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Mathematical models of axon guidance: towards the understanding of a key process in development

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ABSTRACT

In the developing embryo, neurons form connections by projecting axons to appropriate target areas. The complete understanding of this process, still far to be achieved, is yet an important goal, since for example it may pave the way to learning how to repair lesions in the nervous system.

Pathfinding of growing nerves crucially relies on extracellular navigational cues. Guidance by gradients of diffusible ligands has been described for different molecules, including netrins, semaphorins, neurotransmitters [4],[5]. The growth cone (GC), located at the axon tip, is a highly motile structure that mediates detection and transduction of extracellular cues [2]. Concentration gradients induce an asymmetric localization of molecules in the GC. The polaryzed signalling pathway leads to rearrangement of the GC cytoskeleton and, ultimately, to motility.

The benchmark chemotaxis assay studies the response of GCs exposed to steady graded concentrations of a single attractive/repulsive ligand [6]. Turning angles and standard error parameters are measured after a time lapse after the onset of the gradient. Different mathematical and computational models have been developed in the past to account for these data (see [1] and references therein); the common element of such models is the combination of deterministic and stochastic processes to reproduce observed behaviors.

In this talk, we propose a modelization of the process leading to guidance characterizing the different steps by variance and coefficient of variation, and we study their propagation through the transduction chain. This latter is described as a series of functional boxes, which represent gradient sensing, signal transduction and motion actuation. The mathematical model maps input/output signals of each unit, without reproducing complex intracellular chemical processes. The approach is based on the identification of three characteristic times (conceptually corresponding to the ones appearing in the above cited literature works)–independent concentration measure by GC receptors, GC internal reorganization preceding motion and discernible axon turning– which act at separated scales, ranging from smaller to larger. The fundamental tasks of directional response towards a target, memory effect and randomness are traduced in the mathematical form of an Ornstein–Uhlenbeck process, which models the central transduction box.

The results presented will give insight into the deterministic vs. stochastic regime of internal growth cone functions that are not readily accessible from experimental observations. In particular, the model predicts the decrease of the coefficient of variation as one moves down the chain leading to movement. The transduction function is characterized by an equilibrium between deterministic and stochastic regimes (see also [3]). A mechanism that allow for buffering against noise, thus contributing to the production of the relatively straight paths of GCs observed in experiments, will be highlighted in the motor actuator function, which acts as a mechanical smoother of trajectory deviations. An analysis of the origin of the stochastic contribution will also be presented, showing the transduction process to be a main source of noise, more significant than fluctuations in ligand gradient (difference of concentration) measure. Eventually, based on the above results, the sample size of typical statistical experiments will be discussed.

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