Notes from: Antonio R. Damasio, The Feeling of What Happens,
N.Y.: Harcourt Brace & Co., 1999

Absent without Leave (pp 5-6): Damasio briefly describes an experience w/ a patient afflicted w/ epilepsy. The man suffered what is called an "absence seizure" followed by an "absence automatism." He was able to move, drink coffee, and even walk. In Damasio's words:

> "The man had not collapsed on the floor, comatose, and had not gone to sleep either. He was both there and not there, certainly awake, attentive in part, behaving for sure, bodily present but personally unaccounted for, absent without leave." [:6]

Damasio lists ~~four~~ five "facts" from neurological observations and neuropsychological studies which constitute the "starting point" for his ideas. These are:

1) "Some aspects of the processes of consciousness can be related to the operation of specific brain regions and systems ... The regions and systems cluster in a limited set of brain territories and ... there will be an anatomy of consciousness" [:15]

2) "Consciousness and wakefulness, as well as consciousness and low-level attention can be separated. This fact was based on the evidence that patients can be awake and attentive without having normal consciousness" [:15]

3) "Consciousness and emotion are not separable" [:16]

4) "Consciousness is not a monolith ... it can be separated into simple and complex kinds, and the neurological evidence makes the separation transparent" [:16]

Damasio introduces the idea of a core consciousness [:16]. Core consciousness is the simplest kind of consciousness and "provides the organism with a sense of self about one moment — now — and about one place — here. The scope of core consciousness is here and now. ... There is no elsewhere, there is no before, there is no after." [:16]

Complex ~~con~~ or "extended consciousness" has many "levels and grades" and provides the person "with an elaborate sense of self" [:16].

Damasio speaks of "the supersense of core consciousness" ~~[:16]~~ and a "supersense of extended consciousness." [:16-17]. He says there is neurological evidence that impairments (by disease) that affect extended consciousness leaves core consciousness unscathed, but that impairments at the level of core consciousness "demolish the entire edifice of consciousness: extended consciousness collapses as well" [:17]

Along w/ these two ideas, Damasio introduces the ideas of the core self and the autobiographical self [:17]. The core self is impermanent ("transient") and is "ceaselessly recreated for each and every object with which the brain interacts" [:17] (sounds kind of like a goldfish! rbw). The autobiographical self "depends on systematized memories of situations in which core consciousness was involved in the knowing of the most invariant characteristics of an organism's life" [:17]

5) Damasio's "fifth fact" is not a "fact"; he just offers his hypothesis "that the earliest forms of consciousness precede inferences and interpretations — they are part of the biological transition that eventually enables inferences and interpretations" [:18]

Next we come to Damasio's proto-self [:22-23]. He calls the proto-self "the nonconscious forerunner for the levels of self" (meaning the core self and the autobiographical self). His "model of the body-in-the-brain" theory is a "representation" in the brain which "'perceives' nothing and 'knows' nothing ... and it does not make consciousness" [:23]

> "The model is instead a collection of brain devices whose main job is the automated management of the organism's life. ... The management of life is achieved by a variety of innately set regulatory actions — secretion of chemical substances such as hormones as well as actual movement in viscera and in limbs." [:23]

He then comes to what I suppose is the core of his thesis:

> "In a curious way, consciousness begins as the feeling of what happens when we see or hear or touch. ... it is a feeling that accompanies the making of any kind of image ... within our living organisms" [:26]

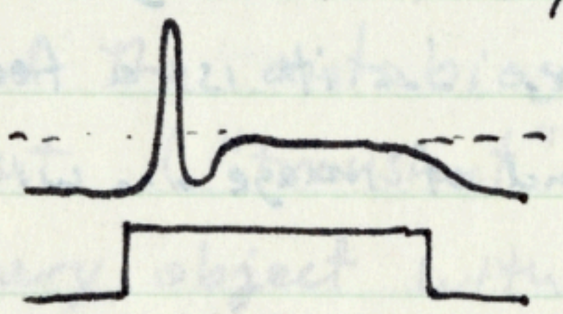
He does not, however, elucidate at this point on what he means by a "feeling" (let alone a "feeling of what happens"). I suspect he uses "feeling" as a verb — some biological process whose act Damasio calls "feeling."

- All open K^+ channels stabilize membrane potential
- Closure of K channels by 2nd messengers is a strategy to enhance excitability.
- Roles of K channels
  1) set the resting potential
  2) Keep fast APs short
  3) terminate periods of intense activity
  4) time the interspike interval during repetitive firing
  5) generally lower the effectiveness of excitatory inputs

- I_K class K channels are rapidly activating Kv class delayed rectifier channels.

- M channels are class KCNQ
  1) regulated by NTXs
  2) do not inactivate
  3) are tonically open (partially activated) at Vrest
  4) are turned OFF by ACh and by substance P & LHRH = GnRH

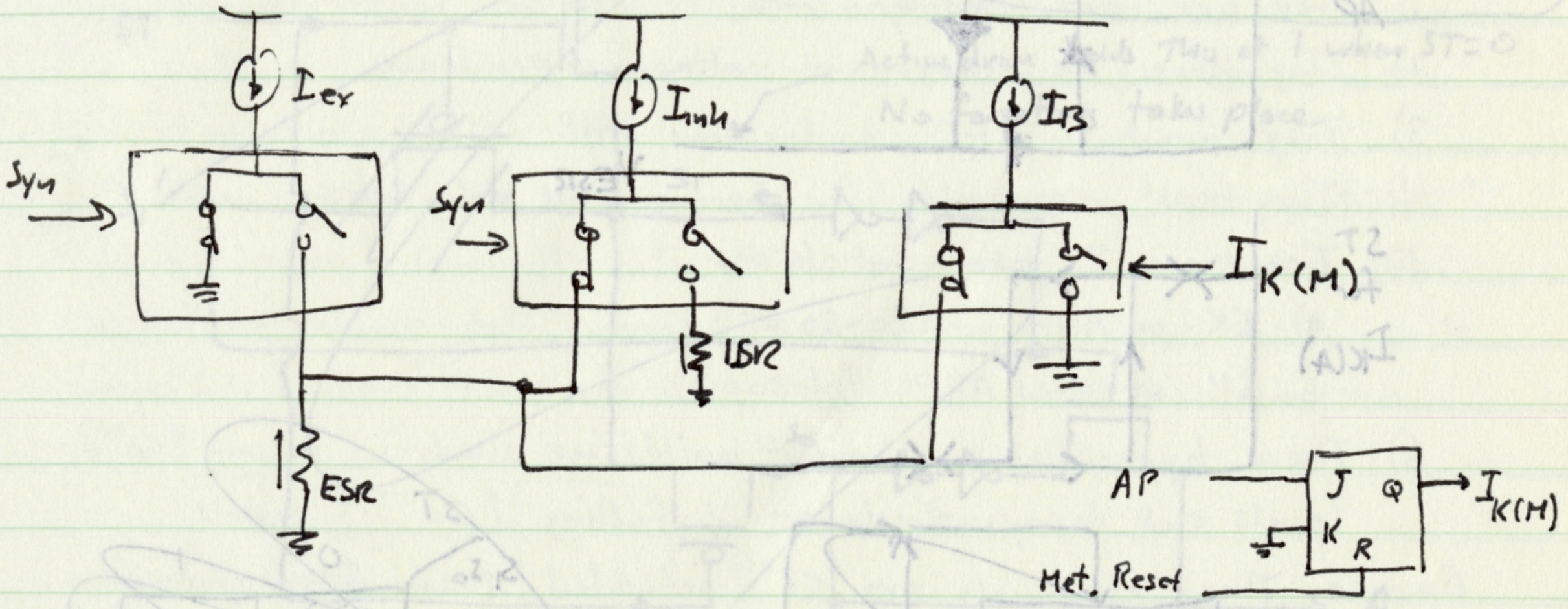
if I remember correctly, M currents produce ON responders and



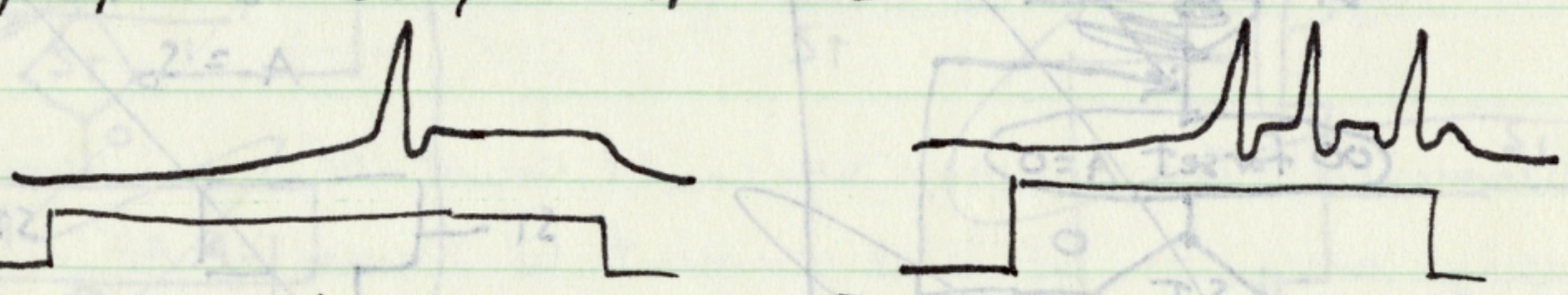
deep hyperpolarization will deactivate the M current.

