

# Sensitivity analysis of a model of lower limb haemodynamics

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**Abstract.** *Post-thrombotic syndrome (PTS) has variable clinical presentation with significant treatment costs and gaps in the evidence-base to support clinical decision making. The contribution of variations in venous anatomy to the risk of complications following treatment has yet to be characterized in detail. We report the development of a steady-state, 0D model of venous anatomy of the lower limb and assessment of local sensitivity of model outputs to variability in venous anatomy. All input vessel radii were varied individually +/- 10 percent from their reference value and the change in output flow was used to compute absolute and normalised measures of sensitivity. An analysis of orthogonal sensitivity was also performed. The analysis was repeated with four degrees of thrombosis in the left common iliac vein. The largest normalised sensitivities were observed in locations associated with the venous return. Ranking of input parameters provided by the magnitude of normalised sensitivities suggests relatively few input parameters are associated with higher sensitivity values for flow in individual vessels where thrombosis is typically observed. Increase in absolute sensitivity was observed in the leg affected by the thrombosis, when this was explicitly included in the model. The results obtained can be used to inform model reduction strategies and to target clinical data collection to maximise the accuracy of model estimates of flow in venous regions prone to thrombus development. In future work it will be informative to extend the analysis to consider global sensitivity of the outputs.*

**Keywords:** Post-thrombotic Syndrome · Venous model · Sensitivity analysis.

## 1 Introduction

Deep vein thrombosis (DVT) of the lower limb is a health condition in which blood clots form in deep veins of the leg due to some pathological changes of the blood vessels or the blood itself [1]. It is estimated to affect 1-2 per 1,000 people each year and between 20 and 50% of them will develop long term complications known as post-thrombotic syndrome, PTS [2, 3]. The condition is not terminal, but it significantly impairs the quality of life. Its highly variable clinical presentation makes it difficult to treat and due to follow-up and repeat interventions treatment pathways are associated with significant cost. The use of stenting has increased in recent years [4], but there are significant gaps in the evidence-base to support clinical decision making [5]. The contribution of venous anatomy to haemodynamics in the region of the thrombosis and resulting risk of complications following stent placement has yet to be characterized in detail.

Reduced order modelling approaches using 1D and 0D formulations have been extensively reported in the literature, particularly in the context of research questions associated with the arterial circulation [6]. In contrast there are relatively few studies which focus on the venous circulation. Müller and Toro [7] describe a 1D model of the both the arterial and venous circulation, with focus on the cerebral vasculature and Keijsers et al. [8] employ a 1D formulation to study the interaction between the venous circulation in the lower limb and the activity of the calf muscle pump.

The assessment of model sensitivity and the quantification of the propagation of uncertainty from model inputs to model outputs has become acknowledged as an essential aspect of model development, particularly when model outputs are used to inform clinical decision making [9].

This study reports the development of a model of venous haemodynamics with focus on the influence of variation in the venous anatomy on the distribution of flow within the veins of the lower limb. This represents the first step towards modelling venous flow of the lower limb to aid clinical decision making in treatment of PTS.

