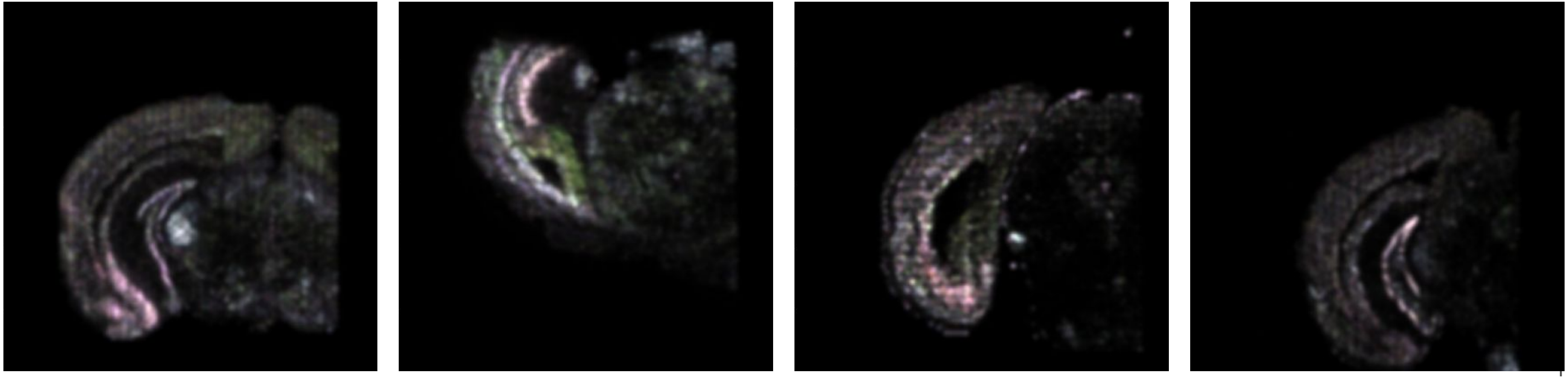
Spatially map single cell RNA-seq to spatial coordinates

without prior knowledge of cell locations for scRNAseq (BAR-seq2)



Motivation

Growing better organoids to form organ tissues for organ repair and regeneration

Mapping single cells to spatial structures improves interpretation of spatial developmental biology

For example, key kidney paper on SIX2 gene in progenitor kidneys involved spatial knowledge:

Six2 activity is required for maintaining the mesenchymal progenitor population in an undifferentiated state by opposing the inductive signals emanating from the ureteric bud.

Six2-expressing cells give rise to all cell types of the main body of the nephron during all stages of nephrogenesis.

THE EMBO JOURNAL

EMBO J. 2006 Nov 1; 25(21): 5214–5228. PMCID: PMC1630416
Published online 2006 Oct 12. doi: 10.1038/sj.emboj.7601381 PMID: 17036046

Six2 is required for suppression of nephrogenesis and progenitor renewal in the developing kidney

Michelle Self,[1] Oleg V Lagutin,[1] Beth Bowling,[1] Jaime Hendrix,[1] Yi Cai,[2] Gregory R Dressler,[2] and Guillermo Oliver[1,a]

Author information Article notes Copyright and License information Disclaimer

Cell Stem Cell
Volume 3, Issue 2, 7 August 2008, Pages 169-181

Article

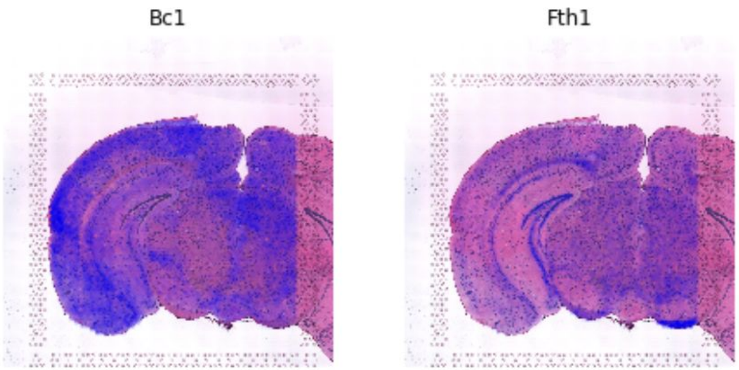
Six2 Defines and Regulates a Multipotent Self-Renewing Nephron Progenitor Population throughout Mammalian Kidney Development

Akio Kobayashi [1], M. Todd Valerius [1], Joshua W. Mugford [1], Thomas J. Carroll [1, 3], Michelle Self [2], Guillermo Oliver [2], Andrew P. McMahon [1]

