Activator-repressor based genetic oscillator in the presence of decoy binding sites

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***Abstract*— Genomic decoys are nonfunctional binding sites on DNA, found ubiquitously, where transcription factors (TFs) can bind with high affinities. By modifying the dynamics of TFs, they indirectly participate in regulatory dynamics of genes. Here, we ask how the decoys' presence affects the oscillatory dynamics of genes. Gene oscillations are essential where precise timekeeping of cellular processes is required. To understand the role of decoys on gene oscillations, we study a genetic oscillator based on an activator-repressor motif. We find that the stability of decoy-bound proteins crucially affects the robustness of the oscillations, and observe contrasting behaviors depending on whether decoys bind to activators or repressors.**

I. Introduction

In the genome, there are numerous nonfunctional binding sites where transcription factors bind with high affinities[1]. Although such genomic decoy binding sites are not actively involved in regulation, it has been shown that they alter the dynamics of various gene regulatory circuits [2], [3], [4]. Here we study the role of genomic decoys on the oscillatory dynamics of gene expression, which is not well understood. Gene oscillations are essential for precise timekeeping of cellular processes. Circadian clocks that organisms use to maintain daily activity and segmentation clocks that are essential for robust formation during embryonic development in higher animals, are two well-known examples. Here, in the presence of decoys, we investigate a genetic oscillator based on an activator-repressor motif, a common mechanism for sustained gene oscillations [3], [4], [5].

II. Model

We consider a genetic oscillator model with two components, an activator and a repressor. Sustained oscillations result from a rapid activator-mediated positive feedback in conjunction with a slow repressor-mediated negative feedback[5]. Fig. 1 shows the schematic of the system. The activator promotes the expression of itself and the repressor. The repressor only inhibits the expression of the activator. Both proteins are able to bind to decoy binding sites and become decoy-bound proteins. Additionally, they can unbind, becoming free proteins. The decoy-bound protein can be either stable or degradable. We solve the dynamics numerically, and utilize the linear stability analysis to obtain analytical insights.

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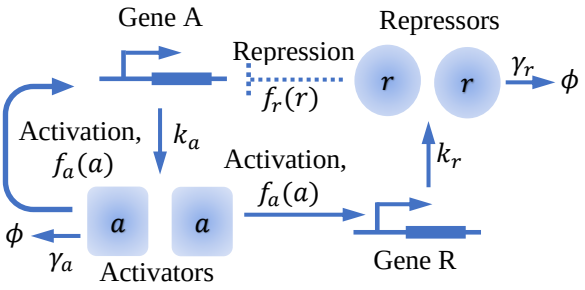

Fig. 1. The schematic of activator-repressor oscillatory system. The positive and negative feedback between the activator and the repressor can generate sustained oscillation.

III. Result and Conclusion

Our result shows that the presence of decoy binding sites slows the gene dynamics whereas the degradation of decoy-bound protein accelerates the dynamics. In the case of a stable decoy-activator complex, we find that activator binding to decoy sites can destroy oscillations by slowing the activator dynamics. In contrast, an unstable decoy-activator complex can expand the oscillatory parameter regime by accelerating the activator dynamics. The opposite pattern is seen for repressor binding to decoys: stable decoy-repressor complexes enhance oscillation, whereas unstable decoy-repressor complexes impinge oscillation.

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