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ENERGETICS BASED SPIKE GENERATION OF SINGLE NEURON

SIMULATION RESULTS & ANALYSIS

Supplementary Material to the Paper submitted to Frontiers in Neuroenergetics

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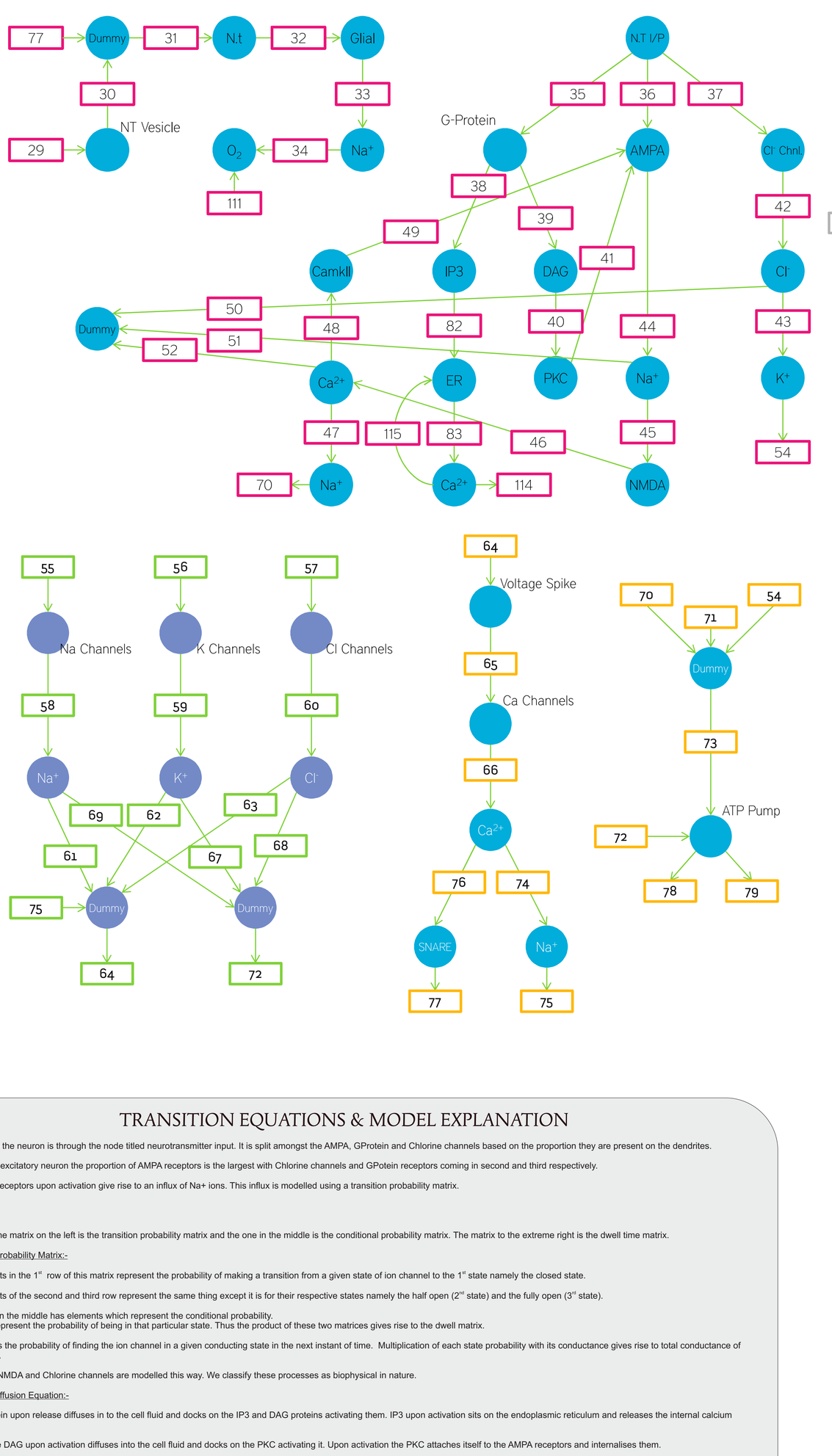
COMPLETE MODEL



TRANSITION EQUATIONS & MODEL EXPLANATION

The input to the neuron is through the node titled neurotransmitter input. It is split amongst the AMPA, GProtein and Chlorine channels based on the proportion they are present on the dendrites.

