uOttawa

L'Université canadienne
Canada's university

**FACULTÉ DES ÉTUDES SUPÉRIEURES ET POSTOCTORALES**

uOttawa

L'Université canadienne
Canada's university

**FACULTY OF GRADUATE AND POSDOCTORAL STUDIES**


Eman Ahmed Ibrahim
AUTEUR DE LA THÈSE / AUTHOR OF THESIS

M.A.Sc. (Electrical Engineering)
GRADE / DEGREE

School of Information Technology and Engineering
FACULTÉ, ÉCOLE, DÉPARTEMENT / FACULTY, SCHOOL, DEPARTMENT


Design of an XML-Based Alerting System Prototype Using Mortality Prediction Models

TITRE DE LA THÈSE / TITLE OF THESIS

M. Frize
DIRECTEUR (DIRECTRICE) DE LA THÈSE / THESIS SUPERVISOR

CO-DIRECTEUR (CO-DIRECTRICE) DE LA THÈSE / THESIS CO-SUPERVISOR

EXAMINATEURS (EXAMINATRICES) DE LA THÈSE / THESIS EXAMINERS

Peter X. Liu

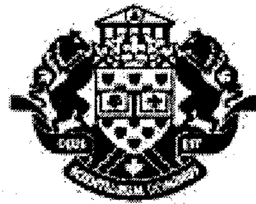
N. Yagoub

Gary W. Slater
Le Doyen de la Faculté des études supérieures et postdoctorales / Dean of the Faculty of Graduate and Postdoctoral Studies

# Design of an XML-Based Alerting System Prototype Using Mortality Prediction Models

Submitted by

Eman Ibrahim




A thesis submitted to the Faculty of Graduate Studies and Research
In partial fulfillment of the requirements for the degree of

Master of Applied Science in Electrical Engineering

School of Information Technology and Engineering

University of Ottawa

© 2007 Ibrahim: Ottawa, Ontario, Canada

Library and
Archives Canada

Published Heritage
Branch

395 Wellington Street
Ottawa ON K1A 0N4
Canada

Bibliothèque et
Archives Canada

Direction du
Patrimoine de l'édition

395, rue Wellington
Ottawa ON K1A 0N4
Canada

*Your file Votre référence*
*ISBN: 978-0-494-49212-3*
*Our file Notre référence*
*ISBN: 978-0-494-49212-3*

NOTICE:
The author has granted a non-exclusive license allowing Library and Archives Canada to reproduce, publish, archive, preserve, conserve, communicate to the public by telecommunication or on the Internet, loan, distribute and sell theses worldwide, for commercial or non-commercial purposes, in microform, paper, electronic and/or any other formats.

The author retains copyright ownership and moral rights in this thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without the author's permission.

AVIS:
L'auteur a accordé une licence non exclusive permettant à la Bibliothèque et Archives Canada de reproduire, publier, archiver, sauvegarder, conserver, transmettre au public par télécommunication ou par l'Internet, prêter, distribuer et vendre des thèses partout dans le monde, à des fins commerciales ou autres, sur support microforme, papier, électronique et/ou autres formats.

L'auteur conserve la propriété du droit d'auteur et des droits moraux qui protège cette thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

In compliance with the Canadian Privacy Act some supporting forms may have been removed from this thesis.

While these forms may be included in the document page count, their removal does not represent any loss of content from the thesis.

Conformément à la loi canadienne sur la protection de la vie privée, quelques formulaires secondaires ont été enlevés de cette thèse.

Bien que ces formulaires aient inclus dans la pagination, il n'y aura aucun contenu manquant.

# Abstract

This thesis presents an XML based clinical alerting system prototype that has the ability to accurately detect and warn medical decision makers of critical events or complications prior to their occurrence.

The alerting system makes use of existing MIRG ANN infant mortality prediction models to develop 'alert generation rule' algorithms using the four most highly ranked variables in each of the mortality prediction models.

Prior to the use of this system, physicians did not have a way of knowing which ANN mortality model was better at predicting infant mortality as these models are similar and there is no currently known method to establish which one is better except by generally computing sensitivity and specificity. This alerting system is a first attempt at finding an alternate way to assess how each model performs in detecting the outcome 'death' and can be used by MIRG researchers in selecting the best model.

# Acknowledgments

I would like to thank my supervisor Dr. Monique Frize for her constant support and encouragement in helping me overcome my obstacles in completing this thesis. Dr.Frize always believed in me and my abilities and helped me look at things in a more positive way and was very patient with me over the last few years.

I would like to thank god and my parents, Tahany and Ahmed Ibrahim, for their support and constantly pushing me to finish my thesis. I couldn't have done this without their blessings. A very special thank you to my mom who spent countless hours with my son to help me concentrate on my work and finally finish after all the hurdles I have come across.

I would also like to thank my MIRG colleagues especially Doaa Swailum, Dajie Zhou, Saadia Kahn, Daphne Townsend and Christina Catley, you all helped me fill in the missing gaps and provided me with the background and support I needed to complete my research.

I am most grateful to my friends Ghada, Amy and Mr. Badr for helping me reach the point of completion. I would have never been able to finish without your great efforts and countless hours of assistance and encouragement.

Finally to my family Sherif, and my boys Ahmad and Omar El-Barbary you were my inspiration to finish this work you motivated me to work long nights to while you were sleeping to complete my thesis. You boys are the light of my life and I dedicate this thesis to you.

# Table of Contents

ABSTRACT ..... II
ACKNOWLEDGMENTS ..... III
TABLE OF CONTENTS ..... IV
LIST OF FIGURES ..... VI
LIST OF TABLES ..... VII
LIST OF EQUATIONS ..... VII
NOMENCLATURE ..... VIII
CHAPTER 1: INTRODUCTION ..... 1
1.1 MOTIVATION AND SIGNIFICANCE OF RESEARCH ..... 3
1.2 DEFINITION OF THE PROBLEM AND THESIS OBJECTIVES ..... 4
1.3 MIRG'S MEDICAL SOFTWARE AND APPLICATION ENVIRONMENT ..... 7
1.4 THESIS OUTLINE ..... 8
CHAPTER 2: LITERATURE REVIEW ..... 10
2.1 CLINICAL EVENT MONITORS ..... 10
*2.1.1 An Excess of False Alarms* ..... *11*
*2.1.2 Efforts to Reduce False Alarms Produced by Event Monitors* ..... *13*
*2.1.3 Integrating Alerting Systems with Intelligent Alarming Schemes* ..... *16*
2.2. APPLICATION OF CLINICAL ALERTING SYSTEMS IN HEALTHCARE ..... 20
*2.2.1 Clinical Laboratory Alerting Systems* ..... *20*
*2.2.2 Physiologic Alerting Systems* ..... *23*
*2.2.3 Computerized Prescriber/Physician Order Entry Systems* ..... *25*
2.3 FROM WIRED TO WIRELESS COMMUNICATION ..... 29
CHAPTER 3: BACKGROUND ..... 33
3.1 CHEO'S NICU REAL-TIME DATA ACQUISITION SYSTEM ..... 34
3.2 CLINICAL DECISION SUPPORT SYSTEMS ..... 35
3.3 ARTIFICIAL NEURAL NETWORKS ..... 36
*3.3.1 ANN Architecture* ..... *37*
*3.3.2 Types of Artificial Neural Networks* ..... *39*
*3.3.3 Weight Decay and Weight Elimination* ..... *40*
*3.3.4 Adaptive Network Parameters* ..... *41*
*3.3.5 Performance Measurements* ..... *43*
3.3.5.1 Correct Classification Rate (CCR) ..... 43
3.3.5.2 Sensitivity ..... 44
3.3.5.3 Specificity ..... 44
3.3.5.4 Confusion Matrix ..... 44
3.4 MIRG'S CLINICAL DECISION SUPPORT TOOLS ..... 45
*3.4.1 MIRG's Artificial Neural Network* ..... *45*
*3.4.2 Case-Based Reasoner* ..... *47*
*3.4.3 K-Nearest Neighbour* ..... *47*
3.5 MIRG ANN PREDICTION MODELS ..... 49
*3.5.1 ANN Mortality Prediction Model 1: Ennett's Model* ..... *50*
*3.5.2 ANN Mortality Prediction Model 2: Qi's Model* ..... *52*
*3.5.3 ANN Mortality Prediction Model 3: Rybchynski's Model* ..... *55*
3.6 STRUCTURAL LANGUAGES ..... 57
*3.6.1 EXtensible Markup Language (XML)* ..... *57*
*3.6.2 Overview of eXtended Markup Language (XML)* ..... *59*

*3.6.3 XML Schema Language* ........ *62*
3.6.3.1 Document Type Definitions ........ 63
*3.6.4 XML Parsers* ........ *64*
*3.6.5 XML Processors* ........ *66*
*3.6.6 Extensible Stylesheet Language Transformations (XSLT)* ........ *67*
*3.6.7 Wireless Markup Language (WML)* ........ *68*
*3.6.8 Short Messaging Service (SMS)* ........ *68*

**CHAPTER 4: ADOPTION OF MOBILE COMPUTING AND WIRELESS TECHNOLOGY IN HEALTHCARE** ........ **70**

4.1 BENEFITS OF WIRELESS AND MOBILE COMPUTING ........ 71
4.2 TECHNOLOGY ASSESSMENT: TECHNOLOGIES USED IN IMPLEMENTING A WIRELESS HEALTHCARE ... 72
*4.2.1 Personal Area Network (PAN - WPAN):* ........ *75*
*4.2.2 Local Area Network (LAN –WLAN):* ........ *75*
*4.2.3 Wide Area Networks (WAN – WWAN)* ........ *76*
4.3 CHALLENGES IN IMPLEMENTING WIRELESS TECHNOLOGIES IN HEALTHCARE ENVIRONMENTS ........ 79
*4.3.1 Interference of Coexisting Technologies and Medical Devices* ........ *79*
*4.3.2 Cultural and Physicians Resistance to Change* ........ *80*
*4.3.3 Interoperability of Medical Devices* ........ *80*
*4.3.4 Privacy* ........ *81*
*4.3.5 Security* ........ *81*

**CHAPTER 5: METHODOLOGY** ........ **83**

5.1 INTEGRATING CLINICAL ALERTS INTO AN XML-BASED HEALTH CARE FRAMEWORK ........ 83
5.2 DESIGN AND IMPLEMENTATION OF EMAN SYSTEM ........ 85
*5.2.1 XML NICU Alert Schema* ........ *86*
*5.2.2 Schema Structure* ........ *87*
*5.2.3 High Level Overview of XML Alerting System Architecture* ........ *89*
5.3 WEB-BASED USER INTERFACE ........ 90
*5.3.1 Design of the User Interface* ........ *91*
*5.3.2 Manage Patient Records* ........ *92*
*5.3.3 Manage Staff Data* ........ *93*
*5.3.4 Manage Thresholds* ........ *93*
*5.3.5 Invoke CDSS* ........ *94*
5.4 ALERTING SYSTEM PROTOTYPE ........ 94
5.5 DATA SOURCE AND INPUT VARIABLES ........ 97
*5.5.1 ANN Input Variables* ........ *98*
*5.5.2 Data Processing for Alert Generation* ........ *98*
*5.5.3 Alert Generation Rules* ........ *99*
5.5.3.1 Basic Rules ........ 99
5.5.3.2 Advanced Rules ........ 100
5.5.3.3 Combination Rules ........ 100
5.6 PROCEDURE FOR TESTING PERFORMANCE OF ALERTING SYSTEM ........ 101

**CHAPTER 6: RESULTS AND DISCUSSION** ........ **104**

6.1 TESTING THE PERFORMANCE OF THE ALERTING SYSTEM ........ 105
6.2 DISCUSSION OF RESULTS ........ 108
*6.2.1 Varying the number of Variables in the Alert Generation Rules* ........ *109*
6.3 ALERTS GENERATED BY ALERTING SYSTEM ........ 111

**CHAPTER 7: CONCLUSION, CONTRIBUTIONS AND FUTURE WORK** ........ **113**

7.1 CONCLUSION ........ 113
7.2 RESEARCH CONTRIBUTIONS ........ 114
7.3 FUTURE WORK ........ 115

**REFERENCES:** ........ **116**

## List of Figures

Figure 3-1: Basic Architecture of a two-layer ANN [Rybchynski, 2005] .............. 38
Figure 3-2: The Basic Neural Unit [Rybchynski, 2005] .............. 39
Figure 3-3: Multi-layered feed-forward ANN [Rybchynski, 2005] .............. 40
Figure 5-1: Architecture of Alerting System .............. 89
Figure 5-2: Structure of Alerting Systems User Interface .............. 92
Figure 5-3: Alerting System Layout .............. 95

## List of Tables

Table 3-1: Confusion Matrix for Two-Value Classification Outcome [Hohavi & Provost, 1998] ..... 45
Table 3-2: Ennett's List of Risk Factors for Predicting Mortality [Ennett 2003] .. 52
Table 3-3: Classification Rate of EPIC database by ANN tool and Physicians [Qi, 2005] ..... 54
Table 3-4: Classification results by physicians vs. ANN tool using the EPIC database [Qi 2005] ..... 54
Table 3-5: Rybchynski's CCVT compared to Qi's ANN Tool [Rybchynski 2005] 56
Table 3-6: MIRGs ANN Mortality Prediction Model Minimal Data Sets ..... 57
Table 4-1: Potential Benefits from Health Care Mobile Computing Applications [Turisco & Case 2001] ..... 74
Table 4-2: Comparison of Wireless Technologies [FCE, 2006] ..... 78
Table 5-1: ANN Inputs and Output used by the alerting system ..... 87
Table 6-1: Confusion Matrix for Alert Generation Rules using 4 variables. ..... 106
Table 6-2: Performance of Alert Generation Rule tests ..... 107
Table 6-3: Rybchynski's Model: Alert generation rule #1 ..... 110
Table 6-4: Qi's Model: Alert Generation Rule #2 ..... 111
Table 6-5: Ennett's Model: Alert Generation Rule #3 ..... 111

## List of Equations

Equation 3-1: Classification Rate [Hohavi & Provost, 1998] ..... 43
Equation 3-2: Sensitivity [Penny & Frost, 1996] ..... 44
Equation 3-3: Specificity [Penny & Frost, 1996] ..... 44
Equation 5-1: Z-score Formula ..... 99

## Nomenclature

| | |
|---|---|
| **ADEs** | Adverse drug events |
| **ADT** | Admission, discharge, and transfer |
| **ANN** | Artificial Neural Networks |
| **ANN RFW** | Artificial neural network research framework |
| **API** | Application programming interfaces |
| **CBR** | Case Based Reasoner |
| **CCR** | Correct Classification Rate |
| **CCVT** | Committee of Classifiers/Verification Tool |
| **CDSS** | Clinical Decision Support System |
| **CHEO** | Children's Hospital of Eastern Ontario |
| **CLAS** | Computerized laboratory alerting system |
| **CNN** | Canadian Neonatal Network |
| **CPOE** | Computerized physician order entry |
| **DOM** | Document Object Model |
| **DOV** | Duration of Ventilation |
| **DTD** | Document Type Definitions |
| **EPIC** | Evidence-based Practice Identification & Change |
| **EMS** | Enhanced messaging service |
| **EPR** | Electronic Patient Record |
| **GUI** | Graphical user interface |
| **HELP** | **H**ealth **E**valuation through **L**ogical **P**rocessing |
| **HIS** | Hospital Information System |
| **HTML** | Hypertext Markup Language |
| **ISP** | Internet Service Provider |
| **JAXP** | Java API for XML parsing |
| **KNN** | k-Nearest Neighbours |
| **LAN** | Local area network |
| **LOS** | Length of Stay |
| **MIRG** | Medical Information Technologies Research Groups |
| **MLP** | MultiLayer Perceptron |
| **MORT** | Mortality |
| **NICU** | Neonatal Intensive Care Unit |
| **ODBC** | Open Database Connectivity |
| **PADS** | PArents Decision Support |
| **PIS** | Patient Information System |
| **PACS** | Picture archiving and communication systems |
| **PAN** | personal area network |
| **PDAs** | Personal digital assistants |
| **RAM** | Random access memory |
| **RF** | Radio Frequency |
| **SAX** | Simple API for XML |
| **SGML** | Standardized Generalized Markup Language |
| **SMS** | Short Messaging Service |
| **SNAP** | Score of neonatal acute physiology |

| | |
|---|---|
| **SNAPPE-II** | Score for Neonatal Acute Physiology version 2 with Perinatal Extension |
| **SOX** | Schema for object oriented XML |
| **TCP/IP** | Transmission control protocol/internet protocol |
| **WAN** | Wide area network |
| **WAP** | Wireless Application Protocol |
| **Wi-Fi** | Wireless Fidelity |
| **WML** | Wireless Markup Language |
| **W3C** | World Wide Web Consortium |
| **XDR** | XML data reduced |
| **XML** | eXtensible Markup Language |
| **XSD** | XML schema Definition |
| **XSL** | eXtensible Stylesheet Language |
| **XSDL** | XML schema definition language |
| **XSLT** | eXtensible Stylesheet Language Transformation |

# Chapter 1: Introduction

"Information overload" in medical settings has long been acknowledged – large volumes of medical information are constantly being processed and generated from several sources and are exponentially increasing. In environments like the neonatal intensive care unit (NICU), medical data are being collected on a continuous basis for each patient. This vast library of data is typically stored in data repositories or databases where it is easily accessible to physicians and other medical staff within the hospital.

In order for physicians to make use of this enormous amount of information in the most meaningful way, many hospitals have increasingly been employing patient information systems (PISs) or clinical decision support systems (CDSSs), which are computer-based information systems used in the processing and management of patient data and in providing more accurate assessment of patient conditions providing for improved decision-making capabilities in patient care [Chen et al. 2002]. PISs are usually interfaced to a diverse set of clinical systems which provide physiological data at the bedside along with laboratory results and medication information thereby providing physicians with enough data for more accurate clinical decision making [Bradshaw et al. 1989]. PISs will eventually replace the traditional paper based method of documenting patient information.

Over the past decade, sophisticated clinical alerting systems have become increasingly prevalent in health care settings and have been implemented into a number of hospital intensive care units' (ICUs) clinical information systems in order to improve patient care, information management, the efficiency of the ICU medical treatment and minimise the number of adverse events from taking place [Rideout 2006]. The clinical

information systems provide physicians with an information base gathered from various types of data acquisition sources such as: administration, laboratory, radiology, and pharmacy systems, picture archiving and communication systems (PACS) as well as physiological monitors, ventilators, pumps and electronic urimeters, along with medication and patient history records. All of this information is retrieved on a continuous basis in real-time and stored in a database which forms the foundation of the patients' electronic patient record (EPR).

Wireless technologies, coupled with advances in mobile computing, are enabling many exciting new applications in the health care setting that can simplify daily routines, increase patient independence, and improve the quality of patient care [Turisco & Case 2001].

In a fast paced environment such as the NICU it is essential for medical decision makers to stay in close contact with each other and have access to vital information anytime and anywhere. Over the past few years the boom in wireless technologies has brought forth ample opportunities in improving patient care. The use of emerging wireless technologies hold the promise of improving access to critical information and reducing the time it takes physicians to respond to critical events in patients [Reddy et al. 2005]. Wireless technology fits in well with the inherent mobile workflow of the medical environment, since physicians and nurses are almost always on the go, which is an important requirement for physicians' adoption and usage of any new technology [Kafeza et al. 2004].

Clinical alerting systems make use of a combination of wireless communication technologies in order to reliably transmit critical alerts to physicians' in a quick and

timely manner. These alerts could be transmitted to decision-makers using a variety of different mobile devices with wireless connectivity such as two way alphanumeric pagers, cellular telephones, personal digital assistants (PDA's), Smart Phones, Tablet PCs and e-mail. Studies have shown that clinical alerting systems have been successful in alerting physicians to adverse events, to a great extent faster than would have been possible through human interpretation of data [Shabot et al. 2000].

This thesis entails the design and implementation of an Electronic Medical Alerting & Notification (EMAN) system prototype that is required to interact with Medical Information Technologies Research Groups (MIRGs) clinical decision support systems, in particular the Artificial Neural Network.

## 1.1 Motivation and Significance of Research

MIRG is a multi-disciplinary group that brings together engineers, physicians, statisticians, computer scientists and students to integrate a number of decision support tools to aid physicians in their decision making, especially in the fast paced NICU environment.

The integration of clinical alerts into an XML based health care framework for the neonatal intensive care unit (NICU) is one of the project areas in which MIRG is involved, along with its primary goal of developing artificial intelligence based clinical decision support systems (CDSSs) using Artificial Neural Networks (ANNs) and k-Nearest Neighbours (k-NN) in order to improve patient health care and enhance the effectiveness of data management in the hospital setting.

MIRG is working in collaboration with the neonatal intensive care unit at the Children's Hospital of Eastern Ontario (CHEO), using the Philips Document Center

server to enable real-time data acquisition of physiological data at the bedside for the purpose of testing MIRG's data processing software systems, such as the ANN, k-NN and additional clinical decision support systems. The use of these trained CDSSs may assist physicians in predicting important outcomes relating to ICU patients such as: mortality, complications, duration of ventilation and length of stay (LOS).

Various studies have shown that real-time clinical alerting systems have made significant improvements in the collaboration between physicians and nurses in the ICU, in providing physicians with more prompt critical event notification and in the delivery of accurate information regarding life-threatening events, providing physicians with concrete information, aiding them in making better and more accurate clinical decisions [Reddy et al. 2003, Mendonça et al. 2004].

The remainder of the thesis is dedicated to the development of the EMAN system prototype that will be interfaced with MIRG's ANN tool and in the future CHEO's data repository collected through the Philips Document Center server. XML schemas are used to describe allowable formats for the XML-based patient clinical alert documents. A customizable web-based graphical user interface (GUI) is designed to enable physicians to interact with the XML-based NICU alerting system.

## 1.2 Definition of the Problem and Thesis Objectives

In the intensive care unit and other critical care settings, patients' physiological state needs to be monitored and data collected on a continuous basis, to help predict or detect and if possible prevent critical events or complications from taking place. Traditionally, alarms are generated by medical devices when data values exceeded or

dropped below pre-programmed threshold values; however this frequently set off false alarms. An excess of these false alarms or "alert fatigue" could cause physicians and nurses to override what could potentially be a critical event or even to shut down the alarms [Van Der Sijs et al. 2006].

Today, clinical alerting systems have been integrated into clinical information systems to automatically monitor patient data and generate clinical alerts when ever abnormal or life-threatening events occur [Chen et al. 2002].

In the context of this thesis, alerts which are classified based on their severity (warning, critical or life-threatening) are generated by either conforming to any of the developed alert generation rules or when physiologic parameter values drop below or exceed patient specific thresholds.

To be effective, clinical alerts must be customizable as physicians have widely varying perspectives on what they perceive to be important information. The more adaptable the software can be made to each individual patient's circumstances, the more accepted the tool will be from the point of view of the physician [Walker 2005].

Inadequate access to information and ineffective communication amongst medical personnel are leading factors in the increased numbers of medical errors. In response to these findings, the integration of wireless communication technologies within the hospital setting has extensively facilitated communication between clinical decision makers by providing the means of transmitting real-time event notifications, and receiving direct responses from physicians to reverse the problems, in a timely manner. As a result, it is hoped that physicians will be able to spend more time interacting with their patients, make less errors, reduce the cost of and improve patient health care.

As aforementioned, the ICU generates large volumes of clinical data. In order to ensure effective patient care, it is important to maintain accurate patient records. This creates "information overload" for physicians and makes it a very complex process for them to analyze and extract vital and critical information to manage their patients. Moreover, there can be a delay between the time when critical information is made available and when physicians review and act on them. In many situations, physicians rely heavily on laboratory results to make accurate medical decisions and can spend excessive time querying the laboratory information system for pending results. A simple mistake can result in an adverse event or even more serious; death. For that reason, doctors and nurses need to document vital patient information. This excessive "paperwork often overwhelms healthcare staff, using about 50-70% of their available time" [Geier 2005].

These challenging issues have led to the research presented in this thesis. It is believed that a solution that may alleviate the majority of these problems is the incorporation of a clinical alerting system into existing hospital information system (HIS) that can be used in wirelessly transmitting warnings or alerts to physicians' mobile devices at the point of care.

