Hybrid (experiment & model) systems for biological experiments

2016 NZMRI Summer School Lecture 3

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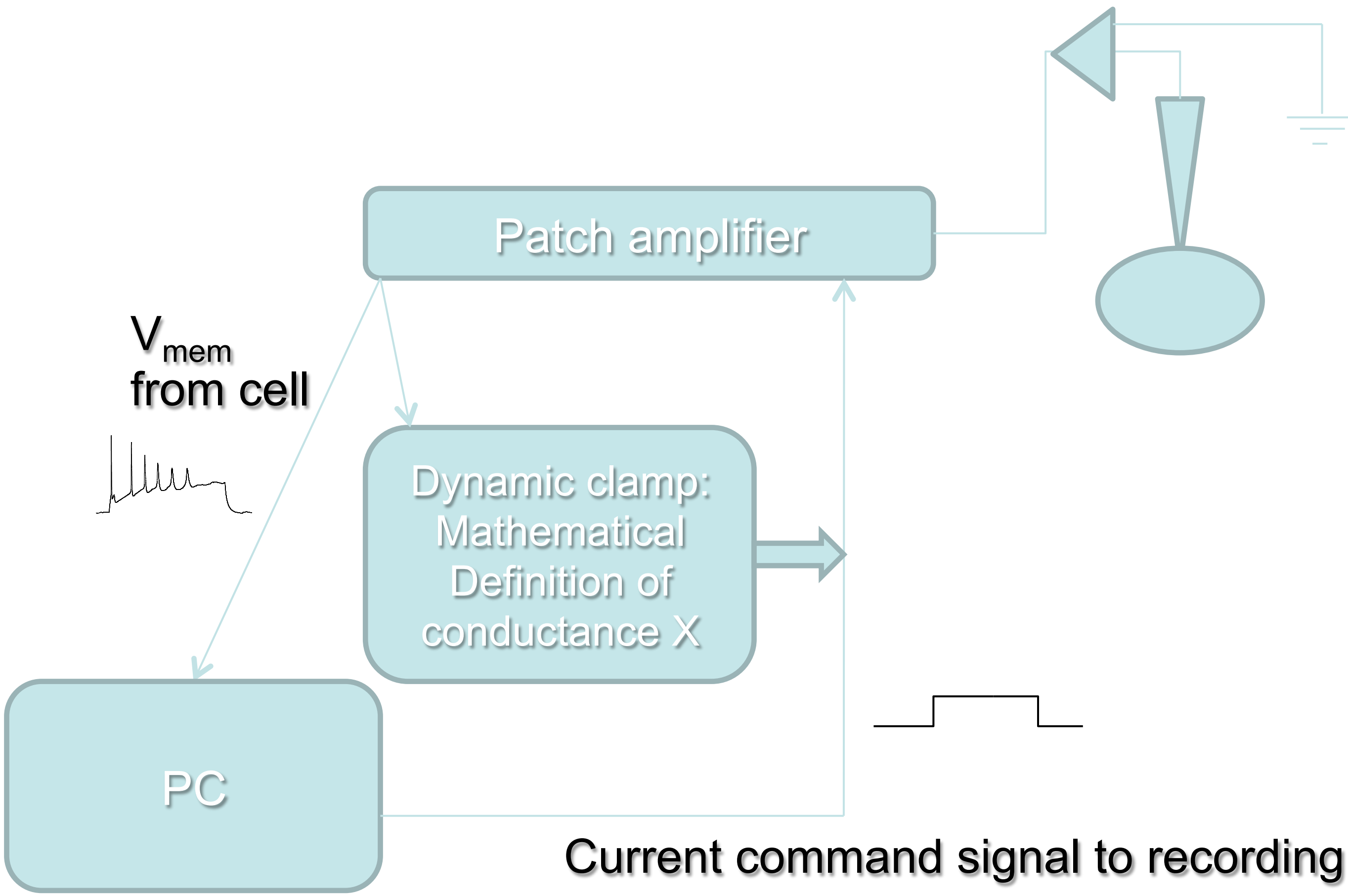
Dynamic clamp: using dynamical systems in real cells

- A method to assess how biophysically-defined ionic conductances shape the firing patterns of neurones

- Dynamic clamp: a small step for an electrophysiology setup, a giant leap forward for neuroscience

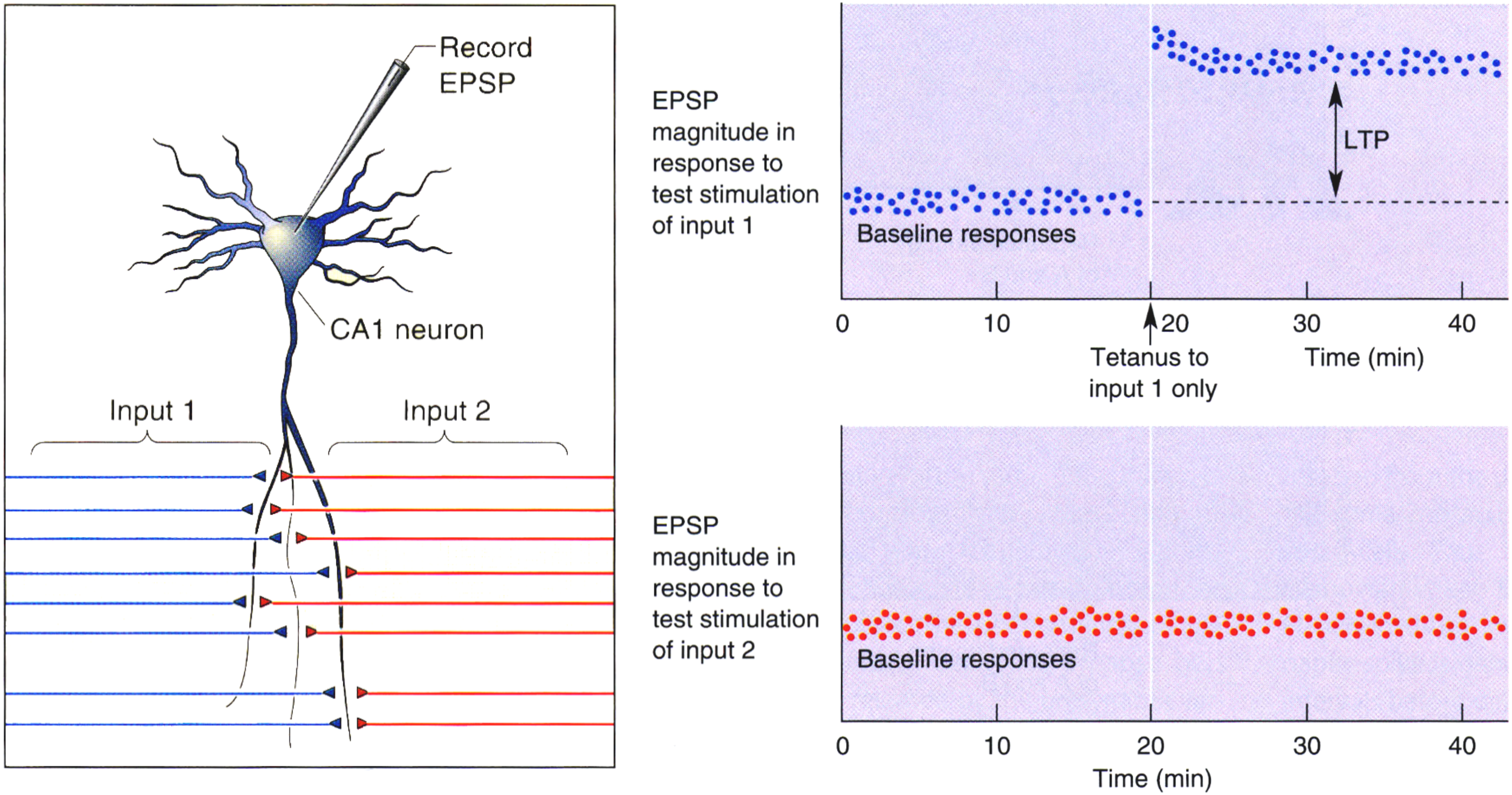
- A Physiologist's dream: Adding and removing defined channel types without having to resort to pharmacology or molecular biology

How would the cell behave if it also had conductance X?



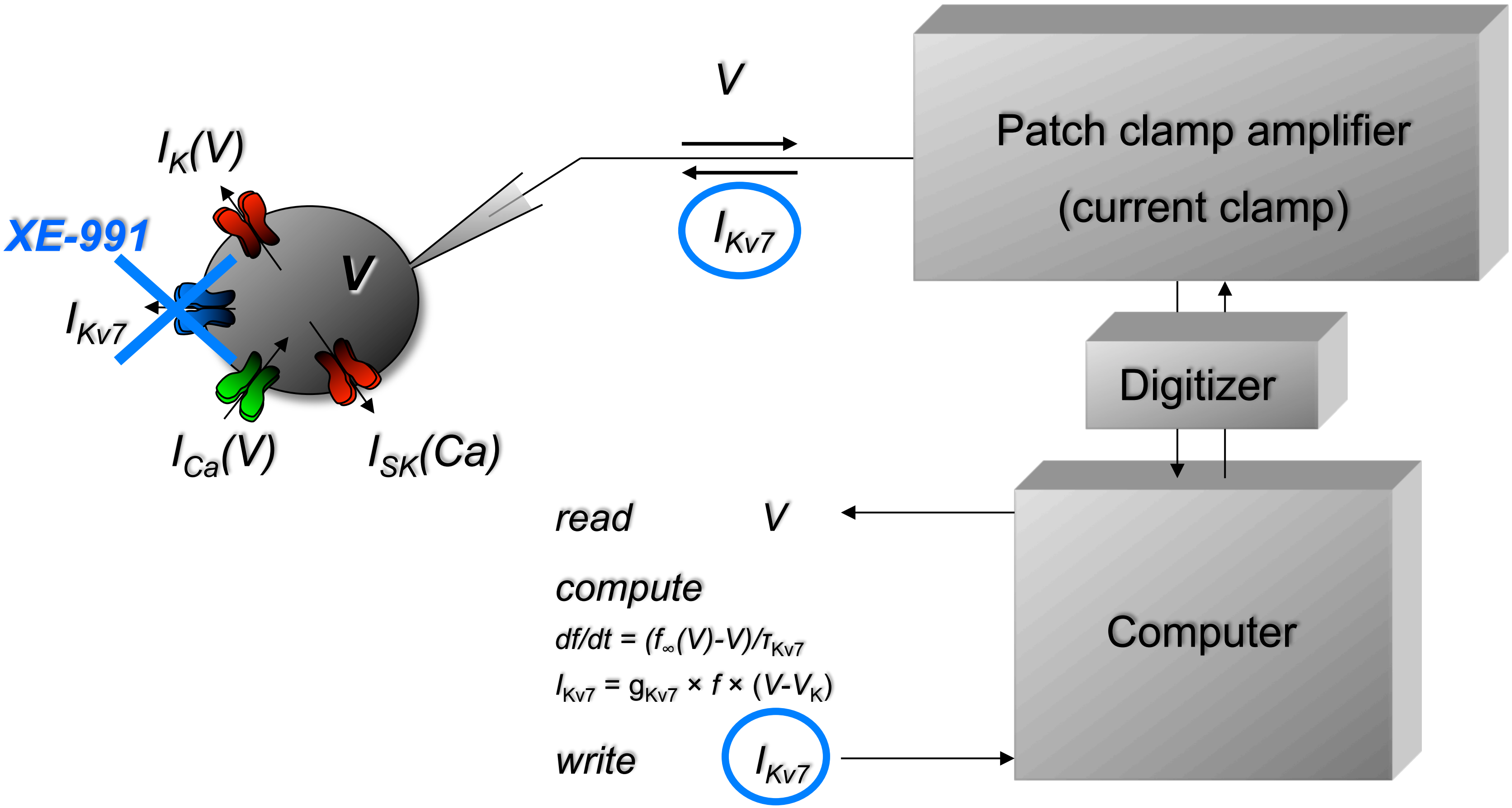
Develop method using cultured hippocampal neurones

Long-term Potentiation in CA1



LTP requires only a brief high frequency stimulation (HFS), is input specific, and can last many weeks!

