

Vesicle-Synapsin Interactions Modeled with Cell-DEVS

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1. INTRODUCTION

The interactions of vesicles and synapsins were modeled using the Cell-DEVS formalism. These interactions take place within a presynaptic nerve terminal of a neuron, which is represented by a circular region in a 2-dimensional cellular automaton. Simulation results show the formation and separation of vesicle-synapsin clusters in response to action potentials.

This paper begins with background information about vesicle-synapsin interactions and Cell-DEVS modeling. In Section 3, the model itself is specified. Section 4 describes the implementation of the model using the CD++ toolkit, and presents selected test results. The paper concludes with a few observations about the model, and a discussion of possible improvements.

2. BACKGROUND

This section describes the vesicle-synapsin interactions in general, briefly introduces the DEVS and Cell-DEVS modeling formalisms, and discusses the application of Cell-DEVS to the biological system.

2.1 Vesicle-Synapsin Interactions

When signals, known as “action potentials” propagate along a neuron, they terminate at presynaptic nerve terminals. These round structures may transmit the signal to other neurons. At the risk of adopting an over-simplistic interpretation of a complex system, one can strive to understand this process by studying the interactions between vesicles and synapsins.

Synaptic “vesicles” move within a presynaptic nerve terminal. If they encounter the “active zone”, a region of the sur-

rounding membrane, they may remain there. When an action potential arrives, these docked vesicles may release neurotransmitters through the membrane, which may in turn trigger an action potential in the adjacent neuron.

Also moving within a presynaptic nerve terminal are proteins known as “synapsins”. Synapsins may tether vesicles together to form clusters. It has been proposed that the clustering of vesicles aids signal transmission by controlling the number of vesicles in the vicinity of the active zone. When an action potential arrives, a chemical reaction takes place during which these clusters tend to break up. The separated vesicles and synapsins then start binding with one another, forming new clusters before the arrival of the next action potential.

The complex chemical interactions that take place at a presynaptic nerve terminal are discussed in far greater detail in [1] and [2].

2.2 DEVS and Cell-DEVS Formalisms

DEVS (discrete event systems specification) is a formalism developed in the 1970’s. It allows a model to be specified in one of two ways. If specified in isolation, a model is referred to as an “atomic model”. If specified as a group of interconnected models, it is a “coupled model”. As a model within a coupled model can itself be a coupled model, complex DEVS models can be organized in hierarchies.

Using DEVS, a programmer can prepare a simulation without implementing loops. All DEVS models are specified independently of the simulator responsible for advancing time. The programmer’s main task is to specify how models are interconnected, and what state transitions can take place.

Cell-DEVS is an extension to DEVS designed for the specification of cellular automata. A “cell”, in this case, is a unit in a cell-space. If a cell-space is 2-dimensional, a cell can be thought of as a square on a grid.

In the Cell-DEVS formalism, each cell of a cell-space has an associated timed DEVS cell model. The cell-space as a whole has an associated DEVS coupled model, which contains all of the cell models. The interconnections between cell models are defined by the “neighborhood”, which is a set of relative coordinates.

An overview of DEVS and Cell DEVS is provided by [3],

which also describes the CD++ implementation of these formalisms.

2.3 Vesicle-Synapsin Interaction Models

Of particular interest in the presented Cell-DEVS model is the formation and separation of vesicle-synapsin clusters, and the motion of these clusters. Reactions triggered by action potentials are modeled as periods of time during which binding probabilities are altered. An active zone is modeled as a region of the membrane adjacent to which any vesicle or synapsin is rendered motionless. The release of neurotransmitters was not modeled.

The presented model is an enhancement of a preexisting model described in [4]. In the original, the locations of vesicles and synapsins were represented by single cells in a 2-dimensional cell-space. When isolated, vesicles and synapsins would move randomly through the space. After each cycle, they would bind to one another to form stationary clusters. Arbitrary probabilities controlled the binding of vesicles and synapsins, as well as their separation from clusters.

The circular region representing the membrane, the active zone, the motion of clusters, and the effect of action potentials were enhancements introduced in the development of the presented model.

3. MODEL SPECIFICATION

This section provides a formal specification of the model. First, the coupled Cell-DEVS model and DEVS cell atomic model are presented. Next, the initial conditions of the cell-space are established, followed by general transition rules. Transition rules specific to action potentials, vesicle-synapsin binding, and cluster motion are subsequently explained.

3.1 Presynaptic Nerve Terminal Model

The function $presynaptic_{GCC}$ results in a Cell-DEVS coupled model that represents a presynaptic nerve terminal. The parameter R , which must be a positive integer, is the inner radius of the terminal. In the absence of an action potential, the probability that a vesicle will bind to an adjacent synapsin is p_{rest} . If they are already bound, then there is a probability of q_{rest} that they will separate. The binding and separating probabilities during an action potential are p_{act} and q_{act} respectively.

$$presynaptic_{GCC}(R, p_{rest}, q_{rest}, p_{act}, q_{act}) = \langle Xlist, Ylist, X_{GCC}, Y_{GCC}, n, [t_1, t_2], N, C, B, Z \rangle$$

The coupled model has one input port, named in , on which to receive a value of either $receiving_{act}$ or $receiving_{rest}$. This represents the arrival of an action potential from the axon of the neuron, or the point at which the action-potential-induced reactions have subsided. The input value is received by the cell $[0, 0]$.

$$Xlist = \{[0, 0]\}$$

$$X_{GCC} = \{[in, \Phi']\};$$

$$\Phi' \in \{receiving_{act}, receiving_{rest}\}$$

There are no output ports.

$$Ylist = \emptyset$$

$$Y_{GCC} = \emptyset$$

The cell-space is a 2-dimensional square grid, just large enough to surround the inner terminal with a membrane layer of at least one cell in any direction.

$$n = 2$$

$$t_1 = t_2 = 2 \cdot R + 1$$

A von Neumann neighborhood is used.

$$N = \{[0, 0], [1, 0], [0, 1], [-1, 0], [0, -1]\}$$

A function named $presynaptic_{TDC}$ results in the DEVS cell atomic model of each cell in the cell-space. It is defined in a section 3.2.

$$C([i_1, i_2]) = presynaptic_{TDC}(p_{rest}, q_{rest}, p_{act}, q_{act});$$

$$(i_1 \in \mathbb{N}) \wedge (0 \leq i_1 < t_1)$$

$$(i_2 \in \mathbb{N}) \wedge (0 \leq i_2 < t_2)$$

Because the vesicle-synapsin interactions take place in a circular region within the cell-space, the conditions of the actual model border are irrelevant. For simplicity, a wrapped border can be used.

$$B = \emptyset$$

The translation function Z is defined by the Cell-DEVS formalism.

