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Integrative approaches to investigate the architecture and assembly of BILBO1, a multidomain cytoskeletal protein from *Trypanosoma brucei*

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Trypanosoma brucei is a protozoan parasite causing sleeping sickness in Africa. At the base of its single flagellum is a bulb-like structure called the flagellar pocket (FP). The FP is responsible for all endo-/exocytosis and thus essential for the survival of the parasite. At the neck of the FP is an electron-dense structure termed the flagellar pocket collar (FPC), which currently has only one known protein component, BILBO1. Bioinformatic analysis indicates that there are four structural domains in the 67-kDa protein, including a globular N-terminal domain, two central EF-hand motifs followed by a long coiled-coil domain, and a C-terminal leucine zipper. BILBO1 forms enormously large oligomers in vitro, which makes it intractable by any single conventional structural study method. We recently carried out structural dissection of *T. brucei* BILBO1 using integrative structural biology approaches including NMR, crystallography, EM, and various biophysical methods. The high-resolution structure of its N-terminal domain reveals a variant ubiquitin-like fold with a conserved surface patch; mutagenesis of this patch causes cell death in vivo. We further found that the EF-hand motifs change their conformation upon calcium binding, the coiled-coil domain forms an antiparallel dimer, and intermolecular interactions between adjacent leucine zippers allow BILBO1 to form extended filaments in vitro. These filaments were additionally shown to condense into fibrous bundles through lateral interactions as demonstrated by our EM studies. Based on all these experimental data, we propose a mechanism for BILBO1 assembly into the flagellar pocket collar.

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An integrated computational platform for whole-heart coronary flow

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Clinical diagnosis of coronary artery disease continues to be a subject of intense investigation. On one hand, questions remain regarding newer imaging technologies such as perfusion MRI due to the difficulties in relating the acquired data to the underlying physiological state. Meanwhile, enhanced invasive indices such as wave intensity analysis (WIA) which has the potential to offer broader diagnostic information on combined coronary and cardiac function, remains poorly understood. A common obstacle in these pursuits is the difficulty of addressing the physiological complexity, quantitatively. In this work, we present new methodological advances based on integrative computational modeling which aims to tackle these conventional limitations. Our framework comprises a multi-scale model of cardiac perfusion encompassing both macro and microcirculation. The varying flow regimes over these scales are addressed by heterogeneous mathematical models (one-dimensional elastic tube flow and poro mechanics) that are coupled together. The regional influence of cardiac motion on coronary flow is captured through actively contracting myocardium. Coronary anatomy and the compartment-averaged microvascular properties are derived from high-resolution imaging. The complete numerical model including systemic hemodynamics is solved via finite element method. The utility of the model is demonstrated through an in silico wave WIA, which is sensitive to both myocardial and coronary function. In particular the effects of QRS duration and aortic valve dynamics on major coronary waves are quantified. Furthermore, the calculated flow field forms the basis for simulation of transport phenomena, allowing in silico perfusion imaging based on the passage of contrast agent through the myocardium.

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