How does the level of GABA in the synapse affect the rate of receptor binding and thus affect the depth of anesthesia a person may feel?

by

Maarika Teose

Wilson High School

(Systems Dynamics Class)

May 19, 2003

Systems Dynamics Advisor: Diana M. Fisher

Mathematics Department

Wilson High School

Portland, OR

Outside Advisor:

Edward J. Gallaher, Ph.D.

Associate Professor
Behavioral Neuroscience MQ280
Oregon Health and Science University
Portland, OR 97201

Introduction

General anesthesia is tricky. Doctors have been using it in operations and medical procedures since the early eighteen hundreds, but despite our technological and medical advances since that time, little more is known about it today than back then. Its effects are measurable, but it's impossible to know exactly what anesthesia does on the cellular level. Anesthesiologists have many theories on how anesthesia affects the nervous system, but even after years of research and testing, nothing has been proven.

It is generally agreed that general anesthesia affects the receptors on a neuron's dendrites. Exactly how the receptors are affected – whether they're activated for longer, whether more of them are open, whether they're closed – no one knows.

One of these theories suggests that anesthesia affects the amount of receptors that become activated, and that the activation of these receptors triggers a release of dopamine into the body, which then sedates the person.

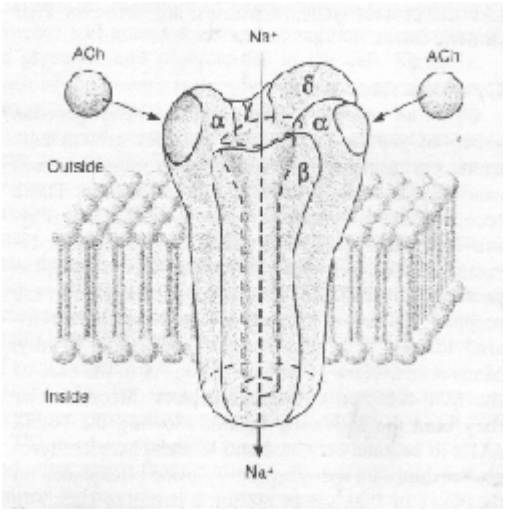


Figure 1: A receptor, also known as a ligand-gated ion channel.

Before modeling the effect of anesthesia on the body, though, it is necessary to model how receptors and neurotransmitters interact when there is no outside influence. A basic

model describing the interaction between GABA (a neurotransmitter) and receptor binding and activation would also be useful to others interested in more than simply anesthesia. Several drugs affect various steps of the neurotransmitter-receptor process, and the specific components connected with these specific drugs can be added and removed from the basic model.

Process of Model Building

At first, I was only interested in the effects of general anesthesia, and was unaware of how the interaction between receptors and neurotransmitters was integral to my topic. My first, rough model focused on the amount of anesthesia in the body, and what variables affected the level of anesthesia in the blood stream.

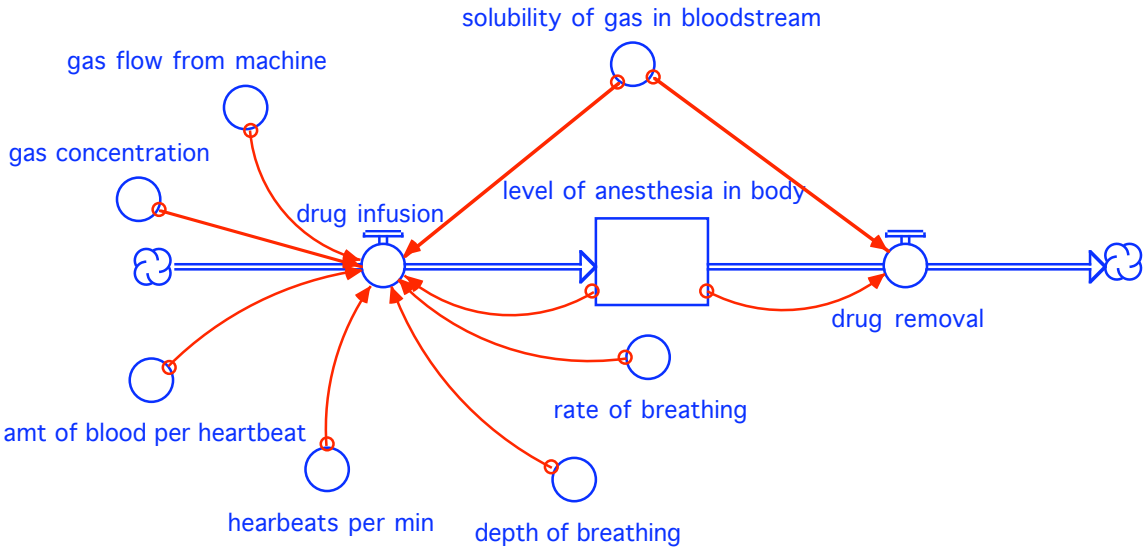


Figure 2: Variables affecting level of anesthesia in body.

As I met and began to talk with my contact, Dr. Edward Gallaher from Oregon Health Sciences University, I realized that before I could even begin to model the effects of anesthesia, I needed to understand that, as a drug, anesthesia affected the normal functioning of neurons. Before deciding which theory to follow, though, I began modeling the interaction between GABA and receptors. The first step in modeling this interaction was to model how GABA was released into and drained from the synapse.

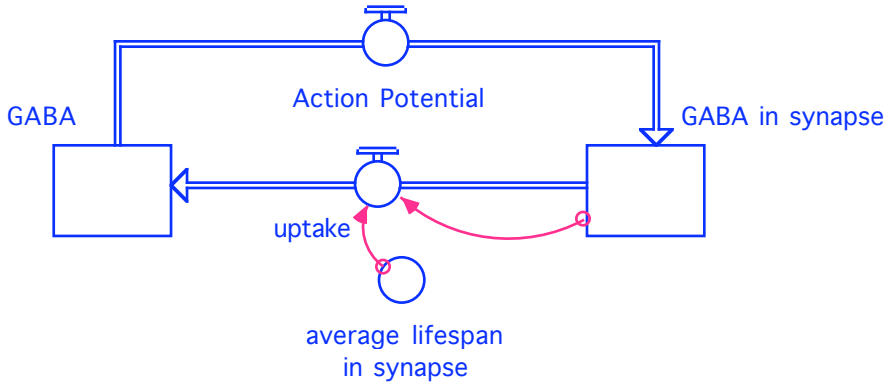


Figure 3: Two-state equilibrium between GABA and GABA_in_synapse

To make the model more conceptual and more accurate, I set up a three-state equilibrium between unbound, bound, and active receptors.

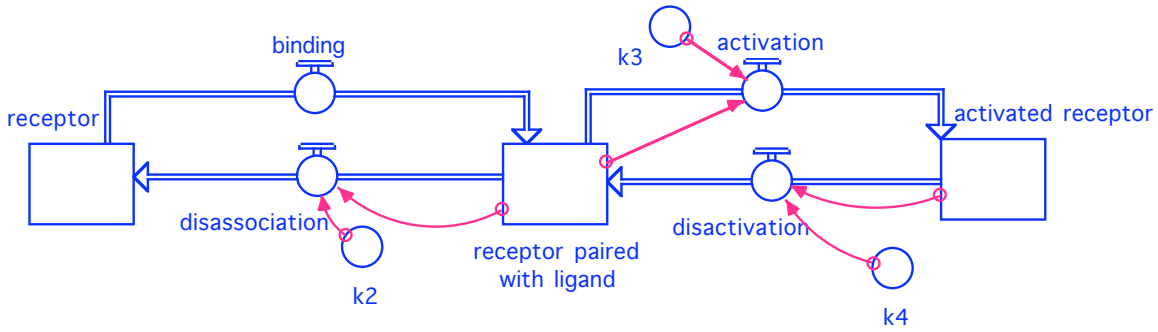


Figure 4: Three-state equilibrium between receptor, receptor_paired_with_ligand, and activated_receptor

As I continued to work on my model, I realized that while the anesthesia component of the model was important to me, modeling the interaction between GABA and receptors was taking priority. Thus, my understanding of how anesthesia affected the body began to come from understanding the way neurotransmitters and receptors interacted.

To connect the two structures – that is, the GABA component and the receptor states component – I first attempted to use a graphical converter to affect the value of k_effective. K_effective is the rate constant that determines how fast receptors become bound, and it depends on the GABA component. I based my graphical converter on the ratio between the number of GABA molecules in the synapse and the number of free receptors.

