แบบจำลองในการทำนายความเข้มข้นของยูเรียและการประเมินความเพียงพอในการฟอกเลือดโดยโครงข่ายใยประสาทเทียม

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MODELING FOR THE PREDICTION OF UREA CONCENTRATION AND HEMODIALYSIS ADEQUACY ASSESSMENT BY ARTIFICIAL NEURAL NETWORK

Mr. Niti Somboonpattanakul

A Thesis Submitted in Partial Fulfillment of the Requirements

for the Degree of Master of Engineering Program in Chemical Engineering

Department of Chemical Engineering

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Thesis Title	MODELING FOR THE PREDICTION OF UREA CONCENTRATION AND HEMODIALYSIS ADEQUACY ASSESSMENT BY ARTIFICIAL NEURAL NETWORK
By	Mr. Niti Somboonpattanakul
Field of Study	Chemical Engineering
Thesis Advisor	Associate Professor Paisan Kittisupakorn, Ph.D.

Accepted by the Faculty of Engineering, Chulalongkorn University in Partial Fulfillment of the Requirements for the Master's Degree

…….. Dean of the Faculty of Engineering
(Associate Professor Boonsom Lerdhirunwong, Dr.Ing.)

THESIS COMMITTEE

…….. Chairman
(Associate Professor Tharathon Mongkhonsi, Ph.D.)

……..……. Thesis Advisor
(Associate Professor Paisan Kittisupakorn, Ph.D.)

…….. External Member
(Wachira Daosud, D.Eng.)

…….. Member
(Assistant Professor Amornchai Arpornwichanop, D.Eng.)

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ในการทำนายความเพียงพอในการฟอกเลือดได้มีผู้เชี่ยวชาญด้านไตวิทยาเสนอแบบจำลองเพื่อทำนายความเพียงพอในการฟอกเลือดหลายแบบจำลอง โดยแบบจำลองที่ได้รับที่ได้รับความนิยมมากคือ แบบจำลองทางจลศาสตร์ของยูเรีย และ เนอเซอรัลล็อกการิธึมของ Daugirdas โดยแบบจำลองทางจลศาสตร์ของยูเรียและสมการของ Daugirdas เป็นวิธีที่ Kidney Disease Outcome Quality Initiative (K/DOQI) แนะนำให้ใช้ในการคำนวณค่าความเพียงพอในการฟอกเลือด เนื่องจากแบบจำลองทางจลศาสตร์ของยูเรียมีความแม่นยำสูง ส่วนสมการของ Daugirdas อยู่ในรูปแบบที่ไม่ซับซ้อนและง่ายในการคำนวณ ในงานวิจัยจึงได้เสนอแบบจำลองในการทำนายความเพียงพอในการฟอกเลือดโดยใช้วิธีโครงข่ายใยประสาทเทียม โดยกำหนดให้แบบจำลองมีจำนวนชั้นซ่อน 2 ชั้น โครงข่ายแบบจำลองจะถูกเลือกหลังจากกระบวนการฝึก การทดสอบและการพิสูจน์ โดยการพิจารณาค่าความผิดพลาดกำลังสองเฉลี่ยที่น้อยที่สุด ซึ่งแบบจำลองที่ได้จะมีโครงสร้าง 8-7-8-1 ซึ่งผลลัพธ์ที่ได้แสดงให้เห็นว่าเมื่อนำชุดข้อมูลที่ไม่ได้ใช้ในการฝึก มาทดสอบกับแบบจำลองโดยวิธีโครงข่ายใยประสาทเทียม แบบจำลองที่ได้จากวิธีโครงข่ายใยประสาทเทียมยังคงมีความสามารถในการทำนายได้ดีใกล้เคียงกับ แบบจำลองทางจลศาสตร์ของยูเรีย โดยมีค่าสัมประสิทธิ์สหสัมพันธ์เท่ากับ 0.955

ภาควิชาวิศวกรรมเคมี ลายมือชื่อนิสิต.....

สาขาวิชา วิศวกรรมเคมี ลายมือชื่ออาจารย์ที่ปรึกษา.....

ปีการศึกษา 2550

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NITI SOMBOONPATTANAKUL : MODELING FOR THE PREDICTION OF UREA CONCENTRATION AND HEMODIALYSIS ADEQUACY ASSESSMENT BY ARTIFICIAL NEURAL NETWORK. THESIS ADVISOR : ASSOC. PROF. PAISAN KITTISUPAKORN, Ph.D., 56pp.

In the prediction of hemodialysis adequacy, nephrologists have proposed several models to predict the hemodialysis adequacy. The most favorite models are the Formal Urea Kinetic Model (Formal UKM) and Daugirdas natural logarithm equation. The Formal UKM and Daugirdas equation are the method which Kidney Disease Outcome Quality Initiative (K/DOQI) recommends to be used in the hemodialysis adequacy assessment because the Formal UKM gives high accuracy while the Daugisdas equation is not complicate and easy to be used. This research proposes an alternative way to model hemodialysis adequacy by Artificial Neural Network (ANN). This network model is developed based on two hidden layers. The network model is selected after training, testing and validation process by considering the least mean square error (MSE). The neural network model structure is 8-7-8-1. Simulation results show that though unseen data are given to test the neural network model, the neural network model can still provide good prediction of the Formal UKM with correlation coefficient equal to 0.955.

Department Chemical Engineering Student's signature……
Field of study Chemical Engineering Advisor's signature……
Academic year 2007

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NOMENCLATURES

A	membrane area (m^2)
C_o	concentration of BUN at beginning of a dialysis treatment (mg/dl)
C_t	concentration of BUN at end of a dialysis treatment (mg/dl)
$CrCl$	creatinine clearance (ml/min)
G	urea generation rate (mg/min)
GFR	glomerular filtration rate (ml/min/1.73 m^2)
J	mass transfer rate (mol/min)
K	dialyzer clearance (ml/min)
K_0	over all mass transfer coefficient (ml/min.m^2)
K_r	residual renal urea clearance (ml/min)
MAE	Mean Absolute Error
MSE	Mean Square Error
P_b	hydrostatic pressure blood compartment (mmHg)
P_d	hydrostatic pressure of dialysate compartment (mmHg)
R	overall mass transfer resistance (min.m^2/ml)
$RMSE$	Root Mean Square Error
R_B	mass transfer resistance in blood boundary layer (min.m^2/ml)
R_D	mass transfer resistance in dialysate boundary layer (min.m^2/ml)
R_m	mass transfer resistance in membrane (min.m^2/ml)
SSE	Sum of Square Error
S_{Cr}	serum creatinine (mg/dl)
TMP	transmembrane pressure (mmHg)
t	duration time in dialysis (min)
UF	ultrafltrate volume (L)
V	volume distribution of urea (L)
W	post dialysis weight (kg)

Greek Letters

π	colloidal osmotic pressure due to protein in plasma (mmHg)
α	rate of interdialytic volume expansion
θ	interdialytic time

CHAPTER I

INTRODUCTION

Recently there have been many end stage renal disease treatments such as hemodialysis, peritoneal dialysis and kidney transplantation. Hemodialysis is one of the acceptable methods that have the objectives to replace the kidney functions in case of removal uremic toxins and to keep balance of water, mineral, acid and base in the human body. However, hemodialysis cannot absolutely replace the kidney functions therefore the adequacy index is specified to assess the quality of hemodialysis. Hemodialysis adequacy can be shown by various indexes such as Kt/v, Urea Reduction Ratio (URR), etc. In the past, many researchers had proposed equations to calculate those indexes, but each model still has the errors. Supporting report from E.A. Fernandez et al (2005) found that it has an error 23.81%, 22.22% and 17.46% from calculation of the standard URR, the Syme and the Cheng equation respectively by comparing with the gold standard index (GSI). Kovavic, et al (2003) compared the calculation value (Kt/V) of many formulas with gold standard index (Formal Urea Kinetic Modeling), the results show significantly different from GSI, the Daugirdas 1.66%, Barth 2.66%, Jindal 3.49%, Keshaviah 6.65%, Basile 6.73%, kerr 9.65%, and Lowrie formulas 19.63%. For this reason, the model has been developed for exactly prediction to reduce an error. One of the popular and efficient methods is Artificial Neural Networks (ANNs). ANNs based on mechanisms of human brain including structure, processing, learning, and adaptation for the error that difference from the empirical models is proposed by previous researches. Since some major variables that affect the system have not been investigated therefore it has an error when used. Therefore, ANNs have been used successfully to solve complex and stochastic problems without the need of mathematical models and a precise understanding of the mechanism involved. The application of ANNs is known as a powerful tool to simulate various non-linear systems and many fields of clinical medicine such as Pharmacodynamic analysis (Veng-Pedersen P. and Modi N.B., 1992), heparin pharmacokinetics during hemodialysis

(Smith B.P., 1998), time-course and diagnosis of chronic nephropathy (Geddes C.C. et al, 1998)

The aim of the study is to create the model of the prediction hemodialysis adequacy by using clinical data pre and post dialysis urea concentration, net ultrafiltration, body weight, blood flow rate and dialysate flow rate from hemodialysis unit, Chulalongkorn hospital. For this research work, modeling is performing by MATLAB program and compares the results from ANNs model with the other models proposed by nephrologists.

1.1 Objective of this research

The objective of this research is to create mathematical model for prediction the hemodialysis adequacy.

1.2 Scopes of this research

1.2.1 The data of 30 patient in duration 6 month to 12 month are collected from medical record in hemodialysis unit, Chulalongkorn hospital.

1.2.2 All of the patients are treated by means of hemodialysis three times a week.

1.2.3 The MATLAB program is used to train, test and validate the networks to create a model.

1.3 Contributions of this research

1.3.1 Apply neural network process in medical field study.

1.3.2 Hemodialysis adequacy assessment is more accurate.

1.4 Procedures of this research

1.4.1 Define variables to study.

1.4.2 Collect patient data from medical record, chulalongkorn hospital.

1.4.3 Study feed-forward neural network with back-propagation learning.

1.4.4 Training network with a set of known input-output patterns.

1.4.5 Testing and validation network.

1.4.6 Create model for the prediction hemodialysis adequacy.

1.4.7 Compare the result with other models.

1.4.8 Discuss the results and conclusion

CHAPTER II

LITERATURE REVIEWS

Hemodialysis is the most common method used to treat advanced and permanent kidney failure. The kidney could be replaced by simple diffusive removal of solute from the blood. Hemodialysis allowed life to continue and patients to prosper even after total loss of the kidneys that a minimum dose of dialysis is required to optimize both the duration and the quality of life. The dose of hemodialysis is best described as the fractional clearance of urea as a function of its distribution volume (Kt/V), standard minimum for adequate dialysis is 1.2. This is the standard adopted by the Dialysis Outcomes Quality Initiative (DOQI) group.

2.1 Hemodialysis

Gotch and Sargent, 1985 analysis the National Cooperative Dialysis Study (NCDS) and suggested that most treatment failures, defined as hospitalization and/or the appearance of de novo clinical abnormalities or worsening of residual morbidity in any organ system, occurred at Kt/V < 0.8 and concluded that a Kt/V of 1.0 was fully adequate.

Prado, et al, 2000 present a new hemodialysis prescribing procedure which calculates the adequate dialyzer clearance to obtain a target time averaged concentration (TAC) of urea. This procedure is supported by a new model that developed: the normalized single-pool urea kinetic model which is able to calculate a good approximation to the real Kt/V based in dialyzer clearance.

Kemp, et al, 2001 review a measure of dialysis adequacy. In this paper presented basic concept of hemodialysis and the calculation of kt/V and Normalized Protein Catabolic Rate using Urea kinetic Modeling.

Kovacic, et al, 2003 demonstrated significant differences between Kt/V Daugirdas (single-pool and equilibrated) and other delivered and prescribed Kt/V values. Additionally, the Daugirdas Kt/V values and Daugirdas Kt/V equilibrated values

were statistically different from all other calculated Kt/V values ($p<0.05$). And found the least difference (i.e., the least mean of the absolute values of the differences) to be between the Barth Kt/V values and the Daugirdas Kt/V values (both single-pool and equilibrated).

