Phys. Biol. **8** (2011) 044001 (4pp) doi:10.1088/1478-3975/8/4/044001

COMMUNICATION

Nucleosome mediated crosstalk between transcription factors at eukaryotic enhancers

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Received 5 February 2011
Accepted for publication 24 May 2011
Published 10 June 2011
Online at stacks.iop.org/PhysBio/8/044001

Abstract

A recent study of transcription regulation in *Drosophila* embryonic development revealed a complex non-monotonic dependence of gene expression on the distance between binding sites of repressor and activator proteins at the corresponding enhancer *cis*-regulatory modules (Fakhouri *et al* 2010 *Mol. Syst. Biol.* **6** 341). The repressor efficiency was high at small separations, low around 30 bp, reached a maximum at 50–60 bp, and decreased at larger distances to the activator binding sites. Here, we propose a straightforward explanation for the distance dependence of repressor activity by considering the effect of the presence of a nucleosome. Using a method that considers partial unwrapping of nucleosomal DNA from the histone octamer core, we calculated the dependence of activator binding on the repressor–activator distance and found a quantitative agreement with the distance dependence reported for the *Drosophila* enhancer element. In addition, the proposed model offers explanations for other distance-dependent effects at eukaryotic enhancers.

S Online supplementary data available from stacks.iop.org/PhysBio/8/044001/mmedia

Introduction

Predicting gene expression from the DNA sequence and arrangement of regulatory proteins on the DNA is a central issue of the current research in quantitative cell biology (Yuh *et al* 1998, Beer and Tavazoie 2004, Jaeger *et al* 2004, Janssens *et al* 2006, Zinzen *et al* 2006, Yuan *et al* 2007, Segal *et al* 2008, Gertz *et al* 2009, He *et al* 2010, Kaplan *et al* 2011). The underlying models are usually constructed assuming the competitive equilibrium binding of multiple proteins at genomic regulatory regions (Bintu *et al* 2005a, 2005b, Garcia *et al* 2010, Teif 2010). However, the main complication encountered in eukaryotes is the organization of the DNA genome in chromatin: about 145–147 bp of DNA are wrapped around a histone octamer protein core to form a nucleosome chain with 10–50 bp linker DNA spacing. Thus, DNA is not equally accessible for transcription factors as assumed in the early models. Integrating the chromatin structure within the framework of probabilistic transcription factor binding is still an unsolved problem that is highly relevant to rationalize the complexity and cooperativity of protein interactions in the genome. Current computational models usually derive a phenomenological potential for TF–TF interactions from fitting the experimental data (He *et al* 2010). However, the predictive power of such approaches is limited since they lack mechanistic molecular details of the underlying processes. Here we address a recent experimental study of *Drosophila* embryonic development, which considered synthetic enhancers with varying distance between binding sites for a repressors/activator transcription regulation module (figure 1(*A*)) (Fakhouri *et al* 2010). Intuitively, one might expect that the effect of the repressor would simply decrease with its target distance. However, the study by Fakhouri *et al* revealed a puzzling non-monotonic distance dependence of

