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Activation and Repression of Transcription by Differential Contact: Two Sides of a Coin*

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Activation and repression of transcription are primarily caused by gene regulatory proteins (activators and repressors), which act by binding to specific sites on DNA. The steps from initial binding of RNA polymerase to the elongating complex are characterized by many intermediates, each with a discrete structure, offering many mechanistic possibilities for regulator actions. It has been shown in some systems that the activator acts by helping RNA polymerase or other associated factors to bind (recruitment) and/or by influencing a postrecruitment step (isomerization, promoter clearance, etc.) (1–7). We have used the term recruitment for referring to assistance only on the initial binding step of RNA polymerase. We caution that a postbinding step may be indistinguishable from the recruitment step if they are in rapid equilibrium. Clearly, all activators do not act at the level of RNA polymerase recruitment to the promoters. There are activators demonstrated to help postbinding steps that have no effect on initial binding (4–7). Promoter-specific repression can occur by sterically hindering the binding of RNA polymerase or of, in principle, another essential transcription factor to the promoter (8, 9). However, other studies in several promoters, as was anticipated (10), point toward repressor action also through contact with promoter-bound RNA polymerase at a postbinding step (11–17). More interestingly, some regulators act as activator in one context and as repressor in another (13, 15). Although the contact regions on the surface of some regulators and of RNA polymerase have been mapped (18, 19), how these contacts cause activation or inhibition of transcription initiation in biochemical terms is not known. In principle, the contact may affect the process of transcription initiation (i) by allosteric modification of RNA polymerase and/or (ii) by energetic stabilization of an intermediate(s). Regulator-induced conformation changes in RNA polymerase by protein-protein contact may contribute to the regulation process. However, a regulator-RNA polymerase contact may play a fundamentally different role in transcription initiation. In this article, we provide a conceptual framework for the process of activator and repressor action through differential stabilization of one or more of the intermediate states of RNA polymerase-promoter complex by its contact with the regulator. We portray regulators as catalysts. From a thermodynamic point, we view that activators, like catalysts, lower the activation energy of some step(s) in the reaction pathway of transcription initiation. As discussed below, a similar energetic argument explains the action of repressors. To make our point, we discuss simple examples of DNA-binding regulators modulating RNA polymerase during transcription initiation in selected prokaryotic systems.

Regulators as Catalysts

The biochemical steps of RNA polymerase binding to the promoter leading to transcription initiation have been discussed extensively (20–22). In principle, any of the steps can be regulated; a rate-limiting step can easily be enhanced by an activator or quenched by a repressor (10, 23, 24). To describe the role of a regulator in the simplest way, we will use, for example, the open complex formation as a two-step chemical reaction that includes the formation of only one transition state,

$$\text{Step 1. } R + P \overset{K_a}{\rightleftharpoons} (R \cdot P)_c$$

$$\text{Step 2. } (R \cdot P)_c \rightarrow [R \cdot P]^{\ddagger} \xrightarrow[k_f]{} (R \cdot P)_o$$

where R is RNA polymerase, P is promoter DNA, $(R{\cdot}P)_c$ is the closed complex of RNA polymerase and DNA; $(R{\cdot}P)_o$ is the open complex of RNA polymerase and DNA; $[R{\cdot}P]^{\ddagger}$ is the transition state between $(R{\cdot}P)_c$ and $(R{\cdot}P)_o$, K_a is the equilibrium constant that characterizes the closed complex, and k_f is the rate constant of the isomerization from closed to open complex. Thus, the reactions can be described by a free energy diagram (25), which has been very useful in explaining catalysis by enzymes that act by lowering the energy barrier(s) during the course of a reaction (26–29). We propose that both activator and repressor modulate the energetics of the reactions steps. This outlook of a regulator action not only provides a common biochemical and thermodynamic basis of its action but also addresses the following questions. (i) What role does DNA play in regulator action? (ii) How can a regulator be bifunctional, *i.e.* activator in one context and repressor in another?

