Neural Optimal Transport for Dynamical Systems
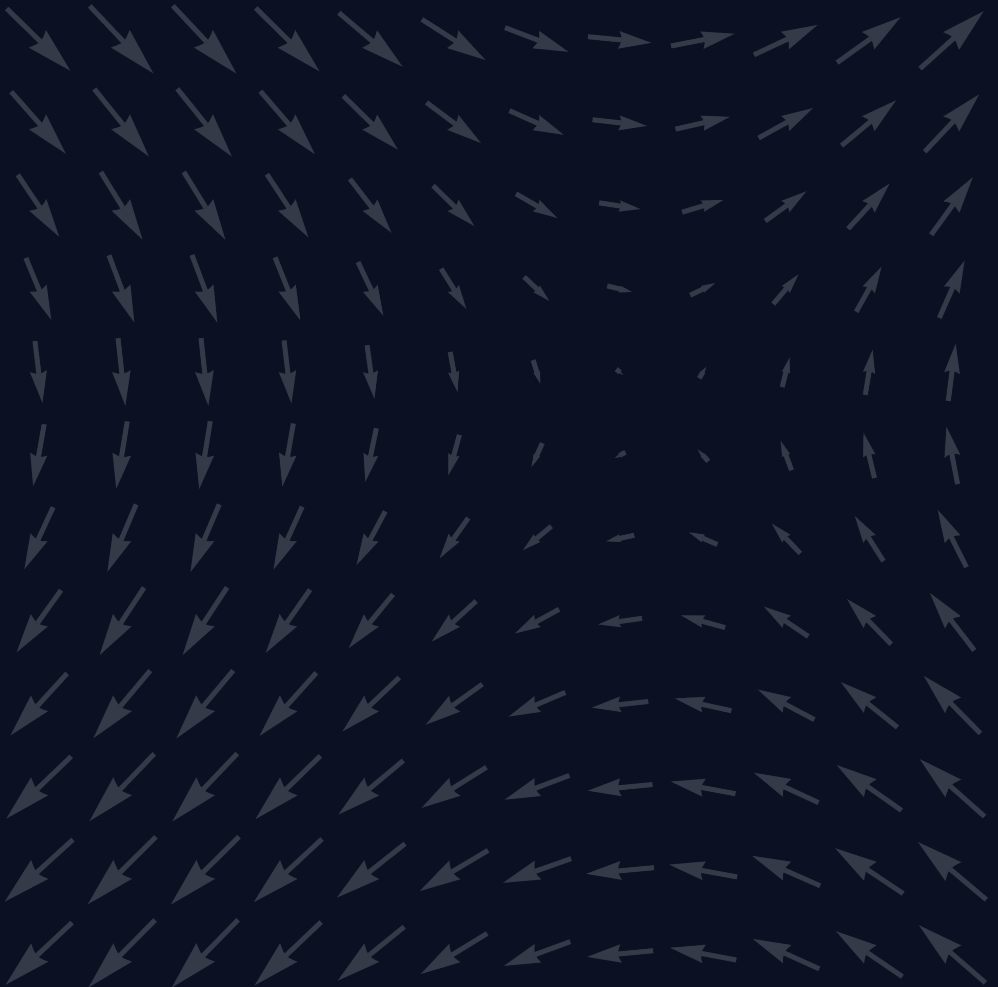
Methods and Applications in Biomedicine

Charlotte Bunne

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NEURAL OPTIMAL TRANSPORT FOR DYNAMICAL SYSTEMS

METHODS AND APPLICATIONS IN BIOMEDICINE

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METHODS AND APPLICATIONS IN BIOMEDICINE

A dissertation submitted to attain the degree of

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presented by

CHARLOTTE BUNNE
M. sc. ETH Zurich

born on 29 August 1995

accepted on the recommendation of

Prof. Dr. Andreas Krause, examiner
Prof. Dr. Marco Cuturi, co-examiner
Prof. Dr. Lucas Pelkmans, co-examiner
Prof. Dr. Jure Leskovec, co-examiner

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Und was in schwankender Erscheinung schwebt,
Befestiget mit dauernden Gedanken.
— Johann Wolfgang von Goethe, *Faust I* (1808)

ABSTRACT

English abstract here.

ZUSAMMENFASSUNG

Deutsche Zusammenfassung hier.

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CONTENTS

NOTATION

Σ_d Probability simplex of size d

ACRONYMS

OT optimal transport.

1

INTRODUCTION

...

— ..., ... (...)

(Bunne et al., 2021) optimal transport

2

BACKGROUND

The results suggest a helical structure (which must be very closely packed) containing probably 2, 3 or 4 coaxial nucleic acid chains per helical unit and having the phosphate groups near the outside.
— Rosalind Franklin, *Report* (1952)

3

RELATED WORK

La vraie générosité envers l'avenir consiste à tout donner au présent.
— Albert Camus, *L'homme révolté* (1951)

4

…

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*Tout va par degré dans la nature, et rien par saut, et
cette regle à l'égard des changements est une partie de
ma loi de la continuité.*
— Gottfried Wilhelm Leibniz, *Nouveaux essais sur
l'entendement humain* (1765)

5

...

Living matter evades the decay to equilibrium.
— Erwin Schrödinger, *What is Life?* (1944)

6

…

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*Ein solches mathematisch-definierbares System ist
überhaupt nicht die Wirklichkeit selbst, sondern nur
ein Schema, welches zur Beschreibung der Wirklichkeit
dienen kann.*

*— Andrey Kolmogorov, Über die analytischen
Methoden in der Wahrscheinlichkeitsrechnung (1931)*

7

CONCLUSION AND FUTURE DIRECTIONS

> *It's odd the way life works, the way it mutates and*
> *wanders, the way one thing becomes another.*
> — Siri Hustvedt, *What I Loved* (2003)

In this work we propose CELLOT, a framework to model single-cell perturbation responses from unpaired treated and untreated cell states using neural optimal transport. By adequately modeling the nature of the problem through the lens of optimal transport, CELLOT determines how perturbations affect cellular properties, reconstructs the most likely trajectory single cells take upon perturbation, and subsequently assists in a better understanding of driving factors of cell fate decision and cellular evasion mechanisms. CELLOT builds on the recent successes of optimal transport applications in single-cell biology (Schiebinger et al., 2019; Lavenant et al., 2021), by introducing a fully parameterized transport map that can be applied to incoming unseen samples. Previous methods (Jacob et al., 2018; Yang and Uhler, 2019; Prasad et al., 2020) rely on an unconstrained parameterization of the *primal* optimal transport map. However, the unconstrained nature of these models makes robust optimization challenging and results in reduced performance (Makkuva et al., 2020, Table 1). Instead, we learn the transformation of unperturbed to perturbed cell states through the *dual* optimal transport problem, parameterized via a pair of neural networks constrained to be convex (Makkuva et al., 2020). These constraints are important inductive biases that facilitate learning and result in a reliable and easy-to-train framework, as evidenced by the consistently strong performance of CELLOT on several problems without the need for extensive hyperparameter tuning (see Online Methods).

CELLOT infers the highly complex and nonlinear evolution of cell populations in response to perturbations without making strong simplifying assumptions on the nature of these dynamics. Unlike current approaches comprising autoencoder-based baselines (Lopez et al., 2018; Lotfollahi et al., 2019; Yang et al., 2020), CELLOT does not necessarily rely on learning meaningful low-dimensional embeddings in which perturbations are modeled as linear shifts. We confirm this advantage through experiments on single-cell responses to different drugs in cancer cell lines obtained with RNA-seq

and spatially resolved 4i measurements, where CELLOT consistently outperforms (Fig. **??** and **??**). Our evaluations went beyond the often-used average treatment effect and correlation analysis across all cells; we analyzed marginals and computed MMD scores, a strong measure of how well predicted and observed distributions match.

Using CELLOT to perform cell-state-aware drug profiling enables us to quantify perturbation effects as a function of the underlying heterogeneity of the studied system, in our cases a co-culture of two melanoma cell lines with different sensitivities to drug treatments. In doing so, we *sharpen* the response profiles of the measured drugs and reveal cell-state-specific responses of multiple signaling pathway in relation to treatment history of the cell line donor. We find the signaling activity associated to the MEK and PI3k pathways to decouple in cells pre-exposed to MEK inhibitors, a known adaptation mechanism for therapy evasion in melanoma cells (Kun et al., 2021). This *pathway rewiring* is associated to alteration in the molecular feedback structure of cells from effectors to receptors (Kun et al., 2021; Turke et al., 2012). Thus, combining CELLOT with a larger set of combination treatments, multiplexed imaging, and cellular systems reflective of disease adaptations may help us to elucidate the molecular mechanisms of signaling pathway evolution in the context of cancer therapy.

We further analyze how well the learned maps generalize beyond samples used for training (o.o.s. setting) and to different sample compositions (o.o.d. setting). In Fig. **??**, we therefore test CELLOT's ability to to predict treatment responses in unseen lupus patients, infer developmental trajectories on stem cells of lower potency, and translate innate immune responses across patients. In all cases, CELLOT's accuracy and precision are superior to current state-of-the-art methods (Fig. **??**). Moreover, the predicted cell states after perturbation are still very close to the actually observed cell states. We consider these results as particularly promising, as it illustrates that accurate o.o.s. and o.o.d. predictions are indeed possible.

The ability to make predictions out-of-distribution, such as on unseen patients, is, however, only feasible if a) similar samples have been observed in the unperturbed setting, and b) the training set contains cases that are similar not only in their unperturbed state but also their perturbation response. An analysis of glioblastoma patients treated with Panobinostat (Zhao et al., 2021) (see **??**a-c) indeed confirms this restriction: CELLOT and the baselines are able to predict treatment outcomes for those patients that are similar to other patients in both unperturbed state as well as perturbation effect (see Fig. **??**f), but fail to capture perturbation effects for

patients that exhibit unique responses (see **??**g). This limitation is important to consider when applying CELLOT in o.o.d. settings. To overcome such problems, larger cohorts, additional meta-information, and methodological extensions are required. Bunne et al. (2022) partially address this issue by deriving a neural optimal transport scheme that can be conditioned on a context, e.g., patient meta-data, when predicting perturbation responses.

We also observe that the predictive performance for CELLOT drops when perturbations are too strong, i.e., the cell distributions before and after perturbations are very different (see Fig. **??**j); a similar drop is observed for the other methods (see **??**). The principle underlying the optimal transport theory is ideally suited for acute cellular perturbations during which single cells do not redistribute entirely and randomly in multidimensional measurement space, but typically only in a few dimensions, such that the overall correlation structure is preserved. While this modeling hypothesis is satisfied when perturbation responses are observed via regularly and frequently sampled snapshots, molecular transitions cannot be reconstructed when perturbation responses have progressed too far. For particularly strong or complicated perturbations, cellular multiplex profiles might change too drastically, violating OT assumptions and making it challenging to reconstruct the alignments between unperturbed and perturbed populations based on the *minimal effort* principle. In such settings, additional information is likely needed, for instance, a model of the underlying biology or models that integrate observations of multiple smaller time steps.

Despite the stochastic nature of cell fate decisions and the fact that cellular dynamics are intrinsically noisy (Wilkinson, 2009), CELLOT models cell responses as deterministic trajectories. Approaches treating cell fate decisions as probabilistic events have previously allowed estimation of the full dynamical model to a greater extent than their deterministic counterparts (Bergen et al., 2020). By connecting OT and stochastic difference equations, recent work (Bunne et al., 2023; Somnath et al., 2023) can build up on CELLOT to account for biological heteroscedasticity, at the cost of added model complexity and other simplifying assumptions.

Despite having provided a proof-of-concept of the capacity of CELLOT to model various chemical perturbations for different data modalities through an in-depth analysis of the nature of the learned mapping as well as a demonstration of its versatility in a broad class of applications, CELLOT's generalization capacity has been evaluated on relatively small datasets. Crucially, large cohorts comprised of patients with different molecular profiles, such as cancer patients with various underlying genetics, could

result in strongly heterogeneous treatment responses. It is evident that approaches addressing these challenges could readily exploit the upcoming availability of large-scale patient cohort studies. The use of neural optimal transport to learn single-cell drug responses makes thus for an exciting avenue for future work, including its use to improve our understanding of cell therapies, study drug responses from patient samples, and better account for cell-to-cell variability in large-scale drug design efforts.

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CURRICULUM VITAE

PERSONAL DATA

Name	Charlotte Bunne
Date of Birth	August 29, 1995
Place of Birth	Karlsruhe, Germany
Citizen of	Germany

EDUCATION

2022-2023 Broad Institute of MIT and Harvard,
Cambridge (MA), USA
Visiting Graduate Student

2016 – 2019 Eidgenössische Technische Hochschule (ETH),
Zürich, Switzerland
Final Degree: Master of Science

2018-2019 Massachusetts Institute of Technology (MIT),
Cambridge (MA), USA
Visiting Student

2013 – 2016 Heidelberg University
Heidelberg, Germany
Final Degree: Bachelor of Science

EMPLOYMENT

2022 Research Intern
Apple,
Paris, France

2020 Research Intern
Google Research,
Zürich, Switzerland

2017 Research Intern
IBM Research,
Zürich, Switzerland

PUBLICATIONS

Charlotte Bunne, Andreas Krause, and Marco Cuturi. Supervised Training of Conditional Monge Maps. In *Advances in Neural Information Processing Systems (NeurIPS)*, 2022.

A

A P P E N D I X

Here be dragons.