1 A Simple Explanation of Cell Volume Control

There are many organic ions inside the cell which do not leak out of the cell membrane. This creates excess osmotic pressure for the inside of the cell. Since the membrane is permeable to water and is not mechanically strong enough to withstand significant osmotic pressure differences, the cell cannot maintain its volume and will tend to burst. Depending on the organism, there are three ways to tackle this problem.

- **Plant Cells**: The mechanically rigid cell wall surrounds the cell membrane, thereby preventing the cell from bursting.
- **Certain Protozoa**: Periodically pump out water using the contractile vacuole.
- **Animal Cells**: Maintain osmotic balance by controlling intracellular and extracellular ionic concentrations and membrane voltage.

The first two strategies above are easy to understand, but the third strategy, used by animal cells, is subtle and requires further explanation.

Suppose there are 10mM of proteins and organic ions inside the cell, and none outside. Proteins and organic ions are mostly negatively charged. Suppose these ions, on average, carry $-10$ charges per molecule. This means that the organic anions contribute $-10 \times 10 = -100$ mEq amount of charge (1Eq is the amount of charge contributed per liter by 1mol/l of monovalent cation). Suppose all the other inorganic ions have either $-1$ or $+1$ charge. Suppose further that the extracellular negative and positive ionic concentrations are 150mM.

Let the intracellular positive ion concentration be $x$ and negative ion concentration be $y$. We argue that $x$ and $y$ are uniquely determined by the constraint of electroneutrality and the condition of osmotic balance (Table 1). Indeed, by intracellular electroneutrality, we must have:

$$-100 + x - y = 0. \quad (1)$$

By osmotic balance, we have:

$$10 + x + y = 300. \quad (2)$$
Cell Volume Control

Table 1: Charge in mEq, osmolarity in mOsm. 1Osm is the osmotic pressure of a 1mmol/l solution. Electroneutrality and osmotic pressure balance determines $x$ and $y$.

<table>
<thead>
<tr>
<th></th>
<th>inside cell</th>
<th>outside cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>charge</td>
<td>$-100$</td>
<td>$0$</td>
</tr>
<tr>
<td>osmolarity</td>
<td>$10$</td>
<td>$0$</td>
</tr>
<tr>
<td>charge</td>
<td>$x$</td>
<td>$150$</td>
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<tr>
<td>osmolarity</td>
<td>$x$</td>
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<tr>
<td>charge</td>
<td>$-y$</td>
<td>$-150$</td>
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<tr>
<td>osmolarity</td>
<td>$y$</td>
<td>$150$</td>
</tr>
<tr>
<td>total</td>
<td>$0$</td>
<td>$300$</td>
</tr>
</tbody>
</table>

We may solve the above equations to find:

$$x = 195, \quad x = 95. \quad (3)$$

This shows that, in order to maintain cell volume, we must lower the concentration of negative ions inside the cell with respect to the outside and increase the concentration of positive ions inside the cell with respect to the outside. One way to do this would be to maintain a negative membrane potential across the cell membrane, so that negative ions will preferentially distribute extracellularly and positive ions intracellularly.

In order to create this negative membrane potential, the cell maintains a $K^+$ concentration differential across the membrane so that the extracellular $K^+$ concentration is low and the intracellular $K^+$ concentration is high. By having $K^+$ channels on the cell membrane, this concentration differential gives rise to a negative membrane potential, as we saw earlier.

2 The Pump-Leak Model

The explanation given above of animal cell volume control offers only a rough explanation. To better understand cell volume control, we introduce the pump leak model. Consider a cell of volume $v$ and let $[\,]_{i,e}$ be the intracellular and extracellular ionic concentrations respectively. We only consider the ions $Na^+$, $K^+$ and $Cl^-$. Let the cell be in a large and well-stirred extracellular bath so that $[\,]_e$ can be assumed constant. We have the following balance equations for the three ionic species.

