A Computer Model of the Transmission of an Action Potential at the Neuro-Muscular Synapse in a Myasthenia Gravis Patient

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Summary:

Myasthenia gravis is a relatively common neurological disease whose symptoms are extreme muscle weakness and fatigue. It is caused by an immune response to neuro-receptors at the junction between nerve and muscle cells which renders the receptors inoperable, reducing the muscle's sensitivity to stimuli. Using an already existing mathematical model of the synapse, I determined a way to simulate the disease's effects and subsequent treatment. I then used the simulation to generate a computer model of the synapse, allowing the chemical changes which occur during the transmission of a signal through the junction to be examined in detail.

Introduction:

Myasthenia gravis is a debilitating neuromuscular disease characterized by a loss of muscular responsiveness in the patient, poorly developed muscle structure, and difficulty maintaining any degree of prolonged physical exertion. The disease was first clinically described at the turn of the century (Jolly, 1895), and since then the effects of myasthenia gravis have been studied in great depth.

Although the cause (or causes, if there are more than one) of myasthenia gravis is not fully understood, the method by which the disease affects its victims is very well-documented. Early recognition that myasthenia gravis bore symptoms similar to poisoning by curare, a toxin used by many South American Indian tribes in hunting, led to the discovery of its treatment. Curare had a known anti-toxin, physostigmine, and experimentation led to the eventual discovery that small doses of physostigmine (and similar chemicals such as neostigmine and pyridostigmine) helped to temporarily negate the disease's affects. (Goodman and Gilman, 1980)

Though the most apparent affects of myasthenia gravis are the changes in the body's stamina and muscle density, the actual change that myasthenia gravis makes in the body occurs on a microscopic level. A normal patient's muscular activity is regulated by a neurotransmitter called acetylcholine (ACh). When an action-potential is received by a motor neuron which regulates a specific set of muscle cells the neuron releases a small amount of acetylcholine into the junction between it and the muscle cell. The muscle cell receives the signal via tiny receptors which attach to the acetylcholine, causing the muscle to contract. In an individual with myasthenia gravis the muscle cell's sensitivity to acetylcholine is reduced because of a reduction in the number of receptors on the cell's surface. This reduction is the result of an abnormal production of antibody which binds to and deactivates the receptors. (Goodman and Gilman, 1980)

Treatment of myasthenia gravis consists of administering a chemical known as an anti-cholinesterase (anti-ChE). Instead of deactivating the antibody, these chemicals reverse the disease's effects by drastically slowing down the rate at which acetylcholine is removed from the synaptic cleft. More specifically, the anti-cholinesterases bind to the cholinesterase enzymes (ChE) which break down acetylcholine, allowing the transmitter to linger in the cleft for a longer amount of time. Though this treatment does not permanently negate

the disease's effects, it does allow the individual to function almost normally as long as the drug is in his or her system.

Because the chemical reactions which occur in myasthenia gravis are so well-documented, I decided to utilize the disease as a case study for a mathematical model developed by my mentor, Charles Peskin (1991). The model was originally created to describe the chemical and physiological reactions which occur at a synapse involved in the transmission of an action potential by means of several simple differential equations. However, I decided that by taking the model and modifying it to simulate the synapse of a myasthenia gravis patient a greater understanding of the disease might emerge.

Method:

The first step in creating the model was identifying the reactants with which I would be dealing. The three basic reactants in the general model for any synaptic reaction are the transmitter, the enzyme which breaks it down, and the receptor to which it binds. These quantities would be represented by the variables T, E, and R, respectively. From these basic reactants the general model derives two additional complexes, the transmitter-enzyme complex and the transmitter-receptor complex, represented by TE and TR, respectively. The original model's emphasis was on representing the transmission of the action potential, and thus differentiated between transmitter-receptor complexes which had opened, perpetuating the action potential, and those which had not. However, since my model dealt solely with the chemical reactions occurring within the cleft, I decided to ignore the distinction between open and shut TR complexes, thereby simplifying the resulting equations. This left me with the basic system of variables shown in Table 1.

