A FUZZY CLASSIFIER FOR DRUG SENSITIVITY IN SEPTIC PATIENTS DURING CARDIOPULMONARY BYPASS

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Abstract: A compartmental model is modified to simulate the capillary leak associated with Sepsis and Cardiopulmonary Bypass (CPB). This involves continuously updating the oncotic pressures with regard to the flows in and out of each compartment. As a result, it is possible to model the effects of administering fluids with different oncotic pressures on filtration. The model allows for simulated infusions of vasoactive and inotropic drugs with a range of sensitivities to these drugs, giving a comprehensive platform for testing various control strategies. Furthermore, a fuzzy logic based system is designed to classify drug responses according to sensitivity, using the drug input and mean arterial pressure (MAP) signals from the model. This can be used as part of a comprehensive drug decision support system to estimate initial sensitivity and/or detect long-term changes in drug sensitivity.

Keywords: Sepsis, Capillary leak, Fuzzy inference, Medical applications, Simulation, Decision support, Discrimination.

1. INTRODUCTION

Starling's hypothesis states that the fluid movement due to filtration across a capillary wall is dependent on the balance between the hydrostatic pressure gradient and the oncotic pressure gradient across the capillary (Klabunde, 2005). This is summarised by the Starling equation (1), where the net fluid movement (J_v) is dependent on the filtration coefficient (K_f), the reflection coefficient (σ) and the hydrostatic (P_x) and oncotic pressures (π_x) on either side of the capillary.

$$J_v = K_f[(P_c - P_i) - \sigma(\pi_c - \pi_i)] \qquad (1)$$

During and after Cardio-pulmonary bypass (CPB) however, this balance is disrupted and there may be a net 'capillary leak' into the interstitial compartment. Capillary leak is one of the symptoms associated with sepsis, which affects a significant proportion of CPB patients. Sepsis is also characterised by increased heart rate and cardiac output, as well as persistent hypotension and hypoperfusion (Astiz and Rackow, 1998).

There are several published circulatory models of various levels of complexity, designed to simulate different conditions. However, only a few of these deal with specifically with capillary leak in a physiological sense. The objective here was to develop a physiologically based model, capable of simulating the key haemodynamic variables used by medical staff during and after CPB.

Model development combined ideas and equations from two previous models by Randall (1986) and Xie *et al* (1995). Randall's model is a lumped parameter, steady flow model representing commonly measured haemodynamic parameters (see Figure 1). It uses simple elements to describe parts of the circulation. Capacitors represent the veins and arteries, a steady flow pump represents the left and right ventricles and

variable resistors represent the systemic and pulmonary vascular resistance. Subscript 'p' denotes pulmonary, 's' systemic, 'a' arterial and 'v' venous. CO_l and CO_r are the left and right cardiac outputs respectively, described by a non-linear function ' f '.

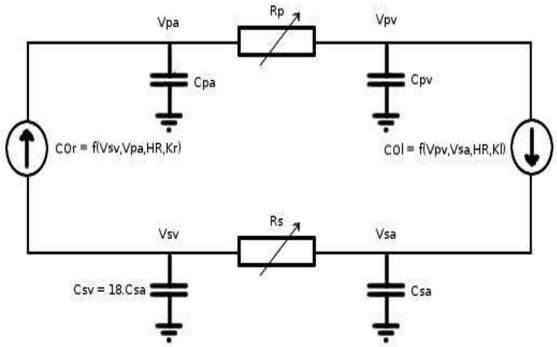

Figure 1: The electrical analogue circuit of the circulatory model where frequency, voltage current and charge are analogues of heart rate, blood pressure, flow rate and volume respectively.

Xie and co-workers developed a compartmental microcirculation model, which describes the transport and distribution of fluid and plasma proteins according to physiologically based, mathematical equations such as the Starling equation (1) and the lymph equation (2) as shown in Figure 2.

$$J_l = J_{l0} + LS\,(P_I - P_{I0}) \qquad (2)$$

Where P_I is the current interstitial pressure, P_{I0} is the nominal interstitial pressure, and LS and J_{l0} are constants determined from their simulations.

