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Modeling the Progression of Discrete Paired Longitudinal Data.

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Modeling the Progression of Discrete Paired Longitudinal Data

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ABSTRACT

Modeling the Progression of Discrete Paired Longitudinal Data

by

Jonathan Wesley Hicks

It is our intention to derive a methodology for which to model discrete paired longitudinal data. Through the use of transition matrices and maximum likelihood estimation techniques by means of software, we develop a way to model the progression of such data. We provide an example by applying this method to the Wisconsin Epidemiological Study of Diabetic Retinopathy data set. The data set is comprised of individuals, all diabetics, who have had their eyes examined for diabetic retinopathy. The eyes are treated as paired data, and we have the results of the examination at the four unequally spaced time points spanning over a fourteen year duration.

DEDICATION

I dedicate this thesis to everyone for their support and patience. I am grateful and will never forget this wild trip.

ACKNOWLEDGMENTS

I would like to thank Dr. Yali Liu for all of her advice, support, and guidance during the preparation of this thesis, my wife, Liz, for being there for me. I would also like to thank the three musketeers, since there are four of us.

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1 INTRODUCTION: DR AND WESDR

Due to the severity of diabetes, the body is susceptible to a multitude of complications. Of these complications, the eyes are prone to be severely effected eventually leading to blindness. Diabetic retinopathy is the leading cause of visual impairment among people of working age in America [6]. In the early 1990's, the cost of medical care for a blind diabetic under the age of sixty-five was on average 12,764 dollars per year. This led to an estimated 500 million dollars a year spent on blind diabetics [6] .

The three leading causes of damage to the eyes for diabetics that can all lead to blindness are cataract, glaucoma, and diabetic retinopathy. Cataracts are characterized by clouding of the eye's lenses [10]. Glaucoma is the increased pressure of fluid in the eye [10]. Diabetic retinopathy, the most common of these complications that affect the eye, is caused by damage, usually leakage or swelling of blood vessels, to the retina, which is the light sensitive tissue located at the rear of the eye [1]. It is a progressive disease, in that it develops over four stages. The first is known as mild nonproliferative retinopathy, in which micro aneurysms, small areas of swelling, begin to occur [1]. The second stage is known as moderate nonproliferative retinopathy, in which some of the blood vessels that nourish the retina begin to become blocked [1]. The third stage, severe nonproliferative retinopathy, is when many more of the blood vessels in the retina are blocked and the retina begins to send signals for new blood vessels to be grown to aid in the loss of blood supply [1]. The end stage of diabetic retinopathy is proliferative retinopathy, in which the new blood vessels, which are often fragile with thin walls, may leak blood causing vision loss and eventual blindness [1]. In Type 1 diabetes, diabetic retinopathy is a common complication and almost

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all patients have a form of retinopathy after a fifteen year duration of diabetes [4].

The classification of diabetic retinopathy is based on a combination of two methods, the Snellen Visual Acuity Chart and the Modified Airlie House Classification Scheme [2]. The Snellen Visual Acuity Chart is a chart with which we are all familiar because it can be found at any optometrist office. It was developed by a nineteenth century Dutch ophthalmologist Herman Snellen (1834-1908), from which it got its name. The Snellen chart measures the clarity of vision. This is the standard protocol for measuring visual clarity and is based on the distance a person is from a letter or number on the chart and the height of that letter or number [10]. The scale is as follows:

Table 1: Grading of Visual Acuity

Grade	Diagnosis
20/20 to 20/40	"good"
20/50 to 20/100	"moderate impairment"
20/200 to 5/200	"severe impairment"
5/200	"blind"

The next method used in classifying diabetic retinopathy is the Modified Airlie House Classification Scheme, which was proposed in the late 1960's [9]. This method consists of a series of seven 30° standard stereoscopic colour fundus photographs used in the grading of the severity level of diabetic retinopathy [1]. The Modified Airlie House Classification Scheme uses the colour fundus photographs to find hemorrhages or micro aneurysms, which may have formed at the retina. Since these lesions caused by the hemorrhaging or micro aneurysms can be identified in the photographs, they

are graded in order to determine the retinopathy severity level. The presence of the lesions is the major factor to be evaluated [1].

The Modified Airlie Classification Scheme was introduced as a way of standardizing the classification of Diabetic Retinopathy, and is still used by clinicians today based on its ease of use [9]. Standard photographs were provided such that a basis of grading hemorrhaging or the micro aneurysms could be established.

It was apparent that a need to understand and study the progression diabetic retinopathy was in order. Many studies have been conducted on the progression of this disease, but it is the Wisconsin Epidemiological Study of Diabetic Retinopathy that has gained the most notoriety [6].

The Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) [1] was founded during the years of 1979-1980. Its purpose was to investigate the prevalence, incidence, and progression of Diabetic Retinopathy. WESDR is the most recognizable name for its efforts in the prolonged study of diabetic retinopathy [6]. This group has conducted an observational study of a random sample of diabetics who all received primary care in an eleven county area of Southern Wisconsin. This sample was comprised of a younger onset group, all taking insulin before the age of thirty, and an older onset group [1]. For the purposes of this paper, we are concerned with only the younger onset group.

The younger onset group is comprised of 996 diabetics examined at four unequally spaced time points. The standard protcols for measuring diabetic retinopathy were used at each time point. These protocols are the Snellen chart and the Modified Airlie Classification Scheme. The first examination took place at the baseline year. The first

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follow-up examination was done four calendar years from the baseline (year four) in which 891 of the baseline year participated. The second follow-up examination was six calendar years after year four (year ten) in which 766 participated. The third follow-up examination was done four years after the second follow up (year fourteen) in which 625 of the original baseline examination were examined [1].

These are time censored intervals, in that we have no idea of the individual's condition or state in between examinations. Since this is an observational study, some subjects experience events such as death and other causes to the natural progression of the retinopathy process [2]. The reasons for non-participation will not be mentioned in this paper and are addressed elsewhere [1].

At each examination, we have the participant's visual acuity score from the Snellen chart and retinopathy severity level from the Modified Airlie House Classification Scheme. The visual acuity scores follow the standard chart as mentioned in Table 1, while the retinopathy severity levels were scaled using an algorithm where the scores range from 10 (no disease) through 85 (proliferate retinopathy) [1]. Table 2 summarizes the grading of diabetic retinopathy severity levels.

Table 2: Severity States

Level	severity
RL < 15	no retinopathy
$15 \leq RL \leq 37$	non proliferative DR
$38 \leq RL \leq 59$	mild non-proliferative DR
$60 \leq RL \leq 84$	active profliferative
RL = 85	end stage proliferative DR

We intend to use the visual acuity score and the retinopathy severity level of each

participant to encode our data. Accompanying these scores, we have the participant's gender and age at the baseline year. We intend to use age as a factor in our model of the progression of diabetic retinopathy.

The WESDR data are a discrete categorical model, in which we use ordinal scales for measurements. We intend to take a frequentist approach to modeling the progression of diabetic retinopathy because of the advantage of using our large sample size to allow for model selection based on the data [2]. Through the use of probability transition matrices to aid in the modeling of the progression form one year to the next and the use of maximum likelihood estimation methods to estimate parameters, we model the discrete paired longitudinal data as separate entities as well as paired. Since computation is numerically difficult by hand, software will be implemented for computation. It is our primary goal to model the progression of discrete paired longitudinal data.

2 METHODOLOGY

We propose to use a Markov chain, a stochastic process, because the conditional distribution of X_{t+1} given $X_0...X_t$ is identical to the conditional distribution of X_{t+1} given X_t. Also, the use of a Markov Chains has been successful and convenient in modeling medical contexts [7]. Our first step in this process was to encode the data into two groups. All non-participants were given a value of NA corresponding to not available. We combined the visual acuity score (VA) and retinopathy severity levels (RL) such that if the individual had a VA>20 or a RL<85, he/she was given a value of zero, which corresponds to not having severe visual impairment. If the individual scores a VA less than 20 and a RL equal to 85, he/she was given a value of one indicating severe visual impairment. A summary of the counts are given in Table 3 and Table 4 for the left and right eye, respectively, for our four time points, which are given in years after the baseline examination.

Table 3: Coded Counts for The Left Eye

Year	0	1
Baseline	914	78
4 years after	815	76
10 years after	721	45
14 years after	611	41

2.1 Modeling Eyes Individually

We now wish to apply a probability transition matrix to the unequally spaced time points separately for each eye. Our assumptions are that all cases are mutually

Table 4: Coded Counts for the Right Eye

Year	0	1
Baseline	916	76
4 years after	814	77
10 years after	715	51
14 years after	605	47

exclusive, an individual's eye is considered not to have severe visual impairment until a value of one is seen, and once the individual has reached the state of visual impairment, that individual is considered to have severe visual impairment for the duration of observed time points. We are treating the probabilities of the transition matrix as constants for the moment, and the transition matrix represents the idea of going from state to state in one-year increments. In the first row, the parameter p represents the probability of going from an eye of non-severe visual impairment to an eye of non-severe visual impairment, $1 - p$ represents that of going from an eye of non-severe visual impairment to that of an eye with severe visual impairment. The second row of the transitions matrix, under our assumptions, gives us a zero for going from an eye with severe visual impairment to an eye with non-severe visual impairment and a 1 for the probability of going from severe impairment to severe impairment. As it should, each row in the transition matrix sums to one. The following represents our transition matrix that we have applied to the data set:

$$\begin{bmatrix} p & 1 - p \\ 0 & 1 \end{bmatrix}$$

We used maximum likelihood estimation to estimate the parameters. Using this

transition matrix, we applied it to all possible finite cases of each eye separately and produced the following results where the first column represents the baseline year and the remaining columns represent four years after the baseline, ten years after the baseline, and fourteen years after the baseline, respectively. In the event that a missing value occured at the baseline year and a value of one occured at the first observed time point, the parameter ν was introduced. We do not know the state of the individual at the baseline year, and ν is the the estimate of having a value of not having severe visual impairment at the baseline year. The transition matrix is applied to each eye separately and the following represents all possible cases under our assumptions and their respective probabilities. We have substituted a value of * for any missing value in the following cases.

$$\text{Cases} \rightarrow \text{Probability}$$

$$0000 \rightarrow p^{14}$$

$$0001 \rightarrow p^{10} - p^{14}$$

$$0011 \rightarrow p^4 - p^{10}$$

$$0111 \rightarrow 1 - p^4$$

$$1111 \rightarrow 1$$

$$*000 \rightarrow p^{14}$$

$$*001 \rightarrow p^{10} - p^{14}$$

$$*011 \rightarrow p^4 - p^{10}$$

$$*111 \rightarrow 1 - \nu p^4$$

$$0*00 \rightarrow p^{14}$$

$$0*01 \rightarrow p^{10} - p^{14}$$

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$$0*11 \rightarrow 1 - p^{10}$$

$$1*11 \rightarrow 1$$

$$00*0 \rightarrow p^{14}$$

$$00*1 \rightarrow 1 - p^{14}$$

$$01*1 \rightarrow 1 - p^{4}$$

$$11*1 \rightarrow 1$$

$$000* \rightarrow p^{10}$$

$$001* \rightarrow p^{4} - p^{10}$$

$$011* \rightarrow 1 - p^{4}$$

$$111* \rightarrow 1$$

$$**00 \rightarrow p^{14}$$

$$**01 \rightarrow p^{10} - p^{14}$$

$$**11 \rightarrow 1 - \nu p^{10}$$

$$0**0 \rightarrow p^{14}$$

$$0**1 \rightarrow 1 - p^{14}$$

$$1**1 \rightarrow 1$$

$$*0*0 \rightarrow p^{14}$$

$$*0*1 \rightarrow p^{4} - p^{14}$$

$$*1*1 \rightarrow 1 - \nu p^{4}$$

$$00** \rightarrow p^{4}$$

$$01** \rightarrow 1 - p^{4}$$

$$11** \rightarrow 1$$

$$0*0* \rightarrow p^{10}$$

$$0*1* \to 1 - p^{10}$$

$$1*1* \to 1$$

$$*00* \to p^{10}$$

$$*01* \to p^{4} - p^{10}$$

$$*11* \to 1 - \nu p^{4}$$

$$0*** \to 1$$

$$1*** \to 1$$

$$*0** \to p^{4}$$

$$*1** \to 1 - \nu p^{4}$$

$$**0* \to p^{10}$$

$$**1* \to 1 - p^{10}$$

$$***0 \to p^{14}$$

$$***1 \to 1 - \nu p^{14}$$

It is now our goal to write the likelihood of the observed cases. We write a function in R, to obtain the counts of the cases and shall denote the counts as n_i such that $\{n_i, i = 1...N\}$ where i denotes the number of the discrete observed cases and the observed probabilities are denoted as $f(x_i)$ from the transition matrix, where $i = 1...N$ is the number of the observed cases. Our likelihood function is

$$L = \prod_{i=1}^{N} f(x_i)^{n_i}.$$

By taking the natural log of our likelihood function, we obtain our log-likelihood function

$$l = \sum_{i=1}^{N} n_i \ln(f(x_i)).$$

We use the log-likelihood to find our estimate of p and ν. This is done since the value of p and ν maximize the likelihood function as well as the log-likelihood function [5]. Once the counts of the cases are obtained from our R program, we take the counts and write our log-likelihood function in Maple version 10 to procure the results. The log-likelihood value is given since the likelihood function may be quite small.