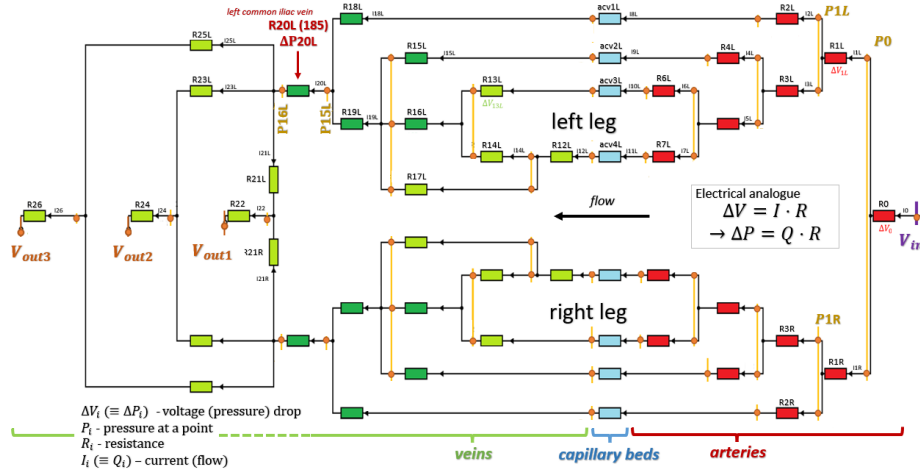
## 2 Methods

### 2.1 Lower limb circulation model

In this study a steady-state, 0D model was used to account for the complicated venous anatomy of the lower limb without considering the pulsatility of arterial or venous flow or vessel wall elasticity. The model topology and input parameters were taken from anatomical data reported by Müller and Toro [7] and the form of the model is shown in Figure 1.

The mean radius and length of each vessel were used to compute the corresponding Poiseuille resistance, given by equation (1).

$$R = \frac{8\mu L}{\pi r^4} \quad (1)$$



**Fig. 1.** Model formulation. Flow in the circulation is from right to left. Red elements represent large arteries, blue elements represent arterioles, capillaries and venules and green elements represent veins. All vessels are modelled as resistive elements.

where  $\mu$  is the viscosity of blood,  $r$  is a radius of the cross section of the considered vessel and  $L$  is its length.

To simplify the form of the model, where vessels were arranged in series in the vascular network they were represented as a single resistive element. The arterial circulation was taken to start at the abdominal aorta (representing flow into the lower limb only) and three pathways were considered to contribute to venous return to the heart (the inferior vena cava, the azygos vein and the vertebral venous plexus). The full model consisted of 50 resistances (15 arterial, 8 capillary beds, 27 venous) informed by 42 input vessel radii and length parameters. The boundary conditions to the model consisted of the pressure gradient between the abdominal aorta and the venous return to the heart. The aortic pressure was set to 80mmHg and the pressure at all outlets was assumed to be zero.

The model uses a data set with length and radii of every vessel from Müller and Toro [7] to calculate the mean radius and Poiseuille resistance. Vessels were assigned to the elements of the model based on a prepared key file to account for some of them being lumped into a single resistor. Resistance of arterioles, capillaries and venules between specific artery-vein pairs was calculated by summing resistance of the three and their distal resistance as provided by Müller and Toro. To simulate thrombosis, resistance of specific blood vessels was recalculated and replaced in the dataset based on a percentage reduction in the mean radius. A system of equations describing the model was constructed using Kirchhoffs' laws. There are 30 unique pathways from inlet to outlet and a pressure drop along each must agree with the specified boundary conditions. At every junction, the

sum of flows in must equal the sum of flows out of the junction. This results in an overspecified system of 66 equations. A row-echelon reduction algorithm was implemented to reduce and solve the system. The solution of the model provides flow at all locations which is post-processed to provide the corresponding pressure everywhere in the model.

## 2.2 Sensitivity analysis

To assess the sensitivity of the model outputs to variability in venous anatomy a local sensitivity analysis was performed. Each of the 42 radii of the blood vessels was varied by  $\pm 10\%$  from the reference value in turn, with all other radii kept constant. The model was solved 3 times for each vessel, with  $r_{base}$  - the original value,  $r_{min} = 0.9 \cdot r_{base}$  and  $r_{max} = 1.1 \cdot r_{base}$ . This produced 3 sets of output flows,  $Q$ , for each of the 42 radii. It is important to note that because some vessels are lumped, two or three radii contribute to the same resistor.

