

Abstract Submitted  
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**Sequence-dependent sliding kinetics of p53** JASON LEITH, ANAHITA TAFVIZI, Harvard University, Massachusetts Institute of Technology, FANG HUANG, Cambridge University, WILLIAM USPAL, PATRICK DOYLE, Massachusetts Institute of Technology, ALAN FERSHT, Cambridge University, LEONID MIRNY, Massachusetts Institute of Technology, ANTOINE VAN OIJEN, Rijksuniversiteit Groningen — Theoretical work has long proposed that one-dimensional sliding along DNA while simultaneously reading its sequence can accelerate transcription factors' (TFs) search for their target sites. More recently, functional sliding has been shown to require TFs to possess at least two DNA-binding modes. The tumor suppressor p53 has been directly observed to slide on DNA, and structural and single-molecule studies have provided evidence for a two-mode model for the protein. If the model is in fact applicable to p53, then the requirement that TFs read while they slide implies that p53's mobility on DNA should be affected by non-cognate sites and thus that its diffusivity should be generally sequence-dependent. Here we confirm this prediction with single-molecule microscopy measurements of p53's local diffusivity on non-cognate DNA. We show how a two-mode model accurately predicts the variation in local diffusivity while a single-mode model does not. Our work provides evidence that p53's sliding is indeed functional and suggests that the timing and efficiency of its activating and repressing transcription can depend on its non-cognate binding properties and its ability to change between multiple modes of binding, in addition to the much better-studied effects of cognate-site binding.

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