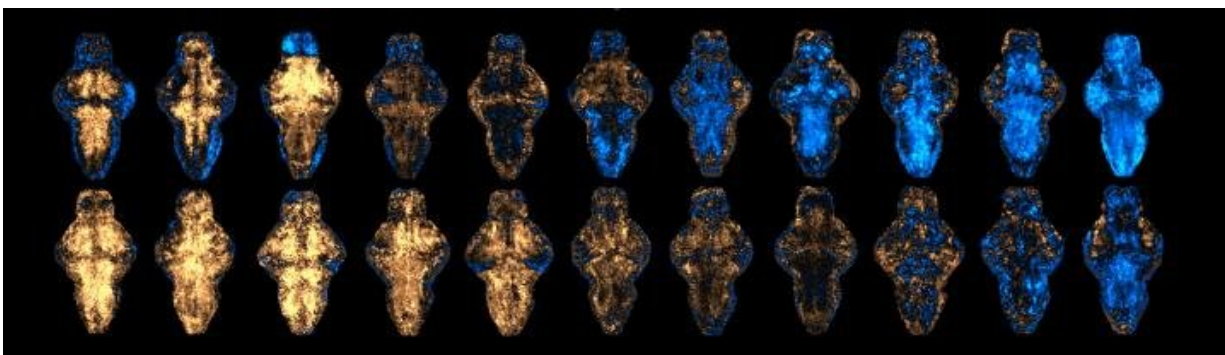


# Shortcut strategy for screening compounds with clinical potentials for drug development

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Examples of T-score brain activity maps used for predicting compounds' neuropharmacology. Credit: City University of Hong Kong

Developing a new drug often takes years and costs hundreds of millions of dollars. A shortcut has now been reported in a study led by City University of Hong Kong (CityU), which can potentially reduce the time and costs of developing new drugs by sorting out the high potential candidates from a long list of chemical compounds.

This breakthrough in neuropharmacology is the result of five years of collaboration by CityU's Department of Biomedical Engineering (BME), its Department of Biomedical Sciences (BMS), and Harvard Medical School. The research is published in *Nature Communications* in an article titled "High-throughput Brain Activity Mapping and Machine Learning

as a Foundation for Systems Neuropharmacology".

Depression, psychosis, epilepsy and Alzheimer's disease are common [brain](#) disorders. But drugs designed to treat them are difficult to develop, and candidate drugs have particularly high failure rates.

The research, led by Dr. Shi Peng, Associate Professor of BME at CityU, seeks to provide a platform to predict compounds with potential for development into [new drugs](#) to treat brain diseases. This platform could help drug developers to identify the compounds with a higher therapeutic and clinical translation potential, so as to prioritize the drug development pipeline and resource allocation. And more importantly, it can help speed up the new drug discovery process and save costs.

"Even a 1 percent increase in the drug development success rate would make a huge difference for CNS disorder patients," Dr. Shi explained.

### **Innovative system for efficient whole-brain activity imaging**

As in other pharmacological research, this study used zebrafish as a working model to conduct whole-brain activity mapping to show how and which part of the brain or central nervous system (CNS) react to the drugs. But Dr. Shi said their innovative system helped to streamline the process, enabling large-scale experiments.

"We have designed an integrative system that makes use of robotics, microfluidics and hydrodynamic force to trap and orient a conscious zebrafish automatically in 20 seconds, instead of spending 20 minutes to prepare and manually position each single fish for a similar experiment. Therefore, we can carry out imaging for many zebrafish in one go to collect a large amount of data efficiently. Importantly, our platform is capable of immobilizing the fish without anaesthesia, which may interfere with the brain activity and hence the evaluation of the chemical

compounds," he explained

By using this platform, the team first built a reference library of brain activity maps for 179 existing CNS drugs. They generated the maps from the brains of thousands of [zebrafish larvae](#), each of which had been treated with a clinically used CNS drug. The maps showed the corresponding brain regions that reacted to those drugs. Solely based on the intrinsic coherence among the maps of all the CNS drugs (without the names or any other information about the drugs), the team then used [machine learning](#) algorithms to classify these drugs into 10 physiological clusters. Some of the clusters were associated with therapeutic categories, such as anti-epileptic, psychoanaleptic and anti-Parkinson's, as defined by the World Health Organization Collaborating Centre for Drug Statistics Methodology (WHOCC).

## **Machine Learning to Predict Neuropharmacology**

With the reference library in hand, in close collaboration with Dr. Wang Xin, assistant professor of BMS Department at CityU and Dr. Stephen Haggarty, associate professor at Harvard Medical School, the team carried out information analysis and employed machine learning strategy to predict the therapeutic potential of 121 new compounds by using the brain activity maps of these new compounds and those of the 179 clinically used drugs in the library.

With a particular focus on anti-epileptics, the machine learning strategy predicted that 30 out of those 121 new compounds had anti-seizure properties. To validate the prediction, the research team randomly chose 14 from the 30 potential anti-seizure compounds to perform behavioural tests with an induced seizure animal model in zebrafish.

"The result showed that seven out of 14 compounds were able to reduce the seizures of the zebrafish without causing any sedative effects,

implying a prediction accuracy of around 50 percent," Dr. Shi said. "With this high-speed in vivo drug screening system combined with machine learning, we can provide a shortcut to help identify new compounds with significantly higher therapeutic potentials for further development, hence speed up the drug development and reduce the failure rate in the process."

Another significant implication of the new screening paradigm is to make use of the physiology of zebrafish's brain activity as an indicator of the therapeutic potentials of the compounds without the need of their biochemical information. "Traditionally, many [drug](#) development efforts were based on the study of the chemical structure or molecular target to identify potent [compounds](#). But using our strategy, we actually found a large heterogeneity in chemical structures or molecular targets even within the drugs of the same classification of [brain activity](#) maps. Our new approach may help widen the pharmacology of certain neurological diseases," said Dr. Shi.

**More information:** Xudong Lin et al, High-throughput brain activity mapping and machine learning as a foundation for systems neuropharmacology, *Nature Communications* (2018). [DOI: 10.1038/s41467-018-07289-5](#)

Provided by City University of Hong Kong

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