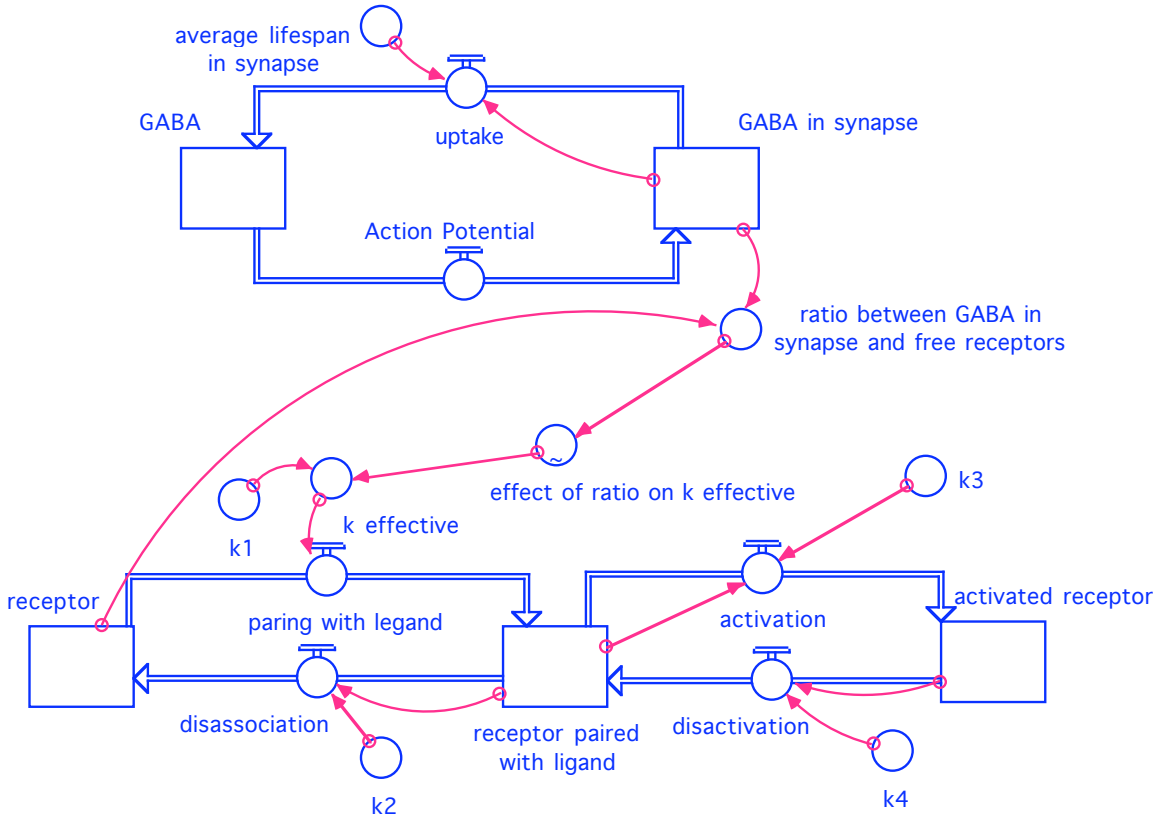


Figure 5: GABA component linked to receptor component via a graphical converter

This method of connecting the GABA component and the receptor component was cumbersome and inaccurate, though, so a simpler and more intuitive connection was in order. Instead of using the actual number of GABA molecules in the synapse to affect k_effective, the molar concentration of GABA in the synapse would affect k_effective more accurately. For this to work properly, though, the volume of the synapse needed to be added to the model. As soon as these changes were made, the model was complete and working properly.

The Finished Model and How It Works

(Of Butterflies and Neurotransmitters)

Explaining the interaction between neurotransmitters and neurons is next to impossible without using highly sophisticated terminology that is completely alien to most people. Instead of trying to explain these concepts using science, it would be better to come up with an analogy that can be grasped easier.

Say that you have an enormous, enclosed space such as an indoor stadium. In this stadium, there are one thousand people spaced apart evenly and waiting quietly. Beside each person, there are two buckets full of beads – one of these buckets is filled mostly with white beads and a handful of blue beads, and the other bucket is filled mostly with white beads and a handful of red beads. Each person also has a hat, but no one is wearing a hat at the start of the experiment.

Next, ten thousand butterflies are released into the stadium. These butterflies are quite tame and are not afraid of humans, so if one of these butterflies comes near a human, it will perch on their outstretched finger. Through prior research, the average "perch time" of a butterfly had been determined, and on average, after this time has elapsed, the butterfly will take flight again.

The people in the stadium are given these instructions: if a butterfly lands on your finger, immediately begin picking beads out of the bucket with the blue beads at a rate of one every five seconds. Only pick beads from the bucket while the butterfly is on your finger; if the butterfly takes flight while you're still picking beads from the bucket with blue beads, stop picking beads. If you pick a white bead, don't do anything. If, however, you pick a blue bead, immediately put on a hat. Once you are wearing your hat, switch to picking beads out of the bucket with the red beads at a rate of one every five seconds. If you pick a white bead, don't do anything, but if you pick a red bead, remove the hat. If,

after removing the hat, the butterfly is still perched on your finger, begin picking beads out of the bucket with the blue beads again.

The butterflies are genetically altered in a way that makes them very comfortable around people wearing hats. If a butterfly lands on a person's finger, and the person dons a hat before the butterfly leaves, the butterfly will not leave as long as the person is wearing a hat. In other words, it is not possible to have a person wearing a hat without a butterfly on their finger.

At the very beginning of the experiment – as soon as you release the butterflies – you turn on a bright light in a corner of the stadium which attracts the butterflies. Gradually, the amount of butterflies flying around in the stadium decreases as they make their way to the bright light, and after one hour, there are no more butterflies flying around in the stadium. You gather the butterflies around this light and save them for reuse. After a period of two hours from the start of the experiment, you release another ten thousand butterflies into the stadium and the process begins again.

This analogy, as cumbersome and fantastical as it is, is a wonderful way to describe how neurotransmitters and receptors interact. The enormous but enclosed space of the stadium stands for the synapse between neurons. Each butterfly represents a GABA particle, so the number of butterflies per cubic foot of stadium is the concentration of GABA in the synapse. Each person is a receptor. A person without a butterfly is an unpaired receptor, a person with a butterfly but no hat is a paired, inactive receptor, and a person with a butterfly and hat is a paired, activated receptor.

In actual neurotransmitter-neuron interaction, the GABA particles are released according to action potentials (electrical signals that travel along a neuron's axon). These action potentials occur in a random fashion instead of at regular intervals, so the concentration of GABA in the synapse fluctuates according to these action potentials. In terms of the analogy, instead of always waiting two hours before releasing a new batch of butterflies

into the stadium, you would release them at random time intervals between, say, ten minutes and five hours.

