Predictions of the effect of drugs on individual cells are now possible

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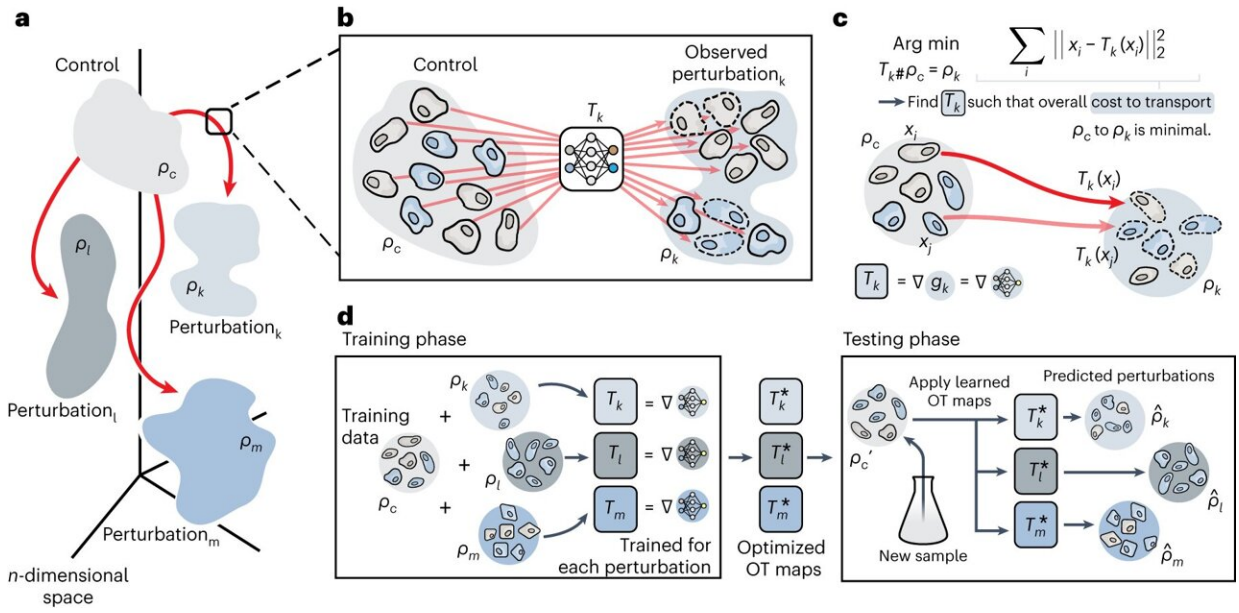

Overview of the CellOT model. **a**, Distributions of single cells were measured in either an untreated control state (ϱ_c) or in one of several perturbed states (ϱ_k, ϱ_l, ϱ_m, …). These distributions lie in a high-dimensional space of profiled features. **b**, For a perturbation k, we aim to model it with a function T_k that maps untreated cells in ϱ_c to their treated counterparts in ϱ_k. **c**, Lacking paired measurements, we assume that the perturbation transforms ϱ_c into ϱ_k under a principle of minimal effort. In particular, we learn T_k using optimal transport theory to directly estimate this distributional mapping as the gradient of the optimal transport dual potential ∇g_θ. **d**, OT maps are learned for all perturbations independently. Because these maps are fully parameterized, CellOT can be trained, for example, on a set of initially provided samples to then make predictions on untreated cells originating from new, previously unseen samples. Credit: *Nature Methods* (2023). DOI: 10.1038/s41592-023-01969-x

Experts from ETH Zurich, the University of Zurich, and the University Hospital Zurich have used machine learning to jointly create an innovative method to predict how individual cells react to specific treatments, offering hope for more accurate diagnoses and therapeutics.

Cancer is triggered by changes in cells that lead to the proliferation of pathogenic tumor cells. In order to find the most effective combination and dosage of drugs, it is advantageous if physicians can see inside the body, so to speak, and determine what effect the drugs will have on individual cells.

An interdisciplinary research team of biomedical and computer scientists from ETH Zurich, the University of Zurich, and the University Hospital Zurich has now developed a machine learning approach that allows such cell changes and drug effects to be modeled and predicted with much greater accuracy and nuance than before.

Understanding the responses of individual cells

In the battle against cancer, a fine-grained understanding of the behavior of individual cells towards a drug is key. After all, a medication ideally should destroy only tumor cells. However, if the effect of a drug is known only as a statistical average of a larger cell population, an analysis of the drug's effect might not detect that certain tumor cells survive the drug due to their nature or obtained resistances, and the cancer will continue to spread.

Researchers from Zurich have devised a pioneering approach that recognizes the distinct reactions individual cells can have to a drug within a larger population. This understanding of cell variation is pivotal for advancing more effective cancer treatments.

"The diversity within a group of cells greatly influences their sensitivity or resistance to changes. Instead of basing our understanding on the average response of a cell group, our method can precisely describe—and even predict—how each cell reacts to disturbances like those from a drug," explains Gunnar Rätsch, Professor of Biomedical Informatics at ETH Zurich and the University Hospital Zurich.

Method works on many cell types

Researchers refer to the molecular reactions with which cells respond to chemical, physical or genetic influences as perturbations. Such disturbances alter the affected cells and can, for example, trigger their death. The effect a given drug has on a cancer cell can also be seen as a perturbation.

Understanding which cancer cells respond to a drug and identifying the traits of those that form resistance to a drug is crucial for developing new treatment approaches and strategies. Such new treatments could be more effective at inhibiting cell growth or even causing pathogenic cells to die.

In their study, published in the current issue of *Nature Methods* along with a Research Briefing on their work, the researchers demonstrate that their method works not only on cancer cells but also on other pathogenic cells—for example, including the case of lupus erythematosus. This autoimmune disease is typically accompanied with a red rash and can lead to inflammation of the chest, heart or ribs.

Predicting reactions of individual cells is now possible

Another key innovation to emerge from this study is the ability to make predictions: the Zurich researchers are calling their new machine

learning method CellOT. Besides evaluating existing cell measurement data and thus expanding the knowledge of cellular perturbation reactions, CellOT can also predict how individual cells will respond to a perturbation whose reactions have not yet been measured in the laboratory.

The new method thus paves the way towards more targeted and personalized treatments: the predictions allow for the forecasting of a perturbation's effect on unseen cells, and thus indicate how well a patient's cells respond to the drug in question. Comprehensive clinical trials are still required before the approach can be used in a hospital setting. At present, the researchers have demonstrated the method's ability to provide highly accurate predictions.

Machine learning is what made such predictions possible. For CellOT, the researchers use novel machine learning algorithms and train these with both data from unperturbed cells and data from cells that changed after a perturbation response. In the process, the algorithm learns how cellular perturbation reactions arise, how they progress and the likely phenotypes of altered cell states.

Optimal transport enables learning

The ETH computer scientists worked closely with the research group led by Lucas Pelkmans, Professor of Cellular Systems Biology at the University of Zurich. Gabriele Gut, formerly a postdoc in Pelkmans' lab and now senior scientist in the Medical Oncology and Hematology Clinic at the University Hospital Zurich, measured the specific cell changes using a technique called 4i multiplex protein imaging. "CellOT works particularly well on data acquired with this technique," Pelkmans points out. In addition, the researchers obtained single-cell RNA data from public databases.

"Mathematically speaking, our machine learning model is based on the assumption that cells change gradually after a perturbation," says Charlotte Bunne, who, along with Stefan Stark and Gabriele Gut, is the lead author of the study and is working on her doctorate under Andreas Krause, Professor of Computer Science and Chair of the ETH AI Center. Bunne's research area is machine learning, and she explains that "these gradual changes in cell states can be described and predicted well using the mathematical theory of optimal transport."

Optimal transport (OT) is the field of mathematics in which ETH mathematics professor Alessio Figalli won the 2018 Fields Medal. In the last four years, optimal transport theory has contributed much to explaining cellular perturbation responses.

CellOT is now the first approach to use optimal transport and machine learning to predict the perturbation responses of cells from new samples. "Established OT methods do not allow for out-of-sample or out-of-measurement predictions. But that's exactly what CellOT can do," Bunne says.

More information: Charlotte Bunne et al, Learning single-cell perturbation responses using neural optimal transport, *Nature Methods* (2023). DOI: 10.1038/s41592-023-01969-x

Neural optimal transport predicts perturbation responses at the single-cell level, *Nature Methods* (2023). DOI: 10.1038/s41592-023-01968-y

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