3.2 Presynaptic DEVS Cell Model

As mentioned above, the timed DEVS cell atomic model for each cell results from the $presynaptic_{TDC}$ function. Its parameters, the four binding and separating probabilities, are the same for each cell.

$$presynaptic_{TDC}(p_{rest}, q_{rest}, p_{act}, q_{act}) = \langle X_{TDC}, Y_{TDC}, S, N, delay, d, \delta_{ext}, \delta_{int}, \tau, \lambda, ta \rangle$$

The cell model's set of input values, X_{TDC} , includes the corresponding set from the coupled model, X_{GCC} , as well as the set of states from changing neighbors, X . A cell's set of output values, Y_{TDC} , includes only those values derived from its own changing state. As the sets X and Y deal only with interacting neighboring cells, their meanings are implied by the Cell-DEVS formalism.

$$X_{TDC} = X \cup X_{GCC}$$

$$Y_{TDC} = Y$$

A cell's state must belong to the set S . It is described by seven variables: $type$, b , Φ , ϕ , v , z , and σ .

$$S = \{[type, b, \Phi, \phi, v, z, \sigma]\}$$

The $type$ variable indicates whether a cell is part of the *empty* region inside the terminal, a *vesicle*, a *synapsin*, part of the neuron's *membrane*, or part of the active *zone* within the membrane.

$$type \in \{empty, vesicle, synapsin, membrane, zone\}$$

The function b is defined for the four vectors pointing from a cell to its adjacent neighbors. For each of these directions, the function result can be either *free*, *seeking*, *unseeking*, *looking*, or *binding*. This information facilitates the modeling of vesicle-synapsin binding and separation.

$$b([i, j]) \in \{free, seeking, unseeking, looking, binding\};$$

$$([i, j] \in N) \wedge ([i, j] \neq [0, 0])$$

The variable Φ indicates whether the cell has received an event external to the coupled model (*receiving_[...]*), is starting or ending an action-potential-induced reaction (*starting_[...]*), or is waiting for a change (*holding_[...]*).

$$\Phi \in \{ \begin{array}{l} receiving_{act}, receiving_{rest}, \\ starting_{act}, starting_{rest}, \\ holding_{act}, holding_{rest} \end{array} \}$$

There are eight phases, which are cycled through in succession each time vesicles and synapsins move. The current phase is indicated by the variable ϕ .

$$\phi \in \{ \begin{array}{l} starting, holding, \\ selecting, bindings, binding_v, \\ aiming, steering, moving \end{array} \}$$

The variable v represents the direction in which a vesicle or synapsin is intending to move. In membrane and active zone cells, which never move, v is always zero. In empty cells, the variable may be used to indicate the intended direction of an approaching vesicle or synapsin.

$$v \in N$$

The priority number z is used to resolve conflicts between moving vesicles and synapsins.

$$0 \leq z \leq 1$$

The time remaining until the next internal transition is represented by σ . As the model uses inertial delays, the transition indicated by σ may be interrupted by a change in a neighboring cell.

$$\sigma \geq 0$$

Aside from one exception, the external transition function δ_{ext} , internal transition function δ_{ext} , and output function λ are defined as in the Cell-DEVS formalism. The exception pertains to an external event representing an action potential, which is described in a section 3.4. The local computing function τ and time advance function ta are also specified further below.

3.3 Initial Conditions

The cell-space is initialized by the function $presynaptic_{init}$, which has four arguments. The parameter R , again, represents the inner radius of the terminal. The size of the active zone is described by the angle θ . The probabilities p_V and p_S provide a convenient way to distribute vesicles

and synapsins within the terminal.

$$presynaptic_{init}(R, \theta, p_V, p_S) = s_{init};$$

$$s_{init}([i_1, i_2]) = [\begin{array}{l} type_{init}([i_1, i_2]), \\ b_{init}, \\ \Phi_{init}, \\ \phi_{init}, \\ v_{init}, \\ z_{init}, \\ \sigma_{init} \end{array}];$$

$$(i_1 \in N) \wedge (0 \leq i_1 < t_1)$$

$$(i_2 \in N) \wedge (0 \leq i_2 < t_2)$$

The radius can be used to partition the cell-space into a region inside the terminal, and a bordering region representing the membrane of the neuron.

$$type_{init}([i_1, i_2]) = \left(\begin{array}{ll} r([i_1, i_2]) \geq R & \rightarrow type_{outer}([i_1, i_2]) \\ r([i_1, i_2]) < R & \rightarrow type_{inner}([i_1, i_2]) \end{array} \right)$$

The function r gives the distance from the center of the cell-space.

$$r([i_1, i_2]) = \sqrt{(i_1 - R)^2 + (i_2 - R)^2}$$

On the outside, all cells encompassed by the angle θ are part of the active zone. Otherwise, they are regular *membrane* cells.

$$type_{outer}([i_1, i_2]) = \left(\begin{array}{ll} i_1 - R > r([i_1, i_2]) \cdot \cos(\frac{\theta}{2}) & \rightarrow zone \\ i_1 - R \leq r([i_1, i_2]) \cdot \cos(\frac{\theta}{2}) & \rightarrow membrane \end{array} \right)$$

On the inside, each cell has a probability p_V of being a vesicle, and a probability p_S of being a synapsin. Otherwise the cell is empty.

$$type_{inner}([i_1, i_2]) = \left(\begin{array}{ll} rand < p_V & \rightarrow vesicle \\ p_V \leq rand < p_V + p_S & \rightarrow synapsin \\ p_V + p_S \leq rand & \rightarrow empty \end{array} \right);$$

$$rand = uniform()$$

The function b initially results in *free* regardless of position and direction. This reflects the absence of vesicle-synapsin clusters. The terminal is not undergoing an action-potential-induced reaction, and the initial phase is *starting*. Initially, the intended direction v is $[0, 0]$, and z and σ are both zero.

$$b_{init}([i, j]) = free$$

$$\Phi_{init} = holding_{rest}$$

$$\phi_{init} = starting$$

$$v_{init} = [0, 0]$$

$$z_{init} = 0$$

$$\sigma_{init} = 0$$

Figure 1 shows one possible initial configuration of cell types.

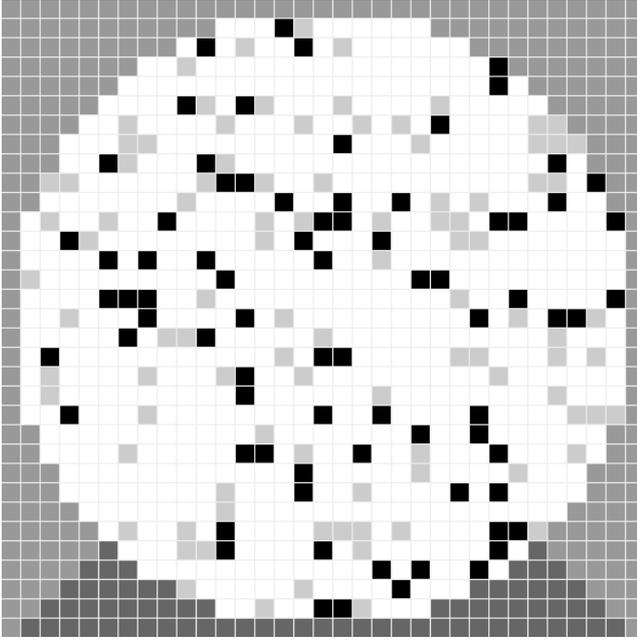


Figure 1: An initial cell-space configuration ($R = 16$, $\theta = 90^\circ$, $p_v = 9\%$, $p_s = 12\%$). On the inside, black cells represent vesicles while the light grey cells are synapsins. White cells are empty. On the outside, the dark region at the bottom is the active zone, while the remainder are normal membrane cells. Though it is not part of the model, one could imagine a connection to the axon of the neuron somewhere near the top.

