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NUCLEAR PHYSICS AS NEW FRONTIER TO BIOLOGISTS AND BIOPHYSICISTS

Shobhit, Govt. P.G. College Hissar

Abstract: The nucleus is physically distinct from the cytoplasm in ways that suggest new ideas and approaches for interrogating the operation of this organelle. Chemical bond formation and breakage underlie the lives of cells, but the nonchemical aspects of cell nuclei present a new frontier to biologists and biophysicists. Here, we are discussing a new era of nuclear physics.

THE NUCLEUS BACK THEN

Classical (pre-1950) biophysics did not worry much about differences between nucleus and cytoplasm, mainly because the focus of physiology was on the latter compartment and in particular on actomyosin function. Francis Crick studied the viscosity of cytoplasm (Crick, 1950; Crick and Hughes, 1950), which is a still-intriguing issue. The nucleus sat in Crick's field of microscope observation as a sideshow, its DNA waiting quietly for his future attentions.

The nucleus was of necessity destroyed in early DNA studies, in which pus-filled bandages were the source and harsh extraction conditions were applied but subsequently, the organelle was isolated and studied. It soon became apparent that nuclei, both isolated and studied within intact cells, had physical properties different from the cytoplasm. For example, the nuclear envelope can display a membrane resting potential of about −15 mV. Electrical and related osmotic responses of isolated and in-cell nuclei when differentially responding to elevated extracellular Na^+, clearly indicate a basal osmotic strength different from cytoplasm. These studies illustrate the key fact that the nucleus is a distinct place not just in macromolecule populations but in basic physical properties.

THE MODERN AND POSTMODERN NUCLEUS

Electron microscopy of the 1950s presented the nucleus in high resolution, revealing that there are no internal membranes and that the chromatin, nucleolus, and other nuclear components are mixed together. This suggested that DNA replication, transcription, RNA processing, and other nuclear functions occurred via a wild melee of molecular interactions. Later this was refined by the realization that many DNA-acting (and some RNA-acting) proteins are confined to nucleic acid by nonspecific interactions that provide efficient kinetic pathways to search for specific targets. The notion followed that many nuclear functions may depend on the tethering of key factors to pre-existing entities.

The scheme of folding of the gigantic lengths of DNA (2 m in the human case) inside the interphase nucleus remains a deep puzzle. Even the question of the physiological relevance of the 30-nm fiber observed in biochemical studies remains open. In at least most differentiated somatic cell nuclei, individual interphase chromosomes lie in close opposition to one or more others, occupying distinct territories. Mapping of contacts by chromosome conformation capture has suggested a space-filling “fractal globule” folding scheme with intriguing functional consequences, most notably reduction of chromosome entanglements relative to the “null hypothesis” of random coil-like polymer organization.

Meanwhile, in the nuclear space not occupied by the genome, RNAs move by, or more precisely by anomalous subdiffusion arising from nuclear cul-de-sacs and short-lived contacts with chromatin. Here, in the interphase nucleoplasm between the chromosomes, various nuclear bodies are found and, in many cases, dynamically accrete and shed their parts. All this choreography is encased within the nuclear envelope and its underlying lamina. After years of being perceived as static, the nuclear lamina has recently become recognized as one of the most dynamic regions of the nucleus.

PHYSICAL BIOLOGY OF THE NUCLEUS

After this lightning review of nuclear biology, we turn to brief consideration of physical perspectives concerning cell nuclei. To date, only occasional efforts along this line have been mounted and it is most timely to take this up once again.

THE CHROMOSOMES

Like all objects at nonzero temperature, chromosomes are subject to random thermal motion Recombination and translocations are depicted in textbooks as neat deterministic processes, but the reality must be much more stochastic. The discoveries that the DNA repair machinery and the internucleosomal histone H1 display remarkably rapid exchange on and off the DNA revealed a highly dynamic molecular dance. This applies also to the conformation of chromatin itself, which must be undergoing thermal agitation of its shape. Remarkably, we still have only a rather poor understanding of the polymer properties of chromatin in vivo—which may be related to the imbroglio of the 30-nm fiber structure—isolated fibers may well behave very differently from fibers in a chromatin-crowded and highly reactive nuclear environment. Even poorer is our understanding of exactly how interphase chromatin is put into and maintained in its folded (fractal globule?) form—a form that requires control of distant site correlations. And how do SMC complexes and topoisomerases achieve the feat of mitotic chromosome compaction with such efficient individualization of chromosomes and resolution of sister chromatids within them in the confinement of the nucleus? These are compelling questions for physical biologists that might be addressed using single-molecule and micromanipulation approaches. These issues bear on how genes might spatially congress or disperse during embryonic development or a cell differentiation pathway. A controversial claim that this involves an intranuclear motor has not been replicated. Yet it would seem that moving a pair of genes, residing on two chromosomes or within one, from distal to vicinal locations within a genome with regulated three-dimensional folding could not be left to diffusion alone—which would be a threat to the fractal architecture. After half a century of skepticism, actin and myosin have been now been convincingly demonstrated in the nucleus but the jury remains out on them having any role in gene relocation.

