

University of Technology Sydney
Faculty of Engineering and Information Technology

**ELECTROCARDIOGRAM AND HYBRID SUPPORT
VECTOR ALGORITHMS FOR DETECTION OF
HYPOGLYCAEMIA IN PATIENTS WITH TYPE 1 DIABETES**

By

NURYANI NURYANI

Student No: 10828960

Supervisor: Prof. Hung Nguyen

Co-Supervisor: Dr. Steve Ling

A thesis submitted in partial fulfillment of the requirement for the Degree of Doctor of
Philosophy

CERTIFICATE OF AUTHORSHIP/ORIGINALITY

I certify that the work in this thesis has not previously been submitted for a degree nor has it been submitted as part of requirements for a degree except as fully acknowledged within the text.

I also certify that the thesis has been written by me. Any help that I have received in my research work and the preparation of the thesis itself has been acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

Nuryani Nuryani

Acknowledgement

I would like to thank Professor Hung T. Nguyen and Dr. Steve Ling from University of Technology Sydney for providing direction and supervision towards the doctoral research. I would also like to thank to the Juvenile Diabetes Research Foundation (JDRF) as this research is supported by a grant from JDRF.

Nuryani Nuryani

Table of Contents

CHAPTER 1. INTRODUCTION	1
1.1 Background.....	1
1.2 The problem statement.....	5
1.3 Objectives	6
1.4 Contribution of the doctoral research	8
1.5 Structure of the dissertation	9
1.6 Publications presented during the doctoral research.....	10
CHAPTER 2. LITERATURE REVIEW	12
2.1 Hypoglycaemia	12
2.2 Effect of hypoglycaemia on the electrical activity of the heart	16
2.3 Existing strategies of hypoglycaemia detection.....	20
2.3.1 Iontophoresis technique.....	24
2.3.2 Near-infrared spectroscopy (NIR) technique	25
2.3.3 Hypoglycaemia detection using skin temperature and skin conductance	26
2.3.4 Hypoglycaemia detection using electroencephalogram	28
2.3.5 Hypoglycaemia detection employing electrocardiogram.....	30
<i>Inputs of the electrocardiogram (ECG) based-hypoglycaemia detection</i>	30
<i>Intelligent techniques for ECG based-hypoglycaemia detection</i>	36
2.4 The proposed strategy of hypoglycaemia detection	38
CHAPTER 3. ELECTROCARDIOGRAPHIC BASED HYPOGLYCAEMIA DETECTION STRATEGY EMPLOYING SUPPORT VECTOR MACHINE	42
3.1 The hypoglycaemia detection model based on support vector machine (SVM)	43
3.1.2 Electrocardiographic acquisition.....	44
3.1.3 Feature extraction	45
<i>Delineation of ECG fiducial points</i>	46
<i>Finding the ECG parameters</i>	49

3.1.4 SVM classification	50
<i>Linear support vector machine</i>	51
<i>Nonlinear support vector machine</i>	54
<i>Soft-margin nonlinear support vector machine</i>	56
3.2 Experimental result	58
3.2.1 Data set	62
3.2.2 Electrocardiogram obtained from the study	63
3.2.3 Performances of hypoglycaemia detections using SVM.....	66
3.3 Discussion	71
3.4 Conclusion	76
 CHAPTER 4. SWARM BASED SUPPORT VECTOR MACHINE FOR HYPOGLYCAEMIA	
DETECTION	77
4.1 Introduction to PSO	79
4.2 Development of a hypoglycaemia detector based on the swarm based support vector machine	82
4.2.1 Optimization of SVM parameters using PSO	83
4.2.2 Fitness function for the optimization.....	86
4.3 Experimental results	87
4.4 Discussion	96
4.5 Conclusion	100
 CHAPTER 5. HYBRID FUZZY INFERENCE SYSTEM SUPPORT VECTOR MACHINE	
FOR HYPOGLYCAEMIA DETECTION	101
5.1 Background	101
5.2 Swarm based fuzzy support vector machine (SFSVM).....	102
5.3 Hypoglycaemia detection using SFSVM.....	104
5.3.1 Fuzzy Inference System	104
<i>Fuzzification</i>	105
<i>Inference engine</i>	106
<i>Defuzzification</i>	106
<i>FIS parameters</i>	107
5.3.2 Hybrid particle swarm optimization with wavelet mutation	107
5.4 Experimental result	111