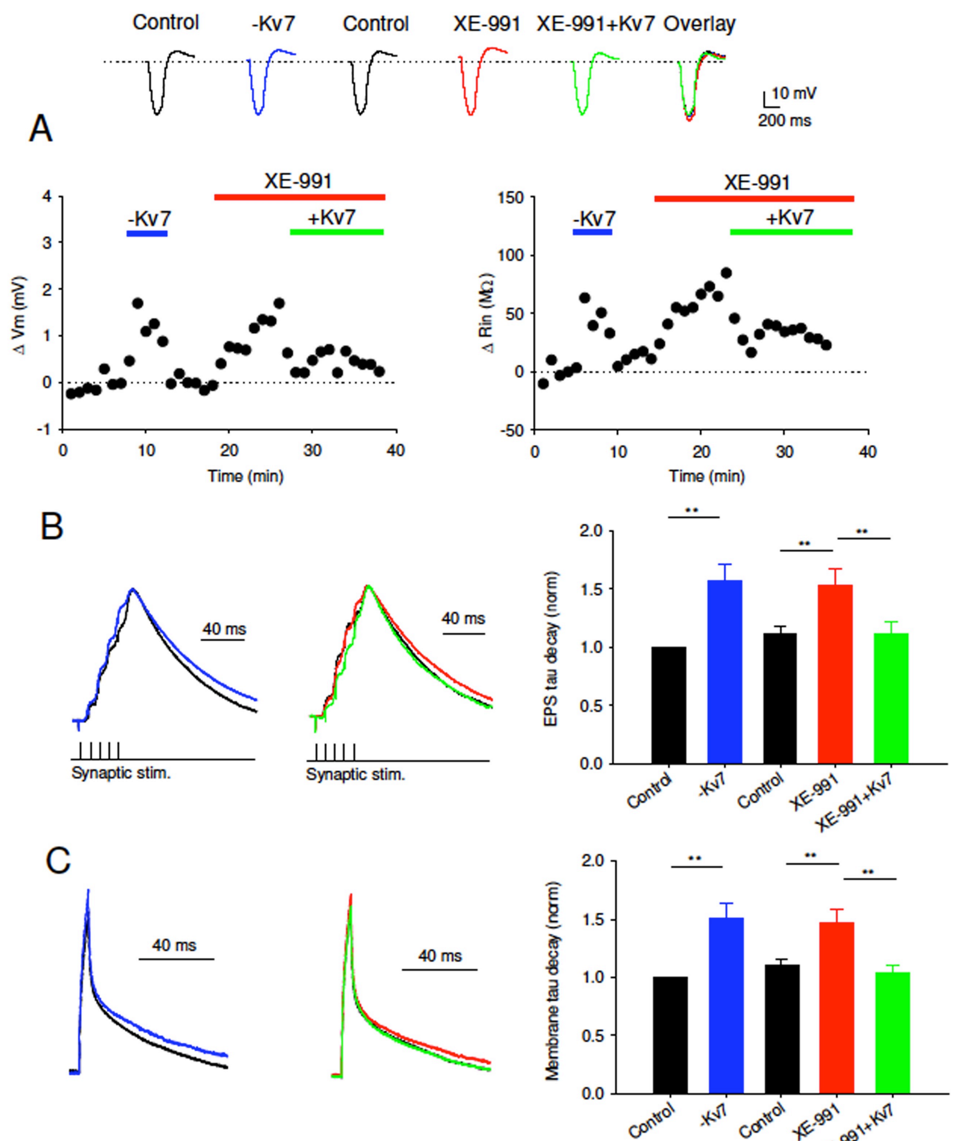
Adding/Subtracting M-current (Kv7) with Dynamic Clamp



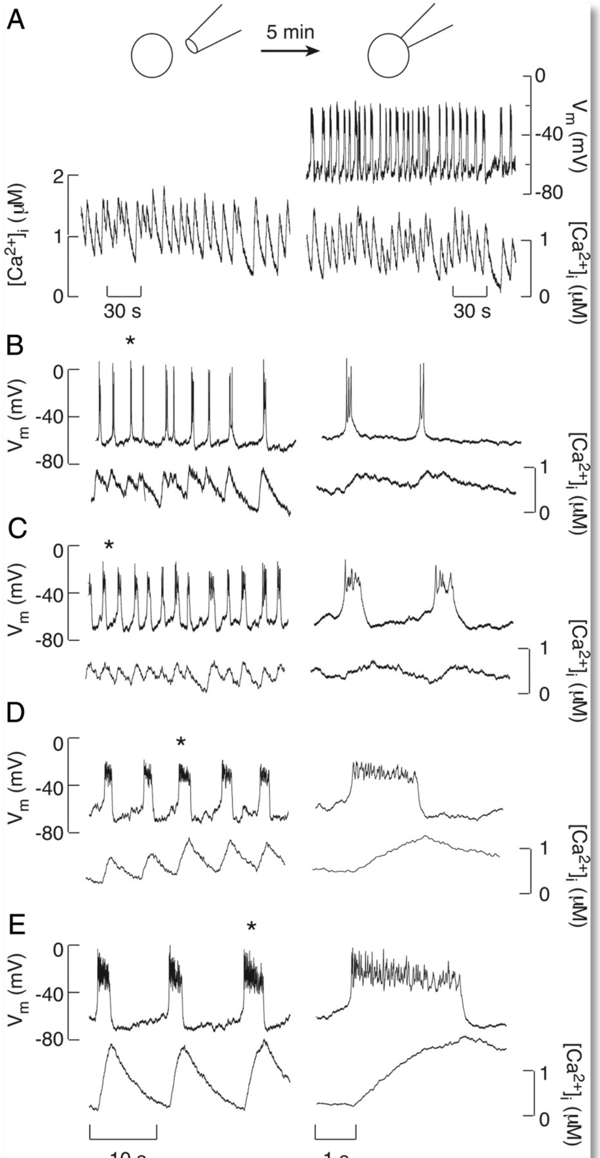
Original concept : Sharp et al, 1993

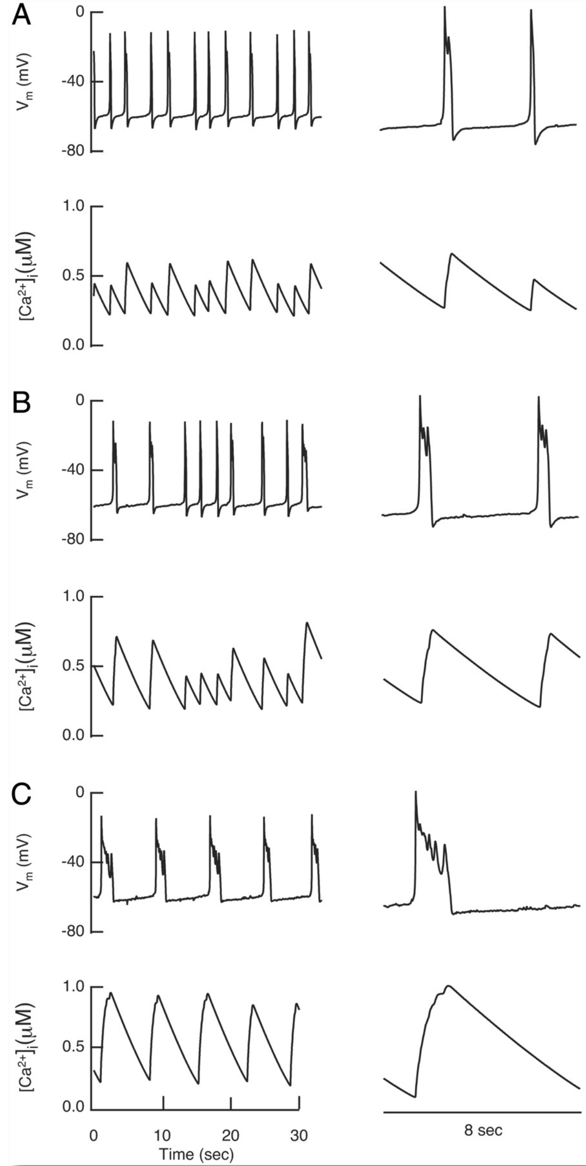
Implementation : **Cambridge Conductance** (Robinson, 2008)

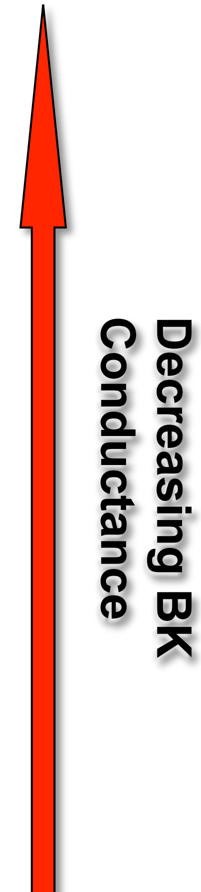
Injection or removal of Kv7 conductance by dynamic clamp reverses or mimics the effects of XE-991.



