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Using decision analytic modelling to simulate pregnancy

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Using Decision Analytic Modelling to Simulate Pregnancy

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USE OF THESIS

The Use of Thesis statement is not included in this version of the thesis.

Abstract

Decision analytic modelling enables decision makers to assess the cost-effectiveness associated with a proposed change in a current system without physically implementing the changes. This can be achieved by formulating a mathematical model that represents all the major events occurring in the system through formulas and algorithms, and estimating the likely outcomes along with their costs.

This type of modelling has been identified by the State Health Research Advisory Council (SHRAC) of the Western Australian Department of Health as an asset for the planning of health care investments in the future. One such area in which the Western Australian Department of Health has identified the need for future planning is in the improvement of perinatal outcomes of Aboriginal women living in rural and remote areas of Western Australia. Various investigations into policy changes that have given some evidence of improving pregnancy outcomes have recently provided the need for an appropriate decision analytic model to be constructed. This requires the formulation of a mathematical model that can simulate the pregnancy events and outcomes consistent with those observed in practice.

This thesis will outline a mathematical model with the objective to simulate a large cohort of individual Aboriginal women going through pregnancy in remote regions of WA that is representative of the populations' current outcomes. The scope of the model is limited to the prediction of clinical outcomes during the antenatal period of pregnancy for individual patients whilst the implementation of costs will not be considered.

The validity of the simulation model will be shown to be very accurate by providing comparisons of simulated outcomes to those from the observed data. A discussion on the benefits of the methods used to construct this model will then be identified, concluding with a range of further uses this model could be applied to.

Acknowledgments

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I would also like to thank my fiancée Samantha Rowse for her understanding and support whilst I spent many antisocial hours preparing this thesis.

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Date 17/12/2009

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Glossary

Adverse event – a non-beneficial outcome measured in a study of an intervention that may or may not have been caused by the intervention.

Antenatal – existing or occurring before birth (also *prenatal*).

Antenatal care – care of women during pregnancy by doctors and midwives in order to predict and detect problems with the mother or the unborn child. Advice is also offered on other matters relevant to pregnancy and birth.

Antenatal clinic – a clinic in a maternity unit where care is provided by midwives, obstetricians and other health professionals.

Antepartum haemorrhage – bleeding from the birth canal in the second half of pregnancy.

Cross-sectional study – the observation of a defined set of people at a single point in time or time period – a snapshot. This type of study contrasts with a longitudinal study, which follows a set of people over a period of time.

Delivery – birth of the baby and the afterbirth.

Diabetes – a disorder with high blood sugar levels caused by inappropriate levels of the hormone insulin.

Gestation age – length of pregnancy

Hypertension – blood pressure which is higher than normal, also used for a disease which is characterized by high blood pressure.

Incidence – the number of new events (new cases of a disease) in a defined population, within a specified period of time.

Induction of labour – starting labour artificially by using drugs or other methods.

Longitudinal study – a study of the same group of people at more than one point in time. (This type of study contrasts with a cross-sectional study, which observes a defined set of people at a single point in time).

Maternal – relates to the mother.

Midwife – a person appropriately educated and licensed in a State or Territory to practice midwifery and who provides care, advice and assistance during pregnancy, labour and delivery and after the baby is born.

Multiparous – having carried more than one pregnancy to a viable stage.

Nulliparous – having never given birth to a viable infant.

Obstetrics – services relating to the management and care of pregnancy and childbirth, for example antenatal appointments, labour, delivery and care after the baby is born.

Parity – number of previous births (live or still born) of at least 20 weeks gestation that a woman has experienced.

Perinatal – refers to the period from 20 weeks of pregnancy to 28 days after birth.

Pre-eclampsia – medical condition of pregnancy marked by high blood pressure, protein excretion in urine, abnormal blood components and water retention in the tissues. (Also called pregnancy induced hypertension)

Pregnancy record – the maternity record held by the woman and completed by the providers of care during her pregnancy.

Preterm labour – labour occurring before 37 weeks of gestational age.

Prelabour Rupture of Membranes – bag of waters breaks or leaks well in advance of the due date and before the commencement of labour.

Abbreviations

APH	Antepartum haemorrhage
ARIA	Accessibility/Remoteness Index of Australia
GA	Gestational age
GDM	Gestational diabetes
MNS	The Western Australia Midwives Notification System
PET	Pre-eclampsia
PROM	Prelabour Rupture of Membranes
TPL	Threatened preterm labour
WA	Western Australia

1 Introduction

1.1 Decision Analytic Modelling

Decision analytic models are rapidly gaining recognition in the health care industry to aid policy decision makers allocate limited health care resources efficiently (Weinstein, 2003). The purpose of decision analytic modelling is to enable decision makers to assess the possible benefits that may be associated with a proposed change in clinical practice without physically implementing the program. It also allows for the selection of the most effective program when two or more competing programs are proposed. When the programs have not been trialled on a population wide basis, these insights are estimated by combining existing data from a variety of clinical and economic sources to produce a mathematical model of the proposed system (Akehurst et al, 2000).

1.2 Why Model Pregnancy

The Western Australia Midwives Notification System (MNS) tracks maternal and perinatal health for the state. In a recent report it has been revealed that Aboriginal women who gave birth in 2005 suffered greater rates of adverse outcomes compared to non-Aboriginal women (Gee et al, 2007). Aboriginal mothers represent approximately 6.5% of all women who give birth in Western Australia (WA) each year with 65% of these women living outside of the Perth metropolitan area. Coincidently, it has been identified that conventional models of antenatal and maternal care in non-metropolitan WA are not meeting the needs of Aboriginal women (WA Department of Health, 2007).

Some small scale innovations have been tried in WA to improve care to pregnant Aboriginal women living in the rural and remote parts of the state. For example, the WA Country Health Service (WACHS) Midwest and the Geraldton Regional Aboriginal Medical Service (GRAMS) initiated a midwife led antenatal service. Although the numbers of women were too small to detect significant differences in maternal or perinatal outcomes, a review of the outcomes for cohorts of women giving birth before and after the establishment of this service showed improved attendance at antenatal services and greater likelihood of receiving essential antenatal services (Bradley, 2006). Moreover, a new antenatal care program designed through collaboration with the Aboriginal community in Townsville, North Queensland, in the past several years has given evidence that the service has influenced reductions in

preterm births and perinatal mortality rates, and an increase in mean birth weight (Panaretto, 2007).

In light of these improvements and possible implications that enhanced antenatal care will have on maternal and perinatal outcomes, an investigation entitled "Models for improved maternal care for rural and remote Aboriginal women: evaluation of clinical benefits and cost-effectiveness" is currently being carried out by the Women and Infants Research Foundation and funded by the State Health Research Advisory Council (SHRAC) of the Western Australian Department of Health. The project will use decision analytic modelling to evaluate the health outcomes and economic implications of proposed changes to maternity care in rural and remote WA by comparing the outcomes and associated costs between two different models of maternity care.

The analytical model required for the project will simulate the events of a hypothetical cohort of Aboriginal women through pregnancy in Western Australia (WA). Not only will the model provide a theoretical record of outcomes at an individual patient level consistent with those recorded in the MNS, but will also provide an estimate of the cost incurred for pregnancy care. These costs range from routine pregnancy tests and care provided by GP's and obstetricians to emergency transport and hospital admission costs for both the newborn and mother.

The idea is to firstly obtain a reference data set by simulating pregnancy outcomes and estimating costs based on the current policies followed in WA. A second model can then be constructed to reflect the change in outcomes observed through clinical studies related to proposed changes in antenatal care practices. An additional data set will then be generated with an identical cohort and will be used to compare the outcomes with those of the reference model. For example, increased attendance to antenatal clinics has been shown to increase birth weight (Panaretto, 2007). Given that the current rates and costs of antenatal attendance are known, a second model can be obtained to include an increase in antenatal attendance along with the benefits of increased birth weight by reducing the likelihood of adverse outcomes related to babies of a lower birth weight. The increase in costs of encouraging and providing an improvement in clinic attendance can then be compared with the magnitude of any decreases in emergency costs associated with adverse outcomes. Decision makers can then access the viability of the proposed changes on both a clinical and monetary scale, even making comparisons amongst sub-cohorts.

1.3 Objectives of this Thesis

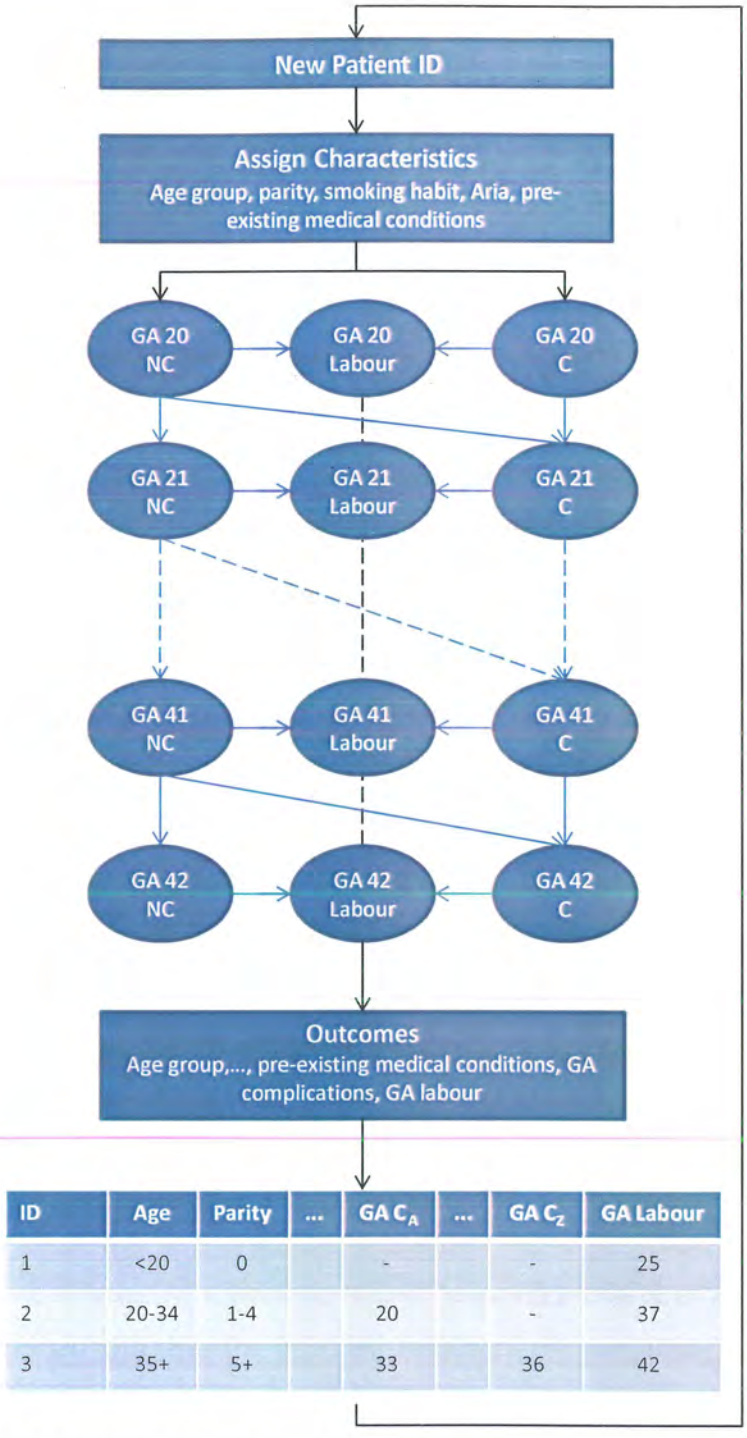
The objective of this thesis is to devise a mathematical model which will simulate a large cohort of individual Aboriginal women going through pregnancy in remote regions of WA that is representative of the populations' current outcomes. The scope of the model is limited to the prediction of clinical outcomes during the antenatal period of pregnancy for individual patients whilst the implementation of costs will not be considered.

An overview of the model represented as a flow chart of events is illustrated in Figure 1.3.1. The construction of the model can be broken down into three stages. Stage one introduces a new patient into the model and assigns them with a set of maternal characteristics. Stage two will use the assigned characteristics as an input to the pregnancy process in which the probability of the particular patient having a complication during any one week can be estimated. If a complication occurs, their maternal risk factors are combined with the adverse effects of their complication to predict the likelihood of labour during the week. If labour does not occur, the patient advances one week of pregnancy and the process is repeated, retaining both maternal and clinical risk factors. This continues until either labour occurs or the patient reaches 42 weeks of pregnancy, at which point it is common practice that labour is induced. Stage three is to record these events for each patient, providing a data set with outcome variables such as patient id, age, parity, smoking habit, level of remoteness, pre-existing medical conditions, gestational age (GA) at the onset of any complications and the GA at labour.

