

A system of transport and diffusion PDE for modeling the spatial organization of cell proliferation in the developing central nervous system.

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Biological introduction

The development of the organizational complexity of the central nervous system (CNS) requires temporally and spatially organized operation of developmental cell behaviors. One of them, the cell proliferation (CP) is involved in the generation of appropriate number of neurons for each CNS area. During the early CNS development cells divide symmetrically, i.e. each cell originates two similar proliferating cells. These dividing cells locate on the inner surface of the CNS forming the generation zone (GZ). As cells proliferate, they increase in number and the GZ thickens and expands tangentially. Later on, cells proliferate asymmetrically, i.e. each cell originates a similar proliferating cell and a neuron. Thus, the number of cells at the GZ stabilizes while neurons accumulate at the underlying pre-migratory zone. By the end of the proliferative phase the number of proliferating cells decreases, the GZ becomes thinner and finally disappears. CP involves an ordered sequence of cyclic events (cell cycle) with typical durations. CP involves two main phases: a) the mitotic (M) phase (kario- and cytocinesis) and b) the inter-M phase or interphase. The latter, in turn, is composed of the G1, S and G2 subphases. For each cell type the cell cycle length oscillates around a mean value. The total length and also that of the different phases, varies depending on the cell type. For each cell type the cell cycle length may significantly change when long periods or time are considered. This work analyzes the spatial organization of the CP during an early and brief developmental period using as experimental model a cortical visual area, the optic tectum (OT) of the chick embryo. OTs obtained from 2, 4 and 6 embryonic days (E2, E4, E6) were used. Between E2-E6 the OT undergoes changes in size and shape. OTs were processed for microscopic observations and proliferation records (PR) were constructed. A PR is defined as a numerical sequence of values of density of mitotic cells in successive ordered 25 um length windows along an intrinsic spatial axis, the OT cephalic-caudal axis. The total number of cells in the GZ was also computed for each 25 um window. The present analysis assumes that between E2-E6: (a) the cells divide symmetrically, (b) the number of neurons in the GZ is negligible and the increase in cell number in the GZ is mainly due to the symmetric divisions and (c) the cell cycle length does not change significantly between E2-E6.

The mathematical model

A system of transport and diffusion PDEs is introduced as a model to describe the spatially organized process of CP during the SNC development. As a prior step before dealing the three-dimensional case, an unidimensional version of the model is presented.

In this work we achieve a validation of the proposed model by means of experiments in accordance with this hypothesis. The differential equations for the unidimensional model are the following:

$$\begin{cases} \frac{\partial n_1}{\partial t} + \frac{\partial [v_1(t)n_1]}{\partial a} = \frac{\partial^2 [D(x)n_1]}{\partial x^2} & v_2(t)n_2(t, a=0, x) = v_1(t)n_1(t, a=1, x) \\ \frac{\partial n_2}{\partial t} + \frac{\partial [v_2(t)n_2]}{\partial a} = \frac{\partial^2 [D(x)n_2]}{\partial x^2} & v_1(t)n_1(t, a=0, x) = [2 - q(t, x)]v_2(t)n_2(t, a=1, x) \\ \frac{\partial n_3}{\partial t} = q(t, x)v_2(t)n_2(t, a=1, x) & \frac{\partial n_1}{\partial x}(t, a, x=x_+(t))=0 \quad \frac{\partial n_2}{\partial x}(t, a, x=x_+(t))=0 \quad \frac{\partial n_3}{\partial x}(t, a, x=x_+(t))=0 \\ n_1(0, a, x) = n_1^0(a, x) \quad n_2(0, a, x) = n_2^0(a, x) \quad n_3(0, a, x) = 0 & \text{boundary and initial conditions} \end{cases}$$

Notation t : time variable

x : abscissa of the transversal section of the neural tube, $0 \leq x \leq x_+$,

$x = 0$ cephalic tip, $x = x_+(t)$ caudal tip at time t

a : phase of the cellular division cycle $0 \leq a \leq 1$ in each of the two phases considered, namely G1-S-G2 and M

$v_1(t)$, $v_2(t)$: time reciprocal of cellular division (velocity of progression within each phase)

$D(x)$: “effective cellular diffusion” along the x -axis in the x – section

$0 \leq q(t, x) \leq 1$: differentiation rate

$n_1(t, a, x)$, $n_2(t, a, x)$: density of neuroepithelial cells in the x – section, time t , at stage a in phases G1-S-G2 and M,

$n_3(t, a, x)$: density of differentiated cells migrating in the x – section

The model length, x_+ , is also an unknown. As first step, only n_1 is considered.

The experimental data for the tectum at E2 were set as initial conditions for the model, which was then run for E4 and E6.

