**Risk Assessment of
Necrotizing Enterocolitis in NICU**

by

Irena Zamboni

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Abstract

Increase in infant survival rates has resulted in an increase of numerous medical complications, such as *necrotizing enterocolitis* (NEC): “acute, self-limiting, inflammatory bowel disease of premature infants of unclear pathogenesis” (Di Lorenzo, 2000).

In order to assist the medical professionals in diagnosis of NEC, this research focuses on three populations of interest to NEC: total neonatal population, very-low-birth-weight and gestation age less than 33 weeks. To obtain the minimum data sets for NEC, the performance of two classifiers was assessed: MIRG’s ANN RFW tool as well as the LIBSVM tool.

The minimum data sets found for the three NEC models were all unique. The ANN RFW performance was superior for NEC modeling in comparison to the SVM tool, which had performance issues when classifying minority cases. This suggests that data resampling should be considered for other data mining tools as it increases classifier performance.

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— 21 —

“We are drowning in information but starved for knowledge.”

~ John Naisbitt ~

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Glossary (definitions)

ANN: Artificial Neural Network

ANN RFW: Artificial Neural Network Research Framework (tool developed by MIRG)

APGAR: Appearance, Pulse, Grimace, Activity, and Respiration score

BPD: Bronchopulmonary dysplasia

C-SVC: C Support Vector Classification

CBR: Case-Based Reasoner

CDSS: Clinical Decision Support System

CHEO: Children's Hospital of Eastern Ontario

CNN: Canadian Neonatal Network

CRIB: Clinical Risk Index for Babies

IR: Infrared Imaging

IVH: Intraventricular hemorrhage

k-NN: k-Nearest Neighbour algorithm

LIBSVM: Library for Support Vector Machines

MIRG: Medical Information technologies Research Group

NEC: Necrotizing enterocolitis

NICU: Neonatal Intensive Care Unit

NTISS: Neonatal Therapeutic Intervention Scoring System

RBF: Radial Basis Function

SNAP: Score for Neonatal Acute Physiology

SNAPPE: Score for Neonatal Acute Physiology Perinatal Extension

SVM: Support Vector Machine

1 INTRODUCTION

1.1 Motivation and Significance of Research

Motivation and significance of this research stems from two equally important perspectives: medical and technical.

From the medical perspective, data collection from patients admitted to a hospital can aid both medical professionals and administration staff. Medical professionals can use previously collected data to analyze trends in medical conditions. Applying this knowledge to patients exhibiting similar symptoms, healthcare staff can act quickly in providing appropriate medical care. With regards to the hospital administrative staff, analysis of patient data can help the hospital in terms of their resource allocations and budget assignments, including equipment management and staff. This is extremely valuable as different hospitals tailor to different patient types and specialize in particular health care divisions; ex. neonatal health, oncology centres etc. Analyzing yearly trends, and even monthly or daily trends, can help hospital administration determine the number of beds it needs to have, specialty units, other equipment resources, and medical staff.

From the technical perspective, in order to assist medical staff and hospital administration in analyzing trends in data and making decisions in a timely manner, data mining tools have come into play. Improvements in computer technology drive the goal to integrate data mining tools with the Clinical Decision Support Systems (CDSSs) so that they may be of use to medical staff in the near future. Medical Information technology Research Group (MIRG) uses the Artificial Neural Network Research Framework Tool (ANN RFW) as the base of its CDSS. MIRG uses the ANN RFW to

find trends in medical data and develop prediction models for medical outcomes such as mortality, bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), length of stay (LOS) and length of ventilation (LOV).

With strong medical and technical perspectives, this thesis looks at an additional medical complication in order to enrich the current MIRC ANN RFW tool: necrotizing enterocolitis (NEC). Understanding the NEC medical problem, as described in section 1.2, is necessary to fully comprehend the choice of models examined in this thesis.

1.2 Medical Impact

Necrotizing enterocolitis, *NEC*, is the most common neonatal gastrointestinal (GI) emergency (Lin & Stoll, 2006), (Panigrahi, 2006). It is a medical complication that has puzzled healthcare professionals for decades, all the while bolstering its ‘enigmatic’ reputation due to intriguing and complex interaction of many physiological factors. Since the disease causes portions of the bowel to undergo necrosis, i.e. tissue death, medical literature occasionally refers to it as intestinal or bowel gangrene (Gupta, Burke, & Herson, 1994). Even more alarming is the fact that although medical and surgical techniques are making great advances, in the last few decades mortality and morbidity due to NEC remain high or have been increasing (Panigrahi, 2006). The increase in NEC over the decades is attributed partially to the increase in the number of low birth babies that are surviving due to significant advances in medical technology. A brief overview of history, epidemiology and pathogenesis, diagnosis, management and prognosis, and the populations of interest for NEC are covered.

1.2.1 History and Epidemiology

The earliest accounts of NEC medical literature dates back to 1888, when Paltauf reported clinical and pathological findings of what is considered consistent with NEC today, along with Generisch in 1891 and the report of abdominal distension in a 45-hour-old neonate (Panigrahi, 2006). Furthermore, Panigrahi (2006) reports that although NEC was reported in medical literature over the span of the century, it was not accepted as a 'distinct disease entity' until the 1950s, and it was not until the late 1960s and early 1970s that it attracted the attention of surgeons, pathologists and physicians. Medical literature also recognizes the fact that because of the wider recognition of this devastating medical complication, and an increase of preterm birth survivals, NEC has become a serious medical challenge and problem worldwide (Panigrahi, 2006).

Medical experts agree on the fact that NEC has a very complex and multifactorial pathogenesis (McAlmon, 2004), (Kling & Hutter, 2003). Studies of the disease indicate that it varies from centre to centre and from year to year, and that there are endemic (regional) and epidemic (widespread) occurrences of it (Luig & Lui, 2005a). It is estimated that anywhere between 0.3 to 2.4 cases occur in every 1,000 live births; more particularly with NEC occurring in 2 to 5% of all NICU admissions and 5 to 10% of VLBW infants (McAlmon, 2004). In an attempt to identify risk factors related to NEC, several clinical studies show that two risk factors in particular lead the increased predisposition to development of NEC because of the immaturity of the gastrointestinal tract – prematurity and low birth weight (LBW). As such, gestational age and birth weight are important determinants of mortality risk in NEC (Di Lorenzo, 2000). Characteristics set the mean gestation age of onset at between 30 – 32 weeks;

approximately 10% of infants are full-term; mean age at onset is 12 days, while mode is 3 days; approximately 90% of infants have been fed prior to disease onset (McAlmon, 2004). According to McAlmon (2004), infants exposed to cocaine are also up to 2.5 times at an increased risk of developing NEC because “the vasoconstrictive and hemodynamic properties of cocaine may promote intestinal ischemia”, resulting in severe intestinal gangrene, perforation and mortality. Even more staggering are mortality statistics of NEC, regardless of medical or surgical interventions: 9 – 28%; with the mortality of infants weighing less than 1,500g being up to 45% (McAlmon, 2004).

1.2.2 Diagnosis

As NEC outcome depends significantly on the time of diagnosis, the earlier that the detection and diagnosis, the better the chance of survival and prognosis. McAlmon’s (2004) summary of clinical characteristics as well as laboratory and radiographic features used for NEC diagnosis can be seen in appendix A, table A-1. There is no single NEC-specific test for diagnosis.

Of the various clinical and laboratory features used in diagnosis of NEC, there are also additional medical features that are not NEC specific. These are used in what is known as ‘differential diagnosis’. The differential diagnosis characteristics that can be potentially helpful in diagnosing NEC are the presence of sepsis and feeding intolerance. Presence of blood in the stool can also often be an indication of an ulcer or other medical problems, not just NEC.

However, the most important diagnostic tool is the imaging modality – abdominal radiography (X-ray) (Epelman et al., 2007). Abdominal radiographs are normally taken at times of acute clinical deterioration every 12 to 24 hours, or once NEC

has been diagnosed, as often as necessary. Two images are usually obtained: a supine image with a vertical beam (patients are flat on their back), and a cross-table lateral image with a horizontal beam, due to concerns of bowel perforations which usually occur within 48 hours of NEC onset (Epelman et al., 2007), (Buonomo, 1999). Although the background of X-ray technology is beyond the scope of this thesis, it is important to note that “excessive number of exposures or very long fluoroscopic times can subject the patient to high exposures [radiation dosages], and the risk versus benefit of the procedure must be considered” (Siedband, 1998). The U.S. Food and Drug Administration (FDA) Center for Device and Radiological Health (CDRH) suggests that X-ray risks with respect to X-ray’s ionizing radiation and harm to living tissues are the following (CDRH, 2008), (Center for Devices and Radiological Health (CDRH), 2008):

1. increase in possibility of patient developing cancer later in life
 - i. risk of cancer increases with larger doses and number of X-ray exams a patient undergoes
 - ii. risk of cancer is larger for patients undergoing X-ray at a younger age
(*ex. babies imaged for NEC*)
 - iii. risk of cancer is larger for women than men
2. cataracts and skin burns (at higher levels of radiation exposure)

Therefore, there is a need for a medical imaging modality that would decrease the risks presented by X-ray imaging, but at the same time be as effective, if not better, at detecting NEC in babies.

Using clinical, laboratory and radiographic features and findings, NEC is further categorized by the ‘Bell Staging Criteria’ (Bell et al., 1978), (Panigrahi, 2006). Babies suspected of NEC are considered Stage I, definite NEC is considered Stage II and advanced NEC (severe abdominal inflammation or perforated bowels) is Stage III. More information about the Bell Staging Criteria can be found in appendix A, table A-2.

1.2.3 Management and Prognosis

NEC is not a simple disease to diagnose. Medical professionals attempt to tackle NEC by trying to diagnose it in its early stage (Stage I), and by taking precautions early on with the population of babies who are at an increased risk of developing it, more specifically premature infants. Constant monitoring of the respiratory function, along with cardiovascular and metabolic function is done for babies suspected of NEC. In addition babies are placed on ‘NPO’ orders (Latin nil per os, or nothing-by-mouth) (Martin & Simone, 2006). As McAlmon (2004) suggests, “therapy is based on intensive-care measures and the anticipation of potential problems”, and the preferred method of treatment is through medication as opposed to surgical intervention that is required for severe cases. This is because surgical cases and “those with Stage II B and Stage III have a higher incidence of growth delay”, as well as being at an increased risk of morbidity and mortality due to infection, respiratory failure, short-bowel syndrome (if parts of intestine were removed due to NEC) among other risks (McAlmon, 2004).

1.2.4 Populations of interest for NEC

In order to understand the complex variable relationships in NEC, medicine focuses research interests on two populations: full-term or near-term infants and

premature ones, more specifically those born before 33 weeks of gestation and those weighing less than 1500g.

1.2.4.1 NEC in full-term or near-term infants

Unlike the very premature infants, term infants have considerably more mature intestinal and immune systems. Literature review confirms that only a few studies have focused particularly on the larger newborns with NEC. Furthermore, the studies suggest that factors that might place full-term infants at risk of NEC include “exchange transfusion, perinatal asphyxia, maternal preeclampsia, smallness for gestational age, polycythemia, respiratory distress and hypoglycaemia” (Martinez-Tallo, Claure, & Bancalari, 1997). In a retrospective study of hospital records at the Jackson Memorial Hospital between January 1, 1990 and December 31, 1993 (average delivery of 10,828 deliveries annually), Martinez-Tallo et al. (1997) found that the ‘most striking’ factors that may set larger infants at risk for NEC are: hypoglycaemia, asphyxia, respiratory problems, CHD (congenital heart disease), exchange transfusion, chorioamnionitis and prolonged rupture of membranes. In addition, the mean age of onset for the group from this study was recorded to be 3.25 days, with gestational age in weeks 38.08 $\pm$ 2.28, and birth weight of 2,668 $\pm$ 718g.

1.2.4.2 NEC in premature infants

Hallstrom et al. (2003), (2006), also set out to identify laboratory findings predictive of necrotizing enterocolitis. While conducting an epidemiological study on a population of 117,892 newborns from the Tampere University Hospital (Finland), they found that 18.3% of the babies diagnosed with NEC were at less than 33 weeks of

gestation. Statistical analysis performed by the group further showed the day of onset of NEC symptoms to be 4, with gestational age in weeks 26 $\pm$ 2, and birth weight 952g $\pm$ 322.4g. From their study, the group found that metabolic acidosis, platelet count, blood glucose, leukocyte levels and pH were useful indicators of NEC in preterm infants (Hallstrom, Koivisto, Janas, & Tammela, 2006). In addition, according to Stall, as reported by (Di Lorenzo, 2000), case fatality rates for infants weighing less than 1500g range from 10-44%; and those infants weighing more than 2500g range from 0-20%". The mortality rate increases to 35-50% for infants weighing less than 1000g, and these NEC babies having serious long-term complications ranging from poor growth to poorer neuro-developmental outcomes (Luig & Lui, 2005b).

1.3 Problem Statement

In response to the variation of pathological signs and symptoms in NEC, there is a growing need to develop a risk assessment model or a scoring system tool that will allow doctors to detect NEC much earlier, and do so for different populations of interest. Combining the hidden and valuable relationships in the medical data that are not necessarily transparent to medical professionals, with the computational power of the ANN RFW data mining tool, the goal is to assist medical professionals in outcome prediction of NEC in the neonatal intensive care units (NICU). In addition, the predictive capabilities of the ANN RFW will be compared to another classifier – the Support Vector Machine (SVM).

1.4 Thesis Objectives

This thesis has 3 objectives:

- 1) Analyze the performance of MIRG's ANN RFW in prediction of NEC, by examining the relationships between variables in day 1 data and developing a day 1 model for NEC for the following populations:
 - a. Total Canadian Neonatal Network database
 - b. 2 risk group subsets of NEC
 - Babies weighing < 1500g (VLBW)
 - Babies with gestational age < 33 weeks
- 2) Analyze the performance of SVM in prediction of NEC, by examining the relationships between variables in day 1 data and developing a day 1 model for NEC for the following populations:
 - c. Total Canadian Neonatal Network database
 - d. 2 risk group subsets of NEC
 - Babies weighing < 1500g (VLBW)
 - Babies with gestational age < 33 weeks
- 3) Compare the predictive power of MIRG's ANN RFW tool to that of SVM for the outcome of NEC.

1.5 Thesis Outline

The scope of this research is covered in 5 chapters.

Chapter 1: Introduction covers significance and research motivation. In order to establish the problem statement and thesis objectives, a medical impact section is introduced to present the seriousness of the medical complication (NEC) of central interest to this research.

Chapter 2: Literature Review covers the concept of data mining in medicine, and looks at the current neonatal scoring models that are used in outcome prediction in medicine. The outcome prediction models cover basic modeling attempts of NEC as well. As part of Clinical Decision Support Tools, ANNs and SVMs are examined next. Lastly, the Canadian Neonatal Network (CNN) database used in this research is introduced along with a brief analysis of issues with respect to database preparation.

Chapter 3: Methodology covers steps taken in preparing the CNN database for modeling NEC. Dataset creation is covered for both the ANN RFW and SVM tool and is done for the 3 populations of interest: total database, VLBW and gestation age less than 33 weeks. The approach used in reaching the minimum data set is established for both tools used.

Chapter 4: Results and Discussion present the results obtained for all of the NEC models examined in this research. This is done for the ANN RFW tool as well as the SVM tool. Model comparison is also done between the tools with respect to their performance and minimum data sets.

Chapter 5 Conclusion summarizes the work and findings of this thesis and provides a summary of contributions to knowledge and future research. Future research is specifically aimed at NEC.

2 LITERATURE REVIEW

Vast amounts of data are collected daily. The overwhelming task is in maximizing the use of the available information and deriving meaning from it – knowledge discovery (KD). The concept of knowledge discovery and data mining (DM) is used hand-in-hand. Data mining is a rapidly growing discipline used in several fields of study: banking and finance, telecommunications, engineering, medicine, pharmacology and sciences (Klosgen & Zytchow, 2002). It is seen as “the process of discovering meaningful new correlations, patterns and trends by sifting through large amounts of data stored in repositories, using pattern recognition technologies as well as statistical and mathematical techniques” (Larose, 2005). Hand et al. (2001) also define data mining as “the analysis of (often large) observational data sets to find unsuspected relationships and to summarize the data in novel ways that are both understandable and useful to the data owner”. The process of data mining and knowledge discovery is often referred to as DMKD. Review of literature and relevant concepts focuses on data mining in medicine with regards to the neonatal severity of illness scoring systems and the use of Clinical Decision Support Systems (CDSSs). CDSSs of interest include the Artificial Neural Networks (ANNs) and Support Vector Machines as part of the data mining cycle. Data preparation for the data mining process is also discussed.

2.1 Data mining in medicine

With respect to the field of medicine, data mining shows remarkable promise. Health care facilities collect patient information on a daily basis, especially for critical patients such as those in the intensive care units. Data collected includes demographic

information, numerical measurements which include lab results and vital signs, as well as recorded signals such as ECG (electrocardiogram) and radiological images. This information is useful for several reasons (Cios & Moore, 2002), (Perreault & Metzger, 1999) :

1. It forms the basis of a patient's medical record history and legal record.
2. It supports communication between health care providers.
3. It identifies deviations from expected trends which is helpful in early diagnosis, as well as patient's prognosis.
4. It supports medical research: based on already existing cases, future cases exhibiting similar trends can be diagnosed.

In response to the complexity of data mining and the lack of a knowledge discovery procedure, in 1996 analysts representing DaimlerChrysler, SPSS and NCR developed a 6-stage standard DMKD process model that is industry-neutral, tool-neutral and application-neutral (Larose, 2005). Using the CRISP-DM model as foundation, Cios and Moore (2002) developed a supplementary data mining model applicable specifically to the field of medicine (figure 2.1).