The end result is to generate a data set of individual patients with records of pregnancy outcomes that are consistent with those in the current population. The validity of the model will be determined by evaluating the accuracy of the simulated outcomes to those from the observed data.

This thesis will be structured in the following manner. A literature review of decision analytic modelling of previous studies and investigation into modelling techniques will be described in Chapter 2. From the literature review, the mathematical methods used to generate individual patients and simulate their corresponding pregnancy outcomes will be outlined in Chapter 3. Chapter 4 will give an analysis of the input data used to estimate the probability distributions required to generate maternal characteristics and simulate pregnancy outcomes. The estimated probability distributions are then

combined with the mathematical methods to describe how the model was implemented followed by a validation of the simulated outcomes through goodness of fit tables. A discussion on the results and implications of the model will be presented in Chapter 5.



ID	Age	Parity	...	GA C_A	...	GA C_Z	GA Labour
1	<20	0		-		-	25
2	20-34	1-4		20		-	37
3	35+	5+		33		36	42

NC = No complications, C = Complication(s)

Figure 1.3.1 – Flow chart of pregnancy model

2 Literature Review of Decision Analytic Modelling

Since Sonnenberg and Beck (1993) published a practical guide to Markov models in decision making, there has been increasing interest in using decision analytic models to provide support for decision makers in health economics to make informed decisions on investments in new treatments or technologies. There have been investigations by several authors (McGabe & Dixon, 2000; Sculpher et al, 2000; Sonnenberg et al, 1994) that offer guidance to the researcher on effective modelling practices in terms of the quality in the structure, inputs, results and the value of the model to the decision maker. However, these guides do not comment on appropriate modelling techniques in which there is a limited amount of literature. Nevertheless, articles by Brennan, Chick and Davies (2006) and Copper, Brailsford and Davies (2007) give an indication as to the main types of modelling techniques used in decision analytic modelling. These include decision trees, Markov models and discrete event simulation (DES), which will be investigated for their relative appropriateness to this thesis.

2.1 Modelling with Decision Trees

Decision trees are the most widely used modelling techniques in the health field (Cooper et al, 2007). They offer a useful way of visually displaying and organising the computational aspects of a problem. Wyer, McGinn, Keitz, Ho, Joynt and Lee (2009) define a decision tree as "...an explicit, quantitative, and systematic approach to decision making under conditions of uncertainty". A set of decisions can be analysed by mapping a path of possible outcomes. The probability of following a particular set of outcomes can then be calculated, giving an indication of the most likely series of events. Often in medical decision making, the outcomes are given a utility value to quantify the difference in quality of life (QoL) from adverse outcomes that may arise from different methods of treatment. In this context, a decision can be made to adopt the method of treatment that offers the highest expected QoL.

However, the solution of a decision tree is based on a choice of events that lead to the highest expected QoL but the intended results of the pregnancy model is a record of pregnancy outcomes, not a utility function. These outcomes will be based on natural events with a particular frequency of occurring for a given patient and there will be no interaction of human decision making. This type of tree is referred to as a probability or event tree, where the solution is derived by finding the product of the frequency of the initiating event with the probabilities of passing along each path leading to each

outcome scenario (Andrews, 2000). Thus, a model of this type will give a probability distribution for all possible pregnancy outcomes.

This is not practical for the pregnancy model when the numbers of combinations of patients' characteristics are considered, where a particular patient can be generated from one of three age groups, three parity groups, four groups of geographical remoteness, smoking or non-smoking during pregnancy, and 2^3 combinations of the three most common pre-existing medical conditions. This equates to 576 ($3 \times 3 \times 4 \times 2 \times 2^3$) possible combinations of maternal characteristics. Thus a probability tree of pregnancy events would need to be defined for each of these 576 possible combinations.

Another major drawback for this technique, cited by Cooper et al (2007); Brennan et al (2006); and Sonnenberg and Beck (1993), is the rapid growth in paths contributed by repetitions of events, such as the weekly pregnancy cycles. Here they suggest using Markov modelling to reduce the complexity of the decision tree.

2.2 Decision Analysis formulated using Markov Modelling

A Markov chain was used by Kapadia et al (2000) in which they wished to study the course of stay in a paediatric intensive care unit as the patients move back and forth between severity of illness states. The study evaluated the proportion of time a patient is expected to spend at a particular state of illness given the total number of days in intensive care. However, the Markov chain had only eight states with the probability of moving back and forth between states predicted for a general cohort.

Brennan et al (2006) indicate that the number of dimensions of the Markov model rises exponentially when the cohort to be modelled has multiple attributes/covariates. The only way of retaining these factors is to define a separate transition probability for each combination of attributes. This is true for the pregnancy model in that it was previously calculated that there is 576 possible sub cohorts based on the different categories of maternal characteristics. Another obstacle to consider is that the outcome of a pregnancy event (such as the onset of a complication) will alter the probabilities of future events.

Papers by Sonnenberg and Beck (1993), and Beck and Pauker (1983), provide a solution for these problems. They suggest the use of a simulated patient-level Markov model (SPLMM) through Monte Carlo simulation. This allows a series of events to be simulated one patient at a time. Thus, a patient with certain characteristics can be

progressed through a Markov process where their probability of transition is compared to a uniform random number at each node to ascertain a particular path. Once the patient reaches an absorbing state (labour), the simulation of that patient finishes and the times spent in each state prior to, are reported. This process is repeated thousands of times to simulate a large cohort of patients required for a comprehensive analysis of the outcomes.

2.3 Modelling with Discrete Event Simulation

Cooper et al (2007) and Brennan et al (2006) describe discrete event simulation (DES) as another way to model the flow of individual patients through a new treatment system. They state two main additions compared to SPLMM. Firstly, this technique enables the researcher to model the effects of interaction between patients such as in the case of physical resource scarcity. For example, one can model the effects of patients having to wait for surgery if there is a queue. Secondly, DES does not require constant time periods for transitions. However, these features are not required for this model and DES was not investigated any further.

2.4 Logistic Regression

Some of the more sophisticated simulation models by Muenz and Rubinstein (1985), and Weinstein, Coxson, Williams, Pass, Stason & Goldman (1987) that included multiple attributes in the cohort to predict events used logistic functions. Logistic regression is a regression technique for predicting a dichotomous dependent variable on the basis of continuous and/or categorical independents (Foster, Barkus & Yavorsky, 2006). Using logistic regression equations in the model with coefficients determined through analysis of the data will enable an easier way to estimate patient attributes, that may affect transition probabilities, and the actual transition probabilities.

3 Methodology used for Pregnancy Simulation

The methods used to construct a model which can simulate a cohort that is representative of the current population of remote Aboriginal women going through the antenatal stage of pregnancy in WA will be discussed in this chapter. The main objective is to introduce the mathematical techniques that were used.

To estimate this population, a set of maternal characteristics needed to be assigned to each patient simulated from a multivariable distribution. This was done by assigning their characteristics in a sequential order such that once the first characteristic was assigned, it could be used to predict the next, and then these two characteristics could be used as covariates to predict the subsequent characteristic and so on. As these characteristics are commonly represented as categorical variables in the obstetric field, logistic, as opposed to linear, regression was used to estimate the likelihood of which group the patient belonged to for each particular characteristic and is described in Section 3.1.

Logistic regression was also used to predict the probability of events occurring during the pregnancy stage of the model. These events included various pregnancy complications and the onset of labour. In fact, if labour occurs the modelling for the purpose of this thesis is complete and the simulation for a new patient begins, on the other hand, if a pregnancy complication occurs, then the probability of labour occurring is affected. Through logistic regression, the adverse affects of maternal complications can be added to the vector of maternal characteristics and used to predict the probability of the next event occurring. For this reason, logistic regression was preferred over using survival analysis to predict the final event of labour as survival analysis assumes that the factors which influenced survival at the start are present throughout the time period observed without additional factors being introduced (Foster et al, 2006). Due to this influential behaviour of pregnancy complications, an assumption was made that the possibility of them occurring should be determined before the probability of labour and therefore, complications were modelled in a sequential order before the prediction of labour. This was done using a probability tree which is outlined in Section 3.2.

The pregnancy stage was modelled in weekly time increments from 20 weeks GA to a maximum of 42 weeks GA (where labour is typically induced). During each week, the model allows for the possibility of the onset of one or more pregnancy complications followed by labour. This was a repetitive process and as such a Markov cycle was used

and is explained in Section 3.3. Solving the model analytically would be extremely difficult and as such, Section 3.4 describes how Monte Carlo simulation can be used to determine outcomes of the model.

3.1 Logistic Regression

Logistic regression is a popular modelling procedure in epidemiologic studies used to describe the relationship of several explanatory variables, which can be continuous and/or categorical, to a dichotomous dependent variable (Kleinbaum, 2002). Estimates from the logistic regression model can also be used to discriminate between two populations. This is preferred over classical discriminant analysis when there are violations to the normality assumptions of classical discriminant analysis, which is often the case when at least one variable is qualitative (Press & Wilson, 1978).

Consider a group of N subjects, each with a set of j covariates $X_i = (x_{i1}, \dots, x_{ij})$ and a dichotomous outcome variable $Y_i \in \{0, 1\}$. The discrimination between two populations is accomplished by the evaluation of the conditional probability $P(Y = 1 \mid X)$ with $P(Y = 0 \mid X) = 1 - P(Y = 1 \mid X)$. By convention $Y_i = 1$ indicates that the i^{th} individual has the condition of interest. The logistic model is formulated in terms of the probability that the i^{th} individual with covariates X_i presents with the outcome of interest given by

$$p_i = P(Y_i = 1 \mid X_i) = \frac{1}{1 + e^{-(\beta_0 + \beta' X_i)}}$$

with parameters $\beta' = (\beta_1, \beta_2, \dots, \beta_j)$.

The parameters β' are derived using maximum likelihood estimation (MLE). Maximum likelihood methods seek to maximize the likelihood (or probability) that the observed values of the dependent, Y, may be predicted from the observed values of the covariates, X. The MLEs for β' are solved by the statistical software package SPSS using a Newton-Raphson type algorithm (SPSS, 2006), which is described in the Appendix.

The logit transformation defined as $\text{logit}(p_i) = \ln\left(\frac{p_i}{1-p_i}\right) = \beta_0 + \beta' x_i$ converts the logistic model into a linear log-odds representation.

When the outcomes of interest contain more than two categories the dependent variable is transformed into multiple dichotomous variables. For example, each simulated patient is assigned one of three possible parity groups consisting of no previous births, between one and four births and more than five births. During the logistic regression analysis this

variable is split in to three separate dependent variables each representing one of the parity groups. For each of the three new dependent variables, the patient from the sample data was coded with a 1 if they belong to the parity group indicated by the new variable or 0 if they belong to one of the other two groups. Thus, each parity group would have a different set of parameter coefficients which would be used to predict the probability that the simulated patient was in the group of interest. The estimated probabilities of belonging to each group could be scaled such that they summed to one and this gives a relevant probability distribution to determine which parity group out of the three that the simulated patient most likely belonged to. This method was preferred over using multinominal logistic regression as most dependent variables were already dichotomous and multinominal logistic regression compares the likelihood that the sample patient belonged to each group separately, compared to a single reference group.

Final covariate selection, in particular those used to predict pregnancy complications, was made trough consultation with clinical experts. This helped minimise the problem of predicting events through independent variables that, although they may be correlated with the complication, do not cause the complication to occur. Moreover, the consultation ensured that any covariates that may not have shown to be highly significant during analysis, were still included.

3.2 Probability Trees

As discussed in the introduction to this section, any pregnancy complication that may occur will significantly affect the GA at labour. For this reason, it was decided that the possibility of one or more pregnancy complications should be evaluated before modelling the chance of labour occurring during a particular week. The simplest way to model this series of events was to use a probability tree.

A probability tree represents the possibilities for the step-by-step evolution of an observer's knowledge (Shafer, 1998). The method of constructing a probability tree involves defining an event and listing the relevant outcomes. The events can be described as event nodes, where a probability distribution, which must sum to one, is assigned to the possible outcomes. The selected outcome may then contain further event nodes that will describe another list of outcomes pertaining to the previous event. In this way, the system branches out like a tree and the event probabilities along each possible path can be summed to give the likelihood of that particular series of events occurring from all those considered in the system.

A diagram of the structure used in the pregnancy model is shown in Figure 3.2.1. The event nodes for the probability tree are represented by circles. The tree illustrates how a patient can possibly accumulate one or more complications during the particular week or none at all. For example, the possible combinations of outcomes shown in the first two stages are complication A and complication B, complication A only, complication B only or no complications. A chance of each complication occuring per pregnancy week must be considered so that the probability of labour can be estimated at the end of that week.

