

Analog Circuit Model of Stimulus-Dependent Synchronization of Visual Responses

Kimberly Reinhold

Advanced Biophysics Lab Class, 2011

Introduction

The gamma frequency oscillation (30-80 Hz) in visual cortex has been extensively studied. However, its neural mechanism is still debated. In particular, while in recent years many researchers have embraced a model of oscillating, weakly coupled neurons and sub-networks as generative, we have a limited understanding of how the nervous system *specifically* implements a circuit to support and sustain such oscillatory activity. Furthermore, we have little intuition regarding the challenges faced by the nervous system in constructing systems of coupled oscillators for robust and efficient computation. To explore these issues, I have built several analog circuits containing coupled, oscillating components, with a plan, first, to recapitulate basic theoretical principles of two-component systems and then to physically implement a proposed model of stimulus-dependent response synchronization in the visual system.

Mathematics developed to describe the effects of coupling in simple oscillating systems have been applied to a wide range of phenomena in neuroscience. For instance, using this approach, researchers have gained insights into central pattern generators for walking, swimming, and breathing (Kopell, 1988), and into pathological oscillatory states including epilepsy (O'Sullivan-Greene, 2009). One phenomenon of particular interest because it may represent cognitive binding of related stimuli is phase-locking of the local field potential (LFP) across some distance in cortex when spatially separated receptive fields (RFs) receive similarly oriented inputs (Fig. 1). A paper from Grannan, Kleinfeld, and Sompolinsky (1993) proposes a model to explain this effect (Fig. 1d). Across cortical columns, groups of similarly feature-tuned neurons may be more densely interconnected than are groups of differentially feature-tuned neurons. If this is true, and some recent evidence is supportive of the idea, driving two similarly feature-tuned populations will recruit their reciprocal connections, possibly leading to phase-locking of the LFP across cortical columns. In the case that the driven populations are not matched in feature specificity, a lack of strong reciprocal connectivity prevents synchronization. I find that even a simple analog circuit of heterogeneous oscillating elements can exhibit cluster-specific phase-locking when the appropriate inputs are matched, given a preset architecture of strong local, intra-cluster connectivity with weaker, sub-network-specific cross-cluster connections. Finally, I find that exhibiting stimulus-dependent synchronization to a subset of the possible inputs is rather robust to weights of the connections, shapes of the waveforms, and intrinsic frequencies of the oscillating elements. However, tuning the six-neuron network to perform the ideal "similar or dissimilar" computation in every case is very difficult, when searching the parameter space without a pre-determined, optimized endpoint. Perhaps, in scaling up from a few elements to a network of many thousands of neurons, the cortex avoids the simple in- or out-of-phase solutions that lock the network in undesired states. Furthermore, coding redundancies in the cortex may compensate for periodic computational failures of a subcircuit.

Methods

Single Neuron Model

The fundamental oscillatory element in my circuit is a two-conductance, Fitzhugh-Nagumo-like neuron (Fig. 2), described in a paper by Maeda and Makino (2000). A stimulus activates the fast inward current by raising the voltage at the gate of the "fast inward" 2n3904 transistor, which allows the connected 2n3906 transistor to pass current (Darlington arrangement). The battery source for the fast inward current charges both "leak" and "delay" capacitors, but the 0.5 microF "leak" capacitor charges up more rapidly than does the 1 microF capacitor. This pushes the "inside" voltage rapidly toward 5 V, the "equilibrium potential" of the fast inward current (rising phase of the action potential). Eventually, the 1 microF capacitor charges up to a voltage able to activate the "delay" 2n3904 transistor. This transistor now conducts a strong current that discharges the inside voltage, driven by the 0.4 V battery with reverse polarity (falling phase of the action potential). To simplify the construction of this element, I have replaced the delayed outward voltage source with a diode that ensures the "fast inward" 2n3904 transistor will activate when the voltage inside the cell rises above 0 V (Fig. 2, diode circuit suggested by Maeda et al., 2005). Now, R_L affects the time constant for charging C_1 and C_2 , thus it sets the intrinsic oscillation frequency of the model neuron. To verify this description of the circuit's activity, I record from each node during spontaneous oscillation, and I vary key circuit parameters (R_L , C_1 and C_2) to observe the effects on oscillation frequency and waveform shape.

Synapse Model

I use an excitatory synapse motif to couple the neuronal elements (design from <http://www.nbb.cornell.edu/neurobio>) (Fig. 3). A diode produces asymmetric transmission modeling the asymmetry of the chemical synapse. A similar Darlington transistor arrangement controls the turning on and off of the synapse, and a capacitor sets the time course of the resulting "excitatory post-synaptic potential" (EPSP). Importantly, R_{syn} controls the strength of the synapse by modulating current flow from the 3 V battery into the post-synaptic cell.

Recapitulating Basic Findings in Coupled Oscillator Theory

Using a pair of neurons with a single, unidirectional, excitatory synapse between them, I investigate the ability of both EPSP strength and timing (phase) relative to the oscillation of the post-synaptic cell to influence the phase shift of the post-synaptic cell's next action potential. Theory suggests that both parameters should have effects (Ermentrout and Chow, 2002). Then, I reciprocally couple a pair of cells to investigate in-phase and anti-phase phase-locking dependent on the strength of the symmetric connection (synapses in both directions are set to have equal weights). According to theory, in the case of two oscillators coupled by a reciprocal excitatory connection, in-phase solutions are stable for lower coupling strengths (Ermentrout and Chow, 2002). As the strength of coupling increases, however, only the anti-phase solution should be stable. I test this in the analog circuit.

Analog Circuit Model of Stimulus-Dependent Synchronization of Ongoing Oscillatory Activity

In the visual system, the presentation of similarly oriented inputs to two different receptive fields can lead to the phase-locking and synchronization of the local field potential at

the spatially corresponding cortical sites. To model this phenomenon in an analog circuit composed of intrinsic oscillators, I designed a six-neuron network with three "clusters", where neurons within a cluster all shared the same receptive field and each neuron in a cluster "preferred" a different type of input (Fig. 4). I controlled each cell's "response" to an input by tuning the value of R_L , which determines the oscillation frequency of the neuronal element. Thus, cells lacking R_L were "OFF" (did not spike unless driven by an active presynaptic cell), while cells with appropriate R_L values were "ON". Neurons within clusters were strongly reciprocally connected, verging on "strong coupling" (able to drive spikes in the post-synaptic cell), with R_{syn} values of 120 kOhms. In contrast, cross-cluster synapses were weak -- all cross-cluster synapses used R_{syn} resistors of 1000 kOhms. While an R_{syn} value of 1000 kOhms might not produce clear EPSPs in a quiescent post-synaptic neuron, such a synapse might be of sufficient strength to push around action potential timing (weak coupling regime).

I explored the ability of this architecture to exhibit stimulus-specific cross-cluster synchronization. I also attempted to tune the network to improve its performance on the task. Specifically, I aimed for the circuit to show strong within-cluster synchrony in all cases and cross-cluster synchrony only when inputs to the two clusters were perfectly matched. For instance, if Clusters A and B received the same input (e.g., ON-ON) but Cluster C received a different input (e.g., ON-OFF), I would expect the all neurons in Clusters A and B to synchronize (in-phase phase-locking), without any A-C or B-C phase-locking. I used the following strategy to tune the network: 1. change R_L , C_1 , and C_2 values within each isolated neuron to match, as much as possible, waveform shape and oscillation frequency across all cells before wiring up the synapses, 2. identify a within-cluster coupling strength that causes phase-locking when both units in a cluster are driven but that is not so strong a unit can drive spikes in its OFF neighbor, 3. choose a cross-cluster coupling strength enabling similar inputs to drive cross-cluster synchrony. Finally, I read in the response of the network to various stimuli, two neurons at a time using a two-channel National Instruments data acquisition system controlled via Matlab.

Results

Single Neuron Model

All predictions about the mechanisms of operation of the circuit were confirmed (Fig. 5). R_L was confirmed as the relevant parameter for turning ON or OFF ($R_L = \text{infinity}$) each neuron.

Synapse Model

As expected, R_{syn} controlled the strength of the synapse, and lower values of R_{syn} more rapidly charged up the post-synaptic cell's membrane voltage to spike threshold (Figs. 6 and 7). Interestingly, while 1000 kOhms produced EPSPs too small to be detected in the single, unidirectional synapse configuration, 1000kOhm synapses were sufficient to alter action potential timing of an intrinsically oscillating element (weak coupling regime) (Figs. 11 and 12).

Recapitulating Basic Findings in Coupled Oscillator Theory

EPSPs arriving about a fourth of a period before the next action potential in the post-synaptic cell (phase ≈ 270 degrees) seemed best able to speed up the onset of the subsequent post-synaptic action potential (Fig. 8). In contrast, EPSPs arriving anti-phase to the oscillation of

the post-synaptic neuron or exactly in-phase with the post-synaptic action potentials had little or no effect on subsequent action potential timing (Fig. 8).

