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Article

Membrane Potential: A Critical Reassessment of Pump Theory and an Electrostatic Adsorption Model

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Abstract

The membrane pump theory (MPT) attributes the resting membrane potential of neurons to ionic diffusion driven by transmembrane concentration gradients, maintained by the Na,K-ATPase. Despite decades of dominance, this model harbours fundamental thermodynamic, kinetic, and geometric inconsistencies that have remained unaddressed in mainstream biophysics. We present a systematic quantitative critique across five independent axes: (1) the electrostatic force exceeds the diffusive force by ∼300-fold under physiological conditions; (2) the peri-axonal space contains 10–100× fewer ions than required by channel-based models; (3) the Na,K-ATPase carries an energy deficit of ∼26% per cycle and operates 5000× too slowly to compensate measured leak fluxes; (4) the Nernst and Goldman–Hodgkin–Katz equations are applied outside their domain of validity; and (5) cell geometry invalidates plane-membrane approximations. In contrast, direct experimental evidence (Tamagawa experiment) demonstrates that a potential of ≈ -40 mV arises from fixed negative charges alone, without any ionic gradient. We formalise this result within a Poisson–Boltzmann/Grahame electrostatic framework, supplemented by Ling's ion adsorption model and Manoj's murburn concept, and obtain $\Delta\psi \approx -65$ to -85 mV from first principles. Four specific experimental predictions distinguish the model from MPT.

Keywords: membrane potential; Na/K-ATPase; Poisson-Boltzmann; ion adsorption; Ling; murburn concept; electrostatics; Goldman equation; Nernst equation

1. Introduction

The membrane potential of excitable cells – typically -65 to -85 mV in neurons – is central to all cellular electrophysiology. The dominant framework, Membrane Pump Theory (MPT), attributes this potential to three interrelated mechanisms: (i) selective ionic diffusion driven by transmembrane concentration gradients, (ii) voltage-gated and leak ion channels providing differential ionic permeability, and (iii) Na,K-ATPase actively restoring ionic gradients dissipated by leak fluxes. This framework, formalized by Goldman [1], Hodgkin and Katz [2], and Hodgkin and Huxley [3], forms the foundation of modern neuroscience.

However, a growing body of work reveals deep incompatibilities within MPT. Ling [4] demonstrated that metabolically dead cells maintain a measurable membrane potential in the absence of any active pump. Tamagawa et al. [6,7] showed that a potential of ≈ -40 mV arises from a cation-exchange resin in a uniform electrolyte, without an ionic gradient. Manoj, Bazhin, and Tamagawa [8,9] demonstrated thermodynamically that Na,K-ATPase cannot function as a classical pump. Manoj et al. [10] proposed that it instead acts as a redox-coupled equilibrating enzyme (murzyme).

The present work consolidates and extends a series of five preliminary preprints by the same authors [16–20] into a unified quantitative analysis. We show that five independent lines of argument, electrostatic dominance, geometric constraints, pump energetics, mathematical inapplicability, and

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direct experimental demonstration, converge on the same conclusion: ionic diffusion driven by Na,K-ATPase is not the primary mechanism of membrane potential generation. We then present a positive alternative: an electrostatic equilibrium potential arising from fixed surface charges, formalized via the Poisson–Boltzmann equation and supplemented by ion adsorption.

2. Electrostatics Dominates Diffusion: A Quantitative Comparison

2.1. Force Balance on a Membrane Ion

The MPT implicitly assumes that ionic diffusion drives charge separation across the membrane. This can be tested by comparing the magnitudes of the electrostatic and diffusive forces that act on a single K^+ ion.

