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Review

# The Cellular Battery: Rethinking the Electrochemical Basis of Transmembrane Potential

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## Abstract

The origin of the transmembrane potential (TMP) in living cells is one of the foundational questions of cellular physiology. The dominant explanatory framework—the ion-pump model—attributes TMP to the active, ATP-dependent displacement of ions (principally Na<sup>+</sup> and K<sup>+</sup>) across the plasma membrane by dedicated protein complexes. This view, consolidated through the seminal work of Hodgkin and Huxley and the structural characterisation of the Na,K-ATPase, has shaped decades of research in neuroscience, cardiology, and cell biology. A competing framework, the *murburn concept* developed by Manoj and colleagues, proposes a fundamentally different mechanism. According to this view, TMP is not the product of mechanical ion pumping but emerges spontaneously from asymmetric redox chemistry at the membrane interface. Diffusible reactive species (DRS), generated continuously during aerobic respiration, accumulate differentially on either side of the membrane, producing effective charge separation analogous to that observed in electrochemical cells. This perspective examines both frameworks critically, identifies the core points of disagreement, and evaluates the explanatory scope and empirical challenges of each. We argue that the *murburn* framework raises legitimate and underexplored questions about the thermodynamic sufficiency of the ion-pump model, and that a productive synthesis may lie in recognising redox chemistry as a primary contributor to membrane polarisation—rather than a secondary consequence of it.

**Keywords:** transmembrane potential; *murburn* concept; reactive oxygen species; bioenergetics; electrophysiology; ion homeostasis; redox metabolism

## 1. Introduction: A Question Hidden in Plain Sight

Every living cell maintains a measurable difference in electrical potential across its plasma membrane. In a resting neuron, the interior is approximately 70 mV more negative than the extracellular space. This potential difference—the resting transmembrane potential—is not a passive equilibrium state. It is actively maintained, metabolically expensive, and biologically essential: it underlies nerve impulse conduction, muscle contraction, hormonal signalling, and a vast array of ion-coupled transport processes.

The question of how this potential is generated and maintained seems, at first glance, to have been settled. The textbook answer invokes the Na,K-ATPase, a membrane-embedded enzyme that hydrolyses ATP to export three sodium ions while importing two potassium ions per cycle, generating a net outward current and sustaining an ion gradient that, in conjunction with selective ion channels, produces the observed TMP. This model is supported by decades of pharmacological, electrophysiological, and structural evidence.

And yet, foundational tensions persist. The thermodynamic accounting of the ion-pump model has been questioned on quantitative grounds. The spatial geometry of ion diffusion within cells presents unresolved complications. The very notion that protein conformational cycling can serve as

the *primary* engine of membrane polarisation has been challenged from multiple directions, including the association-induction hypothesis of Gilbert Ling [5], the phase-transition models of Freeman Cope, and more recently, the murburn framework of Kelath Murali Manoj and collaborators [8–12].

This perspective does not adjudicate between these frameworks with finality—the experimental record does not yet permit that. Instead, we aim to do something more immediately useful: to render the debate legible to biochemists and biologists who have not followed the specialist literature, and to identify the specific empirical and conceptual questions that would most productively distinguish between the competing accounts.

## 2. The Classical Model: Ion Pumps and the Electrochemical Gradient

### 2.1. Core Claims

The membrane theory of cellular electrophysiology rests on three interconnected propositions. First, the plasma membrane is selectively permeable: it allows certain ions to cross more readily than others, either through constitutively open channels or through regulated, gated pores. Second, the Na,K-ATPase actively maintains concentration gradients by coupling ATP hydrolysis to directional ion transport—sodium outward, potassium inward—against their respective electrochemical gradients. Third, the TMP at rest reflects a diffusion potential: the tendency of permeable ions (principally  $K^+$ ) to move down their concentration gradient generates an electrical potential that partially counteracts further diffusion, reaching a steady state described by the Goldman–Hodgkin–Katz equation [3,4].

The action potential—the nerve impulse—is explained as a transient reversal of this resting state: voltage-gated sodium channels open in response to membrane depolarisation,  $Na^+$  rushes inward, the membrane potential briefly reverses, and then potassium channels restore the resting potential by allowing  $K^+$  to exit. The Na,K-ATPase then restores the ion gradients over a longer timescale [1].

