The metabolic cost of Neuronal Activity

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Introduction

Although the brain represents only **2**% **of the body weight**, about **20**% **of the oxygen** and **25**% **of the glucose** consumed by the human body are dedicated to cerebral functions (*Attwell D and Laughlin SB, 2001*).

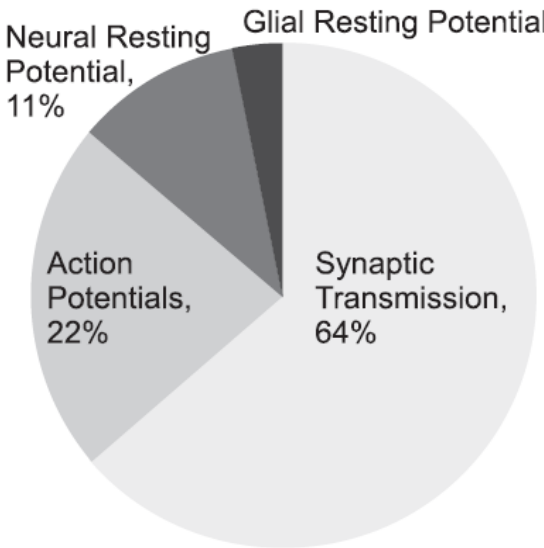

Figure 8. A revised energy budget for signaling in the grey matter of the rat brain. Incorporating the increased efficiency of action potentials in mammalian neurons into Attwell and Laughlin's [1] original energy budget for grey matter in the rat brain reduced the proportion of the energy budget consumed by action potentials. The proportion of the energy budget consumed by synaptic transmission is increased.

Energy substrates

- **Glucose** is the obligatory energy substrate of the adult brain. Nevertheless, under particular conditions the brain has the capacity to use other **blood-derived** substrates:
  - **Ketone bodies** during development, starvation and hypoglycemia (*Magistretti, 2008*);
  - **Lactate** during periods of intense physical activity (*van Hall et al. 2009*).

Why should we care about brain energy metabolism?

- The impaired energy metabolism in the brain detected by neuroimaging studies has been shown to be associated with diseases like bipolar disorder, major depression, cardiac arrythmia or Traumatic brain injury *(Murashita J. et a. 2000; Joanne S. Ingwall 2009; Stephen J. DeVience et al. 2017)*.
- A better understanding would be of great importance and would have widespread consequences not only for biology and medicine but also for psychology, psychiatry, and sociology.

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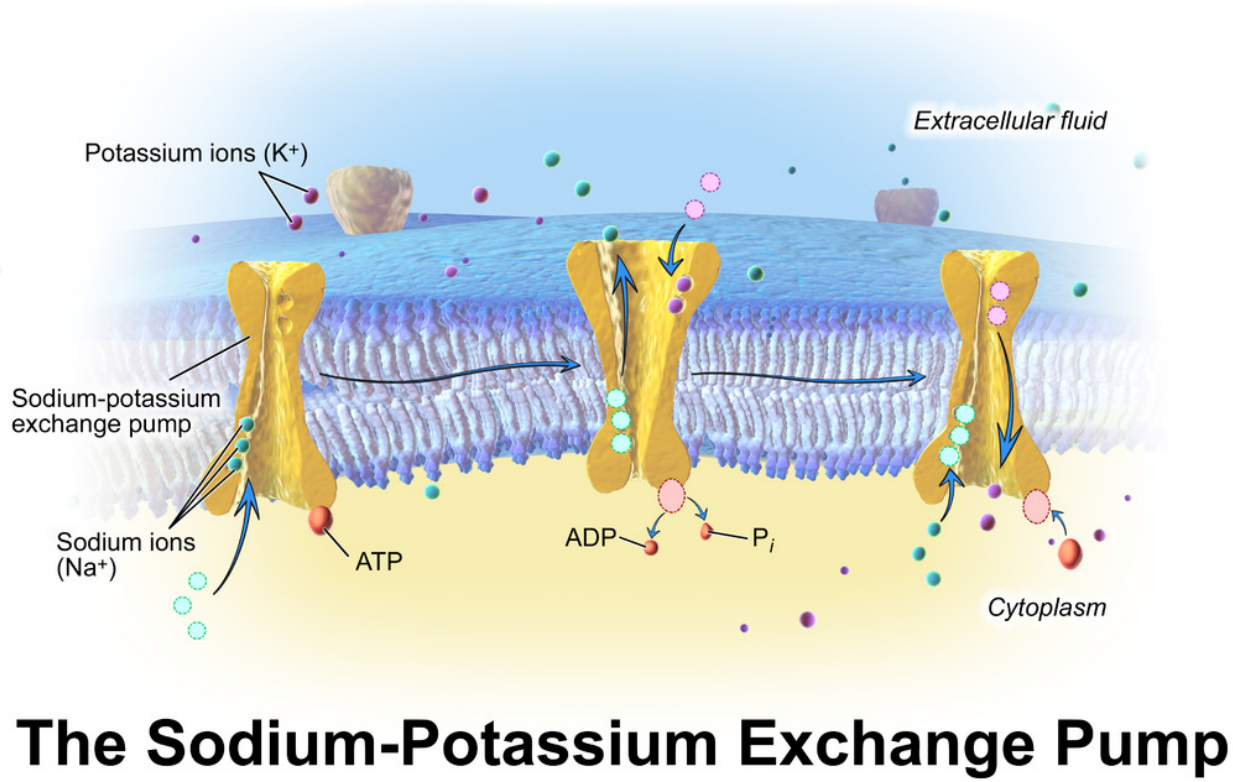
Action potentials generation

