Neuronal oscillations level sets for activity constancy: from single neurons to networks

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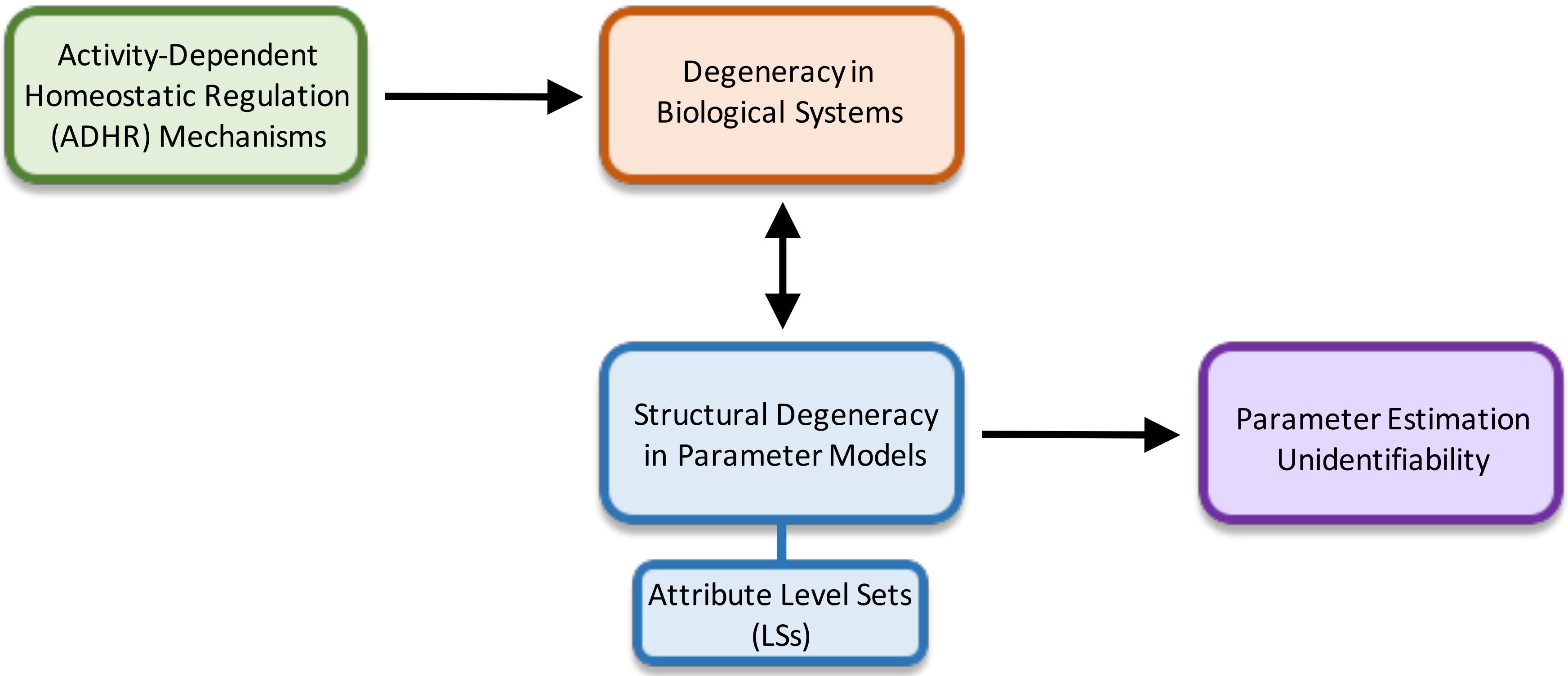
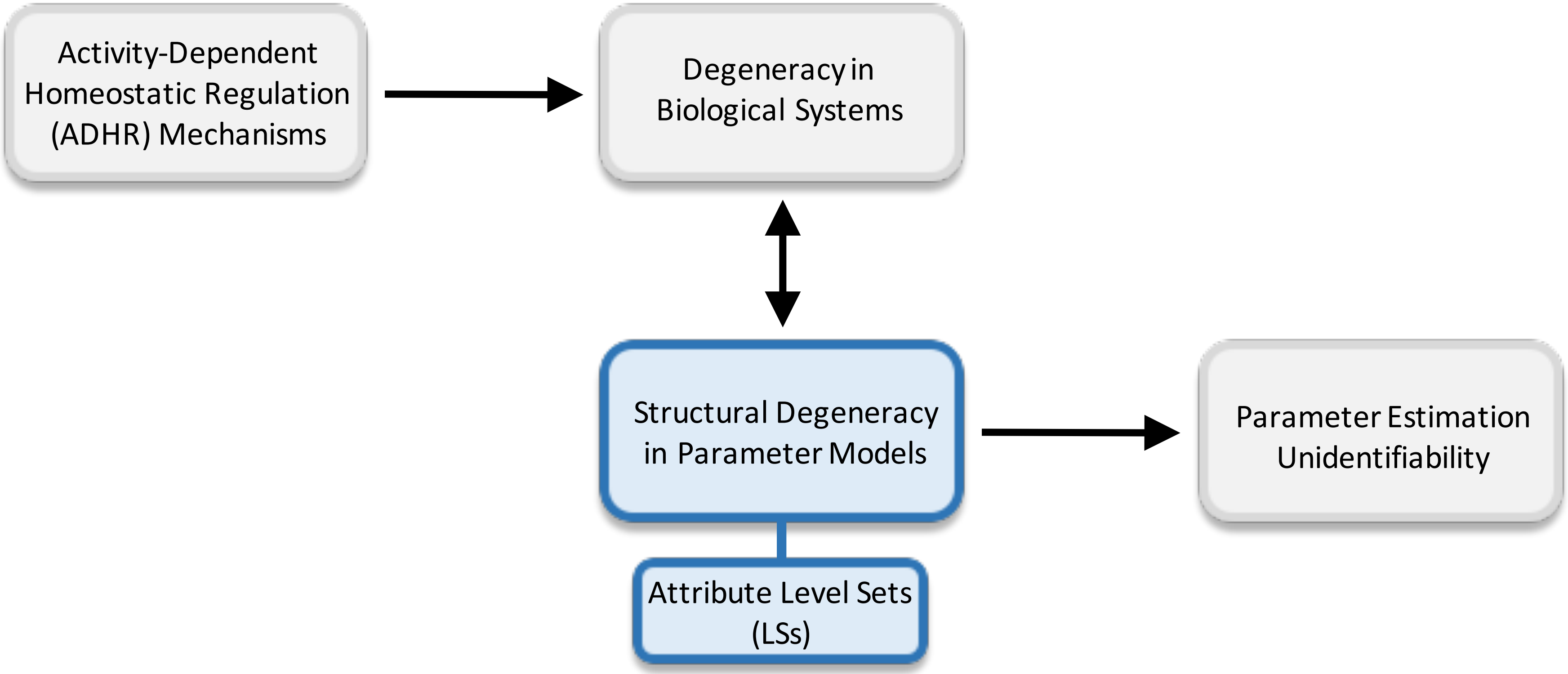
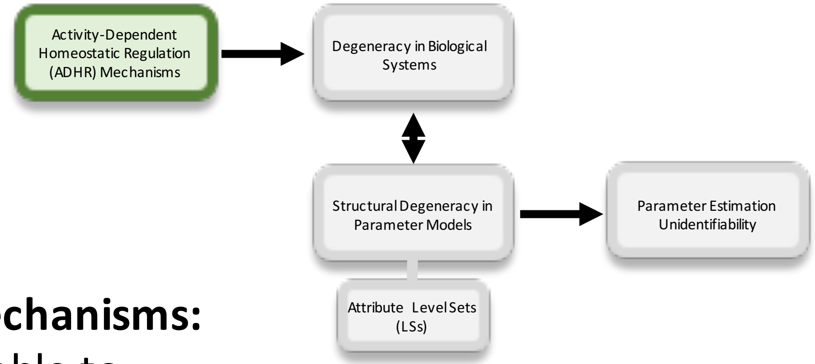