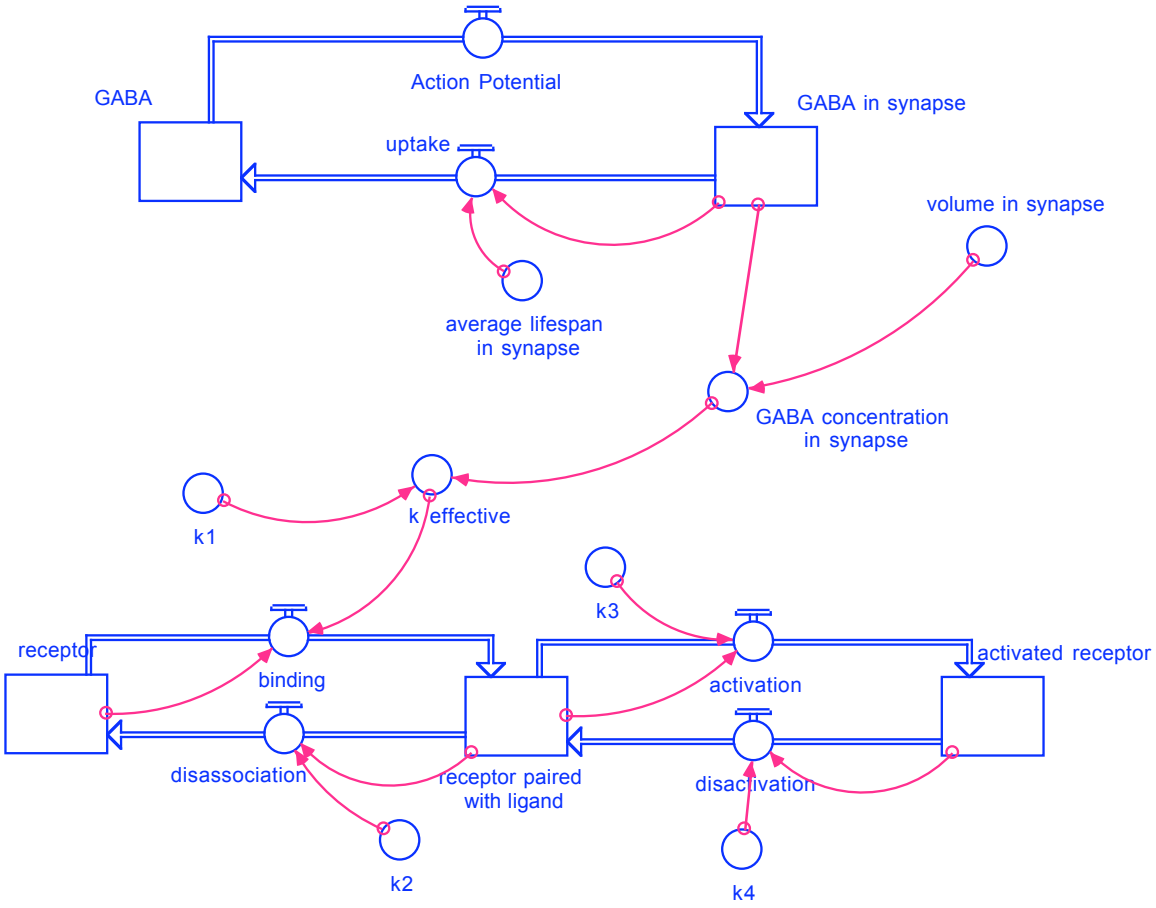


Figure 6: Finished model showing how GABA affects receptor activity

My model begins with the GABA component. Immediately, another discrepancy between the analogy and my model arises. In my model, GABA is not measured in individual molecules; instead, it is measured in moles. At a neuron's terminal, there is a virtually unlimited supply of GABA. Similarly, the number of moles of GABA in the first stock is so large that GABA will never "run out". This GABA is depleted from the terminal and released into the synapse according to action potentials in that neuron. The amount of GABA released per action potential in my model is 10^{-14} moles. In order to simulate action potentials and incorporate the random time intervals between action potentials, the Action Potential flow is a PULSE command that sends 10^{-14} moles of GABA from the terminal into the synapse every 50 to 1000 milliseconds. Thus, the basic equation for the

Action Potential is PULSE(10^{-14}, 0, RANDOM(50,1000)). I have confidence in this equation because the pulse command with the random component makes sense: every time an action potential occurs, the same amount of GABA is released, but the time interval between action potentials is random.

As soon as GABA enters the synapse, the terminal of the nerve begins to "suck" GABA back into the terminal. This part of the process corresponds with the release of the butterflies and their gradual migration to the bright light. In my model, the rate of uptake depends on the number of moles of GABA in the synapse and on the average amount of time the GABA remains in the synapse: "life span" of the GABA in the synapse. The GABA removed from the synapse by this uptake is returned back into the original GABA stock. This corresponds to gathering the butterflies and saving them for later use in the analogy.

The other major component of my model is the receptor binding and activation component. Conceptually, it is much easier to understand if the process of binding and activation is broken up into separate, distinct steps.

Recall the analogy. The people in the stadium represent the receptors, and the butterflies are GABA particles. There are three distinct states that a person can have; no butterfly and no hat, butterfly and no hat, or butterfly and hat. Similarly, a receptor can be either free (not bound to a GABA particle) and inactive, bound to a GABA particle but inactive, or bound and active. In the analogy, the rate of binding (having a butterfly land on an outstretched finger) is dependent on how many butterflies there are in the stadium. The more butterflies per square foot, the more likely it is for one of them to land on an outstretched finger. It is the same in my model. In general, the more GABA there is in the synapse, the more likely it is that a GABA particle will bind to a receptor.

In the analogy, after a butterfly lands on a person's finger, he/she begins picking beads out of a bucket. Much of the time, the person does nothing, but when a blue bead is chosen the person puts on a hat. The rate at which a person puts on a hat depends on how

many blue beads there are compared to how many white beads. The more blue beads there are compared to white beads, the greater the probability the person will put on a hat. This corresponds to k3 in my model. In my model the value for k3 is constant, but in reality, it fluctuates around the constant value. If the value for k3 were to increase, the bound receptors would become activated faster. The idea is the same in the other direction too. When the person is wearing a hat and picking beads again, the amount of red beads compared to white beads determines how fast he/she will take the hat off. Similarly, if k4 became larger, the rate at which activated receptors become inactive would increase.

When a person has a butterfly on his/her outstretched finger (and is not wearing a hat), the rate at which the butterfly will take flight again depends on how probable it is for the butterfly to take flight again. If this probability were to increase, the butterfly would take flight and "unbind" the person faster. This probability is reflected in k2, which, if it were to increase, would cause bound receptors to become unbound at a faster rate.

The GABA and receptor components are connected in a deceptively simple but very important manner. I said earlier that in general, the more GABA there is in the synapse, the more likely it is that a GABA particle will bind to a receptor. This is not entirely true. In fact, as the GABA concentration (molarity) in the synaptic fluid increases, the rate at which receptors will bind to GABA particles will increase. To take this into account, the liquid volume of the synapse needs to be defined. Once this is done, the moles of GABA in the synapse must be divided by the volume of the synapse to find the concentration: GABA_in_synapse/volume_of_synapse {molarity}.

K1 is unlike the other rate constants in the receptor component. The units are (1/mol*msec). In order to incorporate the GABA concentration into the receptor component, k1 is multiplied by the GABA concentration to yield k effective. Thus, if the GABA concentration increases, k effective increases, and receptors become bound at an increased rate.

In truth, all of the other rate constants (k2, k3, and k4) are already k effectives of other components that I have not included. For the sake of simplicity, I have only modeled the process for k1.

The Model Feedback and Loop Story

The first critical feedback loop occurs between GABA_in_synapse and uptake. As the amount of GABA_in_synapse increases, the uptake increases. This causes the amount of GABA_in_synapse to decrease. Thus, it is a balancing feedback loop. This is a very important feedback loop for the rest of the system because GABA_in_synapse affects the receptor component of the model; as GABA_in_synapse increases, the amount of receptors that become bound with a GABA particle increases.

The next feedback loop occurs between the receptor stock and the binding flow. As binding increases (due to a changing k effective), the number of receptors decreases, which causes the binding to decrease. This is another balancing feedback loop. It affects other parts of the model since receptor_paired_with_ligand directly depends on binding, and activated_receptor depends on receptor_paired_with_ligand. Unless receptors become bound, they cannot become activated.

Another critical feedback loop includes receptor_paired_with_ligand, activation, activated_receptor, and disactivation. As receptor_paired_with_ligand increases, activation increases, which causes disactivation to increase, which causes receptor_paired_with_ligand to increase. This is a positive, reinforcing feedback loop because the increase of one causes an increase of all the others. This loop affects the rest of the receptor component, because receptor_paired_with_ligand is part of a similar feedback loop with receptor.

The Model Boundaries

In order to make my model useable, I assumed that GABA was the only neurotransmitter to affect k_effective. I also assumed that the other rate constants (k2, k3, and k4) did not change over the course of the simulation. In actuality, each rate constant varies according to other components that I have not included in my model.

Along with these major modeling assumptions, I made several smaller assumptions regarding the values of stocks and converters. First, the initial values for the GABA and receptor stocks are educated guesses instead of scientifically accurate values. Values for some of the converters are educated guesses as well, such as the average lifespan of GABA in the synapse, the volume of the synapse, and the values of k2, k3, and k4. Finally, the specs for the RANDOM function in the action_potential flow are assumptions; action potentials in real life can occur much more often than 50 milliseconds.

In fact, the time specs for the entire model are a bit skewed. In the same way that the butterfly experiment lasts a very, very long time compared to my model, my model operates much slower than the actual process. My model operates over a course of 10,000 milliseconds (that is, 10 seconds). In actuality, neurotransmitters are binding and activating receptors at a much faster rate than my model suggests. The reason I have "stretched out" the process in my simulation is the same reason I "stretched out" my simulation into the butterfly analogy – so that the observer /reader has time to comprehend and understand the process. So while my model may not be scientifically accurate, the concepts that it depends on and encompasses come across very strongly, which I feel is more important.

Another scientifically inaccurate time component of my model that I justify by valuing understanding over accuracy is that of the time window during which action potentials can occur. It is important to show that the system is stable before the introduction of

action potentials in order to be certain that the only thing affecting a change in the system is the release of GABA into the synapse. This time period before the introduction of action potentials is T=0msec to T=1000msec. Similarly, after action potentials have disrupted the system for a short period of time, I chose to disallow action potentials so that the system could return to the equilibrium state. This time period is T=3000msec to T=10,000msec. Thus, the equation for the action potential flow is an IF, THEN, ELSE statement dependent on time. In short, if TIME is between 1000msec and 3000msec, then the action potential flow becomes the PULSE command at RANDOM time intervals.

