

# **THE USE OF NEURAL NETWORKS FOR CLINICAL DECISION-MAKING IN PSYCHIATRY**

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# ABSTRACT

This thesis investigates the application of Multi-layer Perceptron (MLP) type Neural Networks to clinical decision-making problems in psychiatry. Only a small number of studies have previously investigated their use in psychiatry. More widely though, in the past decade there has been an increasing interest and several hundred investigations of the application of MLPs to clinical decision-making problems, involving diagnosis and prediction, in medicine. Despite this body of research, it is still difficult to reach any conclusions about the potential role of MLPs for clinical decision-making. The studies are highly disjointed, they target specific clinical decision making problems, they generally have not built upon previous studies, there is little or no consideration of either Neural Network Theory or of Statistical Theory and many have methodological problems.

The investigation is conducted in four parts:

Part I is a review of clinical decision-making and an exposition of Neural Network Theory and Statistical Theory, which examines the characteristics of MLPs relevant to the types of clinical decision-making problems found in psychiatry. We extend an earlier empirical review [Sargent 2001], which compared the performance of MLPs with Logistic Regression as classifiers of clinical datasets, and also consider the use of MLPs and Logistic Regression in the context of the theory of the bias-variance trade off. We find that there is qualified empirical and theoretical support for the application of MLP type neural networks to clinical decision making problems

Part II is an exposition of methodological issues involved in comparing and evaluating classifiers in the context of clinical decision making. It concludes with a description of the methodology to be used for the investigation of the application of MLPs to individual clinical decision-making problems.

Part III describes three studies in which MLPs are applied to specific psychiatric clinical decision-making problems and compared to the more commonly used Logistic Regression technique. The three clinical problems investigated are:

- a) Diagnosis of Melancholia amongst patients with Depression
- b) Prediction of response to treatment with stimulant medication in children with Attention Deficit Hyperactivity Disorder (ADHD)
- c) Diagnosis of Autistic Disorder

Part IV, is a synthesis of the previous 3 parts. It is concluded, on theoretical and empirical grounds, that MLPs do have potential applications to some clinical decision-making problems in psychiatry and that a proper evaluation of MLPs, especially in relation to comparison with other classification techniques, needs to take account the effects of tradeoffs between bias and variance related to each model's complexity. Some possible directions for future research are discussed and we outline plans for the continued development of an Autistic Disorder classifier based upon an MLP neural network developed in Chapter 7

# Certificate of Originality

I hereby declare that submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, nor material which to a substantial extent has been accepted for the award of any other degree or diploma at UNSW or any other educational institution, except where due acknowledgement is made in this thesis. Any contribution made to the research by others, with whom I have worked at UNSW or elsewhere is explicitly acknowledged in this the thesis.

I also declare that the intellectual content of this thesis is the product of my own work, except to the extent that assistance from others in the projects design and conception or in style, presentation and linguistic expression is acknowledged.

(Signed).....

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### **Statements of Originality and of collaboration**

The idea of investigating neural networks for clinical decision-making in psychiatry was the original idea of Tony Florio. It predates any publications using or suggesting the use of neural networks for clinical decision-making in psychiatry. It was first elaborated in a published paper [Florio, Einfeld & Levy 1994].

The “Melancholia Diagnosis Study” was a collaboration of Tony Florio and Gordon Parker. The Mood Disorders Unit at the University of NSW had previously collected the data for a series of studies on psychomotor disturbance as a marker for Melancholia. The dataset of 407 patients contained a set of 18 clinician scored CORE items, which assess psychomotor disturbance, 17 traditional endogeneity symptoms of Melancholia again scored by a clinician and three varying diagnostic criteria for Melancholia. As part of their prior study of this data set Prof. Parker and his colleagues had assessed the comparative diagnostic utility of the CORE items and the endogeneity symptoms for classifying the patients into Melancholic and Non-Melancholic diagnostic groups, variously defined by the three diagnostic criteria. The study conducted by Tony Florio

and reported in this thesis extended that analysis, which employed traditional statistical tools, by using Neural Networks to classify the cases. It is reported in a published paper [Florio et al 1998]

The “Prediction of Response to Treatment with Stimulant Medication of Children with ADHD” study was a collaboration of Tony Florio and Florence Levy. Clinical records from Prof Levy’s practice were used to construct a dataset of 225 children with ADHD, who were treated with stimulant medication. The childrens’ scores on a pre-treatment CPT test were extracted, one at a time, from a computer database by Tony Florio. Prof Levy reviewed each child’s clinical record file and rated each child’s response to treatment from her own notes. Tony Florio applied neural Network and traditional statistical classification techniques to the dataset.

The “Autism Diagnosis” study was a collaboration of Tony Florio, Bruce Tonge, Avril Brereton and Stewart Einfeld. An initial dataset of 638 subjects (319 matched pairs, one of each pair having a diagnosis of Autistic Disorder, the other not) was collected by Professor Tonge and Dr Brereton at the Monash Autism Clinic in Melbourne. Tony Florio in Sydney collected an Independent cross-validation data set of 100 subjects from 3 diagnosis and assessment clinics (Grosvenor, Kogorah and Tumbatin). Tony Florio applied neural Network and traditional statistical classification techniques to the dataset



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# LIST OF PUBLICATIONS

Florio T., Einfeld S.L. & Levy F. (1994), Neural Networks and Psychiatry: Candidate Application in Clinical Decision Making. *Australian & New Zealand Journal of Psychiatry*, 28(4):651-666.

Florio TM. Parker G. Austin MP. Hickie I. Mitchell P. Wilhelm K. (1998) Neural network subtyping of depression. *Australian & New Zealand Journal of Psychiatry*. 32(5):687-94.

# GLOSSARY

<b>Az</b>	Area Under the ROC Curve. The volume of the area contained between the ROC Curve generated by a classifier and the bottom and right hand axes of the ROC graph. Az is an index of the classification accuracy of the classifier as a whole.
<b>Back Error Propagation</b>	An algorithm used to find the set of weights for an MLP, which are associated with an error minima. Also known as BackProp.
<b>Bayesian Classification Decision Boundary</b>	Bayes theorem stipulates that we should use knowledge (information) about probabilities to assign a case of unknown class membership to a class. If we know the probability of class membership at all points in an information space, then we can assign all cases at point in this space to the class with the highest probability at that point. If all the points in one region of the space have a higher probability for one class, and all the points in an adjacent region have a higher probability for another class, then there will be a boundary line between the two adjacent regions where the probability of membership of one class is equal to the probability of membership of the other class. This line is the Bayesian Classification Decision Boundary. The boundary can be a straight line an curved line or a ragged line with many twists and turns.
<b>Bootstrap corrected Az</b>	<p>An Az value which is less optimistically biased than a training data set derived Az.</p> <p>The Bootstrap technique is used to generate a large number of samples. The classifier is then individually trained on each bootstrap sample. Az is measured on each bootstrap sample and the bootstrap derived classifier is also applied to the original full data set to obtain a second Az value. The difference between these two values is a measure of the optimistic bias of that particular bootstrap sample. The procedure is repeated for every bootstrap sample. The average difference between the two Az values across all the bootstrap samples is used as an estimator of the size of the optimistic bias. The classifier is then trained on the original full data set. The training data set Az value derived from this classifier is then corrected by subtracting the value of the estimated optimistic bias to produce a Bootstrap corrected value for Az.</p>
<b>Classification Algorithm</b>	The set of equations or rules developed by a classifier to assign cases to classes based upon the values of a set of predictor variables.
<b>Classifier</b>	A method or technique for classifying cases into known classes.
<b>Complexity</b>	The degree of non-linearity of a function and also denotes the number of hidden units in an MLP required to approximate the function. Zero complexity is a linear function or zero hidden units. A complexity of two indicates one turning point in a curved line (i.e. a quadratic) or two hidden units. A complexity of three indicates two turning points in curved line (an equation with a cubed term) and three hidden units. And so on.

<b>Connection</b>	The connection between the output of one unit and the input of another unit. Functionally equivalent to a synapse in a biological neural system.
<b>Early Stopping</b>	The practice of using a holdout data set to estimate the performance of multi-layer perceptron on the population during training and using deterioration in that performance as criteria to stop the training earlier than would otherwise be the case using other criteria for stopping.
<b>Error function</b>	A mathematical function which measures the difference between the actual and predicted values of a variable, usually the variable which signifies class membership.
<b>Error Surface</b>	The manifold surface of average (across all cases) error function values plotted as a function of all the possible values of all the weights in an MLP when applied to a set of cases.
<b>Generalisation</b>	The classification accuracy of a classifier on a population.
<b>Global minima</b>	The point on the error surface of an MLP where error is at minimum value compared to anywhere else on the error surface. The set of weight values which define this point represent the best possible solution for the MLP on that data set using that error function.
<b>“gold standard”</b>	A classifier, which is judged to be the best possible (or best obtainable) in a particular clinical domain. It used as the standard against which other classifiers are evaluated.
<b>Hidden layer</b>	The middle layer(s) of a multi-layer perceptron.
<b>Ill-Posed Problem</b>	A classification problem where it not possible to classify cases, because there is no (or not much) separation of classes in the input space.  The opposite of ill-posed is <b>well-posed</b> .
<b>Input Layer</b>	The first layer of a multi-layer perceptron which receives inputs (input patterns).
<b>Input Pattern</b>	The set of values of a set of predictor variables in a classification data set.
<b>Input space</b>	The space defined by all the possible values of all the input variables.
<b>Input Variable</b>	A variable which is member of the set of predictor variables.
<b>Linear</b>	A line, or function represented by a line, which is a straight line.
<b>Linear model</b>	An equation for a straight line, where the variables represent objects of interest such as the predictor variables and the classification criterion.
<b>Linear Discriminant Function Analysis</b>	A statistical modeling technique which can be used to develop a linear classifier.
<b>Local minima</b>	A point on the error surface of an MLP where error is at minimum value

