \beta \leq 1 - \max CUB_i \\ 0 \leq \gamma \end{gathered} \tag{15}$$

With these constraints the dosage of light to tumorous, critical, and normal tissue is taken in to account. A small enough α, β and γ ensures that most of the tumorous tissue is destroyed, whereas the dosage to the critical and normal tissue is kept within the desired upper bounds the physician desires as much as possible. Hence, we hope for a small α so that we obtain as near to 100% tumor destruction as possible. At the

same time, we hope for a small enough β so that the physician's desired upper bound for critical cell destruction is not breached. Also, we hope for a small enough γ such that the physician's upper bound for normal tissue destruction is not breached.

6 Experimentation

A prototype treatment system developed by Dr. Allen Holder called Radiotherapy optimAl Design, or RAD, was developed from MATLAB and used in this project. The system is available from http://www.trinity.edu/aholder /research/oncology/, and requires MATLAB's optimization toolbox. RAD was set to use a 64×64 grid so that the generated artificial C_{PET} calculations could be easily translated. A tumor was drawn in the RAD program surrounded by critical tissue and normal tissue. The tumor was set so that it would receive 100% of the dose. The normal structure was set so that it received at most 80% of the dose, and the critical tissue was set so that it would receive no more than 30% of the dose. Using the randomly generated Photofrin concentrations, and a randomly drawn tumorous region, the linear programming model was applied, resulting in a dosage plan for the 48-72 hour treatment interval with dosage application every 10 minutes of the entire treatment time. RAD produced 24 contour maps for the 24 hour treatment period(see figures 4-27). In these figures, the tumor region is displayed as as the u-shaped area, and the critical structure is set apart with a box. It also produced a 3-D image for each treatment hour. In the contour plots the tissue destruction to the tumorous region an the minimization of critical tissue destruction is obsrved.

Results showed that the tumor did, in fact, receive more dosage than non-tumorous tissue over the entire treatment time. The optimum treatment time was found to be 58 hours after injection and resulted in a 65% destruction of the tumor (see Figures 28 and 29). The α value was high at 0.7636. This means that some area of the tumor only recieved 24% destruction. The β value was found to be 0, meaning that nore more than 80% of the normal tissue was damaged. The γ value was found to be -.01068. Hence only .1% more damage was found in the critical structure than the physician desired. Becasue the angles for treatment are minimal, a good treatment plan was difficult to achieve. In the future the angles available will be increased and more constraints may be added to the linear program setting.

7 References

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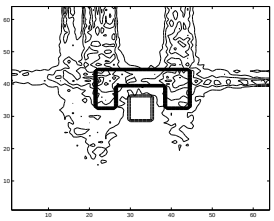