Statistical inferences will be performed to find the best model for the progression of diabetic retinopathy. For model selection, we incorporate age and time until a severe visual impairment occurs as factors. We are operating under the same assumptions that our cases are mutually exclusive. An individual's eye is considered not to have severe visual impairment until a value of one is seen. Once the individual has reached the state of visual impairment, that individual is considered to have severe visual impairment for the duration of the observed time. In the following transition matrix, t represents the time until severe visual impairment is observed or until the end of our observed time and age represents the age of the individual at the baseline year. As before, both rows sum to one. We assume little about the parameters β and γ except that they are less than or equal to zero and hence account for this in our matrix.

$$\begin{bmatrix} pe^{(-\beta age - \gamma t)} & 1 - pe^{(-\beta age - \gamma t)} \\ 0 & 1 \end{bmatrix}$$

After applying the transition matrix, where age and time are factors, we then arrive at all possible cases under our assumptions and they are as follows:

$$\text{Cases} \rightarrow \text{Probability}$$

$$0000 \rightarrow p^{14} e^{(-14\beta age - \gamma \sum_{t=1}^{14} t)}$$

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$$0001 \rightarrow p^{10}e^{(-10\beta age - \gamma \sum_{t=1}^{10} t)} - p^{14}e^{(-14\beta age - \gamma \sum_{t=1}^{14} t)}$$

$$0011 \rightarrow p^{4}e^{(-4\beta age - \gamma \sum_{t=1}^{4} t)} - p^{10}e^{(-10\beta age - \gamma \sum_{t=1}^{10} t)}$$

$$0111 \rightarrow 1\text{- } p^{4}e^{(-4\beta age - \gamma \sum_{t=1}^{4} t)}$$

$$1111 \rightarrow 1$$

$$*000 \rightarrow p^{14}e^{(-14\beta age - \gamma \sum_{t=1}^{14} t)}$$

$$*001 \rightarrow p^{10}e^{(-10\beta age - \gamma \sum_{t=1}^{10} t)} - p^{14}e^{(-14\beta age - \gamma \sum_{t=1}^{14} t)}$$

$$*011 \rightarrow p^{4}e^{(-4\beta age - \gamma \sum_{t=1}^{4} t)} - p^{10}e^{(-10\beta age - \gamma \sum_{t=1}^{10} t)}$$

$$*111 \rightarrow 1\text{-}\nu p^{4}e^{(-4\beta age - \gamma \sum_{t=1}^{4} t)}$$

$$0*00 \rightarrow p^{14}e^{(-14\beta age - \gamma \sum_{t=1}^{14} t)}$$

$$0*01 \rightarrow p^{10}e^{(-10\beta age - \gamma \sum_{t=1}^{10} t)} - p^{14}e^{(-14\beta age - \gamma \sum_{t=1}^{14} t)}$$

$$0*11 \rightarrow 1\text{- } p^{10}e^{(-10\beta age - \gamma \sum_{t=1}^{10} t)}$$

$$1*11 \rightarrow 1$$

$$00*0 \rightarrow p^{14}e^{(-14\beta age - \gamma \sum_{t=1}^{14} t)}$$

$$00*1 \rightarrow p^{4}e^{(-4\beta age - \gamma \sum_{t=1}^{4} t)} - p^{14}e^{(-14\beta age - \gamma \sum_{t=1}^{14} t)}$$

$$01*1 \rightarrow 1\text{- } p^{4}e^{(-4\beta age - \gamma \sum_{t=1}^{4} t)}$$

$$11*1 \rightarrow 1$$

$$000* \rightarrow p^{10}e^{(-10\beta age - \gamma \sum_{t=1}^{10} t)}$$

$$001* \rightarrow p^{4}e^{(-4\beta age - \gamma \sum_{t=1}^{4} t)} - p^{10}e^{(-10\beta age - \gamma \sum_{t=1}^{10} t)}$$

$$011* \rightarrow 1\text{- } p^{4}e^{(-4\beta age - \gamma \sum_{t=1}^{4} t)}$$

$$111* \rightarrow 1$$

$$**00 \rightarrow p^{14}e^{(-14\beta age - \gamma \sum_{t=1}^{14} t)}$$

$$**01 \rightarrow p^{10}e^{(-10\beta age - \gamma \sum_{t=1}^{10} t)} - p^{14}e^{(-14\beta age - \gamma \sum_{t=1}^{14} t)}$$

$$**11 \rightarrow 1\text{-}\nu p^{10}e^{(-10\beta age - \gamma \sum_{t=1}^{10} t)}$$

$$0**0 \rightarrow p^{14}e^{(-14\beta age - \gamma \sum_{t=1}^{14} t)}$$

$$0**1 \rightarrow 1 - p^{14}e^{(-14\beta age - \gamma \sum_{t=1}^{14} t)}$$

$$1**1 \rightarrow 1$$

$$*0*0 \rightarrow p^{14}e^{(-14\beta age - \gamma \sum_{t=1}^{14} t)}$$

$$*0*1 \rightarrow p^{4}e^{(-4\beta age - \gamma \sum_{t=1}^{4} t)} - p^{14}e^{(-14\beta age - \gamma \sum_{t=1}^{14} t)}$$

$$*1*1 \rightarrow 1 - \nu p^{4}e^{(-4\beta age - \gamma \sum_{t=1}^{4} t)}$$

$$00** \rightarrow p^{4}e^{(-4\beta age - \gamma \sum_{t=1}^{4} t)}$$

$$01** \rightarrow 1 - p^{4}e^{(-4\beta age - \gamma \sum_{t=1}^{4} t)}$$

$$11** \rightarrow 1$$

$$0*0* \rightarrow p^{10}e^{(-10\beta age - \gamma \sum_{t=1}^{10} t)}$$

$$0*1* \rightarrow 1 - p^{10}e^{(-10\beta age - \gamma \sum_{t=1}^{10} t)}$$

$$1*1* \rightarrow 1$$

$$*00* \rightarrow p^{10}e^{(-10\beta age - \gamma \sum_{t=1}^{10} t)}$$

$$*01* \rightarrow 1 - p^{10}e^{(-10\beta age - \gamma \sum_{t=1}^{10} t)}$$

$$*11* \rightarrow 1 - \nu p^{4}e^{(-4\beta age - \gamma \sum_{t=1}^{4} t)}$$

$$0*** \rightarrow 1$$

$$1*** \rightarrow 1$$

$$*0** \rightarrow p^{4}e^{(-4\beta age - \gamma \sum_{t=1}^{4} t)}$$

$$*1** \rightarrow 1 - \nu p^{4}e^{(-4\beta age - \gamma \sum_{t=1}^{4} t)}$$

$$**0* \rightarrow p^{10}e^{(-10\beta age - \gamma \sum_{t=1}^{10} t)}$$

$$**1* \rightarrow 1 - \nu p^{10}e^{(-10\beta age - \gamma \sum_{t=1}^{10} t)}$$

$$***0 \rightarrow p^{14}e^{(-14\beta age - \gamma \sum_{t=1}^{14} t)}$$

$$***1 \rightarrow 1 - \nu p^{14}e^{(-14\beta age - \gamma \sum_{t=1}^{14} t)}$$

In writing our likelihood function including age and time as factors, we represent $f(x_i; age, time)$ as the probability of each case. Here we cannot take our counts and use Maple version 10 to compute our estimate, however we write our program in R such that the log-likelihood is added under each iteration of the function. This is done since age is a changing factor for each case, and if more than one case exists then the sum of said case's age is required. Since t is a constant, its value is can easily be computed. Using the optim feature in R, we are able to achieve our best estimate for p, ν, β, and γ.

Another nice feature of using R to write our log-likelihood is that, since we are interested in the best possible model, we can obtain the best estimates for when $\beta = 0$ and when $\gamma = 0$ in order to do statistical inferences. We intend to use a likelihood ratio test to find the best possible model. This will allow us to know if age and/or time plays a factor in the progression of diabetic retinopathy.

2.2 Modeling of Paired Data

It is now our intent to model the eyes as discrete paired longitudinal data. We are still under the previous assumptions but, since pairs of ordered categorical responses tend to be highly correlated, we now incorporate a factor to account for the dependence between the eyes when at least one of the eyes reaches the state of severe visual impairment [3].

We introduce our transition matrix such that the first row represents going from the left and right eye not having sever visual impairment to the left and right eye staying in the same state. In other words, column one represents the left and right

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eye not having severe visual impairment. Column two represents the right eye having severe visual impairment and the left eye not having severe visual impairment. Column three repesents the left eye having severe visual impairment and the right not having severe visual impairment. Column four represents both eyes having severe visual impairment. It is our assumption that if the previous state of the eyes are not severely afflicted then the eyes will have no effect on the next year's state. In other words, the first row represents an independence between the state of the eyes. Row two represents the left eye having no severe visual impaired and the right eye having severe visual impairment. Row two follows the transitions from the four previously mentioned columns. Row three represents the left eye having severe visual impairment and the right eye not having severe visual impairment. Row three follows the same transitions through the columns already mentioned. Row four represents both eyes having severe visual impairment and their transitions through the mentioned columns.

In the matrix, the subscripts l and r apply to left eye and right eye, respectively. The factors e^{β_l} and e^{β_r} are to account for the dependence between the eyes. We take the assumption that β_l and β_r are less than or equal to zero. Therfore we account for this restriction in our transition matrix.

$$
\begin{bmatrix}
p_l p_r & p_l(1 - p_r) & (1 - p_l)p_r & (1 - p_l)(1 - p_r) \\
0 & p_l e^{-\beta_l} & 0 & 1 - p_l e^{-\beta_l} \\
0 & 0 & p_r e^{-\beta_r} & 1 - p_r e^{-\beta_r} \\
0 & 0 & 0 & 1
\end{bmatrix}
$$

There are a multitude of cases in modeling pairs of longitudinal data that consist of every combination of left and right eye, respectively. One must keep in mind that

all cases are mutually exclusive when applying the transition matrix. One must also be sure to include all possible cases that will influence the probability of each case. We again use R to write our log-likelihood function to obtain the best estimates for our parameters.

It is now our intention to include age as a factor in modeling the year-to-year transitions. We allow γ to be our slope for age, which is recorded at the baseline year, and assume that γ is greater than zero since we have accounted for the negative value of γ in our transition matrix. We assume the parameter γ to be the same for the left and right eye, since each individual shares the recorded baseline age.

$$\begin{bmatrix} p_l e^{-\gamma age} p_r e^{-\gamma age} & p_l e^{-\gamma age}(1 - p_r e^{-\gamma age}) & (1 - p_l e^{-\gamma age}) p_r e^{-\gamma age} & (1 - p_l e^{-\gamma age})(1 - p_r e^{-\gamma age}) \\ 0 & p_l e^{-\beta_l - \gamma age} & 0 & 1 - p_l e^{-\beta_l - \gamma age} \\ 0 & 0 & p_r e^{-\beta_r - \gamma age} & 1 - p_r e^{-\beta_r - \gamma age} \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

Using R we are again able to write our log-likelihood function and obtain the best estimates for our parameters, which now consist of $p_l, p_r, \beta_l, \beta_r,$ and γ . This matrix represents the same idea as the previous matrix for modeling eyes jointly, only now the factor for age is in our program and is included at each iteration of the log-likelihood function.

3   RESULTS

In this chapter we present our results. We give the parameter estimates and the value of the log-likelihood function for each trial of our programs. This is important since we are going to conduct the likelihood ratio test.

In the likelihood ratio test, the value of the log-likelihood is obtained for the unconstrained model. In our case, age and time until severe visual impairment represents our unconstrained model. We denote the unconstrained model's log-likelihood value as l_u. When a factor is dropped, the model is the constrained model, and we denote its log-likelihood value as l_c. The test statistic is $X^2 = -2 * (l_u) - 2 * (l_c)$ [8]. This test statistic is compared to a chi-square distribution with 95% confidence and the degrees of freedom equal to the number of parameters dropped from the unconstrained model [11].

3.1   Left Eye Results

We begin with the simpliest case of modeling the left eye transitions that is our first constrained model. It is our intention to use maximum likelihood estimation (MLE) methods to estimate parametes, and we use the following equations to represent the likelihood function with all of cases from the data. Note that ν has a no value because no such cases exist.

$$L = \prod_1^7 f(x)^{n_i} = (1-p^4)^{n_1} * (p^4-p^{10})^{n_2} * (p^{10}-p^{14})^{n_3} * (p^{14})^{n_4} * (p^{10})^{n_5} * (p^4-p^{14})^{n_6} * (p^4)^{n_7}$$

Taking all counts from our R program, we were able to write the likelihood function as follows:

$$L = \prod_1^7 f(x) = (1 - p^4)^{16} * (p^4 - p^{10})^{13} * (p^{10} - p^{14})^{16} * p^{9864} * (p^4 - p^{14})$$

By taking the natural log of the likelihood function we arrive at

$$l = \sum_{i=1}^7 n_i \ln(f(x_i)) =$$

$$16 * \ln((1 - p^4) + 13 * \ln(p^4 - p^{10}) + 16 * \ln(p^{10} - p^{14}) + 9864 * \ln(p) + \ln(p^4 - p^{14}))$$

We are searching for the value that maximizes p, therefore we take the derivative of L with respect to the unknown parameter p and arrive at:

$$\frac{dl}{dp} = \frac{-64*p^3}{(1-p^4)} + \frac{52*p^3}{(p^4-p^{10})} - \frac{130*p^9}{(p^4-p^{10})} + \frac{160*p^9}{(p^{10}-p^{14})} - \frac{224*p^{13}}{(p^{10}-p^{14})} + \frac{9864}{p} + \frac{4*p^3}{(p^4-p^{14})} - \frac{14*p^{13}}{(p^4-p^{14})}$$

By setting the $\frac{dl}{dp} = 0$ we obtain our estimate of p for the left eye to be p=0.995948827. A log-likelihood value of l_c=-227.9330 is computed. Figure 3 shows a graph of the log-likelihood function for the left eye and Figure 4 shows the log-likelihood function's derivative. The figures are provided by Maple version 10.

Our next step is to compute the estimates with age and time until severe visual impairment are observed as factors. When considering these factors, we obtain our unconstrained model. Thanks to the software package R, we are able to obtain the estimates when age or time are dropped from the model. Table 5 summarizes the estimated parameter values for our unconstrained model.

Table 5: Parameter Estimates for Unconstrained Model for Left Eye

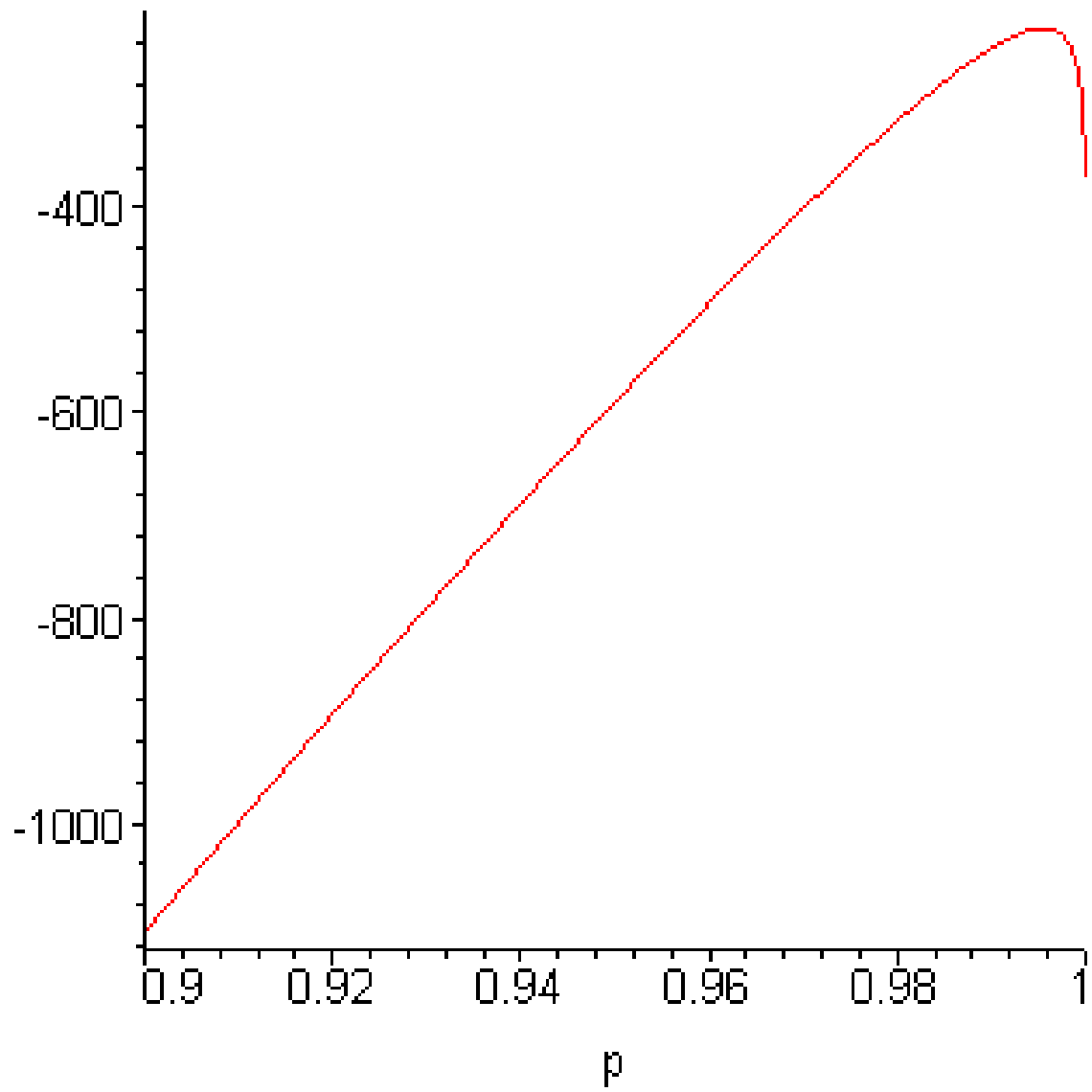| Parameter	Value
p	0.9981274
β	0.00007342678
γ	0.0001084154
ν	NA

