Stochastic and Deterministic Decision in Cell Fate

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Advanced article

Article Contents

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From bacteria to mammals, individual cells from an isogenic population are able to assume roles resulting in phenotypic heterogeneity. The mechanisms used to make these cell fate decisions range from highly deterministic to essentially random. This wide range of behaviour springs from the interplay of intracellular molecular kinetics, the topologies of underlying gene regulator networks, epigenetic control mechanisms and cell–environment interactions. Cells utilise these factors to implement differentiation strategies such as developmental rigidity, which ensures the development of key structures in multicellular organisms, and bet hedging, the introduction of nongenetic variability to promote population fitness. Because decision-making genes in natural systems are integrated with myriad other pathways, they can be difficult to study on their own. Synthetic biology offers a means to study cell differentiation *in vivo* in a manner separated from normal cellular functions.

Introduction

The many processes that comprise gene regulation – transcription, translation, protein and messenger ribonucleic acid (mRNA) degradation, etc. – are inherently stochastic (Kaern *et al*., 2005). This is because, at the molecular level, all cellular decisions are the result of random molecular interactions. These stochastic interactions can give rise to heterogeneity within an otherwise homogenous population. In mice, which have roughly 1000 different olfactory receptors, stochastic differentiation provides a simple mechanism for individual sensory neurons to randomly express a single receptor (Mombaerts, 2004). Stochastic differentiation can also offer functional benefits for a population. When in starvation conditions, *Bacillus subtilis* exhibits a bet-hedging strategy in which members choose randomly between states of sporulation, diauxic growth and lysis (Suel *et al*., 2006; Veening *et al*., 2008). Other stochastic decisions provide a simple method of assigning labour division between associated cells, such as in the random differentiation of photoreceptors to different colour-sensitive variants in *Drosophila* (Wernet *et al*., 2006).

Despite this randomness, however, cell fate determination is often not a stochastic process. Rather, many fate decisions proceed in a highly deterministic manner, often in response to cues from the environment or neighbouring cells. The transition of a fertilised oocyte into a blastocyst demonstrates how precisely cell differentiation can be guided through multiple stages of development (Clift and Schuh, 2013). Similar deterministic developmental processes have been documented in early growth and body segmentation of *Drosophila melanogaster* due to transcription factor gradients (Lee and Orr-Weaver, 2003).

Noise is a fact of life, arising from sources such as cell–cell signalling, intracellular molecular dynamics, and chromatin modification and packaging (Blake *et al*., 2003; Elowitz, 2002). Organisms have adapted to utilise or counteract this noisy expression in a context-dependent manner. Understanding the mechanisms by which they achieve this is of fundamental importance in understanding how cells make decisions. By understanding both the deterministic and stochastic elements of cell decision making, we can open up new venues in cell reprogramming and therapeutics with which scientists and engineers are only beginning to experiment.

Cell Fate Determination

Cellular adaptability and role assignment has allowed life to thrive, in both single cellular and multicellular states. Central to this adaptability is the ability of individual cells to differentiate into specialised variants that complement each other. For example, some cells in a *B. subtilis* population may transition to a state of competency, in which they uptake foreign deoxyribonucleic acid (DNA),

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whereas others retain a tepid relationship with non-native DNA (Maamar *et al*., 2007), increasing diversity to improve overall population fitness. Mating yeast adopt a mating type on cell division, determining viable mating partners and promoting evolutionary diversification (Peisajovich *et al*., 2010). In multicellular organisms, stem cells differentiate into specific lineages unique to the multitude of tissues and organs found throughout the body (Enver *et al*., 2009). Whether as a means to promote population fitness or as a way to form the various parts of a larger organism, cells adopt roles, resulting in phenotypic changes, which cannot be easily reversed (Balazsi *et al*., 2011).