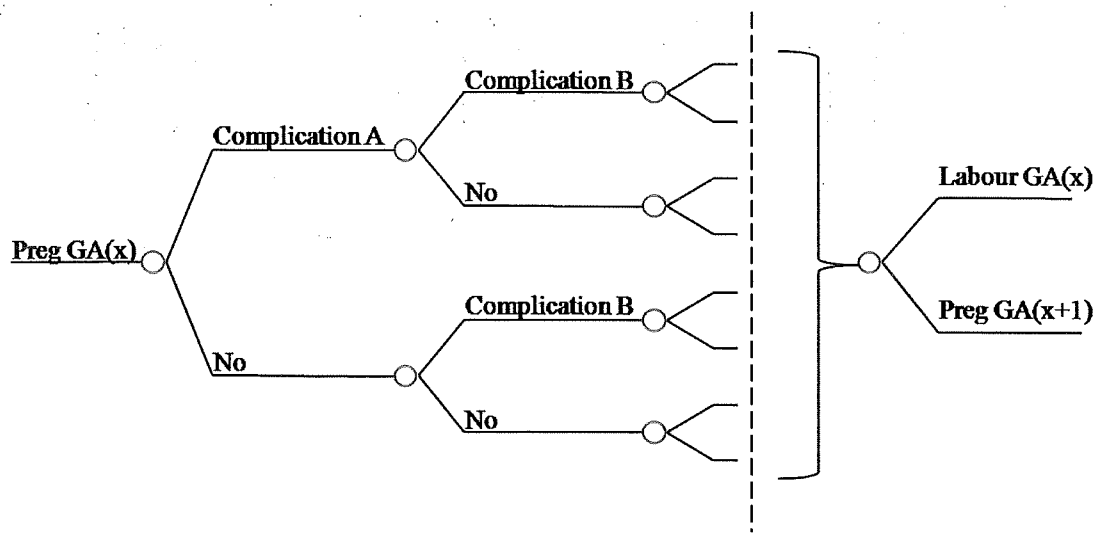


Figure 3.2.1- Graphical representation of the probability tree used in the model

The outcomes to the event nodes were again estimated using logistic functions. The decison analytic software allows for the recording of outcomes for all events encountered. Thus, the outcome of any event node can be recorded by using a vector of binary outcomes to evaluate the implemented logistic equation.

Suppose for example, the probability of a pregnancy complication C_j is to be predicted for a patient with a set of i maternal characteristics $M_i = (m_1, \ldots, m_i)$ andand a set of j-1 previous complications $C_{j-1} = (c_1, \ldots, c_{j-1})$ then

$$P(C_j = 1 \mid M_i, C_{j-1}) = \frac{1}{1 + e^{-(\beta_0 + \beta' M_i + \gamma' C_{j-1})}}$$

with parameters $\beta' = (\beta_1, \beta_2, \ldots, \beta_i)$ and $\gamma' = (\gamma_1, \gamma_2, \ldots, \gamma_j)$..

3.3 Markov Models

A stochastic process is defined to be an indexed collection of random variables $\{X_t\}$, where the index t runs through a given set T. The variable $X_t X$ represents a measureable variable of interest, which is often non-negative, at time t. The system can be observed at particular points of time, thus the stochastic process $\{X_t\} = \{X_0, X_1, X_2,...\}$ provides a mathematical representation of how the status of the system evolves over time (Hillier & Lieberman, 2005). The possible outcomes at any one time are called states. A stochastic process is said to have the Markovian property if;

$$P\{X_{t+1} = j \mid X_0 = k_0, X_1 = k_1,...,X_{t-1} = k_{t-1}, X_t = i\} = P\{X_{t+1} = j \mid X_t = i\},$$

for $t = 0, 1,...$and every sequence $i, j, k_0, k_1,...,k_{t-1}$.

In other words, a stochastic process has the Markovian property if the conditional probability of any future event, given any past events and the present state $X_t = i$, is independent of the past events and depends only upon the present state. In this case, the stochastic process is called a Markov chain (Hillier & Lieberman, 2005).

The transition probability of going from the i^{th} state at time t, given state j, after n transitions is often denoted $P\{X_{t+n} = j \mid X_t = i\} = P_{ij}^{(n)}$, and if

$$P\{X_{t+n} = j \mid X_t = i\} = P\{X_n = j \mid X_0 = i\},$$

then the transition probabilities are said to be stationary.

A state i is said to accessible from state j if there is a path from state j to state i. A state is said to be a transient state if, upon entering the state, the process may never return to the state again. Therefore, state i is transient if and only if there exists a state j ($j \neq i$) that is accessible from state i but state i is not accessible from state j. If the process cannot leave a particular state, the state is said to be an absorbing state.

Given the probability tree system described previously, the pregnancy model can be represented by 23 transient states, pregnancy at GA 20 to GA 42, and one absorbing state of labour. This is made possible as the outcome of the probability tree will provide the complication covariates needed for the transition probability of going from the state of pregnant at time t to either pregnant at $t+1$ or the state of labour (shown in Figure 3.3.1). Without the probability tree as an intermediate step for determining the

transition probabilities, additional states would need to be defined for all possible combinations of being pregnant with complications for each GA.

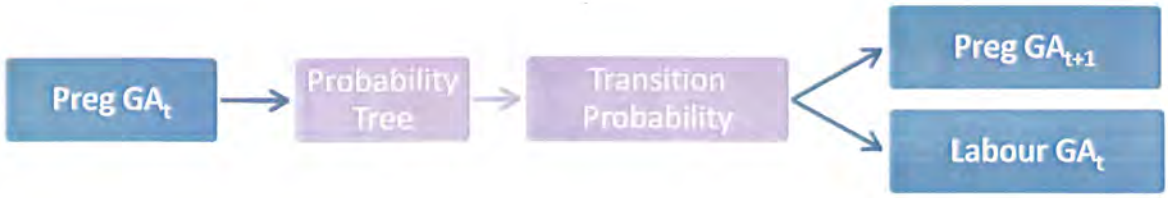


Figure 3.3.1 - Estimating transition probabilities

If S represents a vector of states $S = (s_0, s_1, s_2, \ldots, s_{23})$ where, s_0 = Pregnant at GA 20, s_1 = Pregnant at GA 21, ..., s_{22} = Pregnant at GA 42, and s_{23} = Labour. Then if $P(S_{t+1} = j \mid S_t = i) = P_{ij}$ the transition probabilities for all states can be represented by a transition matrix P and are estimated such that

$$P_{ij} = \frac{1}{1 + e^{-(\beta_0 + \beta' M_i + \gamma' C_j)}}$$

with parameters $\beta' = (\beta_1, \beta_2, \ldots, \beta_i)$ and $\gamma' = (\gamma_1, \gamma_2, \ldots, \gamma_j)$.

A graphical representation of the Markov model and the corresponding transition matrix P of this system are shown in Figure 3.3.2 and Figure 3.3.3 respectively.

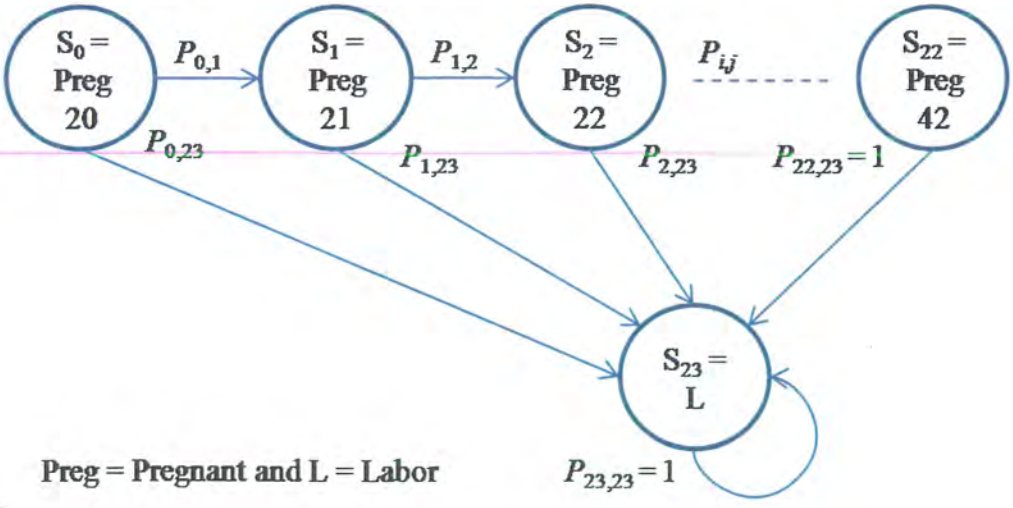


Figure 3.3.2- Graphical representation of the simplified Markov model

$$
P = \begin{array}{c} \text{State} \\ 0 \\ 1 \\ 2 \\ \vdots \\ 21 \\ 22 \\ 23 \end{array}
\begin{array}{c}
\begin{array}{ccccccc} 0 & 1 & 2 & 3 & \dots & 22 & 23 \end{array} \\
\begin{bmatrix}
0 & P_{01} & 0 & 0 & \dots & 0 & P_{0,23} \\
0 & 0 & P_{12} & 0 & \dots & 0 & P_{1,23} \\
0 & 0 & 0 & P_{23} & \dots & 0 & P_{2,23} \\
\vdots & \vdots & \vdots & \vdots & \ddots & 0 & P_{\dots,23} \\
0 & 0 & 0 & 0 & 0 & P_{21,22} & P_{21,23} \\
0 & 0 & 0 & 0 & 0 & 0 & 1 \\
0 & 0 & 0 & 0 & 0 & 0 & 1
\end{bmatrix}
\end{array}
$$

Figure 3.3.3 - Transition matrix of the simplified Markov model

Solutions such as expected time to absorption (or weeks till labour in this case) can be determined through matrix algebra for an absorbing Markov chain. A good description of the techniques for this can be found in Kenny and Snell (1960). However, the dimensions of the full Markov model, without the probability tree, would be too large to solve through these methods and instead, Monte Carlo Simulation will be used.

3.4 Monte Carlo Simulation

A definition of Monte Carlo simulation by Gentle (2003) is 'Monte Carlo simulation is the use of experiments with random numbers to evaluate mathematical expressions'. In this model the random numbers will be used to determine the outcomes of the logistic regression equations used to predict the probability of a patient having particular characteristics, complications and Markov state transition. For yes/no outcomes the following algorithm can be used.

Let $\hat{p}_x$ represent the probability estimated by logistic equation x and $Y_x \in \{0, 1\}$ be the possible outcomes. Then generate a uniform random number $U \sim \mathrm{U}(0,1)$ determining the outcome

$$
Y_x = \begin{cases} 1, & \text{if } U \leq \hat{p}_x \\ 0, & \text{if } U > \hat{p}_x \end{cases}
$$

The outcomes of characteristics with multiple categories are obtained by a simple extension. That is, the otcome Y_{xk} can be determined by probability $\hat{p}_{xk}$ for logistic equation x of category k belonging to a set of K categories, $k = \{1, 2, \dots, K\}$, for the particular maternal characteristic, by

$$Y_{xk} = \begin{cases} 1, & \text{if } 0 \leq U \leq \hat{p}_{x1} \\ 2, & \text{if } \hat{p}_{x1} < U \leq \sum_{k=1}^{2} \hat{p}_{xk} \\ \vdots & \vdots \\ K-1, & \text{if } \sum_{k=1}^{K-2} \hat{p}_{xk} < U \leq \sum_{k=1}^{K-1} \hat{p}_{xk} \\ K, & \text{if } \sum_{k=1}^{K-1} \hat{p}_{xk} < U \end{cases}$$

Each outcome is recorded by the decision analytic software giving a list of outcomes for each event.

In practice, a large number of simulations are required for the comprehensive evaluation of the model.

4 Modelling Pregnancy

The output of the simulation is to reflect pregnancy outcomes consistent with those observed in the population of Aboriginal women living in rural and remote areas of WA. The primary data used for this thesis were extracted from the Western Australian Midwife's Notification System (MNS). The inclusion criterion was for all Aboriginal women residing in a rural setting who gave birth in Western Australia between 1997 and 2007, so that 12,741 pregnancy records were obtained. The variables of interest included maternal characteristics such as age, parity, smoking habits during pregnancy, ARIA[1], and pre-existing medical conditions (hypertension, diabetes and 'other conditions'). Pregnancy complications that are known to have significant adverse effects on pregnancy outcomes included, antepartum haemorrhage due to abruption or other causes (APH), placenta praevia, preeclampsia (PET), gestational diabetes (GDM), threatened preterm labour (TPL), preterm pre-labour rupture of membranes (PROM), and 'other' complications (such as anaemia or sexually transmitted infections) that are routinely recorded as 'other complications' in the Midwives Notification System. The frequency distribution of the GA at onset of these complications is not recorded in the MNS but is required for the model. Summaries of these distributions were obtained from supplementary data, most of which were acquired from the Western Australian Pregnancy Cohort (Raine) Study. Section 4.1 provides descriptive statistics of these variables.

