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# A model of intracellular transport of particles in an axon

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**Abstract.** In this paper we develop a model of intracellular transport of cell organelles and vesicles along the axon of a nerve cell. These particles are moving alternately by processive motion along a microtubule with the aid of motor proteins, and by diffusion. The model involves a degenerate system of diffusion equations. We prove a maximum principle and establish existence and behavior of a unique solution. Numerical results show how the transportation of mass depends on the relevant parameters of the model.

## 1. Description of the model

In this paper we consider a model for intracellular transport of cell organelles and vesicles along the axon. Following the terminology of [17] we shall refer to the cell organelles and vesicles as *particles*. According to experimental studies in [20,21] (see also [1], pp. 812–815) particles bind to motor proteins, which in turn bind to microtubules, and move along them. The motor proteins "walk" along the microtubules, in a processive motion, step-by-step, each step mediated by a mechanochemical ATPase. Typically, a particle is transported along a microtubule for an average distance of about 10 $\mu$m, with an average speed of about 1 $\mu$m/$s$, after which the motor protein detaches from the microtubule (see [17]), until it encounters another nearby microtubule, or the same one, and is again transported along it, and so on.

The average length of a microtubule can be 500 $\mu$m [19], while the average diameter of the microtubule is 0.025 $\mu$m. Therefore the average length of a microtubule is typically 20000 times larger than its diameter.

Since there are dozens of particles in the vicinity of a microtubule [19], we may replace, to a first approximation, the individual particles by a density function. Instead of tracking down the motion of the individual particles we then have to study the time evolution of the density. Indeed, this point of view was taken recently by Smith and Simmons [17]. They divided the particles into two populations: those that are attached to a microtubule and those that are detached from it. The attached particles were still divided into outward going particles (i.e., in anterograde motion,

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from the cell nucleus toward the synaptic end) driven by kinesin motor proteins, and inward going particles driven in retrograde motion by dynein motors. The law of conservation of mass was used to determine the movement of particles attached to the microtubule. The detached particles were assumed to undergo diffusion.

An earlier and quite different model of this transport problem was developed by Blum and Reed [3,4,14], and Blum, Carr and Reed [2]. They introduced concentrations $P$, $E$, $T$, $Q$ of free particles, free kinesin molecules, free binding sites along the microtubules, and moving particles along the microtubules. Using mass reaction laws and conservation of mass, they derived a system of hyperbolic equations and studied (mostly numerically) the particle concentration profile along the axon. Other models of transport are discussed in [11,15,18,23]. In particular, the model of Takenaka and Gotoh [18] introduces three diffusion equations for materials in fast anterograde, slow anterograde, and retrograde motion, in the entire axon, with linear interactions among the three phases. After we describe our model, we shall explain in more detail the differences between our model and the models in [2–4, 14] (Remark 1.2) and [11,15,18,23] (Remark 1.3).

In this paper we introduce a model of transport of particles which may be viewed as a further refinement of the model of Smith and Simmons [17]. The underlying assumptions of our model are the following:

(1) For simplicity, we consider in this paper only outward motion, e.g. the motion induced by kinesin, which transports the particles from the soma into the synaptic end along the axon. Our results however can be extended to include inward transport, as will be explained in item $(A)$ of the Conclusions section.
(2) We assume as in Smith and Simmons [17] that the number of free kinesin molecules is not rate limiting; this is in contrast with the earlier models in [2–4,14].
(3) As is [17], we assume that the number of binding sites where motor proteins can attach onto microtubules is not rate limiting, i.e., there is no "traffic congestion" over microtubules.
(4) The number of binding sites of a particle for motor proteins might exceed 1; for definiteness (and simplicity) we take it to be 2. This assumption is actually believed to be true [17], although it was assumed in [17] that only one binding site is available.
(5) It is known that motor proteins will not attach to microtubules unless they are already bound to a particle. It is believed that the binding of motor proteins to particles is much stronger than the binding of motor proteins to microtubules. To simplify the model we shall assume that the motor proteins bind irreversibly to the particles.
(6) For some neuronal types the microtubules are tightly packed together, see [6]. For other neuronal types the microtubules are relatively sparse (see [19] for an image of an axonal section in this case). As in [17], we shall consider here the latter case.
(7) The motor proteins bind reversibly to microtubules [17]. In view of the previous assumption, we can deal with just one microtubule, since most particles that detach from one microtubule reattach to the same microtubule.

(8) The model used in [17] was one-dimensional, that is, it was assumed that all densities are functions of a variable $x$, which measures the length along the microtubule. In particular, the diffusion of free particles was assumed to take place along the $x$-axis. In the present model include a 3-dimensional diffusion, which takes place in a cylindrical neighborhood of the microtubule. Furthermore, we assume that the translational diffusion coefficient (that is, in the direction parallel to the microtubule axis) may be larger than the diffusion coefficient in the orthogonal cross-section. As in [17], the translational diffusion is taken to be 25% of that of water, a fact validated in a number of experiments [12, 16].

(9) We shall also assume that the rate of attachment of a particle to a microtubule is smaller the further away the particle is from the microtubule.

We denote by $u_{ij}$ the concentration of particles that have $i$ motors attached to them, $j$ of which are attached to the microtubule. We denote by $\lambda_1$ the rate at which a motor protein will get attached to a particle, by $\lambda_2$ the rate at which a motor protein which is attached to a particle but undergoing diffusion will get attached to the microtubule. Consider particles that have two motors attached to them, and just one of the motors attached to the microtubule, and denote by $\lambda_2'$ the rate at which the second motor will attach to the microtubule. On one hand, because a particle in this class is already connected to the microtubule, it might be easy for the second motor to get connected to the microtubule. On the other hand, the rigidity constraints of being already attached to the microtubule by one motor might make it hard for the second particle-bound motor to attach to the microtubule. Thus, it is not clear whether $\lambda_2'$ is larger or smaller than $\lambda_2$. We shall therefore not make any assumptions on the sign of $\lambda_2 - \lambda_2'$. Finally, we denote by $k$ the rate at which a motor protein that is bound to the microtubule will get detached from it.

Note that the rate at which $u_{00}$ particles become $u_{10}$ particles is twice as large as the rate at which $u_{10}$ particles become $u_{20}$ particles, since $u_{00}$ particles have two free binding sites where motor proteins can attach, while for $u_{10}$ particles one such binding site is already occupied. Similarly, the rate at which $u_{22}$ particles become $u_{21}$ particles is twice as large as the rate at which $u_{11}$ particles become $u_{10}$ particles, since for $u_{22}$ particles one or the other of the two bound motor proteins could detach from the microtubule. Finally, the rate at which $u_{20}$ particles become $u_{21}$ particles is twice as large as the rate at which $u_{10}$ particles become $u_{11}$ particles. Thus we have the following flow chart:

$$\begin{array}{ccccc} u_{00} & & & & \\ \downarrow{\scriptstyle 2\lambda_1} & & & & \\ u_{10} & \underset{k}{\overset{\lambda_2}{\rightleftarrows}} & u_{11} & & \\ \downarrow{\scriptstyle \lambda_1} & & \downarrow{\scriptstyle \lambda_1} & & \\ u_{20} & \underset{k}{\overset{2\lambda_2}{\rightleftarrows}} & u_{21} & \underset{2k}{\overset{\lambda_2'}{\rightleftarrows}} & u_{22} \end{array}$$

*Remark 1.1.* Since the vertical arrows in this flow chart are all pointing downward, one expects that as $t$ increases most of the particles will be $u_{20}$, $u_{21}$, or $u_{22}$. Nevertheless, it is important to include the particles $u_{00}$, $u_{10}$, $u_{11}$ in the model. The reason is that one expects most of the particles leaving the soma to have no motor proteins, so that the boundary conditions on the proximal end of the axon is, say, $u_{00} = 1$ and all other $u_{ij} = 0$. We can envision experiments which measure the time-dependent profile of the particles concentration near the soma (cf. [9]) which could then be compared with results of our model.

For clarity, we shall first deal with the case where the diffusion is the same in all directions, and the rate of attachment of particles to the microtubule is independent of their distance to the microtubule; in section 8 we shall consider the more general case, whereby the translational diffusion is larger than the diffusion in the direction orthogonal to the axis of the microtubule, and the rate of attachment of particles to the microtubule decreases with their distance to the microtubule.

Smith and Simmons ([17], p.64) express the opinion that the observed fluctuations in the speed of particles bound to the microtubule by motor proteins could be explained by fluctuations in the number of motor protein molecules bound to the particles and attached to the microtubule. This led us in this paper to work with a model where the velocity $v'$ of particles bound to the microtubule by two motor proteins can be larger than the velocity $v$ of particles bound by one motor protein. It is reasonable to assume that $v \le v' \le 2v$, although our mathematical results do not require this assumption.

Recalling that $u_{i0}$ particles are diffusing, and using the law of mass conservation we derive from the above flow chart the following system of PDEs:

$$
(T)\quad
\begin{aligned}
\frac{\partial u_{00}}{\partial t} &= D\Delta u_{00} - 2\lambda_1 u_{00},\\
\frac{\partial u_{10}}{\partial t} &= D\Delta u_{10} + 2\lambda_1 u_{00} - \lambda_1 u_{10} - \lambda_2 u_{10} + k u_{11},\\
\frac{\partial u_{20}}{\partial t} &= D\Delta u_{20} + \lambda_1 u_{10} - 2\lambda_2 u_{20} + k u_{21},\\
\frac{\partial u_{11}}{\partial t} &= -v\frac{\partial u_{11}}{\partial x} + \frac{\lambda_2}{B}\int_1^b u_{10} r dr - \lambda_1 u_{11} - k u_{11},\\
\frac{\partial u_{21}}{\partial t} &= -v\frac{\partial u_{21}}{\partial x} + \lambda_1 u_{11} + \frac{2\lambda_2}{B}\int_1^b u_{20} r dr - \lambda_2' u_{21} + 2k u_{22} - k u_{21},\\
\frac{\partial u_{22}}{\partial t} &= -v'\frac{\partial u_{22}}{\partial x} + \lambda_2' u_{21} - 2k u_{22}
\end{aligned}
$$

where $D$ is the diffusion coefficient. The transport system $(T)$ is to be considered in a 3-dimensional region

$$\Omega_L = \{(x, r);\ 0 < x < L,\ 1 < r < b\} \qquad (r = \sqrt{y^2 + z^2})$$

where $r = 1$ is the radius of the microtubule and $L$ is its length, $b$ is $O(1)$ (e.g. $b = 5$), and $B = \int_1^b r dr$ is the cross section area.

