Inferring phase and amplitude response of oscillatory systems exploiting test stimulation

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Motivation

- We need these characteristics for modelling oscillatory networks

- We need the phase and amplitude response to optimise control of oscillatory dynamics

Analysis of oscillatory systems

- Active analysis vs. passive analysis

- Model-based analysis vs. non-model-based one

Analysis of oscillatory systems

- Active analysis vs. passive analysis
  - Passive analysis: we observe the system under free-running conditions
  - Active analysis: we perturb the system by a specially designed perturbation and look for the response
- Model-based analysis vs. non-model-based one

Analysis of oscillatory systems

- Active analysis vs. passive analysis

- Model-based analysis vs. non-model-based one
  - Non-model-based: no assumption about the origin of the signal
    (an example: spectral analysis)
  - Model-based: the validity of the technique crucially depends on the assumption about the system under investigation
    (an example: coupling function reconstruction assumes that the signals come from interacting self-sustained oscillators)

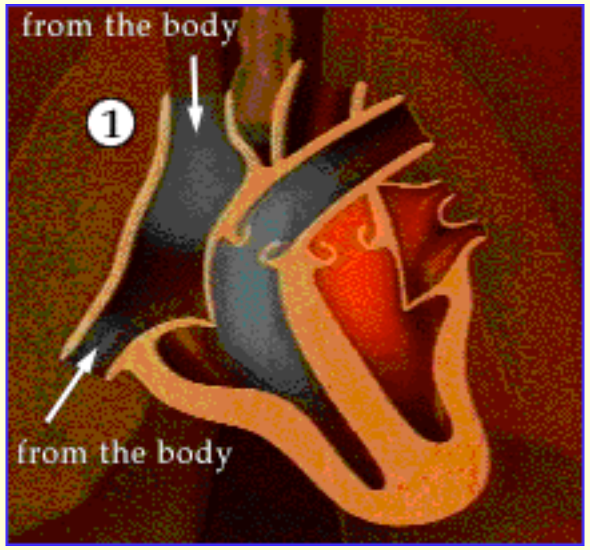
Analysis of oscillatory systems

- Active analysis vs. passive analysis

- Model-based analysis vs. non-model-based one

We present an active analysis technique based
on the model of self-sustained oscillators

Self-sustained oscillators



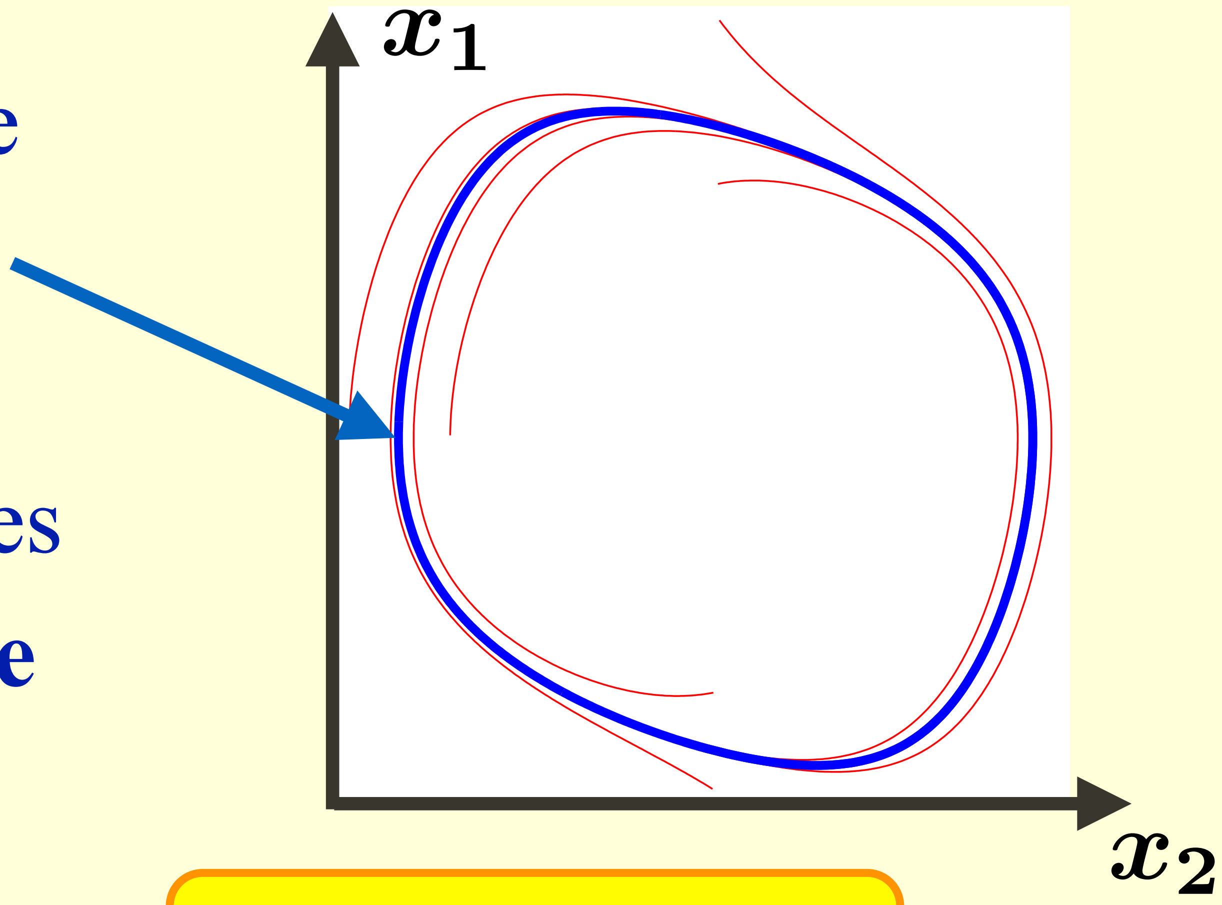
Active oscillators

Biology: systems generating **endogenous** rhythms

Systems of this class:

1. generate stationary oscillations without periodic forces
2. are dissipative nonlinear systems
3. are described by autonomous differential equations
4. are represented by a limit cycle in the phase space

Self-sustained oscillator: limit cycle and phase



Stable limit cycle: an attractive closed curve in the phase space

Phase is a variable that describes the motion along the **limit cycle**

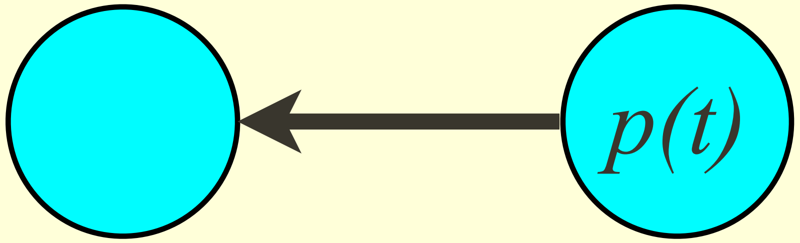
Phase is defined to obey the condition $\boxed{\dot{\varphi} = \omega = 2\pi/T}$

and can be introduced:

1. on the limit cycle

2. in the basin of attraction of the limit cycle

Phase dynamics: the phase sensitivity function



Suppose the oscillator is driven by **weak** perturbation *p(t)*

Then

$$\dot{\varphi} = \omega + Z(\varphi)p(t)$$

Phase Sensitivity function, or Phase Response Curve (PRC)

Phase dynamics equation in the **Winfree form**

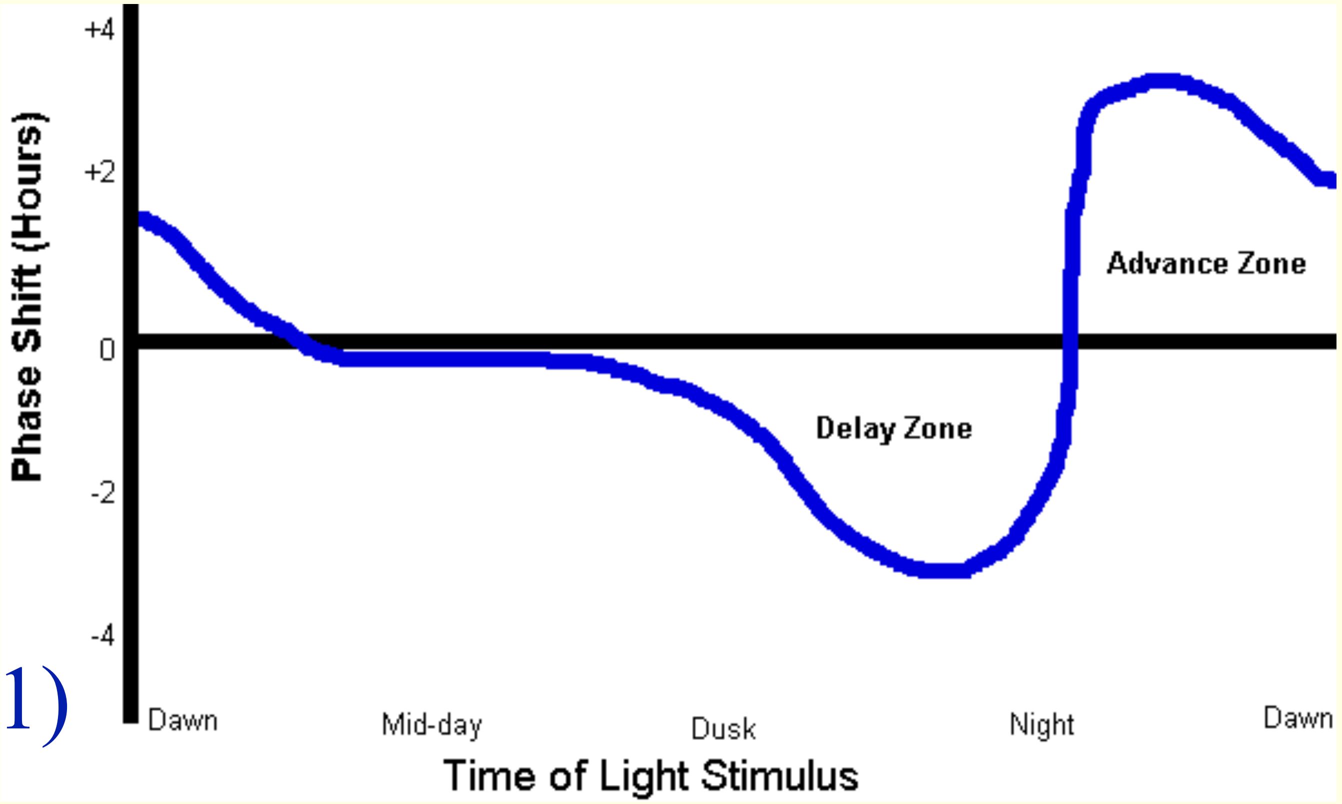
- **PRC** is a basic characteristic of a limit-cycle oscillator
- **PRC** description is widely used, e.g. in neuroscience

