A THEORETICAL APPROACH TO THE ANALYSIS OF AXONAL TRANSPORT

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ABSTRACT A theoretical model of intra-axonal transport is proposed that presupposes a carrier system moving down the axon in a distal direction. Protein and particle transport is achieved by their reversible association with the distally moving carriers. Mathematical equations representing the concentrations of moving carriers and proteins and/or particles within the axon at any position and time are proposed. Analysis of the equations demonstrates that a traveling wave solution for the particle concentration (an experimental fact) is possible provided the chemical interaction between particles and carriers exhibits positive cooperativity. The phase velocity of the wave solution is interpreted as the observed velocity of the intra-axonal transport, known to be independent of position of observation. In addition, the theory predicts a spectrum of transport velocities for different proteins, in agreement with observations. The velocity of a given protein is dependent on its affinity to the carrier.

INTRODUCTION

It is generally agreed that anterograde axonal transport (from cell soma to the synaptic termini) occurs via two processes, referred to for convenience as the slow and fast transport systems (Barondes, 1969; Grafstein, 1969; Lasek, 1970). Slow transport (~1–10 mm/d) occurs at about the same rate as axon regeneration and is thought to represent a bulk transport of axoplasm (Barondes and Samson, 1967), although Ochs (1974*a*, *b*) has challenged this view. Fast transport generally occurs at 10–1,500 mm/d, and, in general, transports particles, e.g., vesicles and mitochondria, although soluble proteins are also transported (Edstrom and Mattson, 1972; Ochs, 1972*a*). An excellent review of the subject of axonal transport is to be found in Grafstein (1977). Some significant properties of the fast transport system are as follows: (*a*) In cat neurons there is no decrement of rate with distance, as illustrated in Fig. 1, and no late-appearing crests of activity which might imply the presence of multiple fast transport systems (Ochs, 1972*b*). (*b*) The rate of transport appears to be independent of fiber diameter, but varies from species to species, ranging from 250 to 400 mm/d in warm-blooded animals (Lasek, 1970; Ochs, 1972*b*). (*c*) Direct evidence that motion is driven by a local motor, uniformly distributed along the length of the axon, comes from experiments showing that transport occurs within a doubly ligatured segment and requires local energy consumption (Banks and Mayor, 1972). (*d*) Recent studies (Willard et al., 1974; Willard and Hulabak, 1977) demonstrate that labeled proteins, comprising more than 40

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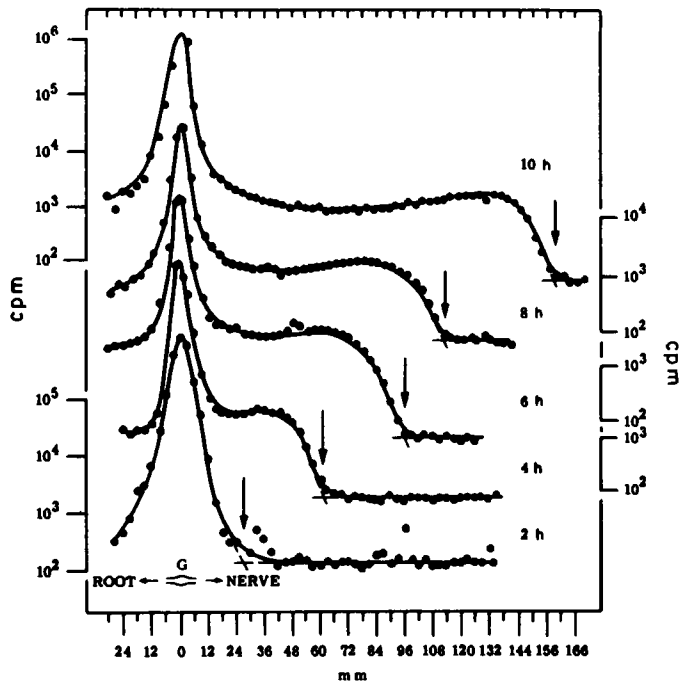

FIGURE 1 The radioactivity in counts per minute is shown as a function of distance in millimeters at various observation times, after injection of [^{3}H]leucine into the L7 ganglia (origin of the abscissa) of the sciatic nerves of five cats. The curves illustrate the traveling wave nature with fixed velocity of the transported radioactive material. The ordinate scale at lower left is for the nerve observed 2 h after injection of the tritiated leucine, whereas the ordinate scales for the observations at 4, 6, 8, and 10 h are shown at the lower right, middle right, upper right, and upper left, respectively. From Ochs (1972*b*), with permission of the publishers of *Science (Wash. D.C.)*.

polypeptides, are transported along axons of the rabbit visual system in at least five groups, with velocities >200, 34–68, 4–8, 2–4, and 0.7–1.1 mm/d. The two fastest groups clearly fall within the range of definition of the fast transport system.