Through the process of differentiation, cells arrive at their fate: a quasi-equilibrium state of gene expression characterised by functional and phenotypic steady states. Cell fate is a complex phenomenon involving the balance of many intracellular interactions (Macarthur *et al*., 2009). One of the primary defining qualities of a cell fate is its invariance to noise, to the extent that many cell fate decisions are considered irreversible (Vierbuchen *et al*., 2010). Although the advent of induced pluripotent stem cells has challenged the absolute irreversibility of differentiated cell fates, cell fate decisions can still be considered invariable to internal noise (Yamanaka, 2009). Without an external force, a cell that has already differentiated to a given fate will not spontaneously dedifferentiate to a previous state.

There are two prevailing analogies for cell fate determination. The first is that of the epigenetic landscape, in which a marble rolls down a hill containing a number of separate valleys (Waddington, 1957). As the marble travels further down the hill, the valleys bifurcate into more and more specific channels. The valleys represent potential cell fates, their walls representing the forces at work that maintain a chosen fate. Cells choose fates based on the layout of this landscape and through random variations that develop along the journey towards a final fate. The second analogy for fate selection is that of a dynamic attractor in high-dimensional gene expression space (Kauffman, 1969). Somewhat less intuitive than Waddington's landscape, this visualisation emphasises the complexity of gene interactions. The state of a genetic system is represented as its location within a multidimensional gene expression space: typically with more than 3 dimensions; hence, nonsimplified visualisation is difficult or impossible. Certain regions in the space are more stable than others, acting as attractors towards which the system will ultimately trend. These stable attractors represent distinct phenotypes (Huang *et al*., 2005). Both analogies have their merits. The epigenetic landscape is easy to understand and is representative of how cells often transition through several distinct phenotypes before ultimately arriving at a terminal fate. The multidimensional genetic space representation more fully captures the complexity of intracellular dynamics and gets beyond phenotypic descriptions, although its increased complexity makes it more difficult to visualise.

Deterministic Cell Fate Decisions

We know through the observation of natural systems that cells are capable of deterministic differentiation. Developmental biology is particularly rife with examples. Perhaps one of the starkest examples is the embryonic development of *Caenorhabditis elegans* (Sulston *et al*., 1983). The development of *C. elegans* has been thoroughly traced from zygote to larva, from a single cell to exactly 671 cells, with such a rigid developmental pattern as for Sulston *et al*. to declare the process 'essentially invariant'. The process is not only invariant in terms of cell count at various stages but also shows remarkable time resolution. For example, under similar experimental conditions, one can expect to see exactly 28 cells and the beginning of gastrulation 100 min after first cleavage. A large number of these cells, 111 or 113 depending on the sex of the nematode, are programmed to ultimately die in the development process, before the nematode's hatching at 800 min after first cleavage. **See also**: *Caenorhabditis elegans* Embryogenesis: Genetic Analysis of Cell Specification

On an intuitive level, deterministic embryonic development makes sense. For a single fertilised egg to reliably divide into an entire multicellular organism, early progenitor cells for the various tissues would need to be placed exactly, both spatially and temporally. It is no surprise then that this sort of strictly deterministic cell fate assignment is commonly observed throughout the biological world. Reduction in variability during development, a process often referred to as canalisation or phenotypic stability, has been observed in blastocyst formation in *D. melanogaster* (Manu *et al*., 2009), the zebra fish dermal skeleton development (DeLaurier *et al*., 2014) and early human embryogenesis (Clift and Schuh, 2013). This lack of variation, like all cellular processes, is due to gene expression regulation. **See also**: Autonomous Cell Fate Specification: Overview

Gene expression and its regulation are inherently stochastic processes (Kaern *et al*., 2005). Despite this, cells have evolved mechanisms to reduce or ignore this noise in order to act in a deterministic fashion. Gene regulatory networks (GRNs) are the key to this behaviour (Davidson and Levine, 2008). GRNs are, both topologically and functionally, composed of small network motifs (Alon, 2007), and several common motifs function to regulate the noise of their output signal. Negative feedback loops have been shown to produce tightly controlled gene expression compared with similar networks without feedback (Becskel and Serrano, 2000). Coherent feedforward loops, in which an input signal mediates an output through two pathways, one direct and one indirect, have similar noise-reducing qualities (Ghosh *et al*., 2005). Examples of these motifs are shown in **Figure 1**. Although noise is never completely eliminated, due to the nature of biochemical reactions, its effect can be reduced enough for the GRN to behave deterministically.