Increasing the strength of a reciprocal, excitatory synapse between two oscillating neuronal elements shifted the activity of the system from uncoupled (uniformly drifting phase offset) to coupled with some attraction of action potential phase to in-phase synchronous to anti-phase phase-locked (Fig. 9). The transition to in-phase synchronous occurred between 43 and 15 kOhms, while the transition from in-phase to anti-phase as a stable solution occurred between 1.1 kOhms and 2000 Ohms.

Analog Circuit Model of Stimulus-Dependent Synchronization of Ongoing Oscillatory Activity

I found that the network often responded as expected; however, in certain cases, a non-ideal computation was performed (Figs. 10, 11 and 12). For instance, turning on both Neurons 1 and 6 drove some spiking in Neuron 2 (3-to-1 Neuron 1 to Neuron 2 spiking). Thus, in this case, the input signal (only 1 and 6 ON) was mostly maintained (Neuron 1 still responded more strongly than Neuron 2) but was degraded. Also, phase-locked units within or across clusters would often settle at some small fixed phase offset (<90 degrees) when, ideally, they would have perfectly synchronized. "Slipping" was also observed in many cases. I define slipping as the appearance of transient phase-locking (not real stability) followed by a rapid precession of the phase difference through the anti-phase configuration to return to a transiently (on the order of seconds) "stable" in-phase configuration. On multiple occasions, I also observed hysteresis, which I confirmed by repeating the same steps in the same order (e.g., turn on Neuron X then Neuron Y, rather than Y then X) to ensure a connection had not accidentally been changed. I found that waveform shape and the intrinsic oscillation frequency of each element were hugely important parameters for tuning the circuit. Given the heterogeneity of the electronic components, I was unable to *perfectly* match every neuronal element, but I was able to tune all elements to *about* the same waveform and to the same oscillation frequency. Finally, an incomplete version of the network (lacking the Neuron 1-5 synapses, and lacking the Neuron 2-6 synapses) was able to perform many of the same computations, but with somewhat less success than the full model.

For every tested input, I was able to tune the network to respond as desired by altering synaptic weights. However, I was unable to arrive at one stable network configuration that could support all the desired functions. In the figures (Figs. 10-12), I show data from two network configurations and discuss the limitations of each.

Conclusions

Analog circuit modeling has provided me with a unique set of insights into the challenges faced by the nervous system in constructing robust, efficient, and computationally useful networks of coupled, oscillating elements. Gamma oscillations in the visual system may indeed be supported by coupled oscillators (e.g., weakly coupled interneurons), and if so, the visual system must overcome or utilize some of the same issues I have encountered during this project. There have been advantages to physically implementing this analog circuit over programming a computer simulation. In addition to my gain in familiarity with circuit techniques, in addition to the circuit's practically *instantaneous* computation of derivatives and integrals, I struggled with the fact that the physical circuit components were non-ideal and

heterogeneous. This meant the network, to be functional, had to be rather robust to physical environmental variations (e.g., temperature) and to dissimilarities between the units (neurons).

Searching the enormous parameter space of this network, with intuition and an attempted systematic approach, made blatant the complexity and non-linearity of the final visual system model. The simpler networks (2 coupled neurons) were easily understood, and their behavior was well-predicted. In scaling up to only six neurons, the behavior of the system became rather unpredictable. I gained a sense, however, for the ways in which certain parameter changes might affect the system. For instance, poorly matched waveforms seemed to push two coupled units toward the anti-phase configuration. This makes sense, given the inherent instability of the phase-locked configuration when two neurons are not able to spike at the same frequency, or one at some integer multiple of the other's frequency (given a particular coupling strength). This observation can even be seen for the simple two-neuron case with reciprocal coupling. As the oscillation frequency increases to the point where the relative and then absolute refractory periods are approached, the in-phase configuration becomes unstable. Each neuron tries to "speed up" the action potential of the other (acceleration phenomenon), and both approach their absolute refractory periods. The in-phase configuration is no longer stable. Fig. 8c also provides information about stability. I found these simpler circuit models to be extremely valuable for this project. Recapitulating basic findings of coupled oscillator theory was an excellent confirmation of correct wiring and of my understanding of the parameters controlling the system dynamics.

In conclusion, the visual system model was able to exhibit stimulus-dependent synchronizaton across clusters as described in the electrophysiology literature. This is, perhaps, quite remarkable, and this may speak to robustness of the concept, given that I had not mathematically optimized circuit parameters prior to building to circuit. The system did not, however, work exactly as I had hoped, probably due in large part to the inhomogeneity of the network and its small size. In the real cortex, many more connections might help to offset some of the pitfalls of variable neuronal elements for this task. That is, many reciprocally connected cells may eliminate some of the undesired static attractor states into which my network was able to fall. Furthermore, the neocortex has the option of redundancy, both at the level of connections onto a single cell (if Cell A's connection with Cell B does not lock it into the appropriate oscillation, it still has connections with C through Z) and at the level of representation. There is likely some redundancy in cortical representation. If I had ten versions of the final visual system model, I might be able to run them all, accepting their flaws, and bootstrap the results to ultimately attain a much better signal-to-noise ratio.

In summary, the clear ability of this network architecture to support stimulus-dependent cross-cluster synchronization suggests this implementation might be a reasonable one to support the described electrophysiological phenomena in cortex and perhaps to more generally serve cognitive functions requiring representation binding.

References

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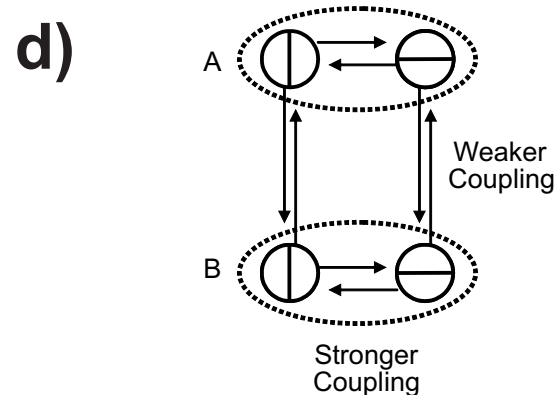
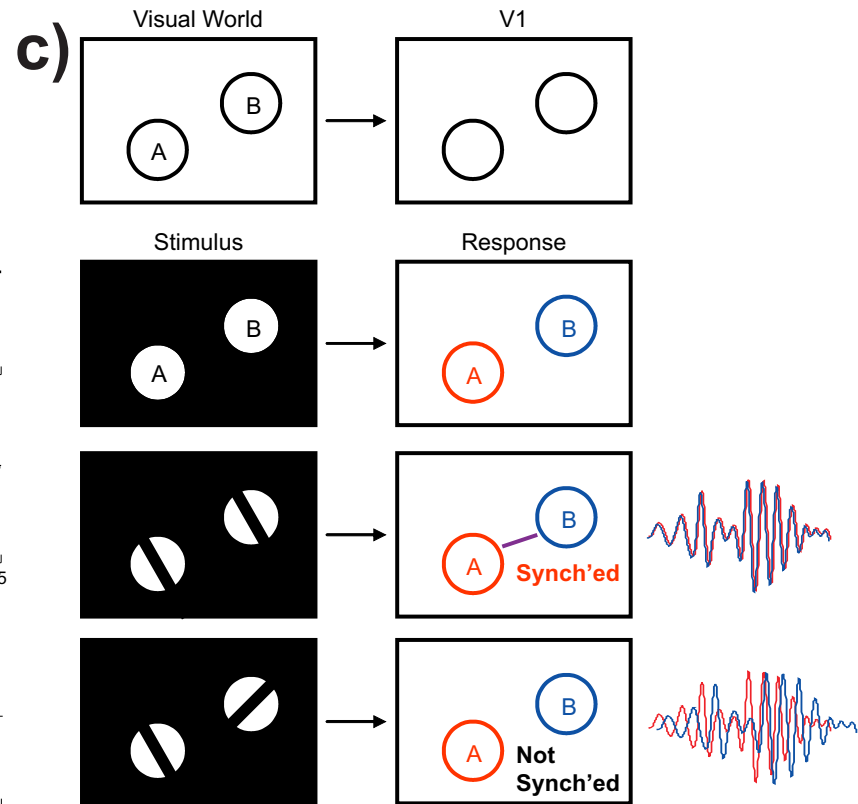
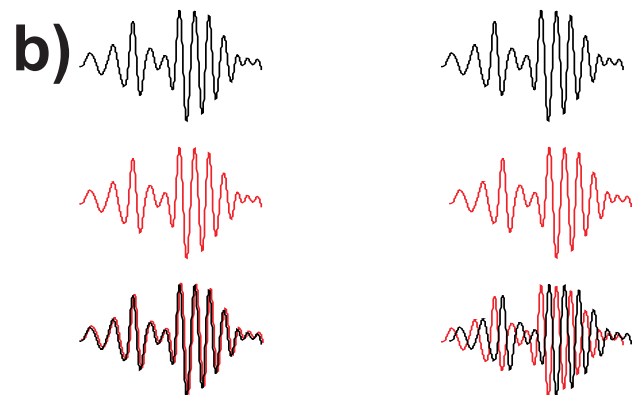
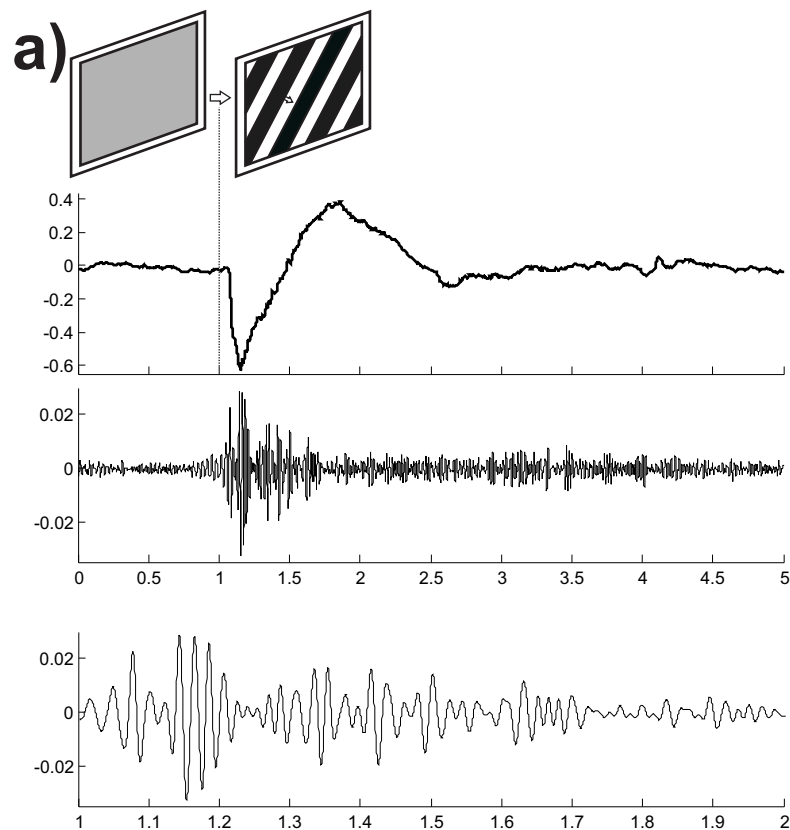