5) M channels activate for Vm > -65mV. Typical V_r is in the range from ~~-70mV to~~ -75 to -60mV.
6) $I_{K(M)}$ has slow gating kinetics.

We can biomimic M channels by diverting bias current

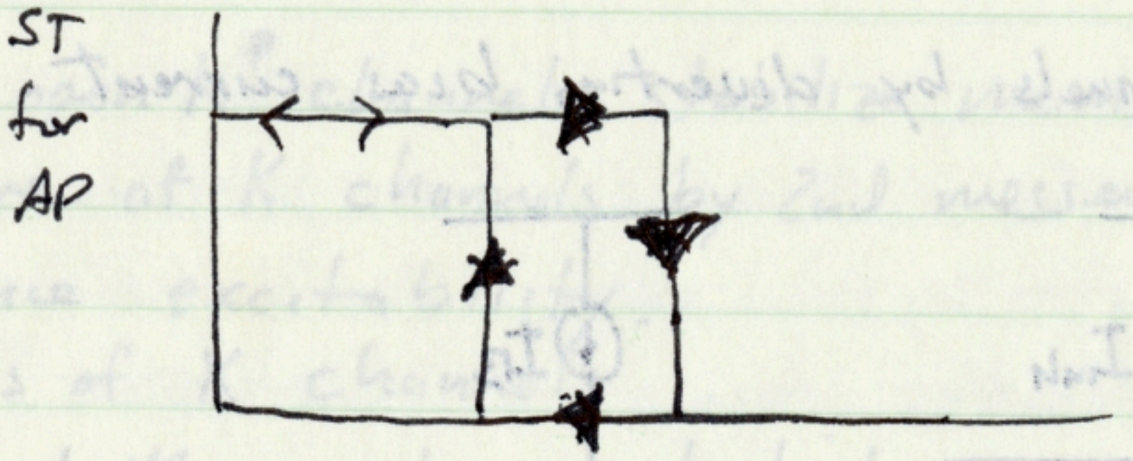


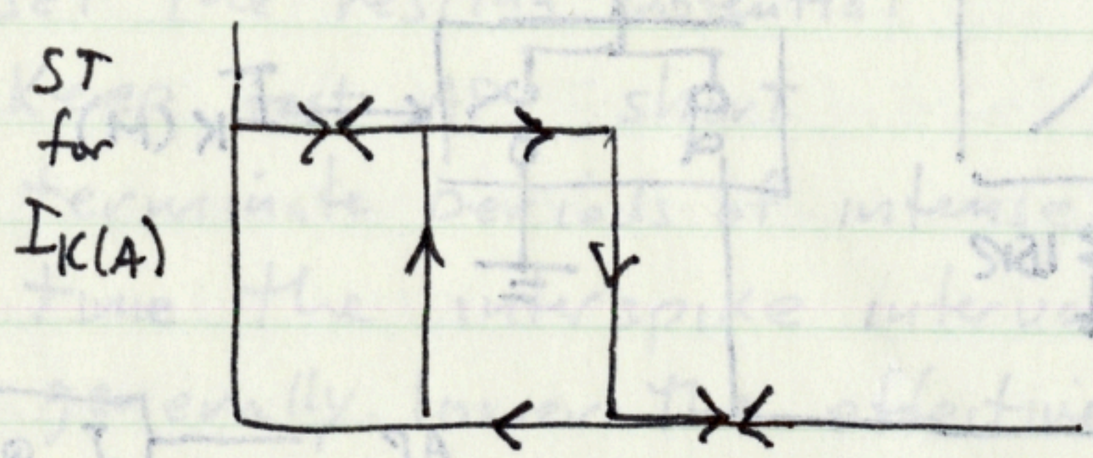
- A channels are members of the Ky class
  1) They are ~~slowly~~ moderately rapidly inactivating transient channels
  2) They activate in the subthreshold region of the APs
  3) They conduct only in a narrow range from -65 to -40mV in <u>Anisodoris</u> (V_r = -45mV)
  4) They produce delayed responders



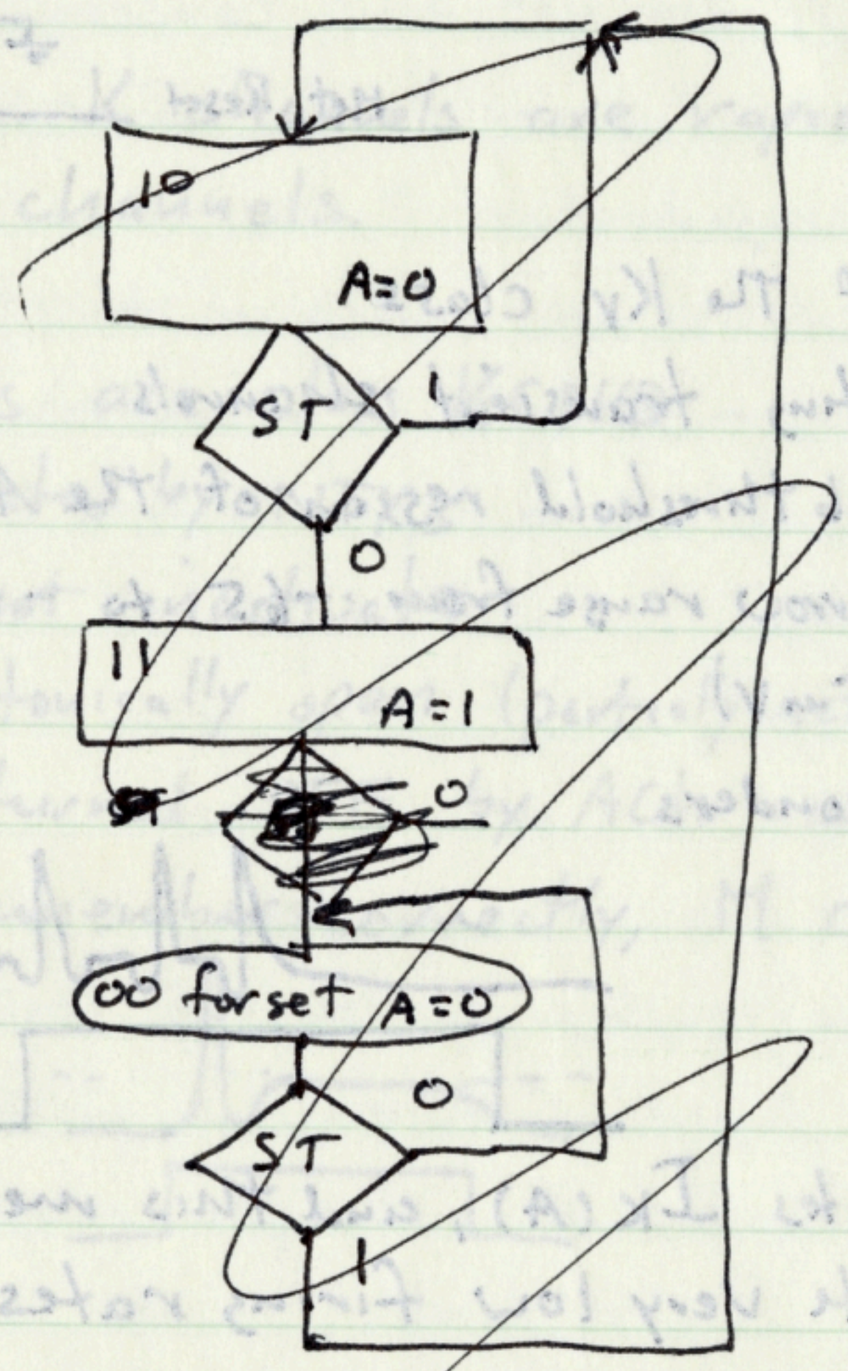
  5) hyperpolarization deactivates $I_{K(A)}$, and this means that A channels can modulate very low firing rates

