PHASE RESPONSE CURVE

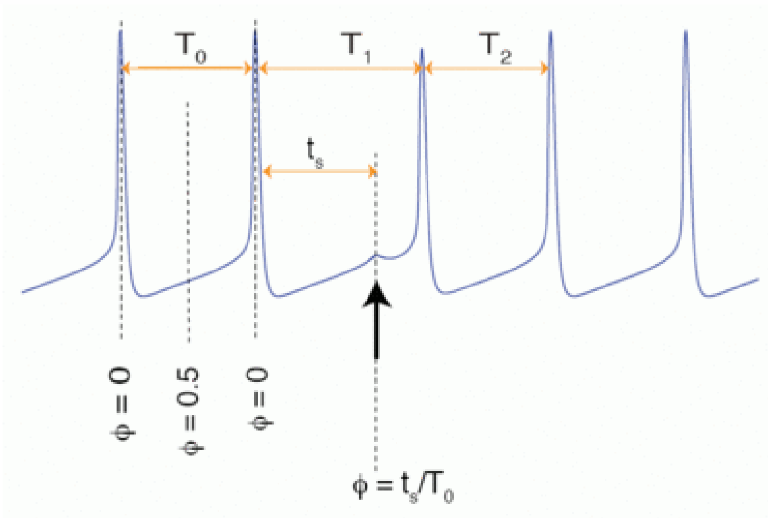

Figure 1: The phase response curve is measured by delivering a precisely timed perturbation to an oscillation and measuring the effect on the cycle period.

A **phase response curve** (PRC) tabulates the transient change in the cycle period of an oscillator induced by a perturbation as a function of the phase at which it is received.

Definition and Methodology

A phase response curve (PRC), also called a **phase resetting curve**, is measured by delivering a precisely timed perturbation to an oscillation and measuring the effect on the cycle period. Examples of biological oscillations are the heartbeat, circadian rhythms, and the regular, repetitive firing observed in some neurons in the absence of noise. The unperturbed, free-running period of the oscillator is T_0 . The period of the oscillation is normalized to 1 (preferred by biologists) or to 2π (preferred by mathematicians), and mapped onto a circle (Winfree, 1980). The former convention will be used here. Thus every point on the oscillation can be uniquely described with a phase ($0 \leq \phi < 1$). An arbitrary reference point is chosen to have a phase of 0 and the point with phase ϕ is the value of the state variables (e.g., the potential, calcium, etc) at a time $t=T_0\phi$ later in the cycle. In a neuralcontext this reference point is often the peak of an action potential or the first action potential in a burst. An arbitrary perturbation is applied at a phase $\phi=t_s/T_0$, where t_s is the time elapsed since the reference phase. The cycle containing the perturbation has a length T_1 . Biologists often define the phase resetting as

$$F(\phi)=(T_1-T_0)/T_0 ,$$

whereas mathematicians usually use the opposite sign convention

$$\Delta\phi=(T_0-T_1)/T_0\ .$$

The latter convention will be used here. If the period is shortened, the trajectory is assumed to have been displaced in the direction of motion, causing an increment in the phase called an **phase advance**. On the other hand, if the period is lengthened, the trajectory is assumed to have been displaced in a direction opposite to the direction of motion causing a decrement in phase called a **phase delay**.

The type of perturbation used to generate the phase resetting curve depends upon how it will be used. Commonly used perturbations approximate either an infinitesimally small (in duration and amplitude) input or an input that the oscillator might receive in a particular system under study. Neural oscillators are usually perturbed by a change in a synaptic conductance, but for weak perturbations this perturbation is sometimes approximated by a current.

The theory of weakly coupled neural oscillators (Ermentrout and Kopell, 1990) requires the **infinitesimal PRC** (iPRC), which is mathematically equivalent to the partial derivative of phase with respect to voltage ($\partial\phi/\partial V$), since generally only perturbations in voltage are considered, and for weak coupling a perturbation in current can be assumed to be equivalent to a perturbation in voltage. Here phase in the neighborhood of the limit cycle oscillation is typically defined in the sense of isochrons. In the theory of weakly coupled oscillators, small perturbations are assumed to sum linearly, thus the phase resetting experienced by a coupled oscillator is obtained by convolving the input waveform (usually a synaptic conductance) with the iPRC.