Phase response curve: examples

PRC quantifies response (phase shift) of an oscillator to a perturbation

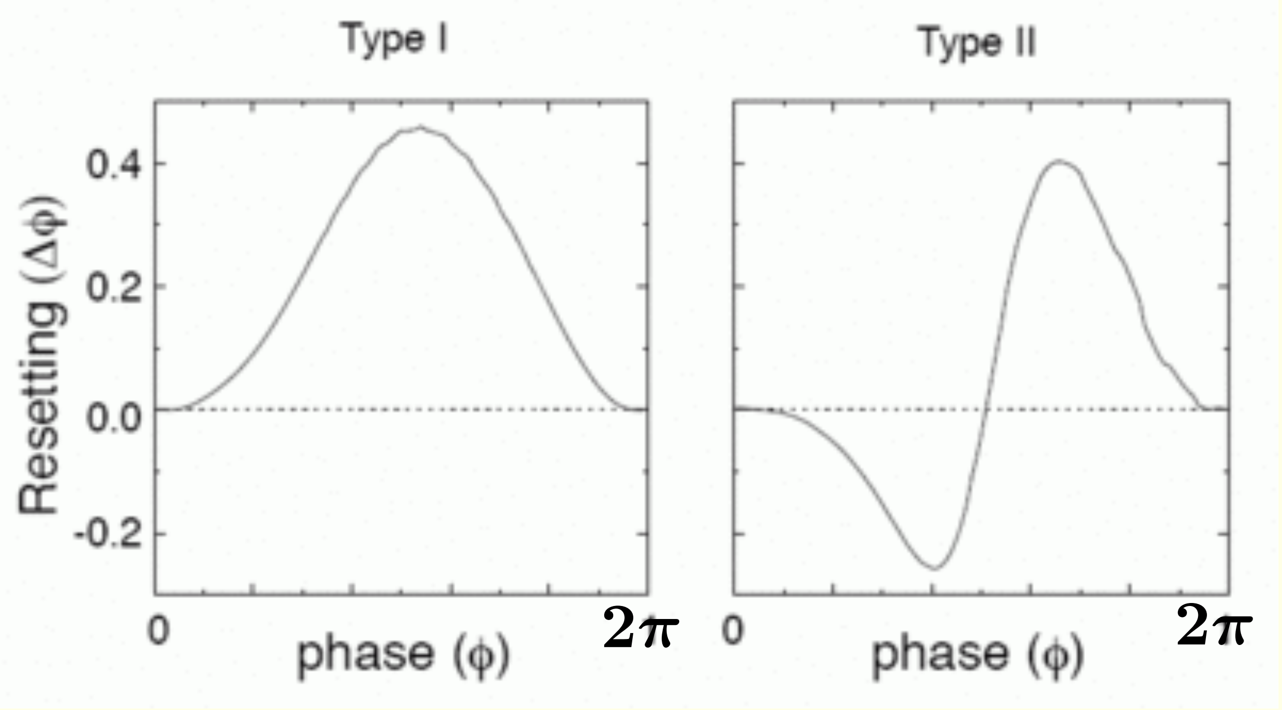
Example: human circadian cycle

- *Delay region: evening light shifts sleepiness later* and
- *Advance region: morning light shifts sleepiness earlier*.



(Wikipedia; Kripke & Loving, 2001)

Example: neural PRCs

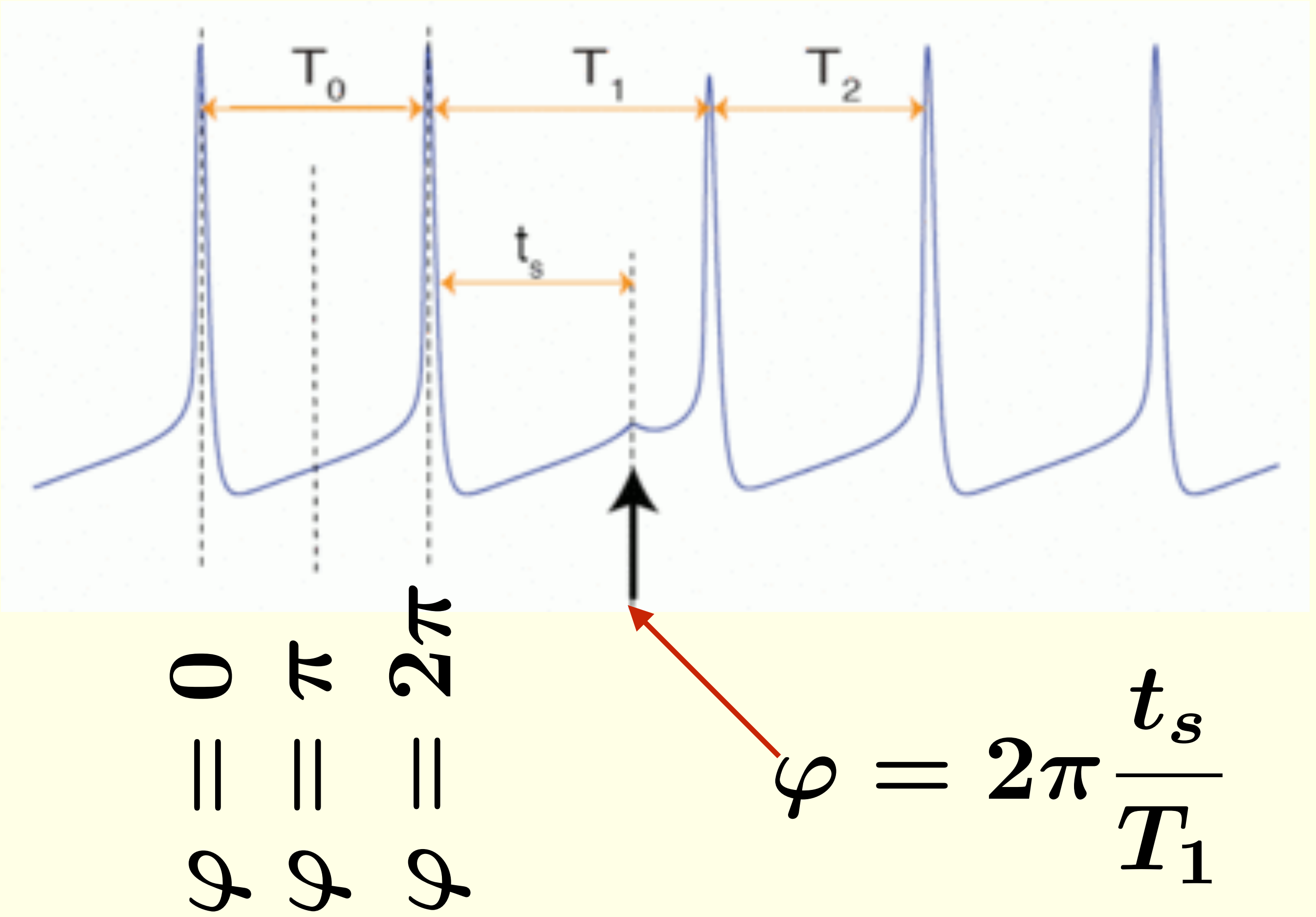


(Scholarpedia)

PRC determination

Traditional approach to PRC determination: repeated stimulation of an isolated oscillator by short pulses

(Picture from Scholarpedia)



$\varphi = 0$ $\quad \varphi = \pi$ $\quad \varphi = 2\pi$

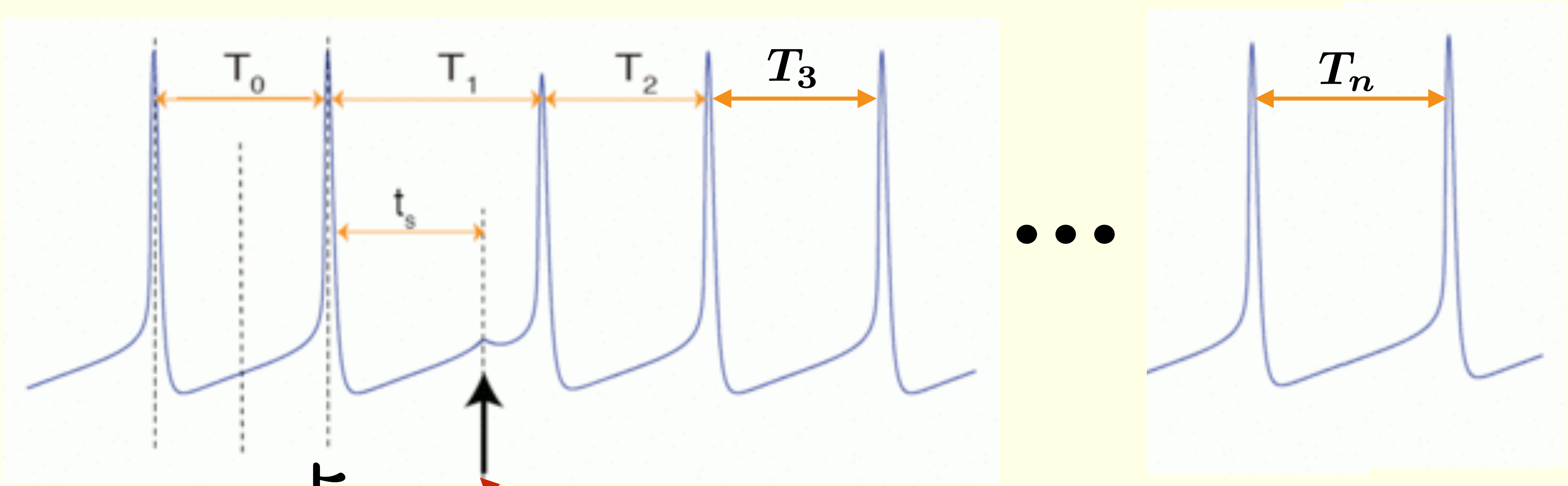
$$\varphi = 2\pi \frac{t_s}{T_1}$$

$$\boxed{Z(\varphi) = 2\pi \frac{T_0 - T_1}{T_0}}$$

This works well with neuronal system that are well-described by integrate-and-fire models

PRC determination II

Generally, one has to follow several periods after the kick



$\varphi = 0$ $\varphi = \pi$ $\varphi = 2\pi$

$$\varphi = 2\pi \frac{t_s}{T_1}$$

$$Z(\varphi) = 2\pi \frac{nT_0 - \sum_{j=1}^{n} T_j}{T_0}$$

(PRC is typically normalized by the amplitude of the kick)

PRC determination: problems

- The standard approach requires narrow pulses that reasonably approximate Dirac’s delta function; however, in biological applications, the pulses frequently must be **charge-balanced**

Pulse $\mathscr{P}(t-t_0)$

We denote theoretical PRC (response to Dirac’s delta) as $Z(\varphi)$

We denote effective PRC (response to arbitrary $\mathscr{P}$) as $Z_{\mathscr{P}}(\varphi)$

→ **We need a technique for re-computation $Z_{\mathscr{P}}(\varphi) \to Z(\varphi)$**