$$\frac{d}{dt} (v[Na^+]_i) = -\gamma_{Na} \left( RT \ln \left( \frac{[Na^+]_i}{[Na^+]_e} \right) + F\phi \right) - 3p, \quad (4a)$$

$$\frac{d}{dt} (v[K^+]_i) = -\gamma_K \left( RT \ln \left( \frac{[K^+]_i}{[K^+]_e} \right) + F\phi \right) + 2p, \quad (4b)$$

$$\frac{d}{dt} (v[Cl^-]_i) = -\gamma_{Cl} \left( RT \ln \left( \frac{[Cl^-]_i}{[Cl^-]_e} \right) - F\phi \right). \quad (4c)$$
Here, $\phi$ is the membrane potential, $\gamma$ are the ion channel permeatilities for each species of ion, $p$ is the strength of the pump current, $F$ is the Faraday constant, and $RT$ is the ideal gas constant times absolute temperature. The pump current for $Na^+$ and $K^+$ has a ratio of $3 : 2$ reflecting the stoichiometry of the Na-K ATPase. The above balance laws are supplemented by the following:

$$0 = [Na^+]_i + [K^+]_i - [Cl^-]_i + \frac{zA}{v}, \quad (4d)$$

$$0 = [Na^+]_e + [K^+]_e - [Cl^-]_e, \quad (4e)$$

$$\frac{dv}{dt} = \zeta RT \left( [Na^+]_i + [K^+]_i + [Cl^-]_i + \frac{A}{v} \right) - ([Na^+]_e + [K^+]_e + [Cl^-]_e) \right). \quad (4f)$$

Equation (4d) is the electroneutrality condition for the intracellular space, where $z$ is the valence on one organic anion, and $A$ is the total amount of organic anion. Equation (4e) is the electroneutrality condition for the extracellular space. We have assumed that there are no organic molecules outside the cell and that they do not pass through the membrane. Equation (4f) says that water flows into or out of the cell according to the osmotic pressure difference across the membrane. Here, $\zeta$ is the membrane permeability to water flow. System (4) forms a system of differential algebraic equations. We would like to see under what condition the above system possesses a stable steady state, representing a cell with a stable cell volume and ionic composition.

It may be somewhat more accurate to replace (4d) with the following equation:

$$C_m \phi = F v \left( [Na^+]_i + [K^+]_i - [Cl^-]_i + zA \right) \quad (5)$$

where $C_m$ is the total membrane capacitance of the cell. Equation (5) states that the total amount of charge inside the cell is equal to the charge stored on the membrane capacitor. Let us take the time derivative of (5):

$$C_m \frac{d\phi}{dt} + i_K + i_{Na} + i_{Cl} = 0, \quad (6)$$

where

$$i_{Na} = -F \frac{d(v[Na^+]_i)}{dt} = F \gamma_{Na} \left( RT \ln \left( \frac{[Na^+]_i}{[Na^+]_e} \right) + F \phi \right) + 3pF \quad (7)$$

and likewise for $i_K$ and $i_{Cl}$. This equation has a convenient interpretation in terms of electrical circuits. It says that the total membrane current and the capacitive current add up to 0, a simple statement of current conservation. Replacing (4d) with (5) is mathematically equivalent to replacing (4d) with (6) in system (4) so long as the initial condition satisfies (5). To examine the effect of replacing (4d) with (6), let us make system (4) and (6) dimensionless. Let:

$$v = v_0 V, \phi = \frac{RT}{F} \hat{\phi}, A = c_0 v_0 \hat{A}, [Na^+]_i = c_0 N_i, \gamma_{Na} = \gamma_0 G_{Na} \quad (8)$$
and likewise for the other ions. Here, \( c_0 \) and \( v_0 \) are the representative ionic concentration and volume respectively.