Datasets

Spatial Transcriptomic data from the Allen Brain Institute is used from:

https://github.com/almaan/spacetx/



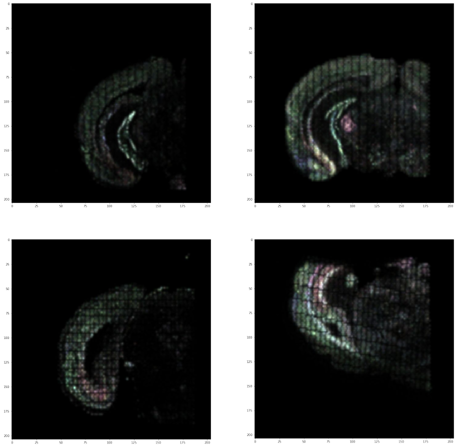
This is purposed for the **BAR-seq2** data of the **Competition from the Allen Brain Institute**:

https://labshare.cshl.edu/shares/gillislab/resource/CellTypeMapping_2022/

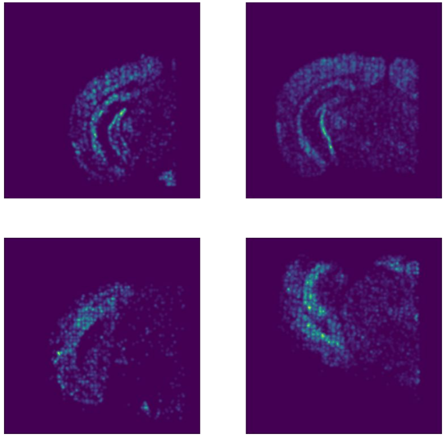
Name	Last modified	Size	Description
Parent Directory		-	
barseq2.hdf5	2022-04-16 11:27	29M	
barseq2.rds	2022-04-16 11:27	27M	
readme.txt	2022-04-16 11:27	1.2K	

Training set

Predicted image tissue histology pixels matched to observed image tissue histology pixels

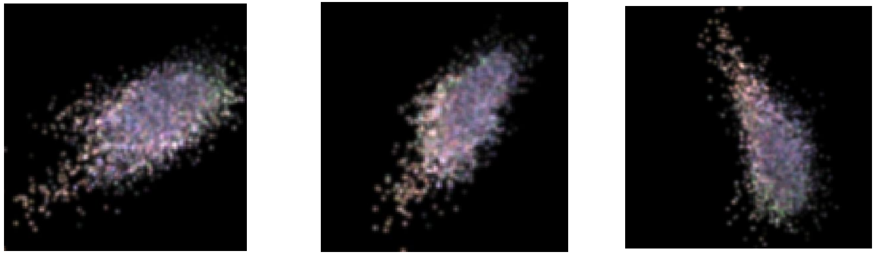


Predicted gene expression of SLC24A2 on spatial histology matched to observed spatial gene expression