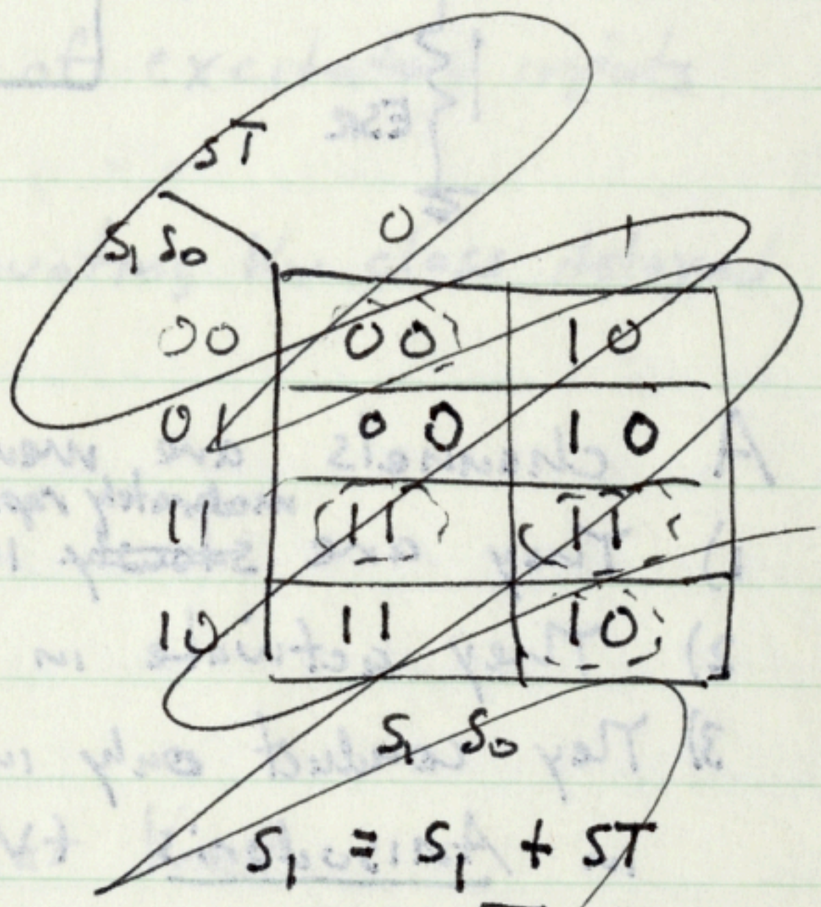
We can biomimic this w/ a S.T. and a forgetful FF. The ST triggers HI before the AP trigger threshold and triggers LOW below the AP S.T.





V_{ESR}



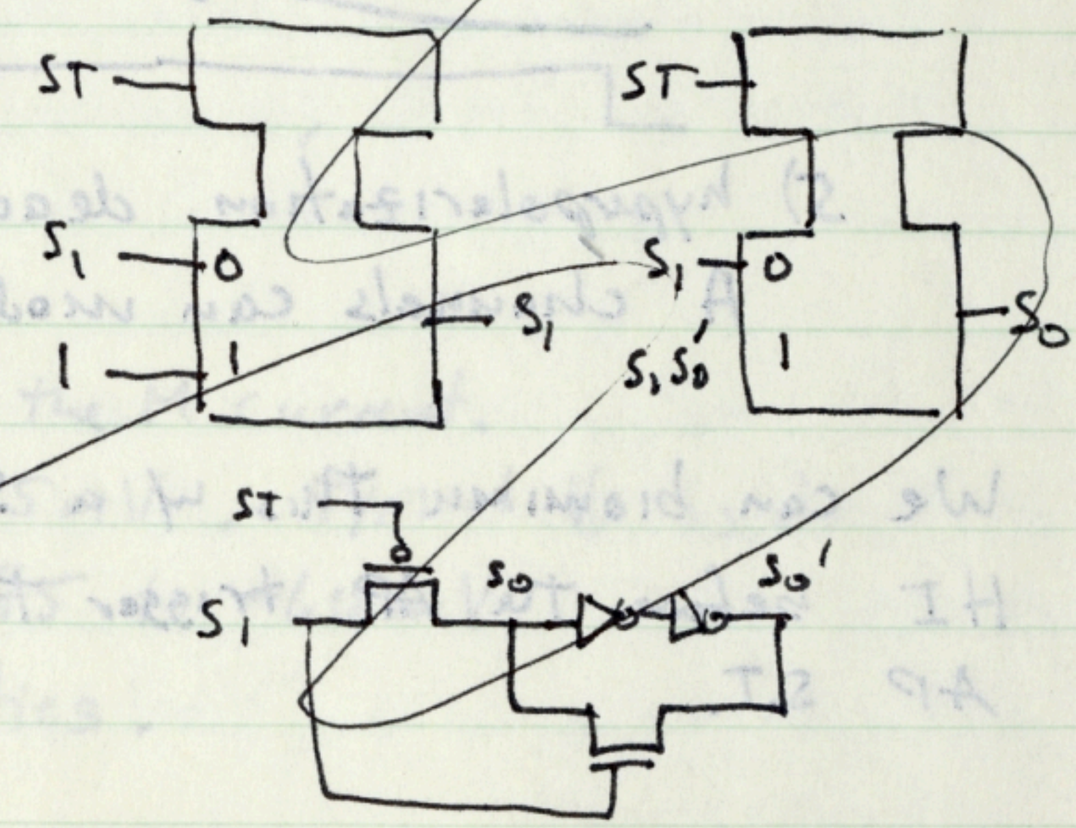


$S_1 = S_1 + ST$

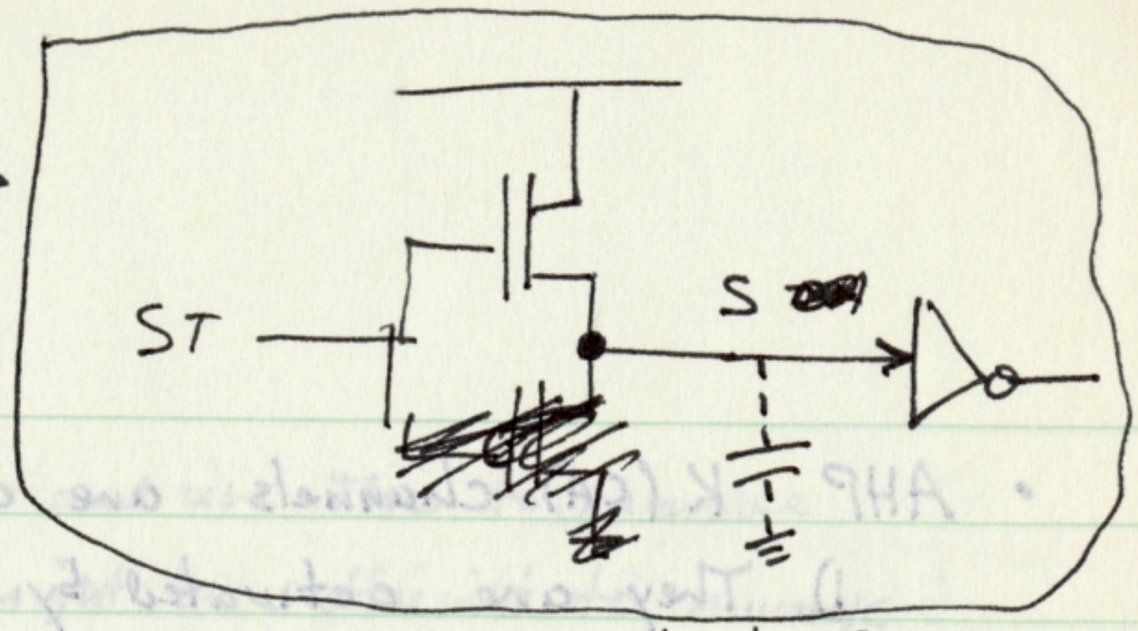
$S_0 = S_1 \cdot \overline{ST} + S_1 S_0$

