CONT. from LNB BIP001

Some Kinetic Responses of Post Synaptic currents

Here are some additional time plots taken from [4] ([KOCH]; see ref.'s LNB BIP001).

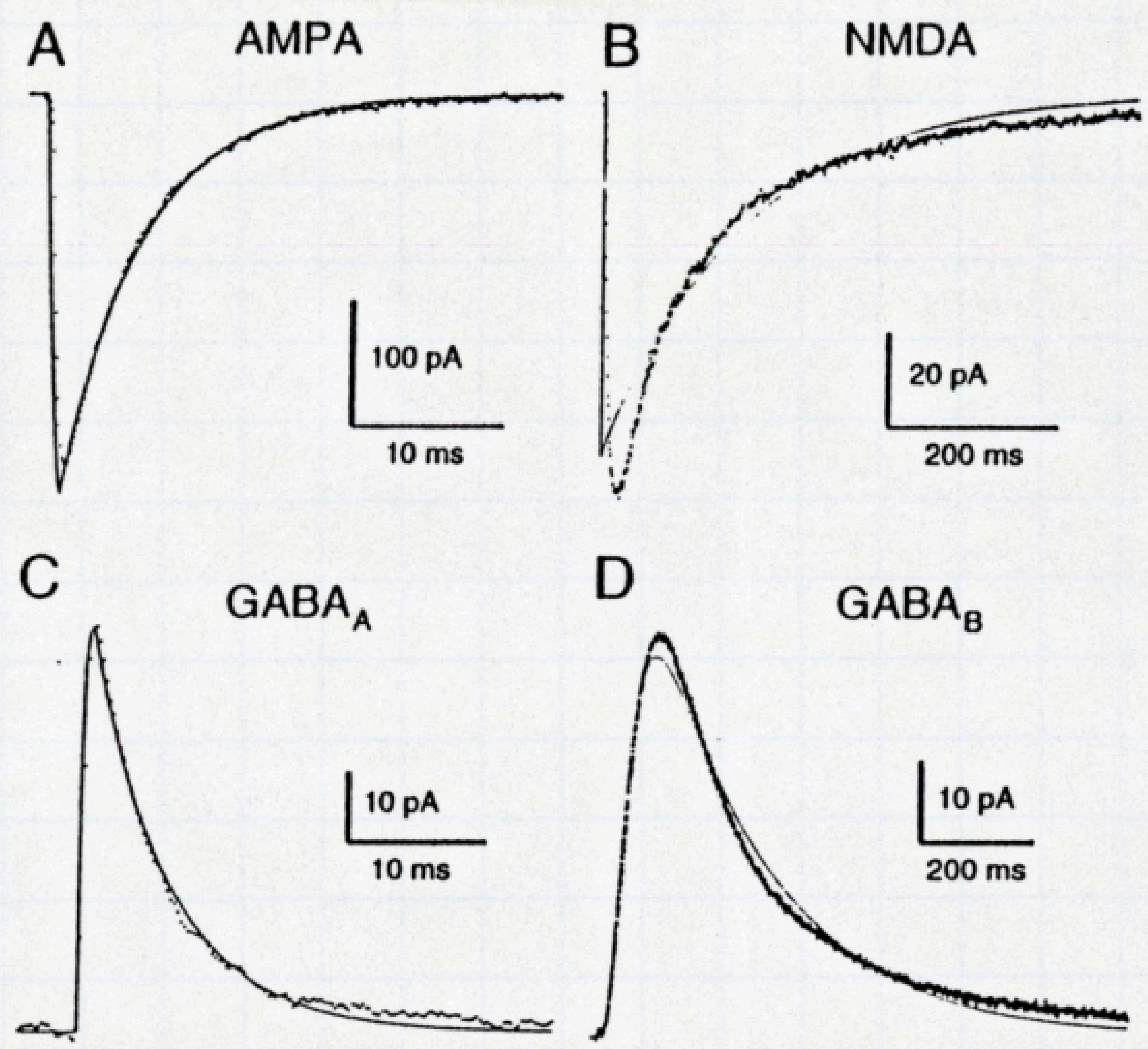

Figure 1.3
Best fits of simplified kinetic models to averaged postsynaptic currents obtained from whole-cell recordings. (A) AMPA/kainate-mediated currents. (B) NMDA-mediated currents. (C) GABA$_A$-mediated currents. (D) GABA$_B$-mediated currents. For all graphs, averaged whole-cell recordings of synaptic currents (noisy traces; identical description as in figure 1.2) are represented with the best fit obtained using the simplest kinetic models (continuous traces). Transmitter time course was a pulse of 1 mM and 1 msec duration in all cases. Panel A modified from Destexhe, Mainen, and Sejnowski 1994b; panel C modified from Destexhe et al. 1994; panel D modified from Destexhe et al. 1996; fitting procedures described in chapter appendix B.

These plots make it appear that the time constants for AMPA and GABA$_A$ are more or less equal, allowing for the difference between

$$1 - e^{-t/\tau} \quad \text{and} \quad e^{-t/\tau},$$

while the same can be said for NMDA and GABA$_B$.

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be an explicit Ca^{2+} variable in the model.

Turning now to the mathematics of H-H, the key assumption is that ionic channels open and close through a first-order reaction determined by <u>rate</u> <u>coefficients</u> α and β

$$\underset{(a)}{\text{gate open}} \underset{\alpha}{\overset{\beta}{\rightleftarrows}} \underset{(b)}{\text{gate closed}}$$

When the gate is voltage dependent the rate coefficients are functions of V_m. The assumed dependence is

$$\alpha(V_m) = \alpha_0 e^{\delta z V_m}$$

$$\beta(V_m) = \beta_0 e^{-(1-\delta) z V_m}$$