Fig. 1 represents a minimal kinetic scheme of a typical open complex formation reaction at a hypothetical promoter that is not regulated, and the associated free energy changes during the course (change in reaction coordinates). RNA polymerase conformation constantly changes depending on the DNA sequence during the course of the reaction (30, 31). We propose a *differential contact*[1] model to explain regulator action. In this model, *a given regulator after binding to DNA interacts with and lowers the free energy of one or more of the DNA-bound RNA polymerase intermediates (including the transition state), each with discrete conformation, during the course of open complex formation.* The differential protein-protein contacts may persist throughout the progression from closed to open complex and lower the free energy level of all states with respect to unbound RNA polymerase. On the other hand, the contact may be specific for some state(s), selectively stabilizing that intermediate and lowering its free energy. Changes in RNA polymerase conformation during the initiation steps may facilitate differential contacts.

As explained below, this provides the regulator the option to enhance or inhibit open complex formation by decreasing or increasing the energetic barrier of the different steps. The presence of two proteins on adjacent DNA sites having the potential for interaction does not ensure that they will interact because of the importance of establishing proper geometry. The net interaction energy and consequent stabilization is a function of several factors: local concentration of the regulator (entropic assistance), free energy of regulator-RNA polymerase interaction, and any required protein and DNA distortion energy. If the geometry is highly unfavorable, the required DNA and protein distortion energy will not be compensated by the entropic gain and protein-protein interaction energy for proper regulator-RNA polymerase contact or stabilization. The variation of orientations of two adjacently bound proteins during the progress of the reaction can permit contacts in some orientation and not in others (differential contacts).

Activation

In the example of an activator action, the concentration of unbound RNA polymerase and free DNA, whose free energy is taken

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[1] Differential contacts are transient contacts, which are made and broken in a temporal manner, between DNA-bound regulators and RNA polymerase.

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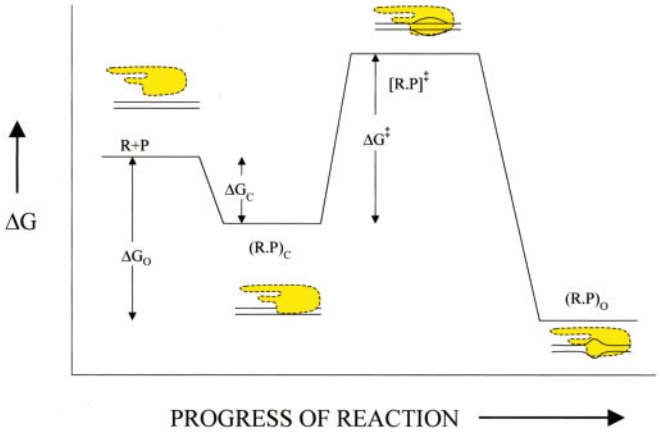

FIG. 1. **Free energy diagram of two-step open complex formation.** ΔG_c, ΔG_o, and $\Delta G‡$ represent free energies of closed complex formation, open complex formation, and "activation," respectively. The cartoon figures illustrate the nature of the states of RNA polymerase (*yellow*) and DNA. Compared with $(R{\cdot}P)_c$, $(R{\cdot}P)_o$ is characterized by partial melting of the promoter region.

as the reference state, is assumed to be slightly higher than the true K_a^{-1} for closed complex formation, and the closed complex is placed at a slightly lower free energy level than that of the unbound RNA polymerase and free DNA (Fig. 2, *A–C*, *black lines*). For simplicity, we have not included a transition state intermediate for closed complex formation and made the transition state of isomerization the rate-limiting step by placing [R·P]‡ at the highest free energy level. A regulator can activate transcription by any of the scenarios described in the following paragraphs.

Plot 1—The regulator has contacts with $(R{\cdot}P)_c$ and [R·P]‡ with the same affinity and lowers their free energy by equal amounts during the progress of the reaction (Fig. 2*A*, *green line*). As shown in the free energy diagram, such interactions will decrease only ΔG_c, and not $\Delta G‡$, the net result being activation because of increased K_a. The net rate enhancement of open complex formation will be most significant if the free energy of $(R{\cdot}P)_c$ in the absence of activator is higher than that of unbound RNA polymerase, *i.e.* K_a^{-1} is greater than the unbound RNA polymerase concentration. If the RNA polymerase concentration is higher than K_a^{-1}, then further stabilization of the closed complex by contact with a regulator would not significantly enhance the net rate of open complex formation. Thus, the maximal effect of such a regulator can only be observed if the RNA polymerase concentration is below K_a^{-1}. A contact between the C-terminal domain of the α-subunit (αCTD)[2] of RNA polymerase and the downstream subunit of CRP was shown in a study employing wild type and mutant proteins where a correlation was established between the ability of CRP to interact with RNA polymerase in solution and its ability to activate the *lac* promoter (32). It has been shown that CRP activates *lac* transcription by increasing the pseudoequilibrium constant[3] as derived from kinetic measurements (2), implying that the contact between CRP and αCTD is held at both closed and transition state complexes with approximately equal free energy.

