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A stochastic model of neurogenesis controlled by a single factor

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HIGHLIGHTS

- We propose a stochastic model of neurogenesis for mammalian.
- It is consistent with experimental data from the murine neocortical neurogenesis.
- The process is controlled by a single factor that is inherited by daughter cells.
- The model contains, as ingredients, asymmetric division and gradual specification.

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ABSTRACT

The researches on cortical neurogenesis reveal that asymmetric division plays a key role in controlling the balance between the self-renewal of stem cells and the beginning of the neural differentiation. In such a process a neural stem cell divides by mitosis, originating a postmitotic neuron and other pluripotent stem cell available for subsequent differentiation events.

In addition, studies of cell lineage trees of cultured neural progenitors reveal tree shapes and subtrees recurrent, consistent with a stochastic model of division symmetrical/asymmetrical. These considerations have led us to develop a stochastic model of neurogenesis in order to explore the possibility that this is controlled primarily by a single factor (i.e. the concentration of mNumb in the cell). We contrast the predictions of our model with experimental data and compare it with other models of neurogenesis.

1. Introduction

The mammalian cerebral cortex is composed of six concentric layers of glutamatergic pyramidal neurons (projection neurons) and GABAergic inhibitory interneurons which form local circuits. Each of the layers of pyramidal neurons is characterized by the number of neurons, their functional properties and innervation patterns. The layer I, closest to the pial surface, is the least populated. The layer II/III (in the mouse both layers are merged) establishes connections between different cortical areas. The fourth layer neurons receive axons from subcortical areas (i.e. the thalamus), while the layers V and VI send projections to such areas (Vetter and Dorsky, 2005). This laminar pattern of cortical organization is essential for normal functioning of the neocortex and there are pathologies associated with disorders in neurogenesis and lamination, such as epilepsy and severe mental retardation (Manzini and Walsh, 2011). The pyramidal neurons and astrocytes of neocortex are originated from pluripotent neural progenitor cells (NPCs) of the neuroepithelium of dorsal telencephalon. These NPCs proliferate as "stem cells", to generate other pluripotent NPCs and postmitotic neurons which initiate differentiation and migrate radially outwardly from the ventricular surface, forming part of cortical layers. Pyramidal neurons originate in a time interval known as neurogenetic interval (NI), while astrocytes originate immediately after this. Moreover, GABAergic interneurons and oligodendrocyte precursors originate from ventral telencephalon. (The oligodendrocyte precursors originate during the postnatal period.)

Pioneering studies (Angevine and Sidman, 1961) using radioactive thymidine pulses on successive days of development show a close correlation between the time of birth of the neuron and their final layer position. Indeed, by this method, in those NPCs in S period, radioactive thymidine is incorporated in the process of synthesis of their DNA. So that if they are in their final mitotic division when the thymidine pulse occurs, they will generate postmitotic neurons with a level of detectable label. Thus the pulse time can be correlated with the observation of the mark in one of the cortical layers. This method has revealed a temporally ordained pattern in cortical histogenesis. Neurons that originate

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first migrate out of the ventricular zone and form the so-called preplate. Later neurons migrate to it forming the cortical plate, to split the preplate in a marginal zone (future layer I) and a deeper layer (the intermediate zone) which containing neurons of the subplate, with transient functions as "guidepoints" for thalamic axons innervating cortical layers. Within the developing cortical plate, different cortical layers (II–VI) are formed from an inside out pattern, so that deeper layers are formed from the first born neurons, followed by radially migrating neurons, to form the shallower layers (Nowakowski and Hayes, 2005). Moreover, the laminar identity of each neuron is determined by its last mitosis (neural birthday): newly generated neural precursors, transplanted after the last mitosis, from brains at early stages (where should form the layer VI) to brains of older embryos (forming the layer II), remain committed and only migrate to layer VI (Mc Connel and Kaznowski, 1991).