5.5	Discussion.....	122
5.6	Conclusion	124
CHAPTER 6. DISCUSSION AND CONCLUSION		126
6.1	Discussion.....	126
	Future works	
	Limitation.....	
6.2	Conclusion	132
APPENDIX A. MARGIN BETWEEN TWO HYPERPLANES		134
APPENDIX B. LAGRANGIAN DUAL OPTIMIZATION		135
APPENDIX C. SOFT-MARGIN NONLINEAR SUPPORT VECTOR MACHINE		137
APPENDIX D. SEQUENTIAL MINIMAL OPTIMIZATION (SMO) FOR SVM		139
APPENDIX E. SCRIPT IMPLEMENTATION OF THE ALGORITHMS		144
REFERENCES	153	

List of Figures

Figure 2.1: Counterregulatory mechanisms including hormones secretion and onset of physiological, symptomatic and cognitive changes in response to different blood glucose level thresholds (Frier and Fisher, 2007).	14
Figure 2.2: QT interval in an electrocardiogram.....	17
Figure 2.2: QT interval in an electrocardiogram.....	17
Figure 2.3: Schematic of a human heart accomplished with typical action potential waveforms in different regions and an electrocardiogram (Nerbonne and Kass, 2005).....	18
Figure 2.4: Illustration of T-wave interval, T-wave amplitude and T-wave area in an electrocardiogram.....	20
Figure 2.5: Methods of glucose sensor [adopted from (Oliver et al., 2008)].....	23
Figure 2.6: Schematic diagram of reverse iontophoresis for glucose extraction through the skin(Sieg et al., 2005).	24
Figure 2.7: GlucoWatch G2 Biographer; Cygnus, Inc., Redwood City, CA (Takahashi et al., 2008).....	25
Figure 2.8: A wristwatch-like Diabetes Sentry (Miller and Evans, 2006).....	26
Figure 2.9: Schematic diagram to measure glucose concentration using near infrared wave (Maruo et al., 2003).....	27
Figure 2.10: Relation of skin impedance and blood glucose level in healthy subjects (group A) and patients with type 1 diabetes (group B) (Ghevondian et al., 1997).....	28
Figure 2.11: EEG of a patient with different blood glucose levels in the study of Pramming et al. (1988).....	29
Figure 2.12: Output of neurone in hypoglycemic and nonhypoglycemic state(Laione and Marques, 2005).....	30
Figure 2.13: Relation of heart rate and BGL in healthy subjects (group A) and patients with type 1 diabetes (group B) (Ghevondian et al., 1997).....	33

Figure 2.14: Heart rate in relation to insulin induced hypoglycaemia of healthy subjects (Hilsted et al., 1984).....	34
Figure 2.15: Alteration of QTc relating to BGL in a diabetic patient participating in the study (Harris et al., 2000)	35
Figure 2.16: A positive and negative skewness	35
Figure 2.17: Distributions with different kurtosis; kurtosis of the left distribution is larger than kurtosis of the right one.	36
Figure 2.18: Fuzzy system for hypoglycaemia detection with input of ECG parameter and the output of hypoglycaemic state. (Ghevondian and Nguyen, 1997).....	37
Figure 2.19: Example of experimental result of hypoglycaemia detection using input of ECG parameter and the output of hypoglycaemic state. (Ghevondian and Nguyen, 1997)	37
Figure 2.20: Architecture of fuzzy neural network for hypoglycaemia detection with input of heart rate and skin impedance (Ghevondian et al. 1997b)..	39
Figure 2.21: The general structure of the proposed hypoglycaemia detection employing SVM.....	41
Figure 3.1: General structure of hypoglycaemia detection which employs a support vector machine and inputs of ECG	43
Figure 3.2: The ECG acquisition from the patients	44
Figure 3.3: The facility for exporting ECG data in Profusion PSG 2	45
Figure 3.4: ECG fiducial points of Q, R, S, To, Tp and Te	46
Figure 3.5: Filtering the ECG signals	47
Figure 3.6: Delineation of R point.	47
Figure 3.7: Delineation of Tp (the peak of T-wave)	47
Figure 3.8: Q and S points are found using wavelet transformation using wavelet scale of 30 (WL30), for Q point, and wavelet scale of 21 (WL21), for S point. Q and S points are at the same time position with the minimum of WL30 and WL21, respectively.	49
Figure 3.9: Delineation of Te using the Phillips method; a line segment was drawn from Tp forward in time to a point, and the Te is a point that has the maximum vertical distance between the point and the line segment (L).	49