Plot 2—The regulator interacts and lowers the free energy of both $(R{\cdot}P)_c$ and [R·P]‡ but decreases the free energy of [R·P]‡ more than that of $(R{\cdot}P)_c$ (Fig. 2*B*, *green line*). The result will be decreases in both ΔG_c and $\Delta G‡$ and thus activation by increasing both K_a and k_f. This type of regulation is exemplified by λcII at the P_{RE} and P_{INT} promoters (33, 34) and by CRP activation of the *gal P1* promoter (35, 36). If, on the other hand, the regulator decreases ΔG_c more than it decreases $\Delta G‡$, the situation will be as described below under "Repression" (Plot 4).

Plot 3—The regulator makes differential contacts and lowers the free energy of [R·P]‡, thus decreasing $\Delta G‡$. The net effect is activation because of an increase in k_f (Fig. 2*C*, *green line*). The stronger the interaction, the lower will be the activation energy for the

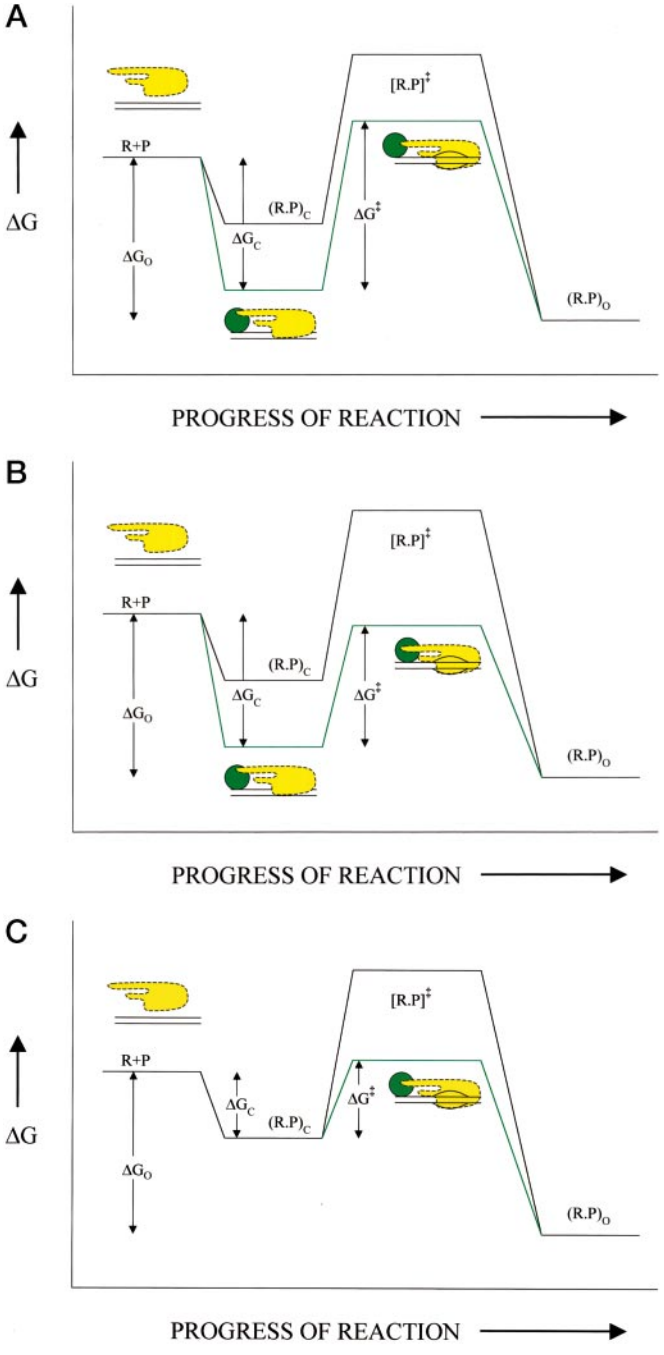

FIG. 2. **Free energy diagrams of different modes of activation of transcription by transcription activators.** Shown are activators (*green*) that affect: *A*, K_a (Plot 1); *B*, both K_a and k_f (Plot 2); and *C*, k_f (Plot 3). Only the relevant icons of the proteins are shown (*cf.* Fig. 1).

