Project Details	
Project Code	MRC22IIAREx Wedgwood
Title	Mathematical Modelling for the Prediction of Aerobic Fitness in Paediatric Patients with Cystic Fibrosis
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	A core goal for treating cystic fibrosis is to improve patients' aerobic fitness, which incorporates function of the cardiovascular, pulmonary and muscular systems. Despite knowledge of these systems in isolation, little is understood about the complex interactions between them. This project aims to construct and analyse dynamic, multi-organ mathematical models to elucidate to assess how the quantitative relationships between these systems impact aerobic fitness.
Description	This project aims to develop an integrated, multi-scale model of cardiac, vascular, muscular and respiratory systems to investigate how aerobic fitness in young patients with CF might be improved. To do this, we will build upon our previously developed Gaussian process regression model, which predicts gas exchange thresholds (GET), a proxy for aerobic fitness, from routinely collected lung function measurements and spirometry data from cardiopulmonary exercise tests (CPET) in paediatric patients. Gaussian process models have three advantages over other types of data-driven mathematical model. Firstly, they can describe nonlinear relationships between variables. Secondly, they provide not only an estimate of output variables, but also the level of uncertainty around this estimate, which is particularly important when dealing with adolescent age groups which tend to display greater variability in physiological parameters compared to adults. Finally, the Bayesian nature of these models means that prior knowledge of distributions of output parameters and uncertainty around the input measurements themselves can naturally be incorporated into the full model, so that all sources of uncertainty are accounted for. In a narrow cohort of 15 patients, this model was shown to be a robust predictor of GET, requiring only limited amounts of patient data. In order for the model to translated into the clinical realm, it must first be validated against a wider and more diverse patient group and against other commonly used biomarkers for aerobic fitness and CF prognosis. In addition, the ability of the model to predict how interventions, including pharmacological and exercise-based treatment strategies, will affect longer-term aerobic fitness needs to be tested. To address these, this project will: 1. Apply our previously developed Gaussian process model to a wider cohort of patients and use it to cluster patients into groups displaying similar quantitative relationships between aerobic fitness and the constitutive physiological organ systems. The clustering of patients will identify which patients are most likely to respond in a similar manner to one another to the same type of clinical intervention. 2. Develop a revised Gaussian process regression taking into account other important biomarkers not included in the initial model, such as haemoglobin count and body composition. The impact of adding additional inputs to the model will be assessed and the model refined down to its simplest, robust form. Gaussian process models using the same inputs to predict other clinically relevant biomarkers, including muscle strength, will be developed and contrasted to the revised models

	for GET using a Bayesian model comparison framework. Importantly, this step will show how the same input variables affect different output biomarkers assessing the same overarching clinical features so that robustness across measurement methodology can be quantified. 3. Use the validated model to predict improvements to aerobic fitness that may arise due to clinical strategies. For example, through in silico analysis using our model, we will test: (i) How does the manipulation of the inspiratory lung pressure training influence whole body total oxygen consumption (VO2)? (ii) How does the manipulation of arteriovenous oxygen difference (simulating endurance training) influence total oxygen consumption (VO2max)? These predictions will be validated against changes observed in GET in patients following an 8-week intervention period, in which they will be assigned an exercise-management strategy focussed on either aerobic, anaerobic or resistance training. Changes in aerobic fitness as computed via CPET tests administered before and after the 8-week period will be compared across the clusters identified in objective 1. In this way, the project will attempt to identify which type of clinical intervention is optimal for a given patient cluster.
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