Figure 2.1: The six-step DMKD process model (Cios & Moore, 2002)

The life cycle consists of 6 phases, which are adaptive and dependent on each other. ‘Adaptivity’ in this process means that the next phase in the sequence can, and does, depend on the outcome(s) associated with a preceding phase (Larose, 2005). The outer circle of the six-step model indicates that the solution to a problem is of iterative nature, as research problems often raise further questions of interest (Larose, 2005). Additional feedback loops to account for changes and decisions made in a particular step and their impact on later steps of the DMKD process (Cios & Moore, 2002).

When developing a DMKD model, it is essential that in the early stages of research emphasis be on *understanding the problem domain* and *data* steps of the cycle. This is followed by the labour intensive *data preparation* and *data mining* stages. To ensure that results obtained in the modeling stage are valid for the domain of interest, *evaluation of the discovered knowledge* evaluation is done next. The *evaluation* stage of the six-step DMKD would have to undergo a clinical study, similar to the one performed by Townsend (2007), where she conducted a survey and performed an analysis on physicians’ ability to accurately identify high, medium and low risk patients with respect to different medical outcomes. Once the results are validated by medical professionals through rigorous medical trials, deployment of the model would be considered (Dorling et al., 2005), (Garg et al., 2005). Cios and Moore have successfully applied their DMKD process model to several medical domains, in particular the automation of the cardiac SPECT (Single-Photon Emission Computer Tomography) diagnosis (Sacha, Cios, & Goodenday, 2000), (Kurgan, Cios, Tadeusiewicz R., Ogiela, & Goodenday, 2001).

2.2 Neonatal (Severity of Illness) Scoring Systems

In an effort to assess the illness severity of newborns, neonatal scoring systems are used extensively in neonatal intensive care units. Also known as neonatal illness/disease scoring systems, scoring systems are epidemiologic tools that attempt to standardize outcome comparison between heterogeneous groups of patients across different hospital environments (Dorling et al., 2005), (Dorling & Field, 2008). Relying on the physiological, demographic, and clinical data collected on newborns, the scoring systems are largely used for mortality and morbidity risk assessments, in addition to other group and individual predictions, as summarized in table 2.1.

Table 2.1: Research uses of predictive scores in neonatology (Dorling et al., 2005)

Group predictions	
1.	Comparing study groups for similarity of risk
2.	Auditing the severity of illness in different units
3.	Comparing performance of different units
4.	Determining trends in results over time
5.	Reviewing if infants are treated appropriately for risk (e.g. number of septic screens or ventilation days)
6.	Comparing rates of complications; are some preventable?
Individual predictions	
1.	Giving prognostic information
2.	Stratifying infants in trials (to ensure similarity of risk)
3.	Determining individual treatment

Of the several systems that are in use today, the most popular ones are the Apgar score, CRIB, NTISS, SNAP (SNAP-II, SNAPPE-II). Dorling et al. (2005) published a review of these systems in which the authors note that: “A balance needs to be drawn between a complex score including many variables, and therefore difficult to complete, and a simpler model that may be easier to use but not as accurate”. Although speaking with respect to morbidity, the authors point out that *no* score can fully quantify the complex factors that make up an infant’s outcome (Dorling et al., 2005).

2.2.1 The Apgar Score

Developed by Dr. Virginia Apgar in 1953, the Apgar Score is a method of evaluating a newborn's condition at birth (Apgar, 1953). It is based on five characteristics: skin colour, heart rate, reflex irritability, muscle tone and breathing. Physicians have adopted the acronym of 'APGAR': Appearance, Pulse, Grimace, Activity, and Respiration respectively. Scored between 0 (min) and 10 (max) and assessed at 1min and 5mins, Apgar score of less than 7 is often associated with a higher risk of mortality (Richardson, Corcoran, Escobar, & Lee, 2001). Out of the four scoring systems discussed, Apgar is the most subjective one, as it relies more on the opinions and assessment of the medical professional rather than being based on the physiological data. Appendix B shows how the Apgar score is calculated.

2.2.2 CRIB

The Clinical Risk Index for Babies, CRIB, is a mortality scoring system for infants born at less than 32 weeks of gestation or weighing less than or equal to 1500g. It is a logistic regression model where parameters are weighted according to their statistical relation to death (The International Neonatal Network, 1993). The development of the CRIB score was performed on data from four UK teaching hospital neonatal units between July 1st, 1988 and June 30th, 1990, on a total of 1548 infants. The score is based on data collected in the first 12 hours of admission for the following six variables: birth weight, gestational age, maximum and minimum fraction of inspired oxygen, maximum base excess and presence of congenital malformations (appendix B). The major advantage of CRIB is the ease of data collection necessary to calculate the score, which

approximately takes 5 minutes; in addition, since the CRIB score is determined in the first 12 hours of life, it is less susceptible to treatment effects compared to other models (Dorling et al., 2005).

Since its original development, CRIB has undergone modifications: CRIB II (Parry et al., 2003). The new model uses a grid system (appendix B) predicting mortality by gestational age along with birth weight, in addition to admission temperature and base excess. The intent is to improve predictions for very premature babies and to exclude variables that are influenced by the primary care provider (Dorling et al., 2005).

2.2.3 NTISS

The Neonatal Therapeutic Intervention Scoring System, NTISS, was created by modifying the existing adult-version TISS (Cullen, Civetta, Briggs B.A, & Ferrara, 1974), and making it suitable for neonatal intensive care (Cullen et al., 1974), (Gray, Richardson, McCormick, Workman-Daniels, & Goldmann, 1992). There are 62 NTISS variables, for which the scores are assigned from 1 to 4 with respect to various intensive care therapies. Gray et al. (1992) found that for the 1643 newborns in their study, between November 1st, 1989 to September 30th, 1990, independent of birth weight, NTISS was a valid measure of neonatal illness severity and resource utilization (Gray et al., 1992). Appendix B shows how the NTISS score is calculated. Unlike other scoring systems, NTISS is based on the treatments received by an infant rather than the measure of physiological factors (Dorling et al., 2005).

2.2.4 SNAP

Unlike the CRIB scoring system, the Score for Neonatal Acute Physiology (SNAP) can be used on all admissions regardless of gestation age or birth weight. SNAP, developed by Richardson et. al (1993), uses 26 variables as outlined in appendix A, for which data is collected in the first 24 hours. Ideally, SNAP's intent is to "score the worst physiologic derangements in each organ system in the first 24 hours" (Richardson et al., 1993). However, the drawbacks of the initial SNAP scoring system is the large number of variables (26) that it needs for calculations, which increases its complexity. Also, the variables are assigned a weight of 0, 1, 3 or 5, as predetermined by expert opinion (Dorling et al., 2005). An additional drawback noted by Dorling et. al (2005) suggests that because the original SNAP model was derived from a population with a very low number of VLBW babies, it has a reduced sensitivity to differences between the most premature infants. Richardson et. al also confirmed this drawback (1993).

In order to compensate for its drawbacks, Richardson et. al. added three more variables to the SNAP model (Perinatal Extension variables): birth weight, small for gestational age (SGA) and 5min Apgar score. Using logistic regression the authors reduced the original SNAP variable set to include only 6 variables, thus developing SNAP-II and SNAPPE-II models as shown in appendix B (Richardson et al., 2001).

2.2.5 NEC Scoring Systems

Although attempts have been made to use scoring systems designed strictly for mortality for predictions of adverse medical outcomes such as chronic lung disease, research suggests that these models perform less well (Dorling et al., 2005). Ideally it

would be preferred if the same models that predict mortality could be used for other medical events; however, medical events are not governed by the same factors. This is not different for NEC. Two NEC risk assessment / scoring systems were found: NEC-Mortality Scoring System and Mathematical modeling in NEC.

2.2.5.1 Presurgical NEC-mortality scoring system

In response to the need of improving NEC outcome, Kessler et. al. (2006) set out to assess the relationship between early-laboratory parameters, disease severity, type of management (surgical or conservative) and outcome in necrotizing enterocolitis. The study includes neonate data collected between 1980 and 2002 at the University Children's Hospital in Mainz, Germany. The parameters recorded were: birth weight (BW), gestational age (GA), sex, type of treatment, severity of NEC (Bell staging criteria), pre-intervention blood parameters (blood cell counts, haemoglobin concentration, lactate, C-reactive protein) and survival (Kessler et al., 2006). Statistical analysis between the NEC and normal groups was done using unpaired t-test, where $p < 0.05$ was considered statistically significant. Table 2.2 summarizes statistical information for the 128 NEC babies eligible for the study.

Table 2.2: Statistical summary of Kessler et. al (2006) study

Birth weight (BW)	Sex
<ul style="list-style-type: none"> • Range: 450 – 3600g • Mean: 1507 +/- 64g 	<ul style="list-style-type: none"> • Male: 72 • Female: 56
Gestational age (GA)	Treatment
<ul style="list-style-type: none"> • Range: 23 to 41 weeks <ul style="list-style-type: none"> ○ 12 full term ○ 116 preterm • Mean: 31.0 +/- 0.4 weeks 	<ul style="list-style-type: none"> • Operative: 91 • Conservative: 37
Mean age of onset = 16.3 +/- 1.1 days	

In addition to comparisons between surgically treated and medically treated (conservative) infants, a comparison is done between NEC survivors and non-survivors. The findings are summarized in tables 2.3 and 2.4 respectively.

Table 2.3: Laboratory values, survival and NEC-score in operated and conservatively treated infants (Kessler et al., 2006)

<i>Parameter</i>	<i>Operated</i>		<i>Conservative</i>		<i>P-value</i>
	<i>N^a</i>	<i>Value</i>	<i>N^a</i>	<i>Value</i>	
Survival (%)	78	82.8	>0.05	-	-
Leukocyte count (x 10 ⁹ /l)	86	10.6 +/- 1.0	34	14.9 +/- 1.0	>0.05
Hemoglobin (g/l)	64	13.6 +/- 0.3	21	12.8 +/- 0.4	>0.05
Platelet count (x 10 ⁹ /l)	86	213 +/- 14	34	221 +/- 27	>0.05
CRP (mg/l)	85	46.8 +/- 4.4	33	43.6 +/- 8.1	>0.05
Lactate (mg/dl)	76	3.6 +/- 0.6	27	3.0 +/- 0.8	>0.05
**NEC-score (Table 2.5)	66	4.1 +/- 0.3	31	4.1 +/- 0.2	>0.05

^aN = number of patients for whom results are available, CPR=C-reactive protein

****NEC-score (Table 2.5)** – score calculated subsequent development of the scoring system

From table 2.3, it can be seen that the percentage of survivals did not differ between operated and conservatively treated babies. Of the parameters of interest, only the leukocyte counts differ significantly between operated and conservatively treated babies (Kessler et al., 2006). In conclusion, the model is not useful for prediction of babies that need operative versus those that need surgical treatment.

Table 2.4: Laboratory value, BW, GA and NEC-score in survivors and non-survivors (Kessler et al., 2006)

<i>Parameter</i>	<i>Survivors</i>		<i>Non-survivors</i>		<i>P-value</i>
	<i>N^a</i>	<i>Value</i>	<i>N^a</i>	<i>Value</i>	
BW (g)	103	1568 +/- 71	25	1199 +/- 125	<0.01
GA (weeks)	103	31 +/- 0.4	25	28.7 +/- 0.8	<0.0001
Leukocyte count (x 10 ⁹ /l)	96	11.2 +/- 0.9	25	13.0 +/- 1.6	>0.05
Hemoglobin (g/l)	65	13.4 +/- 0.3	20	13.3 +/- 0.5	>0.05
Platelet count (x 10 ⁹ /l)	96	220 +/- 14	25	187 +/- 27	>0.05
CRP (mg/l)	87	47 +/- 3.7	24	41 +/- 3.7	>0.05
Lactate (mg/dl)	81	2.6 +/- 0.25	23	7.0 +/- 1.8	<0.05
**NEC-score (Table 2.5)	79	3.7 +/- 0.18	18	5.7 +/- 0.32	<0.001

^aN = number of patients for whom results are available, CPR=C-reactive protein

****NEC-score (Table 2.5)** – score calculated subsequent development of the scoring system

Results in table 2.4 indicate that BW, GA, and lactate levels are all significantly lower in infants who died than those who survived. Adding the value of Bell Staging Criteria to their results, and assigning scores based on expert medical opinion, table 2.5 was developed. Points are scored based on gestational age, Bell Stage, platelet count and lactate levels. Healthy babies would ideally score 0 points, whereas the extremely sick ones can score up to 8 points. Applying the NEC-score to the 128 NEC neonates that were a part of the study, the authors found that the score of 4.5 out of 8 was the ‘optimal cut-off’ with respect to NEC-mortality, i.e. babies scoring more than 4.5 were more likely to die from NEC. The sensitivity and specificity for predicting survival using the NEC-score was 0.71 and 0.72, respectively (Kessler et al., 2006). The conclusion: “The predictive potential for survival was superior using the score than using single parameters” (Kessler et al., 2006).

Table 2.5: NEC-score (Kessler et al., 2006)

<i>Parameter</i>	<i>Score</i>		
	<i>0</i>	<i>1</i>	<i>2</i>
GA (weeks)	>32	30 – 32	<30
Bell stage	I	II	III
Platelets (g/l)	>200	150 – 200	<150
Lactate (mg/dl)	<2.5	2.5 – 3.3	>3.3

However, several issues with this scoring system need to be noted:

1. Data set is relatively small, 128 babies, and some patients have missing data for variables that were analyzed. The authors chose not to impute or remove cases with missing variables.
2. There is a significant number of premature babies (116) with NEC compared to infants considered to be born at term (12).

3. This is a single hospital neonatal cohort, with a span of 20 years, and might now be representative of the population across the entire country.
4. This scoring system has not been properly validated.

2.2.5.2 Mathematical model of inflammation in NEC

Upperman et. al (2007) attempted to develop a “calibrated mathematical model of inflammation and its pathologic consequences in NEC” to predict physiologic and biologic response in infants suffering from it. The researchers focused on developing a model using various biomarkers such as proinflammatory cytokines and products of vasoactive substances present in serum and intestine of infants with NEC. This model is based on system biology, which integrates experimental and computational tools to characterize complex biological phenomena (Upperman et al., 2007). Research focused on contributions of cellular and molecular mechanics to the pathogenesis of NEC. The mathematical model developed by Upperman et. al. incorporates two system compartments: tissue and blood. These are further broken down into smaller pieces to allow for mathematical analysis. For example (equation 2.1), one of the sub-systems developed models the interaction of the active neutrophils in the tissue and blood level of inflammatory cytokines (proteins).

$$\begin{aligned}
 n'_a &= f(c_b) - v \cdot n_a \\
 c'_b &= \gamma \cdot c_b + \frac{d}{d + \eta} (r \cdot n_a - \eta \cdot c_b)
 \end{aligned} \tag{2.1}$$

where,

n_a = active neutrophils in the tissue

c_b = blood level of inflammatory cytokines

$f(c_b)$ = sigmoidal function representing combined production of activated neutrophils by inflammatory cytokines & transport of activated neutrophils to the tissue compartment

ν, γ, η = parameters of degradation rates of neutrophils, blood cytokines and tissue cytokines respectively
 r = rate of production of cytokine by neutrophils in the tissue
 d = diffusivity of cytokines from the blood to the tissue

The complexity of this model is beyond the scope of this research. Furthermore, this has yet to be validated in a clinical setting.

2.3 Clinical Decision Support Systems

While data mining centres around problem solving by analyzing existing data, decision support centres around development of systems aimed at assisting decision makers in problem solving and decision making (Mladenic, Lavrac, Bohanec, & Moyle, 2003). Clinical Decision Support Systems (CDSSs) in particular use data mining techniques to assist physicians and other health care professionals with decision making tasks. Although the debate over the medical usefulness of CDSS (Berner, 1998)s with respect to practitioner performance and patient outcomes is on-going, existing trials of CDSSs include: systems for diagnosis, systems for prevention, systems for disease management, systems for drug dosing and drug prescribing (Garg et al., 2005), (Berner, 1998). To properly assess the value of a system, model evaluation techniques need to be established first. Systems that ‘learn’ by example and over time, i.e. non-knowledge based system such as neural networks and support vector machines, are then discussed.

2.3.1 Model Evaluation Techniques

Frequently used performance measures of data mining techniques include the constant predictor, sensitivity, specificity, classification rate (CR), receiver operating characteristic curve (ROC), and the stopping criterion.

Confusion Matrix

A confusion or contingency $n \times n$ square matrix summarizes the dispositions of true and false positive and negative instances, and is used to evaluate the performance of a classification system (Fawcett, 2006). Table 2.6 is 2-by-2 square matrix, used for a 2-class classification system, such as the one used in this research. In medicine, a less frequent outcome is associated with the positive classification (+1). The ‘normal’ outcome is associated with the negative classification (-1).

Table 2.6: 2×2 confusion matrix for a 2-class classification system

		Actual Class	
		<i>Positive (P)</i>	<i>Negative (N)</i>
Predicted Class	<i>Positive</i>	True Positive (TP)	False Negative (TN)
	<i>Negative</i>	False Positive (FP)	True Negative (TN)

Constant Predictor and Priori Knowledge

In order to ensure consistency with respect to comparisons between various data mining methods, a priori knowledge about the data distribution needs to be established first. A priori knowledge refers to the actual number of positive versus negative cases represented in the population of interest.

$$\text{Positive priori outcome} = \frac{TP + FN}{(TP + TN + FP + FN)} \quad (2.2)$$

$$\text{Negative priori outcome} = \frac{TN + FP}{(TP + TN + FP + FN)} \quad (2.3)$$

Furthermore, the *Constant Predictor (CP)* is established by using a prior knowledge. CP is set as the negative priori outcome i.e. the value which is associated with the ‘normals’

in a population of interest. For example, if 95% of the population is considered to be healthy, while 5% is sick, the CP would be 95%.