Depner, 2005 presented the basic essentials and practical points for the nephrologists in training. In this work focus on the prescription of dialysis, methods of measuring the dose and expressing it in a way that best reflects its therapeutic effect.

2.1 Neural Network

Artificial Neural Network (ANN) is a type of mathematical model that simulates the biological nervous system and draws on analogues of adative biological learning. The most popular ANN is the multi layer perceptron that generally trains the input-output relationship using a back-propagation algorithm. ANN learns when the difference between observed and predicted outputs is minimized by iteratively adjusting connection weights. ANN has been applied to numerous problems of considerable complexity in many fields including engineering and medical science.

Chow, et al, 1997 determined the applicability of using a neural network approach to analyze population pharmacokinetic data. The data were collected retrospectively from pediatric patients who had received tobramycin for the treatment of bacterial infection. The information collected included patient-related demographic variables (age, weight, gender, and other underlying illness) the individual's dosing regimens (dose and dosing interval), time of blood drawn, and the resulting tobramycin concentration. Neural networks were trained with this information to capture the relationships between the plasma tobramycin levels and the following factors: patient-related demographic factors, dosing regimens, and time of blood drawn. The data were also analyzed using a standard population pharmacokinetic modeling program, NONMEM. The observed versus predicted concentration relationships obtained from the neural network approach were similar to those from NONMEM. The residuals of the

predictions from neural network analyses showed a positive correlation with that from NONMEM. Average absolute errors were 33.9 and 37.3% for neural networks and 39.9% for NONMEM. Average prediction errors were found to be 2.59 and -5.01% for neural networks and 17.7% for NONMEM.

Nazario, et al, 1999 presented an artificial neural network is used to model and control the pH of the erythromycin acetate salt which Thirty hours of real data were used to generate the input and output patterns to identify a neural network model and the last 60 observations were used to fit a neural network model by computer program to control the pH of the erythromycin acetate salt.

Basheer and Hajmeer, 2000 has an aims to familiarize the reader with ANN-based computing and to serve as a useful companion practical guide and toolkit for the ANNs modeler. An also review of the various types of ANNs and the related learning rules is presented, with special emphasis on backpropagation (BP) ANNs theory and design. A generalized methodology for developing successful ANNs from conceptualization, to design, to implementation, is described. The most common problems that BPANNs developers face during traning are summarized in conjunction with possible causes and remedies. Finally, as a practical application, BpANNs were used to model the microbial growth curves of *S. Flexneri*. The developed model was reasonably accurate in simulating both training and test time-dependent growth curves as affected by temperature and pH.

Fernandez, et al, 2001 propose a supervised neural network to predict the equilibrated postdialysis blood urea (eqU) at 60 min after the end of hemodialysis. The use of this model is new in this field and is shown to be better than the currently accepted methods (Smye for eqU and Daugirdas for eqKt/V). With this approach achieve a mean difference error of 0.22 +/- 7.71 mg/ml (mean % error: 1.88 +/- 13.46) on the eqU prediction and a mean difference error for eqKt/V of -0.01 +/- 0.15 (mean % error: -0.95 +/- 14.73). The equilibrated Kt/V estimated with the eqU calculated using the Smye formula is not appropriate because it showed a great dispersion. The Daugirdas double-pool Kt/V estimation formula appeared to be accurate and in agreement with the results of the HEMO study.

Hoo, et al, 2002 study on the ability of a neural network to predict the behavior of a nonlinear system accurately ought to be improved if there was some mechanism that allows the incorporation of first-principles model information into their training. This is accomplished by modifying the objective function so as to include an additional term that is the difference between the time derivative of the outputs, as predicted by the neural network, and that of the outputs of the first-principles model during the training phase. The performance of a feedforward neural network model that uses this modified objective function is demonstrated on a chaotic process and compared to the conventional feedforward network trained on the usual objective function that give a good result.

Gaweda, et al, 2003 present a presents a pharmacodynamic population analysis in chronic renal failure patients using Artificial Neural Networks (ANNs). In pursuit of an effective and cost-efficient strategy for drug delivery in patients with renal failure, two different types of ANN are applied to perform drug dose-effect modeling and their performance compared. Applied in a clinical environment, such models will allow for prediction of patient response to the drug at the effect site and, subsequently, for adjusting the dosing regimen.

Yamamura, 2003 used ANN modeling to evaluate the pharmacokinetics of aminoglycosides (arbekacin sulfate and amikacin sulfate) in severely ill patients. The plasma level was predicted by ANN (peak and trough level, r = 0.825 and 0.854 respectively) modeling using parameters related to the severity of the patient's condition and the predictive performance was shown to be better than could be achieved using multiple regression analysis (peak and trough level r = 0.037 and 0.276 respectively).

Gabutti, et al, 2004 studied ANN in predicting the dialysis quality (Kt/V), the follow-up protein catabolic rate (PCR) and the risk of intradialytic hypotension. The ANN were built and then prospectively compared with the ability of six experienced nephrologists to predict the Kt/V and follow-up PCR and to detect a Kt/V < 1.30, a follow-up PCR < 1.00 g/kg/day and the occurrence of hypotension. The result show ANN can achieve a better prediction of follow-up PCR than experienced nephrologists.

Turner, et al, 2004 determine the human pharmacokinetics of known and unknown drug-like compounds is a much sought-after goal in the pharmaceutical

industry. The current study made use of artificial neural networks (ANNs) for the prediction of clearance, fraction bound to plasma protein, and volume of distribution of a series of structurally diverse compounds. Models were trained on one set of compounds and validated with another. Absolute predicted ability was evaluated using a further independent test set of compounds. Correlations for test compounds ranged from 0.855-0.992. Predicted values agree closely with experimental values for total clearance, renal clearance, and volume of distribution, while predictions for protein binding were encouraging.

Strik, et al, 2005 applied the highly energetic biogas from anaerobic digestion into fuel cells will result in a significantly higher electrical efficiency and can contribute to an increase of renewable energy production. The experiments concluded that ammonia in biogas can indeed be present up to 93 ppm. Hydrogen sulfide and ammonia concentrations in biogas were modeled using the MATLAB Neural network Toolbox. The resulted determination coefficients (R^2) were for hydrogen sulfide 0.91 and ammonia 0.83.

Chiu et al, 2005 applied an Artificial Neural Network to Predict Total Body Water in Hemodialysis Patients. The predictive value of TBW based on ANN and five anthropometric equations (58% of actual body weight, Watson formula, Hume formula, Chertow formula, and Lee formula) was evaluated. The results showed the predictive TBW values derived from anthropometric equations were significantly higher than TBW-BIA (31.341 ± 6.033 liters). The only non-significant difference was between TBW-ANN (31.468 ± 5.301 liters) and TBW-BIA ($p = 0.639$). ANN had the strongest Pearson's correlation coefficient (0.911) and smallest root mean square error (2.480). Its peak centered most closely to zero with the shortest tails in an empirical cumulative distribution plot when compared with the other five equations.

CHAPTER III

KIDNEY AND ARTIFICIAL KIDNEY MACHINE

3.1 Kidney

The kidney performs numerous regulatory functions in addition to manufacturing important biochemical. The key separation functions of the kidney are:

- Remove nitrogenous end-products of protein metabolism
- Regulate the volume of body water
- Maintain acid-base and electrolyte composition and get rid of the excess electrolytes
- Assist in red blood cell production (erythropoiesis)

Renal function is provides by paired, fist-sized organs, the kidneys located behind the peritoneum against the posterior abdominal wall on both sides of the aorta. Each kidney is made up of over million parallel mass transfer units which receive their common blood supply from the renal arteries, return the processed blood to the systemic circulation through the renal veins, and collect the waste fluids and solutes through the calyx of each kidney into the ureter and from there into the urinary bladder.

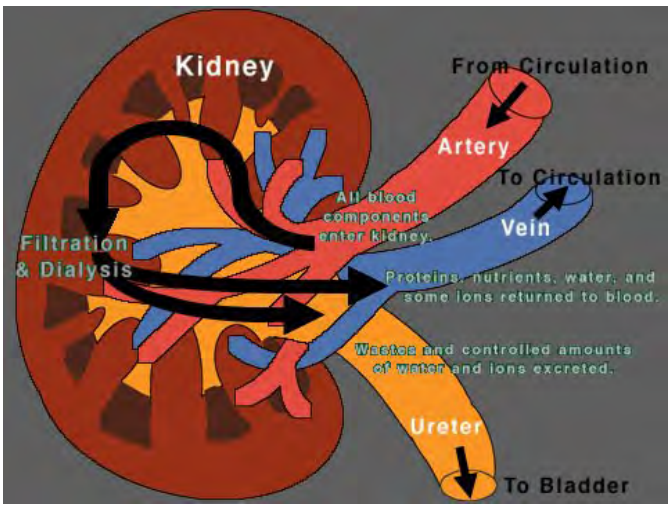

Figure 3.1: Schematic diagram illustrating the kidney ability to separate particles in the blood in order to maintain optimal body chemistry (http://www.chemistry.wustl.edu)

These functional units are called nephrons which is the most basic functional unit of the kidney.

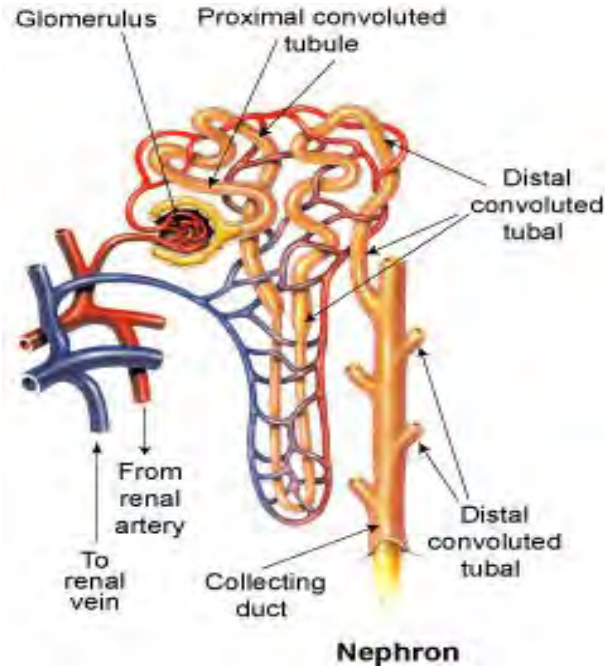

Figure 3.2: Components of nephron (http://www.venofer.com)

In the nephron, capillaries (tiny blood vessels) are intertwined with tubules (urine-carrying tubes) that carry away wastes and water. Blood enters the nephron through the glomerulus, a tuft of capillaries where filtration occurs. During filtration, blood fluid is forced from capillaries into the tubules. As the fluid passes through the tubules, substances needed by the body, including water, sodium, phosphorus, potassium, and glucose, are selectively reabsorbed into the blood by the intertwined capillaries. In this way, the kidneys regulate the level of these vital substances in the blood. The blood exits the nephron through the renal vein. The fluid remaining in the tubules after reabsorption exits as urine into the collecting duct, which eventually leads to the ureter.

3.2 Diagnosis and Treatment of Renal Failure

When the kidneys do not function properly, dialysis must be performed artificially. Without this artificial kidney dialysis, toxic wastes build up in the blood and cannot be filtered out by kidneys. If the kidneys stop working completely, the body fills with extra water and waste products. This condition is called uremia which means literally “urine in the blood”. Hands or feet may swell. Patients will feel tired and weak because body needs clean blood to function properly. Untreated uremia may lead to seizures or coma and will ultimately result in death. Patients will need to undergo dialysis or kidney transplantation to prolong their life. Dialysis is a mechanical filtering process used to cleanse the blood of waste products, draw off excess fluids and regulate body chemistry.

