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REVIEW

Stochasticity and determinism in cell fate decisions

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ABSTRACT

During development, cells need to make decisions about their fate in order to ensure that the correct numbers and types of cells are established at the correct time and place in the embryo. Such cell fate decisions are often classified as deterministic or stochastic. However, although these terms are clearly defined in a mathematical sense, they are sometimes used ambiguously in biological contexts. Here, we provide some suggestions on how to clarify the definitions and usage of the terms stochastic and deterministic in biological experiments. We discuss the frameworks within which such clear definitions make sense and highlight when certain ambiguity prevails. As an example, we examine how these terms are used in studies of neuronal cell fate decisions and point out areas in which definitions and interpretations have changed and matured over time. We hope that this Review will provide some clarification and inspire discussion on the use of terminology in relation to fate decisions.

KEY WORDS: Central nervous system, Fate decisions, Stochasticity

Introduction

In the biological literature, developmental processes are frequently classified as deterministic or stochastic. This classification is often based on the reproducibility of an outcome of a biological experiment. For example, if an experiment yields similar results each time it is repeated, it may be considered to be deterministic. By contrast, if the system responds differently and unpredictably each time an experiment is performed, it is often referred to as stochastic. For example, in the context of cell fate decisions, if a progenitor gives rise to the same cell type at a specific developmental stage, these fate decisions are often regarded as deterministic. However, the physical and chemical events that underlie a fate decision are evidently affected by fluctuations, which need to be overcome to achieve reliable outcomes. Conversely, fate decisions may be considered to be stochastic when no obvious pattern of outcomes is observed. In some cases, patterns may well exist but lie beyond the level of resolution of a specific experiment. In other cases, stochasticity may be used actively by a biological system to generate diversity across outcomes. Thus, the question arises as to how to draw the boundary between stochastic and deterministic behavior, and to what extent such a distinction can be inferred from limited experimental data. Clarification of these concepts and their limitations is important to streamline our terminology and the way we draw conclusions from experimental data.

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In this Review, we address these issues. We first provide a mathematical definition of the term stochasticity (and related terminology) and discuss the potential origins of stochasticity in cellular and developmental systems. We also elaborate on how the depth at which we resolve a biological phenomenon can influence the conclusions drawn. In light of these considerations, we then review and interpret several recent findings relating to cell fate decisions during central nervous system (CNS) development.

A mathematical notion of stochasticity

Consider a hypothetical experiment E with the outcome X. The outcome X could, for example, be the number of cells of a certain type that are quantified at a particular developmental stage under defined experimental conditions. If the underlying system is stochastic, X can take different values from a certain set, which in the field of probability theory is referred to as 'event space'. In the cell counting experiment above, the event space could be the set of positive integer numbers. The particular outcome the system attains is given by chance and thus is unknown *a priori*. Formally, X can be described as a 'random variable', which assigns a number to each element in the event space. A random or stochastic process is a sequence of random variables that can be used to describe time-dependent stochastic phenomena. In mathematics, the terms 'random' and 'stochastic' are often used interchangeably.

Random variables and processes provide a useful means to describe biological phenomena with uncertain outcome. The latter can be summarized in terms of a probability distribution function (PDF). A PDF assigns a probability $P(X)$ to each possible value of X, which reflects how often this outcome occurs when an experiment is repeated over (infinitely) many times. Importantly, stochastic systems are not necessarily entirely unpredictable. For example, a PDF allows the prediction – at least in statistical terms – of which outcomes are more likely to occur than others. Casinos heavily rely on this fact: although individual games are decided by chance, the odds are such that gamblers will almost certainly lose in the long term. The degree of randomness of a system's outcome is captured by the shape of the PDF. If the probability distribution concentrates on one or just a few outcomes, the system can be predicted more reliably than in a situation where all outcomes have the same probability (Fig. 1A). Thus, stochastic systems can range from being entirely unpredictable to being highly reproducible and predictable. By contrast, a deterministic system can be thought of as the limiting case in which a single outcome occurs with a probability of one, whereas all other outcomes have zero probability. For detailed introductions into probability theory and stochastic processes, the reader may refer to Feller (1991) and Van Kampen (2007).

