

Unsupervised learning and adaptation in a model of adult neurogenesis

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Abstract

Adult neurogenesis has long been documented in the vertebrate brain, and recently even in humans. Although it has been conjectured for many years that its functional role is related to the renewing of memories, no clear mechanism as to how this can be achieved has been proposed. Using the mammalian olfactory bulb as a paradigm, we present a scheme in which incorporation of new neurons proceeds at a constant rate, while their survival is activity-dependent and thus contingent upon new neurons establishing suitable connections. We show that a simple mathematical model following these rules organizes its activity so as to maximize the difference between its responses, and can adapt to changing environmental conditions in unsupervised fashion, in agreement with current neurophysiological data.

1 Introduction:

The function of the mature brain is not only to be constantly ready to solve particular tasks, but also to learn new ones, adapt to changes in environmental conditions, and optimize its computational resources accordingly. While synaptic change is regarded as the most common form of modification underlying plasticity (notably in neural network models), it is by no means the only source of functional change in the brain. One alternate source is adult neurogenesis, i.e. the incorporation of new neurons into neural structures that have already passed through development.

It was long thought that neuronal production ended soon after birth, fueling a view of the adult brain as a finalized structure (as far as new neurons are concerned), with further plasticity concentrated on synapses. It took some time to realize and demonstrate that neuronal incorporation can, to different degrees, continue during the entire life of an animal. De-novo neuronal incorporation continues in the adult mammalian brain in the dentate gyrus of the hippocampus, the olfactory bulb and the association cortex [Altman 1965, Lois and Alvarez-Buylla 1994, Alvarez-Buylla and Lois 1995, Gould et al 1999b, Eriksson et al. 1998, Gould et al. 1999c]. Adult neurogenesis also occurs extensively in birds and other vertebrates [Alvarez-Buylla et al. 1992, Goldman 1998].

Based on the experimental evidence, it has been conjectured that adult neurogenesis could be related to brain plasticity and learning [Alvarez-Buylla et al. 1990, Kirn et al. 1994, Barnea and Nottebohm 1994, Gould et al. 1999a, Kempermann et al. 1997]. However, the functional mechanism of neuronal replacement remains elusive, and we do not understand the degree to which it may supersede, compete with or complement better understood plastic mechanisms. The observation of seasonal changes of neuronal incorporation and death in canaries, as they renew their yearly repertoire of songs, has led to the idea that neurons are not indefinitely plastic but that new neurons are needed for new memories. Despite the considerable interest and importance of the phenomenon, no clear mechanism has been described through which this memory renewal process would be implemented.

We describe here a simple model in which adult neurogenesis underlies unsupervised learning and adaptation in sensory processing. We chose the olfactory bulb (OB) as the neuroanatomical locus of the model, for adult neurogenesis has been extensively documented in this system, and the neuronal processing tasks are presumably better circumscribed than in other sensory systems [Mori et al. 1998]. The olfactory bulb is the first relay of the olfactory information. Olfactory receptor neurons express a single olfactory receptor and project to two glomeruli of each bulb in a topographically precise manner [Vassar et al. 1994, Mombaerts et al. 1996]. Each receptor may be activated by more than one odor and each odor may activate more than one receptor [Malnic et al. 1999, Hildebrand and Shepherd 1997]. Mitral and tufted cells (M/T), the output neurons in the bulb, receive their synaptic input from the olfactory receptors within single glomeruli. Odor information seems to be encoded in the spatial as well as the temporal responses of M/T cells. Olfactory discrimination is then dependent on the combinatorial pattern of activation of multiple M/T cells. Given the promiscuous nature of olfactory receptors, the discrimination of odors is importantly dependent on the tuning of the combinatorial response of M/T cells.

