Mathematical Degeneracy Meets Biological Degeneracy: Implications for Dynamical Systems Reconstruction

Horacio G. Rotstein

BioDatanamics Lab
Mathematical Biology and Computational Neuroscience

Federated Department of Biological Sciences
New Jersey Institute of Technology (NJIT) & Rutgers University

(CONICET Argentina, Corresponding Investigator)

Congreso Antonio Monteiro - 2023
Universidad Nacional del Sur
June 8, 2023

@horacerot

web.njit.edu/~horacio

horacio@njit.edu

BioDatanamics Lab (Horax)

Biological Oscillatory Networks

Related Mathematical and Computational Problems

Nervous system (cognition and motor behavior), systems biology, chemistry

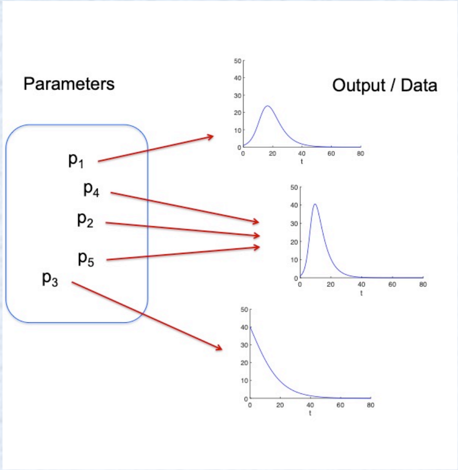
- ☑ How they generate oscillatory patterns (mechanisms)
- ☑ How they process information and perform computations
- ☑ How all this depends on the dynamic properties of nodes, connectivity and topology
- ☑ Resonances / selection of frequencies

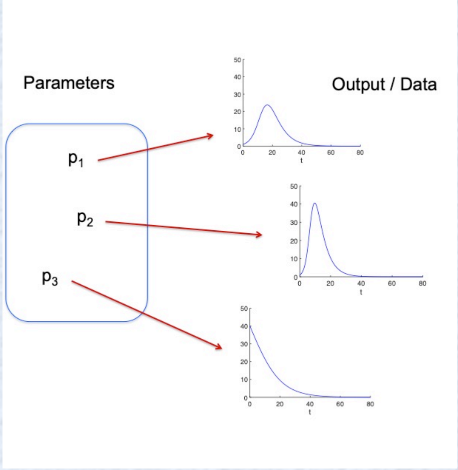
Learning and Inference of Dynamical Mechanisms from Experimental Data

- ☑ Mathematical modeling
- ☑ Numerical simulations
- ☑ Dynamical systems analysis
- ☑ Parameter estimation
- ☑ Inference algorithms

- ☑ Relationship between experimental/observable data and models
- ☑ Unidentifiability
- ☑ Correlations / causality

Collaborators (this project) & Group Members





- Rodrigo F. O. Pena (Biol, NJIT, US)
- Omar Itani (Biol, NJIT, US)
- Dylan Lederman (Biol, NJIT, US)
- Raghav Patel (CS, Applied Math, NJIT, now UTSA, US)
- Juliana Reves-Szemere (UBA, CONICET, Argentina)

- Alejandra Ventura (UBA, CONICET, Argentina)
- Farzan Nadim (NJIT, US)
- Xue Han (Boston University, US)

- Danny Barash (Ben Gurion University of the Negev, Israel)
- Alex Churkin (Shamoon College of Engineering, Israel)
- Harel Dahari (Loyola University, Medical School, US)
- Asher Uziel (Machine Learning, Israel)

Machine learning for mathematical models of HCV kinetics during antiviral therapy
Churkin et al. (2022, *Mathematical Biosciences*)

Parameter Estimation in the age of unidentifiability and degeneracy
Lederman, Patel, Itani, R. (2022, *Mathematics*)

Raíces NE-USA (digression)

Red de Científicos, Investigadores y Profesional del Conocimiento Argentinos en el Noreste de EEUU

- Generación de colaboraciones científicas y tecnológicas entre los miembros de la Red y nuestros colegas en Argentina
- Contribuir a la formación de recursos humanos en Argentina
- Diáspora científica: en el sentido de “miembros de la tribu”

R@ICES NE-USA

Red de Científicos, Investigadores,
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Argentinos en el Noreste de EEUU

@RaicesUnidos

raicesmathbio@gmail.com

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- ☑ Pasantías
- ☑ Investigadores correspondientes del CONICET
- ☑ Federalización de la Ciencia - Focos de investigación en Universidades "menos centrales", en agenda)

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Hacia una nueva noción de diáspora de capital humano: una estrecha integración funcional entre comunidades

Posted on Mayo 5, 2023

Por

Horacio G. Rotstein

y

Laura Galvis

- ☑ https://diplomaciacientifica.org/

DiploCientifica

RED DE DIPLOMACIA CIENTÍFICA LATINOAMÉRICA Y EL CARIBE

Raíces NE-USA (digression)

Workshop: Mathematical Aspects of Brain Computation

- Alan Bush (alan.bush@mgh.harvard.edu)
  - Decomposition and parameterization of local field potentials
- Guillermo Cecchi (gcecchi@us.ibm.com)
  - The many dimensions of brain aging
- Carina Curto (cpc16@psu.edu)
  - Dynamic attractors in inhibition-dominated neural networks
- Soledad Gonzalo Congo (soledad.g.cogno@ntnu.no)
  - Minute-scale periodic sequences in the entorhinal cortex
- Gabriel Kreiman (gabriel.kreiman@tch.harvard.edu)
  - Aprendiendo cosas nuevas sin olvidar lo que ya sabemos
- Sara Solla (solla@northwestern.edu)
  - The prevalence of low-dimensional dynamics in neural populations

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Nuevas preguntas matemáticas

Crear nueva matemática basada en resultados experimentales

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- https://www.youtube.com/watch?v=zECA7JBtcwc&t=1s
- https://www.youtube.com/watch?v=vhFwTeExLeg

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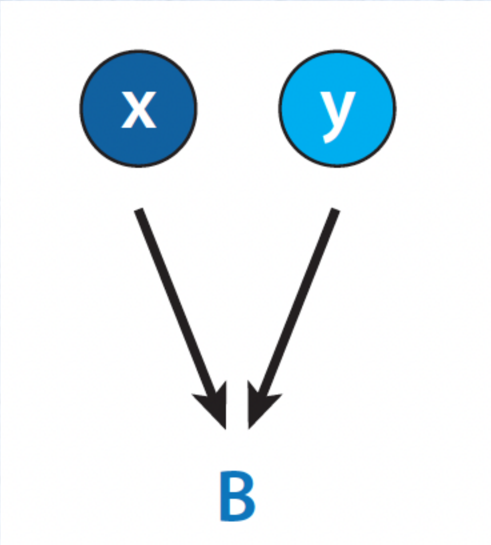
Degeneracy

The ability of elements that are structurally different to perform the same function or yield the same output

Edelman & Gally 2001

Degeneracy



Goaillard & Marder 2021

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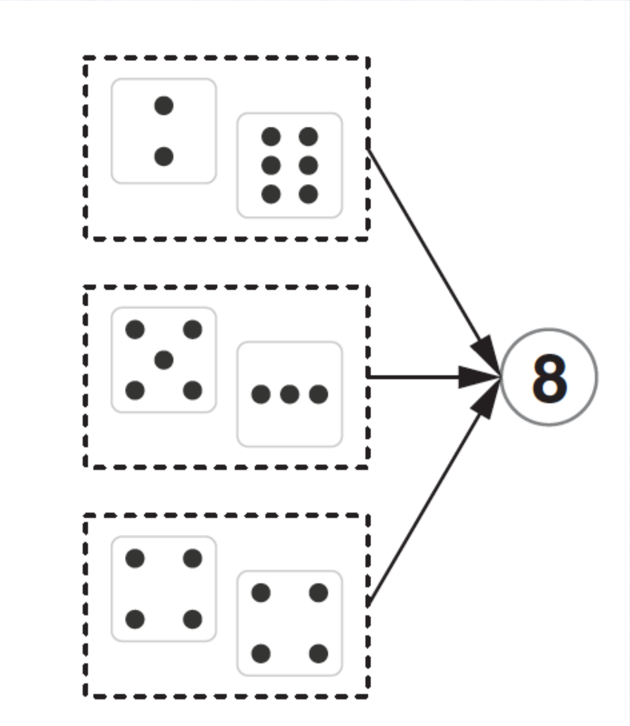

many-to-one

Kamaleddin 2021

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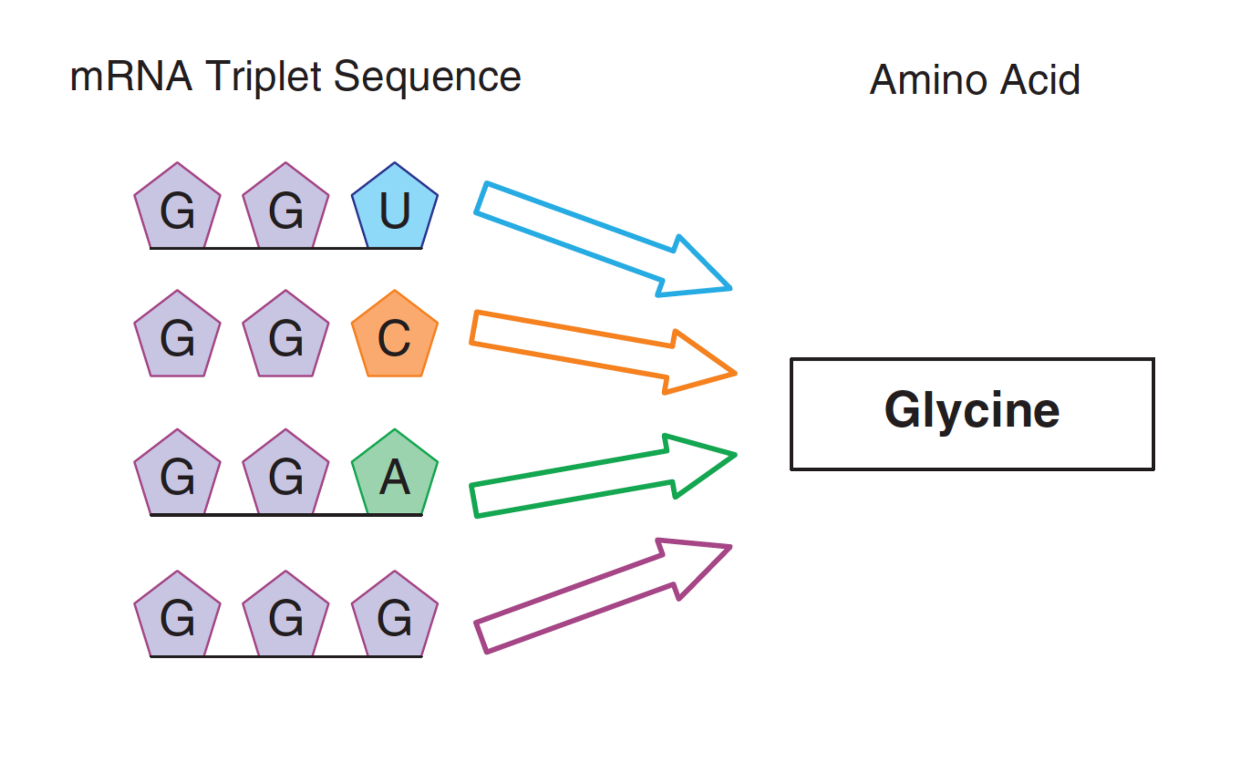
Degeneracy: many-to-one



Genetic code: degeneracy space where some of the amino acids are encoded by more than one mRNA triplet codon sequence

There are more mRNA triple codon sequences compared to the number of translated amino acids

Kamaleddin 2021

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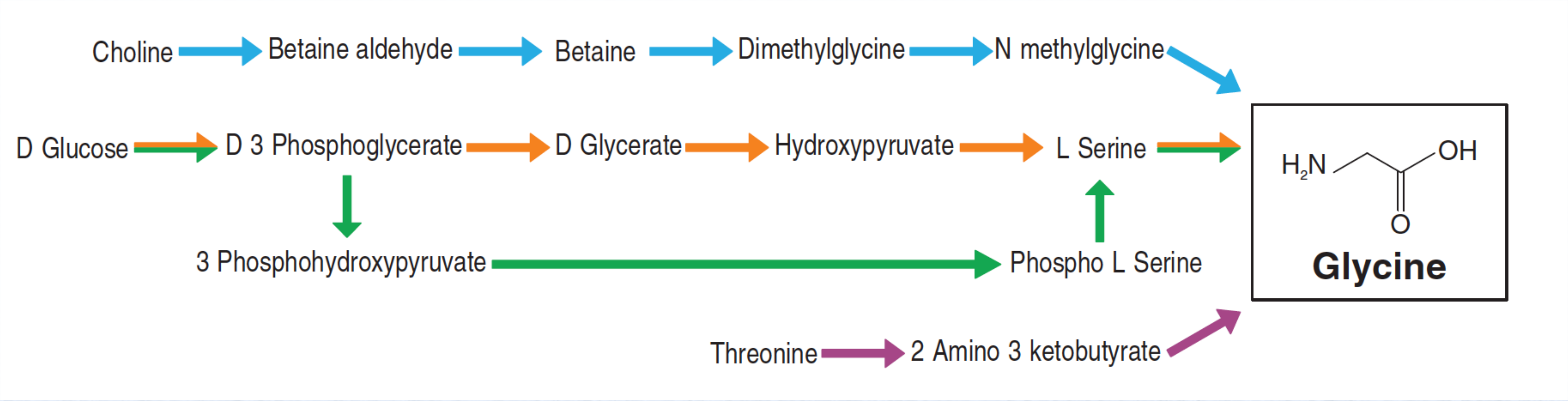
Degeneracy: many-to-one



Different pathways leading to glycine synthesis

Kamaleddin 2021

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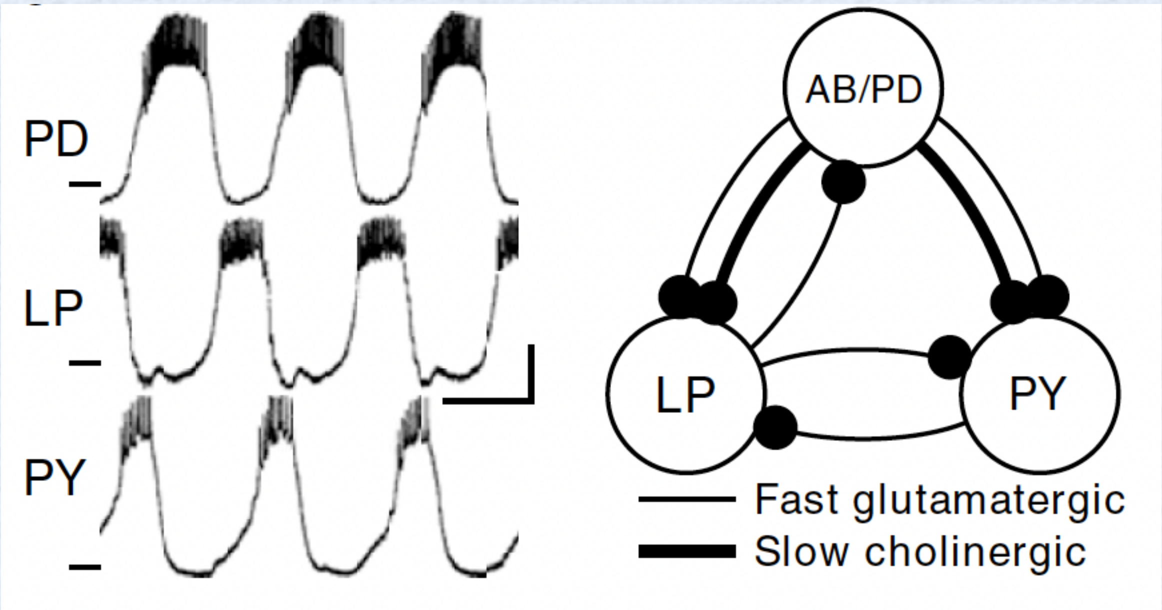
Edelman & Gally 2001

Biological pyloric (triphasic) rhythm

Pyloric circuit architecture

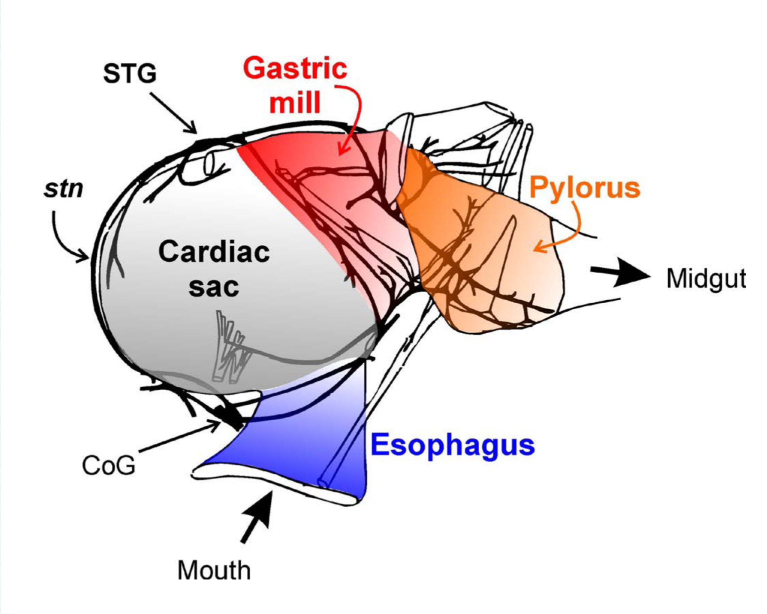


- Scale bars: 1 sec, 10 mV
- Horizontal lines: -60 mV
- All synapses are inhibitory

Prinz et al. 2004

Stomatogastric (STG) circuit

Crab *Cancer Borealis*



https://centers.njit.edu/stglab/sites/stglab/files/Cancer_Guide.pdf

https://sites.google.com/view/golowasch-lab/

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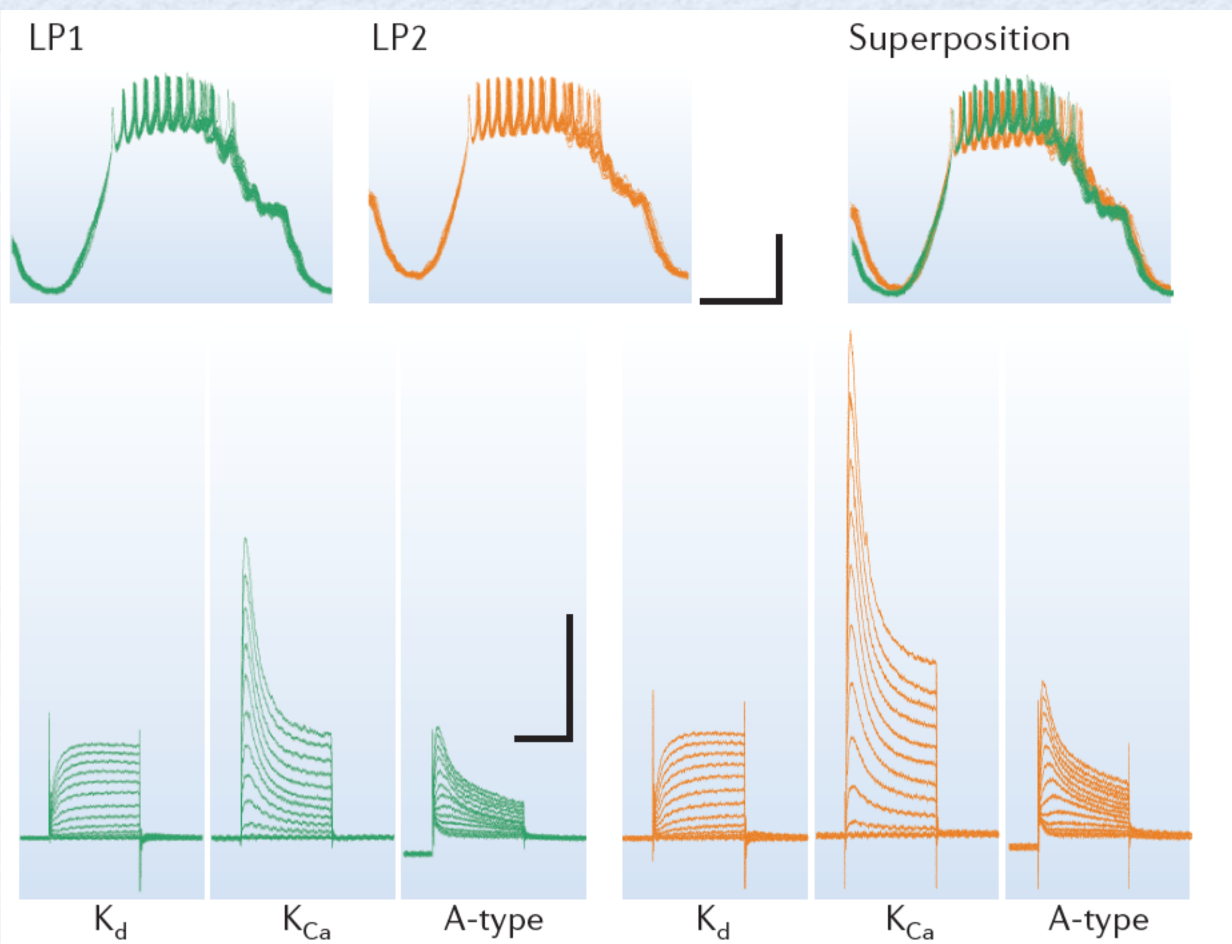
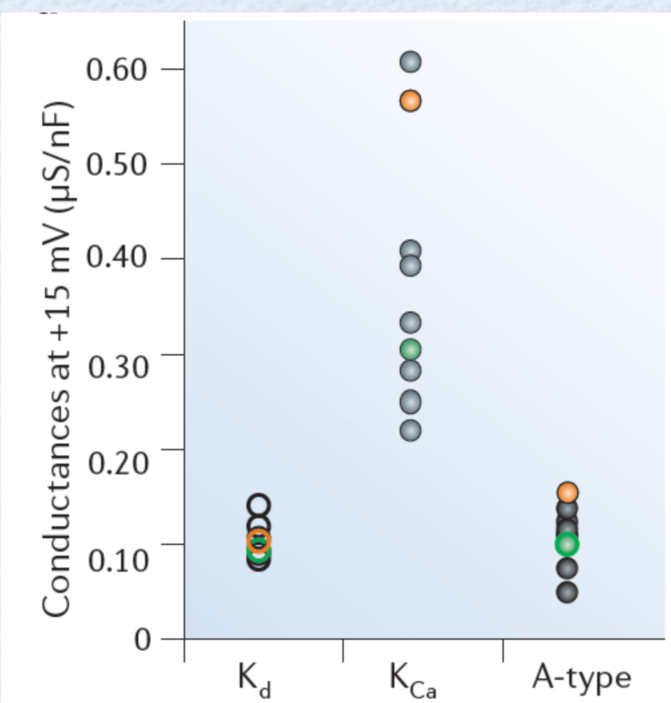


Voltage recordings from two LP cells (spontaneous activity)

Ionic currents



Marder & Goaillard 2006

Scale bars: -60 to -50 mV, 50 nA, 200 ms (top), 100 ms (bottom)

9 different LP cells (maximal conductances)

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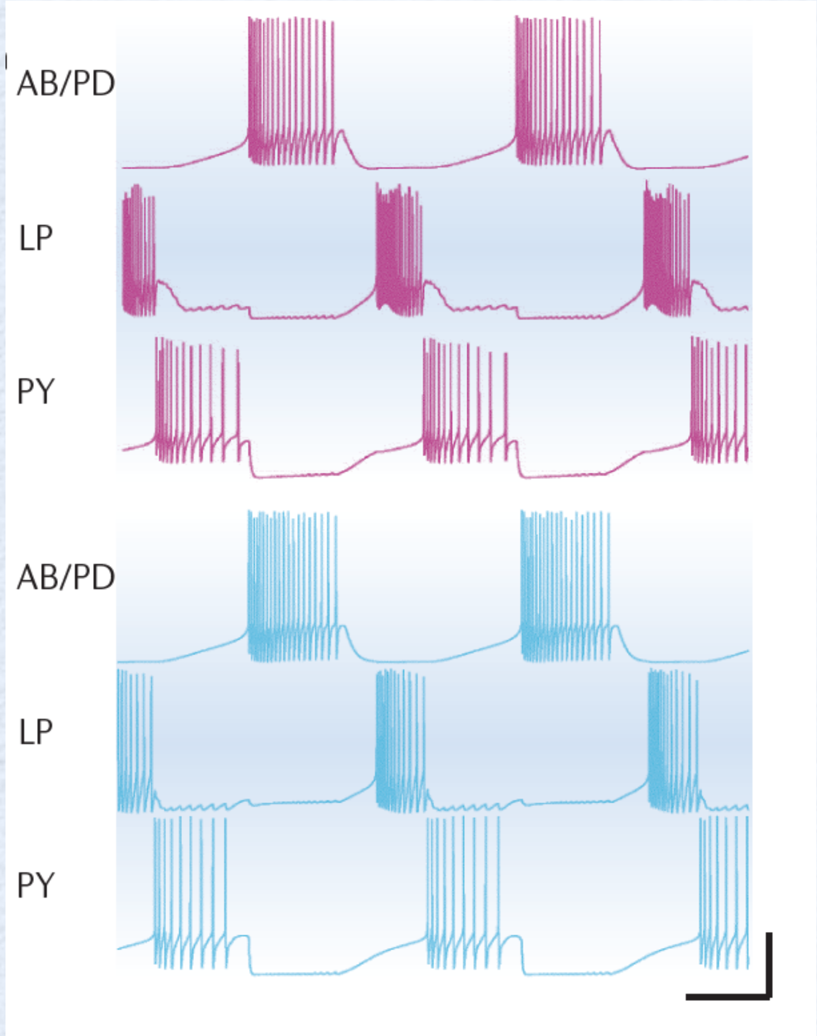
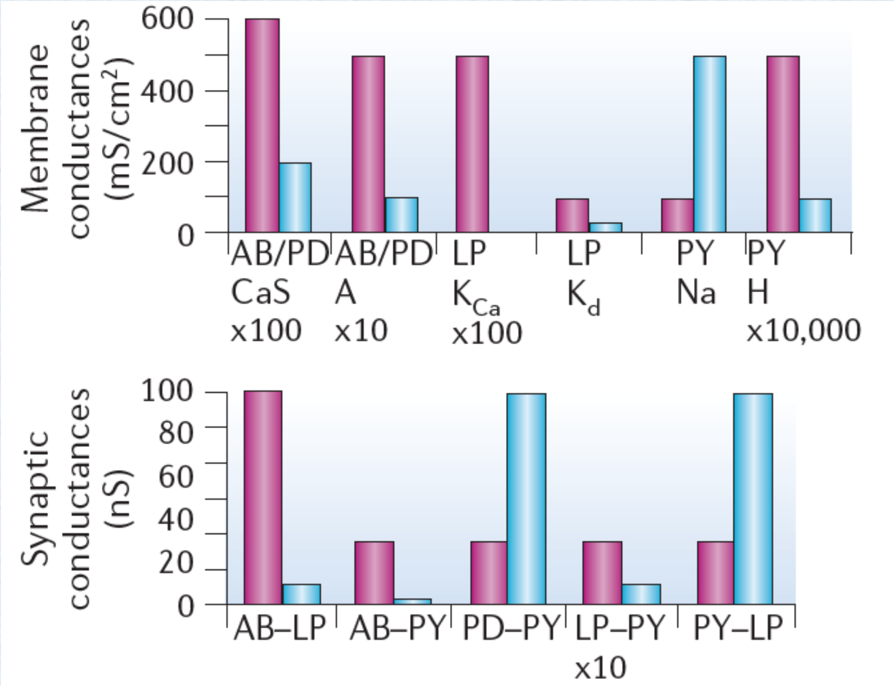