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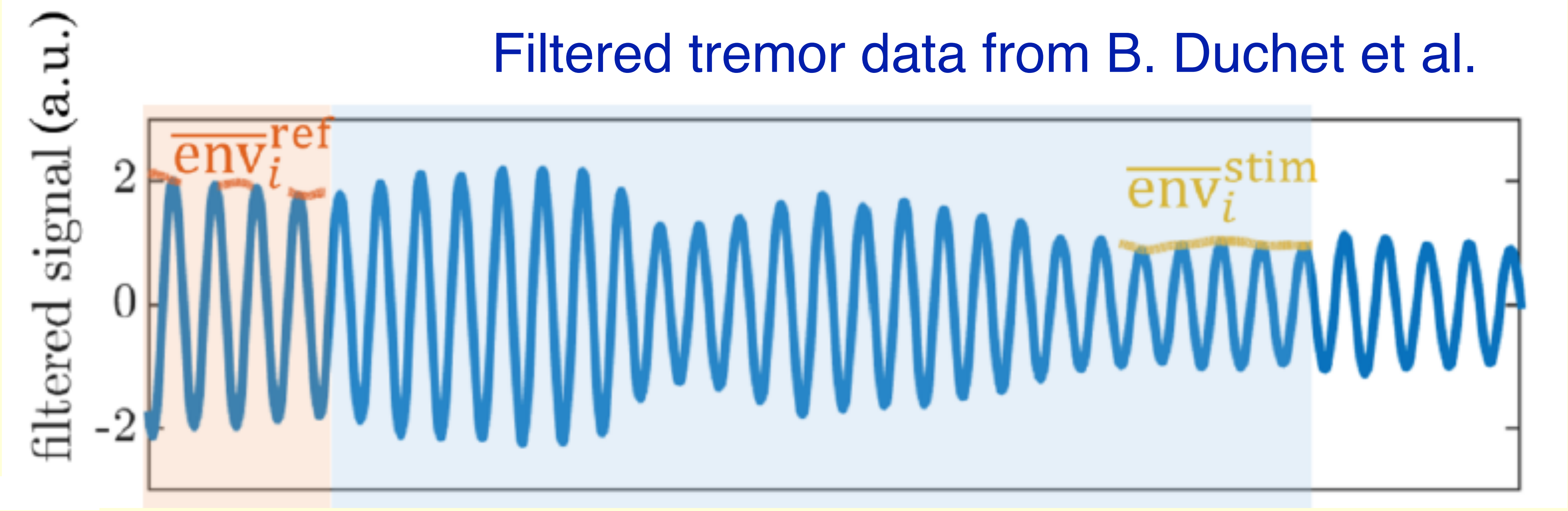
→ **We need a technique for re-computation $Z_{\mathscr{P}}(\varphi) \rightarrow Z(\varphi)$**

… and we provide it!

PRC determination: problems II

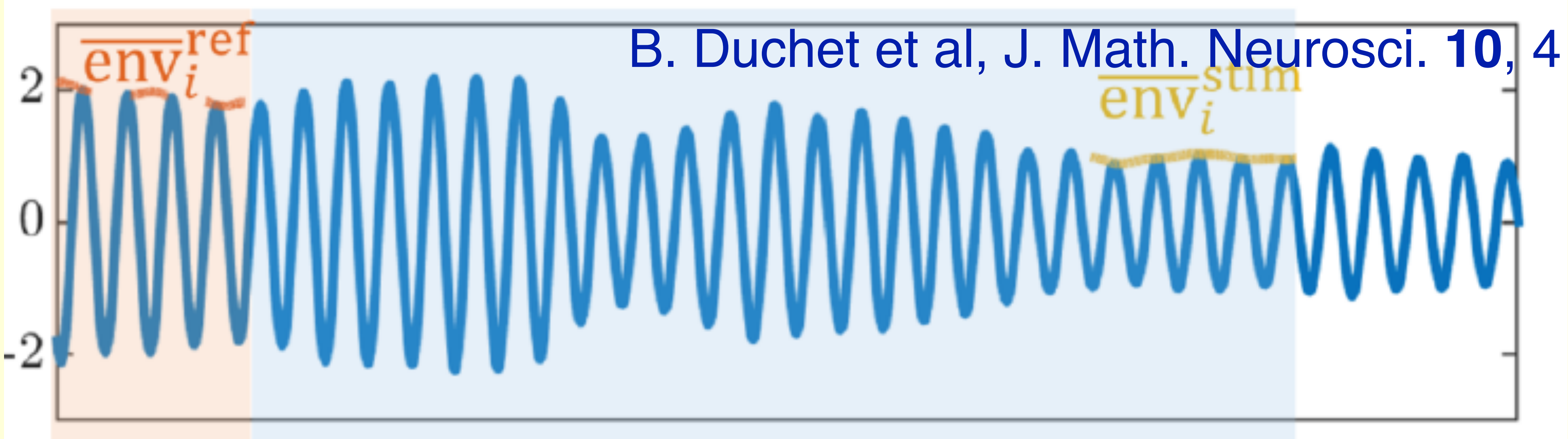
- The standard approach works well if the signal has well-defined marker events that can be assigned a specific phase value



Filtered tremor data from B. Duchet et al.

We need a technique for arbitrary stimulation's and signal's shape

PRC determination: problems II



B. Duchet et al, J. Math. Neurosci. **10**, 4 (2020)

Stimulation by bursts of pulses

Amplitude changes due to stimulation

→ Weakly stable limit cycle

PRC determination: problems II

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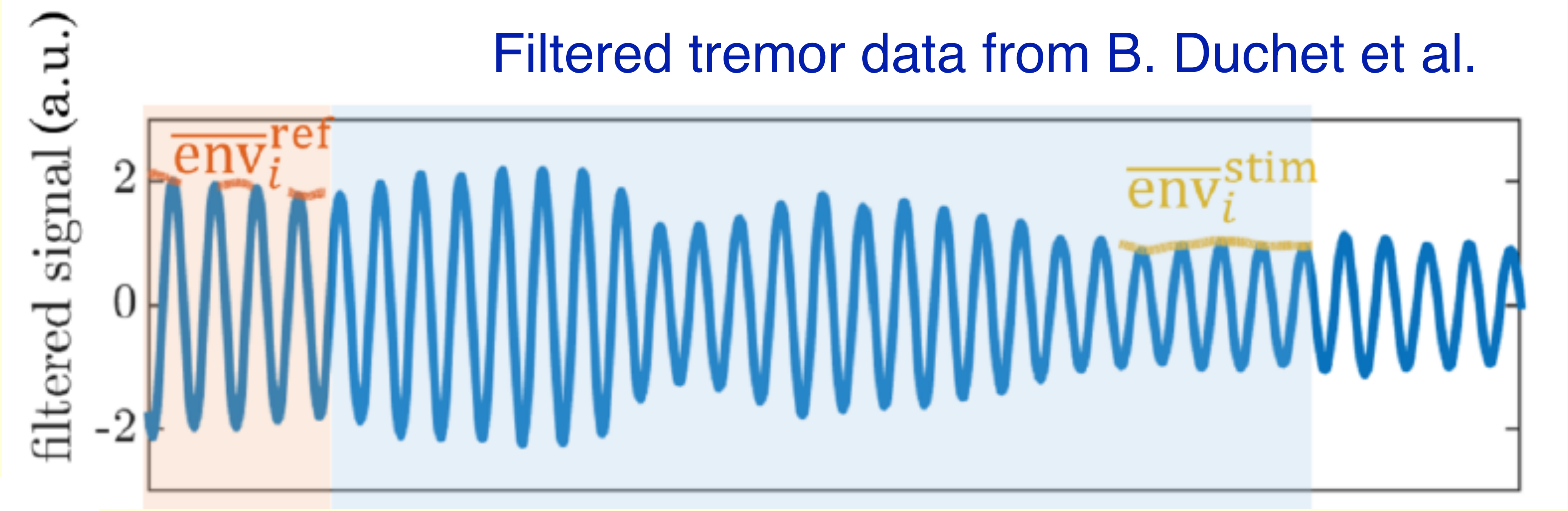


Filtered tremor data from B. Duchet et al.

→ **We need a technique for arbitrary stimulation's and signal's shape**

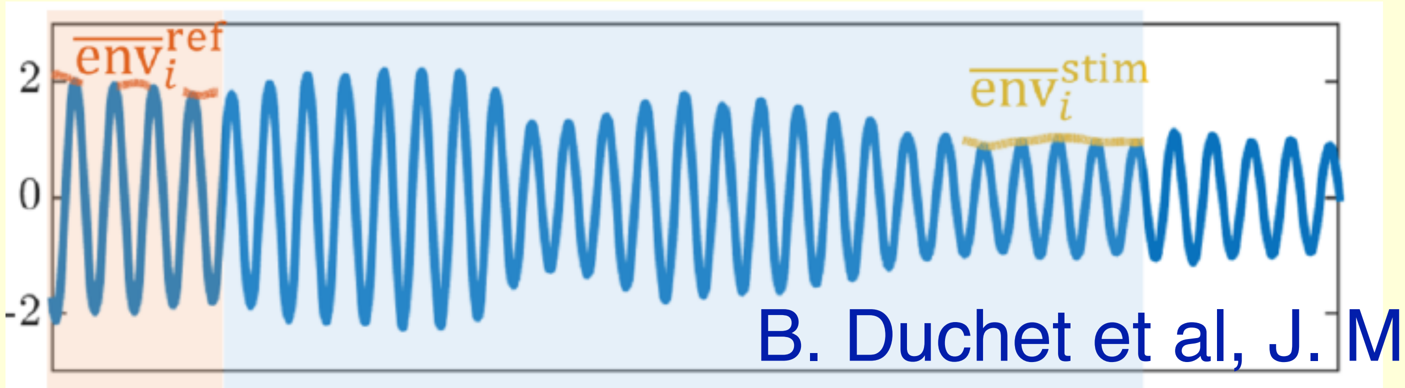
PRC determination in the context of Deep Brain Stimulation (DBS)

- Fitting sine-wave before and after the stimulus

  A. Holt and T. Netoff, J Comput Neurosci **37**, 505 (2014)

  A. Holt et al, PLoS Comput. Biol. **12**, e1005011 (2016)

- Using Hilbert Transform (HT) to evaluate phase (and amplitude) variation due to the pulse



