Neonatal Jaundice-Its Mathematical Model and Treatments*†

Tram Hoang‡, Shazia Khan, and Lorena Ortiz
Advisor: Professor Charles H. Lee

Department of Mathematics
California State University Fullerton

Abstract

Neonatal jaundice (icterus neonatorium) is caused by the excessive accumulation of bilirubin, a byproduct of the red blood cells decomposition. Shortly after birth, newborn babies carry a very high level of red blood cells and thus a high concentration of bilirubin. If a baby's liver is premature, it cannot process the bilirubin as quickly as its body produces. The excessive bilirubin then flows out of the bloodstream and permeates to the body surface causing yellow-colored skin and sclera of the eye and inside lining of the mouth. If jaundice is left untreated, the infant can develop Kernicterus, a form of permanent brain damage. In this paper, we derive a mathematical model for the mass transport of the bilirubin concentration in the human body using the Mass Balance Law. We also incorporate into the model three types of treatments: blood transfusion, phototherapy, and medication. Our goal is, by observing the bilirubin concentration in the blood, to find the optimal treatment(s) to bring the concentration of bilirubin down to a normal level. We will also develop a program that automatically chooses the treatments based on the severity of the bilirubin level.

1

Introduction

Neonatal jaundice is a common medical condition that occurs in 65% of all newborn infants [7]. It is caused by the excessive accumulation of bilirubin in the bloodstream. The normal flow of bilirubin begins with unconjugated bilirubin, also known as a fat soluble, the waste product of the old red blood cells, which is carried to the liver by the protein albumin, where it is converted into conjugated bilirubin a water-soluble form of bilirubin [9]. Conjugated bilirubin is then excreted easily through the urine, stool and sweat glands [9]. In the event that the conjugated bilirubin is not excreted, it builds up in the bloodstream and spreads to the surface of the body causing the skin, eyes and inside lining of the mouth to appear yellow.

There are three common causes for neonatal jaundice. The first one being in the healthy newborn is the high volume of red blood cells, which produces a large amount of bilirubin and then spreads to the skin and eyes. Second, in the case of a premature infant, the baby's premature liver cannot convert bilirubin as quickly as it is being produced, which in turn will accumulate [9]. The third cause is the lack of normal floral bacteria in the gastrointestinal track, which normally aids in breaking down the bilirubin and prevents the bilirubin from being reabsorbed [9]. Without the bacteria, the bilirubin is reabsorbed back into the blood causing more bilirubin accumulation

The common types of neonatal jaundice are physiologic and pathologic. Physiologic jaundice occurs in nearly 50% of term infants and 80% of pre-term infants [9]. It is caused by a rapid destruction of fetal red blood cells in which the amount of bilirubin that is formed is reabsorbed from the intestinal track and is sent back to the liver as unconjugated bilirubin. As a result, the infant's liver is accumulated with fresh red blood cells and used unconjugated bilirubin from the intestinal track. Pathologic jaundice affects an infant's health within the first 24 hours of life. The main cause of pathologic jaundice is hemolytic disease. Hemolytic disease, also known as erythroblastosis fetalis, occurs during the fetal stage in which a maternal antibody passes through the placenta into the fetus and predisposes fetal and neonatal blood cells too early and the bilirubin begins to accumulate. As a result, the infant is born with jaundice and anemia [9]. In this paper, we will investigate the physiologic jaundice since it is more common than pathologic.

An extremely severe form of neonatal jaundice is called Kernicterus. Kernicterus, meaning yellow nucleus, is the deposition of unconjugated bilirubin in the basal ganglia of the brain [9]. The main cause of Kernicterus is the fat-

2

soluble unconjugated bilirubin. If the infant's albumin-binding capacity is exceeded, the fat-soluble unconjugated bilirubin sometimes crosses the blood-brain barrier and enters the brain by diffusion [7]. Other causes include blood group incompatibility, asphyxia, and hemolysis [5], [7]. The long term effects of Kernicterus are choreoathetosis, deafness, and mental retardation [5], [7].

