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Publication Date
2017-12-01

DOI
10.1016/j.gde.2017.09.004

Peer reviewed

HHS Public Access

Author manuscript

Curr Opin Genet Dev. Author manuscript; available in PMC 2019 December 09.

Published in final edited form as:

Curr Opin Genet Dev. 2017 December ; 47: 121–127. doi:10.1016/j.gde.2017.09.004.

The Rewiring of Transcription Circuits in Evolution

Alexander D. Johnson

Abstract

The binding of transcription regulators to cis-regulatory sequences is a key step through which all cells regulate expression of their genes. Due to gains and losses of cis-regulatory sequences and changes in the transcription regulators themselves, the binding connections between regulators and their target genes rapidly change over evolutionary time and constitute a major source of biological novelty. This review covers recent work, carried out in a wide range of species, that addresses the overall extent of these evolutionary changes, their consequences, and some of the molecular mechanisms that lie behind them.

Biologists typically rely on metaphors to describe the inner workings of cells. We call the genome “the blueprint of the organism” and sometimes refer to it as a dictionary or encyclopedia, albeit a disorganized one. Mitochondria are power plants, helicases are rotary engines, and gene expression patterns are produced by circuits or wiring, a reference to “an assemblage of electronic elements.” Although these metaphors are immensely useful for describing the cell at certain depths, they ultimately break down and often cause confusion when reflexively applied at deeper levels of understanding. For example, most biological metaphors are taken from our everyday lives, where there is nothing analogous to diffusion or thermal motion. Moreover, the metaphors almost always invoke products designed and built by humans. Although biologists acknowledge that the workings of the cell were not designed, there often remains an expectation that cell mechanisms should conform to principles of good design, such as orderliness, logic, efficiency, elegance, and even cleverness. When it comes to transcription circuits (the subject of this review), the early work on the *lac* and λ repressors did produce a picture consistent with good design principles. This correspondence was, at least in part, due to the insight of scientists in choosing relatively simple systems with high dynamic ranges of expression. These studies revealed many of the basic principles of gene expression, including positive and negative transcriptional control, recognition of short DNA sequences by regulatory proteins, the modular structures of transcription regulators, DNA looping, and the existence of feedback loops that could be stably maintained through many cell generations (see, for example [1]). However, as more and more transcription circuits were studied, particularly in eucaryotes and especially using full-genome methods, they began to seem less and less intuitive and

Conflict of Interest

The author declares no conflicting interests.

sensible when viewed from a design perspective. The same might be said for the genomes themselves: some bacterial genomes, with their paucity of excess DNA and their genes neatly arranged in operons, make more sense, from a design perspective, than, say, mammalian genomes. Of course, genomes and transcription circuits are products of evolution; although evolutionary forces can produce the illusion of good design, good design should not be an obligatory expectation.

An insightful way of coming to grips with the structures of present-day transcription circuits is through an understanding of the evolutionary processes that produced them. It has been appreciated for many years that gene expression circuits evolve relatively rapidly [2,3]. For example, there are marked differences in transcription circuitry between even closely related species that contain, more or less, the same genes. And many of these circuits seem overly complex when compared to idealized circuits. In this sense, transcription circuits should probably be viewed as works in progress or even as “runaway bureaucracies” [4] rather than perfected, efficient, and logical constructs. This review summarizes a selection of the work (case studies, computational approaches, and theoretical considerations) published in the past two years that further document the extent of evolutionary rewiring among species and provide insights into extant circuits. These studies build on earlier experimental work in animals [5–9], plants [10,11], and fungi [12,13]), and owe a major debt to those biologists who have stressed the importance of neutral evolution (see, for example [4,14–16]).

Nomenclature and General Principles

I refer to sequence-specific DNA binding proteins that regulate the transcription of specific genes by binding to cis-regulatory sequences (located in rough proximity to those genes) as “transcription regulators.” I use this term rather than the more common “transcription factor” because the latter term also includes the large number of proteins that are needed for the processes of transcription initiation and elongation but do not select genes to be transcribed. Although some transcription regulators bind to cis-regulatory sequences on their own, many more assemble on DNA cooperatively with additional regulators. I refer to a given transcription regulator and all the genes that it regulates through direct DNA binding (herein called target genes) a “transcription circuit.” I will call the process through which genetic differences in transcription circuitry are produced across a group of species as “evolutionary rewiring.”

