Computational Modeling of Adult Neurogenesis

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The restriction of adult neurogenesis to only a handful of regions of the brain is suggestive of some shared requirement for this dramatic form of structural plasticity. However, a common driver across neurogenic regions has not yet been identified. Computational studies have been invaluable in providing insight into the functional role of new neurons; however, researchers have typically focused on specific scales ranging from abstract neural networks to specific neural systems, most commonly the dentate gyrus area of the hippocampus. These studies have yielded a number of diverse potential functions for new neurons, ranging from an impact on pattern separation to the incorporation of time into episodic memories to enabling the forgetting of old information. This review will summarize these past computational efforts and discuss whether these proposed theoretical functions can be unified into a common rationale for why neurogenesis is required in these unique neural circuits.

The importance of neurogenesis will be ultimately tied to its impact on the computational function of the overall circuit within which it resides. Notably, the two mammalian regions where neurogenesis is typically studied, the olfactory bulb (OB) and the dentate gyrus (DG) region of the hippocampus, have considerably different functions. The OB is a primary sensory region, essentially the equivalent of the processing layers of the retina, providing an initial transformation of raw olfactory inputs to the brain. In contrast, the hippocampus is one of the deepest structures in the brain, residing many layers away from sensory inputs and vital for episodic memory formation.

Interestingly, as noted throughout this collection, although OB and DG neurogenesis share some similarities, there are sufficient differences to make it difficult to generalize across

the two systems, not the least of which is the recent observation that humans likely lack OB neurogenesis. This is somewhat supported by a comparative perspective. As with mammals, neurogenesis in birds is limited to several structures with certain species, including neurogenesis in well-studied birdsong regions. Vertebrates with arguably less advanced nervous systems, such as reptiles and fish, have more widespread neurogenesis, suggesting that broad evolutionary pressures to attenuate neurogenesis in other areas of the brain led to the relative isolation of the OB and hippocampus as opposed to an evolutionary gain-of-function process common to the OB and DG. This subtle distinction has implications on how far one can hope for a shared function between these areas and, for this reason, it is not surprising that most computational studies investigating

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neurogenesis have focused either on the OB or the DG. However, it is possible that, despite the uniqueness of these two regions, there could be a unique computational paradigm that is common to these two regions that other mechanisms of neural evolution could not usurp. Toward the end of the review, we will return to this possibility.

Understanding neurogenesis from a computational perspective offers at least two benefits. First, characterizing the function of new neurons in a computational framework is invaluable in interpreting existing and future behavioral and physiology experiments of neurogenesis function. Recent debates regarding DG neurogenesis function highlight this value (Aimone et al. 2011; Sahay et al. 2011). Although behavioral tests of varied neurogenesis knockdown animals has suggested a function of “pattern separation” for new neurons (Clelland et al. 2009), there has been an ongoing debate about how this function maps to DG computation. The second benefit of a computational description of neurogenesis is more prospective. Neurogenesis offers one of the most potent opportunities for manipulating neural systems, either biological or in silico. Whether we are seeking a route to cell-replacement therapy or designing a novel neural algorithm for artificial intelligence purposes, understanding the implications of adding a new neuron to an existing functioning network is essential.

Notably, there have been several study-by-study reviews of neurogenesis models in recent years (Aimone and Gage 2011; Nogues et al. 2012). This review will take a slightly different approach, looking at the relationship of neurogenesis to the equivalent nonneurogenic biological system at different scales, and will focus primarily on neurogenesis within the DG with some discussion of the OB. Likewise, adult neurogenesis in the human striatum will receive only a cursory mention, largely because of the fact that the recency of its discovery (Ernst et al. 2014) has not yet motivated substantial theoretical work, a fact that will surely change in the future. However, first, it is useful to describe what the value of a new neuron is within the context of abstract neural networks, in general,

and then progress to the biological systems in which the specific details of adult neurogenesis interact with the existing network.

CAN WE INFER ANYTHING FROM THE VALUE OF NEW NEURONS IN ARTIFICIAL NEURAL NETWORKS?

