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Title: THE REPLICA SET METHOD: A ROBUST, ACCURATE AND HIGH-THROUGHPUT APPROACH TO QUANTITATIVELY MEASURE CAENORHABDITIS ELEGANS LIFESPAN

Abstract

Feeding-based RNAi in Caenorhabditis elegans led to the discovery of hundreds of gerogenes, many of which are evolutionarily conserved, demonstrating the power of C. elegans as a tool for the study of aging biology. Despite these advances, only a handful of these putative gerogenes have been substantially characterized in their aging-associated roles, in part due to the size of experiments necessary to identify genetic interactions and map genes to pathways. Lifespan is an easily quantifiable surrogate measure of aging, and has been traditionally assayed in C. elegans by following a relatively small population sample over time, and recording when animals cease to exhibit any movement in response to a touch stimulus. While this traditional longitudinal method (TLM) provides straightforward estimates of median and maximum lifespan, it is also time-consuming, and involves repeated handling of animals which can introduce contamination or possibly damage aged animals. The Replica Set Method (RSM) is an alternative approach based on assaying independent samples of a population each time an observation is made, which minimizes handling and enables an increase in throughput of at least an order of magnitude. Through in silico simulation of TLM and RSM lifespan experiments, we find that both approaches yield similar accuracy, precision, and statistical power for realistic experiment designs, but that RSM is more robust to experimental scoring error and requires many fewer total observations per condition during the course of an experiment. We also provide a framework for RSM data analysis and comparison in WormLife, a freely available software tool with a graphical interface, based on R. Thus, RSM enables even single investigators to scale lifespan experiments to hundreds of conditions- such as feeding-based RNAi clones- without compromise in accuracy or power, facilitating the generation of large quantitative phenotypic datasets that are necessary for modeling biology at a systems-level.