Biological Psychiatry: CNNI

Stochastic Dynamic Models for Computational Psychiatry and Computational Neurology

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One of the central problems of modern psychiatry is its purely symptom-based nosology. Current diagnostic schemes, such as the DSM or ICD, define diseases as collections of clinical symptoms and signs; this conveys reliability to diagnoses, but also creates heterogeneous patient groups. This heterogeneity, in turn, complicates treatment predictions in clinical practice and hinders research that aims at identifying disease mechanisms in individual patients. As a consequence, the conventional disease classifications have been increasingly criticized, and the field is searching for alternatives that are grounded in a more fundamental understanding of the underlying disease processes (1).

The key challenge for creating a pathophysiologically informed diagnosis and treatment scheme is dealing with the complexity of the brain and its interactions with its surroundings (including both the body and the external world). While different subfields of neuroscience focus on molecular mechanisms, cellular processes, neuronal circuits, or behavior, there is still a large explanatory gap between these levels of investigation and a lacking connection to clinical symptom expression.

Computational models have been promoted as one of the most promising tools to close this gap, as they allow for spanning multiple levels of description (1,2). The spectrum of models and their application is wide: algorithmic models, such as reinforcement learning methods, and Bayesian models have provided explanations for basic computational processes, such as learning, decision making, and perception, and allowed for linking these basic computations to their manifestation in behavior or brain activity. At the other end of the spectrum, generative models of neuroimaging data and biophysically informed neuronal network models operate on a mesoscopic level, linking neuronal population activity to large-scale brain activity measurements and clinical pathologies (3).

In their two-part article series in this issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, Roberts *et al.* (4,5) stress the importance of one class of modeling approaches—stochastic dynamic models (SDMs)—for clinical applications. SDMs rest on stochastic differential equations (SDEs) to describe the evolution of a system that has both deterministic and stochastic components. In the brain, stochastic changes in the current state of the system (state noise) may arise, for example, from sensory channel noise, random fluctuations in microscopic states, or irregular discharges from brainstem nuclei. In the presence of both intrinsic dynamics and noise, SDMs are ideally suited to describe how a specific state of the brain, represented by a set of variables such as neuronal firing rate, membrane potential, or ion channel conductance, evolves over time.

In particular, SDMs can be extremely powerful in describing phenomena in which 1) state changes such as a rapid increase or decrease in neuronal firing rates are driven by stochastic processes or 2) the state noise itself contains relevant information. The most striking examples of the former are multistability and bifurcations. In the case of multistability, multiple states coexist toward which the dynamics gravitate (attractors). Stochastic processes can then drive the system to jump back and forth between these attractor states. Noise-induced alternations between multistable states have been used to explain, for example, the ictal and interictal durations of epileptic seizures (6), abnormal sleep patterns, or working memory deficits (5). Noise plays a similarly important role in the vicinity of bifurcations, where a small change in the parameters can cause a sudden change in attractor states and thus induce an abrupt qualitative change in the system's behavior. The influence of noise becomes prominent at the transition point when the current attractor becomes unstable. There it manifests itself in an increase in variance and correlation that results in slow, high-amplitude fluctuations, called critical slowing. Signatures of critical slowing could serve as early predictors of an upcoming state transition (7), which makes them attractive in the clinical context. In a recent model for depression, for instance, temporal autocorrelation, variance, and fluctuation patterns of emotions akin to critical slowing were related to an increased probability of an upcoming transition between a normal state and a depressed state (8). In general, bifurcations have been related to a broad spectrum of clinical and nonclinical phenomena: the onset and duration patterns of epileptic seizures, mood fluctuations in melancholia, and bipolar disorder or sleep-wake transitions (5). In addition, even if the noise is not directly driving a rapid change in the dynamics, the state noise itself can contain relevant information that yields additional features of potential clinical relevance: 1) noise can capture dynamics that are otherwise not explicitly modeled or plays a role in determining which neuronal activity patterns become excessively strong attractors (9); 2) different noise sources, e.g., intrinsic state noise and measurement noise, can be disentangled and separately dealt with; and finally, 3) noise can represent uncertainty, which has become a core feature in many current models of perception and decision making (10).

While this broad set of applications illustrates the utility of SDMs, their translation to clinical questions also faces some significant challenges: SDMs typically focus on microscopic dynamics, such as the activity pattern of spiking neurons, but clinical measures are usually acquired at a macroscopic level, including electroencephalography time series, functional magnetic resonance imaging scans, or behavioral and cognitive assessments. SDMs thus need to bridge the gap between the

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  http://dx.doi.org/10.1016/j.bpsc.2017.03.003
Biological Psychiatry: Cognitive Neuroscience and Neuroimaging April 2017; 2:214–215 www.sobp.org/BPCNNI ISSN: 2451-9022

levels of hidden neuronal states and observations. A first step to achieve this link is to use SDMs for describing mesoscopic dynamics (neuronal population activity), such as the dynamics of multiple neurons within a cortical column. A problem for this approach is model complexity. Trying to use SDEs to account for the individual behavior of many neurons, one faces an intractable number of parameters that can, in principle, produce every possible behavior, resulting in overly precise models that lack generalizability (overfitting). One solution to this complexity is to consider the average state of multiple neurons, a so-called mean field approximation. That is, instead of representing the dynamics of many individual neurons, one considers the dynamics of their average state (a population density perspective). This approximation makes parameter estimation tractable, even in highly complex systems.