Artificial neural networks (ANNs) have been a focus of computer science and cognitive science research for more than 50 years. ANNs are powerful tools for use in a wide range of applications for the simple reason that their initial design (i.e., their architecture) is, to a great extent, independent of their ultimate function and utility. Typically, ANNs are created with entirely random weights for their connections with subsequent training of the network, either through supervised (external feedback regarding performance) or unsupervised (no feedback regarding accuracy) learning, specializing the network for use in a given problem domain. This paradigm is powerful for at least two reasons. First, the ANN can learn sophisticated functions that are not readily described using conventional algorithms. Second, not all information must be available to the programmer at design-time; once trained, the ANN can be used to classify or process a wide range of inputs that are not part of the initial training set.

Despite their potential, there are a number of practical challenges associated with ANNs that can limit their utility. One such difficulty is balancing the ability of a network to acquire new information with the desire to preserve already trained information. Indeed, well before the existence of neurogenesis in the adult brain was widely appreciated, artificial intelligence researchers had recognized that algorithms, which relied on the introduction of naïve units, offered value in encoding novel information. Two algorithms widely recognized of this variety are the adaptive resonance theory (ART) (Carpenter and Grossberg 1988) and a growing version of the radial basis function (RBF) (Yingwei et al. 1997) classification algorithms. Both ART and RBF are pattern-classification algorithms in which inputs are compared with the receptive fields of a set of nodes. If the input is

significantly far away from all of the nodes' fields, then the network assigns a new, naïve node to represent that input. This process, although never motivated by biological neurogenesis, clearly shares some similarities.

Although the aforementioned specialized algorithms leveraging a neurogenesis-like functionality have proven useful in certain applications, the standard multilayer perceptron (MLP) networks, which are widely used for many applications, do not have structural plasticity. Broadly speaking, MLPs are the prototypical neural network; inputs are fed into a hidden layer of neurons, which perform a transformation and project to a subsequent hidden layer or output layer. Training of MLPs most often uses the backpropagation algorithm, a learning protocol that determines how to update synaptic weights to best achieve a desired outcome. Backpropagation is not intended to mimic learning in the brain; rather, it was designed to optimally configure a network to a desired input–output relationship. More biologically realistic training algorithms leverage unsupervised learning, such as the Hebbian learning rule, or reinforcement learning, such as temporal difference learning rules.

MLPs are a simple model framework, but they are notable, in part, because they are a core computational kernel of “deep learning” networks and illustrative of the limitations of machine learning in handling novelty. MLPs programmed with either supervised or unsupervised learning rules face the aforementioned challenge in balancing the capability to continue to learn new inputs with the preservation of the coding of past inputs. Notably, some of the first computational studies of neurogenesis remained within this ANN framework and showed how turnover within the middle layers of an MLP was sufficient to make the learning of a trained network more flexible in its response to novel inputs. The first such study by Chambers and colleagues (2004) is a somewhat simple example given the success of deep networks today, but it illustrates how neurogenesis provides a unique solution to this challenge. Their small three-layer networks were trained to recognize the Roman alphabet (mapping letters to their

numerical index (i.e., $A \rightarrow 1, B \rightarrow 2, \dots, Z \rightarrow 26$), a task easily learned by a backpropagation network. When the same networks were retrained to learn Greek letters, of which some letters are quite different (i.e., $\Gamma \rightarrow 3, \Delta \rightarrow 4, \dots, \Sigma \rightarrow 19$), the investigators observed that without “neurogenesis” (modeled by replacing middle-layer nodes), the trained networks could never fully learn Greek, whereas networks with neurogenesis became proficient. This result highlighted the effect that has persisted through more recent biological network studies: new neurons provide a capacity for networks to learn novel information that highly trained mature neurons simply cannot provide.

Subsequently, work by both Chambers and Miranker on this initial study further explored the effect of turnover in ANN networks with progressively more biologically realistic learning rules, the inclusion of inhibition, and targeted replacement strategies (Crick and Miranker 2006; Chambers and Conroy 2007). These studies combined illustrate that the effect described in the initial study is not simply a feature of ANNs, but is a general principle that is likely relevant to more biologically realistic networks. A related set of studies by Karl Deisseroth and colleagues took a similar approach using a more biologically based method with much larger networks (500 neurons per layer) with unsupervised Hebbian learning of random inputs. This approach, which was purely statistical learning as opposed to the targeted learning of the Chambers studies, showed very similar results; without neurogenesis, the network was much slower to adapt to more recent inputs, suggesting that neurogenesis was useful in rapidly adapting the network to the more recent statistics of the inputs (Deisseroth et al. 2004; Meltzer et al. 2005).

