Gap junctions and emergent brain rhythms: A mathematical study

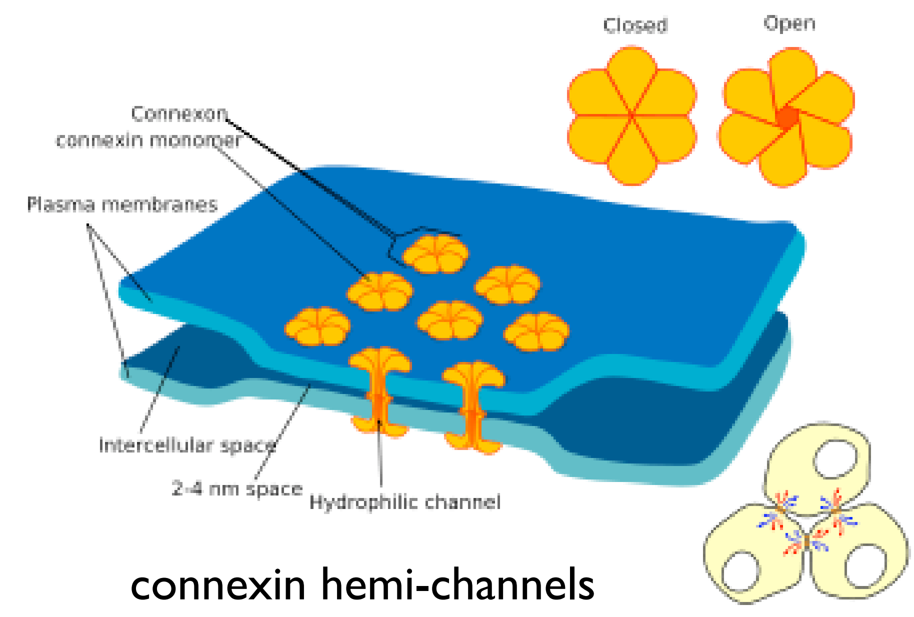
Stephen Coombes

The University of Nottingham

Some motivation

Gap junctions are ubiquitous

- between inhibitory cortical interneurons
- between hippocampal mossy fiber axons
- neuron to glia
- thalamo-cortical cells in LGN



connexin hemi-channels

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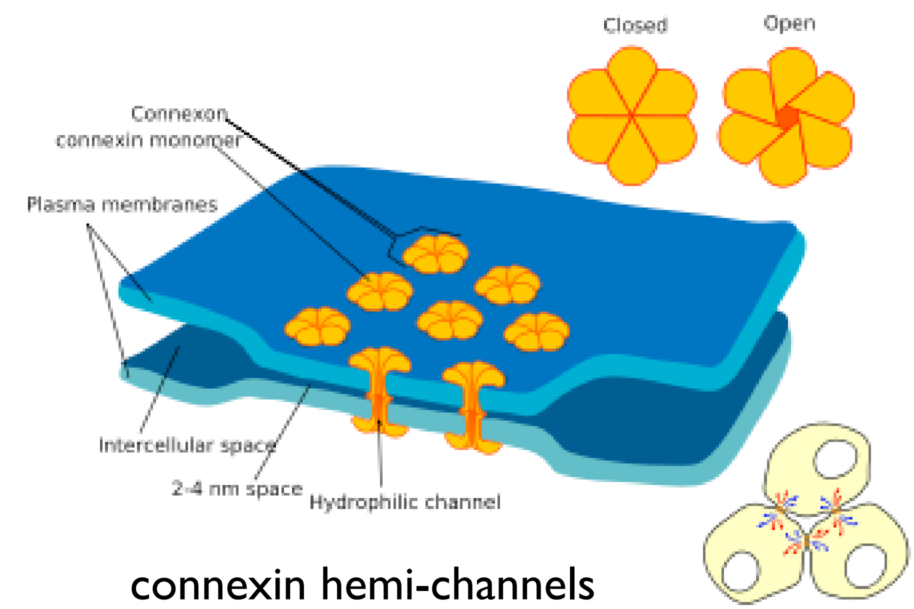

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- to phase-locking ? *Coupled Oscillator Theory*

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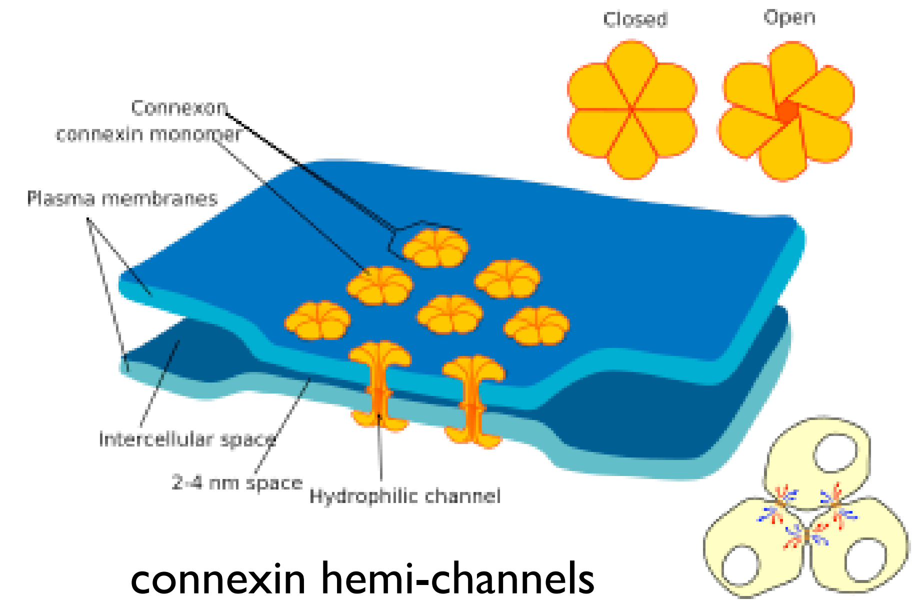

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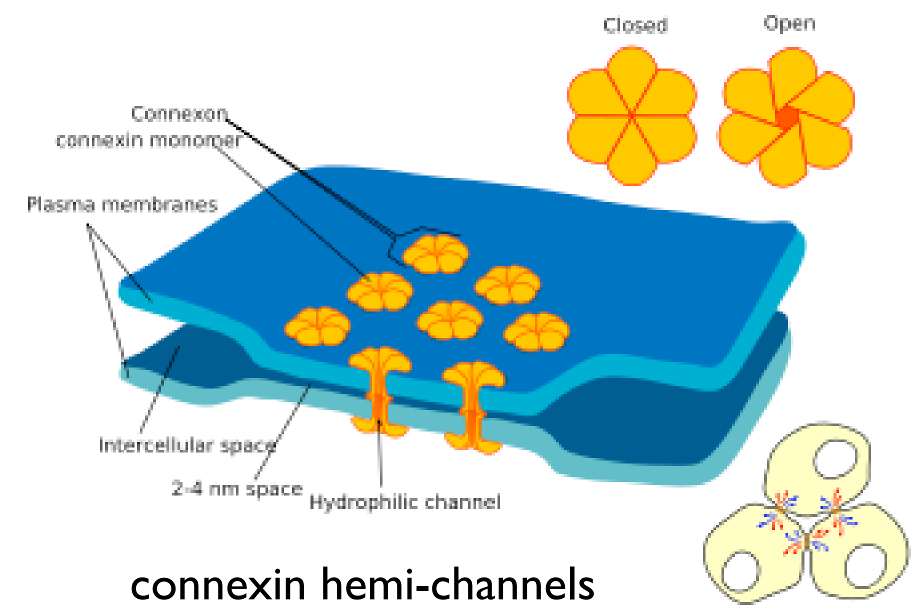

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Theoretical work by

- Kopell
- Ermentrout
- Rinzel
- Chow
- Lewis
- Holmes
- Sherman
- Hansel
- Pfeuty
- Ostojic, Brunel & Hakim
- ....

Fast spiking interneuron model ?

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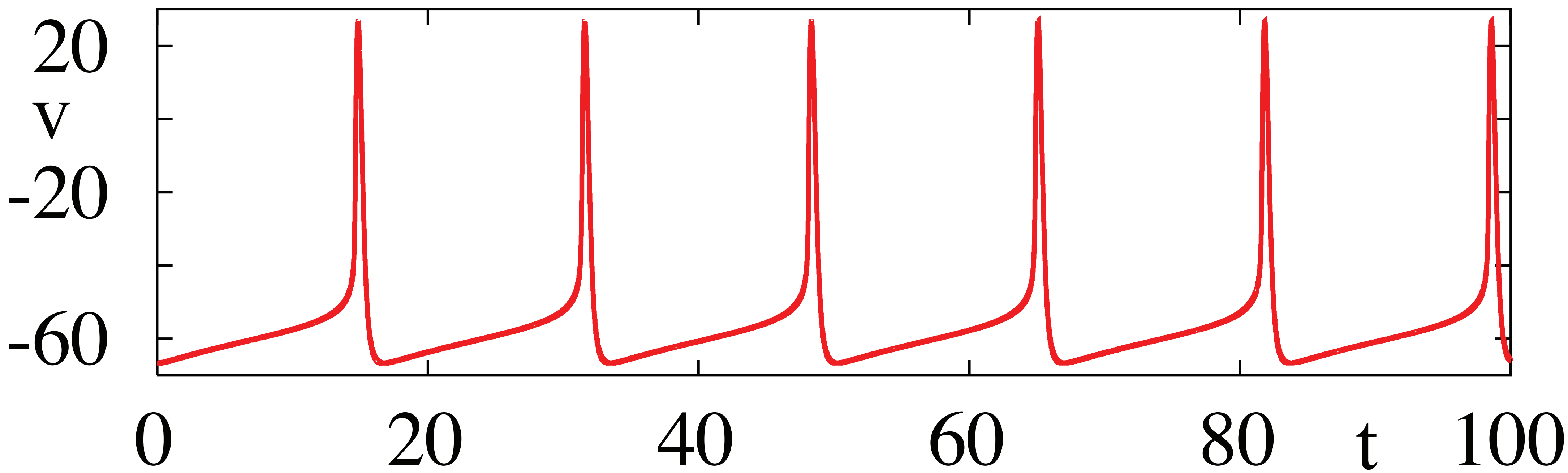
Wang-Buzsaki

X. J. Wang and G. Buzsaki. Gamma oscillation by synaptic inhibition in a hippocampal interneuronal network. Journal of Neuroscience, 16:6402–6413, 1996.



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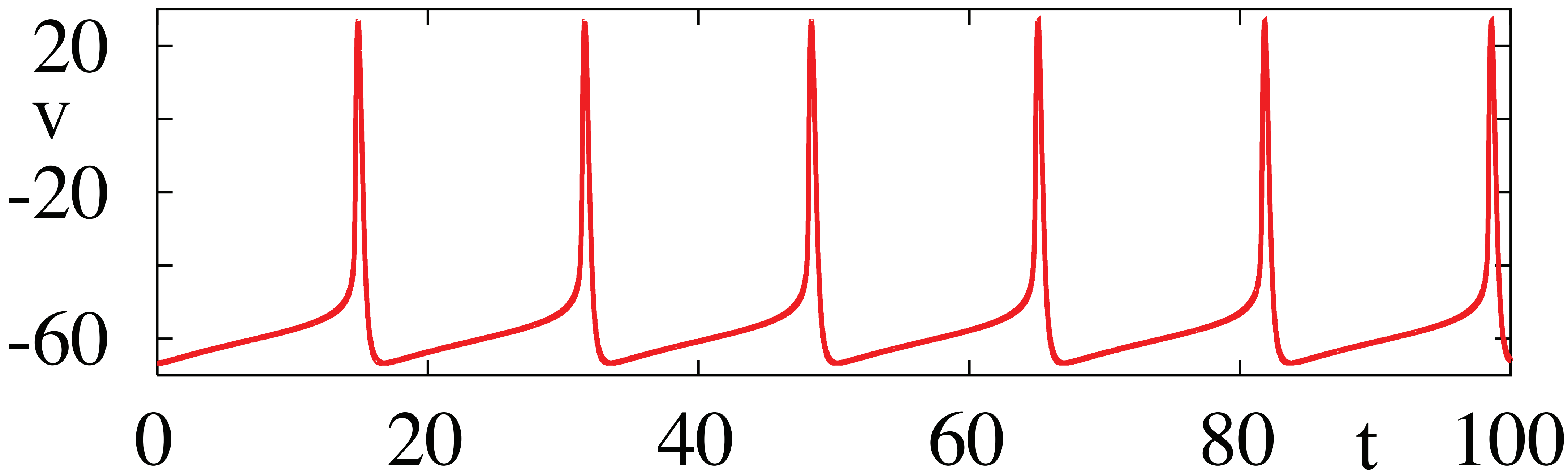
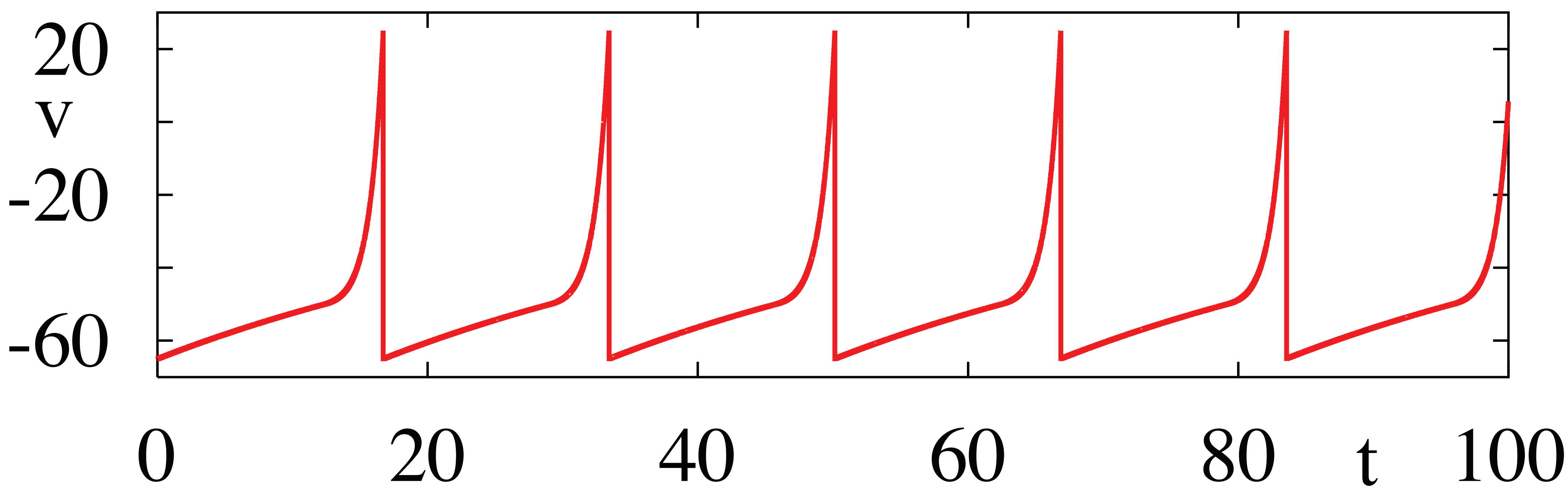
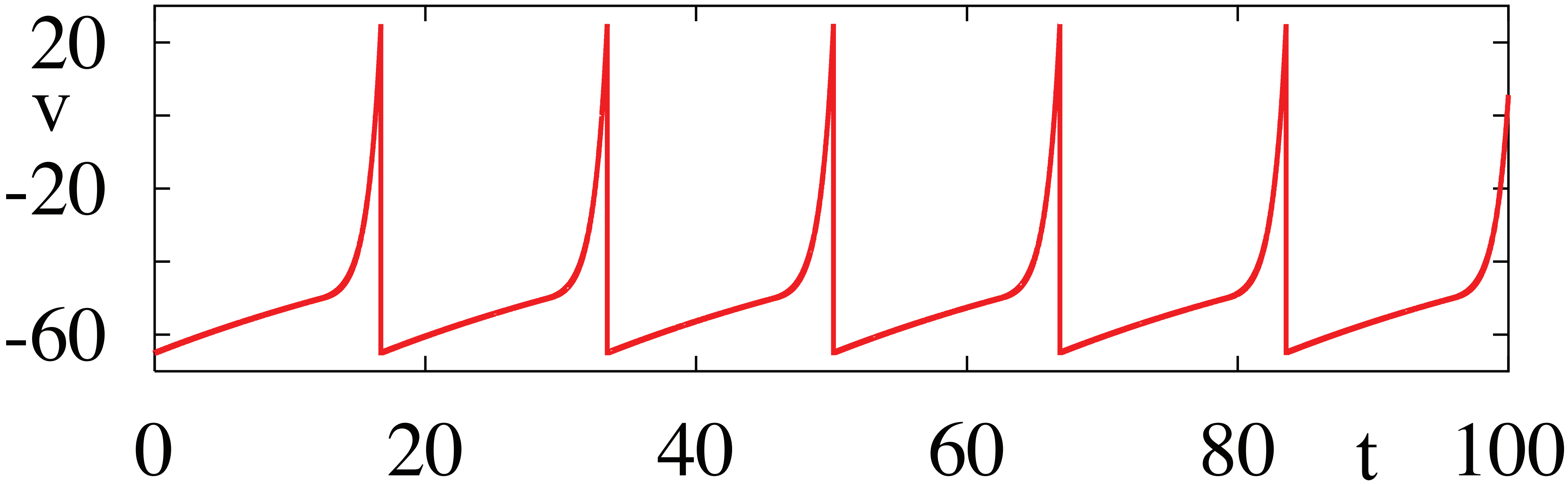