1. Introduction



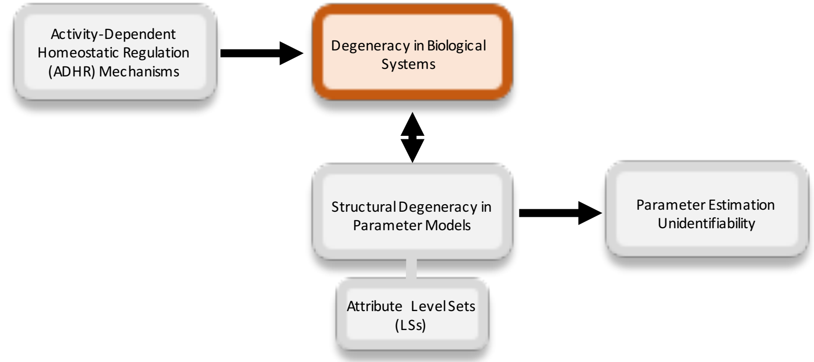


1. Introduction

Activity-Dependent Homeostatic Regulation Mechanisms

- ✓ **Activity-dependent homeostatic regulation (ADHR) mechanisms:** negative feedback systems through which neurons are able to restore their properties and compensate changes due to external perturbations. They allow a neuron to maintain their so-called target activity level.

- ✓ The fact that the **target activity level** of a neuron or neuronal network is presumably an electrical activity pattern and that almost identical activity can arise from different intrinsic or network properties give rise to degeneracy in biological systems.



1. Introduction

Degeneracy in Biological Systems

- ✓ **Similar neuron activity** can be generated with different combinations of ionic currents.

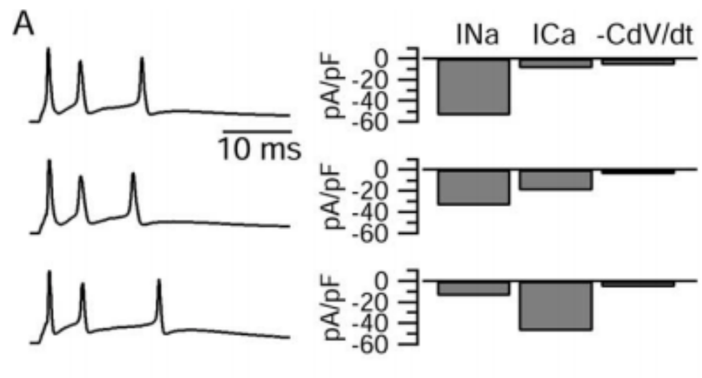
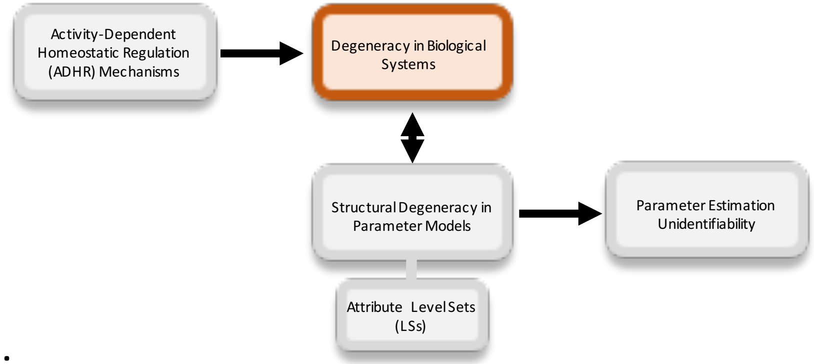


Figure 1.: Individual cerebellar Purkinje neurons show almost identical patterns of electrical activity with different ratios of Na^{+} and Ca^{+} currents, [1].

[1] Swensen AM, Bean BP. Robustness of burst firing in dissociated purkinje neurons with acute or long-term reductions in sodium conductance. *J Neurosci*. 2005;25(14):3509-3520



1. Introduction

Degeneracy in Biological Systems

✓ **Similar network activity** can be generated with several combinations of synaptic strengths and intrinsic properties

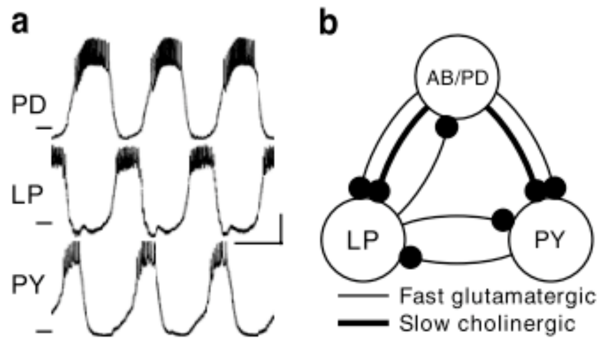


Figure 2.: Pyloric rhythm and pyloric circuit architecture, [2].