Model Testing

K1 is a known value that has been found through experimentation; this value is about 10^{-6} per mol*msec. First off, in order for the rate constant of k_effective to be in the correct units, I needed to have a concentration (moles). I also wanted k_effective to be around .01 so that it would match better with the other rate constants. For this to work, though, the concentration must stay around 10^{-8} mol; this way, when the concentration and k1 are multiplied, they give a value of around .01 per msec. When I run the model, I find that the GABA_concentration_in_synapse stays between 0 and 20^{-8}, and that k_effective stays between 0 and .02. This means that the most important part of the model – the part that connects the GABA component and the receptor component – is working properly.

The overall behavior of the model corresponds with the reference behavior as well. The GABA and receptor components work correctly both separately and together. The moles of GABA in the synapse increases with each action potential, and decreases steadily according to the amount of GABA in the synapse and the average lifespan in the synapse until the next action potential kicks the value up again. The receptor component displays intuitive and correct behavior as well. When the number of free receptors decreases, the number of paired receptors and activated receptors increase. The feedback loops are accurate and make sense.

For the purpose of exercising my model, I have to remove the RANDOM element so that I will be able to reproduce the same situation each time I run the model. Instead of having the action potentials occur randomly between a time interval, I change it to a fixed time interval of 500msec. Now I have a predictable system, and can exercise it.

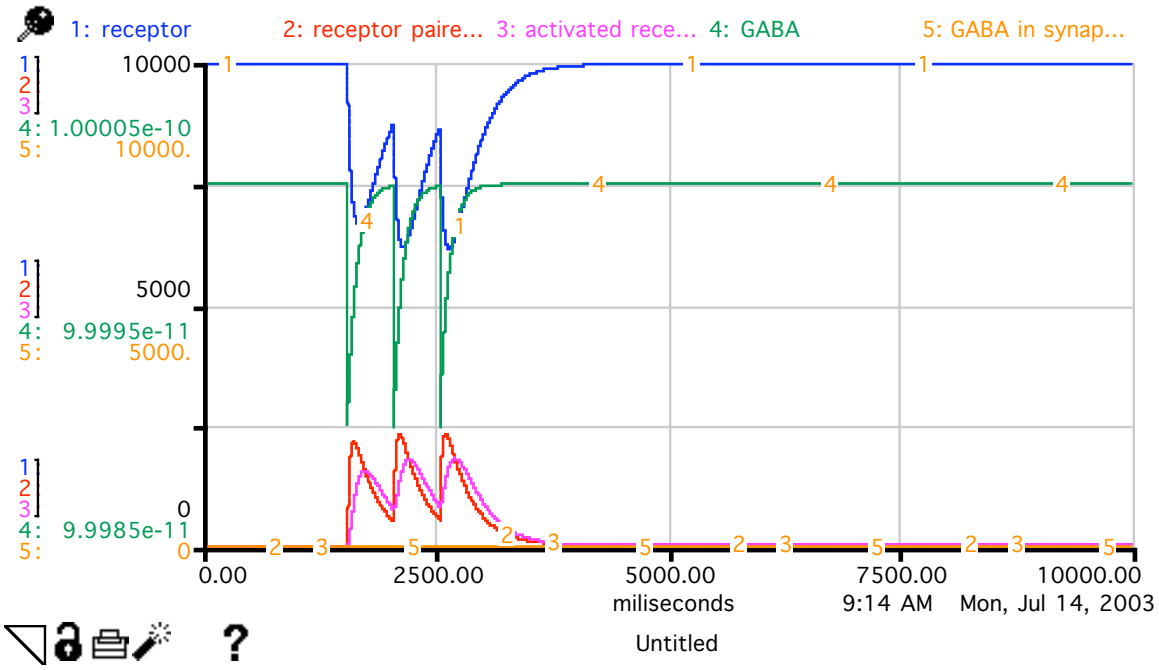


Figure 7: Unexercised model showing levels of GABA, GABA_in_synapse, receptor, receptor_paired_with_ligand, and activated_receptor.

First, I change the values for some of the rate constants. I began by looking at k2. When I change the value of k2 from .01/msec to .05/msec, the results make sense. With a faster disassociation rate, the number of unbound receptors may decrease with each action potential, but the receptors quickly become unpaired again, which causes the average number of free receptors to remain high. Also, since the disassociation happens at such a fast rate, there is little time for the receptors to become activated, and so the average number of activated receptors is quite small.

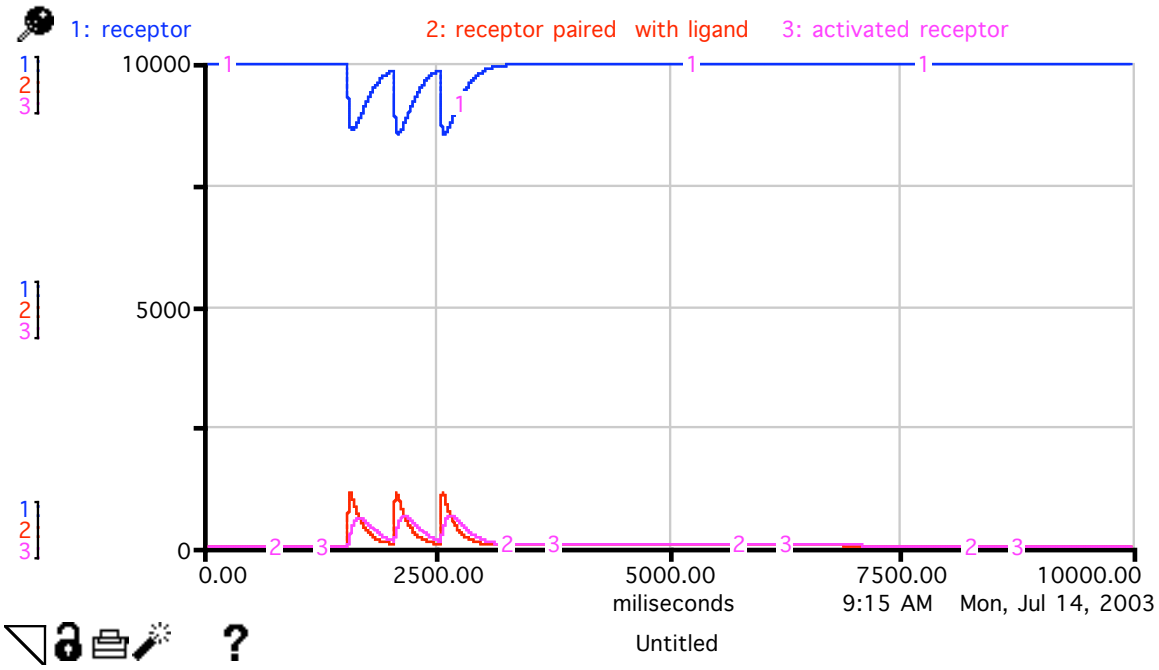


Figure 8: Graph of receptor, receptor_paired_with_ligand, and activated_receptor at k2=.05/msec.

If k2 is, instead, changed to .001/msec, the opposite happens. The rate of disassociation is so slow compared to the other rate constants that when an action potential occurs and receptors become bound, it is almost more likely that they will become activated before they are unbound. In fact, there are more paired receptors and activated receptors at one point than there are unbound receptors. The rate of disassociation is so slow that even after the action potentials stop, it takes a very long time before the system becomes stable again; in fact, even by the end of the 10,000msec simulation, the values are still not at equilibrium.

