Press release

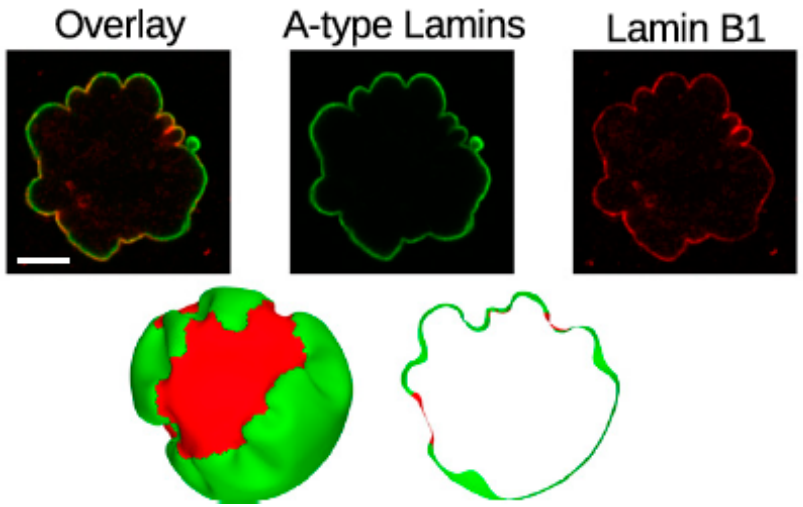
Mechanical model of blebbing in nuclear lamin meshworks

Chloe M. Funkhouser, Rastko Sknepnek, Takeshi Shimi, Anne E. Goldman, Robert D. Goldman, and Monica Olvera de la Cruz

Proc. Natl. Acad. Sci. **110** (9) 3248-3253 (2013); DOI: 10.1073/pnas.1300215110.

Much of the structural stability of the nucleus comes from meshworks of intermediate filament proteins known as lamins forming the inner layer of the nuclear envelope called the nuclear lamina. These lamin meshworks additionally play a role in gene expression. Abnormalities in nuclear shape are associated with a variety of pathologies, including some forms of cancer and Hutchinson–Gilford Progeria Syndrome, and often include protruding structures termed nuclear blebs. These nuclear blebs are thought to be related to pathological gene expression; however, little is known about how and why blebs form.

We have developed a minimal continuum elastic model of a lamin meshwork that we use to investigate which aspects of the meshwork could be responsible for bleb formation. Mammalian lamin meshworks consist of two types of lamin proteins, A type and B type, and it has been reported that nuclear blebs are enriched in A-type lamins. Our model treats each lamin type separately and thus, can assign them different properties. Nuclear blebs have been reported to be located in regions where the fibers in the lamin meshwork have a greater separation, and we find that this greater separation of fibers is an essential characteristic for generating nuclear blebs. The model produces structures with comparable morphologies and distributions of lamin types as real pathological nuclei. Thus, preventing this opening of the meshwork could be a route to prevent bleb formation, which could be used as a potential therapy for the pathologies associated with nuclear blebs.



(Top) Highly lobulated nucleus from a fibroblast of a progeria patient with the E145K-LA mutation. (Bottom) Simulation result showing the surface and a cross-section resembling the lobulated structure in. (Scale bar: 5 µm.)

Funded by the Office of the Director of Defense Research and Engineering (DDR&E) and Air Force Office of Scientific Research (AFOSR) Award FA9550-10-1-0167, the US Department of Energy Award DEFG02-08ER46539, the National Cancer Institute Grant 5R01CA031760-28 and the Progeria Research Foundation.