Unraveling the genetic organization of lifespan and ageing in a life history context: lessons from fruit flies (and other short-lived models)

The challenge
Evolutionary theories of ageing predict that the genetics underlying ageing rates is complex with clear links to life history traits such as development, reproduction, and life span. Notably, the the mutation accumulation (MA) and the trade-off (TO) theories explicitly address the genetic component of ageing. Under MA, new genetic variants solely have negative impact on traits such as lifespan and reproduction, while TO predicts that genetic variants can affect multiple traits differently and may therefore increase fecundity while at the same time lower lifespan. Importantly, these mechanisms are not mutually exclusive, and the genetics of ageing is expected to be a complex “mixed bag” of causes. Moreover, under MA the mechanisms are expected to be “private” and under TO more “public”. Which genetic mechanism is causing variation in lifespan, health, and ageing affects (i) the rationale for selecting and using model organisms and (ii) the comparability of human cohorts. Thus ultimately, whether ageing is the consequence of “trade-offs” or “late-life deleterious mutations” may have consequences for prevention and treatment in humans.

The opportunity
Both theories have supporting experimental evidence, however, to what extent natural genetic variation in lifespan is caused by the mechanisms of MA or TO is yet unknown. We have previously evolved long-lived populations of *Drosophila melanogaster* by selecting for late reproduction, which serves as a resource to study the evolution of lifespan. Through whole-genome sequencing we have identified genomic regions that associate with phenotypic differences between selection regimes, allowing us to uniquely disentangle the role of MA and TO in this system.

We will (I) perform backward selection for populations previously selected for late reproduction using an early reproduction protocol. Then we will (re)sequence all populations to detect genetic variants that either respond to the new selection regime (i.e. consistent with TO), or do not change (i.e. consistent with MA); (II) perform a genetic association study between genetics variants (I) with lifespan; and (III) perform full/ half-sib analysis and targeted genotyping of specific loci (found in I and II) to uncover the genetic underpinning of lifespan and/or age-specific fecundity. Under MA, traits are affected in the same direction, while under TO, genetic variation for one trait antagonistically affects another trait. Under MA, traits are affected in the same direction, while under TO, genetic variation for one trait antagonistically affects another trait.

The offer
Our experimental evolution populations are currently in their 156 and 294 generations for late and early reproduction respectively. They are a unique resource for studies into the genetics of ageing that goes beyond the focus on additive genetic variance and that allow uncovering epistatic interactions and long-range disequilibrium between relevant loci. This might serve as a benchmark for studies into the genetics of lifespan and ageing in humans, allows for the identification of interesting evolutionary conserved genetic interactions, and/or for testing of the role therein of candidate loci from other species, including from humans.