Treatments for jaundice include blood transfusion, phototherapy, and medication. With abnormally high bilirubin levels, doctors may administer blood transfusion, an exchange of the infant's blood with normal blood. Phototherapy is implemented when bilirubin levels are slightly above normal [7]. The infant is exposed to a fluorescent light called bililight, which causes a chemical change in the bilirubin under the skin and makes it easy to excrete through the liver [7]. (Another reason why we do not consider the case of pathologic jaundice is that phototherapy is ineffective in the face of moderate degrees of hemolytic disease.) Infants may also be given medication to reduce the level of bilirubin. The types of medication include phenobarbital, tin-protosoporphyrin (Sn-PP), and tin-mesoporphoryin (Sn-MP). Phenobarbital has been used since the mid-1960s and its function is to increase the conjugation and excretion of bilirubin [3]. The latter two drugs block the production of bilirubin [10]. Heme is an iron-containing constituent of the red-pigmented protein hemoglobin. It carries oxygen throughout the body and as red blood cells are processed for removal from the body, the heme is converted to bilirubin by the heme oxygenase enzyme. Sn-MP and Sn-PP prevent heme oxygenase from working. The effect is that the heme is not converted to bilirubin and is directly excreted from the body. We will consider the use of Sn-MP for three reasons. First, studies have shown Sn-MP to be more effective in reducing the time it takes for bilirubin to reach normal levels, also reducing the need for phototherapy [2], [6]. Second, when babies are treated with phenobarbital, the drug diminishes the oxidative metabolism of bilirubin in the neural tissues, which may increase the risk of neurotoxic effects [3]. Last, while Sn-MP and Sn-PP both block bilirubin production, Sn-MP requires less dosage administration than Sn-PP to yield the same results [2].

Our paper is structured as follows: In the next section, we shall derive a mathematical model to approximate the levels of bilirubin in the body. Particularly, we treat the human body as three separate compartments: blood, body surface, and liver/bile. Using our model, we create a simulation to observe the bilirubin levels in a healthy and jaundiced infant. After our observations, we will incorporate the three treatments mentioned above into

the model and find the optimal treatment(s) that bring the bilirubin concentrations down to normal levels. Furthermore, we will show a cost-effective way of switching on and off the accompanying treatment when the bilirubin levels decline to its normal stage.

1 Mathematical Formulation and Modelling Process
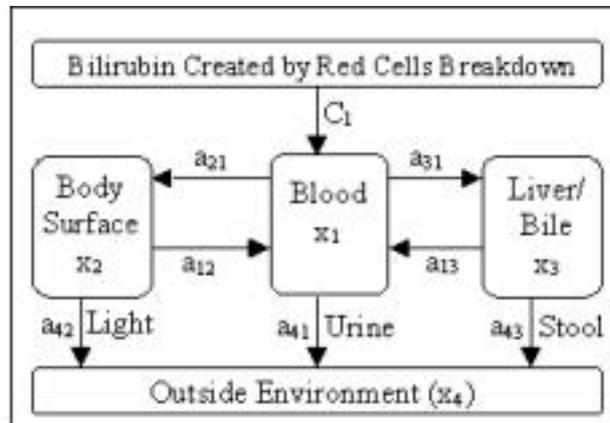
1.1 Bilirubin in a Human Body

Figure 1: Mass transport model for bilirubin in a human body

We cannot microscopically model bilirubin transport from creation to excretion so we will use a simpler model. This model shows the flow of bilirubin in the three main compartments of the bloodstream, body surface and liver/bile. The flow of bilirubin is illustrated in the following diagram called the Compartment Mass Transport Model (Figure 1). The hourly creation of bilirubin by the breakdown of red blood cells denoted by C_1 is measured in units of concentration per hour. The normal bilirubin production rate in a full-term newborn is $0.250 - 0.417$ mg/dl/hour [7]. This rate is two times greater in newborns than in adults since infants have a greater red blood cell mass and shorter red blood cell lifespan [7]. We denote by $x_1(t), x_2(t)$ and $x_3(t)$, the instantaneous concentration of bilirubin in the blood, body surface and liver respectively. Each $x_j(t)$ is a function of time t. The bilirubin transfer rate from compartment j to i is constantly proportional to $x_j(t)$ and

4

the constant of proportionality is denoted by a_{ij} where j is the compartment of concern and i is the connected compartment [1]. The parameters can be estimated based on empirical or clinical findings. We do not include the bilirubin concentrations in the external environment, x_4, since bilirubin does not flow back into the body once excreted nor does any bilirubin flow into the body.