Milos M. Petrovic, Jakub Nowacki, Krasimira Tsaneva-Atanasova, Andrew D. Randall & Jack R. Mellor, 2011, *Inhibition of post-synaptic Kv7/KCNQ/M channels facilitates Long-Term Potentiation in the Hippocampus*, PLoS ONE, 7(2): e30402



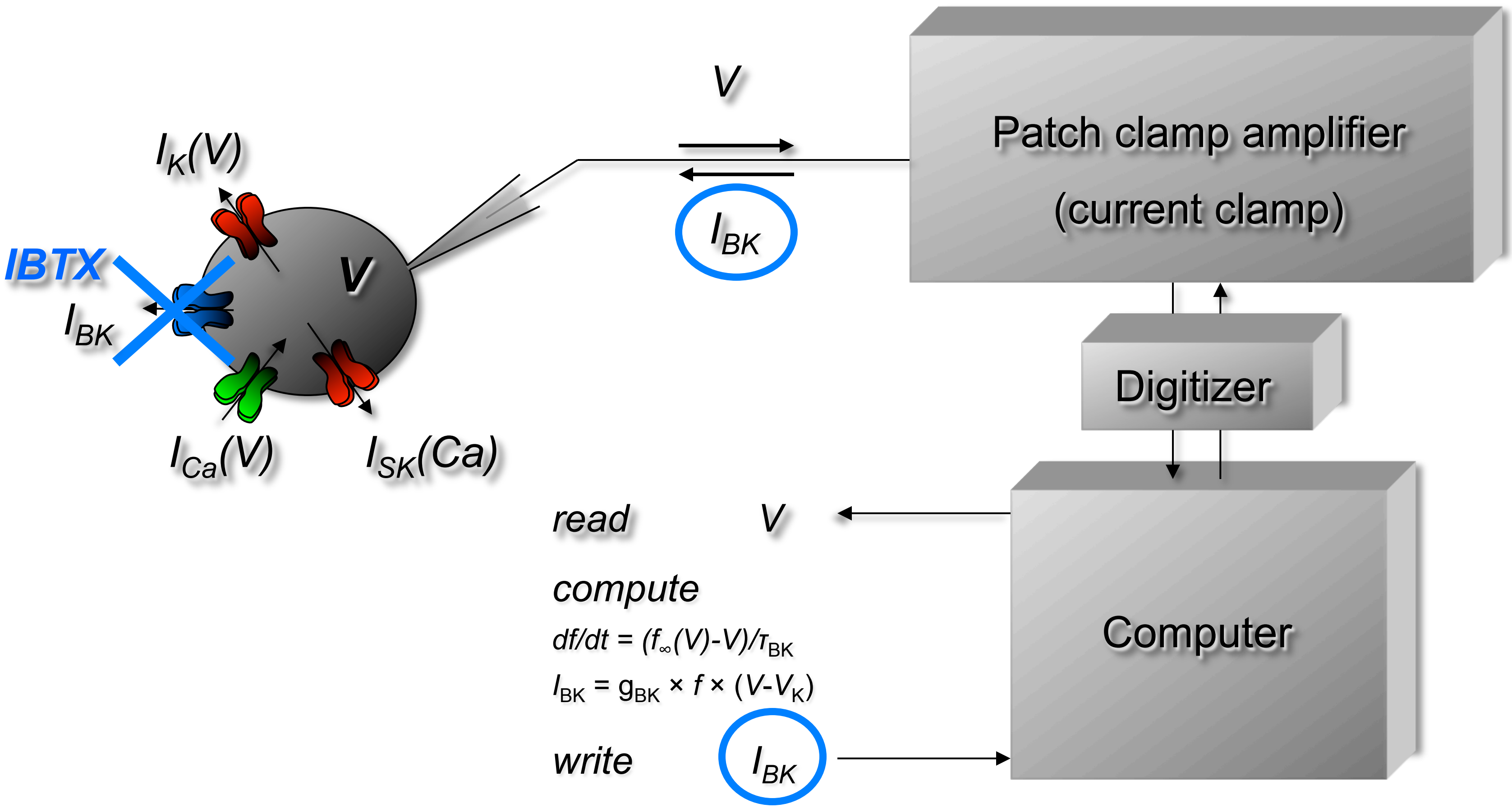




Tsaneva-Atanasova, K. et al. J Neurophysiol 98: 131-144 2007

Journal of Neurophysiology

Adding BK current with Dynamic Clamp

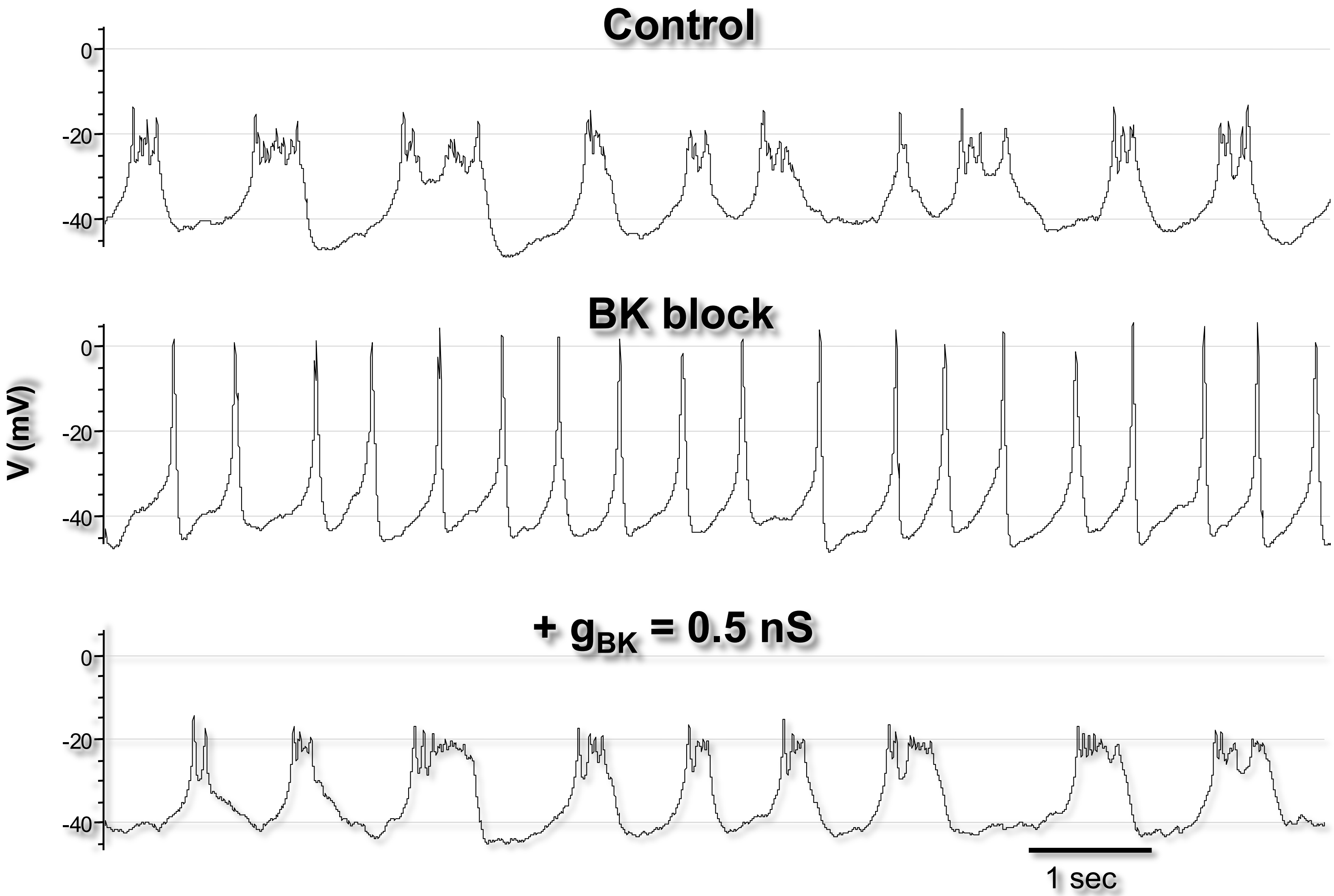


Courtesy of J. Tabak
Florida State University, US

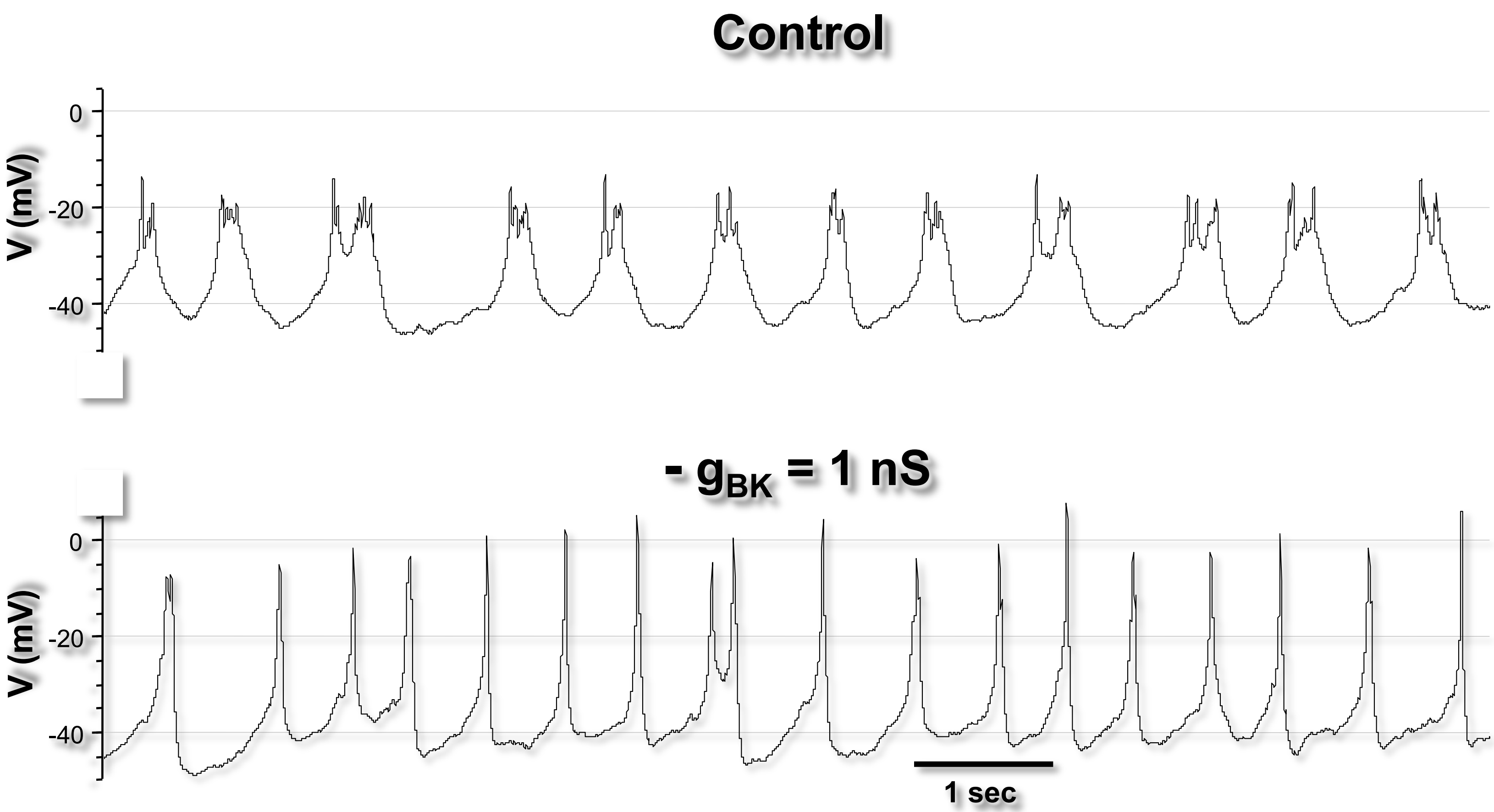
Original concept : Sharp et al, 1993

Implementation : **QuB** (Milescu et al, 2008)