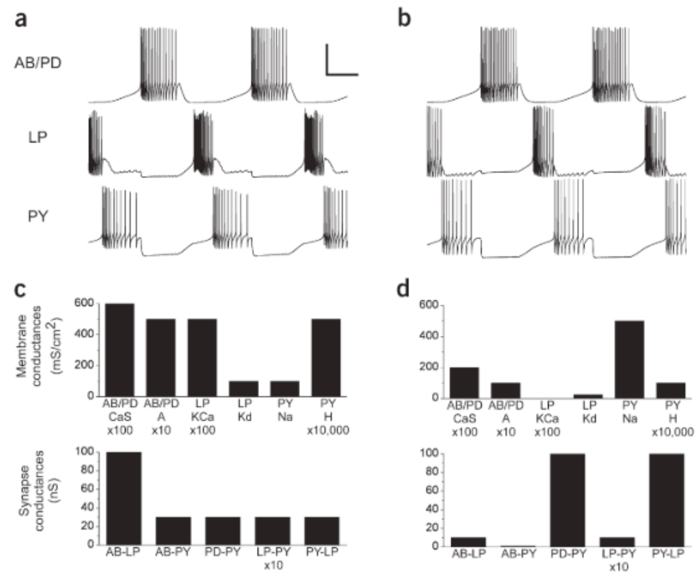
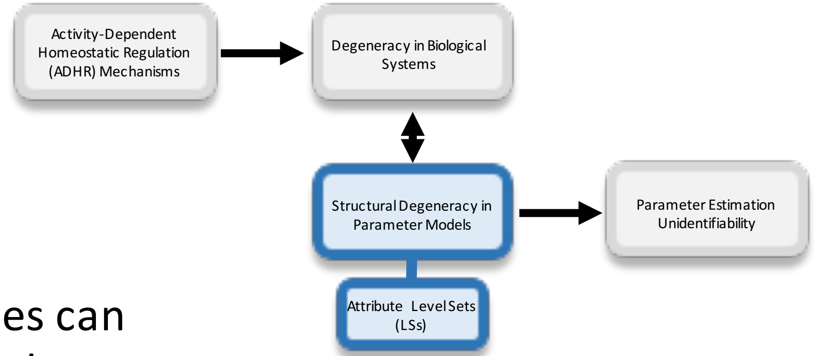


Figure 3.: Symilar pyloric rhythms from different networks, [2].

[2] Prinz AA, Bucher D, Marder E. Similar network activity from disparate circuit parameters. *Nat Neurosci*. 2004;7(12):1345-1352

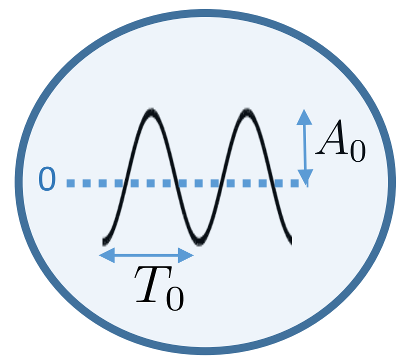


1. Introduction

Structural Degeneracy

- ✓ **Structural degeneracy:** multiple sets of parameters values can produce the same observable output, therefore making the inverse problem ill-posed, i.e., determining the model parameters from observable experimental data is not a well-defined problem. Only based on the inherent structure of a given model.

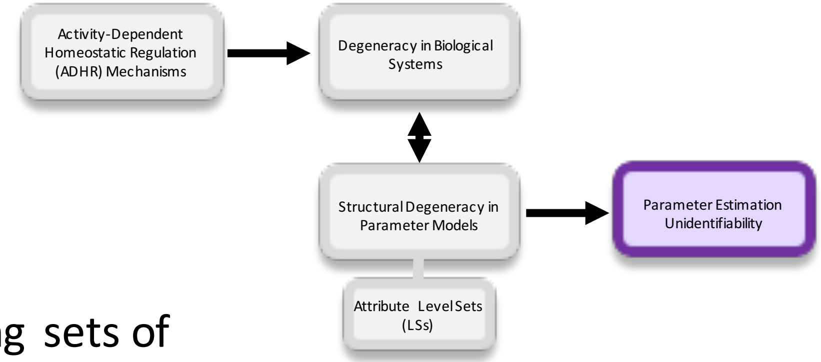
- ✓ **Attribute Level Sets (LSs):** sets of points in parameter space for which a given attribute is constant.