The activity of M/T cells is regulated by inhibitory granular cells. Granular cells

are unpolarized neurons that establish inhibitory dendro-dendritic connections with the M/T cells long secondary dendrites [Woolf et al. 1991], and are indeed thought to play an important role in lateral inhibition and in the tuning of M/T cell responses to different odors [Yokoi et al. 1995]. Each granule cell connects to several mitral cells that can be far away from each other given the extensive length of their secondary dendrites. Experimental results indicate that only inhibitory neurons are replaced in the OB. Whereas M/T cells are born before birth, the large majority of granular neurons continue to be born postnatally and into adult life [Rosselli-Austin and Altman 1979].

Based on the known anatomy and physiology of the OB, we modelled neurogenesis in this structure. It is important to remark that we are not presenting an exhaustive model of olfaction [Hopfield 1991], which would require a delicate understanding of the temporal dynamics of encoding [Laurent et al. 1996], but rather using it to demonstrate the computational potential of neurogenesis for information processing.

Model

We base our model on two fundamental observations. First, neuronal production in the sub-ventricular zone (SVZ) and migration toward the OB continue even in the absence of the bulb [Lois and Alvarez-Buylla 1994]; this suggests that cell birth and migration are not dependent on olfaction or activity within the bulb [Kirschenbaum et al. 1999]. Second, most newly incorporated neurons die within few weeks after differentiation, suggesting that those that do survive have achieved some elusive goal [Petreanu and Alvarez-Buylla 2000, Kirn et al. 1999]. Neuronal activity is known to be necessary for survival during brain development but not for the initial synapse formation [Katz and Shatz 1996, Verhage et al. 2000]. Moreover, activity-dependent mechanisms also seem to play an important role in the recruitment or survival of postnatally generated OB interneurons [Corotto et al. 1994, Frazier-Cierpial and Brunjes 1989, Cummings et al. 1997]. These findings suggest that the survival of the newly-generated neurons is regulated through activity.

Thus we postulate the basic mechanism of the model: neuronal incorporation proceeds at a constant unregulated rate, whereas neuronal survival is modulated through activity-dependent apoptosis. New neurons arrive and establish random connections; those with useless connections fail to participate in relevant processing and soon die off, but neurons that establish useful connections in the context of the network can survive and are therefore incorporated into the final structure. Exactly which feature of neuronal activity ensures survival can then dictate the final function of the network.

The simplest model compatible with the experimental evidence consists of a layer of g glomeruli receiving one-to-one projections from an input or receptor layer and local lateral inhibition due to granular interneurons. The output of the system then equals the input minus the effect of inhibitory connections between the outputs:

$$\mathbf{y}^{(k)} = \mathbf{x}^{(k)} - G\mathbf{y}^{(k)} \quad (1)$$

where $\mathbf{y}^{(k)}$ is the activity of the output layer, $\mathbf{x}^{(k)}$ is the activity of the receptor layer when presented with input k , G is a matrix giving lateral inhibition, and $(y_i$ is the activity of glomerulus number i , Fig. 1). Solving for \mathbf{y} we obtain

$$\mathbf{y}^{(k)} = (1 + G)^{-1} \mathbf{x}^{(k)} \quad (2)$$

We assume that each granular cell has connections to only two projection neurons; therefore, G_{ij} is the density or number of granular neurons connecting M/T cells (or glomeruli) i and j , so that $G_{ij} = G_{ji} \forall i, j$ (connections are symmetric) and $G_{ii} = 0 \forall i$, (there is no self-inhibition). We also assume that the response of each M/T cell is normalized by the total number of synaptic connections [Chechik et al. 1999] and that neuronal responses remain in the linear regime; positive or negative activity should be interpreted in the context of a background level. Explicitly inserting a total synaptic weight normalization term $1 + \sum_j G_{ij}$ and symmetrizing the input, Eq. 1 becomes

$$y_i^{(k)} = \frac{x_i^{(k)} - \sum_j G_{ij}(y_i^{(k)} + y_j^{(k)})}{1 + \sum_j G_{ij}}$$

We finally assume for convenience that the output layer is normalized, $\|\mathbf{y}^{(k)}\| = 1 \forall k$.