Finally, the goal is to obtain parameter estimates that capture clinically relevant mechanisms in an individual person or a group of people, by fitting the model (in a Bayesian context, this is referred to as model inversion). To that end, a representation of mesoscopic dynamics has to be mapped onto macroscopic observations via a measurement function. While measurement functions that link neuronal activity to electroencephalography or functional magnetic resonance imaging activity exist and are widely used, a direct quantitative mapping onto behavior—or clinical symptoms—is more challenging.

Roberts *et al.* (4,5) point out that there is a potentially fruitful way to link neuronal dynamics to a broad spectrum of behaviors by expressing stochastic neural population activity in terms of probability distributions (the population density perspective described above) (4). The primary rationale is the following: while each state may be subject to individual stochastic fluctuations, in an ensemble of stochastic processes some states are more likely to be reached than others. Thus, one can recast SDEs as probability density functions. The mathematical formalism of this mapping, adapted from similar problems in physics, is called the Fokker–Planck equation. While the mathematical derivation of the Fokker–Planck equation from an SDE involves some nontrivial math, the link from SDEs to probability distributions is desirable: many computational models of macroscopic behavior, such as Bayesian models of belief updating or models of decision making (e.g., drift-diffusion models), use some form of probability distributions as their building blocks. Using the same mathematical description for mesoscopic models can link the different levels and may thus represent one of the most principled and promising approaches to take stochastic phenomena into account when addressing neuroscientific and clinical problems.

While the theoretical foundation is promising, in practice, bridging the gap between multiple levels of description and observation continues to represent a major challenge in applying SDMs to clinically relevant questions. It might explain why most progress has been made in the application of SDMs to neurological disorders, such as epilepsy or Parkinson's disease, where it is easier to adopt an exclusive focus on physiology. By contrast, the application of SDMs to psychiatric disorders is still mainly phenomenological. A critical challenge for the future is to find Fokker–Planck equation–based models that unify representations of mesoscopic activity with computational interpretations (e.g., how variance of neuronal populations encodes uncertainty in perception) and link abnormalities at the neuronal level to both measurements of brain activity and behavior in individual patients. If this can be achieved, SDMs will turn into an extremely powerful tool for linking symptoms to the underlying biological processes. In particular, building this bridge could facilitate new drug developments and help predict how pharmacological actions at the cellular level relate to changes in symptoms.

Roberts *et al.* (4,5) provide a much-needed overview of the potential and challenges of the use of SDMs for clinical applications and outline this exciting but challenging path to the future. Their articles provide an excellent and important starting point for future translational neuromodeling research directed at transforming phenomenological descriptions into quantitative assessments of neuropsychiatric disorders.

Acknowledgments and Disclosures

Early Career Investigator Commentaries are solicited in partnership with the Education Committee of the Society of Biological Psychiatry. As part of the educational mission of the Society, all authors of such commentaries are mentored by a senior investigator. This work was mentored by Tiago V. Maia, Ph.D.

I would like to thank Tiago Maia, Klaas Enno Stephan, and Saee Paliwal for helpful comments and suggestions.

The author reports no biomedical financial interests or potential conflicts of interest.

Article Information

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Received Feb 24, 2017; accepted Mar 3, 2017.

References

1. Wang XJ, Krystal JH (2014): Computational psychiatry. Neuron 84: 638–654.
2. Maia TV, Frank MJ (2011): From reinforcement learning models to psychiatric and neurological disorders. Nat Neurosci 14:154–162.
3. Stephan KE, Iglesias S, Heinzle J, Diaconescu AO (2015): Translational perspectives for computational neuroimaging. Neuron 87: 716–732.
4. Roberts JA, Friston KJ, Breakspear M (2017): Clinical applications of stochastic dynamic models of the brain, part I: A primer. Biol Psychiatry Cogn Neurosci Neuroimaging 2:216–224.
5. Roberts JA, Friston KJ, Breakspear M (2017): Clinical applications of stochastic dynamic models of the brain, part II: A review. Biol Psychiatry Cogn Neurosci Neuroimaging 2:225–234.
6. Suffczynski P, Lopes Da Silva FH, Parra J, Velis DN, Bouwman BM, Van Rijn CM, *et al*. (2006): Dynamics of epileptic phenomena determined from statistics of ictal transitions. IEEE Trans Biomed Eng 53:524–532.
7. Scheffer M, Bascompte J, Brock WA, Brovkin V, Carpenter SR, Dakos V, *et al*. (2009): Early-warning signals for critical transitions. Nature 461:53–59.
8. van de Leemput IA, Wichers M, Cramer AOJ, Borsboom D, Tuerlinckx F, Kuppens P, *et al*. (2014): Critical slowing down as early warning for the onset and termination of depression. Proc Natl Acad Sci U S A 111:87–92.
9. Maia TV, Cano-Colino M (2015): The role of serotonin in orbitofrontal function and obsessive-compulsive disorder. Clin Psychol Sci 3:460–482.
10. Petzschner FH, Glasauer S, Stephan KE (2015): A Bayesian perspective on magnitude estimation. Trends Cogn Sci 19:285–293.