Table 3.1: Uremic solutes with potential toxicity (The biomedical engineering handbook, 1995)

Urea	Hippuric acid	Hormones
Guanidines	Benzoates	Parathormone
Methyguanidine	Polypeptides	Natriuetic factor
Guanidine	β_2-microglobulin	Glucagon
β-guanidinipropionic acid	Indoles	Growth hormone
Guanidinosuccinic acid	Indol-3-acetic acid	Gastin
Gamma-guanidinobutyric acid	Indoxyl sulfate	Prolactin
Taurocyamine	5-Hydroxyindol acetic acid	Cateecholamines
Creatinine	Indol-3-acrylic acid	Xanthine
Arginic acid	5- Hydroxytryptophan	Hypoxanthine
Homoarginine	N-acetyltryptophan	Furanpropionic acid
N-alpha-acetylarginine	Tryptophan	Amines
Phenols	Middle molecules	Putrescine
O-cresol	Ammonia	Spermine
P-cresol	Alkaloids	Spermidine
Benzyl alcohol	Trace-metals (brommine)	Dimethylamine
Tyrosine	Uric acid	Polyamines
	Cyclic AMP	Endorphins

Phenolic acids:	Amino acids	Pseudouridine
P-hydroxyphenylacetic acid	Myoinositol	Potassium
β -(m hydroxyphenyl)-	Mannitol	Phosphorus
hydracrylic acid	Oxalate	Calcium
Hippurates	Glucuronate	Sodium
p-(OH)hippuric acid	Glycols	Water
o-(OH)hippuric acid	Lysozyme	Cyanides

In the diagnosis of renal function, the glomerular filtration rate (GFR) is traditionally considered the best overall index of renal function in health and disease. The Modification of Diet in Renal Disease (MDRD) study proposed the equations to estimate GFR based on ages, genders and ethnicities (Andrew S. Levey et al., 1999):

$$GFR = 186 \times (S_{Cr})^{-1.154} \times (Age)^{-0.203} \times (0.742\ if\ \ female) \times (1.21\ if\ \ African-American) \quad (3.1)$$

Table 3.2: Levels of GFR and state of kidney disease (The Nephrology Society of Thailand, www.nephrothai.org)

Level	State	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or increased GFR	= 90
2	Kidney damage with mild decrease in GFR	60-89
3	Moderate decrease in GFR	30-59
4	Severe decrease in GFR	15-20
5	Kidney Failure	< 15 or dialysis

An also considered the estimation of creatinine that show how well your kidneys are working. Creatinine is excreted entirely by the kidneys, and therefore is directly related to renal function. When the kidneys are functioning normally, the serum

creatinine level should remain constant and normal. A high creatinine level may mean your kidneys are not working properly. The Cockcroft-Gault had developed equation to predict creatinine clearance (Cockcroft DW and Gault MH, 1976):

$$CrCl = \frac{[(140 - age\ in\ years) \times (weight\ in\ kg) \times (0.85\ if\ \ female)}{72 \times S_{Cr}} \quad (3.2)$$

Table 3.3: Level of creatinine compared with kidney damage (Wallach J., 1996)

Renal Status	Creatinine clearance (ml/min)
normal (males)	90 – 130
normal (females)	80 – 125
slight	52 - 62.5
mild impairment	42 – 52
moderate impairment	28 – 42
severe impairment	< 28
anuric	0

There are two major types of dialysis:

1) Hemodialysis
2) Peritoneal dialysis

3.2.1 Hemodialysis

Hemodialysis is the process of filtering blood through a device known as an artificial kidney or dialyzer. The blood is continually circulated through a dialyzer by an artificial kidney machine. The patient is connected by a tube to the dialysis machine, which continuously draws blood out, cleanses it, removes excess fluid, and returns the blood back to the patient. Hemodialysis must be performed for 3-4 hours at least three times a week.

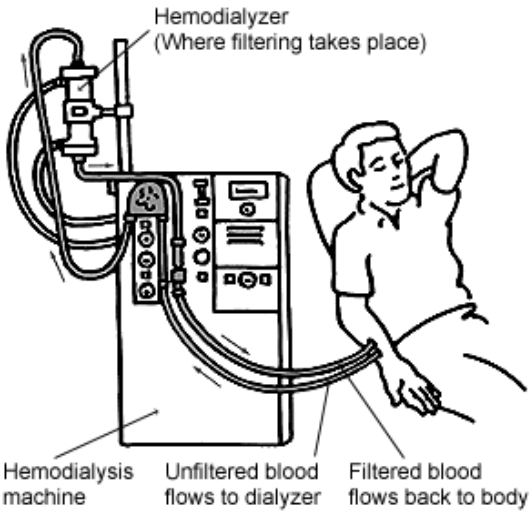

Figure 3.3: Hemodialysis with the artificial kidney machine (http://kidney.niddk.nih.gov)

3.2.2 Peritoneal dialysis

Peritoneal dialysis, a fluid is put into your abdomen. This fluid, called dialysate captures the waste products from your blood. After a few hours, the dialysate containing your body's wastes is drained away. Then, a fresh bag of dialysate is dripped into the abdomen. Patients can perform peritoneal dialysis themselves. Patients using continuous ambulatory peritoneal dialysis (CAPD), the most common form of peritoneal dialysis, change dialysate four times a day. Another form of peritoneal dialysis, however, can be performed at night with a machine that drains and refills the abdomen automatically.

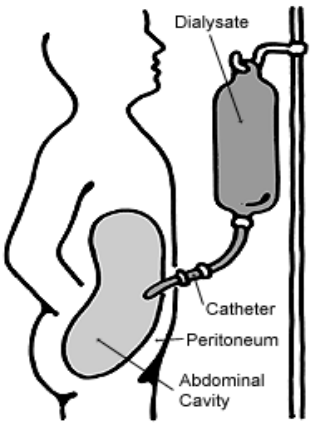

Figure 3.4: Peritoneal dialysis (http://kidney.niddk.nih.gov)

Table 3.4: Standard value of solute concentration in plasma (Handbook of bioengineering, 1987)

Substance	Normal range	Uremic range*
Sodium, meq/L	133-144	138(135-150)
Potassium, meq/L	3.5-5.5	5(4-6)
Phosphorus, inorganic, mg/dL	2.7-4.3	4(3-5)
BUN, mg/dL	7-18	67(50-150)
Creatinine, mg/dL	0.7-1.5	13(5-16)
Uric acid, mg/dL	3.0-6.1	5(4-6)

* Patient undergoing hemodialysis 12 to 15 h/week

3.3 Artificial kidney machine

The artificial kidney is a device which can partially simulate the kidney in three functions:

- Remove nitrogenous metabolic waste products, primarily small molecular weight solutes such as urea, uric acid, and creatinine
- Remove excess body water
- Partially reestablish appropriate plasma acid-base and electrolyte composition and concentrations.

Upon failure of the kidney, the patient's blood must be treated on the artificial kidney for 4 to 5 h per treatment, 3 days a week; the treatment is called hemodialysis.

The artificial kidney is composed of two primary components: a hemodialyzer in which all mass transport takes place, and an automatic dialysate delivery system which continuously supplied an aqueous solution called a dialysate to the hemodialyzer. The dialysate carries away the waste products removed by the hemodialyzer.

3.3.1 Types of dialyzers

The dialyzer consists of a chamber with a support system for a semipermeable membrane which separates blood and dialysate. The semipermeable membrane used in early dialysis systems was cellophane which is still used in some dialyzers. Regenerated cellulose acetate and Cuprophane are new membranes with improved performance characteristics and probably the most used membranes at the present time. Dialyzer is divided in three basic configurations:

3.3.2 Flat –plate hemodialyzer

This dialyzer is composed of multiple layers of two sheets of membrane and plastic spacers. The blood flows between the two sheets of membrane, whereas the dialysate flows on both sides of the blood membrane channel between the membrane and spacer. The plastic spacer has a pattern molded onto its surface to enhance dialysate and blood mixing.

3.3.3 Coil hemodialyzer

In the coil dialyzer, the blood flows through a flattened tubing which is wound, together with a plastic mesh, around a cylindrical core. In operation, blood flowed inside of the cellophane tubing around the coil, while dialysate flowed axially through the space formed by the plastic mesh.

3.3.4 Hollow fiber hemodialyzer

The hollow-fiber dialyzer is the most recent development in dialyzer design. The structure of hollow fibers is composed of; a bundle of hollow fibers is contained in housing and encapsulated at each end forming tubesheets. The blood flows in and out of the lumens of the fibers. Adjacent to each tubesheet is a circumferential header, which directs dialysate flow in and out of the shellside space. The device is geometrically similar to a shell-and-tube heat exchanger.

Table 3.5: Typical values of clearance for standard 1-m^2 dialyzer* (Handbook of bioengineering, 1987)

Substance	Molecular weight	Approximate clearance, mL/min	Approximate variation, mL/min
Urea	60	125	± 15
Creatinine	113	100	± 15
Uric acid	168	80	± 10
Vitamin B_{12}	1355	25	± 6

* $Q_{B,i} \approx$ 200 mL/min, $Q_{D,i} \approx$ 560 mL/min, $Q_v \leq$ 10 mL/min, $c_{D,i} = 0$ and $T = 37^{\circ}\mathrm{C}$

3.3.5 Dialysate

Dialysate is composed of appropriate concentrations of sodium, potassium, chloride, magnesium and calcium, and buffer to develop ideal plasma water. The quantity of each of the constituents of dialysate may vary considerably and the range available is listed in table 3.6 below.

Table 3.6: Range of solute concentrations in dialysate solution

Substance	Normal range
Sodium	130-140 mEq/l
Potassium	0-4 mEq/l
Chloride	96-112 mEq/l
Acetate	33-45 mEq/l
Magnesium	1- 2.5 mEq/l
Calcium	2.0 -3.5 mEq/l
Dextrose	0-250 mg/dl

3.3.6 Mass transfer in dialyzer

In artificial kidney, the removal of water (solvent) and uremic toxin (solute) from the blood stream is achieved by

- Solute diffusion in response to concentration gradients
- Water ultrafiltration and solute convection in response to hydrostatic and osmotic pressure gradients.
- Water migration in response to osmotic gradients

In most cases, these processes occur simultaneously and in the same exchange device, rather than sequentially as they do in the natural kidney with the cascade of glomerular filtration, tubular reabsorption, and final in the collecting duct.

3.3.6.1 Diffusion

Diffusion refers to the process which molecules of substances move from high concentration to low concentration by used concentration gradient as driving force.

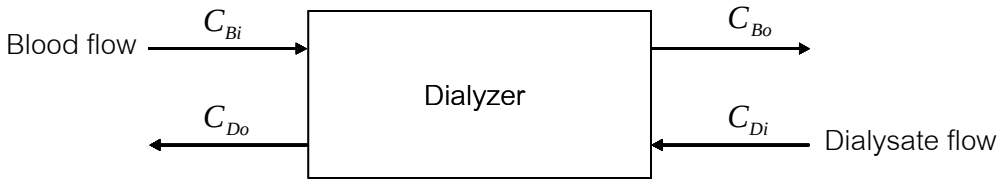

Figure 3.5: Diffusive mass transfer across an element of a membrane of length dz and area dA

Diffusive mass transfer rate, dJ transferred across an element of membrane of length dz and area dA per unit time:

$$dJ = K_0(\Delta C)dA \tag{3.3}$$

Where ΔC is the logarithm mean of the concentration differences prevailing at the inlet and at the outlet

$$J = K_0 A \left(\frac{\Delta C_{z=o} - \Delta C_{z=1}}{\ln \frac{\Delta C_{z=1}}{\Delta C_{z=0}}} \right) \quad (3.4)$$

The parameter $K_0 A$ is represent the efficiency of dialyzer that divided in 3 levels

1. $K_0 A$ <500 ml/min is low efficiency dialyzer
2. $K_0 A$ 500-700 ml/min is moderate efficiency dialyzer
3. $K_0 A$ >700 ml/min is high efficiency dialyzer

3.3.6.2 Convection

Convection is the process used pressure as driving force to remove solute from solution that difference from diffusion and called this pressure as transmembrane pressure (TMP) that equal pressure difference between two sides of semipermeable membrane.

$$TMP = (P_b - P_d) - \pi \quad (3.5)$$

TMP is regulating transportation of water (solvent) across membrane. Each types of membrane have difference property in permeability therefore membrane with large pore allow water transfer across membrane easier than small pore (use higher TMP).