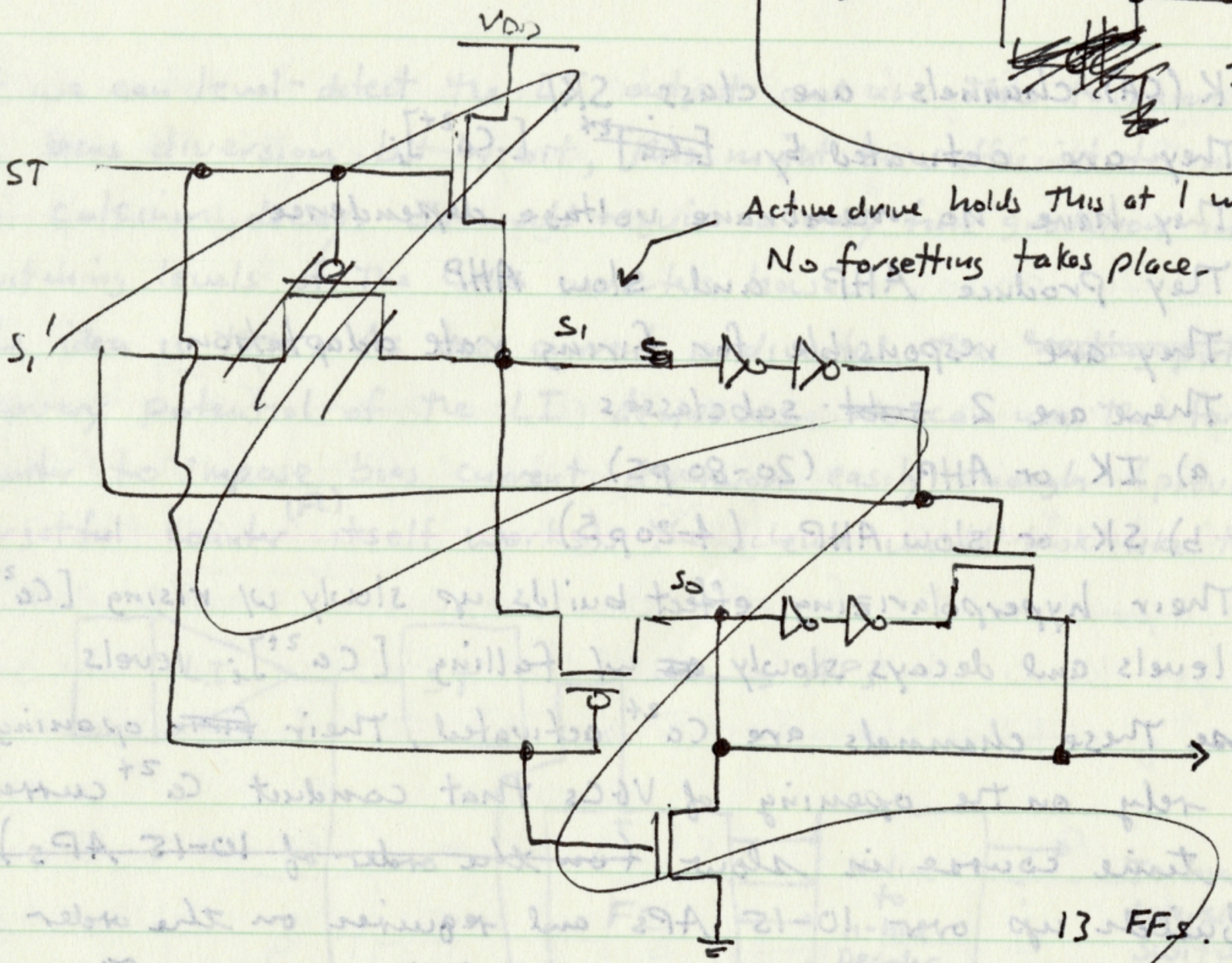
$A = S_0$

$S_0 = S_1 \cdot \overline{ST} + S_1 S_0 = S_1 \cdot (\overline{ST} + S_0)$



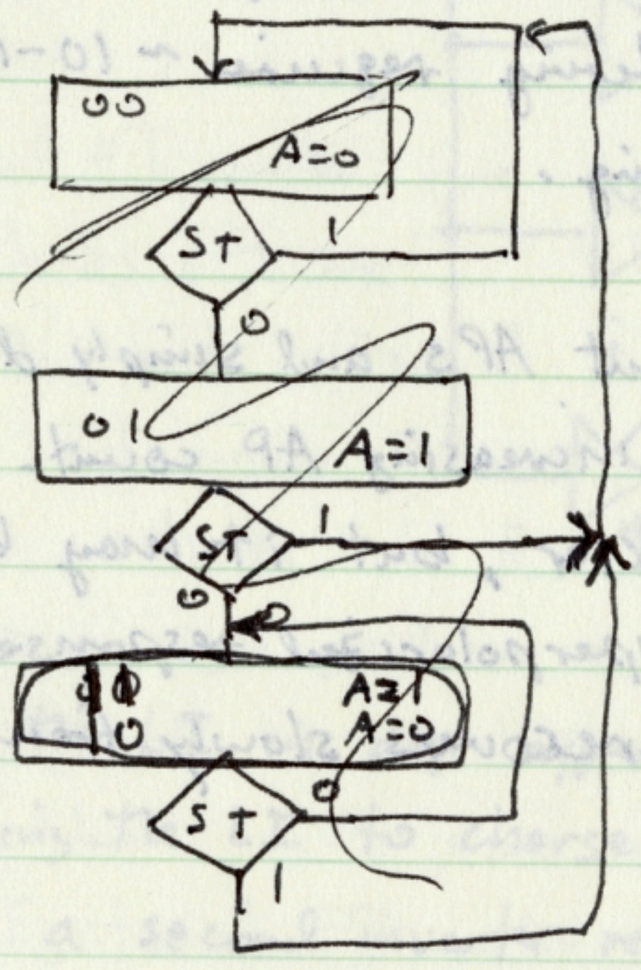
forsetful Register

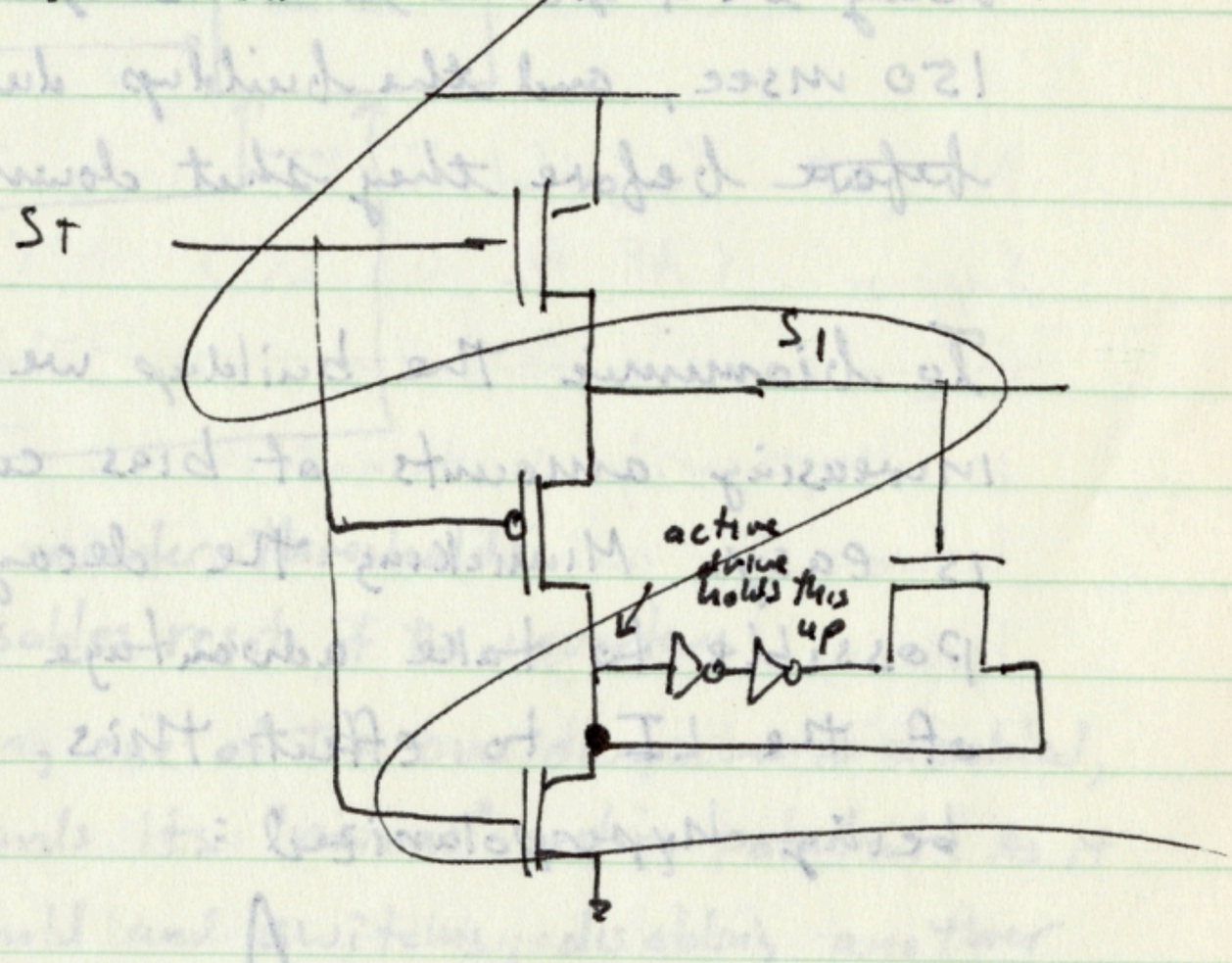




Active drive holds this at 1 when ST=0
No forsetting takes place.