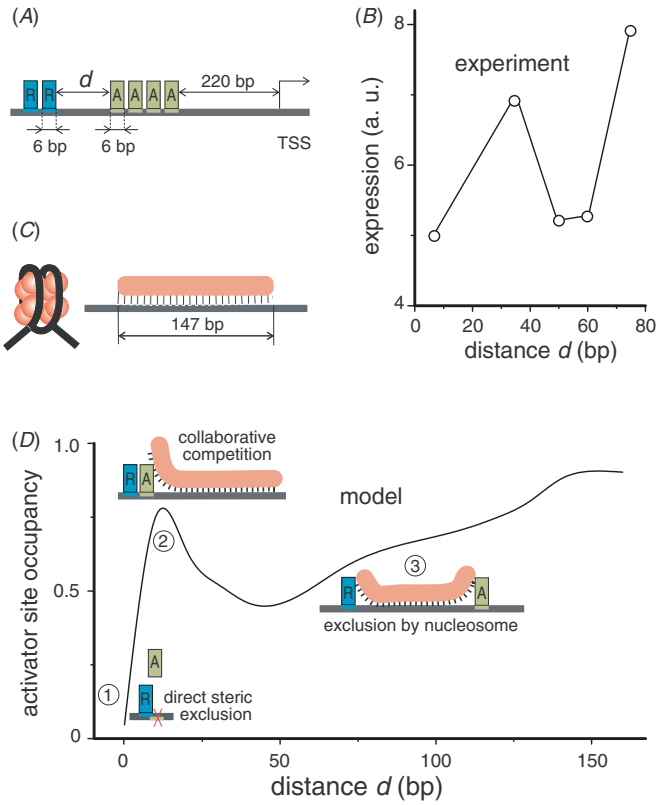

Figure 1. (*A*) Experimental setup investigated (Fakhouri *et al* 2010). The enhancer element contains two binding sites for repressor '*R*' and four for activator 'A_1–A_4'. The distance *d* is varied. (*B*) Gene expression as a function of *d* plotted as $1 - P$, with *P* being the repressor quenching efficiency reported by Arnosti and co-workers (Fakhouri *et al* 2010). (*C*) A lattice model of the nucleosome that allows DNA unwrapping with 1 bp resolution (Teif *et al* 2010). (*D*) Activator binding to the leftmost '*A*' site calculated as a function of distance *d* assuming that the contact of nucleosome '*N*' with repressor is cooperative ($w = 1000$). Repressor and activator cover 6 bp upon binding to DNA and exclude each other at distances < 6 bp. Binding constants: $K(R) = 10^{11}$ M^{-1}; $K(A_1) = K(A_2) = 5 \times 10^9$ M^{-1}, $K(A_3) = K(A_4) = 10^{10}$ M^{-1}; $K(N) = 10^{-8}$ M^{-1}. Concentrations: $[R] = [A] = [N] = 10^{-9}$ M. Nucleosomes form nonspecifically, cover up to 147 bp and can partially unwrap with a homogeneous unwrapping potential (Teif *et al* 2010).

the repression efficiency. The repressor efficiency was high at small separations ∼5 bp, low around 30 bp, reached a maximum at 50–60 bp, and decreased at larger distances to the activator binding sites (figure 1(*B*)). How can the observed distance dependence between activator and repressor binding sites be rationalized? Here, a quantitative explanation of these findings is proposed that takes into account the nucleosomal chromatin structure.

Results

A number of explanations of the distance dependence observed by Fakhouri *et al* can be excluded: (i) proteins with extended tails may interact in a distance-dependent manner but for such large distances that would be unprecedented since these interactions are usually ⩽15 bp (Teif 2007). (ii) A third 'mediator' protein (complex) could insert between the repressor and the activator to quench the activator. The transcription factors in question interact with multicomponent co-repressors and co-activators. Thus, a flexible assembly of proteins with possibly multiple contact surfaces might indeed bridge relatively large distances through direct touching. However, the wide range of distances over which the repressor acts suggests a general mechanism not dependent on a repressor complex with fixed geometry. (iii) Another source of nonlinearity could arise through protein-assisted DNA looping. However, the probability of loop formation has a maximum at 500 bp separation (Rippe 2001) and a 10 bp periodicity below the DNA persistence length of 150 bp (Saiz *et al* 2005). In contrast, the experimental data of Fakhouri *et al* show a peak at 50–60 bp separation, which would be energetically unfavorable for interactions via the looping of a relatively stiff free DNA tether. Thus, we are left with the possibility that the repressor acts indirectly through chromatin rearrangements. Such an assumption is indeed supported by a subsequent recent publication by Li and Arnosti (2011). It was found that upon adding short-range repressors enhancer regions become less susceptible to MNase digestion and histone deacetylation increases. While the latter would increase nucleosome stability (Teif and Rippe 2010), the relation of this process to gene expression remains enigmatic.

Here, we propose a straightforward mechanistic explanation for the distance dependence of repressor action by considering the nucleosome structure of the eukaryotic genome. Specifically, we assume that the repressor binding stabilizes the nucleosome. This can be realized either by the direct repressor interaction with the core nucleosomal DNA (Dowell *et al* 2010) or by recruiting histone modifying enzymes (Teif and Rippe 2010). Although the nucleosome is stabilized, its DNA can partially unwrap to allow activator binding. Using a novel method that considers partial unwrapping of nucleosomal DNA (Teif *et al* 2010) (figure 1(*C*)), we calculated the dependence of activator binding on the repressor–activator distance *d* (figure 1(*D*)). A fixed set of reasonable thermodynamic parameters detailed in the figure legend was applied without further fitting. It was assumed that nucleosomes can assemble at any position along the DNA and can partially unwrap as described by a homogeneous potential (Teif *et al* 2010). Repressor–nucleosome contacts were included via a McGhee–von Hippel cooperativity parameter (McGhee and von Hippel 1974) as described previously (Teif 2007). Furthermore, it was assumed that the simultaneous binding of repressor and activator was prohibited if binding sites were within less than 6 bp from each other. The details of the calculation method are provided in the supplementary materials available at stacks.iop.org/PhysBio/8/044001/mmedia.

