# Local and Personalised Modelling for Renal Medical Decision Support Systems

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**School of Computing and Mathematical Sciences**
**Faculty of Design and Creative Technology**

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## Attestation of Authorship

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person (except where explicitly defined in the acknowledgements), nor material which to a substantial extent has been submitted for the award of any other degree or diploma of a university or other institution of higher learning.

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Tian Min Ma

## Co-Authored Works

### Book Chapter:

Kasabov, N., Song, Q., & Ma, T. M. (2008). Fuzzy-neuro systems for local and personalized modelling. In *Forging New Frontiers: Fuzzy Pioneers II* (Vol. 218, pp. 175-197). Berlin / Heidelberg: Springer.

### Journal Articles:

1. Hossain, F., Kendrick-Jones, J., MA, T. M., & Marshall, M. R. (2012). The estimation of glomerular filtration rate in an Australian and New Zealand cohort. *Nephrology, 17*(3), 285-293.

2. Khanal, N., Marshall, M., Ma, T., Pridmore, P., Williams, A., & Rankin, A. (2012). Comparison of outcomes by modality for critically ill patients requiring renal replacement therapy: a single-centre cohort study adjusting for time-varying illness severity and modality exposure. *Anaesth Intensive Care, 40*, 260-268.

3. Song, Q., Kasabov, N., Ma, T. M., & Marshall, M. R. (2006). Integrating regression formulas and kernel functions into locally adaptive knowledge-based neural networks: A case study on renal function evaluation. *Artificial intelligence in Medicine, 36*(3), 235-244.

4. Marshall, M. R., Song, Q., Ma, T. M., MacDonell, S. G., & Kasabov, N. K. (2005). Evolving connectionist system versus algebraic formulas for prediction of renal function from serum creatinine. *Kidney Int, 67*(5), 1944-1954.

5. Song, Q., Ma, T., & Kasabov, N. (2005). Transductive Knowledge Based Fuzzy Inference System for Personalized Modeling. Fuzzy Systems and Knowledge Discovery. In L. Wang & Y. Jin (Eds.), *Lecture Notes in*

*Computer Science* (Vol. 3614, pp. 485-488): Springer Berlin / Heidelberg.

## Publications in Conference Proceedings:

1. Song, Q., & Ma, T. (2007). GAWDN-NFIS: Neural-Fuzzy Inference System with a Genetic Algorithm Based on Weighted Data Normalization and Its Application in Medicine. Symposium conducted at the meeting of the Fourth International Conference on Fuzzy Systems and Knowledge Discovery (FSKD 2007), Haikou, China.

2. Song, Q., Ma, T., & Kasabov, N. (2006). TTLSC – Transductive Total Least Square Model for Classification and Its Application in Medicine. In X. Li, O. Zaïane, & Z. Li (Chair), Symposium conducted at the meeting of the the 2nd International Conference of Advanced Data Mining and Applications (ADMA 2006), Xi'An, China.

3. Song, Q., Ma, T. and Kasabov, N. (2005). Transductive Knowledge Based Fuzzy Inference System for Personalized Modeling. In: Symposium conducted at the meeting of the 11th World Congress of International Fuzzy Systems Association (IFSA2005), Beijing, China.

4. Ma, T., Song, Q., Marshall, M., & Kasabov, N. (2005). TWNFC – Transductive Neural-Fuzzy Classifier with Weighted Data Normalization and Its Application in Medicine. In M. Mohammadian (Chair), Symposium conducted at the meeting of the International Conference on Computational Intelligence for modelling, Control and Automation 2005 (CIMCA2005), Vienna, Austria.

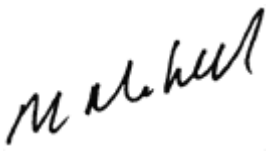
5. Song, Q., Ma, T. M., & Kasabov, N. (2004). LR-KFNN: Logistic Regression-Kernel Function Neural Networks and the GFR-NN Model for Renal Function Evaluation. In M. Mohammadian (Chair), Symposium conducted at the meeting of the International Conference on

Computational Intelligence for Modelling, Control and Automation 2004 (CIMCA2004), Gold Coast, Australia.

6. Song, Q., Ma, T. M., & Kasabov, N. (2004). A Novel Generic Higher-Order TSK Fuzzy Model for Prediction and Applications for Medical Decision Support. In: Symposium conducted at the meeting of the Eight Australian and New Zealand Intelligent Information Systems Conference, Sydney, Australia.

The published papers that I have co-authored contain my contribution in terms of: (1) Participation in the method development and implementation; (2) Experiments on renal data; (3) Analysis of results.

This is confirmed and signed by Professor Nikola Kasabov, Dr. Mark Marshall and Dr. Qun Song.



## List of Abbreviations

| | | |
|---|---|---|
| AI | - | Artificial Intelligence |
| ANFIS | - | Adaptive Neural-Fuzzy Inference System |
| ANNs | - | Artificial Neural Networks |
| ART | - | Adaptive Resonance Theory |
| BP | - | Back-propagation |
| CKD | - | Chronic Kidney Disease |
| DENFIS | - | Dynamic Evolving Neuro-Fuzzy Inference System |
| DOPPS | - | Dialysis Outcome and Practice Patterns Study |
| DSSs | - | Decision Support Systems |
| ECM | - | Evolving Clustering Method |
| ECOS | - | Evolving Connectionist Systems |
| EFuNN | - | Evolving Fuzzy Neural Network |
| EI | - | Evolving Intelligence |
| Errthr | - | Error Threshold |
| ESKF | - | End Stage Kidney Failure |
| FIS | - | Fuzzy Inference System |
| GA | - | Genetic Algorithm |
| GFR | - | Glomerular Filtration Rate |
| ICED | - | Index of Co-Existent Disease |
| IDSSs | - | Intelligent Decision Support Systems |
| KBNN | - | Knowledge Based Neural Network |
| KNN | - | K-nearest Neighbours |
| LM | - | Levenberg-Marquardt |
| LS | - | Least Square |
| LSE | - | Least Square Estimator |
| MAE | - | Mean-Absolute-Error |
| MDRD | - | Modification of Diet in Renal Disease |
| MF | - | Membership Function |
| MLP | - | Multi Layer Perceptron |
| MLP-BP | - | Multi-layer Perceptron with Back-propagation |
| NECOSAD | - | Netherlands Co-operative Study on the Adequacy of Dialysis |
| NN | - | Neural Networks |
| RMSE | - | Root-Mean-Square-Error |

ROC - Receiver Operating Curve
Std - Standard Deviation
Sthr - Sensitivity Threshold
SVM - Support Vector Machine
TLS - Total Least Square Method
TTLSC - Tansductive Total Least Squares Classifier
TWNFC - Transductive Weighted Neuro-Fuzzy Classifier
TWNFI - Transductive Neuro-Fuzzy Inference System with Weighted Data Normalization

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## Abstract

The complexity and the dynamics of real-world problems, such as large Health Informatics data processing, require sophisticated methods and tools for building adaptive and knowledge-based intelligent systems.

This research developed intelligent systems for Health Informatics, and focuses on those local and personalised modelling which perform better local generalisation over new data. The local models are based on the principles of local learning, where the data is clustered and for each cluster a separate local model is developed and represented as a fuzzy rule as a knowledge representation, either of Takagi-Sugeno, or Zadeh-Mamdani types. The personalised modelling techniques are based on transductive reasoning. They develop individual model for each data vector that takes into account the new input vector location in the space. They are adaptive models, in the sense that input-output pairs of data can be added to the data set continuously. This type of personalised modelling is promising for medical decision support systems where a model for each patient is developed to predict an outcome for this patient and to rank the importance of the clinical variables for them.

This thesis presents novel local and personalised modelling and illustrates them on real world medical case studies of renal function evaluation – an important problem of medical decision support. The local and personalised models are compared with statistical, neural network and neural fuzzy global models and show a significant advantage in accuracy and explanation.

Two representative problems in clinical medicine have been explored using the framework of local and personalised modelling. In each case, prediction has been made utilising either clinical, laboratory, or a combination of different types of data where appropriate. Systems has been developed for the following circumstances: (1) prediction appertaining to renal function, using data from 178 Australasian patients with advanced chronic kidney disease (computing procedure GFR-DENFIS, GFR-KBNN, GFR-TWNFI); (2) prediction appertaining to patient longevity after the inception of dialysis for end-stage renal failure,

using data from 6010 patients randomly sampled from United States facility haemodialysis population (computing procedure DOPPS-TWNFC, DOPPS-TTLSC).

The main contribution of this research is to provide immediate and workable methods and tools to augment health care, which are of sufficient accuracy to support good clinical decision-making. Furthermore, this research resulted in technical solutions to the various data modelling problems that exist in health care research. More importantly, personalised modelling developed for renal disease in this research is an adaptive and evolving technique, in which new data sample can be continuously added to the training dataset and subsequently contribute to the learning process of personalised models. The technique of personalised modelling offers a new tool to give a profile for each new individual data sample. Such characteristic makes personalised modelling based methods promising for medical decision system, especially for complex human disease diagnosis and prognosis.

# Chapter 1 : Introduction

This chapter introduces background information on Health Informatics, and explains the potential of evolving intelligent systems for medical prediction. The overall objectives, broad methodology and main contributions of this research are described.

## 1.1 Background

### 1.1.1 Motivation of the Research

Health care generates extensive administrative and clinical data from hospital bureaucracy, clinical trials, patient electronic records and computer supported disease management systems. The recent proliferation of medical information systems and databases exacerbates this situation. However, these data tend to be undervalued as a strategic resource, partly because traditional approaches of data analysis have not allowed their fullest use due to the number, complexities and interrelationships of the data. Many clinical problems in health care have behaviour that is simply impossible to describe or predict reliably by conventional modelling tools. Therefore, traditional approaches to knowledge discovery need to be coupled with newer methods for more efficient computer-assisted analysis.

Advances in health care are facilitated with the use of accurate tools for medical prediction within in the various disciplines of Health Informatics. Such tools allow health care delivery to be optimised to the patient clinical condition, which is in turn critically dependent on three broad requisites at both an individual and population level: (1) accurate assessment of patient health status / organ function; (2) accurate assessment of risk from any given illness; (3) accurate identification of high-risk patients for targeting for either preventative or therapeutic purposes. Without such tools, health care administrators and funders may not be able formulate effective health service delivery plans, and health care providers may misdiagnose the presence and status of disease and thereby risk inappropriate investigation and treatment.

### 1.1.2 Health Informatics and Decision Support Systems

**Health Informatics** is defined as “an evolving scientific discipline that deals with the collection, storage, retrieval, communication and optimal use of health related data, information and knowledge. The discipline utilizes the methods and technologies of the information sciences for the purpose of problem solving, decision making and assuring highest quality health care in all basic and applied areas of the biomedical sciences” (Graham, 1994). The term covers a wide range of applications and research. It is the study of how technology, particularly artificial intelligence, computer science, and informational science relates to the medical field. This field of study is typically applied to clinical care, nursing, public health, and biomedical research, all dedicated to the improvement of patient care and population health. It is one of the fastest growing areas within the health sector.

In the domain of health informatics, **Decision Support Systems (DSSs)** are defined as computer-based information systems or knowledge based systems that support information sciences and decision making activities (Gadomski, Bologna, Costanzo, Perini, & Schaerf, 2001). The first generation of Medical DSSs that attempted to aid the clinician in making medical decisions appeared in the late 1950s. These systems were mainly based on methods that used decision trees or truth tables. Systems based on statistical methods appeared later, followed by expert systems much later. Most early systems remained only prototypes.

DSSs based on evolving intelligence or intelligent agents’ technologies (e.g. Evolving Connectionist Systems), which perform selected cognitive decision-making functions, are called **Intelligent Decision Support Systems (IDSSs)**. The concepts of evolving intelligence, Evolving Connectionist Systems and related techniques are introduced in the following section. The main purpose of this research is to develop artificial intelligence systems based on local and personalised models that might potentially form the basis of practical IDSSs in the future.

### 1.1.3 Artificial Intelligence, Evolving Intelligence and Evolving Connectionist Systems

**Artificial Intelligence (AI)** can be loosely defined as a system that perceives its environment and takes actions that maximize its chance of success. This research focuses on AI which can continuously evolve structure and functionality over time through learning from data and continuous interaction with the environment. Such systems can be denoted further as **Evolving Intelligence (EI)**, meaning that they induce rules rather than using a predefined set; they learn and improve incrementally starting from little knowledge; they develop concepts and abstractions in terms of rules; they "explain" their behaviour in terms of rules; they accommodate, at any time of their operation, knowledge and data – both new and old (N. Kasabov, 2003).

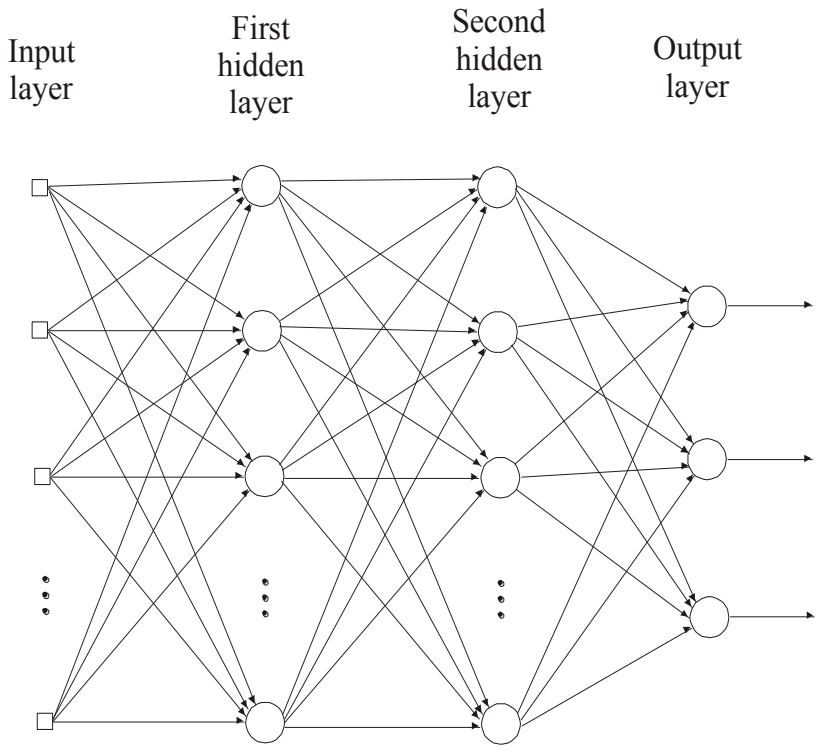
In AI research, **machine learning** has been central to its development from the very beginning. Machine learning is a branch of computer science that is concerned with the development of algorithms that allow computers to learn (Luger & Stubblefield, 2004; Nilsson, 1998; Poole, Mackworth, & Goebel, 1998; Turing, 1950). More details of the different machine learning techniques are explained in Chapter 2.

In the field of machine learning, **connectionist learning procedures** and **connectionist systems** are important parts of it. The term 'connectionism' refers to computational systems for machine learning that simulate neural processes. There are many different connectionist systems, although neural networks (NN) were the first type of connectionist system and are still the most common. (Elman et al., 1996; N. Kasabov, 2003; Marcus, 2001; McClelland & Rumelhart, 1986; Pinker & Mehler, 1988; Rumelhart & McClelland, 1986). Structurally, a NN is a group of nodes ("artificial neurons") interconnected by a network ("artificial synapses"). A prototypical NN is shown in the Figure 1.1. In most cases a NN is an adaptive system that changes its structure based on external or internal information that flows through the network. This information processing and subsequent change in structure is motivated by the artificial neurons based on a connectionist approach, which involves mathematically

defined changes in connection weights over time. Different networks modify their connections differently, but conceptually these changes constitute a given NN's "learning algorithm". In more practical terms, NNs are non-linear statistical data modelling or decision making tools. They can be used to model complex relationships between inputs and outputs or to find patterns in data.

**Figure 1.1 Prototypical neural network architecture.**

*(A structure of a multi-layer perceptron NN with two hidden layers)*




To extrapolate the principles above, the operating characteristics of connectionist systems can be further described by attributes usually applied to human mental processes:

- Any mental state can be described as an (N)-dimensional vector of numeric activation values over neural units in a network.
- Memory is created by modifying the strength of the connections between neural units. The connection strengths, or "weights", are generally represented as an (N×N)-dimensional matrix.

Connectionist systems use a variety of modelling techniques to perform machine learning in this way. The most common strategy in connectionist learning methods is to incorporate gradient descent over an error surface in a space defined by the weight matrix. All gradient descent learning in connectionist models involves changing each weight by the partial derivative of the error surface with respect to the weight. Back-propagation (BP), first made popular in the 1980s, is probably the most commonly known of the connectionist gradient descent algorithms.

The AI developed in the thesis is for the most part based on **evolving connectionist system (ECOS).** An ECOS is a neural network or a collection of such networks that operate continuously in time and adapt their structure and function through a continuous interaction with the environment and with other systems(N. Kasabov, 2003). Each evolving connectionist system contains of four main parts: 1. Data acquisition; 2. Pre-processing and feature evaluation; 3. Connectionist modelling; 4. Knowledge acquisition (N. Kasabov, 2003). Comparing with other AI systems, ECOS have advantage as: fast learning from a large amount of data, real-time incremental adaptation to new data, continuous improving, and the ability to analyze and explain themselves through rule extraction. All these strengths enable them to be promising for their application in health Informatics and medical IDSS.

In this research, ECOS uses a variety of modelling techniques to perform machine learning under several different combinations of frameworks: inductive versus transductive reasoning, and global versus local modelling. The incremental development of different systems ultimately aims to create practical IDSSs based on personalised modelling approach; that is, an ECOS that will create a local model for each new individual data vector (e.g. a patient), that fits the data better than a global model for the whole problem space or a local one based on adaptation of pre-existing clusters.

## 1.2 Research Objectives and Respective Contributions

This research is in the area of Health Informatics. The main purpose of this research is to develop artificial intelligence systems based on local and

personalised models that might potentially form the basis of practical IDSSs in the future.

In this research, EI computing procedures are developed, modified and applied with a view to improving the health care delivery and outcomes (N. Kasabov, Song, & Ma, 2008; Marshall, Song, Ma, MacDonell, & Kasabov, 2005; Qun Song & Kasabov, 2006; Q. Song, Kasabov, Ma, & Marshall, 2006; Qun Song, Ma, & Kasabov, 2006). The accuracy of prediction with these procedures is compared with existing regression formulas, which are the most popular type of prognostic and classification models in medicine. Regression formulas are derived from data gathered from the whole problem space through inductive learning, and are consequently used to deduce the output value for a new input vector regardless of where it is located in the problem space. For many problems, this can result in different regression formulas for the same problem through the use of different datasets and limited accuracy on new data that are significantly different from those used for the original modelling.

Two representative problems in clinical medicine have been studied. Modelling is undertaken using actual biological rather than simulated patient data. In each case, prediction is made using either clinical, laboratory, or a combination of different types of data where appropriate. Systems are developed for following clinical circumstances: (1) prediction appertaining to renal function, using data from 178 Australasian patients with advanced chronic kidney disease (computing procedures GFR-DENFIS, GFR-KBNN, GFR-TWNFI); (2) prediction appertaining to patient longevity after the inception of dialysis for end-stage kidney failure, using data from 6010 patients randomly sampled from United States facility haemodialysis population (computing procedures DOPPS-TWNFC, DOPPS-TTLSC).

For both problems, specific objectives and major research questions of this research are as following:

(a) *Develop a novel local learning method for prediction of renal function based on knowledge-based neural networks: GFR-KBNN*

The primary aim of this and the following two objectives is to develop computing procedures to accurately predict renal function - as assessed by glomerular filtration rate (GFR) - using clinical and laboratory patient data, with a degree of accuracy that is sufficient for clinical and administrative purposes.

Briefly, the analyses utilise an existing contemporary patient database of 178 Australasian patients with advanced chronic kidney disease. The database includes comprehensive clinical and laboratory data including patients' actual GFR as measured by the gold standard technique of renal radioisotope clearance. Prediction algorithms based on a knowledge based neural network (KBNN) are developed to create local models for identified and distinct patient profiles as defined by commonly available clinical variables. KBNNs incorporate and adapt existing knowledge as kernel functions in their structures to improve their learning and adaptation ability. Potentially, these systems offer efficient use of existing knowledge combined with self learning, reasoning and enhanced explanation. In this research, this existing knowledge comprises nine regression formulas that are used by clinicians and administrators for the estimation of GFR in their routine clinical practice.

The KBNN integrates sub-models and new data in each problem space resulting in an incrementally adaptive model and increasing accuracy. Local learning is by the fine-tuning of local models (including modification of the nine existing regression formulas within each local model), and global learning by a gradient descent method on the whole dataset. Training is performed on a randomly selected training subset, and validation on the remaining cohort. The performance of GFR-KBNN will be compared to the existing standard methods for the prediction of GFR in routine clinical practice, again based on conventional regression formulas.

The results of this objective have been published in part by Song et al. (Song, Kasabov, Ma, & Marshall, 2005)

(b) *Develop a novel local learning method for prediction of renal function based on fuzzy inference: GFR-DENFIS (Dynamic Evolving Neuro-Fuzzy Inference System)*

As with the previous objective, the primary aim of this objective is to develop computing procedures to accurately predict GFR. The same patient database as which was used for the previous objective is also used for this one. Prediction algorithms based on fuzzy inference are developed to create local models for identified and distinct patient profiles as defined by commonly available clinical variables. Local learning is by the fine-tuning of each local model, and global learning by the proper aggregation of all local models. Training is performed on a randomly selected training subset, and validation on the remaining cohort. The performance of the novel system will be compared to the existing standard methods for the prediction of GFR as described above.

This resulting contribution has been published in part by Marshall et al. (Marshall, Song, Ma, Macdonell & Kasabov, 2005)

(c) *Develop a novel method for prediction of renal function based on transductive personalised modelling: GFR-TWNFI (Transductive Neuro-Fuzzy Inference System with Weighted Data Normalization)*

The primary aim and data source for this objective are the same as the previous ones. However, prediction algorithms for this objective are based on a novel transductive neural fuzzy procedure and are used to create personalised models for renal function evaluation. GFR-TWNFI is transductive (inferential reasoning from observed, specific training cases is used to move to specific test cases) rather than inductive (reasoning from observed cases is used to move to general rules, which are then applied to the test cases). In response to new information, the TWNFI therefore estimates the value of a potential new model only in a single point of the entire problem space (as defined by the new data vector) utilizing additional information related to this point.

Personalised modelling via transductive reasoning is potentially useful for prediction in medical applications as it can develop a specific model for each data vector (patient) by taking into account the vector's location in the problem space, without the intermediate requirement of solving the more general problem. An individual model for individual patient is promising for Health

Informatics where the focus is often not only on the health of the population, but on the health of the individual. Moreover, the proper aggregation of these individual models can potentially yield greater accuracy to the general model due to the better account of the particularities of each input. In this research, GFR-TWNFI is developed as an adaptive system, in the sense that input-output pairs of data can be added to continuously and immediately made available for transductive inference and subsequent modelling.

Like GFR-KBNN, GFR-TWNFI is knowledge-based insofar as it utilizes medical knowledge in setting initial values for parameters of weighted data normalization. For many practical problems including those in medicine, some input variables have a known place in the hierarchy of importance and will make a different contribution to the model's output. Therefore, it is necessary to find an optimal normalization and assign proper importance factors to the variables. This is especially critical in a special class of models – the clustering based neural networks or fuzzy systems. In such systems, distance between neurons or fuzzy rule nodes and input vectors are usually measured in Euclidean distance, so that variables with a wider range will have more influence on the learning process and on the output value and vice versa. To assist this particular aspect of the model, medical knowledge is used to set the initial value of weight for normalization which is the first step of the steepest descent algorithm used for subsequent training.

As previously, the performance of the novel system will be compared to the existing standard methods for the prediction of GFR as described above.

This resulting contribution has been published in part by Song et al. (Song, Ma, & Kasabov, 2005)

*(d ) Develop a novel method for prediction of survival of patients on dialysis based on transductive personalised modelling: DOPPS-TWNFC (Transductive Weighted Neuro-Fuzzy Classifier )*

The primary aim of this objective is to develop computing procedures to distinguish between clinical profiles in haemodialysis patients that are

associated with different survival rates, with a degree of accuracy that could influence clinical or administrative management.

Prediction algorithms for this objective are based on a transductive neural fuzzy procedure with weighted data normalization. Using transductive reasoning, the system estimates the value of a new classification model (survival) for each data vector (patient) only in a single point of the entire problem space (as defined by the new data vector) utilizing additional information by taking into account the vector's location in the problem space. The performance of the system will be compared to established methods that are based on conventional regression analyses. This work has been published in part by Ma et al. (Ma, Song, Marshall, & Kasabov, 2005).

The secondary aim of this objective is to compare the resulting models with existing medical knowledge. In particular, the predictive clinical variables chosen and modelled by the DOPPS-TWNFC were compared with the collection of clinical variables that are "known" to be predictive of mortality in routine clinical practice or conventional medical research: patient related factors (co-morbid medical conditions such as coronary artery disease, lung disease, malnutrition; patient demographics such as sex, age, race), treatment related factors (haemodialysis practice patterns such as dialysis dose, equipment), and health care provider characteristics (private vs. state-funded). The patterns of association and predictions of the transductive model are potentially not achievable by any traditional approaches to knowledge discovery such as conventional regression. There is potential for the patterns of association within the DOPPS-TWNFC to allow for knowledge discovery in two ways: one is from the identification of high risk patient subgroups based on previously ignored clinical variables; another is from the identification of new biological processes and potentially new therapeutic targets for clinical care.

This work has been published in part by Song et al. (Song, Ma, & Kasabov, 2006).

## 1.3 Overall Contributions of the Research

The main contribution of this research is to provide workable methods and tools to augment health care, which are of sufficient accuracy to support good clinical decision-making. Current tools for the above applications are either inadequate or wholly lacking, and improved methods are needed. This research provides superior modelling strategies and results through the development of EI based on progressively more local and finally personalised models (See Figure 1.2).

Personalised models developed for renal decision support system in this research is an adaptive and evolving technique, in which new data sample can be continuously added to the training dataset and subsequently contribute the learning process of personalised modelling. The techniques of personalised modelling offer a new tool to give a profile for each new individual data sample. They also reveal the most significant input variables (features) for the model that might suggest clinical target for intervention and a change in medical management. These characteristic makes personalised modelling based methods promising for medical decision support system, especially for complex human disease diagnosis and prognosis.

Such personalised systems can also be utilised by hospital funders and administrators to more accurately assess future population disease burden for service planning.

The objectives of this research are concentrate on specific clinical situations (prediction of renal function, prediction of patient survival on haemodialysis), but they will result in generic modelling frameworks. These can then be extrapolated to the future development of other health care applications using local and personalised models (e.g. for accurate prediction of cardiovascular risk), and will serve to catalyse further applications albeit with some modification to methodology.

Furthermore, this research will also result in technical solutions to the various data modelling problems that exist in health care research. For instance, most patient data collected by hospitals for diagnosis and prognosis are limited by

their incompleteness (missing parameter values), incorrectness (systematic or random noise in the data), sparseness (few and/or non-representable patient records available), and inexactness (inappropriate selection of parameters for the given task). To date, there have been few rigorous attempts to develop Health Informatics solutions to these problems, and it is anticipated that the procedures developed in this project will set the benchmark in this area.

## 1.4 Organization of the Thesis

This thesis is organized as follows:

***Chapter 1*** introduces background information on Health Informatics and Evolving Intelligence and their importance in developing medical prediction tools for decision making. The main objectives, plans and contributions of this research are also described in this chapter.

***Chapter 2*** reviews conventional algorithms and techniques of machine learning, with particular emphasis on classic algorithms for global and local learning and neural fuzzy inference techniques for both local and personalised modelling frameworks are reviewed.

***Chapter 3*** presents novel algorithms and techniques of evolving connectionist systems using both local and personalised modelling frameworks.

***Chapter 4*** provides the medical and biological background to the representative problems which will be modelled. To provide context and clinical relevance, the biological role of renal function will be discussed, and the difficulties of renal function evaluation using current tools. The chapter will also provide corresponding background to the problem of mortality for haemodialysis patients, and again the corresponding difficulties with prediction of longevity. The two modelling datasets (GFR, DOPPS) will be introduced and described.

***Chapter 5*** presents the development of GFR- KBNN, a local inductive knowledge-based model, and the performance of the system relative to conventional methods for GFR prediction.

***Chapter 6*** presents the development of GFR-DENFIS, a local inductive neural fuzzy model, and the performance of the system relative to conventional methods for GFR prediction.

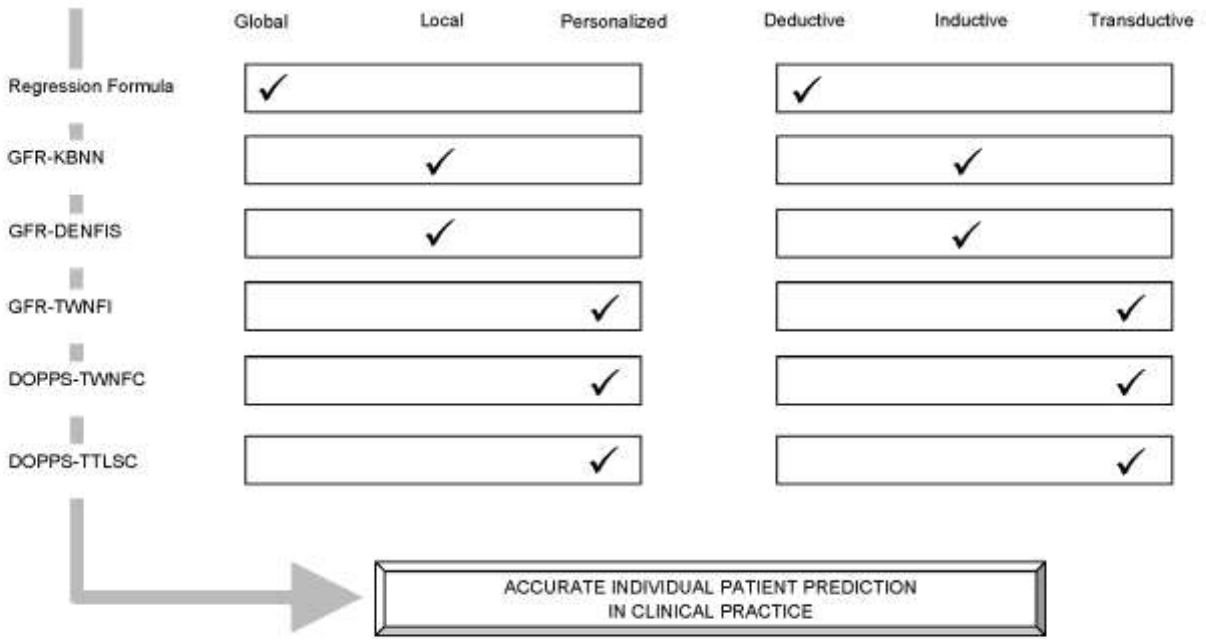
***Chapter 7*** presents the development of GFR-TWNFI, a personalised transductive knowledge-based neural fuzzy model, and the performance of the system relative to conventional methods for GFR prediction.

***Chapter 8*** presents the development of DOPPS-TWNFC, a personalised transductive neural fuzzy classifier, and the performance of the system relative to conventional methods for prediction of survival of Haemodialysis patients.

***Chapter 9*** presents the development of DOPPS-TTLSC, a personalised transductive model, and the performance of the system relative to conventional methods for prediction of survival of Haemodialysis patients.

***Chapter 10*** includes the summary and future work.

**Figure 1.2 Schema of system development in this research, pertaining to the modelling and reasoning frameworks as discussed.**



# Chapter 2 : Review of Selected Machine Learning Methods Relevant to the Thesis

In ***Chapter 1***, Health Informatics and Evolving Intelligence were described, and their potential roles in the area of medical prediction. The main objectives, plans and contributions of this research were also described in the chapter.

This chapter reviews conventional algorithms and techniques of machine learning, with particular emphasis on classic algorithms for global and local learning and neural fuzzy inference techniques for both local and personalised modelling frameworks are reviewed.

## 2.1 Machine Learning Methods

Machine learning is a scientific discipline concerned with the design and development of algorithms that allow computers to evolve behaviours (“learn”) based on empirical data. A commonly quoted definition is as follows: A computer program is said to learn from experience E with respect to some class of tasks T and performance measure P, if its performance at tasks in T, as measured by P, improves with experience E (T. Mitchell, 1997)

A major focus of machine learning research is to automatically learn to recognize complex patterns and make intelligent decisions based on data. At a general level, there are three types of machine learning approaches: deductive, inductive, and transductive.

### 2.1.1 Deductive, Inductive and Transductive Reasoning Methods.

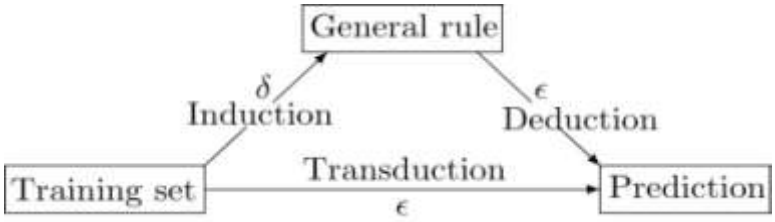
#### *2.1.1.1 Deductive Approaches*

Deductive approaches (knowledge transmission) apply established models with existing facts and knowledge to new data to deduce a prediction. Arguably deductive learning does not generate "new" knowledge at all, it simply

memorises the logical consequences of what is known already and applies this learning to new data. In this research, examples of deductive methods can be found in the existing formulas for prediction of GFR in routine clinical practice.

**Figure 2.1 The deductive, inductive and transductive approaches**

*(Gammerman & Vovk, 2007)*




### *2.1.1.2 Inductive Approaches*

In contrast to deductive learning, inductive approaches (knowledge discovery) use observed cases and generate hypotheses based on the similarities between them. Inductive learning creates computing procedures by extracting **general** rules from patterns of association, which it can then apply to test cases. It should be noted that although pattern identification is important to machine learning, without rule extraction, the process falls more accurately in the field of data mining.

The original theory of inductive inference proposed by(Solomonoff, 1964a, 1964b) in early 1960s is to predict the new data based on the observations for a series of given data. In the context of knowledge discovery, inductive reasoning approach is concerned with the construction of a function (a model) based on the observations, e.g., predicting the next event (or data) based upon a series of historical events (or data) (C. Bishop, 1995; Levey et al., 1999). Plenty of the statistical learning methods, such as: Support Vector Machine (SVM), Multi Layer Perceptron (MLP) and neural network models, have been developed and tested on inductive reasoning problems.

Inductive inference approach is widely used to build models and systems for data analysis and pattern discovery in computer and engineering science. This

approach creates the models based upon known historical data vectors and applicable to represent the entire problem space. However, the created models neglect any information about a particular new data vector. Thus, the inductive learning and inference approach is only efficient when the entire problem space (global space) is required for the solution of new data vector. Inductive models generally neglect any information related to the particular new data sample, which raises an issue that whether a global model is suitable for analyzing the new input data.

#### *2.1.1.3 Transductive Approaches*

Different from inductive learning, transductive approaches creates computing procedures by extracting **local** or **personal** rules from these patterns, which are then applied to test cases depending on the new data vector's location in the problem space. Transductive methods result in specific models for each data vector without the intermediate requirement of solving the more general problem.

Transductive inference introduced by (Vapnik, 1998) is a method that creates a model to test a specific data vector (a testing data vector) based on the observation from a specific group of data vectors (training data). The models and methods created from transductive reasoning are concentrated on a single point of the space (the new data vector), rather than the given entire problem space. Transductive inference systems emphasize the importance of the utilization of the additional information related to the new data point, which brings more relevant information to suit the analysis of the new data. Within the same given problem space, transductive inference methods may create different models specific for testing each new data vector.

In a transductive inference system illustrated in Figure 2.2, an individual model Mi is trained for every new input vector $xi$ with data use of samples Di selected from a data set $D$, and data samples $D0,i$ generated from an existing model (formula) $M$ (if such a model is existing). Data samples in both $Di$ and $D0,i$ are similar to the new vector xi according to defined similarity criteria.

**Figure 2.2 A block diagram of a transductive reasoning system.**

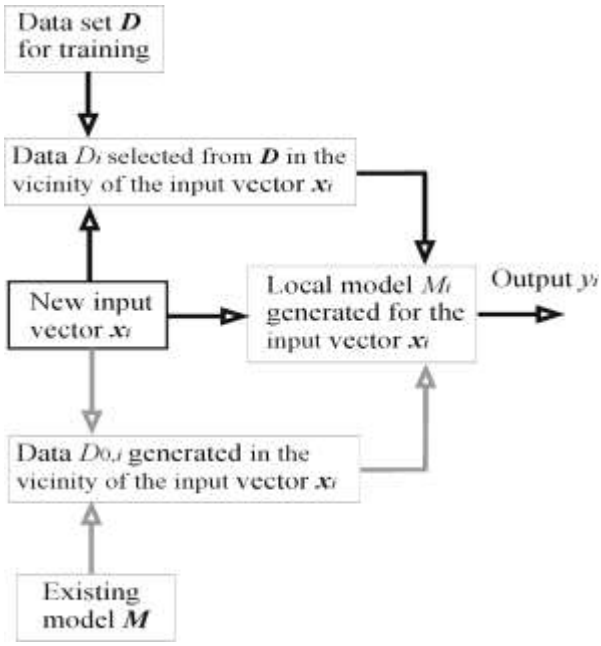
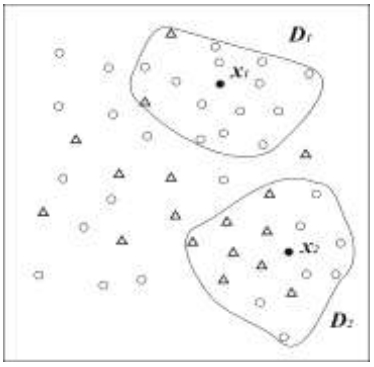



**Figure 2.3. Illustration of a transductive reasoning system.**

*In the centre of the system is the new data vector (here illustrated with two of them – x1 and x2), surrounded by a fixed number of nearest data samples selected from the training data D and generated from an existing model M.*




● – a new data vector

○ – a sample from *D*

Δ – a sample from *M*

Transductive inference is concerned with the estimation of a function in single point of the space only (Vapniak, 1998). In Figure 2.3, for every new input vector $xi$ that needs to be processed for a prognostic task, the $Ni$ nearest neighbours, which form a sub-data set $Di$, are derived from an existing data set $D$. If necessary, some similar vectors to vector $xi$ and their outputs can also be generated from an existing model M. A new model Mi is dynamically created from these samples to approximate the function in the point $xi$ - Figures 2.2 and 2.3. The system is then used to calculate the output value $yi$ for this input vector xi.

Transductive inference systems have been so far applied to a variety of classification problems, such as heart disease diagnostics (Wu, Bennett, Cristianini, & Shawe-taylor, 1999), promoter recognition in bioinformatics (N. Kasabov & Pang, 2004), microarray gene expression data classification(West et al., 2001). Other examples using transductive reasoning systems include: evaluating the predicting reliability in regression models providing additional reliability measurement for medical diagnosis (Kukar, 2002), transductive SVM for gene expression data analysis (Pang & Kasabov, 2004) and a transductive inference based radial basis function (TWRBF) method for medical decision support system and time series prediction (Song & Kasabov, 2004). Most of these experimental results have shown that transductive inference systems outperform inductive inference systems, because the former have the ability to exploit the structural information of unknown data.

Transductive inference approach seems to be more appropriate to build learning models for clinical and medical applications, where the focus is not simply on the model, but on the individual patient's condition. In the nature of complex problems, a new data vector (e.g. a patient to be clinically treated; or a future time moment for a time-series data prediction) may require an individual or a local model that best fits the new data vector, rather than a global model that does not take into account any specific information from the object data(Qun Song & Kasabov, 2006).

### 2.1.2 Supervised Learning vs. Unsupervised Learning

Supervised learning is a machine learning technique for creating a function or a model from training data. The training data consist of pairs of input objects (typically vectors), and desired outputs. The output of the function can be a continuous value (called regression), or can predict a class label of the input object (called classification). The task of the supervised learner is to predict the value of the function for any valid input object after having seen a number of training examples (i.e. pairs of input and target output). To achieve this, the learner has to generalize from the presented data to unseen situations in a "reasonable" way. The parallel task in human and animal psychology is often referred to as concept learning.

Supervised learning can generate models of two types. Most commonly, supervised learning generates a global model that maps input objects to desired outputs. In some cases, however, the map is implemented as a set of local models (such as in case-based reasoning or the nearest neighbor algorithm).

In order to solve a given problem of supervised learning, one has to consider various steps:

- Determine the type of training examples. Before doing anything else, the researchers should decide what kind of data is to be used as training data.
- Gathering a training set. The training set needs to be characteristic of the real-world use of the function. Thus, a set of input objects is gathered and corresponding outputs are also gathered, either from human experts or from measurements.
- Determine the input feature representation of the learned function. The accuracy of the learned function depends strongly on how the input object is represented. Typically, the input object is transformed into a feature vector, which contains a number of features that are descriptive of the object. The number of features should not be too large, because of the curse of dimensionality; but should be large enough to accurately predict the output.

- Determine the structure of the learned function and corresponding learning algorithm. For example, the researchers may choose to use artificial neural networks or decision trees.
- Complete the design. The researchers then run the learning algorithm on the gathered training set. Parameters of the learning algorithm may be adjusted by optimizing performance on a subset (called a validation set) of the training set, or via cross-validation. After parameter adjustment and learning, the performance of the algorithm may be measured on a test set that is separate from the training set.

In supervised learning, we are given a set of example pairs $(x,y), x \in X, y \in Y$ and the aim is to find a function $f: X \to Y$ in the allowed class of functions that matches the examples. In other words, we wish to infer the mapping implied by the data; the cost function is related to the mismatch between our mapping and the data and it implicitly contains prior knowledge about the problem domain.

A commonly used cost is the mean-squared error, which tries to minimize the average squared error between the network's output, f(x), and the target value y over all the example pairs. When one tries to minimize this cost using gradient descent for the class of neural networks called multilayer perceptrons, one obtains the common and well-known back-propagation algorithm for training neural networks.

Tasks that fall within the paradigm of supervised learning are pattern recognition (also known as classification) and regression (also known as function approximation). The supervised learning paradigm is also applicable to sequential data (e.g., for speech and gesture recognition). This can be thought of as learning with a "teacher," in the form of a function that provides continuous feedback on the quality of solutions obtained thus far.

Unsupervised learning is a method of machine learning where a model is fit to observations. It is distinguished from supervised learning by the fact that there is no a priori output. In unsupervised learning, a data set of input objects is gathered. Unsupervised learning then typically treats input objects as a set of random variables. A joint density model is then built for the data set.

In unsupervised learning, some data $x$ is given and the cost function to be minimized, that can be any function of the data $x$ and the network's output, $f$.
The cost function is dependent on the task (what we are trying to model) and our a priori assumptions (the implicit properties of our model, its parameters and the observed variables).

As a trivial example, consider the model $f(x)=a$, where $a$ is a constant and the cost $C=E[(x-f(x))^2]$. Minimizing this cost will give us a value of $a$ that is equal to the mean of the data. The cost function can be much more complicated. Its form depends on the application: for example, in compression it could be related to the mutual information between $x$ and $f(x)$, whereas in statistical modelling, it could be related to the posterior probability of the model given the data. (Note that in both of those examples those quantities would be maximized rather than minimized).

Tasks that fall within the paradigm of unsupervised learning are in general estimation problems; the applications include clustering, the estimation of statistical distributions, compression and filtering.

Unsupervised learning can be used in conjunction with Bayesian inference to produce conditional probabilities (i.e. supervised learning) for any of the random variables given the others.

Unsupervised learning is also useful for data compression: fundamentally, all data compression algorithms either explicitly or implicitly rely on a probability distribution over a set of inputs.

Another form of unsupervised learning is clustering, which is sometimes not probabilistic.

Evaluated with respect to known knowledge, an uninformed (unsupervised) method will easily be outperformed by supervised methods, while in a typical Knowledge Discovery in Databases (KDD) task, supervised methods cannot be used due to the unavailability of training data (C. M. Bishop, 2006).

## 2.2 Global, Local and Personalised Modelling: A Review

Global, local and personalised modelling are currently three main approaches for modelling and pattern discovery in machine learning area. These three types of modelling are derived from inductive and transductive inference that are the most commonly used learning techniques for building the models and systems in the area of data analysis and patter recognition (N. Kasabov, 2007).

• Global modelling builds a model from the data which covers the entire problem space. The model is represented by a single function, e.g. a regression formula, a NN of MLP (Multi-Layer Perceptron) or RBF (Radial Basis Function), Support Vector Machine (SVM), etc. The global model gives the big picture but not the individual profile. It has difficulty in adapting to new data.

• Local modelling creates a set of local models from data, each representing a sub-space (e.g. a cluster) of the whole problem space. These models can be a set of local regressions or a set of rules, etc.

• Personalised modelling uses transductive reasoning to create a model specifically for each single data point (e.g. a data vector, a patient record) within a localized problem space.

A personalised model is created “on the fly” for every new input vector and this individual model is based on the closest data samples to the new samples taken from a data set. The K-nearest neighbours (K-NN) method is one example of the personalised modelling technique. In the K-NN method, for every new sample, the nearest K samples are derived from a data set using a distance measure, usually Euclidean distance, and a voting scheme is applied to define the class label for the new sample (T. Mitchell, Keller, & Kedar-Cabelli, 1986; Vapnik, 1998).

All the three approaches are useful for complex modelling tasks and all of them provide complementary information and knowledge, learned from the data. For

each individual data vector (e.g. a patient), an individual, local model that fits the new data is needed, rather than a global model, in which the data is matched without taking into account any specific information about the new data.

### 2.2.1 Algorithms for Global Learning - Linear Least Square Estimator

The method discussed in this section, called Linear Least Square Estimator (LLSE), is used as part of learning algorithms presented later in the thesis.

For a learning data set composed of data pairs $[x_i ; y_i] = \{([x_{i1}, x_{i2}, ..., x_{iq}], y_i), i = 1, 2, ..., m\}$, which represent desired input-output pairs of the target system to be identified, yi can be defined by a set of m parameterised linear expressions:

$$\begin{cases} \beta_0 + \beta_1 x_{11} + \beta_2 x_{12} + \ldots + \beta_q x_{1q} = y_1, \\ \beta_0 + \beta_1 x_{21} + \beta_2 x_{22} + \ldots + \beta_q x_{2q} = y_2, \\ \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \\ \beta_0 + \beta_1 x_{m1} + \beta_2 x_{m2} + \ldots + \beta_q x_{mq} = y_m, \end{cases} \tag{2.1}$$

where $x_{ij}$'s, $i = 1, 2, ..., m; j = 1, 2, ..., q,$ are elements of input and $\beta_j$'s, $j = 0, 1, 2, ..., q,$ are unknown parameters to be estimated. In statistics, the task of fitting data using a linear model is referred as a *linear regression problem*. Thus equation set (2.1) is called the *regression function set*, and $\beta_i$'s are called the *regression coefficients*.

Using matrix notation, the preceding equation is set in a concise form:

$$\mathbf{A}\,\boldsymbol{\beta} = \boldsymbol{y}, \tag{2.2}$$

where **A** is a $m \times (q + 1)$ matrix:

$$\mathbf{A} = \begin{bmatrix} 1 & x_{11} & x_{12} & \dots & x_{1q} \\ 1 & x_{21} & x_{22} & \dots & x_{2q} \\ . & . & . & . & . \\ . & . & . & . & . \\ . & . & . & . & . \\ 1 & x_{m1} & x_{m2} & \dots & x_{mq} \end{bmatrix} \quad (2.3)$$

$\boldsymbol{\beta}$ is a $(q + 1) \times 1$ unknown parameter vector:

$$\boldsymbol{\beta} = [\beta_0, \beta_1, \beta_2, \dots, \beta_q]^T, \quad (2.4)$$

and $\boldsymbol{y}$ is a $m \times 1$ output vector:

$$\boldsymbol{y} = [y_1, y_2, \dots, y_m]^T. \quad (2.5)$$

The $i$-th row of the joint data matrix [$\mathbf{A}$; $\boldsymbol{y}$], denoted by [$\mathbf{a}_i$ ; $y_i$], is related to the $i$-th input-output data pair ([$x_{i1}$, $x_{i2}$, …, $x_{iq}$], $y_i$), through

$$\mathbf{a}_i = [1, x_{i1}, x_{i2}, \dots, x_{iq}]. \quad (2.6)$$

Sometimes [$\mathbf{a}_i$ ; $y_i$] is referred as the $i$-th data pair of the learning data set.
Usually, there are more data pairs than the fitting parameters, i.e., $m$ is greater than $q + 1$. To obtain uniquely the unknown vector $\boldsymbol{\beta}$, Equation (2.7) is modified by incorporating an *error vector* $\boldsymbol{e}$ to account for random noise or identifying error as follows:

$$\mathbf{A}\,\boldsymbol{\beta} + \boldsymbol{e} = \boldsymbol{y}. \quad (2.7)$$

Now, instead of finding $\boldsymbol{\beta}$ as the exact solution to Equation (2.7), a vector $\boldsymbol{\beta} = \boldsymbol{b}$ which minimises the *sum of squared error* is defined by

$$E(\boldsymbol{\beta}) = \sum^{m} (y_i - \mathbf{a}_i\,\boldsymbol{\beta})^2 = \boldsymbol{e}^T\boldsymbol{e} = (\boldsymbol{y} - \mathbf{A}\,\boldsymbol{\beta})^T(\boldsymbol{y} - \mathbf{A}\,\boldsymbol{\beta}), \quad (2.8)$$

where $\boldsymbol{e} = \boldsymbol{y} - \mathbf{A}\,\boldsymbol{\beta}$ is the error vector produced by a specific choice of $\boldsymbol{\beta}$. (2.9)
The theorem of least square estimator is given in(Draper & Smith, 1981; Hsia, 1977; Kalman, 1960):

The square error in Equation (2.8) is minimised when $\boldsymbol{\beta} = \boldsymbol{b}$, called the Least Square Estimator (LSE), which satisfies the normal equation

$$\mathbf{A}^T\mathbf{A}\,\boldsymbol{b} = \mathbf{A}^T\boldsymbol{y}. \tag{2.10}$$

If $\mathbf{A}^T\mathbf{A}$ is nonsingular, $\boldsymbol{b}$ is unique and is given by

$$\boldsymbol{b} = (\mathbf{A}^T\mathbf{A})^{-1}\,\mathbf{A}^T\boldsymbol{y}. \tag{2.11}$$

### 2.2.2 Fuzzy Logic Systems

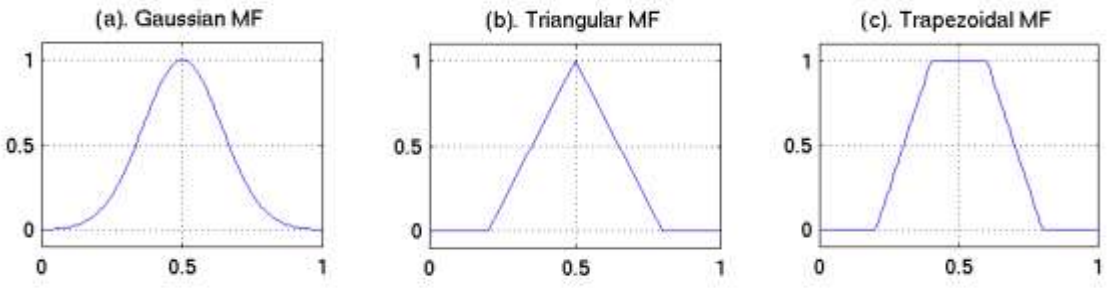
Why do we need fuzzy logic in this research?

Fuzzy logic is one way to represent human-like knowledge in linguistically interpretable concepts and rules. Knowledge representation, in its different forms of global-, local- and personalised-, is one of the goals of this study in relation to renal DSSs (Kaufmann & Gupta, 1985; Kawahara & Saito, 1996; L.A. Zadeh, 1973; H. J. Zimmermann, 1985).

#### *2.2.2.1 Fuzzy Sets and Membership Functions*

If X denotes a universal set, a fuzzy set A is defined by a membership function $\mu_A$: X $\rightarrow$ [0, 1] which describes the membership degree of the elements of A. Larger values denote higher membership degrees.
Some widely used membership functions are shown in Figure 2.4

**Figure 2.4 Examples of fuzzy membership functions**



- **Gaussian membership function**

  The Gaussian membership function depends on two parameters $\sigma$ and $c$, given by

$$\mu(x) = \exp\left(\frac{-(x-c)^2}{\sigma}\right). \qquad (2.12)$$

- **Triangular membership function**

  Triangular membership function depends on three parameters, $a$; $b$; $c$, given by

$$\mu(x) = f(x; a, b, c) = \begin{cases} 0, & x \le a \\ \frac{x-a}{b-a}, & a \le x \le b \\ \frac{c-x}{c-b}, & b \le x \le c \\ 0. & c \le x \end{cases} \qquad (2.13)$$

  The parameters $a$ and $c$ locate the "feet" of the trapezoid and the parameters $b$ and $c$ locate the "shoulders".

- **Trapezoidal membership function**

$$\mu(x) = f(x; a, b, c) = \begin{cases} 0, & x < a \text{ and } x > d \\ (x - a) / (b - a) & a <= x <= b \\ 1 & b <= x <= c \\ (d - x) / (d - c) & c <= x <= d \end{cases} \qquad (2.14)$$

### *2.2.2.2 Operations on Fuzzy Sets*

The operations between two fuzzy sets are actually the degree's operators to each point (Dubois & Prade, 1980; L.A. Zadeh, 1973; L.A. Zadeh, 1988; H. J. Zimmermann, 1985). Let $\mu_A$ and $\mu_B$ be two membership functions that define two fuzzy sets, A and B respectively. There are four fuzzy operations given as follows(Kaufmann & Gupta, 1985; Kawahara & Saito, 1996):

- Subset

  A is contained in B or A is a subset of B, denoted by

  $$A \subseteq B, \text{ if } \mu_A(x) \leq \mu_B(x), \qquad \forall x \in X;$$

  or

  $$A \subset B, \text{ if } \mu_A(x) < \mu_B(x), \qquad \forall x \in X.$$

- Complement, Negation

  The membership function $\mu_{\bar{A}}(x)$ of the complement of A (denoted by $\bar{A}$ ) is defined by:

  $$\mu_{\bar{A}}(x) = 1 - \mu_A(x), \quad \forall x \in X. \tag{2.15}$$

  The relative complement of A with respect to B is defined by:

  $$\mu_{\bar{A}B}(x) = \mu_B(x) - \mu_A(x), \qquad \forall x \in X \quad \text{if } \mu_B(x) > \mu_A(x). \tag{2.16}$$

- Intersection

  The intersection of A and B is defined by:

  $$A \cap B = \{x | x \in A \wedge x \in B\}; \qquad \forall x \in X. \tag{2.17}$$

  Extreme operator: $\mu_{A \cap_1 B}(x) = \mu_A(x) \wedge \mu_B(x) = \min\{\mu_A(x), \mu_B(x)\}; \quad \forall x \in X.$

  Product operator: $\mu_{A \cap_2 B}(x) = \mu_A(x)\, \mu_B(x); \qquad \forall x \in X.$

- Union

  The union of A and B is defined by:

  $$A \cup B = \{x | x \in A \vee x \in B\}. \qquad \forall x \in X.$$

  Extreme operator: $\mu_{A \cup_1 B}(x) = \mu_A(x) \vee \mu_B(x) = \max\{\mu_A(x), \mu_B(x)\}; \quad \forall x \in X.$

  Sum operator: $\mu_{A \cup_2 B}(x) = \mu_A(x) + \mu_B(x) - \mu_A(x)\, \mu_B(x); \qquad \forall x \in X.$

#### *2.2.2.3 Fuzzy Relations*

A relation represents the presence or absence of association, interaction or interconnection between the elements of two or more sets. A fuzzy relation R(x, y) is a fuzzy subset of X × Y (Kaufmann & Gupta, 1985; Kawahara & Saito, 1996; L.A. Zadeh, 1988).

For membership function μ(x, y)

$$R = \{\mu(x, y): X \times Y \rightarrow [0, 1]\} \quad (2.22)$$

or

$$R = \{(x, y), \mu_R(x, y)\} = \cup (x, y)\, \mu_R(x, y). \quad (2.23)$$

A fuzzy relation $R(x_1, x_2, \ldots, x_n)$ on sets $X_1, X_2, \ldots, X_n$, is a fuzzy subset of $X_1 \times X_2 \times \ldots \times X_n$.

$$R = \{\mu(x_1, x_2, \ldots, x_n): X_1 \times X_2 \times \ldots \times X_n \rightarrow [0, 1]\}. \quad (2.24)$$

or

$$R = \cup\{ (x_1, x_2, \ldots, x_n)\, \mu_R(x_1, x_2, \ldots, x_n)\}: X_1 \times X_2 \times \ldots \times X_n \rightarrow [0, 1].$$

A composition relation of fuzzy relations R(x, y) and S(y, z) is a relation C(x, z) obtained after applying relations R and S one after another.
Given:

$$R(x, y), \quad (x, y) \in X \times Y, \quad R: X \times Y \rightarrow [0, 1],$$

$$S(y, z), \quad (y, z) \in Y \times Z, \quad S: Y \times Z \rightarrow [0, 1],$$

Composition C(x, z)

- Max min composition:

  $\mu_c(x, z) = \max\{\min(\mu_R(x, y), \mu_s(y, z))\}; \quad x \in X, y \in Y, z \in Z.$ (2.26)

- Max product composition:

  $\mu_c(x, z) = \max\{\mu_R(x, y) \cdot \mu_s(y, z)\}; \quad x \in X, y \in Y, z \in Z.$ (2.27)

#### *2.2.2.4 Fuzzy If-Then Rules*

A fuzzy if-then rule assumes the form

if x is A then y is B,

where A and B are linguistic values defined by fuzzy sets on universes of discourse X and Y respectively. Usually, “x is A” is called an antecedent or a premise, while “y is B” is called a consequence or a conclusion.

A linguistic variable is defined by Lotfi Zadeh as follows: “By a linguistic variable we mean a variable whose values are words or sentences in a natural or artificial language. For example, ‘Age’ is a linguistic variable if its values are linguistic rather than numerical, i.e. young, not young, very young, quite young, old, not very old and not very young, etc, rather than 20, 21, 22, …” (L.A. Zadeh, 1973).

Several types of fuzzy rules have been used so far (N. Kasabov & Woodford, 1999). Different fuzzy rules will result in different fuzzy inference systems. There are several kinds of fuzzy rules including:

- **Zadeh-Mamdani fuzzy rules:**

  A generalised form of Zadeh-Mamdani fuzzy rules(L.A. Zadeh, 1988) is:

  if $x_1$ is $A_1$ and $x_2$ is $A_2$ and … and $x_n$ is $A_n$, then y is B,
  where “$x_1$ is $A_1$”, “$x_2$ is $A_2$”, … , “$x_n$ is $A_n$” are $n$ fuzzy propositions as the antecedent of the fuzzy rule; $x_i$, $i$ = 1, 2, …, $n$, and y is a fuzzy variable defined over universes of discourse $X_i$, $i$ = 1, 2, …, $n$, and Y respectively; and $A_i$, $i$ = 1, 2, …, $n$, and B are fuzzy sets defined by their fuzzy membership functions $\mu_{Ai}$: $X_i \rightarrow [0, 1]$, $i$ = 1, 2, …, $n$, and $\mu_B$: $Y \rightarrow [0, 1]$.

- Fuzzy rules with confidence degrees (N. Kasabov & Woodford, 1999) :
  Apart from the simple form of Zadeh-Mamdani fuzzy rules mentioned above, fuzzy rules having coefficients of uncertainty have often been used in practice. A fuzzy rule that contains a confidence factor of the validity of the consequence has the form of:

  if x is A then y is B (with a CF).

- **Takagi-Sugeno fuzzy rules:**

  This kind of fuzzy rules was introduced by Takagi and Sugeno in 1985 (Tuck, Song, Kasabov, & Watts, 1999). In the consequent part, a crisp function is used. A generalised form of Takagi-Sugeno fuzzy rules is:

  if $x_1$ is $A_1$ and $x_2$ is $A_2$ and … and $x_n$ is $A_n$, then y is $f(x_1, x_1, …, x_n)$.

if $f(x_1, x_1, \ldots, x_n)$ is C which is a crisp constant, it is called a zero order Takagi-Sugeno fuzzy rule; if function $f(x_1, x_1, \ldots, x_n)$ is linear, the rule is called a first order Takagi-Sugeno fuzzy rule; and, such rule is called a high-order Takagi-Sugeno fuzzy rule if the non-linear function is taken in this rule.

- Generalised fuzzy production rules (N. Kasabov & Woodford, 1999):

These kinds of rules can be seen as weighted rules, where each of the rules contributes to a certain degree to the final decision. Very often the fuzzy propositions in the antecedent part of the rule are not equally important for the rule to infer an output value. A generalised fuzzy production rule with degrees of importance ($DI_i$) of the fuzzy propositions in the antecedent part and certainty factors (CF) of the validity of the consequent part has the form of:

if $x_1$ is $A_1$ ($DI_1$) and $x_2$ is $A_2$ ($DI_2$) and … and $x_n$ is $A_n$, ($DI_n$), then y is B (CF).

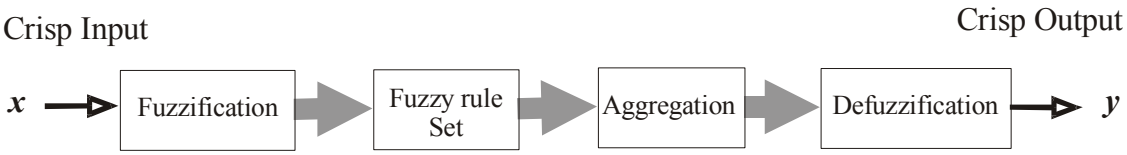
#### *2.2.2.5 Fuzzy Inference Systems*

The Figure 2.5 shows a block diagram of a basic fuzzy inference system, which is composed of four functional parts:

- Fuzzification
  Fuzzification is a process of finding the membership degrees to which input data belong to the fuzzy sets in the antecedent part of a fuzzy rule.
- Fuzzy rule set
  This set contains a number of 'if-then' fuzzy rules.
- Aggregation
  Aggregation performs a fuzzy reasoning operation by aggregating the fuzzy values within the rules with connective operations.
- Defuzzification

Defuzzification is a process of calculating a single-output numerical value to a fuzzy output variable on the basis of the inferred resulting membership function for this variable.

**Figure 2.5 A block diagram of a fuzzy inference system**

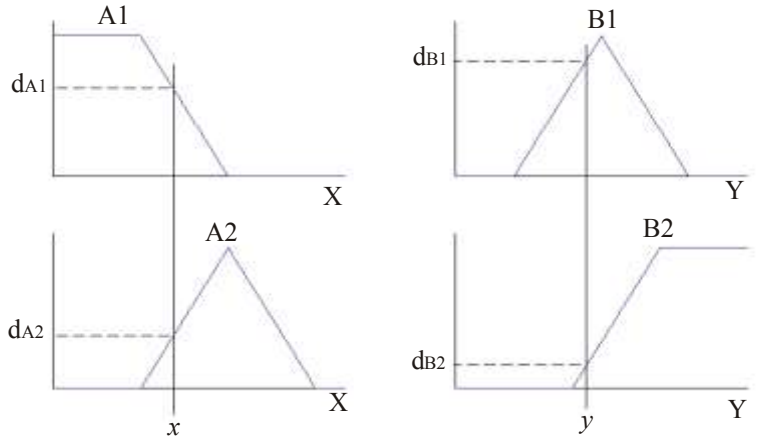



There are several types of fuzzy inference systems, which have been used in various areas. The differences among them lie with the types of fuzzy inferences and the fuzzy if-then rules employed. Two most popular types of fuzzy inference are described as follows:

- **Mamdani inference engine** (H. J. Zimmermann, 1985, 1987)

  Zadeh-Mamdni fuzzy rules are used. The overall fuzzy output is derived by applying the union operation to the qualified fuzzy outputs (each of which is equal to the minimum of firing strength and the output membership function of each rule). This relational type inference engine feature linguistic premises and consequences.

**Figure 2.6 The Takagi-Sugeno fuzzy inference**




$z_1 = f_1(x, y)$

$w_1 = d_{A1} * d_{B1}$

$z_2 = f_2(x, y)$

$w_2 = d_{A2} * d_{B2}$

Rule 1: IF $x$ is A1 and $y$ is B1 THEN $z_1$ is $f_1(x, y)$

Rule 2: IF $x$ is A2 and $y$ is B2 THEN $z_2$ is $f_2(x, y)$

$$z = \frac{w_1 * z_1 + w_2 * z_2}{w_1 + w_2}$$

- **Takagi-Sugeno inference engine** (Uchino, Yamakawa, Miki, & Nakamura, 1992)

  Takagi-Sugeno fuzzy rules are used. The output of each rule is a function of input variables, and the final output is the weighted average of each rule's output. This type inference engine uses a crisp function in the consequences, in contrast to relational type inference engine.

Figure 2.6 shows a Takagi-Sugeno fuzzy inference engine using two rules with two inputs.

#### *2.2.2.6 Input Space Partitioning*

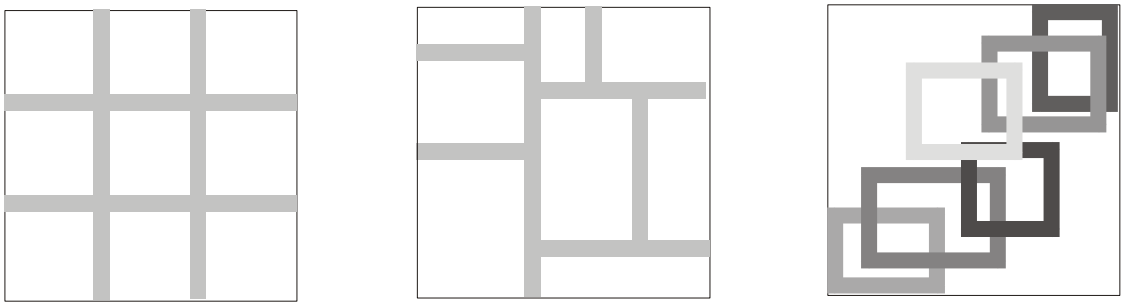
It is known from the preceding sections that different fuzzy inference systems have nearly the same antecedents in their fuzzy rules though their consequent constituents are different. There are three major methods of input space partitioning described as follows and they are suitable for all types of fuzzy inference systems mentioned in preceding section.

- Grid partitioning (shown in Figure 2.7 (a))

  This method is easy to use and usually is chosen for a fuzzy controller, and in some cases, it can be taken as an initial state of partition for some adaptive partitioning methods. Because the number of rules increases exponentially with the number of inputs, if the tasks have comparative large number of inputs, "the curse of dimensionality" will occur.

**Figure 2.7 Three methods of input space partitioning**

*(a) grid partition; (b) tree partition; (c) scatter partition.*



( a ) ( b ) ( c )

- Tree partitioning (shown in Figure 2.7 (b))
  The tree partition can alleviate the problem mentioned above to some extent. In this partition method each region can be uniquely specified along a corresponding decision tree. Usually, it is difficult to express linguistic meanings for the membership functions.
- Scatter partitioning (shown in Figure 2.7 (c))
  The scatter partition has relatively small number of membership functions covering a subset of the input space that characterises a region of possible occurrence of the input vectors. The scatter partition is usually dictated by desired input-output data pairs and generally, orthogonality does not hold (N. Kasabov, 1996). Scatter partitioning is used in DENFIS.

### 2.2.3 Multi-Layer Perceptron Neural Network with Back- Propagation Algorithm

This class of neural networks consists of multiple layers of computational units, usually interconnected in a feed-forward way. Each neuron in one layer has directed connections to the neurons of the subsequent layer. In many applications the units of these networks apply a sigmoid function as an activation function.

The universal approximation theorem for neural networks states that every continuous function that maps intervals of real numbers to some output interval of real numbers can be approximated arbitrarily closely by a multi-layer perceptron with just one hidden layer.

Multi-layer networks use a variety of learning techniques, back-propagation being the most popular. Here the output values are compared with the correct answer to compute the value of some predefined error-function. By various techniques the error is then fed back through the network. Using this information, the algorithm adjusts the weights of each connection in order to reduce the value of the error function by some small amount. After repeating this process for a sufficiently large number of training cycles the network will

usually converge to some state where the error of the calculations is small. In this case one says that the network has learned a certain target function. To adjust weights properly one applies a general method for non-linear optimization task that is called gradient descent. For this, the derivative of the error function with respect to the network weights is calculated and the weights are then changed such that the error decreases (thus going downhill on the surface of the error function). For this reason back-propagation can only be applied on networks with differentiable activation functions.

In general the problem of teaching a network to perform well, even on samples that were not used as training samples, is a quite subtle issue that requires additional techniques. This is especially important for cases where only very limited numbers of training samples are available (Balabin, Safieva, & Lomakina, 2007). The danger is that the network overfits the training data and fails to capture the true statistical process generating the data. Computational learning theory is concerned with training classifiers on a limited amount of data. In the context of neural networks a simple heuristic, called early stopping, often ensures that the network will generalize well to examples not in the training set.

Other typical problems of the back-propagation algorithm are the speed of convergence and the possibility of ending up in a local minimum of the error function. Today there are practical solutions that make back-propagation in multi-layer perceptrons the solution of choice for many machine learning tasks.

#### *2.2.3.1 Artificial Neurons and Activation Functions*

An artificial neural network (ANN), usually simply called a neural network (NN) (Amari & Kasabov, 1998; C. Bishop, 1995; Mackey & Glass, 1977) is a biologically inspired computational model. It consists of processing elements called neurons, and connections between them with coefficients, or weights, which constitute the neuronal structure, and training and recall algorithms attached to the structure (N. Kasabov, 1996; Minsky & Papert, 1969; Rumelhart, Hinton, & Williams, 1986; Saad, 1999). The neurons are created

based on the model of a real neuron. This simple neural model can be seen in Figure 2.8 and expressed in the following form:

$$o = f\left(\sum_{i=1}^{n} w_i x_i\right) \tag{2.28}$$

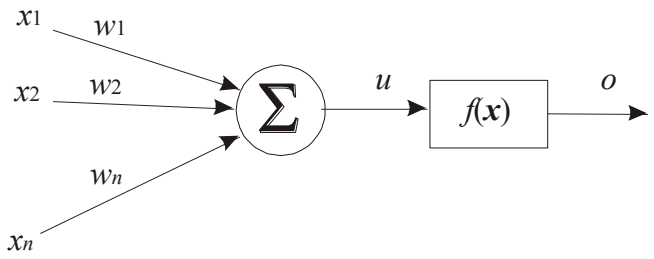
where $f(\bullet)$ is the activation function, $x_i$ are the inputs and $w_i$ are the weights of the neuron.

Some common activation functions are given as follows:

- Linear function (Figure 2.9 (a)):

$$o = u \tag{2.29}$$

**Figure 2.8 A model of an artificial neuron**




- Saturated function (Figure 2.9 (b)):

$$o = \begin{cases} +1 & \text{if } u > 1 \\ u & \text{if } u \in [-1, 1] \\ -1 & \text{if } u < -1 \end{cases} \tag{2.30}$$

- Sigmoid function (Figure 2.9 (c)):

$$o = \frac{1}{1 + \exp(-u)} \tag{2.31}$$

- Hyperbolic tangent function (Figure 2.9 (d)):

$$o = \frac{\exp(u) - \exp(-u)}{\exp(u) + \exp(-u)} \tag{2.32}$$

- Gaussian (bell shape) function (Figure 2.9 (e)):

$$o = \exp\left[\frac{-(u-c)^2}{\sigma}\right] \qquad (2.33)$$

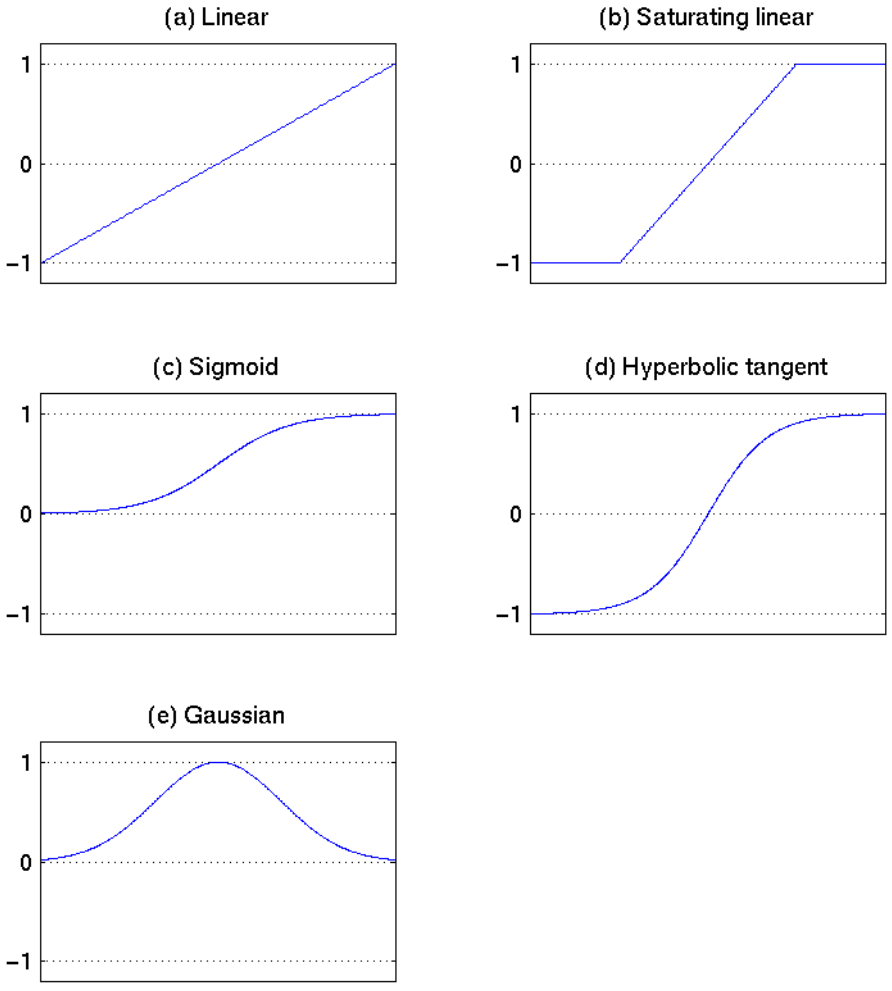



**Figure 2.9 Five common activation functions of a neuron**

### *2.2.3.2 Error Back-Propagation Learning in Neural Networks*

Several kinds of ANNs have been used to solve various problems (N. Kasabov, 1996; N. Kasabov & Woodford, 1999). The multi-layer perceptron trained with back-propagation algorithm (MLP-BP) is one of the most common models (Mitra & Pal, 1995; Rumelhart et al., 1986; Saad, 1999). The Figure 2.10 shows a structure of a multi-layer perceptron with two hidden layers. Two basic signal flows, i.e. function signal flow and error signal flow, in a multi-layer perceptron are shown in Figure 2.11.