B. Duchet et al, J. Math. Neurosci. **10**, 4 (2020)

Both techniques have never been tested on models with known PRC

→ **We need test models**

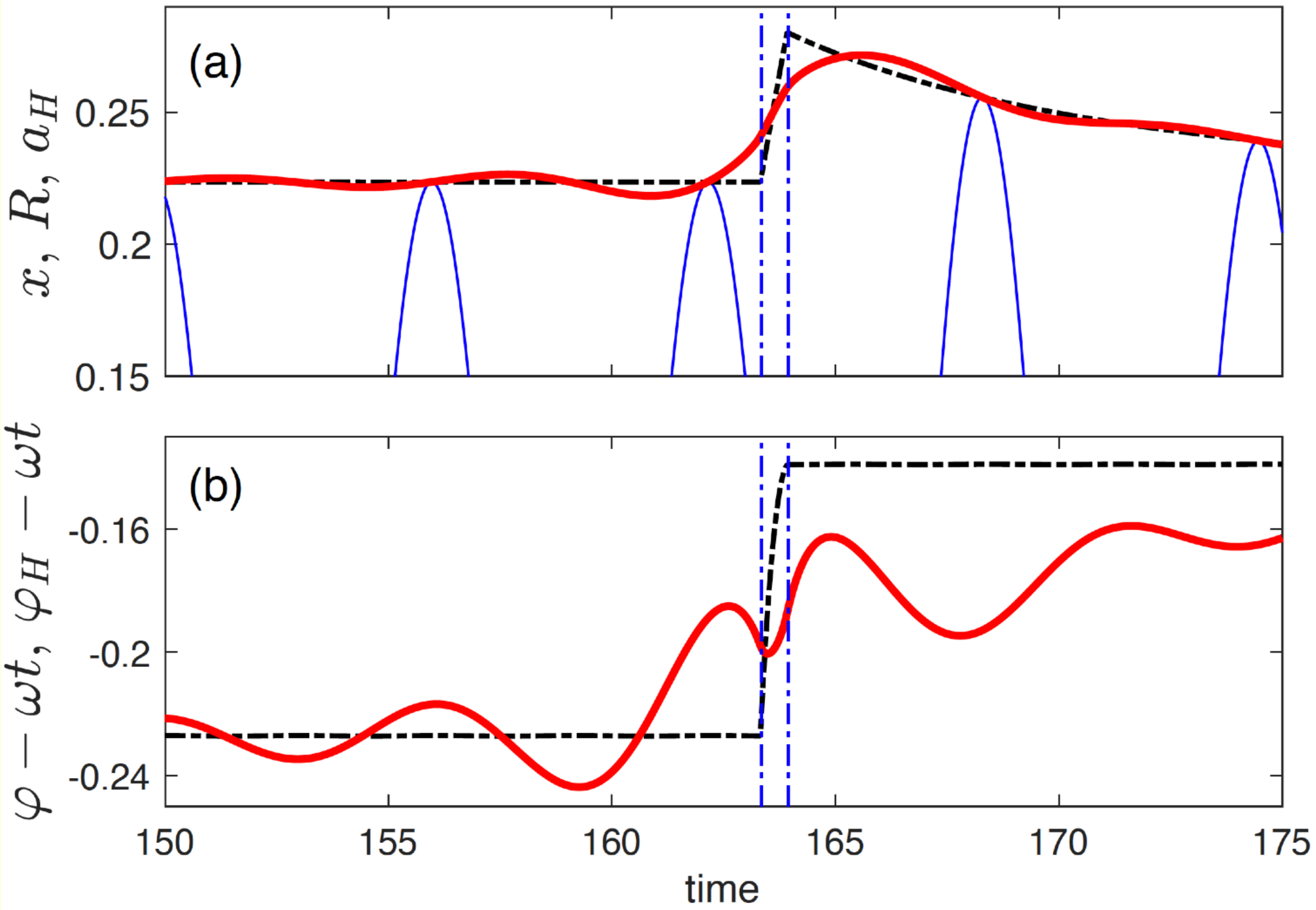
→ **We need a measure of goodness of the PRC determination**

Amplitude response - an unexplored problem

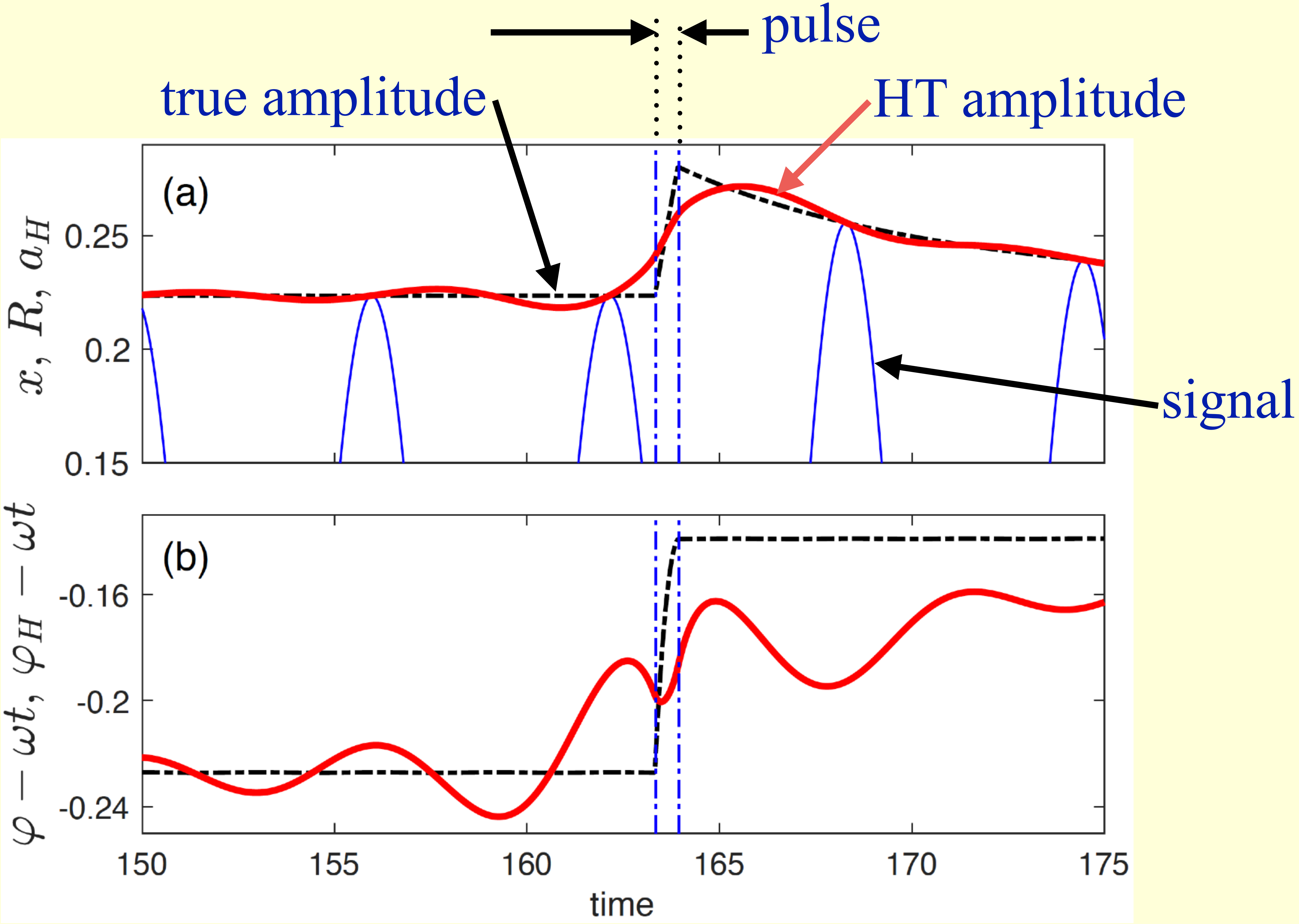
- Irrelevant for neuron-like systems (relaxational oscillators, strongly stable limit cycle); no effect of simulation on the amplitude
- Highly relevant in the context of DBS, where the goal of the stimulation is to suppress the oscillation, i.e., to affect the amplitude. This is possible for a weakly stable cycle only.
- The main problem is the amplitude's definition
- *Ad hoc* approach (B. Duchet et al.): to compute the amplitude response curve as $A(\varphi) = a_{after\ pulse}/a_{before\ pulse}$, where $a(t)$ is the instantaneous amplitude obtained via HT

Tests of known techniques: Hilbert-based

Hilbert transform is non-local, it is known to work poorly with pulse perturbation, here is the test for the SL system