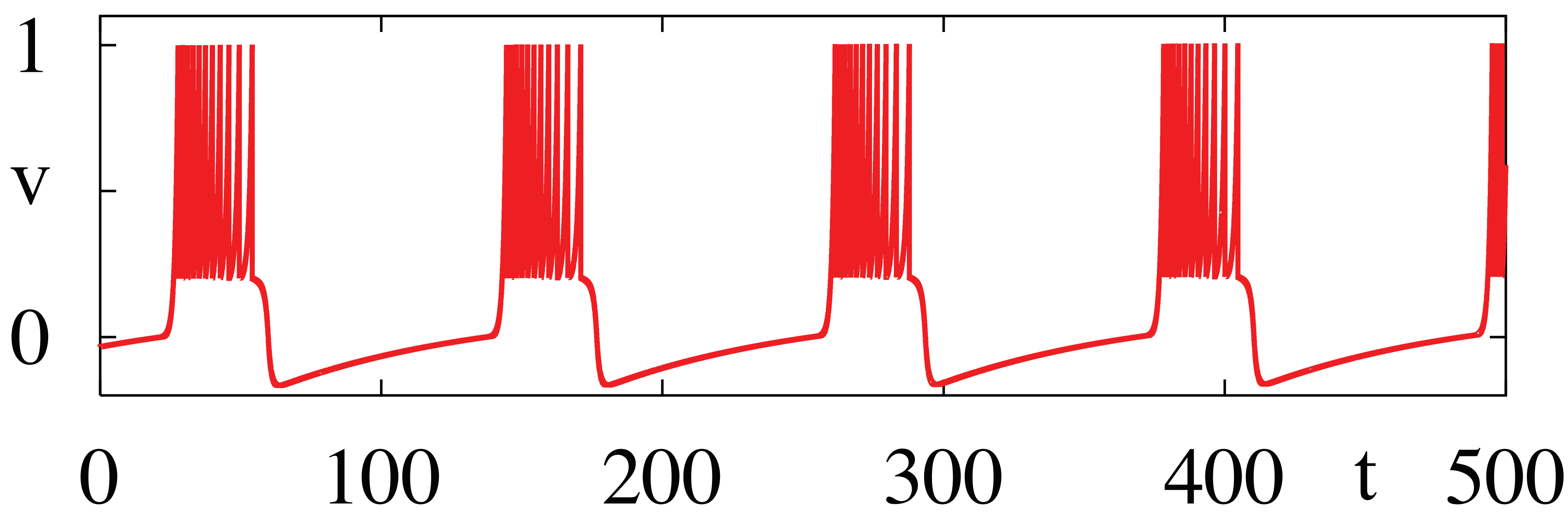
Absolute integrate-and-fire model

J. Karbowski and N. Kopell. Neural Computation, 12:1573–1606, 2000.

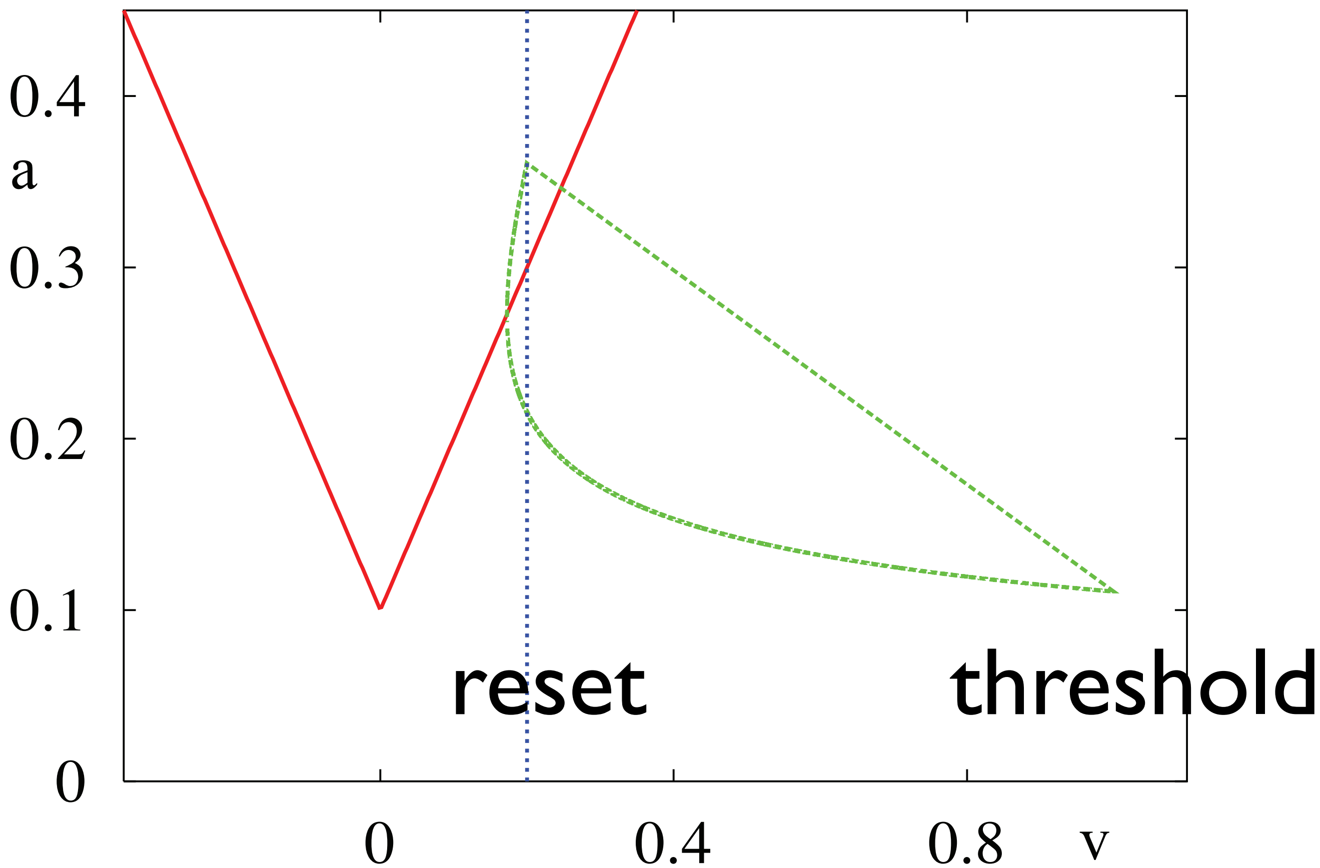


Spike adaptation - tonic *and* burst firing





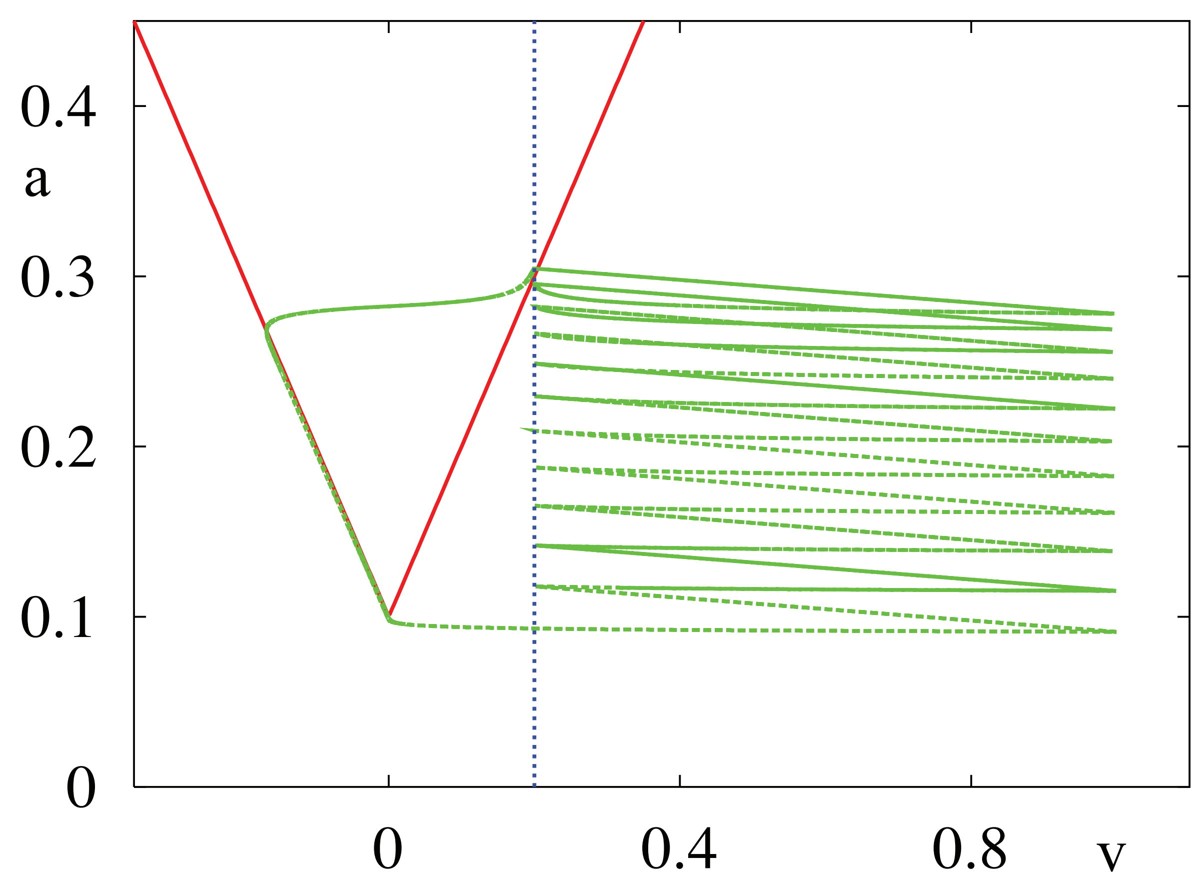
Mathematical structure



$$\dot{v} = |v| + I - a$$

$$\dot{a} = -a/\tau_a$$

$$a(T^m) \rightarrow a(T^m) + g_a/\tau_a$$



Periodic orbits - closed form solution

period Δ

$$v(\Delta) = v_{\mathrm{t}h}$$

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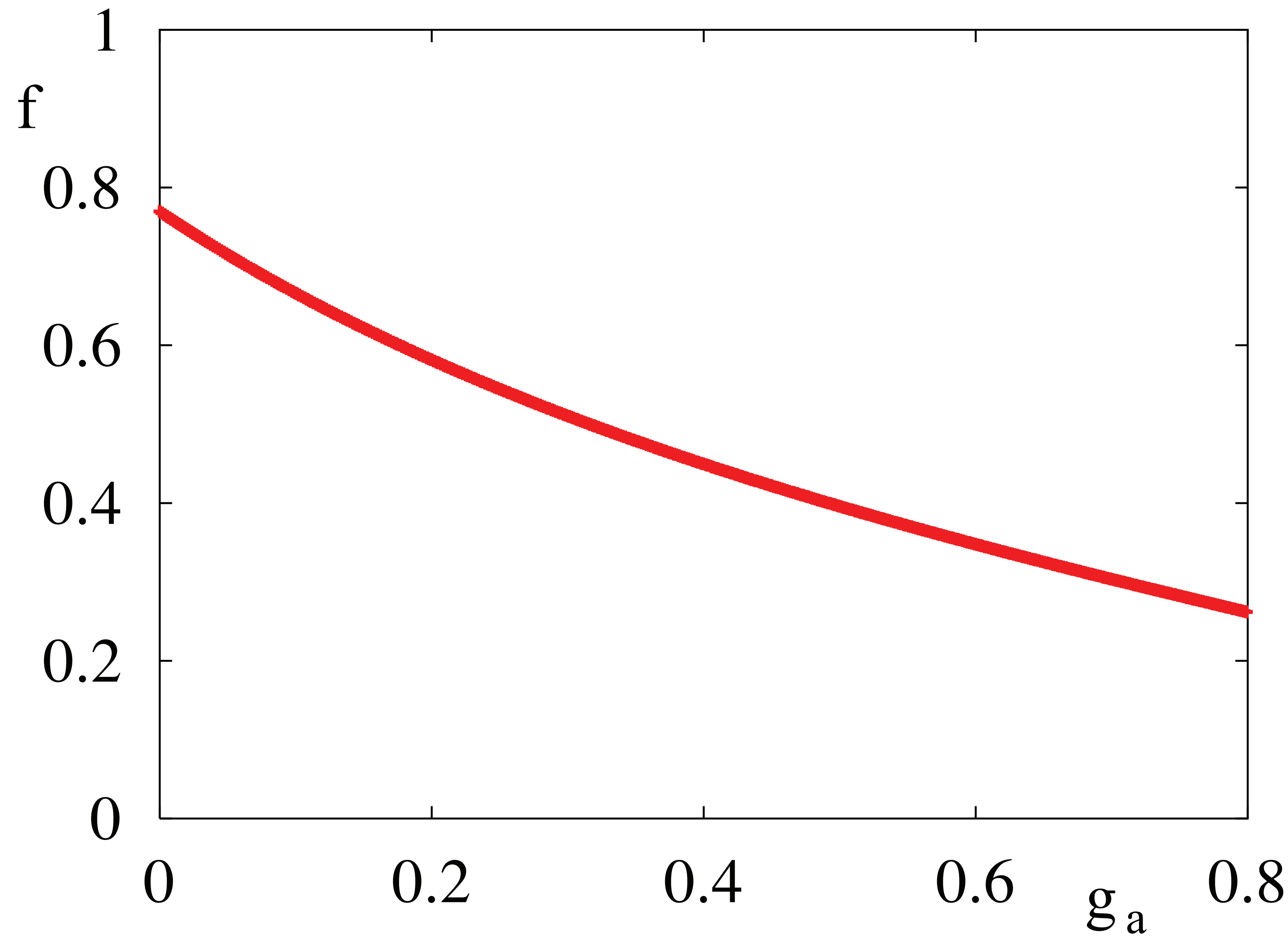
$$v(t) = v_{\mathrm{r}} e^{t} + I(\mathrm{e}^{t} - 1) - \frac{\overline{a}\tau_a}{1 + \tau_a}(\mathrm{e}^{t} - \mathrm{e}^{-t/\tau_a})$$

