HUMAN MICROVASCULAR EXCHANGE FOLLOWING THERMAL INJURY
A MATHEMATICAL MODEL OF FLUID RESUSCITATION

by

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ABSTRACT

A dynamic model is developed to describe the redistribution of fluid and albumin between the human circulation, interstitium and lymphatics following burn injury. The model is based on the assumption that the human microvascular exchange system (MVES) consists of three compartments, the circulation, injured tissue and uninjured tissue compartments, in which the spatial distribution of fluid and albumin properties are homogeneous. Transcapillary exchange in the MVES is described by the Coupled Starling Model (CSM) where fluid is filtered from the capillary to the interstitium according to Starling's Hypothesis and albumin is transported passively by diffusion and convection through the same fluid-carrying channels.

The parameters necessary to fully describe the model are determined by statistical fitting of model predictions with clinical data from burn patients. The parameters include the perturbation to the filtration coefficient in uninjured and injured tissue, $G_{KF, TI}$ and $G_{KF, BT}$ respectively; the relaxation coefficient, $r$, which describes the time it takes for the transport coefficients to return to near-normal values following injury; and the exudation factor, EXFAC, which determines the fraction of the interstitial protein concentration which leaves with exudate from the burn wound. Perturbations to other parameters including the permeability coefficient and the albumin reflection coefficient, in the injured and uninjured tissues are obtained from $G_{KF, TI}$ and $G_{KF, BT}$, utilizing relationships between all three types of parameters and capillary pore size.

Parameters are determined for two groups of burns: burns less than and greater than 25% surface area. The optimum parameters for burns less than 25% surface area are: $G_{KF, TI} = 0.5$, $G_{KF, BT} = 12.0$, $r = 0.025$ h$^{-1}$ and EXFAC = 1.0. For burns greater than 25%, the optimum parameters are: $G_{KF, TI} = 2.0$, $G_{KF, BT} = 9.0$, $r = 0.025$ h$^{-1}$ and EXFAC = 0.75. The
sensitivity of the model predictions to changes in $G_{K,F,II}$ and $G_{K,F,BT}$ for the two burn groups are investigated. For burns less than 25%, $G_{K,F,II}$ and $G_{K,F,BT}$ values beyond the ranges 0.5±0.1 and 12.0±3.0 respectively will significantly affect the model's predictions. The model predictions will be insensitive to $G_{K,F,II}$ and $G_{K,F,BT}$ values in the ranges 2.0±0.8 and 9.0±3.0 respectively for burns larger than 25% surface area.

The model and its associated parameters are validated by comparing the predictions of patient responses to fluid resuscitation, to the clinical data obtained from these patients. The predicted response of the MVES is in generally good agreement with the observed trends and the absolute values of fluid volume and albumin concentration. The model is also used to simulate the response of a hypothetical individual to three common resuscitation formulae, namely the Evans, Brooke and Parkland formulae, following two burn sizes, 10% and 50%. The simulated responses are explained in terms of the transport mechanisms, driving forces and perturbations to the transport coefficients following burn injury. The predictions of the model compare satisfactorily with known clinical behaviour of the human MVES with and without fluid resuscitation. This establishes the potential of the patient simulator developed in the current study to be used as a tool for fluid management of burn patients. The effects of different resuscitation formulae can be compared to suggest possible improvements.

As more reliable clinical data become available, all of the essential model parameters can be more definitely determined. In addition, one significant improvement that may be made to the model is the inclusion of cellular compartments. It is expected that, with more accurate parameters and an improved physiological basis, the usefulness of the mathematical burn patient simulator will be enhanced considerably.
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- Paa Bissue (Sam), thank you for your love and patience and for being that very special part of me. This one is for you.
Burns are a major cause of traumatic injury in all ages of the population. There are many causes of burns and they occur in a variety of settings including the home and the workplace. It has been reported that the majority of burn accidents occur in the home, predominantly in the kitchen and the bathroom [Martyn, 1990; McLaughlin, 1990]. Burns are caused by such activities as cooking, bathing or smoking. Younger children usually suffer scald or grease burns when they pull the handles of pots on the stove, knock over hot foods on the table or play with hot water in the bathtub. An unfortunate reality is that some children are burned due to child abuse. Sources of burn injuries include flame, electrical, chemical and radiation [Harvey et al., 1984]. Flame burns are commonly caused by ignited clothing or a flash from an explosion. Electrical burns are not as common as flame burns but may be more serious due to injury to deeper structures of the body. Chemical burns are uncommon and can be caused by an acid or an alkali. They are usually related to industrial accidents. Extreme exposure to nuclear or solar radiation causes burns of varying severity.

The most immediate and clear evidence of burn injury is damage or destruction to the skin. However, burns affect more than just the skin and can be fatal. The state of homeostasis maintained in the body is also greatly affected following burn injury. There is a rapid shift of fluid from the circulating plasma into the interstitium, resulting in the accumulation of fluid in the interstitial space. This leads to drastic swelling of the tissue or edema, of such magnitude as to distort body features. The loss of plasma results in an abnormally low circulating blood volume, a condition known as hypovolemia. Fluid replacement is
therefore essential in replenishing the lost plasma volume, to avoid the possibility of hypovolemic shock. Approximately thirty years ago, the majority of patients with extensive burns died from hypovolemic shock within the first week following their injuries due to failure of the whole circulatory system [Rylah, 1992]. Today, adoption of the practice of prompt and aggressive fluid resuscitation of the burn victim has resulted in the survival of more patients with severe injury. Consequently, early death can usually be prevented in previously healthy individuals and is only common in patients with near total body surface burns, or in those of advanced age or with major concurrent chronic disease.

Numerous resuscitation formulae have been developed to restore lost body fluid volumes and organ blood flows [Evans et al., 1952; Gillespie et al., 1987; Reiss et al., 1953]. These formulae differ in terms of the amount of colloid or electrolyte solution given and the rate and duration of their administration to stabilize the burned and hypovolemic individual, considering the size of the injury and the time postburn. The fluid resuscitation programmes are intended merely as guidelines and are continually adjusted according to the response of individual patients. The empirical formulae for fluid resuscitation may be considered as simplistic models using a "black box" approach, where all the circulatory and interstitial changes are contained within the "black box", leaving only the fluid inputs and outputs as the manipulated variables. As such, they do not describe the pathophysiological mechanisms which occur following burn injury.

Burn injuries result in complex perturbations to the normal transcapillary transport of fluid and proteins in the human microvascular exchange system (MVES). In the human MVES, fluid and proteins are exchanged between the circulatory system, interstitium and the lymphatics. Consequently, a complete quantitative description of edema formation following a burn injury requires detailed knowledge of a large number of variables describing the normal transcapillary exchange of fluid and proteins as well as the changes.
in these variables following injury. Mathematical modelling has been used to facilitate understanding of the dynamic behaviour and pathophysiology of a burn injury. Elaborate models have been developed based on detailed mathematical descriptions of fluid and protein transport across the capillary membrane [Arturson et al., 1984, 1988, 1989; Bert et al., 1988, 1989, 1991; Hedlund et al., 1988; Roa et al., 1986, 1988, 1990, 1993]. The potential advantages of these models are manifold. They provide a description of the time course of changes in fluid volumes and protein concentrations in the blood and various tissues in the human MVES. These models can be used to validate and hence predict the reaction of the MVES to different empirical resuscitation protocols following a burn injury. Ultimately, mathematical models may be used to suggest a possible optimum form of fluid replacement therapy.

The development of mathematical models to describe the human MVES following thermal injury was pioneered by Arturson et al. [1984] in their description of a computer based burn patient simulator. They have since developed complex multi-compartmental models made up of modules to describe microvascular exchange, hormonal function, renal dynamics and cell volume regulation [Arturson et al., 1988, 1989; Hedlund et al., 1988]. Roa et al. [1986, 1988, 1990, 1993] also modelled the MVES following burn injury and the effect of burn and inhalation injuries on pulmonary capillary dynamics. These groups of workers have made valuable contributions in the area of burn injury computer modelling. Their models are complex in that they attempt to model other systems affected by burn injury, in addition to the MVES. A major fault with their models, however, is that they assume various model parameters and transport mechanisms from the literature, some of which are based on out-dated knowledge regarding the human MVES. Bert et al. [1989, 1991; Bowen et al., 1989] have developed compartmental models to describe the MVES in the burn injured rat. In contrast to the models developed by Arturson et al. and Roa et al., the MVES was emphasized due to the critical role it plays in transcapillary exchange
following burn injury. In addition, the parameters used in their models were determined by statistical fitting of model predictions to experimental data.

The present research involves computer modelling of the human MVES following burn injury and fluid resuscitation. This work is a continuation of the research effort at UBC by Bert, Bowen and colleagues, with vital input from medical professionals in Norway.

The specific objectives of the current study are to:

1. formulate a model to mathematically describe the distribution and transport of fluid and plasma proteins in the human MVES following a burn injury;
2. estimate the model parameters by fitting its predictions to clinical data using suitable optimization techniques;
3. validate the model by comparing its predictions with other data obtained from burn patients; and
4. investigate the model-predicted behaviour of the MVES with regard to burn patient fluid therapy using common empirical resuscitation formulae.

In order to provide a basis for understanding the physiological changes that occur in the MVES following burn injury, Chapter 2 provides a brief physiological review of the system being considered. An overview of mathematical models which have been developed to describe the normal and thermally injured MVES is presented in Chapter 3. In Chapter 4, the formulation of the current model which will be used to represent the system of interest is described. The patient data used in estimating the unknown model parameters and for validation purposes are discussed in Chapter 5. The statistical procedure adopted to determine the parameters is also described. The best-fit parameter estimates are reported in Chapter 6. The validity of the model is investigated by comparing its predictions with all of the available clinical data, including additional information.
withheld from the fitting process for this purpose. In addition, simulations using the statistically determined parameters along with fluid inputs based on common resuscitation formulae are presented and discussed. Finally, the major conclusions drawn from the current study and suggestions for further work are presented in Chapter 7.
CHAPTER 2

PHYSIOLOGICAL OVERVIEW

2.1 INTRODUCTION

The extreme complexity of the human body and its regulation continues to provide great challenges to the medical and engineering professions. The current study seeks to assist in the understanding of the role and response of part of this complex system, the microvascular exchange system (MVES), to burn injuries. A brief overview of the general circulatory system and the MVES will provide a basis for understanding the physiological changes that occur in the MVES following thermal injury.

2.2 THE CIRCULATORY SYSTEM

2.2.1 Description of the Circulatory System

The circulatory system serves to transport and distribute essential substances to the tissues and to remove by-products of metabolism. Oxygen from the lungs and nutritional substances absorbed from the gastrointestinal tract are supplied to the tissues of the body via the circulation. Carbon dioxide is transported from the tissues and exchanged in the lungs while other products of metabolism are removed by the kidneys. The circulatory system also shares in such homeostatic mechanisms as body temperature regulation, humoral communication throughout the body and adjustments of oxygen and nutrient supply in different physiological states.
The system that accomplishes all these tasks is made up of a pump, the heart, a series of distributing and collecting tubes and an extensive system of small vessels that permit rapid exchange between the tissues and the vascular network. Blood is the transport medium which is pumped through the closed system of vessels by the heart. In mammals, the heart may be considered as two pumps in series (see Figure 2.1). Blood rich in oxygen and nutrients leaves the left ventricle of the heart and is pumped through arteries and arterioles to a bed of capillaries. In this capillary bed, the oxygen and nutrients are transported across the capillary wall or membrane, to the surrounding tissue space, or interstitium. There is also exchange of carbon dioxide and other metabolic waste products from the interstitium to the circulating blood. The capillaries drain through venules into veins and back to the right atrium of the heart. Upon leaving the right atrium, this carbon-dioxide-rich blood flows to the right ventricle, which pumps the blood through the vessels of the lungs and the left atrium, to the left ventricle. In the lungs, there is counter-exchange of oxygen and carbon dioxide, so that oxygen-rich blood leaves the lung circulatory system to resume its cyclic journey.

In addition, some tissue fluids enter another parallel circulatory system of vessels, the lymphatics, which drain tissue derived fluid via the thoracic duct and the right lymphatic duct into the venous system. This is the lymphatic circulation which is shown in Figure 2.2. The lymphatics are not part of the blood circulatory system per se, but constitute a one-way route for the movement of interstitial fluid to blood. These thin-walled capillaries have large pores and are permeable to all interstitial fluid constituents, including protein. Thus, the lymphatics carry fluid and proteins from the interstitium to the circulatory system.
Figure 2.1: Human Circulatory System
Figure 2.2: Lymphatic and Blood Vessels in Area of Bat Wing: lymphatics (black), blood vessels (shaded) and blood capillaries (lines)
2.2.2 Composition and Properties of Blood

Blood is the transport medium for oxygen, nutrients, carbon dioxide and metabolic waste products in all mammals. It makes up between 6 and 8% [Berne and Levy, 1988; Ganong, 1991] of the total body weight and is a suspension of various types of cells in a complex aqueous medium known as plasma. The elements of blood serve multiple functions essential for metabolism and the defense of the body against injury.

**Plasma:** The normal adult has an average of 50 mL of plasma per kg of body weight or a total volume of about 3 L [Berne and Levy, 1988; Ganong, 1991; Reference Man ICRP 23, 1975; Vander et al., 1985]. Plasma contains many substances including erythrocytes, proteins, lipids, carbohydrates (particularly glucose), amino acids, vitamins, hormones, nitrogenous breakdown products of metabolism (such as urea and uric acid) and gaseous oxygen, carbon dioxide and nitrogen. Normally, the composition of blood is maintained at biologically regulated levels by a variety of homeostatic mechanisms. The balance may be upset by impaired function following injuries and in a multitude of disorders, particularly those involving the lungs, cardiovascular system, kidneys, liver and endocrine organs.

There are several different proteins that are dissolved in plasma. In all, plasma normally contains about 7 g/dL of protein [Berne and Levy, 1988; Reference Man ICRP 23, 1975; Vander et al., 1985]. The bulk of protein belongs to two groups, albumin and various immunoglobulins, albumin being the most abundant. Albumin, synthesized by the parenchymal cells of the liver, is normally present at an average concentration of about 4 g/dL [Berne and Levy, 1988; Reference Man ICRP 23, 1975]. The exchange of albumin across intact vascular endothelium is restricted and this provides the critical colloid osmotic or oncotic pressure that participates in the regulation of the passage of water and diffusible solutes across the capillaries. A reduction of the albumin concentration in plasma
causes shift of fluid to the surrounding tissue space. Excess fluid accumulation in extravascular tissues is termed edema.

**Blood Cells:** The cellular constituents of blood include red blood cells (erythrocytes), which make up the vast majority of blood cells, a variety of white blood cells (leukocytes) and platelets or cell fragments. Ordinarily, the constant motion of the blood keeps the cells well dispersed throughout the plasma. Centrifugation of a sample of blood to which an anticoagulant is added results in separation of cells from the fluid. This permits determination of the hematocrit or the percentage of the total blood volume which is erythrocytes. The normal hematocrit is approximately between 37 and 49% in men and between 36 and 45% in women [Berne and Levy, 1988; Ganong, 1991; Reference Man ICRP 23, 1975].

The principal protein constituent of the cytoplasm of the mature erythrocyte is hemoglobin, an iron-containing protein which binds oxygen and constitutes approximately one-third of the total weight of the erythrocyte. Normal blood has about 15 g/dL of hemoglobin in adult men and about 13.5 g/dL in adult women [Berne and Levy, 1988].

2.3 THE MICROVASCULAR EXCHANGE SYSTEM

2.3.1 Description of the Microvascular Exchange System
The microvascular exchange system pertains to the portion of the circulatory system that is composed of the capillary network as shown in Figure 2.3. It also comprises the interstitium and the lymphatics. This system is the site of exchange of substances such as fluids and plasma proteins across the capillary membrane.
Figure 2.3: Human Microcirculation
The microcirculation is the part of the circulatory system comprising smaller vessels of diameter up to 100 μm. A description of these blood vessels is presented in Table 2.1. At any given moment, approximately 5% of the total circulating blood is flowing through the capillaries [Berne and Levy, 1988; Reference Man ICRP 23, 1975; Vander et al., 1985]. It is this 5% which is performing one of the most important functions of the entire system, namely, the exchange of nutrients and metabolic end products. The capillaries permeate almost every tissue of the body. There are an estimated 25 000 miles of capillaries in an adult person, each individual capillary being only about 1 mm long [Berne and Levy, 1988; Vander et al., 1985].

In a normal person, the fluid filtered out of the capillaries each day, excluding those in the kidneys, exceeds that reabsorbed by approximately 3 L [Vander et al., 1985]. This excess is returned to the blood via the lymphatics. Partly for this reason, obstruction of the lymphatics leads to increased interstitial fluid or edema. Most capillaries in the body have a slight permeability to protein and accordingly, there is a small, steady movement of protein from the blood to the interstitial fluid. This protein is returned to the circulatory system via the lymphatics. Some protein is normally leaked into the interstitial fluid and failure of the lymphatics to remove it by carrying away the interstitial fluid containing it allows the interstitial protein concentration to increase. This reduces or eliminates the protein-concentration difference and thus water-concentration difference across the capillary wall and permits net movement of increased quantities of fluid out of the capillary into the interstitial space.
**Table 2.1: Classification of Blood Vessels**

<table>
<thead>
<tr>
<th>Blood Vessel</th>
<th>Description/Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artery</td>
<td>Contains a large amount of elastic tissue which is stretched during systole and recoils on the blood during diastole.</td>
</tr>
<tr>
<td>Diameter: 0.4 cm</td>
<td></td>
</tr>
<tr>
<td>Arteriole</td>
<td>Muscular vessel which provides major resistance to blood flow.</td>
</tr>
<tr>
<td>Diameter: 30 μm</td>
<td>Also regulates regional blood flow to the capillary bed.</td>
</tr>
<tr>
<td>Metarteriole</td>
<td>Serves as thoroughfare channels to venules, bypassing the capillary bed.</td>
</tr>
<tr>
<td>Diameter: 10 - 20 μm</td>
<td>Alternatively, serves as conduits to supply the capillary bed.</td>
</tr>
<tr>
<td>Precapillary sphincter</td>
<td>Ring of smooth muscle protecting site where capillary exists from metarteriole.</td>
</tr>
<tr>
<td></td>
<td>Continually opens and closes to allow intermittent flow through any given capillary.</td>
</tr>
<tr>
<td>Capillary</td>
<td>Thin-walled tube of endothelial cells, one-layer thick without any surrounding smooth muscle or elastic tissue.</td>
</tr>
<tr>
<td>Diameter: 5 - 10 μm</td>
<td>Primary site of exchange of water and solutes with interstitial fluid.</td>
</tr>
<tr>
<td>Venule</td>
<td>Has some smooth muscle, the contractions of which influence capillary pressure.</td>
</tr>
<tr>
<td>Diameter: 20 μm</td>
<td>Permits exchange of materials with interstitial fluid.</td>
</tr>
<tr>
<td></td>
<td>Serves as collecting channel and storage or capacitance vessel.</td>
</tr>
<tr>
<td>Vein</td>
<td>Last set of tubes through which blood flows on its journey back to the heart.</td>
</tr>
<tr>
<td>Diameter: 0.5 cm</td>
<td>Also serves as collecting channel and storage or capacitance vessel.</td>
</tr>
</tbody>
</table>
2.4 THE INTERSTITIUM

2.4.1 Structure and Composition of the Interstitium

The interstitium may be defined as the space located between the capillary wall and the cells. The basic structure of the interstitium is similar in all tissues: collagen forms a fibre framework that contains a gel phase made up of glycosaminoglycans and other large macromolecules, a salt solution and proteins derived from plasma. Although the components are principally the same in all tissues, their relative amounts vary greatly. The amount of interstitium varies from about 50% of the wet weight in skin to 10% in skeletal muscle, to even less in the brain [Aukland and Reed, 1993]. The composition and structure of the interstitium has been the subject of several reviews [Aukland and Reed, 1993; Bert and Pearce, 1984; Chapple, 1990; Comper and Laurent, 1978; Gu, 1987; Xie, 1992].

**Collagens**: The collagens are a group of proteins consisting of bundles of tiny fibrils, which combine to form the white glistening inelastic fibres of tendons, ligaments and fascia. Their molecules consist of three separate left-handed coiled polypeptide chains, each containing about 1 000 amino acids. Three molecules are coiled into a right-handed super helix. These three chains constitute the collagen molecule. A collagen fibre consists of an organized array of collagen molecules, arranged in parallel with many stable cross linkages between the molecules. As a result, the collagens have a high tensile strength, resist stretching and maintain the integrity of many different organs.

**Glycosaminoglycans**: The glycosaminoglycans are polyionic polysaccharide chains of variable length made from repeating disaccharide units of hexosamine and uronic acid or galactose. The glycosaminoglycans are widely distributed in the organism, but their
concentration varies between different organs. About two-thirds of the glycosaminoglycan content in skin is hyaluronan, one of the seven subfamilies of glycosaminoglycans.

*Elastic Fibres:* The elastic fibres provide tissues with elasticity, giving some tissues a rubber-like texture. The major part of the elastic recoil of skin after applying tension within physiological limits is attributed to elastin, a three-dimensional network of cross-linked hydrophobic amino acid molecules.

*Interstitial Plasma Proteins:* The plasma proteins contained in the interstitial fluid are the same as those in plasma. The proteins move from the plasma to the interstitium across the capillary wall. The interstitial concentration is a function of the selectivity at the capillary barrier, the transcapillary fluid flux and lymph flow. The physical properties of the plasma proteins in the interstitial space affect the physiology of this space. Due to its relative abundance, relatively low molecular weight and high charge density, albumin is a major contributor to the interstitial colloid osmotic pressure (COP). The interstitial proteins return to the circulation via the lymph and thus, the interstitium acts as a reservoir for colloidal actively molecules.

2.4.2 Physicochemical Properties of Interstitium

Certain properties of the interstitium influence its response to burn injury and will be discussed in the following section.

2.4.2.1 Turnover of Interstitial Plasma Proteins

The rate of disappearance of plasma proteins from the interstitium is described as the turnover rate. The turnover of proteins in the interstitium has been quantified in several ways, most commonly by injecting radiolabelled protein into the tissue and measuring its removal by external gamma-detecting equipment or by estimating the appearance of tracer
in plasma [Hollander et al., 1961; Langgård, 1963; Reed et al., 1990]. In humans, the normal removal rate of radioactive albumin injected subcutaneously has been found to be between 2 and 2.5% per hour [Hollander et al., 1961, Langgård, 1963; Xie, 1992].

2.4.2.2 Interstitial Volume Exclusion

Mutual exclusion between macromolecules occurs because at any particular time, no two of these molecules may occupy the same space, and their centres may not come closer than the sum of their radii. The characteristic components of the interstitium such as collagenous fibres, have diverse geometric shapes. Their presence thus limits the interstitial space accessible to plasma proteins and other macromolecules. In vivo exclusion studies predict fractional albumin excluded volumes ranging from about 25% to 60% [Granger et al., 1980; Parker et al., 1979, 1980; Reed et al., 1990]. Based on these studies and the work of Wiederhielm [1979], Bert and Pinder [1982] determined a constant albumin exclusion fraction of 25% of the normal interstitial volume.

2.4.2.3 Interstitial Compliance

In order to perform any type of quantitative analysis of interstitial fluid dynamics, it is essential to know the relationship between interstitial fluid pressure and volume in the interstitial spaces. The interstitial compliance is defined as the ratio of the change in interstitial fluid volume \(V_I\) to the corresponding change in interstitial hydrostatic pressure \(P_I\), i.e.,

\[
Compliance = \frac{\Delta V_I}{\Delta P_I}.
\]

Information about the compliance of human tissues is lacking. Chapple [1990] developed a compliance relationship for humans based on the work of Strand and Myhre [1982] and Reed and Wiig [1981]. Strand and Myhre [1982], in the only known study of human compliance, measured the compliance of lower limb subcutaneous tissue in 46 patients.
However, the data was too scattered to derive a meaningful relationship for human compliance. Reed and Wiig [1981], after studying the compliance characteristics of skin and skeletal muscle in rat, cat and dog tissues, found that the compliances of both tissues follow a similar trend. During severe tissue dehydration, compliance is low while during severe tissue overhydration, compliance is high. In between the two extremes, moderate compliance characteristics prevail. The general shape of the volume-pressure curve is shown in Figure 2.4 [Reed and Wiig, 1981]. Chapple scaled interstitial hydrostatic pressure and interstitial fluid volume data from the rat based on changes observed in the edematous state by Stranden and Myhre. The flat segment of his compliance relationship, representing overhydration, was considered the region most prone to the influence of experimental error. As such, two other relationships were investigated by arbitrarily increasing the slope of the overhydration segment from $1.8 \times 10^{-5}$ to $5.0 \times 10^{-5}$ and $1.05 \times 10^{-4}$ mmHg/mL. A summary of the three compliance relationships investigated is presented in Table 2.2. The three tissue compliance relationships were used by Xie [1992] in a study to determine normal transport parameters for the human MVES. The best-fit parameters were obtained using compliance relationship #3.

2.5 THE SKIN

In the present study, the properties of the interstitium are assumed to be those of skin and muscle. A brief discussion of the anatomy and function of the skin provides a basis in understanding the microscopic changes that occur in the skin following burn injury.

2.5.1 Anatomy and Function of Skin

The skin is the largest organ of the body and has a surface area that ranges from about 0.025 m² in the newborn to 2.0 m² in the adult [Martyn, 1990; McLaughlin, 1990]. It
Figure 2.4: Tissue Hydrostatic Pressure as a Function of Interstitial Fluid Volume for Skeletal Muscle and Skin in Rat [Reed and Wiig, 1981]
Table 2.2: Mathematical Description of Human Interstitial Compliance Relationship

[Chapple, 1990]

<table>
<thead>
<tr>
<th>Region of Curve</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehydration</td>
<td>[ P_I = -0.7 + 1.96154 \times 10^{-3} \left( V_I - 8.4 \times 10^3 \right) ]</td>
</tr>
<tr>
<td>Moderate Hydration</td>
<td>Mathematical interpolation of experimental P(_I) and V(_I) data</td>
</tr>
<tr>
<td>Overhydration:</td>
<td></td>
</tr>
<tr>
<td>Compliance #1</td>
<td>[ P_I = 1.88 + 1.8 \times 10^{-5} \left( V_I - 1.26 \times 10^4 \right) ]</td>
</tr>
<tr>
<td>Compliance #2</td>
<td>[ P_I = 1.88 + 5.0 \times 10^{-5} \left( V_I - 1.26 \times 10^4 \right) ]</td>
</tr>
<tr>
<td>Compliance #3</td>
<td>[ P_I = 1.88 + 1.05 \times 10^{-4} \left( V_I - 1.26 \times 10^4 \right) ]</td>
</tr>
</tbody>
</table>

consists primarily of two layers, the epidermis and dermis or corium as shown in Figure 2.5. The outermost cells of the epidermis are dead cornified cells that act as a tough protective barrier against the environment. It has high capacity for regeneration. The stratum corneum in the epidermis has a high electrical impedance which restricts the passage of electric current. The second, thicker layer, the dermis, is composed chiefly of fibrous connective tissue. It contains the blood vessels and nerves to the skin and epithelial appendages of specialized function. The dermis is the barrier that prevents loss of body fluids by evaporation and loss of excess body heat. Sweat glands help maintain body temperature by controlling the amount of heat loss by evaporation. Beneath the dermis is subcutaneous or adipose tissue which consists mostly of fat. It serves as a means of heat insulation and as a nutritional source in extreme conditions.
Figure 2.5: Structure of Normal Skin Showing the Categorization of Burn Injury
2.6 TRANSCAPILLARY EXCHANGE

Fluid and proteins move across the capillary endothelial wall by filtration, diffusion and convection. The transcapillary exchange of fluid and protein is determined by the properties of the capillary membrane, the transcapillary pressures and the protein concentrations.

2.6.1 Capillary Filtration

The magnitude and direction of the movement of fluid across the capillary wall is determined by the algebraic differences between the hydrostatic and osmotic pressures existing across the membrane. An increase in intracapillary hydrostatic pressure favours movement of fluid from the blood vessel to the interstitial space, whereas an increase in the concentration of osmotically active agents within the vessels favours movement into the vessels from the interstitial space.

The role of the hydrostatic and colloid osmotic pressures in regulating the passage of fluid across the capillary endothelium was first expounded by Starling in 1896 and constitutes the Starling Hypothesis. It can be expressed by the equation:

\[ J_F = kA \cdot \left[ (P_C - P_I) - \sigma \cdot (\Pi_{PL} - \Pi_I) \right] \]

where \( J_F \) is the transmembrane filtration flow, \( k \) the hydraulic conductivity of the capillary membrane per unit area, \( A \) the surface area available for exchange, \( \sigma \) the capillary reflection coefficient for the plasma proteins, \( P \) and \( \Pi \) are the hydrostatic and colloid osmotic pressures respectively, while the subscripts \( C \), \( PL \) and \( I \) represent capillary, plasma and interstitial respectively. The product \( kA \) is referred to as the capillary filtration coefficient for the capillary membrane. Filtration occurs when the pressure driving force, \( (\Delta P - \sigma \Delta \Pi) \), is positive and re-absorption occurs when it is negative.
2.6.2 Combined Convective and Diffusive Solute Transport

Bresler and Groome [1981] developed an equation for the combined convective and diffusive protein flux across membranes of finite thickness. The transport equation which describes the solute flux generated when a combined hydrostatic and osmotic pressure difference and a concentration difference act conjointly across the membrane is

\[
\dot{Q}_s = J_F \cdot (1 - \sigma) \cdot \left[ \frac{c_{pl} - c_j \cdot \exp(-Pe)}{1 - \exp(-Pe)} \right],
\]

where \(\dot{Q}_s\) is the rate of solute transport across the membrane, \(c\) the concentration of plasma protein and \(Pe\) is a modified Péclet number defined by

\[
Pe = \frac{(1 - \sigma) \cdot J_F}{PS}.
\]

PS is the product of the permeability of the capillary membrane to albumin and the membrane surface area.

2.7 PHYSIOLOGICAL CHANGES FOLLOWING INJURY

The physiological changes that result from a burn injury have been reviewed extensively [Gu, 1987; Lund et al., 1989, 1992]. The typical clinical features of thermal injury include visible swelling of the skin, blister formation and loss of surface-protecting epithelium which leaves wet and weeping surfaces. The swelling is caused by changes in the microvascular exchange system (MVES), in particular, fluid shifts and losses from the circulation. Other macroscopic changes occur with respect to areas not directly affected by the burn. A brief review of these changes will serve as a basis for the formulation of the current model describing the human MVES following burn injury.
2.7.1 Damage to Skin

The continued losses of water and heat through burned skin play major roles in the pathophysiologic changes seen postburn. Significant swelling may also occur in the subcutaneous layer of skin. The degree of impairment in the protective characteristics of normal skin is dependent on the depth of the burn injury and the extent of injury or the size of the burn relative to that of the total skin surface area. Traditionally, burn depth has been classified in degrees of injury: first, second and third degree burns. Currently, the more popular classifications are partial-thickness (first and second degree) and full-thickness (third degree) burns. Both classifications use the same criteria based on the depth of tissue destruction as is shown in Figure 2.5 and described in Table 2.3.

The extent of injury indicates the total percentage of the body surface area (TBSA) involved. The "rule of nines" has been used in evaluating the extent of burns, where each arm is considered to be 9%, each leg 18%, anterior trunk 18%, posterior trunk 18% and head 9% of TBSA as shown in Figure 2.6. A more accurate method is the use of the Lund and Browder chart shown in Figure 2.7 which divides the body surface by regions, while accounting for age group variation [McLaughlin, 1990].