Table 1:

Reactant	**Function in General Model**	**Representation in Model**
acetylcholine	transmitter	T
acetylcholinesterase	enzyme	E
muscle-cell receptor	receptor	R
receptor-bound acetylcholine	transmitter-receptor complex	TR
enzyme-bound acetylcholine	transmitter-enzyme complex	TE

At this point it was necessary to break from the original general model in order to represent the more specific case of the myasthenia gravis patient's neuromuscular junction. The primary difference between an untreated myasthenia gravis patient's synapse and a normal patient's is the presence of anti-receptor antibodies, which bind to some (approx. 75-90%) of the receptors on the muscle side of the neuromuscular junction, preventing them from operating (Goodman and Gilman, 1980). Since at present a way to free receptors from the limiting antibodies is unknown, the change in the number of receptors was treated as a static one: once the antibodies had rendered the receptors inoperable, they would stay that way. Thus, it was unnecessary to

introduce a variable representing the antibody or to chart its changes in concentration. The change in the number of receptors would be introduced later on by simply lowering the number of receptors which the simulator started out with.

While an untreated patient's system of variables warranted no additional changes from the general model, the system describing a patient to whom an anti-cholinesterase agent was being administered did. In order to represent the changes in the system which would occur upon administration of the drug, a new variable representing the anti-cholinesterase agent, denoted in the system by "N," was necessary. The specific breed of anti-cholinesterases which are used to treat myasthenia gravis differ from other anti-cholinesterases in that they act not to destroy the enzyme, but instead to simply slow it down. In fact, the anti-cholinesterase is not so much an inhibitor as it is an incredibly slow substrate. As such, a compound variable "NE," representing a cholinesterase/anti-cholinesterase complex was also necessary in the model.

Once these seven variables were declared I then had to determine the differential equations which would described how the elements in the system affected one another's concentrations. I began by using the same relationships declared in the original model. These relationships assumed three basic things about the nature of the reactions at hand:

1) **The rate of diffusion of transmitter across the synaptic cleft is very fast.**

2) **Transmitter may ONLY be removed from the system by means of enzyme degradation or receptor binding**

3) **Receptors can bind to one transmitter molecule only**.

The first of these assumptions allowed me to ignore the short amount of time required for the transmitter to cross the synapse. The second eliminated any in- or out-flux of transmitter from the system, allowing the pure relationship between the transmitter, the enzyme, and the receptor to emerge. The last insured that there would be a one-to-one correspondence between transmitter and receptor, a relationship which made the differential equations simpler.

The first step made by the original system in declaring the differential equations was determining the chemical and biological reactions taking place between the various elements of the system. Since all the

changes in the system could be described as either the addition or subtraction of some amount of a reactant from the system, the differential equations dealt with the rates of change of the various concentrations of the reactants.

I began by defining the reactions themselves. I took the first three reactions from the original model. The capital letters indicate the reactants involved in a reaction:

1) the release of the transmitter:

—»T

2) binding of transmitter to receptor

T + R «—» TR

3) enzymatic degradation of transmitter

T + E «—» TE —» E

The last set of reactions I needed were the ones describing the bonding of the cholinesterase to the anti-cholinesterase. Since the anti-cholinesterase was basically just a very poor substrate, its reaction would follow the same pattern as the enzymatic degradation of the receptor:

4) bonding of anti-enzyme to enzyme

N + E «—» NE —» E

At this point it was necessary to determine the rates at which the various reactions occurred. The rates at which the reactions occurred were not constant: they varied depending upon the concentrations of the various elements in the system. I decided to declare them at the beginning, allowing me to write the differential equations, and then return to them later and actually determine what they were. The rates in the original model could be placed into two distinct categories: reversible reactions (written as a «—») and non-reversible reactions (written as —»). The non-reversible reactions in the original model were the release of the transmitter into the synaptic cleft and the degradation of the transmitter by the enzyme (—»T and TE —» E) Since they only went in one direction, they were rather easy to define. The rate at which T was released, r_t, was independent of the amount of transmitter in the system, and thus would be expressed in the final differential equation describing the change in the concentration of T (written "[T]") as a simple addition statement. The rate at which TE —» E, however, was dependent upon the amount of TE in the system. Thus, in the original model, the rate at which the

transmitter was degraded was expressed as a rate α_E, which indicated the fraction of the total number of TE complexes which would degrade into E per unit time.