The analysis of the data allows for the estimation of the models probabilities that can be implemented to simulate pregnancy outcomes. Section 4.2 introduces the computer software used for this along with a description and an example of the process. The simulated data are then compared to the observed data in Section 4.3 via validation tables.

4.1 Descriptive Statistics of Maternal Characteristics and Pregnancy Outcomes

The distributions of maternal characteristics for the observed data are shown in Table 4.1.1. The distributions of ages and parity were grouped according to common obstetric risk levels for analysis and it can be seen that the highest percentages of maternal age and parity are amongst the 20 to 34 years (69.9%), and one to four previous births

[1] ARIA, Accessibility/Remoteness Index of Australia (version 2), derived for 1996, 2001 and 2006 data (Australian Bureau of Statistics, 2006). ARIA provides an index between 0 and 15 that reflects a road distance from a fixed locality to the nearest service centres defined as localities with the population greater than 999 persons.

(62.6%) groups respectively. It is less likely that a patient will be 35 years or older (6.1%), or will have had five or more previous births (9.1%). Just over half of Aboriginal women in rural and remote areas of WA can be expected to have been smoking during pregnancy (51.6%). Furthermore, almost two thirds of the population reside in very remote regions, ARIA 5, of WA (65.6%).

Table 4.1.1 - Maternal characteristics in Aboriginal women residing in rural and remote areas

Risk factor	Categories		%
Maternal age	< 20 years		24.0
	20 - 34 years		69.9
	≥ 35 years		6.1
Parity	Parity 0		28.3
	Parity 1 - 4		62.6
	Parity ≥ 5		9.1
Smoking	Any smoking of tobacco during pregnancy		51.6
Medical conditions	Current diabetes		1.3
	Current hypertension		1.0
	Other conditions		18.8
ARIA	ARIA 2: 0.2 – 2.40	Inner Regional	9.3
	ARIA 3: >2.4 – 5.92	Outer Regional	20.9
	ARIA 4: > 5.92 – 10.53	Remote	4.7
	ARIA 5: >10.53	Very Remote	65.6

The expected incidence rates of pregnancy complications are summarised in Table 4.1.2. It can be noticed that 'Other antenatal complications' such as pregnancy induced hypertension, anaemia and sexually transmitted diseases can be expected to occur in almost one quarter (24.0%) of pregnant Aboriginal women in rural and remote areas of WA. Pre-eclampsia, gestational diabetes and threatened preterm labour occurred in 4.9%, 5.0% and 5.6% of cases respectively. The rate of preterm delivery (13.9%) is higher than the average rate (approximately 8%) for all women giving birth in WA (Linacre, 2007).

4.1.2 - Pregnancy complications considered in the model

Complication	Definition	Incidence %
Pre-eclampsia	Gestational hypertension with protein in urine	4.9
Gestational diabetes	Carbohydrate intolerance with onset or first recognition during pregnancy	5.0
Antepartum haemorrhage (APH)	Any bleeding in pregnancy. May be caused by premature separation of the placenta (placenta abruption) or have unknown origin	1.9
Placenta praevia	The placenta overlies or is proximate to the internal os of the cervix, potentially causing bleeding	0.4
Other antenatal complication	Pregnancy induced hypertension, anaemia, sexually transmitted diseases, and otherwise unspecified conditions	24.0
Threatened Preterm Labour	The onset of regular painful contractions before 37 weeks of pregnancy	5.6
Prelabour Rupture of Membranes (PROM)	Rupture of the membranes prior to onset of labour	7.4
Preterm delivery	Birth before 37 completed pregnancy weeks	13.9

Maternal risk factors are known to vary amongst the age and parity groups. Table 4.1.3 shows a summary of the pregnancy complications stratified by age groups. As can be expected, the less than 20 age group are far more likely to be first time mothers (71.6%) compared to those women 35 and over (6.9%). Moreover, Aboriginal women 35 and over are more likely to currently have hypertension (3.6%), diabetes (6.2%) and 'other' medical conditions (23.7%) compared to the under 20 age group with hypertension (0.3%), diabetes (0.3%) and 'other' conditions (16.8%). The 35 and over age group is also, on average, more likely to have a pregnancy complication compared to the other groups.

Table 4.1.3 - Rates of maternal characteristics and pregnancy complications amongst Aboriginal women stratified by age

Characteristic	Age			
	< 20	20-34	≥ 35	All
	3053 (24.0)	8911 (69.9)	777 (6.1)	12741 (100.0)
Parity				
P 0	2185 (71.6)	1361 (15.3)	54 (6.9)	3600 (28.3)
P 1-4	868 (28.4)	6695 (75.1)	414 (53.3)	7977 (62.6)
P 5+	-	855 (9.6)	309 (39.8)	1164 (9.1)
Smoking in pregnancy	1399 (48.8)	4414 (52.7)	374 (50.3)	6187 (51.6)
ARIA Index				
2 (Inner Regional)	212 (7.1)	867 (9.9)	89 (11.6)	1168 (9.3)
3 (Outer Regional)	577 (19.2)	1894 (21.6)	142 (18.6)	2613 (20.9)
4 (Remote)	111 (3.7)	440 (5.0)	33 (4.3)	584 (4.7)
5 (Very Remote)	2103 (70.0)	5552 (63.4)	501 (65.5)	8156 (65.1)
Pre-existing conditions				
Hypertension	10 (0.3)	87 (1.0)	28 (3.6)	125 (1.0)
Diabetes	8 (0.3)	115 (1.3)	48 (6.2)	171 (1.3)
Other	514 (16.8)	1693 (19.0)	184 (23.7)	2391 (18.8)
Pregnancy complications				
TPL	174 (5.7)	488 (5.5)	46 (5.9)	708 (5.6)
PET	188 (6.2)	379 (4.3)	60 (7.7)	627 (4.9)
APH	77 (2.5)	261 (2.9)	23 (3.0)	361 (2.8)
PROM	207 (6.8)	678 (7.6)	56 (7.2)	941 (7.4)
GDM	46 (1.5)	485 (5.4)	106 (13.6)	637 (5.0)
Other	713 (23.4)	2112 (23.7)	236 (30.4)	3061 (24.0)

A summary of maternal characteristics and pregnancy complications stratified by the three parity groups are shown in Table 4.1.4. It can be seen that Aboriginal women with five or more previous births are more likely to be smoking during pregnancy (59.3%) compared with those women who have had no previous births (46.5%) or one to four previous births (52.8%). Also, except for pre-eclampsia, Aboriginal women with five or more previous births are more likely to have a pregnancy complication than women who have had fewer previous births.

Table 4.1.4 - Rates of maternal characteristics and pregnancy complications amongst Aboriginal women stratified by parity

Characteristic	Parity			
	P 0	P 1-4	P 5+	All
	3600 (28.3)	7977 (62.6)	1164 (9.1)	12741 (100.0)
Age				
< 20	2185 (60.7)	868 (10.9)	-	3053 (24.0)
20-34	1361 (37.8)	6695 (83.9)	855 (73.5)	8911 (69.9)
≥ 35	54 (1.5)	414 (5.2)	309 (26.5)	777 (6.1)
Smoking in pregnancy	1576 (46.5)	3953 (52.8)	658 (59.3)	6187 (51.6)
ARIA Index				
2 (Inner Regional)	308 (8.8)	711 (9.0)	149 (13.0)	1168 (9.3)
3 (Outer Regional)	708 (20.1)	1701 (21.6)	204 (17.8)	2613 (20.9)
4 (Remote)	138 (3.9)	380 (4.8)	66 (5.8)	584 (4.7)
5 (Very Remote)	2366 (67.2)	5066 (64.5)	724 (63.3)	8156 (65.1)
Pre-existing conditions				
Hypertension	25 (0.7)	86 (1.1)	14 (1.2)	125 (1.0)
Diabetes	25 (0.7)	118 (1.5)	28 (2.4)	171 (1.3)
Other	654 (18.2)	1501 (18.8)	236 (20.3)	2391 (18.8)
Pregnancy complications				
TPL	188 (5.2)	441 (5.5)	79 (6.8)	708 (5.6)
PET	298 (8.3)	284 (3.6)	45 (3.9)	627 (4.9)
APH	91 (2.5)	232 (2.9)	38 (3.3)	361 (2.8)
PROM	267 (7.4)	578 (7.2)	96 (8.2)	941 (7.4)
GDM	101 (2.8)	431 (5.4)	105 (9.0)	637 (5.0)
Other	855 (23.8)	1846 (23.1)	360 (30.9)	3061 (24)

Also of interest is the number of pregnancy complications that occurred amongst the different maternal characteristics which is presented in Table 4.1.5. The number of pregnancy complications is higher for Aboriginal women in the 35 and over age group with 49.2% having more than one complication compared to the average rate of 39.4%. There is a similar trend for Aboriginal women who have had five or more previous pregnancies (56.3% having one or more complications). Also, those with a pre-existing medical condition were more likely to have one or more complications.

Table 4.1.5 - Number of pregnancy complications stratified by maternal characteristics

Characteristic	Number of Pregnancy Complications			
	0	1	2	3+
	7721 (60.6)	3876 (30.4)	988 (7.8)	156 (1.2)
Age				
< 20	1900 (62.2)	926 (30.3)	203 (6.6)	24 (0.8)
20-34	5426 (60.9)	2692 (30.2)	680 (7.6)	113 (1.3)
≥ 35	395 (50.8)	258 (33.2)	105 (13.5)	19 (2.4)
Parity				
P 0	2161 (60.0)	1121 (31.1)	279 (7.7)	40 (1.1)
P 1-4	4935 (61.9)	2369 (29.7)	584 (7.3)	89 (1.1)
P 5+	625 (53.7)	386 (33.2)	126 (10.8)	27 (2.3)
Smoking in pregnancy	3775 (61.0)	1861 (30.1)	478 (7.7)	73 (1.2)
ARIA Index				
2 (Inner Regional)	685 (58.6)	348 (29.8)	114 (9.8)	21 (1.8)
3 (Outer Regional)	1533 (58.7)	829 (31.7)	208 (8.0)	43 (1.6)
4 (Remote)	355 (60.8)	186 (31.8)	38 (6.5)	5 (0.9)
5 (Very Remote)	5018 (61.5)	2438 (29.9)	613 (7.5)	87 (1.1)
Pre-existing conditions				
Hypertension	37 (29.6)	49 (39.2)	34 (27.2)	5 (4.0)
Diabetes	59 (34.5)	69 (40.4)	38 (22.2)	5 (2.9)
Other	1050 (43.9)	937 (39.2)	332 (13.9)	72 (3.0)

Furthermore, the data were analysed for the impact that the maternal pregnancy risk factors have on the rate of preterm birth (labour before 37 weeks gestation). Underdevelopment of the baby due to labour occurring preterm is a significant problem in obstetrics as preterm birth has been associated with poorer health outcomes (Linacre, 2007). Analysis of the rate of preterm labour for Aboriginal women with particular maternal characteristics is shown in Table 4.1.6. It is clear from this table that those women who have a pre-existing medical condition are much more likely to deliver their baby preterm. The overall rate of preterm delivery for Aboriginal women across the data set was 13.9% while for those with hypertension it was 33.6%, for those with diabetes it was 39.8% and for those with 'other' conditions the rate of preterm delivery was 21.5%.

Table 4.1.6 - Rates of preterm birth stratified by maternal characteristics

		Age		
Characteristic	**< 20**	**20-34**	**≥ 35**	**Total**
Preterm	439 (14.4)	1220 (13.7)	118 (15.2)	1746 (13.9)
		Parity		
Characteristic	**P 0**	**P 1-4**	**P 5+**	**Total**
Preterm	490 (13.6)	1127 (14.1)	160 (13.7)	1746 (13.9)
		Pre-existing condition		
Characteristic	**Hypertension**	**Diabetes**	**Other**	**Total**
Preterm	42 (33.6)	68 (39.8)	515 (21.5)	1746 (13.9)

Also of particular interest are the higher rates of preterm birth stratified by Aboriginal women who have a pregnancy complication. These rates are summarised in Table 4.1.7 and it can be seen that there is a large difference between those women whom did not have a pregnancy complication (5.5%) and those that had any two or more (51.0%). The second lowest rate of preterm delivery is for Aboriginal women who had gestational diabetes, GDM, (8.8%) which is generally associated with babies of increased birth weight. At least one third of the Aboriginal women whom had a threatened preterm delivery (TPL) or prelabour rupture of membranes (PROM) delivered preterm with rates of 39.6% and 35.4% respectively.