2.7.2 Changes to the Microvascular Exchange System (MVES)

The abnormal accumulation of fluid in the interstitial spaces of tissues, or edema, is a major clinical problem after thermal injury. Edema is most prominent in burn tissues or in the region directly surrounding the burn tissues, but is not uncommon in nonburned tissues, including the lungs. It is well known that this swelling of tissue is caused by the shift of fluid from the circulating plasma to the interstitial spaces. This internal loss of plasma volume may result in hypovolemia and eventually in hypovolemic shock. The pathogenesis of this fluid shift has been the subject of many research efforts [Arturson, 1979; Davies, 1982; Leape, 1968], however, it is still not very well understood.
Figure 2.6: Rule of Nines for Burn Estimate
<table>
<thead>
<tr>
<th>Area</th>
<th>Birth-1 yr</th>
<th>1-4 yr</th>
<th>5-9 yr</th>
<th>10-14 yr</th>
<th>15 yr</th>
<th>Adult</th>
<th>Partial thickness 2°</th>
<th>Full thickness 3°</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head</td>
<td>19</td>
<td>17</td>
<td>13</td>
<td>11</td>
<td>9</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior trunk</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior trunk</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right buttock</td>
<td>2½</td>
<td>2½</td>
<td>2½</td>
<td>2½</td>
<td>2½</td>
<td>2½</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left buttock</td>
<td>2½</td>
<td>2½</td>
<td>2½</td>
<td>2½</td>
<td>2½</td>
<td>2½</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genitals</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right upper arm</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left upper arm</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right lower arm</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left lower arm</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right hand</td>
<td>2½</td>
<td>2½</td>
<td>2½</td>
<td>2½</td>
<td>2½</td>
<td>2½</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left hand</td>
<td>2½</td>
<td>2½</td>
<td>2½</td>
<td>2½</td>
<td>2½</td>
<td>2½</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right thigh</td>
<td>5½</td>
<td>6½</td>
<td>8</td>
<td>8½</td>
<td>9</td>
<td>9½</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left thigh</td>
<td>5½</td>
<td>6½</td>
<td>8</td>
<td>8½</td>
<td>9</td>
<td>9½</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right leg</td>
<td>5</td>
<td>5</td>
<td>5½</td>
<td>6</td>
<td>6½</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left leg</td>
<td>5</td>
<td>5</td>
<td>5½</td>
<td>6</td>
<td>6½</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right foot</td>
<td>3½</td>
<td>3½</td>
<td>3½</td>
<td>3½</td>
<td>3½</td>
<td>3½</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left foot</td>
<td>3½</td>
<td>3½</td>
<td>3½</td>
<td>3½</td>
<td>3½</td>
<td>3½</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2.7: Lund-Browder Chart for Burn Estimate: Percentage of Body Area**
Table 2.3: Burn Depth Classifications

<table>
<thead>
<tr>
<th>Classification of Burn</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>First degree or Superficial partial-thickness</td>
<td>Involves only epidermis layer with minimal tissue damage.</td>
</tr>
<tr>
<td></td>
<td>Protective functions of skin in dermis remain intact.</td>
</tr>
<tr>
<td></td>
<td>Causes: overexposure to sunlight or hot liquid scalding.</td>
</tr>
<tr>
<td>Superficial second degree (Deep partial-thickness)</td>
<td>Involves heat destruction of upper third of dermis.</td>
</tr>
<tr>
<td></td>
<td>Microvessels are injured and permeability increases resulting in plasma leakage into the interstitium.</td>
</tr>
<tr>
<td></td>
<td>Blisters form due to loss of epidermis.</td>
</tr>
<tr>
<td>Mid- to deep dermal second degree (Deep partial thickness)</td>
<td>Extends well into dermal layer.</td>
</tr>
<tr>
<td></td>
<td>Plasma leakage in remaining intact blood vessels is evident.</td>
</tr>
<tr>
<td></td>
<td>Blood supply is marginal and the potential for the burn to progress to deeper injury is high.</td>
</tr>
<tr>
<td>Third degree or Full thickness</td>
<td>Destruction of entire epidermis and dermis.</td>
</tr>
<tr>
<td></td>
<td>Formation of avascular tissue due to heat-coagulation of dermal blood vessels.</td>
</tr>
<tr>
<td></td>
<td>Causes: Short exposure to very high temperature or prolonged contact with moderate temperature.</td>
</tr>
</tbody>
</table>

2.7.2.1 Transcapillary Exchange in Injured Tissue

Edema develops when the rate of fluid filtered from the microvessels exceeds the rate at which fluid is drained by the lymphatics or by some other route. Fluid is filtered across the capillary membrane according to Starling's hypothesis, which according to the previous section yields
\[ J_F = kA \cdot \Delta P, \]  
\[ \Delta P = P_C - P_f - \sigma \cdot (\Pi_{PL} - \Pi_f). \]

2.5

where \( \Delta P \) is the net filtration pressure given by

2.6

Lymphatic drainage from the tissue is assumed to be linearly dependent on interstitial fluid pressure, i.e.,

\[ J_L = J_{L,NL} + LS \cdot [P_f - P_{I,NL}]. \]

2.7

\( J_L \) is the rate of lymphatic drainage from tissue, \( LS \) the lymph flow sensitivity coefficient and the subscript \( NL \) represents normal steady-state conditions. The influence of burn injury on each of the parameters in Equations 2.5, 2.6 and 2.7, which affect transcapillary fluid and protein exchange in the injured tissue, is discussed in Table 2.4.

Due to the marked increase in capillary permeability to macromolecules and decrease in the capillary reflection coefficient, there is a high plasma protein content in exudate and blister fluid following burn injury [Arturson, 1979]. This apparent leakiness of the capillaries results in an increase in the pool of plasma proteins outside the circulation. Return of this pool to the circulation depends on lymphatic function. The concentration of plasma proteins in plasma may also be increased through the administration of resuscitation fluids.

2.7.2.2 Transcapillary Exchange in Uninjured Tissue

Swelling or edema of uninjured skin, muscle and internal organs distant from the injured skin areas is also seen following fluid resuscitation of patients with extensive burns. Increases in protein extravasation, tissue protein and fluid content have been reported in uninjured tissue [Carvajal et al., 1979; Lund and Reed, 1986]. These remote effects occur
Table 2.4: Changes to Injured Tissue MVES Properties Following Burn Injury

<table>
<thead>
<tr>
<th>Property</th>
<th>Physiological Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capillary Filtration Coefficient, kA</td>
<td>Conductivity per unit area, k, increases.</td>
</tr>
<tr>
<td></td>
<td>Overall effect on kA is therefore unpredictable.</td>
</tr>
<tr>
<td>Net filtration pressure, ΔP</td>
<td>Normal value of ΔP is between 0.5 and 1 mmHg.</td>
</tr>
<tr>
<td>Capillary hydrostatic pressure, P_c</td>
<td>P_c is normally determined by arterial and venous hydrostatic pressures as well as precapillary and postcapillary resistances.</td>
</tr>
<tr>
<td>Interstitial fluid hydrostatic pressure, P_i</td>
<td>P_i is normally slightly subatmospheric (-1 to -2 mmHg).</td>
</tr>
<tr>
<td></td>
<td>An acute marked decrease of P_i to a strongly negative value of about -150 mmHg has been observed in the first hour postburn [Lund et al., 1988].</td>
</tr>
</tbody>
</table>
### Table 2.4 (Continued): Changes to Injured Tissue MVES Properties Following Burn Injury

<table>
<thead>
<tr>
<th>Property</th>
<th>Physiological Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma colloid osmotic pressure (COP), ( \Pi_{PL} )</strong></td>
<td>A reduction in the value of ( \Pi_{PL} ) has been observed [Lund et al., 1986, 1988; Onarheim et al., 1989; Pitkänen et al., 1987; Watchtel et al., 1983; Zetterström and Arturson, 1980] with or without fluid resuscitation. ( \Pi_{PL} ) is affected by the loss of fluid and proteins out of the circulation, as well as the lymphatic return of fluid poor in protein. The effect on transcapillary fluid exchange is to enhance the net capillary filtration of fluid.</td>
</tr>
<tr>
<td><strong>Interstitial fluid COP, ( \Pi_1 )</strong></td>
<td>Increased extravasation of fluid and protein can effect a theoretical increase or decrease in the value of ( \Pi_1 ) depending on the protein concentration of the filtrate compared to that in interstitial fluid. Increases in the value of ( \Pi_1 ) [Lund and Reed, 1986] and a reversed COP gradient (( \Pi_{PL} - \Pi_1 )) [Pitkänen et al., 1987] have been observed. The reversed COP gradient could enhance fluid filtration, hence plasma volume loss.</td>
</tr>
<tr>
<td><strong>Capillary reflection coefficient, ( \sigma )</strong></td>
<td>Normal ( \sigma ) in skin is reported to be between 0.85 and 0.97 [Taylor and Granger, 1984]. A reduction in the value of ( \sigma ) from 0.87 to 0.45 has been reported [Pitt et al., 1987], associated with increased protein permeability. The normally reabsorptive COP gradient across the capillary membrane is thus reduced.</td>
</tr>
<tr>
<td><strong>Lymphatic drainage, ( J_L )</strong></td>
<td>Increases in the value of ( J_L ) of up to 20 times has been observed [Arturson and Mellander, 1964; Pitt et al., 1987; Taylor and Granger, 1984].</td>
</tr>
</tbody>
</table>
when the burns cover more than 25% to 30% of the total body surface area (TBSA). Reduced blood flow has also been reported following minor burns [Jelenko et al., 1973].

The lungs are of special interest due to the well recognized complication of pulmonary edema in major body burns. Inhalation injury has direct damaging effects on the respiratory tract and lungs. In the absence of this injury, the lungs are protected against edema by their ability to increase lymphatic removal of fluid. An additional edema-preventing mechanism results from the removal and dilution of interstitial proteins due to a normally high interstitial COP in the lungs.

2.7.2.3 Systemic Hemodynamic Changes

Hypovolemia, resulting from the loss of fluid from the circulation, induces a number of hemodynamic changes following thermal injury. Cardiac output is reported to fall markedly soon after extensive burns. In addition, arterial blood pressure and central venous pressure have both been found to decrease. The ratio of the systemic blood pressure to the cardiac output is a measure of the peripheral resistance. It depends mainly on the degree of vasoconstriction and on the viscosity of blood, to a lesser extent. Vasoconstriction causes an overall increase in the peripheral resistance, which may maintain arterial blood pressure for a time, but at the expense of a reduced blood flow through the skin and other vital organs.

2.8 FLUID RESUSCITATION

Hypovolemia resultant from burn injury can rapidly lead to conversion of a viable but ischemic deep dermal burn to a nonviable full-thickness burn, further increasing the possibility of mortality. Death due to the development of hypovolemic shock in the acute phase is also of particular concern. Adequate initial fluid volume resuscitation is therefore
critical to the survival of a major body burn. However, the aggressive correction of the problem of hypovolemia can result in generalized burn edema formation which is less lethal than shock, but can result in serious morbidity nonetheless. The subnormal cardiac output following burn injury also needs to be promptly restored as near as possible to the normal value.

The greatly increased capillary leakage resulting in progressive edema formation is greatest during the first eight hours post-burn. Consequently, the two important goals of early burn care are the prompt initiation of resuscitation and an adequate volume replacement regime. Several empirical formulae exist for resuscitation of the burn patient based on the timing of fluid replacement, as well as on the composition and amount of fluid provided. Crystalloids, hypertonic crystalloids and colloidal solutions have been used for early fluid therapy.

2.8.1 Isotonic Crystalloid Fluid Resuscitation

Crystalloids, in particular isotonic solutions such as lactated Ringer's solution, with a sodium concentration of 130 mEq/L, are the most popular resuscitation fluids [Gillespie et al., 1987]. The loss of large quantities of sodium and water from the vascular space into the burn wound is well recognized. The need for sodium and water replacement to effect successful resuscitation justifies the use of this solution, which closely approximates the composition of the extracellular fluid. The amount of fluid to be given over the first 24 hours is initially estimated by various formulae such as the Parkland formula (4 mL of lactated Ringer's /kg/% TBSA burned). The use of lactated Ringer's solution has been found highly effective in preventing early death due to hypovolemia. However, concerns exist due to complications from the administration of large volumes of fluid.
2.8.2 Hypertonic Crystalloid Fluid Resuscitation

Hypertonic solutions with sodium concentrations between 240 and 260 mEq/L, have become a popular option in minimizing the total fluid volume administered to burn patients in the early phase postburn. These hypertonic saline solutions are used to control cell swelling by increasing extracellular osmotic pressure. Water influx into the cells is thus prevented and fluid extravasation into injured tissue is decreased. Extracellular and hence, intravascular volume is maintained with less fluid. However, as these solutions are still crystalloids, hypoproteinemia and blood volume are not as well maintained as with colloid solutions. The safe use of these fluids as a standard solution has been the subject of many recent research efforts [Griswold et al., 1991; Gunn et al., 1989].

2.8.3 Colloid Fluid Resuscitation

The realization that the fluid lost from the circulation into the burned tissues has the characteristics of plasma is justification for using colloidal solutions for the early fluid therapy. A variety of colloids have been used including human plasma, serum and/or albumin, modified gelatin and the non-protein colloids such as dextrans and starches (hetastarch and pentastarch).

The use of protein solutions has been reported to decrease total fluid requirements [Wilkinson, 1971]. The timing of albumin therapy remains controversial as capillary permeability changes vary considerably in different tissues for different degrees of burn injury. As the fluid requirements and the area of the burn are related, various formulae have been proposed as guidelines to the requirements of a particular burn patient (Evans; Brooke) [Evans et al., 1952; Reiss et al., 1953]. Due to the very high cost of albumin infusions, less expensive colloids, not derived from human plasma provide a significant cost benefit. The potential efficacy of nonprotein colloid plasma expanders in burn resuscitation was suggested by experimental studies with dextran [Demling et al., 1984].
Clinically, dextrans have not been widely used primarily due to their potential to induce allergic reactions and increased bleeding. The safety and efficacy of other plasma substitutes, including gelatins, for burn resuscitation, remain unresolved. The most promising alternative colloid volume expanders are the starches [Waxman et al., 1989]. Hetastarch, which closely mimics 5% albumin in normal saline, has been found to increase clotting and reduce bleeding times in animals. Pentastarch has been found to be a very promising plasma substitute, with hemodynamic effects equal or superior to albumin. However, further study is required to assess the efficacy of pentastarch within the first 24 hours of resuscitation.

Formal resuscitation is generally carried out in all adults with burns over 15 to 20%, with superficial or first degree burns being excluded. The most reliable clinical parameter reported for evaluating the response of the patient to all these resuscitation formulae is urine output, even though this has been disputed [Dries and Waxman, 1991]. In adults, 0.5 to 1.0 mL/kg/h of urine is the optimum goal.

2.9 SUMMARY

In summary, the most important changes that occur following thermal injury which need to be considered when modelling the human microvascular exchange system, are the following:

i) the rapid development of edema in the injured tissue resulting from increased pressure driving forces and the capillary filtration coefficient in this tissue;

ii) a dramatic increase in transcapillary transport of plasma proteins in the injured tissue;

iii) a dramatic loss of fluid and protein from the burn wound; and
iv) a dramatic reduction by about -150 mmHg in interstitial fluid hydrostatic pressure, creating a strong "suction" in the burned tissue. This very negative tissue pressure has been observed in rats.

Burns covering more than about 25% of the total body surface area initiate local and systemic effects different from those initiated by smaller burns. Consequently, two burn groups, less than and greater than 25% burn surface area, need to be considered in the analysis of fluid exchange and resuscitation of burn patients.
CHAPTER 3

COMPUTER MODELLING OF THE MICROVASCULAR EXCHANGE SYSTEM

3.1 INTRODUCTION

In order to replace the loss of plasma volume which results in the microvascular exchange system (MVES) following a burn injury, and hence to improve the survival of burn victims, various empirical formulae for fluid therapy have been developed and implemented with varying degrees of success [Evans et al., 1952; Gillespie et al., 1987; Reiss et al., 1953]. These empirical approaches to treatment are based on clinical observations and medical experience from treating burn patients, with limited understanding of the underlying fluid and protein transport phenomena in the MVES. These treatment formulae give the amount of fluid required to stabilize a burned, hypovolemic individual, based on the size of the injury and the time postburn. Fluid resuscitation has been found to correct hypovolemia or low blood volume, but worsens the edema or swelling process.

Mathematical models have been developed to complement this empirical approach to patient care. These models are based on detailed fluid and protein transport mechanisms across the capillary membrane. The models describe the time course of changes in fluid volumes and the amount and concentration of protein in the blood and tissues following injury. Mathematical models can be used to predict the response of the MVES to different empirical resuscitation protocols to give an indication of a possible optimum form of therapy. In describing the human MVES, two different kinds of models have been considered; the distributed and compartmental models.
In the distributed model, the fluid and tissue properties are considered to be position-dependent. These spatial properties are difficult to determine experimentally and hence are not readily available. In addition, a more complex description of fluid and protein transport is required, resulting in a model that consists of a set of partial differential equations, which are difficult to solve mathematically. Distributed models [Gates, 1992; Taylor et al., 1990; Werner, 1981] approximate the real system under investigation more closely than the compartmental models. However, due to the mathematical complexity of these models and the lack of experimental data required to determine model parameters, it is premature to consider their inclusion in a burn patient simulator.

The compartmental model, as the name suggests, comprises a system of separate, well-mixed compartments in which fluid and proteins are homogeneously distributed. As such, the properties in each compartment represent average values for that compartment. Due to this spatial averaging, the behaviour of fluid and proteins in the MVES can be described by a much simpler set of ordinary differential equations. Several compartmental mathematical models have been developed to describe the distribution and transport of fluid and protein between the circulation, interstitium and lymphatics [Arturson et al., 1984; Bert et al., 1982, 1988; Roa and Gomez-Cia, 1986; Wiederhielm, 1979]. The proposed models generally differ in two aspects: the complexity in the division of the MVES into compartments and the description of fluid and protein exchanges between the compartments. In most models, the MVES is assumed to comprise the plasma compartment and interstitial compartments. Additional compartments to describe intracellular and extracellular distribution or renal function for example, are also considered based on the particular interests of the researchers. Fluid and protein exchange between the compartments is based on Starling's concepts on capillary filtration and exchange [Starling, 1896]. The mathematical equations that describe the model are obtained by carrying out fluid and protein balances around the compartments. This results
in a set of ordinary differential equations where the independent variable is time. The remainder of this chapter will review compartmental models which have been developed to describe the normal or thermally injured MVES in experimental animals and humans.

3.2 MODELLING OF NORMAL MVES

A non-linear computer simulation program was developed by Wiederhielm [1979] to analyze the dynamics of capillary fluid exchange. The simulation program took account of the fact that, in addition to plasma proteins, the interstitium also contains other osmotically active substances such as mucopolysaccharides. These substances exert an osmotic pressure and also exhibit unusual physical characteristics in terms of volume exclusion. The interstitium was therefore partitioned into a mucopolysaccharide-containing gel phase in equilibrium with a free fluid-phase, to which the proteins are restricted. Also included in the simulation was a nonlinear interstitial compliance. Two different modes of transport of plasma proteins and macromolecules from the circulation into the interstitium were considered: bulk flow at the venous end of the capillary and via diffusion. With this model, steady-state and transient responses to a variety of perturbations, including changes in arterial and venous pressures, plasma oncotic pressure, interstitial mucopolysaccharide content and lymphatic obstruction were studied.

Bert and Pinder [1982] modified the model of Wiederhielm to incorporate a different concept of volume exclusion. The excluded volume in Wiederhielm's model which was a variable calculated from the concentration of proteoglycans, including hyaluronate in the gel phase, was replaced by a constant value. This constant value for the excluded volume was based on observations that the volume from which albumin is excluded remains constant, even with swelling of the tissue [Meyer et al., 1977] and was due to the presence of collagenous fibres. The use of this constant value avoided the unprovable assumptions
Wiederhielm was forced to make regarding content, composition and interaction of components of the interstitial space and also simplified the overall model. Bert and Pinder used their model to program perturbations characteristic of different forms of edema, and to record both the transient and steady-state responses, which were found to be in good agreement with Wiederhielm's predictions.

Bert et al. [1988] developed a dynamic mathematical model to describe the distribution and transport of fluid and plasma proteins between the circulation, interstitial space of skin and muscle, and the lymphatics in the rat. They investigated two descriptions of transcapillary exchange: a homoporous 'Starling Model' (SM) and a heteroporous 'Plasma Leak Model' (PLM). In the SM, water and protein exchanges were assigned to a single site in the capillary and were characterized by one pair of transport parameters for each plasma protein investigated and by one value of capillary hydrostatic pressure. The PLM was based on fluid filtration in the arterial end of the capillary, reabsorption in the venous end and convective protein transport through nonsieving channels also in the venous capillaries. Parameters used in these two hypothetical transport mechanisms were determined based on statistical fitting of simulation predictions to selected experimental data. This aspect of the work by Bert et al. differed from previous computer modelling efforts [Bert and Pinder, 1982; Wiederhielm, 1979]. The fully determined model was used to simulate steady-state conditions of hypoproteinemia, overhydration and dehydration, as well as the dynamic response to changes in venous pressure and intravascularly administered protein tracers. It was concluded from these studies that the PLM provided a better description of microvascular exchange in comparison to the SM because it yielded a better statistical fit of the available experimental data.

In order to describe the distribution and transport of fluid and albumin in the human circulation, the interstitium and the lymphatics, Chapple [1990] formulated a mathematical
model to describe the human MVES, continuing the trend set previously by Bert et al. Two transcapillary mass exchange mechanisms, the 'Coupled Starling Model' (CSM), in which transcapillary albumin diffusion and convection are coupled, and the heteroporous PLM, were investigated, as previously studied in the rat [Bert et al., 1988; Reed et al., 1989]. Some of the parameters used in the transport equations were again determined based on statistical fitting between simulation predictions and experimental data from normal humans and nephrotic patients. Due to the facts that the PLM required more estimated parameters than the CSM, and that fewer of the transport parameters had been measured experimentally, the model employing a Starling-type exchange mechanism was favoured for future studies by the group.

In a continuing study, Xie [1992] used the Coupled Starling Model (CSM) to determine a set of transport parameters to describe the transport mechanisms of the normal human MVES. The transport parameters were determined by fitting model predictions to experimental data from normal humans, nephrotic patients and patients who had sustained heart failure. Data from nephrotic and heart-failure patients were selected due to the fact that the MVES is believed to remain in its normal state, altered only by changes in the Starling forces. The fully described model was successfully used to simulate the transient behaviour of normal humans and patients subjected to saline and albumin solution infusions.

3.3 MODELLING OF MVES FOLLOWING BURN INJURY

Compartmental models have also been developed to study changes in the MVES following burn injury. Arturson et al. [1984] pioneered the description and development of these computer-based patient simulators. Based on the analog model by Wiederhielm [1979], modifications were made which described the changes that occur postburn. The interstitial
tissue was divided into two compartments. The injured tissue compartment represented only injured skin and the second tissue compartment comprised intact tissue (i.e. both intact skin and muscle). Exchange of fluids and protein between injured and intact tissue was assumed not to take place. In addition, osmotic effects of electrolytes in plasma, the interstitial space and cells were not taken into account. Wound fluid loss consisting of evaporation and exudation were also considered in the model. Data from three patients with thermal injuries were used to evaluate the model. The validity of the model was assessed by running simulation tests using constants and parameters determined from Wiederhielm's study. Subsequent research efforts [Arturson, 1988; Arturson et al., 1989; Hedlund et al., 1988] involved the development of complex multi-compartmental models made up of modules to describe such systems as hormonal function, renal dynamics and cell volume regulation, all in addition to the MVES. Many unmeasured parameters were required to fully describe these models.

A preliminary mathematical model of plasma water dynamics was developed by Bush et al. [1986] to investigate the relative efficacy of alternative modes of fluid therapy. Fluid input, urine output, burn water loss and insensible water losses via the unburned skin, lung and gastrointestinal tract were incorporated in the model. The model was reported to give reasonable responses to a wide range of burns, body sizes, fluid loss factors and rates of intravenous fluid administration. Due to its comparative simplicity, the model was not realistic enough to provide answers to unsettled questions concerning conflicting treatment methods. Useful additions to improve the predictive capabilities of the model were suggested, such as the inclusion of burn and nonburn interstitial and intracellular spaces along with their electrolyte and albumin contents.

Roa et al. [1986] have also been involved in the development of compartmental burn models. They presented an algorithm for the qualitative and quantitative study of the
variations in the distribution of extracellular fluids and proteins between the vascular and interstitial spaces in burn patients. Measurements of hematocrit, plasma protein concentration, fluid replacement and diuresis were used in the algorithm. Values for plasma, cellular and blood volumes, plasma proteins, evaporative water losses and net fluid and protein shifts were determined using the algorithm. In order to assess the reliability of the algorithm, their results were compared with the clinical progress of patients. In addition, agreement was obtained with the experimental and clinical results obtained by other authors [Arturson et al., 1984]. Roa et al. continued their modelling efforts by developing a non-linear, five-compartment mathematical model [1988]. Control mechanisms were incorporated to describe the interactions between the extra- and intracellular compartments. The different mechanisms that regulate pulmonary capillary dynamics in burn patients were also studied by including the relevant compartments [Roa et al., 1990]. More recently, Roa et al. [1993] have developed a fluid therapy method (BET) designed by computer simulation, using their previous digital simulation techniques. The effectiveness of the BET fluid therapy during the shock phase after burning was investigated and found to show promise.

Extension of the mathematical model developed by Bert et al. [1988] to describe normal microvascular exchange in the rat, enabled them to study microvascular exchange in the rat following a burn injury [Bert et al., 1989; Bowen et al., 1989]. The skin compartment in the previous model was subdivided into two compartments: the burned and the nonburned skin. Perturbations characteristic of relatively small (10% burn surface area) and large (40% burn surface area) burn injuries without fluid resuscitation were incorporated into the model. They estimated the changes that occur to transport coefficients and other system parameters subsequent to burns of these sizes by fitting the model predictions to specific experimental data [Lund and Reed, 1986]. A study by Bert et al. [1991] extended this model further to include the effects of different types of fluid
resuscitation protocols on the circulatory and microvascular exchange systems. They identified the ranges of model parameters that best described the changes in interstitial fluid volume and protein mass in addition to transcapillary protein extravasation for three sets of experiments: no resuscitation, resuscitation with Ringer's or resuscitation with plasma.

The importance of cellular exchange in the MVES following thermal injury was investigated in a preliminary study [Drysdale, 1988] where the model of fluid resuscitation developed by Bert et al. [1991] was extended to include hypertonic resuscitation in the rat. Adequate compartments to account for intra- and extracellular exchange were added to the existing model. Trends predicted by the model indicated that hypertonic fluid resuscitation in thermally injured rats mobilized cellular water in an attempt to maintain plasma volume.

The above mentioned groups have all made valuable contributions in the area of burn injury computer modelling. The models of Arturson et al. and Roa et al. are relatively complex in that they attempt to model other systems also affected by thermal injury, in addition to the MVES. Their description of the MVES is based primarily on the work of Wiederhielm [1979]. However, current knowledge regarding the MVES has superseded that proposed by Wiederhielm. In addition, various parameters necessary to fully describe their models were taken directly from available literature, with no attempt made to estimate them using patient data. Bert et al., on the other hand, have developed compartmental models, with particular emphasis on the MVES, which plays a critical role in transcapillary exchange following burn injury. Their models, unlike those mentioned previously, use model parameters based on statistical fitting of model predictions to experimental data. In addition, the physiological concepts employed in formulating these models are based on up-to-date knowledge regarding the MVES.
In this study, a mathematical model to investigate fluid resuscitation in humans following burn injury is developed, based on the simulation work of Xie [1992] who studied the normal human MVES. In contrast to most previous modelling efforts and continuing the trend set by Bert et al., the transport parameters necessary to fully describe the model are determined based on statistical fitting of model predictions to two specific sets of experimental data [Birkeland, 1969; unpublished data from T. Lund]. Current issues and knowledge regarding the human MVES are also incorporated into the model, in an attempt to give a better and more accurate description of fluid and protein distribution in the human MVES following thermal injury.
4.1 INTRODUCTION

Several mechanisms of transcapillary fluid and albumin exchange have been investigated as discussed in Chapter 3. The Coupled Starling Model (CSM) was found to best describe the normal human microvascular exchange system (MVES) [Xie, 1992]. The model developed in the current study to describe the human MVES following burn injury is an extension of the compartmental model developed by Xie [1992]. The main assumptions, transport mechanisms as well as systemic fluid and protein inputs and outputs for this extended model are discussed in the first part of this chapter. Normal steady-state conditions existing in the average human provide a basis for describing conditions in the patient at the instant the burn takes place. Following burn injury, fluid and proteins in the system are redistributed in the different compartments. This results in changes to physiological properties dependent on the fluid and protein content in the compartments. Additional relationships to describe the postburn physiological properties and transport coefficients necessary for the model formulation are discussed and developed. Fluid and protein losses from the burn wound by exudation as well as evaporative fluid losses are important issues related to burn injury. These are also discussed and incorporated in the model. Finally, a description of the simulation algorithm is presented.
4.2 BASIC ASSUMPTIONS

1. It is assumed that the MVES is divided into three well-mixed compartments in which fluid and proteins are homogeneously distributed. Consequently, the properties in each compartment represent average values for that compartment. In contact with the circulating plasma compartment are two tissue compartments: the uninjured and the injured tissue compartments, as shown schematically in Figure 4.1. In previous modelling studies in the rat [Bert et al, 1988; Reed et al., 1989], the uninjured interstitium was divided into two separate compartments, muscle and skin. This separation was justified in that many of the characteristics of these two tissues, including the colloid osmotic pressure (COP) dependence on protein concentration, the compliance characteristics and the normal steady-state conditions are known. The separation was also possible because separate experimental response data for muscle and skin was available from rat studies by Reed and Wiig [1981]. Due to lack of experimental information on human tissues, it is assumed in this model that the uninjured tissue compartment consists of unburned skin, muscle and other tissues while the injured tissue compartment consists of burned skin. In common with earlier models, it is also assumed that there is no direct exchange of fluid or plasma proteins between the two tissue compartments. Direct exchanges only occur between the circulation and each tissue separately.

2. In order to appreciate the influence of plasma proteins on the regulation of fluid volume, knowledge of the effect of protein concentration on COP in each compartment is necessary. Due to its relative abundance, relatively low molecular weight and high osmotic activity, albumin is the major contributor to the interstitial COP. For these reasons, and because albumin was the only protein whose
Figure 4.1: Schematic of Compartmental Burn Model
concentration was monitored in many experiments on rats, albumin was selected as the representative protein in previous modeling efforts in the rat [Bert et al., 1988; Reed et al., 1989]. In the current study, as in previous modeling studies in humans [Chapple, 1990; Xie, 1992], albumin is again chosen to represent all the plasma proteins.

3. The importance of cellular exchange in the MVES following thermal injury is well recognized, especially with regard to hypertonic fluid resuscitation [Griswold et al., 1991; Gunn et al., 1989]. In the current model, the effect of isotonic fluid resuscitation on the MVES is studied and as such, the transcellular transport of small ions is assumed to be at steady-state conditions. It is also assumed that the concentration of small ions in the blood, interstitium and lymphatics is constant. The effect of cellular damage resulting from burn injury is not considered in this model.

4. Transcapillary exchange in the human MVES is described by the Coupled Starling Model (CSM) or Patlak Model [Patlak et al., 1963]. It is a homoporous model, in which the pores in the capillary membrane are assumed to be of a single size, characterized by the value of the albumin reflection coefficient (σ). A reflection coefficient of unity implies that the membrane is perfectly impermeable to albumin, while a value of zero implies free passage of albumin across the capillary membrane. In addition, the pressure within the capillary is assumed to be uniform and represented by a single hydrostatic pressure term. The fluid and protein transport mechanisms which characterize the CSM are described below.

a) Fluid is transported from capillary to interstitium by filtration, according to Starling's Hypothesis [Starling, 1896] as

\[ J_F = k_F \cdot \left[ P_C - P_I - \sigma \cdot (\Pi_{PL} - \Pi_I) \right], \] 4.1
where \( k_F \) is the capillary filtration coefficient, determined as the product of the hydraulic conductivity of the capillary membrane per unit area and the surface area available for fluid exchange, \( k_A \), as discussed in Chapter 2.

b) Albumin is transported passively by diffusion and convection from capillary to interstitium through the fluid-carrying channels in the capillary membrane according to

\[
\dot{Q}_s = J_F \cdot (1 - \sigma) \cdot \left[ \frac{c_{pl} - c_{i,AV} \cdot \exp(-Pe)}{1 - \exp(-Pe)} \right],
\]

where \( c_{i,AV} \) is the effective interstitial albumin concentration defined by

\[
c_{i,AV} = \frac{Q_i}{(V_i - V_{i,EX})}.\]

\( Q \) is the albumin content and \( V_{i,EX} \) the albumin excluded volume, assumed to represent 25\% of the normal interstitial fluid volume [Bert and Pinder, 1982].

c) Under normal conditions, fluid is assumed to flow from the interstitium into the lymphatic system. The fluid is then drained from the lymphatics into the circulation. It is assumed that the lymph flow rate is always positive. Lymph flow relationships have been developed for rats [Bert et al., 1988] and humans [Chapple, 1990] based on the assumption that lymph flow is a linear function of interstitial fluid pressure. A relationship similar to that adopted by Bert et al. [1988] is employed in the current model. The relationship ensures that lymph flow remains at its normal value under normal conditions, varies linearly with interstitial pressure near normal conditions but ceases when the interstitial fluid volume falls to the excluded volume value.

For overhydrated tissue when \( P_i \geq P_{i,ML} \),

\[
J_L = J_{L,ML} + LS \cdot [P_i - P_{i,ML}],
\]

4.4
during tissue dehydration when $P_{i,\text{EX}} \geq P_i > P_{i,\text{NL}},$

$$J_L = J_{L,\text{NL}} \cdot \left[ \frac{P_i - P_{i,\text{EX}}}{P_{i,\text{NL}} - P_{i,\text{EX}}} \right],$$

while under conditions where $P_i < P_{i,\text{EX}},$

$$J_L = 0.$$  \hspace{1cm} 4.5

$L_L$ represents the lymph flow, LS the lymph flow sensitivity coefficient which expresses the slope of the relationship, $P_{i,\text{EX}}$ the tissue pressure at the excluded volume, and subscript NL refers to normal steady-state conditions.

d) Albumin is also exchanged across the lymphatic wall according to

$$\dot{Q}_L = J_L \cdot c_i.$$  \hspace{1cm} 4.7

4.3 FLUID AND PROTEIN INPUT

Following burn injury, intravenous infusions of clear fluids such as acetated Ringers, normal saline and dextrose are administered in order to replace volume lost from the circulating plasma into the tissue compartments. Colloid-containing fluids are also administered to replace protein loss from the circulating plasma. Based on individual patient responses, the composition, volumes and infusion rate of fluids administered are adjusted accordingly. These inputs to the system are accounted for in the formulation of the model equations.