Neurogenesis is performed by three types of division: non-neurogenic symmetric divisions to generate two NPCs from an original NPC; neurogenic asymmetric divisions, which give a neuron and one NPC and neurogenic symmetrical divisions, in which a NPC originates two neurons. Initially the non-neurogenic symmetrical divisions establish the initial NPCs proliferative population. Asymmetric divisions are more frequent during peak period of neurogenesis, followed by an increase in the proportion of symmetric neurogenic divisions (Takahashi et al., 1996). In the mouse, neurogenesis takes place between embryonic day 10 (ED10) and ED17 (neurogenic interval, NI), comprising a total of 11 cell cycles. In each of them, a fraction of NPCs differentiates as postmitotic neurons (Q fraction) and the complementary fraction remains in proliferative state (P fraction) (Nowakowski and Hayes, 2005). Measuring the relative proportions of NPCs and postmitotic neurons generated along NI, Takahashi et al. (1996) have determined the temporal evolution of P and Q fractions. Their results show that these fractions are time dependent (elapsed cell cycle). In that work, it appears that all NPCs initially divide symmetrically to produce more NPCs, thus establishing the initial proliferating population NPCs ($P=1, Q=0$). Over the cell cycles, an increase of Q (and a decrease in P) occurs, reaching values of $P=0$ and $Q=1$ at the end of NI. Given that the "birthday" of the neuron determines its laminar identity, the evolution of P and Q determines the distribution of the progeny of the NPCs in each of the layers.

In recent years, these histogenetic studies of the neurogenesis have been complemented by lineage tree studies from cultured NPCs at clonal density (Qian et al., 2000; Shen et al., 2002). These studies provide a sharper information about cell division processes and fate determination, since the trace of cell divisions (lineage) of a NPC to its final destination (a differentiated cell that expresses a specific marker) can be followed by video microscopy. These studies reveal recurrent shapes of lineage trees or subtrees. At first glance, this recurrence could be attributed to predetermined patterns of cell division in mammalian neurogenesis, as shown in invertebrates (Skeath, 1999). However, given the large number of cells involved in neurogenesis of mammals, a totally predetermined mechanism is not very credible. This led Slater et al. (2009) to test different stochastic models that incorporate symmetric (stem cell–stem cell and neuron–neuron) and asymmetric (stem cell–neuron) division probabilities. These authors, in their modeling strategy, assume that the nodes of the tree originated by the division may be terminals (type N) or branching (type S), mimicking the evolution of a stem cell lineage, in which the proliferating cells are only NPCs. Their results show that models which include probabilities depending on generation, reproduce imbalance distributions of lineage trees consistent with lineage trees observed in culture. Thus, a stochastic mechanism for neurogenesis of mammals is plausible.

We have not found in the literature models that formulate a cellular mechanism of neurogenesis that accounts for more global aspects of cortical histogenesis: the evolution of P and Q fractions over NI. In this paper, we develop a model which incorporates the stochastic nature assumed for neurogenesis in the work of Slater et al. (2009) and we incorporate a hypothetical mechanism at the cellular level: the synthesis of a "neurogenic factor" and their stochastic distribution between two postmitotic cells. Our model reproduces the evolution of P and Q fractions described in the work of Takahashi et al. (1996).

2. The model

We assume that the cellular concentration of a certain molecule x controls the neurogenesis process. Initially, the first progenitor cell has a concentration $x=x_o$ (which we take as a unit).

The concentrations of x, inherited by both cells after the first division (namely $x_1^1(t=0)$ and $x_2^1(t=0)$) are not independent since they are related by the following link.

$$x_1^1(t=0)+x_2^1(t=0)=2x_o. \tag{1}$$

Here the superscript indicates the generation and the subscript identifies the cells. The constrain Eq. (1) states that if one of the sister cells inherits high concentration of x, his sister will inherit low concentration. We assume that one of the inherited concentrations, $x_1^1(t=0)$, is determined by some probability distribution $P(x)$, whose most probable value is x_o. More precisely, the probability that the concentration inherited by a daughter falls between x and $x+dx$ is $P(x)dx$. The inherited concentration corresponding to the sister ($x_2^1(t=0)$) is automatically determined by Eq. (1). If the inherited concentration ($x_1^1(t=0)$ or $x_2^1(t=0)$) is less than or equal to certain critical value x^*, the daughter cell remains in proliferative state, otherwise the cell leaves the cycle as a neuron. For cells in proliferative state, between cell divisions (cycles), we assume the synthesis of x according to an elemental equation occurs.