- Action potential generation is the process by which a neuron rapidly depolarizes from a negative resting potential to a more positive potential, and is achieved by influx of cations (sodium ions or calcium ions) through ion channels.
- It occurs at the action potential initiation zone region of the soma, and is propagated along the axon to downstream targets.

Action potentials generation

- The energy consumption of mammalian brains is tightly linked to the generation and conduction of action potentials (APs), mainly in axons, and by the ensuing synaptic transmission (*Attwell D and Laughlin SB, 2001*).
- The energy consumption of APs is due to the influx of Na^+ ions and efflux of K^+ ions through voltage-gated ion channels, which charge the membrane capacitance to the peak of the AP and then discharge it back to resting potential.
- To maintain signaling the Na+/K+ ATPase pumps these ions back across the membrane using energy provided by **Adenosine triphosphate (ATP)** (*SKOU JC (1957)*).

Action potentials generation



The Sodium-Potassium Exchange Pump

Source: Wikepedia

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Ion counting approach

- In most previous studies, the metabolic cost of APs was based on Na^+ influx, which was then converted to the total ATP required by Na^+/K^+-ATPase pumps to restore ion gradients after an AP.
- The **Na^+ load** provides an estimate of the **number of pump cycles**, or ATP molecules, that the pump will need to reestablish the resting state of the neuron.

Ion counting approach

- The number of ATP moles(ATPmols) can be computed as

$$ATPmols = \frac{Q_{Na}}{3eNA}$$

where Q_{Na} is the amount of **Na+ load** crossing the membrane during a single AP. $e = 1.60210^{19}$ C is the electric charge and $NA = 6.02210^{23}$ is the Avogadro constant.

- For the other hand, the energy available for chemical work from the ATP concentration is measured by the free energy of ATP hydrolysis (F_{ATP}). This allows an estimate of the metabolic energy associated with ionic pumping as the free energy times the number of ATP moles, that is,

$$\text{Metabolic energy (kJ/mol)} = F_{ATP} * ATPmols$$

.

Ion counting approach: shortcomings

The Na+ counting method is controversial for many reasons:

- it **underestimates** the metabolic costs for neurons in which ions other than Na+ and K+ also play key roles in AP generation.
- Inward Na+ and outward K+ overlap during the action potential generation, introducing an uncertainty in the calculation of Na+ ions.
- In addition, the transmembrane enzyme ATPase moves per cycle **three Na+ ions outside** the cell and only **two K+ ions inside**. This **unbalanced electric exchange** generates controversy about whether to use **one third** or **half** the number of sodium ions to estimate the number of pump cycles.