\[
\frac{d}{d\tau} (VN_i) = -G \left( \ln \left( \frac{N_i}{N_e} \right) + \hat{\phi} \right) - 3\alpha \equiv -I_{Na} \tag{9}
\]

\[
\frac{d}{d\tau} (VK_i) = -G_K \left( \ln \left( \frac{K_i}{K_e} \right) + \hat{\phi} \right) + 2\alpha \equiv -I_K \tag{10}
\]

\[-\frac{d}{d\tau} (VC_i) = -G_{Cl} \left( \ln \left( \frac{C_i}{C_e} \right) - \hat{\phi} \right) \equiv I_{Cl} \tag{11}\]

\[
\epsilon \frac{d\phi}{d\tau} = -(I_K + I_{Na} + I_{Cl}) \tag{12}
\]

\[
d\frac{dV}{d\tau} = \xi \left( N_i + K_i + C_i + \frac{A}{V} - (N_e + K_e + C_e) \right) \tag{13}\]

where

\[
t = t_c \tau = \frac{c_0 v_0}{\gamma_0 RT} \tau, \quad \alpha = \frac{p}{\gamma_0 RT}
\]

\[
\xi = t_c \frac{c_0 RT \zeta}{v_0}, \quad \epsilon = \frac{C_m (RT/F)}{F c_0 v_0}. \tag{15}\]

The dimensionless quantity \( \epsilon \) is about \( 10^{-8} \) and is thus quite small. It is thus an excellent approximation, in the context of volume control, to set \( \epsilon \) to be equal to 0 and use the electroneutrality constraint for intracellular ions. We are thus back to (4d).

We note, however, that this approximation is not justified in all cases. Rescale time in terms of \( \epsilon t_c \) rather than \( t_c \) so that our new time variable \( \tau' \) satisfies \( t = \epsilon t_c \tau' \). Then, we have:

\[
\frac{d}{d\tau'} (VN_i) = -\epsilon G_{Na} \left( \ln \left( \frac{N_i}{N_e} \right) + \hat{\phi} \right) - 3\epsilon\alpha \tag{16}
\]

\[
\frac{d}{d\tau'} (VK_i) = -\epsilon G_K \left( \ln \left( \frac{K_i}{K_e} \right) + \hat{\phi} \right) + 2\epsilon\alpha \tag{17}
\]

\[-\frac{d}{d\tau'} (VC_i) = -\epsilon G_{Cl} \left( \ln \left( \frac{C_i}{C_e} \right) + \hat{\phi} \right) \tag{18}\]

\[
\frac{d\phi}{d\tau'} = -(I_{Na} + I_K + I_{Cl}) \tag{19}
\]

\[
d\frac{dV}{d\tau'} = \epsilon \xi \left( N_i + K_i + C_i + \frac{A}{V} - (N_e + K_e + C_e) \right) \tag{20}\]

As we let \( \epsilon \to 0 \), the only equation that remains is the equation for the membrane voltage. In this regime, we should not neglect effects from membrane capacitance but it is admissible to assume that the concentrations and volumes are constant. The time \( t_c \) is on the order of minutes to hours and consequently \( \epsilon t_c \) is on the order of milliseconds or less. The electroneutrality condition is a valid approximation at long time scales. The \( \epsilon t_c \) timescale becomes relevant
when the membrane permeabilities or the membrane ionic conductances change rapidly in time. This happens in the context of excitable cells, a topic we shall study in the next chapter. Henceforth, in this chapter, we deal exclusively with the electroneutral approximation.

Let us recast problem (4) in a slightly more general form. Consider the following model:

\[
\frac{d(vc_k)}{dt} = -j_k - p_k, \quad k = 1, \ldots, N, \quad (21a)
\]

\[
0 = \sum_{k=1}^{N} z_k c_k + \frac{zA}{v} = \sum_{k=1}^{N} z_k c_k^e = 0, \quad (21b)
\]

\[
\frac{dv}{dt} = -j_w \quad (21c)
\]

where \(c_k\) is the intracellular ionic concentration of the \(k\)-th species of ion, \(c_k^e\) is the extracellular ionic concentration and \(z_k\) is the valence of the \(k\)-th ion. The fluxes \(j_k\) and \(p_k\) are the ion channel and pump fluxes respectively, and \(j_w\) is the water flux. For \(j_k\) and \(p_k\), we let:

\[
j_k = \gamma_k \mu_k, \quad \mu_k = \ln \left( \frac{c_k}{c_k^e} \right) + z_k \phi
\]

\[
j_w = \zeta \pi_w, \quad \pi_w = \left( \sum_{k=1}^{N} c_k^e - \left( \sum_{k=1}^{N} c_k + \frac{A}{v} \right) \right).
\]

We have made the equations dimensionless by rescaling \(\phi\) by \(RT/F\) and \(\gamma_k\) accordingly. Let us require that \(c_k^e > 0\) and \(z_k \neq 0\) for simplicity.