Pyloric rhythm generated by two different model networks



Maximal conductances for 6 different intrinsic conductances and 5 different synaptic conductances

Marder & Goaillard 2006
Prinz et al 2004

Scale bars: 50 mV, 500 ms

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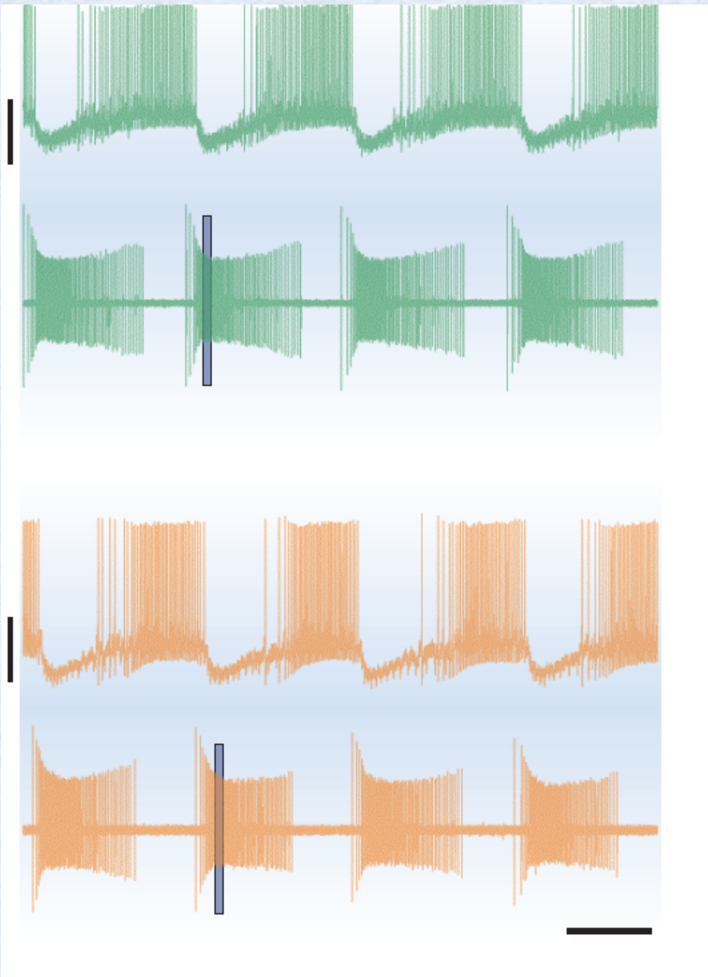
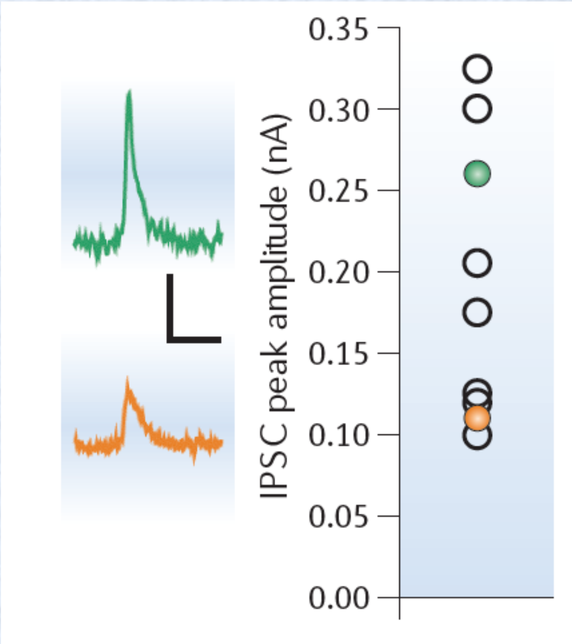


Intracellular (top) and extracellular (bottom) showing the activity of two reciprocally inhibitory leech neurons

Network 1: green
Network 2: orange (?)



IPSCs (inhibitory postsynaptic currents) in the intracellularly recorded interneurons (early phase of the burst

Marder & Goaillard 2006 using data from Tobin & Calabrese 2005

Scale bars: -50 to -40 mV, 500 ms, 100 pA

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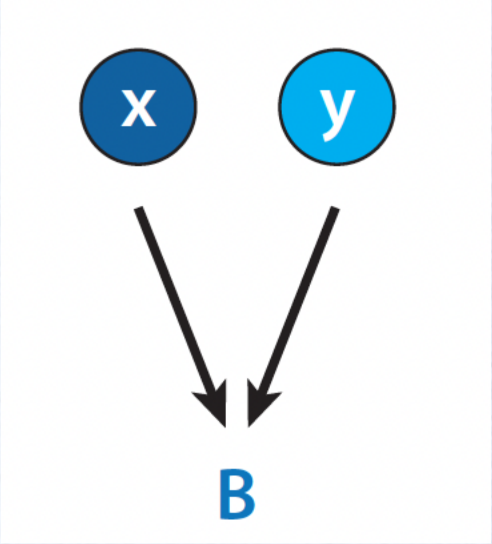
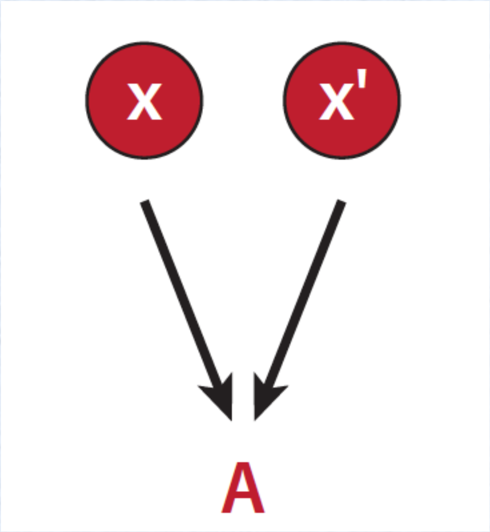


Non-identical components (x, y) perform the same function (B)

Redundancy



Identical components (x, y) perform the same function (B)

Goaillard & Marder 2021

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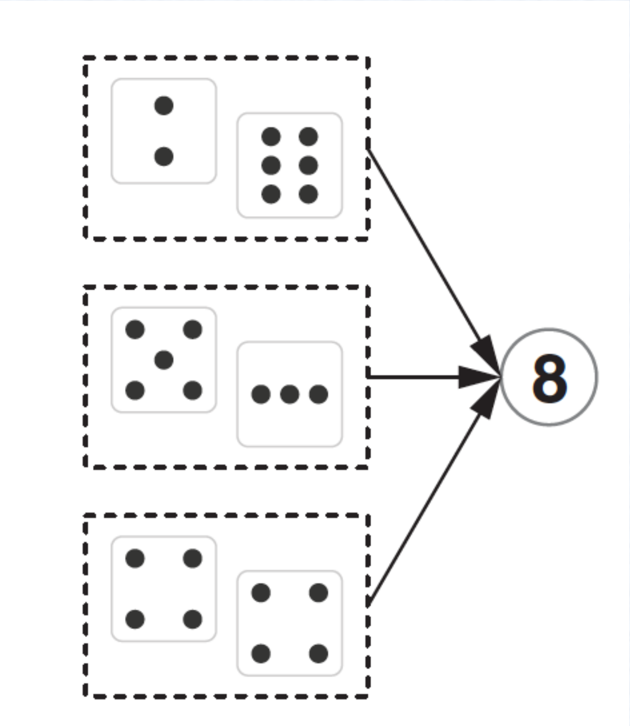
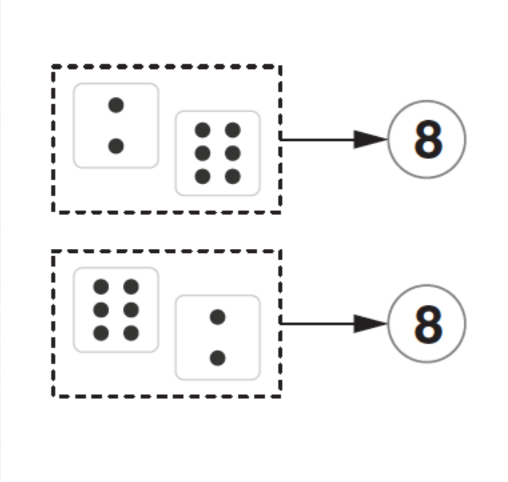
The ability of elements that are structurally different to perform the same function or yield the same output

Degeneracy



many-to-one

Redundancy



one-to-one

Kamaleddin 2021

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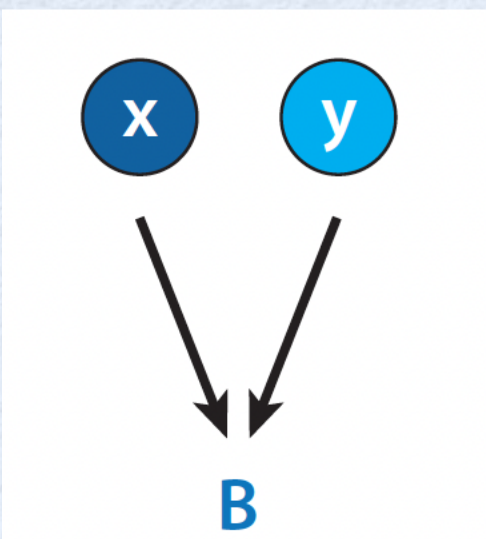
Degeneracy



Non-identical components (x, y) perform the same function (B)

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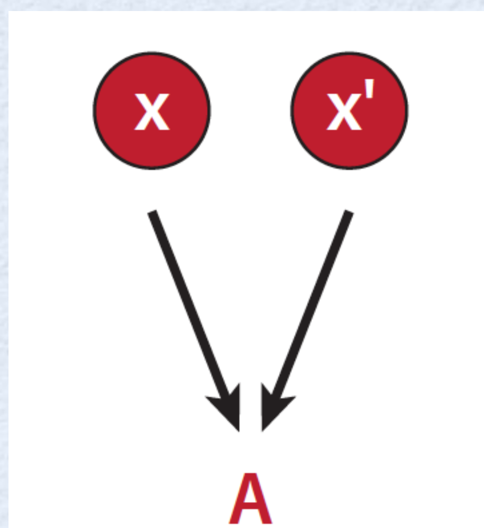
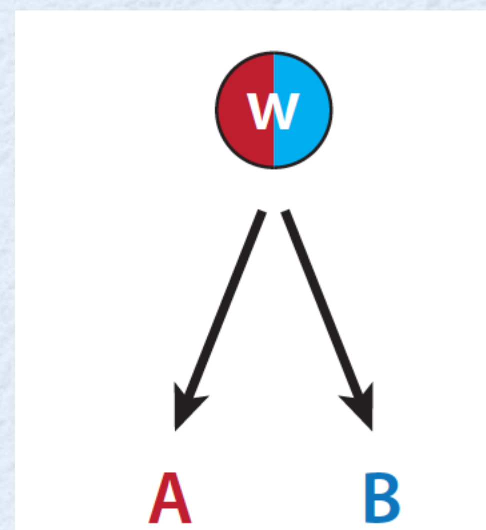


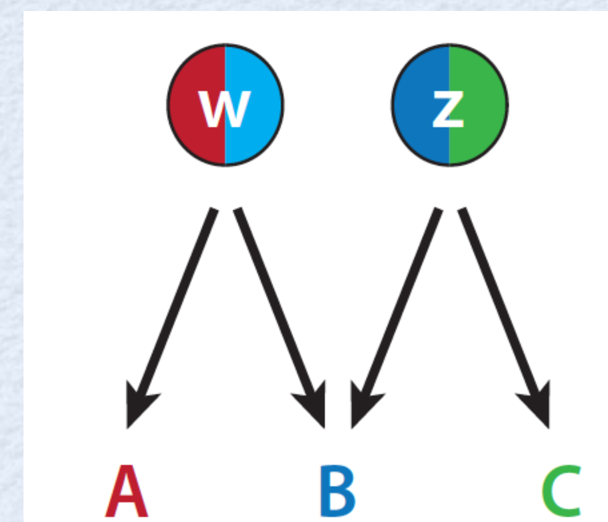
Identical components (x, y) perform the same function (B)

Pleiotropy



One component (w) involved in two (or more) functions (A, B)

Functional overlap



Two pleiotropic components (w, z) partially degenerate and sharing function

Goaillard & Marder 2021

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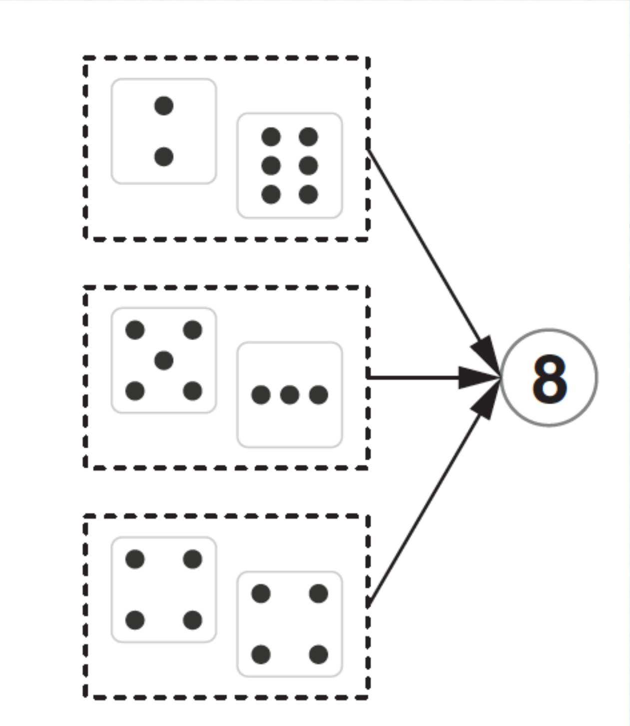
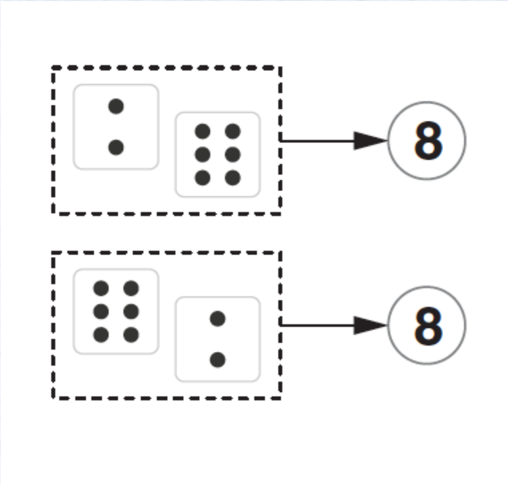


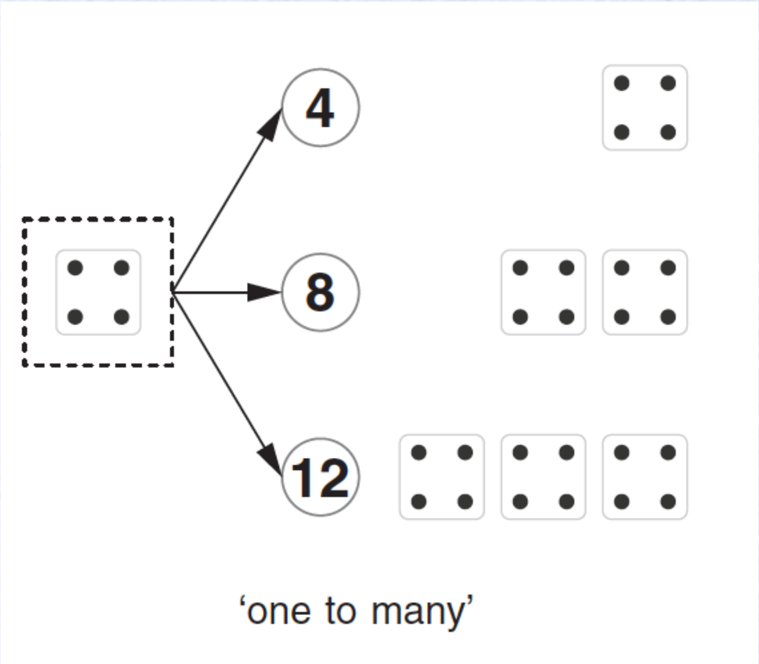
many-to-one

Redundancy



one-to-one

Pluripotentiality



one-to-many

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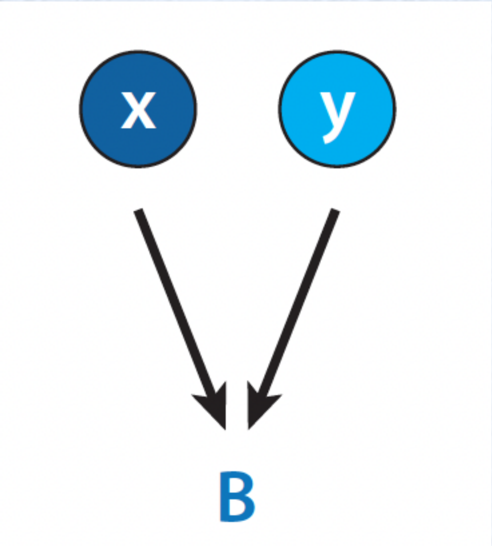
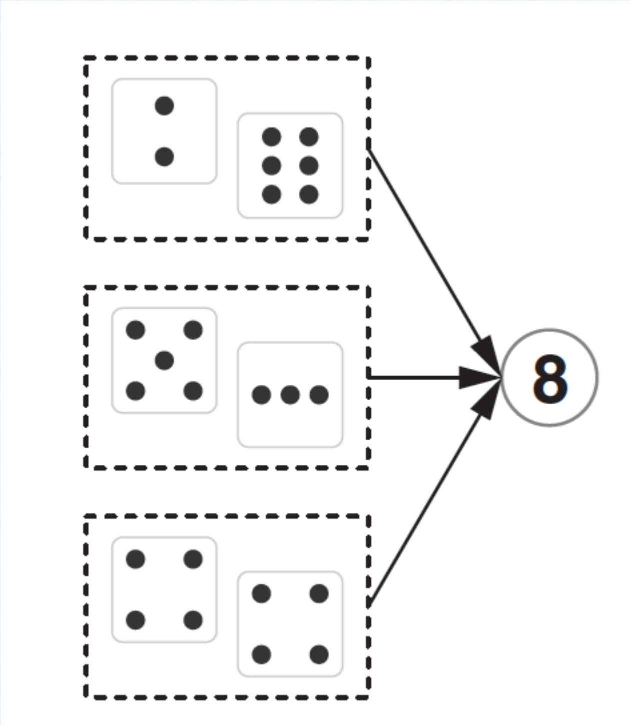
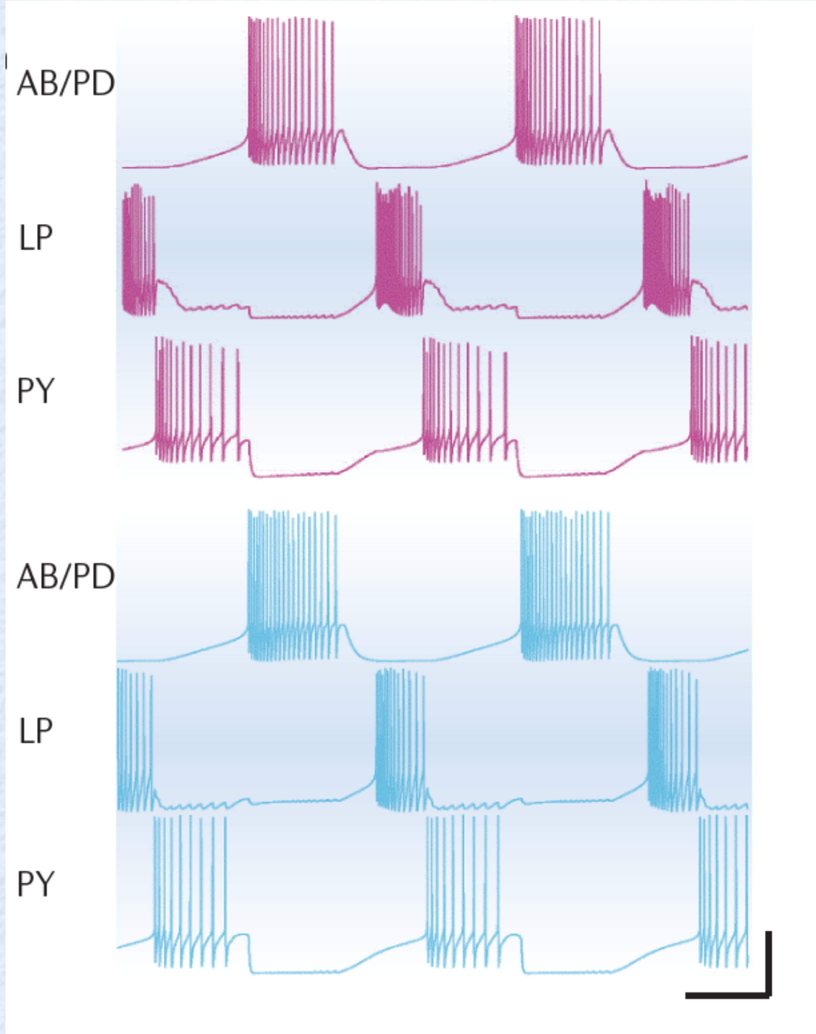
Multiple solutions to the same problem







Kamaleddin 2021

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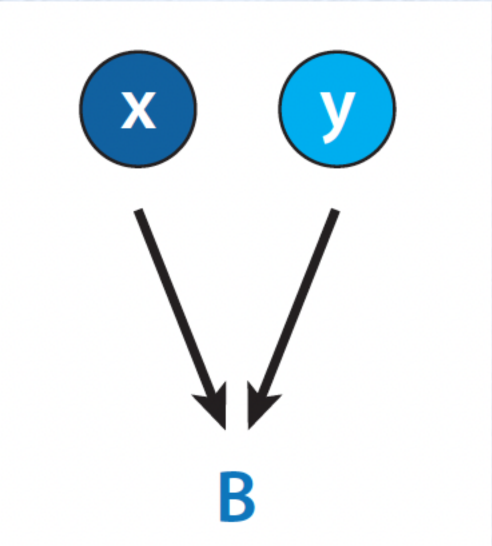

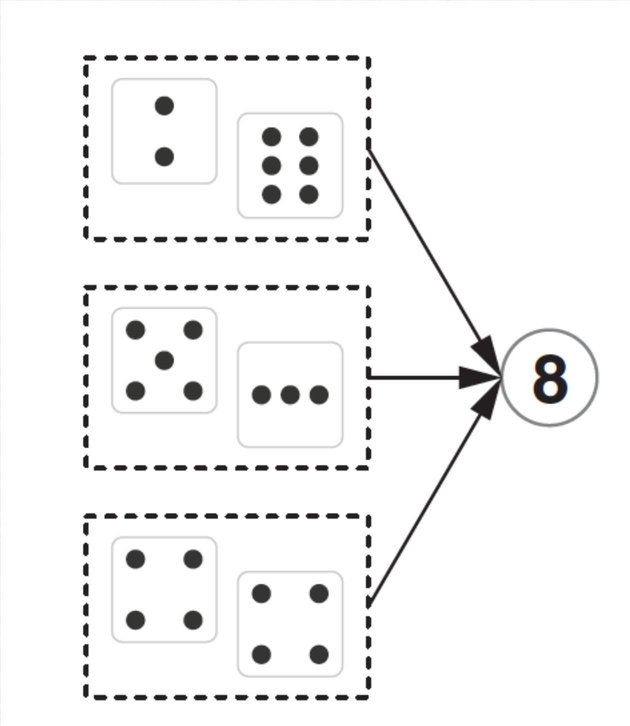

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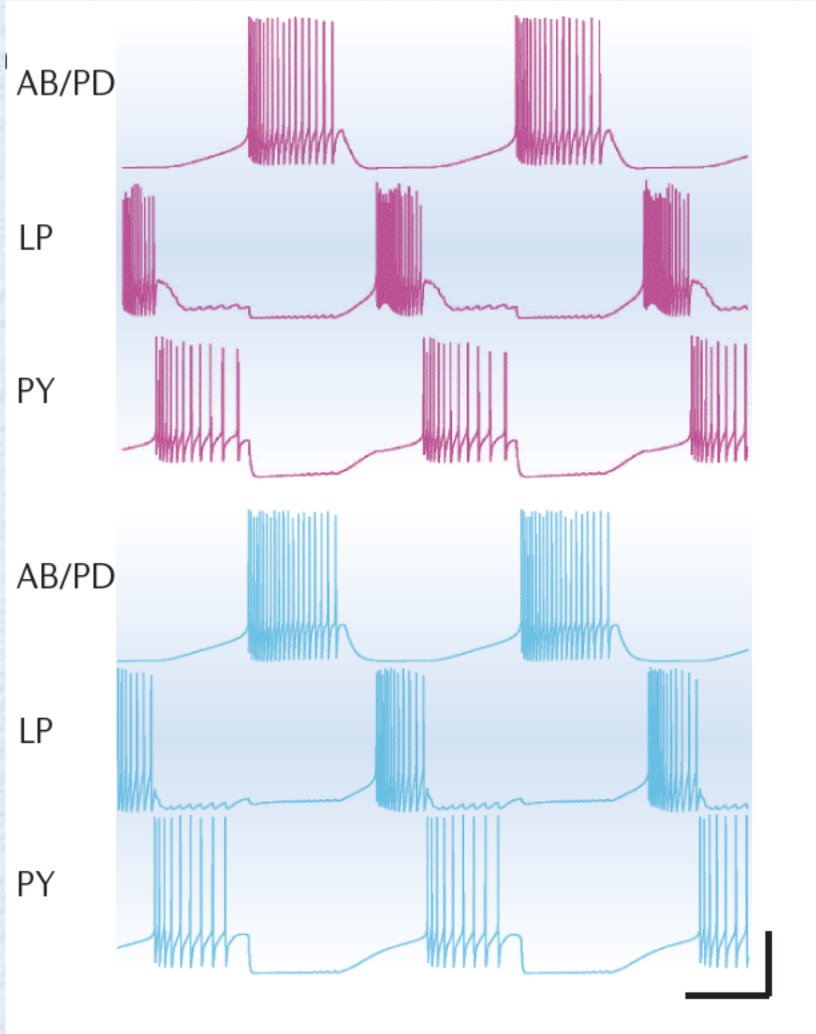