The specific objectives of this thesis are:

1. The main objective is to design an electronic medical alerting and notification (EMAN) system prototype which uses MIRG's ANN infant mortality prediction models to aid researchers in identifying the most suitable mortality model that detects abnormal or life threatening events before they occur and

wirelessly transmits corresponding warnings and alerts to physicians at the point of care.

2. The next objective is to create a complete NICU XML schema used to describe the acceptable formats for the XML-based patient clinical alert documents. The schema will also be validated using the World Wide Web Consortium's online validation tool.
3. The following objective is to develop an alert severity mechanism to transmit alerts based on their severity (i.e warnings, critical alerts, and life threatening alerts) to medical personnel in a timely fashion.
4. The fourth objective is to design a web-enabled graphical user interface to enable physicians to interact with the alerting system by providing them with the ability to input and update patient information, staff data and medical device or ANN thresholds to be used by the alerting system.
5. The final objective is to validate the alerting systems performance in terms of its ability to accurately detect significant events measured in terms of its correct classification rate, specificity and sensitivity.

## 1.3 MIRG's Medical Software and Application Environment

One of MIRG's main objectives is to provide a broad range of applications for its medical decision support tools. As stated by Frize: "Most neural network and expert system developments in medicine, as decision-aid tools, have narrow applications" [Frize et al. 1996]. An overview of artificial neural networks (ANNs), Case-Based Reasoner (CBR) and k-Nearest Neighbour (k-NN) are given in chapter 3. At the present time,

MIRG is focusing on improving the predictive outcomes of its clinical decision making tools based on comparisons with clinical data and physicians' medical knowledge. MIRG is currently working on applying its ANN and k-NN technology to a variety of medical databases, including the perinatal, neonatal and adult intensive care unit (ICU) data and coronary surgery data [Frize et al. 2001, Ennett & Frize 2003a]. The subsequent chapter is a literature review which dicusses some of the existing applications of clinical monitoring and alerting systems and identifies ways in reducing the number of false alarms generated by monitoring devices.

## 1.4 Thesis Outline

This thesis is divided into seven chapters as follows:

**Chapter 1:** Introduction presents the motivation, the problem statement and the objectives of this research.

**Chapter 2:** Provides an in depth literature review on the early use of clinical event monitors, the application of clinical alerting systems and the transition from wired to wireless healthcare.

**Chapter 3:** Background covers important information from CHEO's medical setting, a brief introduction into various clinical decision support systems used by MIRG, and an overview of the structuring language used in the clinical alerting system. The ANN models used in developing 'alert generation rules' are described in detail.

**Chapter 4:** Discusses the adoption of mobile computing and wireless technologies in healthcare as well as the benefits and challenges faced with the implementation of wireless technologies in healthcare.

**Chapter 5:** Provides the methodology used in implementing the alerting system prototype.

**Chapter 6**: Discusses the results obtained from testing the alerting system prototype's ability to accurately detect abnormal or life-threatening events.

**Chapter 7:** Concludes the thesis with a brief discussion, contribution to this research and ideas for future work.

# Chapter 2: Literature Review

There has been extensive literature on the application of clinical monitoring systems in critical care settings such as in anesthesia and in the intensive and surgical care units. These clinical monitoring systems incorporate a clinical alerting mechanism that is used to deliver critical alerts in real-time to physicians at the point of care. Monitoring is essential for the patients' safety in order to recognize the onset of an adverse condition, hence reducing the chances of morbidity and mortality [Beneken & Van der Aa 1989].

Over the past two decades, researchers have been interested in the development and implementation of more sophisticated and intelligent patient monitoring and alerting systems to detect and prevent critical events from taking place [Rind et al. 1994, Shabot & LoBue 1995, Shabot et al. 2000, Chen et al. 2004].

## 2.1 Clinical Event Monitors

The literature suggests that constantly monitoring and evaluating critically ill patients' vital trends and other pertinent physiological parameters is necessary to ensure the management of their health issues. It is difficult for nurses to constantly monitor trends around the clock, and the large amounts of data generated from medical devices can make it very difficult to recognize significant events which occur randomly and infrequently. As stated by Hripcsak "clinical monitors derive their benefit from serving as tireless observers, constantly monitoring clinical events" [Hripcsak et al. 1996]. Clinical event monitors are computing systems that scan clinical information systems

(laboratory, radiology, medication and ADT information) for new clinical and administrative data entered into the system in search of evidence of possible abnormal conditions in patients, thereby notifying physicians by generating critical alerts or warnings.

The use of clinical event monitors are not meant to "replace health care providers, but to make his or her job easier" [Hripcsak et al. 1996]. Clinical event monitors and computerized alerting systems have extensively been used in obtaining critical laboratory results in the detection of medication errors, the detection of life threatening conditions, and in computerized physician order entry (CPOE) [Shabot et al. 2000, Poon et al. 2002, Steele et al. 2005].

### 2.1.1 An Excess of False Alarms

Some of the earlier generations of patient monitoring systems were clinically inappropriate for use in providing accurate information on the true state of a patient. Although some of the alarms generated by these monitors could be used as an indication of a patient's physiological condition deteriorating, most of these alarms are disruptive to medical staff due to the high incidence of clinically insignificant (i.e. movement of patient, signal artifact) and false alarms. This was due to the fact that earlier monitors were designed to monitor the signals being measured from the patient and not the actual patient's state.

Several studies have indicated that a vast majority of the alarms generated by clinical monitors were not useful at portraying the patients' state. In critical care settings for adults, false alarm rates were as high as 89.4%. A study was conducted to determine the significance and the frequency of audible alarms during the postoperative intensive

care of ten cardiac patients in the ICU. The study period per patient was approximately 26 hours; of the 1,307 times an alarm was generated, only 10.6 % (139) were deemed significant [Koski et al. 1990].

Several studies have indicated that medical devices that make use of conventional alarms generally misrepresent the actual information pertaining to the patient's true state. As stated by Schecke, monitor use could possibly be "meaningless in the context of all information about the patient's state" with the use of conventional alarms [Schecke et al. 1992].

One study conducted in a pediatric ICU setting was designed to determine the predictive value of patient monitoring alarms over a seven day period. Out of the 2, 176 alarms generated 68% (1,481) were false, 26.5% (576) were induced by medical procedures, and only 5.5% (119) were significant true alarms that resulted in a change in therapy. It was concluded that overall, 94% of alarms were clinically insignificant, suggesting that the use of these monitoring systems was a poor indicator of the occurring events [Lawless 1994].

Another similar study conducted in a multidisciplinary ICU in a children's teaching hospital recorded the appropriateness of alarms generated by clinical event monitors over a ten week period. The results showed that 86% of total 2,942 alarms (during 298 hours of monitoring) were false positives; an additional 6% were found to be clinically irrelevant true alarms; and only 8% of all the recorded alarms were true alarms with clinical relevance [Tsien 1997].

There were many factors contributing to these high rates of false alarms. The main contributor was single variable limit alarm thresholds that were used in the

monitoring devices, which ultimately caused an alarm to be generated whenever a patient's parameters exceeded thresholds. This approach posed a few problems: there were great difficulties in determining suitable alarm thresholds; the frequency of false positive alarms caused irritation to nurses and physicians; and each signal was evaluated separately without taking its clinical context into consideration (i.e. recent medications or other signal values that may affect the reading).

To effectively use clinical alerting systems the high rates of false alarms must be reduced. The next section suggests some ways of potentially reducing the high rate of false alarms making clinical alerting system more useful in medical settings.

### 2.1.2 Efforts to Reduce False Alarms Produced by Event Monitors

A number of studies were conducted in efforts to reduce the rate of false alarms. Arnell suggested combining several signals together to generate alarms that are more closely related to the patients' true state [Arnell et al. 1983].

Bloom also demonstrated that by examining a variable's interrelationship with other variables, it could improve the interpretation of any single physiological variable, and depending on the state of the patient, the significance of the combination of these variables would vary [Bloom 1993].

Another method of reducing the number of false alarms was devised by Mylrea and colleagues; after examining ten published reports related to operating room critical incidents, accidents, and deaths, it was concluded that by using a fewer number of important (patient airway) variables significant to the patients condition, the monitoring system produced better results than previous systems. It was determined that by integrating and monitoring the five most common airway variables pertaining to the

patient's condition, 47% of the 1,882 anesthesia related incidents could have been identified [Mylrea et al. 1993] since some monitored variables are more significant than others in representing the state of a patient.

An alertnative approach is manually changing the alarm limits during a medical procedure which may result in a decrease in the number of false alarms. The "determination of appropriate limits could be further enhanced using information on the initial patient status and disease" [Mylrea et al. 1993]. In addition, the positive predictive value of alarms would potentially be increased by manually changing the alarm limits.

In a study conducted by Makivirta, the mean limit values observed in postoperative cardiac patients did not vary drastically from the physicians' choice of alarm limits. However, as the variables containing frequent transient excursions increased beyond the defined limit values, the end result was frequent occurrences of false alarms. This study recommended that alarm thresholds be set according to the patient's state as opposed to being based entirely on established predefined limits [Makivirta & Koski 1994].

A different method for reducing false alarms, in addition to multivariable monitoring, is the determination of "safe ranges" of monitored vital signs based on each individual patients state [Koski et al. 1995].

Alberdi et al. performed an investigation on the role of computerized monitoring in neonatal intensive care by conducting interviews with neonatal staff, ward observations, and experimental techniques. It was found that, monitors played a secondary role in clinicians' decision making and that the computer usage by ICU staff was less than anticipated. The study suggested a few ways of improving the use of

computerized monitoring systems through: training of staff, making clinical information available online, improving the user-interface and development of more intelligent alarm algorithms [Alberdi et al. 2000].

A review was conducted by Chambrin discussing the reasons for the high incidence of false alarms (or clinically insignificant alarms) generated by monitoring systems. Physicians are generally interested in the "detection of relevant abnormalities or changes in a patient's condition. This is not easily reflected in a value crossing a limit but rather by the simultaneous evolution of different parameters" [Chambrin 2001].

It was found that some monitoring systems can effectively detect vital problems, but have a low specificity which can result in several adverse consequences. Most monitoring systems generate alarms: when threshold limits are exceeded, when an electrode is positioned incorrectly, due to motion artifacts or in the case of a high level of signal interpretation (i.e arrhythmia) causing a flood of alarms from each monitor connected.

Based on a review of monitoring system use, the author suggested that the "adaptation of the choice of the element of monitoring to each patient, and the development of technical solutions with multiparametric approaches to detect events that are clinically relevant" could potentially reduce the high incidence of false alarms [Chambrin 2001].

The high incidence of false alarms is attributed mostly to the clinical equipment used in monitoring patients and much of the problem arises from normal and sometimes unavoidable practice [Edworthy & Hellier, 2006]. However, the integration of

intelligence in monitoring systems can ultimately reduce the false alarm rate significantly.

### 2.1.3 Integrating Alerting Systems with Intelligent Alarming Schemes

Techniques such as knowledge-based, artificial intelligence including fuzzy logic and expert systems, machine learning, artificial neural networks and decision tree classifiers are all approaches that have been integrated into clinical event monitors or alerting systems in efforts to improve patient monitoring and management systems by replacing conventional alarms with more intelligent alarms. Some of the literature covering these approaches is presented to give an overview of the application of each approach.

The first approach used in the development of more intelligent alerting systems was the knowledge-based (KB) approach. The basic concept behind the knowledge-based approach is a computer program that uses complex guidelines to simulate the process of human reasoning in attempt to distinguish abnormal events. Fukui and colleague mentioned that to achieve this task the following two procedures are required: First, the experts knowledge is presented in a similar way that (s)he thinks using production rules in specific the "if then" format. Second, the procedure from the first step is used in the inference engine for the intelligent alarming scheme used in the recognition of "the event of each signal, relate the events of signals to each other, recognize the time-successive state transition, and finally activate the appropriate alarms" [Fukui & Masuzawa 1989].

The literature refers "to Knowledge- Based (K-B) Systems as those computer systems used for the interpretation of data about a specific problem, in the light of

knowledge represented or contained in the knowledge base, to develop a problem specific model and then to develop plans for problem solution" [Mora et al. 1993] .

Suvkuvaara et al developed and tested a knowledge-based alarm system prototype for intensive care monitoring of cardiac operated patients; it incorporated median filtering, trend estimation and rule-based reasoning, to monitor cardiovascular and pulmonary functions. The system consisted of two components: DataLog signal preprocessor and the InCare knowledge based alarm system that implemented medical knowledge gathered from two physicians into 87 rules. DataLog was used in the continuous monitoring of patient variables, while the InCare system was used to detect specific pathological conditions from estimated trends and from a combination of measured signals. To maintain the reliability of system when data was incomplete, multiple conditions and multiple rules within the 87 rules were combined by logical OR operators. A clinical trial of the alarming system was conducted with 35 patients for 171.9 hours. In the first phase of the trial, the system alarmed 27 times and had a sensitivity of 100% and a specificity of 71% [Suvkuvaara et al. 1993].

Although knowledge-based expert systems have been developed for medicine they have not been readily adopted due to their wide ranges and diverse variations it is nearly impractical to use these systems in identifying specific abnormal situations. Moreover, expert systems are incapable of handling the large flow of data required for comprehensive and widespread patient monitoring. [Mylrea et al. 1993].

Other more popular approaches in the realm of intelligent monitoring are machine learning techniques such as artificial neural networks, fuzzy logic and decision tree induction. Neural networks are well suited in their ability to recognize complex data. In

a study conducted at the University of Utah, a neural network was used in the integration of anesthesia data. After training the neural network with data from an oil/water lung model, the system was tested and found to be 99.5 % accurate in identifying 13 critical events. Further testing resulted in the detection of 94.7% of the events [Mylrea et al. 1993].

Fuzzy logic is an additional approach employed to cope with the vague and incomplete knowledge-based approach. The complex monitoring of a patient state can be supported by the use of fuzzy logic technologies. In fuzzy technologies, common-sense rules are used to describe problem solving techniques [Becker et al. 1994].

Maglaveras et al developed a dynamically changing alarming scheme that uses pairs of important interconnected parameters (i.e. heart rate and blood pressure) in order to accommodate the drastic changes in an ICU patient's condition on a day to day basis. This scheme was implemented using a shrinking generating neural network algorithm for the purpose of training and learning. The algorithm is used to define the borders between normal, abnormal and intermediate in a patients' state. This approach results in an alarming scheme that can be easily updated and adapted to each patient's state and condition. The advantage of this approach is that the neural network can accurately and easily be trained to detect complex events even with a small number of points, as shown in this work [Maglaveras et al. 1998].

A fuzzy inference approach is used in generating intelligent alarms by evaluating the combinations and interdependencies of the patient's vital signs. Since it is difficult to determine the appropriate threshold for individual signals in monitoring devices, the

fuzzy inference approach may be useful in dealing with the vagueness of a particular threshold and in modeling physicians' decision making process.

In an effort to reduce false alarms related to arterial blood pressure (ABP) in the ICU, Zong et al developed an algorithm that used the fuzzy logic approach to examine the relationship between electrocardiogram (ECG) and arterial blood pressure (ABP) waveforms and analyzed the quality of the ABP signal. Results showed that by using this approach the false alarm rate was reduced from 34.9% to 1.7% of ABP alarms while accepting 99.4% of true ABP alarms. The author concluded that this approach was very practical and effective at significantly reducing the number of ABP related false alarms [Zong et al. 1999].

A study conducted by Tsien used the decision tree induction method on multiple signals in order to reduce false alarms in the intensive care unit. This study demonstrated that using machine learning techniques such as classification tree induction on features derived from physiological data could be an interesting approach in distinguishing true positives from false alarms in the intensive care unit [Tsien 2000a].

Tsien went on to detect "true alarm" conditions in the ICU using a pipeline for event discovery in medical time-series data. This study demonstrated that machine learning techniques such as decision tree classifiers, neural networks, logistic regression, radial base function networks, and support vector machines were useful in discovering knowledge from physiological data and their correlation with clinical events [Tsien 2000b].

The idea behind intelligent monitoring is to incorporate the highest level of patient monitoring by utilizing all of the available information generated from bedside

monitors and ventilators as well as patient data found in clinical information systems. Intelligent alarm algorithms that integrate artificial intelligence techniques have the potential to reduce false alarm rates and to improve knowledge representation.

The artificial neural networks approach will be used in this research as MIRG has been actively developing and improving a number of outcome prediction models using ANNs to be used at the CHEO.

## 2.2. Application of Clinical Alerting Systems in Healthcare

The literature indicates that over the past twenty years clinical or computer alerting systems have been used extensively in ordering and obtaining critical laboratory results, monitoring critically ill patients' vital trends for critical or abnormal events and in the most widely used to date, computerized physician order entry (CPOE) systems to prevent injury from adverse drug events due to medication errors.

### 2.2.1 Clinical Laboratory Alerting Systems

Clinical laboratory systems are used to analyze laboratory data in order to identify critically abnormal values and trends. Various studies have indicated that physicians depend heavily on laboratory test results in their decision making process, and can spend a great deal of time querying the laboratory information system for pending results [Bradshaw et al. 1984, Mc Donald et al. 1985]. To make appropriate patient care decisions, complete and accurate laboratory results must be delivered to physicians in a timely manner.

Bradshaw et al developed a computerized laboratory alerting system (CLAS) and integrated it with capabilities of the **H**ealth **E**valuation through **L**ogical **P**rocessing (HELP) medical information system, used in a 520 bed tertiary care teaching hospital. The HELP system evaluated medical knowledge that was embedded into decision frames or modules and used its flexible medical decision making capabilities to evaluate the data within specific time limits. CLAS was used to monitor laboratory data for the presence of life threatening conditions in hospitalized patients using decision modules that incorporated the alert criteria (obtained from a predefined medical knowledge base) and to alert physicians to initiate treatment more rapidly.

Alerts were transmitted to computer terminals on the hospitals nursing division where they were evaluated and acknowledged. CLAS was evaluated for its effectiveness in transmitting alerts to physicians. Initially, the average acknowledgement times ranged from 5.1 to 58.2 hours. After the installation of the flashing lights, the average acknowledgement time decreased to 0.1 hours about 6 minutes [Bradshaw et al. 1989]. Although this method of alerting significantly decreased the physicians' response time, it was still not a viable solution because the average acknowledgement time was still taking several hours and the constant use of flashing lights was distracting and annoying to hospital personnel [Bradshaw et al. 1989].

Shabot et al designed a computerized laboratory ICU decision support alerting system to analyze laboratory and blood gas data for critically abnormal values and/or trends. The study was conducted over an eight month period in which 1, 515 alerts were detected out of 115 000 laboratory data results. Shabot reported that the critical laboratory alerts "were sensitive indicators of severity of illness" and were predictive of

patient outcomes. It was found that patients who had one or more critical lab alert suffered an ICU mortality of 9.52 % and had an average length of stay of 6.62 days, in contrast to 0 % and 1.31 % ICU mortality and an average length of stay of 1.57 days for ICU patients who had no critical lab alerts [Shabot et al. 1990].

Rind and colleagues developed a mechanism to alert physicians via e-mail to rising levels of serum creatinine in hospitalized patients receiving nephrotoxic medications or renally excreted drugs. It was shown that using the clinical laboratory alerting system, medication doses were adjusted or discontinued an average of 21.6 hours earlier when using e-mail alerts as opposed to no alerts [Rind et al. 1994].

Tate et al also developed and evaluated a computerized critical value alerting system which automatically alerted physicians to critical laboratory results via a patient specific digital pager. Results of the study showed that 100 % of the 335 critical value alerts generated were reported to physicians within approximately 38.6 minutes, and 51% of all alerts were acknowledged within twelve minutes. Nurses verified that 308 of the 335 alerts were valid. The researchers concluded that the computerized reporting system decreased the alert acknowledgement time significantly and that 67% of the time nurses were unaware of critical values without the use of the pagers [Tate et al. 1995].

Kuperman et al evaluated the effect of an automatic alerting system on the time required before an appropriate treatment was ordered for patients with critical laboratory results. The results demonstrated that the use of clinical alerting systems has been shown to significantly decrease the time between patients having abnormal status and their clinicians suggesting a treatment plan by 38% [Kuperman et al. 1999].

### 2.2.2 Physiologic Alerting Systems

Physiological alerting systems are used to monitor patient's vital trends for early detection of critical or abnormal trends. Physiologic data is used as one of the main indicators of a patients' condition and this data is used 13% -22 % of the time by physicians in critical decision making [Bradshaw et al. 1984].

In efforts to make ICU alarms more meaningful, Schoenberg et al compared traditional alarms with trend-based (module) algorithms. Schoenberg used a customizable logic engine in the design of a computerized module used to analyze real-time data generated from multiple monitoring devices. Over a period of five days, the module was tested on six ICU patients to evaluate the two different algorithm's performance. The module consisted of alarm algorithms for: heart rate, systolic and diastolic blood pressure and arterial oxygen saturation. The results revealed a ten fold increase in the positive predictive value (PPV) of the alarms from 3% using the alarm algorithm to 32% using the module. Overall the sensitivity of the module was 82% suggesting that the use of such an algorithm can aid in filtering out false and insignificant alarms in the ICU [Schoenberg et al. 1999]

Shabot and LoBue developed an alerting system that sends out real-time alerts to physician's palmtop personal digital assistant (PDA), based on a combination of complex physiologic flow sheet data, incoming source data and medication data. The method of detecting physiologic events was accomplished in defining "exception condition alerts" [Shabot & LoBue 1995]. Exception conditions are "clinical events which may occur over a period of time, as a combination of events (cross-correlated exception) that may occur at one time or over time, or as extraordinarily serious single

events" [Shabot et al. 2000]. For example, a cross-correlated exception indicating insufficient intravascular volume would consist of the combination of systolic blood pressure < 80 mmHg and pulmonary capillary wedge pressure < 10 mmHg [Shabot & LoBue 1995]. These exception alerts are wirelessly transmitted to physicians PDAs to notify them of an abnormal condition in the patient.

Chen et al designed a real-time clinical alerting system using a similar method as the previous authors, of detecting physiologic events using 63 ICU physiologic alert rule definitions. A few of the physiological parameters used in the alert definitions are heart rate, systolic and diastolic blood pressure, respiratory rate, temperature and oxygen saturation rate ($S_pO_2$). The alerting system was evaluated in terms of the time it takes a message to be transmitted to physician's pagers or mobile phones. Results showed that it takes a pager an average of fifteen seconds and a mobile phone an average of ten seconds to receive an alert [Chen et al. 2002].

More recent work on physiologic alerting system was demonstrated by Charbonnier and Gentil. They developed an alarm system based on the trend analysis approach, in which trends were extracted online from physiological data and resultant alarms were generated based on the quantitative information of the trend, while the qualitative information was used to recognize specific situations on-line, such as device disconnections. The authors compared the results of the trend based alarm with the traditional alarm system to detect abnormal physiologic trends based on three physiological values: systolic blood pressure (SBP), oxygen saturation rate ($S_pO_2$) and maximal pressure in the airwarys ($P_{max}$). The system was run on-line and tested on adult patients hospitalized in an ICU, recording 36 hours of data. The performance of the trend

based alarm system surpasses that of a traditional limit alarm system, rejecting 33% of false alarms and detecting all of the clinically relevant alarms. As well the trend based system had a strong ability at recognizing alarm situations that triggered when monitoring devices were disconnected with 100 % sensitivity and specificity [Charbonnier & Gentil, 2007].

### 2.2.3 Computerized Prescriber/Physician Order Entry Systems

Computerized prescriber/physician order entry (CPOE) systems are primarily used to prevent injury from adverse drug events resulting from medication errors. The use of computerized entry systems can aid in detecting and preventing adverse drug events (ADEs) earlier than the spontaneous reporting approach done by hospital staff. Several studies demonstrate the effectiveness of using computerized detection and alerting systems in identifying ADEs.

Classen et al used a computerized alerting system that was programmed to identify signals in specific mismatches of clinical information that suggested the presence of an ADE. The signals consisted of antidote ordering, certain abnormal laboratory values and medication stop orders. A pharmacist evaluated the computerized signals to verify whether an ADE had actually occurred. Over an 18 month period, the computer detected 731 validated adverse drug events, whereas only 101 of the ADEs were reported by the pharmacist. Classen demonstrated that computerized detection of critical medication related events was much more effective than manually detecting and reporting ADEs [Classen et al. 1991].

