



Jonathan Widom , PhD

Professor
Biochemistry, Molecular Biology and Cell Biology
PhD, Stanford

Research Interests

Structure and function of chromosomes, biophysical chemistry of proteins and nucleic acids

Our research is focused on the structure and function of chromosomes and related protein-DNA complexes. The long-term aims of the work are to elucidate the molecular architecture of chromosomes, the mechanisms whereby cells regulate their chromosome structure during the cell cycle, and the relationships of chromosome structure to chromosome function.

We are currently attacking four broadly important questions of topics concerning chromosome function. Three of these are: (a) How do gene-regulatory proteins gain access to their DNA target sites in chromatin? (b) How are RNA and DNA polymerase able to elongate through their natural substrates, which are chromatin, not naked DNA? (c) In what ways are genomic DNA sequences evolved or constrained to facilitate their own packaging into nucleosomes, or to contribute to gene regulation through effects on nucleosome positioning or stability?

Our research in these areas has been predominantly carried out in vitro, on chromatin fragments reconstituted from purified components, using diverse biophysical and biochemical approaches. The advanced instrumentation available in our new Keck Biophysics Facility now makes possible a wealth of exciting new biophysical approaches to these problems. In complementary new studies, we are carrying out experiments in vivo to test remarkable predictions that arise from the in vitro studies of regulatory protein binding and of nucleosome-positioning DNA sequences.

Finally, in a new project, we are working to answer fundamental questions concerning the physico-chemical basis of gene regulation, through quantitative studies on single living cells.

Selected Publications

Garcia, H.G., Grayson, P., Han, L., Inamdar, M., Kondev, J., Nelson, P.C., Phillips, R., Widom, J., and Wiggins, P.A. (2006), "Biological Consequences of Tightly Bent DNA", *Biopolymers* 85: 115-130.

Wiggins, P.A., van der Heijden, T., Moreno-Herrero, F., Spakowitz, A., Phillips, R., Widom, J., Dekker, C., and Nelson, P.C. (2006), "Beyond the wormlike chain: High flexibility of DNA on short lengthscales probed by atomic force microscopy", *Nature Nanotechnology* 1: 137-141. Featured in News & Views.

Segal, E., Fondudé-Mittendorf, Y., Chen, L., Thåström, A., Field, Y., Moore, I.K., Wang, J.Z., and Widom, J. (2006), "A Genomic Code for Nucleosome Positioning", *Nature* 442: 772-778 (full Article). Featured on cover of *Nature* and in News & Views, highlighted in *Nature Reviews Genetics*, and highlighted on front page and summarized in Science section of *The New York Times*, July 25, 2006, and in numerous other popular-press articles internationally. Top-ranked paper in all of biology on Faculty of 1000, September 2006. Highlighted again in *Nature News Feature*, (2006) 244: 259-261, and again in *Nature/Nurture* (Autumn, 2006) as top-most downloaded research paper from *Nature* over current four-month period.

Pyle, A.M. and Widom, J. (2006), "Nucleic Acids", *Curr. Opin. Struct. Biol.* 16: 267-269.

Wang, J.Z. and Widom, J. (2005), "Improved Alignment of Nucleosome DNA Sequences Using a Mixture Model", *Nucleic Acids Res.* 33: 6743-6755.

Widom, J. (2005), "Target site localization by site-specific DNA binding proteins", *Proc. Natl. Acad. Sci. (USA)* 102: 16909-16910.

Meyer, B.J. and Widom, J. (2005), "Chromosomes and gene expression mechanisms: Theory and experiment", *Curr. Opin. Genet. Dev.* 15: 113-115.

Sales-Pardo, M., Guimera, R., Moreira, A.A., Widom, J. and Amaral, L.A.N (2005), "Mesoscopic modeling for nucleic acid chain dynamics", *Phys. Rev. E.* 71: art. no. 051902 (13 pages).

Cloutier, T.E. and Widom, J. (2005), "DNA twisting flexibility and the formation of sharply looped protein-DNA complexes", *Proc. Natl. Acad. Sci. (USA)(Track II)*, 102: 3645-3650. Highlighted in Travers, A. (2005), *Curr. Biol.* 15: R377-379.

Chen, L. and Widom, J. (2005), "Mechanism of Transcriptional Silencing in Yeast", *Cell* 120: 37-48. Highlighted in *Nature Reviews Genetics*, March, 2005.

Li, G., Levitus, M., Bustamante, C., and Widom, J. (2005), "Rapid Spontaneous Accessibility of Nucleosomal DNA", *Nature Struct. Mol. Biol.* 12: 46-53.

J.D. Anderson and J. Widom (2000). "Sequence and position-dependence of the equilibrium accessibility of nucleosomal DNA target sites." *J. Mol. Biol.* 296:979-987.

K.J. Polach, P.T. Lowary, and J. Widom (2000). "Effects of core histone tail domains on the equilibrium constants for dynamic DNA site

accessibility in nucleosomes." *J. Mol. Biol.* 298:211-223.

K.J. Polach and J. Widom (1999). "Restriction enzymes as probes of nucleosome stability." *Methods in Enzymology* 304:278-298.

J. Widom and K. J. Polach (1995). "Mechanism of protein access to specific DNA sequences in chromatin: a dynamic equilibrium model for gene regulation." *J. Mol. Biol.* 254: 130-149.

J. Widom and K. J. Polach (1996). "A model for the cooperative binding of eukaryotic regulator proteins to nucleosomal target sites." *J. Mol. Biol.* 258: 800-812.

J. Widom (1996). "Short-range order in two eukaryotic genomes: relation to chromosome structure." *J. Mol. Biol.* 259: 579-588.

P. T. Lowary and J. Widom (1998), "New DNA sequence rules for high affinity binding to histone octamer and sequence-directed nucleosome positioning", *J. Mol. Biol.*, 276: 19-42.

J. Widom (1998), "Structure, dynamics, and function of chromatin in vitro", *Ann. Rev. Biophys.* 27:285-327.