3.3.6.3 Diffusion resistance

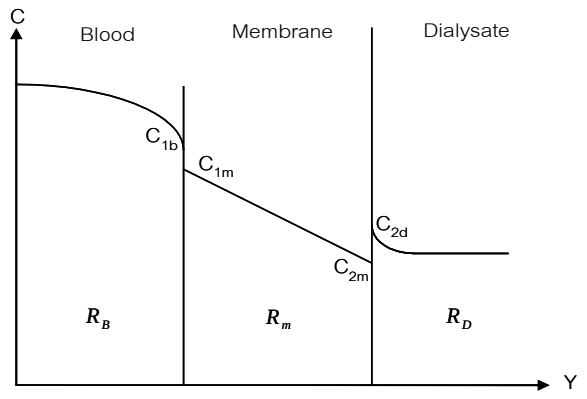

Figure 3.6: Concentration profile and resistance in dialysis

The overall mass transfer resistance R can be expressed as the sum of the resistances associated with each phase:

$$R = R_B + R_m + R_D \quad (3.6)$$

So the overall mass transfer coefficient K is defined as reciprocal of R :

$$K_0 = \frac{1}{R}$$

Thus,

$$\frac{1}{K_0} = \frac{1}{K_B} + \frac{1}{K_m} + \frac{1}{K_D} \quad (3.7)$$

3.3.6.4 Dialyzer mass transport coefficient

As blood and dialysate flow rates increase, the clearance increases in a curvilinear fashion that eventually reaches a plateau as shown in Figure 6. This maximum clearance at infinite blood and dialysate flow rates is the dialyzer mass transfer area coefficient (K_0A), sometimes called the intrinsic clearance of the dialyzer for the measured solute (usually urea). It is a property of the solute and of the dialyzer and is independent of flow rates and concentrations, so it is often used to compare different dialyzers and dialyzer models. K_0A can be measured as a function of clearance and flow rates of blood (Q_B) and dialysate (Q_D) using an equation that can be derived mathematically for countercurrent flow:

$$K_0A = \frac{Q_B \cdot Q_D}{Q_B - Q_D} \ln\left(\frac{Q_D(Q_B - K_D)}{Q_B(Q_D - K_D)}\right) \quad (3.8)$$

Clearance is usually measured instantaneously from pre and post dialyzer blood concentrations as described above. From knowledge of the dialyzer's K_0A, the expected clearance can be calculated from a rearrangement of Equation 8 at any dialysate and blood flow:

$$K_D = Q_B \left[\frac{e^{K_0 A\left(\frac{Q_D - Q_B}{Q_D Q_B}\right)} - 1}{e^{K_0 A\left(\frac{Q_D - Q_B}{Q_D Q_B}\right)} - \frac{Q_B}{Q_D}} \right] \quad (3.9)$$

Equation 9 is often helpful to calculate the prescribed or predicted Kt/V at achievable flow rates for the particular patient, blood access device, and dialyzer.

3.4 Hemodialysis adequacy

Adequacy of hemodialysis is assessment on patients after treatments that have several ways. The most common acceptable methods are: formal urea kinetic model (UKM), Kt/V natural logarithm formula, urea reduction rate (URR), and normalized protein catabolic rate (nPCR)

3.4.1 Formal Urea Kinetic Model (Formal UKM)

Formal kinetic modeling provides a quantitative method for developing a treatment prescription for a specific patient. Because of the complexity of the formula that provides the information for calculation of Kt/V by UKM, computational software is necessary to compute Kt/V using formal UKM. Formal UKM can be used to calculate the exact treatment time required delivering a particular hemodialysis dose at specified blood and dialysate flows with a particular dialyzer. Formal UKM calculates the volume of distribution of urea by a complicated mathematical iteration of two formula that share common terms. The first formula solves for the end dialysis volume, V. The other formula calculates the urea generation rate (G) between consecutive hemodialysis sessions (Sargent JA and Gotch FA, 1980):

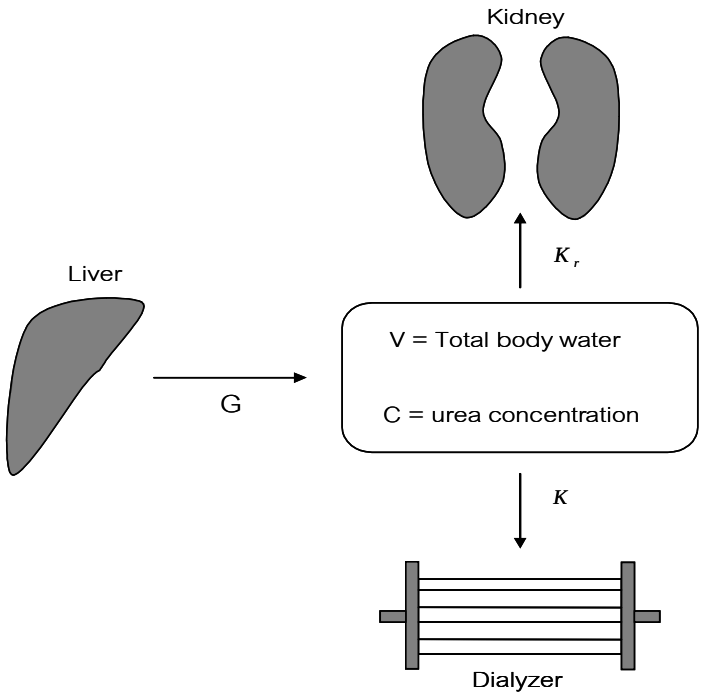

Figure 3.6: Diagram of urea mass balance

The rate of change of urea = urea generation rate – removal rate

$$\frac{d(CV)}{dt} = G - KC \tag{3.10}$$

Integration and rearrange thus

$$V = Q_f \times t\left[\left[1-\left[\frac{G-C_t\left(K+K_r-Q_f\right)}{G-C_o\left(K+K_r-Q_f\right)}\right]^{\frac{Q_f}{K+K_r-Q_f}}\right]^{-1}-1\right] \tag{3.11}$$

$$G = \frac{(K_r+\alpha)\left[C_o - C_t\left(\frac{Vt+\alpha\theta}{Vt}\right)^{-\frac{K_r+\alpha}{\alpha}}\right]}{\left(1-\left(\frac{Vt+\alpha\theta}{Vt}\right)\right)^{-\frac{K_r+\alpha}{\alpha}}} \tag{3.12}$$

The standard value for Kt/V should equal or more than 1.2 (DOQI guidelines, 2000) for the patients under dialysis treatment 3 time per week. Another formula to calculate Kt/V directly without the need for computer program developed by Daugirdas (Daugirdas JT, 1993):

$$Kt/V = \ln(R - 0.008t) + (4 - 3.5 \times R) \times \frac{UF}{W} \quad (3.13)$$

Where $R = \frac{post\ dialysis\ BUN}{pre\ dialysis\ BUN}$

And Barth equation:

$$\frac{Kt}{V} = 0.031 \times \left(\frac{(C_1 - C_2)}{C_1} \times 100 \right) - 0.66 \quad (3.14)$$

3.4.2 Urea Reduction Ratio

The reduction in urea as a result of dialysis, or the URR, is one measure of how effectively a dialysis treatment removed waste products from the body. The URR stands for urea reduction ratio, but it is commonly expressed as a percentage (Owen WF, et al., 1993):

$$URR(\%) = 100 \times \left(1 - \frac{Bunpost}{Bunpre} \right) \quad (3.15)$$

For the patients that treatment 3 times per week URR should higher 65% (DOQI guidelines, 2000).

3.4.3 Normalized Protein Catabolic Rate

The protein catabolic rate ($nPCR$), also called the protein equivalent of nitrogen appearance is the parameter used in hemodialysis units to assess dietary protein intake in patients that correlates with the mortality risk. The $nPCR$ may be calculated by (Borah MD, et al., 1978):

$$nPCR = 9.35G + 0.294V \quad (3.16)$$

The poor nutrition has shown as PCR below 1 g/kg/day and recommended this value should between 1.0-1.2 1 g/kg/day (DOQI guidelines, 2000).

3.5 Neural network

Neural network approaches are inspired by biology with components loosely analogous to the dendrites, cell body and the axon of a living thing. The dendrites are tree-like receptive networks of nerve fibers that carry electrical signals into the cell body. The cell body effectively sums and thresholds these incoming signals. The axon is a single long fiber that carries the signal from the cell body out to other neurons. The point of contact between an axon of one cell and a dendrite of another cell is called a synapse. It is the arrangement of neurons and the strengths of the individual synapses, determined by a complex chemical process that establishes the function of the neural network.

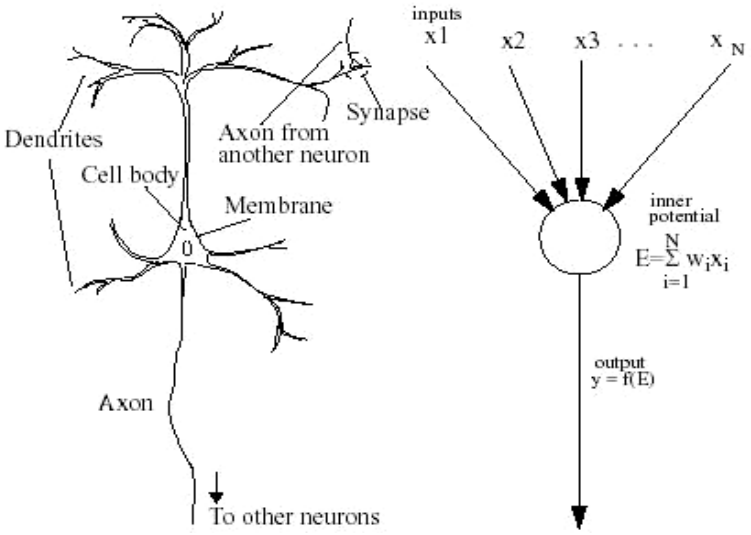

Figure 3.7: Schematic diagram of biological neurons and artificial neural network

A neural network is a parallel distributed processing system (Other names for the field include connectionism, artificial intelligence, and neural computation) composed of processing entities called neurons, the connection strengths between which are weights which are adjusted to store experiential knowledge and make it available for later use in prediction and classification. The goal of a neural network is to map a set of input patterns onto a corresponding set of output patterns. The network accomplishes this mapping by first learning from a series of past examples defining sets

of input and output correspondences for the given system. The network then applies what it has learned to a new input pattern to predict the appropriate output.

The first development of artificial neural networks came in the late 1950s, with the invention of the perceptron network and associated learning rule by Frank Rosenblatt. Rosenblatt and his colleagues built a perceptron network and demonstrated its ability to perform pattern recognition. This early success generated a great deal of interest in neural network research. It was later shown that the basic perceptron network could solve only a limited class of problems. At about the same time, Bernard Widrow and Ted Hoff introduced a new learning algorithm and used it to train adaptive linear neural networks, which were similar in structure and capability to Rosenblatt's perceptron. The Widrow-Hoff learning rule is still in use today.

An application of neural networks in many fields such as electronics, financial, medical, robotics, and engineering. In bioprocessing and chemical engineering the first application papers was by Hoskins and Himmelbrau (1988), who applied a neural network to the fault diagnosis of a chemical reactor system.

3.5.1 Components of a node

The foundation of a neural network is the neuron, or node that in many scientific and engineering applications, this node is frequently called a processing element.