Adverse drug events are frequently linked to medication errors. Although medication errors can occur at any point in the medication administration process: ordering, transcribing, dispensing and administering the medication, the majority of errors that could have prevented an ADE from taking place in the ordering (56%) and administration (34%) stages [Bates et al. 1995a, Bates et al. 1995b, Leape et al. 1995].

In the United States alone, it is estimated that adverse drug events (ADEs) are the leading cause of more than 770,000 patient injuries and or deaths annually, costing hospitals up to $5.6 million [Cullen et al. 1997]. It is said that many of these ADEs could have been reduced if hospitals systems used more efficient methods in preventing and detecting ADEs [Classen et al. 1997].

Jha et al developed a computerized ADE monitor and compared it with two other approaches of detecting ADEs: intensive medical chart review (more expensive method) and stimulated voluntary reporting done by a trained reviewer. Out of 617 ADEs detected, 76 were detected by both the computerized monitor and the medical chart review (MCR) methods. The ADEs that were detected by the computerized monitor were classified as more "severe" than those detected by the chart review. Although, the computerized monitor identified approximately half the ADEs identified by the chart review method, at much lower cost it far exceeded the voluntary reporting method by more than a ten-fold increase [Jha et al. 1998].

A 650 bed community hospital implemented a computer alert system to detect ADEs using 37 drug specific triggers (of situations with increased risk of injury). For example, arrhythmia is caused by digoxin—for which the alerting system looked for patients receiving digoxin who had hypokalaemia. Over a period of six months, the alert

system triggered 1116 times. Alerts were reviewed by pharmacists who then contacted physicians to make appropriate regimen changes. About 53 % (596) of the total alerts were classified as true-positive alerts. Of the 596 true positive alerts, 44% (265) were not recognized by physicians prior to receiving alerts. This study identified opportunities to prevent patient injuries at a rate of 64 per 1000 admissions, suggesting that the use of computer alerting systems as a successful tool in identifying opportunities to prevent ADEs [Raschke RA et al. 1998].

In 1999, a report written by the Institute of Medicine recommended the use of CPOE systems to reduce medical errors, and one study found that the implementation of a CPOE system reduced the number of serious medication errors by 55% [Bates et al. 1998].

Extensive work has been done on improving the use of CPOE systems in order to reduce the number of adverse events related to medication errors. A study conducted in a pediatric critical care unit (PCCU) to study the effects of using computerized alerting systems to reduce medication errors and ADEs at the medication order entry stage. This study was conducted using 514 patients admitted to a 20-bed PCCU in a children's teaching hospital. Medication errors that resulted in the medication ordering stage were classified into three categories: potential ADEs, medication prescribing errors (MPE) and rule violations (RV). Results of the study prior to implementing the computerized alerting system showed that, out of 13 828 medication orders potential ADEs occurred at a rate of 2.2 per 100 orders, MPEs occurred at a rate of 30.1 per 100 orders and RVs occurred at a rate of 6.8 per 100 orders. After the implementation of the alerting system the rate of potential ADEs decreased to 1.3 per 100 orders, MPEs decreased to 0.2 per

100 orders and RVs decreased to 0.1 per 100 orders. The overall error reduction was 95.9%. Potential ADEs were reduced by 40.9%, MPEs and RVs were reduced by 99.4% and 97.4% respectively. This study shows that the uses of an alerting system significantly reduced the rate of error in the medication ordering process [Potts et al. 2004].

With the addition of clinical decision support features to CPOE system, medication errors could be reduced by 81 % [Koppell et al 2005]. In a recent study in a long-term care hospital it was suggested that the use of a CPOE system with clinical decision support (CDS) can significantly improve drug safety by improving physicians' medication prescribing decisions. Using a CPOE-CDS physicians' could be notified promptly of prescribing errors such as the administration of a contraindicated drug, as such a simple prescribing error could lead to a series of errors resulting in a adverse event [Rochon et al. 2006].

In order for an alerting system to be effective the number of false alarms generated must be reduced. Inevitably, this goal is not easily achieved but preliminary studies have suggested several approaches that may reduce the rate of false alarms such as: more enhanced parameter acquisition accuracy, the use of more intuitive graphical user interface, setting patient dependent limits and more enhanced alarm integration and intelligence such as "smart alarms", in which the alerting system takes into account multiple parameters and rate of change of the parameters.

Clinical alerting systems coupled with wireless technologies will enable the transmission of wireless alerts to medical decision makers' mobile devices and will enhance physicians' decision making ability at the point of care.

## 2.3 From Wired to Wireless Communication

In the past, medical decision makers used to query the hospital information system (HIS) using a fixed terminal to look up the information they required; a method that was extremely inefficient because there was no way of knowing whether the information would be available at the time of their search and it interrupted their work flow [Eisenstadt et al. 1998]. A more efficient approach to obtaining critical information is having an alerting system notify a physician when the required information is available.

Over the past few years, there has been a widespread increase in the use of wireless communication systems and handheld technologies in the healthcare industry. Medical institutions are shifting from wired to wireless communications in order to improve communication, provide access to critical information, reduce workload and delays, and increase mobility and the quality of care delivered to patients [Shabot et al. 2000, Poon et al. 2002].

The use of information technology can reduce errors in the following three ways: "by preventing errors and adverse events, by facilitating a more rapid response after an adverse event has occurred, and by tracking and providing feedback about adverse events" [Bates & Gawande, 2003].

A number of studies have identified the inadequate access to patient information and the lack of communication among health care team members as one of the leading causes of medical errors. In order to alleviate these problems information technology can be used to push critical information such as: vital patient trend information (changes in patient status), laboratory results (new or abnormal results) and medication alerts when

and where they are needed, rather than having to periodically check patients records for updates [McKnight et al. 2001, Chen et al. 2004].

For example, the traditional flow of information for obtaining abnormal laboratory results required a lab technician to complete the tests, document them on the computer to update the electronic patient record and phone the head nurse with the results. The nurse would then notify a physician with the latest information in order to take appropriate action [Rind et al. 1994, Tate et al. 1995, Reddy et al. 2005]. With the increasing shortage of nurses, when the ICU is busy, a nurse may not be able to promptly notify a physician with these vital results and because of the life-threatening nature of critical laboratory results, it is important that they are communicated to the physician within a reasonable period of time before the patients condition worsens.

In many ways, the introduction of new technologies into health care has improved the flow of information in providing real-time notification to medical decision makers. The use of wireless alerting systems allows nurses and physicians to learn about vital information and critical events as they occur, helping to alleviate the pressure on nurses and providing quicker response time to reverse adverse events.

For example, the alphanumeric pager is one tool that has been used quite frequently in many studies and has considerably changed the flow of information. Two-way alphanumeric pagers facilitate multidirectional interactions between healthcare workers. Coeira conducted an observational study of clinical communication and noted that when contacting each other, the physicians' favorite tool was the pager because they can get an instant reply to a page [Coeira 2000].

In these studies the pagers had two major roles: "first, they facilitate communication among staff members. Second, pagers serve as real-time clinical event notification mechanisms for hospital staff" [Wagner et al. 1998, Shabot et al. 2000, Norris & Dawant 2001, Poon et al. 2002, Reddy et al. 2005] in improving access to required information.

Another factor affecting the flow of information is the mobility of medical staff. Eisenstadt and colleagues described the integration of two-way alphanumeric pagers into the clinical event monitor (CLEM), developed at the University of Pittsburg Medical Center. The researchers pointed out that without the use of wireless technology; the mobility of the medical workers was a major barrier that prevented them from receiving clinical information in a timely fashion [Eisenstadt et al. 1998, Reddy et al. 2005]. The use of wireless handheld devices can help remedy this problem because they offer portability and mobile access to important patient information.

Mobile devices such as two way pagers, cellular phones, PDAs etc. provide many benefits to the health care industry for improving communication, increasing the mobility of and keeping medical decision makers in touch with each other. The collaborative nature of medical environments requires the use of mobile devices that support multidirectional communication because the flow of information between health care providers must be two-ways.

These studies validate the necessity for integrating clinical alerting systems into hospital information systems; in order to detect abnormal or critical patient events at the earliest time possible as well as improve the flow of information and improve the

decision making capabilities of physicians by using wireless technologies to push vital information to their hand held devices, providing anytime anyplace access to information.

The next chapter describes the medical setting for which this alerting system is designed for as well as the various clinical decision support tools used by MIRG. The MIRG mortality models used in the development 'alert generation rules' for use in the alerting system will be described briefly highlighting the important risk factors in predicting mortality for each model. An overview of the structural languages used in the development of the alerting system will be described.

# Chapter 3: Background

The previous chapter outlined the various uses of clinical alerting systems and suggested methods in reducing the number of false alarms generated by monitoring systems. The integration of a clinical alerting system with intelligent alarming schemes may help reduce medical errors and critical events before they occur. Monitoring devices are an integral part of the intensive care unit. The ICU is known for its extensive use of monitoring devices to gather vital signs of critically ill patients. Typically, these devices use predefined thresholds that are triggered when a given physiological parameter exceeds the threshold values. Standard monitoring devices are highly susceptible to providing large volumes of false alarms (over 90 %); this value takes into account clinically insignificant alarms as well as technology malfunctioning alarms [Shoenberg et al. 1999]. As a result, medical caregivers have a tendency to silence these alarms or set alarm limits that are not likely to be exceeded in order to reduce the number of unnecessary distractions, ultimately increasing the chances of not detecting true occurrences of adverse events [Van Der Sijs et al. 2006].

The data generated by ICU monitoring devices are potentially valuable in detecting physiological trends and pathological diagnoses in critically ill patients and it is expected that providing an early warning of a developing problem or complication will help reduce the rate of mortality and morbidity.

Advances in technology have significantly improved the performance of clinical monitoring devices and tools by incorporating automated signal interpretation and intelligent alarming schemes. This process involves electronically capturing physiological data from the bedside monitors, enabling the sophisticated analysis of the

trends, potentially improving physicians 'ability to predict a patients' state and make better critical decisions.

The introduction of wireless and mobile computing technologies into the health care industry has made it possible for clinicians to wirelessly monitor their patients' state and gain access to critical information wherever and whenever they need it, across the continuum of care without increasing their workload, ultimately increasing the productivity of clinicians, improving patient outcomes and reducing the cost of care [Varshney, 2006].

The first section of this chapter explores relevant technical concepts from the field of medical informatics and information technology related primary to the research conducted by MIRG. This section provides a brief description of CHEO's data acquisition system, followed by a general discussion of clinical decision support systems and artificial neural networks. In addition, a short description of MIRGs clinical decision support tools, in particular the ANN, CBR and k-NN. Finally the main structural languages used in the prototype of the alerting system are examined.

## 3.1 CHEO's NICU Real-time Data Acquisition System

The Neonatal intensive care unit (NICU) at the Children's Hospital of Eastern Ontario (CHEO) is a 20 bed facility that specialises in the treatment of critically ill newborns. The clinical information system implemented to facilitate clinical knowledge management is the Sunrise Clinical Manager System from Eclipsys Corporation. The Sunrise Clinical Manager provides comprehensive displays for real-time diagnosis, patient care and data documentation and analysis. The real-time vital trends generated from monitors and ventilators are collected using the CareNet data acquisition system at

the bedside. The data from each bed is then passed through a common hub connected to the Philips Document Center Server located in the NICU's operating room. This server is connected to the hospital local area network (LAN) along with the following:

- Three client PCs (one each at CHEO, the University of Ottawa, and Carleton University not connected online yet)
- The Open Database Connectivity (ODBC) compliant SQL database, where the collected data is stored.
- The hospital information system (HIS), including the admission, discharge, and transfer (ADT) service.
- The laboratory information system and soon the radiology Picture Archiving and Communication System (PACS).

As of August 2002, the data collection system was fully operational and collecting data, for the purpose of research.

Currently CHEO has not implemented clinical alerting systems for use in the NICU except for the existing alarms from their medical equipment. This thesis aims at developing a prototype system that once interfaced with the data acquisition system in the NICU will provide physicians with up to the minute clinical alerts containing valuable patient information.

## 3.2 Clinical Decision Support Systems

Clinical decision support systems (CDSS) are interactive computer-based systems that integrate medical knowledge, clinical models and clinical patient information into a computer program that uses this explicit knowledge to generate patient specific assessments or recommendations to assist in the clinical decision making process. The

use of computer based systems in health care has not only been driven by the increasing demand for the management of large amounts of data, but also by the necessity to make evidence-based and cost effective decisions.

One of the first clinical decision support systems was designed as early as 1970, to support the diagnosis of acute abdominal pain. This design was based on Bayesian statistical theory, providing crude probabilistic diagnosis based on specific critical values. [Miller 1994]. These days, clinical decision support systems have advanced from a foundation based on statistical algorithms to more complex artificial neural networks and expert systems.

Scoring systems to determine the severity of illness were successful at predicting clinical outcomes for a group of patients, but were not effective for single patients. The success rate on an individual patient by patient basis may be increased significantly through the application of the artificial neural network to clinical decision support systems. Various examples of data driven clinical decision support systems are: artificial neural networks (ANNs), probabilistic (Bayesian) structures and the Case-Based Reasoner (CBR). The next section describes the application of artificial neural networks to clinical decision support systems.

## 3.3 Artificial Neural Networks

Artificial neural networks (ANNs) are powerful mathematical tools that are able to find patterns in data or to capture and represent complex input/output relationships. ANNs typically consist of an interconnected group of artificial neurons that use a mathematical or computational model for information processing based on a

connectionist approach to computation. The ANN behaves much like the human brain in the following two ways:

1. A neural network acquires knowledge through learning from its environment.
2. The ANNs knowledge is stored within inter-neuron connections attached to each other by weighted connections called synapses [Haykin 1999].

Before an ANN can be utilized in any application, it must 'learn' or discover the relationship between input and output patterns, or to analyze, or find the structure of the input patterns. The process of training a neural network involves adjusting the synaptic weights on each neuron until the output of the ANN is consistent with the known output for a particular input data set. Once the ANN is sufficiently trained, it can be used to provide an estimation of selected clinical outcomes of a particular patient based on what it has learned from a training set.

Medical data is often believed to have nonlinear relationships between input variables and outcomes, so the neural network is a good choice for data analysis in the medical environment [Baxt 1994].

### 3.3.1 ANN Architecture

The most basic ANN architecture depicted in figure 3-1 is formed by an input layer made up of several nodes, connected to an output layer consisting of one or more output nodes.

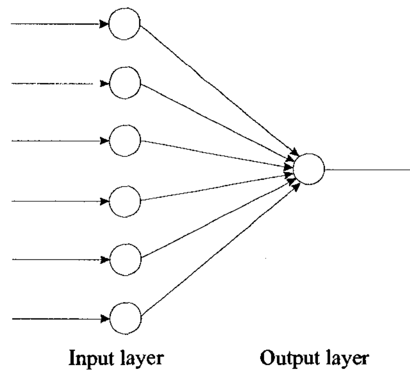



**Figure 3-1: Basic Architecture of a two-layer ANN [Rybchynski 2005]**

The nodes have inputs (x) where the known information is introduced. Both the input nodes and the bias term (which is equal to one) are multiplied by a corresponding weight (w). The input signal values in each processing unit are then summed using an adder at the output layer and then fed through a transfer function or activation function that scales the value of the output within a limited range as seen in figure 3-2 [Ennett 1999]. The role of the bias input is similar to a non-zero intercept in statistics [Kattan & Beck 1995]. The bias weight provides a threshold above which the node is activated [Penny & Frost 1996]. It should be mentioned that although the transfer function shown in figure 3-2 is a step function, many different types of functions such as the sigmoid function are commonly used. During training, the network is presented with inputs and known outcomes. The weights of the links are adjusted based on the relationship identified between the inputs and outcomes in the training set.

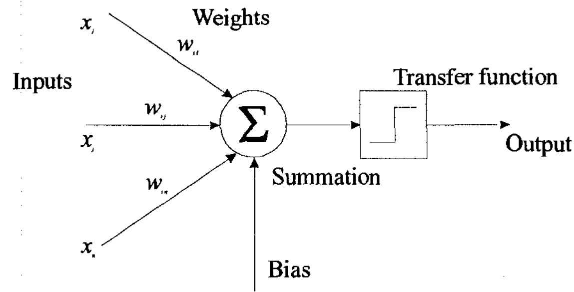



**Figure 3-2: The Basic Neural Unit [Rybchynski 2005]**

### 3.3.2 Types of Artificial Neural Networks

ANNs vary in their distinct architectures and learning process. The three most used architectures for ANNs are:

1. Single-layer feed-forward networks: Consists of an input layer directly connected to the output layer (i.e. networks with no hidden layers).
2. Multilayer feed-forward networks (MLPs): Consists of at least one or more hidden layers between the input and output layers as seen in figure 3-3. The hidden neurons play the role of calculating higher-order statistics and can solve more complex non-linear problems requiring increased training time, however, having more than one hidden layer does not necessarily result in an ANN with better performance [Penny & Frost 1996].

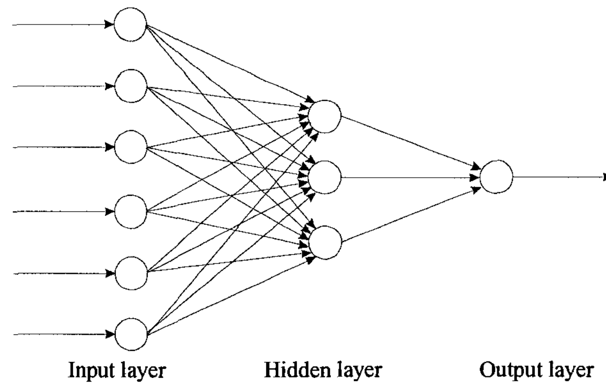



**Figure 3-3: Multi-layered feed-forward ANN [Rybchynski 2005]**

3. Recurrent or feedback networks: Models with bi-directional data flow. Feed-forward networks with at least one feedback loop. The learning capability and performance of such a network is increased with the addition of feedback in the network [Haykin 1999].

The true power and advantage of neural networks lies in their ability to represent both linear and non-linear relationships and in their ability to learn these relationships directly from the data being modeled. Traditional linear models are simply inadequate when it comes to modeling data that contains non-linear characteristics.

### 3.3.3 Weight Decay and Weight Elimination

The weight-elimination and weight decay terms are added to the error function used in the back-propagation algorithm to adjust the weights of the network. Weight decay limits the size of the connection weights by preventing the larger weights from increasing further. The larger weights in weight decay are penalized by the penalty term. The penalty term causes the weights to converge to smaller absolute values. The larger weights can cause excessive variance of the output [Geman et al. 1992]. Therefore, weight decay results in a more stable network.

Weight elimination on the other hand, attempts to reduce the smaller weights to zero and thus its effect on the network to zero. The small weights result in adding unwanted "white noise" to the model. Network pruning is the term used to describe this approach, which serves to simplify the network and possibly eliminate the variables that offer little or no assistance in predicting the correct outcome [Weigend et al. 1990]. "Weight decay and weight elimination work best when using a large initial network structure, small initial weights and a small learning rate" [Ennett & Frize 2003b].

Weight elimination is the key in determining the minimum data set that is required to accurately predict a specific outcome [McGowan et al. 1996; Ennett et al. 2004].

### 3.3.4 Adaptive Network Parameters

The ANN parameters are adjusted during training for optimization of the ANN. There are nine driving parameters used to regulate the way in which the ANN learns from one epoch (single pass through the entire training set, followed by testing of the verification set) to the other. These parameters are adjusted in order to gradually reach the networks optimal performance and to develop the best possible ANN model. The adjustment of these parameters can change the weights and biases of the network as a function of the error between the desired and intended outputs. Following is a brief overview on the role each parameter has on the learning process of the neural network:

"***Learning rate (lr)***: The value of the learning rate determines the speed at which the network attains a minimum in the criterion function so long as it is small

enough to insure convergence. If the learning rate is too high, it may oscillate around the global minimum, and is unable to converge.

***Learning rate increment (lr_inc)*:** The learning rate's incremental value.

***Learning rate decrement (lr_dec)*:** The learning rate's decrement value.

***Weight-decay constant ($\lambda$)*:** The weight-decay constant determines how strongly the weights are penalised.

***Weight-decay constant increment ($\lambda$_inc)*:** The weight-decay constant's incremental value.

***Weight-decay constant decrement ($\lambda$_dec)*:** The weight-decay constant's decrement value.

***Weight-elimination scale factor ($w_o$)*:** Weight-elimination scale factor defines the sizes of "large" and "small" weights. When $w_o$ is small, the small weights will be forced to zero resulting in fewer large weights (i.e., weight-elimination). A large $w_o$ causes many small weights to remain and limits the size of large weights (i.e., weight-decay).

***Momentum (momentum)*:** The momentum parameter adds a proportion of the previous weight-change value to the new value, thereby giving the algorithm some "momentum" to prevent it from getting caught in local minima.

***Error ratio (err_ratio)*:** The error ratio controls how the backpropagation makes adaptive changes in the learning rate, the weight-decay constant, and the momentum term." [Ennett et al. 2004].

### 3.3.5 Performance Measurements

Appropriate measurements are required in order to evaluate the performance of a network. There are several performance measurements for the ANN which are commonly used and are described in the following sections.

#### 3.3.5.1 Correct Classification Rate (CCR)

The number of cases that were predicted accurately with respect to the total number of cases in the data set is referred to as the correct classification rate or CCR. Correct Classification Rate (CCR or CR) is the total number of cases that were predicted correctly. The CCR measures the sensitivity to the frequency distribution of the outcome. The CCR is an accurate measure only if the desired outcome is above 15% of the total cases [Frize et al. 1998]. It is calculated as follows:

$$CCR = \frac{TN + TP}{TN + FN + TP + FP}$$

**Equation 3-1: Classification Rate [Hohavi & Provost, 1998]**

where **TP**: true positive – represents the number of deaths correctly classified.

**TN**: true negative – represents the number of survivals correctly classified.

**FP**: false positive – represents the number of survivals classified as deaths.

**FN**: false negative – represents the number of deaths classified as survivals.

#### 3.3.5.2 Sensitivity

Sensitivity is the true positive rate or the networks ability to correctly classify positive outcomes. The following equation is used to calculate sensitivity:

$$sensitivity = \frac{TP}{TP + FN}$$

**Equation 3-2: Sensitivity [Penny & Frost, 1996]**

#### 3.3.5.3 Specificity

Specificity is the true negative rate or the networks ability to correctly classify negative outcomes. The following equation is used to calculate specificity:

$$specificity = \frac{TN}{TN + FP}$$

**Equation 3-3: Specificity [Penny & Frost, 1996]**

High sensitivity represents a good classification performance in terms of death, whereas high specificity represents a good classification performance in terms of survivals.

#### 3.3.5.4 Confusion Matrix

An ANNs sensitivity and specificity can be calculated by a two by two confusion matrix (contingency table) [Fawcett 2003]. The confusion matrix is a mean to analyze the classification performance of a system. It shows how the outcomes are classified into four categories depending on their predicted and actual outcome as seen in table 3-1.

| | | **Actual Outcome** | |
|---|---|---|---|
| | | **Negative Outcome (-1 or 0)** | **Positive Outcome (+1)** |
| **Predicted Outcome** | **Negative Outcome (-1 or 0)** | True Negative (**TN**) | False Negative (**FN**) |
| | **Positive Outcome (+1)** | False Positive (**FP**) | True Positive (**TP**) |

**Table 3-1: Confusion Matrix for Two-Value Classification Outcome [Hohavi & Provost 1998]**

For example, if an outcome was predicted to be negative (i.e survival when predicting mortality) and the actual outcome was negative, the case is categorized as true negative. In the context of this work, a positive outcome will be the rare outcome (i.e. mortality) and a negative is the dominant outcome (survival).

## 3.4 MIRG's Clinical Decision Support Tools

### 3.4.1 MIRG's Artificial Neural Network

MIRG has been developing artificial neural network (ANN) tools for more than ten years to predict clinical outcomes such as artificial ventilation needs for adult intensive care unit patients [Frize et al. 1995; Tong et al. 2002], post-surgery mortality for coronary artery bypass grafting surgery patients [Ennett & Frize, 2003a] and in-hospital mortality, length of stay (LOS) and duration of artificial ventilation (DOV) for Neonatal Intensive Care Unit (NICU) patients [Frize et al. 2001, Frize et al. 2004], and the occurrence of complications in the clinical environment, based on certain physiological parameters.

