PROJECT TITLE: A personalised automatic approach for assessing and modelling the brain deep tissue waste drainage related structures

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PROJECT DESCRIPTION

Background:

Previous experiments (Kress 2014) have suggested that brain features known as perivascular spaces play an important role in the clearance of metabolic waste from the brain tissue. They extend along arterioles, capillaries and venules, communicating freely with perineuronal and other spaces between glial cells (i.e. the "brain cleaners") and fiber tracts, and contain cerebrospinal fluid. Perivascular spaces (PVS), when enlarged, can be seen in MRI and have attracted the attention of the clinical community as they have been found associated with ageing, vascular risk factors and with a myriad of inflammatory and neurodegenerative diseases (Francis et al. 2019). However, the interaction between PVS and venules and the haemodynamic characteristics of these clearance processes are not known, making difficult (if not impossible) the prognosis and contributing to inefficient treatment strategies.

We have developed computational methods to segment venules, perivascular spaces, main venous drainage pathways and cerebrospinal fluid-filled spaces within the intracranial volume. However, several factors hamper their accuracy and limit their applicability, having these been identified as: motion artefacts, poor tissue-structure contrast, biological tissue inhomogeneities, presence of lesions and features with similar intensity and size characteristics, scanning protocol variations and the lack of ground truth. Therefore, a robust unsupervised or semi-supervised approach to segment and characterise the venules and venous pathways consistently and accurately for multicentre studies and personalised medicine is needed.

Aims:

This project aims to develop a robust state-of-the-art computational approach to segment, model and characterise venules and components of the brain drainage pathways and investigate their association with PVS, lesion progression, and brain tissue loss in patients with small vessel and Alzheimer's diseases.

Hypothesis:

We hypothesise that using state-of-the-art machine learning techniques it will be possible to overcome the limitations of the current methods that segment these venous pathways. Also, that it will be possible to estimate the inflammatory vs. vascular contributions in the pathological features seen in brain MRI if we use an integrated approach that combines the results from the detailed segmentation of venules, perivascular spaces, brain lesions, and main venous drainage pathways and cerebrospinal fluid-filled spaces within the intracranial volume, with textural tissue characteristics, retinal vasculature measurements and relevant clinical information.

Methods:

This project will use data from well-characterised mild stroke patients with long term outcomes, and Alzheimer's disease patients from a publicly available database (http://adni.loni.usc.edu/) from where the necessary data and priors of the segmentations are available. Tissue properties including mineral deposition and extraction of the diffusion characteristics in tissues will be used. The methods to apply involve variants of Hessian filters, combined with the machine learning methods we have evaluated in the past: UResNet, Generative Adversarial Networks, and with the descriptors we have explored and developed in the last five years (see publications of principal supervisor in https://www.research.ed.ac.uk/portal/en/persons/maria-valdes-hernandez(f22f22d9-52bb-4883-bf94-52aa23a691e1).html). All data necessary for this project is already available and has been generated as part of ongoing projects.

Training outcomes:

The student will receive state-of-the-art training in the core disciplines of image analysis, computational modelling, statistical methods, and data science while gaining expert knowledge in the context of brain disease. This highly interdisciplinary approach is well aligned with the "T-shaped researcher" training requirements identified as key in the DTP in Precision Medicine. The student will develop the essential soft and domain-specific skills necessary to design and implement novel quantitative and computational methods that could solve challenging problems across the entire spectrum of clinical brain sciences both in academic and industrial settings. More specifically:

1) Recognise and identify the state-of-art and difficulties of the segmentation of small venules and perivascular spaces

2) Identify and familiarise with the state-of-art image processing methods used in biomedical signal and image analyses and translate them to the task in-hand

3) Identify and familiarise with the role that the structures to be segmented have and their interaction with other disease indicators

4) Acquire skills in data management.

5) Familiarise with and apply clinical research regulations.

References:

Kress BT, Iliff JJ, Xia M, Wang M, Wei HS, Zeppenfeld D, Xie L, Kang H, Xu Q, Liew JA, Plog BA, Ding F, Deane R, Nedergaard M.Impairment of perivascular clearance pathways in the aging brain. Ann Neurol. 2014 Dec;76(6):845-61.

Francis F, Ballerini L, Wardlaw JM. Perivascular spaces and their associations with risk factors, clinical disorders and neuroimaging features: A systematic review and meta-analysis. Int J Stroke 2019; 14(4): 359-371.

Muñoz Maniega et al. Spatial Gradient of Microstructural Changes in Normal-Appearing White Matter in Tracts Affected by White Matter Hyperintensities in Older Age. Front Neurol 2019 https://doi.org/10.3389/fneur.2019.00784

Ballerini et al. Perivascular Spaces Segmentation in Brain MRI Using Optimal 3D Filtering. Scientific Reports (2018) 8:2132

PROJECT TIMEPLAN

Timetable for the first two years (the third year will be wider evaluation, implementation for wider use and writing-up the thesis) Note: <u>the datasets for this projects are already available and have been characterised in detail as part of current projects</u>.

Task		Super-vision (%)	Start	End	Work-ing days	2020	2021			2022	
						Sep - Dec	Jan - Mar	Apr - Sep	Oct - Dec	Jan - Mar	Apr - Sep
1	Induction and training	MVH(40), JMW(20), MOB(40)	01.09.20	31.10.20	45						
2	Acquisition of computational resources	-	01.09.20	31.10.20	45						
3	Training, literature review	MVH(60), JMW(20), MOB(20)	03.11.20	30.01.21	55 (excl Holiday)						
4	Evaluation and modification of existing methods applying transfer-learning techniques	MVH(60), JMW(20), MOB(20)	02.02.21	31.03.21	42						
5	Evaluate outputs and (re)define segmentation pipeline	MVH(60), JMW(20), MOB(20)	01.04.21	30.09.21	135						
Milestone 1: Refined robust automatic segmentation of vessel-like brain structures								◇			
6	Extract texture and signal-based descriptors from the tissues/lesions	MVH(60), JMW(20), MOB(20)	02.02.21	30.09.21	173						
7	Define and extract boundary conditions and initial evaluation of existing model	MVH(30), JMW(20), MOB(50)	01.10.21	31.12.21	56 (excl Holiday)						
Milestone 2: Tissue characterisation and definition of boundary conditions									◇		
8	Drainage pathways modelling (adaptation and re-definition of	MVH(20), JMW(20), MOB(60)	04.01.22	31.03.22	64						

	existing vessel model)										
Milestone 3: Drainage pathways modelling										◇	
9	Integrate the modelling with the clinical indicators / other biomarkers to estimate vascular vs. inflammatory contributions	MVH(33), JMW(33), MOB(33)	01.04.22	31.08.22	119						
Milestone 4: Preliminary estimation of vascular vs. inflammatory contributions											◇

ALIGNMENT WITH MRC DTP THEMES

Medical Informatics x

Computational Biology x

Computational Modelling x

Bioinformatics x

Whole Organism Physiology/Pathology x

Details about the interdisciplinary nature of the project

This is a highly interdisciplinary project that brings together experts across several disciplines (Dr María Valdés Hernández, neuroimaging, image processing, software development; Prof Joanna Wardlaw, cerebral small vessel disease, ischaemic stroke, neuroimaging; Dr Miguel O. Bernabeu, medical informatics, vascular structure and function) in order to tackle a problem of great clinical relevance. The student will receive training across a broad range of topics, most notably: image analysis, computational modelling, statistical methods, and data science. Furthermore, the student will develop first-hand experience in the application of the previous techniques to the early detection of small vessel disease, a leading cause of dementia and stroke worldwide.