A question of dynamics

In response to different stimuli many transcription factors (TFs) display different activation dynamics that trigger the expression of specific sets of target genes, suggesting that promoters have a way to decode dynamics. In order to understand how mammalian promoters decode TF dynamics we needed a way to generate different TF dynamics at will. For this purpose, we constructed a synthetic TF based on the blue light-responsive nuclear localization signal LINuS previously developed in our lab. This way we could directly manipulate the nuclear localization of the synthetic TF in mammalian cells without affecting other processes. We then generated two different pulsatile alongside sustained TF dynamics and employed live cell microscopy and mathematical modelling to analyse the behaviour of a library of reporter constructs. We found that decoding of TF dynamics occurs only when the coupling between TF binding and transcription pre-initiation complex formation is inefficient and that the ability of a promoter to decode TF dynamics gets amplified by inefficient translation initiation. Using the knowledge acquired, we built a synthetic circuit that allows obtaining two gene expression programs depending solely on TF dynamics. Finally, we translated our findings to two natural TFs: p65 and p53. These results help elucidate how gene expression is regulated in mammalian cells and open up the possibility to build complex synthetic circuits steered by TF dynamics.