formation of the transition state and the higher will be k_f. RNA polymerase concentration would not have any effect on this type of activator action.

One example is the activation of P_{RM} promoter by λcI protein (37, 38). cI stimulates P_{RM} by increasing the rate of isomerization of the closed to the open complex, *i.e.* k_f. By the differential contact model, cI contacts the [R·P]‡ complex and decreases $\Delta G‡$ and thus increases k_f (Fig. 2*C*, *green line*). Mutations of cI have indeed been isolated that bind to DNA normally but fail to activate transcription and thus define the proposed region of contact with RNA polymerase (39, 40). Mutants of the σ^{70} subunit of RNA polymerase have also been reported, which have specific effects on cI-stimulated transcription at P_{RM}, suggesting that the proposed contact between cI and (R·P)‡ is through the σ^{70} subunit (41). Another example of an activator regulating through affecting k_f is NtrC. It

[2] The abbreviations used are: αCTD, C-terminal domain of the α-subunit; CRP, cAMP receptor protein.
[3] The measured pseudo-equilibrium constant was $k_1/(k_{-1} + k_f)$.

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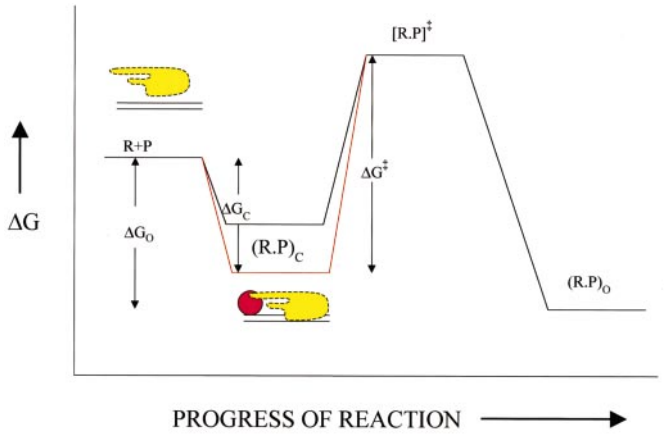

FIG. 3. **Free energy diagram of repression by contact between a repressor (*red*) and RNA polymerase (Plot 4).** Only the relevant icons of the proteins are shown (*cf.* Fig. 1).

acts at the *glnA* promoter, which utilizes a σ^{54}-RNA polymerase (42).

Repression

The general nature of repression by contact with RNA polymerase is likely to be stabilization, by differential contact, of any of the intermediates with respect to the subsequent transition state. The bound RNA polymerase faces an increased energetic barrier to the next step as exemplified by Plot 4.

Plot 4—In the free energy diagram in Fig. 3, a promoter is described that proceeds without much of an energy barrier. The regulator interacts and lowers the free energy of $(R{\cdot}P)_c$ only and not of [R·P]‡, thus increasing $-\Delta G_c$ as well as $\Delta G‡$. Although there will be an accumulation of closed complex $(R{\cdot}P)_c$ (increase of ΔG_c), *i.e.* an increase of K_a, a large increase in $\Delta G‡$ will create an energy trap for the isomerization step. If RNA polymerase concentration is greater than K_a^{-1}, the corresponding decrease in k_f overcompensates for the increase in K_a, and the net effect will be repression. GalR, the repressor of the *Escherichia coli gal* operon, clearly does not act by competing with RNA polymerase for DNA binding (13, 43, 44) as has been suggested for LacI (9). GalR and RNA polymerase form a stable ternary complex at the *galP1* promoter, and repression of *P1* is abolished either by truncation of or by specific amino acid alterations of the αCTD of RNA polymerase. These results show that GalR inhibits RNA polymerase activity at a postbinding step through a direct contact with αCTD. This phenomenon is easily explained if GalR makes a differential contact with the closed complex in the free energy diagram (Fig. 3, *red line*), a net decrease in k_f.