Moving away from the classic MLP design, there have been several other lines of abstract ANN models with neurogenesis. In the first of a series of several models, Wiskott and colleagues (2006) used a three-layer auto-encoder design to encode a series of environments. In contrast to the aforementioned backpropagation studies, the linear training method of these networks resulted in the novel environment being

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coded very well with considerable “catastrophic” interference of the previous memories. The incorporation of new neurons by addition (not replacement) is sufficient to preserve the representation of the prior environment when the novel environment is learned. A later study used model architecture somewhat more similar to the neurogenic EC → DG → CA3 circuit (described below) and explored the relative value of addition versus replacement and different rates of neurogenesis (Appleby and Wiskott 2009). Similar to the earlier study, they observed that addition (at approximately a 30% rate) was ideal for encoding subsequent environments without interference of previous representations. A follow-up study looked further at the value of these networks with biologically realistic grid cell inputs, illustrating that neurogenesis aided in the encoding of spatially constrained information (Appleby et al. 2011).

THE FUNCTION OF BIOLOGICAL NEUROGENESIS

Although the above results describing the effects of neurogenesis on ANNs provides some insight into how new neurons could impact learning in neural networks, the specific function of new cells in the brain should be expected to be very much related to the function and behavior of the region itself. The different biological neural systems vary considerably from the simple ANN architectures described above, as well as from each other.

DG NEUROGENESIS

Ascribing a clear functional role for DG neurogenesis has been a challenge faced by many researchers over the last decade. As with several other neural systems, the DG has experienced a renaissance in attention, not only because of the observation of neurogenesis, but through long overdue *in vivo* physiology observations, optogenetics, and focused behavioral tasks. Not surprisingly, the renewed debate regarding how best to describe the DG’s function has complicated the neurogenesis field’s ability to ascribe a clear function to new neurons.

From a computational perspective, relating the function of new neurons to animal behavior is nontrivial; one must recognize the impact of new neurons on the computation of the DG and, in turn, how the neurogenic DG affects the overall computation of the hippocampus (Fig. 1A). The computations of the hippocampus clearly affect behavior, particularly, in tasks related to spatial or contextual memory in rodents; however, it is necessary to recognize that the hippocampus is acting within the framework of the whole brain during behavior. Recognizing that these interacting functional scales are distinct is an important step for understanding the impact of neurogenesis on each level. Indeed, computational models and theoretical studies of DG neurogenesis have focused at each of the neuronal, DG, and hippocampal levels (Fig. 1B). Here, we walk through these levels, touching briefly on neurogenesis and neurogenesis-independent work at each scale.

Granule Cells, Young and Old

The granule cell (GC) is a deceptively simple-looking neuron. Small with a classic monopolar shape, a GC sits alongside thousands, if not millions, of highly similar looking siblings. However, arguably, dentate GCs are among the most distinct neurons in the forebrain, possessing a highly unique axon, the mossy fiber, which forms giant multisynapse terminals on downstream CA3 neurons and hilar mossy cells. This powerful formation is relatively unique among excitatory neurons and has inspired visions of it as a “detonator synapse” (McNaughton and Morris 1987). Notably, although mossy terminals are the most prominent of GC outputs, mossy fibers also have a different type of synaptic contacts on hilar and CA3 interneurons and hilar mossy cells (Henze et al. 2000). Whereas the mossy fiber appears to make GCs incredibly powerful, this impact on computation appears to be offset by their extremely sparse connectivity (each mossy fiber only connects to a dozen or so downstream CA3 neurons, one of the sparsest connections in the brain) and the GCs’ heavy tonic inhibition.

Figure 1. Overview of different scales relevant to characterizing neurogenesis function in the dentate gyrus (DG). (A) Understanding neurogenesis function involves considering how dynamics of a cellular process propagate up to the behavioral level. (B) There are currently several theories for each of these scale transitions, providing both a framework for understanding DG neurogenesis, as well as a challenge in updating classic models to include new neurons.