Our calculations show that three distance-dependent regimes emerge for such a system, labeled as 1, 2 and 3 in figure 1(*D*). At small separations ($d < 6$ bp, regime 1), activator binding is inhibited directly by the repressor. At 6 bp $< d <$ 50 bp (regime 2), repressor and activator bind cooperatively. The binding of one protein stabilizes the unwrapped state of nucleosomal DNA and facilitates the binding of the second

protein in a so-called collaborative competition (Miller and Widom 2003). This effect decreases with the repressor–activator distance. At larger distances of 50 bp $< d <$ 147 bp (figure 1(*D*), regime 3), a partially unwrapped nucleosome can fit between the repressor and activator making activator binding anticooperative. This effect decreases at larger distances as less unwrapping of nucleosomal DNA is required. Thus, our calculations reproduce the essential features of the nonlinear distance dependence observed experimentally (Fakhouri *et al* 2010) (figures 1(*B*) and (*D*)). The maximum repressor efficiency at 50–60 bp distances corresponds to the inner DNA region in the central part of nucleosome, which is the least accessible to transcription factors. The distance corresponding to the maximum repressor efficiency is mainly determined by the nucleosome geometry and its possibility to unwrap (supplementary figure S2 available at stacks.iop.org/PhysBio/8/044001/mmedia). In contrast, the width and the height of the peak are sensitive to changes in the binding constants of repressor, activator and histone octamer (supplementary figure S3 available at stacks.iop.org/PhysBio/8/044001/mmedia).

Discussion

Cooperative interactions between transcription factors separated by distances less than the nucleosome size seem to be abundant in the eukaryotic genome (Segal *et al* 2008). With respect to *Drosophila* enhancers, three classes of preferred distances between TF binding sites can be roughly distinguished: class I has ∼10 bp separations between homotypic TFs, probably reflecting their in-phase arrangement on the same side of the double helix (Makeev *et al* 2003); class II shows an ∼17 bp separation between heterotypic TFs that are probably located at the opposite sides of the double helix (Makeev *et al* 2003, Papatsenko *et al* 2009); class III is characterized by preferred distances between activators and repressors centered at about 60–80 bp (Papatsenko *et al* 2009). The latter distance cannot be rationalized in terms of the DNA double helix phasing and is likely reflecting structural chromatin features. Our calculations suggest that this class of distance preferences represents regulatory elements that operate via nucleosome-mediated TF interactions. For this class, we have provided here a quantitative description of the nucleosome-dependent regulation of gene expression at short genomic distances. The nucleosome in the lattice model is represented as a protein entity with a characteristic size of the histone octamer that can be wrapped by 147 or less DNA base pairs. Although histones are the most abundant chromatin proteins, one could also imagine protein complexes other than histones, which form an 'enhanceosome' with mathematical properties similar to the nucleosome in terms of DNA accessibility. The nonlinear distance dependence predicted by our model would be present in both cases.

Acknowledgments

We thank David Arnosti and Thomas Höfer for fruitful discussions. This work was funded within project EpiGenSys by the BMBF as a partner of the ERASysBio+ initiative supported under the EU ERA-NET Plus scheme in FP7 and by BRFFI grant B10M-060.

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SUPPLEMENTAL MATERIALS

Nucleosome mediated crosstalk between transcription factors at eukaryotic enchancers

