PLOS | COMPUTATIONAL BIOLOGY

RESEARCH ARTICLE

Representing high throughput expression profiles via perturbation barcodes reveals compound targets

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Tracey M. Filzen, Peter S. Kutchukian, Jeffrey D. Hermes, Jing Li, and Matthew Tudor. Representing high throughput expression profiles via perturbation barcodes reveals compound targets.
PLOS Computational Biology, 13(2):e1005335, February 2017

Perturbation Barcodes

Overview

Goal Representation learning for transcriptomic analysis.

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Methods Metric Learning Network

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Evaluation	Efficacy in various predictive or clustering tasks.
Code	`https://github.com/matudor/siamese`

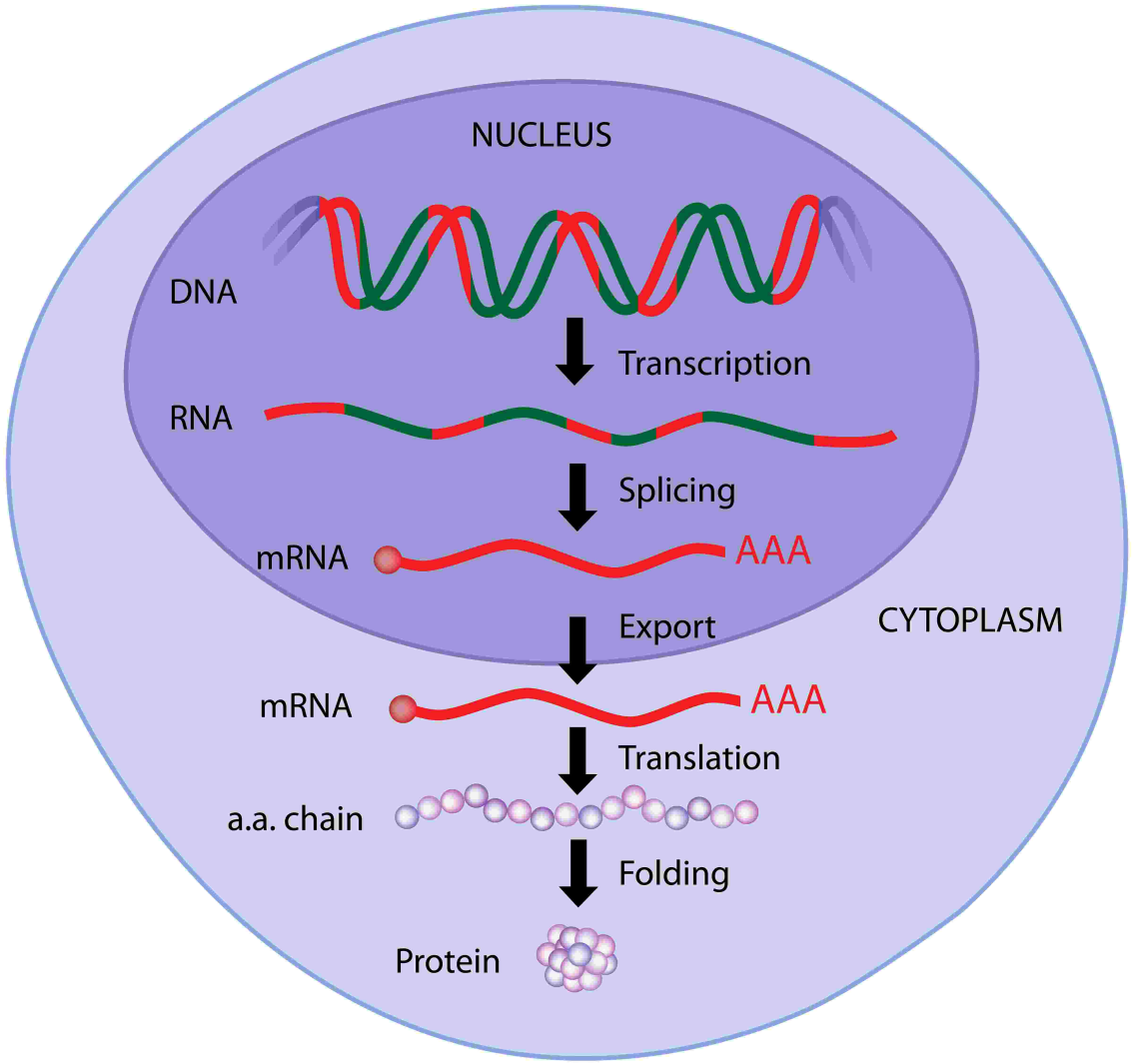
Gene Expression Data

Overview

Transcriptomic/Gene expression data measures counts of transcription factors inside perturbed cells.

