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Modelling cerebral blood flow and perfusion during acute ischaemic stroke

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List of Publications

First Author Papers

1. **R.M. Padmos**, T.I. Józsa, W.K. El-Bouri, P.R. Konduri, S.J. Payne, A.G. Hoekstra. (2021). Coupling one-dimensional arterial blood flow to three-dimensional tissue perfusion models for in silico trials of acute ischaemic stroke. *Interface Focus*. 2021;11(1):20190125. doi:10.1098/rsfs.2019.0125

Authors' contributions: R.M. Padmos has developed the coupling algorithm, the 1-D blood flow model, and written the manuscript under the supervision of A.G. Hoekstra. P.R. Konduri has created segmentations of the circle of Willis based on CT angiography. T.I. Józsa has pre-processed the brain mesh and a vessel encoded arterial spin labelling atlas describing perfusion territories under the supervision of S.J. Payne. R.M. Padmos, T.I. Józsa, W.K. El-Bouri, S.J. Payne, and A.G. Hoekstra have designed the research. All authors have revised the paper.

2. **R.M. Padmos**, N. Arrarte Terreros, T.I. Józsa, G. Závodszy, H.A. Marquering, C.B.L.M. Majoie, A.G. Hoekstra. (2021). Modelling the leptomeningeal collateral circulation during acute ischaemic stroke. *Med Eng Phys*. 2021;91:1-11. doi:10.1016/j.medengphy.2021.03.003

Authors' contributions: R.M. Padmos wrote the manuscript and developed the computational model. N. Arrarte Terreros performed the measurements in stroke patients. T.I. Józsa has post-processed the brain mesh and the vessel-encoded arterial spin labelling MRI atlas describing

perfusion territories. G. Závodszy, H.A. Marquering, C.B.L.M. Majoie and A.G. Hoekstra helped conceive and supervise the project. All authors have contributed to the final manuscript.

3. **R.M. Padmos**, T.I. Józsa, W.K. El-Bouri, G. Závodszy, S.J. Payne, A.G. Hoekstra. Two-Way Coupling Between 1D Blood Flow and 3D Tissue Perfusion Models. In: Paszynski M, Kranzlmüller D, Krzhizhanovskaya V V., Dongarra JJ, Sloot PMA, eds. Vol 12744. Lecture Notes in Computer Science. Springer International Publishing; 2021:670-683. doi:10.1007/978-3-030-77967-2_56

Authors' contributions: R.M. Padmos has developed the coupling algorithm, the 1-D blood flow model and written the manuscript under the supervision of G. Závodszy and A.G. Hoekstra. T.I. Józsa has post-processed the brain mesh, developed the 3-D tissue perfusion model and the optimisation of the model parameters under the supervision of S.J. Payne. All authors have contributed to the design of the research and revision of the paper.

4. **R.M. Padmos**, N. Arrarte Terreros, T.I. Józsa, G. Závodszy, H.A. Marquering, C.B.L.M. Majoie, S.J. Payne, A.G. Hoekstra. (2021). Modelling Collateral Flow and Thrombus Permeability During Acute Ischaemic Stroke (Submitted to International Journal for Numerical Methods in Biomedical Engineering, 2021)

Authors' contributions: R.M. Padmos wrote the manuscript and developed the computational model. N. Arrarte Terreros performed the measurements in AIS patients. T.I. Józsa has post-processed the brain mesh and the vessel-encoded arterial spin labelling MRI atlas describing perfusion territories. G. Závodszy, H.A. Marquering, C.B.L.M. Majoie, S.J. Payne, and A.G. Hoekstra helped conceive and supervise the project. All authors have contributed to the final manuscript.

Co-authored Papers

1. T.I. Józsa, **R.M. Padmos**, N. Samuels, W.K. El-Bouri, A.G. Hoekstra, S.J. Payne. A porous circulation model of the human brain for in silico clinical trials in ischaemic stroke. *Interface Focus*. 2021;11(1):20190127. doi:10.1098/rsfs.2019.0127

Authors' contributions: T.I. Józsa has pre-processed the brain mesh, developed the finite-element models and the optimization of the model parameters, and written the manuscript under the supervision of S.J. Payne. R.M. Padmos has developed the brain territory clustering algorithm under the supervision of A.G. Hoekstra whereas N. Samuels prepared the patient's description and processed the corresponding CT image. T.I. Józsa, W.K. El-Bouri, A.G. Hoekstra and S.J. Payne have designed the research. Every author has contributed to the revision of the paper.