Note that we regard $u_{11}, u_{21}, u_{22}$ as functions of only $x$ and $t$, since they represent concentrations of particles moving along the microtubule, while $u_{00}, u_{10}, u_{20}$ are functions of $x, t$ and $r$, since they represent concentrations of particles diffusing inside the axon, off the microtubule.

The unit of length in $\Omega$ is $0.0125\mu$m, since the diameter of the microtubule is about $0.025\mu$m. The values of $D,\ k$ and $v$ used in [17] are $D$=0.1$\mu$m$^2$/s, $k = 1$ and $0.1\mu$m/s $< v <1\mu$m/s. The parameters $\lambda_1, \lambda_2$ and $\lambda_2'$ depend on the biochemical properties of the particles, motor proteins, and microtubules. As mentioned earlier, $L$ is a large number (typically 40000 units). It is therefore natural to consider the system $(T)$ not only in $\Omega_L$, but also in

$$\Omega_\infty = \{(x, r);\ 0 < x < \infty,\ 1 < r < b\} \qquad (r = \sqrt{y^2 + z^2})$$

In this paper we establish the mathematical foundation for the system $(T)$, i.e., we prove that this system has a unique solution. We shall also give some numerical results which show, in particular, how the transported mass depends on the parameters. In a future work we intend to compare simulations based on our model with a variety of experimental results on transport of organelles, vesicles, and possibly also neurofilaments.

For clarity of exposition we shall first consider the system $(T)$ in the stationary case; this is done in sections 2–8. The time-dependent system can be dealt with in a similar way, so we shall consider it, only briefly, in section 9. A basic tool for proving existence and uniqueness is a maximum principle (see [13]).

In section 2 we introduce a general system of PDEs which we shall study in sections 3–7. We shall then, in section 8, apply the results in order to establish existence and uniqueness of the stationary solution of $(T)$ in $\Omega_L$ and in $\Omega_\infty$; we shall also consider in section 8 the case where the translational diffusion is larger than the diffusion in the orthogonal directions, and the rate of attachment of particles with motor proteins to the microtubule decreases with increased distance to the microtubule. As mentioned above, in section 9 we shall briefly discuss the extension of all the previous results to the time dependent transport system. In section 10 we shall give numerical results which illustrate how the mass transport of particles varies with some of the parameters. Finally, in the concluding section 11 we discuss the extension of our model and state some open problems.

*Remark 1.2.* The basic differences between our model and the models developed in [2–4, 14] are the following:

- $(i)$ In our model we assume that the number of motor proteins and the number of binding sites on the microtubules are not rate limiting, whereas in [2–4, 14] these numbers may be rate limiting. Which one of these assumptions is correct may depend on the type of neuron.
- $(ii)$ In our model the fast transport takes place only as long as the the motor-bound particles are attached to a microtubule. Our model is 3-dimensional: it includes diffusion of detached particles within a cylindrical region about a microtubule. The model in [2–4, 14] is 1-dimensional: it assumes uniform concentrations of particles, motors and microtubule binding sites at any cross

section along the axon, and does not elaborate on the attachment/detachment feature of the transport process.

$(iii)$ In our model we assume sparsely distributed microtubules. This assumption is true for some neuronal types [19], but not true for others [6]. In [2–4, 14] the question of distribution of microtubules does not arise, since only the concentration of free binding sites is introduced, and this concentration is a function of just one variable, the coordinate point on the axis along the neuron. In the conclusions section of this paper we shall comment on how our model might be extended to include compactly distributed microtubules.

*Remark 1.3.* As we mentioned above, the 1984 model of Takenaha and Gotoh [18] assumes both fast and slow transport. In contrast, our model is based on more recently acquired evidence regarding transport of particles, namely, transport occurs only when a motor-bound particle is attached to a microtubule, and these motors get detached from the microtubule from time to time. The models discussed in [11, 15, 23] precede [18], and do not get into the quantitative nature of the transport.

## 2. The basic mathematical problem

Consider the following system of PDEs for functions $u(x,r)$, $v(x)$, $w(x)$ in $\Omega_L$:

$$-\Delta u + \gamma_{11} u - \gamma_{12} v = f_1(x,r), \tag{2.1}$$

$$v_x + \gamma_{21} v - \gamma_{22} w - \frac{\gamma_{11}}{B} \int_1^b u(x,r) r\,dr = f_2(x), \tag{2.2}$$

$$w_x + \theta\gamma_{22} w - \theta\gamma_{32} v = f_3(x) \tag{2.3}$$

with boundary conditions

$$u(0,r) = u_0(r)\ (1 < r < b),\ \ v(0) = v_0,\ \ w(0) = w_0, \tag{2.4}$$

$$\begin{cases} \frac{\partial u}{\partial r}(x,1) = \frac{\partial u}{\partial r}(x,b) = 0\ (0 < x < L), \\ u(1,r) = u_1(r)\ (1 < r < b), \end{cases} \tag{2.5}$$

where $\gamma_{ij}$ are positive constants, $1/2 \le \theta \le 1$, and

$$\gamma_{12} + \frac{1}{\theta}\gamma_{32} \le \gamma_{21}. \tag{2.6}$$

The motivation for the no flux boundary conditions in (2.5) will be given in section 8, where we deal with the full system $(T)$.

We shall prove that if

$$0 \le f_i \le Ce^{-\mu x}\ (\mu > 0),\ \ u_0 \ge 0,\ \ v_0 \ge 0,\ \ w_0 \ge 0,\ \ u_1 \ge 0, \tag{2.7}$$

then there exists a unique solution of (2.1)–(2.5) such that

$$u \ge 0,\ \ v \ge 0,\ \ w \ge 0.$$

Furthermore, under an additional condition on the $\gamma_{ij}$, as $L \to \infty$ the solution converges to a solution in $\Omega_\infty$ of (2.1)–(2.7), with (2.5) replaced by

$$\frac{\partial u}{\partial r}(x,1) = \frac{\partial u}{\partial r}(x,b) = 0 \ (0 < x < \infty), \ u \in L^\infty(\Omega_\infty). \tag{2.8}$$

This solution is unique, and it satisfies the asymptotic behavior

$$|u(x,r) - c\gamma_{12}\gamma_{22}| + |v(x) - c\gamma_{12}\gamma_{22}| + |w(x) - c\gamma_{11}\gamma_{22}| \le Ce^{-\nu x} \tag{2.9}$$

for some positive constants $C, \ \nu$ and nonnegative constant $c$.

In section 3 we establish a maximum principle for the system (2.1)–(2.6). This is used in section 4 to prove existence and uniqueness of a solution to (2.1)–(2.7). In section 6 we establish a bound on the solution, which is independent of the parameter $L$, and this allows us to obtain a solution in $\Omega_\infty$ (by taking $L \to \infty$), and to establish the asymptotic behavior (2.9). The derivation of the bound is based on a construction of a supersolution, given in section 5. The results obtained in sections 3–6 for the system (2.1)–(2.3) are extended in section 7 to another system of two differential equations. In section 8 we use the results derived for the system (2.1)–(2.7) in $\Omega_L$ (or the corresponding system in $\Omega_\infty$ with (2.5) replaced by (2.8)) and the results of section 7 to prove existence, uniqueness, and asymptotic behavior for the stationary solutions of the transport system $(T)$.

## 3. A maximum principle

**Theorem 3.1.** *Let* $(u, v, w)$ *satisfy the differential inequalities*

$$-\Delta u + \gamma_{11}u - \gamma_{12}v \le 0 \text{ in } \Omega_L, \tag{3.1}$$

$$v_x + \gamma_{21}v - \gamma_{22}w - \frac{\gamma_{11}}{B}\int_1^b u(x,r)r\,dr \le 0 \text{ for } 0 < x < L, \tag{3.2}$$

$$w_x + \theta\gamma_{22}w - \theta\gamma_{32}v \le 0 \text{ for } 0 < x < L \tag{3.3}$$

*and*

$$u(0,r) \le 0, \ u(L,r) \le 0 \ (0 < r < b), v(0) \le 0, \ w(0) \le 0, \tag{3.4}$$

$$\frac{\partial u}{\partial r}(x,1) = \frac{\partial u}{\partial r}(x,b) = 0 \ (0 < x < L). \tag{3.5}$$

*Then $u$ cannot take a positive maximum in* $\overline{\Omega}_L$.

*Proof.* We assume to the contrary that

$$M = \max_{\overline{\Omega}_L} u = u(x_0, r_0) > 0 \tag{3.6}$$

for some $(x_0, r_0) \in \overline{\Omega}_L$. Then $0 < x_0 < L$. From (3.2) we have

$$v(x) \le e^{-\gamma_{21}x}v_0 + \gamma_{22}\int_0^x e^{\gamma_{21}(\xi - x)}w(\xi)d\xi + \frac{\gamma_{11}}{B}\int_0^x d\xi \int_1^b e^{\gamma_{21}(\xi - x)}u(\xi, r)r\,dr. \tag{3.7}$$

Since $u(\xi, r) \leq M$ we get

$$v(x) \leq e^{-\gamma_{21}x}(v_0 - \frac{\gamma_{11}}{\gamma_{21}}M) + \frac{\gamma_{11}}{\gamma_{21}}M + \gamma_{22}\int_0^x e^{\gamma_{21}(\xi - x)}w(\xi)d\xi \quad (3.8)$$

Recalling that $v_0 \leq 0$ and $M > 0$ it follows that

$$v(x) \leq A + \gamma_{22}\int_0^x e^{\gamma_{21}(\xi - x)}w(\xi)d\xi, \quad A = \frac{\gamma_{11}}{\gamma_{21}}M. \quad (3.9)$$

Next, by (3.3),

$$w(x) \leq e^{-\theta\gamma_{22}}w_0 + \theta\gamma_{32}\int_0^x e^{-\theta\gamma_{22}(\xi' - x)}v(\xi')d\xi'. \quad (3.10)$$

Recalling that $w_0 \leq 0$ and substituting (3.10) into (3.9), we obtain

$$v(x) \leq A + \gamma_{22}\theta\gamma_{32}\int_0^x I(\xi' - x)v(\xi')d\xi' \quad (3.11)$$

where

$$I(\xi' - x) = \int_{\xi'}^x e^{\gamma_{21}(\xi - x)}e^{\theta\gamma_{22}(\xi' - \xi)}d\xi. \quad (3.12)$$

If $\gamma_{21} \neq \theta\gamma_{22}$ then

$$I(\xi' - x) = \frac{1}{\gamma_{21} - \theta\gamma_{22}}\left(e^{\theta\gamma_{22}(\xi' - x)} - e^{\gamma_{21}(\xi' - x)}\right)$$

and

$$\int_0^x I(\xi' - x)d\xi' = \frac{1}{\gamma_{21}\theta\gamma_{22}} - \frac{1}{\gamma_{21} - \theta\gamma_{22}}f(x),$$

where

$$f(x) = \frac{e^{-\theta\gamma_{22}x}}{\theta\gamma_{22}} - \frac{e^{-\gamma_{21}x}}{\gamma_{21}}.$$