$$\frac{dx}{dt}=\beta(N_c)-\nu\frac{x}{k+x}, \tag{2}$$

where $\beta(N_c)=\alpha N_c+\beta_o$ is the rate of synthesis of x which depend on the number of cell cycle (N_c) and we assume a Michaelis–Menten degradation process of parameters ν and k. Hence, if $x_1^1(t=0)\le x^*$ (and/or $x_2^1(t=0)\le x^*$), to determine the concentration of x just before the second division, we integrate Eq. (2) starting from $x_1^1(t=0)$ (and/or $x_2^1(t=0)$) to obtain $x_1^1(t=T_1)$ (and/or $x_2^1(t=T_1)$). Here T_1 is the time between the first and second cell division, i.e. the duration of the cell cycle. For the second cellular division, the progenitor has a concentration $x_1^1(t=T_1)$ (and/or $x_2^1(t=T_1)$). Hence the daughters will have concentrations linked by

$$x_1^2(t=0)+x_2^2(t=0)=2x_1^1(t=T_1); \tag{3}$$

and/or

$$x_3^2(t=0)+x_4^2(t=0)=2x_2^1(t=T_1). \tag{4}$$

Now, the probability of inheritance for $x_1^2(t=0)$ (and/or $x_3^2(t=0)$) will be given by $P'(x)$ similar to $P(x)$ but will have its maximum value at $x_1^1(t=T_1)$ (or $x_2^1(t=T_1)$).

The value of $x_2^2(t=0)$ (and/or $x_4^2(t=0)$) is determined by the link Eq. (3) (and/or Eq. (4)). Each time the concentration of x is less than or equal to the critical value x^*, we repeat this procedure on each of subsequent cell divisions (see Fig. 1). That is, if the cell k cell of generation j inherits $x_k^j(t=0)\le x^*$, it remains in proliferate state. Then we evolve x_k^j, from $t=0$ to $t=T_j$ through Eq. (2). When mitosis occurs, the concentrations for the daughters will be bound by