This ~~was a~~ poor State assignment. How about

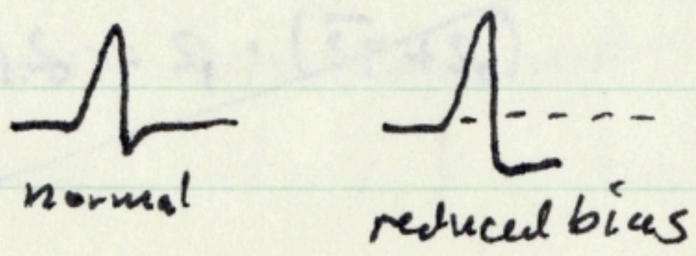




- AHP K (CA) channels are class SKI
  1) They are activated by ~~$[Ca]^{2+}$~~ $[Ca^{2+}]_i$.
  2) They have no membrane voltage dependence
  3) They produce AHP and slow AHP
  4) They are responsible for firing rate adaptation
  5) There are 2 ~~subt~~ subclasses
     a) IK or AHP (20-80 pS)
     b) SK or slow AHP (4-20pS)
  6) Their hyperpolarizing effect builds up slowly w/ rising $[Ca^{2+}]_i$; levels and decays slowly ~~as~~ w/ falling $[Ca^{2+}]_i$ levels

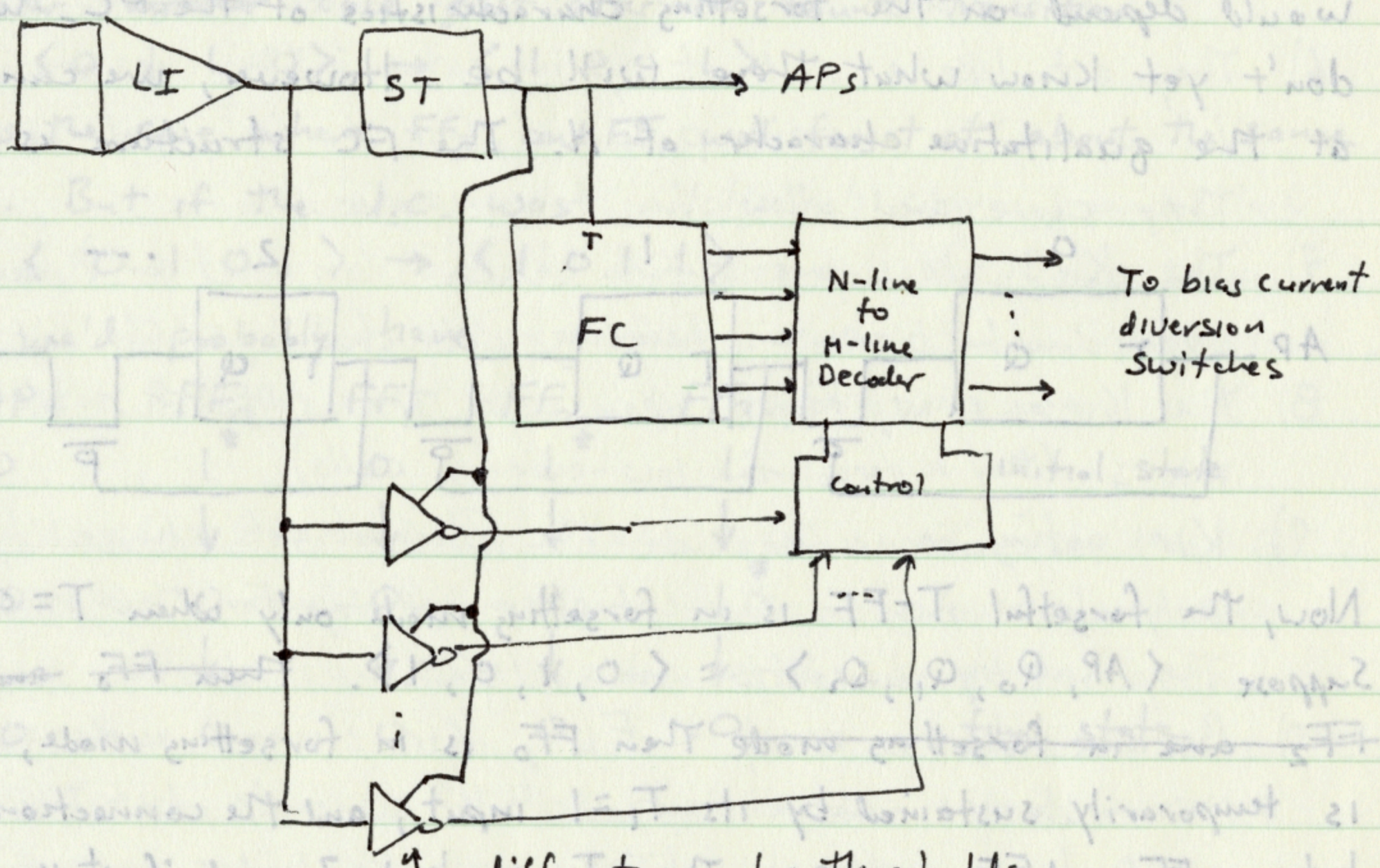
Because these channels are Ca^{2+} activated, their ~~firin~~ opening must rely on the opening of VGCs that conduct Ca^{2+} current. ~~Their time course is slow, (on the order of 10-15 APs).~~ It builds up over 10-15 APs and requires on the order of a few seconds to decay after AP firing stops. The decay in response to a single AP is on the order of about 150 msec, and the buildup during AP firing requires ~ 10-15 APs ~~before~~ before they shut down AP firing.

To biomimic the buildup we could count APs and simply divert increasing amounts of bias current w/ increasing AP count. This is easy. Mimicking the decay is trickier, but it may be possible to take advantage of the hyperpolarized response of the LI to effect this. The LI recovers slowly from being hyperpolarized:



If we can level-detect the LI output and use this to remove the bias diversion bit-by-bit, this might be sufficient to mimick the calcium decay. It would require a very fine gradation in the switching levels of the CMOS inverters however.

The idea is this. As bias current is diverted, the ~~"resting potential"~~ recovery potential of the LI decreases. We can use the forsetful counter to impose bias current diversion easily enough (provided the forsetful counter (FC) itself works). The scheme would look like this:

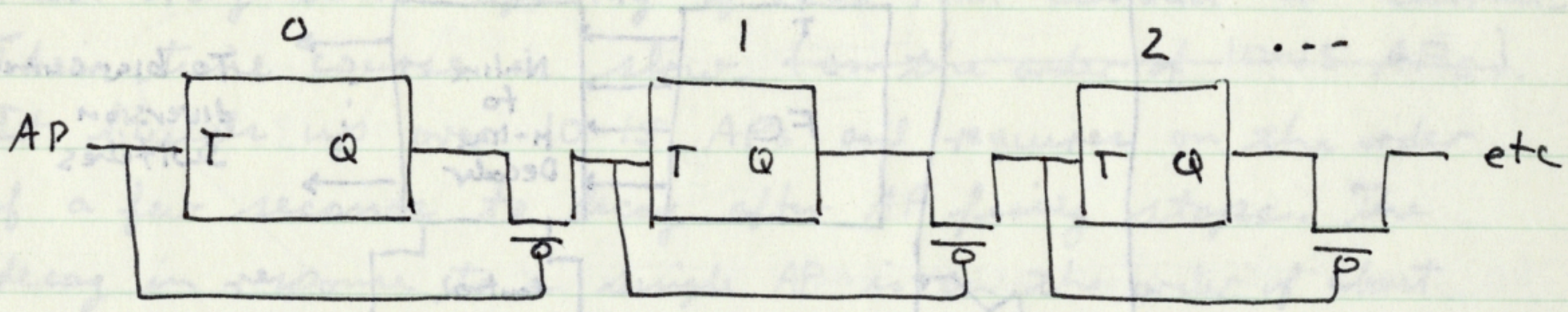


AP=H disables reset of the inverters

With the LI in deep hyperpolarization, one of the bias diversions is disabled, allowing the LI to charge back towards its "normal" resting potential. As it does, a second inverter reaches threshold and switches, disabling another bias diversion, allowing the LI to increase some more, etc., until all the bias diversion is disabled.

This requires a fairly fancy ASM because we have to distinguish between the buildup phase and the decay phase. The FC does not count when there is no AP firing, so it can only participate in the buildup phase.

One way to view it is that the FC is monitoring $[Ca^{2+}]$ buildup. ∴ a more realistic mimick might be to just use the FC's "forgetfulness" to mimic $[Ca^{2+}]$ decline as well. All this would depend on the forgetting characteristics of the FC. We don't yet know what these will be. However, we can get at the qualitative character of it. The FC structure is



Now, the forgetful T-FF is in forgetting mode only when T=0. Suppose $\langle AP, Q_0, Q_1, Q_2 \rangle = \langle 0, 1, 0, 1 \rangle$. ~~Then FF_0 and FF_2 are in forgetting mode~~ Then FF_0 is in forgetting mode, FF_1 is temporarily sustained by its $T_1 = 1$ input, and the connection between FF_1 and FF_2 is open. Thus T_2 is high-Z and if it is holding a charge on T_2 as well as its charge on Q_2, Q_2 is not in forgetting mode until T_2 decays to a 0 level. At that time, FF_2 enters forgetting mode. In such a case, FF_0 should forget first and FF_2 should forget later. When FF_0 forgets, $T_1 \to 0$ and $T_2 \to 0$ (because $Q_1 = 0$ already). Therefore, forgetting should ripple up from the lower bits to the higher bits of the FC.

Consider another case

* denotes forsetting mode

AP	FF_0	FF_1	FF_2	FF_3	
0	1^*	0	0	1^*	initial state
	↓	↓	↓	↓	
0	0	0	0	0	decayed state

In this case, the LSB and the MSB forset at the same time (more or less; in fact, FF_3 will probably forset first because it will usually have been in forsetting mode longer than FF_0).

