Resolving degeneracy in a neuronal dynamic model via transient activation in response to perturbations: Examination of different metrics

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In a scientific context, degeneracy refers to the idea that several scenarios (e.g., mechanisms, structures, network architectures) produce the same experimental or observational outcome [1] [2]. Therefore, the inverse function mapping these data back to the original scenarios is not injective, and consequently they cannot be uniquely determined.

Biologically, degeneracy is associated with the notions of system complexity and variability [3], allowing the system to develop robustness to external factors and adaptability, but obscuring the multi-stranded relationships between cause and effect for the observer, which can lead to apparent indeterminacy and failure of the average [4].

Mathematically, the parameters of a putative model proposed to describe or explain a dataset are unidentifiable [5] [6]. This is linked to the idea of mathematical indeterminacy, where a system possesses multiple solutions. In the case of parameter estimation, these solutions are not the values of the variables that satisfy the system for a fixed set of parameters, but rather the parameter values that satisfy the system for a given dataset.

In this project, we view the notions of degeneracy and unidentifiability as two faces of the same coin. We focus on dynamic models using differential equations. In this context, degeneracy can be thought of as a constraint imposed by the "amount of information" that can be extracted from a dataset and the number of parameters governing the dynamics that one wishes to identify (once parameter redundancy has been eliminated). This raises a mathematical questions regarding the relationship between the mathematical structures of both the information present in a given dataset and the models, as well as the metrics required to disambiguate degeneracy in the presence of system perturbations.

In this work, we address these issues using a simple spiking neuronal model that exhibits an unequivocal case of degeneracy: the *leaky integrate-and-fire* (LIF) model [7]. Briefly, this model describes the dynamics of the voltage V in the presence of an intrinsic current I_L (with maximal conductance G_L and resting potential E_L) and a constant external current I_{app}. The subthreshold dynamics are described by

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

where C is the cellular membrane capacitance. When the voltage reaches a threshold value V_th, a spike (action potential) is said to occur and immediately after that the value of V is reset to a value $V\_rst < V\_th$ and the dynamics resume following the previous equation. The spiking dynamics are not explicitly modeled in this framework, only the spike time is recorded.

Typically, one has access to a sequence of interspike intervals (ISIs) from which one can compute the firing rate (in the simplest case, they are reciprocal quantities and the firing rate is equivalent to the frequency). We found the firing rate patterns of the LIF model exhibit degeneracy. Assuming that the transient dynamics do not exhibit the same type of degeneracy, we hypothesize that perturbations to the model would reduce, if not resolve, the degeneracy (and decrease or eliminate the model's unidentifiability).

To test this hypothesis, we proceed as follows: (i) we identify a series of N (different and well-distributed) parameter sets that produce firing patterns with the same (constant) frequency in the absence of noise, (ii) for each of these parameter sets, we simulate the firing patterns in the presence of white noise and calculate the corresponding firing rate patterns, which now exhibits a certain degree of variability depending on the noise variance, (iii) we compare the results using different metrics (distances, divergences), (iv) we evaluate which aspects of the differences between firing patterns are captured by each of the metrics [8].

The chosen metrics are based on the geometry of the firing patterns (Victor-Purpura [9] , Van Rossum [10]) and on the structure of the probability distribution of the firing rate patterns approximated by the corresponding histograms (Wasserstein, Kullback-Leibler, Hellinger).

Our results allow us to understand how each of the proposed metrics and their combinations contribute to reducing the degree of degeneracy of the model, and therefore increase the degree of identifiability, and to generate hypothesis for more complex models.

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