Since $f(\infty) = 0$ and $f'(x) < 0$ ($> 0$) if $\gamma_{21} > \theta\gamma_{22}$ ($\gamma_{21} < \theta\gamma_{22}$), we conclude that $f(x)/(\gamma_{21} - \theta\gamma_{22}) > 0$, so that

$$\int_0^x I(\xi' - x)d\xi' < \frac{1}{\gamma_{21}\theta\gamma_{22}} \quad \text{if } x > 0. \quad (3.13)$$

If $\gamma_{21} = \theta\gamma_{22}$ then $I(\xi' - x) = (x - \xi')e^{\gamma_{21}(\xi' - x)}$ and (3.13) can again be easily verified. From (3.13) we get

$$\int_0^x I(\xi' - x)d\xi' \int_0^{\xi'} I(\xi'' - \xi')d\xi'' < \frac{1}{(\gamma_{21}\theta\gamma_{22})^2}. \quad (3.14)$$

Iterating $v$ in (3.11) and using (3.13), (3.14) and the obvious successive iterations, we obtain

$$v(x) < A\sum_{n=0}^{\infty}\left(\frac{\gamma_{22}\gamma_{32}}{\gamma_{21}\theta\gamma_{22}}\right)^n = A\frac{\theta\gamma_{21}}{\theta\gamma_{21}-\gamma_{32}} \le \frac{\gamma_{11}}{\gamma_{12}}M \tag{3.15}$$

by (2.6), so that

$$\gamma_{12}v(x) - \gamma_{11}u(x_0, r_0) < 0 \text{ in } \Omega_L.$$

Then, by (3.1), $-\Delta u(x,r) < 0$ in some $\Omega_L$-neighborhood of $(x_0, r_0)$. But since $u$ takes maximum at $(x_0, r_0)$, we have $-\Delta u(x_0, r_0) \ge 0$ if $1 < r_0 < b$, which is a contradiction, whereas if $r_0 = 1$ or $r_0 = b$ then $\frac{\partial u}{\partial r}(x_0, r_0) \ne 0$ (by the strong maximum principle for elliptic equations, see [13]), which is again a contradiction to (3.5). □

**Corollary 3.2.** *There exists at most one solution of (2.1)–(2.5).*

Indeed, if $(u_i, v_i, w_i)$ $(i = 1, 2)$ are two solutions, then by the maximum principle (i.e., by Theorem 3.1) $u_1 - u_2 \equiv 0$, and then also, by ODE theory, $v_1 - v_2 \equiv 0$, $w_1 - w_2 \equiv 0$.

**Corollary 3.3.** *There exists at most one solution of (2.1)–(2.4), (2.8).*

*Proof.* For any $\epsilon > 0$ define $(\tilde{u}, \tilde{v}, \tilde{w})$ by $\tilde{u} = \epsilon x$,

$$-\Delta\tilde{u} + \gamma_{11}\tilde{u} - \gamma_{12}\tilde{v} = 0, \tag{3.16}$$

and

$$\tilde{v}_x + \gamma_{21}\tilde{v} - \gamma_{22}\tilde{w} - \gamma_{11}\tilde{u} = 0. \tag{3.17}$$

One can verify, using (2.6), that

$$\tilde{w}_x + \theta\gamma_{22}\tilde{w} - \theta\gamma_{32}\tilde{v} \ge 0. \tag{3.18}$$

Let $(u, v, w)$ denote the difference of two bounded solutions $(u_i, v_i, w_i)$ in $\Omega_\infty$. If $L_0$ is sufficiently large then

$$|u(x,r)| < \epsilon x \text{ on } x = L_0.$$

Recalling (3.16)–(3.18) and noting that $\tilde{u}(0) = 0$, $\tilde{v}(0) = 0$, $\tilde{w}(0) > 0$ we can then apply the maximum principle to $(\hat{u}, \hat{v}, \hat{w}) \equiv (u - \tilde{u}, v - \tilde{v}, w - \tilde{w})$ in $\Omega_{L_0}$ and conclude that

$$\hat{u}(x,r) < \epsilon x \text{ in } \Omega_{L_0},$$

Fixing $(x, r)$ and letting $\epsilon \to 0$, we get $\hat{u}(x,r) \le 0$. Similarly $\hat{u}(x,r) \ge 0$, and the desired assertion follows. □

## 4. Existence in $\Omega_L$

Consider the system (2.1)–(2.6) and assume that

$$f_1 \in L^\infty(\Omega_L),\ f_2 \in L^\infty([0, L]),\ f_3 \in L^\infty([0, L]),\ u_0(r) \text{ and } u_1(r) \text{ belong to } C^\alpha[1, b] \text{ for some } 0 < \alpha < 1. \tag{4.1}$$

**Theorem 4.1.** *Under the assumption (4.1) there exists a unique solution* $(u, v, w)$ *of (2.1)–(2.6) in* $C^0(\overline{\Omega}_L)$*, and it belongs to* $C^\beta(\overline{\Omega}_L)$ *for some* $0 < \beta < 1$.

*Proof.* Without loss of generality we may assume that $f_2 \equiv f_3 \equiv 0,\ v(0) = w(0) = 0$. Indeed, otherwise we work with the functions $(u, v + \tilde{v}, w + \tilde{w})$ instead of $(u, v, w)$, where $(\tilde{u}, \tilde{v}, \tilde{w})$ form the solution of the ODE system (2.2),(2.3) with $u \equiv 0$ and with $\tilde{v}(0) = v_0, \tilde{w}(0) = w_0$.

Let $U = \{u \in L^\infty(\Omega_L), |u| \le M\}$, where $M$ is a large constant to be chosen later on. For any $u \in U$ we solve the ODE system (2.2),(2.3) with $u(0) = w(0) = 0$, $f_2 \equiv f_3 \equiv 0$. As in (3.8)

$$v(x) \le \frac{\gamma_{11}}{\gamma_{21}} M(1 - e^{-\gamma_{21} L}) + \gamma_{22} \int_0^x e^{\gamma_{21}(\xi - x)} w(\xi) d\xi.$$

Proceeding as in (3.10)–(3.15) we arrive at the inequality

$$v(x) \le \frac{\gamma_{11}}{\gamma_{21}} M(1 - e^{-\gamma_{21} L}). \tag{4.2}$$

We next solve

$$-\Delta\tilde{u} + \gamma_{11}\tilde{u} - \gamma_{12} v = f_1 \text{ in } \Omega_L, \tag{4.3}$$

subject to the boundary conditions in (2.4),(2.5). We can do this by applying the Dirichlet principle in order to get a unique solution $\tilde{u}$ in $H^1(\Omega_L)$. The solution is then Hölder continuous away from the corner points $x = 0, L,\ r = 1, b$. We shall prove that $\tilde{u}$ is in $C^\beta$ in a neighborhood of these points. To do this, say for $x = 0,\ r = b$, we reflect the solution across $r = b$. The extended function, which shall be denoted again by $\tilde{u}$, then satisfies

$$-\Delta\tilde{u} + \tilde{g}\frac{\partial\tilde{u}}{\partial r} = \tilde{f}, \text{ in } 1 < r < 2b, 0 < x < L,$$

where $\tilde{g},\ \tilde{f}$ are bounded functions, and $\tilde{u}(0, r)$ is in $C^\alpha$. By Theorem 8.29 in [8] $\tilde{u}$ is then in $C^\beta$ near $x = 0,\ r = b$, for some $\beta > 0$.

Consider the mapping $T : u \to \tilde{u}$ $(u \in U)$. From (4.2),(4.3) we see that

$$-\Delta\tilde{u} + \gamma_{11}\tilde{u} = \gamma_{12} v + f_1 < \gamma_{12}\frac{\gamma_{11}}{\gamma_{12}} M = \gamma_{11} M,$$

if $M$ is sufficiently large ($M$ depends on $L$). If $M$ is also larger than $\max\{|u_0| + |u_1|\}$, then, by comparison, $\tilde{u} < M$. It follows that $T$ maps $U$ into itself. It is also easily seen that $T$ is continuous in the $L^\infty$ norm. Finally, by the $C^\beta$ estimate on $\tilde{u}$ it follows that $T$ maps $U$ into a compact subset of $U$ (with respect to the $L^\infty$ norm). Applying the Schauder fixed point theorem we conclude that $T$ has a fixed point. This establishes the existence of a solution to (2.1)–(2.6). Uniqueness was proved in Corollary 3.2. □

## 5. ODE system

Consider the case where the solution of (2.1)–(2.6) is independent of $r$, i.e., $u(x, r) \equiv u(x)$. We then have an ODE system which we can write in the form

$$U_x = AU + F \text{ in } \mathbb{R}^+ = \{0 < x < \infty\} \tag{5.1}$$

where $U = (u, \tilde{u}, v, w)$, $\tilde{u} = u_x$,

$$A = \begin{pmatrix} 0 & 1 & 0 & 0 \\ \gamma_{11} & 0 & -\gamma_{12} & 0 \\ \gamma_{11} & 0 & -\gamma_{21} & \gamma_{22} \\ 0 & 0 & \theta\gamma_{32} & -\theta\gamma_{22} \end{pmatrix},$$

$F = (0, -f_1, f_2, f_3)$, with the initial conditions

$$u(0) = u_0, \ v(0) = v_0, w(0) = w_0. \tag{5.2}$$

We shall be interested in the case where

$$f_j = C_j e^{-\mu_j x} \ \ (C_i > 0, \ \mu_j > 0) \tag{5.3}$$

and the $\gamma_{ij}$ are such that the eigenvalues $\beta_j$ of $A$ satisfy

$$\beta_1 < \beta_2 < \beta_3 = 0 < \beta_4. \tag{5.4}$$

**Theorem 5.1.** *Under the assumptions (5.3),(5.4) there exists a unique bounded solution of (5.1),(5.2) and*

$$|(u, v, w) - c(\gamma_{12}\gamma_{22}, \gamma_{11}\gamma_{22}, \gamma_{11}\gamma_{32})| \le Ce^{-\mu x} \tag{5.5}$$

*for some positive constant $\mu$ and a constant $c$ that depends only on $u_0, v_0, w_0$. Furthermore, if $u_0 > 0, v_0 > 0, w_0 > 0$ then $u(x) > 0, v(x) > 0, w(x) > 0$ for $0 < x < \infty$ and the constant $c$ is positive.*

This solution will be used in section 6 to estimate the solution of the PDE system (2.1)–(2.6) as $L \to \infty$.