**Figure 2.10 A structure of a multi-layer perceptron NN with two hidden layers**

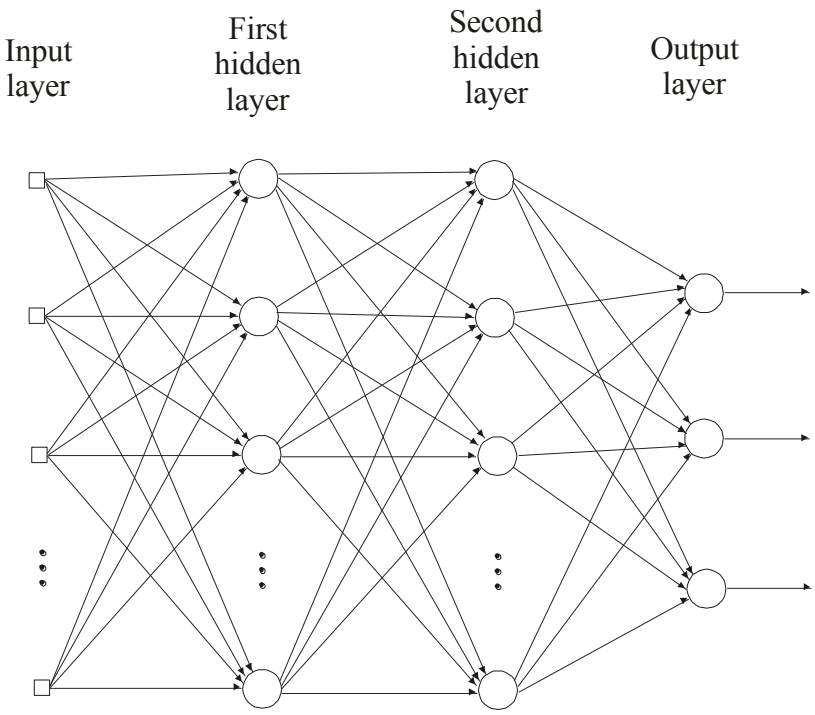


**Figure 2.11 Two basic signal flows in a multi-layer perceptron**

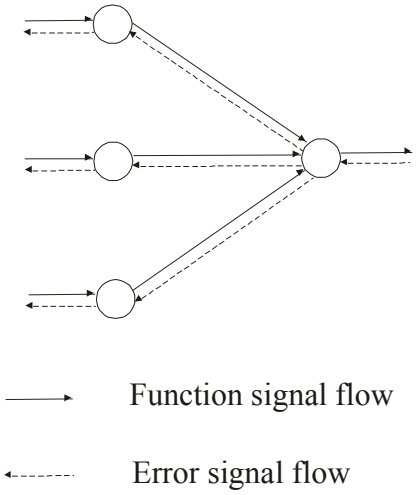
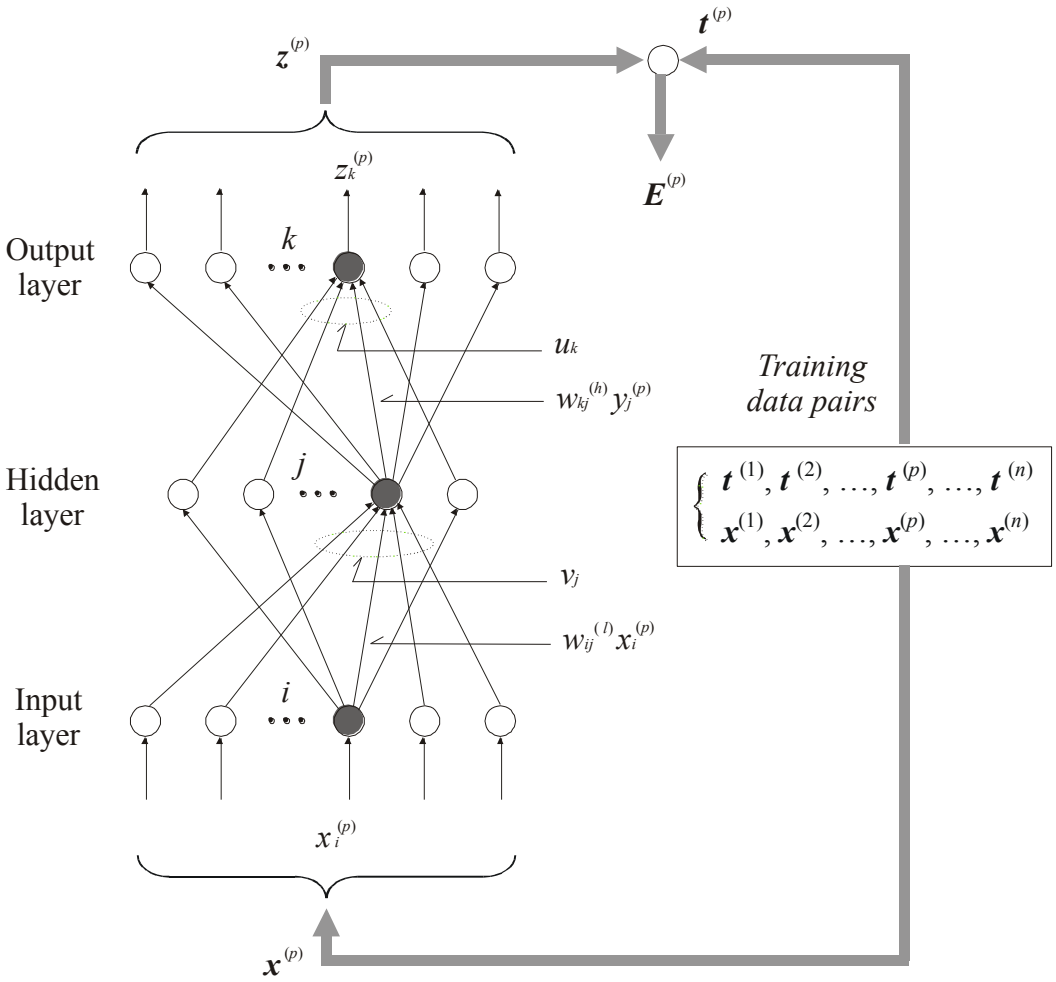



**Figure 2.12 A three-layer back-propagation neural network**



A typical back-propagation training algorithm employed in a three-layer perceptron is described as follows (Figure 2.12):

Here, $\boldsymbol{x}^{(p)}$ and $\boldsymbol{t}^{(p)}$ denote the $p$-th training data pair; $\boldsymbol{z}^{(p)}$ denotes the actual output of the network; $w_{ji}^{(l)}$ denotes the weight from neuron $i$ to neuron $j$, and $w_{kj}^{(h)}$ denotes the weight from neuron $j$ to neuron $k$. A sigmoid transfer function (Equation 2.31) is taken as the activation function in the neurons of hidden layer and output layer. The goal of training is to get the minimum value of error $E$:

$$E = \sum_{p=1}^{p} E^{(p)} = \sum_{p=1}^{p} \{ \sum_{k=1}^{m} ( t_k^{(p)} - z_k^{(p)} )^2 / 2 \}. \qquad (2.34)$$

- step 1: initiation

  Set the maximum error $e_{max}$; the maximum number of training epochs $eps_{max}$; the current number of training epochs $Eps = 0$; the learning rate $\varepsilon$; and the initial values of the weights.

- step 2: input

  Select one data pair [$\boldsymbol{x}^{(p)}$, $\boldsymbol{t}^{(p)}$] from the training data set as current input and desired output, and set $Eps = Eps + 1$.

- step 3: forward calculation

  Calculate $\boldsymbol{y}^{(p)}$ and $\boldsymbol{z}^{(p)}$, outputs of the hidden layer and output layer

$$\begin{cases} y_j^{(p)} = f(v_j) = 1 / (1 + \exp(-v_j)) \\ z_k^{(p)} = f(u_i) = 1 / (1 + \exp(-u_i)) \end{cases} \qquad (2.35)$$

  where

$$\begin{cases} v_j = \sum_i w_{ji}^{(l)} x_i^{(p)} \\ u_k = \sum_j w_{kj}^{(h)} y_j^{(p)} \end{cases} \qquad (2.36)$$

- step 4: backward calculation (1)

Update the weights $w^{(h)}$ between hidden layer and output layer

$$\begin{cases} \delta_k^{(h)} = (t_k^{(p)} - z_k^{(p)}) z_k^{(p)} (1 - z_k^{(p)}) \\ \Delta w_{kj}^{(h)} = \varepsilon \delta_k^{(h)} y_j^{(p)} \\ w_{kj}^{(h)} \leftarrow w_{kj}^{(h)} + \Delta w_{kj}^{(h)} \end{cases} \qquad (2.37)$$

- step 5: backward calculation (2)

  Update the weights $\boldsymbol{w}^{(l)}$ between the hidden later and input later using the updated $\boldsymbol{w}^{(h)}$

$$\begin{cases} \delta_j^{(l)} = \left( \sum_k \delta_k^{(h)} w_{kj}^{(h)} \right) y_j^{(p)} \left(1 - y_j^{(p)}\right) \\ \Delta w_{ji}^{(l)} = \varepsilon \delta_j^{(l)} x_i^{(p)} \\ w_{ji}^{(l)} \leftarrow w_{ji}^{(l)} + \Delta w_{ji}^{(l)} \end{cases} \tag{2.38}$$

  if there are more hidden layers, the step 5 will be repeated to calculate the weights.

- step 6: terminal decision

  The training session is terminated if $E < e_{max}$ or , $Eps > eps_{\max}$, and otherwise, a new training epoch is initiated by going to step2.

The derivation, which leads to the preceding algorithm, is described in the next lines:

To decrease the error $E^{(p)}$ (Equation 2.34), it is necessary to adjust $\boldsymbol{w}^{(h)}$ and $\boldsymbol{w}^{(l)}$ and the *steepest descent method* is used for this. In order to obtain the increasing value of weights $\boldsymbol{w}$ :

$$\Delta w_{kj}^{(h)} = \varepsilon \frac{\partial E^{(p)}}{\partial w_{kj}^{(h)}} \tag{2.39}$$

and

$$\Delta w_{ji}^{(l)} = \varepsilon \frac{\partial E^{(p)}}{\partial w_{ji}^{(l)}} \tag{2.40}$$

From Equation 2.35, then

$$-\frac{\partial E^{(p)}}{\partial w_{kj}^{(h)}} = -\frac{\partial E^{(p)}}{\partial u_k} \frac{\partial u_k}{\partial w_{kj}^{(h)}} \tag{2.41}$$

$$-\frac{\partial E^{(p)}}{\partial u_k} = -\frac{\partial E^{(p)}}{\partial z_k^{(p)}}\frac{\partial z_k^{(p)}}{\partial u_k} \qquad (2.42)$$

$$= (t_k^{(p)} - z_k^{(p)})\, f'(u_k)$$
$$= (t_k^{(p)} - z_k^{(p)})\, z_k^{(p)} (1 - z_k^{(p)}) = \delta_k{}^{(h)}.$$

Form Equation 2.39, 2.40, and 2.41, then

$$\frac{\partial u_k}{\partial w_{kj}^{(h)}} = y_j^{(p)} \qquad (2.43)$$

the next equation can be obtained as:

$$\Delta w_{kj}^{(h)} = \varepsilon\, \delta_k{}^{(h)}\, y_j^{(p)} = \varepsilon\, (t_k^{(p)} - z_k^{(p)})\, z_k^{(p)} (1 - z_k^{(p)})\, y_j^{(p)}. \qquad (2.44)$$

The output of the neurons in the hidden layer can be expressed as Equation 2.35:

$$v_j = \sum_i w_{ji}^{(l)}\, x_i^{(p)}$$
$$y_j^{(p)} = f(v_j)$$

in this case

$$-\frac{\partial E^{(p)}}{\partial w_{ji}^{(l)}} = -\frac{\partial E^{(p)}}{\partial v_j}\frac{\partial v_j}{\partial w_{ji}^{(l)}} = \delta_j{}^{(l)}\, x_i^{(p)} \qquad (2.45)$$

$$\delta_j{}^{(l)} = -\frac{\partial E^{(p)}}{\partial v_j} = -\frac{\partial E^{(p)}}{\partial y_j^{(p)}}\frac{\partial y_j^{(p)}}{\partial v_j} = -\frac{\partial E^{(p)}}{\partial y_j^{(p)}}\, y_j^{(p)} (1 - y_j^{(p)})$$

$$\frac{\partial E^{(p)}}{\partial y_j^{(p)}} = \sum_k \frac{\partial E^{(p)}}{\partial u_k} \frac{\partial u_k}{\partial y_j^{(p)}} = -\sum_k \delta_k{}^{(h)} w_{kj}^{(h)}$$

so

$$\delta_j{}^{(l)} = \left( \sum_k \delta_k{}^{(h)} w_{kj}^{(h)} \right) y_j^{(p)} (1 - y_j^{(p)}) \qquad (2.46)$$

From Equation 2.40, 2.45 and 2.46, then

$$\Delta w_{ji}^{(l)} = \varepsilon \delta_j{}^{(l)} x_i^{(p)} = \varepsilon \left( \sum_k \delta_k{}^{(h)} w_{kj}^{(h)} \right) y_j^{(p)} (1 - y_j^{(p)}) x_i^{(p)} \qquad (2.47)$$

### 2.2.4 Neuro-fuzzy Networks

A neuro-fuzzy network is a fuzzy inference system (FIS) in the body of an artificial neural network. Depending on the FIS type, there are several layers that simulate the processes involved in a fuzzy inference like fuzzification, inference, aggregation and defuzzification. Embedding an FIS in a general structure of an ANN has the benefit of using available ANN training methods to find the parameters of a fuzzy system.

## 2.3 Summary

This chapter reviews some classic algorithms for global and local learning. Main neural fuzzy inference techniques are presented in details. They are the basic functions for both local and personalised modelling developed in this thesis.

In ***Chapter 3***, novel algorithms and techniques of evolving connectionist systems will be presented, with particular emphasis on local and personalised modelling frameworks.

# Chapter 3 : Evolving Connectionist Systems (ECOS)

In ***Chapter 2***, conventional algorithms and techniques of machine learning were reviews, with particular emphasis on classic algorithms for global and local learning and neural fuzzy inference.

In this chapter, novel algorithms and techniques called ECOS are reviewed, with particular emphasis on local and personalised modelling frameworks. These generic techniques are further developed as specific methods applied on renal data.

## 3.1 Introduction

The complexity, uncertainty and the dynamics of real-world problems, such as adaptive speech recognition and language acquisition (Furlanello, Giuliani, & Trentin, 1995; N. Kasabov, 1998b; N. Kasabov et al., 1999), adaptive intelligent prediction and control systems (Albus, 1975), intelligent agent-based systems and adaptive agents on the Web(Woldrige & Jennings, 1995), mobile robots(Fukuda, Komata, & Arakawa, 1997), visual monitoring systems and multi-modal information processing(N. Kasabov, 1998a; Massaro & Cohen, 1983), large Bio-informatics data processing, and many more(Amari & Kasabov, 1998; Arbib, 1995), require sophisticated methods and tools for building on-line, adaptive, knowledge-based intelligent systems (IS). Such systems should be able to: (1) learn fast from a large amount of data (using fast training); (2) adapt incrementally in an on-line mode; (3) dynamically create new modules – have open structure; (4) memorise information that can be used at a later stage; (5) interact continuously with the environment in a “life-long” learning mode; (6) deal with knowledge (e.g. rules), as well as with data; (7) adequately represent space and time(Amari & Kasabov, 1998; Blanzieri & Katenkamp, 1996; N. Kasabov, 1996; N. Kasabov, 1998; N. Kasabov, 1998a; Platt, 1991; Schaal & Atkeson, 1998)

**Evolving connectionist systems (ECOS)** are multi-modular connectionist architectures that facilitate modelling of evolving processes and knowledge discovery. Each evolving connectionist system contains of four main parts: 1. Data acquisition; 2. Pre-processing and feature evaluation; 3. Connectionist modelling; 4. Knowledge acquisition (N. Kasabov, 2003). Comparing with other AI systems, ECOS have advantage as: fast learning from a large amount of data, real-time incremental adaptation to new data, continuous improving, and the ability to analyze and explain themselves through rule extraction. All these strengths enable them to be promising for their application in health Informatics and medical IDSS.

## 3.2 Methods and Techniques

### 3.2.1 Local Learning in ECOS

Evolving connectionist systems (ECOS) are modular connectionist-based systems that evolve their structure and functionality in a continuous, self-organised, on-line, adaptive, interactive way from incoming information; they can process both data and knowledge in a supervised and/or unsupervised way(N. Kasabov, 2001).

ECOS learn local models from data through clustering of the data and associating a local output function for each cluster. Clusters of data are created based on similarity between data samples either in the input space (this is the case in some of the ECOS models, e.g. the Dynamic Neuro-fuzzy Inference System (DENFIS)(N. Kasabov & Song, 2002), or in both the input space and the output space (this is the case in the EFuNN models)(N. Kasabov, 2001). Samples that have a distance to an existing cluster centre (rule node) N of less than a threshold Rmax (for the EfuNN models it is also needed that the output vectors of these samples are different from the output value of this cluster centre in not more than an error tolerance E) are allocated to the same cluster *Nc*. Samples that do not fit into existing clusters, form new clusters as they arrive in time. Cluster centres are continuously adjusted according to new data samples, and new clusters are created incrementally.

The similarity between a sample $S = (\boldsymbol{x,y})$ and an existing rule node $N = (W_1,W_2)$ can be measured in different ways, the most popular of them being the normalized Euclidean distance:

$$d(S,N) = [\Sigma_{(i=1,..,n)} \ (x_i - W_1(i))^2 \ ] /n \qquad (3.1)$$

where n is the number of the input variables.

ECOS learn from data and automatically create a local output function for each cluster, the function being represented in the $W_2$ connection weights, thus creating local models. Each model is represented as a local rule with an antecedent – the cluster area, and a consequent – the output function applied to data in this cluster, e.g.:

*IF (data is in cluster Nc)*
*THEN (the output is calculated with a function Fc* (3.2)

Implementations of the ECOS framework require connectionist models that support these principles. Such model is the evolving fuzzy neural network (EFuNN).

### 3.2.2 The Evolving Fuzzy Neural Network (EFuNN) Model

#### *3.2.2.1 The Principles and Architecture of Evolving Fuzzy Neural Networks (EFuNNs)*

EFuNNs adopt some known techniques from(N. Kasabov, Kim, Watts, & Gray, 1997), but here all nodes in an EFuNN are created /connected during learning. The nodes representing membership functions (MF) can be modified during learning. In EFuNNs, each input variable is represented here by a group of spatially arranged neurons to represent a fuzzy quantization of this variable. For example, three neurons can be used to represent “small”, “medium” and “large” fuzzy values of the variable. Different MFs can be attached to these neurons. New neurons can evolve in this layer if, for a given input vector, the

corresponding variable value does not belong to any of the existing MFs to a degree greater than a set threshold. A new fuzzy input neuron, or an input neuron, can be created during the adaptation phase of an EFuNN. An optional short-term memory layer can be used through feedback connections from the rule node layer (see Figure 3.1). The layer of feedback connections could be used if temporal relationships between input data are to be memorised structurally.

The third layer contains rule nodes that evolve through supervised / unsupervised learning. The rule nodes represent prototypes of input-output data associations, graphically represented as an association of hyper-spheres from the fuzzy input and fuzzy output spaces. Each rule node *r* is defined by two vectors of connection weights – $W_1(r)$ and $W_2(r)$, the latter being adjusted through supervised learning based on the output error, and the former being adjusted through unsupervised learning based on a similarity measure within a local area of the problem space. The fourth layer of neurons represents fuzzy quantization for the output variables, similar to the input fuzzy neurons representation. The fifth layer represents the real values for the output variables.

**Figure 3.1 An EFuNN architecture with a short term memory and feedback connections**

*(figure from Kasabov N, 2002, 2007)*

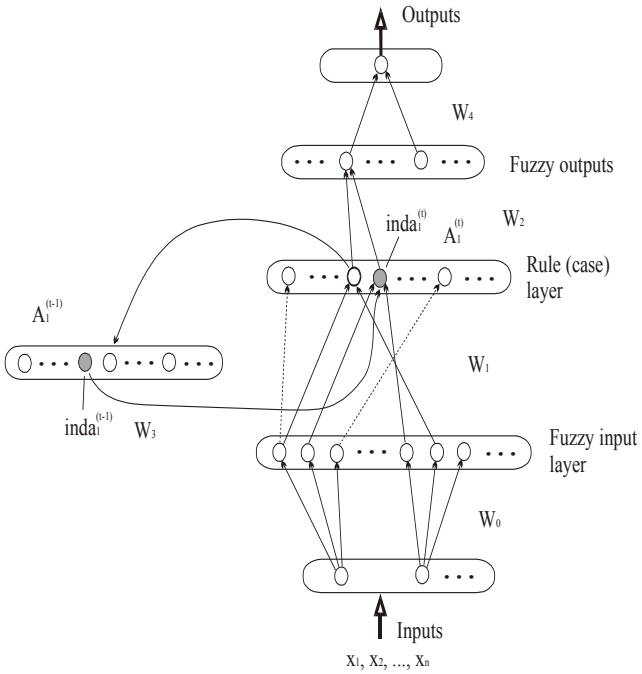
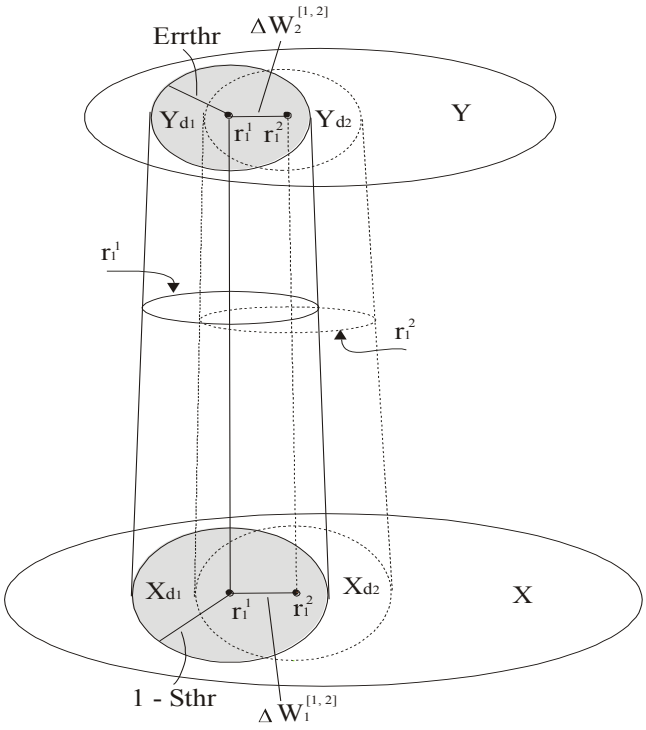


**Figure 3.2 Rule creation in an EFuNN**

*Each rule created during the evolving process associates a hyper-sphere from the fuzzy input space to a hyper-sphere from the fuzzy output space. Through accommodating new nodes the centre of the rule node moves slightly (figure from Kasabov N, 2002)*




The evolving process can be based on two assumptions, that either no rule nodes exist prior to learning and all of them are created during the evolving process, or there is an initial set of rule nodes that are not connected to the input and output nodes and become connected through the learning process.

Each rule node (e.g., $r_1$) represents an association between a hyper-sphere from the fuzzy input space and a hyper-sphere from the fuzzy output space (see Figure 3.2), the $W_1(r_j)$ connection weights representing the co-ordinates of the centre of the sphere in the fuzzy input space, and the $W_2(r_j)$ – the co-ordinates in the fuzzy output space. The radius of an input hyper-sphere of a rule node is defined as (1 – *Sthr*), where *Sthr* is the *sensitivity threshold* parameter defining the minimum activation of a rule node (e.g., $r_1$) to an input vector (e.g., ($Xd_2$, $Yd_2$)) in order for the new input vector to be associated to this rule node.

Two pairs of fuzzy input-output data vectors $d_1$ = ($Xd_1$, $Yd_1$) and $d_2$ = ($Xd_2$, $Yd_2$) will be allocated to the first rule node $r_1$ if they fall into the $r_1$ input sphere and in the $r_1$ output sphere, i.e. the local normalised fuzzy difference between $Xd_1$ and $Xd_2$ are correspondingly smaller than the radius $r$ and the local normalised fuzzy difference between $Yd_1$ and $Yd_2$ is smaller than an *error threshold* (*Errthr).*

The local normalised fuzzy difference between two fuzzy membership vectors $d_{1f}$ and $d_{2f}$ that represent the membership degrees to which two real values $d_1$ and $d_2$ data belong to the pre-defined *MF* are calculated as $D(d_{1f}, d_{2f}) = \sum |d_{1f} - d_{2f}| / \sum (d_{1f} + d_{2f})$. For example, if $d_{1f}$ = [0, 0, 1, 0, 0, 0] and $d_{2f}$ = [0, 1, 0, 0, 0, 0], then $D(d_{1f}, d_{2f})$ = (1 + 1) / 2 = 1 which is the maximum value for the local normalised fuzzy difference. If data example $d_1$ = ($Xd_1$, $Yd_1$) where $Xd_1$ and $Yd_1$ are correspondingly the input and the output fuzzy membership degree vectors, and the data example is associated with a rule node $r_1$ with a centre $r_1^1$, then a new data point $d_2$ = ($Xd_2$, $Yd_2$), that is within the shaded area as shown in Figure 3.2, will be associated with this rule node too.

Through the process of associating (learning) new data points to a rule node, the centre of this node hyper-sphere is adjusted in the fuzzy input space depending on a *learning rate* $lr_1$ and in the fuzzy output space depending on a *learning rate* $lr_2$, as it is shown in Figure 3.2 on two data points. The adjustment of the centre $r_1^1$ to its new position $r_1^2$ can be represented mathematically by the change in the connection weights of the rule node $r_1$ from $W_1(r_1^1)$ and $W_2(r_1^1)$ to $W_1(r_1^2)$ and $W_2(r_1^2)$ as it is presented in the following vector operations:

$$W_1(r_1^2) = W_1(r_1^1) + lr_1 * Ds(Xd_1, Xd_2) \qquad (3.3)$$

$$W_2(r_1^2) = W_2(r_1^1) + lr_2 * Err(Yd_1, Yd_2) * A_1(r_1^1) \qquad (3.4)$$

where: $Err(Yd_1, Yd_2) = Ds(Yd_1, Yd_2) = Yd_1 - Yd_2$ is the signed value rather than the absolute value of difference vector; $A_1(r_1^1)$ is the activation of the rule node $r_1^1$ for the input vector $Xd_2$.

The idea of dynamic creation of new rule nodes over time for a time series data is graphically illustrated in Figure 3.3. While the connection weights from $W_1$

and $W_2$ capture spatial characteristics of the learned data (centres of hyper-spheres), the temporal layer of connection weights $W_3$ from Figure 3.1 captures temporal dependences between consecutive data examples. If the winning rule node at the moment ($t$ – 1) (to which the input data vector at the moment ($t$ – 1) was associated) was $r_1 = inda_1(t - 1)$, and the winning node at the moment $t$ is $r_2 = inda_1(t)$, then a line between the two nodes is established as follows:

$$W_3(r_1, r_2)^{(t)} = W_3(r_1, r_2)^{(t-1)} + lr_3 * A_1(r_1)^{(t-1)} * A_1(r_2)^{(t)} \qquad (3.5)$$

where: $A_1(r)^{(t)}$ denotes the activation of a rule node $r$ at a time moment ($t$); $lr_3$ defines the degree to which the EFuNN associates links between rules (clusters, prototypes) that include consecutive data examples (if $lr_3$ = 0, no temporal associations are learned in an EFuNN).

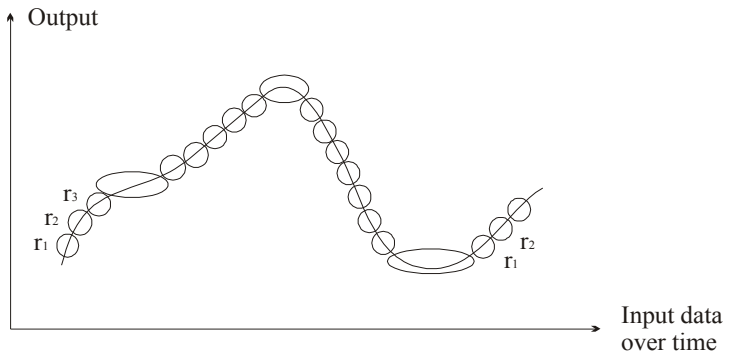
The learned temporal associations can be used to support the activation of rule nodes based on temporal, pattern similarity. Here, temporal dependences are learned through establishing structural links. These dependences can be further investigated and enhanced through synaptic analysis (at the synaptic memory level) rather than through neuronal activation analysis (at the behavioural level). The ratio (spatial – similarity) / (temporal – correlation) can be balanced for different applications through two parameters *Ss* and *Tc* such that the activation of a rule node $r$ for a new data example $d_{new}$ is defined as the following vector operations:

$$A_1(r) = f(Ss * D(r, d_{new}) + Tc * W_3(r^{(t-1)}, r)) \qquad (3.6)$$

where: $f$ is the activation function of the rule node $r$, $D(r, d_{new})$ is the normalised fuzzy difference value and $r^{(t-1)}$ is the winning neuron at time moment ($t$ – 1).

**Figure 3.3 Rule nodes in an EFuNN**

*The rule nodes in an EFuNN evolve in time depending on the similarity in the input data (figure from Kasabov N, 2002)*




Several parameters were introduced so far for the purpose of controlling the functioning of an EFuNN. Some more parameters will be introduced later, that will bring the EFuNN parameters to a comparatively large number. In order to achieve a better control of the functioning of an EFuNN structure, the three-level functional hierarchy is used, namely: genetic level, long-term synaptic level, and short-term activation level.

At the genetic level, all the EFuNN parameters are defined as genes in a chromosome, these are:

(a) Structural parameters, e.g., number of inputs, number of *MF* for each of the inputs, initial type of rule nodes, maximum number of rule nodes, number of *MF* for the output variables, number of outputs.

(b) Functional parameters, e.g., activation functions of the rule nodes and the fuzzy output nodes; mode of rule node activation ('one-of-n', or 'many-of-n') depending on how many activation values of rule nodes are propagated to the next level); learning rates $lr_1$, $lr_2$ and $lr_3$; sensitivity threshold (*Sthr)* for the rule layer; error threshold (*Errthr)* for the output layer; forgetting rate; various pruning strategies and parameters, as explained in the EFuNN algorithm below.

### *3.2.2.2 The Basic EFuNN Algorithm*

In an EFuNN, a new rule node $r_n$ is connected and its input and output connection weights are set. The EFuNN algorithm, to evolve EFuNNs from incoming examples, is given below as a procedure of consecutive steps(N. Kasabov, 1998a). Vector and matrix operation expressions are used to simplicity of presentation.

1. Initialise an EFuNN structure with maximum number of neurons and no (or zero-value) connections. Initial connections may be set through inserting fuzzy rules in the structure. If initially there are no rule nodes connected to the fuzzy input and fuzzy output neurons, then create the first node $r_n$ = 1 to represent the first example $d_1$ and set its input $W_1(r_n)$ and output $W_2(r_n)$ connection weight vectors as follows:

   <create a new rule node>: $W_1(r_n) = EX$; $W_2(r_n) = TE$, where $TE$ is the fuzzy output vector for the current fuzzy input vector $EX$.

2. WHILE <there are examples in the input stream> DO
   Enter the current example ($Xd_i$, $Yd_i$), $EX$ denoting its fuzzy input vector. If new variables appear in this example, which are absent in the previous examples, create new input and / or output nodes with their corresponding membership functions.

3. Find the normalised fuzzy local distance between the fuzzy input vector $EX$ and the already stored patterns (prototypes, exemplars) in the rule (case) nodes, $r_j$, $r_j = r_1, r_2, \ldots, r_n$,

   $$D(EX, r_j) = \sum |EX - W_1(j) / 2| / \sum (W_1(j))$$

4. Find the activation $A_1(r_j)$ of the rule (case) $r_j$, $r_j = r_1, r_2, \ldots, r_n$. Here, radial basis, *radbas*, activation, or a saturated linear one, *satlin*, can be use, i.e.

$A_1(r_j) = radbas(D(EX, r_j))$, or $A_1(r_j) = satlin(1 - D(EX, r_j))$

The former may be appropriate for function approximation tasks, while the latter may be preferred for classification tasks. In case of the feedback variant of an EFuNN, the activation is calculated as explained above:

$A_1(r_j) = radbas(Ss * D(EX, r_j) – Tc * W_3)$, or

$A_1(r_j) = satlin(1 - Ss * D(EX, r_j) + Tc * W_3)$

Update the pruning parameter value for the rule nodes, e.g. *age*, *average activation* as pre-defined in the EFuNN chromosome.

Find all case nodes $r_j$ with an activation value $A_1(r_j)$ above a sensitivity threshold *Sthr*.

If there is no such case node, then <create a new rule node> using the procedure from step 1.

ELSE

8. Find the rule node $inda_1$ that has the maximum activation value (e.g., $maxa_1$).
9. There are two modes: '*one-of-n*' and '*many-of-n*'.
   (a) In case of '*one-of-n*' EFuNNs, propagate the activation $maxa_1$ of the rule node $inda_1$ to the fuzzy output neurons.
   $A_2 = satlin(A_1(inda_1)) * W_2(inda_1))$
   (b) In case of '*many-of-n*' mode, the activation values of all rule nodes that are above an activation threshold of *Athr* are propagated to the next neuronal layer.
10. Find the winning fuzzy output neuron $inda_2$ and its activation $maxa_2$.
11. Find the desired winning fuzzy output neuron $indt_2$ and its value $maxt_2$.
12. Calculate the fuzzy output error vector: $Err = TE – A_2$.
13. IF ($inda_2$ is different from $indt_2$) or ($D(A_2, TE) > Errthr$), <create a new rule node>

    ELSE
14. Update: (a) the input, (b) the output, and (c) the temporal connection vectors (if such exist) of the rule node $k = inda_1$ as follow:
   (a) $Ds(EX, W_1(k)) = EX – W_1(k)$; $W_1(k) = W_1(k) + lr_1 * Ds(EX, W_1(k))$, where $lr_1$ is the learning rate for the first layer;

(b) $W_2(k) = W_2(k) + lr_2 * Err * maxa_1$, where $lr_2$ is the learning rate for the second layer;

(c) $W_3(l, k) = W_3(l, k) + lr_3 * A_1(k) * A_1(l)^{(t-1)}$, here $l$ is the winning rule neuron at the previous time moment ($t$-1), and $A_1(l)^{(t-1)}$ is its activation value kept in the short term memory.

15. Prune rule nodes $j$ and their connections that satisfy the following fuzzy pruning rule to a pre-defined level:

    IF (a rule node $r_j$ is *OLD*) AND (average activation $A_{1av}(r_j)$ is *LOW*) AND (the density of the neighbouring area of neurons is *HIGH* or *MODERATE* (i.e. there are other prototypical nodes that overlap with $j$ in the input-output space; this condition apply only for some strategies of inserting rule nodes as explained in a sub-section below) THEN the probability of pruning node ($r_j$) is *HIGH*.

    The above pruning rule is fuzzy and it requires that the fuzzy concepts of *OLD*, *HIGH*, etc., are defined in advance (as part of the EFuNN's chromosome). As a partial case, a fixed value can be used, e.g. a node is *OLD* if it has existed during the evolving of an EFuNN from more than 1000 examples. The use of a pruning strategy and the way the values for the pruning parameters are defined depends on the application tasks.

16. Aggregate rule nodes, if necessary, into a smaller number of nodes (see the explanation in the following subsection).
17. END of the while loop and the algorithm.
18. Repeat steps 2 to step 17 for a second presentation of the same input data or for Eco training if needed.

With good dynamic characteristics, the EFuNN model is a novel efficient model especially for on-line tasks. The EFuNN model has the following major strong points: (1) incremental, fast learning (possibly 'one pass'); (2) on-line adaptation; (3) 'open' structure; (4) allowing for time and space representation based on biological plausibility; (5) rule extraction and rule insertion.

### 3.2.3 Dynamic Evolving Neural Fuzzy Inference System (DENFIS)

#### *3.2.3.1 General Principle of DENFIS*

The Dynamic Evolving Neural-Fuzzy Inference Systems (DENFIS) is also based on the ECOS principle and motivated by EFuNNs. DENFIS has an approach similar to EFuNNs especially similar to EFuNNs' *m-of-n* mode. DENFIS is a kind of dynamic Takagi-Sugeno type fuzzy inference systems. An evolving clustering method (ECM) is used in DENFIS models to partition the input space for creating the fuzzy rules. DENFIS evolve through incremental, hybrid (supervised/unsupervised), learning and accommodate new input data, including new features, new classes, etc. through local element tuning. New fuzzy rules are created and updated during the operation of the system. At each time moment the output of DENFIS is calculated through a fuzzy inference system based on *m*-most activated fuzzy rules which are dynamically selected from the existing fuzzy rule set. As the knowledge, fuzzy rules can be inserted into DENFIS before, or during its learning process and, they can also be extracted during the learning process or after it. The fuzzy rules used in DENFIS are indicated as follows:

$R_l$: if $x_1$ is $F_{11}$ and $x_2$ is $F_{12}$ and … and $x_P$ is $F_{1P}$,
then $y_l = b_{l0} + b_{l1}x_1 + b_{l2}x_2 + \ldots + b_{lP}x_P$ (3.7)

where "$x_j$ is $F_{lj}$", $l$ = 1, 2, … $m$; $j$ = 1, 2, … $P$, are $M \times P$ fuzzy propositions that form $m$ antecedents for $m$ fuzzy rules respectively; $x_j$, $j$ = 1, 2, …, $P$, are antecedent variables defined over universes of discourse $X_j$, $j$ = 1, 2, …, $P$, and $F_{lj}$, $l$ = 1, 2, … $M$; $j$ = 1, 2, …, $P$ are fuzzy sets defined by their fuzzy membership functions $\mu_{Flj}$: $X_j \rightarrow [0, 1]$, $l$ = 1, 2, … $M$; $j$ = 1, 2, …, $P$. In the consequent parts of fuzzy rules, $y_l$ , $l$ = 1, 2, … $m$, are the consequent variables defined by linear functions.

In DENFIS, $F_{lj}$ are defined by the following *Gaussian* type membership function

$$GaussianMF = \alpha \exp\left[-\frac{(x-m)^2}{2\sigma^2}\right] \quad (3.8)$$

When the model is given an input-output pair ($\boldsymbol{x}_i$, $d_i$), it calculates the following output value:

$$f(\boldsymbol{x_i}) = \frac{\sum_{l=1}^{M} y_l \prod_{j=1}^{P} \alpha_{lj} \exp\left[-\frac{(x_{ij} - m_{lj})^2}{2\sigma_{lj}^2}\right]}{\sum_{l=1}^{M} \prod_{j=1}^{P} \alpha_{lj} \exp\left[-\frac{(x_{ij} - m_{lj})^2}{2\sigma_{lj}^2}\right]} \tag{3.9}$$

The goal is to design the system from (8) so that the following objective function is minimized:

$$E = \frac{1}{2}\left(f(\boldsymbol{x_i}) - d_i\right)^2 \tag{3.10}$$

For optimizing the parameters $b_{lj}$, $m_{lj}$, $\alpha_{lj}$ and $\sigma_{lj}$ in DENFIS, the steepest descent algorithm can be used:

$$\varphi(k+1) = \varphi(k) - \eta_\varphi \frac{\partial E}{\partial \varphi} \tag{3.11}$$

here, $\eta$ is the learning rate and $\varphi$ can represent $b$, $m$, $\alpha$ or $\sigma$ respectively. DENFIS has following characteristics:

- Building a Takagi-Sugeno fuzzy inference engine dynamically.
  The Takagi-Sugeno fuzzy inference engine is used in both on-line and off-line modes of DENFIS. The difference between them is that for forming a dynamic inference engine, only first-order Takagi-Sugeno fuzzy rules are employed in DENFIS on-line mode and both first-order Takagi-Sugeno fuzzy rules and expanded high-order Takagi-Sugeno fuzzy rules are used in DENFIS off-line modes. To build such a fuzzy inference engine, several fuzzy rules are dynamically chosen from the existing fuzzy rule set depending on the position of current input vector in the input space.
- Dynamic creation and updating of fuzzy rules.
  All fuzzy rules in the DENFIS on-line mode are created and updated during a 'one-pass' training process by applying the *Evolving Clustering Method* (ECM) and the *Weighted Recursive Least Square Estimator with Forgetting Factors* (WRLSE).

- Local generalisation.
  Similar to EFuNNs, DENFIS model has local generalisation to speed up the training procedure and to decrease the number of fuzzy rules in the system.
- Fast training speed.
  In the DENFIS on-line mode, the training is a 'one-pass' procedure and in the off-line modes, WLSE and small-scale MLPs are applied, which lead DENFIS to have the training speed for complex tasks faster than some common neural networks or hybrid systems such as multi-layer perceptron with back-propagation algorithm (MLP-BP) and *Adaptive Neural-Fuzzy Inference System* (ANFIS), both of which adopt global generalisation.
- Satisfactory accuracy.
  Using DENFIS off-line modes, we can achieve a high accuracy especially in non-linear system identification and prediction.

#### *3.2.3.2 Dynamic Takagi-Sugeno Fuzzy Inference Engine*

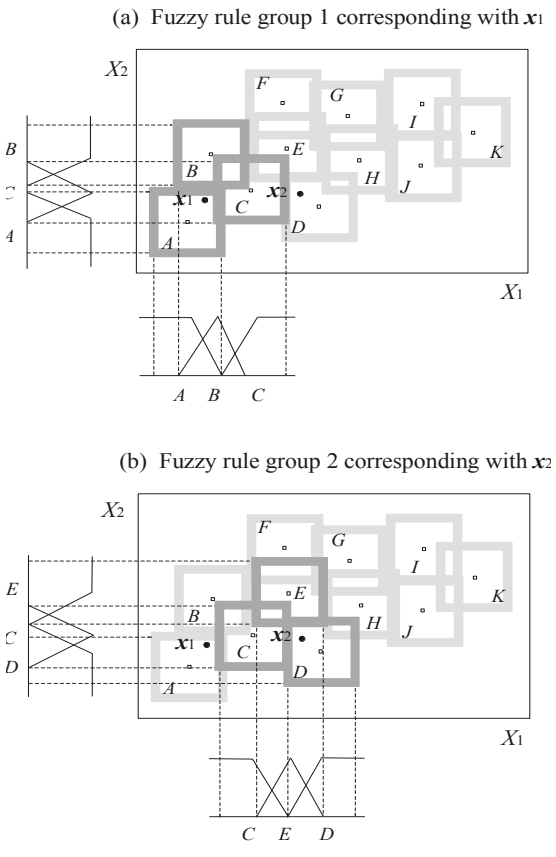
The Takagi-Sugeno fuzzy inference engine(Takagi & Sugeno, 1985) utilised in DENFIS is a dynamic inference model. In addition to dynamically creating and updating fuzzy rules in the DENFIS on-line mode, the major differences between such inference engine and the general Takagi-Sugeno fuzzy inference engine are described as follows:

First, depending on the position of the current input vector in the input space, different fuzzy rules are chosen from the fuzzy rule set, which has been estimated during the training procedure, for constructing an inference engine. If there are two input vectors very close to each other, especially in DENFIS off-line modes, two identical fuzzy inference engines are established and they may be exactly the same. In the on-line mode, however, although sometimes two inputs are exactly same, their corresponding inference engines are probably different. This is because these two inputs come into the system from the data stream at different moments and the fuzzy rules probably have been updated during this interval.