Goaillard & Marder 2021

Reviews & Seminal papers

Tononi et al 1999
Edelman & Gally 2001
Marder & Goaillard 2006
Marder 2011
Calabrese et al 2011
Cropper et al 2016
Goaillard & Marder 2021
Kamaleddin 2022
Marder et al 2022

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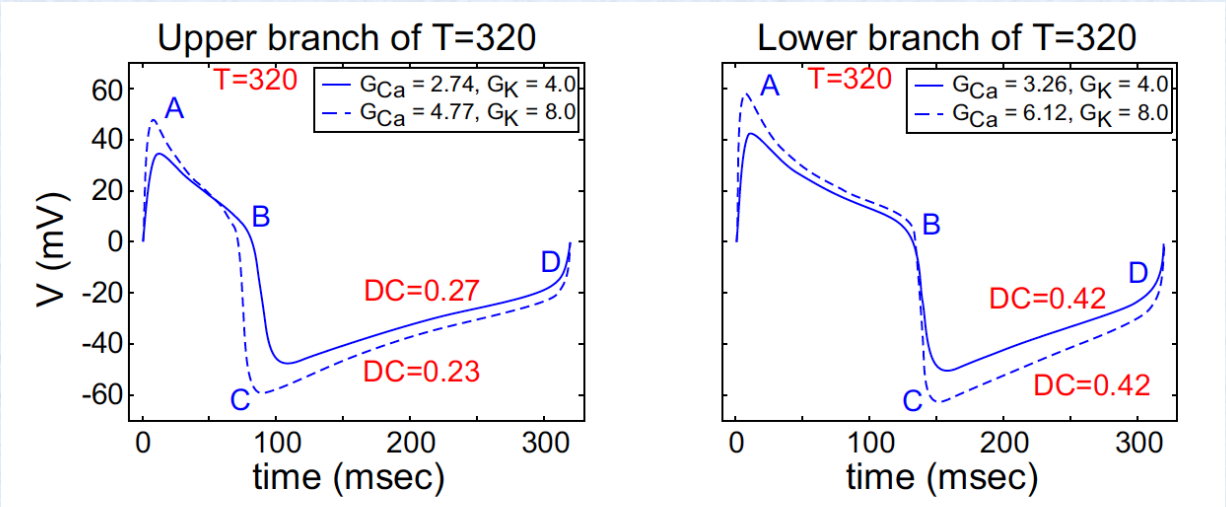
Multiple solutions to the same problem

- ☑ A target pattern for the observable variable (s)
- ☑ A pattern with a number of target attributes (e.g., oscillations frequency, burst length, firing rate distribution)

Model: Multiple combination of parameters produce patterns with the same attribute values



R et al 2016

Morris-Lecar model

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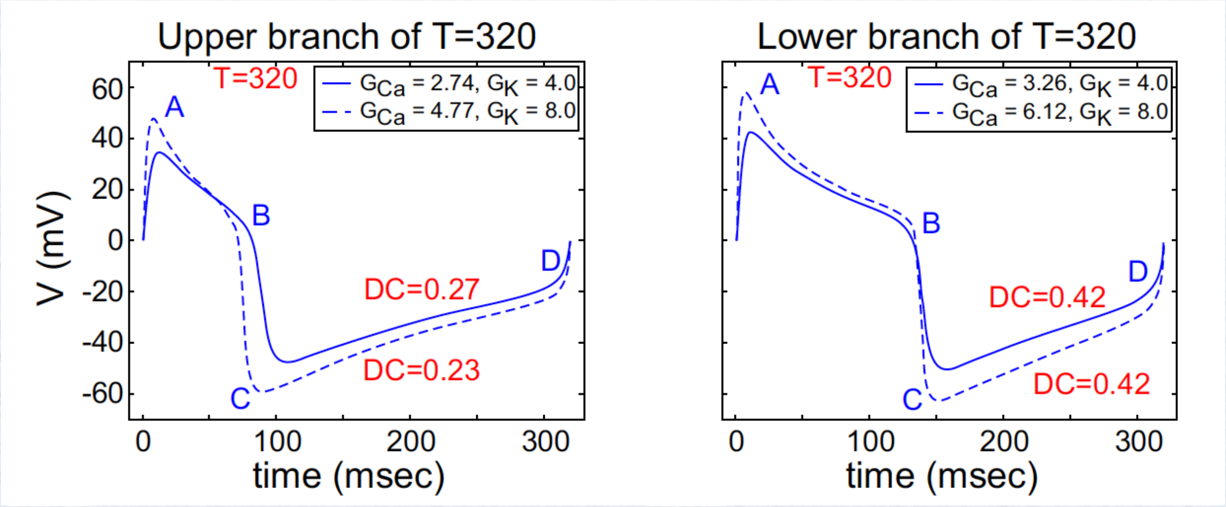
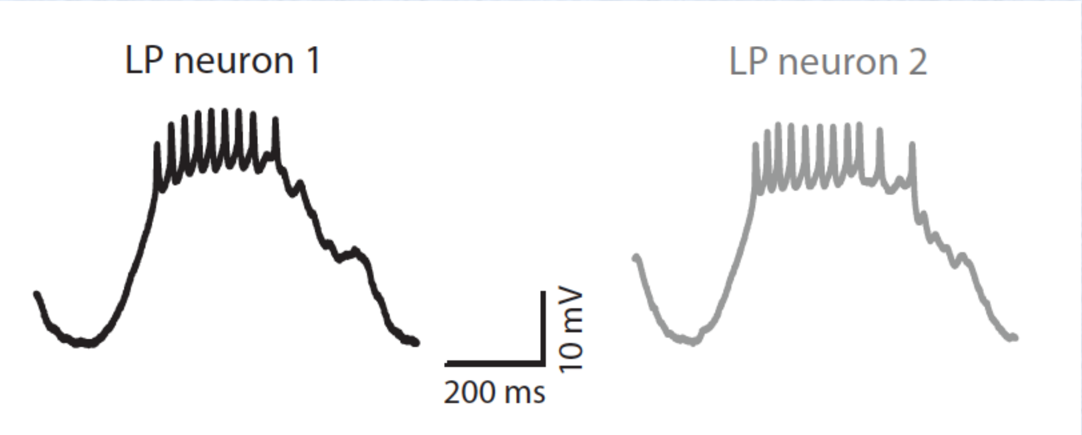
Model: Multiple combination of parameters produce patterns with the same attribute values

Experiments: Multiple combination of parameters (e.g., ionic/synaptic current densities) produce patterns with almost indistinguishable attribute values





R et al 2016

Morris-Lecar model

Goaillard & Marder 2021

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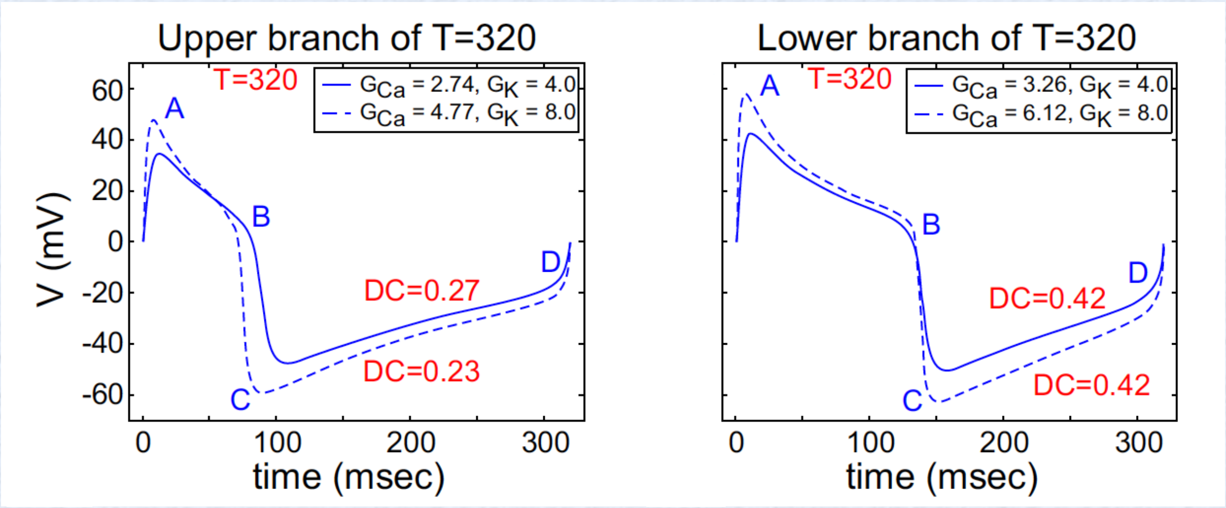
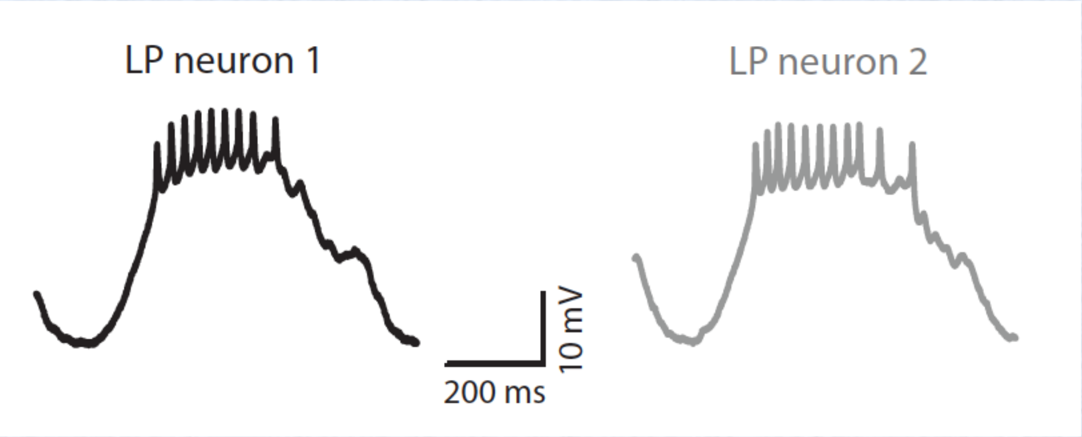
Model: The variability of the target attribute values is smaller than the variability of the system's parameter values





R et al 2016

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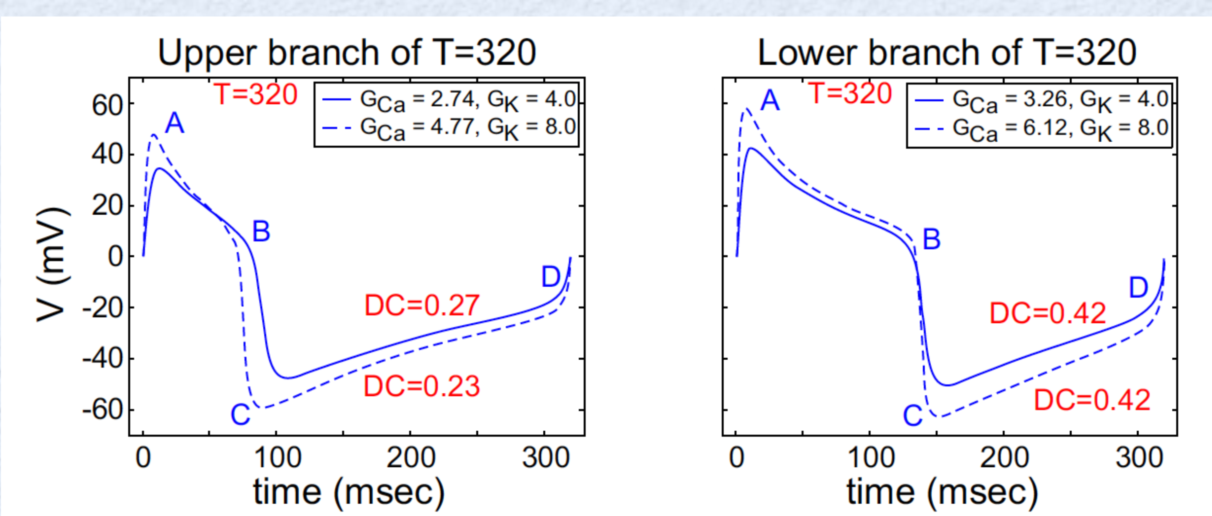
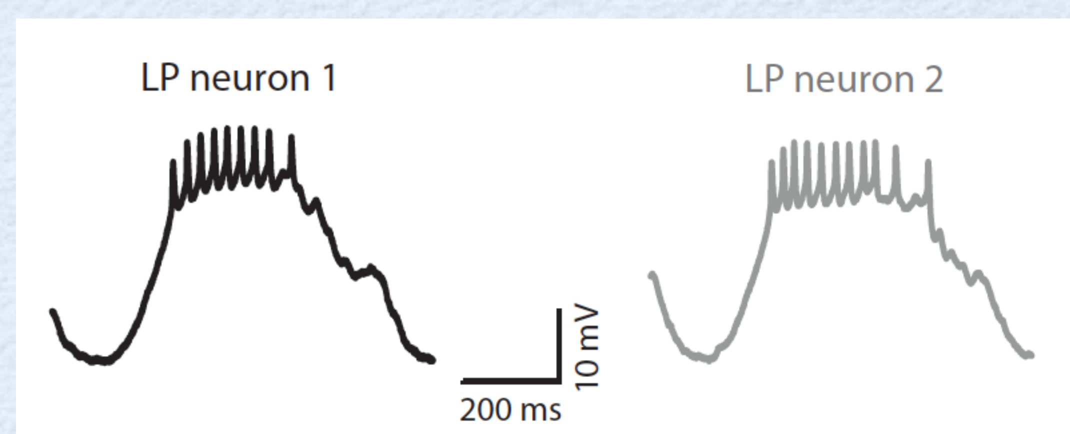
Multiple solutions to the same problem

Degeneracy & (mathematical) singularity:

In the simplest case of a linear system, the matrix of the coefficients linking data and parameters (the coefficients represent the data and the variables represent the parameters) is degenerate (or singular) and therefore the system admits multiple solutions





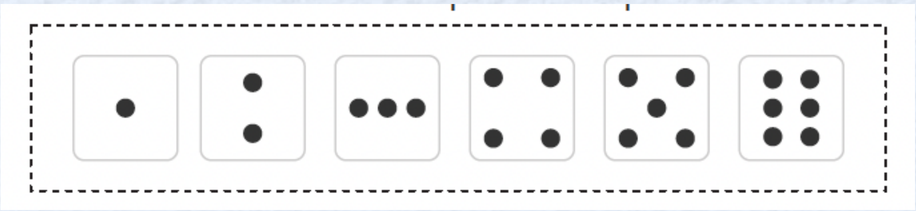
R et al 2016 Morris-Lecar model

Goaillard & Marder 2021

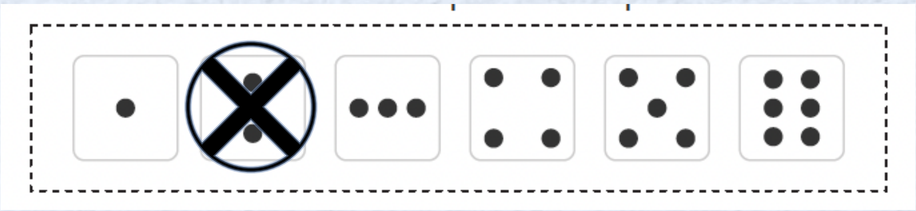
Degeneracy

Degeneracy and robustness

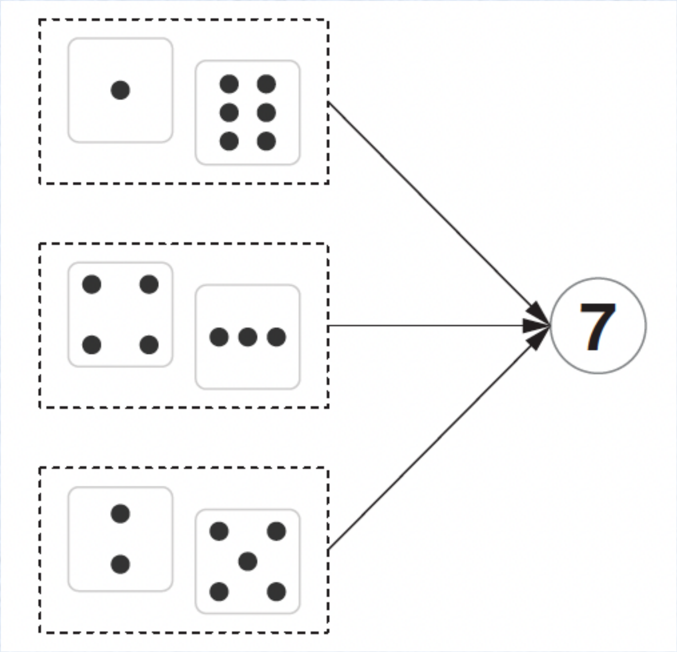
Elements in the parametric space



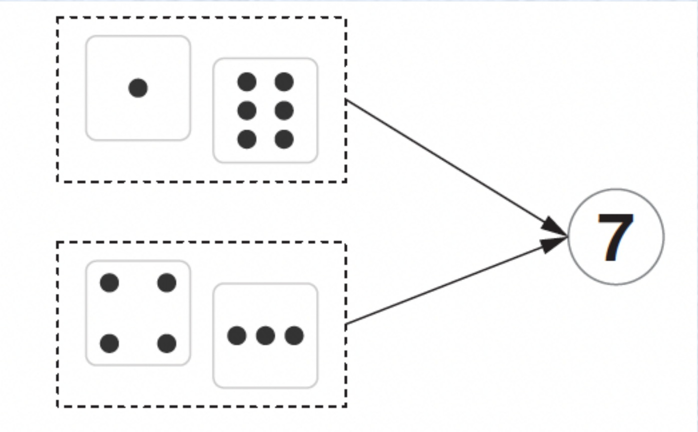
Elements in the perturbed parametric space



Different combinations produce the same output



The outcome can still be produced



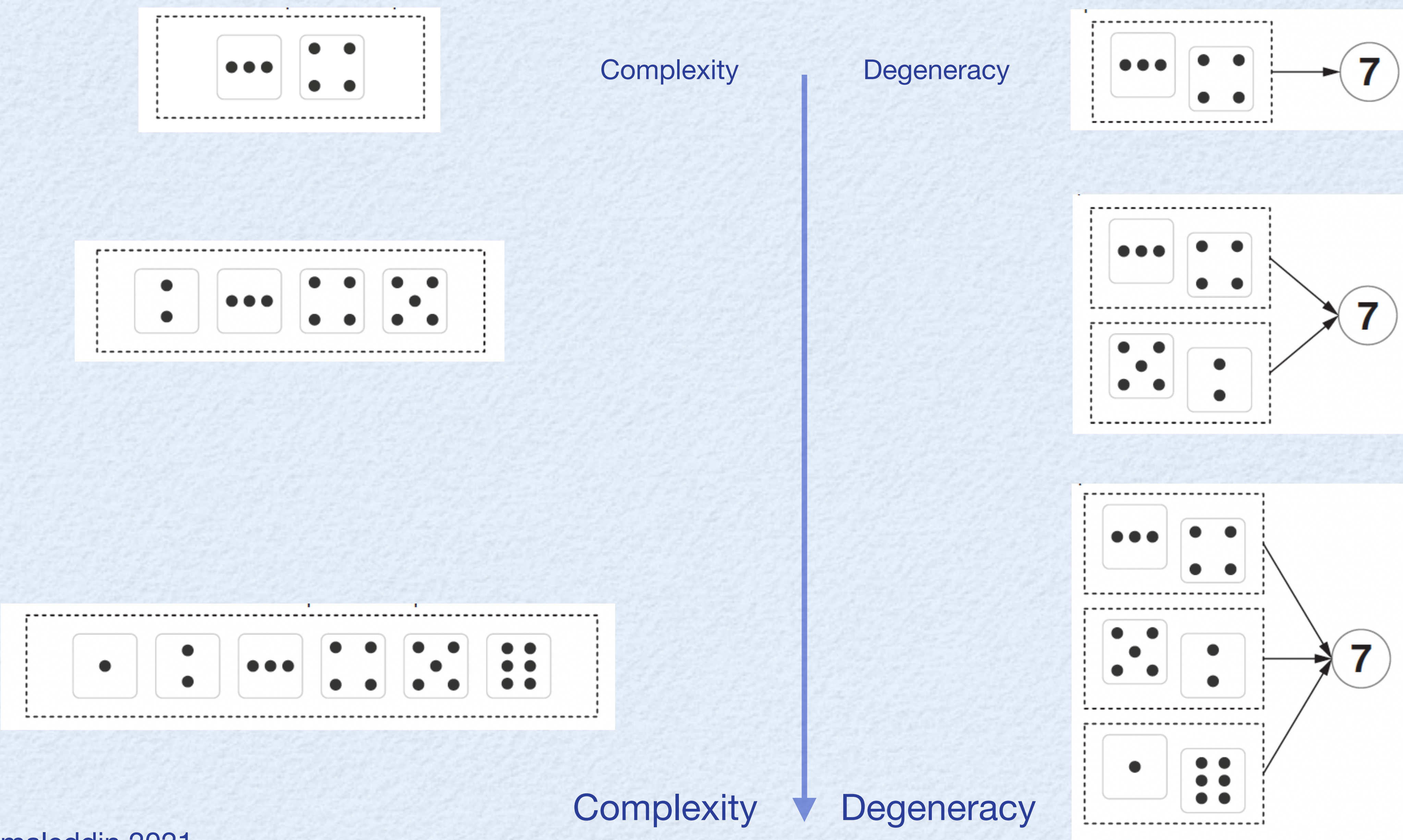
Kamaleddin 2021

Degeneracy

Degeneracy and complexity

Elements in the parametric space

Solutions to the problem of producing the outcome 7



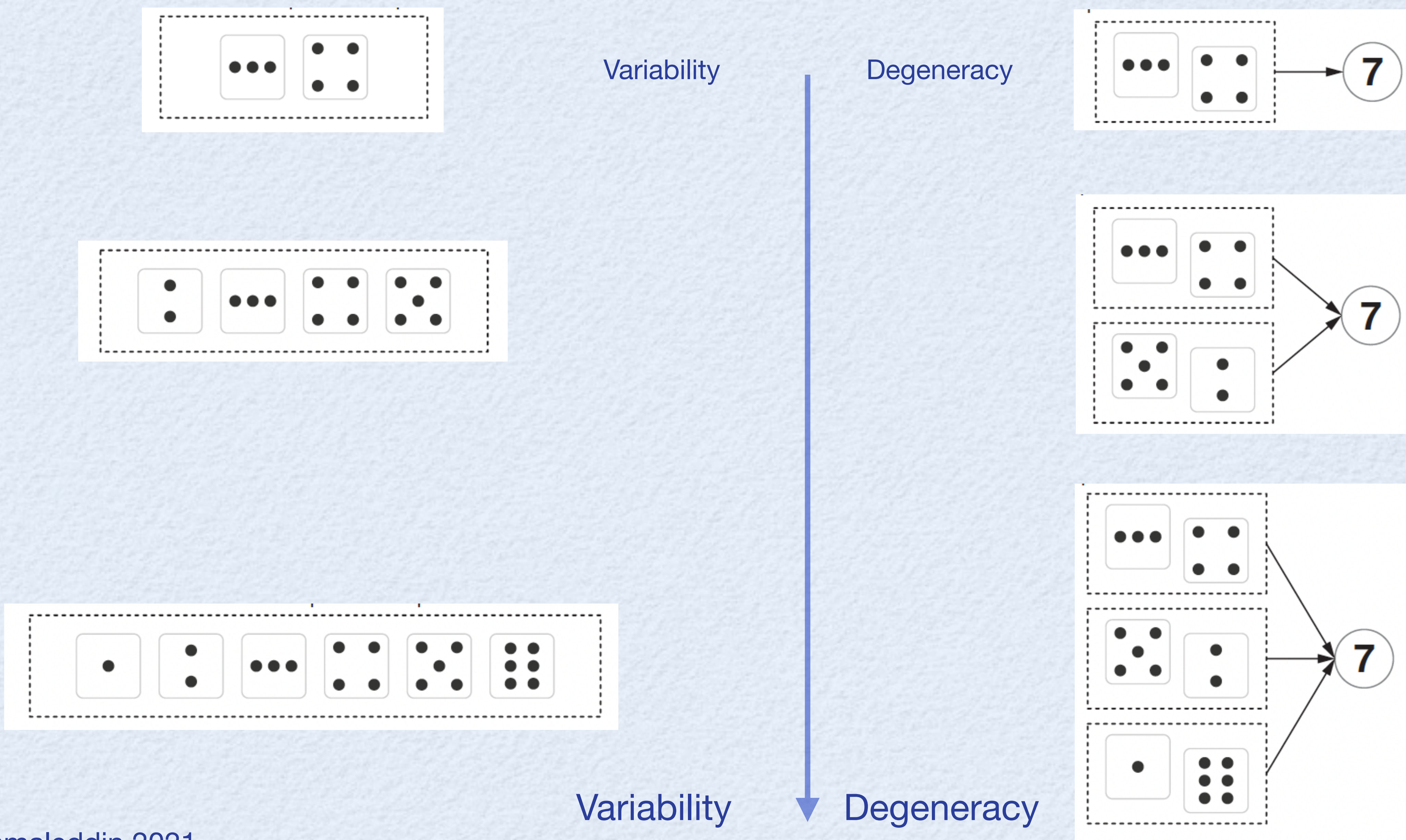
Kamaleddin 2021

Degeneracy

Degeneracy and variability (interindividual)

Elements in the parametric space

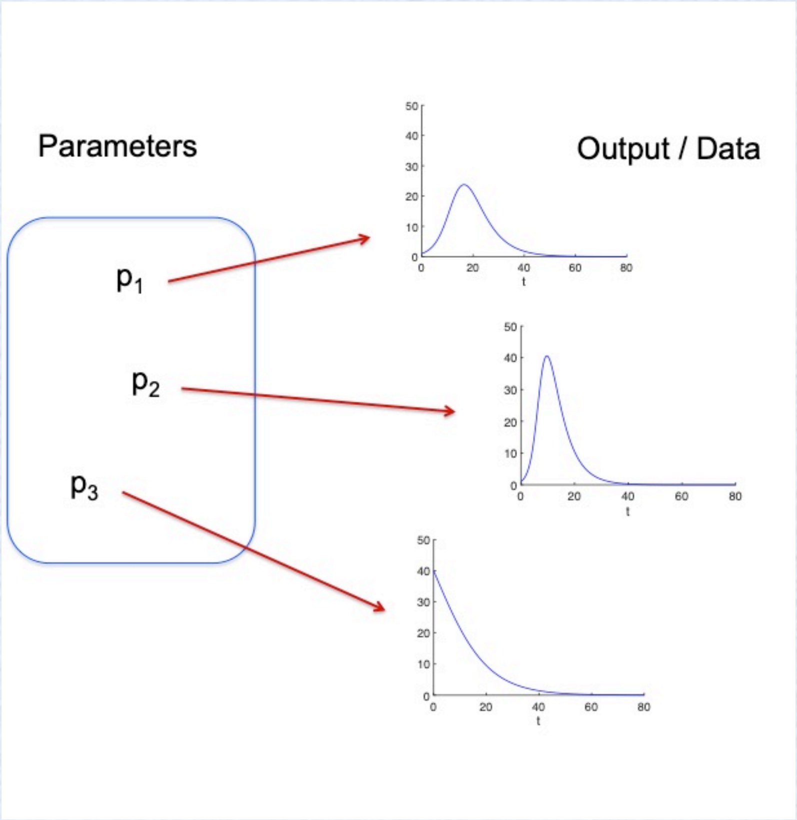
Solutions to the problem of producing the outcome 7



Kamaleddin 2021

Unidentifiability in dynamic models

- ☑ Is it possible to uniquely determine the model parameters from the available data?



