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Aggregation–fragmentation model of vesicular transport in neurons

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Abstract

We develop a mathematical model of the motor-based transport and delivery of vesicles to synaptic targets of an axon. Our model incorporates the 'stop-and-go' nature of bidirectional motor transport (which can be modeled in terms of advection–diffusion) and the reversible exchange of vesicles between motors and targets, both of which have been observed experimentally. Since motor-target interactions are reversible, it is necessary to keep track of the cluster size of vesicles bound to each motor-complex. This naturally leads to a modified version of the Becker–Doring model of aggregation–fragmentation processes. We analyze steady-state solutions of the transport model and obtain an explicit solution that supports a uniform distribution of synaptic resources along an axon. We thus establish a possible mechanism for the democratic distribution of synaptic resources along the length of an axon, based on reversible motor-target interactions. In the irreversible case, one finds that the motor-driven transport of newly synthesized proteins from the soma to pre-synaptic targets along the axon tends to favor the delivery of resources to more proximal synapses.

Keywords: intracellular transport, molecular motors, aggregation–fragmentation models, Becker–Doring equations, synaptic democracy

(Some figures may appear in colour only in the online journal)

1. Introduction

Neurons are highly polarized cells with extensively branched input dendrites and a single long output axon [1]. Communication between neurons is primarily mediated by highly regulated, protein-rich subcellular compartments known as synapses. Each synapse consists of a pre-synaptic active zone located either at an axon terminal or partway along an axon (en passant

synapse), which is apposed to a postsynaptic density located on a dendritic branch. The active zone is the site of neurotransmitter release, whereas the postsynaptic density contains receptors to which neurotransmitter binds, resulting in local changes in the membrane voltage of the postsynaptic cell. The formation of new synapses (synaptogenesis) and the modification of existing synapses (synaptic plasticity) in response to synaptic activity from other neurons, requires the transport of newly synthesized proteins along the axon and dendrites. The long distances between the soma and distal synapses means that diffusion is too slow and thus necessitates the packaging of proteins into vesicles, which are then actively transported by molecular motors along microtubular filament tracks. Microtubules are directionally polarized polymeric filaments with biophysically distinct (+) and (−) ends, and this polarity determines the preferred direction in which an individual molecular motor moves. For example, kinesin moves towards the (+) end, whereas dynein moves towards the (−) end [2]. Since microtubules tend to be aligned with the same polarity along axons and distal regions of dendrites, it follows that kinesin (dynein) transports cargo from (towards) the cell body, that is, in the anterograde (retrograde) direction.

In experiments where fluorescent labeling and live-cell imaging have been used to track the position of vesicular cargo, the movement along a dendrite or axon is typically seen to randomly pause and switch direction [3–5]. The random switching between different motile states can be explained using a biophysical model of the cargo and microtubule interacting via multiple molecular motors [6]. The motors interact through the forces they each place on the cargo. If the set of motors transporting a cargo is comprised of motors with opposing directional preference then they may compete in a tug-of-war [6, 7]. (Alternatively, there is some signaling mechanism that switches between kinesin-based and dynein-based transport.) Movement of the cargo is then ultimately determined by the random binding and unbinding of the motors to the microtubule. The unbinding rate depends on the force applied to the motor. If a force is applied opposite to the preferred direction of a motor, then it is more likely to unbind from the microtubule. One can consider all of the motors attached to a cargo as a motor-complex such that the different motile states of the motor-complex represent different configurations of bound and unbound motors.

A major challenge for a neuron is to ensure an even distribution of synaptic material among neighboring synapses. Experimental studies in *drosophila* and *C elegans* indicate that one mechanism for achieving 'synaptic democracy' is to combine bidirectional transport with inefficient (reversible) capture of mobile vesicles by synapses, in order to prevent excessive aggregation at any particular synapse [8–11]. For example, in the case of the transport of synaptic vesicle precursors in axons, motor-cargo complexes make frequent stops at potential synaptic sites where certain GTPases such as ARL-8 regulate the kinetics of association and dissociation [9]. Recently, we developed a mathematical model of motor-driven vesicular transport and showed quantitatively that a combination of 'stop-and-go' transport and reversible interactions between motors and targets provides a biophysically plausible mechanism for the democratic distribution of molecular cargo among synapses [12]. In particular, we considered a pair of advection–diffusion equations for the concentration of motor-complexes with or without a vesicle, which included kinetic mass-action terms that represented the reversible exchange of a vesicle with synaptic targets. However, one major simplification of our previous model was to assume that each motor-complex could only carry at most one vesicle. In this paper, we extend our model by allowing motor-complexes to carry an arbitrary number of vesicles. We show that the kinetic part of the equations become a modified version of the Becker–Doring (BD) equations for aggregation–fragmentation processes [13–17]. We exploit this connection to analyze the existence of steady-state solutions, and derive

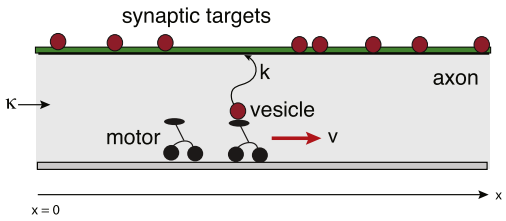

Figure 1. Schematic diagram of the motor transport and irreversible delivery of vesicles to presynaptic targets along an axon (not to scale). Bidirectional transport is modeled in terms of an advection–diffusion equation with mean speed v and diffusivity D. For ease of visualization, we represent each motor-complex by a single motor in this and subsequent figures. However, in order to undergo bidirectional transport, a complex will typically consist of several kinesin and dynein motors.

conditions for the uniform distribution of synaptic resources along an axon. In particular, the rate of exchange of vesicles between motors and targets has to be sufficiently fast.

2. Vesicular transport model

In order to highlight the basic problem we wish to solve, consider a population of motor-complexes moving bidirectionally along a semi-infinite axonal domain, see figure 1. Suppose that there is a uniform, continuous distribution of presynaptic targets along the axon, and that each motor-complex can irreversibly deliver its cargo to a presynaptic target at a uniform rate k. Let $u(x, t)$ denote the density of motor-complexes carrying a vesicle at position x at time t. Neglecting any interactions between distinct complexes, we take $u(x, t)$ to evolve according to the advection–diffusion equation

$$\frac{\partial u}{\partial t} = -v\frac{\partial u}{\partial x} + D\frac{\partial^2 u}{\partial x^2} - ku, \quad x > 0, \tag{2.1}$$

where v is the mean speed of the complex and D is an effective diffusivity. This transport equation can be derived from more detailed biophysical models of bidirectional motor transport under the assumption that the rates at which motor-complexes switch between different motile states are relatively fast [12, 19], see also the appendix. The mean speed will depend on the relative times that the complex spends in different anterograde and retrograde states, whereas the diffusivity D reflects the underlying stochasticity of the motion. Suppose that there is a constant flux of complexes injected at the end $x = 0$, so that equation (2.1) is supplemented by the boundary condition

$$-D\frac{\partial u(0, t)}{\partial x} + vu(0, t) = \kappa. \tag{2.2}$$

Let $c(x, t)$ denote the density of vesicles delivered to the presynaptic targets, with

$$\frac{\partial c}{\partial t} = ku(x, t) - \gamma_c c(x, t). \tag{2.3}$$

Here γ_c is the rate of vesicle degradation within a presynaptic target. (If we were to neglect degradation of vesicles, then it would be necessary to impose by hand a maximum capacity of presynaptic targets, otherwise $c(x, t)$ could become unbounded.) A basic limitation of this model follows from the observation that the steady-state distribution of vesicles decays exponentially with respect to distance from the soma with a correlation length $\overline{\xi}$. That is

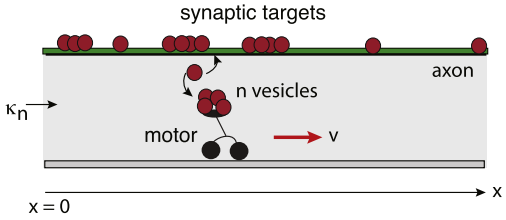

Figure 2. Schematic diagram of reversible vesicular transport model. Each motor-complex can reversibly exchange a vesicle with a synaptic target, and there is clustering of vesicles bound to motors and bound to targets.

$$c(x) = \frac{k}{\gamma_c}\frac{J_1 e^{-x/\overline{\xi}}}{D/\overline{\xi} + v}, \qquad \overline{\xi} = \frac{2D}{-v + \sqrt{v^2 + 4Dk}}. \tag{2.4}$$

Taking the typical values $D = 0.1\ \mu\text{m s}^{-1}$ for cytoplasmic diffusion and $v = 0.1 - 1\ \mu\text{m s}^{-1}$ for motor transport [2], and assuming that $k \ll 1\ \text{s}^{-1}$, we see that $\overline{\xi} \approx (v/k)\mu\text{m}$. Thus, in order to have correlation lengths comparable to axonal lengths of several millimeters, we would require delivery rates of the order $k \sim 10^{-5}\ \text{s}^{-1}$, whereas measured rates tend to be of the order of a few per minute [20, 21]. This simple calculation establishes that injecting motor-complexes from the somatic end of the axon leads to an exponentially decaying distribution of synaptic resources along the axon.

Recently we showed that a more uniform distribution of presynaptic vesicles can be achieved by taking the synaptic delivery of vesicles to be reversible [12], as has been observed experimentally [8, 10], see figure 2. This requires generalizing the above advection–diffusion equation in order to keep track of the number of vesicles the motor-complexes are carrying. In our previous model we restricted each complex to carry at most one vesicle, whereas here we relax this assumption and show how the resulting model is described by a modified version of the BD equations for aggregation–fragmentation [13–17]. Let $u_n(x, t)$, $n = 0, 1$,.., denote the concentration of motor complexes at position x at time t that are carrying n vesicles. It is mathematically convenient to assume that there is no upper bound for the carrying capacity of a motor-complex—this is not a major issue since, as we shall show in section 3, the steady-state solution satisfies $\lim_{n\to\infty} u_n = 0$. Our next assumption is that motor-complexes can only exchange one vesicle at a time with synaptic targets. We thus have the following reaction scheme

$$X + U_n \underset{a_n}{\to} U_{n+1}, \qquad U_n \underset{b_n}{\to} X + U_{n-1}, \qquad n \geqslant 1 \tag{2.5}$$

and

$$X + U_0 \underset{a_0}{\to} U_1. \tag{2.6}$$

Here X denotes a membrane bound vesicle, U_n denotes a motor-complex with n vesicles, b_n is the rate at which a vesicle is transferred from the complex to a synaptic target, and a_n is the rate of the reverse process. Next, we model the one-dimensional bidirectional transport of the population of motor-complexes with n vesicles in terms of an advection–diffusion equation with an effective diffusivity D_n and mean velocity v_n; we are allowing for the possibility that the mean speed and diffusivity of a motor-complex depends on the number of vesicles it is carrying. This is based on the idea that motors carrying more vesicles tend to move more slowly due to the increased load. (In the appendix, we use a quasi-steady-state (QSS) diffusion approximation to derive the advection–diffusion equation from a more detailed

biophysical model of active motor transport.) When this is combined with the exchange of vesicles with synaptic targets, we obtain the following system of equations

$$\frac{\partial u_n}{\partial t} = D_n \frac{\partial^2 u_n}{\partial x^2} - v_n \frac{\partial u_n}{\partial x} + b_{n+1} u_{n+1} + a_{n-1} c\, u_{n-1} - [b_n + a_n c] u_n, \quad n \geqslant 1. \tag{2.7}$$

and

$$\frac{\partial u_0}{\partial t} = D_0 \frac{\partial^2 u_0}{\partial x^2} - v_0 \frac{\partial u_0}{\partial x} + b_1 u_1 - a_0 c u_0. \tag{2.8}$$

For the moment, suppose that there are reflecting boundary conditions at $x = 0, L$:

$$I_n(0, t) = I_n(L, t) = 0, \quad I_n(x, t) \equiv -D_n \frac{\partial u_n}{\partial t} + v_n u_n, \tag{2.9}$$

with $I_n(x, t)$ denoting the flux of complexes carrying n vesicles. Ignoring any degradation of vesicles, we have

$$\frac{\partial c}{\partial t} = \sum_{n \geqslant 0} [b_n u_n(x, t) - a_n c(x, t) u_n(x, t)] \tag{2.10}$$

with $b_0 \equiv 0$. Note that we are keeping track of the discrete number of vesicles attached to a motor-complex, but treating the vesicles incorporated into synaptic targets as a continuous density.

3. Analysis of non-spatial model

In order to gain insights into the behavior of the full model, we first focus on the kinetic part of the equations by assuming we have a well-mixed 1D domain, so that all concentrations are independent of x. This situation could occur if there is initially a uniform distribution of membrane-bound vesicles and motor-complexes, and the axon or dendrites of a neuron are globally activated. The latter could be implemented by bathing the neuron in potassium chloride, for example. Equations (2.7), (2.8) and (2.10) then reduce to the system of ODEs

$$\frac{\mathrm{d}u_n}{\partial t} = J_{n-1} - J_n, \quad n \geqslant 1, \tag{3.1a}$$

$$\frac{\mathrm{d}u_0}{\partial t} = -J_0, \tag{3.1b}$$

$$\frac{\mathrm{d}c}{\mathrm{d}t} = -\sum_{n \geqslant 0} J_n, \tag{3.1c}$$

where we have introduced the vesicle fluxes

$$J_n = a_n c u_n - b_{n+1} u_{n+1}. \tag{3.2}$$

The system of equations (3.1*a*)–(3.1*c*) is a modified version of the BD equations for aggregation–fragmentation processes. The latter equations were originally proposed as a model for nucleation [13], in which clusters form by individual particles (monomers) colliding with each other then grow via subsequent collisions between clusters and monomers. The main simplifying assumption is that interactions between clusters are ignored, which is reasonable when the cluster density is relatively small. If $\widehat{u}_n$, $n \geqslant 2$ denotes the concentration of clusters of size n and $\widehat{u}_1$ denotes the concentration of monomers then the BD equations take the form

$$\frac{\mathrm{d}\widehat{u}_n}{\partial t} = \widehat{J}_{n-1} - \widehat{J}_n, \quad n \geqslant 2, \tag{3.3a}$$

$$\frac{\mathrm{d}\widehat{u}_1}{\partial t} = -\widehat{J}_1 - \sum_{n\geqslant 1}\widehat{J}_n, \tag{3.3b}$$

with

$$\widehat{J}_n = a_n\widehat{u}_1\widehat{u}_n - b_{n+1}\widehat{u}_{n+1}. \tag{3.4}$$

Now a_n and b_n denote the rates of aggregation and partial fragmentation of a cluster of size n. More precisely, equations (3.3*a*) and (3.3*b*) are a slightly modified version of the original BD equations whereby the total mass of the system is conserved [15]—the original model took the monomer concentration $\widehat{u}_1$ to be fixed [13].

In our transport model, membrane bound vesicles play the role of monomers and motor-complexes play the role of clusters, with n now labeling the number of motor-bound vesicles rather than cluster size. Another major difference between our transport model and cluster formation models is that the fastest diffusing element in the latter is a monomer, whereas in our model the 'monomer' is membrane bound and does not diffuse. In recent years the BD equations (3.3*a*) and (3.3*b*) have been applied to a wide range of chemical and biological processes including micelle and vesicle formation [22, 23], viral capsid assembly [24], and robust protein concentration gradient formation [25]. There have also been several mathematical studies of the existence and uniqueness of steady-state solutions and large-time asymptotics [14–17]. In the following we will adapt these analytical results to our model of vesicular transport.

First, adding equations (3.1*a*)–(3.1*c*) shows that the total concentration of motor-complexes $U = \sum_{n\geqslant 0} u_n$ is conserved:

$$\frac{\mathrm{d}U}{\mathrm{d}t} = \sum_{n\geqslant 0}\frac{\mathrm{d}u_n}{\mathrm{d}t} = -J_0 + (J_0 - J_1) + (J_1 - J_2) + \cdots = 0. \tag{3.5}$$

This yields the motor conservation condition

$$M = \sum_{n\geqslant 0} u_n(t). \tag{3.6}$$

Furthermore

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}t}\sum_{n\geqslant 0} nu_n &= \sum_{n\geqslant 1} n\,(J_{n-1} - J_n)\\ &= J_0 - J_1 + 2(J_1 - J_2) + 3(J_2 - J_3) + \cdots\\ &= J_0 + J_1 + J_2 + \cdots\\ &= \sum_{n\geqslant 0} J_n.\end{aligned}$$

Hence the total number of vesicles is conserved:

$$\rho = c(t) + \sum_{n\geqslant 1} nu_n(t). \tag{3.7}$$

One subtlety regarding the above derivation of the conservation equations is that we have assumed that we can reverse the order of infinite summation and differentiation. It turns out that for certain choices of the n-dependent transition rates a_n, b_n, reversibility breaks down, reflecting the fact that a steady-state solution no longer exists [14, 15]. However, we will not consider such possibilities here.

Therefore, we now look for steady-state solutions $J_n(t) = J$ for all $n \geqslant 0$. In the absence of vesicle degradation, the only physical solution is the equilibrium solution $J = 0$, since $\mathrm{d}c/\mathrm{d}t \to \infty$ otherwise. Hence

$$b_{n+1}u_{n+1} = a_n c u_n,$$

which on rearranging and iterating gives

$$u_n = Q_n c^n u_0, \quad Q_n = \frac{a_{n-1}a_{n-2}\ldots a_0}{b_n b_{n-1}\ldots b_1}. \tag{3.8}$$

The conservation equations (3.6) and (3.7) then yield the results

$$M = u_0\left(1 + \sum_{n\geqslant 1} Q_n c^n\right) \equiv u_0(1 + F_0(c)), \tag{3.9}$$

and

$$\rho = c + \left(\sum_{n\geqslant 1} n Q_n c^n\right) u_0 = c + \frac{F_1(c)}{1 + F_0(c)} M, \tag{3.10}$$

where

$$F_0(c) = \sum_{n\geqslant 1} Q_n c^n, \quad F_1(c) \equiv c F_0'(c) = \sum_{n\geqslant 1} n Q_n c^n. \tag{3.11}$$

We will assume that for a given choice of a_n and b_n the infinite series defining $F_1(c)$ has a finite radius of convergence $c = z$—the corresponding series expansion of $F_0(z)$ also then converges. There will then exist a steady-state solution provided that equation (3.10) has a solution for which $c \leqslant z$.

The approach to equilibrium can be established by constructing an appropriate Liapunov function. Adapting the analysis of Penrose [15], consider the function

$$\widehat{L} = \sum_{n=0}^{\infty} u_n[\log(u_n/Q_n c^n) - 1], \tag{3.12}$$

with $Q_0 = 1$. One finds that

$$\frac{\mathrm{d}\widehat{L}}{\mathrm{d}t} = \sum_{n\geqslant 0} \frac{\mathrm{d}u_n}{\mathrm{d}t} \log(u_n/Q_n c^n) - \sum_{n\geqslant 1} \frac{n u_n}{c} \frac{\mathrm{d}c}{\mathrm{d}t}. \tag{3.13}$$

Now we have

$$\begin{aligned}
\text{first term on rhs} &= -J_0 \log u_0 + \sum_{n\geqslant 1} (J_{n-1} - J_n)\log(u_n/Q_n c^n) \\
&= -J_0 \log u_0 + J_0 \log(u_1/Q_1 c) + J_1 \log(u_2/Q_2 c) - J_1 \log(u_1/Q_1 c) + \cdots \\
&= -J_0 \log u_0 + J_0 \log(u_1 b_1/a_0 c) + J_1 \log(u_2 Q_1/u_1 Q_2 c) + \cdots \\
&= J_0 \log(u_1 b_1/a_0 c u_0) + J_1 \log(u_2 b_2/u_1 a_1 c) + \cdots \\
&= J_0 \log(u_1 b_1/a_0 c u_0) + \sum_{n\geqslant 1} (a_n c u_n - b_{n+1} u_{n+1}) \\
&\quad \times \log(b_{n+1} u_{n+1}/a_n c u_n) \leqslant 0,
\end{aligned}$$

and

$$\text{second term on rhs} = -\sum_{n\geqslant 1}\frac{nu_n}{c}\frac{\mathrm{d}c}{\mathrm{d}t} = -\frac{\rho - c}{c}\frac{\mathrm{d}c}{\mathrm{d}t},$$
$$= -\frac{\mathrm{d}}{\mathrm{d}t}[\rho \log c - c].$$

The above suggests considering the modified Liapunov function

$$L = \widehat{L} + \rho \log c - c$$
$$= \sum_{n=0}^{\infty} u_n[\log(u_n/Q_n c^n) - 1] + \rho \log c - c, \tag{3.14}$$
$$= \sum_{n=0}^{\infty} u_n[\log(u_n/Q_n) - 1] - (\log c)\sum_{n=0}^{\infty} nu_n + \rho \log c - c, \tag{3.15}$$
$$= \sum_{n=0}^{\infty} u_n[\log(u_n/Q_n) - 1] + c \log c - c, \tag{3.16}$$
$$\equiv L_0 + c \log c - c. \tag{3.17}$$

It immediately follows that

$$\frac{\mathrm{d}L}{\mathrm{d}t} = \sum_{n\geqslant 0}(a_n c u_n - b_{n+1}u_{n+1})\log(b_{n+1}u_{n+1}/a_n c u_n) \leqslant 0. \tag{3.18}$$