Importantly, although the GC has historically been among the most heavily studied neurons in the brain, the discovery that GCs are actually a mixed population of immature and mature neurons occurred after the DG received much of this attention. For instance, although there have been several studies of dendritic integration of individual GCs (Carnevale et al. 1997; Aradi and Holmes 1999; Schmidt-Hieber et al. 2007), there have not been equivalent studies of individual young neurons using computational single-neuron models with high levels of biological fidelity. This is in spite of considerable anatomical and physiological characterization of developing neurons showing that they are unique at different ages (Esposito et al. 2005;

Zhao et al. 2006; Marin-Burgin et al. 2012). Nonetheless, these experimental studies paint a convincing picture of the “excitable” young neuron. This presumed excitability arises from several different, presumably complementary, sources. First, young neurons, particularly those <2–3 wk old, have a weaker and even depolarizing response to γ -aminobutyric acid (GABA) (Ge et al. 2006). Second, immature neurons maintain a distinct set of ion channels, contributing to both a higher overall resistance and a differential spiking response (Mongiat et al. 2009). Finally, using a computational model far simpler than the multicompartmental GC models mentioned above, we have presented evidence that the reduced synaptic input, both

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inhibitory and excitatory, is sufficient to bias a typically silenced immature GC to fire more often than mature neurons (Li et al. 2012).

One recent study of ours considered from a theoretical perspective how the properties of individual young neurons could affect the timing of their activity in the network as opposed to that of mature neurons (Rangel et al. 2013). Briefly, we hypothesized that the decreased thresholds of young neurons will enable them to be activated at broader temporal ranges of θ , whereas mature neurons will tend to be “locked” to phases of θ that maximize total EC inputs. Although there is some in vivo evidence that this relationship of young and old neurons indeed exists in the DG, the computational implications of neurogenesis on phase coding in the hippocampus deserve more extensive exploration, and more focused experimentation will likely be necessary to conclusively show the hypothesis.

Impact of New Neurons on the DG

The DG, as a whole, has long attracted the attention of both neurobiologists and computational neuroscientists (Treves et al. 2008). As the input layer to the hippocampus and one of the most readily identifiable structures in the rodent brain, not to mention the unique properties of GCs described above, the DG was the site of numerous classic experimental neurobiological studies. For instance, long-term potentiation (LTP) was first observed in vivo in the mammalian brain by Lømo and Bliss in the DG (Bliss and Lømo 1973). Nonetheless, the ease of identifying clear place cells in the CA3 and CA1 regions, coupled with difficulty recording in vivo within the DG, directed much of the systems level hippocampus region downstream. Through both behavioral studies and computational studies following Marr’s seminal work on the hippocampus (Marr 1971), the DG was generally assumed to have two related roles in hippocampal function: the decorrelation of cortical inputs to facilitate downstream memory formation (“pattern separation”) and the integration of cortical information from different modalities, such as space and object informa-

tion (“conjunctive encoding”) (O’Reilly and McClelland 1994; Rolls and Kesner 2006; Kesner 2007). Both of these functions arise from the properties of GCs described above combined with their sheer number; roughly, a million sparsely active, powerful neurons receiving inputs from the lateral “what” and medial “where” entorhinal cortices would make for an ideal pattern-separating encoding system.

Computational perspectives of the DG have ranged from theoretical or abstract work along the above lines (Treves and Rolls 1992; O’Reilly and McClelland 1994) to highly realistic conductance-based models (Santhakumar et al. 2005; Dyhrfeld-Johnsen et al. 2007; Schneider et al. 2012) to less-biologically detailed phenomenological models of DG function (de Almeida et al. 2009; Myers and Scharfman 2009; Cerasti and Treves 2010; Rennó-Costa et al. 2010). Notably, the behaviors examined within these models vary considerably; some have focused on pattern separation, others on spatial processing and effectively conjunctive encoding, whereas the epilepsy models by Soltesz and colleagues have focused mostly on activity propagation and seizure generation.

Examining the effects of neurogenesis within these models is nontrivial. There is, typically, not a clear path by which to fit neurogenesis into existing phenomenological models. One example in a more theoretical context would be Lisman (2011), which described how progressively “retiring” GCs could fit in with his previous winner-take-all framework for the DG (Alme et al. 2010; Lisman 2011). In principle, the incorporation of new neurons into an existing circuit to observe what the function of neurogenesis is should be better suited for more detailed mechanistic models. However, this approach suffers from challenges caused by the different time scales of most models and neurogenesis. For instance, the sophisticated high-resolution conductance-based models of the DG used for epilepsy studies operate by necessity at very small time scales; incorporating neurogenesis would thus require the addition of an extra, much longer time scale into the model.