Sensitivity and Specificity Analysis

Using the data from the confusion matrix, sensitivity, specificity and classification rate are also calculated. *Sensitivity* is defined as the true positive rate, and is also known as a *hit rate* or a *recall*.

$$Sensitivity = \frac{TP}{(TP + FN)} \quad (2.4)$$

Specificity, on the other hand, is the measure of the true negative rate.

$$Specificity = \frac{TN}{(TN + FP)} \quad (2.5a)$$

OR

$$Specificity = 1 - \text{false positive rate} = 1 - \frac{FP}{(FP + TN)} \quad (2.5b)$$

Classification Rate

The classification rate, also known as accuracy, is the overall success rate with respect to the number of correct classifications, both positive and negative, over the entire population (Witten & Frank, 2005). For imbalanced medical data, where negative a priori is much higher than positive a priori, CR measure is not a good indicator of performance (Maimon & Rokach, 2005). MIRG has found that CR is an accurate

measure of performance only in cases where the desired outcome is above 15% (Frize et al., 1998).

$$\text{Classification rate} = \frac{TP + TN}{TP + TN + FP + FN} \quad (2.6)$$

Receiver Operating Characteristic (ROC) Curve

According to Fawcett (2006) “A receiver operating characteristic (ROC) graph is a technique for visualizing, organizing and selecting classifiers based on their performance”. In addition, ROC curves are popular in medical decision making where they are used in assessment of risk scores (Dorling & Field, 2008). An ROC curve is generated by plotting the true positive rate, i.e. the sensitivity, versus the false positive rate, or $1 - \text{specificity}$. It is the area under the curve (AUC) that is of most interest in analysis. Figure 2.2 is an example of an ROC graph showing five (A, B, C, D, E) discrete classifier points, with corresponding (*false positive rate, true positive rate*) co-ordinate pairs.

Figure 2.2: An ROC graph (Fawcett, 2006)

With respect to (TP rate, FP rate) coordinate pairs, the general assumption is that one point is better than the other if it is located in the 'northwest' corner of the graph, maximizing the TP rate and minimizing the FP rate (Fawcett, 2006). The ideal point on the ROC curve is represented by point D (0,1), where all positive samples are identified correctly and no negative examples are misclassified. As such, point D is considered a 'perfect' classifier. 'Conservative' classifiers, those in the proximity of the bottom left-hand side, have lower FP errors but often have low TP rates as well. On the diagonally opposite end, classifiers within proximity of (1,1) coordinate pair are considered more 'liberal' as they classify nearly all positives correctly, but also have a high rate of false positives. Point A compared to point B is more conservative; however, point A might be a more appropriate classifier as it has a lower rate of false positives. This depends on the application and on the balance of training samples present in each class (Maimon & Rokach, 2005). Any classifier located on the line $y=x$, ex. point C, represents a 'random guess' classifier and is considered useless. A classifier worse than a random guess is the one identified by point E, and in general any classifier found below the $y=x$ line. With respect to the value of the ROC curve in medicine, medical literature reports that any scoring systems with a value for the area under the ROC curve yielding 80% and greater, may be useful in clinical practice (Dorling et al., 2005), (Dorling & Field, 2008).

Stopping Criteria

In order to ensure that overtraining and overfitting (memorizing) of data is not taking place, stopping criteria is used to identify the optimal performance of data mining algorithms (Ennett, 2003). Classification rate and the minimum square error are often

used as a stopping criteria; however, due to the sensitive nature of medical problems, where it is of higher priority to correctly identify the outcomes of rare occurrence, the preferred stopping criteria was found to be the *logarithmic-sensitivity index* (logsens) (Scales, 2001; Ennett, 2003). Unlike the classification rate and minimum square error, the logsens index strives to find an optimal balance between the sensitivity and the specificity classifications, while slightly favouring the higher sensitivity at the expense of specificity (Scales, 2001). By varying the value of n , the weight in favour of sensitivity is monitored. This is currently used by MIRG for the ANN RFW tool.

$$\text{logsens} = -\text{sensitivity}^n * \log_{10}(1 - \text{sensitivity} * \text{specificity}) \quad (2.6)$$

2.3.2 Artificial Neural Networks

Mimicking the function of the biological neural networks, because of their non-knowledge-based learning abilities artificial neural networks (ANNs) are gaining attention as classification algorithms (Berner, 1998). Viewed as an adaptive machine, Haykin (1999) defines the neural network as:

“A neural network is a massively parallel distributed processor made up of simple processing units, which has a natural propensity for storing experiential knowledge and making it available for user. It resembles the brain in two respects:

1. *Knowledge is acquired by the network from its environment through a learning process.*
2. *Interneuron connections strengths, known as synaptic weights, are used to store the acquired knowledge. “*

The smallest information processing unit of the neural network is the neuron, as seen in figure 2.3. The three basic elements of the neuron model are (Haykin, 1999):

1. The ‘synapses’, characterized as the *weights* (w_{in}) which lie in the range that includes both positive and negative numbers.

2. The ‘adder’, which sums the input signals ($x_1 \dots x_n$) as they are weighed by their respective weights ($w_{i1} \dots w_{in}$), in addition to the externally applied *bias*, which increases/decreases the input to the activation function.
3. The ‘activation function’ or the *transfer function*, which limits the amplitude of the output of the neuron.

Figure 2.3: Information processing unit – the neuron (Pan, 2002)

The output of the neuron i , based on figure 2.3, is given as:

$$\text{Output} = \text{TransferFunction} \left[\left(\sum_{j=1}^n w_{ij}x_j \right) + \text{bias} \right] \quad (2.7)$$

Multiple neurons are further grouped together to form networks which can be made up of different structures. Haykin (1999) identifies three fundamentally different classes of neural network architectures (structures): single-layer feedforward, multi-layer feedforward and recurrent networks. Further classification can be done based on the type of learning algorithm used to train the network (supervised, unsupervised, recurrent), as well as the application, connection type and computational modeling (Haykin, 1999).

Of interest to this research are the single and multi-layer neural networks (classifier networks), as seen in figure 2.4.

Figure 2.4: (a) 2-layer network; (b) 3-layer network

The networks can also be fully connected, figure 2.4(b), where each node in the layer is connected to a node in the subsequent layer; or, connections can be partial so that not every input connects to every subsequent node. The type of connections shown in figure 2.4 make up a feedforward neural network, where information flow is in only one direction: from the input nodes, through the hidden layer (if it exists), ending at the output layer. In general, the computing power of the ANNs is achieved through the parallel distributed structure, in addition to the network's ability to learn and *generalize* outputs for inputs not encountered during the training (Haykin, 1999), (Hertz, Krogh, & Palmer, 1991). The input-output mapping is attained with a learning paradigm known as *supervised learning*, where each sample from a training set and its input signals map to a desired response (outcome). This also makes the network adaptable, as retraining is necessary to account for changes in the operating environment (Haykin, 1999). By modifying the weights during training, the differences between the expected response and the actual response are minimized. ANNs using the backpropagation learning algorithm attempt to minimize the error (mean squared error), by updating the connection weights and biases after the error is propagated backwards through the network (Haykin, 1999).

In addition to the ‘classifier’ multi-layer neural network used in this thesis, computational models include association, optimization and self-organization networks (Haykin, 1999). An example of an associative network is the Hopfield model, which is a symmetric recurrent architecture ANN, i.e. the data flow is bidirectional. The units of this network take on binary thresholds values for their states, as determined by whether or not the unit input exceeds a certain threshold (Hertz et al., 1991). The Boltzmann Machine is an example of an optimization network, which makes use of stochastic transfer functions and introduces ‘random’ variations into the network (Haykin, 1999). Self-organizing networks such as the Kohonen network use a form of unsupervised learning (network provided with inputs, but not outputs). The network ‘decides’ what features are used to group input data (Haykin, 1999).

2.3.2.1 Transfer functions

There are various types of activation functions used for ANN training: threshold function (step function), piecewise-linear function, and sigmoid function. The type of activation function used determines if the network model is linear or non-linear, regardless of the number of hidden layers. For example, multi-layer networks with fixed weights and a linear activation function are equivalent to a 2-layer network (Russell, 1993), (Haykin, 1999). “A linear system with any number n of layers is equivalent to a single-layer linear system whose weight matrix is the product of the n intermediate weight matrices” (Russell, 1993). If a simple linear model is desired, the activation function used has to be linear. However, non-linear mapping functions are used more often for multi-layer networks as they provide more computational capability (Haykin, 1999), (Rybchynski, 2005). MIRG uses the non-linear hyperbolic transfer function for its

multi-layer ANN tool, equation 2.8 and figure 2.5, because of the sharper transition between output values which permits faster learning (Buskard, 1994), (Ennett, 2003).

$$f(x) = \frac{e^x - e^{-x}}{e^x + e^{-x}} = \frac{e^{2x} - 1}{e^{2x} + 1} \quad (2.8)$$

The function ranges (-1,1), and offers a sharp sigmoid-like transition thus minimizing output values near and at zero (Fausett, 1994). As such, the output of the neural network is either on the -1 side of the 1 side of the threshold value (zero).

Figure 2.5: Hyperbolic transfer function

2.3.2.2 ANN RFW tool & driving parameters

ANN Research Framework Tool (RFW), developed by MIRG, uses nine driving parameters for the feedforward backpropagation algorithm used for training of the network. These parameters control the rate at which the weights and the biases of the network are updated, while attempting to minimize the error between the actual and the desired outputs. MIRG researcher, Eliane Charette worked on automation of the driving parameters for the ANN RFW tool in order to improve the performance with respect to speed and calculation of optimal parameters (Frize, Ennett, & Charette, 2000). Removal of researcher interaction was achieved by allowing the software to automatically progress

from one parameter run to the next, while carrying forward the best parameter values (Rybchynski, 2005).

Learning rate (lr)

While attempting to minimize the average squared error of the network's output, the learning rate determines the step size and thus the speed with which the network achieves its minimum in the criterion function, resulting in convergence (Witten & Frank, 2005). If the learning rate is too high and the error function has several minima, the search can overshoot and miss the minimum entirely, or it can result in oscillations. On the contrary, if the learning rate is too small, convergence will eventually happen, but may take a very long time; this is the main reason backpropagation networks are slow (Masters, 1993). In the search for the minimum, MIRG's ANN RFW also uses the learning rate increment (lr_inc) and learning rate decrement (lr_dec) values as the driving parameters.

Momentum

In order to enhance the performance of the network and speed up the learning process, the momentum term is introduced in the update of network weights. The term adds a proportion of the update value from the previous iteration to the new weight change and as such "smooths the search process by making changes in direction less abrupt" (Witten & Frank, 2005). This in turn helps ensure that the learning algorithm does not get caught up in a local minimum (Masters, 1993).

Weight-decay constant (λ) & Weight-elimination scale factor (w_0)

The purpose of the weight-decay constant is to limit the influence of non-meaningful connections on the network. The constant penalizes large weights by preventing them from increasing since they might not contribute a correspondingly large reduction in the error (Witten & Frank, 2005). Depending on the network performance, the ANN RFW uses weight-decay constant increment (λ_{inc}) or decrement (λ_{dec}) to penalize connections.

Like the weight-decay constant, the weight-elimination scale factor is used for network pruning and regularization of the network training, i.e. minimize overfitting to the noise on the training data (Bishop, 1995). The weight-elimination scale factor sets the scale for the ‘large’ and ‘small’ weights. “When w_0 is small, the small weights will be forced to zero resulting in a fewer large weights (i.e. weight-elimination). A large w_0 causes many small weights to remain and limits the size of large weights (i.e. weight-decay)” (Ennett, 2003).

Combining the effects of the weight-decay constant and the weight weight-elimination scale factor with the mean squared error function, the weight-elimination cost function is obtained (Weigend, Rumelhart, & Huberman, 1990), (Ennett & Frize, 2003).

$$E(W) = E_0(W) + \lambda \times \sum_{ij} \frac{\frac{w_{ij}^2}{w_0^2}}{1 + \frac{w_{ij}^2}{w_0^2}} \quad (2.9)$$

where,

E_0 = SSE (sum squared error).

λ = weight-decay constant

w_{ij} = weight of connecting node i and j.

w_0 = weight elimination scale factor

Error ratio (err_ratio)

User-defined value, error ratio is used to “measure the change from the current to previous error to determine how the learning rate, weight decay constant and momentum will be adapted to improve the network performance” (Ennett, 2003). With improvement in performance of the network, error ratio should decrease.

2.3.2.3 Network structure

Medical data is generally not linear, and is not easily mathematically characterized. As such, linear neural networks are not the best for modeling the medical domain; hence non-linear networks with one or more hidden layers are a preferred choice. The literature indicates that there is no reason why more than one hidden layer should be used for ANNs, as it does not add more knowledge to the network (Hertz et al., 1991), (Masters, 1993), (Ennett, 2003). In addition, multiple hidden layers slow training dramatically because of error backpropagation and constant changes to the gradient and hence the weights (Masters, 1993).

Finding the optimal number of hidden nodes in a hidden layer is a brute force and a time-consuming task. The use of too many hidden nodes not only increases the training time, but it can potentially lead to overfitting as the network learns “insignificant aspects of the training set, aspects that are irrelevant to the general population” (Masters, 1993). On the contrary, too few hidden nodes might be insufficient for learning and solving the problem. While Hertz et. al. (1991) state that the necessary number of hidden ‘units’ is not known in general, and may grow exponentially with the number of input units, Masters (1993) states that the rough guideline for choosing the number lies in the *geometric pyramid* rule:

$$hidden\ nodes = \sqrt{TotalOutputNodes * TotalInputNodes} \quad (2.10)$$

Masters (1993) also reiterates that this number should only be used as a rough guideline and might not be considered sufficient for networks with a smaller number of input and output variables. Two other guidelines are considered for determining the number of hidden nodes: Livingstone's and Manallack's method (Livingstone & Manallack, 1993) as well as Kolmogorov's Theorem (Bishop, 1995), equations 2.11 and 2.12 respectively.

$$hidden\ nodes = \frac{TotalTrainingCases * TotalOutputNodes}{TotalNetworkWeights} \quad (2.11)$$

where,

$hidden\ nodes > 3$ to ensure good generalization

Livingston's and Manallack's method produces a large number of hidden nodes, and for a database the size of the CNN's, it is not considered a viable solution with regards to determining the network structure. Past MIRG researchers have also found that the neural networks using the CNN database did not require as many hidden nodes as Livingstone and Manallack suggest (Khan, 2006).

$$hidden\ nodes = 2n + 1, \text{ where } n = \# \text{ of input variables} \quad (2.12)$$

Kolmogorov's Theorem, as adapted to neural networks, states that mapping $y(x)$ from n input variables x_i to the output variable y can be represented exactly by a three-layer neural network having $(2n+1)$ units in the hidden layer (Bishop, 1995). MIRG's ANN RFW tool is setup to use a modified version of Kolmogorov's Theorem to determine the max number of hidden nodes. ANN RFW attempts classification on structures with the number of hidden nodes ranging from 0 to $2n+1$, after which the structure with the best

criteria is chosen as the model. As variables are removed, the number of hidden nodes decreases, which in turn reduces the network complexity and computational time.

2.3.3 Support Vector Machines

Support Vector Machines (SVMs) are a set of supervised learning methods that can be used for both classification and regression problems (Vapnik, 1995). Developed by Vapnik (1995), SVM goal is to implement principles of statistical “learning theory that addresses the fundamental issue of how to control the generalization ability” and produce input-output mapping of data instances (Haykin, 1999). Consider a set of empirical data:

$$(x_1, y_1), \dots, (x_m, y_m) \in \mathbb{R} \times Y, Y = \{-1, 1\}$$

where,

$$i = 1 \dots m$$

x_i = patterns (input data)

y_i = labels or targets (output)

Vapnik (1995) introduced the concept of the N-dimensional hyperplane used to separate instances of two different classes, $Y = \{-1, 1\}$. The hyperplane is bound by a *margin*, which is defined as “the minimal distance of an example to a decision surface” leading to the idea that the “risk is minimized when the margin is maximized” (Maimon & Rokach, 2005). The subset of training examples that constrain the width of the margin and the optimal hyperplane are known as *support vectors* (Vapnik, 1995). In the simplest of hyperplane classifications, a 2-dimensional model (figure 2.6), the class of hyperplanes for linearly separable patterns takes the form (Chen et al., 2005):

$$(\mathbf{w} \cdot \mathbf{x}) + b = 0 \quad \mathbf{w} \in \mathbb{R}^N, b \in \mathbb{R} \quad (2.12)$$

where,

$\mathbf{w}$ = adjustable weight vector
 $\mathbf{x}$ = input vector
 b = bias

This class of hyperplanes correspond to decision functions:

$$f(\mathbf{x}) = \text{sign}((\mathbf{w} \cdot \mathbf{x}) + b) \quad (2.13)$$

For two samples, $\mathbf{x}_1$ and $\mathbf{x}_2$, belonging to a different class such that $(\mathbf{w} \cdot \mathbf{x}_1) + b = 1$ and $(\mathbf{w} \cdot \mathbf{x}_2) + b = -1$, respectively, the distance of $\mathbf{x}_1$ and $\mathbf{x}_2$, measured perpendicularly to the hyperplane, gives the margin of:

$$\frac{\mathbf{w}}{\|\mathbf{w}\|} \cdot (\mathbf{x}_1 - \mathbf{x}_2) = \frac{2}{\|\mathbf{w}\|} \quad (2.14)$$

Figure 2.6: The optimal hyperplane for a linear 2-class classifier, represented by circles and diamonds (Chen et al., 2005).

