Title: Human Brain Organoids on a Chip Reveal the Physics of Folding

The origin of human brain wrinkling remains an open fundamental problem, with implications to neurodevelopmental disorders.
Studies in polymer gel models suggest that wrinkling emerges spontaneously due to the development of compression forces during differential swelling,
however these ideas have not been tested in a living system.
Here, we report the appearance of surface folds during in vitro development and self-organization of human brain organoids, in a micro-fabricated compartment,
which supports in situ imaging over weeks.
We observed the emergence of convolutions at a critical cell density, and maximal nuclear strain, which are indicative of a mechanical instability.
We identified two opposing forces which contribute to differential growth; cytoskeletal contraction at the organoid core, and cell-cycle dependent nuclear expansion at the organoid perimeter.
The wrinkling wavelength exhibited linear scaling with tissue thickness and with a slope of 0.8, consistent with an equilibrium between bending and stretching energies.
Finally, lissencephalic (smooth brain) organoids displayed reduced convolutions, linear scaling with an increased slope and reduced elastic modulus.
Our on-chip approach reveals a rich, dynamic system offering means for studying the collective and physical aspects of organoid development, with implications
to embryonic human brain.