

that determined from tracer flux⁸⁻¹⁰, a method which does not use a kinetic model.

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LANDOWNE AND COHEN REPLY—Goldman *et al.*¹ state that they find no serious discrepancy between the measured temperature dependence of the extra sodium flux during an action potential and that computed from Hodgkin-Huxley kinetics.

We have discussed² this discrepancy, or the lack thereof, in a qualitative fashion and both we² and Fitzhugh and Cole³ concluded that there is still a discrepancy even when the effect of temperature on the maximum conductances was included. Although Hodgkin and Huxley succeeded in predicting the electrical behaviour of the axon membrane based on their measurements of currents resulting from potential steps, they noted that at room temperature there was disagreement between the computed ion fluxes and those found experimentally⁴. We have also computed the fluxes predicted by the Hodgkin-Huxley equations and find there is considerable disagreement with experimental data at many temperatures.

The Hodgkin-Huxley equations were solved every three degrees from 3 to 27 °C and the calculated extra unidirectional tracer fluxes for membrane action potentials are shown as the solid curves in Fig. 1, together with the experimental data. Curve 1 represents the fluxes predicted by the unmodified Hodgkin-Huxley equations with a Q_{10} of 3.0 on the rate constants and 1.0 on the conductances. These calculated fluxes are within 1% of those given in Table 5 of Hodgkin and Huxley's original calculations at 6.3 and 18.5 °C (ref. 4). Curve 2 shows the effect of including a Q_{10} of 1.5 on the conductances and curve 3 was generated by using the Q_{10} s given by Goldman *et al.*¹. By taking the ratio of the net fluxes at 5 and 15 °C from the calculations for curve 3, a Q_{10} of 1.8 is obtained, similar to that of Goldman *et al.*¹. Clearly, none

of the curves fits the experimental data very well although, as suggested previously^{2,3} and by Goldman *et al.*¹, the fit is improved by including the effect of temperature on the maximum conductances. All the computed action potentials look qualitatively similar to experimental action potentials. Thus it seems that the appearance of the computed action potentials is not a good criterion for prediction of the appropriate fluxes.

The experimentally observed Q_{10} s were 1/1.4, 1/0.7 and 1/1.6 for the extra Na influx and 1/1.0, 1/1.3 and 1/1.2 for the extra Na efflux, for a variety of experimental conditions. We think that it is quite possible that these numbers are smaller than 1/1.8.

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Equivalence principle

BOTH Bishop and Landsberg¹ and Kilminster in his review² use the argument

- Gravitational redshift
- Retardation of clocks
- Space-time curvature

where we have identified the "non-Minkowskian metric"¹ and the phrase "the geometry of space-time is modified"² with space-time curvature. We have shown³ this argument (which is due to Schild^{4,5}) to be invalid and gave the rather obvious counterexample of a uniform gravitational field where space-time is flat (since the Riemann curvature tensor vanishes).

Einstein's 1911 paper is not, of course, in the framework of Newtonian physics. The argument

- Equivalence principle
- Retardation of clocks

cannot be applied in Newtonian physics because of the existence of an absolute time. The principle of equivalence itself is only partly contained in Newtonian physics in that "fictitious forces" can be equated with gravitational forces. Since the equivalence principle requires, in addition, that the behaviour of clocks under the influence of a gravitational field and an (locally equivalent) acceleration field be indistinguishable at a point, it may not be fully incorporated into Newtonian physics.

The redshift which arises in the treat-

Fig. 1 Extra unidirectional sodium fluxes associated with nerve impulses in squid giant axons. *a*, Influx: the curves represent predictions made by the equations of Hodgkin and Huxley⁴ solved by a computer program similar to that of Moore and Ramon⁵ with modifications as described in the text. The experimental data (points) are the mean values \pm s.e. from Tables 1 and 2 of Cohen and Landowne². *b*, Efflux: the experimental points represent the mean values \pm s.e. from Table 3 of Cohen and Landowne². The experimental data are plotted against the right hand vertical axis which was obtained from the left hand axis using a diameter of 476 μ m and an internal sodium concentration of 65 mM. The dashed lines were fitted to the experimental points by eye.

