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Control of Gene Expression by a Deep Model in Thousands of Individual Cells

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DESCRIPTION

Differences in gene expression dynamics can generate diverse cell phenotypes in genetically identical populations. These fluctuations can encode signals, provide temporal organization, and diversify communities, providing populations with the flexibility required to respond and adapt to environmental changes and stresses. For example, recent studies have demonstrated that the dynamics of entry into stationary phase in bacteria influence the emergence of antibiotic-tolerant persister cells, fluctuations in transcription factors can underlie bet-hedging strategies, and stochastic transcriptional bursts impact plasticity and drug resistance of cancer cells. These examples highlight the critical role that single-cell gene expression dynamics can play in cell function and survival. In this study, we use deep model predictive control to break the current limitations of throughput and dynamic control for single-cell gene expression. We first develop a high-throughput experimental platform to grow, observe, and ontogenetically stimulate bacteria at the single-cell level. We demonstrate that it is possible to accurately predict gene expression in single cells with deep learning models. We then use these models to control dynamic gene expression in thousands of cells in parallel with a high degree of precision, both at the population level and in single cells. Finally, we apply single cell control to expression of an antibiotic resistance gene, producing high resolution data about the relationships between expression levels, growth rate, and survival. Overall, these findings demonstrate the broad applicability of deep model predictive control for driving single-cell gene expression dynamics. Recently, studies have begun to circumvent this second issue by imposing expression dynamics with single-cell feedback control platforms. With this approach, a gene of interest is made externally inducible, for example by using an ontogenetic system and its expression level is measured every few minutes fluorescence microscopy. These data are processed on-the-fly by a control algorithm that decides whether to activate or repress expression of the gene in order to drive it towards a desired dynamic objective. Then, light is applied to stimulate single cells independently. This process is repeated every few minutes in a real-time feedback loop. Algorithms that have been used to control gene expression dynamics include traditional proportional integral strategies and bespoke designs to test synthetic circuits or cell interactions. However, to date only approaches based on model predictive control have been used to assign time varying dynamics to single cells, resulting in high levels of control accuracy. In this type of controller, several candidate ontogenetic stimulation strategies are considered and a model, often based on ordinary differential equations, is used to predict how the cell will respond to each strategy. Based on these predictions, the stimulation strategy that is expected to bring the expression level closest to a desired objective is applied to the cell. Recently, major milestones in control engineering outside of the field of biology have been achieved by algorithms that couple traditional control theory with machine learning. One such approach is deep model predictive control, which uses deep neural networks to predict system responses to potential control strategies based on training data and without the need for an expert to construct the predictive model. These models have shown impressive accuracy at predicting the behaviour of nonlinear and chaotic systems. They can also incorporate high-dimensional data, and because neural network computations can be massively parallelized, they are orders of magnitude faster than traditional prediction models such as those based on ordinary differential equations.

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CONFLICT OF INTEREST

There are no conflicts of interest.

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