Although the detailed mechanism(s) of axonal transport are unknown, three proposals seem to dominate present thinking. First, the particles attach to a stationary cytoskeletal framework, and, when attached, slide along the stationary filaments (Schmitt, 1968). Second, the particles attach to a moving system of filaments, and are carried along at the speed of the filaments (Ochs, 1974*a, b*). A third possibility which has recently been suggested is that the particles are propelled through the cytoskeletal meshwork by a process akin to an unzipping-zipping process (Melenchuk, 1979). In this paper we examine the consequences of the second proposal from a quantitative viewpoint, and ask whether such a mechanism is, in fact, consistent with the above-listed properties of the fast axonal transport system.

Odell (1977) has presented a theoretical analysis of fast axon transport based on the idea that the neurotubules comprise an anisotropic medium which, by moving back and forth, causes the fluid to move in a coherent bidirectional manner that could carry particulate and soluble materials with it. Odell's continuum model requires that the dimensionless wave

number which characterizes the hypothetical traveling wave of microtubular motility be very close to a particular numerical value if the system is to operate without developing potentially catastrophic pressure gradients. Even if this is so, the fast transport rate is computed to be ~56,000 cm/d, about three orders of magnitude faster than the observed fast transport rates.

The theoretcal model which we examine in this paper presupposes a set of carriers, for example filaments or microtubules that are sliding relative to one another, moving in a distal direction parallel to the axonal axis. We further suppose that particles and/or proteins to be carried interact chemically with the carriers to form a complex. The particles are permitted to diffuse, but not so the carriers. We ask whether the equation system (which we develop below) can support a traveling wave solution moving with constant velocity down the axon. It will be shown that the answer to this question is yes, provided that there are many binding sites for the particle and/or protein on each carrier, and that the interaction between them is positively cooperative.

FORMULATION

We assume that the axon of a neuron is a long tube containing a fluid medium, the axoplasm, with x representing position along the axis of the tube, and t the time. For definiteness, the soma of the neuron is located at $x = -\infty$, and the synaptic terminals at $x = +\infty$ (Fig. 2). According to the proposal of Ochs (1974*a*, *b*), the particles can attach to a moving system of carriers. Here we do not wish to prejudge the identity of the carrier, which may be a filament, microtubule, vesicle, or something yet unknown. Let the concentrations of moving carriers and particles (or proteins) in the axoplasm be denoted by $m(x, t)$ and $p(x, t)$, respectively. In addition, m and p may interact at a rate $r(x, t)$ to form a complex whose concentration is denoted by $c(x, t)$.

The particles or protein molecules can diffuse, but because of the massiveness of the carriers or because they are constrained to a cytoskeletal "track," diffusion of either the bare or the complexed carriers is neglected. (This assumption simplifies the mathematical analysis.) Carriers are presumed to move in the positive x direction with a mean velocity v. Thus the fundamental equations satisfied by $p(x, t)$ and $c(x, t)$ are:

$$\frac{\partial p}{\partial t} = D\frac{\partial^2 p}{\partial x^2} - r, \tag{1}$$

$$\frac{\partial c}{\partial t} = -v\frac{\partial c}{\partial x} + r, \tag{2}$$

where D is the diffusion constant of the particles in the axoplasm. The concentration $m(x, t)$ is determined from $c(x, t)$ by the conservation equation

$$m + c = m_o, \tag{3}$$

where m_o represents the constant total concentration of carriers in the axon, whether bare or in complexed form. To account for the presumed steady flux of carriers in the positive x direction, a source of carriers must exist in the soma and a sink in the synaptic terminals.