Lederman, R et al 2022

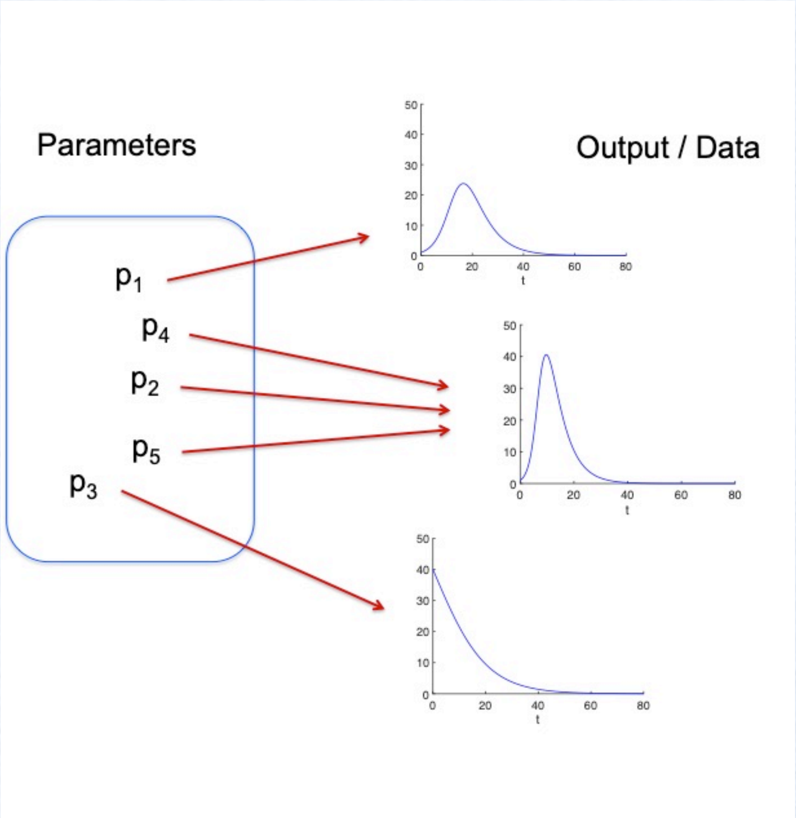
Unidentifiability in dynamic models

- ☑ Is it possible to uniquely determine the model parameters from the available data?

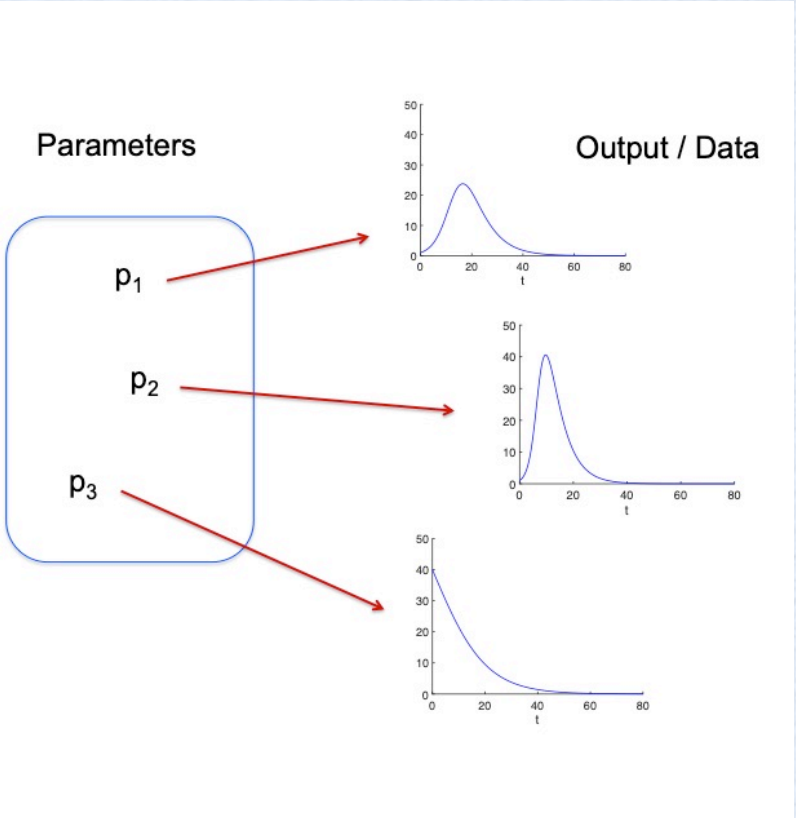
- ☑ What are the factors that affect our ability to do it?

- ☑ Accuracy
- ☑ Reliability
- ☑ Predictions

Unidentifiability



Identifiability



Lederman, R et al 2022

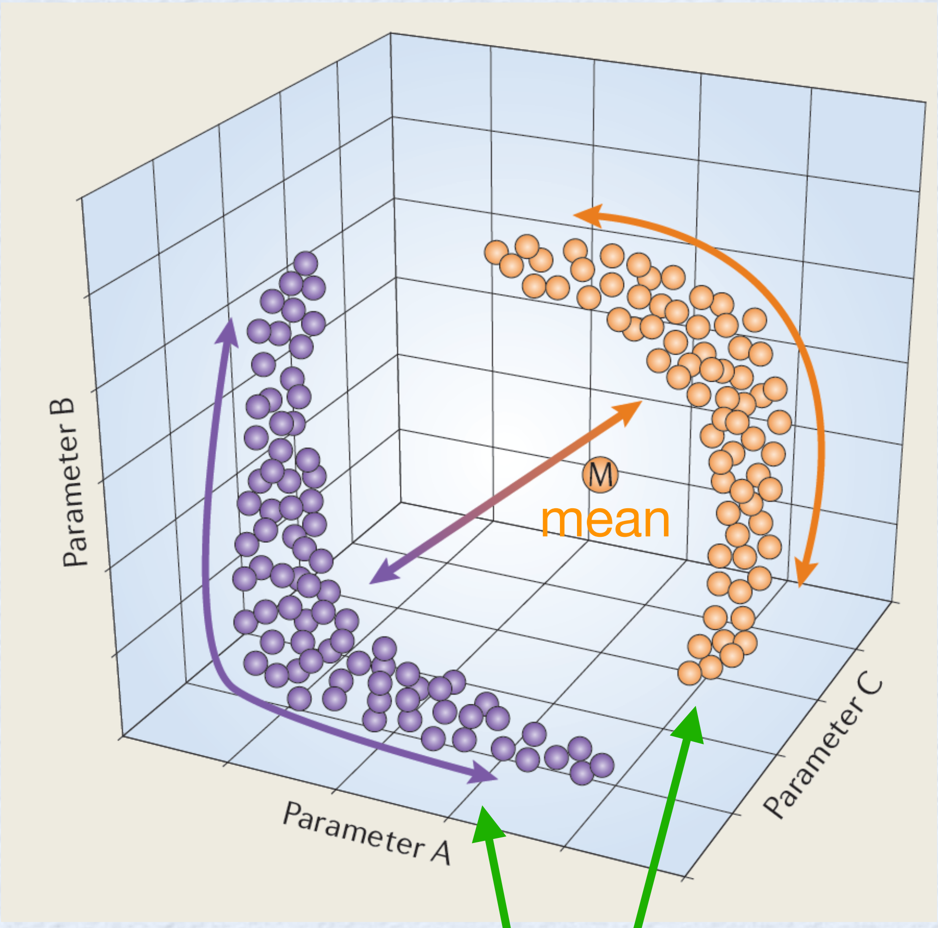
Degeneracy & unidentifiability

Parameters: A, B, C (e.g, conductances for three different ion channels)

Behaviors: purple, yellow (e.g, bursts with different length)

Homeostatic rules may operate within colored regions

Neuromodulators may operate by moving neurons from one region to another



Marder & Goaillard 2006

Level sets of activity

Whether or not the means of the parameters capture the behavior of the individuals in the mean depend on the shape of the level sets

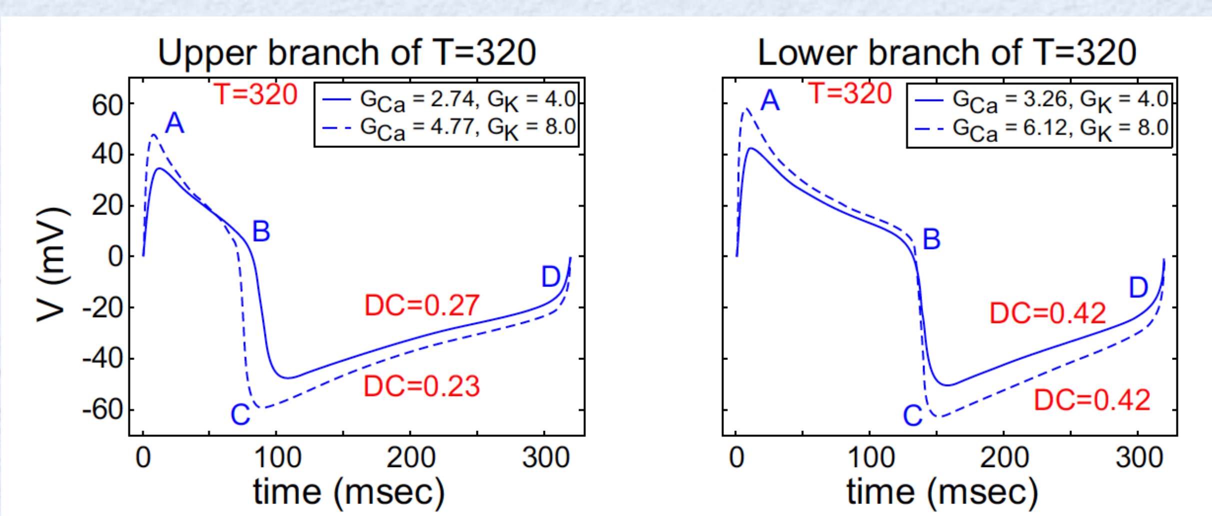
Golowasch et al 2002; Taylor et al 2001

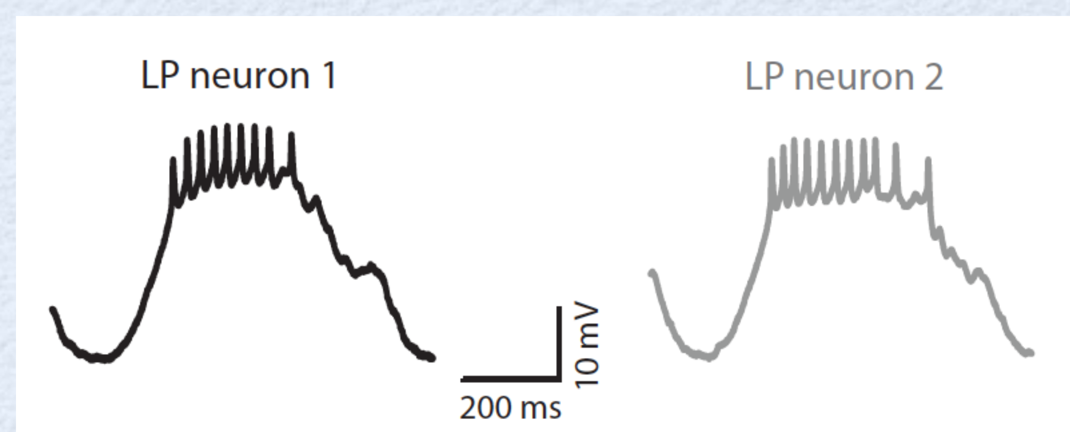
Degeneracy & unidentifiability

The ability of elements that are structurally different to perform the same function or yield the same output

Multiple solutions to the same problem

Bower & Koch 1992; Foster et al 1993





R et al 2016

Morris-Lecar model

Goaillard & Marder 2021

Degeneracy & unidentifiability

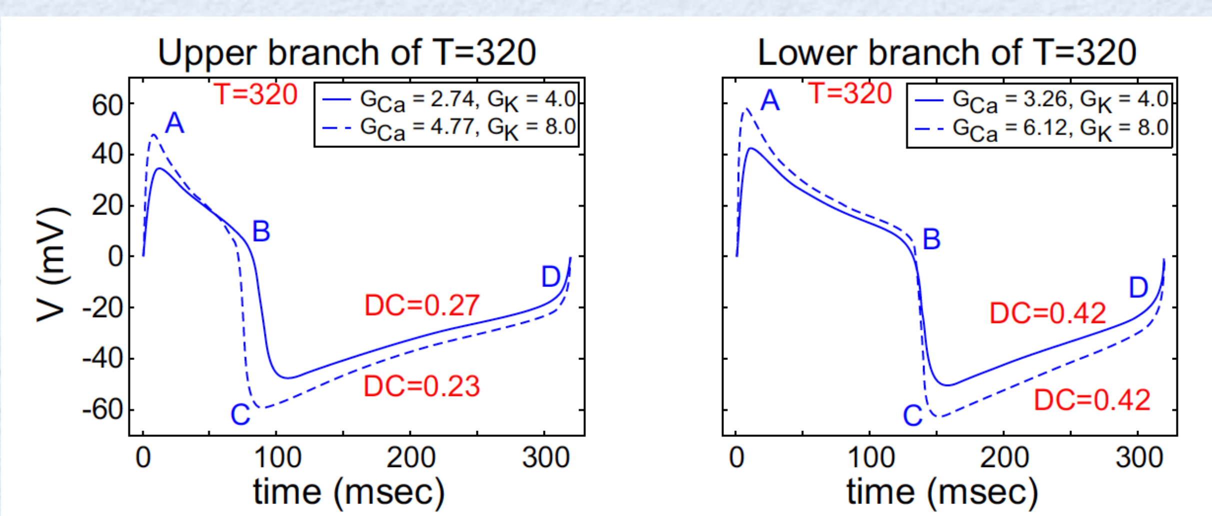
The ability of elements that are structurally different to perform the same function or yield the same output

Multiple solutions to the same problem

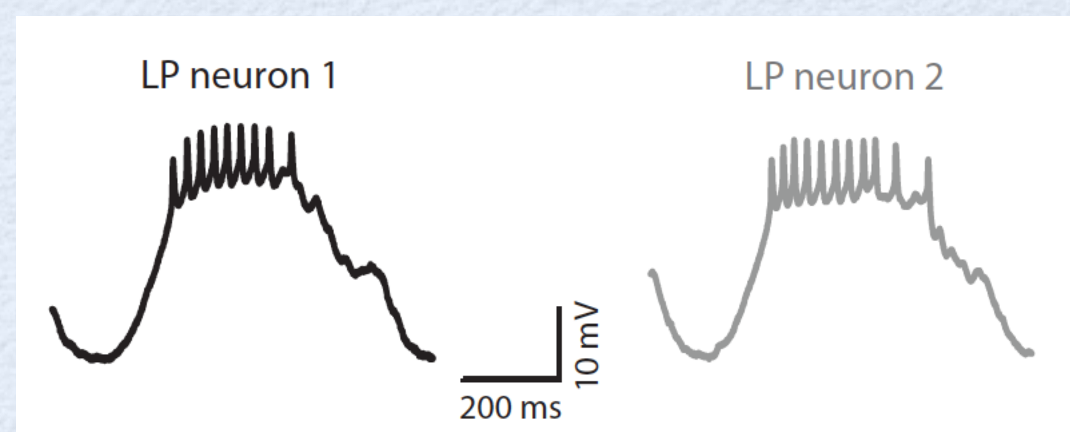
Consequences for modeling

Experimental results should be captured by determining parameter ranges, rather than specific values (e.g., mean values) and the parameter variability

Bower & Koch 1992; Foster et al 1993



R et al 2016 Morris-Lecar model



Goaillard & Marder 2021

Degeneracy & unidentifiability

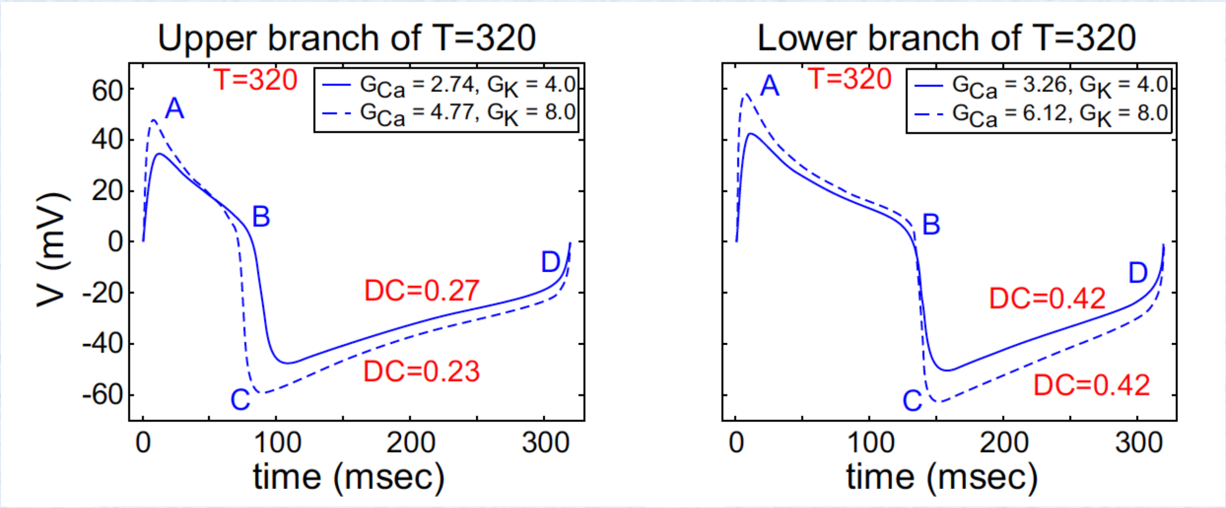
The ability of elements that are structurally different to perform the same function or yield the same output

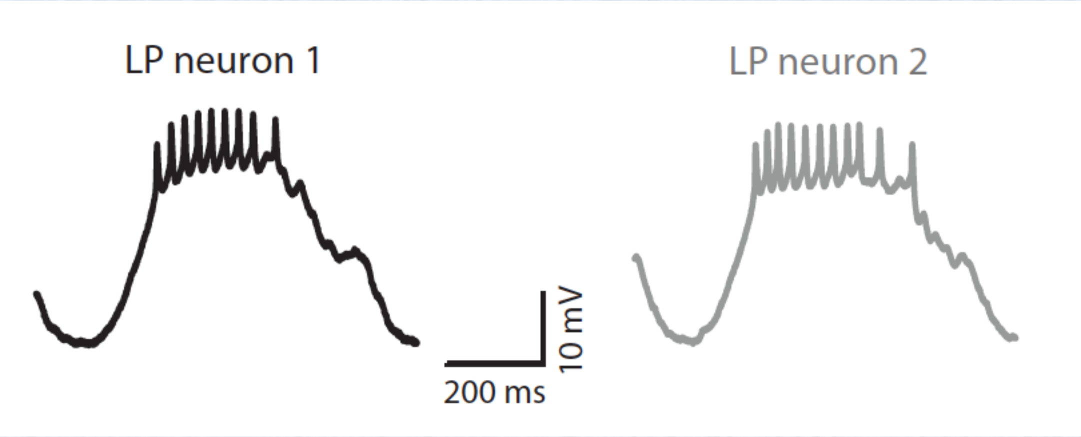
Multiple solutions to the same problem

Consequences for modeling

Averaging may fail because the distribution of data points is poorly characterized by its mean and variance (and higher order statistics)

Golowasch et al 2002





R et al 2016 Morris-Lecar model

Goaillard & Marder 2021

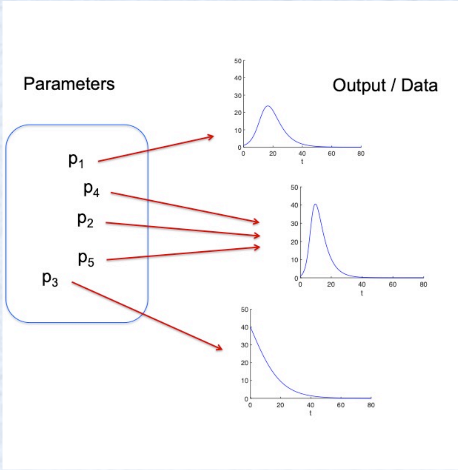
Degeneracy & unidentifiability

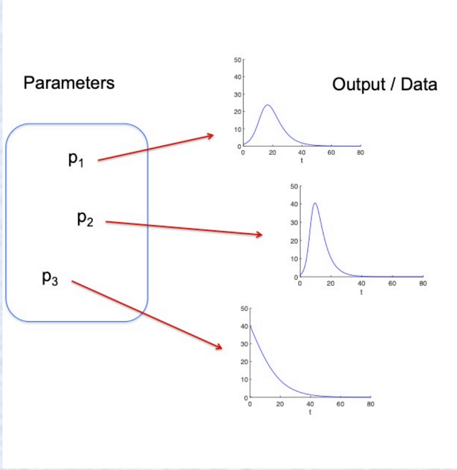
- ☑ Experimental / observational data: Attributes (e.g., oscillations frequency, mean firing rate)
- ☑ Model: Parameters

Fit parameters using the available data (attributes) for the observable variables

- ☑ Predictions
- ☑ Mechanisms
- ☑ Decisions

Is it possible to uniquely determine the model parameters from the available data?