Thus for an excitatory neuron the proportion of AMPA receptors is the largest with Chlorine channels and GPotein receptors coming in second and third respectively.

The AMPA receptors upon activation give rise to an influx of Na+ ions. This influx is modelled using a transition probability matrix.

Over here the matrix on the left is the transition probability matrix and the one in the middle is the conditional probability matrix. The matrix to the extreme right is the dwell time matrix.

Transition Probability Matrix:-

The elements in the 1st row of this matrix represent the probability of making a transition from a given state of ion channel to the 1st state namely the closed state.

The elements of the second and third row represent the same thing except it is for their respective states namely the half open (2nd state) and the fully open (3rd state).

The matrix in the middle has elements which represent the conditional probability.
Its values represent the probability of being in that particular state. Thus the product of these two matrices gives rise to the dwell matrix.

It represents the probability of finding the ion channel in a given conducting state in the next instant of time. Multiplication of each state probability with its conductance gives rise to total conductance of the channel.

The AMPA,NMDA and Chlorine channels are modelled this way. We classify these processes as biophysical in nature.

Langevin Diffusion Equation:-

The G-protein upon release diffuses in to the cell fluid and docks on the IP3 and DAG proteins activating them. IP3 upon activation sits on the endoplasmic reticulum and releases the internal calcium reserves.

Similarly the DAG upon activation diffuses into the cell fluid and docks on the PKC activating it. Upon activation the PKC attaches itself to the AMPA receptors and internalises them.

Each individual transition in this process just described has been modelled using the Langevin Diffusion Equation. It is also a biophysical process.

$$\frac{d(x,y,z)}{dt} = \frac{1}{D}\left(\frac{d(E_g(x,y,z,t))}{dt} + f_b\right)$$

where

E_g represents the Electric Gradient
D represents the diffusion coefficient
f_b represents stochastic forces

The chlorine ions are transported out with the help of the potassium gradient. This gradient is then restored by the ATPase pump.

Similarly the Sodium-Calcium exchanger pushes the calcium out and the sodium in. This sodium is then pushed back out using the ATPase pump.

Thus the above mentioned processes all consume ATP. There will be a transition which connects these Sodium and Potassium ions to the ATPase pump. The transition equation governing that will be explained later.

Here the plasticity effects on the AMPA receptors are brought about by the CAMKII.
As the calcium concentration inside the cell increases the number of activated CAMKII.

Based on the amount of activated CAMKII the conditional probability of the ion channels in the open states increases and that in the closed state decreases.
Morever the number of AMPA receptors also increases.

Similarly base on the amount of PKC activated the conditional probability of the ion channels in the closed state increases and in the open state decreases. The equations governing the ATPase activation are given by

d(Na+-3)d(k+-2). Only if there are 3 or more sodium ions or two or more potassium ions, will the equation return true. And everytime it does, an ATP is consumed.

The ATP is mainly consumed when the ATPase pumps try to restore the ionic gradients. They are also consumed while packaging the neurotransmitters and pumping it with Hydrogen ions. This is why there is a transition from the Golgi apparatus to the ATP. This transition is a linear equation given by

$$\frac{d[PRODUCT]}{dt} = K[SUBSTRTATE]$$

where K is the proportionality constant. In this case since were not modelling a chemical reaction it is the ratio of number of ATP's used per neurotransmitter packaging by a golgi apparatus. The value stored inside the Golgi node will be the level of activity of the the Golgi apparatus. Thus by multiplying these two values we get the total ATP's used per unit time.