Alternatively, one could say that carriers arrive at the synaptic end, discharge their protein molecule or particle "passengers" and return to the soma to resume their role as protein

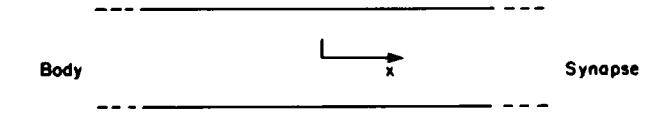

FIGURE 2 Representation of an axon of a neuron as an infinitely long one-dimensional tube. The body of the neuron is located at $x = -\infty$, whereas the synaptic terminal of the axon is located at $x = +\infty$.

carriers. During this return trip, they are presumably in a different state, incapable of acting as carriers for the anterograde system, but by a mechanism identical to that to be analyzed below, the returning carriers could account for retrograde transport (Ochs, 1974*a*, *b*). The returning carriers, however, play no role in the present theory, which does not concern itself with this aspect of carrier dynamics, nor with what is occurring at the body end or synaptic end of the axon.

Because we wish to allow for cooperativity in the reaction of protein with the carriers, we shall assume that there are n binding sites for the protein molecule or particle on each carrier with $n > 1$, and that n protein molecules act in all-or-none fashion to bind reversibly with a carrier molecule. Thus, the reaction rate r is represented as

$$r = k_+{}^n p_m^n - k_-{}^n c, \tag{4}$$

where k_+ and k_- represent in some sense forward and back reaction rate constants for a single particle. Here again, in the interests of mathematical simplicity, we have adopted the simplest reaction law known to exhibit the property of cooperativity. Because of Eqs. 3 and 4, our fundamental Eqs. 1 and 2 take the form:

$$\frac{\partial p}{\partial t} = D\frac{\partial^2 p}{\partial x^2} - nk_+{}^n p^n(m_o - c) + nk_-{}^n c, \tag{5}$$

$$\frac{\partial c}{\partial t} = -v\frac{\partial c}{\partial x} + k_+{}^n p^n(m_o - c) - k_-{}^n c. \tag{6}$$

The above two reaction-diffusion equations constitute a nonlinear parabolic system. We shall not solve these equations at this time because we are only interested in the question as to whether the model system can sustain a traveling wave solution. The existence of such a solution is required by the observed existence of the fast transport system in axons. In other words, we want the solution $p(x, t)$ to exhibit, for a given time t, the same functional dependence on position that it had at time zero, but translated in the positive x direction by an amount proportional to t (Fig. 3).

Thus we look for solutions $p(x, t)$ and $c(x, t)$ of Eqs. 5 and 6 of the form

$$p(x, t) = p(z),\ c(x, t) = c(z),\ z = x - at, \tag{7}$$

where a is a constant called the wave velocity. Then Eqs. 5 and 6 become

$$-ap' = Dp'' - nk_-{}^n p^n(m_o - c) + nk_-{}^n c, \tag{8}$$

$$(v - a)c' = k_+{}^n p^n(m_o - c) - k_-{}^n c, \tag{9}$$

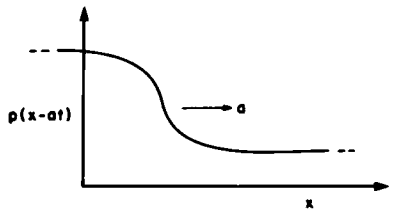

FIGURE 3

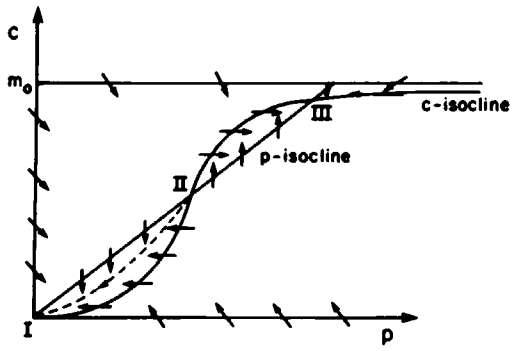

FIGURE 4

FIGURE 3 Schematic illustration of the desired traveling waveform of the protein concentration as a function of distance at a given fixed time. The waveform moves in the positive x direction with velocity a and without change in shape.

FIGURE 4 Schematic phase plane diagram of the system of Eqs. 9 and 11, for the case $n = 2$. The critical points of Eqs. 15–17 are labeled I, II, and III, respectively. The isoclines are the curves on which the derivative, either c' or p', is constant. The dashed curve or trajectory leading from critical point II to critical point I represents the desired traveling wave solution of Eqs. 5 and 6. The arrowhead in the curve indicates how the trajectory is traversed as z (and therefore x) goes from $-\infty$ to $+\infty$.

where the prime (′) denotes differentiation with respect to argument. By adding n times Eq. 9 to Eq. 8, it follows that

$$Dp'' = -ap' + n(v - a)c'. \tag{10}$$

This equation holds true regardless of the assumed form of r. Eq. 10 can be integrated once to yield the relation

$$Dp' = -ap + n(v - a)c. \tag{11}$$

In obtaining Eq. 11, we have set the constant of integration equal to zero because of the conditon $p(+\infty) = c(+\infty) = 0$ (Fig. 3).

