Journal of Neuroscience Methods 206 (2012) 151–157

Contents lists available at SciVerse ScienceDirect

Journal of Neuroscience Methods

journal homepage: www.elsevier.com/locate/jneumeth

Basic Neuroscience

Direct interaction with no correlation: An experimental pitfall in neural systems

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ARTICLE INFO

Article history:
Received 16 December 2011
Received in revised form 11 February 2012
Accepted 14 February 2012

Keywords:
Correlation
Interaction
Dynamical systems
Steady-state
t-test
ANOVA
Generalized linear model (GLM)

ABSTRACT

Neural systems continuously optimize how organisms process their environment and are highly dynamic. Building predictive models of these systems is challenging due to the large number of their elements. Therefore, in experimental and descriptive neurobiology the researcher typically does not seek to catalogue all variables that affect one another, but rather tries to isolate variables that interact directly. Because of methodological limitations, observed variables are often measured near equilibrium. The presented analysis demonstrates that statistical tests performed on such equilibrium values are fundamentally incapable of detecting direct interactions in a large subset of simple dynamical systems. Some of these problems can be avoided by using explicit statistical models that include time as a variable.

1. Introduction

At all organizational levels, biological systems tend to be highly dynamic. This property lies at the core of their self-organization and self-maintenance that are driven by irreversible processes, or the "arrow of time" (Nicolis and Prigogine, 1989; Prigogine, 1997). Neural systems take this time-dependence to the next level, since their very function requires that they continuously update themselves in evolving and even stable environments.

This presents great challenges for experimental neuroscience which seeks to isolate neural system elements that directly affect one another. These elements can be molecules, cells, or entire brain regions. Due to the complexity of neural systems, often entire studies are devoted to the demonstration of a single hypothesized link. Fundamentally, this approach reveals functional networks that are analogous to anatomical or social networks and can be formalized as graphs, in which each node (vertex) represents an element of the system and each link (edge) represents a direct causal link between two elements (Fig. 1). The mathematical graph theory has already provided new insights into the organization of neural systems, such as their small-world properties (Buzsáki, 2006; Hagmann et al., 2008; Feldt et al., 2011; Hu et al., 2011; Power et al., 2011; Sporns, 2011; Wig et al., 2011).

Why does current methodology place so much emphasis on direct effects? If a neural system was given sufficient time, it is likely that any of its elements would eventually affect any of its other elements (Fig. 1A). This conclusion follows from the almost trivial observation that biological systems are complex, adaptive, and dynamic (Meehl, 1967; Gros, 2008). The distinction between indirect and direct effects is important because indirect effects can be highly sensitive to the current state of other elements in the system. While indirect effects may be useful in some standardized applications (e.g., in a clinical setting), they cannot be expected to generalize to other, untested conditions. In contrast, direct effects are relatively insensitive to the current state of other elements that do not participate in the process. Therefore, direct effects are superior to other effects in that they can segment a complex system into simpler, independent components. The knowledge of direct links among elements is especially important if the researcher seeks to model the system and predict its behavior in situations that have never been studied experimentally. It is understood that such flexible control will eventually require information about how directly interacting elements affect each other in time, or about the dynamics of the entire network (Palsson, 2006; Barrat et al., 2008; Feldt et al., 2011).

This sequential approach implicitly assumes that one can make a complete inventory of direct connections among the system's elements and deal with their dynamic relationships later. The first part of this program is typically carried out by experimentalists who seek black-or-white *P*-values (and who rarely present the numerical estimates of the underlying model). The second part is typically

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doi:10.1016/j.jneumeth.2012.02.012