To derive our model we used the Mass Balance Law [4], which governs the Compartment Mass Transport Model:
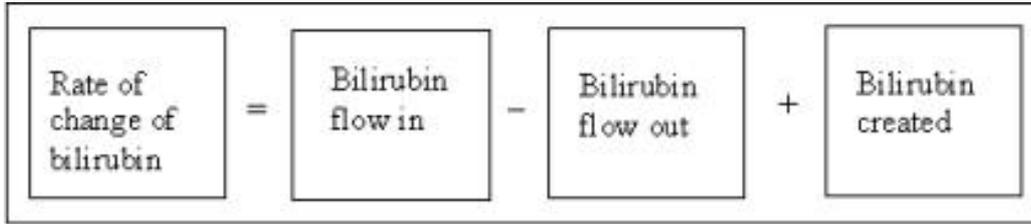

Figure 2: Mass Balance Law

Using the Mass Transport Model in Figure 1 and the Mass Balance Law in Figure 2, the resulting bilirubin concentration is a set of ordinary differential equations:

$$\frac{dx_1}{dt} = -(a_{21} + a_{31} + a_{41})x_1 + a_{12}x_2 + a_{13}x_3 + C_1 \tag{1}$$

$$\frac{dx_2}{dt} = a_{21}x_1 - (a_{12} + a_{42})x_2 \tag{2}$$

$$\frac{dx_3}{dt} = a_{31}x_1 - (a_{13} + a_{43})x_3. \tag{3}$$

Let $x_1(0) = x_1^0$, $x_2(0) = x_2^0$, $x_3(0) = x_3^0$ be the initial bilirubin concentrations in the body surface, blood, liver, respectively. The ordinary differential equations (1)-(3) along with these initial conditions can be solved numerically. In our simulations, we employed a Matlab function, called "ode45", to perform the calculations.

1.2   Functionality and Prematurity

Due to our assumption of physiologic jaundice, we will suppose a baby's ability to excrete bilirubin from the liver/bile into the stool at birth is P_0, a percentage of the normal functioning liver/bile, and the liver improves over

a period of time t at a maturity rate of r_m. The mathematical formulation for such percentage can be modeled as

$$P(t) = \frac{P_0}{P_0 + (1 - P_0)\exp(-r_m t)}.$$ (4)

A sample of different maturity rates for a fixed P_0 is displayed in Figure 3. The larger r_m is, the faster the recovery rate.
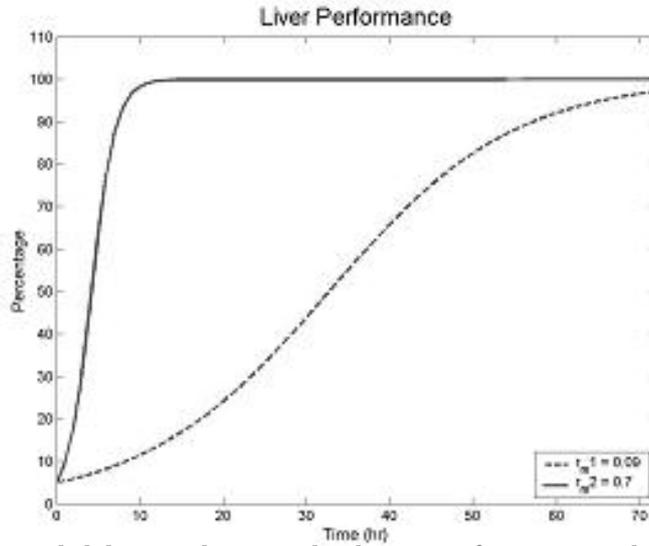

Figure 3: The solid line indicates the liver performance when the recovery rate is high. The broken line shows its behavior at a much slower rate.

As a result, some coefficients in our model in equations **??** become time dependent. In fact the transport rates of bilirubin concentration out of the liver are modified as follows

$$a_{43} \rightarrow P(t)a_{43}$$ (5)

$$a_{13} \rightarrow \frac{1}{\sqrt{P(t)}}a_{13}$$ (6)

Since a_{43} is excreting bilirubin at a reduced rate, more bilirubin is cumulated in the liver and thus the rate of bilirubin flowing back to the blood compartment is increased. Hence, such overflow is expressed by equation 6.