The Role of DNA

What part does DNA play in the action of a regulator? Several roles have been suggested before (25, 45). (i) Having a regulator-specific DNA binding site brings specificity to the regulator. Most DNA-binding gene regulatory proteins have unique sequences to which they bind. (ii) DNA binding near a promoter increases the local concentration of the regulator. (iii) DNA binding changes the structure of the regulator allosterically making it more "potent" for differential contacts. (iv) DNA bending induced by a regulator can directly affect transcription initiation by correctly aligning interacting groups of proteins and DNA in space. Although some or all of these roles of DNA may be essential for the function of a given regulator, the following suggests that such roles may not be sufficient (46). When a 4-nucleotide single-stranded gap is introduced in the DNA segment intervening the CRP binding site and the *lac* promoter, CRP not only failed to activate but also repressed the basal transcription. DNA binding results, nevertheless, showed normal, if not better, formation of CRP·DNA·RNA polymerase ternary complex under such conditions, demonstrating that protein-protein contact-mediated RNA polymerase recruitment was not affected by the DNA structural alteration. It was proposed that either the CRP·RNA polymerase complex is formed by a wrong, *i.e.* nonproductive, contact or the intervening DNA plays a more direct role and must be normal and intact. The differential contact model suggests that both proposals are valid. In this model, double-stranded DNA provides the proper rigidity to the nucleoprotein complex, allowing only the desired contacts. On the other hand, the single-stranded DNA either allows an unwanted contact creating an energy trap because of its flexibility or prevents an essential contact between the regulator and RNA polymerase because of change in geometry. Because CRP activates the *lac* promoter by increasing K_a (2), as discussed above, in the differential contact model the αCTD contact by the regulator must be held at both closed and transition state complexes. By introduction of a single-stranded gap, the intervening DNA loses rigidity and consequently its ability to make the "right" contacts shown in Fig. 2*A*. In this model, CRP now contacts either $(R{\cdot}P)_c$ more strongly than [R·P]‡ or contacts $(R{\cdot}P)_c$ only (Plot 4), leading to repression. Such stabilization at the $(R{\cdot}P)_c$ state is likely to be considerable because the establishment of the contact is no longer required to overcome the DNA distortion energy (47, 48).

The Dual Behavior of Regulators

GalR—Under specific conditions, binding of the GalR protein to the site O_E in the *gal* operon of *E. coli* regulates transcription from two promoters *P*1 and *P*2 (13, 43, 44). GalR represses transcription from *P*1, which is located on the same face of DNA as the DNA-bound GalR, and stimulates that from *P*2, which is located on the opposite side. Gel electrophoretic studies and DNase protection experiments of *gal* DNA in the presence of GalR and RNA polymerase have shown that GalR forms a characteristic GalR·DNA·RNA polymerase ternary complex at each promoter because of putative interaction between GalR and RNA polymerase.

GalR binding to O_E increases open complex formation at *P*2 by stimulating RNA polymerase binding (13, 43, 44). Although it is not known that GalR stimulation at *P*2 is through increasing K_b or k_f, or both, GalR behavior can be explained by Plots 1, 2, or 3 in Fig. 2. The proposed interaction of RNA polymerase with GalR is through αCTD, which is connected with the rest of the RNA polymerase by a flexible hinge (49, 50). Consistently, RNA polymerases missing either portions of αCTD or containing specific amino acid substitutions are insensitive to GalR-mediated activation at *P*2 but are normal in basal transcription (43).