Eqs. 9 and 11 are nonlinear ordinary differential equations that we can analyze by phase-plane methods (see, for example, Stoker, 1950). Thus the c-isocline locus and the p-isocline locus of the equation system, at which $c' = 0$ and $p' = 0$, respectively, are given from Eqs. 9 and 11 as

$$c = \frac{K^n p^n}{1 + K^n p^n} m_o, \tag{12}$$

$$p = n\left(\frac{v}{a} - 1\right)c, \tag{13}$$

where $K \equiv k_+/k_-$ is the equilibrium association constant of the reaction. Note that Eq. 12 is the familiar Hill equilibrium law for the reaction of an n-mer with a ligand (Hill, 1910). Because p and c must always be positive, it follows from Eq. 13 that

$$a < v. \tag{14}$$

Hence, the wave velocity of protein transport is always less than the bare carrier velocity.

On the p-isocline locus, the tangents to the trajectories in the phase plane are locally vertical, because $p' = 0$ there, while on the c-isocline locus, the tangents to the trajectories in the phase plane are locally horizontal, because $c' = 0$ there (Fig. 4). The intersections of the two isoclines, Eqs. 12 and 13, determine the critical points, labeled I, II, and III in Fig. 4. For the simple case $n = 2$, they can be determined explicitly, and are given as

$$(c, p) = (0, 0), \quad \text{I}, \tag{15}$$

$$(c, p) = (m_o - \sqrt{m_o^2 - b^2})\left(\frac{1}{2}, \frac{v}{a} - 1\right), \quad \text{II}, \tag{16}$$

$$(c, p) = (m_o + \sqrt{m_o^2 - b^2})\left(\frac{1}{2}, \frac{v}{a} - 1\right), \quad \text{III}, \tag{17}$$

where

$$b = \left[K\left(\frac{v}{a} - 1\right)\right]^{-1} \tag{18}$$

These critical points represent the equilibrium states of the system. Critical point I corresponds to the state of affairs that we wish our traveling wave solution to represent at $x = +\infty$, and critical point II corresponds to the required solution at $x = -\infty$. Physical reality of critical points II and III requires that $m_o \geq b = 1/K(v/a - 1)$, or, rearranging,

$$0 < a \leq v\frac{Km_o}{1 + Km_o}. \tag{19}$$

We shall assume this condition is satisfied, because otherwise a traveling wave solution is certainly not possible. Note that Eq. 19 yields a lower upper bound to a than that given by Eq. 14. Because of the behavior of the trajectories on the isoclines, we can infer that there is a unique trajectory leading from critical point II at $z = -\infty$ to critical point I at $z = +\infty$. This trajectory, in fact, represents the desired traveling wave solution to the partial differential equation system (Eqs. 1–4) with $n = 2$. This trajectory is represented by the dashed line in Fig. 4. The trajectory leading from critical point II to critical point III is of no interest because it represents a solution that is incompatible with the required boundary conditions on c and p at $z = +\infty$.

It is intuitively clear that similar considerations are applicable for $n > 2$ because the sigmoidal shape of the equilibrium Eq. 12 is unchanged if p^2 is replaced by p^n there. However, if $n = 1$, there are only two critical points, as follows,

$$\begin{aligned} &(c, p) = (0, 0), \quad \text{I}, \\ &(c, p) = (m_o - b)\,(1, v/a - 1), \quad \text{II}. \end{aligned} \tag{20}$$

Reality of critical point II requires that the c-isocline lie above the p-isocline in the region of interest between the two critical points (Fig. 5). The trajectory connecting the two critical points now leads from critical point I at $z = -\infty$ to critical point II at $z = +\infty$. This trajectory