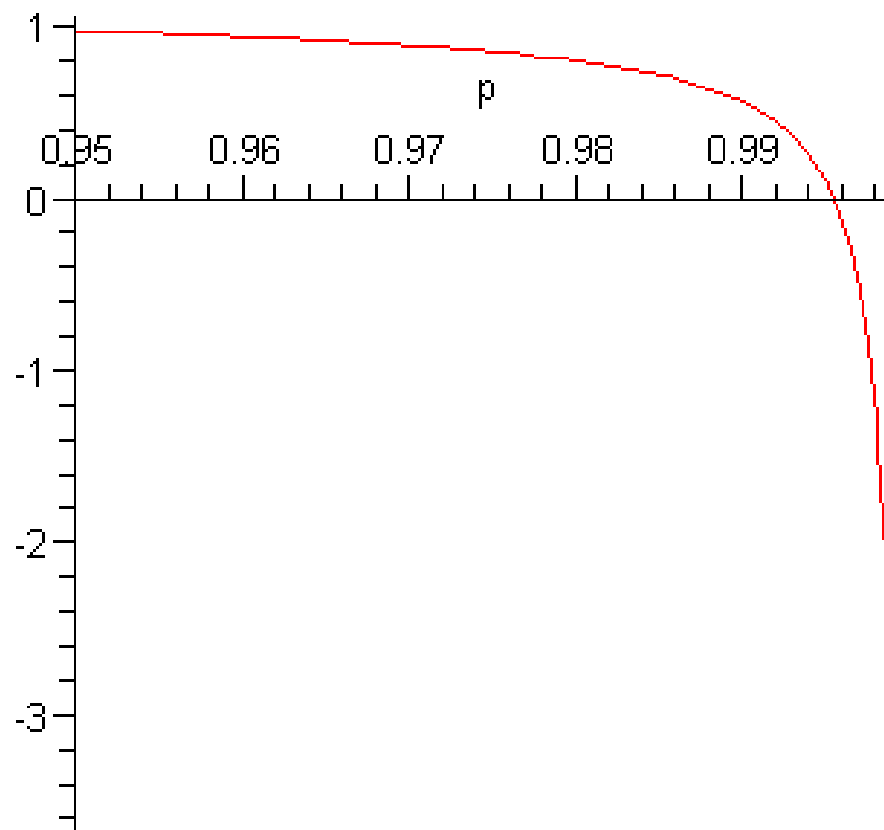Figure 1: Graph of the Log-Likelihood Function of Left Eye Treated as a Constant

Figure 2: Derivative of Log-Likelihood Function for Left Eye Treated as a Constant

Through MLE methods in R, we obtain parameter estimates to be p=0.9981274, the slope for age β=0.00007342678, the slope for the time until severe visual impairment, γ=0.001084154. The parameter ν receives a value of "NA". The unconstrained model gives l_u= -224.8931.

We are now able to give the best results for when time until severe visual impairment is not a factor in the model, γ=0. Table 6 summarizes our estimates of our parameters for when time until severe visual impairment is not a factor.

Table 6: Parameter Estimates for γ=0 for Left Eye

Parameter	Value
p	0.99699653
β	0.00005879746
γ	0
ν	NA

We see that the parameter p=0.99699653 and the parameter β=0.00005879746. We obtain a value for l_c= -225.7362 for the constrained model.

We can also remove age as a factor from the model. This gives us our third constrained model. Table 7 summarizes our estimates for when β equals to zero.

Table 7: Paramter Estimates for β=0 for Left Eye

Parameter	Value
p	0.9958837
β	0
γ	0.00006702342
ν	NA

The parameter p=0.9958837 and the parameter γ=0.00006702342. This con-

strained model gives l_c= -227.3449. With this information, we are now able to perform our likelihood ratio test with our possible models. The first test is done for when β and γ are dropped from the unconstrained model.

$$H_0:\ \beta=0\ \gamma=0$$

$$H_a:\ \text{at least one slope does not equal zero}$$

$$X^2=2*(-224.8931)-2*(-227.9330)=6.0798$$

$$\chi^2_{(.95,2)}=5.99146$$

$$X^2 > \chi^2_{(.95,2)}\ \text{Conclude } H_a$$

From this test, we have evidence that at least one parameter can be included in our model of the progression of diabetic retinopathy. The following test will determine which factor we shall include.

Test for time being dropped form the model, $\gamma=0$.

$$H_0:\ \gamma=0$$

$$H_a:\ \gamma \neq 0$$

$$X^2=2*(-224.8931)-2*(-225.7362)=1.6862$$

$$\chi^2_{(.95,1)}=3.84146$$

$$X^2 < \chi^2_{(.95,1)}\ \text{Conclude } H_0$$

This test gave us supporting evidence for the idea that time until severe visual impairment should not be included in our model. The following test is to see if we have evidence that the age of individual is appropriate for our model. This would support our first test that at least one parameter should be included in the model.

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$$\text{H}_0\text{: } \beta = 0$$

$$\text{H}_a\text{: } \beta \neq 0$$

$$X^2 = 2*(-224.8931) - 2*(-227.3449) = 4.9036$$

$$\chi^2_{(.95,1)} = 3.84146$$

$$X^2 > \chi^2_{(.95,1)} \text{ Conclude } \text{H}_a$$

From this test, we have evidence that age should be included in our model of the progression of diabetic retinopathy. This also supports our previous test results. We can interpret these results to mean that the older an individual, the more susceptible the individual is to severe visual impairment. The following table summarizes the results of the likelihood ratio tests:

Table 8: Likelihood Ratio Test Results

H_0	Test Statistic	p-value
$\beta=0$ $\gamma=0$	6.0798	0.04783967
$\gamma=0$	1.6862	0.1941027
$\beta=0$	4.9036	0.0268077

3.2 Right Eye Results

We begin, similar to how we analyzed the left eye results, by treating the transition matrix as a constant. We begin by showing our equation for the liklihood fucntion of the right eye. This will be our first constrained model for the right eye. As with the left eye, the parameter ν will not be estimated since no such cases exist.

$$L = \prod_1^7 f(x)^{n_i} = (1-p^4)^{n_1}*(p^4-p^{10})^{n_2}*(p^{10}-p^{14})^{n_3}*(p^{14})^{n_4}*(p^{10})^{n_5}*(p^4-p^{14})^{n_6}*(p^4)^{n_7}$$

Taking all of our counts from our R program, we were able to write the likelihood function as follows:

$$L = \prod_1^7 f(x) = (1 - p^4)^{22} * (p^4 - p^{10})^{17} * (p^{10} - p^{17})^{16} * p^{9696} * (p^4 - p^{14})^3$$

Taking the natural log of the likelihood function we arrive at

$$l = \sum_{i=1}^7 n_i \ln(f(x_i)) =$$

$$22 * \ln((1 - p^4) + 17 * \ln(p^4 - p^{10}) + 17 * \ln(p^{10} - p^{14}) + 9696 * \ln(p) + 3 * \ln(p^4 - p^{14}))$$

Since we desire the value that maximizes p, we take the derivative of L with respect to the unknown parameter p and arrive at:

$$\frac{dl}{dp} = \frac{-88*p^3}{(1-p^4)} + \frac{68*p^3}{(p^4-p^{10})} - \frac{170*p^9}{(p^4-p^{10})} + \frac{170*p^9}{(p^{10}-p^{14})} - \frac{238*p^{13}}{(p^{10}-p^{14})} + \frac{9696}{p} + \frac{12*p^3}{(p^4-p^{14})} - \frac{42*p^{13}}{(p^4-p^{14})}$$

By setting the $\frac{dl}{dp} = 0$ we obtain the parameter p, for the right eye modeled as a constant to the value of 0.9941692577. Our log-likelihood function gives a value $l_c =$ -273.7965. Figure 5 shows the graph obtained from Maple version 10 of the log-likelihood function for the right eye and Figure 6 shows its derivative.

We include age and time until severe visual impairment as factors to obtain our unconstrained model. The following table represents the results from our MLE methods in the R program. By optimizing our log-likelihood function to obtain the best estimates for our parameters as well as for when $\beta=0$ and $\gamma=0$, we arrive at the following tables.

Table 9 shows results from when age and time are factors. We see that our probability $p=0.9962208$, $\beta=0.00006593282$, $\gamma=0.00005152787$. This gives us our unconstrained model for the right eye and has a log-likelihood value l_u=-269.7488.
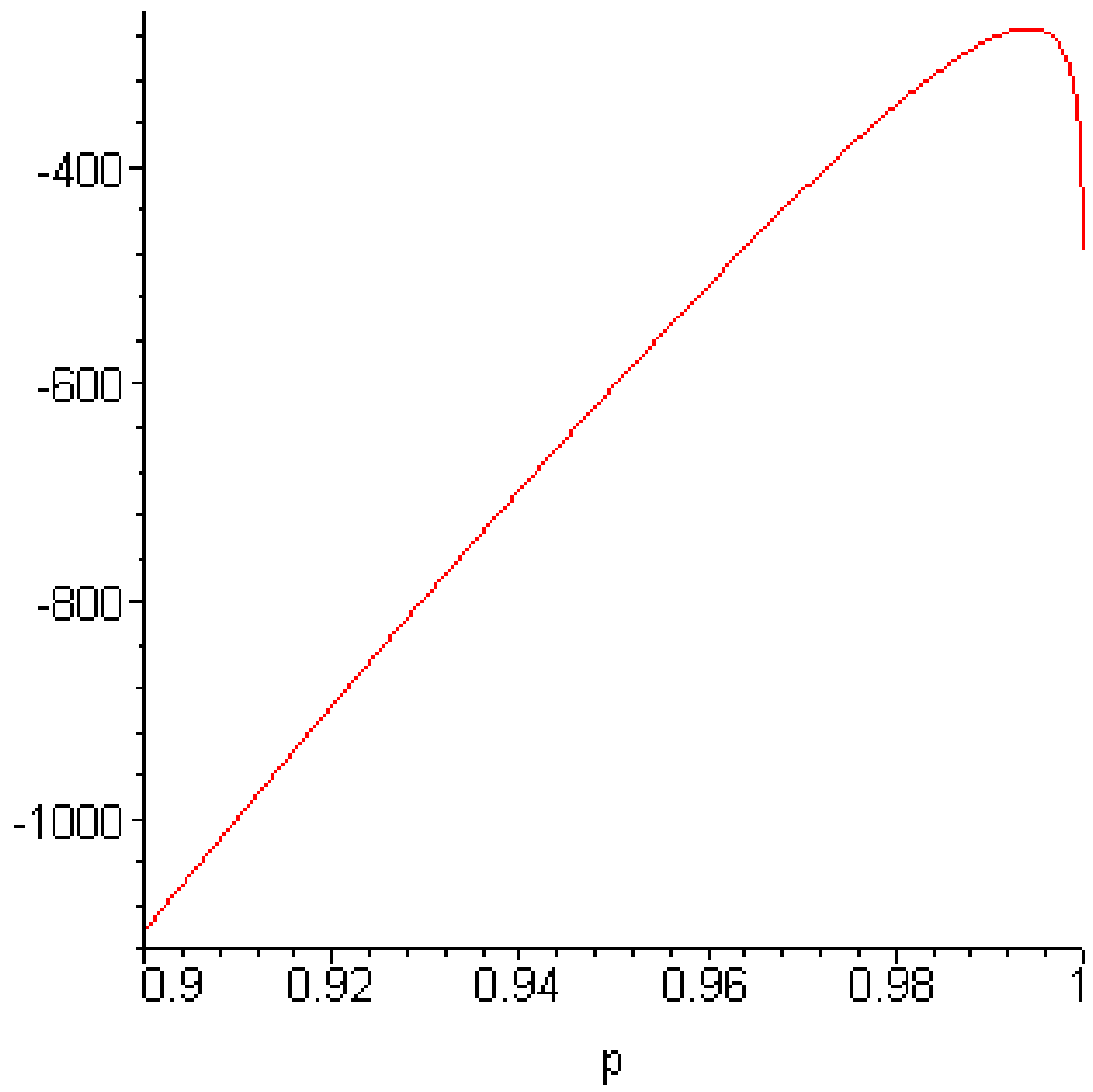
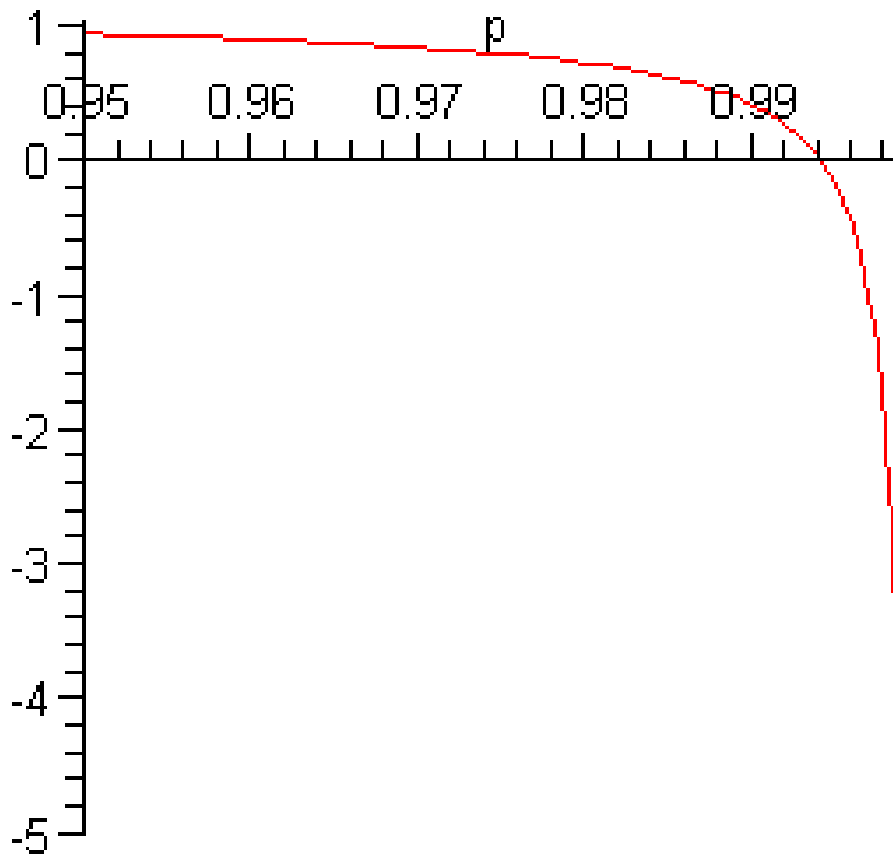Figure 3: Graph of the Log-Likelihood Function of Right Eye Treated as a Constant

Figure 4: Derivative of Log-Likelihood Function for Right Eye Treated as a Constant

Table 9: Parameter Estimates for Unconstrained Model for Right Eye

Parameter	Value
p	0.9962208
β	0.00006593282
γ	0.00005152787
ν	NA

We now obtain the best estimates for when time until severe visual impairment is not a part of our model. This is the case when γ is equal to zero, and the results are summarized in Table 10.