Table 4.1.7 - Rates of preterm birth stratified by pregnancy complication

Complication	**None**	**TPL**	**PET**	**APH**
N	7589	369	340	144
Preterm	414 (5.5)	146 (39.6)	63 (18.5)	36 (25.0)
Complication	**PROM**	**GDM**	**Other**	**Any Multiple**
N	449	363	2145	1210
Preterm	159 (35.4)	32 (8.8)	303 (14.1)	617 (51.0)

A graph of the cumulative distribution of the GA at labour for a given pregnancy complication is shown in Figure 4.1.1. It illustrates that Aboriginal women with either multiple complications, or those with TPL, PROM or APH were more likely to deliver at an earlier GA then those without. However, it can also be seen that a much larger percentage of Aboriginal women with APH delivered before 28 weeks of pregnancy

compared to any other single complication. From GA 28 to GA 34 the percentage is stable indicating that the remaining cases can be managed effectively through obstetric care, or only a small percentage of women incurred APH during this time period.

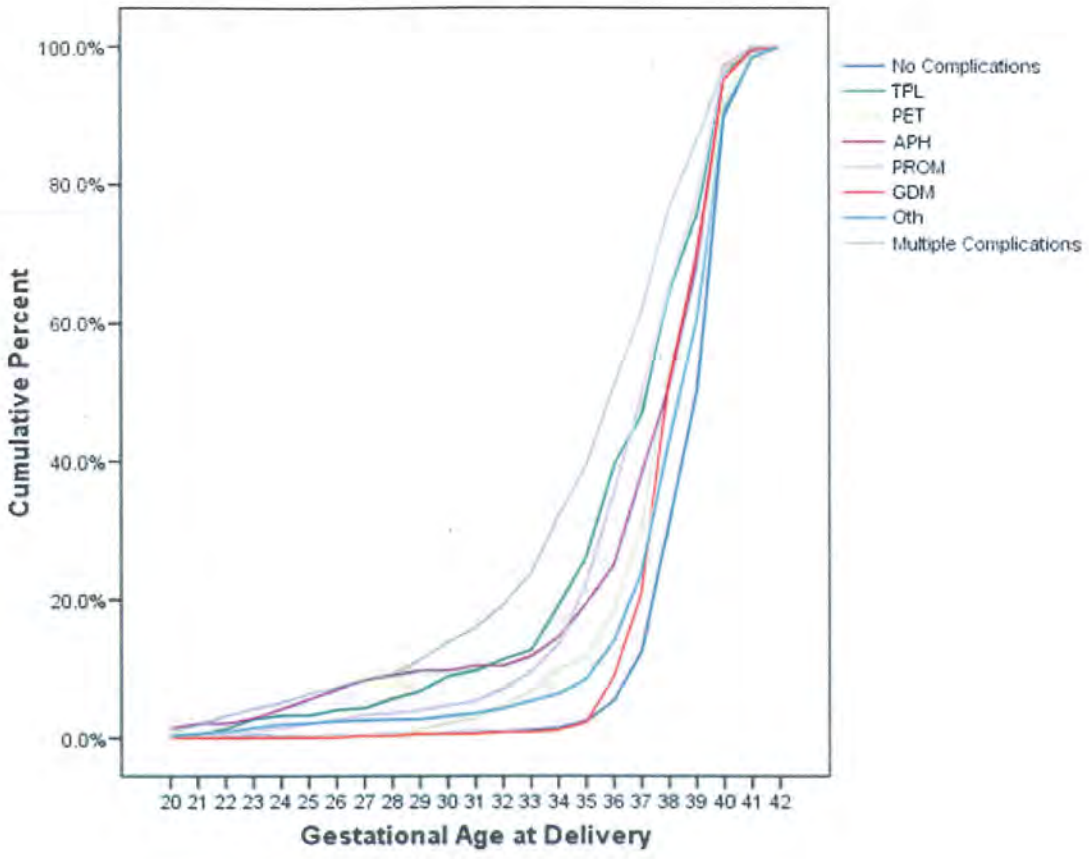


Figure 4.1.1 - Cumulative distribution of the GA at delivery depending on pregnancy complication

To investigate the difference between the rates over time of the onset of a complication compared to the onset of labour, supplementary data sets with records of these distributions of the GA at the onset of a pregnancy complication were analysed. Accurate capture of the GA at the onset of each complication of pregnancy is an important consideration during the modelling of pregnancy because they change the probabilities of the onset of labour. Pregnancy complications also have significant cost implications (not in the scope of this thesis).

An example of the time lag between the expected GA at the onset of a complication and the GA at labour for two complications is given in Figure 4.1.2. The graphs show the cumulative distribution of the onset of a complication from the supplementary data sets together with the cumulative distribution of the GA at labour from the MNS data. The graph of the GA at the onset of TPL and the graph of the GA at labour for those women

who had TPL during pregnancy illustrate that between the GA of 26 and the GA of 32, an additional 45% (from 20% to 65%) of these women incurred the onset of the pregnancy complication. For the same GA range, an additional 8% (from 7% to 15%) of women with TPL went into labour. In comparison, for those women with APH during pregnancy, an additional 26% (from 26% to 52%) had incurred the onset of TPL between GA 26 and GA 32, whilst an additional 10% (from 12% to 22%) went into labour. Since there was a lower percentage of women with the onset of APH but a higher percentage of them going into labour compared to TPL over the selected GA range, it could be said that the likelihood of going into labour after the onset of APH is higher that than of TPL.

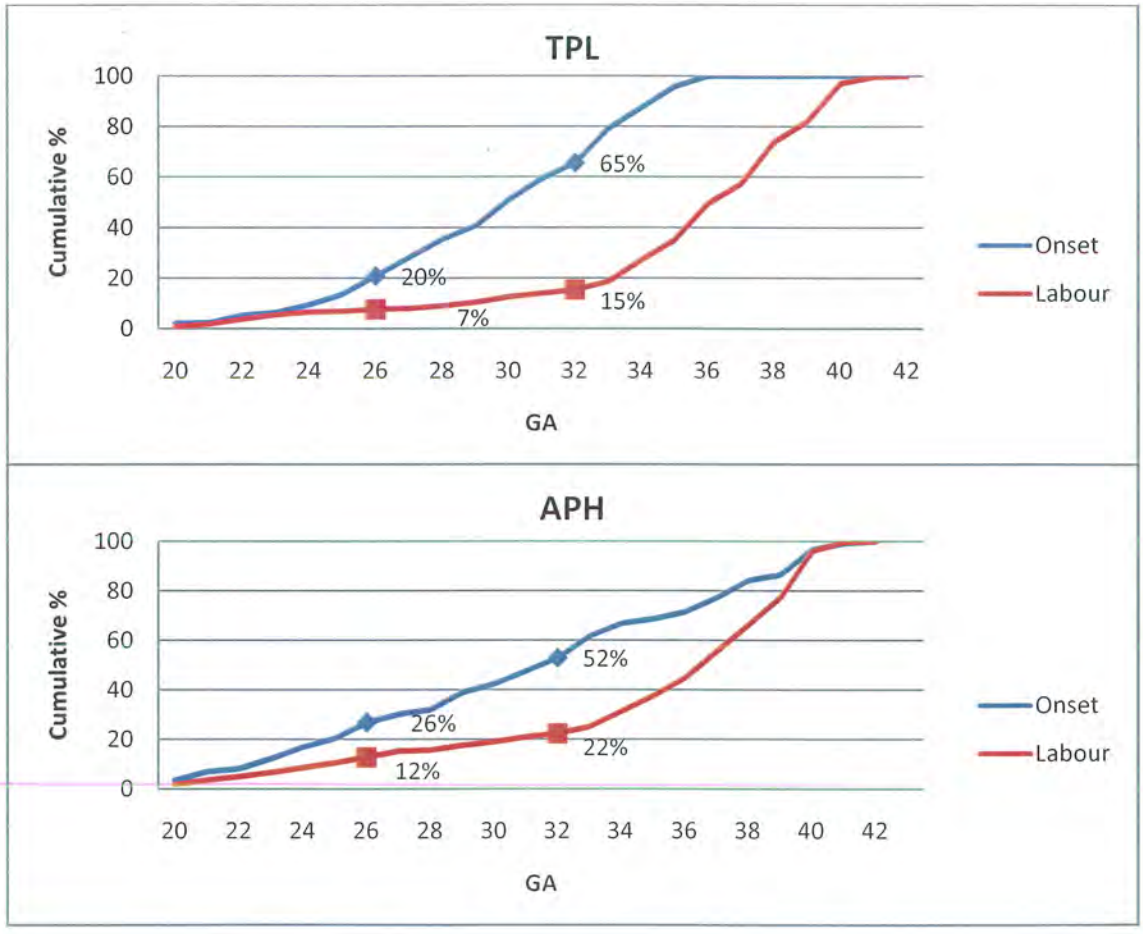


Figure 4.1.2 – Time lag between the GA at onset of a complication and corresponding GA at delivery

4.2 Model Implementation

The pregnancy simulation was implemented with the use of computer software called TreeAge Pro Health Care Module (TreeAge, 2009). TreeAge Pro Health Care is

specifically designed for constructing decision analytic models tailored to health care applications. Researchers can make use of decision trees and Markov models which produce both outcome and cost variables along with associated cost-effectiveness results for analysis. An important feature of this software in the context of this model is the ability to run patient level Monte Carlo simulations. This can be done through the use of 'Tracker' variables which allow the user to record events modelled to generate a data set which can be exported and analysed with other statistical software.

To describe the implementation of the pregnancy model, the generation of maternal characteristics and simulation of pregnancy will be outlined in separate steps. Section 4.2.1 will describe the model designed and used in TreeAge to generate the maternal characteristics, giving the output of one such patient. Section 4.2.2 will describe the same for the pregnancy stage and the example patient generated in Section 4.2.1 will be used in a simulation of pregnancy outcomes.

4.2.1 Generating Maternal Characteristics

The initial part of the model was to generate a set of maternal characteristics for each patient to be simulated. This was done by sequentially assigning maternal characteristics, thus, the age group of the patient is generated first. The age group is then used as a predictor for assigning a parity group with the probability of being in a particular group estimated from the logistic equation. The process continues to successively assign smoking habit, ARIA region, and the possibility of any or all of the pre-existing medical conditions.

Except for maternal age, the input probabilities for assigning maternal characteristics will be predicted using logistic regression. Estimation of the age group probabilities is simply those analysed from the sample data. Namely, the probability of being under 20 years of age is 0.240, between 20 to 34 years is 0.699, and 35 years and over is 0.061. As binary logistic regression estimates the probability for a dichotomous outcome, each maternal characteristic will have a logistic equation with coefficients. In the case of predicting a characteristic pertaining to a group, such as the three parity groups, the estimated probabilities from the logistic equation will be scaled such that the cumulative probabilities for the group sum to one.

The coefficients of the predictor covariates are shown in Table 4.2.1. The table is constructed such that the dependent column describes the characteristic to be predicted

and the other columns show the coefficients for the relevant predictor variables, as each new characteristic is predicted from the previously assigned characteristics. The constant represents the predictor coefficient for the baseline (or reference) group, which is updated as the next characteristic is assigned. For example, when predicting parity the baseline group for age is 20 to 34, thus to estimate the probability of the patient having no previous births, the logit equation (log transform of the logistic regression equation, giving the linear log-odds form) is simply the constant (-1.713) if the patient was assigned the age group of 20-34. This gives a probability of $p = P(\text{Para } 0{=}1 \mid \text{Age } 20\text{-}34) = \frac{1}{1+e^{-(-1.713)}} = 0.153$. If the patient was assigned to the under 20 age group, then the logit equation would be the constant plus the coefficient estimate for being in that age group (-1.713 + 2.637). This yields an estimated probability of $p = P(\text{Para } 0{=}1 \mid \text{Age}{<}20) = \frac{1}{1+e^{-(-1.713+2.637)}} = 0.716$. This is consistent with Table 4.1.3 from the data analysis section (15.3% of Aboriginal women between 20 to 34 and 71.6% in the under 20 age group have no previous births).Then, the baseline group for predicting smoking status becomes maternal age 20 to 34 and parity one to four. For assigning ARIA, non-smoking is included as the baseline group, then ARIA 2 is included for predicting pre-existing conditions.

An example of the steps computed in TreeAge for one patient is given in Figure 4.2.1 and calculated in Table 4.2.2. The age group is assigned first. A uniform random number $U \sim \text{U}(0,1)$ is compared against the cumulative probability of being in any of the three age categories. Here U = 0.711 which is less than the cumulative probability of being in one of the under 20 and the 20 to 34 age groups ($0.240 < \text{U} < 0.939$). Thus the patient is assigned the age group 20 to 34. From there, the probabilities of the parity groups are estimated using only the coefficients of the constants, as age 20 to 34 is a baseline group, such that for $\text{U} < 0.153$ corresponds to P0, $0.153 < \text{U} < 0.904$ corresponds to P1-4 and $\text{U} > 0.904$ indicates P5+. Since U = 0.636, the parity group of one to four previous births is assigned. The patient was considered to smoke tobacco during pregnancy as $\text{U} = 0.185 < \text{P(Smoker)} = 0.530$. This patient was then assigned ARIA 5 and the presence of 'other' pre-existing medical conditions. Once these maternal characteristics are assigned, the pregnancy simulation model uses the recorded vector of outcomes (age, parity, smoking status, ARIA, hypertension, diabetes, other) = (2, 2, 1, 5, 0, 0, 1) .

