

MODELING THE DYNAMICS OF SECOND MESSENGER PATHWAYS

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Abstract: Understanding the effect of neuromodulators requires modeling the dynamics of second messenger pathways and their effects on channel properties. Chemosis is software for modeling enzyme reactions, stoichiometric reactions, diffusion, and ligand gating of channels and is used in conjunction with GENESIS, the software program for neuronal modeling. This chapter explains the differential equations and corresponding Chemosis objects that implement these reactions. Glutamate stimulated IP₃ production and calcium waves are examples of the second messenger pathways that can be implemented in Chemosis.

Keywords: diffusion, calcium, second messengers, enzymes, dynamics

1. INTRODUCTION

The importance of neuromodulators in neurological disorders such as Parkinson's Disease is generally accepted, (e.g. Albin et al. 1989; Blandini et al. 2000). Neuromodulators act through second messenger pathways, (e.g. Nishi et al. 1997; Choi et al. 1999) which influence neuronal behavior by their effect on membrane and channel properties, (e.g. West and Grace 2002; Levine et al. 1996; Kitai and Surmeier 1993; Surmeier and Kitai 1993). Most studies only evaluate steady state changes in channel properties, and, similarly, most compartmental models only include steady state effects of neuromodulation, (e.g. Seamans et al. 1998); but it is improbable that steady state concentrations occur *in vivo*. The release of neurotransmitters is a transient event, with rapid fluctuation in concentration mediated by release, re-uptake and degradation. Thus, to understand neural function in response to neuromodulators, it is necessary to study the dynamics of second messenger pathways and their effects on channel properties.

A technique to bridge this knowledge gap is computer modeling of the dynamics of second messenger pathways and their effects on membrane properties (e.g. Kotter et al. 1998; Kotter and Schirok 1999). Chemosis is software for modeling biochemical reaction pathways and is used in conjunction with GENESIS (Bower and Beeman 1998), a software program for neuronal modeling. Chemosis contains objects for describing enzyme reaction, stoichiometric reactions, diffusion, and ligand gating of channels. Creating models requires setting up the reaction pathways and assigning values for the

parameters using standard GENESIS commands. Chemiesis overlaps with Kinetikit, another set of GENESIS objects for simulating biochemical reactions, but Chemiesis also contains objects for diffusion and calcium release.

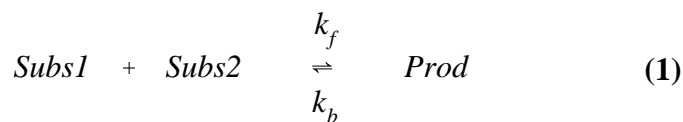
The details of biochemical reaction pathways and kinetic parameters are maintained in several enzyme databases accessible via the internet such as ExPASy (<http://www.expasy.ch/enzyme>) and BRENDA (<http://www.brenda.uni-koeln.de/>). For additional information it is necessary to refer to the original literature, much of which is published in the *Journal of Biological Chemistry*, <http://www.jbc.org/>. An explanation of how to extract reaction rate constants from the published experiments is provided in Chapter 10 of *The Book of Genesis* (Bower and Beeman 1998). Some of the neuron specific reaction pathways, with rate constants extracted from the literature, is provided in <http://doqcs.ncbs.res.in/>.

These databases, along with tools for modeling of biochemical reactions within compartmental models of neurons, allows the study of the dynamics of second messenger effects on neuronal function. The purpose of this chapter is to explain how to use Chemiesis to model second messenger pathways, and to integrate these models with traditional compartmental models.

2. FROM CHEMISTRY TO MATHEMATICS

2.1 Equations Governing Biochemical Reactions

Biochemical reactions are interactions between substrate molecules to form product molecules, e.g.:

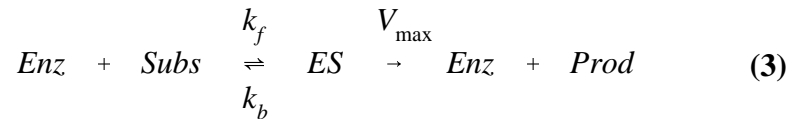


The rate of the reaction is given by the forward rate constant, k_f , that describes the frequency with which product is formed, and the backward rate constant, k_b , which describes the frequency with which the substrates are regenerated. The quantity of each species in the reaction is determined from differential equations, which describe the change in quantity (or concentration) with time.

$$\frac{dProd}{dt} = k_f \cdot Subs1 \cdot Subs2 - k_b \cdot Prod \quad (2)$$

A similar equation describes the change in substrate with time. These equations are commonly called “mass action kinetics”, because they describe the behavior of large groups of molecules, and ignore the probabilistic interactions between individual molecules. Conservation of mass implies that, on the time scale of the reactions, there is no change in the total quantity of a particular molecule. In the example above, this implies that substrate and product are two forms of the same molecule; thus, they sum to a constant.