where δ is an energy barrier "asymmetry factor," $z = F/RT$ with $F = 96{,}480$ cal/mol = Faraday constant, T = temperature in °K, and $R = 1.98$ cal/°K-mol = gas constant. The coefficients α_0 and β_0 are

$$\alpha_0 = A e^{-\Delta G_0/RT} \quad , \; A = \text{some proportionality constant}$$

$$\beta_0 = A e^{-\Delta G_0/RT} \quad (\text{which implies } \alpha_0 = \beta_0)$$

$+\Delta G_0$ in cal/mol = activation energy

H-H defines the "open" or "a" state as the "permissive" state and the "closed" state as the non-permissive state. The probability of being in the permissive state at time t is $y(t)$, leaving $1-y(t)$ as the probability of being in the non-permissive state. $y(t)$ is assumed to follow a first order Markov process

$$\begin{tikzcd} y(t) \arrow[r, bend left, "\beta"] & 1-y(t) \arrow[l, bend left, "\alpha"] \end{tikzcd}$$

with flow rates α and β acting like arrival and service rates in a queueing model. The flow rate into the $y(t)$ state is $\alpha(1-y)$; the flow rate out of it is βy. Therefore

$$\frac{dy(t)}{dt} = \alpha\,(1-y(t)) - \beta\, y(t)$$

Now, when V_m is a function of time then so are α and β and this equation has no closed-form solution. But if V_m is constant or we consider intervals Δt small enough that $V_m(t)$ can be regarded as constant over this interval then

$$y(t) = y_\infty - (y_\infty - y_0)\, e^{-(\alpha+\beta)t}$$

where $y_0 = y(t=0^-)$ and $y_\infty = \frac{\alpha}{\alpha+\beta}$

Finally, for p statistically-independent "gating particles" (the fictitious "particles" H-H used ~~to~~ as the name for whatever actually determines the physical motion of the gate), the total "activation function" becomes

$$Y(t) = [\,y(t)\,]^p$$

where the "activation function" accounts for the time-varying channel conductance

$$g(t) = Y(t)\,\bar{g} \quad , \quad \bar{g} = \text{maximum conductance}$$
$$0 \le Y \le 1.$$