$$x_i^{j+1}(t=0)+x_{i+1}^{j+1}(t=0)=2x_k^j(t=T_j). \tag{5}$$

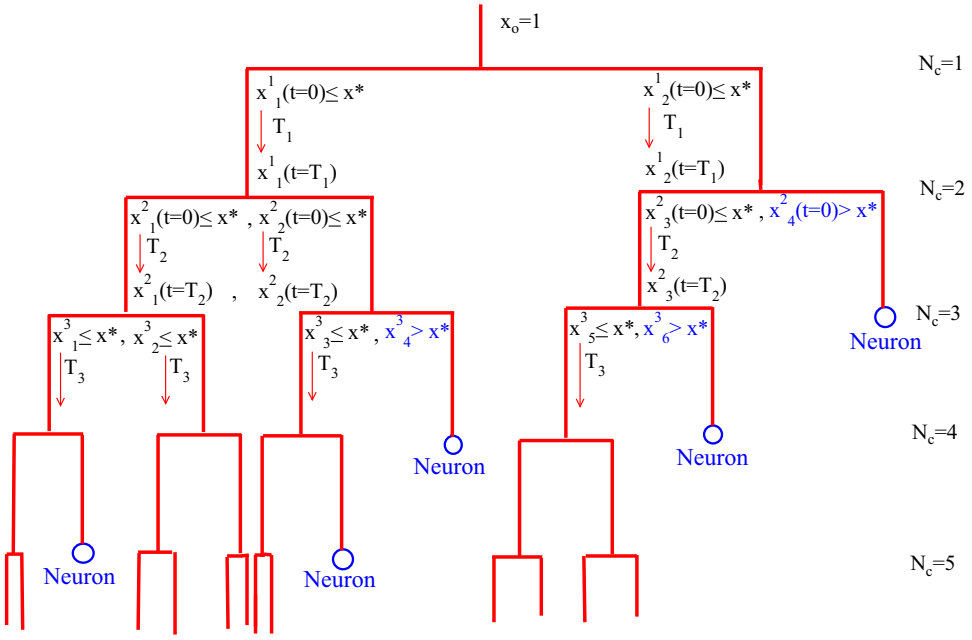

Fig. 1. Rules for the generation of cell lineage trees.

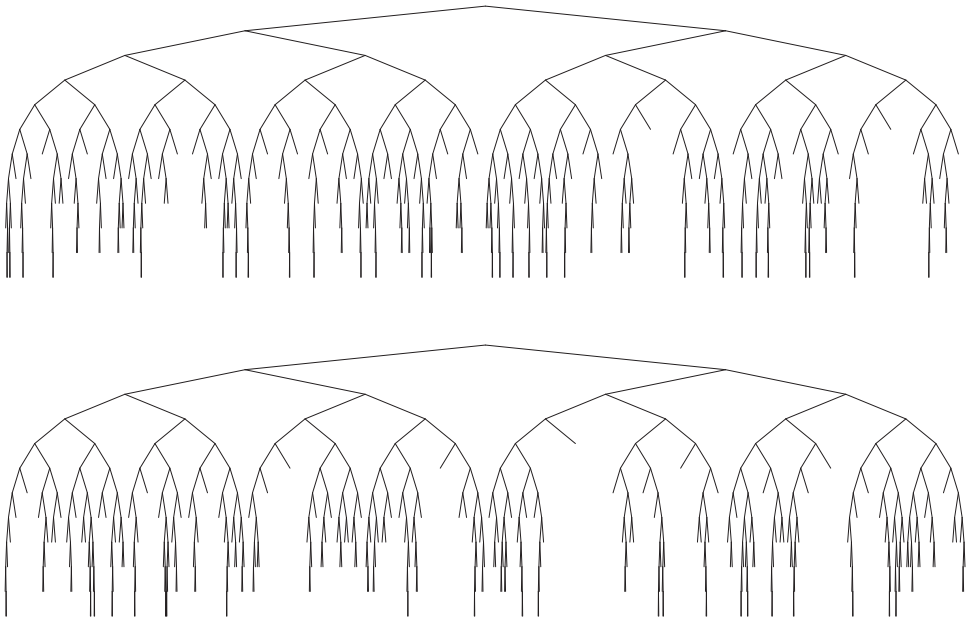

Fig. 2. Two realizations for cell lineage trees according to the rules explained in the text.

The concentration $x_i^{j+1}(t=0)$ is determined through the probability distribution $P(x)$ whose maximum is at $x_k^j(t=T_j)$. The second concentration $x_{i+1}^{j+1}(t=0)$ is determined by Eq. (5). Thus we obtain similar lineage trees to those shown in Fig. 2.

The quantities of interest are

- $Q(N)$, the fraction of differentiated cells as a function of cell cycle number N_c.
- $\Pi_{s,s}(N)$, the probability of symmetric divisions that lead to both daughters as proliferating cells.
- $\Pi_{q,q}(N)$, the probability of symmetric divisions that produce neurons.
- $\Pi_{s,q}(N)$, probability of asymmetric divisions (one stem cell, one neuron).

We used three different probability distributions, all of them with a width proportional to the most probable value. In that way, we avoid possible non-biological values for x (i.e. $x<0$). In the graphs of Fig. 3 it is shown schematically such distributions.

- $P_g(x)$ is a Gaussian of width $\sigma=(a/2)x_o$.
- $P_c(x)$ is an uniform distribution for $x_o(1-a/2)\le x\le x_o(1+a/2)$.
- $P_t(x)$ is an asymmetric triangular distribution for $x_o(1-a/3)\le x\le x_o(1+2a/3)$.