Numerical simulation of a case where the baby's initial ability to excrete bilirubin is 5% and a rate of liver maturity of 0.04 with initial bilirubin concentrations

$$x_1(t) = 1.65 \ mg/dl \tag{7}$$
$$x_2(t) = 0.25 \ mg/dl \tag{8}$$
$$x_3(t) = 5.70 \ mg/dl \tag{9}$$

is shown in Figure 4 below. The bilirubin concentration in each of the three compartments increases over the 72-hour period. In particular, the concentration in the blood rises above the alarming level of 20 mg/dl around the 10th hour. Under our assumption that the liver improves by itself, after the 10th hour the bilirubin concentration levels off steadily; however, without any medical treatments, the concentration remains in the danger zone for over a period of 24 hours, which indicates a harmful scenario. Thus, we are motivated to investigate the different types of treatments to bring down the bilirubin concentration as soon as it escalates above the normal level.
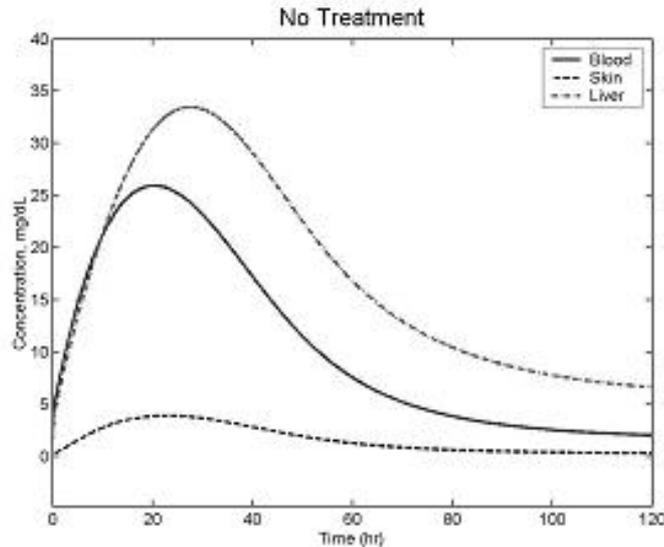

Figure 4: Bilirubin concentration in the blood, liver, and body surface after 72 hours with $P_0 = 0.05$ and $r_m = 0.04$.

Realistically, doctors diagnose jaundice based on the intensity of the serum bilirubin level and measure its concentration by a complete blood count. However, our mathematical model gives us a measurement of the

bilirubin concentration in the body surface and liver as well. Although the bilirubin levels in the liver and body surface may not be realistically known, they will be shown throughout our model.

2 Treatments

As mentioned, high levels of bilirubin concentration may cause many damages to a jaundiced baby. Thus, we want to examine several types of treatments hopefully to bring the abnormal bilirubin levels down to stable conditions. We will consider the following treatments:

1. exchanging the patient's blood with normal blood, and/or

2. exposing the patient to a spectrum of bililight,

3. administering a drug to block the production of bilirubin.

2.1 Treatment 1: Blood Transfusion

A severe case of neonatal jaundice, in which the bilirubin concentration ranges from $15 - 20$ mg/dl, requires immediate medical attention [6]. In this situation, blood transfusion is usually administered. Blood transfusion is the exchange of an infant's blood with new blood that has a normal level of bilirubin. This implies that along with the hourly bilirubin being created by the body, C_1, the new blood carries some bilirubin into the blood compartment. However the removal of the patient's blood carries out the bilirubin already present in the body. Thus, blood transfusion causes bilirubin to flow in and out of the blood compartment. This rate of transfusion is then modelled as the flow rate of the new blood divided by the blood volume of the infant. Referring back to equation (1), we have that this treatment affects C_1:

$$C_1 \quad \rightarrow \quad C_1 + \frac{r_{blood}}{V}(c_0 - x_1)\delta_1(t) \tag{10}$$

where V, c_0, and r_{blood} denote the volume of blood in the body, bilirubin concentration in the new blood, and transfusion rate, respectively. Note that this change only occurs when the infant is being treated, therefore we denote

$\delta_1(t)$ as the treatment 1 indicating function. Blood transfusion is turned "on" when $\delta_1(t) = 1$ and it is "off" when $\delta_1(t) = 0$. Therefore the hourly bilirubin rate will be (7) whenever the infant is being treated with blood transfusion.