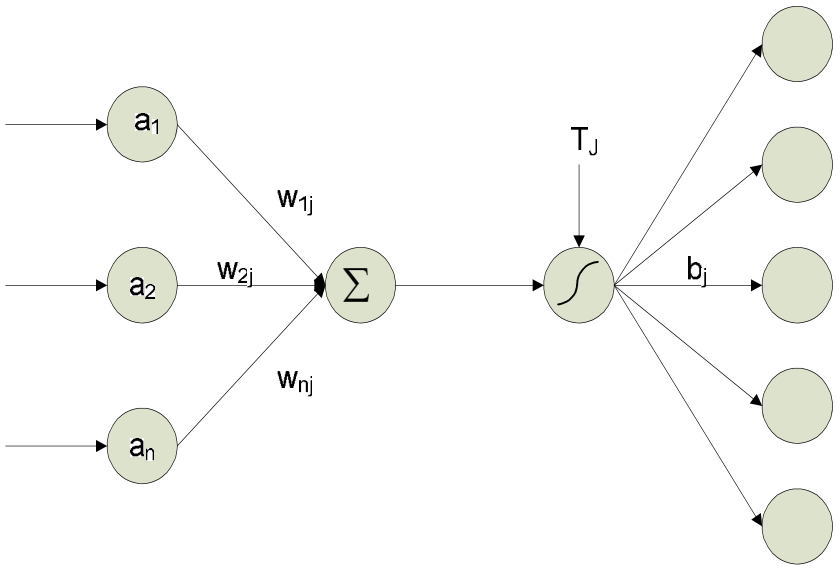

Figure 3.8: Components of node

- Inputs and outputs

The inputs to the J^{th} node are represented as an input vector, with components a_i (i = 1 to n). The node manipulates these inputs, or activities, to give the output, b_j, which can then form the part of the input to other nodes.

- Weight factors

Weights, w_{ij} determine the relative strength of the connection from an input neuron to the neuron under consideration. Weights inputs must be aggregated by the neuron through a summation function which computes the net input. That is, for target neuron j, the basic summation is simply the sum of the path weights from all its neurons i time the outputs of these i neurons:

$$\text{Net input}_i = \sum_{i=1}^{n} (w_{ij} a_i) \quad (3.15)$$

Weights factor can have either an inhibitory or an excitatory effect. Weights are positive if the connection is excitatory and negative if the connection is inhibitory.

- Internal threshold

The internal threshold or bias for the J^{th} node, denoted T_j, controls activation of that node. The node calculates all its $W_{ij} a_i$ sums the terms together and then calculates the total activation, x_j, by subtracting the internal threshold value:

$$\text{Total activation} = x_j = \sum_{i=1}^{n} (w_{ij} a_i) - T_j \quad (3.16)$$

If T_j is large and positive, the node has a high internal threshold, which inhibits node-firing. Conversely, if T_j zero (or negative, in some cases) is, the node has a low internal threshold, which excites node-firing and if no internal threshold T_j is to be zero.

- Transfer functions

The summed weights are forwarded to the next layer of neurons by an activation function, also called transfer function. The node calculates the dot product of vector $w_j = [w_{1j}, w_{2j} \ldots w_{nj}]$ with vector a, and subtracts the threshold T_j and pass this result to a transfer function so, the complete node calculation is:

$$f(w_j \cdot a - T_j) \quad = \quad f(\sum_{i=1}^{n}(w_{ij} a_i) - T_j) \tag{3.17}$$

Table 3.7: Transfer functions of neural network

Type of functions	Relation	Characteristic
Step function	$f(x) = \begin{cases} 1 & \text{if } x \geq 0 \\ 0 & \text{if } x < 0 \end{cases}$	Linear
Ramp Function	$f(x) = \begin{cases} 1 & \text{if } x \geq 1 \\ x & \text{if } x < 1 \\ -1 & \text{if } x \leq -1 \end{cases}$	Linear
Sigmoid Function	$f(x) = \frac{1}{1+e^{-x}}$	Nonlinear
Gaussian Function	$f(x) = \frac{1}{1+e^{\frac{-x^2}{2}}}$	Nonlinear

3.5.2 Network Architecture

- Single layer feed-forward neural networks (perceptrons)

The perceptron is the simplest type of neural network that compose of an input connected directly to the output layer of neurons so, each output node is independent of the others, each weight affects only one of the outputs.

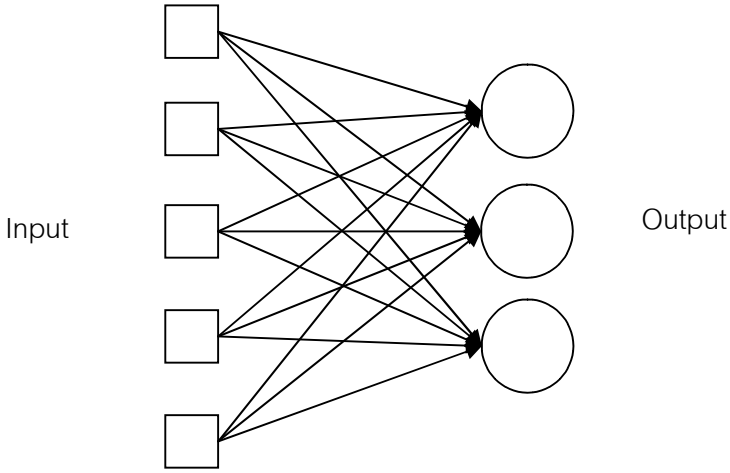

Figure 3.9: A perceptron network

- Multilayer feed-forward networks

A general multilayer feed-forward network is illustrated in figure 3.13. This is a forward, fully connected hierarchical network consisting of an input layer, one or more middle or hidden layers and an output layer. The internal layers are called hidden because they only receive internal inputs (inputs from other processing units) and produce internal outputs (outputs to other processing units). Most neural networks contain one to three hidden layers and typical three hidden layer feed-forward network used in bioprocessing and chemical engineering.

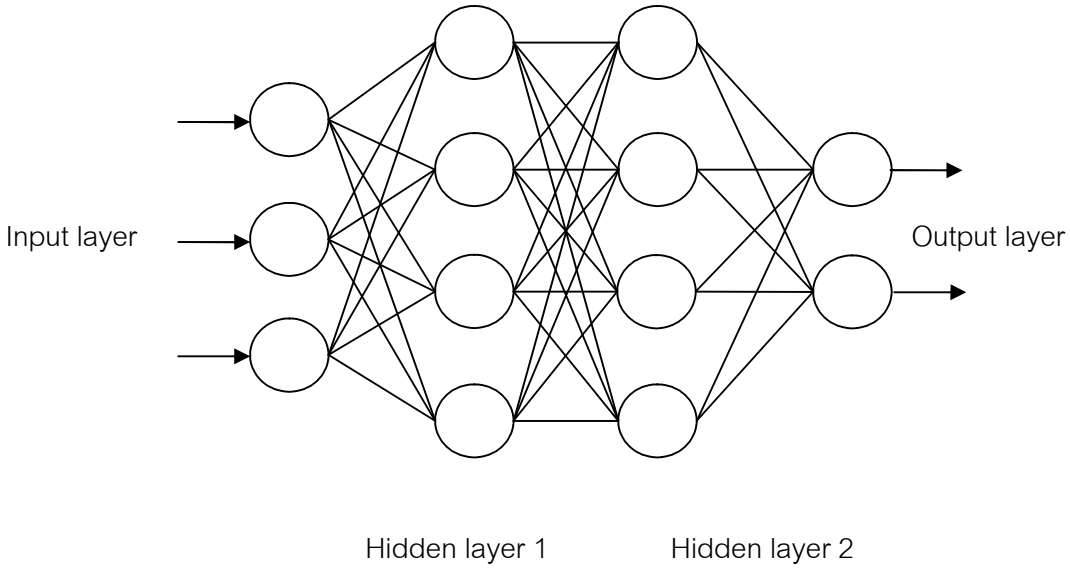

Figure 3.10: Feed-forward networks with two hidden layer

3.5.3 Learning function

Learning function is the actual process of adjusting weight factors base on trial and error. There are many different approaches to training neural networks:

3.5.3.1 Supervised learning

An external teacher controls the learning and incorporates global information. The teacher is able to provide the neural network with desired or target response for that training vector. The network parameters are adjusted under the combined influence of the training vector and the error. This adjustment is carried out iteratively in a step-by-step with the aim of eventually making the neural network emulate the teacher. Examples of supervised learning algorithm include the Least-Mean-Square (LMS) algorithm, Adaptive Linear Neural Element (ADALINE) and Backpropagation (BP) algorithm that the backpropagation has widely used and successful algorithm for the design of multilayer feed-forward networks.

3.5.3.2 Unsupervised learning

In unsupervised or self-organized learning there is no external teacher is used and instead, the neural network relies upon both internal control and local information. That is, networks trained by unsupervised learning cluster input examples according to similarity. Kohonen networks, Learning Vector Quantization (LVQ) are example of implementation of unsupervised learning.

3.5.4 Performance measure

In measurement network performance the error function is an importance index to choose the optimal network. The smaller the value of error, the better is the model's prediction. The error function has several types but the most common used in process modeling are MAE (Mean Absolute Error) MSE (Mean Square Error) or $RMSE$ (Root Mean Square Error) and SSE (Sum of Square Error). The definition of these functions is given as follows. Let $\hat{Y}$ is an estimate of a parameter Y

$$MAE = \frac{1}{N}\sum_{i=1}^{N}\left|\hat{Y}-Y\right|$$

$$MSE = \frac{1}{N}\sum_{i=1}^{N}\left(\hat{Y}-Y\right)^2$$

$$SSE = \sum_{i=1}^{N}\left(\hat{Y}-Y\right)$$

$$RMSE = \sqrt{MSE}$$

CHAPTER IV

ARTIFICIAL NEURAL NETWORK FOR HEMOIALYSIS ADEQUACY

This chapter presents method to find mathematical model for predict hemodialysis adequacy and post dialysis urea concentration.

4.1) Collection Data

The 30 patients' data in duration 6 months to 12 months were obtained from hemodialysis units in Kasikorn building, Chulalongkorn hospital. All patients must receive hemodialysis treatment three times a week. The group of patients received treatment with hemodialysis machine Fresenius model 4008H and used low flux polysulphone hemodialyzers (F8). The dialysate flow rate is 800 ml/min and 240 min for dialysis time.

4.2) Selection Input Variables

In the prediction of hemodialysis adequacy The parameter is selected base on many factors that influenced hemodialysis dose compose of Blood urea nitrogen at the beginning $(Pre\ BUN\ 1)$ and the end $(Post\ BUN\ 1)$ at first hemodialysis session, Blood urea nitrogen at the beginning of next treatment $(Pre\ BUN\ 2)$. Pre $(Pre\ BW\ 1)$ and post $(Post\ BW\ 1)$ body weight after the first hemodialysis treatment of a week. The pre body weight before $(Pre\ BW\ 2)$ the second of treatment. Ultrafiltration volume (UF) and Blood flow rate (BFR). Time and Dialysate flow rate were not included as input to model because it fixed at constant value.