Two matrices were constructed and compared to visualise the relationships between the change in radii with the change in flows. The first was a matrix of absolute changes, with elements described by equation (2).

$$a_{ij} = \frac{\Delta Q_j}{\Delta r_i} = \frac{[Q_{max} - Q_{min}]_j}{[r_{max} - r_{min}]_i} \quad (2)$$

$Q_{max}$  corresponds to flows obtained by changing radius of a vessel to  $r_{max}$ , and  $Q_{min}$  to  $r_{min}$ . The second matrix reports relative changes, with respect to the base values of the radii and flows, with elements described by equation (3). Changes  $\Delta Q$  and  $\Delta r$  are calculated in the same way as in equation (2).

$$s_{ij} = \frac{\left[ \frac{\Delta Q}{Q} \right]_j}{\left[ \frac{\Delta r}{r} \right]_i} \quad (3)$$

The left common iliac vein, a deep vein of the ilio-femoral region, is a likely place for thrombus development. In the Müller and Toro dataset it corresponds to vessel no. 185 (resistor  $R20L$  in the current model) and is associated with flow  $Q20L$ . The relative influence of each input parameter on this flow value was evaluated using the sensitivity vector for this particular output value.

An analysis of orthogonal sensitivity was also performed. If the set of flow changes for variation of a given radius (input  $i$ ) is treated as a sensitivity vector the inner product of each vector with every other vector (input  $j$ ) provides an indication of the similarity between each vector pair. If the output scalar is close to  $\pm 1$ , the input parameter pair has a similar effect on the system, if it is close to zero, their effects are independent.

Finally, four different degrees of thrombosis were introduced in the left common iliac vein. An absolute sensitivity matrix of radii and flow changes was

constructed for each case, by repeating the procedure of radii variation. For each level of thrombosis, these matrices were compared to the original absolute sensitivity matrix.

### 3 Results

A comparison of absolute and normalised (relative) sensitivity matrices is shown in Fig. 2. Input and output parameters corresponding to cells of highest sensitivity value are highlighted in orange and yellow.

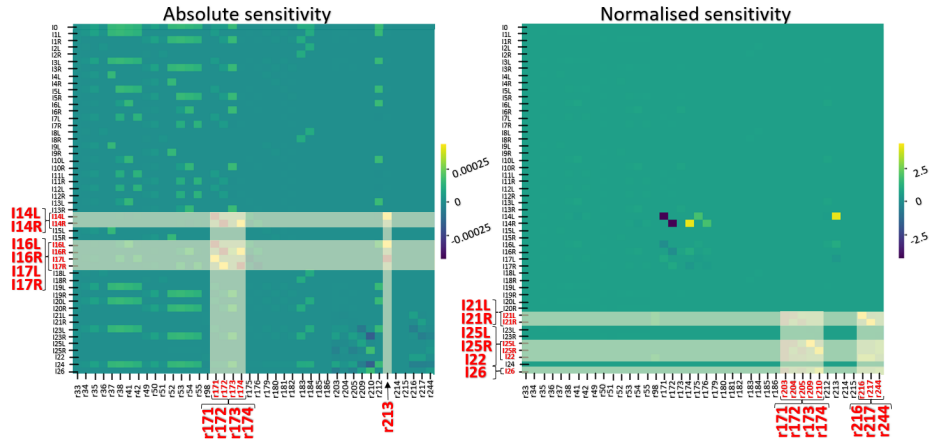
The two matrices vary in that the most significant radii in the absolute sensitivity belong to veins in the middle of the model, whereas for relative sensitivity, vessels close to the venous return appear to be more significant. It is worth noting that cells of highest values in the absolute sensitivity matrix are still significant in the relative sensitivity matrix, but not as much as those in the bottom right corner.

Ranked normalised sensitivity for flow  $Q_{20L}$  is shown in Fig. 3. This is a flow in left common iliac vein - a potential site of thrombosis. Out of 42 radii, 13 display influence on the flow and the first 5 belong to arterial network of the left leg.

