**Career Development Plan**

Name of ESR:Peter Marinov

Name of lead supervisor: Blanca Rodriguez

Date: 04/03/2020

**Brief overview of research project and major accomplishments so far**

The goal of the project is to assess the effect of tissue and cellular level remodelling on the 12-lead ECG in Arrhythmogenic Cardiomyopathy using in-silico techniques.

Twenty patient geometries were reconstructed from MRI data.

Accomplished work:

Using the patient-specific geometries, two Arrhythmogenic Cardiomyopathy (ACM) patient QRS phenotypes were mechanistically explained using MRI-based computer simulation and modelling. Simulated ECGs found that the classical right ventricular predominant ACM patient was confirmed to have conduction slowing in the anterior/anterolateral free wall due to fibrotic replacement and consequent conduction slowing of 40-50% in the region identified by LGE MRI. A more complex phenotype involving loss of R-wave progression and a fibrotic patch in the left ventricle anterior free wall was found to be attributed to a 60% slowing of the Purkinje-endocardial layer. Features were extracted from the QRS complexes of a cohort of patients and were found to display a spectrum of abnormalities, in terms of QRS and terminal activation durations.

A paper with the above results was submitted to the journal Circulation Arrhythmia and Electrophysiology. The work was presented at the Cardiac Physiome Symposium in the Netherlands.

To be executed:

The aim is explore T-wave inversion and QRS complex morphological changes in precordial ECG leads in a subset of patients due to ACM related substrates.

More specifically, the goal is to test the effects of fibrous myocardial scar tissue location, size, geometry and density as well as localised APD prolongation on the precordial leads ECG using whole ventricular modelling and simulation of ACM subjects.

**Long-term career objectives (over 5 years)**

1. Goals:

To become more independent as a researcher, improving on skills such as research planning, execution and setting of research direction. Further developing soft skills such as group work and nurturing collaborations.

1. What further research activity or other training is needed to attain these goals?

Find a novel research topic in academia/industry and learn novel research tools.

**Short-term objectives (1-2 years)**

1. Research results: anticipated publications and conference, workshop, courses, and /or seminar presentations:

Publication on the role of fibrous myocardial scar tissue location, size, geometry and density as well as localised APD prolongation on the precordial lead ECG. Building software to help clinicians discern ACM from other clinical entities from the 12-lead ECG is another possibility.

1. Research skills and techniques. Training in specific new areas, or technical expertise etc.

Statistical and/or imaging methods for data processing alongside the implementation of novel computational methods for healthcare. Learning how to use combined modelling and statistical approaches to answer healthcare related questions.

1. Research management: Fellowship or other funding applications planned (indicate name of award if known; include fellowships with entire funding periods, grants written/applied for/received, professional society presentation awards or travel awards, etc.)

Collaboration with Phillips where the aim is an implementation of 12-lead ECG reconstruction software in their R&D pipeline.

1. Communication skills:

Effective collaboration with clinicians, industry and other partners. Presenting at conferences, transfer of knowledge within the lab.

1. Other professional training (course work, teaching activity):

NA

**Progress Review Committee (PRC)**

**Meeting minutes – student feedback form**

Early Stage Researcher: Peter Marinov

Date of PRC Meeting: 05/03/2020

Committee Chair: Pyotrp Platanov

**Comments from the PRC about progress and next steps**

pyotr is interested in disease progression in time. He asked to see how fibrosis extent modulates the T-wave area. He observed in longitudinal data of ARVC patients that the T-wave area decreases before becoming negative. He asked about T-wave inversion in inferior leads as this is unexplained and doctors **may** already know about T-wave inversion in precordial leads in ARVC. He recommends working on ARVC rather than ACM due to lack of clarity in ACM. Another question is also when to start worrying about asymptomatic disease carriers based in the 12-lead ECG? The atrial substrate in ARVC shows P-wave abnormalities. T-wave inversion is non specific. He has a large dataset of longitudinal data. Pyotr is happy to send the data on epsilon waves to us imminently.

Pyotr showed great interest in understanding the mechanisms underlying T-wave amplitude changes in ARVC patients. These changes have been observed to occur occasionally during the initial stages of the disease and as the disease progresses T-wave inversion appears with higher frequency.

He mentioned that T-wave inversion during medical training is a sign that the protocol should be repeated as it is usually due to heart position, so asking the subject to take a deep breath should prevent the inversion from appearing in a second recording.

However, persistency in occurrences of this feature is considered a clinical biomarker that deserves further attention.

Pyotr mentioned that a patient can have T-wave inversion one day and not have it on the following week during the initial stages of the disease.

It may be that “periodical” variability in the heart state which is usually considered constant in simulation studies has an important role with the on-off manifestation of T-wave inversion in ARVC patients. As first Alan showed in his lectures relating it to the circadian rhythm and then Hanna emphasised in her presentation with extracellular concentrations, it could be that T-wave abnormalities in ARVC patients is linked to long term periodicities in the state of the cardiac system.

 If this hypothesis was to be plausible, introducing this variability in the models could trigger T-wave inversion for personalised cases while the clinical records were unable to capture it yet. Thus, help in finding features which could identify risk indicators in early stages of the disease.

This idea could serve to answer Pyotr’s question: When should we start to worry about patients who have the mutation but still don’t show severe risk related biomarkers?

Following on the idea that heart position can produce T-wave inversion in the inferior leads, Pyotr also mentions other mechanisms for T-wave inversion, such as right bundle branch block. So, how do we know that the manifestation of T-wave inversion in a patient is a sign of conductance perturbations due to fibrosis? Pyotr believes that modelling could help in order to discard alternative explanations and increase the confidence in the source of the abnormality.

**Recommendations for the Career Development Plan**

Discussion on academia vs industry. The assessor believes computational healthcare will transition into the clinic and that its the right time to be working in the field. No specific suggestions on institutes or companies to consider.

Pyotr believes that close collaborations with clinicians that research in the same topic should be encouraged for computational biologists to keep them in the clinically relevant research path.

Date & Signature of ESR: Date & Signature of PRC chair:

Date & Signature of SB member: