The sodium-potassium pump is an information processing element in brain computation

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Brain neurons can transmit signals using a flow of Na$^+$ and K$^+$ ions, which produce an electrical spike called an action potential (AP) (Hodgkin and Huxley, 1952). After an AP, the Na$^+$/K$^+$ pump resets the arrangement of Na$^+$ and K$^+$ ions back to their original positions so that the neuron is then ready to relay another AP when it is called upon to do so (Glitsch, 2001). So, the Na$^+$/K$^+$ pump has a "housekeeping" role rather than a direct role in brain signaling. This is the long-held, entrenched viewpoint. However, novel research upon cerebellar Purkinje neurons suggests that the Na$^+$/K$^+$ pump may have a direct role in brain coding and computation (Forrest, 2008, 2014a,b; Forrest et al., 2009, 2012). This research was conducted in 2006–2007, and presented in a 2008 Ph.D. thesis (Forrest, 2008), but has only been published relatively recently. In the intervening period it was serially rejected by reviewers and journals that were uncomfortable with this re-appraisal of Na$^+$/K$^+$ pump function. Purkinje neurons are found in the cerebellum, responsible for motor control (Ito, 1984).

The Na$^+$/K$^+$ pump uses the energy of one ATP molecule to exchange three intracellular Na$^+$ ions for two extracellular K$^+$ ions (Glitsch, 2001). Thus, the pump is electrogenic, extruding one net charge per cycle to hyperpolarize the membrane potential. *In vitro*, the Na$^+$/K$^+$ pump has been shown to control and set the intrinsic activity mode of Purkinje neurons (Forrest, 2008, 2014a; Forrest et al., 2009, 2012). It dictates whether the Purkinje neuron is quiescent or spontaneously firing in a continuous tonic, continuous burst, bimodal (tonic and quiescent), trimodal (tonic, burst, quiescent), or bimodal (burst and quiescent) repeat pattern. In the bimodal and trimodal repeat patterns, the Na$^+$/K$^+$ pump sets the length of each constituent mode. So, at the foundation of the Purkinje cell's intrinsic multimodality, there is the working of just a single molecular species: the Na$^+$/K$^+$ pump.

Numerical modeling of experimental data suggests that, *in vivo*, the Na$^+$/K$^+$ pump produces long quiescent punctuations ($>>1$ s) to Purkinje neuron firing (Forrest, 2014a). The Na$^+$/K$^+$ pump is an enzyme and its activity is dependent on the concentration of its substrates: intracellular Na$^+$ and extracellular K$^+$ (Glitsch, 2001). Na$^+$ flows into and accumulates in the Purkinje cell during firing; Forrest's numerical model proposes that intracellular Na$^+$ concentration is a memory element, which records firing history (Forrest, 2014a). Furthermore, that the Na$^+$/K$^+$ pump "reads" this memory setting to dictate the timing and duration of long quiescent periods. To speculate, these long quiescent periods, on the scale of seconds and minutes, may be computationally advantageous. By conferring an access to longer time scales, they may permit storage and short-term processing of sensory information in the cerebellar cortex. To elaborate, they may permit different dynamical states to be sustained in the cerebellar cortex for extended periods. Each of these states is associated with a specific configuration of firing and quiescent states in different Purkinje cells. These network states could store information and perform computations. So, these network computations sit upon the proposed intracellular Na$^+$ ion computation, mediated by the Na$^+$/K$^+$ pump, which dictates the activity state of individual Purkinje neurons (firing or quiescent). Forrest terms this hypothesis: "ion to network" computation (Forrest, 2014a). There could be further layers of control and regulation: the Na$^+$/K$^+$ pump is a receptor for the endo-ouabain signaling molecule (Xie and Cai, 2003) and Na$^+$/K$^+$ pump activity might be modulated by intracellular signaling cascades (Therien and Blostein, 2000; Bagrov and Shapiro, 2008). Relevantly, a mutation in the Na$^+$/K$^+$ pump causes rapid onset dystonia parkinsonism, which has symptoms to indicate that it is a pathology of cerebellar computation (Cannon, 2004; de Carvalho et al., 2004). Furthermore, an ouabain block of Na$^+$/K$^+$ pumps in the cerebellum of a live mouse results in it displaying movement disorders: ataxia and dystonia (Calderon et al., 2011).