Consider ~~another~~ initial condition case just after the count transition

$$\langle 0\ 1\ 1\ 0 \rangle \rightarrow \langle 1\ 0\ 0\ 1 \rangle$$

This is the case where FF_3 and FF_1 will forset at about the same time. But if the i.c. was

$$\langle 0\ 1\ 0\ 1 \rangle \rightarrow \langle 1\ 0\ 1\ 1 \rangle$$

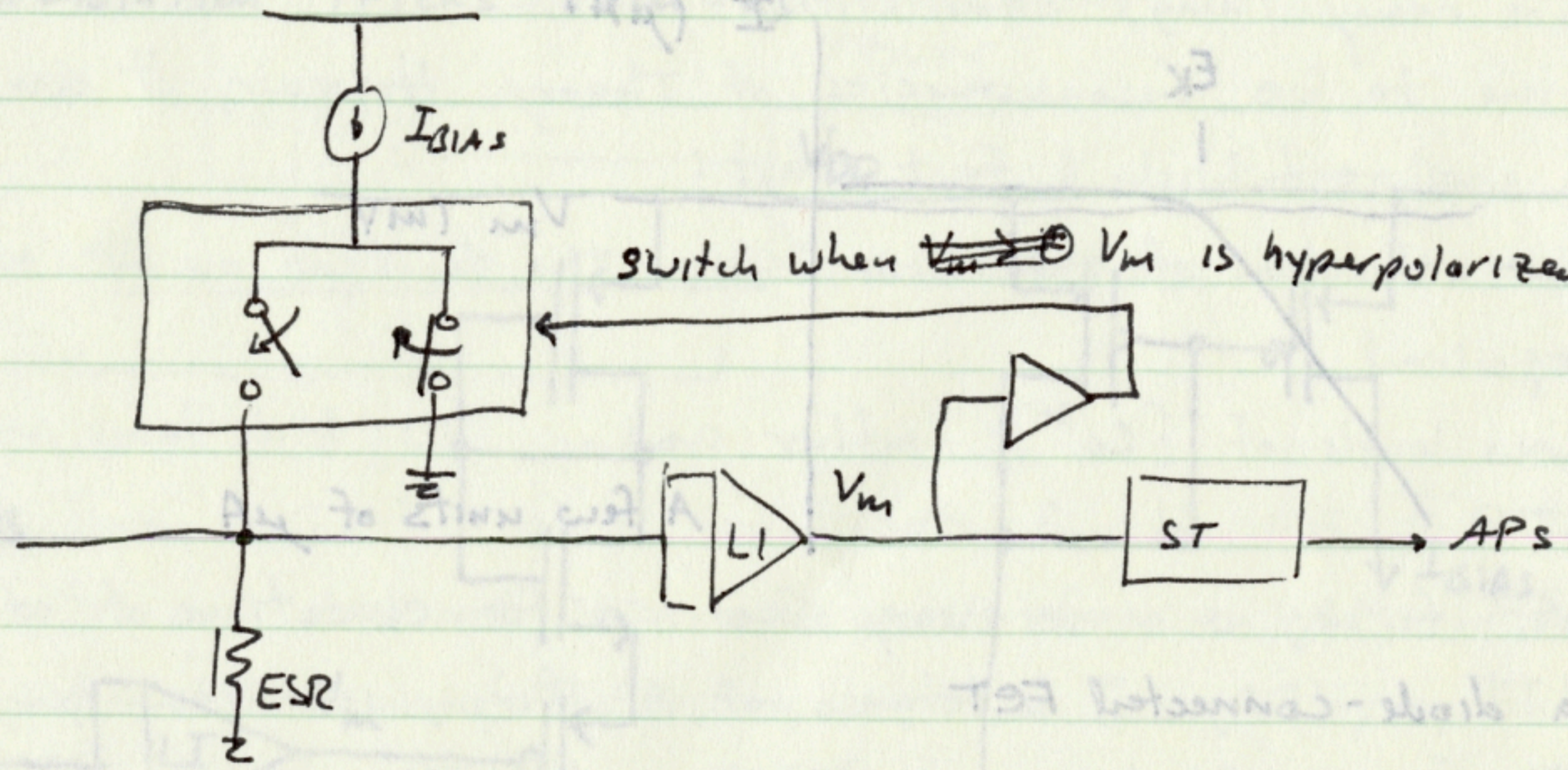
then we'd probably have

AP	FF_0	FF_1	FF_2	FF_3	
0	1^*	0	1^*	1	initial state
	↓	↓	↓	↓	
0	0	0	0	1^*	final state

- Inward rectifiers are a diverse family of 2TM, class Kir channels
  1) There are 5 subfamilies of "classical" Kir channels
  2) There is an ATP-sensitive Kir class (Kir 6.1)
  3) There is a G-protein-coupled Kir class (Kir 6.1)
  4) Kir channels stop conducting during depolarization and increase conductance during hyperpolarization
  5) They have a steep voltage dependence on hyperpolarization, depend on $[K^+]_o$, and have a very fast time constant (< 1 msec) plus additional long time constant modes.
  6) They act like a sort of spring/latch; they maintain Vm near the resting potential, but during depolarization they close and allow Vm to change.
  7) The Kir3 class are A.K.A. K_{ACh} (in the heart), and open due to G-protein-coupling activated by ACh.
  8) The Kir6 class, K_{ATP}, open when the ADP/ATP ratio rises (they hyperpolarize low-energy cells)
  9) Kir gating occurs because the channel gets plugged by polyvalent ions in the cytoplasm. ~~or by~~ For this reason they are by convention not VGCs.
  10) Because V_m is rarely < E_K, Kir channels under normal circumstances conduct <u>outward</u> K^+ currents, but their conductance is small. (They are like diodes conducting Isat when $V_m > E_K$; they are "ON" diodes when $V_m < E_K$).

So, it would appear that Kir action models as an increase in bias current that occurs during ~~depolarization~~ hyperpolarization. It also appears that Kir3 when activated metabotropically by ACh models as decrease in I_{BIAS}. It also appears that K_{ATP} channels should open (decrease I_{BIAS}) in response to high firing activity.

It seems like the model should look like so:

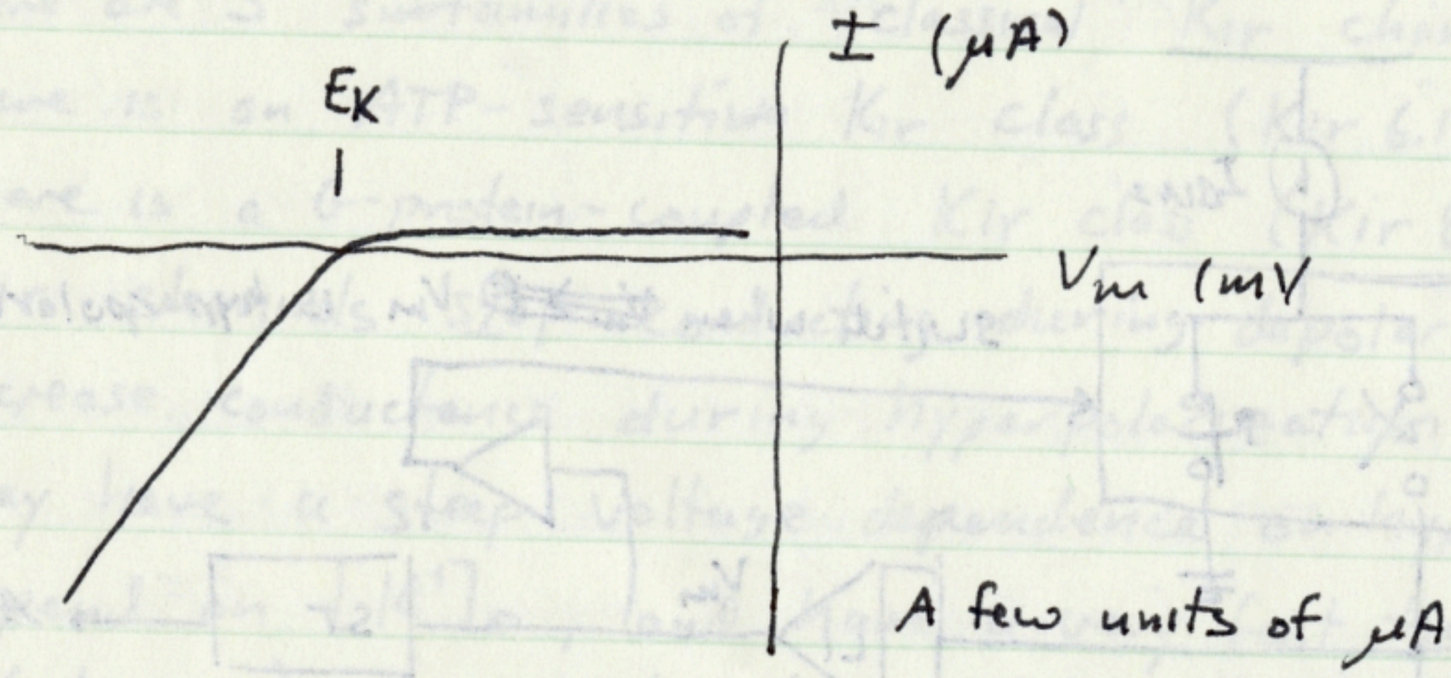


However, it is not clear that Kir channels play any particularly important role in actual signal processing. Their role seems primarily to set the resting potential (conduct when hyperpolarized) but more so to control basic cell metabolic processes.