Neuron

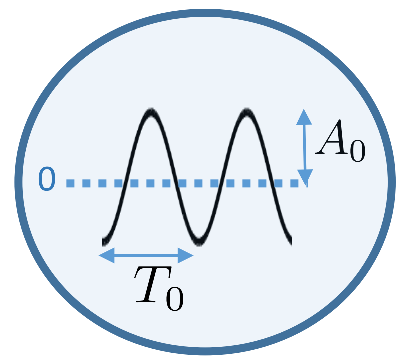
1. Introduction

Parameter Estimation Unidentifiability



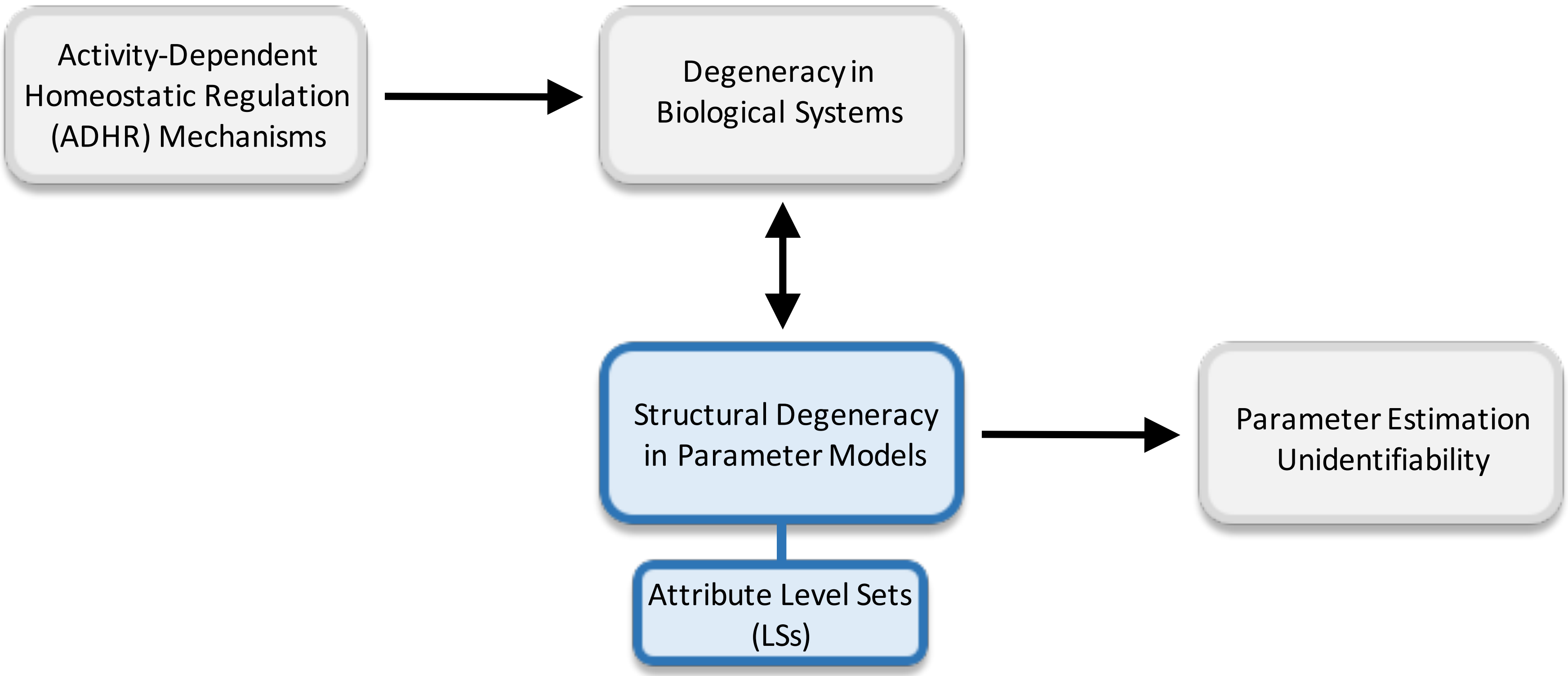
- ✓ **Neuronal parameter optimization**: process of identifying sets of parameters that lead to a desired electrical activity pattern in a given neuron or neuronal network model that is not fully constrained by experimental data.

- ✓ Which parameters produce a given activity pattern?



Neuron

1. Introduction



2. Background on Computational Neuroscience

Mathematical Models for Neuronal Networks

- ✓ Conductance-Based Models
- ✓ Synaptic Dynamics Models
  - ✓ Electrical Synapses or gap-junction
  - ✓ Chemical Synapses

3. Previous Work on Attribute Level Sets

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First published September 12, 2007; doi:10.1152/jn.00842.2007.

Innovative Methodology

Using Constraints on Neuronal Activity to Reveal Compensatory Changes in Neuronal Parameters

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Submitted 27 July 2007; accepted in final form 5 September 2007

Olypher AV, Calabrese RL. Using constraints on neuronal activity to reveal compensatory changes in neuronal parameters. *J Neurophysiol* 98: 3749–3758, 2007. First published September 12, 2007; doi:10.1152/jn.00842.2007. In this study, we developed a general description of parameter combinations for which specified characteristics of neuronal or network activity are constant. Our approach is based on the implicit function theorem and is applicable to activity characteristics that smoothly depend on parameters. Such smoothness is often intrinsic to neuronal systems when they are in stable functional states. The conclusions about how parameters compensate each other, developed in this study, can thus be used even without regard to the specific mathematical model describing a particular neuron or neuronal network. We showed that near a generic point in the parameter space there are infinitely many other points, or parameter combinations, for which specified characteristics of activity are the same as in the original point. These parameter combinations form a smooth manifold. This manifold can be extended as long as the gradients of characteristics are defined and independent. All possible variations of parameters compensating each other are simply all possible charts of the same manifold. The number of compensating parameters (but not parameters themselves) is fixed and equal to the number of the independent characteristics maintained. The algorithm that we developed shows how to find compensatory functional dependencies between parameters numerically. Our method can be used in the analysis of the homeostatic regulation, neuronal database search, model tuning and other applications.

INTRODUCTION

Numerous studies, both experimental and theoretical, have revealed myriad factors underlying neuronal and network activity. These factors range from neuronal morphology and distribution of ionic current channels to structural properties of networks such as the average number of synaptic connections per neuron. Experiments show that despite the variability in these factors and the complexity in their interactions, some characteristics of neuronal activity, and in particular those related to appropriate function, are maintained (Buzsaki et al. 2002; MacLean et al. 2003; Marder and Goaillard 2006; Swensen and Bean 2005). These maintained functional characteristics could be constancy in the period of a network producing rhythmic output, the time interval between the stimulus onset and the response of a neuron, or many others.

Various factors compensate each other to maintain function. An example of such compensation has been discovered recently in neurons of the lobster stomatogastric ganglion (MacLean et al. 2003; Schulz et al. 2006). In neurons with similar firing properties, there was a linear correlation between the conductances of transient potassium (I_A) and hyperpolarization-activated inward (I_h) currents. This correlation accounted for the commonly observed variability of these two currents across preparations. Importantly, the correlation appears to reflect a homeostatic mechanism that regulates I_A and I_h. Experimental (MacLean et al. 2003; Swensen and Bean 2005) and modeling (Achard and De Schutter 2006; Goldman et al. 2001; MacLean et al. 2005; Prinz et al. 2004) studies in vertebrates and invertebrates show that multiple combinations of conductances can underlie similar neuronal behavior, suggesting that multiple complex compensatory mechanisms are possible. A traditional approach for finding compensatory mechanisms is based on sensitivity analysis (MacLean et al. 2005; Nygren et al. 1998; Olsen et al. 1995; Paulsen et al. 1982; Weaver et al. 2007). In this analysis, the sensitivity of a specified characteristic to a certain parameter is a ratio of the normalized change in the characteristic to the underlying normalized change in the parameter. Sensitivities can be used to determine approximately how much one parameter must change from its original value to compensate a change of the other parameter. That multiple compensatory covariations exist is well documented (Marder and Goaillard 2006; Rich and Wenner 2007; Ward 2006); what is lacking are systems for determining and understanding these covariations.