Recent efforts to validate the use of ANN's in accurately predicting clinical

outcomes have been made by comparing results with other methods such as fuzzy logic classifiers [Frize et al. 2004] and radial basis functions with principal component analysis [Li 2005; Ouyang 2006].

An ethical decision making aid tool called PADS (PArents Decision Support) uses outcome prediction results from the ANN to aid clinicians and parents/guardians interactive participation in the decision on whether or not to initiate, withdraw or withhold their child from intensive care treatment [Yang 2004; Frize et al. 2005].

One of the most significant contributions was the latest update of MIRG's ANN tool to include the classification-based MultiLayer Perceptron (MLP) ANN tool, into an artificial neural network research framework (ANN RFW) in efforts to improve the functionality, learning curve and operating time of the previous ANN [Rybchynski 2005]. The MLP ANN uses a feed forward back propagation learning algorithm with weight elimination as an option. There are nine network parameters that influence the ANNs learning capabilities as aforementioned in section 3.3.4.

MIRG is working towards achieving its goal of developing an online outcome prediction system that receives input data and computes outcomes in real-time using various CDSS and then send out alerts or warnings when predefined thresholds are exceeded or alert rules are triggered. Once all of the components for this system are completed they can be integrated into the hospital information system at the Children's Hospital of Eastern Ontario (CHEO).

Neural Networks are used extensively in the development of intelligent alarm algorithms in real time using patient specific data. In one study conducted by Maglaveras and colleagues they designed a smart alarming scheme using neural networks for use in

the ICU. Since a patient's status changes significantly on a daily basis, it is essential to have an alerting scheme that is user-friendly and learned quickly by medical decision makers with the ability to customize thresholds that are applicable to each individual patient's condition. In order to update the knowledge-base used in detecting critical events, and subsequently the data used in the training algorithm, it is essential to continuously update the alarming scheme with real time data generated from the bedside monitoring devices [Maglaveras et al. 1998].

### 3.4.2 Case-Based Reasoner

The case-based reasoner (CBR) is an extension of the knowledge-based system (KBS). It draws on past experience from a case base and is able to adapt a successful solution from the past to a similar problem. The CBR, in contrast with the KBS, uses reasoning instead of defined rules and is therefore the method of choice when working in domains that have no concrete rules [Watson & Marir 1994].

The CBR uses a retrieval algorithm to find the most similar case in its case base. One example of a retrieval algorithm and the one that is used by many MIRG researchers is the k-nearest neighbour algorithm.

### 3.4.3 K-Nearest Neighbour

K-nearest neighbor distance algorithms calculates the weighted distance by effectively plotting all points in k-dimensional space. This algorithm calculates the weighted distance from the target case to all other cases in the case-base. Hence, the cases with the smallest distance to the target case are chosen as the closest.

A weighted k-NN algorithm takes into account weights assigned for each input variable of the case. Input variables with greater weights are plotted along an elongated axis forcing the difference in values along the axis to be more important. Conversely, input variables with lower weights are plotted along a shrunken axis on the plot [Cotea & Jiwani 2003; Rybchynski 2005].

One of the main advantages of the k-NN algorithm lies in its ability in dealing with missing values. Although the missing values are not plotted, the k-NN is still able to find the closest matching cases and a distance is still calculated. It should be noted that cases with more than four out of nine SNAPPE-II variables missing is disregarded. The three perinatal extension variables: small for gestantial age (sga), low APGAR score (apgar5) and birth weight (bthwt) are absolutely necessary for the development of mortality prediction models as they are strong indicators of severity of illness and mortality risk.

A weakness of the k-NN is that it requires a predefined knowledge of the inputs of the query and their associated weights [Rynchynski 2005]. An additional weakness is the exponential increase in computation time of the k-NN with a larger number of cases. Therefore, it is most efficient when used with smaller case bases [Ennett 2003; Frize et al. 1993].

The k-NN algorithm used by MIRG, implements a weighted matching algorithm that allows external sources to provide weights for each input variable, so more significance can be given to certain variables when cases are matched by the k-NN. To obtain the weights of the input variables, the k-NN is used in conjunction with a second data mining tool.

The k-NN tool can provide several functions including the following [Rybchynski 2005]:

1. Matching closest cases for inspection by a clinician: This function allows the ten closest matching cases to be viewed and analyzed by the clinician. The relevant inputs and corresponding weights have been defined with the assistance of a domain expert. [Frize et al. 1993]
2. Imputing missing values into patient cases: This function imputes the mean of the ten closest matching cases into the missing value of the specific case. Imputation can be done in the following two ways:
    a. Vertically: to impute missing values to increase the number of complete cases or
    b. Horizontally: to impute missing variables to increase the number of variables for each case. The assistance of a domain expert is required in order to define the weights and inputs to be used for imputation [Ennett & Frize 2003b].
3. Extending datasets to include missing minimum data set variable when merging databases to create a multi-source test set: This function allows a dataset missing variables to impute the missing values using horizontal expansion as aforementioned. The variables included in the data set and their corresponding k-NN weights need to be set.
4. Predicting outcomes: Since the ANN cannot deal well with continuous outcomes without the continuous input and output being classified, the k-NN can be used instead to predict outcomes by outputting the mean of the continuous outcome for the ten closest matching cases. The inputs and relative weights must be predefined for each outcome [Rybchynski 2005].

## 3.5 MIRG ANN Prediction Models

MIRG makes use of an artificial neural network application written in MatLab for mining medical data. MIRG researchers have used the application extensively to

develop prediction models for clinical and administrative outcomes for medical databases. In some cases a list of risk factors or the most influential input variables (minimum dataset) is the desired result. On the other hand, the prediction model can be intended for use in a clinical environment as a case-by-case outcome prediction model.

Three seperate mortality prediction models developed by MIRG researchers will be used in the design of the alerting system prototype which will aid researchers in selecting the model that is best suited at predicting infant mortality. Since physicians have a high tendency to overestimate mortality (i.e predict death with a high sensitivity), a model which correctly classifies more patients who will survive (i.e predicts survival with a high specificity) would be beneficial and complementatry to the way physicians think [Walker 2003].

The three models used will be described briefly and their application to the clinical alerting system in efforts to detect abnormal or critical events.

The data used to develop the ANN prediction models comes from the Canadian Neonatal Network (CNN) database which contains 20,488 admissions collected from seventeen NICU's from across Canada between January 8, 1996 and October 31, 1997. Data was collected on day 1 (admission to NICU) and days 3, 14 and 28 (or discharge).

### 3.5.1 ANN Mortality Prediction Model 1: Ennett's Model

Ennett developed a hybrid ANN-CBR system to impute missing values in order to achieve a better ANN mortality prediction model than the statistically based models in the literature [Ennett 2003]. The ANN-CBR system could impute values that were closer

to the actual missing value than the value obtained by the mean or random imputation methods.

The CNN database using day 1 data collected within the first twelve hours of admission to the NICU was used to evaluate the hybrid system. Any cases missing (mortality) data or any of the perinatal extension variables considered important (bthwt, sga or apgar5), were excluded, resulting in 19,427 cases remaining.

The hybrid system was used to train and test only the cases that had complete data of a database on an ANN to determine the relative weights of the input variables. The database was first expanded "vertically" to included cases missing one to four of the SNAPPE-II (Score for Neonatal Acute Physiology Perinatal Extension-II) variables to ensure all nine SNAPPE-II variables were imputed for all cases. Next, expanding the dataset "horizontally" increased the number of cases with complete data for more input variables in addition to the SNAPPE-II variables. This resulted in an imputed/complete case database which increased from 5102 to 19,403 cases consisting of 30 variables [Ennett 2003].

Using the database consisting of 5102 cases with 30 complete variables, Ennett used the ANN and the weight elimination cost function to reduce the 30 variables and determine a minimal dataset for the prediction of mortality consisting of 13 variables found in table 3-2 compared with the nine SNAPPE-II variables.

| Ennett's Hybrid model | SNAPPE-II |
|---|---|
| Po2/FiO2 ratio | Po2/FiO2 ratio (po2fio2r) |
| Lowest urine output | Lowest urine output (lurine) |
| Lowest serum pH | Lowest serum pH (lserum) |
| Apgar score at 5 minutes | Apgar score at 5 minutes (apgar5) |
| Lowest platelet count (lplt) | Small for gestational age (sga) |
| Small for gestational age | Birth weight (bthwt) |
| Highest sodium concentration | Lowest temperature (ltempf) |
| Highest respiratory rate | Lowest blood pressure (lbloodp) |
| Highest pCO2 reading | Multiple seizures (seizure) |
| Birth weight | |
| Lowest glucose concentration | |
| Lowest temperature | |
| Highest blood pressure | |

**Table 3-2: Ennett's List of Risk Factors for Predicting Mortality [Ennett 2003]**

A new ANN neonatal mortality model containing 19,427 cases with complete/imputed data for all thirteen of the ANN-CBR hybrid systems mortality model was developed. The model included all of the SNAPPE-II variables with the exception of the occurrence of multiple seizures *(seizure)* and the lowest blood pressure *(lbloodp)* [Ennett 2003].

The resultant model classified the patients better than or equally as well as the statistically based scoring models in the literature.

The classification rate of Ennett's model was 96.8% when specificity was optimized and 84.2% when sensitivity was optimized, while the SNAPPE-II model's classification rates for the same test were 96.4% and 85.2% respectively [Ennett 2003].

### 3.5.2 ANN Mortality Prediction Model 2: Qi's Model

Qi developed an ANN prototype tool using the nine SNAPPE-II variables to predict the likelihood of infants' survival, duration of ventilation and length of stay in the

NICU. The results discussed will only be limited to mortality model presented in this work.

The CNN database was used to train the ANN, and consisted of 20,488 cases on day 1 (admission to NICU) data collected within the first 12 hours. Any cases missing (mortality, length of stay or length of ventilation) data, moribund babies or any of the perinatal extension variables considered important (bthwt, sga or apgar5), were excluded, resulting in 19,398 cases. Qi used the CNN database with Ennett's imputed values for the 19,398 cases to build an ANN model.

This particular database had a high imbalance of the mortality outcome only 3.74%, hence the ANN would classify all the cases as belonging to the outcome with the highest a priori probability (survival). To improve the classification performance of the ANN, the cases with the rare outcome (death) were randomly re-sampled back into the data creating a training set with an artificially increased representation of mortality [Qi 2005]. Training an ANN with an increased number of rare outcomes, produces a test set with better performance [Ennett 2003]. Hence, the 725 mortality cases were extracted from the database, duplicated to create 1450 cases and re-sampled back into the data increasing the total number of cases to 20,848 [Qi 2005]. This larger database was divided into a training set of 13,899 (2/3) cases and test set using 6,949 (1/3) cases.

The Evidence-based Practice Identification and Change (EPIC) 2002 database is a small repository of cases which have been submitted from tertiary care centers that contain 59 patient cases was used as a further validation set. Many of the variables collected in the CNN database were collected in the EPIC database.

To validate the ANN model, Qi extracted the nine SNAPPE-II variables used in testing and training of the ANN model. "For nine input variables, five of them had complete values for 59 cases ... The missing values must be replaced because the tool required nine complete input values for each case" [Qi 2005]. It was suggested that these missing values be replaced with normal values to complete the cases.

Each of the nine input variables were put into the ANN tool and predictions were made for each of the 59 cases. The predicted results were compared with the real results for each patient along with physicians predicted results as summarized in table 3-3.

| | Mortality | | |
|---|---|---|---|
| | Qi's ANN Tool (CNN) | ANN Tool (EPIC) | Physicians (EPIC) |
| Sensitivity (%) | 70.2 | 25 | 50 |
| Specificity (%) | 93 | 98 | 92 |
| CCR (%) | 90.6 | 88.1 | 86.4 |

**Table 3-3: Classification Rate of EPIC database by ANN tool and Physicians [Qi 2005]**

The results in table 3-3 show that the ANN tool using the CNN database had a slightly higher performance than the physicians at classifying mortality. When using the EPIC database as a validation set the the physicians predicted mortality better than the ANN tool.

| | Mortality | |
|---|---|---|
| | Death (+1) | Survival (-1) |
| Real outcome | 8 | 51 |
| Physicians' Predictions | 4 | 47 |
| ANN tool outcome | 2 | 50 |

**Table 3-4: Classification results by physicians vs. ANN tool using the EPIC database [Qi 2005]**

When the EPIC database was used to verify the ANNs predictive ability, the performance of the physicians was much better as shown in table 3-4. This may be due to the fact that the EPIC database was small in size and contained only eight 'deaths', as such the results may not be representative of a larger study. Also in this particular research the EPIC database was imputed with normal values so it is possible that these normal values were not accurate in representing the patients' state.

### 3.5.3 ANN Mortality Prediction Model 3: Rybchynski's Model

Rybchynski used the nine SNAPPE-II variables to develop mortality, length of stay (LOS) and length of ventilation (LOV) models and tested these models using the ANN research framework (ANN RFW), the ANN Committee of Classifiers Verification tool (CCVT) and the Case Based Reasoning System (CBRS) using k-Nearest Neighbours (k-NN) matching algorithm.

The CNN database that was used in Rybchynski's work consisted of 19,377 cases with complete data in all nine SNAPPE-II input variables as well as the outputs mortality, length of stay and length of ventilation. The original CNN database contained 5088 cases with complete data in the SNAPPE-II variables after being imputed by Ennett [Rybchynski, 2005]. The EPIC database was used as a further verification database.

For each outcome, the database was split into training, testing and verification set. The verification set was made up of 1/3 of the data (6459 cases), the remaining 2/3 (12918) of the cases was split again, 2/3 (8612 cases) for training and the remaining 1/3 (4306 cases) as a test set.

As aforementioned, this database contained a high imbalance of mortality outcome so re-sampling was preformed to increase the number of positive outcomes (i.e

death) to 10%. The total number of cases increased to 20,739. Rybchynski later mentioned that to provide effective results, re-sampling for each outcome should have been at least 20% [Rybchynski 2005].

Rybchynski pointed out that the results "seen from the CCVT for mortality are better than for VENT and LOS. The nine input variables used to train the ANNs were from the SNAPPE-II sub-set of the 37 variable SNAP.... the SNAPPE-II variables were chosen from the SNAP as those best able to predict mortality" [Rybchynski 2005]

The results using the CCVT were compared with the work of Qi for the mortality prediction found in table 3-5. Both Rybchynski and Qi used the EPIC database to validate their ANN mortality prediction models.

| | Mortality | |
|---|---|---|
| | CCVT | Qi [2005] |
| Sensitivity (%) | 62.5 | 25.0 |
| Specificity (%) | 94.1 | 98.0 |
| CCR (%) | 89.8 | 88.1 |

**Table 3-5: Rybchynski's CCVT compared to Qi's ANN Tool [Rybchynski 2005]**

As seen in table 3-5 the CCVT's classification rate was slightly higher than Qi's model. The CCVT had a significantly higher sensitivity rate than Qi, which represents a model with better classification performance in terms of mortality which is ideal in a mortality prediction model.

The risk factors (minimal data set) for each of the three ANN mortality models chosen for this work is shown in table 3-6. All three models share similar variables but in different order. The order of the variables is important in that the variable with the highest value (100) is the most influential at predicting mortality.

| Ennett's [2003] Model (n=5102) | | Rybchynski's [2005] Model (n= 19377) | | Qi's [2005] Model (n=20848) | |
|---|---|---|---|---|---|
| **po2fio2r** | 100 | **po2fio2r** | 100 | **apgar5** | 100 |
| **Lurine** | 72 | **apgar5** | 96 | **po2fio2r** | 93 |
| **Lserum** | 36 | **lurine** | 67 | **Bthwt** | 61 |
| **apgar5** | 33 | **lbloodp** | 65 | **Lurine** | 50 |
| Lplt | 29 | ltempf | 59 | Sga | 44 |
| Sga | 28 | bthwt | 58 | Lserum | 43 |
| hsodium | 28 | lserum | 56 | lbloodp | 41 |
| Hrespr | 24 | seizure | 54 | Ltempf | 37 |
| hpco2 | 22 | sga | 51 | Seizure | 36 |
| Bthwt | 21 | | | | |
| Lgluc | 20 | | | | |
| Ltempf | 18 | | | | |
| mbloodp | 18 | | | | |

**Table 3-6: MIRGs ANN Mortality Prediction Model Minimal Data Sets**

For each of the mortality models described above a corresponding 'alert generation rule' algorithm will be developed using the first four highly ranked variables from each model for use in the alerting system prototype in efforts to aid researchers in selecting the model that most accurately predicts mortality.

## 3.6 Structural Languages

There are three main structural languages used to represent the content of a document: Hypertext Markup Language (HTML), Extensible HTML and Extensible Markup Language (XML). The outlined framework will focus on the use of XML and its family of standards.

### 3.6.1 EXtensible Markup Language (XML)

In a clinical environment, medical experts are often faced with the problem of non-standardized and unstructured clinical data such as electronic medical records,

medical reports (tests), treatment guidelines and scientific publications. This lack of structure hinders the processing, extraction and exchange of pertinent information contained within these resources.

To solve some of these issues, the introduction of the eXtensible Markup Language (XML) (a popular standard for the web) into the health care industry holds great promise in the exchange and representation of clinical information "emerging from the convergence of data processing, communication, and publishing technology" [Sokolowski & Dudeck 1999].

The health care industry has experienced a widespread increase in the use of the World Wide Web (WWW), fostering the need for XML to standardize medical data for the purpose of structuring of web resources. The World Wide Web (WWW) fosters an increased number of medical patient record systems, knowledge-based resources, clinical decision support systems (CDSS) and educational tools, and is poised to change the nature of medical practice as we know it [Kahn et al. 1998].

The majority of web based applications are dependent on the use of the Hypertext Markup Language (HTML), for information exchange. HTML is a specific application of the Standardized Generalized Markup Language (SGML). However, due to its fixed format, (i.e. each introduction to new element types requires a new version of HTML) it is inflexible. The creation of a subset of SGML, the eXtensible Markup Language was easier to handle and this encouraged its widespread adoption.

XML was adopted by the World Wide Web Consortium (W3C) to enhance HTML for the processing and exchange of data. XML is a meta-language that is not

meant to replace HTML, but to complement its ability to transport structured data [Kahn et al. 1998].

Amongst the markup languages, XML is the most appropriate choice for interoperability and data portability as it allows the user to avoid the stringent complexity of SGML and the rigid tag set of HTML [Hulse et al. 2005]. The use of XML provides a valuable means of exchanging data in the most flexible and efficient way, and it adds structure to existing documents. One of the most noted advantages of XML is in its ability to separate content from presentation [Hoelzer et al. 2001, Hulse et al. 2005]. When using XML, the user has the ability to define the tags for the description of data for each specific use [Seol et al. 1998].

This thesis explores the use of XML with its schema definitions and related technologies (namely XSLT, and parsers DOM) in creating XML-based alerts from a predefined NICU schema and XML-based patient information offering the flexibility needed to enhance the sharing of medical data, and advantages over the use of other markup languages such as HTML and SGML.

The subsequent sections give an overview of XML, followed by an explanation of how this technology is significant in the context of this thesis.

### 3.6.2 Overview of eXtended Markup Language (XML)

Currently the predominant format for the exchange of information over the Internet depends primarily on the Hypertext Markup Language (HTML). However, as web applications become more sophisticated, the use of HTML does not suffice as it is limited by its simplicity. Adequate facilities are not provided for the transportation of structured data using HTML. Also, HTML is not suitable for situations where

applications are used to interpret and process data because HTML is presentation rather than semantic content oriented. Additionally, the creation of new data tags is not permitted by HTML to facilitate information exchange between organizations that share common data types. The full text retrieval feature within HTML documents is not very helpful because it often results in too many irrelevant hits that are listed in uncategorized structure.

In order to overcome these shortcomings and handle the emerging needs, the leading body on XML, the World Wide Web Consortium (W3C) introduced the extended Markup language family of standards, which became an official recommendation in February 1998 [Data 2007]. Since then, several initiatives to drive the adoption of XML in structuring documents on the Internet have emerged.

Over the past couple of years the eXtensible Markup Language has received tremendous publicity. The key attraction to XML is it enables the user to create a single representation of a document and present it in many different ways, independent of the display device. XML provides a mechanism for labeling sets of data so that they can be shared between systems. XML is being used in a variety of different systems including palm pilots, mobile telephones and Web applications.

The primary application of XML within the medical fields has focused on a standardized solution to the problems of structure, storage, retrieval, and exchange of patient data. "XML was devised to provide SGML's extensibility, structure, and data checking to create for robust, large scale Web applications" [Kahn et al. 1998].

XML makes data portable by separating data from presentation and logic, ultimately provides a clean logical representation of information enabling the author to

modify information at any time. Users are able to define original content by creating new XML schemas or Document Type Definitions (DTDs).

The four principle components that enable XML applications to process an XML document are:

- the XML document
- XML schemas or Document Type Definitions (DTDs)
- Processors and Parsers
- Stylesheets

Each of these components will be discussed in the subsequent sections in more detail.

Hoelzer describes the process as follows: "XML allows for the addition of structure to existing test (.xml), validating each document against a corresponding schema (.xsd), changing the schema and related XML documents, querying the document's specific context, and finally displaying content according to the users needs" [Hoelzer et al. 2001].

Recognizing the limitations of SGML, mainly its breadth and complexity, the W3C proposed XML as a simplified subset of SGML, inherit all of SGMLs strengths of extensibility, structure and data checking and discard the more complex and less used traits to create robust, large scale Web applications.

When seeking to produce interoperability, component reuse is very important. XML is a major enabling technology that supports global interoperability as it has the ability to extend, rename, reuse, and refine other individual components.

With every XML document, there is usually an XML schema or Document Type Definition (DTD) associated with it which serves to define a set of rules applicable to that

XML document. These rules are used in determining whether the XML document is valid or not. The following section discusses the schema language and DTD.

### 3.6.3 XML Schema Language

XML presents a means of attaching metadata to describe data representations and semantics through the use of XML schema language, also known as the XML schema Definition (XSD) language. The schema language constrains a set of rules used for describing and constraining the structure and content of an XML document [Beech et al. 1999]. An XML schema is analogous to a data definition language for a relational data base, as it serves to specify the valid structures, data types and constraints for XML documents [Roy & Ramanujun 2001].

There are several schema languages such as: schema for object oriented XML (SOX), XML data reduced (XDR) schema, and XML schema definition language (XSDL) that can be used in the structuring of text based data and in updating already existing documents. The schema language can be used to describe custom data types and have the "inherent capabilities for reusing components by doing the kind of importing and referencing that are found in programming languages such as JAVA" [Gregory 2000].

A schema definition represents the overall document model. To describe how the receiving application will interpret the markup tags, XML schemas or DTDs are sent with the data (referenced from an external source or included within the XML document) thereby creating self describing data. XML document models with human readable material are enhanced by the application of the standard syntax provided by XML schema specification.

As mentioned by Catley, the "XML schema language supports the rich data types associated with object oriented programming languages and provides support for data validation to ensure that the XML data conforms to its attached schema. This rigorous data checking is imperative in medical applications where data integrity is essential" [Catley & Frize, 2002a].

Inheritance is a feature supported by the XML schema language. This feature is of particular interest to MIRG's ANN application since it allows automatic generation of new schemas based on existing schemas. In addition, XML schemas are used as a basis of comparison in determining whether or not an XML document structure is well formed (i.e. conforms to rules of XML) as well as identify errors in the data itself. The flexibility of adding new elements where required is possible by changing the XML schema definition.

In the prototype of the clinical alerting system, XML schemas are used to describe the allowable formats for XML based patient records. The creation of XML-based clinical alerts will form the basis of a predefined NICU schema and XML based patient information. MIRGs ANN tool will be interfaced with the NICU schema in order to support clinical decision support system (CDSS) alert generation.

#### 3.6.3.1 Document Type Definitions

Document Type Definitions (DTDs) are extensively used in describing the structure of XML documents. Typically a set of custom tags and attributes are defined within a DTD. Similarly to schemas, DTDs can either be attached to an XML document or referenced from an external location. DTDs are also designed for the purpose of validating an XML document.