We assume that only interneurons are replaced, arriving at a constant rate with randomly distributed connectivity; rules in which granular cells connect to more than two neurons and whose survival depends on the product of multiple inputs lead to combinatorial encoding strategies, but this is an issue outside the scope of the present paper. The regulation of the survival rate of the interneurons is implemented as a function of their activity, which indicates how well they are connected to active output cells, so that active cells survive and inactive cells do not. Our key assumption is that the survival of the granular cells depends on the product of the inputs, so that granular cells connecting glomeruli i and j will survive if the value of $y_i y_j$, averaged over the time of presentation of the entire set of stimuli, is greater than or equal to zero; this amounts to a somatic coincidence rule. Thus, when $\langle y_i y_j \rangle \gg 0$ all newly arrived neurons survive, and so ΔG_{ij} has its full value; while $\langle y_i y_j \rangle < 0$ results in massive death and $\Delta G_{ij} < 0$. This leads to a simplified update equation given by

$$\Delta G_{ij} \sim \langle y_i y_j \rangle, \quad (i \neq j) \quad (3)$$

where $\langle \rangle$ denotes the average over the ensemble of inputs $k = 1 \dots N$. A non-linearity is introduced through the condition that G be positive definite, $G_{ij} > 0 \ i \neq j$, i.e. the population of granular cells cannot be negative.

Results

Based on the previous considerations, we implemented a simulation of the process of *training* the network with the activity based replacement of the inhibitory interneurons. The left panel of Fig. 2 shows a set of 10 odors represented as different mixtures of receptor bindings. The right panel shows the result of iterating a cycle of presentation of the set of odors followed by neuronal replacement on a model network with 10 M/T cells. The result of the update rule specified by Eq.3 is to *orthogonalize* the output, which can be seen by analyzing the fixed point of the system: $\Delta \mathbf{y} = 0 \Rightarrow \Delta G_{ij} = \langle y_i y_j \rangle = 0 \forall i, j$ and given the normalization of \mathbf{y}_i , $\langle y_i y_j \rangle \sim \mathbf{I}$, where \mathbf{I} is the

identity matrix. The simulation displays a very sharp orthogonalization of the output vectors, which can be further appreciated in the evolution of the response to a single odor (Fig. 3). The orthogonalization of the output maximizes, to linear order, the separation between output vectors and is the simplest way of achieving discrimination. An orthogonal set of neural responses is robust to the presence of noise because the representatives are maximally distant from each other [Shannon 1993]. In this case, an orthogonal set of responses from the output of the M/T cell layers corresponds to the maximal difference in the the spatial response in the layer for each odor. So it is possible to implement a simple algorithm based on neurogenesis and neuronal replacement that achieves a complex mapping of input stimuli in neural space.

To quantify the orthogonalization process, we computed the determinant of the 10×10 matrix of odors and M/T cells (see Methods). The determinant of a set of n normalized vectors of n components has the property that it is maximal ($= \pm 1$) when the vectors are mutually orthogonal, and becomes zero whenever the vectors are linearly dependent. Thus, the determinant is a good indicator of the ability of a system to maximally separate responses to linear order. The evolution of the determinant and the total number of granular cells incorporated are depicted in Fig. 4, together with the rate of incorporation, as a function of the iteration number.

The other functional property of the algorithm is its adaptability to changes in the input ensemble, i.e. a change in the set of odors the network is presented with. This is a feature of paramount importance for early odor sensory processing, given the intense seasonal changes produced, e.g., by blooming, migration and foraging, and because the presence of a single odorant in high concentrations is enough to upset the output of a system like the OB, due to the promiscuous nature of the olfactory receptors. In our model, training is unsupervised, and consists simply of exposing the system to the environment until a balance between cell incorporation and death is established. Continued exposition to a constant environment does not result in over-training. If the environment is changed, the balance is upset and the system evolves until a new balance is achieved. To see how our model copes with a changing environment, we simulated a periodic renewal of the odor ensemble, on a time-scale similar to that of the convergence of the orthogonalization process. The initial update rule was modified to include a slow death process,