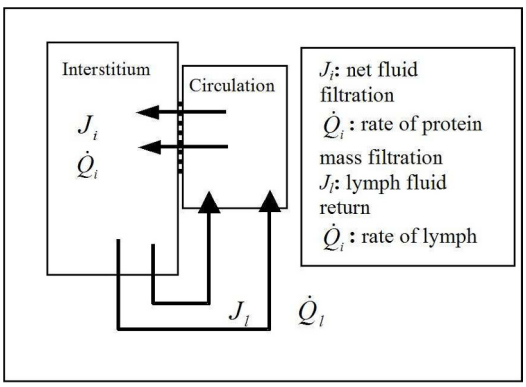

Figure 2: A Schematic of the fluid and protein exchange model by Xie et al [4].

The new model has an additional circulatory compartment, the capillaries, to act as the site of exchange between the circulation and the interstitium (Figure 3). The capillary pressure in this new compartment takes the place of the 'circulation' pressure in Xie's model. Each compartment has a continuously updated oncotic pressure. It was assumed that all capillary leak took place in the systemic circulation. All compartments were assumed to be well mixed, i.e., all properties were considered uniform throughout each compartment. As in Xie's model, at steady state, the transcapillary exchange rate of protein is equal to its removal rate via the lymph.

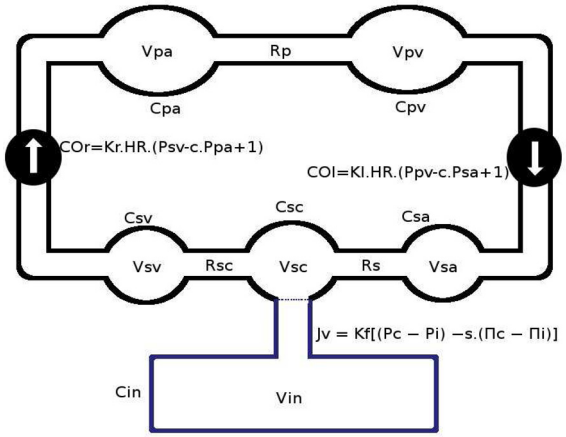

Figure 3: A Schematic diagram of the modified cardiovascular model

Mason (1989) has modelled the effects of vasoactive and inotropic drugs on systemic vascular resistance (SVR) and ventricular function (Rs and Kl/Kr respectively in Figure 3). A transport delay of 30 seconds was assumed for all drugs, representing the average time for the blood flow to transport the drug to its action sites. This was followed by an exponential change in ventricular function or SVR towards the dose-response curve. Based on his clinical experience, the time constant for vasodilator effects was set at 1 minute, and that for inotropic and vasoconstrictive agents to 2 minutes. The gain of the drug effects was adjusted until a response was produced which agreed with clinical experience and data presented by Greenway (1982). However, patients may show a wide range of responses to drugs. These differences can be simulated by adjusting the dose-response curve for each drug. Mason's piecewise linear dose-response curve was replaced with a sigmoidal one, while keeping the slope at the median effect the same.

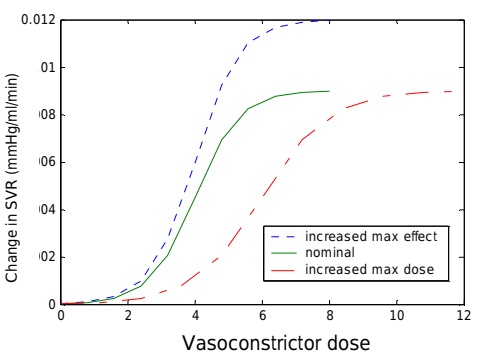

Figure 4: Dose response curve for vasoconstrictor on SVR, altered using max effect and max dose.