The number of golgi apparatus activated depends on the number of neurotransmitters produced by the Krebs cycle at a particular instant. It is modelled using the same equation given above, where the K is the proportionality constant. In reality what it represents is the how the golgi apparatus activity changes per neurotransmitter packaged. For the time being due to a lack of experimental evidence we are assuming these processes to be linear time variant. As we garner more information through experiments our models will also improve to incorporate this new information. The neurotransmitters are produced from the alpha-keto glutarate in the Krebs cycle.
This is a chemical reaction and the proportionality constant is calculated from the gibbs free energy value.

The ATP is produced by the ATPase enzyme using the ADP and the H+ ions. Only if the H+ ions have a high enough concentration can enough energy be provided to the ATPase enzyme to produce the required ATP.

The equation used to model this transition is

$$\frac{d[ATP]}{dt} = K[ADP]$$

The K value is always lies between 0 and 1. As the Calcium and Hydrogen ions inside mitochondria increase the amount of ATP formed also increases as the K value is suitably adjusted. Similarly as the Calcium and Hydrogen ions decrease the formation of ATP decreases as the K value reduces.
The gibbs free energy for ADP+ADP is calculated and using this the rate reaction constant is obtained.

$$\frac{d[AMP]}{dt} = K[ADP]^2$$

This AMP is used to activate the AMPK(metabolic switch). This process is also modelled using the Langevin diffusion equation. This AMPK activation leads to the activation of acetyl coa carboxylase. The activation of acetyl coa carboxylase leads to the inhibition of malanoyl coa carboxylase production. This thus increases the number of CPTI enzymes which move across the mitochondria membrane and increase the transport of fatty acids into the mitochondria. These fatty acids are then broken down by beta oxidation to increase the number of NADH and $FADH_2$.

AMPK also increases the number of glutamate transporters and hence increases the amount of glucose transported into the neuron.

This motion of glucose transporters and CPTI enzymes across the membrane is done using the Michelis Menten kinetics given by the equation

$$J = \frac{E_0 K_d K_+ K_- ([G_{out}] - [G_{in}])}{(G_{out} + K_d)(G_{in} + K_d)(K_+ + K_-)}$$

K_d = disassociation constant
K_+ = rate of motion in the forward direction
K_- = rate of motion in the backward direction
E_0 = total concentration of enzyme
G_{out} = concentration of molecules outside
G_{in} = concentration of molecules inside
J = total flux
The beta oxidation process has been modeled using the equation

$$\frac{d[length]}{dt} = -K[length][substrate]$$

This is based on the fact that longer the molecule lower the stability and hence faster the cleaving of two carbon atoms. But as the length of the fatty acid decreases the rate at which it is broken down also decreases. The FADH2, NADH and acetyl coa produced depend directly on the amount of fatty acid produced. It is modeled using the equation

$$\frac{d[PRODUCT]}{dt} = K[SUBSTRTATE]$$

The Krebbs cycle rate increases with the amount of Acetyl CoA produced. This increase is modelled using the gibbs free energy for acetyl CoA to citrate. The rate of formation of the NADH and FADH2 is modelled using the gibbs free energy obtained from the transition malate to oxaloacetate. This is the transition responsible for the rate of H+ ions released. So based on the rate of this reaction we determine the rate of formation of NADH and FADH2. The H+ ions formation from FADH2 and NADH is also modelled using the above stated equation.