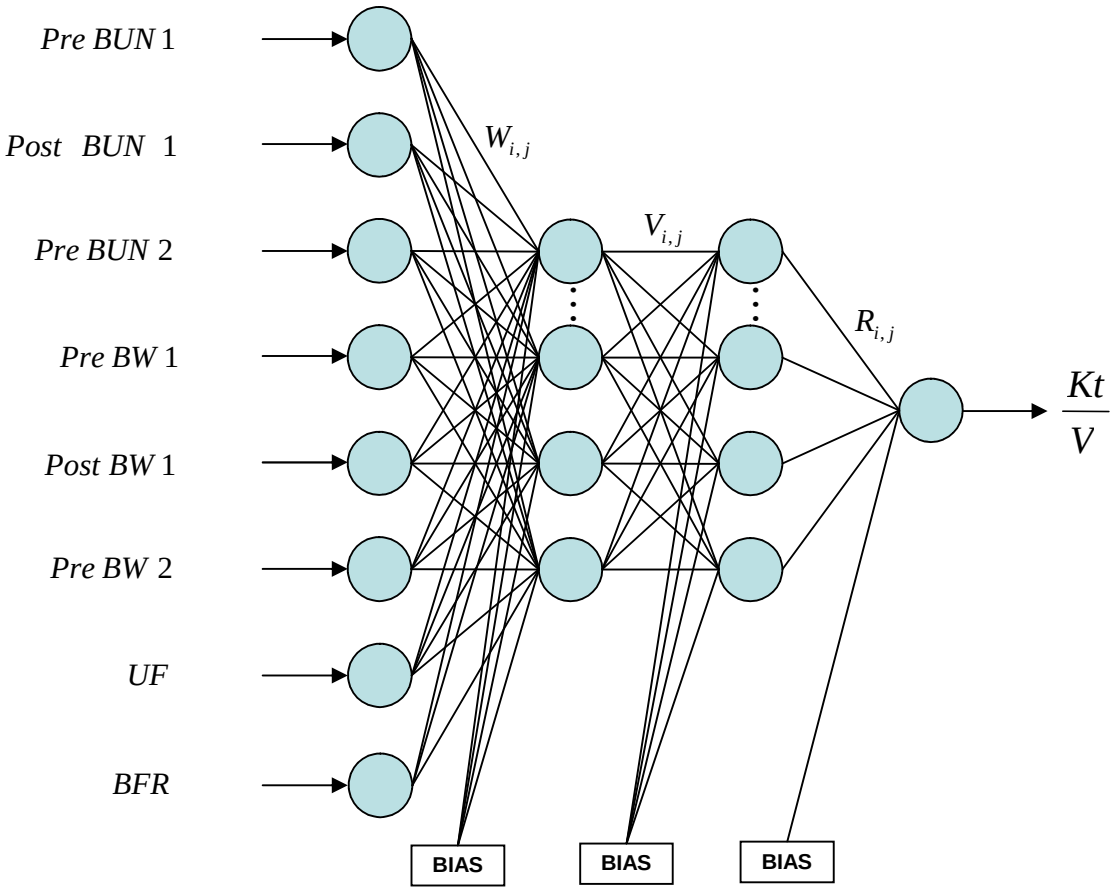

Figure 4.1: Structure of neural network model

$W_{i,j}$ denoted weight between i^{th} node of input layer to j^{th} node 1st hidden layer

$V_{i,j}$ denoted weight between i^{th} node of 1st hidden layer to j^{th} node of 2nd hidden layer

$R_{i,j}$ denoted weight between i^{th} node of 2nd hidden layer to j^{th} node of output layer

4.3) Neural Network Procedure

Apply MATLAB Neural Network Toolbox to develop model that has follow each steps below

1) Data are divided into three subsets consist of training, testing and validation. Looney (1996) recommends 65% of the database to be used for training, 25% for testing, and 10% for validation. The training data should include all the data belonging to the problem domain. The testing data should be different from those used in the training for check the performance of the model. The validation data should

distinct from those two subsets. This validation data is used after selecting the best network to confirm the accuracy of the model.

2) Pre processing data by normalize input and output data in a uniform range (0,1) for adjust the data has same order of magnitude.

3) Applied feed-forward neural network with backpropagation learning as a structure and Choose two hidden layer. The number of neuron in hidden layer may varied depend on capability in prediction function. Use sigmoid Transfer function in 1^{st} and 2^{nd} layer and linear transfer function in output layer.

4) The parameters associated with the training algorithm like error goal, maximum number of epochs (iterations), etc, are defined.

5) Initialized weight and bias for training network.

6) Training network until the error between the estimated value and the desired output is minimized. The criteria used to stop training are Mean Square Error (MSE).

7) Given the optimum weight, bias and number of neuron in hidden layer under stopping criteria.

8) Create neural network model and test network with unseen data

10) Compare the result with Formal Urea Kinetic modeling, Daugirdas equation and Barth equation.

11) Analysis output from Neural Network Model with principle of Statistics by SPSS 16.0 program

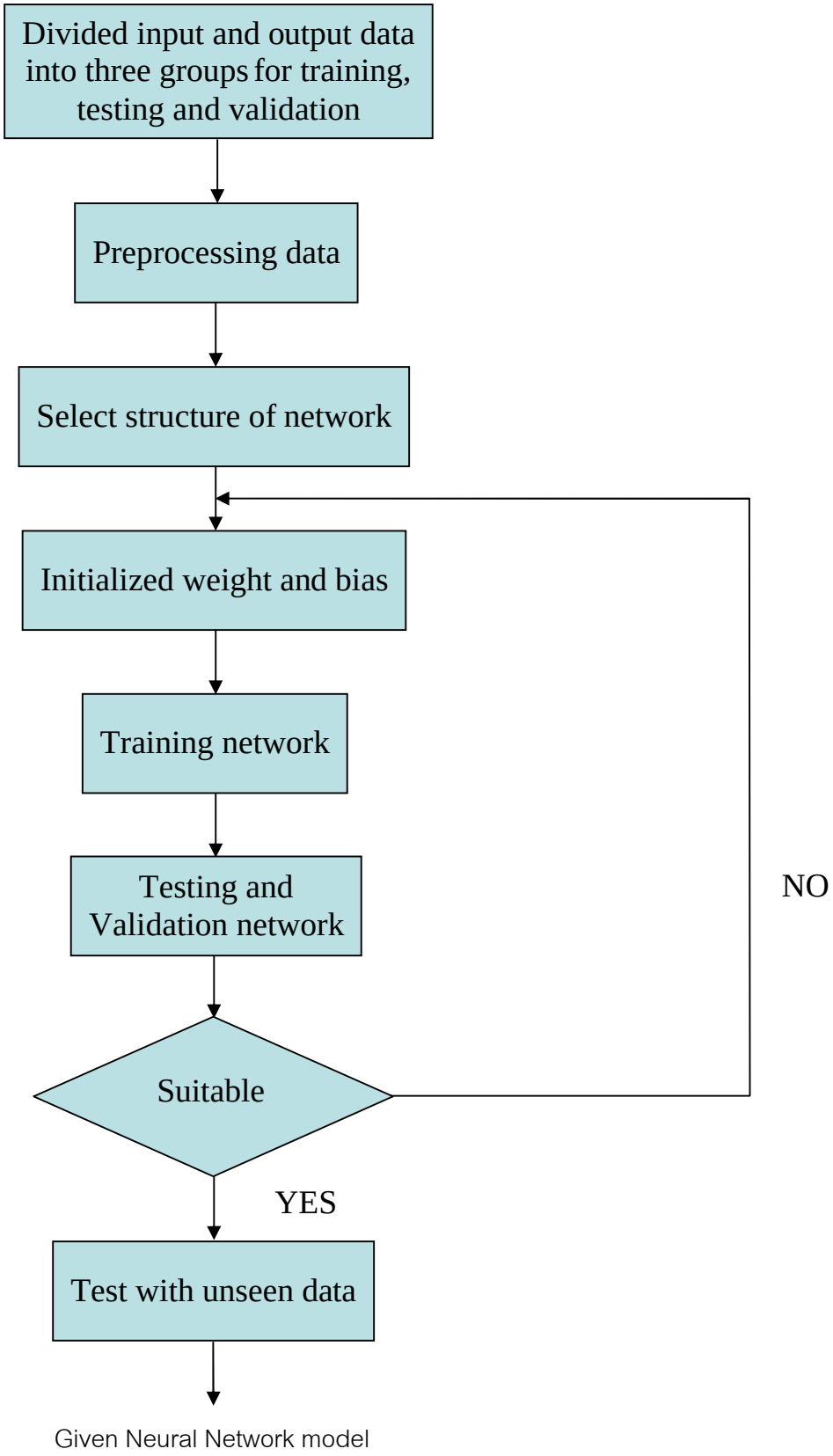

Figure 4.2: Schematic for Neural network

CHAPTER V

RESULTS AND DISCUSSION

To develop Neural Network (NN) Model the dataset is divided into 8 groups, 4 groups for training set, 2 groups for testing set, 1 group for validation set and the last group to confirm network accuracy before the end of process. Before training the network number of hidden layer and number of hidden node must be specified. No any rules for the determination of these sizes. Trial and error process is applied to find suitable network parameters. In this work based on 2 hidden layers and the numbers of hidden node are varied in the Table 5.1 to choose the optimal structure.

Table 5.1: Neural Network configuration varied by the number of hidden node

No. of node in hidden layer 1	No. of node in hidden layer 2	MSE	SSE
7	8	0.0094	0.3009
4	10	0.0098	0.3143
5	10	0.0106	0.3396
6	6	0.0135	0.4318
4	8	0.0144	0.4594
6	10	0.0160	0.4172
5	5	0.0177	0.5654
8	8	0.0189	0.6044
8	10	0.0211	0.6759
3	6	0.0269	0.8616

From Table 5.1 select the number of nodes in 1st and 2nd hidden layer equal to 7 and 8 respectively that give the minimum value of MSE . So the optimum network is 8-7-8-1.

5.1) Neural Network Modeling

From the previous section the selection structure of network by training network under stopping criteria to give optimum network composed of the number of hidden node, weight and bias. The information of neural network model that used for training are showed in Table 5.2. The weights and biases after select suitable network are given in Table 5.3-5.6 and the schematic of neural network model with 8-7-8-1 structure showed in Figure 5.1.

Table 5.2: Basic information of neural network model

No. of Input	8
No. of output	1
No. of Hidden layer	2
No. of nodes in Hidden layer 1	7
No. of nodes in Hidden layer 2	8
Transfer function in Hidden layer 1	Sigmoid
Transfer function in Hidden layer 2	Sigmoid
Transfer function in output layer	Linear
Learning rule	Supervised learning - Backpropagation learning
Training algorithm	Gradient Descent

Table 5.3: Weight from input layer to 1st hidden layer of neural network model

i \ j	1	2	3	4	5	6	7	8
1	0.6129	-0.8360	2.4215	1.9517	-1.6358	-1.0156	-1.3701	0.5633
2	-3.2986	3.5691	0.7811	0.4931	-1.0166	1.3853	0.3111	-0.3323
3	-3.2628	0.0794	-2.7680	1.4318	0.5891	-0.6052	1.6909	0.2610
4	-0.1563	3.9092	0.6972	-0.5348	-1.7081	0.5675	-1.1315	0.8020
5	3.4935	2.9929	-0.0801	-1.9192	-0.2058	0.4993	1.2288	0.4546
6	1.3741	-0.3391	0.0302	-1.8433	1.6531	-1.6572	-1.5925	1.1953
7	2.4201	-2.3817	-1.2577	-0.4696	-0.1562	1.6780	-1.4688	1.3196

Table 5.4: Weight from 1st hidden layer to 2nd hidden layer of neural network model

i \ j	1	2	3	4	5	6	7
1	-0.8342	4.3767	1.5855	3.5602	2.4039	-3.7289	-1.7152
2	-0.2073	-2.6109	0.0088	-2.4899	1.9942	2.9751	-5.6389
3	-2.0787	1.8701	-1.2241	-5.2675	2.4089	2.0542	3.1093
4	4.1155	3.4301	0.0739	2.4505	-3.8242	-0.1409	-2.7355
5	-0.3055	-0.0428	3.7701	-2.9532	-1.1863	-5.6682	0.4905
6	-3.6093	-2.4683	2.0408	-3.0775	-1.0027	-3.3004	3.5183
7	-3.3160	0.4357	-1.8309	3.9711	-1.1991	-5.0221	-0.1351
8	1.1020	0.2400	4.5941	-0.3503	1.0350	-3.9839	-4.1387

Table 5.5: Weight from 2nd hidden layer to output layer of neural network model

i \ j	1	2	3	4	5	6	7	8
1	-1.1149	0.9123	0.5622	-0.3981	0.4381	0.1341	-0.0359	-0.3933

Table 5.6: Bias added to 1st, 2nd hidden layer and output layer of neural network model

BIAS		
1st hidden layer	2nd hidden layer	Output layer
-2.7478	1.1945	-0.3109
1.2509	5.4171	
-1.0828	1.1434	
1.4534	-2.1477	
3.4821	2.0222	
2.9897	2.2016	
3.6674	0.6913	
	4.5086	

