Machine learning used to understand and predict dynamics of worm behavior

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The roundworm C. elegans is a well-established laboratory model system. While the worm is a fairly simple living system, it is complicated enough to serve as "a kind of sandbox" for testing out methods of automated inference, says Emory biophysicist Ilya Nemenman. Credit: Emory University

Biophysicists have used an automated method to model a living system—the dynamics of a worm perceiving and escaping pain. The *Proceedings of the National Academy of Sciences (PNAS)* published the results, which worked with data from experiments on the *C. elegans* roundworm.

"Our method is one of the first to use machine-learning tools on experimental data to derive simple, interpretable equations of motion for a living system," says Ilya Nemenman, senior author of the paper and a professor of physics and biology at Emory University. "We now have proof of principle that it can be done. The next step is to see if we can apply our method to a more complicated system."

The model makes accurate predictions about the dynamics of the worm behavior, and these predictions are biologically interpretable and have been experimentally verified.

Collaborators on the paper include first author Bryan Daniels, a theorist from Arizona State University, and co-author William Ryu, an experimentalist from the University of Toronto.

The researchers used an algorithm, developed in 2015 by Daniels and Nemenman, that teaches a computer how to efficiently search for the laws that underlie natural dynamical systems, including complex biological ones. They dubbed the algorithm "Sir Isaac," after one of the most famous scientists of all time—Sir Isaac Newton. Their long-term goal is to develop the algorithm into a "robot scientist," to automate and speed up the scientific method of forming quantitative hypotheses, then testing them by looking at data and experiments.

While Newton's Three Laws of Motion can be used to predict dynamics for mechanical systems, the biophysicists want to develop similar predictive dynamical approaches that can be applied to living systems.

For the PNAS paper, they focused on the decision-making involved when *C. elegans* responds to a sensory stimulus. The data on *C. elegans* had been previously gathered by the Ryu lab, which develops methods to measure and analyze behavioral responses of the roundworm at the holistic level, from basic motor gestures to long-term behavioral programs.

C. elegans is a well-established laboratory animal model system. Most *C. elegans* have only 302 neurons, few muscles and a limited repertoire of motion. A sequence of experiments involved interrupting the forward movement of individual *C. elegans* with a laser strike to the head. When the laser strikes a worm, it withdraws, briefly accelerating backwards and eventually returning to forward motion, usually in a different direction. Individual worms respond differently. Some, for instance, immediately reverse direction upon laser stimulus, while others pause briefly before responding. Another variable in the experiments is the intensity of the laser: Worms respond faster to hotter and more rapidly rising temperatures.

The researchers fed the Sir Isaac platform the motion data from the first few seconds of the experiments—before and shortly after the laser strikes a worm and it initially reacts. From this limited data, the algorithm was able to capture the average responses that matched the experimental results and also to predict the motion of the worm well beyond these initial few seconds, generalizing from the limited knowledge. The prediction left only 10 percent of the variability in the worm motion that can be attributed to the laser stimulus unexplained. This was twice as good as the best prior models, which were not aided by automated inference.

"Predicting a worm's decision about when and how to move in response to a stimulus is a lot more complicated than just calculating how a ball will move when you kick it," Nemenman says. "Our algorithm had to account for the complexities of sensory processing in the worms, the neural activity in response to the stimuli, followed by the activation of muscles and the forces that the activated muscles generate. It summed all this up into a simple and elegant mathematical description."

The model derived by Sir Isaac was well-matched to the biology of *C. elegans*, providing interpretable results for both the sensory processing and the motor response, hinting at the potential of artificial intelligence to aid in discovery of accurate and interpretable models of more complex systems.

"It's a big step from making predictions about the behavior of a worm to that of a human," Nemenman says, "but we hope that the worm can serve as a kind of sandbox for testing out methods of automated inference, such that Sir Isaac might one day directly benefit human health. Much of science is about guessing the laws that govern natural systems and then verifying those guesses through experiments. If we can figure out how to use modern machine learning tools to help with the guessing, that could greatly speed up research breakthroughs."

More information: Bryan C. Daniels et al. Automated, predictive, and interpretable inference of Caenorhabditis elegans escape dynamics, *Proceedings of the National Academy of Sciences* (2019). DOI: 10.1073/pnas.1816531116

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