Learning interpretable embeddings for *in vivo/in vitro* comparison of endometrial epithelium

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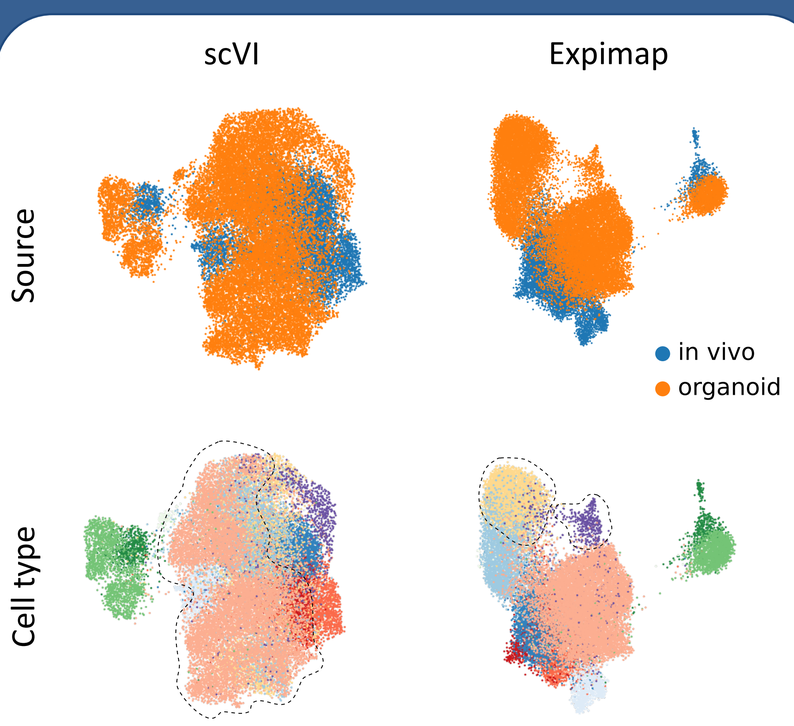
Background

- The endometrium is the mucosal lining of the uterus. It plays a key role in female reproductive health and disease.
- Endometrial organoids derived from glandular tissue reproduce key features of endometrial biology *in vitro.*[1,2]
- Deep learning models can be used to learn low dimensional representations of single cell omic data. Expimap[3] learns interpretable embeddings by mapping the gene expression matrix to known gene programs (GP).

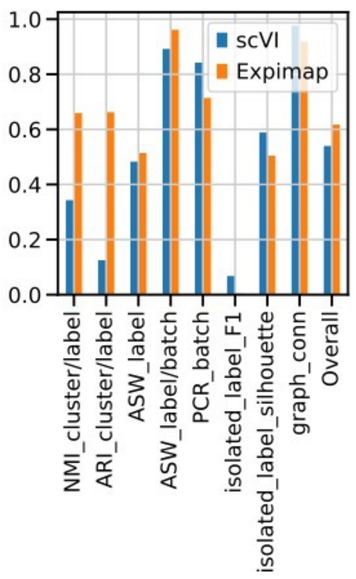
Expimap outperforms unconstrained models



Over-correction loses separation of organoid secretory cells

Successful separation of organoid populations which do not have *in vivo* counterparts

scIB[7] benchmarking



- in vivo_SOX9
- in vivo_SOX9_LGR5
- organoid_Estrogen Induced
- in vivo_Pre-ciliated
- in vivo_Ciliated
- organoid_Pre-ciliated
- organoid_Ciliated
- in vivo_Glandular_secretory
- in vivo_Glandular
- organoid_Secretory
- organoid_Inflamatory
- organoid_NH_Day0

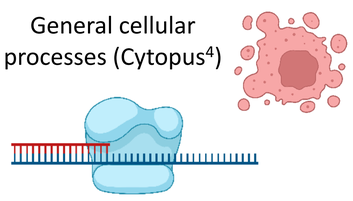
Future directions

- Extension to scRNA-seq datasets from organoids cultured according to different protocols
- Extension to multiple modalities (eg chromatin accessibility)
- Comparison to attention-based methods
- Perturbing differentially active pathways *in silico* and experimentally

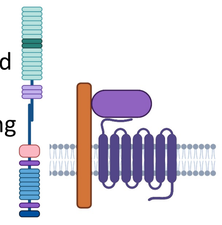
Building the Expimap model

Curated gene programs in the bottleneck layer:

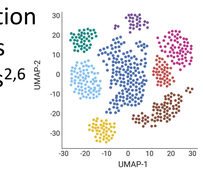
General cellular processes (Cytopus[4])

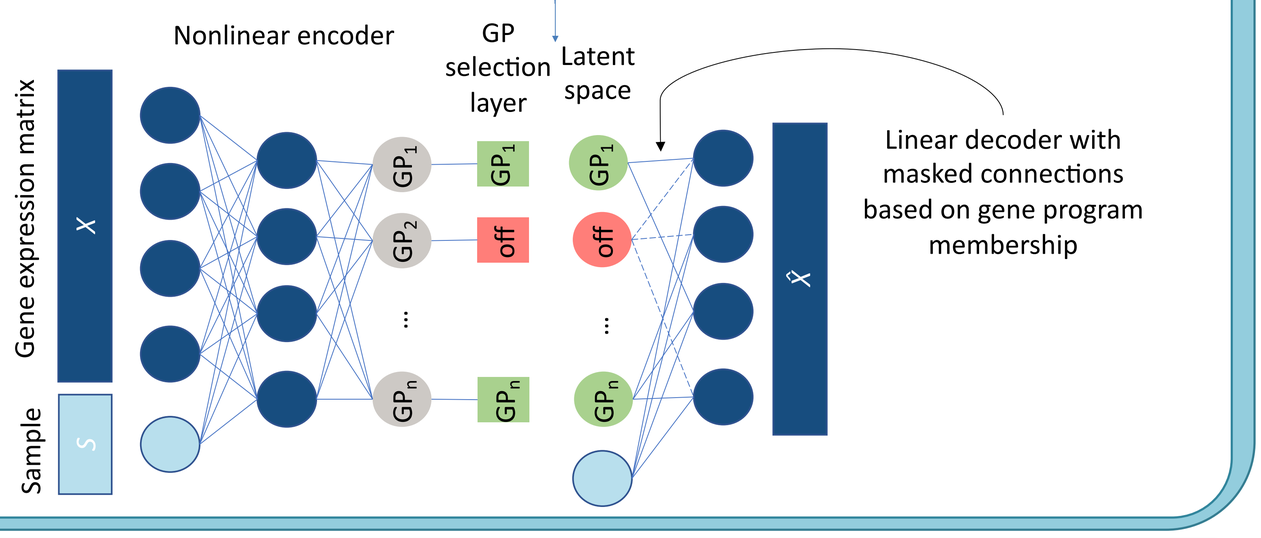


Pathways related to organoid culture conditions, Wnt, Notch and hormonal signaling (from Reactome[5])

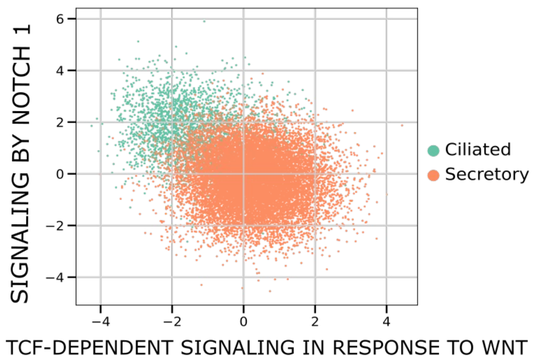


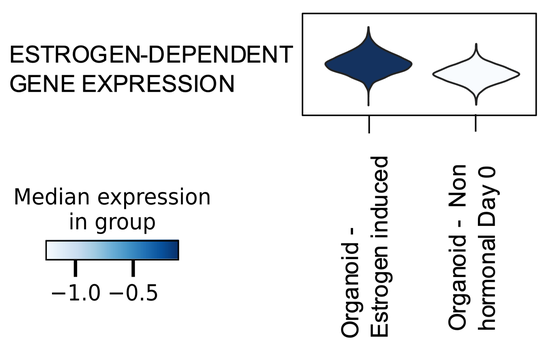
Cell-type specific markers and transcription factors regulons[2,6]





Expimap recovers expected biological patterns



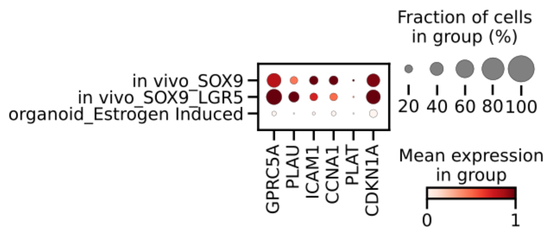


Expimap identifies *in vivo/in vitro* differences

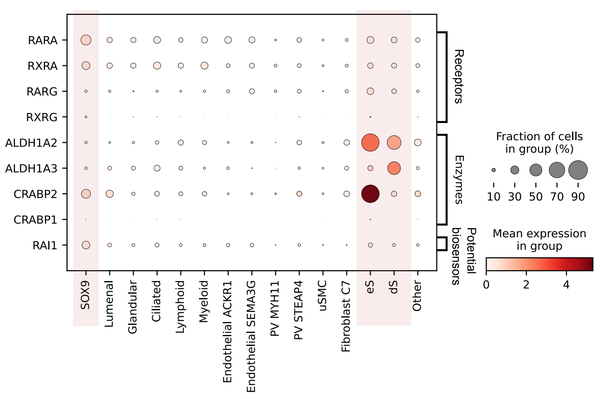
Differentially active GP are linked to cell division and proliferation, as well as organoid culture conditions and absence of stromal cell interactions

Retinoic acid

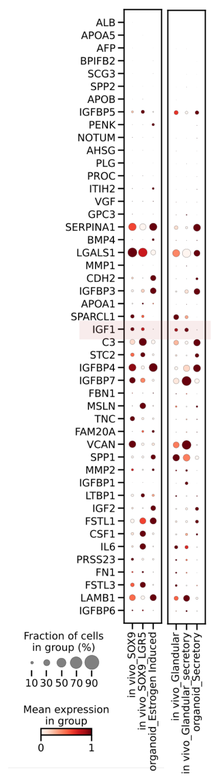
- Increased expression of retinoic acid receptor α target genes *in vivo*



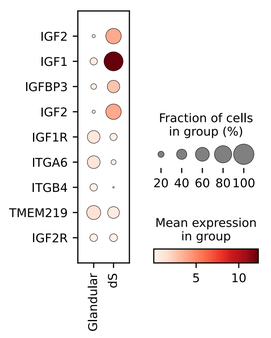
- *In vivo*, stromal cells signal to epithelial cells via RA



Insulin growth factor



- Differential activity of genes involved in regulation of IGF transport and uptake by IGFBP5
- Stromal cells signal to epithelial cells via IGF *in vivo :*



➢ Do these differences remain in organoids cultured with media containing vitamin A and insulin?

References:

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