

# Neuronal energy consumption: biophysics, efficiency and evolution

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Electrical and chemical signaling within and between neurons consumes energy. Recent studies have sought to refine our understanding of the processes that consume energy and their relationship to information processing by coupling experiments with computational models and energy budgets. These studies have produced insights into both how neurons and neural circuits function, and why they evolved to function in the way they do.

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## Introduction

*Neurons consume energy.* Appreciating that they do so is essential for understanding and interpreting the function and evolution of neurons, neural circuits and, ultimately, whole brains. Yet we must go beyond mere appreciation by relating specific molecular components and processes to the energy they consume and the work they contribute to processing information and generating behavior. This permits determination of both ‘how’ and ‘why’ processes consume energy, and an understanding of the key trade-offs that have influenced neural evolution (reviewed in [1,2]). Although neuronal energy consumption has been studied for over 80 years [3,4], conceptual and methodological breakthroughs [5–9] have prompted renewed interest in the causes and consequences of neuronal energy consumption over the last ~20 years. Here I review this recent progress in our understanding of how the physiology and anatomy of neurons and neural circuits reflect fundamental relationships between energy consumption, biophysics and performance.

## Major energy consuming processes in neural tissue

The nervous system is a major energy consumer; the human brain, for example, consumes 20% of basal metabolic rate, whilst accounting for just 2% of the body mass [10]. Experimental, theoretical and computational approaches (Box 1) have shown that the primary processes within adult neurons and neural networks that consume energy are the generation and maintenance of electrical signaling and synaptic transmission [7–9,11–15]. The vast numbers of ions moving across the cell membrane to produce electrical signals, whether post-synaptic/graded potentials or action potentials, must be restored by the  $3\text{Na}^+/2\text{K}^+$  pump [16]. For every three  $\text{Na}^+$  ions extruded an ATP molecule is hydrolyzed to provide energy for the work of the pump. Other processes, such as neurotransmitter re-uptake or  $\text{Ca}^{2+}$  extrusion, are often linked to the work of the pump through symporters and antiporters that co-transport  $\text{Na}^+$  or  $\text{K}^+$  ions. One exception to this is the loading of synaptic vesicles, which involves a V-ATPase [17].

## Resting, ‘housekeeping’ and developmental costs

Costs are incurred even when a neuron is ‘at rest’ just to maintain the resting potential because ions are moving across the membrane, albeit at a lower rate than when signaling [8,12]. These resting costs are typically substantially lower than the signaling costs, though there are exceptions such as vertebrate photoreceptors [15]. The precise relationship between resting and signaling costs can influence the way in which information is coded within populations of neurons, relatively low resting costs favoring large populations that are rarely active producing sparse coding (see below) [1,7,18].

Even in adult neurons processes linked to ‘housekeeping’ or cellular maintenance also consume energy [19,20]. The specific processes and their contributions have yet to be identified fully, and those that have been investigated have revealed some surprises. For example, protein synthesis appears to consume relatively little energy, whilst lipid synthesis consumes a higher proportion of the cellular housekeeping costs [20]. Another factor likely to be contributing a substantial amount to non-signaling energy consumption is mitochondrial proton leak, which erodes the proton motive force established by the respiratory electron transport chain [1,20,21].

In developing neural tissue, the division of costs is likely to be rather different because the production of new

**Box 1 Measuring energy consumption**

Key to determining 'how' and 'why' processes consume energy is coupling the experimental measurement of neuronal energy consumption with energy budgets for particular tissues and computational modelling. This combination of approaches is crucial because direct experimental measurements of single neuron energy consumption are extremely challenging due to their size, highly-branched structure, and embeddedness within networks. Consequently, experimental measurements of oxygen consumption, carbon dioxide production or other proxies of neuronal energy consumption are typically made from larger volumes of tissue from the retina [11,13,14] to the entire brain [10,70]. With sufficient knowledge of the structure and activity of the neural tissue being measured, the energy consumed can be apportioned to various processes such as action potential transmission, synaptic transmission or transmitter recycling: a so-called 'top-down' approach.