The description of the document model that will be used in this work is the XML schema definition as oppose to the DTD. The reasons for this decision are: firstly the main advantage of XML schemas over DTDs lies in the fact that XML schemas are XML documents that support data types and namespaces [Schweiger et al. 2001]. Hence, existing XML tools such as parsers and transformation engines are used in processing an XML schema. "DTD's on the other hand, have non-XML syntax. For example, we cannot feed a DTD into a (Extensible Stylesheet Language Transformation) XSLT engine" [Schweiger et al. 2001]. The XSLT will be described in the later of the context. Secondly, in comparison to DTDs, "XML schema approach supports more abstraction concepts thus allowing for a higher reuse of definitions" [Hoelzer et al 2001]. Finally, XML schema syntax is generally more detailed (richer and more useful) than DTDs. This offers a very detailed documentation of the document model. Once the schemas are complete, they are transmitted with the data and interpreted and subsequently validated by XML parsers. The use of XML parsers and processors are discussed in the next section.

### 3.6.4 XML Parsers

An XML parser is responsible for reading and interpreting an XML document to create its document tree, so that it can be used by other applications. The main role of the parser is to process an XML document. The parser interprets the documents by extracting data from its contextual representation and then creates either new data structures or events from them. It is essential for parsers to check whether documents are well-formed and whether they comply with a specific XML standard as a process towards the automatic processing of XML documents.

XML parsers fall under two separate categories: validating and non-validating parsers; they support standard application programming interfaces (APIs), either the Document Object Model (DOM) or the Simple API for XML (SAX).

Validating parsers are responsible for checking the "well-formedness" [Bray et al. 2006] constraints of a document and to verify that it conforms to a certain schema or DTD (either internal or external to the XML file in question). In contrast, non-validating parsers are not required to compare the document to the schema or DTD [Sall 2000] but only need to check the well-formedness of the document.

There are many different parsers available in the market. They not only vary in their support for transforming and checking documents but also in the way they interpret a document. For example, the simple API for XML (SAX) is an event driven rather than structure oriented parser that reads text sequentially. Whenever a start or end tag appears within the document, the parser alerts the application that an event has been generated. The DOM is a W3C recommendation that works in a similar fashion as an HTML document tree in a Web browser. A hierarchical data structure is built from the content of the document by the parser. The Xerces4J is a popular parser created by the Apache XML project. It forms the basis for IBM's XML parser for Java (XML4J) and Sun's Java API for XML parsing (JAXP).

The choice of a particular parser is dependent on the particular uses of the data. The SAX parser is well suited for applications that work with large amounts of data with speed as a requirement. Whereas the DOM is well suited for applications that involve the parsing and storing of information for use at a later time. In this thesis the Xerces DOM parser was used to parse XML files in the alerting and warning system prototype.

### 3.6.5 XML Processors

Software programs that are used to parse XML documents and provide access to their structure and content are known as XML processors. Typically, XML processors are fixed within the application that is used to view the XML document. The XML processor's role is to validate the structure of an XML file or document and confirm that all the rules defined in the schema of DTD are followed. Additionally, XML processors can transform documents into a diverse set of formats.

There are two classes of conforming XML processors, validating and non-validating. The validating XML processor reads and processes every part of the document including the schema (or DTD) and all external entities referenced in the document, and report on all violations and well-formedness. On the other hand, non-validating processors are only required to check the validity of the document. When using non-validating processors, well-formedness errors many go undetected, especially in the case where external entities must be read. Several different components may be required by XML processors to accomplish their tasks.

One example of an XML processor is the eXtensible Stylesheet Language (XSL) Transformations (XSLT) processor. There are many components that make up the XSLT processor, one of which is the parser. An XML document is separated into meaningful parts using the parsing components, so that other XSLT components can operate on the individual components.

Initially, when an XML processor first loads an XML document, it parses the elements within a document and stores them in the form of a Document Object Model (DOM) in the random access memory (RAM).

The DOM is a W3C recommendation that describes the structure of dynamic HTML and XML documents and provides a way for manipulating the documents structure through a Web browser. In the case where an XSLT is associated with an XML document, the XML processor can be used to apply the XSLT to the document to produce a specified output format.

The next section discusses the use of the eXtensible Sytlesheet Language Transformations (XSLT).

### 3.6.6 Extensible Stylesheet Language Transformations (XSLT)

In order to be human readable, XML documents are required to be displayed in a Web browser. The mechanism used to describe how an XML document should be displayed is the eXtensible Stylesheet Language (XSL). XSL is the preferred stylesheet language of XML and it is far more sophisticated than the simple cascading stylesheet language used by HTML.

XSL consists of three parts:

- XSLT – most important part of XSL; is a language for transforming XML documents into other documents
- XPath – is a language for navigating through XML documents
- XSL-FO – is a language for formatting XML documents.

The focus here is on the eXtensible Stylesheet Language Transformations (XSLT). XSLT is a language used in transforming an XML document into another XML document, or another type of document that is recognized by a browser.

XSLT uses XPath to find information by navigating through elements and attributes within an XML document. XSLT enables the transformation of data centric

XML documents into a variety of different output formats, such as an HTML page, Java Code, a C++ file, simple text file, PDF or even modified XML, a format suitable for the purpose of presentation. These transformations are processed by an XML processor as previously described.

In the context of this thesis, the XSLT is used to convert XML documents representing patient data into a format that can be processed by the ANN.

### 3.6.7 Wireless Markup Language (WML)

WML or the Wireless Markup Language, is a markup language similar to HTML, except WML is based on XML so it is more flexible and highly structured than HTML. WML follows the same rules as XML. WML is the most dominant language used with wireless devices.

The purpose of WML is to create and control the presentation of Web pages to be displayed in a Wireless Application Protocol (WAP) browser typically found in WAP devices such as mobile phones, PDAs, and other wireless connection devices. Pages in WML are structured within decks, allowing for several pages (also know as cards) to be defined within a file. The WAP standard is based on Internet standards such as HTML, XML and transmission control protocol/internet protocol (TCP/IP).

### 3.6.8 Short Messaging Service (SMS)

The short messaging service (or SMS) simply put, is a protocol used for sending and receiving short text messages to and from cellular phones, or from a personal computer connected to the internet or a handheld device such as a Blackberry to a cell phone. SMS messages are limited to 160 alphanumeric characters that can be transmitted

in one message. If a message contains more than 160 characters, some phones are able to break down the messages into several smaller messages and send them as single messages. The recipient's cellular phone is then able to combine all of the received messages into one long message.

SMS provides its users with a convenient and low cost way of communication as it uses a control channel rather than a voice channel to transmit messages. Service providers often provide their customers with text messaging packages or a small charge is applied for sending text messages.

Since SMS is a low-bandwidth messaging service that does not overload the network as much as phone calls it is most commonly used in alert and notification applications such as: stock market alerts, weather report alerts, remote system monitoring, and most recently TV show polls.

SMS will be used in this research to send wireless alerts to physician's mobile devices. Other alternatives of transmitting alerts to physicians exist such as the enhanced messaging service (EMS) used to send formatted text, sound effects and small pictures and multimedia messaging service (MMS), in addition to text it can send animations, and audio and video files. Not all phones are enabled to use these standards so for the sake of simplicity SMS is the method of choice that will be used and the easiest to implement for the current stage of this research. In the future other technologies can be implemented such as WML to transmit alerts using a WAP gateway.

The next chapter briefly discusses the benefits of wireless and mobile computing technologies in healthcare and gives and overview of some of the challenging issues that need to be addressed before implementing a wireless network in medical settings.

# Chapter 4: Adoption of Mobile Computing and Wireless Technology in Healthcare

The health care process involves generating significant amounts of vital and sensitive information that is critical in providing the most appropriate delivery of patient care. Traditionally this information has been documented in paper based records (patient charts) which has been said to be the most inefficient way of storing and retrieving such critical information and does not help in improving the health care delivery process.

For years, the health care industry has implemented "wired" patient information systems (PIS) with some degree of acceptance and success. Timely access to information is evidently important in critical care settings such as hospital emergency (ER) and operating rooms (OR), and intensive care units (ICU) in order to deliver the most appropriate care to patients. The main problem with wired healthcare is it does not provide physicians with the mobility and flexibility which are so inherent in their workflow.

One of the most critical issues faced in health care is due to the high rate of medication errors which harms about 770,000 people a year and amounts to $5.6 billion annually to treat drug related injuries in the US alone, as previously mentioned.

All of the above factors have driven the adoption of wireless technology and mobile computing into healthcare as some applications can potentially aid in reducing medical errors, increasing the management and accuracy of patient data while reducing missing information, increasing the efficiency of healthcare providers and overall, improving the quality of care through enhanced communication and management of medical information.

Wireless technology may succeed in healthcare where other applications have failed, for one main reason that is that wireless technology blends in well with the inherent mobile nature of the medical environment, a key requirement for physician acceptance and usage of any new technology. [Parekhji 2002].

## 4.1 Benefits of Wireless and Mobile Computing

"Mobile healthcare, also known as m-health, is the development, dissemination and application of mobile information and wireless telecommunication technologies in the area of healthcare" [Siau & Shen 2006]. Mobile healthcare technologies promise a new era of benefits for both patients and physicians alike in reducing errors, providing real-time access to patient information, improving communication between physicians and patients, improving the productivity of medical personnel and ultimately reducing the cost of care.

The use of powerful hand held devices such as cellular smart phones, PDAs, tablet personal computers (PCs), and blackberries are harnessing the power of the internet and wireless technologies to provide secure access to accurate and instantaneous medical information that will enable physicians to provide improved patient care by having up to the minute information in the palm of their hands. Not only does the use of medical technologies greatly reduce paperwork, but it also reduces the likelihood of errors associated with paper based information systems, as some information could be incomplete or missing as a result of misplacing test results or the filing of important information in another patients file.

Research has indicated that many medical errors occur due to inadequate access to and having complete information at the time and place it is needed, resulting in incorrect diagnosis and drug interaction problems. A way of reducing these errors was the incorporation of CPOE into hospital information systems. Also the pairing of mobile devices with physicians and nurses who are almost always on the go could reduce the number of errors by allowing information to be accessed and entered at the patient's bedside. Providing real-time access to patient information increases the decision making ability of physicians who are then able to make better and well informed choices.

The use of mobile and wireless technologies also improve communication amongst physicians, nurses and patients, providing a more flexible and mobile way of communication. Traditionally, information was broadcasted over a paging system. This method of communication has some obvious drawbacks in that it overloads the paging system, it is relatively slow in tracking down the physician, physicians might not hear a page due to dead areas in the hospital and this is a one-way mode of communication.

The use of wireless technologies and mobile computing frees healthcare personnel from being tied to a desktop, potentially improving the workflow and efficiency, allowing physicians to spend more time in providing the patient care itself.

The following section will discuss the wireless technologies available in connecting physicians with vital information.

## 4.2 Technology Assessment: Technologies Used in Implementing a Wireless Healthcare

There are three main components required when considering the implementation of a wireless system in hospitals: 1) the clinical application that is being supported 2)

devices that run the application and 3) the network infrastructure over which these devices communicate.

In efforts to improve patient safety and the health care delivery process, wireless technologies have been integrated into many clinical applications. A few of the most widely used applications are:

Charge capture and coding applications: allows the entry of diagnostic and procedure codes and fee schedules at the time of the visit. These applications may interface with a legacy system and send information to a billing system.

Clinical Decision Support System applications such as CPOE, that assist physicians in determining and delivering the correct therapy or intervention to patients by providing, for example, drug-drug interactions checking, drug allergy checking, dose checking, and duplicate therapy for prescriptions.

Laboratory order-entry results reporting applications that facilitate ordering of laboratory tests and/or routing of test for view and sign off by user.

Clinical alerting systems and communication applications that capture clinical alert messages generated by patient monitoring devices, clinical decision support systems or legacy applications, and transmit the information to the physician's mobile device. The potential benefits of wireless clinical applications in health care are summarized in table 4-1.

**Potential Benefits from Health Care Mobile Computing Applications**

| Mobile Computing Application | Positive Financial Impact | Improved Documentation and Coding | Decreased Wait Times for Patients | Decreased Wait Time for MDs | Improved Workflow | Decreased Number of Manual Tasks/Phone | Improved MD Satisfaction | Decreased Variation/ Improved Care Quality |
|---|---|---|---|---|---|---|---|---|
| Alert Messaging / Communication | | | ✖ | ✖ | | ✖ | ✖ | |
| Charge Capture and Coding | ✖ | ✖ | | | ✖ | ✖ | | |
| Clinical Documentation | | ✖ | | | ✖ | ✖ | | |
| Decision Support | ✖ | | | | | | ✖ | ✖ |
| Lab Order Entry and Results Reporting | | | ✖ | ✖ | | ✖ | ✖ | |
| Medication Administration | | ✖ | | | ✖ | ✖ | | ✖ |
| Prescription Writer | ✖ | | ✖ | ✖ | ✖ | ✖ | ✖ | |

**Table 4-1: Potential Benefits from Health Care Mobile Computing Applications [Turisco & Case 2001]**

This thesis focuses on the design and implementation of a web-enabled XML based clinical alerting system prototype that will aid in detecting abnormal events and generate alerts and or warnings, which will be wirelessly transmitted to physicians' mobile devices, a Java GUI or e-mail depending on the severity of the alert.

Due to limited resources, the mobile devices used in the system will be restricted to cellular telephones in the future as more devices are made available they can be easily integrated into the system.

The last of the three components for implementing a wireless system is the network infrastructure. There are three possible network infrastructures that can be used: personal area network (PAN), local area network (LAN) and wide area network (WAN), a brief introduction of each type of network will be given.

### 4.2.1 Personal Area Network (PAN - WPAN):

A personal area network (PAN) is a computer network that is organized around a person. It is the smallest-scale network. PANs can consist of a mobile computer, a cell phone and/or a handheld computing device such as a PDA. A PAN allows these devices to communicate with each other over short distances. These networks can be used to transfer files including email and calendar appointments, digital photos etc. Personal area networks can be constructed using cables or they can be wireless PANs. A universal serial bus (USB) and Firewire (a high performance networking standard based on a serial bus architecture similar to USB) technologies are often used to link a wired PAN together, while wireless PANs typically use Bluetooth or sometimes infrared connections such as IrDA. PANs generally cover a range of less than 10 meters (about 30 feet).

### 4.2.2 Local Area Network (LAN –WLAN):

A local area network (LAN) is a network of computers in close proximity to each other, are supplied with high speed data networking capabilities. Generally these computers or networking devices are in the same general physical location usually within an office building, a hospital, a school campus, or a home. A LAN is useful in offering users with shared access to resources like files, printers, servers, games or applications through connecting workstations, personal computers, and other devices. A LAN in turn often connects to other LANs, and to the Internet or other wide area networks. Most

LANs are built with relatively inexpensive hardware such as Ethernet cables, network adapters and hubs.

A wireless LAN (WLAN) on the other hand, is a flexible data communications system implemented as an extension to or as an alternative for, a wired LAN. WLANs use radio frequency (RF) communication technologies to accomplish the same functionality as its wired counterpart, except the transmission and receiving of data is over the air, minimizing the need for wired connections. Thus, wireless LANs combine data connectivity with user mobility. With wireless LANs, users can access shared information without looking for a place to plug in, and a network can be set up or augmented without installing or moving wires. This gives users the mobility to move around within a broad coverage area and still be connected to the network.

### 4.2.3 Wide Area Networks (WAN – WWAN)

A Wide Area Network or WAN is a computer network that spans a large geographical area and provides broader connectivity across countries. Typically, a WAN consists of linking two or more local area networks, so that users and computers in one location can communicate with users and computers in another location. Computers connected to a WAN are often connected trough public networks, such as the telephone system they can also be connected through satellites or leased lines. The largest and most well-known example of a WAN in existence is the Internet.

Several WAN's are built for one specific organization and are usually private. Others may be built by an Internet service provider (ISP) to provide a connection from an organization's LAN to the Internet.

In addition, WAN's also refer to Mobile Data Communications, such as GSM, GPRS and 3G.

A wireless wide area network (WWAN) uses cellular network technologies such as **W**orldwide **I**nteroperability for **M**icrowave **A**ccess (WiMAX), **U**niversal **M**obile **T**elecommunications **S**ystem (UMTS), **G**eneral **P**acket **R**adio **S**ervice (GPRS), **G**lobal **S**ystem for **M**obile communication (GSM), and **C**ellular **D**igital **P**acket **D**ata (CDPD) to transmit data over a wireless signal over a range of several miles to a mobile device. The devices used to access the wireless applications need to have a modem that interacts with the wireless network via radio signals

Amongst the wireless networks, the WLAN is the most commonly implemented network infrastructure for wireless healthcare solutions as it enables very high data transmission rates critical for the data intensive needs of healthcare.

The NICU at the Children's Hospital of Eastern Ontario has implemented a wireless LAN in specific 802.11 b for wireless transmission of information. The WLAN is the most suitable network infrastructure for transmission of the data from the clinical alerting system to mobile devices compared to other wireless technologies such as Bluetooth and Zigbee as they have low data rates 1 Mbps (721 kbps) and 0.25 Mbps data rate respectively, compared to Wi-Fi 11 Mbps. A comparision of the three competiting technologies that can be used in a hospital setting is found in table 4-2.

| Technologies | Wi-Fi | Bluetooth | Zigbee |
|---|---|---|---|
| **Standard** | IEEE 802.11 b/g/a | IEEE 802.15.1 | IEEE 802.15.4 |
| **Network type** | WLAN | WPAN | WPAN |
| **Modulation** | DSSS and OFDM | FHSS | DSSS |
| **RF Frequency Band** | 2.4 and 5 GHz bands | 2.4 GHz | 915 MHz, 2.4 GHz, 898 MHz in Europe |
| **Number of Channels** | 11 | 79 | 16 |
| **Topology** | Star-access point | Peer to Peer | Mesh Network |
| **Coverage area (m)** | < 100 | < 10 | < 10 |
| **Range** | 100 m | 8 m (Class II, III) to 100 m (Class I) | 10 – 75 m |
| **Current** | 350 mA | 65- 179 mA | 30 mA |
| **Data Rate (Mb/s)** | 11 (b) to 54 (a,g) | 1 (721 kbps actual) | 0.25 |
| **Battery Life** | 1 – 3 hours | 4-8 hours (streaming audio) | Years (at low duty cycle) |
| **Adoption of Technology** | Mature technology (widely used) | | Relatively new |
| **Applications** | Internet access, Computer Networking, Wireless Networking, Bedside charting, Wireless Alerting | Streaming audio, Hands-free, Computer peripheral, ECG Monitoring, Multimedia | Wireless sensors, Industrial controls, Wireless switches, Remote patient monitoring, Meter reading |

**Table 4-2: Comparison of Wireless Technologies [FCE 2006]**

In the medical domain it is important to have a secure, reliable network to transmit confidential patient information without compromising the privacy of the patient for these reasons not all hospitals have been quick to implement a wireless network infrastructure. In the next section some of the arising issues and challenges with deploying wireless technologies in hospitals are discussed.

## 4.3 Challenges in Implementing Wireless Technologies in Healthcare Environments

Although there are numerous benefits in deploying wireless technologies in healthcare, there are also some challenges that need to be addressed before wireless technologies can be applied on a wide scale within the healthcare continuum. As with any relatively new technology, there are many issues that affect the implementation and utilization of wireless networks in hospitals and clinics. There are both common and specific issues depending on the type of wireless network. Some of the common factors are related to interference of coexisting technologies and medical devices and physicians' resistance to change while others are more specific, such as interoperability of medical devices, privacy and security.

### 4.3.1 Interference of Coexisting Technologies and Medical Devices

The Industry, Scientific, Medical (ISM) band is available for medical usage but shared with other users. All of the wireless technologies mentioned above also use the same 2.4 GHz ISM band. The sharing of wireless channels causes interference. There was much concern that radio-frequency (RF) devices such as cell phones and PDAs and wireless networking devices could potentially interfere with critical medical equipment such as apnea monitors, ventilators, infusion pumps and EEG machines. To alleviate this problem, many medical centers have responded by limiting the operation of wireless devices in areas where patients and medical devices are in use. Also, wireless devices can be restricted to operate in ranges outside of certain limits depending on the transmitted power of the device.

In terms of interference due to the coexistence of other wireless technologies it has been shown that when Bluetooth and 802.15.4 (Zigbee) are used simultaneously the result is severe interference and performance degradation [Chevrollier & Golmie 2005]. To reduce or avoid interference between WLANs and Zigbee, channels of the ISM band can be manually configured by selecting only those channels that do not overlap in frequency [Cyper et al. 2006].

### 4.3.2 Cultural and Physicians Resistance to Change

In a fast paced environment like a hospital, physicians are under a lot of pressure to respond rapidly to critical events. Although wireless technology and mobile computing are intended to ease the workload of physicians, sometimes they do the opposite and may cause physicians to be reluctant to try new applications if they are perceived as slowing them down, or are “unreliable, inaccurate or even, at times, hostile” [Clemmer 2004]. Medical device vendors must keep in mind the end user when designing wireless devices because ease of use and speed are extremely important features to physicians’ acceptance to change. If the system is not intuitive they will not take the time to learn it, and “if a new technology provides little benefit and requires major disruptions in current practice, then health-care workers will resist the change” [Reddy et al. 2005].

### 4.3.3 Interoperability of Medical Devices

The interoperability among various devices is an issue related to the implementation of wireless network. Due to the fact that many wireless devices are

manufactured by various different vendors which follow different standards or in some cases no standards, it is sometimes difficult to ensure that all of these devices will work together and work reliably, resulting in segmented solutions.

### 4.3.4 Privacy

Patient records are sensitive, so hospitals have to protect their patients' information and ensure privacy. Healthcare data should be available anywhere, anytime, but only for authorized persons. To ensure patient privacy over a wireless network, various methods such as: encrypting data through user IDs and passwords, a secure Virtual Private Network (VPN) and data encryption and authentication methods have been put into place. In addition to encryption from mobile devices to the wireless provider, there is also encryption from the provider to the service gateway and from the gateway to the wireless server.

### 4.3.5 Security

Security is a major issue faced in the deployment of wireless systems in hospitals. Given that these systems will be transmitting highly sensitive information, namely patient data, implicit in their use is a need for a high level of end-to-end security. Many individuals are concerned that wireless technologies do not provide the same level of security as wired LANs.

In an attempt to ensure electronic data is secure in the United States (US), the **H**ealth **I**nsurance, **P**ortability and **A**ccountability **A**ct (HIPAA) was designed and enacted giving guidelines of various security requirements. The standard indicates that during the transfer of wireless data, there needed to be absolute certainty that patient records were

not put into jeopardy. In Canada there is a similar privacy act protecting the privacy of medical health records known as the **P**ersonal **I**nformation **P**rotection and **E**lectronic **D**ocuments **A**ct (PIPEDA).

There are many different types of users who will require access to the wireless network within hospitals. For example doctors, nurses and other caregivers (residents or visiting physicians) need access to patient records, charts and test results. Other users such as hospital technicians, parents or relatives do not need access to sensitive patient information. The use of Virtual Private Networks (VPNs) allows an authorized wireless LAN user to gain access to only the information they require.

In order to establish the highest level of security to protect patient information when implementing wireless systems throughout the healthcare continuum, a multi-layered security protection scheme is required in order to protect the air, the data, the network and the user simultaneously, by authenticating and checking any user or device attempting to connect to the corporate system for potential threats before being allowed access to the network inevitably complying with the stringent requirements of the international security standards/policies in Canada the PIPEDA and the HIPAA in the US.

The next chapter describes the methodology used in the design and development of the EMAN system. The performance of the system will be discussed in detail in chapter six.

# Chapter 5: Methodology

## 5.1 Integrating Clinical Alerts into an XML-Based Health Care Framework

This thesis extends the previous research work of Christina Catley. Catley developed an XML based health care framework in order to promote medical data interoperability (to facilitate the sharing of medical data) and integrate diverse clinical decision support systems in the NICU at CHEO [Cately & Frize 2002b].

Catley makes use of XML and its associated schema language to develop a prototype system that standardized medical data to support the exchange of electronic patient information within hospital information systems (HIS). MIRGs future goal is to integrate artificial intelligent based software such as the ANN, k-NN and other artificial intelligence (AI) approaches into CDSSs and use this system with an online data repository for CHEO's NICU. As expressed by Dr. Robin Walker, former head of CHEO's NICU "the ultimate objective would be to transmit infant data from the hospital to diverse, external ANN or CBR systems, and to receive a reply in real-time" [Cately & Frize 2002b]. This thesis will extend this work by taking the predicted outcomes generated from the ANN and in the future other CDSSs and interface them with the clinical alerting system to enable the detection of adverse events and wirelessly transmit these alerts to physicians to aid them in making well informed decisions.