Hidden variables and apparent stochasticity

In practical situations, variations in an experimental outcome generally cannot be attested to a single stochastic event or process, but rather emerge from a conglomeration of (possibly unknown) factors that contribute to the observed outcome. Cell fate choices,

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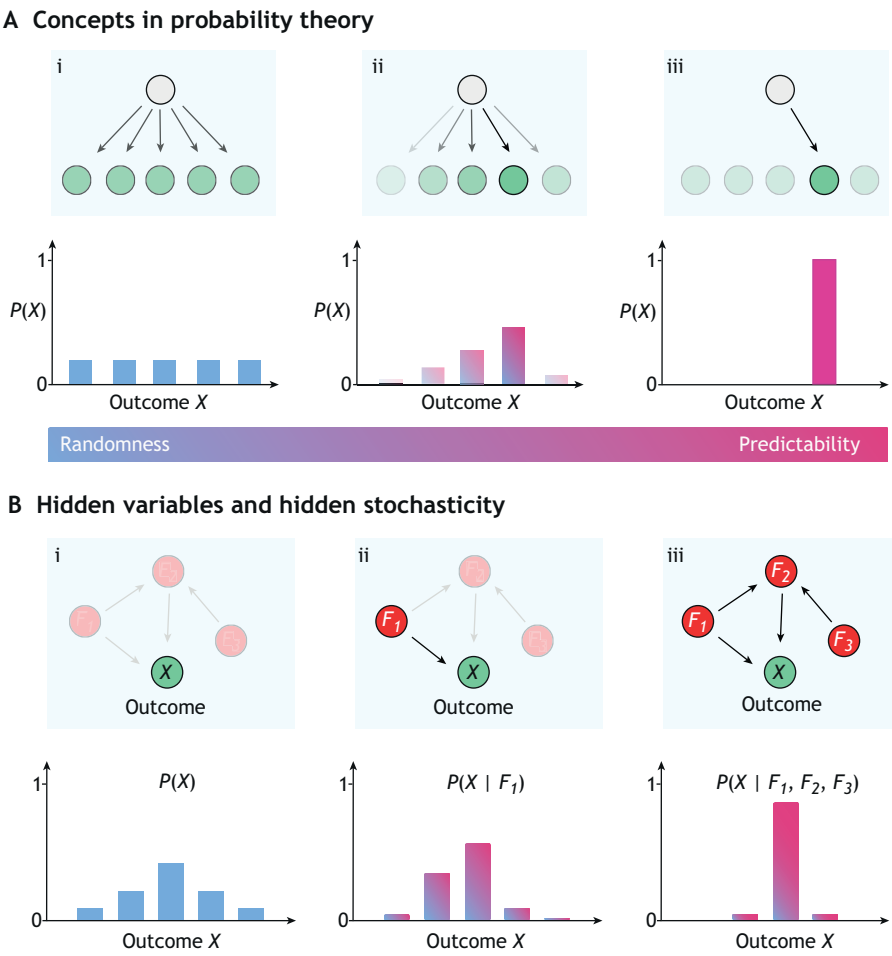

Fig. 1. Concepts in probability theory. (A) Schematics illustrating randomness and predictability of experimental outcomes. Outcomes X of an experiment E can range from entirely random (i) to completely predictable (iii), as captured by the shape of the respective PDF. (B) Schematics illustrating hidden variables and apparent stochasticity. The outcome X of an experiment E depends on multiple variable factors (F_1-F_3) (i). As more information is obtained about these factors, the outcome of the system becomes more predictable (ii,iii). In the absence of this information, the outcome can appear to be more random than is actually the case, i.e. it may display 'apparent stochasticity'.

for example, integrate a multitude of chemical and mechanical factors, which often vary with time and space. As a consequence, even in cases in which fate decisions appear stochastic when considered in isolation, they may become more predictable if detailed knowledge about the intra- and extracellular context of a cell was available. In other words, hidden variables that cannot be accessed experimentally can cause variations in cellular behaviors that make these behaviors appear to be random (Fig. 1B). In this Review, we refer to this phenomenon as 'apparent stochasticity', as it is rooted in a lack of knowledge about the underlying factors that affect the observed outcome. Similar concepts play a pivotal role in statistical physics, in which they are used to derive statistical laws of large deterministic systems that are too complicated to handle otherwise (Landau and Lifshitz, 2013).

An important consequence of apparent stochasticity is that experimental outcomes can appear more or less random depending on how much is known about the system (Fig. 1B). In mathematical terms, this can be illustrated using the notion of conditional probability. A conditional PDF, $P(X|F)$, captures the uncertainty of an outcome X once a second random variable F is known. If X and F are statistically dependent, then measuring F will, on average, decrease our uncertainty about X. In other words, X appears more or less random depending on whether F is hidden or not.