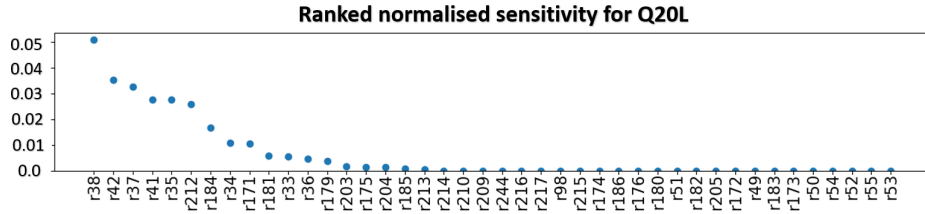
The vector in equation (4) expresses the relative sensitivity of all outputs (flows) to the  $i^{th}$  input (radius).

$$\underline{s}_i = (s_{i1}, s_{i2}, s_{i3}, \dots, s_{iN}). \quad (4)$$

The normalised inner product in equation (5) therefore measures the orthogonality (effective independence) of the  $i^{th}$  and  $j^{th}$  input parameters [10].



**Fig. 2.** Absolute vs normalised sensitivity. The most sensitive parameters and outputs are highlighted in both figures.

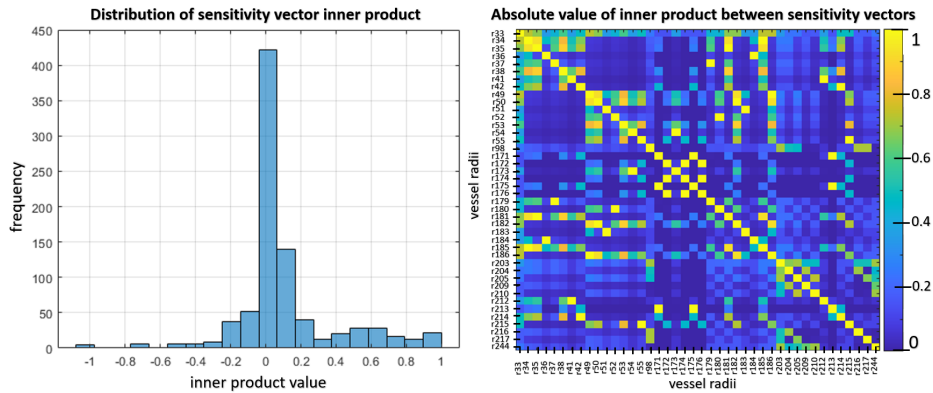


**Fig. 3.** Relative influence of input parameters on Q20L flow.

$$p_{ij} = \frac{\underline{s}_i \cdot \underline{s}_j}{|\underline{s}_i| \times |\underline{s}_j|}. \quad (5)$$

The distribution of these inner product values and a heatmap of their absolute values are presented in Fig. 4. This distribution has a clear peak at zero, demonstrating that many of the sensitivity vectors are independent of one another. The clustering of entries close to  $-1$  and  $1$  represent parameters which induce similar response of the system.

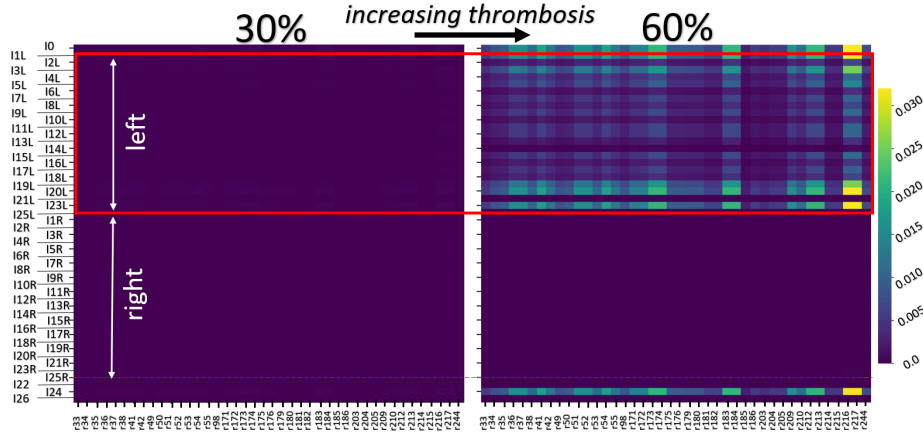
The heatmap can be used to identify the identity of these parameters. The heatmap is symmetric along the diagonal where all values equal 1, as expected. The majority of cells are blue which suggests weak or no dependence. Relatively few yellow spots off the diagonal imply dependence of some parameters and hence, a possibility of parameter space reduction after further analysis.