*Proof.* Consider first the case where all of the $f_j$ vanish. We can write the general bounded solution of $U_x = AU$ as a linear combination

$$U = c_1U_1 + c_2U_2 + c_3U_3, \tag{5.6}$$

where $U_j$ is a constant vector times $e^{\beta_j x}$, i. e.

$$U_j = (u_j, \tilde{u}_j, v_j, w_j)^T e^{\beta_j x}.$$

Note that $\tilde{u}_j = \beta_j u_j$; hence if we set

$$\tilde{U}_j = (u_j, v_j, w_j)^T e^{\beta_j x}, \ \tilde{U} = (u, v, w)^T,$$

then (5.6) is equivalent to

$$\tilde{U} = c_1\tilde{U}_1 + c_2\tilde{U}_2 + c_3\tilde{U}_3.$$

To prove that there exists a bounded solution satisfying (5.5) we need to show that we can implement the initial conditions (5.2) by some choice of the $c_j$. This can be done if and only if the vectors $\tilde{U}_1, \tilde{U}_2, \tilde{U}_3$ at $x = 0$ are linearly independent. We shall assume that this is not the case and derive a contradiction. Note that, since $\beta_3 = 0$, we can take

$$U_3 = (\gamma_{12}\gamma_{22}, \gamma_{11}\gamma_{22}, \gamma_{11}\gamma_{32})^T \equiv (\delta_1, \delta_2, \delta_3)^T. \tag{5.7}$$

From the linear dependence of $\tilde{U}_1, \tilde{U}_2, \tilde{U}_3$ we then have (after rescaling $\tilde{U}_1, \tilde{U}_2$)

$$\tilde{U}_2 = \tilde{U}_1 + \lambda\tilde{U}_3, \text{ for some } \lambda \in \mathbb{R}. \tag{5.8}$$

From $AU_j = \beta_j U_j$ we also have

$$\gamma_{11}u_j - \gamma_{12}v_j = \beta_j^2 u_j, \tag{5.9}$$

$$\gamma_{11}u_j - \gamma_{21}v_j + \gamma_{22}w_j = \beta_j v_j, \tag{5.10}$$

$$\theta\gamma_{32}v_j - \theta\gamma_{22}w_j = \beta_j w_j \tag{5.11}$$

for $j = 1, 2$.

If we substitute the relations (5.7), (5.8) into (5.9)–(5.11) for $j = 2$, we get

$$\gamma_{11}(u_1 + \lambda\delta_1) - \gamma_{12}(v_1 + \lambda\delta_2) = \beta_2^2(u_1 + \lambda\delta_1), \tag{5.12}$$

$$\gamma_{11}(u_1 + \lambda\delta_1) - \gamma_{21}(v_1 + \lambda\delta_2) + \gamma_{22}(w_1 + \lambda\delta_3) = \beta_2(v_1 + \lambda\delta_2), \tag{5.13}$$

$$\theta\gamma_{32}(v_1 + \lambda\delta_2) - \theta\gamma_{22}(w_1 + \lambda\delta_3) = \beta_2(w_1 + \lambda\delta_3). \tag{5.14}$$

Comparing (5.10) for $j = 1$ with (5.13) we find that

$$v_1 = \lambda\frac{\beta_2\delta_2}{\beta_1 - \beta_2}.$$

Similarly, from (5.11) for $j = 1$ and (5.14)

$$w_1 = \lambda\frac{\beta_2\delta_3}{\beta_1 - \beta_2}.$$

Since, from (5.11) for $j = 1$, we have

$$\theta\gamma_{32}v_1 = (\theta\gamma_{22} + \beta_2)w_1,$$

we conclude that

$$\theta\gamma_{32}\delta_2 = (\theta\gamma_{22} + \beta_2)\delta_3,$$

or $\gamma_{22} = \gamma_{22} + \beta_2/\theta$, a contradiction. This completes the proof of existence of a bounded solution satisfying (5.5) in the special case $F \equiv 0$, with $\mu = -\beta_2$.

The general case will follow by constructing a special solution which decreases exponentially to zero as $x \to \infty$. To do that we take $U = \sum_{j=1}^3 c_j U_j$ and choose $c_j = c_j(x)$ such that

$$\sum_{j=1}^{3} c_j' U_j = F,\ c_j(0) = 0.$$

We find that

$$|c_j(x)U_j(x)| \le C(1+x)|F(x)| \le Ce^{-\mu x}$$

for any $\mu < \min\{\mu_j\}$.

Suppose next that $u_0 > 0, v_0 > 0, w_0 > 0$. Let $\tilde{U}_4 = (u_4, v_4, w_4)e^{\beta_4 x}$ be a nonzero solution of (5.1) with $F \equiv 0$. It is easily seen that $u_4 \neq 0$ and we may therefore take $u_4 = 1$. Introduce the solution of (5.1)

$$(\tilde{u}, \tilde{v}, \tilde{w}) \equiv (u, v, w) - u(L)e^{-\beta_4 L}\tilde{U}_4 \text{ in } 0 < x < L. \tag{5.15}$$

Then $\tilde{u}(L) = 0$ and, since $u(L)$ is uniformly bounded for $0 < L < \infty$,

$$\tilde{u}(0) > 0,\ \tilde{v}(0) > 0,\ \tilde{w}(0) > 0,$$

if $L$ is sufficiently large. Applying the maximum principle, we conclude that $\tilde{u}(x) > 0$ in $0 < x < L$, and then also, from (2.2),(2.3),(5.3),

$$\tilde{v}_x + \gamma_{21}\tilde{v} > \gamma_{22}\tilde{w},\quad \tilde{w}_x + \theta\gamma_{22}\tilde{w} > \theta\gamma_{32}\tilde{v}. \tag{5.16}$$

We can now easily deduce that also $\tilde{v}(x) > 0,\ \tilde{w}(x) > 0$, in $0 < x < L$. Indeed, otherwise there is a smallest $x = x_0$ such that either $\tilde{v}(x)$ or $\tilde{w}(x)$ becomes zero. Suppose $\tilde{v}(x_0) = 0$. Then $\tilde{v}_x(x_0) \le 0$, and since $\gamma_{22}\tilde{w}(x_0) \ge 0$, this is a contradiction to the first inequality in (5.16).

Having proved that $\tilde{u}(x, r) > 0,\ \tilde{v}(x) > 0,\ \tilde{w}(x) > 0$ if $0 < x < L,\ 1 < r < b$, we now take $L \to \infty$ in (5.15) and conclude that $u \ge 0,\ v \ge 0,\ w \ge 0$, and then, by Theorem 3.1, $u > 0,\ v > 0,\ w > 0$ in $\Omega_\infty$. The assertion that $c > 0$ in (5.5) follows by applying the maximum principle to $(u, v, w) - \epsilon\tilde{U}_3$ for small enough $\epsilon > 0$. □

*Example.* Consider the system for $(u, v, w) \equiv (u_{20}, u_{21}, u_{22})$ in $(T)$, where $u_{10}$ and $u_{11}$ are assumed to be known functions. We can rescale $(x, r)$ to make the parameters $D$ and $v$ equal, so that

$$D\gamma_{11} = 2\lambda_2,\ D\gamma_{12} = k,\ D\gamma_{21} = \lambda_2' + k,\ D\gamma_{22} = 2\theta k,\ D\gamma_{32} = \theta\lambda_2'.$$

Then the matrix $A$ is given by

$$A = \frac{1}{D}\begin{pmatrix} 0 & 1 & 0 & 0 \\ 2\lambda_2 & 0 & -k & 0 \\ 2\lambda_2 & 0 & -\lambda_2' - k & 2k \\ 0 & 0 & \theta\lambda_2' & -2\theta k \end{pmatrix}$$

where $\theta = \frac{v}{v'}$. Note that $\gamma_{12} + \frac{1}{\theta}\gamma_{32} = \gamma_{21}$, so that (2.6) is satisfied. The characteristic polynomial $\det(A - \beta I)$ is equal to $\beta f(\beta)$, where

$$f(\beta) = \beta^3 + (2k\theta + k + \lambda_2')\beta^2 + (2k^2\theta - 2\lambda_2)\beta - (4k\lambda_2\theta + 2\lambda_2\lambda_2'),$$

so that

$$f(-\infty) = -\infty,\ f(+\infty) = +\infty,\ f(0) < 0,\ \text{and}$$
$$f(-(2k\theta + \lambda_2')) = 2k^2\theta\lambda_2' + k(\lambda_2')^2 > 0.$$

It follows that $f(\beta)$ has real roots $\beta_1, \beta_2, \beta_4$ such that $\beta_1 < -(2k\theta + \lambda_2') < \beta_2 < 0 < \beta_4$. Hence the condition (5.4) is satisfied.

## 6. Existence in $\Omega_\infty$

Consider the system (2.1)–(2.4),(2.8) under the assumption that $f_i$ are measurable functions and

$$|f_1(x,r)|, |f_2(x)|, |f_3(x)| \le Ce^{-\mu_0 x} \ (\mu_0 > 0),\ u_0 \in C^\alpha[1,b] \text{ for some } 0 < \alpha < 1. \tag{6.1}$$

**Theorem 6.1.** *If the $\gamma_{ij}$ satisfy (2.6) and (5.4) then there exists a unique solution to (2.1)–(2.4),(2.8), and*

$$|(u(x,r), v(x), w(x)) - c(\gamma_{12}\gamma_{22}, \gamma_{11}\gamma_{22}, \gamma_{11}\gamma_{32})| \le Ce^{-\mu x} \tag{6.2}$$

*for some positive constants $C$, $\mu$ and a constant $c$. Furthermore, if*

$$f_i \ge 0, u_0 \ge 0, v_0 \ge 0, w_0 \ge 0, \tag{6.3}$$

*then also*

$$u \ge 0, v \ge 0, w \ge 0 \tag{6.4}$$

*and $c \ge 0$.*

*Proof.* Consider first the case where (6.3) holds. Let us denote by $(u_L, v_L, w_L)$ the solution established in Theorem 4.1 in the special case where $u(L,r) \equiv 0$, and by $(\hat{u}(x), \hat{v}(x), \hat{w}(x))$ the solution of the ODE system in $\mathbb{R}^+$ established in Theorem 5.1 in the case

$$f_i = Ce^{-\mu_0 x} \ (i = 1, 2, 3), \text{ and}$$
$$\hat{u}(0) = 1 + \max_{1 \le r \le b} u_0(r),\ \hat{v}(0) = 1 + v(0),\ \hat{w}(0) = 1 + w(0).$$

Since, by the last part of Theorem 5.1, $\hat{u}(L,r) > 0 > u(L)$, we can apply the maximum principle to $(\hat{u}, \hat{v}, \hat{w}) = (u_L - \tilde{u}, v_L - \tilde{v}, w_L - \tilde{w})$ and conclude that $u_L - \hat{u} < 0$ in $\Omega_L$. Then, by the argument following (5.16), also $v_L - \hat{v} < 0$, $w_L - \hat{w} < 0$ in $0 < x < L$. Hence

$$0 \le u_L \le C,\ 0 \le v_L \le C,\ 0 \le w_L \le C,$$

where $C$ is a constant independent of $L$.