$$\Delta G_{ij} \sim \langle y_i y_j \rangle - \mu_{ij} \quad (4)$$

where μ_{ij} is a stochastic variable representing a constant rate of *unregulated* and *non-specific* death, independent for each granular unit, $\mu_{ij} = \hat{\mu} \forall ij$. The results can be appreciated in Fig. 5, which depicts the evolution of the output determinant, the total number of granular cells, and the number of granular cells connected to one arbitrary pair of glomeruli. After the initial rise, the total number of granular cells remains relatively constant during ensemble changes, whereas any one particular location in the granular network fluctuates more tightly with the changes. The orthogonalization process, although dependent on the identity of the ensemble, is basically unaffected by the changes, as the determinant is increased several orders of magnitude. Importantly, the non-specific death term in the update equation, though small, is essential to assure adaptability. Its absence leaves the network prone to preserve traces of previous

ensembles, which hinder the capability of orthogonalizing new ensembles (data not shown).

Unlike synapses, which connect only two neurons, interneurons connect a large number of M/T cells. Expanding the connection rule to higher connectivities leads to combinatorial encoding, which will be explored in detail elsewhere. Here we shall only mention the basic principle. Consider a connection structure where granule cells connect to three M/T cells, and where survival depends on coincidences between all three inputs. There will be various pairwise terms as described above, and in addition, a novel term will appear with the form $\langle y_i y_j y_k \rangle$. Please notice that the set of y that satisfy $\langle y_i y_j y_k \rangle = 0$ is no longer a linear space of dimension g , since collections where at most two y are nonzero satisfy this criterion, and so the solution set now may become much larger, of order $g^2/2$ elements. It is not difficult to see that for higher connectivities, as found in the real system, this can lead to combinatorial properties, but these models have to be explored numerically.

Discussion

We have modelled a simplified olfactory bulb circuit based on its known anatomy and physiology in which granule cells are constantly replaced. We have shown that by having the young neurons to connect randomly and to survive in an activity dependent basis, as experimental evidence suggests, neurogenesis is capable of maximizing the discrimination of odors in an unsupervised manner. Moreover, this discrimination task is robust to a changing environment by adding a small random cell death rule.

Several physiological considerations are in order here. In the first place, the implementation of the proposed survival rule implies only a *local* or somatic computation [Koch 1998] (for instance, a biochemical mechanism involving a high stoichiometry or cooperative reaction, such as the CamK-II/Ca⁺⁺ pathway), and so requires a completely different molecular machinery than synapse-specific modification mechanisms [Bailey et al. 1996]. One may think then that in evolutionary terms, the selection of different strategies of plastic modification may depend both on their computational possibilities and on ease of implementation, as well as accessibility: neurogenesis was already available to build the structure in the first place.

The second consideration concerns the apparently random distribution of brain areas where adult neurogenesis has been documented. Although our model was not intended to solve this puzzle, it suggests a possible answer. The replacement of entire neurons is a rather violent event, in network terms, and rather unlike smoother and more gradual rules like Hebbian changes or back-propagation. The relationship between our algorithm and such gradual rules is similar to that between Monte Carlo methods and gradient descent. In the former, the minimization of an objective or cost function is done by randomly searching the configuration space and thus avoiding trappings in local minima, whereas the latter performs the minimization by downhill descent on the steepest directions of the function. In these methods, the dimensionality and degree of smoothness of the function to be optimized plays a substantial role as to which performs best. Thus we hypothesize that the dimensionality of the input in competition with the amount of computational resources dedicated to a task is what determines the

existence of adult neurogenesis. For instance, in the visual pathway there are several layers of processing before reaching the cortex, whereas the OB, whose input space has an intrinsic high dimensionality [Hopfield 1991], projects directly to the olfactory cortex. If synaptic plasticity is implemented by a diffusive substance, a trophic factor for instance, then the diffusive process coupled with the normal excursion of axonal and dendritic extensions can mislead the guidance process. This will be particularly true if very distant locations in the network must be connected, a very likely scenario in the case of olfaction, where statistical correlations in the input do not possess a smooth topographic projection, i.e. there is no simple sense of “neighborhood”. According to this hypothesis, the incorporation of new neurons can be correlated more precisely with changes affecting global aspects of the input statistics.