Fig. 1: Oriented stimuli produce gamma frequency responses in V1 cortex, and presenting similarly oriented stimuli to two different receptive fields synchronizes the local field potential (LFP) at spatially corresponding cortical locations. a) A transition from a gray screen to a drifting grating elicits an LFP response (top). Gamma-filtering (between 30 and 80 Hz) shows an increase in gamma power during this response (middle). (Bottom) Zoomed in on middle gamma-filtered trace. b) Two LFP oscillations can be in-phase, anti-phase or out of phase. Left column shows in-phase. Right column shows anti-phase. c) Stimulus-dependent synchronization of visual responses. Two receptive fields (RFs), A and B, see two different regions of space. Stimuli here elicit responses in corresponding cortical locations (A and B in right column). Showing these two RFs the same orientation causes synchronization of their LFP responses, while opposite orientation do not lead to LFP synch'ing. d) Grannan et al. explanatory model for phenomenon in (c). Within-cluster cells are synchronized by strong within-cluster coupling, while clusters are synchronized by weaker connections that exist only between cells tuned to the same orientation. In this way, only similar inputs to the two clusters will recruit the cross-cluster synapses, allowing cross-cluster synchrony.

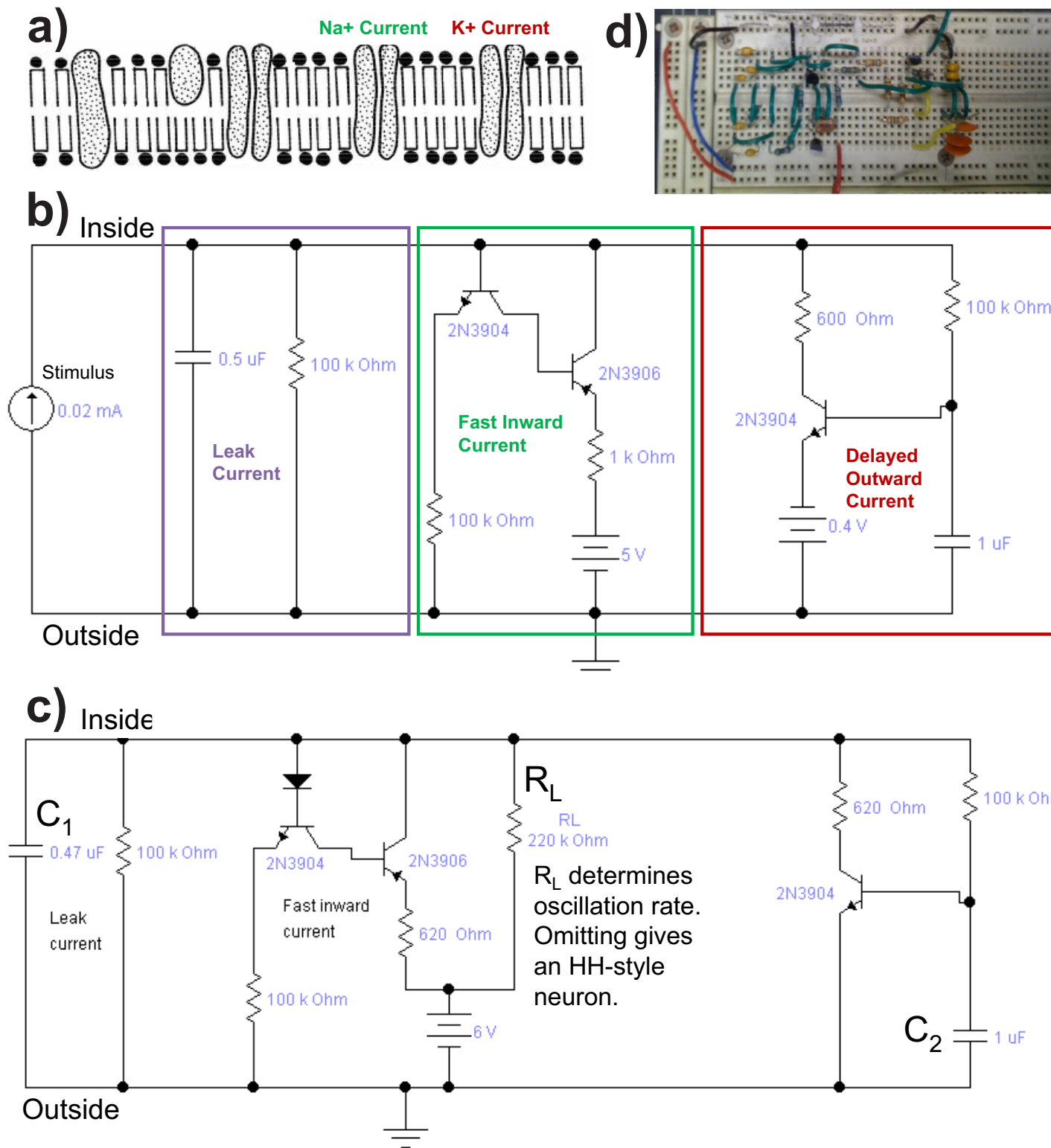


Fig. 2: Analog circuit model of a two-conductance, Fitzhugh-Nagumo-like neuron. a) Schematic of cell membrane with ion channels that allow current flow from the extracellular environment into the cell (Na⁺ current) and vice versa (K⁺ current). b) Maeda and Makino circuit model of neuron. Fast inward current corresponds to the Na⁺ current (rising phase of action potential), while delayed outward current corresponds to K⁺ current (falling phase of action potential), roughly. See text of paper for explanation of circuit operation. c) Modified version of (b) for easier construction. Delayed outward voltage source has been replaced by a diode that sets the threshold for action potential generation at just above 0 V. d) Photograph of my electronic circuit corresponding to the one neuron in (c).