Table 10: Right Eye Estimates for $\gamma=0$

Parameter	Value
p	0.9961130
β	0.00006592568
γ	0
ν	NA

We have $p=0.9961130$ and $\beta=0.00006592568$ as estimates for our parameters. The log-likelihood function gives a value of l_c=-269.7613, and gives us a second constrained model.

Table 11 summarizes the best estimates for when age is not a part of the model. This is the case when β equals to zero. The values of the paramters are $p=0.9958837$ and $\gamma=0.000047637$. The log-likelihood function gives a value of l_c=-273.7672.

Since we now have estimates for our unconstrained and constrained models, we can perform the likelihood ratio test and select the best model.

Our first test is done for when β and γ are not a part of the unconstrained model.

Table 11: Right Eye Estimates for $\beta=0$

Parameter	Value
p	0.9958837
β	0
γ	0.000047637
ν	NA

$$H_0: \ \beta=0 \ \gamma=0$$

$$H_a: \text{ at least one slope does not equal zero}$$

$$X^2=2*(-269.7488)-2*(-273.7965)=8.0954$$

$$\chi^2_{(.95,2)}=5.99146$$

$$X^2 > \chi^2_{(.95,2)} \text{ Conclude } H_a$$

From this test, we have evidence that at least one parameter can be included in our model of the progression of diabetic retinopathy. The following test will determine which factor we shall include.

Test for time until severe visual impairment is observed is not a part of the model.

$$H_0: \ \gamma=0$$

$$H_a: \ \gamma \neq 0$$

$$X^2=2*(-269.7488)-2*(-269.7613)=0.25$$

$$\chi^2_{(.95,1)}=3.84146$$

$$X^2 < \chi^2_{(.95,1)} \text{ Conclude } H_0$$

This test gave us supporting evidence for the idea that time until severe visual impairment should not be included in our model. The following test is to see if we

have evidence that the age of the individual is appropriate for the model, and this supports our first test that at least one parameter should be included in the model.

Test for age not being a part of the model.

$$H_0: \beta=0$$

$$H_a: \beta \neq 0$$

$$X^2=2*(-269.7488)-2*(-273.7672)=8.0368$$

$$\chi^2_{(.95,1)}=3.84146$$

$$X^2 > \chi^2_{(.95,1)} \text{ Conclude } H_a$$

This test led us to conclude that we have evidence that age should be included in our model, much like what was seen analyzing data for the left eye. We conclude that the best model for the left and right eye should be the one in which age is included and is based on the model selected by the data. We can interpret these results to mean that the older an individual, the more susceptible the individual is to severe visual impairment. Table 12 summarizes the results of our likelihood ratio tests and gives their respective p-values.

Table 12: Likelihood Ratio Test for Right Eye

H_0	Test Statistic	p-value
$\beta=0$ $\gamma=0$	8.0954	0.01746249
$\gamma=0$	.025	0.874367
$\beta=0$	8.0368	0.004583644

3.3 Joint eyes

We now show results for modeling the progression of the discrete paired longitudinal data. We begin with the simplest case of treating the transition matrix as a constant, and allowing this to represent the first constrained model. Using the optim feature in R, we were able to obtain the estimates that maximize our log-likelihood function and a summary of the results are in the following table.

Table 13: Parameter Estimates for Joint Eyes: Constrained Model

Parameter	Value
p_l	0.99733348
p_r	0.99625972
β_l	0.02388120
β_r	0.053444210

The parameters to account for the dependence between the eyes are allowing us to look at how the eyes change over a one-year interval. The left eye's dependence value is $e^{-\beta_l}$=0.9764016994, and the right eye's dependence value is $e^{-\beta_r}$=0.9479588262. This model gives us a l_c= -388.8224 for our constrained model's log-likelihood value.

At this time, we would like to test our model for independence. It was our assumption that a dependence structure was present between the eyes and, by allowing β_l=0 and β_r=0 in our transition matrix, we were able to optimize our log-likelihood function and acheive the parameter estimates for to be p_l=0.9960828 and p_r=0.9947730. Under the restriction that β_l=0 and β_r=0 and p_l=0.9960828 and p_r=0.9947730, we achieve a log-likelihood value, which shall be denoted l_i=-455.8831, where i represents our independence structure. We shall again use the likelihood ratio test and it is as

follows:

$$H_0: \beta_l=0 \; \beta_r=0$$

$$H_a: \text{at least one slope does not equal zero}$$

$$X^2=2*(-388.8224)-2*(-455.8831)=134.1214$$

$$\chi^2_{(.95,2)}=5.99146$$

$$X^2 > \chi^2_{(.95,2)} \text{ Conclude } H_a$$

We can conclude that at least one slope does not equal zero with strong evidence since we have a p-value $<$ 0.0001. From this test, it is clear that a dependence structure is present and therefore we shall include β_l and β_r in our model of the joint progression of the discrete paired longitudinal data.

Since it is our primary goal to obtain the best model, we include age as a factor. We are interested in seeing if age is also a factor to consider for the progression of diabetic retinopathy in both eyes.

Table 14: Parameter Estimates for Age Included for Joint Eyes

Parameter	Value
p_{left}	0.9983295
p_{right}	0.9973444
β_{left}	0.02913909
β_{right}	0.05621652
γ	0.00003510966

We achieve a log-likelihood value of $l_u=$ -386.3605 for our log-likelihood value from this model and consider it to be our unconstrained model. Age was included as a factor and γ=0.00003510966 and this allows us to conclude that the older you are

the more likely the eyes are to be severely impaired. Now we wish to conduct our likelihood ratio test to this model, to test if age should be dropped from modeling the eyes as a pair.

$$H_0: \gamma=0$$

$$H_a: \gamma \neq 0$$

$$X^2=2*(-388.8224)-2*(-386.3605)=4.9238$$

$$\chi^2_{(.95,1)}=3.84146$$

$$X^2 < \chi^2_{(.95,1)} \text{ Conclude } H_a$$

We can conclude from this likelihood ratio test, that we have evidence to support that age should be included in modeling of the eyes jointly. In other words, $\gamma \neq 0$. We obtain a p-value equal to 0.026489. We can interpret this as meaning that age plays a role in the progression of diabetic retinopathy in that the older an individual is, the more likely he/she is to obtain the state of severe visual impairment.

4 CONCLUSION

The Wisconsin Epidemological Study of Diabetic Retinopathy has gained much acclaim for their efforts in the study of incidence, prevalence, and progression of diabetic retinopathy [6]. Using the Wisconsin Epidemological Study of Diabetic Retinopathy data set as an example, it was our intention to derive a methodology to model discrete paired longitudinal data.

In modeling discrete paired longitudinal data, we began by modeling the pairs seperately, in the case of the WESDR data, the left and right eye, respectively. We introduced a Markov Chain process in which we implemented a transition matrix to model from one state to the next state. The purpose of taking such an approach was that we may perfom statistical inferences and arrive at the most appropriate model.

In the case of treating the pairs seperately, we see that the most appropriate model is the one that includes age as a factor, information we have for the baseline examination year of each individual. In the following transition matrix, we have β restricted such that the sign is negative.

$$
\begin{bmatrix} pe^{(-\beta age)} & 1 - pe^{(-\beta age)} \\ 0 & 1 \end{bmatrix}
$$

It was our primary goal to determine a methodology to model discrete paired longitudinal data. We first treated the model for the paired data as a constant, which includes a value to account for the dependence between the eyes. This dependence is common with most paired medical, model contexts [3]. The value that was included to account for the dependece was $e^{-\beta_l}$ for the left eye and $e^{-\beta_r}$ for the right eye. We

took the assumption that β_l and β_r was negative and accounted for this in our model. This led us to the restriction that β must be greater than zero in our estimate. We included age as a factor, to see if age has a role in the model, as it has with treating the pairs individually. We arrived at the conclusion that we do have enough evidence to say age is a factor to be included in the model based on the likelihood ratio test. The following transition matrix represtents our model for the discrete paired longitudinal data.

$$
\begin{bmatrix}
p_l e^{-\gamma age} p_r e^{-\gamma age} & p_l e^{-\gamma age}(1 - p_r e^{-\gamma age}) & (1 - p_l e^{-\gamma age}) p_r e^{-\gamma age} & (1 - p_l e^{-\gamma age})(1 - p_r e^{-\gamma age}) \\
0 & p_l e^{-\beta_l - \gamma age} & 0 & 1 - p_l e^{-\beta_l - \gamma age} \\
0 & 0 & p_r e^{-\beta_r - \gamma age} & 1 - p_r e^{-\beta_r - \gamma age} \\
0 & 0 & 0 & 1
\end{bmatrix}
$$

Through the use of software, we are able to optimize our parameters by means of maximum likelihood estimation methods. The likelihood ratio test performed on all our models was chosen as the test since the natural log of the value of the likelihood function was easily computed.

BIBLIOGRAPHY

[1] B. Craig, A Bayesian Approach to Modelling the Natural History of a Chronic Condition From Observations with Intervention. *Statistics in Medicine*, **18** (1999), 1355-1371.

[2] J. Angers, A Bayesian Analysis of the 4-year Follow-up Data of the Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Statistics in Medicine*, **23** (2004), 601-615.

[3] J. Williamson, A Global Odds Ratio Regression Model for Bivariate Ordered Categorical Data From Ophthalmologic Studies. *Statistics in Medicine*, **15** (1996), 1507-1518.

[4] M.Lövestam-Adrian, Diabetic Retinopathy, Visual Acuity, and Medical Risk Indicators. A continuous 10-year Follow-up Study in Type 1 Diabetic Patients Under Routine Care. *Journal of Diabetes and Its Compicatons*, **15** (2001) 287-294.

[5] *Regression Models for Categorical and Limited Dependent Variables*, by J. Scott Long, Published by Sage Publication, Inc. 1997.

[6] M. Porta, Diabetic retinopathy: A Clinical Update. *Diabetologia*, **45** (2002) 1617-1634.

[7] *Analyzing Categorical Data*, by J. S. Simonoff, Published by Springer, New York, 2003.

[8] *Categorical Data Analysis*, by A. Agresti, Published by Wily-Interscience Publicaton, New York, 1990.

[9] *Symposium on the Treatment of Diabetic Retinopathy*, by M. Goldberg, Published by Public Health Service Publicaton, Arlington, 1968.

[10] *Merriam-Webster's Medical Desk Dictionary Revised Edition*, Published by Merriam-Webster Incorporated, New York , 2005.

[11] *Applied Linear Statistical Models*, by M. Kutner, Published by McGraw-Hill Irwin, Boston, 2005.

APPENDICES

Appendix A presents the code for the left eye's log-likelihood function in which age and time have been considered as factors. The right eye was done similarly. We began by coding the data into a matrix after it has been read into R. The matrix represents the state of the eye from one observed time point until the next. We denoted our log-likelihood function for the left eye as lefteyefunction2, where p represents the probability in our transition matrix, b represents β in our transition matrix, g represents *gamma* in our transition matrix, and v represtn ν.

In Appendix B, we introduce the code for computing the value of the parameters for when age is incorporated as a factor into the modelling of eyes jointly. Here s represents the left eye, t represents the right eye, B represents β_l, G represents β_r, and K represents γ, the slope for our factor time.