4.4 FLUID AND PROTEIN OUTPUT

Fluid and proteins are also lost from the system following burn injury. These losses must also be taken into account in developing the mass balances.
4.4.1 Water Loss by Evaporation

In a normal adult, the water loss through the skin excluding that lost as sweat is about 750 mL/day, as reported by Davies [1982]. The destruction of the stratum corneum and lipids in the skin following burn injury allows increased evaporation of water through the burn eschar. Water lost through burned skin via evaporation adds considerably to that normally lost through the lungs [Martyn, 1990]. The evaporative water loss from skin following burn injury may be estimated from the following formula reported by Sundell [1971],

\[ J_{\text{EVAP}} = [25 + \text{DEG}] \cdot \text{TBSA}, \]  

4.8

where \( J_{\text{EVAP}} \) is the rate of evaporative fluid loss from injured and uninjured tissue, DEG the percentage of body surface burned and TBSA the total body surface area in m², defined by

\[ \text{TBSA} = W^{0.425} \cdot H^{0.725} \cdot 71.84 \times 10^{-4}. \]  

4.9

In Equation 4.8, \( W \) and \( H \) represent the patient's preburn weight in kg and height in cm, respectively.

4.4.2 Fluid Loss by Exudation

Significant volumes of fluid are lost as exudate from the burned surfaces of the body of injured patients [Arturson et al., 1984; Davies, 1982]. Knowledge of the loss of sodium into dressings and soiled bed linen gives an indication of the volume of exudate. Exudation rates of between 400 and 1000 mL/day have been reported [Davies, 1982] for burns of up to 50% of the total body surface area.

In this study, estimates of fluid loss by exudation are made based on fluid balances on individual patients. The fluid balance is performed between successive times when measurements were available, i.e.,

\[ \text{Change in patient weight} = \text{Volume of fluids given} - \text{Volume of fluids lost} \]
The fluids given include clear fluids (acetated Ringers, normal saline, dextrose) and protein-containing fluids (iso-oncotic and hyperoncotic fluids as well as plasma). The fluids lost include urine, blood loss and evaporative and exudative fluid losses. The fluid loss due to exudation can be estimated from the balance knowing the changes in the other quantities between two successive times. The exudative fluid loss from patients for which weight changes were not monitored is estimated from a linear relationship between average exudate output and the area of burn injury. This relationship is obtained by linear regression of clinical data reported by Davies [1982]. The detailed calculations for each patient are presented in Appendices E and G.

4.4.3 Protein Loss via Exudate

Losses of labelled proteins in exudate have been measured by application of absorbent dressings to all burned areas and assay of radioactivity in the dressings after their removal [Davies, 1982]. The exudate losses are directly related to the extent of the burn. Between 5 and 10 g of albumin/day have been reported to be lost via exudate with burns covering between 25 and 35% of the body surface [Davies, 1962]. In patients with more severe burns, the equivalent of the albumin content of the normal adult plasma volume has been reported to be lost over the first week. Protein losses of at least 2 to 3 g of protein/1% of body surface burned/day up to 7 to 8 g/1% burn/day have also been reported [Davies, 1962]. The rate of albumin loss via exudate is assumed to be described by the following modified relationship proposed by Arturson et al. [1984],

\[ \dot{Q}_{\text{EXUD}} = J_{\text{EXUD}} \times c_{\text{BT}} \times \text{EXFAC}, \]

\[ \text{4.10} \]

where \( \dot{Q}_{\text{EXUD}} \) is the rate of albumin loss via exudate, EXFAC a factor ranging from 0 to 1 and subscript BT represents the injured tissue.
4.4.4 Blood Loss

Early excision and grafting of the burn wound as soon as the patient is hemodynamically stable, remain the keys to survival for patients with major thermal injuries. Surgical incisions in the form of escaratomies and fasciotomies are necessary to prevent edema from building up sufficient interstitial pressure to impair capillary blood flow, thus causing ischemia. Blood loss occurs as burn tissue is removed. The volume and rate of blood loss depend on the depth of the burn, the area excised and the clotting profile of the patient. Although rates vary between patients, blood losses of as high as 250 mL/min have been encountered [Martyn, 1990].

Data regarding initial volumes of blood lost due to surgical procedures were provided for some of the patients considered in the current study. The blood losses were clinical estimates based on the extent of escaratomies. In addition, 10 mL blood samples were assumed to be taken every 6 hours for laboratory analyses. In order to incorporate these blood losses in the model equations, the losses were assumed to occur over a period of time and expressed as blood loss per hour, $Q_{BLOOD}$.

4.5 MODEL EQUATIONS

The equations that describe the model are obtained by carrying out fluid and protein (albumin) balances around each compartment in Figure 4.1, i.e.,

Rate of Accumulation = Input Rate - Output Rate.

Uninjured Tissue Balances:

$$\frac{dV_{TI}}{dt} = J_{F,TI} - J_{L,TI} - J_{EVAP,TI}$$  \hspace{1cm} 4.11
Injured Tissue Balances:

\[
\frac{dQ_{BT}}{dt} = Q_{S,BT} - Q_{L,BT} - Q_{EXUD,BT}
\]

Circulatory Balances:

\[
\frac{dV_{PL}}{dt} = J_{RESUSC} - J_{F,LT} + J_{F,LT} - J_{F,BT} + J_{L,BT} - J_{URINE} - J_{BLOOD}
\]

\[
\frac{dQ_{PL}}{dt} = Q_{RESUSC} - Q_{S,LT} + Q_{S,LT} - Q_{S,BT} + Q_{L,BT} - Q_{BLOOD}
\]

The subscripts TI, BT and PL refer to the uninjured tissue, injured tissue and plasma compartments respectively. In Equations 4.15 and 4.16, \(J\) and \(\dot{Q}\) are the rates of fluid and albumin flow respectively, while the subscripts RESUSC, URINE and BLOOD represent the resuscitation fluids, urine and blood respectively.

4.6 PROPERTIES OF THE MICROVASCULAR EXCHANGE SYSTEM

A set of six ordinary differential equations result from these balances on fluid and albumin. In order to solve these equations the following properties are required:

i) hydrostatic pressure relationships for circulatory and tissue compartments (compliance or pressure versus volume relationships);

ii) colloid osmotic pressure relationships for circulatory and tissue compartments \(\Pi = fn(c)\); and

iii) transport coefficients.
Some of these properties experience changes from their normal values immediately following burn injury. In order to facilitate the quantitative analysis of these changes, the normal steady-state conditions and the initial conditions that prevail in the patient immediately postburn will first be presented.

4.6.1 Normal Steady-State Conditions

In order to establish reasonable values to describe the physiological conditions that exist in the average human, a "reference man" has been defined [Reference Man ICRP 23, 1975]. This "reference man" is described as a healthy male, 170 cm in height, 70 kg in weight and supine in position. These normal steady-state conditions in a combined tissue compartment and the general circulation are those employed by Xie [1992] and are summarized in Table 4.1.

Table 4.1: Normal Steady-State Conditions in "Reference Man"

<table>
<thead>
<tr>
<th></th>
<th>Tissue</th>
<th>Circulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid volume, $V$, L</td>
<td>8.4</td>
<td>3.2</td>
</tr>
<tr>
<td>Excluded volume, $V_{ex}$, L</td>
<td>2.1</td>
<td>-</td>
</tr>
<tr>
<td>Albumin content, $Q$, g</td>
<td>141.1</td>
<td>126.1</td>
</tr>
<tr>
<td>Albumin concentration, $c$, g/L</td>
<td>16.8</td>
<td>39.4</td>
</tr>
<tr>
<td>Available albumin concentration, $c_{AV}$, g/L</td>
<td>22.4</td>
<td>-</td>
</tr>
<tr>
<td>Hydrostatic pressure, $P$, mmHg</td>
<td>-0.7</td>
<td>11.0</td>
</tr>
<tr>
<td>Colloid osmotic pressure, $\Pi$, mmHg</td>
<td>14.7</td>
<td>25.9</td>
</tr>
</tbody>
</table>
In order to account for the fact that the patients considered in this study differ from the "reference man" in terms of weight, fluid volume and albumin content amongst many other properties, the extensive physiological properties are scaled by a weight ratio, WR, where

\[ WR = \frac{\text{Weight of Patient}}{\text{Weight of "Reference Man"}}. \]  

4.17

Albumin concentration, hydrostatic and colloid osmotic pressures in the interstitial fluid and plasma are intensive properties and therefore are unaffected by changes in patient weight.

4.6.2 Initial Conditions

The initial conditions are the conditions that prevail in the patient immediately prior to injury. Immediately postburn, the tissue compartment is divided into two separate compartments: the injured tissue and the uninjured tissue compartments as shown in Figure 4.1. The uninjured tissue compartment comprises unburned skin, muscle and all other tissues, while the injured tissue compartment is made up of only burned skin. Partition of body tissue in the two tissue compartments following injury is based on the interstitial fluid distribution in the "reference man" [Chapple, 1990] described in Appendix A.

Let RELSM be the fraction of the total body made up of skin and DEG be the degree of burn. The fraction of tissue burned is

\[ VAFBT = RELSM \times DEG. \]  

4.18

The fraction of tissue that remains uninjured is

\[ VAFTI = [RELSM \times (1-DEG)] + [1-RELSM] = 1-VAFBT. \]  

4.19

The extensive properties of the tissue must therefore be modified by the fraction of tissue in each compartment following the injury as follows:

Initial value = Weight corrected normal value \times VAFTI (or VAFBT).  

4.20
4.6.3 Compliance Relationships

Compliance relationships are essential for the determination of the hydrostatic pressure from the fluid volume in the compartments. The hydrostatic pressures in the compartments have important roles in redistributing fluid and albumin following a burn injury.

4.6.3.1 Circulatory Compliance

Due to lack of data from humans, the exact circulatory compliance relationship is not as yet established. As a consequence, a linear relationship is assumed between the capillary hydrostatic pressure and plasma volume, where the rate of the change in plasma volume to the change in capillary hydrostatic pressure is constant, i.e.,

$$P_c = P_{c,0} + \frac{1}{C_{COMP}} \cdot [V_{pl} - V_{pl,0}],$$

where $P_{c,COMP}$ is the reciprocal of circulatory compliance and subscript O refers to initial conditions. $P_{c,COMP}$ has not been measured in humans. An estimate based on scaling up values reported for the rat [Bert et al., 1989] yields $P_{c,COMP} = 0.009659 \text{ mmHg/mL}$.

4.6.3.2 Interstitial Compliance

Information concerning the compliance of human tissues is scarce. Based on the studies of Reed and Wiig on rat tissues [1981] and Stranden and Myhre on human lower limb subcutaneous tissue [1982], Chapple [1990] developed the following "most-likely" compliance relationships for humans.

Under conditions of dehydration where $V_i \leq 8.4 \times 10^3 \text{ mL}$,

$$P_i = -0.7 + 1.96154 \times 10^{-3} \cdot [V_i - 8.4 \times 10^3],$$

while during conditions of tissue overhydration where $V_i \geq 12.6 \times 10^3 \text{ mL}$,

$$P_i = 1.88 + 1.05 \times 10^{-4} \cdot [V_i - 1.26 \times 10^4].$$

In the intermediate range, the compliance relationship is obtained by interpolating experimental $P_i$ and $V_i$ data by means of cubic splines.
Following burn injury, the interstitial compliance in uninjured and injured tissue is modified to account for the partition of tissue in each of the compartments.

**Uninjured Tissue:**

During tissue dehydration where $V_T \leq (8.4 \times 10^3 \times WR \times VAFTI)$ mL,

$$P_T = -0.7 + \frac{1.96154 \times 10^{-3}}{VAFTI \times WR} \left[ V_T - (8.4 \times 10^3 \times WR \times VAFTI) \right].$$  \hfill (4.24)

During tissue overhydration where $V_T \geq (12.6 \times 10^3 \times WR \times VAFTI)$ mL,

$$P_T = 1.88 + \frac{1.05 \times 10^{-4}}{VAFTI \times WR} \left[ V_T - (12.6 \times 10^3 \times WR \times VAFTI) \right].$$  \hfill (4.25)

For intermediate values of $V_T$, the compliance relationship is obtained by cubic spline interpolation of pressure and volume data for normal humans, with the volume data modified by $(WR \times VAFTI)$ to account for tissue partition, i.e.,

$$P_T = fn[V \times WR \times VAFTI].$$  \hfill (4.26)

Additional relationships are required for the injured tissue compartment to account for the very negative tissue pressure which has been observed in the burned skin of rats immediately postburn [Lund et al., 1988]. Due to lack of data from humans, pressure data from these experiments on rats are used to describe the change in interstitial pressure with time in the first 2.5 hours postburn. Data from unresuscitated rats is used in the initial period postburn when no form of fluid treatment is given to the patient. Following this initial period up to 2.5 hours postburn when data is available, data from resuscitated rats is used. After 2.5 hours, modified forms of the normal interstitial compliance relationships given above are employed.
Injured Tissue:

During the first 2.5 hours postburn, interstitial fluid pressure in injured skin versus time data from experiments on both unresuscitated and resuscitated rats by Lund et al. [1988] are interpolated by cubic splines according to the general relation

\[ P_{BT} = fn(t) \].

Following this initial 2.5 hour period, the compliance relationships are based on the relationships developed for normal humans, with modifications to account for the injury, i.e.,

during tissue dehydration where \( V_{BT} \leq (8.4 \times 10^3 \times WR \times VAFBT) \) mL,

\[
P_{BT} = -0.7 + \frac{1.96154 \times 10^{-3}}{VAFBT \times WR} \left[ V_{BT} - (8.4 \times 10^3 \times WR \times VAFBT) \right]
\]

and during tissue overhydration where \( V_{BT} \geq (12.6 \times 10^3 \times WR \times VAFBT) \) mL,

\[
P_{BT} = 1.88 + \frac{1.05 \times 10^{-4}}{VAFBT \times WR} \left[ V_{BT} - (12.6 \times 10^3 \times WR \times VAFBT) \right].
\]

For intermediate values of \( V_{BT} \), the compliance relationship is again determined by passing cubic splines through the interstitial pressure and volume data for normal humans, with the volume data modified by \((WR \times VAFBT)\), i.e.,

\[ P_{BT} = fn[V \times WR \times VAFBT]. \]

4.6.4 Colloid Osmotic Pressure (COP) Relationships

Colloid osmotic pressure results because the protein molecules cannot transfer freely through the semi-permeable capillary membrane. The following relationship between plasma albumin concentration and COP was determined by least squares fitting of data from the circulatory compartment of patients with nephrotic syndrome by Chapple [1990]:

\[ c_{PL} = 1.522 \times 10^{-3} \cdot \Pi_{PL}. \]

This relationship is assumed applicable to the plasma compartment following burn injury. The proteins contained in interstitial fluid are the same as those in plasma. Assuming that
the osmotic pressure exerted by the plasma proteins in plasma is the same as that exerted by proteins in interstitial fluid, similar relationships are applied to the interstitial compartments following burn injury.

Thus, for uninjured tissue,

$$c_{TI, AV} = 1.522 \times 10^{-3} \cdot \Pi_{TI}$$

and for injured tissue,

$$c_{BT, AV} = 1.522 \times 10^{-3} \cdot \Pi_{BT}$$

The effective albumin concentration is used in Equations 4.32 and 4.33, since albumin is excluded from some of the tissue space.

4.6.5 Transport Coefficients

The transcapillary fluid and protein fluxes depend on the following five transport coefficients:

i) fluid filtration coefficient, \( k_F \), reflects the hydraulic conductivity of the capillary membrane;

ii) permeability coefficient, \( PS \), expresses the permeability of the capillary membrane to albumin;

iii) albumin reflection coefficient, \( \sigma \), reflects the relative impediment of this membrane to the passage of albumin;

iv) lymph flowrate under normal steady-state conditions, \( J_{L,NL} \); and

v) lymph flow sensitivity, \( LS \), characterizes the efficiency of the lymphatic system in removing accumulated interstitial fluid.

Following burn injury, the transient response of these transport coefficients is generally expressed as an exponential function of time postburn. Based on the work of Arturson et al. [1984], Bert et al. [1989] proposed the form:
\[ kA = k_{NL} \cdot A_{NL} \cdot \left[ 1 + G \cdot e^{-\tau} \right], \quad 4.34 \]

where \( kA \) represents the overall transport coefficient, \( k_{NL} \) the normal or preburn value of the time-dependent coefficient per unit area, \( A \) the surface area available for exchange, \( G \) the perturbation to the transport coefficient immediately postburn and \( r \) the relaxation coefficient, indicating the time required for the transport coefficient to return to normal. The form of Equation 4.34 allows the transport coefficient values to return to normal after a long period of time, i.e., as the patient's wounds heal.

The transport coefficient is the product of an area available for exchange term and a conductivity per unit area term, as in previous studies in the injured rat [Bert et al., 1989]. It is assumed that, as the plasma volume changes, there is a proportional change in the area available for mass exchange in the tissues. In addition, it is assumed that burn causes a fractional destruction of the capillary beds in the injured tissue, further reducing the area available for mass transport in this tissue. Consequently, in the uninjured tissue which is made up of unburned skin, muscle and other tissues in the body, the overall transport coefficient, \( kA_{TI} \) becomes

\[ kA_{TI} = k_{NL} \cdot \left[ FA_{TI} \times VAFTI \times WR \right] \cdot \left[ 1 + G_{TI} \cdot e^{-\tau} \right] \quad 4.35 \]

and the overall transport coefficient in the injured tissue, \( kA_{BT} \) becomes

\[ kA_{BT} = k_{NL} \cdot \left[ FA_{BT} \times VAFBT \times WR \right] \cdot \left[ 1 + G_{BT} \cdot e^{-\tau} \right] \quad 4.36 \]

where \( FA_{TI} \) is the fractional area available for exchange in the uninjured tissue, which changes with changing plasma volume, and is given by

\[ FA_{TI} = \frac{V_{pl}}{V_{pl0}} \cdot \frac{\text{VFRAC}}{1 - \text{VFRAC}} \quad 4.37 \]

and \( FA_{BT} \) is the fractional area available for exchange in the injured tissue, given by
FABT = \left[ \frac{V_{PL}}{V_{RL0}} \cdot \frac{-VFRAC}{1-VFRAC} \right] \cdot AFRAC. \quad 4.38

VFRAC is the fractional plasma volume at which perfusion in tissues is zero and AFRAC is the fractional perfusion in injured tissue immediately following a burn injury. Bert et al. [1991], determined values for VFRAC and AFRAC by statistical fitting of model predictions to experimental data from rats. They found values that produced good fits were VFRAC = 0.50 and AFRAC = 0.50. These values were also used in the current study.

The Fluid Filtration Coefficient, $k_F$, depends on the area available for exchange and hence in uninjured tissue becomes

$$k_{F,TI} = k_{F,NL} \cdot [FA_{TI} \times VAFTI \times WR] \cdot [1 + G_{kF,TI} \cdot e^{-\sigma}] , \quad 4.39$$

while in injured tissue,

$$k_{F,BT} = k_{F,NL} \cdot [FA_{BT} \times VAFBT \times WR] \cdot [1 + G_{kF,BT} \cdot e^{-\sigma}] . \quad 4.40$$

The Permeability Coefficient, $PS$, also depends on the area available for exchange and thus in uninjured tissue is

$$PS_{TI} = PS_{NL} \cdot [FA_{TI} \times VAFTI \times WR] \cdot [1 + G_{PS,TI} \cdot e^{-\sigma}] , \quad 4.41$$

and in injured tissue,

$$PS_{BT} = PS_{NL} \cdot [FA_{BT} \times VAFBT \times WR] \cdot [1 + G_{PS,BT} \cdot e^{-\sigma}] . \quad 4.42$$

The Albumin Reflection Coefficient, $\sigma$, does not depend on the available area for exchange as it indicates the relative impediment to the passage of albumin through the capillary membrane. In addition, the perturbation to $\sigma$ is negative as this coefficient has
been found to decrease rather than increase following burn injury [Pitt et al., 1987]. Thus, in uninjured tissue, it is assumed that
\[
\sigma_{TI} = \sigma_{NL} \cdot [1 - G_{\sigma,TI} \cdot e^{-\eta}],
\]
while in injured tissue,
\[
\sigma_{BT} = \sigma_{NL} \cdot [1 - G_{\sigma,BT} \cdot e^{-\eta}].
\]

The *Lymph Flowrate under normal steady-state conditions*, \(J_{L,NL,TI}\), does not depend on the fractional area available for exchange which changes with plasma volume. It does however, depend on the fractional destruction of the capillary beds in the injured tissue. Thus, in uninjured tissue, \(J_{L,NL,TI}\) is given by
\[
J_{L,NL,TI} = J_{L,NL} \cdot [VAFTI \times WR] \cdot [1 + G_{JL,NL,TI} \cdot e^{-\eta}],
\]
while for injured tissue,
\[
J_{L,NL,BT} = J_{L,NL} \cdot [AFRAC \times VAFBT \times WR] \cdot [1 + G_{JL,NL,BT} \cdot e^{-\eta}].
\]

The *Lymph Flow Sensitivity Coefficient*, \(LS\), also depends only on the fractional destruction of the capillary beds in the injured tissue. Consequently, in uninjured tissue, \(LS_{TI}\) is given by
\[
LS_{TI} = LS_{NL} \cdot [VAFTI \times WR] \cdot [1 + G_{LS,TI} \cdot e^{-\eta}],
\]
while for injured tissue,
\[
LS_{BT} = LS_{NL} \cdot [AFRAC \times VAFBT \times WR] \cdot [1 + G_{LS,BT} \cdot e^{-\eta}].
\]

The normal values for these transport coefficients have been determined for the "reference man" by Xie [1992] (see Appendix B.1). The capillary membrane parameters that determine the exchange of albumin are \(k_F\), \(\sigma\) and \(PS\). These individual transport coefficients are not independent, but are linked to each other via changes in the capillary pore radius. Thus, once the perturbation to \(k_F\) is known for the injured and uninjured
tissue, the perturbations to $\sigma$ and PS for both tissues may be estimated based on these interrelationships (see Appendix B.2). Current knowledge regarding changes in the lymphatic system following thermal injury is very limited. Consequently, the perturbations to $J_{L,NL}$ and LS in the injured and uninjured tissue postburn are assumed to be zero.

4.7 NUMERICAL SOLUTION OF MODEL EQUATIONS

For given patient data (degree of burn, weight and height of patient) and resuscitation protocol (fluid and protein input), simulation of the MVES following injury involves solving the six first-order ordinary differential equations (Equations 4.11 - 4.16), arising from the fluid and albumin balances. These differential equations must be solved simultaneously with the relationships defining interstitial and plasma hydrostatic and colloid osmotic pressures as well as the other auxiliary equations. Due to the nonlinearity of some of these relationships, the differential equations cannot be solved analytically. Consequently, the classic fourth-order Runge-Kutta numerical integration method is used to solve the equations, with a global accuracy of 0.001 mL and 0.001 mg for fluid and albumin contents respectively. The computer program is documented in Appendix K.
Chapter 5: Parameter Estimation

CHAPTER 5

PARAMETER ESTIMATION

5.1 INTRODUCTION

The model equations developed in Chapter 4 contain unknown parameters which need to be determined in order to simulate the behaviour of the microvascular exchange system following a burn injury. In the first part of this chapter, the parameters to be determined are presented. This is followed by a description of the clinical data used for the identification of the parameters and the validation of the model. Finally, the optimization procedure is discussed.

5.2 PARAMETERS TO BE DETERMINED

The transcapillary fluid and protein fluxes depend on five transport coefficients: the fluid filtration coefficient, \( k_F \), permeability coefficient, \( PS \), albumin reflection coefficient, \( \sigma \), lymph flowrate under normal steady-state conditions, \( J_{LNL} \) and lymph flow sensitivity coefficient, \( LS \). The transient response of these transport coefficients to burn injury is expressed as an exponential function of time postburn as described in Chapter 4. In general, the time-dependent transport coefficients have the form:

\[
kA = k_{NL} \cdot A_{NL} \cdot [1 + G \cdot e^{-\eta}].
\]

The unknown parameters identified from the above relationship include the perturbations to the transport coefficients in both the injured and uninjured tissues and the relaxation coefficient as follows:
i) perturbation to the fluid filtration coefficient: $G_{kF, Ti}$, $G_{kF, BT}$ (in Equations 4.39 and 4.40);

ii) perturbation to the permeability coefficient: $G_{PS, Ti}$, $G_{PS, BT}$ (in Equations 4.41 and 4.42);

iii) perturbation to the albumin reflection coefficient: $G_{\sigma, Ti}$, $G_{\sigma, BT}$ (in Equations 4.43 and 4.44);

iv) perturbation to the lymph flowrate: $G_{jL, NI, Ti}$, $G_{jL, NI, BT}$ (in Equations 4.45 and 4.46);

v) perturbation to the lymph flow sensitivity: $G_{LS, Ti}$, $G_{LS, BT}$ (in Equations 4.47 and 4.48); and the

vi) relaxation coefficient: $r$.

The factor, EXFAC, in Equation 4.10 describing the protein loss via exudate was estimated by Arturson et al. [1984] to be one fourth of the proteins originally associated with the exuded fluid. Fluid loss due to exudation has been reported by Davies [1982] to account for 5 to 10 g of albumin per day when the burn covers between 25 and 35% of the body surface. Protein losses in exudate from the burn wound are therefore significant and contribute to a decrease in albumin concentration observed during the early phase postburn. The basis for the estimation of EXFAC by Arturson et al. is unclear and as such, EXFAC was also considered as an unknown parameter to be determined.

The capillary membrane parameters which determine the exchange of albumin are $k_F$, $\sigma$ and PS. As discussed in Appendix B.2, these transport parameters are not independent, but are linked to each other via changes in the capillary pore radius. Based on relationships reported by Reed et al. [1991], the perturbations to the albumin reflection coefficient and permeability coefficient in injured and uninjured tissues can be determined from the values of the perturbations to the filtration coefficient in both tissues, $G_{kF, Ti}$ and $G_{kF, BT}$. The
mathematical manipulations are presented in Appendix B.2. $G_{NL,TI}$, $G_{NL,BT}$, $G_{LS,TL}$ and $G_{LS,BT}$ are assumed to be equal to zero due to the lack of information concerning changes to the lymphatics following injury. In the final analysis, only four parameters remained to be determined, namely $G_{k,T}$, $G_{k,B}$, $r$ and $EXFAC$.

5.3 CLINICAL DATA

The most common measurements made to monitor burn patient conditions include venous hematocrit and plasma protein or albumin concentration. The response of the patient to fluid replacement is also monitored through the hourly production of urine, vital signs, plasma electrolyte concentrations such as sodium, potassium or chloride ions, and the value of hematocrit. Other measurements including central venous and arterial pressures are also made when the state of the patient requires it. Four different sets of clinical data were used in this study for parameter estimation or model validation. These are presented below.

5.3.1 National Burn Centre (NBC) Data

Dr. T. Lund and his colleagues working at the National Burn Centre in Norway, kindly provided specific information for five patients admitted to the Burn Centre, who had suffered deep cutaneous burns. This patient information was unique in that, in addition to the most commonly made measurements mentioned in the previous section, they also measured the transcapillary colloid osmotic pressures (COPs) in injured and non-injured skin of these seriously burned patients. The raw data were manipulated to convert them into a form that could be used in this study. The manipulations included the determination of plasma volume from hematocrit and the estimation of exudative fluid loss from the burn wound by fluid balances. These are detailed in Appendices D and E respectively. The final form of the patient data and the individual resuscitation protocols are also presented in
Appendix C. This patient information was used directly in the parameter estimation procedure.

5.3.2. Birkeland Data

Dr. Birkeland, in a collection of articles published in the Journal of the Oslo City Hospitals [1969], reported results from a study of over 100 patients. The burn patients were grouped according to the percentage burn surface area sustained and were observed prior to start of replacement therapy. Data of direct interest in the current study were the plasma volume changes in five groups of burn patients as presented in Appendix F. These data were especially useful for investigating the response of the microvascular exchange system during the initial period postburn, when no form of fluid therapy was administered. As such, it was also used directly in the parameter estimation procedure.

Due to lack of information concerning urine production, it was assumed that the kidneys shut down in the initial period postinjury. In addition, due to the unavailability of specific admission information concerning the weight and height of the patients studied, standard weights and heights of 70-kg and 170-cm respectively were assumed. The normal steady-state conditions in each of the patients were also assumed to be those in the reference man which are presented in Table 4.1. Exudative fluid losses were estimated based on data available from a study by Davies [1982]. The rate of exudative fluid loss from patients with different burn areas was monitored during the initial period postburn before fluid therapy was initiated. To the best of the author's knowledge, these were the only suitable data that could be used to estimate the initial exudative fluid loss from the patients studied by Birkeland. The details of this estimation are presented in Appendix G.
5.3.3. Arturson Data

Published information by Dr. Arturson and his colleagues in Sweden [1989] concerning the treatment of a patient with thermal injury was used to validate the predictions of the model developed in this study. The monitored physiological variable of direct application to the current study was the erythrocyte volume fraction or hematocrit. The patient data and the fluid resuscitation protocol are presented in Appendix H. Based on the fluid therapy, cumulative urine production and change in body mass information, it was possible to estimate exudative fluid loss by fluid balances as described in Appendix E.

5.3.4. Roa Data

Dr. Roa and her colleagues in Spain have also been actively involved in the development of mathematical models to investigate microvascular exchange in burn patients. The treatment of two burn patients and clinical data collected from these patients were presented in a publication by this group [1990]. This information, together with information provided by Dr. Roa through personal communications were also used to independently validate the predictions of the model developed in this study. The relevant information including the resuscitation protocol, urine volume, hematocrit and plasma protein concentration is presented in Appendix I.

5.3.5. Normalization of Data

The four different data sets described previously consist of one or more of the following quantities: plasma volume, $V_{PL}$, albumin concentration in plasma, $c_{PL}$ and colloid osmotic pressures (COPs) in plasma, injured and uninjured tissues, $\Pi_{PL}$, $\Pi_{PT}$ and $\Pi_{TI}$ respectively. In order to make these quantities comparable so that they could be used collectively in the parameter estimation procedure, it was first necessary to normalize them. The plasma volumes and albumin concentrations were normalized with respect to their preburn values.
Chapter 5: Parameter Estimation

based on normal steady-state values for the reference man, scaled to account for differing preburn weights where appropriate, i.e.,

\[ X = \frac{X_t}{X_o} \text{,} \tag{5.1} \]

where \( X \) refers to the measured physiological quantity and subscripts \( O \) and \( t \) refer to the preburn and postburn times, respectively.

The availability of COP data made it possible to investigate the distribution of protein in plasma and the injured and uninjured tissue compartments. However, there appears to have been a systematic error in the COP measurements made by Lund et al. The measured values were lower than what were generally expected. In order to use these data, the injured and uninjured tissue COPs were normalized with respect to the plasma COP to nullify the effect of the systematic errors in the measurements, i.e.,

\[ X = \frac{\frac{\Pi_t}{\Pi_{PL,t}}}{\frac{\Pi_o}{\Pi_{PL,O}}} \text{.} \tag{5.2} \]

5.4 PARAMETER ESTIMATION PROCEDURE

The proposed method to determine the identified model parameters was based on the fitting of predicted results from the model to clinical data. The adopted procedure entailed finding the parameters which gave the best statistical fit between the model predictions and the clinical data based on the weighted least-squares criterion. The optimum parameters were those which would minimize an objective function, OBJFUN, which is the sum of the squares of the deviations of the normalized clinical data from the predicted values, i.e.,
\[
OBJFUN = \sum_{i=1}^{N} \sum_{j=1}^{M} WF_{i,j} \left( X_{\text{EXP}_{i,j}} - X_{\text{PRED}_{i,j}} \right)^2,
\]

where \( N \) represents the number of data points for the \( i \)th variable, \( M \) the number of variables monitored, \( X_{\text{EXP}_{i,j}} \) the experimental or clinical value, and \( X_{\text{PRED}_{i,j}} \) the predicted value from the simulation and \( WF_{i,j} \) is the weight for each data point.

In order to indicate the significance or relative importance attached to each data point within a data set, each point was assigned a weighting factor, \( WF \). Normally, \( WF \) is set equal to the inverse of the error in measurement (or the standard deviation squared) of each data point. Due to the unavailability of information concerning the experimental errors involved in the clinical measurements, it was not possible to assign weighting factors to the data in this manner. As a result, each data point was weighted equally by assigning a weight of unity to each point.

A standard constrained optimization technique was selected to estimate the unknown parameters by finding the minimum of the nonlinear objective function, subject to constraints, if any. This technique is a slightly modified version of K. Schittkowski's implementation of the recursive quadratic approximation method of Wilson, Han and Powell [1981].