The assumption of a strongly attracting limit cycle allows perturbations in amplitude to be ignored. Only perturbations in phase are considered, reducing the oscillator to a single dimension. In the case of a model neuron, the iPRC can be computed by XPPAUT using the adjoint method instead of using perturbations.

Another approach is to use a spike or a burst as the perturbation that drives the synaptic conductance and approximates the input that will be received in a network. A PRC generated in this manner can be used to predict the activity exhibited by a network of pulse-coupled oscillators without an assumption of weak coupling (Oprisan et al. 2004, Goel and Ermentrout, 2002). PRCs generated using an action potential to drive the change in postsynaptic conductance are often called **spike time response curves**.

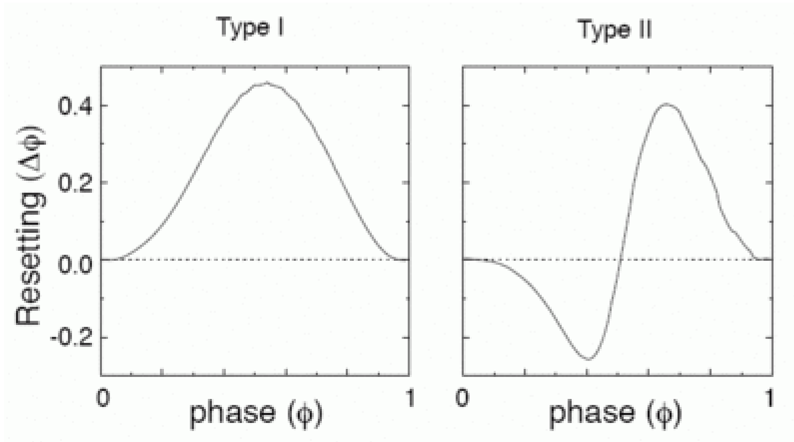

Figure 2: Two types of PRCs based on bifurcation structure.

Classification of PRCs by Bifurcation Structure

Hansel et al. (1995) identified two types of neural phase resetting curves:

- in Type I, the phase is only advanced by a small depolarization produced by excitatory postsynaptic potentials, whereas
- in Type II either an advance or delay could be produced depending upon the timing of the perturbation.

A small hyperpolarization similarly produces only delays in Type I PRCs but can produce either an advance or delay in Type II. Ermentrout (1996) showed that for the infinitesimal PRC this classification of phase response curves is closely related to the classification of excitable membranes(Hodgkin, 1948). Excitable membranes can undergo a transition from quiescence to repetitive firing of action potentials in two ways as the applied depolarizing currents is increased.

- Type I excitable membranes can fire arbitrarily slowly near the onset of firing.
- Type II excitable membranes have an abrupt onset of repetitive firing at a threshold frequency, and cannot be induced to fire at any frequency below the threshold frequency.

Type I membrane excitability is exhibited by models near a saddle-node on invariant circle bifurcation, and Type II near a Andronov-Hopf bifurcation (Rinzel and Ermentrout, 1989). Ermentrout's conclusion was that Type I resetting is associated with Type I excitability and Type II resetting with Type II excitability. Since an abrupt onset of firing may also be observed in the case of a saddle-node bifurcation away from the limit cycle (Izhikevich 2007), it may be more accurate to say that Type I resetting is associated with an integrator and Type II with a resonator.

Classification of PRCs by Winding Number

The classification scheme described above assumes weak perturbations, but the following scheme classifies PRCs based on whether the perturbation is strong or weak. The classification assumes topological equivalence of the limit cycle to the radial isochron clock (Glass and Winfree, 1984; Glass and Mackey, 1988). The radial isochron clock has been proposed as a simplified model for the circadian rhythm and for neural and cardiac oscillators. One form of the radial isochron clock is the topological normal form for any system near an Andronov-Hopf bifurcation.