MODEL EQUATIONS & INITIAL CONDITIONS OF SIMULATION

List of Transition Equations

Transition Number	Equation
1, 2, 3, 6, 8, 10, 11, 12, 13, 14, 15, 16, 18, 23, 24, 26, 27, 29, 31, 32, 33, 34, 38, 39, 40, 45, 48, 49, 55, 56, 57, 64, 65, 72, 73, 76, 78, 79, 82, 83, 85, 86, 98, 99, 100, 111, 114, 116, 117, 118, 119, 120	$\frac{d(product)}{dt} = K[Substrate]$
5, 7, 19, 20, 28, 41, 78, 84, 115, 90	$\frac{d(product)}{dt} = -K[Substrate]$
67, 68, 69, 70, 54, 71, 112, 21, 22, 47, 50, 51, 52, 54, 25, 30, 77, 74, 35, 36, 37, 75	Direct Pass On
8, 17	$\frac{d(length)}{dt} = -K[Length] * [Substrate]$
42, 44, 46, 58, 59, 60, 66	Markovian Process (Transition Probability Matrix)

Table 1 : Transition Equations

List of Parameter Values (Initial State Conditions)

In situations where realistic values were not available for parameter values, we use a method of optimization combining simulated annealing [Kirk83] and game theory [Behavioral Game Theory] to arrive at the values listed. These values are listed in the table given at the end of the discussion.

We now describe in brief, the optimization approach employed. Simulated Annealing is a popular optimization strategy that is effective in situations where there less number of parameters over a larger period of time to arrive at better correlation with the cost function. Game Theory is combined with this approach previously presented by WARFT. [Mohan08] Game Theory is based on the combination of highly inter related parameters that vary heavily based on the change in the other. Game Theory is then used to select parameters or groups of parameters for the next round of optimization. This approach leads to better convergence and faster optimization [Mohan08].

This method is used to optimize the energetics model by combining parameters by the method mentioned above. Thereafter, the optimization methodology is used to tweak/optimize the parameters by repeatedly simulating and comparing the results with a predefined cost function. (In our case, The Voltage spike of the neuron is compared with experimental Spike distribution functions) The modification of parameters is done based on the optimization algorithm. [Thiagarajan11]

Concentration of Parameters

The initial concentration is based on the following two assumptions.

1. We assume the input to the system is realistic
2. We assume the transitions that represent the system is realistic

Based on the above two assumptions, we can say that the values obtained for individual parameters by a single traversal of the system will also be realistic. Thus, Parameters for which realistic concentrations were obtained are used as such. For other parameters, we use the above method (based on the assumptions to arrive at suitable values)

Compound	Initial Concentration (µM)
Na^+_i	15000
Na^+_e	180000
K^+_i	150000
K^+_e	70000
ATP	10800
ADP	1200
AMP	100
PDH	1328.241
Neurotransmitter I/P	$1.328241 * 10^{-11}$

Reaction Coefficients

We detail the values of 'K' (as described by the transition equations) used to obtain the simulated results. These values are obtained by the method described above.

Reaction Constants	Value
NMDA – Na Selectivity	0.8
Ca^{2+} Diffusion Coefficients	1.251
ATP Diffusion Coefficients	0.15 x 10-5 cm2/sec
DAG Diffusion Coefficients	1.7
PKC Diffusion Coefficients	1.8
IP3 Diffusion Coefficients	2.5
G-Protein Diffusion Coefficients	2.5
Neurotransmitter – Gprotein Dependence	0.1
Neurotransmitter – AMPA Dependence	0.7
Neurotransmitter – Cl Dependence	0.2
Glucose Transporter AMPk Dependence	0.8899
Pyruvate Glucose Rate Dependece	0.3559
Pyruvate Acetly COA Rate Dependence	0.4601
Acetyl COA Carboxylate Dependence	0.8394
CPTI Transporter Dependence	0.1912
Super Oxide Formation ETC Dependence	0.0211
Acetyl COA Krebs Cycle Factor	0.75,0.3
NADH,FADH PDH Inhibition Factor	0.4521
ETC Rate Factor	0.3500
UCP Uncoupling Factor	0.1492
ATP AMPK Factor	0.0091
BetaOxidation Factor	0.0102