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CALCULATION METHOD

Transcription factor binding to nucleosomal DNA was calculated using a statistical-mechanical DNA lattice model and deriving the partition function with the transfer matrix formalism (Teif *et al.*, 2010). In this approach the partition function is obtained by sequentially multiplying the transfer matrices (weight matrices) assigned to each DNA unit (Hill, 1957; Magee *et al.*, 1963; Magee *et al.*, 1965; Crothers, 1968; Gurskii *et al.*, 1972; Chen, 1987; Woodbury, 1988; Di Cera and Kong, 1996; Chen, 2004; Teif, 2007; Teif and Rippe, 2009; Teif, 2010; Teif *et al.*, 2010; Teif and Rippe, 2010). This approach was first used for describing DNA duplex melting, both for the case of the all-or-none binding (Magee *et al.*, 1963) and for partial binding (Magee *et al.*, 1965). Although the partial binding of an oligonucleotide and partial nucleosome unwrapping are very different processes they can be described by similar mathematical formalisms (Teif *et al.*, 2010). The transfer matrices are constructed so that each matrix element $Q_n(i, j)$ contains the probabilities to find the lattice unit n in a state i provided the unit $n+1$ is in state j. Prohibited combinations of states are characterized by zero weights. We consider reversible binding of proteins of f types to the DNA with the DNA base pairs numbered by index $n = (1, N)$. A protein of type $g = (1, f)$ covers up to m_g lattice units upon binding to the DNA. The value m_g corresponds to the length of the DNA binding site in the conventional all-or-none model. However, in our approach intermediate binding states with effective binding site length less than m_g are also allowed. Thus, for a binding event it is not necessary that all interaction sites of the protein are in contact with the DNA, e.g. one or more protein-DNA contacts may remain in the unbound state. This is represented in the model by splitting the protein-DNA interactions into discrete contacts, one per each DNA lattice unit, which are characterized by their microscopic binding constants. The microscopic binding constants $k(n,g,h)$ assigned for each DNA unit $h = (1, m_g)$ covered by the protein are chosen such that their product yields the macroscopic binding constant $K(n,g)$ for the whole protein binding to its target DNA sequence $(n, n + m_g - 1)$. In the calculations performed here we define the elementary DNA unit to be one base pair and set microscopic protein-DNA binding constant as $k(n,g,h) = \sqrt[m_g]{K(n,g)}$, i.e. interactions are equally distributed over all protein-DNA contacts. For the nucleosome, incomplete binding corresponds to the unwrapping of the DNA from the histone octamer protein core. The interaction between DNA-bound proteins is characterized by a parameter $w(l, g_1, g_2)$ that represents the interaction potential between the proteins of type g_1 and g_2 separated by the distance l. At $l = 0$, w is equivalent to the McGhee-von Hippel contact cooperativity parameter (McGhee and von Hippel, 1974; Teif *et al.*, 2002). Each protein is characterized by the maximum interaction distance V_g. Proteins do not interact at distances larger than V_g, $w(l > V_g, g_1, g_2) = 1$. Anticooperativity corresponds to $w = 0$. In particular, as the model $w(l \leq 6, g_1, g_2) = 0$ was used in the calculations to take into account mutual exclusion of DNA-bound activator and repressor molecules. The algorithm used to assign non-zero elements of the transfer matrix taking into account intermediate bound states was described in details in our previous publication (Teif *et al.*, 2010).

For predicting repression efficiency, we used the simplest model assuming that transcription initiation involves equal contributions of all activators bound at the enhancer. For the enhancer with four activator binding sites A_1, A_2, A_3, A_4 (numbered left to right in Figure 1 in the main manuscript), the probability of transcription initiation is considered to be proportional to $c(A_1) + c(A_2) + c(A_3) + c(A_4)$, where $c(A_i)$ is the probability that a binding site A_i is occupied by the activator. From the occupancy of activator binding sites the repressor efficiency R_{eff} is then calculated as:

$$R_{eff} = Const \times (1 - (c(A_1) + c(A_2) + c(A_3) + c(A_4))/4) \quad (1)$$

where *Const* is the normalization constant chosen from fitting.