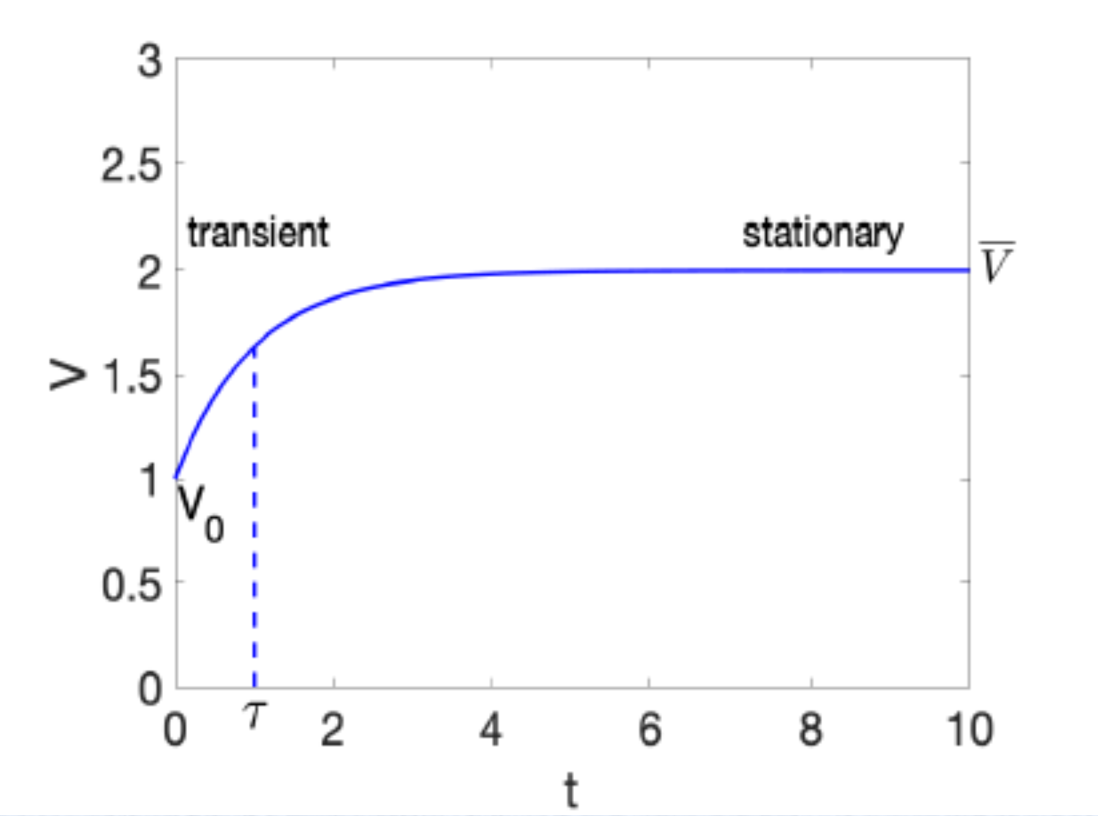


Unidentifiability in dynamic models

Simple example: One-dimensional linear model

$$\tau \frac{dV}{dt} = -V + \bar{V} \qquad V(0) = V_0$$

$$V(t) = \bar{V} + (V_0 - \bar{V})e^{-t/\tau}$$

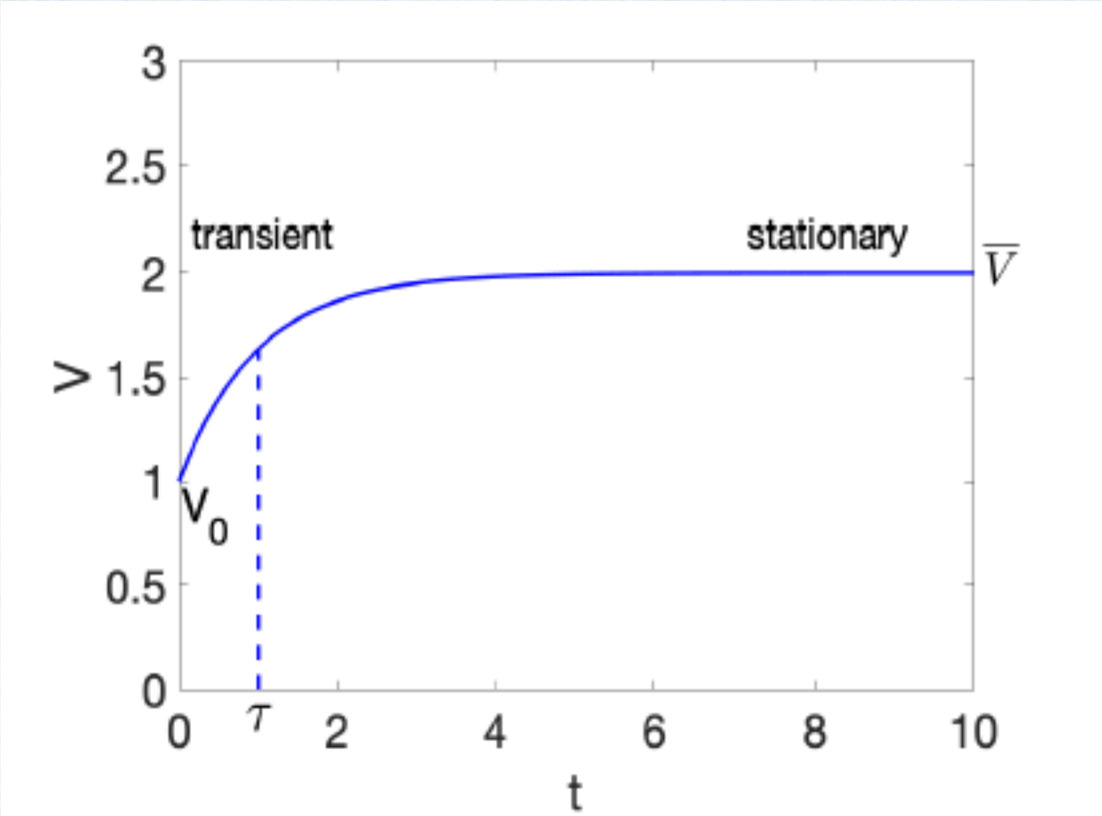


Parameters and attributes are identical

Unidentifiability in dynamic models

One-dimensional linear model: identifiability

- V_0 can be estimated from the initial conditions
- $\bar{V}$ can be estimated from the steady state response $\lim_{t\to\infty} V(t)$
- τ can be estimated by computing the time it takes to V to reach 63 % of the gap between V_0 and $\bar{V}$



Parameters and attributes are identical

Unidentifiability in dynamic models

One-dimensional linear model: unidentifiability

The passive membrane equation

Model

$$C \frac{dV}{dt} = -G_L (V - E_L) + I_{app} \qquad V(0) = V_0$$

Rescaling

$$\tau \frac{dV}{dt} = -V + \bar{V} \qquad \tau = \frac{C}{G_L}, \quad \bar{V} = E_L + \frac{I_{app}}{G_L}$$

- V_0 can be estimated from the initial conditions
- $\bar{V} = E_L + I_{app}/G_L$ can be estimated from the steady state response $\lim_{t\to\infty} V(t)$
- $\tau = C/G_L$ can be estimated by computing the time it takes to V to reach 63 % of the gap between V_0 and $\bar{V}$

More parameters than attributes: redundancy in the biophysical parameters

Unidentifiability in dynamic models

Two-dimensional linear model

$$\frac{d^2Y}{dt} + b\frac{dY}{dt} + cY = A, \qquad Y(0) = Y_0, \quad \frac{dY}{dt}(0) = Y_0'$$

$$\bar{Y} = \frac{A}{c}$$

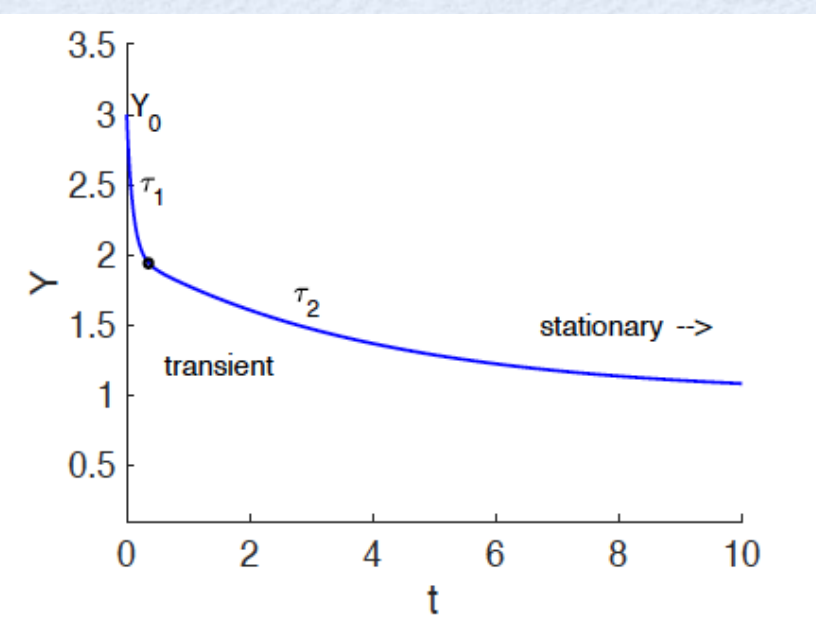
$$r_{1,2} = \frac{-b \pm \sqrt{b^2 - 4c}}{2}$$

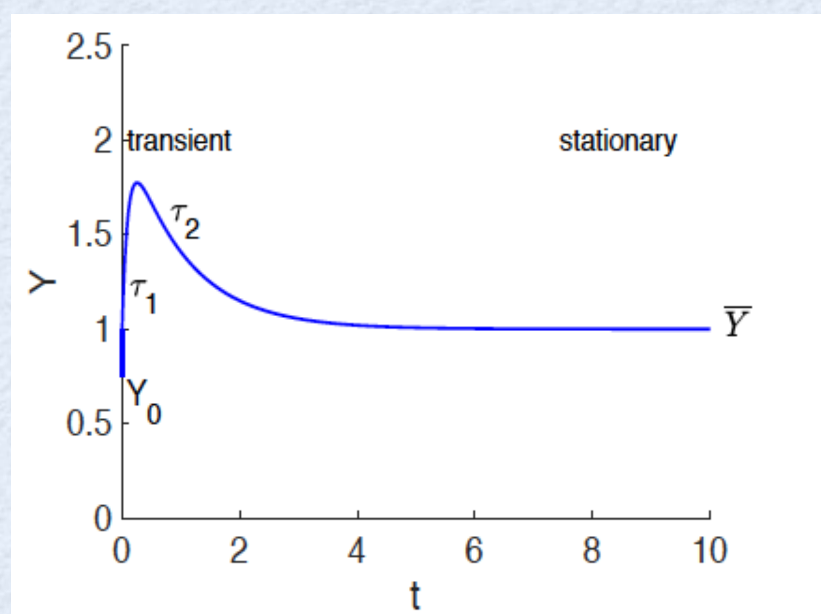
Parameters and attributes
are not the same

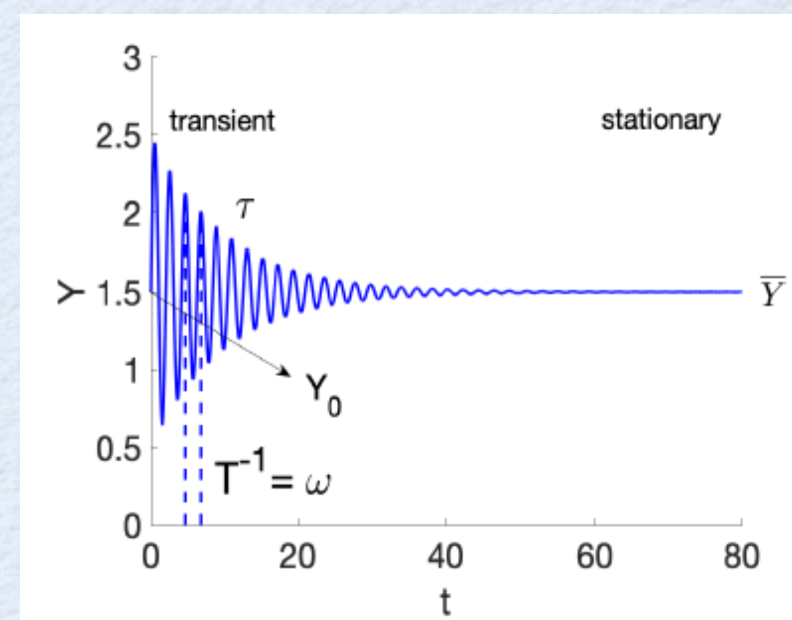
$$\tau_{1,2} = r_{1,2}^{-1}$$

$$\tau = -\frac{2}{b}$$

$$\omega = \frac{\sqrt{b^2 - 4c}}{2}$$







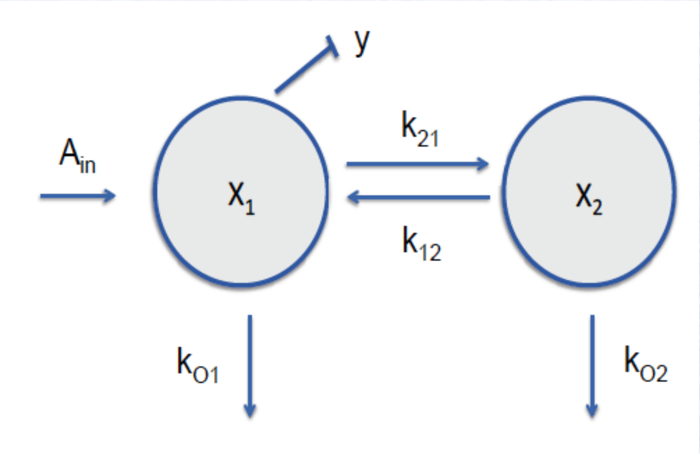
Unidentifiability in dynamic models

Two-dimensional linear model: unidentifiability

$$\frac{dX_1}{dt} = A_{in} + k_{12}\,X_2 - (k_{O,1} + k_{21})\,X_1,$$

$$\frac{dX_2}{dt} = k_{21}\,X_1 - (k_{O,2} + k_{12})X_2.$$

$$Y = Q\,X_1$$



Linear network

More parameters than attributes: redundancy in the network parameters

Unidentifiability in dynamic models

Two-dimensional linear model: unidentifiability

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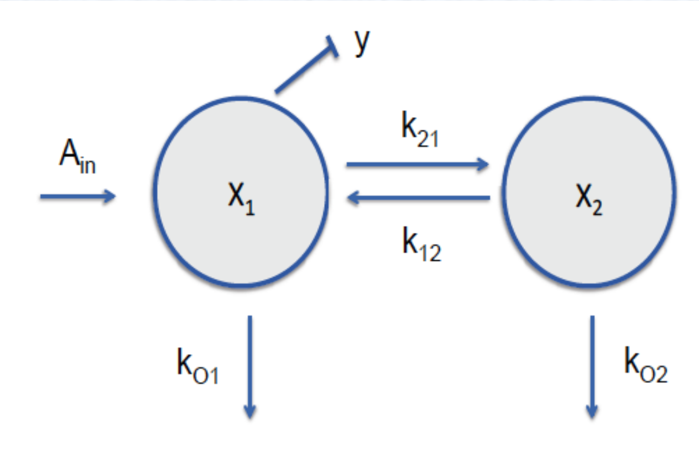


Linear network

$$\frac{d^2Y}{dt} + b\frac{dY}{dt} + cY = A$$

$$b = k_{O,1} + k_{O,2} + k_{12} + k_{21}$$

$$A = (k_{O,2} + k_{12})QA_{in}$$

$$c = (k_{O,1} + k_{21})\,(k_{O,2} + k_{12}) - k_{12}k_{21}$$

More parameters than attributes: redundancy in the network parameters

Unidentifiability in dynamic models

Two-dimensional linear model: unidentifiability

$$\frac{dV}{dt} = -c\,V + (1-\epsilon)\,\frac{c\,\delta}{\beta\,T_0}\,I, \qquad V(0) = V_0$$

$$\frac{dI}{dt} = (1-\eta)\,\beta\,T_0\,V - \delta\,I, \qquad I(0) = V_0 T_0 \beta/\delta$$

Hepatitis C virus

More parameters than attributes: redundancy in the biological parameters

Unidentifiability in dynamic models

Two-dimensional linear model: unidentifiability

$$\frac{dV}{dt} = -c\,V + (1-\epsilon)\,\frac{c\,\delta}{\beta\,T_0}\,I, \qquad V(0) = V_0$$

$$\frac{dI}{dt} = (1-\eta)\,\beta\,T_0\,V - \delta\,I, \qquad I(0) = V_0 T_0 \beta/\delta$$

Hepatitis C virus

$$\frac{d^2V}{dt} + (c+\delta)\frac{dV}{dt} + c\,\delta\,[\,1-(1-\epsilon)(1-\eta)\,]V = 0$$

$$V(0) \;=\; V_0 \qquad dV/dt(0) \;=\; -c\,V_0\,\epsilon$$

$$\frac{d^2Y}{dt} + b\frac{dY}{dt} + cY = A$$

More parameters than attributes: redundancy in the biological parameters

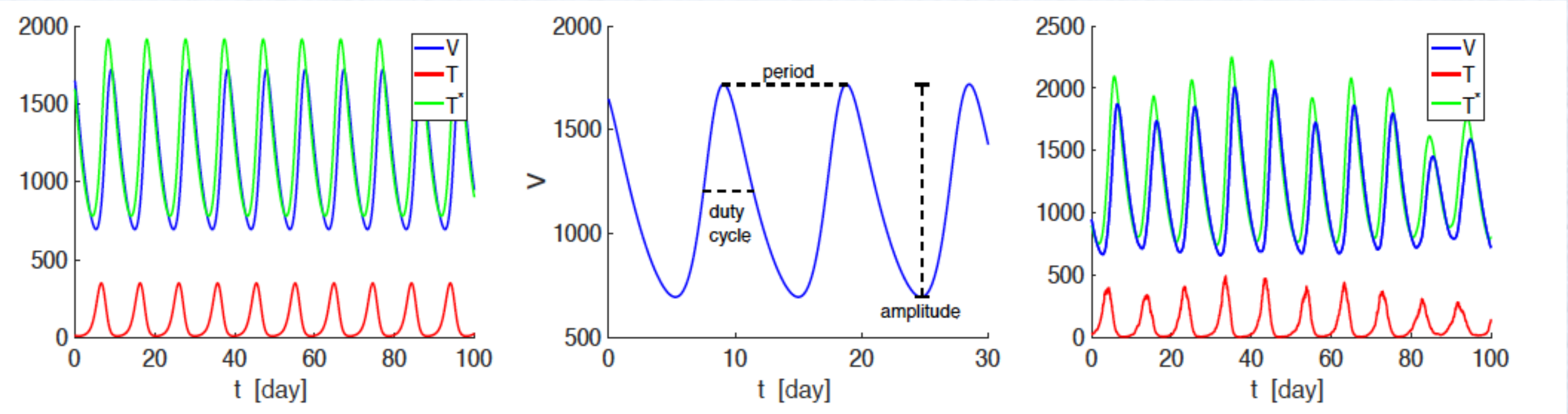
Unidentifiability in dynamic models

Some issues that compromise identifiability / produce degeneracy (and lead to unidentifiability)

☑ Undertainty / Noise

Regular

Irregular



HIV-1 patterns

V: viral load
T: uninfected cells
T*: infected cells

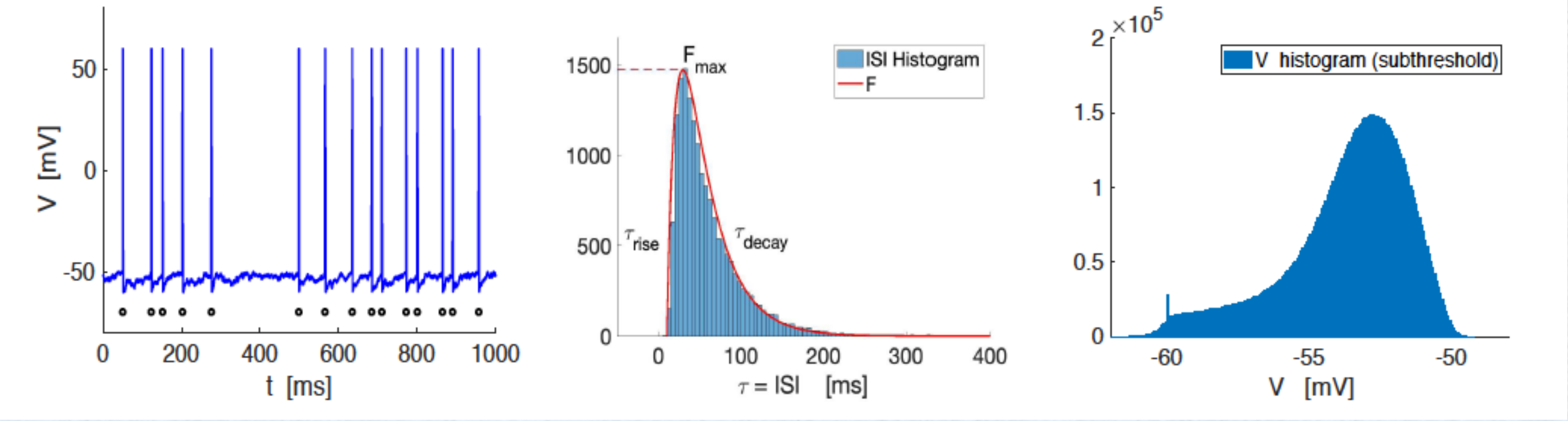
Attributes:

Period
Amplitude
Duty cycle

Unidentifiability in dynamic models

Some issues that compromise identifiability / produce degeneracy (and lead to unidentifiability)

- ☑ Lack of experimental/observational access to all the state variables (hidden variables)



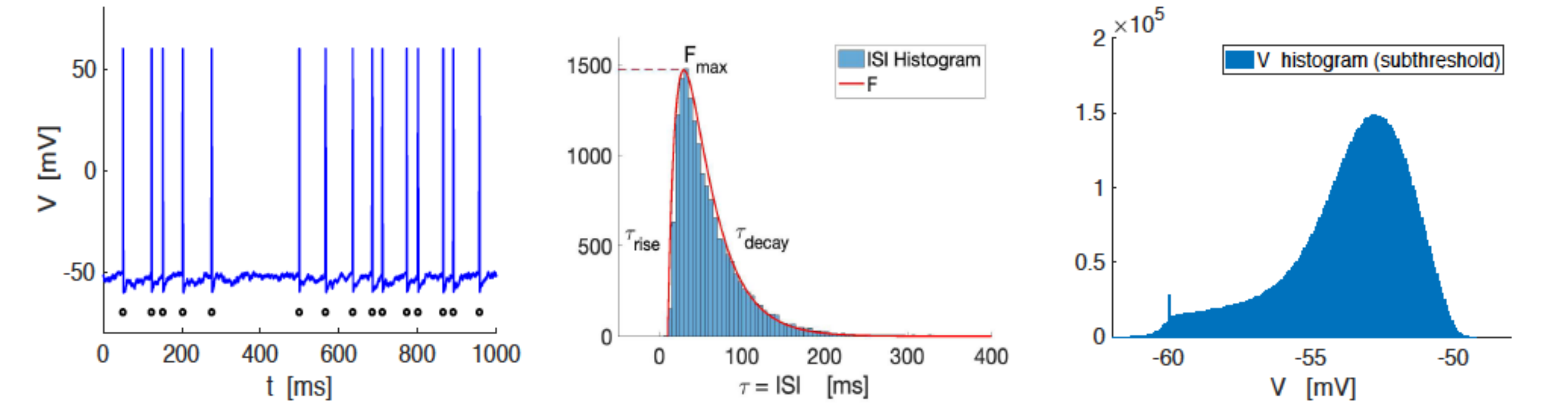
Neuronal spiking pattern

V: membrane potential
ISI: Interspike intervales

Unidentifiability in dynamic models

Some issues that compromise identifiability / produce degeneracy (and lead to unidentifiability)

☑ Lack of experimental/observational access to the continuous events (e.g., membrane potential), but only to discrete events (e.g., spikes)



Neuronal spiking pattern

V: membrane potential
ISI: Interspike intervales

Attributes:

F_{max}
F_{peak}
τ_{raise}
τ_{decay}

Unidentifiability in dynamic models

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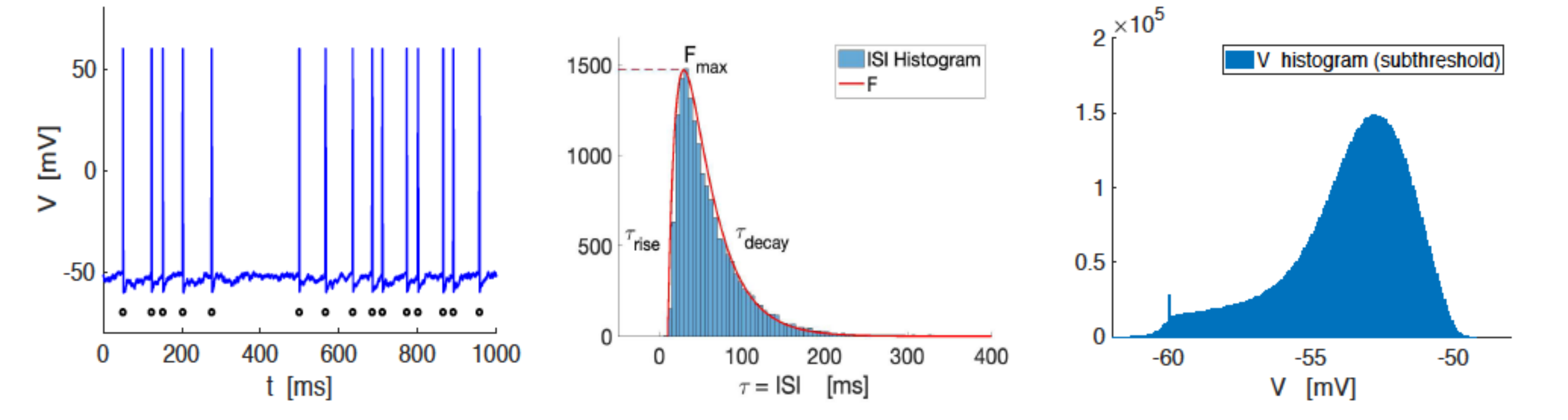
☑ Lack of experimental/observational access to the continuous events (e.g., membrane potential), but only to a number of attributes attributes (e.g., ISI attributes)



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Attributes:

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F_{peak}
τ_{raise}
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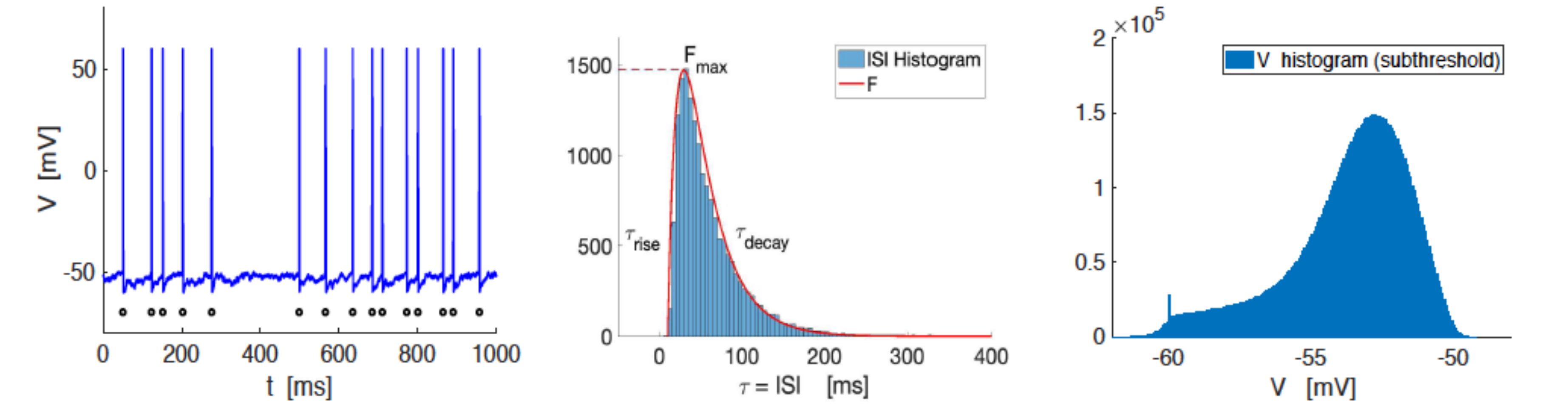
Unidentifiability in dynamic models

Some issues that compromise identifiability / produce degeneracy (and lead to unidentifiability)

- ☑ There may be gaps in the data set and these gaps may be inconsitent across trials (requiring imputation)



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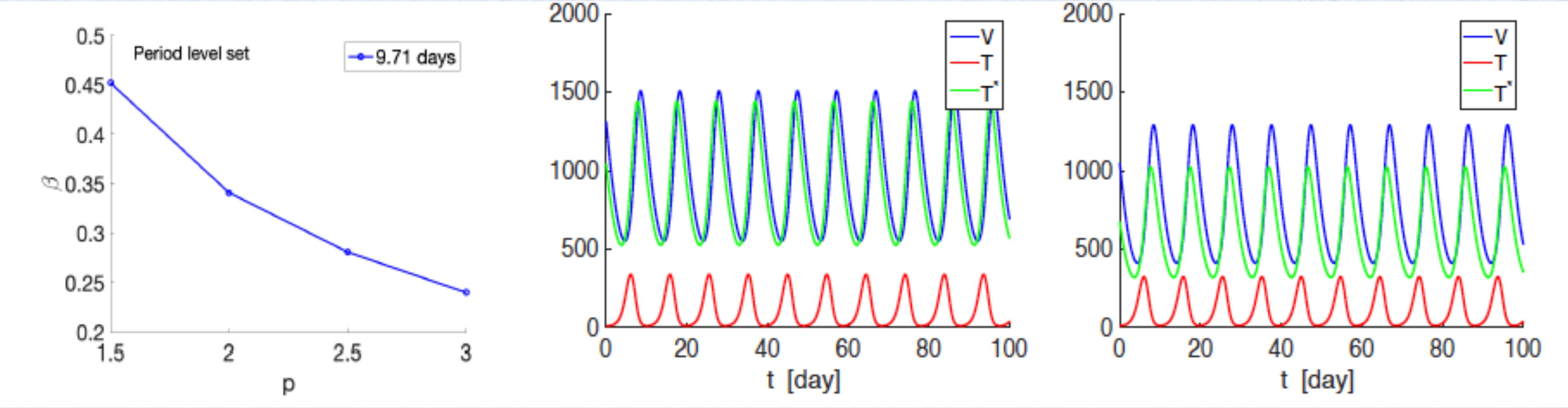
Unidentifiability in dynamic models

Some issues that compromise identifiability / produce degeneracy (and lead to unidentifiability)

- ☑ Parameter degeneracy: multiple parameter sets give rise to the same observable pattern



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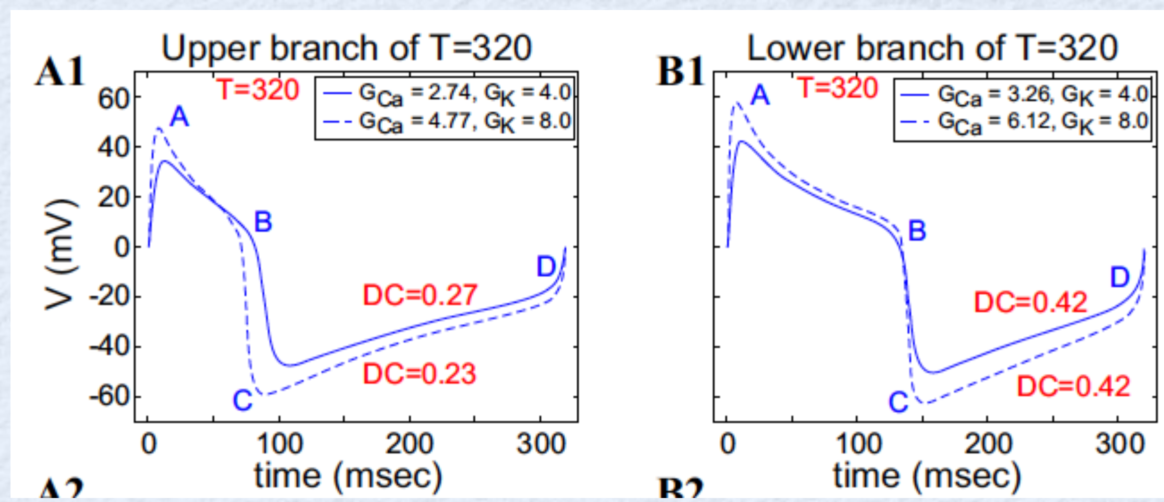
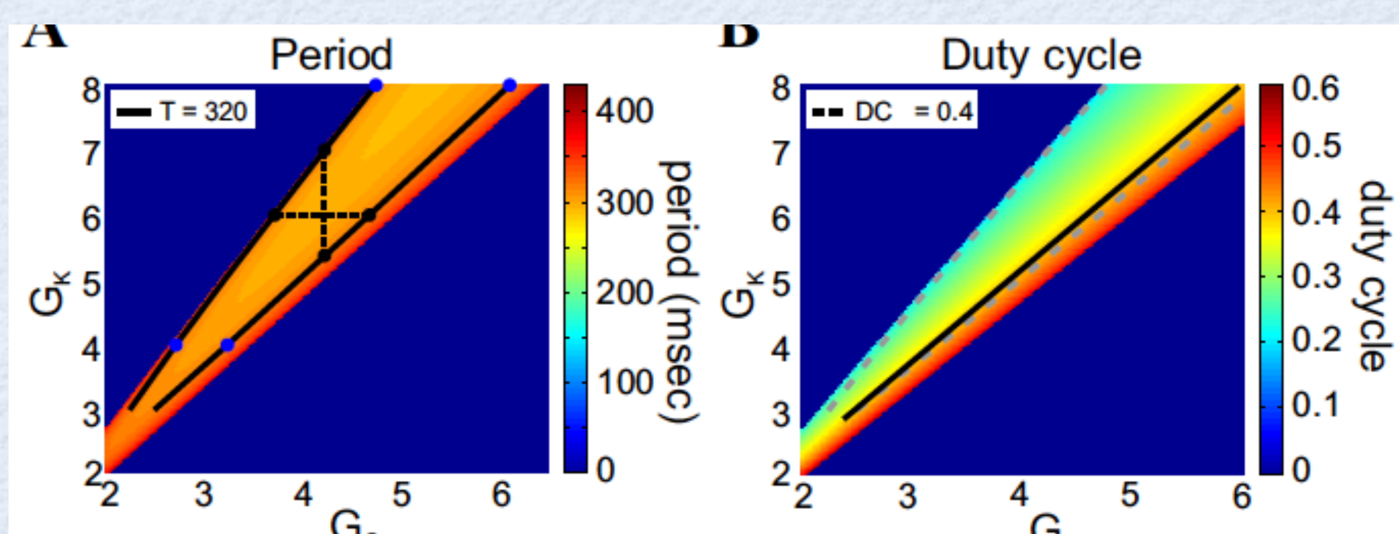


Neuronal model

G_{Ca}: Calcium conductance
G_K: Potassium conductance



Prinz, Bucher, Marder (2004)
Olypher & Calabrese (2010)
R, Olarinre, Golowasch (2016)

Unidentifiability in dynamic models

Some issues that compromise identifiability / produce degeneracy (and lead to unidentifiability)

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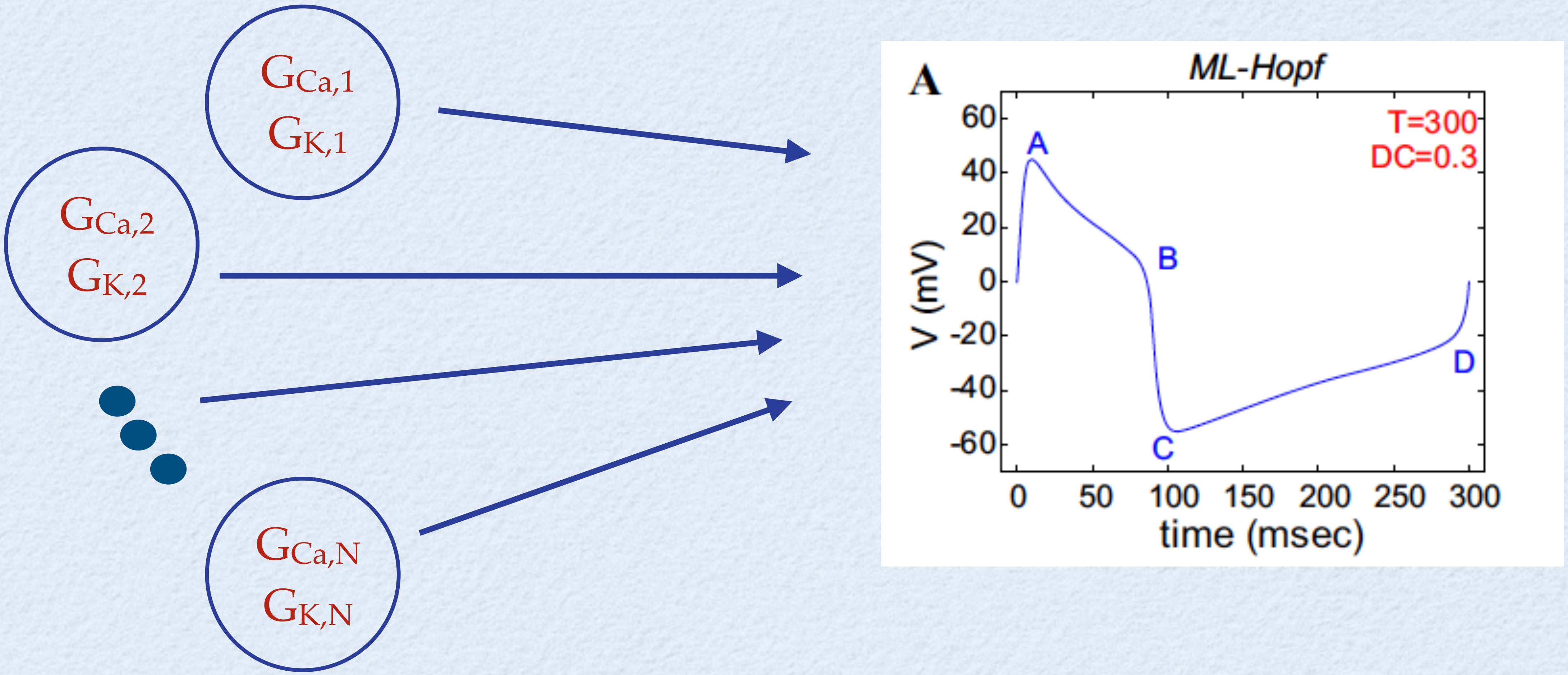

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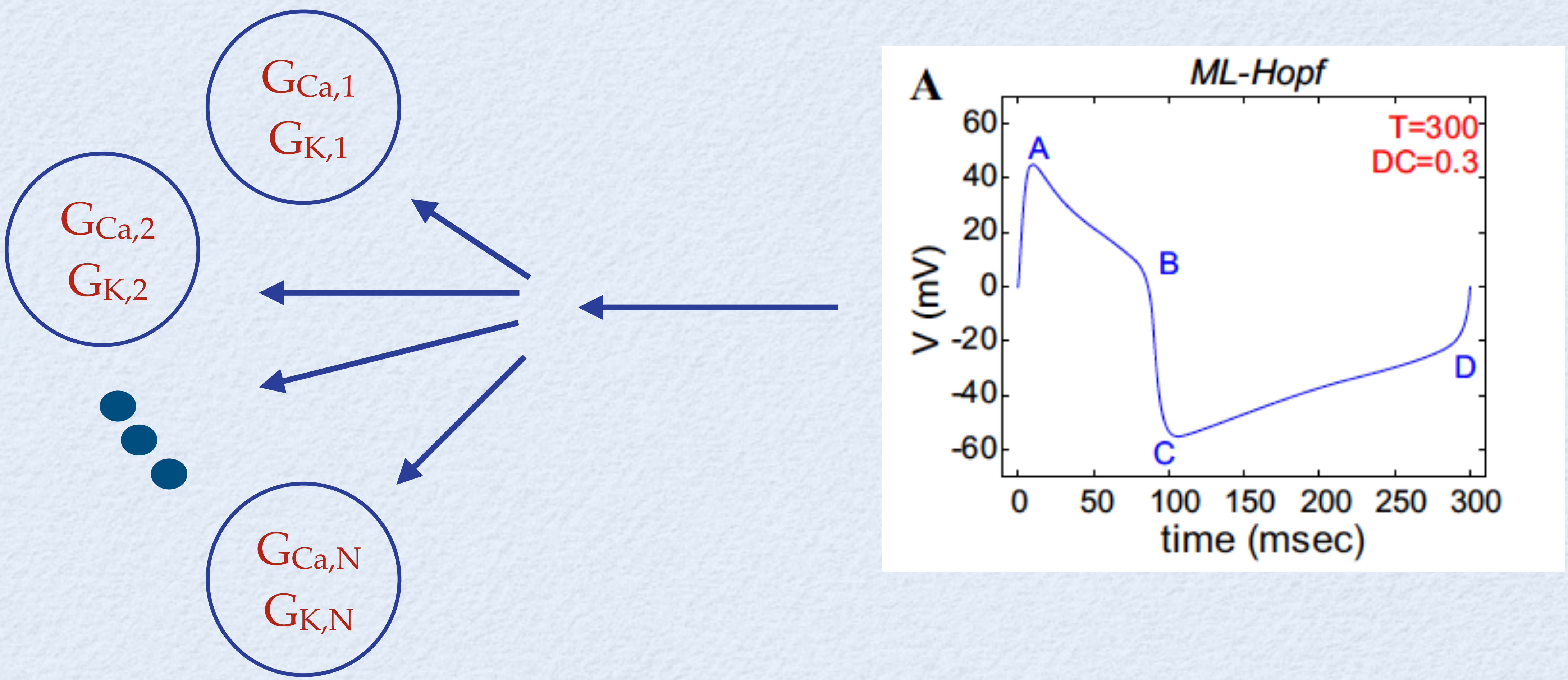

Unidentifiability in dynamic models

Some issues that compromise identifiability / produce degeneracy (and lead to unidentifiability)

- ☑ Parameter degeneracy: multiple parameter sets give rise to the same observable pattern
- ☑ Classical parameter degeneracy: one can at most identify combinations of unidentifiable model parameters
- ☑ This is due to an excess in the number of parameters with physical meaning as compared to the numbers of parameters necessary to describe the data

Identifiability: Numerical Approaches

Fisher information
Profile likelihood
Hessian method
Data cloning
Bayesian analysis

Parameter estimation

Maximum likelihood
Profile likelihood
Genetic algorithms
Gradient descents
Bayesian methods (e.g., SNBI and neural density estimators)

Unidentifiability

Ollivier 1990
Ljung & Glad 1994
Evans & Chappell 2000
Audibly et al 2003
Hengl et al 2007
Chis et al 2011

Nonlinear systems / models

Taylor series: Pohjanpalo 1978

Similarity transformations: Tunali & Tarn 1987; Vajda et al 1989

Differential algebra tools: Fliess & Glad 1993; Ljung & Glad 1994

Global unidentifiability: Chappell et al 1990

Degeneracy & Unidentifiability

Questions

- **Canonical model.** Can one find an oscillator with a higher degree of degeneracy?
  - Identical oscillations (oscillatory solutions) can be found for multiple parameter sets
  - Same limit cycle and same speed along the limit cycle
  - —> Same level set of all attributes (e.g., frequency, amplitude, dutyc cycle).
- **Disambiguation.** What type of perturbations will allow to identify the differences between different oscillators in a level set?
  - This perturbations should be able to activate the transients
  - Noise
  - Periodic (entrainment)

Degeneracy & Unidentifiability

Questions

- ☑ **Implications.** What are the consequences of the existence of level sets at the single cell level for network dynamics?
  - ☑ How should on design the network questions?
    - ☑ Homogeneity: All oscillators in the network are identical
    - ☑ Heterogeneity I: All oscillators in the network belong to the same level sets
    - ☑ Heterogeneity II: At least two oscillators in the network belong to different level sets
  - ☑ Can network and single cell levesl sets coincide?
  - ☑ Given certain connectivity, how different can the oscillators be (in the level sets metric) to generate newtork level sets?
- ☑ **Disambiguation.** What type of perturbations will allow to identify the differences between different oscillators in a network level set?

Degeneracy: canonical model

Canonical level sets emerge because of an “excess” of symmetries

$$\frac{dx}{dt} = (\lambda - b\,r^2)\,x - (\omega + a\,r^2)\,y,$$

$$\frac{dy}{dt} = (\omega + a\,r^2)\,x + (\lambda - b\,r^2)\,y,$$

$$r^2 = x^2 + y^2$$

Poincaré oscillator

Real value special cases of the Ginzburg-Landau equation

Degeneracy: canonical model

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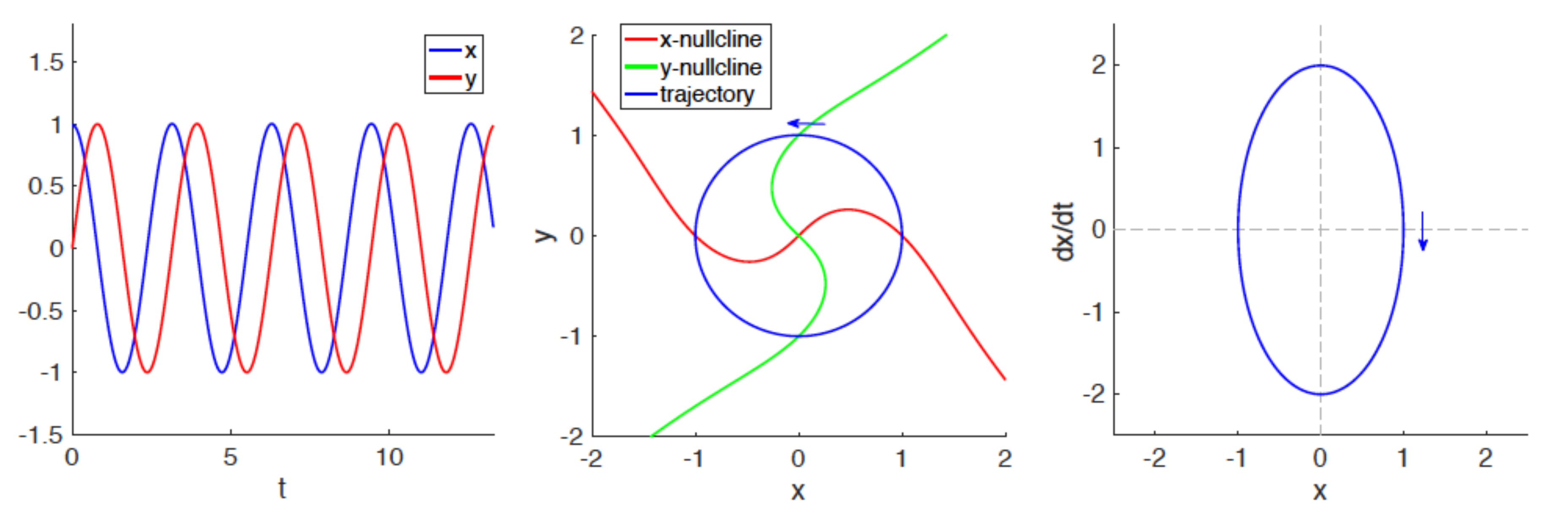

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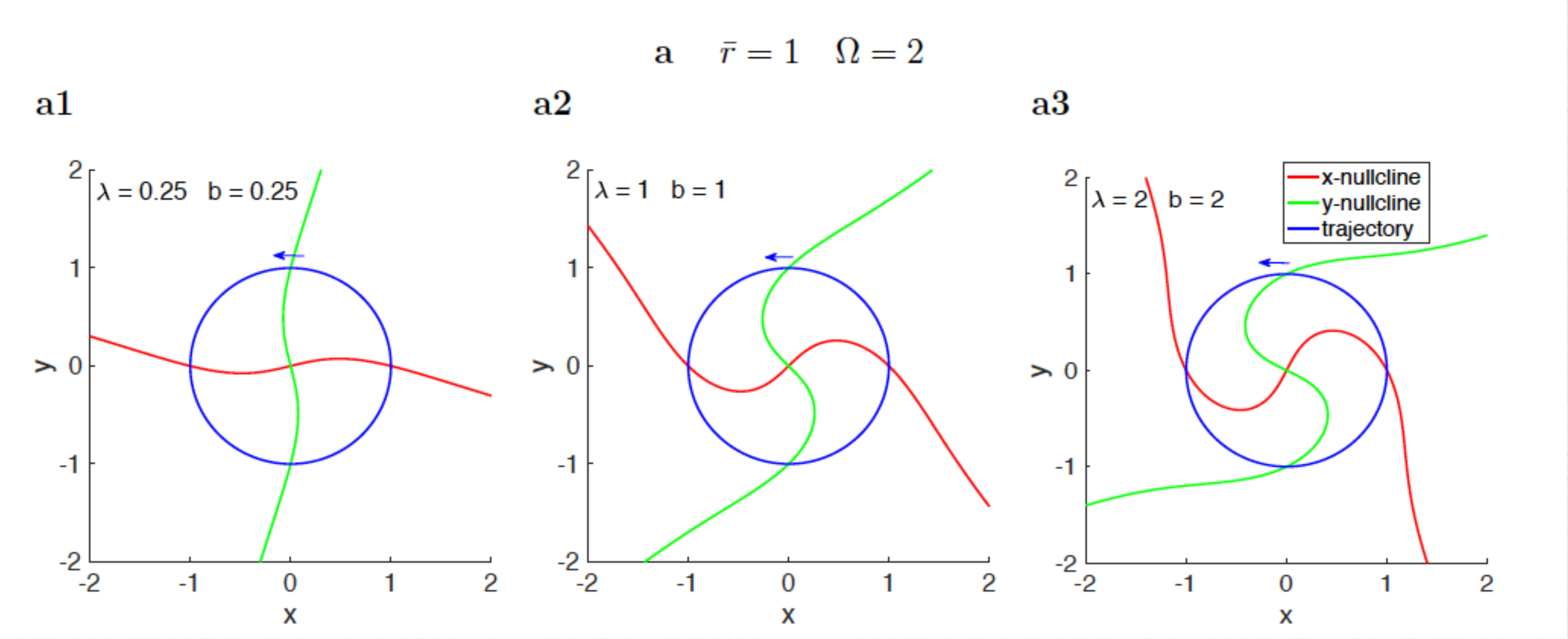

Degeneracy: canonical model

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$$r^2 = x^2 + y^2$$

$$\frac{dx}{dt} = \Lambda(r)\,x - \Omega(r)\,y,$$

$$\frac{dy}{dt} = \hat{\Omega}(r)\,x + \hat{\Lambda}(r)\,y,$$

$x = r\,\cos(\theta)$ and $y = r\,\sin(\theta)$,

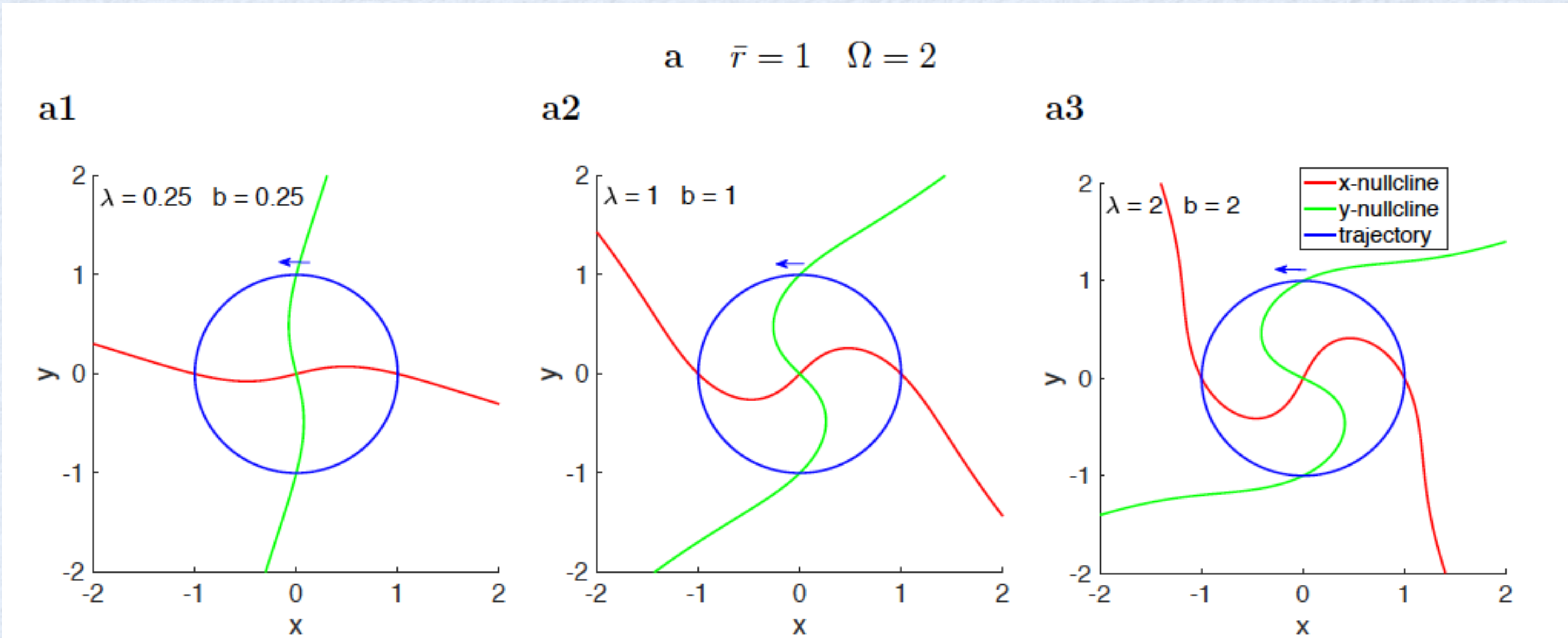
$$\frac{dr}{dt} = r\,\Lambda(r),$$

$$\frac{d\theta}{dt} = \Omega(r).$$

$\Lambda(\bar{r}) = 0$ $\quad \Lambda(r) = \lambda - b\,r^2$ $\quad \bar{r} = \sqrt{\frac{\lambda}{b}},$ $\quad \bar{\omega} = \omega + a\frac{\lambda}{b}$