Although there may be several hyperplanes separating the two classes of data, the unique hyperplane defining the maximum margin of separation for the two classes is defined as:

$$\max_{\mathbf{w}, b} \min \{ \|\mathbf{x} - \mathbf{x}_i\| : \mathbf{x} \in \mathcal{R}^N, (\mathbf{w} \cdot \mathbf{x}) + b = 0, i=1, \dots, m \} \quad (2.15)$$

The optimal hyperplane is achieved by solving the optimization problem:

$$\min_{\mathbf{w}, b} \frac{1}{2} \|\mathbf{w}\|^2 \quad (2.16)$$

$$\text{subject to : } y_i((\mathbf{w} \cdot \mathbf{x}_i) + b) \geq 1, \text{ for } i = 1, \dots, n \quad (2.17)$$

Beyond the scope of this research, the optimization is solved by introducing the Lagrange multipliers $\alpha_i \geq 0$ and the Lagrange function:

$$L(\mathbf{w}, b, \alpha) = \frac{1}{2} \|\mathbf{w}\|^2 - \sum_{i=1}^n \alpha_i (y_i((\mathbf{w} \cdot \Phi(\mathbf{x}_i)) + b) - 1) \quad (2.18)$$

L is maximized with respect to primal variables $\{\mathbf{w}, b\}$ and minimized with respect to dual variables α_i . By finding the derivatives of L with respect to the $\mathbf{w}$ and b , the primal variables can be replaced by:

$$\sum_{i=1}^n \alpha_i y_i = 0 \quad \text{and} \quad \mathbf{w} = \sum_{i=1}^n \alpha_i y_i \mathbf{x}_i = 0 \quad (2.19)$$

Furthermore, the *support vector* correspond to non-zero α_i , which by the Karush-Kuhn-Tucker (KKT) complimentary conditions of optimization means that all other constraints in equation 2.17 must be zero (Maimon & Rokach, 2005):

$$\alpha_i (y_i((\mathbf{w} \cdot \mathbf{x}_i) + b) - 1) = 0, \quad \text{for } i = 1, \dots, n \quad (2.20)$$

The original hyperplane decision function equation 2.12 can then be written as:

$$f(\mathbf{x}) = \text{sign} \left(\sum_{i=1}^n \alpha_i y_i (\mathbf{x} \cdot \mathbf{x}_i) + b \right) \quad (2.21)$$

2.3.3.1 Kernel functions

By far the simplest way to divide two classes is to use a linear classifier, as described in the previous section. However, linear classifier functions often have a limited functionality as data is not always linearly separable, resulting in a classifier under fitting the data. To deal with this predicament, SVM makes use of kernel functions which map the data into a feature space where maximum-margin hyperplanes can be

constructed (Maimon & Rokach, 2005). According to Cortes and Vapnik (1995), “to construct a hyperplane in a feature space one first has to transform the n -dimensional input vector x into an N -dimensional feature vector through a choice of an N -dimensional vector function $\Phi: \mathbb{R}^n \rightarrow \mathbb{R}^N$.” The N -dimensional linear weight vector w and bias b is constructed for the set of transformed vectors $\Phi(x_i) = \Phi_1(x_i), \Phi_2(x_i), \dots, \Phi_N(x_i)$ (for $i=1, \dots, l$) as a modified equation 2.12 (Cortes & Vapnik, 1995):

$$f(x) = w \cdot \Phi(x) + b \quad (2.22)$$

Determining the best kernel function is the subject of active research, as different functions give similar classification accuracy and sets of support vectors (Vapnik, 1998), (Schölkopf & Smola, 2002). The most commonly used kernel functions, as summarized in table 2.7 are Polynomial (degree d), Radial Basis Function (RBF), and sigmoid (Schölkopf & Smola, 2002).

Table 2.7: Common SVM kernel functions

Kernel function	$K(x, x_i)$
Radial Basis Function	$\exp(-\gamma \ x - x_i\ ^2), \gamma > 0$
Polynomial (degree d)	$((x^T x_i) + \eta)^d$
Sigmoid	$\tanh(\gamma (x^T x_i) + \eta), \gamma > 0$

Literature review suggests that RBF is a ‘reasonable first choice’ with respect to SVM kernels and classification (Maimon & Rokach, 2005), (Chen et al., 2005), (Schölkopf & Smola, 2002). As such, it was the kernel of choice in this research. Incorporating the kernel function with equation 2.21, by replacing the dot product of $(x \cdot x_i)$, the following hyperplane decision function is obtained:

$$f(x) = \text{sign} \left(\sum_{i=1}^n \alpha_i y_i K(x, x_i) + b \right) \quad (2.23)$$

The optimization problem is then:

$$\max_{\alpha} \sum_{i=1}^n \alpha_i - \frac{1}{2} \sum_{i,j=1}^n \alpha_i \alpha_j y_i y_j K(x_i, x_j) \quad (2.24)$$

$$\text{subject to: } \alpha_i \geq 0, \quad i = 1, \dots, n, \quad \sum_{i=1}^n \alpha_i y_i = 0 \quad (2.25)$$

2.3.3.2 Soft Margin Support Vector Classifier: C-SVC

An ideal SVM classifier introduces a hyperplane that fully separates two classes of data. Nonetheless, this is often impossible as data samples frequently ‘violate’ constraints of the optimal hyperplane. To allow flexibility for such issues, Cortes and Vapnik (1995) introduced a slack variable ξ_i (modification to equation 2.17) whose purpose is to ‘relax’ the margin constraints:

$$y_i ((\mathbf{w} \cdot \Phi(x_i)) + b) \geq 1 - \xi_i, \quad \xi_i \geq 0, \quad i = 1, \dots, n \quad (2.26)$$

By controlling the classifier capacity ($\|\mathbf{w}\|$) and the sum of the slack variables ξ_i , the soft margin classifier minimizes the following objective function (Maimon & Rokach, 2005):

$$\min_{\mathbf{w}, b, \xi} \frac{1}{2} \|\mathbf{w}\|^2 - C \sum_{i=1}^n \xi_i, \quad \text{where } C > 0 \quad (2.27)$$

The regularization constant, C , is used to control the trade-off between the training errors and rigid margins, by permitting some misclassifications (Vapnik, 1995), (Schölkopf & Smola, 2002). Because of the high level of non-linearity in medical data, this thesis uses the C-SVM classifier (C-SVC). Lastly, incorporating C with the Lagrange multipliers from equation 2.24 and 2.25, the Lagrange multiplier α_i is subject to $0 \leq \alpha_i \leq C$, $i=1, \dots, n$,

$$\sum_{i=1}^n \alpha_i y_i = 0.$$

2.4 Data preparation

Medical data is unique and requires consideration of the following heterogeneity issues before it is used (Cios & Moore, 2002):

1. Volume and complexity
2. Physician's interpretation
3. Sensitivity and specificity analysis
4. Poor mathematical characterization
5. Canonical form (same concept represented with different terminology)

Consistency in data collection is necessary to minimize the impact of the above issues and in order to ensure good quality data is used in research. MIRG research is conducted on medical data collected by the Canadian Neonatal Intensive Care Unit Network (CNN), which includes 17 tertiary care NICUs, or approximately 80% of the tertiary care NICU beds in Canada (McMillan, Chan, & Lee, 1997). The data collection was funded by the Medical Research Council of Canada, and was done between January 8th, 1996 and October 31st, 1997. It includes 20,488 baby admissions. Data was collected for day 1 (admission day), day 3, 14, and 28 or discharge. However, issues of missing values, data imbalance with respect to *a priori* levels and data dimensionality reduction all have to be addressed by the users of this database before commencing data mining.

2.4.1 Missing values

Missing values and class imbalance are challenges for data mining techniques. Data that medical professionals consider irrelevant for diagnosis or that is not recorded because a medical test was not performed, are considered '*do not care*' conditions. On the contrary, values that were misplaced, forgotten or mistakenly erased are considered *lost* values. Regardless of type, both 'do not care' and 'lost' data are considered

important to medical data mining as each patient case offers valuable knowledge. The CNN database used by MIRG is no exception to the issue of missing values and incomplete data sets. Literature further classifies methods to handle this issue as *sequential* (or *pre-processing*) *methods* and *parallel methods* (Maimon & Rokach, 2005). Unlike the sequential methods, parallel methods take into account the attributes with missing values during the main process of acquiring knowledge by using rule induction (for example decision trees). However, ANN and SVM cannot perform well on databases with missing values (Ennett, 2003); hence for this thesis, parallel methods are not considered a valid solution for the missing value problem.

Instead, MIRG uses sequential methods to deal with missing values in the CNN database. While deleting cases with missing attribute values, method known as *listwise/casewise deletion* or *complete case analysis*, is considered legitimate, the process itself strips the database of valuable information (Ennett, 2003), (Maimon & Rokach, 2005). With respect to the CNN database, cases that have the least amount of missing values are those of the sickest infants, and removing less sick babies would result in a model that is not representative of the entire population (Ennett, Frize, & Walker, 2001). Several of the MIRG researchers have worked on validating methods for imputation of missing values in the CNN database, which include the following:

1. *Statistical imputation*

- Missing values were replaced with mean and median values for the particular variable, for the outcome of mortality. However, the database was found to be biased towards the survivors and non-survivors were not classified correctly (Tong, 2000).

2. Normal distribution replacement

- Missing values were replaced by a random value from the normal distribution.

3. Case-Based Reasoner (CBR)

- This knowledge base system uses a retrieval algorithm (k-Nearest Neighbour) to determine the most similar cases in the case base (Ennett, 2003). By plotting the data points in an n-dimensional space, the k-NN calculates the weighted distance between the cases in the repository to that of the target. The mean of the 10 closest matching cases are used to impute the value of the missing variable. Ennett (2003) validated the imputation of missing values using linear ANN weights for the day 1 data with missing values, while Khan (2006) performed the imputations using both linear and non-linear ANN weights on day 1 and day 3 CNN data. The imputations were done using variable weights biased towards the output of mortality, as determined by: a) a physician domain expert, and b) linear and non-linear neural networks (Ennett, 2003), (Khan, 2006). Townsend (2007) performed the imputation of missing values for the day 1 data as well; however, the imputations were done by using uniform weights for all variables as opposed to the weights determined by the ANNs or assigned by physicians. Townsend (2007) reasoned that this was to avoid a bias towards a particular outcome, such as mortality, as done in previous work.

2.4.1.1 CBR uniform weight imputation

The original CNN database used in this thesis contains 20488 patient files. Prior to proceeding with model development, the database had to be screened and analyzed.

Transfer of babies between hospital sites and re-admissions resulted in duplicate cases of patient files. After removal of duplicate files, cases with extreme outliers, missing outcome information (originally mortality), birth weight and variable ‘small for gestational age’ the total number of cases included 19814 babies (Townsend, 2007). The summary of missing value statistics for the 30 SNAP variables in the CNN Database is seen in table 2.8.

Table 2.8: CNN (19814 cases) database missing value statistics (Townsend, 2007)

Parameter description	Variable	Percent missing
Small for gestational age	SGA	0.00
Birth weight	bthwght	0.00
Presence of apnea	apnea	0.02
Stool guaiac	guaiac	0.02
Presence of seizures	seizure	0.03
Highest heart rate	hheartr	0.22
Lowest heart rate	lheartr	0.26
Highest respiratory rate	hrespr	0.36
Lowest temperature	ltempf	0.41
Apgar score at 5 minutes	Apgar5	1.73
Highest glucose	hgluc	8.72
Highest mean blood pressure	hbloodp	12.70
Lowest glucose	lgluc	14.51
Lowest mean blood pressure	lbloodp	16.07
Lowest white blood cell count	LWBC	17.42
Highest hematocrit	hhema	18.56
Lowest platelet count	lplt	28.55
Lowest absolute neutrophil count	LANC	28.57
Lowest hematocrit	lhema	33.53
Highest immature/total neutrophil ratio	hitnrat	35.77
Lowest serum pH	lserum	39.85
Highest pCO ₂	hpco2	40.26
Lowest urine output	lurine	52.68
Highest sodium	hsodium	59.53
Highest potassium	hpotass	62.65
Lowest pO ₂	lpo2po2	63.14
Lowest pO ₂ /FiO ₂ ratio	Po2fio2r	64.11
Lowest sodium	lsodium	66.00
Lowest potassium	lpotass	68.04
Highest oxygenation index	OI	72.76

The next step was to deal with missing values present in the database by imputing data in order to ensure sufficient number of cases are present for training and testing of the learning algorithms. Prior to imputation and upon feedback from the collaborating

CHEO neonatologist, Dr. Erika Bariciak (2006), variables ‘stool guaiac’, ‘highest potassium’ and ‘lowest potassium’ were removed from the database as they are normally not measured within the first 12 hours of admission. Missing values for the remaining 27 day 1 variables used in this thesis were next imputed by Townsend (2007) using uniform weights. In order to minimize the error from imputation of missing values, Townsend (2007) imputed up to 8 missing variables per case (i.e. up to 30% of a particular case is potentially imputed). Patient cases with more than 8 missing variables were discarded, resulting in the final database of 13584 complete cases after imputation. Table 2.9 summarizes pre-imputation variable statistics for the 13584 cases that qualified for imputation of missing values.

Table 2.9: Distribution of missing values in the 13584 CNN database (Townsend, 2007)

Variable	Min	Max	Mean	St. Dev.	# Missing	% Missing
SGA	0	1	0.04	0.20	0	0.00
birth weight	280	6320	2338.65	1042.19	0	0.00
apnea	1	4	1.17	0.56	0	0.00
seizure	1	3	1.05	0.29	0	0.00
hhearttr	60	327	161.84	18.00	1	0.01
lhearttr	0	197	126.73	15.52	3	0.02
ltempf	68	113	97.43	1.21	3	0.02
hrespr	0	180	58.61	29.06	18	0.13
Apgar5	0	10	7.83	1.74	33	0.24
hbloodp	0	121	49.07	11.31	260	1.91
hgluc	0.9	65.3	5.44	2.59	341	2.51
lbloodp	0	100	36.71	9.54	392	2.89
LWBC	0.39	1442	15.17	22.37	483	3.56
hhema	0	82	49.37	8.84	624	4.59
lgluc	0	20.7	3.42	1.63	988	7.27
lplt	0.22	3337	212.63	102.80	1594	11.73
LANC	0	686000	8599.17	12648.83	1888	13.90
lserum	4.4	7.79	7.31	0.11	2535	18.66
hpcO2	4.44	172	46.80	14.06	2600	19.14
lhema	0	80	48.45	9.23	2796	20.58
hitnrat	0.00	1	0.16	0.16	2999	22.08
lurine	0	11.73	0.89	0.82	5471	40.28
hsodium	106	182	136.20	5.06	6395	47.08
lpo2po2	0	434	61.09	33.47	6476	47.67
Po2fio2r	0	12.42	1.90	1.27	6642	48.90
lsodium	86	180	135.51	5.19	7392	54.42
OI	0	275	9.10	16.13	8297	61.08

Majority of the variables used had less than 25% missing values. Variables with a large percent of missing values (ex. OI, Isodium) were kept because they were deemed important, and due to the reasonable standard deviation (Bariciak, 2006). As mentioned in section 2.4.1, the imputations were done using the k-NN algorithm, thus only the 10 closest matching cases were used to impute the value of the missing variable. Once the imputations were complete, the 13584 database then had to be processed, adjusted and analyzed with respect to NEC. This is discussed in the methodology section.

2.4.2 Data imbalance

In addition to the issue of missing values, data mining also has to consider data imbalance. Rare cases are of most interest to, as the goal is to uncover patterns that are hidden in vast amounts of data (Maimon & Rokach, 2005). With respect to neural network training, “if some classes have much fewer samples, i.e. a priori level, compared to other classes, the neural network system may respond wrongly for minority classes because the overwhelming samples in the majority classes dominate the adjustment procedure in training” (Wang & Xiuju, 2005). This in turn makes generalization difficult (Maimon & Rokach, 2005). Obtaining more medical data to increase the *a priori* of the rare cases is not an option, so the data imbalance must be dealt with in other ways. While it is possible to randomly remove some of the majority cases (*random undersampling method*), this solution is not considered beneficial as the entire population is not correctly represented. Removal of useful data is risked when cases are removed due to missing values as well as undersampling (Ennett, 2003). MIRG instead resorts to boosting the numbers of minority cases by *random oversampling*, and does so for the rare cases of the training data sets. Ennett (1999) performed several ANN trials to ensure that

oversampling the rare cases does not lead to data overfitting, and found that resampling the rare case up to 20% for training was optimal for training.

2.4.3 Data dimensionality reduction (DDR)

Medical databases have a large amount of data and variables. Although it is beneficial to have as much information as possible, the high-dimensionality of data makes it difficult to analyze and model due to irrelevant and redundant information that often interferes with useful values and attributes (Wang & Xiuju, 2005). As Wang and Xiuju (2005) suggest, “the problem of DDR is to select a subset of attributes which represent the concept of data without losing important information”. The attribute space search is performed in one of two ways: *forward selection* or *backward elimination* (Witten & Frank, 2005). Forward selection requires a use of a predetermined attribute subset, as deemed important by the domain expert. This attribute set is not the minimum data set; instead it is used as a starting point to which additional attributes are added one by one. For example, the 9 SNAPPE-II variables can be considered a subset to which additional attributes are added in order to expand the attribute set and improve performance. On the contrary, backwards elimination starts off with the entire attribute set, for example all of the SNAP variables, from which attributes are removed one-by-one, or several at a time. There are tradeoffs for either method: forward selection requires a domain knowledge and thus might be biased, whereas backwards elimination can be extremely inefficient for working with large-scale databases with many variables (Maimon & Rokach, 2005). MIRG uses backwards elimination, and in previous research has created minimum data sets for various outcomes and complications: mortality, length of stay, ventilation, preterm birth, BPD, and IVH.

