The Effects of Voltage-Gated Gap Junctions on Phase-Locking in Neuronal Networks

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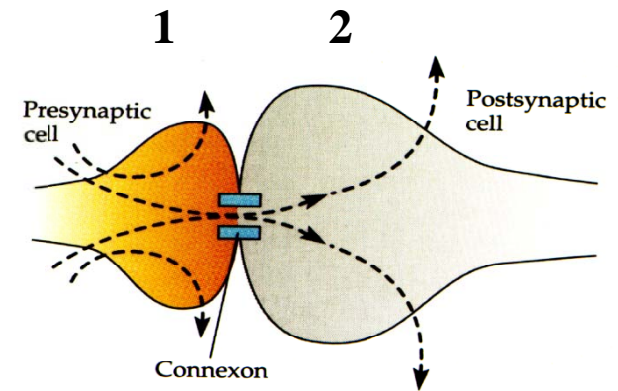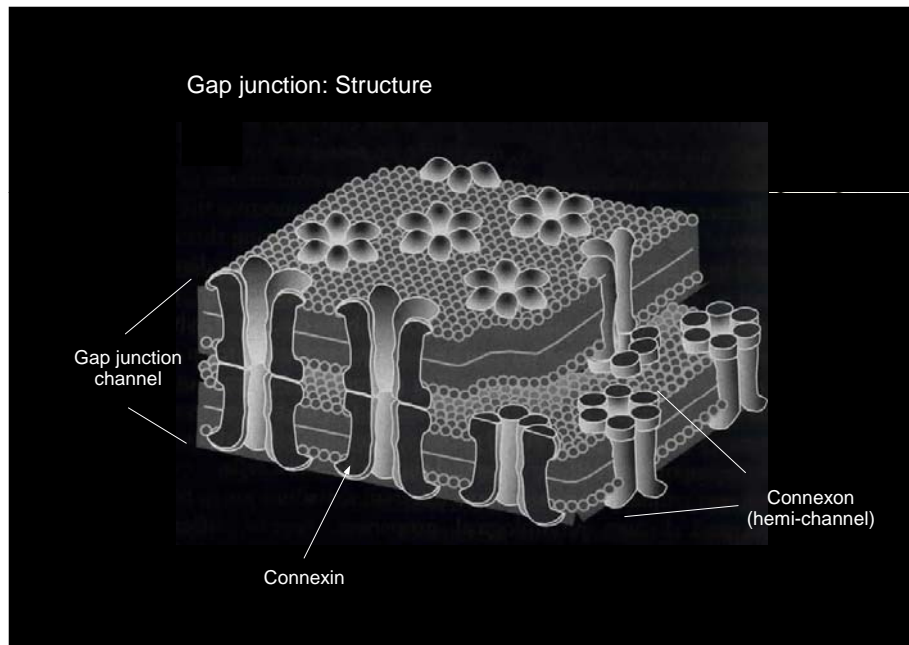University of California, Davis

with

Donald French

Department of Mathematics,
University of Cincinnati

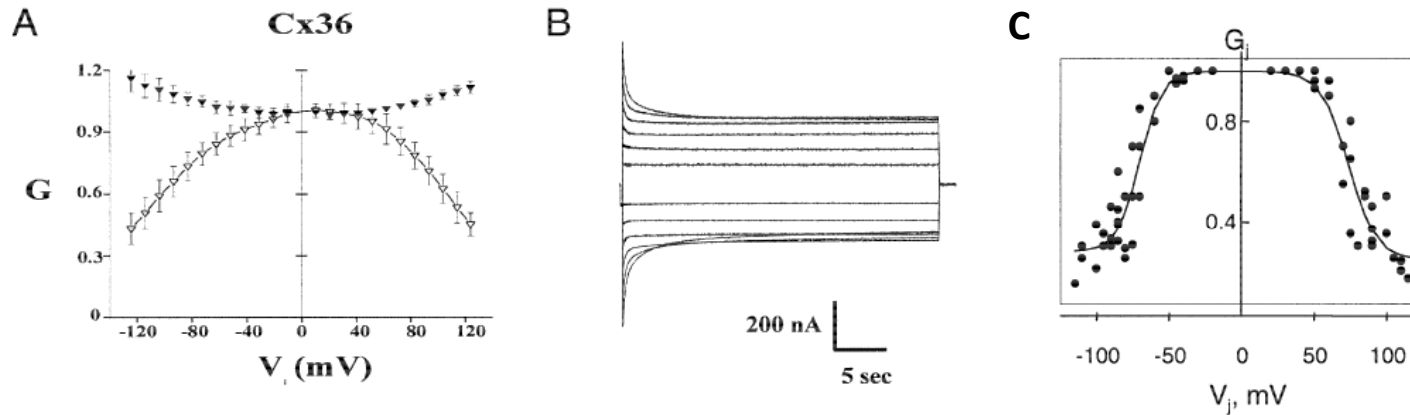**CNS*2010 Workshop: Phase Locking in the Presence of Biological Noise**

gap junction/electrical synapse/electrical coupling

Gap junction: Structure

Gap junction channel

Connexin

Connexon (hemi-channel)

1   **2**

Presynaptic cell

Postsynaptic cell

Connexon

$$I_{coup,12} = g_c \left(V_1 - V_2 \right)$$

~ 20 different connexins

VOLTAGE-GATING OF GAP JUNCTIONS

From **Teubner et al (2000)** J. Membrane. Biol. 176: 249-262: Voltage gating of (homotypic) **Cx36** gap junctions expressed in *Xenopus Oocytes* (A,B) and transfected HeLa cells (C). **(A,C)** initial and steady state normalized gap junction conductance (filled and open symbols respectively) as a function of transjunctional potential V_j. **(B)** Representative junctional current for voltage clamp steps up to +120mV in 20mV increments.

$$I_{coup,12} = g_c \left(V_1 - V_2 \right)$$

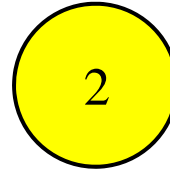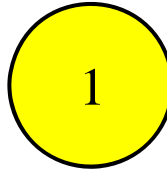voltage- (and time-) dependent

goal:

Explore the effects of gap junction voltage-gating on phase-locking in networks of coupled cells.