3.4 Transitions

Used as an argument in transition functions, the state function s gives the cell state for each cell in a neighborhood. The expression $s([1, 0])$, for example, represents the state of the cell with coordinates $[1, 0]$ relative to the cell in question.

$$s([i, j]) \in S;$$

$$[i, j] \in N$$

The functions $type$, b , Φ , ϕ , v , z , and σ are defined implicitly by the equation below. It will be assumed that they are all available in whatever context the state function s is available. The expression $z([1, 0])$, for example, gives the priority number of the cell with coordinates $[1, 0]$ relative to the cell in question.

$$s([i, j]) = [$$

$$type([i, j]),$$

$$b([i, j]),$$

$$\Phi([i, j]),$$

$$\phi([i, j]),$$

$$v([i, j]),$$

$$z([i, j]),$$

$$\sigma([i, j])]$$

For convenience, the variables $type_0$, b_0 , Φ_0 , ϕ_0 , v_0 , z_0 , and σ_0 will be used to represent the state of the cell in question. The expression Φ_0 , for example, will be used as an

alternative to $\Phi([0, 0])$.

$$s([0, 0]) = [type_0, b_0, \Phi_0, \phi_0, v_0, z_0, \sigma_0]$$

The time advance function ta is defined as follows.

$$ta(s) = \sigma_0$$

The local computing function τ is partially defined below. The eight phase-specific local computing functions ($\tau_{starting}$, $\tau_{holding}$, etc.) will be defined in subsequent subsections.

$$\tau(s) = \begin{pmatrix} \phi_0 = starting & \rightarrow \tau_{starting}(s) \\ \phi_0 = holding & \rightarrow \tau_{holding}(s) \\ \phi_0 = selecting & \rightarrow \tau_{selecting}(s) \\ \phi_0 = bindings & \rightarrow \tau_{bindings}(s) \\ \phi_0 = bindingv & \rightarrow \tau_{bindingv}(s) \\ \phi_0 = aiming & \rightarrow \tau_{aiming}(s) \\ \phi_0 = steering & \rightarrow \tau_{steering}(s) \\ \phi_0 = moving & \rightarrow \tau_{moving}(s) \end{pmatrix}$$

Several functions are defined here for convenience. The function any_{type} indicates whether any of the adjacent cells are of the indicated type.

$$any_{type}(s, type') =$$

$$(type([1, 0]) = type') \vee (type([-1, 0]) = type') \vee$$

$$(type([0, 1]) = type') \vee (type([0, -1]) = type')$$

The function any_{b_0} indicates whether the state function b_0 contains the indicated binding-related value.

$$any_{b_0}(s, b'_0) =$$

$$(b_0([1, 0]) = b'_0) \vee (b_0([-1, 0]) = b'_0) \vee$$

$$(b_0([0, 1]) = b'_0) \vee (b_0([0, -1]) = b'_0)$$

If any of the adjacent cells have the indicated action state, any_Φ will yield a truthful result.

$$any_\Phi(s, \Phi') =$$

$$(\Phi([1, 0]) = \Phi') \vee (\Phi([-1, 0]) = \Phi') \vee$$

$$(\Phi([0, 1]) = \Phi') \vee (\Phi([0, -1]) = \Phi')$$

If any of the adjacent cells have the indicated phase, any_ϕ will be true.

$$any_\phi(s, \phi') =$$

$$(\phi([1, 0]) = \phi') \vee (\phi([-1, 0]) = \phi') \vee$$

$$(\phi([0, 1]) = \phi') \vee (\phi([0, -1]) = \phi')$$

The function $uniform$ results in a random value based on a uniform probability distribution. The range lies between, but does include, 0 and 1.

$$uniform()$$

The expression below results in a value randomly selected from the vector V . All values of V are given an equal probability.

$$random(V)$$

3.5 Action Potentials

Action potentials are triggered by events external to the Cell-DEVS coupled modeled. The input is received on the port in , which is directed to cell $[0, 0]$. Any other membrane cell could have been used. The receipt of an action potential changes the cell's action state, as indicated by the equation

below. Also note the change in σ , the time remaining until the next internal event.

$$\begin{aligned}\delta_{ext}(s, e, [in, \Phi']) &= [type_0, b_0, \Phi'_0, \phi_0, v_0, z_0, \sigma'_0]; \\ \Phi'_0 &= \Phi' \\ \sigma'_0 &= \sigma_0 - e\end{aligned}$$

Action-potential-related information is propagated in the *starting* phase, and sustained during the *holding* phase. Because the *starting* phase has instantaneous events, the conditional formula below is necessary. It states that if any of a cell's adjacent neighbors is in the *holding* phase, that cell must itself transition to the *holding* phase without delay. This need to immediately update the phase is a recurring theme in the model.

$$\begin{aligned}\tau_{starting}(s) &= \left(\begin{array}{ll} any_\phi(s, \phi'_0) & \rightarrow s'_{now} \\ \neg any_\phi(s, \phi'_0) & \rightarrow \tau'_{starting}(s) \end{array} \right); \\ \phi'_0 &= holding \\ s'_{now} &= [type_0, b_0, \Phi_0, \phi'_0, v_0, z_0, \sigma'_0]; \\ \sigma'_0 &= 0\end{aligned}$$

If the cell is in a *holding*[...] action state, but at least one of its adjacent neighbors is *starting*[...], then the cell adopts the new state without delay. It also adopts the appropriate *starting*[...] value if the neighbor's value is *receiving*[...]. Once a cell's action state value changes, it then propagates this information to other neighboring cells.

A transition from *holding*_{rest} to *starting*_{act} indicates the beginning of an action potential. The transition from *holding*_{act} to *starting*_{rest} indicates that the chemical reactions induced by the action potential have subsided. This simple "ON-or-OFF" model of action potentials suffices to break up vesicle-synapsin clusters.