Mathematically, deterministic cell fate assignment can be described by a system of ordinary differential equations

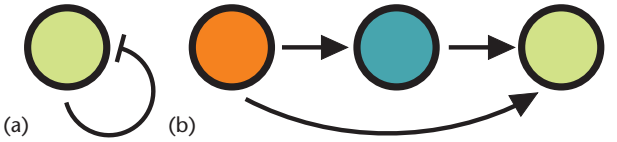

Figure 1 Several genetic motifs have been shown to reduce expression noise. Shown here are two of the most common noise buffering motifs. (a) Negative feedback loop (NFBL). (b) Coherent type-1 feedforward loop (C1FFL).

(ODEs) without loss of descriptive power regarding cell-switching dynamics. ODE models can offer insights into how changing concentrations of important molecules affect changes within a biological system. Populations that exhibit hysteresis are those that can occupy one of two or more steady expression states. Which state they choose is dependent on their starting conditions and the dynamics of other interrelated protein populations. Hysteresis, illustrated in **Figure 2**, is the foundation of cell decision making, because it allows a single cell or population to have more than one mode in which it operates. Because all cells of an organism are almost genetically identical – they contain exactly the same DNA – the ability to maintain multiple different stable gene expression states is necessary (Gardner *et al*., 2000).

A network typically only exhibits hysteresis within a range of some input or combination of inputs. Inputs are commonly proteins made by other components in the GRN, signalling ligands from other cells, or small molecules dictated by environmental conditions. Shifting these conditions can alter the points at which a GRN will switch between possible steady states, and it can alter the shape of the bifurcation curve that describes when and how robustly a system can maintain a given state (Chen and Arkin, 2012). Because state switching is such a dynamic process, affected by so many different elements, maintaining a differentiated state is as important as the initial differentiation process. In addition to GRN topologies that naturally reduce the noise of their output, cells have a number of other tools at their disposal to reduce the possibility of undesirable state transitions.

Because cells have no control over the levels of extrinsic noise, many receptors on the plasma membrane have developed to ignore short fluctuations in signalling molecules, responding instead to more prolonged signals (Ladbury and Arold, 2012). This is seen in the multimerisation of receptors, which reduce the chance of activation of a signalling pathway by a single errant ligand (Ghim and Almaas, 2008). Other receptors, including many receptor tyrosine kinases, include other thresholding measures, such as endogenous phosphatase activity, which deactivates the receptor in the absence of a strong external signal (Östman and Böhmer, 2001). These mechanisms work in parallel to reduce the amount of noise from an external signal that is transmitted into the cell. **See also**: Transmembrane Signalling

A final powerful tool that eukaryotic cells have at their disposal is the ability to modulate – to the point of absolute