To account for different gates, H-H represents the different activation functions using the letters n, m, and h where

$$g_K = n^4\,\bar{g}_K \quad , \quad g_{Na} = m^3 h\,\bar{g}_{Na}$$

with m representing activation by depolarization, h representing inactivation by depolarization and

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

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

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

Because h corresponds to inactivation, the constant-V_m solutions are

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

$$m(t) = m_\infty - (m_\infty - m_0)\, e^{-t/\tau_m}$$

$$h(t) = h_\infty + (h_0 - h_\infty)\, e^{-t/\tau_h}$$

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$$x_\infty = \frac{\alpha_x}{\alpha_x + \beta_x} \qquad \tau_x = \frac{1}{\alpha_x + \beta_x} .$$

~~Since n, m, and h represent probabilities, if the membrane is in a steady-state condition and a step change is made to V_m, then we always have~~

$$\cancel{n_0 = m_0 = 1 \quad , \quad h_0 = 0}$$

~~if the gates are~~

It is not uncommon to see $n(t)$ or $m(t)$ equivalently expressed as

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

$$m(t) = m_0 - (m_0 - m_\infty)(1 - e^{-t/\tau_m})$$

which more clearly shows that n_0 and m_0 are initial probabilities.

with $\alpha_0 = \beta_0$ from pg 8,

$$\alpha + \beta = \alpha_0\, e^{\delta \gamma V_m} (1 + e^{-\gamma V_m}) = 1/\tau$$

and therefore

$$x_\infty = \frac{1}{1 + e^{-\gamma V_m}} \quad , \quad x = n \text{ or } m$$

$$= \frac{1}{1 + e^{\gamma V_m}} \quad , \quad x = h$$

where the h_∞ result again comes from reversing the roles of α and β in the case of h

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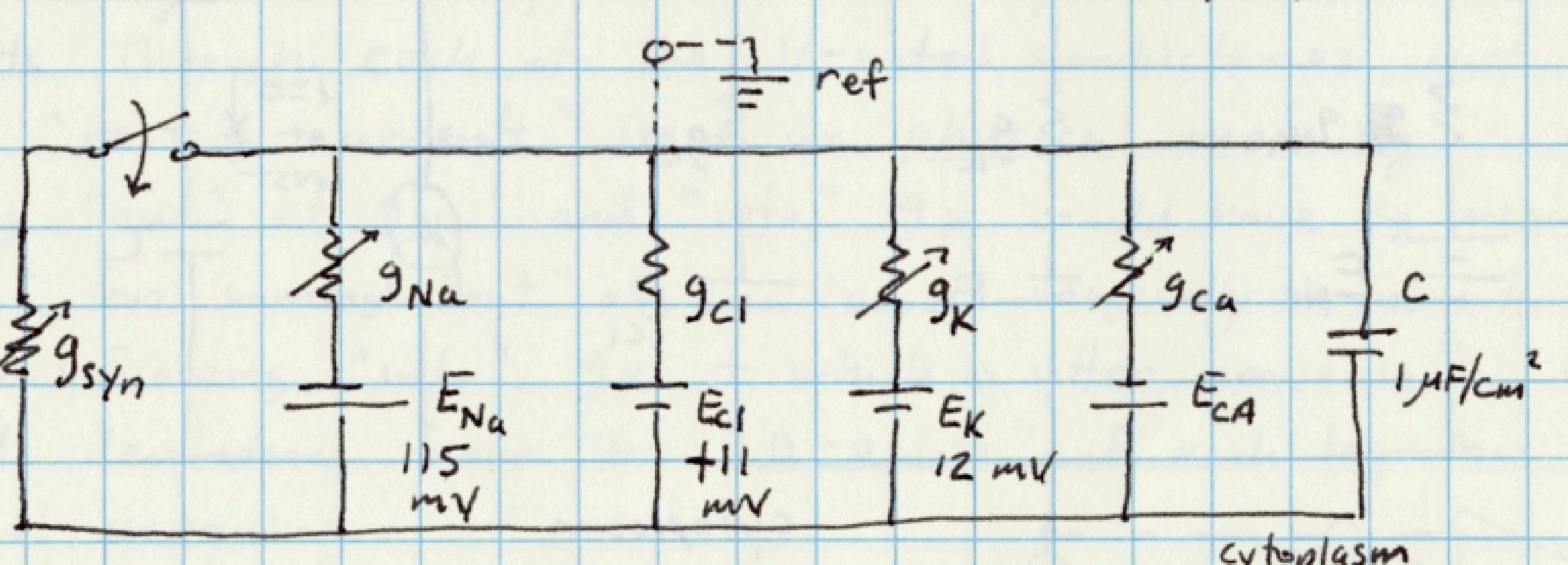
To get the initial conditions right, we must remember that $y(t)$ is the probability of the permissive (open) state. If the gate is open, n_o or $m_o = 1$; if it is closed, n_o or $m_o = 0$. If it is inactivated $h_o = 0$, otherwise $h_o = 1$.