In recent times, other groups have shown the Na$^+$/K$^+$ pump to be a computational element in other neuron types, in other systems. For example, the Na$^+$/K$^+$ pump produces an afterhyperpolarization (AHP) to each burst in the motor neurons of Drosophilia larvae; AHP amplitude is dependent on the number of spikes in the burst (Glanzman, 2010; Pulver and Griffith, 2010). So the Na$^+$/K$^+$ pump generated AHP acts as a spike counter and is a form of short-term memory.

Locomotion in Xenopus tadpoles, as in vertebrates generally, is produced by a central pattern generator (CPG) network

within the animal's spinal cord and hindbrain. In these CPG neurons the Na^+/K^+ pump produces an AHP; the amplitude/hyperpolarization (and therefore duration) of which is proportional to the intensity and duration of previous spiking activity (Simmers, 2012; Zhang and Sillar, 2012). So, again, a Na^+/K^+ pump generated AHP acts as a spike counter and a form of short-term memory. This system ensures that if the tadpole has recently swum intensively (many spikes per unit time) the next swimming bout is shorter; whereas if prior swimming was weaker (less spikes) then the next swimming bout can be longer. This presumably ensures that the animal is not overexerted. So, the Na^+/K^+ pump generated AHP system remembers prior spiking/motor activity to dictate the nature of future spiking/motor activity.

Aplysia interneurons can exhibit a prolonged inhibitory synaptic potential, produced by synaptic activation of an electrogenic Na^+ pump (Pinsker and Kandel, 1969). In sensory neurons of the lamprey, and tactile (T) sensory neurons of the leech, the Na^+/K^+ pump produces an AHP (Baylor and Nicholls, 1969; Jansen and Nicholls, 1973; Van Essen, 1973; Catarsi and Brunelli, 1991; Catarsi et al., 1993; Parker et al., 1996; Scuri et al., 2007). Activation of a leech's T neurons produces swimming behavior; serotonin quickens the swimming response to touch (reaction time) (Scuri et al., 2007). It negatively modulates Na^+/K^+ pumping, leading to less AHP, and more spikes being transmitted across a synaptic connection between two T neurons i.e., there results a functional, plastic change at a synapse (learning).

The leech T neuron responds to step-stimuli on the skin with a burst code (Arganda et al., 2007). The code doesn't seem to contain any amplitude information, only the velocity of the skin displacement. With Gaussian white-noise stimuli, stimulus velocity is encoded in burst duration. The greater the velocity, the longer the burst (and the greater the spike rate within the burst). However, a given velocity does not always produce the same length of burst; the length depends on the nature of other velocities coded for in the same period. The burst length codes the ratio of that velocity to the standard

deviation of the velocity distribution. This means that a burst of given size is first produced in response to low velocities, but after 1 min of stimulation it is only produced in response to higher velocities i.e., there is adaptation to the stimulus. Numerical simulations and experiments indicate that the Na^+/K^+ pump is responsible for this adaptive scaling. When the pump is blocked by strophantidin it cannot occur. Under normal conditions: the larger the stimulus velocity variance, the greater the AHP amplitude and, with this decreased excitability, bursts are smaller.

Forrest and co-workers have shown, by experiment and modeling, that the Na^+/K^+ pump can produce AHPs in cerebellar Purkinje neurons (Forrest, 2008, 2014a,b; Forrest et al., 2009, 2012). Other groups have shown that the Na^+/K^+ pump can produce AHPs in other mammalian neurons: in presynaptic and postsynaptic neurons at the calyx of Held in the medial nucleus of the trapezoid body (Kim et al., 2007; Kim and von Gersdorff, 2012), in spinal cord neurons (Ballerini et al., 1997), in cerebellar Golgi cells (Botta et al., 2010), in hippocampal pyramidal (Gustafsson and Wigström, 1981, 1983; Thompson and Prince, 1986; Gulledge et al., 2013), and in neocortical layer 5 (Koike et al., 1972; Gulledge et al., 2013) neurons.