Figure 3.10: ECG parameters of RR , QT , RTp , STo , $TpTe$ and $ToTe$	50
Figure 3.11: Two-out-of-many separating lines; (a) with smaller margin and (b) with larger margin	52
Figure 3.12: Margin m between two supporting hyperplanes	53
Figure 3.13: Illustration of mapping using a transform $\Psi: \mathbb{R}^2 \rightarrow \mathbb{R}^3$	54
Figure 3.14: Introducing slack variable ξ in soft-margin SVM	56
Figure 3.15: The approaches A1–A5; the hypoglycaemia detection employs SVM (SVMR, SVMP, SVML); the SVM parameters are given as presented in Table 3.1. The input is ECG parameters and the output is hypoglycaemia/nonhypoglycaemia	59
Figure 3.16: The ECG signal recorded from the study (left) and the associated frequency spectrum (right)	61
Figure 3.17: The ECG signal after the Notch filtering (left) and the associated frequency spectrum (right)	61
Figure 3.18: The ECG signals before the high pass filtering (left) and after the high pass filtering (right). The inserted figures are the signals in frequency of less than 1 Hz.	62
Figure 3.19: Example of the ECG fiducial points from the delineation	65
Figure 3.20: The profiles of the blood glucose levels of the diabetic patients.....	66
Figure 3.21: The effects of the increase in C from 1 to 10^6 to the performance in the training and the testing.	69
Figure 3.22: Bad ECG signals found from the study	72
Figure 3.23 Epicardial, endocardial and the M cell action potentials and $TpTe$ interval in ECG	73
Figure 4.1: A Grid with two parameters and five points in each parameter.	78
Figure 4.2: Local and global minimum of a function.	80
Figure 4.3: Hypoglycaemia detection using swarm based support vector machine	83
Figure 4.4: The pseudo of the PSO for the SVM parameter optimization.....	84
Figure 4.5: The particles of the PSO	85
Figure 4.6: Hypoglycaemia detection using SSSVM with the input of all the six ECG parameters (Approach I)	88

Figure 4.7: Hypoglycaemia detection using SVM with its parameters generated randomly (Approach II)	89
Figure 4.8: Hypoglycaemia detection using swarm based multiple regression with the input of all the six ECG parameters (Approach III).....	90
Figure 4.9: Hypoglycaemia detection using SSVM with inputs are varied by the combinations of the six ECG parameters (Approach V).	90
Figure 4.10: The geometric mean of the SSVMR with different inputs. The x axis indicates the combinations of ECG parameters. The best geometric mean is 80.46% when the inputs are <i>HR and ToTe_c</i>	94
Figure 4.11: ROC of the hypoglycaemia detection using swarm based support vector machine	96
Figure 5.1: FMR developed in (Ling and Nguyen, 2011).....	101
Figure 5.2: SFSVM for hypoglycaemia detection with input of ECG parameters	104
Figure 5.3 Fuzzy Inference System.....	104
Figure 5.4: Fuzzy input and the associated membership degree.....	105
Figure 5.5: Pseudo code of PSOWM	108
Figure 5.6: The swarm of PSOWM for the SFSVM.....	109
Figure 5.7: The geometric means of SFSVM with the different ECG parameters for the FIS input. The rest of ECG parameters for the SVM inputs. (x_1 :HR, x_2 : <i>QTe_c</i> , x_3 : <i>TpTe_c</i> , x_4 : <i>ToTe_c</i> , x_5 : <i>RTp_c</i> , and x_6 : <i>QTp_c</i> .)	114
Figure 5.8: The ROC curve of SFSVM with the FIS inputs are HR, <i>TpTe_c</i> and <i>ToTe_c</i> and the SVM inputs are <i>QTe_c</i> , <i>RTp_c</i> and <i>QTp_c</i>	115
Figure 5.9: The geometric means of FMR with the different ECG parameters for the FIS input. The rest of ECG parameters are for the SVM inputs. (x_1 :HR, x_2 : <i>QTe_c</i> , x_3 : <i>TpTe_c</i> , x_4 : <i>ToTe_c</i> , x_5 : <i>RTp_c</i> , and x_6 : <i>QTp_c</i> .)	116
Figure 5.10: The fitness function value of the global best obtained in the optimization of the SFSVM with 200 iterations	117
Figure 5.11: The fitness function value of the global best obtained in the optimization of the SFSVM with 250 iteration.....	118
Figure 5.12: The fuzzy membership functions of heart rate, <i>TpTe_c</i> and <i>ToTe_c</i>	118

