**Learning lineage dynamics by coherent sparse optimization**

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**Abstract**

Single-cell genome-wide profiling offers an approach to map transitional cell states during cell differentiation, disease onset, and drug response. Lineage-tracing, in which cells are labeled with hereditary markers, offers an approach to establishing dynamic relationships between cell states. Here, we develop a computational approach to predict cell dynamics and fate decision boundaries from single-cell genomic data with lineage tracing. To do so, we infer stochastic dynamics by extending the statistical problem of compressed sensing to enforce coherent, sparse clonal relationships in time series data (CoSpar). In simulation and two published ground-truth datasets, CoSpar is robust to severe down-sampling of clonal data. It is compatible with one or more clonal time points. In datasets representing hematopoiesis, reprogramming, and in vitro differentiation, CoSpar identifies fate biases not previously detected, consistent with heterogeneity in the expression of transcription factors. CoSpar is available at <https://cospar.readthedocs.io/>.

**Introduction**

In tissue development, regeneration, and disease, cells differentiate into distinct, reproducible phenotypes. A ubiquitous challenge in studying these processes is to order the sequence of events in differentiation1–3, and to identify events that drive cells towards one phenotype or another. This challenge is common to understanding mechanisms in embryo development, stem cell self-renewal, cancer cell drug resistance, and tissue metaplasia1–3.

At least two observational strategies help to order cellular events. Single-cell genome-wide profiling – such as by single-cell RNA sequencing (scRNA-seq) – offers a universal and scalable approach to establishing dynamic states by densely sampling cells at different stages3–10. Alone, however, scRNA-seq does not establish which early differences between cells drive or correlate with future fate2,11–13. Lineage tracing offers a complementary family of methods that can clarify long-term dynamic relationships across multiple cell cycles. To carry out lineage tracing, individual cells are labeled naturally or experimentally at an early time point1–3. The state of their clonal progeny is analyzed at one or more later time points (Fig. 1**a**).

Recently, a number of efforts from us and others have integrated lineage-tracing with single-cell genome-wide profiling (hereafter LT-scSeq), using unique, heritable, and expressed DNA barcodes2,13–21. These technologies identify cells that share a common ancestor and define their genomic state in an unbiased manner. LT-scSeq experiments have been used successfully to identify when fate decisions occur13,14, novel markers for stem cells16, and pathways whose manipulation alters cellular outcomes14,16. The simplest of these methods label cells at one time point13 (Fig. 1**b**); more complex methods allow the accumulation of barcodes over successive cell divisions and can thus reveal the sub-structure of clones2,13–21 (Fig. 1**c**).

Emerging LT-scSeq methods have been successful at revealing novel regulators of cell fate14,16 and the potency of early progenitors13,14. But they also present challenges that may limit their utility in practice. We identified at least five technical and biological challenges that affect design and interpretation, detailed in (Fig. 1**f**). These include stochastic differentiation and variable expansion of clones22 (Fig. 1**f-i**); cells loss during analysis (Fig. 1**f-ii**); barcode homoplasy wherein cells acquire the same barcode despite not having a lineage relationship2 (Fig. 1**f-iii**); access to clones only at a single time point23,24 (Fig. 1**f-iv**); and clonal dispersion due to a lag time between labeling cells and the first sampling (Fig. 1**f-v**).

Here we develop an approach to analyze LT-scSeq experiments in a manner that is robust to these problems. To do so, we begin with a generalized model of clonal dynamics in which cells can divide, differentiate, or be lost from the sampled tissue in a stochastic manner, with rates that are state-dependent (Supplementary Fig. 1**a**). Defining the features of this model can be considered the goal of LT-scSeq. We make it our narrower goal to learn the fraction of progeny of cells, initially in one state, which are found to occupy a second state after some time interval (Supplementary Fig. 1**bc**). When calculated across all pairs of initial and final states, these fractions encode differentiation bias and fate hierarchies (Fig. 1**d**). They can reveal genes whose early expression is predictive of future fate choice.