The formulas below specify the propagation of action states. If none of a cell's neighbors are *starting* a new action state, then the cell transitions to the *holding* phase in 1 time unit. Note that this delayed transition will be interrupted if a

neighbor's state changes within that time.

$$\tau'_{starting}(s) = \left(\begin{array}{ll} any_{act} & \rightarrow s_{act} \\ any_{rest} & \rightarrow s_{rest} \\ \neg any_{start} & \rightarrow s_{later} \end{array} \right);$$

$$\begin{aligned}any_{act} &= \\ & ((\Phi_0 = holding_{act}) \wedge any_\Phi(s, starting_{act})) \vee \\ & (\Phi_0 = receiving_{act}) \\ any_{rest} &= \\ & ((\Phi_0 = holding_{rest}) \wedge any_\Phi(s, starting_{rest})) \vee \\ & (\Phi_0 = receiving_{rest})\end{aligned}$$

$$any_{starting} = any_{act} \vee any_{rest}$$

$$s_{act} = [type_0, b_0, \Phi'_0, \phi_0, v_0, z_0, \sigma'_0];$$

$$\Phi'_0 = starting_{act}$$

$$\sigma'_0 = 0$$

$$s_{rest} = [type_0, b_0, \Phi'_0, \phi_0, v_0, z_0, \sigma'_0];$$

$$\Phi'_0 = starting_{rest}$$

$$\sigma'_0 = 0$$

$$s_{later} = [type_0, b_0, \Phi_0, \phi'_0, v_0, z_0, \sigma'_0];$$

$$\phi'_0 = holding$$

$$\sigma'_0 = 1$$

Once a *starting*[...] action state has been propagated during the *starting* phase, it must be converted to a corresponding *holding*[...] state during the *holding* phase. For example, suppose the presynaptic nerve terminal is at rest. When an action potential arrives, the Φ_0 of cell [0,0] becomes *receiving*_{act}. Sometime later, during the *starting* phase, every cell becomes *starting*_{act}. After 1 time unit, during the *holding* phase, every cell becomes *holding*_{act}. A similar process takes place when the cell-space returns to the rest state.

As indicated below, a cell in the *holding* phase enters the *selecting* phase if any of its adjacent neighbors is in the *selecting* phase. The $B_{selecting}$ function will be explained in section 3.6.

$$\tau_{holding}(s) = \left(\begin{array}{ll} any_\phi(s, \phi'_0) & \rightarrow s_{now} \\ \neg any_\phi(s, \phi'_0) & \rightarrow \tau'_{holding}(s) \end{array} \right);$$

$$\phi'_0 = selecting$$

$$s_{now} = [type_0, b'_0, \Phi_0, \phi'_0, v_0, z_0, \sigma'_0];$$

$$b'_0 = B_{selecting}(s)$$

$$\sigma'_0 = 0$$

The formulas below convert $starting_{[...]}$ action states into corresponding $holding_{[...]}$ action states.

$$\tau'_{holding}(s) = \left(\begin{array}{l} iS_{starting_{act}} \rightarrow s_{act} \\ iS_{starting_{rest}} \rightarrow s_{rest} \\ \neg iS_{starting} \rightarrow s_{later} \end{array} \right);$$

$$iS_{starting_{act}} = (\Phi_0 = starting_{act})$$

$$iS_{starting_{rest}} = (\Phi_0 = starting_{rest})$$

$$iS_{starting} = iS_{starting_{act}} \vee iS_{starting_{rest}}$$

$$s_{act} = [type_0, b_0, \Phi'_0, \phi_0, v_0, z_0, \sigma'_0];$$

$$\Phi'_0 = holding_{act}$$

$$\sigma'_0 = 0$$

$$s_{rest} = [type_0, b_0, \Phi'_0, \phi_0, v_0, z_0, \sigma'_0];$$

$$\Phi'_0 = holding_{rest}$$

$$\sigma'_0 = 0$$

$$s_{later} = [type_0, b'_0, \Phi_0, \phi'_0, v_0, z_0, \sigma'_0];$$

$$b'_0 = B_{selecting}(s)$$

$$\phi'_0 = selecting$$

$$\sigma'_0 = 1$$

If, or when, there are no $starting_{[...]}$ values to convert, a delay of 1 time unit elapses and the cell enters the *selecting* phase. This is the first step in the vesicle-synapsin binding process.

3.6 Vesicle-Synapsin Binding

After handling information related to action potentials, but before vesicles and synapsins move, vesicle-synapsin bindings are permitted to change. Adjacent but unbound vesicle and synapsins may bind together, while those that are already bound may separate.

When a cell enters the *selecting* phase, its b_0 function is replaced with the result of the $B_{selecting}$ function. The b_0 value is only changed if the cell is either a synapsin or a vesicle. If it is a synapsin, then the result of b_0 becomes *free* in any direction that does not point to an adjacent vesicle. If it does point to a vesicle, b'_S must be evaluated. For vesicles, b_0 results in *looking* for each direction that points to

an adjacent synapsin. Otherwise, the result is *free*.

$$B_{selecting}(s) = \left(\begin{array}{l} type_0 = synapsin \rightarrow b_S \\ type_0 = vesicle \rightarrow b_V \\ \neg iS_{particle} \rightarrow b_0 \end{array} \right);$$

$$iS_{particle} = type_0 \in \{vesicle, synapsin\}$$

$$b_S([i, j]) = \left(\begin{array}{l} type([i, j]) \neq vesicle \rightarrow free \\ type([i, j]) = vesicle \rightarrow b'_S(s, [i, j]) \end{array} \right)$$

$$b_V([i, j]) = \left(\begin{array}{l} type([i, j]) \neq synapsin \rightarrow free \\ type([i, j]) = synapsin \rightarrow looking \end{array} \right)$$

In the case of a synapsin with an adjacent vesicle, the corresponding result of b_0 depends first on whether the pair are already bound. If so, the result becomes *unseeking*, which can be interpreted as "seeking separation". If the pair are not already bound, then the b_{free} function is evaluated.

$$b'_S(s, [i, j]) = \left(\begin{array}{l} b_0([i, j]) = binding \rightarrow unseeking \\ b_0([i, j]) = free \rightarrow b_{free}(s, [i, j]) \end{array} \right)$$

Complications arise from the fact that a synapsin can only bind in two opposite directions. If the synapsin is binding in the direction $[-i, -j]$, then it may seek a vesicle in direction $[i, j]$. In this case, $b_0([i, j])$ becomes *seeking*. Otherwise, b'_{free} is evaluated.

$$b_{free}(s, [i, j]) = \left(\begin{array}{l} b_0([-i, -j]) = binding \rightarrow seeking \\ b_0([-i, -j]) = free \rightarrow b'_{free}(s, [i, j]) \end{array} \right)$$

In the case that the synapsin is not binding in the direction opposite $[i, j]$, the two perpendicular directions are checked. If the synapsin is binding in either of these directions, its alignment prohibits binding in the direction $[i, j]$. The result of $b_0([i, j])$ therefore becomes *free*. Otherwise, b''_{free} is evaluated.