Periodic orbits - closed form solution

period Δ

$$v(\Delta) = v_{th}$$

frequency f



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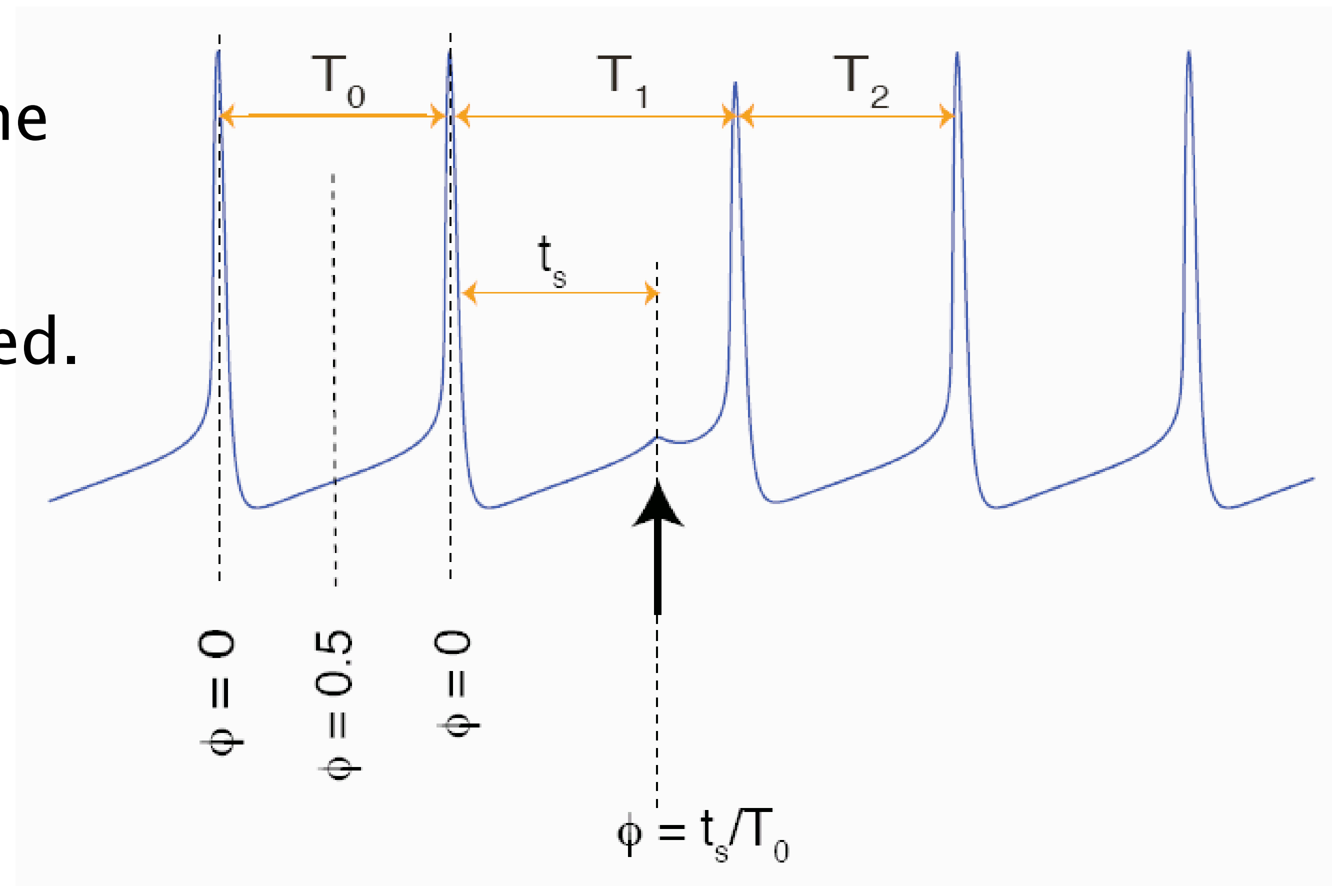
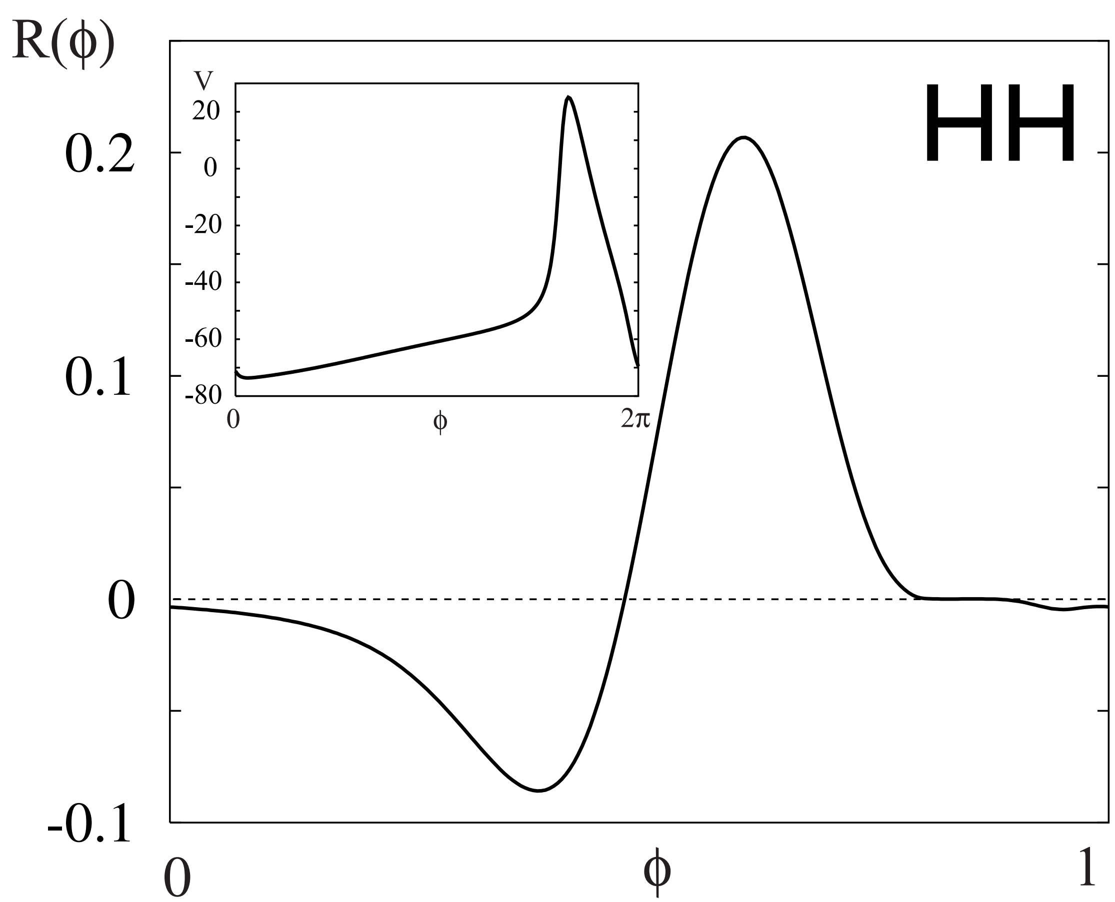
Phase Response Curve (PRC)

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.





Easy to compute numerically with XPPaut

Nice discussion at Scholarpedia :
http://www.scholarpedia.org

PRC - exact solution

Call the orbit $z = Z(t)$ where $\dot{z} = F(z)$

Introduce a phase (isochronal coordinates) θ

Adjoint $Q = \nabla_Z \theta$ (Ermentrout and Kopell 1991)

$$\frac{\mathrm{d}Q}{\mathrm{d}t} = D(t)Q, \qquad D(t) = -DF^T(Z(t))$$

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$$\nabla_{Z(0)} \cdot F(Z(0)) = 1/T \qquad Q(\Delta^+) \ = \ Q(0)$$

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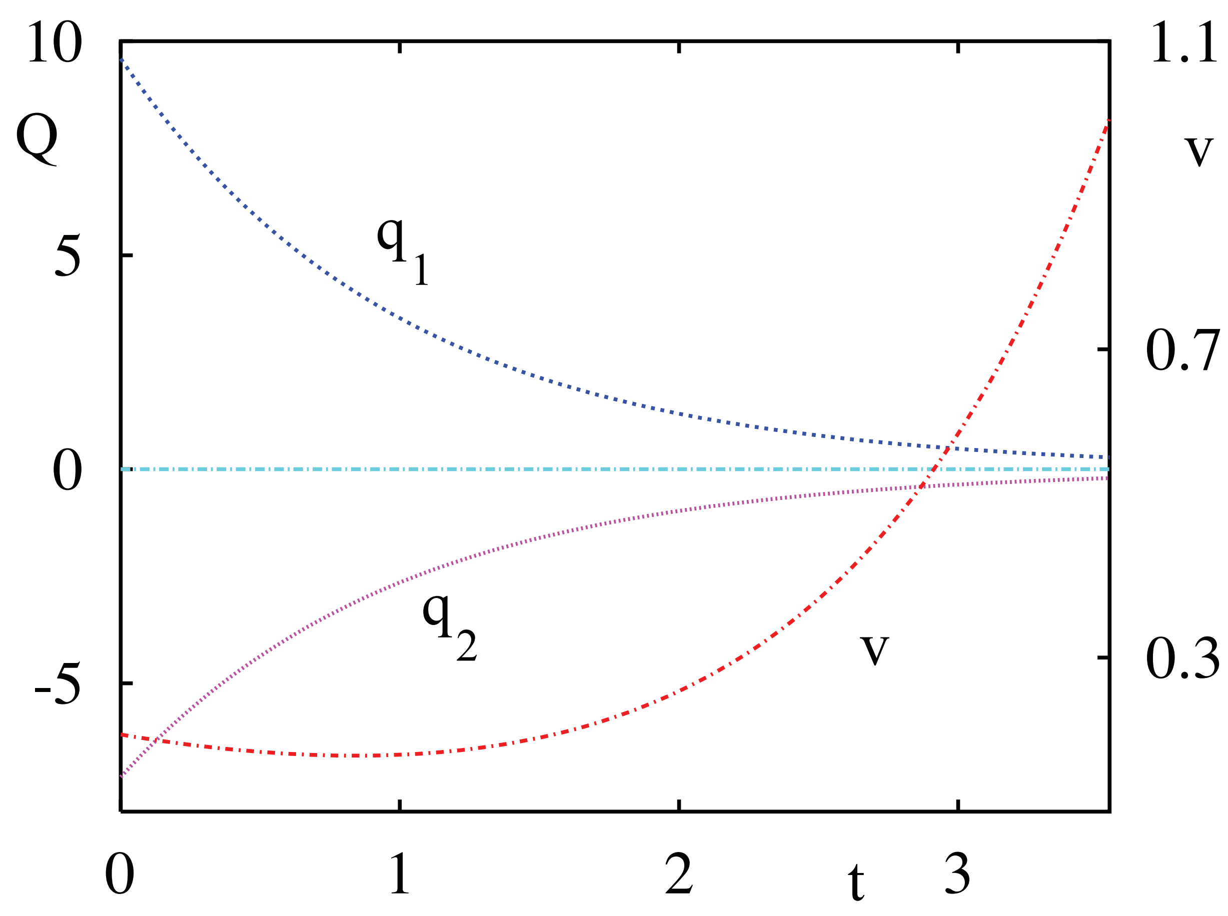
$$Q(t) = \frac{\kappa}{\Delta} \mathrm{e}^{-t} \begin{bmatrix} 1 \\ -\tau_a/(1+\tau_a) \end{bmatrix}$$

$$\kappa = [v_\mathrm{r} + I - \overline{a}\tau_a/(1+\tau_a)]^{-1}$$



Gap junction coupling

$$I_{\text{gap}} = g_{\text{gap}}(v_{\text{post}} - v_{\text{pre}})$$

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Analyse phase locked states

period T

$$z_i(t) = z(t - \phi_i T), \; z(t) = z(t + T)$$

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N eqns distinguished by their drive:

$$N^{-1} \sum_{j=1}^{N} g_{ij}(v(t + (\phi_i - \phi_j)T) - v(t))$$

Existence of the asynchronous state

globally coupled network $g_{ij} = g$ and large N

network averages ~ time averages

$$\lim_{N\to\infty} \frac{1}{N} \sum_{j=1}^{N} v(t + j\Delta/N) = \frac{1}{\Delta} \int_0^{\Delta} v(t)\mathrm{d}t$$

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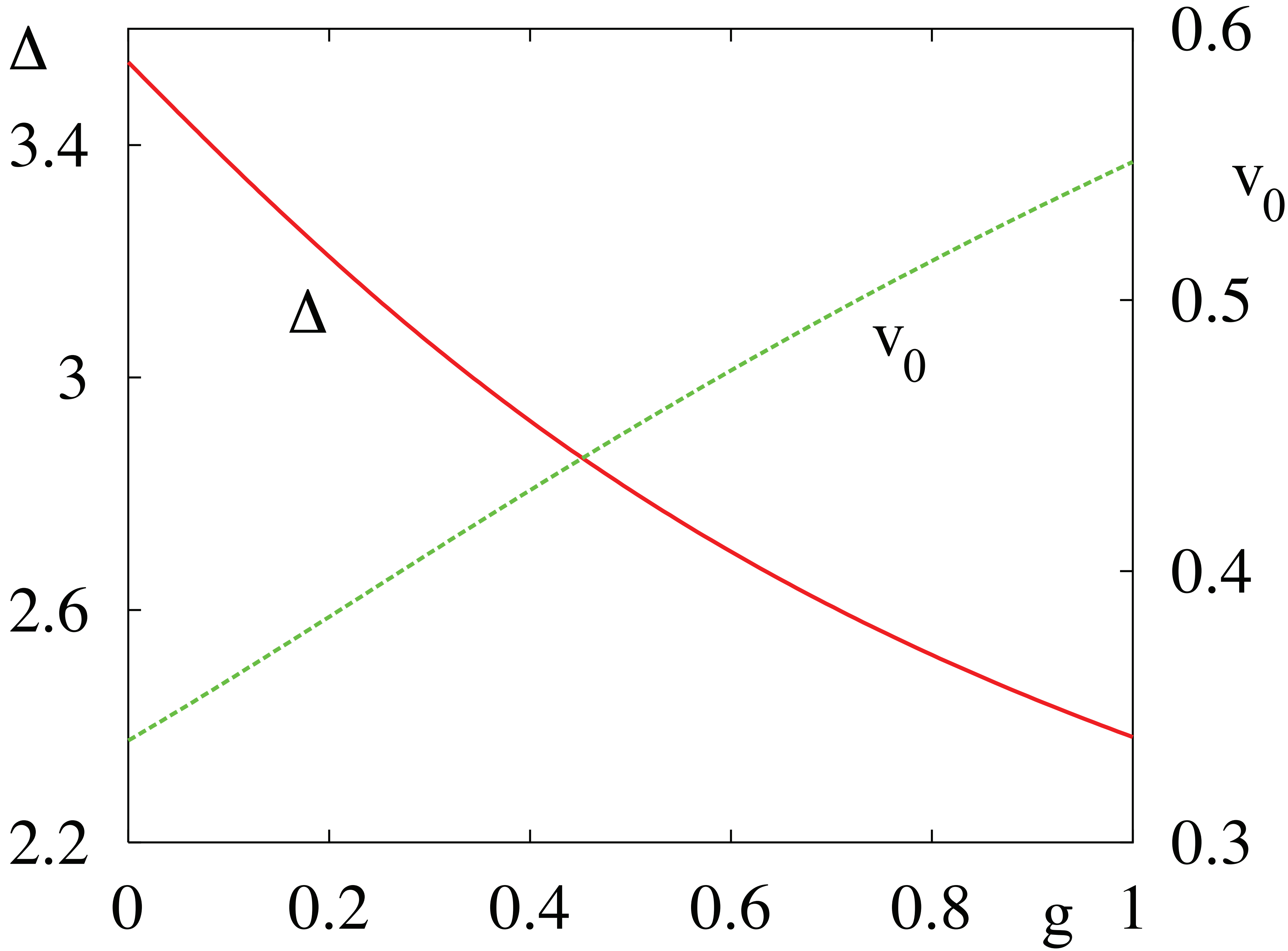
advanced-retarded ode - self-consistent periodic solution

$$v(\Delta) = v_{\mathrm{t}h} \qquad v_0 = \Delta^{-1} \int_0^{\Delta} v(t)\mathrm{d}t$$

splay state as a function of coupling



Stability of the asynchronous state

Stability - generalise approach for synapses.

e-values as zeros of

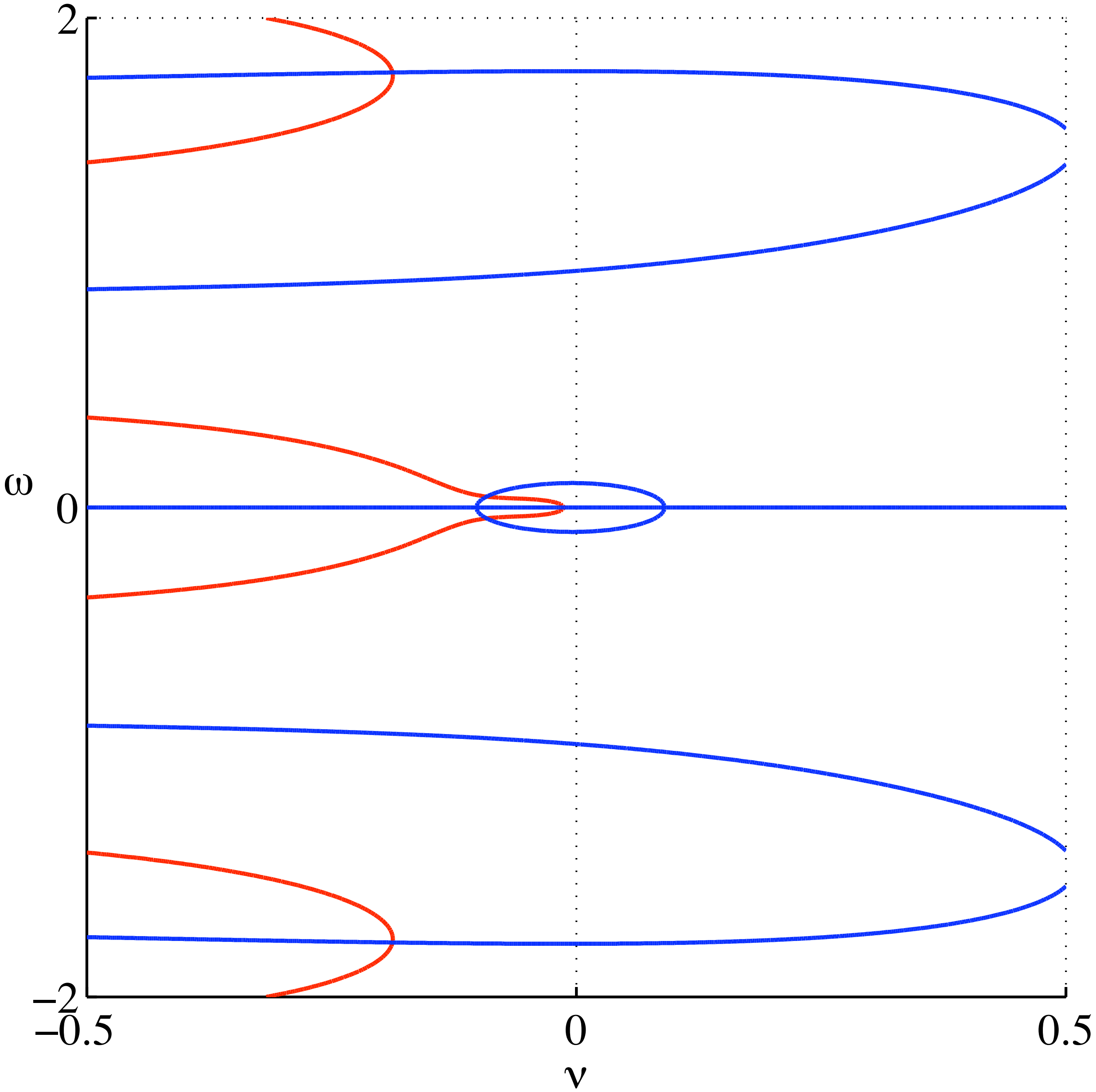
$$\mathcal{E}(\lambda) = \frac{\mathrm{e}^{\lambda T}}{\widetilde{v}(\lambda)} + g\lambda T \int_0^1 R(\theta)\mathrm{e}^{\lambda\theta T}\mathrm{d}\theta$$

