Computational modeling using a novel continuum approach coupled with Pathway-informed neural networks to optimize Dynein-mediated centrosome positioning in Polarized cells

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Microtubules (MTs) are cytoskeletal polymers that interact with motor proteins such as dynein to position the centrosomes and nucleus within a cell. Centrosome positioning specifies the cell's division plane by determining the location and orientation of the mitotic spindle. In polarized cells, centrosome alignment along the polarity axis causes the cell to divide asymmetrically, producing unequal daughter cells. Proper centrosome positioning is critical during development where it is required for important processes such as cell fate specification. Improper centrosome positioning is implicated in disease processes: cancer cells often exhibit abnormal centrosome positioning prior to division. While many studies have focused on centrosome movement during mitosis, centrosomes are often positioned prior to mitosis. This movement prior to mitosis when the centrosomes are associated with the intact pronuclear envelope is not well understood. Many aspects of dynein-mediated centrosome movement are highly nonlinear and rely on biochemical, mechanical and geometric features in the cell that are difficult to investigate experimentally. Mathematical modeling can easily deal with this complexity, bridging the varying time and space scales, and provide a fundamental understanding of the mechanisms of positioning centrosomes. This model provides the key features required to integrate modeling and experiments on early embryos of the *C. elegans* to elucidate the interplay between biochemical, mechanical and geometric signals that act to position centrosomes in polarized cells through the following aims. The same non-linear framework for confined geometries is extended to create a pathway-informed comprehensive data driven digital twin of an individual's mental health profile and analyze spatiotemporal behavior. Although dynamic study and modeling of depression-related behavior exist in literature, we employ a novel digital twin model that combines Sensitive, Exposed, Induced and Excluded models with Disease-informed neural networks to identify progression and intensity of depression related behavior.