Appendix A: Code for Modeling Left Eye with Age and Time as Factors

```
va0 <- 20

leye<- matrix(1, n, 4)

leye[vale0<=va0, 1]<-1

leye[vale0>va0 & rlle0 < 85, 1]<-0

leye[is.na(vale0), 1] <- 2

leye[vale4<=va0, 2]<-1

leye[vale4>va0 & rlle4 < 85, 2]<-0

leye[is.na(vale4), 2] <- 2

leye[vale10<=va0, 3]<-1
```

```r
leye[vale10>va0 & rlle10 < 85, 3]<-0

leye[is.na(vale10), 3] <- 2

leye[vale14<=va0, 4]<-1

leye[vale14>va0 & rlle14 < 85, 4]<-0

leye[is.na(vale14), 4] <- 2

lefteyefunction2 <-function(para, n, age0) {

p<-para[1]

b<-para[2]

g<-para[3]

v<-para[4]

loglike <- 0

for (i in 1:n){

if (leye[i,1]==0 &leye[i,2]==0 & leye[i,3]==0 & leye[i,4]==0){

loglike <- loglike + 14*log(p)+14*b*age0[i]+g*sum(1:14)

}

if (leye[i,1]==0 &leye[i,2]==0 & leye[i,3]==0 & leye[i,4]==1){

loglike<- loglike + log(p^10*exp(10*b*age0[i])*exp(g*

sum(1:10))-p^14*exp(14*b*age0[i])*exp(g*sum(1:14)))

}

if (leye[i,1]==0 &leye[i,2]==0 & leye[i,3]==1 & leye[i,4]==1){

loglike<-loglike + log(p^4*exp(4*b*age0[i])*exp(g*sum(1:4

))-p^10*exp(10*b*age0[i])*exp(g*sum(1:10)))

}
```

```
if (leye[i,1]==0 &leye[i,2]==1 & leye[i,3]==1 & leye[i,4]==1){

loglike<- loglike + log(1-p4^*exp(4*b*age0[i])*exp(g*sum(1:4)))

}

if (leye[i,1]==1 &leye[i,2]==1 & leye[i,3]==1 & leye[i,4]==1){

loglike<-loglike + 0

}

if (leye[i,1]==2 &leye[i,2]==0 & leye[i,3]==0 & leye[i,4]==0){

loglike <-loglike + 14*log(p)+14*b*age0[i]+g*sum(1:14)

}

if (leye[i,1]==2 &leye[i,2]==0 & leye[i,3]==0 & leye[i,4]==1){

loglike<-loglike + log(p10^*exp(10*b*age0[i])*exp(g*

sum(1:10))-p14^*exp(14*b*age0[i])*exp(g*sum(1:14)))

}

if (leye[i,1]==2 &leye[i,2]==0 & leye[i,3]==1 & leye[i,4]==1){

loglike<-loglike + log(p4^*exp(4*b*age0[i])*exp(g*sum(1:4))

-p10^*exp(10*b*age0[i])*exp(g*sum(1:10)))

}

if (leye[i,1]==2 &leye[i,2]==1 & leye[i,3]==1 & leye[i,4]==1){

loglike<-loglike + log(1-v*p4^*exp(4*b*age0[i])*exp(g*sum(1:4)))

}

if (leye[i,1]==0 &leye[i,2]==2 & leye[i,3]==0 & leye[i,4]==0){

loglike <-loglike + 14*log(p)+14*b*age0[i]+g*sum(1:14)

}
```

```
if (leye[i,1]==0 &leye[i,2]==2 & leye[i,3]==0 & leye[i,4]==1){

loglike<-loglike + log(p1̂0*exp(10*b*age0[i])*exp(g*sum(1:10))

-p1̂4*exp(14*b*age0[i])*exp(g*sum(1:14)))

}

if (leye[i,1]==0 &leye[i,2]==2 & leye[i,3]==1 & leye[i,4]==1){

loglike<-loglike + log(1-p1̂0*exp(10*b*age0[i])*exp(g*sum(1:10)))

}

if (leye[i,1]==1 &leye[i,2]==2 & leye[i,3]==1 & leye[i,4]==1){

loglike<-loglike + 0

}

if (leye[i,1]==0 &leye[i,2]==0 & leye[i,3]==2 & leye[i,4]==0){

loglike <-loglike + 14*log(p)+14*b*age0[i]+g*sum(1:14)

}

if (leye[i,1]==0 &leye[i,2]==0 & leye[i,3]==2 & leye[i,4]==1){

loglike<-loglike + log(p4̂*exp(4*b*age0[i])*exp(g*sum(1:4))-

p1̂4*exp(14*b*age0[i])*exp(g*sum(1:14)))

}

if (leye[i,1]==0 &leye[i,2]==1 & leye[i,3]==2 & leye[i,4]==1){

loglike<-loglike + log(1-p4̂*exp(4*b*age0[i])*exp(g*sum(1:4)))

}

if (leye[i,1]==1 &leye[i,2]==1 & leye[i,3]==2 & leye[i,4]==1){

loglike<-loglike + 0

}
```

```
if (leye[i,1]==0 &leye[i,2]==0 & leye[i,3]==0 & leye[i,4]==2){

loglike <-loglike + 10*log(p)+10*b*age0[i]+g*sum(1:10)

}

if (leye[i,1]==0 &leye[i,2]==0 & leye[i,3]==1 & leye[i,4]==2){

loglike<-loglike + log(p4̂*exp(4*b*age0[i])*exp(g*sum(1:4))

-p1̂0*exp(10*b*age0[i])*exp(g*sum(1:10)))

}

if (leye[i,1]==0 &leye[i,2]==1 & leye[i,3]==1 & leye[i,4]==2){

loglike<-loglike + log(1-p4̂*exp(4*b*age0[i])*exp(g*sum(1:4)))

}

if (leye[i,1]==1 &leye[i,2]==1 & leye[i,3]==1 & leye[i,4]==2){

loglike<-loglike + 0

}

if (leye[i,1]==2 &leye[i,2]==2 & leye[i,3]==0 & leye[i,4]==0){

loglike <-loglike + 14*log(p)+14*b*age0[i]+g*sum(1:14)

}

if (leye[i,1]==2 &leye[i,2]==2 & leye[i,3]==0 & leye[i,4]==1){

loglike<-loglike + log(p1̂0*exp(10*b*age0[i])*exp(g*sum(1:10))-

p1̂4*exp(14*b*age0[i])*exp(g*sum(1:14)))

}

if (leye[i,1]==2 &leye[i,2]==2 & leye[i,3]==1 & leye[i,4]==1){

loglike<-loglike + log(1-v*p1̂0*exp(10*b*age0[i])*exp(g*sum(1:10)))

}
```

```
if (leye[i,1]==2 &leye[i,2]==0 & leye[i,3]==2 & leye[i,4]==0){

loglike <-loglike + 14*log(p)+14*b*age0[i]+g*sum(1:14)

}

if (leye[i,1]==2 &leye[i,2]==0 & leye[i,3]==2 & leye[i,4]==1){

loglike<-loglike + log(p^4*exp(4*b*age0[i])*exp(g*sum(1:4))

-p^14*exp(14*b*age0[i])*exp(g*sum(1:14)))

}

if (leye[i,1]==2 &leye[i,2]==1 & leye[i,3]==2 & leye[i,4]==1){

loglike<-loglike + log(1-v*p^4*exp(4*b*age0[i])*exp(g*sum(1:4)))

}

if (leye[i,1]==2 &leye[i,2]==0 & leye[i,3]==0 & leye[i,4]==2){

loglike <-loglike + 10*log(p)+10*b*age0[i]+g*sum(1:10)

}

if (leye[i,1]==2 &leye[i,2]==0 & leye[i,3]==1 & leye[i,4]==2){

loglike<-loglike + log(p^4*exp(4*b*age0[i])*exp(g*sum(1:4))

-p^10*exp(10*b*age0[i])*exp(g*sum(1:10)))

}

if (leye[i,1]==2 &leye[i,2]==1 & leye[i,3]==1 & leye[i,4]==2){

loglike<-loglike + log(1-v*p^4*exp(4*b*age0[i]+g*55))

}

if (leye[i,1]==0 &leye[i,2]==2 & leye[i,3]==0 & leye[i,4]==2){

loglike <-loglike + 10*log(p)+10*b*age0[i]+g*sum(1:10)

}
```

```
if (leye[i,1]==0 &leye[i,2]==2 & leye[i,3]==1 & leye[i,4]==2){

loglike<-loglike + log(1-p1̂0*exp(10*b*age0[i])*exp(g*sum(1:10)))

}

if (leye[i,1]==1 &leye[i,2]==2 & leye[i,3]==1 & leye[i,4]==2){

loglike<-loglike + 0

}

if (leye[i,1]==0 &leye[i,2]==0 & leye[i,3]==2 & leye[i,4]==2){

loglike <-loglike + 4*log(p)+4*b*age0[i]+g*sum(1:4)

}

if (leye[i,1]==0 &leye[i,2]==1 & leye[i,3]==2 & leye[i,4]==2){

loglike<-loglike + log(1-p4̂*exp(4*b*age0[i])*exp(g*sum(1:4)))

}

if (leye[i,1]==1 &leye[i,2]==1 & leye[i,3]==2 & leye[i,4]==2){

loglike<-loglike + 0

}

if (leye[i,1]==0 &leye[i,2]==2 & leye[i,3]==2 & leye[i,4]==0){

loglike <-loglike + 14*log(p)+14*b*age0[i]+g*sum(1:14)

}

if (leye[i,1]==0 &leye[i,2]==2 & leye[i,3]==2 & leye[i,4]==1){

loglike<-loglike + log(1-p1̂4*exp(14*b*age0[i])*exp(g*sum(1:14)))

}

if (leye[i,1]==1 &leye[i,2]==2 & leye[i,3]==2 & leye[i,4]==1){

loglike<-loglike + 0
```

```
}

if (leye[i,1]==0 &leye[i,2]==2 & leye[i,3]==2 & leye[i,4]==2){

loglike<-loglike + 0

}

if (leye[i,1]==1 &leye[i,2]==2 & leye[i,3]==2 & leye[i,4]==2){

loglike<-loglike + 0

}

if (leye[i,1]==2 &leye[i,2]==0 & leye[i,3]==2 & leye[i,4]==2){

loglike <-loglike + 4*log(p)+4*b*age0[i]+g*sum(1:4)

}

if (leye[i,1]==2 &leye[i,2]==1 & leye[i,3]==2 & leye[i,4]==2){

loglike<-loglike + log(1-v*p4̂*exp(4*b*age0[i])*exp(g*sum(1:4)))

}

if (leye[i,1]==2 &leye[i,2]==2 & leye[i,3]==0 & leye[i,4]==2){

loglike <-loglike + 10*log(p)+10*b*age0[i]+g*sum(1:10)

}

if (leye[i,1]==2 &leye[i,2]==2 & leye[i,3]==1 & leye[i,4]==2){

loglike<-loglike + log(1-v*p1̂0*exp(10*b*age0[i])*exp(g*sum(1:10)))

}

if (leye[i,1]==2 &leye[i,2]==2 & leye[i,3]==2 & leye[i,4]==0){

loglike <-loglike + 14*log(p)+14*b*age0[i]+g*sum(1:14)

}

if (leye[i,1]==2 &leye[i,2]==2 & leye[i,3]==2 & leye[i,4]==1){
```

```
loglike<-loglike + log(1-v*p̂14*exp(14*b*age0[i]+g*sum(1:14)))

}

if (leye[i,1]==1 & leye[i,2]==0){

loglike<-loglike + 0

}

else if (leye[i,2]==1 & leye[i,3]==0){

loglike<-loglike + 0

}

else if (leye[i,3]==1 & leye[i,4]==0){

loglike<-loglike + 0

}

else if (leye[i,1]==1 & leye[i,4]==0){

loglike<-loglike + 0

}

else if (leye[i,2]==1 & leye[i,4]==0){

loglike<-loglike + 0

}

else if (leye[i,1]==1 & leye[i,3]==0){

loglike<-loglike + 0

}

if (leye[i,1]==2 &leye[i,2]==2 & leye[i,3]==2 & leye[i,4]==2){

loglike<-loglike + 0

}
```

```
}

return(loglike)

}

optim(c(9.964941e-01 ,-3.936488e-05 ,-5.386775e-05 , 0.000000e+00),

lefteyefunction2,method="L-BFGS-B", control = list(maxit=6000,

fnscale =-1), n=n,age0=age0,lower=c(0.001, -1, -1,0),

upper=c(.999999999, 0,0,1 ))
```

Appendix B: Code for Modeling Eyes Jointly

```
joint2<-function(para,n,age0){

s<-para[1]

t<-para[2]

B<-para[3]

G<-para[4]

K<-para[5]

loglike<-0

for (i in 1:n){


   if (leye[i,1]==0 &leye[i,2]==0 & leye[i,3]==0 & leye[i,4]==0
& reye[i,1]==0 &reye[i,2]==0 & reye[i,3]==0 & reye[i,4]==0)
{
loglike<- loglike + log(s^(14)*((exp((-K*age0[i])))^(28)*t^(14))
}
if (leye[i,1]==0 &leye[i,2]==0 & leye[i,3]==0 & leye[i,4]==0
& reye[i,1]==0 &reye[i,2]==0 & reye[i,3]==0 & reye[i,4]==1)
{
loglike<-loglike + log((-1)*s^(14)*((exp((-K*age0[i])))^(24)
*t^(10)*(-1+t*exp((-K*age0[i])))*(exp((-B))+t*exp((-K*age0[i]))
)*((((exp((-K*age0[i]))))^(2)*t^(2)+((exp((-B))))^(2)))
}
if (leye[i,1]==0 &leye[i,2]==0 & leye[i,3]==0 & leye[i,4]==0
```