If we are allowing $V_m(t)$ to vary (in a numerical solution), n_o, m_o, and h_o are determined from the initial condition at the beginning of the calculation and by $n(t)$, $m(t)$, and $h(t)$ at the end of each calculation interval for setting up the calculation of the next interval.

This is all simple enough for purely V-gated channels. The real complexity in H-H calculations comes in determining Esyn and gsyn. This is the factor being addressed in the synaptic receptor table on pg 115 of LNB BIP 001.

Let us consider an example of a simple ionotropic excitation due to glutamate. From the table on pg 115 of BIP001, $E_{syn} = 0$ and we have



$g_{Na} = 120\, m^3 h \qquad g_K = 36\, n^4 \quad g_{Cl} = 0.3 \quad m\mho \qquad g_{Ca} = 0 \quad E_{Ca} = 0$

$$\frac{dm}{dt} = \frac{0.1(25-V_m)}{e^{.1(25-V_m)} - 1}(1-m) - 4m\, e^{-V_m/18}, \quad m_o = .05$$

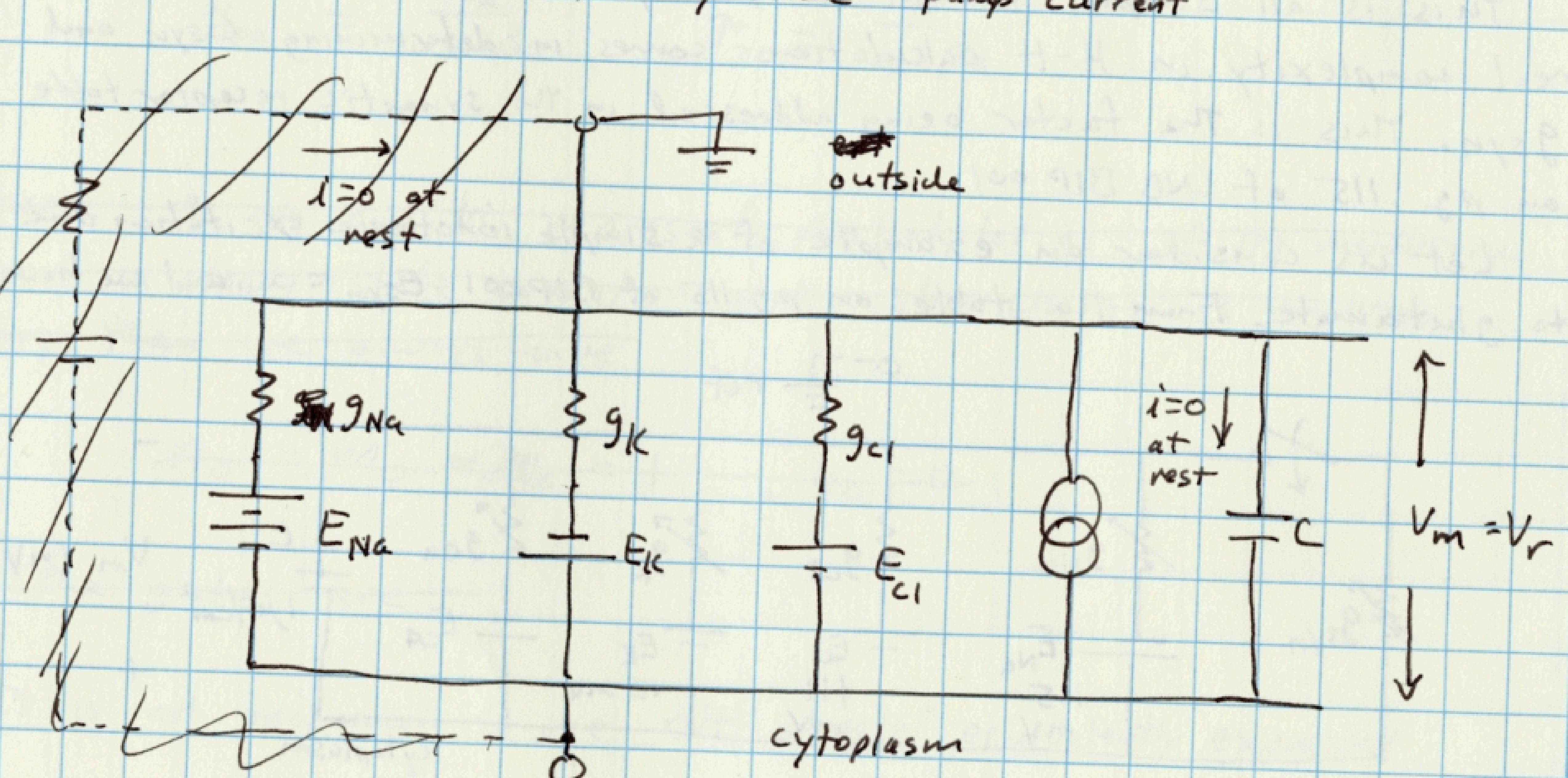
$$\frac{dh}{dt} = 0.07\, e^{-V_m/20}(1-h) - \frac{h}{\exp[0.1(30-V_m)]+1}, \quad h_o = .60$$

$$\frac{dn}{dt} = \frac{0.01(10-V_m)}{\exp[0.1(10-V_m)]-1}(1-n) - 0.125\, e^{-V_m/80}\cdot n, \quad n_o = .32$$

The numerical values given here Hodgkin & Huxley's fit to the giant squid axon [DEUT: 54-55], and so this example is fictitious (the squid axon has no ionotropic synapses). With these numbers, the initial values are $g_{Na} = 9\,\mu\mho$, $g_{Cl} = 0.3\, m\mho$, $g_K = .38\,\mu\mho$ $V_m(0^-) =$ ~~14 mV~~ -7.3. Switching in g_{syn} produces an initial current surge (~~out of~~ into the cell) of $V_m \cdot g_{syn}(0)$, which is depolarizing in the sense that it will reduce V_m toward zero.
~~(Deutsch's model of this Esyn gives numbers inconsistent w/ the direction of Na^+ current flow, which should be into the cell).~~

As we might expect from biologists who develop circuit models, the standard conventions in the H-H model take some getting used to:

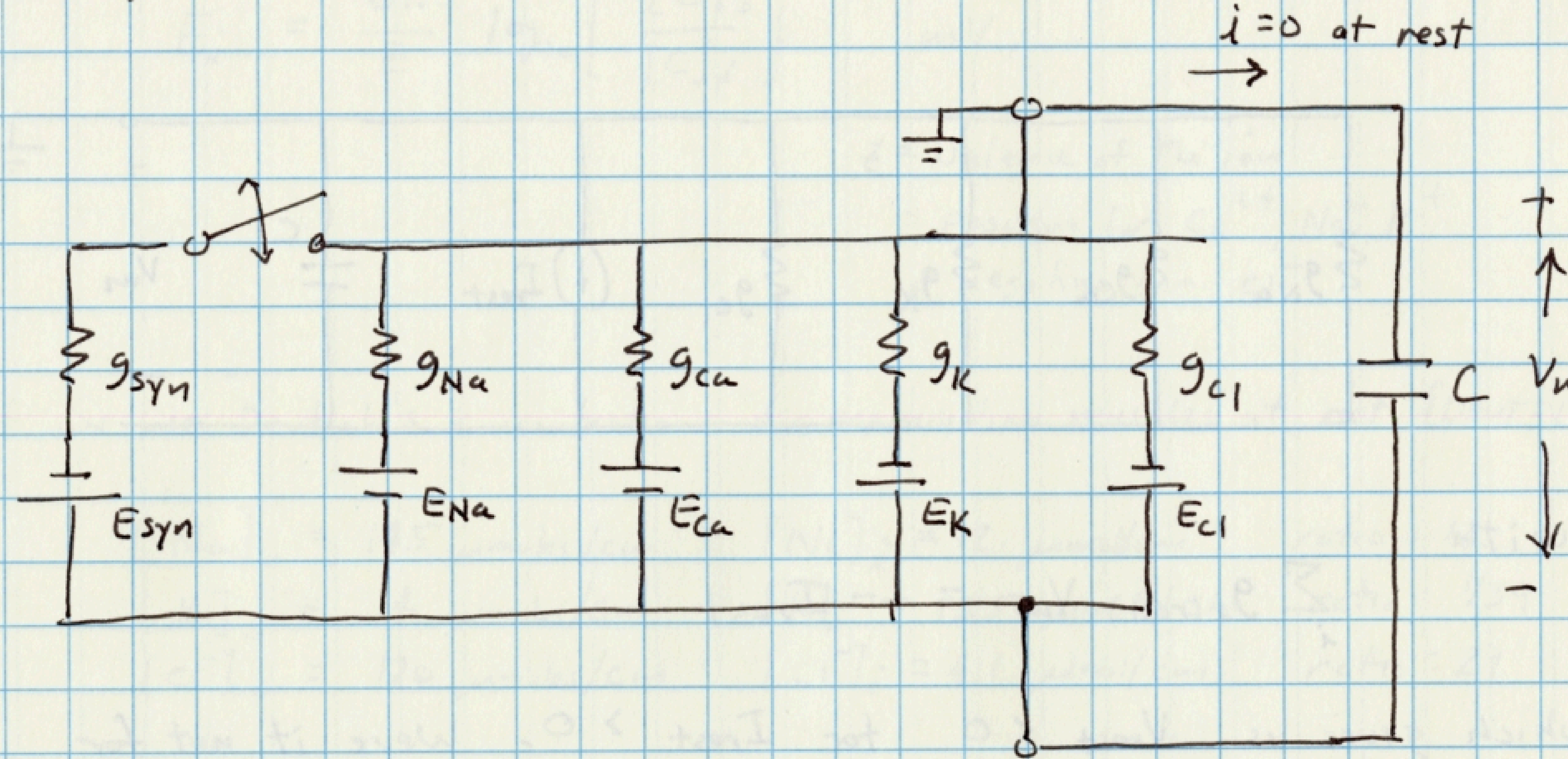
1) Ground reference is always the outside of the cell
2) The "batteries" representing the ion flows are always arranged so that ion flow at $V_m = V_{rest}$ is zero.
3) V_{rest} always places the cytoplasm at a negative potential compared to ground
4) zero current flow through the various g_i when $V_{rest} \neq E_i$ has to be accounted for by some "pump current"