**Results**

**Dynamic inference from clonal data with state information.**

One formalization of dynamic inference is to identify a transition map, a matrix , which describes the probability of a cell, initially in some state at time , giving rise to progeny in a state at time (Fig. 1**d**)7,25. We define specifically as the fraction of progeny from state *i* that occupy state *j* (Supplementary Fig. **1c**). This transition matrix does not capture all we can learn about cell dynamics: it already combines the effects of cell division, loss, and differentiation (Supplementary Fig. **1d**). As will be seen, even learning will prove useful for several applications (Fig. 1**d**).

The transition map has properties that make it amenable to inference. We expect it to be a sparse matrix, since most cells can access just a few states during an experiment (Fig. 1**e**, left panel). And we expect it to be locally coherent, meaning that neighboring cell states share similar fate outcomes (Fig. 1**e**, right panel). These constraints could improve robustness in map inference (see illustration in Supplementary Fig. 1**e**). Box 1 formalizes these constraints and establishes the technical foundation for inferring a transition map by coherent sparse (CoSpar) optimization (see schema in Fig. 2**a**; Supplementary Fig. 2). As inputs, CoSpar requires a clone-by-cell matrix that encodes the clonal information at time , and a data matrix for observed cell states (e.g. from scRNA-seq).

CoSpar is formulated assuming that we have information on the same clones at more than one time point. When we observe clones at only one time point , we jointly optimize the transition map and the initial clonal data (Fig. 2**b**; Methods). In this joint optimization, one must initialize the transition map, and we have shown that the final result is robust to initialization (Supplementary Fig. 3**e**; Supplementary Fig. 4**cd**). This approach can be used for clones with nested structure (Supplementary Fig. 4**f-h**). Finally, coherence and sparsity provide reasonable constraints when no clonal information is available, offering an approach to infer transition maps from state heterogeneity alone. We have extended CoSpar to this case.

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| **Box 1: Coherent Sparse Optimization**  To learn the transition map, we denote as a clone-by-cell matrix and introduce *S* as a matrix of cell-cell similarity over all observed cell states, including those lacking clonal information. In a model of stochastic differentiation, the transition map directly links any two density profiles at two time points:  where the density profiles are estimated as .  Since the matrices are determined directly from data, with enough information could be learnt by matrix inversion. However, in most cases, the number of clones is far less than the number of states. To constrain the map, we require that: 1) is a sparse matrix (Fig. 1**e**, left panel); 2) is locally coherent (Fig. 1**e**, right panel); and 3) is a non-negative matrix. With these requirements, the inference becomes an optimization problem:    quantifies the sparsity of the matrix through its L1 norm, and quantifies the local coherence of ( being the Graph Laplacian of the cell state similarity graph, and being the local divergence). The remaining constraints enforce the observed clonal dynamics, non-negativity of , and map normalization, respectively. At , the minimization takes the form of *Lasso*26, an algorithm for compressed sensing. Our formulation extends compressed sensing from vectors to matrices, and to enforce local coherence. The local coherence extension is reminiscent of the *fused Lasso* problem27. An iterative, heuristic approach solves the CoSpar optimization efficiently (Fig. 2**a**; Supplementary Fig. 2). See Methods and Supplementary Notes 1-3 for further details. |

**CoSpar infers dynamics robustly in simulations.**

We used computer simulations to establish the basic performance of CoSpar. We modeled cells progressing through a sequence of gene expression states either towards a single fate (Fig. 3**a**) or bifurcating into two fates (Fig. 3**e**), with clones sampled in a manner representative of LT-scSeq experiments13,14. We then used the simulated data to infer the transition rates and fate biases of the simulated process. With 1000 clones, mean transition rates inferred by CoSpar were within 3 standard deviations () of the actual transition rate distribution 98% of the time (TPR>98%, Fig. 3**d**). In simulations of bifurcating dynamics, CoSpar predicted the distribution of progeny fates with 85% Pearson correlation to ground truth (Fig. 3**j**). Inferences remained similarly accurate with as few as 30 clones (Fig. 3**d**). These results established that CoSpar can quantitatively infer transition maps in idealized conditions.

We examined how two errors typical of LT-scSeq -- barcode homoplasy, and clonal dispersion -- would alter dynamic inference. Enforcing sparsity and local coherence should make inference insensitive to both sources of errors. To simulate homoplasy, we allowed different clones to acquire the same barcode (Fig. 3**a**). CoSpar only detectably lost accuracy when all lineage barcodes mixed more than ten clones on average (Fig. 3**b-d**) – a degree of homoplasy far higher than expected in most experiments. The method should thus be robust to most LT-scSeq applications, and may even be suitable for parsing lineage-tracing experiments with very few barcodes28,29. To study clonal dispersion, we simulated sampling clones at increasing times post-barcoding. CoSpar proved largely insensitive to dispersion resulting from lag time: even after five cell cycles it recovered fate biases and mean transition rates with no loss of accuracy (Fig. 3**g-i**).

CoSpar performance can be contrasted with that of approaches used in previous work, which average the transitions between cells observed in each clone at different time points13. While this approach works for perfect data, it is severely affected by both lag time and barcode homoplasy (Fig. 3**dgi**).

**CoSpar predicts early fate bias in hematopoiesis.**

We applied CoSpar to published datasets from three independent experiments. The first experiment tracked hematopoietic progenitor cells (HPCs) differentiating in culture, with clones sampled on days 2, 4 and 6 post-barcoding (Fig. 3**ab**)13. During this time, cells progressed from a heterogeneous pool of HPC states into ten identifiable differentiated cell types. We used all clonal data to generate a ground truth for the early fate bias towards either the Monocyte or Neutrophil fate, using the simple method from Weinreb et.al.13 (Fig. 4**c**). Below, we evaluated the accuracy of fate prediction using its Pearson correlation with the ground truth.

As a baseline for comparison, we applied CoSpar to predict HPC fate bias using state information alone (Fig. 1**d**). Even without access to any clonal data, CoSpar could resolve early fate bias at a performance close to the upper bound defined by cross-validation of the ground-truth data (CoSpar correlation R=0.69; ground-truth R=0.72) (Fig. 4**eg**; Supplementary Fig. 6**a**). This performance reflects improvements from enforcing coherence and sparsity (R=0.51-0.54 prior to CoSpar; Fig. 4**d**; Supplementary Fig. 3**f**). However, the prediction based on state information alone is limited because it is sensitive to the choice of distance metric used in analysis (Fig. 4**g**; Supplementary Fig. 3**e**).

Clonal information eliminated the sensitivity to distance metric. To show this, we applied CoSpar to data restricted in time, or restricted in its quality and depth. Using even a single time point of clonal data (day-6), CoSpar recovered the early fate bias (Fig. 4**f**; R=0.68), and it did so robustly over a range of parameters and choices of distance metrics (Fig. 4**g**;Supplementary Fig. 3**e**). Further, it recovered the differentiation hierarchy seen in the correlation of clonal barcodes across all cell types (Supplementary Fig. 3**cd**). When using a sub-sampled dataset from the top 15% most dispersed clones as ranked by day-4 intra-clone distance (Fig. 4**b**), CoSpar performed similarly well, and outperformed the original method used to analyze this data13 (Fig. 4**hi**;Supplementary Fig. 3**ab**)**.** Thus, CoSpar successfully facilitates analysis of clones at a single time point, or using a fraction of the original data collected in this example.

These benchmarks suggest that CoSpar should be able to predict fate biases not previously recognized. We investigated fate biases in the Gata1+ states that give rise to five mature fates: Megakaryocyte (Mk), Erythrocyte (Er), Mast cell (Ma), Basophil (Ba), and Eosinophil (Eos) (Fig. 4**ak**). In culture, Mk and Er arise from a common progenitor (MEP), while Ba, Eos and Ma are produced by a different progenitor (BEMP)30,31. Existing studies of these progenitors are hampered by the lack of good markers. While molecular signatures of FACS-sorted MEP have been explored recently32, less is known about the transcriptome identity of BEMPs. This dataset provides an opportunity to predict the molecular identity of these early progenitors. The original method used to analyze this data finds very few genes distinguishing BEMPs and MEPs (Supplementary Fig. 3**g-i**). Yet using all clonal information, CoSpar predicts an early fate decision boundary between MEP and BEMPs (Fig. 4**jk**). Differences between the putative BEMPs and MEPs are evident in scRNA-seq data alone, but clonal data provide confidence that the differences are associated with functional fate bias. The fate bifurcation correlates with the expression of known marker genes (*Slc14a1* for Mk32, *Thy1* for Ba33; Fig. 4**l**), and a transcription factor (TF) *Cebpa* that regulates Eos and Ba differentiation30. We identified 377 known and novel putative fate-associated genes (Fig. 4**m**; Supplementary Table 1).

**CoSpar reveals early fate bias in reprogramming.**

The second experiment we analyzed tracked cells during the reprogramming of fibroblast cells over 28 days into endoderm progenitors (Fig. 5**a**)14. In this experiment, approximately 30% of cells successfully reprogrammed; the remainder failed. Clonal analysis with cumulative barcoding was used to identify these cells early and predicted features that regulate their fate (Fig. 5**bc**). We used clones strongly enriched in one of the two fates, identified by the original study, to generate the ground truth for early fate bias, and we then used it to benchmark CoSpar.

To evaluate CoSpar, we revisited this experiment after discarding over 90% of clones, and we specifically retained clones that show the least bias in reprogramming outcomes. Despite deliberately using down-sampled low-quality data, CoSpar recapitulated fate bias: the predicted progenitors of reprogrammed cells share 73 out of 100 marker genes with the ground truth population (Fig. 5**f**). Established marker genes are among our top predictions: *Apoa1*, *Spint2*, *Col1a2*, *Peg3*, as well as *Mettl7a1*, which was found to improve reprogramming14. These genes could be associated with fate bias using as few as 5% of the original clones, even when deliberately selecting clones with minimal fate bias (Fig. 5**de**;). By contrast, the analytical approach used in the original study14 failed to identify fate-predictive gene expression after such severe reduction in data quality (Fig. 5**ef**; Supplementary Fig. 4**b**). Further, CoSpar performed robustly when using only clonal data from the final time point of the experiment (Fig. 5**gh**; Supplementary Fig. 4**cde**).

As in hematopoiesis, it is instructive to see the information encoded in clonal relationships. When applying CoSpar without clonal data, we found that CoSpar predicts the same early fate biases (Fig. 5**g**, Middle panel), but is again sensitive to the distance metric used (Fig. 5**h**). A different distance metric performs best here from the hematopoiesis dataset, suggesting that there is no simple ‘best-practice’ approach to dynamic inference in the absence of clonal data.

Finally, we applied CoSpar to predict fate bias at the earliest available time point after reprogramming is initiated (day 3), where no clonal information is available and fate bias remains unexplored14. Using clonal information, CoSpar predicts strong fate biases (Fig. 5**i**), arguing that future reprogramming success is established very early on. This prediction is supported by the differential expression of transgene *FoxA1-HNF4a* (a TF cocktail to induce reprogramming), the reprogramming marker gene *Apoa1,* and failed trajectory marker *Col1a2* and *Dlk1*14. We also found other known and putative drivers or marker genes that correlate with fate bias on day 3 (Fig. 5**k**; Supplementary Table 2).

**CoSpar predicts early fate bias during direct lung differentiation.**

In the third experiment, human pluripotent stem cells were cultured to differentiate directly todistal lung alveolar epithelial cells (specifically, induced alveolar epithelial type 2 cells, or iAEC2)23. Here, clonal and transcriptomic information were profiled jointly on day 27 after initial barcoding on day 17, and a separate time-course experiment produced scRNA-seq data for day 17 and 21(Fig. 6**a**). In this study, the authors reported the existence of multipotent clones on day 17, but they did not investigate fate biases within this population. A re-examination of their clonal data, however, suggests strong fate biases as early as day 17. Out of the 272 clones, 25% are enriched in either the iACE2 or non-iACE2 cluster (FDR=0.01), and the fate bias profile differs significantly from that of randomized clones (Fig. 6**b**). The enriched fraction becomes 78% for the large clones (10 cells) analyzed in the original study. Accordingly, clonal representation of iACE2 cells anti-correlates with other fates (Supplemental Fig. 6**bc**). We investigated signatures that could predict effectors of fate bias among day 17 progenitors.