5.4.1 Preliminary Tests

The model was tested by performing a simulation with assumed, but physiologically reasonable values of the four parameters, \( G_{kF,Ti} \), \( G_{kF,BT} \), \( r \) and \( \text{EXFAC} \). Predictions of the response of one of the NBC Patients to fluid therapy are presented in Figure 5.1. Patient 1, a 30-year old male who sustained a 21% burn surface area injury, was treated according to the fluid resuscitation protocol presented in Table C.2. The trends predicted by the model
Figure 5.1: Simulation of MVES for NBC Patient 1
GKFTI=0.5; GKFBT=10.0; r=0.025 /h; EXFAC=1.00
were in agreement with trends observed clinically. Following burn injury, fluid is lost from the burn wound due to exudation and evaporation and protein is also lost via exudate. However, immediately postburn and prior to the start of fluid therapy, large amounts of fluid and protein are transferred to the injured tissue from the circulating plasma. This results in edema formation as well as a considerable increase in the albumin content in the injured tissue compartment. The circulating plasma experiences a loss in fluid volume and protein content due to the increased rate of transfer into the injured tissue. The uninjured tissue compartment experiences a loss in fluid volume, resulting in an increase in albumin concentration. Fluid resuscitation is started one hour after injury and soon afterwards, the decrease in plasma volume is reversed, increasing towards its normal volume of about 4023 mL. The injured tissue however, continues to increase in its fluid volume but starts to resolve after about 1.5 days. The uninjured tissue responds to the fluid therapy almost immediately and becomes swollen, but to a lesser extent than the injured tissue. After 1.5 days, the uninjured tissue volume starts decreasing towards its normal volume of about 630 mL. The albumin concentration in plasma continues to decrease during the first day following fluid resuscitation but then starts to increase in the second day. A detailed discussion of these trends will be presented in Chapter 6. These initial results confirmed the adequacy of the model to describe the phenomena which occur in the MVES following burn injury. A steady-state simulation was also performed by solving the model equations over a long period of 480 hours (20 days). The results are shown in Figure 5.2. The most important observation was the ability of the model to predict the return of the system variables to their normal values after a long period. The model was also able to predict the equalization of the opposing fluid and protein fluxes in the injured and non-injured tissues in the steady state. This further confirmed the ability of the model to correctly predict the response of the microvascular exchange system to burn injury. As such, the model could be confidently used in the parameter estimation algorithm.
Figure 5.2: Steady-State Simulation of MVES for NBC Patient I

\(GKFTI=0.5; \ GKFBLT=10.0; \ r=0.025/\text{h}; \ EXFAC=1.00\)
The optimization technique was also tested in two ways. Plasma volume and albumin concentration as well as plasma, injured and uninjured tissue COP data were generated by simulating the response of NBC Patient 1 to fluid therapy with assumed values of $G_{k,F,TI}$, $G_{k,F,BT}$, $r$ and EXFAC. In the first test, these "error-free" data were used in estimating the model parameters which were assumed unknown. The optimization technique required that initial values for the parameters be provided from which the search for the optimum values could begin. The optimizer successfully identified the parameter values used to generate the "error-free" data set, irrespective of the initial values provided to initiate the search. For example, the "error-free" data set was generated using the following parameter values: $G_{k,F,TI} = 0.50$; $G_{k,F,BT} = 10.0$; $r = 0.025$ h$^{-1}$ and EXFAC = 1.00. These data were then used in the optimization program to obtain "best-fit" values for $G_{k,F,TI}$ and $G_{k,F,BT}$ starting with initial estimates of 1.0 and 15.0 respectively. Optimum values and confidence intervals estimated for $G_{k,F,TI}$ and $G_{k,F,BT}$ were $0.37\pm0.30$ and $11.2\pm2.3$ respectively. The expected good fits between the clinical data and the model predicted responses are illustrated in Figure 5.3. The optimization procedure was then repeated using perturbed data values obtained by generating random errors on the "error-free" data. The optimizer identified the following optimum parameter values and confidence intervals: $G_{k,F,TI} = 0.70\pm0.31$ and $G_{k,F,BT} = 11.5\pm3.2$. The clinical data and the model predicted responses are shown in Figure 5.4. It was observed however, that using the "noisy" data, as the number of parameters to be determined increased to include $r$ and EXFAC, the optimizer was unable to identify the expected optimum values.

Following on from these tests, the optimization technique was next used to determine parameter values based on the clinical data obtained from the NBC patients. Different initial estimates were provided to the program from which the search for the optimum values could begin. The optimizer was unsuccessful in determining global optimum values for all the parameters. Different "optimum" values were obtained from the routine
Figure 5.3: Model Predicted Response of MVES and "Error-free" Data for NBC Patient 1
Figure 5.4: Model Predicted Response of MVES and "Noisy" Data for NBC Patient 1
depending on the initial values specified. Ideally, the initial values should be as close to the
global optimum values as possible to reduce the chances of encountering local optima and
of false convergence. The results therefore suggested that the "multi-dimensional surface"
of the objective function had several saddle-points or shallow depressions. The nature of
this objective function surface for Patient 1 is shown in Figure 5.5.

The results from this preliminary study suggested the need to:

i) introduce constraints to ensure physiologically feasible predictions by the model;
ii) develop a more appropriate optimization scheme;
iii) further scrutinize the patient data; and
iv) re-assess the parameters to be determined by the statistical procedure.

5.4.2 Constraints

Simulation predictions based on parameters determined from the preliminary studies using
the real patient data indicated that certain trends predicted were either not physiologically
feasible or were not consistent with clinical observations. Consequently, constraints were
imposed such that:

i) $G_{kF,\text{BT}}$ is always greater than $G_{kF,\text{TI}}$ due to the fact that following injury, it is
    observed that the injured tissue undergoes relatively larger changes than the
    uninjured tissue; and

ii) the injured tissue volume at any time postburn, $V_{\text{BT}}$, is always greater than its
    initial volume, $V_{\text{BT,O}}$. This ensures that the injured tissue compartment is not
dehydrated at any time postburn, in accordance with clinical observations.
Figure 5.5: Objective Function Surface for NBC Patient 1

$GKFTI = 0.5; GKFBT = 10.0; r = 0.025\, /h; EXFAC = 1.0$

(The shallow depressions represent local minima)
5.4.3 Modified Optimization Strategy

5.4.3.1 Re-assessment of Parameters to be Determined

Analysis of the clinical data used in the optimization procedure revealed that the quality and in particular, the quantity of the data did not justify estimating all four parameters, $G_{k_F, TI}$, $G_{k_F, BT}$, $r$ and EXFAC by statistical fitting. Consequently, it was proposed that $G_{k_F, TI}$ and $G_{k_F, BT}$ be determined by the fitting procedure, while $r$ and EXFAC were investigated only at discrete values.

*Relaxation Coefficient, $r$.* Information concerning the time it takes for the transport coefficients to return to normal is sparse. Bert et al. in their studies concerned with rats [1989] assumed that the transport coefficients approximately return to their normal values after about 12 hours. Due to the larger body size of humans as compared to rats, a longer response time would be anticipated. Arturson et al. [1984] assumed that normal plasma leakage occurs after about 70 hours postburn in the case of local edema. Roa et al. [1988] reported that the capillary permeability coefficient in burned tissue returns to its normal value in between 48 and 72 hours postinjury. In the current study, two values of $r$ were considered, 0.025 h$^{-1}$ and 0.008 h$^{-1}$, suggesting that the transport coefficients return to 95% of their normal values in 5 and 15 days respectively.

*Exudation Factor, EXFAC.* The exudation factor, which is the fraction of protein in the injured tissue interstitial fluid which is lost with the exudate, must range from 0 to 1. In determining the optimum value, four values of EXFAC were considered: 0.25, 0.50, 0.75 and 1.00.

With these redefined search levels for $r$ and EXFAC, the strategy of the parameter estimation procedure was to determine the pair of values of $G_{k_F, TI}$ and $G_{k_F, BT}$ which gave
the minimum objective function for each of the eight possible combinations of \( r \) and EXFAC in the experimental design shown in Table 5.1. The optimum \( G_{kF,TI} \) and \( G_{kF,BT} \) for a given patient were then determined as the pair which yielded the minimum objective function amongst the eight combinations of \( r \) and EXFAC.

5.4.3.2 Optimization Scheme: "Gridding Approach"

It was also evident from the initial tests that the quality and quantity of clinical data available did not warrant a formal optimization technique. As such, an approach was devised to ensure that global optima as opposed to local optima, were obtained. This approach was based on a "surface gridding" technique described below.

Table 5.1: Factorial Experiment Study

<table>
<thead>
<tr>
<th>EXFAC</th>
<th>0.25</th>
<th>0.50</th>
<th>0.75</th>
<th>1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>( r )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.008</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>0.025</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

The major steps in the search method were as follows:

i) Select wide ranges for \( G_{kF,TI} \) and \( G_{kF,BT} \) which are physiologically acceptable and within which the optimum values can be located. Ranges of 0 - 10 and 0 - 100 were selected for \( G_{kF,TI} \) and \( G_{kF,BT} \) respectively.

ii) Divide the ranges of \( G_{kF,TI} \) and \( G_{kF,BT} \) with variable step sizes to form a coarse grid: step sizes of 1.0 and 10.0 for \( G_{kF,TI} \) and \( G_{kF,BT} \) respectively.
iii) Determine the objective function for all the nodes ($G_{kF,TI}$, $G_{kF,BT}$) in the grid, which satisfy the conditions that $G_{kF,TI} < G_{kF,BT}$ and $V_{BT} > V_{BT,O}$. This resulted in a surface with several depressions or minima.

iv) Select a narrower range of values for $G_{kF,TI}$ and $G_{kF,BT}$ which contains the shallowest depression.

v) Construct a finer grid by subdividing the narrow ranges with smaller step sizes.

vi) For all the grid nodes which satisfy the constraints $G_{kF,TI} < G_{kF,BT}$ and $V_{BT} > V_{BT,O}$, calculate the objective function values. This resulted in a surface with a single depression.

vii) The pair of values of $G_{kF,TI}$ and $G_{kF,BT}$ corresponding to the shallowest point is considered the optimum.

Using this successive gridding process, a well defined single depression was obtained in all the cases considered in the current study. For each burn patient or group, the search scheme was applied to each of the eight combinations of $r$ and EXFAC in the factorial design shown in Table 5.1. The optimum values for a given patient or group were considered to be those corresponding to the minimum objective function for values amongst the eight cases.

5.5 SUMMARY

In summary, a simple but reliable method was developed to determine the model parameters. The method ensured that the selection of the optimum parameters was based on the global minima as opposed to local minima. The model parameters determined using this method and the model validation are discussed in Chapter 6.
CHAPTER 6

RESULTS AND DISCUSSION

6.1 INTRODUCTION

Simulation of the response of the human microvascular exchange system (MVES) to fluid resuscitation following thermal injury is only feasible if all the model parameters are known. Based on the procedure discussed in Chapter 5, it was possible to determine the model parameters required to fully describe the model. The parameters obtained using the National Burn Centre (NBC) and Birkeland data sets independently are first presented followed by a discussion of the global parameters obtained using a combination of the two data sets. A description of sensitivity tests conducted to investigate the influence of these global parameters on the model predictions is then presented. Using the global parameters, the ability of the model to satisfactorily predict the response of patients monitored in other independent studies is examined. As this latter patient information was not used in the parameter estimation procedure, this constitutes independent validation of the model. Finally, the model is used to predict patient response to three commonly used resuscitation formulae.

6.2 ESTIMATED PARAMETERS

6.2.1 Parameters Determined Using NBC Data

The objective function value (OBJFUN) described in Chapter 5 was estimated using plasma volume, albumin concentration and colloid osmotic pressure data from five patients receiving various forms of fluid therapy. For each patient, the values of $G_{kF,T1}$ and
GBT which gave the minimum objective function value for all eight combinations of \( r \) and EXFAC were determined. The results are presented in Appendix J. The four parameters, \( G_{kF,TI} \), \( G_{kF,BT} \), \( r \) and EXFAC, which gave the minimum objective function value were considered the optimum for each patient. These patient results are presented in Table 6.1.

Table 6.1: Optimum Parameters Determined Using NBC Data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Degree, %</th>
<th>( G_{kF,TI} )</th>
<th>( G_{kF,BT} )</th>
<th>( r ), h(^{-1} )</th>
<th>EXFAC</th>
<th>OBJFUN</th>
<th>NEXP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21</td>
<td>0.0</td>
<td>8.0</td>
<td>0.025</td>
<td>1.0</td>
<td>0.48</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>51</td>
<td>0.5</td>
<td>4.0</td>
<td>0.025</td>
<td>1.0</td>
<td>1.63</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>0.0</td>
<td>6.0</td>
<td>0.025</td>
<td>1.0</td>
<td>3.65</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>59</td>
<td>1.0</td>
<td>5.0</td>
<td>0.025</td>
<td>1.0</td>
<td>2.83</td>
<td>21</td>
</tr>
<tr>
<td>5</td>
<td>72</td>
<td>0.5</td>
<td>5.0</td>
<td>0.025</td>
<td>0.75</td>
<td>3.75</td>
<td>30</td>
</tr>
</tbody>
</table>

Clinical observations [Arturson, 1961; Lund et al., 1992] indicate that burns which exceed 25% of the total body surface area initiate both systemic and localized changes which differ from burns less than 25%. Burns less than 25% of the total body surface area generally cause smaller changes in the uninjured tissue as compared to burns exceeding 25%. Generalized edema has been observed [Arturson, 1961] when the extent of the burned tissue is greater than 25% of the total body surface area. Consequently, the five NBC patients were separated into two groups: less than 25% and greater than 25% of the total body surface area. Patient 1 was the only patient with a less than 25% burn. The remaining four patients sustained burns greater than 25%. The combination of the four parameters which gave the minimum objective function was then determined for each of the two groups. This was based on the sum of the objective function values for the
individual patients in a particular group for the same values of the four parameters. The results are shown in Table 6.2.

Table 6.2: Optimum Parameters for Two Burn Groups Using NBC Data

<table>
<thead>
<tr>
<th>Burn Group, %</th>
<th>(G_{k,T1})</th>
<th>(G_{k,BT})</th>
<th>(r, h^{-1})</th>
<th>EXFAC</th>
<th>OBJFUN</th>
<th>NEXP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 25</td>
<td>0.0</td>
<td>8.0</td>
<td>0.025</td>
<td>1.0</td>
<td>0.48</td>
<td>12</td>
</tr>
<tr>
<td>25 - 100</td>
<td>0.5</td>
<td>5.0</td>
<td>0.025</td>
<td>1.0</td>
<td>12.47</td>
<td>93</td>
</tr>
</tbody>
</table>

6.2.2 Parameters Determined Using Birkeland Data

The burn patients studied by Birkeland were grouped according to the percentage burn surface area and monitored prior to the start of fluid replacement therapy. The objective function values for each burn group were based on plasma volume data only. The values of \(G_{k,T1}\) and \(G_{k,BT}\) which yielded the minimum objective function value for all eight combinations of \(r\) and EXFAC for each burn group are detailed in Appendix J. The four parameters which gave the minimum objective function value for each of the five groups of patients are presented in Table 6.3.

Table 6.3: Optimum Parameters Determined Using Birkeland Data

<table>
<thead>
<tr>
<th>Burn Group</th>
<th>Degree, %</th>
<th>(G_{k,T1})</th>
<th>(G_{k,BT})</th>
<th>(r, h^{-1})</th>
<th>EXFAC</th>
<th>OBJFUN</th>
<th>NEXP</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>2 - 9</td>
<td>0.6</td>
<td>3.0</td>
<td>0.008</td>
<td>0.25</td>
<td>2.01\times10^{-4}</td>
<td>6</td>
</tr>
<tr>
<td>II</td>
<td>10 - 19</td>
<td>1.1</td>
<td>8.0</td>
<td>0.025</td>
<td>1.00</td>
<td>0.86\times10^{-3}</td>
<td>6</td>
</tr>
<tr>
<td>III</td>
<td>20 - 30</td>
<td>3.4</td>
<td>8.0</td>
<td>0.008</td>
<td>0.25</td>
<td>7.73\times10^{-3}</td>
<td>5</td>
</tr>
<tr>
<td>IV</td>
<td>39 - 49</td>
<td>5.8</td>
<td>6.0</td>
<td>0.008</td>
<td>0.25</td>
<td>5.68\times10^{-3}</td>
<td>4</td>
</tr>
<tr>
<td>V</td>
<td>54 - 90</td>
<td>5.8</td>
<td>6.0</td>
<td>0.008</td>
<td>0.25</td>
<td>4.09\times10^{-2}</td>
<td>4</td>
</tr>
</tbody>
</table>
The five groups were then separated into two large groups of burns less than 25% and burns greater than 25%, as for the NBC data set. Patients in burn groups I and II sustained burns less than 25% while patients in groups II, IV and V suffered burns greater than 25%. The parameters giving the minimum objective function for each of these two groups are presented in Table 6.4.

Table 6.4: Optimum Parameters for Two Burn Groups Using Birkeland Data

<table>
<thead>
<tr>
<th>Burn Group, %</th>
<th>$G_{KF,TI}$</th>
<th>$G_{KF,BT}$</th>
<th>$r$, h$^{-1}$</th>
<th>EXFAC</th>
<th>OBJFUN</th>
<th>NEXP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 25</td>
<td>0.5</td>
<td>12.0</td>
<td>0.008</td>
<td>0.25</td>
<td>$9.02 \times 10^{-3}$</td>
<td>12</td>
</tr>
<tr>
<td>25 - 100</td>
<td>3.8</td>
<td>8.0</td>
<td>0.008</td>
<td>0.25</td>
<td>$6.56 \times 10^{-2}$</td>
<td>13</td>
</tr>
</tbody>
</table>

6.2.3 Parameters Determined Using Combination of NBC and Birkeland Data

The NBC and Birkeland data sets were combined to determine global parameters which would be representative for any patient in the two burn groups, less than and greater than 25%. The procedure was based on the sum of the objective function values of the same combinations of $G_{KF,TI}$, $G_{KF,BT}$, $r$ and EXFAC for each patient in a given group.

The magnitudes of the objective function values based on Birkeland's data differed from those based on the NBC data because of differences in the quantity and type of data used in their estimation. The objective function values determined using the NBC patient data were about two orders of magnitude higher than those obtained using Birkeland's data because a greater amount and different types of patient data were available. Thus, optimization based on the direct summation of objective function values from the two individual data sets would be erroneous. The higher values from the NBC data would dominate the overall objective function value and thus mask any meaningful contribution.
from Birkeland's data. As such, a scaling factor was applied to the objective function values from Birkeland's burn groups before combining the two independent data sets. It was necessary to find a suitable factor that would give equal weighting to the two data sets. The results obtained using three different scaling factors, 30, 100 and 200, are presented in Tables 6.5 and 6.6.

Table 6.5: Optimum Parameter Values for Burns Less Than 25%

<table>
<thead>
<tr>
<th>Factor</th>
<th>$G_{k_F,TT}$</th>
<th>$G_{k_F,HT}$</th>
<th>$r$, h$^{-1}$</th>
<th>EXFAC</th>
<th>OBJFUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>0.5</td>
<td>10.0</td>
<td>0.025</td>
<td>1.0</td>
<td>1.19</td>
</tr>
<tr>
<td>100</td>
<td>0.5</td>
<td>12.0</td>
<td>0.025</td>
<td>1.0</td>
<td>2.00</td>
</tr>
<tr>
<td>200</td>
<td>0.5</td>
<td>13.0</td>
<td>0.025</td>
<td>1.0</td>
<td>3.08</td>
</tr>
</tbody>
</table>

Table 6.6: Optimum Parameter Values for Burns Greater Than 25%

<table>
<thead>
<tr>
<th>Factor</th>
<th>$G_{k_F,TT}$</th>
<th>$G_{k_F,HT}$</th>
<th>$r$, h$^{-1}$</th>
<th>EXFAC</th>
<th>OBJFUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>1.0</td>
<td>8.0</td>
<td>0.025</td>
<td>0.75</td>
<td>26.26</td>
</tr>
<tr>
<td>100</td>
<td>2.0</td>
<td>9.0</td>
<td>0.025</td>
<td>0.75</td>
<td>37.01</td>
</tr>
<tr>
<td>200</td>
<td>2.5</td>
<td>9.0</td>
<td>0.025</td>
<td>0.75</td>
<td>46.64</td>
</tr>
</tbody>
</table>

Using a scaling factor of 100, the magnitude of the objective function values determined using Birkeland's patient data were comparable with the values determined using the NBC patient data. In other words, direct summation of the objective function values from both data sets resulted in an approximately equal contribution to the overall objective function value for burns less than and greater than 25% of the total body surface area. The NBC patient data had a larger influence on the overall objective function value with a factor of
30, while Birkeland's patient data were more influential with a factor of 200. The results obtained with a factor of 100 were therefore chosen as the optimum global parameters.

Clinical data from Birkeland's patients were available for up to 12 hours postburn in the case of patients from burn groups I, II and III and 4 hours postburn from burn groups IV and V. On the other hand, data from the NBC patients were available for up to 72 hours postburn during which fluid therapy was administered. Using the two data sets independently gave different results with regards to the relaxation coefficient, \( r \) and the exudation factor, \( \text{EXFAC} \). The relaxation coefficient represents the time it takes for the transport coefficients to return to their normal values. Two discrete values were investigated in the current study, 0.025 h\(^{-1}\) and 0.008 h\(^{-1}\), suggesting that the transport coefficients return to 95% of their normal values in 5 and 15 days respectively. With the NBC patient data, a value of 0.025 h\(^{-1}\) for \( r \) was obtained while Birkeland's patient data resulted in a value of 0.008 h\(^{-1}\). EXFAC values of 1.00 and 0.25 were obtained for the two data sets respectively. The NBC patient data, which spanned 3 days, had a larger influence on the final results for \( r \) and EXFAC when the two independent data sets were combined. During this longer time period, more information concerning the response of the transport coefficients to burn injury and protein loss from the burn wound via exudate could be inferred. In addition, Birkeland's data contained no information about protein behaviour. Thus, EXFAC values estimated using the NBC patient data would be more meaningful.

6.2.4 Summary of Parameters

As discussed in Chapter 5, the other model parameters \( G_{\text{PSTI}} \), \( G_{\text{PSBT}} \), \( G_{\text{OTI}} \) and \( G_{\text{OBT}} \) can be determined from the values of \( G_{k_f,Ti} \) and \( G_{k_f,BT} \). A summary of optimum model parameters found in this study is presented in Table 6.7.
Table 6.7: Coupled Starling Model Parameters

<table>
<thead>
<tr>
<th></th>
<th>Burns less than 25%</th>
<th>Burns greater than 25%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Uninjured Tissue</td>
<td>Injured Tissue</td>
</tr>
<tr>
<td>$G_{KF}$</td>
<td>0.5</td>
<td>12.0</td>
</tr>
<tr>
<td>$G_{PS}$</td>
<td>6.3</td>
<td>45.9</td>
</tr>
<tr>
<td>$G_{\sigma}$</td>
<td>0.1</td>
<td>0.8</td>
</tr>
<tr>
<td>$G_{II,NI}$</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>$G_{L,NI}$</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>$r$, h$^{-1}$</td>
<td>0.025</td>
<td>0.025</td>
</tr>
<tr>
<td>EXFAC</td>
<td>-</td>
<td>1.00</td>
</tr>
</tbody>
</table>

The results obtained indicate that following burn injury, the injured tissue generally undergoes a much greater change than the uninjured tissue. Immediately following burns less than 25%, the filtration coefficient in uninjured tissue increases to 1.5 times its normal value while the injured tissue experiences a greater change by a factor of 13. Burns in excess of 25% cause more pronounced changes in the uninjured tissue as compared to those experienced following smaller burns where the uninjured tissue filtration coefficient increases to 3 times its normal value. The injured tissue coefficients on the other hand, experience changes similar to those experienced following smaller burns. The filtration coefficient increases to 10 times its normal value immediately postburn. Perturbations to the normal lymph flowrate and lymph flow sensitivity coefficient were set to zero in both tissues and for both degrees of burn due to lack of pertinent information.
As discussed previously, due to the fact that data from the NBC patients were available for a longer period postburn as compared to data from Birkeland's patients, the contribution of the latter data set to the global value of $r$ was minimal. Using the NBC patient data independently, a value $0.025$ h$^{-1}$ was obtained for $r$ while Birkeland's patient data resulted in a value of $0.008$ h$^{-1}$. A global value of $0.025$ h$^{-1}$ was obtained when the two sets were combined for both burn groups, less than and greater than $25\%$. This suggests that irrespective of the size of the burn injury, the tissue transport properties return to $95\%$ of their normal values in about 5 days. As was the case with the relaxation coefficient, the global value of the exudation factor, EXFAC, was more strongly influenced by the NBC data set. The rate of exudative protein loss from the injured tissue following smaller burns was found to be similar to that lost following large burns.

To the best of the author's knowledge, no clinical data are available with which to directly compare these estimated parameters. However, best fit perturbed parameter values have been reported in burn injured rats with and without fluid resuscitation [Bert et al., 1989, 1991]. In studies of nonresuscitated injury in rats, the filtration coefficient in injured tissue was found to decrease to $50\%$ of the normal value at time zero, decaying with a time constant of $0.231$ h$^{-1}$ following a $10\%$ surface area injury. Following burns of $40\%$ surface area, the filtration coefficient in the injured skin was found to be reduced to $5\%$ of the normal value and return to normal after about 12 hours as for the smaller burn. Studies of fluid resuscitated rats resulted in a perturbation in the fluid filtration coefficient in the injured tissue of the order of a factor of 10 in the best-fit region. No changes in filtration in intact tissue were required to obtain a good fit of the data, therefore the perturbation was considered to be zero.

Based on the results obtained from the rat studies, the parameters obtained in the current study are encouraging. However, the only way of validating these model parameters is to
investigate how well the model predicts the response of burn patients to fluid resuscitation using the parameters determined. The influence of the individual parameters on the predictability of the model is discussed in the next section.

6.3 SENSITIVITY ANALYSES

The method employed in determining the model parameters made it impossible to give an accurate estimate of the confidence intervals for the parameters. Therefore, sensitivity analyses were performed to investigate the influence of the model parameters on the objective function values. In order to assess the effect of one of the four parameters on the objective function value, the other three were maintained at their optimum values, while the parameter being investigated was varied on either side of its optimum and the corresponding objective function value determined.

6.3.1 Sensitivity Analysis of $G_{kF, TI}$

For burns less than 25%, varying $G_{kF, TI}$ from 0 to 1.4 reveals a deep and almost symmetrical distribution of the objective function values about the minimum as shown in Figure 6.1. A 25% change in $G_{kF, TI}$ from its optimum value of 0.5 yields a 27% change in the objective function value. Consequently, the model predictions would be very sensitive to changes in the value of $G_{kF, TI}$.

For values of $G_{kF, TI}$ in the range selected, which satisfy the constraint that $V_{BT} > V_{BTO}$, the sensitivity curve for burns greater than 25%, given in Figure 6.2, shows an asymmetric distribution about the optimum value of 2.0. For values of $G_{kF, TI}$ less than 1.0, the objective function value changes by about 14 per unit change in $G_{kF, TI}$. For values between 1.0 and 1.5, the objective function value changes by about 7 per unit change in $G_{kF, TI}$. This suggests that values of $G_{kF, TI}$ less than 1.5 will greatly influence the model predictions. On
Figure 6.1: Sensitivity Plots for Burns Less Than 25%
Figure 6.2: Sensitivity Plots for Burns Greater Than 25%
the other hand, for values of $G_{kF, TI}$ between 1.5 and 2.5, the objective function value changes by only about 0.8 per unit change in $G_{kF, TI}$. This suggests that for burns exceeding 25%, the model predictions would be relatively insensitive to values of $G_{kF, TI}$ near the optimum value in the range of about 2.0±0.8.

The range of values of $G_{kF, TI}$ which will produce only a 10% change in the objective function value and therefore not significantly affect the model's predictions are therefore estimated to be 0.5±0.1 for burns less than 25% of the total body surface area and 2.0±0.8 for larger burn injuries. The differing behaviour of the uninjured tissue in each burn group is an encouraging outcome of the current study. In practice, the uninjured tissue experiences greater changes following large burns as compared to smaller burns due to the release of circulating factors in more extensive burns [Lund et al., 1992].

6.3.2 Sensitivity Analysis of $G_{kF, BT}$

A very shallow distribution of the objective function values about the minimum with varying $G_{kF, BT}$ is depicted in Figure 6.1 for burns less than 25%. A 20% change in $G_{kF, BT}$ from its optimum value of 12.0 results in a 6% change in the objective function value. The extensive plateau of objective function values around the optimum $G_{kF, BT}$ value suggests that for burns less than 25%, a wide range of values spanning the optimum $G_{kF, BT}$ could be considered without an appreciable change in the model predictions.

For burns greater than 25%, the sensitivity curve in Figure 6.2 depicts symmetry about the minimum of 9.0 and in the range 9.0±3.0 for $G_{kF, BT}$. A change of about 20% in $G_{kF, BT}$ from its optimum value also results in a change in the objective function of 8%. However, for values of $G_{kF, BT}$ beyond 12.0, there is a significant increase in the objective function values with $G_{kF, BT}$ by about 1.6 per unit change in $G_{kF, BT}$. Hence, for burns greater than
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25% the model predictions would be relatively insensitive to $G_{k, BT}$ values within the range 9.0±3.0 and very sensitive to values greater than about 12.0.

The model predictions would therefore be insensitive to values of $G_{k, BT}$ for burns less than 25% and greater than 25% in the ranges 12.0±3.0 and 9.0±3.0 respectively. These ranges represent the values of $G_{k, BT}$ that produce a 10% change in the objective function value. It has been generally observed that the changes experienced in the injured tissue following small burns are similar to those experienced following larger burns [Lund et al., 1992]. The results obtained from the current study are therefore consistent with what is expected.

### 6.3.3 Sensitivity Analysis of EXFAC and r

As mentioned in Chapter 5, EXFAC and r were only investigated using relatively coarse discrete changes and were not rigorously estimated using the optimization technique adopted. Four discrete values of EXFAC ranging from 0.25 to 1.0 and two values of r, 0.008 h⁻¹ and 0.025 h⁻¹ were investigated. As such, the sensitivity curves obtained for these parameters may not necessarily provide sufficient information concerning the sensitivity of the model predictions to r and EXFAC.

The curves obtained for burns less than 25% shown in Figure 6.1 depict a slight steady decrease in the objective function with increasing values of EXFAC and r. For burns exceeding 25%, the steady decrease in the objective function is more pronounced with increasing values of EXFAC and r. In the case of EXFAC, there is a reversal in the trend at the optimum value of 0.75. Therefore, irrespective of the size of the burn injury, the injured and uninjured tissue transport coefficients return to near-normal values after about 5 days while the exudation factor lies between 0.75 and 1.0.
6.4 VALIDATION OF MODEL PREDICTIONS

The optimum model parameters can be used to predict the response of the MVES to specific fluid replacement therapy in a burn patient. These model predictions can then be compared to the actual monitored responses of the patient to investigate how well the model performs.

6.4.1 Partial Validation

The global parameters obtained by combining the data sets from the NBC and Birkeland were used in simulating the response of the MVES of the individual patients and groups in these two sets. Since these data were used in the identification of the parameters, comparison of the model predictions with the monitored physiological variables was not considered true validation. However, the predictive capabilities of the model, as well as the valicity of the global parameters could be investigated from these simulations.

6.4.1.1. NBC Data

Simulation results for the NBC patients and the measured data and are presented in Figures 6.3 to 6.7. Plasma volume, albumin concentration and colloid osmotic pressures (COPs) in plasma and injured and uninjured tissues were monitored over 3 days. The only patient with burn injuries of less than 25% of the total body surface area was Patient 1. All the other patients sustained injuries greater than 25%.

Almost immediately following burn injury, the injured tissue becomes edematous due to fluid shifts from the circulating plasma and to a lesser extent from the uninjured tissue. Subsequent to fluid resuscitation, the injured tissue fluid volume continues to increase while the plasma and uninjured tissue volumes start to increase for all degrees of burn injury. After 24 hours, the fluid resuscitation protocol was adjusted so that reduced
Figure 6.3: Simulation of MVES for NBC Patient 1 Using Global Model Parameters
Figure 6.4: Simulation of MVES for NBC Patient 2 Using Global Model Parameters
Figure 6.5: Simulation of MVES for NBC Patient 3 Using Global Model Parameters
Figure 6.6: Simulation of MVES for NBC Patient 4 Using Global Model Parameters
Figure 6.7: Simulation of MVES for NBC Patient 5 Using Global Model Parameters
volumes of fluid were given to the patients. This results in the uninjured and injured tissue volumes decreasing towards their normal values. Additionally, the increased flux of albumin from the circulating plasma into the tissues results in an initial decrease in albumin concentration in plasma and a corresponding increase in the injured and uninjured tissue albumin concentration. Introduction of fluid therapy results in a continuing decrease in the plasma albumin concentration and a decrease in the injured and uninjured tissue albumin concentrations towards their normal values. After 24 hours, the albumin concentration in plasma starts to increase towards its normal value as less protein-poor fluids are administered. Due to proportionality between the effective albumin concentration and the colloid osmotic pressure, COP, the trends in albumin concentration are reflected in the COP predictions. In general, the model predictions of plasma volume changes were in good agreement with the actual monitored changes. The model also successfully predicted the monitored trends in plasma protein concentration and hence, colloid osmotic ratios, despite the scarceness of this data.

6.4.1.2 Birkeland's Data
Simulations of Birkeland's patient groups and the data monitored are presented in Figure 6.8. Plasma volume was monitored over the first 12 hours postburn in the smaller burns and over the first 4 hours postburn in the larger burns. This data made it possible to investigate the response of the MVES in the initial period postburn when no form of fluid therapy was started. Patients in burn groups I and II sustained burn injuries to less than 25% of their total body surface area, while patients in groups III, IV and V sustained larger burns.

Immediately postburn, the circulating plasma and uninjured tissue compartments undergo losses in fluid volume as fluid is shifted to the injured tissue compartment. The injured tissue experiences an increase in its fluid volume. The rate of fluid loss from the circulating
Figure 6.8: Simulation of MVES for Birkeland Patient Groups Using Global Model Parameters
plasma increases with increasing severity of the burn injury. Generally, this trend is well predicted by the model. In the larger burns however, the model slightly underestimates the loss in plasma volume at later times.

6.4.2 Independent Validation

Clinical data from two other patient studies were considered to test the model further. These patient data were not used in the identification of the parameters. Hence, the ability of the model to predict the response of these patients to fluid therapy provides an independent validation of the model and its parameters.