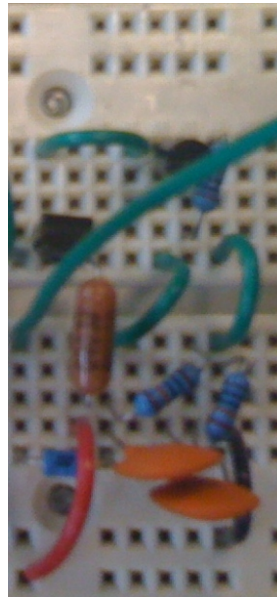
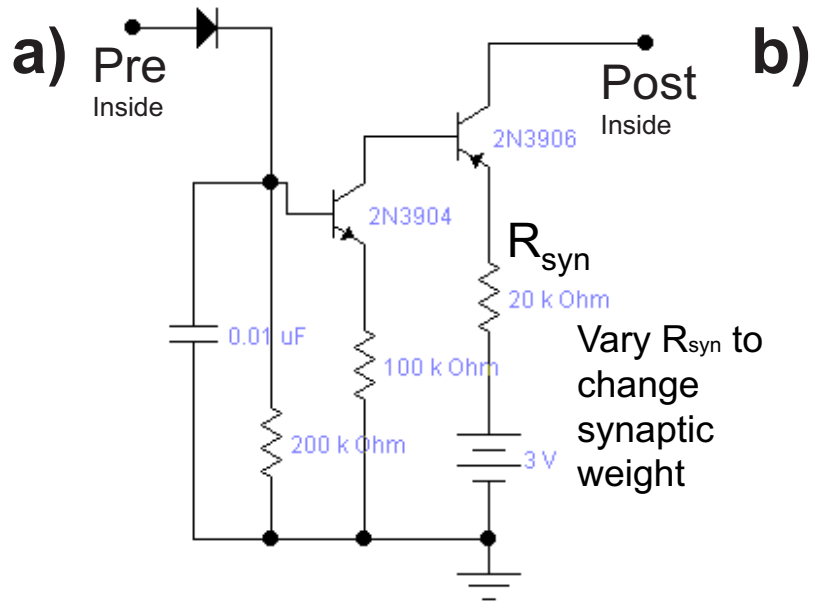
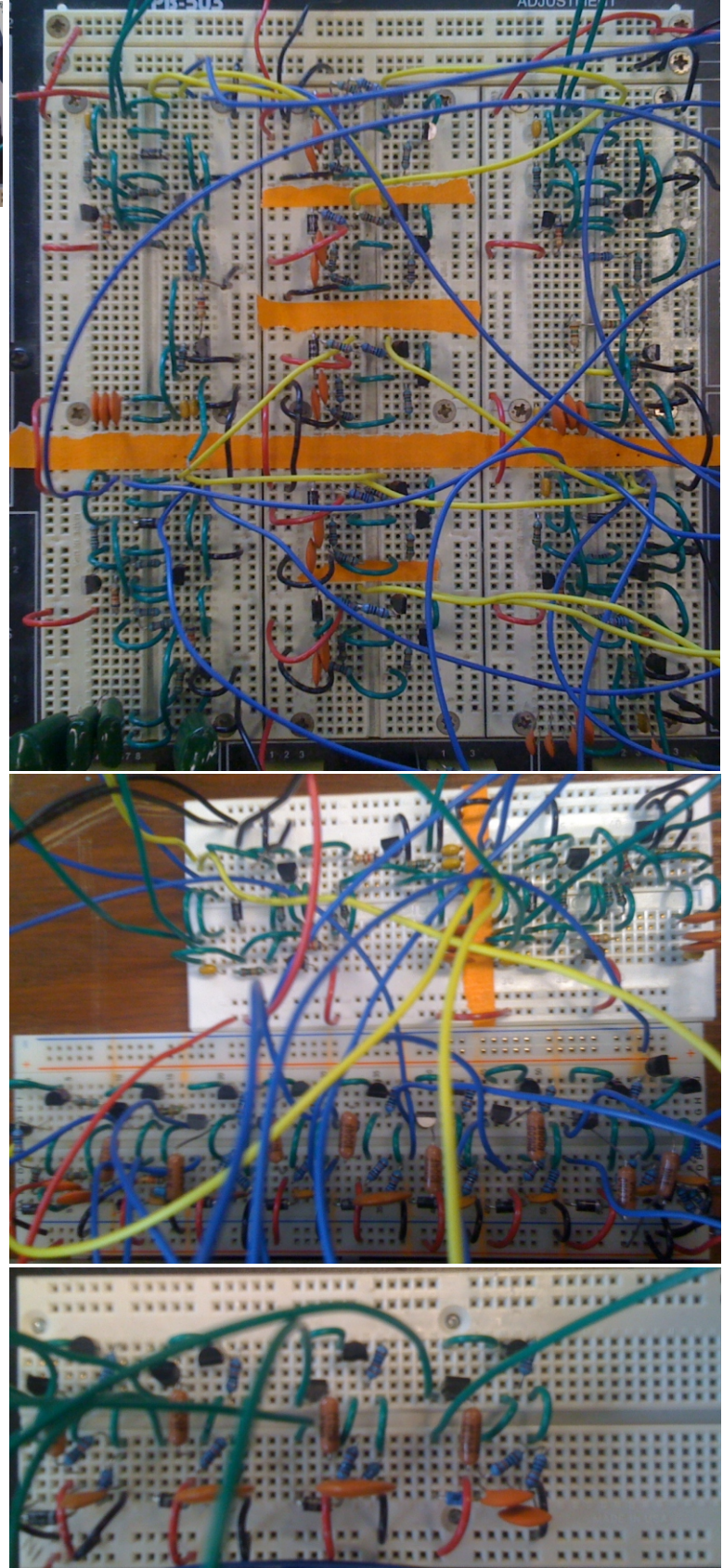