$$b''_{free}(s, [i, j]) = \left(\begin{array}{l} binding_{perp} \rightarrow free \\ \neg binding_{perp} \rightarrow b''_{free}(s, [i, j]) \end{array} \right);$$

$$binding_{perp} = (b_0([j, i]) = binding) \vee (b_0([-j, -i]) = binding)$$

In the final case, the synapsin is not binding in any direction. If then has a 50% chance of *seeking* the vesicle at $[i, j]$ as a candidate for binding.

$$b''_{free}(s, [i, j]) = \left(\begin{array}{l} iS_{aligned} \rightarrow seeking \\ \neg iS_{aligned} \rightarrow free \end{array} \right);$$

$$iS_{aligned} = ((|i| = 1) \wedge iS_{vertical}) \vee ((|j| = 1) \wedge \neg iS_{vertical})$$

Note that the random value of $iS_{vertical}$ is evaluated once per cell, not once per direction.

$$iS_{vertical} = uniform() < 0.5$$

The complex $B_{selecting}$ function is evaluated during the transition into the *selecting* phase. Once this phase begins, its

sole purpose is to waste 1 time unit to ensure that $B_{selecting}$ has been evaluated on each cell.

$$\begin{aligned}\tau_{selecting}(s) &= [type_0, b_0, \Phi_0, \phi'_0, v_0, z_0, \sigma'_0]; \\ \phi'_0 &= binding_S \\ \sigma'_0 &= 1\end{aligned}$$

The *bindings* phase is when the synapsins firmly decide whether they will bind with adjacent vesicles. It is followed by the *binding_v* phase, in which vesicles identify bindings by looking at the synapsins. The formula below indicates an immediate transition to the *binding_v* phase in the event that any of a cell's adjacent neighbors is already in that phase. Otherwise, $\tau'_{binding_S}$ is evaluated.

$$\begin{aligned}\tau_{binding_S}(s) &= \left(\begin{array}{l} any_\phi(s, \phi'_0) \rightarrow s_{now} \\ \neg any_\phi(s, \phi'_0) \rightarrow \tau'_{binding_S}(s) \end{array} \right); \\ \phi'_0 &= binding_V \\ s_{now} &= [type_0, b_0, \Phi_0, \phi'_0, v_0, z_0, \sigma'_0]; \\ \sigma'_0 &= 0\end{aligned}$$

An unresolved direction, in the case of a synapsin, is one for which the b_0 function results in *seeking* or *unseeking*. If there are any unresolved directions, $\tau''_{binding_S}$ is evaluated.

$$\begin{aligned}\tau'_{binding_S}(s) &= \left(\begin{array}{l} any_{unresolved} \rightarrow \tau''_{binding_S}(s) \\ \neg any_{unresolved} \rightarrow s'_{later} \end{array} \right); \\ any_{unresolved} &= \\ &any_{b_0}(s, seeking) \vee any_{b_0}(s, unseeking) \\ s'_{later} &= [type_0, b_0, \Phi_0, \phi'_0, v_0, z_0, \sigma'_0]; \\ \phi'_0 &= binding_V \\ \sigma'_0 &= 1\end{aligned}$$

When $\tau''_{binding_S}$ is evaluated, b_0 is changed in each unresolved direction. If it results in *seeking* for one direction, there is a probability p that it will become *binding*. Otherwise it will become *free*. If b_0 results in *unseeking* for a direction, there is a probability q that it will become *free*. Otherwise, it becomes *binding*. Here p and q depend on the action state. If the presynaptic nerve terminal is at rest, the model parameters p_{rest} and q_{rest} are used. If the terminal is responding to an action potential, then p_{act} and q_{act} are

used.

$$\begin{aligned}\tau''_{binding_S}(s) &= [type_0, b'_0, \Phi_0, \phi_0, v_0, z_0, \sigma'_0]; \\ b'_0([i, j]) &= \left(\begin{array}{l} b_0([i, j]) = seeking \rightarrow b_p([i, j]) \\ b_0([i, j]) = unseeking \rightarrow b_q([i, j]) \\ resolved \rightarrow b_0([i, j]) \end{array} \right); \\ resolved &= \\ &(b_0([i, j]) \neq seeking) \wedge \\ &(b_0([i, j]) \neq unseeking) \\ b_p([i, j]) &= \left(\begin{array}{l} rand < p \rightarrow binding \\ rand \geq p \rightarrow free \end{array} \right); \\ p &= \left(\begin{array}{l} \Phi_0 = holding_{rest} \rightarrow p_{rest} \\ \Phi_0 = holding_{act} \rightarrow p_{act} \end{array} \right) \\ rand &= uniform() \\ b_q([i, j]) &= \left(\begin{array}{l} rand < q \rightarrow free \\ rand \geq q \rightarrow binding \end{array} \right); \\ q &= \left(\begin{array}{l} \Phi_0 = holding_{rest} \rightarrow q_{rest} \\ \Phi_0 = holding_{act} \rightarrow q_{act} \end{array} \right) \\ rand &= uniform() \\ \sigma'_0 &= 0\end{aligned}$$

Once synapsins have chosen their binding directions, and the cell-space transitions from *bindings_S* to *binding_v*, the vesicles respond. The first thing specified is the condition where a cell's neighbor has already transitioned to the *aiming* phase, in which case that cell must also transition. Otherwise $\tau_{binding_V}$ is evaluated. The functions V_{aiming} and Z_{aiming} are explained in section 3.7.

$$\begin{aligned}\tau_{binding_V}(s) &= \left(\begin{array}{l} any_\phi(s, \phi'_0) \rightarrow s_{now} \\ \neg any_\phi(s, \phi'_0) \rightarrow \tau'_{binding_V}(s) \end{array} \right); \\ \phi'_0 &= aiming \\ s_{now} &= [type_0, b_0, \Phi_0, \phi'_0, V_{aiming}(s), Z_{aiming}(s), \sigma'_0]; \\ \sigma'_0 &= 0\end{aligned}$$

In the case of a vesicle, an unresolved direction is one for which b_0 results in *looking*. The function $\tau''_{binding_V}$ is evaluated if any directions are unresolved.

$$\begin{aligned}\tau'_{binding_V}(s) &= \left(\begin{array}{l} any_{unresolved} \rightarrow \tau''_{binding_V}(s) \\ \neg any_{unresolved} \rightarrow s'_{later} \end{array} \right); \\ any_{unresolved} &= any_{b_0}(s, looking) \\ s'_{later} &= [type_0, b_0, \Phi_0, \phi'_0, V_{aiming}(s), Z_{aiming}(s), \sigma'_0]; \\ \phi'_0 &= aiming \\ \sigma'_0 &= 1\end{aligned}$$

When $\tau''_{binding_V}$ is evaluated, the result is a change in $b_0([i, j])$ for each unresolved direction $[i, j]$. Suppose the adjacent synapsin, in direction $[i, j]$, is binding in the opposite direction, $[-i, -j]$. In that case, $b_0([i, j])$ is *binding*. Otherwise

it is *free*.

$$\begin{aligned}\tau''_{binding_V}(s) &= [type_0, b'_0, \Phi_0, \phi_0, v_0, z_0, \sigma'_0]; \\ b'_0([i, j]) &= \begin{pmatrix} b_0([i, j]) = looking & \rightarrow b''_0([i, j]) \\ b_0([i, j]) \neq looking & \rightarrow b_0([i, j]) \end{pmatrix} \\ b''_0([i, j]) &= \\ & \begin{pmatrix} b_{adj}([-i, -j]) = binding & \rightarrow binding \\ b_{adj}([-i, -j]) = free & \rightarrow free \end{pmatrix}; \\ b_{adj} &= b([i, j]) \\ \sigma'_0 &= 0\end{aligned}$$

By the time the cell-space transitions into the *aiming* phase, all bindings between vesicles and synapsins have been resolved.