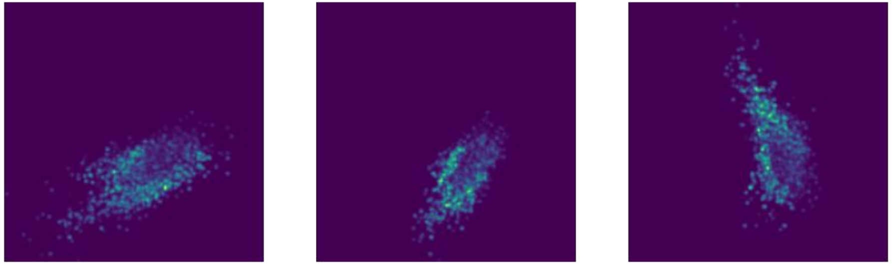


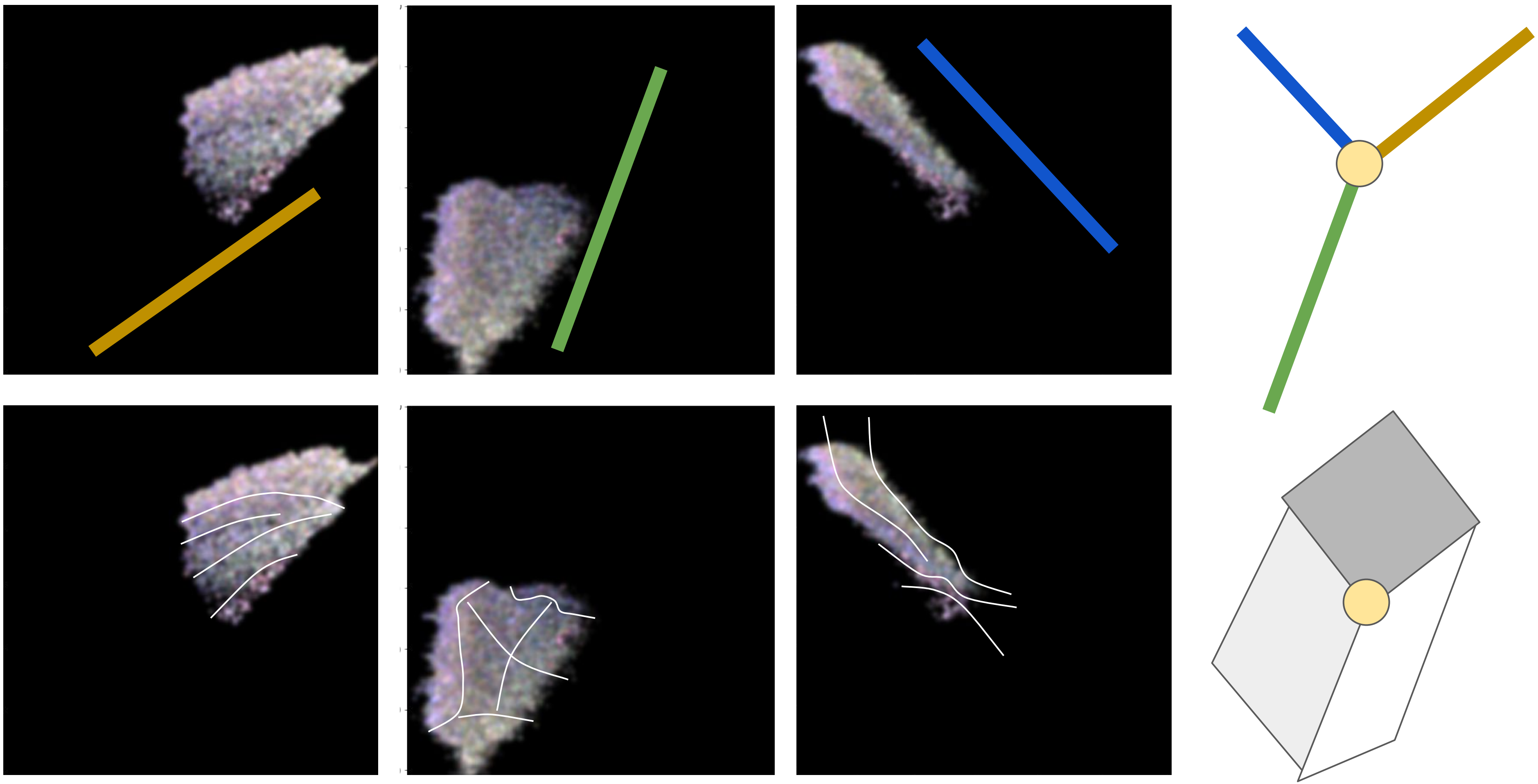
Test set

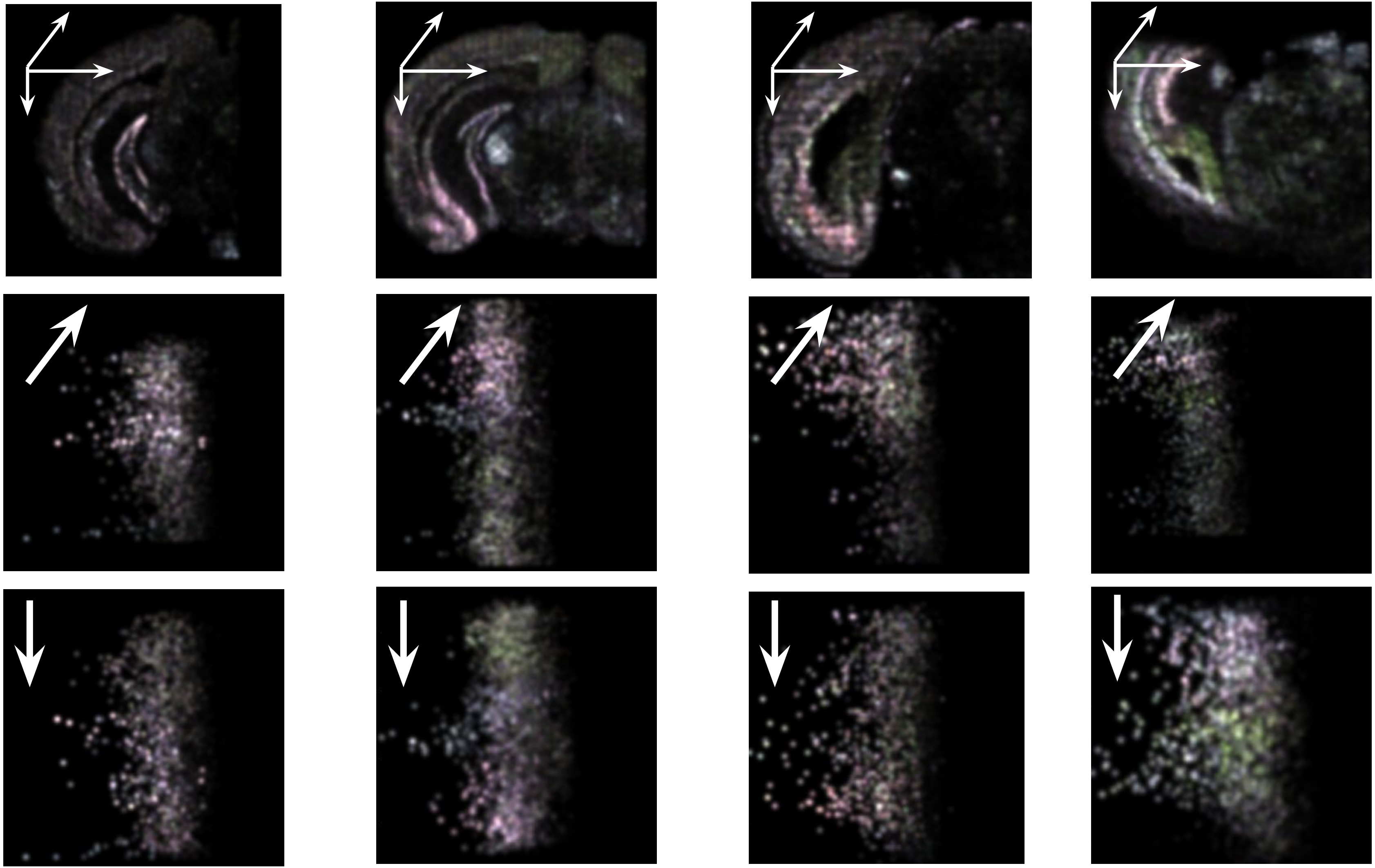