Adding I_{BK} (fast) back with dynamic clamp restores bursting

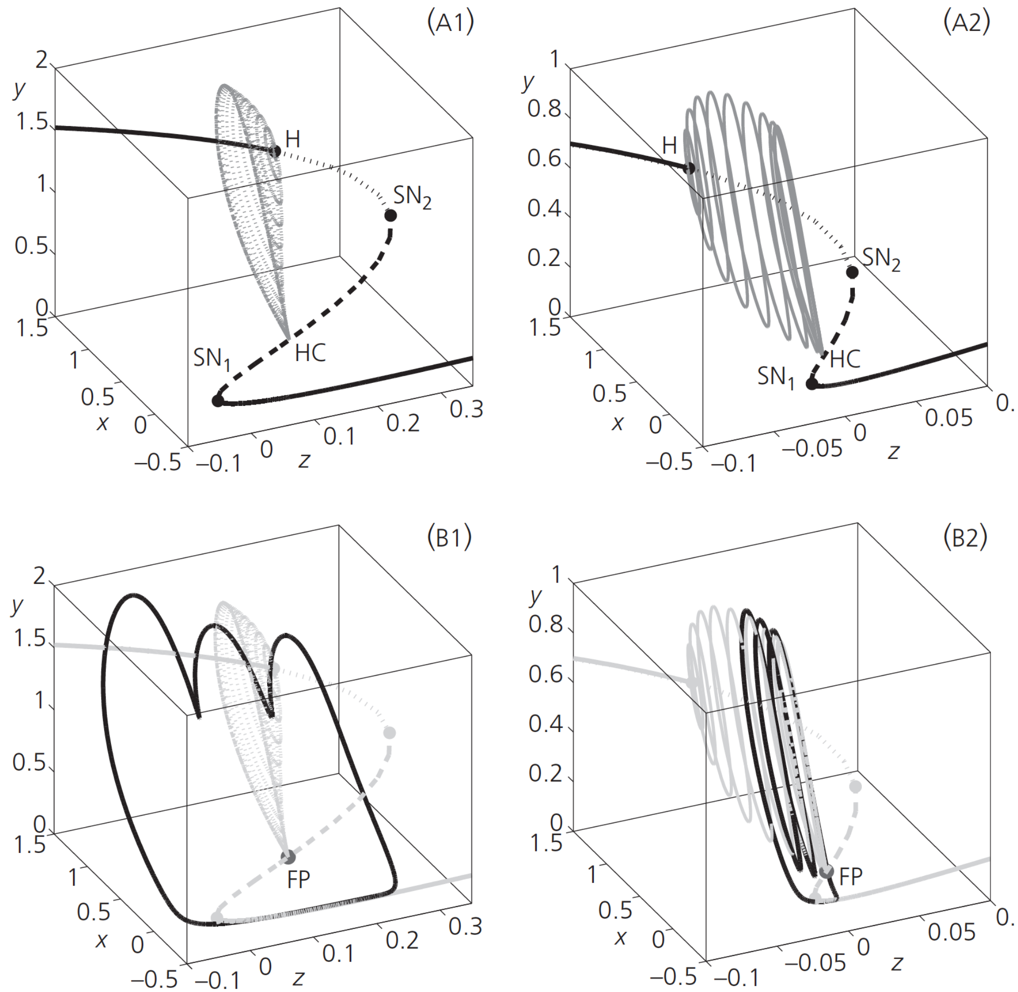


Subtracting I_{BK} converts bursting into spiking



Courtesy of J. Tabak
Florida State University, US

$$\begin{cases} \dot{x} = f(x,y,z) \coloneqq sax^3 - sx^2 - y - bz, \\ \dot{y} = \varphi g(x,y) \coloneqq \varphi(x^2 - y), \\ \dot{z} = \varepsilon h(x,y) \coloneqq \varepsilon(sa_1 x + b_1 - kz). \end{cases}$$



Towards a normal form for bursting

Golubitsky et al. showed that fold/homoclinic bursting appears for the first time in the unfolding of a codimension-three singularity, namely a degenerate Bogdanov–Takens point. They used the following normal form, which is of Liénard type

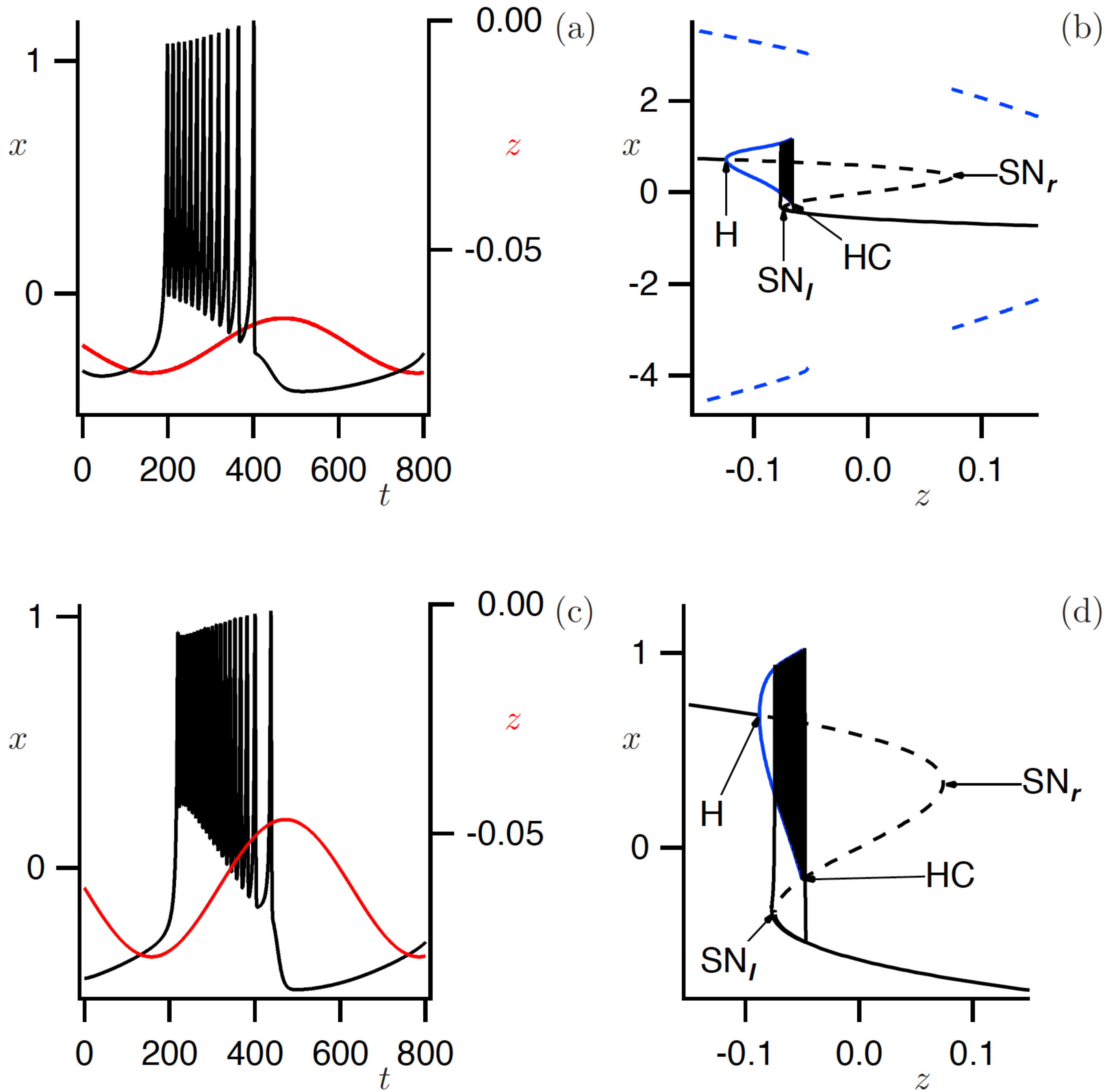
$$\begin{cases} \dot{x} = y, \\ \dot{y} = -\mu_1 + \mu_2 x - x^3 + y(\nu + bx + x^2). \end{cases}$$

In order to make the normal form into a burster, the μ_1 is assumed to slowly oscillate and identify μ_1 with the slow variable $z(t)$ in (1). Hence $\mu_1 = \mu_1(t) = z(t)$, where

$$z(t) := \bar{\mu}_1 - A\sin(\varepsilon t).$$

The fold/homolinic burst path identified by Golubitsky et al. has the dis-advantage that system (2) exhibits an unstable limit cycle of large amplitude surrounding the region in phase space that is involved in the burst; this is not seen in the biophysical models.