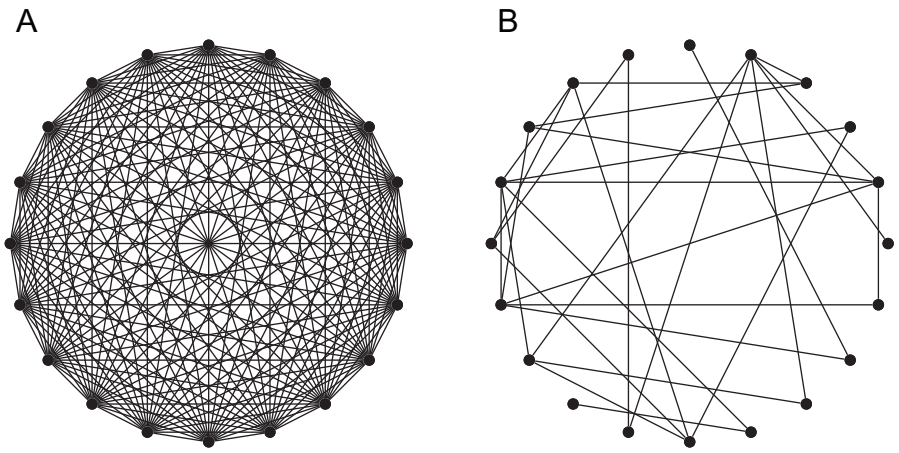

Fig. 1. In a neural system, any element can affect any element if the system is given sufficient time. Such indirect interactions are the "expected" and carry little information for fundamental neuroscience (A). Controlled experiments can show that some of the effects are indirect, thus reducing the system to a network of direct effects that are relatively independent of one another (B).

left to theoretical neuroscientists (e.g., Izhikevich, 2007). The following analysis shows that this program is deeply flawed in that a large proportion of direct interactions among elements can elude experimental detection unless their temporal dynamics is considered. Conversely, time-independent statistical tests cannot provide proof that elements do not directly interact. These problems cannot be solved by simply using large samples, but they can be greatly alleviated by proper care in experimental designs and analyses.

2. Methods

In experimental neuroscience, variables are typically controlled by the researcher or measured near equilibrium to avoid rapid transients and/or repetitive invasive procedures. The relationships among the variables are then investigated with standard statistical tests (the *t*-test, ANOVA, or other types of regression). Since these statistical tests are based on correlation, the researcher effectively assumes that if two variables interact, their values can be expected to strongly correlate. However, it can be demonstrated that if a system is measured at equilibrium and its two variables interact directly, their correlation can take on any value (including zero). Importantly, these values are theoretically exact and are not related to the statistical power of the sample.

The equilibrium value of one variable cannot *directly* affect the equilibrium value of another variable because it would imply an instantaneous communication between entities located at different points on the time continuum. Such assumptions may be acceptable in practical applications, but they are fundamentally incapable of giving an accurate description of reality. A variable can only have an effect on the *trajectory* of another variable; in particular, a change in one variable can make another variable move from its current equilibrium (with time, the second variable can stabilize at another value).

Based on these considerations, a direct interaction between two variables (X and Y) can be formalized as follows:

$$\frac{dX}{dt} = f(X, Y) \text{ and } \frac{dY}{dt} = g(X, Y) \quad (1)$$

where dX/dt and dY/dt are the rates of change of X and Y, respectively, and f and g are some functions of the two variables.

In experimental and descriptive research, the relationship between two variables is studied by observing the system's behavior as it undergoes artificial or natural perturbations. Both of these scenarios are examined.

All numerical simulations were carried out in Mathematica 8 (Wolfram Research, Inc.). For the analysis of two-dimensional stochastic systems, a closed-form solution was used (Gardiner, 2010). The simulation code is available in Supplementary Material.

3. Results

3.1. Direct interaction with no correlation in descriptive research

In descriptive research, perturbations are produced by genetic and environmental factors. If the simplest, linear interaction is assumed, one obtains

$$\frac{dX}{dt} = a_X + a_{XX}X + a_{YX}Y \text{ and } \frac{dY}{dt} = a_Y + a_{YY}Y + a_{XY}X \quad (2)$$

where all a's are coefficients. Note that if $a_{YX} \neq 0$ or $a_{XY} \neq 0$, it immediately implies that X and Y interact.

Two natural scenarios are considered, both of which lead to qualitatively similar conclusions. In the first scenario, X and Y are sampled in a population in which all coefficients vary slightly from individual to individual around their population means. In biological systems, such variability of parameters can be due to genetic polymorphisms of receptors, transporters and ion channels, accumulated memory, and other factors. If the only available information is that X and Y interact, the correlation between their equilibrium values can fall anywhere between −1 and 1, including zero (Fig. 2A). This finding continues to hold if only strong interactions between X and Y are allowed (Fig. 2B) and if the coefficient of variation (the standard deviation divided by the mean) is allowed to randomly vary among the coefficients (Fig. 2C and D).