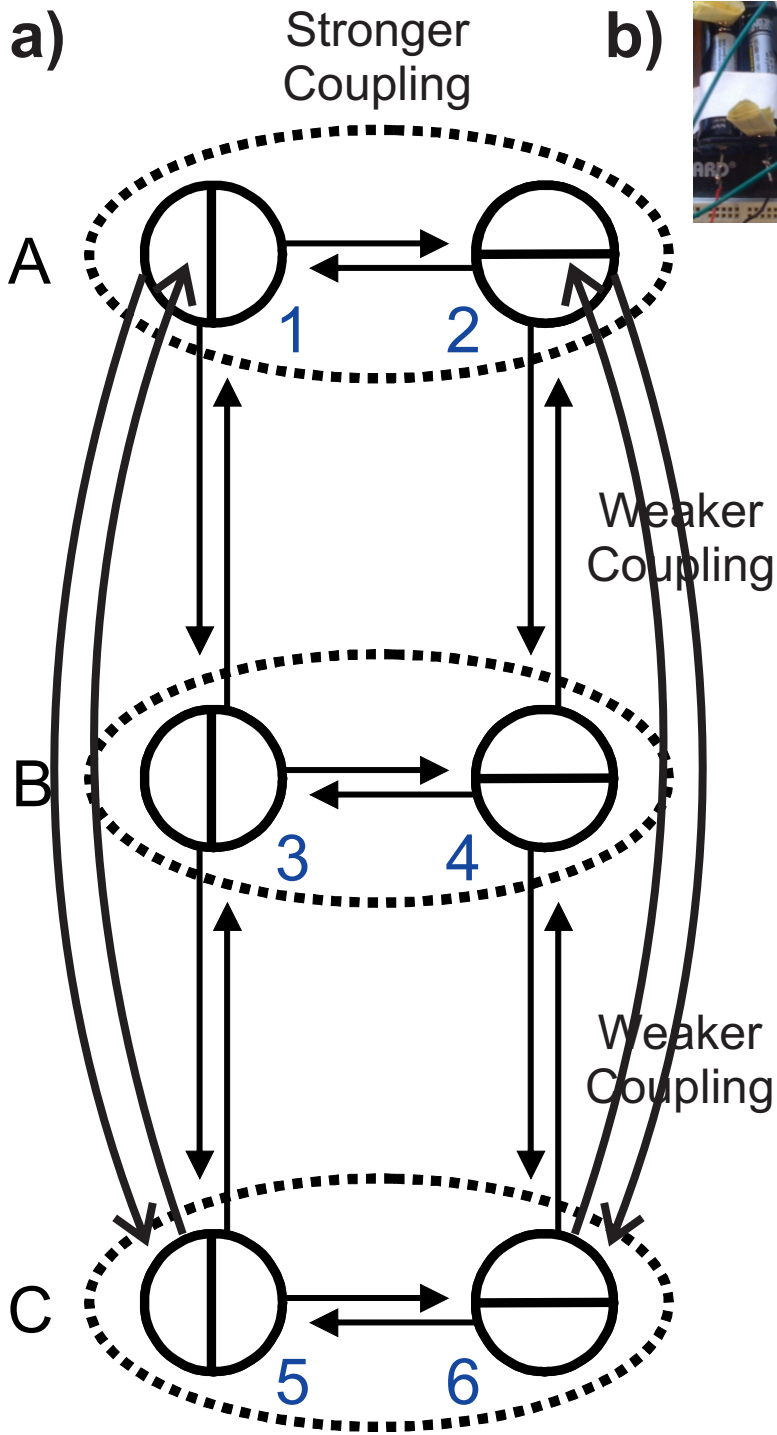
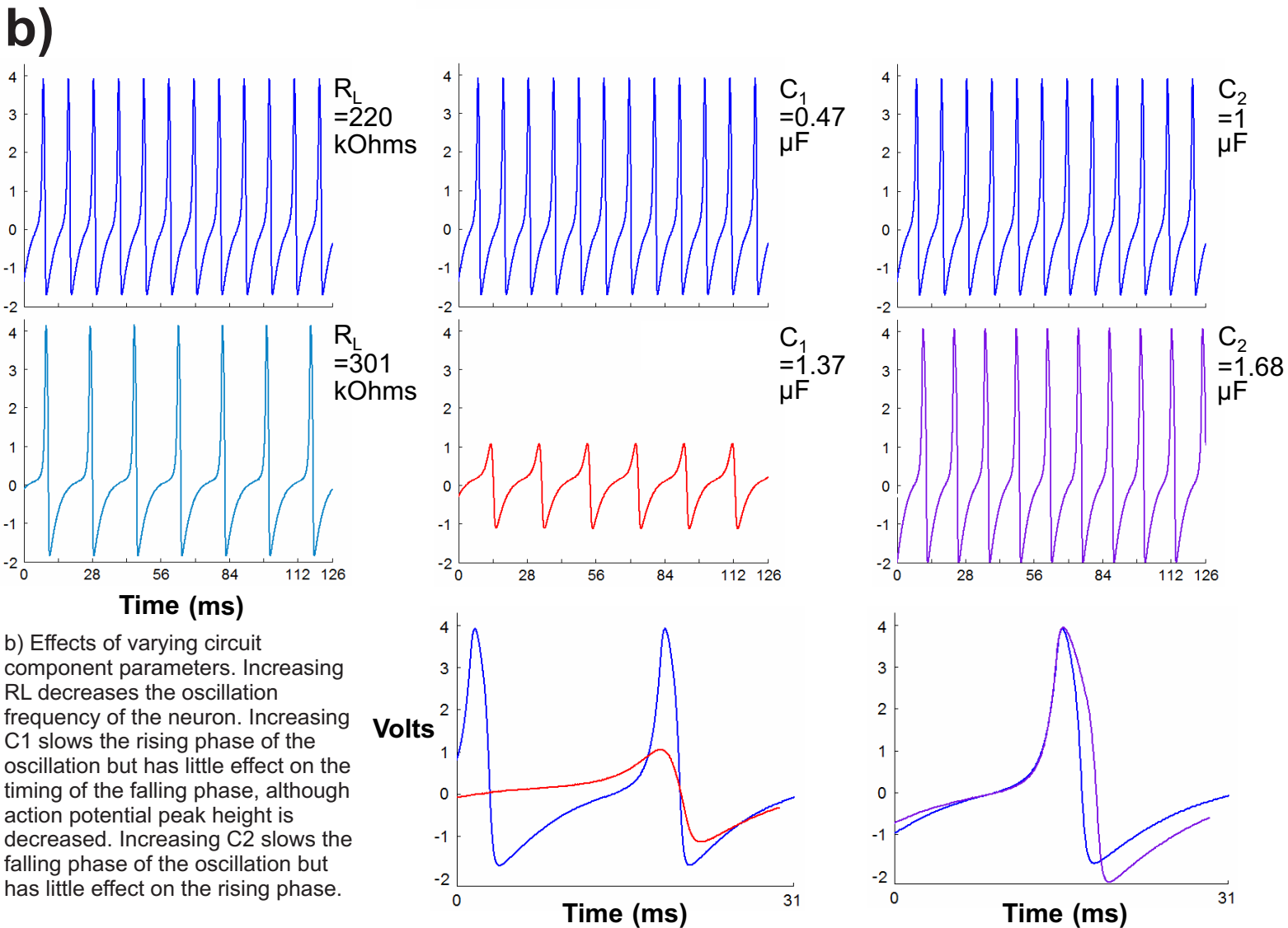
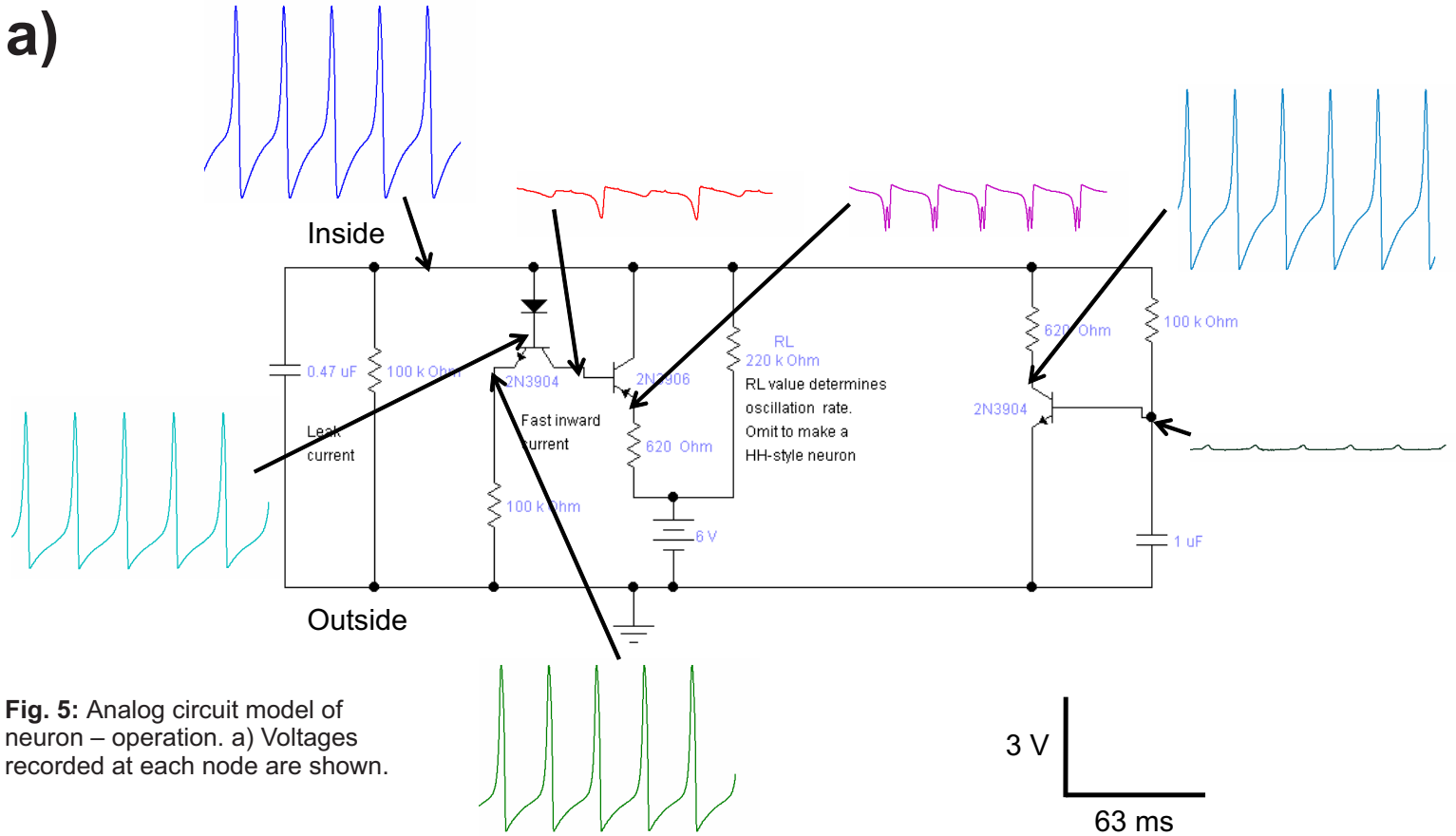


