Oscillations in the expression of a self-repressed gene: interaction of a transport delay with transcriptional response

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Mathematical models of gene networks often assume that transcription reacts instantaneously to variations in regulatory protein concentrations. However, some experiments have evidenced a slow transcriptional dynamics at time scales comparable to other biochemical processes. It is thus important to understand how trancriptional response can modify the dynamical behavior of gene circuits.

Recently, we have revisited the dynamics of a self-repressed gene where transcription rate is not a function of protein concentration but a dynamical variable converging to the usual equilibrium value over a finite time, playing the role of a delay. To understand the interplay of this delay with nonlinearity in the degradation processes, we considered arbitrary degradation mechanisms for RNA and protein. Remarkably, the oscillation threshold of this model can be computed analytically, and depends only on normalized gene response time and degradation rates. We also found that when gene response time is equal to a characteristic time whose expression can also be computed analytically, oscillations can be induced by degradation mechanisms much less nonlinear than for infinitely fast regulation.

To determine if this behavior is robust, we have studied a model including an additional delay, describing cellular transport or transcription/translation. We considered both the case of an explicit delay and of a delay resulting from an extra reaction step, to understand the influence of the modeling choice. Again, we could find analytical criteria for the appearance of oscillations.

These results allow us not only to characterize quantitatively the interplay of delay and nonlinear degradation, but also to study how two delays interact. In particular, we found that two delays in sequence can be more destabilising than a single delay of equivalent duration, and that a small delay added on top of a large delay can suffice to trigger oscillations.