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1 Introduction

The term degeneracy has two different and distinct meanings (Mason et al., 2015). Degeneracy in everyday language denotes deviance and decay, while degeneracy in scientific language is defined as the ability of elements that are structurally different to perform the same function (Tononi et al., 1999; Edelman and Gally, 2001). Neuronal degeneracy at the molecular scale is then defined as the ability for a same identified neuron to maintain the same electrophysiological features from different combinations of these components (*e.g.* ion channels). Abundance of experimental evidences, using RNA sequencing and other molecular measurements, reveal such properties (Goaillard and Marder, 2021). In a physiological context, degeneracy is known to endow the system with robustness: the impairment of one element can be compensated by another. This allows the system to have multiple pathways to achieve the same outcome. However, in a pathological context, degeneracy could prove to be a difficulty in the treatment of some neurological disorders, since targeting a specific element that contributes to the pathological behavior of the system could be compensated by other elements (Kamaleddin, 2021). For all these reasons, identifying all the underlying elements in a degenerate system appears today both crucial and challenging (Price and Friston, 2002; Kamaleddin, 2021).

Many valuable works deal with the concept of degeneracy from the computational and modeling perspective (Golowasch et al., 2002; Achard and De Schutter, 2006; Migliore et al., 2018; Alonso and Marder, 2019; Onasch and Gjorgjieva, 2020; Alonso and Marder, 2020) using conductance-based models (CBMs). Using optimization algorithms, such works determine various distinct set of parameters (*e.g.* different combinations of maximal conductances) of the CBM, for which the model behaves similarly or identically for some inputs. In this Perspective, we discuss such a

methodology to determine degenerate solutions. Our hypothesis is the following: *different solutions that behave identically or similarly do not guarantee that they are degenerate*. Then, we propose a necessary condition from the dynamical systems' viewpoint for different solutions of a CBM to be considered as degenerate: they should share the same *complete* bifurcation structure in their physiological range of functioning. To support our claims, neurons of the *C. elegans* worm are used as canonical examples. *C. elegans* is a well-known model organism in neuroscience with a relatively simple nervous system (White et al., 1986) that shares many general principles with more sophisticated ones (Chalasani et al., 2007).

2 Degenerate parametric solutions of a conductance-based model should endow the model with the same bifurcation structure

Neuronal development rules in *C. elegans* (Hobert, 2018; Taylor et al., 2021) imply that a same identified neuron always displays a qualitatively similar phenotype although quantitatively different from one measurement to another, partly due to multiple sources of intrinsic and extrinsic noises (Faisal et al., 2008; Destexhe and Rudolph-Lilith, 2012; Gerstner et al., 2014). This has a direct implication for degenerate solutions from the dynamical systems' viewpoint: degenerate solutions should exhibit the same bifurcation structure. Indeed, the qualitative changes that the model's behaviors undergo following a change in stimuli is explained by the appearance of bifurcations of the resting and spiking states. Therefore, the bifurcation structure of a neuron, that is, the set of bifurcations and their types that occur in the neuron, determines the neurocomputational properties of the excitable system (Izhikevich, 2000).

The conservation of the same bifurcation structure for the same identified neuron in *C. elegans* can be observed from the recently conducted electrophysiological survey on the non-spiking RIM, AIY and AFD neurons (Liu et al., 2018). Non-spiking neurons have the advantage of having bifurcation structures that are easy to analyze, directly from the steady-state current (Naudin et al., 2022). To sum up: (i) a monotonic steady-state current confers to the neuron a *near-linear* behavior (defined by smooth depolarizations or hyperpolarizations from the resting potential), and (ii) a N-shaped steady-state current endows the neuron with a *bistable* behavior (characterized by a voltage jump between the resting potential and a depolarized potential). The near-linear neurons do not exhibit bifurcations, while the bistable ones do display two saddle-node bifurcations, responsible for the voltage jump (Naudin et al., 2021). For the RIM, AIY and AFD neurons, numerous whole-cell current recordings have been carried out (RIM: n = 3; AIY: n = 7; AFD: n = 3) from which the steady-state currents were obtained (Liu et al., 2018)[1]. For each measurement, the steady-state current displays the same qualitative shape, allowing us to safely conclude that these neurons always display the same qualitative behavior. As a consequence, degenerate parametric solutions of a CBM of these neurons should endow the model with the

[1]Raw electrophysiological recording traces and data are available at https://doi.org/10.17632/tngf9w3pgd.1

same bifurcation structure. Based on a recent result by Naudin et al. (2022), we point out in the next section that different parametric solutions of the AFD neuron CBM (Naudin et al., 2020) that behave identically do not necessarily satisfy this condition.