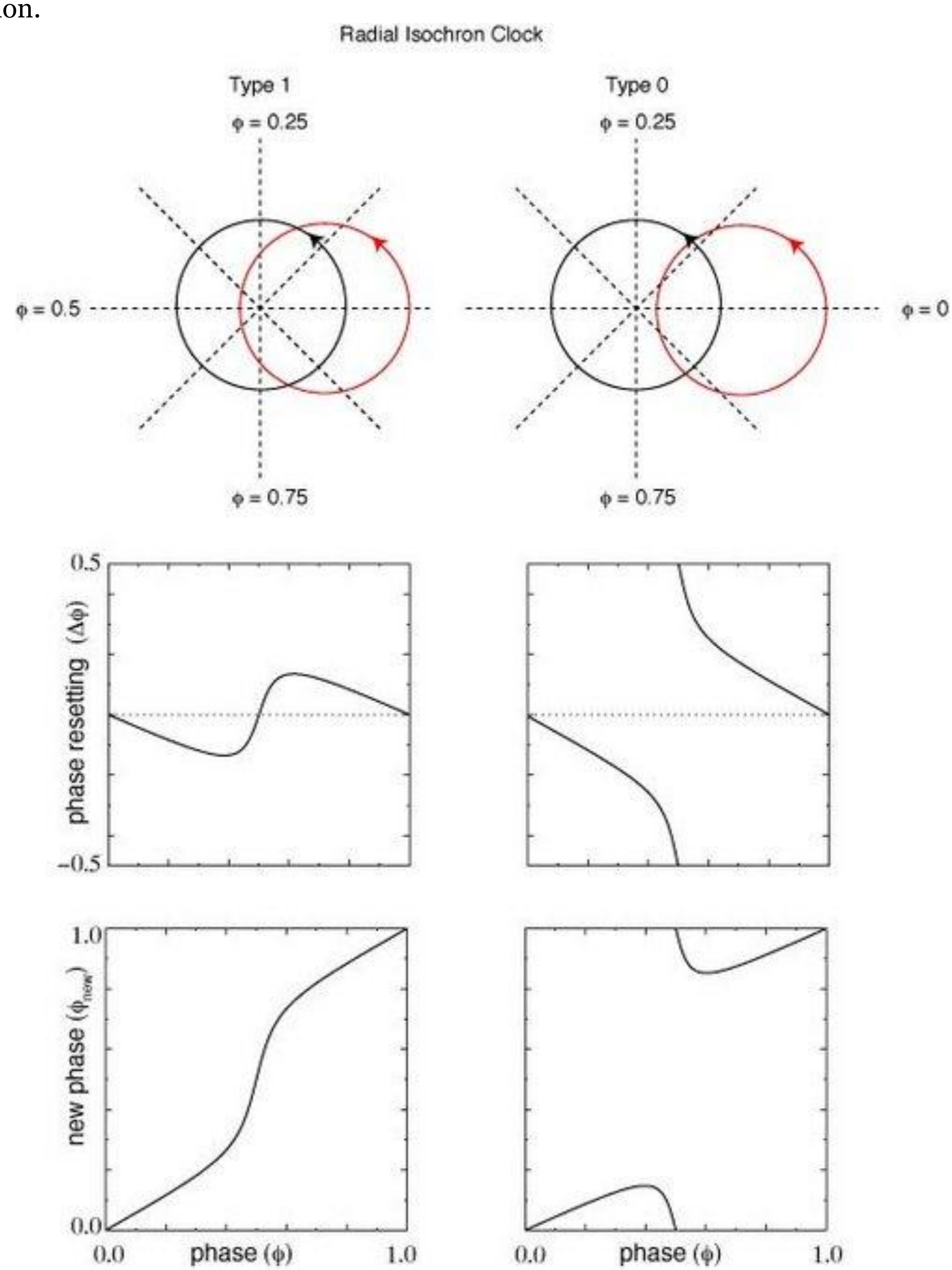

Figure 3: Two types of PRCs based on winding number. Top: Shifted limit cycles relative to the isochrons of the original limit cycle. Middle: Phase Response Curves. Bottom: Phase Transition Curves.