During developmental programs, it is impossible to capture the entire state of a cell and its context. This means that, in many situations, hidden variables likely contribute significantly to variations in cellular outcomes. Indeed, the potential impact of hidden variables has been demonstrated experimentally in various contexts of cellular decision making. In cell culture experiments, for example, some studies show that, although cellular outcomes and responses can vary substantially between identical cells, much of the variability correlates with the context of a cell, including its growth rate, cell cycle stage, neighborhood or morphology (Colman-Lerner et al., 2005; St-Pierre and Endy, 2008; Snijder et al., 2009). This indicates that large parts of the variations due to regulated or predetermined factors, for example stochastic events in transcription, seem to play less of a role. Another recent study used concepts from information theory in combination with single cell sequencing data to formally test for hidden variables in cell fate choices during hematopoiesis (Weinreb et al., 2020). Specifically, the authors tested whether variations in transcriptional state are sufficient to explain stochastic fate choices. Their analysis revealed that cell fates can be predicted from transcriptomic data to a large extent, but that a considerable amount of uncertainty remains (Weinreb et al., 2020). This suggests that variations in fate choices can be explained only partly by gene expression variability and that additional hidden factors can bias cell fate choices towards certain outcomes. Another example in which stochasticity in fate choices might be linked to hidden variables is in the context of epidermal stem cells (Mesa et al., 2018). Although it was previously thought that these cells decide between self-renewal or differentiation in a cell-autonomous and stochastic manner, a recent study showed that outcomes could be predicted from differentiation events of neighboring cells. Thus, although from a clonal perspective these fate choices appear stochastic, they turned out to be predictable from the environment of the cell.

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These studies underpin the fact that, when dealing with systems that can only be partially observed, stochastic behavior cannot be interpreted as an objective property of the system. This is because it generally depends on how comprehensively we can measure the state of the system. In other words, not all of the uncertainty in cellular behaviors is necessarily caused by randomness in the underlying events. Yet, as these studies demonstrate, this can be leveraged to identify the key factors that control cell fate decisions, by testing how predictive they are in terms of cellular outcomes. A combination of theoretical approaches with image-based and single cell transcription analyses will therefore be a promising strategy to move forward in this direction.

Physiological origins of stochasticity in cell fate decisions

From a physiological point of view, stochasticity in cell fate choices can arise from mesoscopic fluctuations in the mechanical and chemical processes that orchestrate cellular outcomes. Generally speaking, fluctuations affect all processes that take place on mesoscopic scales. For example, reactions among molecules take place at random times and positions. Similarly, the force generated by motor proteins exhibits random fluctuations. The extent to which these individual sources of stochasticity contribute to variations in cell fate choices, however, remains only poorly understood.

One origin of stochasticity that is frequently associated with cell fate decisions is gene expression noise (Johnston and Desplan, 2008; Raj and van Oudenaarden, 2008; Raj et al., 2010; Urban and Johnston, 2018). It arises from intrinsic fluctuations in transcription and translation as well as variations in the microenvironment of a cell, also termed extrinsic noise (Elowitz et al., 2002). In combination, intrinsic and extrinsic sources of noise can cause substantial variations in gene product concentrations among genetically identical cells. In recent years, much work has been dedicated to studying how cells can buffer gene expression noise (Lestas et al., 2010; Little et al., 2013; Battich et al., 2015; Keskin et al., 2018; Klosin et al., 2020) or even utilize it to generate heterogeneity across fates (Johnston and Desplan, 2014). However, a detailed understanding of how gene expression noise propagates to the level of fate decisions is still lacking and will require more work in the future.

Molecular fluctuations also play an important role in cell signaling. Extracellular signals themselves, for example, can exhibit spatial and temporal fluctuations (Gregor et al., 2007; Durrieu et al., 2018), as do the biomolecular pathways that process these signals and transduce them to their downstream targets (Cheong et al., 2011). For example, significant work has been conducted to understand how fluctuations in the gradient of Bicoid (a morphogen) affect the precision at which cells can make position-dependent cell fate choices along the anterior-posterior axis of *Drosophila* embryos (Gregor et al., 2007; Dubuis et al., 2013; Tkačik et al., 2015; Huang et al., 2017). In addition, a direct demonstration of how signaling noise impacts cell fate stochasticity has been provided in *Caenorhabditis elegans*, in which fluctuations in Wnt signaling activity determine whether P3.p cells fuse with the hypodermis or become vulva precursors (Kroll et al., 2020). Although these studies have provided insights into biochemical sources of stochasticity, it is known that mechanical processes and properties such as cell shape, migration or division can also exhibit fluctuations, yet their impact on cell fate choices remains largely unexplored. Thus, despite the progress that has been made in understanding the role of stochasticity in fate decisions, many environmental factors that are most likely involved in this process have not yet been extensively probed and present an exciting avenue for future studies.