Table 4.2.1 – Coefficients of maternal predictors from logistic regression

	Predictors								
Dependant	Constant#	< 20	35+	P 0	P 5+	Smoking	ARIA 3	ARIA 4	ARIA 5
P 0	-1.713	2.637	-0.881						
P 1-4	1.106	-2.974	-0.974						
P 5+	-2.243	-18.96	1.828						
Smoking	0.12	0.033	-0.215	-0.278	0.316				
ARIA 2	-2.192	-0.471	0.064	0.186	0.317	-0.126			
ARIA 3	-1.223	-0.165	-0.097	-0.02	-0.194	-0.076			
ARIA 4	-2.911	-0.197	-0.249	-0.143	0.245	-0.11			
ARIA 5	0.491	0.322	0.089	-0.027	-0.05	0.124			
Hypertension	-4.388	-1.203	1.418	0.092	-0.391	0.147	-1.015	0.082	-0.401
Diabetes	-4.286	-1.535	1.626	-0.154	-0.095	0.164	-1.244	0.22	-0.211
Other	-1.315	-0.158	0.287	0.039	-0.021	-0.106	-0.107	-0.285	0.148

The constant represents the baseline characteristics for the given logistic equation. The baseline variables correspond to maternal age 20-34, parity group 1-4, non-smoker and ARIA 2.

Figure 4.2.1 - Sequential order of assigning maternal characteristics

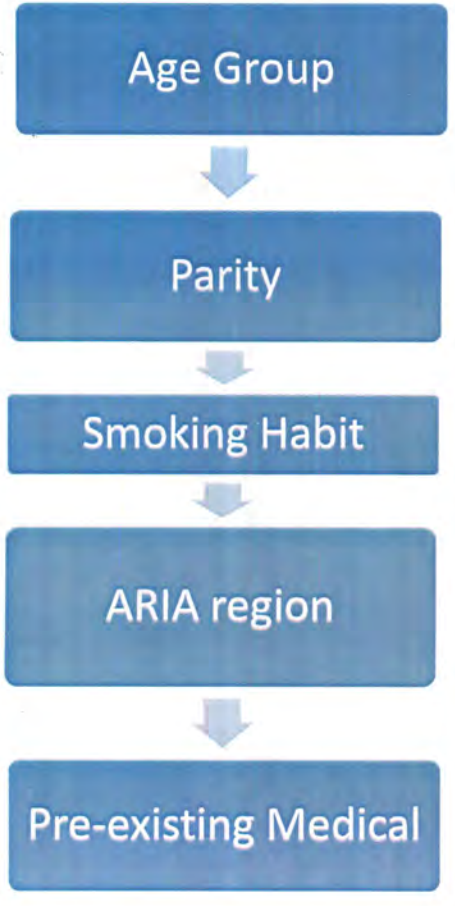


Table 4.2.2 - Example of generating maternal characteristics

Maternal Characteristic to be Assigned	Logit	Est. Prob	Cum P	U	Outcome	Vector
Age < 20	NA	0.240	0.240	0.711	Age 20-34	2
Age 20 - 34	NA	0.699	0.939			
Age 35+	NA	0.061	1.000			
Para 0	-1.713	0.153	0.153	0.636	P 1- 4	2
Para 1-4	1.106	0.751	0.904			
Para 5+	-2.243	0.096	1.000			
Smoker	0.12	0.530	0.530	0.185	Smoker	1
ARIA 2	-2.192 – 0.126	0.090	0.090	0.909	ARIA 5	5
ARIA 3	-1.233 – 0.076	0.213	0.303			
ARIA 4	-2.911 – 0.11	0.046	0.350			
ARIA 5	0.491 + 0.124	0.649	1.000			
Hypertension	-4.388 + 0.147 – 0.401	0.008	0.008	0.368	No	0
Diabetes	-4.286 + 0.164 – 0.211	0.011	0.018	0.527	No	0
Other	-1.315 – 0.106 + 0.148	0.237	0.240	0.077	Yes	1

Est. Prob = Estimated probability from logistic equation. Cum P = Cumulative probability scaled to equal one.

4.2.2 Simulating Pregnancy Outcomes

Pregnancy outcomes are simulated beginning at 20 weeks up to 42 weeks of pregnancy. At each pregnancy week, the probability of having one or more pregnancy complications is given. This information along with their characteristics is then used to determine the probability of labour at the end of the week. If labour does not occur, they advance one week of pregnancy. Like the generation of maternal characteristics, logistic regression was used to estimate the probability of having a pregnancy complication and the probability of labour. The estimated coefficients for predicting the probability of a complication for a given set of maternal characteristics and prior pregnancy complications is shown in Table 4.2.3. The logistic coefficients used in the modelling were obtained as a result of a comprehensive analysis of the data set. In this analysis, statistically significant indicators of pregnancy outcomes were identified. Only predictors that made clinical sense were retained. Furthermore, some of the maternal characteristics were included despite the lack of statistical significance to preserve the difference between age, parity and ARIA groups.

As has been seen in the data analysis, the rates of onset of a pregnancy complication were not uniform over all pregnancy weeks. The distribution of onsets from the supplementary data will be used to estimate the probability of onset of a pregnancy complication for a given GA. For complications where the overall rate differed from the observed, this rate was scaled to reflect the Aboriginal pregnancies and was suitably apportioned among all simulated pregnancy weeks. The estimated cumulative probability of the onset of each pregnancy complication is plotted in Figure 4.2.2. TPL can only occur in the preterm GA range and therefore the probability of onset form 37 weeks of pregnancy and on is zero.

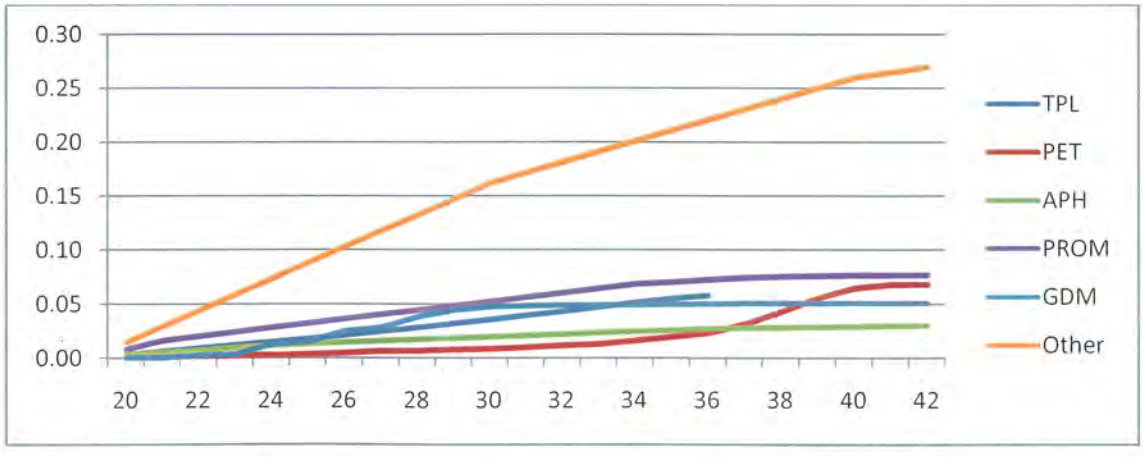


Figure 4.2.2 - Estimated cumulative probability of onset of a particular complication

It was also shown that these pregnancy complications have a large influence on the onset of labour. Therefore, each complication should contribute to the estimation of the GA at labour. Therefore, for each complication the probability of going into labour needs to be represented by a conditional probability distribution. This was achieved by taking the joint probability of labour and having a pregnancy complication for each GA, and using the basic laws of probability to transform that distribution into a distribution of conditional probabilities.

Once the conditional probability distribution of labour given a pregnancy complication was determined, Bayes' rule was used to calculate the Markov transition probabilities. This is the probability of going from the state of pregnant to labour given it is known how many more weeks of labour are possible. The transition probabilities are changed to logistic predictor coefficients so that the probability of labour given multiple factors can be computed in the model. Table 4.2.4 shows the logistic regression coefficients for estimating the transition probabilities to labour over each GA for the predictor variables. The constant represents the probability of labour given the patient has no pregnancy complications. The coefficients extend to 41 pregnancy weeks as the transition probability of going from 42 weeks of pregnancy to labour is one, due to the fact that labour will be induced. The distribution of labour coefficients generated using logistic regression are not uniformly increasing or decreasing in pattern as they reflect the distribution obtained from the raw data.

An example of simulating pregnancy outcomes for the patient generated in the last section is shown in Table 4.2.5. It can be recalled that the patient was assigned the age group of 20 to 34, one to four previous births, smoking during pregnancy, an ARIA index of five and had 'other' pre-existing medical conditions. For this set of characteristics, the overall probability of the onset of TPL can be estimated by

$$p = P(\text{TPL}{=}1 \mid \text{maternal characteristics}) = \frac{1}{1 + e^{-(-3.431+0.247+0.243+0.362)}} = 0.070$$

This probability is then apportioned to a weekly probability through the use of the estimated weekly onset distribution of TPL such that at 20 weeks of pregnancy, the probability of this patient having TPL is 0.0037. Since U = 0.454 > p = 0.0037, TPL was simulated not to occur in week 20 for this patient. The procedure illustrated for deciding whether or not the complication TPL occurs in week 20, is repeated for the other complications in that week. The probability of going into labour is determined last

given the complications that may have occurred. The pregnancy characteristics are not used to determine the probability of labour directly but their influence operates by their effects on the probability of a complication occurring. A random number is drawn to decide whether or not the patient goes into labour based.

The process is repeated for subsequent weeks. If a complication occurs, such as in week 37 where the patient had 'other' pregnancy complications, the probability of labour is estimated with the addition of the pertinent coefficient (1.12) for week 37. Thus

$$p = P(\text{Lab=1} \mid \text{pregnancy complications}) = \frac{1}{1 + e^{-(-3.01+1.12)}} = 0.131$$

The patient then retains this complication for the rest of their pregnancy, affecting all future probabilities. The outcome of the pregnancy simulation for this patient is that they had 'other' pregnancy complications occurring at week 37 and delivered at week 39.

These events were estimated from the MNS data, however, these data are cross-sectional and the pregnancy simulation model required the prediction of events on a weekly time scale. Therefore, the probability of events occurring from one week to the next are estimated by combining secondary data sources and transforming the prior incidence rates of the primary data to conditional probabilities given the outcomes of previous events. As such, the outcomes of the simulation model need to be calibrated and this was done by continuously comparing the observed rates with those simulated. When these rates did not agree, the conditional probabilities were adjusted empirically using the criterion of minimising the difference in major outcomes between observed and simulated values.