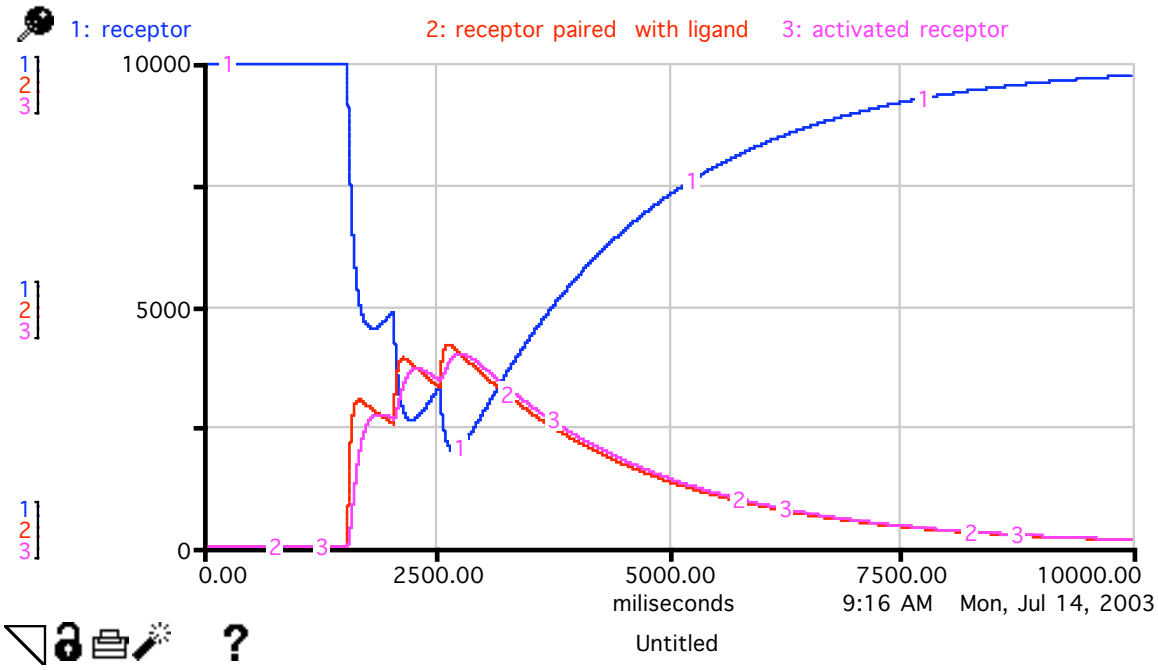


Figure 9: Graph of receptor, receptor_paired_with_ligand, and activated_receptor at k2=.001/msec.

Similarly, when I change the value of k3, the results are intuitive. When k3 becomes .05/msec instead of .01/msec, the rate of activation increases. Since the other rate constants remain the same, and activation is a flow from the paired_receptor stock to the activated_receptor stock, the value of paired_receptor decreases and the number of activated_receptors increases compared to the unexercised system. There are even a few times during which there are more activated receptors than free ones.

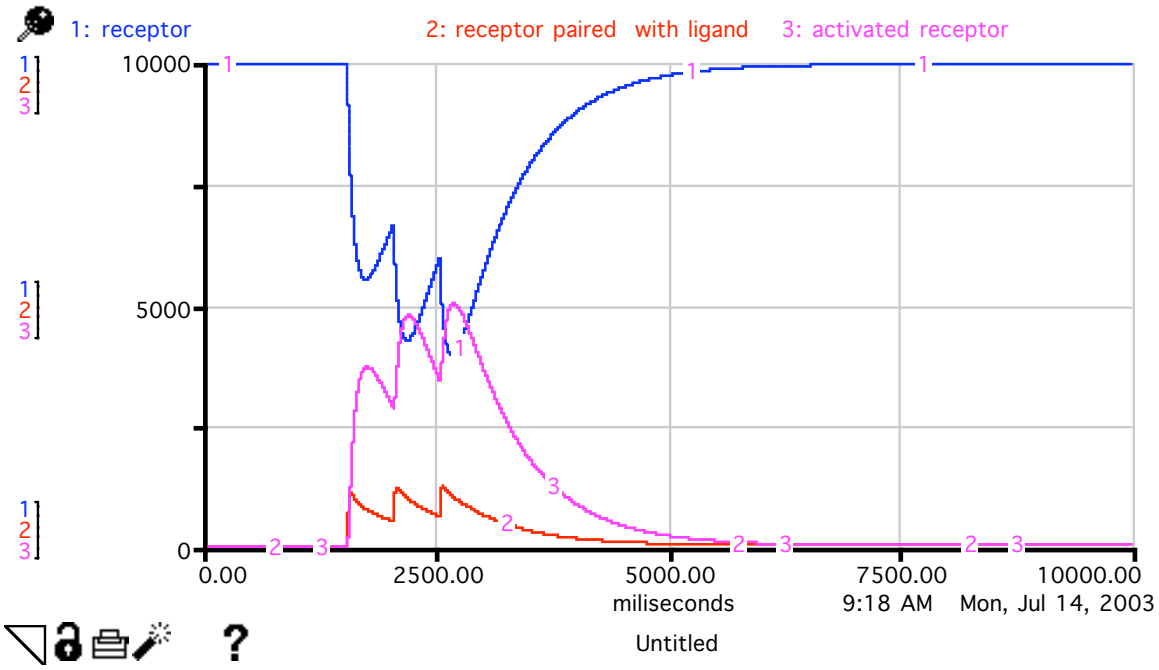


Figure 10: Graph of receptor, receptor_paired_with_ligand, and activated_receptor at k3=.05/msec.

When k3=.001/msec, the rate of activation is very small compared to the other rates, and so hardly any receptors become activated, and so the number of paired but inactive receptors increases.

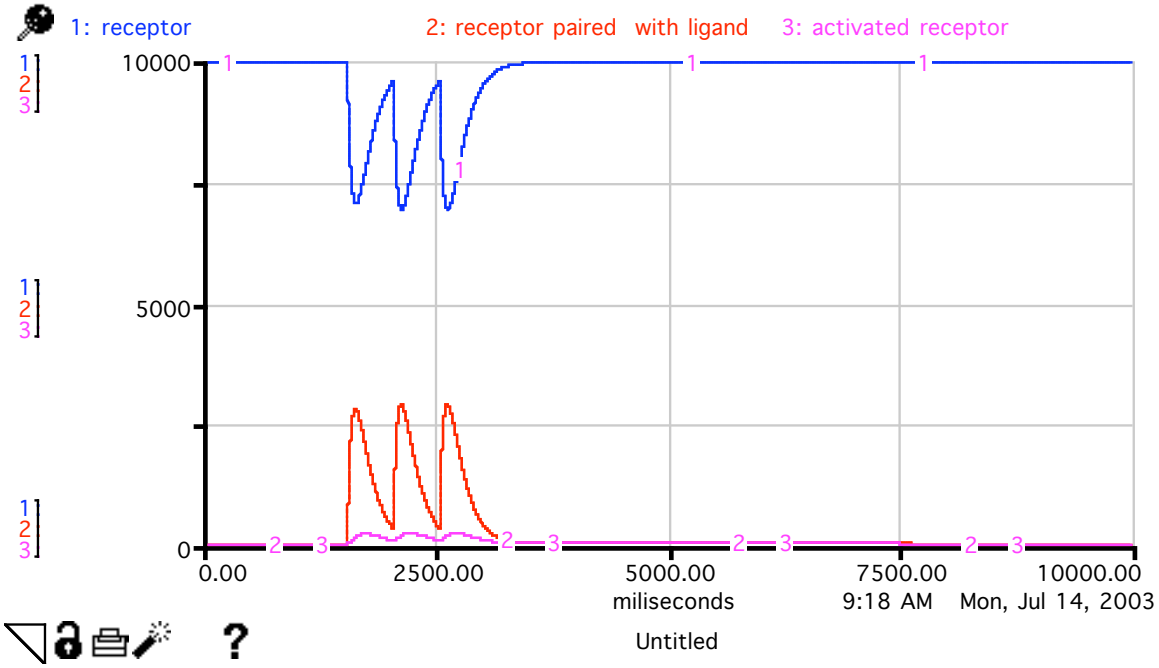


Figure 11: Graph of receptor, receptor_paired_with_ligand, and activated_receptor at k3=.001/msec.

Next, I exercise other values besides the receptor rate constants. If I increase the volume_of_synapse from $1*10^{-6}$L to $5*10^{-6}$L, the GABA_concentration_in_synapse will decrease (since there is the same number of moles of GABA spread through a larger space), which will cause k_effective to decrease, which will cause receptor binding to decrease. Thus, a larger volume of the synapse – unaccompanied by any other change – will cause fewer receptors to get bound and therefore fewer receptors to get activated.