The other type of reaction in the general model were *fast reversible reactions*. These reactions were not one-way, but could go back and forth from one state to another, such as the binding and release of T from R. Though these reactions were effectively infinitely fast in either direction, they did maintain a certain ratio to one another in the frequency with which they occurred which could be expressed as an equilibrium constant, K. In order to further simplify this type of reaction, the original model utilized the concept of *net rates*. (Peskin, 1991) Though the reaction occurs in both directions, at any one time there is a net rate in either the forward or backward direction. Thus, at any specific time, the rate at which T + R «—» TR could be expressed as a single rate per unit volume r_R and T + E «—» TE as r_E. The direction of the reaction was interpreted numerically as the sign of the rate, with positive being forward (formation of the complex) and negative being backward (the dissociation of that complex into its two components.

At this point I had to again break from the original model in order to establish the rates for the anti-cholinesterase reactions. Since it very was similar to the cholinesterase/acetylcholine reaction it followed the same basic set up. Since it was a fast reversible reaction, I reduced the N + E «—» NE portion in the same way as before, resulting in a net rate r_N. However, the second portion of the equation, the NE —» N part, posed a problem. Since the entire purpose of the anti-cholinesterase agent is to render the enzyme molecule it binds to inoperable by making the process of catalyzation excessively long (Wilson and Harrison, 1961), I decided to follow the same format as for the TE —» E reaction, but to set $\alpha_N = 0$, since the speed of that reaction would be negligible. Thus, there is no parameter α_N in the model described below.

With these rates and reactions defined, I was able to move on to actually declaring the differential equations. The differential equations for each respective reactant's concentration were written by taking into account the various reactions in which the reactant's concentration changed, and then adding or subtracting that rate from the differential equation. The result is table 3.

Table 3:

$d[T]/dt = r_T - r_R - r_E$

$d[TR]/dt = r_R$

$d[R]/dt = - r_R$

$d[TE]/dt = r_E - \alpha_E [TE]$

$d[E]/dt = -r_E + \alpha_E [TE] - r_N$

$d[N]/dt = -r_N$

$d[NE]/dt = r_N$

These are 7 equations in the seven unknown concentrations [T], [TR], [R], [TE], [E], [N], and [NE]. Note, however, that there are three additional unknowns, the net rates of the fast reversible reactions, r_R, r_E, and r_N. (The rate of transmitter release, r_T, is considered a given function of time in this model.) Three additional equations for these additional unknowns are obtained from the equilibrium relationships of the fast reversible reactions, as given in Table 4.

Table 4:

$[T] [R] = K_R [TR]$

$[T] [E] = K_E [TE]$

$[N] [E] = K_N [NE]$

These relationships hold at all times because, though the time frame which we are considering is very small (the amount of time required for the synapse to transmit the action potential; about 200 milliseconds) the rate at which the equation balances itself can be considered to be almost infinitely fast.

I differentiated each of the equations with respect to time:

$$(d[R]/dt) \cdot [T] + [R] \cdot (d[T]/dt) = K_R \cdot d[TR]/dt$$

$$(d[E]/dt) \cdot [T] + [E] \cdot (d[T]/dt) = K_E \cdot d[TE]/dt$$

$$(d[E]/dt) \cdot [N] + [E] \cdot (d[N]/dt) = K_R \cdot d[NE]/dt$$

This established a relationship between the various derivatives. Substituting with the derivatives from Table 3 produced:

$$(- r_R) \cdot [T] + [R] \cdot (r_T - r_R - r_E) = K_R \cdot (r_R)$$

$$(- r_E + \alpha_E \cdot [TE] - r_N) \cdot [T] + [E] \cdot (r_T - r_R - r_E) = K_E \cdot (r_E - \alpha_E \cdot [TE])$$

$$(- r_E + \alpha_E \cdot [TE] - r_N) \cdot [N] + [E] \cdot (- r_N) = K_N \cdot (r_N)$$

I then rearranged the equations to produce a set of linear equations with the net rates as the variables:

Table 5:

$$([R] + [T] + K_R) \cdot r_R - [R] \cdot r_T + [R] \cdot r_E = 0$$

$$(- [E]) \cdot r_R + [E] \cdot r_T + (- [E] - [T] - K_E) \cdot r_E + (- [T]) \cdot r_N = (- [T] - K_E) \cdot \alpha_E \cdot [TE]$$

$$(- [N]) \cdot r_E + (- [N] - [E] - K_N) \cdot r_N = - [N] \cdot \alpha_E \cdot [TE]$$

This left a system of 3 linear equations in the 3 unknowns r_R, r_E, and r_N. The rate of transmitter release r_T is considered to be a known quantity. In fact, since transmitter is released so quickly from the presynaptic neuron, I decided to simplify the situation by assuming that all of the released transmitter is already in the synaptic cleft at the beginning of each computer experiment. With this assumption, $r_T = 0$ for $t > 0$, and can be used to simplify the equations given in Table 5.

At this point I needed to write the computer program which would simulate what occurred in the synapse. I wrote the program on a Sun Sparc Workstation in Matlab version 5.0. My basic strategy for writing the program was to use a large loop which would simulate the passage of time, and then use a method for approximating changes in a function known as *Euler's Method* to determine the changes in variable concentration. Euler's Method consists of taking very small time steps, determining the rate of change for the function at that point in time, and then adding the rate of change of the function times the time step to the previous value of the function. I created a loop with 400 steps of length dt = 1 millisecond; at each step the program calculated the new rates of change using the data from the previous time step. The actual calculation of the rates was done by using Matlab to solve the above system of linear equations and then substituting the values back into the differential equations. Determining the initial values of the reactants was somewhat harder, for

though the total amount of each reactant, with the exception of the receptors, remained constant in all cases, the initial concentration of free reactant changed depending on each situation in order to fulfill the equilibrium equations. In order to determine the initial concentrations of all the reactants I took advantage of the fact that the total concentration of each reactant was equal to the sum of the concentrations of all complexes containing that reactant. Thus,

Total T = [T] + [TE] + [TR]

Total E = [E] + [TE] + [NE]

Total R= [R] + [TR]

Total N= [N] + [NE]

Then, using the equilibrium equations (Table 4) I expressed the total amounts of E and T strictly in terms of [E] and [T]. I then rearranged them to produce two functions

$E = K_E \cdot (\text{total T} / [T] - 1 - \text{total R} / (K_R + [T]))$

$T = K_E \cdot (\text{total E} / [E] - 1 - \text{total N} / (K_N + [E]))$

I then graphed the two functions simultaneously. The point where the curves intersected provided me with the initial concentrations which satisfied both equations, and thus satisfied the system.

I used the program itself to simulate three separate situations: the synapse of a healthy individual, the synapse of a diseased individual, and the synapse of diseased individual treated with anti-cholinesterase. The healthy individual served as a control, and I simulated it by entering in normal data for the constants and taking out those parts of the equations which introduced anti-cholinesterase (Thus effectively running the original model.). Simulating the disease was done by running the normal simulation but reducing the number of receptors by 80%, mimicking the 75-80% drop in receptors which actually occurs. The last situation simply entailed running the diseased simulation with anti-cholinesterase present.

Results:

After running the simulations of the healthy, diseased, and diseased but treated synapses, I graphed the concentrations of all reactants versus time. These graphs, which display the first 400 milliseconds after the release of the transmitter, indicate that the experiment achieved its overall goal, simulating the physical effects of both the disease and its treatment.

The simulation of the healthy synapse behaved as follows. The concentration of transmitter (which was introduced suddenly at t=0) fell throughout the entire simulation (figure 1), the initial linear decay being due to the combined efforts of the receptors and enzymes, and the ensuing slow, exponential decay owing to the gradual release of transmitter from receptors as the overall concentration of transmitter in the system decreased. The plots for the concentration of TR and TE (figures 5 and 6) verified this general trend; as transmitter was removed from the system by the enzyme, the concentration of the two compounds decreased in order to fulfill the requirements of the equilibrium equations. Thus, the model successfully replicated the general effect of an action potential on the synapse, mimicking the return to the resting state after the addition of transmitter to the system.