Fig. 3: Analog circuit representing an excitatory synapse. a) Schematic of synaptic motif circuit. See paper text for explanation of circuit operation. R_{syn} decides synaptic strength. Greater R_{syn} gives weaker synapse. b) Photograph of one synapse implemented as in (a).

Fig. 4: Analog circuit model of the visual system's stimulus-dependent synchronization of response. a) Schematic of my architecture. Each circle represents a neuron as in (2c); arrows represent synapses as in (3a). Dotted ovals indicate clusters. "Similarly tuned" neurons are connected to each other (that is, 1, 3 and 5 are all reciprocally connected; and 2, 4 and 6 are all reciprocally connected). Within-cluster R_{syn} is 120 kOhms. Across-cluster R_{syn} is 1000 kOhms. Neurons are numbered for ease of reference. b) Photographs of my analog circuit implementation of full model in (a).





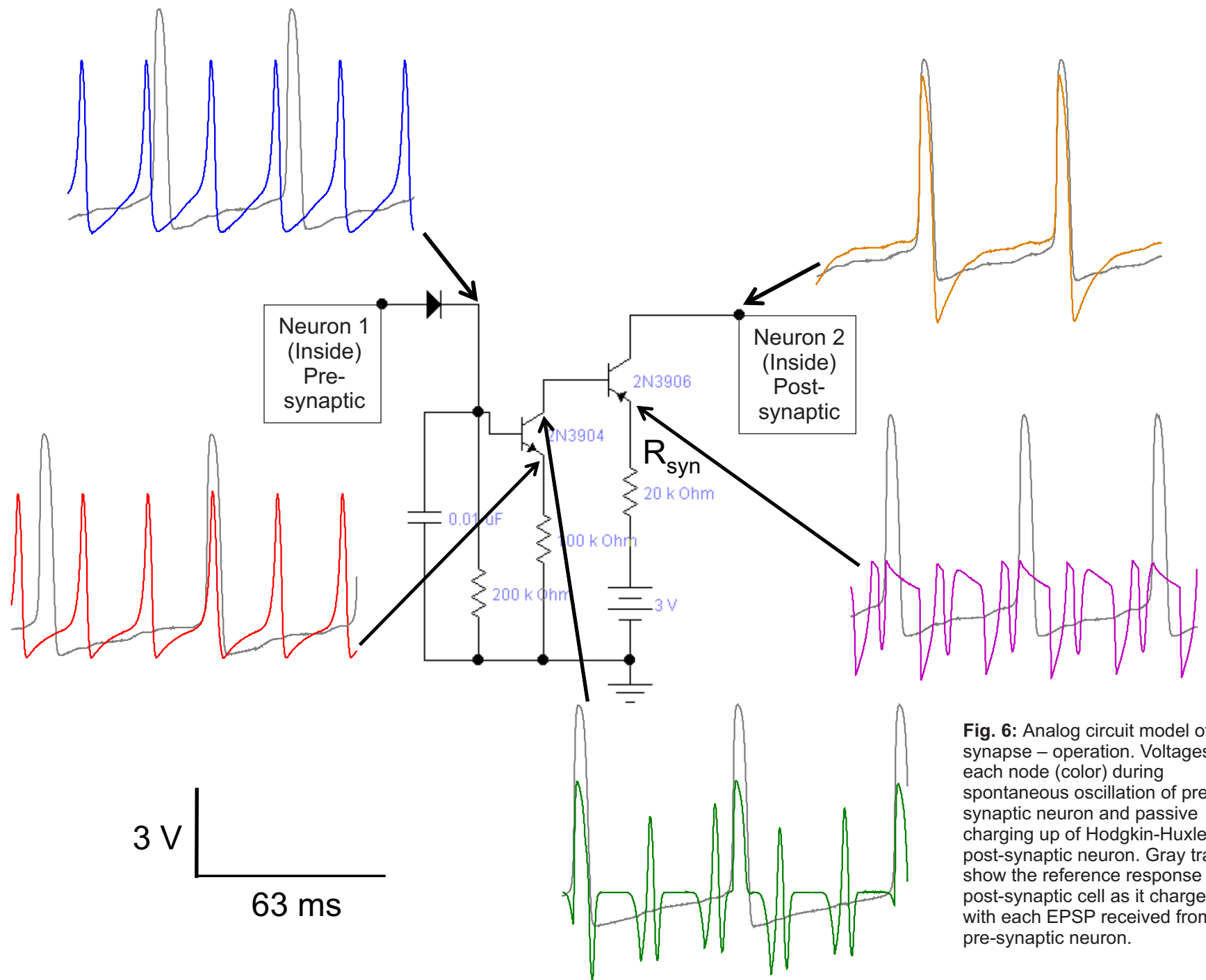


Fig. 6: Analog circuit model of synapse – operation. Voltages at each node (color) during spontaneous oscillation of pre-synaptic neuron and passive charging up of Hodgkin-Huxley-like post-synaptic neuron. Gray traces show the reference response of the post-synaptic cell as it charges up with each EPSP received from the pre-synaptic neuron.

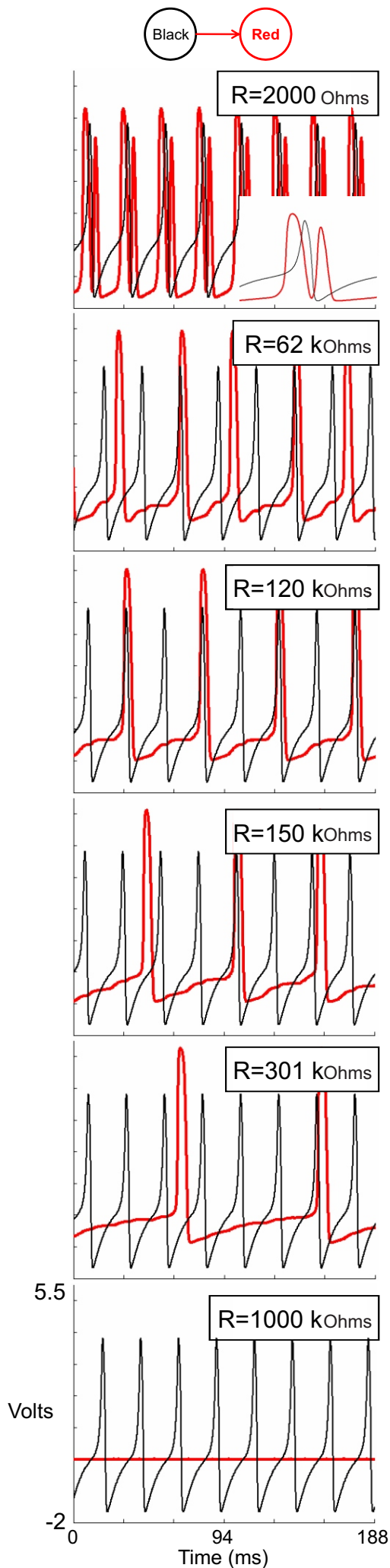


Fig. 7: Effects of varying synaptic strength of post-synaptic response. The black neuron (pre-synaptic) oscillates spontaneously ($RL > 0$), but the red neuron (post-synaptic) has $RL = 0$, so it acts like a passive Hodgkin-Huxley-like membrane, charging up until it reaches its threshold for action potential generation. Stronger synapse (smaller $R = R_{syn}$) charges up post-synaptic neuron more rapidly. At 2000 Ohms, see doublets. These doublets nicely show the absolute refractory period of the post-synaptic neuron, during which the voltage cannot remain high. 1000 kOhms does not give an obvious EPSP in the post-synaptic (red) cell, but this voltage is enough to affect action potential timing (see Figs. 11 and 12).

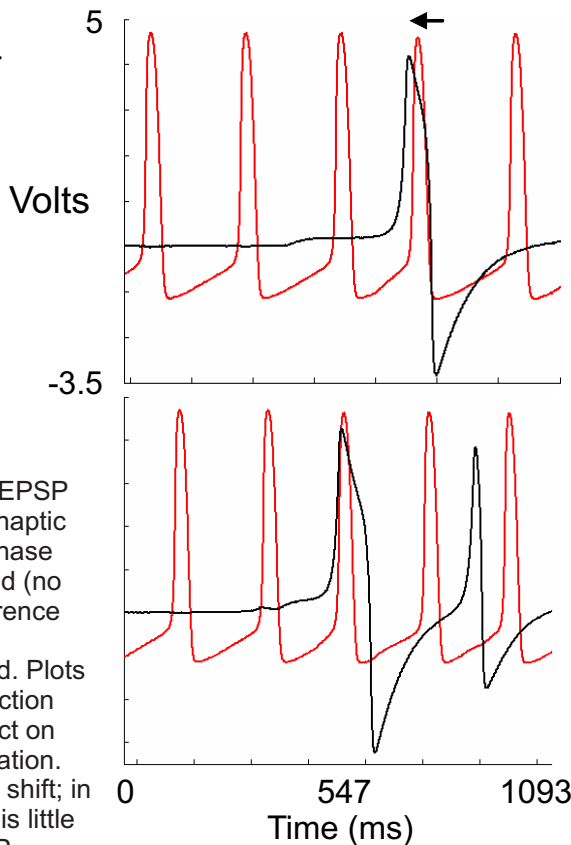
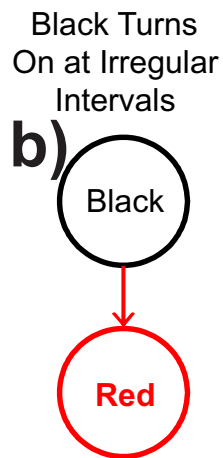
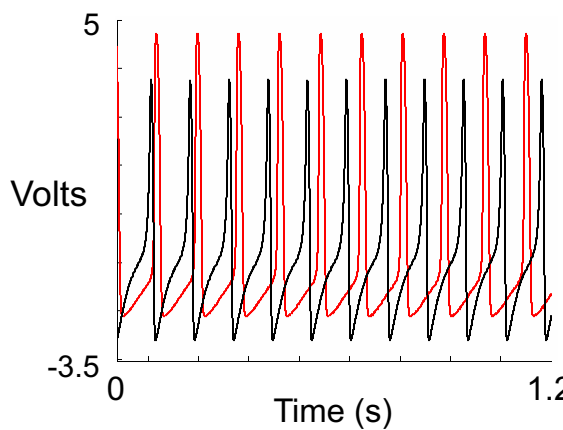
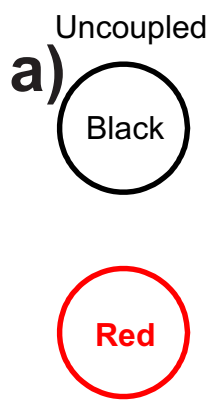


Fig. 8: Effects of EPSP timing on post-synaptic action potential phase shift. a) Uncoupled (no synapse) for reference with (b). b) Black synapses onto red. Plots show first black action potential and effect on intrinsic red oscillation. Top shows phase shift; in bottom plot there is little effect of the EPSP.