The electrostatic force in the transmembrane field is the following.

$$F_{\text{elec}} = qE = e\frac{\Delta V}{d} = \frac{(1.6\times10^{-19}\,\text{C})(70\times10^{-3}\,\text{V})}{7\times10^{-9}\,\text{m}} \approx 1.6\times10^{-12}\,\text{N} \tag{1}$$

The diffusive force from the concentration gradient is:

$$F_{\text{diff}} = \frac{k_B T}{c}\frac{dc}{dx} \approx \frac{4\times10^{-21}\,\text{J}}{150\times10^{-3}\,\text{mol/L}} \cdot \frac{145\times10^{-3}\,\text{mol/L}}{7\times10^{-9}\,\text{m}} \approx 5.5\times10^{-15}\,\text{N} \tag{2}$$

The ratio $F_{\text{elec}}/F_{\text{diff}} \approx 300$. The electric force exceeds the diffusive force by approximately three orders of magnitude under physiological conditions. Diffusion cannot be the primary determinant of membrane potential.

2.2. The Electroneutrality Constraint

The charge per unit area required to establish $-70\,\text{mV}$ across the membrane is:

$$\sigma_Q = C_m \cdot \Delta V = (10^{-2}\,\text{F/m}^2)(70\times10^{-3}\,\text{V}) = 7\times10^{-4}\,\text{C/m}^2 \approx 7\,\text{pmol/cm}^2 \tag{3}$$

This corresponds to $\sim 10^{-13}\,\text{mol/cm}^2$, far below any measurable change in the bulk concentration of ionics. Even the initial departure of a few K^+ ions generates a field that immediately opposes further efflux. Thermodynamic equilibrium, not ongoing diffusion, governs the charge distribution.

2.3. The Cell Growth Paradox

During growth and protein synthesis, intracellular K^+ concentration increases — K^+ enters the cell. MPT requires a net K^+ efflux to maintain the negative interior potential. These two fluxes are mutually contradictory within the MPT framework.

3. Ion Channels and the Na,K-ATPase Cannot Function as Described

3.1. The Peri-Axonal Space: An Ionic Deficit

The myelinated axon is surrounded by a peri-axonal space of ≈12 nm thickness. At 150 mM the ionic concentration is, the available ion count per unit of membrane area is:

$$N = [\text{ion}] \cdot N_A \cdot d \approx 150\times10^{-3}\,\text{mol/L} \cdot 6\times10^{23} \cdot 12\times10^{-9}\,\text{m} \approx 10^{9}\,\text{ions/m}^2 \tag{4}$$

A single channel with conductance ∼10 pS and driving force 70 mV carries ∼0.7 pA, i.e. ∼ 4×10^6 ions/s. The peri-axonal reservoir would be depleted in ∼250 μs without bulk replenishment. Given the geometry and tortuosity of this narrow space, the required diffusive supply is kinetically untenable.

3.2. Energetic Incompatibility of the Na,K-ATPase

Na, K-ATP.e is assigned the task of extruding 3 Na^+ and importing 2 K^+ per cycle, consuming one ATP. A quantitative audit reveals three independent incompatibilities (Table 1).

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Table 1. Quantitative incompatibilities between MPT requirements and measured pump parameters.

Parameter	Required by MPT	Actually measured	Discrepancy
Free energy/cycle	68.2 kJ/mol (37.1 for $3\,Na^+$ + 31.1 for $2\,K^+$)	≈54 kJ/mol (1 ATP, physiological)	×1.26 — thermodynamic deficit
Pump cycle rate	$\sim 10^6$ cycles/s per neuron	100–200 cycles/s	×5000 too slow
ATP consumption (10^{11} neurons)	$\sim 10^{17}$ ATP/s — lethal	Compatible with life	$\gg 10^3$

The energy deficit (∼26%) means that the pump cannot thermodynamically perform its assigned task with a single ATP. The speed deficit (×5000) means that it cannot compensate measured K^+ leak fluxes even if it is energetically feasible. Consistent with this analysis, inhibition of Na, K-ATPase by ouabain reduces the resting potential by only ∼5% in most cell types.