Secondly, also depending on the position of current input vector in the input space, the antecedents of fuzzy rules, which have been chosen from the fuzzy rule set for forming an inference engine, may different. An example is illustrated in Figure 3.4, where two fuzzy rule groups, FG1 and FG2, are estimated depending on two input vectors x1 and x2 respectively in a 2-D input space. We can know from this example that, for instance, the region C represents a linguistic meaning 'large' in FG1 on the X1 axis but it represents a linguistic meaning 'small' on that in FG2. Also, the region C is presents as different membership functions respectively in FG1 and FG2.

**Figure 3.4 Two fuzzy rule groups corresponding with input $x_1$ and $x_2$ in a 2-D space**

*(figure from Kasabov N, 2002)*



#### *3.2.3.3 Fuzzy Rule Set, Rule Insertion and Rule Extraction*

Fuzzy rules in a DENFIS are created during a training procedure, or come from rule insertion. In the on-line mode, the fuzzy rules in the rule set can also be updated as new training data appear in the system(N. Kasabov & Woodford, 1999).

As the DENFIS uses a Takagi-Sugeno fuzzy inference engine the fuzzy rules inserted to or extracted from the system are Takagi-Sugeno type fuzzy rules. These rules can be inserted into the rule set before or during the training procedure and they can also be exacted from the rule set during or after the training procedure.

The inserted fuzzy rules can be the rules that are extracted from a fuzzy rule set created in previous training of DENFIS, or they can also be general Takagi-Sugeno type fuzzy rules. In the latter, the corresponding nodes of the general Takagi-Sugeno fuzzy rules have to be found and located in the input space. For an on-line learning mode, their corresponding radiuses should also be defined. The region can be obtained from the antecedent of a fuzzy rule and the centre of this region is taken as the node corresponding with the fuzzy rule. A value of (0.5 ~ 1)Dthr can be taken as the corresponding radius.

#### *3.2.3.4 Comparison of DENFIS On-line Mode and EFuNN*

Similar to EFuNN, the DENFIS on-line mode applies a one-pass, on-line training algorithm and adopts local generalisation that make both DENFIS performs its training procedure very fast.

The EFuNN is a fuzzified neural network and it updates the system by using a method similar to an on-line gradient descent method(Biehl, Freking, Holzer, Reents, & Schlosser, 1998; Freeman & Saad, 1997; J. Moody & Darken, 1988;

John Moody & Darken, 1989; Rummery & Niranjan, 1994). The EFuNN algorithm is a simple one so that the rule insertion, rule extraction and rule aggregation are easy to realize, however, the EFuNN normally requires more rules than a DENFIS on-line mode for achieving the similar result.

The DENFIS model is a neural fuzzy inference system with capability of learning. The DENFIS on-line mode updates the system by using a weighted recursive least square estimation algorithm which makes the DENFIS more effective and more accurate than EFuNN. Instead of the data space partitioning in both input space and output space, the DENFIS on-line mode applies the ECM that performs the partition in input space only.

## 3.3 Summary

This chapter reviews novel algorithms and techniques called ECOS, with particular emphasis on local and personalised modelling frameworks. These techniques will be used in the thesis either as part of the developed new techniques in the following chapters or for comparison of experimental results.

In ***Chapter 4***, medical and biological background will be presented as it relates to the representative problems modelled in this research. The biological relevance of renal function will be discussed, and the limitations of current tools for its evaluation. The modelling datasets (GFR and DOPPS) used in this current chapter will also be introduced and described.

# Chapter 4 : Medical and Biological Background - The Evaluation of Kidney Function and the Survival with Patients with End-Stage Kidney Failure on Dialysis

In ***Chapter 3***, novel algorithms and techniques using evolving connectionist systems were reviewed, with particular emphasis on local and personalised modelling frameworks. These generic techniques are further developed as specific methods applied on renal data introduced in current chapter.

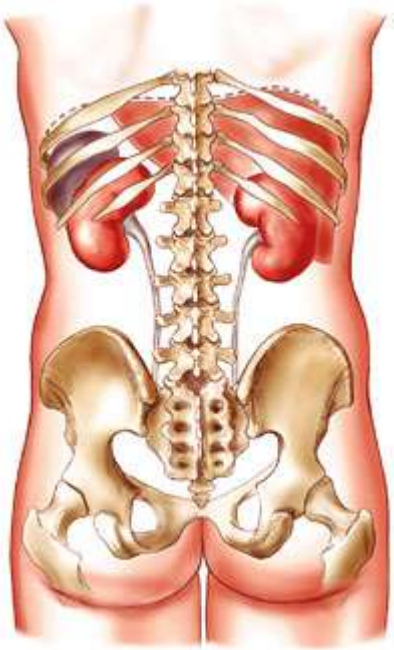
In this chapter, medical and biological background is presented as it relates to the representative problems modelled in this research. To provide context and clinical relevance, the biological role of kidney function will be discussed, and the difficulties of evaluation using current tools. This chapter will also provide corresponding background to the problem of mortality for haemodialysis patients, and again the corresponding difficulties with prediction of longevity. The two modelling datasets (GFR, DOPPS) will be introduced and described.

## 4.1 Problem Description and Review

### 4.1.1 Normal Renal Function

The human kidneys are two bean-shaped organs, one on each side of the backbone (Figure 4.1). They represent about 0.5% of the total weight of the body, but receive 20-25% of the total arterial blood pumped by the heart. The kidneys play a key role in eliminating metabolic waste and maintaining fluid and electrolyte homeostasis. They are also an endocrine organ, generating hormones such as renin and angiotensin that regulate blood pressure, vitaminD that maintains calcium balance and bone integrity, and erythropoietin which regulates red blood cell production in bone marrow(Kriz & Elger, 2010).

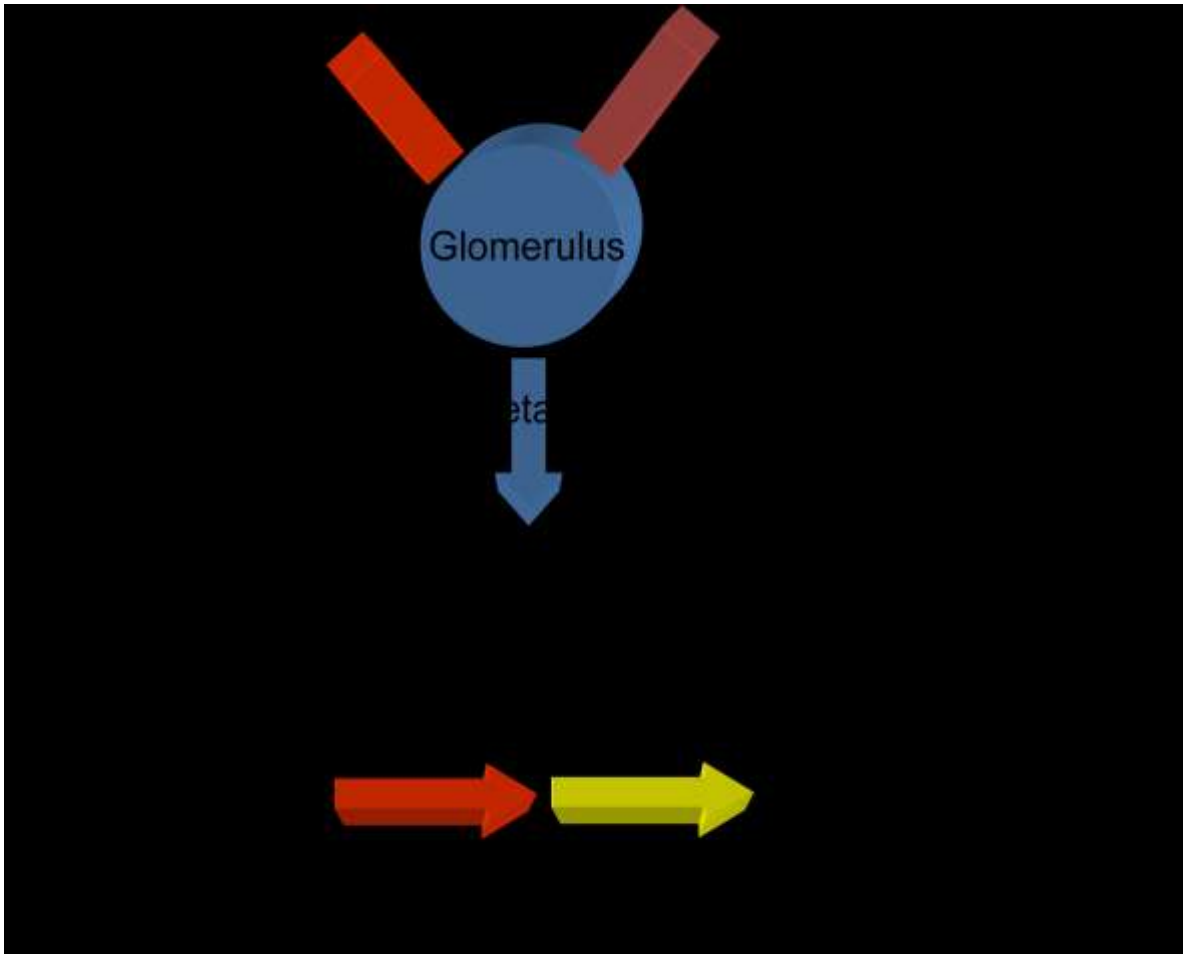
**Figure 4.1 Anatomical location and relationships of the kidneys.**



The most important function of the kidney is the elimination of metabolic waste and the maintenance of normal fluid and electrolyte homeostasis. This occurs through a process of filtration by the kidneys, which separate cellular and proteinaceous material (e.g. red blood cells, immunoglobulins) in the blood from the fluid in which they are suspended (the plasma). The filtration itself occurs within organic filters called glomeruli (singular glomerulus). Each human kidney contains between 600,000-800,000 glomeruli. As is shown in Figure 4.2, unfiltered blood enters each glomerulus via the afferent arteriole and exits after filtration via the efferent arteriole. Aggregating the function of all of these glomeruli together, the normal kidney filters 125-150mL of blood per minute, or 75-90 ml/min/1.73m$^2$ when corrected for body surface area to account for the size of the person. This latter figure is referred to as the glomerular filtration rate (GFR). The filtered blood leaving each glomerulus is reconstituted with purified plasma which is generated by the proximal and distal tubules of the kidney, which reclaim water and electrolytes as necessary from the glomerular filtrate.

By the end of all these processes, the remaining fitrate containing all the metabolic waste and excess water and electrolytes is passed down larger conduits called collecting ducts into the ureters and then to the bladder for excretion as urine(Shirley & Unwin, 2010).

**Figure 4.2 Schematic representing the filtering unit of the kidney, namely a glomerulus and the tubules that serve it.**




In the healthy population, kidney function declines with physiological ageing at a rate of about 1 ml/min/1.73m$^2$ per year after the age of 30 years (Coresh, Astor, Greene, Eknoyan, & Levey, 2003; D. F. Davies & Shock, 1950; Rule et al., 2004). Most people, however, do not experience clinical consequences from normal aging, since the effects of age impair kidney function only very mildly, and in a manner that is insufficient to causes direct morbidity or mortality.

### 4.1.2. Overview of Kidney Disease

Impaired kidney function can occur in two contexts. The impairment may occur over days to weeks in so-called “acute kidney injury”, a condition that is often reversible. On the other hand, the impairment may occur over months to years in so-called “chronic kidney disease”, a generally progressive and irreversible condition. In both conditions, renal impairment can arise as a result of local organ or remote disease. Local organ diseases include congenital conditions such as polycystic kidney disease, and acquired ones such as glomerulonephritis and interstitial nephritis. Remote diseases include either a reduction of blood flow to the organ as a result of shock (severe blood loss, sepsis, heart failure) in acute kidney injury, or direct glomerular injury as a result of diabetes mellitus and hypertension in chronic kidney disease. Certain insults can cause both acute kidney injury and chronic kidney disease, such as medication side effects, vascular disease affecting perfusion of the kidney beds, and blockages to urinary outflow due to tumours or kidney stones.

Impaired kidney function causes morbidity and mortality from lack of urine production and the accumulation of both metabolic waste in the blood (so-called “uraemic toxins”) and also excess salt and water in the body. The clinical concept of “uraemia” or “urine in the blood” as a result of kidney failure has remained constant since its origins in the 1700’s (Richet, 1988). Then as now, untreated uraemia results in death at anytime within days to months once toxicity manifests, depending on the rate of deterioration in kidney function and degree of concurrent medical co-morbidity (Carter, 1888; Garcia et al., 2007; Smith et al., 2003). When kidneys fail altogether, patients die from complications of fluid overload (pulmonary oedema, heart failure), complications of electrolyte and acid-base perturbation (arrhythmia from hyperkalaemia, organ failure from acidosis), and classical manifestations of terminal uraemia attributed to the various wastes retained in renal failure (neuro-encephalopathy, pericarditis, cardiomyopathy).

The clinical consequences of less severe degrees of renal impairment are in general proportional to the degree of kidney dysfunction. Overall, chronic kidney disease is strongly associated with cardiovascular morbidity and mortality. There is clear evidence that this is due to both atherosclerotic coronary artery disease probably as a direct result of retained uraemic toxins, as well as left ventricular hypertrophy secondary to hypertension and progressive salt and water retention. Both of these conditions predispose to myocardial ischaemia and sudden cardiac death. In chronic kidney disease, the risk of death associated with mild chronic kidney disease is probably not greatly increased over the general population without chronic kidney disease. However, in moderate and severe chronic kidney disease the risk of death is 20% and 80% higher than the general population, even after statistical adjustment for conventional cardiovascular risk factors(Go, Chertow, Fan, McCulloch, & Hsu, 2004).

End-stage kidney failure (ESKF) occurs when the kidneys fail completely. Most but not all patients will receive some kind of renal replacement therapy with dialysis or renal transplantation once their kidneys fail. Dialysis in general prolongs life by several years, and transplantation by several decades (Figure 4.3)(Oniscu, Brown, & Forsythe, 2005). However, both treatments come at the cost of a heavy predisposition to cardiovascular and infectious diseases which between them account for the vast majority of deaths in such patients. Dialysis patients have up to a 100-fold increased risk of death compared to the general population, and transplant patients a 10-fold risk(Foley, Parfrey, & Sarnak, 1998). As an example, a 30 year old New Zealander on dialysis has the same survival as an 80 year old with normal kidney function (Figure 4.4). The prognosis of patients on renal replacement therapy is approximately the same as those people who are diagnosed with bowel cancer(Foley et al., 1998; Howlader et al., 2001; U S Renal Data System, 2011). It is therefore vital to preserve kidney function.

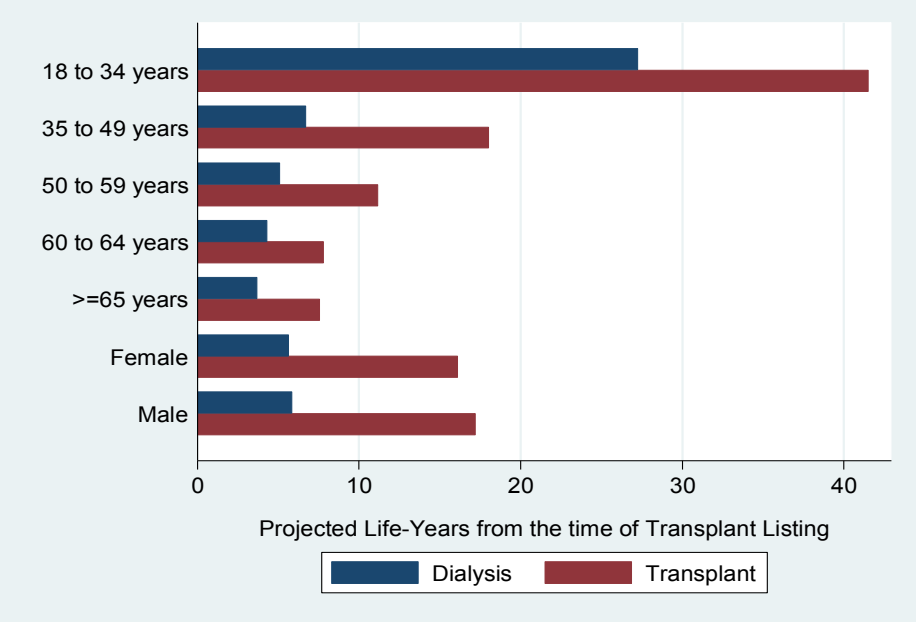
### 4.1.3 The Burden of Kidney Disease

After standardization of methods of assessment, the NHANES III survey found a chronic kidney disease prevalence of 4.7% in the adult American population

(Coresh et al., 2003). Using non-standardized methods, other studies have found a prevalence of between 4.9% and 13%(Chadban et al., 2003; Clase, Garg, & Kiberd, 2002; de Lusignan et al., 2005; Viktorsdottir et al., 2005). Recently, a large primary care study from the UK also using standardized methods found a chronic kidney disease prevalence of 8.5% in the adult population (10.6% in females, 5.8% in males)(Stevens et al., 2007). The higher prevalence in the UK is probably as a result of the large South Asian population in this country, who are more prone to kidney disease than the white population. Of note, there are no reported prevalence data for chronic kidney disease within the general New Zealand population, or even the Pacific / New Zealand Maori communities. It is widely assumed that the prevalence of chronic kidney disease will be on the higher rather than the lower side in this country because of our high risk ethnic minorities.

**Figure 4.3 The longevity of dialysis patients who receive a transplant versus those who remain on dialysis waiting for one**

*(Oniscu et al., 2005)*




As mentioned above, renal replacement therapy for ESKF can be undertaken using either dialysis or renal transplantation. Both therapies are life-saving and life-sustaining. The vast majority of patients will only ever be treated with dialysis due to a shortfall in available organs for transplantation and the inability of many sick patients with ESKF to survive such major surgery. For instance, in

New Zealand only 13% of those with ESKF are ever listed as waiting for transplantation, and only half of those will actually be transplanted(Clayton, Excell, Campbell, McDonald, & Chadban, 2010).

It has been estimated that there are 2-3 million people are treated with renal replacement therapy for ESKF around the world(Grassmann, Gioberge, Moeller, & Brown, 2005; U S Renal Data System, 2011). The prevalence of renal replacement therapy in New Zealand can be estimated using the Australian and New Zealand Dialysis and Transplant (ANZDATA) Registry, which has prospectively collected data on ESKF patients in these countries since 1963 (www.anzdata.org.au). According to the most recent census, there are between 3000 and 4000 patients treated with renal replacement therapy in New Zealand at 31st December 2010 (Figures 4.5). The leading cause of ESKF is diabetes mellitus, accounting for more than half the cases.

**Figure 4.4 Mortality in patients treated by dialysis and transplantation in New Zealand compared to the general population.**


The number of ESKF patients continues to grow around the world, and is around 4.8% per annum in New Zealand and the current time(Clayton et al., 2010). This growth has arisen from improvements in technology and an aging

population, with both factors leading to a broadening of the criteria for acceptance of patients for dialysis. At the same time, increased awareness of the availability of a life-saving technology has led to an increase in demand for dialysis by patients, their relatives and the public at large. Globally, the veritable explosion in the end-stage kidney failure population is compounded by the increasing access of previously poor nations to technically advanced treatments as their economic fortunes increase and the cost of technology falls.

In New Zealand, the treatment of ESKF costs more than $150 million annually representing around 1-2% of total public health expenditure. As practiced, dialysis costs on average $46,000 per patient per annum in NZ. Costs for transplantation are relatively higher in the first year of treatment (~$90,000) and substantially lower in later years (~$9,000 per annum ongoing). In the long-term, transplantation is approximately 2-3 times less expensive than dialysis on a per-patient per-year basis (Figure 4.6)(Ashton & Marshall, 2007). Developments to provide clinically superior and more financially viable replacement therapies than dialysis and transplantation are not expected in the foreseeable future.

## 4.2 Problem Statement - Evaluation of Kidney Function

### 4.2.1 Measurement and Estimation

The early detection of renal impairment is therefore vital to allow for the institution of appropriate diagnostic and therapeutic measures, and potentially maximise preservation of residual renal function in the setting of kidney disease. Monitoring the progression and severity of renal impairment is just as important since it allows practitioners to monitor the response of kidney disease to therapy. Finally, the evaluation of greater degrees of kidney impairment is useful to determine the onset of ESKF and provide additional information to the clinician to facilitate the timely initiation of dialysis before lethal complications ensue. Estimating the presence and degree of kidney disease is therefore an

important patient and population health priority, and fundamental to the wellbeing of New Zealanders.

The most intuitive way of estimating the presence and degree of kidney disease is by measurement of uraemic toxins in the blood. Unfortunately, however, our knowledge about the specific solutes in blood responsible for uraemic toxicity remains inconsistent and incomplete. Urea, for instance, has come to be recognized as useful marker of general uraemic solute retention, having been first isolated from urine in 1773 by Hilaire Marin Rouelle(Richet, 1988). However, urea is not a uraemic toxin per se due to its relatively low toxicity and the variable relationship of urea concentrations with clinical characteristics of the uraemic syndrome. It is now well accepted that the uraemic syndrome is instead the result of the accumulation of multiple factors rather than one single substance, as well as the deficiency of an important few such as vitamin D, erythropoietin and opsonins(Glorieux, Schepers, & Vanholder, 2007; Vanholder & Massy, 2009; Vanholder, Meert, Schepers, & Glorieux, 2008; Vanholder, Van Laecke, & Glorieux, 2008). To date, a 100 or so uraemic toxins have been formally identified although the total number is probably in the thousands or millions (www.uremic-toxins.org/). Practically, most of these toxins are very difficult to measure. Moreover, the relationship between their blood levels and clinical disease is reasonably predictable for a given patient, but very variable between individuals.

For this reason, GFR itself has come to be best index of renal function in both health and disease(Walser, 1998). GFR is most accurately measured by clearance measurements of administrated tracers filtered by the kidneys. The best tracer for the measurement of GFR is generally considered to be inulin, although radioisotopes such as $^{99}$Tc-DTPA, $^{55}$Cr-EDTA, and $^{125}$I-iothalamate are more accessible and of comparable accuracy, and are now accepted as reference methods for the measurement of GFR in clinical research(Levey et al., 1993). All of the methods are still associated with a small degree of error. Various investigators have reported intra-test coefficients of variation of approximately 5-6%

**Figure 4.5 Prevalence of ESKF treated with either dialysis or renal transplantation at 31st December 2010 in New Zealand, by treating centre.**

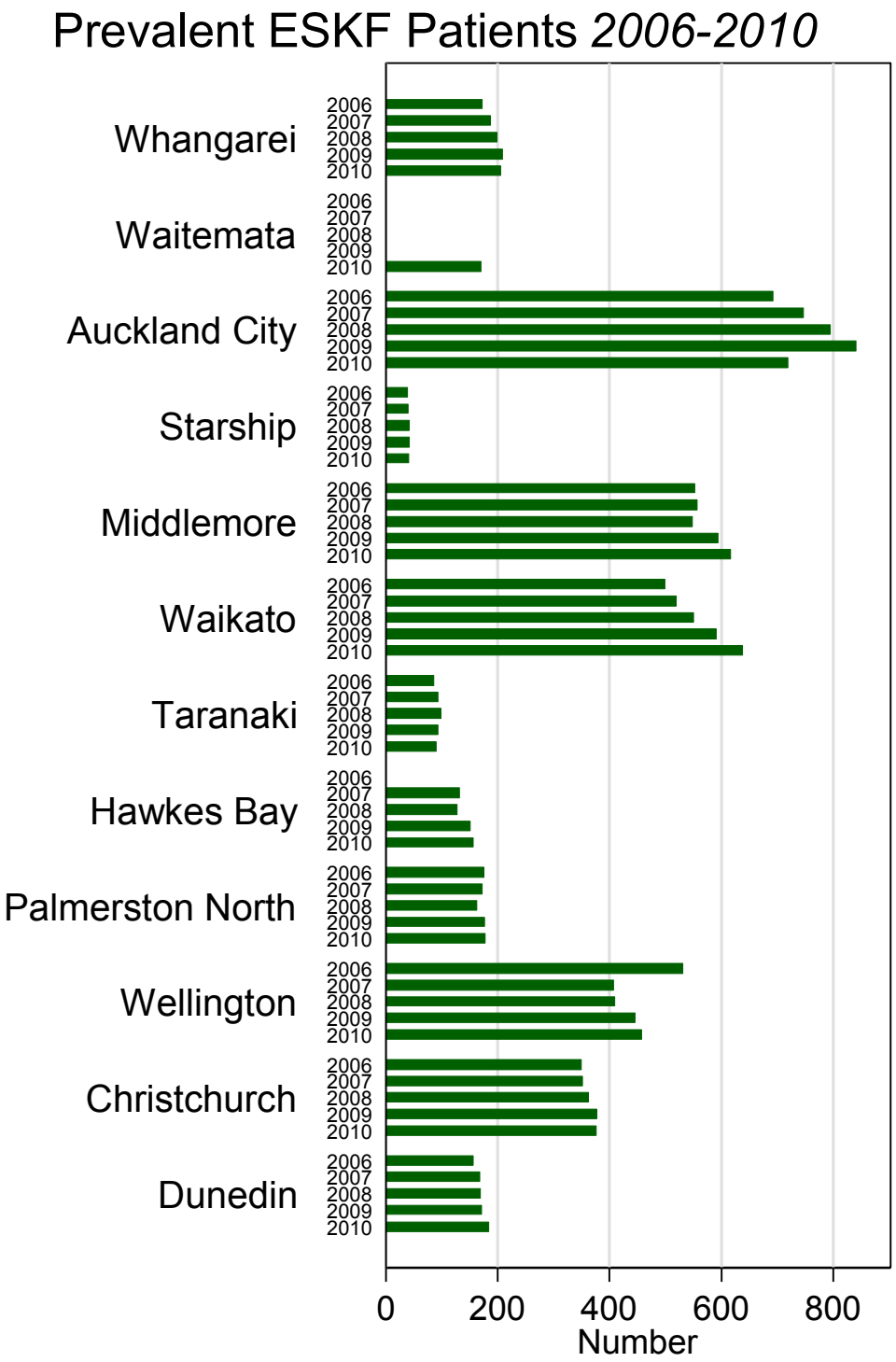
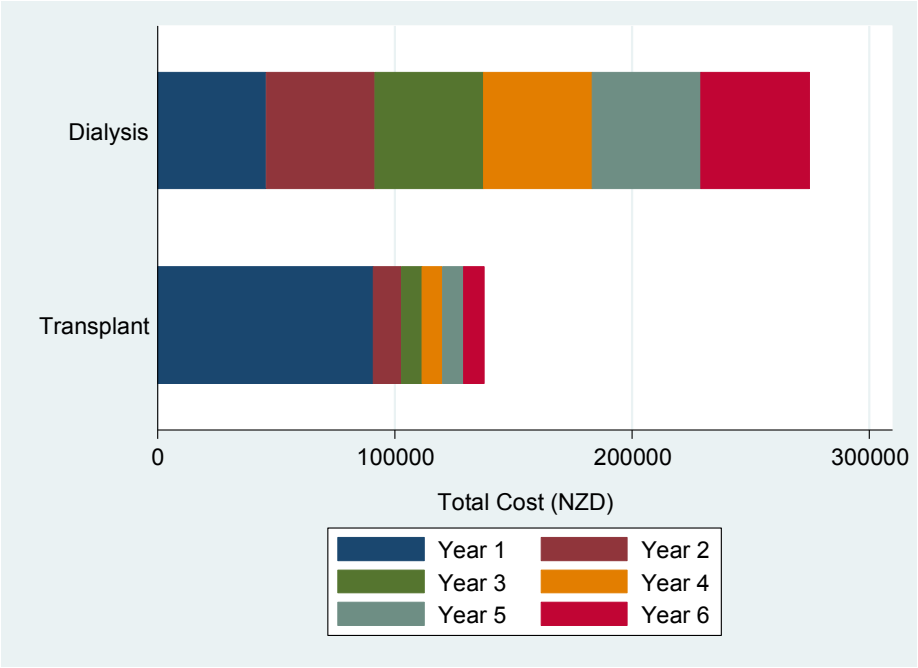


**Figure 4.6 Costs of dialysis renal transplantation over the medium term.**




(Levey et al., 1993; Perrone et al., 1990; Roger et al., 2004; Walser, Davidson, & Orloff, 1955), although they have a high degree of reproducibility across different centres as long as computing algorithms are similar(Cosgriff et al., 2003; Cosgriff et al., 2002; Fleming et al., 1998; White, Houston, Sampson, & Wilkins, 1999). These methods have been recommended as routine by some authors(Mariat C et al., 2004), although they are time consuming and expensive and probably unsuitable for routine assessment of GFR in clinical settings(Levey et al., 1993).

Estimation of GFR from the clearance measurements of creatinine is based on the same principles as the “gold-standard” methods, but avoids the need for administered tracers. Creatinine is an endogenously produced protein originating from muscle. It is predominantly filtered by the kidneys and is progressively retained as kidney function declines. It therefore fulfils the major criteria as a tracer and marker of GFR. However, due to a variable degree of secretion, creatinine clearance tends to systematically overestimate GFR. This discrepancy is negligible for mild degrees of renal impairment, but becomes significant at lower levels of GFR. Accuracy can be enhanced by the

administration of cimetidine, which can block this secretion, during collection of the specimen, thereby providing a creatinine measurement in the urine that is derived from glomerular filtration alone(Walser, 1998). Accuracy can also be enhanced by using the averaged measured urea and creatinine clearance since the former tends to underestimate GFR and the latter overestimate, with the average being more accurate than both(Levey et al., 1999). Collection of an accurate 24-hour urine sample is essential for all of these tests, requiring a high degree of discipline by the patient. Studies have shown collection to be much less accurate and reproducible in routine clinical practice, and when such errors are not eliminated the day-to-day variation in measured creatinine clearance may be as high as 70%(Levey et al., 1999).

Alternatively, GFR can be estimated by a number of empirical formulas that have been derived from correlational analysis with measured GFR in various datasets of patients with chronic renal disease. Over the last 30 years, medical practitioners have come to rely on a number of regression formulas to estimate GFR from demographic and common laboratory variables including levels of serum creaitine. These formulas predict either creatinine clearance as measure of GFR, or less commonly GFR directly depending on the original study design for formula development and validation. They represent a compromise between exactitude and convenience, since they have the advantage of easy bedside calculation without the requirement for direct tracer measurement, but at the price of reduced accuracy. Given the barriers to measuring GFR directly, formulas such as these have become clinically indispensable in routine medical practice. Previously, the most frequently used formula for predicting renal function in adults was the Cockcroft-Gault (CG) formula(Cockcroft & Gault, 1976), which was originally developed for predicting creatinine clearance but widely utilised instead for predicting GFR. A number of other less commonly used formulas for predicting creatinine clearance or GFR (Table 4-1) have also been developed(Bjornsson, 1979; Cockcroft & Gault, 1976; Gates, 1985; Hull et al., 1981; Jelliffe, 1971, 1973; Levey et al., 1999; Mawer, Lucas, Knowles, & Stirland, 1972; Walser, 1994; Walser, Drew, & Guldan, 1993). When compared to reference methods, the prediction error of these formulas in the literature averages 21.3%.

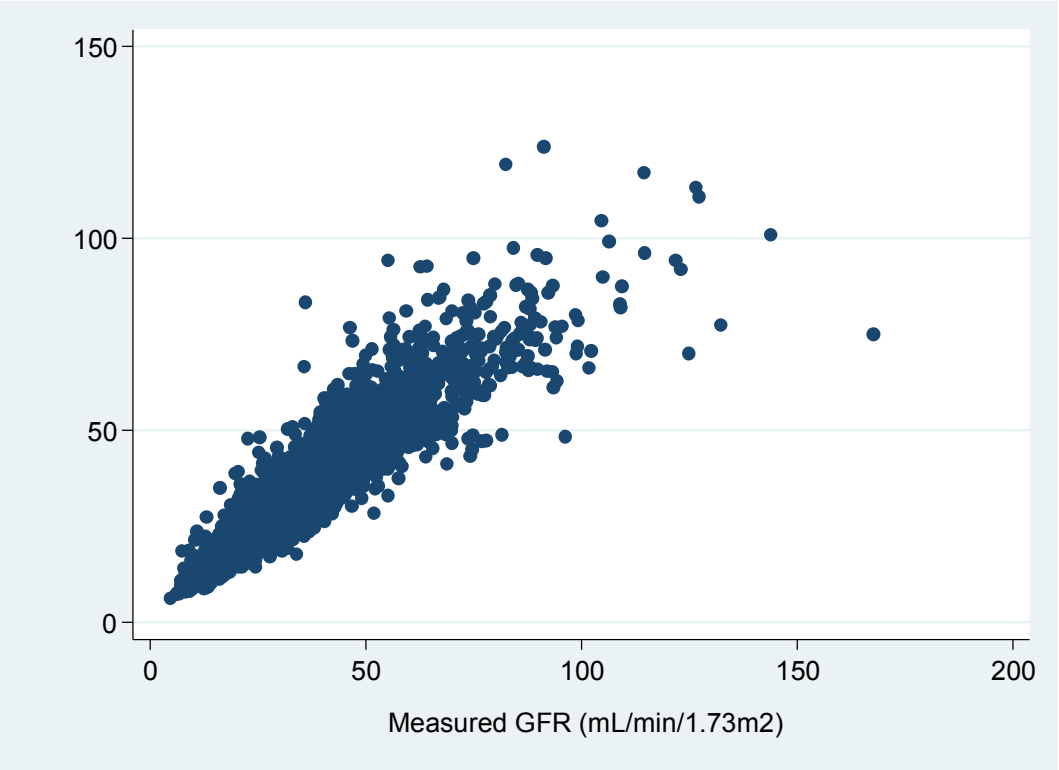
Recently, the Modification of Diet in Renal Disease (MDRD) study resulted in several new formula for more accurate evaluation of GFR(Levey et al., 1999). Since they predict GFR as opposed to creatinine clearance, accuracy is maintained over the entire range of renal function, including in particular low GFR. All these formulas require the input of serum creatinine and various other laboratory or demographic variables. The most commonly used MDRD formulas estimate GFR from serum creatinine more accurately than the other formulas in Table 1-1. For instance, the prediction error of the most accurate MDRD formula in the original article (MDRD equation #7) was reported to be 11.5% and about half that of the CG formula to which it was directly compared(Levey et al., 1999). Although the MDRD investigators did not compare their formulas to all the others in Table 4-1, scatter graphs suggest that the MDRD formulas outperform these as well (See Figure 4.7). The most accurate MDRD formula uses the following variables: age, race, gender, serum creatinine (Scr in mg/dl), serum albumin (Alb in g/dl) and blood urea nitrogen concentrations (BUN in mg/dl). This so-called MDRD equation #7 is used in this research as the gold standard formula for the estimation of GFR, and will be henceforth referred to as the MDRD formula.

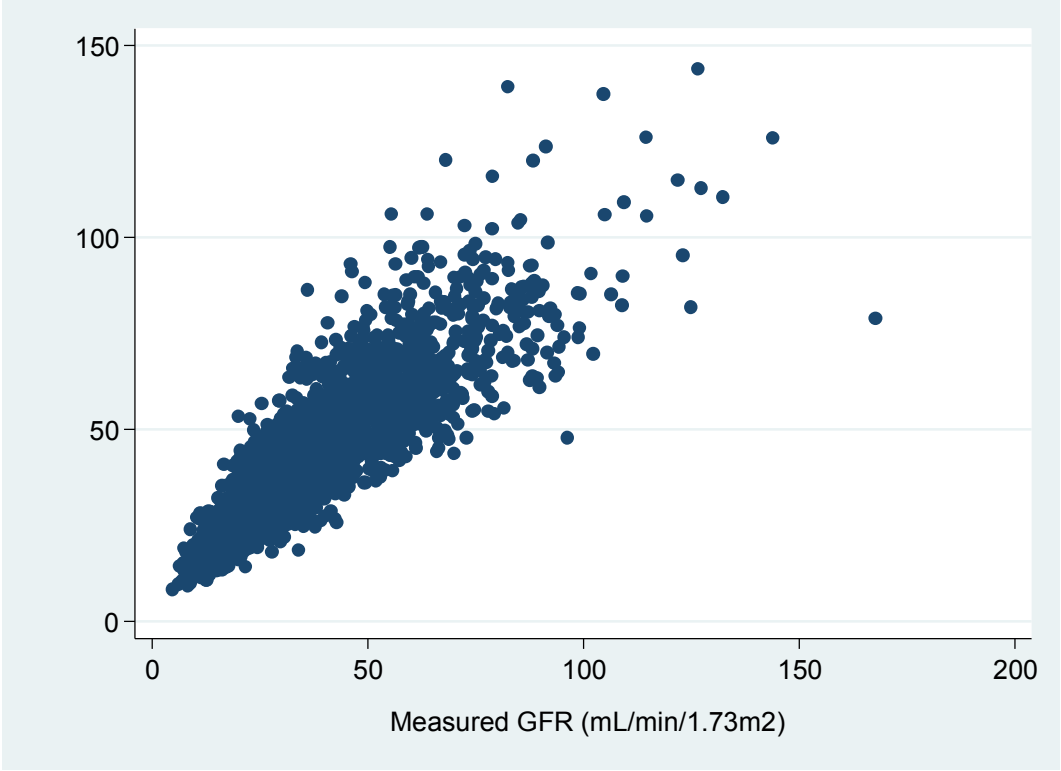
### 4.2.2 Better Systems are Needed for Estimating GFR.

All of the formulas in Table 4-1, including the MDRD formula, are derived from regression. Regression formulas are the most popular type of prognostic and classification models in medicine. Technically, they are derived from data gathered from the whole problem space through inductive learning, and are consequently used to calculate the output value for a new input vector regardless of where it is located in the problem space. For the estimation of GFR, this can result in different regression formulas for the same problem through the use of different datasets as can be seen in Table 4-1. As a result, all of these formulas have limited accuracy on new data that are significantly different from those used for the original modelling.