compared to other points in its near vicinity on the error surface. The set of weight values which define this point represent a relatively good solution for the MLP on that data set using that error function.

<b>Logistic Regression</b>	A statistical modeling technique which can, amongst other things, be used to develop a linear classifier. Also known as a <b>Logistic Discriminant</b> when used as a classifier.
<b>Multi-layer Perceptron (MLP)</b>	A type of neural network consisting of 3 or more layers of units, in which information feeds forward from inputs in the first layer to outputs in the last layer. Also Known as an MLP.
<b>NevProp</b>	Software for implementing and training MLPs, developed by Dr P Goodman at the Centre for Biomedical Modeling Research at the University of Nevada, Reno Nevada, USA.
<b>Non-Linear</b>	A line, or function represented by a line, which is not a straight line. It has at least one, possibly more kinks or curved sections.
<b>Non-Linear model</b>	An equation for a curved or kinked line, where the variables represent objects of interest such as the predictor variables and the classification criterion.
<b>Optimistic bias</b>	The bias present in measures of classification accuracy derived from a training data set, which come about as a result of capitalisation upon chance relationships (inherent in any sample) by training algorithms. The bias is always optimistic (that is towards indicating greater accuracy).
<b>Output layer</b>	The final or last layer of a MLP which generates an output(s).
<b>Output value</b>	The value of the output of a unit in the output layer of a MLP.
<b>Production</b>	After a classifier has been trained, it can be used to classify cases for which predictors are known but class membership is not. This phase is known as production.
<b>QuickProp</b>	An algorithm used to find the set of weights for a MLP which locate an error minima, but does so much quicker than BackProp.
<b>ROC Curve</b>	Receiver Operating Characteristics Curve. A particular graph, with origins in signal detection theory, which is drawn by plotting variations in Sensitivity (y axis) and 1 – Specificity (x-axis) across the full range of possible cut-off values of the output values of a classifier.
<b>Shrinkage</b>	The difference between a training data set derived measure of classification accuracy (e.g. $A_z$ ) and a test data set derived measure of classification accuracy. It is a measure of the amount of optimistic bias contained in the training data set derived measure.

If all the available data is used for training, then  $A_z$  shrinkage can be estimated by subtracting Bootstrap corrected  $A_z$  (see above) from training data set derived  $A_z$ .

<b>SYSTAT</b>	A software package for statistical analysis sold by the SPSS corporation.
<b>Test data set</b>	A data set of cases with predictor variables and known class membership, which is used to measure the performance of a classifier by applying the classifier to the data set and recording the accuracy of classification. Also known as a cross-validation data set.
<b>Training</b>	The process of applying an optimisation algorithm, such as BackProp, to an MLP to locate a set of weights for the MLP which minimises the error function
<b>Training algorithm</b>	An algorithm, for example BackProp, which used for training an MLP.
<b>Training data set</b>	A data set of cases with predictors and known class membership, which is used for the training of a classifier.
<b>Weight</b>	Also known as a “connection weight”. A positive or negative number used to multiply input connections to a unit in a multi-layer perceptron. The term Weight in an MLP corresponds directly to the term “coefficient” as used in regression and statistics.
<b>Weight Decay</b>	An addition to optimisation algorithms such as BackProp, which subtracts a constant small proportion from weights, on each pass of the algorithm and so biases the solution towards containing smaller rather than larger weights. This improves generalisation.
<b>Well-Posed Problem</b>	<p>A classification problem where it is possible to classify all (or almost all) cases, because there is good separation of classes in the input space.</p> <p>The opposite of well-posed is <b>ill-posed</b>.</p>
<b>Unit</b>	A single artificial neuron, which is part of a neural network.