55

```
& reye[i,1]==0 &reye[i,2]==0 & reye[i,3]==1 & reye[i,4]==1)

{

loglike<-loglike + log((-1)*s^(14)*((exp((-K*age0[i])))))^(18)*

t^(4)*(-1+t*exp((-K*age0[i])))*((exp((-B))))^(4)*(exp((-B))+t*

exp((-K*age0[i])))*(((exp((-B))))^(2)+exp((-B))*t*exp((-K*age0[i]

))+((exp((-K*age0[i]))))^(2)*t^(2))*(((exp((-B))))^(2)-exp((-B))

*t*exp((-K*age0[i]))+((exp((-K*age0[i]))))^(2)*t^(2)))

}

if (leye[i,1]==0 &leye[i,2]==0 & leye[i,3]==0 & leye[i,4]==0

& reye[i,1]==0 &reye[i,2]==1 & reye[i,3]==1 & reye[i,4]==1)

{

loglike<-loglike + log((-1)*s^(13)*((exp((-B))))^(9)*((exp(

(-K*age0[i])))))^(13)*(-1+t*exp((-K*age0[i])))*(exp((-B))+t*

exp((-K*age0[i])))*(((exp((-K*age0[i]))))^(2)*t^(2)+((exp

((-B))))^(2)))

}

if (leye[i,1]==0 &leye[i,2]==0 & leye[i,3]==0 & leye[i,4]==0

& reye[i,1]==1 &reye[i,2]==1 & reye[i,3]==1 & reye[i,4]==1)

{

loglike<- loglike + log(s^(14)*((exp((-K*age0[i])))))^(14)*((

exp((-B))))^(14))

}

if (leye[i,1]==0 &leye[i,2]==0 & leye[i,3]==0 & leye[i,4]==1
```

```
& reye[i,1]==0 &reye[i,2]==0 & reye[i,3]==0 & reye[i,4]==0)

{

loglike<-loglike + log(-s^(10)*((exp((-K*age0[i])))))^(24)*

t^(14)*(-1+s*exp((-K*age0[i])))*(exp((-G))+s*exp((-K*age0[i])

))*(((exp((-K*age0[i])))))^(2)*s^(2)+((exp((-G))))^(2)))

}

if (leye[i,1]==0 &leye[i,2]==0 & leye[i,3]==0 & leye[i,4]==1

& reye[i,1]==0 &reye[i,2]==0 & reye[i,3]==0 & reye[i,4]==1)

{

loglike<- loglike + log(s^(10)*((exp((-K*age0[i])))))^(20)*

t^(10)*(1+s^(4)*((exp((-K*age0[i])))))^(7)*t^(3)*exp((-B))

-s^(4)*((exp((-K*age0[i])))))^(6)*t^(2)*exp((-B))+s^(4)*(

(exp((-K*age0[i])))))^(5)*((exp((-B))))^(3)*t-s^(4)*((exp(

(-K*age0[i])))))^(5)*t*((exp((-B))))^(2)+s^(4)*((exp((-K*

age0[i])))))^(6)*t^(2)*((exp((-B))))^(2)+s^(3)*((exp((-K*

age0[i])))))^(7)*t^(4)*exp((-G))-s^(2)*((exp((-K*age0[i])

))))^(6)*t^(4)*exp((-G))+t^(4)*((exp((-K*age0[i])))))^(5)*

((exp((-G))))^(3)*s+s^(2)*((exp((-K*age0[i])))))^(6)*t^(4)

*((exp((-G))))^(2)-s*((exp((-K*age0[i])))))^(5)*t^(4)*((exp

((-G))))^(2)-s^(3)*((exp((-K*age0[i])))))^(7)*t^(4)-s^(4)

*((exp((-K*age0[i])))))^(7)*t^(3)+s^(4)*((exp((-K*age0[i]))

))^(8)*t^(4)-s^(4)*((exp((-K*age0[i])))))^(4)*((exp((-B)))

)^(3)-t^(4)*((exp((-K*age0[i])))))^(4)*((exp((-G))))^(3)))
```

```
}
if (leye[i,1]==0 &leye[i,2]==0 & leye[i,3]==0 & leye[i,4]==1

& reye[i,1]==0 &reye[i,2]==0 & reye[i,3]==1 & reye[i,4]==1)

{

loglike<-loglike + log(s^(10)*t^(4)*((exp((-K*age0[i])))))^(14)

*(-1+t*exp((-K*age0[i])))*(exp((-B))+t*exp((-K*age0[i])))*(((exp(

(-B))))^(2)+exp((-B))*t*exp((-K*age0[i]))+((exp((-K*age0[i])))

)^(2)*t^(2))*((((exp((-B))))^(2)-exp((-B))*t*exp((-K*age0[i]))+

((exp((-K*age0[i])))))^(2)*t^(2))*(s*exp((-K*age0[i]))*exp((-B))

-1)*(s*exp((-K*age0[i]))*exp((-B))+1)*(s^(2)*((exp((-K*age0[i])))

)^(2)*((exp((-B))))^(2)+1))

}

if (leye[i,1]==0 &leye[i,2]==0 & leye[i,3]==1 & leye[i,4]==1

& reye[i,1]==0 &reye[i,2]==0 & reye[i,3]==0 & reye[i,4]==0)

{

loglike<-loglike + log(-s^(4)*((exp((-K*age0[i])))))^(18)*t^(14)

*(-1+s*exp((-K*age0[i])))*((exp((-G))))^(4)*(exp((-G))+s*exp((-K

*age0[i])))*(((exp((-G))))^(2)+exp((-G))*s*exp((-K*age0[i]))+

s^(2)*((exp((-K*age0[i])))))^(2))*(((exp((-G))))^(2)-exp((-G))*

s*exp((-K*age0[i]))+s^(2)*((exp((-K*age0[i])))))^(2)))

}

if (leye[i,1]==0 &leye[i,2]==1 & leye[i,3]==1 & leye[i,4]==1

& reye[i,1]==0 &reye[i,2]==1 & reye[i,3]==1 & reye[i,4]==1)
```

```
{
loglike<-loglike + log(1+2*s*((exp((-K*age0[i])))))^2*t-s*exp(
(-K*age0[i]))-t*exp((-K*age0[i]))-t^3*((exp((-K*age0[i])))))^4
*((exp((-G))))^2*s-s*((exp((-K*age0[i])))))^5*t^4*((exp((-G)))
)^2-s^2*((exp((-K*age0[i])))))^5*t^3*exp((-G))-s^2*((exp((-K*
age0[i])))))^6*t^4*exp((-G))+s^3*((exp((-K*age0[i])))))^7*t^4*
exp((-G))-s^3*((exp((-K*age0[i])))))^4*((exp((-B))))^2*t-s^4*
((exp((-K*age0[i])))))^5*t*((exp((-B))))^2+s^4*((exp((-K*age0[i]
)))))^6*t^2*((exp((-B))))^2-s*((exp((-K*age0[i])))))^3*t^2-s^2
*((exp((-K*age0[i])))))^3*t+2*s^2*((exp((-K*age0[i])))))^4*t^2+
t^3*((exp((-K*age0[i])))))^3*((exp((-G))))^2+s^3*((exp((-K*
age0[i])))))^3*((exp((-B))))^2+t^4*((exp((-K*age0[i])))))^5*((exp
((-G))))^3*s+s^2*((exp((-K*age0[i])))))^6*t^4*((exp((-G))))^2+
s^4*((exp((-K*age0[i])))))^5*((exp((-B))))^3*t-s^4*((exp((-K*
age0[i])))))^6*t^2*exp((-B))+s^4*((exp((-K*age0[i])))))^7*t^3*
exp((-B))-s^3*((exp((-K*age0[i])))))^5*t^2*exp((-B))+s^3*((exp
((-K*age0[i])))))^4*t*exp((-B))-s^3*((exp((-K*age0[i])))))^7*t^4
-s^4*((exp((-K*age0[i])))))^7*t^3+s^4*((exp((-K*age0[i])))))^8*
t^4-t^4*((exp((-K*age0[i])))))^4*((exp((-G))))^3-s^4*((exp((-K
*age0[i])))))^4*((exp((-B))))^3+s*((exp((-K*age0[i])))))^4*t^3*
exp((-G)))
}
if (leye[i,1]==0 &leye[i,2]==1 & leye[i,3]==1 & leye[i,4]==1
```

```
& reye[i,1]==1 &reye[i,2]==1 & reye[i,3]==1 & reye[i,4]==1)

{

loglike<-loglike + log(-(s*exp((-K*age0[i]))*exp((-B))-1)*(s*exp

((-K*age0[i]))*exp((-B))+1)*(s^(2)*((exp((-K*age0[i]))))^(2)*((

exp((-B))))^(2)+1))

}

if (leye[i,1]==1 &leye[i,2]==1 & leye[i,3]==1 & leye[i,4]==1

& reye[i,1]==0 &reye[i,2]==0 & reye[i,3]==0 & reye[i,4]==0)

{

loglike<-loglike + log(t^(14)*((exp((-K*age0[i]))))^(14)*((exp

((-G))))^(14))

}

if (leye[i,1]==1 &leye[i,2]==1 & leye[i,3]==1 & leye[i,4]==1

& reye[i,1]==1 &reye[i,2]==1 & reye[i,3]==1 & reye[i,4]==1)

{

loglike<-loglike +0

}

if (leye[i,1]==1 & leye[i,2]==0 || reye[i,1]==1 & reye[i,2]==0)

{

loglike<-loglike + 0

}

else if (leye[i,2]==1 & leye[i,3]==0 ||reye[i,2]==1 & reye[i,3]==0 )

{
```

```
loglike<-loglike + 0

}

else if (leye[i,3]==1 & leye[i,4]==0 ||reye[i,3]==1 & reye[i,4]==0 )

{

loglike<-loglike + 0 }

if (leye[i,1]==0 &leye[i,2]==0 & leye[i,3]==0 & leye[i,4]==2

& reye[i,1]==0 &reye[i,2]==0 & reye[i,3]==0 & reye[i,4]==2)

{

loglike<-loglike + log(s^(10)*((exp((-K*age0[i])))))^(20)*t^(10))

}

if (leye[i,1]==0 &leye[i,2]==0 & leye[i,3]==0 & leye[i,4]==2

& reye[i,1]==0 &reye[i,2]==0 & reye[i,3]==1 & reye[i,4]==2)

{

loglike<-loglike + log(-s^(10)*((exp((-K*age0[i])))))^(14)*t^(4)

*(-1+t*exp((-K*age0[i])))*(exp((-B))+t*exp((-K*age0[i])))*(((exp(

(-B))))^(2)+exp((-B))*t*exp((-K*age0[i]))+((exp((-K*age0[i])))

)^(2)*t^(2))*(((exp((-B))))^(2)-exp((-B))*t*exp((-K*age0[i]))+

((exp((-K*age0[i])))))^(2)*t^(2)))

}

if (leye[i,1]==0 &leye[i,2]==0 & leye[i,3]==0 & leye[i,4]==2

& reye[i,1]==0 &reye[i,2]==1 & reye[i,3]==1 & reye[i,4]==2)

{

loglike<- loglike + log(-s^(14)*((exp((-B)))))^(10)*((exp((-K*
```

```
age0[i]))))^(14)*(-1+t*exp((-K*age0[i])))*(exp((-B))+t*exp((-K*
age0[i])))*(((exp((-K*age0[i]))))^(2)*t^(2)+((exp((-B))))^(2)))
}
if (leye[i,1]==0 &leye[i,2]==0 & leye[i,3]==0 & leye[i,4]==2
& reye[i,1]==1 &reye[i,2]==1 & reye[i,3]==1 & reye[i,4]==2)
{
loglike<- loglike + log(s^(10)*((exp((-K*age0[i]))))^(10)*((exp
((-B))))^(10))
}
if (leye[i,1]==0 &leye[i,2]==0 & leye[i,3]==1 & leye[i,4]==2
& reye[i,1]==0 &reye[i,2]==0 & reye[i,3]==0 & reye[i,4]==2)
{
loglike<- loglike + log(-s^(4)*((exp((-K*age0[i]))))^(14)*t^(10)
*(-1+s*exp((-K*age0[i])))*(exp((-G))+s*exp((-K*age0[i])))*(((exp((-G)
))))^(2)+exp((-G))*exp((-K*age0[i]))*s+s^(2)*((exp((-K*age0[i])))
)^(2))*(((exp((-G))))^(2)-exp((-G))*exp((-K*age0[i]))*s+s^(2)*(
(exp((-K*age0[i]))))^(2)))
}
if (leye[i,1]==0 &leye[i,2]==0 & leye[i,3]==1 & leye[i,4]==2
& reye[i,1]==0 &reye[i,2]==0 & reye[i,3]==1 & reye[i,4]==2)
{
loglike<-loglike + log(s^(4)*((exp((-K*age0[i]))))^(8)*t^(4)
*(1-s*((exp((-K*age0[i]))))^(2)*t+t^(3)*((exp((-K*age0[i])))
```

)^(4)*((exp((-G))))^(2)*s-s*((exp((-K*age0[i]))))^(5)*t^(4)

((exp((-G))))^(2)+s^(2)((exp((-K*age0[i]))))^(5)*t^(3)*exp

((-G))-s^(2)*((exp((-K*age0[i]))))^(6)*t^(4)*exp((-G))+s^(3)*

((exp((-K*age0[i]))))^(7)*t^(4)*exp((-G))+s^(3)*((exp((-K*

age0[i]))))^(4)*((exp((-B))))^(2)*t-s^(4)*((exp((-K*age0[i])))

)^(5)*t*((exp((-B))))^(2)+s^(4)*((exp((-K*age0[i]))))^(6)*

t^(2)*((exp((-B))))^(2)+s*((exp((-K*age0[i]))))^(3)*t^(2)+2*

s^(2)*((exp((-K*age0[i]))))^(3)*t-2*s^(2)*((exp((-K*age0[i])))

)^(4)*t^(2)-t^(3)*((exp((-K*age0[i]))))^(3)*((exp((-G))))^(2)

-s^(3)*((exp((-K*age0[i]))))^(3)*((exp((-B))))^(2)+t^(5)*((exp

((-K*age0[i]))))^(5)*((exp((-G))))^(4)-s^(6)*((exp((-K*age0[i]))

))^(7)*t*((exp((-B))))^(4)-s^(5)*((exp((-K*age0[i]))))^(7)*t^(2

)*((exp((-B))))^(3)+s^(6)*((exp((-K*age0[i]))))^(8)*t^(2)*((exp

((-B))))^(4)-s^(6)*((exp((-K*age0[i]))))^(8)*t^(2)*((exp((-B)))

)^(3)+s^(6)*((exp((-K*age0[i]))))^(9)*t^(3)*((exp((-B))))^(3)-

s*((exp((-K*age0[i]))))^(7)*t^(6)*((exp((-G))))^(4)-s^(2)*((exp(

(-K*age0[i]))))^(7)*t^(5)*((exp((-G))))^(3)+s^(2)*((exp((-K*

age0[i]))))^(8)*t^6*((exp((-G))))^(4)-s^(2)*((exp((-K*age0[i])))

)^(8)*t^(6)*((exp((-G))))^(3)-s^(3)*((exp((-K*age0[i]))))^(8)*

t^(5)*((exp((-G))))^(2)+s^(3)*((exp((-K*age0[i]))))^(9)*t^(6)*(

(exp((-G))))^(3)+s^(5)*((exp((-K*age0[i]))))^(8)*t^(3)*exp((-B))-

s^(5)*((exp((-K*age0[i]))))^(9)*t^(4)*exp((-B))-s^(5)*((exp((-K*

age0[i]))))^(6)*((exp((-B))))^(4)*t+s^(6)*((exp((-K*age0[i])))

```
)^(7)*((exp((-B))))^(5)*t+s^(5)*((exp((-K*age0[i]))))^(6)*t*((
exp((-B))))^(3)+s*((exp((-K*age0[i]))))^(6)*t^(5)*((exp((-G)))
)^(3)+s^(2)*((exp((-K*age0[i]))))^(7)*t^(5)*((exp((-G))))^(2)
-s^(6)*((exp((-K*age0[i]))))^(10)*t^(4)*exp((-B))+s^(6)*((exp((
-K*age0[i]))))^(11)*t^(5)*exp((-B))+s^(3)*((exp((-K*age0[i])))
)^(8)*t^(5)*exp((-G))-s^(5)*((exp((-K*age0[i]))))^(11)*t^(6)-s
^(6)*((exp((-K*age0[i]))))^(11)*t^(5)+s^(6)*((exp((-K*age0[i])))
)^(12)*t^(6)-s^(6)*((exp((-K*age0[i]))))^(6)*((exp((-B))))^(5)-
t^(6)*((exp((-K*age0[i]))))^(6)*((exp((-G))))^(5)+s^(5)*((exp((
-K*age0[i]))))^(5)*((exp((-B))))^(4)-s^(3)*((exp((-K*age0[i])))
)^(6)*t^(3)*exp((-G))*exp((-B))+s^(3)*((exp((-K*age0[i]))))^(7)
*t^(4)*((exp((-G))))^(2)*exp((-B))-s^(4)*((exp((-K*age0[i]))))^(9
)*t^(5)*exp((-G))-t^(5)*((exp((-K*age0[i]))))^(6)*((exp((-G))))^(4)
*s+t^(6)*((exp((-K*age0[i]))))^(7)*((exp((-G))))^(5)*s-s^(4)*((exp
((-K*age0[i]))))^(10)*t^(6)*exp((-G))+s^(5)*((exp((-K*age0[i])))
)^(11)*t^(6)*exp((-G))-2*s^(6)*((exp((-K*age0[i]))))^(9)*t^(3)*
((exp((-B))))^(2)+2*s^(6)*((exp((-K*age0[i]))))^(10)*t^(4)*((exp(
(-B))))^(2)-2*s^(3)*((exp((-K*age0[i]))))^(9)*t^(6)*((exp((-G)))
)^(2)+2*s^(4)*((exp((-K*age0[i]))))^(10)*t^(6)*((exp((-G))))^(2)))
}
if (leye[i,1]==1 &leye[i,2]==1 & leye[i,3]==1 & leye[i,4]==2
& reye[i,1]==0 &reye[i,2]==0 & reye[i,3]==0 & reye[i,4]==2)
{
```

```
loglike<- loglike + log(t^(10)*((exp((-K*age0[i])))))^(10)*((exp

((-G))))^(10))

}

if (leye[i,1]==1 &leye[i,2]==1 & leye[i,3]==1 & leye[i,4]==2

& reye[i,1]==0 &reye[i,2]==1 & reye[i,3]==1 & reye[i,4]==2)

{

loglike<- loglike + log((-1)*(t*exp((-K*age0[i]))*exp((-G))-1)*

(t*exp((-K*age0[i]))*exp((-G))+1)*(t^(2)*((exp((-K*age0[i])))

)^(2)*((exp((-G))))^(2)+1))

}

if (leye[i,1]==1 &leye[i,2]==1 & leye[i,3]==1 & leye[i,4]==2

& reye[i,1]==1 &reye[i,2]==1 & reye[i,3]==1 & reye[i,4]==2)

{

loglike<-loglike+0

}

if (leye[i,1]==0 &leye[i,2]==0 & leye[i,3]==2 & leye[i,4]==0

& reye[i,1]==0 &reye[i,2]==0 & reye[i,3]==2 & reye[i,4]==0)

{

loglike<- loglike + log(s^(14)*((exp((-K*age0[i])))))^(28)*t^(14))

}

if (leye[i,1]==0 &leye[i,2]==0 & leye[i,3]==2 & leye[i,4]==0

& reye[i,1]==0 &reye[i,2]==0 & reye[i,3]==2 & reye[i,4]==1)

{
```

```
loglike<-loglike + log(s^(4)*((exp((-K*age0[i]))))^(8)*t^(4)*

(s^(10)*((exp((-K*age0[i]))))^(10)*(1-t*exp((-K*age0[i])))*((exp

((-B))))^(9)+s^(10)*((exp((-K*age0[i]))))^(11)*t*(1-t*exp((-K*

age0[i])))*((exp((-B))))^(8)+s^(10)*((exp((-K*age0[i]))))^(12)*

t^(2)*(1-t*exp((-K*age0[i])))*((exp((-B))))^(7)+s^(10)*((exp((-

K*age0[i]))))^(13)*t^(3)*(1-t*exp((-K*age0[i])))*((exp((-B))))^(6)

+s^(10)*((exp((-K*age0[i]))))^(14)*t^(4)*(1-t*exp((-K*age0[i])))*

((exp((-B))))^(5)+s^(10)*((exp((-K*age0[i]))))^(15)*t^(5)*(1-t*

exp((-K*age0[i])))*((exp((-B))))^(4)+s^(10)*((exp((-K*age0[i])))

)^(16)*t^(6)*(1-t*exp((-K*age0[i])))*((exp((-B))))^(3)+s^(10)*(

(exp((-K*age0[i]))))^(17)*t^(7)*(1-t*exp((-K*age0[i])))*((exp((-B))

))^(2)+s^(10)*((exp((-K*age0[i]))))^(18)*t^(8)*(1-t*exp((-K*

age0[i])))*exp((-B))+s^(10)*((exp((-K*age0[i]))))^(19)*t^(9)*(1-t

*exp((-K*age0[i])))))

}

if (leye[i,1]==0 &leye[i,2]==0 & leye[i,3]==2 & leye[i,4]==1

& reye[i,1]==0 &reye[i,2]==0 & reye[i,3]==2 & reye[i,4]==1)

{

loglike<- loglike + log(s^(4)*((exp((-K*age0[i]))))^(8)*t^(4)

*(1-s*((exp((-K*age0[i]))))^(2)*t+s^(2)*((exp((-K*age0[i])))

)^(12)*t^(10)*((exp((-G))))^(8)+t^(3)*((exp((-K*age0[i])))

)^(4)*((exp((-G))))^(2)*s-s*((exp((-K*age0[i]))))^(5)*t^(4)

*((exp((-G))))^(2)+s^(2)*((exp((-K*age0[i]))))^(5)*t^(3)*exp
```