Three kinds of evolutionary changes in transcription regulation are summarized in Figure 1. Although gains and losses of cis-regulatory sequences are widespread, evolutionary changes in the transcriptional regulators themselves are also important. Transcription regulators have modular structures, and although the DNA-binding specificity is often preserved over long evolutionary times, other domains of these proteins can more rapidly gain and lose interactions with partner proteins. Although not the focus of this review, it should be noted that promoter sequences (that is, sequences near the start point of transcription that guide the assembly of RNA polymerase and its associated factors) also change over evolutionary timescales [17–19]. Finally, although this review is limited to transcriptional circuitry, many of the principles discussed here apply to other steps in gene expression [20,21].

Evolutionary rewiring is extensive in all clades examined

Although this basic idea is now generally accepted, the past two years have provided new examples and added important insights. Specifically, there is new evidence from bacteria [22], fungi [23–31], worms [32,33] sea urchins [34,35], flies [36–38], plants [39], and mammals [40–45] that evolutionary rewiring—that is, genetic changes in the connections between a regulator and its targets genes—is frequent. Using a common methodology to evaluate transcription evolution across a variety of animal species, Carvunis et al. [46] concluded that evolutionary rewiring occurred at roughly similar rates (using years of divergences from a common ancestor as the denominator) in insects, birds, and mammals. As pointed out by the authors, this equivalent rate is surprising, given the differences among these animals in generation times, population sizes, and genome sequence evolution rates. In very rough terms (and based on small sets of transcription regulators in mammals and insects), for two species diverged by 100 million years, the majority of the DNA-binding patterns of a given regulator in one species are not preserved in the other species; genome-wide correlations converge on about 10%. Although this number depends on the transcriptional regulator, the clade examined, and the methodologies employed, it is a useful starting place, particularly as it indicates that the majority of regulator-target gene connections are not preserved across this timescale.

Estimates from the fungal ascomycete lineage, which nominally spans 300 million years of diversity, fall within this range. For example Nocedal et al. [27] showed, for a particular regulator (Ndt80) that controls many target genes, 3–12% of the connections (considering only orthologous target genes) were preserved in two species (*S. cerevisiae* and *C. albicans*) that span this timescale. The variation in the number depends on the stringency of the criteria used to integrate experimental and computational results. Using computational cis-regulatory sequence detection across many transcriptional regulators, Habib et al. [47] estimated that, on average, about 16% of the regulator-target gene connections are preserved between these same two species. Sarda and Hanneholli [31], using computational approaches, also document extensive rewiring among fungal species over this same timescale. The extent of rewiring will obviously vary from one regulator to the next and from one clade to the next. Moreover, all of these numbers are dependent on the methodologies and criteria used to generate them [48]. However, as rough as they are, they at least provide a framework for thinking about the overall frequency of evolutionary rewiring.

In any case, it seems a solid conclusion that, on average, a given transcription regulator-target gene connection in one species is probably not preserved in a second species that last shared a common ancestor 100–300 million years ago. Given that the DNA-binding specificities of transcriptional regulators often remain relatively constant and that many target genes are also deeply conserved over this timescale, it is perhaps surprising that the connections between them change so rapidly. However, gene expression patterns are often preserved over these same timescales, indicating that the regulator-target gene interactions underlying a gene expression program may change while the output of a program itself can remain relatively stable [12,27,30,47–50]. This phenomenon has been termed “developmental system drift” [51] and several recent examples are discussed below.