Model: Pairs of oscillating spiking cells.
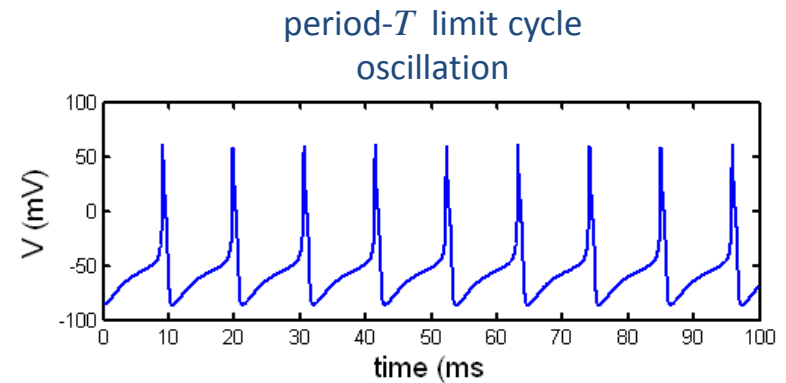**Technique:** Theory of weak coupled oscillators.
Conditions: A. no voltage-gating
      B. fast voltage-gating
      C. slow voltage-gating

MODEL

intrinsic dynamics:

conductance-based HH model
e.g. fast-spiking (FS) interneuron model
(Erisir et al 1999; Mancilla et al 2007) .
Oscillatory for $I_1 < I < I_2$; I controls
the T-period of the oscillations

period-T limit cycle oscillation

$$C \frac{dV_j}{dt} = -I_{ion}(V_j, w_j) + I$$

$$\tau_w \frac{dw_j}{dt} = w_\infty(V_j) - w_j$$

$$V_j(t) = V_0(t + \theta_j)$$

relative phase

$$j, k = 1, 2; \quad j \neq k$$

MODEL

intrinsic dynamics:

conductance-based HH model
e.g. fast-spiking (FS) interneuron model
(Erisir et al 1999; Mancilla et al 2007) .
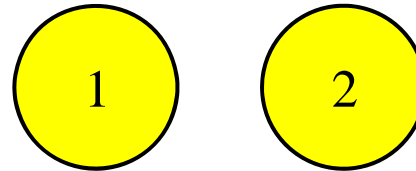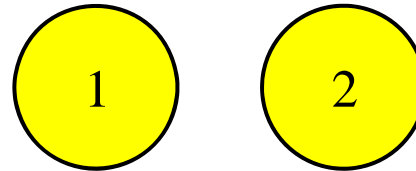Oscillatory for $I_1 < I < I_2$; I controls
the T-period of the oscillations

heterogeneity

("weak")

$$C\frac{dV_j}{dt} = -I_{ion}(V_j, w_j) + I + (-1)^j \frac{\Delta I}{2}$$

$$\tau_w \frac{dw_j}{dt} = w_\infty(V_j) - w_j$$

$$j, k = 1, 2; \quad j \neq k$$

MODEL

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Oscillatory for $I_1<I<I_2$; I controls
the T-period of the oscillations

noise
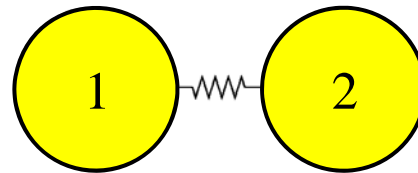
("weak")

$$C\frac{dV_j}{dt} = -I_{ion}\left(V_j, w_j\right) + I + \sigma\eta_j(t)$$

$$\tau_w\frac{dw_j}{dt} = w_\infty\left(V_j\right) - w_j$$

$$j,k = 1,2; \;\; j \neq k$$

MODEL

intrinsic dynamics:

conductance-based HH model
e.g. fast-spiking (FS) interneuron model
(Erisir et al 1999; Mancilla et al 2007) .
Oscillatory for $I_1 < I < I_2$; I controls
the T-period of the oscillations

heterogeneity
("weak")

coupling current
("weak")

$$C \frac{dV_j}{dt} = -I_{ion}(V_j, w_j) + I + (-1)^j \frac{\Delta I}{2} + \overline{g}_c s (V_k - V_j)$$

$$\tau_w \frac{dw_j}{dt} = w_\infty (V_j) - w_j$$
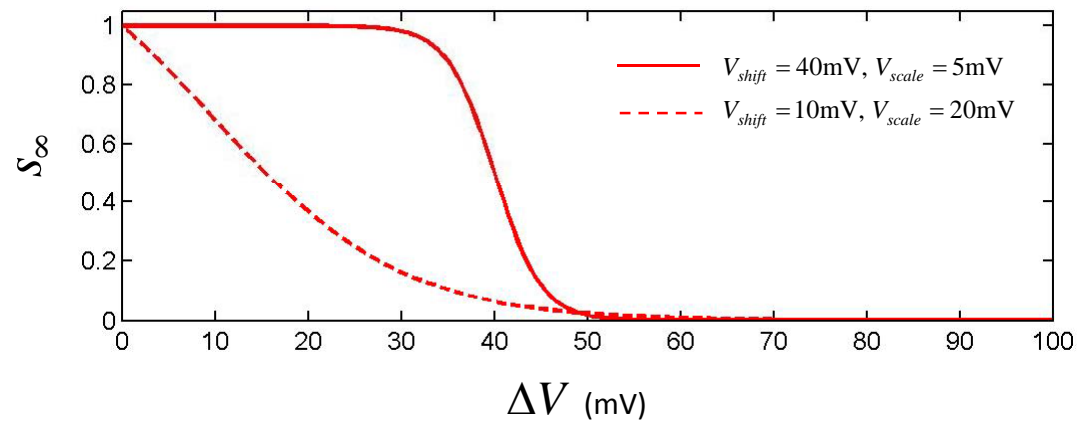
$$j, k = 1, 2; \quad j \neq k$$

MODEL

Electrical coupling voltage-gating dynamics:

$$\tau_s \frac{ds}{dt} = s_\infty (V_k - V_j) - s$$

$$s_\infty(\Delta V) = \left(1 - \tanh\left(\frac{|\Delta V| - V_{shift}}{V_{scale}} \right) \right) s_{scale}$$
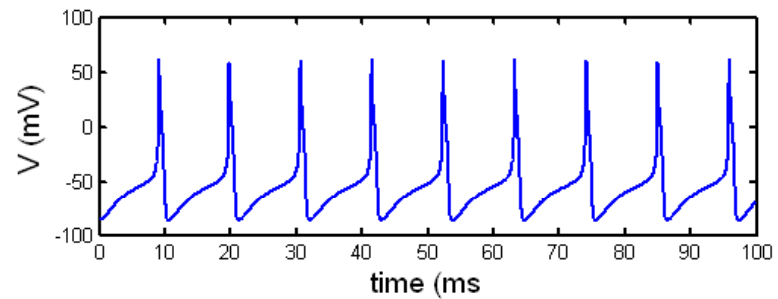
*scaled to set $s_\infty(0)=1$

THEORY OF WEAK COUPLING

general: Malkin; Neu; Kuramoto; Ermentrout & Kopell; Hansel et al, …, **Schwemmer & Lewis**
electrical coupling: Lewis & Rinzel, Mancilla et al, Pfeuty et al, …, **Lewis & Skinner**