Nonetheless, there have been several models at intermediate levels of biological detail

designed to examine neurogenesis directly. We described a moderately biologically realistic model that showed several distinct effects of young neurons (Aimone et al. 2009). First, it illustrated that new neurons interact with the presumed pattern-separation function of the DG in a complex manner, most likely by contributing a strong temporal component whereby events close in time are “integrated” together, and whereas events far apart in time are even more separated. This temporal coding, which was hypothesized by us and others several years prior (Aimone et al. 2006; Becker and Wojtowicz 2007), is an example of a *de novo* function that would not have been identified by simply incorporating young neurons into existing functional frameworks. Our model further hypothesized that young neurons born at different times will specialize to better encode (and, presumably, eventually better discriminate) features that were salient at the times when they were young, a prediction that has also inspired directed experimentation in rodents (Rangel et al. 2014). Subsequently, a study by the Argibay group followed up by investigating spatial processing in the Aimone et al. (2009) model (Cuneo et al. 2012).

The Neurogenic Hippocampus

Since David Marr’s seminal studies in the early 1970s (Marr 1971), there have been numerous attempts to model the full hippocampal circuit. Much of this work has arisen from the view of the hippocampus as a fairly simple trisynaptic loop: the EC represents cortical information from different domains, the DG performs pattern separation on those inputs, the CA3 attractor network is where information is bound together into memories, the CA1 performs temporal associations of these representations, and the information is sent back to the EC (Rolls and Kesner 2006). Not surprisingly, the actual hippocampal anatomy is considerably more complex than this simple trisynaptic loop, with feedback from the CA3 to DG, and direct connections from the EC to the CA3 and CA1. Furthermore, the role of the subiculum as an output (both intermediate to EC, as well as to

other brain areas) has received little exploration, as has the computational involvement of the CA2. Last, the hippocampus is tightly coupled to subcortical structures with substantial reciprocal connections to the septum, as well as other limbic areas (mammillary bodies, hypothalamus, and modulatory circuitry) (Andersen et al. 2007). It is worth noting that the increased consideration of neurogenesis’s role in affective processing would potentially involve these latter circuits that have received little computational attention.

Although there have been few attempts to relate neurogenesis computationally to affective circuits, there have been several models of neurogenesis in the classic hippocampal memory circuit. The first such model was by Sue Becker (2005), which incorporated new neurons into a four-layer $EC \rightarrow DG \rightarrow CA3 \rightarrow CA1 \rightarrow EC$ loop model and assessed the efficacy of memory encoding and retrieval in the overall circuit. The primary result of this model is that the turnover of new neurons is necessary for effective hippocampal coding of representationally similar inputs. This result is quite related to the results described in the abstract models above, and it is one of the first demonstrations of how neurogenesis could impact the separability of information coded within the hippocampus. Becker and colleagues (2009) followed this work several years later with a subsequent modeling study that showed that preferential recruitment of new neurons over time was useful in minimizing network forgetting and maintaining paired associations in a task that the investigators argue is portable to human cognitive studies.

Subsequently, a set of studies by Weisz and Argibay (2009, 2012) took a similar approach with a full hippocampal network loop, but with treating neurogenesis as an additive, as opposed to a replacement, one-shot process. Because neurogenesis did not result in replacement, the postneurogenic networks had a clear mix of young and mature neurons. As also observed in other modeling studies, the young neurons tended to represent more of the activity as a result of novel inputs, effectively separating memories that were pre- and postneurogenesis. However, as with Aimone et al. (2009), the

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Weisz and Argibay model showed signs of impaired pattern separation in neurogenic networks. As a follow-up study in a later model, they examined the effect of neurogenesis on forgetting within their 2009 model, indicating the new neurons help the system eliminate older memories from the system (Weisz and Argibay 2012). Notably, their prediction that new neurons are useful for forgetting was supported by recent evidence from the Frankland laboratory (Akers et al. 2014).

Summary of DG Impact and Relevance to Pattern Separation

Despite its relatively short existence as a research field, DG neurogenesis has been the focus of several notable debates. One of the most pronounced has been its function: first, whether it even was functionally important and, more recently, what this function is (Aimone et al. 2011; Sahay et al. 2011). Increasingly, both models and behavioral studies of neurogenesis have often focused on this presumed pattern-separation function; however, it is increasingly clear, at the very least, that the terminology as applied to different perspectives is problematic.

As mentioned previously, most models of neurogenesis touch on this putative separation function in one manner or another. Indeed, what appears to vary between models is not whether pattern separation and neurogenesis are related, but rather what differs are the aspects of a representation that are actually being separated. This has led to some debate in the community about whether pattern separation is the correct lens through which to view neurogenesis function (Sahay et al. 2011), or whether there is a more precise function that could be described computationally (Aimone et al. 2011).

