# Temporal precision of regulated gene expression

Shivam Gupta[1], Julien Varennes[1], Hendrik C. Korswagen[2] and Andrew Mugler[1,*]

**Cells trigger events with high timing precision, but how do they so with inherently noisy molecular components remains unclear. We investigate this question using a first-passage-time approach, for an event triggered by a molecule that crosses an abundance threshold and that is regulated by either an accumulating activator or a diminishing repressor. We find that the optimal strategy arises from a tradeoff between minimizing the extrinsic noise of the regulator and minimizing the intrinsic noise of target molecule itself. Our results explain the low noise of mig-1 gene expression in migrating neuroblast cells during *Caenorhabditis elegans* development, and suggest that mig-1 regulation is dominated by repression for maximal temporal precision.**

***Keywords*** **— First-passage time | Gene regulation | Cell migration.**

## I. Background

Proper timing is crucial for biological processes, including cell division [1], cell differentiation [2], cell migration [3], and embryonic development [4]. These processes are governed by molecular events inside cells, i.e., production, degradation, and interaction of molecules. Molecular events are subject to unavoidable fluctuations, because molecule numbers are small and reactions occur at random times [5]. Cells combat these fluctuations using networks of regulatory interactions among molecular species. This raises the fundamental question of whether there exist regulatory strategies that maximize the temporal precision of molecular events and, in turn, cellular behaviors. A canonical mechanism by which a molecular event triggers a cellular behavior is accumulation to a threshold [2, 6]: molecules are steadily produced by the cell, and once the molecule number crosses a particular threshold, the behavior is initiated. Recent work has investigated the impact of auto-regulation (i.e., feedback) on the temporal precision of threshold crossing [6]. Interestingly, it was found that auto-regulation generically decreases the temporal precision of threshold crossing, meaning that the optimal strategy is a linear increase of the molecule number over time with no auto-regulation [6]. However, in many biological processes, such as the temporal control of neuroblast migration in *Caenorhabditis elegans* [3], the molecular species governing the behavior increases nonlinearly over time. This suggests that other regulatory interactions beyond auto-regulation may play an important role in determining temporal precision. In particular, the impact of activation and repression on temporal precision, where the activator or repressor has its own stochastic dynamics, remains unclear.

## II. Results

Here we investigate the temporal precision of threshold crossing for a molecule that is regulated by either an accumulating activator or a degrading repressor. Using a first-passage-time approach [6] and a combination of computational and analytic methods. We find that the optimal regulatory strategy for either an activator or a repressor corresponds to a non-linear increase in the regulated molecule number over time. We elucidate the physical mechanism behind these optimal strategies, which stems from a tradeoff between reducing the noise of the regulator and reducing the noise of the target molecule. Motivated by data from migrating neuroblast cells in *C. elegans* larvae [3], we also consider the effects of cell division, and find that activation (repression) is optimal if cell division occurs early (late) in the temporal process. Our results are quantitatively consistent with both the temporal precision and nonlinearity of the *mig-1* mRNA dynamics in the macroblasts, and we predict that *mig-1* regulation is dominated by repression for maximal temporal precision.

## III. Conclusion

We demonstrate that regulation increases the timing precision of threshold crossing by a target molecule beyond the precision achievable with constitutive expression alone. Our minimal model is sufficient to explain both the nonlinearity rise in molecules and low degree of noise in dynamics of mig-1 in *C. elegans*.

## References

[1] Bean JM et.al (2006) Coherence and timing of cell cycle start examined at single-cell resolution. Molecular Cell 21(1):3-14.

[2] Carniol K, Eichenberger P, Losick R (2004) A threshold mechanism governing activation of developmental regulatory protein σf in bacillus subtilis. Journal of biological chemistry 279(15):14860-14870.

[3] Mentlink RA et al. (2014) Cell intrinsic modulation of Wnt signaling controls neuroblast migration in C. elegans. Developmental Cells 31(2):188-201.

[4] Meinhardt H (1982) Models of biological pattern formation. (Academic Press Inc).

[5] Van Kampen N (1992) Stochastic processes in physics and chemistry. (Elsevier) Vol. 1.

[6] Ghusinga KR, Dennehy JJ, Singh A (2017) First-passage time approach to controlling noise in timing of cellular events. PNAS 114(4):693-698.

Acknowledgements: This work was funded by HFSP RGP0030/2016.

[1]Department of Physics, Purdue University.
[*]Email: amugler@purdue.edu.
[2]Hubrecht Institute, Netherlands. Email: r.korswagen@hubrecht.eu