Gene Expression Data

Overview



http://www.biology-questions-and-answers.com/images/Protein-Synthesis.jpg

Gene Expression Data

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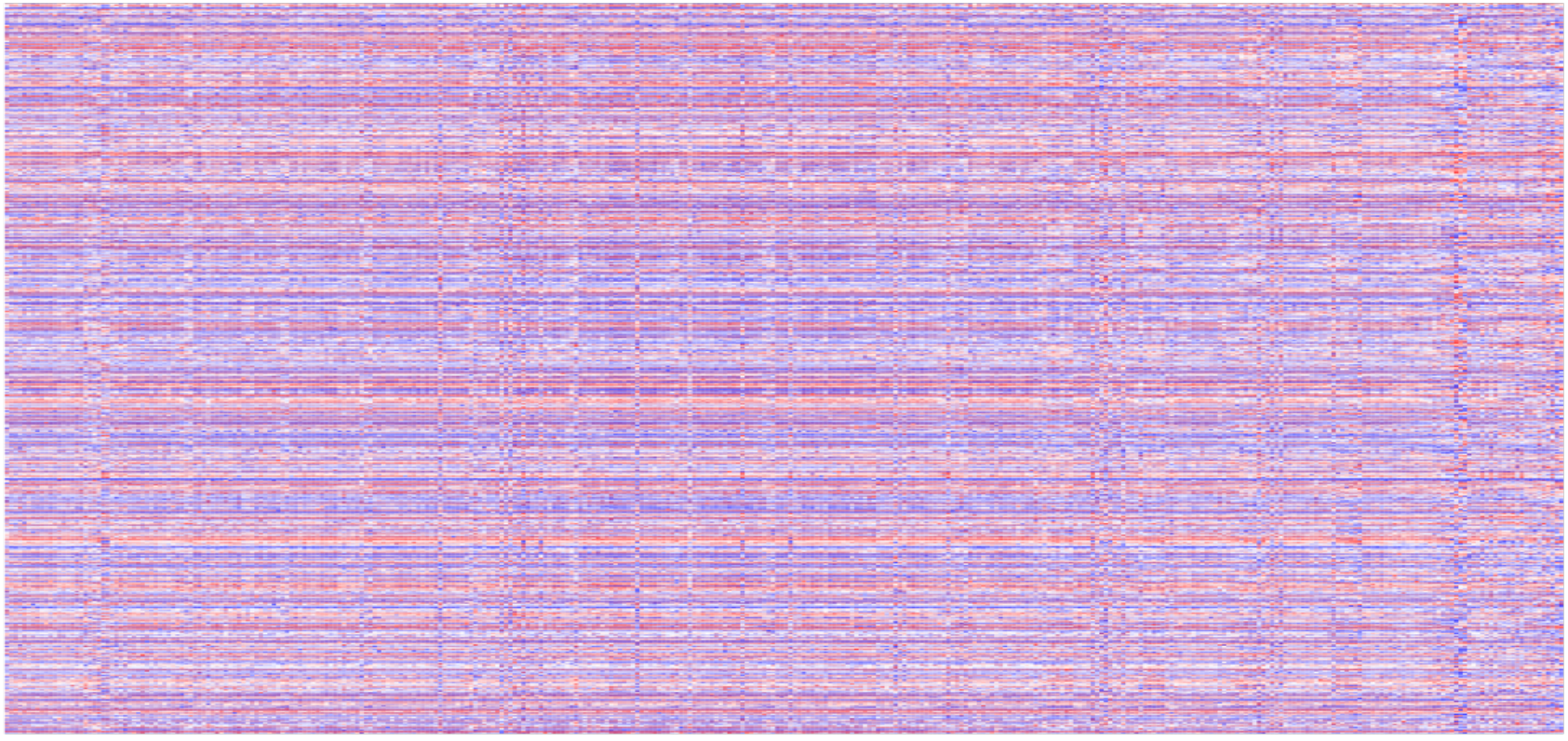

Gene Expression Data

Why we care

Gene expression vectors give a picture of the internal state of the cell at the time of measurement.