3 Solutions displaying identical behaviors for some inputs are not necessarily degenerate

Reproducing the behavior of the neuron only for some inputs is not sufficient to capture the right underlying bifurcation structure of the neuron. Figure 1.A shows the experimental voltage behavior of the AFD bistable neuron of *C. elegans* (in green), against two different sets of parameters of the $I_{Ca,p} + I_{Kir} + I_{K,t} + I_L$-model (in blue). In both cases, the outcome of the solution overlaps the experimental voltages for the inputs used in the optimization process, *i.e.* inputs from -15 pA to 25 pA by 5 pA increments. When considering the resulting steady-state current of each solution in Figure 1.B, it can be observed that the first solution reproduces the experimental steady-state current well, while the second one deteriorates completely for stimuli higher than 25 pA which remain physiologically plausible stimuli, *i.e.* stimuli that the neuron is able to withstand (the neuron does not burst in response to these stimuli) (Liu et al., 2018). Since the steady-state current determines the bifurcation structure of non-spiking CBMs, this implies radically different bifurcation structures for the two solutions, displayed in Figure 1.C. Two saddle-node bifurcations occur for the first solution, whereas the second solution displays four saddle-node bifurcations. The existence of unexpected saddle-node bifurcations for the second solution explains the drastic and non-physiological rise of the membrane potential trajectory to a new stable state of aberrant higher voltage for $I > 28.4$ pA (Figure 1.D).

At first glance, we could have concluded that these two solutions were degenerate if we considered only their behaviors for stimuli used in the optimization process. Indeed, two different solutions behave identically in the training set (Figure 1.A). Nevertheless, a further analysis of their bifurcation structure shows us that these two solutions have a radically different behavior when novel stimuli are applied (Figure 1.D). The second solution exhibits two saddle-node bifurcations for high stimulus values, while the first does not. Therefore, their bifurcation structure is different (Figure 1.C). From then on, based on the previous section, their degenerate character can no longer be held.

The electrophysiological signature of a CBM is determined by the occurrence of its bifurcations (Izhikevich, 2007). And it is essential to keep in mind that *a bifurcation occurs at a local value of the bifurcation parameter (injection currents in our case), and this does not imply anything on the appearance of other bifurcations for other values of this parameter.* In other words, the occurrence of a same bifurcation in a given value of the bifurcation parameter for different solutions does not imply that these share the same bifurcations for other values. We observe that numerous existing works omit this basic point by building solutions with identical behavior for a limited

set of stimuli, making the erroneous implicit assumption that similarity in their behaviors for other biologically relevant inputs naturally follows. This point cannot be overlooked in view of the complexity of CBMs that we discuss in the next section.

4 Complexity of models and degenerate parametric space

CBMs are complex models in the sense that they exhibit strong nonlinearities with a large number of equations and parameters. Therefore, CBMs with a high number of ion channels have a high dimensionality in their parametric solution space. This has an important consequence for the determination of degenerate solutions: the more complex the model is, the greater is the ability for the optimization algorithm to find various solutions in the parametric space that behave similarly, as complex as we want, for some inputs. As an example, Onasch and Gjorgjieva (2020) found 750 apparent parameter solutions that have a significant degree of degeneracy, and about 400 000 solutions for Prinz et al. (2004). Nevertheless, how many solutions among them are really degenerate, or even just viable for the system? Indeed, the complexity of CBMs has its common downside as previously seen: it increases the probability that these solutions exhibit radically and qualitatively different behaviors, likely aberrant, when confronted with novel stimuli not considered during the parameter calibration stage (Naudin et al., 2022; Druckmann et al., 2011; Gerstner and Naud, 2009). This concern is classically referred to as the generalization capability. Figure 2 proposes a diagram of a parametric space in which degenerate and non-degenerate solutions coexist. If we consider a restricted training set of stimuli, the optimization algorithm will produce many parameter combinations that are falsely degenerate, behaving identically for that set of stimuli but unable to generalize the neuron responses for other stimuli. In fact, we propose that the set of degenerate solutions will be a subset of these solutions that share the same bifurcation structure.