Tests of known techniques: Hilbert-based



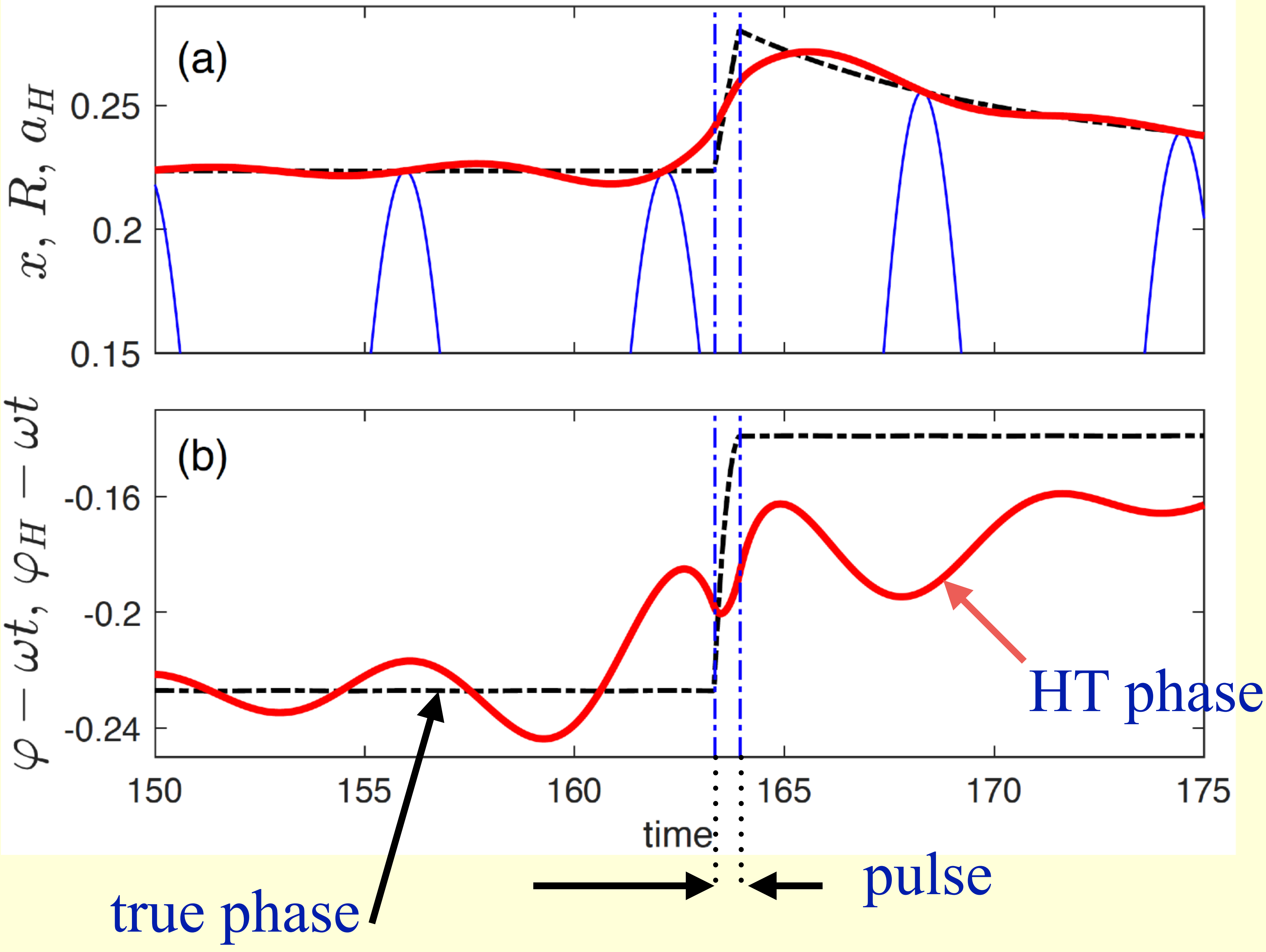
pulse

true amplitude

HT amplitude

signal

Tests of known techniques: Hilbert-based



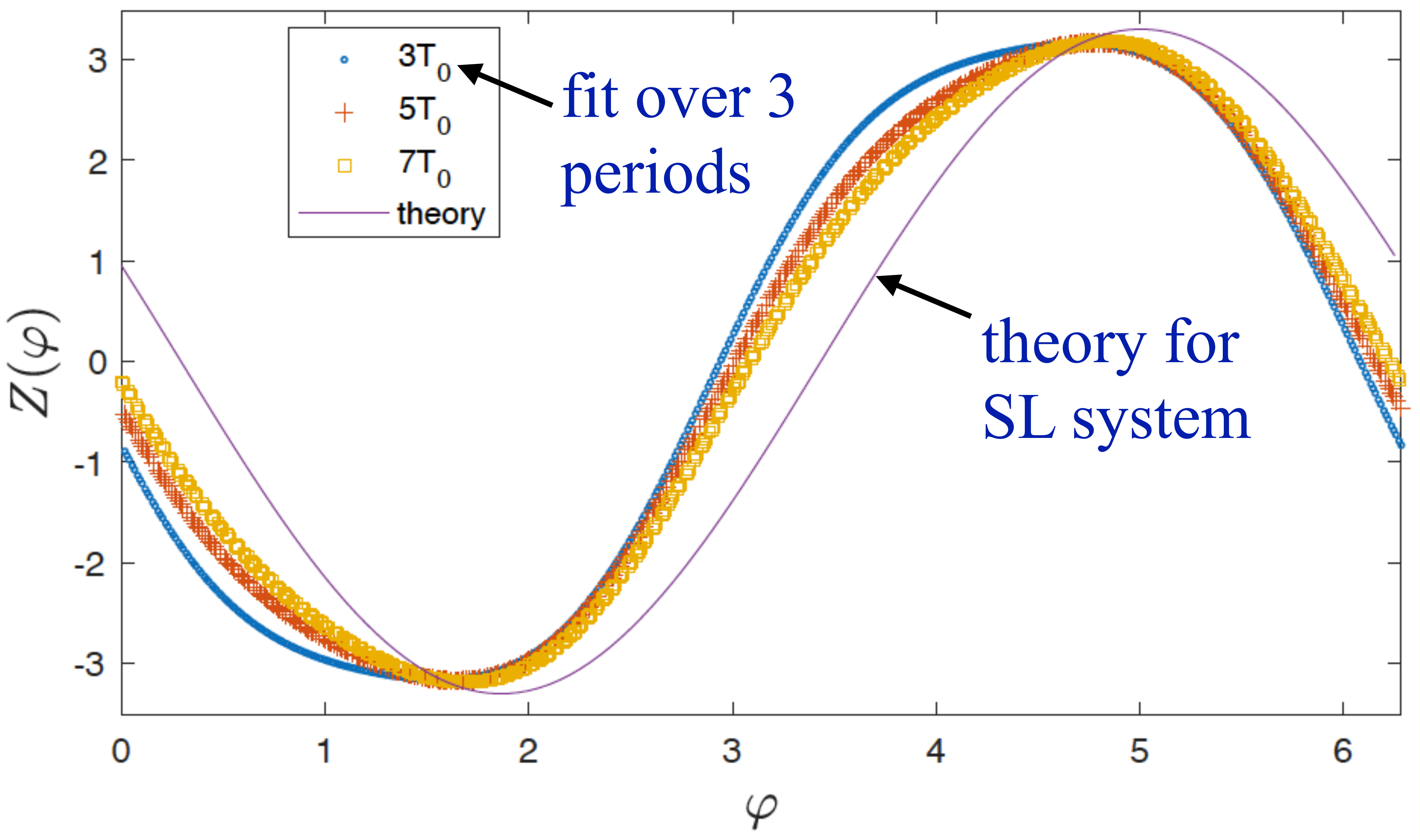
Hilbert-based technique: summary

- the results depend on the observable (not shown)

- works only with nearly harmonic signals

- can be improved (not shown), but remains imprecise

Tests of known techniques: sine-fitting



fit over 3 periods

theory for SL system

- works only with nearly harmonic signals
- is imprecise
- requires long time series

Phase - isostable variable representation

For an autonomous 2-dimensional system:

$$\dot{\varphi} = \omega\,, \quad \dot{\psi} = \kappa\psi$$

Floquet exponent

Isostable variable

ψ **quantifies deviation from the limit cycle**

For a perturbed system (1st approximation!):

$$\boxed{\dot{\varphi} = \omega + Z(\varphi)p(t)\,, \quad \dot{\psi} = \kappa\psi + I(\varphi)p(t)}$$

Isostable response curve (IRC)

The description applies to multidimensional systems if relaxation in one direction is much slower than in others

For details, see Wilson and Moehlis, PRE **94**, 052213 (2016)
Wilson and Ermentrout, SIAM J on Appl Dyn Sys **17**, 2516 (2018)
Wilson, PRE **99**, 022210 (2019)

Phase - isostable variable representation

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Isostable response curve (IRC)

We present an algorithm for inferring these equations from an observation of the perturbed system

Computing PRC from a known input

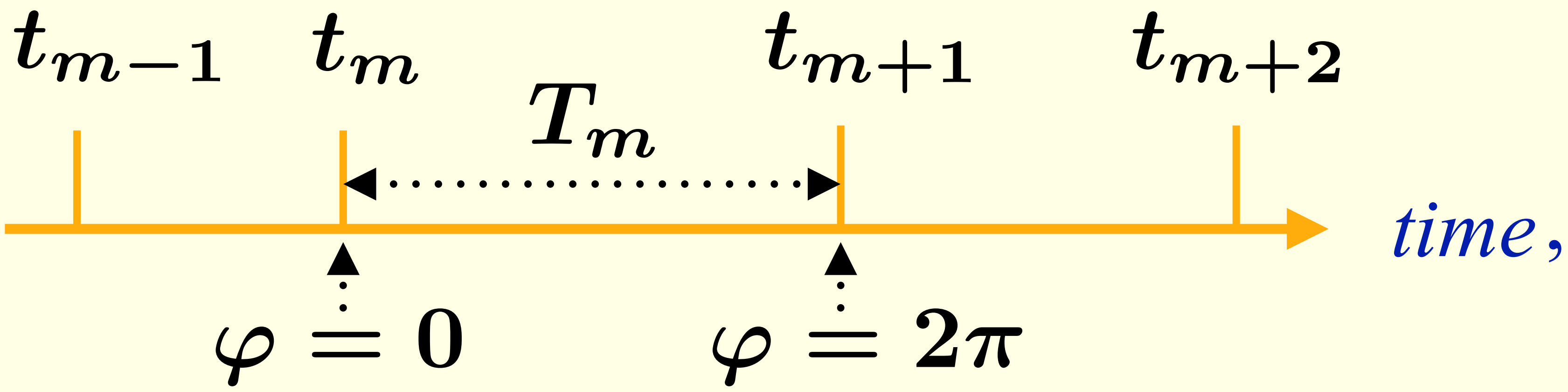
We adapt our approach from

Rok Cestnik & M. R. Sci Rep **8,** 13606, 2018

We perturb the oscillator by the pulse train $p(t) = \sum_k \mathscr{P}(t - t_k)$

We define events via thresholding, e.g., $x(t) = x_{threshold}, \dot{x} > 0$

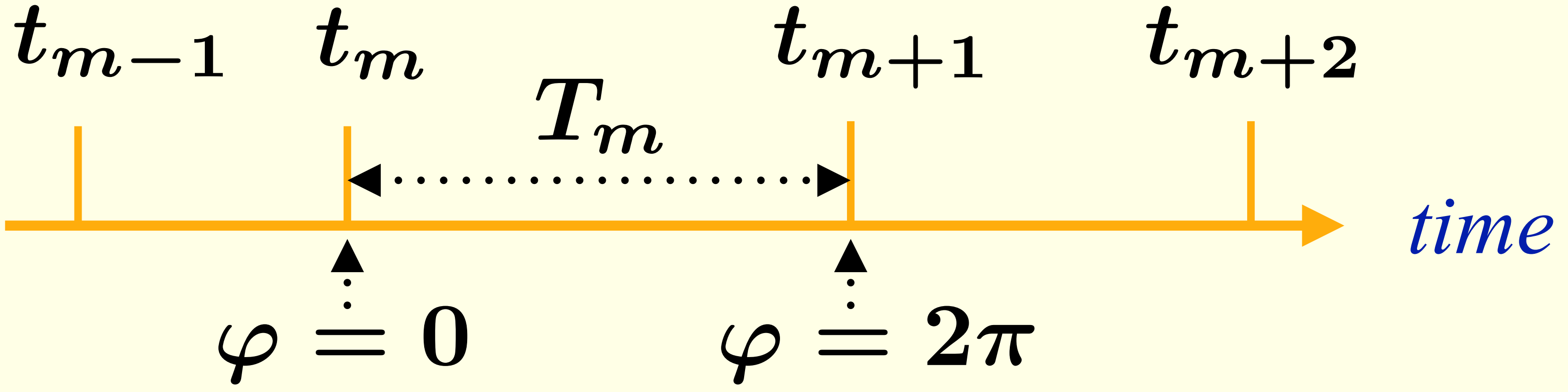
Notations



The choice of the threshold can be optimised

Computing PRC from a known input

Notations



Winfree model $\dot{\varphi} = \omega + Z(\varphi)p(t)$

$$\int_0^{2\pi} \mathrm{d}\varphi = \int_{t_m}^{t_m+T_m} [\omega + Z(\varphi)p(t)]\mathrm{d}t$$

Substituting PRC as a finite Fourier series,

$$Z(\varphi) = a_0 + \sum_{n=1}^{N} [a_n \cos(n\varphi) + b_n \sin(n\varphi)]$$

we obtain ***m*** equations:

$$2\pi = \omega T_m + a_0 \int_{t_m}^{t_m+T_m} p(t)\mathrm{d}t + \sum_{n=1}^{N} \left[a_n \int_{t_m}^{t_m+T_m} p(t)\cos[n\varphi(t)]\mathrm{d}t + b_n \int_{t_m}^{t_m+T_m} p(t)\sin[n\varphi(t)]\mathrm{d}t \right]$$

Computing PRC from a known input

$$2\pi = \omega T_m + a_0 \int_{t_m}^{t_m+T_m} p(t)\mathrm{d}t + \sum_{n=1}^{N} \left[a_n \int_{t_m}^{t_m+T_m} p(t)\cos[n\varphi(t)]\mathrm{d}t + b_n \int_{t_m}^{t_m+T_m} p(t)\sin[n\varphi(t)]\mathrm{d}t \right]$$

$\boldsymbol{Eq.(*)}$

We solve the problem by iterations: first we take

$$\boldsymbol{\varphi^{(0)}(t) = 2\pi(t - t_m)/T_m \in [t_m, t_m + T_m]}$$

Computing PRC from a known input

$$2\pi = \omega T_m + a_0 \int_{t_m}^{t_m+T_m} p(t)\mathrm{d}t + \sum_{n=1}^{N} \left[a_n \int_{t_m}^{t_m+T_m} p(t)\cos[n\varphi(t)]\mathrm{d}t + b_n \int_{t_m}^{t_m+T_m} p(t)\sin[n\varphi(t)]\mathrm{d}t \right]$$

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iteration

Computing PRC from a known input

$$2\pi = \omega T_m + a_0 \int\limits_{t_m}^{t_m+T_m} p(t)\mathrm{d}t + \sum_{n=1}^{N}\left[a_n \int\limits_{t_m}^{t_m+T_m} p(t)\cos[n\varphi(t)]\mathrm{d}t + b_n \int\limits_{t_m}^{t_m+T_m} p(t)\sin[n\varphi(t)]\mathrm{d}t\right]$$