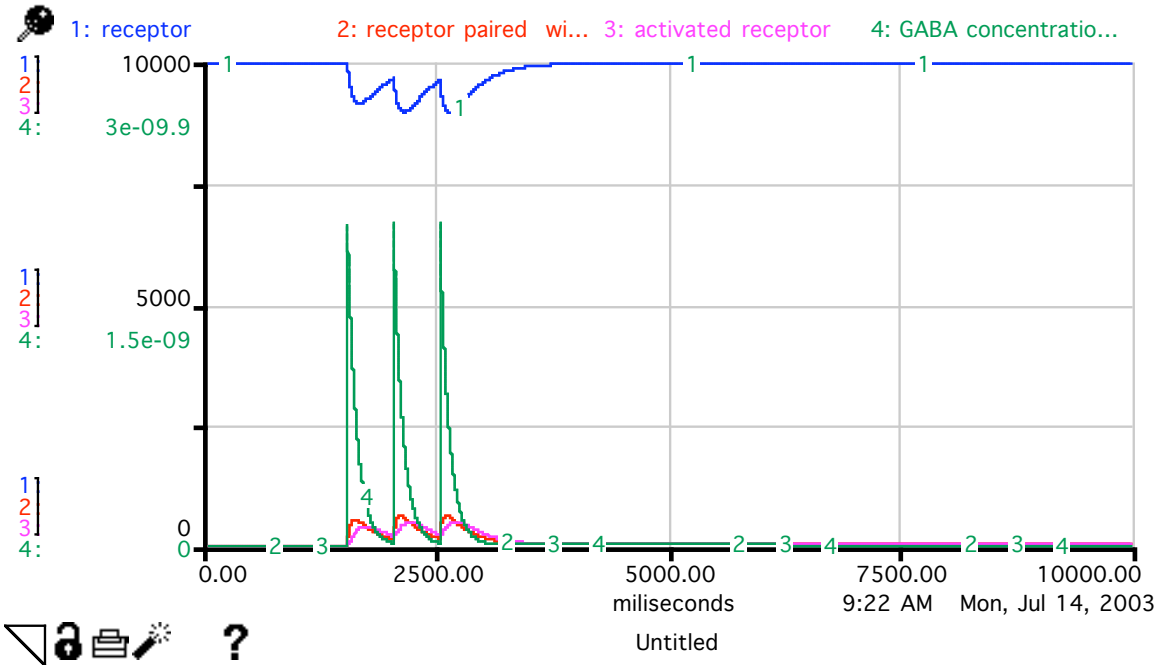


Figure 12: Graph of receptor, receptor_paired_with_ligand, activated_receptor, and GABA_concentration_in_synapse when volume_of_synapse=$5*10^{-6}$L

Finally, if the average lifespan of GABA_in_synapse is exercised, the entire system becomes affected, not just one part. When I increase the average lifespan from 100msec to 500msec, GABA remains in the synapse longer than it did before. Every time an action potential occurs, this altered lifespan causes a buildup of GABA_in_synapse. The level of GABA_in_synapse becomes larger than the level of GABA. This causes GABA_concentration_in_synapse to increase, which causes k_effective to increase, causing an increase in binding.

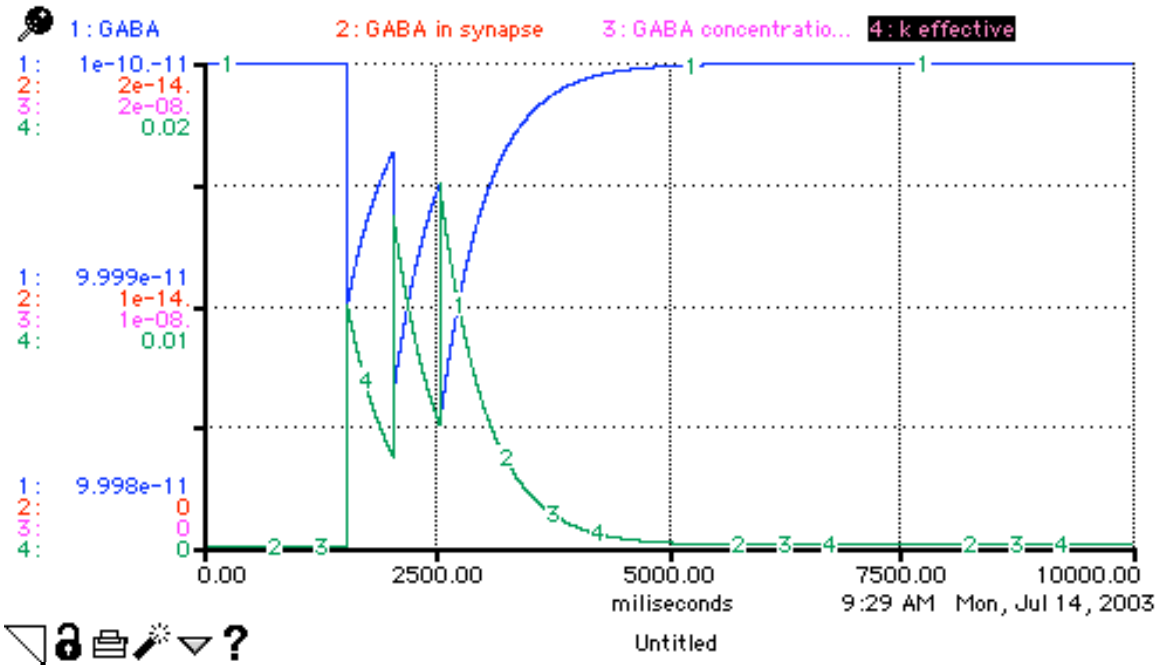


Figure 13: Graph of GABA, GABA_in_synapse, GABA_concentration_in_synapse, and k_effective when average_lifespan_in_syanpse=500msec.

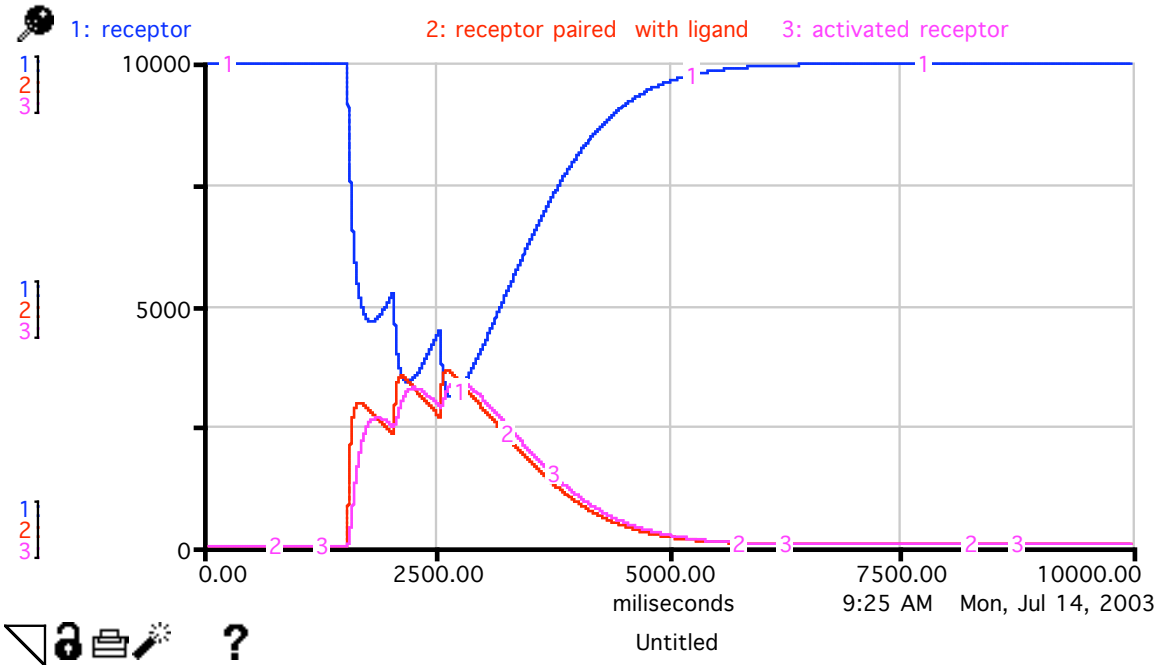


Figure 14: Graph of receptor, receptor_paired_with_ligand, and activated_receptor when average_lifespan_in_synapse=500msec.

In general, I know that my model is working properly because of the behavior that all graphs show prior to T=1000msec, and after T=3000msec. All of the graphs are stable at these times, which means that nothing besides action potentials are affecting the system. This is exactly the behavior that should occur, because action potentials are what start the whole process going in real life as well.

The Results of Modeling and Thinking

From the graphs and tables, I see that the model I have created to simulate the interaction between GABA and the receptors is a valid representation of what actually occurs on the cellular level between neurotransmitters and receptors. In order for a receptor to become bound and activated, GABA must be present in the synapse. The higher the GABA concentration is in the synapse, the more likely it is that the receptor will get bound. Action potentials determine the concentration of GABA in the synapse. Therefore, without an action potential, nothing happens. All of this is evident in my model.