Furthermore in order to evaluate the importance of each variable, ANNs use the relative weight reduction as modified by Rybchynski (2005).

2.4.3.1 Relative Weight Reduction Method (ANN)

With the introduction of non-linear network to the ANN RFW, Rybchynski (2005) investigated weight reduction methods necessary for the data dimensionality reduction and creation of a minimum data set. For a linear network, weight extraction is a fairly straightforward process: scale the magnitude of the connection weights between the input and output nodes between 0 and 100, and remove the input nodes with the smallest weights (Frize, Ennett, & Hebert, 2001), (Rybchynski, 2005). The network is retrained again, and the process is repeated. For a non-linear network, the introduction of hidden layers complicates this calculation as it requires a series of computations that take into account the hidden layer and the nodes associated with it, and their relationship to the input and output of the network. Rybchynski adopted a weight reduction method developed by Garson and modified by Goh (1995), and modified it so as to “integrate the hidden-output weights into the algorithm while maintaining the basic approach of Garson-Goh’s relative weight calculation” (Rybchynski, 2005). The equations associated with the modifications to Garson-Goh are the following (Rybchynski, 2005):

- 1) Calculation of the relative weight of the hidden-output connections into the output node ($k=1$):

$$rw_{jk} = \frac{abs(w_{jk})}{\sum_j abs(w_{jk})}$$

- 2) Calculation of the relative weight of the input-hidden connections into each hidden node *(for each hidden node j)*:

$$rw_{ij} = \frac{abs(w_{ij})}{\sum_i abs(w_{ij})}$$

- 3) Multiplication of each relative weight input-hidden connection value by the relative weight value of its connected hidden-output weight *(for each input i)*:

$$P_{ik} = rw_{ij} * rw_{jk}$$

- 4) Summation of the final relative weight products *(for each input i)*:

$$S_i = \sum_i P_{ik}$$

- 5) Division of the sum of the final relative weights for each input node by the total of all relative weights *(for each input i)*:

$$RI_i = \frac{S_i}{\sum_i S_i}$$

where,

i: # of input nodes

j: # of hidden nodes

k: # of output nodes (*k=1* for MIRG research)

w_{ij}: connection weight between input node *i* and hidden node *j*

w_{jk}: connection weight between hidden node *j* and output node *k*

rw_{ij}: relative connection weight between input node *i* and hidden node *j*

rw_{jk}: relative connection weight between hidden node *j* and output node *k*

RI_i: Relative Importance of input node *i*

3 METHODOLOGY

Several factors are considered in the development of the NEC outcome prediction model(s) and are based on the following findings in the medical literature:

1. Can scores for predicting mortality be used as markers of disease severity for other outcomes, such as NEC (Dorling & Field, 2008)?
2. NEC is a *multivariable* complication with an unclear pathogenesis.
3. Clinical characteristics and laboratory features are believed to be different for neonatal population of infants born preterm and those born at term.

In response to these issues, three NEC models are explored in this thesis:

1. NEC model for the total population
 - a. model with gestation as a binary variable
(GestAge < 33 weeks = 1, GestAge ≥ 33 weeks = -1)
 - b. model with normalized gestation age (between -1 and 1)
2. NEC in very low birth weight (VLBW) population
3. NEC in population with gestation < 33 weeks

Model development, with the goal of achieving a minimum data set for NEC outcome prediction, is attempted with MIRG's ANN RFW, and the Library for Support Vector Machines (LIBSVM C-SVC v.2.86) tool developed by Chang and Lin (2001). ANN RFW tool has been used by MIRG for development of mortality, length of stay, ventilation, BPD and IVH scoring models. The SVM classification has to date been used by MIRG only for segmentation and extraction of regions of interest in clinical thermal

infrared images (Herry, 2008). As such the methodology described here with respect to the LIBSVM C-SVC tool is new to MIRG.

3.1 Data Understanding and Preparation

After the imputation of missing values was completed by Townsend (2007), the 13584 case CNN database was further modified for NEC. Outcome information for NEC was added to the 13584 cases, as were the variables gestational age and neonate *gender*, which were not considered important for Townsend’s analysis, but are relevant in NEC outcome (Bariciak, 2006). Dr. Bariciak (2006) also suggested that high blood pressure be removed from NEC analysis as it is not relevant to the outcome itself, as well as the SGA variable since it is derived from the birth weight and gestational age variables. Lastly, any of the 13584 cases with missing NEC outcome, and missing information/ambiguity for the neonate gender were also removed at this point. The resulting NEC database had 13133 patient cases with 27 variables, as summarized in table 3.1. With respect to Ennett’s (2001) conclusion that “patients who have fewer missing values have a higher mortality rate than patients with more missing values”, this was found to be true for NEC as well. The original CNN database (20488 cases) has a total of 344 NEC patients whereas the processed and final database has 312.

Table 3.1: Day 1 variables used in NEC modeling

	Variable	Variable Description
1	CASELINK	Patient ID – <i>administrative variable</i>
2	LURINE	Lowest urine output
3	HRESPR	Highest respiratory rate
4	LPLT	Lowest platelet count
5	SGA	<i>Small for gestational age (SNAPPE-II model only)</i>

6	HGLUC	Highest glucose
7	LHEMA	Lowest hematocrit (Hct, Ht)
8	APGAR5	Apgar score @ 5min
9	LBLOODP	Lowest mean blood pressure
10	HHEMA	Highest hematocrit
11	LGLUC	Highest glucose
12	BTHWT	Birth weight
13	HSODIUM	Highest sodium
14	HITNRAT	Highest immature/total neutrophil ratio
15	LWBC	Lowest white blood count
16	LANC	Lowest absolute neutrophil count
17	LHEARTR	Lowest heart rate
18	HHEARTR	Hearth rate high
19	OI	Oxygenation index
20	APNEA	Presence of apnea
21	LTEMPF	Lowest temperature
22	SEIZURE	Presence of seizure
23	LSODIUM	Lowest sodium
24	LPO2PO2	Lowest pO2
25	LSERUM	Lowest pH
26	PO2FIO2R	Lowest pO2/FiO2 ratio
27	HPCO2	Highest pCO2 recorded
28	GEST	Gestational age
29	SEX	Baby's gender
30	NEC	<i>Outcome variable</i>

**** NOTE:** SNAPPE-II variables are highlighted in bold

To understand the complex interaction of the variables used in modeling NEC, Statistical Package for Social Sciences (SPSS) is used to determine the correlation between input and output variables. The correlation used, Spearman Rank Correlation (ρ), is performed to test the strength of the relationships between any two variables. Spearman correlation is used instead of the Pearson correlation for the reason that: 1) it does not require linear relationship assumptions between variables, 2) it can be used for ordinal and nominal data, and 3) and it does not require knowledge about the variable frequency distribution (SPSS 16.0 for Windows, 2007). To assess the statistical significance of ρ between any two variables, the 2-tailed significance test is performed in

SPSS. The probability value $p < 0.05$ from the 2-tailed significance test is taken to imply statistical significance. Ideally, the minimum data set would *not* be made up of variables that are significantly correlated, i.e. the variables are independent.

3.1.1 ANN RFW vs. C-SVC datasets for outcome prediction

MIRG's ANN RFW uses two datasets for training: the training set and the test set. The training set is used by the network to 'learn' and obtain the best parameters and structure with respect to network weights and biases. The test set evaluates the performance of the network after it has been trained. Optimal network parameters found during training and testing are validated with a third dataset – a verification dataset. Emphasizing that “in many respects, proper validation is more important than proper training”, Masters (1993) states that it is *imperative* that *no* part of the verification data is used as training. Using the same data for training and validation “biases the indication of what can be expected of the network when it is used in general population” (Masters, 1993). A large difference in training versus validation results can indicate that the overtraining has occurred and that the network does not generalize well. Rybchynski (2005) incorporated ten verification sets as part of the ANN RFW validation.

The Library for Support Vector Machines (LIBSVM) C-SVC v2.86 tool by Chang and Lin (2001), makes use of the cross-validation method for training the classifier, and thus integrates the training and test sets as one dataset. The *leave-one-out* or *n*-fold cross-validation, performed in this research with the LIBSVM C-SVC tool is the following:

1. A training set is divided into n subsets of equal size, where $n = 5$.

2. The classifier is trained n times, where on the i -th iteration ($i = 1, \dots, n$), the classifier is trained on all subsets except the i -th one.

A separate dataset is then used for verification, just as is done with the ANN RFW tool. The difference in training methods is taken into account when developing datasets for ANN RFW and LIVSVM C-SVC tools. MIRG uses the convention of splitting the original dataset into $\frac{2}{3}$ for training and testing, with the remaining $\frac{1}{3}$ of the data from the original database used for verification (Witten & Frank, 2005). Because CNN variables have different orders of magnitude, scaling is performed to equalize the importance of all input variables. Variables that are binary, such as *SEX*, have a value of either 1 or -1. For all other variables, MIRG uses the z-score normalization (Olden & Jackson, 2002) :

$$z_n = \frac{x_n - \bar{x}}{\sigma} \quad (3.1)$$

where,

- z_n = normalized value of variable x_n
- x_n = original variable x
- $\bar{x}$ = mean of the variable x
- σ = standard deviation of variable x

NEC model for the total population

For the ANN RFW tool datasets, the 13133 case database is divided into three datasets: training, testing and verification. As suggested by Ennett (2001), to deal with the data imbalance due to the low number of NEC cases, the training set is resampled using *random oversampling* to increase the number of NEC babies to 20%. Resampling involves:

1. From the 13133 database, randomly selecting the NEC cases used in training
2. Making multiple copies of the NEC case selected for the training dataset

3. Ensuring that all NEC cases (i.e. only NEC cases in the training set) are represented at least once in the training database.

This resampling is done for all models (VLBW and GestAge<33weeks). Table 3.2 summarizes the cases distribution for the three total population datasets.

Table 3.2: ANN RFW data distribution – NEC model for the total population

	NEC cases		Normal cases		TOTAL
	#	%	#	%	#
Original database	312	2.38	12821	97.62	13133
DATASETS					
Training	1428	20.0	5712	80.0	7140
Testing	69	2.36	2849	97.64	2918
Verification	100	2.30	4260	97.70	4360

Due to the n -fold cross-validation training of the LIBSVM C-SVM classifier, two training/testing dataset have been created for C-SVC training. The network is first trained and verified with the distribution of NEC and normal cases as found in the original 13133 database. Training and verification is then performed using a resampled training/testing dataset as summarized in table 3.3.

Table 3.3: LIBSVM C-SVC data distribution – NEC model for the total population

	NEC cases		Normal cases		TOTAL
	#	%	#	%	#
Original database	312	2.38	12821	97.62	13133
DATASETS					
Training/Testing	212	2.42	8561	97.58	8773
Training/Testing (resampled)	2140	20.00	8561	80.00	10701
Verification	100	2.30	4260	97.70	4360

It should be pointed out that the *exact* same cases are used in the training sets for both the ANN RFW and the LIBSVM C-SVM classifier. In addition, the verification sets for both classifiers are made up of identical cases and data distributions. This holds true for the datasets created for subsequent NEC models as well (VLBW and gestation<33weeks). Lastly, the training, testing and verification datasets are independent of one another, i.e. the datasets do *not* have the same patient records. The datasets were created only once for each tool (ANN and SVM). The work undertaken in thesis does *not* investigate data resampling on a different training NEC case subset. This can be considered part of future work in terms of database preparation techniques.

NEC in VLBW population

On the stipulation of literature that different risk factors are associated with NEC in preterm neonates versus those considered term, a NEC model for VLBW babies was considered a valid path to explore. The database used for this model involves a subset of the 13133 case CNN database, where the selection criterion is based on the birth weight being limited to babies $\leq 1,500\text{g}$. Tables 3.4 and 3.5 summarize the data split for ANN RFW and LIBSVM C-SVC classifiers respectively.

Table 3.4: ANN RFW data distribution – NEC model for the VLBW population

	NEC cases		Normal cases		TOTAL
	#	%	#	%	#
Original database	233	6.85	3170	93.15	3403
DATASETS					
Training	353	20.0	1414	80.0	1767
Testing	52	6.86	706	93.14	758
Verification	80	7.08	1050	92.92	1130

Table 3.5: LIBSVM C-SVC data distribution – NEC model for the VLBW population

	NEC cases		Normal cases		TOTAL
	#	%	#	%	#
Original database	233	6.85	3170	93.15	3403
DATA SETS					
Training/Testing	153	6.73	2120	93.27	2273
Training/Testing (resampled)	530	20.00	2120	80.00	2650
Verification	80	7.08	1050	92.92	1130

NEC in population with gestation <33 weeks

In addition to the VLBW population that comprises primarily of preterm neonates, the last population of interest considered for the preterm group are the neonates born at less than 33 weeks of gestation. This dataset is also a subset of the 13133 cases CNN database, and just like the VLBW subset database, it has a considerably smaller population of the normal cases, as seen in tables 3.6 and 3.7.

Table 3.6: ANN RFW data distribution – NEC model for gestation age <33 weeks

	NEC cases		Normal cases		TOTAL
	#	%	#	%	#
Original database	254	5.42	4436	94.58	4690
DATA SETS					
Training	494	20.0	1977	80.0	2471
Testing	54	5.18	989	94.82	1043
Verification	90	5.76	1470	94.23	1560

Table 3.7: LIBSVM C-SVC data distribution – NEC model for gestation age <33 weeks

	NEC cases		Normal cases		TOTAL
	#	%	#	%	#
Original database	254	5.42	4436	94.58	4690
DATASETS					
Training/Testing	164	5.24	2966	94.76	3130
Training/Testing (resampled)	741	20.00	2966	80.00	3707
Verification	90	5.76	1470	94.23	1560

3.2 Finding the Minimum Data Set

Misuse of current medical scoring systems, for outcomes for which they were not developed, drives the need to develop a minimum data set used in outcome prediction for NEC. Development of the NEC model follows two methodologies: ANN RFW and LIBSVM C-SVC.

3.2.1 ANN RFW

Automation of the ANN RFW by Rybchynski (2005) gives the tool the capability to perform an exhaustive search for network parameters and structures. This is done for both the single layer (0 hidden layers) and double layer (1 hidden layer) structure. As such, linear and non-linear ($2n+1$, $n>0$) structures are used and analyzed in the development of all the three NEC models. Network training starts with all 27 input variables, and uses weight decay and weight elimination (section 2.3.2.2) to determine the weights of least significance. Although the process is automated, researcher interaction is necessary to ensure that the best structure is selected by the network and that only structures where learning has occurred are selected as those of 'best' performance. Next, the modified Garson-Goh weight reduction method, as developed by Rybchynski (2005), uses the network weights and biases to determine the importance of network input variables. Variables are assigned weights from 0 (lowest) to 100 (highest) and are ranked in descending order of importance. The variables with the lowest weight are considered least significant and are removed from the network. The entire process is repeated, and variables are reduced until network performance degrades. The ANN RFW methodology steps are summarized:

1. For N -input variables, train and validate the network for all $2n+1$ structures, where n =# of input variables and $0 < n \leq N$.
2. Examine the log sensitivity, sensitivity and specificity graphs to ensure network convergence. Discard structures where oscillation occurs in the graphs. Discard structures where there is a large difference between the training and testing sets. These structures over generalize and validate poorly with respect to the verification dataset.
3. Given that the test epoch is not less than 100 (set by MIRG to ensure sufficient network training (Khan, 2006) , ensure that the ‘best test epoch’ is taken from a steady state on the log sensitivity graph.
4. Upon selecting the ‘best structure’ obtain the network performance by averaging the results of the 10 verification sets:
 - i. Sensitivity
 - ii. Specificity
 - iii. Classification rate

NOTE: Presence of zero value entries in the validation results suggest that the network has not converged. This means that network validation was not performed. If this is the case, a search for the ‘best structure’ has to be repeated for the N -input variables and another structure selected.

5. Upon successful completion of steps 1 to 4, invoke Rybchynski’s weight reduction method on the weights and biases of the best performing structure.

6. Rank the N -input variables in descending order of importance, as determined by the weights from step 5.
7. Remove the variable(s) i_k (where $k = 1, \dots, N$) with the smallest weight, as determined in step 6.
8. Repeat the entire procedure for $(N-i_k)$ -input variable set. The minimum data set is obtained when performance from one structure to the next degrades.

3.2.2 LIBSVM C-SVC

The radial basis function kernel used in this research, where $K(x, x_i) = \exp(-\gamma \|x - x_i\|^2)$, $\gamma > 0$, requires optimization of the C and γ parameters prior to commencing classification with the LIBSVM C-SVC tool, as these are not known beforehand. The C parameter is weighed with respect to the distribution of the rare and normal outcomes; whereas the gamma parameter (γ) is proportional to the width of the Gaussian basis function. It is of highest interest to determine the best (C, γ) parameters so that the classifier can be used for prediction. Chang and Lin (2001) suggest the use of n -fold cross-validation and grid search to identify suitable C and γ , which give a classification rate with a balance between sensitivity and specificity classifications. The authors reported that exponentially increasing sequences of C and γ is a practical way of identifying 'good' parameters; hence the grid search is done using $\log_2 C$ and $\log_2 \gamma$. Once valid (C, γ) parameters are found, the network is trained and tested on them for the different datasets.

A grid search for parameters is a time-consuming and computation-heavy task. By approximation alone, it is impossible to determine the correct starting point for the

parameter search. Using exponentially growing sequences for C and γ saves time, as does using a ‘coarse’ grid search with a step size of 1. Chang and Lin recommend this approach (Chang & Lin, 2001). For large datasets, such as the one used in this study, the authors also suggested taking a representative set of the population and determining the (C, γ) parameter pair for this subset of the original data first. With this in mind, VLBW and GestAge less than 33 weeks data sets are trained and tested first. A ‘fine’ grid search for the ideal (C, γ) parameter pair is performed once the region of interest is identified successfully with a coarse grid search. The fine grid search is performed with step sizes 0.5 and 0.1 respectively, in order to obtain better classification results.