2. T.I. Józsa, **R.M. Padmos**, W.K. El-Bouri, A.G. Hoekstra, S.J. Payne. On the Sensitivity Analysis of Porous Finite Element Models for Cerebral Perfusion Estimation. *Ann Biomed Eng*. Published online June 21, 2021. doi:10.1007/s10439-021-02808-w

Authors' contributions: T.I. Józsa carried out the research and prepared a draft of the manuscript under the supervision of S.J. Payne. R.M. Padmos developed the brain territory clustering algorithm under the supervision of A.G. Hoekstra. T.I. Józsa, W.K. El-Bouri, and S.J. Payne designed the research and every author contributed to the revision of the paper.

3. C. Miller, M. van der Kolk, **R.M. Padmos**, T.I. Józsa, A.G. Hoekstra. Uncertainty Quantification of Coupled 1D Arterial Blood Flow and 3D Tissue Perfusion Models Using the INSIST Framework. In: Paszynski M, Kranzlmüller D, Krzhizhanovskaya V V., Dongarra JJ, Sloot PMA, eds. Vol 12747. Lecture Notes in Computer Science. Springer International Publishing; 2021:691-697. doi:10.1007/978-3-030-77980-1_52

Authors' contributions: C. Miller carried out the research and wrote the manuscript under the supervision of A.G. Hoekstra. M. van der Kolk developed the framework and contributed to the research. R.M. Padmos developed the 1D blood flow model. T.I. Józsa developed the 3D tissue perfusion model. Every author has contributed to the revision of the paper.

4. M. van der Kolk, C. Miller, **R.M. Padmos**, V. Azizi, A.G. Hoekstra. des-ist: A Simulation Framework to Streamline Event-Based In Silico Trials. In: Vol 1. Springer International Publishing; 2021:648-654. doi:10.1007/978-3-030-77967-2_53

Authors' contributions: M. van der Kolk developed the framework and wrote the manuscript under the supervision of A.G. Hoekstra. C. Miller, R.M. Padmos, and V. Azizi have contributed to the design of the framework. Every author has contributed to the revision of the paper.

5. C. Miller, **R.M. Padmos**, M. van der Kolk, T.I. Józsa, N. Samuels, Y. Xue, S.J. Payne, A.G. Hoekstra. (2021). In Silico Trials for Treatment of Acute Ischemic Stroke: Design and Implementation. *Computers in Biology and Medicine*, 104802. doi:10.1016/j.combiomed.2021.104802

Authors' contributions: Claire Miller: Investigation, Writing - Original Draft, Visualization. Raymond Padmos: Methodology, Writing - Original Draft, Visualization. Max van der Kolk: Software, Investigation, Writing - Review and Editing. Tamás István Józsa: Methodology, Writing - Review and Editing. Noor Samuels: Methodology, Writing - Review and Editing. Yidan Xue: Methodology, Writing - Review and Editing. Stephen Payne: Supervision. Alfons Hoekstra: Conceptualisation, Writing - Review and Editing, Supervision, Funding acquisition.

Summary

The work within this thesis focuses on modelling cerebral arterial blood flow and tissue perfusion during acute ischaemic stroke. Several models have been developed that are able to model blood flow and tissue perfusion during a stroke. Understanding the changes in blood flow and tissue perfusion during an acute ischaemic stroke is important to better understand how tissue infarction develops. This can be used to, for instance, predict patient outcome, help with (clinical) decision-making, and improve treatment development. This thesis starts with a short introduction to the cerebral vascular system and the motivation behind modelling blood flow and perfusion.

Chapter two focuses on modelling blood flow through the cerebral arteries and the mapping of model outlets to perfusion territories on the surface of the brain. The pulsatility of blood flow, caused by the beating of the heart, gradually decreases away from the heart. This work therefore argues that compared to the timescale of tissue infarction, the pulsatility of blood (flow) can be ignored if one is mainly interested in tissue perfusion. This provides one-way coupling between arterial blood flow and tissue perfusion. A stroke is modelled as the complete blockage of a cerebral artery in the arterial blood flow model and leads to zero flow at the boundary of the cerebral tissue model.

