These advances bestow mathematical models with the quantitative insight required to generate testable predictions for further experimental validation.

\section{Quantitative analysis of cell fate decisions}

Quantitative measurements and mathematical models have proven invaluable to studies of GRN behavior in a wide variety of biological systems. Most modeling efforts fall into one of two categories; those that recapitulate molecular mechanism, and those that empirically capture systems-level behavior.

The first class of models strive to parameterize specific biomolecular interactions by fitting a model directly to data. They typically describe the time-evolution of transcripts and proteins using systems of coupled ordinary differential equations (ODEs) reminiscent of those familiar to chemical engineers and ecologists. Despite the illusion of mechanistic detail, these models still deploy a healthy dose of abstraction. None of the commonly used rate represent true elementary reactions, instead opting for empirical representations such as linear degradation and cooperative binding kinetics. Nevertheless, many novel GRN behaviors and functions have been elegantly proposed and tested in this manner \cite{Yu2008,Paulsen2011}.

The second class of models forego molecular detail in favor of a coarse-grained mathematical representation of a particular phenomenon. These approaches provide a powerful means to identify, characterize, and predict behaviors that span a broad variety of biological contexts. Among the common modeling frameworks, control theory has proven particularly fertile for generating and testing hypotheses related to GRN dynamics. Bacterial chemotaxis offers a compelling example in which a history of experimentally-inspired molecular models were supplanted by a simple integral control framework. Analogous strategies have drawn inspiration from various disciplines to further our understanding of threshold response \cite{Melen2005,Graham2010}, signal transduction \cite{Benziger2018}, fold-change detection \cite{Adler2018}, and many other functions of GRNs.

Quantitative analysis has similarly reinvigorated the study of cell fate decisions, with many models having sought to explain how cell fates are reliably resolved from the spatiotemporal signaling cues encoded in GRN activity. Melen et al used a simple system of ODEs to explore how cells generate all-or-none responses to morphogen gradients in the \textit{Drosophila} ventral ectoderm \cite{Melen2005}. They proposed that an ultrasensitive response mechanism dictates the expression of Yan, a transcriptional repressor responsible for impeding cell fate transitions. Graham et al later used a different system of ODEs to argue that Yan plays a different role in the larval eye, instead forming a bi-stable switch by antagonizing a transcriptional activator named Pointed (Pnt) \cite{Graham2010}. Shwartz et al refined the model to include autoregulatory interactions between each the Pnt isoforms that drive the sustained induction of Pnt needed to flip the switch \cite{Shwartz2013}. Pelaez et al then published quantitative measurements of Yan expression that contradict all of these models \cite{Pelaez2015}.

Development is an inherently dynamic process, as each stage of gene expression is responsible for triggering subsequent events in the developmental program. Unsurprisingly, many genes involved in the coordination of cell fate decisions have been shown to be transiently expressed within a given context.

round of cell fate decisions must trigger subsequent events in the developmental program.

and it becoming increasingly obvious that gene expression dynamics play

Mathematical models have also revealed that

As nuanced changes in expression yield abnormal morphologies in vivo, differences in protein levels manifest as differences in phenotype penetrance(Raj et al., 2010). I aim

Raj et al

Oodenarden

Anderson

Yi et al

\section{Negative feedback in developmental GRNs}

Together, these results indicate that tightly coordinated competition between Yan and Pnt lies at the heart of neuronal fate commitment. These observations are consistent with the notion that Yan and Pnt compete for occupancy of shared binding sites in the promoter region of downstream effectors of neuronal differentiation(Gabay et al., 1996; O’Neill et al., 1994). Consequently, altering the expression dynamics of either protein is expected to increase the frequency of erroneous fate commitment, and subsequently increase the likelihood of a roughened eye phenotype.