At rest

$$\begin{tikzcd} \text{open } (n) \arrow[r, bend left, "\beta"] & (1-n) \text{ closed} \arrow[l, bend left, "\alpha"] \end{tikzcd}$$

in: $\alpha(1-n)$ out: βn

$$\frac{dn}{dt} = \alpha(1-n) - \beta n = \alpha - (\alpha+\beta)n$$

let $\alpha+\beta = \gamma$

$$sN - n_0 = \frac{\alpha}{s} - (\alpha+\beta)N(s)$$

$$(s+\gamma)N = n_0 + \frac{\alpha}{s} \Rightarrow N = \frac{n_0}{s+\alpha} + \frac{\alpha}{\alpha+\beta}\frac{1}{s} - \frac{\alpha}{\alpha+\beta}\frac{1}{s+\gamma}, \quad \tau_n \triangleq \frac{1}{\alpha+\beta}$$

$$\frac{\alpha}{s(s+\gamma)} = \frac{A}{s} + \frac{B}{s+\gamma}$$

$$A = \frac{\alpha}{\gamma} \quad B = -\frac{\alpha}{\gamma}$$

$$n(t) = n_0 e^{-t/\tau_n} + n_\infty - n_\infty e^{-t/\tau_n}, \quad n_\infty \triangleq \frac{\alpha}{\alpha+\beta} = \tau_n \alpha$$

$$= n_0 e^{-t/\tau_n} + n_\infty(1 - e^{-t/\tau_n})$$

eq 3-13 pg 55 $\Rightarrow$

$$\alpha = \frac{0.01(10-V)}{e^{0.1(10-V)} - 1} \qquad \beta = 0.125 e^{-V/80}$$

This would model the statistics of the energy barrier and the probability of the gating particle overcoming this barrier.

If the neuron is at rest at $t=0$, ~~$a_0 = 0$~~ $n(0) = n_\infty \Rightarrow n_0 = n_\infty \Rightarrow n(t) = n_\infty$ ~~and no firing could take place.~~

$$g_K = \bar{g}_K n_\infty^4 = \bar{g}_K (\tau_n \alpha)^4$$

$$\tau_n \alpha = \frac{\alpha}{\alpha+\beta} = \frac{0.01(10-V)}{0.01(10-V) + 0.125 e^{-V/80}(e^{0.1(10-V)} - 1)} = n_\infty < 1$$

This is all incorrect because $n \neq Pr[\text{firing}]$. It is $Pr[\text{open}]$; physically, it is the fraction of ion channels that are open & conducting at any particular time.

~~$\frac{dn}{dt} = \alpha - (\alpha+\beta)n_\infty$~~ ~~$sN - n_\infty = \alpha - (\alpha+\beta)n_\infty$~~

$$\frac{dn}{dt} = 0 \Rightarrow 0 = \alpha - (\alpha+\beta)n \Rightarrow n = \frac{\alpha}{\alpha+\beta} = n_\infty \checkmark$$

This merely says that the probability of firing at any given t is constant.

$$\begin{tikzcd} \text{open } F \arrow[loop left, "n_\infty"] \arrow[r, bend left, "1-n_\infty"] & \text{closed } R \arrow[loop right, "1-n_\infty"] \arrow[l, bend left, "n_\infty"] \end{tikzcd}$$

$Pr[R] \triangleq \pi_R(t)$, w/ $\pi_R(0) = 1$

$Pr[F] \triangleq \pi_F(t)$

$$\begin{bmatrix} \pi_F(t+1) \\ \pi_R(t+1) \end{bmatrix} = \begin{bmatrix} n_\infty & n_\infty \\ 1-n_\infty & 1-n_\infty \end{bmatrix} \begin{bmatrix} \pi_F(t) \\ \pi_R(t) \end{bmatrix}; \quad \begin{bmatrix} \dot\pi_F \\ \dot\pi_R \end{bmatrix} = \begin{bmatrix} n_\infty & n_\infty \\ 1-n_\infty & 1-n_\infty \end{bmatrix} \begin{bmatrix} 0 \\ 1 \end{bmatrix} = \begin{bmatrix} n_\infty \\ 1-n_\infty \end{bmatrix}$$

