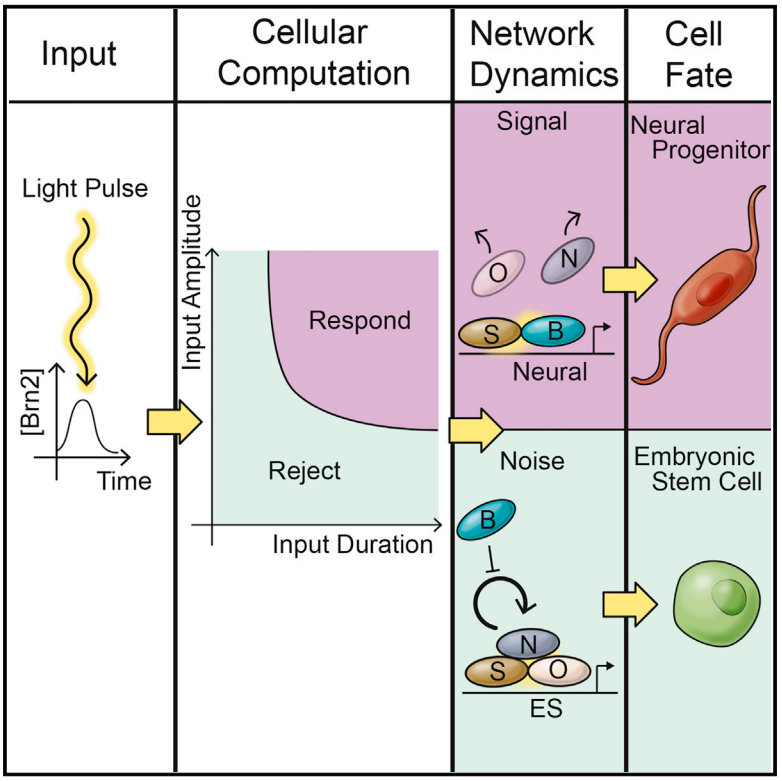
Article

Cell Systems

Transcription Factor Competition Allows Embryonic Stem Cells to Distinguish Authentic Signals from Noise

Graphical Abstract



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In Brief

By controlling the neural differentiation of embryonic stem cells optogenetically, Sokolik et al. identify a network-level mechanism that allows the embryonic stem cell to distinguish developmental signals from background gene expression noise.

Highlights

- Optical induction of Brn2 drives neural differentiation in embryonic stem cells
- The pluripotency network applies magnitude and duration thresholds to Brn2 inputs
- Nanog half-life determines minimum Brn2 input duration required to designate the input as "signal"
- Mathematical model predicts response of ESC to complex, time varying inputs

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Transcription Factor Competition Allows Embryonic Stem Cells to Distinguish Authentic Signals from Noise

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SUMMARY

Stem cells occupy variable environments where they must distinguish stochastic fluctuations from developmental cues. Here, we use optogenetics to investigate how the pluripotency network in embryonic stem cells (ESCs) achieves a robust response to differentiation cues but not to gene expression fluctuations. We engineered mouse ESCs to allow quantitative control over the endogenous mechanism of neural differentiation through a light-inducible Brn2 transgene and monitored differentiation status through a genome-integrated Nanog-GFP reporter. By exposing cells to pulses of Brn2, we find that the pluripotency network rejects Brn2 inputs that are below specific magnitude or duration thresholds, but allows rapid differentiation when both thresholds are satisfied. The filtering properties of the network arise through its positive feedback architecture and the intrinsic half-life of Nanog, which determines the duration threshold in the network. Together our results suggest that the dynamic properties of positive feedback networks might determine how inputs are classified as signal or noise by stem cells.

INTRODUCTION

All cells experience fluctuations in the concentrations of internal regulatory molecules and external molecular cues (Kumar et al., 2014a; Ohnishi et al., 2014; Raj et al., 2006; Raj and van Oudenaarden, 2008). In undifferentiated stem cells, internal gene expression fluctuations are particularly strong due to a permissive chromatin configuration that allows stochastic, unregulated bursts of transcription to occur broadly across the genome. Transcriptional bursting leads to the premature expression of differentiation-promoting genes in stem cells even prior to differentiation (Chang et al., 2008; Hu et al., 1997; Kumar et al., 2014b; Weishaupt et. al 2010). Embryonic stem cells, as an example, stochastically express a number of lineage-specific transcription factors including core regulators of neural differentiation in the pluripotent state (Kumar et al., 2014b). Stem cells, therefore, confront a critical challenge: cells must simultaneously avoid responding to these stochastic fluctuations while retaining a capacity to differentiate in response to appropriate developmental cues (Figure 1A) (Hornung and Barkai, 2008).

In control theory and engineering, the problem of distinguishing fluctuations (noise) from input commands (signal) is typically solved by feedback control (Bechhoefer, 2005; Muzzey et al., 2009; Yi et al., 2000). The regulatory principles and network architectures that facilitate this process in stem cells are not well understood (Figure 1A). Microorganisms typically employ autoregulatory negative-feedback loops to stabilize transcriptional regulatory networks against the stochastic activation of key regulatory molecules (Becskei and Serrano, 2000; Dublanche et al., 2006; Hornung and Barkai, 2008; Prill et al., 2005; Simpson et al., 2003; Thieffry et al., 1998; Yi et al., 2000). However, metazoans present a quandary: instead of negative feedback, stem cell regulatory networks are dominated by positive feedback regulation (Fong and Tapscott, 2013; Hnisz et al., 2013; Jaenisch and Young, 2008; Kueh et al., 2013; Niwa, 2007; Whyte et al., 2013). It is not clear how positive feedback networks allow stem cells to reject fluctuations but also differentiate in response to developmental cues. Rather, in stem cell biology, discussions of noise tolerance have focused on models of cell fate regulation through "Waddington landscapes" (Waddington, 1957) where abstract energy barriers between cell types prevent transitions due to stochastic fluctuations (Ferrell, 2012; François and Siggia, 2012; Pujadas and Feinberg, 2012). Despite the intuitive appeal of landscape models of cell fate regulation, they have not been validated, and it is not clear how cell fate landscapes are implemented by underlying protein regulatory networks (Ferrell, 2012; François and Siggia, 2012).

Embryonic stem (ES) cells provide a well-characterized model system for quantitative analysis of stem cell differentiation and cell fate regulation. In the pluripotent state, a group of transcription factors including Oct4, Sox2, and Nanog form a complex that blocks the expression of differentiation-specific genes