LT of orbit

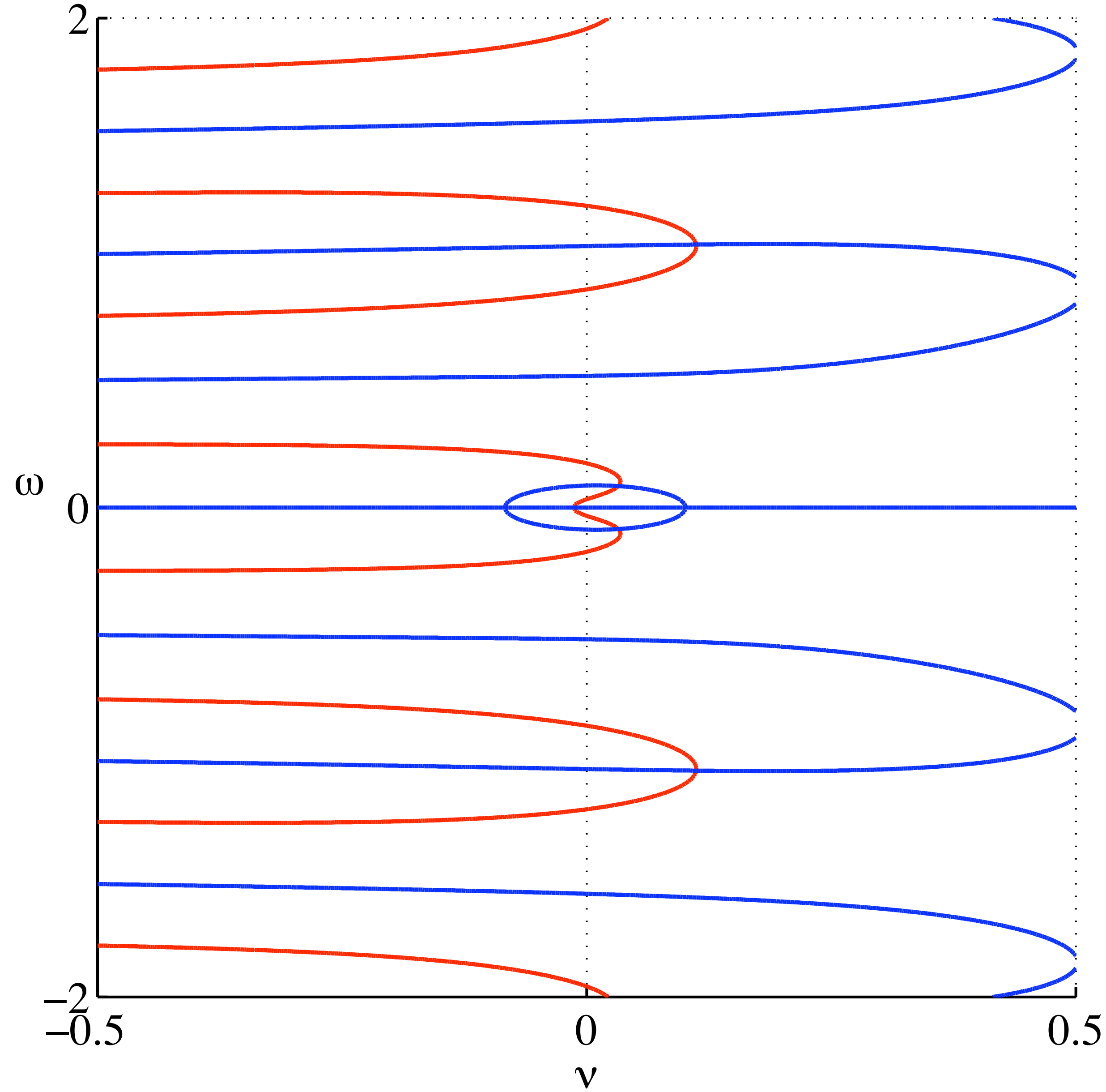
PRC of splay

C. van Vreeswijk, Analysis of the asynchronous state in networks of strongly coupled oscillators, Physical Review Letters, 84 (2000), pp. 5110–5113.

