The Neural model with Energy constraint

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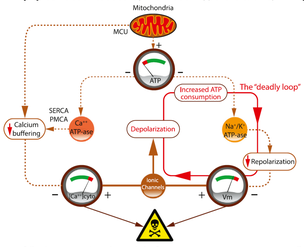
Background & Objective

The importance of energetics of neurons

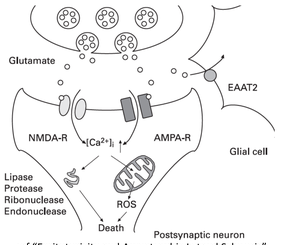
The brain takes much cost of energy as the consumption occupies 20% of the whole human body's one while the neural tissue's weight is only 2% of whole body[1]. Neurons are requiring high energy demands and maintaining homeostatic ATP level[2]. But if such a fundamental function is corrupted, they get malfunctions leading to cell deaths **(A)(B)** which is strongly related to neurodegenerative diseases such as ALS, Parkinson disease and Alzheimer disease[3)4)5)6)]. So studying the effect of ATP on neural activities has a huge benefit on understanding underlying mechanism of such diseases.

(A) Cell death caused by individual hyperexcitability



ref "A Computational Model of Motor Neuron Degeneration"

(B) Cell death caused by presynaptic hyperexcitability



ref "Excitotoxicity and Amyotrophic Lateral Sclerosis"

Despite such an importance, **the vast majority of previous neural models have been ignoring ATP kinetics of neurons** while others are considering it in the level of single neurons[7)8)9)] but because of their complexity, they don't allow us to simulate the network consisting of thousands of neurons. Actually, there are a few models explaining ATP effect on neural network[10)11)], but the problem is that they only consider about Na/K ATPase's ATP consumption even though neurons have various processes such as housekeeping, Glutamate or GABA recycling and Ca activities[12)13)14)15)] and didn't link ATP kinetics to individual behaviors either.

Objective

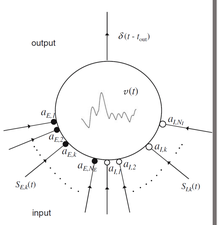
"To explore the relationship between the energetics of neurons and their behaviors constructing biologically plausible single neural model with low-running cost."

Leaky Integrate-and-Fire (LIF) model[16)]

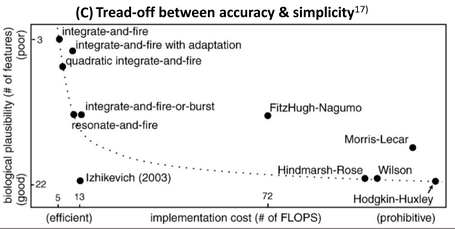
The model integrates presynaptic inputs, and the integrated input changes the membrane potential V_m following a R-C circuit during subthreshold (V_m<V_{th}). Also, V_m follows the rules below;

・If $V_m > V_{th}$, the neuron fires $V_m \rightarrow V_{ap}$.
・After the spike, $V_m \rightarrow V_{reset}$.

This model is the simplest model among many neural models **(C)** and can be extended with some specific factors such as adaptation and partial reset.



(C) Tread-off between accuracy & simplicity[17)]

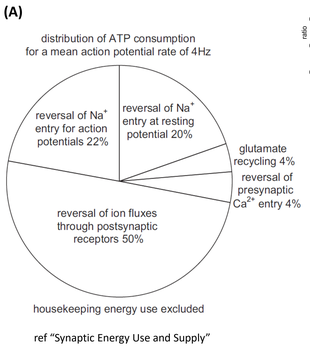


Method

EDLIF: Energy-Dependent Leaky Integrate-and-Fire model

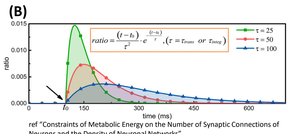
Formalization of ATP consumption (A_c)

(A)



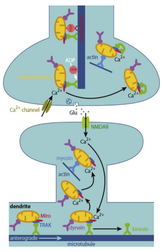
ref "Synaptic Energy Use and Supply"

(B)



ref "Constraints of Metabolic Energy on the Number of Synaptic Connections of Neurons and the Density of Neuronal Networks"

(C)



ref "Synaptic Energy Use and Supply"

We calculated the amount of ATP consumption required for each neural activity **(A)** based on values estimated by a previous article[13)].

