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Generalized Fourier series solution of equations governing molecular-motor-assisted transport of adenoviral vectors in a spherical cell ☆

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Abstract

This paper presents an analytical solution of one-dimensional transient molecular-motor-assisted transport equations that describe transport of adenoviruses in a spherical cell. The model of intracellular trafficking of adenoviruses is based on molecular-motor-assisted transport equations suggested by Smith and Simmons [D.A. Smith, R.M. Simmons, Models of motor-assisted transport of intracellular particles, Biophysical Journal 80 (2001) 45–68.]. These equations are presented in spherical coordinates and extended by accounting for the random component of motion of viral particles bound to filaments. This random component is associated with the stochastic nature of molecular motors responsible for the locomotion of viral particles bound to filaments. Utilizing the method of separation of variables, a generalized Fourier series solution for this problem is obtained. The solution uses two different orthogonal sets of eigenfunctions to represent the concentration of free viral particles transported by diffusion and the concentration of microtubule-bound viral particles transported by kinesin-family molecular motors away from the cell nucleus. Binding/detachment kinetic processes between the viral particles and microtubules are specified by first rate reaction constants; these lead to coupling between the two viral concentrations. The obtained solution simulates viral transport between the cell membrane and cell nucleus during initial stages of viral infection.

Keywords: Molecular motors; Motor-assisted transport; Viral trafficking; Separation of variables; Generalized Fourier series solution

1. Introduction

During infection, some DNA viruses utilize the cell's own molecular-motor-assisted microtubule (MT)-based transport mechanism to deliver viral DNA to the nucleus of a target cell, where they use cellular reproductive machinery to replicate themselves (Leopold and Pfister [2], Mabit et al. [3], Alberts et al. [4]). A recent paper by Dinh et al. [5] presents a comprehensive numerical model of intracellular trafficking of adenoviruses; the model is based on equations governing molecular-motor-assisted transport of intracellular particles developed in Smith and Simmons [1]. According to this model, a fraction of intracellular space is occupied by filaments (such as microtubules or actin cables); the remaining space allows for diffusion of unbound particles.

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Nomenclature

D_0	dimensionless diffusivity of a free viral particle $\tilde{D}_0\,\tilde{k}_+/\tilde{v}_+^2$
$\tilde{D}_0$	diffusivity of a free viral particle
D_+	dimensionless diffusivity of MT-bound viral particles, $\tilde{D}_+\,\tilde{k}_+/\tilde{v}_+^2$
$\tilde{D}_+$	diffusivity of MT-bound viral particles
$\tilde{k}_+$	first order rate constant for binding of viral particles to microtubules
k_+'	dimensionless detachment rate constant of viral particles from microtubules, $\tilde{k}_+'/\tilde{k}_+$
$\tilde{k}_+'$	first order rate constant for detachment of viral particles from microtubules
n_0	dimensionless free viral particles concentration $\tilde{n}_0\,\tilde{v}_+^3/\tilde{k}_+^3$
$\tilde{n}_0$	free viral particles concentration
n_+	dimensionless concentration of viruses moving on microtubules, $\tilde{n}_+\tilde{v}_+^3/\tilde{k}_+^3$
$\tilde{n}_+$	concentration of viruses moving on microtubules
N_C	dimensionless concentration of viruses at the cell membrane, $\tilde{N}_C\tilde{v}_+^3/\tilde{k}_+^3$
$\tilde{N}_C$	concentration of viruses at the cell membrane
N_N	dimensionless concentration of viruses at the nucleus membrane, $\tilde{N}_N\tilde{v}_+^3/\tilde{k}_+^3$
$\tilde{N}_N$	concentration of viruses at the nucleus membrane
$\tilde{r}$	radial coordinate
r	dimensionless radial coordinate, $\tilde{r}\,\tilde{k}_+/\tilde{v}_+$
$\tilde{R}_C$	cell radius
R_C	dimensionless cell radius, $\tilde{R}_C\tilde{k}_+/\tilde{v}_+$
$\tilde{R}_N$	radius of cell nucleus
R_N	dimensionless radius of cell nucleus, $\tilde{R}_N\tilde{k}_+/\tilde{v}_+$
t	dimensionless time, $t\tilde{\tilde{k}}_+$
$\tilde{t}$	time
$\tilde{v}_+$	velocity of a viral particle moving on a microtubule

Greek symbols

σ_N	degree of loading at the nucleus membrane

Microtubules radiate out in all directions from the centrosome (the cell center) where their minus-ends are anchored. Different kinds of intracellular particles (such as transport vesicles loaded with specific proteins, intracellular vesicles carrying different types of cargo between intracellular compartments, or viral particles) are carried away from the cell center toward the cell membrane by kinesin-family molecular motors (this family of molecular motors is responsible for the transport on microtubules toward their plus-ends). Intracellular organelles are also carried from the cell membrane toward the cell center by dynein-family molecular motors (this family of molecular motors is responsible for the transport on microtubules toward their minus-ends) (Alberts et al. [4], Pollard and Earnshaw [6]).

Unbound (free) viruses may bind to filaments; viruses bound to filaments may detach from them; the binding/detachment kinetic processes are specified by the first rate constants. Dinh et al. [7] and Pangarkar et al. [8] applied the developed model to investigating spatial patterns of intracellular particles. Other aspects of intracellular transport of cell organelles and vesicles along microtubules were considered in Friedman and Craciun [9] and Welte [10]. Recently, Kuznetsov [11] obtained an analytical solution of Smith–Simmons equations through generalized Fourier series using a set of non-orthogonal eigenfunctions.

Dinh et al. [5] solved molecular-motor-assisted transport equations in a cylindrical coordinate system, assuming elongated cells. This paper presents a formulation of the molecular-motor-assisted transport equations in a spherical coordinate system, assuming a spherically symmetric cell. Modeling is carried out under the assumption that molecular-motor-assisted transport of viral particles is only powered by kinesin-family molecular motors and occurs toward microtubules plus-ends, from cell nucleus to cell membrane. Molecular-motor-assisted transport of viral particles powered by dynein-family molecular motors (from cell membrane to cell nucleus) is neglected in this paper.