spectrum for fixed g

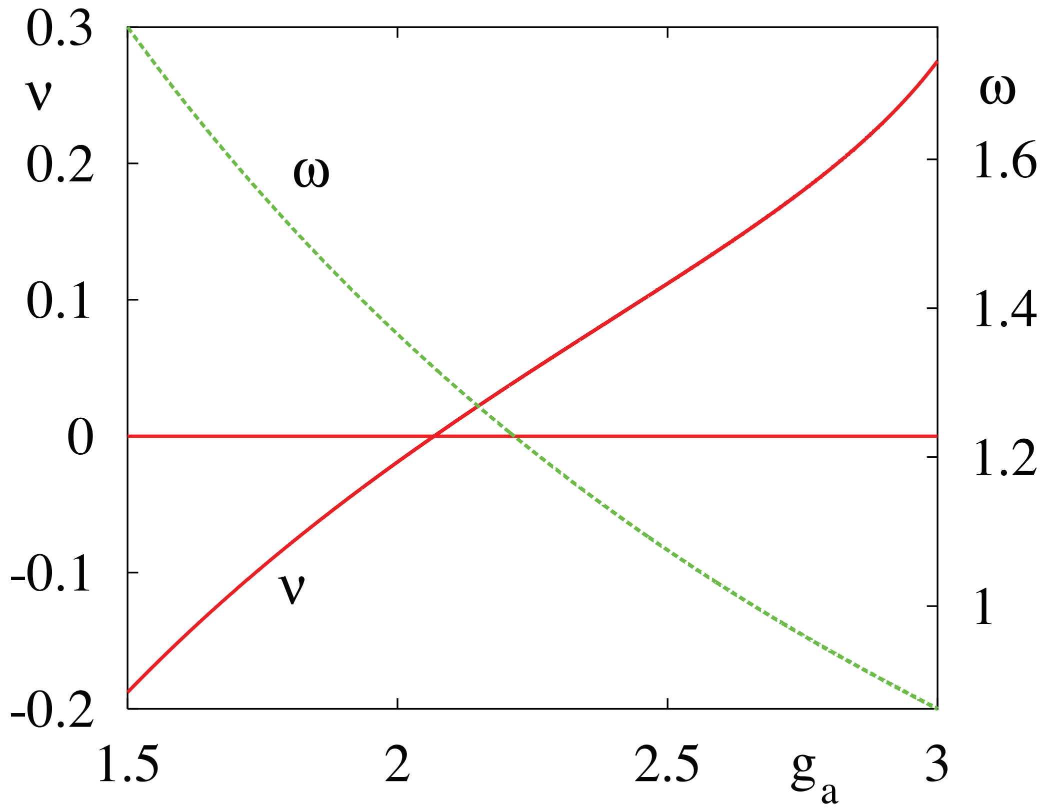


$g_a = 1.5$



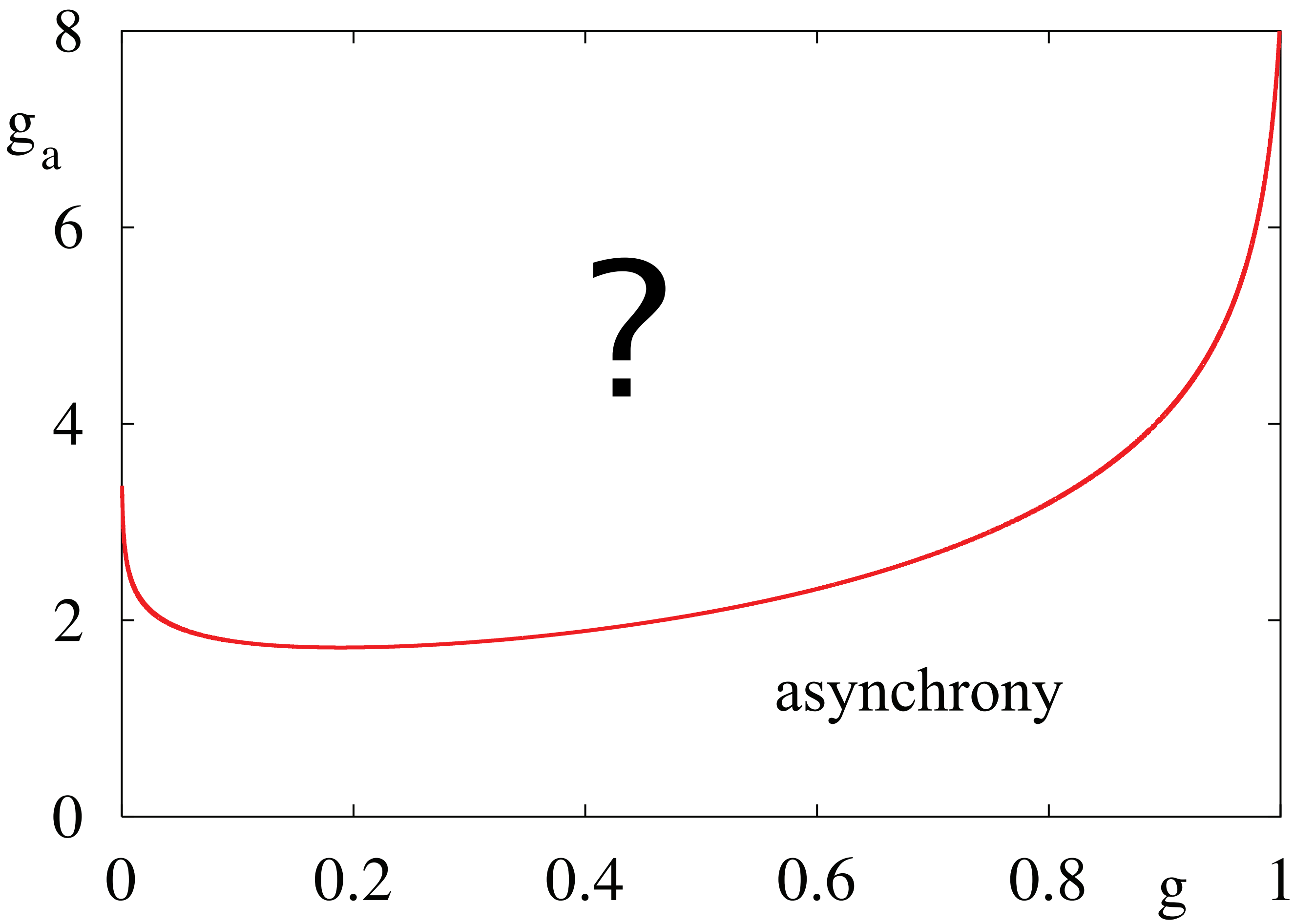
$g_a = 2.5$

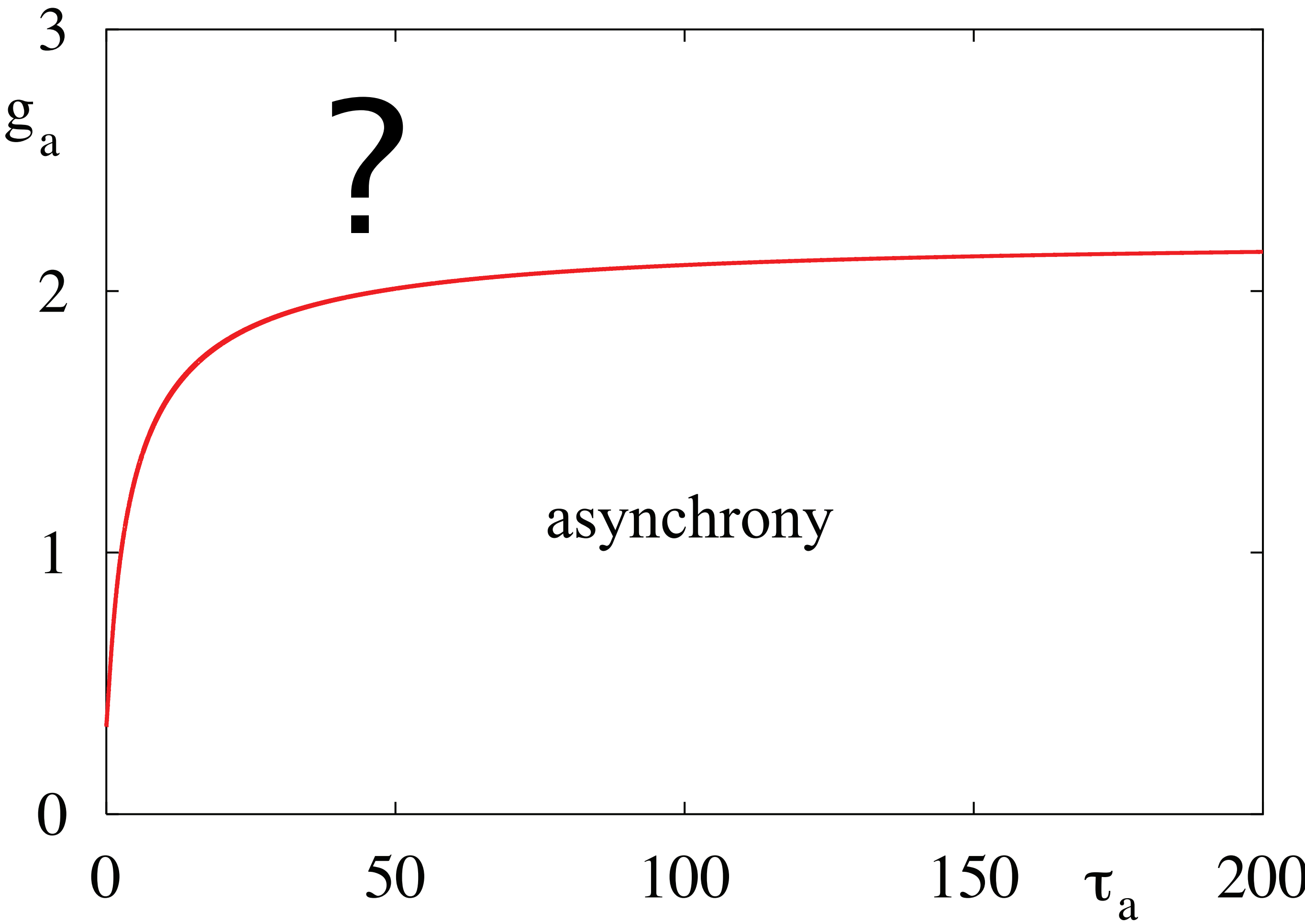
Bifurcation



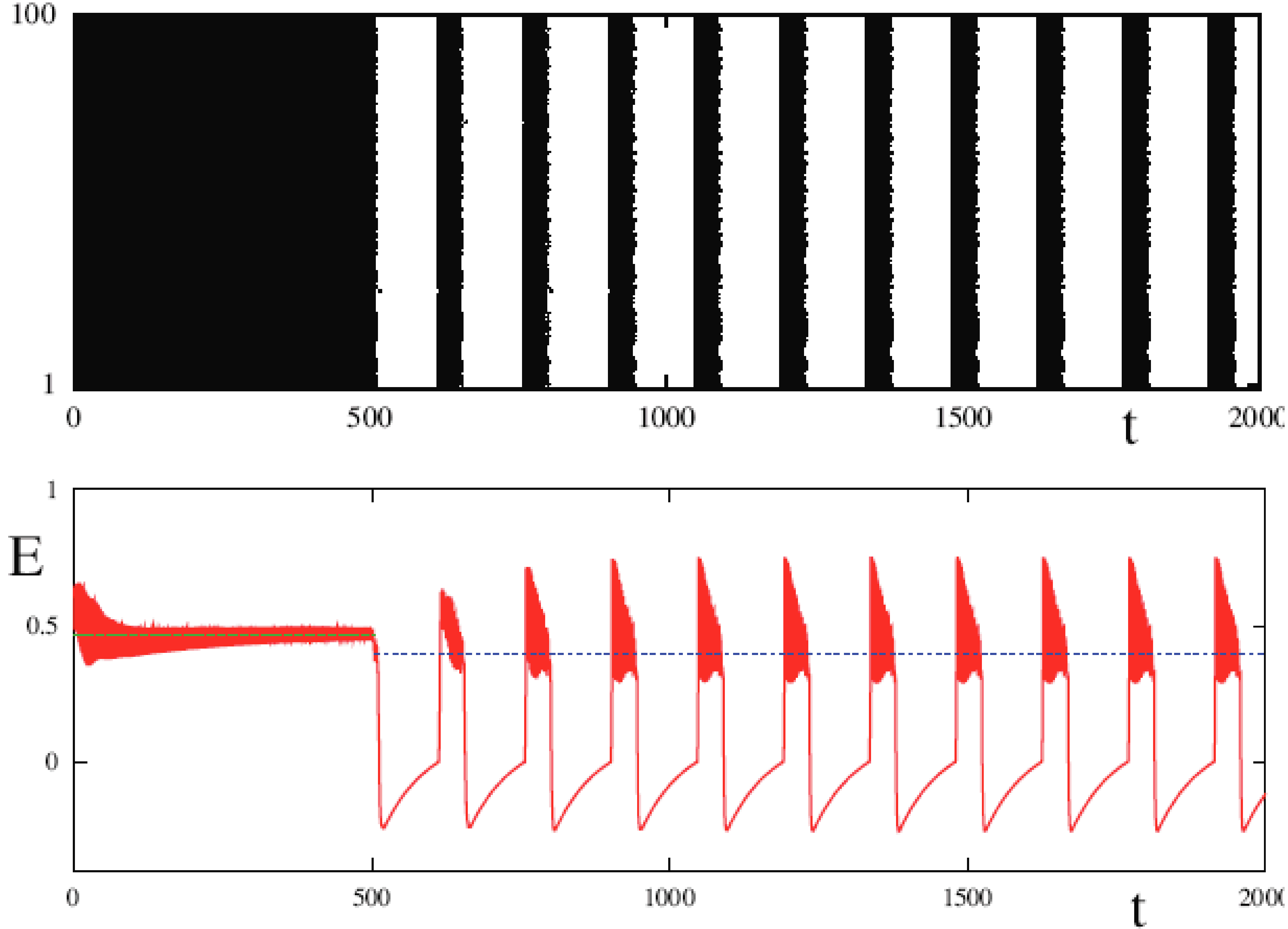
$$\lambda = \nu + i\omega$$

$$\mathrm{Re}\ (\lambda) = \nu = 0$$





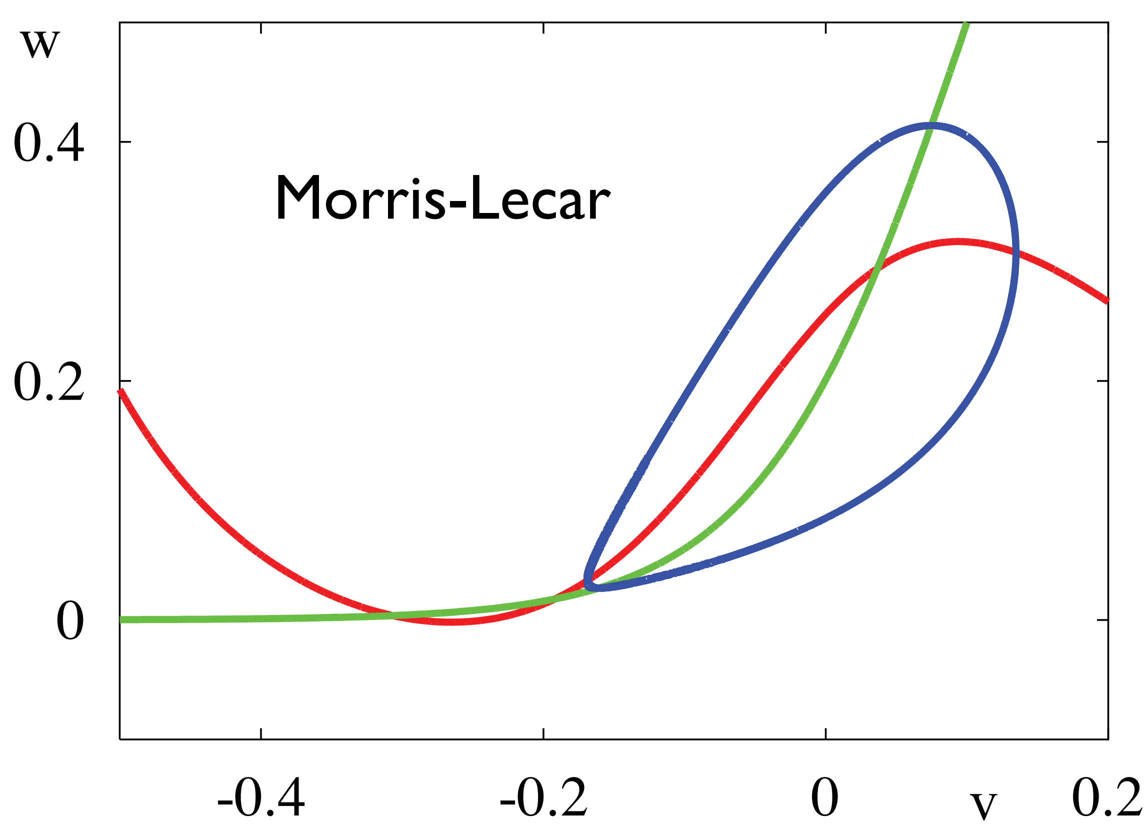
Synchronised bursting

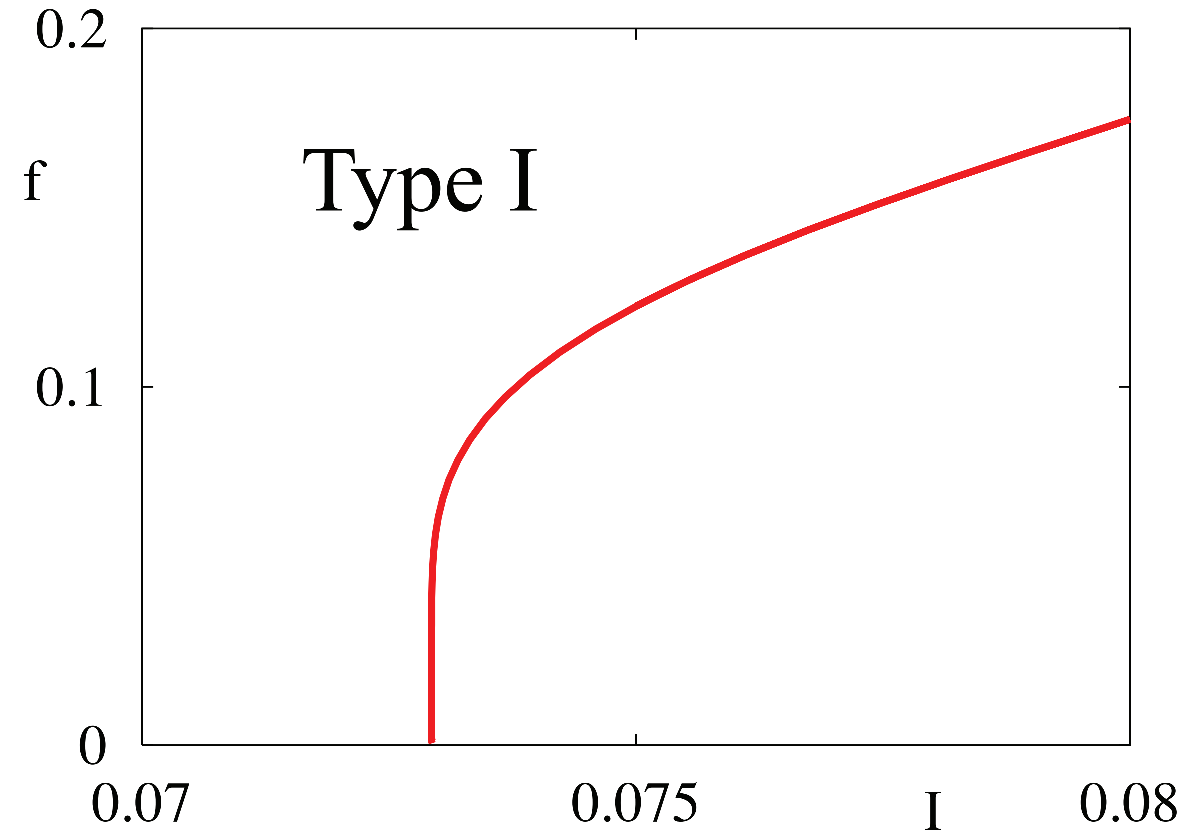


$$E(t) = \frac{1}{N}\sum_{i=1}^{N} v_i(t)$$

Mean field rhythms

S. K. Han, C. Kurrer, and Y. Kuramoto, Dephasing and bursting in coupled neural oscillators, Physical Review Letters, 75 (1995), pp. 3190–3193.





global coupling - mean field signal as average membrane potential

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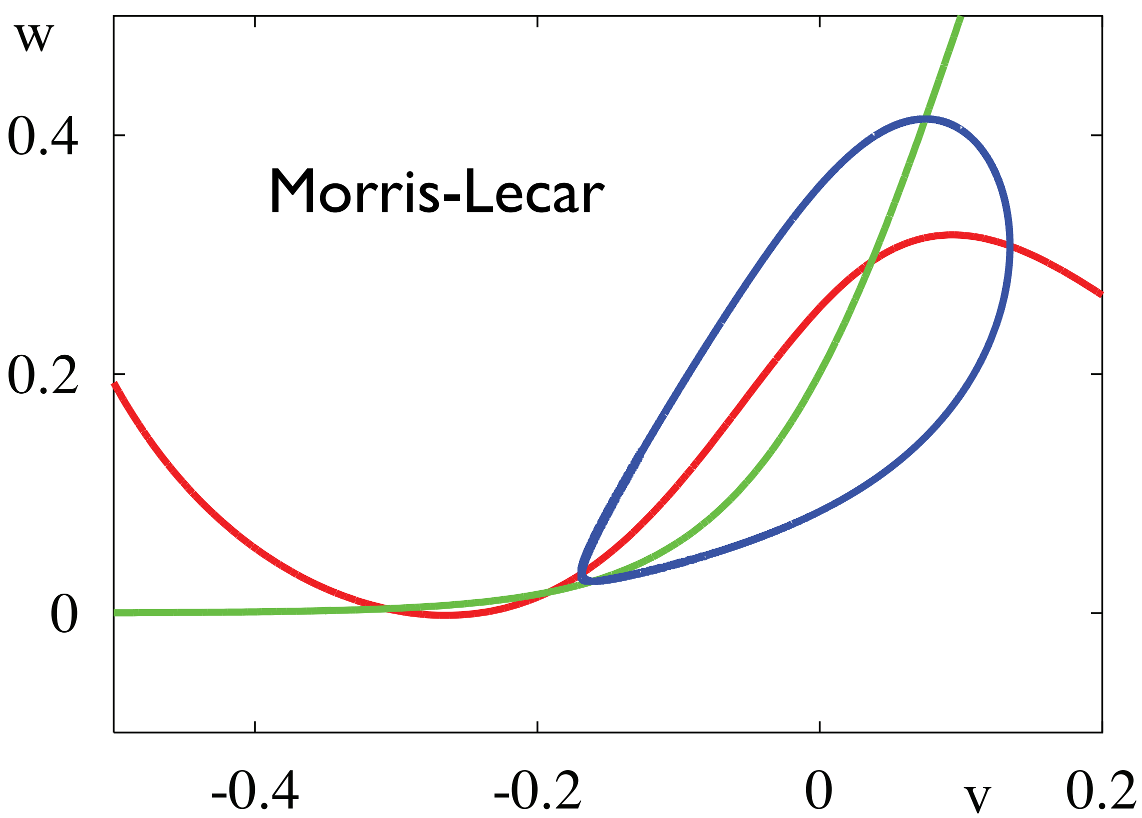

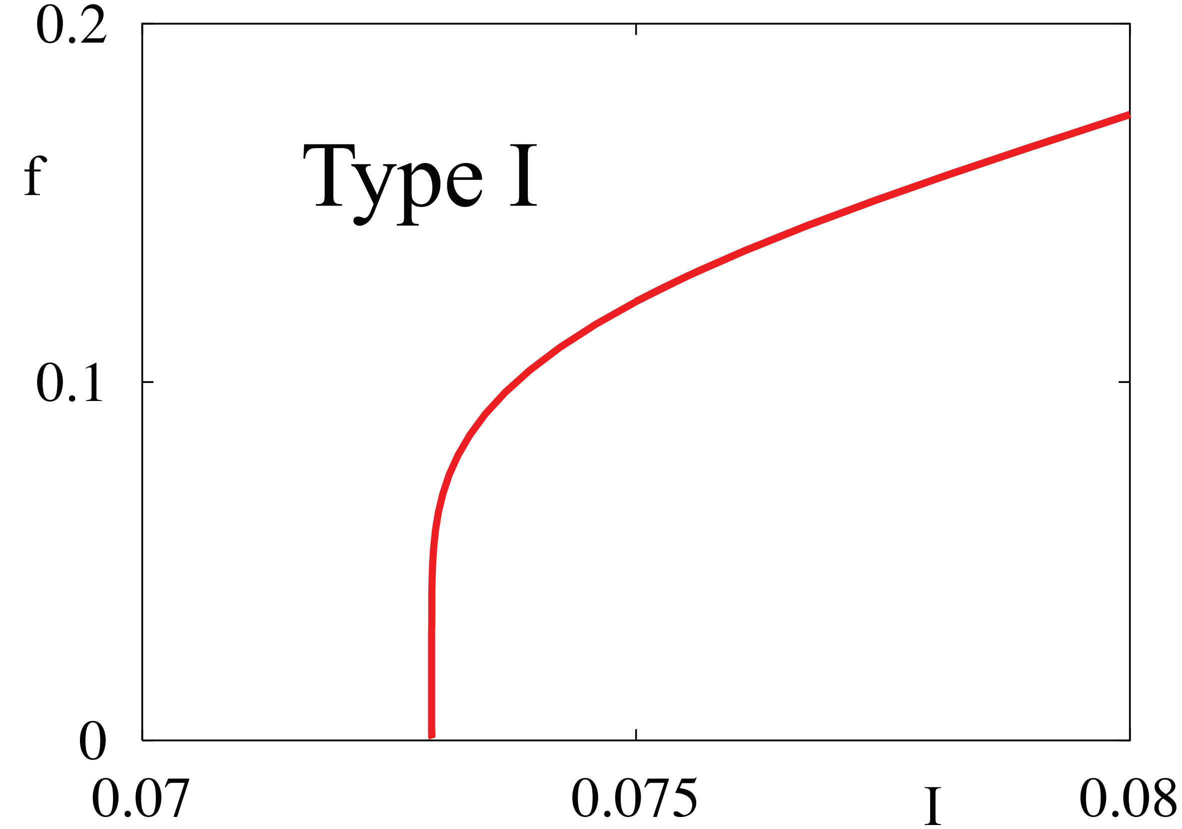

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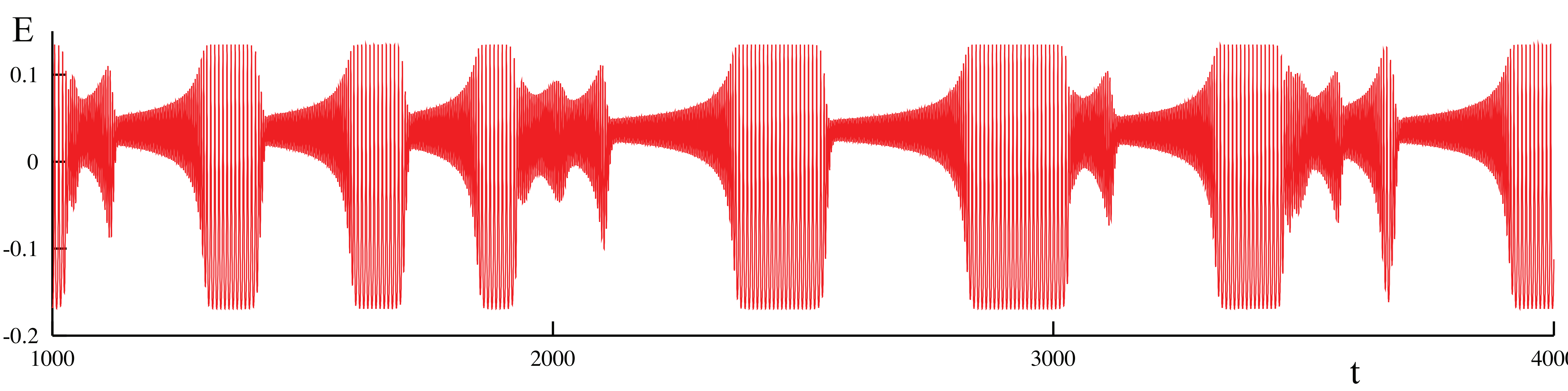
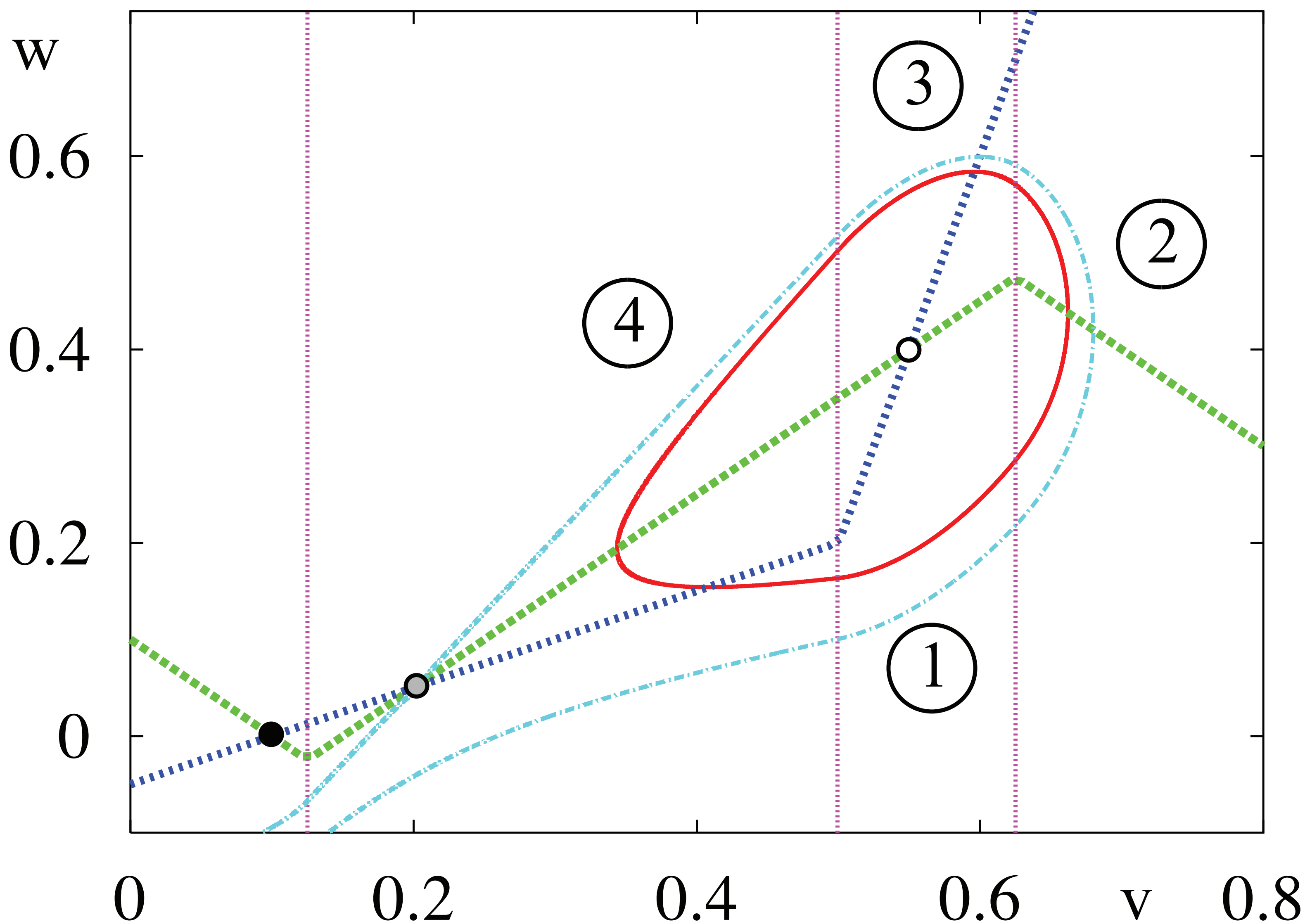