6.4.2.1 Arturson's Patient Data

In a study by Arturson et al. [1989], a 62-year old, 77-kg man who had sustained a 58% total area burn was treated during the first 48 hours postburn. Information concerning fluid therapy of the patient, cumulative urine production and the changes in body mass over the initial 48-hour period is reported. The patient information is presented in Appendix H. Predictions of the erythrocyte volume fraction (or hematocrit) using the model developed in this study were compared with the monitored response in the patient, as shown in Figure 6.9. In the first hour postburn, the model predicts an elevated (30%) hematocrit resulting from plasma volume loss. The start of fluid therapy results in the rapid fall of hematocrit as indicated by the patient's response and the model prediction. Between 26.5 and 30 hours postburn, primary excision and grafting with synthetic skin was performed. The model could not be used to predict the response of the patient both during and after the operation since information concerning this operation period was unavailable. It can be envisaged that inclusion of the volume of blood lost during the operation would enable the model to correctly predict the lower erythrocyte volume fraction observed clinically. The close agreement between the model predicted and
Figure 6.9: Simulation of MVES for Arturson's Patient Using Global Model Parameters
clinically monitored erythrocyte volume fraction prior to the operation however, is satisfactory validation of the model and its associated parameters.

6.4.2.2 Roa’s Patient Data

The treatment of two burn patients and the clinical data collected from these patients were reported by Roa et al. [1990] and are presented in Appendix I. Patients 1 and 2 sustained burn injuries to 75 and 80% of their total body surface areas respectively. Intravenous and colloid input, as well as the urine produced by these two patients were used to predict the changes in hematocrit and plasma protein concentration in the MVES following injury. Predictions using the model and clinically monitored responses of the two patients are presented in Figure 6.10. The initial elevation in hematocrit and the subsequent gradual return to normal observed in both patients is well predicted by the model. Clinically, reduced plasma protein concentrations are usually observed soon after burning as was the case in the two patients treated. The model successfully predicted this reduction, however, it slightly overestimated the rate of reduction in Patient 2.

Hence, using the global parameters determined for large burns exceeding 25% of the total body surface area, the model was able to predict the response of the MVES following fluid therapy in patients treated by Arturson et al. [1989] and Roa et al. [1990]. The model predictions agreed favourably with the clinical data available from individual patients. As the clinical data were not used in the parameter estimation procedure, the ability of the model to simulate the response of the patients constituted independent validation of the model. The successful outcome of this independent validation establishes some confidence in the ability of the model and its associated parameters to predict patient responses to fluid therapy following burn injury.
Figure 6.10: Simulation of MVES for Roa's Patients Using Global Model Parameters.
6.5 SIMULATION OF FLUID RESUSCITATION ACCORDING TO DIFFERENT FORMULAE

The use of resuscitation formulae in the treatment of burn patients was discussed in Chapter 2. In order to illustrate the potential use of a model such as that developed in the current study, the response of the MVES, following burn injury, to three common resuscitation formulae was simulated. The response of the MVES to no fluid resuscitation was also simulated to clearly show the influence of fluid resuscitation on the behaviour of the MVES following burn injury.

The amounts of fluid to be given according to the Evans, Brooke and Parkland formulae during the first two 24-hour periods are shown in Table 6.8. These general formulae were applied to a 70-kg man with two different total body surface area burns: 10% and 50% full-thickness burns. The model was used to simulate the response of the MVES to the three different resuscitation formulae following the two burns.

The Parkland formula for fluid resuscitation differs markedly from the Evans and Brooke formulae. During the first 24-hour period, the Evans formula uses a slightly hypertonic sodium chloride solution and colloid solution in equal volumes. Brooke's formula includes an isotonic lactated Ringer's solution and colloid solution in proportions 3:1. Parkland's formula on the other hand, only uses isotonic lactated Ringer's solution in very large quantities. In addition, about 2000 mL of 5% glucose in water is given per day according to the Evans and Brooke formulae, but not in the Parkland protocol.

During the second 24-hour period, half of the amount of electrolytes and colloids compared with the first 24-hours is given according to the formulae of Evans and Brooke. Colloids only are given according to the Parkland formula. 2000 mL of 5% glucose in
water is again given during the second day according to Evans' and Brooke's formulae, while the amount required to maintain adequate urine output is administered according to Parkland's formula.

Table 6.8: Common Fluid Resuscitation Formulae [Arturson et al., 1989]

<table>
<thead>
<tr>
<th>Fluids</th>
<th>Evans Formula</th>
<th>Brooke Formula</th>
<th>Parkland Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First 24 hours</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrolytes</td>
<td>1.0 mL/kg/%</td>
<td>1.5 mL/kg/%</td>
<td>4.0 mL/kg/%</td>
</tr>
<tr>
<td>Glucose/water</td>
<td>2000 mL</td>
<td>2000 mL</td>
<td>None</td>
</tr>
<tr>
<td>Plasma</td>
<td>1.0 mL/kg/%</td>
<td>0.5 mL/kg/%</td>
<td>None</td>
</tr>
<tr>
<td><strong>Second 24 hours</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrolytes</td>
<td>0.5 mL/kg/%</td>
<td>0.75 mL/kg/%</td>
<td>None</td>
</tr>
<tr>
<td>Glucose/water</td>
<td>2000 mL</td>
<td>2000 mL</td>
<td>As required for urine output</td>
</tr>
<tr>
<td>Plasma</td>
<td>0.5 mL/kg/%</td>
<td>0.25 mL/kg/%</td>
<td>500 - 2000 mL as required to maintain urine output</td>
</tr>
</tbody>
</table>

6.5.1 Simulations of 10% Burn

Simulations of the response of the MVES to no fluid resuscitation and the Evans, Brooke and Parkland formulae following a 10% burn injury are depicted in Figures 6.11 to 6.14. It was assumed that the fluid resuscitated patient lost 1.5 L of urine each day over the 2-day period simulated. Fluid loss due to evaporation was determined using Equation 4.7. Exudative fluid loss from the burn wound was estimated based on the relationship derived from the NBC patient data (Equation E.1) as described in Appendix E. In addition,
Figure 6.11: Simulation of MVES with no Fluid Resuscitation Following a 10% Burn
Figure 6.12: Simulation of MVES According to Evan's Formula Following a 10% Burn
Figure 6.13: Simulation of MVES According to Brooke's Formula Following a 10% Burn
Figure 6.14: Simulation of MVES According to Parkland's Formula Following a 10% burn
200 mL of blood were assumed to be lost in the first hour postburn due to surgical procedures. The perturbations which describe the changes to the transport coefficients following a 10% burn surface area injury were those obtained for burns less than 25% and are presented in Table 6.7.

Immediately following burn injury, fluid and albumin are transferred from the circulating plasma compartment to the injured tissue compartment due to increased conductance and permeability of the capillary membrane. Edema results in the injured tissue, with its volume approximately doubling within 2 hours. The patient plasma volume decreases due to the low circulating blood volume which results from the fluid shift. The uninjured tissue also experiences a small decrease in fluid volume as it also acts as a source of fluid for the plasma compartment. The concentration of albumin in the circulating plasma also decreases as albumin is shifted into the tissue compartments. The albumin concentration therefore increases steadily following injury in both tissue compartments, but to a greater extent in the injured tissue. Fluid therapy according to all three formulae was started 1 hour after injury in order to replace the lost fluid volume and albumin content from plasma.

The transcapillary fluid shifts of fluid and albumin following burn injury can be explained by analyzing the fluid and albumin fluxes in the three compartments. The hydrostatic and colloid osmotic pressures in the plasma and tissue compartments are the forces that drive the fluid and albumin exchange. These pressures and the fluid and albumin fluxes are also shown in Figures 6.11 to 6.14.

The very strong negative pressure in the injured tissue, $P_{BT}$, in the first few hours postburn, as well as the initial increase in the filtration coefficient results in an increased rate of fluid and albumin transport from the circulating plasma into the injured tissue.
Reduction of the capillary reflection coefficient, $\sigma_{BT}$, associated with increased protein permeability, also influences the increased filtration rate. Lymph flow from the injured tissue which is restricted to non-negative values, is virtually nonexistent also due to the very negative tissue pressure. However, the injured tissue loses fluid by evaporation and exudation and albumin via exudate from the burn wound. Despite these losses, the great increase in the rate of fluid and albumin transfer into the injured tissue results in a rise in both fluid volume and plasma protein content in this tissue during this initial period postburn. Consequently, edema develops in the injured tissue because the rate of fluid filtration from the capillaries exceeds the rate at which fluid is removed from the tissue via the lymphatics and other routes. In addition, the injured tissue albumin concentration, $c_{BT}$ and hence the colloid osmotic pressure, $\Pi_{BT}$, increase while the plasma albumin concentration, $c_{PL}$ and colloid osmotic pressure, $\Pi_{PL}$ decrease. Immediately postburn, the uninjured tissue experiences a decrease in its hydrostatic pressure due to loss of fluid volume from this compartment. In the first few hours postburn, the hydrostatic pressure in the capillary falls much more markedly than that in the uninjured tissue compartment. This causes a reduction in the filtration rate despite the small increase in the filtration coefficient. The uninjured tissue fluid volume therefore decreases while its albumin concentration increases.

Fluid therapy, where applicable, was started 1 hour postinjury. The interstitial fluid pressure in the injured skin of rats has been observed to approach normal values within 2 to 3 hours [Lund et al., 1988]. During the first 2.5 hours postburn, interstitial pressure versus time data from experiments on both unresuscitated and resuscitated rats [Lund et al., 1988] were used to describe the injured tissue compliance. After 2.5 hours, the injured tissue hydrostatic pressure was linked to changes in interstitial fluid volume resulting in an increase in $P_{BT}$, approaching more positive values between 2.5 and 3 hours postburn. This influences the rate at which fluid and albumin is shifted from the circulating plasma
compartment. Transcapillary fluid and albumin transport also continually readjust depending on the fluid and colloid input to the system. Fluid resuscitation according to Evans' and Brooke's formulae results in similar responses by the MVES. The injured tissue fluid volume starts to decrease approaching normal values. However, the albumin concentration, \( c_{BT} \), continues to increase. The plasma volume on the other hand, remains low despite the input of fluid to the system and the albumin concentration also continues to decrease despite colloidal infusions. This results in the injured tissue COP, \( \Pi_{BT} \), exceeding that of plasma, \( \Pi_{PL} \), early in the postburn phase. These trends could be a reflection of the resuscitation protocol with regards to protein replacement. In contrast to the generally accepted view that colloids should be withheld for the first 12 to 24 hours postburn, the Evans and Brooke formulae require that colloids be administered in the first 24 hours. It appears that there is continued protein transfer into the injured tissue resulting in the continued increase in \( c_{BT} \) and hence \( \Pi_{BT} \) as predicted by the model. Pitkänen et al. [1987], in their studies in burn injured patients, found a higher injured skin COP than plasma COP up to 12 hours postburn. Voluminous crystalloid infusions were sited as being partially responsible for the postburn incidence of hypoproteinemia [Pitkänen et al., 1987]. Spontaneous decreases in plasma COP have also been reported following burn injuries in man [Davies, 1982] and in anaesthetized and unresuscitated burned rats [Lund and Reed, 1986]. Later in the resuscitation period, the uninjured tissue compartment experiences a slight increase in tissue volume, out of phase with the injured tissue edema as shown in Figures 6.12 to 6.14. During the second 24-hour period, the uninjured tissue volume starts to decrease, tending towards its normal value. This ensures continued increase in albumin concentration, \( c_{TI} \) and hence COP, \( \Pi_{TI} \), but to a lesser degree than that experienced in the injured tissue.

Fluid resuscitation according to Parkland's formula resulted in a slightly different response in the MVES in the second 24-hour period postburn. The large volume of only protein-
poor fluid infusions in the first 24-hour period resulted in a larger decrease in the albumin concentration in the circulating plasma than with Evans' and Brooke's formulae. However, plasma as well as a significantly reduced volume of glucose in water were administered in the second 24-hour period. This resulted in an increase in the plasma albumin concentration and hence the plasma COP.

6.5.2 Simulations of 50% Burn

Figures 6.15 to 6.18 show predictions of the response of the MVES to no fluid resuscitation, the Evans, Brooke and Parkland formulae following a 50% burn. Similar assumptions regarding fluid and albumin losses from the patient following a 10% burn were applied in this case. In order to describe the changes to the transport coefficients following a burn of this size, perturbed parameter values determined for burns exceeding 25% of the total body surface area were applied.

The response of the MVES without fluid therapy is shown in Figure 6.15. The extent of the burn injury results in a relatively greater shift of fluid and albumin from the circulating plasma into the injured tissue as compared to the smaller burn. Edema results in the injured tissue despite the loss of fluid due to exudation and evaporation. This is due to increased filtration from the circulating plasma, encouraged by a very strong negative injured tissue pressure, an initial increase in $k_f$ and a decrease in the capillary reflection coefficient associated with increased protein permeability. The uninjured tissue compartment acts as a source of fluid for the depleting plasma compartment and hence its fluid volume also decreases. In addition, albumin is transferred to both tissue compartments from plasma. This results in an increase in the concentration of albumin and hence COP in the tissues, while the plasma albumin concentration and hence COP decrease as in the smaller burn.
Figure 6.15: Simulation of MVES with no Fluid Resuscitation Following a 50% Burn
Figure 6.16: Simulation of MVES According to Evans' Formula
Following a 50% Burn
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Figure 6.17: Simulation of MVES According to Brooke's Formula Following a 50% Burn
Figure 6.18: Simulation of MVES According to Parkland's Formula Following a 50% burn
As was the case for the smaller burn, fluid therapy was started 1 hour postinjury. The injured tissue hydrostatic pressure returns to more positive and near-normal values and the transcapillary fluid and albumin fluxes continually readjust depending on the fluid and albumin input to the system. As a result, the injured tissue volume starts to decrease while the plasma volume starts to increase, tending towards their normal volumes. Fluid resuscitation with the larger volumes of fluid results in more extensive edema formation in the uninjured tissue as compared to that experienced following a 10% burn injury. A reversal of plasma and injured tissue COP is again predicted as the injured tissue albumin concentration exceeds that in the circulating plasma following resuscitation according to all three formulae. However, the redistribution of albumin in the three compartments differs following fluid resuscitation according to the three formulae after about 10 hours postburn. Discontinuities in the predicted trends 24-hours postburn are reflections of the change in resuscitation protocol and are more evident following the larger burn.

Resuscitation according to the Evans formula results in similar trends in $c_{BT}$ and $\Pi_{BT}$ as observed following the 10% burn. The albumin concentration in injured tissue continued to increase while that in plasma continued to decrease up until 10 hours postburn. The trend in plasma was then reversed and continued to increase in the second 24-hour period. The injured tissue on the other hand experienced slight fluctuations in fluid volume resulting in a continued increase in $c_{BT}$ and $\Pi_{BT}$ but at a greatly reduced rate. Administration of fluid and plasma according to Brooke's formula results in similar behaviour in the circulating plasma. The injured tissue albumin concentration however, decreases after 10 hours postburn and continues to decrease steadily in the second 24 hours. The decrease in $c_{PL}$ and the increase in $c_{BT}$ are more pronounced using Parkland's formula in the first 24 hour period. It is widely accepted that resuscitation with colloid-free solutions produces a decrease in $\Pi_{PL}$ due to dilution of plasma proteins. In the second 24-hour period, $c_{PL}$ starts to increase rapidly as protein-rich fluid is administered according
to Parkland's formula. The injured tissue albumin concentration also starts to increase following fluid therapy but at a reduced rate.

6.5.3 Simulations by Other Authors

Arturson et al. [1989] and Roa et al. [1993] used their models to simulate the response of the standard 70-kg man with a 40% burn surface area to one or more of the resuscitation formulae discussed previously. The predictions made by the models of these authors are discussed and compared to those obtained with the model developed in the current study.

A mathematical model developed by Arturson et al. [1989] was used to simulate the response of a 70-kg man with a 40% full thickness burn to fluid therapy according to the Evans, Brooke and Parkland formulae. The model described the distribution of body fluids in vascular, interstitial and intracellular compartments, influenced by the flows of fluids, electrolytes and colloids, taking place across the capillary beds and cell membranes. Changes in plasma volume and interstitial volume in noninjured and injured tissue were simulated. Their model predicted the decrease in plasma and uninjured tissue volume and the increase in injured tissue volume that is experienced postburn with no fluid therapy. Treatment according to Evans' formula resulted in an increase in the plasma volume during the first eight hours followed by a slow and steady decrease towards its normal value. Edema in the injured tissue started to resolve 18 hours postburn while the uninjured tissue continued to experience a decrease in its fluid volume. Use of the Brooke formula resulted in a continued slow and steady decrease of the plasma and uninjured tissue volumes from their normal values. The increased injured tissue volume however, started to decrease 18 hours postburn. Fluid therapy according to Parkland's formula caused a reversal in the decreasing trend, increasing towards the normal plasma volume during the second 24-hour period. Edema in the injured tissue was more pronounced with Parkland's formula but started to resolve during the second 24 hour period. The uninjured tissue however,
experienced an increase in fluid volume following fluid resuscitation and continued to increase over the 2-day period. The shift of fluid into the injured tissue causing edema and the subsequent decrease towards normal values predicted by the current model is in agreement with Arturson's predictions. Fluid therapy according to Parkland's formula is able to restore the lost plasma volume but causes extensive edema in the uninjured tissue. However, the redistribution of fluid in the uninjured tissue and plasma using Evans' and Brooke's formulae differ between the two studies. With Arturson's model, a steady decrease in uninjured tissue fluid volume is predicted following resuscitation with the two formulae. This is in contrast to the predicted increase in fluid volume in the first 24 hours followed by a decrease towards the normal value by the current model.

A simulator developed by Roa and Gomez-Cia [1993] was recently used to design a fluid therapy method for burn patients during the acute phase following burn. The interactions between the intracellular and extracellular compartments, normal and burned capillary dynamics, hemodynamic regulation of the systemic circulation, lymphatic systems in the normal and burned areas and renal function were all considered in the simulation. The response of a 70-kg, 170-cm tall individual with a 40% burn to the Brooke and Parkland formulae were simulated and compared to the fluid therapy method designed. The trends in plasma and uninjured tissue volumes predicted by their simulator were similar to those obtained in the current study. Fluid resuscitation according to the Brooke and Parkland formulae resulted in an increase in the plasma volume following the initial decrease when no form of fluid therapy was administered. The Parkland formula caused a greater increase in the uninjured tissue fluid volume as compared to Brooke's formula, as also predicted by the current model.
6.6 SUMMARY

In the current study, clinical data were used to estimate transport parameters and other significant parameters in the model. This aspect of the current study represents a significant difference in the approach to model formulation as compared to the models of Arturson et al. [1984, 1988, 1989] and Roa et al. [1986, 1988, 1990, 1993]. Additionally, in contrast to the other models discussed, microvascular exchange was emphasized and the formulation of the current model was based on up-to-date information and concepts. However, despite the relative complexity of the models developed by Arturson et al. and Roa et al. as compared to that developed in the current study, the simulations show many similar trends in terms of the response of the human MVES to fluid therapy according to the Evans, Brooke and Parkland formulae. Inclusion of cellular compartments as in the case of the other models would be an improvement to the model, to further enhance its predictive capabilities. As more clinical data become available, a more accurate parameter estimation procedure can be adopted in the development of a model that will better reflect the dynamic behaviour of fluid and proteins in the MVES following a burn injury.
CHAPTER 7

CONCLUSIONS AND RECOMMENDATIONS

7.1 CONCLUSIONS

A compartmental model has been developed to describe the human microvascular exchange system following burn injury. One of the objectives of the current study was to determine the unknown model parameters by statistical fitting of model predictions to clinical data. An optimization scheme was implemented to determine the "best-fit" parameters. The scheme ensured that the optimum model parameters were those which yielded the global minimum of the objective function value.

Clinical observations indicate that burns less than 25% of the total body surface area initiate systemic and localized changes which differ from those caused by burns exceeding 25%. Therefore global parameters were determined for burns less than and greater than 25%. The results obtained indicate that, immediately postburn, the injured tissue undergoes greater change compared to the uninjured tissue for all degrees of burn injury. Immediately following burns less than 25%, the filtration coefficient in uninjured tissue increases to 1.5 times its normal value while the injured tissue transport coefficient changes by a factor of 13. Burns in excess of 25% initiate more pronounced changes in the uninjured tissue filtration coefficient, by a factor of 3 while the injured tissue coefficient increases to 10 times its normal value. Therefore burns exceeding 25% of the total body surface area cause greater changes in the uninjured tissue as compared to smaller burns. However, the injured tissue undergoes similar changes for all burns. The transport coefficients were found to return to near-normal values in about 5 days following burn
injuries of all sizes. The exudation factor, which determines the fraction of the interstitial protein concentration which leaves with exudate from the burn wound, was found to be in the range 0.75 to 1.00 for all degrees of burn injury.

The sensitivity of the model's predictions to changes in the model parameters from their optimum values was also investigated. The analyses revealed that for burns less than 25%, the model predictions would be more sensitive to smaller changes in $G_{KF,T1}$ compared to $G_{KF,BT}$. The model predictions would not be significantly affected by values of $G_{KF,T1}$ within the range ±0.1 about the optimum value of 0.5 and values of $G_{KF,BT}$ within the range ±3.0 about the optimum value of 12.0. Beyond these ranges, appreciable changes in the model predictions would be observed. Values of $G_{KF,T1}$ within the range ±0.8 about the optimum value of 2.0 and values of $G_{KF,BT}$ within the range ±3.0 about the optimum value of 9.0 would not significantly affect the model's predictions. As the model parameters EXFAC and $r$ were investigated using relatively coarse discrete changes, limited information could be inferred concerning the sensitivity of the model predictions to EXFAC and $r$.

The model and its associated parameters were validated by comparing model predictions of patient responses to fluid therapy, to the clinical data obtained from those patients. Simulation of the response of patients whose clinical data was not used in estimating the parameters constituted independent validation of the model and its parameters. The model predicted response of the MVES to burn injury was in agreement with the observed trends and the absolute values of fluid volume and plasma protein concentration. Immediately postburn, there was an initial elevation in hematocrit due to fluid loss from the circulating plasma. Administration of fluid therapy initiated the return of hematocrit to normal values. In addition, the reduction in plasma protein concentration observed clinically soon after burn injury was successfully predicted by the model.
The other major objective of the current study was to develop a burn patient simulator. The model could be used to investigate the response of the MVES to fluid resuscitation following a particular burn injury. The patient simulator could also be used to compare the effects of different recommended resuscitation formulae, to suggest possibilities for the design of optimal fluid resuscitation programs in terms of the fluid composition, volume and infusion rate. Areas of further investigation with respect to fluid management of burn patients could also be suggested using the model. To this end, the model was used to simulate the response of the MVES following burn injury to no form of fluid therapy and then to three common resuscitation protocols, namely the Evans, Brooke and Parkland formulae. The simulated responses of the MVES were explained in terms of the transport mechanisms, driving forces and perturbations to the transport coefficients following two degrees of burn injury, 10% and 50%. In general, it was found that the very strong negative injured tissue pressure as well as the initial increase in the filtration coefficient and the reduction of the capillary reflection coefficient resulted in an increased flux of fluid and albumin from the circulating plasma into the injured tissue. This resulted in the injured tissue becoming edematous, while the circulating plasma continued to lose fluid volume. The concentration of albumin in the injured tissue also increased steadily while that in plasma decreased following injury. This resulted in a reversal of the colloid osmotic pressure difference between the injured tissue and plasma. The response of the MVES to fluid therapy according to the Evans and Brooke formulae was similar. The injured tissue hydrostatic pressure increased approaching normal values and the transcapillary flux of fluid and albumin continually readjusted depending on the fluid and colloid input to the system. Parkland's formula initiated slightly different and more pronounced responses due to the large volume of colloid-free fluid given in the first 24-hours followed by colloidal infusions in the second 24-hours. The major difference between the two burn degrees was the relative greater shift of fluid and albumin from the circulating plasma into the injured
and uninjured tissues following the 50% burn injury as compared to the 10% injury. Similar predictions from models developed by other workers confirmed the ability of the present model to adequately predict the response of the human MVES to fluid therapy following burn injury.

The model parameters estimated in the current study may be considered as estimates due to the extreme complexity of the MVES and the lack of experimental data. As more reliable and useable clinical data becomes available, more accurate parameters may be estimated to better reflect the dynamic behaviour of the MVES. However, the simulated results illustrate the utility of the model in predicting non-measureable variables in the MVES.

7.2 RECOMMENDATIONS

The various problems encountered as well as the results obtained in the current study form the basis for the following recommendations for future developments to the current model.

1) The use of clinical data to estimate transport coefficients and other significant model parameters sets the current model apart from those developed by other workers. There is therefore absolute need for more reliable clinical data in terms of both quantity and quality, to enable a more detailed identification of all the model parameters including the relaxation coefficient and exudation factor. This would undoubtedly improve the ability of the model to adequately predict the response of the complex system to fluid resuscitation following thermal injury.

2) In order to verify the model predictions, additional clinical data or information is required:
• measurements of the changes to the injured and uninjured tissue transport coefficients following burn injury;
• estimates of burn wound fluid and protein loss due to exudation; and
• estimates of fluid loss due to evaporation.

3) Improvements to the current model might include:
• replacement of the "most-likely" human tissue compliance relationship with clinically determined relationships for the injured and uninjured tissue as the data becomes available;
• investigation of the possible change in the vascular compliance during the course of fluid resuscitation;
• determination of the lymph flow changes in the injured and uninjured tissues following burn injury as this information becomes available;
• subdivision of the uninjured tissue compartment comprising uninjured skin, muscle and other tissues into the individual components. This will only be possible when clinical data regarding the colloid osmotic pressure dependence on protein concentration, the compliance characteristics and the normal steady-state conditions of the individual tissues become available; and
• extension of the current model to include intra- and extracellular compartments to allow for fluid, protein and small ion exchange between compartments. This would enable the simulation of the response of the MVES to hypertonic fluid resuscitation following thermal injury.
### NOMENCLATURE

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Ratio of albumin molecule radius to pore radius</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Surface area available for exchange</td>
<td>m²</td>
</tr>
<tr>
<td>AFRAC</td>
<td>Fractional perfusion in injured tissue immediately following burn injury</td>
<td></td>
</tr>
<tr>
<td>Alb$_{to}$</td>
<td>Albumin turnover rate</td>
<td>h⁻¹</td>
</tr>
<tr>
<td>AR</td>
<td>Acetated Ringers solution</td>
<td></td>
</tr>
<tr>
<td>BV</td>
<td>Blood Volume</td>
<td>mL</td>
</tr>
<tr>
<td>c</td>
<td>Albumin concentration</td>
<td>g/L</td>
</tr>
<tr>
<td>COP</td>
<td>Colloid osmotic pressure</td>
<td>mmHg</td>
</tr>
<tr>
<td>CSM</td>
<td>Coupled Starling Model</td>
<td></td>
</tr>
<tr>
<td>CV</td>
<td>Cell Volume</td>
<td>mL</td>
</tr>
<tr>
<td>DEG</td>
<td>Percentage of body surface burned</td>
<td>%</td>
</tr>
<tr>
<td>Dₕ</td>
<td>Solute free diffusion coefficient</td>
<td>cm²/s</td>
</tr>
<tr>
<td>DSW</td>
<td>Dextrose</td>
<td></td>
</tr>
<tr>
<td>EXFAC</td>
<td>Exudation factor</td>
<td></td>
</tr>
<tr>
<td>FA</td>
<td>Fractional area available for exchange</td>
<td></td>
</tr>
<tr>
<td>fn()</td>
<td>Function of</td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>Perturbation to the transport coefficient</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>Patient height</td>
<td>cm</td>
</tr>
<tr>
<td>Hct</td>
<td>Hematocrit</td>
<td>%</td>
</tr>
<tr>
<td>HR</td>
<td>Hypertonic Ringer's solution</td>
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</tr>
<tr>
<td>Symbol</td>
<td>Description</td>
<td>Units</td>
</tr>
<tr>
<td>--------</td>
<td>-------------</td>
<td>-------</td>
</tr>
<tr>
<td>J</td>
<td>Fluid transport rate</td>
<td>mL/h</td>
</tr>
<tr>
<td>k</td>
<td>Time-dependent coefficient</td>
<td></td>
</tr>
<tr>
<td>kA</td>
<td>Overall transport coefficient</td>
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<tr>
<td>k_F</td>
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</tr>
<tr>
<td>k_i α_i</td>
<td>Steric fractional drag coefficient</td>
<td></td>
</tr>
<tr>
<td>LS</td>
<td>Lymph flow sensitivity coefficient</td>
<td>mL/mmHg-h</td>
</tr>
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<td>M</td>
<td>Number of variables monitored</td>
<td></td>
</tr>
<tr>
<td>MVES</td>
<td>Microvascular Exchange System</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Number of data points</td>
<td></td>
</tr>
<tr>
<td>NBC</td>
<td>National Burn Centre</td>
<td></td>
</tr>
<tr>
<td>NEXP</td>
<td>Number of experimental data points</td>
<td></td>
</tr>
<tr>
<td>NS</td>
<td>Normal saline</td>
<td></td>
</tr>
<tr>
<td>OBJFUN</td>
<td>Objective function value</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>Hydrostatic pressure</td>
<td>mmHg</td>
</tr>
<tr>
<td>P_{C,COMP}</td>
<td>Reciprocal of circulatory compliance</td>
<td>mmHg/mL</td>
</tr>
<tr>
<td>Pe</td>
<td>Modified Péclet number</td>
<td></td>
</tr>
<tr>
<td>PS</td>
<td>Membrane permeability coefficient</td>
<td>mL/h</td>
</tr>
<tr>
<td>PLM</td>
<td>Plasma Leak Model</td>
<td></td>
</tr>
<tr>
<td>PV</td>
<td>Plasma volume</td>
<td>mL</td>
</tr>
<tr>
<td>Q</td>
<td>Albumin content</td>
<td>mg</td>
</tr>
<tr>
<td>\dot{Q}</td>
<td>Albumin transport rate</td>
<td>mg/h</td>
</tr>
<tr>
<td>r</td>
<td>Relaxation coefficient</td>
<td>h^{-1}</td>
</tr>
<tr>
<td>r_{pore}</td>
<td>Radius of pore</td>
<td>m</td>
</tr>
<tr>
<td>r_{solute}</td>
<td>Radius of solute</td>
<td>m</td>
</tr>
<tr>
<td>RELSM</td>
<td>Fraction of total body comprising skin</td>
<td></td>
</tr>
<tr>
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<td>Starling Model</td>
<td></td>
</tr>
<tr>
<td>Symbol</td>
<td>Description</td>
<td>Units</td>
</tr>
<tr>
<td>--------</td>
<td>------------------------------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>SM</td>
<td>Starling Model</td>
<td></td>
</tr>
<tr>
<td>t</td>
<td>Time</td>
<td>h</td>
</tr>
<tr>
<td>TBSA</td>
<td>Total body surface area</td>
<td>m²</td>
</tr>
<tr>
<td>V</td>
<td>Fluid volume</td>
<td>mL</td>
</tr>
<tr>
<td>VAFTI</td>
<td>Fraction of tissue which remains uninjured</td>
<td></td>
</tr>
<tr>
<td>VAFBT</td>
<td>Fraction of tissue which is injured</td>
<td></td>
</tr>
<tr>
<td>VFRAC</td>
<td>Fractional plasma volume at which perfusion in tissues is zero</td>
<td></td>
</tr>
<tr>
<td>W</td>
<td>Patient body weight</td>
<td>kg</td>
</tr>
<tr>
<td>WR</td>
<td>Weight ratio</td>
<td></td>
</tr>
<tr>
<td>WF</td>
<td>Weighting factor for each data point</td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>Data point</td>
<td></td>
</tr>
<tr>
<td>Π</td>
<td>Colloid osmotic pressure</td>
<td>mmHg</td>
</tr>
<tr>
<td>σ</td>
<td>Albumin reflection coefficient</td>
<td></td>
</tr>
<tr>
<td>μ</td>
<td>Viscosity of water</td>
<td>g/cm-s</td>
</tr>
<tr>
<td>(1 - a)</td>
<td>Partition coefficient</td>
<td></td>
</tr>
<tr>
<td>Δ</td>
<td>Change</td>
<td></td>
</tr>
<tr>
<td>ΔX</td>
<td>Thickness of capillary membrane</td>
<td>cm</td>
</tr>
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### Subscripts and Superscripts

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
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<tbody>
<tr>
<td>AV</td>
<td>Volume available to albumin</td>
</tr>
<tr>
<td>BLOOD</td>
<td>Blood loss</td>
</tr>
<tr>
<td>BT</td>
<td>Injured tissue</td>
</tr>
<tr>
<td>C</td>
<td>Capillary</td>
</tr>
<tr>
<td>CLF</td>
<td>Clear fluid</td>
</tr>
<tr>
<td>end</td>
<td>End of time period</td>
</tr>
<tr>
<td>EVAP</td>
<td>Evaporation</td>
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<tr>
<td>EX</td>
<td>Excluded</td>
</tr>
<tr>
<td>EXP</td>
<td>Experimental</td>
</tr>
<tr>
<td>EXUD</td>
<td>Exudation</td>
</tr>
<tr>
<td>F</td>
<td>Filtration</td>
</tr>
<tr>
<td>I</td>
<td>Interstitium</td>
</tr>
<tr>
<td>L</td>
<td>Lymph</td>
</tr>
<tr>
<td>NL</td>
<td>Normal steady-state conditions</td>
</tr>
<tr>
<td>O</td>
<td>Initial conditions</td>
</tr>
<tr>
<td>PB</td>
<td>Postburn</td>
</tr>
<tr>
<td>PCF</td>
<td>Protein-containing fluid or colloidal fluid</td>
</tr>
<tr>
<td>PL</td>
<td>Plasma</td>
</tr>
<tr>
<td>PRED</td>
<td>Predicted</td>
</tr>
<tr>
<td>RESUSC</td>
<td>Resuscitation</td>
</tr>
<tr>
<td>S</td>
<td>Solute</td>
</tr>
<tr>
<td>start</td>
<td>Start of time period</td>
</tr>
<tr>
<td>TI</td>
<td>Uninjured tissue</td>
</tr>
<tr>
<td>URINE</td>
<td>Urine</td>
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REFERENCES


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Appendices

Appendix A: Interstitial Fluid Distribution

Appendix B: Transport Parameters

Appendix C: NBC Patient Data

Appendix D: Estimation of Plasma Volume from Hematocrit Data

Appendix E: Estimation of Exudation Rate Based on NBC Patient Data

Appendix F: Birkeland's Patient Data

Appendix G: Determination of Exudation Rate for Birkeland's Patients

Appendix H: Clinical Data from Arturson's Patient

Appendix I: Clinical Data from Roa's Patient

Appendix J: Minimum Objective Function Value Results

Appendix K: Computer Program Listing
Appendix A: Interstitial Fluid Distribution

The interstitial fluid distribution in the "Reference Man" has been reported [Chapple, 1990] as shown in Table A.1.