Briefly, a challenge to computational neurogenesis researchers is that there are several potential mechanisms by which new neurons can affect pattern separation at a behavioral level. What most models have suggested is a population effect in which new cells represent novel information, and because of their distinct connections to the CA3 network, memories are encoded with less interference (Fig. 2A). However,

there are other possibilities that equally could yield a similar behavioral effect with a drastically different computational effect. For instance, if new neurons preferentially contacted local inhibitory interneurons, their increased activity would effectively silence the whole DG through increasing feedback GABA (Lacefield et al. 2012). This process would create sparser, and thus likely more orthogonal, activity by mature neurons (Fig. 2B). Similarly, young neurons could differentially activate CA3 interneurons, effectively activating feedforward inhibition in CA3 and “priming” the recurrent network to be trained by mature cells (Fig. 2C) (Rangel et al. 2013).

Ultimately, it is likely that more integration between computational studies, which are effective at showing sufficiency, and behavioral studies, which are better suited for establishing necessity, will be necessary to improve the resolution of neurogenesis function. Of particular importance will be the identification of more specific hypothesized functions, which are difficult to map into multiple mechanistic computational models. For instance, the time coding theory helped motivate the recent design of a novel behavioral task in rodents, showing that there is, indeed, a previously unappreciated timescale in episodic memory that depends on the DG (Morris et al. 2013) and the presence of young neurons (Kesner et al. 2014).

OB NEUROGENESIS

Although this article is primarily focused on neurogenesis in the DG, it is worth touching on the recent computational studies that look at neurogenesis in the OB. As alluded to in the Introduction, the OB is a considerably different neural circuit, receiving primary sensory input from olfactory receptor neurons (ORNs), which are themselves a turning-over population. Information is passed from the ORNs to excitatory mitral and tufted cells in complex structures called glomeruli. In between these glomeruli are inhibitory neurons known as periglomerular cells, and in between mitral cells are interneurons called granule cells (OGCs, to distinguish from DG GCs). Both the periglomerular cells

Figure 2. Overview of potential mechanisms for neurogenesis effect on pattern separation. (A) Common hypothesis in which increased activity and plasticity of new neurons represent novel information, allowing progressive events to be better separated (*left*). Without neurogenesis, a mature population must represent all events (*right*). (B) Alternative mechanism whereby young neurons increase feedback inhibition in the dentate gyrus (DG) (*left*). Without new neurons, mature neuron activity is higher, decreasing separation (*right*). (C) Another mechanism in which young neurons activate feedforward inhibition in the CA3, which decreases the density of attractors and reduces interference. Notably, none of these mechanisms are exclusive and all may be occurring simultaneously.

and OGCs turnover through neurogenesis process; however, unlike DG neurogenesis, the stem cells for these populations reside far away in the subventricular zone and migrate through the forebrain along the rostral migratory stream to the OB.

The periglomerular cells have received relatively little attention from a computational perspective, so this discussion will focus primarily on the OGC population. There are several significant differences between the OGCs and similarly named DG GCs. OGCs are inhibitory neurons, and dendrites of OGCs form synapses onto the same neurons that excite them;

this dendrodendritic communication supports a very rapid feedback and lateral inhibition. As with most interneurons in the brain, computationally, their function is not obvious; although it increasingly appears that the inhibitory framework provided by OGCs is important for decorrelation of olfactory glomerular inputs, the mechanism behind this is not clear. Further, evidence from insect olfactory systems suggests that the representation of olfactory information is highly dynamic, so it would not be surprising if OGCs are important for shaping the temporal trajectories of information that is presented to the cortex.

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Like the hippocampus, there has been a long tradition of modeling the OB (Cleland and Sethupathy 2006; Cleland 2010), although the number of models looking at OB neurogenesis is itself fairly small (Lepousez et al. 2013). In one of the earliest computational studies of biological neurogenesis in any system, Cecchi and colleagues (2001) modeled the activity-dependent survival of OGCs providing lateral inhibition between mitral and tufted cells, observing that new neurons do aid in orthogonalization. A more recent study by Chow and colleagues (2012) explored, in detail, the role of OGC turnover in a relatively realistic biological model of the OB. As with the Cecchi study, the activity dependence of OGC survival was an important component of the network's function, with the Chow study showing, in some detail, how the decorrelation provided by newborn OGCs could potentially map to experimentally observed results from OB recordings.