A tractable model



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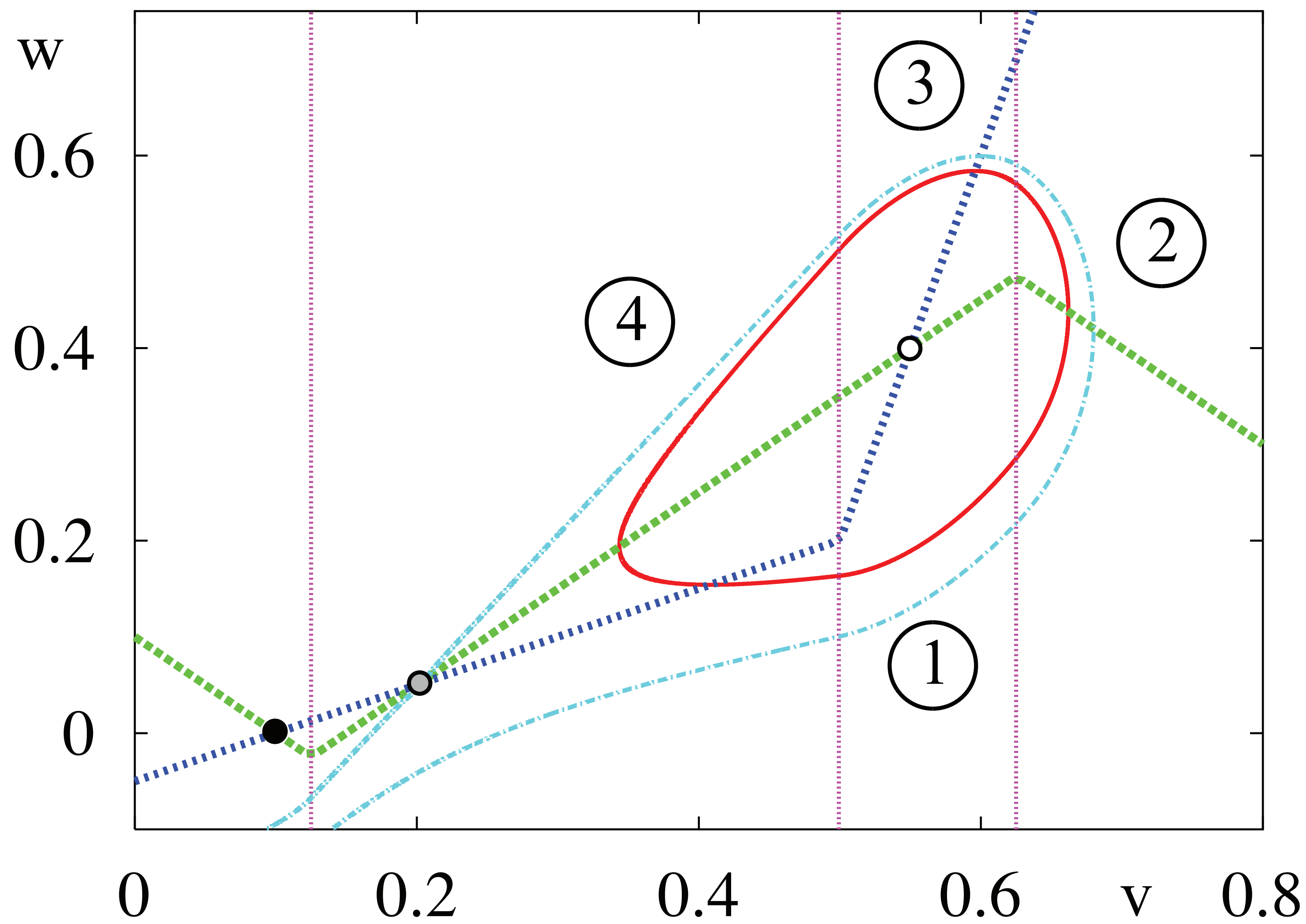

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$$\dot{w} = g(v, w),$$

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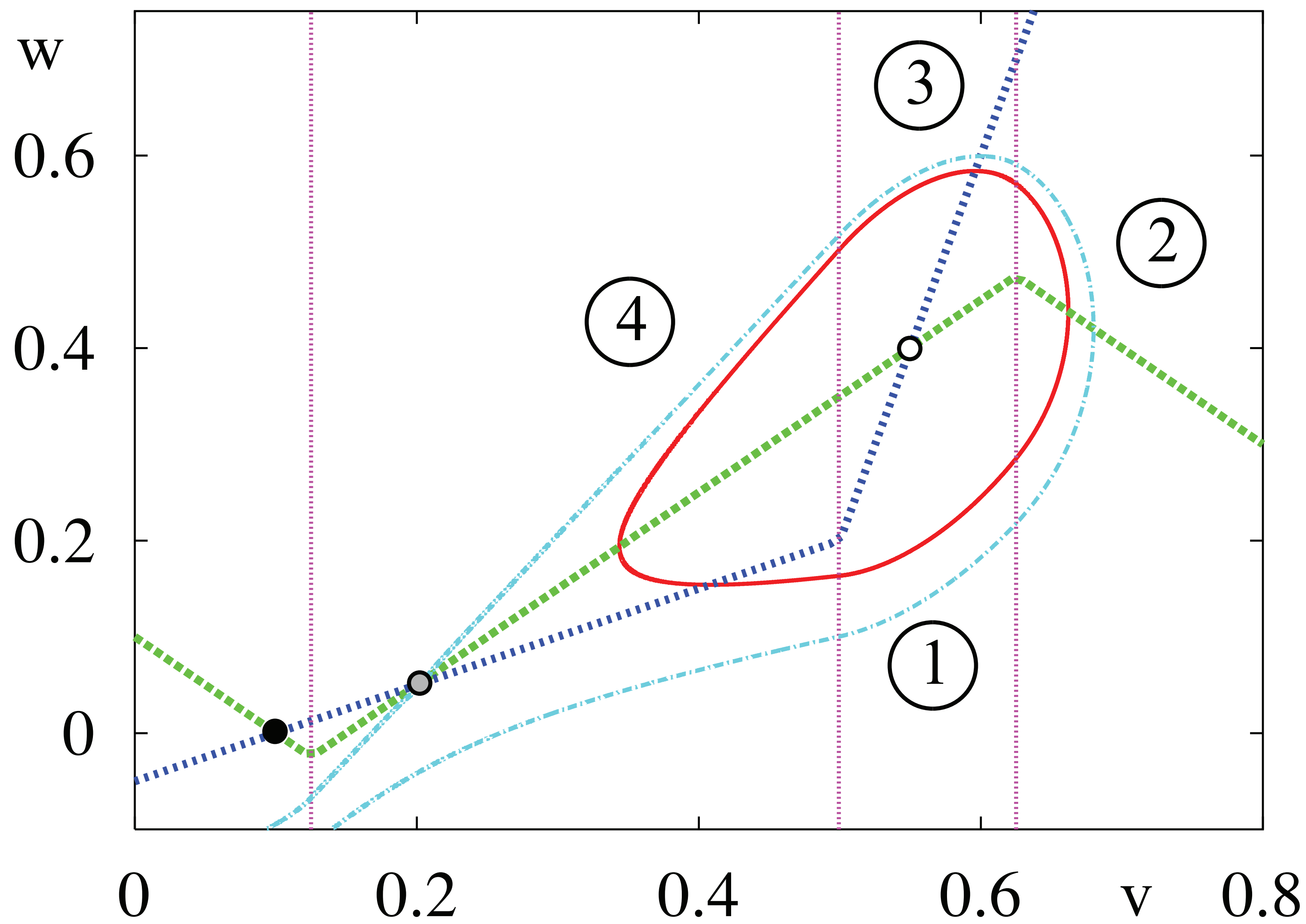

$$\mu \dot{v} = f(v) - w + I,$$
$$\dot{w} = g(v, w),$$

$$f(v) = \begin{cases} -v, & v < a/2 \\ v - a, & a/2 \leq v \leq (1+a)/2 \\ 1 - v, & v > (1+a)/2 \end{cases},$$

$$g(v, w) = \begin{cases} (v - \gamma_1 w + b^* \gamma_1 - b)/\gamma_1, & v < b \\ (v - \gamma_2 w + b^* \gamma_2 - b)/\gamma_2, & v \geq b \end{cases},$$

Periodic orbits - PWL systems

$$\dot{z} = Az + b, \qquad z = \begin{bmatrix} v \\ w \end{bmatrix}$$

$$z(t) = G(t)z(0) + K(t)b, \qquad G(t) = \mathrm{e}^{At}, \qquad K(t) = \int_0^t G(s)\mathrm{d}s$$

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Introduce 4 labels and write $z_\mu(t) = G_\mu(t)z_\mu(0) + K_\mu(t)b_\mu$

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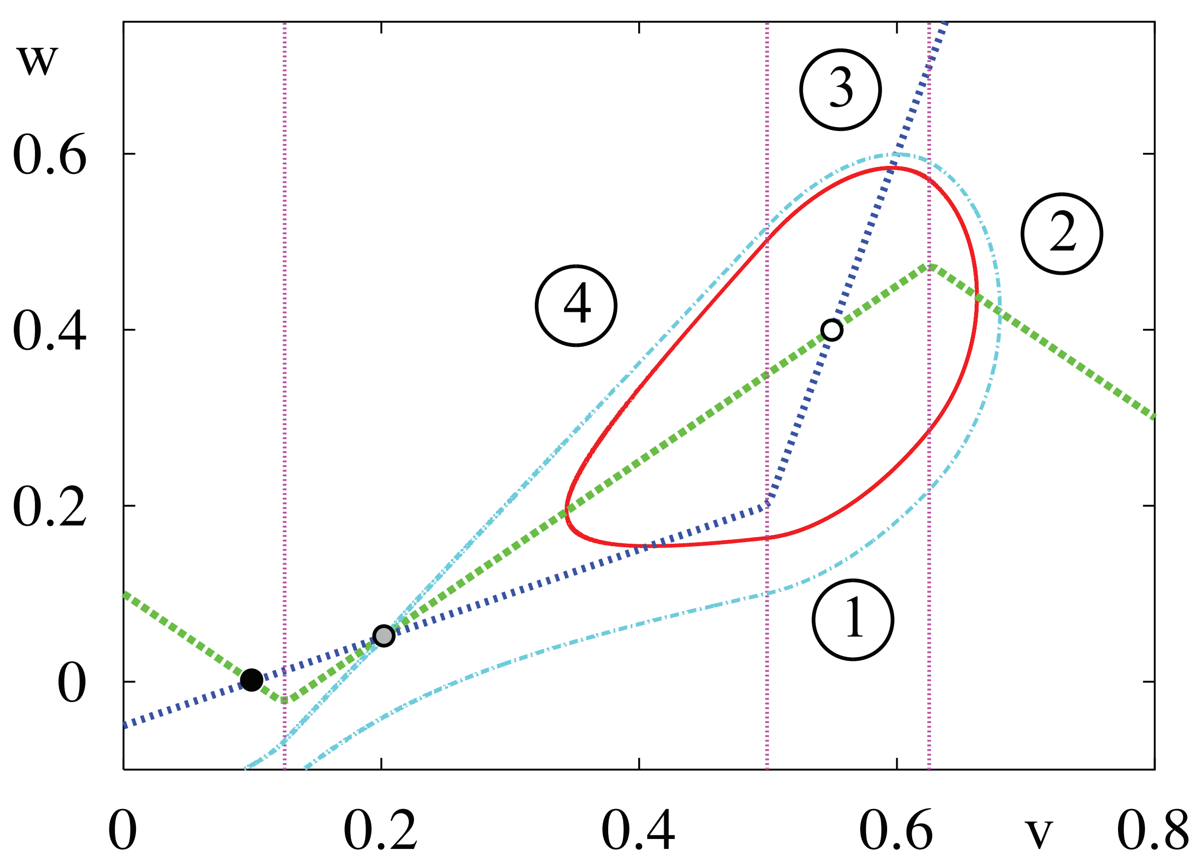


Continuous and periodic

- Choose initial data

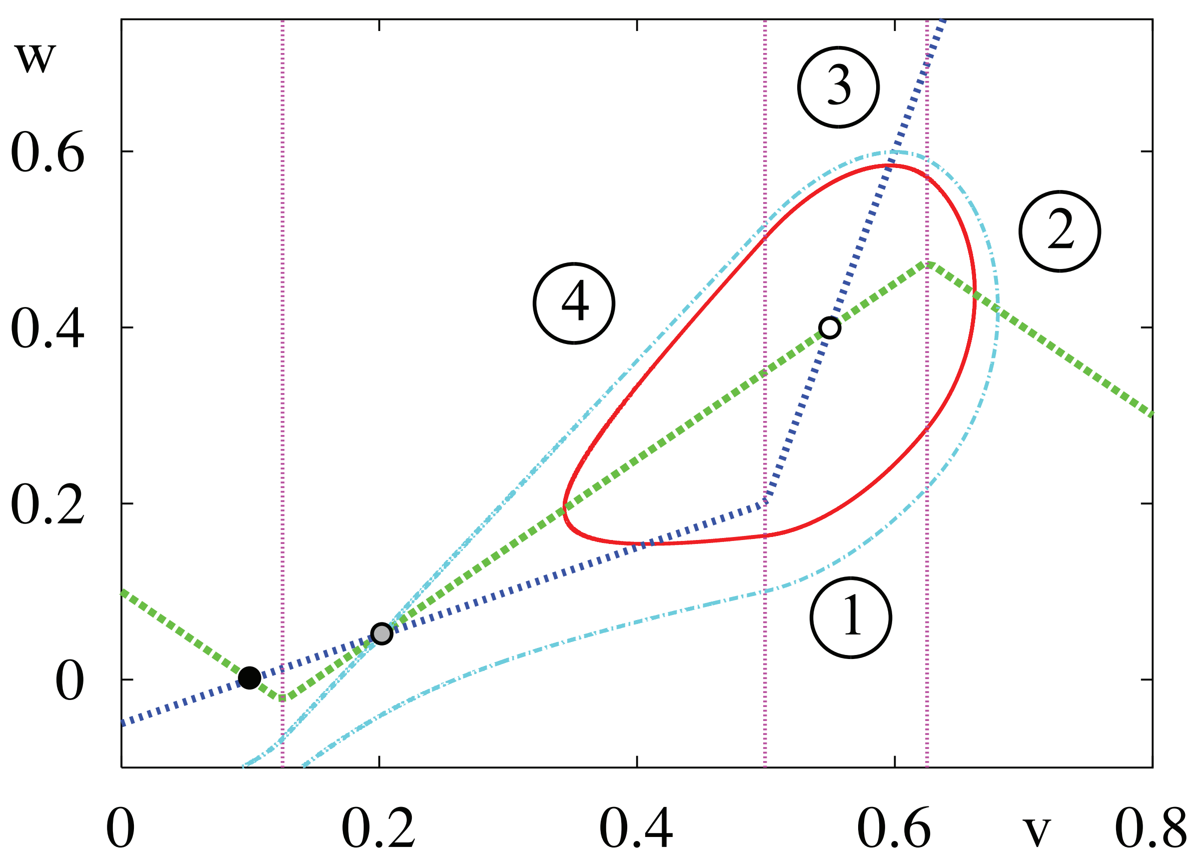
$$z_1(0) = (v_{\text{th}}^1, w^*)$$

- "Times of flight" determined by threshold crossings

$$v_1(T_1) = v_{\text{th}}^2,\ v_2(T_2) = v_{\text{th}}^2,\ v_3(T_3) = v_{\text{th}}^1, \text{ and } v_4(T_4) = v_{\text{th}}^1$$