List of Tables

Table 2.1: Studies of alterations in ECG during hypoglycaemia. <i>a, b, c, d, e, f, g, h, i, j</i> represent the studies as listed in the bottom of the table. "x" is to show that the associated ECG parameter is significant to indicate hypoglycaemia in the associated study.....	16
Table 2.2: Specification of continuous glucose monitoring [adopted from Klonoff (2005)]	22
Table 2.3: ECG parameter and algorithm used for hypoglycaemia detection	32
Table 3.1: Hypoglycaemia detection with different SVM algorithms and different SVM parameters.....	60
Table 3.2: The comparison of the ECG parameters obtained in the hypoglycaemic phase against the nonhypoglycaemic phase.....	65
Table 3.3: The performances of the detection algorithm using A1; all the parameters are set to be 1, except the degree of the polynomial kernel function d which is set to be 2.....	67
Table 3.4: The performances of the detection algorithm in A2; all the parameters are set to be 1, except the degree of the polynomial kernel function d which is set to be 2, and $C = 100$	68
Table 3.5: The performances of the detection algorithm using Approach A3; all the parameters are set to be 1, except the degree of the polynomial kernel function d which is set to be 2, and $C = 10^4$	68
Table 3.6: The performances of the detection algorithm using the approach A4; all the parameters are set to be 1, except the degree of the polynomial kernel function d which is set to be 2, and $C = 10^6$	70
Table 3.7: The performances of the detection algorithm using the E5; w_0 was set in such a way that the sensitivities were about 70%. The other SVM parameters were set to be the same with the A1.....	70
Table 4.1: The performance of the hypoglycaemia detection using different techniques of SSVM and using the same input that is all six ECG parameter.....	91

Table 4.2: The testing performance of the hypoglycaemia detections without PSO (input: all six ECG parameter).....	92
Table 4.3: Comparison of the performance of the swarm based SVM with the other methods	93
Table 4.4: The performance the SSVM hypoglycaemia detection using single input.....	93
Table 4.5: The best performance of the hypoglycaemia detection using SSVMR with the inputs of HR and $ToTe_c$	95
Table 4.6: The optimal parameters of SSVM with the input of HR and $ToTe_c$	95
Table 5.1: The input combinations which provide the best performance of SFSVM for each FIS input number. x_1 :HR, x_2 : QTe_c , x_3 : $TpTe_c$, x_4 : $ToTe_c$, x_5 : RTp_c and x_6 : QTp_c (the values in %)	115
Table 5.2: The performance of SFSVM in the variation of the SVM inputs; x_2 : QTe_c , x_5 : RTp_c and x_6 : QTp_c (the values in %).....	116
Table 5.3: The performance of FMR in the variation of the SVM inputs; x_1 :HR, x_2 : QTe_c and x_4 : $ToTe_c$ (the values in %).....	117
Table 5.4: The Fuzzy rule tables	119
Table 5.5: The optimal SVM parameters of the SFSVM with the input of HR, $TpTe_c$ and $ToTe_c$	120
Table 5.6: The performance of SFSVM with different fuzzification.....	121
Table 5.7: Performance comparison of the SVM–based algorithms	122

