LETTER

An ill-posed boundary condition was inadvertently implemented when deriving the expression to characterize deformation of neurons

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Ling et al. (1) suggest that the exquisite subnanometer voltage-dependent motility observed in cultured neurons results in part from voltage-dependent tension changes at the membrane and are pseudolinear with the transmembrane potential, Ψ. Unfortunately, they (1) modeled the tension change with an expression by Zhang et al. (2) that was derived with ill-posed boundary conditions (3) and has been subsequently overlooked by others (4).

The starting expression used by Zhang et al. (2) arises from electro-capillary phenomena that described charging at a polarizable electrode that is initially uncharged (polarization charge density, $q \equiv 0$), and forms an electrical double layer upon application of an external electric field ($q \neq 0$). Upon changing the potential, U, at the electrode, the electrical double layer adjusts itself to change the interfacial tension, τ, according to $q = -(\partial\tau/\partial U)_{T,\mu,P}$ (T, temperature; μ, chemical potential; P, pressure). Integration of this expression requires knowledge of the relationship between q and U (5) and the potential of zero charge, U_0, which is measurable for a polarizable electrode like mercury, hence $\tau(U) = \tau_0 - (1/2C) \times (U - U_0)^2$ (C, specific capacitance of double layer). In contrast, biological membranes are naturally charged and double layers form spontaneously at the interfaces when immersed in solutions (6). The difficulty is to establish the potential of zero charge for biological membranes. Zhang et al. (2) wrote the Lippmann expression by equating the charge density at each plasma membrane leaflet in terms of the surface potential at each interface and the tension of each leaflet. They then integrated these two expressions with the same boundary condition used to integrate a polarizable electrode, namely that the membrane behaves like an electric condenser with a plate spacing equal to the Debye length. They defined the condition for the potential of zero charge when the membrane tension at each leaflet is at a maximum, i.e., $\tau = \tau_0$, then $q \equiv 0$, where the surface potentials on each leaflet are equivalent to zero, but they did this without showing when, how, or whether this condition becomes true. They then used the Poisson–Boltzmann (PB) equation to write a separate expression for the surface potential at each interface, while without justification, they made the assumption that voltage drop across the membrane is equivalent to Ψ. This assumption requires that the surface potential of each leaflet is identical. They then derived an expression for tension by substituting the PB expressions into their integrated relationships. This expression, the right-hand side of equation **2**, was used by Ling et al. (1).

We showed (3) that tension change is parabolic with respect to the transmembrane potential, as also reported (7) to explain voltage-dependent pressure differences in squid, and by theorems that describe action potentials in neurons (8). This is also in agreement with interfacial tension at droplet interface bilayer membranes (9) and for electrowetting of dielectrics (10). The continued use of an expression that was poorly constructed and suggests that tension is pseudolinear with the transmembrane potential serves only to confuse the interpretation of such motility (1) measurements.

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1 T. Ling *et al.*, High-speed interferometric imaging reveals dynamics of neuronal deformation during the action potential. *Proc. Natl. Acad. Sci. U.S.A.* **117**, 10278–10285 (2020).
2. P.-C. Zhang, A. M. Keleshian, F. Sachs, Voltage-induced membrane movement. *Nature* **413**, 428–432 (2001).
3 B. Farrell, C. Do Shope, W. E. Brownell, Voltage-dependent capacitance of human embryonic kidney cells. *Phys. Rev. E Stat. Nonlin. Soft Matter Phys.* **73**, 041930 (2006).
4 T. D. Nguyen *et al.*, Piezoelectric nanoribbons for monitoring cellular deformations. *Nat. Nanotechnol.* **7**, 587–593 (2012).

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5. E. J. W. Verwey, J. TH. G. Overbeek, *Theory of the Stability of Lyophobic Colloids* (Elsevier, New York, 1948).
6. J. Lyklema, *Fundamentals of Interface and Colloid Science II: Solid-liquid Interfaces* (Academic, London, 1995).
7 V. V. Malev, A. I. Rusanov, Thermodynamics, mechanical and electrical properties of biomembranes. *J. Theor. Biol.* **136**, 295–307 (1989).
8 A. El Hady, B. B. Machta, Mechanical surface waves accompany action potential propagation. *Nat. Commun.* **6**, 6697 (2015).
9 S. Punnamaraju, A. J. Steckl, Voltage control of droplet interface bilayer lipid membrane dimensions. *Langmuir* **27**, 618–626 (2011).
10 F. Mugele, J. C. Baret, Electrowetting: From basics to applications. *J. Phys. Condens. Matter* **17**, R705–R774 (2005).