3.2.2.1 Sensitivity analysis (SVM)

Finding the minimum data with LIBSVM C-SVC tool is a brute force procedure compared to the relative weight reduction method used by the ANN RFW. The standard SVM, as is the case for LIBSVM C-SVC, “can not select variables automatically and therefore its solution typically utilizes all the input variables without discrimination” (Zhang, Liu, Wu, & Zhu, 2008). Because input variable weights are not calculated, it is difficult to identify important predictor variables. To deal with this issue, this research uses sensitivity analysis in to reduce the initial variable set and obtain the minimum data set. Backward elimination is executed for all input variables, by removing one input variable at a time and training the algorithm. Once the algorithm is trained without a particular input variable, the removed variable is then reinstated to the set, the next variable is removed and the algorithm retrained. The model with the least amount of degradation with respect to specificity, sensitivity and classification rate is selected before the procedure of retraining the SVM is repeated with a smaller variable set.

Assuming that C and γ have been optimized, the steps performed to obtain the minimum data set with SVM are the following:

1. Train the C-SVC network with the N -input variable training dataset ($N=27$ for all NEC datasets, except the SNAPPE-II datasets where $N=9$).
2. Perform validation with the N -input variable verification dataset.
3. Obtain network performance for the verification dataset:
 - i. Sensitivity
 - ii. Specificity
 - iii. Classification rate
4. Remove input variable i_k (where $k = 1, \dots, N$) from the N -input variable training and verification datasets.
5. Repeat steps 1 to 3: training and validating the network on $N-i_k$ variables.
6. Replace variable i_k removed in step 4.
7. Repeat steps 4 to 6 for all N -input variables: $i_{k+1}, \dots, i_N$
8. Once training and validation is completed for all N -input variables, remove variable i_k which gives the best network performance with respect to specificity, sensitivity and classification rate.
9. Repeat the entire procedure for $(N-i_k)$ -input variable set. The minimum data set is obtained when performance from one structure to the next degrades.

3.2.3 Model Comparison

With respect to result analysis, model comparison is first performed within each of the two tools. ANN RFW models obtained for the total population (13133 cases), VLBW and less than 33 weeks gestation are compared to each other. The same is done for the models obtained with the LIBSVM C-SVC tool. Comparisons are done with respect to:

1. Performance of the tools for each population
 - a. network structure
 - b. sensitivity, specificity and classification rate; where specificity $\geq 85\%$ is chosen as the selection criteria in order to minimize the number of misclassifications
2. Variables in the minimum data set
 - a. common variables
 - b. variables of highest importance
 - c. SNAPPE-II variables

Once this is complete, performance of the tools is done with respect to each other. Comparison between the two tools is done based on the results from the verification sets, which were kept identical for the ANN RFW and the LIBSVM C-SVC tools.

4 RESULTS

4.1 Statistical analysis

Spearman analysis was performed in order to get a better understanding of how the input variables are related to the outcome of NEC. The level of correlation significance was taken as $p < 0.05$. From table 4.1 it can be seen that 25 out of 27 input variables had a fairly negligible ρ correlation coefficient, with the exception of birth weight ($\rho = -1.63$) and gestational age ($\rho = -158$). This is not a surprise as both low birth weight and low gestational age are associated with a higher risk of NEC. Variables *lurine*, *lgluc*, *lsodium*, *hpcO2* and *SEX* all had large p values (.680, .144, .225, .536 and .274 respectively), leading to the conclusion that these variables are independent and not correlated with NEC.

Table 4.1: Spearman correlation and 2-tailed statistical significance of input variables with respect to the outcome of NEC

Variable	SNAPPE-II variable (✓)	NEC	
		Correlation Coefficient ρ (rho)	Sig. (2-tailed)
<i>lurine</i>	✓	-.004	.680
hrespr		-.097**	.000
lplt		-.027**	.002
sga	✓	.038**	.000
hgluc		.044**	.000
lhema		-.081**	.000
Apgar5	✓	-.060**	.000
lbloodp	✓	-.097**	.000
hhema		-.075**	.000
<i>lgluc</i>		.013	.144
birthweight	✓	-1.63**	.000
hsodium		-.020*	.023
hitnrat		.058**	.000

LWBC		-.082**	.000
LANC		-.083**	.000
lheartr		.076**	.000
hheartr		.073**	.000
OI		.049**	.000
apnea		.025**	.005
ltempf	√	-.034**	.000
seizure	√	-.026**	.003
lsodium		-.011	.225
lpo2po2		.020*	.019
lserum	√	-.036**	.000
Po2fio2r	√	-.048**	.000
hpcO2		.005	.536
GestAGE		-.158**	.000
SEX		-.010	.274

** . Correlation is significant at the 0.01 level (2-tailed).

* . Correlation is significant at the 0.05 level (2-tailed).

4.2 ANN RFW Models

4.2.1 Total population model

Two NEC models were analyzed for the 13133 case database. In the first model, model A, the *GestAge* variable was classified with respect to 33 weeks of gestation. A value of -1 was assigned to babies born at or above 33 weeks of gestation; a value of 1 was assigned to babies born at less than 33 weeks of gestation. The purpose of differentiating by gestational age using categories, as opposed to scaling the variable with the z-score normalization, was to enhance the performance of the network. This is due to the fact that most babies with NEC were found to be born at less than 33 weeks of gestation (254 out of 312). The gestational split is considered significant primarily because NEC is thought to be more abundant in preterm babies. ANN results and variables sets for this model are shown in table 4.2 and 4.3 respectively.

Table 4.2: ANN RFW results for Model A*

# of Variables	27	23	20	19	18	17
Best test epoch	711	672	1201	921	1069	1080
Best structure	43	25	7	6	10	30
Log sensitivity	Best test	0.2666	0.4169	0.3327	0.4081	0.4110
	Verification avg.	0.2229	0.3196	0.2518	0.3561	0.2649
Sensitivity (%)	Best test	71.01	82.61	76.81	82.61	82.61
	Verification avg.	68.00	74.00	71.00	76.00	73.00
Specificity (%)	Best test	81.50	83.19	82.17	82.24	82.24
	Verification avg.	79.80	83.92	79.81	82.16	81.76
CCR (%)	Best test	81.25	83.17	82.04	82.25	82.25
	Verification avg.	79.54	83.69	79.61	82.02	81.56
ROC	Best test	80.49	84.99	84.89	86.95	84.78
	Verification avg.	71.88	69.71	72.53	75.69	72.40

*Model A – GestAge category of [-1,1]

Table 4.3: Variables and weights for best performance structures for Model A*

27 variables		23 variables		20 variables		19 variables		18 variables		17 variables	
lgluc	100	lgluc	100	GEST	100	bthwt	100	bthwt	100	bthwt	100
seizure	96	hrespr	93	Apgar5	72	seizure	67	hrespr	86	LWBC	99
Lurine	94	OI	90	Po2fio2r	67	hrespr	63	hpcO2	58	hrespr	90
Apgar5	94	lpo2po2	89	hrespr	63	Apgar5	61	Po2fio2r	53	GEST	86
hitnrat	93	hpcO2	86	hpcO2	62	lserum	51	hgluc	49	apnea	86
hrespr	93	LWBC	86	bthwt	57	hitnrat	50	Apgar5	44	seizure	86
hsodium	92	Lurine	84	lplt	57	hsodium	44	ltempf	41	OI	84
Po2fio2r	90	hgluc	82	hsodium	52	apnea	40	hitnrat	40	hitnrat	84
apnea	89	hsodium	80	apnea	47	OI	39	lserum	39	hsodium	84
hheartr	89	hitnrat	77	seizure	44	ltempf	38	Lurine	37	hgluc	83
GEST	86	seizure	76	ltempf	43	lplt	34	LWBC	37	hpcO2	79
lheartr	85	Po2fio2r	76	lgluc	42	lgluc	33	apnea	37	Po2fio2r	79
hpcO2	85	bthwt	76	hgluc	37	Lurine	29	GEST	34	lserum	78
ltempf	85	GEST	73	lserum	36	hpcO2	24	lgluc	34	Lurine	75
LANC	85	lserum	73	lpo2po2	34	Po2fio2r	21	OI	34	ltempf	73
hgluc	84	apnea	71	OI	33	GEST	20	seizure	30	Apgar5	65
OI	83	Apgar5	66	Lurine	33	LWBC	17	hsodium	27	lgluc	59
hhema	83	ltempf	66	hitnrat	32	hgluc	16	lplt	17		
lserum	82	lplt	65	LWBC	31	lpo2po2	14				
LWBC	81	hhema	65	hhema	27						
bthwt	80	hheartr	59								
lpo2po2	80	LANC	57								
lplt	80	lheartr	57								
lhema	79										
SEX	78										
lbloodp	75										
lsodium	67										

*Model A – GestAge category of [-1,1]

From table 4.2 it can be seen that the reduction of variables results in a fairly steady network performance with respect to the sensitivity, specificity and classification rates. The testing specificity and sensitivity values are nearly matching each other within each structure. However, this is not the case for the verification results. The difference between the testing and verification sensitivities is the smallest in the 27 variable dataset, coming in at 71.01% to 68.00% respectively. The conclusion here is that the network overtrains and does not generalize well to the rest of the population. The most significant variables for the model were *hrespr*, *lgluc*, and *birthweight*. *Hrespr* stayed fairly significant for the entire variable reduction, whereas *lgluc* level of significance decreased over the duration of the experiments. *Birthweight* picked up significance as the variable dataset decreased in size; in fact *birthweight* remained as the top variable in the 19, 18 and 17 variable models.

The second model, model B, had the gestation variable scaled using the z-score normalization equation (section 3.1.1, equation 3.1) instead of using the category split of Model A. This was done to improve on the verification results, which Model B lacked in. The results can be seen in table 4.4 and 4.5.

Table 4.4: ANN RFW results for Model B*

# of Variables		27	25	24	22	21	20	19
Best test epoch		1494	239	540	1055	708	1014	783
Best structure		11	12	43	13	9	13	10
Log sensitivity	Best test	0.2706	0.1856	0.3024	0.2387	0.3018	0.3271	0.2994
	Verification avg.	0.1864	0.1805	0.1706	0.1461	0.1814	0.2390	0.1917
Sensitivity (%)	Best test	68.12	59.42	71.02	65.22	71.01	73.91	71.01
	Verification avg.	64.00	61.00	67.00	63.00	65.00	67.00	64.00
Specificity (%)	Best test	88.00	86.31	88.00	87.33	87.89	86.45	87.47
	Verification avg.	87.75	78.85	81.20	84.79	85.94	86.74	86.95
CCR (%)	Best test	87.56	85.68	87.59	86.81	87.49	86.15	87.08
	Verification avg.	87.20	78.44	80.87	84.29	85.46	86.28	86.42
ROC	Best test	83.06	84.79	84.31	83.68	83.63	83.73	84.52
	Verification avg.	72.51	75.38	76.61	74.30	74.24	74.61	74.64

*Model B – GestAge scaled by z-score normalization

Table 4.5: Variables and weights for best performance structures for Model B*

27 variables		25 variables		24 variables		22 variables		21 variables		20 variables		19 variables	
GEST	100	lgluc	100	lbloodp	100	lgluc	100	bthwt	100	GEST	100	bthwt	100
OI	87	lserum	88	hitnrat	92	Po2fio2r	99	hhema	91	bthwt	85	Po2fio2r	99
hhema	84	hitnrat	79	lheartr	88	OI	99	LANC	90	seizure	77	GEST	98
lsodium	84	lsodium	77	Apgar5	87	apnea	95	lbloodp	86	lsodium	76	hitnrat	83
lgluc	84	OI	67	LANC	86	GEST	88	hheartr	84	hpc2	70	hhema	80
lserum	83	lbloodp	64	lsodium	84	lheartr	82	lsodium	77	OI	68	LANC	73
Lurine	83	GEST	63	Lurine	83	Apgar5	82	GEST	75	LANC	66	lbloodp	71
SEX	82	lhema	63	lgluc	81	hheartr	79	Apgar5	74	apnea	62	OI	66
hheartr	80	lheartr	63	OI	81	hitnrat	78	lhema	72	Po2fio2r	57	apnea	64
hpc2	78	ltempf	62	bthwt	81	lsodium	72	lserum	71	lserum	54	lhema	63
apnea	78	Lurine	60	lserum	80	ltempf	71	OI	71	lgluc	54	hpc2	63
lplt	76	LANC	60	lpo2po2	78	LANC	70	apnea	71	Lurine	53	lserum	62
seizure	76	hheartr	59	GEST	77	bthwt	68	hpc2	70	ltempf	51	Apgar5	57
LANC	75	hhema	56	apnea	77	hhema	68	hitnrat	66	lhema	50	Lurine	56
lbloodp	74	hpc2	56	hheartr	76	lbloodp	68	seizure	66	Apgar5	49	lgluc	52
hsodium	73	lplt	55	Po2fio2r	75	hpc2	66	lgluc	62	lbloodp	48	lsodium	45
lpo2po2	71	apnea	54	ltempf	72	lserum	63	Lurine	59	hhema	46	seizure	45
lhema	68	lpo2po2	53	lhema	71	seizure	61	ltempf	58	lheartr	43	ltempf	38
Po2fio2r	67	seizure	52	hhema	70	lplt	61	lheartr	57	hitnrat	36	lheartr	37
ltempf	66	Po2fio2r	50	hpc2	70	lhema	57	Po2fio2r	46	<i>hheartr</i>	26		
bthwt	66	bthwt	47	seizure	65	Lurine	39	<i>lplt</i>	37				
lheartr	63	hgluc	46	lplt	65	<i>lpo2po2</i>	38						
Apgar5	61	Apgar5	41	<i>hsodium</i>	64								
hitnrat	61	hsodium	40	<i>hgluc</i>	61								
hgluc	61	<i>SEX</i>	37										
<i>hrespr</i>	60												
<i>LWBC</i>	57												

*Model B – GestAge scaled by z-score normalization

The performance of Model B with respect to verification sensitivity across the minimum data sets (range from 61% to 67%) was worse than that of Model A (range from 68% to 76%). However, the verification results were much better when compared to the testing sensitivity, which means that the Model B network did not overtrain like the Model A network. Both *lgluc* and *birthweight* variables were of high importance, just like in the previous model. *GestAge* also seemed to carry more importance for Model B than Model A.

4.2.2 VLBW model

The VLBW model had the least number of cases of the three models. However, it still met the requirement of having at least 10 times the number of cases as it does variables, so it was considered valid (Masters, 1993). The performance measures and variable reduction are shown in tables 4.6 and 4.7 respectively.

Table 4.6: ANN RFW results for the VLBW model

# of Variables		27	24	23	22	21
Best test epoch		350	243	478	289	1784
Best structure		18	24	13	18	22
Log sensitivity	Best test	0.0458	0.0566	0.0589	0.0254	0.0459
	Verification avg.	0.0848	0.0674	0.0298	0.0825	0.0226
Sensitivity (%)	Best test	30.77	34.62	34.62	23.077	30.77
	Verification avg.	28.75	31.25	32.50	27.50	28.75
Specificity (%)	Best test	94.48	90.65	93.63	97.02	94.48
	Verification avg.	92.76	88.10	87.05	92.95	92.86
CCR (%)	Best test	90.10	86.81	89.58	91.95	90.11
	Verification avg.	88.23	84.07	83.19	88.32	88.32
ROC	Best test	54.21	58.57	68.03	64.15	62.33
	Verification avg.	56.84	54.46	60.63	52.32	58.64

Table 4.7: Variables and weights for best performance structures of the VLBW model

27 variables		24 variables		23 variables		22 variables		21 variables	
bthwt	100	hpc2	100	bthwt	100	bthwt	100	lhema	100
OI	88	lserum	84	Apgar5	94	Apgar5	90	hitnrat	90
Po2fio2r	84	Apgar5	82	GestAge	88	apnea	89	hheartr	90
lheartr	81	bthwt	79	SEX	87	hitnrat	86	SEX	88
GestAge	80	hgluc	77	lheartr	80	OI	86	lserum	85
LWBC	80	LANC	76	hgluc	80	lsodium	80	lplt	84
Apgar5	80	lsodium	71	hheartr	77	lhema	78	ltempf	80
lhema	78	lhema	71	ltempf	75	hgluc	78	LWBC	79
SEX	74	hhema	69	LWBC	71	lheartr	75	OI	76
hitnrat	74	ltempf	69	Lurine	71	SEX	72	lpo2po2	76
lbloodp	74	lgluc	69	lhema	67	LANC	72	hpc2	74
hgluc	72	apnea	66	lplt	66	lpo2po2	68	lsodium	71
lplt	71	lheartr	66	LANC	65	lplt	67	Lurine	68
hheartr	71	Lurine	66	hitnrat	62	ltempf	65	bthwt	64
lsodium	70	lplt	65	lserum	61	hheartr	63	lheartr	64
hhema	70	SEX	65	Po2fio2r	61	hhema	63	LANC	63
apnea	68	GestAge	64	hhema	59	hpc2	62	hhema	63

Lurine	65	hitnat	63	lpo2po2	59	lserum	62	GestAge	60
lpo2po2	64	LWBC	62	OI	58	GestAge	60	hgluc	59
LANC	62	Po2fio2r	62	hpcO2	57	LWBC	60	apnea	58
hpcO2	60	lpo2po2	61	apnea	54	Lurine	56	Apgar5	52
lgluc	58	hheartr	61	lsodium	49	<i>Po2fio2r</i>	52		
lserum	57	OI	56	<i>lgluc</i>	33				
ltempf	52	<i>lbloodp</i>	46						
<i>seizure</i>	47								
<i>hrespr</i>	47								
<i>hsodium</i>	45								

There was a drastic change in the sensitivity level of the VLBW model compared to sensitivities observed in models A and B. In fact, sensitivity of this model was nearly one half of Model A. This could potentially be attributed to the fact that the VLBW population is made up of babies that have additional medical complications. The complications may confound with those of NEC, making it hard for the network to distinguish between the two populations. However, this is a speculation that needs further investigation. The importance of *Apgar5* and *bthwt* variables was particularly pronounced in the VLBW model. Both of the variables ranked high for the 27, 24, 23 and 22 variable models.