Datasets

Genometry Data (private)

- Two cell lines (PC3, ME180).
- 3699 known or potential bioactive compounds used (6h).
- Some compounds had multiple replicates, others did not.
- 14 months total of data collection.
- After quality control, 7573 total L1000 vectors.

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- After quality control, **7573** total L1000 vectors.

Datasets

LINCS Data (public)

- 15 cell lines
- 273 compounds, 2 doses, 24h.
- Data more heavily pre-processed.
- Data available: `https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE70138`

Model

Side Task Representation Learning

Biological replicates vary widely:

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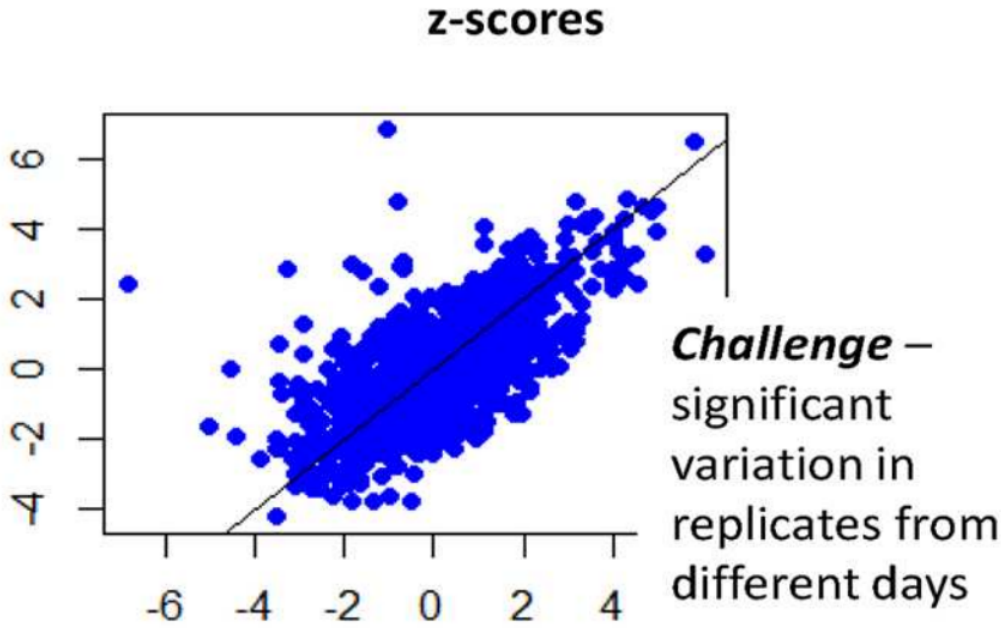

