Modelling Neuromodulated Information Flow and Energetic Consumption at Thalamic Relay Synapses*

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Abstract. Recent experimental and theoretical work has shown that synapses in the visual pathway balance information flow with their energetic needs, maximising not the information flow from the retina to the primary visual cortex (bits per second), but instead maximising information flow per concomitant energy consumption (bits of information transferred per number of adenosine triphosphate molecules necessary to power the corresponding synaptic and neuronal activities) [10, 5, 11]. We have previously developed a biophysical Hodgkin-Huxley-type model for thalamic relay cells, calibrated on experimental data, and that recapitulates those experimental findings [10]. Here, we introduce an improved version of that model to include neuromodulation of thalamic relay synapses’ transmission properties by serotonin. We show how significantly neuromodulation affects the output of thalamic relay cells, and discuss the implications of that mechanism in the context of energetically optimal information transfer at those synapses.

Keywords: Brain energetics · Information theory · Energetic optimality · Neuromodulation.

1 Introduction

The brain consumes an inordinate amount of energy with respect to its size. It is responsible for about 20% of the whole body baseline energy metabolism at rest, while representing usually only 2% of its mass [9]. Over the last couple of years, attempts at theoretically or experimentally determining an energetic budget for the brain have all pointed to synapses as the locus where most of brain energy is being spent [7], with estimates putting their share of the brain’s signalling energy budget at roughly 60% [1, 13, 9]. A better understanding of brain energetics is essential because abnormal energy metabolism is an early

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2 Mathematical model of information transmission and concomitant energy consumption in thalamic relay cells

2.1 Hodgkin-Huxley formalism

We have previously published an experimentally calibrated biophysical single-compartment model of the Hodgkin-Huxley-type for thalamic relay cells [10]. Briefly, the model is written as follows: The Hodgkin-Huxley formalism describes
the dynamics of the membrane voltage $V$ as:

$$C_m \frac{dV}{dt} = - \sum_j i_j - i_{Hold} - i_{syn},$$  \hspace{1cm} (1)$$

with $C_m$ the membrane capacitance, $i_j$ the intrinsic currents, $i_{Hold}$ an experimentally injected holding current (see ref. [10] for further details) and $i_{syn}$ the synaptic currents. Following Bazhenov and colleagues [2], the intrinsic currents include a leak current $i_L$, a potassium leak current $i_{KL}$, an A-type potassium current $i_A$, a T-type low threshold calcium current $i_T$, an h-current $i_h$, a fast sodium current $i_{Na}$ and a fast potassium current $i_K$. All the intrinsic currents have the same general form:

$$i = g m^M h^N (V - E),$$  \hspace{1cm} (2)$$

where for each current $i$, $g$ is the maximal conductance, $m(t)$ is the activation variable, $h(t)$ is the inactivation variable, $E$ is the reversal potential, and $M$ and $N$ are the number of independent activation and inactivation gates.

The intracellular calcium dynamics is defined by:

$$\frac{dCa^{2+}}{dt} = - \frac{1}{\tau_{Ca}} (Ca^{2+}_{t,0} - Ca^{2+}_t) - A i_T,$$  \hspace{1cm} (3)$$

with $Ca^{2+}_{t,0} = 2.4 \times 10^{-4} \text{ mM}$, the baseline intracellular calcium concentration, and $A = 5.18 \times 10^{-5} \text{ mM cm}^2 \text{ ms}^{-1} \mu\text{A}^{-1}$, a constant. The time dependence for $m$ and $h$ is defined by:

$$\frac{dx}{dt} = \alpha_x (1 - x) - \beta_x x,$$  \hspace{1cm} (4)$$

where $x$ stands for either $h$ or $m$.

We refer the interested reader to ref. [10] for all further details of the model, and for a detailed description of experimental and calibration procedures.

### 2.2 Modelling synaptic input, synaptic depression and neuromodulation

In order to model the strong paired-pulse depression and neuromodulation that is known to happen at thalamic relay synapses, we use the formalism introduced by Tsodyks and Markram [20].