Table 4.2.3 - Maternal and clinical beta coefficients for predicting pregnancy complications

	Predictors									
Dependent	Constant	Age <19	Age 35+	P0	P5+	Smoking	ARIA 2	ARIA 3	ARIA 4	ARIA 5
TPL	-3.431	0.138	-	-	0.186	0.247	-	0.416	-0.171	0.243
PET	-3.542	-	0.354	1.044	-	-0.528	0.225	-	-	-
APH	-4.074	-	0.022	-	-	-	0.528	0.439	0.417	-
PROM	-2.904	-0.221	-0.123	0.153	-	0.121	-	-	-0.334	-
GDM	-2.647	-1.189	0.807	-0.250	0.273	-0.370	-0.354	-	-0.116	-
OTHER	-1.300	-	-	-	0.347	-	-	-0.121	-0.071	-0.238

	Predictors								
	Existing	Existing	Existing						
Dependant	Hypertension	Diabetes	Other	TPL	PET	APH	PROM	GDM	Other
TPL	-	0.701	0.362	-	-0.563	1.159	0.929	-	-
PET	1.754	1.213	0.623	-0.580	-	-	-	1.089	0.167
APH	-	0.014	0.349	1.260	-	-	-	-0.619	0.553
PROM	-	0.135	0.465	0.931	-0.412	0.846	-	-0.343	0.536
GDM	0.846	-	-	-	1.007	-	-	-	-
OTHER	0.739	0.906	0.857	-	0.200	0.495	0.554	0.167	-

Table 4.2.4 - Pregnancy complication coefficients for predicting the transition from pregnancy to labour

GA	Constant	TPL	PET	APH	PROM	GDM	Other
20	-10.09	8.51	-0.96	8.64	7.63	0.79	6.61
21	-9.88	7.92	-1.69	7.78	6.95	0.06	6.91
22	-6.93	4.49	3.02	3.43	3.17	-4.72	3.28
23	-9.79	7.13	6.41	6.08	5.94	-2.09	6.18
24	-8.03	4.78	3.91	4.14	4.04	1.06	4.04
25	-9.46	5.89	5.82	5.24	5.18	2.17	5.43
26	-7.75	4.14	4.21	3.50	3.48	0.06	3.58
27	-7.60	3.70	4.03	3.11	3.26	-0.36	3.12
28	-9.82	5.76	6.17	5.21	5.36	1.53	4.83
29	-6.10	2.41	3.07	1.90	2.06	-1.86	1.50
30	-6.15	2.80	3.93	2.38	2.57	-1.37	1.98
31	-5.61	1.77	2.93	0.69	1.60	-1.60	1.02
32	-5.53	2.21	3.16	1.18	2.12	-0.36	1.54
33	-5.04	2.19	2.75	0.90	2.43	-0.33	1.01
34	-4.57	2.30	2.65	0.93	2.55	0.84	1.09
35	-4.90	3.04	2.51	1.53	3.39	1.66	1.57
36	-3.32	2.32	1.94	0.68	2.14	0.94	0.83
37	-3.01	1.30	2.09	1.47	1.79	1.24	1.12
38	-1.72	1.27	1.54	0.76	1.01	1.22	0.81
39	-1.30	0.52	0.89	-0.10	0.84	1.30	0.59
40	1.13	0.49	0.26	-2.10	0.60	0.45	0.11
41	1.76	0.03	0.88	-7.86	7.72	0.72	-0.16

Table 4.2.5 - Example of simulating pregnancy for patient 20-34 years of age, 1-4 previous births, smoker, ARIA 5 and 'other' pre-existing medical conditions

GA		Initial Comps	TPL	PET	APH	PROM	GDM	Other	End Comps	P(Labour | Comp)
20	U		0.4540	0.7532	0.0497	0.7722	0.3125	0.0324		0.1990
	E(P)	None	0.0037	0.0004	0.0024	0.0098	0.0002	0.0206	None	<0.0001
	Outcome		0	0	0	0	0	0		0
21	U		0.7944	0.8489	0.5796	0.0397	0.9493	0.4309		0.5768
	E(P)	None	0.0037	0.0004	0.0020	0.0098	0.0002	0.0206	None	<0.0001
	Outcome		0	0	0	0	0	0		0
...										
37	U		0.3228	0.0714	0.4572	0.8811	0.8513	**0.0181**		0.4512
	E(P)	None	0.0000	0.0050	0.0007	0.0020	0.0007	**0.0197**	**Other**	0.1312
	Outcome		0	0	0	0	0	**1**		0
38	U		0.5267	0.2523	0.4379	0.9711	0.0153	0.9383		0.7975
	E(P)	**Other**	0.0000	0.0086	0.0006	0.0024	0.0000	0.0137	Other	0.2870
	Outcome		0	0	0	0	0	0		0
39	U		0.3201	0.7799	0.6845	0.4972	0.7732	0.9560		**0.0356**
	E(P)	Other	0.0000	0.0095	0.0006	0.0016	0.0000	0.0137	Other	**0.3296**
	Outcome		0	0	0	0	0	0		**1**

U = a random number $U \sim U(0,1)$. E(P) = expected probability of event occurring. Outcome = 1 if U < E(P), otherwise 0. Comps = Pregnancy Complications.

4.3 Goodness of Fit

The final data set included the simulation of 200,000 patients. This number of simulations was derived empirically by assessing the magnitude of the percentage difference in simulated outcomes upon successively increasing the number of generated patients. It was discovered that generating 200,000 patients would be sufficient to produce a consistent data set of outcomes. The difference in simulated outcomes between generating one million patients and 200,000 was on average less than a 0.1% change whereas, between 100,000 and 200,000 the difference could be up to 1%.

The outcomes of the pregnancy simulation model against the observed outcomes from the MNS data are presented in the following tables. Table 4.3.1 gives a validation of the generated maternal characteristics. It can be seen that almost half these outcomes are within one tenth of a percent difference and the largest difference of 0.6% is between the observed percentage of under 20 year olds living in ARIA 5 (70.0%) and simulated (70.6%).

Table 4.3.2 presents a validation of the rates of incidence of pregnancy complications stratified by maternal characteristics for the observed data against simulated. GDM by definition cannot occur in patients with pre-existing diabetes and this is reflected in the simulated data with an incidence rate of zero. The largest discrepancies occur in stratified groups where both the incidence of a complication and maternal characteristic are rare. For example, the age group of 35 and over represent only 6.1% of all ages and there is a difference of just over 2% between the observed rates of GDM with 13.6% and 'Other' complications with 30.4%, compared with the simulated rates of 11.4% and 28.0% respectively. However, almost half of the differences between observed and simulated values are within, at most, one tenth of a percent difference and over three quarters did not exceed half of a percent difference.

Comparisons between the observed and simulated number of pregnancy complications stratified by maternal characteristics are shown in Table 4.3.3. The overall percentage of the number of pregnancy complication for the simulated cohort agree with those observed with 60.7% having no pregnancy complications, 30.4% having one complication, 7.8% having two complications and 1.1% having three or more complications, compared with the observed values of 60.6%, 30.4%, 7.8% and 1.2% respectively. Overall, more than half of the stratified groups have a difference between

observed and simulated of less than or equal to half a percent, and just over three quarters did not exceed a one percent difference.

The validation of the GA range at labour stratified by maternal characteristics is shown in Table 4.3.4. The variation between observed and simulated values is largest in the pre-existing medical conditions of hypertension and diabetes, with a difference of 4.5% for hypertension in the GA at labour of between 37 and 40 weeks, where the observed percentage is 62.4% and the simulated is 66.9%, and a difference of 8% for diabetes in the GA range at labour of 41 weeks and over, where the observed percentage was nil and the simulated percentage was 8%. These large variations occur due to the small incidence of hypertension (1.0%) and diabetes (1.3%) in the data. The variations over all the stratified groups are minimal with approximately two thirds of the groups having a difference between observed and simulated vales of less than or equal to half a percent, and over four fifths have a difference of, at most, one percent.

Table 4.3.5 shows the similarity between the observed GA range of labour stratified by pregnancy complication and that simulated. The variation in simulated against observed values is expected to be larger than for previous indicators as the outcome of labour at a particular GA for a given complication required calibration of the rates of different data sets simultaneously. However, the difference between the values simulated and those observed were sufficiently small with over two thirds of the stratified groups not exceeding a one percent difference. The largest variations occurred in APH, which also had the lowest rate of incidence (2.7%), with 10.5% difference at the GA at labour of between 37and 40 weeks and 11.3% at the GA at labour of 41 weeks or more. This is not of great concern however, as labour at any time term leads to greater health outcomes for the baby compared with those delivered preterm. The difference between the observed percentages of mothers going into labour with APH at term (51.4% + 3.9% = 55.3%) compared to those simulated (40.9% + 15.2% = 56.1%) is only 0.8%.

Most variation between observed and simulated values occurred for rare events and particularly when stratified by other rare events, such as complications stratified by the age group of 35 years and over. This is due to the low number of cases available for analysis in the observed data leading to differences between other groups not being significant, in which case an average rate was assumed.

Table 4.3.1 - Validation of simulated pregnancy characteristics stratified by age groups

Maternal	Observed age group (%)				Simulated age group (%)			
Characteristic	<20	20-34	35+	**Overall**	<20	20-34	35+	**Overall**
P0	71.6	15.3	6.9	**28.3**	71.6	15.3	7.0	**28.3**
P1-4	28.4	75.1	53.3	**62.6**	28.4	75.1	53.6	**62.6**
P5	0.0	9.6	39.8	**9.1**	0.0	9.6	39.4	**9.1**
Smoking	48.8	52.7	50.3	**51.6**	48.6	52.7	50.4	**51.7**
ARIA 2	7.1	9.9	11.6	**9.3**	6.8	9.8	11.2	**9.2**
ARIA 3	19.2	21.6	18.6	**20.9**	18.9	21.5	18.9	**20.7**
ARIA 4	3.7	5.0	4.3	**4.7**	3.7	4.8	4.1	**4.5**
ARIA 5	70.0	63.4	65.5	**65.1**	70.6	63.9	65.8	**65.6**
Hypertension	0.3	1.0	3.6	**1.0**	0.3	1.0	3.5	**1.0**
Diabetes	0.3	1.3	6.2	**1.3**	0.3	1.3	5.9	**1.3**
Other	16.8	19.0	23.7	**18.8**	16.6	19.1	24.2	**19.1**
Overall	**24.0**	**69.9**	**6.1**	**100.0**	**24.0**	**69.9**	**6.1**	**100.0**

Table 4.3.2 – Validation of simulated incidence of pregnancy complication stratified by maternal characteristics

Maternal	Observed pregnancy complication (%)						Simulated pregnancy complication (%)					
Characteristic	TPL	PET	APH	PROM	GDM	Other	TPL	PET	APH	PROM	GDM	Other
Age <20	5.7	6.2	2.6	6.8	1.5	23.4	5.9	6.4	2.6	6.8	1.5	22.3
Age 20-34	5.5	4.3	2.9	7.6	5.4	23.7	5.5	4.3	2.7	7.7	5.3	24.0
Age 35+	5.9	7.7	3.0	7.2	13.6	30.4	5.9	7.0	3.0	7.2	11.4	28.0
P0	5.2	8.3	2.6	7.4	2.8	23.8	5.7	8.3	2.7	7.5	2.7	23.1
P1-4	5.5	3.6	2.8	7.2	5.4	23.1	5.5	3.6	2.7	7.4	5.2	23.3
P5	6.8	3.9	3.3	8.2	9.0	30.9	6.3	4.2	2.8	7.5	8.1	29.9
Smoking	6.7	3.5	2.8	8.0	4.4	23.8	6.3	3.6	2.8	7.9	4.0	23.8
ARIA 2	4.6	5.7	4.1	7.8	4.1	28.4	4.5	5.7	3.8	7.8	3.7	27.1
ARIA 3	6.6	4.9	3.7	6.9	5.3	25.3	6.8	5.2	3.6	7.8	5.0	25.4
ARIA 4	3.6	4.3	3.6	5.5	4.6	25.9	3.7	4.4	3.7	5.5	4.6	25.2
ARIA 5	5.5	4.8	2.3	7.7	5.1	22.8	5.6	4.9	2.2	7.3	4.8	22.7
Hypertension	5.6	27.2	3.2	7.2	18.4	44.8	5.7	27.5	4.5	8.3	17.6	44.8
Diabetes	11.1	16.4	4.1	11.1	-	50.3	9.1	16.4	3.6	11.4	0.0	50.2
Other	7.7	8.2	4.3	11.3	5.5	39.3	7.4	8.4	4.1	11.0	4.9	39.3
Overall	**5.6**	**4.9**	**2.9**	**7.4**	**5.0**	**24.0**	**5.6**	**5.0**	**2.7**	**7.4**	**4.8**	**23.8**

Table 4.3.3 - Validation of number of pregnancy complications stratified by maternal characteristics

Maternal	Observed number of pregnancy complications (%)				Simulated number of pregnancy complications (%)			
Characteristic	0	1	2	3+	0	1	2	3+
Age < 20	62.2	30.3	6.6	0.8	63.0	29.4	6.9	0.8
Age 20-34	60.9	30.2	7.6	1.3	60.6	30.4	7.8	1.2
Age 35+	50.8	33.2	13.5	2.4	52.2	34.8	11.1	1.9
P0	60.0	31.1	7.7	1.1	60.5	30.4	8.0	1.1
P1-4	61.9	29.7	7.3	1.1	61.7	29.9	7.3	1.1
P5	53.7	33.2	10.8	2.3	54.2	34.3	9.8	1.7
Smoking	61.0	30.1	7.7	1.2	61.0	30.4	7.5	1.1
ARIA 2	58.6	29.8	9.8	1.8	58.4	31.8	8.6	1.2
ARIA 3	58.7	31.7	8.0	1.6	57.8	31.8	9.0	1.5
ARIA 4	60.8	31.8	6.5	0.9	60.9	31.0	7.1	1.0
ARIA 5	61.5	29.9	7.5	1.1	61.9	29.8	7.3	1.0
Hypertension	29.6	39.2	27.2	4.0	27.9	42.6	23.2	6.3
Diabetes	34.5	40.4	22.2	2.9	33.4	47.2	17.4	2.1
Other	43.9	39.2	13.9	3.0	43.5	40.0	13.9	2.5
Overall	**60.6**	**30.4**	**7.8**	**1.2**	**60.7**	**30.4**	**7.8**	**1.1**