Figure 1 (partial), Page 4

Model

Side Task Representation Learning

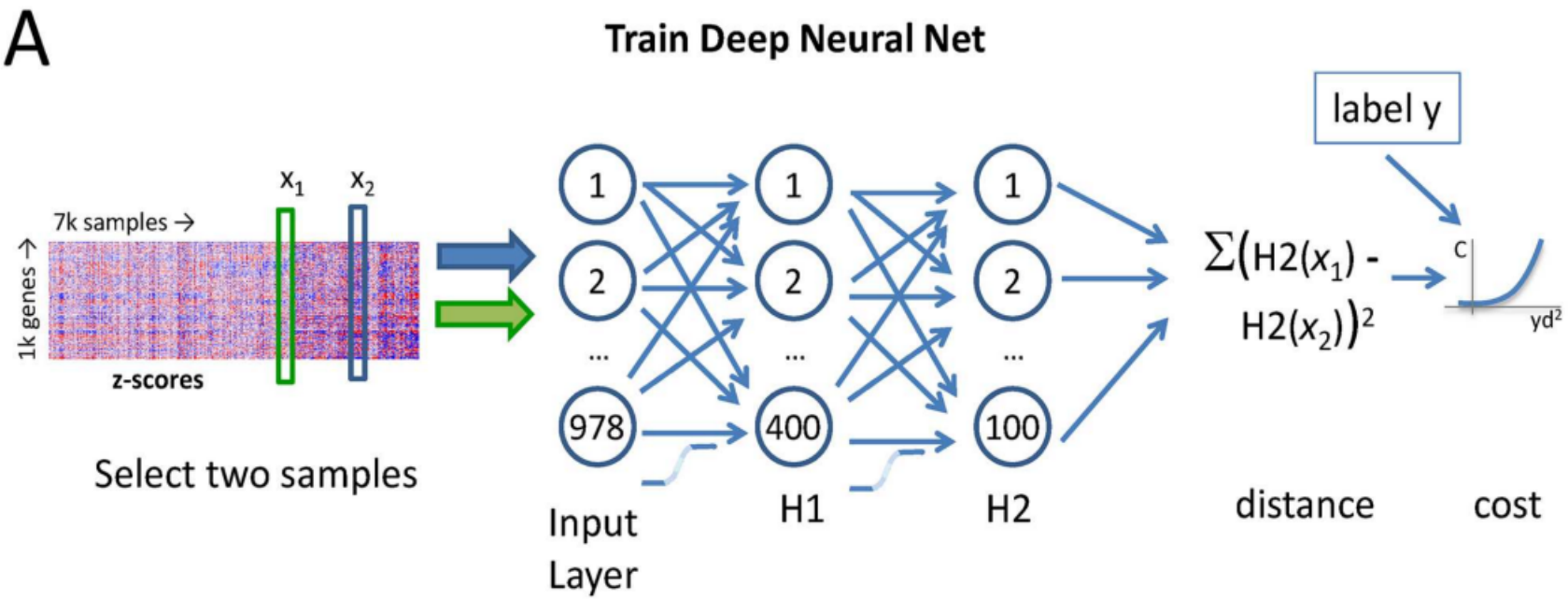

Figure 2 (partial), Page 6

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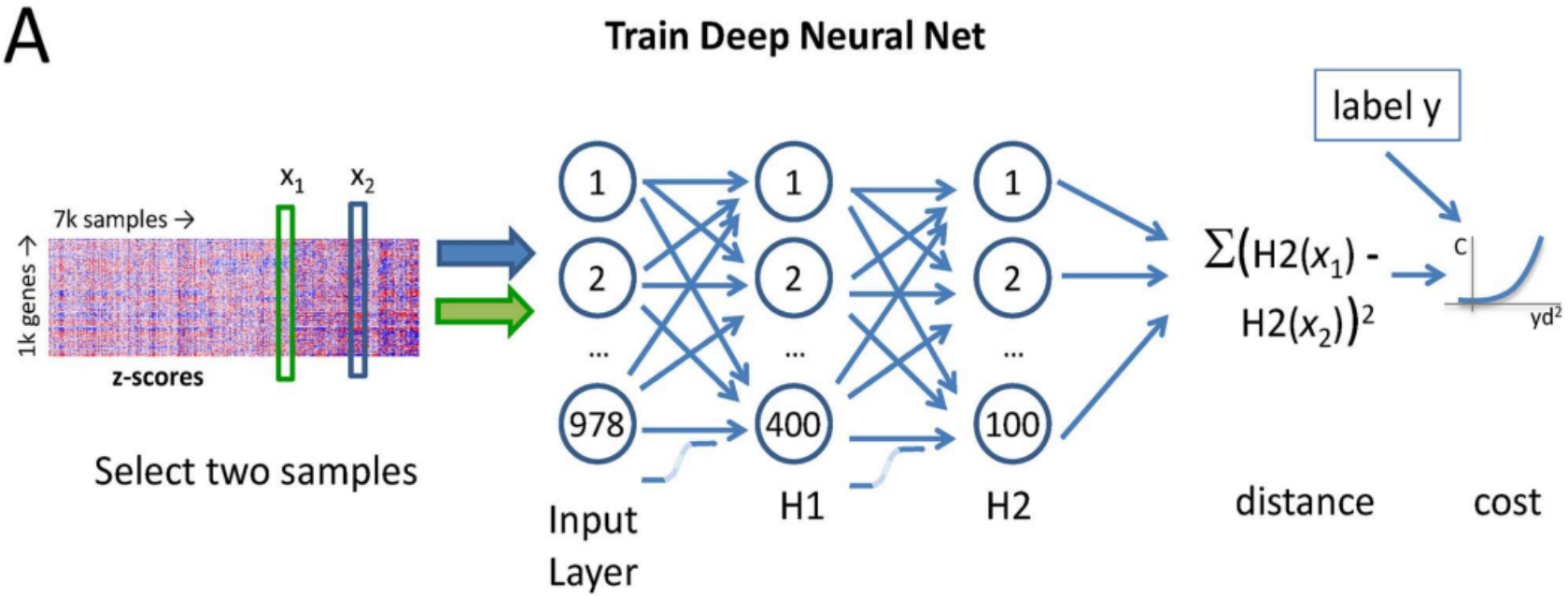
Side Task Representation Learning



$$c = \text{softplus}\left(1 - y\left(5 - \|\text{H2}(\boldsymbol{x}_1) - \text{H2}(\boldsymbol{x}_2)\|^2\right)\right).$$