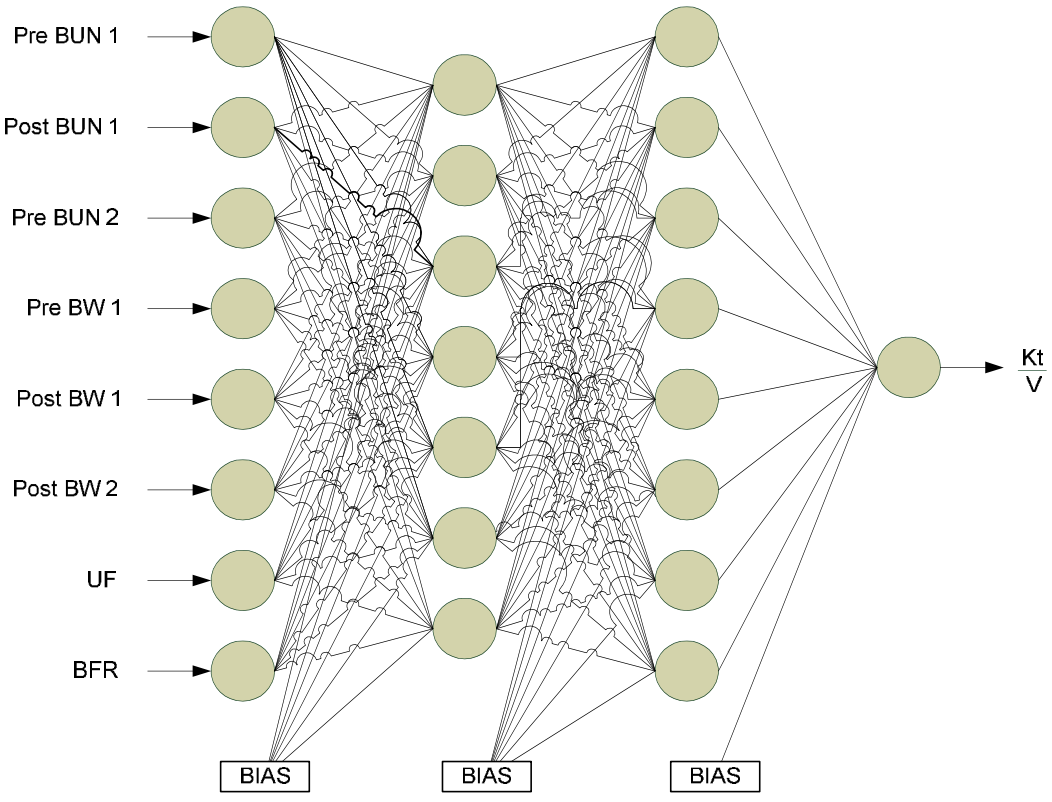

Figure 5.1: Neural Network Model with the structure 8-7-8-1

5.2 Compare the results

In this section used Neural Network model to predict hemodialysis adequacy ($\frac{Kt}{V}$) with group of data not used in training to check the performance of network. The results from Neural Network model are compared with Formal Urea Kinetic Model (Formal UKM), Daugisdas equation and Barth equation shown in figure 5.2. The plot between outputs forms neural network model and Formal UKM from Figure 5.3 showed the correlation coefficient (R) equal to 0.955.

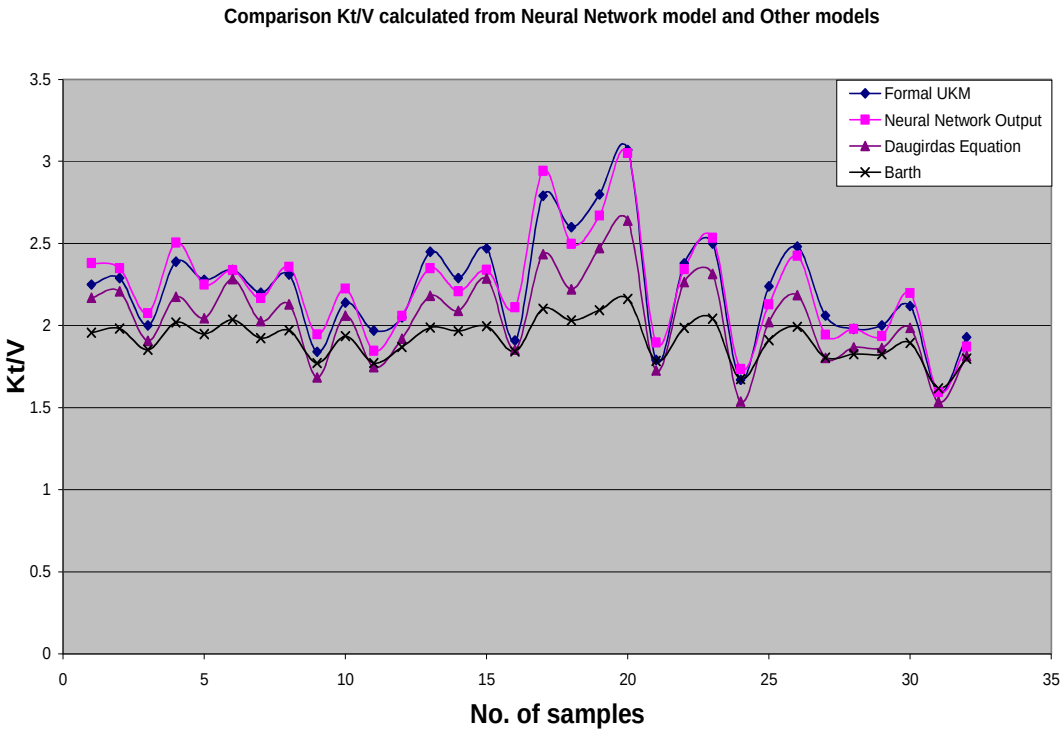

Figure 5.2: Compared the prediction of $\frac{Kt}{V}$ from Neural Network model, Formal Urea Kinetic Model and Daugirdas equation

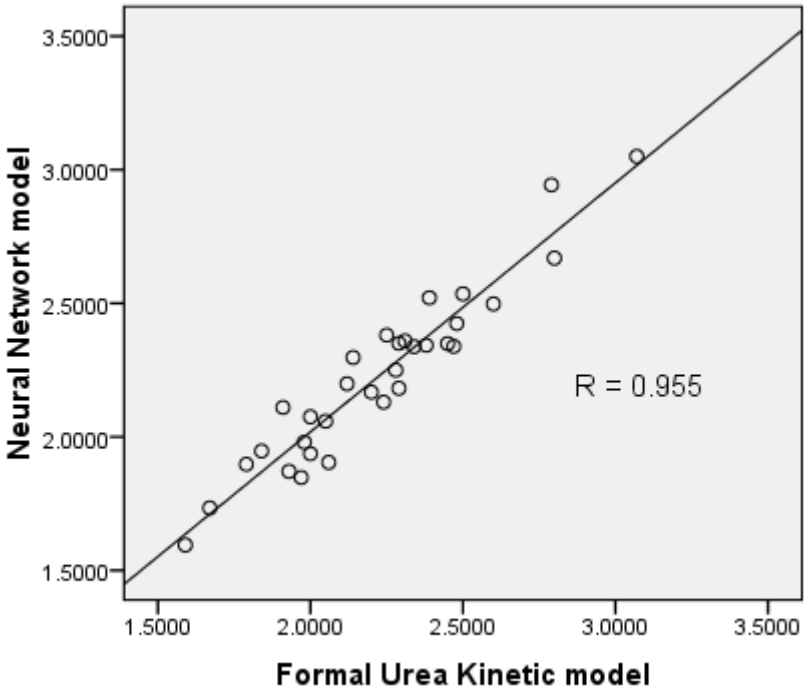

Figure 5.3: Comparison between outputs calculated from Neural Network model and Formal Urea Kinetic model

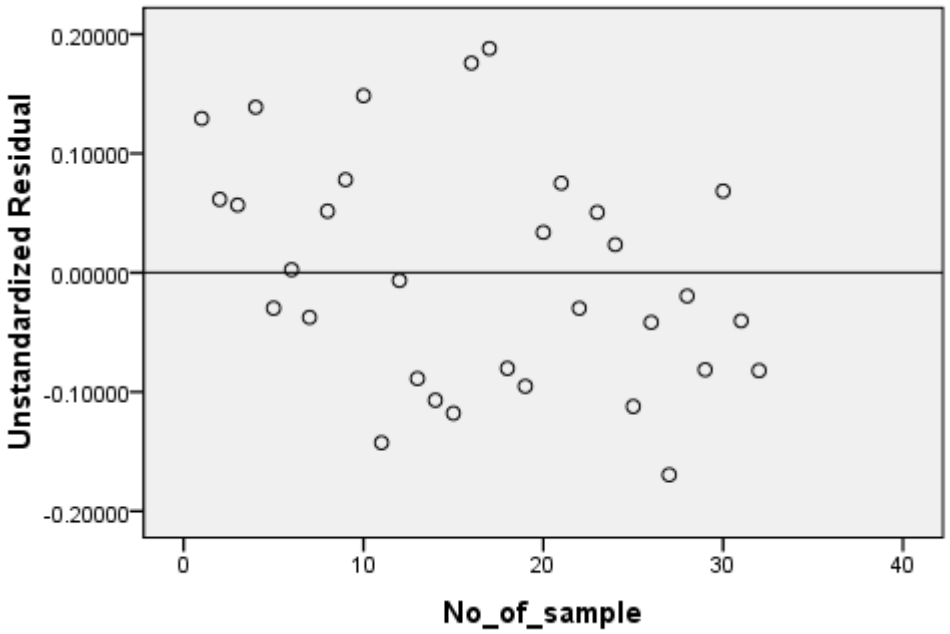

Figure 5.4: Residual plots, the difference between Neural Network outputs with Formal Urea Kinetic Model

From Figure 5.2 Neural Network model has ability in the prediction value of $\frac{Kt}{V}$ close to Formal Urea Kinetic Model more than Daugirdas equation and Barth equation. Moreover, the residual plot from Figure 5.4 showed with no trend or systematic pattern in the error. The residuals randomly distributed around the line of the error = 0.

CHAPTER VI

CONCLUSION AND RECOMMENDATION

6.1 Conclusion

This research applied Artificial Neural Network (ANN) to predict the hemodialysis adequacy ($\frac{Kt}{V}$) and compared the performance of the ANN with Formal Urea Kinetic Model (Formal UKM) and Daugisdas natural log equation. The network model is selected after training, testing and validation process by considering the minimum mean square error (MSE). The selected ANN model is the Multilayer feed-forward with backpropagation learning and the structure of network is 8-7-7-1. The result showed the ANN model is an ability in prediction of the hemodialysis adequacy as same as Formal UKM although unseen data are given to test the neural network model. The predictions of $\frac{Kt}{V}$ between Neural Network model and Formal UKM showed that the predicted values from Neural Network model are closed to Formal UKM with correlation coefficient equal to 0.955.

6.2 Recommendation

In the future work the ANN model in this research should be test with patient data from the other hemodialysis unit. Moreover, the data will be added more data to train ANN model to improve the accuracy. The ANN model will take the data from other Hemodialysis unit to training process and testing validation from another.

APPENDICES

APPENDIX A

A.1 Expand of backpropagation learning

The backpropagation learning method can be applied to any multilayer network that uses differentiable functions and supervise learning. This is an optimization procedure based on gradient descent that adjusts weights to minimize error or cost function. The name backpropagation arises from the method in which corrections are made to the weights. During the learning phase, input patterns are presented to the network in some sequence. Each training pattern is propagated forward layer by layer until an output pattern is computed. The computed output is then compared to a desired or target output and an error value is determined. The errors are used as inputs to feedback connections from which adjustments are made to the weights layer by layer in a backward direction. Figure 3.11 illustrates multilayer feed-forward network with backpropagation learning. The backward linkages are used only for the learning phase, whereas the forward connections are used for both the learning and the operational phases.

