Jonathan Widom 1955–2011

Jeffrey Hayes

This past month, many of us in the biochemistry and structural biology communities were shocked and saddened to learn of the untimely death of Jon Widom at the too-early age of 55. Jon was a leading scientist working at the forefront of understanding how genomes are organized into arrays of nucleosomes and higher-order chromatin structures. His research spanned the biology and physical chemistry of macromolecular interactions, especially as applied to DNA mechanics and DNA-histone complexes, and he published numerous seminal works.

Jon Widom was trained as a chemist, receiving a BA from Cornell University in 1977. He pursued doctoral research with Robert L. (Buzz) Baldwin at Stanford University, where he focused on cation-induced condensation of DNA as a model for understanding compaction of phage DNA into toroidal conformations[1]. This work introduced Jon to the physical chemistry and mechanics of DNA and, perhaps more apropos of his life's work, to the problem of fitting a genome's worth of DNA into a functionally confining space such as a phage capsid or a eukaryotic nucleus[2]. Upon receiving his PhD in biochemistry in 1982, Jon ventured to the famed Laboratory of Molecular Biology at the Medical Research Council Laboratory in Cambridge, England, to work with Nobel laureate Sir Aaron Klug on the structure of eukaryotic chromatin. Specifically, Jon applied low-angle X-ray scattering and other techniques to study the conformation and nucleosome packaging arrangements in the so-called 30-nm-diameter chromatin fiber, providing evidence for the proposed solenoid model of the fiber[3]. Of special note was Jon's seminal study of cation-induced chromatin compaction, published as a single-author paper from his postdoctoral work, which set the stage for a multitude of modern analyses of salt-dependent folding and compaction of model chromatin systems[4].

In 1985 Jon joined the Departments of Chemistry and Biochemistry at the University of Illinois at Urbana-Champaign, where he initiated studies of the structure and biophysical behavior of yeast chromatin. Although his training was in a different field, he was undaunted by the prevailing lore regarding the difficulty of extracting unproteolyzed yeast chromatin and was intrigued by the short nucleosome repeat length found in many yeasts as well as the possibility of exploiting the power of yeast genetics to test prevailing models for the structure of the 30-nm fiber. He first showed that yeast has a higher-order structure resembling that of the 30-nm fiber of metazoan chromatin, and he did this despite the short repeat length of the chromatin and the lack of an abundant histone H1 (refs. 5,6). Jon realized that understanding the behavior of linker DNA was crucial to understanding how the 30-nm fiber was formed, and he demonstrated that structures as small as a dinucleosome can condense with a presumably bent linker and appear to require a specific twist in the condensed state[7,8]. Of special note, Jon's analysis of all nucleosome repeat lengths catalogued in van Holde's *Chromatin* provided evidence for a quantization of linker DNA twist values, supporting the idea of a defined orientation between nucleosomes in chromatin[6].


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In 1991 Jon joined Northwestern University, where he continued to pursue interests in the physical chemistry of chromatin, making several major contributions to the field. First, in a string of exceptional papers applying classical kinetic analyses and other biophysical approaches, he demonstrated that, contrary to popular perception, nucleosomes were indeed dynamic structures that present primarily a thermodynamic rather than a kinetic impediment to DNA accessibility, and he provided a useful theoretical framework to explain this behavior[9,10]. These results have important implications for how transcription factors invade nucleosomes and imply an inherent cooperativity between factors invading the same nucleosome[11]. His lab extended this concept to show that nucleosomes within long arrays exhibit the same dynamics[12] and that heterochromatin gene silencing in yeast cells is unlikely to be due to simple steric interference with DNA-binding transcription factors[13]. Second, as part of a series of superb studies to learn more about the rules and mechanics of DNA bending in the nucleosome, Jon's lab used the SELEX approach to isolate what has come to be the most widely used DNA for *in vitro* chromatin reconstitution, the 601 high-affinity nucleosome positioning sequence[14,15]. This sequence has an affinity for the core histone octamer that is several hundred–fold greater than in natural sequences and results in nearly unique translational positioning of reconstituted nucleosomes, a feature of enormous utility to chromatin biochemists.

Jon's interest in sequence-dependent positioning naturally led him to consider the role of the sequence in defining how whole genomes are organized into nucleosomes. While many other workers were mapping nucleosome positions, Jon, in collaboration with Erin Segal's group, developed methods to predict how the sequence might define the global location of nucleosomes, and he discovered that about 50% of all nucleosome positions in the yeast genome could be predicted with reasonable certainty[16]. This work demonstrated that the yeast genome contains DNA-encoded information to define chromatin structure, and it provided a powerful demonstration that global nucleosome organization is biologically relevant[17]. Further analysis of the data supported his earlier results indicating that linker DNA lengths are constrained by higher-order chromatin structure and that the bulk of the nucleosome pattern could be recapitulated by simple reconstitution of the yeast genome. Most recently, Jon and his group have pushed both the science

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and technology to even greater heights by combining a nucleosome-dependent chemical cleavage approach[18] with paired-end sequencing to produce nucleosome maps of unparalleled accuracy. Unfortunately, this work, sure to set a new standard in the field, was still in preparation at the time of his death.

Jon hails from a truly extraordinary family. His mother is a protein biochemist and his father is a professor (emeritus) in physical chemistry at Cornell University and a member of the National Academy of Sciences. Both his brother Michael and his sister Elisabeth are university professors, at Carnegie-Mellon University and Miami University (Ohio), respectively. At Northwestern, Jon served as chair of the Department of Biochemistry, Molecular Biology and Cell Biology, director of the University Molecular Biophysics Training Program, director of the Keck Biophysics Facility and director of the Center for Structural Biology. Perhaps most important of all, Jon was a stellar teacher and mentor for numerous graduate students and postdoctoral fellows. Jon's first graduate student (in chemistry), Patricia Draves (Vice President for Academic Affairs, Dean of the College and professor of chemistry at the University of Mount Union in Ohio), recalling their conversation about his research, relates, "I was struck by his passion, his intellect, and his dedication; needless to say, the choice was easy. He was a phenomenal mentor and was committed to all of his students' growth as scientists and people. I had never experienced such an excitement and pace of learning." His first biochemistry graduate student, James Godde (professor and chair of biology at Monmouth College), reports that "Jon was a great human being as well as an outstanding scientist; he had all the qualities one could ask for in an advisor—he had a seemingly infinite amount of patience as well as an infectious enthusiasm for science, qualities that I have tried to emulate as a professor." Like many, I have had the great pleasure of Jon's company and the chance to enjoy his razor-sharp and physical chemistry–tinged wit. When I asked him about strategies for interfacing with administration as a department chair, he responded, "Deal with zero or one dean." During a recent trip to Japan that I was fortunate enough to spend with Jon, I was reminded again of his gentle demeanor, his ready laugh and his patented phrase (as he poured the sake), "Your glass is getting dangerously low!".

Jon contributed so much to our understanding of the basic biochemical behavior of chromatin that many of his papers are required reading for those in the chromatin field. Moreover, Jon was motivated by the simple love and passion that are stirred by the search for truth and by discoveries about our physical world, qualities emblematic of the true scientist. We are certainly much the poorer for his passing.

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