Applying CoSpar, we assigned a putative fate bias to each of the cells seen on day 17. This analysis predicts that these endodermal progenitors are already heterogenous in a manner that is strongly correlated with fate (Fig. 6**c**). CoSpar also predicts the existence of unbiased multipotent states; these strongly overlap with highly proliferating cell states on day 17 and are consistent with large clones hosting multiple endodermal lineages on day 27 (Supplementary Fig. 5**d**). We expected weaker fate biases in cells earlier in their differentiation, which is confirmed by applying CoSpar to day-15 cells in this experiment (Supplementary Fig. 5**e-g**). Among genes differentially expressed between the two biased populations on day 17, we identified several established TFs that regulate lung differentiation: *CEBPD, NKX2-1, SOX9, SOX11* (Fig. 6**de**;Supplementary Table 3)23,34–36.

**Discussion**

Here we have developed a mathematical framework for systematically inferring dynamic transitions by integrating state and clonal information. Extending compressed sensing, our method takes advantage of reasonable assumptions on the nature of biological dynamics: that cells in similar states behave comparably, and that cells limit their possible dynamics to give sparse transitions. Using reference datasets, we demonstrated that coherent sparse optimization relates molecular heterogeneity of cells to their future fate outcomes, in a manner that is robust to typical sources of experimental error (Fig. 1**f**), using as little as 5-10% data originally collected. The computational methods used in each original study to analyze clonal data were not similarly robust. CoSpar also robustly recovered early fate biases in these datasets using only clonal information from the last time point. Without clonal information, fate biases could be recovered well, but results were sensitive to the choice of distance metric, and no single approach reliably inferred fate choices across all data sets when clonal data was absent.

The robustness of CoSpar could greatly simplify the design of LT-scSeq experiments, by enabling experiments with fewer cells, fewer clones, or fewer time points. In all three datasets considered here, CoSpar reveals clear early fate boundaries that were not previously reported, yet in agreement with the heterogeneity of key transcription factors and fate determinants. We predicted novel transcription factors and markers in each case, and they could facilitate enriching and manipulating the desired fate outcomes.

The examples we have analyzed specifically relate to LT-scSeq implemented using LARRY13,23 and CellTagging14, but CoSpar is not limited to these technologies. The state measurement can be transcriptomic (via scRNA-seq or RNA fluorescence in situ hybridization (FISH)37), as shown above, as well as proteomic and epigenomic; and lineage tracing can be achieved with static DNA barcodes13,23, endogenous mutations38, or exogenous DNA constructs that accumulate mutations over time, like CRISPR-based editing2,17,18,39,40. CoSpar can thus facilitate interpretation of the rapidly evolving field of LT-scSeq, and thus accelerate exploration of development and disease.

CoSpar also has limitations, which directly follow from its central assumption. By enforcing coherent fate choices between similar cells, CoSpar becomes sensitive to choices in measuring cell-cell similarity (Fig. 2**a**; Supplementary Fig. 7**a**), and to the degree of smoothing used in implementing the algorithm. Thus, CoSpar will fail to identify fate biases when heterogeneity relevant to cell fate is not measured, or when it is filtered out during data analysis, or due to over-/under-smoothing. In addition, when inferring progenitor bias from clones observed at a single late time point, CoSpar performs by matching heterogeneity in initial states to the structure of clones observed later. CoSpar can fail in this case when heterogeneity in the later population cannot be related to heterogeneity in the initial population (Supplementary Fig. 7**b**). Despite these caveats, CoSpar provided sensible predictions in the cases examined here.

We expect coherent sparse optimization to be useful for applications beyond dynamic inference. Several problems require learning locally coherent maps from few and noisy measurements. Such problems occur, for example, when: integrating two sets of measurements in the same system41,42 (batch correction and multi-omics); decoding spatial transcriptomes from composite FISH measurements43; and inferring responses of a system to individual perturbations from composite perturbation readouts44–46. Outside of biology, the association of measurements in one modality with sparse measurements in another can occur in marketing and social networks47. Forcing coherence and sparsity constraints could greatly improve map inference in general, reducing the cost of data acquisition and enabling new discoveries.

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