Table A.1: Interstitial Fluid Distribution in the "Reference Man"

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Interstitial Fluid Volume, L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Skin</td>
<td>2.39</td>
</tr>
<tr>
<td>Skeletal Muscle</td>
<td>4.51</td>
</tr>
<tr>
<td>Other Tissue</td>
<td>1.50</td>
</tr>
<tr>
<td>Total Body</td>
<td>8.40</td>
</tr>
</tbody>
</table>
Appendix B: Transport Parameters

B.1 Normal Transport Parameters for "Reference Man"

Normal values for five transport coefficients have been determined using the Coupled Starling Model (CSM) for the normal 70-kg man by Xie [1992]. Values for the lymph flow sensitivity coefficient, LS and the albumin reflection coefficient, σ, were determined by statistical fitting of the CSM model predictions to experimental human MVES response data. The lymph flowrate, J_L, permeability coefficient, PS and filtration coefficient, k_F are calculated from the following relationships based on the estimated values of LS and σ:

\[
J_{L,NL} = \frac{Alb_{TO}}{(1-\sigma_{NL}) \cdot \exp(-Pe_{NL}) \cdot \frac{1}{[1-\exp(-Pe_{NL})] \cdot [V_{I,NL} - V_{I,EX}]}} V_{I,NL}
\]

B.1

\[
PS_{NL} = \frac{(1-\sigma_{NL}) \cdot J_{L,NL}}{\ln \left[ \frac{c_{I,NL} - (1-\sigma_{NL}) \cdot c_{I,AV,NL}}{c_{I,NL} - (1-\sigma_{NL}) \cdot c_{PL,NL}} \right]}
\]

B.2

\[
k_{F,NL} = \frac{J_{L,NL}}{P_{C,NL} - P_{I,NL} - \sigma_{NL} \cdot (\Pi_{PL,NL} - \Pi_{I,NL})}
\]

B.3

where Pe is a modified Péclet number which can also be shown to be

\[
Pe_{NL} = \ln \left[ \frac{c_{I,NL} - (1-\sigma_{NL}) \cdot c_{I,AV,NL}}{c_{I,NL} - (1-\sigma_{NL}) \cdot c_{PL,NL}} \right]
\]

B.4

Subscript NL refers to normal steady-state values and Alb_{TO} is the albumin turnover rate, which expresses the rate of disappearance of albumin from the interstitial compartment and has been found to be between 2 and 2.5% per hour [Hollander et al., 1961; Langgård, 1963]. In the current study, a value of 0.025 h^{-1} is used.
The normal values of the transport coefficients, as estimated from the above relationships from the values of LS and σ found by Xie are as follows:

\[ \text{LS}_{\text{NL}} = 43.08 \text{ mL/mmHg-h} \]
\[ \text{PS}_{\text{NL}} = 72.98 \text{ mL/h} \]
\[ k_{F,\text{NL}} = 120.64 \text{ mL/mmHg-h} \]
\[ J_{L,\text{NL}} = 75.46 \text{ mL/h} \]
\[ \sigma_{\text{NL}} = 0.9888. \]

As explained in Chapter 4, these transport coefficients, with the exception of the albumin reflection coefficient, are scaled with respect to the weight ratio, WR, to account for the "real patient".

B.2 Transport Coefficients Following Burn Injury

Most proteins in plasma cross capillary walls, diffuse through tissues and return to the plasma via the lymphatic system. It is well known that the concentration of a macromolecule in lymph is a function of its molecular size and that capillaries are heteroporous, i.e., both small and large pores are necessary to describe the movement of large molecules across capillary walls [Taylor and Granger, 1984]. The capillary membrane parameters which determine the exchange of plasma proteins, represented by albumin in the current study, are \( k_F \), \( \sigma \) and PS. These transport parameters are not independent, but are linked to each other via changes in the capillary pore radius. Reed et al. [1991] report the following relationships for the transport coefficients \( k_F \), \( \sigma \) and PS, based on the radius of the capillary pore and the radius of solute, which is albumin in this case:

\[ k_F' = \frac{r_{\text{pore}}^2}{8 \cdot \mu \cdot \Delta X} \quad \text{B.5} \]
\[ \sigma = \frac{16}{3} \cdot a^2 - \frac{20}{3} \cdot a^3 + \frac{7}{3} \cdot a^4 \quad \text{B.6} \]
\[ PS' = \frac{(1-a)^2 \cdot D_s}{k_i \alpha_i \cdot \Delta X} \]  

where \(a\) is the ratio of the solute radius, \(r_{\text{solute}}\), to the pore radius, \(r_{\text{pore}}\), i.e.,

\[ a = \frac{r_{\text{solute}}}{r_{\text{pore}}} \]  

\(\mu\) is the viscosity of water (\(\mu = 0.006915 \text{ g/cm-s at } 37^\circ\text{C}\)), \(\Delta X\) the thickness of the capillary membrane (\(\Delta X = 5000 \text{Å} = 5 \times 10^{-5} \text{ cm}\)), \((1-a)\) the partition coefficient, \(D_s\) the solute free diffusion coefficient in \(\text{cm}^2/\text{s}\) and \(k_i \alpha_i\) is the steric fractional drag coefficient which is dimensionless. The units of \(k_F\) and \(PS'\) are \(\text{cm/s-mmHg}\) and \(\text{cm/s}\) respectively, while \(\sigma\) is dimensionless.

A normal value for \(a\) is determined from Equation B.6, based on normal values for the radius of the albumin molecule [Taylor and Granger, 1984] and the albumin reflection coefficient:

\[ \sigma_{NL} = 0.9888 = \frac{1}{3} \left[ 16 \cdot a_{NL}^2 - 20 \cdot a_{NL}^3 + 7 \cdot a_{NL}^4 \right]. \]

Solving this equation yields:

\[ a_{NL} \equiv 0.89 \]

Recall that following burn injury, the transient response of the transport coefficients is expressed in the following general form:

\[ kA = k_{NL} \cdot A_{NL} \cdot [1 + G \cdot e^{-n}] \]  

Considering \(k_F\), by the definition above, at time \(t = 0\),

\[ \frac{k_F}{k_{F,NL}} = 1 + G_{k_F} \]

In the current study, it is assumed that following burn injury, the capillary membrane pores experience changes in radii. From equation B.5, \(k_F \propto r_{pore}^2\). Thus:
Where \( r_{\text{pore,NL}} \) is the normal capillary pore radius. Setting \( r_{\text{pore}} = r \), and \( r_{\text{pore,NL}} = r_{\text{NL}} \), Equation B.9 can be expressed as

\[
r = r_{\text{NL}} \left[ 1 + G_k \right]^{\frac{1}{2}}. 
\]

From Equations B.8 and B.10, the ratio of albumin and capillary pore radii following burn injury may be defined as follows:

\[
\alpha_{PB} = \frac{r_{ab}}{r} = \frac{r_{ab}}{r_{NL} \left( 1 + G_k \right)^{\frac{1}{2}}}. 
\]

In addition, under normal conditions,

\[
\alpha_{NL} = \frac{r_{ab}}{r_{NL}}. 
\]

From equations B.11 and B.12,

\[
\frac{\alpha_{PB}}{\alpha_{NL}} = \frac{r_{ab}}{r_{NL} \left( 1 + G_k \right)^{\frac{1}{2}}} = \frac{1}{r_{ab}} \frac{r_{NL} \left( 1 + G_k \right)^{\frac{1}{2}}}{\left( 1 + G_k \right)^{\frac{1}{2}}}.
\]

Hence, the ratio of the albumin molecule radius to pore radius, postburn is

\[
\alpha_{PB} = \frac{\alpha_{NL}}{(1 + G_k)^{\frac{1}{2}}}. 
\]

Consider PS. Again, by definition, at time \( t = 0 \),

\[
\frac{PS}{PS_{NL}} = 1 + G_{PS}
\]

From Equation B.7, \( PS \propto (1 - \alpha)^2 \). Therefore

\[
\frac{(1 - \alpha_{PB})^2}{(1 - \alpha_{NL})^2} = 1 + G_{PS}.
\]
Hence:

\[ G_{PS} = \frac{(1 - a_{PB})^2}{(1 - a_{NL})^2} - 1, \quad \text{B.14} \]

where \( a_{NL} = 0.89 \) and \( a_{PB} \) can be expressed in terms of \( G_{KF} \) as in Equation B.13.

Consider \( \sigma \). Once again, by definition, at time \( t = 0 \):

\[ \frac{\sigma}{\sigma_{NL}} = 1 - G_\sigma. \]

Hence:

\[ G_\sigma = 1 - \frac{\sigma}{\sigma_{NL}}. \]

Substituting for \( \sigma \) by Equation B.6:

\[ G_\sigma = 1 - \left\{ \frac{\sqrt{3} \left[ 16 \cdot a_{PB}^2 - 20 \cdot a_{PB}^3 + 7 \cdot a_{PB}^4 \right]}{0.9888} \right\}. \quad \text{B.15} \]

Again, \( a_{PB} \) can be expressed in terms of \( G_{KF} \) as in Equation B.13.

Hence postburn, \( a_{PB} \) may be determined based on a value of \( G_{KF} \) for uninjured tissue \( (G_{KF, TI}) \) and injured tissue \( (G_{KF, BI}) \). The perturbations to PS and \( \sigma \) in uninjured and injured tissue may then be determined using Equations B.14 and B.15.
The information provided by Dr. T. Lund for each of the 5 patients studied at the National Burn Centre were as follows:

i. Patient data on admission:
   - Age and sex
   - Total burn surface area or degree of burn

ii. Laboratory data:
   - Hematocrit
   - Plasma albumin concentration
   - COPs in plasma and interstitial fluid from injured and uninjured skin

iii. Weight changes with time postburn

iv. Resuscitation protocol:
   - Clear fluids: Acetated Ringers, AR
     Hypertonic Ringers, HR
     Normal Saline, NS
     5% Dextrose, D5W
   - Colloidal fluids: Iso-oncotic
     Hyperoncotic
   - Blood transfusions

v. Urine produced

vi. Initial blood loss due to surgical procedures

The original patient data sheets provided for the current study are presented in Figures C.1 to C.5. Summaries of the patient information for Patients 1, 2, 3, 4 and 5 are shown in Tables C.1 to C.10. Most of the information was taken from the patient data sheets in Figures C.1 to C.5 with the exception of the following:
Figure C.1: NBC Patient 1 Data Sheet
Figure C.2: NBC Patient 2 Data Sheet
Figure C.3: NBC Patient 3 Data Sheet
Figure C.4: NBC Patient 4 Data Sheet
Figure C.5: NBC Patient 5 Data Sheet
• patient preburn weight estimated based on fluid balances, discussed in Appendix E; and
• plasma volumes estimated from hematocrit data, discussed in Appendix D.

Table C.1: Admission and Laboratory Data for NBC Patient 1

30 year old male

Preburn weight = 88 kg

Total burn surface area = 21%

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<th>Time, hrs postburn</th>
<th>Hct, %</th>
<th>VPL, mL</th>
<th>cPL, g/L</th>
<th>ΠTP, mmHg</th>
<th>ΠBT, mmHg</th>
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Table C.2: Fluid Inputs and Outputs for NBC Patient 1

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<th>$J_{\text{PCF}}$, mL/h</th>
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$T_{\text{start}}$ and $T_{\text{end}}$ represent the time at which fluid resuscitation starts and ends respectively, $J_{\text{CLF}}$ and $J_{\text{PCF}}$ the resuscitation rates of clear and colloidal fluids respectively and $J_{\text{URINE}}$ is the rate of urine production.

i) Between 0 and 1 hour postburn, 200 mL of blood was lost due to surgical procedures.

ii) Exudation Rate = 45.09 mL/h
### Table C.3: Admission and Laboratory Data for NBC Patient 2

- **42 year old female**
- **Preburn weight = 65 kg**
- **Total burn surface area = 51%**

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<thead>
<tr>
<th>Time, hrs postburn</th>
<th>Hct, %</th>
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<th>$c_{PL}$, g/L</th>
<th>$\Pi_{TD}$, mmHg</th>
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### Table C.4: Fluid Inputs and Outputs for NBC Patient 2

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<th>$J_{\text{PCF}}$, mL/h</th>
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</table>

i) Between 0 and 1 hour postburn, 400 mL of blood was lost due to surgical procedures.

ii) Between 61 and 63 hours, 500 mL of blood was given to this patient.

iii) Between 1 and 2.5 hours, 500 mL of hyperoncotic fluid was given. To determine the albumin content of this fluid, an "equivalent volume" of 750 mL was assumed.

iv) Exudation Rate = 80.89 mL/h
Table C.5: Admission and Laboratory Data for NBC Patient 3

55 year old male

Preburn weight = 70 kg

Degree = 80%

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<th>Hct, %</th>
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<th>( c_{PL} ), g/L</th>
<th>( \Pi_{TI} ), mmHg</th>
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Table C.6: Fluid Inputs and Outputs for NBC Patient 3

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<th>$J_{\text{PCF}}$, mL/h</th>
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i) Between 0 and 0.8 hours postburn, 200 mL of blood was lost due to surgical procedures.

ii) Exudation Rate = 136.64 mL/h
Table C.7: Admission and Laboratory Data for NBC Patient 4

57 year old male

Preburn weight = 72 kg

Total burn surface area = 59%

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Table C.8: Fluid Inputs and Outputs for NBC Patient 4

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</tr>
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<td>8.0</td>
<td>14.0</td>
<td>772.22</td>
<td>166.67</td>
<td>74.50</td>
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<td>772.22</td>
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<tr>
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<td>166.67</td>
<td>74.50</td>
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<tr>
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<td>74.50</td>
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<td>250.00</td>
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<td>48.0</td>
<td>72.0</td>
<td>233.33</td>
<td>31.25</td>
<td>68.96</td>
</tr>
</tbody>
</table>

i) Between 0 and 0.5 hours postburn, 100 mL of blood was lost due to surgical procedures.

ii) Exudation Rate = 103.65 mL/h
Table C.9: Admission and Laboratory Data for NBC Patient 5

31 year old male

Preburn weight = 78 kg

Total burn surface area = 72%

<table>
<thead>
<tr>
<th>Time, hrs postburn</th>
<th>Hct, %</th>
<th>$V_{PL}$, mL</th>
<th>$c_{PL}$, g/L</th>
<th>$\Pi_{TI}$, mmHg</th>
<th>$\Pi_{BT}$, mmHg</th>
<th>$\Pi_{PL}$, mmHg</th>
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<tbody>
<tr>
<td>0.0</td>
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<tr>
<td>12.0</td>
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<td>-</td>
<td>-</td>
<td>7.5</td>
<td>8.5</td>
<td>8.0</td>
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<tr>
<td>13.0</td>
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<td>-</td>
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<td>4042.08</td>
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<td>41.0</td>
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<td>6866.93</td>
<td>18.0</td>
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<td>45.0</td>
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<td>59.0</td>
<td>-</td>
<td>-</td>
<td>20.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>72.0</td>
<td>32</td>
<td>5489.94</td>
<td>19.0</td>
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</tr>
</tbody>
</table>
Table C.10: Fluid Inputs and Outputs for NBC Patient 5

<table>
<thead>
<tr>
<th>$T_{\text{start}}$, hours postburn</th>
<th>$T_{\text{end}}$, hours postburn</th>
<th>$J_{\text{CLF}}$, mL/h</th>
<th>$J_{\text{PCF}}$, mL/h</th>
<th>$J_{\text{URINE}}$, mL/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>1.25</td>
<td>0.00</td>
<td>0.00</td>
<td>138.54</td>
</tr>
<tr>
<td>1.25</td>
<td>8.0</td>
<td>1037.04</td>
<td>74.07</td>
<td>138.54</td>
</tr>
<tr>
<td>8.0</td>
<td>12.0</td>
<td>1025.00</td>
<td>0.00</td>
<td>138.54</td>
</tr>
<tr>
<td>12.0</td>
<td>15.0</td>
<td>1025.00</td>
<td>229.17</td>
<td>138.54</td>
</tr>
<tr>
<td>15.0</td>
<td>24.0</td>
<td>1115.91</td>
<td>229.17</td>
<td>138.54</td>
</tr>
<tr>
<td>24.0</td>
<td>26.0</td>
<td>486.74</td>
<td>156.25</td>
<td>43.83</td>
</tr>
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<td>38.0</td>
<td>395.83</td>
<td>156.25</td>
<td>43.83</td>
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<tr>
<td>38.0</td>
<td>40.0</td>
<td>645.83</td>
<td>156.25</td>
<td>43.83</td>
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<td>156.25</td>
<td>43.83</td>
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<td>48.0</td>
<td>50.0</td>
<td>229.17</td>
<td>52.08</td>
<td>92.50</td>
</tr>
<tr>
<td>50.0</td>
<td>52.0</td>
<td>229.17</td>
<td>175.83</td>
<td>92.50</td>
</tr>
<tr>
<td>52.0</td>
<td>72.0</td>
<td>229.17</td>
<td>52.08</td>
<td>92.50</td>
</tr>
</tbody>
</table>

i) Between 0 and 1.25 hours postburn, 200 mL of blood was lost due to surgical procedures.

ii) Between 1.25 and 8 hours, 500 mL of macrodex (dextran 70, 6%) was given. To determine the albumin content of this fluid, an "equivalent volume" of 750 mL was assumed.

iii) Exudation Rate = 137.03 mL/h
Appendix D: Estimation of Plasma Volume from Hematocrit Data

Hematocrit, Hct, is a measure of the packed cell volume of red blood cells and is expressed as a percentage of the total blood volume, BV. Thus:

\[ Hct = \frac{\text{Cell Volume}}{\text{Blood Volume}} = \frac{CV}{BV}. \] \hspace{1cm} \text{(D.1)}

The plasma and cellular elements of the blood together constitute the total blood volume, i.e.,

\[ BV = PV + CV. \] \hspace{1cm} \text{(D.2)}

Consequently,

\[ PV = BV \cdot [1 - Hct] = \frac{CV}{Hct} [1 - Hct]. \] \hspace{1cm} \text{(D.3)}

Based on the above relationships and assuming a normal hematocrit of 45% and 41% for the standard male and female respectively [Reference Man ICRP 23, 1975], and a normal plasma volume of 3200 mL, normal values of cell and blood volume for the standard 70-kg male and female can be estimated and are shown in Table D.1.

Table D.1: Normal Values for 70-kg, 170-cm Individual

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit, Hct, %</td>
<td>45</td>
<td>41</td>
</tr>
<tr>
<td>Plasma Volume, PV, mL</td>
<td>3200.00</td>
<td>3200.00</td>
</tr>
<tr>
<td>Cell Volume, CV, mL</td>
<td>2618.18</td>
<td>2223.73</td>
</tr>
<tr>
<td>Blood Volume, BV, mL</td>
<td>5818.18</td>
<td>5423.73</td>
</tr>
</tbody>
</table>
In order to account for differing preburn weights of the patients, the various volumes are modified by a weight ratio, WR, where

\[ WR = \frac{\text{Preburn weight of patient}}{70}. \]

However, the weight of the patients before injury were unknown on admission. In most of the patients studied, the first few weights were recorded 12 hours and then 24 hours postburn. It was possible to estimate the preburn weight for each patient, based on fluid balances on the patient between two successive times when measurements of weight, fluids given and fluids lost were available, from

\[
\text{Change in patient weight} = \text{Volume of fluids given - Volume of fluids lost}
\]

The procedure is described in detail in Appendix E.

Following from personal communication with Dr. T. Lund, Patients 1 and 2 were considered to be slightly unusual in that their normal hematocrit were below the normal population value. It was concluded that a value of 37% should be used for the normal hematocrit for these two individuals.

Initial blood losses due to escharatomies and fasciotomies were clinically estimated for each patient and were also provided [personal communication with Dr. T. Lund]. In addition, it was assumed that for laboratory purposes, 10 mL blood samples were taken from each patient, four times each day over the three-day period. Associated with these blood losses from the circulating plasma is cell loss, and as such, the changing cell volume was taken account of in estimating the changing plasma volume.

Two patients, 2 and 5, received blood transfusions. This addition to the blood volume and the resulting change in cell volume was considered in estimating the plasma volume. An example of how plasma volumes were estimated is presented in Example D.1.
Example D.1: Estimation of Plasma Volume for Patient 1

a. Time of injury, $t = 0$

Normal values for Hct, CV, PV and BV

b. Time of admission, $t = 13$ hours post-injury

200 mL of blood estimated to be lost 1-hour postinjury

Therefore:

$$CV = 2362.63 - (200 \times 0.37) = 2288.63 \text{ mL}$$
$$PV = \frac{2288.63}{0.40} \times [1 - 0.40] = 3432.95 \text{ mL}$$
$$BV = PV + CV = 5721.58 \text{ mL}$$

c. $t = 31$ hours post-injury

30 mL of blood taken for laboratory analysis

Therefore:

$$CV = 2288.63 - (30 \times 0.40) = 2276.63 \text{ mL}$$
$$PV = \frac{2276.63}{0.35} \times [1 - 0.35] = 4228.03 \text{ mL}$$
$$BV = 6504.66 \text{ mL}$$

d. $t = 55$ hours post-injury

40 mL of blood taken for laboratory analysis

Therefore:
\[ CV = 2276.63 - (40 \times 0.35) = 2262.63 \text{ mL} \]
\[ PV = \frac{2262.63}{0.37} \times (1 - 0.37) = 3852.59 \text{ mL} \]
\[ BV = 6115.22 \text{ mL} \]

e. \ t = 66 \text{ hours post-injury}

20 mL of blood taken for laboratory analysis

Therefore:

\[ CV = 2262.63 - (20 \times 0.37) = 2255.23 \text{ mL} \]
\[ PV = \frac{2255.23}{0.35} \times (1 - 0.35) = 4188.28 \text{ mL} \]
\[ BV = 6443.51 \text{ mL} \]
Appendix E: Estimation of Exudation Rate Based on NBC Patient Data

The rate of exudation from the injured tissue was determined by performing a fluid balance on each of the 5 patients between two successive measurement times, from

"Volume" of fluid in patient = Volume of fluids given - Volume of fluids lost

where the "Volume" of the patient is the product of the weight change of the patient and the density of fluids in the body, which is assumed to be 1 kg/L.

The fluids given include:

(i) clear fluids such as acetated Ringers, hypertonic Ringers and dextrose; and
(ii) protein-containing fluids such as iso-oncotic fluids, hyper-oncotic fluids and blood transfusions.

The fluids lost include:

(i) urine produced;
(ii) blood losses;
(iii) evaporative fluid, discussed in Chapter 4 and defined as:

\[ J_{EVAP} = [25 + DEG] \times TBSA \]  \hspace{1cm} 4.8

(iv) exudative fluid.

Therefore, knowing the change in weight of the patient between two times, the fluids given, urine, blood and evaporative fluid lost, the exudative fluid loss may be determined from the above fluid balance.

As discussed previously, preburn patient weights were not known on admission. This weight is necessary in estimating the total body surface area, TBSA, to determine the evaporative fluid loss. In most of the patients studied, the first few weights were recorded 12 hours postburn and then 24 hours postburn. In order to determine the preburn weight for each patient, it was assumed that the exudation and evaporation rate during the first
indicated times when the patient's weight was recorded, was the same as that in the first few hours postburn. For example,

\[
\text{Rate between 12 and 24 hours postburn} = \text{Rate between 0 and 12 hours postburn.}
\]

The resulting preburn weight could then be used to estimate the fluid loss due to evaporation and hence, that due to exudation. The sample calculation, Example E.1, illustrates this procedure.

**Example E.1: Sample Calculation - Estimation of Exudation Rate**

In Patient 1, the first weights were measured 24 and 48 hours postburn.

At \( t = 24 \) hours, weight = 92.4 kg

At \( t = 48 \) hours, weight = 89.5 kg

Hence, change in weight = -2.9 kg

Assuming the density of the fluids in the body is 1 kg/L;

\[
\text{Change in body volume} = -2900 \text{ mL}
\]

Fluids given in this period = 3840 mL D5W + 750 mL Iso-oncotic fluid = 4590 mL

Fluid losses measured in this period = 2558 mL urine + 40 mL blood = 2598 mL

Fluid lost due to evaporation = \((25 + 21) \times W^{0.425} \times 170^{0.725} \times 71.84 \times 10^{-4}\)

The preburn weight, \( W \), is unknown.

Therefore:

\[
\text{Fluid loss due to both evaporation and exudation} = -2900 - 4590 + 2598 = 4892 \text{ mL in 24 hours} = 203.83 \text{ mL/h}
\]

To determine the preburn weight, consider the period between 0 and 24 hours postburn.

Assume the rate of evaporative and exudative fluid loss between 24 and 48 hours is the same as that between 0 and 24 hours postburn.

Change in body weight = \((92.4 - W) \text{ kg} = (92.4 - W) \times 10^3 \text{ mL}\)
Fluids given in this period = \((4500 + 7000)\) mL AR + 150 mL Iso-oncotic fluid
\[= 11650\] mL

Fluids lost in this period = \((600 + 1958)\) mL urine + \((200 + 20)\) mL blood = 2778 mL

Fluid loss due to evaporation and exudation = 4892 mL
\[92400 - W = 11650 - 2778 - 4892\]
\[W = 88420 \text{ ml} \approx 88.4 \text{ kg}\]

Therefore fluid lost due to evaporation:
\[J_{EVAP} = (25 + 21) \times 88^{0.425} \times 170^{0.725} \times 71.84 \times 10^{-4} \approx 91.75 \text{ mL/h}\]

Hence, fluid lost due to exudation, \(J_{EXUD} \approx \frac{4892}{24} - 91.75 \approx 112.08 \text{ mL/h}\)

Exudation rates during the subsequent time periods were also determined from fluid balances as previously described. However, discussions with Dr. T. Lund indicated that the patient weights were not taken in a consistent manner. As such, there was variability in the exudation rates determined for each patient. However, considering the five patients collectively would give more reasonable estimates for the exudation rate. Consequently, the exudation rate for each of the five patients was estimated based on the first set of recorded weights, usually between 12 and 24 hours postburn. It was then assumed that the rate of exudation was proportional to the percentage burn surface area or degree of burn. The data from the five patients and the fitted relationship are shown in Figure E.1. The fitted relationship was forced to pass through the point \(J_{EXUD} = 0\) when \(DEG = 0\%). The relationship obtained was
\[J_{EXUD} = 0.0244 \times DEG \times W,\]  
E.1

where \(J_{EXUD}\) is the fluid loss due to exudation, \(DEG\) the degree of burn and \(W\) the patient's preburn weight. Based on this relationship, an exudative rate was determined and assumed constant for each patient during the first three days postburn.
Figure E.1: Exudation Relationship based on NBC Patient Data
Appendix F: Birkeland's Patient Data [1969]

This data was used directly in the parameter estimation procedure. The data which could be directly applied in the current study were the plasma volumes of five sets of burn patients, grouped according to percentage burn surface area as presented in Table F.1. The curved lines shown in Figure F.1 represent graphical estimates of the plasma volumes as a function of time for each burn group. The postburn times and corresponding plasma volumes shown in Table F.2 were manually extracted from the solid lines shown in Figure F.1.

Table F.1: Grouping of Birkeland's Patients

<table>
<thead>
<tr>
<th>Burn Group</th>
<th>Percentage Burn, %</th>
<th>Number of Burn Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>2 - 9</td>
<td>11</td>
</tr>
<tr>
<td>II</td>
<td>10 - 18</td>
<td>21</td>
</tr>
<tr>
<td>III</td>
<td>20 - 30</td>
<td>17</td>
</tr>
<tr>
<td>IV</td>
<td>39 - 49</td>
<td>7</td>
</tr>
<tr>
<td>V</td>
<td>54 - 90</td>
<td>11</td>
</tr>
</tbody>
</table>
Figure F.1: Patient Blood and Plasma Volume Observations on Admission and Prior to Start of Fluid Therapy by Birkeland
Table F.2: Plasma Volume Data (mL) for Groups of Birkeland's Patients

<table>
<thead>
<tr>
<th>Time, hours postburn</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Group IV</th>
<th>Group V</th>
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</thead>
<tbody>
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<td>3200.00</td>
<td>3200.00</td>
<td>3200.00</td>
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<td>-</td>
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<td>1550.78</td>
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<td>4.0</td>
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<td>1351.11</td>
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<td>6.0</td>
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<td>1706.67</td>
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<td>-</td>
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<td>10.0</td>
<td>2540.00</td>
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<td>1617.78</td>
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<td>-</td>
</tr>
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<td>12.0</td>
<td>2506.67</td>
<td>2270.00</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Appendix G: Determination of Exudation Rate for Birkeland's Patients

Exudative fluid losses from Birkeland's patients were estimated based on data available from a study by Davies [1982]. In this study, it was assumed that the sodium concentration in the fluid leaking from the burned surface is the same as that of serum. As a result, chemical analysis of sodium extracted with water from the dressings covering burned tissue gave an indication of the volume of exudate. The rate of exudative fluid loss from patients with different burn areas was monitored during the initial period postburn before fluid therapy was initiated. These patient data [Davies, 1982] are presented in Table G1. To the best of the author's knowledge, this is the only available data that could be used to estimate the initial exudative fluid loss from the patients studied by Birkeland.

Table G.1: Area of Burn and Exudation Rate Postburn

<table>
<thead>
<tr>
<th>Area of Burn, cm²</th>
<th>Average Exudate Output, mL/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>7400</td>
<td>26.92</td>
</tr>
<tr>
<td>7960</td>
<td>25.67</td>
</tr>
<tr>
<td>5624</td>
<td>36.71</td>
</tr>
<tr>
<td>7164</td>
<td>22.63</td>
</tr>
<tr>
<td>5890</td>
<td>38.50</td>
</tr>
<tr>
<td>5220</td>
<td>38.79</td>
</tr>
<tr>
<td>4400</td>
<td>12.83</td>
</tr>
<tr>
<td>2970</td>
<td>24.58</td>
</tr>
</tbody>
</table>

A linear relationship was determined based on the assumption that the rate of exudation was proportional to the area of the burn. The clinical data and the fitted relationship are
shown in Figure G.1. The fitted relationship was forced to pass through the point $J_{\text{EXUD}} = 0$ when $\text{DEG} = 0\%$. The relationship obtained was

$$ J_{\text{EXUD}} = \frac{8.85}{8 \times 10^3} \times A $$

where $J_{\text{EXUD}}$ is the rate of exudation and $A$ the area of burn in cm$^2$ given by

$$ A = \text{DEG} \times \text{TBSA}. $$

The rate of exudative fluid loss for each group was determined as the $J_{\text{EXUD}}$ value corresponding to the mid-point value of the percentage burn surface area of that group. The exudation rates estimated from the NBC patient information were about 8 times greater than those reported by Davies for the same burn surface area. This difference may be explained by the fact that the NBC patients received fluid therapy, while fluid resuscitation had not been initiated in the patients studied by Davies in the period under consideration. Similarly, the patients in the various groups investigated by Birkeland received no fluid therapy during the postburn times indicated in Table F.2.
Appendix H: Clinical Data from Arturson's Patient [Arturson et al., 1989]

Information regarding the treatment and care of a patient included:

i) fluid therapy consisting of acetated Ringers, 5% glucose, plasma and albumin infusions;

ii) cumulative urine production;

iii) erythrocyte volume fraction; and

iv) change in body mass.

A summary of this information is presented in Tables H.1 and H.2. These data were used to validate the model once the best-fit parameters were determined.

The patient, a 62-year-old man with a body mass of 77-kg and a 58% total burn area, was treated during the first 48 hours. Primary excision and grafting with synthetic skin was performed between 26.5 and 30 hours after burn injury.

Table H.1: Erythrocyte Volume Fraction Data [Arturson et al., 1989]

<table>
<thead>
<tr>
<th>Time, hours postburn</th>
<th>Erythrocyte Volume Fraction, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>50</td>
</tr>
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Table H.2: Fluid Inputs and Outputs to Patient [Arturson et al., 1989]

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Appendix I: Clinical Data from Roa's Patients [Roa et al., 1990; personal communication]

The information pertaining to two patients included:

i) intravenous fluid and colloid input;

ii) urine volume;

iii) hematocrit; and

iv) plasma protein concentration.