An alternative 'bottom-up' approach is to determine the energy consumption from the biophysical and structural properties of single neurons, synapses and molecular components [e.g., 8,9]. Such an approach depends upon electrophysiological measurements of currents and conductances, as well as membrane capacitance. Recently, traditional electrophysiological methods have been augmented by live imaging of molecules that are directly involved in energy metabolism, such as ADP/ATP or NADH-NAD<sup>+</sup> [71–74]. This imaging has enormous potential for estimating energy consumption within spatially extensive neurons and specific structures such as synapses [73,74], providing bounds for cellular-level and subcellular-level bottom-up energy budgets. When combined with details of molecular processes that occur within neurons, such as the structure of second messenger cascades, this approach can yield detailed energy budgets for neurons that quantify the consumption of specific processes. Moreover, when coupled with dynamic computational models [26\*\*,29,41], this approach can allow the energy consumption of neurons to be estimated on a fine temporal scale equivalent to that of the electrical signals within neurons themselves.

Both approaches, top-down and bottom-up, have advantages and disadvantages in isolation but ideally bottom-up energy budgets should be corroborated with experimental measurements of energy consumption [9]. Even so, each assumption must be carefully examined.

tissue will consume substantial amounts of energy, though these costs may still be small in comparison to long-term operation of neural tissue. For example, incorporating developmental energy consumption into an energy budget of cortical white matter suggests that the cost of building myelin could be repaid rapidly through savings in action potential energy consumption were it not for the energy cost of maintaining the oligodendrocyte resting potential [22\*]. This suggests that the role of myelin is in increasing propagation speed rather than in reducing energy consumption.

**Linking energy consumption to performance**

Energy consumption within neurons and neural networks is linked to their performance through signaling speed, noise, and propagation (reviewed in [1,2]). The signaling speed (or bandwidth) of a neuron depends upon its membrane time constant. Reducing the time constant increases the bandwidth but requires an increase in conductance, which increases the ionic current that flows.

This inflates energy consumption because more ions are moved across the membrane creating more work for the 3Na<sup>+</sup>/2K<sup>+</sup> pump.

Noise, random fluctuations or distortions that interfere with a signal, may arise from stimuli extrinsic to a neuron (e.g. sensory stimuli or neurotransmitter molecules), or from intrinsic processes (e.g. spontaneous activation of voltage-gated ion channels) (reviewed in [23]). Signals can be protected from noise through amplification but this involves greater numbers of molecules and, consequently consumes more energy. Noise can also be removed by averaging across signaling events, provided that the noise is independent in each of the events being averaged. Averaging to remove noise can be implemented on different scales from increasing the number of ion channels generating a signal within a neuron or the number of vesicles released at a synapse, to the number of neurons within a circuit signaling in parallel. Irrespective of the scale, however, greater numbers of events consume more energy.

Once generated, signals must be propagated to permit information processing and transmission. Irrespective of whether these signals are graded potentials or action potentials, propagation consumes energy because ions flow across the cell membrane. The precise amount of energy consumed depends upon the distance over which signals are propagated as well as the biophysical properties of the neuron, emphasizing that the effects of bandwidth, noise and propagation on neural energy consumption cannot be fully disentangled from one another.

**Action potential energy consumption**

Most, though not all [24], neurons use action potentials to transmit information over long distances. This is not, however, their sole function; action potentials are also important for preventing noise accumulation in successive layers of information processing in neural circuits. The energy consumption of a single action potential within a single neuron would be challenging to measure directly, so typically it is estimated by converting the electrical signals into the total amount of work the 3Na<sup>+</sup>/2K<sup>+</sup> pump must do to restore ion gradients (Box 1) [9,25,26\*\*,27,28\*\*,29–36]. Estimates of action potential energy consumption are, consequently, dependent upon accurate measurement of biophysical parameters including channel kinetics, conductance magnitudes and membrane capacitances.

**Heterogeneity in action potential costs**

Initial estimates of action potential energy consumption were based upon that of the squid giant axon [9,25]. It was assumed that the energy consumption of this action potential was broadly representative all others [9]; however, this was dispelled by combining experimental

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