$\boxed{\boldsymbol{Eq.(*)}}$

We solve the problem by iterations: first we take

$$\varphi^{(0)}(t) = 2\pi(t - t_m)/T_m \in [t_m, t_m + T_m]$$

iteration

substitute into $\boldsymbol{Eq.(*)}$, compute numerically all integrals

system of ***M*** linear equations for ***2N+2*** coefficients

for ***M>2N+2*** we solve the system using l.m.s. optimisation

first approximation for frequency and PRC $\omega^{(1)}, Z^{(1)}$

Next approximation for the phase

We integrate numerically $\dot{\varphi}^{(1)} = \omega^{(1)} + Z^{(1)}\left(\varphi^{(0)}(t)\right)p(t)$

for each inter-spike interval with initial condition $\varphi^{(1)}(t_m) = 0$

It is, for $0 \leq \tau \leq T_m$ we compute

$$\varphi^{(1)}(t_m + \tau) = \omega^{(1)}\tau + \int_{t_m}^{t_m+\tau} Z^{(1)}\left(\varphi^{(0)}(t)\right)p(t)\mathrm{d}t$$

Since everything is approximate, generally

$$\varphi^{(1)}(t_m + T_m) = \psi_m^{(1)} \neq 2\pi$$

Therefore we **rescale the phase:** $\varphi^{(1)}(t) \to 2\pi\varphi^{(1)}(t)/\psi_m^{(1)}$

Quantities $\psi_m^{(k)}$ will be used to monitor convergence of iterations

Second iteration

$$2\pi = \omega T_m + a_0 \int_{t_m}^{t_m+T_m} p(t)\mathrm{d}t + \sum_{n=1}^{N} \left[a_n \int_{t_m}^{t_m+T_m} p(t)\cos[n\varphi(t)]\mathrm{d}t + b_n \int_{t_m}^{t_m+T_m} p(t)\sin[n\varphi(t)]\mathrm{d}t \right]$$

$\boldsymbol{Eq.(*)}$

We obtained $\boldsymbol{\varphi^{(1)}(t)}$

substitute into $\boldsymbol{Eq.(*)}$, compute numerically all integrals

system of ***M*** linear equations for ***2N+2*** coefficients

for ***M>2N+2*** we solve the system using l.m.s. optimisation

second approximation for frequency and PRC $\boldsymbol{\omega^{(2)}, Z^{(2)}}$

Second and further iterations

$$2\pi = \omega T_m + a_0 \int_{t_m}^{t_m+T_m} p(t)\mathrm{d}t + \sum_{n=1}^{N} \left[a_n \int_{t_m}^{t_m+T_m} p(t)\cos[n\varphi(t)]\mathrm{d}t + b_n \int_{t_m}^{t_m+T_m} p(t)\sin[n\varphi(t)]\mathrm{d}t \right]$$

$\boldsymbol{Eq.(*)}$

We obtained $\boldsymbol{\varphi^{(1)}(t)}$

substitute into $\boldsymbol{Eq.(*)}$, compute numerically all integrals

system of ***M*** linear equations for ***2N+2*** coefficients

for ***M>2N+2*** we solve the system using l.m.s. optimisation

second approximation for frequency and PRC $\boldsymbol{\omega^{(2)}, Z^{(2)}}$

$$\boxed{\boldsymbol{\omega^{(k)}, Z^{(k)}, \psi_m^{(k)}}}$$

Monitoring convergence

Recall:

$$\varphi^{(1)}(t_m+\tau)=\omega^{(1)}\tau+\int_{t_m}^{t_m+\tau} Z^{(1)}\left(\varphi^{(0)}(t)\right)p(t)\mathrm{d}t$$

Since everything is approximate, generally

$$\varphi^{(1)}(t_m+T_m)=\psi_m^{(1)}\neq 2\pi$$

and similarly for further iterations, $\psi_m^{(k)}$

We introduce the average error $\Delta_\psi=\langle(\psi_m-2\pi)^2\rangle^{1/2}$

to be compared with

$$\Delta_{\psi_T}=\langle(\langle\omega\rangle T_m-2\pi)^2\rangle^{1/2}\text{ where }\langle\omega\rangle=\langle 2\pi/T_m\rangle$$

(error of trivial prediction with average period)

Quality of the PRC estimation

We introduce the average error $\boldsymbol{\Delta_\psi = \langle (\psi_m - 2\pi)^2 \rangle^{1/2}}$

to be compared with

$$\boldsymbol{\Delta_{\psi_T} = \langle (\langle \omega \rangle T_m - 2\pi)^2 \rangle^{1/2}} \text{ where } \boldsymbol{\langle \omega \rangle = \langle 2\pi / T_m \rangle}$$

(error of trivial prediction with average period)

The measure $E = \Delta_\psi / \Delta_{\psi_T}$ quantifies the quality of the estimation

This measure can and shall be used with any inference technique!

Inferring 1st-order phase-isostable dynamics (IPID-1 technique)

First, we infer PRC; this also yields $\varphi(t)$.

From $\varphi(t)$ we obtain time events τ_i of equal phase, $\varphi(\tau_i) = \text{const}$

For a noise-free unperturbed system, the observed signal would be $s(\tau_i) = \text{const} = s_0$

For the perturbed system, we write in the 1st order:

$$\psi_i = c(\psi(\tau_i) - s_0) \qquad (*)$$

Generally, $c = c(\varphi)$, $s_0 = s_0(\varphi)$. However, at points τ_i phase is the same. Hence, c and s_0 in Eq. (*) are constants.

Additionally, ψ is defined up to a constant factor $\Longrightarrow$ $c = 1$

IPID-1 technique

We integrate the isostable dynamics $\dot{\psi} = \kappa\psi + I(\varphi)p(t)$

$$\psi_{i+1} - \psi_i = \kappa \int_{\tau_i}^{\tau_{i+1}} \psi(t)\,\mathrm{d}t + \int_{\tau_i}^{\tau_{i+1}} I(\varphi)p(t)\,\mathrm{d}t$$

Using $\psi_i = c(\psi(\tau_i) - s_0)$, we write the l.h.s. as $s(\tau_{i+1}) - s(\tau_i)$

Substituting $I(\varphi)$ as a finite Fourier series, we obtain a linear system, but we have to compute the integral $\kappa \int_{\tau_i}^{\tau_{i+1}} \psi(t)dt$

We write it as

$$\kappa \int_{\tau_i}^{\tau_{i+1}} \psi(t)\,\mathrm{d}t = -\kappa s_0(\tau_{i+1} - \tau_i) + \kappa \int_{\tau_i}^{\tau_{i+1}} (\psi(t) + s_0)\,\mathrm{d}t$$

IPID-1 technique II

We write it as

$$\kappa \int_{\tau_i}^{\tau_{i+1}} \psi(t)\,\mathrm{d}t = -\kappa s_0(\tau_{i+1} - \tau_i) + \kappa \int_{\tau_i}^{\tau_{i+1}} \underbrace{(\psi(t) + s_0)}\,\mathrm{d}t$$

becomes another variable for the linear system

this function is known in endpoints:

$\psi(\tau_i) + s_0 = s(\tau_i)$

$\psi(\tau_{i+1}) + s_0 = s(\tau_{i+1})$

we approximate $\int_{\tau_i}^{\tau_{i+1}} (\psi(t) + s_0)\,\mathrm{d}t \approx [s(\tau_i) + s(\tau_{i+1})]/2$

we solve the linear system and obtain the 1st-approximation

$$s_0^{(1)}, \kappa^{(1)}, I^{(1)}(\varphi)$$

IPID-1 technique III

we solve the linear system and obtain the 1st-approximation

$s_0^{(1)}, \kappa^{(1)}, I^{(1)}(\varphi)$

again, we use iterations to obtain next approximations

starting with $s_0^{(m)}, \kappa^{(m)}, I^{(m)}(\varphi)$, we compute

$$\psi^{(m)}(t) = \underbrace{s(\tau_i) - s_0^{(m)}}_{\psi^{(m)}(\tau_i)} + \int_{\tau_i}^{t} [\kappa^{(m)}\psi^{(m)}(t') + I^{(m)}(\varphi)p(t')]\,\mathrm{d}t'$$

and solve the linear system to obtain $s_0^{(m+1)}, \kappa^{(m+1)}, I^{(m+1)}(\varphi)$

Monitoring the inference's error

starting with $s_0^{(m)}$, $\kappa^{(m)}$, $I^{(m)}(\varphi)$, we compute

$$\psi^{(m)}(t) = \underbrace{s(\tau_i) - s_0^{(m)}}_{\psi^{(m)}(\tau_i)} + \int_{\tau_i}^{t} \left[\kappa^{(m)}\psi^{(m)}(t') + I^{(m)}(\varphi)p(t')\right] \mathrm{d}t'$$

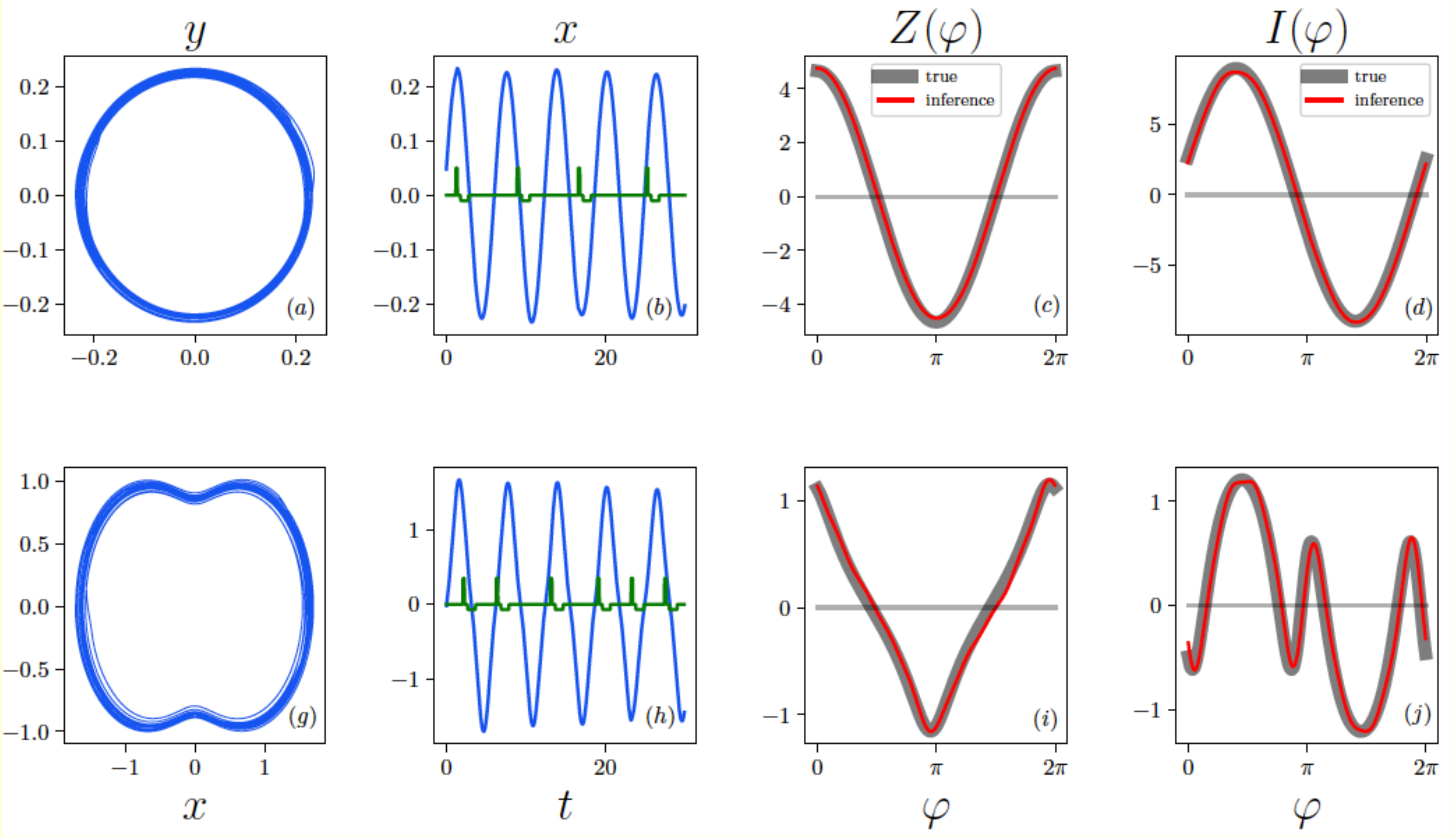
Our model is not exact, hence $\Psi_i^{(m)} = \lim_{t\uparrow\tau_{i+1}} \psi^{(m)}(t) \neq s(\tau_{i+1}) - s_0^{(m)}.$