Let us remember that the distribution $P(x)$ is updated before each cell division so that the most probable value (here denoted as x_o) becomes the concentration of progenitor cell. In all cases we set the

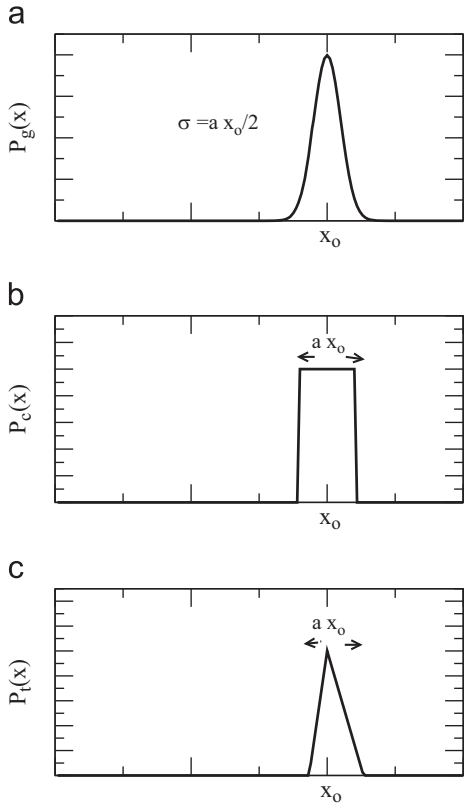

Fig. 3. The graphs show the probability distributions (a) Gaussian, (b) uniform, (c) asymmetric triangular.

value of $a=0.2$, which leads to fluctuations in the inherited x from about 10% of the most probable value.

3. The murine neocortical neurogenesis

We apply this model to the mouse neocortical neurogenesis. It is known that during the process, which lasts 6 days, there are 11 cell cycles of varying duration. During the first day, there are about three cycles while in the latter, the length of the cycle is nearly a day. That is, the cell cycle length varies from 8 h to 18 h. First, we determine how the time of integration for Eq. (2) depends on cycle number (N_c). From the experimental data shown in Fig. 7 of Takahashi et al. (1996), we obtain the graph depicted in Fig. 4 where the embryonic days (ED) vs. number of cell cycle (N_c) is plotted. The stars are experimental data while the solid curve corresponds to the following fit:

$$ED(N_c) = 0.237N_c^{1.345} + 11. \quad (6)$$

Then, we evaluate the length of cell cycle (in days) as the derivative

$$T(N_c) = d(ED)/dN_c = 0.319N_c^{0.345}. \quad (7)$$

In Fig. 5, we show the plot corresponding to the fraction of differentiated cells Q as a function of the number of cell cycles N_c for the three distribution of probabilities $P_g(x), P_c(x)$ and $P_t(x)$.

The stars correspond to the experimental values taken from Takahashi et al. (1996). Unfortunately, the authors do not provide the errors. The curves in black correspond to the mean values taken over 2600 realizations. The error bars show how the results of each realization are dispersed around the average, do not indicate the error in this, which is, for 2600 realizations, non-visible on the scale of the graph.

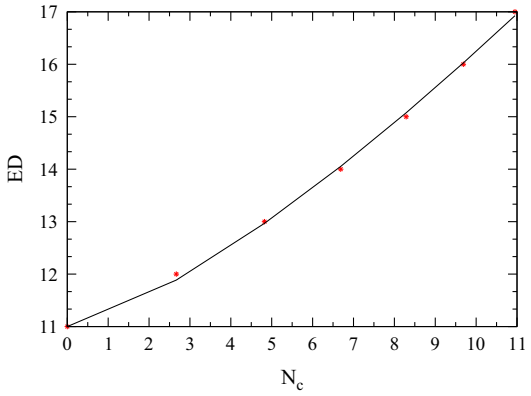

Fig. 4. Embryonic days (ED) vs. number of cell cycles. The stars correspond to experimental values, taken of Takahashi et al. (1996). The solid line corresponds to the fit $ED(N_c) = 0.237N_c^{1.345} + 11$.