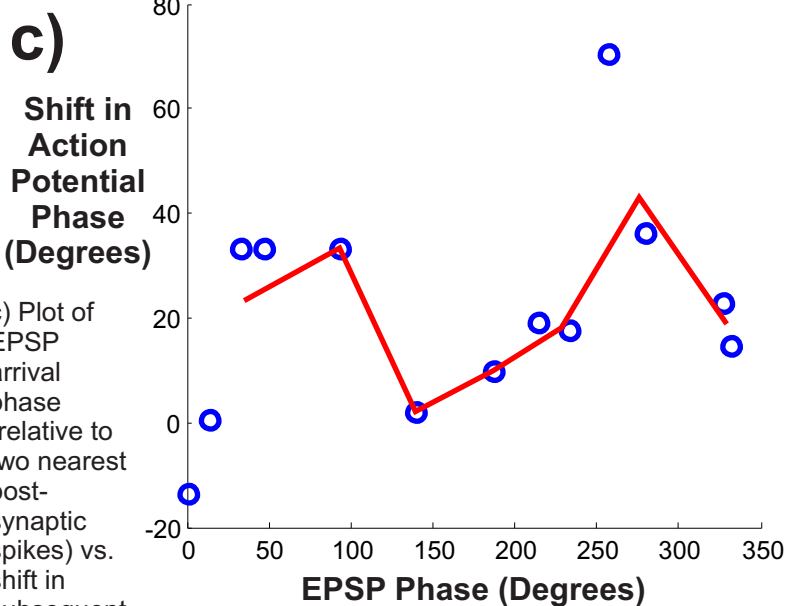
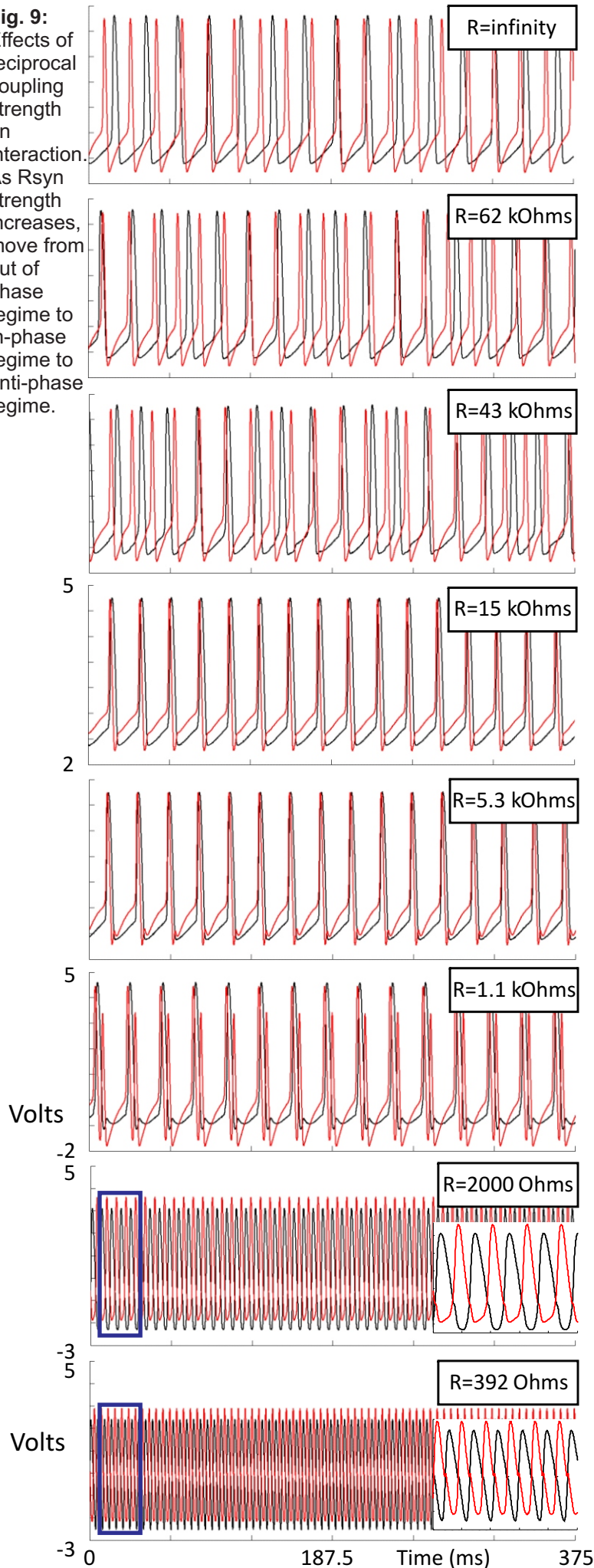


Fig. 9: Effects of reciprocal coupling strength on interaction. As R_{syn} strength increases, move from out of phase regime to in-phase regime to anti-phase regime.



