Notes from: W.G. Regehr & C.F. Stevens, "Physiology of synaptic transmission and short-term plasticity," in Synapses, W.M. Cowan, T.C. Südhof, & C.F. Stevens (eds.), Baltimore, Maryland: The Johns Hopkins University Press, 2001, pp. 135-175

- ∃ 3 key variables that characterize quantal NTX release:
  - number of release sites, N
  - probability of quantal release, p
  - size of quantal response, q
- the number of active zones per synaptic contact site ranges from one to hundreds
- At some synapses a single AP reliably triggers vesicle fusion at a single contact site, whereas at others an AP rarely triggers vesicle fusion ($p < 0.1$).
- For some synapses each quantum produces a large postsynaptic depolarization (large q) whereas at others q is small.
- Synapses in the calyx of Held or the climbing fiber-Purkinje cell synapse are high-N and high-p.
- Most of what we know of synaptic function and plasticity is based on recordings from populations of neurons (extracellular recording).

Regehr & Stevens " (cont)

- individual synapses in hippocampus are very unreliable (low p)
- hippocampal neurons receive synaptic inputs w/ diverse individual properties.
- one axon might make multiple synaptic connections to one postsynaptic cell, and this would tend to increase p.
- however, often a neuron makes only a single synaptic contact w/ its target cells.
- increasing extracellular Mg^{2+} tends to block synaptic transmission. (when accompanied by lowering extracellular Ca^{2+}).
- Katz et al. proved that the amplitude of postsynaptic response follows a binomial distribution (N, p, q)
- in central synapses, spontaneous mPSCs vary greatly in amplitude from one to the next. This variation is large enough to tend to mask the quantal nature of synaptic transmission at central synapses.

Reseler & Stevens (cont)

My comment: If it is true that central synapses show a large spontaneous miniature post synaptic currents (mPSCs), then it is reasonable to suspect that individual synapses have their own "bias" contribution to postsynaptic membrane potential.

- An important but unresolved question is whether or not NTX released by a single vesicle can saturate postsynaptic receptors.

- It has been found that at some central synapses, the vesicle interior (after NTX release) remains exposed to the extracellular medium for about 20 seconds. Vesicle recycling requires about 1 minute.

- All available data indicates that members of a population of synapses, even those made by a single axon, have very different release probabilities.

- New experiments have confirmed that a single active zone can normally release only one vesicle per AP. The dead time for release persists for about 10 msec.

Regehr & Stevens (cont)

- Synapses greatly vary in their release probabilities. In ~~a study~~ studies of hippocampal cultures and slices it was found that a population of synapses had an average $\bar{p} = 0.3$ with a skew toward the low end and a peak in the distribution at $p = 0.15$.
- A typical hippocampal synapse has around 5-10 docked vesicles (the readily releasable pool), and p depends on the size of the RRP. Under rapid stimulation, p declines to a small steady-state value, which has been classically interpreted to mean the RRP is being depleted faster than it can be re-supplied w/ docked vesicles. Some references on how p and the size of the RRP are related are:

L.E. C.F.
Dobrunz & Stevens (1997), Heterogeneity of release probability, facilitation, and depletion at central synapses, Neuron 18:995-1008

Murthy, V.N. et al. (1997), Heterogeneous release properties of visualized hippocampal synapses, Neuron 18:599-612

- Recovery of p following rapid stimulation induced depression takes several seconds.

Regehr & Stevens (cont)

Wells' comment: The relatively low values of p and its depression under rapid stimulation must have some tie-in w/ how the neural network functions. Low p implies that for any synapse w/ a small EPSP response to APs, a <u>train</u> of APs <u>must</u> be required if the info presented by the presynaptic cell is to play any significant role in the post-synaptic cell (in the case of ionotropic synapses; the situation is different for the metabotropic synapse, where even one NTX event can trigger significant reactions in the target cell).

This would tend to support the coding hypothesis that cell signaling encodes significant activity as synchronized firing of cell groups. It also implies that after a cell has been firing at a sustained high rate, it "takes itself out of the picture" by depletion of the RRP. Therefore, if a single cell is firing and fails to produce a response, its signal path effectively gets turned off for several seconds. Because one cell signals to many targets, this further implies the primacy of the correlation-encoding hypothesis. The reason I think so is that the response or non-response of a cell <u>assembly</u> just might depend on the depression of p in the cells that act as the assembly's info source.

