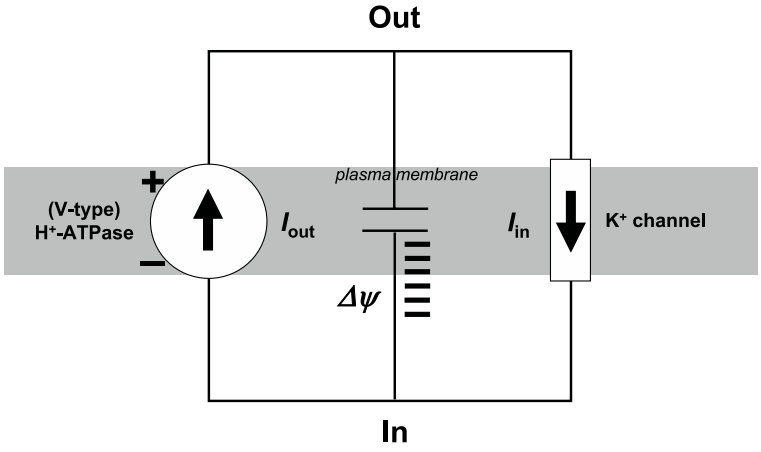
A current source and a cation conductance are components of an electrical circuit connected across the plasma membrane of the malaria parasite *Plasmodium falciparum*

R.J. W. Allen, K.J. Saliba and K. Kirk, School of Biochemistry and Molecular Biology, Linnaeus Way, Australian National University, Canberra, ACT 0200, Australia.

Like most cells, the intraerythrocytic malaria parasite *Plasmodium falciparum* requires a high intracellular concentration of K^+ (~135 mM) for normal development. Using $^{86}Rb^+$ and the potential-sensitive compound ^3H-TPP^+, we have shown that the parasite's mechanism of K^+ uptake is electrophoretic, mediated by a pathway with characteristics of a K^+ channel. The driving force, the parasite's membrane potential, $\Delta\psi$, originates from the extrusion of H^+ by a (V-type) H^+-ATPase on the plasma membrane. However, we have also shown that $\Delta\psi$ is modulated (partially offset) by extracellular K^+, indicating an interdependence between K^+ influx and $\Delta\psi$.

Investigations into the kinetics of K^+ uptake have shown that between 5 mM – 130 mM K^+, the influx of K^+ remains constant, despite there being a reduction in $\Delta\psi$ with increasing concentrations of extracellular K^+.

These phenomena may be reconciled by considering the H^+-ATPase as an 'ideal' current source, and the K^+ channel as a 'variable' conductance, the latter a function of the extracellular concentration of K^+ (see figure). In this electrical model, the inward current carried by K^+ influx through the K^+ channel, 'I_{in}', is equal to the outward current carried by the (*net*) export of H^+ via the H^+-ATPase, 'I_{out}' (*i.e.* $I_{in} = I_{out}$). As the K^+ conductance of the membrane is varied by altering the extracellular concentration of K^+, the offset to $\Delta\psi$ caused by the influx of K^+ also varies, so that the equality $I_{in} = I_{out}$ remains satisfied.



Requirement for steady state $\Delta\psi$: $I_{in} = I_{out}$

During its growth phase, the accumulation of K^+ by the parasite is achieved in the context of a >10-fold decrease in the concentration of K^+ (from ~140 mM) within the host red cell (itself a result of the parasite manipulating the permeability of the host cell membrane). The mechanism we describe is able to explain the parasite's ability to generate a stable influx of K^+, neither overwhelmed by, nor starved of, K^+, as the concentration of K^+ within the red cell undergoes a dramatic reduction.

Largely on the basis of sequence homology to the canonical selectivity filter of homotetrameric K^+ channels, two putative K^+ channel genes have been identified in the *Plasmodium falciparum* genome database. Hydropathy profiles suggest that both channels have additional transmembrane domains over and above the 6 characteristic of voltage-gated K^+ channels, a feature shared by several members of the 'slo' K^+ channel family. The function of these domains is unknown. Both channels are unusual for their great size (the larger has ~2000 residues per subunit), and have large hydrophilic domains which are predicted to reside cytosolically, the functions of which are also unknown. The larger protein has an 'S4' segment containing 3 regularly spaced arginines, in a pattern consistent with a (perhaps degenerate?) voltage sensor of a voltage-gated K^+ channel. Immunofluorescence studies demonstrate localisation of this protein to be predominantly at the host cell membrane, suggesting that it is not the K^+ uptake pathway in the parasite membrane discussed above, but perhaps plays a role in the alteration of the ionic makeup of the host cell cytosol by the parasite. No data currently exists for the location of the smaller protein. These putative K^+ channels are the subject of continuing investigations.