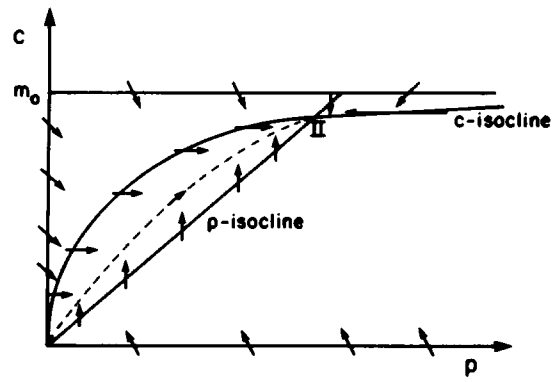

FIGURE 5 Schematic phase plane diagram of the system of Eqs. 9 and 11, for the case $n = 1$. The trajectory connecting the critical points now leads from I to II as z goes from $-\infty$ to $+\infty$, and is not compatible with the traveling wave solution of Fig. 3.

does not represent a traveling wave solution of the form shown in Fig. 3, and is clearly undesirable. The above analysis shows that the carrier must be multisited with respect to the protein it carries, and that the biochemical reaction between protein and carrier must display positive cooperativity, in order for the mathematical system to possess the desired traveling wave solution.

The phase-plane analyses we have made do not determine the phase velocity a of the traveling wave solution, which is to be identified with the observed velocity of the fast transport system. Such a determination necessitates an explicit calculation of the solution to Eqs. 1–4. However, the fact that K and m_o are parameters of the model equation system, and the fact that the upper bound on a given by Eq. 19 depends on the nondimensional parameter Km_o, suggests that those proteins that have a greater affinity for the carriers (larger K value) will possess a faster transport velocity.

DISCUSSION

The simple mathematical theory of axonal transport that we have presented indicates that a carrier system which is able to react chemically in a reversible manner with proteins and/or particles is compatible with a fixed velocity transport system such as is observed. The theory predicts that the set of all proteins and/or particles that are able to react chemically with the carriers will display a spectrum of transport velocities, depending on the rate constants for association and dissociation of the proteins and/or particles with the carriers. Those proteins with a higher affinity will presumably have a greater transport velocity, although we have not proved that this is the case. That a spectrum of transport velocities is observed by Willard and co-workers (1974, 1977) is supportive of the model. The predicted wave motion in particle concentration is also consonant with observed saltatory behavior of moving particles (Rebhun, 1972), which is interpretable as individual particles attaching to and detaching from moving carriers.

The present model could, in principle, explain slow as well as fast transport; an appropriately low affinity constant would automatically lead to a very slow transport rate, an idea that was first introduced by Ochs (1974*b*) on the basis of the kinetics of the slow

transport system. Support for the concept that the slow and fast transport rates are mediated by different systems appears to come from the observation that administration of β, β'-iminodipropionitrile to rats blocked slow transport in the sciatic nerve without interfering with fast anterograde (or retrograde) transport (Griffin et al., 1978). However, this observation does not rule out the possibility that transport rate is determined only by affinity of the transported component to the carriers, because the drug could selectively interfere only with binding to the low affinity sites.

Although the present model does not presuppose a knowledge of the identity of the carriers, it is pertinent to know whether possible carriers are present in axons. A number of observations suggest that microtubules play a central role in the fast transport process. Banks and Mayor (1972) noted that: (*a*) longitudinally arranged bundles of microtubules are prominent in axons; (*b*) a clear association between presumptive synaptic vesicles and microtubules has been seen in lamprey axons; (*c*) topical applications of low concentrations of colchicine prevents norepinephrine-containing vesicles from being transported in many nerves, stops transport in doubly ligatured segments, and decreases the number of microtubules present. Although the evidence implicating microtubules in the fast axonal transport system is suggestive, it is not conclusive, as emphasized by Byers (1974). Exposure of axons to very high concentrations of Ca^{++} (Brady and McClure, 1979) causes an apparently complete loss of microtubules without loss of fast transport. Ochs et al. (1978), however, reported that very high external concentrations of Ca^{++} blocked fast axonal transport and caused some loss of microtubules. The work of Brimijoin et al. (1979) shows that the number of microtubules per unmyelinated axon declined considerably with decreasing temperature before transport was impaired. On the other hand, although these studies did not indicate a close correlation between microtubule function and fast axon transport, it has been shown that when more than half the microtubules in frog sciatic nerve are destroyed, transport of mitochondria is then diminished in proportion to the further destruction of microtubules (Friede and Ho, 1977).