3.3. Electrostatic Obstruction in the Selectivity Filter

MacKinnon's structural work [5] revealed that the K^+ channel selectivity filter is lined with carbonyl oxygens, creating an intense negative electrostatic field that stabilizes K^+ over Na^+. However, this same field constitutes an energy barrier to rapid ion transit. Selectivity and high conductance are under fundamental tension: the structural requirements for the discrimination of K^+ / Na^+ imply electrostatic interactions incompatible with the transit rates of near-diffusion-limited assumed in models based on GHK.

3.4. Geometric Invalidation of Standard Models

All standard models (Nernst, GHK, Hodgkin–Huxley) assume a planar membrane of infinite extent with a uniform one-dimensional electric field. Real cell membranes are curved. This has two consequences: (i) field lines are not parallel, introducing off-axis force components; and (ii) membrane-embedded proteins experience mechanical stress from bending that modifies their conformational dynamics. Neither effect is negligible at the nanometer scale of ion channels.

4. Experimental Demonstration: Potential Without Diffusion

4.1. The Tamagawa Experiment

Tamagawa et al. [6,7] measured the potential in a system containing only an ion-exchange resin and a bathing electrolyte, under three conditions:

1. **Cation exchange resin** (fixed negative charges) in uniform KCl: measured potential ≈ −40 mV.
2. **Anion exchange resin** (fixed positive charges) in uniform KCl: measured potential ≈ +35 mV.
3. **KCl concentration gradient alone** (no resin, no fixed charges): measured potential ≈ 0 mV.

The conclusion is unambiguous: fixed charges alone generate a substantial potential; an ionic gradient alone generates none. This directly falsifies the central claim of MPT.

4.2. Donnan–Poisson–Boltzmann Interpretation

The result is immediately explained by the Donnan potential at any charged interface. For a cation-exchange phase with fixed charge density X (mol/L) in contact with a concentration KCl solution c:

$$\Delta\psi_{\text{Donnan}} = -\frac{RT}{F}\,\text{arcsinh}\left(\frac{X}{2c}\right) \tag{5}$$

For $X \approx 0.1$ mol/L and $c = 150$ mM, this yields $\Delta\psi \approx -20$ to -40 mV, in quantitative agreement with Tamagawa's measurements and with the neuronal resting potentials.

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4.3. Dead Cells and the Absence of Pumping

Ling's observation [4] that metabolically dead cells maintain a residual potential is inexplicable within MPT, which requires continuous pump activity driven by ATP. This is naturally explained by the electrostatic model: fixed charges persist after death, and the equilibrium potential they establish does not require metabolic maintenance.

5. The Standard Equations Are Applied Outside Their Domain of Validity

5.1. Nernst: Equilibrium Versus Steady State

The Nernst equation

$$E_i = \frac{RT}{z_i F} \ln \frac{[i]_o}{[i]_i} \tag{6}$$

Theoretically rigorous for a system at *electrochemical equilibrium*. The membrane potential of a living neuron is a *non-equilibrium steady state* maintained by continuous energy expenditure. The Nernst potential for K^+ ($\approx -94\,\mathrm{mV}$) differs from the measured resting potential ($\approx -70\,\mathrm{mV}$), confirming that the system is not in Nernst equilibrium. Applying an equilibrium equation to a non-equilibrium system and treating the result as a mechanistic explanation is a category error.

5.2. Activity Coefficients: A Systematic Neglected Correction

The Nernst equation uses electrochemical *activities* $a_i = \gamma_i[C_i]$, not concentrations. At physiological ionic strength ($I \approx 0.16\,\mathrm{M}$):

$$\gamma_{K^+} \approx 0.75 \qquad \text{(Davies equation)} \tag{7}$$

This introduces a systematic correction:

$$\Delta E = \frac{RT}{F} \ln \frac{\gamma_{\text{out}}}{\gamma_{\text{in}}} \approx -7.4\,\mathrm{mV} \tag{8}$$

This correction ≈10% is never discussed in the MPT literature, but follows directly from applying the Nernst equation correctly.