This proposition is in agreement with many computational works studying how various features of the target data provide different constraints on model parameters. As an example, using a machine learning tool to perform Bayesian inference on the Hodgkin–Huxley model parameters, Gonçalves et al. (2020) show that as more features of the data to be fitted are used, the more the posterior distribution of estimated parameters is centered on the ground truth parameters. Furthermore, simulations of the posterior solutions match the observed data only in the features that have been taken into account in the parameter estimation procedure. For instance, applying optimization algorithms to fit spike counts alone only identifies parameters that produce the correct number of spikes, but for which the timing of the spikes and the time course of the subthreshold voltage are incorrect (Gonçalves et al., 2020). This again shows that capturing a given phenomenology does not necessarily imply that other quantitative and qualitative characteristics of the dynamics are captured at the same time.

Beyond the characteristics of the electrical signal, neurons and neural systems are subject to many additional constraints to maintain good neural coding, such as the requirement to be

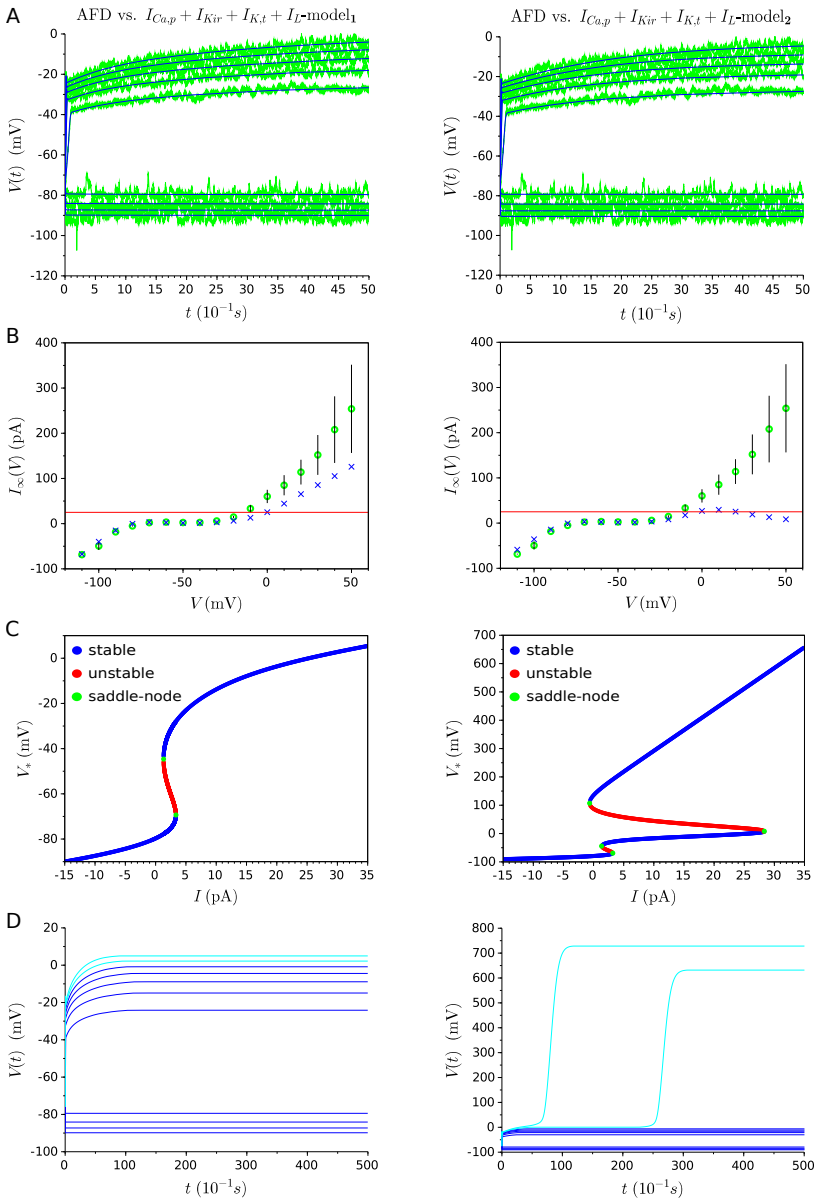

Figure 1: **Two apparent degenerate solutions that are not**. **(A)** Two different set of parameters of the $I_{Ca,p}$+I_{Kir}+$I_{K,t}$+I_L-model (represented in blue) overlap the AFD experimental voltages (represented in green) for a series of current injection starting from −15 pA and increasing to 25 pA by 5 pA increments. **(B)** Experimental steady-state current (green circles) against estimated steady-state currents (blue crosses). The experimental steady-state current results from voltage-clamp experiments, while the estimated steady-state currents result from the fitting of membrane potentials evolution in (A). The red line is associated with a stimuli of 25 pA. **(C)** Bifurcation diagram for each model. **(D)** Dark blue curves represent the evolution of voltages for the same values of current injection than in (A) (*i.e.* stimuli starting from −15 pA and increasing to 25 pA by 5 pA increments), whereas light blue ones represent the change of voltage traces for novel stimuli (30 pA and 35 pA). Results have been reproduced from Naudin et al. (2022) with the consent of the authors.