This applies to the even the MDRD formulas, which as described are the best ones available. Visual inspection of the validation data for the MDRD formula (Figure 4-7) shows still overall poor prediction and accuracy. This inaccuracy may under certain circumstances impair good clinical decision-making and mislead as to the presence or progression of renal disease. In the validation study, over 90% of estimated values by MDRD formula were within 30% of measured GFR, an accuracy that was generally maintained for most degrees of renal impairment. In relative terms, this degree of accuracy is certainly better than other regression formulas(Levey et al., 1999). In absolute terms, this degree of accuracy is not always acceptable. A new tool for accurate assessment of GFR is therefore desirable.

**Figure 4.7 Accuracy of MDRD formula #7¸ the Cockcroft & Gault formula, and the Walser formula for the prediction of GFR from the MDRD data as presented in the original publication.**




150
100
50
0
0
50
100
150
200
Measured GFR (mL/min/1.73m2)

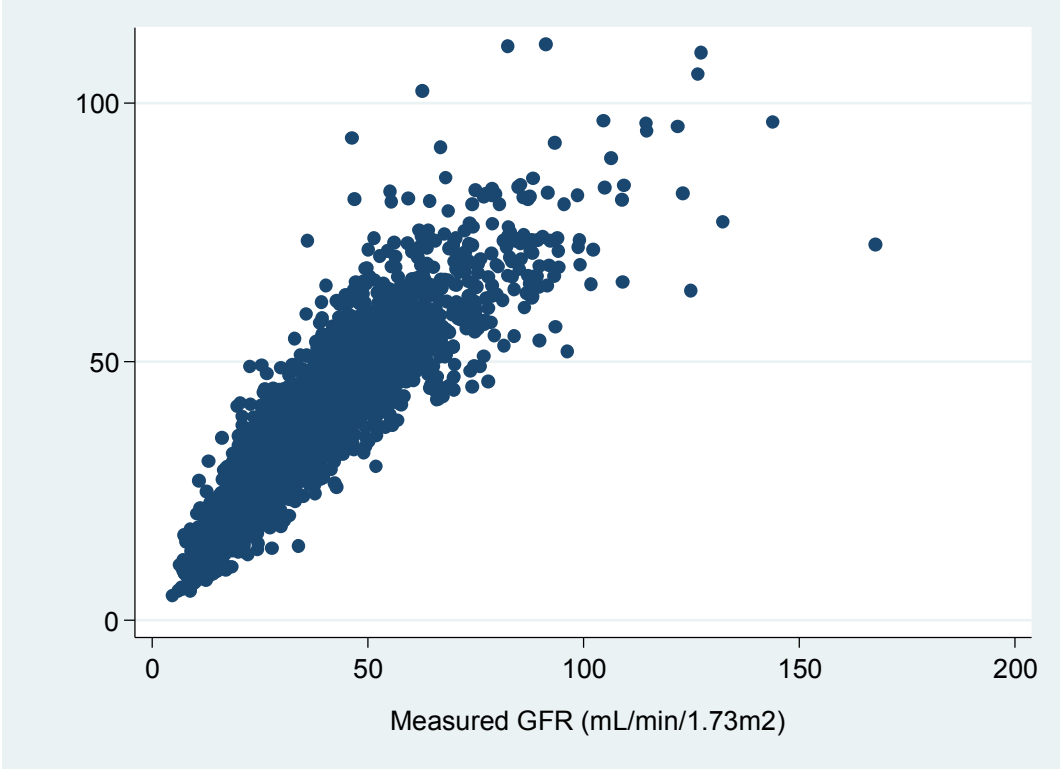

100
50
0
0
50
100
150
200
Measured GFR (mL/min/1.73m2)

**Table 4-1 Equations for estimating renal function**

| | |
|---|---|
| Jelliffe Equation (1971) | Men: Ccr (ml/min/1.73m$^2$ ) $= \frac{100}{Scr} - 12$<br>Women: Ccr (ml/min/1.73m2 ) $= \frac{80}{Scr} - 7$ |
| Mawer Equation (1972) | Men: Ccr (ml/min/70 kg) $= \frac{Weight \times [29.3 - (0.203 \times Age)] \times [1 - (0.03 \times Scr)]}{(14.4 \times Scr)} \times \frac{Weight}{70}$<br>Women: Ccr (ml/min/70 kg) $= \frac{Weight \times [25.3 - (0.175 \times Age)] \times [1 - (0.03 \times Scr)]}{(14.4 \times Scr)} \times \frac{Weight}{70}$ |
| Jelliffe Equation (1973) | Ccr (ml/min/1.73m$^2$) $= \frac{98 - 0.8 \times (Age - 20)}{Scr} \times$ (0.9 if female) |
| Cockcroft-Gault Equation (1976) | Ccr (ml/min) $= \frac{(140 - Age) \times Weight}{72 \times Scr} \times (0.85 \, if \, female)$ |
| Hull Equation (1981) | Ccr (ml/min/70kg) $= \left(\frac{145 - Age}{Scr} - 3\right) \times \frac{Weight}{70} \times (0.85 \, if \, female)$ |
| Bjorasson Equation (1984) | Men: Ccr (ml/min) $= \frac{27 - (0.173 \times Age) \times Weight \times 0.07}{Scr}$<br>Women: Ccr (ml/min) $= \frac{25 - (0.175 \times Age) \times Weight \times 0.07}{Scr}$ |
| Gates Equation (1985) | Men: Ccr (ml/min) $= (89.4 \times Scr^{-1.2}) + [(55 - Age) \times (0.447 \times Scr^{-1.1})]$<br>Women: Ccr (ml/min) $= (60 \times Scr^{-1.1}) + [(56 - Age) \times (0.3 \times Scr^{-1.1})]$ |
| Walser Equation (1994) | Men: GFR (ml/min/1.73m$^2$) $= \frac{7570}{Scr} - (0.103 \times Age) + (0.096 \times Weight) - 6.66$<br>Women: GFR (ml/min/1.73m$^2$) $= \frac{6050}{Scr} - (0.08 \times Age) + (0.08 \times Weight) - 4.81$ |
| MDRD Equation #7 (1999) | $GFR = 170 \times Scr^{-0.999} \times Age^{-0.176} \times 0.762 \, (if \, Sex \, is \, female)$<br>$\times 1.18 \, (if \, Race \, is \, black) \times BUN^{-0.17} \times Alb^{0.318}$ |
| | where *Age* in in years, *Weight* is in kg and *Scr* is in mg/dL. |

There are also other potential theoretical problems applying the MDRD formulas to the New Zealand population. The formula was developed in a sample from the United States population. A feature of all of the MDRD formulas is a factor used to account for black race, 1.18 in the MDRD equation #7. In this research, the ethnic mix of "black" patients in Australia and New Zealand includes Maori, Polynesian, and Aboriginal patients, who are quite distinct from African Americans. It should not be assumed that creatinine generation is higher in these ethnic groups as is the case in African Americans. In the GFR dataset that will be used for modelling in the research, the mean measured GFR was 18.73 mL/min/1.73m$^2$ and the mean serum creatinine 0.42 mmol/L for patients classified as “black”. The corresponding values were were 22.9 mL/min/1.73m2 and 0.34 mmol/L for patients classified as “white”. If one equates GFR with creatinine clearance and assumes a steady state, the mean 24-hour creatinine generation is 11.3 mmol for both blacks and whites. The only other available published data support this finding. The relationship between calculated creatinine clearance and urine creatinine was not different in Pacific People, New Zealand Maoris, and Europeans (P.A. Metcalf, personal communication, July 26, 2004)(Metcalf, Scragg, & Dryson, 1997). This issue highlights again the potential in applying formulas such as the MDRD formulas in a population that is different from that in which they have been developed.

## 4.3 Problem Statement - The Prediction of Mortality in Dialysis Patients

### 4.3.1 Predicting Prognosis in Dialysis Patients

As described above, the prognosis of patients on dialysis is poor. In New Zealand, the average survival of dialysis patients is approximately 5 years(Marshall et al., 2011). The need for more sensitive and specific prognostic information is motivated by several main principles. Each discussed in the following sections.

### 4.3.2 Principle 1: Prospective Identification of High Risk Dialysis Patients

To be effective in supporting patients with this disease, intervention must aim to prevent catastrophic complications of ESKF rather than treating them. An accurate prognostic system will allow for prospective identification of high risk dialysis patients, who are likely to require increased health service resource. This will in turn allow more opportunity to intervene with potential to improve outcomes. This may also lead to the identification of characteristics associated with such a poor outcome such that withdrawal of dialysis, now the third most common cause of death in New Zealand(S McDonald, Excell, & Livingston, 2010), can be carefully managed and in some cases anticipated.

### 4.3.3 Principle 2: Provision of Equitable and Improved Clinical Outcomes to through Robust Benchmarking

Recent evidence from New Zealand and elsewhere has highlighted apparently significant differences in patient survival across countries and dialysis units. For instance, the reported five-year mortality rates for end-stage kidney disease in Europe and Japan are 20-35% lower than those reported in the United States, even when adjusted for age, sex, and diabetic status(Held et al., 1990). Within the United States, there is a five-fold variation in both crude and adjusted mortality reported across facilities(Hulbert-Shearon, Loos, Ashby, Port, & Wolfe, 1999; McClellan, Flanders, & Gutman, 1992). Similar results have been shown in the UK (Ansell & Feest, 2002). Recent analysis of units in Australia and New Zealand has showed significant centre variation in outcomes after accounting for both risk factors predictive of poor outcomes between centres, as well as potential bias due to sampling variability(Ansell & Feest, 2002; MacDonald, 2003)(Figure 4.8).

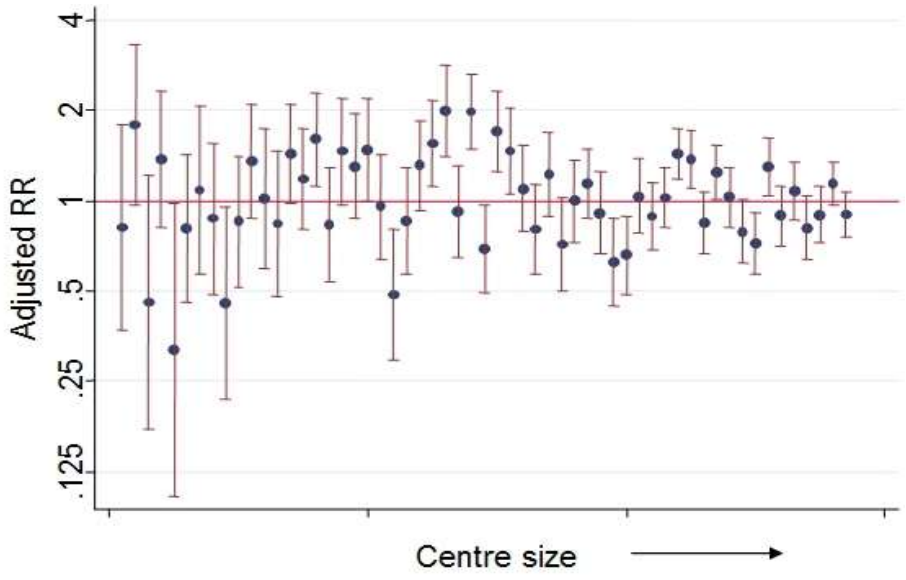
These observations have led to vigorous debate as to the relative effects of patient-related versus treatment-related factors(Keane & Collins, 1994; Lowrie & Lew, 1990; Marcelli et al., 1996), although the impact of differing practice patterns in contributing to these variations is disputed by few. However, a league table approach to this problem is flawed due to imprecise and overly sensitive statistical models. Without exception, these models are very sensitive

to minor differences in adjustment for predictive baseline characteristics producing inappropriately large changes in estimates of treatment effect on survival. Despite this, increasing scrutiny of the performance of health care providers has led to an increasing number of initiatives on a regional or unit basis, with these inadequate statistical tools providing the basis for the assessment of the quality of care in order to identify centres for possible regulatory intervention.

The provision of equitable and improved clinical outcomes to a heterogeneous group of patients on dialysis will only be achieved through harmonization of clinical care to evidence-based best practice, and also reliable monitoring of mortality rates in dialysis units whilst accounting for the proportion of high risk patients in their population. To date, the league table approach using either time series analysis or standardized mortality ratios have not been reliable enough for this task, and as a consequence have not been adopted. Better predictive tools for acute benchmarking between dialysis units are required.

**Figure 4.8 Significant centre variation in relative risk of mortality after accounting for both patient-level risk factors predictive of poor outcome and potential bias due to sampling variability**

(*SP McDonald, 2003*).



### 4.3.4 Principle 3: Provision of Renal Replacement Therapy for All Those Who will Benefit from Treatment

Funding agencies are faced with the task of allocating the necessary resources to provide access to renal replacement therapy for all those who will benefit from the treatment. In turn, dialysis providers must provide more accurate clinical assessments that dialysis will meaningfully prolong life and provide an acceptable quality of life in individual cases. While there is some variation in practice as indicated above, most dialysis services in New Zealand do not accept patients for dialysis whose life prolongation is estimated to be less than 6 months. In this situation, dialysis providers are critically dependent on a scoring system or clinical intuition to accurately predict death soon after starting dialysis, and unless this can be achieved with certainty then limiting dialysis on the basis of likely short survival is almost certainly inappropriate(JF Collins, 1998; Khan & Macleod, 1995; Kjellstrand & Moody, 1994).

### 4.3.5 Principle 4: Accurate Clinical Assessments as to the Prolongation of life, and the Provision of an Acceptable Quality of Life for Dialysis Patients

All patients with ESKF are offered dialysis treatment provided it will meaningfully prolong their life and provide an acceptable quality of life. A system that can accurately predict death soon after starting dialysis will allow for dialysis providers and patients to make a robust clinical evaluation as to whether dialysis will provide clinical benefit, and therefore allow a more objective and informed decision as to whether dialysis should be either offered or accepted. Approximately 50% of patients who reach ESKF are not offered or do not engage an offer of dialysis. The most common reason is a perception by either the dialysis provider or the patient of a low quality of life on dialysis for a only short prolongation of life. Although no such data are available for a complex therapy such as dialysis, patients who are asked to imagine themselves as incompetent with a poor prognosis decide against cardiopulmonary resuscitation about 70% of the time(Emanuel, Barry, Stoeckle, Ettelson, & Emanuel, 1991; Finucane, Shumway, Powers, & D'Alessandri, 1988; Frankl, Oye, & Bellamy, 1989; Lo, McLeod, & Saika, 1986; Shmerling, Bedell, Lilienfeld, & Delbanco, 1988; Uhlmann, Pearlman, & Cain, 1988;

Wagner, 1984). A system that allows for accurate prediction of outcomes will potentially allow dialysis providers to withhold dialysis, and potential dialysis patients to refuse dialysis when the therapy merely serves to prolong death as opposed to prolonging life. Such a system may also provide data on characteristics that identify patient who are already on dialysis with a very poor prognosis. This would in turn allow the withdrawal of dialysis, now the second or third most common cause of death in both the United States and Australasia(S McDonald et al., 2010; U S Renal Data System, 2011), can be carefully managed and in some cases anticipated.

### 4.3.6 Principle 5: Identification of Novel Factors or Novel Interactions between Factors to Improve Patient Care.

Accurate models of patient survival may identify new factors or new interactions between factors that place patients on dialysis at increased risk, such as the elderly or those in certain ethnic minorities such as the New Zealand Maori. This will allow for new strategies and interventions for their medical, social and economic problems in order to improve outcomes.

### 4.3.7 How can Dialysis Patients be Risk Stratified?

Prognostic indices to identify mortality risk in advance should be based on those variables that independently predict mortality in prospective studies, or have independent associations with mortality in cross-sectional studies. Many such patient-related or treatment-related variables have been identified in the literature. Notwithstanding differences in data definitions between studies, omitted variables, the time-dependent nature of many risk factors, and issues around external validity, the following variables have been identified as being independent correlates of mortality in dialysis patients:

- **Age**(Avram, Mittman, Bonomini, Chattopadhyay, & Fein, 1995; Barrett et al., 1997; Byrne, Vernon, & Cohen, 1994; Churchill et al., 1992; Fernandez, Carbonell, Mazzuchi, & Petruccelli, 1992; Foley et al., 1994; Garcia-Garcia et al., 1985; Hutchinson, Thomas, & MacGibbon, 1982; Keane & Collins, 1994; Khan & Macleod, 1995; Lowrie & Lew, 1990; MacDonald, 2002; Wright, 1991)

- **Diabetes mellitus**(Avram et al., 1995; Byrne et al., 1994; A. J. Collins, Hanson, Umen, Kjellstrand, & Keshaviah, 1990; S. J. Davies, Russell, Bryan, Phillips, & Russell, 1995; Garcia-Garcia et al., 1985; Hutchinson et al., 1982; Keane & Collins, 1994; Khan et al., 1993; Lowrie & Lew, 1990; Lowrie, Lew, & Huang, 1992; MacDonald, 2002; Wright, 1991),
- **Poor nutrition** as indicated by body mass index, subjective global assessment, serum creatinine, serum albumin, serum cholesterol, total lymphocyte count(Acchiardo, Moore, & Latour, 1983; Avram et al., 1995; Chertow, Johansen, Lew, Lazarus, & Lowrie, 2000; S. J. Davies et al., 1995; Leavey et al., 2001; Leavey, Strawderman, Jones, Port, & Held, 1998; Lowrie et al., 1992; Owen, Lew, Liu, Lowrie, & Lazarus, 1993; Pifer et al., 2002)
- **Race**(Lowrie et al., 1992; Owen, Chertow, Lazarus, & Lowrie, 1998)
- **Blood pressure**(Fernandez et al., 1992; Foley, Parfrey, et al., 1996c; Port et al., 1999)
- **Vintage** (time on dialysis)(Avram et al., 1995; Chertow et al., 2000; Lowrie & Lew, 1990)
- **Primary renal disease** (Byrne et al., 1994; Garcia-Garcia et al., 1985; Lowrie & Lew, 1990; Wolfe, Port, Hawthorne, & Guire, 1990)
- **Left ventricular hypertrophy**(Foley et al., 2000)
- **Left ventricular ejection fraction**(Foley et al., 2000)
- **Congestive heart failure**(Foley et al., 2000; Hutchinson et al., 1982; Keane & Collins, 1994)
- **Ischaemic heart disease**(Churchill et al., 1992; S. J. Davies et al., 1995; Fernandez et al., 1992; Foley, Parfrey, et al., 1996a; Foley et al., 1994; Keane & Collins, 1994)
- **Treated arrhythmia**(Foley et al., 1994)
- **Peripheral vascular disease**(A. J. Collins et al., 1990; S. J. Davies et al., 1995; Foley et al., 1994; Keane & Collins, 1994)
- **Chronic lung disease**(A. J. Collins et al., 1990; Keane & Collins, 1994)
- **Central nervous system disease**(A. J. Collins et al., 1990; Foley et al., 1994)

- **Smoking**(Keane & Collins, 1994), non-cutaneous malignancy(Barrett et al., 1997; A. J. Collins et al., 1990; S. J. Davies et al., 1995; Foley et al., 1994; Keane & Collins, 1994)
- **Liver disease**(Beddhu, Bruns, Saul, Seddon, & Zeidel, 2000; Foley et al., 1994; van Manen et al., 2002)
- **Systemic collagen vascular disease**(van Manen et al., 2002)
- **Dialysis schedule and duration**(Charra et al., 1992; Lowrie & Lew, 1990; Marshall, Byrne, Kerr, & McDonald, 2006)
- **Dialysis dose**(Avram et al., 1995; A J Collins, Ma, Umen, & Keshaviah, 1994; S. J. Davies et al., 1995; Fernandez et al., 1992; Gotch & Sargent, 1985; R.M. Hakim, Breyer, Ismail, & Schulman, 1994; Keshaviah & Collins, 1988; Lowrie, Laird, Parker, & Sargent, 1981; Owen et al., 1993; Parker, Husni, Huang, Lew, & Lowrie, 1994) (Marshall et al., 2006)
- **Haemodialysis access**(Combe et al., 2001), haemodialyser membrane characteristics(Eknoyan et al., 2002; R. M. Hakim, 1998; R. M. Hakim et al., 1996; Leypoldt et al., 1999)
- **Inflammatory markers**(R.M. Hakim et al., 1994; Yeun, Levine, Mantadilok, & Kaysen, 2000; J. Zimmermann, Herrlinger, Pruy, Metzger, & Wanner, 1999)
- **Haemoglobin**(Besarab et al., 1998; Foley, Parfrey, et al., 1996b)
- **Serum calcium**(Foley, Parfrey, Harnett, Kent, Hu, et al., 1996)
- **Serum phosphate**(Block, Hulbert-Shearon, Levin, & Port, 1998; Block & Port, 2000)
- **Acid-base status**(Lowrie & Lew, 1990), patient compliance(Leggat et al., 1998)
- **Depression and quality of life**(Lopes et al., 2003; Lopes et al., 2002)
- **Haemodialysis unit ownership**(Garg, Frick, Diener-West, & Powe, 1999)
- **Pre-dialysis care**(Cass, Cunningham, Snelling, Wang, & Hoy, 2002; Jungers et al., 1993)
- **Functional status**(Chandna, Schulz, Lawrence, Greenwood, & Farrington, 1999; Keane & Collins, 1994; Lopes et al., 2003; McClellan, Anson, Birkeli, & Tuttle, 1991)

- **Socioeconomic status**(Cass et al., 2002; Lopes et al., 2003; Young, Mauger, Jiang, Port, & Wolfe, 1994)
- **Health insurance**(Garcia-Garcia et al., 1985).

### 4.3.8 What Systems are Currently Available to Predict Outcomes?

The numerous studies cited above have examined the influence of patient-related and treatment-related variables on mortality in dialysis patients. The combined risk of having multiple single co-morbid medical conditions has been investigated less often and for only a limited number of diseases(Barrett et al., 1997; Churchill, Thorpe, Vonesh, & Keshaviah, 1997; S. J. Davies et al., 1995; Gokal & Mallick, 1999; Khan et al., 1993; Mailloux et al., 1996; Mallick & Gokal, 1999; van Manen et al., 2002; Van Manen et al., 2003). There are four simple, quantitative or semi- quantitative scoring systems in the literature that are generally regarded as being potentially useful. In essence, these scores attempt to summarise medical co-morbidity into a risk score.

The first method was developed by Khan and colleagues in 1993(Khan et al., 1993), derived from 375 incident haemodialysis and peritoneal dialysis patients from two centres for whom they had collected 2 years of survival data. Based on a combination of age and co-morbidity, patients were classified to have a low, medium and high mortality risk. The second method was developed by Davies and colleagues in 1995(S. J. Davies et al., 1995), derived from 97 prevalent peritoneal dialysis patients from a single centre for whom they had collected 30 months of survival data. Based on the number of co-morbid medical conditions without age, patients were classified to have either no, intermediate, or severe co-morbidity. The third method is the Charlson co-morbidity index, which is designed to deal with prognostic co-morbidity in longitudinal studies of all kinds of patients. Based on different weights for separate age classes and co-morbid medical conditions, a risk score can be calculated (Charlson, Pompei, Ales, & MacKenzie, 1987). This method was utilised by Beddhu and colleagues in 2000(Beddhu et al., 2002), adapted in 268 incident and prevalent patients from a single centre for whom had collected 2 years of survival data. The fourth method was developed by Foley in

1994(Foley et al., 1994), derived in 325 patients incident haemodialysis and peritoneal dialysis patients from a single centre for whom they had collected up to 11 years of survival data.

In addition to these four indices, there has been a recent report from the Netherlands Co-operative Study on the Adequacy of Dialysis (NECOSAD) Study Group, who has explored the performance of new scoring systems derived from regression analyses of their own dataset. Several prognostic indices were developed from the combination of regression coefficients from Cox proportional hazard analysis and values of chosen variables. This study provided the opportunity to develop a scoring system in a large (*n* = 1205) prospective follow-up study of all incident dialysis patients in the majority of centres in the Netherlands, with data that allowed for the inclusion of more medical co-morbidity (15 conditions) and explicit graded severity for four of the most weighted co-morbid medical conditions(van Manen et al., 2002; Van Manen et al., 2003). This methodology can be utilised for the development of a prognostic index in any dataset that has been subject to appropriate regressions analysis, and has been proposed but not tested in other settings(J. Collins & Metcalf, 2003; MacDonald, 2002).

One other index used in patients with ESKF is the Index of Co-Existent Disease (ICED)(Athienites et al., 2000; Miskulin et al., 2001; Miskulin et al., 2002; Nicolucci et al., 1992). The ICED summarizes co-morbidity by adding the peak score of the disease severity of co-morbidities and the peak score for impact of co-morbidities on physical impairment. Because the degree of physical impairment of the patient is rated for this index, the ICED seems more equivalent to a health status instrument, and therefore somewhat different from those indices above.

### 4.3.9 Better Systems for Predicting Survival are Needed.

The reference method for predicting outcomes in dialysis patients remains clinical intuition by the medical team. Surprisingly, this has been tested robustly in only one study, in which nephrologists performed as well the prognostic

indices at predicting early death(Barrett et al., 1997). Nevertheless, both clinical intuition and available scoring systems do not predict outcomes with a degree of accuracy that would influence clinical or administrative management. For instance, the system presented by Foley and colleagues was applied prospectively by Barrett and colleagues to 822 incident haemodialysis and peritoneal dialysis patients at 11 Canadian centres(Barrett et al., 1997). It was found that 52% of those classified as high risk died within 6 months, although 23% were still alive after more than a year of treatment. Further refinement and adjustment of the model did not result in improved performance. The treating nephrologists provided a separate intuitive prediction of survival, which were as accurate as the scoring system up to 6 months, above which they tended to overestimate risk. The authors concluded that the inability of a scoring system or clinical intuition to accurately predict death soon after starting dialysis suggested limiting dialysis on the basis of likely short survival was inappropriate.

Contrary to expectations, the NECOSAD index did not result in improved performance over the Khan, Davies or Charlson indices. This was despite a large number of patients, precise data, and inclusion of a large number of co-morbid medical conditions with graded severity. The authors concluded further fine tuning of the NECOSAD index was unlikely to produce a superior scoring system, and that the Khan, Davies and Charlson indices were all appropriate for the expressing the prognostic impact of co-morbidity on mortality.

Why then are these systems so limited? It has been speculated that the inclusion of yet other variables such as functional status may improve the predictive accuracy of these models(Barrett et al., 1997). In addition, these prognostic indices do not include potentially important variables relating to practice patterns at either a patient level such as details of dialysis procedures and medications, or at a facility level such as physician contact time or staffing ratios. However, it is more likely that simple regression is unable to account for variables which are interrelated in a multidimensional manner within the patient clinical profile, or account for variables which have a non-linear or complex

relationship with survival. A better system for predicting survival is likely to require a paradigm shift in modelling, and motivates the sue

## 4.4. Study Datasets.

### 4.4.1 The GFR Dataset.

The EPO AUS-14 study was a prospective multi-centre randomised clinical trial conducted from 1998 to 2002 to determine if maintenance of serum haemoglobin between 120 and 130 g/L prevented and/or delayed the development of left ventricular hypertrophy in patients with advanced kidney disease. The coordinating centre did the original selection of 12 centres in Australia and New Zealand, and all incident patients fulfilling the criteria for study were screened for participation. These criteria were: (1) age between 18 and 75 years, (2) GFR between 15 to 50 mL/min, and (3) demonstrated historical decline in haemoglobin concentration to 110 - 130 g/L for males and 100 - 120 g/L for females. Full details of the methods and results of the study have been reported elsewhere(Roger, McMahon et al. 2003). EPO AUS-14 was approved by ethical review committees at respective institutions and informed consent was obtained from all patients in accordance with the guidelines proposed in the Declaration of Helsinki(1997).

A sample of patients was drawn from EPO AUS-14 for research. In the original study, 296 patients were consented and screened for randomisation. We excluded patients from this research if the date of GFR measurement by the reference method did not coincide with the date of laboratory testing, or if the protocol employed for this GFR measurement differed from that stated below. A total of 178 patients from the original cohort were included in this study. The demographic and clinical characteristics of these patients are provided in Table 4-2.

Reference GFR measurements were made for all patients at baseline and then yearly intervals for the duration of the study. GFR was measured as the plasma clearance of chromium-51 ethylenediamine tetraacetic acid (51Cr-EDTA) corrected for body surface area (GFR-EDTA). Clearance was determined by either two or three point sampling at variable intervals between 0.5 and 4.5 hours after tracer injection, with or without a correction for the monoexponential assumption. Samples were processed in the nuclear medicine laboratories in each of the respective centres. Median intra-test and inter-test coefficients of variation within and between these centres were not studied and are therefore unavailable. A total of 441 GFR-EDTA measurements were available for this study.

A limitation of this dataset is that multiple GFR measurements are included for each patient. This methodology has occasionally been a feature of previous research of this nature17, since estimates derived from any analysis in the dataset will be weighted by the characteristics of patients with more frequent measurements. To examine this further, demographic, clinical, and laboratory characteristics of the patients in this dataset have been compared between those with patients one or two GFR measurements, versus those with three or four measurements. There were no demonstrable differences in any of these parameters, indicating that the average frequency of 2.4 GFR measurements per patient was unlikely to have confounded our results. The other limitation of this dataset is its sample size: the MDRD study used 1070 and 558 GFR measurements for training and validation, respectively, compared with 309 and 132 corresponding GFR measurements in this study. This will inevitably limit the power of the analyses presented in this research.

A fundamental strength of this dataset is that it is sourced from multiple centres using the centres' own clinical and laboratory measurements. This study design reproduces routine clinical practice, as opposed to previous studies which have usually been undertaken in single centres, or in multiple centres but using central laboratories.

**Table 4-2 Baseline clinical characteristics of study participants in the GFR dataset**

| Parameter | n (% of total) | Mean | Standard Deviation |
|---|---|---|---|
| | | | |
| Number of patients | 178 | - | - |
| Number of GFR measurements | 441 | - | - |
| Male | 93 (52%) | - | - |
| Female | 85 (48%) | - | - |
| White race | 160 (89%) | - | - |
| Asian race | 3 (2%) | - | - |
| Black race | 15 (9%) | - | - |
| Angiotensin converting enzyme inhibitor use | 130 (74%) | - | - |
| HMG CoA reductase inhibitor use | 69 (39%) | - | - |
| Loop diuretic use | 76 (43.3%) | - | - |
| Diabetes mellitus | 47 (26.4%) | - | - |
| Hypertension | 165 (93.0%) | - | - |
| Congestive heart failure | 4 (2.2%) | - | - |
| Ischaemic heart disease | 30 (16.9%) | - | - |
| Age | - | 53.2 | 13.7 |

| | | | |
|---|---|---|---|
| Weight (kg) | - | 77.1 | 15.9 |
| Height (cm) | - | 167.8 | 9.6 |
| Systolic blood pressure | - | 141.2 | 21.5 |
| Diastolic blood pressure | - | 79.5 | 11.7 |
| Serum creatinine (mmol/L) | - | 0.35 | 0.21 |
| Serum urea (mmol/L) | - | 20.4 | 7.6 |
| Serum albumin (g/L) | - | 38.8 | 4.7 |
| Haemoglobin | - | 111.7 | 10.0 |
| Left ventricular ejection fraction | - | 65 | 7.4 |
| Left ventricular mass (gm) | - | 162.8 | 57.7 |
| Left ventricular mass index ( g/m2) | - | 86.9 | 26.1 |

### 4.4.2 The DOPPS Dataset

The Dialysis Outcomes and Practice Patterns Study (DOPPS, www.dopps.org) is a prospective observational longitudinal cohort study which has been ongoing since 1996. The research plan of the DOPPS is to assess the relationship between haemodialysis treatment practices and patient outcomes, and the relationship between different patient outcomes, all for the purpose of improving treatments and survival of patients on haemodialysis. The DOPPS studies a stratified random sample of haemodialysis patients from the United Sates, 8 European countries (United Kingdom, France, Germany, Italy, Spain, Belgium, Netherlands, and Sweden), Japan, Australia and New Zealand. There have

been four phases of data collection since 1996, and a fifth phase is currently just beginning. At the time of this thesis, the DOPPS had enrolled 27880 incident and prevalent patients (approximately 33% and 66% respectively) in the study, representing approximately 75% of the world's haemodialysis patients. Prevalent patients are defined as those patients who had received maintenance haemodialysis prior to the study period, while incident patients are those who had not previously received maintenance haemodialysis.

The DOPPS collects detailed practice pattern data, demographics, cause of end-stage renal disease, medical and psychosocial history, and laboratory data at enrolment and then at regular intervals during the period of observation. Baseline characteristics of patients at study enrolment are provided in Table 6.2. Numerous patient outcomes are studied, although the outcomes of main interest are death, frequency of hospitalisation, vascular access, and health related quality of life.

The DOPPS dataset for this case study contains 6100 samples from the DOPPS phase 1 in the United States, collected from 1996-1999. Each record includes 24 patient and treatment related variables (input): demographics (age, sex, race), psychosocial characteristics (mobility, summary physical and mental component scores (sMCS, sPCS) using the Kidney Disease Quality of Life (KD-QOL®) Instrument), co-morbid medical conditions (diabetes, angina, myocardial infarction, congestive heart failure, left ventricular hypertrophy, peripheral vascular disease, cerebrovascular disease, hypertension, body mass index), laboratory results (serum creatinine, calcium, phosphate, albumin, hemoglobin), haemodialysis treatment parameters (Kt/V, haemodialysis angioaccess type, haemodialyser flux), and vintage (years on haemodialysis at the commencement of the DOPPS). The outcome is patient survival at 3 years post study enrolment.

A fundamental strength of this dataset is that it is representative of most of the world's dialysis population other than for China. Patients are randomly chosen

from a random selection of dialysis units within countries, with the random selection of units being stratified by type of dialysis unit (hospital based versus community satellite, publicly funded versus private). Of note, 20 dialysis units in Australia and two in New Zealand participate in the DOPPS. As such, the data in the DOPPS dataset are directly applicable to both our local dialysis population and also the wider global population.

**Table 4-3 Baseline clinical characteristics of study participants in the DOPPS dataset**

| Parameter | n (% of total) | Median | Inter-quartile range |
|---|---|---|---|
| | | | |
| Number of patients | 6010 | | |
| Age (years) | | 62 | 49-62 |
| Vintage (years) | | 0.6 | 0.02-2.73 |
| Male | 3282 (54.6%) | | |
| Female | 2728 (45.4%) | | |
| Race: | | | |
| White | 3071 (51.1%) | | |
| Black | 2054 (34.2%) | | |
| Asian | 178 (3.0%) | | |
| Native American | 49 (0.8%) | | |
| Hispanic | 580 (9.7%) | | |
| Other | 78 (1.3%) | | |
| Primary renal disease: | | | |
| Diabetes mellitus | 2257 (40%) | | |
| Hypertension | 1723 (30.5%) | | |
| Glomerulonephritis | 553 (9.8%) | | |
| Neoplasms | 93 (1.7%) | | |
| Obstruction | 152 (2.7%) | | |
| Polycystic kidney disease / interstitial nephritis / hereditary | 561 (9.9%) | | |

| | | | |
|---|---|---|---|
| Other | 305 (5.4%) | | |
| Smoking: | | | |
| Active | 2478 (52.6%) | | |
| Former (<1 year) | 1015 (21.5%) | | |
| Former (>1 year) | 237 (5.0%) | | |
| Non-smoker | 985 (20.1%) | | |
| Angina: | | | |
| None | 3867 (64.4%) | | |
| Exertional | 1464 (24.4%) | | |
| At rest | 679 (11.3%) | | |
| Previous myocardial infarction | | | |
| None | 4790 (79.7%) | | |
| > 3 months | 1087 (18.1%) | | |
| < 3 months | 133 (2.2%) | | |
| Previous coronary surgery / intervention | 863 (14.8%) | | |
| Previous cardiac arrest | 149 (2.5%) | | |
| Congestive heart failure | | | |
| None | 2821 (48.2%) | | |
| Previous | 917 (15.7%) | | |
| Dyspnoea at rest | 2115 (36.14) | | |
| Left ventricular hypertrophy | 1685 (28.7%) | | |
| Cancer: | | | |
| None | 5271 (87.7%) | | |
| >10 years ago | 298 (5.0%) | | |

| | | | |
|---|---|---|---|
| 5-10 years ago | 91 (1.5%) | | |
| 1-5 years ago | 143 (2.4%) | | |
| <1 year ago | 207 (3.4%) | | |
| Hypertension: | | | |
| None | 892 (15.4%) | | |
| Current | 4795 (82.5%) | | |
| Current + retinopathy | 123 (2.1%) | | |
| Previous cerebrovascular disease | | | |
| None | 4962 (84.4%) | | |
| TIA | 123 (2.3%) | | |
| Stroke, no deficit | 492 (8.4%) | | |
| Stroke, deficit | 291 (5.0%) | | |
| Peripheral vascular disease | | | |
| None | 4388 (74.7%) | | |
| Intermittent claudication | 460 (7.8%) | | |
| Previous bypass / AAA | 208 (3.5%) | | |
| Rest pain / gangrene | 500 (8.5%) | | |
| Previous amputation | 321 (5.5%) | | |
| Diabetes mellitus | | | |
| None | 3072 (52.6%) | | |
| Current | 1293 (22.1%) | | |
| Current + microvasculopathy | 1479 (25.3%) | | |
| Lung disease | | | |
| None | 5095 (87.4%) | | |

| | | | |
|---|---|---|---|
| Current | 522 (9.0%) | | |
| Current + home oxygen | 215 (3.7%) | | |
| Dementia | 230 (3.9%) | | |
| Peripheral neuropathy | 1119 (18.9%) | | |
| Atrial fibrillation | 629 (10.6%) | | |
| Alcohol abuse | 320 (7.5%) | | |
| Previous parathyroidectomy | 140 (2.4%) | | |
| Gastrointestinal bleeding: | | | |
| None | 4933 (83.2%) | | |
| Previous | 537 (9.1%) | | |
| <12 months | 457 (7.7%) | | |
| AIDS | 71 (2.6%) | | |
| Hepatitis B: | | | |
| None | 5886 (97.9%) | | |
| Current | 121 (2%) | | |
| Current + ascites | 3 (0.1%) | | |
| Hepatitis C: | | | |
| None | 5608 93.31 | | |
| Current | 392 (6.5%) | | |
| Current + ascites | 10 (0.2%) | | |
| High flux haemodialysis | 2277 (43.5%) | | |
| Vascular access: | | | |
| Fistula | 1208 (20.8%) | | |
| Graft | 2353 (40.4%) | | |

| | | | |
|---|---|---|---|
| Bovine graft | 129 (2.2%) | | |
| Tunnelled CVL | 1139 (19.6%) | | |
| Non-tunnelled CVL | 992 (17.0%) | | |
| Malnutrition | 439 (8.6%) | | |
| Mobility: | | | |
| Walks and eats normally | 3784 (67.2%) | | |
| Walks with assistance | 912 (16.2%) | | |
| Wheelchair, can transfer | 361 (6.4%) | | |
| Wheelchair, cannot transfer | 449 (8.0%) | | |
| Cannot eat independently | 126 (2.2%) | | |
| Marital status | | | |
| Single | 1072 (18.5%) | | |
| Married | 2887 (49.8%) | | |
| Widowed | 1039 (17.9%) | | |
| Divorced | 635 (11.0%) | | |
| Separated | 163 (2.8%) | | |
| Living status | | | |
| Living alone | 1014 (17.3%) | | |
| Lives with family or friends | 4519 (77.0%) | | |
| Nursing home/ institution | 311 (5.3%) | | |
| Homeless | 15 (0.3%) | | |
| Prisoner | 8 (0.1%) | | |
| Education: | | | |
| <12 years | 1655 (34.9%) | | |

| | | | |
|---|---|---|---|
| High school | 1806 (38.1%) | | |
| Incomplete tertiary | 716 (15.1%) | | |
| Graduate tertiary | 570 (12.0%) | | |
| Employment / homemaker /retired: | | | |
| Current | 2412 (57.6%) | | |
| Unemployed | 541 (12.9%) | | |
| Disabled | 1234 (29.5%) | | |
| Residual renal function | 1329 (39.5%) | | |
| Blood pressure (mmHg): | | | |
| Pre-dialysis systolic | | 153 | 137-168 |
| Pre-dialysis diastolic | | 79 | 70-88 |
| Post-dialysis systolic | | 142 | 126-159 |
| Post-dialysis diastolic | | 75 | 66-84 |
| Haemodialysis Rx / week | | 3 | 3-3 |
| Heamodialysis Rx time (hours) | | 210 | 180-240 |
| Dialysate $K^+$ (mmol/L) | | 2 | 2-2.5 |
| Dialysate $Na^+$ (mmol/L) | | 140 | 140-143 |
| Dialysate bicarbonate (mmol/L) | | 35 | 35-39 |
| Daily protein intake (g) | | 80 | 71-92 |
| Daily calorie intake (kcal) | | 2000 | 1800-2000 |
| 3-mo mean serum creatinine (mg/dL) | | 8.4 | 6.3-11 |
| 3-mo mean serum BUN (mg/dL) | | 63.3 | 51-78.5 |
| 3-mo mean serum $K^+$ (mmol/L) | | 4.7 | 4.3-5.2 |
| 3-mo mean serum $Ca^{2+}$ (mg/dL) | | 9 | 8.4-9.6 |

| | | | |
|---|---|---|---|
| 3-mo mean serum albumin (mg/dL) | | 3.7 | 3.3-3.9 |
| 3-mo mean serum $PO_4$ (mg/dL) | | 5.6 | 4.6-6.7 |
| 3-mo mean serum Hb (g/dL) | | 10.5 | 9.5-11.4 |
| 3-mo mean serum $Na^+$ (mmol/L) | | 138 | 135-140 |
| 3-mo mean serum $HCO_3^-$ (mmol/L) | | 21 | 18-24 |
| 3-mo mean serum ferritin (ug/L) | | 236 | 105-480 |
| 3-mo mean total cholesterol (mg/dL) | | 166 | 140-197 |
| 3-mo mean HDL cholesterol (mg/dL) | | 37 | 31-49 |
| 3-mo mean LDL cholesterol (mg/dL) | | 102 | 76-138 |
| 3-mo mean triglycerides (mg/dL) | | 143 | 100-212 |
| Kt/V | | 1.3 | 1.15-1.42 |
| Normalized protein catabolic ratio | | 0.9 | 0.7-1.1 |
| Predialysis weight (Kg) | | 73.5 | 62.7-87.2 |
| Postdialysis weight (Kg) | | 71.2 | 60.5-84.6 |
| BMI | | 24.7 | 21.5-29 |
| Summary physical component score | | 31.9 | 24.7-40.1 |
| Summary mental component score | | 47.4 | 37.5-56.1 |
| Depression | 1133 (19.1%) | | |

## 4.5 Regression Formulas and Connectionist Systems

As discussed above, kidney disease is a lethal and expensive calamity for both the patient and the nation. Better predictive tools would help lessen the burden of disease to both sufferers of kidney disease and the population at large.

As is also discussed above, regression formulas are the stalwart of prediction in medical issues related to kidney disease. However, their accuracy is limited with incremental improvement with addition data and modelling complexity. One reason for their poor performance is that they are global models, in which statistical functions or mathematical formulas are developed and applied uniformly to the entire patient population. For example, the MDRD formula implicitly assumes that relationships between predictive variables and GFR are the same for every patient within a given cohort.

In contrast, a framework of multiple local models, in which different statistical models or mathematical formulas are developed and applied in different clusters of patients, may be more fruitful. As described in the previous chapters of this research, connectionist systems can be provided with a self-mapping function by which new patient data are allocated to whichever cluster or clusters are closest in terms of the associated predictive variables. From there, the local models unique to the allocated cluster or clusters can be applied to the new data in a weighted fashion. Moreover, these self-mapping functions may be used for a transductive approach to develop new models for each new patient using a framework of multiple personal models. Overall, it is likely that connectionist computing structures using these frameworks will generate more accurate output than regression analysis. A further benefit of connectionist systems is the easy implementation of adaptive modelling: when new patient training data are provided, the system will optimize both clustering and local or personal models until error cannot be reduced further. This is not possible to implement with classical regression analysis.

Regression analysis is often unsuited for noisy medical data, and limited by assumptions regarding data distribution. In contrast, connectionist systems tolerate noisy data well and do not require assumptions regarding data distribution. They outperform classical regression analysis in situations where input variables are interrelated. They are potentially suitable for the prediction of both GFR in chronic kidney disease and survival in dialysis patients, where the

complex interrelation of patient factors make the evaluation of renal function and prediction of prognosis very difficult.

## 4.6 Summary

This chapter provides the medical and biological background to the representative problems which will be modelled in this research. It presents context and clinical relevance, the biological role of renal function, and the difficulties of renal function evaluation using current tools. The chapter also provides corresponding background to the problem of mortality for haemodialysis patients, and again the corresponding difficulties with prediction of longevity. The two modelling datasets (GFR, DOPPS) has be introduced and described.

In ***Chapter 5***, a local knowledge-based model - GFR- KBNN will be introduced. The development and the performance of this inductive neural model ar also presented.

# Chapter 5 : A Knowledge Based Neural Network for the Prediction of Renal Function (GFR - KBNN)

In ***Chapter 4***, medical and biological background was presented as it relates to the representative problems modelled in this research. The biological relevance of renal function was discussed, and the limitations of current tools for its evaluation. The modelling dataset (GFR and DOPPSt) used in this current chapter was also introduced and described.

In this chapter, a novel KBNN for the prediction of GFR is presented (GFR-KBNN). GFR-KBNN is a neural system in which prediction occurs based on global and local learning. As described in Chapter 4, there are several existing regression formulas commonly used by medical practitioners to predict GFR in both clinical and research settings. These formulas constitute global and fixed models, and each of them is characterised by different and varying degrees of prediction error distributed across the problem space. Nevertheless, these regression formulas represent accumulated knowledge that might be accurate in at least some sub-space of the whole problem space.

The GFR-KBNN incorporates several conventional regression formulas and kernel functions in its structure for improved accuracy and adaptation. Unlike standard feed-forward NNs, the GFR-KBNN model uses several different non-linear functions as neurons in its hidden layer. Each hidden neural node has a pair of such functions, comprised of one conventional regression formula that represents existing knowledge, and one Gaussian kernel function that defines a sub-space of the whole problem space, in which the formula is locally adapted to new data. All these functions are aggregated through incremental learning. The GFR-KBNN model is trained using the GFR dataset as described in Chapter 4, which contains observed measurements patient GFR and associated demographic and laboratory variables for modelling. In this case study, the regression function for each cluster is selected by the model from conventional regression formulas that are commonly used by medical practitioners to predict GFR (Table 4.1). As will be demonstrated, GFR-KBNN

predicts GFR with ≥10% greater accuracy compared to any of the individual regression formulas or other NN models. Furthermore, the model derives locally adapted formulas with the best performance within each cluster. In summary, using existing knowledge the GFR-KBNN model can manifest better accuracy and extract adapted formulas on new data.

The material of the chapter was published in (Song, Kasabov, Ma, & Marshall, 2005).

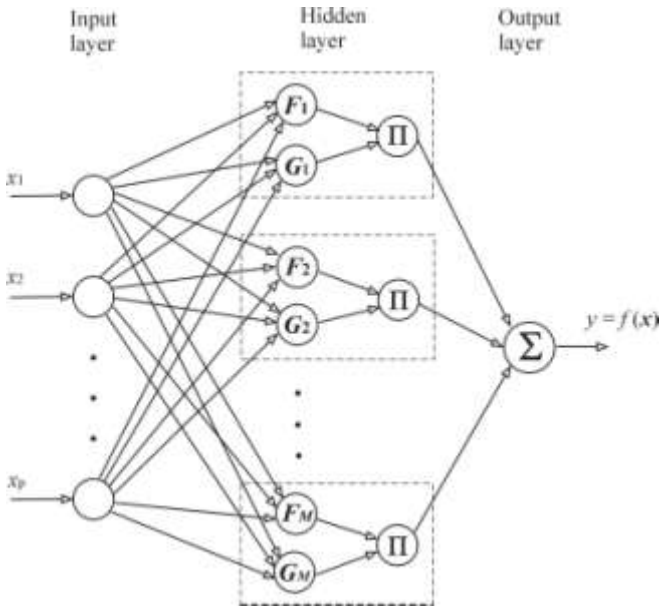
## 5.1 Introduction to GFR-KBNN: Integrating Regression Formulas and Kernel Functions into a Locally Adaptive KBNN

So long as there are sufficient data, both general NNs (including kernel-based function NNs) and KBNNs can generate accurate output after appropriate training (Cloete & Zurada, 2000; N. Kasabov, 1996; John Moody & Darken, 1989; Q. Song, Ma, & Kasabov, 2004). Kernel-based NNs have radial based function (RBF) kernels attached to their nodes that are adjusted through learning from data in terms of their centres and radius(John Moody & Darken, 1989). They are trained as a set of local models that are integrated at the output.

KBNNs are a distinct type of NN structured to “capture” knowledge from data in different formats, but most often as IF-THEN rules (Cloete & Zurada, 2000; Jang, 1993; N. Kasabov, 1996). In (N. Kasabov, 2003; N. Kasabov & Song, 2002), special types of KBNN are presented where the model evolves its structure from data and can adapt to new data in an incremental mode facilitating rule extraction (that is, an evolving connectionist system). However, this approach as applied so far has a limited capability as it “ignores” the accumulated knowledge in the regression formulas that might be useful at least in some sub-space of the whole problem space.

We propose a new type of KBNN that is represented by the following generic structure in Fig. 5.1 and generic function in Eq. 5.1:

**Figure 5.1 A generic structure for the proposed KBNN**




$$y(\boldsymbol{x}) = G_1(\boldsymbol{x})\, F_1(\boldsymbol{x}) + G_2(\boldsymbol{x})\, F_2(\boldsymbol{x}) + \ldots + G_M(\boldsymbol{x})\, F_M(\boldsymbol{x}) \qquad (5.1)$$

where, $\boldsymbol{x} = [x_1, x_2, \ldots, x_P]$ is the input vector; $y$ is the output vector; $G_I$ are kernel functions; and $F_I$ are knowledge-based transfer functions, e.g. regression formulas, $I = 1, 2, \ldots M$.

Eq. 5.1 can be regarded as a functional regression function. Using different $G_I$ and $F_I$, Eq. 5.1 can represent different kinds of neural networks, and describe the different functions associated with neurons in their hidden layer(s). $G_I$ are *Gaussian* kernel functions and $F_I$ are constants in the case of RBF NNs (John Moody & Darken, 1989). $G_I$ are sigmoid transfer functions and $F_I$ are constants in the case of a generic three-layer MLP NN (Jang, 1993; N. Kasabov, 1996; N. Kasabov, 2003; "Neural Network Toolbox user's guide," 1996). $G_I$ are fuzzy membership functions and $F_I$ are linear functions in the case of a first-order Takagi-Sugeno-Kang (TSK) fuzzy inference model (Jang, 1993); and in the simplest case, $G_I$ represents a single input variable and $F_I$ are constants in the case of a linear regression function.

The KBNN structure illustrated in Fig. 5.1 is distinct from these other NNs (*Fuzzy Logic Toolbox User's Guide* 2002). $F_I$ are non-linear functions that

represent the knowledge in local areas, and $G_l$ are *Gaussian* kernel functions that control the contribution of each $F_l$ to the system output. The further an input vector is from the centre of the Gaussian function, the less contribution to the output is produced by the corresponding $F_l$.

The KBNN model has a cluster-based, multi-local model structure. Every transfer function is selected from existing knowledge (conventional regression formulas), and it is trained within a cluster (local learning), so that it becomes a modified formula that can optimally represent this area of data. These formulas are taken as knowledge-based transfer functions to be integrated into the KBNN model. The KBNN aggregates a number of transfer functions and Gaussian functions to compose a neural network and such a network is then trained on the whole training data set (global learning). The GFR-KBNN model uses the medical dataset of observed patient GFR measurements to select the most accurate formula within each patient cluster and incorporate it within the local model.

## 5.2 Proposed Method

In this experiment, we compare the prediction of GFR from KBNN models with the prediction using individual regression formulas and other NN models. We use the GFR dataset as described in Chapter 4.

### 5.2.1 Learning Procedures for the Integrated Regression – Kernel Function of KBNNs

Suppose there are $Q$ functions $f_h$, $h$ = 1, 2, ..., $Q$, globally representing existing knowledge that are selected as functions $F_l$ (see Fig.1). The KBNN learning procedure performs the following steps:

(1) Cluster the whole training data set into $M$ clusters.
(2) In each cluster $l$, $l$ = 1, 2, …, $M$, $Q$ functions $f_h$ are modified (local learning) with a gradient descent method on the sub-dataset and the best one (with the minimum root-mean-square error – RMSE) is chosen as the transfer function $F_l$ for this cluster.

(3) Create a Gaussian kernel function $G_l$ as a distance function: the centre and radius of the clusters are respectively taken as initial values of the centre and width of $G_l$.

(4) Aggregate all $F_l$ and $G_l$ as per Eq. 5.1 and optimize all parameters in the KBNN (including parameters of each $F_l$ and $G_l$) using a gradient descent method on the whole data set.

In the KBNN learning algorithm, the following indexes are used:

- Training data : $i = 1, 2, \ldots, N$ ;
- Sub-training data set: $i = 1, 2, \ldots, N_l$ ;
- Input variables: $j = 1, 2, \ldots, P$ ;
- Neuron pairs in the hidden layer: $l = 1, 2, \ldots, M$ ;
- Number of existing functions: $h = 1, 2, ..., Q$ ;
- Number of parameters in $F_l$ $pf = 1, 2, ..., L_{pf}$;
- Learning iterations: $k = 1, 2, \ldots$

The equations for parameter optimisation are described below. Consider the system having $P$ inputs, one output, and $M$ neuron pairs in the hidden layer, the output value of the system can be calculated on input vector $\boldsymbol{x}_i = [x_{i1}, x_{i2}, \ldots, x_{iP}]$ by Eq. 5.1:

$$y(\boldsymbol{x}_i) = G_1(\boldsymbol{x}_i)\, F_1(\boldsymbol{x}_i) + G_2(\boldsymbol{x}_i)\, F_2(\boldsymbol{x}_i) + \ldots + G_M(\boldsymbol{x}_i)\, F_M(\boldsymbol{x}_i) \qquad (5.2)$$

Here, $F_l$ are transfer functions and each of them has parameters $b_{pf}$ , $pf = 1, 2, ..., L_{pf}$ ,

and $G_l(\mathbf{x}_i) = \alpha_l \prod_{j=1}^{P} \exp[-\frac{(x_{ij} - m_{lj})^2}{2\sigma_{lj}^2}]$ are Gaussian kernel functions. (5.3)

Here, $\boldsymbol{\alpha}$ represents a connection vector between the hidden layer and the output layer; $\boldsymbol{m}_l$ is the centre of $G_l$. $\boldsymbol{\sigma}_l$ is regarded as the width of $G_l$, or a 'radius' of the cluster $l$. If a vector $\boldsymbol{x}$ is the same to $\boldsymbol{m}_l$, the neuron pair $G_l(\boldsymbol{x})F_l(\boldsymbol{x})$ has the maximum output – $F_l(\boldsymbol{x})$; the output will be between (0.607 ~ 1)$\times F_l(\boldsymbol{x})$ if the distance between $\boldsymbol{x}$ and $\boldsymbol{m}_l$ is smaller than $\boldsymbol{\sigma}_l$; the output will be close to 0 if $\boldsymbol{x}$ is far away from $\boldsymbol{m}_l$.

Suppose the KBNN is given the training input-output data pairs [$\boldsymbol{x}_i$, $t_i$], the local learning minimizes the following objective function for each transfer function on the corresponding cluster:

$$E_l = \frac{1}{2}\sum_{i=1}^{Nl}[f_h(\mathbf{x}_i) - t_i]^2 \tag{5.4}$$

Here, $N_l$ is the number of data that belong to the $l$-th cluster, and the global learning minimizes the following objective function on the whole training data set:

$$E = \frac{1}{2}\sum_{i=1}^{N}[y(\mathbf{x}_i) - t_i]^2 \tag{5.5}$$

A gradient descent algorithm (BP algorithm) is used to obtain the recursions for updating the parameters $\boldsymbol{b}$, $\boldsymbol{\alpha}$, $\boldsymbol{m}$ and $\boldsymbol{\sigma}$, so that $E_l$ of Eq.5.4 and $E$ of Eq.5.5 are minimized. The initial values of these parameters can be obtained from original functions (for $\boldsymbol{b}$), random values or least-squares method (for $\boldsymbol{\alpha}$) and the result of clustering (for $\boldsymbol{m}$ and $\boldsymbol{\sigma}$):

$$b_{pf}(k+1) = b_{pf}(k) - \eta_b \frac{\partial E_l}{\partial b_{pf}} \quad \text{(for local learning)} \tag{5.6}$$

$$b_{pf}(k+1) = b_{pf}(k) - \eta_b \frac{\partial E}{\partial b_{pf}} \quad \text{(for global learning)} \tag{5.7}$$

$$\alpha_l(k+1) = \alpha_l(k) - \frac{\eta_\alpha}{\alpha_l(k)}\sum_{i=1}^{N}\{G_l(\boldsymbol{x}_i)F_l(\boldsymbol{x}_i)[y(\boldsymbol{x}_i) - t_i]\} \tag{5.8}$$

$$m_{lj}(k+1) = m_{lj}(k) - \eta_m\sum_{i=1}^{N}\left\{\frac{G_l(x_i)F_l(x_i)[y(x_i) - t_i](x_{ij} - m_{lj})}{\sigma_{lj}^2}\right\} \tag{5.9}$$

$$\sigma_{lj}(k+1) = \sigma_{lj}(k) - \eta_{\sigma} \sum_{i=1}^{N} \left\{ \frac{G_l(\mathbf{x}_i) F_l(\mathbf{x}_i)[y(\mathbf{x}_i) - t_i](x_{ij} - m_{lj})^2}{\sigma_{lj}^3} \right\} \quad (5.10)$$

Here, $\eta_b$, $\eta_\alpha$, $\eta_m$, and $\eta_\sigma$ are learning rates for updating the parameters $\boldsymbol{b}$, $\boldsymbol{\alpha}$, $\boldsymbol{m}$ and $\boldsymbol{\sigma}$ respectively;

$\frac{\partial E_l}{\partial b_{pf}}$ and $\frac{\partial E}{\partial b_{pf}}$ respectively depend on existing and selected functions, e.g. the MDRD function, which has been introduced in Chapter 4, can be defined as follows:

$$f(\boldsymbol{x}) = \text{GFR} = b_0 \times x_1^{b1} \times x_2^{b2} \times x_3^{b3} \times x_4^{b4} \times x_5^{b5} \times x_6^{b6} \quad (5.11)$$

In this function, $x_1$, $x_2$, $x_3$, $x_4$, $x_5$ and $x_6$ represent Scr, age, gender, race, BUN and Alb respectively. So that, for the local learning:

$$\frac{\partial E_l}{\partial b_0} = \sum_{i=1}^{Nl} [f(x_i) - t_i] \quad (5.12)$$

$$\frac{\partial E_l}{\partial b_p} = x_p^{b_p} \ln b_p \sum_{i=1}^{Nl} [f(x_i) - t_i], \; p = 1, 2, ..., 6 \quad (5.13)$$

and for the global learning (suppose the MDRD function is selected for the $l$-th cluster):

$$\frac{\partial E}{\partial b_0} = G_l(x_i) \sum_{i=1}^{N} [y(x_i) - t_i] \quad (5.14)$$

$$\frac{\partial E}{\partial b_p} = G_l(x_i) x_p^{b_p} \ln b_p \sum_{i=1}^{N} [y(x_i) - t_i], \quad p = 1, 2, ..., 6 \quad (5.15)$$

For both local and global learning, the following iterative design method is used:

(1) Fix the maximum number of learning iterations ($maxK_l$ for the local learning and $maxK$ for the global learning) and the minimum value of the error on training data ($minE_l$ for the local learning and $minE$ for the global learning );

(2) Perform Eq. 5.6 repeatedly for the local learning until the number of learning iterations $k > maxK_l$ or the error $E_l <= minE_l$ ($E_l$ is calculated by Eq. 5.4);

(3) Perform Eq. 5.7 – 10 repeatedly for the global learning until the number of learning iterations $k > maxK$ or the error $E <= minE$ ($E$ is calculated by Eq. 5.5).

In this learning procedure, we use a clustering method called *ECM* (Evolving Clustering Method) for clustering and a gradient descent algorithm for parameter optimization(N. Kasabov & Song, 2002; Q. Song & Kasabov, 2001). Although some other clustering methods can be used such as *K-means*, *Fuzzy C-means* or the *Subtractive* clustering method (*Fuzzy Logic Toolbox User's Guide* 2002), *ECM* is more appropriate because it is a fast one-pass algorithm and produces well-distributed clusters. The number of clusters, M, depends on the data distribution in the input space and it can be set up by experience, probing search or optimization methods (e.g. the genetic algorithm – GA). In this research, we do not use any optimization method to adjust M. For generalisation and simplicity, we give the KBNN learning algorithm a general gradient descent method. The Levenberg-Marquardt (LM), one-step secant BP algorithm (*Fuzzy Logic Toolbox User's Guide* 2002), Least-squares method, SVD-QR method or some others (Mendel, 2001) can be applied in the KBNN for parameter optimization instead of a general gradient descent algorithm.

### 5.2.2 Statistical Evaluation

The performance of GFR-KBNN models and individual regression formulas and other NN models are compared using the *Root-Mean-Square-Error* (RMSE) and the *Mean-Absolute-Error* (MAE), as defined as the following equations:

$$RMSE = \left[ \sum_{i=1}^{N} (y_i - t_i)^2 \Big/ N \right]^{1/2} \quad (5.16)$$

$$MAE = \sum_{i=1}^{N} |y_i - t_i| \Big/ N \quad (5.17)$$

where $N$ is the number of testing samples, $y_i$ and $t_i$ are the actual output. $y_i$ is calculated by a model or a function, and $t_i$ is the desired output for the $i$-th testing sample.

The statistical assessment of agreement is philosophically related to the assessment of model fit, although there are all sorts of aspects of agreement and model fit that are better illustrated with one method than the other.

In regression analysis, the RMSE is an assessment of the residuals around a line of best fit. This can be directly converted into 95% confidence intervals by a number of different methods. The RMSE is also known as the standard error of the estimate in regression analysis. This is the statistic whose value is minimized during the parameter estimation process, and it is the statistic that determines the width of the confidence intervals for predictions. The 95% confidence intervals for prediction are approximately equal to the point prediction "plus or minus 2 standard errors"--i.e., plus or minus 2 times the RMSE

95% confidence intervals are the standard way of expressing accuracy in medical fields, although Bland and Altman analyses and concordance correlation coefficient are also used. In Chapter 6 of the GFR-DENFIS model, all of these methods of describing accuracy were used. These are sufficient for all regulatory bodies, and are the basis for which the MDRD formula was adopted by NZ over and above of previous ones.

### 5.2.3 Data Source

The GFR-KBNN models are trained using the GFR dataset as described in Chapter 4, and all testing is also using the same dataset. Ideally, a training dataset should be used to train a model for testing on an independent testing dataset. When the data set is comparably small, a Leave-One-Out cross-validation method is usually used (Leave-One-Out cross-validation: for each experiment, one sample is taken out from the data set as the testing data and the remains as the training data). In this experiment, all results of the models listed in Table 5-1 (including GFR-KBNN models) are based on Leave-One-Out cross-validation experiments on the whole data set. We did not use parameter optimization the connectionist models, but used instead different parameter sets for each model to optimise output, and the best results produced by the

respective models are shown in Table 5-1. For instance, we used LM learning algorithm for MLP (*Neural Network Toolbox User's Guide*, 2002), and selected different number of neurons in the hidden layer from [4, 8, 12, 16, 24, 32] and different number of learning iterations from [60, 120, 200, 500]. The parameters of the MLP producing the best results (as shown in Table 5-1) are 12 neurons and 200 learning iterations.

## 5.3 Results

The GFR-KBNN models generate more accurate outputs than the existing formulas or other well-known connectionist models. The results of all comparisons are listed in Table 5-1, including those obtained using the nine conventional regression formulas, standard NN models such as MLP and RBFNNs (*Neural Network Toolbox User's Guide*, 2002), and the adaptive neural fuzzy inference system (ANFIS) (*Fuzzy Logic Toolbox User's Guide* 2002; Jang, 1993). The results include the number of fuzzy rules (for ANFIS), or neurons in the hidden layer (for KBNN, RBF and MLP), testing RMSE, testing MAE and Std (standard deviation).

For the GFR-KBNN models, we found that the number of clusters – M, and the initial values for the BP algorithm affect the training results. If M is too small, e.g. $M < 6$, the results are similar to that of using a certain formula. This is because the KBNN cannot derive optimal local models under such conditions. If M is too large, e.g. $M > 30$, some clusters are so small that the data in these clusters are not adequate for the local learning. In this study, the best range for M was 12 – 20.

With regard to the BP algorithm, random values were used as initial parameter values, and for every experiment we implemented GFR-KBNN for three times and then selected the best result (the MLP and RBF were implemented in the same way).

The testing results (using Leave-One-Out cross-validation) of different phases of GFR-KBNN are listed in Table 5-2. From the results we can see that:

(1) Using original formulas locally is better than using them globally;

(2) Local learning adapts original formulas to local data;

(3) The optimal local models are changed a little after the global learning;

(4) Both local learning and global learning are necessary for the KBNN model to improve its accuracy.

Through training the KBNN model, new knowledge can be extracted, which includes the modified formulas for each cluster (location). When the whole data set (441 samples) is used to train the KBNN, the whole input space is partitioned into 17 clusters and 17 corresponding modified formulas are obtained: one Cockcroft-Gault, two Gates, five MDRD and nine Walser. Four of these 17 formulas are listed in Table 5-3 to Table 5-5. The formulas listed in Table 5-3 are four optimal formulas for corresponding local areas (clusters). After the local learning and global learning, the formulas change as listed in Table 5-4, and they comprise the final KBNN model that can be used to obtain better results. Table 5-5 shows the parameters of four related Gaussian kernel functions. From the experimental results, we can see that four formulas (Walser, MDRD, Gates and Cockcroft-Gault) are selected as the most important to KBNN model in this case study. It can be inferred that these formulas are also the most suitable for use in New Zealand and Australia.

**Table 5-1 Experimental results (testing) on GFR data with different methods.**

| *Model* | *Neurons or Rules* | *RMSE* | *MAE* | *Std* |
|---|---|---|---|---|
| Jelliffe71 | – | 9.13 | 7.21 | 12.42 |
| Mawer | – | 11.01 | 8.09 | 13.34 |
| Jelliffe73 | – | 7.84 | 5.90 | 9.66 |
| Cockcroft-Gault | – | 7.97 | 6.16 | 10.45 |
| Hull | – | 9.50 | 7.12 | 12.43 |
| Bjorasson | – | 10.29 | 7.83 | 12.07 |
| Gates | – | 7.49 | 5.62 | 9.92 |
| Walser | – | 7.36 | 5.58 | 10.19 |
| MDRD | – | 7.76 | 5.87 | 9.27 |
| MLP | 12 | 8.44 | 5.74 | 9.06 |
| ANFIS | 36 | 7.43 | 5.46 | 8.97 |
| RBF | 32 | 7.18 | 5.39 | 9.36 |
| GFR-KBNN | 17 | 6.86 | 5.07 | 8.55 |

**Table 5-2 Experimental results (testing) on GFR data with different modes of operation of GFR-KBNN.**

| *Model* | *RMSE* | *MAE* |
|---|---|---|
| Local Models (original formulas) | 7.28 | 5.51 |
| Modified local models (after local learning) | 7.09 | 5.26 |
| Modified local models (after local and global learning) | 7.12 | 5.30 |
| KBNN with global learning only | 7.05 | 5.19 |
| KBNN with both local and global learning | 6.86 | 5.07 |

**Table 5-3 Four selected formulas (after local learning)**

| *Cluster Number* | *Best Formula For The Cluster* | *Modified Formula Through Local Adaptation In The KBNN Model* |
|---|---|---|
| 1 | MDRD | $121.5 \times Scr^{-0.842} \times Age^{-0.058} \times 0.834$ (if *Sex* is female) $\times 0.915$ (if *Race* is black) $\times BUN^{-0.101} \times Alb^{0.014}$ |
| 3 | Walser | Men: $6319 / Scr - (0.046 \times Age) + (0.081 \times Weight) - 1.90$<br>Women: $4747 / Scr - (0.175 \times Age) + (0.056 \times Weight) + 7.28$ |
| 5 | Gates | Men: $(83.21 \times Scr^{-1.2}) + (55 - Age) \times (0.805 \times Scr^{-1.1}) + 5.34$<br>Women: $(49.64 \times Scr^{-1.1}) + (56 - Age) \times (0.271 \times Scr^{-1.1}) + 5.88$ |
| 7 | Walser | Men: $6288 / Scr - (0.047 \times Age) + (0.091 \times Weight) - 1.91$<br>Women: $4402 / Scr - (0.0287 \times Age) + (0.077 \times Weight) + 0.349$ |

**Table 5-4 Four selected formulas (after local learning and global learning)**

| *Cluster Number* | *Best Formula For The Cluster* | *Modified Formula Through Local Adaptation In The KBNN Model* |
|---|---|---|
| 1 | MDRD | $121.5\times Scr^{-0.846}\times Age^{-0.055}\times 0.834$ (if *Sex* is female) $\times 0.915$ (if *Race* is black) $\times BUN^{-0.099}\times Alb^{0.011}$ |
| 3 | Walser | Men: $6306 / Scr - (0.044\times Age) + (0.085\times \text{Weight}) - 1.92$<br>Women: $4759/ Scr - (0.178\times Age) + (0.058\times \text{Weight}) + 7.40$ |
| 5 | Gates | Men: $(83.58\times Scr^{-1.2}) + (55 - Age) \times (0.801\times Scr^{-1.1}) + 5.58$<br>Women: $(49.53\times Scr^{-1.1}) + (56 - Age) \times (0.275\times Scr^{-1.1}) + 5.87$ |
| 7 | Walser | Men: $6306 / Scr - (0.044\times Age) + (0.085\times Weight) - 1.92$<br>Women: $4393/ Scr - (0.0351\times Age) + (0.076\times Weight) + 0.347$ |

**Table 5-5 Four Gaussian functions (after local learning and global learning) associated with four clusters.**

| *Cluster Number* | *Parameters of Gaussian functions* | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 1 | $\alpha$ | 0.113 | | | | | | |
| | $\boldsymbol{m}$ | 36.5, | 0, | 0.61, | 3.67, | 0, | 19.4, | 162, | 61.8 |
| | $\boldsymbol{\sigma}$ | 7.12, | 0.155, | 0.41, | 4.10, | 0.16, | 2.82, | 8.0, | 5.0 |
| 3 | $\alpha$ | -0.122 | | | | | | |
| | $\boldsymbol{m}$ | 27.8, | 1, | 1.24, | 18.6, | 0, | 16.8, | 155, | 47.7 |
| | $\boldsymbol{\sigma}$ | 6.30, | 0.15, | 0.33, | 4.0, | 0.15, | 6.0, | 8.0, | 5.89 |
| 5 | $\alpha$ | -0.193 | | | | | | |
| | $\boldsymbol{m}$ | 69.1, | 0, | 1.37, | 15.7, | 0, | 16.8, | 171, | 58.9 |
| | $\boldsymbol{\sigma}$ | 7.04, | 0.15, | 0.39, | 4.0, | 0.15, | 6.0, | 8.0, | 5.0 |
| 7 | $\alpha$ | 0.288 | | | | | | |
| | $\boldsymbol{m}$ | 51.2, | 1, | 0.77, | 7.61, | 0, | 5.44, | 178, | 61.2 |
| | $\boldsymbol{\sigma}$ | 6.97, | 0.15, | 0.50, | 4.0, | 0.15, | 6.0, | 8.0, | 6.02 |

## 5.4 Conclusions

In this case study, the local learning GFR-KBNN model performed better than any of existing conventional regression formulas, MLP, RBFNNs, and ANFIS neural fuzzy models as global models. This is a result of a fine-tuning of each local model and a proper aggregation of all local models in the KBNN system.

The KBNN integrates existing regression formulas as sub-models with new data related to the same problem resulting in an incrementally adaptive model. The KBNN performs the local learning to find an optimal formula (local model) for each cluster defined by a kernel function. Global learning was subsequently performed to integrate all local models, thus facilitating knowledge insertion, knowledge-modification, and knowledge extraction. New knowledge can be extracted from the KBNN as follows:

(1) A modified function (or local model) that represents the current knowledge in each cluster (local area).
(2) The importance of the local models and how they can be aggregated to obtain better accuracy.
(3) For a new input vector, the contribution from each local function can be estimated.

The KBNN method is considered suitable for medical applications because:

(1) Related existing regression formulas can be used as local models, or local models can be created depending on the related knowledge;
(2) Through local learning and global learning, a KBNN model can achieve a better accuracy;
(3) New knowledge can be extracted from a KBNN model, which may be valuable for users.

## 5.5 Summary

In this chapter, a novel local inductive knowledge-based neural network based model was presented. Its performance was superior to existing global regression formulas commonly used by medical practitioners.

In ***Chapter 6*** the development of another local inductive neural fuzzy model is presented (GFR-DENFIS), and its performance compared to conventional methods for GFR prediction. This direction represents an incremental advance in the techniques of Health Informatics towards progressively more localized and personalised modelling frameworks with the expectation of a better accuracy and a more specialised knowledge discovery.

# Chapter 6 : An ECOS Based Method for Local Learning for Renal Function Evaluation (GFR - DENFIS)

In ***Chapter 5***, GFR-KBNN was presented as a local inductive knowledge-based model for the prediction of renal function. The GFR-KBNN models predict GFR with ≥10% greater accuracy compared to any of the individual regression formulas or other NN models.

In this chapter, another novel local modelling method for the prediction of GFR is presented (GFR-DENFIS). GFR was predicted using the dynamic evolving neuro-fuzzy inference system (DENFIS) (N. Kasabov & Song, 2002), an ECOS that optimizes its generated output by learning from training data using multiple local models. In this case, the generated output was GFR, and the training vectors were each comprised of the target output (GFR-EDTA) and the clinical and laboratory variables to be associated with this target output and therefore to be used for computational modelling. DENFIS was engineered to report GFR as the average of ten performed internal modelling experiments for both training and testing vectors.

The material of the chapter was published in (Marshall, Song, Ma, Macdonell & Kasabov, 2005)

## 6.1 Introduction to GFR-DENFIS

Detailed descriptions of DENFIS are provided in Chapter 3.

## 6.2 The Proposed Method

In this experiment, we compare the prediction of GFR from GFR-DENFIS models with the prediction the MDRD formula, which as described in Chapter 4 is the best of the available conventional regression formulas for the prediction of GFR. We use the GFR dataset as described in Chapter 4.

GFR were predicted also using a modified MDRD formula (mMDRD formula) containing the same variables, but different regression coefficients and multiplicative constants developed using multiple regression analyses in the GFR dataset. Successive mMDRD formulas were derived during each phase of the GFR-DENFIS modelling described below.

The rationale for modification of the original MDRD formula is as follows. As described in Chapter 4, the original formula was developed in a sample of the United States population to predict GFR as measured by renal clearance of $^{25}$I-iothalamate. In the GFR dataset, patients were sampled from an Australian and New Zealand population and GFR was measured by plasma clearance of $^{51}$Cr-EDTA. The original MDRD formula cannot therefore be expected to perform as well in this dataset as the original, due to patient related factors and also the inter-test variability between the two techniques for radioisotope GFR measurement. A meaningful comparison between the MDRD equation and GFR-DENFIS (which has been developed in the new dataset) requires that the original MDRD formula be remodelled to optimize accuracy under the new conditions. In this way, the comparison now becomes more valid in that both the algebraic formula and local models are products of the same dataset, and neither has the disadvantage of being developed under one set of conditions and tested under another.

### 6.2.1 Modelling Phases for GFR-DENFIS and mMDRD Formulas.

Three phases of modelling were performed. The purpose of the first phase of modelling was conventional validation of both the DENFIS and modified MDRD formula. Variables used in the training of DENFIS and modification of the MDRD formula were the same six as were used in original formula. The GFR dataset was randomly divided into training and testing sub-datasets, comprising 70% (309 renal function measurements) and 30% (132 renal function measurements, randomly selected) respectively of the total. The mMDRD formula was derived from the training dataset using stepwise multiple regression analyses. The model for GFR-DENFIS was derived from the training dataset within the neural fuzzy systems described in Chapter 3 and (N. Kasabov & Song, 2002). Even modified according to the new data, the mMDRD formula is a global model and

it is difficult to adapt to data in every sub-space of the problem space. The DENFIS model, being a set of local models, may be expected to perform better.

For the second phase of modelling, additional clinical variables were used for the training of DENFIS. The purpose of this phase of modelling was to evaluate the effect of adaptive properties of DENFIS in clinical practice. As previously, the GFR dataset was randomly divided into training and testing sub-datasets, but this time comprising 80% (353 renal function measurements) and 20% (88 renal function measurements) respectively of the total. The mMDRD formula was again derived from the now expanded training dataset using stepwise multiple regression analyses and the usual six variables per vector. The modelling of DENFIS was performed in a manner to closest reproduce its use in clinical practice. The likeliest clinical scenario is that centres would be sequentially recruited to the local model over time, to join other centres already using the trained system. The recruitment of the new centre would involve provision of some centre-specific training data to DENFIS, after which one could expect accurate prediction of GFR for the new patients.

The "leave one out" method is the modelling protocol that best reflects this clinical scenario. This protocol involved dividing the EPO AUS-14 dataset into 12 sub-datasets according to the centre of origin of the renal function measurement. For a given centre of interest, GFRDENFIS was initially modelled by training on the other 11 centres. GFRDENFIS was then further modelled in the centre of interest by retraining on a random sample comprising 80% of renal function measurements from that centre. This protocol was applied for each of the 12 centres. The overall prediction error was then calculated as the average error across the 12 centres from testing in the remaining 20% of the measurements from each centre. This modelling protocol provides the most realistic reflection of the ECOS performance with sequential recruitment of centres to the system over time.

The purpose of the third and final phase of modelling was to develop the most accurate local model and algebraic formula possible, and compare the limits of optimization for both frameworks. It should be noted that virtually all algebraic formulas in common clinical use, including the original MDRD as published,

have been optimized by using the entire respective data sets for concurrent training and testing(Cockcroft & Gault, 1976; Hull et al., 1981; Jelliffe, 1971; Kampmann, Siersbaek-Nielsen, Kristensen, & Hansen, 1974; Levey et al., 1999; Mawer et al., 1972; Walser et al., 1993). The third phase of modelling in this study was similarly undertaken using the entire GFR data set for both training and testing of both the neural fuzzy model and algebraic formula. The variables used in the training of DENFIS and modification of the MDRD formula were the same six as were used in the original MDRD formula.