5.3. Goldman–Hodgkin–Katz: Three Unverified Assumptions

The GHK equation rests on three assumptions: (i) a constant, uniform electric field across the membrane (Goldman's "constant field" hypothesis); (ii) complete independence of ionic fluxes; and (iii) spatial homogeneity of ionic concentrations within the membrane. None of these has been verified experimentally under physiological conditions. The constant-field assumption has never been directly measured; indirect evidence consistently suggests a strongly non-linear potential profile in biological membranes.

5.4. Hodgkin–Huxley: Description Without Mechanism

The Hodgkin–Huxley model [3] reproduces action potential waveforms with impressive fidelity. However, the gating variables m, h, and n are phenomenological parameters fitted to voltage-clamp data, not quantities derived from a physical mechanism. The model's descriptive success is consistent with many different underlying physical mechanisms, including electrostatic adsorption dynamics.

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6. Alternative Model: Electrostatic Adsorption and Fixed Charges

6.1. The Poisson–Boltzmann Framework

We propose that the membrane potential is primarily an electrostatic equilibrium potential established by fixed negative surface charges. The spatial distribution of mobile ions near a charged surface is governed by the Poisson–Boltzmann (PB) equation:

$$\frac{d^2\psi}{dx^2} = \frac{2Fc^\infty}{\varepsilon\varepsilon_0}\sinh\left(\frac{F\psi}{RT}\right) \tag{9}$$

For a membrane surface with fixed surface charge density σ (C/m^2), the surface potential ψ_0 is given by the *Grahame equation*:

$$\sinh\left(\frac{F\psi_0}{2RT}\right) = -\frac{\sigma}{2c^\infty}\sqrt{\frac{F}{2\varepsilon\varepsilon_0 RT}} \tag{10}$$

6.2. Quantitative Application to the Neuronal Membrane

Using measured biological parameters (Table 2), the calculation yields an external surface potential $\psi_0 \approx -25$ to -35 mV. The intracellular face carries a higher density of fixed charges (cytoskeletal proteins, nucleic acids, anionic phospholipids), giving $\psi_{\text{intra}} \approx -40$ to -50 mV. The transmembrane potential is then:

$$\Delta\psi = \psi_{\text{intra}} - \psi_{\text{extra}} \approx -65 \text{ to } -85\,\text{mV} \tag{11}$$

This range is in quantitative agreement with measured neuronal resting potentials (≈ -70 mV), derived from first principles with no adjustable parameters and without invoking ionic diffusion or pump activity.

Table 2. Parameters used in the Poisson–Boltzmann calculation.

Parameter	Value	Source
Surface charge density σ	-0.020 C/m^2	Measured [13]
External ionic concentration	150 mM	Physiological
Dielectric constant ε	80	Aqueous solution
Temperature	310 K (37 °C)	Physiological

6.3. Ion Selectivity Via Adsorption: The Ling Model

Ling [4] proposed that intracellular K^+ is predominantly adsorbed on fixed anionic sites of cytoplasmic proteins. The selectivity of these sites for K^+ over Na^+ follows from the difference in ionic hydration energies (Table 3). The preferential adsorption of K^+ naturally explains the high intracellular $[K^+]/[Na^+]$ ratio without requiring selective channels or active transport. The site occupancy follows a competitive Langmuir isotherm:

$$\theta_K = \frac{K_{\text{ads}}[K^+]}{1 + K_{\text{ads}}[K^+] + K_{\text{ads,Na}}[Na^+]} \tag{12}$$

Table 3. Hydration energies and adsorption behaviour of the main physiological ions.