We now ask whether the above system has a steady state. Let us set the right hand side of (21a) equal to 0. We have:

\[
\mu_k = \ln \left( \frac{c_k}{c_k^e} \right) + z_k \phi = -\frac{p_k}{\gamma_k} \equiv q_k.
\]

From here, we see that:

\[
c_k = c_k^e \exp(-q_k - z_k \phi).
\]

Substituting this into (21c) and (21b), we have:

\[
f(\phi) + \frac{A}{v} = 0, \quad (24)
\]

\[
-\frac{df}{d\phi} + \frac{zA}{v} = \sum_{k=1}^{N} z_k c_k^e \exp(-q_k - z_k \phi) + \frac{zA}{v} = 0, \quad (25)
\]

where \(f(\phi)\) is given by:

\[
f(\phi) = \sum_{k=1}^{N} c_k^e \left( \exp(-q_k - z_k \phi) - 1 \right), \quad (26)
\]
We must find solutions \( \phi \) and \( v > 0 \) to the above system. Note that:

\[
\frac{d^2 f}{d\phi^2} = \sum_{k=1}^{N} z_k^2 c_k^e \exp(-q_k - z_k \phi) > 0, \quad \lim_{\phi \to \pm \infty} \frac{df}{d\phi} = \pm \infty. \quad (27)
\]

The second property comes from the fact that there are ions with negative and positive valences among the \( N \) species of ions and that \( c_k^e > 0 \). We can thus solve (25) for \( \phi \) uniquely in terms of \( v \). Let this function be \( \phi = \varphi(v) \). We have:

\[
\frac{d\varphi}{dv} = -\left( \frac{d^2 f}{d\phi^2} \right)^{-1} \frac{zA}{v^2}. \quad (28)
\]

Consider the left hand side of (24) and substitute \( \phi = \varphi(v) \) into this expression:

\[
R(v) \equiv f(\varphi(v)) + \frac{A}{v} = 0. \quad (29)
\]

Our problem of finding steady states is reduced to the question of whether the above equation in \( v \) has a positive solution. We have:

\[
\frac{dR}{dv} = \frac{df}{d\phi} \frac{d\varphi}{dv} - \frac{A}{v^2} = -\left( \frac{d^2 f}{d\phi^2} \right)^{-1} \frac{(zA)^2}{v^3} - \frac{A}{v^2} \leq -\frac{A}{v^2} < 0 \quad (30)
\]

where we used (25) and (28) in the second equality and (27) in the first inequality. Therefore, \( R(v) \) is monotone decreasing. Note that:

\[
R(e) = R(1) - \int_e^1 \left( \frac{dR}{dv} \right) dv \geq R(1) + \int_e^1 \left( \frac{A}{v^2} \right) dv = R(1) + A(e^{-1} - 1). \quad (31)
\]

Therefore, \( R(v) \to \infty \) as \( v \) tends to 0 from above. Thus, (29) has a unique positive solution if:

\[
\lim_{v \to \infty} R(v) < 0, \quad (32)
\]

and otherwise, there is no solution. Let \( \varphi_{\infty} = \lim_{v \to \infty} \varphi(v) \). Note that this limit exists since, by (28), \( \varphi(v) \) is monotone if \( z \neq 0 \) and constant if \( z = 0 \). Taking the limit \( v \to \infty \) on both sides of (25), we see that \( \varphi_{\infty} \) is the unique solution to \( df/d\phi = 0 \) as an equation for \( \phi \). Given (29), condition (32) can be written as \( f(\varphi_{\infty}) < 0 \).