3.7 Cluster Motion

While it would be relatively straightforward to allow isolated single-cell particles to move randomly through the presynaptic nerve terminal, it is challenging to specify the motion of vesicle-synapsin clusters. A cluster is any group of vesicles and synapsins connected through *binding* links defined by the b_0 functions. Clusters move randomly, remaining intact and avoiding obstacles such as other clusters. The algorithm designed to accomplish this is based on priority numbers.

Upon transitioning to the *aiming* phase, the intended direction v_0 and priority number z_0 of each cell may be changed. The new values are obtained from the V_{aiming} and Z_{aiming} functions respectively. If a cell is a vesicle or synapsin, and if it is not adjacent to the active zone, then both the direction and priority number are randomized. Otherwise the direction is $[0, 0]$, indicating no motion. In this case, the priority number given to empty cells is 1, which is the weakest number. If the motionless cell is not empty, the priority number is zero, which is the strongest.

$$\begin{aligned}V_{aiming}(s) &= \begin{pmatrix} ismovable(s) & \rightarrow V_{random}() \\ \neg ismovable(s) & \rightarrow [0, 0] \end{pmatrix} \\ Z_{aiming}(s) &= \begin{pmatrix} ismovable(s) & \rightarrow Z_{random}() \\ \neg ismovable(s) & \rightarrow Z_{frozen}(s) \end{pmatrix} \\ ismovable(s) &= \\ & (type_0 \in \{vesicle, synapsin\}) \wedge \\ & \neg any_{type}(s, zone) \\ V_{random}() &= random([[1, 0], [0, 1], [-1, 0], [0, -1]]) \\ Z_{random}() &= uniform() \\ Z_{frozen}(s) &= \begin{pmatrix} type_0 = empty & \rightarrow 1 \\ type_0 \neq empty & \rightarrow 0 \end{pmatrix}\end{aligned}$$

The first phase associated with cluster motion is *aiming*. A cell, with any neighbors that have already advanced to the

steering phase, must itself advance.

$$\begin{aligned}\tau_{aiming}(s) &= \begin{pmatrix} any_\phi(s, \phi'_0) & \rightarrow s'_{now} \\ \neg any_\phi(s, \phi'_0) & \rightarrow \tau'_{aiming}(s) \end{pmatrix}; \\ \phi'_0 &= steering \\ s'_{now} &= [type_0, b_0, \Phi_0, \phi'_0, v_0, z_0, \sigma'_0]; \\ \sigma'_0 &= 0\end{aligned}$$

During the *aiming* phase, directions and priority numbers are repeatedly shared within each cluster. A cell will adopt these values from an adjacent neighbor, provided that the neighbor has a lower priority number than that of the cell itself. The process ends when each vesicle and synapsin has the same direction and priority number as any other component in the same cluster.

It is useful to define a function g_{aiming} , which results in a truthful value if a neighbor at $[i, j]$ has a lower priority number and is bound to the cell. Another function, G_{aiming} , is truthful if all neighbors have advanced past the *binding_V* phase, and $g_{aiming}([i, j])$ is true for any $[i, j]$ describing an adjacent cell.

$$g_{aiming}(s, [i, j]) = (z([i, j]) < z_0) \wedge (s_0([i, j]) = binding)$$

$$\begin{aligned}G_{aiming}(s) &= \neg any_\phi(s, binding_V) \wedge (\\ & g_{aiming}(s, [1, 0]) \vee g_{aiming}(s, [-1, 0]) \vee \\ & g_{aiming}(s, [0, 1]) \vee g_{aiming}(s, [0, -1]))\end{aligned}$$

So long as the result of G_{aiming} is false, there is nothing to do other than transition to the *steering* phase after 1 time unit.

$$\begin{aligned}\tau'_{aiming}(s) &= \begin{pmatrix} G_{aiming}(s) & \rightarrow \tau''_{aiming}(s) \\ \neg G_{aiming}(s) & \rightarrow s'_{later} \end{pmatrix}; \\ s'_{later} &= [type_0, b_0, \Phi_0, \phi'_0, v_0, z_0, \sigma'_0]; \\ \phi'_0 &= steering \\ \sigma'_0 &= 1\end{aligned}$$

If G_{aiming} is true, the lower priority number and direction are copied from the adjacent neighbor.

$$\tau''_{aiming}(s) = \begin{pmatrix} g_{aiming}(s, [1, 0]) & \rightarrow obey(s, [1, 0]) \\ g_{aiming}(s, [0, 1]) & \rightarrow obey(s, [0, 1]) \\ g_{aiming}(s, [-1, 0]) & \rightarrow obey(s, [-1, 0]) \\ g_{aiming}(s, [0, -1]) & \rightarrow obey(s, [0, -1]) \end{pmatrix}$$

The copying is specified by the *obey* function below.

$$\begin{aligned}obey(s, [i, j]) &= [type_0, b_0, \Phi_0, \phi_0, v'_0, z'_0, \sigma'_0]; \\ v'_0 &= v([i, j]) \\ z'_0 &= z([i, j]) \\ \sigma'_0 &= 0\end{aligned}$$

By the time the cell-space transitions beyond the *aiming* phase, all particles and clusters have an intended direction. That direction may change, however. Vesicles and synapsins must not collide, and must not enter the membrane. All possible collisions are to be resolved during the *steering* phase.

First, cells are to transition to the *moving* phase if adjacent neighbors have already done so.

$$\tau_{steering}(s) = \left(\begin{array}{l} any_{\phi}(s, \phi'_0) \rightarrow s'_{now} \\ \neg any_{\phi}(s, \phi'_0) \rightarrow \tau'_{steering}(s) \end{array} \right);$$

$$\phi'_0 = moving$$

$$s'_{now} = [type_0, b_0, \Phi_0, \phi'_0, v_0, z_0, \sigma'_0];$$

$$\sigma'_0 = 0$$

As was the case in the *aiming* phase, a direction and priority number are copied from an adjacent cell only if the priority number is lower. In the case of *steering*, any one of three conditions must also be met. One of those case is the same as in the case of *aiming*; specifically, that the cell is bound to the adjacent neighbor. Clearly, the two particles must have the same direction.