Most second messenger pathways are described as a cascade of such biochemical reactions. For example, the product in reaction 1 may be the substrate for the next reaction. Enzyme reactions are a special type of two step reaction, in which the enzyme is regenerated (and product formed) in the second step with rate V_{max} . Furthermore, the backward reaction rate for the second step is zero:



Equations describing this cascade of two reactions are written as for the first reaction:

$$\begin{aligned} \frac{dES}{dt} &= k_f \cdot Enz \cdot Subs - (V_{max} + k_b) \cdot ES \\ \frac{dProd}{dt} &= V_{max} \cdot ES \end{aligned} \quad (4)$$

If the reaction has certain properties, i.e. the enzyme substrate complex (ES) rapidly reaches equilibrium, then it is said to exhibit Michaelis-Menton kinetics (Schulz 1994). Given that the amount of free enzyme is the difference between the total amount of enzyme (E_{tot}) and the ES complex, then the equations simplify to:

$$\frac{dProd}{dt} = \frac{V_{max} \cdot E_{tot} \cdot Subs}{Subs + K_M}, \quad \text{where } K_M = \frac{V_{max} + k_b}{k_f} \quad (5)$$

2.2 Equations for Other Processes Affecting Concentration

Not all changes to molecules can be described using these biochemical reactions. In particular, movement of ions between compartments cannot be described using bimolecular reactions. One type of ion movement is flow from the extracellular space into the cell interior through channels such as the voltage gated calcium channel. This ion movement is described in terms of current flow, $I_{Ca}(V_M)$, with units of amperes. To determine the change in calcium per unit time (flux) produced by a given current flow, the following equation is used:

$$\Phi_I = \frac{-I_{Ca}(V_M)}{2 F} \quad (6)$$

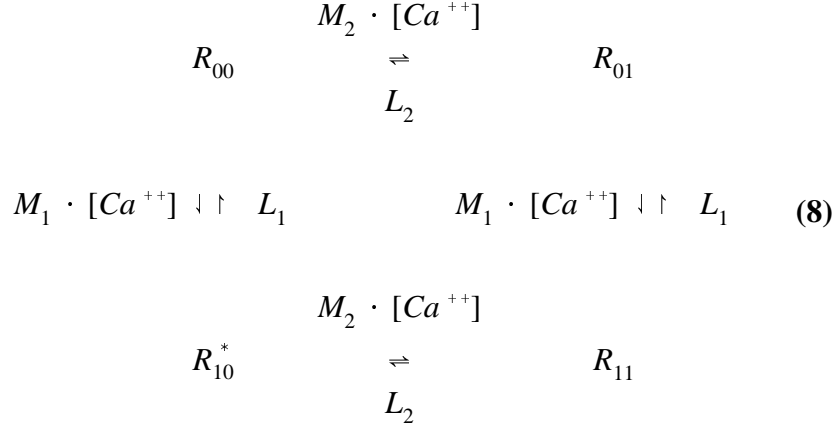
where F is Faraday's Constant, which specifies the moles of an ion per coulomb (charge), and Φ_I is the flux due to current flow.

A second type of movement is flow from the endoplasmic reticulum (ER) to the cell interior through calcium release channels. Similar to the flow of ions across ionic channels, the flow of ions across the membrane is governed by the permeability of the channel, and the driving force or difference between the inside and outside concentration. In contrast to the flow of ions across ionic channels, it is assumed that there is no potential difference between these compartments.

$$\Phi_R = P \cdot X_{open}^n \cdot ([Ca_{ER}^{++}] - [Ca^{++}]) \quad (7)$$

P , permeability of channel, is in units of volume/time; X_{open} is the open state of a calcium release channel, such as the ryanodine sensitive or IP_3 sensitive release channels, both of which depend on calcium concentration; n is an integer indicating how many independent subunits control the open state, and $[Ca_{ER}^{++}]$ $[Ca^{++}]$ are the calcium concentration in the ER and cytoplasm, respectively.