First, a sequence of binarized input action potentials is generated with a temporal resolution $\Delta t = 3 \text{ ms}$. In order to generate sequences with the same temporal statistics than recorded in vivo, we use sequences recorded in vivo (available from ref. [10]) to calculate the non-Poissonian in vivo inter-spike interval distribution. From this distribution, we calculate the cumulative distribution function of inter-spike intervals, and in turn, use that cumulative distribution function to generate synthetic binary sequences.
Each input is then used to trigger an AMPA and a NMDA conductance with the generic form:

\[
g(dt) = A \left( \exp(-dt/\tau_{\text{rise}}) - \exp(-dt/\tau_{\text{decay}}) \right),
\]

with \( \tau_{\text{rise}} \) and \( \tau_{\text{decay}} \) some time constants, \( dt \) the time elapsed since the input action potential and \( A \) an amplitude. Consecutive contributions are summed up.

In each case, the effective amplitude \( A \) of the triggered conductance is modulated by synaptic depression. To model this, we use a slight adaptation of the Tsodyks-Markram model [20], whereby the amplitude of the conductance is given by:

\[
A_{n+1} = A_n (1 - U) \exp(-\Delta t/\tau_{\text{rec}}) + AU (1 - \exp(-\Delta t/\tau_{\text{rec}})),
\]

with \( U \) and \( \tau_{\text{rec}} \) some parameters. Fitting that model on experimental data from ref. [10] yields \( U = 0.7 \) and \( \tau_{\text{rec}} = 620 \text{ ms} \) (to be described in details somewhere else). These parameters predict a paired-pulse depression of \( \sim 0.4 \) for consecutive pulses at 100 ms interval, in excellent agreement with what was observed in electrophysiological recordings [10]. Additionally, that procedure yields \( \tau_{\text{rise}} = 0.75 \text{ ms} \) and \( \tau_{\text{decay}} = 2 \text{ ms} \) for the AMPA conductance, and \( \tau_{\text{rise}} = 9 \text{ ms} \) and \( \tau_{\text{decay}} = 22 \text{ ms} \) for the NMDA conductance, and a ratio between the peak amplitudes of the NMDA and AMPA conductances of 0.1.

Thus, \( i_{\text{syn}} \) (see Eq. 1) is given by:

\[
i_{\text{syn}} = -g_{\text{AMPA}} (V - E_{\text{excitatory}}) - g_{\text{NMDA}} \left( \frac{9.69}{1 + 0.1688 e^{-0.0717V}} \right) (V - E_{\text{excitatory}}),
\]

with \( E_{\text{excitatory}} = 0 \text{ mV} \), the reversal potential of AMPA and NMDA receptors. The additional term in the description of the NMDA conductance is added to describe the nonlinear I-V relation of NMDA receptors due to the Mg\(^{2+}\) block [10]. In each case, \( g_{\text{AMPA}} \) and \( g_{\text{NMDA}} \) are determined by the procedure mentioned above combining Equations [5] and [6]. An example of what that procedure yields can be observed in the top two panels of Fig. 1 below.