Changes in the cis-regulatory sequences of a single gene can have profound effects on development

Often, a “master regulator” that sets in motion a developmental program [52] is expressed in a new place or new time in development through simple gains or losses of the cis-regulatory sequence that control expression of the regulator. Early work documenting this principle in humans, flies, stickleback fish and maize (reviewed by [5–7,36]) has been complemented by many new studies. Recent examples include the repeated co-option of the regulator Optix in butterfly wing patterning [53], changes in the regulation of *Shh* in the loss of limbs in snakes [54], changes in the cis-regulatory sequences of FOXO1 in the “invention” of residual stromal cells [55], changes in Tbx5 regulation in the evolution of fins [56], changes in *PAX3* and *PAX7* regulation in craniofacial evolution in humans [57], and changes in *GDF6* regulation in the evolution of the human foot [58]. Evolutionary changes in the expression of master regulators is a key concept in understanding how transcription circuits change over evolutionary timescales; indeed the cis-regulatory sequences of such master regulators are sometimes referred to as hotspots for evolutionary change [5–9,59]. Gains and losses of cis-regulatory sequences controlling a single regulator are relatively simple to understand mechanistically. In the next section, more complex situations, in which each member of a whole set of co-regulated genes acquires the same cis-regulatory sequence, will be discussed.

“Handoffs” of a set of genes from one transcription regulator to another

A strength of the work in fungi is the relative ease in determining the function, mapping the connections, and assessing the effect of knockouts for an orthologous transcription regulator across multiple species. This type of analysis has revealed several instances where a regulon (a set of co-regulated genes) has been handed off from one transcription regulator to another over evolutionary time. Although the first cases were documented nearly a decade ago (reviewed in [12,13]), recent work has uncovered additional examples, indicating that such handoffs are quite common [60]. New examples include a handoff of the sterol biosynthetic genes from an SREB-like protein (a helix-loop-helix member) to Upc2 (a Zn-finger protein) [24]; a handoff of the *GAL* genes (needed to convert galactose to glucose) from Rgt1-Rtg3 (helix-loop helix proteins) to Gal4 (a Zn finger protein) [25]; and a handoff of the allantoin degrading enzymes from Prp1 (a Zn-finger protein) to Dal82 (an uncharacterized structural class) [26] (Figure 2). Each of these changes required the destruction of old and the formation of new cis-regulatory sequences controlling each member of a set of target genes; often the new sequences are unrelated to the ancestral sequences, as evidenced by the fact that these handoffs occurred between transcriptional regulators belonging to different structural classes. What are the consequences, if any, of these handoffs? In at least some cases, the handoff occurred without a dramatic change in gene expression of the regulon. For example, despite the handoff, the *GAL* genes are still induced by galactose in the species examined. Although some handoffs could be neutral, others could have had roles in the restructuring of gene expression patterns that accompanied shifts in respiration and metabolism that occurred several times in fungi [13,61]. In the case of the *GAL* genes, the rewiring was correlated with a change in many of the quantitative parameters (for example

the dynamics of gene induction) as well as a shrinking of the size of the regulon containing the *GAL* genes. Although such handoffs might seem counterintuitive, they appear to be quite common, at least in fungi.

How might these regulon handoffs occur? As most biological processes require the coordinated expression of many genes, it is not immediately obvious how a whole regulon could lose one cis-regulatory sequence and gain another. However, a common feature of transcriptional regulators is their ability to bind DNA cooperatively with other transcriptional regulators, and the biophysics of cooperative binding provides a model that can account for the rewiring of regulons [50,62,63]. In its simplest form, and considering only a pair of transcriptional regulators, the idea is that the energy of binding can be shared between protein-DNA interactions and protein-protein interactions in many ways. This means that there are many different solutions for a transcription regulator to efficiently occupy a given cis-regulatory sequence, and different solutions can be sampled through neutral evolution (Figure 3). When small increases and decreases in the intracellular concentrations of the regulatory proteins themselves are added, there are even more possibilities for systems drift. If clusters of low affinity sites, which are found at many animal enhancers, are also taken into account, the potential for circuit “movement” is even greater [64], particularly if the regulators exhibit weak cooperativity. In the limit case, a regulon could move, over evolutionary time, from control by one protein to cooperative binding with a second protein to elimination of the first protein (Figure 3). This entire scenario could occur through neutral evolution, if the binding of either or both regulatory proteins was sufficient to maintain proper expression of the target genes. Many of the protein-protein interactions that mediate cooperative binding are weak (on the order of 2–3 kcal/mole), and this type of interaction is relatively easy to gain and lose through mutation [50]. Thus, the acquisition of a new, relatively low-specificity, protein-protein interaction could initiate the rewiring process across a whole set of genes. As cooperative binding could allow extensive neutral excursions without disrupting regulation, it provides a simple mechanism through which a circuit could move through a dual control intermediate during a handoff, thereby preserving regulation at each step in the transition [47,50,62]. It should be noted, however, that there are constraints in circuit movement, as some types of change will compromise regulation. These constraints are probably crucial in shaping permissive pathways of transcription circuit evolution [65].