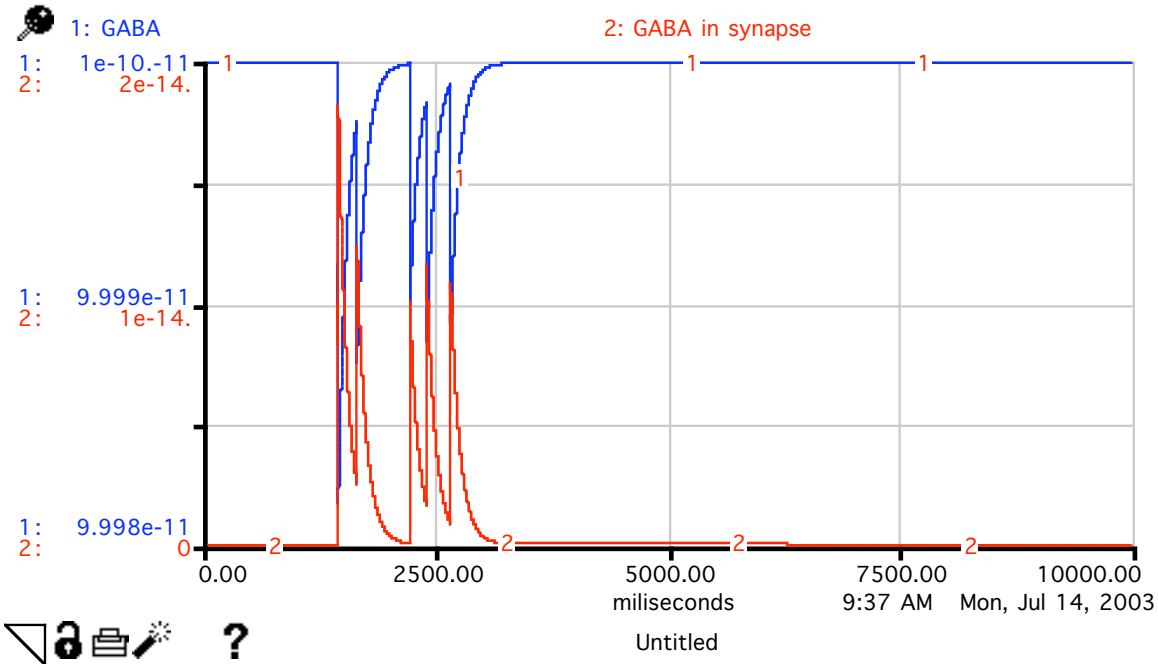


Figure 15: Graph of GABA and GABA_in_synapse.

Because of the RANDOM command in the action potential flow, no two runs are identical. The general behavior of the system is predictable, though. Before T=1000msec, the system is stable. The number of moles of GABA stays at 1*10-10{mol}(10000*10-14{mol}) until at least T=1000msec, and the number of moles of GABA_in_synapse stays at 0 {mol}until then as well. This means that without action potentials, the system doesn't kick into action. This is how it is supposed to be, because in actuality, GABA is unable to enter the synapse without first being released as a result of an action potential.

As soon as t=1000 has passed, though, action potentials begin to occur, releasing GABA into the synapse. The level of GABA drops sharply after every action potential, and then immediately begins to increase and approach its initial value – that is, it approaches the equilibrium value (it is important to realize that this does not mean it is a converging process; see below). GABA continues to increase and approach this value until another action potential occurs and causes the value of GABA to drop substantially. This process is repeated any number of times between T=1000msec and T=3000msec, at which point the action potentials cease. After this, the amount of GABA approaches the equilibrium value and remains there for the entire rest of the simulation, which again proves that without action potentials, there is no neurotransmitter activity.

The graph of GABA_in_synapse is the exact mirror of the GABA graph. This makes perfect sense. When GABA is released, it goes into the synapse, and when GABA leaves the synapse, it is taken back up into the first neuron. From T=0msec to T=1000msec, GABA_in_synapse remains at 0 {mol} because no action potential occurs during this time. When, after T=1000msec, action potentials do begin to occur, GABA_in_synapse increases sharply with each action potential. Immediately after this, it begins to decrease. This decrease is an exponential decay, because it depends on a rate constant (average lifespan in synapse) and the current amount in the stock at that moment. The curve of the graph of GABA_in_synapse after each action potential confirms this. Note: because the GABA graph is the exact mirror of the GABA_in_synapse graph, it may look like the GABA graph is displaying converging behavior, but in actuality it is displaying the mirror of an exponential decay on the part of GABA_in_synapse. After T=3000msec, the action potentials cease, and, as dictated by exponential decay, the graph of GABA_in_synapse approaches its equilibrium state value of 0 {mol}.

I chose to include the graphs of GABA and GABA_in_synapse because this two-state equilibrium is vital to understanding the rest of the model. Without action potentials – which are a direct upshot of the GABA component of my model – the rest of the system would not function.

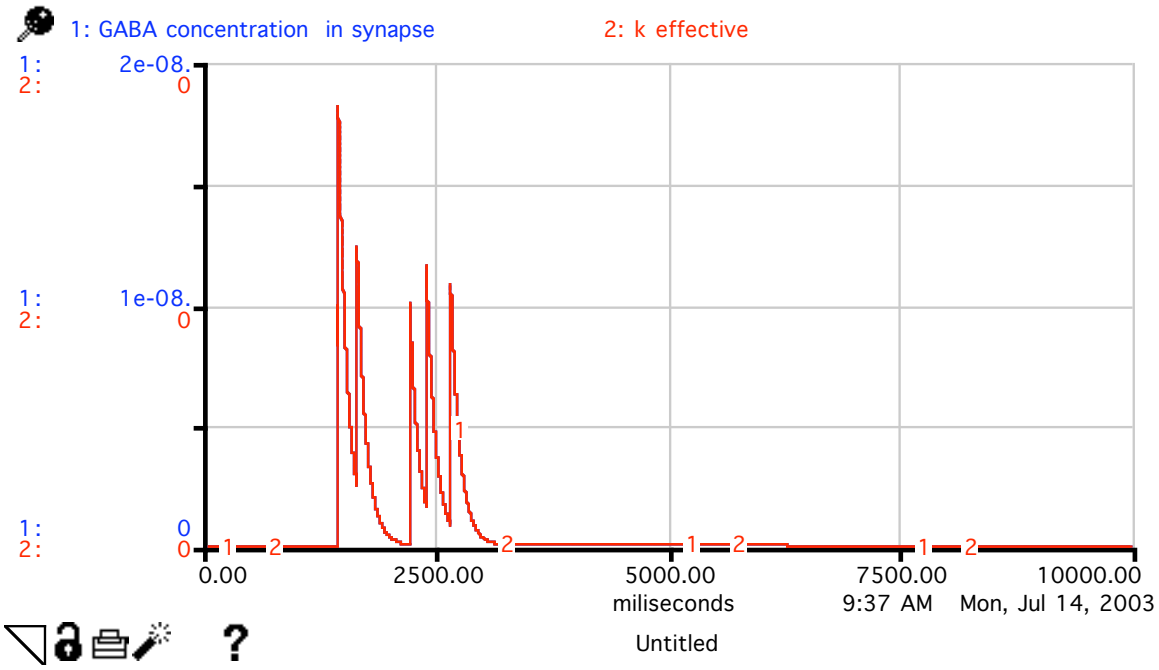


Figure 16: Graph of GABA_concentration_in_synapse and k_effective.

As has already been stated, prior to T=1000msec, all values are at equilibrium because there are no action potentials before then. This includes GABA_concentration_in_syanpse and k_effective. Both values are at zero from T=0msec to T=1000msec. When action potentials do begin occurring, the values of both GABA_concentration_in_synapse and k_effective change accordingly.

Every time an action potential occurs, the GABA_concentration_in_synapse increases sharply and then immediately begins to decrease. It mimics the graph of GABA_in_syanpse. This is because GABA_concentration_in_synapse is directly dependent on GABA_in_synapse. Since volume_of_synapse is constant and doesn't change during the simulation, the only thing affecting the shape of the GABA_concentration_in_synapse graph is GABA_in_synapse; therefore, the shape of the graph of GABA_concentration_in_synapse looks similar to the graph of GABA_in_synapse. After T=3000msec, GABA_concentration_in_synapse once again approaches its equilibrium state of 0 {Molar}.

The graph of k_effective looks very similar to the graph of GABA_concentration_in_synapse, for the same reason the GABA_concentration_in_synapse looks very similar to the GABA_in_synapse graph; k_effective is proportionally dependent on two things, one of which does not change. Thus, the one that does change (GABA_concentration_in_synapse) dictates the shape of the graph. After each action potential, the value of k_effective increases sharply and then begins to decrease depending on the GABA_concentration_in_synapse.