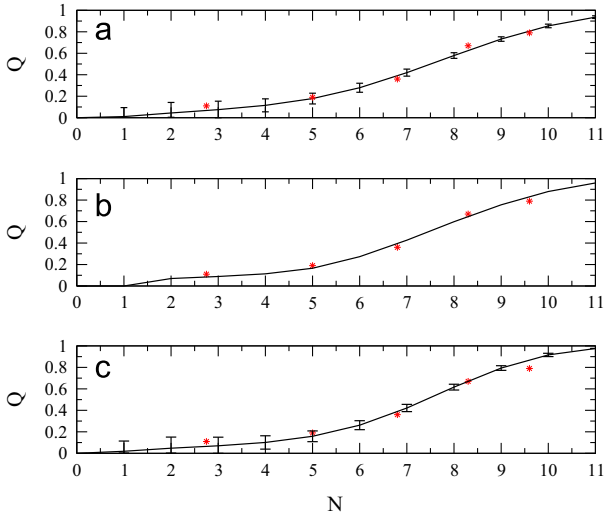

Fig. 5. The fraction of differentiate neurons (Q) vs. number of cell cycles (N_c) for three distribution of probabilities. (a) P_g, Gaussian distribution, (b) P_c, uniform distribution, (c) P_t, triangular distribution. The stars correspond to experimental values, taken of Takahashi et al. (1996) while the curves correspond to the results of our model using the parameters shown in Table 1.

The graphics shown in Fig. 6 are the probabilities of stem cell–neuron asymmetric division $\Pi_{s,q}$, stem cell–stem cell symmetric division $\Pi_{s,s}$ and neuron–neuron symmetric division $\Pi_{q,q}$ for the three distribution $P_g(x)$ (a), $P_c(x)$ (b) and $P_t(x)$ (c). The parameters used for the calculations are shown in Table 1.

4. Discussion and conclusions

The model presented here takes into account two phenomena occurring in the process of neurogenesis. During lineage progression, elapses a gradual process of neural specification (modeled as a dependency of the rate of synthesis of x on the number of cell cycles). Furthermore, the phenomenon of asymmetric inheritance by which the division of a stem cell originates another stem cell of equal level of pluripotency and a specified cell (postmitotic neuron) or more committed in neural specification (basal progenitor cell) (Knoblich, 2008). The latter is introduced by means of the link between inherited concentrations of an x factor by sister cells and its effect becomes noticeable between the sixth and the tenth cell cycle. The results show that our model is consistent with experimental data. This indicates that the process of neurogenesis could be controlled, at least in first approximation, by a single factor.

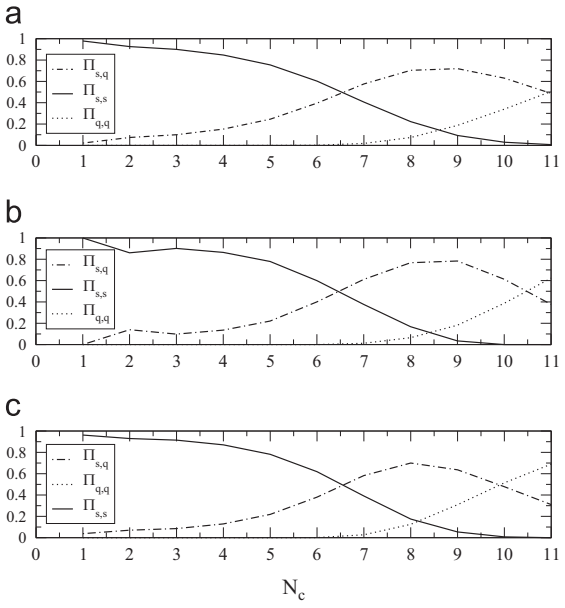

Fig. 6. Probabilities of symmetric division stem–stem ($\Pi_{s,s}$), neuron–neuron ($\Pi_{q,q}$) and asymmetric division ($\Pi_{s,q}$) as a function of N_c. (a) Distribution P_g, (b) distribution P_c, (c) distribution P_t.