1. Intrinsic dynamics of the neurons *dominate*:

~ period T
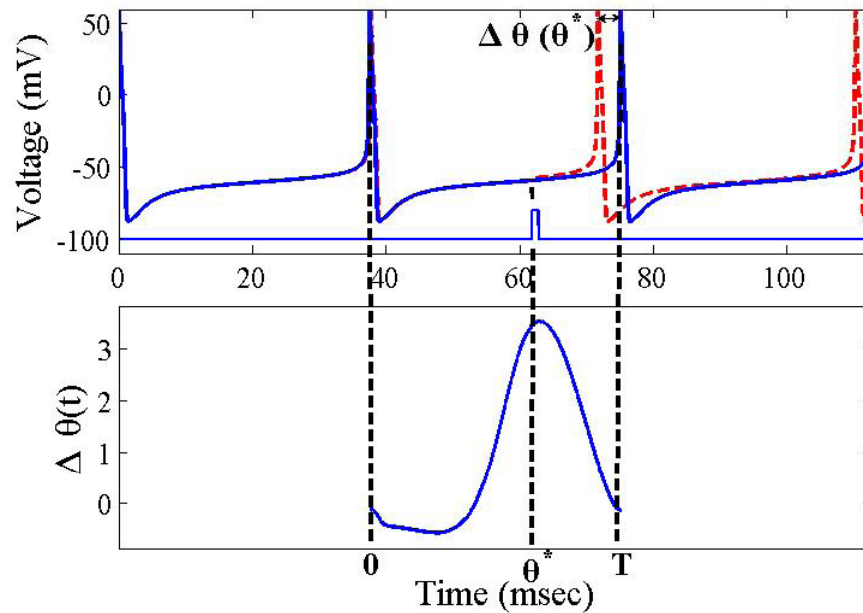**~ intrinsic limit cycle**
oscillation:

$$V_j(t) \cong V_0\big(t + \theta_j(t)\big)$$

slowly evolving relative phase

THEORY OF WEAK COUPLING

2. Response (phase-shift) of a single cell to a "small" δ-function-like current stimulus:

Infinitessimal phase resetting curve (iPRC) Z(t): the normalized phase shift $\Delta\theta_j$ of a cell in response to a small δ-*function* current stimulus of amplitude (total charge) $I_{stim}\,\Delta t$ that is delivered at phase $t+\theta_j$.

$$Z\left(t+\theta_j\right)=\frac{\Delta\theta_j}{I_{stim}\Delta t}$$

THEORY OF WEAK COUPLING

3. The effects of small continuously applied perturbations (*coupling* and *heterogeneity*) add sequentially according to the iPRC

$$Z\left(t+\theta_j\right)=\frac{\Delta\theta_j}{I_{stim}\Delta t}$$

$$\downarrow$$

$$\frac{\Delta\theta_j}{\Delta t}=Z\left(t+\theta_j\right)I_{stim}$$

$$\downarrow$$

$$\frac{d\theta_j}{dt}=Z\left(t+\theta_j\right)I_{stim}\left(t,\theta_j,\theta_k\right)$$

THEORY OF WEAK COUPLING

3. The effects of small continuously applied perturbations (*coupling* and *heterogeneity*) add sequentially according to the iPRC

$$\frac{d\theta_j}{dt} = Z(t+\theta_j) I_{stim}(t,\theta_j,\theta_k) \qquad \text{phase equations}$$

$$= Z(t+\theta_j)\left[\overline{g}_c\, s\left(V_0(t+\theta_k)-V_0(t+\theta_j)\right)+(-1)^j \frac{\Delta I}{2}\right]$$

↑ coupling current

↑ heterogeneity

$$\tau_s \frac{ds}{dt} = s_\infty\left(V_0(t+\theta_k)-V_0(t+\theta_j)\right) - s$$

$$j,k=1,2;\ \ j\neq k$$

THEORY OF WEAK COUPLING

4. Averaging over an oscillation cycle:

Average RHS of equations for the phases over period T to capture average rate of phase shift due to effect of the coupling and heterogeneity:

$$\frac{d\theta_j}{dt} = \frac{1}{T}\int_0^T Z(\tilde{t}+\theta_j)\left[\overline{g}_c s\left(V_0(\tilde{t}+\theta_k)-V_0(\tilde{t}+\theta_j)\right)+(-1)^j\frac{\Delta I}{2}\right]d\tilde{t}$$

$$= \frac{1}{T}\int_0^T Z(\tilde{t})\,\overline{g}_c s\left(V_0(\tilde{t}-(\theta_j-\theta_k))-V_0(\tilde{t})\right)d\tilde{t}+(-1)^j\frac{\Delta I}{2}\frac{1}{T}\int_0^T Z(\tilde{t})\,d\tilde{t}$$

$$\underbrace{\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad}\qquad\underbrace{\qquad\qquad\qquad\qquad}$$

$\uparrow$ **effects of coupling current**

$\uparrow$ effects of heterogeneity

$$\overline{g}_c H\left(-(\theta_j-\theta_k),s\right)$$

$$(-1)^j\frac{\Delta I}{2}Q$$

A. <u>NO VOLTAGE-GATING</u>

i.e., constant $s=s_0=1$
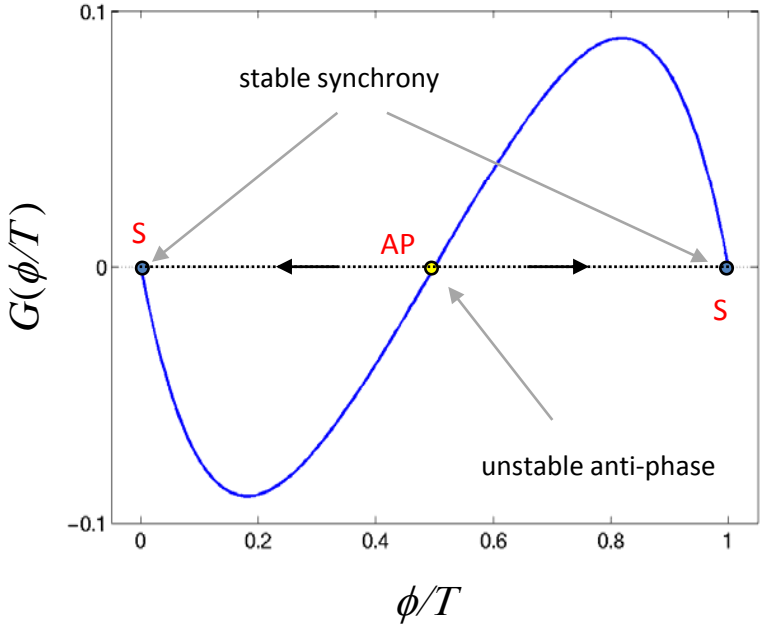
$$\frac{d\theta_j}{dt} = \frac{1}{T}\int_0^T Z(\tilde{t})\,\overline{g}_c s_0 \left(V_0(\tilde{t}-(\theta_j-\theta_k))-V_0(\tilde{t})\right) d\tilde{t} + (-1)^j \frac{\Delta I}{2}\frac{1}{T}\int_0^T Z(\tilde{t})\,d\tilde{t}$$

$$= \overline{g}_c\,H\left(-(\theta_j-\theta_k)\right)+(-1)^j\frac{\Delta I}{2}Q$$

$$j,k=1,2;\;\; j\neq k$$

$\phi = \theta_1 - \theta_2$ = phase difference between cells

$$\frac{d\phi}{dt} = \left(\overline{g}_c H(-\phi)+\frac{\Delta I}{2}Q\right)-\left(\overline{g}_c H(\phi)-\frac{\Delta I}{2}Q\right) = -2\overline{g}_c H_{odd}(\phi)+\Delta I\,Q$$