The simulation of the diseased individual produced similarly admirable results. The reduction in receptor concentration modeled well (figures 9 and 10), the lower concentration causing the receptors to return to the equilibrium state much earlier than in the healthy model. The overall change in the other parts of the system was as one would expect (figures 6-8) The initial concentration of transmitter increased approximately 7%, a result of the fact that there was less receptor to bind to. The enzyme concentration stayed approximately the same, the change in transmitter concentration being not nearly enough to affect it.

The addition of the anti-cholinesterase to the system in the final simulation produced results which are consistent with the beneficial effects of this type of drug. The anti-cholinesterase behaved as to be expected, its concentration decreasing similar to the transmitter's (figure 14) However, due to the fact that it is not being degraded after binding, its concentration approaches the equilibrium constant K_N instead of zero. The effect it had on the enzyme was quite large: the sudden addition of the extra substrate resulted in an overall decrease in the concentration of the enzyme, which grew back towards its rest state at a much slower rate than in the

previous two simulations (figure 12). More important, however, was the result it had on the receptors, particularly the transmitter-receptor complex. In order to successfully treat the disease, the addition of the anti-cholinesterase would have to slow the TR complex's return to rest. Figure 18 shows the concentration of TR from the diseased individual plotted on the same axes and the concentration of TR from the treated individual. The difference in the rate at which the complex dissociates is obvious, with the complex dissociating noticeably slower in the treated individual than in the diseased. While the change is not very large, the fact that it did occur indicates that the addition of the anti-cholinesterase produced the desired effects, and that a greater change could easily be brought about via a higher initial concentration of the anti-enzyme.

Overall, the experiment was quite successful. The data generated fit into our understanding of the processes of the disease, and my addition of the anti-cholinesterase agent proved to successfully mimic the physiological effects of the disease's treatment. The greatest problems in the simulation were those elements left out during the formulation of the simulation, namely the release of transmitter and the effects on the system, caused by outside sources, such as the diffusion of reactants into and out of the cleft. These could be easily solved with some additional research, resulting in an even more complete picture of the disease.

The experiment obviously leaves itself open to further research in this field. Besides solving the aforementioned problems, one could also seek to extrapolate on the system to simulate other situations. For instance, certain muscle cells are particularly hard-hit by the effects of myasthenia gravis. The muscles which control the eyelids are one such group of cells, and it is those cases in which the disease causes eyelid muscles to sag, resulting in the condition known as ptosis, for which myasthenia gravis is best known. Redesigning the model to simulate the disease's effects on the eyelid muscles could yield some very interesting results, and certainly promises to be an interesting area for further research. Similarly, anti-cholinesterases seem to have a promising future in the treatment of Alzheimer's, as the class of drugs has been found to help restore memory in certain individuals in certain cases. In general, future research in the area of mathematical neurobiology seems to hold great promise, promoting a greater understanding of the body and how it works.

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Appendix: Matlab code

Code enclosed in a box was included only in the healthy and diseased individual simulation

Code in double parenthesis was included only in the diseased individual simulation.

Code in square brackets was included only in the diseased individual being treated with anti-cholinesterase simulation

Everything after the % sign indicates a comment in the code, explaining its function

Basicsim:

```
%RUNS THE SIMULATION
setvars   % Sets all variables to initial state
n=1;
tsave(n)=n*dt;
saveconc;
nmax=400;  %Each timestep indicates one millisecond
        for n=2:nmax
          nuround;
        end
```