In the second scenario, X and Y are sampled in a population in which the coefficients are constant in all individuals, but the equilibrium values of X and Y in each individual are continuously perturbed by random noise. A formal description of this situation is given by the stochastic Ornstein-Uhlenbeck process (Gardiner, 2010). Again, the correlations between the X and Y values cover the entire range from −1 to 1 and appear to be nearly uniformly distributed if the ends of the interval are excluded (Fig. 2E and F).

These results demonstrate that, if only equilibrium values are used, a direct and strong interaction between two variables can

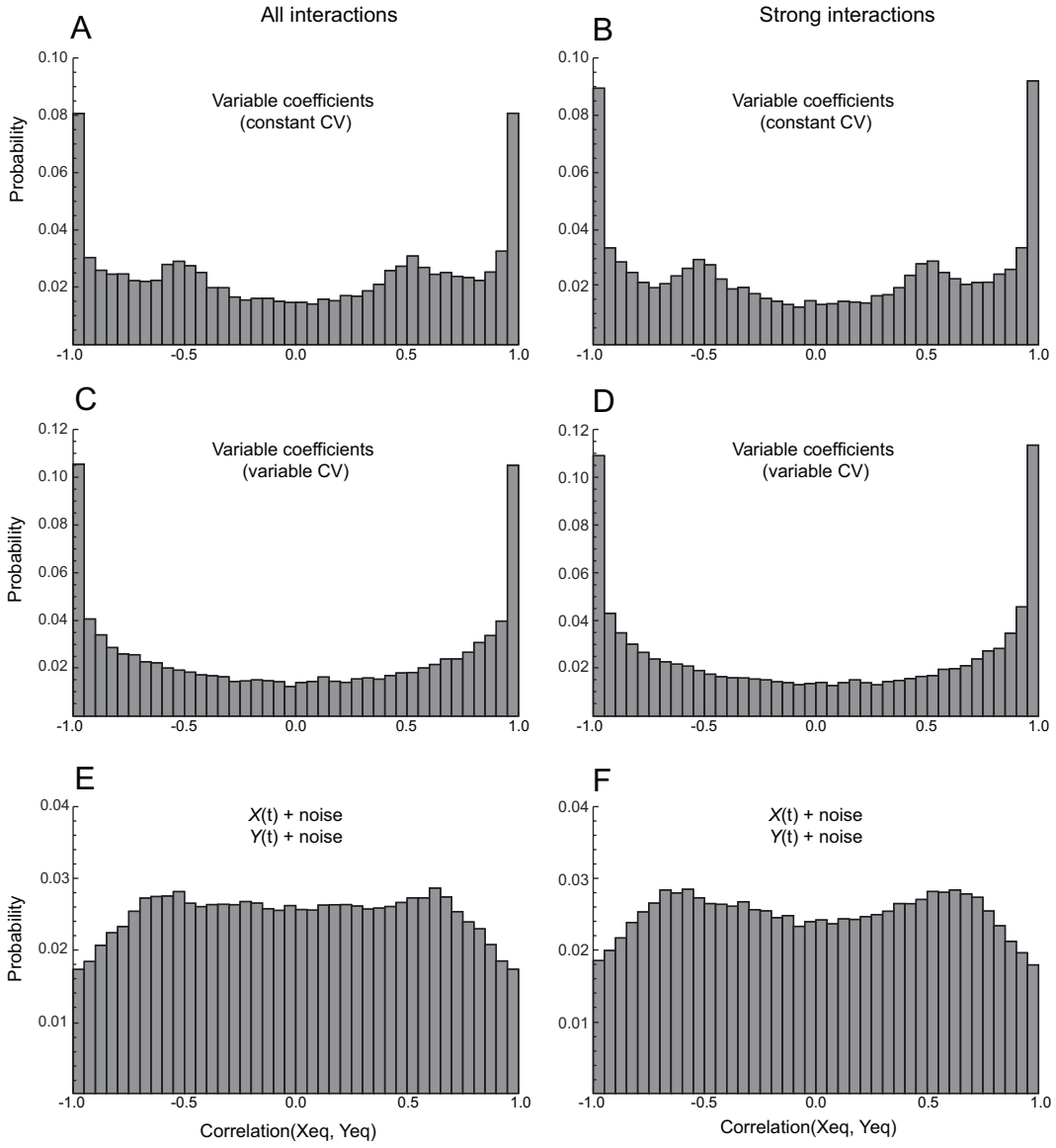

Fig. 2. The distribution of the correlation coefficients between the equilibrium values of two interacting variables (X and Y) in randomly generated linear dynamical systems (25 000 in A–D and 100 000 in E and F). Each system was generated by assigning each a-coefficient (Eq. (2)) a random value from the uniform distribution on the interval $[-1, 1]$, and only stable systems were used (i.e., the real parts of both eigenvalues had to be negative). In A, C and E, no other restrictions were placed on a_{YX} and a_{XY} (the "all interactions" condition). In B, D and F, an additional restriction was placed on a_{YX} and a_{XY}: at least one of them had to be greater than or equal to 0.4 (the "strong interactions" condition). In A–D, the correlation for each system was obtained by allowing each coefficient to independently vary around its original value (m) according to the normal distribution with the mean = m and the standard deviation = 0.05 m (A, B) or the standard deviation = αm (C, D), where α was assigned (for each coefficient of the system) a random value from the uniform distribution on the interval [0,0.10]. Therefore, the coefficient of variation (CV) was the same for all coefficients in A and B, but varied among the coefficients in C and D. In A–D, the correlation coefficient of a system was estimated by analytically calculating the X and Y equilibrium values after 300 perturbations (for technical details, see Janušonis, in press). In E and F, the values of X and Y were perturbed around the