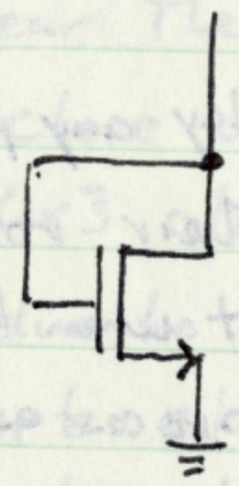
- Hyperpolarization channels I_h (a.k.a. I_f, I_q, and I_{AR}) one class NCNI
  1) Like Kir channels, They open in response to hyperpolarization and initiate slow depolarization if Vm has become very negative.
  2) They respond directly to cAMP by shifting the voltage-dependence of their gating threshold. Elevated cAMP promotes ~~depolarization~~ depolarization
  3) These channels produce pacemakers.

It may also be the case that we can use this notion ~~of~~ for closed-loop bias control of the BAN. The hyperpolarizing channels in a sense act like diode clamps. Their V-I curve

has the basic form



For a diode-connected FET

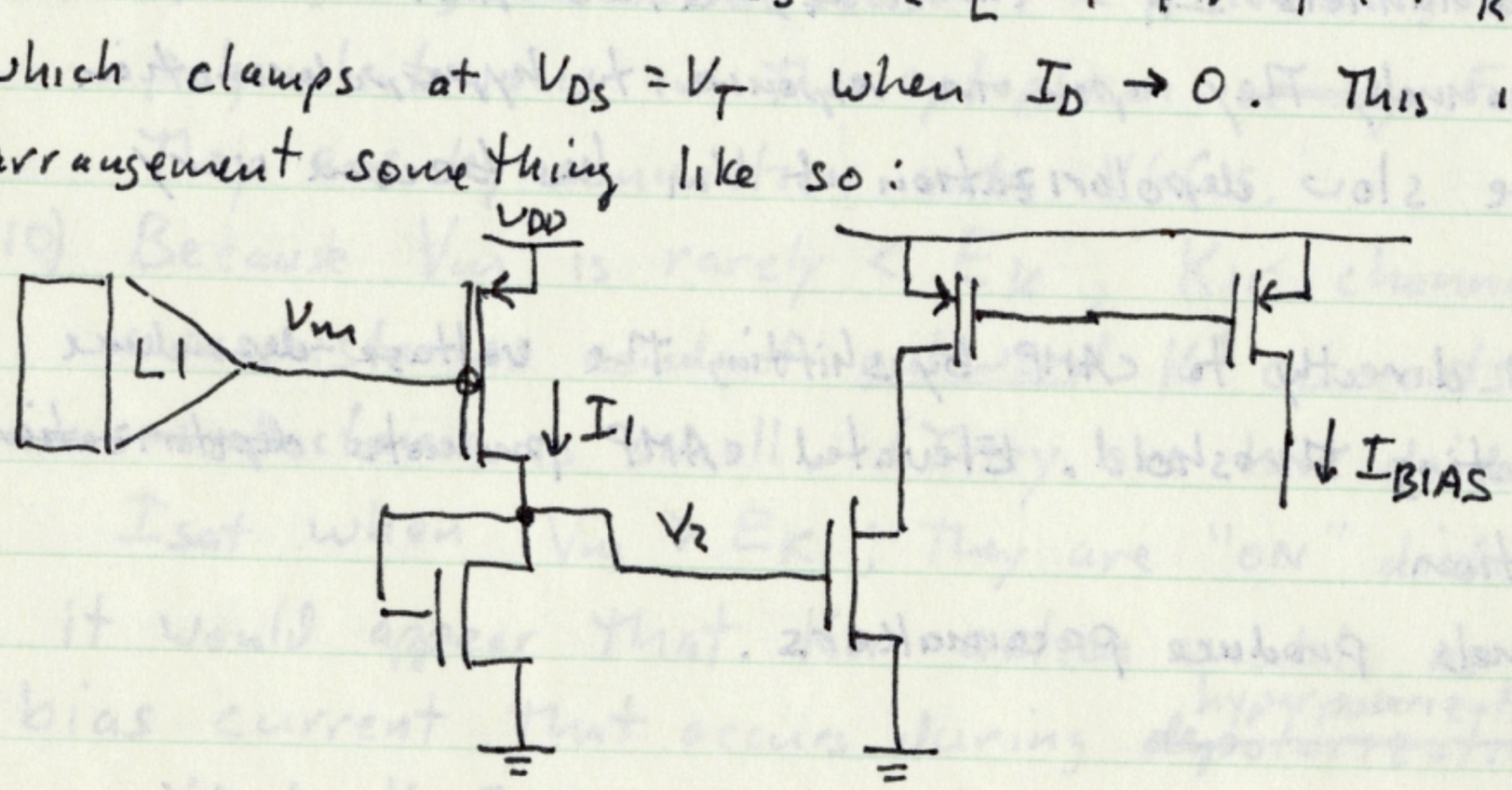


$$I_D = K \frac{W}{L} (V_{DS} - V_T) V_{DS} \quad , V_{DS} > V_T$$
$$0 \quad , V_{DS} < V_T$$

$$V_{DS}^2 - V_T V_{DS} - \frac{L I_D}{KW} = 0$$

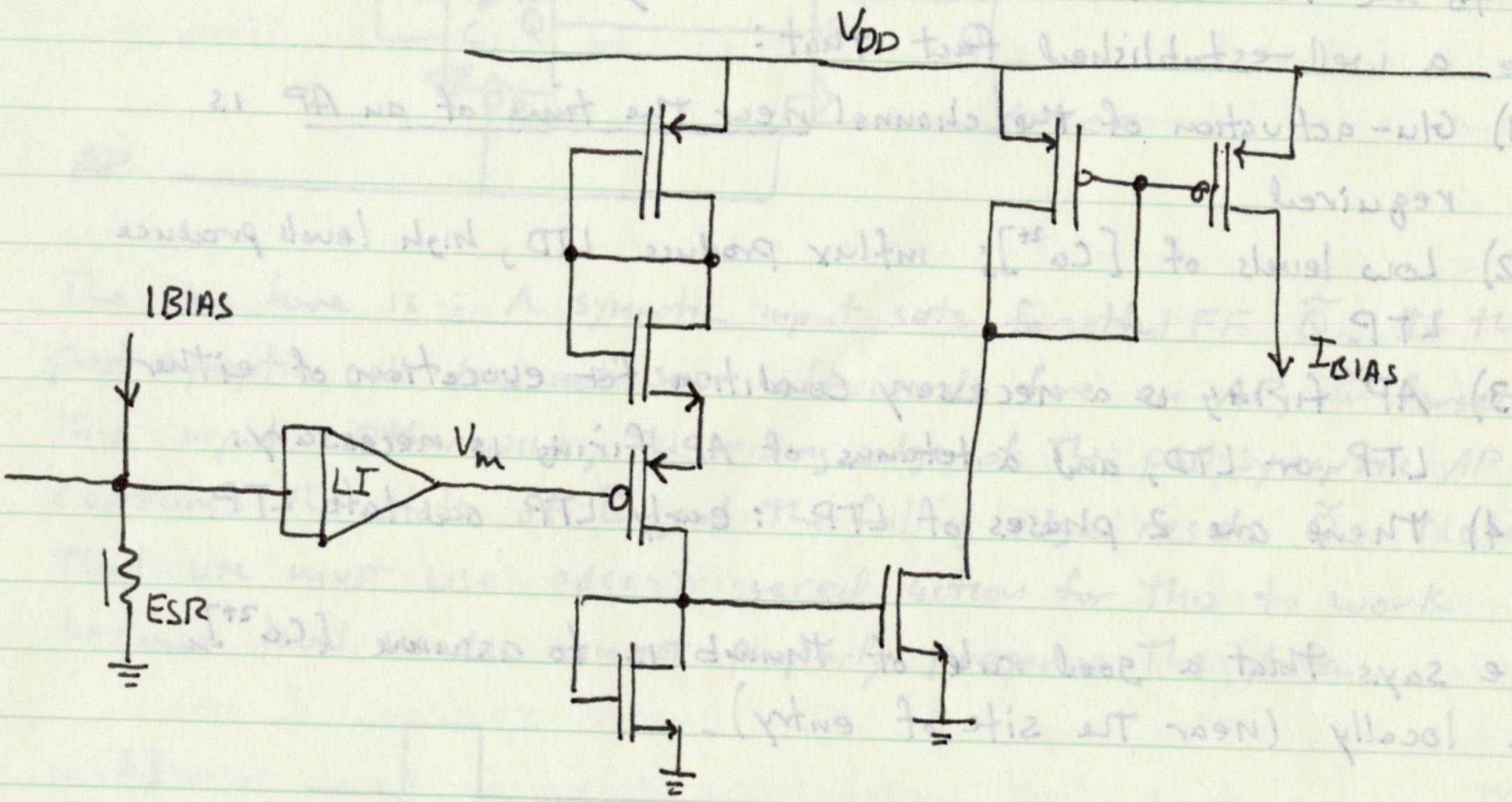
$$V_{DS} = \frac{1}{2} \left[V_T + \sqrt{V_T^2 + 4 \frac{L I_D}{KW}} \right] \quad , V_{DS} > 0$$

which clamps at $V_{DS} = V_T$ when $I_D \to 0$. This implies an arrangement something like so:



As $V_m \uparrow$ I_1 decreases and V_2 drops toward V_T. To get the bias

point into the proper range, we'll probably have to do some level-translation tricks such as



The LI, of course, will require a large T_f so that I_{BIAS} feedback does not cancel excitatory PSP effects. We'll also want to see to it that we set a nice, relatively slow charge-up to the proper Q-point in recovery from extreme hyperpolarization.