I chose to include the graphs of GABA_concentration_in_synapse and k_effective because these two values connect the GABA component to the receptor component, and it is important to see how both values depend on action potentials.

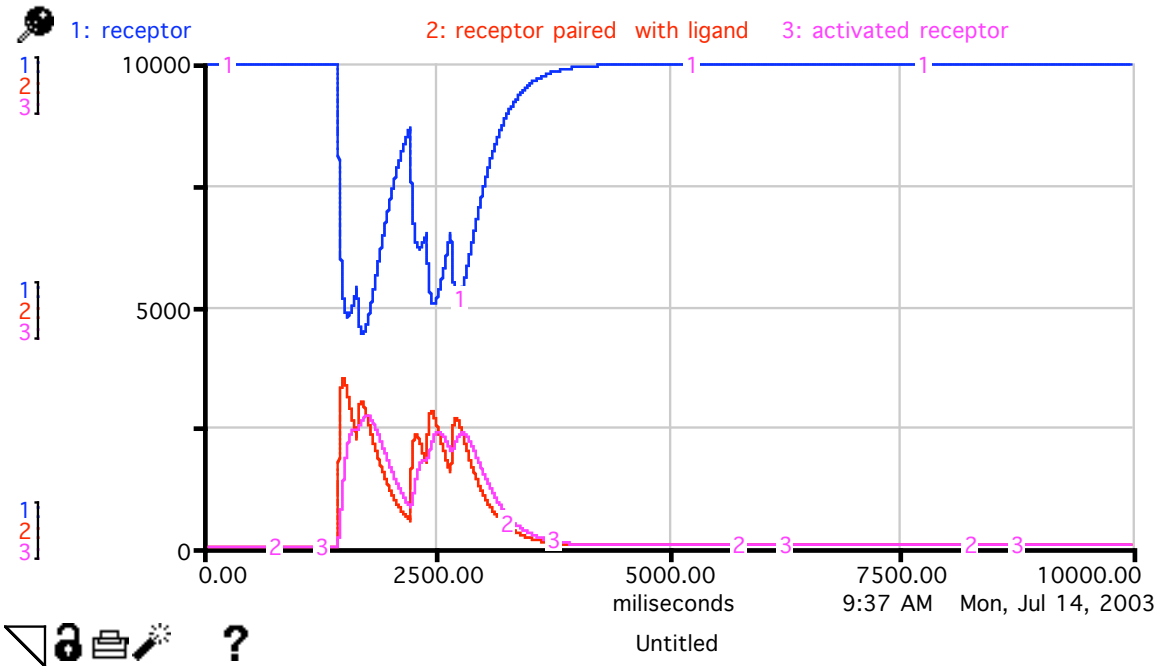


Figure 17: Graph of receptor, receptor_paired_with_ligand, and activated_receptor.

Finally, I've included the graphs of the receptor, paired receptor, and activated receptor because they are perhaps the most interesting part of my model. The three-state equilibrium between them is similar to – but much more complicated than – the two-state equilibrium between GABA and GABA_in_synapse. Action potentials cause free receptors to decrease (they become bound). Because of the disassociation flow, though,

as soon as receptors decrease, they begin to increase again until the next action potential. Receptor_paired_with_ligand increases as soon as the number of free receptors decreases, since every free receptor becomes a paired receptor.

Key Learning from the Modeling Process

- Receptors have three separate and defined states: unbound and inactive, bound and inactive, and bound and activated.
- The rate of receptor binding depends on the molar concentration of GABA in the synapse between neurons.
- Action potentials release neurotransmitters into the synapse.
- As soon as GABA (or any neurotransmitter, for that matter) is released into the synapse, the first neuron begins to "suck" the neurotransmitter back into its terminal.
- The rates of activation, disactivation, and unbinding are not constants, but are also dependent on other systems and components.
- The system is stable before action potentials, which means that action potentials are the sole instigators of change in the system.
- The system desires to go back to the stable state after each action potential; that is, GABA tends to return to the terminal after each action potential, and receptors tend to become inactive and unbound.
- If a long enough time passes between action potentials, the system will return to the pre-action potential state.
- K effective depends on the molar concentration of GABA in the synapse, and not on the actual number of GABA molecules in the synapse.

As the concentration of GABA in the synapse increases, the number of bound – and activated – receptors increases. According to the theory that I have chosen, the activation of these receptors triggers a release of dopamine into the system, which increases the level of anesthesia a person feels.

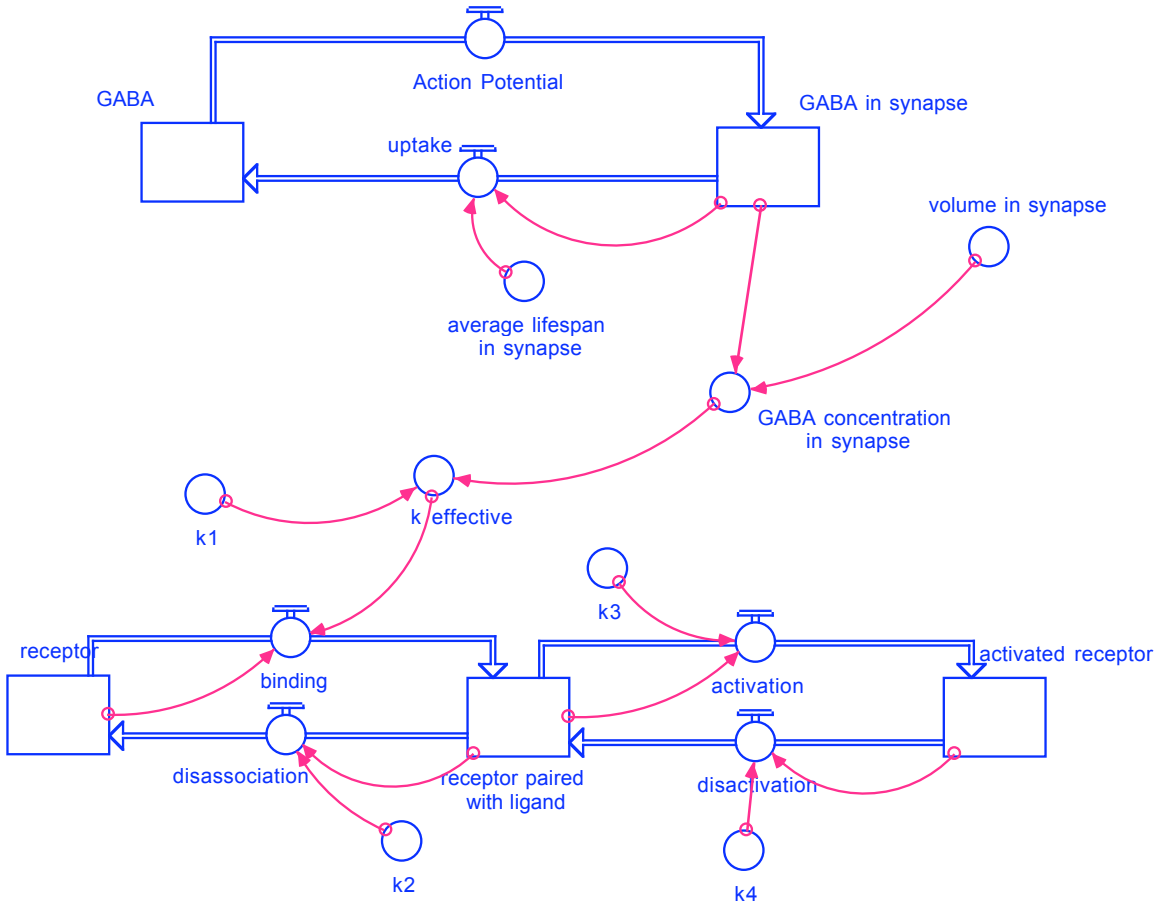
My model is a good jumping-off point for others interested in how neurons interact. Each of the rate constants that I chose are actually dependent on other factors which could be added on to my model. Various drugs affect different parts of the system, and if someone is interested in modeling how a certain drug affects neurons, they can adapt my model to display the affect of the drug.

Bibliography

Katzung, Bertram G., MD, PhD. Basic& Clinical Pharmacology. 8th ed. New York: Lange Medical Books/McGraw-Hill, 2001.

Gallaher, Edward J., PhD. Associate Professor, Behavioral Neuroscience MQ280, Oregon Health and Science University, Portland, OR 97201, gallaher@ohsu.edu

Appendix: Completed Model and Equations



Equations: Omitted