We can now choose a sequence $L = L_n \to \infty$ for which $(u_{L_n}, v_{L_n}, w_{L_n})$ converges uniformly on compact subsets of $\Omega_\infty$ to a solution $(u, v, w)$ of (2.1)–(2.4),(2.8), and $u \ge 0$, $v \ge 0$, $w \ge 0$.

The proof of existence for general $f_j, u_0, v_0, w_0$ follows by splitting these data into positive and negative parts ($f_j = f_j^+ - f_j^-$, etc.) and applying the above proof for each of the two sets of data. Since uniqueness was already established in Corollary 3.3, it remains to prove (6.2).

We begin by noting that

$$\left(\frac{1}{B}\int_1^\infty u(x,r)r\,dr,\ \ v(x),\ \ w(x)\right) \tag{6.5}$$

is a solution of the ODE system (5.1) with

$$|f_j| \le Ce^{-\mu_0 x}$$

and initial data

$$\bar{u}_0 = \frac{1}{B}\int_1^\infty u_0(r)rdr,\, v_0,\, w_0. \tag{6.6}$$

We compare this solution with the two solutions of (5.1) corresponding to

$$f_j = Ce^{-\mu_0 x} \ \text{ or } \ f_j = -Ce^{-\mu_0 x}$$

and having the same initial values (6.6). If we denote these two solutions by $(u^\pm, v^\pm, w^\pm)$, then, by the maximum principle,

$$u^-(x) \le \frac{1}{B}\int_1^b u(x,r)rdr \le u^+(x).$$

and by the argument following (5.16)

$$\begin{aligned} v^-(x) &\le v(x) \le v^+(x), \\ w^-(x) &\le w(x) \le w^+(x). \end{aligned} \tag{6.7}$$

By Theorem 5.1

$$|(u^\pm, v^\pm, w^\pm) - c(\gamma_{12}\gamma_{22}, \gamma_{11}\gamma_{22}, \gamma_{11}\gamma_{32})| \le Ce^{-\mu x} \tag{6.8}$$

for some $\mu > 0$. Consequently, the same asymptotic bound holds for the solution (6.5). In particular, we get from (2.1)

$$-\Delta u + \gamma_{11}u = \tilde{f}_1(x,r), \tag{6.9}$$

where

$$|\tilde{f}_1(x,r) + c\gamma_{12}\gamma_{11}\gamma_{22}| \le Ce^{-\nu x},\ \ \nu = \min\{\mu, \mu_0\}. \tag{6.10}$$

If we multiply (6.9) by $u$ and integrate over $\Omega_L$, and then take $L \to \infty$, we find that

$$\iint_{\Omega_\infty} (|\nabla u|^2 + \gamma_{11}u^2)rdrdx < \infty; \tag{6.11}$$

here we used the boundary condition $\partial u/\partial r = 0$ at $r = 1, b$. We are now in a position to apply Theorem 6.3 of [7] to (6.9) and deduce that

$$u(x,r) = \bar{u}(r) + O(e^{-\nu_0 x}) \text{ for some } \nu_0 > 0 \tag{6.12}$$

and some function $\bar{u}(r)$. Taking $x \to \infty$ in equation (2.1) we deduce that $\bar{u}(r)$ satisfies

$$-\frac{1}{r}\frac{\partial}{\partial r}(r\frac{\partial \bar{u}}{\partial r}) + \gamma_{11}\bar{u} = \gamma_{12}c\gamma_{11}\gamma_{22},$$

so that, by uniqueness, $\bar{u}(r)$ must coincide with the constant $c\gamma_{12}\gamma_{22}$. The assertion (6.8) now follows from (6.12) and (6.7), (6.8). □

## 7. Another subsystem of $(T)$

The subsystem of $(T)$ for $u = u_{10},\ v = u_{11}$ (with $u_{00}$ assumed to be known) can be written in the form

$$-\Delta u + \gamma_{11} u - \gamma_{12} v = f_1, \tag{7.1}$$

$$v_x + \gamma_{11} v - \frac{\gamma_{22}}{B} \int_1^b u(x,r) r dr = f_2, \tag{7.2}$$

where

$$\gamma_{11} = \lambda_1 + \lambda_2,\ \gamma_{12} = k,\ \gamma_{21} = \lambda_1 + k,\ \gamma_{22} = \lambda_2. \tag{7.3}$$

This system is not a special case of (2.1)–(2.3) (with $w \equiv 0$) since $\gamma_{22} \neq \gamma_{21}$. However, the results obtained in sections 3–6 can easily be extended to this system.

Consider first the maximum principle. We assume that

$$-\Delta u + \gamma_{11} u - \gamma_{12} v \le 0 \text{ in } \Omega_L, \tag{7.4}$$

$$v_x + \gamma_{11} v - \frac{\gamma_{22}}{B} \int_1^b u(x,r) r dr \le 0 \text{ in } 0 < x < L, \tag{7.5}$$

and that $u, v$ satisfy the same boundary conditions as in (3.4),(3.5). We claim that $u \le 0$ in $\Omega_L$.

Indeed, suppose $u$ takes a positive maximum $M$, say at $(x_0, r_0)$. As in (3.9) (with $w \equiv 0$) we get

$$v(x) < \frac{\gamma_{22}}{\gamma_{21}} M,$$

so that by (7.4)

$$-\Delta u + \gamma_{11} u < \gamma_{12} \frac{\gamma_{22}}{\gamma_{21}} M.$$

Assuming that

$$\gamma_{12}\gamma_{22} < \gamma_{11}\gamma_{21}, \tag{7.6}$$

we obtain the inequality $-\Delta u < 0$ in a neighborhood of $(x_0, r_0)$, from which we derive a contradiction, as before.

Note finally that the inequality (7.6) is satisfied for $\gamma_{ij}$ as in (7.3).

Next we turn to the ODE system corresponding to (7.1),(7.2). In the present case

$$A = \frac{1}{D} \begin{pmatrix} 0 & 1 & 0 \\ \gamma_{11} & 0 & \gamma_{12} \\ \gamma_{22} & 0 & -\gamma_{21} \end{pmatrix}$$

and

$$\det(A - \lambda I) = -\beta^3 - (\lambda_1 + k)\beta^2 + (\lambda_1 + \lambda_2)\beta + (\lambda_1^2 + \lambda_1\lambda_2 + \lambda_1 k) \equiv f(\beta).$$

Since

$$f(-\infty) = +\infty,\ f(+\infty) = -\infty,\ f(0) > 0, \text{ and}$$
$$f(-(\lambda_1 + k)) = -\lambda_2 k < 0,$$

$f(\beta)$ has three real zeros $\beta_j$, and

$$\beta_1 < -(\lambda_1 + k) < \beta_2 < 0 < \beta_3.$$

We can now easily extend the proof of Theorem 5.1 to the present case, and then also the proof of Theorem 6.1. Thus the system (7.1),(7.2), under the same boundary conditions on $u$, $v$ and on the $f_j$ as in (6.1), has a unique bounded solution, and

$$|u(x, r)| + |v(x)| \leq Ce^{-\mu x}$$

for some positive constants $C$, $\mu$; under the additional conditions $f_j \geq 0, u_0 \geq 0$, $v_0 \geq 0$, we also have $u \geq 0$, $v \geq 0$.

## 8. The system $(T)$ and its generalization

The results obtained in sections 2–7 enable us to solve the system $(T)$ (in the stationary case) either in $\Omega_L$ or in $\Omega_\infty$. To avoid repetition we shall consider the stationary system $(T)$ only in $\Omega_\infty$, with boundary conditions

$$\begin{aligned} &u_{i0}(0, r)\ (1 < r < b), u_{i1}(0), u_{i2}(0), \\ &\frac{\partial u_{i0}}{\partial r}(x, 1) = \frac{\partial u_{i0}}{\partial r}(x, b) = 0, \quad 0 < x < \infty, \\ &u_{i0} \in L^\infty(\Omega_\infty); \end{aligned} \tag{8.1}$$

note that the last condition may be viewed as a boundary condition at $x = \infty$.

The boundary condition $\frac{\partial u_{i0}}{\partial r}(x, 1) = 0$ simply means that there is no flux of particles into the microtubule. The boundary condition $\frac{\partial u_{i0}}{\partial r}(x, b) = 0$ means that the net flux of particles from the $(b - 1)$-neighborhood of the microtubule is negligible.

We first solve for $u_{00}$ and observe, by comparison, that

$$|u_{00}(x, r)| \leq Ce^{-\sqrt{2\lambda_1}x}. \tag{8.2}$$

Next we solve for $(u_{10}, u_{11})$ in $\Omega_\infty$. Using the results of section 7 we find that there exists a unique solution, and

$$|u_{10}(x, r)| + |u_{11}(x)| \leq Ce^{-\mu_0 x} \quad (\mu_0 > 0). \tag{8.3}$$

Finally, we apply Theorem 6.1 to $(u_{20}, u_{21}, u_{22})$ and conclude that there exists a unique solution such that

$$|(u_{20}, u_{21}, u_{22}) - c(2k^2, 4k\lambda_2, 2\lambda_2\lambda_2')| \leq Ce^{-\mu_1 x} \quad (\mu_1 > 0), \tag{8.4}$$

for some constant $c$.

Consider next the more general situation where the diffusion terms are given by

$$D\frac{\partial^2 u_{i0}}{\partial x^2} + \rho^2 D\frac{1}{r}\frac{\partial}{\partial r}(r\frac{\partial u_{i0}}{\partial r}), \quad 1 < r < b, \tag{8.5}$$

for some constant $0 < \rho < 1$.

By a change of variables

$$r' = \frac{r}{\rho}, \quad u'_{i0}(x, r') = u_{i0}(x, r),$$

the expression (8.5) becomes

$$D\left(\frac{\partial^2 u'_{i0}}{\partial x^2} + \frac{1}{r'}\frac{\partial}{\partial r'}\left(r'\frac{\partial u'_{i0}}{\partial r'}\right)\right), \quad \frac{1}{\rho} < r' < \frac{b}{\rho}. \tag{8.6}$$

Thus the transport system reduces to the system $(T)$ in the region $\Omega_L^\rho = \{(x, r),\ 0 < x < L,\ \frac{1}{\rho} < r < \frac{b}{\rho}\}$, and all our previous results remain true.