$$= \overline{g}_c G(\phi)+\Delta I\,Q$$

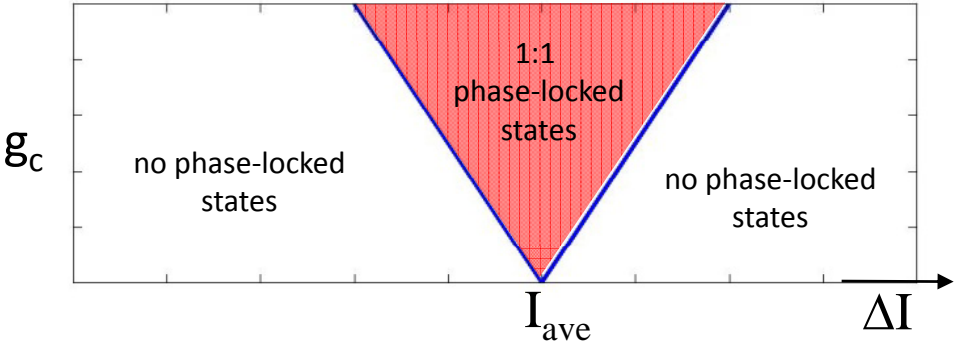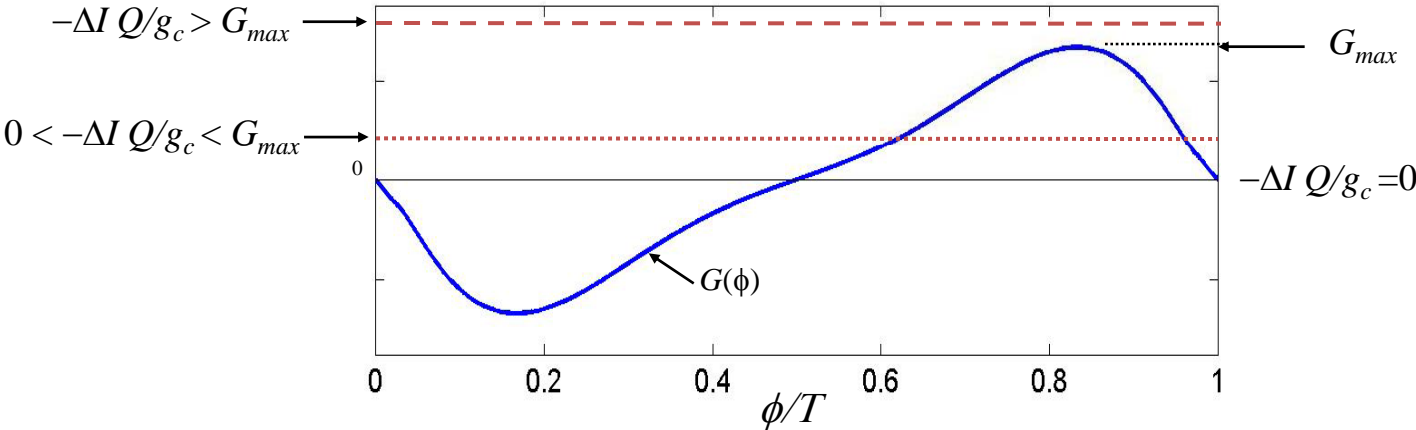$$\frac{d\phi}{dt} = \bar{g}_c G(\phi)$$

Phase-locking (according to the theory of weakly coupled oscillators) with $\Delta I = 0$:

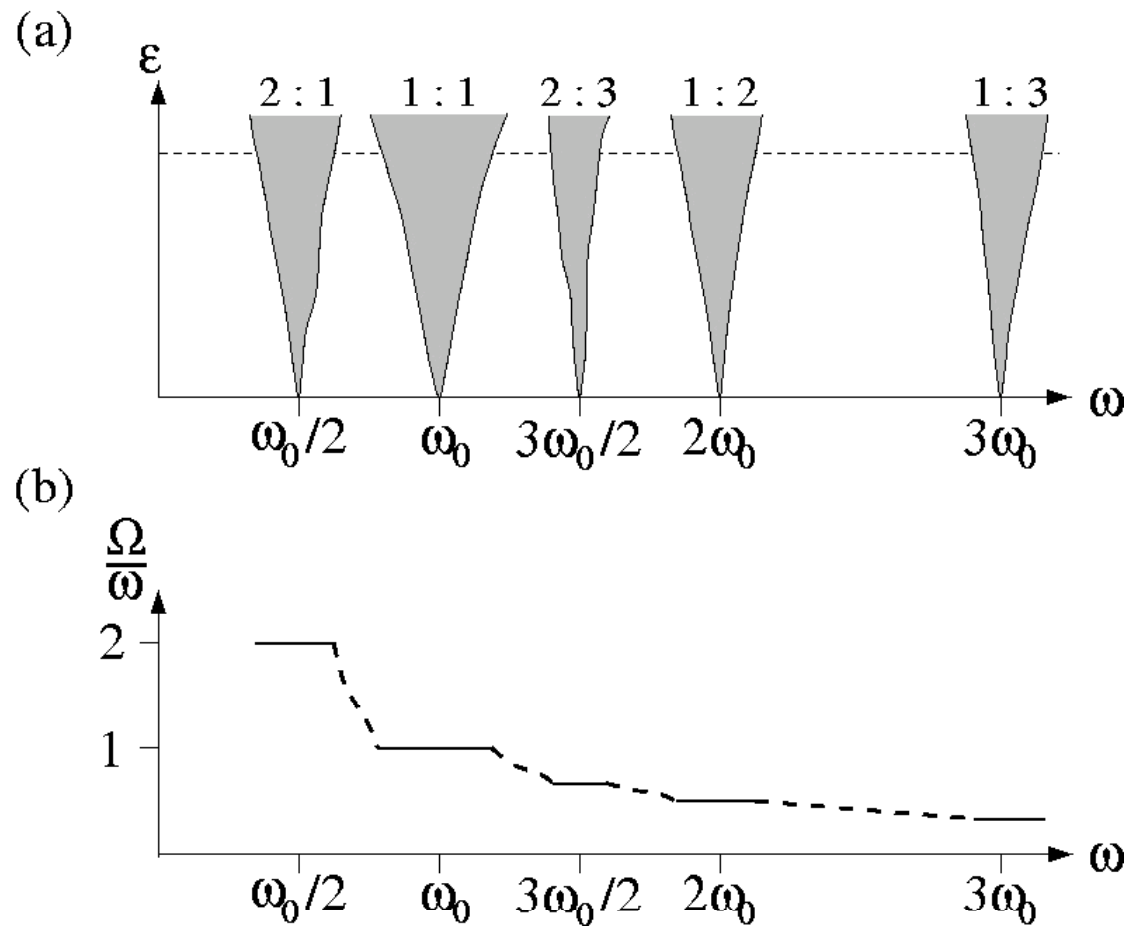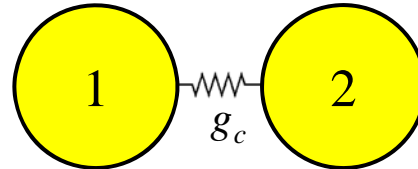$$\frac{d\phi}{dt} = \bar{g}_c G(\phi) + \Delta I\, Q$$