2.2 Treatment 2: Phototherapy

An infant with bilirubin levels ranging from $10 - 15$ mg/dl is considered to have a mild case of jaundice. Usually at this stage, doctors will conduct phototherapy, where the baby is exposed under a spectrum of bililight. Bilirubin is bleached through the action of light, thus it becomes water-soluble. This process also changes the structure of the bilirubin, hence increases the excretory capacity through the sweat glands. Three factors that influence the effectiveness of phototherapy include the blue-green spectrum, power output of the bililight, and the surface area of the infant exposed to the light. In our model, the light intensity will affect the bilirubin flow rate from the body surface (x_2) to the external environment (x_4).

Referring back to equation (2), we will have

$$-(a_{12} + a_{42})x_2 \rightarrow -(a_{12} + a_{42})x_2 - (a_{12}k_{12} + a_{42}k_{42})x_2\delta_2(t) \qquad (11)$$

where k_{12} and k_{42} denote the intensity of the bililight which will affect compartments 1 and 2 and compartments 4 and 2, respectively. It should be noted that too much bililight might cause an adverse effect to a baby, so it is important stop phototherapy whenever the bilirubin concentration falls below a certain normal level.

Thus, let us denote $\delta_2(t)$ as the treatment 2 indicating function. That is, it is switched "on" or $\delta_2(t) = 1$ while phototherapy is given and switched "off" or $\delta_2(t) = 0$ when it is not.

This means that when phototheraphy is "off," the rate of bilirubin flowing into compartment 4 from compartment 2 is the original rate, but as soon as phototherapy is "on," the new rate will be (8).

2.3 Treatment 3: Medication

The third treatment we will consider is medication. The three types of medication available are Phenobarbital, tin-protoporphyrin(Sn-PP) and tin-mesoporphyrin(Sn-MP). Phenobarbital increases the conjugation and excre-

tion of bilirubin, and both Sn-PP and Sn-MP block the production of bilirubin. In our treatment model, we will use Sn-MP because it reduces the time for bilirubin to reach stable levels faster than the other two medications. Moreover, Phenobarbital increases the risk of neurotoxic effects. Furthermore, infants do not require phototherapy after the use of Sn-MP, and Sn-MP requires less dosage administering than does Sn-PP.

Since Sn-MP decreases the bilirubin production rate, C_1 in our model will be altered. We will administer Sn-MP every D hours and give N_3 amount of doses. The Sn-MP will alter C_1 as follows:

$$C_1 \quad \rightarrow \quad C_2 + (C_1 - C_2)\cos^8[\frac{(t - T_3)\pi}{D}]\delta_3(t) \tag{12}$$

The cosine function is used to model the behavior of the bilirubin level. That is, when the drug is given it slows down the hourly created bilirubin C_1, thus we will see a decline in the concentration level. As time passes, the drug wears out causing the bilirubin to increase and this behaves like the cosine curve.

3   Case Studies

Earlier we examined the case where an infant's initial ability to excrete the bilirubin is reduced to 5% and its liver maturity rate is 4%. Treatments are implemented under this case and are compared individually and in combinations. Because the bilirubin elevates above the alarming level of 20 mg/dl at the 10th hour, we set the initiation time for all treatments at this hour. When the level of bilirubin ranges from $16 - 20$ mg/dl, blood transfusion is prompted (see the first graph in Figure 5). The second graph of Figure 5 monitors the treatment's time and duration; when the switch is "on," a bar appears at 1 and at 0 when it is "off". Notice that the second round requires less time than the first.