Hinke M Osinga, Arthur Sherman and Krasimira Tsaneva-Atanasova, 2012, *Cross-Currents Between Biology And Mathematics: The Codimension Of Pseudo-Plateau Bursting*, Discrete and Continuous Dynamical Systems - Series A (DCDS-A), 32(8): 2853–2877


(a)
x
z
t
0
200
400
600
800
1
0
0.00
-0.05
(b)
x
z
2
0
-2
-4
-0.1
0.0
0.1
SN$_r$
H
SN$_l$
HC
(c)
x
z
t
0
200
400
600
800
1
0
0.00
-0.05
(d)
x
z
1
0
-0.1
0.0
0.1
SN$_r$
H
HC
SN$_l$

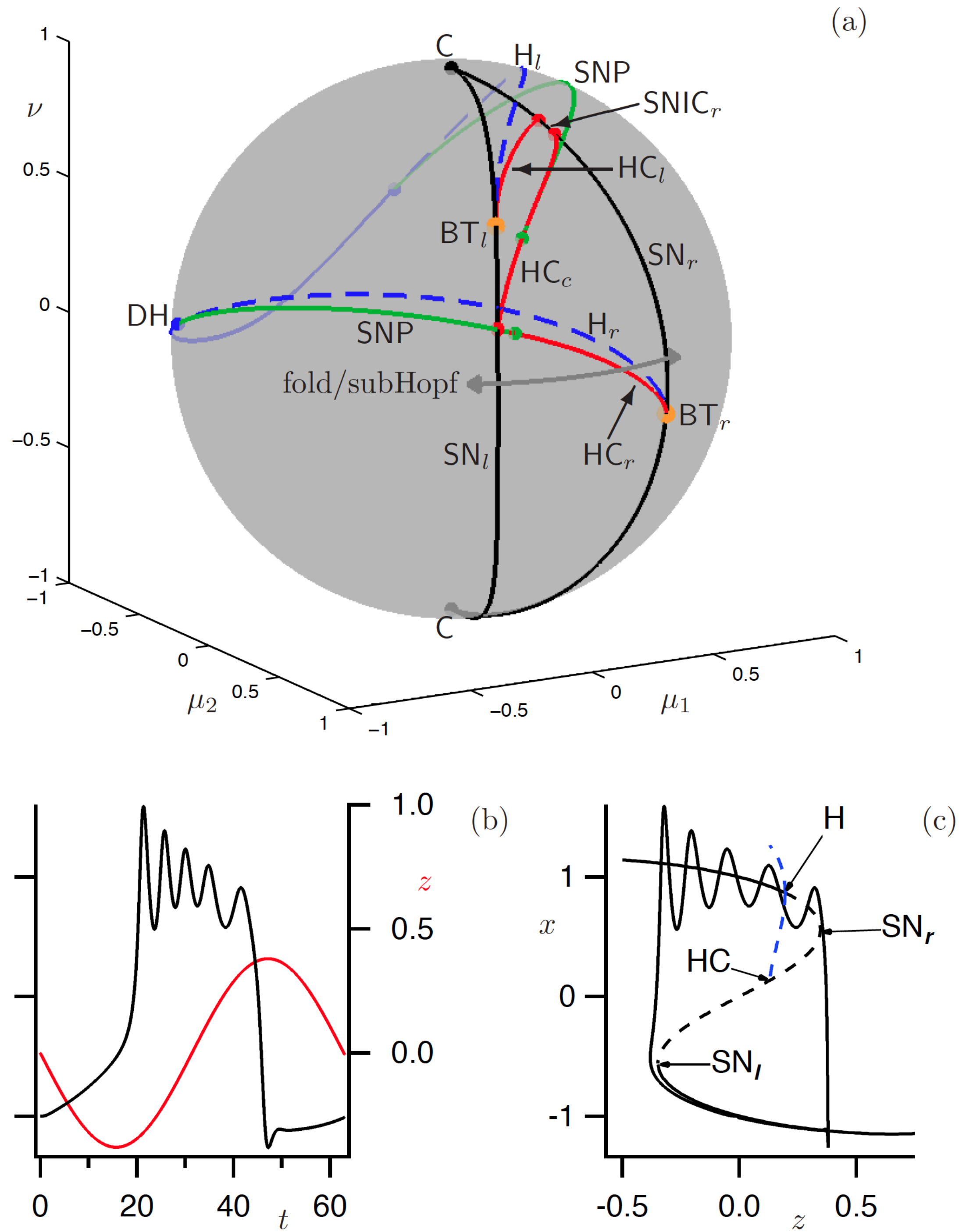
Towards a normal form for bursting

A ‘clean’ fold/homolinic burst path can be found in the time-reversed system

$$\begin{cases} \dot{x} = y, \\ \dot{y} = -\mu_1 + \mu_2 x - x^3 + y(\nu + bx - x^2). \end{cases}$$

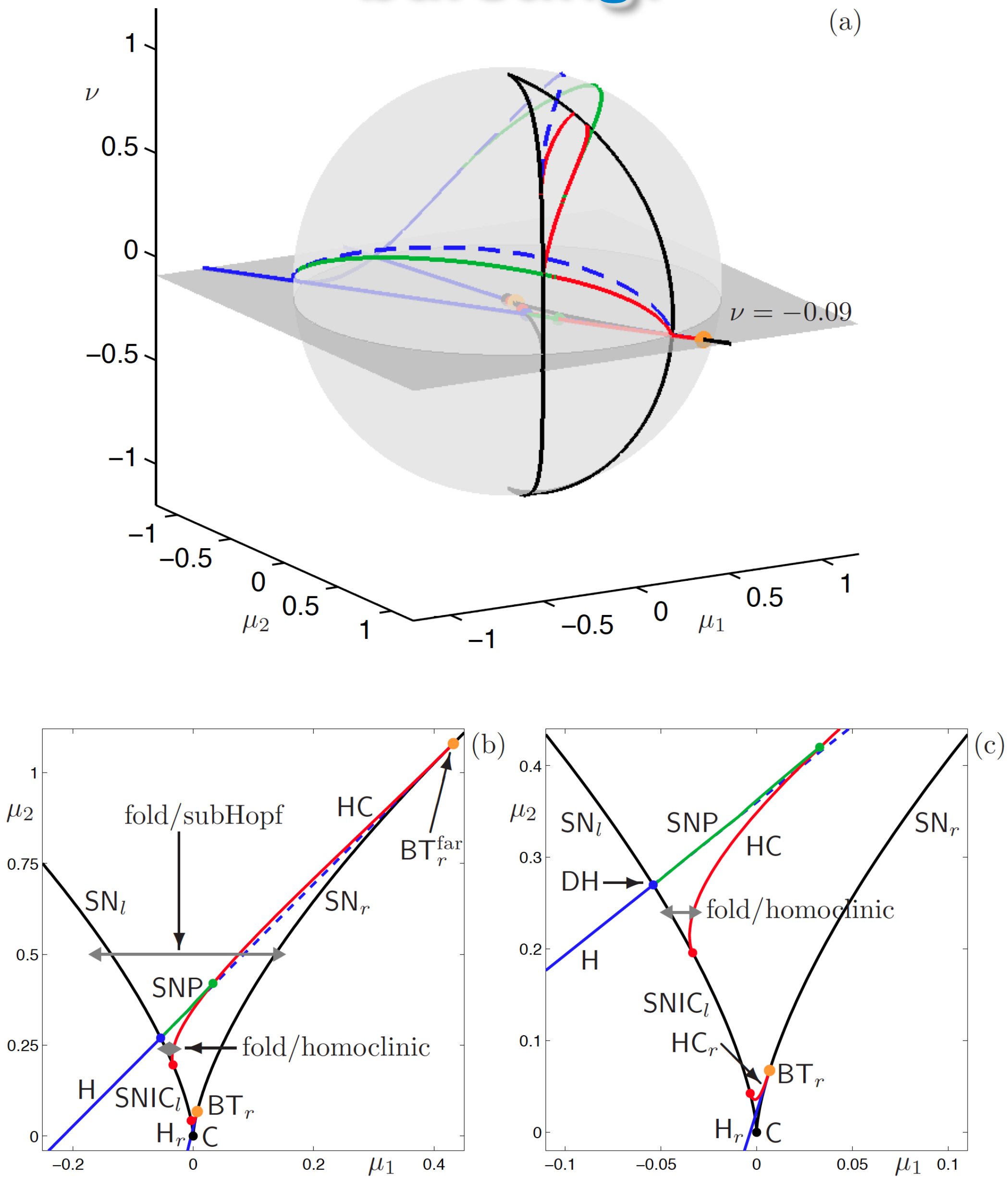
Technically we also reverse the orientations of μ_1, v and x, so that the net effect is only a change of sign for the term yx^2, and the Hopf bifurcation again occurs on the “upper” branch. We consider codimension-four unfolding where the parameter b is no longer fixed and we study the entire four-dimensional parameter space.

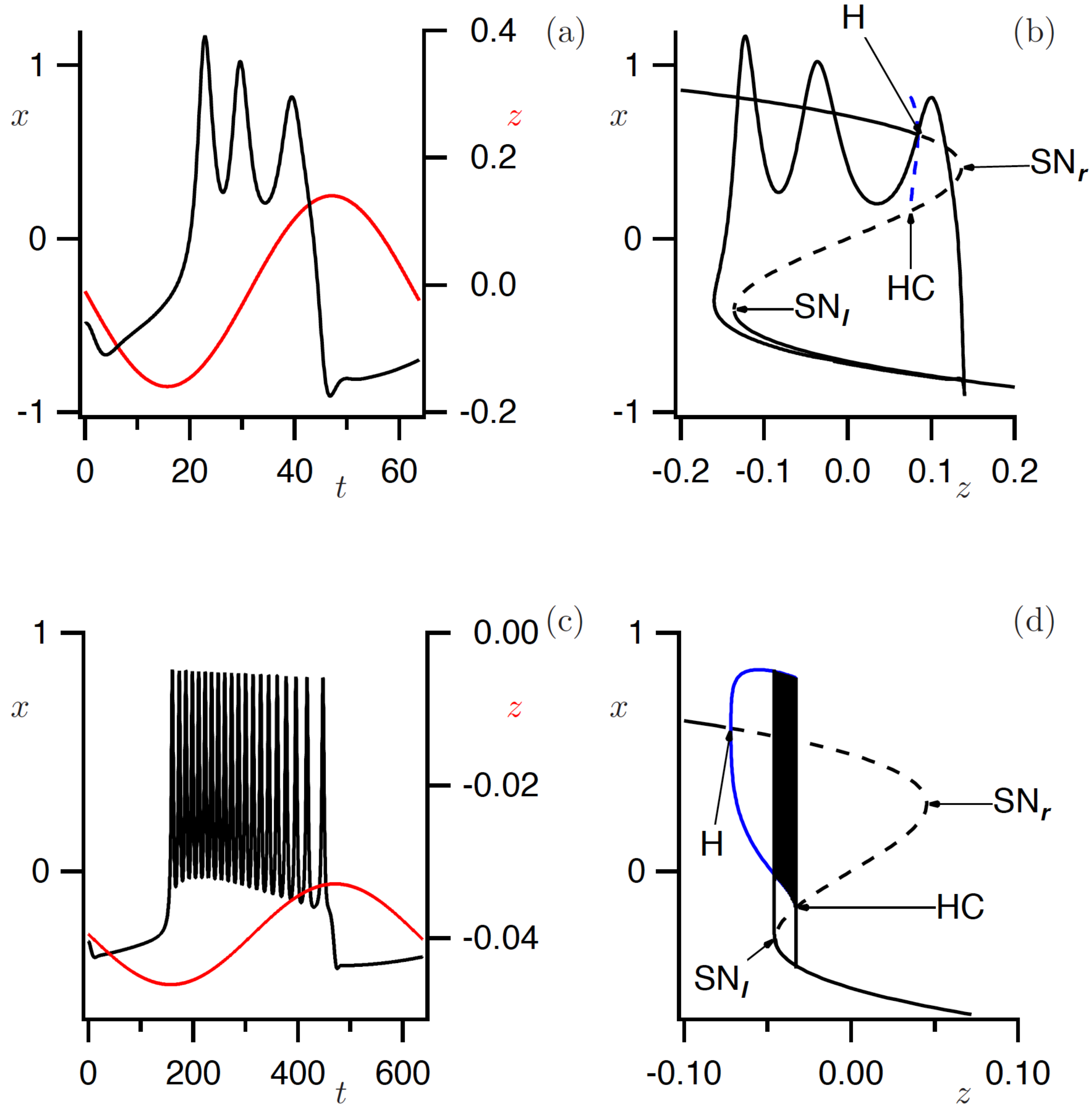
We consider the unit sphere, that is, a sphere with radius one centered around the origin in (μ_1, μ_2, v)-space, as the boundary of a fixed neighborhood. We find that b = 0. 75 is small enough such that we can identify a fold/subHopf burst path on this unit sphere.