We may summarize our result as follows. The function \( f(\phi), \phi \in \mathbb{R} \) has a unique minimizer \( \phi = \phi_{\min} \). Our system has a unique steady state if this minimum value is negative:

\[
f_{\min}(q, c^e, z) \equiv f(\phi_{\min}) < 0. \quad (33)
\]

Otherwise, the system does not have any steady states.

The above condition can be interpreted as follows. At steady state, \( c_k \) must be equal to \( c_k^* = c_k^e \exp(-q_k - z_k \phi^*) \) where \( \phi^* \) is the value of \( \phi \) at steady state. We need \( f(\phi^*) = \sum_{k=1}^{N}(c_k^* - c_k^e) < 0 \) since there must be “osmotic room” for
the impermeable solutes. This is only possible if the minimum of \( f(\phi), \phi \in \mathbb{R} \) is negative. It is interesting that this necessary condition is in fact sufficient.

Let us apply the above result to system (4). The function \( f(\phi) \) in this case is given by:

\[
f(\phi) = \left( [Na^+]_e \exp\left(-\frac{3p}{\gamma_{Na}RT}\right) + [K^+]_e \exp\left(\frac{2p}{\gamma_{K}RT}\right) \right) \exp\left(-\frac{F\phi}{RT}\right) + [Cl^-]_e \exp\left(\frac{F\phi}{RT}\right) - ([Na^+]_e + [K^+]_e + [Cl^-]_e)
\]

(34)

where we have restored dimensional units. To obtain the minimum value of \( f(\phi) \) when \( \phi \) varies over all real numbers, we may apply the arithmetic-geometric mean inequality to the first two terms in the above:

\[
f(\phi_{\text{min}}) = 2\left(\left([Na^+]_e \exp\left(-\frac{3p}{\gamma_{Na}RT}\right) + [K^+]_e \exp\left(\frac{2p}{\gamma_{K}RT}\right) \right) |Cl^-]_e\right)^{1/2} - ([Na^+]_e + [K^+]_e + [Cl^-]_e).
\]

(35)

This quantity has to be negative. Noting that:

\[
[Na^+]_e + [K^+]_e = [Cl^-]_e
\]

(36)

by electroneutrality (4d), we conclude that the condition for existence of a steady state is:

\[
\frac{[Na^+]_e \exp (-3p/(\gamma_{Na}RT)) + [K^+]_e \exp (2p/(\gamma_{K}RT))}{[Na^+]_e + [K^+]_e} < 1.
\]

(37)

Let us view the left hand side of the above as a function of \( p \) and call this function \( g(p) \). Note that \( g(0) = 1 \) and that \( d^2g/dp^2 > 0 \). This shows that, \( g(p) < 1 \) is satisfied for some value of positive \( p \) if and only if \( dg/dp < 0 \) at \( p = 0 \). This leads to the condition:

\[
\frac{2[K^+]_e}{\gamma_{K}} < \frac{3[Na^+]_e}{\gamma_{Na}}.
\]

(38)

This condition is clearly satisfied under physiological conditions. Indeed, the extracellular concentration of Na\(^+\) is more than ten-fold higher than the extracellular K\(^+\) concentration and the cell membrane is far more permeable to K\(^+\) ions than to Na\(^+\) ions. One may argue that the cell is making sure that the above inequality is satisfied by a wide safety margin.

3 Stability of Steady States

The next question we should turn to is the stability of the steady state. For this, we first establish a free energy identity. Multiply (21a) by \( \mu_k \) on both sides. We
have:

\[
\mu_k \frac{dv_{c_k}}{dt} = \ln \left( \frac{c_k}{c_k^r} \right) + z_k \phi \frac{d(v_{c_k})}{dt} = \frac{d}{dt} \left( v \left( c_k \ln \left( \frac{c_k}{c_k^r} \right) - c_k \right) \right) + c_k \frac{dv}{dt} + z_k \phi \frac{d(v_{c_k})}{dt}
\]  

\[= - \mu_k (j_k + p_k). \tag{39} \]

Now, let us take the summation in the above equation in \(k\).

