Do our muscles tire because we get old or because they do: The Worm Workout Gymnasium

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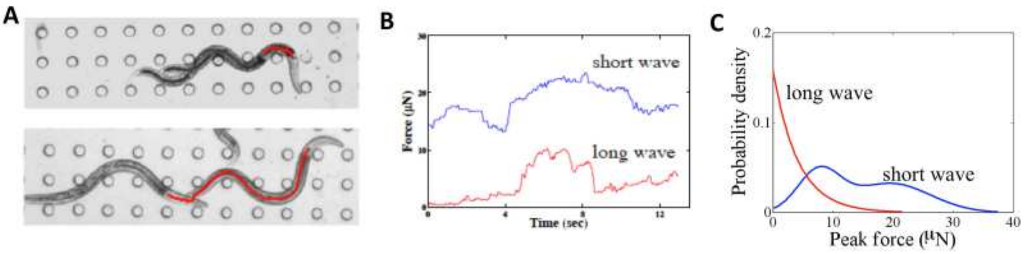
Life expectancy in the UK is increasing at an unprecedented rate. Within 20 years the fraction of the population aged 65 and over is predicted to rise from the one sixth it is today to over one quarter. This increasing ageing human population, and in particular the disparity between lifespan and healthspan, is a grand societal challenge impacting on social wellbeing, the economy, productivity, health service provision, housing, indeed all areas of life of the Nation. Understanding the process of ageing and the decline in muscular capability is crucial to the development of appropriate preventative, care and treatment therapies. Preserving musculoskeletal mass and function with age is important to strength, power and endurance, as well as metabolic health. Physical activity decreases with age, contributing significantly to loss of musculoskeletal mass and function which limit activities of daily living. Similar alterations in muscle strength occur through biological adaptations to changes in the environment, in response to space flight for example.

The unit of biological energy, the molecule ATP, is produced in the mitochondrial 'power stations' within most cells. Mitochondrial activity and mass both decrease with age. **Is this reduction in mitochondrial activity and mass caused by ageing *per se* or the decline in physical activity levels in adulthood?** Addressing this issue is clear to successful ageing. It is impossible to study connections between life-long physical activity, mitochondrial function and muscle strength in humans. Fortunately, the soil nematode *Caenorhabditis elegans* has been developed successfully into a model system to study the regulation of muscle protein degradation. A significant problem with these as experimental subjects, however, is their unresponsiveness to questions about their physical state and strength and their complete lack of compliance with even the simplest requests. Here, we will engineer and apply tools that will permit the accurate measurement of nematode muscle strength in both passive and active situations, throughout their life-course. **The studentship will develop the 'Worm Workout Gymnasium'; an ageing platform that provides readouts on, muscle forces, locomotion and muscle structure in C. elegans, to understand and quantify the relation between aging, muscle-strength decline and genetics**. This research is an important and necessary step towards soft technology for measuring cell/organ mechanical properties that may have a role in the monitoring of atrophy and ageing.



Two modes of locomotion of *C. elegans* in a square array of micropillars. (A) Inefficient locomotion with short undulation wave (top) and efficient locomotion with long undulation wave (bottom). (B) Time profile of the force exerted by *C. elegans* on the pillars for the short-wave and long-wave locomotion modes and (C) the corresponding force probability distribution.

Our proposed platform will be used to comprehensively probe integrative muscle physiology in aging *C. elegans*. Using this multi-readout platform, we will determine whether force declines with age in normal worms, and if it is delayed in long-lived mutant worms. We will test if the transcription factor FOXO (daf-16) is required for delayed onset of force decline in long-lived worms.

The research will grow from proof-of-concept studies in which elastomeric posts have been used as levers on which nematodes pass. Whilst able to record a deflection to the beam, an absolute measurement of force is precluded since both the accurate deflection spring constant of the post and the position on the post at which the nematode is in contact are unknown. Here, we will research the fabrication, use and assessment of engineered 3D precision structures, expanding on the proof-of-principle ideas and tests of the applicants, to study nematode strength. We will explore the engineering and design space available to the multi-photon fabrication facility to refine measurement architectures capable of assessing both low and high force (deflection) regimes. The student will be trained in systems design and simulation, multi-photon and other 3D fabrication technologies, and silicon-nitride cantilever methods of force and mechanical property measurements. Later, the project will explore and develop the application of active transducers, such as the fabrication of activate transducers (piezo-electric, micro-fluidic hydraulic, pneumatic) on which the response of the nematodes to controlled dynamic forces can be assessed.