Simulation of a Presynaptic Nerve Terminal with a Tethered Particle System Model

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Abstract—**Presynaptic nerve terminals are located at the ends of nerve cells; a signal propagating through a nerve cell reaches one of these compartments before being transmitted to an adjacent nerve cell.**

A tethered particle system (TPS) is a type of impulse-based model recently developed for the simulation of deformable biological structures. In a TPS, collisions can cause approaching particles to rebound outwards, as one would expect, but they can also caused separating particles to retract inwards.

This paper demonstrates how a TPS can be used to simulate biological systems by presenting its application to a presynaptic nerve terminal. The model captures the clustering of sacs called vesicles in the presence of protein called synapsin. Both rigid and deformable membranes are also described. The simulated presynaptic nerve terminal may be used, for example, to predict how a change in synapsin concentration affects the size of vesicle clusters.

I. Introduction

The simulation of deformable structures is used for a wide range of applications in the biomedical field, including the study of physiology, the analysis of joint replacements, and the planning of surgeries. Though the finite element method is likely the most popular method for such applications, the recently-developed tethered particle system (TPS) is a relatively simple alternative. Whereas [1] provides a more detailed description of the TPS, including key formulas, this paper demonstrates its application to a specific biological system.

An action potential, a signal that propagates along the axon of a nerve cell, will ultimately arrive at a presynaptic nerve terminal. Inside this compartment are dozens of neurotransmitter-containing sacs called synaptic vesicles. Some of those vesicles are docked to a region of the membrane called the active zone. When an action potential arrives, those docked vesicles may release their neurotransmitters outside of the membrane, which can provoke another action potential in an adjacent nerve cell.

Also present in a presynaptic nerve terminal are protein called synapsin. Synapsins, which may number in the hundreds within the compartment, bind with vesicles to form clusters. An action potential triggers chemical reactions that cause synapsins to lose their affinity for vesicles. This disrupts the clusters, freeing vesicles. Clusters may reform before the next action potential arrives.

Figure 1 illustrates the clustering of vesicles and other features of a presynaptic nerve terminal. More information on the biology of these compartments can be found in [2].

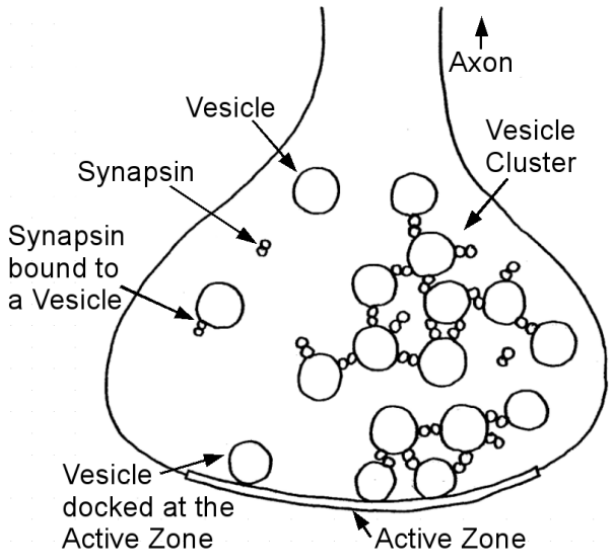

Fig. 1. An illustration of a presynaptic nerve terminal.

The simulation of a presynaptic nerve terminal is motivated by a desire to answer questions that are difficult to address with experimentation alone. One may be able to use simulation results, for example, to predict how a decreased synapsin concentration affects the size of vesicle clusters. Such results could prove useful to biologists and medical researchers, as the formation and disruption of vesicle clusters is important in the regulation of neurotransmitter release.

The simulation in [3] captures the reaction and diffusion of chemicals around vesicles docked on a presynaptic membrane, but allows neither the vesicles nor the membrane to move. The cellular models of [4] and [5] allow vesicles to move and form clusters, but the clusters behave as rigid bodies. Here we use a TPS instead of a cell space, allowing vesicle clusters and cell membranes to deform. The problem is approached from a software design perspective, and this paper focuses on the representation of biological structures. After providing background information on the TPS in general, its application to vesicle clusters and nerve cell membranes is discussed. The same modeling techniques used to design the presented TPS model of a presynaptic nerve terminal could be applied to simulations of other biological systems.

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II. Tethered Particle System Models

The simplicity of the TPS contributes significantly to its appeal. A TPS model consists of a large number of moving particles. Two types of collisions occur between pairs of particles: blocking collisions and tethering collisions.

A blocking collision is the more familiar type. It occurs when two approaching particles reach an inner limiting distance $\Delta u_{blocking}$, as illustrated in Figure 2, and causes the particles to rebound outwards.

