Chapter 28
A Multiscale Computational Model of Chemotactic Axon Guidance

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ABSTRACT

In the development of the nervous system, the migration of neurons driven by chemotactic cues has been known since a long time to play a key role. In this mechanism, the axonal projections of neurons detect very small differences in extracellular ligand concentration across the tiny section of their distal part, the growth cone. The internal transduction of the signal performed by the growth cone leads to cytoskeleton rearrangement and biased cell motility. A mathematical model of neuron migration provides hints of the nature of this process, which is only partially known to biologists and is characterized by a complex coupling of microscopic and macroscopic phenomena. This chapter focuses on the tight connection between growth cone directional sensing as the result of the information collected by several transmembrane receptors, a microscopic phenomenon, and its motility, a macroscopic outcome. The biophysical hypothesis investigated is the role played by the biased re-localization of ligand-bound receptors on the membrane, actively convected by growing microtubules. The results of the numerical simulations quantify the positive feedback exerted by the receptor redistribution, assessing its importance in the neural guidance mechanism.

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INTRODUCTION

The ability of cells of responding to chemical signals present in the environment is of utmost importance for life, for example to recognize peers or locating food sources. Chemical cues also serve to mark pathways, which lead cells to a target (attractive cues) as well as repel them from selected regions (repulsive cues). Pathfinding by chemical cues is a key mechanism in the embryo, where sets of cells have to organize and reach specific areas to form the different body tissues. Cells crawl along the concentration gradient, towards (or away from) the direction of increasing diffusible chemical signal, moving from the peripheries to the source. This phenomenon is known as chemotaxis and its discovery dates back to the 18th century, allowed by the invention of the microscopy. An interesting example of chemotaxis is found in the developing nervous system, where axons, long and slender projections of nerve cells, find the targets they will innervate navigating in the extracellular environment through a chemotactic guidance mechanism (see, *e.g.*, Tessier-Lavigne & Goodman, 1996; Mueller, 1999; Song & Poo, 2001). Detection and transduction of navigational cues in chemotactic axon guidance is mediated by the growth cone (GC), a highly dynamic structure located at the axon tip (see, *e.g.*, Guan & Rao, 2003 and refer to Figure 1). From the microscopic point of view, directional sensing is initiated by differential binding with the extracellular ligand (the chemical cue) of the specialized receptors located on the opposite sides of the GC membrane. In order to respond to the very shallow ligand gradients observed in nature, the GC must optimize concentration measurements, overcoming the surrounding noise. Several mathematical models investigate this concept. In the seminal work of Berg & Purcell (1977), each receptor is considered as a "measuring device" which provides an estimation of the local ligand concentration based on its average time of permanence in the binding state during a certain period. In Mortimer et al. (2009b), it is shown that, if - in addition - the number of unbound-to-bound transitions is also signalled by the receptor, a more precise measure of the ligand concentration is yielded. When coming to consider the complete pool of receptors present on the GC, a strategy to weight the whole set of binding measurements should also be envisaged. In Mortimer et al. (2009a), it is shown that the optimal measuring strategy gives to each receptor a weight proportional to its distance from the geometrical center of the GC. In the present work, we propose a modification of this latter concept, introducing a weighting strategy depending on the distance of the single receptor from the center of mass of the receptor pool, a quantity dynamically varying according to the activity level of each single receptor (as will be defined more thoroughly in the following). The biophysical fact which motivates this hypothesis is the recent finding of Bouzigues et al. (2007a, 2007b) that, in presence of an attractive gradient of the diffusible cue GABA, ligand-bound GC receptors undergo two fundamental types of motion on the membrane: the first kind of motion is free diffusion, which is present even under an uniform external field, while the second kind of motion is a biased drift toward the side facing the attractive ligand source. This latter motion is driven by the physical interaction of bound receptors with the GC microtubules, which serve as conveyor belts (Saxton, 1994; Saxton & Jacobson, 1997). The overall effect of this mechanism is the establishment of an autocatalytic loop: bias in receptor localization induces, via internal polarization of molecules, preferential growth of the microtubules toward the leading edge of the GC and this, in turn, enhances convey of receptors on that same side (Bouzigues et al., 2007b). Once a weighting strategy for the receptor measurements is established, one should model the subsequent internal polarization chain leading to motion. Mathematical models in this context most often do not enter into the details of the extremely complex biochemical signalling cascade, but rather adopt phenomenological