- Ensure periodicity

$$w_4(T_4) \ = \ w_1(0)$$



Continuous and periodic

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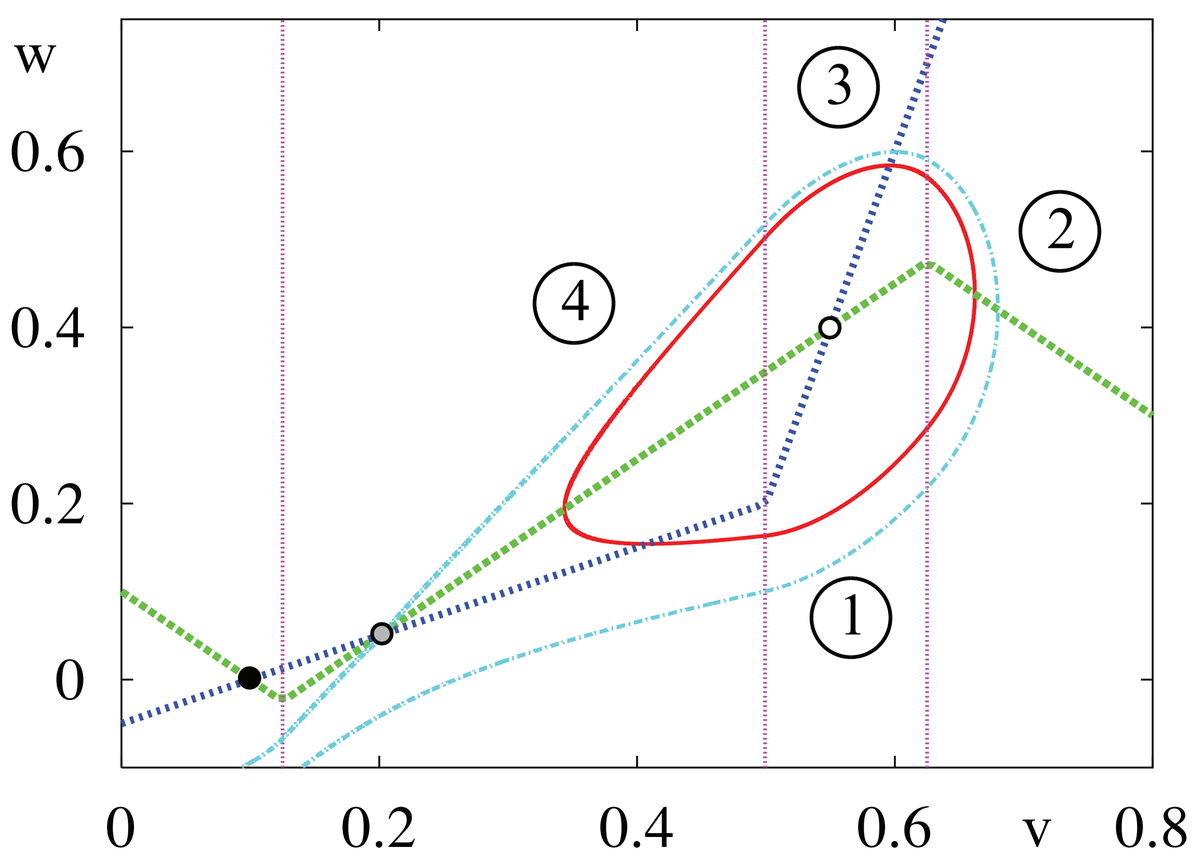
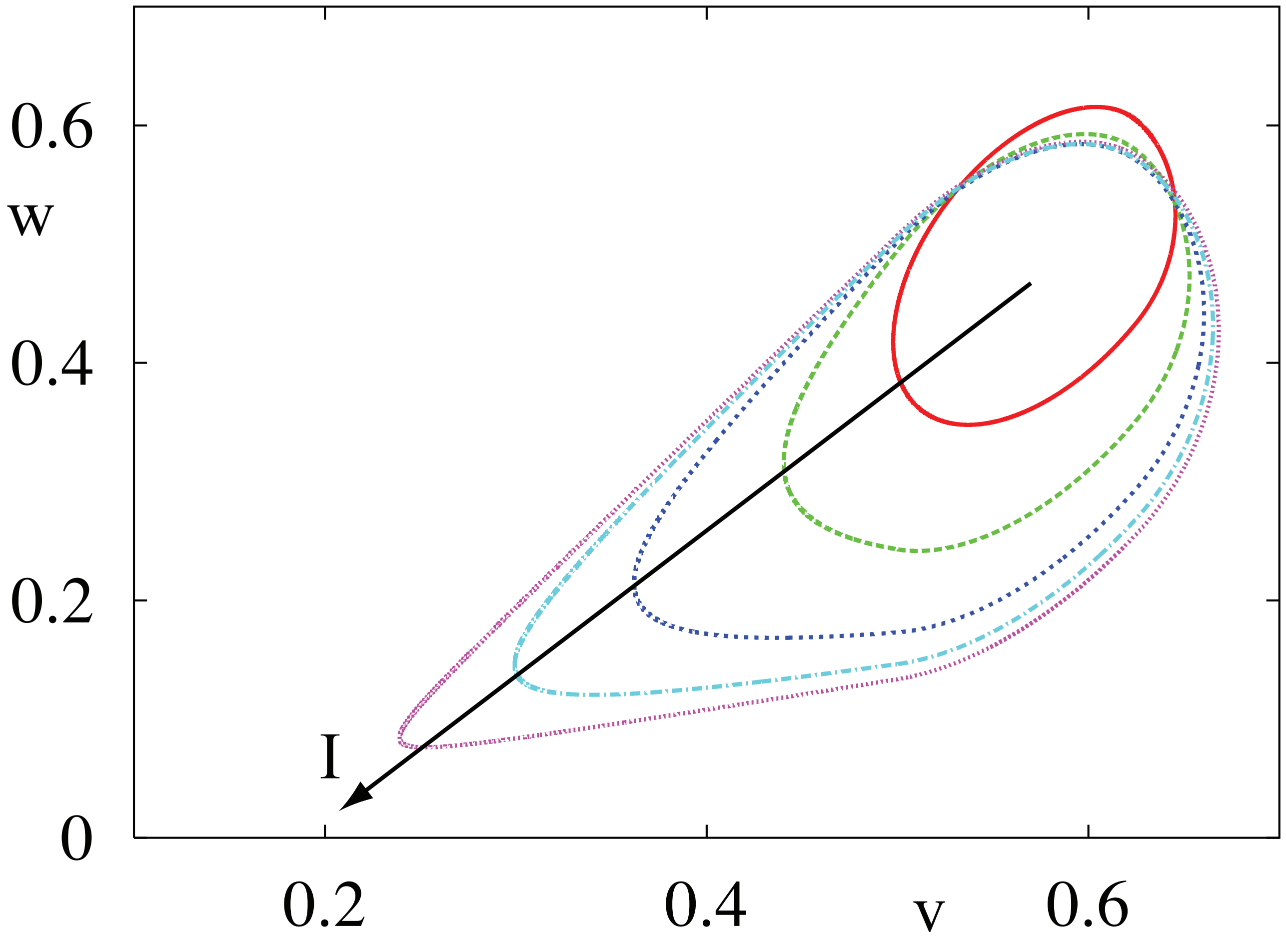


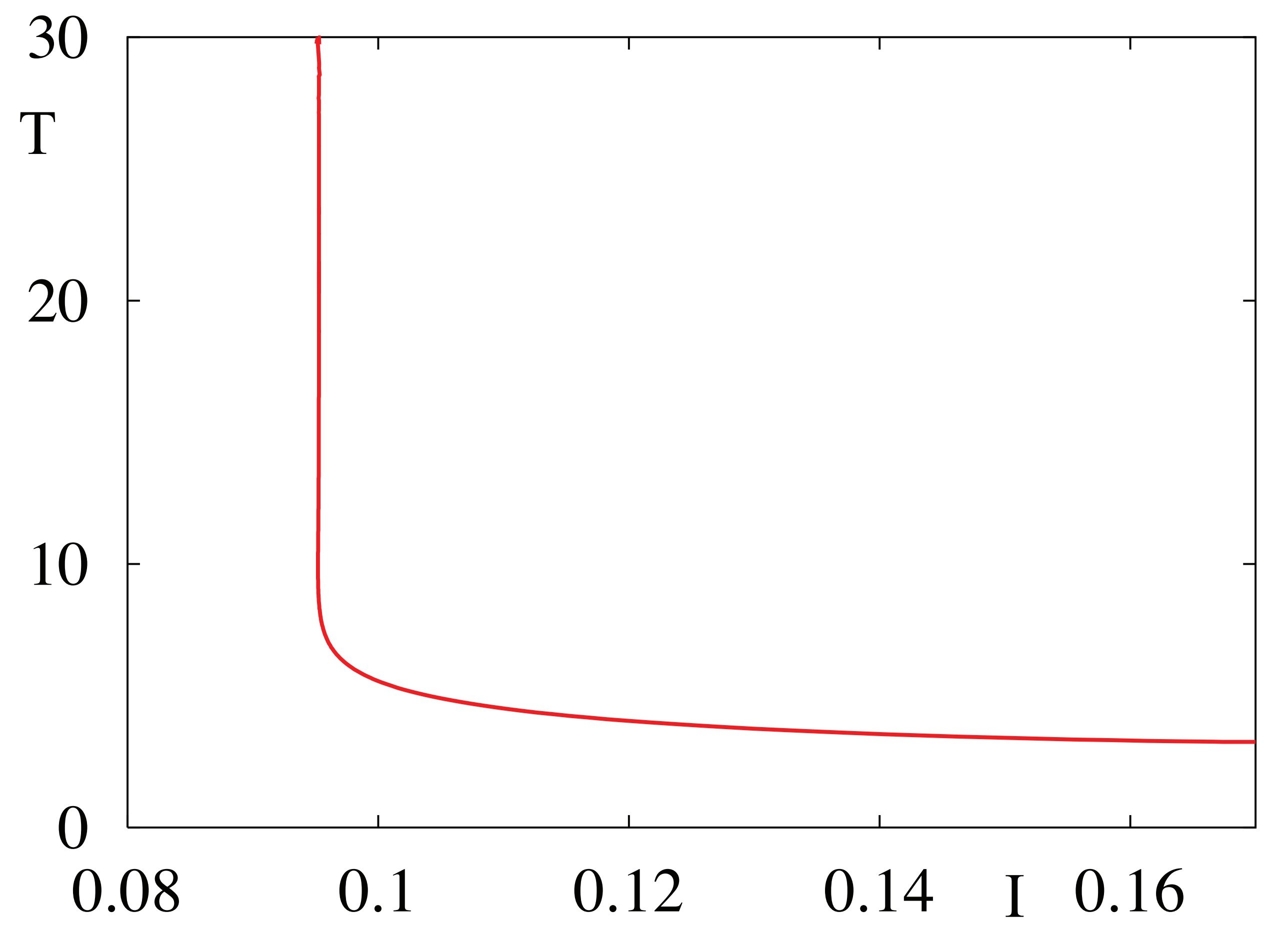
Yielding w^*

and the period

$$T = \sum_{\mu=1}^{4} T_\mu$$

Orbit and period





PRC - exact solution

Call the orbit $z = Z(t)$ where $\dot{z} = F(z)$

Introduce a phase (isochronal coordinates) θ

Adjoint $Q = \nabla_Z \theta$ (Ermentrout and Kopell 1991)

$$\frac{\mathrm{d}Q}{\mathrm{d}t} = D(t)Q, \qquad D(t) = -DF^T(Z(t))$$

$$\nabla_{Z(0)}\theta \cdot F(Z(0)) = 1/T \text{ and } Q(t) = Q(t+T)$$

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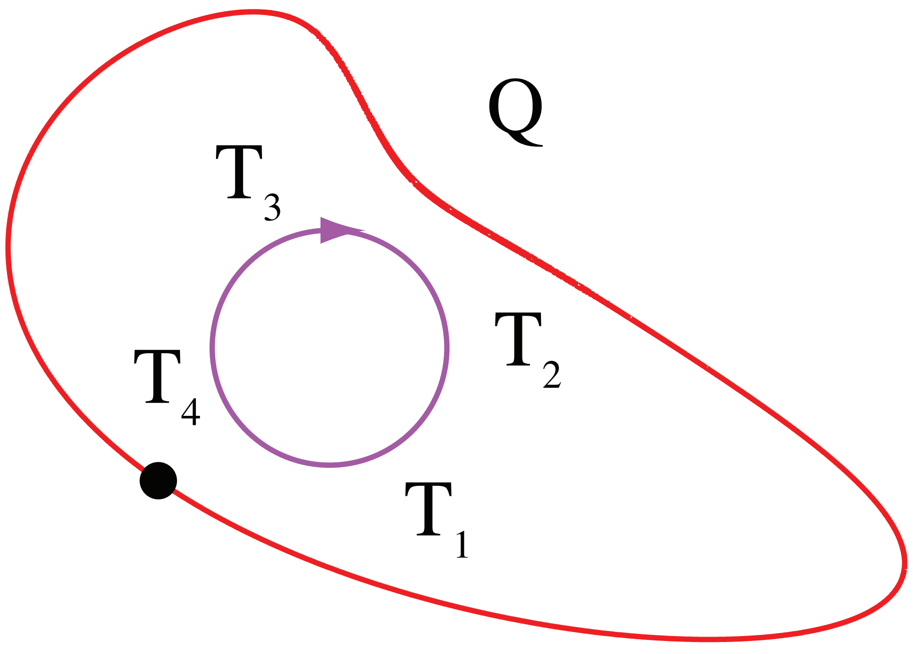
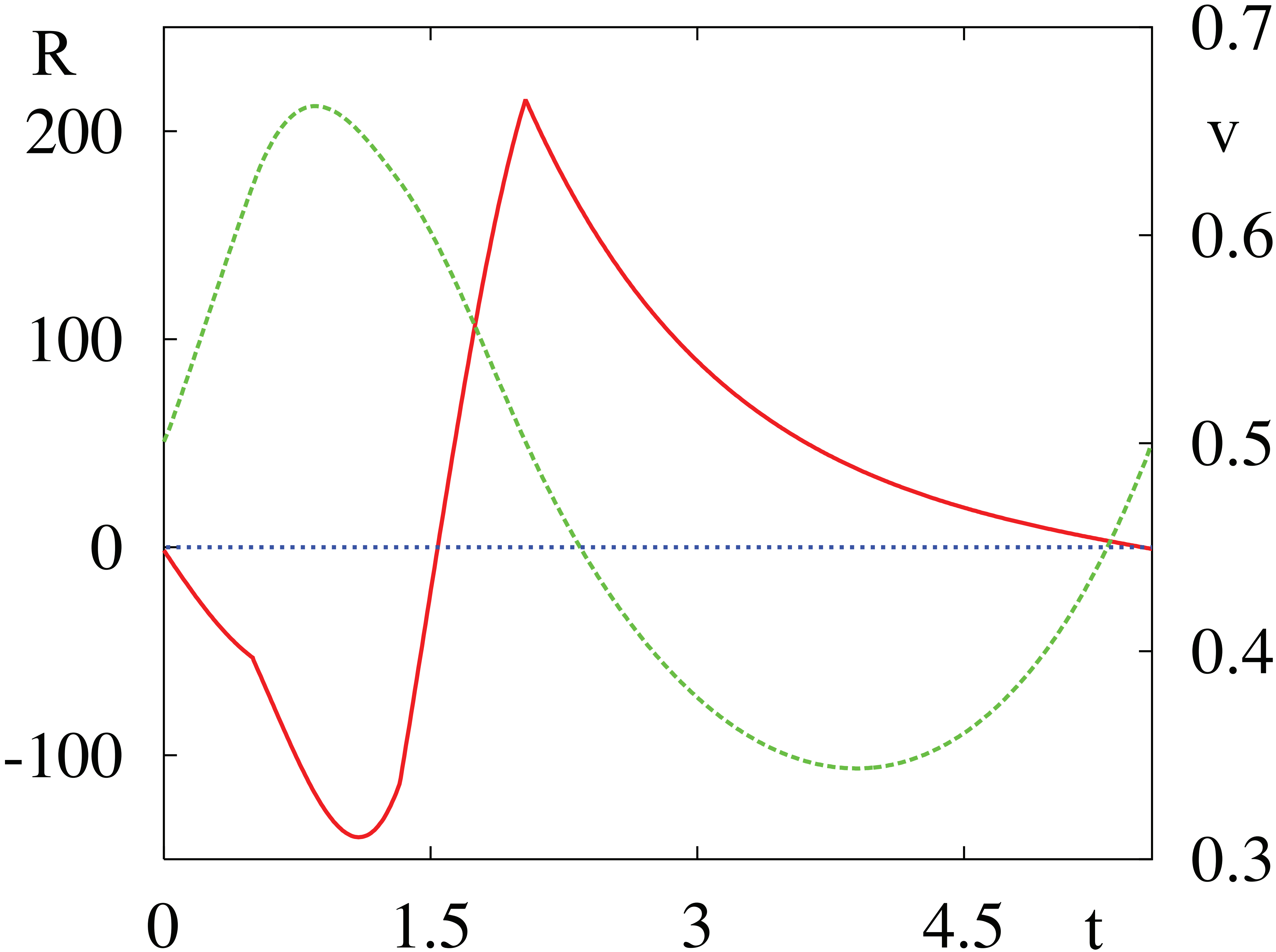
Another pwl system with 4 labels!