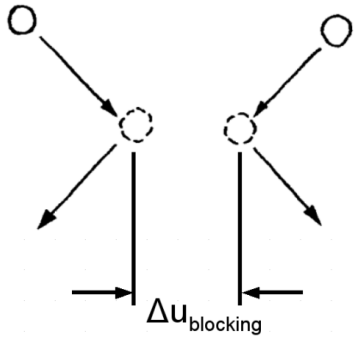

Fig. 2. A blocking collision. Two approaching particles reach an inner limiting distance $\Delta u_{blocking}$, then rebound outwards.

When a blocking collision occurs, the two particles involved may become tethered to one another. If two separating tethered particles reach an outer limiting distance $\Delta u_{tethering}$, and if the particles remain tethered, then a tethering collision causes the particles to retract. The unraveling cord in Figure 3 illustrates this effect, but is not explicitly modeled by the TPS.

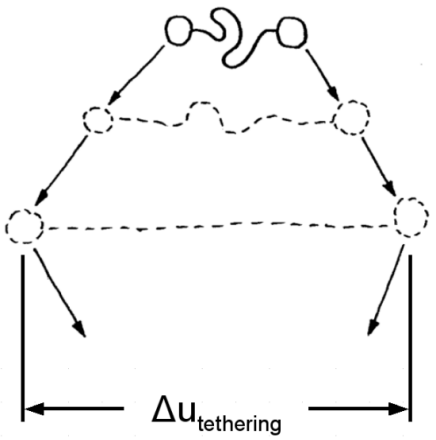

Fig. 3. A tethering collision. Two separating tethered particles reach an outer limiting distance $\Delta u_{tethering}$, then retract inwards.

Although particles are shown as circles or spheres in illustrations throughout the paper, only the blocking and tethering distances are explicitly defined in a TPS model. Particles need not be given radii. By constraining the distances between particles with suitably chosen $\Delta u_{blocking}$ and $\Delta u_{tethering}$ parameters, various deformable structures may be represented.

III. Representation of Vesicle Clusters

A simple way to organize a TPS model is to assign each particle a species. A pair of blocking and tethering distances $\Delta u_{blocking}$ and $\Delta u_{tethering}$ is then associated with each pair of species.

The presynaptic nerve terminal model includes three species that play an intuitive role in the representation of vesicle clusters. The species identified by *V*, *S*, and *D* represent, respectively, vesicles, halves of synapsins, and docking sites in the active zone. Two tethered *S* particles represent one synapsin. The rendering in Figure 4 shows a cluster of two vesicles, which are tethered to opposite ends of a synapsin.

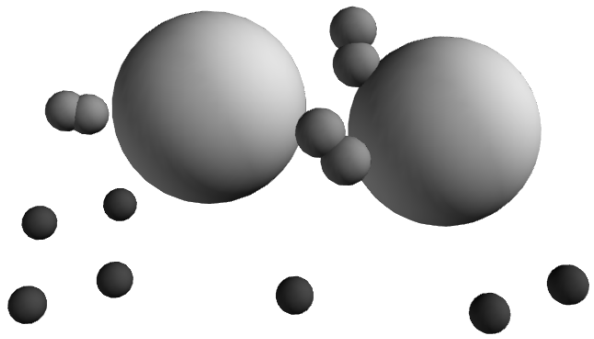

Fig. 4. A snapshot of a simulation showing two vesicles (*V* particles), three synapsins (pairs of *S* particles) and seven docking sites (*D* particles).

If a blocking collision occurs between a *V* particle and a *D* particle, and if the *D* particle is not already tethered to a vesicle, then they become tethered. Similarly, a *V* particle and an *S* particle become tethered after a blocking collision, provided the *S* particle is still without a vesicle. A *V* particle may not become tethered to both *S* particles of the same synapsin.

Table I lists the blocking and tethering distances for *V*, *S*, and *D* particles in the presynaptic nerve terminal model. As indicated, approaching docking site and vesicle particles collide and rebound at 24 nm. If tethered and separating, they retract at 28 nm. The distances were chosen to reflect the sizes of actual structures. The diameter of a vesicle is roughly 40 nm, for example, the value used for the vesicle-vesicle blocking distance. Note that a blocking distance of 0 indicates that blocking collisions never occur between those species, whereas a tethering distance of ∞ indicates that tethering collisions never occur.

TABLE I
Blocking/Tethering Distances for Vesicles, Synapsins, and Docking Sites

Particle Species Pair	$\Delta u_{blocking}$ (nm)	$\Delta u_{tethering}$ (nm)
V - *V*	40	∞
S - *S*	2.5	7.5
S - *V*	22.5	25
D - *D*	8	∞
D - *V*	24	28
D - *S*	0	∞

IV. Representation of Rigid Spherical Membranes

In order to model the formation, disruption, and motion of vesicle clusters, it is necessary to constrain the *V*, *S*, and *D* particles to a region representing the presynaptic nerve terminal compartment. The simplest way to achieve this is to model the nerve cell membrane as a rigid sphere. This is done by adding two particles to the model, one with species *M* and one with species *Z*. Both of these particles are given infinite mass, which ensures that they remain stationary.