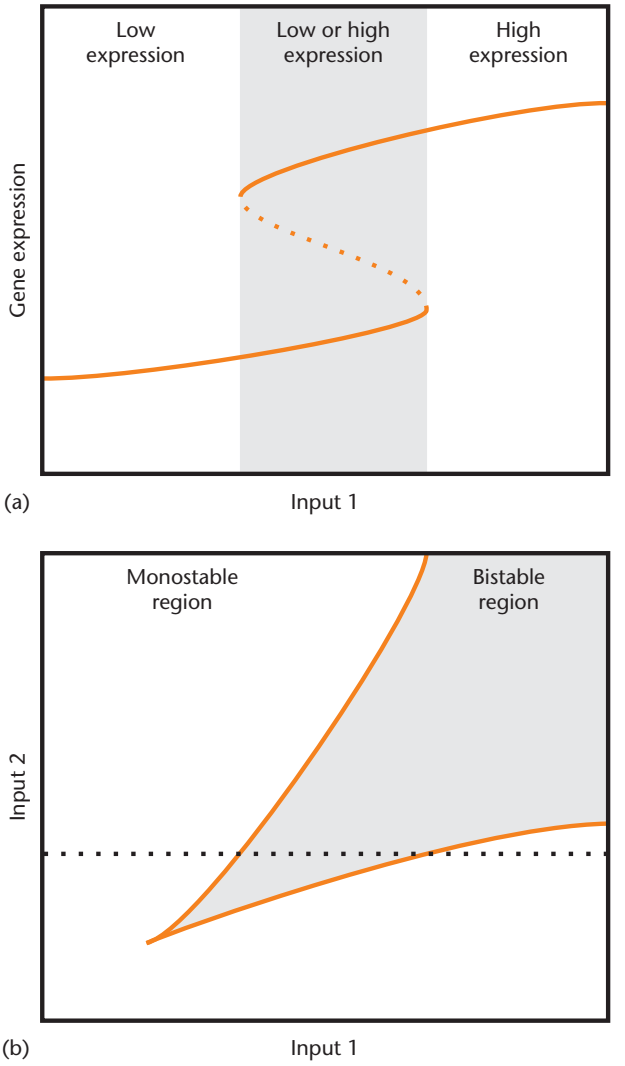

Figure 2 Genetic decision making is often characterised by hysteresis, where gene expression can be either high or low depending on the concentration of some input: usually another protein population or a small molecule species in the environment. (a) Varying the concentration of Input 1 reveals a region in which gene expression has two possible steady states. In a noise-free system, this choice depends on the system's initial conditions. (b) If the bistable region is dependent on 2 inputs, their effects on the bistable region's shape can be plotted as a stability map. The dotted line indicates the concentration of Input 2 that would produce plot (a).

repression – gene activity through histone binding and chromatin organisation (Meshorer and Misteli, 2006). Histones can impede mRNA transcription on their own through steric hindrance, and when coiled densely together into the various chromatin structures they can make genes completely inaccessible to transcription machinery, essentially turning them off. This type of epigenetic control of gene activity is clearly evident on a tissue level, and it is responsible for much of the striking array of genetic expression levels observed throughout multicellular organisms (Akashi *et al*., 2003). **See also**: Tissue-specific Locus Control: Structure and Function

Stochastic Cell Fate Decisions

Given that cells often employ genetic topologies to reduce the noise in their outputs, it is perhaps unsurprising that other networks and developmental pathways have evolved to utilise the inherently noisy nature of biological networks (Balazsi *et al*., 2011). Many organisms use stochastic processes to make long-reaching decisions. Many bacterial species exhibit the phenomenon of persistence, in which a small subset of a population survives antibiotic treatment by entering a dormant state (Allison *et al*., 2011). It is also suggested that gene expression noise may increase cell–cell variability and help the cells hedge the environmental risk to increase their survival possibility (Bennett *et al*., 2008). Stochastic fluctuations in the mouse blastocyst are reinforced, ultimately leading to distinct cell lineages (Ohnishi *et al*., 2014), and the differentiation of haematopoietic stem cells into the myeloid or lymphoid pathways is driven by stochastic gene expression (Miyamoto *et al*., 2002).

There are several primary contributors to stochastic gene expression. In a broad sense, gene expression is governed by two categories of noise: intrinsic and extrinsic (Elowitz, 2002). Extrinsic noise is the result of fluctuations in the cellular environment over which a cell has no direct control, although the intracellular response to a noisy input can still be mediated, as discussed in the previous section. Alternatively, intrinsic noise is the result of biochemical interactions within an individual cell. Key interactions include those of transcription factors (TFs), which bind to the promoter region upstream of a gene to modulate its expression, and the dynamics of mRNA transcripts, which contain the message for a cell to create new proteins. **See also**: Transcription Activation in Eukaryotic Cells

On an intrinsic level, it is important to understand cells and the various structures inside them as 3-dimensionally distributed spaces. The majority of gene regulation within a single cell is carried out by TFs (Rosenfeld *et al*., 2005). The active state – monomer, dimer, tetramer, etc. – of a given TF can strongly influence its noise kinetics by making DNA interactions more or less specific. Additionally, TFs, being proteins, are made in the cell's cytoplasm and must be imported into the nucleus for eukaryotic cells in order to interact with DNA. Translocation of transcription factors across the nuclear membrane can also a source of noise (Cai *et al*., 2008). Many genes are present in only a single copy. The probability of any single transcription factor finding and interacting with that gene's promoter is very low. Given that many transcription factors are present only in low concentration, a system with noisy expression is created. **See also**: Gene Duplication: Evolution; Transcriptional Gene Regulation in Eukaryotes