Activation of serotonin receptors at thalamic relay synapses modulates the release probability of presynaptic vesicles. Specifically, the release probability is reduced and while this tends to lead to smaller postsynaptic potentials (PSPs), it makes consecutive PSPs more similar to each other in amplitude. The literature and preliminary experimental data (courtesy of D. Attwell, E. Engl and J.J. Harris) show that the presence of serotonin receptor agonists experimentally lead to reduced paired-pulse depression with the ratio of consecutive PSPs at 100 ms interval to be about \( \sim 0.8 \) (instead of \( \sim 0.4 \) in control conditions). This can be easily achieved in the model presented here by changing the value of the parameter \( U \) to 0.2, yielding an elegant and simple framework to study the effect of neuromodulation at thalamic relay synapses. An example of what that procedure yields can be observed in Fig. 2 below and can be directly compared with the results in Fig. 1.
Fig. 1. Model dynamics in absence of neuromodulation ($U = 0.7$). **Top row:** Binarized input sequence at time resolution $\Delta t = 3$ ms. Input action potentials are generated at approximately 20 Hz and their temporal dynamics follows experimental data recorded *in vivo* in rodents, i.e. their inter-spike interval distribution matches the inter-spike interval distribution observed *in vivo*. **Second row:** The dynamics of the AMPA and NMDA conductances with parameter values for amplitudes, time constants and synaptic depression derived from experimental recordings and following the Tsodyks-Markram model [20]. With $U = 0.7$, synaptic conductances display significant depression. A paired-pulse depression of $\sim 0.4$ is predicted in these circumstances (consecutive pulses at 100 ms interval), matching what was observed in electrophysiological recordings [10]. **Third row:** Dynamics of the membrane voltage of the thalamic relay cell predicted in response to the input sequence. **Bottom row:** Binarized output sequence at time resolution $\Delta t = 3$ ms. The thalamic relay cell model only produces 4 output action potentials in response to the top input sequence (the average output frequency is $\sim 4$ Hz). In general, those are synchronous with the first input following a relatively long silent period.
Fig. 2. Model dynamics with strong neuromodulation by serotonin ($U = 0.2$). **Top row:** Binarized input sequence at time resolution $\Delta t = 3$ ms. Input action potentials are generated at approximately 20 Hz and their temporal dynamics follows experimental data recorded *in vivo* in rodents. This is the same sequence as in Fig. 1. **Second row:** The dynamics of the AMPA and NMDA conductances with parameter values for amplitudes, time constants and synaptic depression derived from experimental recordings and following the Tsodyks-Markram model [20]. With $U = 0.2$, synaptic conductances display much less depression than in Fig. 1. A paired-pulse depression of $\sim 0.8$ is predicted in these circumstances (consecutive pulses at 100 ms interval), matching what was observed in preliminary electrophysiological recordings. **Third row:** Dynamics of the membrane voltage of the thalamic relay cell predicted in response to the input sequence. **Bottom row:** Binarized output sequence at time resolution $\Delta t = 3$ ms. The thalamic relay cell model now produces 6 output action potentials in response to the top input sequence. That output sequence is significantly different than the one at the bottom of Fig. 1.
2.3 Information flow and neuroenergetics

In order to assess information flow at the modelled feed-forward synapse, we collect the binarized input and output sequences with a temporal resolution of $\Delta t = 3\,$ms (see Fig. 1 top and bottom panels). We then apply the so-called direct method by Strong et al. [19] to compute the mutual information between those input and output sequences, similar to what has been done in [16] and [10]. A detailed description of how to use this method and others for the analysis of spike trains can be found in ref. [15]. Note also that it is possible to use the so-called transfer entropy to measure information flow between neurons [17], instead of the mutual information as we do here. We refer the reader to refs. [11, 6] for a comparative discussion of these measures in a context similar to the one discussed here.

The energy consumption in thalamic relay cells in this scenario arises from presynaptic activity and from the generation of output action potentials. Transport of ions across membranes during neural activity leads to the activation of the Na,K-ATPase electrogenic pump, which consumes adenosine triphosphate (ATP) molecules to maintain and reestablish normal ionic gradients [9, 1, 13]. It is thus possible to compute the energetic cost of neuronal activity (number of ATP molecules consumed in response to that activity) using biophysics as described in [1, 10, 11].

3 Modulation of transmission properties by the neuromodulator serotonin

Figure 1 shows typical data generated by the model in the scenario corresponding to the control experimental situation described in ref. [10], i.e. with strong paired-pulse depression ($U = 0.7$). Strong depression is apparent in the second panel from the top, where each input action potential following the first action potential after a long period of silence only evokes a much reduced conductance. As a result, the model, like the cells it is based on, tends to generate outputs only when two input action potentials come in close succession to each other (this is not always the case, however, as a single input action potential can be seen to trigger an output spike at time bin 7000). While the model receives input action potentials at a frequency of $\sim 20\,$Hz, it generates output action potentials at only $\sim 4\,$Hz.

Figure 2 shows typical data generated by the model in the scenario corresponding to application of serotonin, i.e. with weak paired-pulse depression ($U = 0.2$). The binary input sequence is the same as the one used in Fig. 1. Weak depression is apparent in the second panel from the top, where each input action potential triggers in average smaller conductances, but with amplitudes more evenly distributed over time. A comparison between Figs. 1 and 2 reveals that even though the model is driven in both cases by the same binary input sequence, the voltage trajectory of the cell is very significantly affected by changing the value of $U$, and the binary output sequence of the cell is now largely different.
These results suggest that neuromodulation at these synapses could have a significant effect on the quantity and type of information that reaches the primary visual cortex.

