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On stochastic spatial patterns and neuronal polarity

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Abstract. Polarization refers to asymmetric changes in cellular organization that occur in response to external or internal signals. Although neurons can spontaneously establish and maintain asymmetric distributions of signaling molecules on the plasma membrane, it is not clear how intrinsic noise affects neuronal polarization. In this work we present a stochastic model based on endocytosis, exocytosis and lateral diffusion, to study the effects of low number of molecules (high noise intensity), on neuronal polarization. Numerical results were obtained by solving the master equation using Gillespie's algorithm. Our model suggests that the formation of a single pole of molecular asymmetry is very robust to noise; furthermore, in the presence of noise, neuronal polarization could occur even with reduced feedback strength.

1 Introduction

During the first stage of neuronal polarity a symmetry breaking event takes place [1]. Before the first neurite starts growing, some membrane proteins and members of the Rho GTPases family show spatially localized distributions on the cell membrane [2]. These asymmetric distributions are established spontaneously and can be maintained even without the action of external cues. Some mechanisms, such as positive feedbacks, are thought to be central to the process of polarized domain formation. Although neuronal polarity also occurs in very controlled environments, as it is the case of in vitro experiments, it is impossible to avoid intrinsic noise.

Several mathematical models have shown the importance of positive feedback loops in cell polarity. In particular, some of them state that feedback alone can spontaneously establish a single site of polarity [3,4]. However, it is also suggested that polarization could be very sensitive to stochastic fluctuations. One of the issues giving rise to controversy is the relationship between the amount of involved particles and polarization. Altschuler et al. presented a stochastic model where cells could polarized only when the number of molecules is small [3]. Although using the same model, Grupta showed that it is possible to obtain cell polarity in the infinite population limit, if the feedback strength increases linearly with the population size [5]. Walther et al. determined a threshold number of molecules required for robust polarization [6] and Freisinger and co-workers found that polarity establishment does not depend on the quantity of molecules [7].

In this work we present a model to analyze how intrinsic noise affects neuronal polarity. As intrinsic noise is scaled with the system size, our model allows us to analyze how molecule number fluctuations affect cell polarity in systems with a finite number of molecules. The model itself is the stochastic version of that presented in reference [8]. This model considers the interaction between membrane proteins and modulators of endocytosis (for instance, members of the Rho GTPases family). In order to formulate the stochastic version, we write down a master equation considering the reactions between molecules. Its linear noise approximation is derived using van Kampen's system size expansion [9,10]. Our approach indicates that Turing patterns are not spoiled by intrinsic noise and quasi-pattern structures can be formed with less positive feedback intensity. Since in this approach more noise intensity is associated to a small number of particles, we found that Turing pattern formation does not depend on the number of molecules, but quasi-patterns are not well established if the amount of molecules is too large or too small. Our model suggests that neuronal polarity is very robust to noise, furthermore, in the presence of noise it could occur even with reduced feedback strength.

2 The model

We formulate our model considering two different kinds of molecules, one that represents a typical integral membrane protein endocytosed by a canonical clathrin-mediated process (e.g., cadherin); and another one, representing a modulator of endocytosis (e.g., p. 120-catenin or Rho GTPases). As described in reference [8], we consider the following biological events:

1. *Spontaneous membrane association:* Membrane proteins are tethered spontaneously to the cell membrane [11,12].

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