One area in which environmental factors have been linked to fate decisions in combination with cell intrinsic elements is developmental neurobiology. Here, both stochastic and deterministic aspects of cell fate decisions and cell lineages have been explored for several decades. In the following sections, we discuss the current state of this area of neuroscience and explain how paradigms have shifted in recent years, taking the conceptual thoughts outlined so far in this Review into consideration.

Stochastic and deterministic aspects of cell fate decisions during development

How a fertilized egg evolves into a complex organism containing a vast variety of cell types is a key question in developmental biology and raises many questions with regard to reproducibility, plasticity and robustness in development. Robustness can be reached in different ways. For example, if a system is completely deterministic, this would always lead to a robust outcome. The prime example of organismal development that mainly relies on robust, deterministic fate choices is found during embryonic development of the roundworm *C. elegans* (Sulston et al., 1983). Here, a deterministic lineage tree forms all 671 embryonic cells, some of which become reproducibly apoptotic. However, such perfectly predictable cell behavior appears to be less common in most other developmental contexts. In systems with thousands of cells and cell types, the production of which is more error prone, it is most likely of advantage to buffer possible errors in development by correction mechanisms and underlying stochasticity. To understand the balances between deterministic and stochastic fate decisions, it is thus important to dissect how multipotent cells choose their fate before differentiation in an ever-changing environment.

To enable a comprehensive discussion on these factors, we shall focus on cell fate decisions in the developing CNS. The CNSs of invertebrates and vertebrates exhibit an amazing diversity of neuronal cell types, and producing the right types of neurons in the correct proportions in a spatially and temporally controlled manner is fundamental for generating functional neuronal networks. For decades, a key aim of developmental neurobiology has been to examine how this diversity arises. Multiple studies have identified some of the factors that influence cell cycle exit and neuronal commitment in different brain areas of diverse model systems. In addition, the balance between intra- and extracellular influences has been intensely probed. Some studies have argued that, in certain systems, cell fate decisions are predetermined in progenitor cells (Fig. 2A). However, examples in which stochasticity influences lineage decisions have also been put forward recently (Fig. 2B). Findings understandably vary depending on the CNS area studied and on the complexity of the model system used but, even within the same system, interpretations have differed. Below, we summarize recent literature and approaches that classify cell fate decisions and other phenomena as deterministic or stochastic processes and discuss where these processes occur concurrently, taking the above outlined frameworks into account.

Cell fate decisions in the *Drosophila* nervous system

Owing to its fast generation time and accessibility, the developing *Drosophila* nervous system is an excellent model in which to study neuronal fate decisions. Diverse areas of the *Drosophila* nervous system have been studied and, depending on the region, the influence of deterministic or stochastic processes has been highlighted when interpreting experiments.

In the *Drosophila* retina for example, photoreceptors that discriminate colors (the R7 and R8 cells, which are randomly

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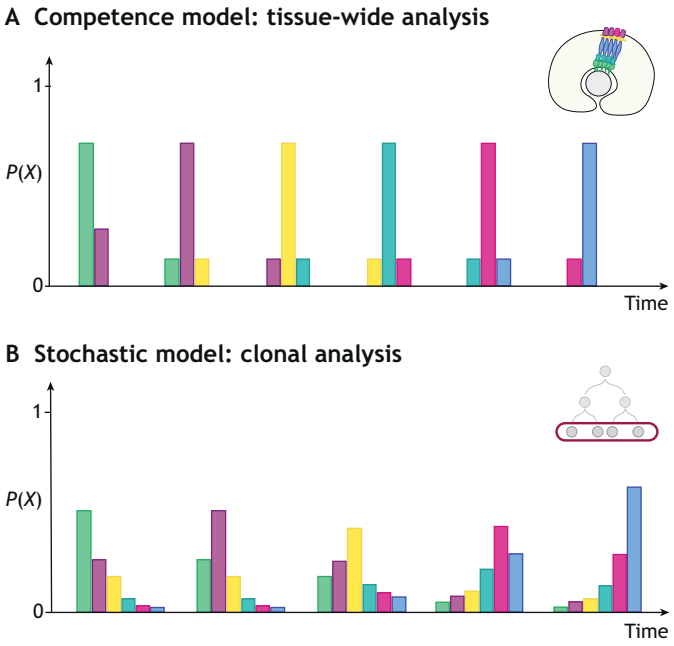