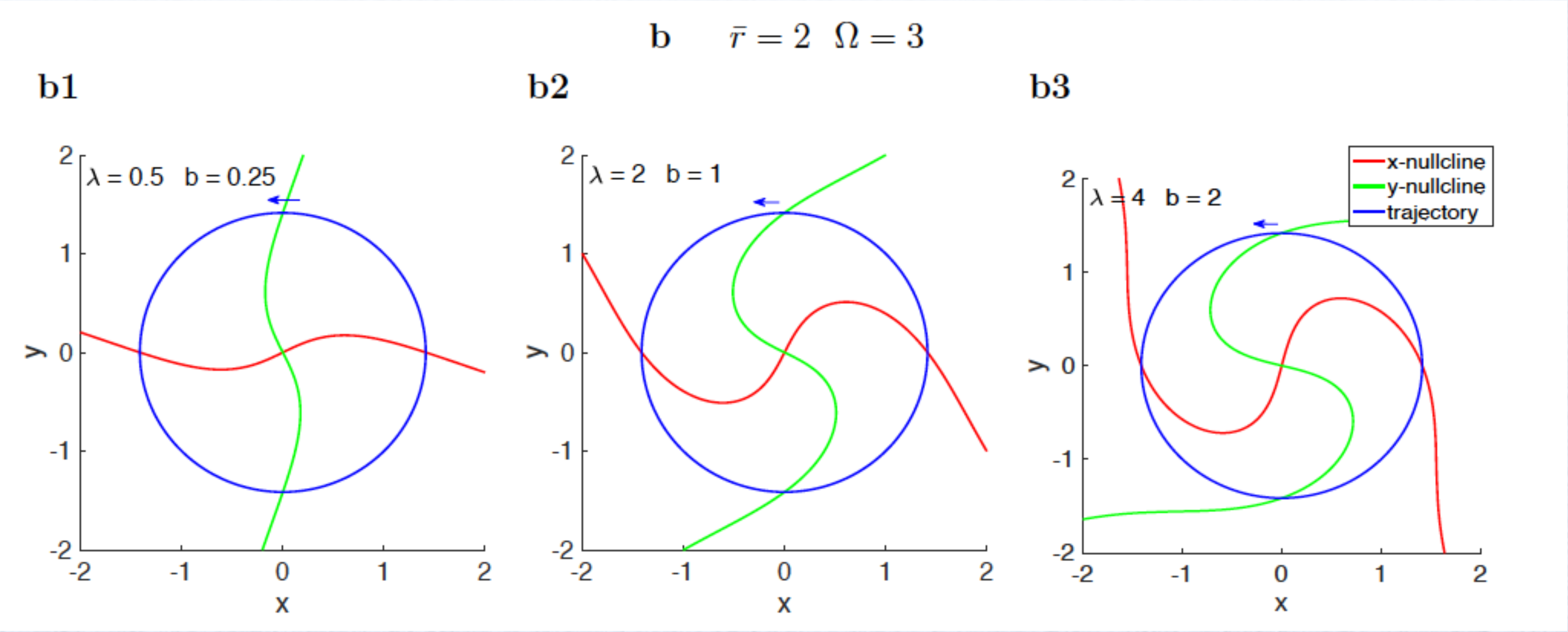
Degeneracy: canonical model

Lambda-omega systems (models): oscillations canonical level sets



Degeneracy: canonical model

Lambda-omega systems (models): oscillations canonical level sets



Degeneracy: canonical model

Lambda-omega systems (models): “structural level sets”

$$\frac{dx}{dt} = f(x, y; p),$$

$$\frac{dy}{dt} = g(x, y; p),$$

$$f(x,y;p) = \lambda\, x - \omega\, y - (b\, x + a\, y)\,(x^2+y^2) - c\, y\left(1 + \frac{x}{\sqrt{x^2+y^2}}\right) - d\,\frac{y^3}{x^2+y^2},$$

$$g(x,y;p) = \omega\, x + \lambda\, y + (a\, x - b\, y)\,(x^2+y^2) + c\, y\left(1 + \frac{x}{\sqrt{x^2+y^2}}\right) + d\,\frac{x\, y^2}{x^2+y^2}.$$

Degeneracy: canonical model

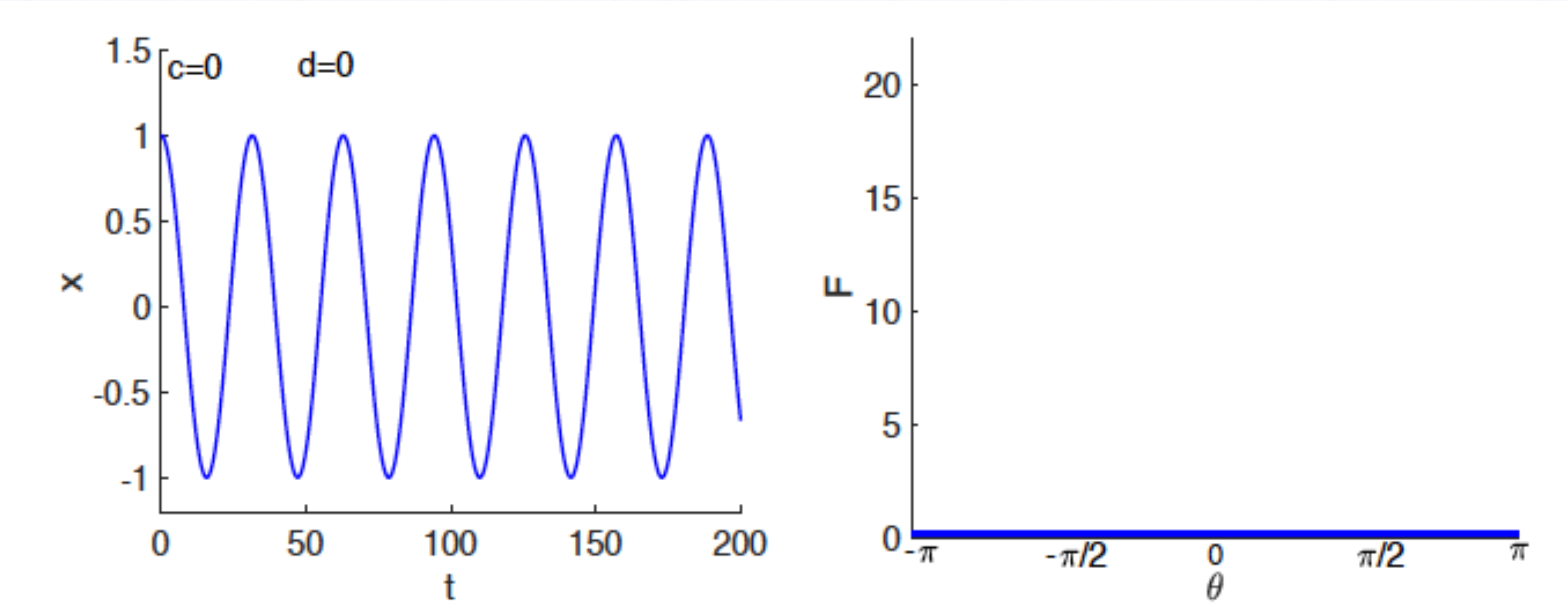
Lambda-omega systems (models): "structural level sets"

$$\frac{dr}{dt} = (\lambda - b\,r^2)\,r,$$

$$\frac{d\theta}{dt} = \omega + a\,r^2 + 2\,c\cos^2(\theta/2) + d\sin^2(\theta),$$

$r^2 = x^2 + y^2$ Polar coordinates

$$F(\theta) = \omega + a\frac{\lambda}{b} + 2c\cos^2(\theta/2) + d\sin^2(\theta)$$



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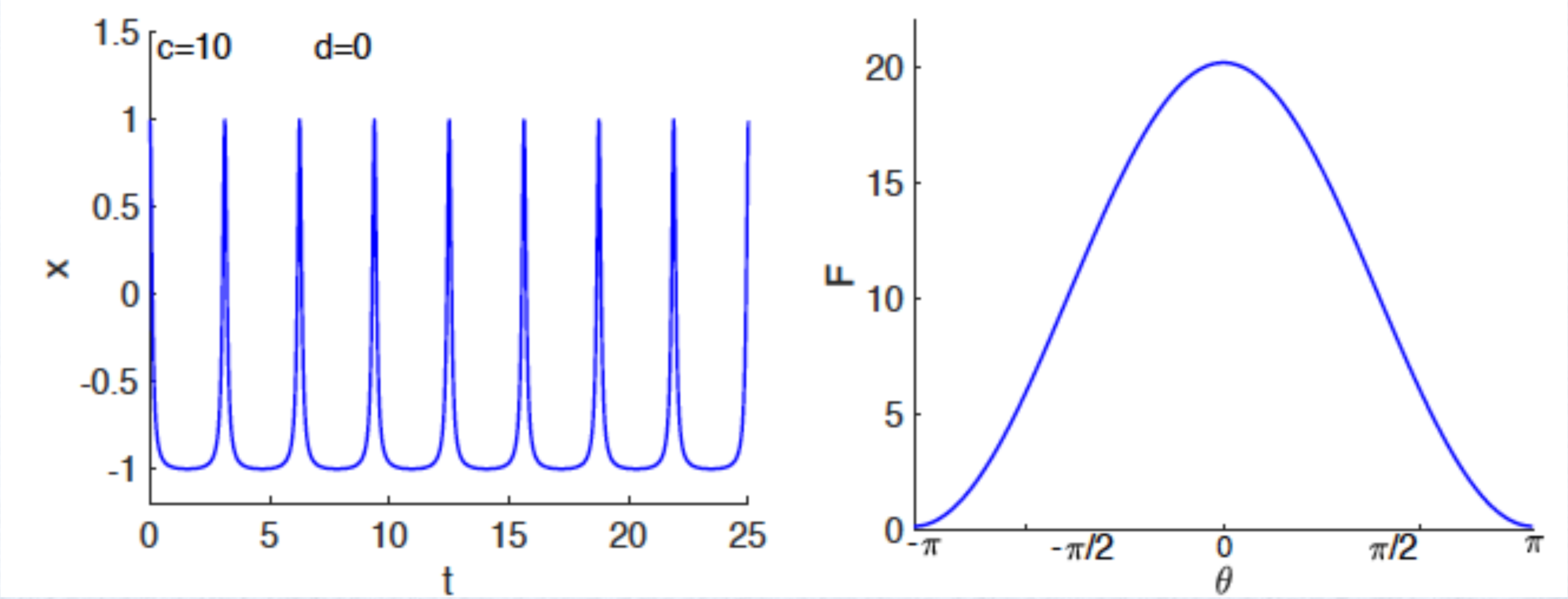

Degeneracy: canonical model

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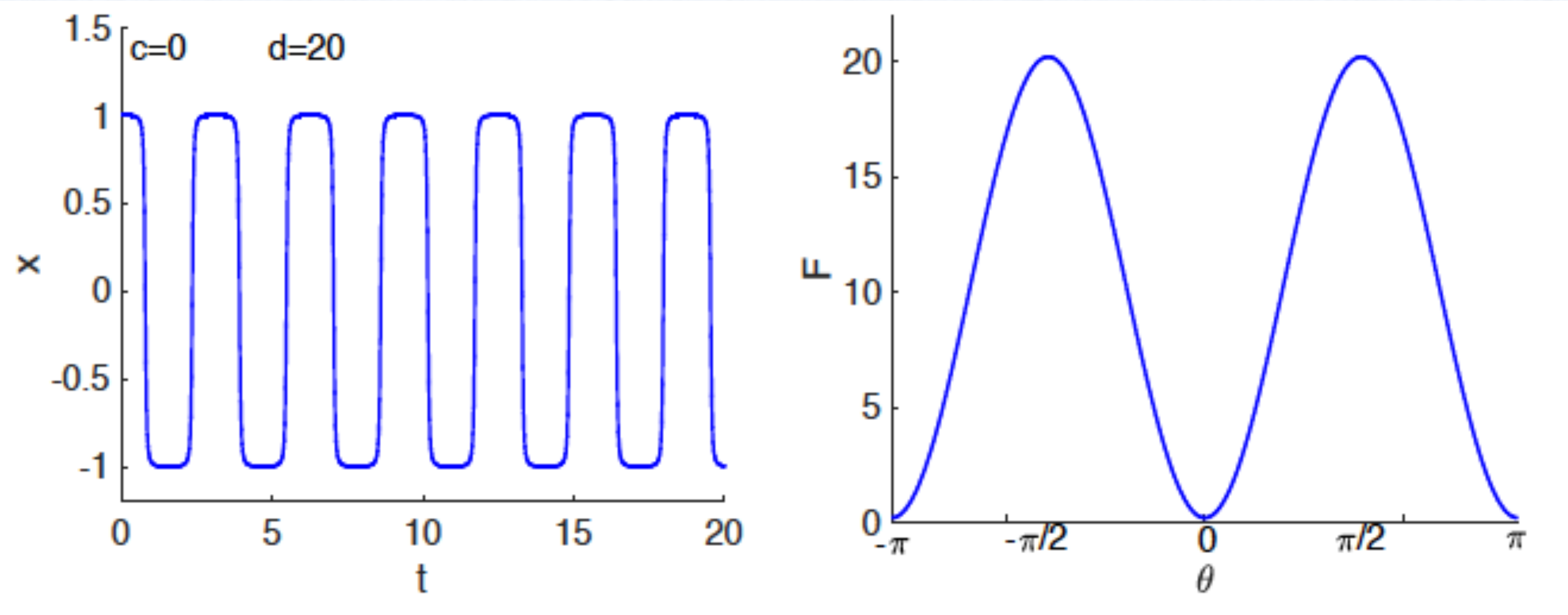


Degeneracy: canonical model

Lambda-omega systems (models) of order 4: Degeneracy, Hopf bifurcations and the emergence of bistability

$$\frac{dx}{dt} = \Lambda(r)\,x - \Omega(r)\,y,$$

$$\frac{dy}{dt} = \hat{\Omega}(r)\,x + \hat{\Lambda}(r)\,y,$$

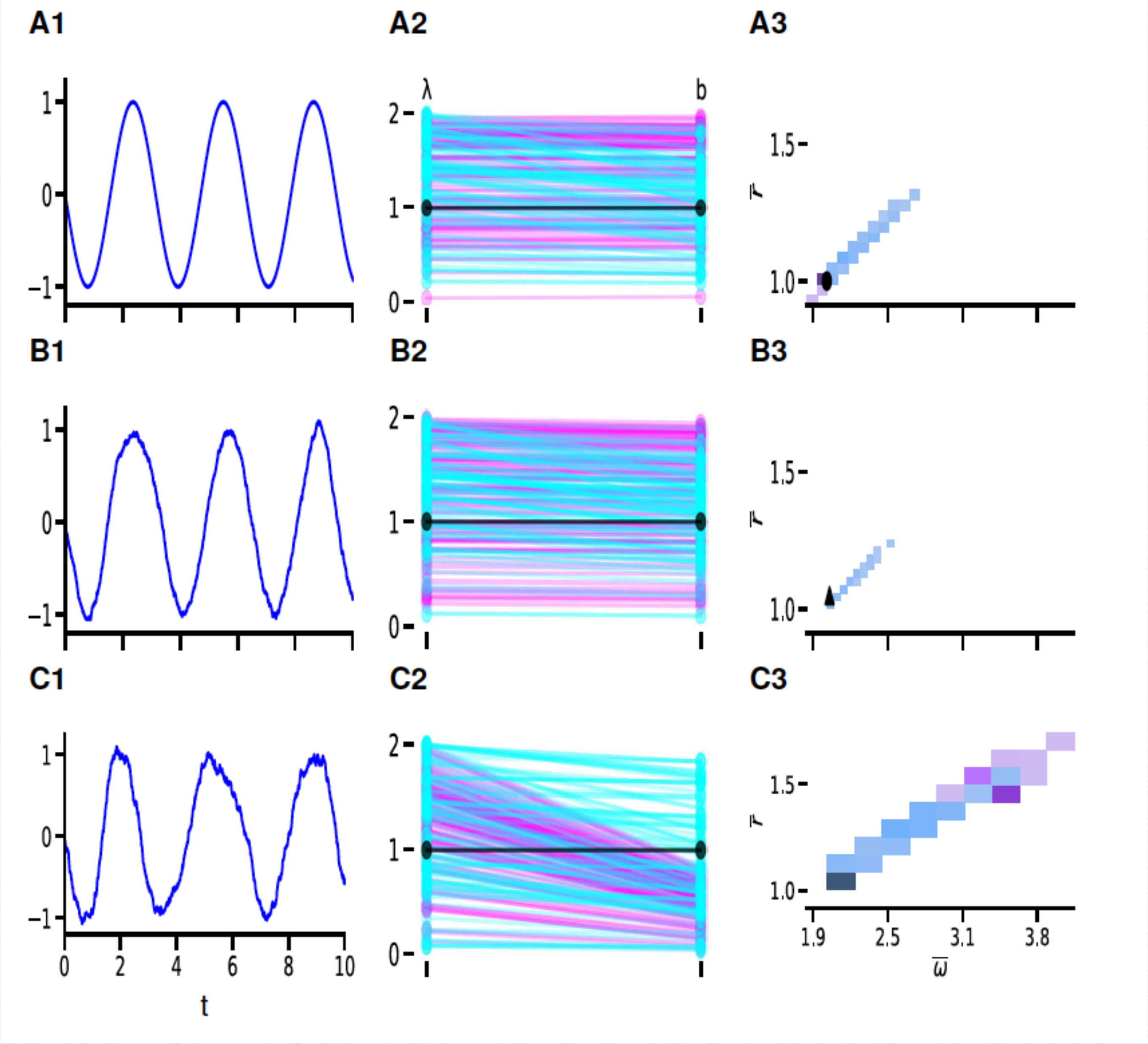
$\Lambda(r) = \lambda - b\,r^2 + c\,r^4$ and $\Omega(r) = \omega + a\,r^2 + d\,r^4$

$$\bar{r} = \sqrt{\frac{b \pm \sqrt{b^2 - 4\lambda c}}{2\lambda}}$$

$$\bar{\omega} = \omega + a\,\bar{r}^2 + d\,\bar{r}^4.$$

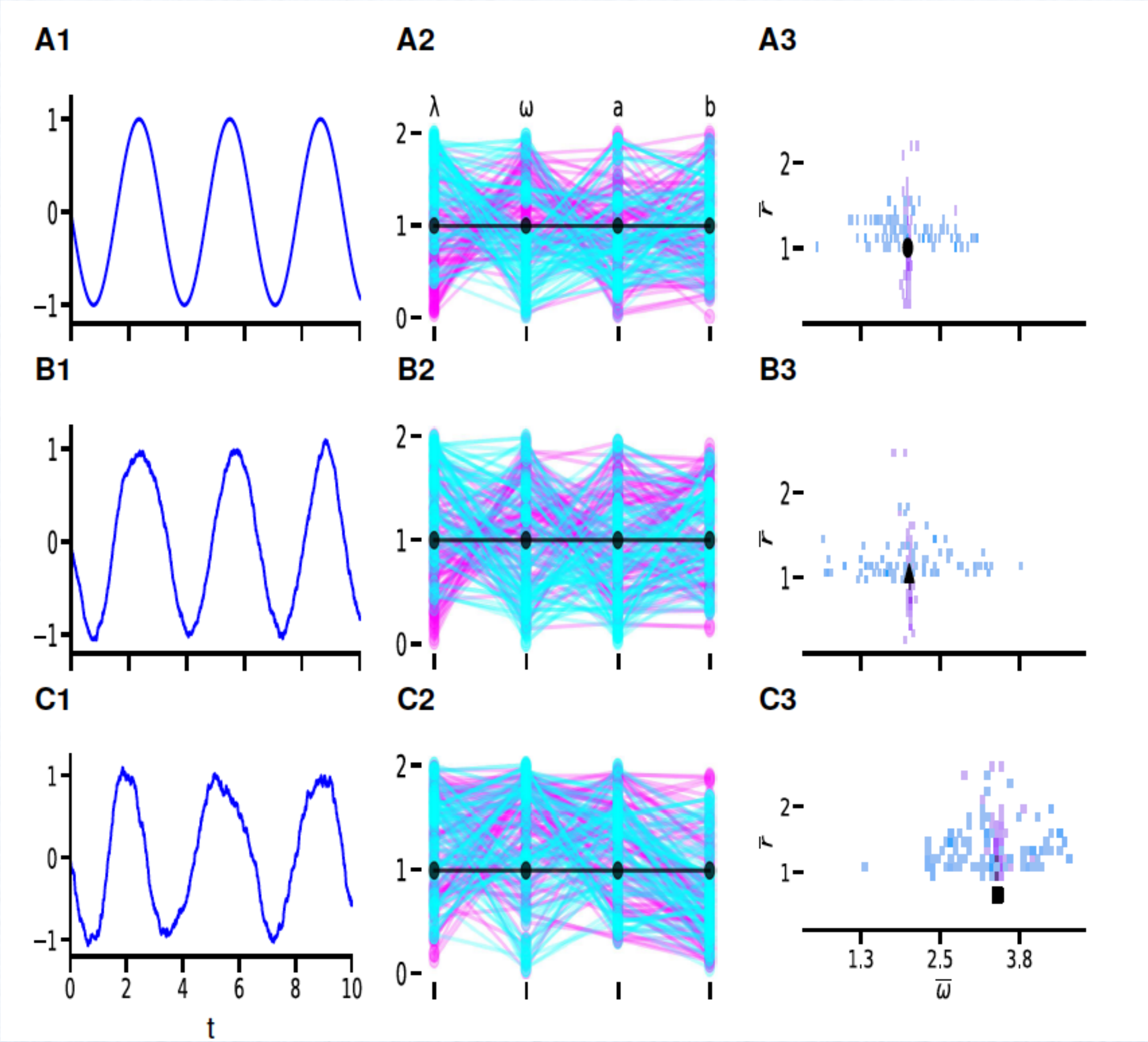
Degeneracy: canonical model

Parameter estimation algorithms: Genetic algorithm (GA) and Sequential Neural Posterior Estimation (SNPE)

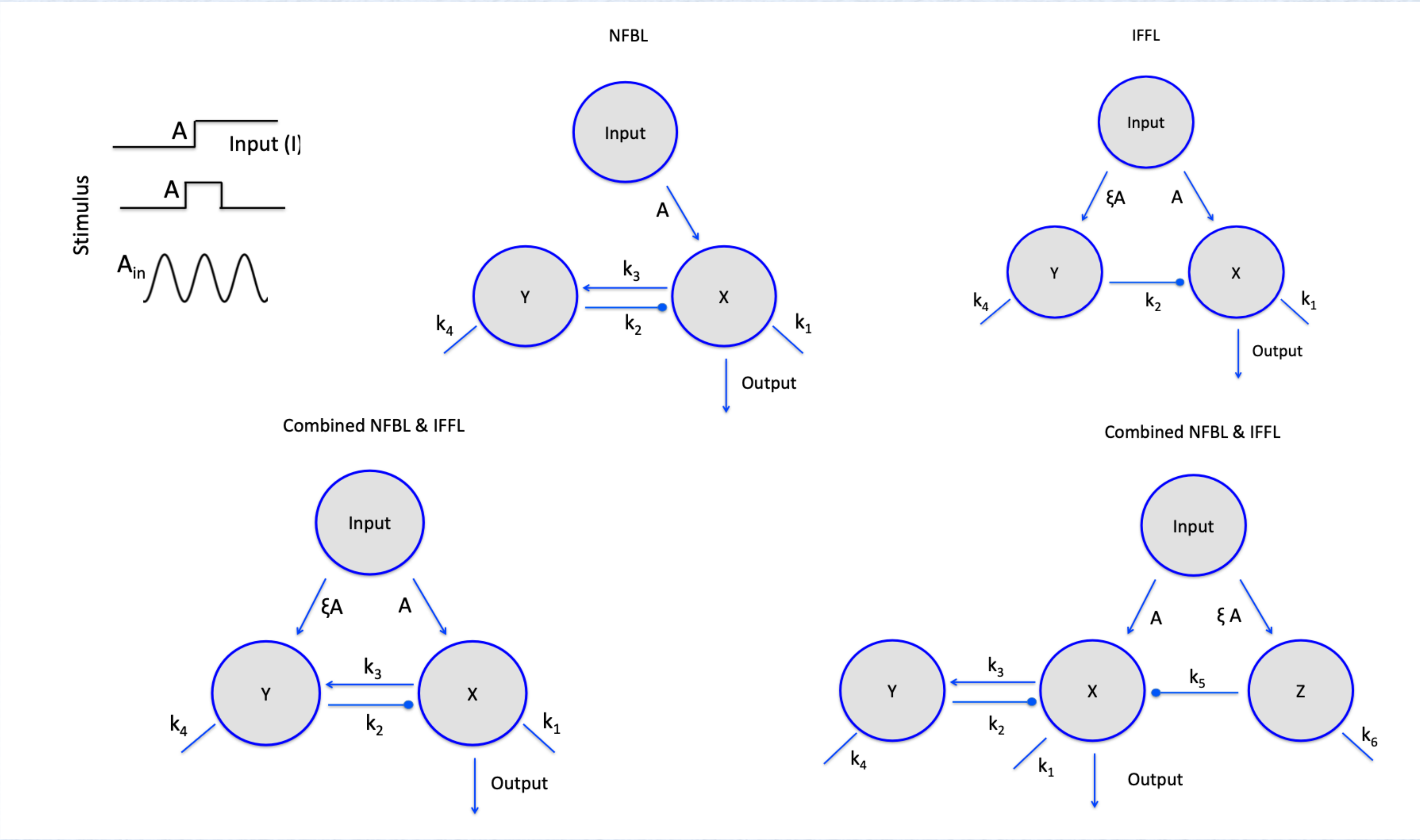


Degeneracy: canonical model

Parameter estimation algorithms: Genetic algorithm (GA) and Sequential Neural Posterior Estimation (SNPE)