The effects of heterogeneity (phase shifts and the loss of 1:1 phase-locking):

Schematic of Arnold Tongues:

A. <u>NO VOLTAGE-GATING</u>
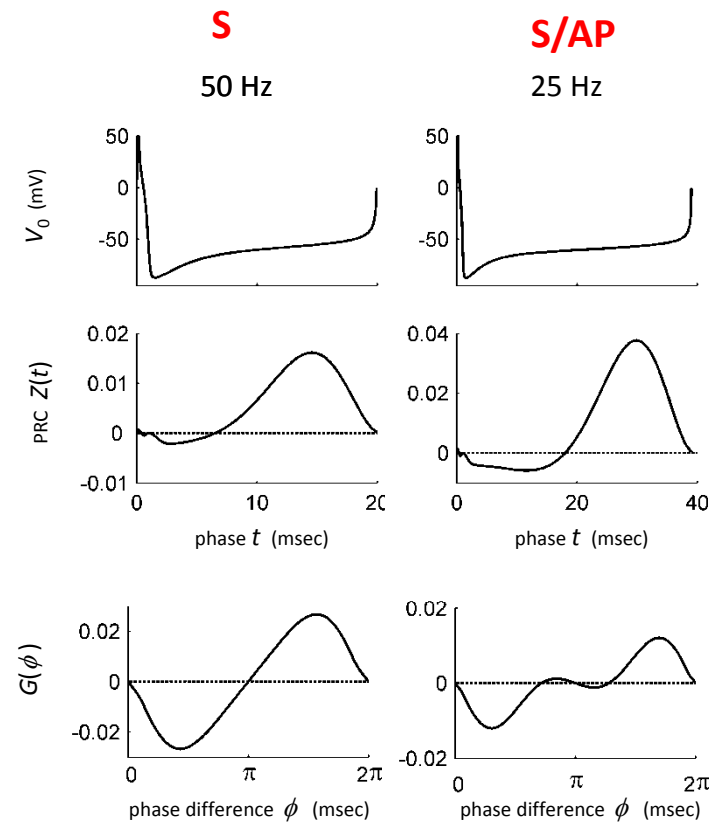

$$C\frac{dV_1}{dt} = -I_{ion}(V_1, m_1, h_1, n_1) + I_{applied} + g_c\,(V_2 - V_1)$$

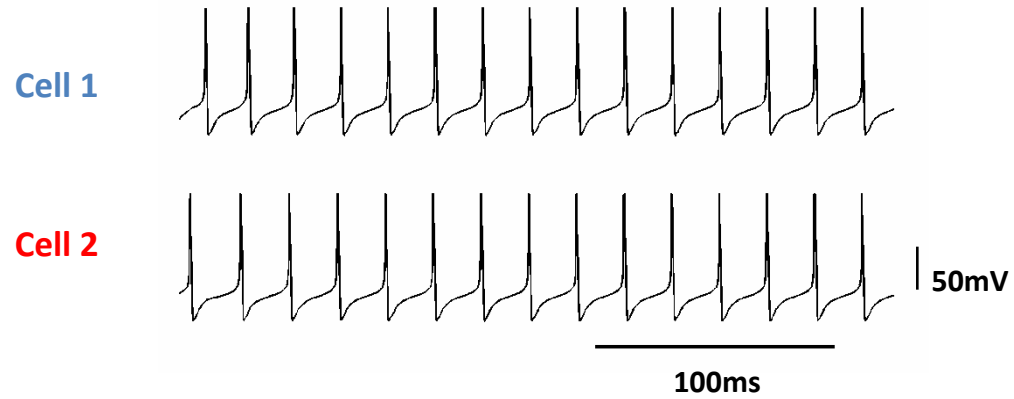$$C\frac{dV_2}{dt} = -I_{ion}(V_2, m_2, h_2, n_1) + I_{applied} + g_c\,(V_1 - V_2)$$

Intuition: electrical coupling promotes synchrony.

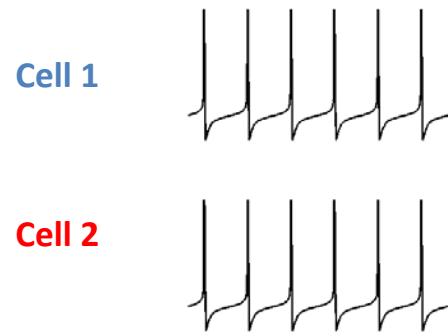# PRCs and phase-locking "predictions" for electrically coupled neurons
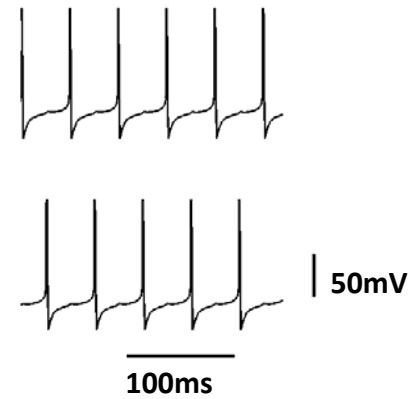

*Mancilla, Lewis et al. (2007) J. Neurosci.

50 *Hz* Synchrony

Cell 1

Cell 2
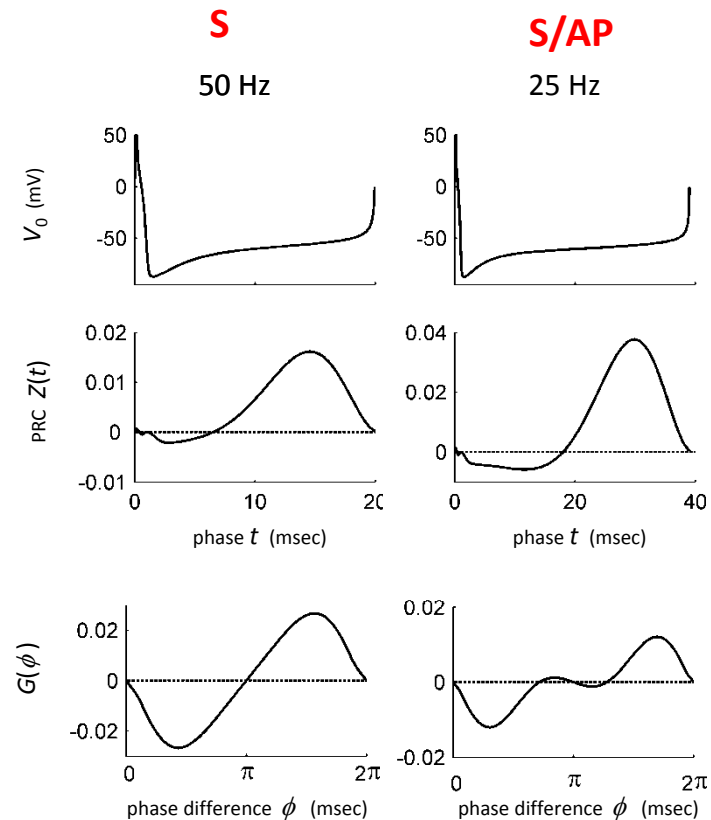
50mV

100ms

25 *Hz* Synchrony

Cell 1

Cell 2

25 *Hz* Anti-phase

50mV

100ms

*Mancilla, Lewis et al. (2007) J. Neurosci.