The approximate solution of the model for E4 and E6 was computed by finite differences. The discretization scheme was the following:

$$u(k+1, i, j) = u(k, i, j) - v \frac{\Delta t}{\Delta a} (u(k, i, j) - u(k, i-1, j)) + D \frac{\Delta t}{(\Delta x)^2} (u(k, i, j+1) - 2u(k, i, j) + u(k, i, j-1)) \quad (1)$$

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where $u(k, i, j) = u(k \Delta t, i \Delta a, j \Delta x)$

is the density of neuroepithelial cells at the section of the neural tube with abscissa $x = j \Delta x$, at time $t = k \Delta t$, and where $a = i \Delta a$ ($0 \leq a \leq 1$) is the stage in the sequence of phases G_1 , S , G_2 at which the cells are, with $a = 0$ corresponding to the beginning of G_1 and $a = 1$ to the end of G_2 .

Parameters ν and D were assumed constant, be it in E2-E4 or in E4-E6. The stability of the methodology was shown upon the following Stability Condition:

$$\nu \frac{\Delta t}{\Delta a} + 2D \frac{\Delta t}{(\Delta x)^2} \leq 1 \quad (2)$$

Model evolution between E2 and E4

A first value of the length in E4 was obtained based on cycle duration and cell density. We used the following parameter values:

$$\nu = 0,54 \frac{1}{h} \quad \Delta t = \frac{1}{6} h \quad D = 6 \frac{(\mu m)^2}{h} \quad \Delta x = 25 \mu m \quad \Delta a = 0,1$$

where h =hour, μm =micron .

These values comply with the Stability Condition (2) and allow obtaining the following equation:

$$U(k+1, j) = (1 + 0,9\alpha)U(k, j) + 0,0032 \left(\frac{U(k, j+1) + U(k, j-1)}{2} - U(k, j) \right) \quad (3)$$

with $\alpha = 0,0095$ (obtained from experimental data)

$$\text{and} \quad U(l, r) = \sum_{i=0}^l u(l, i, r) \quad (4)$$

is the total number of cells that at time $l \Delta t$ and in the section $r \Delta x$ are at some stage of the cycle $G_1 + S + G_2$.

Figure 1 shows the model response (blue) for E4 and the empirical data (magenta) obtained from E4 OT.

Model evolution between E4 and E6

A first value of the length in E6 was obtained based on cycle duration and cell density. Equation (1) was then applied to run the model between E4 and E6. We used the following parameter values

$$\nu = 1,53 \frac{1}{h} \quad \Delta t = \frac{1}{6} h \quad D = 2,4 \frac{(\mu m)^2}{h} \quad \Delta x = 25 \mu m \quad \Delta a = \frac{1}{3}$$

Notice that these values also satisfy the Stability Condition (2) and allow obtaining the following equation:

$$U(k+1, j) = (1 + 0,765\alpha(j)) U(k, j) + 0,00064 \left(\frac{U(k, j+1) + U(k, j-1)}{2} - U(k, j) \right) \quad (5)$$

with $\alpha(j)$ obtained from experimental data, and where $U(l, r)$ is the same as defined in (4).

Figure 2 shows the model response (blue) for E6 and the empirical data (magenta) obtained from E6 OT.

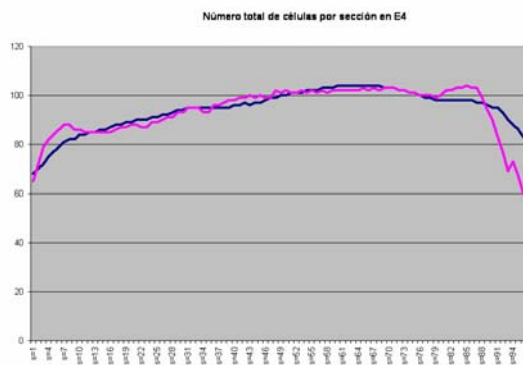


Fig.1

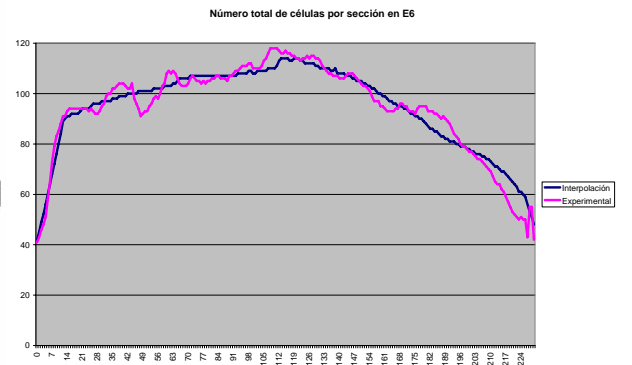


Fig. 2

It can be concluded that the total number of cells calculated by the model, for the defined temporal windows (E2-E4 and E4-E6), closely coincide with the empirical values recorded from samples histological sections of developing CNS. Besides, the model appropriately describes the empirically observed position-dependency of total number of cells along the OT cephalic-caudal axis, thus implying that the model appropriately describes the spatial organization of the proliferation activity

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