There are several models describing open state as a function of IP_3 and calcium. According to the model of the ryanodine receptor (RyR) channel (Tang and Othmer 1994), the RyR may reside in one of four different states, depending on the occupancy of the two calcium binding sites. The open state (R_{10}^*) occurs when the excitatory site is bound. There are three closed states, occurring when either both calcium binding sites are unoccupied (R_{00}), the inhibitory calcium binding site is occupied (R_{01}), or both calcium binding sites are occupied (R_{11}):



where M_1 , M_2 , L_1 and L_2 are reaction rate constants.

Yet a third type of ion movement is diffusion from a region of high concentration to a region of low concentration. The latter does not really occur between compartments, but when modeling spatially extended structures, it is convenient to conceptualize such a structure as a series of discrete well-mixed compartments. I.e. within the compartment, no concentration gradients exist, and all the concentration gradient exists between adjacent compartments. This approximation of a spatially extended structure as a series of isoconcentration compartments is identical to that made for dendritic and axonal cables. The flux of ions between these pseudo compartments depends on the concentration gradient between compartments, the calcium diffusion coefficient (D_{Ca}) and also the geometry of the compartment. Thus, diffusional flux, Φ_D , increases with an increase in surface area ($area_j$) connecting compartments, and decreases as the length (distance separating the centers, $dist_j$) of compartments increases:

$$\Phi_D = -D_{Ca} \sum_j \frac{area_j ([Ca^{++}] - [Ca_j^{++}])}{dist_j} \quad (9)$$

where the summation is over all adjacent compartments, j . The form of this equation allows for two- and three-dimensional diffusion.

The change in calcium for a compartment is the sum of the fluxes due to release, Φ_R , diffusion, Φ_D , ionic current, Φ_I , and bimolecular reactions with buffers or other molecules, Φ_B :

$$\frac{dCa^{++}}{dt} = \Phi_R + \Phi_D + \Phi_I + \Phi_B \quad (10)$$

3. HOW TO USE CHEMESIS OBJECTS

Chemesis is a library of objects written in the GENESIS programming language (Bower and Beeman 1998) for use with GENESIS simulations. It can be downloaded from <http://www.krasnow.gmu.edu/avrama/chemesis.html>. A makefile is provided with instructions on compiling and installing the software on various UNIX platforms. Chemesis has objects for modeling the types of ion movement and biochemical reactions described above. Most second messenger pathways are described as a set of biochemical reactions, with diffusion of one or more species between compartments. The biochemical reactions are modeled using four Chemesis objects: rxnpool, conservepool, reaction, and enzyme; diffusion is modeled with an object called diffusion. For molecules such as calcium, which can flow into the cytosol through release channels in the ER, there are several additional objects: mmpump, cicr, and cicrflux. The following section explains the computations performed by each of these objects and their use with GENESIS commands.

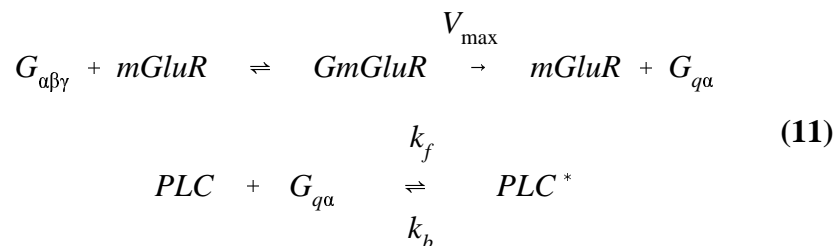
3.1 Chemesis Objects for Bimolecular Reactions

Chemesis has two objects to keep track of the quantity and concentration of molecules. One of them is called rxnpool; the other is called conservepool. rxnpool accumulates the changes to molecule quantity due to various reactions, diffusion, etc. It then computes quantity from the equation $dC/dt = \sum A - \sum B \cdot C$, where A represents a change in quantity due to a reaction or other ion movement, and B represents a rate of change, e.g. degradation, which is proportional to the present quantity. The summation is over all processes that affect the quantity of the molecule, C. Conservepool is used to calculate the quantity and concentration of a molecule as the remainder after all other forms are accounted for: $C = C_{tot} - \sum C_i$.