We shall now generalize the transport model $(T)$ in two directions: $(i)$ taking the diffusion coefficient in the direction orthogonal to the microtubule to be $\gamma D$, where $\gamma < 1$; $(ii)$ assuming that the rate of attachment of particles with motor protein to the microtubule decreases as the distance $r - 1$ increases, say according to $e^{-\alpha(r-1)}$ for some $\alpha > 0$.

Thus instead of $(T)$ we get the system

$$(T_{\gamma\alpha}) \quad \begin{aligned}
\frac{\partial u_{00}}{\partial t} &= D\frac{\partial^2 u_{00}}{\partial x^2} + \gamma D\frac{1}{r}\frac{\partial}{\partial r}(r\frac{\partial u_{00}}{\partial r}) - 2\lambda_1 u_{00} \\
\frac{\partial u_{10}}{\partial t} &= D\frac{\partial^2 u_{10}}{\partial x^2} + \gamma D\frac{1}{r}\frac{\partial}{\partial r}(r\frac{\partial u_{10}}{\partial r}) + 2\lambda_1 u_{00} - \lambda_1 u_{10} - \lambda_2 u_{10} + k u_{11} \\
\frac{\partial u_{20}}{\partial t} &= D\frac{\partial^2 u_{20}}{\partial x^2} + \gamma D\frac{1}{r}\frac{\partial}{\partial r}(r\frac{\partial u_{20}}{\partial r}) + \lambda_1 u_{10} - 2\lambda_2 u_{20} + k u_{21} \\
\frac{\partial u_{11}}{\partial t} &= -v\frac{\partial u_{11}}{\partial x} + \frac{\lambda_2}{B_\alpha}\int_1^b e^{-\alpha(r-1)} u_{10} r\,dr - \lambda_1 u_{11} - k u_{11} \\
\frac{\partial u_{21}}{\partial t} &= -v\frac{\partial u_{21}}{\partial x} + \lambda_1 u_{11} + \frac{2\lambda_2}{B_\alpha}\int_1^b e^{-\alpha(r-1)} u_{20} r\,dr \\
&\quad -\lambda'_2 u_{21} + 2k u_{22} - k u_{21} \\
\frac{\partial u_{22}}{\partial t} &= -v'\frac{\partial u_{22}}{\partial x} + \lambda'_2 u_{21} - 2k u_{22}
\end{aligned}$$

where $B_\alpha = \int_1^b e^{-\alpha(r-1)} r\,dr$.

One can easily extend the proof of Theorem 3.1 to this case and then establish existence and uniqueness in $\Omega_L$ (for the stationary case) as before.

## 9. The time-dependent problem

Consider the system

$$u_t - \Delta u + \gamma_{11} u - \gamma_{12} v = f_1(x, r, t), \tag{9.1}$$

$$v_t + v_x + \gamma_{21} v - \gamma_{22} w - \frac{\gamma_{11}}{B} \int_1^b u(x, r) r dr = f_2(x, t), \tag{9.2}$$

$$\theta w_t + w_x + \theta \gamma_{22} w - \theta \gamma_{32} v = f_3(x, t) \tag{9.3}$$

with boundary conditions

$$u(0, r, t) = u_0(r, t)\ (1 < r < b),\ v(0, t) = v_0(t),\ w(0, t) = w_0(t), \tag{9.4}$$

$$\begin{cases} \frac{\partial u}{\partial r}(x, 1, t) = \frac{\partial u}{\partial r}(x, b, t) = 0\ (0 < x < L), \\ u(1, r, t) = u_1(r, t)\ (1 < r < b), \end{cases} \tag{9.5}$$

and initial condition

$$u(x, r, 0) = u_*(r, t) \quad (0 < x < L,\ 1 < r < b). \tag{9.6}$$

**Theorem 9.1.** *If* $f_j \le 0,\ u_0 \le 0,\ v_0 \le 0,\ w_0 \le 0,$ *and* $u_* \le 0$*, then* $u \le 0$ *in* $\overline{\Omega}_L \times \{t > 0\}$.

*Proof.* Consider first the case $\theta = 1$ and proceed as in the proof of Theorem 3.1, setting

$$M = \max_{\overline{\Omega}_L \times [0,T]} u = u(x_0, r_0, t_0) > 0 \tag{9.7}$$

for some $T > 0$. Analogously to (3.7)

$$v(x_1 + t, t) \le e^{-\gamma_{21} t} + \gamma_{22} \int_0^t e^{\gamma_{21}(\tau - t)} w(x_1 + \tau, \tau) d\tau$$
$$+ \frac{\gamma_{11}}{B} \int_0^t d\tau \int_1^b e^{\gamma_{21}(\tau - t)} u(x_1 + \tau, \tau, r) r dr.$$

for $(x_1 + t, t)$ in a neighborhood of $(x_0, t_0)$, so that

$$v(x_1 + t, t) \le A + \gamma_{22} \int_0^t e^{\gamma_{21}(\tau - t)} w(x_1 + \tau, \tau) d\tau. \tag{9.8}$$

Strictly speaking, this formula is valid only if the interval $\{(x_1 + \tau, \tau); 0 < \tau < t\}$ belongs to $\Omega_L \times (0, t)$; otherwise we have to replace

$$\int_0^t e^{\gamma_{21}(\tau - t)} w(x_1 + \tau, \tau) d\tau$$

by

$$\int_s^t e^{\gamma_{21}(\tau - t)} w(x_1 + \tau, \tau) d\tau,$$

where $x_1 + s = 0$. Alternatively, we can still use the above formula but set $u(x, r, t) = v(x, t) = w(x, t) \equiv 0$ for $x < 0$. We shall use the second alternative since then the formulas take a simpler form.

Similarly,

$$w(x_1 + \tau, \tau) \leq \gamma_{32} \int_0^\tau e^{-\gamma_{23}(s-\tau)} v(x_1 + s, s) ds. \tag{9.9}$$

Substituting (9.9) into (9.8) we get, as in (3.11)–(3.15),

$$v(x_1 + t, t) < A \frac{\gamma_{21}}{\gamma_{21} - \gamma_{32}} = \frac{\gamma_{11}}{\gamma_{12}} M, \tag{9.10}$$

so that

$$(u_t - \Delta u)(x, r, t) < 0$$

in some neighborhood of $(x_0, r_0, t_0)$. This contradicts the maximum principle for the heat equation.

Consider next the case where $0 < \theta < 1$. Then, instead of (9.9) we have

$$w(x_2 + \theta\tau, \tau) \leq \gamma_{32} \int_0^\tau e^{-\gamma_{23}(s-\tau)} v(x_2 + \theta s, s) ds, \tag{9.11}$$

for any $x_2$. For each $0 < \tau < t$ let $x_2 = x_2(\tau)$ be such that

$$x_2(\tau) + \theta\tau = x_1 + \tau, \quad \text{i.e., } x_2(\tau) = x_1 + (1 - \theta)\tau.$$

For each $\tau$, we now substitute $w(x_2 + \theta\tau, \tau)$ from (9.11) into (9.8) and obtain

$$\begin{aligned} v(x_1 + t, t) \leq A + A \frac{\gamma_{22}\gamma_{32}}{\gamma_{21}\theta\gamma_{22}} \\ + \text{ an iterated integral containing } w(x_2(\tau) + \theta s, s). \end{aligned}$$

We can now proceed as before to replace $w(x_2(\tau) + \theta s, s)$ by a formula similar to (9.10), where the new $x_2$ depends on both $\tau$ and $s$. Similarly, by step-by-step iteration, we arrive at the inequality (9.10), from which we derive a contradiction as before. □

Theorem 9.1 can now be used to establish existence in $\Omega_L \times (0, \infty)$. We can also use the same ODE system as in section 5 to derive an a priori bound independent of $L$, and thus establish existence of a bounded solution in $\Omega_\infty \times (0, \infty)$ for the transport system $(T)$. Uniqueness is proved by comparison, as in Corollary 3.3. Finally, the maximum principle extends also to the system $(T_{\gamma\alpha})$.

## 10. Numerical results

For our numerical work we take the standard values of $D$ and $v, v'$ as in [17]: $D = 0.1\mu\text{m}^2/\text{s}$, $v = v' = 0.1\mu\text{m/s}$. The detachment rate $k$ is an unknown variable; we take an average value $k = 0.5\text{s}^{-1}$ from Table 2 of [17]; the value of the attachment rate $\lambda_2$ corresponding to this choice of $k$ in [17] is $\lambda_2 = 1\text{s}^{-1}$. Also, we take $\lambda_2' = \lambda_2$, and finally, to allow for a larger affinity of the motor/particle attachment, we take $\lambda_1 = 2\text{s}^{-1}$. We take the length scale to be $0.0125\mu$m, so that the boundary of the microtubule is at $r = 1$. Also, we take $b = 5$.

Although $L$ is actually very large (i.e., typically 40000 units; see section 1), the numerical results show asymptotic convergence already for $L = 200$. We are especially interested in the effect of varying the values of $\lambda_1, \lambda_2', v'$ and $\gamma, \alpha$; the parameters $\lambda_1, \lambda_2'$ and $v'$ are related to the fact that our model allows more than one motor to bind to a particle, and $\gamma, \alpha$ are related to the three dimensional nature of the domain $\Omega_L$; recall that $v \le v' \le 2v$. The parameters $\lambda_1,\ \lambda_2,\ v'$ do not appear at all in the model introduced in [17].

We shall derive numerical results for the following situations:

(1) stationary system $(T)$ with constant boundary values,
(2) time dependent system $(T)$,
(3) stationary system $(T_{\gamma\alpha})$.

We are interested in stationary solutions since these are the solutions one expects to see in the steady state of a living cell. On the other hand, we are also interested in time dependent solutions because these solutions can be compared with experiments (e.g., by looking at radioactivity profiles during axonal transport).

Note that in the case (1) the solution of the system is independent of the variable $r$, i.e., $(T)$ reduces to an ODE system (cf. section 5). Thus there is no dependence on the diffusion coefficient in the orthogonal direction to the microtubule.

Figures 1–3 illustrate the case (1). The initial values at $x = 0$ are $u_{ij} = 0$ except for $u_{00} = 1$, i.e., we consider the case where the particles supplied by the soma have no motors attached to them initially.

In Figure 1 we show the effect of varying $\lambda_1$ on the total concentration $\sum u_{ij}$, and on the ratio between the mass transported by processive motion, $u_{11}+u_{21}+u_{22}$, and the mass transported by diffusive motion, $u_{00} + u_{10} + u_{20}$.