discrete

$$\begin{bmatrix} \dot\pi_F \\ \dot\pi_R \end{bmatrix} = \begin{bmatrix} n_\infty & n_\infty \\ 1-n_\infty & 1-n_\infty \end{bmatrix} \begin{bmatrix} \pi_F \\ \pi_R \end{bmatrix} \quad \text{or} \quad \dot\pi = A\pi$$

$$\lambda I - A = \begin{bmatrix} \lambda - n_\infty & -n_\infty \\ n_\infty - 1 & \lambda - 1 + n_\infty \end{bmatrix}$$

$-n_\infty(-1+n_\infty) = -n_\infty(n_\infty - 1) = +n_\infty(1-n_\infty)$

$$|\lambda I - A| = 0 \Rightarrow (\lambda - n_\infty)(\lambda - 1 + n_\infty) + n_\infty(n_\infty - 1) = 0$$

~~$\lambda^2 + 2\underbrace{n_\infty(n_\infty - 1)}_{\sigma}\lambda + \underbrace{n_\infty(n_\infty-1)}_{\sigma} \cdot 2 = 0$~~

~~$\lambda = -\sigma \pm \frac{1}{2}\sqrt{4\sigma^2 - 4 \cdot 4 \cdot \sigma^2} = -\sigma \pm \sigma\sqrt{-4}$~~

~~$= -\sigma \pm j\sqrt{3}\sigma$~~

~~But $n_\infty < 1 \Rightarrow \sigma < 0 \Rightarrow Re\{\lambda\} > 0$~~

~~$\lambda^2 - 2n_\infty(1-n_\infty) - 2n_\infty(1-n_\infty) = 0$~~

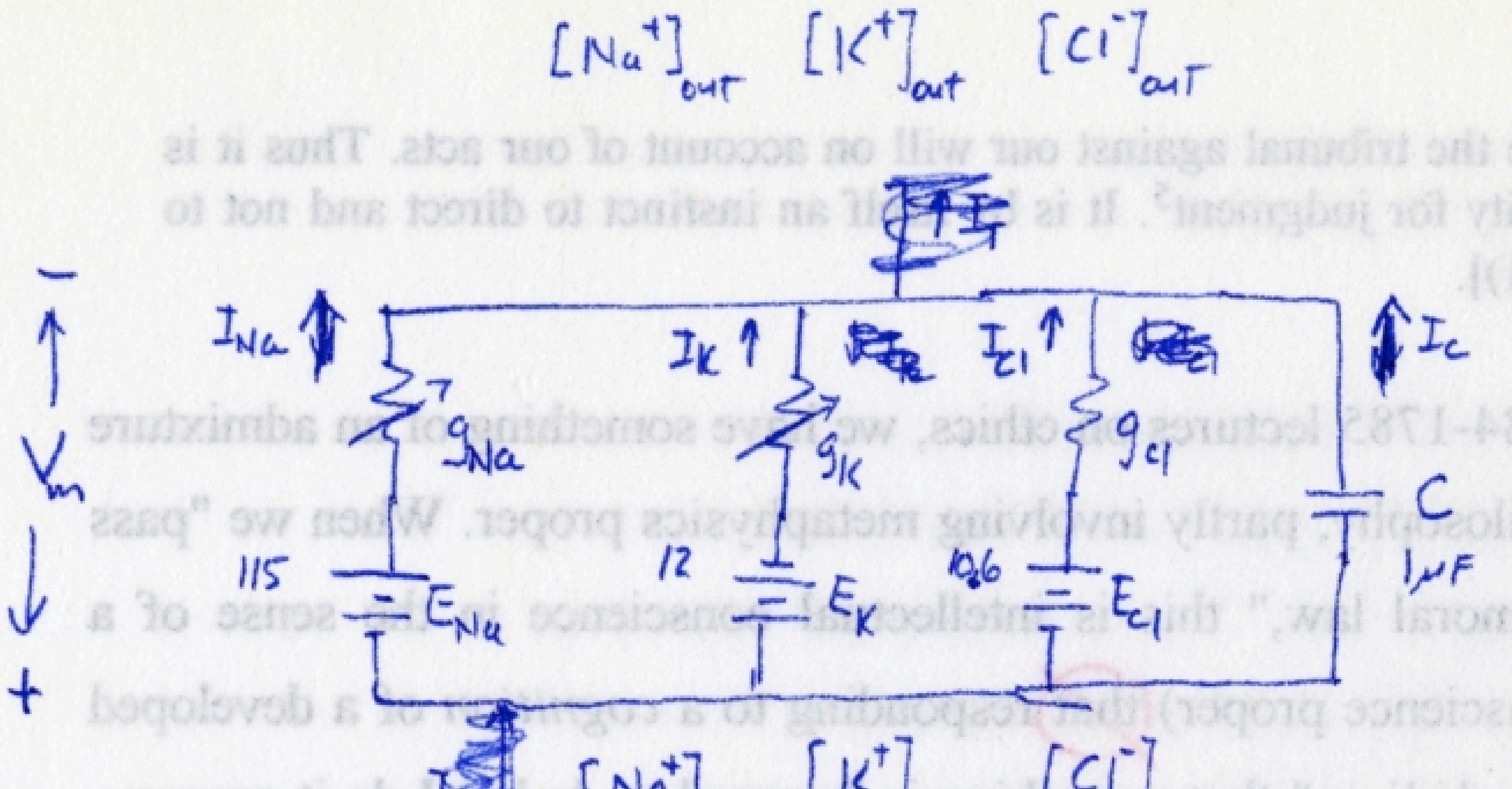
~~$\lambda = n_\infty(1-n_\infty) \pm \sqrt{n_\infty^2(1-n_\infty)^2 + 2n_\infty(1-n_\infty)}$~~