### 2.2. Strengths of the Model

The ion-pump model accounts for an impressive range of phenomena with quantitative precision. The Hodgkin–Huxley equations, developed from voltage-clamp experiments on the squid giant axon, accurately predict the shape and propagation velocity of action potentials. Patch-clamp techniques have directly measured currents through individual ion channels. Ouabain, a specific inhibitor of the Na,K-ATPase, reliably depolarises cells and disrupts ion homeostasis. Crystal structures of the Na,K-ATPase have been resolved at atomic resolution, revealing the conformational states associated with ion binding and ATP hydrolysis [6].

This body of evidence is not trivial. Any alternative framework must account for it, or provide a compelling reason why the apparent confirmations of the classical model reflect confounded measurements rather than direct support.

### 2.3. Unresolved Tensions

Notwithstanding its successes, the ion-pump model carries unresolved tensions that have been noted—and largely set aside—by mainstream electrophysiology.

The first is *quantitative*. The Na,K-ATPase turns over approximately 100–200 cycles per second under physiological conditions, transporting 300–600 ions per pump per second. Given the surface density of pumps on most cell membranes, the rate of ion displacement falls short, by some estimates, of what would be required to maintain observed concentration gradients against the measured permeability of the membrane to the relevant ions. This discrepancy has been addressed by invoking additional regulatory mechanisms and by revising permeability estimates, but the accounting has never been fully transparent.

The second is *geometric*. The standard model treats cellular cytoplasm as a dilute aqueous solution in which ions diffuse freely. This is an approximation. The cytoplasm is a crowded, structured medium in which proteins, cytoskeletal elements, and organelle membranes impose constraints on diffusion. The behaviour of ions in such an environment may differ substantially from their behaviour in bulk

solution, and the relevance of equilibrium thermodynamics derived from dilute-solution chemistry is not self-evident.

The third is *evolutionary*. The emergence of a system in which resting membrane potential depends on the continuous hydrolysis of ATP—requiring the prior existence of ATP synthesis machinery, ion pumps of appropriate stoichiometry, and regulated ion channels—presents a complex chicken-and-egg problem for evolutionary biology. How did the earliest cells maintain membrane potential before each of these components was in place?

### 3. The Murburn Framework: Redox Chemistry as Primary Driver

#### 3.1. Central Proposition

The murburn concept, developed over two decades of research on heme and flavin enzymes by Manoj and colleagues, begins from a different starting point. Rather than treating reactive oxygen species (ROS) as pathological byproducts of aerobic metabolism to be minimised and scavenged, the murburn framework positions them as physiological intermediates whose controlled production and distribution are integral to cellular function [7].

In the murburn view, aerobic respiration is not merely a source of ATP. It is a continuous generator of diffusible reactive species (DRS)—principally superoxide ( $\text{O}_2^{\bullet-}$ ), hydrogen peroxide ( $\text{H}_2\text{O}_2$ ), and hydroxyl radicals—that participate in equilibrium reactions distributed throughout the cell and at the membrane interface. These species are charged, short-lived, and asymmetrically distributed by the geometry of the respiratory apparatus embedded in the inner mitochondrial membrane or, in prokaryotes, the plasma membrane.

#### 3.2. The Battery Analogy

The physical intuition behind the murburn model is best captured by an electrochemical analogy. A battery generates a potential difference not because a mechanical pump moves charges from one terminal to the other, but because a redox reaction proceeds spontaneously at two spatially separated interfaces: oxidation at the anode, reduction at the cathode. The potential difference is a thermodynamic consequence of the reaction chemistry, not its mechanical cause.

The murburn framework proposes that the cell is, in an analogous sense, a living battery. The asymmetric reduction of oxygen at the membrane interface generates an effective charge separation—an accumulation of negatively charged reactive species on the interior face, and a relative depletion on the exterior face. This *effective charge separation* (ECS) produces a transmembrane potential that does not depend on the prior existence of ionic gradients or ATP-dependent pumps [8].

#### 3.3. Implications for Ion Distribution

If the murburn model is correct, the differential distribution of ions across the membrane—more  $\text{K}^+$  inside, more  $\text{Na}^+$  outside—is not the cause of TMP but a consequence of the pre-existing potential established by redox chemistry. Ions distribute themselves in response to an electrical field that was already there. The Na,K-ATPase, in this account, is not a pump that generates a gradient but a *murzyme*—an enzyme that modulates redox equilibria at the membrane interface, contributing to homeostasis without serving as the primary electromotive force [10].

This reframing has significant implications. It suggests that the apparent effectiveness of ouabain as a depolarising agent reflects not the loss of the primary TMP-generating mechanism, but the disruption of a modulatory system whose absence cannot be fully compensated by the remaining redox machinery. It also suggests that the empirical correlations between Na,K-ATPase activity and membrane potential, while real, are correlational rather than mechanistically primary.