We approximated the energy demand during subthreshold by that required for resting potential maintenance and assumed it as constant. We also assumed that housekeeping energy demand is constant over time. For our current research is focusing only on single neurons, we don't have synaptic input and thus neglected the synaptic transmission energy demands. During action potential, the abundant amount of sodium is intruding into the soma and Na pumps respond to the increase in intracellular sodium extruding the same amount of it with ATP consumption. Inspired by Ye Yuan et al[11)], we used an exponential function **(B)** to describe the time-delay spent on extruding all Na intruded during action potential.

Formalization of ATP supply (A_s)

ATP is provided mainly by mitochondria[18)] conveyed along microtubules **(C)**. Based on this assumption and Le Masson model, we used a simple equation of A_s dependent on the homeostatic ATP level ($[ATP]_h$) affected by mitochondrial state.

$$A_s = K([ATP]_h - [ATP]) \qquad (K = recovery\ rate)$$

K denotes the degree of recovery to homeostatic ATP level and set to 1.

ATP kinetics

$$\frac{d[ATP]}{dt} = A_s - A_c$$

ATP kinetics & Neuronal behavior

We incorporated the ATP kinetics into the reset potential V_{reset} considering Na^+/K^+ ATPase inactivation. Specifically, Na pump is described by the kinetic scheme[7)];

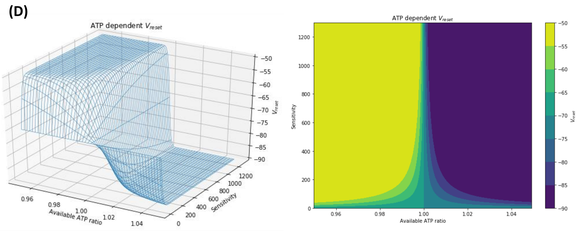
$$pump + 3Na_i^+ + 2K_o^+ + ATP \underset{kp2}{\overset{kp1}{\leftrightarrow}} pumpworking$$
$$pumpworking \underset{kp4}{\overset{kp3}{\leftrightarrow}} pump + 3Na_o^+ + 2K_i^+ + ADP + P$$

As this scheme proved explicitly, less ATP deactivates the pump and thus decreases the Na^+/K^+ ion gradient. This decrease reduces the amount of K outward after the spike prohibiting full-resetting of V_m. Based on this assumption we formalized ATP-dependent V_{reset} as below;

$$\alpha = \frac{V_{reset}}{V_{th}} - 1$$
$$\beta([ATP]) = 1 + \alpha \cdot (2 - (\frac{2}{1 + e^{-\frac{|ATP|_h - [ATP]}{|ATP|_h} sensitivity}}))$$
$$V_{reset}([ATP]) = \beta([ATP]) \cdot V_{th}$$

where "***sensitivity***" is assumed to denote the degree of deactivation depending on the density of pumps, morphological features, and other characteristics of the cell.

(D)



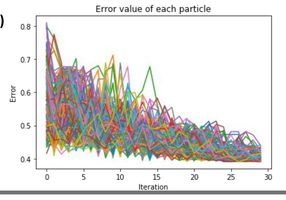
As shown above **(D)**, it's obvious that high sensitivity sharpens the sigmoidal curve indicating V_m is more sensitive to ATP changes in this condition.

Optimization

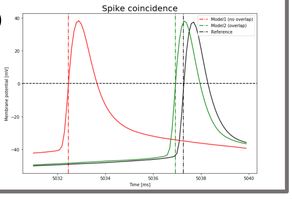
To fit our model to real spike trains and compare performances between our model and LIF model, we optimized both models using the dataset supplied by "Quantitative Single-Neuron Modeling: Competition 2009"[19)]. The data consists of 1 current stimulation profile and 13 voltage responses to it with 39s of duration. We used first 5s of voltage data for calculating g_{leak}, V_{reset}, EL and divided the rest into 80% for training and 20% for test to optimize other parameters (C_m, t_{ref}, V_{th} for LIF, C_m, t_{ref}, V_{th} & *sensitivity* for EDLIF).