Chapter three addresses two-way coupling between a steady state blood flow model and a cerebral tissue model. This work expands upon the work in chapter two in multiple ways. Firstly, the arterial blood flow model is replaced by a steady state model that captures the average state variables over a heartbeat. This step improves the execution time and simplifies the modelling of blood flow. Secondly, the models are two-way coupled such that the tissue perfusion model

can affect the arterial blood flow model, and vice versa. Two-way coupling requires the estimation of the pressure drop, or equivalently the resistance, between the models. The coupling resistance is caused by vessels that fall in between the two models and are therefore not captured by either. The two-way coupled model captures retrograde flow during an acute ischaemic stroke. In addition, the tissue perfusion drops less compared to the one-way coupled model.

Chapter four looks at the effect of the leptomeningeal collateral circulation during a stroke. The collateral circulation provides residual blood flow to tissue at risk during a stroke. This residual flow has a significant effect on infarct volume and penumbra [16]. The steady state blood flow model, presented in the previous chapter, is extended with vessels leading to the start of the cerebral tissue. Outlets are generated on the surface of the brain and connected to a hexagonal vessel network representing the pial surface vessel network covering the surface. The leptomeningeal collateral vessels are the vessels of the pial surface network that connect different perfusion territories of the brain. By varying the density of these vessels, using a collateral vessel probability, different degrees of collateral flow can be modelled. The model is compared to two experimental measurements in acute ischaemic stroke patients: the pressure drop across the clot and the time delay over the clot. Contrast transport is simulated in the model by a simple advection scheme using the average velocity of blood flow inside the vessels. The model results are similar to those measured experimentally.

Chapter five continues with the leptomeningeal collateral model from chapter four. This chapter investigates the effect of thrombus permeability on residual blood flow during a stroke. A permeable thrombus is modelled as a porous medium using Darcy's law. Flow through the thrombus depends on the thrombus resistance and is given by the permeability and length of the thrombus. Infarct volumes are estimated by assigning each outlet on the pial surface a small volume of cerebral tissue. The collateral vessel probability used in the model is mapped to the clinical collateral score: absent, poor, moderate, and good. This is achieved by matching the estimated infarct volumes in the

model with those measured for acute ischaemic stroke patients for the different collateral scores. Measurements in these patients of contrast flowing through the thrombus are used to estimate thrombus permeability for the different collateral scores. Flow through the thrombus is relatively minor compared to that provided by the collaterals. The collaterals are a dominant factor in providing residual blood flow to tissues at risk during a stroke. Approximating a thrombus as impermeable is therefore a valid approximation based on the amount of flow through it.

Finally, the thesis is concluded with a brief summary of the main conclusions and an outlook on applications and future work.

Samenvatting

Dit proefschrift richt zich op het modelleren van cerebrale arteriële bloedstroming en wefselperfusie tijdens een acute ischemische beroerte. Er zijn verschillende modellen ontwikkeld die de bloedstroom en wefseldoorbloeding tijdens een beroerte kunnen modelleren. Inzicht in de veranderingen in bloedstroming en wefselperfusie tijdens een acute ischemische beroerte is belangrijk om beter te begrijpen hoe wefselinfarcten ontstaan. Dit kan bijvoorbeeld worden gebruikt om de uitkomst voor de patiënt te voorspellen, te helpen bij (klinische) besluitvorming en de ontwikkeling van behandelingen te verbeteren. Het proefschrift begint met een korte inleiding over het cerebrale vasculaire systeem en de motivatie achter het modelleren van bloedstroming en perfusie.

Hoofdstuk twee richt zich op het modelleren van bloedstroming door de cerebrale slagaders en het berekenen van de uitgangen naar perfusiegebieden op het hersenoppervlak. De pulsatiliteit van de bloedstroom, veroorzaakt door het kloppen van het hart, neemt geleidelijk af weg van het hart. In dit werk wordt daarom beargumenteerd dat in vergelijking met de tijdschaal van wefselinfarct groei, de pulsatiliteit van bloed(stroming) kan worden genegeerd als men hoofdzakelijk geïnteresseerd is in wefselperfusie. Hierdoor ontstaat een eenrichtingskoppeling tussen arteriële bloedstroming en wefselperfusie. Een beroerte wordt gemodelleerd als de volledige blokkering van een cerebrale slagader in het arteriële bloedstroommodel en leidt tot nul doorstroming in het cerebrale wefselmodel.