energy efficient (Hasenstaub et al., 2010). By adding such metabolic efficiency constraints to select acceptable degenerate solutions from tens of thousands that match the experimental data of the pyloric network model, Deistler et al. (2022) show that some conductance values need to be more strongly constrained. This significantly reduces the number of candidate degenerate parameter sets. Moreover, it is worth noting that the metabolic cost is only one of many properties that the neurons or the neural systems must regulate. Additional constraints are protein levels, osmolarity, pH, etc., and the neuron faces the challenge to coregulate all these properties simultaneously. In this regard, Yang et al. (2022) show that tuning an ion channel to regulate one property risks disrupting other properties. Moreover, they show that only a few combinations of ion channels that produce the target value for one property also produce the target value for a second property, thus further restricting the set of acceptable possible degenerate parametric solutions of a CBM.

Finally, even though some recent works use the generalization capability as an essential criteria to select acceptable CBM solutions reproducing raw data (Druckmann et al., 2011; Markram et al., 2015; Gouwens et al., 2018; Iavarone et al., 2019; Naudin et al., 2022; Schürmann et al., 2022), it remains that these works seem to represent only a small part of the existing studies. This can be surprising at least in one way, when compared with the methodology used in artificial intelligence (A.I.). In this field, the selection and adoption of a solution is almost systematically based on the ability of this solution to predict new data unused in the parameter estimation procedure (Le Cun, 2019). If the notion of *overfitting* is omnipresent in A.I., it seems to us that it is still too little taken into account in computational neuroscience to select viable solutions, in particular degenerate solutions, even though the objective of both fields is often similar to some extent: tuning the parameters of a model to reproduce a set of data or target behaviors, in order to gain insight into their underlying mechanisms (Alexandre et al., 2020; Macpherson et al., 2021).

5 Summary

In this Perspective, we argued that different parameter solutions of a CBM that behave identically or similarly for a given set of stimuli are not necessarily degenerate. In other words, the fact that solutions share the same phenomenology for a restricted set of stimuli is not sufficient to conclude that they are degenerate, since their behavior could be qualitatively divergent for other stimuli. To put it simply, the take-home message is that we should not conclude that solutions are degenerate because they look degenerate. Thus, from the dynamical systems' viewpoint, for different solutions to be considered as degenerate, we proposed the following necessary condition: degenerate solutions should share the same *complete* bifurcation structure in their physiological range of functioning. To verify such a condition, the development of automated procedures and tools to determine the complete bifurcation structure of CBMs could be of valuable help.