Chemesis has two objects for biochemical reactions. One is called reaction; the other is called enzyme. Reaction takes as input the concentration or quantity of substrates and products (an arbitrary number of substrates and products can be specified), and calculates the rate of the forward reaction: the forward rate constant times the substrates, and the rate of the backward reaction: the backward rate constant times the products. Enzyme implements equation 5: it takes as input the concentration of substrate and enzyme, and calculates the

change in the product molecule due to the enzyme reaction.

Standard GENESIS commands (Bower and Beeman 1998) are used to create a simulation of biochemical reactions. These commands are illustrated using the enzyme reaction that occurs after glutamate binds to the metabotropic glutamate receptor (mGluR) and catalyzes the production of the GTP bound form of the $G_{q\alpha}$ subunit, and the bimolecular reaction of active $G_{q\alpha}$ binding to PLC to activate it (Bockaert et al. 1993; Pin et al. 1994).



1. Create pools of molecules using the GENESIS command *create*. The syntax for this command is: `create object_name element_name`

```

create rxnpool mGluR
create rxnpool Gqa
create conservepool Gprot /* for Gαβγ */
create conservepool PLCtot /* for PLC */
create rxnpool PLCstar

```

2. Create bimolecular and enzyme reactions using *create*:

```

create reaction react1
create enzyme enz1

```

3. Assign parameter values such as rate constants, compartment volumes (to calculate concentration from quantity and vice versa), and initial quantities using the genesis *setfield* command. The syntax for this command is: `setfield element_name field_name value`

```

setfield PLCstar volume 1e-15 Qinit 0
setfield react1 kf {kfvalue} kb {kbvalue}

```

In this command you have the option of specifying the value, or specifying a variable, in curly brackets, which has been given the value in an assignment statement: `kfvalue = 3.5`

4. Send molecule concentrations to the reactions using the GENESIS command *addmsg*. The syntax for this command is:

addmsg sending_object receiving_object message_type field_name

```
addmsg PLC react1 SUBSTRATE conc
addmsg Gqa react1 SUBSTRATE conc
addmsg PLCstar react1 PRODUCT conc
```

```
addmsg mGluR enz1 ENZYME conc
addmsg Gprot enz1 SUBSTRATE conc
```

5. Send the results of these calculations back to the rxnpools, for them to calculate their concentrations:

```
addmsg react1 Gqa RXN2 kbprods kfsubs
addmsg react1 PLCstar RXN2 kfsubs kbprods
```

```
addmsg enz1 Gqa MMPUMP kbprods
```

6. Last, send the messages to conservpool so it can calculate the amount of free substrate

```
addmsg Gqa Gprot CONC conc
addmsg PLCstar PLCtot CONC conc
addmsg PLCstar Gprot CONC conc
```

These commands implement the following equations:

$$\frac{dG_{qa}}{dt} = \frac{V_{\max} \cdot mGluR \cdot G_{\alpha\beta\gamma}}{G_{\alpha\beta\gamma} + K_M} - k_f \cdot PLC \cdot G_{qa}$$

$$\frac{dPLC^*}{dt} = k_f \cdot PLC \cdot G_{qa} - k_b \cdot PLC^* \quad (12)$$

$$G_{\alpha\beta\gamma} = G_{prot} - G_{qa} - PLC^*$$

$$PLC = PLC_{tot} - PLC^*$$

To run the simulation standard GENESIS commands are used: *reset*, to initialize everything, then *step n*, to run the simulation for *n* time steps. The size of the time step is adjusted using the *setclock* and *useclock* commands.

3.2 Chemesis Objects for Diffusion and Flux Through Membranes

Chemesis has several objects for computing the flux between compartments. One object, called `mmpump`, is for calculating the amount of calcium (or optionally any other ion) pumped out of the cytosol by voltage independent pumps. This object implements the following equation:

$$\Phi_P = \frac{V_{pump} \cdot [Ca^{++}]^n}{[Ca^{++}]^n + K_D} \quad (13)$$

where n is the Hill coefficient, K_D is the concentration at which the pump rate is half maximal, and V_{pump} is the maximal rate of the pump. A second object is `diffusion` and implements Eqn 9. A third object, `cicrflux`, computes the flux across the membrane through a calcium release channel (Eqn 7). This object also can implement a constant flux, independent of channel state, such as a constant leakage. Lastly, the object `cicr` combines functions of both `rxnpool` and reaction to calculate the open state of calcium release channels. `Cicr` contain all the information about a single state of the release channel. It stores the reaction rates of the forward reactions, and calculates the fraction of molecules in that state. Both the model of De Young and Keizer (1992) for IP_3 induced calcium release (IICR), or Eqn 8 (Tang and Othmer 1994) for calcium induced calcium release (CICR) may be implemented with the `cicr` object.