Regehr & Stevens (cont)

This suggest that at the network level, the primitive information processing unit is the specialized cell assembly which responds only to a limited set of input firing patterns. p-reduction would be one mechanism by which the network elastically re-configures itself to ~~encode~~ time-encode complex events.

- The body of experimental evidence makes it clear that synapses are info-processing units and not merely info-relay stations. In the brain many neuron types fire at high frequencies and often in bursts. Synapses exhibit mechanisms, such as paired-pulse facilitation and paired-pulse depression, that in some sense "encode for" specific firing patterns. Synaptic strength can increase or decrease more than ten-fold by use-dependent mechanisms.

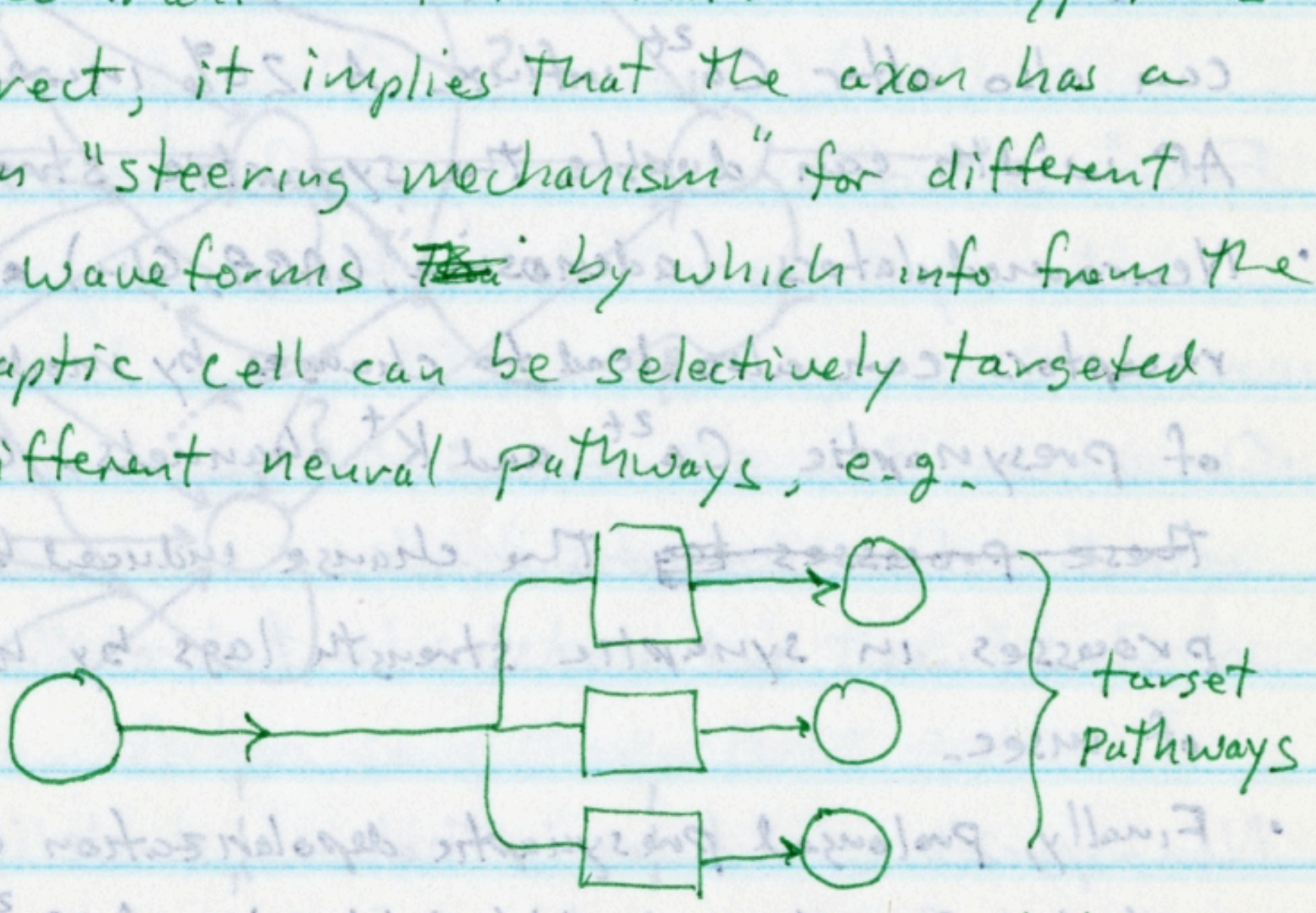
- R&S describe the synapse as a complex time-varying filter. It would appear that:

1. Synapses are "tuned" to respond to a narrow range of firing rates with a specific degree of post-synaptic excitation, but
2. Despite their variability, responses for a given synapse are highly stereotyped.

Regehr & Stevens (cont)

- I had always assumed that presynaptic modulation mechanisms would be productive of more or less the same response at each terminal of a given axon. This is not true. Different terminals on the same axon can exhibit quite different plasticity properties. In my terminology, the set of presynaptic terminals might exhibit a type of signal processing that could be called a filter bank.

Wells' comment: If the filter bank hypothesis is correct, it implies that the axon has a built-in "steering mechanism" for different signal waveforms by which info from the presynaptic cell can be selectively targeted for different neural pathways, e.g.



If this is true, then we should not approach PCNNs via a "one synapse fits all" model. This implies a greater role for dendritic integration logic as well as a somatic inhibitory synapse logic. This synapse logic would have to be time-selective, i.e. a tuned asynch. ASM.

Regehr & Stevens (cont)

- Experiments have shown that

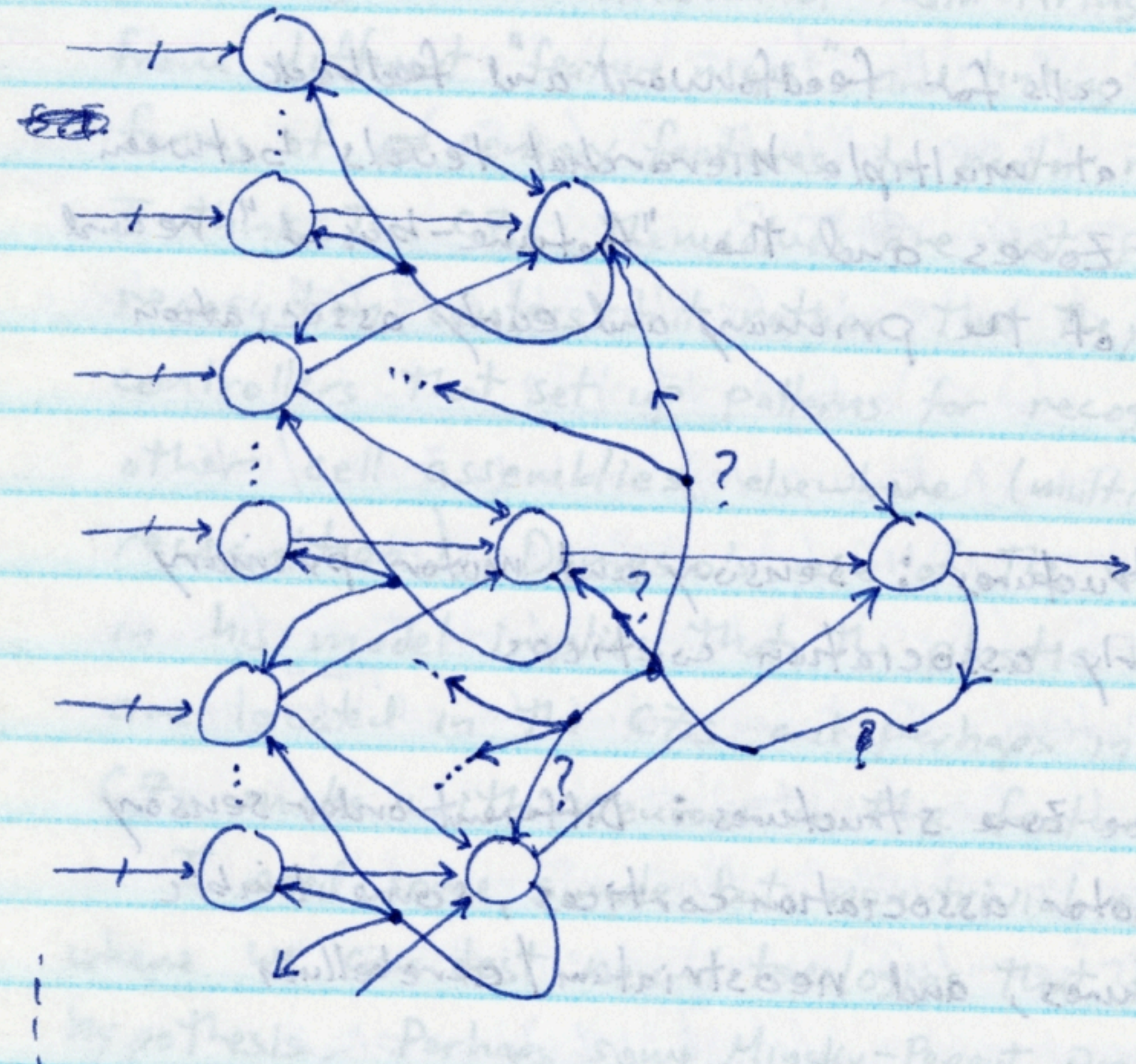
$$EPSC = \text{constant} \times (Ca^{2+}\ \text{influx})^n$$