THE NUCLEOPLASM

The fluid viscosity of the nucleoplasm has been measured to be five times that of water and as mentioned above, proteins and RNA move within the nucleoplasm by anomalous diffusion. The nucleoli and histone locus bodies arise from activity of proximal genes, with their activities producing proximal cytological entities.

Cajal bodies, which are not always located near chromosomes, can be induced to form by artificially tethering their protein components to a chromosomal site indeed, various nuclear bodies can be nucleated by chromosome-tethered coding or noncoding RNAs. In a related study, it was demonstrated that one type of nucleoplasmic body, the paraspeckle, can be nucleated by a nascent RNA transcript, implying that the aforementioned experiments targeting proteins or RNAs artificially to chromosomes are mimicking the in vivo situation. While it is possible that these nuclear body assembly processes involve solely second-order (molecular collision–dependent) kinetics, one is reminded of how molecular crowding can influence such events and we would point to (bio)physical chemistry as a fertile ground for new explorations in the nucleus. In general, the problem of programmed self-assembly of nuclear structures, including the influence of nonthermal reactions, is one that merits increased experimental and theoretical study.

Another quite recent development has been the notion that some nuclear structures might arise by actual phase transitions. The first example of this new line of thinking arose in a study of the extrachromosomal, amplified nucleoli in the germinal vesicle (nucleus) of *Xenopus* oocytes in which the investigators observed these organelles to possess a liquid droplet-like behavior and a size distribution indicative of a scale-free power law Subsequent studies have suggested that phase transition–based phenomena may be at play in the assembly of RNA–protein complexes in the nucleus, although these latter biochemical studies still need to be related to the in vivo situation. A key finding by Kato *et al.* was that simple amino acid sequence repeats in the amyolateral sclerosis–implicated protein used in this study underlie the in vitro assembly of RNA granules, which raises the possibility that amyloid-like protein associations with RNA may be a factor in this and other neurodegenerative diseases. We suggest that, like

macromolecular crowding, phase-transition principles need consideration in current research on nuclear organization and dynamics.

THE NUCLEAR PERIPHERY

The nucleus is surrounded by a double membrane, the nuclear envelope, the outer membrane of which is contiguous with the endoplasmic reticulum, forming a structure of impressive complexity (what is the topological genus of the nuclear envelope–endoplasmic reticulum structure—how many "handles" does it have?). A plausible but unproven idea is that the inner nuclear membrane of eukaryotic cells is an artifact of the cell membrane of an ancient protist, whose invasion of another anucleate cell triggered the evolution of the Eukarya. The inner and outer nuclear membranes are compositionally distinct, as are their physical properties. Lying beneath, on the nucleoplasmic side, is the nuclear lamina, an assembly of type V intermediate filament proteins. As mentioned above, the nuclear lamina was once thought to be relatively static but is now known to be highly dynamic and perhaps rather less dense than implied by the pictures in many cell biology textbooks. Stationed within the nuclear envelope are nuclear pores, more recently known as nuclear pore complexes due to their molecular complexity, through which pass RNA and proteins in either direction.

Given the enabling history of physics-oriented plasma membrane research, the nuclear envelope is a domain of the nucleus in which thinking in terms of physics might have been anticipated to be especially lively. And yet, overall, this had not been the case. That said, recent studies illuminate how physics can be applied. In a creative study, tugging on the nuclear envelope with a glass harpoon has been used to get a sense of its resistance to deformation. Cytoplasm incursions deep into the nucleus bear on issues of nucleo-cytoplasmic transport and make one wonder just how pure a nuclear fraction can be obtained from cells if such invaginations seal off during "nuclear" isolation. Because of the wealth of physical chemistry foundations in membrane research, the nuclear envelope, and its dynamics particularly, await the input of physics going forward.

Physics had arguably its greatest moment in biology in the application of X-ray diffraction to biological molecules, first by Dorothy Crowfoot Hodgkin and later by legions of those who followed. Cell biology has had certain tributaries from physics (recall Francis Crick's cytoplasmic viscometry), and the current momentum in the application of physics to the cell is exciting to see. In this paper, we have presented a number of perspectives that convey our belief that the time is now at hand when considering the nucleus as a physical landscape can and will be exciting and enabling.

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