Once again, standard GENESIS commands are used to create simulations of calcium dynamics. These commands are illustrated using a three compartment model of a soma with a single dendrite, and an ER compartment located within the soma compartment. The soma has a voltage dependent calcium channel. The ER has a ryanodine receptor channel and a pump. Calcium is free to diffuse from the soma to the dendrite.

1. It is necessary to specify the dimensions of the compartments, and compute the volume and various surface areas given a certain geometry. For spherical compartment, radius and surface area are specified. For cylindrical compartments, radius, length, outer surface area and side surface area are specified. In the following example, it is assumed that compartments are cylindrical. Furthermore, it is assumed that the ER volume is 0.185 times the soma volume. The syntax is: `type variable_name {= variable_value}` type can be either float, int (for integer) or str (for a string). The variable can be set to a value as part of the command, or with an assignment statement later.

```
float soma_rad = 6e-6
float soma_len = 12e-6
float soma_vol = PI · soma_rad · soma_rad · soma_len
float soma_SA = 2 PI · soma_rad · soma_len
float soma_side = PI · soma_rad · soma_rad
```

SI units are used in this and subsequent examples. A similar set of commands is required for the dendrite and ER compartments.

2. Create pools of calcium molecules and assign values to fields that specify geometry

```
create rxnpool somaCa
create rxnpool CaER
create rxnpool dendrite Ca
```

In this following command, the `\` is used to indicate a continuation of the command on the next line.

```
setfield somaCa volume {soma_vol} length {soma_len} \
  SAout {soma_SA} SAside {soma_side}
```

3. Create the diffusion object, set the value of the diffusion coefficient (in units of m^2/sec), and setup messages.

```
create diffusion dend_soma
setfield dend_soma D 0.006
```

The diffusion object expects two incoming messages, one from each of two adjacent compartments. Each message must contain three values: the concentration of the compartment, the area of the shared surface, and the length of the compartment. If the two adjacent compartments have different areas, the diffusion object uses the mean value of the two areas. The distance between two adjacent compartments is assumed to be the distance between the centers of the compartments, which is the mean of their lengths.

```
addmsg somaCa dend_soma CONC1 Conc SAside length
addmsg dendCa dend_soma CONC2 Conc SAside length
```

The diffusion object sends messages back to each compartment:

```
addmsg dend_soma somaCa DIFFUSION difconc2 difconc1
```

```
addmsg dend_soma dendCa DIFFUSION difconc1 difconc2
```

These messages have the values of flux within them, and are used by rxnpool to compute the new concentration. The two different pools get opposite messages because diffusion causes an increase in the concentration of one pool and a decrease in the concentration of the other.

4. Create an mmpump from the cytosol to the ER to represent the smooth endoplasmic reticulum Calcium-ATPase (SERCA). The mmpump formulation has the undesired side effect of eventually reducing calcium concentration to zero. To compensate, it is assumed that there is a slow leak of calcium from the ER, which is equal and opposite to the pump rate when calcium concentration is at its rest level. Thus, both an mmpump and a cicrflux (with a constant flux rate) are created:

```
create mmpump SERCA
setfield SERCA power 2 half_conc 0.1e-3 max_rate {Y}

create cicrflux leak
setfield leak maxflux {X} power 1
```

In this case Y is the maximal rate of pumping by the SERCA pump, and X is the permeability of the leak channel, and is calculated from the equation:

$$X = \frac{Y \cdot [C_{rest}^{++}]^2}{[C_{rest}^{++}]^2 + 0.0001^2} \quad (14)$$

where $[C_{rest}^{++}]$ is the resting value of calcium concentration, 0.0001 mM is the half concentration of the pump, and the factor of 2 is the power of the pump.