Clinical alerts are commonly used in intensive care settings such as the NICU, surgical intensive care unit (SICU) and adult intensive care unit (AICU). Alarms can be generated from medical devices when a specified threshold value is exceeded, in most cases producing an excess of alarms. As aforementioned, false alarm rates are typically

very high with clinical equipment, as monitoring systems are equipped with limit alarm systems using the "better safe than sorry" logic which generates large numbers of alarms providing for unnecessary distractions resulting in alarms being turned off, and hindering rather than enhancing the performance of the task. Frequently ignoring alarms could result in: an increase in time before intervention, prolonged hospital stay, and potentially increasing mortality and morbidity [Blum & Rosenberg 2006].

There are many factors that contribute to medical errors such as: information overload, lack of vigilance, varying expertise and human error. The level of expertise varies significantly from one expert to another which frequently results in errors in diagnosis and selection of treatment.

In order to reduce the number of alarms generated by monitoring devices and to improve clinical outcomes through the reduction in error rates or in the optimization of the delivery of treatment the development of an intelligent alerting system is essential.

For this thesis an intelligent alerting system will incorporate specific alarms for specific physiological functions and will be used to monitor patient trends and a combination of important risk factors as opposed to single valued parameters. The current trend in the use of clinical alerting systems is moving towards a more sophisticated approach of integrating real-time data collection with clinical decision support systems (i.e ANN in the scope of this research).

The drive for this integration arises from the potential to incorporate trend based event detection algorithms into an alerting system in order to provide early detection of abnormal or critical events, or in the best case situation, a warning of an abnormal event before it occurs.

Two of the main requirements for the successful acceptance of an alerting system from the perspective of physicians are flexibility and customizability.

1. Alerting software must be able to be adaptable to an individual patient's needs and preferences and customized to suit a particular task at hand.

2. If there are too many false positive alerts, more serious alerts may be ignored. It is often necessary to include real-time delays and to take into account the number of times in a specific period a threshold has been exceeded before generating an alert. For example it is quite common for a premature baby to cease breathing for short periods of time, therefore alerts should not be sent until the baby stops breathing for a predetermined time period (i.e 10 seconds or more).

The steps taken to develop and validate the alerting systems performance will be decribed further in the following sections.

## 5.2 Design and Implementation of EMAN System

The Electronic Medical Alerting and Notification system was developed using Java as the main software development tool. The reason for choosing Java is because it can be run on many different platforms (i.e Windows, Linux etc.) so different versions of the program are not required when different platforms are used. A future goal of this system is to be accessible to physicians as a web-service. Since Java is robust, easy to use and includes security features required to transit medical data over the Internet, it is an excellent choice for this work. Java also has capabilities of parsing XML documents using the DOM parser that was previously mentioned in chapter 2. In this thesis, XML is

used to standardize patient records, staff contact information and threshold information that are used by the clinical alerting system.

### 5.2.1 XML NICU Alert Schema

Developed for this thesis the NICU alerting schema is one of the most important elements in the success of the clinical alerting system, as it is used to define and constrain medical data, CDSS inputs and outputs and clinical alerts. The schema constrains minimum and maximum values or thresholds for all elements to avoid the possibility of extraneous or missing values, therefore reducing the potential for medical errors caused by human inputs.

The values chosen for threshold range limitation are based on the statistical analysis of values from a large NICU database of approximately 20 000 values. Physicians can adjust the threshold values used based on individual patients status.

The schema developed for this work contains structures for patient information (such as administrative data and vital signs) and clinical data used by the ANN. The ANN has been used extensively by MIRG researchers to predict outcomes such as Mortality, Length of Stay (LOS) and the required length of ventilation (LOV). As such, the XML schema must accommodate both the input and output values required by the ANN as found in table 5-1.

| ANN Inputs | |
|---|---|
| Parameter | Description |
| Patient ID | Patient's unique identifier, characters or numbers |
| LBLOODP | Lowest mean arterial pressure (blood pressure) |
| LTEMPF | Lowest body temperature, in degrees Fahrenheit |
| PO2FIO2R | Lowest ratio of blood oxygen to fraction of inspired oxygen |
| LURINE | Lowest urine level output in CCs |
| LSERUM | Blood gas analysis results, lowest serum in pH |
| SEIZURE | Occurrence of seizures. None =1, One seizure =2, Multiple seizures =3 |
| BTWHT | Baby's weight at birth |
| SGA | Small for gestational age Yes =1 and No =0. |
| APGAR5 | APGAR score at 5 minutes after birth. |
| ANN Output | |
| Mortality | Patient death or survival (death = +1, survival = -1) |

**Table 5-1: ANN Inputs and Output used by the alerting system**

The data found in table 5-1 consists of a mix of fixed one data point values (i.e APGAR5 and bthwt) and ANN inputs obtained from periodic real-time device driven data. For example, the patient ID, the APGAR score recorded five minutes after the baby is born, and the birth weight are only required to be documented once. The remaining input variables are measured on a periodic basis; hence to accommodate this mixture of data the structure of the schema must be flexible.

### 5.2.2 Schema Structure

The data structure implemented in the schema developed for the NICU patient record is as follows:

- *Top level: NICU_database:*

  Technically, NICU database is rarely used in the alerting system as the base tends to be the patient record, but for transmission of a series of

patient records in one XML file, it was envisioned that in the future a NICU_database root might be required.

- *Second level: patient_record:*

  This is the root of the xml files containing the patient information used by the alerting system. It is generally a complex structure containing third-level elements.

- *Third level: Patient information, Vital trend sets, and patient CDSS outputs:*

  Patient information may only be collected once because it is administrative information. However, vital sets and CDSS results may be updated on a periodic basis. All the data collected on a patient must be kept in an archive; therefore the schema must accommodate this requirement. For each of the possible vital signs and CDSS outputs included in the schema, the minimum and maximum values are restricted to a specific range. This is done to avoid out of range or missing values, thus reducing the probability for medical errors due to human input errors or technical difficulties in using the ANN.

With the exception of boolean and predefined scales such as APGAR5, the values chosen for thresholds of the vital signs are based on a statistical analysis of values obtained from a large database. The minimum and maximum acceptable values are defined as the valid minimum and maximum values found in the database, plus an additional 10%. The only exception to this is the body temperature, where the upper limit is fixed to 103˚F (39.5˚C).

The schema was designed to be extensible and in the future it can be updated to include more sophisticated data from other CDSS results, laboratory information or diagnositic information.

### 5.2.3 High Level Overview of XML Alerting System Architecture

This section explains the steps in which data is processed and analyzed to detect whether a warning or critical alert should be generated from the data collected or the CDSS predicted outcomes.

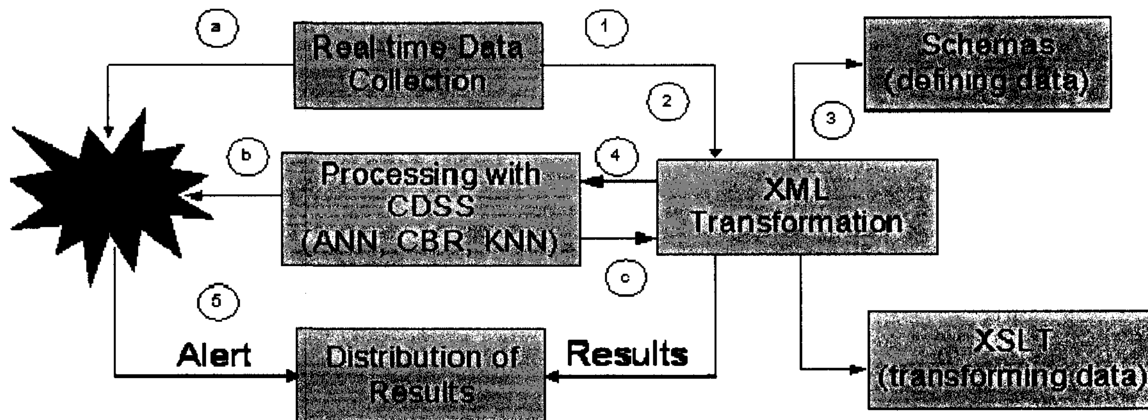



**Figure 5-1: Architecture of Alerting System**

The high level overview of the alerting system is illustrated in figure 5.1. The following is a description of how the alerting system processes data.

1. **Real-time Data Collection block**: The Sunrise Clinical Manager system will be used to collect the real-time patient data generated from medical devices and information contained in electronic patient records.
2. The patient device data is passed to the **XML transformation** block for pre-processing.
3. XML data pre-processing consists of the parsing, validating and transforming of clinical data based on an XML schema and associated eXtended Stylesheet Language Transforms (XSLTs) into a format suitable for the clinical decision support system in question. The schema developed for the NICU data defines

how the document should be structured and defines the minimum and maximum allowable ANN values.

a) It is also possible that the real-time data generated may exceed predetermined threshold values and generate a device alarm.

4. **Processing with CDSS** block: After the real-time data has been transformed into XML, the standardized and preprocessed data is fed into the **processing with CDSSs block**, where the physicians can invoke any of the CDSSs specified by the physicians (i.e ANN invocation). After processing with CDSSs there are two possible events that can occur:

   b) If CDSS output thresholds are exceeded an alarm will be generated. Or

   c) The CDSS output is sent for further XML processing and is converted into an XML document ready for transmission to physicians.

5. **Distribution of Results block**: CDSS alerts and XML based CDSS outcomes are passed to the distribution of results block, where the final result is an XML document containing patient information (electronic patient record), latest output values from the CDSS, alerts and patients latest vital signs obtained from medical devices, ready for transmission to physicians.

## 5.3 Web-based User Interface

A customizable web-based user interface (UI) was developed using Perl as the programming language of choice, as it is commonly used in web based applications in the form of common gateway interface (CGI) scripts. Perl is ideal in this type of application as it has the ability to parse text documents and it interfaces well with HTML (in

processing user input from an HTML form) which is used in the UI design. Perl also has a parsing module XML::Parser, a Perl implementation of a Simple API for XML (SAX) used extensively in automatically creating the XML generated documents required by the alerting system once it receives input information from both the CDSSs and physicians. These generated XML documents were then parsed to generate Perl data structures, in order to display their content on the web page in a visually appealing manner.

The UI was imperative in giving physicians and nurses the ability to interact with the XML-based NICU alerting system. The user interface has the following features that will enable the user to: automatically create XML patient documents from both physician and CDSS inputs, customize thresholds limits corresponding to specific patients, retrieve generated XML documents and display information via a web-browser.

### 5.3.1 Design of the User Interface

The user interface is designed in such a way to make it easy to navigate as the pages all link back to the central home page. Presently there are four options available from the central control page but not all of them are fully functional:

- Manage Patient Data
- Manage Staff Data
- Manage Thresholds
- Invoke CDSS tools Automatically (future work)

Figure 5-2 below shows the structure of the UI.

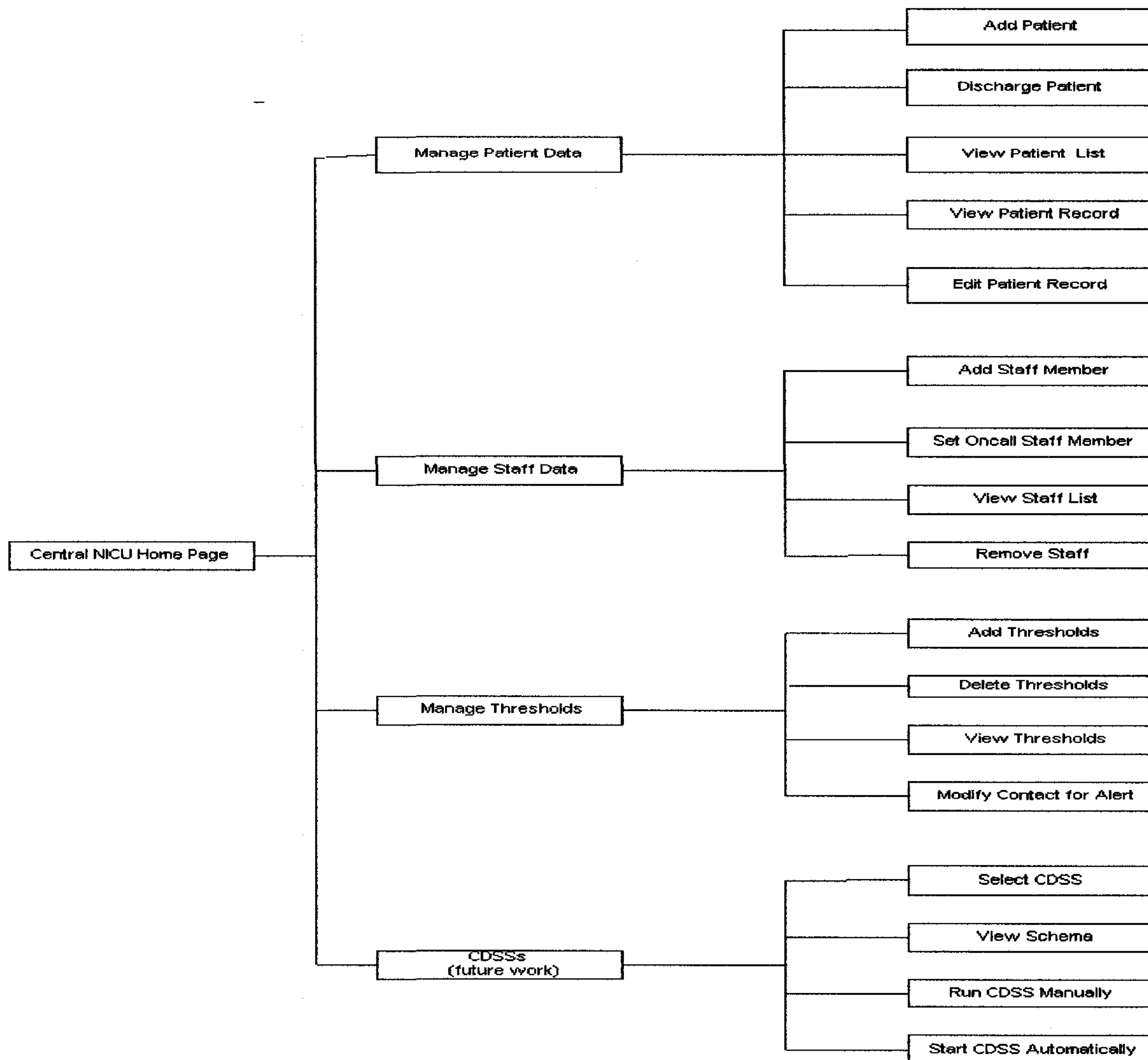



**Figure 5-2: Structure of Alerting Systems User Interface**

A description of each of theses services is detailed below

## 5.3.2 Manage Patient Records

The UI gives the user the ability to add new patients to the database, remove old patient records and place them in the archive, view a list of existing patients and edit patient records. Each patient is assigned a patient id for which a corresponding XML document is created with the name patientID.xml (i.e 23456.xml). The patient ID is

determined by the Perl script; when a new patient is added it updates automatically with the next valid patient ID found in the *ids.txt* file. When a patient is discharged, the file is not removed from the system; it is just removed from the working directory and stored in an archive subdirectory. The resulting patient record is examined by the alerting system for further analysis. If any of the physiologic parameters are above their existing thresholds or if one of the alert generation rules are detected, the program will generate an alert message and send it to the staff member responsible for that particular patient.

### 5.3.3 Manage Staff Data

This module allows the user to keep track of the staff members available during the day. All staff members will be kept in the database; so when a particular staff member is on-call, he/she can be selected from a drop down menu and the time of the shift is entered along with their preferred method (i.e pager, cell phone, PDA, e-mail etc.) for receiving alerts. The complete list of staff members found in the *staff.xml* file can be displayed to the user in a tabular format on the Web page. Whenever a new staff member is added or set to 'on-call', this information is appended to two files *staff.xml* and *shifts.xml.* These corresponding files are used by the alerting system to send alerts to the appropriate staff member, based on the severity of alert and the staff member's on-call schedule. The staff member's information can be updated or removed as required.

### 5.3.4 Manage Thresholds

The user has the ability to set new, update and remove thresholds as necessary for a particular patient. There are three sources with corresponding thresholds values that are

used by the alerting system: CDSSs outputs, latest vitals signs and equipment alarms. When a new threshold is set, it is displayed to the user in tabular format with all the essential information. As well, the new or updated threshold information is appended to the *thresholds.xml* file which the alerting system uses to notify the correct staff member of the updated threshold information.

### 5.3.5 Invoke CDSS

This feature is not functional at the present time. As more clinical decision support systems are made available for use with the clinical alerting system, this feature will enable the user to invoke the CDSS tool of choice from the user-interface and have the data go through the analysis and processing as described in section 5.2.3.

All of the standardized XML documents generated from the UI, for example patient records, staff records containing contact information and shift times, and updated threshold setting records are all transferred to the alerting system for further analysis.

## 5.4 Alerting System Prototype

The alerting system discussed thus far is a prototype used as a "proof of concept"- that is integrating artificial intelligence from CDSS such as MIRG's ANN (predicted outcome models) and medical device data outputs, produces an intelligent alerting system capable of defining and detecting adverse events earlier, and generating appropriate alerts to the responsible decision maker's mobile devices. To realize this goal, the alerting system mechanism is discussed further below.

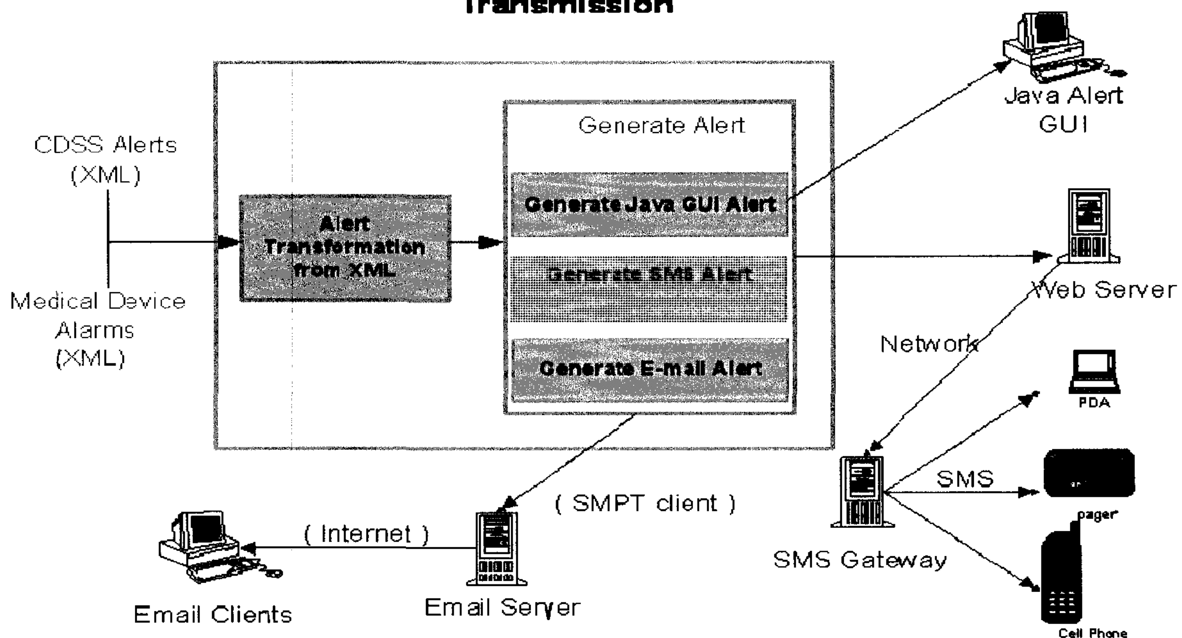



**Figure 5-3: Alerting System Layout**

The alerting system layout in figure 5-3 illustrates the functionality of the proposed system and how each module works together to send out the appropriate alerts. At the present time, the steps leading up to the "generate alerts module" are not yet functioning in real-time. This work is currently being done manually in order to provide the necessary information required for the alerting system and validate its classification performance.

It is envisioned that the alert transformation and generation system will receive, process and transmit XML based alerts as follows. Using the web-enabled UI, as a new patient is admitted to the NICU, the patient's personal and demographic information is entered at the administration desk (i.e patient's first and last name, gender, time, date and location of birth); this process will automatically generate an xml file assigned to this patient and correspondingly assign a new patient id. Once this process is completed, the

patient's physiological parameters are monitored closely in real-time for the first twelve hours after admission to the NICU for the purpose of assessment.

Having a complete patient record containing all of the latest vital information in place, the patient record is analyzed by the alerting system in accordance with the existing ANN models. The predicted models generated by the ANN can then be applied to each specific patient case to generate an output which can be used to predict mortality, length of stay or duration of ventilation as possible ANN outcomes.

First, either CDSS or medical device information regarding possible alerts enters the system via a complete XML patient record. Next, the information is passed through to the Alert transformation from XML block which uses XML Java-based parsers to parse data into the Java program for interpretation. The system then invokes the generate alerts block which generates the appropriate alert.

Warnings will generate Java GUI alerts coded in green, which indicate that a patient may potentially be at risk of their condition worsen. Critical events will generate a Java GUI alert coded in yellow as well as e-mail alerts which use the Java simple mail transfer protocol (SMTP) class, (which allows the Java application to connect to the external e-mail server) suggesting to physicians that this patient should be monitored closely and may require intervention if their condition becomes more severe. Life-threatening events generate Java GUI alerts coded in red and SMS alerts which are passed to the cellular providers SMS gateway and then transmitted to the physicians' mobile device suggesting that immediate action is required as the patient may suffer a mortality.

The alerting system's role is to process this information based on customized alert generation rules and predefined data thresholds and detect if an alert is warranted. If the input data conforms to any of the existing alert generation rules or drops below or exceeds the predefined data thresholds, an alert is generated and sent to the physician's preferred method of receiving alerts, whether by cell phone, PDA, pager or e-mail, as well as to a Java alert GUI (depending on severity) displayed on the computer monitor found behind the administration desk at CHEO in the NICU.

The use of such a system should aid in providing physicians with vital information on a patient status in real-time, allowing them to better assess a patient's needs and to potentially prevent an adverse event from taking place or to manage such an occurrence quickly.

## 5.5 Data Source and Input Variables

The patient data used in this research comes from two databases: the Canadian Neonatal Network (CNN) database and the CNN extension database Evidence-based Practice Identification and Change (EPIC) 2002. The CNN database contains patient records collected from seventeen NICUs across Canada collected from January 8, 1996 to October 31, 1997. The original database contained 20488 patient records during the collection period, for which data was categorized by day 1 (admission to the NICU), and day 3, 14 and 28 (or discharge). In this thesis, only day 1 (admissions- data collected within the first 12 hours) data was considered for the mortality prediction models used.

The EPIC database contains 59 real patient data cases collected at CHEO in 2002. All of the 59 cases were premature infants (gestational age less than or equal to 32 weeks) and were babies transferred from other hospitals.

### 5.5.1 ANN Input Variables

This research uses the nine Score for Neonatal Acute Physiology version 2 with Perinatal Extension (SNAPPE-II) prediction score variables used to predict in-hospital mortality [Richardson et al. 2001] as inputs for the alerting system, found in table 5-1 with their description.

The alerting system can accommodate more input variables as it is easily customizable and not limited to the nine variables used in this work. As more prediction models are developed, for various outcomes the variables corresponding to those models could be easily added to this alerting system.

### 5.5.2 Data Processing for Alert Generation

The 59 real patient EPIC cases used to validate the best ANN prediction model will be used to test the capability of the alerting system in detecting the mortality cases and transmitting wireless alerts to physician's mobile devices.