In this study, we introduce a general method for describing all putative compensatory covariations of neuronal and network parameters given specified characteristics of neuronal activity to be maintained. The method rigorously specifies exact covariations and linear approximations to them. It is based on a fundamental and powerful mathematical tool, the implicit function theorem. We show that compensatory covariations are possible charts of manifolds composed of parameter sets for which specified characteristics are constant. In particular, we show that to maintain N independent characteristics of neuronal activity affected by a change of one or more parameters, at least N other parameters should change appropriately.

To illustrate the method, we apply it to a model of the smallest functional network of the leech heartbeat central pattern generator (CPG) consisting of two mutually inhibitory neurons (Cymbalyuk et al. 2002; Hill et al. 2001; Olypher et al. 2006; Sorensen et al. 2004) (Fig. 1*A*). In particular, we show how certain parameters must covary to maintain the period of the network activity and the average spike frequency in bursts. Finally, we discuss applications of our method to the analysis of the homeostatic regulation, model tuning and other problems.

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[3]

- ✓ Prove the existence (locally) of attribute LSs in complex neuronal systems and networks.
- ✓ Technique mainly based on the implicit function theorem.
- ✓ Algorithm to compute attribute LSs (problem dependent).
- ✓ Predictions: If m attributes are preserved on a given level set in a n-dimensional parameter space, the level set has dimension n-m.

[3] Olypher AV, Calabrese RL. Using constraints on neuronal activity to reveal compensatory changes in neuronal parameters. J Neurophysiol. 2007;98(6):3749-3758

4. Methods

ΛΩ Systems

ΛΩ Systems

Cartesian coordinates

$$\begin{cases} \dfrac{dx}{dt} = \Lambda(r)x - \Omega(r)y \\ \dfrac{dy}{dt} = \Omega(r)x + \Lambda(r)y \end{cases}$$

Polar coordinates

$$\begin{cases} \dfrac{dr}{dt} = r\Lambda(r) \\ \dfrac{d\theta}{dt} = \Omega(r) \end{cases}$$

$$\Lambda(r) = \lambda - br^2$$

$$\Omega(r) = \omega + ar^2$$

$\Lambda\Omega_2$ Systems

Cartesian coordinates

$$\begin{cases} \dfrac{dx}{dt} = \lambda x - \omega y - (bx + ay)(x^2 + y^2) \\ \dfrac{dy}{dt} = \omega x + \lambda x + (ax - by)(x^2 + y^2) \end{cases}$$

Polar coordinates

$$\begin{cases} \dfrac{dr}{dt} = r(\lambda - br^2) \\ \dfrac{d\theta}{dt} = \omega + ar^2 \end{cases}$$

4. Methods

$\Lambda\Omega_2$ Systems

✓ Dynamics of $\Lambda\Omega_2$ systems

- Single limit circle for $\bar{r} = \sqrt{\frac{\lambda}{b}}$

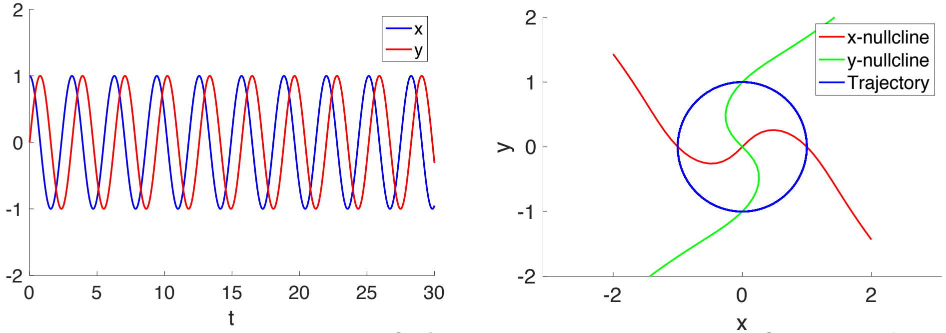

Figure 4.: Dynamics of the $\Lambda\Omega_2$ Systems. Left: x and y traces. Right: x- and y-nullclines and a trayectory on the phase plane.

✓ Degeneracy in $\Lambda\Omega_2$ systems

Attribute Level Sets (LSs)

$$\text{Amplitude level sets } \rightarrow \frac{\lambda}{b} = K_a$$

$$\text{Frequency level sets } \rightarrow \omega + a\frac{\lambda}{b} = K_f$$

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4. Methods

$\Lambda\Omega_2$ Networks

Self-connected Cell

$$\begin{cases} \dfrac{dx}{dt} = \lambda x - \omega y - (bx + ay)(x^2 + y^2) + \alpha x \\ \dfrac{dy}{dt} = \omega x + \lambda y + (ax - by)(x^2 + y^2) \end{cases}$$