PRCs and phase-locking "predictions" for electrically coupled neurons

S   **S/AP**

50 Hz   25 Hz

*Mancilla, Lewis et al. (2007) J. Neurosci.

Q: mechanism of antiphase? (see Lewis and Skinner review).

Q: What does voltage-gating do to the synchronous and anti-phase states?
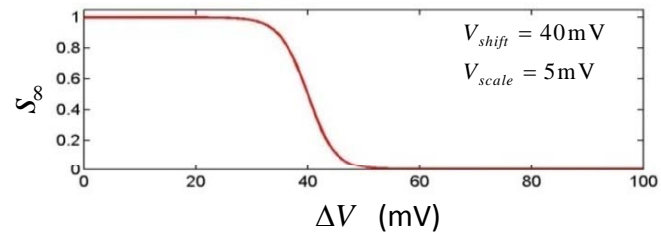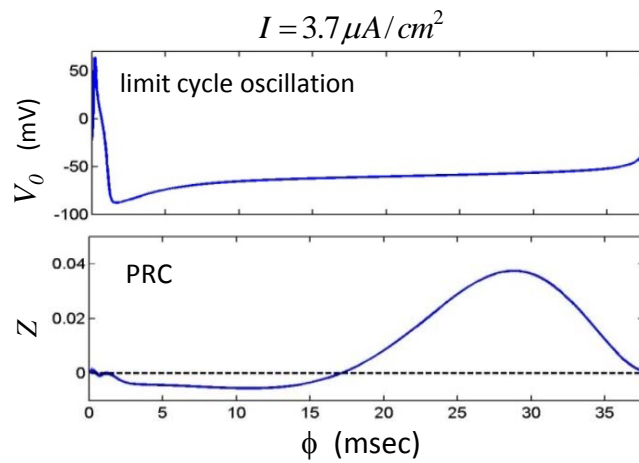
"FAST" VOLTAGE-GATING

$$\tau_s \frac{ds_0}{dt} = s_\infty \left(V_0(t+\theta_k) - V_0(t+\theta_j) \right) - s_0 \qquad \longrightarrow \qquad s_0 = s_\infty \left(V_0(t+\theta_k) - V_0(t+\theta_j) \right)$$

$$\frac{d\theta_j}{dt} = \frac{1}{T} \int_0^T Z(t)\, \overline{g}_c\, s_\infty \left(V_0\left(t-(\theta_j-\theta_k)\right) - V_0(t) \right) \left(V_0\left(t-(\theta_j-\theta_k)\right) - V_0(t) \right) dt \; + (-1)^j \frac{\Delta I}{2} \frac{1}{T} \int_0^T Z(t)\, dt$$

$$\frac{d\phi}{dt} = \left(\overline{g}_c\, H_f(-\phi) + \frac{\Delta I}{2} Q \right) - \left(\overline{g}_c\, H_f(\phi) - \frac{\Delta I}{2} Q \right) = \overline{g}_c\, G_f(\phi) + \Delta I\, Q$$
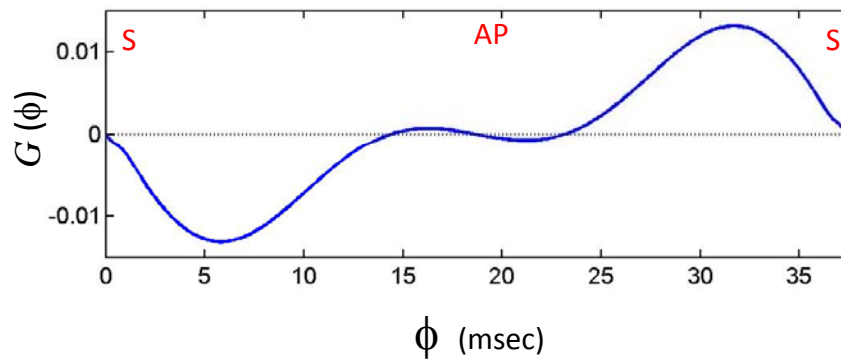
## prediction from theory : voltage-gating can promote anti-phase activity.

$I = 3.7 \mu A / cm^2$

limit cycle oscillation

V_0 (mV)

PRC

Z

ϕ (msec)

S_∞

$V_{shift} = 40 \, mV$

$V_{scale} = 5 \, mV$

ΔV (mV)

prediction from theory : voltage-gating can promote anti-phase activity.

no voltage-gating

voltage-gating

Without voltage-gating, the theory predicts a stable synchronous activity (S) and a marginally stable anti-phase state.
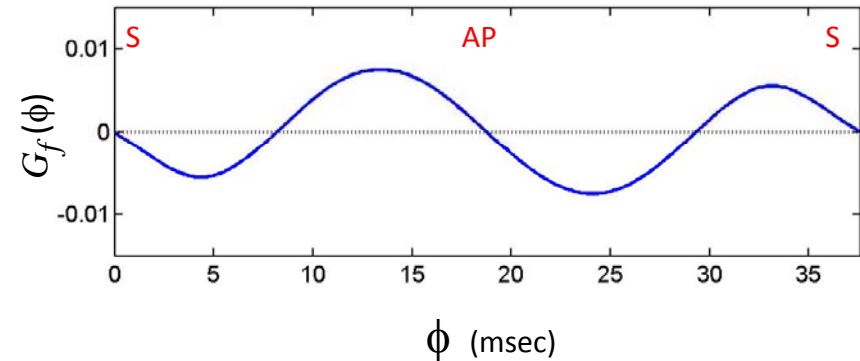
With voltage-gating, the synchronous state (S) and the anti-phase state (AP) appear to be 'equally' stable.

