Regulatory motif movement in promoter regions

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Abstract

We are studying how neutral evolution can generate functional sites *de novo*, and how those new sites can replace existing functional regions. We are focusing on transcription factor binding sites in upstream promoter regions of yeast genomes. Promoter regions often contain protein binding sites which are composed of specific sequences of nucleotides. But because promoter regions contain long stretches of poorly conserved bases, neutral evolution can occasionally lead to formation of new, identical binding sites elsewhere within the promoter. These new sites can then take over the function of the original binding site. We call this type of non-local movement of genomic information 'Genomic Tunneling.'

One such event can be observed in the upstream promoter region of the yeast gene YHR078W. Here, an ABF1 binding site moves about 70 bp downstream in *S. mikatae*.

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                    CGTNNNNNRYGAY
Scer        GGCTCCATCAATTCGTATCAAGTGATAATT-AT------CACATAAATTATATAATTGTA
Spar        AACCCTATTAATTCGTAAGCAGTGATATAA-AT-AGAATAACCTAACTTATACAACTGTA
Smik        AACCCTATGAATTCCTAGTAAGCCACCTATTATAGAGATAACCTAAGTAGTATAGTAGTA
Sbay        AGCCCTATACATTCGTACCAAGTGATAAAT-ATTATTAAGACCTAACATTTAAAACAGTT
              * * **  **** **   **  *      **       ** ***    ** *   **

                              CGTNNNNNRYGAY
Scer        AACCT------ATTAATAACCCTAAT-ATCATCCTCATGCCCTA-AGAAATATTCAATAT
Spar        TCCCTTTTAAACCCCCTAATATTACC-ATCTAAGACCTAACTAATATCAA----GGGAAA
Smik        A-CCTATTAAAATTAAAAACGTTAACCATGATGCCCTAACAATATAATGA-----AGGAA
Sbay        ACCCT-----ACCCTAAAATCGGAAC-ATAAAACACAAACCCTATATAAACGTAGAGAAA
              ***            **    *   **      *       * *   *        *
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These events are likely to be preserving function, without necessarily preserving the exact sequence of a promoter. They can be thought of as silent substitutions, much like changing the 3rd codon position typically preserves the amino-acid sequence of a protein. Genomic tunneling events, like the one shown above, are silent mutations in the structure of a promoter region, which preserve function without preserving the sequence at any particular site.

Another class of movements observed are 'local moves.' In a local move, the binding site moves without being recreated from scratch. Instead, neutral evolution takes advantage of symmetries in a binding site to create a new, nearby site. These sites can then take over the function of the original site, replacing it. An example is found in the yeast YJL194W gene, where the near palindromic MBP1 binding site appears on opposite strands in *S. mikatae* and *S. bayanus*. A single point mutation creates the new motif, and a single point mutation annihilated the now redundant original.

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                        ACGCGTNA
                       TNACGCGT
Smik          GAGGAAAACAGACGCGTGAGCC-CTCGCGT
Sbay          AAGGAAAACTCACGCGTGGAAAGCTCGCGT
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Using both analytic and bioinformatic approaches, we show how genomic tunneling and local moves can substantially alter the sequence of a promoter without affecting its function.

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