REPLY TO KOTLER ET AL.:

Changing ion concentrations in conductance-based models

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We thank Kotler et al. (1) for their response to our paper in PNAS (2). Kotler et al. (1) are correct that the Goldman–Hodgkin–Katz (GHK) formulation (3, 4) is often more appropriate when the ionic concentrations are changing, because ion channel conductance varies with the concentration of the permeant ions (5–7). This is often underappreciated because of the historical success of Hodgkin–Huxley's ohmic formulation (8), as the properties of the squid axon obviated many of the conditions that would ordinarily call for the GHK equations (5–7). Most self-respecting biophysicists would prefer to study ion channel permeation and conductance under symmetric ionic conditions, thus removing the rectification caused by asymmetries in ionic concentrations that would call for the use of the GHK equations. But there are also conditions in which the GHK formalism has important limitations, some of which decrease the difference between results of the GHK and ohmic models (5). As outstandingly successful as the Hodgkin–Huxley (8) formulation has been for the entire field, there are conditions in which the GHK formulation may be better, assuming that one would have a way to estimate the relative limitations of the GHK and linear models in relatively complex geometries or circuit contexts.

Kotler et al. (1) argue that the problem we studied in Zang and Marder (2) would have been better modeled by GHK than the ohmic mode. In Fig. 1, we show that the qualitative effect we report is preserved using the GHK formalism. Fig. 1 makes the additional point that the large pump current plays a key role in the phenomena we report. Our goal was to point out the differences in the profile of Na^+ ion concentrations in the myelinated and unmyelinated axons of various diameters, and to highlight the important effects of the cable structure and the Na/K pump on resilience. Thus, as intuited by Kotler et al. (1), the essential messages of our paper are preserved independently of how the Na^+ currents

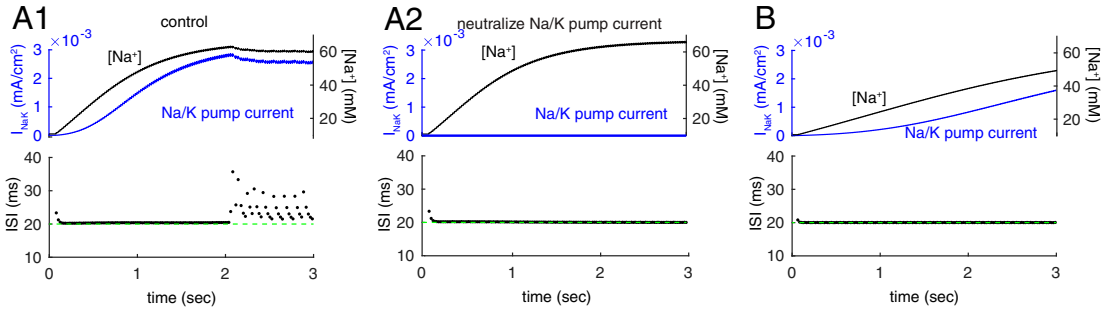

Fig. 1. Na^+ accumulation triggers spike propagation failure in the thin unmyelinated axon by enhanced Na/K pump current. (*A1*) Na^+ accumulation (*Top*, black) enhances outward Na/K pump current (*Top*, blue) to trigger the gradual failure of spike propagation in the 0.2-μm-thick axon, as shown by interspike intervals (ISIs, bottom) recorded at 50 μm distant from the distal end. (*A2*) After neutralizing the Na/K pump, the Na/K pump still removes intracellular Na^+, but, when carrying zero net current (*Top*, blue), Na^+ accumulation (*Top*, black) no longer triggers spike propagation failure in the 0.2-μm-thick axon, as shown by ISIs (*Bottom*). (*B*) In the 0.6-μm-thick axon, enhanced Na/K pump current (*Top*, blue) by Na^+ accumulation (*Top*, black) did not trigger propagation failure, as shown by ISIs (*Bottom*). In all simulations, spikes were triggered at 50 Hz at the starting end of the axon. Na/K pump density is 0.5 pmol/cm^2, and Na^+ current calculation was updated with the GHK equation.

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Author contributions: Y.Z. performed research and E.M. wrote the paper.

The authors declare no competing interest.

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Published March 14, 2022.

are modeled. That said, we join with Kotler et al. (1) to remind those building conductance-based models that consider cases of changing ionic concentrations to compare, directly, the effects of using GHK and a classical Hodgkin–Huxley (8) formalization.

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