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Some biophysical aspects of the nucleus and mitotic chromosomes

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Nearly 100 years ago Alexander Oparin observed that "The vast majority . . of the substances of which protoplasm is made up have very large and complicated particles and therefore must give colloidal solutions" (1). Now, concepts from colloidal systems and their interactions with polymers like chromosomes are providing new paradigms for understanding the structure and activities of nuclei. Macromolecules are so concentrated in the nucleus (>100 mg/ml) that their close proximity leads to strong and subtle entropic forces between them, which are not seen in experiments *in vitro*. Their effects include: Crowding may cause separate phases (coacervates) to form in a mixture of particles or of particles and polymers, by increasing their effective concentration (2). This phase separation was proposed in 1938 to cause the formation of compartments in the nucleus: "Nucleolus formation must be considered as an accumulation of karyolymph proteins .until a droplet rich in proteins is formed" (3), and "the nucleolus is a separated phase out of a saturated solution. Its globular shape and the absence of discontinuities as well as its mode of deformation . . suggest that it is a drop" (4). The effects of entropic forces on polymers elucidate how chromosomes are highly compacted in the nucleus to avoid entanglements and to remain accessible for replication and transcription. Looped conformations in crowded conditions are central to regulation of gene expression, and entropic repulsion between looped polymers can explain the confinement of each chromosome to a discrete territory in the nucleus (5). Nuclei and mitotic chromosomes are exposed *in vivo* to crowding by diffusible macromolecules in the cytoplasm. When this crowding effect is reproduced *in vitro*, isolated nuclei and chromosomes are stable without the cations and/or polyamines used in common buffers (6, 7), raising questions about how far these buffers are "physiological".

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