We define the error as $E_I^{(m)} = \langle(\Psi_i^{(m)} - (s(\tau_{i+1}) - s_0^{(m)}))^2\rangle^{1/2}$

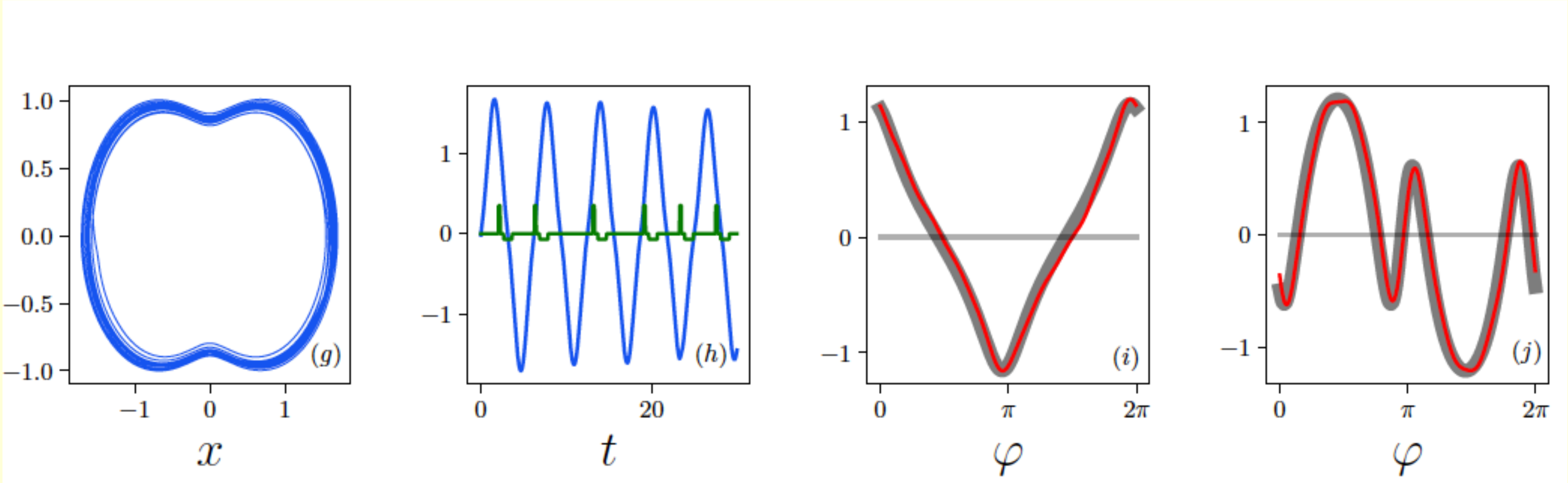
and compare it with the signal's variability at events

$$E_{I0} = \langle(s(\tau_i) - \langle s(\tau_i\rangle))^2\rangle^{1/2}$$

Results for test models with known $Z(\varphi), I(\varphi)$



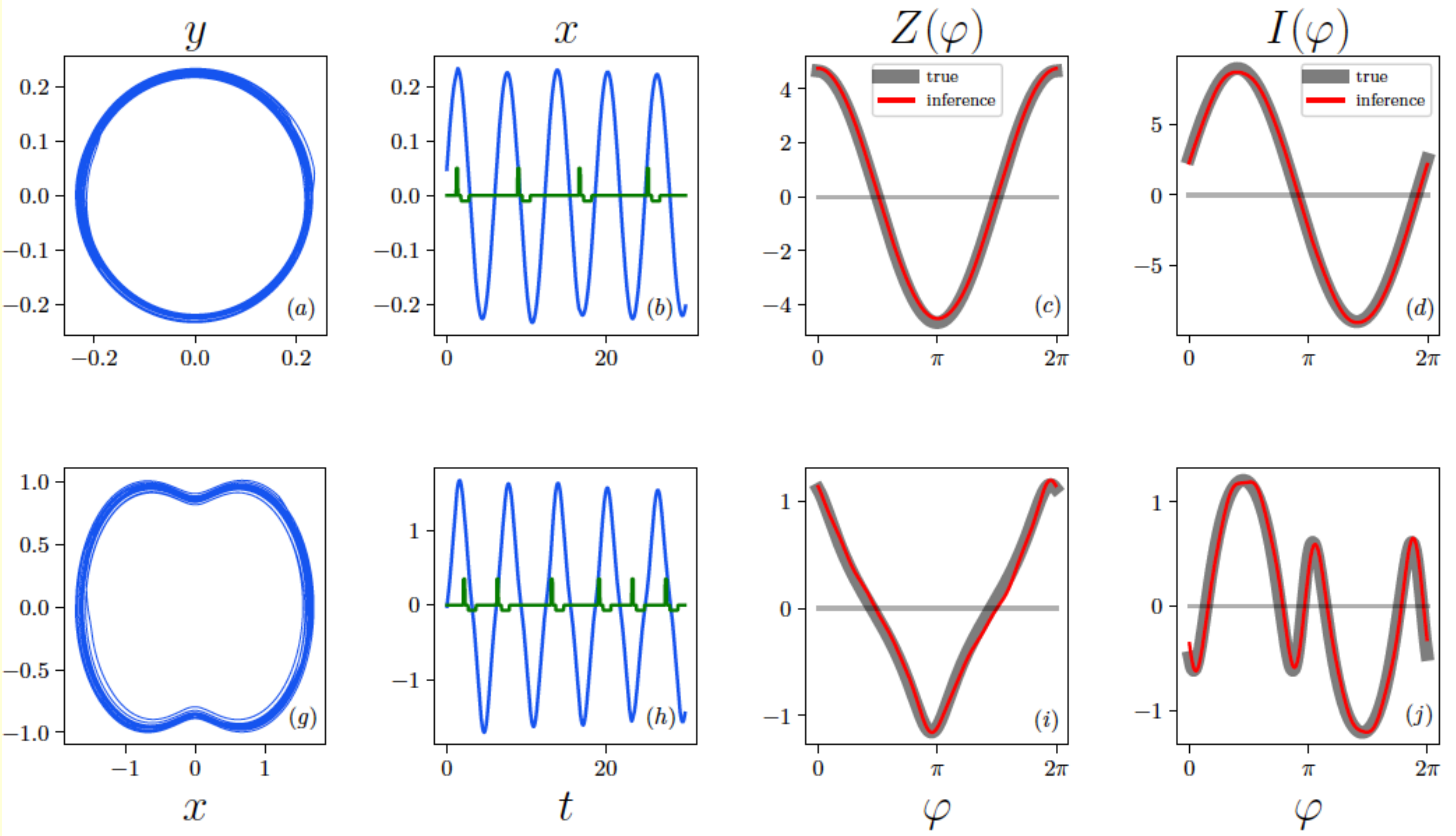
Results for test models with known $Z(\varphi), I(\varphi)$



We constructed test models with known $Z(\varphi)$ and $I(\varphi)$

These models generate different waveforms

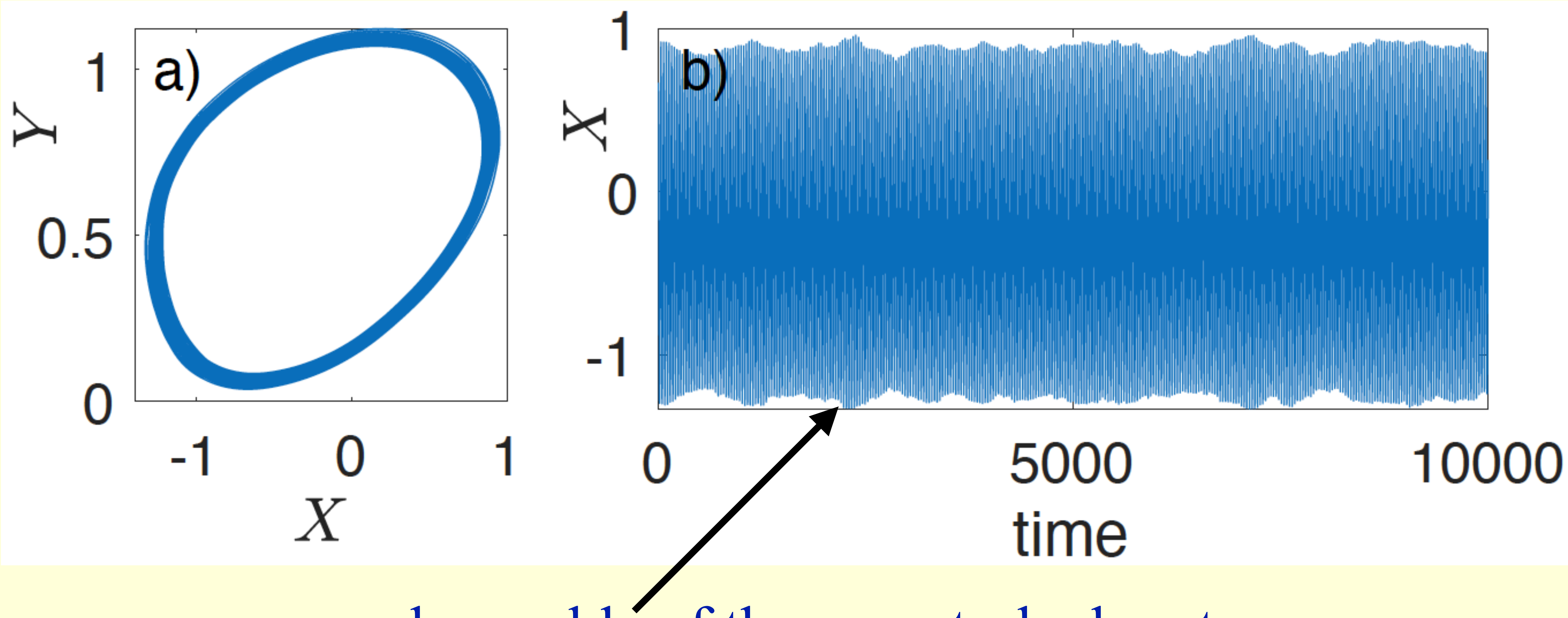
Results for test models with known $Z(\varphi), I(\varphi)$