Fig. 2. Analysis and models of fate decisions in the CNS. (A,B) Schematics illustrating analyses of the vertebrate retina. Different colors refer to different neuronal cell types. The competence model (A), based on classical birth-dating studies at the tissue level, can be described as a PDF that evolves in time. At each time point, progenitors can commit to a certain fate, depending on their competence state. Competence states partially overlap during the neuronal birth order. The stochastic model (B) is generally based on clonal analyses and *in vitro* lineage tracing studies. At each time point during development, retinal progenitors can commit to different fates stochastically according to some PDF. As a result, a stochastic combination of cell types is produced at each time point.

distributed in the fly eye in a 70% to 30% ratio) are thought to emerge in a stochastic pattern with regard to their lineage decisions (although positional information is fixed). This phenomenon depends on fate decisions taking place in the R7 cells that in turn influence R8 cell fate. It was initially shown that R7 cells are arranged randomly and independently in a cell autonomous manner (Bell et al., 2007). This random mosaic arrangement of R7 cells is determined by the stochastic expression of the transcription factor Spineless that is thought to act as an integrator of noise (Johnston and Desplan, 2008; Thanawala et al., 2013) via changing binding site affinity for transcriptional repressors that in turn regulate transcription factor levels (Anderson et al., 2017). In addition to the experimental work, a recent stochastic mathematical model indeed showed that very different patterns of R7/R8 photoreceptors in diverse fly species can be recapitulated by changing the expression patterns of spineless (Ebadi et al., 2018).

A more deterministic mode of neuronal fate decisions prevails for neurogenesis in the *Drosophila* nerve cord and medulla, a part of the optic lobe. Here, neuroblasts undergo multiple rounds of asymmetric divisions that give rise to one maintaining neuroblast and one ganglion mother cell. The ganglion mother cell then divides to generate two neurons (or glia at later developmental stages) (Doe and Technau, 1993). Owing to the precise expression of different transcription factor cascades (Kohwi and Doe, 2013), these ganglion mother cells acquire a precise temporal identity that leads to determined neurogenesis events. These temporal identities are suggested to lead to reproducible fate decisions, such that only defined neuronal cell types are generated at a given developmental position and time (Fig. 2A). Interestingly, each of these neuronal identity factors can activate the next factor, leading to sequential expression of the temporal identity factors and thereby a reproducible sequence of fate choices (Brody and Odenwald, 2000). This deterministic fate acquisition goes so far that exact neuroblasts and their progeny can be singled out from one fly to the other (Cleary and Doe, 2006).

It is thought that, in addition to these temporal cues, spatial cues can contribute to the neuronal diversity seen in the *Drosophila* nervous system (e.g. the up to 80 neuronal cell types in the medulla; Morante and Desplan, 2008). However, the spatial influences are more complex than the temporal transcription factor cascades (Kohwi and Doe, 2013). For example, it has been shown that, in the medulla, complex inputs of diverse additional transcription factors along a spatial axis in addition to a temporal axis promote the neuronal diversity that produces the more than 80 types of neurons observed in 800 organized columns (Li et al., 2013; Erclik et al., 2017). However, it has been noted that some fate plasticity can be observed upon heterochronic transplantation (Berger et al., 2001; Pearson and Doe, 2003). This indicates that, although neuroblasts mainly undergo deterministic cell fate decisions, they remain competent to interpret extrinsic signaling and that stochastic elements in surrounding tissues can lead to plasticity in cell fate decisions.

Cell fate decisions in the mammalian neocortex

The mammalian neocortex is the area of the CNS that influences important higher order brain functions including cognition, motor commands and, in humans, speech. It consists of diverse types and subtypes of neurons, the cell fate decisions of which have been intensely studied. About 20 years ago, it was shown, using retrovirus labeling experiments, that early rodent cortical progenitor cells are multipotent (Desai and McConnell, 2000) and that a single progenitor can produce neurons that function in different layers of the maturing brain. Similar to the situation in the *Drosophila* CNS, it was postulated that, although early progenitors are multipotent, these progenitors lose competence over consecutive cell cycles and can only produce late-stage neurons once this occurred (Fig. 2A). Further experiments suggested that this loss of potency results from changes in environmental factors and not only the counting of cell divisions (Desai and McConnell, 2000). The multipotency of cortical neurons was later confirmed using mouse embryonic stem cells *in vitro* (Gaspard et al., 2008), which recapitulate *in vivo* cortical development and also exhibit a temporal fate pattern. However, owing to the lack of external cues and input from other brain areas in this *in vitro* set-up, this temporal order was attributed to cell intrinsic properties (Gaspard et al., 2008). Another *in vitro* study, using clonal cultures, came to similar conclusions, showing that cortical progenitor cells undergo repeated asymmetric cell divisions, thereby giving rise to characteristic neural lineage trees; in addition, this study touched on the fact that plasticity in these lineage trees might exist, at least for early lineages (Shen et al., 2006).