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```
((-G))-s^(2)*((exp((-K*age0[i]))))^(6)*t^(4)*exp((-G))+s^(3)*

((exp((-K*age0[i]))))^(7)*t^(4)*exp((-G))+s^(3)*((exp((-K*

age0[i]))))^(4)*((exp((-B))))^(2)*t-s^(4)*((exp((-K*age0[i])))

)^(5)*t*((exp((-B))))^(2)+s^(4)*((exp((-K*age0[i]))))^(6)*t^(2)

*((exp((-B))))^(2)+s*((exp((-K*age0[i]))))^(3)*t^(2)+2*s^(2)*

((exp((-K*age0[i]))))^(3)*t-2*s^(2)*((exp((-K*age0[i]))))^(4)*

t^(2)-t^(3)*((exp((-K*age0[i]))))^(3)*((exp((-G))))^(2)-s^(3)

*((exp((-K*age0[i]))))^(3)*((exp((-B))))^(2)-s^(5)*((exp((-K*

age0[i]))))^(15)*t^(10)*((exp((-G))))^(4)+s^(6)*((exp((-K*

age0[i]))))^(16)*t^(10)*((exp((-G))))^(4)-s^(10)*((exp((-K*

age0[i]))))^(19)*t^(9)+s^(10)*((exp((-K*age0[i]))))^(20)*

t^(10)-t^(10)*((exp((-K*age0[i]))))^(10)*((exp((-G))))^(9)-

s^(10)*((exp((-K*age0[i]))))^(12)*t^(2)*((exp((-B))))^(7)-

s^(4)*((exp((-K*age0[i]))))^(14)*t^(10)*((exp((-G))))^(5)-

s^(8)*((exp((-K*age0[i]))))^(18)*t^(10)*exp((-G))+s^(9)*((

exp((-K*age0[i]))))^(19)*t^(10)*exp((-G))+s^(5)*((exp((-K*

age0[i]))))^(15)*t^(10)*((exp((-G))))^(5)-s^(10)*((exp((-

K*age0[i]))))^(13)*t^(3)*((exp((-B))))^(6)+s^(10)*((exp((-

K*age0[i]))))^(14)*t^(4)*((exp((-B))))^(6)+s^(10)*((exp((-

K*age0[i]))))^(13)*t^(3)*((exp((-B))))^(7)+s^(4)*((exp((-

K*age0[i]))))^(14)*t^(10)*((exp((-G))))^(6)-s^(3)*((exp((-

K*age0[i]))))^(13)*t^(10)*((exp((-G))))^(6)+s^(3)*((exp((-

K*age0[i]))))^(13)*t^(10)*((exp((-G))))^(7)-s^(2)*((exp((-
```

K*age0[i]))))^(12)*t^(10)*((exp((-G))))^(7)-s^(10)*((exp((-

K*age0[i]))))^(14)*t^(4)*((exp((-B))))^(5)+t^(5)*((exp((-K*

age0[i]))))^(5)*((exp((-G))))^(4)+s^(10)*((exp((-K*age0[i])))

)^(17)*t^(7)*((exp((-B))))^(3)-s^(10)*((exp((-K*age0[i])))

)^(18)*t^(8)*exp((-B))+s^(10)*((exp((-K*age0[i]))))^(19)*

t^(9)*exp((-B))+s^(7)*((exp((-K*age0[i]))))^(17)*t^(10)*(

(exp((-G))))^(3)-s^(10)*((exp((-K*age0[i]))))^(16)*t^(6)*(

(exp((-B))))^(3)-s^(10)*((exp((-K*age0[i]))))^(15)*t^(5)*(

(exp((-B))))^(4)+s^(10)*((exp((-K*age0[i]))))^(16)*t^(6)*(

(exp((-B))))^(4)-s^(10)*((exp((-K*age0[i]))))^(17)*t^(7)*(

(exp((-B))))^(2)+s^(10)*((exp((-K*age0[i]))))^(18)*t^(8)*(

(exp((-B))))^(2)-s^(7)*((exp((-K*age0[i]))))^(17)*t^(10)*(

(exp((-G))))^(2)-s^(6)*((exp((-K*age0[i]))))^(16)*t^(10)*(

(exp((-G))))^(3)+s^(8)*((exp((-K*age0[i]))))^(18)*t^(10)*(

(exp((-G))))^(2)+s^(10)*((exp((-K*age0[i]))))^(15)*t^(5)*(

(exp((-B))))^(5)-s^(5)*((exp((-K*age0[i]))))^(7)*t^(2)*(

(exp((-B))))^(3)-s^(2)*((exp((-K*age0[i]))))^(7)*t^(5)*(

(exp((-G))))^(3)-s^(3)*((exp((-K*age0[i]))))^(8)*t^(5)*(

(exp((-G))))^(2)+s^(5)*((exp((-K*age0[i]))))^(8)*t^(3)*exp

((-B))-s^(5)*((exp((-K*age0[i]))))^(9)*t^(4)*exp((-B))-s^(5)

*((exp((-K*age0[i]))))^(6)*((exp((-B))))^(4)*t+s^(5)*((exp((-K

*age0[i]))))^(6)*t*((exp((-B))))^(3)+s*((exp((-K*age0[i]))))^(6)

t^(5)((exp((-G))))^(3)+s^(2)*((exp((-K*age0[i]))))^(7)*t^(5)*

```
((exp((-G))))^(2)+s^(3)*((exp((-K*age0[i]))))^(8)*t^(5)*exp((-G
))+s^(5)*((exp((-K*age0[i]))))^(5)*((exp((-B))))^(4)-s^(3)*((
exp((-K*age0[i]))))^(6)*t^(3)*exp((-G))*exp((-B))+s^(3)*((exp(
(-K*age0[i]))))^(7)*t^(4)*((exp((-G))))^(2)*exp((-B))-s^(4)*(
(exp((-K*age0[i]))))^(9)*t^(5)*exp((-G))-t^(5)*((exp((-K*age0[i]
))))^(6)*((exp((-G))))^(4)*s-s^(6)*((exp((-K*age0[i]))))^(9)*
t^(3)*((exp((-B))))^(2)+s^(6)*((exp((-K*age0[i]))))^(10)*t^(4)
*((exp((-B))))^(2)-s^(3)*((exp((-K*age0[i]))))^(9)*t^(6)*((exp
((-G))))^(2)+s^(4)*((exp((-K*age0[i]))))^(10)*t^(6)*((exp((-G))
))^(2)-s^(10)*((exp((-K*age0[i]))))^(10)*((exp((-B))))^(9)+
s^(10)*((exp((-K*age0[i]))))^(11)*((exp((-B))))^(9)*t+t^(10)
*((exp((-K*age0[i]))))^(11)*((exp((-G))))^(9)*s-s^(10)*((exp(
(-K*age0[i]))))^(11)*t*((exp((-B))))^(8)+s^(10)*((exp((-K*
age0[i]))))^(12)*t^(2)*((exp((-B))))^(8)-s*((exp((-K*age0[i])
)))^(11)*t^(10)*((exp((-G))))^(8)-s^(9)*((exp((-K*age0[i])))
)^(19)*t^(10)))
}
if (leye[i,1]==0 &leye[i,2]==2 & leye[i,3]==0 & leye[i,4]==0
& reye[i,1]==0 &reye[i,2]==2 & reye[i,3]==0 & reye[i,4]==0)
{
loglike<- loglike + log(s^(14)*((exp((-K*age0[i]))))^(28)*t^(14))
}
if (leye[i,1]==2 &leye[i,2]==0 & leye[i,3]==0 & leye[i,4]==0
```

```
& reye[i,1]==2 &reye[i,2]==0 & reye[i,3]==0 & reye[i,4]==0)

{

loglike<- loglike + log(s^(14)*((exp((-K*age0[i])))))^(28)*t^(14))

}

if (leye[i,1]==0 &leye[i,2]==2 & leye[i,3]==2 & leye[i,4]==0

& reye[i,1]==0 &reye[i,2]==2 & reye[i,3]==2 & reye[i,4]==0)

{

loglike<- loglike + log(s^(14)*((exp((-K*age0[i])))))^(28)*t^(14))

}

if (leye[i,1]==0 &leye[i,2]==0 & leye[i,3]==2 & leye[i,4]==2

& reye[i,1]==0 &reye[i,2]==0 & reye[i,3]==2 & reye[i,4]==2)

{

loglike<- loglike + log(s^(4)*((exp((-K*age0[i])))))^(8)*t^(4))

}

if (leye[i,1]==0 &leye[i,2]==0 & leye[i,3]==2 & leye[i,4]==2

& reye[i,1]==0 &reye[i,2]==1 & reye[i,3]==2 & reye[i,4]==2)

{

loglike<-loglike + log(s^(4)*((exp((-K*age0[i])))))^(4)*(1-t*exp

((-K*age0[i])))*((exp((-B))))^(3)+s^(4)*((exp((-K*age0[i])))

)^(5)*t*(1-t*exp((-K*age0[i])))*((exp((-B))))^(2)+s^(4)*((exp

((-K*age0[i])))))^(6)*t^(2)*(1-t*exp((-K*age0[i])))*exp((-B))+

s^(4)*((exp((-K*age0[i])))))^(7)*t^(3)*exp((-B)))

}
```

```r
if (leye[i,1]==0 &leye[i,2]==0 & leye[i,3]==2 & leye[i,4]==2
& reye[i,1]==1 &reye[i,2]==1 & reye[i,3]==2 & reye[i,4]==2)
{
loglike<-loglike + log(s^(4)*((exp((-K*age0[i])))))^(4)*((exp(
(-B))))^(4))
}
if (leye[i,1]==0 &leye[i,2]==1 & leye[i,3]==2 & leye[i,4]==2
& reye[i,1]==0 &reye[i,2]==0 & reye[i,3]==2 & reye[i,4]==2)
{
loglike <- loglike + log(s*((exp((-K*age0[i])))))^(4)*(1-t*exp((
-K*age0[i])))*t^(3)*((exp((-G))))^(3)+s*((exp((-K*age0[i])))
)^(5)*t^(4)*(1-s*exp((-K*age0[i])))*((exp((-G))))^(2)+s^(2)*
((exp((-K*age0[i])))))^(6)*t^(4)*(1-s*exp((-K*age0[i])))*exp((-G
))+s^(3)*((exp((-K*age0[i])))))^(7)*t^(4)*exp((-G)))
}
if (leye[i,1]==0 &leye[i,2]==1 & leye[i,3]==2 & leye[i,4]==2
& reye[i,1]==0 &reye[i,2]==1 & reye[i,3]==2 & reye[i,4]==2)
{
loglike<- loglike + log(1+2*s*((exp((-K*age0[i])))))^2*t-s*exp(
(-K*age0[i]))-t*exp((-K*age0[i]))-t^3*((exp((-K*age0[i])))))^4*
((exp((-G))))^2*s-s*((exp((-K*age0[i])))))^5*t^4*((exp((-G)))
)^2-s^2*((exp((-K*age0[i])))))^5*t^3*exp((-G))-s^2*((exp((-K*
age0[i])))))^6*t^4*exp((-G))+s^3*((exp((-K*age0[i])))))^7*t^4*
```

```
exp((-G))-s^3*((exp((-K*age0[i]))))^4*((exp((-B))))^2*t-s^4*

((exp((-K*age0[i]))))^5*t*((exp((-B))))^2+s^4*((exp((-K*age0[i]

))))^6*t^2*((exp((-B))))^2-s*((exp((-K*age0[i]))))^3*t^2-s^2*

((exp((-K*age0[i]))))^3*t+2*s^2*((exp((-K*age0[i]))))^4*t^2+t^3

*((exp((-K*age0[i]))))^3*((exp((-G))))^2+s^3*((exp((-K*age0[i])))

)^3*((exp((-B))))^2+t^4*((exp((-K*age0[i]))))^5*((exp((-G))))^3

*s+s^2*((exp((-K*age0[i]))))^6*t^4*((exp((-G))))^2+s^4*((exp((-

K*age0[i]))))^5*((exp((-B))))^3*t-s^4*((exp((-K*age0[i]))))^6*

t^2*exp((-B))+s^4*((exp((-K*age0[i]))))^7*t^3*exp((-B))-s^3*(

(exp((-K*age0[i]))))^5*t^2*exp((-B))+s^3*((exp((-K*age0[i]))))^4

*t*exp((-B))-s^3*((exp((-K*age0[i]))))^7*t^4-s^4*((exp((-K*age0[i]

))))^7*t^3+s^4*((exp((-K*age0[i])))))^8*t^4-t^4*((exp((-K*age0[i]

))))^4*((exp((-G))))^3-s^4*((exp((-K*age0[i])))^4*((exp((-B))))^3

+s*((exp((-K*age0[i]))))^4*t^3**exp((-G)))
}
if (leye[i,1]==0 &leye[i,2]==1 & leye[i,3]==2 & leye[i,4]==2

& reye[i,1]==1 &reye[i,2]==1 & reye[i,3]==2 & reye[i,4]==2)

{

loglike<-loglike + log((-1)*(s*exp((-K*age0[i]))*exp((-B))-1)*(s*

exp((-K*age0[i]))*exp((-B))+1)*(s^(2)*((exp((-K*age0[i]))))^(2)*

((exp((-B))))^(2)+1))