\[
\frac{d}{dt} \left( \sum_{k=1}^{N} v \left( c_k \ln \left( \frac{c_k}{c_k^r} \right) - c_k \right) \right) + \sum_{k=1}^{N} c_k \frac{dv}{dt} = - \sum_{k=1}^{N} \mu_k (j_k + p_k). \tag{40} \]

Note that the term involving \(\phi\) vanishes by the electroneutrality condition (21b). Next, multiply both sides of (21c) with \(\pi_w\).

\[
\pi_w \frac{\partial v}{\partial t} = - \left( \sum_{k=1}^{N} c_k \right) \frac{dv}{dt} + \frac{d}{dt} \left( \sum_{k=1}^{N} c_k v + A \ln \frac{A}{v} \right) = - \pi_w \dot{j}_w. \tag{41} \]

We may now add (40) and (41) to conclude that:

\[
\frac{dG}{dt} = - \sum_{k=1}^{N} \mu_k (j_k + p_k) + \pi_w \dot{j}_w, \tag{42} \]

\[G = \sum_{k=1}^{N} v \left( c_k \ln \left( \frac{c_k}{c_k^r} \right) - c_k + c_k^r \right) + A \ln \frac{A}{v}. \]

Note that, if \(p_k = 0\) for all \(k\), the right hand side of the first line of the above equality is non-positive, and thus, \(G\) is monotone non-increasing.

The function \(G\) above should be interpreted physically as the free energy of the system. When there is no external energy input \((p_k = 0\) for all \(k\)), then the free energy never increases. We may turn this argument around and say that the requirement that the free energy decrease in the absence of active currents (the second law of thermodynamics) forces us to adopt the requirement:

\[
\sum_{k=1}^{N} \mu_k j_k + \pi_w \dot{j}_w \geq 0. \tag{43} \]

Prescriptions (21d) and (21e) are the easiest ways that guarantee this inequality to hold.

The fact that \(G\) is monotone non-increasing suggests that we might use this as a Lyapunov function to study stability of the steady state. Indeed, if \(p_k = 0\) for all \(k\), \(dG/dt = 0\) when the right hand side of (21a) and (21c) is equal to 0 and is monotone decreasing otherwise. Unfortunately, equality (42) by itself is useless in examining stability of the steady state. When \(p_k = 0\) for all \(k\),
there are no steady states in the first place. An easy computation shows that $f_{\text{min}}$ in (33) is equal to 0 in this case. We must thus look for a function that is monotone decreasing even when $p_k \neq 0$ and there is a steady state.

Now, suppose that (33) is satisfied so that there is indeed a steady state. Let $(c_1^*, \cdots, c_N^*, v^*, \phi^*)$ be the steady state values of the ionic concentration, volume and membrane potential respectively. At steady state, the right hand side of (21a) is equal to 0 and using (21d) we find,

$$\gamma_k \left( \ln \left( \frac{c_k}{c_k^*} \right) + z_k \phi^* \right) + p_k = 0. \quad (44)$$

We may therefore rewrite (21a) as:

$$\frac{d v c_k}{d t} = -\gamma_k \tilde{\mu}_k, \quad \tilde{\mu}_k = \ln \left( \frac{c_k}{c_k^*} \right) + z_k (\phi - \phi^*). \quad (45)$$

We may now multiply both sides of the above equation by $\tilde{\mu}_k$ and perform the same calculation leading to (42) to conclude that:

$$\frac{d \tilde{G}}{d t} = -\left( \sum_{k=1}^{N} \gamma_k \tilde{\mu}_k^2 + \zeta \pi_w^2 \right), \quad \tilde{G} = \sum_{k=1}^{N} v \left( c_k \ln \left( \frac{c_k}{c_k^*} \right) - c_k + c_k^* \right) + A \left( \ln \left( \frac{v^*}{v} \right) - 1 + \frac{v}{v^*} \right), \quad (46)$$

where we used:

$$\sum_{k=1}^{N} c_k^2 = \sum_{k=1}^{N} c_k^* + A. \quad (47)$$

The above function $\tilde{G}$ may be thought of as measuring the free energy of the system relative to the ionic concentrations in the steady state in contrast to $G$, which measures the free energy relative to the ionic concentrations in the extracellular space.

