Single compartment model with volume and chloride dynamics

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We calculate time series for a single compartment including the following variables: intracellular concentrations of sodium, potassium, chloride and impermeable anions (Na_i, K_i, Cl_i and X_i, with charge z); membrane voltage (V); cellular volume. The steady state should occur in the presence of both a pump leak mechanism (sodium-potassium ATPase) and chloride-potassium extrusion (type 2 potassium-chloride co-transporter, KCC2, subject to some constant conductance g_{KCC} and the reversal potentials of potassium and chloride, while taking into account the usual passive forces across the membrane on each ion.

The compartment is initialised as a cylindrical compartment with a fixed radius. Extracellular ionic concentrations, which are shown with subscript e where relevant, are set (and remain constant), as are the conductance parameters for the ionic flux equations, and the scaling constant A_m (surface area per unit volume). The initial intracellular concentrations are calculated assuming charge neutrality and osmotic equilibrium, i.e. they satisfy (1) and (2) below. The charge z represents the average intracellular charge of the impermeant anions, here represented by an X_i.

$$0 = K_i + Na_i - Cl_i + zX_i \tag{1}$$

$$ose = osi = K_i + Na_i + Cl_i + X_i \tag{2}$$

At each time step, we calculate first the membrane potential V_m, then the changes in ionic concentrations, and finally an update of the cellular volume.

V_m is calculated using Equation 3, the "Charge Difference" approach introduced by Fraser and Huang (2004). Roughly, it assumes that voltage over the membrane is equivalent to difference in charge over the membrane as a ratio of the capacitance C_m across the membrane — of course, the small accumulation of charge near the membrane magnified by the capacitance accounts for the membrane potential in traditional terms, too. This approach

is favourable because the initial voltage can be calculated without assuming a steady state and then consistently updated using the same equation. It also allows for some analytical solutions. Note that the formulation below incorporates the scaling constant A_m, which will be explained later, for the first time.

$$V_m = \frac{F(Na_i + K_i - Cl_i + zX_i)}{C_m} \cdot \frac{volume}{s.area}$$

$$V_m = \frac{F(Na_i + K_i - Cl_i + zX_i)}{A_m C_m} \tag{3}$$

From the voltage equation, ionic flux is calculated and added to each ion's intracellular concentration. This is done using the standard equivalent circuit model, which behaves very similarly to the constant field equations, and includes the influence of KCC2 and the sodium-potassium ATPase.

The ATPase transports two potassium ions inside the cell for three sodium ions moved outside the cell. The pump rate J_p (here in units of flux per square cm) is a function of the sodium gradient, as then it has less activity when the intracellular sodium concentration depletes. A cubic function has been shown to approximate more accurate kinetic models reliant on ATP concentration. Thus

$$J_p = P\big(Na_i/Na_e\big)^3 \tag{4}$$

where P is some initial pump rate (a constant).

KCC2 is calculated using Fraser and Huang's formulation in Equation 5 (but can easily be changed to another model).

$$J_{KCC2} = g_{KCC2} \cdot g_K(Cl_e \cdot K_e - Cl_i \cdot K_i) \tag{5}$$

Thus for each ion:

$$\frac{dI_{Na}}{dt} = g_{Na}(V - E_{Na}) - 3p \tag{6}$$

$$\frac{dI_K}{dt} = g_K(V - E_{Na}) + 2p - J_{KCC2} \tag{7}$$

$$\frac{dI_{Cl}}{dt} = g_{Cl}(V - E_{Cl}) - J_{KCC} \tag{8}$$

In practical terms, to calculate the flux for the entire cell at a time step each flux equation is multiplied by A_m and dt, the interval of time between each time step (usually 1 ms). Each ionic concentration is then updated by adding the relevant flux to the current intracellular concentration.

Next, volume is updated. Change in volume is assumed to be instantaneous and expressed by changing the previous volume by a driving force given by the ratio of intracellular to extracellular osmolarity (Equation 9). Of note here is the role of A_m, since a changed volume ought to change the surface area and hence cellular capacitance. It is assumed that changes in volume are only represented by changes in the length of the cell, but not its radius. Thus we have $\frac{s.area}{volume} = \frac{2\pi rad \cdot len}{\pi rad^2 \cdot len} = \frac{2}{r} = A_m$, which gives us the constant scaling ratio in (3).

$$volume = volume \frac{osmo_i}{osmo_e} \tag{9}$$

Finally, intracellular concentrations are updated in the new volume. Either here or at the beginning of the time loop, concentrations, V_m and volume (relative to the initial volume) are appended to arrays for storage.