Nobel prize notwithstanding, H-H is a pretty strange circuit model; it is as if the life science boys never heard that current always has to have a closed loop. You can't just stick terminals out of the two sides as if the extracellular side and the cytoplasmic side were some sort of "ion baths" from which Na^+, K^+, Cl^-, Ca^{2+} magically appear and into which they magically disappear. ~~Ea~~.

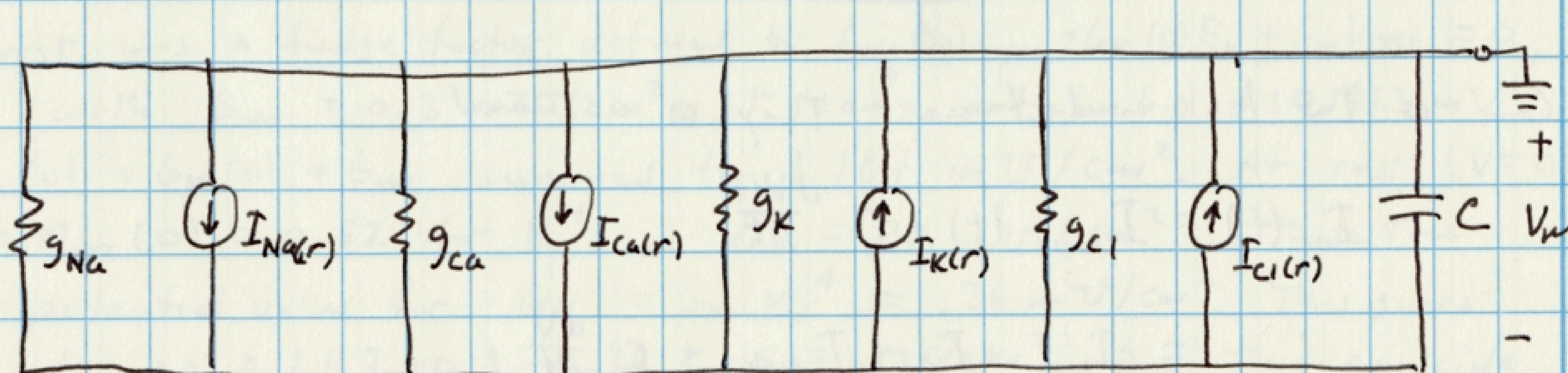
To make physical sense out of the model, it is the capacitor that makes H-H work. It is when the capacitor current is zero that we can say the transmembrane ion currents are zero.

Taking this point of view, H-H "feels better" if we draw the model this way:



Under resting conditions, a circuit analysis will give us non-zero currents through each of the V-gated conductances, but ~~this~~ these "resting currents" have no <u>physical</u> meaning. (A "current" flowing "out" of g_{Na} and "into" g_K would have to mean that a Na^+ ion coming "out" of g_{Na} would magically transmute into a K^+ ion flowing "into" g_K — which is utter nonsense). Only current deviations from the "Q-points" of each leg has a physical meaning.

From this we see that H-H is just as much a phenomenological model as my PMAN mimic. The only issue is how well the two phenomenological behaviors match each other. A more "physical" model of the H-H type (one that did not transmute elements) could be represented as follows (neglecting synapses)



where the "bias currents" $I_{i(r)}$ are invariant dc current sources

$I_i = g_i\,(E_i - V_{rest})$, for Na^+, Ca^{2+};

$I_i = -g_i\,(-E_i - V_{rest}) = g_i\,(E_i + V_{rest})$ for K^+, Cl^-

where all E_i are <u>positive</u> numbers and $V_{rest} < 0$.

Positive current direction is as depicted in the figure.