The mmpump object expects one incoming messages from the soma cytosolic compartment. It sends messages back to the soma, because it decreases the concentration in the soma, and to the ER, because it increases concentration in the ER. The leak object expects three incoming messages, one for soma cytosolic calcium, one for ER calcium, and one for open fraction. Sending the value of 1.0 indicates that permeability is constant. The leak sends messages back to the soma and ER using the rxnpool message DIFFUSION, because the values it sends have the same effect on concentration as a diffusion object.

```
addmsg somaCa SERCA CONC Conc
```

```
addmsg SERCA somaCa MMPUMP moles_out
addmsg SERCA CaER MMPUMP moles_in
```

```
addmsg somaCa leak CONC1 Conc
addmsg CaER leak CONC2 Conc
addmsg somaCa leak IP3R 1
addmsg leak somaCa DIFFUSION fluxconc2 fluxconc1
addmsg leak CaER DIFFUSION fluxconc1 fluxconc2
```

5. Set up calcium induced calcium release through the RyR channel by creating four calcium release objects, one for each state of the RyR. The commands for creating the R_{00} state are illustrated. Commands for the other three states are the same. The fields *alpha_state*, *beta_state* and *gamma_state* take values of 0 or 1, corresponding to the 0 or 1 subscripts in Eqn 8. *Alpha*, *beta* and *gamma* are the forward rate constants, M_1 and M_2 in Eqn 8. Both *alpha_state* and *alpha* are unused (i.e. 0) for the RyR, but they are used for the IP_3 receptor. The field *conserve* indicates whether this state is computed as 1 - sum of other states. *xinit* is the initial value.

```
create cicr R00
setfield R00 alpha_state 0 beta_state 0 gamma_state 0 \
alpha 0 beta {M1} gamma {M2} conserve 0 xinit {init00}
```

Each of the four states sends a message to the states to which it transitions containing the value of the backward rate constant of the transition and the fraction of channels in that state.

```
addmsg R10 R00 BSTATE beta fraction
addmsg R01 R00 GSTATE gamma fraction
addmsg R00 R10 BSTATE beta fraction
addmsg R11 R10 GSTATE gamma fraction
addmsg R11 R01 BSTATE beta fraction
addmsg R00 R01 GSTATE gamma fraction
```

The state which is conserved receives the message CONSERVE from all other states, e.g.:

```
addmsg R00 R11 CONSERVE fraction
```

In addition to these messages, each of the non-conserved states needs a calcium concentration message from somaCa, e.g.:

```
addmsg somaCa R00 CALCIUM Conc
```

Lastly, a `cicrflux` object is created to calculate the calcium flux from the ER to the soma. It requires messages not only from the `somaCa` and `CaER` objects, but also from the `R10` object, which is the open state of the channel.

```
create cicrflux ryanflux
setfield ryanflux power {expon} maxflux {maxcond}
```

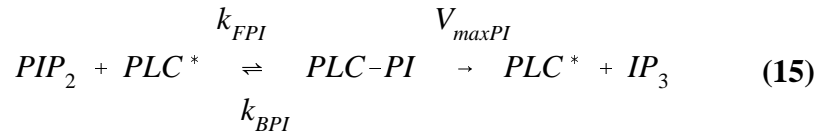
```
addmsg somaCa ryanflux CONC1 Conc
addmsg CaER ryanflux CONC2 Conc
addmsg R10 ryanflux IP3R fraction
```

```
addmsg ryanflux somaCa DIFFUSION fluxconc2 fluxconc1
addmsg ryanflux CaER DIFFUSION fluxconc1 fluxconc2
```

Combining ion movement such as diffusion with biochemical reactions makes it possible to model and simulate any second messenger pathway. The effect of second messengers on ionic channels, such as ligand gated or modulated channels, can be modeled by sending messages from the second messenger `rxnpool` to a GENESIS channel object.

4. EXAMPLES

The utility of Chemesis is illustrated with simulations of IP_3 production after stimulation of a metabotropic receptor on the head of a Purkinje cell spine (Finch and Augustine 1998). The biochemical reactions include those in Eqn 11, plus production of IP_3 from the active PLC enzyme acting on PIP_2 :



Degradation of IP_3 is included, and the equation describing Eqn 15 includes a volume term in the denominator to convert quantity to concentration:

$$\frac{d[IP_3]}{dt} = \frac{V_{maxPI} \cdot PLC^* \cdot [PIP_2]}{vol \cdot ([PIP_2] + K_{M-PI})} - D_{IP_3} \cdot [IP_3] \quad (16)$$

Figure 1 illustrates the change in concentration of (A) bound mGluR, (B) $G_{q\alpha}$, (C) PLC* and (D) IP_3 in response to a single action potential and a short sequence of action potentials, each releasing a single vesicle of glutamate. Notice that IP_3 production is considerably slower than $G_{q\alpha}$ production and the contribution of individual vesicles is not visible.