At the 10th hour, again, the bilirubin level passes above the danger zone, so phototherapy is switched "on" and will be kept on until the level declines below 10 mg/dl. Unlike blood transfusion, phototherapy was on for almost 10 hours the first time. However, both treatments brought the bilirubin concentration down to the same level on the 120th hour. This is shown in Figure 6.
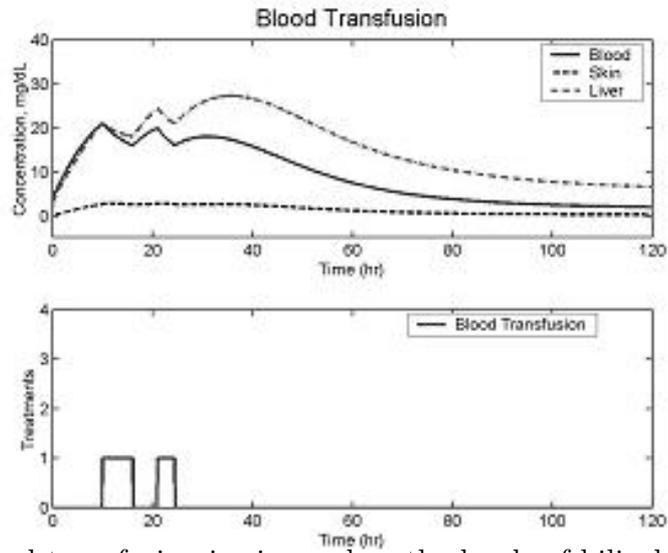
10

Figure 5: Blood transfusion is given when the levels of bilirubin range from 16 to 20 mg/dl
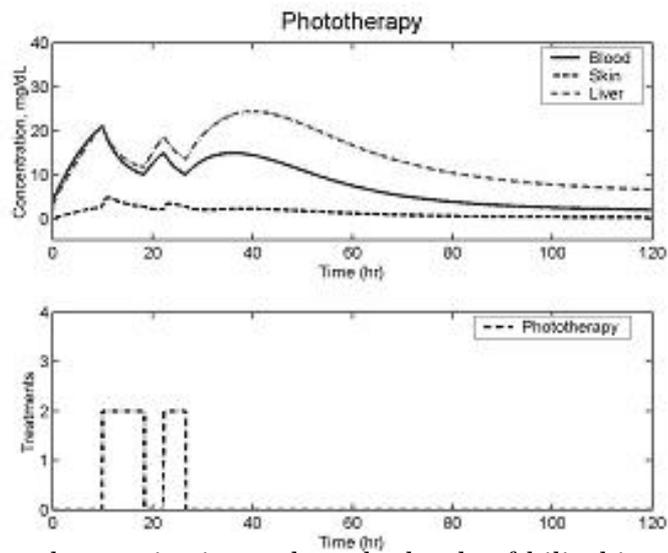

Figure 6: Phototherapy is given when the levels of bilirubin range from 10 to 15 mg/dl. The dashed bar of height 2 in the second figure indicates that phototherapy is "on."

11

Medication is administered at the 10th hour. Five dosages are given; each dose lasts for 8 hours and is given simultaneously. Comparing to the previous treatments, Figure 7 shows that medication is "on" much longer but the bilirubin concentration at the 120th hour is approximately the same.

Now, we will combine these treatments to see their effectiveness. When combining blood transfusion and phototherapy (see Figure 8), the patient has to undergo three rounds of treatments. Although the duration of each round was shorter than the individual treatments, the concentration level at the end is still the same.

Figure 9 shows the case when blood transfusion and medication are combined and Figure 10 illustrates the case of phototherapy and medication. Because both treatments start at the 10th hour, the duration of blood transfusion and phototherapy are shortest compared to the previous treatments.

Figure 11 shows the last case of combining blood transfusion, phototherapy and medication. With the help of medication, the duration of blood transfusion and phototherapy is relatively short. For all the cases though, the bilirubin levels at the 120th hour are parallel.
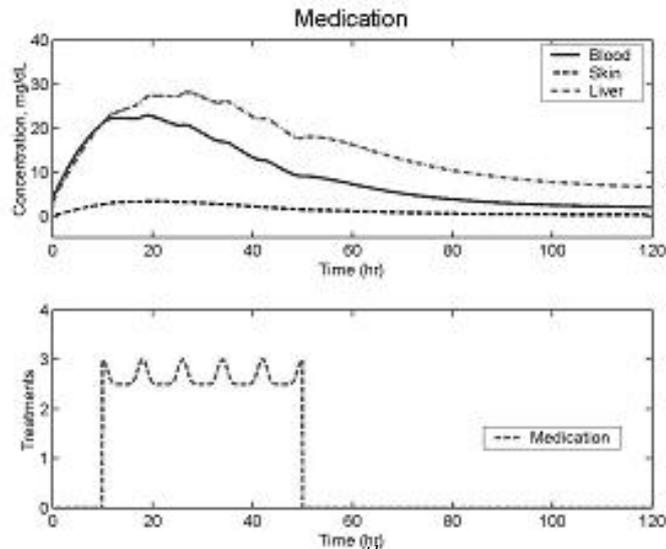