How much of the observed transcriptional rewiring is adaptive?

It seems likely—based on population genetics and experimental case studies—that much of the observed transcription rewiring arose neutrally. In any case, this is a useful null hypothesis [4,14–16]. Such neutral changes could, of course, continually generate new circuit configurations that could ultimately lead to new phenotypes. This is an attractive idea, as it implies that different circuit configurations (as long as they do not destroy the output of the circuit) could be sampled, without the requirement that each step have a selective advantage [4,14–16]. This concept is consistent with experimental studies in which a transcription regulator maintains a conserved function (e.g. liver specification in mammals [66] or meiosis and sporulation in fungi [27]), yet the target genes bound by the regulator differ considerably across even closely related species. Although some of these changes may

well be adaptive, the work to date suggests that there are many alternative, equivalent ways of generating a particular gene expression pattern and that circuits can move neutrally between different solutions without disrupting regulation. In a sense, this idea lies almost at the opposite end of the spectrum from the single-gene examples discussed earlier in the review. Here, it seems that, despite large-scale rewiring, overall circuit output may remain more or less constant. Clearly, a coherent view of evolutionary transcription rewiring must encompass both of these extremes, as well as the continuum between them.

Conclusion

Since the original proposals that changes in gene expression underlie much evolutionary novelty [2,3], many concrete examples have now been explored, some to a high level of detail. One of the more surprising findings is the high frequency of transcriptional rewiring that occurs despite the overall patterns of gene expression remaining relatively stable. An important challenge for the future is understanding the extent to which transcription rewiring occurs neutrally and understanding what types of circuit architectures are commonly formed from such neutral excursions. It is also a future challenge to systematically identify—in the midst of a high background of presumed neutral circuit movement—those changes that were truly adaptive.

Acknowledgments

The author thanks David Morgan, Naomi Ziv, Liron Noiman and Kyle Fowler for valuable comments and Kyle Fowler for drawing the figures.

