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Estimating the life-span of oligodendrocytes from clonal data on their development in cell culture

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Abstract

This paper presents a new method to analyze clonal data on oligodendrocyte development in cell culture. The process of oligodendrocyte generation from precursor cells is modelled as a multi-type Bellman–Harris branching process as suggested in an earlier paper [K. Boucher, A. Zorin, A.Y. Yakovlev, M. Mayer-Pröschel, M. Noble, An alternative stochastic model of generation of oligodendrocytes in cell culture, J. Math. Biol. 43 (2001) 22]. This model has been extended to allow for death of oligodendrocytes as well as a dissimilar distribution of the first mitotic cycle duration as compared to the subsequent cycles of precursor cells, which lengths are assumed to be independent and identically distributed random variables. Since the time-span of oligodendrocytes is not directly observable in clonal data, plausible parametric assumptions are invoked to make estimation problems tractable. In particular, the time to cell death follows a two-parameter gamma distribution, while the lapse of time between the event of cell death and the event of cell disintegration is assumed to be exponentially distributed. A simulated pseudo maximum likelihood method for estimation of model parameters has been developed using simulation-based approximations of the expected numbers and variance-covariance matrices for different types of cells. Finite sample properties of the estimation procedure are studied by computer simulations. The proposed method is illustrated with an analysis of the clonal development of O-2A progenitor cells isolated from the rat optic nerve and the corpus callosum.

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1. Introduction

The problem of quantitative inference from clonal data on oligodendrocyte development in cell culture has been addressed in several publications [1–9]. All these papers employed a multi-type Bellman–Harris branching process to model proliferation of oligodendrocyte precursor cells, known as O-2A progenitor cells, and their transformation into terminally differentiated oligodendrocytes. In the earlier version of the model, it was assumed that the initial population of progenitors is a mixture of subpopulations with different numbers of 'critical' cycles. In each of these subpopulations the probability of division is 1 until the critical number is reached and drops sharply to a fixed value $p < 0.5$ afterwards. The number of critical cycles is not directly observed, and one can only verify this basic assumption by fitting the model to experimental data on the evolution (in time) of clones consisting of two distinct types of cells. However, if one considers the whole population of cells, there is a more gradual decline in the division probability from 1 to p, suggesting that an alternative model in which there is a single population of progenitor cells with a gradually decreasing division probability is also plausible [3]. The model presented in [3] has a more parsimonious structure than its earlier version, while both models are in almost equally good agreement with the available experimental data.

In the present paper, we develop further the latest model characterized by a gradual decline in the probability of progenitor cell division. This model can be represented by a Bellman–Harris branching process with countably infinite number of cell types [3]. Our focus will be on the following two extensions of this basic model:

1. In order to estimate the life-span of oligodendrocytes in cell culture, the process of cell death needs to be incorporated into the stochastic model of proliferation and differentiation of O-2A progenitor cells. Among the two cell types, oligodendrocytes appear to be more susceptible to death. It is commonly believed that the death of oligodendrocytes normally begins on day 7 after plating and its rate increases with time. Furthermore, as our independent observations show, the proportion of cells (both progenitor cells and oligodendrocytes) surviving by day 8 is no more than 80%. The range of experimental data analyzed thus far has been inadequate for estimation purposes because the event of oligodendrocyte death is very rare during the first six days of culturing [10].

   In this paper, we present a new set of experiments specially designed to make the necessary quantitative inferences based on the proposed model. The existing experimental methods allow determination of the incidence of cell death at a given time point. No experimental techniques are currently available for directly gauging the cumulative rate at which oligodendrocyte die over extended periods of time. This difficulty can be surmounted by indirect quantitative inferences from cell counts. To this end, we consider the following possible settings: (1) no distinction is made between live and dead oligodendrocytes in a given study so that only a single count is available for the sum of these two types of cells, (2) distinct counts of live