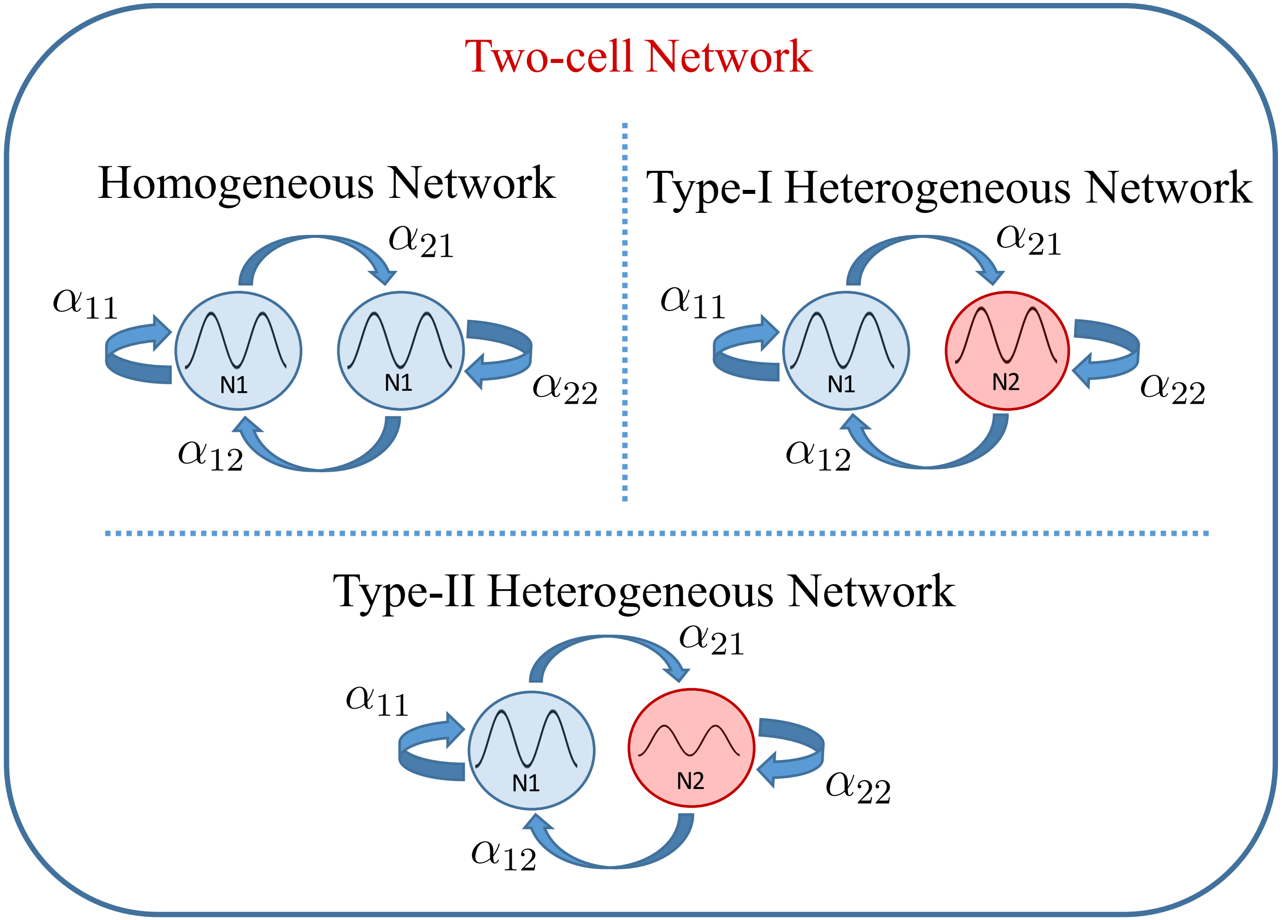
Two-cell Network

$$\begin{cases} \dfrac{dx_1}{dt} = \lambda_1 x_1 - \omega_1 y_1 - (b_1 x_1 + a_1 y_1)(x_1^2 + y_1^2) + \alpha_{11} x_1 + \alpha_{12} x_2 \\ \quad \dfrac{dy_1}{dt} = \omega_1 x_1 + \lambda_1 y_1 + (a_1 x_1 - b_1 y_1)(x_1^2 + y_1^2) \\ \dfrac{dx_2}{dt} = \lambda_2 x_2 - \omega_2 y_2 - (b_2 x_2 + a_2 y_2)(x_2^2 + y_2^2) + \alpha_{21} x_1 + \alpha_{22} x_2 \\ \quad \dfrac{dy_2}{dt} = \omega_2 x_2 + \lambda_2 y_2 + (a_2 x_2 - b_2 y_2)(x_2^2 + y_2^2) \end{cases}$$

Connectivity matrix $\begin{pmatrix} \alpha_{11} & \alpha_{12} \\ \alpha_{21} & \alpha_{22} \end{pmatrix}$

4. Methods

$\Lambda\Omega_2$ Networks



5. Level Sets Preservation in $\Lambda\Omega_2$ Networks

✓ The self-connected cell do not preserve individual LSs

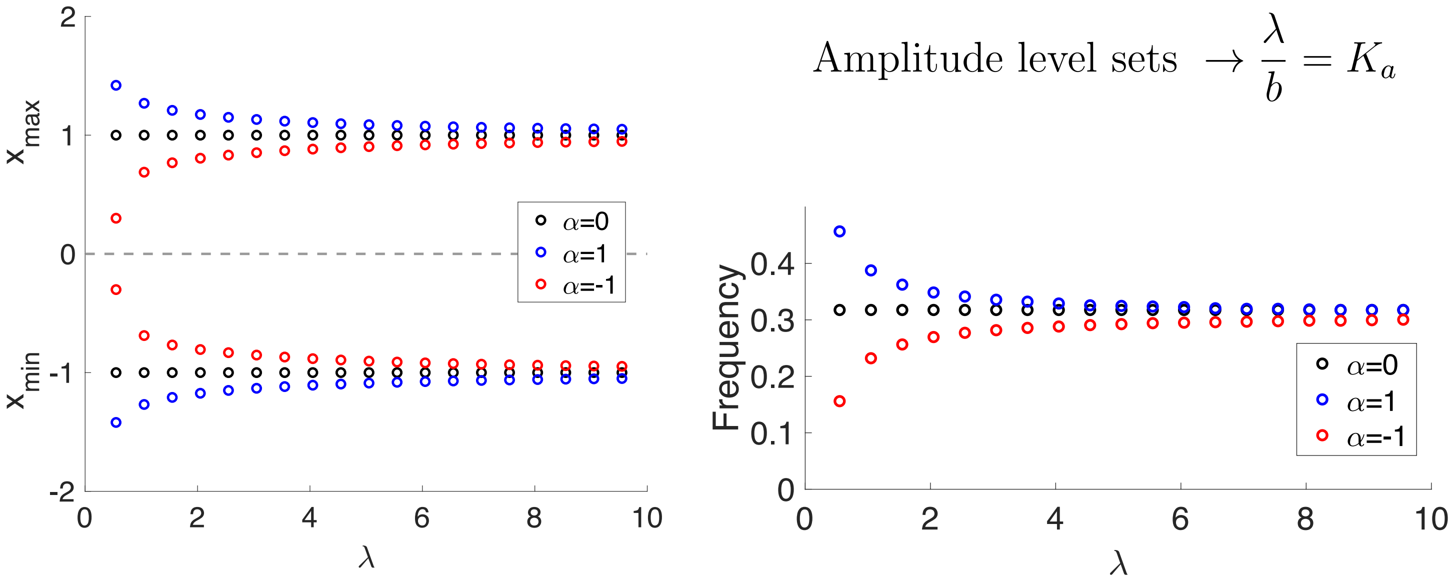


Figure 5.: The individual cells belong to the same amplitude (and frequency) LS (K_a=1). Left: amplitude envelope diagram as a function of λ. Right: frequency diagram as a function of λ.