Ion counting approach: shortcomings

The clarification of these controversies is important,

1. at the cellular level giving the **correct estimates of energy use** associated with the different neural processes,
2. at the level of noninvasive imaging methods based on local metabolic rate changes (**to know how energy utilization contributes to the signals detected by these techniques**).

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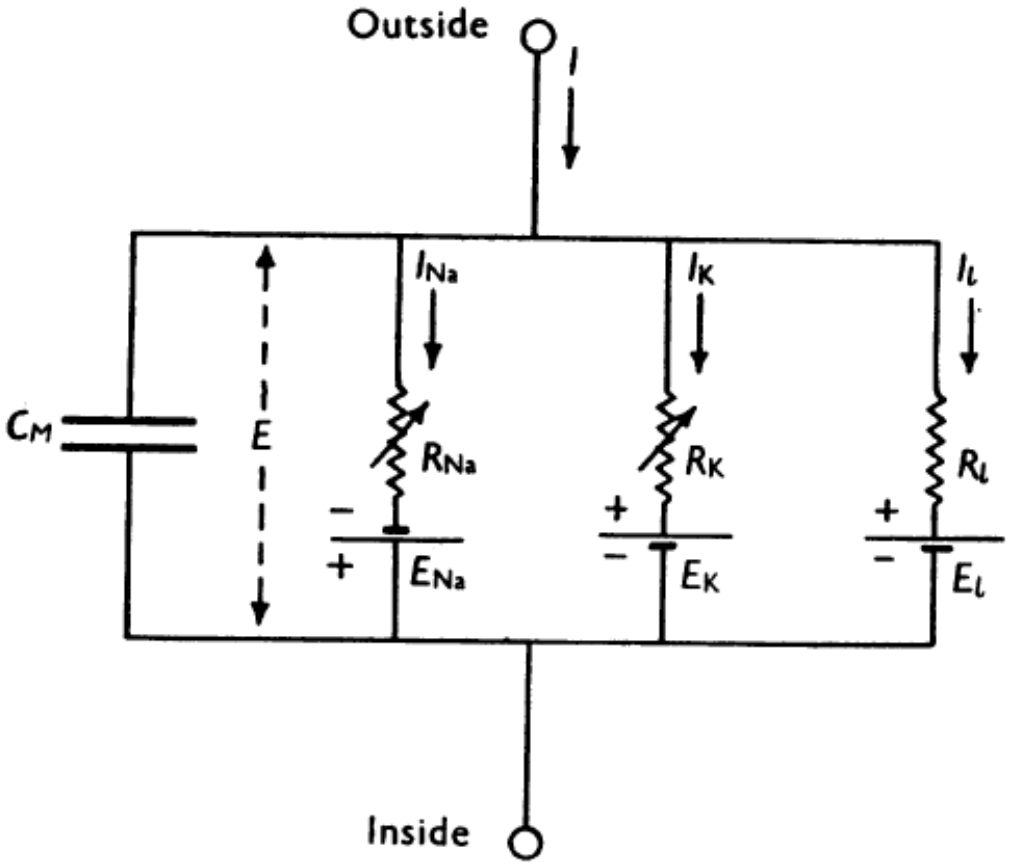
Hodgkin-Huxley neuron model

- Neuron models are frequently used to represent the dynamics of real neurons **but hardly ever to evaluate the electrochemical energy required to maintain that dynamics**.
- We consider that if the Hodgkin-Huxley electric circuit is **a valid tool** to investigate the dynamics and electrical properties of neurons, it will be also valid to analyze the actual energy the neurons demand to produce that dynamics.
- The classical Hodgkin-Huxley description was not only accurate, it was also readily extensible to many other voltage-dependent currents.

Hodgkin-Huxley circuit



The Hodgkin-Huxley circuit (Hodgkin, A.L., and Huxley 1952).

