Modelling the transfer of therapeutic agents from the vascular space to the tissue compartment (a continuum approach)

Project number: GQ6  
Qualifying fellow: Katherina Baber  
Supervisors: Prof. Dr.-Ing. Rainer Helmig, Dr. rer. nat. Bernd Flemisch, Dipl. Ing. Klaus Mosthaf, Dipl. Ing. Karin Erbertseder  
Period of scholarship: 01.10.2008 – 31.03.2009

Modelling the distribution processes in the human body can be of great help in the development and testing of new therapeutic agents. Apart from the distribution in the circulatory system and in the tissue space, the flow and transport processes across the microvascular wall have to be considered (Michel and Curry, 1999; Curry, 1984). Since the microvascular wall is one of the main barriers to substance exchange, a detailed description of its structure and of the occurring processes is the focus of this thesis.

The bio-system involved in transvascular processes can be divided into three compartments: the vascular space, the tissue compartment, and the microvascular wall. All three are highly complex biological structures and must be simplified in order to derive a suitable model concept that allows for a mathematical description and numerical modelling.

The complex flow and fluid properties of blood flow (compartment I) are approximated by the steady, laminar flow of a Newtonian fluid. Tissue (compartment III) is made up of fixed and mobile tissue cells, different kinds of fibres, and the amorphous ground substance. This elastic medium with its various components is described as a rigid, porous medium by applying a continuum approach. The compartment of interest, the microvascular wall (compartment II), is made up of four layers. The main component is the endothelium, which is the principal barrier to and regulator of material exchange. The microvascular wall exhibits a variety of paracellular and transcellular pathways: interendothelial clefts, fenestrations, transcellular pores, vesicles, and transcellular transport mechanisms (Sugihara-Seki and Fu, 2005). The composition and influence of the four layers as well as the distribution of these pathways depend on the anatomic location and on the physiological or pathological conditions. Furthermore, the physico-chemical properties of a transported substance determine the availability of these pathways. Three main types of capillaries can be identified, differing in structure and permeability: continuous, fenestrated, and discontinuous capillaries. A volume-averaging process or continuum approach is applied, so that the microvascular wall is also treated as a porous medium. However, the applicability of this approach is
highly questionable, and it has to be considered only a first approximation. The different properties of the different layers occur across only one layer of cells, and a volume-averaging procedure cannot be applied to such a thin and heterogeneous structure.

The abstract description of the three compartments provides a basis for a mathematical description of the system. The Stokes equation is used to describe the free-flow region in the capillary, and Darcy’s law describes the porous medium regions. Amongst other coupling conditions, the Beavers-Joseph-Saffman condition is chosen for the approximation of the tangential velocity at the interface (Beavers and Joseph, 1967). Since neither values for the Beavers-Joseph slip coefficient nor for the magnitude of the shear stresses and the tangential velocity are known, the applicability needs to be assessed. Discretisation of the resulting system of numerical equations is done with the BOX-method.

Finally, the flow processes are implemented in the modelling toolbox DuMu² (Flemisch et al., 2007) using parameters of subcutaneous tissue. It was possible to obtain flow and pressure fields that match the conception of the respective parameter distributions in the bio-system.

![Distribution of x- and y-component of the velocity and pressure distribution](image)

Furthermore, the influence of the Beavers-Joseph slip coefficient was assessed. The model showed strong interdependencies of the slip coefficient, the velocities, net filtration, and the pressure gradient. To what extent the model results reflect the interdependencies present in the bio-system needs to be further investigated.

In the future, the main task will be to find a more suitable description for the microvascular wall. The capillary wall should be described on the microscale, and the transvascular pathways and individual layers should be resolved. The microscopic description of the wall will then be combined with a macroscopic description of the surrounding compartments. Hence, a multi-scale approach is envisaged.

References