~~$= n_\infty(1-n_\infty) \pm n_\infty(1-n_\infty)\sqrt{1 + \frac{2}{n_\infty(1-n_\infty)}}$~~

~~$\lambda = n_\infty(1-n_\infty)\left[1 \pm \sqrt{1 + \frac{2}{n_\infty(1-n_\infty)}}\right]$; one pole in RHP; one pole in LHP~~

~~$n_\infty = .3 \Rightarrow \lambda = .21\left[1 \pm \sqrt{1 + \frac{2}{.21}}\right] = .21 \cdot \begin{cases} -2.244 \\ +4.244 \end{cases} = \begin{cases} -.471 = \lambda^- \\ +0.891 = \lambda^+ \end{cases}$~~

(2)



$g_{Na} = 120\ m^3h$

$g_K = 36\ n^4$

$g_{Cl} = 0.3$

$$\frac{dm}{dt} = \alpha_m(1-m) - \beta_m m$$

$$\frac{dh}{dt} = \alpha_h(1-h) - \beta_h h$$

$$\frac{dn}{dt} = \alpha_n(1-n)\ \beta_n n$$

$$m(t) = m_0 e^{-t/\tau_m} + m_\infty(1-e^{-t/\tau_m}) \qquad m_\infty = \frac{\alpha_m}{\alpha_m+\beta_m} \qquad \tau_m = \frac{1}{\alpha_m+\beta_m}$$

$$n(t) = n_0 e^{-t/\tau_n} + n_\infty(1-e^{-t/\tau_n}) \qquad n_\infty = \frac{\alpha_n}{\alpha_n+\beta_n} \qquad \tau_n = \frac{1}{\alpha_n+\beta_n}$$

$$h(t) = h_0 e^{-t/\tau_h} + h_\infty(1-e^{-t/\tau_h}) \qquad h_\infty = \frac{\alpha_h}{\alpha_h+\beta_h} \qquad \tau_h = \frac{1}{\alpha_h+\beta_h}$$

$$V_m = \frac{kT}{q} \ln\left[\frac{P_{Na}[Na^+]_o + P_K[K^+]_o + P_{Cl}[Cl^-]_i}{P_{Na}[Na^+]_i + P_K[K^+]_i + P_{Cl}[Cl^-]_o}\right]$$