We used PSO algorithm which was inspired by flocking behavior of birds where individuals are sharing the best positions for getting food and finally converges to that point[20)] **(E)**. As cost function, we measured spike-coincidence **Γ** between two spike trains based on the competition method[19)]. One coincidence is counted if the spike of model exists within ±4ms (precision) from that of reference **(F)**.

(E)



(F)



Results & Discussions

Performance

EDLIF model predicted spike timings better than LIF model. After the optimizations, *sensitivity* value got 558.62. Note that simulations of EDLIF were carried out with normal ATP condition ($[ATP]_h$ = 0.1 [mM]).

	C_m	V_{th}	t_{ref}	*sensitivity*	Test score
LIF	271.82	-51.36	1.00		0.57856
EDLIF	288.58	-51.77	10.00	558.62	0.61653

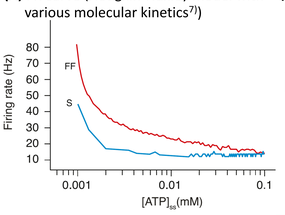
We could show that partial reset function contributes to generating accurate spikes suggesting that Na pump inactivation is an underlying mechanism of individual spiking during normal ATP condition.

ATP & Firing rate

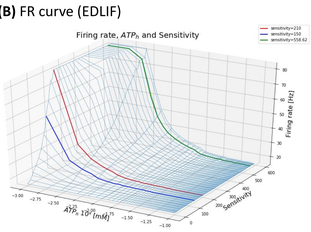
The figure **(A)** shows ATP dependent Firing-Rate (FR) curves of two types of neurons (FF, S) defined by different morphological features, obtained from Le Masson et al[7)]. Figure **(B)** shows ATP dependent FR curve of EDLIF with various sensitivity values and optimized parameters except sensitivity.

Regardless of the simplicity of our model, we succeeded to replicate various ATP-dependent Firing rate with different sensitivity values, e.g., 2 curves with sensitivity = 210,150 (red & blue) can be assigned to FF and to S respectively. The optimized sensitivity value 558.62 (green) suggests the neuron with that value is more sensitive to ATP deficit than FF cell. We could conceptualize the characteristics of cells using different values of sensitivity.

(A) FR curve (Hodgkin-Huxley model with various molecular kinetics[7)])



(B) FR curve (EDLIF)



Limitations & Future work

1) Collect the real data relating to intracellular ATP kinetics which is lacking so far.
2) Incorporate Ca kinetics and its effect on mitochondrial state in a computationally efficient way.
3) Validate more detailed model with the real data of ATP-dependent neural activities.
4) Combine single neural models with ATP-dependent neural plasticity and construct neural network.
5) Analyze the network dynamics and explore the effect of individual energy constraint on network level.

References

1) "Energetic basis of brain activity: implications for neuroimaging."
2) "The Energy Homeostasis Principle: Neuronal energy regulation drives local network dynamics generating behavior. "
3) "Excitotoxicity and Amyotrophic Lateral Sclerosis"
4) "The Function of the Mitochondrial Calcium Uniporter in Neurodegenerative Disorders"
5) "Mitochondrial Calcium Handling in Physiology and Disease"
6) "Mitochondrial dysfunction and intracellular calcium dysregulation in ALS"
7) "A Computational Model of Motor Neuron Degeneration"
8) "A Computational Model of Neuro-Glio-Vascular Loop Interactions"
9) "Neural Energy Supply-Consumption Properties Based on Hodgkin-Huxley Model"
10) "The Energy Coding of a Structural Neural Network Based on the Hodgkin–Huxley Model"
11) "Constraints of Metabolic Energy on the Number of Synaptic Connections of Neurons and the Density of Neuronal Networks"
12) "An Energy Budget for Signaling in the Grey Matter of the Brain"
13) "Evaluating the gray and white matter energy budgets of human brain function"
14) "Non-signaling energy use in the brain"
15) "The Energetics of CNS White Matter"
16) "A review of the integrate-and-fire neuron model: I. Homogeneous synaptic input"
17) "Which Model to Use for Cortical Spiking Neurons?"
18) "Synaptic Energy Use and Supply"
19) "Quantitative Single-Neuron Modeling: Competition 2009"
20) "Optimizing Particle Swarm Optimization Algorithm"