Hodgkin-Huxley dynamics

In the original Hodgkin-Huxley model, the dynamics governing the membrane potential is described by the following membrane equation:

$$C\frac{dV}{dt} = -i_{Na} - i_K - i_l + I, \tag{1}$$

where
$i_{Na} = g_{Na}m^3h(V - E_{Na})$ is the Sodium current.
$i_K = g_K n^4(V - E_K)$ is the Potassium currrent.
$i_l = g_l(V - E_l)$ is the leakage current.
I is the total membrane current density

Hodgkin-Huxley dynamics

The gating variables m,h and n, representing respectively Na+ channels activation and deactivation variables, and K+ channels activation variable, obey the standard kinetic equation $\frac{dx}{dt} = \alpha_x(1-x) - \beta_x x$, $(x = m, h, n)$, where α_x and β_x are voltage-dependent variables. For sodium channels, the activation and deactivation rates are given by,

$$\begin{aligned}
\alpha_m(V) &= (2.5 - 0.1V)/(\exp(2.5 - 0.1V) - 1), \\
\beta_m(V) &= 4\exp(-V/18), \\
\alpha_h(V) &= 0.07\exp(-V/20), \\
\beta_h(V) &= 1/(\exp(3 - 0.1V) + 1).
\end{aligned}$$

and for potassium channels,

$$\begin{aligned}
\alpha_n(V) &= (0.1 - 0.01V)/(\exp(1 - 0.1V) - 1), \\
\beta_n(V) &= 0.125\exp(-V/80).
\end{aligned}$$

The electrochemical energy function

The total electrical energy accumulated in the circuit at a given moment in time is,

$$H(t) = \frac{1}{2} CV^2 + H_{N_a} + H_K + H_l, \tag{2}$$

where the first term in the summation gives the **electrical energy accumulated in the capacitor** and represents the energy needed to create the membrane potential V of the neuron.
The other three terms are the respective **energies in the batteries needed to create the concentration jumps in sodium, potassium, and chloride**.

The electrochemical energy function

Thus, the total derivative with respect to time of the above energy will be,

$$\dot{H}(t) = CV\dot{V} + i_{N_a}E_{N_a} + i_K E_K + i_l E_l. \tag{3}$$

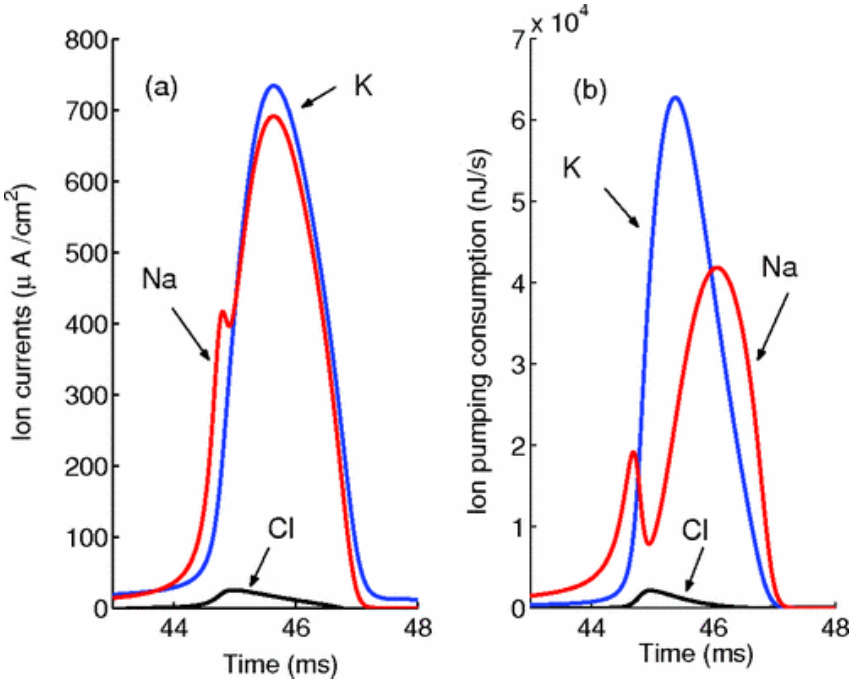
If we substitute Eqs. (1) and the corresponding expressions of i_{Na}, i_K and i_l in Eq. (3), we have for the energy rate in the circuit,

$$\dot{H} = VI - g_{N_a}m^3h(V - E_{N_a})^2 - g_K n^4(V - E_K)^2 - g_l(V - E_l)^2, \tag{4}$$

The electrochemical energy function

- The first term in the right hand summation represents **the electrical power given to the neuron via the different junctions** reaching the neuron;
- the other three terms of the summation represent the **energy consumed by the ion channels**.
- his equation permits evaluation of the total energy consumed by the neuron and also gives information about the consumption associated to each of the sodium, potassium and leaking channels.