$P_{Na} = .07 \quad [Na^+]_o = 455 \quad [Na^+]_i = 72$

$P_K = 1.8 \quad [K^+]_o = 10 \quad [K^+]_i = 345$

$P_{Cl} = 0.8 \quad [Cl^-]_o = 540 \quad [Cl^-]_i = 61$

$$E_{Na} = \frac{kT}{q}\ln\left[\frac{[Na^+]_o}{[Na^+]_i}\right] \times 2.4 \quad (2.4 = \text{fudge factor})$$

$$E_K = \frac{kT}{q}\ln\left[\frac{[K^+]_i}{[K^+]_o}\right] \times 0.13 \quad (0.13 = \text{fudge factor})$$

$$E_{Cl} = \frac{kT}{q}\ln\left[\frac{[Cl^-]_o}{[Cl^-]_i}\right] \times 0.186 \quad (0.186 = \text{fudge factor})$$

→ fudge factors picked to force E_i above to agree w/ concentrations given here.

$V_m = -61.7$ (mV)

$$\alpha_m = \frac{0.1(25-V)}{e^{0.1(25-V)} - 1} \cong .0015 \qquad \beta_m = 4e^{-V/18} = 123 \text{ bogus!}$$

$$\alpha_h = .07e^{-V/20} \qquad \beta_h = \frac{1}{e^{0.1(30-V)}+1}$$

$$\alpha_n = \frac{.01(10-V)}{e^{0.1(10-V)}-1} \qquad \beta_n = 0.125\,e^{-V/80}$$

I'm not getting possible values for α and β from this mix of numbers. Either "V" must be entered as a positive number (β_m, β_n) or else it is not V_m. If we take $V = 61.7$, $\alpha_m > 1$, which is impossible.

Setting aside the failure of the α and β equations, the model is incomplete until we write concentration equations to account for ion flow through the gates because it is the relative ion concentrations that determine V_m, E_{Na}, E_K, and E_{Cl}. In H-H, current and conduction units are in $\mu A/cm^2$ and $m\mho/cm^2$ so

$$\frac{d[C]_o}{dt} = I_{[C]} \qquad \frac{d[C]_i}{dt} = -I_{[C]}$$

were it not for the capacitor term. How do we handle this? Is the cap suppose to absorb the ion currents? This doesn't work unless we distinguish them. The H-H model used "clamps" and applied a potential to the membrane. In this sense, it is not representative (It was, after all, a model of an axon, not a neuron soma). I'll have to see how the Koch, et al. model handled this.

Perhaps the answer is that the "batteries" actually represent the ion concentrations. Suppose

$$E_i = f \ln\left[\frac{[C_i]_o}{[C_i]_i}\right]$$

$$\Rightarrow \frac{dE_i}{dt} = f\frac{[C_i]_i}{[C_i]_o}\frac{d}{dt}\left[\frac{[C_i]_o}{[C_i]_i}\right] = f\frac{[C_i]_i}{[C_i]_o}\left(\frac{1}{[C_i]_i}\frac{d[C_i]_o}{dt} - \frac{[C_i]_o}{[C_i]_i^2}\frac{d[C_i]_i}{dt}\right)$$

$$= f\frac{[C_i]_i}{[C_i]_o}\left(\frac{I_i}{[C_i]_i} + \frac{[C_i]_o}{[C_i]_i^2}I_i\right) = f\frac{[C_i]_i}{[C_i]_o}\left(\frac{1}{[C_i]_i} + \frac{[C_i]_o}{[C_i]_i^2}\right)I_i$$

The units on this appear to be incorrect. The "effective capacitance" would be

$$C_{eff}^{-1} = \underset{\substack{\uparrow \\ \text{volts}}}{f}\;\underset{\substack{\uparrow \\ \text{dimensionless}}}{\frac{[C_i]_i}{[C_i]_o}}\;\underset{\substack{\uparrow \\ 1/\text{concentration}}}{\left(\frac{1}{[C_i]_i} + \frac{[C_i]_o}{[C_i]_i^2}\right)}$$

But $cap \sim \frac{\text{amp-sec}}{\text{volt}} = \frac{\text{coul}}{\text{volt}}$