GalR forms a stable ternary complex with RNA polymerase at *galP1* and causes repression (13, 43). The effect of GalR at one promoter is independent of GalR action at the other promoter; GalR exerts its specific regulatory effect on one when the other is mutationally inactivated. As discussed earlier, repression at *P*1 can be explained if GalR makes a differential contact with the closed complex. Mutation in the αCTD results in loss of repression, and it is clear from the spectrum of amino acids whose alterations resulted in deregulation that both the activating and the inhibitory contacts involve the same region of αCTD. However, the activator complex at *P*2 is in an open complex form, whereas the repressing complex at *P*1 is in a closed complex state. Actually, the *P*1·GalR·RNA polymerase complex, by DNA footprinting studies, appears to be in a form between closed and open complexes (12). Interestingly, the mechanism of activation of *P*2 or repression of *P*1 is not an intrinsic property of the promoter in question. The face of DNA occupied by RNA polymerase relative to the face of DNA occupied by GalR seems to play a role; the regulation can be reversed by switching the orientation of the promoters relative to O_E (13, 43). The use of the concept of differential contacts between a regulator and an RNA polymerase·DNA complex in understanding regulation of transcription initiation explains how a single regulatory protein exhibits dual roles, activation transcription in one context and repression in another. GalR interacts with αCTD of the $(R{\cdot}P)_c$ when located on the same face of DNA to cause repression and with [R·P]‡ or with both [R·P]‡ and $(R{\cdot}P)_c$ when located on the opposite face to cause activation.

MerR—The *E. coli* transcription regulator, MerR, provides another example of a context-dependent dual behavior (17, 51). The differential contacts with RNA polymerase depend upon the state of the regulator and the DNA sequence. MerR binds to a site between the −10 and the −35 of the P_{mer} TPCAD promoter. In the absence of Hg(II), MerR represses transcription from the promoter. In the presence of Hg(II), the DNA·MerR RNA polymerase ternary

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complex is converted from a state of repression to a state of activation. Thus, allosterically changing the structure of a regulator can convert it from a repressor to an activator.

λcI—As previously mentioned, λcI activates the P_{RM} promoter by enhancing k_f, *i.e.* by making a contact with [R·P]‡. It acts also as a repressor of the P_R promoter. A mutational change in RNA polymerase can change the effect of cI. Recently, it has been shown that a mutation in the σ subunit of RNA polymerase can cause λcI to switch from increasing k_f to increasing the pseudo-equilibrium constant K_b (52). Presumably, the mutation enables cI to interact with RNA polymerase in the $(R{\cdot}P)_c$ in addition to the [R·P]‡, leading to a predominant K_b effect. In this case, the mutation may change the strength of the contact and/or orientation of the surface, allowing an interaction at a different point(s) in the reaction pathway.

ϕ29 p4—Protein *p4* of the *Bacillus subtilis* bacteriophage *ϕ29* repressess the transcription of early promoters, *e.g. A2C*, and simultaneously activates transcription of an *A3* promoter for late genes. Both the activation and the repression require contacts between p4 and the α subunit of RNA polymerase. Repression of the A2c promoter is by inhibition of a later step, promoter clearance. The p4 protein allows RNA polymerase to bind but prevents the elongation step of transcription initiation (15). Activation at the A3 promoter is through stabilization of the closed complex between RNA polymerase and DNA (12). It has also been shown that p4-mediated regulation also depends upon the strength of RNA polymerase-promoter interactions; increasing the strength by changing the −35 sequence converts p4 from an activator to a repressor (53) (see "Plot 4").

We have explained the mechanism of action of transcription regulators by comparing with the mechanisms of enzymes. After binding to DNA, a transcription regulator makes *differential contacts* and lowers the free energy of one or more of the DNA-bound RNA polymerase intermediates, each with discrete conformation, during the course of transcription initiation at a promoter. The nature of the differential contacts determines the outcome of a regulator's action, repression or activation. This differential contact model gives a thermodynamic explanation for the biochemical action of both transcription activators and repressors and explains how one regulator can be both an activator and a repressor. We emphasize the important role of DNA in determining the differential contacts between a regulator and various promoters, RNA polymerase intermediates.

Perspective

The basic concept of differential contacts discussed here can easily be applied to any of the steps of not only prokaryotic but eukaryotic complex regulatory systems. Indeed, a number of examples of eukaryotic dual function regulators have been identified (54–58) and are likely to act by differential stabilization of intermediate states through protein-protein contact. The model can be extended to explain the known examples of activator (4) or repressor (15) action at the levels of post-open complex formation of transcription initiation.

The differential contact model of gene transcription can be tested. It predicts that one will be able to isolate mutations in the regulator, RNA polymerase, or promoter, which will define the state(s) of the regulator contacts, and some of the mutations may switch the state to which the regulator binds and alter the regulatory outcome.

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