4.2.3 GestAge < 33 weeks model

The last model analyzed was for the CNN population whose gestational age was less than 33 weeks. The results of this model can be seen in table 4.8 and 4.9 respectively. The model encompasses majority of the cases from the VLBW model, and because of that, the minimum data sets are expected to be similar for the two models. Results observed with respect to sensitivity, specificity and classification rates in the VLBW model are expected for this one as well.

Table 4.8: ANN RFW results for the GestAge < 33 weeks population

# of Variables		27	22	21	20	19
Best test epoch		538	919	631	609	1409
Best structure		10	8	8	6	5
Log sensitivity	Best test	0.0682	0.0511	0.0636	0.0670	0.0976
	Verification avg.	0.0911	0.0584	0.1179	0.0840	0.0390
Sensitivity (%)	Best test	37.04	33.33	34.01	37.04	44.44
	Verification avg.	33.33	31.11	30.00	33.33	37.78
Specificity (%)	Best test	93.33	89.28	89.18	92.01	89.28
	Verification avg.	89.05	88.30	88.57	86.26	86.46
CCR (%)	Best test	90.41	86.38	85.52	89.17	86.96
	Verification avg.	85.83	85.00	85.19	83.21	83.65
ROC	Best test	63.07	60.59	56.89	60.77	63.73
	Verification avg.	60.28	50.07	59.28	60.08	57.57

Table 4.9: Variables and weights for best performance structures of the GestAge <33 weeks model

27 variables		22 variables		21 variables		20 variables		19 variables	
lgluc	100	GEST	100	hitnrat	100	bthwt	100	lbloodp	100
hitnrat	100	LWBC	78	lserum	85	Po2fio2r	99	hhema	89
Lurine	98	bthwt	73	Apgar5	69	lhema	90	bthwt	82
Apgar5	98	ltempf	68	bthwt	67	lgluc	87	hitnrat	78
hsodium	95	lserum	67	GEST	66	hheartr	84	Apgar5	75
LWBC	91	Lurine	67	hrespr	66	hgluc	79	GEST	68
ltempf	91	lhema	65	SEX	63	Apgar5	76	LWBC	68
lbloodp	90	hrespr	63	hhema	62	lbloodp	75	hgluc	66
hhema	89	hsodium	61	LWBC	61	Lurine	70	lserum	64
bthwt	86	Apgar5	60	lhema	59	GEST	69	Po2fio2r	61
hrespr	82	hitnrat	58	ltempf	55	lserum	65	lgluc	61
lheartr	80	LANC	58	hgluc	54	lpo2po2	60	SEX	60
lplt	79	hgluc	57	LANC	53	hrespr	53	hrespr	60
GEST	77	hheartr	55	lpo2po2	49	LANC	52	hheartr	58
Po2fio2r	76	lgluc	52	Po2fio2r	47	LWBC	51	Lurine	57
hheartr	74	SEX	51	Lurine	45	hhema	45	lpo2po2	54
lpo2po2	73	Po2fio2r	49	lgluc	45	SEX	45	lhema	43
LANC	72	lplt	48	hsodium	44	hsodium	43	hsodium	34
SEX	72	lpo2po2	46	hheartr	42	hitnrat	43	LANC	20
lserum	71	lbloodp	43	lbloodp	37	<i>ltempf</i>	28		
hgluc	71	hhema	41	<i>lplt</i>	33				
lhema	70	<i>lheartr</i>	34						
<i>seizure</i>	67								
<i>hpcO2</i>	67								
<i>apnea</i>	64								
<i>lsodium</i>	64								
<i>OI</i>	60								

As expected, the performance of the GestAge<33 weeks model was fairly similar to the VLBW model. The GestAge< 33weeks also placed a high emphasis on the *Apgar5* variable, as well as the *bthwt*. However, the same variables were not removed from the VLBW and GestAge<33 models.

4.3 LIBSVM C-SVC Models

The results and analysis of the LIBSVM C-SVC models for NEC are reported in the inverse order, compared to the results obtained with the ANN RFW tool. The reason for this is the order in which the grid search was performed for obtaining the optimal C and γ parameters for the three models. C , a regularization constant that determines the trade-off between training errors and rigid margins, is vital for allowing misclassifications (i.e. slightly favouring sensitivity to specificity). The gamma parameter (γ) is used by the RBF kernel function. The search for these parameters was initially attempted with the complete database. However, this proved to be a complex task as the grid search is what determines the computational time of the SVM experiments. In order to find the starting point for the search, the preliminary grid search needs to cover a large area. This is a very costly search for large datasets. As such, a smaller subset of the original data was taken, such as the VLBW dataset, in order to establish a grid search starting point. There are two benefits to this approach: 1) it makes much less computational time as the dataset is smaller resulting in faster training, and 2) it is a good estimator of the starting point in the grid search. The preliminary grid searches are considered ‘coarse’ searches, as they cover a large area.

As per the suggestion of Chang and Lin (2001), a ‘fine’ grid search was attempted for all models once the optimal C and γ were found. The step size used was both 0.5 and 0.1. An improvement to the classification rate from the two ‘fine’ grid searches was minimal.

4.3.1 VLBW model

Table 4.10: Grid search for the C and γ parameters for VLBW

	Parameters				Classification
	C	$\log_2 C$	γ	$\log_2 \gamma$	Rate (%)
Original training (NEC=6.73%)	4096	12.0	0.0078123	-7.0	93.40
Resampled training (NEC=20%)	1.0	0.0	16.0	4.0	99.06
SNAPPE training (NEC=20%)	0.5	-1	4.0	2.0	93.27

The original VLBW NEC population was 6.73%. This distribution was used in the preliminary ‘coarse’ grid search for the C and γ parameters (table 4.10). With the LIBSVM C-SVC tool, the user has the ability to assign a *penalty* weight for the normals in the population. This penalty is determined by the ratio of the NEC babies to the normal population. Just like the *logsens* index in the ANN RFW tool favours sensitivity at the expense of specificity, the penalty weight is meant to do the same. After finding the optimal parameters, and obtaining a classification rate of 93.40%, the LIBSVM C-SVC was invoked to test and verify the parameters. Verification results were less than satisfactory: classification rate for training and testing was observed to be 92.92%. However, this was only representative of the normals in the population (specificity=100%) as none of the NEC babies were classified correctly (sensitivity=0%).

To overcome this obstacle, the SVM training data set was resampled in order to increase the distribution of the NEC babies. The classification rate for the 27 variables with the resampled training dataset was 99.06%. However, the VLBW failed in validation once again. The removal of variables one by one, did not seem to improve the sensitivity of the network, which was consistently 0-2%. As such, sensitivity analysis to determine a minimum data set was rendered useless for the VLBW model.

4.3.2 GestAge < 33 weeks model

GestAge <33 weeks model encountered the same problems observed in the VLBW model. Validation of the results was rendered impossible after finding the optimal C and γ parameters (table 4.11).

Table 4.11: Grid search for the C and γ parameters for GestAge<33weeks

	Parameters				Classification
	C	$\log_2 C$	γ	$\log_2 \gamma$	Rate (%)
Original training (NEC=5.42%)	4.0	2.0	0.5	-1.0	94.95
Resampled training (NEC=20%)	1.0	0.0	16.0	4.0	99.73
SNAPPE training (NEC=20%)	2.0	1.0	1.0	0.0	94.76

4.3.3 Total population model

The total population SVM model was of limited success as well. The original dataset with NEC = 2.42% was essentially invalid as the verification was giving sensitivity of less than 3%, and specificity of 100%. Once again it was impossible to determine the variables of importance, and the minimum data set search was deemed futile. Results improved drastically once the database was resampled to increase the

number of NEC cases from 2.42% to 20%. Table 4.12 shows the optimum values for parameters of C and γ ; table 4.13 shows the performance measures of the models given in table 4.14, as obtained by the LIBSVM C-SVC tool.

Table 4.12: Grid search for the C and γ parameters for the total population

	Parameters				Classification
	C	$\log_2 C$	γ	$\log_2 \gamma$	Rate (%)
Original training (NEC=2.42%)	2.5	1.32	2.0	1.0	97.62
Resampled training (NEC=20%)	2.0	1.0	2.0	1.0	99.74
SNAPPE training (NEC=20%)	2.0	1.0	2.0	1.0	99.58

Table 4.13: LIBSVM C-SVC results for the total population model

	TN	FP	TP	FN	TOTAL training	SENSITIVITY %	SPECIFICITY %	CR %
27 variables	4196	64	26	74	4360	26.00	98.50	96.83
26 variables	4190	70	26	74	4360	26.00	98.36	96.70
25 variables	4194	66	28	72	4360	28.00	98.45	96.83
24 variables	4197	63	28	72	4360	28.00	98.52	96.90
23 variables	4197	63	28	72	4360	28.00	98.52	96.90
22 variables	4207	53	29	71	4360	29.00	98.76	97.16
21 variables	4208	52	29	71	4360	29.00	98.78	97.18
20 variables	4207	53	30	70	4360	30.00	98.76	97.18
19 variables	4202	58	31	69	4360	31.00	98.64	97.09
18 variables	4202	58	31	69	4360	31.00	98.64	97.09
17 variables	4201	59	32	68	4360	32.00	98.62	97.09
16 variables	4202	58	31	69	4360	31.00	98.64	97.09

Table 4.14: LIBSVM C-SVC results for the total population model

27 variables	26 variables	25 variables	24 variables	23 variables	22 variables
hrespr	lhema	lhema	lhema	lhema	hitnrat
hsodium	lgluc	lgluc	lgluc	hitnrat	apnea
SEX	hitnrat	hitnrat	hitnrat	lgluc	lgluc
bthwt	hrespr	hrespr	hsodium	apnea	SEX
hitnrat	apnea	apnea	hrespr	GestAge	lhema
Po2fio2r	SEX	SEX	apnea	hsodium	GestAge
LWB	lbloodp	lbloodp	lbloodp	SEX	Po2fio2r
lserum	lserum	lserum	SEX	bthwt	hgluc
OI	lheartr	OI	LWB	Po2fio2r	LWB
LANC	OI	hheartr	lheartr	hpcO2	bthwt
hheartr	hheartr	hpcO2	hheartr	hgluc	lheartr
lgluc	Po2fio2r	Po2fio2r	lurine	lserum	lbloodp
lhema	ltempf	lurine	lserum	lurine	lsodium
lbloodp	hpcO2	lheartr	lplt	LWBC	hpcO2
lurine	hgluc	lsodium	OI	lplt	hsodium
lsodium	LWB	hsodium	ltempf	lsodium	lplt
lplt	lurine	ltempf	hpcO2	lpo2po2	OI
hgluc	lpo2po2	hgluc	Po2fio2r	hheart	lpo2po2
lheartr	Apgar5	LWB	lsodium	OI	hheartr
seizure	hsodium	lplt	hgluc	lheartr	lserum
GestAge	lplt	lpo2po2	lpo2po2	ltempf	lurine
ltempf	lsodium	bthwt	bthwt	lbloodp	ltempf
apnea	bthwt	GestAge	GestAge	hrespr	
hpcO2	GestAge	Apgar5	Apgar5		
Apgar5	LANC	LANC			
lpo2po2	seizure				
hhema					

Table 4.14 continued

21 variables	20 variables	19 variables	18 variables	17 variables	16 variables
apnea	hitnrat	hitnrat	hitnrat	hitnrat	lhema
SEX	lhema	apnea	lgluc	lhema	hitnrat
lhema	lgluc	lgluc	apnea	Lgluc	lgluc
hitnrat	apnea	lhema	lhema	apnea	apnea
lgluc	SEX	Po2fio2r	SEX	SEX	lheartr
GestAge	GestAge	SEX	lheartr	lheartr	Po2fio2r
hpcO2	lheartr	lheartr	Po2fio2r	Po2fio2r	hheartr
po2fio2r	Po2fio2r	GestAge	hheartr	hheartr	GestAge
lheartr	bthwt	hheartr	GestAge	GestAge	hsodium
hgluc	lsodium	hgluc	lpo2po2	hsodium	SEX
bthwt	hpcO2	bthwt	hsodium	lpo2po2	lpo2po2
lbloodp	hgluc	lsodium	hgluc	hpcO2	bthwt
lplt	lurine	hpcO2	lsodium	bthwt	hpcO2
hsodium	hsodium	lurine	bthwt	hgluc	hgluc
lsodium	lpo2po2	lpo2po2	lurine	lsodium	lsodium
lpo2po2	lplt	hsodium	OI	lurine	lurine
LWBC	LWB	OI	hpcO2	OI	
OI	OI	lplt	lplt		
hheartr	hheartr	LWB			
lurine	lbloodp				
lserum					

The variables that dominated the LIBSVM C-SVC data sets were *lhema*, *hitnrat* and *lgluc*. Sensitivity analysis performed showed that their removal from the data set caused the most degradation in performance with respect to sensitivity. The best performance was observed with a 17 variable data set which gave a sensitivity of 32.00%, specificity of 98.63% and classification rate of 97.09%.

4.4 Model Comparison: ANN vs. SVM

The best performance with respect to verification results was found with the ANN RFW tool minimum data set (20 variables) from Model B. Sensitivity was 67.00%, specificity 86.74% and classification rate 86.28%. For the same population, the best SVM results for sensitivity, specificity and classification rate were 32.00%, 98.63%, and 97.09% respectively. The ANN RFW tool obtains a higher sensitivity at the expense of a lower of specificity. However, in case of NEC this might be more appropriate as the complication has devastating consequences if it is not diagnosed in due time. It was also very interesting to note that although the number of NEC cases was fairly similar between all three models examined by the ANN RFW tool, especially for VLBW and GestAge<33weeks, different minimal datasets were obtained.

The VLBW and GestAge<33 weeks models could not be compared between the ANN RFW and LIBSVM C-SVC tool as the models were not obtainable by SVM. This could be attributed to several factors which need further investigation:

1. The small number of minority cases (NEC) might not be enough to train the SVM properly due to the fact that the cases are not similar in nature.

Ensuring that sufficient number of cases is kept for validation of training, potentially robs the network of additional information. Although this holds true for both ANN RFW and LIBSVM C-SVC, it was more of a problem for the later tool. ANN RFW performance did degrade for both the VLBW and GestAge<33 weeks models, compared to performance achieved by the total database model.

2. It is also very possible that babies making up the VLBW and GestAge<33 weeks populations are similar with respect to normal and NEC babies in those two populations of interest. Both of the classes might be exhibiting similar symptoms, making it hard for either tool to extract information about them and hence classify NEC correctly. This could explain why some of the variables deemed as 'independent' for the outcome of NEC using Spearman correlation (*lurine*, *lgluc*, *lsodium*, *hpcO2*, *SEX*) are still present in the minimum data sets.

Lastly, the use of LIBSVM C-SVC needs to be validated for additional medical outcomes, ex. mortality, before conclusive observations can be made about the tool performance. The nature of NEC in general, from disease complexity to the small number of cases, makes it difficult to model and analyze. This results in misclassification of minority cases and was seen in the performance of the LIBSVM C-SVC tool.

4.4.1 Additional ANN & SVM models

SNAPPE-II models contain only 9 input variables. Both the ANN RFW and LIBSVM C-SVC tools attempted to use just these variables to model NEC in the three populations of interest. The results of the findings are summarized in table 4.15.

Table 4.15: SNAPPE-II performance of the ANN RFW and LIBSVM C-SVC tools

		SENSITIVITY (%)	SPECIFICITY (%)	CR (%)
ANN RFW	Total data	64.00	66.85	66.78
	VLBW	59.80	54.85	55.22
	GestAge <33wks	n/a*	n/a*	n/a*
LIBSVM C-SVC	Total data	6.00	98.94	94.63
	VLBW	4.44	99.66	94.17
	GestAge <33wks	5.00	98.59	93.27

n/a* - model did not converge

Both ANN RFW and LIBSVM C-SVC performed poorly with only SNAPPE-II variables, compared to the results obtained when the full set of 27 variables was used. However, one thing was apparent: other than the *SGA* SNAPPE-II variable which was removed from NEC modeling, all ANN RFW models had at least 5 out of 8 SNAPPE-II variables present in their minimum data set (table 4.16). This suggests that although on their own SNAPPE-II variables are not sufficient to predict the outcome of NEC, some of them have an influence on the outcome. LIBSVM C-SVC model contained only 3 of the 8 SNAPPE-II variables.

Table 4.16: Occurrence of SNAPPE-II variables in minimum datasets

SNAPPE-II variable	ANN RFW tool				LIBSVM C-SVC
	Total population Model A	Total population Model B	VLBW model	GestAge<33wks model	Total population
lbloodp	x	√	x	√	x
ltempf	√	√	√	√	x
po2fio2r	√	√	x	√	√
lserum	√	√	√	√	x
seizure	√	√	x	x	x
lurine	√	√	√	√	√
bthwt	√	√	√	√	√
Apgar5	√	√	√	√	x
SGA	n/a	n/a	n/a	n/a	n/a

5 CONCLUSION

The pathology of NEC is extremely complicated compared to other medical outcomes studied by MIRG. This medical complication is multivariable and effects different populations of babies in different ways. In response to this, the goal of this research was to develop a day 1 model for NEC for the following three populations: total CNN database, VLBW babies, and those born at less than 33 weeks of gestation.