# GENERAL INTRODUCTION TO THE INVESTIGATION

## Clinical Decision Making

Clinical decision-making is the cornerstone of all clinical practice. Before an intervention is commenced, before a referral is made and even before further assessment is undertaken, the clinician must make a decision(s) about the nature of the clinical problems that are being presented.

Improved clinical decision-making leads to improved clinical outcomes [Knottnerus et al, 2002]. The most effective intervention is only effective when it is applied to an appropriate case. Many interventions have side effects or carry other risks. In the best-case scenario, inappropriate intervention is a waste of clinical resources. In the worst case, inappropriate intervention causes unnecessary harm. Inappropriate referral and inappropriate further assessment are similarly problematic.

Improvements in clinical decision-making practices offer the potential to improve clinical practices as a whole. Improvements to clinical decision-making practices have usually come about through clinical problem based research, in which the investigators have sought to gain a better understanding of the clinical entity(ies) at hand. Through this better understanding of specific clinical problems better clinical decision making practices have been suggested. These suggested practices are then empirically compared

to pre-existing practices and if they are found to be better, it is usually recommended that they be adopted in place of the previous practices. Through this mechanism of one-clinical-problem-at-time investigation, clinical decision-making practices as a whole have gradually improved.

An alternate approach is to attempt to improve clinical decision making, by focusing research efforts more directly on better understanding the clinical decision making process itself, rather than on understanding specific clinical problems. Such an approach has the potential to produce results that can be broadly applied to many clinical decision making problems. The investigations reported in this thesis take this approach.

There are at least two basic components to clinical decision-making. These are: Information Gathering and Decision Making. For both these components there can be many alternatives. Combinations of the available alternatives for these two components produce many possibilities for clinical decision making for any particular clinical problem. The alternatives for information gathering tend to be closely tied to the clinical problem. The nature of the clinical problem, our conceptualisation and understanding of the clinical problem and the available technology, strongly dictate the range of information that can be gathered. On the other hand the alternatives for decision-making are generally independent of the clinical problem. Instead they are related more to information theory and/or to statistical technologies. This distinction makes it more likely that general improvements to clinical decision making practices will be found by

researching alternatives for the decision making component rather than alternatives for information gathering component.

## **Neural Networks**

Artificial neural networks, hereafter referred to as neural networks, are a recently developed, biologically inspired, form of computation modelled upon the functioning of neurons and nervous systems in biological organisms. Traditional computing has developed since the 1940's along the lines of centralised processing of information, known formally as the "Von Neuman Architecture" after its creator the mathematician John Von Neuman [Dayhoff 1990]. There has been a phenomenal pace of development in computing since World War II. The main aspects of this have been faster and faster Central Processing Units (CPU), increases in the amounts of faster Random Access Memory (RAM), larger and faster Hard Disks, Local Area networking (LAN), Wide Area Networking (WAN), the Internet and more user friendly user interfaces. The range of applications, such as complex calculation, word-processing and electronic communication, for which computers are now used is also phenomenal. In Western societies they have become an integral part of the workplace and are progressing towards becoming an integral part of all aspects of life in those societies.

None the less, it is generally recognised that such computers, based upon the Von Newman Architecture, are only one of a large range of possible computing architectures. It is also generally recognised that they have little resemblance to neural systems in

biological organisms, such as the brain. These biological systems are composed of many simple information-processing units (neurons), which are linked together in networks and perform computation on information by parallel and distributed processing, rather than by centralised processing [Rummelhart & McClelland, 1986].

Amongst other things, biological neural systems are capable of complex pattern recognition and classification tasks that traditional computers with centralised processing architecture, have found difficult to emulate. Examples of tasks, which humans, with their biological neural systems, are capable of, but which traditional computers are not as good at, are visual recognition of persons, objects and symbols, speech recognition and clinical diagnosis [Dayhoff, 1990].

This has led to efforts amongst artificial intelligence researchers to develop artificial neural networks that use parallel and distributed information processing as an alternative to centralised information processing [Rummelhart & McClelland, 1986]. Amongst other things, it has been found that such neural networks can be used in pattern recognition tasks, such as visual recognition of persons, objects and symbols, speech recognition and clinical diagnosis [Dayhoff 1990; Cross, Harrison & Kennedy 1995; Price, Sptitznagel, Downey, Meyer, Risk & el-Ghazzaway 2000], and that they have much in common with statistical classification and pattern recognition techniques [Cheng & Titterington 1994, Ripley 1994, 1996, Sarle 1994, Bishop 1995, Reed & Marks 1999]. As well there are now a number of well established applications of neural network to clinical decision making in medicine (e.g. Diagnosis of Myocardial Infarction [Baxt

1990,1991]; detection of cervical cancer in Pap Smears [Kok & Boon, 1996, Kok et al 2001, Cenci et al 2000, Halford et al 1999]; staging of prostate cancer [Babaian & Zhang 2001, Jung et al 2002]; Prediction of survival after colon carcinoma treatment [Snow, Keerr, Brandt & Rodvold 2001]). All this raises the question of their potential applicability to clinical decision-making problems in psychiatry.