Long Term Potentiation

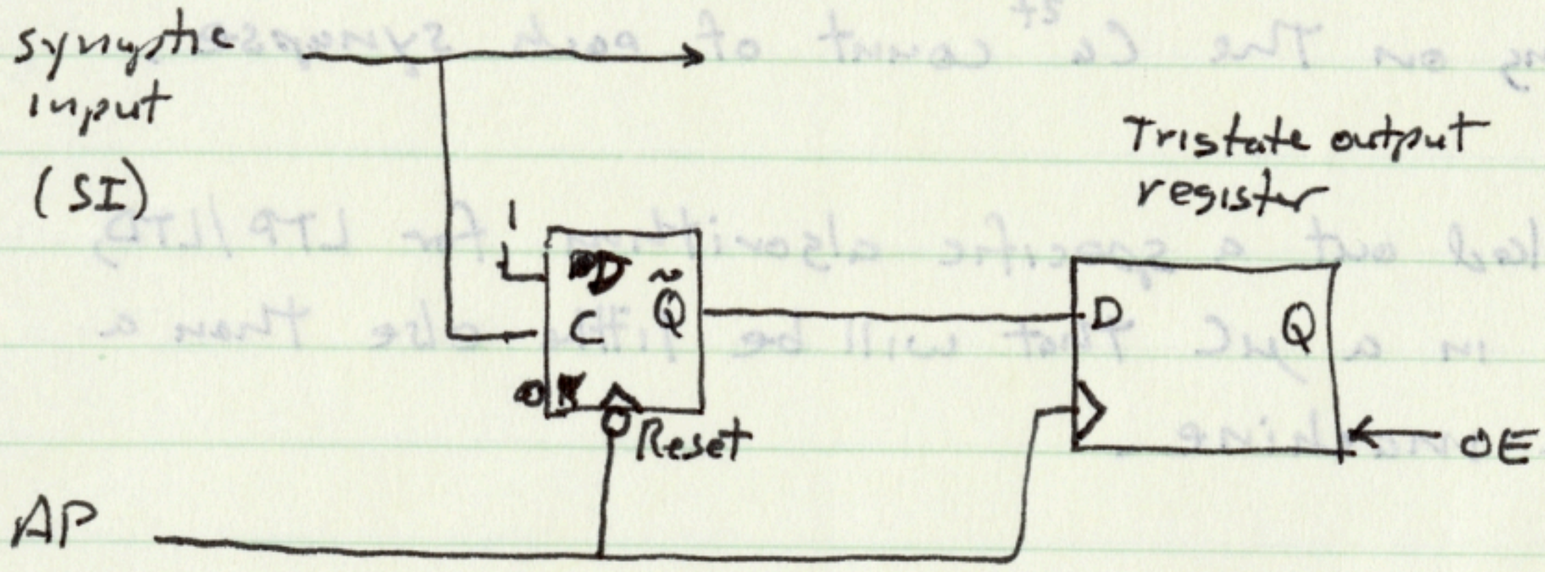
There are many things about NMDA-mediated LTP that present what seem to me to be inconsistencies of theory. However, it does seem to be a well-established fact that:

1) Glu-activation of the channel <u>near the time of an AP</u> is required
2) Low levels of $[Ca^{2+}]_i$ influx produce LTD, high levels produce LTP
3) AP firing is a necessary condition for evocation of either LTP or LTD, and a tetanus of AP firing is necessary.
4) There are 2 phases of LTP : early LTP and late LTP.

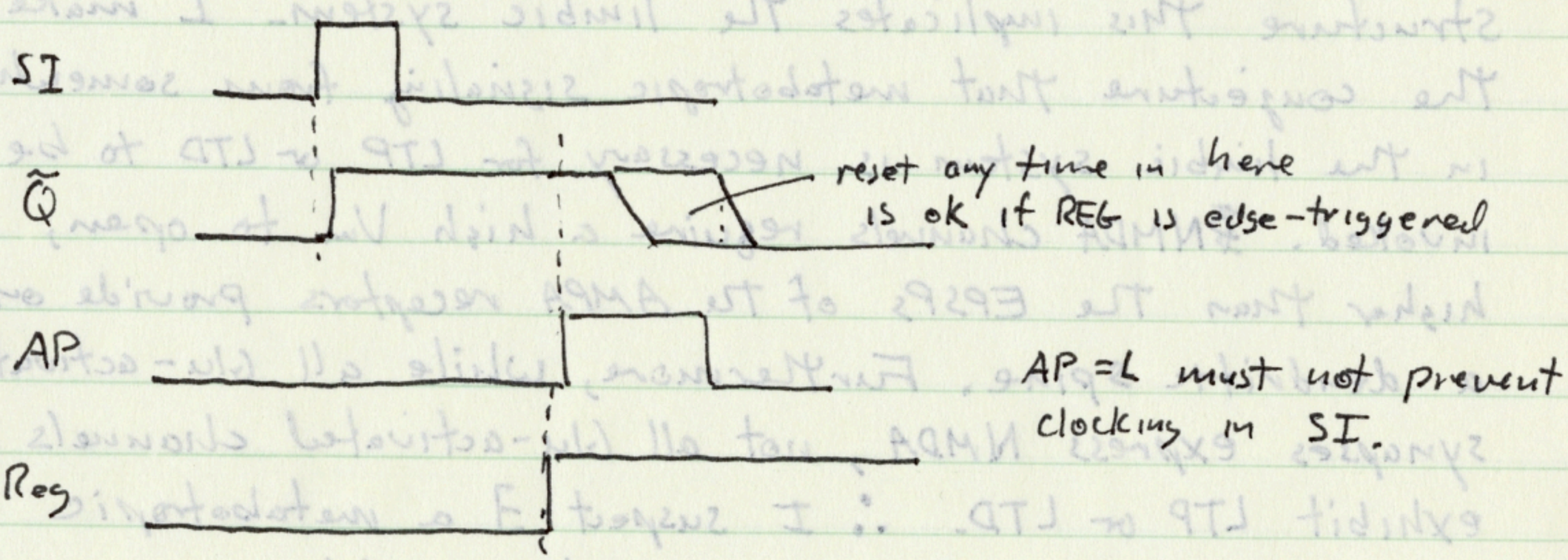
Hille says that a good rule of thumb is to assume $[Ca^{2+}]_i$ acts locally (near the site of entry).

Characteristic (2) is the real tricky feature. Short of putting an LI on every synapse, which is absurdly impractical, the best way to procede seems to me to be: employ a local μcontroller to execute an LTP/LTD algorithm. If the μcontroller is fast enough, it could handle many neurons and thereby distribute the cost. Since LTP and LTD are slow processes, the time lag seems to not be an important factor provided that the μcontroller time lag is not extremely large.

The first trick is to instrument the state of the synapse. Here what we need to know is whether or not the synapse was Glu-activated in close proximity to the time just prior to an AP. To this end we can use a forgetful FF



The idea here is: A synaptic input sets forsetful FF $\tilde{Q}$. If the post synaptic cell does not soon afterwards fire an AP, $\tilde{Q}$ forsets this input. Otherwise, the rising edge of the post synaptic AP captures the state of $\tilde{Q}$, and the falling edge resets $\tilde{Q}$. Note that we must use edge-triggered action for this to work because level mode cannot properly preserve the data.



Every time an AP fires, the μcontroller would scan the contents of REG. REG contains data on all the excitatory synapses of that neuron. If a synapse bit is set, the μC increments a Ca^{2+} count for that synapse. Otherwise it decrements that count until the count = 0. When the neuron's forsetful counter (that controls facilitation) signals tetanus firing, the μC implements LTD or LTP or no change on each

synapse, depending on the Ca^{2+} count of each synapse.

Once we've worked out a specific algorithm for LTP/LTD, we'll implement it in a μC that will be little else than a hard-wired state machine.

- One consideration I haven't seen discussed in the physiology literature is the issue of whether or not an additional metabotropic signal is needed to evoke learning. The question is speculative, but here's where I'm coming from on it. My theory of mental physics says that cognitive action via determining judgment does not take place w/o a prior ~~of~~ reflective judgment. In brain structure this implicates the limbic system. I make the conjecture that metabotropic signaling from somewhere in the limbic system is necessary for LTP or LTD to be invoked. $NMDA channels require a high Vm to open, higher than the EPSPs of the AMPA receptors provide on a dendritic spine. Furthermore, while all Glu-activated synapses express NMDA, not all Glu-activated channels exhibit LTP or LTD. ∴ I suspect ∃ a metabotropic signal of some kind reaches LTP/LTD active neurons and is required to stimulate NMDA channels into opening at a lower level of Vm.