(a)
C
H_l
SNP
$SNIC_r$
HC_l
BT_l
HC_c
SN_r
DH
SNP
H_r
fold/subHopf
BT_r
SN_l
HC_r
C
ν
μ_2
μ_1
(b)
z
t
(c)
H
SN_r
HC
SN_l
x
z

Transition from pseudo-plateau to square-wave bursting.





(a)
x
z
1
0
-1
0.4
0.2
0.0
-0.2
0
20
40
t
60
(b)
H
SN$_r$
HC
SN$_l$
-0.2
-0.1
0.0
0.1
z
0.2
(c)
0.00
-0.02
-0.04
0
200
400
600
(d)
-0.10
0.00
0.10

First-order Approximation of the Cubic Liénard Normal Form

The approach considered in [1] applies a truncated Fourier series to the Duffing equation. We apply a similar analysis to the cubic Liénard normal form equations. This yields an approximation for the system solutions in terms of **sin** and **cos** functions. The derivation of the approximation consists of the following: equations (1) are rearranged into second order form; solutions are assumed in the form of a first-order Fourier approximation; these solutions are substituted into equations (1); coefficients are compared and the resulting expressions rearranged to obtain expressions for the approximation, $x = p(\tau) + a(\tau)\cos(\varepsilon\tau) + b(\tau)\sin(\varepsilon\tau)$, where

$$\textbf{(1)} \begin{cases} \dot{x} = y, \\ \dot{y} = A\sin(\varepsilon t) - \bar{\mu}_1 + \mu_2 x - x^3 + y(\nu + Bx + x^2). \end{cases}$$

[1] Mann B. P.-Burrow S. G. Barton, D. A. W. Control-based continuation for investigating nonlinear experiments. Journal of Vibration and Control, 18:509520, 2012.

First-order Approximation of the Cubic Liénard Normal Form

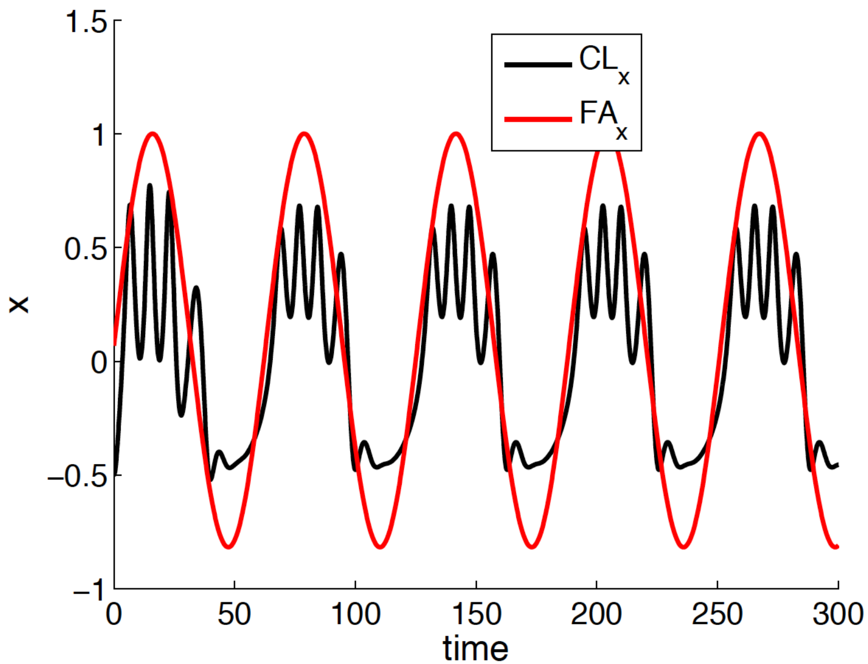


Figure 3.12: Example firing patterns using the cubic Liénard normal form (CL_x) and the first-order approximation (FA_x). Parameter values used for the cubic Liénard normal form are: $b = 0.75$; $v = -0.09$; $\overline{\mu_1} = -0.01$; $\Gamma = A = 0.15$; $n = \varepsilon = 0.1$; $\mu_2 = -0.1$.

Pseudo-Arclength Continuation in *n* = *ε*

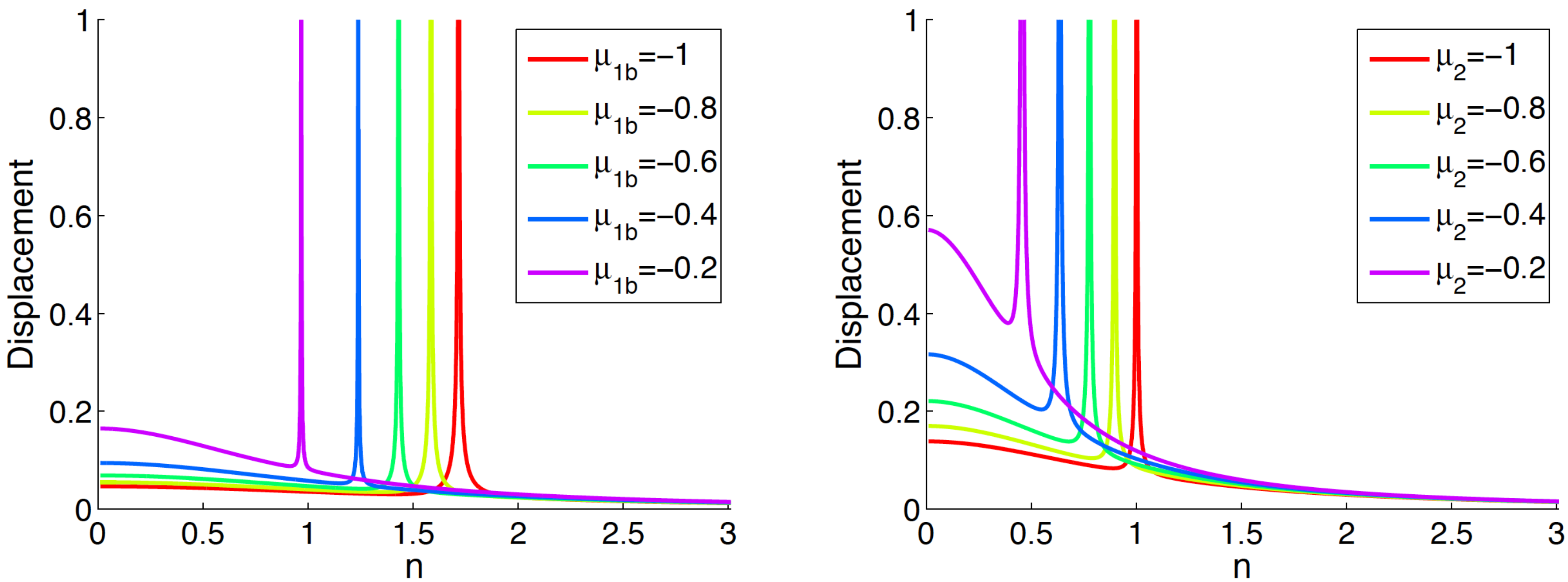
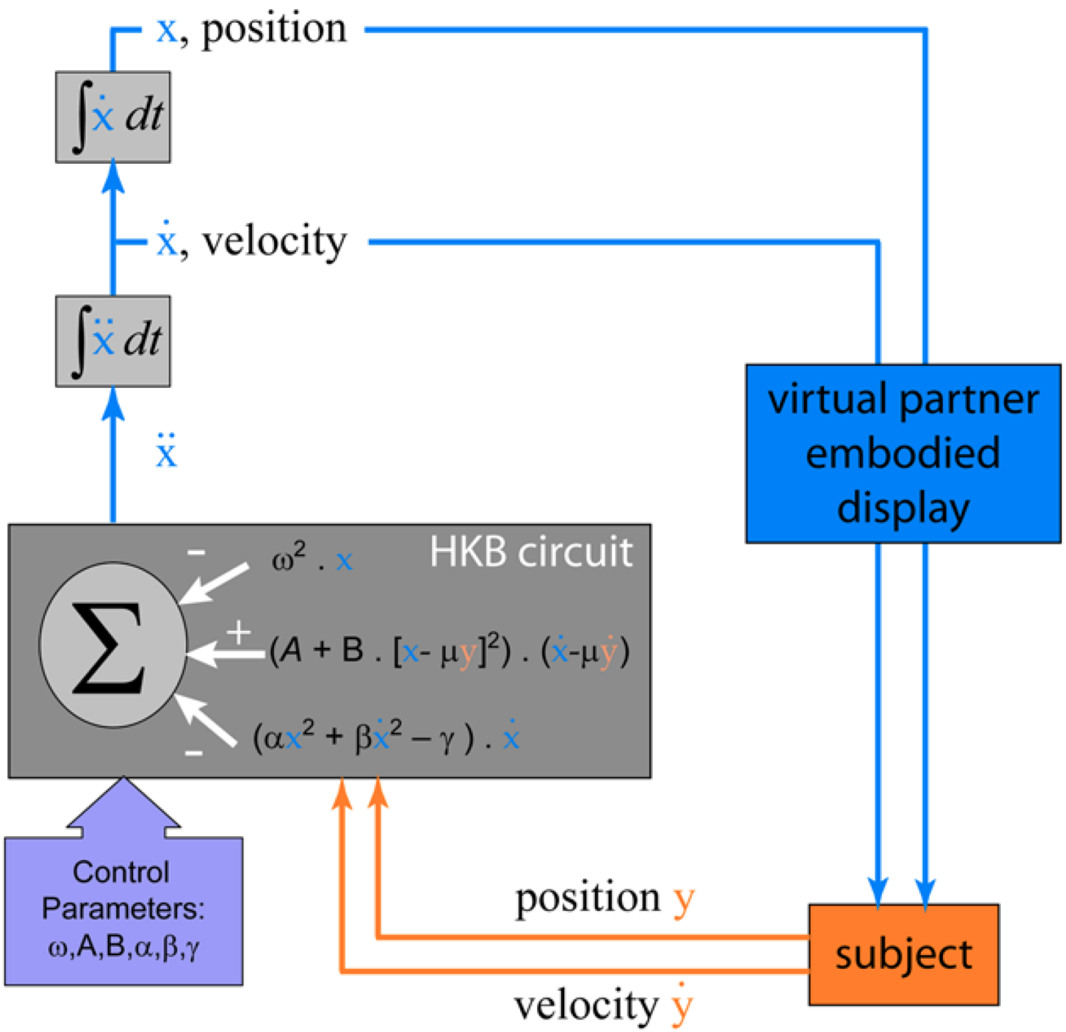