Table 4.3.4 - Validation of GA ranges at delivery stratified by maternal characteristics

Maternal	Observed GA ranges at delivery (%)						Simulated GA ranges at delivery (%)					
Characteristic	20-21	22-27	28-32	33-36	37-40	41+	20-21	22-27	28-32	33-36	37-40	41+
Age <20	0.5	1.5	2.4	9.8	76.2	9.4	0.5	1.7	2.5	9.6	77.1	8.7
Age 20-34	0.4	1.3	2.0	10.1	77.9	8.4	0.4	1.3	2.0	10.0	77.5	8.8
Age 35+	0.9	1.8	2.8	9.7	77.3	7.5	1.1	2.1	2.5	10.3	75.6	8.4
P0	0.6	1.5	2.3	9.3	75.2	11.2	0.6	1.5	2.5	10.1	76.9	8.3
P1-4	0.4	1.4	2.1	10.2	78.5	7.4	0.4	1.4	2.0	9.8	77.4	9.0
P5	0.3	1.1	1.7	10.6	77.1	9.1	0.4	1.4	1.7	10.2	77.4	8.9
Smoking	0.4	1.4	1.4	11.0	76.9	8.0	0.5	1.4	2.1	10.4	77.2	8.4
ARIA 2	0.6	2.0	2.1	10.1	76.9	8.3	0.7	1.7	2.4	10.0	76.4	8.9
ARIA 3	0.3	1.3	2.3	9.9	77.2	9.0	0.3	1.4	2.4	10.6	76.8	8.6
ARIA 4	1.0	1.4	2.4	9.6	76.4	9.2	1.1	1.6	2.0	8.8	77.2	9.4
ARIA 5	0.4	1.3	2.0	10.0	77.7	8.5	0.5	1.4	2.0	9.8	77.6	8.8
Hypertension	-	4.8	9.6	19.2	62.4	4.0	1.0	4.1	5.4	15.6	66.9	7.0
Diabetes	-	4.1	7.0	28.7	60.2	-	1.0	4.4	5.1	17.7	63.8	8.0
Other	0.3	2.3	4.2	14.7	70.8	7.6	0.2	2.5	3.9	13.2	72.0	8.1
Overall	**0.4**	**1.4**	**2.1**	**10.0**	**77.4**	**8.6**	**0.5**	**1.4**	**2.1**	**9.9**	**77.3**	**8.8**

Table 4.3.5 - Validation of GA ranges at delivery stratified by pregnancy complication

Pregnancy	Observed GA ranges at delivery (%)						Simulated GA ranges at delivery (%)					
Complication	20-21	22-27	28-32	33-36	37-40	41+	20-21	22-27	28-32	33-36	37-40	41+
TPL	1.7	6.2	7.3	34.2	47.8	2.0	1.3	5.4	7.3	36.4	46.9	2.6
PET	-	2.1	8.1	19.9	65.1	4.8	0.0	4.9	8.9	14.1	65.1	7.0
APH	3.4	11.8	7.0	22.5	51.4	3.9	2.2	11.5	7.9	22.2	40.9	15.2
PROM	1.9	5.5	9.9	36.8	43.7	2.2	1.4	4.5	8.6	39.9	43.3	2.4
GDM	-	0.5	1.9	14.8	78.8	4.1	0.0	0.9	2.5	13.5	79.6	3.4
Other	0.8	3.3	4.8	18.3	67.5	7.3	0.8	3.1	4.8	16.9	67.0	7.4
Overall	**0.4**	**1.4**	**2.1**	**10.0**	**77.4**	**8.6**	**0.5**	**1.4**	**2.1**	**9.9**	**77.3**	**8.8**

5 Discussion

The objective of the simulation was to generate a large cohort of aboriginal women whose pregnancy outcomes reflect the observed rates of pregnancy outcomes in Aboriginal women residing in rural and remote regions of WA. The validation tables indicate that the methods used to do this were appropriate as the simulated values are very close to those observed, allowing the simulation model to be used confidently as the mathematical representation part of a decision analytic model to evaluate the hypothesised changes in maternity care practices.

The pregnancy simulation model takes a lot of factors into account and appears to be the largest simulation model in terms of scope and complexity than those that were discussed in the literature. Outcomes can be simulated for a strata of 576 combinations of maternal characteristics given there are three age groups, three parity groups, smoking during pregnancy or not, four ARIA regions, and the possibility of having different combinations of three pre-existing medical conditions (3 x 3 x 2 x 4 x 2 x 2 x 2 = 576). The benefit of this is that any of these maternal characteristics can be adjusted and the difference in simulated pregnancy outcomes can be examined. For example, the average age of first time mothers has been seen to be increasing and by adjusting the percentage of patients with no previous births for the older age groups, changes in outcomes can be predicted for a cohort of Aboriginal women by running a new simulation of pregnancy events with this adjustment.

Another advantage of simulating pregnancy outcomes based on a large combination of maternal characteristics is that analysis of different subgroups can be undertaken. This will be of particular use when costs and changes in antenatal care practices are applied to the pregnancy simulation model. One could investigate the incremental cost-effectiveness of these changes in practices and identify subgroups of Aboriginal women for which the changes may not be cost-effective, thereby giving motivation to investigate further improvements in health care policies specific to this group.

The disadvantage to basing the pregnancy model on such a large range of maternal characteristics is that model calibration is an extremely time consuming process. It can be seen from the various tables of simulated results against observed that there are many stratified groups that need to be accessed when an adjustment in rates are made. These adjustments often cause a chain of other groups to be affected along with the group that

may have called for the initial adjustment. This flow on effect of changes can be predicted after some experience in calibrating the model.

The pregnancy simulation model also has some limitations in respect to the validity of results simulated for stratified outcomes in which there are rare, or sometimes no, observed cases. In these situations, the true rate of incidence cannot be accurately estimated. However, there are very few stratified groups with this problem and most provide an accurate simulation of pregnancy outcomes.

Appendix

The MLE of the coefficients of the logistic equation can be solved using the Newton-Raphson method.

First recall, the group of N subjects, each with a set of j covariates $X_i = (x_{i1}, \dots, x_{ij})$ and a dichotomous outcome variable $Y_i \in \{0, 1\}$. Also

$$p_i = P(Y_i = 1 \mid X_i) = \frac{1}{1 + e^{-(\beta' X_i)}}$$

with parameters $\beta' = (\beta_1, \beta_2, \dots, \beta_j)$.

To simplify calculations, it is convenient to aggregate the data such that each row represents one distinct combination of values of the covariates. These rows can be referred to as populations (Czepiel, n.d.). Therefore, redefine N to represent the total number of populations and let n be a column vector with elements n_k representing the number of observations in population k for $k = 1$ to N. Let the column vector y contain elements y_k representing the observed frequency of the number of outcomes equal to one for each population. Let p_k be a column vector of length N with elements $p_k = P(y_k = 1 \mid k)$, the probability that $y_k = 1$ for any given observation in the k^{th} population. Also, let X be a matrix of N rows and J columns such that each population k has a set of j covariates. Lastly, let

$$p_k = P(y_k = 1 \mid X_{kj}) = \frac{1}{1 + e^{-(\sum_{j=0}^{J} \beta_j X_{kj})}} = \frac{e^{\eta_{kj}}}{1 + e^{\eta_{kj}}}$$

where $\eta_k = \sum_{j=0}^{J} \beta_j X_{kj}$.

The goal is to estimate the K unknown parameters β with maximum likelihood estimation which involves finding the set of parameters for which the probability of the observed data is greatest. For this, as presented by SPSS (2006), the likelihood function to estimate the βs for the logistic model is

$$l(\beta) = \prod_{k=1}^{N} {p_k}^{n_k y_k} (1 - p_k)^{n_k (1 - y_k)}$$

and it follows that the logarithm of $l(\beta)$ is

$$L(\beta) = \ln\left(l(\beta)\right) = \sum_{k=1}^{N} (n_k y_k \ln(p_k) + n_k(1 - y_k)\ln\left(1 - p_k\right))$$

Through calculus, the critical points of $L(\beta)$ can be found by setting the first derivative with respect to each β equal to zero. To evaluate the first derivative, it can first be shown

$$\frac{\partial \eta_k}{\partial \beta_j} = \frac{\partial}{\partial \beta_j}\left(\sum_{j=0}^{J} \beta_j X_{kj}\right) = X_{kj}$$

and since

$$p_k = \frac{e^{\eta_{kj}}}{1 + e^{\eta_{kj}}}$$

we have

$$e^{\eta_{kj}} = \frac{p_k}{1 - p_k}$$

Differentiating with respect to β_j then

$$\frac{\partial p_k}{\partial \beta_j} = \frac{\partial}{\partial \beta_j}\left(\frac{e^{\eta_{kj}}}{1 + e^{\eta_{kj}}}\right)$$

$$= \frac{\frac{\partial \eta_k}{\partial \beta_j} e^{\eta_{kj}}(1 + e^{\eta_{kj}}) - \frac{\partial \eta_k}{\partial \beta_j} e^{\eta_{kj}} e^{\eta_{kj}}}{(1 + e^{\eta_{kj}})^2}$$

$$= \frac{\frac{\partial \eta_k}{\partial \beta_j} e^{\eta_{kj}}}{(1 + e^{\eta_{kj}})^2}$$

$$= X_{kj} p_k \frac{1}{1 + e^{\eta_{kj}}}$$

$$= X_{kj} p_k \frac{1}{1 + \frac{p_k}{1 - p_k}}$$

$$= X_{kj} p_k (1 - p_k)$$

therefore

$$\frac{\partial l(\beta)}{\partial \beta_j} = \frac{\partial}{\partial \beta_j}\left[\sum_{k=1}^{N}(n_k y_k \ln(p_k) + n_k(1-y_k)\ln(1-p_k))\right]$$

$$= \sum_{k=1}^{N}(n_k y_k \frac{1}{p_k}\frac{\partial p_k}{\partial \beta_j} - n_k(1-y_k)\frac{1}{1-p_k}\frac{\partial p_k}{\partial \beta_j})$$

$$= \sum_{k=1}^{N}(n_k y_k \frac{1}{p_k} X_{kj} p_k(1-p_k) - n_k(1-y_k)\frac{1}{1-p_k} X_{kj} p_k(1-p_k))$$

$$= \sum_{k=1}^{N}(n_k y_k X_{kj}(1-p_k) - n_k(1-y_k) X_{kj} p_k)$$

$$= \sum_{k=1}^{N}(n_k X_{kj}(y_k - y_k p_k - p_k + y_k p_k))$$

$$= \sum_{k=1}^{N}(n_k X_{kj}(y_k - p_k))$$

The critical point will be a maximum if the matrix of second partial derivatives is negative definite; that is, if every element on the diagonal of the matrix is less than zero. Therefore

$$\frac{\partial^2 l(\beta)}{\partial \beta_j \partial \beta_{j'}} = \frac{\partial}{\partial \beta_{j'}}\sum_{k=1}^{N}(n_k X_{kj}(y_k - p_k))$$

$$= \frac{\partial}{\partial \beta_{j'}}\sum_{k=1}^{N}(n_k X_{kj} y_k - n_k X_{kj} p_k)$$

$$= -\sum_{k=1}^{N} n_k X_{kj'}\frac{\partial p_k}{\partial \beta_j}$$

$$= -\sum_{k=1}^{N} n_k X_{kj'}(X_{kj} p_k(1-p_k))$$

Therefore, given n_k, X_{kj} and p_k all contain positive elements, the critical point is guaranteed to be the global maximum.

Setting the partial derivatives of the log likelihood equation $L(\beta)$ equal to zero results in a system of J non-linear equations with J unknown variables. The solution to this system is a vector with elements, β_j. However, given the equations are non-linear, the Newton-Raphson method is applied. This method, as described by (Hughes-Hallet et al, 2005), is to solve the equation $f(x) = 0$, by choosing an initial estimate x_0 and computing the sequence x_1, x_2, x_3 ... using the rule

$$x_{n+1} = x_n - \frac{f(x_n)}{f'(x_n)}$$

For the MLEs, the solution to $f(x) = \frac{\partial l(\beta)}{\partial \beta_j} = 0$ is required. Thus, let $\beta^{(s)}$ represent the vector of initial approximations for each β_j, then the first step of Newton-Raphson method can be expressed as

$$\beta^{(s+1)} = \beta^{(s)} + \left[-\frac{\partial^2 l(\beta^s)}{\partial \beta_j \partial \beta_{j'}}\right]^{-1} \cdot \frac{\partial l(\beta^s)}{\partial \beta_j}$$

The algorithm continues until it converges to the actual solution or the difference between $\beta^{(s+1)}$ and $\beta^{(s)}$ is less than some predetermined tolerance level.

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