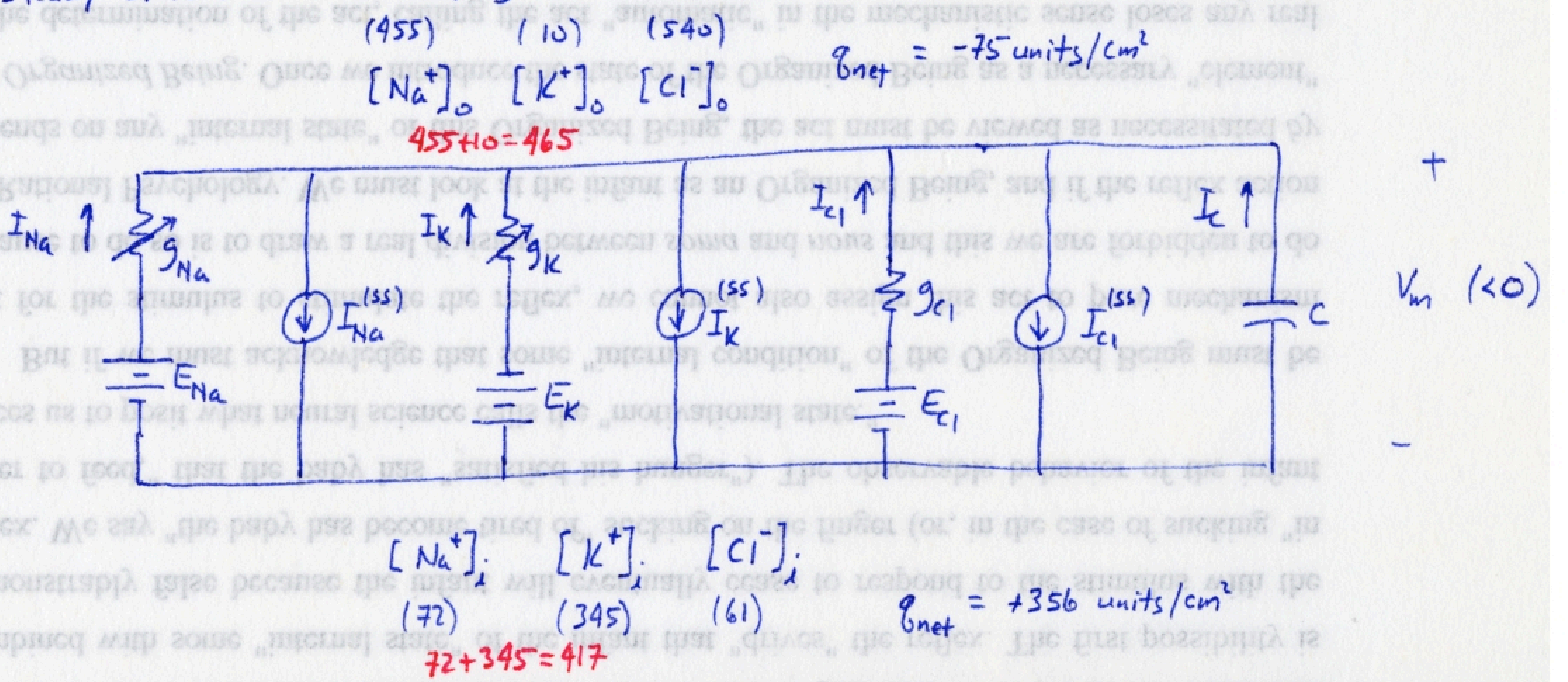
So the concentration would have to have units of coulombs$/cm^2$ = charge density. This can be taken care of by multiplying each concentration by z = charge multiplier. Since $[Na^+]$ and $[K^+]$ have equal valence multipliers, this cancels out in E_i but shows up in the effective capacitance expressions.