equilibrium with random noise and were modeled as a multivariate Ornstein-Uhlenbeck process $d\mathbf{V} = -\mathbf{A}\cdot\mathbf{V}dt + \mathbf{B}\cdot d\mathbf{W}(t)$, where $\mathbf{V} = \{X, Y\}$, $-\mathbf{A}$ is a square matrix $\{\{a_{XX}, a_{YX}\}, \{a_{YY}, a_{XY}\}\}$ generated as described above, $\mathbf{B}$ is a diagonal matrix with its diagonal elements independent and uniformly distributed on the interval [0,2], and $\mathbf{W}(t)$ is the Wiener process. The stationary covariance matrix was analytically calculated by using a closed-form expression available for the two dimensions (Gardiner, 2010); $[(\mathrm{Det}\mathbf{A})\mathbf{B}\cdot\mathbf{B}^{\mathrm{T}} + (\mathbf{A} - (\mathrm{Tr}\mathbf{A})\mathbf{I})\cdot\mathbf{B}\cdot\mathbf{B}^{\mathrm{T}}\cdot(\mathbf{A} - (\mathrm{Tr}\mathbf{A})\mathbf{I})^{\mathrm{T}}]/2(\mathrm{Tr}\mathbf{A})(\mathrm{Det}\mathbf{A})$, where Det$\mathbf{A}$ and Tr$\mathbf{A}$ are the determinant and trace of $\mathbf{A}$, respectively, and $\mathbf{I}$ is the 2×2 identity matrix). Note that the scales of the Y-axes are not the same in A–F.

be fundamentally undetectable (i.e., it can consistently yield zero-correlations irrespective of the sample size).

3.2. Direct interaction with no correlation in experimental research

In experimental research, a system is typically strongly perturbed by transiently or permanently "clamping" one variable at a certain value (or a series of values), and allowing other variables to freely settle down to their new equilibrium values. If the system is pushed far away from its equilibrium (a typical situation in experimental science), the function g (Eq. (1)) can be approximated by a Taylor series with some of the higher order terms:

$$\frac{dY}{dt} = a_Y + a_{YY}Y + a_{XY}X + a_{(YY)Y}Y^2 + a_{(XX)Y}X^2 + a_{(XY)Y}XY + (\mathrm{hot}) \tag{3}$$

where all a's are coefficients and (hot) denotes still higher order terms that may be important (e.g., Y^3, XY^2, with appropriate coefficients). Note that if $a_{XY} \neq 0$ or $a_{(XX)Y} \neq 0$ or $a_{(XY)Y} \neq 0$, it implies that X and Y interact. The importance of second-order terms is obvious in biological processes in which the growth/decay rate of one