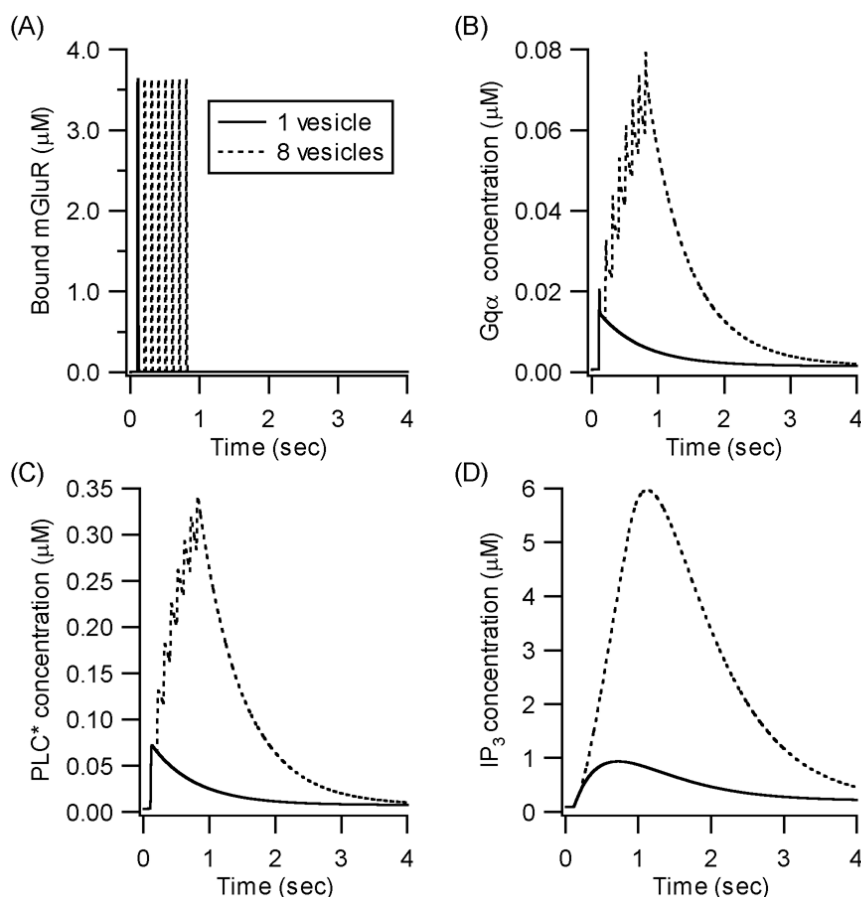


Figure 1 Concentration of molecules in biochemical reactions leading from mGluR activation to IP_3 production

Using ChemoSis to Model Calcium Dynamics

ChemoSis is not limited to single compartment models. Spatially extended structures may be modeled as a series of rxnpool compartments which communicate with each other via diffusion objects and with an ER via calcium release objects. ChemoSis has been used to create multicompartment models to investigate calcium dynamics in classical conditioning (Blackwell 2002).