Letting z_i = valence multiplier for $[C_i]$, we get

$$C_{eff}^{-1} = \frac{f}{z_i}\frac{[C_i]_i}{[C_i]_o}\left(\frac{1}{[C_i]_i} + \frac{[C_i]_o}{[C_i]_i^2}\right) = \frac{f}{z_i[C_i]_i}\frac{[C_i]_i}{[C_i]_o}\left(1 + \frac{[C_i]_o}{[C_i]_i}\right)$$

④

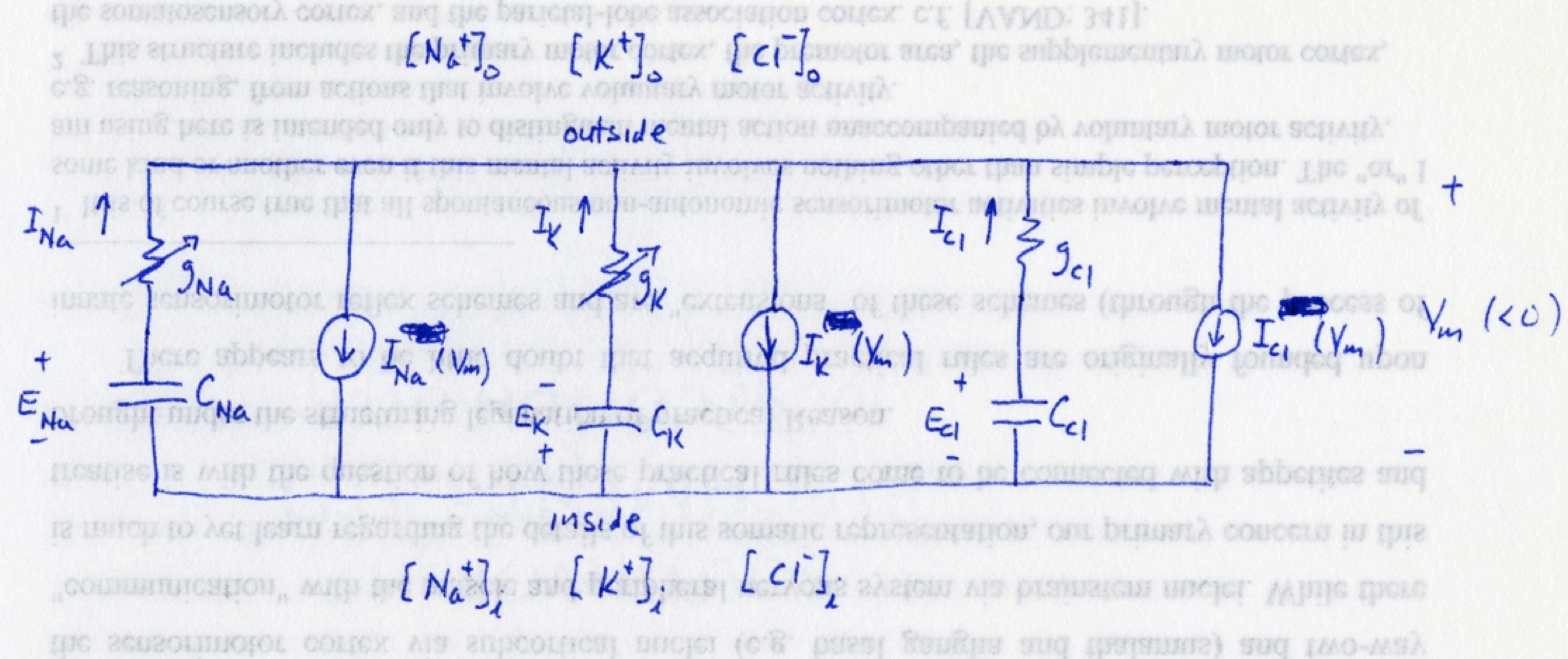
But there is still another problem. V_m is not equal to any of the E_i's in the H-H model and ∴ each legs of the model has currents flowing all the time. This makes it impossible to associate ion currents I_i with specific "legs" of the H-H circuit. We would have, for instance, current I_{Na} flowing into the E_K leg of the model. This makes no physical sense whatsoever. The only circuit model way to deal with this is to introduce the idea of "pumps" that could absorb these steady-state "currents" to maintain the $[C_i]_o/[C_i]_i$ ratio in steady-state. But these "pumps" do not pump ions across the cell membrane; they are complete fictions since their only role is to keep the steady-state ionic "bookkeeping" in balance:



When a "gate" opens, ion flow is allowed to take place. This works by diffusion of ions into the membrane's "gate"; once there, they are presumably accelerated through the gate by the potential difference across the membrane. The questions then becomes: 1) do we leave $I_i^{(ss)}$ at a constant value? 2) how do we model the resulting change in ionic charge density?