Figure 3.15: Bifurcation diagrams in n as $\overline{\mu_1}$ is varied (left) and bifurcation diagrams in n as μ_2 is varied (right). In the left diagram different values of $\overline{\mu_1}$ are given in the legend as μ_{1b}, and in the right the different values of μ_2 used are stated. All other values are the same as those in figure (3.12).

Human Dynamic clamp: using models in human-computer interaction

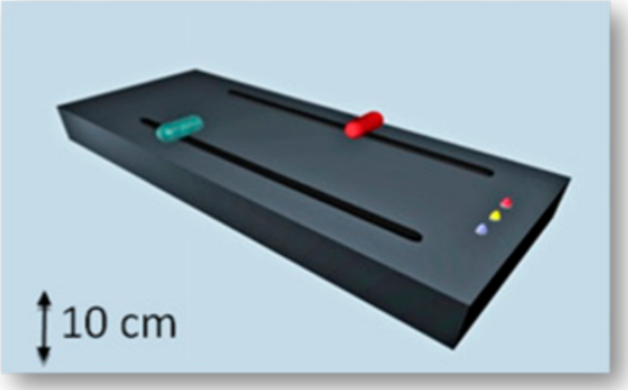


"Modifying the dynamics of the virtual partner with the purpose of inducing a desired human behavior (e.g. as in learning a new skill or as a tool for therapy and rehabilitation) is another useful possibility. On a more basic level, there is also a great deal of interest in engineering complex dynamic structures to produce desired states."

Kelso JAS, de Guzman GC, Reveley C, Tognoli E (2009) Virtual Partner Interaction (VPI): Exploring Novel Behaviors via Coordination Dynamics. PLoS ONE 4(6): e5749

The Mirror Game

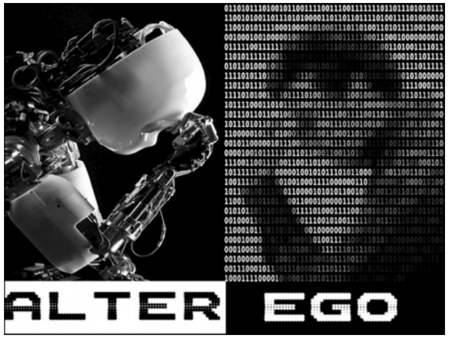
- We use the mirror game as a simple yet effective paradigm
- In its simplest formulation, the mirror game features two people imitating each other's movements at high temporal and spatial resolution.
- It can be played in different conditions:
  - *Leader-Follower* (LF)
  - *Joint Improvisation*
- We focus on the problem of exploring how differences in the kinematic signatures of the players affect their interaction



Noy, Lior, Erez Dekel, and Uri Alon. "The mirror game as a paradigm for studying the dynamics of two people improvising motion together." Proceedings of the National Academy of Sciences 108.52 (2011): 20947-20952.

Motivation

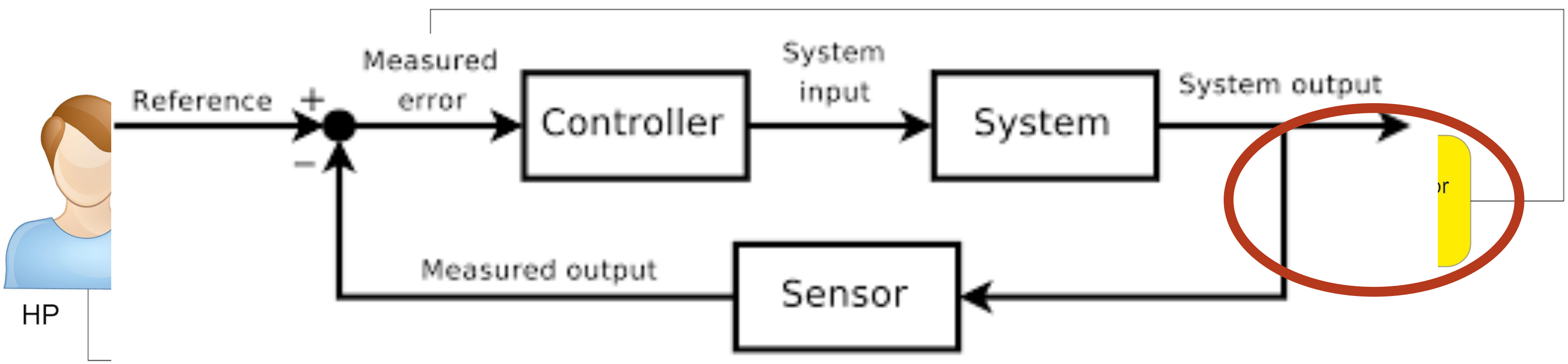
- Coordination games can be used to help people suffering from social disabilities (as for example schizophrenia) improve their social skills.
- In order to implement an effective rehabilitation, the patient should ideally interact first with people who are similar to him/her, and then gradually with someone who is totally different
- To implement this scenario it is necessary to create an avatar or virtual player (VP) able to play the mirror game
- This is the goal of the EU project ALTEREGO
- The aim of our research is to *design a control architecture (or cognitive architecture) able to drive the virtual player* as:
  - leader
  - follower
  - joint-improvisation



www.euromov.eu/alterego

Why feedback control?

- The problem of designing a virtual player able to coordinate its motion with a human player can be seen as a **control design problem**
- The goal is that of designing a *cognitive architecture* able to drive the motion of the VP interacting with a human player in **real-time** while exhibiting different features (e.g. different kinematic signatures)
- This is a typical nonlinear control design problem…

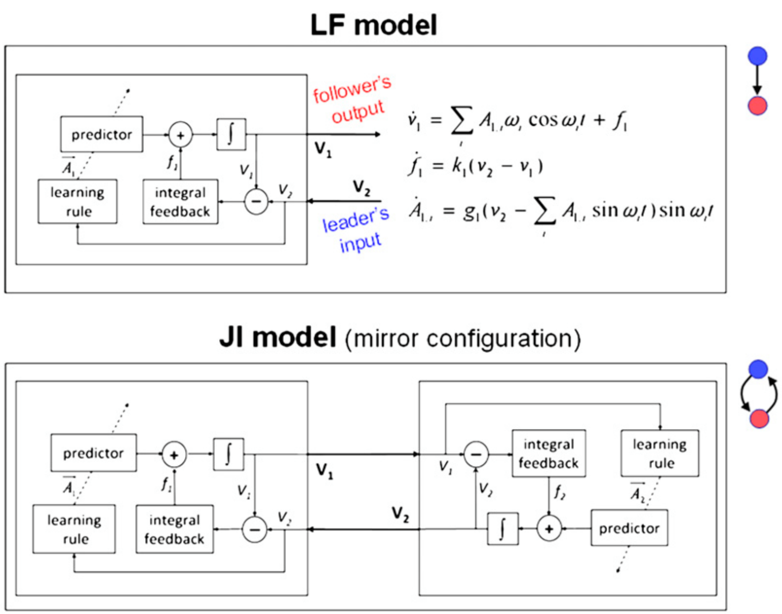


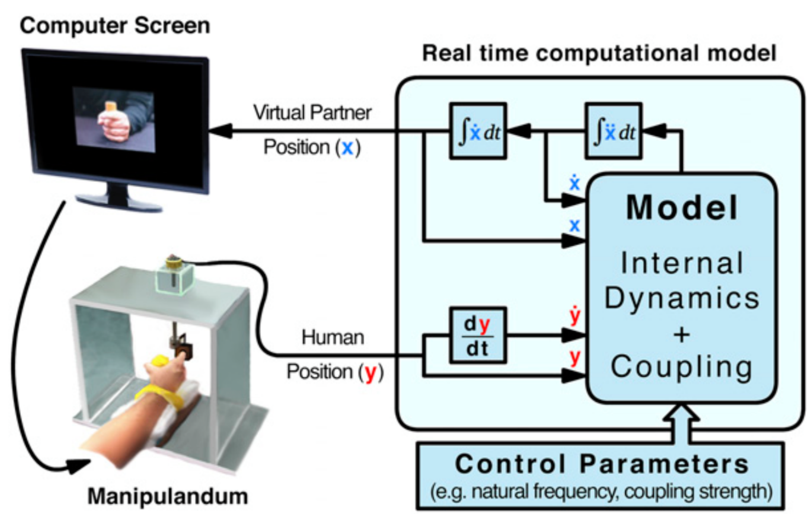
Control = sensing + computation + actuation