In Figure 2 we show the effect of varying $\lambda_2'$, and in Figure 3 we show the effect of varying $v'$.

Since at $x = 0$ no particles are attached to the microtubule, the ratio of processive to diffusive concentrations is very small for small $x$, as shown in Figures 1$(b)$–3$(b)$. As a result, since diffusion alone tends to spread the concentration, total concentration actually decreases in $x$ for $x$ small (approximately for $0 < x < 5$), as shown in Figures 1$(a)$–3$(a)$.

In Figure 1 both the total concentration $\sum u_{ij}(x)$ as well as the relative mass transfer by processive motion are monotone increasing in $\lambda_1$, for any $x$. Figure 2$(b)$ shows that as $\lambda_2'$ decreases, i.e., as the conformation constraint increases, the relative mass transported by the processive motion decreases. Figure 2$(a)$ shows that the transport of the total mass also decreases slightly as $\lambda_2'$ decreases, but only after

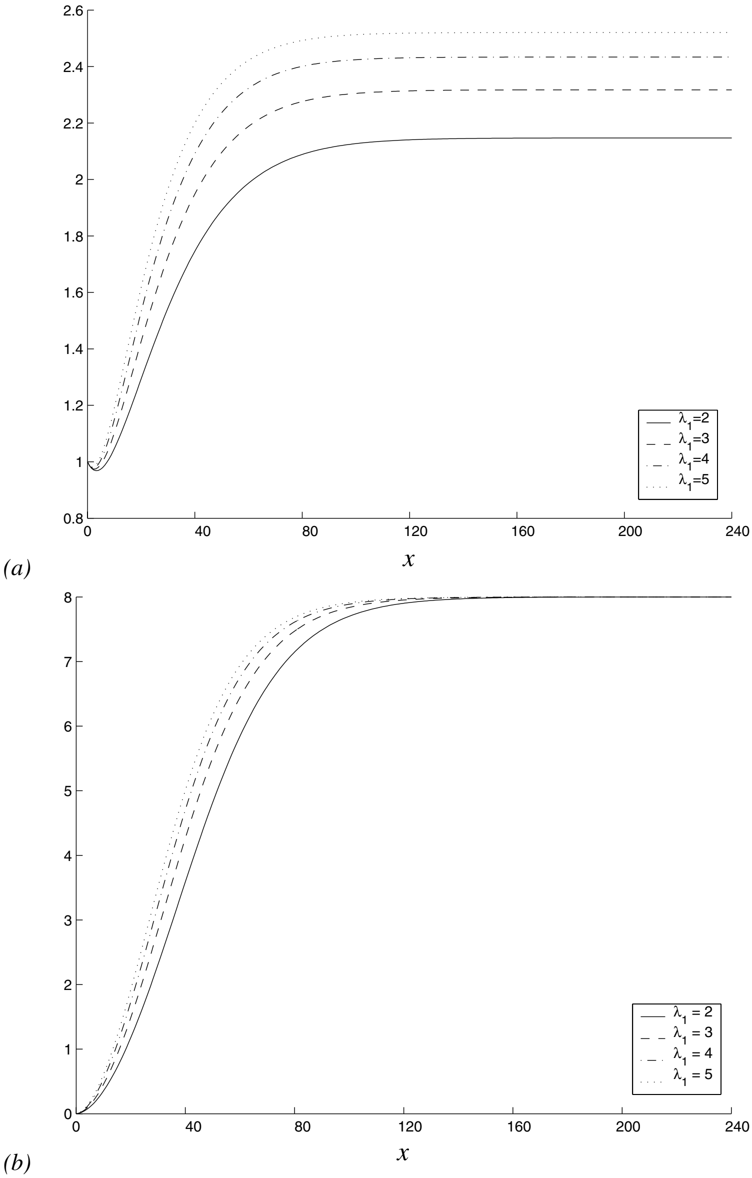
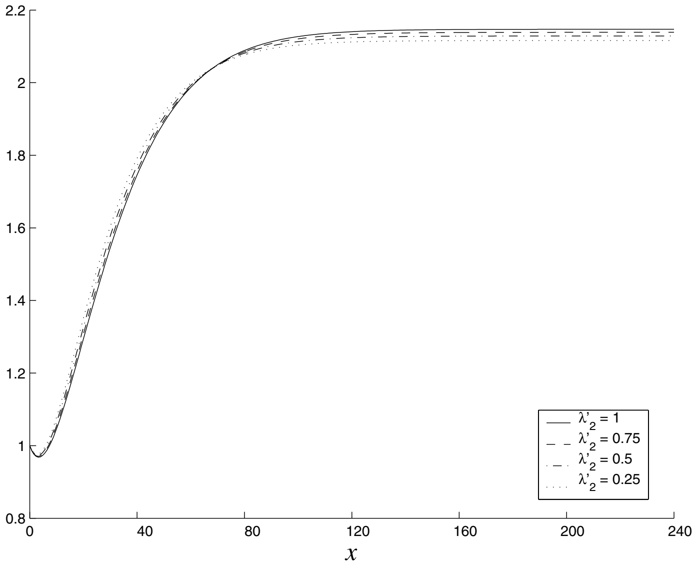
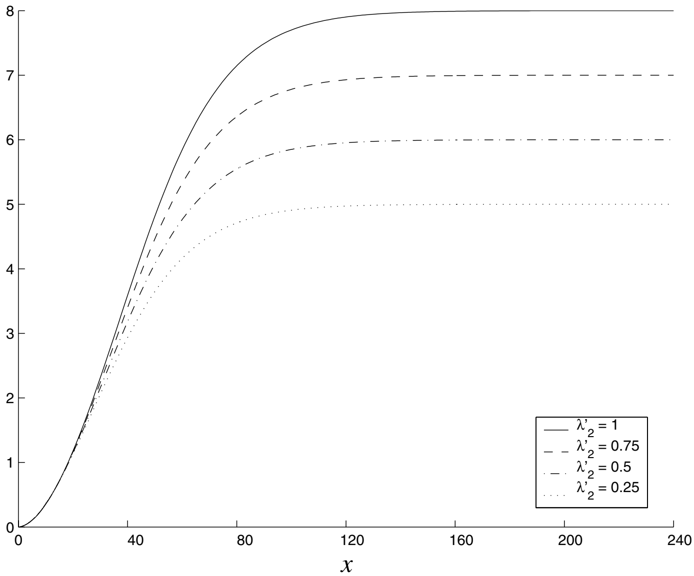



**Fig. 1.** The effect of varying $\lambda_1$ for the stationary solutions of $(T)$: (a) on the total sum of the concentrations $u_{ij}$ (b) on the ratio between total processive and total diffusive concentrations.

some distance away from the soma, i.e., approximately for $x > 70$. Figure 3 shows that as $v'$ increases, the total transported mass decreases, and the relative mass transported by processive motion decreases too. This is apparently a semblance of conservation of mass in the processive motion (roughly, mass concentration times velocity is constant).




*(a)*




*(b)*

**Fig. 2.** The effect of varying $\lambda_2'$ for the stationary solutions of $(T)$: (a) on the total sum of the concentrations $u_{ij}$ (b) on the ratio between total processive and total diffusive concentrations.

Figure 4 illustrates case (2): we look at time dependent solutions of the system $(T)$, for initial conditions $u_{ij} = 0$ at $t = 0$, except for $u_{00}$ which is 1 on a small interval centered 160 units away from the soma; for boundary conditions we take $u_{ij} = 0$ at $x = 0$, for all $i$, $j$. As the initial rectangular profile propagates, it becomes flatter and takes the shape of a Gaussian, similar to experimental results

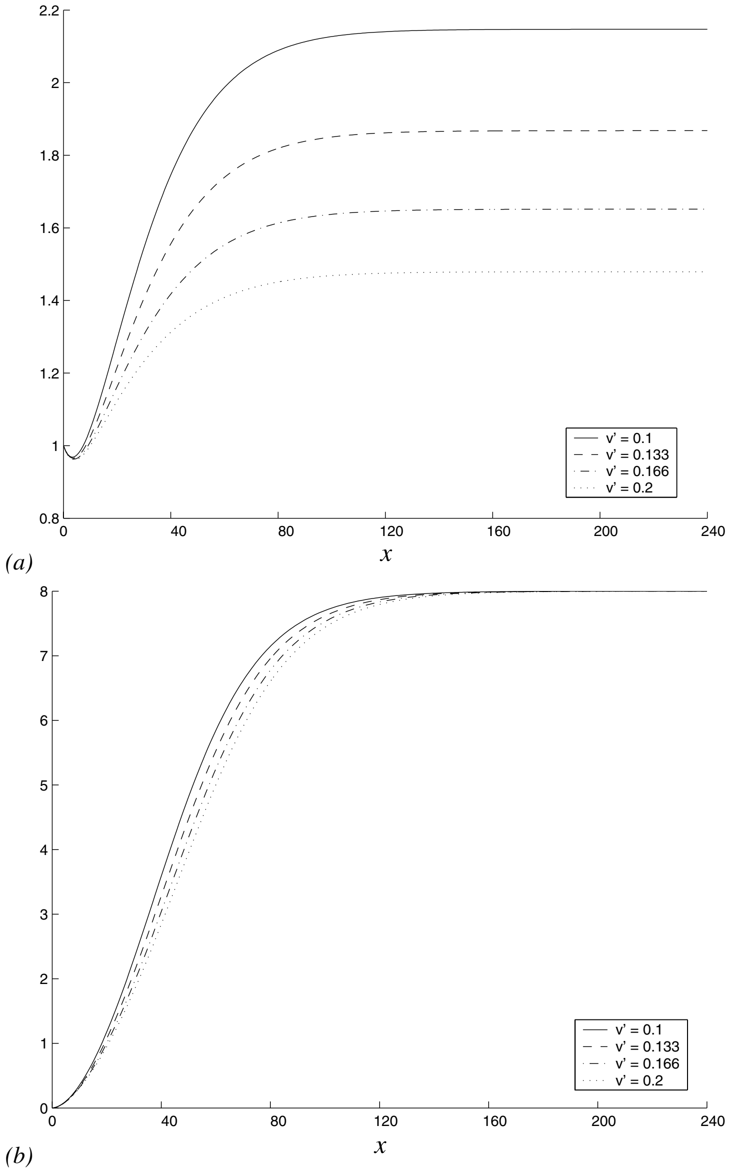



**Fig. 3.** The effect of varying $v'$ between $0.1\mu$m/s and $0.2\mu$m/s for the stationary solutions of $(T)$: (a) on the total sum of the concentrations $u_{ij}$ (b) on the ratio between total processive and total diffusive concentrations.

reported by Gross and Beidler [9] (see also Blum and Reed [3]); there is an obvious difference between the results in [9] and the profiles in Figure 4, since we did not include deposition of particles on the axonal membrane in our model. Note that at $t = 0$ there is no mass in processive motion.