In line with the loss of potency model, another study reported that progenitors of cortical neurons, the radial glia cells, form sub-lineages with distinct fate potentials in mice (Franco et al., 2012). This work, in accordance with an earlier study (Shen et al., 2006), suggested that the generation of upper-layer neurons is driven exclusively by cell intrinsic factors and is independent of extrinsic influences such as the location or time of neurogenesis. Overall, although the combination of these reports did not completely agree on the extent to which intrinsic versus extrinsic factors influence cortical lineage decisions, they all postulated a mainly deterministic

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mode of cell fate choice for cortical neurons in rodents, with only some temporal plasticity. This was also the outcome of a study in mice (Gao et al., 2014) that used a powerful labeling technique termed mosaic analysis with double markers (MADM) (Hippenmeyer et al., 2010), which enables clonal analysis at single cell resolution. This work revealed the distribution of the numbers of neurons that are produced by radial glia cells between deep and superficial layers. The authors noted that all progenitors generate eight to nine neurons that are distributed in deep and superficial layers. This reproducible output was interpreted as an orderly deterministic program for cortex progenitor fate decisions (Gao et al., 2014). A very recent report elaborated on these findings by complementing MADM labeling with retroviral labeling and tamoxifen-induced fate mapping (Llorca et al., 2019). In contrast to the MADM-based study, this study showed that, when all three methods are analyzed in relation to each other, variations in clone sizes and lineage compositions are observed, thereby challenging a completely deterministic mode of neuronal output. The authors instead interpreted their findings as stochastic, similar to a model that has been suggested based on studies in the mammalian retina (discussed below). It was further proposed that stochastic mechanisms based on probabilistic rules define neuronal output. This idea is underlined by a set of elegant mathematical modeling approaches that validate this interpretation (Llorca et al., 2019). In another recent study, it was further confirmed that, as in *Drosophila* (Berger et al., 2001; Pearson and Doe, 2003), temporal plasticity exists for some, albeit not all, types of cortical progenitors (Oberst et al., 2019). This study revealed that, when apical progenitors from older mice are transplanted into a younger environment, they can readjust to this environment and display 'younger' features. However, the same is not true for young progenitors transplanted into older embryos, similar to what had already been suggested in an earlier report upon Foxg1 knockdown (Shen et al., 2006).

Overall, although a lot of emphasis has been placed on showing predictable aspects of cell fate decisions in cortical progenitors, current work has started to unveil stochastic influences. Thus, more experimental research – in combination with statistical modeling – will be required to clarify the interpretation of old and new data and to disentangle the key factors that drive cell fate diversity and heterogeneity in the neocortex.

Cell fate decisions in the vertebrate neural retina

The vertebrate neural retina is the part of the CNS responsible for the perception of the visual environment. It consists of five main types of neurons subdivided into diverse subtypes. These neurons have to be arranged in specific layers for optimal connectivity. Thus, producing the correct number of neurons at the right time is of crucial importance for the formation of a functioning retina (Amini et al., 2018). Interestingly, retinal neuronal layering is highly conserved between diverse vertebrates, including humans, underscoring the importance of these cellular arrangements (Hoon et al., 2014). As in the neocortex, cell fate determination and the factors that influence cell fate decisions have been intensely studied in different vertebrate model systems.

In the late 1980s, studies in *Xenopus* and rodents revealed that retinal progenitors are multipotent (Turner and Cepko, 1987; Holt et al., 1988; Wetts and Fraser, 1988), a finding that was later confirmed in zebrafish (Fadool, 2001). Specifically, birth-dating experiments in *Xenopus* showed that the offspring of one retinal progenitor can generate neurons of all sectors and layers in the future retina (Holt et al., 1988; Wetts and Fraser, 1988). The study by Holt et al. even proposed the general birth order of retinal neurons, a feature conserved in many, if not all, vertebrate species. However, this early study already noted that fate might not strictly be determined by this birth order, as significant overlap between lineages was observed. This study also raised important questions in the field, including the issue of whether temporal cell intrinsic programs are necessary for fate decisions. It was speculated that such programs could involve the differential segregation of intracellular factors or stochastic events within the cell, or that factors in the extracellular environment could guide fate choices.