The membrane particle of species *M* is tethered to all vesicle, synapsin, and docking site particles. For the sake of convenience, the parameter r_M approximates the radius of the compartment, r_V approximates that of a vesicle, and r_S approximates the radius of half of a synapsin. As illustrated in Figure 5, a membrane-vesicle tethering distance of $r_M - r_V$ keeps vesicles in the compartment, and a membrane-synapsin tethering distance of $r_M - r_S$ does the same for synapsins. Because vesicles and synapsins move freely within the compartment, the *M*-*V* and *M*-*S* blocking distances are both zero.

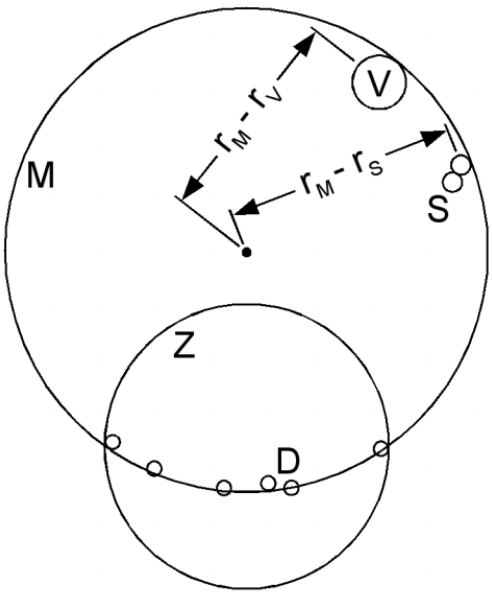

Fig. 5. A diagram illustrating the relationships between the five particle species in the presynaptic nerve terminal model.

The *D* particles, representing docking sites on the membrane, must be constrained to the spherical surface representing the cell membrane. The *M*-*D* blocking and tethering distances are therefore both chosen to be near r_M, with $\Delta u_{tethering}$ slightly greater than $\Delta u_{blocking}$. Another constraint on the docking sites is that they must all be located in that region of the membrane known as the active zone. Hence, all *D* particles are tethered to the *Z* particle shown in Figure 5. With the exception of this tethering, the *Z* particle has no influence on any other particle.

A couple aspects of the model have been neglected thus far for the sake of brevity. Particles lose kinetic energy in collisions according to the various coefficients of restitution described in [1]. In order to maintain some amount of kinetic energy in the system, impulses of randomized magnitude and direction are delivered at randomized times to various particles.

Figure 6 shows a snapshot of a simulation performed with the presynaptic nerve terminal model. The cell membrane *M* particle is shown as a sphere of radius r_M, which in this case is 250 nm. The larger spheres inside the membrane are vesicles, and the pairs of smaller particles tethering vesicles together represent synapsins. Though initially isolated with randomized positions, vesicles and synapsins formed clusters during the simulation. The small dark particles at the bottom represent docking sites; one or more vesicles in the large cluster on the bottom left are tethered to them. The *Z* particle is not shown.

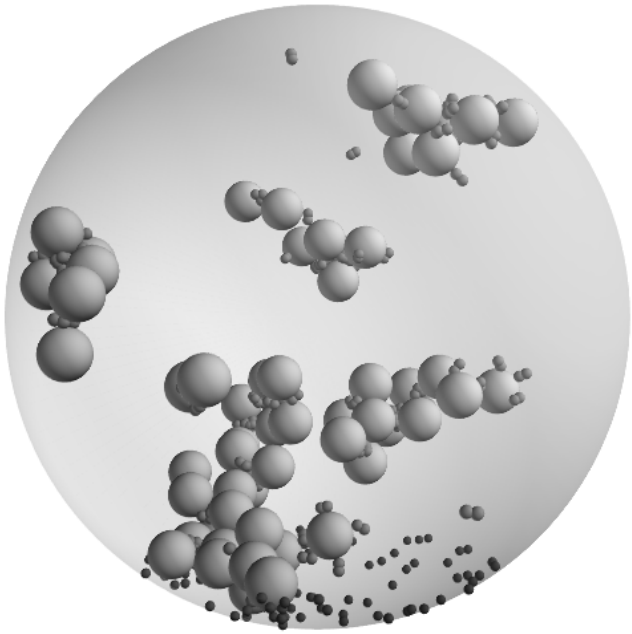

Fig. 6. A snapshot of a simulated presynaptic nerve terminal with a rigid spherical membrane.

Although the cell membrane surrounding a presynaptic nerve terminal is neither rigid nor perfectly spherical, this approximation may well be adequate for the investigation of certain aspects of the real system. If one wishes to predict the relationship between synapsin concentration and vesicle cluster size, for example, a deformable membrane model may be unnecessarily complex.