**Fig. 4.** Distribution of inner product values (left) and absolute value of the inner product (right).

Four different degrees of thrombosis were introduced to the left common iliac vein (no. 185) by reducing its radius, in turn, by 30%, 40%, 50% and 60%. A sensitivity matrix was constructed for each case as before, for  $\pm 10\%$  changes to every radius, and compared to the no-thrombus case. A difference in absolute

sensitivity between the no-thrombus sensitivity and two representative thrombosis cases is shown in Fig. 5. The higher the degree of thrombosis, the bigger the difference in absolute sensitivity. This is observed for the flows of the left leg, marked by a red frame in the plot, and for the output flow  $Q_{24}$  which corresponds to the *inferior vena cava*. These results demonstrate that sensitivity of the system is dominated by the effects of the thrombus when the reduction of the vessel lumen is  $\geq 40\%$  while *anatomical* variation is 10%.



**Fig. 5.** Difference between absolute sensitivity matrix for no-thrombosis case and two different degrees of thrombosis in the left common iliac vein.

## 4 Discussion

The focus of this study is on the assessment of the influence of anatomical variability on the distribution of flow within a model of the lower limb circulation with model parameters taken from Müller and Toro [7]. The sensitivity analyses reported here are an important step in examining the behaviour of the model, prior to further development including personalisation with clinical data.

The comparison of absolute and normalised sensitivity provided in Fig. 2 highlights the variation of radii and flows within the network. Both output measures provide useful information about the system and it is reasonable that the largest normalised change in flow is observed in locations associated with the venous return, as the flow in these vessels results from flow through all other vessels in the network.

The ranking of input parameters provided by the results shown in Fig. 3 is useful when the focus of the model operation is on predicting the flow in a specific location in the network (in this example the left common iliac vein). If such a model is personalised using clinical measurements of vascular anatomy

then this ranking can be used to identify the most important radii for direct measurement and reduce the effort in assessing vasculature which has a small effect on the flow in the location of interest. Fig. 3 suggests such an approach is likely to be feasible for the current network, as relatively few input parameters are associated with higher sensitivity values for this specific model output.

The visualisation of orthogonal sensitivity of the model input parameters shown in Fig. 4 has the potential to inform approaches to reduce the complexity of the model. Although this is not necessary in the current model due to low computational cost (a single operation of the model takes less than a second) it may provide advantages in terms of both interpretation of the model behaviour and efficiency of model personalisation. However, some care is required in interpretation of Fig. 4 as the approach taken here assigns the same significance to all model outputs. For specific clinical applications this may not be appropriate as some model outputs will inform the detail of haemodynamics associated with patient outcomes more than others.

The results provided in Fig. 5 demonstrate the significance of the occlusion of a vessel due to the formation of a thrombus. Although thrombus formation is represented in the same manner as variation in anatomy, by varying the vessel radius, it is worth noting that this variation is of a larger range than that assumed for anatomical variation. The figure shows an increase in absolute sensitivity in the leg affected by the thrombosis. Changes in relative sensitivity were also observed, but only became significant for thrombosis greater than 60%.

This study performs a local sensitivity analysis. To assess global sensitivity of model outputs it is necessary to vary several parameters simultaneously which provides information about interactions between input parameters. The role of such an analysis to inform model personalisation for clinical translation is discussed in detail by Huberts et al. [9]. A global sensitivity analysis will be undertaken in future work and will allow inclusion of additional input parameters including the degree and location of thrombosis and the magnitude of the pressure gradient applied to the model.

## 5 Conclusion

This study demonstrates the value of local sensitivity analysis to inform development of a model of lower limb haemodynamics. The results obtained can be used to inform model reduction strategies and to target clinical data collection to maximise the accuracy of model estimates of flow in venous regions prone to thrombus development.

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