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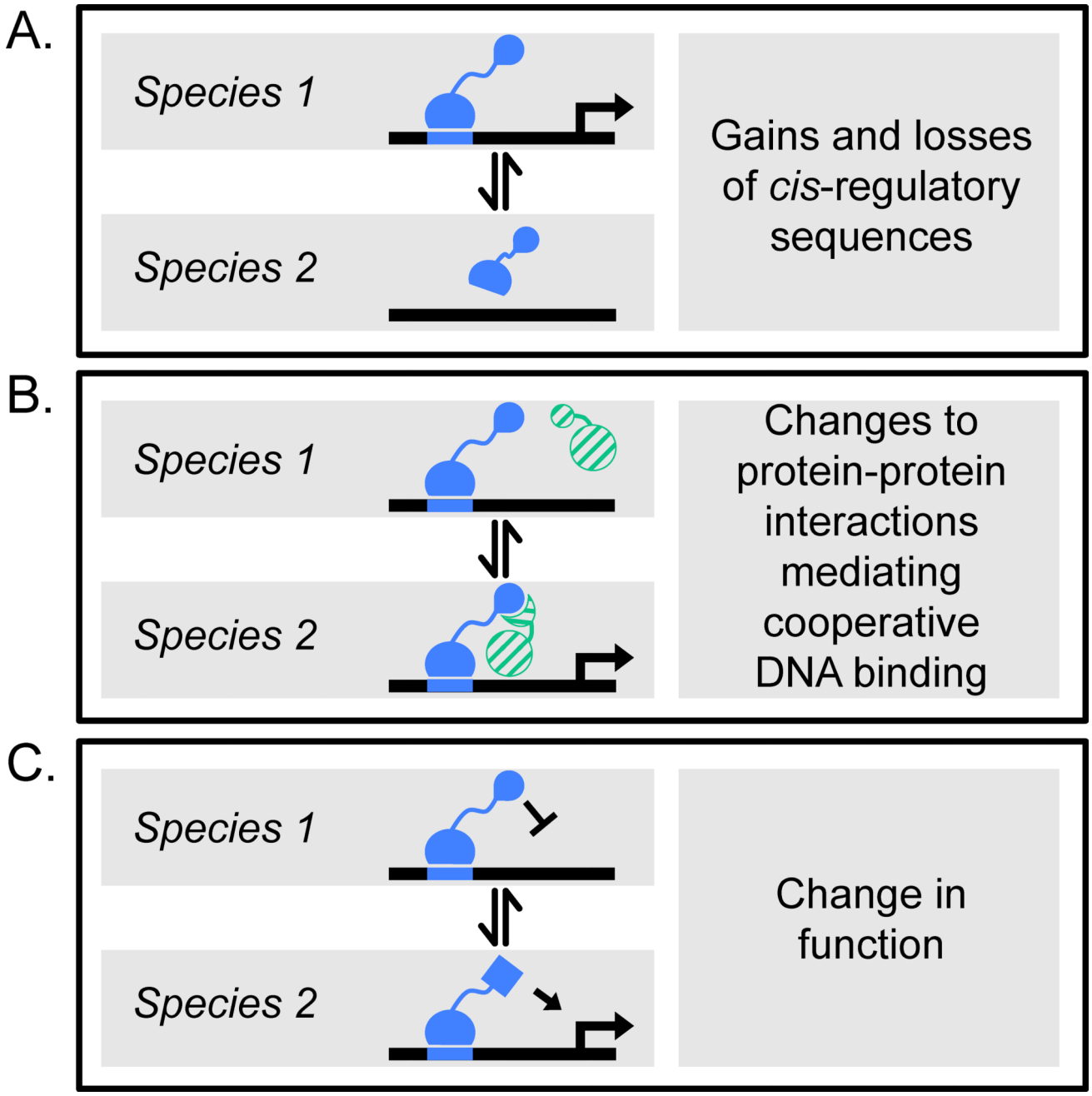

Figure 1.

Three common types of evolutionary changes that can alter transcription circuits:

A. Gains and losses of cis-regulatory sequences by simple mutation. Because cis-regulatory sequences are typically short and can function from multiple positions with respect to a target gene, gains probably occur nearly as frequently as losses.

B. The gain of a favorable protein-protein interaction can occur through a small number of point mutations.

C. Through mutations in its “effector” domain, a transcription regulator can be converted from an activator to a repressor or vice versa.