The original values in the EPIC database are required for use in the alerting system. Since these values were normalized using the z-score formula [Olden & Jackson 2002] found in equation 5.1, prior to validating for use in the ANN, they must be un-normalized for application to the alerting system.

$$zn = \frac{xn - X}{3\sigma}$$

**Equation 5-1: Z-score Formula**

where zn: normalized value of variable x
xn: original value of variable
X: mean of variable X
σ: standard deviation

The 59 patient cases were entered into the system via the UI in order to generate XML based patient records which are required by the alerting system. Along with the ANN outputs (in this case mortality), the nine SNAPPE-II variables used have minimum and maximum threshold values as mentioned in section 5.2.1 that are coded in the alerting system. An alarm threshold class is developed in the alerting system and includes all the minimum and maximum values pertaining to each input variable.

### 5.5.3 Alert Generation Rules

In order to assess the capability of the alerting system in defining and detecting adverse events, different types of alert generation rules have been developed using the monitored physiological parameters. These rules are classified under three general categories: basic rules, advanced rules and combination rules.

#### 5.5.3.1 Basic Rules

Basic rules are based on the minimum and maximum threshold values specific to each parameter. There are three basic rules:

1. parameter > max threshold (i.e ltempf > 103)
2. parameter < min threshold (i.e ltempf < 96)
3. parameter is approaching the minimum or maximum threshold (i.e ltempf = 101.5)

In the first two cases the alerting system would detect that the thresholds for the monitored parameters have dropped below or exceeded the threshold and generate a critical alert and transmit it to the Java alert GUI and medical personnels e-mail.

The third case would generate a warning and transmit it to the Java alert GUI for further monitoring of the patients status. Life-threatening alerts have priority over warnings, and thus are immediately transmitted to physician's mobile devices upon detection and to the Java GUI coded in red indicating the severity of the alert.

#### 5.5.3.2 Advanced Rules

Advanced rules are similar to the basic rules except with the addition of time intervals. There are two possible rules incorporated in the system:

1. parameter > value for 5 minutes (i.e lbloodp > 100 for 5 minutes)
2. parameter > value or < value (i.e po2fio2r < 4 three times in 30 minutes)

It should be noted that these rules cannot be applied to all of the parameters because not all variables have critical durations associated with them. These advance rules generate critical and life-threatening alerts depending on the variable being monitored.

#### 5.5.3.3 Combination Rules

Combination rules are used to "identify novel combinations that have more diagnostic power than does any individual variable" [Laramee et al. 2006]. This may not be medically correct but just as an example of a combination rule, if (lowest blood pressure < 20 && lowest ratio of blood oxygen to fraction of inspired oxygen > 13.662) the patient could suffer from heart failure. This is considered a life-threatening alert. Once the alerting system detects this combination, it would parse the staff.xml and

shifts.xml files to locate the appropriate physician and immediately transmit an alert to his/her mobile device.

## 5.6 Procedure for Testing Performance of Alerting System

Using the MIRG ANN models described in sections 3.5.1-3.5.3 'alert generation rule' algorithms are developed to determine which ANN mortality model most accurately detects infant mortality. Each of the models developed listed the most influential risk factors (variables) used to predict mortality in the NICU. Alert generation rules were developed by integrating up to four of the highest ranked variables from each ANN mortality model and coded in the alerting system to detect abnormal or critical events.

The typical structure of each of the 'alert generation rule' algorithm's are described and will be shown below. Using Ennett's ANN model the highest ranked four variables are: lowest ratio of blood oxygen to fraction of inspired oxygen (po2fio2r), lowest urine level (lurine), lowest serum in pH (lserum) and APGAR score five minutes after birth (apgar5).

The 'alert generation rule' combines the first four variables in the order they appear in table 3-6 in section 3.5.3. The mean of each of the variables is used as the threshold value in the alert generation rule, the threshold values can be varied depending on the state of the patient being monitored. To show how multiple variables can be used at detecting a critical event, the following is the structure of the 'alert generation rule' corresponding to Ennett's model:

if ((po2fio2r <1.9)&&(lurine <4.133)&&(lserum<7.312)) then check apgar5 < 8

The above combination rule is coded in the alerting system and is used to detect clinically significant events as follows: the 59 patient cases are entered into the database and the alerting system scans each patient's file individually checking to see if the first three conditions of the 'alert generation rule' are satisfied. For example if the lowest ratio of blood oxygen to fraction inspired oxygen is less than 1.9 and lowest urine level is less than 4.133 and lowest serum in pH is less than 7.312 then a critical event is detected and the alerting system will generate a Java GUI alert coded in yellow as well as an e-mail alert recommending that the fourth variable in the combination rule be monitored closely. If the fourth condition is satisfied a life-threatening event is detected and the alerting system will generate a Java GUI alert coded in red and a wireless alert will be transmitted to the physician's mobile phone. It should be noted that the threshold values can be varied according to the patients' condition, as some patient's physiological state is more unstable than others depending on the severity of their illness.

Rybchynski's ANN model was developed using the nine SNAPPE-II variables. The four highest ranked variables used to develop the 'alert generation rule' are lowest ratio of blood oxygen to fraction of inspired oxygen, APGAR score at five minutes after birth, lowest urine level and lowest blood pressure. The structure of the 'alert generation rule' is shown:

if ((po2fio2r <1.9)&&(apgar5<8)&&(lurine <4.133)) then check lbloodp <35

Similarly, the alerting system will scan the patient records in attempt to detect if the first three conditions are satisfied the alerting system will generate and transmit critical alerts and then it continues to scan the patient records to see whether the fourth condition is satisfied to detect a life-threatening event and generate a wireless alert.

The third 'alert generation rule' was developed as follows for Qi's ANN model:

if ((apgar5<8)&&(po2fio2r<1.9)&&(bthwt<1000)) then check lurine <4.133

Each 'alert generation rule' algorithm was tested seperately in order to determine which ANN mortality model could detect life-threatening events more accurately. The alerting systems classification performance was measured in terms of sensitivity which is the true positive rate of the system's ability to correctly classify positive outcomes whereas specificity is the true negative rate or the systems ability to correctly classify negative outcomes and the correct classification rate identifies the percentage of correctly classified cases, it is the sum of the number of cases that were correctly classified into their respective classes out of all cases.

The number of variables in each of the 'alert generation rule' algorithm was varied to see whether or not the performance of the system improved or degraded. The results of the test will be discussed in the following chapter, and the model that is most accurate at predicting mortality will be identified.

# Chapter 6: Results and Discussion

The literature pertaining to alert and warning systems points out that the impact of clinical alerting system is best realized through the use of an integrated group of applications with access to a large variety of patient data (i.e. physiologic, medication, laboratory data) and well-defined alert generation rules [Zielstorff RD 1998, Barnett et al. 1983]. Alert rules or logic modules are typically stored in either a rules repository or knowledge database that can be regularly accessed and updated as medical knowledge changes or new evidence becomes available [Teich et al. 1999, Gardner et al. 1999]. A particular event such as sudden increase/decrease in a patient's blood pressure may trigger one of the alert rules and generate a corresponding alert or warning message that is transmitted to the responsible medical personnel immediately.

Warnings are generated when a variable is approaching a threshold value (by 2%). Critical alerts are generated when three out of four condition statements of an 'alert generation rule' are satisfied and life-threatening alerts are generated when all four of the condition statements in an 'alert generation rule' algorithm are satisfied.

In this chapter the 'alert generation rule' algorithms developed in chapter 5 will be coded in the EMAN system in order to test its performance.

The Evidence-based Practice Identification and Change (EPIC) fifty-nine complete patient cases were used to verify the system's ability to correctly detect cases in the database which had the outcome "death". The mortality rate in the EPIC database is 13.6 % (8/59). The specificity, sensitivity and correct classification rate (CCR) of each 'alert generation rule' was recorded and compared in order to determine which model was more suitable for predicting infant mortality.

## 6.1 Testing the Performance of the Alerting System

The highest ranked four variables from each model were used to develop an 'alert generation rule' (in terms of condition statements) corresponding to each model to validate whether or not these variables were sufficient in detecting mortality. The order of the variables will determine whether a life-threatening event or critical event is generated. For example, if three of the four conditions in the 'alert generation rule' are satisfied, the alerting system will examine the fourth condition. If the fourth condition is satisfied the system will generate a life-threatening alert; else it will generate a critical alert suggesting that the fourth condition be monitored closely.

For an alert to be generated using the 'alert generation rule' algorithm, at least the first three conditions must be true. The system then checks the fourth condition to determine the severity of the alert (critical or life-threatening).

The number of variables used was varied in the testing stage to see how much of an effect the number of variables used has on the alerting system's ability to correctly detect a life-threatening event.

The alert generation rule developed for Ennet' mortality model was tested first. The alerting system scanned all fifty nine patient cases and detected six out of eight mortality patient cases accurately, that is, representing true positives (TP). Three survival cases were incorrectly classified as death representing the false positives (FP), and two patient death cases were classified as survivals representing the false negatives (FN). The remaining forty eight patient cases were correctly classified as survivals representing true negatives (TN).

When Qi's model was used for the 'alert generation rule', the alerting system detected five out of eight mortality patient cases representing the true positves. Three patient death cases were classified as survivals representing the false negatives, and two patient survival cases were classified as death. The remaining forty nine cases were correctly classified as survivals representing true negatives.

Finally when Rybchnski's model was used in the 'alert generation rule', the alerting system detected seven out of eight mortality patient cases representing true positives. One patients' death was classified as a survival and three patient survival cases were classified as death representing the false positives. The remaining forty eight cases were correctly classified as survivals representing true negatives.

These results are summarized in the confusion matrix found in table 6-1 using the four highest ranked variables from each model.

| | | **Actual Outcome Ennett's Model** | | **Actual Outcome Qi's Model** | | **Actual Outcome Rybchynski's Model** | |
|---|---|---|---|---|---|---|---|
| | | Negative Outcome (-1 or 0) | Positive Outcome (+1) | Negative Outcome (-1 or 0) | Positive Outcome (+1) | Negative Outcome (-1 or 0) | Positive Outcome (+1) |
| **Predicted Outcome** | Negative Outcome (-1 or 0) | 48 (TN) | 2 (FN) | 49 (TN) | 3 (FN) | 48 (TN) | 1 (FN) |
| | Positive Outcome (+1) | 3 (FP) | 6 (TP) | 2 (FP) | 5 (TP) | 3 (FP) | 7 (TP) |

**Table 6-1: Confusion Matrix for Alert Generation Rules using 4 variables.**

The confusion matrix is a means to analyze the classification performance of a system. It shows how the outcomes are classified into four categories depending on their predicted and actual outcome.

As aforementioned each of the ANN mortality models were developed using the Canadian Neonatal Network (CNN) database as described in sections 3.5.1 – 3.5.3, and Rybchynski and Qi used the EPIC database as a validation set for their ANN models.

Using the values in the confusion matrix in table 6-1, the specificity, sensitivity and correct classification rate (CCR) for the three 'alert generation rule' algorithms are summarized in table 6-2.

Recall that the specificity is systems ability to correctly classify negative outcomes (survival), sensitivity is the systems ability to correctly classify positive outcomes (death) and the CCR is the number of cases that were predicted accurately with respect to the total number of cases in the database.

| | Alert Generation rule #1 (Rybchynski's Model) | Alert Generation rule #2 (Qi's Model) | Alert Generation rule #3 (Ennett's Model) |
|---|---|---|---|
| Sensitivity (%) | 87.5 | 62.5 | 75.0 |
| Specificity (%) | 94.1 | 96.1 | 94.1 |
| CCR (%) | 93.2 | 91.5 | 91.5 |

**Table 6-2: Performance of Alert Generation Rule tests**

From table 6-2 it is apparent that the alerting system was able to correctly classify the survival cases accurately with a high rate for all three of the 'alert generation rules'. But, Rybchynski's model was the best at accurately detecting seven of the eight rare

outcome cases (i.e. mortality), followed by Ennett's and then Qi's model. These results are conforming to the actual results of the ANN prediction models.

By examining the three ANN mortality models it is obvious that they share common variables but these appear in different order. Physicians did not have a way of knowing which model was better at predicting infant mortality as these models are similar and there is no currently known method to establish which one is better except by generally computing sensitivity and specificity. This alerting system is a first attempt at finding an alternate way to assess how each model performs in detecting the outcome 'death' and can now be used by MIRG researchers in selecting the model that best predicts infant mortality.

To further examine the performance of the alerting system the number of variables used were varied to three and five to see whether the number of variables used affects the performance of the alerting system.

## 6.2 Discussion of Results

To further test the performance of the system, the number of variables used in the 'alert generation rules' were varied to see whether there was a significant impact on the alerting systems performance.

Each alert rule was tested individually and the outcome of the system was recorded. The three mortality models used data coming from the CNN database and were verified using the EPIC database for validation purposes.

### 6.2.1 Varying the number of Variables in the Alert Generation Rules

In order to validate the choice of selecting the four highest ranked variables used in developing the 'alert generation rules' the number of variables were varied to observe the impact they have on the performance of the system.

| | Three Variables | Four Variables | Five Variables |
|---|---|---|---|
| Sensitivity (%) | 87.5 | 87.5 | 87.5 |
| Specificity (%) | 90.1 | 94.1 | 94.1 |
| CCR (%) | 89.8 | 93.2 | 93.2 |

**Table 6-3: Rybchynski's Model: Alert generation rule #1**

As can be seen from table 6-3 when the number of variables in the 'alert generation rule' was decreased to three, the number of false (false positive) alarms generated increased. Hence, causing the correct classification rate to decrease from 93.2% to 89.8% and the specificity to decrease from 94.1 % to 90.1 %. The sensitivity remained the same at 87.5%, which is a good indicator that changing the number of variables does not affect the alerting systems ability to detect the mortality cases for this particular model.

In contrast, increasing the number of variables to five produces the exact same results as observed with four variables suggesting that using more variables produces better or at least similar performance results as with four variables. This may also signify that the mortality prediction model must contain four variables or more to accurately detect and classify mortality with the least false positives.

| | Three Variables | Four Variables | Five Variables |
|---|---|---|---|
| Sensitivity (%) | 62.5 | 62.5 | 50 |
| Specificity (%) | 88.2 | 96.1 | 100 |
| CCR (%) | 86.4 | 91.5 | 93.2 |

**Table 6-4: Qi's Model: Alert Generation Rule #2**

Similar observations were noticed for alert generation rule # 2 when decreasing the number of variables to three the number of false positives increased from two to six, generating three times the number of false alarms than when using four variables. The correct classification rate (CCR) dropped from 91.5% to 86.4% and the specificity decreased from 96.1% to 88.2%. Similarily, the sensitivity for the alert generation rule remained the same at 62.5 %.

On the other hand, when increasing the number of variables from three to five the number of false positives decreased to zero hence increasing the correct classification rate and the specificity to 93.2% and 100% respectively.

Alert generation rule # 3 showed similar results as the other two alert generation rules as can be seen from table 6-5.

| | Three Variables | Four Variables | Five Variables |
|---|---|---|---|
| Sensitivity (%) | 87.5 | 75 | 75 |
| Specificity (%) | 82.4 | 94.1 | 94.1 |
| CCR (%) | 83.1 | 91.5 | 91.5 |

**Table 6-5: Ennett's Model: Alert Generation Rule #3**

Reducing the number of variables used to three significantly increased the number of false alarms (from three to nine) generated by the alerting system. This suggests that the number of variables used has a direct impact on the alerting system's ability to correctly classify the mortality and survival cases accordingly. The correct classification

rate decreased from 91.5% to 83.1 % and as a result the specificity decreased from 94.1% to 82.4 %. The system's sensitivity however increased from 75% to 87.5 %.

On the other hand, when increasing the number of variables to five, the performance of the system remained the same as observed in the performance of alert generation rule #1. Although the sensitivity increased by about 10% when the three variables were used, the number of false alarms increased significantly which becomes more of a distraction rather than an aid to physicians.

It can be concluded that combining four or more variables has a direct impact on the alerting system's ability to accurately detect survival and mortality cases, with far less false positive alarms which is inevitably the goal of implementing such a system in the neonatal intensive care unit at CHEO.

Rybchynski's model was best at predicting infant mortality as it detected seven of the eight mortality cases accurately.

## 6.3 Alerts Generated by Alerting System

The alerting system generated multiple alerts during the testing of the 'alert generation rules'. Recall that critical alerts were transmitted to the Java alert GUI and e-mail, while life-threatening alerts were transmitted to cellular telephones and the Java alert GUI.

The transmission of alerts was tested using various cellular telephone providers such as Rogers Wireless, Bell Mobility and Fido. The three cellular phones were receiving SMS alerts simultaneously. This was not part of the testing of the system but it was noticed that the Rogers Wireless phone received alerts quicker than the other two

cellular providers. This could be due to having better coverage from the cellular provider. The alerts were received on each of the cellular phones within 10 seconds of being transmitted by the alerting system to the web server and then to the telephone service providers SMS gateway, which is considered acceptable for such a system. The use of other handheld devices can be integrated in the future to work with this system as they are made available.

The alerting system made use of the University of Ottawa's server to transmit wireless alerts to e-mail using the SMTP client in Java and to the wireless provider's network. When the wireless alerts were transmitted to the cellular provider's network they were transmitted to the cellular telephones via the SMS gateway as SMS text messages. Upon receipt of an alert, the phones set off an alarm indicating that a message had arrived. Messages were accurately received and the user had the ability to reply to the message if warranted using the return address provided in the message which would go the computer located in the NICU's central station.

# Chapter 7: Conclusion, Contributions and Future Work

## 7.1 Conclusion

The primary goal of this thesis was to design and develop an XML based clinical alerting system prototype that aids researchers in selecting the most appropriate ANN mortality prediction model that has the ability to accurately detect and warn physicians of life-threatening events or complications prior to their occurrence.

The alerting system's performance was tested using a variety of 'alert generation rules' from basic rules (dropping below or exceeding thresholds) to combination rules. Using three previously developed MIRG ANN mortality outcome prediction models, the four variables with the highest rank in each of the models were used in developing three separate 'alert generation rule' algorithms corresponding to each model.

Each of the 'alert generation rules' were tested separately to measure the alerting system's performance in detecting significant events. The results revealed that the alerting system's performance was closely correlated with the predictive ability of the developed ANN models, suggesting that such an alerting system could be used in validating future outcome prediction models such as: complications, length of stay and duration of ventilation. The model that produces the least number of false alarms and was best at predicting mortality with the highest accuracy was determined using the alerting system.

The results also indicated that combining greater than three variables as discussed in chapter six, can assist in accurately detecting a patient's true state, and generating the least number of false positive alarms which is ideal in a fast paced environment such as

the NICU where an excess of false alarms can cause physicians to ignore or silence the alerting system making it useless.

This type of alerting system which integrates knowledge from artificial intelligence and alert rules that combine important risk factors in detecting significant events is necessary for the successful deployment of such a system providing physicians with pertinent information on the true status of the patient as opposed to simply monitoring single parameters that drop below or exceed predefined thresholds as was the case in most of the existing patient monitoring and alerting systems.

## 7.2 Research Contributions

1. Designed an XML-based alerting system prototype which is the first of its kind to issue alerts using an ANN tool that predicts mortality of NICU patients.
2. Developed a mechanism to test the effectiveness of various ANN models that predict mortality developed by MIRG students
3. Created alert generation rules for use in the alerting system first from basic rules that approached, dropped below or exceeded threshold values; then proceeded to advanced rules using time interval and then by combining rules. The approach separates warnings, critical alerts and life-threatening alerts based on their severity. Warnings are transmitted to the Java alert GUI, critical alerts are transmitted to e-mail and the Java alert GUI and life-threatening alerts are transmitted to the Java alert GUI and mobile devices.

4. Designed a simple user friendly web-based GUI providing physicians the ability to interact with the alerting system by generating XML encoded patient records, staff information and threshold settings used by the alerting system.

## 7.3 Future Work

Designed as a proof of concept the alerting system requires some improvements in order to be integrated into a hospital setting:

1. Security and encryption: are important features that need to be integrated into the alerting system before it is deployed into CHEO as it contains confidential patient information and the transmission of this information to physicians requires the data to be encrypted.
2. Interfacing the alerting system with a laboratory information system and medication information system would be able to provide more valuable information in the alerts.
3. Test the alerting system with other ANN outcome prediction models such as length of stay, duration of ventilation and potential clinical complications would be valuable.
4. The use of various wireless technologies and an assessment of the most suitable technology in transmitting wireless alerts would be valuable to the application of the alerting system in a medical setting.
5. Testing the alerting system using real-time data in a hospital setting would be the ultimate goal of MIRG.

## References:

[Alberdi et al. 2000]

Alberdi E, Gilhooly K, Hunter J, Logie R, Lyon A, McIntosh N, Reiss J. "Computerisation and decision making in neonatal intensive care: A cognitive engineering investigation." *Journal of Clinical Monitoring and Computing* 2000; 16:85-94.

[Arnell et al. 1983]

Arnell WJ, Schultz DG. "Computers in anesthesiology - a look ahead." *Medical Instrumentation* 1983; 17:385-393.

[Barnett et al. 1983]

Barnett GO, Winickoff RN, Morgan MM, Zielstorff RD. "A computer-based monitoring system for follow-up of elevated blood pressure." *Med Care* 1983; 21(4):400-409.

[Bates et al. 1995a]

Bates DW, Cullen DJ, Laird NM, Petersen LA, Small SD, Servi D, Laffel G et al. "Incidence of adverse drug events and potential adverse drug events: implications for prevention." *JAMA* 1995; 274:29–34.

[Bates et al. 1995b]

Bates DW, Boyle DL, VanderVliet M, et al. "Relationship between medication errors and adverse drug events." *J Gen Int Med* 1995; 10:199–205.

[Bates et al. 1998]

Bates DW, Leape LL, Cullen DJ, et al. "Effect of computerized physician order entry and a team intervention on prevention of serious medication errors." *JAMA* 1998; 280:1311-1316.

[Bates & Gawande 2003]

Bates DW, and Gawande AA. "Improving Safety with Information Technology." *N Engl J Med* 2003; 348:2526-2534.

[Baxt 1994]

Baxt WG. "Complexity, chaos and human physiology: the justification for non-linear neural computational analysis." *Cancer Lett* 1994; 77:85-93.

[Becker et al. 1994]

Becker K, Rau G, Kaesmacher H, Petermeyer M, Kalff G, Zimmermann H. "Fuzzy logic approaches to intelligent alarms." *IEEE Eng in Med & Bid* 1994; 13(4):710-716.

[Beech et al. 1999]
Beech D, Lawerence S, Maloney M, Mendlesohn N, Thompson H. W3C. "XML Schema Part 1: Structures." http://www.w3.org/1999/05/06-xmlschema-1/ (Last accessed: August 23, 2007).

[Beneken & Van der Aa 1989]
Beneken JEW and Van der Aa JJ. "Alarms and Their Limits in Monitoring." *Journal of Clinical Monitoring* 1989; 5(3):205-210.

[Bloom 1993]
Bloom MJ. "Techniques to identify clinical contexts during automated data analysis." *International Journal of Clinical Monitoring and Computing* 1993; 10(1):17-22.

[Blum & Rosenberg 2006]
Blum, J and Rosenber, A. "An Open System for Development of Derived Physiologic Alarms" *AMIA Annu Symp Proc* 2006; 2006:856.

[Bradshaw et al. 1984]
Bradshaw KE, Gardner RM, Clemmer TP, Orme JF, Thomas F, West BJ. "Physicians Decision-making --Evaluation of Data used in a Computerized ICU." *International Journal of Clinical Monitoring and Computing* 1984; 1(2):81-91.

[Bradshaw et al. 1989]
Bradshaw KE, Gardner RM, Pryor TA. "Development of a computerized laboratory alerting system." *Comput Biomed Res* 1989; 22:575-587.

[Bray et al. 2006]
Bray T, Paoli J, Sperberg-McQueen et al. http://www.w3.org/TR/2006/REC-xml-20060816/ (Last accessed: August 23, 2007).

[Catley & Frize 2002a]
Catley C, Frize M. "A Prototype XML-Based Implementation of an Integrated 'Intelligent' Neonatal Intensive Care Unit." *Proc IEEE ITAB (Information Technology Applications in Biomedicine) Conf.* 2003; 322-325.

[Catley & Frize 2002b]
Catley C, Frize M. "Design of a Health Care Architecture For Medical Data Interoperability and Application Integration." *Proc. Joint BMES/EMBS Conference, Houston* 2002; 1952-1953.

[Chambrin 2001]
Chambrin MC. "Alarms in the intensive care unit: how can the number of false alarms be reduced." *Critical Care* 2001; 5(4):184-188.