Predicted image tissue histology based on **scRNAseq + model**



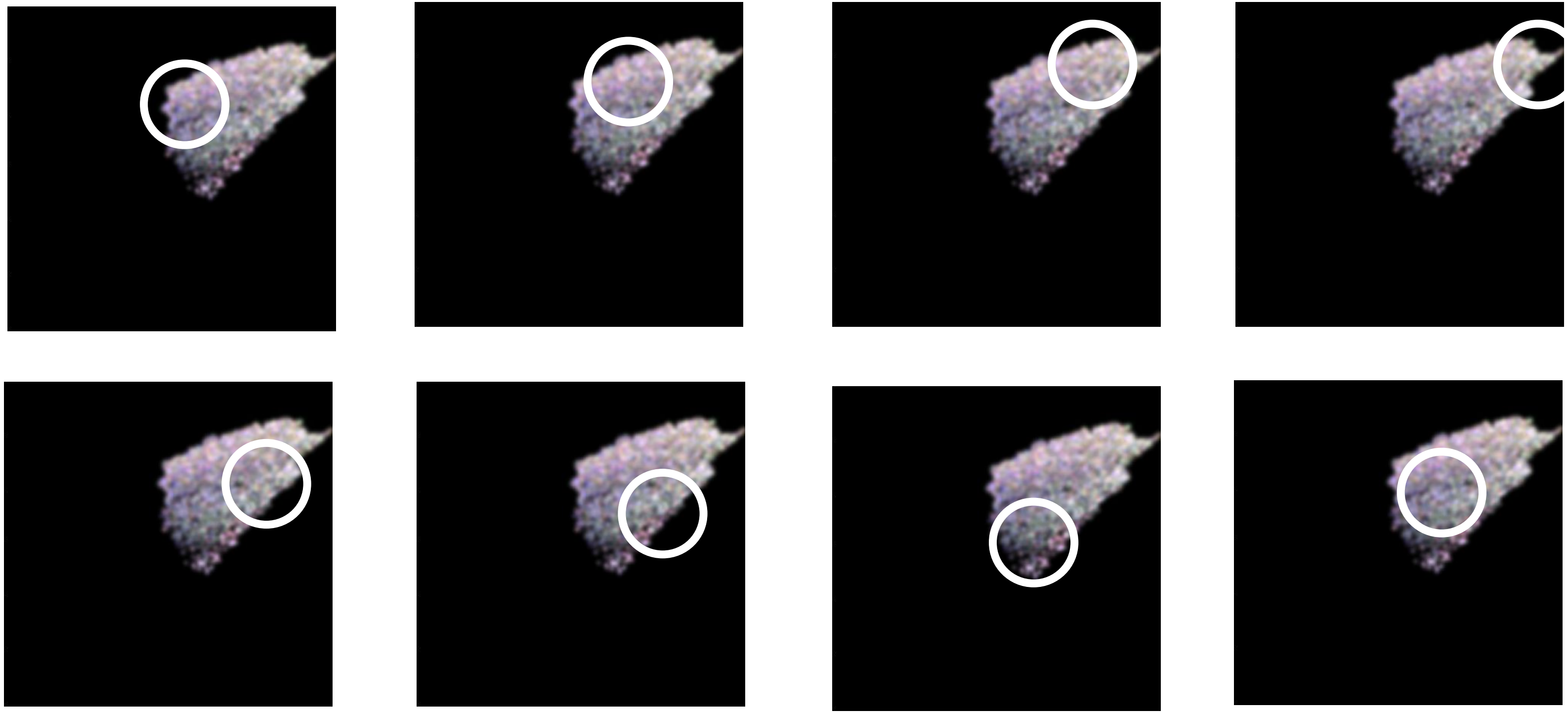
Predicted gene expression for SLC24A2 based on **scRNAseq + model**