List of Abbreviations

DCCT	: Diabetes Control and Complications Trial
ECG	: Electrocardiographic
FIS	: Fuzzy Inference system
FMR	: Fuzzy Inference System Multiple Regression
Gm	: Geometric mean
IDDM	: Insulin-dependent diabetes mellitus
MR	: Multiple regression
PSO	: Particle swarm optimization
PSOWM	: Particle swarm optimization with wavelet mutation
RBF	: Radial basis function
ROC	: Receiver operating characteristic
rSVML	: SVM (with linear kernel function) in which their parameters are determined randomly.
rSVMP	: SVM (with polynomial kernel function) in which their parameters are determined randomly.
rSVMR	: SVM (with RBF kernel function) in which their parameters are determined randomly.
rSVMS	: SVM (with sigmoid kernel function) in which their parameters are determined randomly.
Sensitivities	: Sensitivity
SFSVM	: Swarm based fuzzy inference system support vector machine
SMR1	: Swarm based multiple regression (order 1)
SMR2	: Swarm based multiple regression (order 2)
SMR3	: Swarm based multiple regression (order 3)
Specificity	: Specificity
SSVML	: Swarm based support vector machine with linear kernel function
SSVMP	: Swarm based support vector machine with polynomial kernel

	function
SSVMR	: Swarm based support vector machine with RBF kernel function
SSVMRF	: Swarm based support vector machine with RBF kernel function with the input of ECG parameter corrected using Fridericia formula
SSVMS	: Swarm based support vector machine with sigmoid kernel function
SSVMw	: Swarm based support vector machine without weight optimization
SVM	: Support vector machine
SVML	: Support vector machine with linear kernel function
SVMP	: Support vector machine with polynomial kernel function
SVMR	: Support vector machine with RBF kernel function
SVMS	: Support vector machine with sigmoid kernel function

List of Symbols

Q	: the start of QRS complex
R	: the peak of QRS complex
S	: the end of QRS complex
To	: the starting point of T -wave
Tp	: the peak of T -wave
Te	: the end of T -wave
$TpTe_c$: interval from the peak of T -wave Tp to the end of T -wave Te
$ToTe_c$: the interval from the beginning of T -wave To to the end of T -wave Te
$R Tp_c$: the interval from R point to the peak of T -wave Tp
$Q Te_c$: the interval from Q point to the end of T -wave Te
$Q Tp_c$: the interval from Q point to the peak of T -wave Tp
$S To_c$: the interval from S point to the beginning of T -wave To and
D	: polynomial degree of polynomial kernel function
γ	: The width of RBF kernel function
α	: Lagrangian multiplier
$k()$: Kernel function
ξ	: A slack variable introduced for soft margin SVM
C	: The SVM parameter “cost”
\tilde{z}	: Personal best position in particle swarm optimization
\hat{z}	: Global best parameter in particle swarm optimization
φ	: Inertia weight in particle swarm optimization
$\varphi_{\max}, \varphi_{\min}$: Upper and lower bound of inertia weight
c_1, c_2	: Acceleration constants in particle swarm optimization
β	: Coefficient of independent variables of multiple regression
m	: Mean of Gaussian membership function
σ	: Standard deviation of Gaussian membership function
η	: The output of fuzzy inference system
h	: The fuzzy singleton in the if-then part of the inference engine (FIS)

- ρ : Rule number of rules in the if-then part of the inference engine (FIS)
- q : Constriction factor in particle swarm optimization with wavelet mutation (PSOWM)
- ρ_{\max}, ρ_{\min} : The upper and lower boundary, respectively, of the element of particle.
- $\mathfrak{S}_{tr}, \mathfrak{S}_v$: Sensitivity of training and validation, respectively
- $\mathcal{S}_{tr}, \mathcal{S}_v$: Specificity of training and validation
- δ : Morlet wavelet function
- $\mathcal{P}_{\max}, \mathcal{P}_{\min}$: The upper and lower boundary of the element of particle in PSOWM
- β_{wm} : The shape parameter of the monotonic increasing function in PSOWM

ABSTRACT

Hypoglycaemia is the most acute and common complication of type 1 diabetes. Physiological changes occur when blood glucose concentration falls to a certain level. A number of studies have demonstrated that hypoglycaemia causes electrocardiographic (ECG) alteration.