Ion	Hydration energy (kJ/mol)	Consequence
K^+	-322	Readily dehydrates; adsorbs to protein sites
Na^+	-406	Strongly hydrated; less available for adsorption
Cl^-	-340	Repelled by fixed negative charges

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6.4. The Dynamic Component: Murburn-Mediated Redox

Manoj and colleagues [8–10] demonstrated that the Na,K-ATPase functions as a *murzyme* — a redox enzyme facilitating thermodynamic equilibration at the membrane interface via diffusible reactive oxygen species (DRS) generated by mitochondrial respiration. In the murburn framework, DRS accept electrons from the intracellular milieu, producing a transient excess of negative charges inside the cell. This couples the membrane potential to cellular metabolism without requiring dedicated ion pumping:

$$\Delta\psi_{\text{total}} = \underbrace{\Delta\psi_{\text{fixed charges}}}_{\text{Ling + Tamagawa}} + \underbrace{\Delta\psi_{\text{redox}}}_{\text{Manoj/murburn}} \tag{13}$$

This explains why the potential tracks metabolic activity while remaining largely independent of pump inhibition: the dominant component ($\Delta\psi_{\text{fixed}}$) persists at thermodynamic equilibrium.

7. Testable Predictions Distinguishing the Two Models

The electrostatic adsorption model makes four specific quantitative predictions distinguishable from MPT.

Prediction 1 — Phospholipid charge density controls resting potential

Progressive replacement of anionic phospholipids (phosphatidylserine, phosphatidylinositol) by neutral phospholipids (phosphatidylcholine) in reconstituted liposomes should reduce the surface potential in proportion to the reduction in σ, as computed from the Grahame equation. MPT predicts no effect in the absence of channels.

Prediction 2 — Partial metabolic inhibition produces partial potential reduction

Graded inhibition of mitochondrial respiration should reduce the potential by ∼20–30% (the murburn component), leaving ∼70–80% intact (the fixed-charge component). MPT predicts near-total potential collapse. Literature data already show only ∼5% reduction on Na,K-ATPase inhibition with ouabain — consistent with our model, incompatible with MPT.

Prediction 3 — Cross-cell correlation of charge density and potential

In a panel of cell types with independently measured surface charge densities, the resting potential should correlate linearly with σ as predicted by the Grahame equation. No such systematic comparison exists in the literature.

Prediction 4 — Protein-free lipid vesicles exhibit surface potential

Liposomes reconstituted with a neuronal lipid composition (including ∼20 mol% anionic phospholipids) but containing no membrane proteins should display a negative surface potential of ~ -20 to -30 mV, measurable by zeta-potentiometry. MPT predicts zero potential.

8. Discussion

8.1. Descriptive Success Versus Mechanistic Validity

The enduring influence of MPT rests substantially on the descriptive success of the Hodgkin–Huxley model. However, descriptive adequacy does not imply mechanistic correctness. A model that correctly predicts waveforms from empirically fitted parameters provides no guarantee that its underlying physical assumptions are valid. The convergence of five independent quantitative arguments against MPT — each sufficient individually to raise serious concerns — demands a re-examination of the foundational assumptions.

8.2. What Our Model Does Not Yet Explain

The electrostatic adsorption model accounts quantitatively for the resting potential but does not yet provide a complete account of action potential propagation and rapid excitability dynamics. Rapid

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changes of potential during an action potential require a mechanism for fast modulation of either the surface charge distribution or the DRS dynamics. This remains an open question that we identify as a priority for future work.

8.3. Continuity with the Critical Literature

Our analysis builds on Ling's association-induction hypothesis [4], Tamagawa's experimental work [6,7], and Manoj's murburn framework [8–11]. Three independent research programmes, using different approaches, converging on the same conclusion strengthens the case for reconsidering the canonical model.

9. Conclusion

The membrane potential of neurons is quantitatively compatible with the electrostatic surface potential established by fixed negative membrane charges, as described by the Poisson–Boltzmann/Grahame framework supplemented by Ling's ion adsorption model and the murburn dynamic redox component. This model reproduces the resting potential from first principles, explains the persistence of potential in metabolically dead cells, and makes four experimental predictions distinguishing it from MPT. The five independent quantitative inconsistencies identified in MPT — electrostatic dominance, ionic deficit, pump energetics, mathematical inapplicability, and geometric invalidity — constitute a prima facie case for a fundamental revision of the theory of membrane potential generation.

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