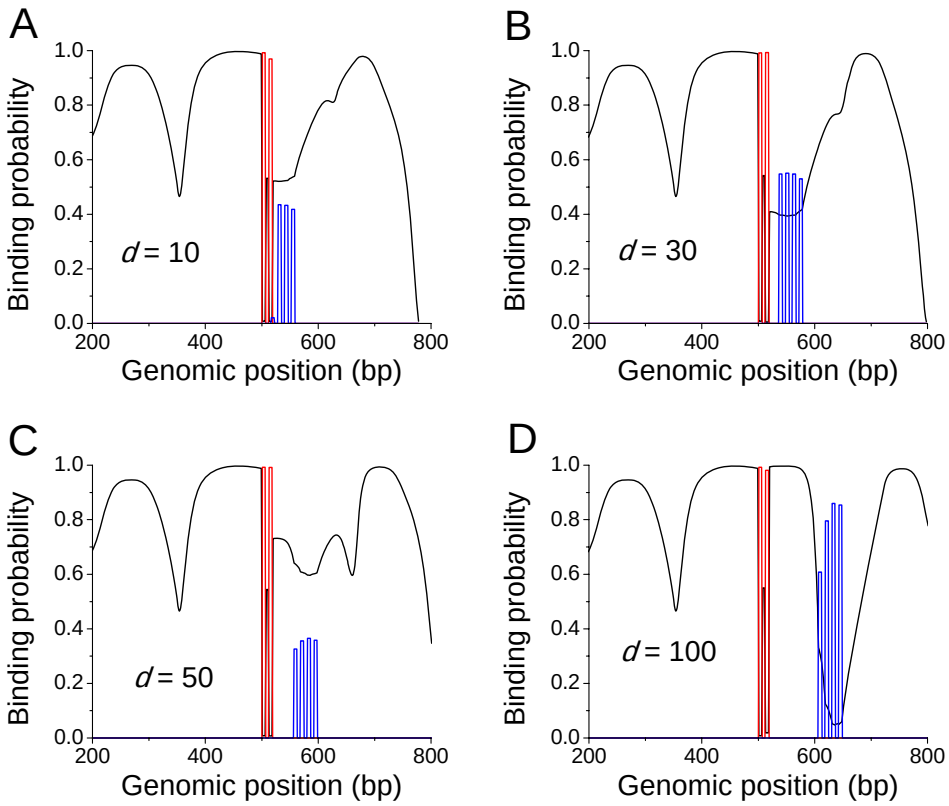

Figure S1. Representative binding maps for enhancer elements that differ with respect to the distance of activator and repressor binding sites. Binding probabilities were calculated for nucleosomes (N, black line), activator (A, blue line) and repressor (R, red line). The DNA fragment used for the analysis comprised 1000 bp of DNA followed by two repressor binding sites, a linker *d* of variable length, the activator block and another 220 bp DNA. The repressor sites were two 6 bp long and separated by 6 bp. The activator block was composed of four binding sites of 6 bp in length and 6 bp separation. The length of the linker *d* was 10 bp (A), 30 bp (B), 50 bp (C) and 100 bp (D). Calculations were made with binding constants of $K(\mathrm{R}) = 10^{11}$ M^{-1}, $K(\mathrm{A}) = 10^{10}$ M^{-1} and $K(\mathrm{N}) = 10^{-9}$ M^{-1} and protein concentrations of $[\mathrm{R}] = [\mathrm{A}] = [\mathrm{N}] = 10^{-9}$ M. Repressor-nucleosome contacts were cooperative with $w(l=0, N, R) = 1000$. Repressor and activator exclude each other at distances less than 6 bp as described by $w(l<6, R, A) = 0$.