The serious harmful effects of hypoglycaemia on the body motivate research groups to find an optimal strategy to detect it. Detection of hypoglycaemia can be performed by puncturing the skin to measure the blood glucose level. However, this method is unsuitable as frequent puncturing may produce anxiety in patients and periodic puncturing is difficult to conduct, not to mention inconvenient, while the patient is sleeping. Therefore, a continuous and non-invasive technique can be considered for hypoglycaemia detection. Several techniques have been reported, such as reverse iontophoresis and absorption spectroscopy.

Another approach to hypoglycaemia detection is based on the physiological effects of hypoglycaemia on the various parts of the body such as the brain, heart and skin. Physiological effects of hypoglycemia to the brain are studied by investigating electroencephalography (EEG) features. Hypoglycemic effects to the heart include alteration of electrocardiographic (ECG) parameters such as heart rate, *QT* intervals and *T*-wave amplitude alteration.

Several algorithms were developed to process ECG parameters for hypoglycemia detection. The algorithms include neural network and fuzzy system based intelligent algorithms. Furthermore, hybrid systems were also developed, such as fuzzy neural network and genetic-algorithm-based multiple regression with fuzzy inference systems.

So far, hypoglycaemia detection systems which are based on the physiological effects still require extensive validation before they can be adopted for worldwide clinical practices.

The research in this thesis introduces several ECG parameters especially which relate to the repolarization phase and could contribute to hypoglycaemia detection. Furthermore, this research aims to introduce novel computational intelligent techniques for hypoglycaemia detection. The detection is based on electrocardiographic (ECG) parameters. A support vector machine (SVM) is the first algorithm introduced for hypoglycaemia detection in this research. The second algorithm is a hybrid of SVM with particle swarm optimization (PSO), which is called an SSVM algorithm. This algorithm is intended to improve the performance of the first algorithm. PSO is an evolutionary technique based on the movement of swarms. It is employed to optimize SVM parameters in order that the SVM perform well for hypoglycaemia detection. The third algorithm is for the improvement of the second algorithm where a fuzzy inference system (FIS) is included. This algorithm involves SVM, FIS and a PSO, which is called SFSVM. The FIS is used to process some ECG parameters to find a better performance of hypoglycaemia detection. FIS is an effective intelligent system which employs fuzzy logic and fuzzy set theory. Its frameworks are based on the concepts of fuzzy set theory, fuzzy if-then rules, and fuzzy reasoning. In addition, the proposed algorithms are compared with the other algorithms. All the algorithms are investigated with clinical electrocardiographic data. The data is collected from a hypoglycaemia study of type 1 diabetic patients.

This study shows that the selected ECG parameters in hypoglycaemia differ significantly from those in nonhypoglycaemia ($p < 0.01$). This difference might consider that the ECG parameters are part of repolarization, in which repolarization prolongs hypoglycaemia. It implies that the ECG parameters are important parameters which possibly contribute to hypoglycaemia detection. Therefore, the ECG parameters are used for inputs of hypoglycaemia detection in this study.

The result also shows that the hypoglycaemia detection strategy which uses SSVM performs better than that which uses SVM (80.04% vs. 73.63%, in terms of geometric mean). Furthermore, the SFSVM performs better than the SSVM (87.22% vs. 80.45% in terms of sensitivity and 79.41% vs. 79.64% in terms of specificity). In summary, SFSVM performs better than the other two algorithms (SVM and SSVM), with acceptable sensitivity, specificity and geometric mean of 87.22%, 79.41% and 83.22%, respectively.