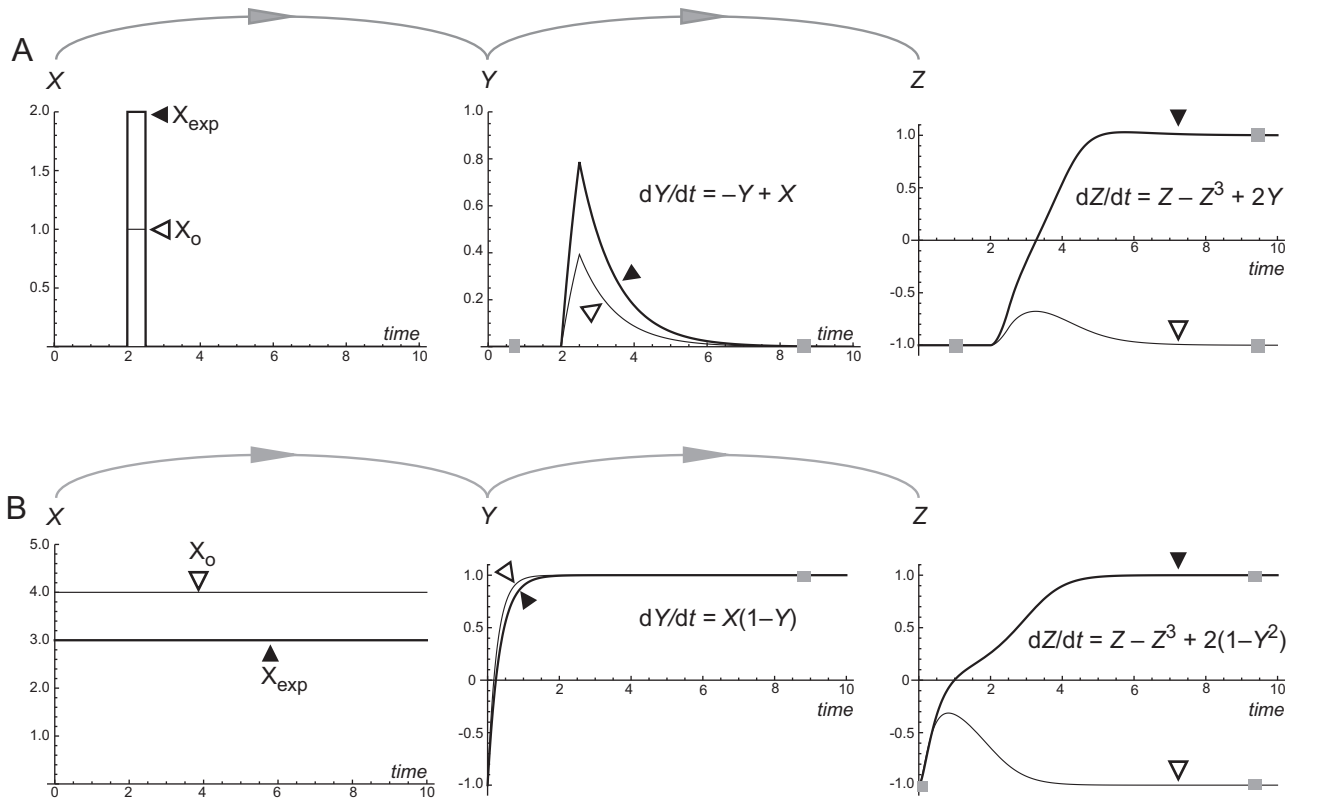

Fig. 3. By experimentally fixing X at X_{exp}, the researcher may observe no change in the equilibrium value of Y, but a strong change in the equilibrium value of Z. If the dynamic relationships among the variables are ignored, the researcher may conclude that X controls Z but not Y, even though the opposite is true. Both transient (A; e.g., a drug injection) and sustained (B; e.g., a gene mutation) change in X has no effect on the equilibrium value of Y, but the dynamics of Y controls the equilibrium value of Z (which does not directly interact with X). The equations in the middle panels represent a simple homeostatic mechanism (A) and development or growth (B). The equations in the right panels (A and B) represent a simple switch (Strogatz, 2001). All of these dynamic relationships naturally describe a number of biological processes, some of which are of clinical importance (Janušonis, in press). The gray arrows at the top represent the direct causal links between the variables. The gray squares mark the stable equilibrium states (i.e., the homeostatic states to which the variables automatically return after small perturbations). These equilibrium states are a product of the system dynamics and do not require external variables.

variable is controlled by another variable, such as in the accelerated postnatal brain growth in autism (Courchesne et al., 2011).