- We also need a **model of the system we wish to control**

Previous work

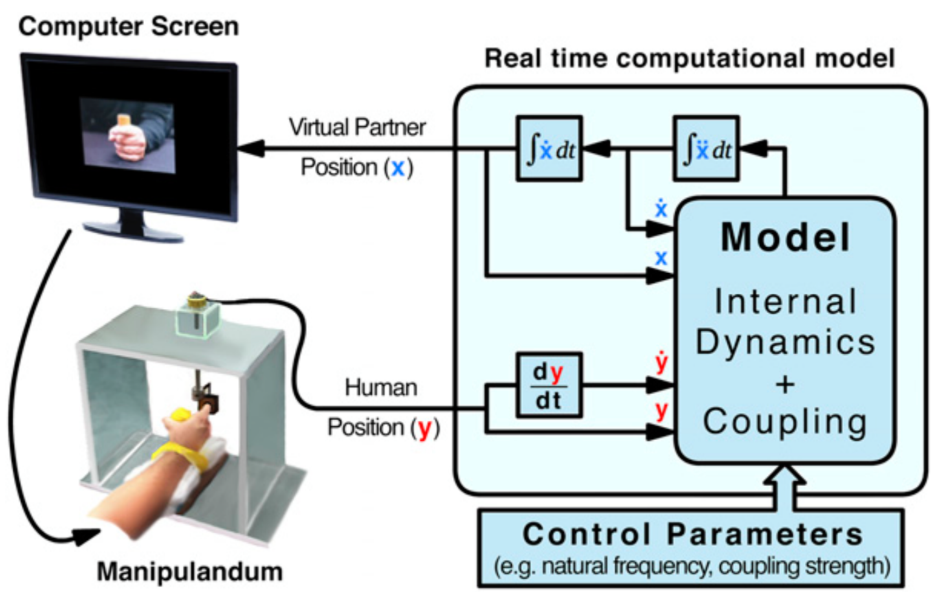
- Two main modelling approaches have been proposed in the literature that relate to this control architecture
  - The **reactive-predictive control (RPC)** proposed by Noy et al (2011)
  - The **Human Dynamic Clamp (HDC)** proposed by Dumas et al (2009; 2014)





Human Dynamic clamp

- The HDC paradigm is introduced to directly manipulate the interaction between a HP and a VP based on the use of a mathematical model
- It is used to model the interactions between HP and VP in different scenarios:
  - ✦ rhythmic behavior
  - ✦ discrete behavior
  - ✦ adaption to changes of pacing;
  - ✦ behavioral skill learning as specified by a virtual "teacher"
- In each scenario a different model is used



Dumas, de Guzman, Tognoli, Kelso. "The human dynamic clamp as a paradigm for social interaction". Proceedings of the National Academy of Sciences, 111.35 (2014): 3726-3734.

HDC – Rhythmic Behaviour

HKB model

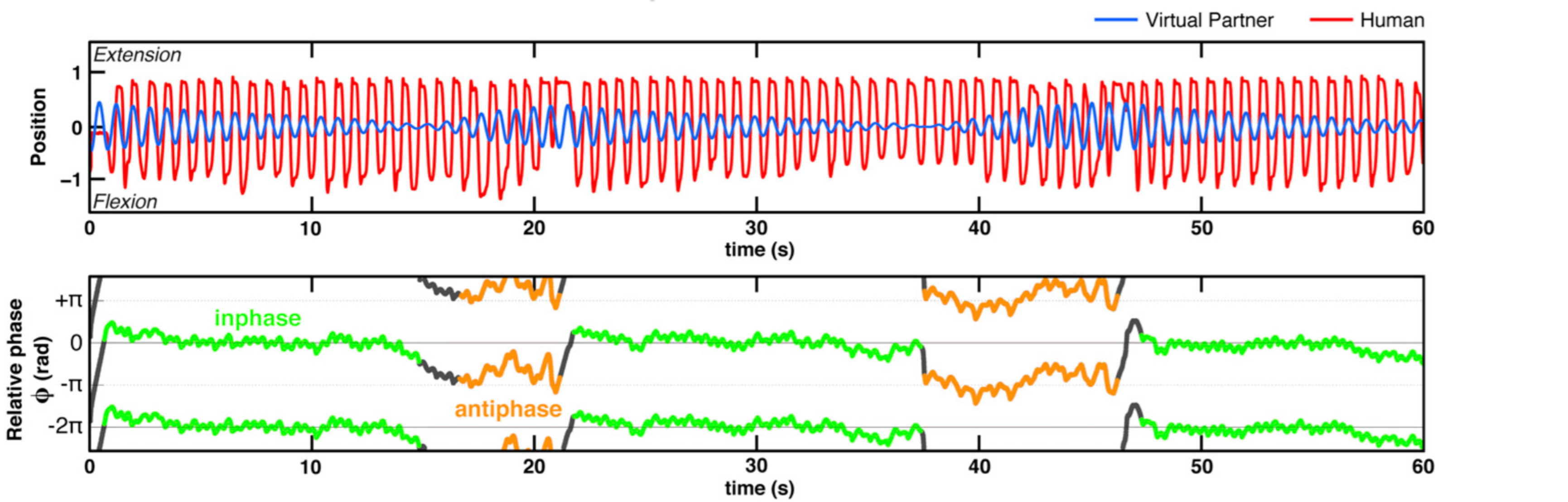
Control input

$$\ddot{x}+(\alpha x^2+\beta\dot{x}^2-\gamma)\dot{x}+\omega^2 x=\left[a+b(x-\mu y)^2\right](\dot{x}-\mu\dot{y})$$

- $x,\dot{x}$ position and velocity of the VP;
- $y,\dot{y}$ position and velocity of the HP;
- μ tunable parameter;

- $\alpha,\beta,\gamma,\omega$ intrinsic properties of the VP oscillator;
- a,b coupling parameters;
- μ determines in phase (1) or anti-phase (-1) coordination.

Anti-phase coordination $\mu=-1$: HP is supposed to follow VP



HDC – Discrete Behaviour

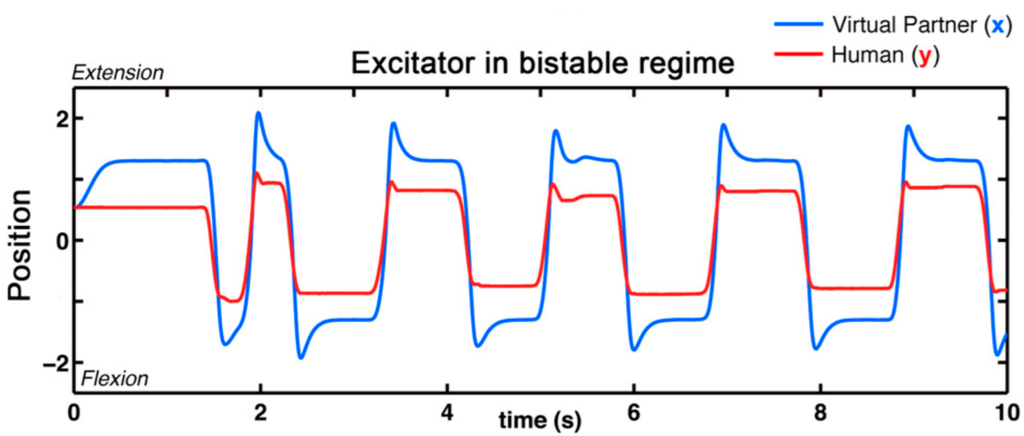
Jirsa-Kelso excitator model

Control input

$$\ddot{x}+\tau\omega(x^2+x^4-1)+\omega^2\left(x-A-B\left(\frac{\dot{x}}{\tau\omega}-x+\frac{1}{3}x^3+\frac{1}{5}x^5-y\right)\right)=\left[a+b(x-\mu y)^2\right](\dot{x}-\mu\dot{y})$$

- $x,\dot{x}$ position and velocity of the VP;
- $y,\dot{y}$ position and velocity of the HP;
- μ tunable parameter;
- A,B,τ,ω intrinsic properties of the VP oscillator;
- a,b coupling parameters;
- μ determines in phase (1) or anti-phase (-1) coordination.

In phase coordination $(\mu=-1)$: VP is supposed to follow HP



HDC – Adaption to changes of pacing

Jirsa-Kelso excitator model

Control input

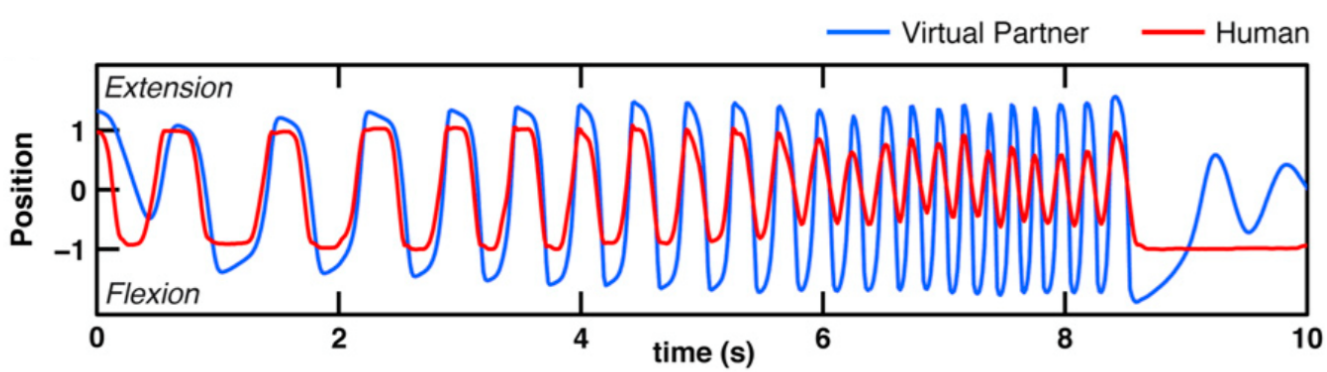
$$\ddot{x}+\tau\omega(x^2+x^4-1)+\omega^2\left(x-A-B\left(\frac{\dot{x}}{\tau\omega}-x+\frac{1}{3}x^3+\frac{1}{5}x^5-y\right)\right)=\left[a+b(x-\mu y)^2\right](\dot{x}-\mu\dot{y})$$

$$\dot{\omega}=\nu(\omega_0-\omega)\omega\ \pm\kappa F(t)\frac{x_2}{\sqrt{x_1^2+x_2^2}}$$

Adaptive parameter

- κ strength of the adaptation;
- ω_0 preferred frequency;
- ν strength of the preferred frequency.

In phase coordination $(\mu=-1)$: VP is supposed to follow HP



Mirror Game as a Control Problem

- We want to design a different control strategy for the VP able to achieve:
  1. the desired game condition (L, F or JI);
  2. bounded tracking of the human player motion (temporal correspondence)
  3. desired kinematic properties, e.g. a given kinematic signature (velocity pdf)
- We also want to make it able to change the motor signature of the VP continuously during the game
- As a model of the VP movement we use an HKB oscillator but redesign the control input to achieve the control goals:

$$\ddot{x} + (\alpha x^2 + \beta \dot{x}^2 - \gamma)\dot{x} + \omega^2 x = u(t, x, \dot{x}, y, \dot{y})$$

- Let's start with controlling temporal correspondence between the players.

The AlterEgo Experiment

Experimental validation of the adaptive tracking algorithm at the hospital in Montpellier, France.

Mirror Game Set-up