Personal data was collected on admission and is summarized in Table I.1. These data were used to validate the model once the best-fit parameters were determined.

Table I.1: Personal Data from Roa's Patients [Roa et al., 1990]

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Table I.3: Fluid Input and Output for Patient 2 [Roa et al., 1990]

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</table>
Table I.4: Monitored Clinical Data for Patient 1 [Roa et al., 1990]

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<th>Hematocrit, %</th>
<th>c_{PL}, g/L</th>
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<td>30.00</td>
</tr>
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<td>-</td>
</tr>
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<td>-</td>
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<td>-</td>
</tr>
<tr>
<td>17.73</td>
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<td>-</td>
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</tr>
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<td>-</td>
<td>30.00</td>
</tr>
<tr>
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<td>43.33</td>
<td>-</td>
</tr>
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<td>33.33</td>
</tr>
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<td>34.55</td>
<td>42.22</td>
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<td>37.78</td>
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<td>36.36</td>
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</tbody>
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Table I.4 Continued: Monitored Clinical Data for Patient 1 [Roa et al., 1990]

<table>
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<th>Time, hours postburn</th>
<th>Hematocrit, %</th>
<th>$c_{PL}$, g/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>36.82</td>
<td>-</td>
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</tr>
<tr>
<td>37.27</td>
<td>44.44</td>
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<td>-</td>
<td>36.67</td>
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<td>38.64</td>
<td>44.44</td>
<td>-</td>
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<td>39.09</td>
<td>-</td>
<td>36.67</td>
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<td>42.73</td>
<td>42.22</td>
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<td>46.36</td>
<td>38.89</td>
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<td>47.27</td>
<td>-</td>
<td>38.89</td>
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</tbody>
</table>

Table I.5: Monitored Clinical Data for Patient 2 [Roa et al., 1990]

<table>
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<th>Hematocrit, %</th>
<th>$c_{PL}$, g/L</th>
</tr>
</thead>
<tbody>
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<td>1.82</td>
<td>56.67</td>
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<td>11.36</td>
<td>60.00</td>
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<td>-</td>
<td>35.56</td>
</tr>
<tr>
<td>18.18</td>
<td>55.56</td>
<td>-</td>
</tr>
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<td>26.36</td>
<td>60.00</td>
<td>32.22</td>
</tr>
<tr>
<td>35.46</td>
<td>-</td>
<td>28.89</td>
</tr>
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<td>41.82</td>
<td>51.11</td>
<td>-</td>
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<tr>
<td>44.55</td>
<td>53.33</td>
<td>-</td>
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<tr>
<td>45.46</td>
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<td>30.00</td>
</tr>
</tbody>
</table>
Appendix J: Minimum Objective Function Value Results

Table J.1: Minimum OBJFUN Values for NBC Patient 1 Based on 12 Data Points

<table>
<thead>
<tr>
<th>EXFAC</th>
<th>r, h⁻¹</th>
<th>$G_{kF,TL}$</th>
<th>$G_{kF,RT}$</th>
<th>OBJFUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.008</td>
<td>0.00</td>
<td>4.00</td>
<td>0.71</td>
</tr>
<tr>
<td>0.50</td>
<td>0.008</td>
<td>0.00</td>
<td>5.00</td>
<td>0.65</td>
</tr>
<tr>
<td>0.75</td>
<td>0.008</td>
<td>0.00</td>
<td>6.00</td>
<td>0.60</td>
</tr>
<tr>
<td>1.00</td>
<td>0.008</td>
<td>0.00</td>
<td>6.00</td>
<td>0.55</td>
</tr>
<tr>
<td>0.25</td>
<td>0.025</td>
<td>0.00</td>
<td>6.00</td>
<td>0.68</td>
</tr>
<tr>
<td>0.50</td>
<td>0.025</td>
<td>0.00</td>
<td>6.00</td>
<td>0.60</td>
</tr>
<tr>
<td>0.75</td>
<td>0.025</td>
<td>0.00</td>
<td>7.00</td>
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<td>1.00</td>
<td>0.025</td>
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<td>0.48</td>
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</table>

Table J.2: Minimum OBJFUN Values for NBC Patient 2 Based on 20 Data Points

<table>
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<tr>
<th>EXFAC</th>
<th>r, h⁻¹</th>
<th>$G_{kF,TL}$</th>
<th>$G_{kF,RT}$</th>
<th>OBJFUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.008</td>
<td>0.00</td>
<td>3.00</td>
<td>2.91</td>
</tr>
<tr>
<td>0.50</td>
<td>0.008</td>
<td>0.00</td>
<td>4.00</td>
<td>2.67</td>
</tr>
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<td>0.008</td>
<td>0.00</td>
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<td>2.56</td>
</tr>
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<td>3.00</td>
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<td>0.50</td>
<td>3.00</td>
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<td>0.025</td>
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<td>4.00</td>
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</table>
Table J.3: Minimum OBJFUN Values for NBC Patient 3 Based on 22 Data Points

<table>
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<tr>
<th>EXFAC</th>
<th>$r$, h^{-1}</th>
<th>$G_{k_{TIP}}$</th>
<th>$G_{k_{RT}}$</th>
<th>OBJFUN</th>
</tr>
</thead>
<tbody>
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<td>0.008</td>
<td>0.00</td>
<td>4.00</td>
<td>5.38</td>
</tr>
<tr>
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<td>5.00</td>
<td>5.06</td>
</tr>
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<td>0.00</td>
<td>5.00</td>
<td>4.76</td>
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<td>0.00</td>
<td>5.00</td>
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<tr>
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<td>0.025</td>
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<td>0.025</td>
<td>0.00</td>
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Table J.4: Minimum OBJFUN Values for NBC Patient 4 Based on 21 Data Points

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<th>$G_{k_{TIP}}$</th>
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<th>OBJFUN</th>
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</tr>
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<td>3.00</td>
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</tr>
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<td>0.008</td>
<td>1.00</td>
<td>3.00</td>
<td>2.90</td>
</tr>
<tr>
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<td>0.008</td>
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<td>4.00</td>
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<td>0.25</td>
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<td>3.00</td>
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</tr>
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<td>1.00</td>
<td>4.00</td>
<td>2.99</td>
</tr>
<tr>
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<td>4.00</td>
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Table J.5: Minimum OBJFUN Values for NBC Patient 5 Based on 30 Data Points

<table>
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<th>$G_{kFT}$</th>
<th>$G_{kFT}$</th>
<th>OBJFUN</th>
</tr>
</thead>
<tbody>
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<td>5.00</td>
<td>3.99</td>
</tr>
<tr>
<td>0.75</td>
<td>0.008</td>
<td>0.00</td>
<td>5.00</td>
<td>3.99</td>
</tr>
<tr>
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<td>6.00</td>
<td>4.00</td>
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<td>0.50</td>
<td>4.00</td>
<td>3.86</td>
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Table J.6: Minimum OBJFUN Values for Combination of NBC Patients 2, 3, 4 and 5
(Degrees of Burn Greater Than 25%)

<table>
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<th>EXFAC</th>
<th>r, h⁻¹</th>
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<th>$G_{kFT}$</th>
<th>OBJFUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.008</td>
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<td>4.00</td>
<td>16.56</td>
</tr>
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<td>0.00</td>
<td>5.00</td>
<td>15.80</td>
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<td>0.008</td>
<td>0.00</td>
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<td>15.15</td>
</tr>
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<td>0.008</td>
<td>0.00</td>
<td>5.00</td>
<td>14.67</td>
</tr>
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<td>0.025</td>
<td>0.50</td>
<td>3.00</td>
<td>14.68</td>
</tr>
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<td>0.025</td>
<td>0.50</td>
<td>4.00</td>
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<td>0.025</td>
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<td>4.00</td>
<td>13.01</td>
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<td>0.025</td>
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</tr>
</tbody>
</table>
Table J.7: Minimum OBJFUN Values for Birkeland Burn Group I Based on 6 Data Points

<table>
<thead>
<tr>
<th>EXFAC</th>
<th>$r$, h$^{-1}$</th>
<th>$G_{ke,TL}$</th>
<th>$G_{ke,BT}$</th>
<th>OBJFUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.008</td>
<td>0.60</td>
<td>3.00</td>
<td>$2.005 \times 10^{-4}$</td>
</tr>
<tr>
<td>0.50</td>
<td>0.008</td>
<td>0.60</td>
<td>4.00</td>
<td>$2.100 \times 10^{-4}$</td>
</tr>
<tr>
<td>0.75</td>
<td>0.008</td>
<td>0.60</td>
<td>4.00</td>
<td>$2.124 \times 10^{-4}$</td>
</tr>
<tr>
<td>1.00</td>
<td>0.008</td>
<td>0.60</td>
<td>4.00</td>
<td>$2.156 \times 10^{-4}$</td>
</tr>
<tr>
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<td>0.70</td>
<td>3.00</td>
<td>$3.569 \times 10^{-4}$</td>
</tr>
<tr>
<td>0.50</td>
<td>0.025</td>
<td>0.70</td>
<td>3.00</td>
<td>$3.562 \times 10^{-4}$</td>
</tr>
<tr>
<td>0.75</td>
<td>0.025</td>
<td>0.70</td>
<td>3.00</td>
<td>$3.560 \times 10^{-4}$</td>
</tr>
<tr>
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<td>0.025</td>
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<td>5.00</td>
<td>$4.941 \times 10^{-4}$</td>
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</tbody>
</table>

Table J.8: Minimum OBJFUN Values for Birkeland Burn Group II Based on 6 Data Points

<table>
<thead>
<tr>
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<th>$r$, h$^{-1}$</th>
<th>$G_{ke,TL}$</th>
<th>$G_{ke,BT}$</th>
<th>OBJFUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.008</td>
<td>0.90</td>
<td>9.00</td>
<td>$1.185 \times 10^{-3}$</td>
</tr>
<tr>
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<td>0.008</td>
<td>0.90</td>
<td>9.00</td>
<td>$1.164 \times 10^{-3}$</td>
</tr>
<tr>
<td>0.75</td>
<td>0.008</td>
<td>0.90</td>
<td>9.00</td>
<td>$1.151 \times 10^{-3}$</td>
</tr>
<tr>
<td>1.00</td>
<td>0.008</td>
<td>0.90</td>
<td>10.00</td>
<td>$1.128 \times 10^{-3}$</td>
</tr>
<tr>
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<td>0.025</td>
<td>1.00</td>
<td>9.00</td>
<td>$0.958 \times 10^{-3}$</td>
</tr>
<tr>
<td>0.50</td>
<td>0.025</td>
<td>1.10</td>
<td>8.00</td>
<td>$0.918 \times 10^{-3}$</td>
</tr>
<tr>
<td>0.75</td>
<td>0.025</td>
<td>1.10</td>
<td>8.00</td>
<td>$0.882 \times 10^{-3}$</td>
</tr>
<tr>
<td>1.00</td>
<td>0.025</td>
<td>1.10</td>
<td>8.00</td>
<td>$0.855 \times 10^{-3}$</td>
</tr>
</tbody>
</table>
Table J.9: Minimum OBJFUN Values for Birkeland Burn Group III Based on 5 Data Points

<table>
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<tr>
<th>EXFAC</th>
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<th>( G_{\text{FETI}} )</th>
<th>( G_{\text{FEBT}} )</th>
<th>OBJFUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.008</td>
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<td>7.733\times10^{-3}</td>
</tr>
<tr>
<td>0.50</td>
<td>0.008</td>
<td>3.40</td>
<td>8.00</td>
<td>7.886\times10^{-3}</td>
</tr>
<tr>
<td>0.75</td>
<td>0.008</td>
<td>3.40</td>
<td>8.00</td>
<td>8.039\times10^{-3}</td>
</tr>
<tr>
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<td>0.008</td>
<td>3.20</td>
<td>8.00</td>
<td>8.571\times10^{-3}</td>
</tr>
<tr>
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<td>0.025</td>
<td>3.80</td>
<td>8.00</td>
<td>9.027\times10^{-3}</td>
</tr>
<tr>
<td>0.50</td>
<td>0.025</td>
<td>3.60</td>
<td>8.00</td>
<td>9.281\times10^{-3}</td>
</tr>
<tr>
<td>0.75</td>
<td>0.025</td>
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<td>9.00</td>
<td>9.874\times10^{-3}</td>
</tr>
<tr>
<td>1.00</td>
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<td>7.20</td>
<td>12.00</td>
<td>36.42\times10^{-3}</td>
</tr>
</tbody>
</table>

Table J.10: Minimum OBJFUN Values for Birkeland Burn Group IV Based on 4 Data Points

<table>
<thead>
<tr>
<th>EXFAC</th>
<th>( r, \text{ h}^{-1} )</th>
<th>( G_{\text{FETI}} )</th>
<th>( G_{\text{FEBT}} )</th>
<th>OBJFUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.008</td>
<td>5.80</td>
<td>6.00</td>
<td>5.682\times10^{-3}</td>
</tr>
<tr>
<td>0.50</td>
<td>0.008</td>
<td>5.80</td>
<td>6.00</td>
<td>5.728\times10^{-3}</td>
</tr>
<tr>
<td>0.75</td>
<td>0.008</td>
<td>5.80</td>
<td>6.00</td>
<td>5.773\times10^{-3}</td>
</tr>
<tr>
<td>1.00</td>
<td>0.008</td>
<td>5.80</td>
<td>6.00</td>
<td>5.819\times10^{-3}</td>
</tr>
<tr>
<td>0.25</td>
<td>0.025</td>
<td>5.80</td>
<td>6.00</td>
<td>6.242\times10^{-3}</td>
</tr>
<tr>
<td>0.50</td>
<td>0.025</td>
<td>5.80</td>
<td>6.00</td>
<td>6.301\times10^{-3}</td>
</tr>
<tr>
<td>0.75</td>
<td>0.025</td>
<td>5.80</td>
<td>6.00</td>
<td>6.359\times10^{-3}</td>
</tr>
<tr>
<td>1.00</td>
<td>0.025</td>
<td>5.80</td>
<td>6.00</td>
<td>6.418\times10^{-3}</td>
</tr>
</tbody>
</table>
Table J.11: Minimum OBJFUN Values for Birkeland Burn Group V Based on 4 Data Points

<table>
<thead>
<tr>
<th>EXFAC</th>
<th>r, h⁻¹</th>
<th>$G_{F,TI}$</th>
<th>$G_{F,HT}$</th>
<th>OBJFUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.008</td>
<td>5.80</td>
<td>6.00</td>
<td>4.091 × 10⁻²</td>
</tr>
<tr>
<td>0.50</td>
<td>0.008</td>
<td>5.80</td>
<td>6.00</td>
<td>4.114 × 10⁻²</td>
</tr>
<tr>
<td>0.75</td>
<td>0.008</td>
<td>5.80</td>
<td>6.00</td>
<td>4.137 × 10⁻²</td>
</tr>
<tr>
<td>1.00</td>
<td>0.008</td>
<td>5.80</td>
<td>6.00</td>
<td>4.160 × 10⁻²</td>
</tr>
<tr>
<td>0.25</td>
<td>0.025</td>
<td>5.80</td>
<td>6.00</td>
<td>4.259 × 10⁻²</td>
</tr>
<tr>
<td>0.50</td>
<td>0.025</td>
<td>5.80</td>
<td>6.00</td>
<td>4.284 × 10⁻²</td>
</tr>
<tr>
<td>0.75</td>
<td>0.025</td>
<td>5.80</td>
<td>6.00</td>
<td>4.309 × 10⁻²</td>
</tr>
<tr>
<td>1.00</td>
<td>0.025</td>
<td>5.80</td>
<td>6.00</td>
<td>4.334 × 10⁻²</td>
</tr>
</tbody>
</table>

Table J.12: Minimum OBJFUN Values for Combination of Birkeland Burn Groups I and II (Degree of Burn Less Than 25%)

<table>
<thead>
<tr>
<th>EXFAC</th>
<th>r, h⁻¹</th>
<th>$G_{F,TI}$</th>
<th>$G_{F,HT}$</th>
<th>OBJFUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.008</td>
<td>0.50</td>
<td>12.00</td>
<td>9.021 × 10⁻³</td>
</tr>
<tr>
<td>0.50</td>
<td>0.008</td>
<td>0.50</td>
<td>12.00</td>
<td>9.175 × 10⁻³</td>
</tr>
<tr>
<td>0.75</td>
<td>0.008</td>
<td>0.50</td>
<td>12.00</td>
<td>9.324 × 10⁻³</td>
</tr>
<tr>
<td>1.00</td>
<td>0.008</td>
<td>0.50</td>
<td>12.00</td>
<td>9.470 × 10⁻³</td>
</tr>
<tr>
<td>0.25</td>
<td>0.025</td>
<td>0.60</td>
<td>12.00</td>
<td>9.688 × 10⁻³</td>
</tr>
<tr>
<td>0.50</td>
<td>0.025</td>
<td>0.60</td>
<td>12.00</td>
<td>9.827 × 10⁻³</td>
</tr>
<tr>
<td>0.75</td>
<td>0.025</td>
<td>0.60</td>
<td>12.00</td>
<td>9.964 × 10⁻³</td>
</tr>
<tr>
<td>1.00</td>
<td>0.025</td>
<td>0.60</td>
<td>12.00</td>
<td>10.10 × 10⁻³</td>
</tr>
</tbody>
</table>
Table J.13: Minimum OBJFUN Values for Combination of Birkeland Burn Groups

III, IV and V (Degrees of Burn Greater Than 25%)

<table>
<thead>
<tr>
<th>EXFAC</th>
<th>( r, \text{ h}^{-1} )</th>
<th>( G_{k,F,TL} )</th>
<th>( G_{k,F,RT} )</th>
<th>OBJFUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.008</td>
<td>3.80</td>
<td>8.00</td>
<td>6.557 \times 10^{-2}</td>
</tr>
<tr>
<td>0.50</td>
<td>0.008</td>
<td>3.60</td>
<td>8.00</td>
<td>6.735 \times 10^{-2}</td>
</tr>
<tr>
<td>0.75</td>
<td>0.008</td>
<td>3.40</td>
<td>8.00</td>
<td>6.994 \times 10^{-2}</td>
</tr>
<tr>
<td>1.00</td>
<td>0.008</td>
<td>3.80</td>
<td>9.00</td>
<td>7.110 \times 10^{-2}</td>
</tr>
<tr>
<td>0.25</td>
<td>0.025</td>
<td>3.80</td>
<td>8.00</td>
<td>6.905 \times 10^{-2}</td>
</tr>
<tr>
<td>0.50</td>
<td>0.025</td>
<td>3.60</td>
<td>8.00</td>
<td>7.158 \times 10^{-2}</td>
</tr>
<tr>
<td>0.75</td>
<td>0.025</td>
<td>4.00</td>
<td>9.00</td>
<td>7.274 \times 10^{-2}</td>
</tr>
<tr>
<td>1.00</td>
<td>0.025</td>
<td>5.20</td>
<td>10.00</td>
<td>11.88 \times 10^{-2}</td>
</tr>
</tbody>
</table>

Table J.14: Minimum OBJFUN Values for Combination of NBC and Birkeland Data

for Burns Less Than 25% for Factor of 30

<table>
<thead>
<tr>
<th>EXFAC</th>
<th>( r, \text{ h}^{-1} )</th>
<th>( G_{k,F,TL} )</th>
<th>( G_{k,F,RT} )</th>
<th>OBJFUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.008</td>
<td>0.50</td>
<td>7.00</td>
<td>2.53</td>
</tr>
<tr>
<td>0.50</td>
<td>0.008</td>
<td>0.50</td>
<td>7.00</td>
<td>2.18</td>
</tr>
<tr>
<td>0.75</td>
<td>0.008</td>
<td>0.50</td>
<td>8.00</td>
<td>1.89</td>
</tr>
<tr>
<td>1.00</td>
<td>0.008</td>
<td>0.50</td>
<td>8.00</td>
<td>1.65</td>
</tr>
<tr>
<td>0.25</td>
<td>0.025</td>
<td>0.50</td>
<td>8.00</td>
<td>1.92</td>
</tr>
<tr>
<td>0.50</td>
<td>0.025</td>
<td>0.50</td>
<td>9.00</td>
<td>1.63</td>
</tr>
<tr>
<td>0.75</td>
<td>0.025</td>
<td>0.50</td>
<td>9.00</td>
<td>1.39</td>
</tr>
<tr>
<td>1.00</td>
<td>0.025</td>
<td>0.50</td>
<td>10.00</td>
<td>1.19</td>
</tr>
</tbody>
</table>
Table J.15: Minimum OBJFUN Values for Combination of NBC and Birkeland Data
for Burns Greater Than 25% for Factor of 30

<table>
<thead>
<tr>
<th>EXFAC</th>
<th>$r$, h$^{-1}$</th>
<th>$G_{k_F, T}$</th>
<th>$G_{k_F, H}$</th>
<th>OBJFUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.008</td>
<td>0.50</td>
<td>7.00</td>
<td>36.36</td>
</tr>
<tr>
<td>0.50</td>
<td>0.008</td>
<td>0.50</td>
<td>7.00</td>
<td>33.91</td>
</tr>
<tr>
<td>0.75</td>
<td>0.008</td>
<td>0.50</td>
<td>8.00</td>
<td>31.75</td>
</tr>
<tr>
<td>1.00</td>
<td>0.008</td>
<td>0.50</td>
<td>9.00</td>
<td>29.86</td>
</tr>
<tr>
<td>0.25</td>
<td>0.025</td>
<td>0.50</td>
<td>8.00</td>
<td>30.80</td>
</tr>
<tr>
<td>0.50</td>
<td>0.025</td>
<td>1.00</td>
<td>7.00</td>
<td>28.44</td>
</tr>
<tr>
<td>0.75</td>
<td>0.025</td>
<td>1.00</td>
<td>8.00</td>
<td>26.26</td>
</tr>
<tr>
<td>1.00</td>
<td>0.025</td>
<td>1.00</td>
<td>9.00</td>
<td>28.05</td>
</tr>
</tbody>
</table>

Table J.16: Minimum OBJFUN Values for Combination of NBC and Birkeland Data
for Burns Less Than 25% for Factor of 100

<table>
<thead>
<tr>
<th>EXFAC</th>
<th>$r$, h$^{-1}$</th>
<th>$G_{k_F, T}$</th>
<th>$G_{k_F, H}$</th>
<th>OBJFUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.008</td>
<td>0.50</td>
<td>10.00</td>
<td>3.44</td>
</tr>
<tr>
<td>0.50</td>
<td>0.008</td>
<td>0.50</td>
<td>10.00</td>
<td>3.04</td>
</tr>
<tr>
<td>0.75</td>
<td>0.008</td>
<td>0.50</td>
<td>11.00</td>
<td>2.70</td>
</tr>
<tr>
<td>1.00</td>
<td>0.008</td>
<td>0.50</td>
<td>11.00</td>
<td>2.43</td>
</tr>
<tr>
<td>0.25</td>
<td>0.025</td>
<td>0.50</td>
<td>11.00</td>
<td>2.82</td>
</tr>
<tr>
<td>0.50</td>
<td>0.025</td>
<td>0.50</td>
<td>11.00</td>
<td>2.50</td>
</tr>
<tr>
<td>0.75</td>
<td>0.025</td>
<td>0.50</td>
<td>12.00</td>
<td>2.22</td>
</tr>
<tr>
<td>1.00</td>
<td>0.025</td>
<td>0.50</td>
<td>12.00</td>
<td>2.00</td>
</tr>
</tbody>
</table>
Table J.17: Minimum OBJFUN Values for Combination of NBC and Birkeland Data
for Burns Greater Than 25% for Factor of 100

<table>
<thead>
<tr>
<th>EXFAC</th>
<th>( r, \text{ h}^{-1} )</th>
<th>( G_{kF,TL} )</th>
<th>( G_{kF,BT} )</th>
<th>OBJFUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.008</td>
<td>1.00</td>
<td>10.00</td>
<td>54.62</td>
</tr>
<tr>
<td>0.50</td>
<td>0.008</td>
<td>1.50</td>
<td>9.00</td>
<td>49.60</td>
</tr>
<tr>
<td>0.75</td>
<td>0.008</td>
<td>2.0</td>
<td>8.00</td>
<td>44.83</td>
</tr>
<tr>
<td>1.00</td>
<td>0.008</td>
<td>2.50</td>
<td>8.00</td>
<td>40.49</td>
</tr>
<tr>
<td>0.25</td>
<td>0.025</td>
<td>1.50</td>
<td>9.00</td>
<td>45.56</td>
</tr>
<tr>
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<td>0.025</td>
<td>2.0</td>
<td>9.00</td>
<td>41.10</td>
</tr>
<tr>
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<td>0.025</td>
<td>2.0</td>
<td>9.00</td>
<td>37.01</td>
</tr>
<tr>
<td>1.00</td>
<td>0.025</td>
<td>2.50</td>
<td>10.00</td>
<td>44.20</td>
</tr>
</tbody>
</table>

Table J.18: Minimum OBJFUN Values for Combination of NBC and Birkeland Data
for Burns Less Than 25% for Factor of 200

<table>
<thead>
<tr>
<th>EXFAC</th>
<th>( r, \text{ h}^{-1} )</th>
<th>( G_{kF,TL} )</th>
<th>( G_{kF,BT} )</th>
<th>OBJFUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.008</td>
<td>0.50</td>
<td>11.00</td>
<td>4.40</td>
</tr>
<tr>
<td>0.50</td>
<td>0.008</td>
<td>0.50</td>
<td>11.00</td>
<td>4.00</td>
</tr>
<tr>
<td>0.75</td>
<td>0.008</td>
<td>0.50</td>
<td>11.00</td>
<td>3.68</td>
</tr>
<tr>
<td>1.00</td>
<td>0.008</td>
<td>0.50</td>
<td>12.00</td>
<td>3.41</td>
</tr>
<tr>
<td>0.25</td>
<td>0.025</td>
<td>0.50</td>
<td>12.00</td>
<td>3.87</td>
</tr>
<tr>
<td>0.50</td>
<td>0.025</td>
<td>0.50</td>
<td>12.00</td>
<td>3.55</td>
</tr>
<tr>
<td>0.75</td>
<td>0.025</td>
<td>0.50</td>
<td>12.00</td>
<td>3.29</td>
</tr>
<tr>
<td>1.00</td>
<td>0.025</td>
<td>0.50</td>
<td>13.00</td>
<td>3.08</td>
</tr>
</tbody>
</table>
Table J.19: Minimum OBJFUN Values for Combination of NBC and Birkeland Data
for Burns Greater Than 25% for Factor of 200

<table>
<thead>
<tr>
<th>EXFAC</th>
<th>r, h⁻¹</th>
<th>$G_{k_F,TI}$</th>
<th>$G_{k_F,BT}$</th>
<th>OBJFUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.008</td>
<td>2.00</td>
<td>9.00</td>
<td>67.21</td>
</tr>
<tr>
<td>0.50</td>
<td>0.008</td>
<td>2.50</td>
<td>8.00</td>
<td>60.68</td>
</tr>
<tr>
<td>0.75</td>
<td>0.008</td>
<td>3.00</td>
<td>8.00</td>
<td>54.53</td>
</tr>
<tr>
<td>1.00</td>
<td>0.008</td>
<td>2.50</td>
<td>9.00</td>
<td>49.59</td>
</tr>
<tr>
<td>0.25</td>
<td>0.025</td>
<td>2.50</td>
<td>9.00</td>
<td>57.30</td>
</tr>
<tr>
<td>0.50</td>
<td>0.025</td>
<td>2.50</td>
<td>9.00</td>
<td>51.43</td>
</tr>
<tr>
<td>0.75</td>
<td>0.025</td>
<td>2.50</td>
<td>9.00</td>
<td>46.64</td>
</tr>
<tr>
<td>1.00</td>
<td>0.025</td>
<td>3.00</td>
<td>11.00</td>
<td>60.03</td>
</tr>
</tbody>
</table>
This program was written in Fortran and run on an IBM 486 Personal Computer using the Microsoft Compiler.

PRINT*, 'ENTER SURFACE DATA FILE'
READ*, SURFILE

c CALCULATE / ASSIGN VARIOUS CONSTANTS

CALL CONSTA

C FIT COMPLIANCE DATA

CALL COMSPL

C ADJUST/CALCULATE NORMAL VALUES

CALL NORMAL

C ASSIGN/CALCULATE INITIAL VALUES

CALL INITV

C PERFORM OPTIMIZATION

C SET INITIAL VALUES AND LIMITS OF PARAMETERS TO BE DETERMINED

IF (IFLOP.EQ.1) THEN
  XXL(1)=XL(1)
  XXL(2)=XL(2)
  XXL(3)=XL(3)
ELSE IF (IFLOP .EQ. 2) THEN
  XXL(1)=XL1
  XXL(2)=XL2
  XXL(3)=XL3
ELSE IF (IFLOP .EQ. 3) THEN
  XXL(1)=XL1
  XXL(2)=XL2
  XXL(3)=XL3
ENDIF
**Subprogram PAROUT: Outputs estimated parameters and results**

```fortran
SUBROUTINE PAROUT
  IMPLICIT REAL*8 (A-H,O-Z)  
  INCLUDE 'outputcmn'       
  INCLUDE 'inputcmn'       
  INCLUDE 'normal.cmn'     
  INCLUDE 'expdatcmn'      
  CONTINUE               
  WRITE(6,100)           
  WRITE(6,103)           
  WRITE(6,102) (GKFTI = 'GKFTI',GKFTI)  
  WRITE(6,102) (RCOF5 = 'RCOF',RCOF5)  
  WRITE(6,102) (EXFAC = 'EXFAC')  
  WRITE(6,107)           
  WRITE(6,108)           
  DO 10 I=1,NUMEXP       
    IF (IPAR(1) .EQ. 1) THEN    
      IF (IRATIO .EQ. 1) THEN 
        PRINT *, EXPIBT(I),APIBT(I)*PIPLO/(APIPL(I)*c 
        WRITE(6,205)(EXPIBT(I),APIBT(I),APIBT(I)*piplo)  
      ENDIF    
    ENDIF    
    IF (IPAR(2) .EQ. 1) THEN    
      IF (IRATIO .EQ. 1) THEN 
        PRINT *, EXPIBT(I),APIBT(I)*PIPLO/(APIPL(I)*c 
        WRITE(6,205)(EXPIBT(I),APIBT(I),APIBT(I)*piplo)  
      ENDIF    
    ENDIF    
  END  
  WRITE(6,107)           
  WRITE(6,108)           
  RETURN                 
END
```

**Subprogram FUNC: Calculates values of objective function and constraint functions at current value of X**

```fortran
SUBROUTINE FUNC(M,EM,MAX,N,FF,G,X)    
  IMPLICIT REAL*8 (A-H,O-Z)  
  INCLUDE 'outputcmn'       
  INCLUDE 'inputcmn'       
  INCLUDE 'expdatcmn'      
  INCLUDE 'initvacmn'      
  DIMENSION X(N),G(MAX)    
  REAL *8 FF             
  CALL SIMOPT with current guesses X (N) 
  CALL SIMOPT(X,N)        
  c —— Calculate objective function value
```
**Appendix K**

\[ FF=0.0 \]

\[ \text{DO } i=1, \text{NUMEXP} \]

\[ \text{IF (IFPAR(1).EQ.1) THEN} \]

\[ \text{IF (EXVPL(I).GT.VAL.) THEN} \]

\[ \text{IF (IRATIO.EQ.1) THEN} \]

\[ \text{ERROR} = \left( \text{EXVPL(I)} - \text{AVPL(I)} \right) / \text{VPLO} \]

\[ \text{ELSE} \]

\[ \text{ERROR} = \left( \text{EXVPL(I)} - \text{AVPL(I)} \right) \]

\[ \text{ENDIF} \]

\[ \text{ERROR} = \text{ERROR} / \text{SDVPL(I)} \]

\[ FF=FF+ERROR \]

\[ \text{ENDIF} \]

\[ \text{ENDIF} \]

\[ \text{IF (IFPAR(2).EQ.1) THEN} \]

\[ \text{IF (EXPIBT(I).GT.VAL.) THEN} \]

\[ \text{IF (IRATIO.EQ.1) THEN} \]

\[ RVAL = \frac{\text{APIBT(I)} \cdot \text{PIBTO}}{\text{APIPL(I)} \cdot \text{PITIO}} \]

\[ \text{ERROR} = \left( \text{EXPIBT(I)} - \text{RVAL} \right) \]

\[ \text{ELSE} \]

\[ \text{ERROR} = \left( \text{EXPIBT(I)} - \text{APIBT(I)} \right) \]

\[ \text{ENDIF} \]

\[ \text{ERROR} = \text{ERROR} / \text{SDPIBT(I)} \]

\[ FF=FF+ERROR \]

\[ \text{ENDIF} \]

\[ \text{IF (IFPAR(3).EQ.1) THEN} \]

\[ \text{IF (EXPITI(I).GT.VAL.) THEN} \]

\[ \text{IF (IRATIO.EQ.1) THEN} \]

\[ RVAL = \frac{\text{APITI(I)} \cdot \text{PITIO}}{\text{APIPL(I)} \cdot \text{PITIO}} \]

\[ \text{ERROR} = \left( \text{EXPITI(I)} - \text{RVAL} \right) \]

\[ \text{ELSE} \]

\[ \text{ERROR} = \left( \text{EXPITI(I)} - \text{APITI(I)} \right) \]

\[ \text{ENDIF} \]

\[ \text{ERROR} = \text{ERROR} / \text{SDPITI(I)} \]

\[ FF=FF+ERROR \]

\[ \text{ENDIF} \]

\[ \text{IF (IFPAR(4).EQ.1) THEN} \]

\[ \text{IF (EXCPL(I).GT.VAL.) THEN} \]

\[ \text{IF (IRATIO.EQ.1) THEN} \]

\[ \text{ERROR} = \left( \text{EXCPL(I)} - \text{ACPL(I)} \right) / \text{CPLO} \]

\[ \text{ELSE} \]

\[ \text{ERROR} = \left( \text{EXCPL(I)} - \text{ACPL(I)} \right) \]

\[ \text{ENDIF} \]

\[ \text{ERROR} = \text{ERROR} / \text{SDCPPL(I)} \]

\[ FF=FF+ERROR \]

\[ \text{ENDIF} \]

\[ \text{ENDIF} \]

\[ \text{10} \text{ CONTINUE} \]

\[ \text{RETURN} \]

\[ \text{END} \]