Figure 2 (partial), Page 6

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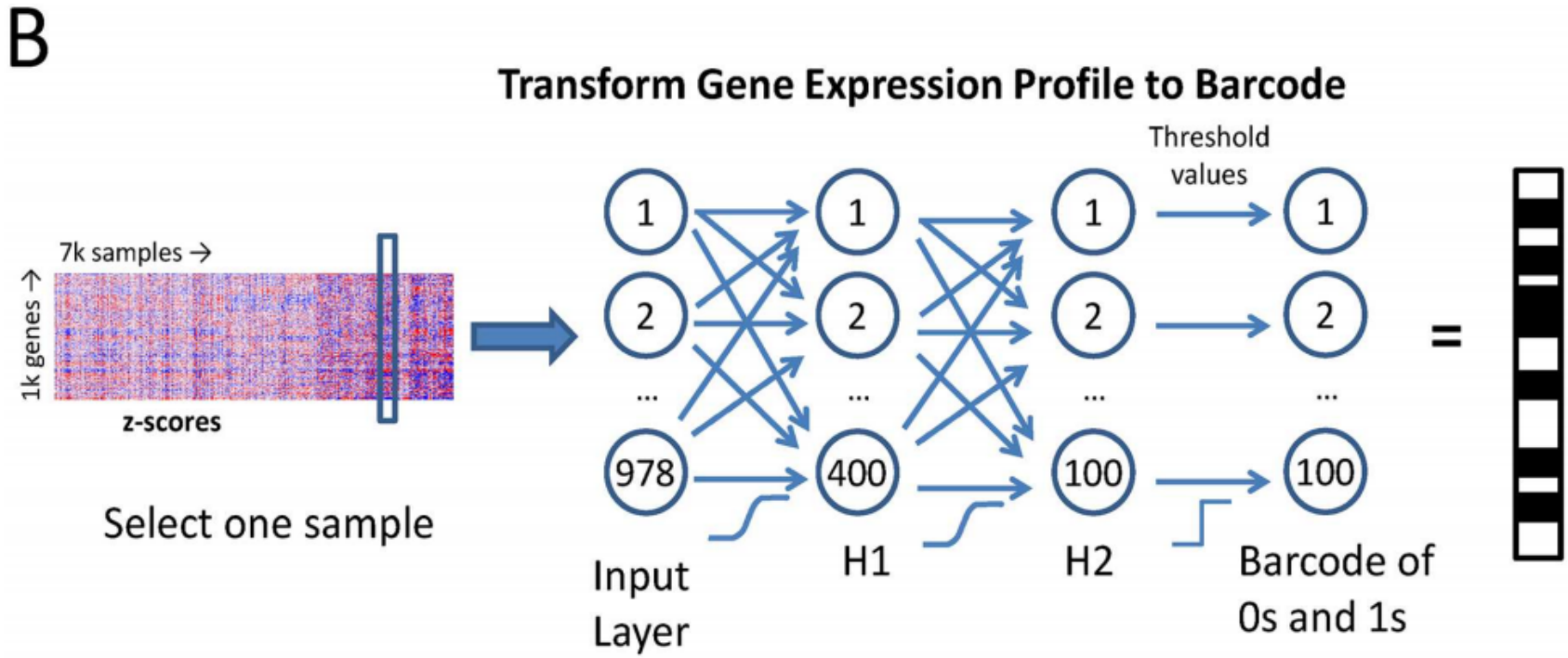

Figure 2 (partial), Page 6

Evaluation

Comparitive Tasks

Median rank of replicates How many samples on average are closer to a query sample than its replicates?

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Promiscuity prediction How well do the various representations predict compound promiscuity?