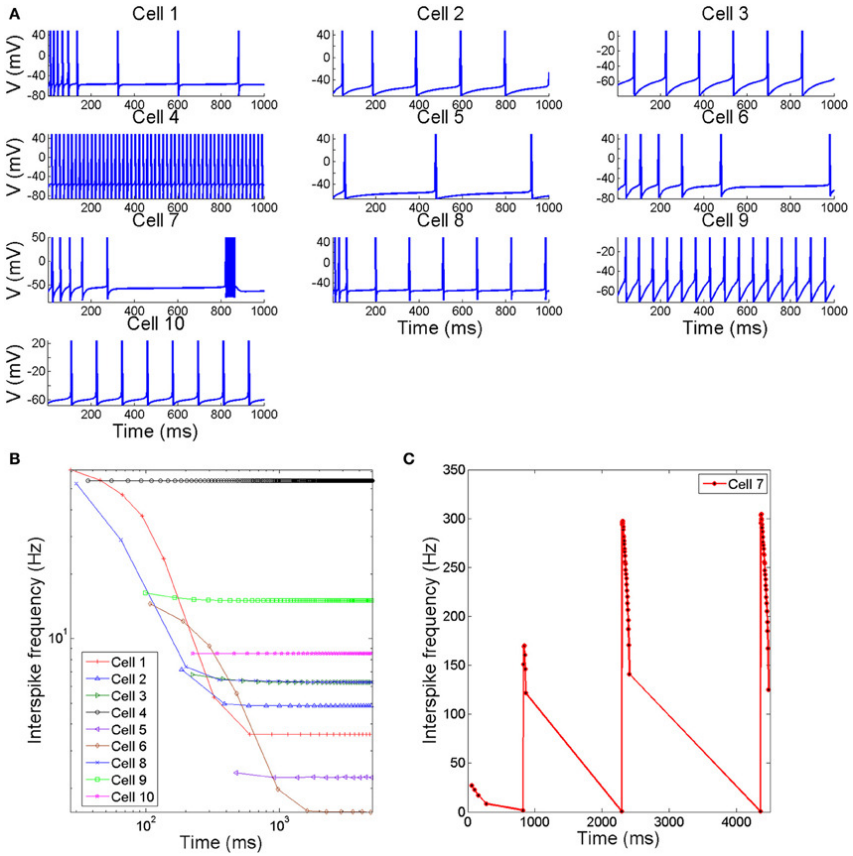
The electrochemical energy function



The electrochemical energy function: some results

- Moujahid, A. et al. Energy and information in Hodgkin-Huxley neurons (2011) Physical Review E - Statistical, Nonlinear, and Soft Matter Physics, 83 (3), art. no. 031912.
- Moujahid, A., d'Anjou, A. Metabolic efficiency with fast spiking in the squid axon (2012) Frontiers in Computational Neuroscience, (NOVEMBER 2012), art. no. 95
- Moujahid, A. et al. Energy demands of diverse spiking cells from the neocortex, hippocampus, and thalamus (2014) Frontiers in Computational Neuroscience, 8 (1 APR), art. no. 41,

The electrochemical energy function: some results



The electrochemical energy function: some results

Table 3 | Ionic flux and energy demands of single action potentials from different spiking cells when stimulated by prolonged current stimulus slightly greater than threshold.