Modelling for both algebraic formulae and DENFIS was performed using Matlab® V6 software (Natick, Massachusetts, USA).

### 6.2.2 Statistical Evaluation

The accuracy of predicted GFR values (GFR-MDRD, GFR-mMDRD, GFR-DENFIS) was determined by their bias and precision in relation to reference GFR measurements (GFR-EDTA). Absolute agreement or bias was assessed by the mean difference between the predicted GFR values and GFR-EDTA, which is the systematic difference between the methods. Relative agreement or precision was assessed by the fluctuation of these differences around the mean. The standard deviation of these differences can be quantified as the RMSE, which can be expressed in mL/min/1.73m$^2$ or as a percentage of GFR. The Bland-Altman procedure was also used which defines range of agreement. This is the mean difference +/- 1.96 standard deviations, and represents how far apart predicted GFR values are likely to be from reference GFR measurements for 95% of individuals (Bland & Altman, 1986, 1995). Analyses were made using Analyse-It® V1.62 software (Leeds, UK), and presented as scatter and bias plots.

## 6.3 Experimental Results

Results are presented as mean +/- standard deviation (range) unless otherwise specified. GFR-EDTA in the cohort was 22.6 +/- 10.7 (0.2 – 70) mL/min/1.73m$^2$. GFR-MDRD was 19.1 +/- 9.3 (3.3 – 46.9) mL/min/1.73m$^2$. GFR-mMDRD was 21.0 +/- 8.0 (4.2 – 40.8) mL/min/1.73m$^2$ after the first phase of modelling, 22.3

+/- 8.0 (3.0 – 45.4) mL/min/1.73m$^2$ after the second, and 21.4 +/- 7.8 (6.4 – 41.2) mL/min/1.73m$^2$ after the third. The mMDRD formula for Australians and New Zealanders generated using the entire GFR dataset was (analytes other than serum albumin in mg/dL, serum albumin in g/dL, age in years):

$$GFR - mMDRD = 120.4 \times (serum\ creatinine)^{-0.825} \times (age)^{-0.159} \times 0.837\,(if\ sex\ is\ female) \times 0.913\,(if\ race\ is\ black) \times (serum\ urea\ nitrogen)^{-0.0114} \times (serum\ albu\min)^{+0.0651}$$

GFR-DENFIS was 23.2 +/- 8.6 (5.0 – 47.6) mL/min/1.73m$^2$ after the first phase of modelling, and 22.6 +/- 8.7 (0.0 – 48.7) mL/min/1.73m$^2$ after the second. GFR-DENFIS was 22.5 +/- 9.9 (5.0 – 64.6) mL/min/1.73m$^2$ after the third phase of modelling.

Statistical assessments of bias and precision of predicted GFR values are presented in Table 6.1 and Figures 6.1 to 6.4. The prediction error of GFR-DENFIS versus mMDRD from the second phase of modelling for each of the 12 centres is shown in Figure 6.5. It can be seen that the local model outperformed the algebraic formula in only certain centres. This finding can be further explored considering Centre 2 as a case study. Patients from Centre 2 had a marginally higher serum creatinine (0.40 ±0.10 mmol/L) but a markedly lower GFR-EDTA (12.1 ±6.7 mL/min/1.73 m2) when compared to the other centres. The relationship between these two variables was therefore different in patients from Centre 2, explaining the improved prediction with local modelling via GFR-DENFIS in comparison to global modelling via the mMDRD. There are several possible hypotheses to explain this observation. Perhaps the patients from Centre 2 were biologically different with lower rates of creatinine production. Indeed, patients from Centre 2 did tend to be female (60% of patients), older (mean age 60 years), and none were black. Alternatively, laboratory assays for serum creatinine or measurements of GFR-EDTA may be systematically lower in Centre 2 than other centres. Irrespective of the reason, improved performance of GFR-DENFIS in this second phase of modelling is due to additional clustering and local model optimization, and allows for improved prediction for patients within centres by accounting for such centre disposition.

Figure 6.6 shows the GFR-DENFIS interface, with one of the fuzzy rules generated by the trained DENFIS. Each rule represents a local model associating predictive variables with the generated output within a given cluster. All rules together represent the equivalent of a global model that can be applied for the prediction of GFR for any new patient.

**Table 6-1 Agreement between predicted GFR values and reference GFR measurements.**

*Accuracy is reported for the testing sub-datasets for the modelling phases 1 and 2, and for the entire dataset for GFR-MDRD and modelling phase 3.*

| *Versus GFR-EDTA* | *Bias (95% CI) (mL/min/1.73m2)* | *RMSE (mL/min/1.73m2)* | *RMSE (% of GFR)* | *95% limits of agreement (mL/min/1.73m2)* | |
|---|---|---|---|---|---|
| | | | | *Lower* | *Upper* |
| GFR-MDRD | -3.5 [-4.2, -2.9] | 7.75 | 34.5% | -17.2 | 10.1 |
| ***Modelling Phase 1*** | | | | | |
| GFR-mMDRD | -1.6 [-2.3, -0.9] | 7.59 | 33.6% | -16.1 | 13.0 |
| GFR-DENFIS | 0.7 [0.0. 1.3] | 7.36 | 32.6% | -13.7 | 15.0 |
| ***Modelling Phase 2*** | | | | | |
| GFR-mMDRD | -0.3 [-0.9, 0.4] | 7.08 | 31.3% | -14.2 | 13.6 |
| GFR-DENFIS | 0.1 [-0.6, 0.6] | 6.75 | 29.9% | -13.2 | 13.3 |
| ***Modelling Phase 3*** | | | | | |
| GFR-mMDRD | -1.2 [-1.8, -0.6] | 7.03 | 31.1% | -14.8 | 12.4 |
| GFR-DENFIS | -0.1 [-0.4, 0.3] | 3.73 | 16.6% | -7.4 | 7.2 |

**Figure 6.1 Agreement of MDRD with GFR-EDTA.**

*In the scatter plot (left panel), the dotted line (·····) represents the line of identity between methods. In the bias plot (right panel), the dotted lines represent the bias between methods, and the broken lines (− · − ·) represent the range of agreement).*

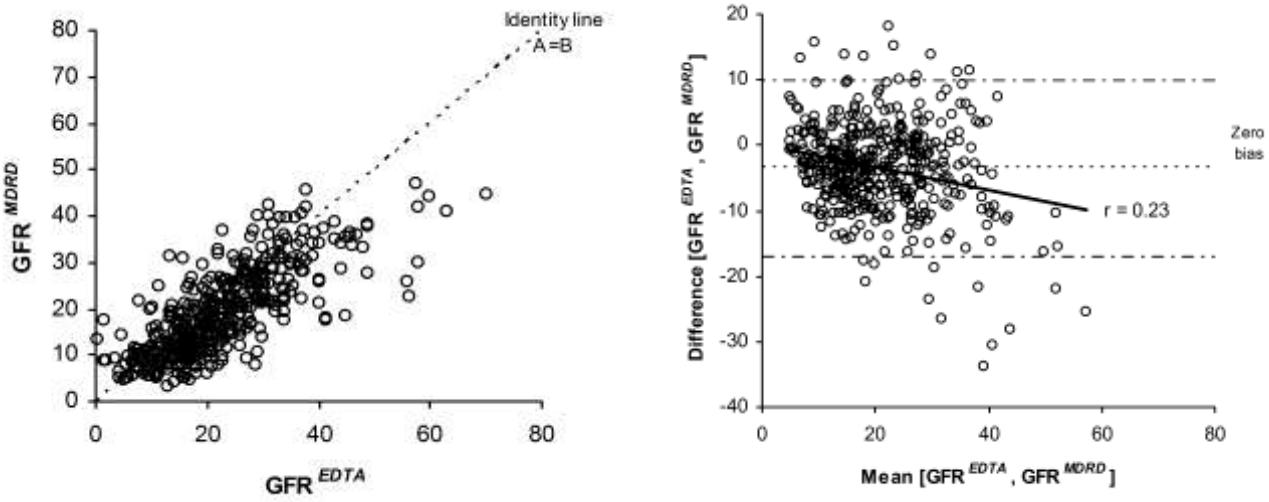


**Figure 6.2 Agreement of mMDRD and GFR-DENFIS with GFR-EDTA from Modelling Phase 1.**

*In the scatter plots (left panels), the dotted lines (·····) represent the line of identity between methods. In the bias plots (right panels), the dotted lines represent the bias between methods, and the broken lines (− · − ·) represent the range of agreement.*

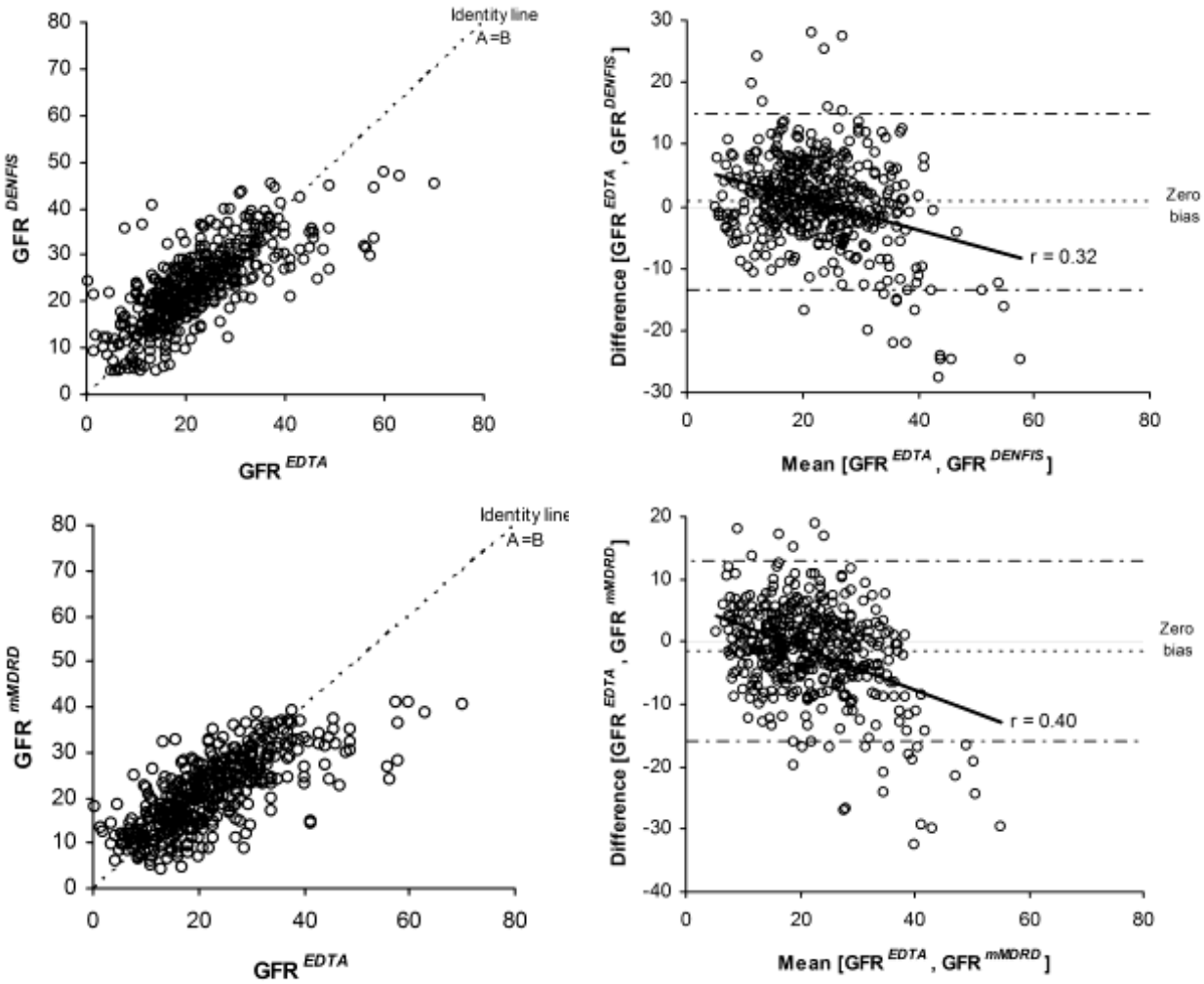


**Figure 6.3 Agreement of GFR-mMDRD and GFR-DENFIS with GFR-EDTA from Modelling Phase 2.**

*In the scatter plots (left panels), the dotted lines (·····) represent the line of identity between methods. In the bias plots (right panels), the dotted lines represent the bias between methods, and the broken lines (− · − ·) represent the range of agreement.*

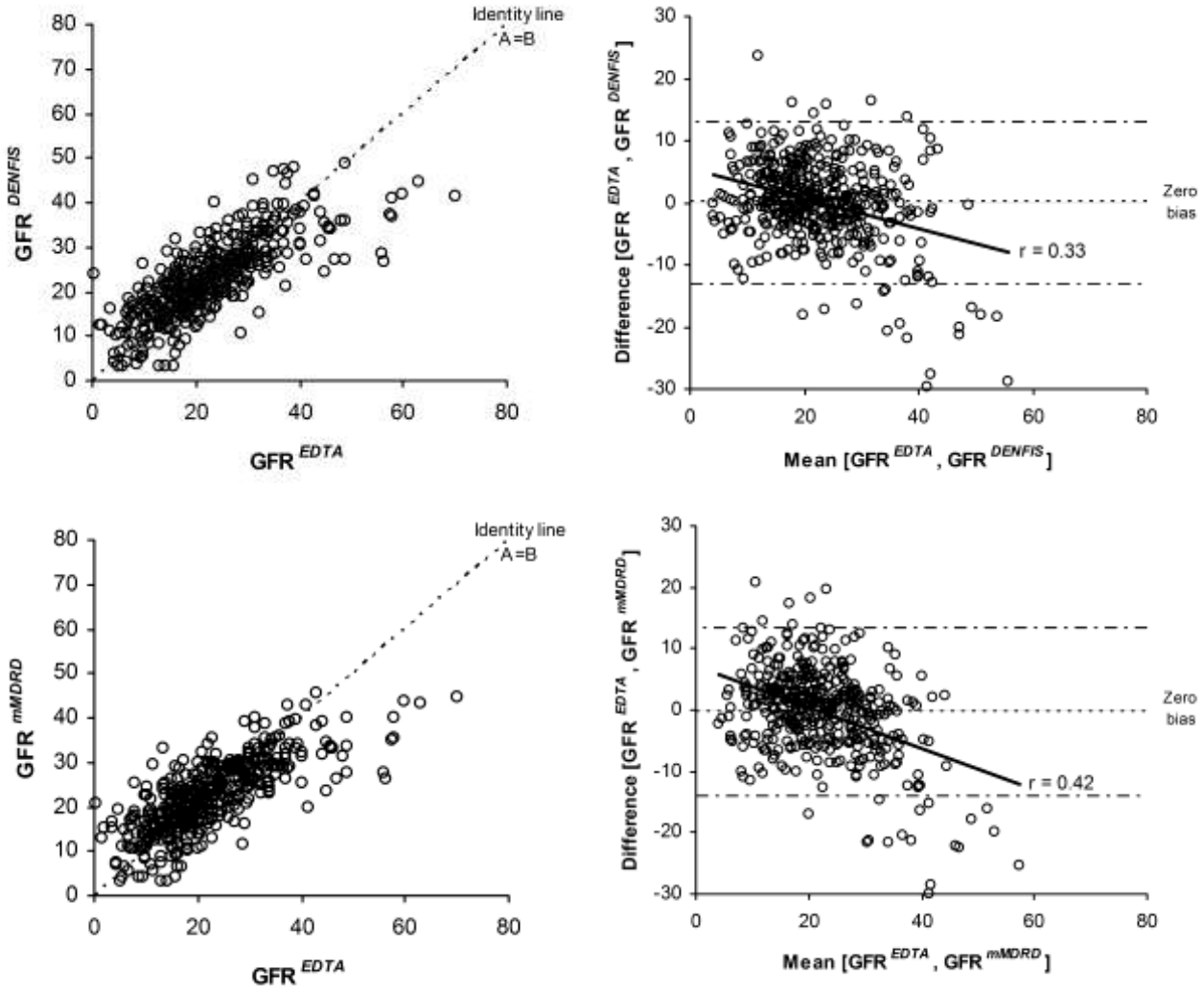


**Figure 6.4 Agreement of GFR-mMDRD and GFR-DENFIS with GFR-EDTA from the Modelling Phase 3.**

*In the scatter plots (left panels), the dotted lines (·····) represent the line of identity between methods. In the bias plots (right panels), the dotted lines represent the bias between methods, and the broken lines (− · − ·) represent the range of agreement.*

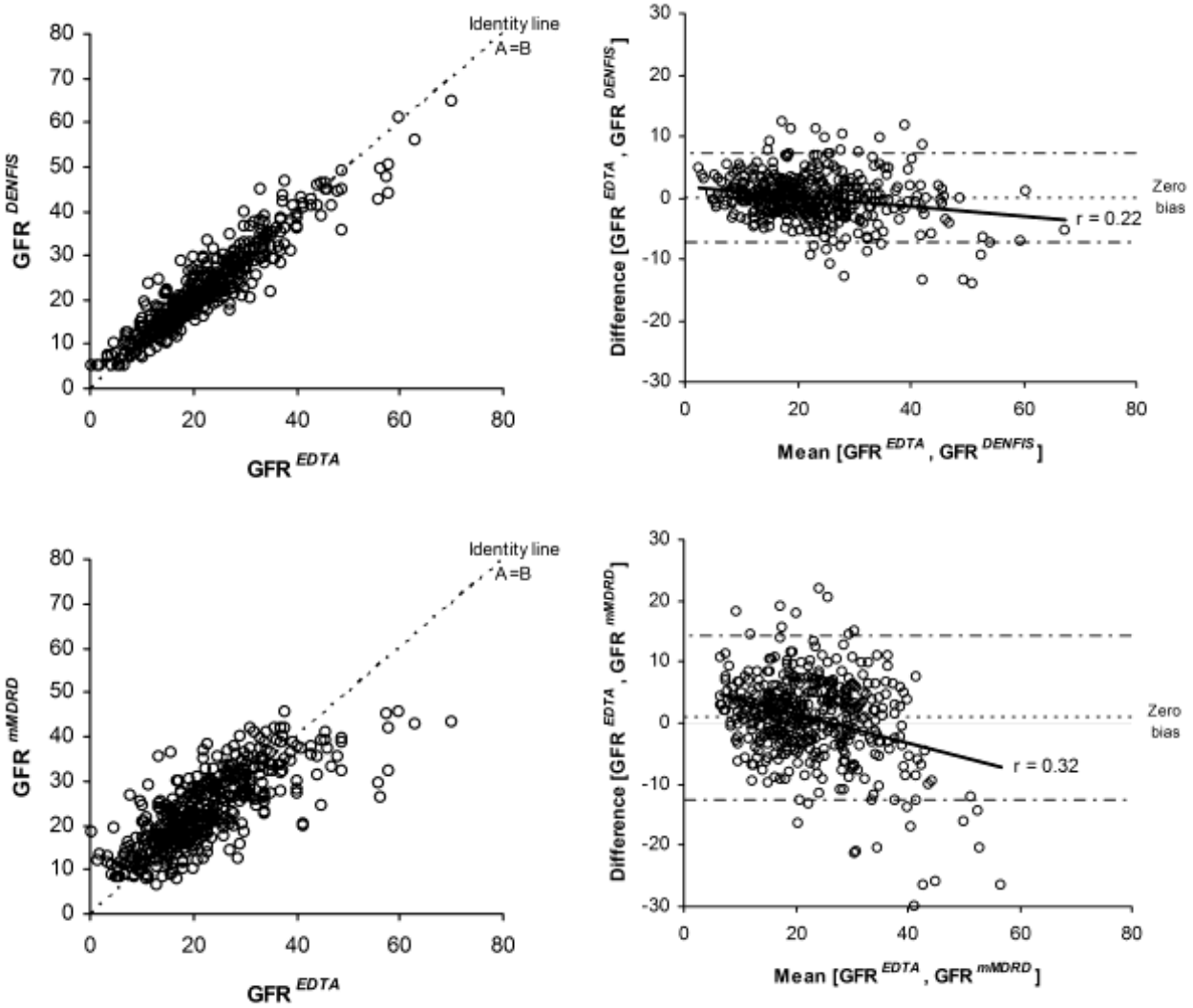


**Figure 6.5 Prediction error for glomerular filtration rate.**

*GFR-DENFIS is represented by the square, and the mMDRD the triangle, and refer to results in each of the 12 centres from modelling phase 2.*

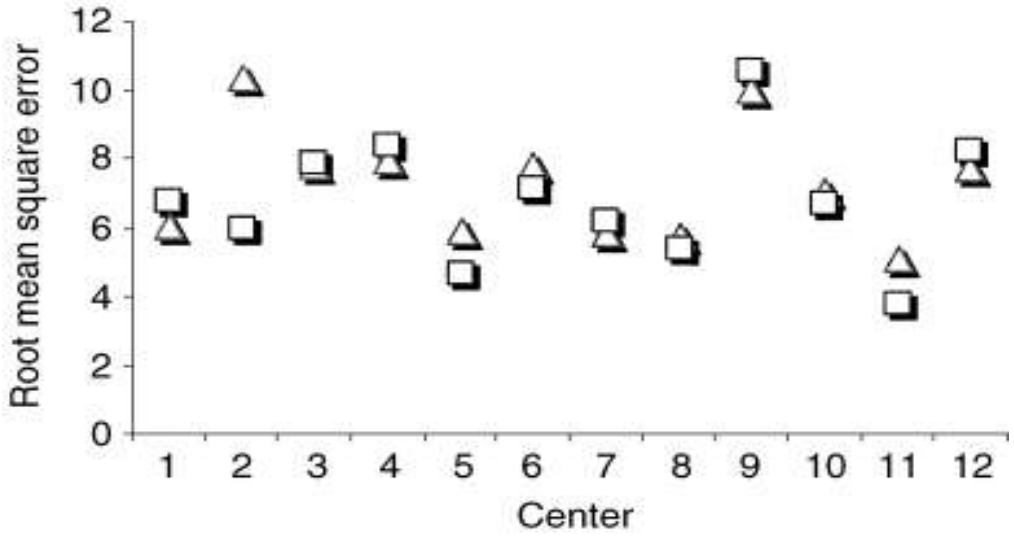
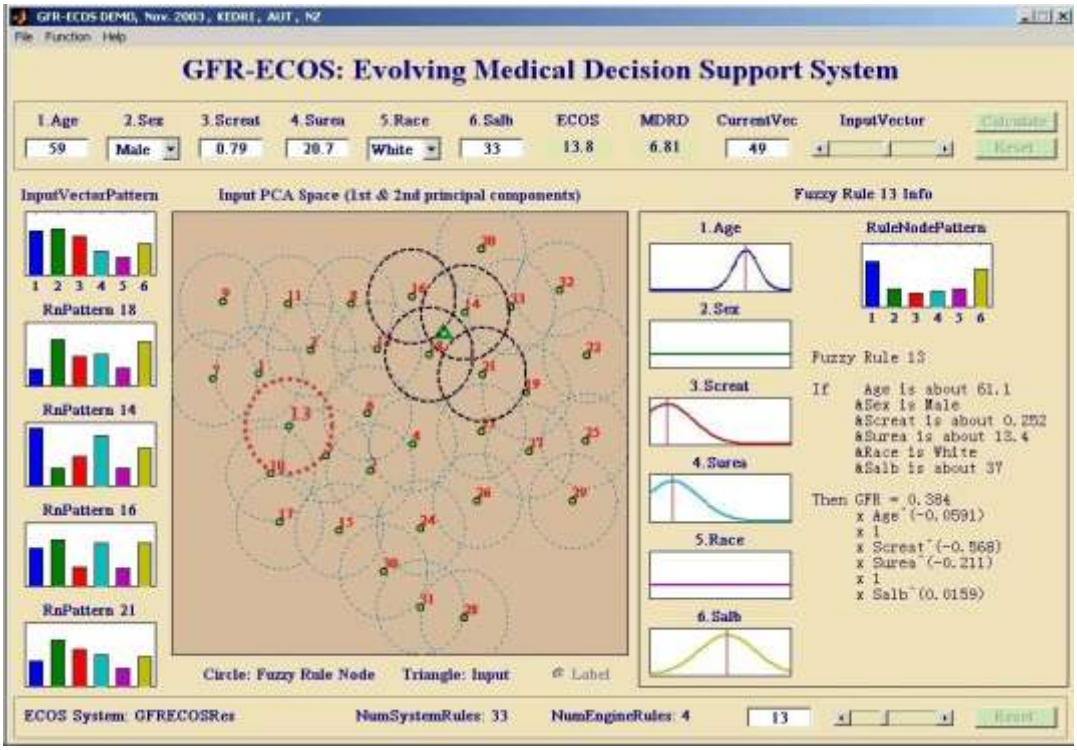


**Figure 6.6 Illustration of the GFR-DENFIS computer interface.**

*The problem space is visualised, as is the progressive partitioning of the space for the ongoing creation of fuzzy rules. At each moment, GFR-DENFIS is calculated through a fuzzy inference system based on the most activated fuzzy rules that are dynamically selected from the existing fuzzy rule set. New fuzzy rules are created and updated during the operation of the system. As an example, rule 13 is illustrated in this interface.*



## 6.4. Conclusions

The results of this experiment indicate that conventional regression formulas will be less accurate than expected in routine clinical practice. However, modification of the original MDRD formula by multiple regression analyses within the GFR dataset did achieve some improvement in absolute prediction error (bias) from -3.5 to -1.2 mL/min/1.73m$^2$, and in relative prediction error (precision) from 34.5% to 31.1%. This represents the best accuracy that can be achieved in the study dataset by a conventional regression formula developed using the MDRD formula template.

GFR-DENFIS predicts GFR with greater accuracy (bias -0.1 mL/min/1.73m$^2$, precision 16.6%), even with the modification of the MDRD formula as described. Moreover, the second phase of modelling in the experiment illustrates the potential beneficial of adaptive modelling with sequential recruitment of centres to the system. The model did not however develop single discrete models for each centre: within each centre, up to 21 models were used to calculate GFR-DENFIS, with renal function measurements often allocated to areas of the problem space partitioned to several overlapping clusters. It is the weighted application of these local models within the ECOS framework that provides improved accuracy over and above global models such as algebraic formulas.

The second phase of modelling also demonstrated an important limitation of GFR-DENFIS in clinical practice. In the case study of Centre 2, DENFIS was unable to distinguish whether the discrepancy between MDRD and the corresponding GFR-EDTA arose from patient-related factors or measurement error in laboratory parameters or radioisotope tracer clearance. ECOS is still a tool based on association rather than causality. However, unlike conventional artificial neural networks it is still possible to examine relationships among input and output variables within the ECOS. The local models are in the form of fuzzy rules that can be extracted and studied. Such rules may allow for generation of hypotheses for further laboratory or clinical testing, and also have the potential to directly add to understanding of underlying biologic processes.

There is potential to engineer machine intelligence into tools of medical practice, and the computer interface of GFR-DENFIS gives a glimpse of this potential. Many medical devices already have such systems embedded in them such as arrhythmia detectors. Alternatively, the systems can be placed on a central server as an internet or intranet-based utility. If such computing resources were not available, these systems are amenable to rule extraction as described. Such rules may be imported in a non-evolving form into a hand-held device, although they would need updating whenever advances in predictive modelling were made.

In summary, this experiment strongly suggests that published conventional regression formulas for the prediction of GFR will be less accurate than expected in routine clinical practice, and confirms that their performance can be improved somewhat by additional regression analyses prior to clinical use in diverse populations. Furthermore, there is potential to enhance modelling further within the ECOS framework by the addition of further variables and training vectors in the future. The web-based implementation of GFR-DENFIS is suitable for clinical use either for research or patient care. Finally, the computational models developed in this experiment may in turn shed light upon biological processes that influence renal function and mitigate renal disease.

## 6.6 Summary

In this chapter, a novel inductive knowledge-based neural fuzzy model was presented in which prediction occurs by local modelling. Its performance was superior to the most accurate of the regression formulas commonly used by medical practitioners, even when they are modified by multiple regression analyses within the GFR dataset. Despite optimization, such formulas are still global and fixed models across the whole problem space. The DENFIS model, being a set of local models, as expected performs better.

In ***Chapter 7***, the development of a transductive neural fuzzy model is presented (GFR-TWNFI) in which prediction occurs by individual or personalised modelling. Its performance is compared to other methods for GFR

prediction. As previously, this direction represents an incremental advance in the techniques of Health Informatics towards progressively more localized and ultimately personalised modelling frameworks.

# Chapter 7 : Personalised Modelling for Renal Function Evaluation (GFR - TWNFI)

In ***Chapter 6***, GFR-DENFIS was presented as an ECOS based model using neural fuzzy inference for local learning and the prediction of renal function. The GFR-DENFIS models predict GFR with greater accuracy than the most widely utilized and accurate conventional regression formula, even after enhanced of the formula through further statistical modelling within the GFR dataset.

In this chapter, a novel transductive neuro-fuzzy inference model (GFR-TWNFI) is presented for personalised modelling. In GFR-TWNFI, prediction occurs by personalised or individual modelling. In transductive systems, a local model is developed for every new input vector, based on data closest to this vector from the training data set. The weighted data normalization method (WDN) optimizes the data normalization ranges for the input variables in the model. A steepest descent algorithm is used for training the TWNFI model. In this chapter, the performance of GFR-TWNFI for the prediction of GFR is compared the MDRD formula and other neural fuzzy systems. The GFR-TWNFI model not only results in a personalised model with a better accuracy of prediction for a given person, but also depicts the most significant input variables (features) for the model that may be used for a personalised medicine.

The material of the chapter was published in (Kasabov, N., Song, Q., & Ma, T. M., 2008).

## 7.1 Introduction to Transductive versus Inductive Modelling

As introduced in Chapter 2, most of learning models and systems in artificial intelligence developed and implemented so far are based on inductive methods, where a model is derived from data representing the problem space and this model is further applied on new data. The model is usually created without taking into account any information about a particular new data vector (test

data). An error is measured to estimate how well the new data fits into the model. The inductive learning and inference approach is useful when a global model ("the big picture") of the problem is needed even in its very approximate form. In contrast to the inductive learning and inference methods, transductive inference methods estimate the value of a potential model (function) only in a single point of the space (the new data vector) utilizing additional information related to this point. This approach seems to be more appropriate for clinical and medical applications of learning systems, where the focus is not on the model, but on the individual patient. Each individual data vector (e.g.: a patient in the medical area; a future time moment for predicting a time series; or a target day for predicting a stock index) may need an individual, local model that best fits the new data, rather than a global model, in which the new data is matched without taking into account any specific information about this data.

## 7.2 Weighted Data Normalization

In many NN and fuzzy models and applications, raw (not normalized) data is used. This is appropriate when all the input variables are measured in the same units. Normalization, or standardization, is reasonable when the variables are in different units, or when the variance between them is substantial. However, a general normalization means that every variable is normalized in the same range, e.g. [0, 1] with the assumption that they all have the same importance for the output of the system.

For many practical problems, variables have different importance and make different contribution to the output(s). Therefore, it is necessary to find an optimal normalization and assign proper importance factors to the variables. Such a method can also be used for feature selection or for reducing the size of input vectors through keeping the most important ones (Q. Song & Kasabov, 2003). This is especially applicable to a special class of neural networks or fuzzy models – the clustering based models (or also: distance-based; prototype-based) such as: RBF (Poggio, 1994), Adaptive Resonance Theory (ART) (Carpenter & Grossberg, 1991), ECOS (N. Kasabov, 2001, 2003; N. Kasabov & Song, 2002). In such systems, distance between neurons or fuzzy rule nodes

and input vectors are usually measured in Euclidean distance, so that variables with a wider normalization range will have more influence on the learning process and vice versa.

## 7.3 Principles of the TWNFI

### 7.3.1 Structure of the TWNFI

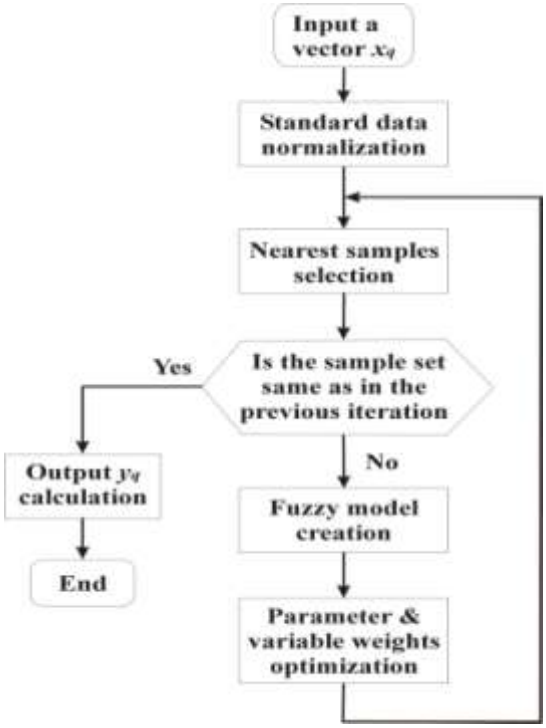
TWNFI is a dynamic neural-fuzzy inference system with a local generalization, in which, either the Zadeh-Mamdani type fuzzy inference engine(L.A. Zadeh, 1965; L.A. Zadeh, 1988) or the Takagi-Sugeno fuzzy inference (Takagi & Sugeno, 1985) is applied. Here, the former GFR data is introduced. The local generalization means that in a sub-space of the whole problem space (local area) a model is created that performs generalization in this area. In the TWNFI model, Gaussian fuzzy membership functions are applied in each fuzzy rule for both the antecedent and the consequent parts. A steepest descent (BP) learning algorithm is used for optimizing the parameters of the fuzzy membership functions (Lin & Lee, 1996; Wang, 1994). The distance between vectors x and y is measured in TWNFI in weighted normalized Euclidean distance defined as follows (the values are between 0 and 1):

$$\|\boldsymbol{x}-\boldsymbol{y}\| = \left[\frac{1}{P}\sum_{j=1}^{P} w_j |x_j - y_j|^2\right]^{\frac{1}{2}} \tag{7.1}$$

where: x, y $\in$ RP and wj are weights.

To partition the input space for creating fuzzy rules and obtaining initial values of fuzzy rules, the ECM (Evolving Clustering Method) is applied (N. Kasabov & Song, 2002; Q. Song & Kasabov, 2001) and the cluster centres and cluster radiuses are respectively taken as initial values of the centres and widths of the Gaussian membership functions. Other clustering techniques can be applied as well. A block diagram of the TWNFI is shown in Figure 7.1.

**Figure 7.1 A block diagram of the TWNFI**




### 7.3.2 The TWNFI Learning Algorithm

For each new data vector $\boldsymbol{x_q}$, the TWNFI learning algorithm performs the following steps:

1) Normalize the training data set (the values are between 0 and 1) with the initial weights of input variables.
2) Search in the training data set in the input space to find $\boldsymbol{N_q}$ training examples that are closest to $\boldsymbol{x_q}$. The value for $\boldsymbol{N_q}$ can be pre-defined based on experience, or - optimized through the application of an optimization procedure. Here we assume the former approach.
3) Calculate the distances $\boldsymbol{d_i}$, $i$ = 1, 2, …, $\boldsymbol{N_q}$, between $\boldsymbol{x_q}$ and each of these $\boldsymbol{N_q}$ data samples . Calculate the vector weights $\boldsymbol{v_i}$ = 1 – ($\boldsymbol{d_i}$ – min($\boldsymbol{d}$)), $i$ = 1, 2, …, $\boldsymbol{N_q}$, min($\boldsymbol{d}$ ) is the minimum value in the distance vector $\boldsymbol{d}$, $\boldsymbol{d}$ = [$d_1, d_2, \ldots, d_{Nq}$].
4) Use the ECM clustering algorithm to cluster and partition the input sub-space that consists of $\boldsymbol{N_q}$ selected training samples.
5) Create fuzzy rules and set their initial parameter values according to the results of ECM clustering procedure. For each cluster, the cluster centre is taken as

the centre of a fuzzy membership function (Gaussian function) and the cluster radius is taken as the width.

6) Apply the steepest descent method (Bp) to optimize the parameters of the fuzzy rules in the local model $\boldsymbol{M_q}$ following Eq. (7.6 – 13).
7) Search in the training data set to find $\boldsymbol{N_q}$ nearest samples (same to Step 2), if the same samples are found, as the last search, the algorithm turns to Step 9, otherwise, Step 3.
8) Calculate the output value $\boldsymbol{y_q}$ for the input vector $\boldsymbol{x_q}$ applying fuzzy inference over the set of fuzzy rules that constitute the local model $\boldsymbol{M_q}$.
9) End of the procedure.

The weight and parameter optimization procedure is described below:

Consider the system having P inputs, one output and M fuzzy rules defined initially through the ECM clustering procedure, the l-th rule has the form of:

$R_l$ : If $x_1$ is $F_{l1}$ and $x_2$ is $F_{l2}$ and … $x_P$ is $F_{lP}$, then $y$ is $G_l$. (7.2)

Here, $\boldsymbol{F_{lj}}$ are fuzzy sets defined by the following Gaussian type membership function:

$$GaussianMF = \alpha \exp\left[-\frac{(\boldsymbol{x}-\boldsymbol{m})^2}{2\sigma^2}\right] \tag{7.3}$$

$\boldsymbol{G_l}$ are of a similar type as $\boldsymbol{F_{lj}}$ and are defined as:

$$GaussianMF = \exp\left[-\frac{(\boldsymbol{y}-\boldsymbol{n})^2}{2\delta^2}\right] \tag{7.4}$$

Using the modified centre average defuzzification procedure, the output value of the system can be calculated for an input vector $\boldsymbol{x_i} = [\, \boldsymbol{x_1}, \boldsymbol{x_2}, \ldots, \boldsymbol{x_P} \,]$ as follows:

$$f(\boldsymbol{x_i}) = \frac{\sum_{l=1}^{M} \frac{G_l}{\delta_l^2} \prod_{j=1}^{P} \alpha_{lj} \exp\left[-\frac{w_j^2 (x_{ij}-m_{lj})^2}{2\sigma_{lj}^2}\right]}{\sum_{l=1}^{M} \frac{1}{\delta_l^2} \prod_{j=1}^{P} \alpha_{lj} \exp\left[-\frac{w_j^2 (x_{ij}-m_{lj})^2}{2\sigma_{lj}^2}\right]} \tag{7.5}$$

Here, $w_j$ are weights of the input variables.