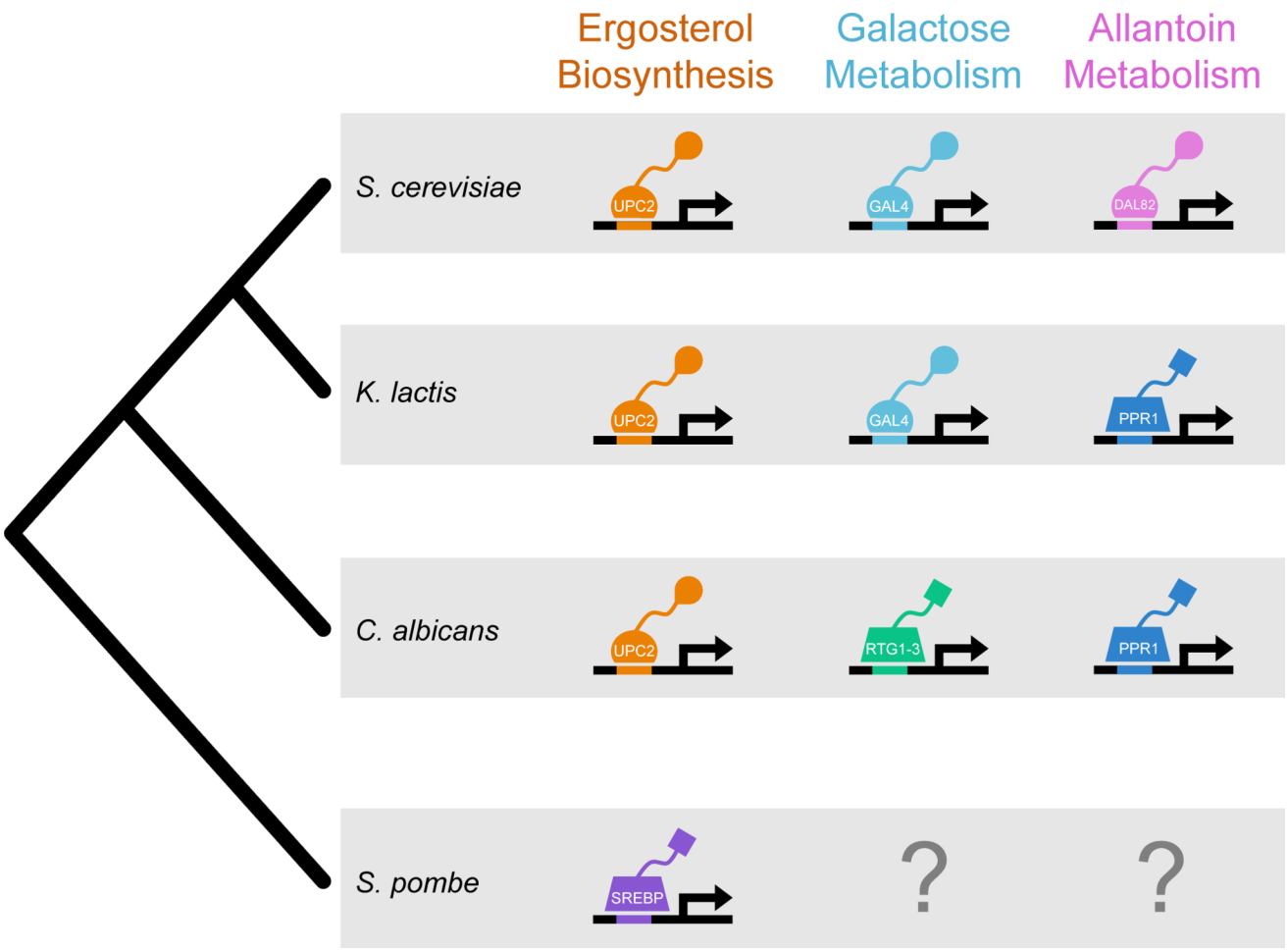

Figure 2.
Three handoffs of sets of metabolic genes from one transcriptional regulator to another occurred during fungal evolution [24–26].

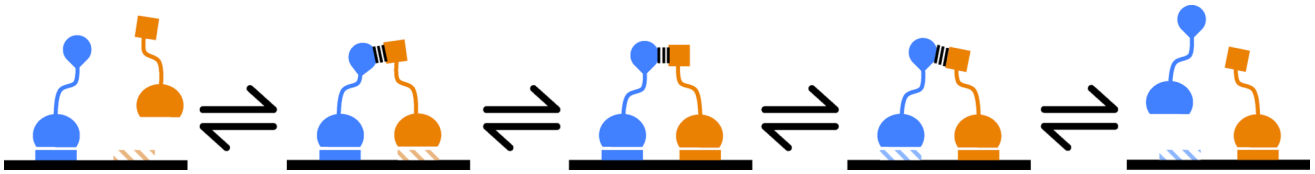

Figure 3.

Circuit movement mediated by cooperative DNA binding. Although only a single target gene is shown, this proposed process, which begins with the evolution of a new protein-protein interaction, could lead to rewiring of a whole set of co-regulated genes. This scenario could also occur in more complex enhancers, where one regulator could substitute for another while other regulators bound to the enhancer remain unchanged. The cis-regulatory sequences indicated with diagonal bars represent low-affinity sequences that are present by chance.