Simulations like the one in Figure 6 have been used to produce animations, and the behavior of vesicle clusters in those animations appear realistic. One possible model enhancement would be the addition of long chains of tethered particles. These chains would represent actin, filaments that affect the dynamics of vesicle clusters. A quantitative assessment of the model would require the optimization of model parameters, as well as suitable techniques for comparing experimental observations with simulation results.

V. Representation of Deformable Membranes

Although the rigid spherical membrane is likely adequate for a number of investigations involving vesicle clusters, the representation of deformable membranes may capture other features of a presynaptic nerve terminal. Deformable membranes may also be useful for models of entire nerve cells, networks of nerve cells, tissues, blood vessels, and perhaps even large organs.

A simple way to represent a membrane with a TPS is illustrated in Figure 7. Particles are positioned on a surface, and each particle is tethered the nearest neighboring particles. To avoid excessively-sharp folds and other anomalous features, a membrane should have at least two layers; that is, there should be two or more parallel surfaces of particles, and corresponding particles on adjacent surfaces should be tethered together.

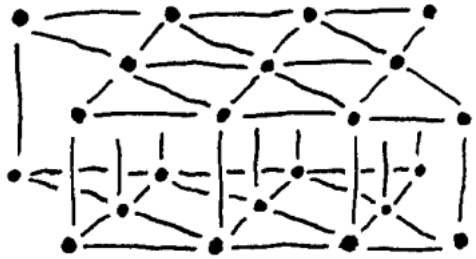

Fig. 7. An illustration of how deformable membranes may be represented. Dots are particles, and lines indicate pairs of tethered particles.

Particles on a membrane surface need not be coplanar, and need not be arranged in the triangular grid pattern shown in Figure 7. One alternative is demonstrated in Figure 8, which shows an initially spherical membrane deforming in response to an impact with an initially downward-moving particle. The particles in the membrane were arranged in two concentric icosahedral grids, each constructed by interpolating a 20-sided regular polyhedron.

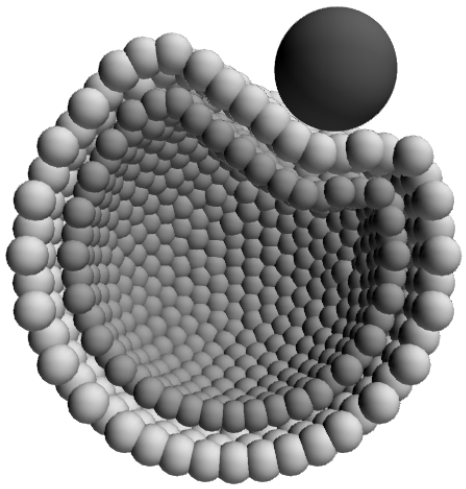

Fig. 8. A simulation in which a deformable membrane suffers an impact. The membrane was closed, but the front half is not shown.

The design of a satisfactory deformable membrane for a presynaptic nerve terminal model is an ongoing effort. Presented below is one attempt to coerce the icosahedral-grid-based membrane into a pear-like shape similar to that in Figure 1. It is used to contain vesicles, synapsins, and docking site particles. Figure 9 shows the majority of vesicles clustering above the somewhat flattened active zone at the bottom. A few vesicles and synapsins drift around the narrow upper end of the compartment.

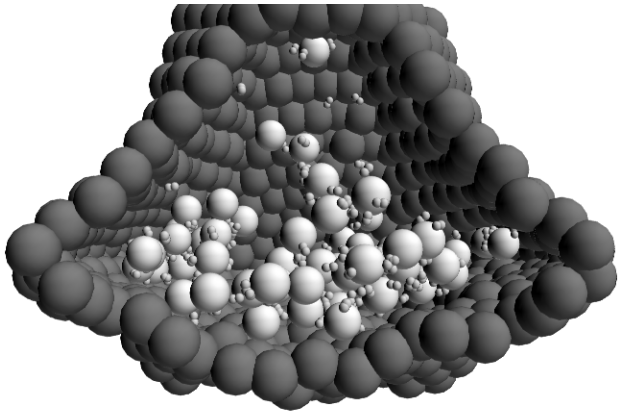

Fig. 9. A simulated presynaptic nerve terminal with a deformable membrane. The outer layer and front of the membrane are not shown.

An icosahedral grid is an artificial structure, arguably, and its use in a TPS tends to result in an undesirable protrusion of the edges of the underlying 20-sided polyhedron. Nevertheless, the simulations of Figures 8 and 9 exhibit believable processes of membrane deformation, suggesting that the TPS might be suitable for a range of different biological structures. Quantitative analyses remain necessary to assess the validity of such models.

VI. Acknowledgment

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References

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