Model development was performed using MIRG's ANN RFW tool that has been validated on outcome predictions for morality, ventilation, length of stay, BPD and IVH. The structures that performed best in all three models were non-linear, but made up of different variable sets. In the minimum data sets for all of the NEC models, at least five out of the 8 SNAPPE-II variables were retained.

NEC was also modeled with a support vector machine tool. Modeling with the LIBSVM C-SVC v2.86 tool, using the radial basis function kernel did not provide valid results for the VLBW and gestation age less than 33 weeks models. Efforts to produce a minimum data set for these two populations proved futile as majority of NEC cases were misclassified. The total database model gave better results, but only after minority cases for the training set were resampled to 20%.

5.1 Summary of Contributions

1. NEC modeling was performed for the first time with the ANN RFW tool that has to date been used by MIRG for mortality, ventilation, length of stay, BPD and IVH

models of outcome prediction. Three different ANN RFW models were developed: total population, VLBW and gestation age less than 33 weeks.

2. From the three ANN RFW models, it was shown that NEC is governed by different variables in premature infants, compared to the total population.
3. While searching for the minimum data set, the ANN RFW tool did not select a single linear structure as the 'best performing' one for NEC. This proves that non-linear models are better at modeling such a multivariable medical complication.
4. NEC modeling was attempted with an SVM tool, and it was found that the tool performed better when rare outcomes were resampled up to 20%. This suggests that data resampling needs to be considered for other data mining systems and not just for ANNs.
5. Performance of SNAPPE-II variables was assessed for NEC outcome prediction. As literature review suggested, it was confirmed that scoring system variables (SNAPPE-II) can not be expected to perform well for an outcome for which they were not developed.

5.2 Future Research

Additional NEC models and validation

1. MIRG is currently involved in the process of obtaining the latest CNN database. The database of interest involves data from 24 tertiary NICU members of the CNN. The data collected between January 5th, 2005 and December 31st, 2005 includes 11,424 admissions (including transfers and re-admissions between NICUs) for a total of 11,004 patient admissions (Zhang, Lee, & Wingert A., 2006). As

occurrences of NEC are suspected to vary from centre to centre and from year to year, the 2005 CNN database would be used to validate the findings of current research.

2. NEC is often diagnosed post day 3. However, this model was not examined in the current research due to the large number of missing values in the day 3 data of the 1996-1997 CNN database. The aim is to develop a day 3 NEC model using the 2005 CNN database.

Support Vector Machines

3. The SVM tool used in this study needs to be validated for additional outcome prediction, among which are mortality, length of stay and ventilation, before further conclusions can be drawn about its performance.
4. In order to improve the performance of the standard SVM tools, weight reduction techniques for SVM tools need to be analyzed. These should then be applied to the LIBSVM C-SVC tool used in this research, as the current tool does not support this.

Diagnostic imaging for NEC

5. NEC is currently diagnosed and confirmed through X-ray imaging. In response to the need of a safer alternative imaging modality, MIRM and the author began collaboration with neonatologist Dr. Erika Bariciak in studying the performance of medical infrared imaging for NEC. Medical infrared imaging has to date been used in clinical diagnosis for breast cancer, extra-cranial vessel disease, neuro-musculo-skeletal disorders and vascular disease, among others. For NEC, research protocols

and ethical clearance have been obtained for the NICUs at the Children's Hospital of Eastern Ontario, as well as the Ottawa General Hospital. Data collection began in May 2007 and is in progress. Future work in this area deals with:

- i. Validating the use of clinical infrared imaging in NEC
- ii. Extracting features from the infrared images and using them to enrich the medical files with information, with the hope of improving the prediction performance of the CDSS tools (ANN RFW tool in particular)

Additional data mining tools

6. MIRG has established collaboration with Dr. Julio Valdés from the National Research Council of Canada (NRC) Institute for Information Technology. Dr. Valdés conducts research in the field of artificial intelligence, data mining and pattern recognition. The aim is to apply Dr. Valdés' hybrid neural network model to the CNN database that MIRG uses. Dr. Valdés' tool will aid in data mining of multivariate heterogeneous databases, such as the CNN, as the network has the ability to tolerate missing values, and use imaging information as input variables.

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APPENDIX A: Features of NEC

Table A-1: Clinical Characteristics and Laboratory & Radiographic Features of NEC
(McAlmon, 2004)

Clinical Characteristics	Laboratory & Radiographic Features
<i>Systemic signs:</i> <ul style="list-style-type: none"> • Respiratory distress • Apnea or bradycardia (or both) • Lethargy • Temperature instability • Irritability • Poor feeding • Hypotension (low BP, shock) • Decreased peripheral perfusion • Acidosis • Oliguria (reduced urine output) • Bleeding diathesis (hemorrhage) 	<i>Radiographic features:</i> <ul style="list-style-type: none"> • Dilated bowel loops • Abnormal gas pattern (consistent with ileus) • Bowel wall edema (swelling) • Pneumatosis intestinalis (gas within bowel wall; KEY radiographic trademark to confirm NEC diagnosis) • Portal / hepatic venous gas • Pneumoperitoneum (air in abdominal cavity)
<i>Abdominal signs:</i> <ul style="list-style-type: none"> • Bloody stool (occult or gross blood) • Abdominal distension / tenderness • Gastric aspirates (feeding residuals) • Vomiting (blood, bile or both) • Decreased / absent bowel sounds • Abdominal wall erythema (redness of skin due to inflammation), or induration (hardening / thickening of tissue) • Abdominal mass • Ascites (fluid in abdomen) 	<i>Blood studies:</i> <ul style="list-style-type: none"> • Thrombocytopenia (low platelet count) • Persistent metabolic acidosis • Severe refractory hyponatremia (abnormally low concentration of sodium (Na⁺) ions in blood)
<i>Course of the disease:</i> <p>a) Severe / aggressive onset and rapidly progressive presentation of signs</p> <p>b) Slow and sudden presentation of abdominal distension, ileus (loss of bowel motility, possible infection)</p>	<i>Analysis of stool:</i> <ul style="list-style-type: none"> • Presence of blood and carbohydrate malabsorption indicate changes in intestinal integrity • Gross blood <i>may</i> be an indication of NEC while occult can be present for other medical reason

Table A-2: Modified Bell Staging Criteria (Bell et al., 1978), (Panigrahi, 2006)

Stage	Findings
Stage I A (NEC suspect)	<ul style="list-style-type: none">• Temperature instability, apnea, bradycardia, lethargy• Abdominal distension, gastric residuals, poor feeding, bilious vomiting, occult (hidden) blood in stool• X-ray shows mild ileus
Stage I B (NEC suspect)	<ul style="list-style-type: none">• As for stage I A with gross (visible) blood in stool
Stage II A (definite NEC, mildly ill)	<ul style="list-style-type: none">• As for stage I B, with pneumatosis intestinalis, absent bowel sounds +/- abdominal tenderness
Stage II B (definite NEC, moderately ill)	<ul style="list-style-type: none">• As for stage II A with metabolic acidosis, mild thrombocytopenia, leukocytosis or leukopenia• Abdominal cellulitis or right lower quadrant mass• Portal venous gas, with or without ascites (peritoneal cavity fluid)
Stage III A (advanced NEC, severely ill infant, bowel intact)	<ul style="list-style-type: none">• As for stage II B with hemodynamic changes, hypotension, respiratory acidosis, neutropenia, disseminated intravascular coagulation• Abdominal cellulitis or right lower quadrant mass
Stage III B (advanced NEC, severely ill infant, perforated bowel)	<ul style="list-style-type: none">• Same radiologic findings as in stage II B, with definite ascites• Same as stage III A with ruptured bowel and pneumoperitoneum

Figure A-1: (a) Supine and (b) cross-table lateral X-ray images of a NEC patient's abdomen (Epelman et al., 2007)

APPENDIX B: Neonatal Scoring Systems

Table B-1: The Apgar Score (Beachy & Deacon, 1993)

COMPONENT	SCORE		
	0	1	2
Appearance (skin colour)	blue, pale	body pink, extremities blue	pink
Pulse (heart rate)	absent	<100bpm	>100bpm
Grimace (reflex irritability)	no response	grimace	cough/sneeze/cry
Activity (muscle tone)	flaccid	some flexion	well flexed
Respiration (breathing)	absent	weak, irregular	good, crying

Table B-2: CRIB (The International Neonatal Network, 1993)

Factor	Score
Birthweight (g)	
> 1350	0
851-1350	1
701-850	4
≤ 700	7
Gestation (wk)	
> 24	0
≤ 24	1
Congenital malformations	
None	0
Not acutely life-threatening	1
Acutely life-threatening	3
Maximum base excess in first 12h (mmol/L)	
> -7.0	0
-7.0 to -9.9	1
-10.0 to 14.9	2
≤ -15.0	3
Minimum appropriate FIO₂ in first 12h	
≤ 0.40	0
0.41 – 0.60	2
0.61 – 0.90	3
0.91 – 1.00	4
Maximum appropriate FIO₂ in first 12h	
< 40	0
0.41 – 0.80	1
0.81 – 0.90	3
0.91 – 1.00	5

*Measured during first 12h; Infants of birthweight ≤1500g or gestational age <31 weeks.

Table B-3: CRIB II (Parry et al., 2003)

Birthweight (g) and gestation (weeks):
The maximum (worst) score for birthweight and gestation is 15, which is obtained for a 22 week male infant of less than 501 g birthweight

Male Infants													Female Infants												
Birthweight (g)	Gestation (weeks)												Birthweight (g)	Gestation (weeks)											
	22	23	24	25	26	27	28	29	30	31	32	22		23	24	25	26	27	28	29	30	31	32		
2751 to 3000											0											0			
2501 to 2750											1	0										1	0		
2251 to 2500											2	0	0								2	0	0		
2001 to 2250											3	0	0								3	0	0		
1751 to 2000											4	0	0								4	0	0		
1501 to 1750											5	0	0								5	0	0		
1251 to 1500											6	0	0								6	0	0		
1001 to 1250											7	0	0								7	0	0		
751 to 1000											8	0	0								8	0	0		
501 to 750											9	0	0								9	0	0		
251 to 500											10	0	0								10	0	0		

Temperature at admission (°C)	
<29.6	5
29.7 to 31.2	4
31.3 to 32.8	3
32.9 to 34.4	2
34.5 to 36	1
36.1 to 37.5	0
37.6 to 39.1	1
39.2 to 40.7	2
>40.8	3

Base excess (mmol/L):	
< -26	7
-26 to -23	6
-22 to -19	5
-17 to -13	4
-12 to -8	3
-7 to -3	2
-2 to 2	1
>3	0

Sex, birthweight (g) and gestation (weeks): _____

Temperature at admission (°C): _____

Base excess (mmol/L): _____

Total CRIB II Score

The logistic regression equation relating CRIB II to mortality (CRIB II algorithm) is:

Log odds of mortality = $\ln 0.476 + 0.460 \times \text{CRIB II}$

Probability of mortality = $\exp(\ln 0.476 + 0.460 \times \text{CRIB II}) / [1 + \exp(\ln 0.476 + 0.460 \times \text{CRIB II})]$

The range of possible CRIB II scores is 0 to 27

Table B-4: NTISS scoring system (Ennett, 2003)

Item	Subscore	Item	Subscore
RESPIRATORY		MONITORING (con't)	
Supplemental oxygen	1 ^a	Thermoregulated environment	1
Surfactant administration	1	Noninvasive oxygen	1
Tracheostomy care	1 ^b	Arterial pressure	1
Tracheostomy placement	1 ^b	Central venous pressure	1
Continuous positive airway pressure administration	2 ^a	Urinary catheter	1
Endotracheal intubation	2	Quantitative intake and output	1
Mechanical ventilation	3 ^a	Extensive phlebotomy (>10 blood draws)	2 ^h
Mechanical ventilation with muscle relaxation	4 ^a	METABOLIC/NUTRITION	
High-frequency ventilation	4 ^a	Gavage feeding	1
Extracorporeal membrane oxygenation	4	Intravenous fat emulsion	1
CARDIOVASCULAR		Intravenous amino acid solution	1
Indomethacin administration	1	Phototherapy	1
Volume expansion (<= 15 mL/kg)	1 ^c	Insulin administration	2
Vasopressor administration (1 agent)	2 ^d	Potassium infusion	3
Volume expansion (> 15 mL/kg)	3 ^c	TRANSFUSION	
Vasopressor administration (>1 agent)	3 ^d	Intravenous gamma globulin	1
Pacemaker on standby	3 ²	Red blood cell (<=15 mL/kg)	2 ⁱ
Pacemaker used	4 ^e	Partial volume exchange	2
Cardiopulmonary resuscitation	4	Red blood cell (>15 mL/kg)	3 ⁱ
DRUG THERAPY		Platelet	3
Antibiotic (<=2 agents)	1 ^f	White blood cell	3
Diuretic (enteral)	1 ^g	Double volume exchange	3
Steroid (postnatal)	1	PROCEDURAL	
Anticonvulsant	1	Transport of patient	2
Aminophylline	1	Single chest tube in place	2 ^j
Other unscheduled medication	1	Minor operation	2 ^k
Antibiotic (> 2 agents)	2 ^f	Multiple chest tubes in place	3 ^j
Diuretic (parenteral)	2 ^g	Thoracentesis	3
Treatment of metabolic acidosis	3	Major operation	4 ^k
Potassium binding resin	3	Pericardiocentesis	4 ^l
MONITORING		Percardial tube in place	4 ^l
Frequent vital signs	1	Dialysis	4
Cardiorespiratory	1	VASCULAR ACCESS	
Phlebotomy (5-10 blood draws)	1 ^h	Peripheral intravenous line	1
		Arterial line	2
		Central venous line	2

*Subscript letters represent mutually exclusive variables.

Table B-5: SNAP scoring system (Richardson et al., 1993)

Variable		Point Range			
		0	1	3	5
Mean blood pressure, mmHg	High	<66	66-80	81-100	>100
	Low	>35	30-35	20-29	<20
Heart rate	High	<180	180-200	201-250	>250
	Low	>100	80-100	40-79	<40
Respiratory rate	High	<60	60-100	>100	—
Temperature (°F)	Low	>96	95-96	92-94.9	<92
pO ₂ , mmHg	Low	>65	50-65	30-50	<30
pO ₂ /FiO ₂ ratio	Low	>3.5	2.5-3.5	0.3-2.49	<0.3
pCO ₂ , mmHg	High	<50	50-65	66-90	>90
Oxygenation index (OI)	High	<0.07	0.07-0.2	0.21-0.40	>0.40
Hematocrit, %	High	<66	66-70	>70	—
	Low	>35	30-35	20-29	<20
White blood cell count (x1000)	Low	>5.0	2.0-5.0	<2.0	—
Immature/total neutrophil ratio	High	<0.21	≥0.21	—	—
Absolute neutrophil count	Low	>999	500-999	<500	—
Platelet count (x1000)	Low	>100	30-100	0-29	—
Blood urea nitrogen, mg/dL	High	<40	40-80	>80	—
Creatinine, mg/dL	High	<1.2	1.2-2.4	2.5-4.0	>4.0
Urine output, mL/kg/h	Low	>0.9	0.5-0.9	0.1-0.49	<0.1
Indirect bilirubin (birth weight)					
- >2kg: mg/dL		<15	15-20	>20	—
- ≤2kg: mg/dL		<5	5-10	>10	—
Direct bilirubin, mg/dL		<2.0	>2.0	—	—
Sodium, mEq/L	High	<150	150-160	160-180	>180
	Low	>130	120-130	<120	—
Potassium, mEq/L	High	<6.6	6.6-7.5	7.6-9.0	>9.0
	Low	>2.9	2.0-2.9	<2.0	—
Calcium (ionized), mg/L	High	<1.4	≥1.4	—	—
	Low	>1.0	0.8-1.0	<0.8	—
Calcium (total), mg/L	High	<12	≥12	—	—
	Low	>6.9	5.0-6.9	<5.0	—
Glucose, mg/L	High	<150	150-250	>250	—
	Low	>40	30-40	<30	—
Serum bicarbonate, mEq/L	High	<33	≥33	—	—
	Low	>15	11-15	≤10	—
Serum pH	Low	>7.30	7.20-7.30	7.10-7.19	<7.10
Presence of seizures		None	Single	Multiple	—
Presence of apnea		None	Responsive to stimulation	Unresponsive to stimulation	Complete apnea
Stool guaiac		Negative	Positive	—	—

*Perinatal Extension (PE) variable points:

Birth weight	
≤ 749g	30 points
750 – 799	10 points
Apgar <7 (at 5min)	10 points
SGA (5 th percentile)	5 points

Where assignment of points corresponds to the following:

Point 0: normal physiologic range/missing data

Point 1: physiologic deviation was sufficiently abnormal to merit careful monitoring

Point 3: deviation was such that most clinicians would alter therapy to correct it

Point 5: acutely life-threatening

Table B-6: SNAPPE-II scoring system (Ennett, 2003)

Variable	Range	Points
Lowest blood pressure	MBP ^a 20-29 mmHg	9
	MBP ^a <20 mmHg	19
Lowest temperature	95-96 °F	8
	<95 °F	15
Lowest PO2/FiO2 ratio	1.0-2.49	5
	0.3-0.99	16
	<0.3	28
Lowest serum pH	7.10-7.19	7
	< 7.10	16
Multiple seizures	>1	19
Lowest urine output	0.1-0.9 mL/kg/h	5
	<0.1 mL/kg/h	18
Birth weight	750-999 g	10
	<750 g	17
Small for gestational age	< 3 rd percentile	12
Apgar score at 5 minutes	< 7	18

*^aMBP = mean arterial blood pressure