The second possible condition is that the cell is either a vesicle or a synapsin, and is currently intending to move towards the adjacent neighbor with the lower priority number. This condition helps to prevent collisions.

The third possible condition is that the adjacent neighbor is a vesicle or synapsin, and the adjacent neighbor is intending to move towards the cell. This also helps to prevent collisions. Note that in this case, the cell in question may be empty. In the *steering* phase, empty cells can adopt directions from vesicles and synapsins.

The conditions described above are defined formally in the function $g_{steering}$.

$$g_{steering}(s, [i, j]) = (z([i, j]) < z_0) \wedge (s_0([i, j]) = binding) \vee ((type_0 \in \{vesicle, synapsin\}) \wedge (v_0 = [i, j])) \vee ((type([i, j]) \in \{vesicle, synapsin\}) \wedge (v([i, j]) = [-i, -j]))$$

Suppose that an empty cell has an approaching vesicle on either side. Suppose also that the one on the right has a lower priority number. The empty cell in the middle will adopt the direction and priority number from the right. In this case, the direction is pointing to the left. The vesicle on the left will then adopt this lower priority number as well, and reverse its direction. This example illustrates how a possible collision is avoided.

Continuing the example above, suppose that the vesicle on the right in now pushed upwards by a synapsin with a lower priority number. The empty cell now has no approaching particles. In order to reset its direction and priority number, this condition checked using the function $\gamma_{steering}$.

$$\gamma_{steering}(s, [i, j]) = (type_0 = empty) \wedge (v_0 = [i, j]) \wedge (v([i, j]) \neq [-i, -j])$$

All the conditions described above are combined into the single function $G_{steering}$.

$$G_{steering}(s) = \neg any_{\phi}(s, aiming) \wedge (g_{steering}(s, [1, 0]) \vee g_{steering}(s, [-1, 0]) \vee g_{steering}(s, [0, 1]) \vee g_{steering}(s, [0, -1]) \vee \gamma_{steering}(s, [1, 0]) \vee \gamma_{steering}(s, [-1, 0]) \vee \gamma_{steering}(s, [0, 1]) \vee \gamma_{steering}(s, [0, -1]))$$

As long as $G_{steering}(s)$ is false, a cell has nothing to do except wait 1 time unit then transition to the *moving* phase.

$$\tau'_{steering}(s) = \left(\begin{array}{l} G_{steering}(s) \rightarrow \tau''_{steering}(s) \\ \neg G_{steering}(s) \rightarrow s'_{later} \end{array} \right);$$

$$s'_{later} = [type_0, b_0, \Phi_0, \phi'_0, v_0, z_0, \sigma'_0];$$

$$\phi'_0 = moving$$

$$\sigma'_0 = 1$$

If $G_{steering}(s)$ is true, then one of the conditions that requires a change of direction and priority is also true. These possible changes are specified below. The function *obey* is the same as in the *aiming* phase, while *obeyall* resets empty cells.

$$\tau''_{steering}(s) = \left(\begin{array}{l} g_{steering}(s, [1, 0]) \rightarrow obey(s, [1, 0]) \\ g_{steering}(s, [0, 1]) \rightarrow obey(s, [0, 1]) \\ g_{steering}(s, [-1, 0]) \rightarrow obey(s, [-1, 0]) \\ g_{steering}(s, [0, -1]) \rightarrow obey(s, [0, -1]) \\ \gamma_{steering}(s, [1, 0]) \rightarrow obeyall \\ \gamma_{steering}(s, [0, 1]) \rightarrow obeyall \\ \gamma_{steering}(s, [-1, 0]) \rightarrow obeyall \\ \gamma_{steering}(s, [0, -1]) \rightarrow obeyall \end{array} \right);$$

$$obeyall = [type_0, b_0, \Phi_0, \phi_0, v'_0, z'_0, \sigma'_0];$$

$$v'_0 = [0, 0]$$

$$z'_0 = 1$$

$$\sigma'_0 = 0$$

The final phase is *moving*. At this point, all vesicles and synapsins have intended directions. These directions will not break bindings, and will not cause collisions. The function g_{moving} indicates whether a cell has an incoming particle in a given direction. The function G_{moving} indicates whether a cell has an incoming particle in any direction.

$$g_{moving}(s, [i, j]) = (type([i, j]) \in \{vesicle, synapsin\}) \wedge (v([i, j]) = [-i, -j])$$

$$G_{moving}(s) = g_{moving}(s, [1, 0]) \vee g_{moving}(s, [-1, 0]) \vee g_{moving}(s, [0, 1]) \vee g_{moving}(s, [0, -1])$$

If a cell has an incoming particle, τ'_{moving} is evaluated. Otherwise, its future state depends on a function named *move*.

$$\tau_{moving}(s) = \left(\begin{array}{l} G_{moving}(s) \rightarrow \tau'_{moving}(s) \\ \neg G_{moving}(s) \rightarrow move(s) \end{array} \right)$$

The τ'_{moving} function obtains the $type_0$ and b_0 values from the cell with the incoming vesicle or synapsin. The transition

occurs after 1 time unit.

$$\tau''_{aiming}(s) = \begin{pmatrix} g_{moving}(s, [1, 0]) & \rightarrow from(s, [1, 0]) \\ g_{moving}(s, [0, 1]) & \rightarrow from(s, [0, 1]) \\ g_{moving}(s, [-1, 0]) & \rightarrow from(s, [-1, 0]) \\ g_{moving}(s, [0, -1]) & \rightarrow from(s, [0, -1]) \end{pmatrix};$$

$$from(s, [i, j]) = [type'_0, b'_0, \Phi_0, \phi'_0, v'_0, z'_0, \sigma'_0];$$

$$type'_0 = type([i, j])$$

$$b'_0 = b([i, j])$$

$$\phi'_0 = starting$$

$$v'_0 = [0, 0]$$

$$z'_0 = 0$$

$$\sigma'_0 = 1$$

If there are no incoming particles, the one condition to check is whether the cell represents a vacating vesicle or synapsin. If so, the cell becomes empty. Otherwise, its type remains as is.

$$move(s) = \begin{pmatrix} vacating & \rightarrow from_{none} \\ \neg vacating & \rightarrow s'_{later} \end{pmatrix};$$

$$vacating = (type([i, j]) \in \{vesicle, synapsin\}) \wedge (v \neq [0, 0])$$

$$from_{none} = [type'_0, b'_0, \Phi_0, \phi'_0, v'_0, z'_0, \sigma'_0];$$

$$type'_0 = empty$$

$$b'_0([i, j]) = free$$

$$\phi'_0 = starting$$

$$v'_0 = [0, 0]$$

$$z'_0 = 0$$

$$\sigma'_0 = 1$$

$$s'_{later} = [type_0, b_0, \Phi_0, \phi'_0, v'_0, z'_0, \sigma'_0];$$

$$\phi'_0 = starting$$

$$v'_0 = [0, 0]$$

$$z'_0 = 0$$

$$\sigma'_0 = 1$$

4. IMPLEMENTATION AND TESTING

This sections discusses the implementation of the model, and presents the results of a selected test.