Finally, degeneracy is an unifying subject which allows the convergence and the use of knowledge and expertise from different scientific fields to deepen our understanding: experimental and

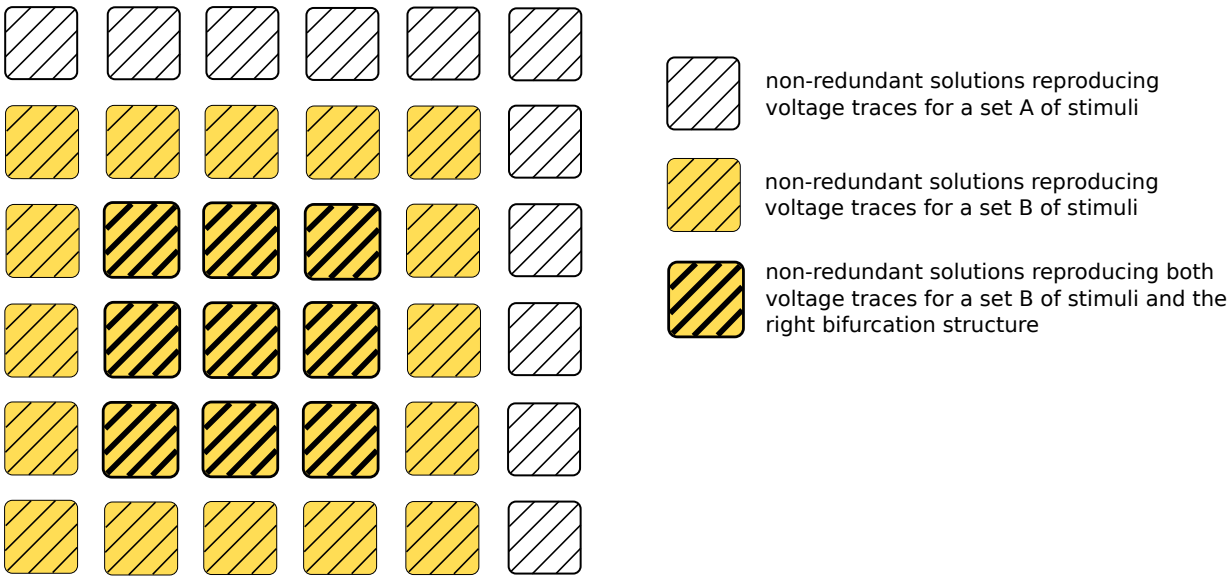

Figure 2: Diagram of degenerate and non-degenerate solutions in the parameter solution space. Each square is a local (possibly global) minimum of this space, representing one parametric solution of a CBM that reproduces the neuron behavior. In particular, the striped squares represent all the different solutions that reproduce the neuron behavior for a set of stimuli A, while the yellow striped squares are solutions that capture its behavior for a set of stimuli $B \supset A$ (*i.e.* a larger set than A). A reduced number of solutions should be obtained for the set of stimuli B. Indeed, some parametric solutions that allow the model to correctly reproduce the behavior of the neuron for a restricted set of stimuli (A) are unable to capture its behavior for larger sets of inputs (B), as in the example shown in Figure 1. In other words, the larger the stimulus set, the smaller the number of solutions obtained. Finally, we propose that the viable and degenerate solutions of the system are those that share the same bifurcation structure, represented by yellow striped squares in bold.

theoretical biologists, mathematicians, computer scientists, and so on. As of today, these complementary viewpoints appear to be necessary. Indeed, to quote Grothendieck (2022), *"it is when the complementary viewpoints on the same reality combine that, thanks to the multiplication of such "eyes", our penetrating gaze can gain a better understanding of the true nature of things. The more complex and rich that reality we wish to understand proves to be, the greater the need is for several "I / eyes" that can provide a more extensive and subtle appraisal thereof."*

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Declaration of Competing Interests

The authors declare no competing interests.

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