A similar study in rat (Turner and Cepko, 1987) came to the conclusion that cell fate decisions in the rodent retina are driven by competence states, similar to what was observed in the *Drosophila* nervous system (discussed above, Fig. 2A). It was proposed that the progenitor cell, as well as its environment, change over time, and that this induces transient 'competence states' (reviewed by Cepko, 2014). The idea of an intrinsic element to fate decisions was also examined in a study using *Xenopus*, which showed that when young or old progenitors are exposed to a developmentally different stage, they nevertheless keep their 'age' and differentiation program (Rapaport et al., 2001), in contrast to recent findings in the rodent neocortex (Llorca et al., 2019). Thus, the authors suggested a 'competence clock' (Fig. 2A). Taking all these findings together, it was proposed that, although all retinal progenitor cells are born equal, extrinsic and cell intrinsic cues induce fate in a reproducible deterministic manner over developmental time (Cepko, 2014).

The idea that stochastic factors are also involved in retinal neurogenesis gathered traction when a study using dissociated rat retinal progenitor cells revealed that clones can vary highly in size and composition (Gomes et al., 2011). These findings were well recapitulated by a simple stochastic model. The conclusion was that these single cells in culture, which exhibit no interactions with other cells, follow a stochastic pattern when committing to a specific fate. Overall, this finding argues against a fundamental role of signaling cues for these decisions. However, it was shown that the probabilities of fate choices reflect the abundance of each cell type in the mature retina, indicating the presence of some type of fate decision bias (Gomes et al., 2011). This finding prompted the authors to suggest a model for cell fate decisions in which a dice is thrown and determines the outcome of progenitors with each throw. However, in the case of retinal fate decisions, this dice appears to be 'loaded' so that certain outcomes are more likely than others. The authors further postulated that such a stochastic influence of a 'loaded dice' could be an important mechanism to buffer fate distributions in the case of developmental defects (Gomes et al., 2011).

This *in vitro* work was followed by a series of elegant studies using the imaging potential of zebrafish in combination with clonal analysis (He et al., 2012; Boije et al., 2015). This set-up allows retinal cell fate decisions to be followed for over three consecutive divisions in a plethora of embryos. One such study proposed a stochastic probability model of retinal fate decisions (He et al., 2012) (Fig. 2B). The authors based this interpretation on the fact that, when following hundreds of lineages from diverse embryos, more than 30 different lineage species are observed (He et al., 2012). These lineages exhibit different clone sizes, composition and division patterns, making stochastic influences likely. However, the authors noted that they could not absolutely exclude the possibility that this variety of clone attributes could follow some early specification programs in progenitors that they did not have the resolution to observe. Thus, it is possible, albeit not very likely, that this is an example of hidden variables and that, in the case that all relevant parameters could be measured, some predictable themes would emerge.

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A complementary study from the same lab further postulated that probabilistic firing of different transcription factor combinations could explain the clonal variability observed (Boije et al., 2015). If this interpretation was correct, this would imply that retinal progenitors are equivalent at birth but that the probabilistic and independent firing of transcription factors drive differences in clone size and composition, underlining the stochastic nature of fate decisions.

It is important to note that the stochastic clone sizes and lineages observed in both studies (He et al., 2012; Boije et al., 2015) are most abundant at early stages of retinal neurogenesis. At later stages of retinal development, by contrast, more deterministic division patterns become prominent, at least in zebrafish. These often arise from a different type of progenitor, the so-called committed precursor, which gives rise to later born neurons (Godinho et al., 2007; Suzuki et al., 2013; Weber et al., 2014). In zebrafish, committed precursors give rise to bipolar (Weber et al., 2014; Engerer et al., 2017), horizontal (Godinho et al., 2007; Weber et al., 2014) and photoreceptor (Suzuki et al., 2013; Weber et al., 2014) cells. Importantly, all of these committed precursors vary from the multipotent progenitors found at early stages of neurogenesis as they show different morphologies, gene expression patterns or division locations. Furthermore, all of these committed precursors give rise to two cells of the same type (i.e. two bipolar cells, two horizontal cells, two photoreceptors). However, their subtype specificity has not yet been explored. As these late deterministic divisions were not yet taken into account when modeling zebrafish retinal fate decisions (He et al., 2012; Boije et al., 2015), it is unclear whether and how they could influence the purely stochastic models that have been proposed to date. It is also not completely clear whether committed precursors are a non-mammal-specific phenomenon (note that committed precursors giving rise to two horizontal cells are also observed in chick; Boije et al., 2009) or whether they are present during retinogenesis in mammals. A study on mouse retinal progenitors that express the transcription factor Olig2 indicates that a similar concept might also be at play in rodents (Hafler et al., 2012). Specifically, it was shown that at late developmental stages, progenitors expressing Olig2 show a strong bias to produce two horizontal or cone photoreceptor cells, similar to committed precursors in zebrafish. These progenitors have even been compared with *Drosophila* ganglion mother cells, although whether these cells indeed reflect committed precursors needs further investigation. Thus, an important step in the future will be to follow specific lineages over time, and in different species, in order to take different types of progenitors and committed precursors into account (Fig. 3).