Suppose the experimenter changes X from its normal value (X_0) to X_{exp} and holds it there (e.g., knocks out a gene). Will the equilibrium value of Y change? Despite the fact that X and Y directly interact, the answer sensitively depends on the values of the coefficients. Assume (hot) = 0 (i.e., the higher order terms can be neglected). If $a_Y = a_{XY} = a_{(YY)Y} = a_{(XX)Y} = 0$, the experimental treatment will have no effect on the Y equilibrium value. In another simple scenario, if $a_{(XY)Y} = a_{(YY)Y} = 0$ and all other coefficients are non-zero, the equilibrium value of Y will change if $a_Y + a_{XY}X_{exp} + a_{(XX)Y}(X_{exp})^2$ differs from $a_Y + a_{XY}X_0 + a_{(XX)Y}(X_0)^2$. However, it may be possible to find (or accidentally choose) such $X_{exp} \neq X_0$ that $a_Y + a_{XY}X_{exp} + a_{(XX)Y}(X_{exp})^2 = a_Y + a_{XY}X_0 + a_{(XX)Y}(X_0)^2$. This leads to the conclusion that a change in X may or may not result in a change in the Y equilibrium value (if the only available information is that X directly controls Y). Therefore, a t-test performed on the conditions ($X = X_0$ and $X = X_{exp}$) effectively assesses the consistency of the data with the following compound null-hypothesis: {X does not control Y} OR {the set of coefficients is not "fortuitous"}. Importantly, there is no equivalence between the strength of the interaction and the coefficient set being "fortuitous." As shown in Fig. 3, X can strongly control Y with no effect on its equilibrium value. Redefining "interaction" as effects on equilibrium values only does not solve the problem and can result in severe inferential errors. Specifically, the researcher may conclude that X directly controls Z but not Y, when in reality the opposite may be true (Fig. 3). This has important implications for theoretical and applied neuroscience fields, including developmental neurobiology and neuropharmacology.

4. Discussion

4.1. Statistical tests estimate mathematical models

The presented analysis shows that statistical tests cannot reliably detect direct interactions among variables if these variables are measured at equilibrium and no constraints are placed on their possible dynamics. This problem arises not because of flaws in statistical tests as mathematical procedures, but because they are used to estimate "time-less" models. Since this observation is important for the following discussion and it also suggests potential solutions, it is helpful to briefly review how statistical tests operate.

If the researcher has performed a statistical test, however simple, it implies the following:

- The researcher has proposed a mathematical model of the studied process. If the model is explicitly specified (e.g., by a formula), its biological relevance can be immediately examined. If the model is not explicitly specified, it is likely to be a standard, premade model (e.g., ANOVA). Since many standard models are built on computational convenience rather than biological relevance, they are generally less safe than models constructed by using evidence-based decisions.
- The researcher has verified that the mathematical structure of the proposed model is consistent with the observed data. For

example, small values of a biological variable can have smaller variances than its large values. While this situation is biologically natural (the variance is proportional to the value), it is inconsistent with the standard ANOVA model.
- The experimenter has numerically estimated the coefficients of the model. A significant *P*-value typically means that some of the model's coefficients are likely to have non-zero values. Obviously, this information is meaningful only if the model is correct (or, more precisely, if the model's mathematical structure is consistent with the data structure).

These considerations show that statistical testing is a type of mathematical modeling. Mechanistically, it is not different from mathematical modeling used to understand physical laws in exact sciences. For example, Newton's second law of motion ($F = ma$) is a simple version of the model that underlies the standard *t*-test ($Y = bX + b_0 + \varepsilon$); the former can be obtained from the latter by assuming a zero intercept ($b_0 = 0$) and a negligible random error ($\varepsilon = 0$). While statistical models often differ from models of physical laws in that they are more empirical or ad hoc, this difference is not fundamental and simply reflects the depth of scientific understanding. It is not unusual to start with empirical models that work reasonably well in fixed or highly controlled settings and then proceed to generalized predictive models that include all essential variables (therefore minimizing the need to control for other variables).