Hoofdstuk drie behandelt de koppeling in twee richtingen tussen een steady state bloedstromingsmodel en een cerebraal wefselmodel. Dit werk breidt op meerdere manieren uit op het werk in hoofdstuk twee. Ten eerste wordt

het arteriële bloedstroommodel vervangen door een steady state model dat de gemiddelde variabelen gedurende een hartslag berekent. Deze stap verbetert de uitvoeringstijd en vereenvoudigt de modellering van de bloedstroom. Ten tweede zijn de modellen in twee richtingen gekoppeld, zodat het weefselperfusiemodel het arteriële bloedstroommodel kan beïnvloeden, en omgekeerd. Voor tweerichtingskoppeling moet de drukval, of equivalent de weerstand tussen de modellen worden berekend. Deze koppelingsweerstand wordt veroorzaakt door bloedvaten die tussen de twee modellen vallen en hierdoor in geen van beide modellen wordt gevangen. Het in twee richtingen gekoppelde model modelleert de retrograde stroming tijdens een acute ischemische beroerte. Bovendien daalt de weefseldoorbloeding minder in vergelijking met het eenzijdig gekoppelde model.

In hoofdstuk vier wordt gekeken naar het effect van de leptomeningeale collaterale circulatie tijdens een beroerte. De collaterale circulatie zorgt tijdens een beroerte voor een restbloedstroom naar weefsel dat risico loopt. Deze reststroom heeft een significant effect op het infarctvolume en de penumbra [16]. Het steady state bloedstromingsmodel, gepresenteerd in het vorige hoofdstuk, wordt uitgebreid met bloedvaten die naar het begin van het hersenweefsel leiden. Model uitstroomopeningen worden gegenereerd aan het oppervlak van de hersenen en verbonden met een hexagonaal vaatnetwerk dat het oppervlak bedekt. De leptomeningeale collaterale vaten zijn de vaten van het piaale oppervlaktenetwerk die verschillende perfusiegebieden van de hersenen met elkaar verbinden. Door de dichtheid van deze bloedvaten te variëren met behulp van een waarschijnlijkheidsparameter van de collaterale bloedvaten, kunnen verschillende gradaties van collaterale stroming worden gemodelleerd. Het model wordt vergeleken met twee experimentele metingen bij patiënten: de drukval over het stolsel en de tijdvertraging over het stolsel. Contrasttransport wordt in het model gesimuleerd door een eenvoudig advectionschema dat gebruik maakt van de gemiddelde snelheid van bloed in de bloedvaten. De modelresultaten zijn vergelijkbaar met experimentele waarden gemeten in patiënten.

Hoofdstuk vijf gaat verder met het leptomeningeale collaterale model uit hoofdstuk vier. Dit hoofdstuk onderzoekt het effect van de doorlaatbaarheid van

de trombus op de resterende bloedstroom tijdens een beroerte. Een doorlatende trombus wordt gemodelleerd als een poreus medium met behulp van de wet van Darcy. De doorstroming door de trombus hangt af van de weerstand van de trombus en wordt gegeven door de permeabiliteit en de lengte van de trombus. De infarctvolumes worden geschat door aan elke uitstroomopening op het piaal hersenoppervlak een klein volume hersenweefsel toe te kennen. De waarschijnlijkheid van de collaterale vaten die in het model wordt gebruikt, wordt gekoppeld aan de klinische collaterale score: afwezig, slecht, matig, en goed. Dit wordt bereikt door de geschatte infarctvolumes in het model af te stemmen op de volumes die zijn gemeten bij patiënten voor de verschillende collaterale scores. Metingen bij patiënten van de bloedstroom door de trombus worden gebruikt om de doorlatendheid van de trombus te schatten voor de verschillende collaterale scores. De bloedstroming door de trombus is relatief gering in vergelijking met de bloedstroom door de collateralen. De collateralen zijn een dominante factor in het leveren van de resterende bloedstroming naar weefsels die risico lopen tijdens een beroerte.

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