direct simulations
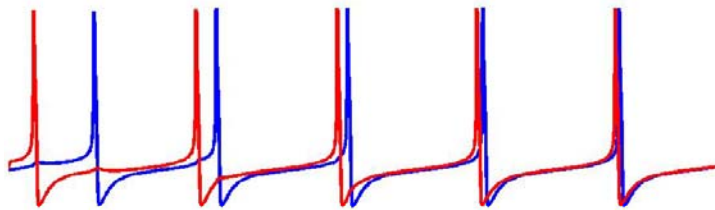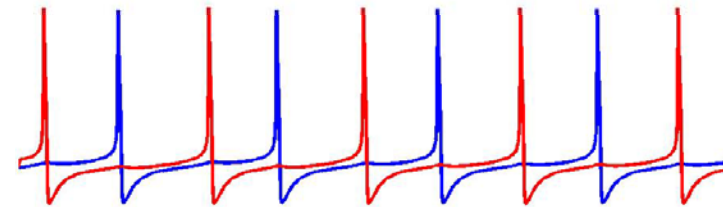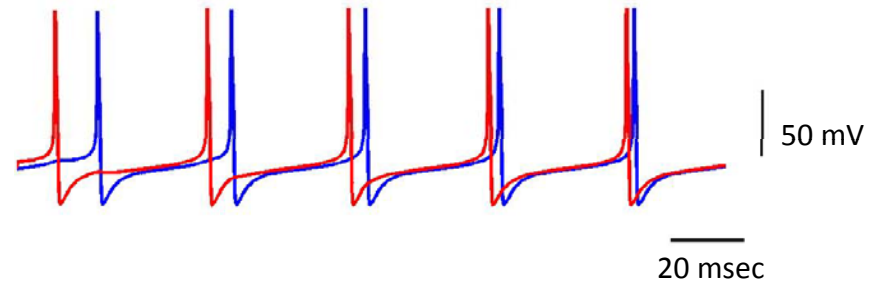
$$\overline{g}_c = 0.03,\, I = 3.7\,\mu A/cm^2$$

$$\Delta I = 0.01\,\mu A/cm^2$$

voltage-gating

no voltage-gating

Without voltage-gating, synchrony (S) was the only stable phase-locked state observed for all initial conditions tried.

50 mV

20 msec

With voltage-gating, both synchrony (S) and anti-phase (AP) activity were stable.

Phase model with (weak) additive white noise:

$$\frac{d\phi}{dt} = \overline{g}_c G(\phi) + \Delta I\, Q + \sigma_T \eta(t)$$

$$\sigma_T = \left(\frac{\sigma^2}{T} \int_0^T [Z(\tilde{t})]^2\, d\tilde{t} \right)^{1/2}$$
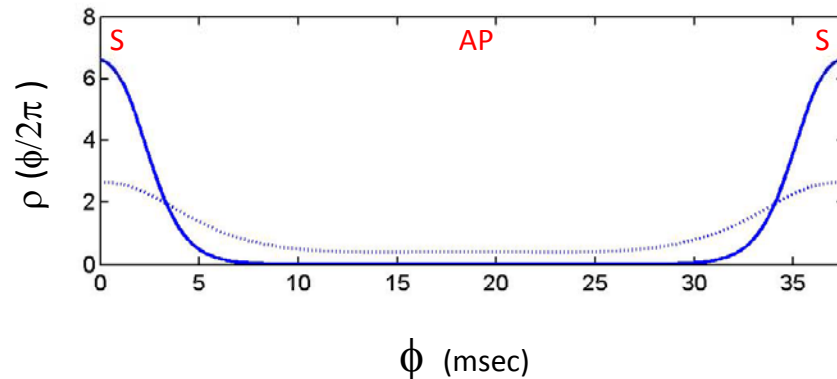
Fokker-Planck equation for distribution of phase difference:

$$\frac{\partial \rho}{\partial t}(\phi, t) = -\frac{\partial}{\partial \phi}\left[(\overline{g}_c G(\phi) + \Delta I\, Q)\rho(\phi, t) \right] + \sigma_T^2 \frac{\partial^2 \rho}{\partial \phi^2}(\phi, t)$$
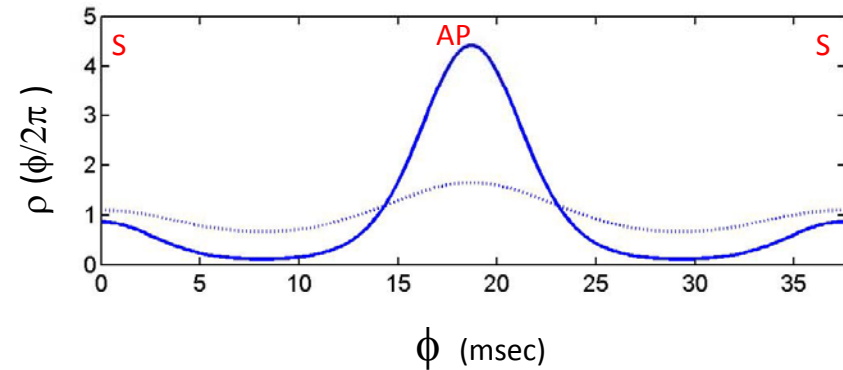
$\rho(\phi, t)$ = prob. that cells will have phase difference ϕ at time t.

effect of noise

no voltage-gating

voltage-gating

Steady state cross-correlogram $\rho(\psi)$ for two level of noise (solid - 'low' noise; dotted – 'high' noise).
$\rho(\psi)$ is determined using the theory of weakly coupled oscillators (Pfeuty et al., 2005):

$$\rho(\psi) = \frac{\exp(K(\psi))}{\int_0^1 \exp(K(\tilde{\psi}))\, d\tilde{\psi}}, \quad \text{where} \quad K(\psi) = \frac{g_c}{\sigma_T^{\,2}} \int_0^{\psi} G(\tilde{\psi})\, d\tilde{\psi}, \quad \psi = \frac{\phi}{2\pi}$$
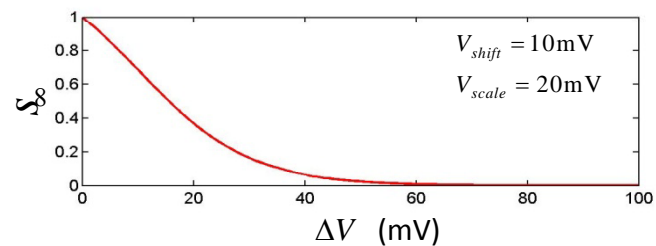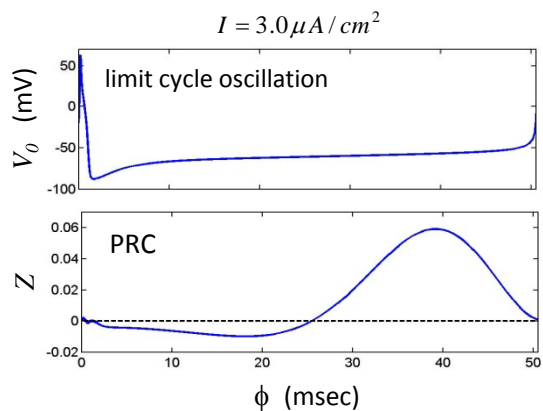
C. "SLOW" VOLTAGE-GATING

For slow voltage-gating, both the relative phases and S evolve on time scales much slower than the period T. Therefore, we can average their dynamics over the period T.