Figure 4: 48 Hours

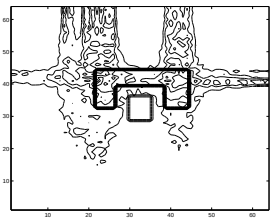

Figure 5: 49 Hours

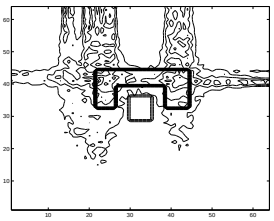

Figure 6: 50 Hours

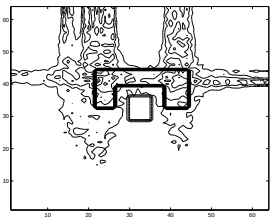

Figure 7: 51 Hours

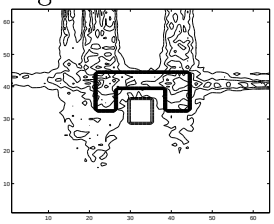

Figure 8: 52 Hours

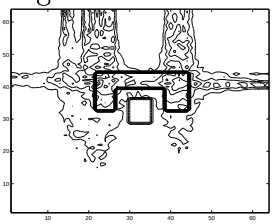

Figure 9: 53 Hours

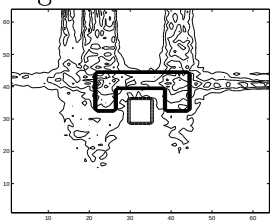

Figure 10: 54 Hours

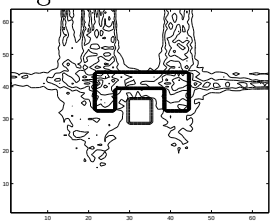

Figure 11: 55 Hours

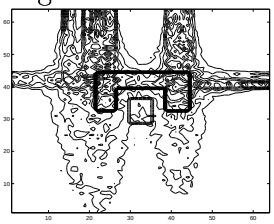

Figure 12: 56 Hours

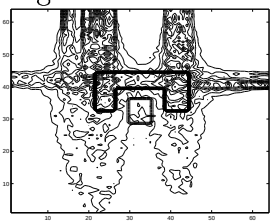

Figure 13: 57 Hours

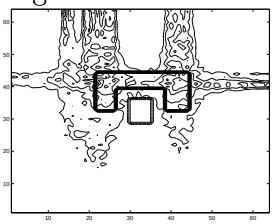

Figure 14: 58 Hours

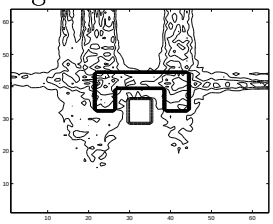

Figure 15: 59 Hours

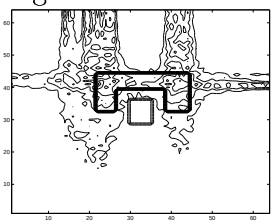

Figure 16: 60 Hours

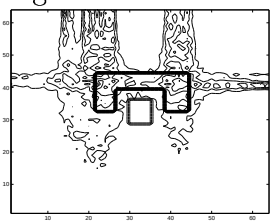

Figure 17: 61 Hours

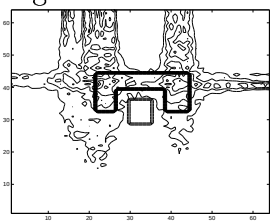

Figure 18: 62 Hours

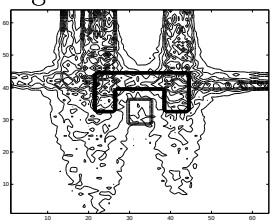

Figure 19: 63 Hours

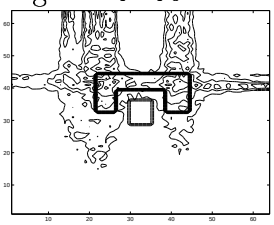

Figure 20: 64 Hours

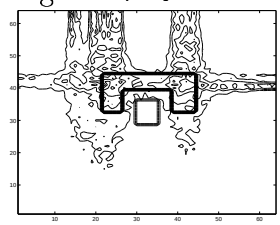

Figure 21: 65 Hours

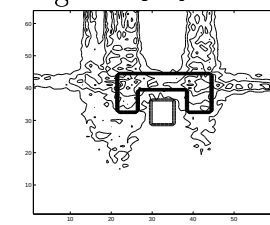

Figure 22: 66 Hours

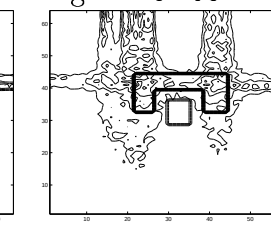

Figure 23: 67 Hours

Figure 24: 68 Hours Figure 25: 69 Hours Figure 26: 70 Hours Figure 27: 71 Hours

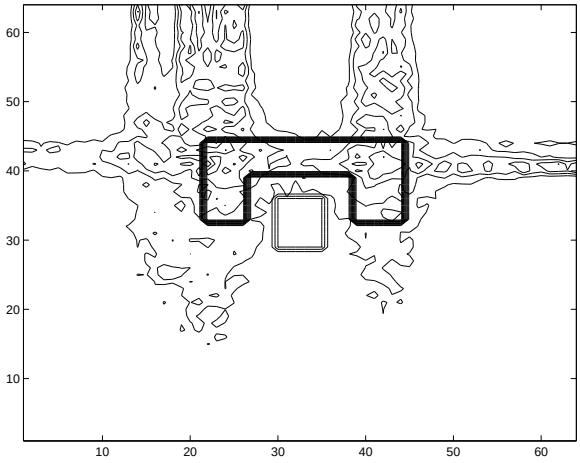

Figure 28: 58 Hours

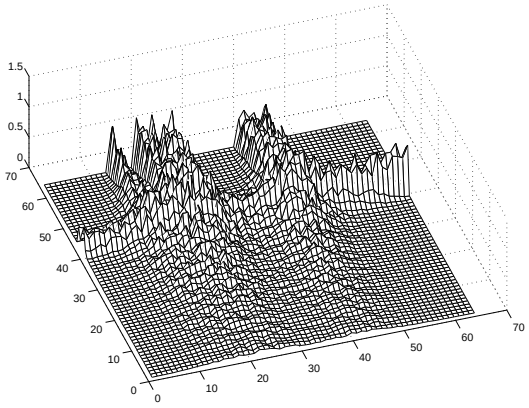

Figure 29: 58 Hours