Setvars:

```
%   SETS ALL VARIABLES AND MATRICES TO INITIAL STATE
V=1.5*10^(-13)          %volume of cleft
%Rates
  Kr=.0001   %Equilibrium constant for receptor and transmitter
  Ke=.0025   %Equilibrium constant for enzyme and transmitter
aE=1     % αE, the rate at which TE —» E
rT=0   %rate  —» T per unit time
rR=0   %rate T «—» TR per unit time
rE=0   %rate E «—» TE per unit time
%Reactants:
 %Transmitter
    totalT=2.5*10^(-3)    % Total concentration of transmitter in the system
    concT= 1.3*10^(-3)  % Concentration of released transmitter
          ((  concT= 1,425*10^(-3)  ))
          [  concT= 1.51*10^(-3) ]
 %Enzyme
    totalE=1.1*10^(-3)    % Total concentration of enzyme in the system
    concE=Ke*totalE/(Ke+concT)          %conc of free enzyme
    concTE=concT*totalE/(Ke+concT)    %concentration of enzyme/substrate packets
[ %Anti-Enzyme
[    totalN=1.0*10^(-3);
[    concNE= totalN*concE/(concE+Kn);
[    concN= concNE*Kn/concE
 %Receptor
    totalR=1.5*10^(-3)   (( totalR = 1.5*10^(-3) * .2 ))
                % concentration of receptors in muscle cell
    concR=Kr*totalR/(Kr+concT)
       %concentration of empty receptors
    concTR=concT*totalR/(Kr+concT)
      %concentration of receptors containing transmitter
%Time
 dt=.01
```

Nuround:

```
        %DETERMINES WHAT HAPPENS IN ONE STEP DT
        tsave(n)=n*dt;  %Saves time variable to allow it to graph
        detrates;       %Determines rates r_E, r_R, and r_N
        detconcT;
        detconcR;
        detconcE;
        detconcTE;
        detconcTR;
        [detconcN;]
        [detconcNE;]    %Determines concentrations of all variables using r_E, r_R, and r_N
        saveconc;
Saveconc:
        %SAVES VARIABLE CONCENTRATIONS IN ARRAYS
        concTsave(n)=concT;
        concEsave(n)=concE;
        concTEsave(n)=concTE;
        concRsave(n)=concR;
        concTRsave(n)=concTR;
        concNsave(n)=concN;
        concNEsave(n)=concNE;
Detrates:
        %CONVERTS THE DATA INTO A SYSTEM OF LINEAR EQUATIONS AND SOLVES IT
        A=zeros(3,3); %creates a 3 by 3 matrix, empty
        A(1,1)=concR+concT+Kr;      A(1,2)=concR;           A(1,3)=0;
        A(2,1)=-concE;              A(2,2)=-concE-concT-Ke; A(2,3)=-concT;
        A(3,1)=0;                   A(3,2)=-concN;          A(3,3)=-concN-concE-Kn;
                        %Enters the left sides of the three linear equations found in table 5
        b=zeros(3,1);
        b(2,1)=aE*concTE*(-Ke-concT);
        b(3,1)=-concN*aE*concTE;
                        %Enters the right sides of the three linear equations found in table 5
        z=A\b;
        rR=z(1,1);
        rE=z(2,1);
        rN=z(3,1);
                        %Gives rE, rR, and rN the values of r_E, r_R, and r_N as calculated at that
                        point in time
detconcT:
        %Determines the amount of T
        dTdt=rT-rR-rE;          %Determines dT/dt, as given in Table 3
        concT=concT+dTdt*dt;    %Application of Euler's Method
detconcE:
        %Determines the amount of E
        dEdt=-rE-rN+aE*concTE;  %Determines dE/dt, as given in Table 3
        concE=concE+dEdt*dt;    %Application of Euler's Method
detconcR:
        %Determines the amount of R
        dRdt=-rR;               %Determines dR/dt, as given in Table 3
        concR=concR+dRdt*dt;    %Application of Euler's Method
detconcN:
        %Determines the amount of N
        dNdt=-rN        ;       %Determines dN/dt, as given in Table 3
```

```
        concN=concN+dNdt*dt;                %Application of Euler's Method
detconcTE:
        %Determines the amount of TE
        dTEdt=rE-aE*concTE;         %Determines dTE/dt, as given in Table 3
        concTE=concTE+dTEdt*dt;     %Application of Euler's Method
detconcTR:
        %Determines the amount of TR
        dTRdt=rR;                   %Determines dTR/dt, as given in Table 3
        concTR=concTR+dTRdt*dt;     %Application of Euler's Method
detconcNE:
        %Determines the amount of NE
        dNEdt=-rN;                  %Determines dNE/dt, as given in Table 3
        concNE=concNE+dNEdt*dt;             %Application of Euler's Method
```

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