	RS cells			FS cells		IB cells			TCR	RHI
	Cell 1	Cell 2	Cell 3	Cell 4	Cell 5	Cell 6	Cell 7	Cell 8	Cell 9	Cell 10
Frequency (Hz)	5	5	6	54	2	2	15	7	15	9
Na^+ load	174	207	134	162	217	132	103	147	69	163
K^+ load	141	214	150	156	197	137	117	133	79	127
Capacitive minimum	65	108	70	22	129	37	15	51	55	125
Overlap load (nC/cm^2)	109	99	64	140	88	95	88	96	14	38
Charge separation	0.38	0.52	0.52	0.14	0.60	0.28	0.14	0.35	0.79	0.77
ATP Pmole	0.60	0.72	0.46	0.56	0.75	0.46	0.36	0.51	0.24	0.56
Metabolic Energy (ion-counting method) (nJ/cm^2)	30	36	23	28	38	23	18	25	12	28
Ionic Energy (From Equation 7) (nJ/cm^2)	30	34	20	24	38	23	18	30	12	23
ATP Hydrolysis (kJ/mol)	49.14	47.03	43.93	41.96	51.15	49.70	51.91	59.95	48.78	40.82
Stimulus (μ A/cm^2)	1.4	0.7	0.15	1.75	0.8	0.25	0.25	2.25	0.44	0.20

The metabolic energy refers to the energy computed according to the ion-counting approach (section 2.3), and the ionic energy accounts for the electrochemical energy computed as the integral of the energy functions given by Equation (7).

The electrochemical energy function: some results

Cell 1:	RS cell as observed from ferret Visual Cortex in vitro
Cell 2:	RS excitatory cell as observed from somatosensory cortex in vitro
Cell 3:	RS inhibitory cell as observed from somatosensory cortex in vitro
Cell 4:	FS cell as observed from ferret Visual Cortex in vitro
Cell 5:	FS cell as observed from somatosensory cortex in vitro
Cell 6:	IB cell as observed from guinea pig somatosensory cortex in vitro (Initial burst followed by adaptive action potentials)
Cell 7:	IB cell as observed from guinea pig somatosensory cortex in vitro (Repetitive bursting)
Cell 8:	IB cell as observed from cat visual cortex
Cell 9:	TCR cell as observed from Mouse thalamocortical relay neuron
Cell 10:	RHI cell as observed from Rat hippocampal interneuron

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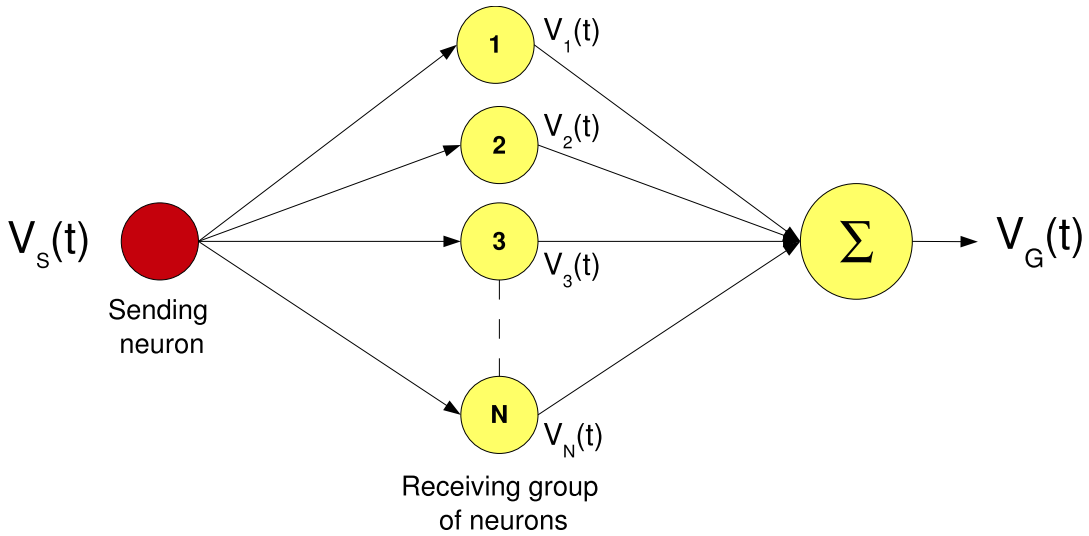
Energy efficiency