Figure 7: Medication is given at the 10th hour. The bowl-shaped curves in the second figure illustrate the number of drug dosage.
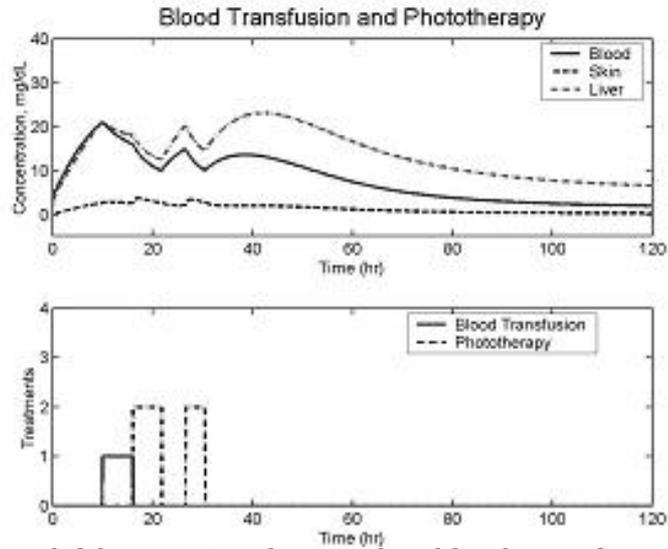
Figure 8: The solid bar at 1 indicates that blood transfusion is "on"; it is switched "off" when the bilirubin level falls below 16 mg/dl. Phototherapy is then turned "on."
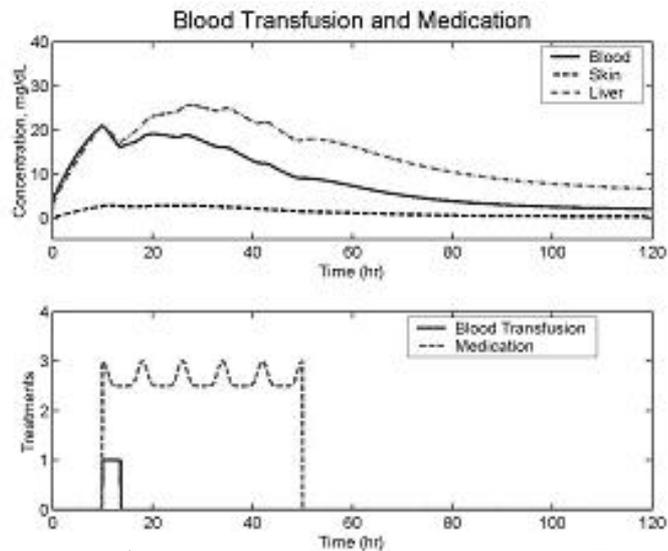

