Energy Efficiency and Neural Function

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Zoology
Overview

- Nervous systems use significant quantities of metabolic energy
- Much of this energy is used for signalling
- Energy demands limit representational capacity
- Nervous systems have evolved energy efficient neural codes and circuits
Energy usage by mammalian brain

- Human brain 2% of body mass
  20% of BMR
- Brain has high Specific Metabolic Rate (rate per gram)
  - SMR, cortical grey matter ≈ heart muscle
- Blocking signaling depresses total brain MR by 50%
- Blocking Na/K pump depresses total brain MR by 60%
- Signaling costs, esp. ions fluxes, are significant
  - How are these costs incurred?
- So are fixed costs
  - macromolecular synthesis (10-20%), resting potentials (10%)
    intracellular transport? mitochondrial proton leak?
Two ionic conductances (sets of ion channels), $g_L$ and $g_K$

with different reversal potentials $E_L$ and $E_K$

carry ions L and K across the membrane to produce currents $i_L$ and $i_K$

$E_L$ and $E_K$ are generated by differences in the concentration of ions L and K

To maintain $E_L$ and $E_K$ the ions that flowed across the membrane are pumped back by an ion pump that is powered by the hydrolysis of ATP to ADP

Involvement of energy in electrical signalling - a basic circuit
Sokoloff’s Method

- Measures local rates of glucose utilisation, averaged over minutes and hours
- 2-Deoxyglucose – transported into cells but not broken down
- Accumulation of radioactively labeled $[^{14}\text{C}]-2\text{DG}$ measures total glucose uptake
- Autoradiography provides reasonable spatial resolution
- Temporal resolution is poor
Sokoloff’s 2-[\textsuperscript{14}C]-deoxyglucose method

Macaque V1, incubated with \textsuperscript{14}C-DG and exposed to radial stimulus for 45’.

Expt. by Roger Tootell,

Figure from Eye, Brain & Vision
David Hubel, Sci.Am Library
1988
Orientation columns in V1

Incubated with $^{14}$C-DG and stimulated with vertically moving Stripes

From Hubel, *op.cit.*
functional imaging - fMRI
Sokoloff’s conclusions

• Neuronal glucose uptake is increased by stimulating neural activity, and reduced by depressing activity
• Energy consumption rises progressively with the level of activity
• Uptake is local - glucose is being used by active neurons

Which neural mechanisms consume energy and how much?
Bottom-up energy budgets
(Attwell & Laughlin, 2001; Lennie 2003)

• Use biophysical data to establish how much ATP is used when a signal is transmitted by a particular component
  – e.g. a synapse

• Use anatomical data to establish how many components are involved
  – e.g. number of synapses per mm$^3$

• Use physiological data to establish how many signals are generated by active components
  – e.g. spike rate x probability that a spike activates vesicle release at a synapse
Neocortex contains \(10^{10}\) neurons

(human body contains \(10^{13} - 10^{14}\) cells)

making circuits using \(10^{14}\) synaptic connections
Peep inside; a lot of it looks like this

Dendrites (D) of CA1 pyramidal cells – EM section by Dr J. Spacek, Charles Univ Czech Rep. Visit Synapse Web [http://synapses.mcg.edu](http://synapses.mcg.edu) for more details
Average pyramidal cell in mouse neocortex
(Braitenberg & Schuz)

Receives @8000 synapses
Transmits @8000 synapses
Using 4.5 cm connections in grey matter (axon collaterals)
Wiring density 3-4 km/mm³
Total wiring in human cortical grey matter $10^5 - 10^6$ km
Anatomical data and simplifying approximations that enabled by Attwell and Laughlin to construct an energy budget for cortical grey matter

A pyramidal neuron receives 8000 glutamatergic synapses, from other pyramidal neurons

80% of neurons are pyramidal cells
90% of synapses are glutamatergic
10% of synapses enter an area of grey matter from outside

We are dealing with a closed system in which, to a first approximation, all neurons are pyramidal cells and all synapses are identical glutamatergic boutons
Energy is used to

1. send spikes (a.p.'s) to synapses and
2. drive signals across synapses

The average neuron, signals by sending an action potential to its 8000 output synapses

This spike traverses the 4.5 cm of axon collateral laid out in grey matter by the average cell.