5. Level Sets Preservation in $\Lambda\Omega_2$ Networks

✓ Type-I (cells belong to the same amplitude and frequency LS) and type-II (cells belong to different amplitude LSs, but the same frequency LS) two-cell networks preserve individual LSs on 2-dimensional manifolds on the connectivity parameter space.

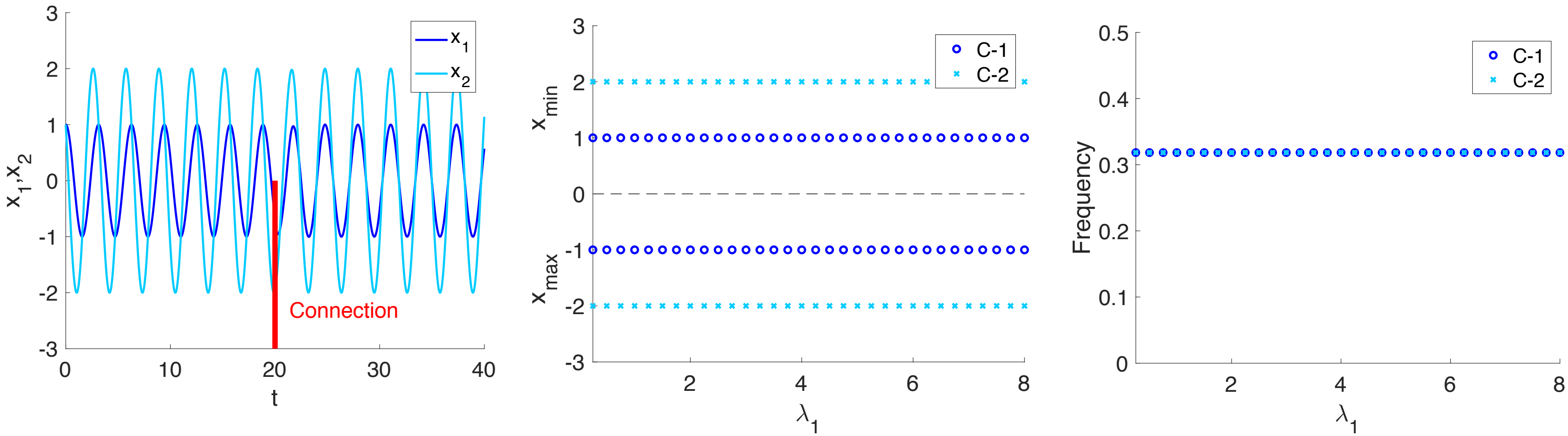


Figure 6.: Synchronized network preserving LSs. Left: voltage traces before and after the connection. Middle: amplitude envelope diagram for values (λ_1, b_1) belonging to the same individual amplitude LS (K_a=1). Left: frequency diagram for the same values of (λ_1, b_1).

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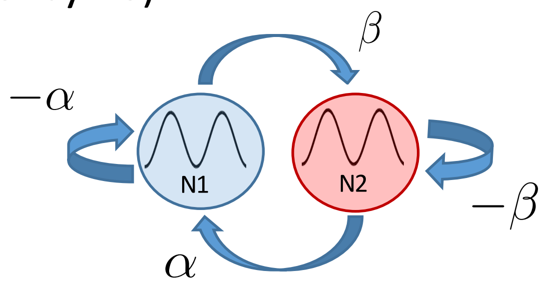
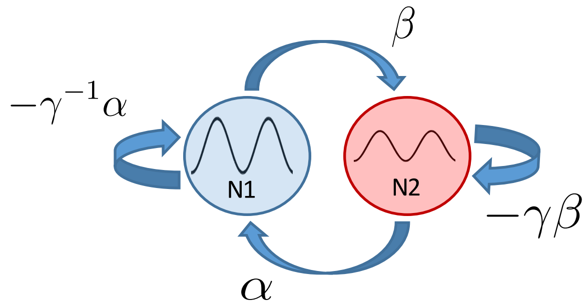
5. Level Sets Preservation in $\Lambda\Omega_2$ Networks

- ✓ Gap-junctions preserve individual LSs in type-I heterogeneous networks (cells belong to the same amplitude and frequency LS)

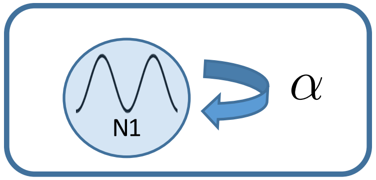


- ✓ Gap-junctions do not preserve individual LSs in type-II heterogeneous networks (cells belong to different amplitude LSs)



$$\gamma = \frac{\text{Amplitude cell-1}}{\text{Amplitude cell-2}}$$

6. Newly Emerged Network Level Sets



- ✓ The self-connected cell show 2-dimensional total-degenerated LSs on the intrinsic parameter space.
- ✓ When the cell is self-connected new parameter dependencies emerge.

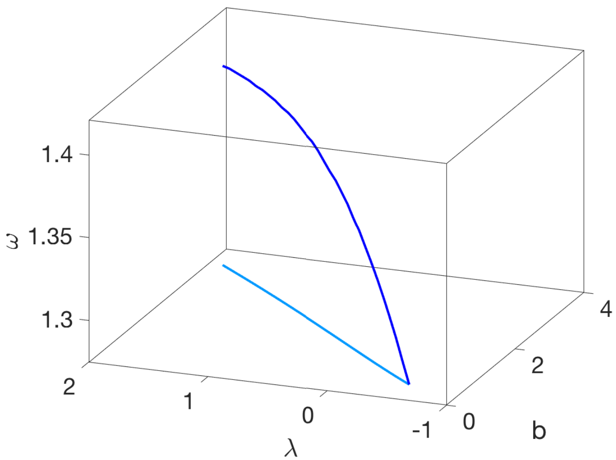
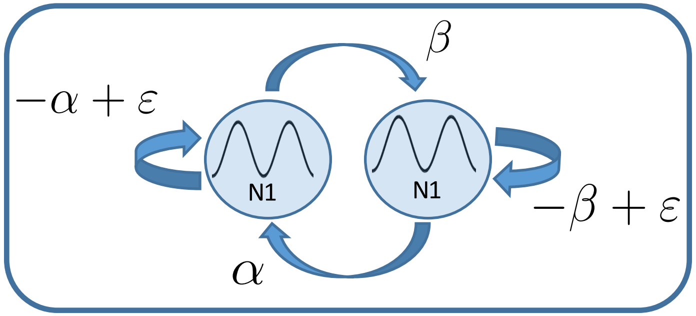


Figure 7.: Total degenerated LSs on the $(b - \lambda - \omega)$ parameter space

6. Newly Emerged Network Level Sets

✓ Symmetrical homogeneous two-cell networks show 2-dimensional total-degenerated LSs on the connectivity parameter space.



