

THE SALK INSTITUTE

October 6, 1981

Dear Tommy,

Thank you so much for your long and helpful letter, the manuscripts and the paper from TINS. I discovered yesterday that the latter idea is not entirely new, since it is fairly clearly stated in the discussion (p. 332) in Peters and Kaiserman-Abramof, *Am. J. Anat.* (1970), 127:321-356. I enclose a copy. They make the point, which I think Nick Swindale missed, that if the scheme is to work the spines must, in some sense, "reach out to the axon", otherwise, as far as I can see, nothing is gained. In the simplest scheme this would imply that the spines only formed after the axons were there. I will check with Max Cowan if this is the case. However one could always argue that the spines in the critical period are constantly disappearing (when not used) and others reforming, in which case they could reach out at that stage.

Now as to the main points of your letter. Both Graeme and I had concluded, with you, that the rhythm idea should be left out. In fact I have cut the last page almost entirely. I note your point about the multiplicative term but notice that for two excitatory synapses, each on a spine, this term, in the simple case, is negative. For rapid modification we need a positive term (i.e., the two synapses should reinforce each other), so some special mechanism is needed.

Now about Rall. I don't really like your division into the two terms, A and S, since both depend on the dimensions of the spine. It seems to me you are making heavy weather of a simple problem. As I see it you have

$$V_s = \frac{g K_{1s} E}{1 + g K_{11}}$$

and since $K_{1s} \approx K_{2s}$, and $K_{11} = R + K_{22}$

$$\text{we have } V_s \approx \frac{g K_{2s} E}{1 + g(R + K_{22})}$$

$$= \frac{K_{2s} E}{\frac{1}{g} + R + K_{22}}$$

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Now since K_{25} depends very little on the shape of the spine, for any given position of the spine on the dendrite, we can consider it independent of g and R .

Now Rall wished to express the condition that the (absolute) change in V_s was a maximum for a given percentage change in R . Thus we need

$$dV_s / \left(\frac{dR}{R} \right)$$

to be a maximum. As far as I can see this implies that

$$R = \frac{1}{g} + K_{22}$$

As you rightly point out, if g is large, this gives us

$$R \approx K_{22}$$

which is Rall's impedance-matching condition. As one can see, if g is smaller, the condition is a little different, but in the same direction, as Rall points out by giving numerical examples. Cristof's notes (pp 10 and 11) come to the same general conclusion; his figures for optimal spine dimensions (p. 11) seem to me to be in the same ballpark as what is observed. (Though I suspect that the dimensions of spines are a little bigger and the specific resistance of the spine neck cytoplasm a little higher.) However I am not clear what value of g Cristof assumed for these calculations, though several values are given in his Fig. 6.

The other factor is "range compression." To avoid this, as you say, you must have gK_{11} (which is $g(R+K_{22})$) small compared to unity. Another way of looking at it is to ask that the absolute change in V_s be a maximum for a given percentage change in g , keeping R and K_{22} fixed. This assumed that memory is at last partly coded by changes in the value of g . Then one obtains (as one might expect from the symmetry of the problem)

$$\frac{1}{g} = R + K_{22}$$

Clearly one cannot satisfy both this condition and the previous one

$$R = \frac{1}{g} + K_{22}$$

unless K_{22} is much smaller than the other terms and $Rg \approx 1$. In other words, R must be big and g must be small, for any given K_{22} . However R must not be made enormous or the approximation that

$$K_{15} \approx K_{25}$$

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breaks down, because appreciable current will leak out through the spine membrane.

We can reasonably ask, what is the diminutive^m factor produced by the spine. If the synapse were on the dendritic shaft, we have (putting $R=0$ in our usual equation)

$$V_s = \frac{g K_{25} E}{1 + g K_{22}}$$

Thus the diminutive^m factor is

$$\frac{1 + g K_{22}}{1 + g K_{22} + g R}$$

If we obey the condition for maximum change due to R ($Rg = 1 + gK_{22}$) thus becomes $1/2$. That is, the synapse on the spine is half as effective as a corresponding one on the dendrite. This is not too bad.

Unfortunately the condition that g is small means that the punch of the synapse (in either position) is also small, so that some compromise is necessary. For example, we might take

$$\left. \begin{aligned} R &= 2 K_{22} \\ g K_{22} &= \frac{1}{2} \end{aligned} \right\}$$

so that $gR = 1$

thus gives a diminutive factor of 0.6. Whether these values are reasonable I don't know since I have not fully digested Cristof's notes. The value of g is really an unknown but I suspect that the ratio of R to K_{22} is largely a geometrical factor (i.e., it doesn't depend too much on the choices for R_m and R_i). Cristof must have data on this.

As you can see, the two requirements conflict, in that for R to have any effect it must be large enough to choke back the input and, if it does do this, some range-compression is inevitable.

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This all assumes that one wants V_s to vary as g varies. However if long-term memory is in the neck of the spine (and more or less independent of the value of g_1 , provided g is large enough) then there is no conflict, although the system is "wasteful" in that the synaptic punch is not fully used, but then that is often Nature's way. It would also have the advantage that statistical variations in g (due to random fluctuations in the number of packets of transmitter released) would be smoothed out. However this leaves us with the problem of how to preserve long-term memory for a long time in the face of metabolic fluctuations, etc. To approach this we have to know what molecular structure determines the shape of the neck of the spine.

I suppose another solution is to assume that long-term memory is represented by all the synapses without spines. On pyramidal cells, these are all inhibitory ones. On non-spiney stellates (most of which produce inhibition) they can be either on the soma or on the dendrites. This would imply that long-term memory is especially tied to inhibitory effects, leaving the spines to handle ultra-short memory. I can't say I feel happy with any of this.

I have not yet had time to think carefully about the active membrane case, though I can see I shall have to.

I don't know quite what to say about the old spine note. It comes to much the same conclusion as Rall's but it could be expressed perhaps a little more clearly. Perhaps we should talk about this.

I am still hoping you will be coming to the NRP meeting at La Jolla, but just in case you don't I am sending this to MIT. I'll keep an extra copy here in case you arrive here without having seen it.

Graeme and I are having some fun speculating about sleep and dreams but still too early to say much about it.

Odile is in fine form. We have had an ex-au-pair girl (now 40) staying with us for a few weeks. She is very vivacious so it's been a lively time.

Our love to Barbara and Martino,

Yours ever,

F. H. C.

F. H. C. Crick

FHCC/bml

Enclosure

P.S. Another way to alter synaptic weight is to alter α , the time course of synaptic activity. I think this gets over the difficulty that the choking back effect, needed to make the neck of the spine have some effect, reduces the effect of changing g .