Estimated noise-driven phenotypic switching rates depend on cell division rates

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The ability of cells to change their phenotype can allow a cell population to adapt to different environments. For a clonal cell population, phenotypic change can occur in response to environmental cues or due to noisy gene expression events. We asked if we could determine how quickly stochastic cell differentiation occurs for cells in static environments based on stationary distributions of protein concentrations. We found that cells in different states divided at different rates, confounding our attempts to infer stochastic switching rates between phenotypes. After accounting for cell division rates, we could infer stochastic switching rates based on stationary distributions.

***Keywords* — systems biology, escape rate, fitness, autoregulation, phenotype switching**

I. Introduction

The capacity of cells to change their phenotype can significantly affect the overall fitness of a cell population. For a cell population, environmental cues may provide the signals by which cells commit to a phenotype. However, even isogenic cells within a static environment may commit to drastically different phenotypes due to noisy gene expression[1].

Biochemical processes involved in gene expression include (but are not limited to) the production and degradation/dilution of mRNA and protein molecules. The stochastic nature of these processes is commonly assumed to determine the rates of stochastic phenotype switching and the distributions of gene products within a cell population. We sought to solve the reverse problem: to infer the rates at which cells switched stochastically between different phenotypes based on their stationary distributions. We found that stochastic switching rates could be inferred from stationary distributions only after accounting for state-dependent differences in cell division rates.

II. Methods & Results

We observed experimentally stochastic phenotype switching of yeast cells with chromosomally integrated inducible synthetic gene circuits. The gene circuits consisted of the reverse tetracycline Trans-Activator (*rtTA*) activating its own expression and the expression of a fluorescent reporter gene from identical promoters in the presence of the inducer ATc. Cells grown in constant levels of inducer relaxed to stationary bimodal fluorescence distributions. Traditional techniques (neglecting inducer-dependent differences in growth rates) incorrectly predicted the rates of switching between high- and low-expressor subpopulations based on these distributions.

Since we observed a decrease in overall cell population division rates with rtTA expression, we developed a new method to estimate switching rates by incorporating this information. We modeled cell division rates as a decreasing function of ATc activated rtTA and estimated the rate at which cells crossed an arbitrary fluorescence boundary. This net "cellular current" resulted from movements towards decreasing and increasing fluorescence. For cells whose division rates are unaffected by their cell state, the increasing current is equal to the decreasing current. However, when cell division rate changes with the cell state, disequilibrium between the increasing and decreasing currents arises, which was quantified based on our model of cell division rates[2].

We inferred the decreasing currents by assuming that concentrations of stable proteins (such as GFP) decreased due to dilution from cell growth. We calculated the increasing current from the net current arising from cellular fitness differences. Finally, we used these currents to estimate the rate at which cells leave a given state. Tiny differences in cell division times more than one order of magnitude shorter than stochastic switching times masked large differences between stochastic switching rates.

We developed models of growing cell populations incorporating division rates and protein production/dilution rates that recaptured experimental distributions. Intriguingly, these stochastic models implied that bimodal distributions may emerge even for deterministically mono-stable systems.

III. Conclusion

Expression-dependent differences in growth rates can drastically alter estimated rates of stochastic switching.

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