Once the necessary transcription factors have found the genes that they modulate, binding dynamics and the recruitment of the RNA polymerase introduce another source of noise (Singh *et al*., 2012). Transcriptional activity – whether the RNA polymerase complex is assembled, attempting to start making an RNA transcript, paused in the middle of elongation, or terminating transcription – is highly variable (Hammer *et al*., 1999). This leads directly to fluctuations in mRNA concentrations, which are further randomised by fluctuating decay rates. **See also**: Transcription Activation in Eukaryotic Cells

Finally, there is a growing body of work that there may be epigenetic sources of noise within cells. Variation in histone methylation across several cancer types is one distinguishing factor of cancerous cells versus normal tissue and most likely plays a role in the vast heterogeneity seen in cancer populations (Hansen *et al*., 2011). Similar epigenetic modifications, although within much more limited areas of the genome, have also been implicated in epithelial to mesenchymal transition: an important cell reprogramming process in development and wound repair (McDonald *et al*., 2011). Although not yet widely accepted as a definite cause of random cell fate assignment, this field is bound to grow and offer new insights in cellular decision making in the future. **See also**: Chromatin Remodelling and Histone Modification in Transcription Regulation; Nucleosomes: Structure and Function

Despite the stochasticity of gene expression, pathways dictating stochastic differentiation are still tightly regulated. Expression is not completely random; instead, cells are allowed to randomly choose between a number of fates in a weighted manner. These systems, when viewed on a population level, typically exhibit consistent distributions. For example, although the colour-sensitive photoreceptors in the eye of *Drosophila* are randomly assigned to one of two variants, under natural conditions there is consistently a 30%/70% distribution between them (Wernet *et al*., 2006). This weighted distribution is best represented by a cell's potential landscape, a concept that has emerged as an iteration of Waddington's epigenetic landscape (Wang *et al*., 2010). At its most basic level, the potential landscape is represented as a 2-dimensional curve, with local minima representing stable expression states, similar to that shown in **Figure 3**. In this model, a gene's expression is akin to a ball rolling along this landscape. It is driven both by a deterministic force, like gravity, which draws it towards the nearest local minimum, and stochastic fluctuations, which bat it randomly from side to side. The peaks between the landscape's valleys buffer against random switching between valleys, but they do not prevent it entirely. In the case of stochastic fate assignment, the heights of the peaks between valleys determine the probability of choosing one fate over another.

This model can be scaled up to 3 or more dimensions, each dimension representing the activity level of another gene within the GRN. Because all fate decisions are typically influenced by changes in multiple genes' expressions, this model has become more and more popular. Essentially, a high-dimensional version of this model is the dynamic attractor model mentioned previously (Kauffman, 1969).

Once a cell has differentiated stochastically, maintenance of the chosen fate proceeds through the same mechanisms as if it had differentiated deterministically. Noise reduction strategies – GRN motifs, protein