Recent experiments suggest that the function of the OB circuitry is to reduce the overlap of the odor representation at the M/T layer, therefore maximizing olfactory discrimination [Friedrich and Laurent 2001]. Our model suggests that this function of the OB circuitry might be achieved and optimized by a slow but continuous activity dependent survival of newly-generated granule neurons. This activity dependent incorporation of neurons optimizes olfactory discrimination, reducing the overlap in the odor representation in the M/T cell layer for the particular ensemble of odors present in the environment, even as it changes. As the differentiation and activity-dependent selection of neurons spans days or weeks [Petreanu and Alvarez-Buylla 2000, Kirn et al. 1999], this neurogenesis-mediated sensory optimization is hypothesized to take place on the same time scale, similarly to other observed plastic changes. Coincidentally with the predictions of the model, experimental evidence suggests that interfering with olfactory bulb neurogenesis affects olfactory discrimination [Gheusi et al 2000]. Olfactory deprivation, which is known to reduce the survival of new granule neurons, also disrupts the representation of odors in the M/T layer in a way consistent with this model [Guthrie et al. 1990]. Moreover, brief olfactory exposures to a single odor during several days can dramatically alter mitral cell responsiveness to odors, as predicted by the model [Buonviso and Chaput 2000]. It remains to be shown whether these experience mediated alterations of neuronal representations are dependent on the incorporation of new neurons into the OB.

We have presented the first mechanistic model in which adult neurogenesis provides the scaffold underlying a computational task. Postulating an activity-dependent survival signal for the newly-generated granular cells, the model predicts the orthogonalization of the neural responses of the OB to changing odor ensembles, the differential incorporation of neurons in particular regions of the OB upon olfactory environmental changes, and the necessity of a background of constant non-specific cell death to achieve an efficient adaptation. It also suggests that the structure of the input space determines to some extent the existence of this mechanism in particular brain areas, thus providing a series of predictions for future experimental manipulation.

Methods

The update of the granular layer was computed from Eq. 2 with $\Delta G_{ij} = \gamma \langle y_i y_j \rangle$ where the average is computed over the cycle of presentations of the odors; $\gamma = 5 \times 10^{-3}$ in all simulations. The steady-state solution is computed for each odor, and then normalized

to $|\vec{g}| = 1$. The orthogonalization is quantified in Fig. 4 by computing the rank-1 determinant $\Delta_{\mathcal{O}}$ of the output matrix $\mathcal{O} = \{\mathbf{y}^k\}$, where k ranges over the ensemble of odors. In general, Δ_A is the determinant of the largest non-singular submatrix of A . It can be computed for any rectangular matrix from the singular value decomposition $A = U\Lambda V$, as $\Delta_A = \prod_{\Lambda_{ii} \neq 0} \Lambda_{ii}$. In our simulations A always has rank 10, which is the maximal rank, because it is nonsingular. The evolution of the total number of granular cells in the network shows a monotonic increase, although the incorporation rate slows dramatically after the stabilization of the orthogonalization is reached. For the purpose of this demonstration, the rate of non-specific death was kept equal to zero. For the simulation of Eq. 4 depicted in Fig. 5 the random death is defined as a stochastic variable which can take the values $\hat{\mu} = 5 \times 10^{-3}$ with probability $p = 5 \times 10^{-3}$ and $\hat{\mu} = 0$ with probability $1 - p$ in each iteration of the algorithm.