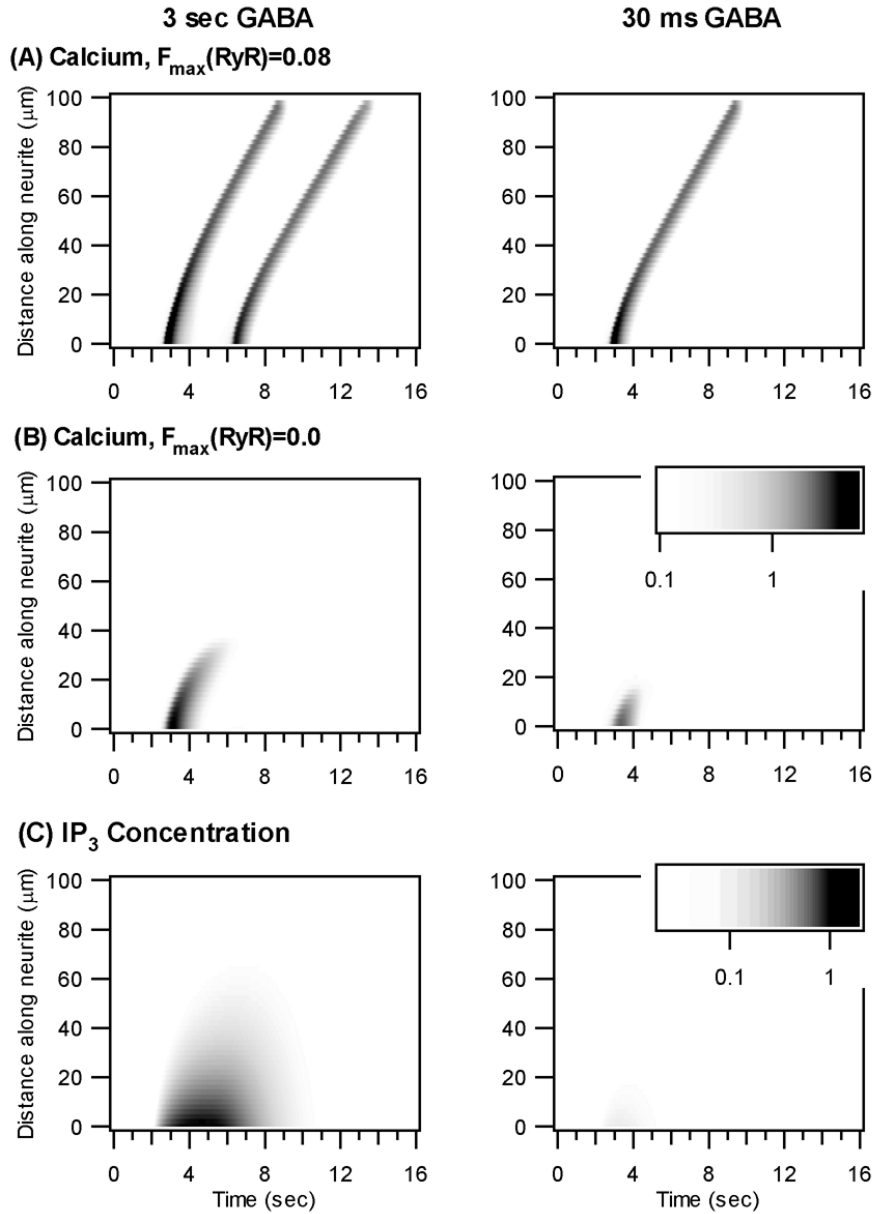


Figure 2 Calcium concentration (A and B) and IP_3 concentration (C) along type B photoreceptor neurite in response to GABA stimulation of terminal branches. Inset shows the concentration in μM corresponding to the gray shade of the figures.

The sea slug, *Hermissenda crassicornis*, is an animal model of classical conditioning and learns to associate light (the conditioned stimulus) with turbulence (the unconditioned stimulus). The memory of the association is

stored in the type B photoreceptors and critically depends on an elevation of intracellular calcium concentration. Turbulence causes hair cells to release GABA onto the terminal branches of the type B photoreceptor and may produce a wave of calcium that propagates from the terminal branches to the soma. Chemesis objects were used to construct a model to determine if GABA stimulation can contribute a calcium signal that propagates along the 100 μm neurite separating the terminal branches from the soma. The model included the second messenger pathways from GABA stimulation to IP_3 production, and included release of calcium from stores through IP_3R and RyR channels. The neurite was divided into 100 isoconcentration compartments of 1 μm length.

Fig 2 illustrates the calcium concentration along the neurite in response to a 3 s (Left) and 30 ms (Right) GABA stimulation. The calcium wave propagates the entire length when RyR channels are present (A). With only IP_3R channels, the calcium wave does not propagate the entire distance (B), but only propagates the distance that IP_3 diffuses (C). Even a 30 ms GABA stimulus produces sufficient IP_3 to initiate a calcium wave.

To analyze the effect of calcium or IP_3 on membrane channels, the *addmsg* command is used to provide the second messenger concentration to a ligand gated channel, such as a calcium dependent potassium channel. Similarly, an *addmsg* command, from the calcium current to the calcium concentration rxnpool allows the traditional compartmental model to influence the second messenger pathway. Thus, the integration of second messenger pathways into GENESIS multi-compartmental neuronal models (Kotter and Schirok 1999), is extended and facilitated by using Chemesis.

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