4.1 CD++ Implementation

The model was implemented using CD++. This toolkit was developed in conjunction with a language designed specifically for the implementation of Cell-DEVS models. Macros

were written to separate the model parameters from the code, and to facilitate the reuse of certain expressions.

While the specification defines a single Cell-DEVS coupled model, the implementation also included an “axon” model to provide external events at regular intervals. The axon model was given two parameters: one to represent the number of cycles between action potentials, and one to specify the duration of each reaction triggered by an action potential. A “cycle” is a complete rotation through each of the eight phases, a time period during which vesicles and synapsins can move at most once. For convenience, the axon model was itself defined as a Cell-DEVS coupled model containing a single cell. A DEVS atomic model could have been implemented instead.

Extra conditions were added to the implementation to address the possibility that two randomly-generated priority numbers might be equal in value. Mathematically this is an impossibility, so the specification is not incorrect for neglecting the issue. In the code, in the event that conflicting directions and priority numbers are encountered, a vesicle or synapsin is rendered motionless with a priority number of zero.

4.2 Test Results

Tests demonstrated that the model captures the desired qualitative behaviour of vesicles and synapsins. One such test involved the simulation of a cell-space with the following initial conditions.

$$R = 8$$

$$\theta = 90^\circ$$

$$p_V = 9\%$$

$$p_S = 12\%$$

In the model, vesicles and synapsins were given a 100% chance of binding while the terminal was at rest. The probability of adjacent vesicles and synapsins binding was actually closer to 50%, as synapsins bind in only two of four directions. A 1% probability of separation was added to discourage the formation of extremely long and narrow clusters. During an action-potential-induced reaction, the binding probability was lowered to 10%, while the probability of separation was raised to 50%.

$$p_{rest} = 100\%$$

$$q_{rest} = 1\%$$

$$p_{act} = 10\%$$

$$q_{rest} = 50\%$$

At the beginning of the simulation, vesicles and synapsins were randomly distributed in the terminal. Although this initial condition does not represent reality, clusters began forming within the first few cycles. As intended, the clusters mostly broke up after the arrival of an action potential, but regrouped thereafter.

Figure 2 shows three snapshots from the simulation: one

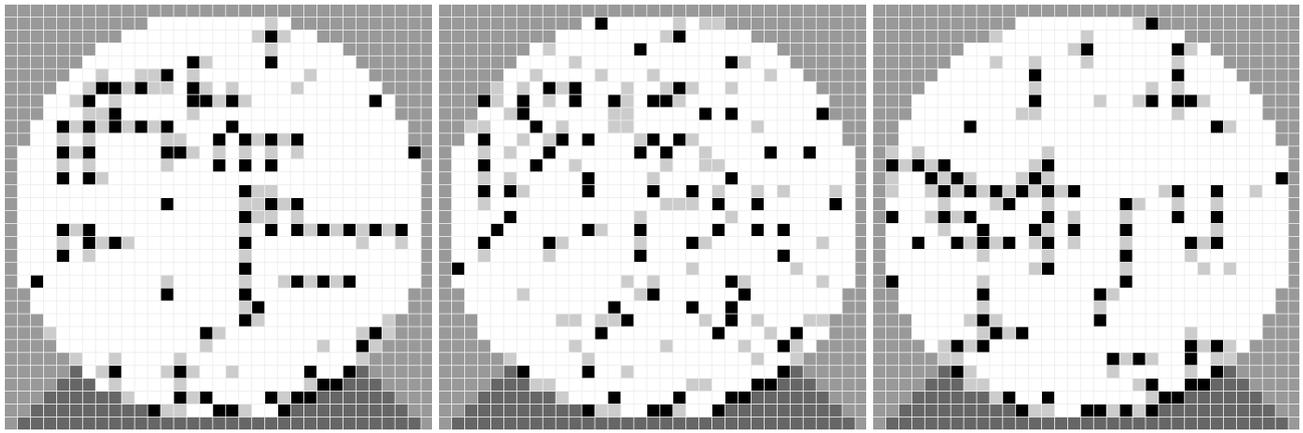


Figure 2: Three snapshots from the test described in the text. The one on the left shows clusters formed after 75 cycles. The first action potential arrived immediately after, and the resulting reaction lasted 5 cycles. Immediately after these 5 cycles, as shown in the center image, the vesicles and synapsins in the large clusters dispersed. Different clusters reformed, as shown on the right, after an additional 75 cycles. Black cells represent vesicles, while the light grey cells are synapsins.

immediately before the first action potential, the next immediately following the resulting reaction, and the third immediately prior to the second action potential. One can also observe vesicles and synapsins in the vicinity of the active zone at the bottom.

Clusters are smaller and more numerous than they appear in the snapshots. Noting that synapsins may bind to at most two vesicles, one can identify groups of adjacent, small clusters that at first appear as single, large clusters. The tendency for clusters to form in straight lines was not intended, but is a logical consequence of the binding rules. A greater value of q would likely result in rounder clusters, as the linear clusters would be rendered unstable.

5. CONCLUSIONS

Simulations demonstrated that the model captured the desired qualitative behaviour of vesicles and synapsins in presynaptic nerve terminals. Specifically, test results showed the formation and break-up of clusters in response to action potentials, the random motion of clusters, and the docking of vesicles and synapsins near the active zone. No efforts have yet been made to assess the validity of the model, nor to optimize the models parameters.

The Cell-DEVS formalism proved particularly useful for the propagation of action-potential-related information, and for the avoidance of collisions during cluster motion. These aspects of the model relied on instantaneous transitions. In retrospect, the specification may have been simpler if the zero-delay transitions used for binding had been avoided.

The cluster motion algorithm is the most interesting and perhaps the most novel aspect of the model. Unfortunately, it has two drawbacks: inefficiency and asymmetry. It is inefficient because many random directions and priority numbers are propagated, most of which are to be replaced with other directions and smaller priority numbers. The motion of clusters is asymmetric because, in the *steering* phase, the final combination of directions depends on the order in which

simultaneous events are resolved. If the order of events was itself randomized, there would be no bias. But as the order of events depends on positions and directions, clusters will likely have a tendency to favour certain directions over others. The effect of this bias was neither studied nor observed.

Possible future enhancements include the adaptation of the model to a 3-dimensional cell-space, and the fusion and formation of vesicles on the membrane. It may also be possible to change the vesicle-synapsin binding rules to better reflect reality. One drawback of the Cell-DEVS approach is that it would be difficult to allow a cluster to rotate. Representing long actin structures, which are known to influence vesicle-synapsin clusters, would also be a challenge.

6. REFERENCES

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