The winding number classification is based on the assumption that during a sufficiently strong perturbation, a distinct, shifted limit cycle is traversed. At the end of the perturbation, phase resetting is assumed to occur via the relaxation of the trajectory along theisochrons, or lines of constant phase, of the original limit cycle. For relatively weak perturbations, the shifted limit cycle still contains the fixed point at which all isochrons terminate. In the absence of a threshold phenomenon, the PRC will be continuous. The **phase transition curve** (PTC) tabulates the new phase (ϕ_{new}) after a perturbation as a function of the old phase (ϕ) before the perturbation.

$$\phi_{new}=\phi+\Delta\phi\ .$$

In this case the PTC will also be continuous because the shifted limit cycle crosses isochrons leading to every possible new phase. On the other hand, for a sufficiently strong perturbation, the shifted limit cycle will no longer include the fixed point, thus it will not cross all the isochrons. The PRC will be discontinuous because a point on the shifted limit cycle just before 0.5 relaxes to a phase slightly greater than 0 causing a large delay whereas a point just after a phase of 0.5 on the shifted limit cycle relaxes to a phase slightly less than 1, causing a large advance. The PTC will be discontinuous because the new phases corresponding to the isochrons that are not crossed cannot be accessed from any old phase. The **winding number** is defined as the number of times that the shifted limit cycle traverses a complete cycle as defined by the isochrons of the original cycle. If the shifted limit cycle contains the singularity at the center of the original limit cycle, then the winding number is 1 (Type 1 PRC), if not, the winding number is zero (Type 0 PRC).

In the presence of a threshold phenomenon such as action potential, a discontinuity can result. In the radial isochron clock, a subthreshold cycle delays the phase by an additional period. Since the new phase is modulo the period, the new phase is the same with or without the subthreshold cycle (Glass and Winfree 1984), hence this type of discontinuous PRC does not produce a discontinuous PTC.

Advanced PRC Methodology

Although the bifurcation structures represented by Type I and II PRCs are most applicable to models of spiking neurons, other bifurcation structures are possible (supercritical Andronov-Hopf, homoclinic) and have their own characteristic PRCs (Brown et al, 2004). In addition to bifurcation structure, oscillators can also be classified by whether the time scales of the state variables are comparable or much different. A relaxation oscillator contains one variable that is significantly slower than any other.

For infinitesimal perturbations, the iPRC depends only on the reciprocal of the derivative of the slow variable at a given phase (Izhikevich, 2000). A comparably simple expression can only be derived for the iPRC for an oscillator that acts like an integrator with Type I phase resetting; the iPRC depends only on the reciprocal of the derivative of membrane potential at a given phase (Hansel et al. 1995). Since the membrane potential is almost always increasing, each point on a type I iPRC has the same sign.

The assumption of weak coupling may not apply in many biological situations; for example, bursting neurons that participate in central pattern generation appear to receive strong inputs that cannot be decomposed into trains of infinitesimal pulses that sum linearly. Large deviations from the limit cycle may cause the resetting to occur in a direction that is normal rather than tangential to the limit cycle. For example, the resetting in one such bursting neuron could be explained by assuming that an inhibition induced switches from the depolarized branch to the hyperpolarized branch of a relaxation oscillator (Oprisan et al,2003)

The large nonlinear deviations from the limit cycle caused by strong coupling may persist into at least one cycle beyond the one containing the perturbation (Guevara et al, 1986). A second order resetting term can be defined as

$$(T_2 - T_0)/T_0 ,$$

where T_2 is the length of the cycle after the cycle T_1 containing the perturbation. This term can also become important in coupled bursting oscillators (Oprisan et al, 2004), for example.

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