Table 1
Parameters used in the calculations corresponding to the three probability distributions P_g, P_c and P_t.

Distribution	x^*	β_o (1/day)	α (1/day)	v (1/day)	k
P_g	1.225	1.91	4.778×10^{-2}	3.45	0.765
P_c	1.1	1.885	3.33×10^{-2}	3.45	0.755
P_t	1.1	1.925	2.62×10^{-2}	3.45	0.755

Regarding the gradual specification, in spite of its known role of the bHLH proneural factors, as Ngn2, as master genes of neural determination (Bertrand et al., 2002) there are no known mechanisms which regulate the timing of this process. In that sense, in recent years there have been researches directed toward understanding the mechanism of regulation of the balance between self-renewal and neural differentiation. In this direction, evidence has been obtained that the relative amount of Pax6 (a paired-domain transcription factor homeodomain-containing) controls the balance between the self-renewal and neurogenesis in neocortical stem cells (Sansom et al., 2009). In relation to the second aspect (asymmetric division), in the development of neocortex different molecules have been identified whose asymmetric segregation is associated with different cell fate between daughter cells after mitosis, including Numb, EGFR, Staut between others (Zhong et al., 1996; Shen et al., 2002; Sun et al., 2005; Ferron et al., 2010; Kusek et al., 2012).

In this paper we present a phenomenological model that does not refer to a specific circuit of known molecules. It is based on two characteristic facts of the neurogenesis (a progression in the specification process and the asymmetric inheritance) associated with a postmitotic stochastic distribution of a master regulator.

Concerning this point, in the model we do not assume that x is a neurogenic factor intracellularly produced which is differentially segregated. In fact, a molecule that affects neurogenic factor values and it is differentially segregated will produce equivalent results.

This consideration is pertinent because some molecules asymmetrically secreted do not determine the destination directly, but other molecules involved in the same pathway do. Such is the case of the mNumb protein (a putative protein that activates Notch receptor degradation (Gulino et al., 2010; McGill and McGlade, 2003). Indeed, in cultures of telencephalic NPCs immunostaining has revealed that cells Numb + are Hes1 (a repressor of proneural gene Ngn2, activated by the Delta-Notch pathway) and vice versa (Ohtsuka et al., 2006), suggesting that the degradation of Notch by mNumb inhibits expression of Hes 1, initiating neural differentiation (Kageyama et al., 2008), a hypothesis that is supported by results of a mathematical model (Barton and Fendrik, 2013).

This simple view of neurogenesis does not rule out at all the existence of complex mechanisms that may occur in the process. For example, the simple dynamics assumed for the synthesis of x, Eq. (2) may represent, effectively, a complex regulatory network in which several factors act contemporaneously to control the neurogenesis. The results do not seem to depend too much on the type of probability distribution assumed for the inheritance of the factor x. What is remarkable is that the individual realizations for P_c are remarkably less scattered around the average than the other two distributions.

A characteristic of the cortical neurogenesis is the evolution of the proportions of the type of cell division. Initially symmetrical non-neurogenic divisions prevail. Near the end, they do symmetrical neurogenic divisions. The asymmetrical divisions are significant in the middle.

In our model, the inclusion of a constraint between the values of x that inherence between daughter cells, naturally generates such development. In our model, the inclusion of a constraint between the values of x that inherit the daughter cells, naturally generates such development. Finally, at the end of neurogenesis, there is a slight discrepancy between our results and what is expected: after the end of development (cell cycle 11), we would expect the fraction of stem cells present was 0 ($Q=1$). However, as can be seen in Fig. 5, there is still a small fraction ($Q \approx 0.93$–0.96). This small discrepancy could disappear if we include apoptosis processes in our model, that are known, occur during neurogenesis (de La Rosa and de Pablo, 2000).

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