In rats, small-diameter neurons of the dorsal root ganglion (DRG) secrete follistatin-like 1 (FSTL1) at their axon synapse, in a spontaneous and depolarization dependent manner. This FSTL1 feeds back and activates their hyperpolarizing Na^+/K^+ pumps (Li et al., 2011). This reduces their excitability and their excitatory transmission to downstream neurons. This appears to be a feedback loop, which keeps the transmission at this synapse in the correct range.

Interestingly, Na^+/K^+ pump generated AHPs can be observed in canine coronary sinus fibers (Wit et al., 1981). What is their role in these cardiac cells? Are they a mechanism to prevent over-excitation (and perhaps arrhythmias)? Or are they without function here; are Na^+/K^+ pump generated AHPs a nuanced by-product of how some excitable cells work, which certain neural cells have seized to their advantage for coding strategies?

There is not likely a single, definitive neural code; different neuron types probably employ different strategies. We have discussed how some neurons, in some systems, utilize the Na^+/K^+ pump. However, for some other neurons, Na^+/K^+ pump activity doesn't seem to be a major determinant of their firing pattern. For example, with a substantial proportion of Na^+/K^+ pumps blocked by ouabain, the rat motor neuron shows no appreciable change in firing pattern or rate (Sawczuk et al., 1997). By contrast, a much smaller ouabain concentration can produce a dramatic sequence of changes in the firing pattern of cerebellar Purkinje neurons (Forrest et al., 2012). Impaired Na^+/K^+ pump function in Drosophila (Ashmore et al., 2009), through mutation or ouabain application, doesn't appear to universally corrupt all brain functions but a specific few: again, suggesting that only some—and not all—neuron types employ it in a coding role. A complicating factor in interpreting these experiments is that there can be different Na^+/K^+ pump isoforms in different cell types in different species and these can have different ouabain sensitivities (the Na^+/K^+ pump is made up of an α and a β subunit; four isoforms of the α and three of the β are known and these can admix in different combinations; Blanco and Mercer, 1998).

In this paper we have listed a number of systems in which the Na^+/K^+ pump may be directly involved in computation. To repeat the case for the cerebellar Purkinje neuron (Forrest, 2014a); electrogenic Na^+/K^+ pump activity hyperpolarises the membrane potential, acting to drive its value more negative, and thus it directly inputs and contributes to the computational variable of the brain cell: its membrane voltage. Pump activity is enzymatically dependent upon intracellular Na^+ and extracellular K^+ concentrations, which are a record of prior membrane voltage values as they are a function of voltage-dependent ion conductances. So, Na^+/K^+ pump "reads" membrane voltage history to shape future membrane voltages. It mediates a form of cellular memory. Its activity can dramatically change the membrane potential; for example, switching off spiking to render a long period of hyperpolarized

quiescence ($>> 1$ s). Indeed, it can act as a spike integrator, memorizing past firing activity to dictate the timing, amplitude, and duration of quiescent periods (AHPs). So, information may be encoded in quiescent periods, in addition to spiking parameters. This may be especially salient for inhibitory neurons, where quiescence conveys disinhibition to downstream neurons. For example, Purkinje cells provide inhibitory input to the Deep Cerebellar Nuclei (DCN). Quiescent periods may be important in cerebellar functioning because numerous Purkinje neurons converge upon and inhibit a single DCN neuron (∼40:1). If all these Purkinje neurons are continuously, simultaneously active then it might be that the DCN neuron is unable to fire in any meaningful way. With a proportion of the Purkinje cells quiescent, only a fraction of the population is active and relevant. The members making up this relevant subset can be switched and changed in a controlled fashion, which can be utilized as a computational feature.

In summary, there is a growing body of work suggesting that Na^+/K^+ pumps can sub-serve information processing roles in some neurons. This is perhaps not surprising given that time and again evolution has shown herself to be a master of turning cost to advantage. Na^+/K^+ pumping in the brain accounts for the overwhelming majority of an animal's energy (ATP) consumption (Laughlin et al., 1998; Attwell and Laughlin, 2001); it seems that the brain may have furthered what information it can process from this cost in some neurons.

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