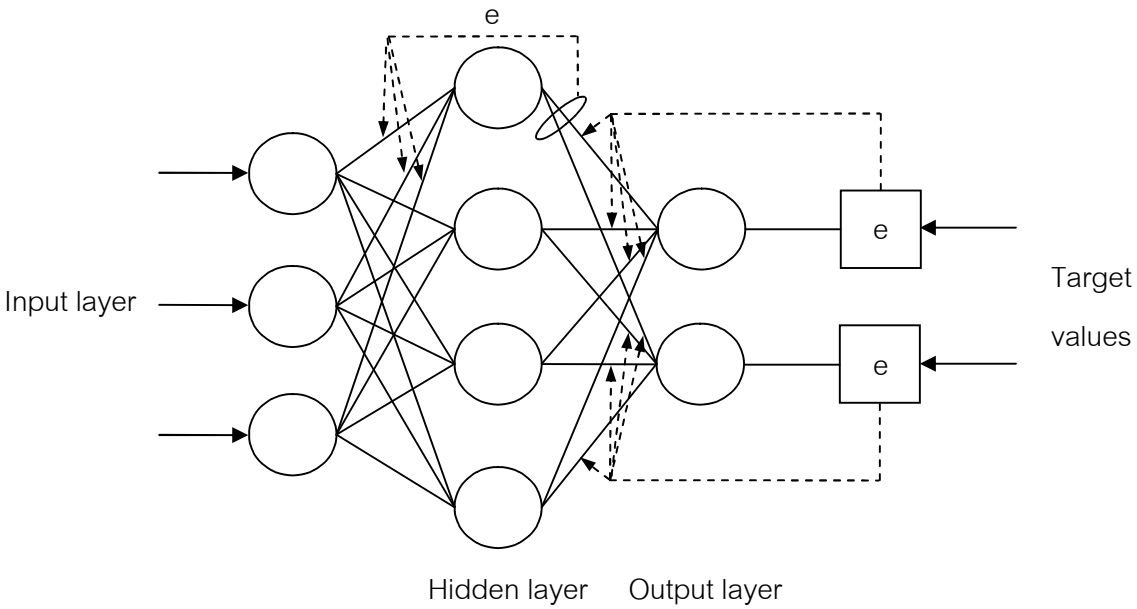

Figure A.1: Multilayer feed-forward with backpropagation learning

To simplify the derivation of backpropagation, begin with a multilayer feed-forward having a single hidden layer. Weight connections between input layer unit i and hidden layer j are denoted by v_{ij}, $i = 1,2,...,n$, $j = 1,2,...,h$ while weight connections between hidden layer unit j and output unit k are designated as w_{jk}, $k = 1,2,...,m$. The n-dimensional input training pattern p is denoted as a^p, $p = 1,2,...,P$ and the output of the hidden layer unit j for input pattern a^p is denoted as y_j^p. Likewise, the output from unit k of the output layer for input pattern a^p is z_k^p, whiles the desired or target output is denoted as t_k^p and also use he same nonlinear activation function f for each of the hidden layer and output layer units.

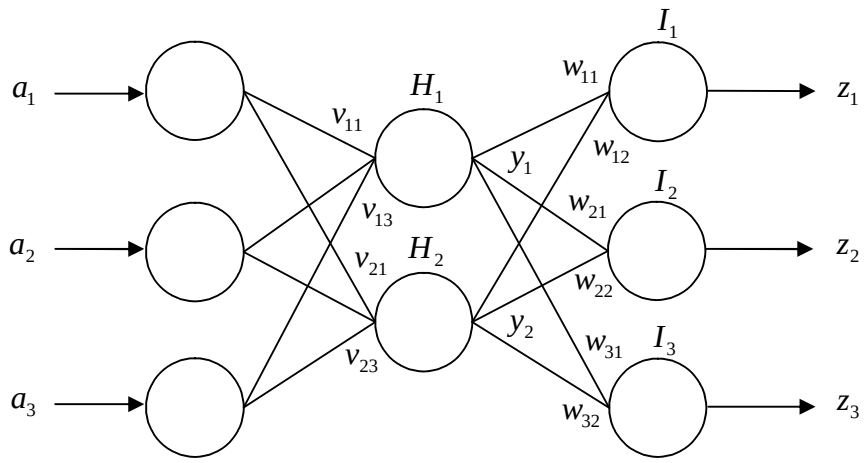

Figure A.2: Multilayer feed-forward network connections and variables

Define the following terms:

$$H_j = \sum_i v_{ij} a_i \qquad j = 1, 2, ..., h \qquad \text{(A.1)}$$

$$I_k = \sum_j w_{jk} y_j \qquad k = 1, 2, ..., m \qquad \text{(A.2)}$$

where H_j is the combined net input to hidden layer unit j

I_k is the net input to unit k of the output layer

Outputs computed by unit j of the hidden layer and unit k of the output layer are given by

$$y_j = f(H_j) \qquad j = 1, 2, ..., h \qquad \text{(A.3)}$$

$$z_k = f(I_k) \qquad k = 1, 2, ..., m \tag{A.4}$$

so,

$$\begin{aligned} z_k = f(I_k) &= f(\sum_j w_{jk} y_j) \\ &= f\left((\sum_j w_{jk} f(H_j)\right) \\ &= f\left(\sum_j w_{jk} f\left(\sum_i v_{ij} x_i\right)\right) \end{aligned} \tag{A.5}$$

For the initial development of backpropagation, the error function E^p, $p = 1, 2, ... P$ can be defined in the sum of squared error over all training pattern:

$$E^p = \frac{1}{2}\sum_{k=1}^{m}(t_k^p - z_k^p)^2 \tag{A.6}$$

Thus, at step $n+1$ of the training process, the weight adjustment by used optimization technique, gradient descent should be proportional to the derivative of the error E^p, computed on iteration n. This can be written as:

$$\Delta w(n+1) = -\eta \frac{\partial E^p}{\partial w(n)} \tag{A.7}$$

Where η is a learning rate

- For weight between hidden layer and output layer, w_{jk}:

$$w_{jk}(n+1) = w_{jk}(n) + \Delta w_{jk} = -\eta \frac{\partial E^p}{\partial w_{jk}(n)} \tag{A.8}$$

Apply the chain rule then,

$$\begin{aligned} \frac{\partial E^p}{\partial w_{jk}} = \frac{\partial E^p}{\partial I_k}\frac{\partial I_k}{\partial w_{jk}} &= \frac{\partial E^p}{\partial I_k}\left(\frac{\partial}{w_{jk}}\sum_j y_j w_{jk}\right) \\ &= \frac{\partial E^p}{\partial I_k} y_k \end{aligned} \tag{A.9}$$

Using the chain rule again,

$$\frac{\partial E^p}{\partial I_k} = \frac{\partial E^p}{\partial z_k}\frac{\partial z_k}{\partial I_k} = -(t_k - z_k) f'(I_k) \quad \text{(A.10)}$$

And defined,

$$\delta_k = (t_k - z_k) f'(I_k) \quad \text{(A.11)}$$

Combining (A.8), (A.9), and (A.11) then

$$\Delta w_{jk} = -\eta \delta_k y_j \quad \text{(A.12)}$$

Therefore

$$w_{jk}^{new} = w_{jk}^{old} + \eta y_j (t_k - z_k) f'(I_k) \quad \text{(A.13)}$$

- For weight between input layer and hidden layer, v_{ij} :

$$\Delta v_{ij} = -\eta \frac{\partial E^p}{\partial v_{ij}} = -\eta \frac{\partial E^p}{\partial H_j}\frac{\partial H_j}{\partial v_{ij}} \quad \text{(A.14)}$$

Can use the chain rule repeatedly to relate the output errors to these weights

$$\frac{\partial H_j}{\partial v_{ij}} = \sum_i \frac{\partial}{\partial v_{ij}}(v_{ij} a_i) = a_i \quad \text{(A.15)}$$

And

$$\frac{\partial E^p}{\partial H_j} = \frac{\partial E^p}{\partial y_j}\frac{\partial y_j}{\partial H_j} = \frac{\partial E^p}{\partial y_j} f'(H_j) \quad \text{(A.16)}$$

Differentiating $\frac{\partial E^p}{\partial y_j}$ directly now we obtain (from (A.2), (A.4), and (A.6))

$$\frac{\partial E^p}{\partial y_j} = \frac{1}{2}\sum_k \frac{\partial (t_k - f(\sum_j w_{jk} y_j))^2}{\partial y_j}$$

$$= -\sum_k (t_k - z_k) f'(I_k) w_{jk} \quad \text{(A.17)}$$

And defined

$$\delta_k = (t_k - z_k) f'(I_k) \quad \text{(A.18)}$$

Then

$$\begin{aligned} \Delta v_{ij} &= (-\eta)(-\sum_k (t_k - z_k) f'(I_k) w_{jk})(f'(H_j))(a_i) \\ &= \eta a_i f'(H_j) \sum_k \delta_k w_{jk} \end{aligned} \quad \text{(A.19)}$$

Thus

$$v_{ij}^{new} = v_{ij}^{old} + \eta a_i f'(H_j) \sum_k \delta_k w_{jk} \quad \text{(A.20)}$$

APPENDIX B

B.1 MATLAB Neural Network Toolbox

In this research used Neural Network Toolbox with Backpropagation algorithm that the MATLAB commands used in this procedure are *newff* , *train* and *sim* . The MATLAB command *newff* generates a Multi Layer Perceptron (MLP) network neural network, which is called *net* .

$$net = newff(PR, [S1, S2, ...SN], \{TF1, TF2, ...TFN\}, BTF, BLF, PF) \quad \text{(B.1)}$$

PR = Rx2 matrix of min and max values for R input elements

S_i = Size of the i^{th} layer

TFi = Activation (or transfer function) of the i^{th} layer, (default = '*tansig* ')

BTF = Network training function, (default = '*trainlm* ')

BLF = Backpropagation weight/bias learning function (default = '*learngdm* ')

PF = Performance function (default = '*mse* ')

After initializing the network, the network training is originated using *train* command. The resulting MLP network is called *net* .

$$[net, tr] = train(net, P, T, Pi, Ai, VV, TV) \quad \text{(B.2)}$$

P = Network inputs

T = Target outputs

Pi = Initial input delay conditions (default = zeros)

Ai = Initial layer delay conditions (default = zeros)

VV = Structure of validation vectors (default = [ ])

TV = Structure of test vectors (default = [ ])

To test the result sim command is applied. The output of the MLP network is called a.

$$a = sim(net, P) \tag{B.3}$$

The measured output T and the output of the MLP network a can now be compared to see how good the result is.

APPENDIX C

C.1 Training algorithm

Training algorithm functions are mathematical procedures used to automatically adjust the network's weights and biases. Neural Network Toolbox supports a variety of training algorithms, including several gradient descent methods, conjugate gradient methods, the Levenberg-Marquardt algorithm (LM), and the resilient backpropogation algorithm (Rprop). This research used gradient descent as training algorithm for training the network. A MATLAB command used in this procedure is *traingd* .

The method of gredient descent is given by the following expression:

$$x^{k+1} = x^k + \Delta x^k \quad \text{(B.1)}$$

$$= x^k + \alpha^k s^k \quad \text{(B.2)}$$

For minimization, the search direction (s^k) is the negative of the gradient

$$s^k = -\nabla f(x^k) \quad \text{(B.3)}$$

Therefore

$$x^{k+1} = x^k - \alpha^k \nabla f(x^k) \quad \text{(B.4)}$$

Where

Δx^k = vector from x^k to x^{k+1}

s^k = search direction, the direction of steepest descent

α^k = scalar that determines the step length in direction s^k

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VITA

Mr. Niti Sombonpattanakul was born in Chachoengsao on 31 August 1979. Education levels are high school in 1995-1998 from Saint Gabriel College, Bangkok and Bachelor Degree in Chemical Engineering from King Mongkut's Institute of Technology North Bangkok, Bangkok in 1999-2003. The last education is studying in Master Degree in Chemical Engineering, Chulalongkorn University that began in May 2004.