Figure 9: Blood transfusion and medication are given. The solid bar at 1 appears inside the dotted curves, indicating that both treatments start at the same time.
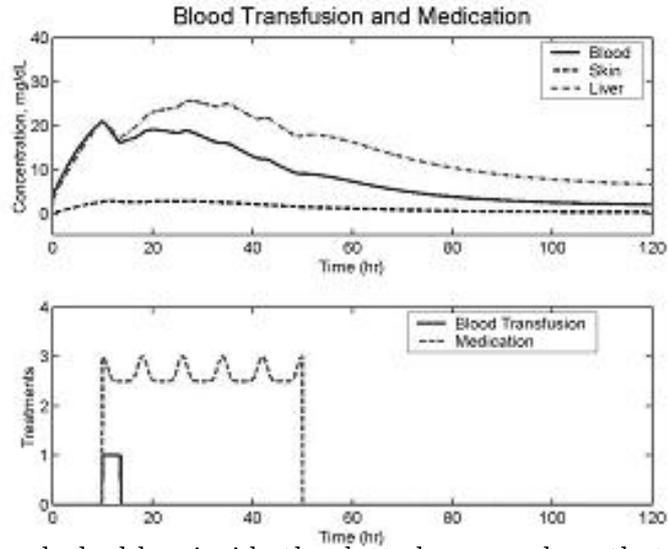
Figure 10: The dashed bar inside the dotted curves show that the patient is concurrently being treated with phototherapy and medication.
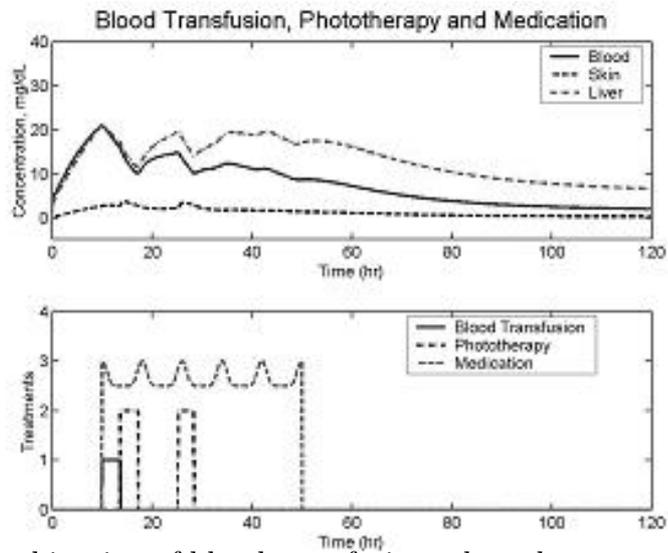

Figure 11: Combination of blood transfusion, phototherapy and medication.

4   Conclusion

The model that we derived along with certain assumptions gives us a good estimate of the behavior of bilirubin concentration and the effectiveness of the treatments. Overall, the combination of the three treatments seems to be most effective because each round of treatments require less time and the bilirubin concentration levels off more steadily. However, we would need to collaborate with hospitals to get data and estimated parameters to improve the accuracy of our model. Furthermore, we want to carefully study the effectiveness of medication, i.e. the lasting effect of the drug to see whether it behaves like a v-shaped or u-shaped curve. We want to be able to predict the liver function to provide or suggest the type of treatments depending on the condition of the child.

References

[1] Robert L. Borrelli. *Differential Equations: A Modelling Perspective.* John Wiley & Sons, Inc, 1996.

[2] Cooke, RWI. "New Approach to Prevention of Kernicterus." The Lancet 1999; 353: 1814-1815.

[3] Dennery PA, Seidman DS, Stenvenson DK. "Neonatal Hyperbilirubinemia." New England Journal of Medicine 2001; 344: 580-589.

[4] Stephen Goode. *Differential Equations* & *Linear Algebra.* Prentice Hall, 1999.

[5] Hansen TWR. "Bilirubin Oxidation in Brain." Molecular Genetics and Metabolism 2000; 71: 411-416.

[6] Hitchey, Tim. "New Drug May Prevent Jaundice in Newborns." New York Times 18 Jan. 1994, rec. c: 3.

[7] Jenson, Hal B. *Behrman Nelson Textbook of Pediatrics* 16_{th} *Edition.* Eds. R. Behrman, R. Kliegman. New Jersey: W.B. Saunders Co., 2000, 515-519.

[8] Kappas A, Drummond GS, Henschke C, Valaes T. "Direct comparison of Sn-mesporphyrin, an inhibitor of bilirubin production, and phototherpay in controlling hyperbilirubinemia in term and near-term newborns." Pedicatrics 1995; 468-74.

[9] Ladewig, Patricia W, London, Marcia L, Olds, Sally B. *Maternal-newborn nursing care: the nurse, the family, and the community.* Maryland: Addison-Wesley, 1998, 509-512, 692-696.

[10] Martinez JC, Garcia HO, Drummond GS, Kappas A. "Control of Severe Hyperbilirubinemia in full-term newborns with the inhibitor of bilirubin production in Sn-mesoporphyrin." Pediatrics 1999; 103: 1-5.