Further results for the IPID-1 technique

It is most reliable technique in the presence of noise

It performs better for a high-dimensional chaotic system (ensemble of globally-coupled Bonhoeffer -van der Pol systems with chaotic mean field)



observable of the unperturbed system

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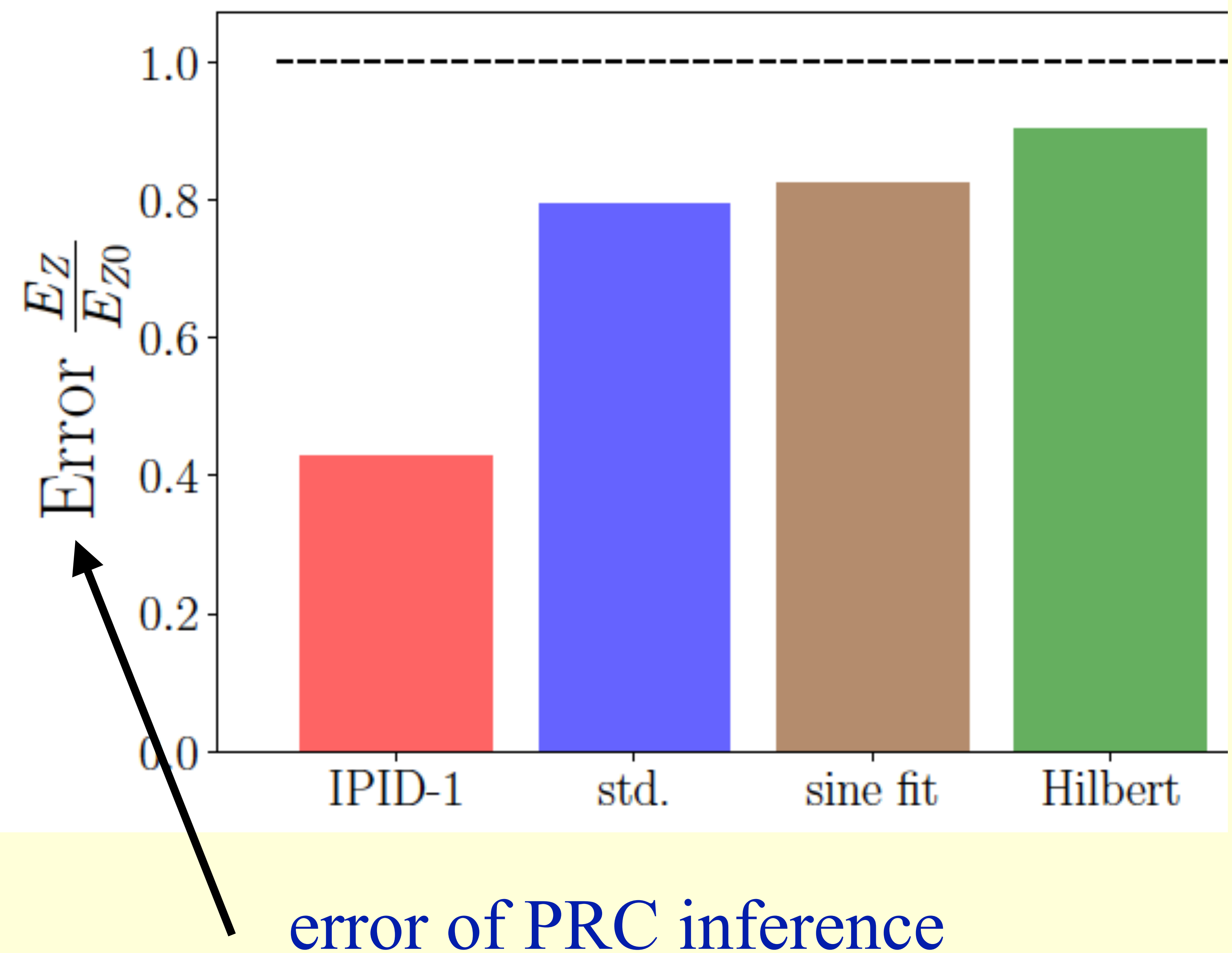
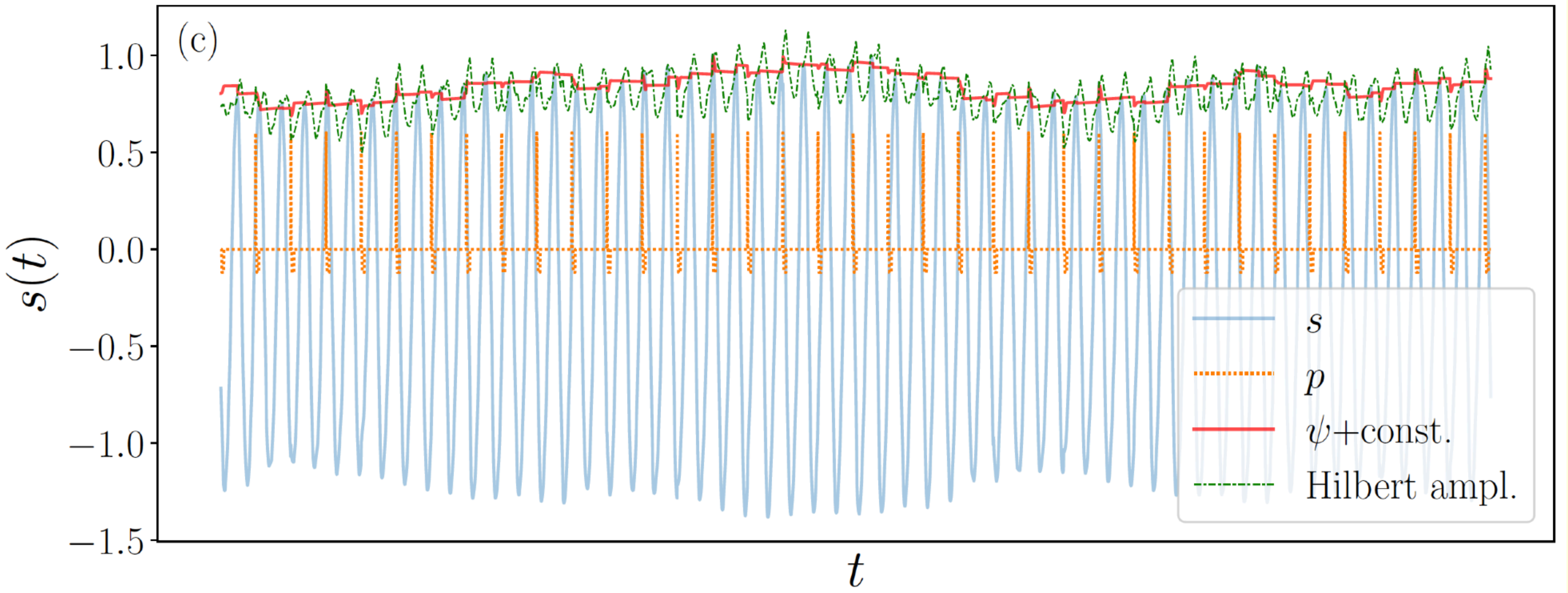


error of PRC inference

Further results for the IPID-1 technique

It yields better envelope than the Hilbert Transform



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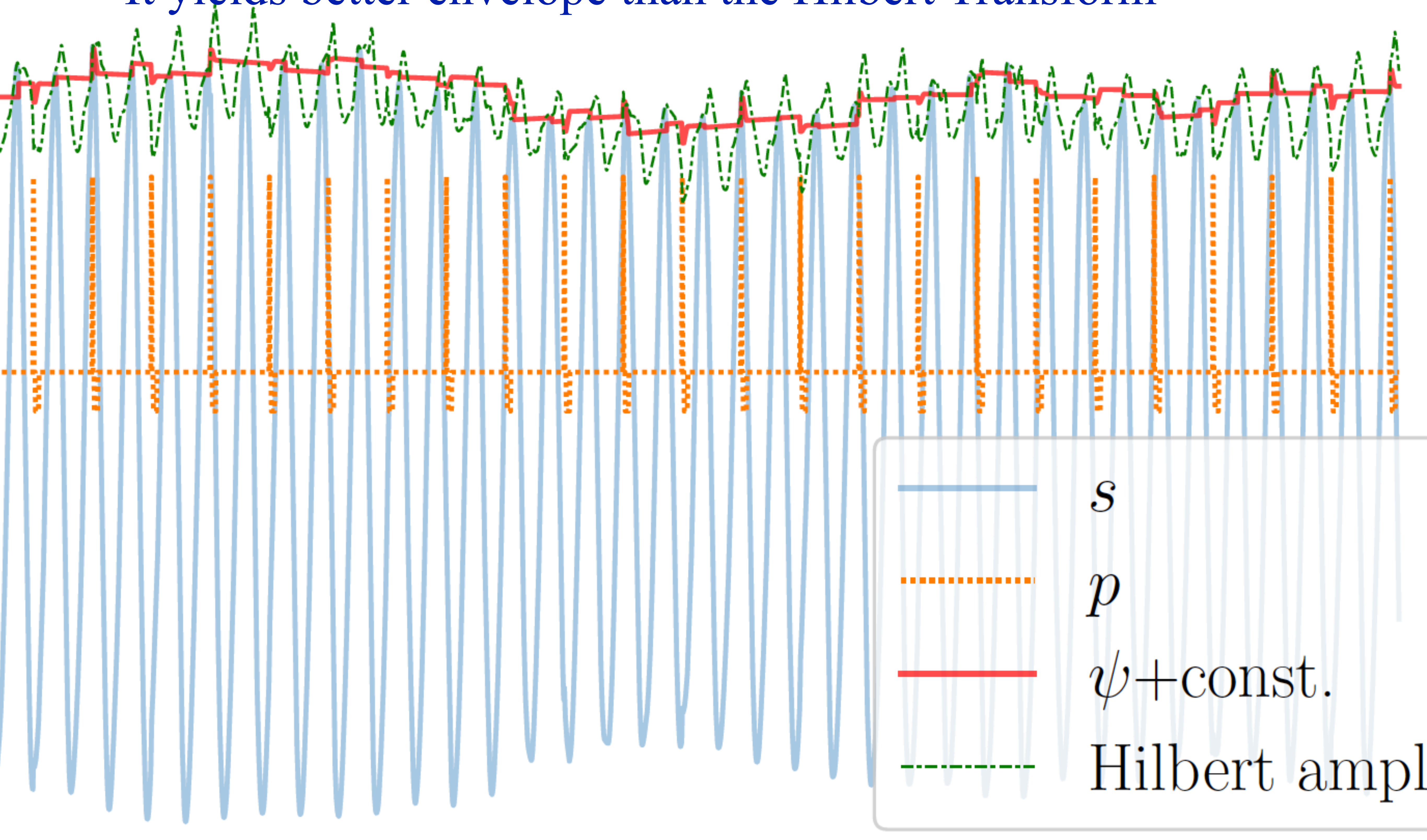

Conclusions

- Reconstruction of the phase - isostable dynamics
  - is independent of the observable
  - robust against noise
  - requires shorter time series
- Inference of the PRC for arbitrary pulse shape
- Test models with known ground truth
- Estimation of the inference error from data

Rok Cestnik, E. Mau, M. Rosenblum, arXiv:2206.09173 (June 2022)

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