Here it seems to me that the proper model is more like a "FET" than the H-H model. The E_i's should become capacitors (C_{eff}'s) and the ionic charge density difference would be what is modeled by their voltages (E_i's). The $I_i^{(ss)}$ on the other hand should be based on the diffusion equation and be a function of V_m. Furthermore, the membrane capacitance C is ~~not~~ now rather superfluous since the displacement current it represents is now accounted for by the C_{eff} terms.

This model looks like so:



Here the trick is that in order to ~~keep~~ "keep the ionic bookkeeping straight," the current sources must at all times absorb 100% of the I_i flowing. This immediately calls into question the H-H expressions for the g_i terms. Are these still to be viewed as voltage-dependent conductances? Because the proteins mechanically responsible for the gating are likely to be voltage-sensitive, the answer is probably "yes." Are they still likely to be functions of the "gating particles"? Here I think this is not so likely. First the idea of a "gating particle" is pretty speculative to begin with. Second, g_i should really only model the mobility of the ions and the fraction of open channels to total channels.

It's tempting to think of the $I_i(V_m)$ sources in terms of the diffusion constant D, but here the problem is that D and mobility μ are related by the Einstein equation, which in its simplest form is $D = (kT/q)\mu$, which assumes the carrier concentration is much less than the effective density of states in the material. Conductivity is $\sigma = (q[C])\mu$ (or, in my earlier notation, $z_i[C]_i\,\mu$) and drift velocity is $v_d = \mu E$.

Diffusion current density is

$$J_{i,\,diff} = qD\frac{\partial [C]}{\partial x}$$

The diffusion constant actually has a complicated relationship

$$D = 2\left(\frac{kT}{q}\mu\right)\frac{F_{1/2}(\Delta U/kT)}{F_{-1/2}(\Delta U/kT)}$$

where ΔU = energy difference between Fermi level and conduction band and $F_{1/2}(\cdot)$, $F_{-1/2}(\cdot)$ are Fermi-Dirac integrals.

~~$F_{1/2}(\cdot)$, for instance is~~

$$F_{1/2}(\eta_f) = \int_0^\infty \frac{\sqrt{\eta}\,d\eta}{1+\exp(\eta-\eta_f)}, \quad \eta_f \triangleq \frac{\Delta U}{kT}$$

~~I don't know what $F_{-1/2}(\cdot)$'s expression is.~~ $\int_0^{-\infty}(\cdot)$ perhaps? I don't know.