Suppose the TWNFI is given a training input-output data pair [$x_i$, $t_i$] , the system minimizes the following objective function (a weighted error function):

$$\mathrm{E} = \frac{1}{2} v_i \left[ f(x_i) - t_i \right]^2 \tag{7.6}$$

($v_i$ are defined in Step 3)

Then the steepest descent algorithm (BP) is used to obtain the formulas for the optimization of the parameters $G_l$, $\delta_l$, $\alpha_{lj}$, $m_{lj}$, $\sigma_{lj}$ and $w_j$, so that the value of $E$ from Eq. (7.6) is minimized:

$$G_l(k+1) = G_l(k) - \frac{\eta_G}{\delta_l^{\,2}(k)} v_i \Phi(\mathbf{x}_i) \left[ f^{(k)}(\mathbf{x}_i) - t_i \right] \tag{7.7}$$

$$\delta_l(k+1) = \delta_l(k) - \frac{\eta_\delta v_i \Phi(\boldsymbol{x}_i)}{\delta_l^{\,3}(k)} \left[ f^{(k)}(\boldsymbol{x}_i) - t_i \right] \left[ f^{(k)}(\boldsymbol{x}_i) - G_l(k) \right] \tag{7.8}$$

$$\alpha_{lj}(k+1) = \alpha_{lj}(k) - \frac{\eta_\alpha v_i \Phi(\boldsymbol{x}_i)}{\delta_l^2(k)\, \alpha_{lj}(k)} \left[ f^{(k)}(\boldsymbol{x}_i) - t_i \right] \left[ G_l(k) - f^{(k)}(\boldsymbol{x}_i) \right] \tag{7.9}$$

$$m_{lj}(k+1) = m_{lj}(k) - \frac{\eta_m w_j^2(k) v_i \Phi(\mathbf{x}_i)}{\delta_l^2(k)\, \sigma_{lj}^{\,2}(k)} \left[ f^{(k)}(\mathbf{x}_i) - t_i \right] \left[ G_l(k) - f^{(k)}(\mathbf{x}_i) \right] \left[ x_{ij} - m_{lj}(k) \right] \tag{7.10}$$

$$\sigma_{lj}(k+1) = \sigma_{lj}(k) - \frac{\eta_\sigma w_j^2(k) v_i \Phi(\boldsymbol{x}_i)}{\delta_l^2(k)\ \sigma_{lj}^{\,3}(k)} \left[ f^{(k)}(\boldsymbol{x}_i) - t_i \right] \left[ G_l(k) - f^{(k)}(\boldsymbol{x}_i) \right] \left[ x_{ij} - m_{lj}(k) \right]^2 \tag{7.11}$$

$$w_j(k+1) = w_j(k) - \frac{\eta_w w_j(k) v_i \Phi(\boldsymbol{x}_i)}{\delta_l^2(k)\, \sigma_{lj}^{\,2}(k)} \left[ f^{(k)}(\boldsymbol{x}_i) - t_i \right] \left[ f^{(k)}(\boldsymbol{x}_i) - G_l(k) \right] \left[ x_{ij} - m_{lj}(k) \right]^2 \tag{7.12}$$

$$\Phi(\boldsymbol{x}_i) = \frac{\prod_{j=1}^{\mathrm{P}} \alpha_{lj} \exp\left\{-\frac{w_j^2(k)[x_{ij} - m_{lj}(k)]^2}{2\sigma_{lj}^2(k)}\right\}}{\sum_{l=1}^{\mathrm{M}} \frac{1}{\delta_l^2} \prod_{j=1}^{\mathrm{P}} \alpha_{lj} \exp\left\{-\frac{w_j^2(k)[x_{ij} - m_{lj}(k)]^2}{2\sigma_{lj}^2(k)}\right\}} \tag{7.13}$$

where: $\eta_G$ , $\eta_\delta$ , $\eta_\alpha$ , $\eta_{\mathrm{m}}$ , $\eta_\sigma$ and $\eta_w$ are learning rates for updating the parameters $\boldsymbol{G_l}$, $\delta_l$, $\alpha_{lj}$, $\boldsymbol{m_{lj}}$, $\sigma_{lj}$ and $\boldsymbol{w_j}$ respectively.

In the TWNFI training–simulating algorithm, the following indexes are used:

- Training data samples: $i$ = 1, 2, … , N;
- Input variables: $j$ = 1, 2, … , P;
- Fuzzy rules: $l$ = 1, 2, …, M;
- Training epochs: $k$ = 1, 2, ….

## 7.4 The Proposed Method

In this experiment, the performance of GFR-TWNFI for the prediction of GFR is compared to several well-known methods using the GFR dataset as previously described in Chapter 4.

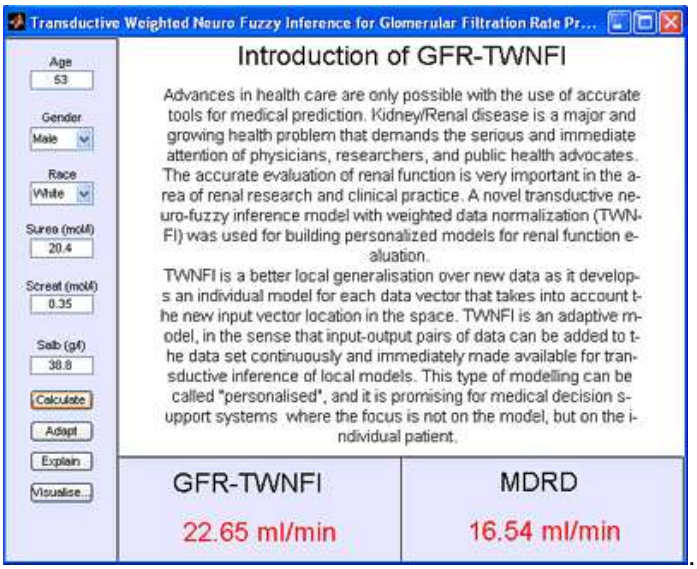
For methods for comparison include the MDRD formula, MLP neural network, ANFIS, and GFR-DENFIS.

All results reported for neural fuzzy systems listed in Table 7-1 (including GFR-TWNFI) are based on 10-cross validation experiments with the same model and parameters and the results are averaged. In each experiment 70% of the whole data set is randomly selected as training data and another 30% as testing data.

Two experiments with TWNFI are conducted. The first one is the TWNFI without WDN: all weights' values are set as '1' and will not be changed during the learning. Another employs the TWNFI learning algorithm described in Section 7.3.

The performance of GFR-TWNFI and other methods are compared using the testing RMSE and MAE. The results also include the number of fuzzy rules (fuzzy models), or neurons in the hidden layer (MLP).

**Figure 7.2 Illustration of the computing interface of GFR-TWNFI**




## 7.5 Results and Conclusions

What follows below is an exemplar personalised model for the prediction of GFR in a patient through use of the TWNFI:

***Rule 7:***

if

Age is around 60.5

Gender is Male

Screat is around 0.31

Surea is around 20.7

Race is White

Salb is around 35.0

then GFR = 12.14 * Age^0.280 * Screat^-0.858 * Surea^0.029 * Salb^0.001

***Rule 8:***

if

Age is around 54.7

Gender is Male
Screat is around 0.45
Surea is around 24.9
Race is White
Salb is around 35.9
then GFR = 12.45 * Age^0.270 * Screat^-0.858 * Surea^0.038 * Salb^-0.003

Variable importances:
Age(0.80); Gender(0.60); Screat(1.00); Surea(0.60); Race(0.30); Salb(0.31)

These fuzzy rules represent *knowledge* that is comprehensible to professional healthcare provider. They illustrate the efficiency of TWNFI on knowledge discovery vi fuzzy rules extraction. Besides the rules for GFR evaluation, which identifies different groups of input vectors that are unique and should be treated differently, there are also rules to show the importance of different variable for this individual patient. The term “about” in the rules can be more precisely described as the degree of membership.

The results of the experiment are provided in Table 7-1. They indicate that normalization of the training data set (the values are between 0 and 1) with weighting of input variables resulted in better prediction. GFR-TWNFI not only resulted in a “personalised” model with a better accuracy of prediction for every single person, but also depicts the most significant input variables (features) for the model that may be used for a personalised medicine and improved treatment.

In conclusion, the GFR-TWNFI performs a better local generalisation over new data as it develops an individual model for each data vector that takes into account the new input vector location in the space. It is an adaptive model, in the sense that input-output pairs of data can be added to the data set continuously and immediately made available for transductive inference of local models. This type of modelling can be called “personalised”, and it is promising for medical decision support systems. As the TWNFI creates a unique sub-model for each data sample, it usually needs more computational time than other inductive models, especially in the case of training and simulating on large

data sets. Of note, this personalised modelling can also be applied to other distance-based, prototype learning neural network or fuzzy inference models.

**Table 7-1 Experimental results (testing) on GFR data with different methods.**

| | | | | *Weights of Input Variables* | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Model** | **Neurons or Rules** | **Testing RMSE** | **Testing MAE** | **Age** | **Sex** | **Scr** | **Surea** | **Race** | **Salb** |
| MDRD | - | 7.74 | 5.88 | 1 | 1 | 1 | 1 | 1 | 1 |
| MLP | 12 | 8.44 | 5.75 | 1 | 1 | 1 | 1 | 1 | 1 |
| ANFIS | 36 | 7.49 | 5.48 | 1 | 1 | 1 | 1 | 1 | 1 |
| DENFIS | 27 | 7.29 | 5.29 | 1 | 1 | 1 | 1 | 1 | 1 |
| TNFI | 6.8 (average) | 7.31 | 5.30 | 1 | 1 | 1 | 1 | 1 | 1 |
| TWNFI | 6.8 (average) | 7.11 | 5.16 | 0.89 | 0.71 | 1.00 | 0.92 | 0.31 | 0.56 |

## 7.6 Summary

In this chapter, a personalised tranductive neural fuzzy model is presented (GFR-TWNFI), and its performance compared to other methods for GFR prediction including other machine learning techniques.

In ***Chapter 8***, the personalised modelling approach is extended to another clinical medical problem involving the prediction of a binary outcome rather than a continuous one. This direction is intended to determine the potential utility of advanced personalised models for problems that involve classification, a common scenario for health informatics applications.

# Chapter 8 : Personalised Modelling for the Prediction of Survival of Haemodialysis Patients (DOPPS-TWNFC)

In ***Chapter 7***, GFR-TWNFI was presented as a transductive model using neural fuzzy inference for personalised modelling and the prediction of renal function. The GFR-TWNFI model predicts GFR with greater accuracy than other methods, including GFR-DENFIS, indicating that personalised modelling are potentially superior to those local models.

In this chapter, the personalised modelling approach is further developed and applied on another clinical medical problem involving the prediction of a binary outcome rather than a continuous one. A tranductive model using neural fuzzy inference is trained on the DOPPS dataset to predict the survival of patients on haemodialysis at 3 years. As previously described in Chapter 4, the DOPPS dataset contains observed mortality status and associated demographic, clinical and laboratory variables for modelling. In this case study, very similar models and modelling techniques to the GFR-TWNFI are used to demonstrate the flexibility of this approach for other prediction problems that arise in medicine. In this clinical medical problem, the TWNFI model is developed for classification, a common scenario for health informatics applications whether the classification is related to death or other sorts of outcomes. The material of the chapter was published in (Ma, Song, Marshall & Kasabov).

## 8.1 Introduction to a Novel Transductive Neuro-fuzzy Classifier with Weighted Data Normalization (TWNFC)

For this task, a novel transductive neuro-fuzzy classifier with weighted data normalization (TWNFC) is developed. As with the previous transductive system in Chapter 7 (GFR-TWNFI), a local model is

developed for every new input vector, based on the closest data to this vector from the training data set. As with GFR-TWNFI, the WDN optimizes the data normalization ranges for the input variables of a system. A steepest descent algorithm is used for training the TWNFC model. The TWNFC is illustrated on the DOPPS dataset as described in Chapter 4: a medical problem of predicting the survival of haemodialysis patients.

## 8.2 Proposed Method

### 8.2.1 Structure and Learning Algorithms of the TWNFC

The structure and learning algorithms of the TWNFC are identical to those described for the GFR-TWNFI in Chapter 7 with the following additions / exceptions only:

In this dynamic neural-fuzzy inference system with a local generalization, the Zadeh-Mamdani type fuzzy inference engine (L.A. Zadeh, 1965; L.A. Zadeh, 1988) is applied. The Zadeh-Mamdani fuzzy logic operator is presented in details in Chapter 3.

All results reported for different models (including GFR-TWNFC) are based on 10-cross validation experiments with the same model and parameters and the results are averaged. In each experiment 70% of the whole data set is randomly selected as training data and another 30% as testing data.

The output is patient survival at 3 years from study enrolment (yes/no).

### 8.2.2 Statistical Evaluation

The output of the DOPPS-TWNFC was compared with prediction from several more common and well-known methods of classification, such as SVM, ECF, MLP, RBF, and multiple linear regression.

For model fit of a dichotomous variable, it was necessary to choose a statistic that reflects the goodness-of-fit, rather than a statistic such as the Chi-square which allows a hypothesis tests with a simple yes-no answer. With the many thousands of vectors available, the Chi-square test (whether for discrimination of the binary outcome of death and life, or for calibration over various increased categories of risk) gives a poor fit for all of the models, with a significant difference between the predicted values and observed values for every technique (all Chi square > 74 at best).

An additional statistic is needed to enable a comparison between models and allow some assessment of the models as to what might be an acceptable model and what is not.

There are several statistics available for this:

The Akaike Information Criterion and the Bayesian Information Criterion allow some sort of discernment between models and allows the observer to choose between two models. They do not, however, allow for the assessment of a model as being good enough for clinical use.

There are really two statistics which do this. The first is the Kappa statistic, which was developed to assess the agreement between two methods, raters or observers, when the observations are measured on a categorical scale (Altman, 1991). The degree of agreement is indicated by K, which allows some sort of idea of whether the agreement is clinically useful and can be roughly interpreted as follows: $K < 0.20$, agreement quality poor; $0.20 < K < 0.40$, agreement quality fair; $0.40 < K < 0.60$, agreement quality moderate; $0.60 < K < 0.80$, agreement quality good; $K > 0.80$, agreement quality very good. Confidence intervals for K were constructed using the goodness-of-fit approach of Donner & Eliasziw (Donner & Eliasziw, 1992). There is no universally agreed method for comparing K between multiple tests of agreement. In this

study, K for different classification methods was compared using the permutation or Monte Carlo resampling routine of McKenzie (McKenzie, Mackinnon, & Clarke, 1997; McKenzie et al., 1996).

Agreement refers to the quality of the information provided by the classification device and should be distinguished from the usefulness, or actual practical value, of the information. Agreement provides a pure index of accuracy by demonstrating the limits of a test's ability to discriminate between alternative states of health over the complete spectrum of operating conditions. To date, prognostic systems based on simple logistic regression or principle component analysis for the prediction of haemodialysis patient survival have published accuracy of 60-70%.

Perhaps the more conventional way of reporting model fit might be with a receiver operating curve (ROC). Similarly to the Kappa statistic, the area under the ROC curve has an element which allows some sort of qualitative judgement of mdoel fit: .90-1 = excellent (A), .80-.90 = good (B), .70-.80 = fair (C), .60-.70 = poor (D), .50-.60 = fail (F). The AUROC is derived from the specificity and sensitivity which are included in Table 8.1 and Table 9.1

We believe the AUROC and other statistics (including the Brier and Shapiro scores) do not add to the Kappa statistic in understanding the practical accuracy of the predictive model.

## 8.3 Results

The experimental results in Table 8-1 illustrate that the DOPPS-TWNFC provides incrementally better results with agreement quality moderate, towards a K of > 0.60 and a level of accuracy ~80%, which are generally regarded as thresholds for clinical utility.

The AUROC statistics are very similar to the Kappa statistics: they indicate fair prediction with the DOPPS-TWNFC, but nevertheless better prediction than the other models.

For every patient, a personalised model is created and can be used to estimate the importance of the variables for this patient. Two examples are shown in Table 8-2. The DOPPS-TWNFC not only results in a better accuracy for the prediction of mortality of patients, but also shows variables selected by the model for each vector that may result in a more efficient personalised treatment for the patient which the vector represents.

## 8.4 Conclusions

The DOPPS-TWNFC performs a better local generalisation over new data as it develops an individual model for each data vector, and this model takes into account the location of new input vector in the problem space. As for GFR-TWNFI, this approach seems to be superior to inductive AI approaches using global models. As with GFR-TWNFI, the approach also focuses on the individual patient and as an adaptive model, where input-output pairs of data can be added and made available for transductive inference of local models. The clinical plausibility of this approach for the prediction of mortality and its results are satisfactory in this study. As GFR-TWNFI, DOPPS-TWNFC creates a unique sub-model for each data sample and usually needs more computational time than other inductive models.

## 8.5 Summary

In this chapter, a personalised tranductive neural fuzzy model is presented (DOPPS-TWNFC), and its performance compared to other methods for GFR prediction including other machine learning techniques. In particular, prediction is superior to conventional statistical and other approaches based on global or local learning.

In ***Chapter 9***, the personalised modelling approach is applied using novel transductive model to the same clinical problem as for Chapter 8. The model, however, is enhanced further through the use of the Total Least Square method (TLS) for optimal fitting, potentially resulting in improved model development for every new input vector.

**Table 8-1 Experimental Results on the DOPPS Data**

| *Model* | *Kappa (95% Confidence Intervals)** | *P-value* | *Agreement (%)* | *Specificity (%)* | *Sensitivity (%)* |
|---|---|---|---|---|---|
| RBF | 0.1675 (0.1268 - 0.2026) | <0.001 | 59.1 | 67.51 | 49.08 |
| ECF | 0.1862 (0.1469 - 0.2224) | <0.001 | 59.9 | 66.74 | 51.76 |
| MLP | 0.3833 (0.3472 - 0.4182) | <0.001 | 69.44 | 72.56 | 65.72 |
| Multiple Linear Regression | 0.4020 (0.3651 - 0.4357) | <0.001 | 70.55 | 76.7 | 63.21 |
| SVM | 0.4110 (0.3748 - 0.4449) | <0.001 | 70.93 | 76 | 64.88 |
| TWNFC | 0.4503 (0.4152 - 0.4837) | Reference | 72.64 | 73.3 | 71.8 |

*Kappa values and confidence intervals ascertained with Stata Intercooled V 8.2 (StataCorp, College Station, TX), and P-values with KAPCOM (McKenzie et al., 1997).

**Table 8.2 DOPPS-TWNFC Models of Single Patients**

| | *Patient 1* | | *Patient 2* | |
|---|---|---|---|---|
| Input variables | Values of input | Weights of input variables | Values of input | Weights of input variables |
| Years on Dialysis prior to Study | 0.34 | 0.49 | 0.5175 | 0.63 |
| Age | 88 | 0.85 | 66 | 1 |
| Sex | Female | 0.05 | Female | 0.62 |
| Race | Black | 0.59 | White | 0.72 |
| Diabetes | No | 0.96 | No | 0.56 |
| Angina | Angina at rest within 12 months of enrolment date | 1 | No | 0.89 |
| Myocardial Infarction | Yes | 0.77 | No | 0.62 |
| Chronic Heart Failure | Dyspnea at rest or pulmonary edema | 0.54 | No | 0.71 |
| Left Ventricular Hypertrophy | Yes | 0.79 | No | 0.33 |
| Serum Albumin | 3.8667 | 0.54 | 3.7 | 0.94 |
| Peripheral Vascular Disease | No | 0.37 | No | 0.68 |
| Cerebrovascular Disease | No | 0.73 | No | 0.21 |
| Hypertension | Yes | 0.76 | Yes | 0.7 |
| Kt/V | 1.3 | 0.52 | 1.31 | 0.68 |
| Serum Phosphate | 4.9333 | 0.56 | 3.77 | 0.57 |
| Serum Haemoglobin | 11.3333 | 0.42 | 9.9 | 0.66 |

| | | | | |
|---|---|---|---|---|
| Type of access for Dialysis | Synthetic graft | 0.95 | Native A- V fistula | 0.24 |
| Mobility | Can walk with assistance | 0.69 | Can walk without assistance | 0.5 |
| sPCS | 32.02 | 0.98 | 51.82 | 0.64 |
| sMCS | 50.99 | 0.77 | 43.99 | 0.69 |
| Body Mass Index | 23.5 | 0.6 | 17.5 | 0.6 |
| Hi-flux | No | 0.82 | Yes | 0.66 |
| Serum Creatinine | 6.8 | 0.6 | 5.93 | 0.8 |
| Serum Calcium | 8.53 | 0.52 | 9.07 | 0.6 |
| Output | Survive | Predicting result: Survive | Non-survive | Predicting result: Non-survive |

# Chapter 9 : Personalised Modelling for the Prediction of Survival of Haemodialysis Patients (DOPPS-TTLSC)

In ***Chapter 8***, DOPPS-TWNFI was presented as a transductive model using neural fuzzy inference for personalised modelling and the prediction of mortality in haemodialysis patients. The DOPPS-TWNFI model predicts mortality with greater accuracy than other methods based on global or local learning.

In this chapter, another novel method is proposed. A change is made to the learning algorithms for the personalised modelling approach. The enhanced transductive model uses the Total Least Square method (TLS) for optimal fitting, potentially resulting in improved model development for every new input vector, based on more appropriate selection of data closest to this vector from the training data set. In this chapter, we compare the performance of the transductive total least squares classifier (DOPPS-TTLSC) for the prediction of mortality in haemodialysis patients

The material in this chapter was published in (Song, Q., Ma, M. and N.Kasabov, 2006).

## 9.1 Transductive Model and Total Least Square Method

The principle and algorithm of TWNFI system has been introduced in Chapter 7. Here I will emphasize the rationale and details of TLS method.

The rationale for the use of the TLS method arises from it being one of the optimal fitting methods that can be used for curve and surface fitting. It is known to outperform the commonly used Least Square (LS) fitting methods in resisting both normal noise and outliers. The problems of using a model of line (curve), plane (surface), or hyperplane (hypersurface) to fit a given data

set are often encountered in many engineering applications. For solving such classical statistical problems, the conventional method is the LS fitting method. However, in many cases, LS is suboptimal. The optimal least square method is the so called Total Least Square (TLS) method (Golub & Van Loan, 1996; Oja, 1982; Xu, Oja, & Suen, 1992). In contrast to the usual LS method, the TLS method yields a function, which can be a line (curve), plane (surface), or hyperplane (hypersurface), on the given data set, and to minimize the sum of the distances between each data point to the estimated function.

In contrast to the usual LS method, computations to obtain the solution of TSL are generally quite burdensome. In the case of linear fitting, however, the problem of optimal fitting in the TLS sense is not so intricate. When the linear models are expressed as:

$$b_0 + b_1 x_1 + b_2 x_2 + \ldots + b_m x_m = 0. \qquad (9.1)$$

where xj, j = 1, 2, …, m, are variables and b0 is an arbitrary constant. For Eq. 9.1, the TLS fitting problem is to minimize the following total least square error E:

$$E = \sum_{i=1}^{n} r_i^2, \qquad r_i = \frac{\left|b_0 + b_1 x_{i1} + b_2 x_{i2} + \ldots + b_m x_{im}\right|}{\sqrt{b_1^2 + b_2^2 + \ldots + b_m^2}} = \left|b_0 + \sum_{j=1}^{m} b_j x_{ij}\right| \Big/ \left(\sum_{j=1}^{m} b_j^2\right)^{1/2} \qquad (9.2)$$

where n is the number of vectors in the data set.

Either a linear neural network using a constrained Hebbian learning rule (Xu et al., 1992) or a steepest descent algorithm can be used to solve such a problem. In our current research, we use the latter.

We apply the transductive technology to the TLS method for more accurate classification: for each class, one TLS function is created on the local area that is based on the position of the new data in the training data space, and the new data belongs to such a class – the related TLS function has the shortest distance to the new data point.

## 9.2 Proposed Method

### 9.2.1 The TTLSC Structure and Learning Algorithm

TTLSC is a TLS method using the transductive technology for solving classification problems. The distance between vectors x and y is measured in TTLSC in normalized Euclidean distance defined as follows (the values are between 0 and 1):

$$\|\boldsymbol{x} - \boldsymbol{y}\| = \frac{1}{P}\left[\sum_{j=1}^{P}|x_j - y_j|^2\right]^{\frac{1}{2}} \tag{9.3}$$

where: $\boldsymbol{x}, \boldsymbol{y} \in \boldsymbol{R}^P$

Consider the classification problem has two classes and *m* variables, for each new data vector $\boldsymbol{x_q}$, the TTLSC learning algorithm performs the following steps:

1) Normalize the training data set and the new data (the values are between 0 and 1).
2) Search in the training data set in the whole space to find $D_q$ that includes $\boldsymbol{N_q}$ training samples closest to $\boldsymbol{x_q}$. The value of $\boldsymbol{N_q}$ can be pre-defined based on experience, or - optimized through the application of an optimization procedure. Here we assume the former approach.
3) If all training samples in $D_q$ belong to the same class, the new data belongs to this class and the procedure ends. Otherwise,
4) Calculate the distances $d_i$, $i$ = 1, 2, …, $\boldsymbol{N_q}$, between $\boldsymbol{x_q}$ and each of data samples in $D_q$ and calculate the vector weights $w_i = 1 - (d_i - \min(\boldsymbol{d}))$, here, $i$ = 1, 2, …, $\boldsymbol{N_q}$, $\min(\boldsymbol{d})$ is the minimum value in the distance vector $\boldsymbol{d}$, $\boldsymbol{d} = [d_1, d_2, \ldots, d_{Nq}]$.
5) Use the Weighted Least Square method (Hsia, 1977; N. Kasabov & Song, 2002) to create a function as Eq.9.4 with the data pairs $[\boldsymbol{x_i}, y_i]$ and $w_i$, $i$ = 1, 2, …, $\boldsymbol{N_q}$ ,

$$y = a_0 + a_1 x_1 + a_2 x_2 + \ldots + a_m x_m \quad (9.4)$$

where, $y_i = 0$ if training data sample xi belongs to class 1 and, $y_i = 1$ if $\boldsymbol{x_i}$ belongs to class 2.

6) Create two initial TLS functions for two classes respectively

$$f_1(\boldsymbol{x},\boldsymbol{B}^{(0)}) = B_0^{(0)} + B_1^{(0)} x_1 + B_2^{(0)} x_2 + \ldots + B_m^{(0)} x_m = 0;$$

$$B_j^{(0)} = a_j, \; j = 0,1, 2, \ldots, m. \quad (9.5a)$$

$$f_2(\boldsymbol{x},\boldsymbol{b}^{(0)}) = b_0^{(0)} + b_1^{(0)} x_1 + b_2^{(0)} x_2 + \ldots + b_m^{(0)} x_m = 0;$$

$$b_0^{(0)} = a_0 - 1 \text{ and } b_j^{(0)} = a_j \, , j = 1, 2, \ldots, m. \quad (9.5b)$$

7) Apply the steepest descent method to optimize the parameters *B* and *b* for two TLS functions following Eq. 9.6 – 9.8.
8) Calculate the distances $r_1$ and $r_2$, from the new data point to $f_1$ and $f_2$ respectively, the new data belongs to class1 if $r_1 < r_2$ and otherwise, it belongs to class 2.
9) End of the procedure.

The parameter optimization procedure is described as following:

Suppose there are $N_{q1}$ class 1 training data $D_{q1}$ and $N_{q2}$ class 2 training data $D_{q2}$ in the $D_q$. The $f_1$ and $f_2$ are optimized on $D_{q1}$ and $D_{q2}$ respectively. The optimization for $f_1$ is showed following (it is the same manner for $f_2$):

The optimization minimizes the following objective function (the re-written Eq.9.2):

$$E = \sum_{i=1}^{Nq1} r_i^2 \, , \quad r_i = \frac{\left|B_0 + B_1 x_{i1} + B_2 x_{i2} + \ldots + B_m x_{im}\right|}{\sqrt{B_1^2 + B_2^2 + \ldots + B_m^2}} = \left|B_0 + \sum_{j=1}^{m} B_j x_{ij}\right| \Big/ \left(\sum_{j=1}^{m} B_j^2\right)^{1/2} \quad (9.6)$$

Then the steepest descent algorithm is used to obtain the formulas for the optimization of the parameters $\boldsymbol{B}$, so that the value of $\boldsymbol{E}$ from Eq. (9.6) is minimized:

$$B_0(k+1) = B_0(k) - \eta \sum_{i=1}^{Nq1} \left\{ \left( B_0(k) + \sum_{j=1}^{m} B_j(k) x_{ij} \right) \Big/ \left( \sum_{j=1}^{m} B_j^2(k) \right)^{1/2} \right\} \quad (9.7)$$

$$B_j(k+1) = B_j(k) - \eta \sum_{i=1}^{Nq1} \left\{ x_{ij} \left[ \left( B_0(k) + \sum_{j=1}^{m} B_j(k) x_{ij} \right) \Big/ \left( \sum_{j=1}^{m} B_j^2(k) \right)^{1/2} \right] - B_j(k) r_i^2(k) \right\} \quad (9.8)$$

where, $\eta$ is the learning rate.

In the TTLSC algorithm, the following indexes are used:

- data samples: $i$ = 1, 2, … , $N_{q1}$ *or* $N_{q2}$;
- variables: $j$ = 1, 2, … , $m$;
- optimization iterations: $k$ = 1, 2, ….

All results reported for different models (including DOPPS-TTLSC) are based on 10-cross validation experiments with the same model and parameters and the results are averaged. In each experiment 70% of the whole data set is randomly selected as training data and another 30% as testing data.

The output is patient survival at 2.5 years from study enrollment (yes/no)

### 9.2.2 Statistical Methods

The output of the DOPPS-TTLSC was compared with prediction from several more common and well-known methods of classification, such as SVM, ECF, MLP, RBF, and multiple linear regression. The Kappa statistic described in Chapter 8 is also used in this experiment.

## 9.3 Results

The experimental results in Table 9-1 illustrate that the DOPPS-TTLSC provides incrementally better results, towards a K of > 0.60 and a level of accuracy ~80% ,which are generally regarded as thresholds for clinical utility.

**Table 9-1 Experimental Results on the DOPPS Data**

| *Model* | *Kappa (95% Confidence Intervals)** | *P-value* | *Agreement (%)* | *Specificity (%)* | *Sensitivity (%)* |
|---|---|---|---|---|---|
| **RBF** | 0.1675 (0.1268 - 0.2026) | <0.001 | 60.4 | 65.3 | 49.08 |
| **ECF** | 0.1862 (0.1469 - 0.2224) | <0.001 | 61.5 | 63.4 | 51.76 |
| **MLP** | 0.3833 (0.3472 - 0.4182) | <0.001 | 62.8 | 65.6 | 58.72 |
| **Multiple Linear Regression** | 0.4000 (0.3651 - 0.4357) | <0.001 | 69.9 | 71.6 | 60.21 |
| **SVM** | 0.4240 (0.3748 - 0.4449) | <0.001 | 72.6 | 76 | 62.4 |
| **TTLSC** | 0.4503 (0.4152 - 0.4837) | Reference | 73.5 | 74.6 | 68.6 |

## 9.4 Conclusions

This chapter presents a transductive total least square method for classification – TTLSC. The TTLSC performs a better local generalization over new data as it develops individual models for each data vector that takes the location of new input vector in the space into account.

As with the other transductive approaches in this research, this personalised approach seems appropriate for clinical and medical applications where the focus is often not on the population but on the individual patient. At the same time, it is an adaptive model, in the sense that data can be added to the data set continuously and immediately, and made available for transductive TTLSC models. The clinical plausibility of the approach and its results are also satisfactory, along with the other transductive models in this study.

In ***Chapter 10***, conclusions and recommendations for future directions are included.

# Chapter 10 : Conclusion and Future Directions

This last chapter of the thesis includes a summary of the thesis, the main contributions of this study in the field of Health Informatics and renal DSS and some future directions that I would like to follow in my future research and practice.

## 10.1 Summary of the Thesis

This research develops AI for Health Informatics, and focuses on those which can continuously evolve structure and functionality over time through learning from data and continuous interaction with the environment. This thesis presents novel neuro-fuzzy models for local and personalised modelling and illustrates them on real world medical case studies.

The local modelling techniques are based on the principles of ECOS, where the data is clustered and for each cluster a separate local model is developed and represented as a fuzzy rule, either of Takagi-Sugeno, or Zadeh-Mamdani types. The local models compare favourably with global models. As the archetypal local model, the output from DENFIS was more accurate as one might expect given that it is a set of local models. Moreover, DENFIS shows a significant advantage in potential explanation through rule extraction within patient clusters.

The personalised modelling techniques are based on transductive reasoning, where a local model is developed for every new input vector, based on data closest to this vector from the training data set. The performance of these models for prediction of GFR and the prediction of mortality in haemodialysis patients is superior to regression formulas, and other neural fuzzy systems in which prediction is made by either local or global modelling. These transductive systems allow for personalised modelling with a better accuracy for a given individual patient. They also reveal the most significant input

variables (features) for the model that might suggest clinical target for intervention and a change in medical management.

Two representative problems in clinical medicine have been explored using the framework of local and personalised modelling. In each case, prediction has been made utilising either routinely available data of a clinical, laboratory, or a combined nature. Systems has been developed for the following circumstances: (1) prediction appertaining to renal function, using data from 178 Australasian patients with advanced chronic kidney disease (computing procedure GFR-DENFIS, GFR-KBNN, GFR-TWNFI); (2) prediction appertaining to patient longevity after the inception of dialysis for end-stage renal failure, using data from 6010 patients randomly sampled from United States facility haemodialysis population (computing procedure DOPPS-TWNFC, DOPPS- TTLSC).

Five novel modelling have been developed during this course of study:

- *GFR- KBNN*: a novel local modelling for GFR Evaluation based on KBNN. KBNNs incorporate and adapt existing knowledge as kernel functions in their structures to improve their learning and adaptation ability. The system performed better than any existing conventional regression formula in common clinical practice. The system also performed better than other NNs and fuzzy models, which occurs as a result of the fine-tuning of each local model in KBNN and by the proper aggregation of all local models.

- *GFR-DENFIS*: a novel modelling for prediction of renal function based on neuro-fuzzy inference system with capability of learning. This direction represents an incremental advance in the techniques of Health informatics towards progressively more localized and personalised modelling frameworks.

- *GFR-TWNFI*: a transductive personalised modelling for prediction of

renal function with better local generalizations over new data. It utilizes medical knowledge efficiently as setting initial values for parameters of weighted data normalization and develops individual model for individual patient.

- *DOPPS-TWNFC*: a transductive personalised modelling for prediction of survival of patients on dialysis. This personalised modelling can also be applied to solve other classification or clustering problems.

- *DOPPS*- TTLSC: a novel transductive modelling based on total least square classification method with better results for medical diagnosis and prognosis.

However, taking more insights on critical review of the methods applied in this research, there are challenges as following:

1) External validity

   Most regression formulas have been validated in unrelated datasets. New models developed in this research have only been validated in the dataset in which they are developed using 10-flod cross validation, leave one out, etc. There is a possibility that there is overfitting which needs to be explored through analyses on new datasets.

2) Accuracy

   - In most areas of medicine, AI has not resulted in greatly better prediction than competent and contemporary statistical models. Both AI and regression analysis cannot make predictions on omitted covariates, and the degree of residual variation in all of these models suggest that there are important predictors which are simply not captured in existing databases and therefore impossible to model (accepting that there might be some instrumental variables that might reduce unmeasured

confounding). However, irrespective of this, AI predicts more accurately than regression.

- This is a preliminary research emphasized on the application of local and personalised models for medical decision support system. Through future optimizations of the models, we target on the improvement on accuracy.

3) Practicality
    - Is the improvement in accuracy with AI of sufficient magnitude to be important? How much better does prediction have to be before it is clinically useful?
    - Most regression formulas can be implemented using simple software. Connectionist models are more complex to implement, and if they used multiple fixed formulae then this is fine, but they won't be able to evolve outside of a mathematical program.
    - Already, Information System in hospitals is painfully slow and often crippled by old servers and outdated software. How resource hungry are these applications, and are they cost-effective? Is the benefit of better prediction worth the outlay of expenditure or is the money better spent elsewhere?

## 10.2 Main Contributions of the Research

The main contribution of this research is to provide immediate and workable methods and tools to augment health care, which are of sufficient accuracy to support good clinical decision-making.

Current tools for the above applications are either inadequate or wholly lacking, and the new systems compare favourably. Such systems can be utilised by hospital funders and administrators to more accurately assess future population disease burden for service planning, and also by health care providers to more accurately assess actual or potential patient disease burden to assist with diagnostic and therapeutic decision-making. The objectives of

this research are concentrated on specific clinical situations (prediction of renal function, prediction of patient survival on haemodialysis), but they result in generic modelling frameworks. These can then be extrapolated to the future development of other health care applications using ECOS (e.g. for accurate prediction of cardiovascular risk) using local and personalised models, and will serve to catalyse further applications albeit with some modification to methodology.

Furthermore, this research resulted in technical solutions to the various data modelling problems that exist in health care research. For instance, most patient data collected by hospitals for diagnosis and prognosis are limited by their incompleteness (missing parameter values), incorrectness (systematic or random noise in the data), sparseness (few and/or non-representable patient records available), and inexactness (inappropriate selection of parameters for the given task). To date, there have been few rigorous attempts to develop Health Informatics solutions to these problems, and it is anticipated that the procedures developed in this project will set the benchmark in this area.

More importantly, personalised modelling developed for renal decision support system in this research is an adaptive and evolving technique, in which new data sample can be continuously added to the training dataset and subsequently contribute the learning process of personalised modelling. The technique of personalised modelling offers a new tool to give a profile for each new individual data sample. Such characteristic makes personalised modelling based methods are promising for medical decision system, especially for complex human disease diagnosis and prognosis.

## 10.4 Future Directions

Health Informatics is an area with increasing data and emergence of knowledge. The problems in Health Informatics are too complex to be adequate modelled with the use of a single approach. New methods are needed in the future for data and model integration and for personalised

modelling to be applied in medical practice. Future directions for my research include:

1) Further Modification:

    - Working on parameter optimization of different systems, e.g. optimal number of clusters and number of learning iterations for KBNN, optimal number of nearest neighbours for TWNFC and TTLSC, etc.
    - Searching for more effective optimization algorithms.
    - Using different formulas in fuzzy rules as their consequent parts to create new fuzzy inference system.

2) Further Development:

    - Integration of these novel methods into Health Care Decision Support Systems to manage health knowledge and patient data for promoting cost-effective and high-quality medical care.
    - Offering patients personalised, actionable wellness information to improve their health.
    - Contributing to the development of new generation of systems and tools which are aimed at health care administrators and other professionals - to support education, communication, decision making, and many other aspects of professional activity.

3) Further Application: Applying these novel methods to different medical decision support systems for solving other healthcare problems, such as: cardio-vascular risk prognosis; biological processes modelling and predictions based on gene expression micro-array data, etc.

    - Applications in Health Informatics and Bioinformatics for building embedded systems in biological environments, for personalised drug design and personalised medical services, etc.

- Applications in Genomics and Proteomics for computational modelling of gene/ protein expression data and gene regulatory networks related to diagnosis and prognosis of disease and drug marker discovery, for prevention of genetic disease and gene therapy.
- Applications in Neuroinformatics and neuroscience for solving complex problems of artificial intelligence, such as multimodal information processing. A promising direction is computational neurogenetic modelling which integrating genetic and brain data to model brain functions (Nikola Kasabov, Benuskova, & Wysoski, 2005).

As we know, Chronic Kidney Disease (CKD) is a global health problem leading to a substantial burden of illness and premature mortality. The burden of CKD is high worldwide.

The application of the novel local and personalised models for renal medical decision support system developed in this research will allow earlier detection and management of CKD, which could be an important strategy to reduce the increase burden of CKD; In addition, personalised models will effectively help identify risk factors in individual patient which might lead to further personalised medical monitoring and treatment.

This research is not an endpoint, but a beginning and an enabling within the field of personalised modelling for Health Informatics and knowledge discovery. Now clinical studies for prospective validation of these systems in independent datasets are planned.

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