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Within the cell nucleus of eukaryotic organisms, chromosomes are organized in a complex, non-random three-dimensional (3D) spatial structure, which is intimately linked to vital functional purposes. Indeed, a correct folding allows an efficient communication between genes and their distal regulatory elements while, if altered, can cause severe diseases. Here I will discuss how Polymer Physics, combined with Molecular Dynamics simulations and Machine Learning based inference, represent a powerful tool to quantitatively investigate the complexity of 3D organization of real genomes, as highlighted by recent microscopy and biochemical experiments. I will show that simple physical processes, widely studied in Statistical Mechanics, such as phase-separation of molecular aggregates and symmetry breaking mechanisms, allow us to make sense of recent experimental observations including the in olfactory receptor choice in olfactory sensory neurons (OSN). Finally, polymer models can be used to study the impact of disease-linked genetic mutations or the effect of viral infections as SARS-CoV-2, opening the way to new potential tools in Biomedicine.

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