Again, following along analogous lines to [15], we can also establish that L_0 is bounded below, and, hence that L is bounded below. First note that each term

$$f(u_n) \equiv u_n[\log(u_n/Q_n) - 1]$$

is a convex function of u_n so that at an arbitrary value u_n^*,

$$f(u_n) - f(u_n^*) \geqslant f'(u_n^*)[u_n - u_n^*],$$

which implies that

$$L_0 \geqslant \sum_{n\geqslant 0}(u_n^*[\log(u_n^*/Q_n) - 1] + (u_n - u_n^*)\log(u_n^*/Q_n)).$$

Let us choose $u_n^* = Q_n z^n$ so that

$$L_0 \geqslant \sum_{n\geqslant 0}(nu_n \log z - Q_n z^n)$$
$$= (\rho - c)\log z - \sum_{n\geqslant 0} Q_n z^n$$
$$= (\rho - c)\log z - F_0(z) > -\infty.$$

We have now established that L must approach a limit as $t \to \infty$ such that $\mathrm{d}L/\mathrm{d}t \to 0$. Since every term on the right-hand side of equation (3.18) is non-positive, it follows that the individual terms approach zero:

$$J_n \equiv a_n c u_n - b_{n+1}u_{n+1} \to 0 \quad \text{as } t \to \infty, \quad n \geqslant 0.$$

Therefore

$$u_n - Q_n c^n u_0 \to 0 \quad \text{as } t \to \infty, \quad n \geqslant 1. \tag{3.19}$$

However, we still need to determine how u_0 and c behave as $t \to \infty$. From the conservation equations, we have

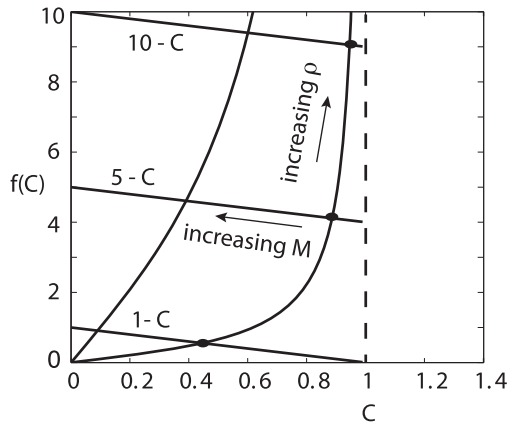

Figure 3. Graphical construction of rescaled steady-state density $C = ac/b$. For given M, ρ, C is determined by the intercept of the straight line $a\rho/b - C$ with the function $f(C) = (aM/b)C/(1 - C^2)$.

$$\lim_{t\to\infty} \sum_{n\geqslant 0} u_n(t) = M, \tag{3.20}$$

and

$$\lim_{t\to\infty} \sum_{n\geqslant 1} n u_n(t) + \lim_{t\to\infty} c(t) = \rho. \tag{3.21}$$

On the other hand, equation (3.19) tells us that

$$\sum_{n\geqslant 0} \lim_{t\to\infty} u_n(t) = \lim_{t\to\infty} u_0(t) + \sum_{n\geqslant 1} Q_n[\lim_{t\to\infty} u_0(t)c(t)^n], \tag{3.22}$$

and

$$\sum_{n\geqslant 1} \lim_{t\to\infty} n u_n(t) = \sum_{n\geqslant 1} n Q_n[\lim_{t\to\infty} u_0(t)c(t)^n]. \tag{3.23}$$

If we can interchange the two limit operations $t \to \infty$ and $n \to \infty$, then we obtain the asymptotic results

$$\lim_{t\to\infty} c(t) = c, \quad \lim_{t\to\infty} u_0(t) = u_0, \tag{3.24}$$

with u_0, c satisfying equations (3.9) and (3.10).

As a simple example, suppose that $a_n = a$, $b_n = b$ for all n, that is, the exchange rates of vesicles between motor-complexes and synaptic targets are independent of the cluster size n. Then $Q_n = (a/b)^n$ and

$$F_0(c) = \frac{ac/b}{1 - ac/b}, \quad F_1(c) = \frac{ac/b}{(1 - ac/b)^2} \tag{3.25}$$

provided that $ac/b < 1$. That is, $F_1(c)$ has the radius of convergence $c = (b/a)^-$, which means that there is an upper bound to the steady-state membrane-bound vesicle concentration. Moreover, for all finite M (total density of motor-complexes) and ρ (total density of motor-bound vesicles) the steady-state concentration c is given by the unique solution to equation (3.10), which becomes

$$\rho = c + \frac{ac/b}{1-(ac/b)^2}M.$$

Existence of a unique solution can be demonstrated graphically, as illustrated in figure 3. Note that for fixed M, we have $\rho \to \infty$ as $c \to b/a$. On the other hand, increasing M for fixed ρ decreases the steady-state concentration.

4. Effects of advection–diffusion

There has been relatively little rigorous work on aggregation–fragmentation models with diffusion. Most studies have considered convergence to partially uniform steady-state solutions, see for example [26–30]. Here we will proceed formally by summing the full equations over n, under the assumption that we can reverse the operations of differentiation and infinite summation. Therefore, let us return to the full model equations given by (2.7) and (2.8). For simplicity, we assume that $D_n = D$ and $v_n = v$ and take $b_n = b$, $a_n = a$ for all $n \geqslant 0$:

$$\frac{\partial u_n}{\partial t} = D\frac{\partial^2 u_n}{\partial x^2} - v\frac{\partial u_n}{\partial x} + bu_{n+1} + ac\, u_{n-1} - [b+ac]u_n - \gamma u_n, \quad n \geqslant 1 \tag{4.1}$$

and

$$\frac{\partial u_0}{\partial t} = D\frac{\partial^2 u_0}{\partial x^2} - v\frac{\partial u_0}{\partial x} + bu_1 - acu_0 - \gamma u_0. \tag{4.2}$$

We have also included degradation terms, which takes into account the fact that motors can be removed from active transport and recycled to the soma. We impose reflecting boundary conditions at $x = L$ and constant flux conditions at $x = 0$,

$$J(u_n(0,t)) = \kappa_n, \quad J(u_n(L,t)) = 0, \quad n \geqslant 0,$$

where $J(u) = -D\partial_x u + vu$. It is important to emphasize that the injected motor-complexes are not necessarily newly synthesized from the cell body. For it has been found experimentally that motor-complexes recycle between the distal and somatic ends of the soma [8, 10]. In the case of a finite axon, we could model recycling by imposing an absorbing boundary condition at the distal end and reinjecting the distal flux into the somatic end. If the axon is much longer than the range of vesicular delivery necessary to supply synapses, then the effects of the absorbing boundary can be ignored and we can treat the axon as semi-infinite.

The concentration of vesicles in presynaptic targets evolves as

$$\begin{aligned}\frac{\partial c}{\partial t} &= \sum_{n\geqslant 0}[bu_n(x,t)[1-\delta_{n,0}] - ac(x,t)u_n(x,t)] \\ &= bu(x,t) - aU(x,t)c(x,t),\end{aligned} \tag{4.3}$$

where

$$u(x,t) = \sum_{n\geqslant 1} u_n(x,t), \quad U(x,t) = \sum_{n\geqslant 0} u_n(x,t) = u(x,t) + u_0(x,t). \tag{4.4}$$

Following the analysis of section 3, we assume that we can reverse the operations of differentiation and infinite summation for n-independent exchange rates. Summing both sides of equations (4.1) with respect to n and adding equation (4.2) then yields the following equation for $U(x,t)$:

$$\frac{\partial U}{\partial t} = D\frac{\partial^2 U}{\partial x^2} - v\frac{\partial U}{\partial x} - \gamma U, \quad U = u + u_0 \tag{4.5}$$

with $J(U(0,t)) = \kappa \equiv \sum_n \kappa_n$ and $J(U(L,t)) = 0$. Similarly, multiplying both sides of equation (4.1) by n and then summing over n, $n \geqslant 1$ gives

$$\frac{\partial \bar{n}}{\partial t} = D\frac{\partial^2 \bar{n}}{\partial x^2} - v\frac{\partial \bar{n}}{\partial x} - \gamma \bar{n} - bu(x,t) + aU(x,t)c(x,t), \tag{4.6}$$

where

$$\bar{n}(x,t) = \sum_{n \geqslant 1} n u_n(x,t), \tag{4.7}$$

and $J(\bar{n}(0,t)) = \sum_n n\kappa_n$, $J(\bar{n}(L,t)) = 0$.

Note from equations (4.3), (4.5) and (4.6) that we recover the spatially uniform conservation conditions (3.6) and (3.7) when $\gamma = 0$ and $\kappa = 0$. Unfortunately, the system of equations (4.3), (4.5) and (4.6) for $U(x,t)$, $c(x,t)$, $\bar{n}(x,t)$ is not closed, since one needs to determine $u_0(x,t)$ (in order to obtain $u(x,t) = U(x,t) - u_0(x,t)$), which means that we have to solve the full hierarchy of equations (4.1) and (4.2). In the case of spatially uniform steady-state solutions with $\gamma = \kappa_n = 0$ for all n, we can proceed iteratively, as shown in section 3. It turns out that for a special choice of the boundary fluxes κ_n, we can also construct a non-spatially uniform steady-state solution of equations (4.1) and (4.2) that supports a uniform distribution of membrane-bound vesicles. First, setting $c(x,t) = c_0$ in equation (4.3) yields the steady-state condition

$$u(x) = \frac{c_0 a}{b} U(x), \tag{4.8}$$

where $U(x)$ is the steady-state solution of equation (4.5):

$$D\frac{\partial^2 U}{\partial x^2} - v\frac{\partial U}{\partial x} - \gamma U = 0, \tag{4.9}$$

with $J(U(0)) = \kappa$ and $J(U(L)) = 0$. This is identical to the steady-state version of equation (2.1) with the delivery rate k replaced by the degradation rate γ. Hence, $U(x)$ decays exponentially with respect to distance from the soma with a modified correlation length ξ (assuming a semi-infinite cable):

$$U(x) = \frac{\kappa e^{-x/\xi}}{D/\xi + v}, \quad \xi = \frac{2D}{-v + \sqrt{v^2 + 4D\gamma}}. \tag{4.10}$$

Since the rate of exchange of vesicles between motors and targets is typically much faster than the degradation or removal rate of motors from the axon ($\gamma \ll k$), it follows that the new model greatly increases the correlation length of the motor-complex concentration. Moreover, as we now demonstrate, for a particular choice of boundary fluxes κ_n, an exponentially decaying concentration of motor-complexes can support a spatially uniform concentration of membrane-bound vesicles. First, it immediately follows from equation (4.8) that

$$u_0(x) = \left(1 - \frac{c_0 a}{b}\right) U(x).$$

Substituting this solution into equation (4.2) and using equation (4.9) shows that

$$u_1(x) = \frac{c_0 a}{b}\left(1 - \frac{c_0 a}{b}\right) U(x).$$

Similarly substituting for $u_1(x)$ into equation (4.1) for $n = 1$ and iterating shows that

$$u_n(x) = \left(\frac{c_0 a}{b}\right)^n \left(1 - \frac{c_0 a}{b}\right) U(x). \tag{4.11}$$