## 4. A Critical Comparison

### 4.1. Where the Frameworks Agree

Both frameworks accept that the plasma membrane separates two compartments with different ionic compositions, and that this compositional difference is associated with a transmembrane potential. Both accept that membrane proteins—channels, pumps, and redox enzymes—play essential roles in establishing and maintaining this state. Neither framework denies that ATP is consumed in maintaining cellular homeostasis. The disagreement is about mechanism: which process is primary, and which is modulatory or secondary.

### 4.2. Where They Diverge

The classical model is deterministic in the sense that it attributes TMP to specific, identifiable molecular machines operating in defined stoichiometric cycles. This makes it highly tractable: one can, in principle, account for every ion moved and every ATP consumed. The murburn framework is probabilistic and thermodynamic: it invokes equilibria among reactive species whose individual trajectories are stochastic. This makes it more difficult to test by conventional electrophysiological methods, which measure ensemble averages rather than single-molecule events.

The classical model has the advantage of established experimental methodology: patch clamp, voltage clamp, radiotracer flux assays, and structural biology have all been applied with precision. The murburn framework, by contrast, requires measurement of DRS concentrations and distributions at the membrane interface at physiologically relevant timescales—a considerably more demanding experimental challenge. Much of the evidence cited in support of the murburn concept is indirect: anomalies and inconsistencies in the classical account, rather than direct demonstrations of DRS-mediated charge separation.

### 4.3. The Question of Falsifiability

A productive framework must be falsifiable. The classical model has been extensively tested, and although tensions remain, its core predictions—that blocking the Na,K-ATPase depolarises cells, that increasing membrane  $K^+$  permeability hyperpolarises them, that the action potential shape follows from Hodgkin-Huxley kinetics—are robustly reproducible.

The murburn framework has not yet been subjected to comparably rigorous testing. The key falsifiable prediction would be: if TMP is generated by redox chemistry at the membrane, then eliminating oxygen from a cell (and thus DRS production) should abolish TMP *before* it abolishes ATP production—because the murburn model places DRS upstream of ion gradients, while the classical model places ATP hydrolysis upstream of both. Designing a clean experiment to test this prediction is technically difficult but not obviously impossible, and would be considerably more informative than the rhetorical and thermodynamic arguments that have dominated the debate to date.

## 5. Toward a Synthesis

The history of science is replete with cases in which a dominant framework, well-supported by accumulated evidence, was revealed to have been over-specified: correct in its description of experimental observations, but wrong in its mechanistic interpretation of them. The classical model of gastric ulcers—attributed to stress and excess acid—was similarly robust and similarly resistant to revision until Marshall and Warren demonstrated the centrality of *Helicobacter pylori*.

We do not claim that the murburn framework will prove correct in its current form. The evidence is insufficient to support that claim. What we do argue is that the asymmetry of investment between the two frameworks—an enormous experimental literature supporting the classical model, a comparatively sparse literature testing the murburn predictions—does not constitute evidence *against* the murburn framework. It constitutes an absence of evidence, which is a different thing.

The most productive path forward is neither to dismiss the murburn framework as heterodox nor to accept it as an established alternative. It is to take its most specific and testable predictions

seriously and to design experiments capable of distinguishing between them. The question of whether DRS-mediated charge separation contributes quantitatively to resting TMP is an empirical question. It has an answer. We do not yet know what it is.

What seems plausible, even on current evidence, is a partial integration: that the resting potential is maintained by a combination of ion-gradient-dependent diffusion potentials *and* DRS-mediated charge separation, with the relative contributions varying by cell type, metabolic state, and oxygen availability. Such a model would preserve the explanatory achievements of the classical account while accommodating the anomalies that the murburn framework has, at minimum, identified clearly.

## 6. Conclusion

The transmembrane potential is not a solved problem. The ion-pump model provides a powerful and well-supported account of membrane electrophysiology, but it rests on thermodynamic and geometric assumptions that have not been fully validated under physiological conditions. The murburn framework challenges those assumptions by placing redox chemistry, rather than mechanical ion pumping, at the centre of the electromotive process.

This perspective has attempted to render that challenge legible without resolving it prematurely. The value of the murburn framework, at its current stage of development, lies less in its specific mechanistic claims than in its insistence on asking a question that mainstream electrophysiology has been too comfortable not asking: is the Na,K-ATPase truly the primary electromotive engine of the cell, or is it a modulator of a potential that chemistry generates on its own?

A cell, after all, is not a machine. It is a chemistry. The distinction matters.

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