A distinguishing characteristic of statistical models is that in addition to usual deterministic variables they include random variables. These random variables are typically assumed to be unchanging in time (e.g., measurement errors). Random variables that evolve in time are usually studied in the theory of stochastic differential equations. It is revealing that these equations are not considered to represent any "tests." They are models, the parameters of which can be optimally estimated based on previous observations and then used to predict the future of cellular, ecological, or financial processes (Øksendal, 2003; Letinic et al., 2009; Gardiner, 2010).

In summary, statistical tests cannot directly "test" biological reality. Rather, they are mathematical models that can yield deeper insights into the mechanisms of the observed phenomena and may allow predictions. As such, they are meaningful only to the extent that their mathematical structure is biologically relevant. Since neural systems never stop evolving in time, ignoring time in their statistical models may lead to serious problems. Some of these problems are beyond the scope of the present study and have been discussed elsewhere (Janušonis, in press).

4.2. Null-hypothesis significance testing yields uninformative model estimates

Null-hypothesis significance testing (NHST) dates back to the pre-computer era and has many problems as a methodological approach (Meehl, 1967; Cohen, 1994; Cohen et al., 2003; Kline, 2004; Nakagawa and Cuthill, 2007). Two of these problems are immediately relevant to the presented results.

First, the correlation between the equilibrium values of two variables is highly sensitive to the baseline numerical values of the coefficients that couple the variables (Eqs. (2) and (3)). However, a significant *P*-value merely means that the confidence intervals of some coefficients do not include zero. If large experimental samples are used, this information becomes nearly trivial, as no coefficients can be precisely 0.00000..., with zeros extending into infinity. It can be more useful if sample sizes are relatively small, since large (not merely non-zero) effect sizes are needed to reject the well-protected null-hypothesis (the Type I error is usually set at $\alpha = 0.05$). Still, this reasoning is an unnecessarily convoluted alternative to confidence intervals that, based on the data, assign each model coefficient a range of possible numerical values (Tukey, 1969; Cohen, 1994; Cohen et al., 2003; Nakagawa and Cuthill, 2007). The latter interpretation is intuitive and mathematically obvious (these estimates can be immediately plugged into the model and used to predict untested outcomes).

It follows that, even if one starts with a statistical model that includes time, NHST fails to report key pieces of information. Specifically, if the only available information is that some model coefficients are non-zero, virtually no prediction can be made about the association strength among the equilibrium values of the variables. Since these equilibrium values are likely to have been studied by other researcher groups, it greatly diminishes the potential for meta-analysis and cross-verification.

In addition, NHST has another undesirable property: it treats the complete absence of an effect as the "normal" or "expected" situation. Consequently, the Type I error ($\alpha = 0.05$) is set such that tests default to this conclusion unless there is strong evidence to the contrary. However, this default conclusion is extraordinary from the biological point of view. In fact, it is difficult to imagine a biological system a perturbation of which would produce a zero effect on some of its variables (small effects already violate the null-hypothesis assumption). In this regard, true weak or near-zero effects are of great value in that they can refine the system's graph by pruning away its links that do not represent direct interactions (Fig. 1). The need for greater flexibility in the construction of the initial hypothesis has been discussed by other authors, some of whom have called for "reversal of the usual scientific burden of proof" (Meehl, 1967; Dayton, 1998; Hoenig and Heisey, 2001).

This approach is perilous if conclusions about weak or near-zero effects are based on associations between equilibrium values (the variables may actually directly interact) or NHST (which automatically defaults to the absence of interaction if the evidence is insufficient). It is interesting that the practice of treating "negative" experimental results as low in scientific value is directly connected with these methodological flaws. If well-designed statistical models are estimated with reliable experimental data, both "negative" and "positive" results are equally useful, since they reveal the connectivity of the system's elements.

Nakagawa and Hauber (2011) is an excellent review of modern statistical models, most of which are not based on NHST. A powerful application of these approaches to the relationship between hippocampal neurogenesis and behavior is given in Lazic (in press).