}
if (leye[i,1]==1 &leye[i,2]==1 & leye[i,3]==2 & leye[i,4]==2
```

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```
& reye[i,1]==0 &reye[i,2]==0 & reye[i,3]==2 & reye[i,4]==2)

{

loglike<-loglike + log(t^(4)*((exp((-K*age0[i])))))^(4)*((exp(

(-G))))^(4))

}

if (leye[i,1]==1 &leye[i,2]==1 & leye[i,3]==2 & leye[i,4]==2

& reye[i,1]==0 &reye[i,2]==1 & reye[i,3]==2 & reye[i,4]==2)

{

loglike<-loglike + log(t^(10)*((exp((-K*age0[i])))))^(10)*((exp

((-G))))^(10))

}

if (leye[i,1]==1 &leye[i,2]==1 & leye[i,3]==2 & leye[i,4]==2

& reye[i,1]==1 &reye[i,2]==1 & reye[i,3]==2 & reye[i,4]==2)

{

loglike<- loglike+0

}

if (leye[i,1]==2 &leye[i,2]==0 & leye[i,3]==0 & leye[i,4]==2

& reye[i,1]==2 &reye[i,2]==0 & reye[i,3]==0 & reye[i,4]==2)

{

loglike<-loglike + log(s^(10)*((exp((-K*age0[i])))))^(20)*t^(10))

}

if (leye[i,1]==0 &leye[i,2]==2 & leye[i,3]==0 & leye[i,4]==2

& reye[i,1]==0 &reye[i,2]==2 & reye[i,3]==0 & reye[i,4]==2)
```

```
{
loglike<- loglike + log(s^(10)*((exp((-K*age0[i])))))^(20)*t^(10))
}
if (leye[i,1]==0 &leye[i,2]==2 & leye[i,3]==1 & leye[i,4]==2
& reye[i,1]==0 &reye[i,2]==2 & reye[i,3]==1 & reye[i,4]==2)
{
loglike<-loglike + log((1-s*exp((-K*age0[i])))*(1-t*exp((-K*
age0[i])))+s*((exp((-K*age0[i])))))^(2)*t*(1-s*exp((-K*age0[i]))
)*(1-t*exp((-K*age0[i])))+s^(2)*((exp((-K*age0[i])))))^(4)*t^(2)
*(1-s*exp((-K*age0[i])))*(1-t*exp((-K*age0[i])))+s^(3)*((exp((-K*
age0[i])))))^(6)*t^(3)*(1-s*exp((-K*age0[i])))*(1-t*exp((-K*age0[i]
)))+s^(2)*((exp((-K*age0[i])))))^(5)*t^(3)*(1-s*exp((-K*age0[i]))
)*(1-t*exp((-K*age0[i]))*exp((-G)))+s^(3)*((exp((-K*age0[i])))))^(5)
*t^(2)*(1-t*exp((-K*age0[i])))*(1-s*exp((-K*age0[i]))*exp((-B)))+s*
exp((-K*age0[i]))*(1-t*exp((-K*age0[i])))*(1-s*exp((-K*age0[i]))*exp
((-B)))+(1-s*exp((-K*age0[i])))*t*exp((-K*age0[i]))*(1-t*exp((-K*
age0[i]))*exp((-G)))+s^(4)*((exp((-K*age0[i])))))^(8)*t^(4)*(1-s
*exp((-K*age0[i])))*(1-t*exp((-K*age0[i])))+s^(5)*((exp((-K*age0[i]
)))))^(10)*t^(5)*(1-s*exp((-K*age0[i])))*(1-t*exp((-K*age0[i])))+
s^(2)*((exp((-K*age0[i])))))^(3)*t*(1-t*exp((-K*age0[i])))*(1-s*
exp((-K*age0[i]))*exp((-B)))+s^(4)*((exp((-K*age0[i])))))^(7)*
t^(3)*(1-t*exp((-K*age0[i])))*(1-s*exp((-K*age0[i]))*exp((-B)))+
s^(5)*((exp((-K*age0[i])))))^(9)*t^(4)*(1-t*exp((-K*age0[i])))*
```

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```
(1-s*exp((-K*age0[i]))*exp((-B)))+s*((exp((-K*age0[i]))))^(3)*t^(2)

*(1-s*exp((-K*age0[i])))*(1-t*exp((-K*age0[i]))*exp((-G)))+s^(3)

*((exp((-K*age0[i]))))^(7)*t^(4)*(1-s*exp((-K*age0[i])))*(1-

t*exp((-K*age0[i]))*exp((-G)))+s^(4)*((exp((-K*age0[i]))))^(9)

*t^(5)*(1-s*exp((-K*age0[i])))*(1-t*exp((-K*age0[i]))*exp((-G))

)+s*exp((-K*age0[i]))*(1-t*exp((-K*age0[i])))*((s*exp((-K*age0[i]

))*exp((-B))))^((1-s*exp((-K*age0[i]))*exp((-B))))+(1-s*exp((-K*

age0[i])))*t*exp((-K*age0[i]))*((t*exp((-K*age0[i]))*exp((-G)))

)^((1-t*exp((-K*age0[i]))*exp((-G))))+2*s^(9)*((exp((-K*age0[i])

)))^(17)*t^(8)*(1-t*exp((-K*age0[i])))*(1-s*exp((-K*age0[i]))*

exp((-B)))+s^(9)*((exp((-K*age0[i]))))^(14)*t^(5)*(1-t*exp(

(-K*age0[i])))*((exp((-B))))^(3)*(1-s*exp((-K*age0[i]))*exp(

(-B)))+s^9*((exp((-K*age0[i]))))^(13)*t^(4)*(1-t*exp((-K*

age0[i])))*((exp((-B))))^(4)*(1-s*exp((-K*age0[i]))*exp((-B)

))+s^9*((exp((-K*age0[i]))))^(15)*t^(6)*(1-t*exp((-K*age0[i]

)))*((exp((-B))))^2*(1-s*exp((-K*age0[i]))*exp((-B)))+s^(9)*(

(exp((-K*age0[i]))))^(10)*t*(1-t*exp((-K*age0[i])))*((exp((-B))

))^(7)*(1-s*exp((-K*age0[i]))*exp((-B)))+s^(9)*((exp((-K*

age0[i]))))^(11)*t^(2)*(1-t*exp((-K*age0[i])))*((exp((-B)))

)^(6)*(1-s*exp((-K*age0[i]))*exp((-B)))+s^(9)*((exp((-K*

age0[i]))))^(12)*t^(3)*(1-t*exp((-K*age0[i])))*((exp((-B))

))^(5)*(1-s*exp((-K*age0[i]))*exp((-B)))+s^(6)*((exp((-K*

age0[i]))))^(11)*t^(5)*(1-t*exp((-K*age0[i])))*(1-s*exp
```

```
((-K*age0[i]))*exp((-B)))+s^(7)*((exp((-K*age0[i]))))^(13)*
t^(6)*(1-t*exp((-K*age0[i])))*(1-s*exp((-K*age0[i]))*exp((-B)))
+s^(8)*((exp((-K*age0[i]))))^(15)*t^(7)*(1-t*exp((-K*age0[i]))
)*(1-s*exp((-K*age0[i]))*exp((-B)))+2*s^(8)*((exp((-K*age0[i])))
)^(17)*t^(9)*(1-s*exp((-K*age0[i])))*(1-t*exp((-K*age0[i]))*
exp((-G)))+s^(5)*((exp((-K*age0[i]))))^(11)*t^(6)*(1-s*exp(
(-K*age0[i])))*(1-t*exp((-K*age0[i]))*exp((-G)))+s^(6)*((exp(
(-K*age0[i]))))^(13)*t^(7)*(1-s*exp((-K*age0[i])))*(1-t*exp(
(-K*age0[i]))*exp((-G)))+s^(7)*((exp((-K*age0[i]))))^(15)*
t^(8)*(1-s*exp((-K*age0[i])))*(1-t*exp((-K*age0[i]))*exp((-G)))
+s^(9)*((exp((-K*age0[i]))))^(16)*t^(7)*(1-t*exp((-K*age0[i])))
*exp((-B))*(1-s*exp((-K*age0[i]))*exp((-B)))+s^(6)*((exp((-K*
age0[i]))))^(12)*t^(6)*(1-s*exp((-K*age0[i])))*(1-t*exp((-K*
age0[i])))+s^(7)*((exp((-K*age0[i]))))^(14)*t^(7)*(1-s*exp(
(-K*age0[i])))*(1-t*exp((-K*age0[i])))+s*((exp((-K*age0[i])))
)^(10)*t^(9)*(1-s*exp((-K*age0[i])))*((exp((-G))))^(7)*(1-t*
exp((-K*age0[i]))*exp((-G)))+s^(2)*((exp((-K*age0[i]))))^(11)*
t^(9)*(1-s*exp((-K*age0[i])))*((exp((-G))))^(6)*(1-t*exp((-K*
age0[i]))*exp((-G)))+s^(3)*((exp((-K*age0[i]))))^(12)*t^(9)*
(1-s*exp((-K*age0[i])))*((exp((-G))))^(5)*(1-t*exp((-K*age0[i])
)*exp((-G)))+s^(8)*((exp((-K*age0[i]))))^(16)*t^(8)*(1-s*exp
((-K*age0[i])))*(1-t*exp((-K*age0[i])))+s^(9)*((exp((-K*age0[i])
)))^(18)*t^(9)*(1-s*exp((-K*age0[i])))*(1-t*exp((-K*age0[i])))+
```

```
s^(5)*((exp((-K*age0[i])))))^(14)*t^(9)*(1-s*exp((-K*age0[i])))*

((exp((-G)))))^(3)*(1-t*exp((-K*age0[i]))*exp((-G)))+s^(4)*((exp

((-K*age0[i])))))^(13)*t^(9)*(1-s*exp((-K*age0[i])))*((exp((-G)))

)^4*(1-t*exp((-K*age0[i]))*exp((-G)))+s^(6)*((exp((-K*age0[i])))

)^(15)*t^(9)*(1-s*exp((-K*age0[i])))*((exp((-G))))^(2)*(1-t*exp(

(-K*age0[i]))*exp((-G)))+s^(7)*((exp((-K*age0[i])))))^(16)*t^(9)*

(1-s*exp((-K*age0[i])))*exp((-G))*(1-t*exp((-K*age0[i]))*exp((-G))))

}


   if (leye[i,1]==1 &leye[i,2]==2 & leye[i,3]==1 & leye[i,4]==2

& reye[i,1]==1 &reye[i,2]==2 & reye[i,3]==1 & reye[i,4]==2)

{

loglike<-loglike+0

}

if (leye[i,1]==0 &leye[i,2]==2 & leye[i,3]==2 & leye[i,4]==2

& reye[i,1]==0 &reye[i,2]==2 & reye[i,3]==2 & reye[i,4]==2)

{

loglike<-loglike+0

}

if (leye[i,1]==0 &leye[i,2]==2 & leye[i,3]==2 & leye[i,4]==2

& reye[i,1]==1 &reye[i,2]==2 & reye[i,3]==2 & reye[i,4]==2)

{

loglike<-loglike + 0
```

```
}
if (leye[i,1]==1 &leye[i,2]==2 & leye[i,3]==2 & leye[i,4]==2
& reye[i,1]==0 &reye[i,2]==2 & reye[i,3]==2 & reye[i,4]==2)
{
loglike<-loglike + 0
}
if (leye[i,1]==1 &leye[i,2]==2 & leye[i,3]==2 & leye[i,4]==2
& reye[i,1]==1 &reye[i,2]==2 & reye[i,3]==2 & reye[i,4]==2)
{
loglike<-loglike + 0
}
if (leye[i,1]==2 &leye[i,2]==2 & leye[i,3]==2 & leye[i,4]==2
& reye[i,1]==2 &reye[i,2]==2& reye[i,3]==2 & reye[i,4]==2)
{
loglike<-loglike + 0
}
if (leye[i,1]==0 &leye[i,2]==1 & leye[i,3]==1 & leye[i,4]==2
& reye[i,1]==0 &reye[i,2]==0 & reye[i,3]==1 & reye[i,4]==2)
{
loglike<-loglike + log(t^(4)*((exp((-K*age0[i])))^(7)*(t*exp
((-K*age0[i]))*exp((-G))-1)*(s*exp((-K*age0[i]))-1)*(t^(5)*((
exp((-G))))^(5)*s^(3)*((exp((-K*age0[i]))))^(5)+((exp((-K*
age0[i]))))^(4)*t^(4)*s^(3)*((exp((-G))))^(4)+t^(2)*((exp
```

```
((-G))))^(2)*s^(3)*((exp((-K*age0[i]))))^(2)+t*exp((-G))*

s^(3)*exp((-K*age0[i]))+s^(3)+((exp((-K*age0[i]))))^(4)*

t^(5)*s^(2)*((exp((-G))))^(6)+((exp((-K*age0[i]))))^(3)*

t^(5)*s*((exp((-G))))^(7)+((exp((-K*age0[i]))))^(2)*t^(5)

*((exp((-G))))^(8)))

}

if (leye[i,1]==0 &leye[i,2]==1 & leye[i,3]==1 & leye[i,4]==2

& reye[i,1]==0 &reye[i,2]==1 & reye[i,3]==1 & reye[i,4]==2)

{

loglike<-loglike + log(1+2*s*((exp((-K*age0[i]))))^2*t-s*exp(

(-K*age0[i]))-t*exp((-K*age0[i]))-t^3*((exp((-K*age0[i]))))^4*

((exp((-G))))^2*s-s*((exp((-K*age0[i]))))^5*t^4*((exp((-G)))

)^2-s^2*((exp((-K*age0[i]))))^5*t^3*exp((-G))-s^2*((exp(

(-K*age0[i]))))^6*t^4*exp((-G))+s^3*((exp((-K*age0[i]))))^7

*t^4*exp((-G))-s^3*((exp((-K*age0[i]))))^4*((exp((-B))))^2*t

-s^4*((exp((-K*age0[i]))))^5*t*((exp((-B))))^2+s^4*((exp((-K*

age0[i]))))^6*t^2*((exp((-B))))^2-s*((exp((-K*age0[i]))))^3*

t^2-s^2*((exp((-K*age0[i]))))^3*t+2*s^2*((exp((-K*age0[i])))

)^4*t^2+t^3*((exp((-K*age0[i]))))^3*((exp((-G))))^2+s^3*(

(exp((-K*age0[i]))))^3*((exp((-B))))^2+t^4*((exp((-K*age0[i])

))))^5*((exp((-G))))^3*s+s^2*((exp((-K*age0[i]))))^6*t^4*((

exp((-G))))^2+s^4*((exp((-K*age0[i]))))^5*((exp((-B))))^3*t

-s^4*((exp((-K*age0[i]))))^6*t^2*exp((-B))+s^4*((exp((-K*
```

```
age0[i]))))^7*t^3*exp((-B))-s^3*((exp((-K*age0[i]))))^5*t^2

*exp((-B))+s^3*((exp((-K*age0[i]))))^4*t*exp((-B))-s^3*((exp

((-K*age0[i]))))^7*t^4-s^4*((exp((-K*age0[i]))))^7*t^3+s^4

*((exp((-K*age0[i]))))^8*t^4-t^4*((exp((-K*age0[i]))))^4*((

exp((-G))))^3-s^4*((exp((-K*age0[i]))))^4*((exp((-B))))^3+s

*((exp((-K*age0[i]))))^4*t^3**exp((-G)))
}
}
return(loglike)
}
optim(c(.998,.997,.0311,.05701,.00002510),joint2,method="L-BFGS-B",

control = list(maxit=6000, fnscale =-1), n=n, age0=age0,lower=

c(0.99 ,0.99, 0, 0, 0), upper=c(0.99999 ,0.999999, 1, 1, 1 ))
```

VITA

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