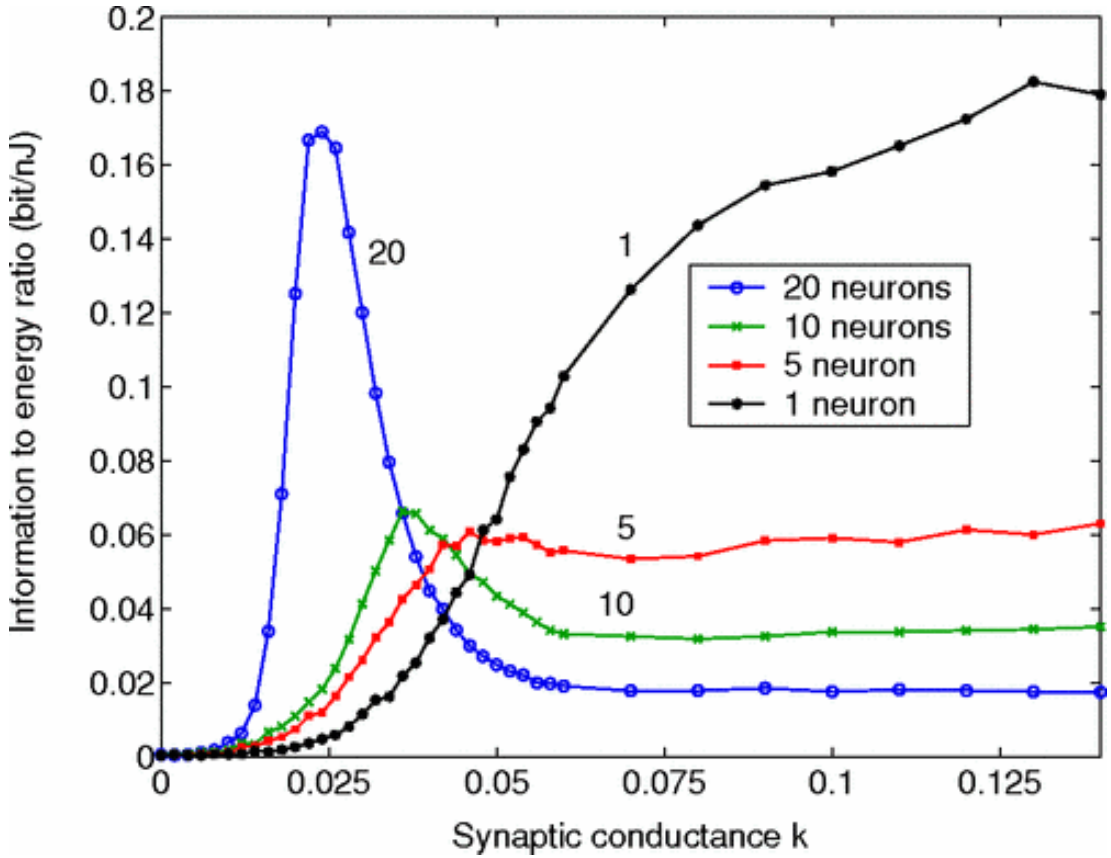
- The evaluation of the cost of information requires the knowledge of both **the metabolic energy cost** and **the amount of information transmitted** by a train of action potentials.
- Shannon's information theory provides a framework to quantify the amount of information that neurons can convey during its signaling activity.

Energy efficiency: A first approximation



Entropy and mutual information are calculated for variables $V_S(t)$, train of spikes of the sending presynaptic neuron, and $V_G(t)$, sum over all individual $V_i(t)$ receiving postsynaptic trains of spikes.

Energy efficiency



Phys. Rev. E 83, 031912

Energy efficiency

- when **the receptor is a single neuron** the increase in mutual information with the coupling conductance is faster than the corresponding increase in metabolic energy consumption. This results in a monotonic increase of the energy efficiency with the coupling conductance.
- On the contrary, **for groups of receiving neurons** there are values of the synaptic conductance, with relatively low consumption, **that optimize the ratio of mutual information to metabolic energy consumption**. For groups of receiving neurons maximum efficiency does not require maximum energy consumption.

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What about the brain energy demands during sleep.

- The main goal is to investigate the energy demands of the brain under different sleep stages and compare them to those corresponding to the waking state.

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