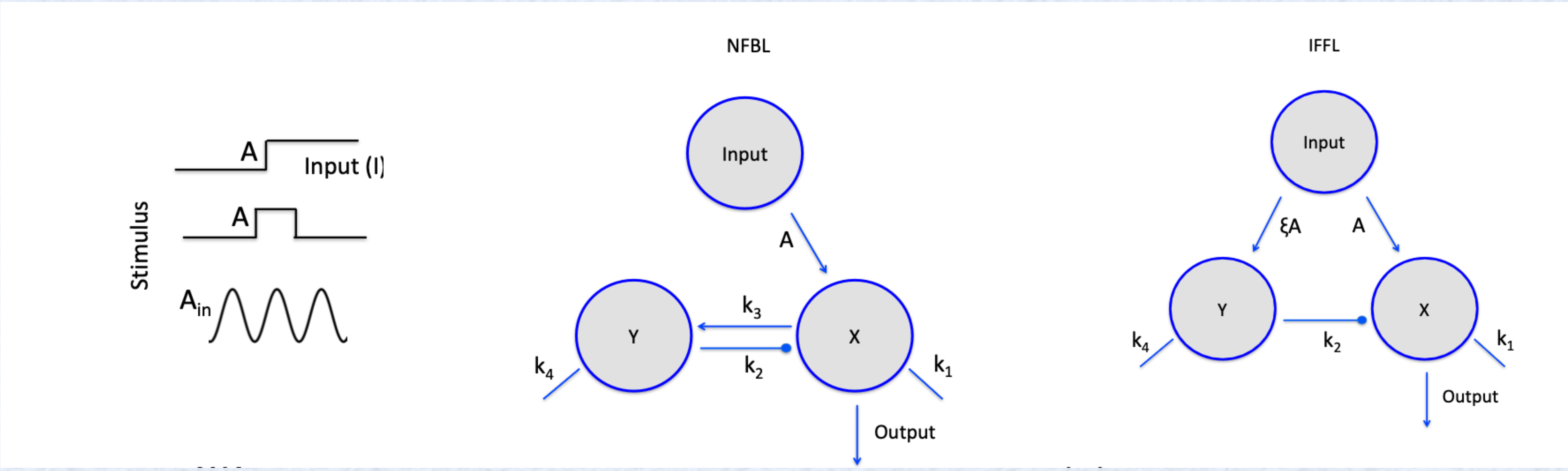
Degeneracy: NFBL & IFFL circuits



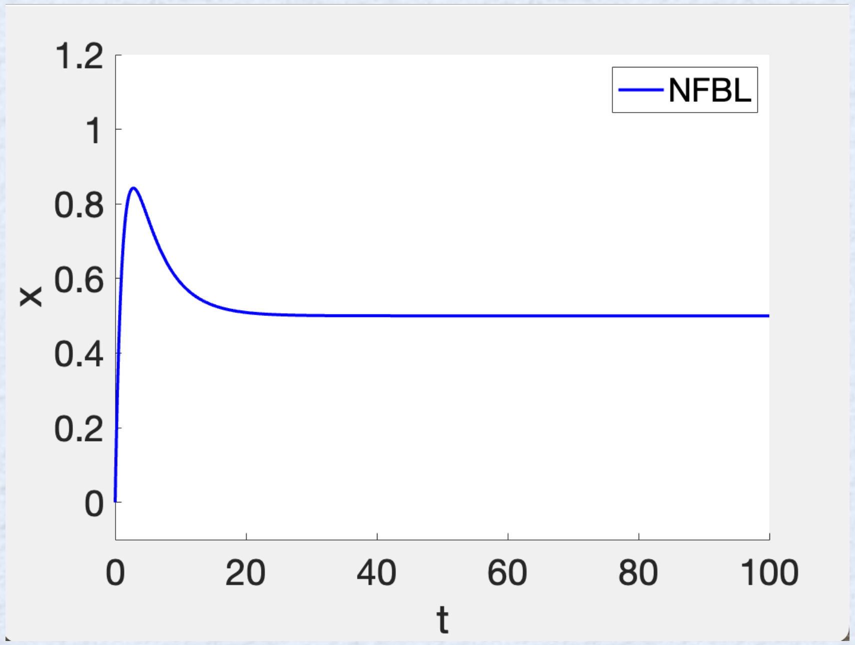
NFBL: Negative feedback loop

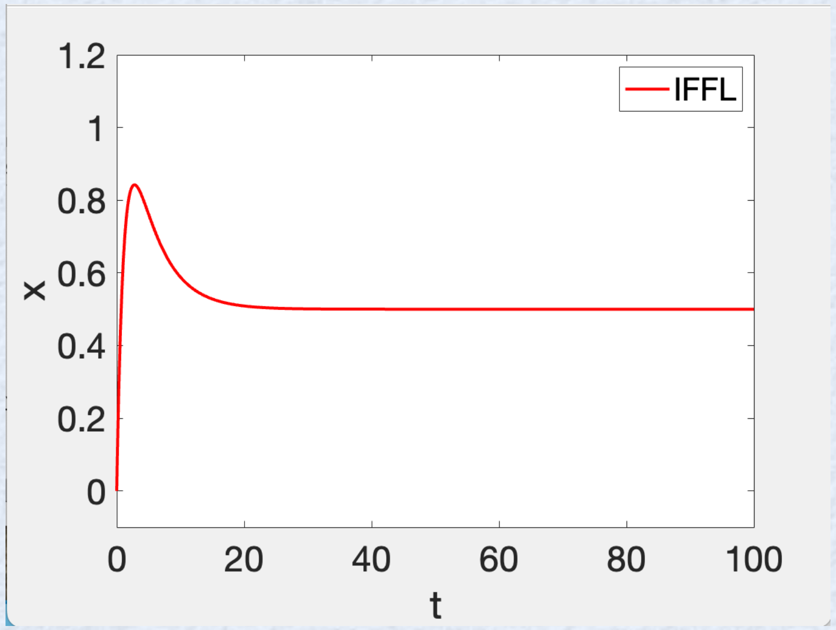
IFFL: Incoherent feedforward loop

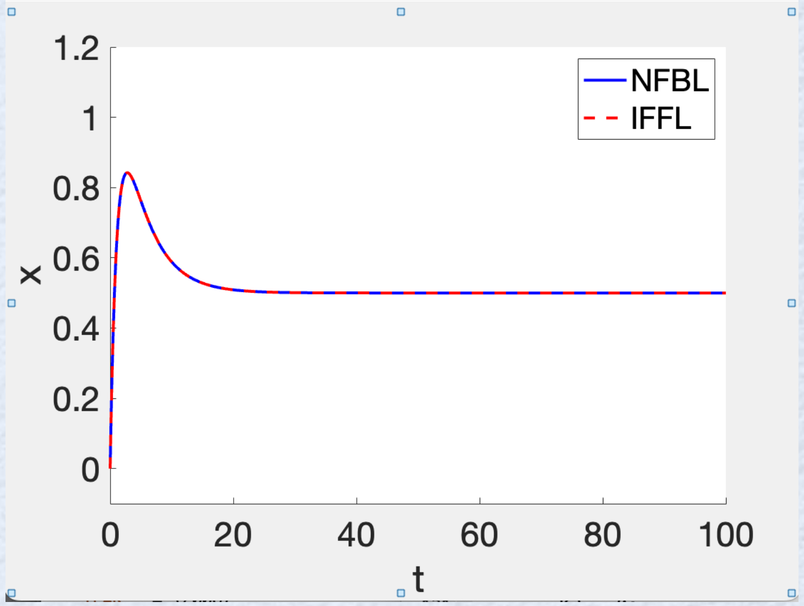
Degeneracy: NFBL & IFFL circuits



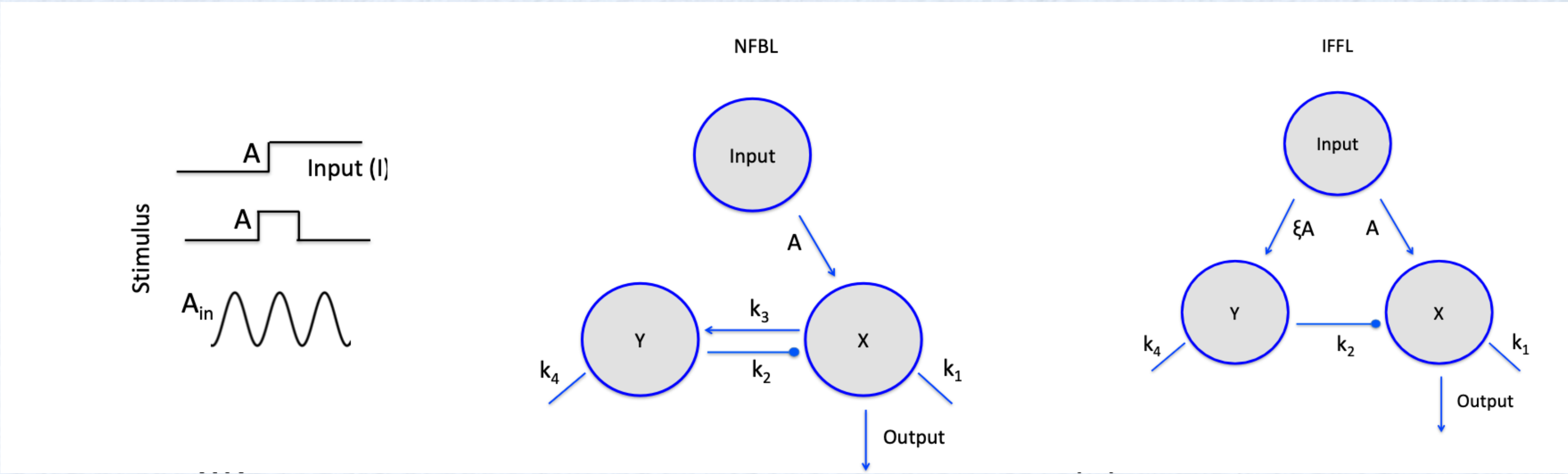
Responses to a constant input



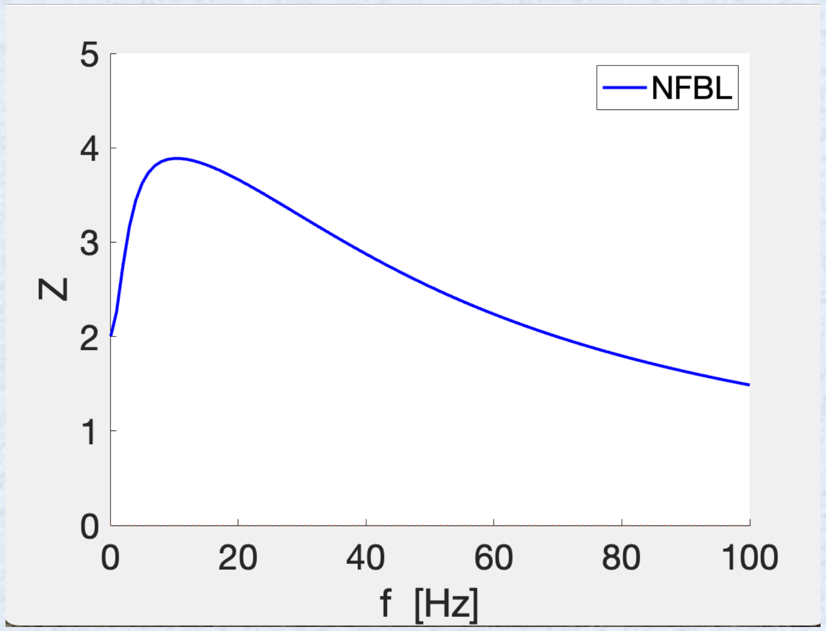


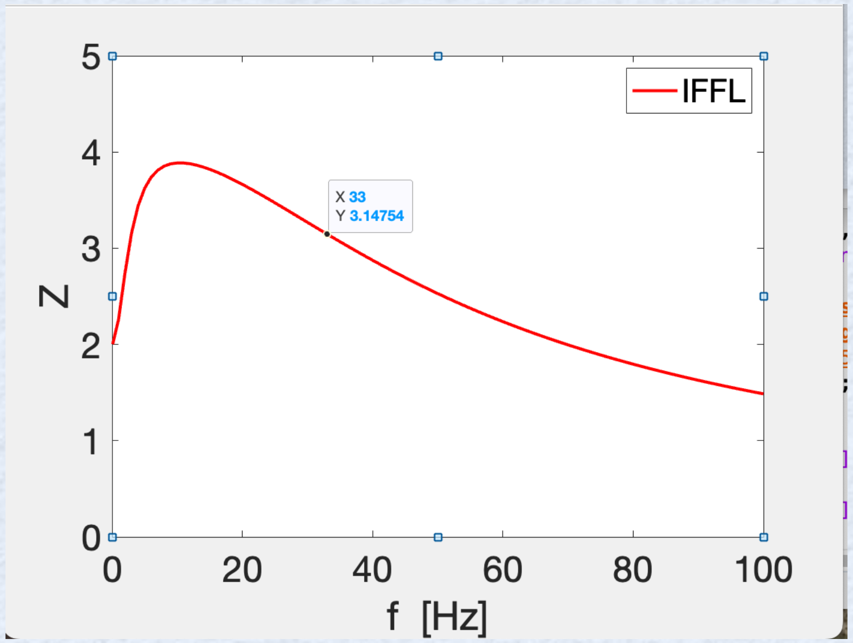


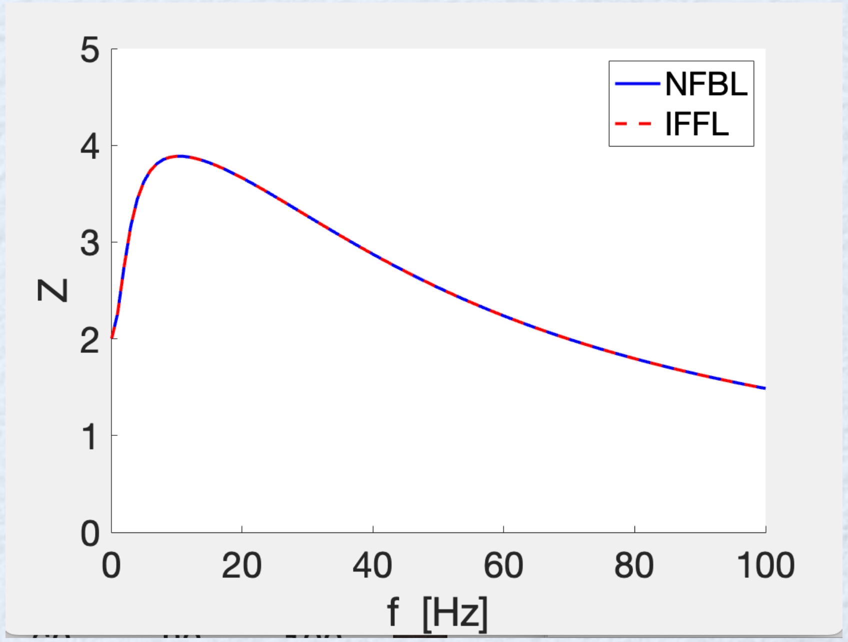
Degeneracy: NFBL & IFFL circuits



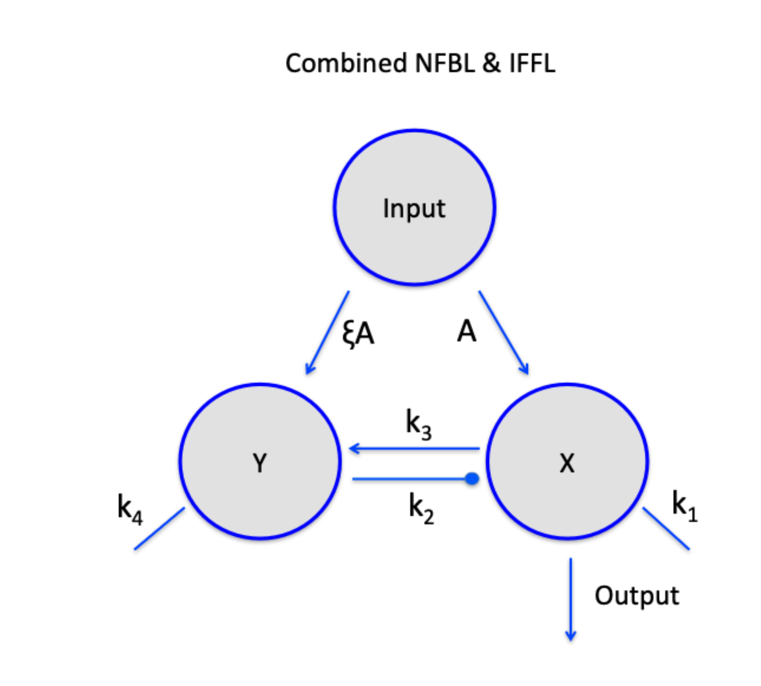
Impedance profiles (x): response to oscillatory inputs

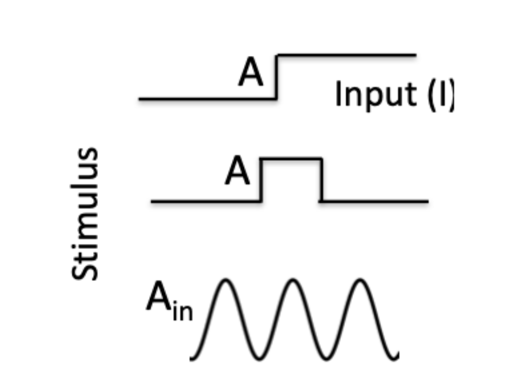






Degeneracy: NFBL & IFFL circuits





$$\frac{dx}{dt} = -k_1 x - k_2 y + A + A_{in}\sin(2\pi\omega t), \qquad x(0) = x_0,$$

$$\frac{dy}{dt} = k_3 x - k_4 y + \xi A + \xi A_{in}\sin(2\pi\omega t), \qquad y(0) = y_0,$$

$$\frac{d^2x}{dt} + b\,\frac{dx}{dt} + c\,x = Q,$$

$x(0) = x_0$ and $dx/dt(0) = -k_1 x_0 - k_2 y_0 + A,$

$$b = k_1 + k_4, \qquad c = k_1 k_4 + k_2 k_3 \qquad \text{and} \qquad Q = (k_4 - k_2\xi)A.$$

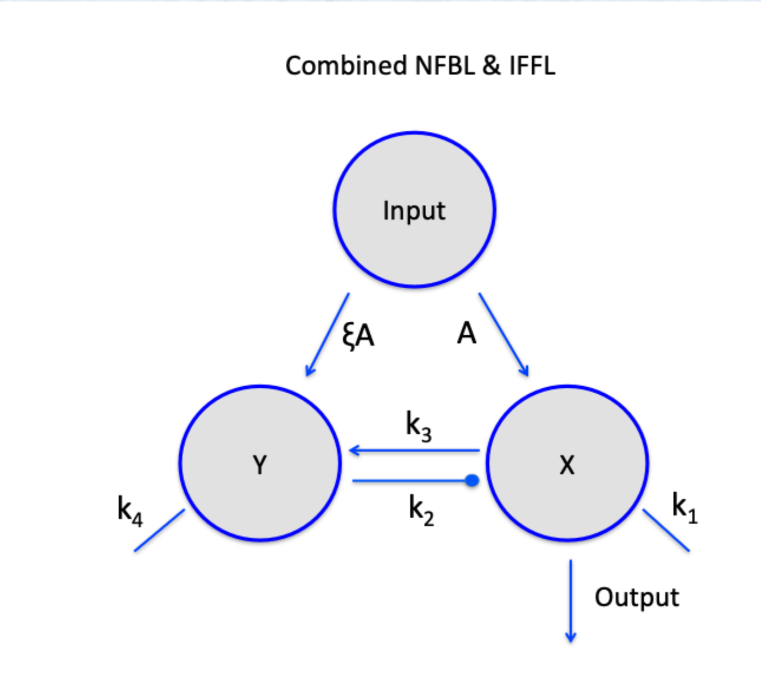
NFBL ($\xi = 0$),

$$b = k_1 + k_4, \qquad c = k_1 k_4 + k_2 k_3, \qquad \text{and} \qquad Q = k_4 A$$

IFFL ($k_3 = 0$)

$$b = K_1 + K_4, \qquad c = K_1 K_4, \qquad \text{and} \qquad Q = (K_4 - K_2\xi)A$$

Degeneracy: NFBL & IFFL circuits



Degeneracy within circuit types

NFBL ($\xi = 0$),

$$b = k_1 + k_4, \qquad c = k_1 k_4 + k_2 k_3, \qquad \text{and} \qquad Q = k_4 A$$

IFFL ($k_3 = 0$)

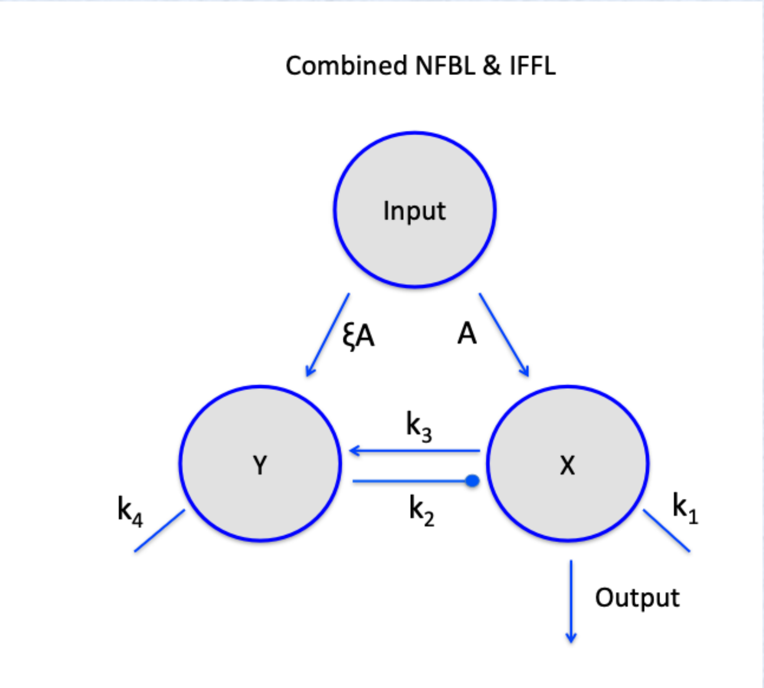
$$b = K_1 + K_4, \qquad c = K_1 K_4, \qquad \text{and} \qquad Q = (K_4 - K_2 \xi) A$$

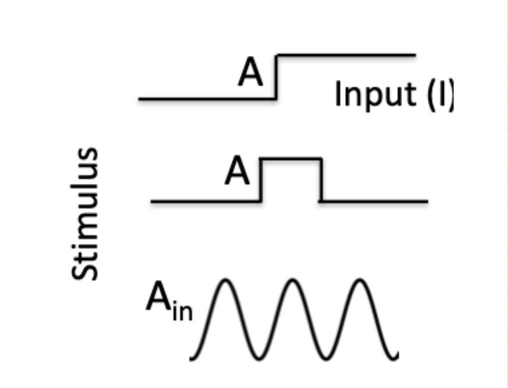
Degeneracy between circuit types

$$K_2 = \frac{K_4 - k_4}{\xi}, \qquad K_4 = b - K_1 \qquad \text{and} \qquad K_1 = \frac{b \pm \sqrt{b^2 - 4c}}{2}$$

$$k_4 = K_4 - K_2\,\xi, \qquad k_1 = b - k4, \qquad \text{and} \qquad k_2 k_3 = c - k_1 k_4$$

Degeneracy: NFBL & IFFL circuits





$$\frac{dx}{dt} = -k_1 x - k_2 y + A + A_{in} \sin(2\pi\omega t), \qquad x(0) = x_0,$$

$$\frac{dy}{dt} = k_3 x - k_4 y + \xi A + \xi A_{in} \sin(2\pi\omega t), \qquad y(0) = y_0,$$

$$\frac{d^2x}{dt} + b\,\frac{dx}{dt} + c\,x = Q,$$

$$x(0) = x_0 \text{ and } dx/dt(0) = -k_1 x_0 - k_2 y_0 + A,$$

$$b = k_1 + k_4, \qquad c = k_1 k_4 + k_2 k_3 \qquad \text{and} \qquad Q = (k_4 - k_2 \xi) A.$$

Degeneracy in the (observable) variable x in response to both constant and oscillatory inputs

If the impedance profiles in the variable x are degenerate, then noise cannot disambiguate (break the degeneracy)

Discussion

What we did and what we did not do/show

- ☑ We discovered a new type of structural unidentifiability / degeneracy in relatively simple models (canonical)
- ☑ Rich family of models that can display a variety of realistic patterns
- ☑ Degeneracy emerges from an “excess” of symmetries
- ☑ Unidentifiability is conceptually connected to the notion of degeneracy
- ☑ Breaking up degeneracy (identifiability) requires the development of new approaches combining experimental and theoretical tools
- ☑ Breaking these symmetries lads to more realistic models and maintain some, but not all the degeneracies
- ☑ These models can be used to ask fundamental questions about unidentifiability / degeneracy in relation to parameter estimation algorithms and machine learning tools
- ☑ How do we disambiguate by adding external perturbations? (for parameter estimation purposes)