Discovering Regulators of the *Drosophila* Cardiac Hypoxia Response Using Automated Phenotyping Technology

JACOB D. FEALA[1], JEFFREY H. OMENS[1], GIOVANNI PATERNOSTRO[1,2], ANDREW D. MCCULLOCH[1]

[1]Dept of Bioengineering, Univ of California, San Diego, La Jolla, CA, [2]The Burnham Inst Medical Research, , La Jolla, CA

ABSTRACT: Necrosis and apoptosis during acute myocardial infarction result in part from the inability of hypoxic cardiac myocytes to match ATP supply and demand. In contrast, hypoxia tolerant organisms such as *Drosophila* can rapidly regulate cellular metabolism to survive large oxygen fluctuations. A genetic screen of fly heart function during acute hypoxia can be an unbiased way to discover essential enzymes and novel signaling proteins involved in this response. We have developed a prototype to show proof of concept for a genome-scale screen, using computer automation to rapidly gather *in-vivo* hypoxic heart data in adult *Drosophila*. Our system automatically anesthetizes flies, deposits them on a microscope slide, and locates the heart organ of each fly. The system then applies a hypoxia stimulus, acquires time-space (M-mode) images of the heart walls, and analyzes heart rate and rhythm. The prototype can produce highly controlled measurements of up to 55 flies per hour, which we demonstrated by characterizing the effect of temperature, oxygen content, and genetic background on the hypoxia response. We discuss the possible applications of a genome-wide cardiac phenotype dataset in systems biology analyses of hypoxic metabolism, using genome-scale interaction networks and constraint-based metabolic models.

KEYWORDS: **cardiac hypoxia, systems biology, automated microscopy, *Drosophila melanogaster*, genomic phenotyping**

Address for correspondence*:* Prof Andrew McCulloch, PhD, Dept of Bioeng, Univ of California, San Diego, 9500 Gilman Drive, La Jolla, CA, 92093-0412, USA, Fax: 858 534 5722
Email: amcculloch@ucsd.edu