Overall, these recent data provide evidence for stochasticity in retinal fate decisions. But at what level might this stochasticity arise? As already described in this Review, the potential origins of stochasticity in cell fate decisions are diverse. Multiple recent studies have started to investigate the role of variations in the extracellular environment on fate outcomes. One factor that has been put forward is nuclear positioning (Baye and Link, 2007; Del Bene et al., 2008; Azizi et al., 2019 preprint). In the retina, as well as in other neuroepithelia, nuclei are distributed along the apico-basal axis of the epithelium during cell interphase. Before mitosis, however, nuclei need to translocate to the apical surface where they undergo division (Norden, 2017). Two studies have postulated that the maximum basal position that nuclei reach during this process of nuclear translocation (termed interkinetic nuclear migration) is an indication of whether a cell will become neurogenic after the next division (Baye and Link, 2007; Del Bene et al., 2008). In this model,

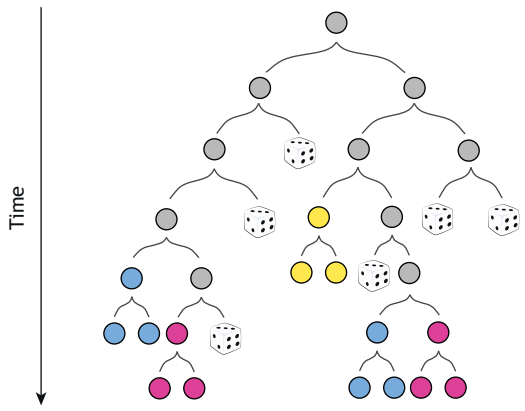

Fig. 3. *In vivo* lineage analysis as a method to study cell fate decisions. Schematic illustrating *in vivo* lineage analysis as an approach to study cell fate decisions. With this approach, purely stochastic fate decisions (represented as a dice) can be taken into consideration as well as late deterministic divisions of committed precursors (colored circles). This type of description of cell fate decisions will help untangle the contribution of stochastic and deterministic processes.

the decision is linked to an assumed apico-basal Notch gradient. Specifically, it has been postulated that when nuclei are positioned towards the apical surface, neurogenic fate could be suppressed by Notch signaling; in turn, at more basal positions, neurogenic potential at the next division would rise. So far, however, no direct proof for a Notch gradient has been presented at the protein or signaling level. In addition, the fact that basal nuclear positioning exhibits stochasticity itself (Norden et al., 2009; Azizi et al., 2019 preprint), and the fact that nuclei show non-predictable trajectories before directed apical migration that span some distance along the apico-basal axis (Norden et al., 2009; Leung et al., 2011; Azizi et al., 2019 preprint), makes it hard to imagine how a stable gradient could influence neurogenesis. Thus, this issue needs further investigation.

Conclusions

Overall, it is clear that stochasticity in fate decisions occurs along a range. This can be illustrated when thinking about a coin toss. Only a probability of one for either heads or tails would correspond to a fully deterministic outcome, but such a situation is rarely observed in biological fate decisions. If both outcomes have the same probability of 0.5, then the coin is entirely random and unpredictable. However, what is often observed in biological fate decisions is more similar to a ‘weighted coin’, which lies somewhere in between those two extremes.

There are many possible factors in cells that can contribute to ‘weighing the coin’, most of which we are just beginning to understand. Determining these factors and dissecting how they influence variability across decisions is a challenging frontier in this exciting era of developmental biology. Nonetheless, although experimental techniques (e.g. gentler imaging techniques that allow following cells over many divisions, improved labeling techniques, fate mapping in rodents, single cell transcriptomics, etc.) are rapidly improving, we are still far from measuring all relevant parameters involved in these decisions and it is unclear whether this will ever be possible. Therefore, as long as we cannot fully resolve the complex milieu that dictates cell behavior, it remains unclear whether the observed stochasticity is caused by random fluctuations in the underlying processes, or whether it is due to hidden factors that have not been captured experimentally.

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Competing interests
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