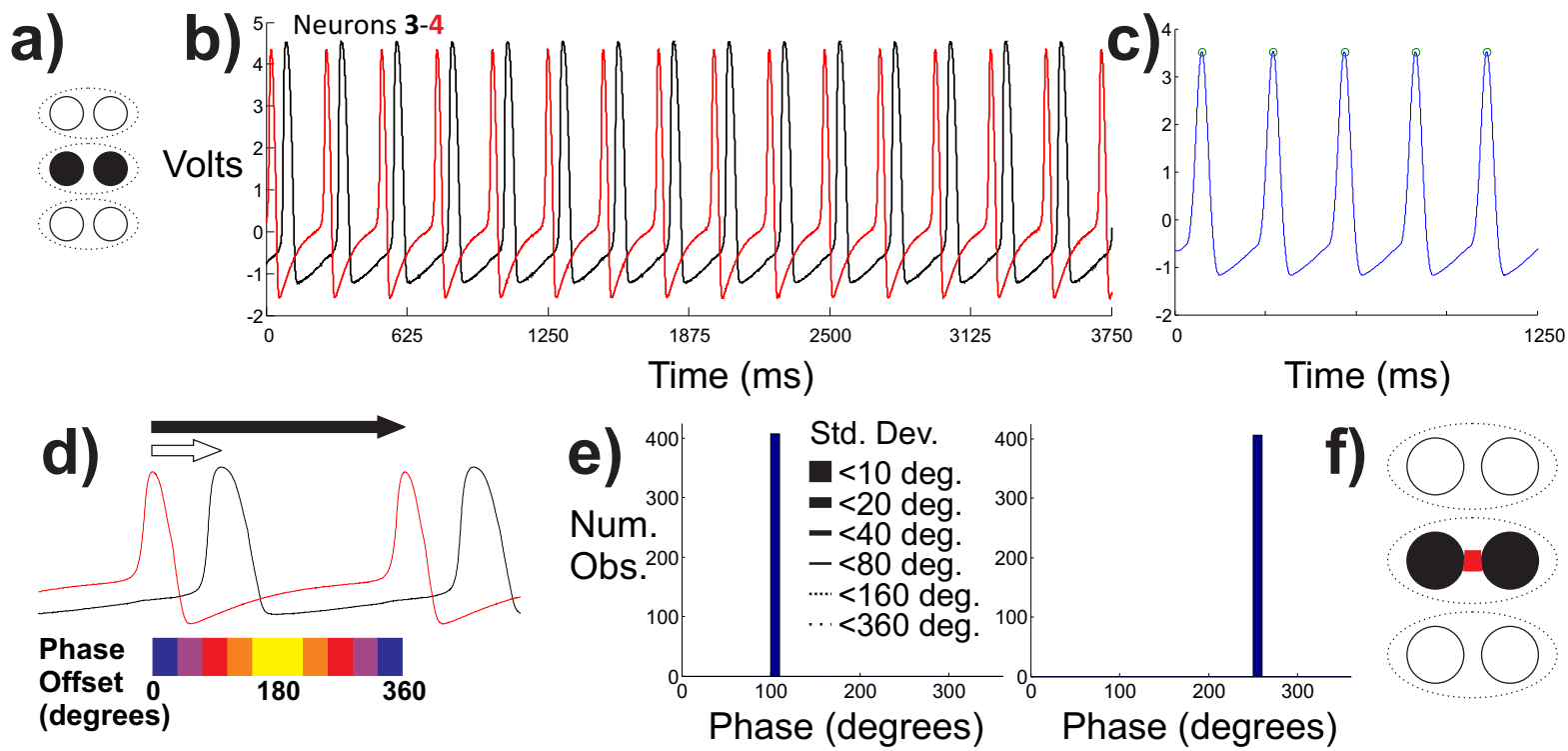


Fig. 10: Analysis methods for the results of the final circuit model of stimulus-dependent synchronization of visual responses. a) Input stimulus. Dark black circle indicates that neuron is ON. White circle indicates that neuron is OFF. Neurons 3 and 4 are ON; all others are OFF. b) Simultaneous recording from Neurons 3 (black) and 4 (red) shows that these oscillators are phase-locked, but at some phase offset. c) To analyze this phase offset, I need to automatically identify action potentials (done using Matlab, where I've defined an action potentials "time" as the time at which its peak occurs). This means that phase relationship data can be shifted by some arbitrary constant depending on when the action potential is considered to start. Blue trace is oscillating neuron. Green dots indicates points at which Matlab identified an action potential. d) How to calculate action potential phase. If we are calculating the phase of the black action potential situation between the two red spikes, we calculate the time from the first red spike to the action potential of interest, and we calculate the time between red spikes. We divide this first value by the second value and multiply the result by 360 degrees to get the phase of the black action potential. The color map below gives the convention for displaying information about phase relationships in subsequent figures. If the phase difference between two cells is less than 36 degrees, connecting line between neurons in the diagram will be blue. If the phase different between two cells is less than 72 degrees, connecting line between neurons in the diagram will be purple; and so forth. e) We can also plot the phase difference distribution for these two interacting oscillators. On the left is the black cell's phase relative to the red cell; on the right is the red cell's phase relative to the black cell. As you can see, the second phase difference is 360 degrees minus the first phase difference. Here, the cells are well phase-locked, so all observations occurred at the indicated phases. The thickness of the line connecting two neurons on the diagram gives the strength of phase-locking. As shown on the left in (e), thinner or dashed lines indicate less reliable phase-locking. f) Summary diagram of this network's activity in response to the stimulus in (a). Neurons 3 and 4 and well phase-locked (thick line) at a phase offset of about 100 degrees (red line).

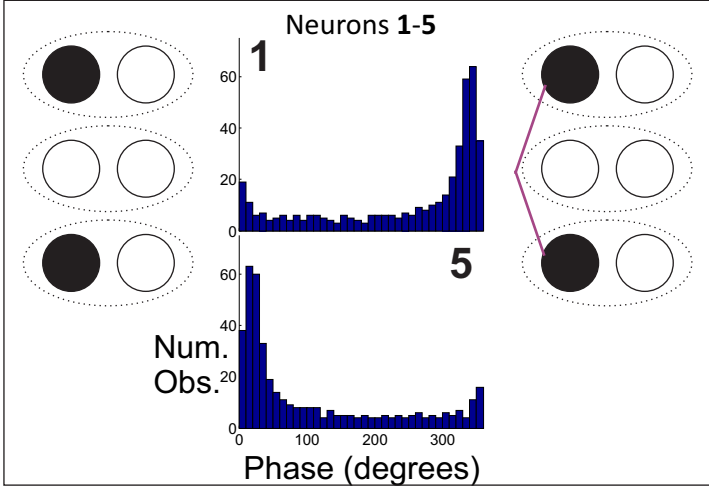
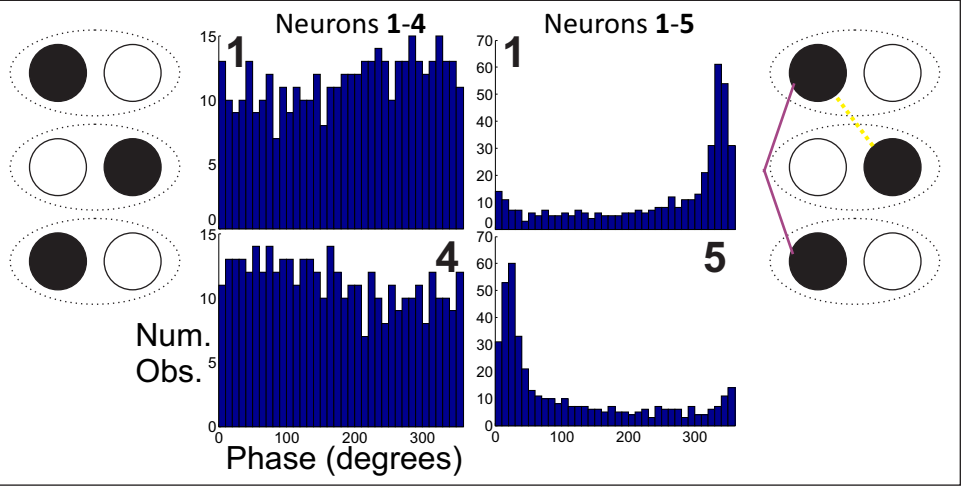
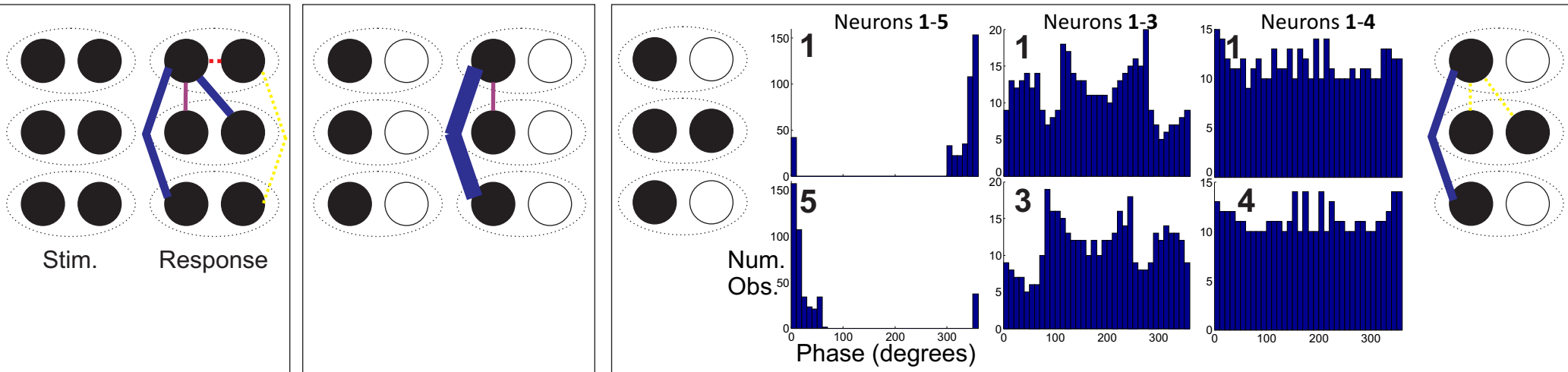


Fig. 11: Results of final circuit model of stimulus-dependent synchronization of visual responses. For each box, the left diagram shows the input to the network and the right-most circle diagram shows the output of the network, according to the conventions discussed in Fig. 10. Filled black circles indicate a neuron is responding fully. Gray circles show a neuron is responding less than the neuron in the network with the highest firing rate (black). Lines indicate phase relationship of two oscillators and strength of phase-locking (see Fig. 10 for key). For some boxes, I also show the histogram of phases for each cell, relative to the other. Each column shows a set of two cells that were simultaneously recorded. Neurons were recorded in a pairwise fashion. In-phase activity is shown by, for instance, the top right box's results for the phase relationship of Neurons 1 and 5. In this box, Neurons 1 and 4 do not have a strong phase relationship (either in phase or anti-phase).

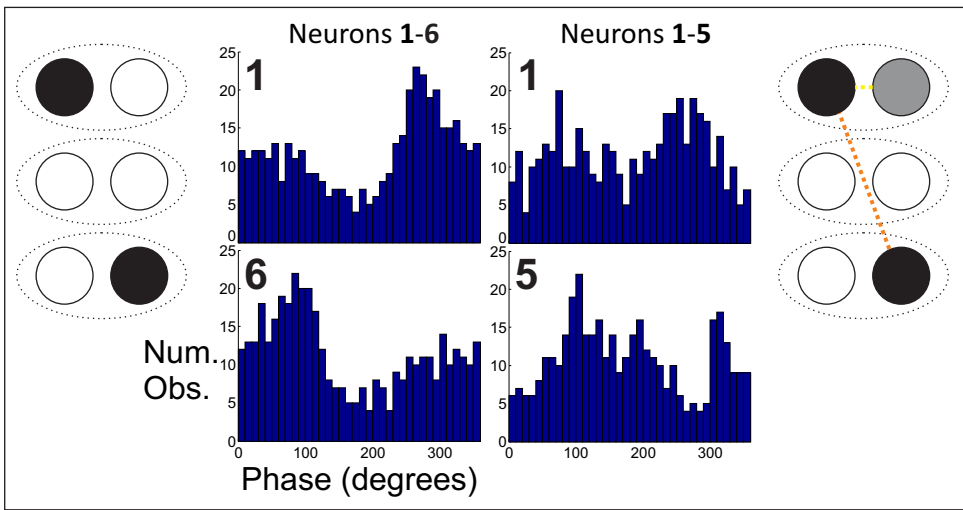


Fig. 12: Results of final circuit model of stimulus-dependent synchronization of visual responses. Same as in Fig. 11. See Figs. 10 and 11 for explanation. This model is the same as in Fig. 11, except that here the synapse from Neuron 6 to Neuron 5 is 200 kOhms rather than 120 kOhms. Other than that, networks are the same. This small change can have dramatic effects on network response. Compare bottom box on this page to leftmost upper box in Fig. 11.