It remains to impose the boundary conditions on the fluxes at the ends $x = 0, L$. Self-consistency yields the following condition on κ_n:

$$\kappa_n = \left(\frac{c_0 a}{b}\right)^n \left(1 - \frac{c_0 a}{b}\right) \kappa, \quad n \geqslant 0. \tag{4.12}$$

This has the unique solution

$$\kappa_n = \left(\frac{c_0 a}{b}\right)^n, \quad n \geqslant 0, \quad \kappa = \sum_{n \geqslant 0} \kappa_n = \left(1 - \frac{c_0 a}{b}\right)^{-1} \tag{4.13}$$

provided that $c_0 < b/a$. In conclusion, in the special case that the constant flux of motor-complexes carrying n vesicles is of the form $\kappa_n = \Gamma^n$, $0 < \Gamma < 1$, the steady-state concentration of membrane-bound vesicles is spatially uniform with $c_0 = b\Gamma/a$.

Of course, the specific form of the fluxes κ_n assumed in the above construction is non-generic. Nevertheless, it is a 'proof of principle' that incorporating reversible interactions between motors and targets, which has been observed experimentally, provides a possible mechanism for a more democratic distribution of synaptic resources along the axon or dendrite of a neuron. It is consistent with the more analytically tractable case considered in our previous work [12], where we restricted each motor-complex to carry at most one vesicle.

5. Discussion

In this paper, we introduced a new application of aggregation–fragmentation models of the BD form, namely, to molecular motor-driven vesicular transport in axons and dendrites of neurons. This type of model naturally arises when the delivery of vesicles to synaptic targets is reversible, which has been observed in a number of experiments. That is, one has to keep track of the cluster size of vesicles bound to each motor-complex. By adapting methods for analyzing the BD equations, we determined steady-state solutions of our transport model and found an explicit solution for which there is a uniform distribution of synaptic resources along an axon. Note, however, that there are some significant differences between our model and the standard BD model. In the latter model monomers are simply identified as clusters of size $n = 1$, whereas in our model monomers correspond to membrane-bound vesicles that are distinct from n-clusters of motor-bound vesicles. It also follows that there can exist a cluster of size zero (motor-complex with no cargo). There are number of possible extensions of our model, which we hope to explore in future work:

(1) One simplification of our model concerns the kinetic interactions between motors and targets; we used simple first-order kinetics, neglected the range of interactions, and assumed that only single vesicles are exchanged. Unfortunately, there is very little known experimentally regarding the interactions between motors and targets, other than the identity of important molecular players such as ARL-8 [9]. Therefore, we will investigate a variety of possible models regarding the association and dissociation of vesicles at synaptic targets. A related issue concerns the simplifying assumption that the capacity of each motor-complex is unbounded so that it can carry an arbitrary number of vesicles n. In the case of n-independent exchange rates, $a_n = a$, $b_n = b$, this was not a severe approximation, since the stationary motor-complex densities in the non-spatial model

rapidly decrease with n, that is, $u_n \sim (ac/b)^n$ with $ac/b < 1$. However, this result could break down when more complicated forms of motor-target kinetics are considered, in which case we would need to impose an explicit upper bound on motor capacity. Yet another extension would be to take D_n and v_n to be n-dependent in the full model equation (4.1), rather than $D_n = D$ and $v_n = v$ for all n.

(2) Another simplification of our model is that it ignores the discrete and inhomogeneous nature of the distribution of synaptic targets—we simply treated the target concentration c as continuous and assumed vertical interactions between motors and targets. One method for handling the discrete nature of synaptic targets is homogenization theory, which we have previously used to analyze the diffusive transport of signaling molecules along spiny dendrites [31]. It should be possible to extend this approach to the more complex advection–diffusion model. There is also heterogeneity at a longer spatial scale, since certain regions of an axon do not have any synaptic targets. Following [10], this can be handled by partitioning the axon into compartments.

(3) The advection–diffusion model given by equations (4.1) and (4.2) is deterministic. There are two levels of stochasticity that could be introduced. First, rather than approximating bidirectional motor transport in terms of advection–diffusion equations, we could consider a more detailed biophysical model that keeps track of different motile states and the switching between them. This was illustrated in the appendix using a simple three-state model of bidirectional motion. A second source of stochasticity would arise when the number of motors is sufficiently small, resulting in demographic noise. One would then have to develop a master equation description that tracks transitions between different motile states and sizes of aggregates.

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Appendix

In this appendix, we consider a more biophysically detailed model of motor transport, in which a motor-cargo complex executes bidirectional transport by switching between different motile states. Using a QSS diffusion approximation, we will show will how the transport model can be reduced to a system of advection–diffusion equations of the form (2.7). For the sake of illustration, consider a simple three-state transport model of a single motor-complex moving on a semi-infinite 1D track as shown in figure A1 . (Although we represent the complex in terms of a single motor, in practice bidirectional transport is mediated by several molecular motors attached to the same cargo.) The motor complex is taken to be in one of three motile states labeled by $j = 0, \pm$: stationary or slowly diffusing ($j = 0$), moving to the right (anterograde) with speed v_+ ($j = +$), or moving to the left (retrograde) with speed $-v_-$ ($j = -$); transitions between the three states are governed by a discrete Markov process. In addition, the motor complex can carry a variable number of vesicles n, which can be reversibly exchanged with membrane-bound synaptic targets when in the state $j = 0$. Let $p_{nj}(x, t)$ denote the probability density that at time t the complex is at position x, $x \in (0, \infty)$, is in motile state j, and is carrying n vesicles. The evolution of the probability density is described by the following system of partial differential equations:

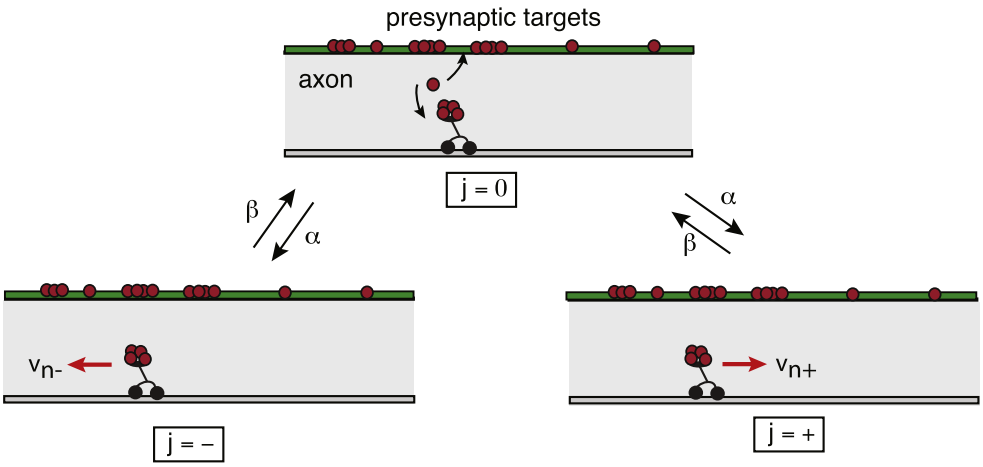

Figure A1. Three-state model of the bidirectional transport of a motor-cargo complex. The particle switches between an anterograde state ($j = +$) of speed v_+, a stationary or slowly diffusing state ($j = 0$), and a retrograde state ($j = -$) of speed v_-. The motor-complex can only exchange vesicles with presynaptic targets when in the state $j = 0$.

$$\frac{\partial p_{n\pm}}{\partial t} = \mp v_{n\pm}\frac{\partial p_{n\pm}}{\partial x} - \beta p_{n\pm} + \alpha p_{n0}$$

$$\frac{\partial p_{n0}}{\partial t} = D_{n0}\frac{\partial^2 p_{n0}}{\partial x^2} + \beta p_{n+} + \beta p_{n-} - 2\alpha p_{n0}, \tag{5.1a}$$

$$+ b_{n+1}p_{n+1,0} + a_{n-1}cp_{n-1,0} - [b_n + a_n c]p_{n0}. \tag{5.1b}$$

For concreteness, we take the end $x = 0$ to be reflecting so that $v_{n+}p_{n+}(0, t) = v_{n-}p_{n-}(0, t)$. Here α, β are the transition rates between the slowly diffusing and ballistic states, and D_{n0} is the diffusivity in the state $j = 0$. As in the model of section 2, we are assuming that there is a continuous distribution c of presynaptic targets along the axon, which can exchange vesicles with the motor-complex at the rates a_n, b_n. (Note that $a_{-1} = b_0 = 0$.)

For intracellular transport, one finds that the transition rates α, β are fast compared to the exchange rates a_n, b_n, and the effective displacement rate $v_{n\pm}/l$, where l is a fundamental microscopic length-scale such as the size of a synaptic target ($l \sim 1\ \mu$m). One can then use a QSS diffusion approximation to derive an advection–diffusion equation for the total probability density

$$p_n(x, t) = \sum_{j=0,\pm} p_{nj}(x, t). \tag{5.2}$$

This involves a relatively straightforward extension of our previous analysis of a three-state molecular motor model with irreversible target delivery [12, 18, 19]. That is

$$\frac{\partial p_n}{\partial t} = -v_n\frac{\partial p_n}{\partial x} + D_n\frac{\partial^2 p_n}{\partial x^2} + b_{n+1}p_{n+1} + a_{n-1}cp_{n-1} - [b_n + a_n c]p_n \tag{5.3}$$

with mean velocity $v_n = (v_{n+} - v_{n-})\rho_+$, effective diffusivity D_n given by

$$D_n = D_{n0}\rho_0 + \frac{\alpha}{\beta(2\alpha + \beta)}((v_{n+} - v_n)^2 + (v_{n-} + v_n)^2),$$

and the rescaled exchange rates a_n, $b_n \to \rho_0 a_n$, $\rho_0 b_n$. Here

$$\rho_0 = \frac{\beta}{2\alpha + \beta}, \quad \rho_\pm = \frac{\alpha}{2\alpha + \beta} \tag{5.4}$$

are the stationary probabilities of the three-state Markov process describing transitions between the motile states $j = 0$ and $j = \pm$, respectively. The basic idea of the QSS reduction is to fix units so that $v_{n\pm}$, a_n, $b_n = O(1)$ and α, $\beta = O(1/\epsilon)$ with $0 < \epsilon \ll 1$. In this regime, there are typically a large number of transitions between different motor-complex states j while the position x and number of vesicles n do not change. Therefore, we expect the three-state Markov process to rapidly converge to the steady-state ρ_n, which is then perturbed as x, n slowly evolve. This motivates decomposing the probability densities as $p_{nj}(x, t) = p_n(x, t)\rho_j + \epsilon w_{nj}(x, t)$ with $\sum_j w_{nj}(x, t) = 0$. Substituting such a solution into equations (5.1*a*) and (5.1*b*), and performing an asymptotic expansion in w_{nj} then yields equation (5.3) to leading order in ϵ. In particular, $D_n - D_{n0}\rho_0 = O(\epsilon)$.

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