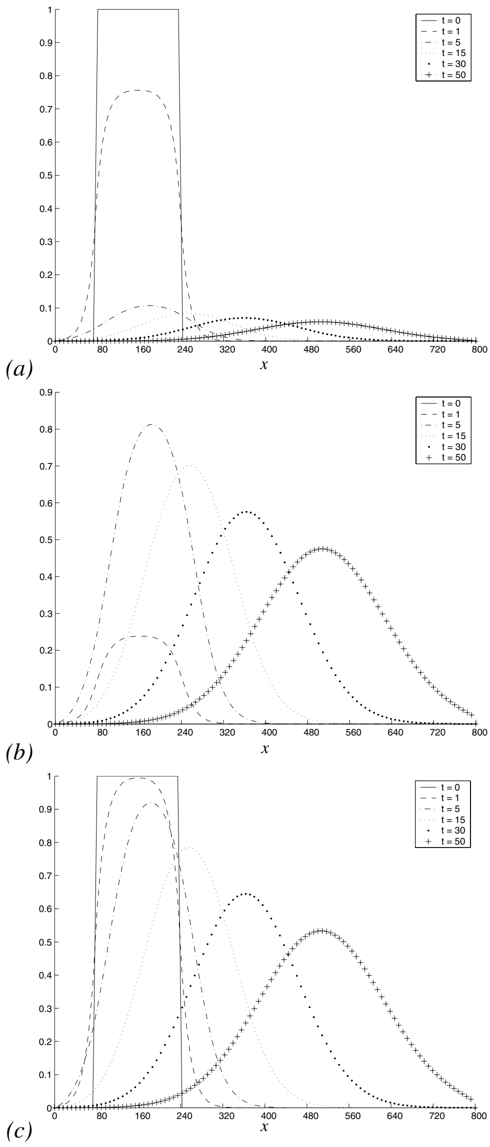



**Fig. 4.** Time dependent solutions of $(T)$: (a) temporal evolution of the sum of the concentrations for diffusive $u_{ij}$ (i.e., $u_{00} + u_{10} + u_{20}$); (b) temporal evolution of the sum of the concentrations for processive $u_{ij}$ (i.e., $u_{11} + u_{21} + u_{22}$); (c) temporal evolution of the sum of all concentrations $u_{ij}$.

Figures 5 and 6 illustrate case (3): we look at stationary solutions of the system $(T_{\gamma\alpha})$. The boundary values $u_{00}(0, r)$ decrease linearly with $r$, while the remaining $u_{ij}(0, r)$ are zero. In Figure 5$(a)$ we see that for $\gamma = 1$ the concentrations of the diffusive $u_{ij}$ at $r = 5$ and $r = 1$ converge to the common limit faster than they do for the case $\gamma = 0.1$. Figure 5$(b)$ shows that the effect of $\gamma$ on the concentrations of

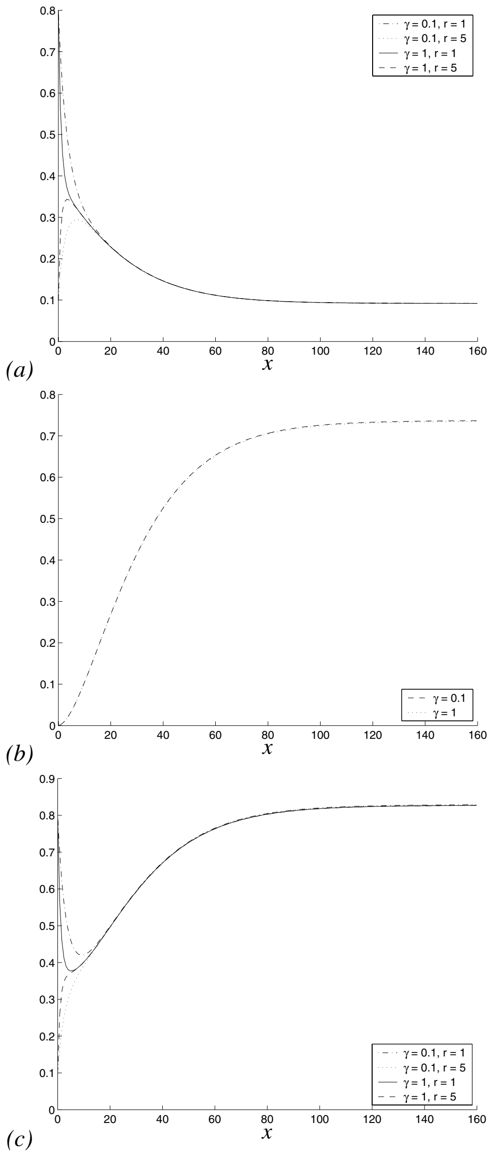



**Fig. 5.** The effect of varying $\gamma$ on the stationary solutions of $(T_{\gamma\alpha})$ at $r = 1$ and $r = 5$: (a) on the total sum of the concentrations for diffusive $u_{ij}$ (i.e., $u_{00} + u_{10} + u_{20}$); (b) on the total sum of the concentrations for processive $u_{ij}$ (i.e., $u_{11} + u_{21} + u_{22}$); (c) on the total sum of the concentrations for all $u_{ij}$.

the processive $u_{ij}$ is very small. Also, the effect of $\alpha$ on the various concentrations is very small, as shown in Figure 6 for the sum of all concentrations. This is due to the fact that the diffusion coefficient is relatively large.

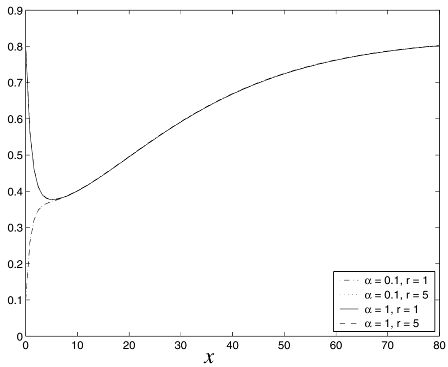



**Fig. 6.** The effect of varying $\alpha$ on the stationary solutions of $(T_{\gamma\alpha})$ at $r = 1$ and $r = 5$, on the total sum of the concentrations for all $u_{ij}$.

## 11. Conclusions

In this paper we developed a rather generic transport model of vesicles and organelles along microtubules in axon. These particles – when bound by motor proteins (kinesin) to the surface of a microtubule – move in processive motion toward the synaptic end; from time to time this motion is disrupted as the motors detach from the microtubule, and then the particles undergo diffusion, until they become reattached to the microtubule.

Our model allows two motor proteins to bind to each particle, and subsequently also to the microtubule. The model consists of a system of six populations with concentrations $u_{ij}$ $(0 \le i \le j \le 2)$, satisfying six PDEs with some boundary and initial conditions. We proved that the system has an unique solution, and discussed the asymptotic behavior of the $u_{ij}$ near the far end of the microtubule.

We presented numerical simulations showing how the transport of mass (both by processive motion and by diffusion) depends on the various parameters of the PDE system. For example, we have shown that if the conformation constraints of the particle bound to microtubule by one motor protein become more restrictive (i.e., $\lambda_2'$ decreases), then the ratio between processive and diffusive mass decreases. We have also shown that, as an initial rectangular profile propagates, it becomes flatter and takes the shape of a Gaussian distribution, somewhat similar to experimental results by Gross and Beidler [9].

Some of the parameters in our model cannot be determined experimentally at this time. Nor is it clear that the factor $e^{-\alpha(r-1)}$ in the system $(T_{\gamma\alpha})$ is the most appropriate one. In future work we intend to consider more recent experimental results on axonal transport of vesicles, organelles, as well as neurofilaments [5,22,24], and attempt to validate our model, or a variant of it, by making suitable choices of parameters and perhaps suitable assumptions on the distribution of microtubules.

With conclude with several challenging problems:

($A$) The model developed in this paper can be extended to include both anterograde and retrograde transport. Suppose no particle can be attached to one anterograde and one retrograde motor at the same time. Then, if we denote by $u_{ij}^*$ the concentration of particles in retrograde motion, we get a system of equations for the $u_{ij}^*$ similar to that for the $u_{ij}$. The only coupling between the two systems occurs among the particles which are unattached to a motor, namely $u_{00} = u_{00}^*$, and we have to introduce rates

$$u_{10}^* \xleftarrow{2\lambda_1^*} u_{00} \xrightarrow{2\lambda_1} u_{10}$$

The analysis of each system then proceeds in the same way as before. If, however, particles may be attached to one anterograde and one retrograde motors, then we get additional "mixed" populations, say $\tilde{u}_{2j}$, and the system becomes more complicated. It would be interesting to explore this system.

($B$) One of the shortcomings of our model is the fact that it deals with only one isolated microtubule. If we take into account the distribution of the population of microtubules in the axon, then the profile of the transported concentration will depend on whether the microtubules are uniformly distributed or are clustered in some regions. Neuronal types where microtubules are compactly distributed are mentioned in [6]. If the microtubules are distributed along the axis in a periodic way, then one may be able to use the method of homogenization [10] in order to compute the "effective" diffusion coefficients for particles $u_{00}$, $u_{10}$, $u_{20}$, as the distance $\varepsilon$ between neighboring microtubules becomes arbitrarily small. One will also have to replace the integrals

$$\int_1^b u_{j0} r dr$$

in ($T$), or

$$\int_1^b e^{-\alpha(r-1)} u_{j0} r dr$$

in ($T_{\gamma\alpha}$), by integrals of $u_{j0}$ (with suitable weight functions) taken along $\delta$-neighborhoods of microtubules, where $\delta$ is a new small parameter. It would be interesting to see how the mathematical and numerical results will depend on the quotient $\delta/\varepsilon$.

($C$) We have assumed in ($T$) that $v$ and $v'$ are deterministic quantities. Actually, because of fluctuations in the cellular environment (including the motion of the microtubules) and the oscillatory nature of the motion of motor proteins, the gliding velocity of motor proteins is a fluctuating quantity. Thus $v$ and $v'$ are undergoing a stochastic process. It would be interesting to model this process and to determine whether it makes a significant change in the results obtained for the model where $v$ and $v'$ are assumed to be the average values of the fluctuating velocities.

($D$) When $v$ and $v'$ are taken as random variables, as suggested in ($C$), the parabolic-hyperbolic system ($T$) becomes a system of stochastic partial differential equations. It would be interesting to try to establish a maximum principle for such a system, which in some average sense is similar to Theorem 3.1.

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