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An analytical solution describing retrograde viral transport in an axon ☆

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ABSTRACT

An analytical solution representing a wave of viral concentration as it propagates from the axon synapse toward the neuron soma is obtained. The obtained solution is based on a model of molecular motor-assisted retrograde transport of a neurotropic virus in an axon of a peripheral nervous system. It is established that the velocity of the viral concentration wave is almost independent of the rate of viral destruction in the axon, but depends on viral diffusivity, especially right after viral uptake at the synapse, when viral concentration gradient is large. As time progresses, the velocity of the viral concentration wave approaches that of a dynein motor, which indicates that for a large time viral transport in an axon is almost exclusively motor-driven.

1. Introduction

It is well known that many neurotropic viruses utilize the axonal transport machinery to invade neurons of the nervous system. This machinery is designed to move large organelles along microtubule (MT) tracks; the organelles are pulled by kinesin molecular motors in the anterograde direction and by dynein molecular motors in the retrograde direction [1–7]. The reason why viruses rely on motor-driven transport along MTs is that viruses are too large to be effectively transported by diffusion alone. West Nile virus, for example, spreads in both retrograde and anterograde directions via axonal transport [8]. Rabies virus, herpes virus, and polio virus enter the neuron via endocytosis at the axon synapse and then utilize the axonal retrograde transport machinery in order to gain access to the neuron soma [9–12].

It is interesting that although retrograde axonal transport is fast (the average rate of retrograde axonal transport is 200 mm/day), for many viruses it is not very efficient, meaning that a large amount of virus is destroyed on its way to the neuron soma. For example, for poliovirus the inefficiency of retrograde transport is identified as one of the major barriers limiting the spread of poliovirus from peripheral to central nervous system. Experimental research has shown that the uptake of poliovirus at the neuromuscular junction is 87% efficient; however, retrograde transport in axons of the peripheral nervous system is only 28% efficient. This is believed to be one of major reasons why only 1% of unvaccinated individuals infected by the poliovirus developed a serious form of disease [9].

The purpose of this paper is to develop a model of retrograde viral trafficking in an axon of a peripheral nervous system resulting from a viral invasion of the axon synapse. The model accounts for the destruction of virus as it travels from the axon terminal toward the neuron soma. An analytical solution of a governing equation subjected to an appropriate boundary condition modeling a viral exposure of limited duration is obtained.

2. Mathematical model and analytical solution

The model developed in this paper is based on equations of active motor-assisted transport in cells developed in Ref. [13], but to make an analytical solution possible it accounts for only one cargo population. It is assumed that the virus (the cargo) can be transported by motor-driven transport (in that mode, it is most likely transported on MTs inside endosomes), but it can also experience diffusion-driven transport.

A schematic diagram of the problem is displayed in Fig. 1a. The virus enters the axon of the peripheral nervous system at the synapse (located at $\tilde{x}=0$). It is assumed that the synapse is exposed to a constant viral flux, $\tilde{j}_0$, for a limited time, $\tilde{t}_c$ (the boundary condition at the synapse is illustrated in Fig. 1b). The diffusivity models transport of a free virus in the cytoplasm of the cell, as well as the situation when an endosome containing viral particles detaches from an MT. Diffusivity can also be caused by cargo navigation around obstacles during motor-driven transport. The rate of viral destruction is accounted for by the first-order decay rate. Under these assumptions, retrograde transport of viruses in an axon is governed by the following equation:

$$\frac{\partial \tilde{n}}{\partial \tilde{t}} = \tilde{D}\frac{\partial^2 \tilde{n}}{\partial \tilde{x}^2} - \tilde{v}\frac{\partial \tilde{n}}{\partial \tilde{x}} - \tilde{k}\tilde{n} \tag{1}$$

Abbreviations: MT, microtubule.

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