The axonal transport of mitochondria does not appear to be related to the presence of neurofilaments or of smooth endoplasmic reticulum. The absence of neurofilaments from microtubule-containing regions in which saltatory particle movements were demonstrated further supports the view that the neurofilaments are not necessary for fast transport (Breuer et al., 1975). The association of a dynein-like protein with microtubules from guinea pig, calf, and pig brain has been reported (Gaskin et al., 1974), so that the conditions postulated in the present model, i.e., a uniformly distributed sliding filament system, could exist. Furthermore, it has been demonstrated that microtubules can interact with phospholipid vesicles (Caron and Berlin, 1979). Finally, for the highly organized dynein-microtubule sliding system of flagella, v is $\simeq 10$ μm/s (Gibbons, 1975), or $\simeq 860$ mm/d, which is comparable to observed fast transport rates. Thus the weight of evidence at present does not exclude the possibility that microtubules are the elements involved in fast axonal transport. It should be added, however, that in Ochs' view microtubules have the role of tracks, rather than trains.

A surprising requirement of the model is the positive cooperative behavior of the reaction between the particles and the filament. Breuer et al. (1975) have noted that published electron micrographs show that mitochondria are associated with more than one microtubule in axons, and raise the possibility that microtubules cooperate in organelle translocation. Alternatively, because the fast axonal transport system transports mostly particles, which are large by

definition, one could envisage that multiple sites on the particle (and hence on the microtubules if they are the carriers) would be required for adequate binding. If so, positive cooperativity of such binding would be likely.

As noted above, there is no compelling evidence that microtubules are necessary and sufficient for fast axonal transport. Recently it has become clear that actin, a major component of neurons, is itself transported by one of the slower transport systems (system I of Willard et al., 1974), as is the myosin of the axon (Willard et al., 1979). In addition to a dynein-microtubule system, therefore, the axon also contains a myosin-actin sliding filament system which could provide the functional force generating unit. The model developed in the present paper is, of course, compatible with either (or both) of these systems or with any other filamentous sliding system that might be present in the axoplasm.

The most serious challenge to our model, as well as to other related models, is the identity of the putative carrier. Of course, that is strictly a question to be answered by biological investigation, rather than by our theoretical considerations which are independent of the identity of the carrier. However, a plausible conjecture to be made from the present study is that the carrier is to be identified with one or more of the fastest moving proteins in the axon. As discussed above, likely contenders for the molecular components of the carrier appear to be tubulin and actin. Both these proteins are carried at slow rates, actin ~ 3 mm/d (Willard et al., 1979) and tubulin at ~ 1 mm/d (Hoffman and Lasek, 1975). This would appear to rule out their role as carrier components in such a strict interpretation of the model.

However, the carrier could still consist of actin or tubulin if the carrier had to become activated before it commenced to interact with potentially transportable particles and to move with velocity v. If only a small fraction of the carriers was activated at any one time, then the conditions of the model could still be satisfied, but the mass of carrier that actually traveled at the fast rate might escape detection by present methods. Of course, this discussion is speculative, and we recognize the possibility that carrier considerations mediated by chemical reaction might simply be a wrong concept.

Although we have stressed the roles of microtubules and/or of actin filaments as possible carriers, "there is no shortage of fibrous proteins from which to construct several transport systems" (Porter et al., 1979). These authors point out that rapid motion of the microtrabecular system constrained by a relatively static framework of microtubules and/or microfilaments might supply the motive force for fast axonal transport. They speculate that local conformational changes, perhaps caused by calcium release from a transport compartment of the smooth endoplasmic reticulum could cause local contraction of polyanionic side chains of the microtrabeculae. How such a mechanism might operate to yield up to five distinct rates of nondispersive transport remains unexplained.

We present our model considerations tentatively, not so much with the conviction that they are correct, but with the utility of such mathematical calculation in mind: They suggest a variety of questions to be answered by investigation that will refute (or support) the assumptions that underlie the model. Thus the model requires that the carriers and the transported particles must react chemically to achieve transport and that such reactions must exhibit positive cooperativity. It suggests that the hierarchy of observed transport velocities of the carried substances are ordered in the same sequence as their chemical affinities for the carrier. Finally, we mention that Eq. 19 indicates that transport velocity should be

proportional to the concentration of carriers at low carrier concentrations, as observed for the relation between microtubule content and the transport of mitochondria in the experiments of Friede and Ho (1977). Although evidence supporting any of these points would not necessarily prove the correctness of the model, consideration of these points may prove helpful in the design of experiments to provide further information on the mechanism(s) of axonal transport.

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