4.3. Explicit modeling and numerical estimation minimize inferential pitfalls

In order to avoid the discussed pitfalls, it is best to start with an explicit statistical model. This approach is used in modern statistical techniques, such as generalized linear modeling (Zuur et al., 2009; Nakagawa and Hauber, 2011) and structural equation modeling (SEM). In SEM, the researcher proposes a model and seeks to validate it with real-life data (thus hoping that the null-hypothesis will *not* be rejected) (Kline, 2011). For the same reason, running a two-way ANOVA in *R* (www.r-project.org) can become an unexpected challenge, because this forward-looking statistical platform requires an exact specification of the underlying model, including a precise definition of the "main effects" in the presence of an interaction (which otherwise can be mathematically ambiguous; by default, most software packages give only one version).

An added benefit of this approach is that it forces the researcher to study the structure of the experimental data. For example, if measurements have been made in animals from different litters, it immediately raises questions about how these data points may

be related to one another (e.g., whether they are truly independent). This may invalidate the standard ANOVA model and suggest a model that is both more relevant and can provide richer biological information (e.g., a mixed-effects model).

While the importance of the data covariance structure has been emphasized in statistical literature (Zuur et al., 2009; Lazic, 2010; Nakagawa and Hauber, 2011), the inherent time-dependence of biological variables is often overlooked. Nevertheless, the researcher has to also decide how time should be included in the model. Since a biological system without time cannot exist, problems at this stage may reveal serious flaws in the experimental design (e.g., the value of a variable was measured, but the selected independent variables affect its rate of change). If a generalized linear model is used, time can be included in the intercept (e.g., if all experiments were conducted at the same time), as an independent variable (which may or may not interact with other independent variables), or as the velocity (rate of change) of the dependent variable.

Including time in the model also forces the researcher to take a disciplined approach to possible linear relationships among the variables. Many emergent properties of biological systems depend on non-linearities among variables (Babloyantz, 1986; Nicolis and Prigogine, 1989; Buzsáki, 2006). The assumption of linearity as an approximation is safe only in special circumstances – namely, when variables stay close to their equilibrium values (due to the Taylor series expansion). Most experimental approaches grossly violate this assumption (typically, the researcher moves the system far away from its equilibrium in the hope of obtaining a large effect size detectable with a relatively small sample). In many cases, a linear relationship automatically implies non-linearity in associated processes (e.g., if $Y = dX/dt = aX$, then it follows that $X = X_0 e^{at}$, where t is time and X_0 is the initial value of X). Finally, assuming linearity among any variables in a dynamical system is logically inconsistent (e.g., if $v \sim t$, then it follows that $s \sim t^2$, where v is velocity, s is traveled distance, t is time, and $\sim$ is the proportionality sign).

It is worth noting that despite these inherent difficulties many successful models in physics and chemistry are linear. It is possible because these models establish relationships between the *rate of change* of the dependent variable and the *current state* of the independent variables (Eq. (1)). This approach takes advantage of the trivial observation that change requires continuity in time and, therefore, can be described locally with respect to time. It also immediately disposes of the problem of "direct interaction with no correlation," since time is already included in the definition of "rate of change." Velocity has been modeled in ecological research (Blumstein, 1992), but it is still rarely considered in neurobiology (with the prominent exception of electrophysiology).

In numerical estimations of the final statistical model, time can be folded into other variables. However, the overall transparency of the analysis can help other researchers to avoid premature generalizations and may facilitate collaborative and meta-analysis efforts. For example, the absence of an effect in adulthood does not imply that the same factor has no effect in early development. Similarly, the absence of an effect on the equilibrium value of a variable does not imply that the factor has no effect on how fast the variable can change (Fig. 3).

Several approaches can be used to validate the final model. One can verify that the structure of the residuals is consistent the specification of the statistical model (Zuur et al., 2009) or use Bayesian-based posterior predictive checking (Gelman et al., 2003). It is worth repeating that the usual *P*-values of statistical tests do not carry this information, since they estimate the coefficients of the underlying models, not their relevance or quality.

5. Conclusions

A direct interaction between elements of a neural system cannot be reliably established unless these elements are analyzed in time. Consequently, statistical models of neurobiological processes should include time as a variable, unless experimental evidence exists to support their time-invariance.

Acknowledgments

This study was supported by Hellman Family Faculty Fellowships and UCSB Academic Senate Grants. I thank Paul J. Atzberger (UCSB Department of Mathematics) for advice on stochastic processes.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jneumeth.2012.02.012.

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