---

**Subprogram SIMOPT: Simulates the Microvascular Exchange Process**

- **XX(N)** = Array of values of parameters
- **NUMP** = Number of parameters

---

**EXTERNAL MODEL**

- **NN** = Data for the resolution of model
- **NEQ** = Number of differential equations to be solved
- **YA(NEQ)** = Input array into subroutines MODEL and DESOLV or RK4C
- **YB(NEQ)** = Output array from subroutines DESOLV or RK4C (holds values of fluid volume and protein contents at the end of each time step)
- **DYDX(NEQ)** = Output array from subroutine MODEL (holds values of derivatives)
- **HMIN,HMAX,HSTART,EPS,DEL,TD2** = Data for Runge Kutta Fehlberg algorithm
- **CURRENT VALUES OF PARAMETERS TO BE DETERMINED**

---

**IF (IFLOPT.EQ.1) THEN**

\[ \text{GKFTI} = \text{XX(1)} \]

\[ \text{GKFBT} = \text{XX(2)} \]

**ELSE IF (IFLOPT.EQ.2) THEN**

\[ \text{GKFTI} = \text{XX(1)} \]

\[ \text{GKFBT} = \text{XX(2)} \]

\[ \text{RCOF} = \text{XX(3)} \]

**ELSE IF (IFLOPT.EQ.3) THEN**

\[ \text{GKFTI} = \text{XX(1)} \]

\[ \text{GKFBT} = \text{XX(2)} \]

\[ \text{RCOF} = \text{XX(3)} \]

\[ \text{EXFAC} = \text{XX(4)} \]

**ENDIF**

**NFNT=0**

**TIME(1)=1.00**

**XI=TIME(1)**

**YA(1)=VTIO**

**YA(2)=QTO**

**YA(3)=VTO**
Appendix K

YA(4)=QBTOIF(EXPT).GT.XL AND.
YA(5)=VPLOEXT(IEXPT).LE.XL AND.
YA(6)=QPLOTHEN
ISUPER=I
IPERIOD=1

--- Solve model equations using RKF algorithm
---
IEXPT=1
NFUN=0
--- Set excess/deficient makeup rates to zero since no steady state
period
VEXREM=0.D0
QEXREM=0.D0
--- Number of periods
NPERIOD=NPETUB
TFINAL=TEND(NPETUB)
--- Loop over the periods
DO 100 IP=1,NPERIOD
   ISUPER=ISUP(IP)
   A=START(IP)
   B=TEND(IP)
   XRES(IP)=XCLF(IP)+XPCF(IP)
   X1=A
   X2=X1
--- Change AFRAC after some time
IF (X1 .GE. 72.000) THEN
   AFRAC=1.0
ELSE
   AFRAC=0.5
ENDIF
900 CONTINUE
X1=X2
--- Blood removal
IF (X1 .L.T. BLSTIM .OR. X1 .GE. BLEND) THEN
   VBLOOD=0.0
ELSE
   VBLOOD=BLOOD(BLEND-BLSTIM)
ENDIF
--- Check if a step of DTAU will overshoot the final time for this
period TEND(IP)
C IF it overshoots adjust STEP else STEP = DTAU
IF (X1+DTAU .GT. TEND(IP)) THEN
   STEP= TEND(IP) - X1
ELSE
   STEP= DTAU
ENDIF
--- Check if there is an experimental point between X1 and
X1+STEP
C IF there is an experimental point between X1 and X1+STEP
   adjust DX else DX= step size STEP calculated above.
   IF (EXTIME(IEXPT) .GT. X1 AND.
   EXTIME(IEXPT) .LE. X1+STEP AND.
   IEXPT .LE. NUMEXP)
   THEN
      DX= EXTIME(IEXPT) - X1
   ELSE
      DX= STEP
   ENDIF
   X2=X1+DX
   DEPS=(DX/TFINAL)*EPS
   CALL RK4C (MODEL, NEQ, X1, X2, YA, DEPS,
   YB, NFUN, IFLAG)
--- If integration failed( IFLAG .EQ. 0) exit else save results
IF (IFLAG .EQ. 0) THEN
   WRITE(6,15) X1,X2
   STOP
ELSE
   DO 5 K=1,NEQ
      YA(K)=YB(K)
   5 CONTINUE
--- Save results
IF (DABS(X2-EXTIME(IEXPT)) .LE. 1.0D-6) THEN
   CALL MODEL (X2,YB,DYDXNEQ)
   CALL SAVRES (X2,YB,DYDXNEQ)
   IEXPT=IEXPT+1
   ENDIF
   ENDIF
IF (X2 .LT. TEND(IP)) GO TO 900
100 CONTINUE
5000 CONTINUE
15 FORMAT (" No solution between ,F18.5, and ,F18.5")
RETURN
END
--- Subprogram MODEL: Supplies derivatives of differential equations
to be solved, to RKF algorithm.
---
SUBROUTINE MODEL (X,Y,DYDX,N)
IMPLICIT REAL*8 (A-H,O-Z)
include 'input.cmn'
include 'compli.cmn'
include 'initva.cmn'
include 'normal.cmn'
include 'cursnt.cmn'
REAL*8 X,Y(N),DYDX(N)
--- Calculate fractional areas
FATI=((Y(5)/VPLO)-VFRAc)/(1.D0-VFRAc)
FAST=AFRAc*FATI
---
--- PLASMA
---
--- Calculation of Cpl
CPL=Y(6)/Y(5)
Appendix K

--- Calculate osmotic pressure in plasma
\[ \text{P}_{\text{PI}} = \text{C}_{\text{PI}} \times \text{P}_{\text{L}}^{1.522} \]

--- Calculate capillary pressure
\[ \text{P}_{\text{CI}} = \text{P}_{\text{CO}} - \text{F}_{\text{COMP}} \times (\text{Y}(1) - \text{V}_{\text{PL}}) \]

\[ \text{IF} (\text{P}_{\text{CI}} \leq 3.0) \text{THEN} \]

--- UNINJURED TISSUE

--- Calculation of \( C \) and \( C_{\text{av}} \) for uninjured tissue
\[ \text{CTI} = \text{Y}(2)/\text{Y}(1) \]
\[ \text{CTI}_{\text{av}} = \text{Y}(2)/(\text{Y}(1) - \text{V}_{\text{ETI}}) \]

--- Calculate hydrostatic pressure for uninjured tissue
\[ \text{P}_{\text{HTI}} = \text{F}_{\text{COMP}} \times (\text{Y}(1)) \]

--- Calculate HPTI EX
\[ \text{HPTI}_{\text{EX}} = \text{F}_{\text{COMP}} \times \text{V}_{\text{ETI}} \]

--- Calculate osmotic pressure in uninjured tissue
\[ \text{P}_{\text{UTI}} = \text{CTI}_{\text{av}} \times 1.522 \times 10^0 \]

--- Calculate fluid fluxes for uninjured tissue

--- Pore radii changes postburn
\[ \text{RTI} = \text{RPNL} \times (1.0 + \text{GK} \times \text{DEXP}(-\text{RCOEF} \times \text{X})) \times 0.5 \times \text{DO} \]

--- ATIPB = \( \text{RPL}/\text{RTI} \)

--- Lymph flow sensitivity
\[ \text{XLSTI} = \text{XLSNORM} \times (1.0 + \text{GLSTI} \times \text{DEXP}(-\text{RCOEF} \times \text{X})) \]

--- Fluid filtration coefficient
\[ \text{XKFTI} = \text{XKFNORM} \times \text{CORRTI} \times (1.0 + \text{GKFTI} \times \text{DEXP}(-\text{RCOEF} \times \text{X})) \times \text{FATI} \]

--- Lymph fluid flow
\[ \text{XIJLTI} = \text{XJLNORM} \times \text{XLSTI} \times (\text{HPBT} - \text{HPTINL}) \]
\[ \text{X2JLTI} = \text{XJLNORM} \times (\text{HPBT} - \text{HPTI}) \times (\text{HPTINL} - \text{HPTI}_{\text{EX}}) \]

\[ \text{IF} (\text{HPBT} \geq \text{HPTINL}) \text{THEN} \]

\[ \text{XJLTI} = \text{XIJLTI} \times \text{CORRTI} \]

\[ \text{ELSEIF} (\text{HPBT}. \text{GE}. \text{HPTI}_{\text{EX}} \text{AND}. \text{HPBT}. \text{LT}. \text{HPTINL}) \text{THEN} \]

\[ \text{XJLTI} = \text{XIJLTI} \times \text{CORRTI} \]

\[ \text{ELSEIF} (\text{HPBT}. \text{LT}. \text{HPTI}_{\text{EX}}) \text{THEN} \]

\[ \text{XJLTI} = 0 \times \text{DO} \]

--- Fluid filtration flow
\[ \text{XJFTI} = \text{XKFTI} \times \text{P}_{\text{CHPT}} \times \text{SIGBT} \times (\text{Pl}_{\text{PL}} / \text{PI}_{\text{BT}}) \]

--- Calculate protein fluxes for uninjured tissue

--- Sigma
\[ \text{TOPTI} = 16 \times \text{ATIPB}^2 \times 10^{-2} - 20 \times \text{ATIPB}^3 \times 10^{-3} + 7 \times \text{DO} \times \text{ATIPB}^4 \times 10^{-1} \]

--- SIGHT = \( \text{TOPTI}/3 \times \text{DO} \)

--- Fluid filtration flow
\[ \text{XIJFTI} = \text{XKFTI} \times \text{SIGTI} \times \text{P}_{\text{L}} / \text{P}_{\text{STI}} \]

--- Lymph protein flow
\[ \text{QLTI} = \text{XJLTI} \times \text{CTI} \]

--- Calculate protein fluxes for injured tissue

--- Sigma
\[ \text{TOPTI} = 16 \times \text{ATIPBT}^2 \times 10^{-2} - 20 \times \text{ATIPBT}^3 \times 10^{-3} + 7 \times \text{DO} \times \text{ATIPBT}^4 \times 10^{-1} \]

--- SIGHT = \( \text{TOPTI}/3 \times \text{DO} \)

--- Fluid filtration flow
\[ \text{XIJFBT} = \text{XKFBT} \times (\text{PC} - \text{HPTI}_{\text{SIGTI}} \times \text{PIPL} \times \text{PIBT}) \]

--- Lymph protein flow
\[ \text{QLBT} = \text{XJLBT} \times \text{CTI} \]

--- INJURED TISSUE

--- Calculate hydrostatic pressure for injured tissue
\[ \text{IF} (\text{SUPER}. \text{EQ}. 1) \text{THEN} \]

\[ \text{DO} = 30 \times 1 - 1,12 \]

--- IF (\( X \). LT. \text{BTIMERH(D)}) \text{THEN} \]

\[ \text{IM} = 1 - 1 \]

--- SLOPE = \( \text{BPRESRH(D)} - \text{BPRESRH(M)} \)

\[ \text{BPBT} = \text{BPRESRH(M)} + \text{SLOPE} \times (\text{X} - \text{BTIMERH(M)}) \]

--- GO TO 100

\[ \text{ENDIF} \]

\[ \text{30 CONTINUE} \]

--- ELSE IF (\( \text{SUPER}. \text{EQ}. 2 \)) \text{THEN} \]

\[ \text{HPBT} = \text{F}_{\text{COMPBT}}(\text{Y}(3)) \]

--- ENDIF

\[ \text{100 CONTINUE} \]

--- Calculate HPTI EX
\[ \text{HPBT}_{\text{EX}} = \text{F}_{\text{COMPBT}}(\text{VEBT}) \]

--- Calculate osmotic pressure in injured tissue
\[ \text{P}_{\text{B}} = \text{CTI}_{\text{AV}} \times 1.522 \times 10^0 \]

--- Calculate fluid fluxes for injured tissue

--- Pore radii changes postburn
\[ \text{RPBT} = \text{RPNL} \times (1.0 + \text{GKFTI} \times \text{DEXP}(-\text{RCOEF} \times \text{X})) \times 0.5 \times \text{DO} \]

--- ATIPBT = \( \text{RPL}/\text{RPBT} \)

--- Lymph flow sensitivity
\[ \text{XLSTBT} = \text{XLSNORM} \times (1.0 + \text{GLSTI} \times \text{DEXP}(-\text{RCOEF} \times \text{X})) \]

--- Fluid filtration coefficient
\[ \text{XKFTBT} = \text{XKFNORM} \times \text{CORRTBT} \times (1.0 + \text{GKFTI} \times \text{DEXP}(-\text{RCOEF} \times \text{X})) \times \text{FATBT} \]

--- Lymph fluid flow
\[ \text{XIJLBTI} = \text{XJLNORM} \times \text{XLSTBT} \times (\text{HPBT} - \text{HPTINL}) \]
\[ \text{X2JLBTI} = \text{XJLNORM} \times (\text{HPBT} - \text{HPTI}_{\text{EX}}) \times (\text{HPTINL} - \text{HPTI}_{\text{EX}}) \]

\[ \text{IF} (\text{HPBT} \geq \text{HPTINL}) \text{THEN} \]

\[ \text{XJLBTI} = \text{XIJLBTI} \times \text{CORRTBT} \]

\[ \text{ELSEIF} (\text{HPBT} \geq \text{HPTI}_{\text{EX}} \text{AND} \text{HPBT} < \text{HPTINL}) \text{THEN} \]

\[ \text{XJLBTI} = \text{XIJLBTI} \times \text{CORRTBT} \]

\[ \text{ELSEIF} (\text{HPBT} < \text{HPTI}_{\text{EX}}) \text{THEN} \]

\[ \text{XJLBTI} = 0 \times \text{DO} \]

--- Fluid filtration flow
\[ \text{XJFTBT} = \text{XKFTBT} \times \text{P}_{\text{CHPT}} \times \text{SIGBT} \times (\text{Pl}_{\text{PL}} / \text{PI}_{\text{BT}}) \]

--- Calculate protein fluxes for injured tissue

--- Sigma
\[ \text{TOPTI} = 16 \times \text{ATIPBT}^2 \times 10^{-2} - 20 \times \text{ATIPBT}^3 \times 10^{-3} + 7 \times \text{DO} \times \text{ATIPBT}^4 \times 10^{-1} \]

--- SIGHT = \( \text{TOPTI}/3 \times \text{DO} \)

--- Fluid filtration flow
\[ \text{XIJFBT} = \text{XKFBT} \times (\text{PC} - \text{HPTI}_{\text{SIGTI}} \times \text{PIPL} \times \text{PIBT}) \]

--- Calculate protein fluxes for injured tissue

--- Sigma
c —— Diffusion coefficient

PSBT = ((1.D0 - ABTPB)**2.D0) * CONST * CORRB * FABT

c —— Peclet number

PRCLBT = ((1.D0 - SIGBT) * XJFBT / PSBT)
RATIOTBT = (CPL-CTAV*DEXP(-PECLBT)) / (1.D0 - DEXP(-PECLBT))

QSBT = ((1.D0 - SIGBT) * XJFBT * RATIOTBT)

QLBT = XJLBT * CBT

ENDIF

FLUID AND PROTEIN BALANCES

In actual periods

IF (IPEROD.EQ.1 AND NEPTUB) THEN

Fluid out = urine + wound fluid loss + evaporative fluid loss

QJEVTI = 25.D0*TBSA
QJEVBT = DEG4100.D0*TBSA
XJMAIN = 0.D0
QURINE = 0.D0
QREMQ = QXEXUD + QEVA + QURINE

Protein out = protein in urine + protein in wound fluid loss

QXEXUD = QURINE * CBTL * EXFAC
QEVAP = 0.D0
QURINE = 0.D0

ELSEIF (IBLANKEQ.2) THEN

XJMAIN = 0.000
QURINE = 0.000
QPLO = 0.000
QEVAP = 0.000
QXEXUD = 0.000

ENDIF

Fluid and protein balances in uninjured tissue

DYDX(1) = XJFTI - XJLTI - XJEVTI

DYDX(2) = QSTI - QLTI

Fluid and protein balances in injured tissue

IF (DEG .GT. 0) THEN

DYDX(3) = XJFBT - XJLBT - XJEVBT - EXUDN

DYDX(4) = QSBT - QLTI - QURINE

ELSE

DYDX(3) = 0.0

DYDX(4) = 0.0

ENDIF

Fluid and protein balances in plasma

DYDX(5) = XJRE = (XJFFI - XJLTI) - (XJFBT - XJLBT) - URINE - VEXREM - VLOOD

DYDX(6) = CRES(IPEROD) * XEQPLV(IPEROD) * QSTI - QLTI - (QSBT - QLTI) - QURINE - QXRE - VLOOD * CPL0

RETURN

END

SUBROUTINE INITV

IMPLICIT REAL*8 (A-H O-Z)

INCLUDE "output.cmn"

INCLUDE "input.cmn"

INCLUDE "compli.cnsn"

INCLUDE "initva.cmn"

INCLUDE "normal.cmn"

INCLUDE "curent.cmn"

INCLUDE "expdat.cmn"

c —— Assi and/or calculate various initial values

SUBROUTINE INITV

IMPLICIT REAL*8 (A-H O-Z)

INCLUDE "output.cmn"

INCLUDE "input.cmn"

INCLUDE "compli.cnsn"

INCLUDE "initva.cmn"

INCLUDE "normal.cmn"

INCLUDE "curent.cmn"

INCLUDE "expdat.cmn"

C —— Assign and/or calculate various initial values

C PLASMA (CIRCULATION)

C —— V and Q

VPLO=VPLNL
QPLO=QPLNL

C —— Calculation of CPL0

C —— Calculation of BVO AND BVF

BV=VPLO/(1.0-HCTO)
BV=VLOOD/(1.0-HCTO)
Appendix K

---

c Calculate initial osmotic pressure

\[ \text{PIPLO} = \text{CPLO} / 1.522 \]

c Calculate initial capillary pressure

\[ \text{PCO} = \text{PCNL} \]

c UNINJURED TISSUE

---

c Calculate \( V \) and \( Q \) for uninjured tissue

\[ \begin{align*}
\text{VTIO} &= \text{VTINL} \* \text{RELSM} \* \text{DEG} + \text{VTINL} \* \text{RELM} \\
\text{VETI} &= \text{VETINL} \* \text{RELSM} \* \text{DEG} + \text{VETINL} \* \text{RELM}
\end{align*} \]

c Calculation of \( C_0 \) and \( C_{av,o} \)

\[ \begin{align*}
\text{CTIO} &= \text{QTIO} / \text{VTIO} \\
\text{CTIAVO} &= \text{QTIO} / (\text{VTIO} - \text{VETI})
\end{align*} \]

c Calculate hydrostatic pressure

\[ \text{HPTIO} = \text{FCOMP}(\text{VTIO}) \]

c Calculate initial osmotic pressure

\[ \text{PITIO} = \text{CTIAVO} / 1.522 \]

c INJURED TISSUE

---

IF (DEG GT 0.00D0) THEN

c \( V \) and \( Q \)

\[ \begin{align*}
\text{VBTO} &= \text{VTINL} \* \text{RELSM} \* \text{DEG} \\
\text{VBET} &= \text{VETINL} \* \text{RELSM} \* \text{DEG} \\
\text{QBTO} &= \text{QTINL} \* \text{RELSM} \* \text{DEG}
\end{align*} \]

c Calculation of \( C_0 \) and \( C_{av,o} \)

\[ \begin{align*}
\text{CBTO} &= \text{QBTO} / \text{VBTO} \\
\text{CBTAVO} &= \text{QBTO} / (\text{VBTO} - \text{VETB})
\end{align*} \]

c Calculate hydrostatic pressure

\[ \text{HPTBO} = \text{FCOMBT}(\text{VBTO}) \]

c Calculate initial osmotic pressure

\[ \text{PITBO} = \text{CBTAVO} / 1.522 \]

ELSE

\[ \begin{align*}
\text{VBTO} &= 0.00D0 \\
\text{VBET} &= 0.00D0 \\
\text{QBTO} &= 0.00D0 \\
\text{CBTO} &= 0.00D0 \\
\text{CBTAVO} &= 0.00D0 \\
\text{HPTBO} &= 0.00D0 \\
\text{PITBO} &= 0.00D0
\end{align*} \]

ENDIF

RETURN

END

---

SUBROUTINE RATION: Normalizes quantities with respect to their initial values

SUBROUTINE RATION

IMPLICIT REAL*8(A-H,O-Z)

include 'output.cmn'

include 'input.cmn'

include 'initva.cmn'

include 'normal.cmn'

include 'expdat.cmn'

PARAMETER (N=2, M=0, ME=0, MMAX=1)

PARAMETER (IMAX=100)

DIMENSION XTI(IMAX), XET(IMAX)

DIMENSION X(N)

CHARACTER*20 CDATA(10)

CHARACTER*10 SURFILE

COMMON CHSUR/SURFILE

OPEN(UNIT=7, FILE=SURFILE)

READ(7,10) NUMTI

READ(7,11) (XTI(I), I=1, NUMTI)

READ(7,10) NUMBT

READ(7,11) (XET(I), I=1, NUMBT)

CLOSE(7)

OPEN (UNIT=8, FILE='C:\AMVRES\SURF.DAT') \n\# RUNITD/SURF.DAT)

DO 1 I=1, NUMTI

X(I)=XTI(I)

DO 2 J=1, NUMBT
.test
read(5,*) dtau
write(6,201) comment,dtau
*time step for saving for output
read(5,*) comment
read(5,*) outtime
write(6,201) comment,outtime
*data for type of run
read(5,*) comment
read(5,*) istedy
write(6,201) comment,istedy
*flag for steady state run
read(5,*) comment
read(5,*) istedy
write(6,201) comment,istedy
*flag for blank run; if blank run, iblink=1 otherwise, iblink=0
read(5,*) comment
read(5,*) iblink
write(6,201) comment,iblink
*data for steady state run
read(5,*) comment
read(5,*) stdtim
write(6,201) comment, stdtim
*time to start addition/removal of fluid/protein
read(5,*) comment
read(5,*) remsta
write(6,201) comment,remsta
*time period for removal/addition of fluid/protein
read(5,*) comment
read(5,*) cpmpl
write(6,201) comment, cpmpl
*flag for "compliance" data
read(5,*) comment
read(5,*) icmpl
write(6,201) comment, icmpl
*graph plotting data
read(5,*) comment
read(5,*) iplot
write(6,201) comment, iplot
*flag to indicate if ratios are to be used for optimization
read(5,*) comment
read(5,*) iratio
write(6,201) comment, iratio
*flag to indicate if experimental data should be randomized
read(5,*) comment
read(5,*) irand, ranfac
write(6,212) comment, irand, ranfac
*experimental data
if(ipar(1).eq.1) then
open(unit=5, file=pvfile)
c-number of experimental data points to be fitted
read(5,*) numexp
c—experimental time (extime), value (expvl) and standard deviation (sdpvl)
if(numexp.gt.0) then
read(5,*) (extime(i), expvl(i), sdpvl(i)), i=1, numexp
endif
endif
if(ipar(2).eq.1) then
open(unit=5, file=ptfile)
c—number of experimental data points to be fitted
read(5,*) numexp
c—experimental time (extime), value (expb) and standard deviation (sdp) at (1, 1, numexp)
if(numexp.gt.0) then
read(5,*) (extime(i), expbi(i), sdpbi(i)), i=1, numexp
endif
endif
if(ipar(3).eq.1) then
open(unit=5, file=ttfile)
c—number of experimental data points to be fitted
read(5,*) numexp
c—experimtitinal time (extime), value (expitt) and standard deviation (dptune)
if(numexp.gt.0) then
read(5,*) (extime(i), expitt(i), sdpit(i)), i=1, numexp
endif
endif
endif
if(ipar(4).eq.1) then
open(unit=5, file=cfpfile)
c-number of experimental data points to be fitted
read(5,*) numexp
*experimental time (extime), value (expcl) and standard deviation (sdcpl)
if(numexp.gt.0) then
read(5,*) (extime(i), expcl(i), sdcpl(i)), i=1, numexp
endif
endif
endif
"flag for compliance data
read(5,*) comment
read(5,*) icmpl
write(6,201) comment, icmpl
"flag for "compliance" data
read(5,*) comment
read(5,*) iratio
write(6,201) comment, iratio
"flag to indicate if experimental data should be randomized
read(5,*) comment
read(5,*) irand, ranfac
write(6,212) comment, irand, ranfac
*experimental data
if(ipar(1).eq.1) then
open(unit=5, file=pvfile)
c-number of experimental data points to be fitted
read(5,*) numexp
c—experimental time (extime), value (expvl) and standard deviation (sdpvl)
if(numexp.gt.0) then
read(5,*) (extime(i), expvl(i), sdpvl(i)), i=1, numexp
endif
endif
if(ipar(2).eq.1) then
open(unit=5, file=ptfile)
c—number of experimental data points to be fitted
read(5,*) numexp
c—experimental time (extime), value (expb) and standard deviation (sdp)
if(numexp.gt.0) then
read(5,*) (extime(i), expbi(i), sdpbi(i)), i=1, numexp
endif
endif
if(ipar(3).eq.1) then
open(unit=5, file=ttfile)
c—number of experimental data points to be fitted
read(5,*) numexp
c—experimtitinal time (extime), value (expitt) and standard deviation (dptune)
if(numexp.gt.0) then
read(5,*) (extime(i), expitt(i), sdpit(i)), i=1, numexp
endif
endif
endif
if(ipar(4).eq.1) then
open(unit=5, file=cfpfile)
c-number of experimental data points to be fitted
read(5,*) numexp
*experimental time (extime), value (expcl) and standard deviation (sdcpl)
if(numexp.gt.0) then
read(5,*) (extime(i), expcl(i), sdcpl(i)), i=1, numexp
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APPENDIX K

Fluid volume correction factors for compliance data

\[ \text{VAFTI} = \text{RELMS} \times \text{DEGM} + \text{RELM} \]

\[ \text{VAFBTh} = \text{RELMS} \times \text{DEG} \]

Correction factors for \( \text{KFNORM}, \text{LSNORM}, \text{PSNORM} \) and \( \text{JLNORM} \)

\[ \text{CORRTI} = \text{WTRATI} \times \text{VAFTI} \]

\[ \text{CORRBT} = \text{WTRATI} \times \text{VAFBT} \]

RETURN

END

SUBROUTINE OUTPUT

IMPLICIT REAL*8(A-H,O-Z)

INCLUDE 'output.cmn'

INCLUDE 'input.cmn'

INCLUDE 'initva.cnmn'

INCLUDE 'normal.cmn'

INCLUDE 'current.cnmn'

INCLUDE 'grfile.cmn'

CHARACTER*10 CADATA(10)

PARAMETER (SAVDIR='C:\AMVRES\')

... (remaining code continues)
WRITE (8,1900) (TIME(I), APTI(I), APIBT(I), APIPL(I), I=1,NPNT)
CLOSE(8)
// Run I:
WRITE (8,1910) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run II:
WRITE (8,1920) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run III:
WRITE (8,1930) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run IV:
WRITE (8,1940) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run V:
WRITE (8,1950) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run VI:
WRITE (8,1960) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run VII:
WRITE (8,1970) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run VIII:
WRITE (8,1980) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run IX:
WRITE (8,1990) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run X:
WRITE (8,2000) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XI:
WRITE (8,2010) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XII:
WRITE (8,2020) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XIII:
WRITE (8,2030) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XIV:
WRITE (8,2040) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XV:
WRITE (8,2050) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XVI:
WRITE (8,2060) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XVII:
WRITE (8,2070) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XVIII:
WRITE (8,2080) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XIX:
WRITE (8,2090) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XX:
WRITE (8,2100) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XXI:
WRITE (8,2110) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XXII:
WRITE (8,2120) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XXIII:
WRITE (8,2130) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XXIV:
WRITE (8,2140) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XXV:
WRITE (8,2150) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XXVI:
WRITE (8,2160) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XXVII:
WRITE (8,2170) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XXVIII:
WRITE (8,2180) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XXIX:
WRITE (8,2190) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XXX:
WRITE (8,2200) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XXXI:
WRITE (8,2210) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XXXII:
WRITE (8,2220) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XXXIII:
WRITE (8,2230) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XXXIV:
WRITE (8,2240) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XXXV:
WRITE (8,2250) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XXXVI:
WRITE (8,2260) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XXXVII:
WRITE (8,2270) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XXXVIII:
WRITE (8,2280) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XXXIX:
WRITE (8,2290) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XXXX:
WRITE (8,2300) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XXXXI:
WRITE (8,2310) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XXXXII:
WRITE (8,2320) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XXXXIII:
WRITE (8,2330) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XXXXIV:
WRITE (8,2340) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XXXXV:
WRITE (8,2350) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XXXXVI:
WRITE (8,2360) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XXXXVII:
WRITE (8,2370) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XXXXVIII:
WRITE (8,2380) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XXXXIX:
WRITE (8,2390) (TIME(I), APTI(I), APIBT(I), APIPL(I), TQPO, I=1,NPNT)
CLOSE(8)
// Run XXXX:
SUBROUTINE NORMAL
IMPLICIT REAL*8 (A-L,H-O-Z)
include 'input.cmn'
include 'omn.cmn'
include 'initva.cmn'
include 'normal.cmn'
CTNL = QTNL/VTNL
CTIAVNL = QTNL/(VTNL-VEHNL)
CPLNL = QPLNL/VPLNL
PENORM = DLOG(TOP/BOT)
c—Calculate normal modified Peclet number, PENORM
TOP = CTNL-(1.00-SIGNL)*CTIAVNL
BOT = CTNL-(1.00-SIGNL)*CPLNL
PENORM = DLOG(TOP/BOT)
c—CalculatenormalJL,XJLNORM
AA=(1.00-SIGNL)*DEXP(PENORM)
RB=(1.00-DEXP(-PENORM))*(VTNL-VETNL)
CC=1.00/VTNL
DIV=AA/BB+CC
XJLNORM=ALBTO/DIV

c—CalculatenormalPS,PSNORM
PSNORM=(1.00-SIGNL)*XJLNORM/PENORM

c—CalculatenormalKF,XKFNORM
DELP=PCNL-HPTNL-SIGNL*(PIPLNL-PITNL)
XKFNORM=XJLNORM/DELP

c—Adjustproteinandfluidcontentsinrealpatientasopposedto
standardhuman
VTNL=VTNL*WTRATI
VETNL=VETNL*WTRATI
QTrNL=QTINL*WTRATI

END
FUNCTION FCOMP: Interpolation function for uninjured tissue compliance relationship

DOUBLE PRECISION FUNCTION FCOMP(Z)
IMPLICIT REAL*8 (A-H,O-Z)
include 'compli.cmn'
include 'input.cmn'
IF (Z.LT.X(I)) THEN
FCOMP=-0.7D0+AS/CORRTI*(Z-CORRTI*8.4D+3)
ELSEIF (Z.GT.X(N)) THEN
FCOMP=1.88D0+BS/CORRTI*(Z-CORRTI*12.6D+3)
ELSEIF (Z.GE.CORRTI*8.4D+3 AND Z.LE.CORRTI*12.6D+3) THEN
FCOMP=FCTI(Z)
ENDIF
RETURN
END

FUNCTION FCTI: Uninjured tissue compliance relationship

DOUBLE PRECISION FUNCTION FCTI(Z)
IMPLICIT REAL*8 (A-H,O-Z)
COMMON/BLKTII/X(101),Y(101),N,NM
COMMON/BLKTI2/Q(100),R(101),S(100)
IF (Z.LT.X(I)) THEN
I=1
WRITE(6,10)Z
ELSEIF (Z.GT.X(N)) THEN
I=NM
WRITE(6,10)Z
ELSE
I=1
J=N
20 K=(I+J)/2.D0
IF (Z.LT.X(K)) J=K
IF (Z.GE.X(K)) I=K
IF (J.GT.I+1) GO TO 20
ENDIF
DX=Z-X(I)
FCTI=Y(I)+DX*(Q(I)+DX*(R(I)+DX*S(I)))
RETURN
END

FUNCTION FCBT: Interpolation function for injured tissue compliance relationship

DOUBLE PRECISION FUNCTION FCBT(Z)
IMPLICIT REAL*8 (A-H,O-Z)
COMMON/BLKBTI/X(101),Y(101),N,NM
COMMON/BLKBT2/Q(100),R(101),S(100)
IF (Z.LT.X(I)) THEN
I=1
WRITE(6,10)Z
ELSEIF (Z.GT.X(N)) THEN
I=NM
WRITE(6,10)Z
ELSE
I=1
J=N
20 K=(I+J)/2.D0
IF (Z.LT.X(K)) J=K
IF (Z.GE.X(K)) I=K
IF (J.GT.I+1) GO TO 20
ENDIF
DX=Z-X(I)
FCBT=Y(I)+DX*(Q(I)+DX*(R(I)+DX*S(I)))
RETURN
END