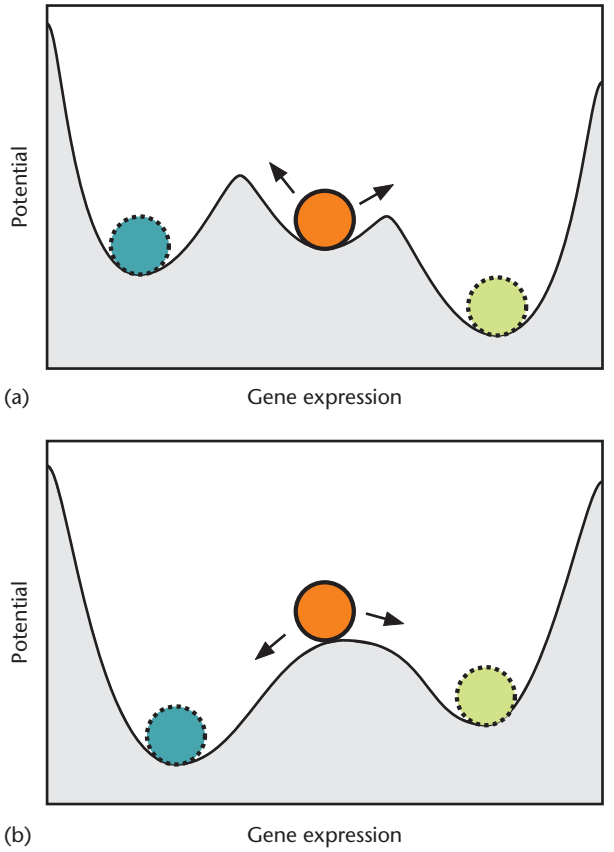

Figure 3 Cell fate determination and stability can be thought of as a potential landscape. (a) In a noiseless system, the orange ball will remain in the central valley. As noise is added, the ball's motion may overcome the peaks to either side of it, allowing it to differentiate into either the teal or green states. Because there is a lower potential barrier to the right, the ball is more likely to jump to the green state. (b) The other means of differentiation is in changing the landscape itself. If the central well is removed, in the absence of noise the ball will roll to the left. Adding a small amount of noise allows the ball to occasionally be pushed right. This makes differentiation in both directions possible, although a higher incidence of the ball settling in the teal state is expected.

multimerisation and epigenetic control – remain as important in a system that chooses a fate stochastically as in one that evolves deterministically.

Synthetic Biology Approaches

Cell fate determination of any kind is a complex process that poses unique obstacles for researchers. The interrelatedness of genetic systems is one of the most confounding barriers, as changes in one gene's expression can induce systemic changes. Altering cell fates in existing systems tends to have high incidence of cell death (Yamanaka, 2009). Using a synthetic biology approach, genetic expression patterns of decision-making networks can be studied *in vivo* while reducing the studied network's interaction with other cellular functions. The rational design and integration of non-native genetic machinery into cells offers the potential to observe the behaviour of small genetic motifs (Austin *et al*., 2006), quantify the noise dynamics of individual network components (Blake *et al*., 2006) and craft GRNs that determine cell fate (Chen and Arkin, 2012), utilising components that act orthogonally to most other cellular machinery.

Using fluorescent reporters, cell fate determination can be simulated without interrupting important cellular processes. Behaviours of numerous similar genetic components can be analysed both in individual expression and in how their expression influences the overall activity of a larger network (Ellis *et al*., 2009). Starting from individual components, behaviours of small motifs can be thoroughly characterised and used to create more and more complex topologies (Guido *et al*., 2006). This 'bottom-up' approach to genetic network construction, paired with synthetic biology's emphasis on mathematical modelling, offers unparalleled insight into gene regulation and cell fate determination from multiple perspectives.

The power of this approach is demonstrated in the construction of a stochastic and irreversible cell fate determining GRN in *Saccharomyces cerevisiae* (Wu *et al*., 2013). The topology created is that of mutual inhibition between two genes. From a neutral state, the system will settle into a state of either green or red fluorescence, but not both. The probability of differentiating to one state or the other can be modulated by altering the cells' environment with inducers specific to each regulatory gene, and the accompanying mathematical model accurately captures the shifting potential landscape caused by these environmental changes. In addition to demonstrating and mathematically explaining protein dynamics, this construct illustrates ways in which synthetic networks might be integrated into natural systems in the future. Through exploiting the highly regulated Gal1 promoter, the researchers were able to obtain initial conditions that would have been difficult to produce with a construct that did not interact with the native genetic architecture. This is a clear illustration of how synthetic biology could be used to interface novel circuits with existing GRNs to robustly produce a desired behaviour.

Our understanding of the complex processes involved in cell fate decisions is constantly expanding. With its combination of molecular genetics and mathematical modelling, synthetic biology has begun to plumb the depths of this topic, offering insight into both how decisions are made and how cell fates can be directed artificially. As more knowledge is gained on the function of individual components and network motifs, the creation of larger, more intricately controlled systems will become possible. Understanding these regulatory networks will open up new therapeutic venues, with applications throughout medical science.

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