| Project Details | |
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| Project Code | MRCPHS25Br Biglino |
| Title | Novel morphological markers of congenital heart disease: from computational modelling to population data |
| Research Theme | Population Health Sciences |
| Summary | Congenital heart disease (CHD) affects 1/110 births, causes 220,000 deaths/year and affects 13+ million worldwide. The aetiology of CHD is complex, with evidence of both genetic and environmental causes, and identifying sub-phenotypes of CHD remains challenging. These defects present with anatomical changes at birth and/or following surgical repair. Such changes over time (e.g. enlargements, narrowings) are key indicators of remodelling and disease progression. Patient-specific computational modelling can generate predictive remodelling and progression data. This project will develop a statistical shape modelling framework for cardiovascular structures based on a unique biobank in Bristol, then extending the observations to larger cohort studies. |
| Description | **Background.** The aetiology of CHD is complex and the identification of specific sub-phenotypes of CHD remains challenging. Patients with CHD require treatment and life-long medication and follow-up but therapies are ineffective in up to 50% of cases. Morphological abnormalities and/or changes in cardiovascular morphology over time (e.g. enlargement, narrowing) are key indicators of remodelling and disease progression. Computational modelling can aid in studying patient-specific anatomies, generating descriptive and predictive data through a statistical shape modelling (SSM) framework for morphological assessment of cardiovascular structures. The creation of image-databases, such as the Cardiac Atlas Project, enables population-based studies processing and analysing large amounts of 3D information for the creation of average population shapes ("atlases") and calculating variability around such averages. Unlocking the potential of shape analysis in heart disease can improve risk stratification, allow personalising management and follow-up strategies. Computational techniques like SSM show promise to quantify 3D variations in shape rather than qualitatively observe them from a (potentially misleading) 2D perspective.<br>**Aim.** The overarching aim is to develop novel non-invasive indices of cardiovascular morphology and generate new knowledge on remodelling, disease progression and onset of complications in CHD patients. Specific objectives: 1) developing normative models of growth and remodelling for both ventricles and the aorta; 2) modelling cross-sectional datasets (>1,000 scans) for the automatic identification of sub-groups with adverse remodelling in two important clinical scenarios, a) tetralogy of Fallot (most common cyanotic CHD) and b) bicuspid aortic valve (most common CHD); 3) developing machine learning and regression strategies to identify sub-groups with accelerated disease progression; 4) testing the findings in larger cohort studies.<br>**Approach.** The work is divided into three key parts. 1) Identifying unfavourable shape features. The student will develop cross-sectional models to unravel associations with clinical data (favourable vs. unfavourable shape features), including implementing unsupervised machine learning tasks to automatically identify natural groups in large |

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| | datasets. Using 3D anatomical models for clustering techniques, with appropriate distance metric and linkage function settings, can be used to automatically divide a bulk of unlabelled clinically acquired input shapes into subgroups of clinical relevance. This will be applied to generate a normative model and test two clinically relevant scenarios, a) left/right ventricles in tetralogy of Fallot, and b) aorta in patients with BAV aortopathy, including sub-populations with/without aortic coarctation. This can uncover previously unreported features and/or patterns within a disease, in line with current Precision Medicine or "Precision Imaging" strategies. 2) Growth patterns and adverse remodelling. The student will develop longitudinal models to construct growth trajectories of both heart chambers and main vessels, analysing >1,000 scans (2+ scans per patient to capture changes over time). They will develop aortic growth models with BAV +/- aortic coarctation and explore ventricular remodelling in ToF comparing growth trajectories within subgroups, identifying those patients at higher risk of adverse remodelling such as ascending aortic dilatation (in BAV) or ventricular enlargement (in ToF). They will also compare against the previously generated normative data. 3) Testing in larger cohorts. The data for components #1 and #2 for the project will be derived from the Bristol biobank generated as part of Children OMACp (Outcome monitoring after cardiac procedure in congenital heart disease), a multicentre prospective cohort study recruiting children with CHD undergoing a cardiac procedure. Having developed the methodologies and tools using OMACp data, the student will apply the models to larger datasets, starting from the Avon Longitudinal Study of Parents and Children (ALSPAC) data. Extending the methods and validating the previous observations in larger datasets will reinforce observations whilst providing additional methodological learning.<br>**Methodological considerations.** As highlighted in The Lancet Digital Health, current AI systems can sometimes establish opaque associations between inputs and outputs, particularly in approaches based on deep learning. Whilst identifying patterns is appealing, the risk of observing spurious relationships has been defined as "considerable". This hampers clinical applications. A "medical algorithmic audit framework" has been proposed in order to consider algorithmic errors in the context of a clinical task, mapping components that may contribute to such errors, and anticipating their consequences. This will be considered in this project.<br>**Ownership.** The student will be exposed to different computational methods and will be able to steer the research by building on our available pilot data and implement their own approaches to the datasets. Depending on the initial results, in-depth analysis of specific markers in the OMACp data will be guided by the students' insights together with the project supervisors. Because of the nature of the results from this work, the student will have the opportunity to determine variables to test in the latter part of the project (larger datasets) based on their own critical thinking and analysis of the data gathered in the first part of the project, as such we feel the project offers good opportunity for the student to take ownership. |

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