Each synapse delivers current to a neuron that is sitting at the average membrane potential of a pyramidal neuron, recorded to be -65mV

On average a neuron receives as much synaptic current as it delivers
Energy usage per synapse per spike

- 4000 glutamates @ 2.67 ATP per glu
  11,000 ATP

- 12,000 Ca$^{2+}$ @ 1 ATP per Ca$^{2+}$
  12,000 ATP

**NMDA**
- 180,000 Na$^{+}$ @ 0.33 ATP per Na$^{+}$
- 10,000 Ca$^{2+}$ @ 1 ATP per Ca$^{2+}$
  70,000 ATP

**Non-NMDA**
- 200,000 Na$^{+}$ @ 0.33 ATP per Na$^{+}$
  67,000 ATP
energy used by a synapse

A

energy use per vesicle released

ATPs consumed per vesicle

% energy consumed per vesicle

non-NMDA

NMDA

mGlur

glu recycling

endol/exocytosis

presyn Ca
Energy required to transmit an action potential

1. Area of membrane and level of depolarisation defines the capacitative current

2. Total Na\(^+\) influx
\[ \approx 4 \times \text{capacitative current} \]
(because Na and K currents overlap)

3. BUT recent papers show that energy efficient a.p.’s reduce overlap to less than 20% (Alle et al, Science, 2009; Carter and Bean, Neuron, 2009; Sengupta et al, PLoS Comp.Biol 2010)
Energy used to transmit the a.p. to the pyramidal cell’s synapses

- a.p. propagates throughout neuron’s collaterals (4 cm x 0.3 microns dia.) and depolarises membrane by 100mV
- Add to this the passive and/or active depolarisation of the dendrites and cell body by the back-propagating a.p.
Usage per a.p. per neuron
(4cm axon, 8000 synapses, p-release = 0.25)

energy use per action potential

ATPs per action potential (x10^6)

% energy per action potential

AP  non-NMDA  mGluR  glu recycling  presyn Ca
Energy consumption limits average spike rate in rodent grey matter to $\approx 4$ Hz
Energy efficient codes, Levy and Baxter – Case 1

$n$ “binary” neurons that fire a spike in a given time interval with probability $p$

Available signal states
\[ n! / [(np)!(n - np)!] \]

In bits
\[
C(n, np) = \log_2 \left[ \frac{n!}{(np)!(n - np)!} \right]
\]
\[
= nH(p) - \log_2 (\sigma \sqrt{2\pi}) \approx nH(p)
\]

$\sigma = \text{s.d. of binomial} = [np(1-p)]^{0.5}$

$H(p) \equiv -p \log_2 p - (1 - p) \log_2 (1 - p)$

Define energy used when resting for a unit time as 1 unit
A spike increases consumption by a factor $r$

\[ E = n(1 - p) + np r = n[1 + p(r - 1)] \]

Efficiency
\[
\frac{C}{E} \approx \frac{H(p)}{1 + p(r - 1)} \quad \text{Bits per unit energy}
Levy and Baxter – Case 1
energy efficiency, $C/E$, and firing probability, $p$
at different ratios of resting cost to spike cost, $r$

The effect of $r$ on efficiency

the optimum $p$ falls as $r$ rises
Levy and Baxter Case 2

$n$ “analogue” neurons – each capable of signalling several levels as frequency, $f$, measured as number of spikes, $j$, over time $T$, up to a maximum of $N/T$ spikes

$$f_j = \{0, 1/T, 2/T, \ldots, N/T\}$$

For the $i^{th}$ neuron

$$C_i = -\sum_{j=0}^{N} p_j \log_2 p_j$$

For $n$ neurons

$$C \approx nC_i, \quad C_{\text{max}} = n\log(N+1)$$

To derive $C_i$ as a function of average firing frequency, $\mu$, use the discrete probability distribution $p_j$ that maximises entropy, the geometric distribution

$$p_j = \frac{\mu^j}{(1+\mu)^{j+1}}$$

giving

$$C_i = -\mu \log_2 \mu + (1+\mu) \log_2 (1+\mu) \quad \text{where} \quad \mu = \bar{f}T,$$

$$C = nC_i$$
Case 2 energy cost & efficiency

\[ E = \sum_{i=1}^{n} (1 + k \tilde{f}_i) = \sum_{i=1}^{n} (1 + k \tilde{f}) = n(1 + k \tilde{f}) \]

where \( k = (r - 1)/f_N \)
Conclusions

1. The energy cost of signalling with synapses and spikes is significant.
2. Energy efficiency can be analysed using information theory to relate representational capacity to the distribution of signals and their cost.
3. The optimum distribution of firing rates depends on the ratio between the cost of generating a signal (the signal cost) and the cost of remaining silent (the fixed cost).
4. Sparse codes in which neurons spike infrequently on average, are energy efficient when, as suggested by energy budgets, the signalling:fixed ratio is >10:1.
5. Real neurons may fire even less frequently than predicted. This reduces energy costs but at the expense of not using the available circuitry efficiently.
6. Are there are other reasons for having a multiplicity of circuits (salience, complexity)?