Equation (46) shows that $d\tilde{G}/dt$ is negative except at steady state, and that both $G$ and $dG/dt$ are equal to 0 at steady state. This suggests that we may use $\tilde{G}$ as a Lyapunov function of this system to conclude that the steady state is indeed stable. To do so, it is sufficient to show that $\tilde{G}(c_1, \cdots, c_N, v, \phi)$ under the electroneutrality constraint (21b) attains its unique minimum at $(c_1^*, \cdots, c_N^*, v^*, \phi^*)$.

For this, it is easiest to change our variables from $(c_1, \cdots, c_N, v, \phi)$ to

$$(a_1, \cdots, a_N, v, \phi), \quad a_k = v c_k, k = 1, \cdots, N. \quad (48)$$

To find the minimizer of $\tilde{G}(a_1, \cdots, a_N, v)$ under the electroneutrality constraint

$$\sum_{k=1}^{N} z_k a_k + z A = 0 \quad (49)$$
we may use the method of Lagrange multipliers. This shows immediately that the only stationary point of $\hat{G}$ when restricted to the hyperplane given in (49) is the steady state $(a^*_1, \cdots, a^*_N, v^*) = (v^* c^*_1, \cdots, v^* c^*_N, v^*)$. To conclude that this is a minimum rather than a saddle or a maximum, we may examine the convexity of $\hat{G}$. The Hessian of $\hat{G}$ with respect to $(a_1, \cdots, a_N, v)$ turns out to be positive definite. Therefore, a stationary point of the restriction of $\hat{G}$ to any hyperplane can only be a minimum.

The fact that $\hat{G}$ is positive everywhere except at the steady state suggests that the steady state is not only (locally) asymptotically stable but globally asymptotically stable. This is in fact true. To prove this fact, one has to rule out the possibility that the concentrations $c_k$ and $v$ may come arbitrarily close to 0 in finite time. This requires a some further computations.

What happens when $f_{\text{min}}$ in (33) is non-negative so that there are no steady states? Then, it turns out that the cell bursts in the sense that

$$\lim_{t \to \infty} v(t) = \infty$$

for any initial value. This result can be shown using the same kind of argument that we used above, the argument here is somewhat technical.

The pump-leak model we studied above, then, has the striking property that there is a unique globally stable steady state if and only if (33) is satisfied. If not, the cell bursts. Cell volume control under the above pump-leak model is robust in the following sense. Suppose the cell experiences a sudden change in pump strength, ion channel conductance and/or extracellular ionic concentration within a range satisfying (33). Then the cell will proceed to the new steady state since the new steady state is still globally asymptotically stable. The cell will not be jolted into losing control of its volume.

4 Problems

1. Suppose the extracellular $K^+$ concentration is suddenly increased. What will happen to cell volume? Explain in biophysical terms.

2. Consider the pump-leak model (21). Show that there are no steady states if the pump currents $p_k$ are all 0.

3. Consider the pump-leak model (21). Suppose that the parameters are chosen such that the model has a steady state. Suppose $A$ is increased. Will the model still have a steady state? If the model still has a steady state, what can you say about the cell volume at the new steady state compared to the older one?

4. For model (4), show that, if there is a steady state, the voltage at steady state is negative so long as $z \leq 0$.

5. Check that $\hat{G}$ of (46) is a convex function in $(a_1, \cdots, a_N, v) = (c_1 v, \cdots, c_N v, v)$. 


6. Suppose that the cell membrane has some mechanical strength, so that (21e) is modified as follows:

\[ j_w = \zeta (\pi_w + p_w), \quad p_w = h(v) \]  \hspace{1cm} (51)

where \( h(v) \) is the membrane mechanical force, given as a function of \( v \). Consider the pump-leak model (21) except that we set \( p_k = 0 \) for all \( k \) in (21a) and replace (21e) with (51).

(a) Is it possible to have a steady state?

(b) Find a Lyapunov function for this system and discuss stability of the steady state if there is one.