w/ $2 \leq n \leq 4$ and the Ca^{2+} influx being influx into the presynaptic terminal. The dependence of the EPSC on Ca^{2+} influx is believed to be due to increases in NTX release.

- Ca^{2+} influx$^{\text{per AP}}$ can either increase or decrease during a train of APs. One mechanism for this is plasticity in Ca^{2+} VGCs in the terminal. But this does not appear to be the dominant mechanism.
- Changes in AP waveform (use-dependent changes) can also alter Ca^{2+} influx. A 20% increase in AP width can double the synaptic strength.
- Neuromodulators (adenosine, GABA, Glu) at metabotropic receptors can also lead to changes by modulation of presynaptic Ca^{2+} and K^+ channels. Generally ~~these processes lag~~ the change induced by these processes in synaptic strength lags by hundreds of msec.
- Finally, prolonged presynaptic depolarization can relieve G-protein-mediated blocking of Ca^{2+} VGCs

A.R. Damasio, "Time-locked multiregional retroactivation: A systems-level proposal for the neural substrates of recall and recognition," Cognition, 33 (1989) 25-62

As best as I can make out, Damasio's hypothesis calls for a network of networks structure something along the following lines



other neuroanatomical substrates include limbic structures (entohinal cortex, hippocampus, amygdala, cingulate cortices) neostriatum/cerebellum, non-specific thalamic nuclei, hypothalamus,

basal forebrain, and brainstem nucleii. These are in addition to primary and early association cortices (both sensory and motor), which are substrates for feature-based records, and association cortices of different orders which constitute the substrate for convergence zones.

Damasio calls for feedforward and feedback connections at multiple hierarchal levels between convergence zones and the "feature-based" record structures of the primary and early association cortices.

Feature structures: sensory and motor primary and early association cortices

Convergence zone structures: Different order sensory and motor association cortices, some limbic structures, and neostriatum/cerebellum

Non-specific structures: thalamic nucleii, hypothalamus, basal forebrain, brainstem nucleii.

The representation of "entities" (neural code) is to be based on time and space synchronous firing patterns.

Con[illegible] Time-locked patterns of different firing rates can in principle be distinguished by particular neurons if the weight distributions are such as to be

information-lossless. If synapses are capable of functioning as banks of waveform filters, this implies that interconnected cell assemblies can do feature extraction based on synchronous firing rates. Feedback from CTs might act to reinforce and stabilize certain integrated feature patterns by promoting the combination of their firing patterns from different "feature maps" and linking the firing of ~~a~~ sensory features to motor responses. I think the CTs themselves are not perceptual recognition centers but rather that they ~~control~~ are controllers that set up patterns for recognition by other cell assemblies elsewhere (multi-region recognition). Damasio's use of the word "records" in his model implies that the plastic weights are located in the CTs and perhaps in the synapses CTs make with neurons in the feature assemblies.

I need some simple but non-trivial application where we can test neural topologies that fit Damasio's hypothesis. Perhaps some Minsky-Papert problems?