A UNIFYING VIEW OF “WHY NEUROGENESIS?”

From a distance, the well-studied mammalian neurogenic systems, the OB and DG, are not obviously related to one another, thus, often inspiring the question of why these and why not other regions? One perspective is that these regions all share one key feature in common; the semantic space in which they are encoding is either unbounded or changing dramatically. For example, the mouse OB has roughly 1000 different ORNs, suggesting that the combinatorial space is $\sim 2^{1000}$; whereas the animal will only be exposed to a relatively small subset of these possibilities, there is the potential for being exposed to entirely novel odors and needing to isolate and distinguish them from similar odors. A similar argument could be made for the hippocampus. The hippocampus must have the capacity for encoding entirely novel episodes throughout life, many of which could not be anticipated a priori.

Similar arguments could be made for other neurogenic regions not discussed here, such as

the adult fish cortex and cerebellum, the post-natal mammalian cerebellum, and the birdsong system. Overall, one could potentially describe the need for new neurons to be related to the extent future information will relate to previously experienced information. Clearly, during development, a period in which neurogenesis is obviously needed, the experienced past explains little of the future. And in the case of extended cerebellum neurogenesis (and even broader fish neurogenesis), long-term physical growth likely stretches out the need for highly dynamic proprioceptive sensing. However, if one takes the case of vision as an example, once an organism reaches a certain age, it is unlikely they will be exposed to novel color or simple shapes. Higher level representations typically associated with hearing or vision, such as language or objects, can be novel throughout life, but also involve more sophisticated forms of learning, potentially even incorporating DG neurogenesis. Ultimately, this last point may explain the recent recognition that humans may not have robust OB neurogenesis (Bergmann et al. 2012); the diminished importance of olfaction in human behavior compared with other modalities may have made it sufficient for DG neurogenesis to handle the novelty in the olfactory world as well.

If the aforementioned speculation on the rationale for neurogenesis's limited locations has some validity, the next question is likely then “why the striatum?” Indeed, the recent observation that humans experience lifelong neurogenesis of a select population of striatal calretinin-positive interneurons is intriguing from a theoretical perspective (Ernst et al. 2014); however, the computational function of these interneurons is not well understood even without considering their neurogenic nature. However, based on the discussion above, one possibility is that the striatum (as opposed to the OB) is tasked with a greater computational burden in humans. Indeed, the striatum is known to be a key component of decision making and action planning (Guitart-Masip et al. 2014), functions that, presumably, are far more sophisticated in humans and other primates relative to smaller mammals.

WHAT IS NEXT FOR NEUROGENESIS MODELING?

Computational studies of neurogenesis have arguably been quite effective to date in impacting the dialog regarding neurogenesis function, and it is likely that they will continue to do so going forward. Although the impact of new neurons on DG is becoming clearer, the relationship of the DG to the CA3 as a whole is being reconsidered. Indeed, many of the classic models of the hippocampus have assumed a role for the DG that the current set of neurogenic DG models does not necessarily support. As a result, future studies more explicitly assessing how a heterogeneous DG population impacts CA3 coding will be invaluable in understanding the role of neurogenesis on broader hippocampal function. A similar challenge awaits OB and striatum models, as understanding the role of interneuron turnover will likely require an appreciation of how downstream regions are affected.

Furthermore, two other questions stand out for computational studies. First is the question of scale. The level of neurogenesis in humans has always been somewhat controversial, and recent advances in quantifying new neurons using C14 radiolabeling have only amplified the debate (Spalding et al. 2013). As we have suggested in previous work (Li et al. 2012), the scaling of numbers of synapses, such as the increase from young to old neurons, but also between small and large networks, has substantial statistical implications, making it highly likely that the effect of new neurons is scale dependent, which is notable given the relatively small sizes of all published neurogenesis models. The second challenge is that of affect. The observation that new neurons are related to antidepressant function has provided both excitement and uncertainty with regard to the function of neurogenesis. Aside from a few references (Becker and Wojtowicz 2007; Aimone et al. 2009), computational studies have not explicitly modeled the relationship of new neurons to the affective state of an animal. Nonetheless, as computational resources and techniques advance alongside ever-increasing biological data, it is highly likely that the future will enable computational

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studies of neurogenesis that can address these challenging questions.

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