![Graph](image.png)

**Fig. 3.** Energetic optimality of information transfer at thalamic relay synapses. Mutual information (bits/sec) divided by concomitant energetic costs (ATP/sec), factoring the cost of reverting ionic flows across the cellular membrane resulting from the activation of postsynaptic receptors (top curves), or resulting from the activation of postsynaptic receptors and from the generation of action potentials (bottom curves). The parameter $U$ is chosen to be either $U = 0.7$ to match control experimental conditions or $U = 0.2$ to model the application of serotonin receptor agonists. An overall gain factor is applied to the synapse with gain $= 1$ matching the experimental physiological gain in control conditions. The curves reveal the presence of an optimum at, or slightly above, gain $= 1$ [10]. Shifting from $U = 0.7$ to $U = 0.2$ appears to shift the peak of each curve slightly to the right, and to slightly broaden the peak.

We then tested whether this type of neuromodulation affects the energetic optimality of information transmission at these synapses. To this end, we ran simulations varying the overall gain of the thalamic relay synapse and measured the mutual information between the input and output sequences [10, 11] using the direct method [19]. We additionally computed the equivalent energetic budget using standard biophysical methods developed in ref. [1]. We observed that, while changing the value of $U$ does affect absolute values, the energetic...
consumption (measured in ATP/sec) associated with the generation of postsynaptic potentials, or with the generation of postsynaptic potentials and action potentials, scales more or less linearly with the gain of those synapses, whatever the value of $U$ (not shown). This matches what has been observed elsewhere [9–11]. We also observed that, while changing the value of $U$ does affect absolute values, information flow across the relay synapse (measured in bits/sec) scales sigmoidally with the gain of those synapses (not shown). Again, this matches what has been observed elsewhere [9–11].

We then computed in each scenario the ratio of information flowing through the synapse to the concomitant energy consumption necessary to power the synaptic and neuronal activity of the thalamic relay neuron. Preliminary results displayed in Figure 3 show that this results in curves with a relatively well-defined energetic optimum for information transmission, whether $U = 0.7$ or $0.2$, and whether the energy budget includes the cost of postsynaptic potentials alone (top curves), or also includes the cost of postsynaptic potentials and action potentials (bottom curves). In all cases, the energetic optimum stood at, or close to, gain = 1, the physiological gain of the synapse in control conditions. This is in excellent accordance with experimental findings and a previous version of this model (driven by experimentally-recorded conductances). Despite its significant effect on the actual output sequences generated by the thalamic relay neuron, neuromodulation (shifting from $U = 0.7$ to $U = 0.2$) only appears to shift the peak of each curve slightly to the right, and to slightly broaden said peak.

4 Discussion

Here, we have introduced a carefully-calibrated mechanistic [14] model of synaptic depression and neuromodulation by serotonin at thalamic relay synapses. We have described how to build and calibrate such a model using experimental data, and together with the work in ref. [10], we have established that it qualitatively, and to some extent quantitatively, captures the behaviour of biological thalamic relay neurons, in particular here, with respect to modelling in vivo-like synaptic inputs, including their modulation by serotonin.

The results presented here suggest that neuromodulation by serotonin does not very significantly affect the energetic optimality of information transmission at thalamic relay synapses. The fact that neuromodulation does not very strongly affect the position of the peak in the information over energy curves, and the fact that this peak sits at the experimentally observed physiological gain for those synapses (gain = 1), reinforces the notion that this principle might be a relatively generic design principle in the brain. This model thus also contains normative (energetic) aspects [14]. It is our contention that synaptic activity has evolved under, and is to an extent shaped by, energetic constraints [9–11, 5].

Neuromodulation does, however, very significantly affect what output sequences are sent out to the primary visual cortex in response to a given input sequence. In other words, it appears to change the encoding of visual information. Our model thus opens now the possibility to systematically investigate what
kind of input sequences will maximise under different circumstances information flowing from the retina to the primary visual cortex.

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