The Fermi-Dirac integral is

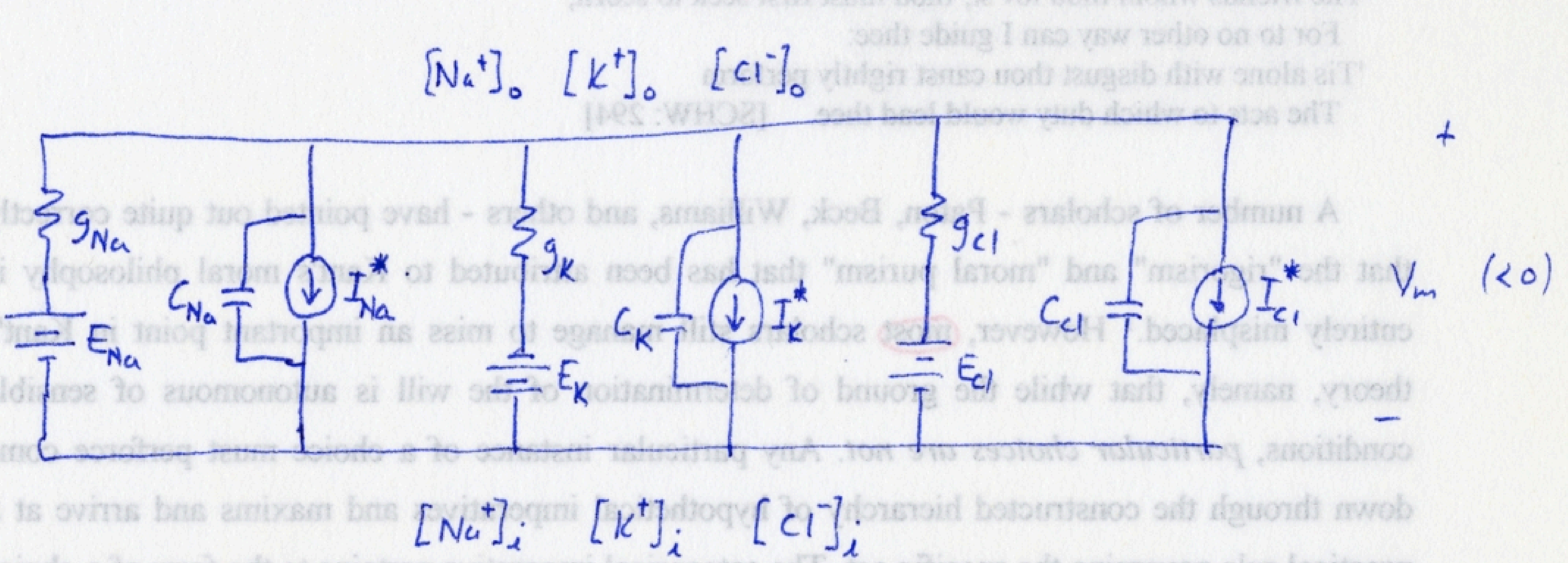
$$F_j(\eta) \triangleq \frac{1}{\Gamma(j+1)}\int_0^\infty \frac{\mu^j\,d\mu}{1+\exp(\mu-\eta)}$$

In ~~generally~~ general, it must be numerically evaluated.

see Leonard & Martin pg 430.

This reveals the flow in the model of pg 5 (which has in addition another serious flaw: E_i will be driven by $I_i(V_m)$ and cannot possibly achieve a steady-state value). We must leave the H-H "batteries" in place because they are responsible for the "effective" E that drives the drift velocity. But here's another question: if this drift velocity is trans-membrane, we're back to having the problem of charge non-conservation that started this whole thing.

Ignoring this for the moment, we can model the charge difference across the membrane as follows:



where now the C_i are effective capacitances which model the $\frac{\partial [C]}{\partial x}$ across the membrane. The I_i^* model the diffusion current plus the fictitious current $I_i = -g_i(V_m - E_i)$ (note the sign reversal; this current is fictitious, so it doesn't matter what "direction" we attribute to it. It's only purpose is to account for $V_m \neq E_i$)

We let $I_i^* = I_{diff} + g_i(E_i - V_m) = \nu_i D_i \frac{\partial [C]}{\partial x} + g_i(E_i - V_m)$

But, again this is not correct because now we have voltage accumulation on Ceff. Instead, we write the diffusion term as

$$I_{i\,diff} = \nu_i D_i \frac{\partial [C_i]}{\partial t} \frac{dt}{dx} = \frac{\nu_i D_i}{v_{d_i}} \frac{\partial [C_i]}{\partial t}$$

where $v_{d_i} = \mu_i \mathcal{E}$, μ_i = mobility and $\mathcal{E}$ = electric field in the membrane. $\mathcal{E} = V_m / l$ where l = membrane thickness so

$$I_{i\,diff} = \frac{\nu_i D_i l}{\mu_i V_m} \frac{\partial [C_i]}{\partial t} = \frac{D_i l}{\mu_i V_m} \frac{\partial \rho_i}{\partial t}, \quad \rho_i \triangleq \nu_i [C_i]$$

But this $[C_i]$ is actually $[C_i]_o - [C_i]_i = \Delta [C_i]$

This whole H-H model turns out to be a ghastly non-physical hodgepodge – I'm forced to conclude that there is simply no way to get any physical sense out of it when multiple ionic carriers are involved.