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Figures

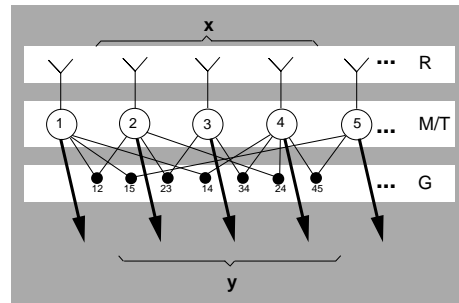


Figure 1: Simplified anatomy of the Olfactory Bulb used in the model. The vector \mathbf{x} represents the activity of the receptor layer R, and \mathbf{y} the activity of the mitral cell layer M/T. Granular inhibitory cells G establish pairwise connections with the mitral cells.

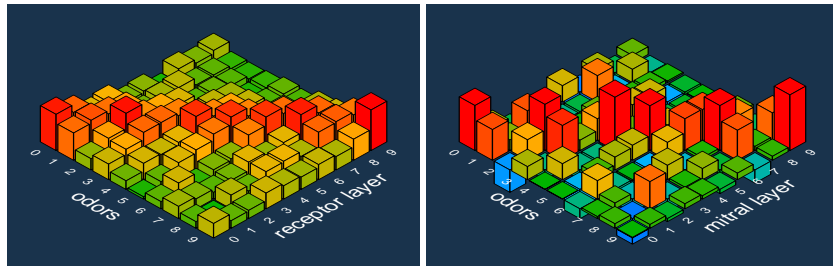


Figure 2: Representation of the smell matrix before and after application of the proposed algorithm. Left panel: an instance of odor ensemble with different degrees of mixing between receptors. Right panel: the steady state achieved as a result of repeated application of the algorithm; the mitral cell layer organizes to segregate topographically the outputs.

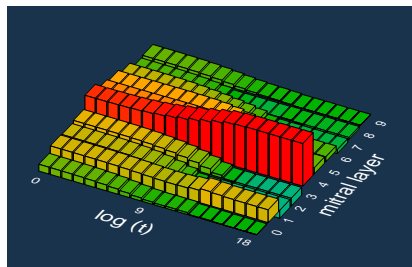


Figure 3: Evolution of the mitral cell layer response to one odor.

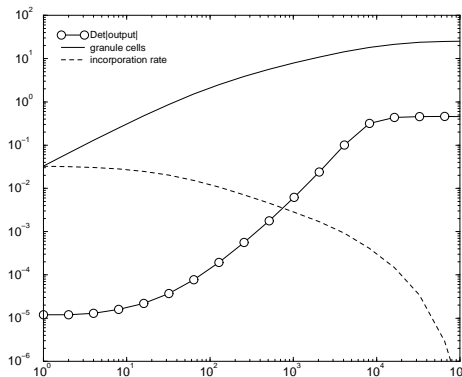


Figure 4: Evolution of the network. Initially, the mitral cell layer matrix determinant equals the small odor matrix determinant. As the algorithm advances, the determinant (circle) as well as the total number of granular cells in the network (solid line) grow until a plateau is reached, after which the incorporation slows (dotted line, representing the derivative of granular cell incorporation) and finally approaches zero.

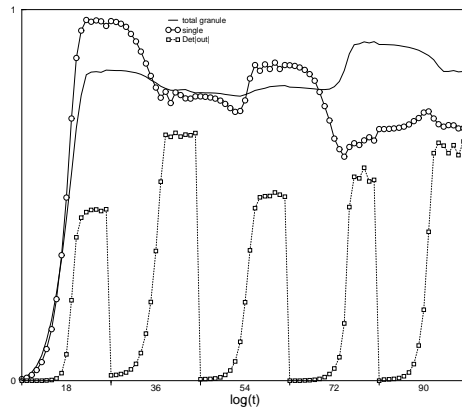


Figure 5: Adaptation of neurogenesis to environmental changes. Each tick in the horizontal axis represents the exposure of the network to a new odor ensemble; the time axis is in a logarithmic scale which is reset after each new exposure. Symbols correspond to: solid line, total number of granular cells; circles, number of cells at one arbitrary position in the granular network; and squares, mitral cell layer matrix determinant.