$$\dot{Q}_\mu = D_\mu Q_\mu, \text{ where } D_\mu = -A_\mu^T$$

Solve using $Q_\mu(t) = G_\mu^T(T_\mu - t)Q_\mu(T_\mu)$

PRC



Weak coupling

Consider a family of weakly connected systems

$$\dot{X}_i = F_i(X_i) + \epsilon G(X), \qquad i = 1, \ldots, n$$

such that each equation in the uncoupled system ($\epsilon = 0$) has an exponentially orbitally stable limit cycle $\gamma_i \subset \mathbb{R}^m$ having natural frequency $\Omega_i \neq 0$. Then the oscillatory weakly connected system can be reduced to a phase model of the form

$$\dot{\theta}_i = \Omega_i + \epsilon g_i(\theta_1, \ldots, \theta_n), \qquad \theta_i \in S^1, \quad i = 1, \ldots, n$$

defined on the n-torus $T^n = S^1 \times \ldots \times S^1$. ie there is an open neighbourhood W of $M = \gamma_1 \times \ldots \times \gamma_n \subset \mathbb{R}^{mn}$ and a continuous function $h : W \to T^n$ that maps solutions of the full model to those of the phase model. ■

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Drive

$$\boxed{\dot{\theta}_i = \Omega_i + \epsilon R_i(\theta_i) G_i(\Gamma(\theta))}$$

PRC

Averaging

$$\frac{\mathrm{d}\theta_i}{\mathrm{d}t} = \frac{1}{T} + \frac{1}{N}\sum_{j=1}^{N} g_{ij} H(\theta_j - \theta_i)$$

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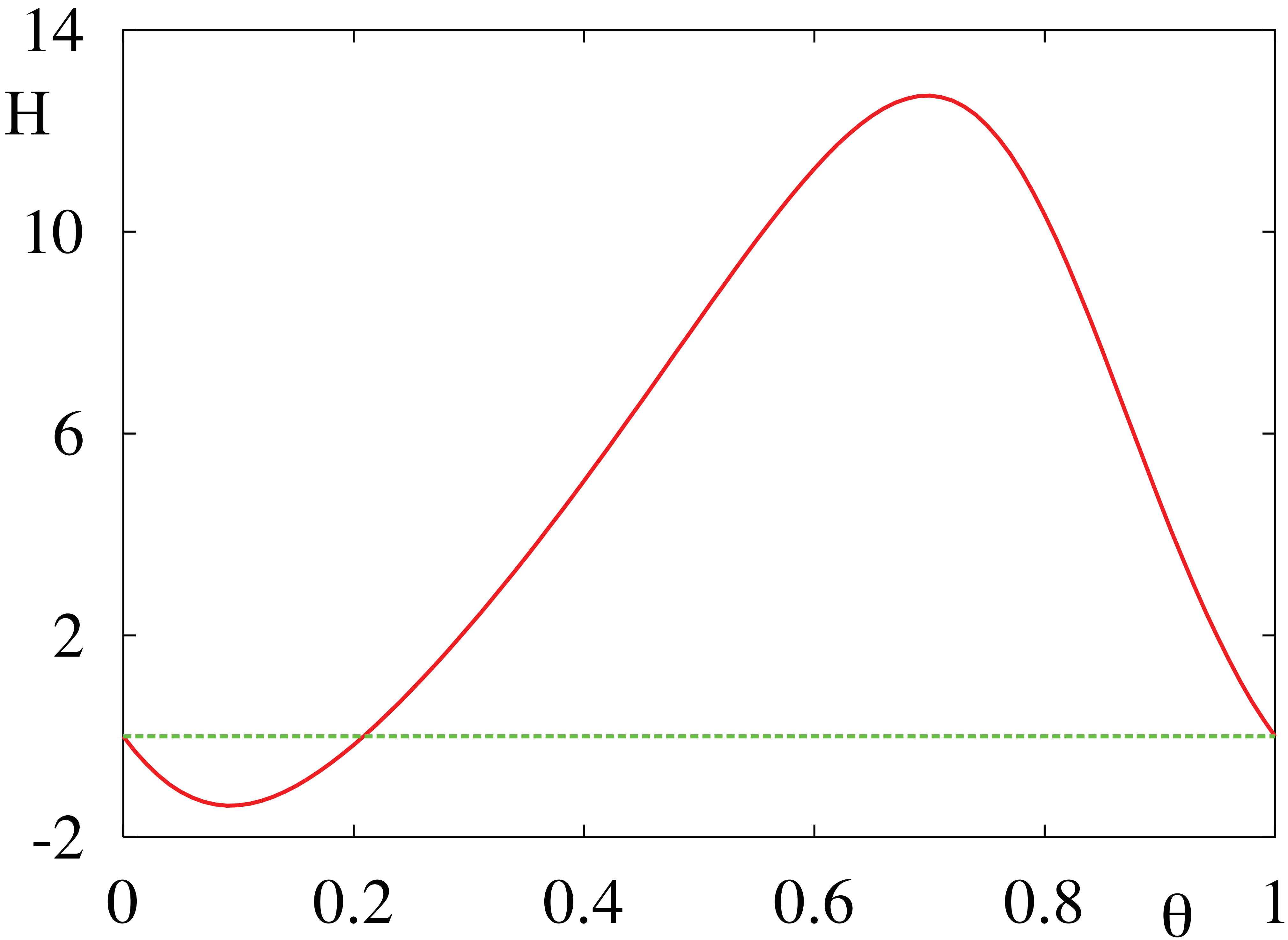
For the pwl model we can obtain the Fourier coefficients in closed form (spare the details!)

Phase interaction function H



Global coupling and large N

Synchrony (relative): $\phi_i(t) = 0,\ \Omega = 1/T$

eigenvalue $\lambda = -gH'(0)$ (multiplicity N-1)

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Synchronous and splay state unstable

Beyond weak coupling

Synchrony - existence as for uncoupled model

Stability - Floquet theory shows restabilisation with increasing g

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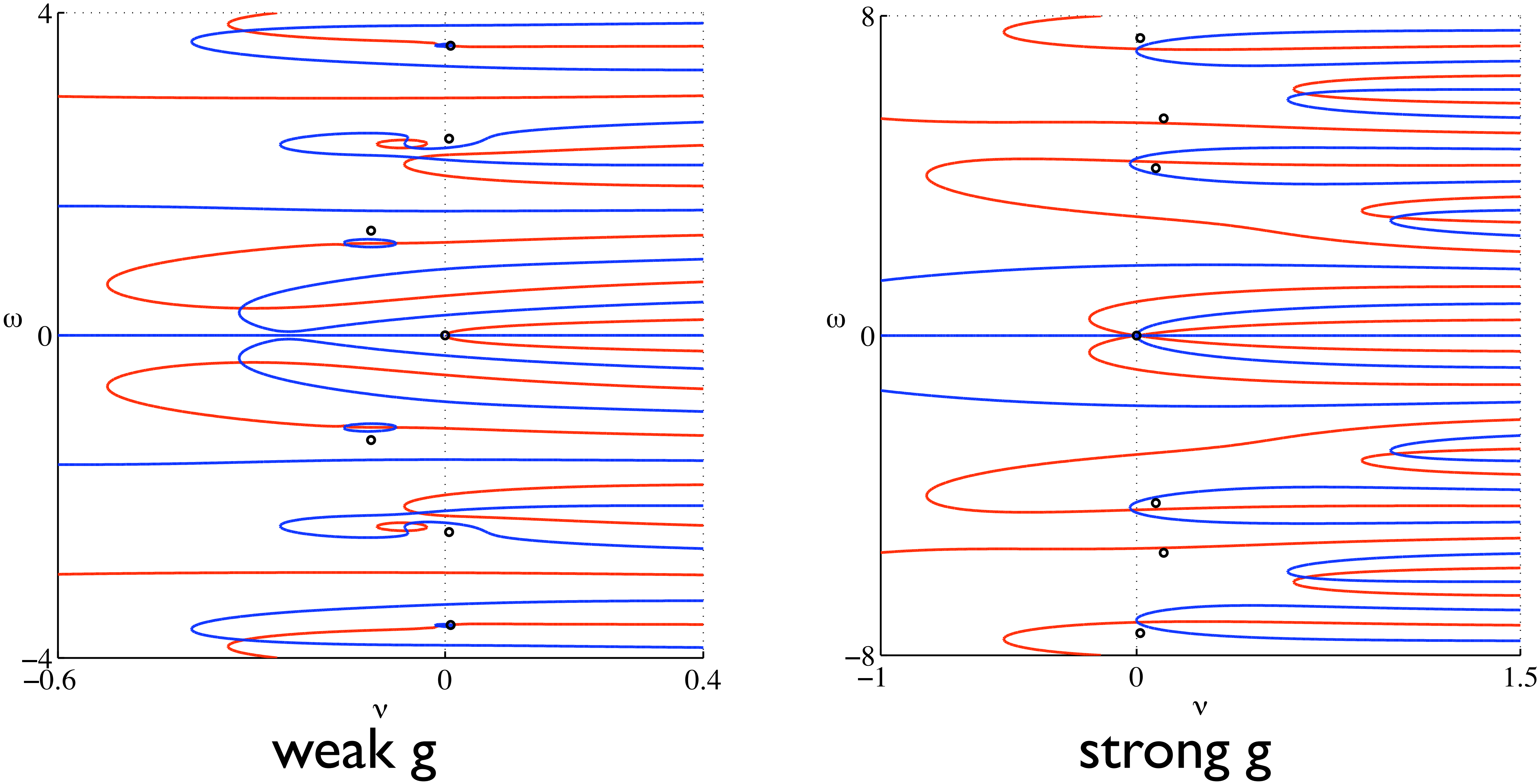
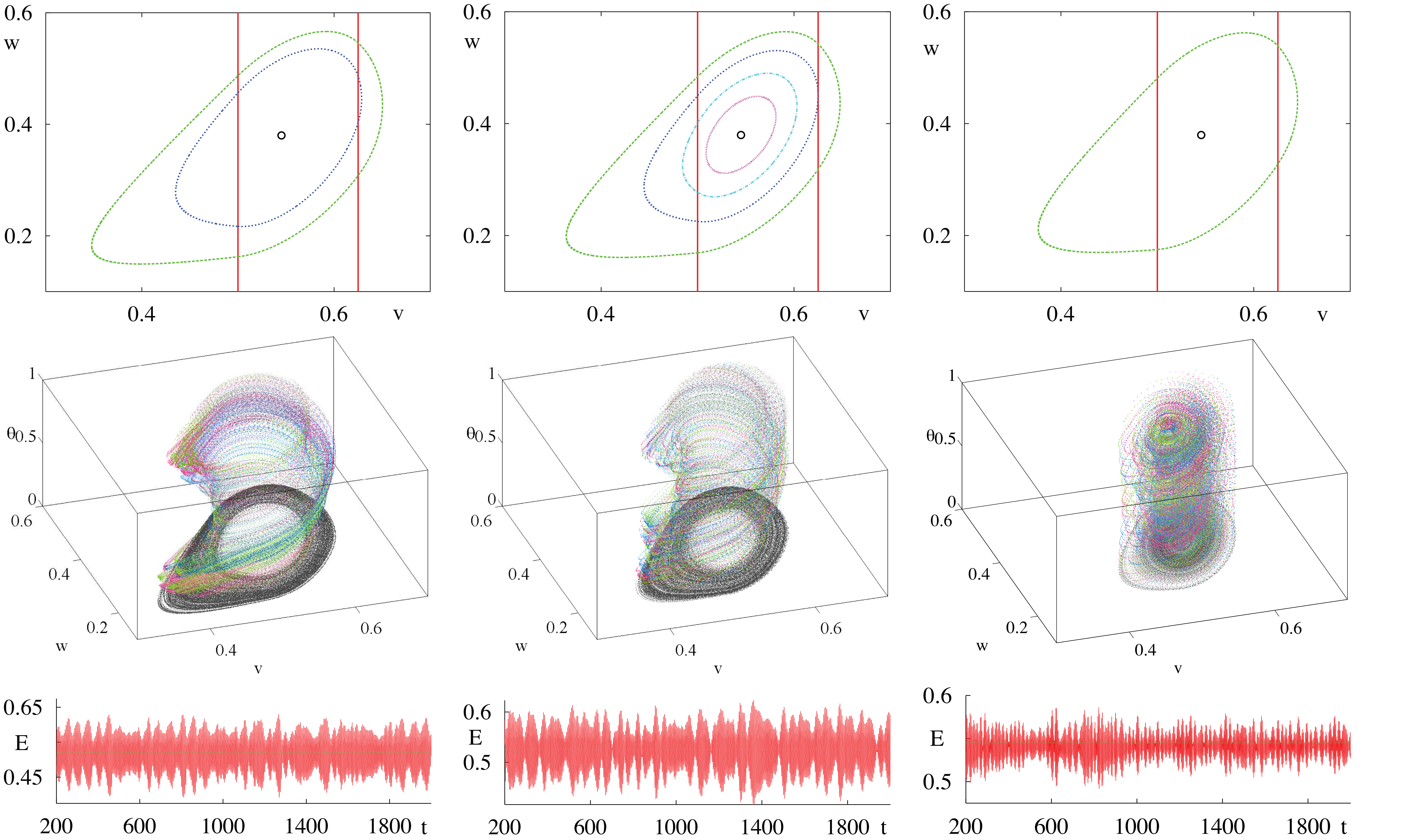
Synchrony - existence as for uncoupled model

Stability - Floquet theory shows restabilisation with increasing g

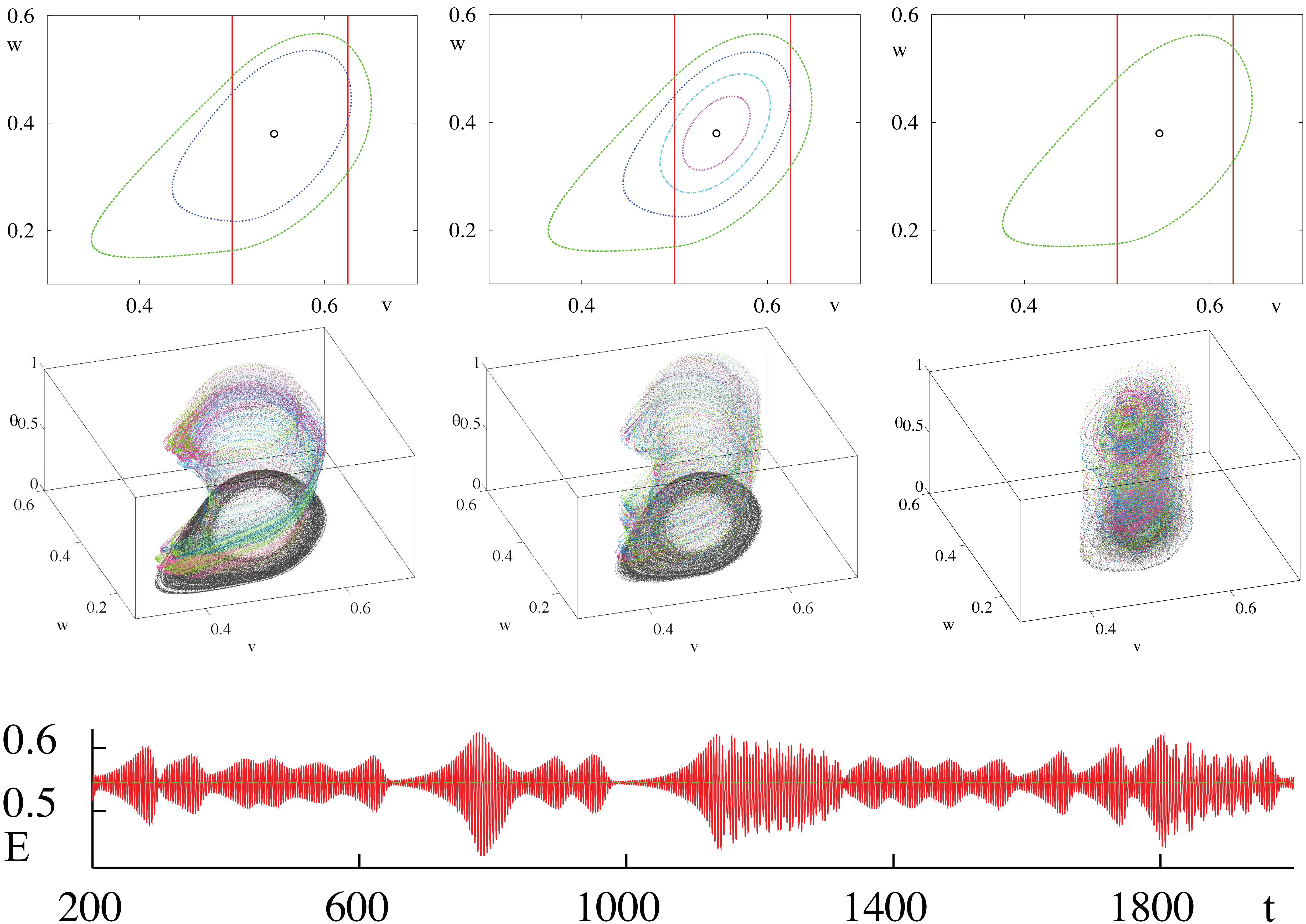
Splay - analysis as for absolute integrate-and-fire model



Understanding rhythms



Understanding rhythms



Future Challenges

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Wilson-Cowan style model with gaps?

“Equation Free Modelling” - role of architectecture, and allowing spatio-temporal pattern analysis

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Gaps on distal dendrites

already known to “tune” network dynamics

2nd Annual meeting of the UK Mathematical Neuroscience Network: 22-25 Mar 2009, Edinburgh.

http://icms.org.uk/workshops/mathneuro2009

Ad Aertsen
Michael Breakspear
Carson Chow
Geoff Goodhill
Vincent Hakim
Viktor Jirsa
Carlo Laing
Peter Latham

Andre Longtin
Stefano Panzeri
David Pinto
Horacio Rotstein
Andrey Shilnikov
Dan Tranchina
Krasimira Tsaneva-Atanasova
Carl Van Vreeswijk