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Comparitive Tasks

Table 1. Performance of learned perturbation barcodes compared to z-scores and GSEA scores.

metric	z-score	GSEA	perturbation barcode
Median rank of replicates (of 7573)	225	72	**24**
Distance by shared target, t statistic	-1	-38	**-43**
Structural clustering overlap with expression clustering	0.01	0.03	**0.17**
Correlation of HTS profiles with expression	0.04	0.02	**0.12**
Promiscuity prediction by SVR, R^2	0.21	0.16	**0.34**

Evaluation

Exploratory Evaluation

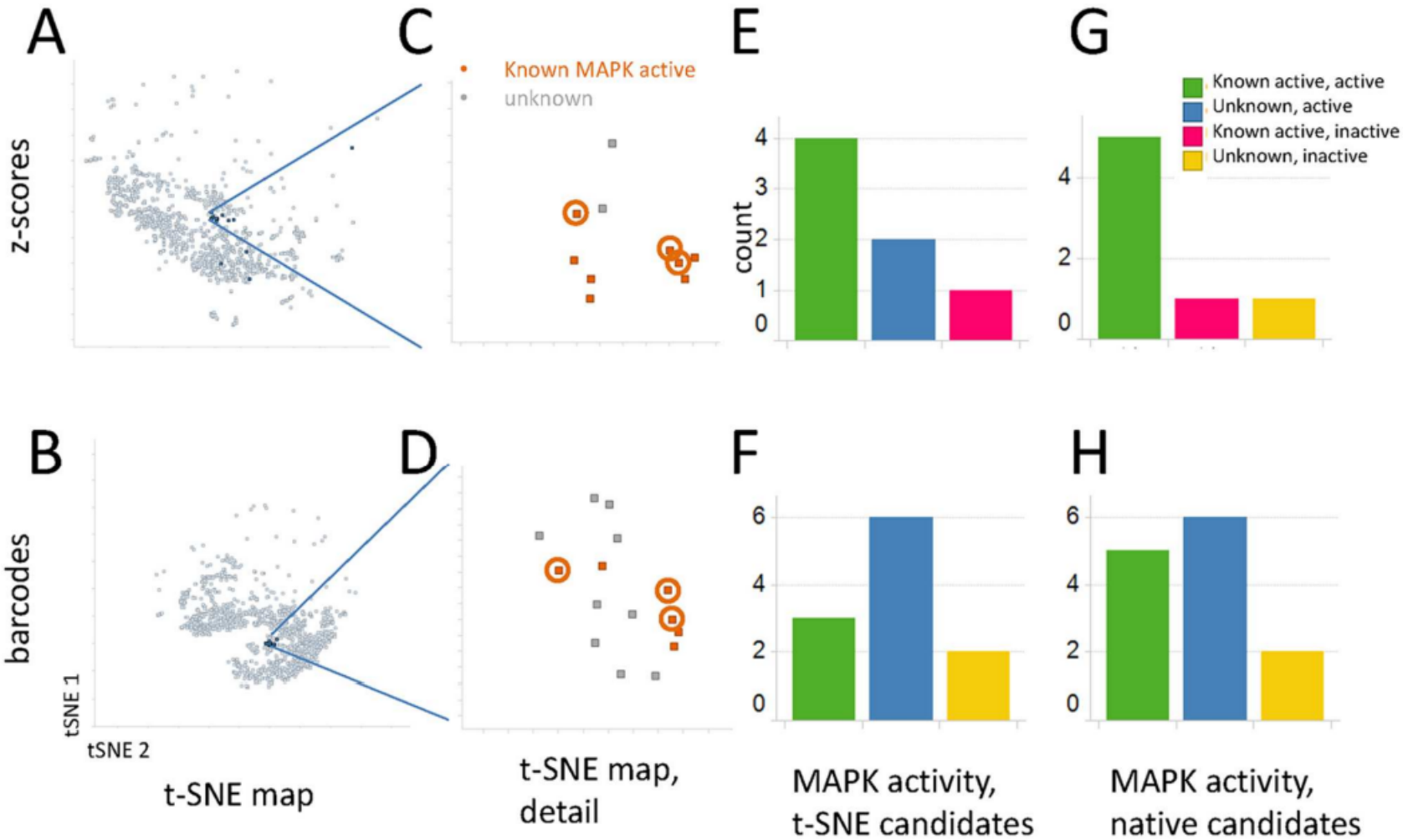

Figure 3, Page 11

Concluding Thoughts

Pros:

- Broad evaluation

Cons:

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Pros:

- Broad evaluation
- Good choice of side task

Cons:

- Questions remain about network design.
- Main results on private data.
- Small population size raises concerns about generalizability.
- Generalizability not really tested.

Conclusion

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