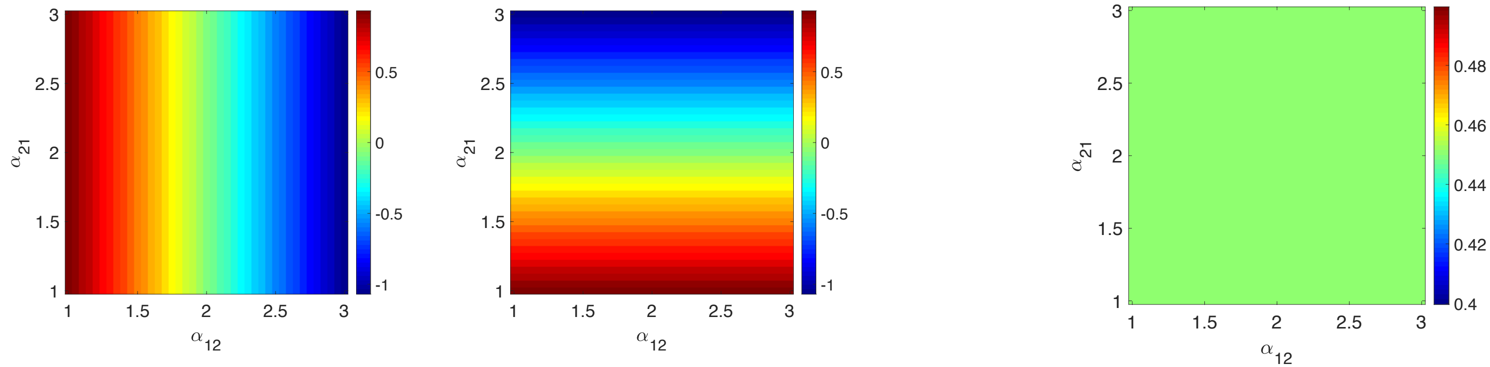


Figure 8.: Left and Middle: amplitude LS on connectivity parameter space. For each pair of cross-connectivity parameters there are the values of the self connectivity parameter α_{11} (Left) and α_{22} (Middle) such as the network amplitude is preserved. Right: frequency for each point of the amplitude LS

6. Newly Emerged Network Level Sets

- ✓ Type-II heterogeneous two-cell networks show 1-dimensional total-degenerated LSs on the intrinsic parameter space of a single cell.

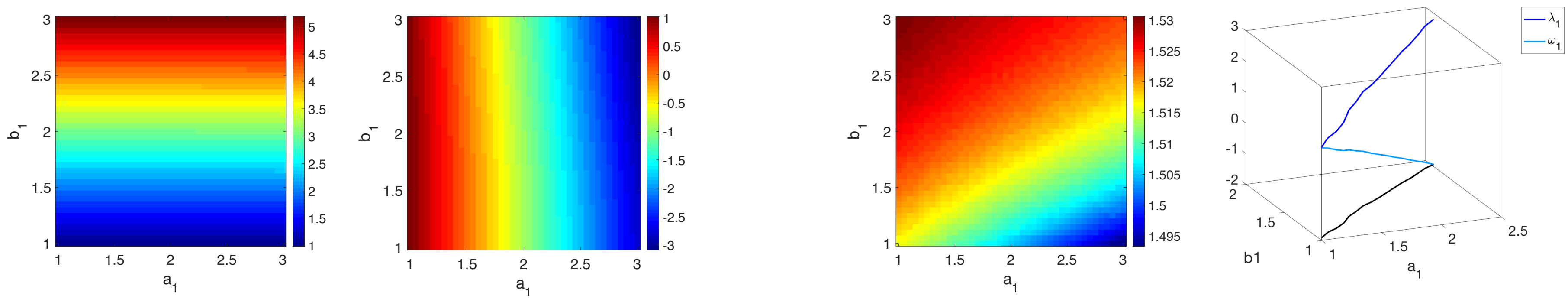


Figure 9.: Left and Middle-left: amplitude LS on intrinsic parameter space of a single cell. For each pair of parameters a_1 and b_1, there are the values parameters λ_1 (Left) and ω_1 (Middle-left) such as the network frequency and the amplitude of cell-1 is preserved. Middle-right: amplitude value of cell-2 for each point of the amplitude LS. Right: 1-dimensional total-degenerated LS on the intrinsic parameter space of a single cell.

7. Conclusion

- ✓ Conditions for LSs preservation in $\Lambda\Omega_2$ networks (two-cell networks)
- ✓ Gap-junctions preserve individual LSs only in type-I heterogeneous networks.
- ✓ Several total-degenerated LSs have been computed (1,2-dimensional LSs on 2,3 or 4-dimensional parameter spaces).
- ✓ The type of network (connectivity architecture, homogeneous, heterogeneous, symmetry,…) affects predictions in [3].
    - Predictions in [3]: if m attributes are preserved on a given level set in a n-dimensional parameter space, the level set has dimension n-m.

Future Work

- ✓ Relation between model symmetries and the preservation of individual LSs
- ✓ Methods for desambiguation of degeneracy (noise, entrainment,…)
- ✓ Robust, non model-dependent and optimized algorithms to compute LSs
- ✓ The notion of a network LS.

[3] Olypher AV, Calabrese RL. Using constraints on neuronal activity to reveal compensatory changes in neuronal parameters. J Neurophysiol. 2007;98(6):3749-3758

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Thank you!

References

[1] Swensen AM, Bean BP. Robustness of burst firing in dissociated purkinje neurons with acute or long-term reductions in sodium conductance. *J Neurosci*. 2005;25(14):3509-3520

[2] Prinz AA, Bucher D, Marder E. Similar network activity from disparate circuit parameters. *Nat Neurosci*. 2004;7(12):1345-1352

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