## **Problem Statement**

In recent years Neural Networks have been successfully applied to a large number of classification and pattern recognition problems [Mjosness & DecCoste 2001]. There is also a growing body of published research investigating the potential application of neural networks to a wide range of clinical decision-making problems [Cross et al. 1995]. A small number of these investigations have been in the area of psychiatry.

Motivation for many of these investigation comes from the notion that Neural Networks may provide a better solution than a traditional statistical techniques (e.g. Linear Discriminant Function Analysis or Logistic Regression) commonly used in clinical decision making practices, because they can recognise patterns in data in much the same ways as an experienced clinician (who is presumably using his/her biological neural network).

This notion is both true and misleading. Under certain conditions a neural network may provide a good solution to a particular clinical decision making problem and the

underlying basis of this good solution is pattern recognition. However a neural network can also be conceptualised as a solution based upon well understood principles of statistical approximation and estimation. It has much in common with Logistic Regression and other related statistical regression and classification techniques [Ripley 1996]. Neural networks can be seen as one of a range of techniques, which can be applied to clinical decision-making problems. The real issue is not “Are they better?”, but “Under what conditions should they be considered and how can they be applied?”

Despite a large number of studies which investigated the application of neural networks to individual clinical decision-making problems, a clear picture about their applicability to clinical decision-making problems has yet to emerge. There are several reasons for this.

Firstly, the literature as a whole is not cohesive. Most investigations have tended to be “one offs” that have examined the application of a neural network to a specific clinical decision-making problem. They have not built upon previous work and as such they are not part of a thread which has progressively illuminated different aspects of a specific application<sup>1</sup> or of the application of neural networks to clinical decision-making in general.

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<sup>1</sup> With a couple of notable exceptions, for example PAPNET - a neural network based system for diagnosing cervical cancer in PAP smears, which has been serially studied and developed.

Secondly, much of the literature on the application of neural networks to clinical decision-making has failed to consider neural networks from a statistical viewpoint [Ripley, 1996].

Finally, most investigations fail to consider a large body of knowledge and research that exists about clinical decision-making [Florio et al 1994].

The objective of this thesis is to study the applicability of neural networks to clinical decision-making problems in psychiatry, in a systematic fashion and from both a statistical and a clinical decision-making viewpoint.

## Research Questions

The central question of this thesis is:

*Are MLP type neural networks applicable to clinical decision-making problems in Psychiatry?*

More specifically the thesis investigates the following:

- *Can MLP type neural networks be applied to clinical decision-making problems in psychiatry?*
- *Under what conditions can MLP type neural networks be applied to clinical decision-making problems in psychiatry?*
- *How should the application of MLP type neural networks to clinical decision-making problems in psychiatry be evaluated?*
- *What are the implications of applying MLP type neural networks to clinical decision-making problems in psychiatry for psychiatric taxonomy and for our theoretical understanding of psychiatric disorders?*



## General Plan of the Thesis

- Part I.*** Examines the historical debate on clinical and statistical decision making, which has been the main focus of researchers to date.
- Introduces neural networks and reviews some of the literature on the application of neural networks to clinical decision making problems in medicine.
- Describes neural networks and their implementation in detail. Concludes that MLP type neural networks can be used to solve non-linear classification problems.
- Uses the theoretical framework of the bias-variance tradeoff to compare MLPs and Logistic Regression, and to elucidate important aspects of comparing and evaluating classifiers.
- Extends a review, of 28 studies, by Sargent [2001], which examines the comparative application of MLPs and Logistic Regression to large clinical datasets ( $N > 200$ ), by adding 21 new studies published since his review.
- Concludes that it is worthwhile to explore the use of neural networks for clinical decision making in psychiatry.
- Part II*** Discusses methodological issues relevant to the evaluation of classifiers (including MLP type Neural Networks) for clinical decision-making problems. Concludes by outlining, in detail, a framework for such evaluations, which are applied later in the thesis
- Part III.*** Individually describes three sets of empirical studies of the application of MLP type neural networks to three clinical decision-making problems. These are:
- Diagnosis of Melancholia amongst depressed patients
  - Prediction of response to stimulant medication in children with Attention Deficit Hyperactivity Disorder
  - Diagnosis of Autistic Disorder
- Part IV*** Provides a general conclusion on the overall findings of the investigation