$$
\begin{cases}
\dfrac{d\theta_j}{dt} = \dfrac{1}{T}\int_0^T Z(\tilde{t})\,\overline{g}_c s_0\left(V_0(\tilde{t}-(\theta_j-\theta_k))-V_0(\tilde{t})\right)d\tilde{t} + (-1)^j\,\dfrac{\Delta I}{2}\,\dfrac{1}{T}\int_0^T Z(\tilde{t})\,d\tilde{t} \\[4mm]
\qquad = \overline{g}_c s_0\,H\left(-(\theta_j-\theta_k)\right) + (-1)^j\,\dfrac{\Delta I}{2}\,Q \\[6mm]
\tau_s\,\dfrac{ds_0}{dt} = \dfrac{1}{T}\int_0^T S_\infty\left(V_0(\tilde{t}-(\theta_j-\theta_k))-V_0(\tilde{t})\right)d\tilde{t} - s_0 \\[4mm]
\qquad = S_\infty\left(-(\theta_j-\theta_k)\right) - s_0
\end{cases}
$$

$$
\frac{d\phi}{dt} = \left(\overline{g}_c s_0\,H(-\phi)+\frac{\Delta I}{2}Q\right) - \left(\overline{g}_c s_0\,H(\phi)-\frac{\Delta I}{2}Q\right) = \overline{g}_c s_0\,G(\phi)+\Delta I\,Q
$$

$$
\tau_s\,\frac{ds_0}{dt} = S_\infty(\phi) - s_0
$$

predictions from theory : voltage-gating always decreases the robustness
of anti-phase activity.

$I = 3.0 \mu A / cm^2$

limit cycle oscillation

V_0 (mV)

PRC

Z

ϕ (msec)

S_∞

$V_{shift} = 10 \text{mV}$

$V_{scale} = 20 \text{mV}$

ΔV (mV)

no voltage-gating

S   AP   S

$G(\phi)$

ϕ (msec)

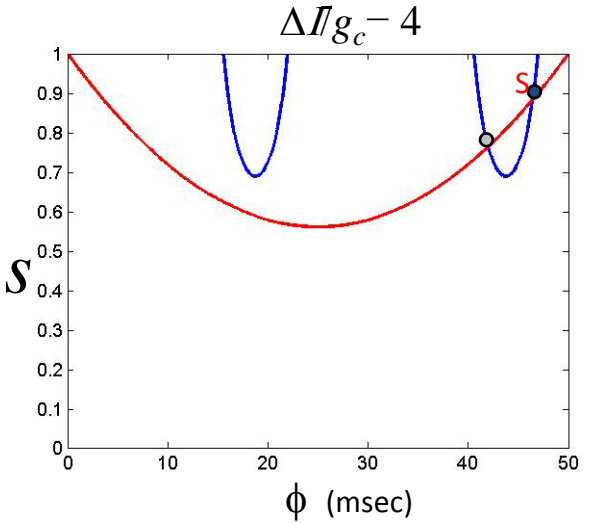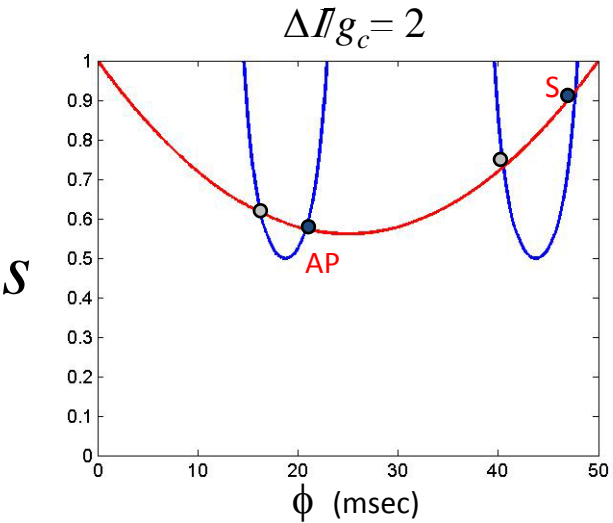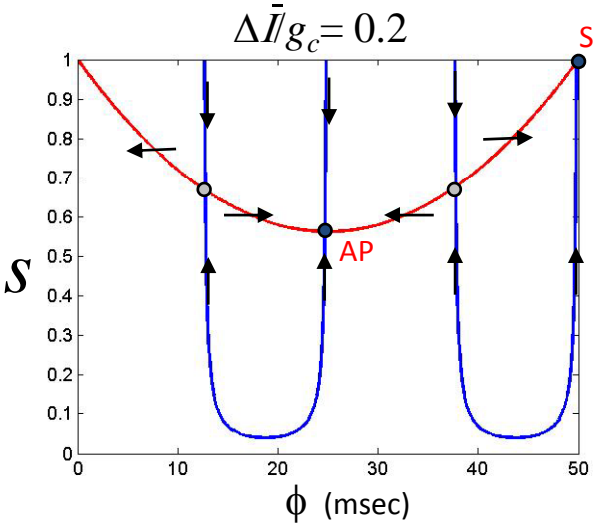## **effect of heterogeneity** : examining dynamics in the phase plane

$$\frac{d\phi}{dt} = \bar{g}_c s_0 \, G(\phi) + \Delta I \, Q$$

$$\tau_s \frac{ds_0}{dt} = S_\infty(\phi) - s_0$$
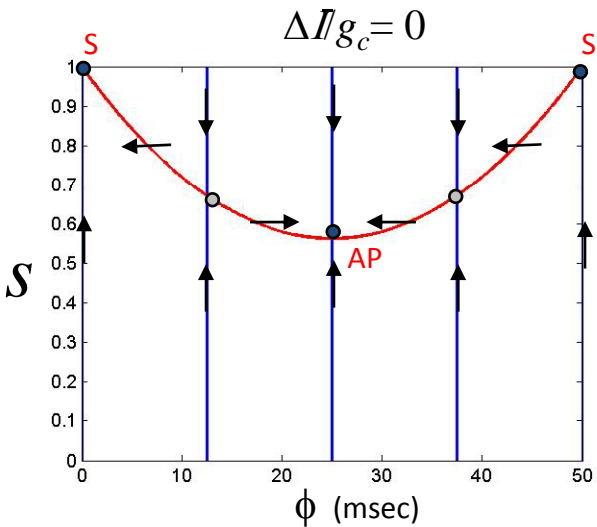
effect of heterogeneity : examining dynamics in the phase plane

$\Delta I/g_c = 0$

$\Delta \bar{I}/g_c = 0.2$

$\Delta I/g_c = 2$

$\Delta I/g_c - 4$

SUMMARY

We have found a variety of effects that depend on the degree and type of voltage-gating as well as the intrinsic dynamics of the cells. Here, we include two examples of the effects of voltage-gated electrical coupling in pairs of spiking neurons:

[1] **When the voltage-gating process is "fast", it can promote anti-phase activity.** This is a result of a diminished synchronizing effect of the spikes.

[2] **When the voltage-gating process is "slow", it always promotes synchronous activity.** Because it decreases the coupling strength only, slow rectification has no effect on the existence of phase-locked states in homogeneous, noiseless networks. However, it alters the robustness of these states. The synchronous state is relatively unaffected by the rectification, but the coupling strength can decrease substantially during asynchronous activity. Thus, the effective robustness of synchronous state increases in the presence of noise and heterogeneity.