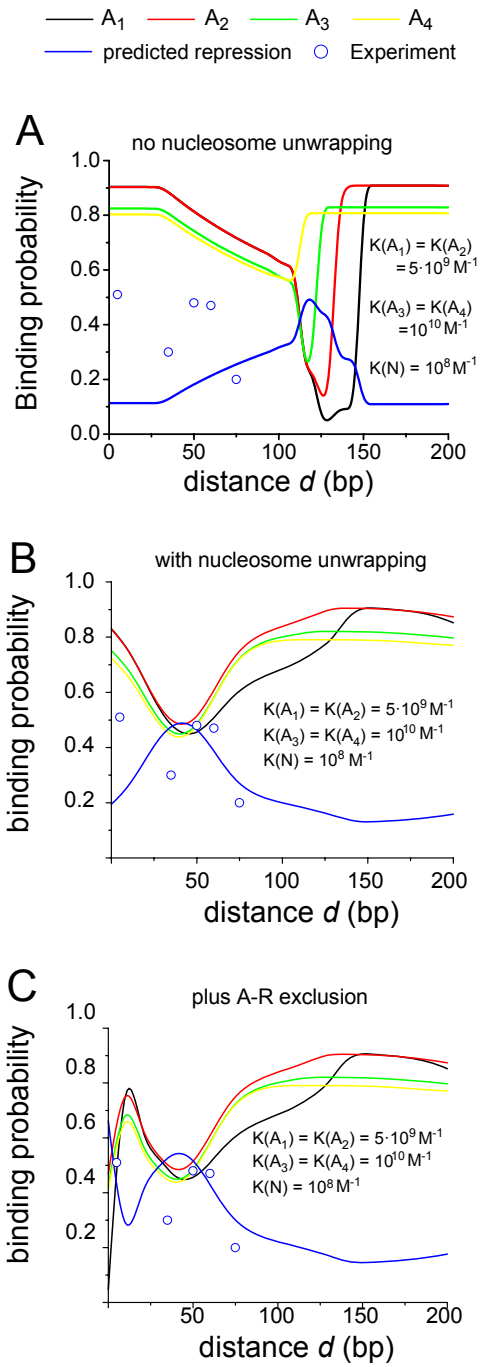

Figure S2. Activator binding and repression efficiency predicted for different binding models. The activator ("A") binding probability is calculated for the four binding sites numbered A_1 (black line), A_2 (red line), A_3 (green line), A_4 (yellow line), numbered from left to right as shown in Figure 1A, as a function of distance d between the leftmost activator site and the rightmost repressor site. The blue line shows the predicted repression efficiency calculated according to Eq. 1 and scaled to fit the data. Open circles correspond to the experimental data of Fakhouri et al, 2010 (Fakhouri *et al.*, 2010). The contact of nucleosome "N" with repressor is cooperative ($w = 1000$). Concentrations: $[R] = [A] = [N] = 10^{-9}$ M. $K(R) = 10^{11}$ M^{-1}. Other binding constants are indicated in the figure. In panel A, partial nucleosome unwrapping was not allowed. This resulted in a peak at d ~147 bp that is incompatible with the experiments. In panel B, nucleosome unwrapping was taken into account, yielding a peak at $d \approx$ 50-60 bp consistent with experiments. In panel C the exclusion between activator and repressor is additionally taken into account (repressor and activator cover 6 bp upon binding to DNA and exclude each other at $d < 6$ bp).

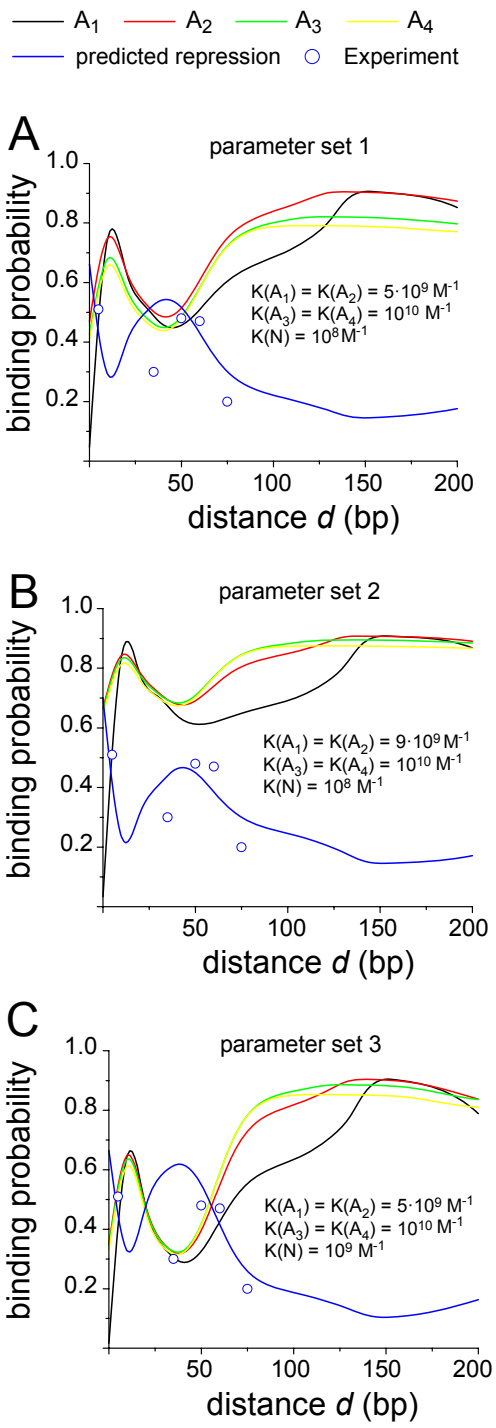

Figure S3. Activator binding and repression efficiency predicted for different binding parameters. The color coding of curves is the same as in Fig. S2. The contact of nucleosome "N" with repressor is cooperative ($w = 1000$). Repressor and activator cover 6 bp upon binding to DNA and exclude each other at distances < 6 bp. Concentrations: [R] = [A] = [N] = 10^{-9} M. K(R) = 10^{11} M^{-1}. Other binding constants are indicated in the figure.

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