[Charbonnier & Gentil 2007]

Charbonnier S. & Gentil S. "A trend based alarm system to improve patient monitoring in intensive care units." *Control Engineering Practice* 2007; 15(9):1039-1050.

[Chen et al. 2002]

Chen HT, Ma WC, Liou DM. "Design and implementation of a real-time clinical alerting system for intensive care unit." *Proc AMIA Symp* 2002; 131-135.

[Chen et al. 2004]

Chen ES, Mendonca EA, McKnight LK, Stetson PD, Lei J, Cimino JJ. "PalmCIS: A Wireless handheld application for satisfying clinician information needs." *J Am Med Inform Assoc* 2004; 11(1):19-28.

[Chevrollier & Golmie 2005]

Chevrollier N, & Golmie, N "On the Use of Wireless Network Technologies in Healthcare Environments." *Proc ASWN '05* Paris France 2005; 147-152.

[Classen et al. 1997]

Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP. "Adverse drug events in hospitalized patients: excess length of stay, extra costs, and attributable mortality." *JAMA* 1997; 277:301-306.

[Classen et al. 1991]

Classen DC, Pestornik SL, Evans RS, et al. "Computerized surveillance of adverse drug events in hospital patients." *JAMA* 1991; 266:2847-2851.

[Clemmer 2004]

Clemmer TP: "Computers in the ICU: Where we started and where we are now." *J Critical Care* 2004; 19:201-207.

[Coeira 2000]

Coiera E. "When conversation is better than computation." *J Am Med Inform Assoc* 2000; 7(3):277-286.

[Cotea & Jiwani 2003]

Cotea, C. Jiwani, S. A Case-Based Reasonsing (CBR) System for the Neonatal Intensive Care Unit (NICU). Bachelor of Science in Engineering Thesis. University of Ottawa, Ottawa, ON, Canada, 2003.

[Cullen et al. 1997]

Cullen DJ, Sweitzer BJ, Bates DW, Burdick E, Edmondson A, Leape LL. "Preventable adverse drug events in hospitalized patients: a comparative study of intensive care and general care units." *Crit Care Med* 1997; 25:1289-1297.

[Cyper et al. 2006]
Cypher, D; Chevrollier, N; Montavont, N; Golmie, N "Prevailing over wires in healthcare environments: benefits and challenges." *IEEE Communications Magazine* 2006; 44(4):56-63.

[Data 2007]
Data R. "Introduction to XML"; http://www.w3schools.com/xml/xml_whatis.asp, (Last accessed: May 14, 2007).

[Edworthy & Hellier 2006]
Edworthy, J. and Hellier, E. "Alarms and human behaviour: implications for medical alarms." *British Journal of Anaesthesia* 2006; 97(1):12-17.

[Eisenstadt et al. 1998]
Eisenstadt SA, Wagner MM, Hogan WR, Pankaskie MC, Tsui FC, Wilbright W. "Mobile workers in healthcare and their information needs: are 2-way pagers the answer?" *Proc AMIA Symp.* 1998; 26(5-6):135-139.

[Ennett & Frize 2003a]
Ennett, C. M., and Frize, M. "Weight-Elimination Neural Networks Applied to Coronary Surgery Mortality Predcition." *IEEE Transactions on Information Technology in Biomedicine* 2003; 7(2):86-92.

[Ennet & Frize 2003b]
Ennett, C. M., and Frize, M. "Validation of a Hybrid Approach for Imputing Missing Data." *Proc IEEE Engineering in Medicine and Biology.* 2003; 2:1268-1271.

[Ennett 2003]
Ennett, C. M. Imputation of Missing Values by Integrating Artificial Neural Networks and Case-based Reasoning. PhD in Electrical Engineering Thesis, Carleton University, Ottawa, ON, Canada, 2003.

[Ennett et al. 2004]
Ennett, C. M., Frize. M., and Charette, E. "Improvement and Automation of ANNs to Estimate Medical Outcomes." *Medical Engineering Physics* 2004; 26(4):321-328.

[Ennett 1999]
Ennett CM. "Coronary surgery mortality prediction using artificial neural networks". M.A.Sc. Thesis, School of Information Technology and Engineering (Electrical Engineering), University of Ottawa, Ottawa, ON. 1999.

[Fawcett 2003]
Fawcett, Tom, "ROC Graphs: notes and practical considerations for data mining Researchers." *HP Laboratories* 2003: 1-28.

[FCE 2006]
First Contact Engineering "Wireless Technology Comparison." http://www.firstcontactengineering.com/fce_comparison.htm 2006; (Last accessed: August 23, 2007).

[Frize et al. 2005]
Frize, M.; Yang, L.; Walker, R.C.; "Conceptual Framework of Knowledge Management for Ethical Decision-Making Support in Neonatal Intensive Care." *IEEE Transactions on Information Technology in Biomedicine* 2005; 9(2):205-215.

[Frize et al. 2004]
Frize, M. Ibrahim, D. Seker, H. Walker, R. Odetayo, M.O. Petrovic, D. Naguib, R.N.G. "Predicting Clinical Outcomes for Newborns Using Two Artificial Intelligence Approaches." *Proc IEEE Engineering in Medicine and Biology* 2004; 2:3202-3205.

[Frize et al. 2001]
Frize M, Ennett CM, Stevenson M, Trigg HCE. "Clinical decision-support systems for intensive care units using artificial neural networks." *Medical Engineering and Physics* 2001; 23(3):217-225.

[Frize et al. 1998]
Frize, M. Wang, L. Ennett, CM. Nickerson, B. Solven, FG. Stevenson, M. "New advances and validation of knowledge management tools for critical care using classifier techniques." *Proc AMIA Symp* 1998; 553-558.

[Frize et al. 1996]
Frize M, Solven FG, Stevenson MH, Nickerson BG. "Computer-Assisted Decision Support Systems for Medical Applications." *Proc. of the 10th International Conference of Women Engineers and Scientists* 1996; 91-93.

[Frize et al. 1995]
Frize M, Solven FG, Stevenson MH, Nickerson BG, Buskard T, Taylor K. "Computer-Assisted Decision Support Systems for Patient Management in an Intensive Care Unit." *Proc. of Medinfo* 1995; 1009-1012.

[Fukui & Masuzawa 1989]
Fukui Y, Masuzawa T. "Knowledge-based approach to intelligent alarms." *Journal of Clinical Monitoring* 1989; 5(3):211–216.

[Gardner et al. 1999]
Gardner RM, Pryor TA, Warner HR. "The HELP hospital information system: update 1998." *Int J Med Inf* 1999; 54:169-182.

[Geier 2005]
Geier, J: "Wireless LANs in Hospitals"
http://www.wirelessnetworkingacademy.com/learning_center/tutorials/Wireless_LANs_in_Hospitals.htm (Last accessed: August 23, 2007).

[Geman et al. 1992]
Geman S, Bienenstock E, and Doursat R: "Neural Networks and the Bias/Variance Dilemma." *Neural Computation* 1992; 4:1-58.

[Gregory 2000]
Gregory, Arofan "XML schema design for business-to-business e-commerce." 2000. http://www.gca.org/papers/xmleurope2000/papers/s21-01.html (Last accessed August 23, 2007).

[Haykin 1999]
Haykin, Simon. Neural Networks: A Comprehensive Foundation. Prentice-Hall, New Jersey, 1999.

[Hohavi & Provost, 1998]
Hohavi, R. Provost, F. "Glossary of Terms. Special Issue on Application of Machine Learning and the Knowledge Discovery Process." *Machine Learning* 1998; 30: 271-274.

[Hoelzer et al. 2001]
Hoelzer S.; Schweiger R. K.; Boettcher H. A.; Tafazzoli A. G.; Dudeck J. "Value of XML in the implementation of clinical practice guidelines- the issue of content retrieval and presentation." *Med Inform Internet Med.* 2001; 26(2):131-46.

[Hripcsak et al. 1996]
Hripcsak G, Clayton PD, Jenders RA, Cimino JJ, Johnson SB. "Design of a clinical event monitor." *Comput Biomed Research* 1996; 29:194–221.

[Hulse et al. 2005]
Hulse NC, Rocha RA, Del Fiol G, Bradshaw RL, Hanna TP, Roemer LK. "KAT: A Flexible XML-Based Knowledge Authoring Environment." *J Am Med Inform Assoc* 2005; 12(4):418-430.

[Jha et al. 1998]
Jha AK, Kuperman GJ, Teich JM et al. "Identifying adverse drug events: Development of a computer-based monitor and comparison with chart review and stimulated voluntary report." *JAMIA* 1998; 5:305-314.

[Kafeza et al. 2004]
Kafeza E, Chiu D K W, Cheung, S.C. Kafeza, M "Alerts in Mobile Healthcare Applications: requirements and pilot study." *IEEE Transactions on Information Technology in Biomedicine* 2004; 2:173-181.

[Kahn et al. 1998]
Kahn CE Jr, de la Cruz NB. "Extensible Markup Language (XML) in Health Care: Integration of Structured Reporting and Decision Support." *Proceedings of the AMIA Annual Symposium* 1998; 725-729.

[Kattan & Beck 1995]
Kattan MW, Beck JR. "Artificial neural networks for medical classification decisions." *Arch Pathol Lab Med* 1995; 119:672-677.

[Kickert & Mamdani 1978]
Kickert, W. J. M. and Mamdani, E. H., "Analysis of a fuzzy logic controller." *Fuzzy Sets and Systems* 1978; 12:29-44.

[Koppel et al. 2005]
Koppel R, Metlay JP, Cohen A et al. "Role of computerized physician order entry systems in facilitating medication errors." *JAMA.* 2005; 293:1197-1203.

[Koski et al. 1995]
Koski EMJ, Makivirta A, Sukuvaara T, Kari A. "Clinicians' opinions on alarm limits and urgency of therapeutic responses." *International Journal of Clinical Monitoring and Computing.* 1995; 12(2):85-88.

[Koski et al. 1994]
Koski EM, Sukuvaara T, Mäkivirta A, Kari A: "A knowledge-based alarm system for monitoring cardiac operated patients: assessment of clinical performance." *Int J Clin Monit Comput* 1994; 11:79-83.

[Koski et al. 1990]
Koski EMJ, Makivirta A, Sukuvaara T, Kari A. "Frequency and reliability of alarms in the monitoring of cardiac postoperative patients." *International Journal of Clinical Monitoring and Computing.* 1990; 7:129-133.

[Kuperman et al. 1999]
Kuperman GJ, Teich JM, Tanasijevic MJ, Ma'Luf N, Rittenberg E, Jha A, Fiskio J, Winkelman J, Bates DW. "Improving response to critical laboratory results with automation: results of a randomized controlled trial." *JAMIA* 1999; 6:512-522.

[Laramee et al. 2006]
Laramee, C.B. Lesperance, L. Gause, D. Mcleod, K. "Intelligent Alarm Processing into Clinical Knowledge" EMBS 06. The 28th Annual International Conference of IEEE. 2006; 6657-6659.

[Lawless 1994]
Lawless ST: "Crying wolf: false alarms in a pediatric intensive care unit." *Crit Care Med* 1994; 22:981-985

[Leape et al. 1995]
Leape LL, Bates DW, Cullen DJ, et al. "Systems analysis of adverse drug events." *JAMA.* 1995; 274:35-43.

[Li 2005]
Li, H. Assessment of two AI approaches to predict mortality in adult intensive care units. Master of Applied Science, Carleton University, Ottawa, ON, Canada, 2005.

[Maglaveras et al. 1998]
Maglaveras N, Stamkopoulos T, Chouvarda T, Kakas P and Strintzis M.G. "Smart Alarming Scheme for ICU Using Neural Networks" *IEEE Computers in Cardiology Conference* 1998; 493-496.

[Major et al. 2002]
Major, K., Shabot, M. M. & Cunneen, S. "Wireless Clinical Alerts and Patient Outcomes in the Surgical Intensive Care Unit." *The American Surgeon* 2002; 68(12): 1057-1060.

[Makivirta & Koski 1994]
Makivirta A, Koski EMJ. "Alarm-inducing variability in cardiac postoperative data and the effects of prealarm delay." *Journal of Clinical Monitoring* 1994; 10:153-162.

[Mc Donald et al. 1985]
McDonald C, Wheeler LA, Glazener T, Blevins L. "A data base approach to laboratory computerization." *Am J Clin Pathol* 1985; 83:707-715.

[McGowan et al. 1996]
McGowan, HCE. Stevenson, M. Frize, M. "The Need for Standardized Reporting of Medical Applications of Artificial Neural Networks" CMBEC, Charlottetown 1996; 26-29.

[McKnight et al. 2001]
McKnight L, Stetson PD, Bakken S, Curran C, Cimino JJ. "Perceived information needs and communication difficulties of inpatient physicians and nurses." *Proc AMIA Symp.* 2001; 453-457

[Mendonca et al. 2004]
Mendonca, E. Chen, P. Stetson, L. McKnight, J. Lei, and J. Cimino. "Approach to mobile information and communication for health care." *Int. Journal of Medical Informatics* 2004;73: 631-638.

[Miller 1994]
Miller RA. "Medical diagnostic decision support systems--past, present, and future: a threaded bibliography and brief commentary." *J Am Med lnformatics Assoc.* 1994; 1:8-27.

[Mora et al. 1993]
Mora FA, Passariello G, Carrault G, Le Pichon JP, "Intelligent patient monitoring and management systems: a review." *IEEE Eng in Med & Bio,* 1993; 12(4):23-33.

[Mylrea et al. 1993]
Mylrea KC, Orr JA, Westenskow DR. Integration of monitoring for intelligent alarms in anesthesia: neural networks – can they help? *Journal of Clinical Monitoring.* 1993; 9(1):31-37.

[Norris & Dawant 2001]
Norris P, Dawant BM. "Closing the loop in ICU decision support: physiologic event detection, alerts, and documentation." *Proc. AMIA Annual Symp* 2001; 498-502.

[Olden & Jackson 2002]
Olden, J.D, Jackson, DA. "Illuminating the 'black box': a randomization approach for understanding variable contributions in artifical neural networks" Ecological Modeling, 2002; 154:135-150.

[Ouyang 2006]
Ouyang, H. Comparing Relative Weight Reduction and Principal Component Analysis Methods Applied to Perinatal Outcome Classification ANN Models. Masters of Applied Science in Electrical Engineering Thesis, School of Information Technology and Engineering, University of Ottawa, Ottawa, ON, Canada. 2006.

[Parekhji 2002]
Parekhji, Manish. Infrastructure analysis of wireless technology in healthcare with market analysis of wireless clinical applications. Masters in Medical Informatics Thesis. Division of Medical Informatics and Outcomes Research, Oregon Health & Science University, Southwest Portland. USA 2002.

[Penny & Frost 1996]
Penny, W. Frost, D. "Neural networks in clinical medicine." *Med Decis Making* 1996; 16:386-398.

[Poon et al. 2002]
Poon E, Kuperman G, Fiskio J, Bates D. "Real-time notification of laboratory data requested by users through alpha-numeric pagers." *J Am Med Inform Assoc* 2002; 9(3):217-222.

[Potts et al. 2004]

Potts AL, Barr FE, Gregory DF, Wright L, Patel NR. "Computerized physician order entry and medication errors in a Pediatric critical care unit." *Pediatrics*. 2004;113(1 Pt 1):59-63.

[Qi 2005]

Qi Lili. Evaluation of an Artificial Neural Network Tool for Neonatal Intensive Care Units. Master of Science in Information and System Science Thesis. Department of Systems and Computer Engineering, Carleton University, Ottawa ON, Canada, 2005.

[Raschke RA et al. 1998]

Raschke RA, Gollihare B, Wunderlich et al. "A computer alert system to prevent injury from adverse drug events: development and evaluation in a community teaching hospital." *JAMA* 1998; 280:1317-1320.

[Reddy et al. 2005]

Reddy MC, McDonald DW, Pratt W, Shabot MM. "Technology, work and information flow: Lessons from the implementation of a wireless alert pager system." *J Biomed Informatics* 2005; 38:229-238.

[Reddy et al. 2003]

Reddy MC, Pratt W, McDonald DW, Shabot MM. "Challenges to physicians' use of a wireless alert pager." *AMIA Annu Symp Proc* 2003; 544-548.

[Richardson et al. 2001]

Richardson DK, Corcoran JD, Escobar GJ, Lee SK "SNAP-II and SNAPPE-II: Simplified newborn illness severity and mortality risk scores." *J Pediatr* 2001; 138:92-100.

[Rideout 2006]

Rideout, K. Adverse Medical Event Reduction Technologies Identification of Primary Risk Factors of Adverse Medical Events Using Artificial Neural Networks. Master of Applied Science Thesis. Department of Systems and Computer Engineering, Carleton University, Ottawa ON, Canada. 2006.

[Rind et al. 1994]

Rind DM, Safran C, Phillips RS et al. "Effect of computer based alerts on the treatment and outcomes of hospitalized patients." *Arch Intern Med* 1994; 154:1511-1517.

[Rochon et al. 2006]

Rochon P., Field T., Bates D., et al. "Clinical application of a computerized system for physician order entry with clinical decision support to prevent adverse drug events in long-term care." *CMAJ* 2006; 174:52-54.

[Roy & Ramanujun 2001]
Roy J, Ramanujan A. "XML Schema Language: Taking XML to the Next Level." *IT Proc* 2001; 37-40.

[Rybchynski 2005]
Rybchynski, D. Design of an Artificial Neural Network Research Framework: Efficient Development of More Effective Prediction Models for Medical Outcomes. Master of Applied Science in Electrical Engineering Thesis, School of Information Technology and Engineering, University of Ottawa, Ottawa, ON, Canada. 2005.

[Sall 2000]
Sall, K; XML Software Guide: XML Parsers, http://wdvl.internet.com/Software/XML/parsers.html 2000. (Last accessed May 14, 2007).

[Schecke et al. 1992]
Schecke T, Langen M, Popp HJ, Rau G, Kasmacher H, Kalff G. "Knowledge-based decision support for patient monitoring in cardioanesthesia." *International Journal of Clinical Monitoring and Computing* 1992; 9(1):1-11.

[Schweiger et al. 2001]
Schweiger R, Hoelzer S, Heitmann KU, Dudeck J. "DTDs go XML Schema—a tools perspective." *Med. Inform Internet Med* 2001; 26(4):297-308.

[Seol et al. 1998]
Seol YH, Johnson SB, Starren J. "Use of the Extensible Stylesheet Language (XSL) for medical data transformation." *Proc AMIA Symp* 1999; 142-146.

[Shabot et al. 2000]
Shabot MM, LoBue M, Chen J. "Wireless clinical alerts for physiologic, laboratory and medication data." *Proc AMIA Symp* 2000; 355(1402):789-793.

[Shabot & LoBue 1995]
Shabot MM, LoBue M. "Real-time Wireless Decision Support Alerts on a Palmtop PDA." *Proc Annu Symp Comput Appl Med Care* 1995; 112(2):174-177.

[Shabot et al. 1990]
Shabot MM, LoBue M, Leyerle BJ: "Decision support alerts for clinical laboratory and blood gas data." *Int J Clin Mon Comput* 1990; 7:27-31.

[Shoenberg et al. 1999]
Schoenberg R, Sands DZ, Safran C. "Making ICU alarms meaningful: a comparison of traditional versus trend-based algorithms." *Proc AMIA Symp* 1999; 379-383.

[Siau & Shen 2006]
Siau K, Shen Z. "Mobile Healthcare Informatics." *Medical Informatics and the Internet in Medicine* June 2006; 31(2):89-99.

[Sokolowski & Dudeck 1999]
Sokolowski, RJ. Dudeck. "XML and its impact on content and structure in electronic health care documents." *JAMIA (Symposium Supplement)* 1999; 6:147-151.

[Steele et al. 2005]
Steele A W, Eisert, S Witter J, Lyons P, Jones MA et al. "The Effect of Automated Alerts on Provider Ordering Behavior in an Outpatient Setting." *PLoS Med* 2005; 2(9):864-870.

[Suvkuvaara et al. 1993]
Sukuvaara T, Koski EMJ, Makivirta A, Kari A. "A knowledge-based alarm system for monitoring cardiac operated patients - technical construction and evaluation." *International Journal of Clinical Monitoring and Computing* 1993; 10(2):117-126.

[Tate et al. 1995]
Tate KE, Gardner RM, Scherting K. "Nurses, pagers, and patient-specific criteria: three keys to improved critical value reporting." *Proc Annu Symp Comput Appl Med Care* 1995; 7(5):164-168

[Teich et al. 1999]
Teich JM, Glaser J, Beckley R, Aranow M, Bates D, Kuperman G, et al. "The Brigham integrated computing system (BICS): advanced clinical systems in an academic hospital environment." *Int J Med Inf* 1999; 54:197-208.

[Tong et al. 2002]
Tong Y, Frize M, Walker, R. "Extending Ventilation duration estimations approach from adult to neonatal intensive care patients using artificial neural networks." *IEEE Trans Info Technol Biomed* 2002; 6(2):188-191.

[Tsien 2000a]
Tsien Christine. TrendFinder: Automated detection of alarmable trends. Doctor of Philosophy in Electrical Engineering and Computer Science Thesis, Department of Electrical Engineering and Computer Science Massachusetts Institue of Technology, USA 2000.

[Tsien 2000b]
Tsien CL, Kohane IS, McIntosh N. "Multiple signal integration by decision tree induction to detect artifacts in the neonatal intensive care unit." *Artificial Intelligence in Medicine.* 2000; 19(3):189-202.

[Tsien 1997]
Tsien CL. "Reducing false alarms in the intensive care unit: a systematic comparison of four algorithms." *Proceedings of the American Medical Informatics Association Annual Fall Symposium* 1997.

[Tsien & Fackler 1997]
Tsien CL, Fackler JC: "Poor prognosis for existing monitors in the intensive care unit." *Crit Care Med* 1997; 25:614-619.

[Turisco & Case 2001]
Turisco F and Case Joanna"Wireless and Mobile Computing" First Consulting Group. http://admin.chcf.org/documents/ihealth/WirelessAndMobileComputing.pdf 2001. (Last accessed August 23, 2007).

[Van Der Sijs et al. 2006]
Van der Sijs H, Aarts J, Vulto A, Berg M. "Overriding of drug safety alerts in computerized physician order entry." *J Am Med Inform Assoc.* 2006; 13(2):138-47.

[Varshney 2006]
Varshney, Upkar. "Enhancing Wireless Patient Monitoring by Integrating Stored and Live Patient Information." *CBMS* 2006; 501-506.

[Wagner et al. 1998]
Wagner MM, Eisenstadt SA, Hogan WR, Pankaskie MC. "Preferences of interns and residents for E-mail, paging, or traditional methods for the delivery of different types of clinical information." *Proc AMIA Symp* 1998; 26(5–6):140-144.

[Walker 2003]
Walker CR [MBBS,FRCPC]. Chief Neonatologist, Children's Hospital of Eastern Ontario (CHEO), Ottawa Hospital –General Campus, Ottawa, ON. Personal communication, May 20, 2003.

[Walker 2005]
Walker, CR [MBBS, FRCPC]. Chief Neonatologist, Children's Hospital of Eastern Ontario (CHEO), Ottawa Hospital – General Campus, Ottawa, ON. Personal communication, June 1, 2005.

[Watson & Marir 1994]
Watson I, Marir F. "Case-based reasoning: A review." *The Knowledge Engineering Review* 1994; 9(4);355-381.

[Weigend et al. 1990]
Weigend, AS, Rumelhart DE, Huberman BA, "Back-propagation, weight-elimination and time series prediction." *Proc Connectionist Models Summer School.* 1990; 105-116.

[Yang 2004]
Yang, L. Pilot Usability Study of UI Prototype for Collaborative Adaptive Decision Support in Neonatal Intensive Care Unit. Masters of Applied Science Electrical Engineering Thesis, University of Ottawa. Ottawa, Ontario, Canada 2004.

[Zielstorff RD, 1998]
Zielstorff RD. "On line practice guidelines: State of our knowledge and a look to the future". *J Am Med Inform Assoc* 1998; 5(3):227-236.

[Zong et al. 1999]
Zong W, Moody GB, Mark RG. "Reduction of False Blood Pressure Alarms by use of Electrocardiogram Blood Pressure Relationships". *Computers in Cardiology.* 1999; 26:305-308.