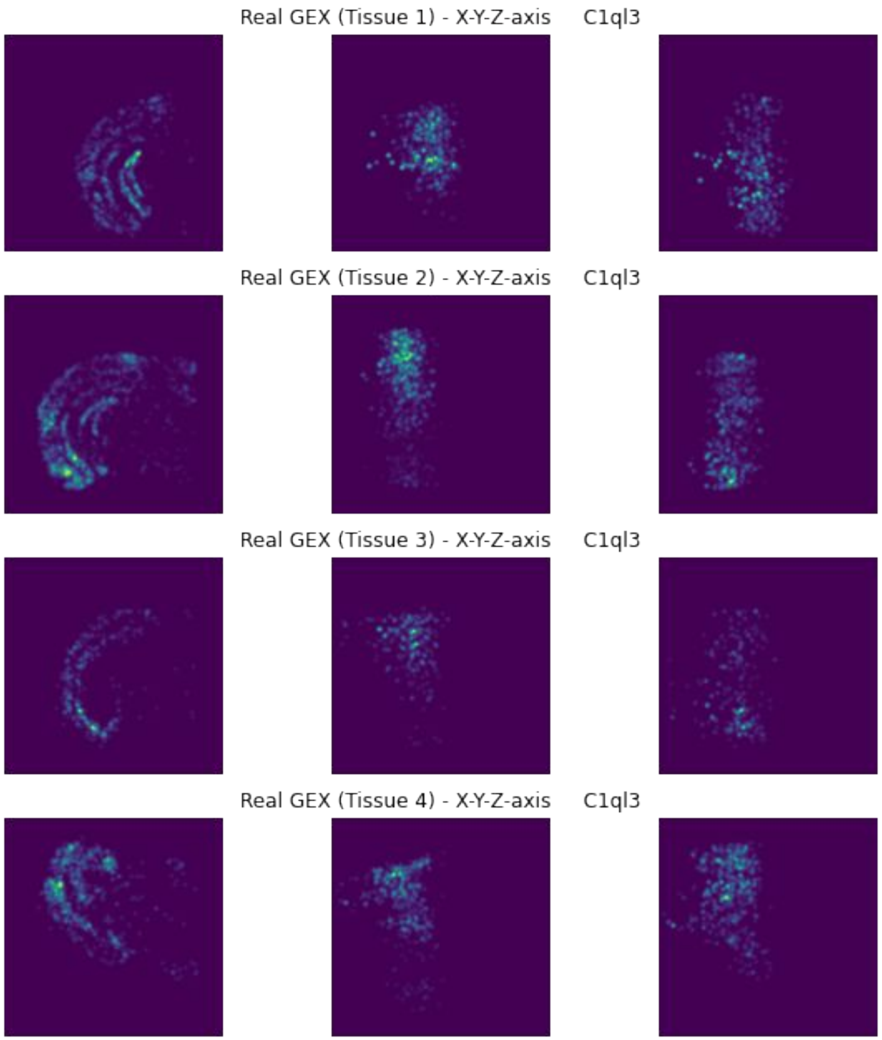


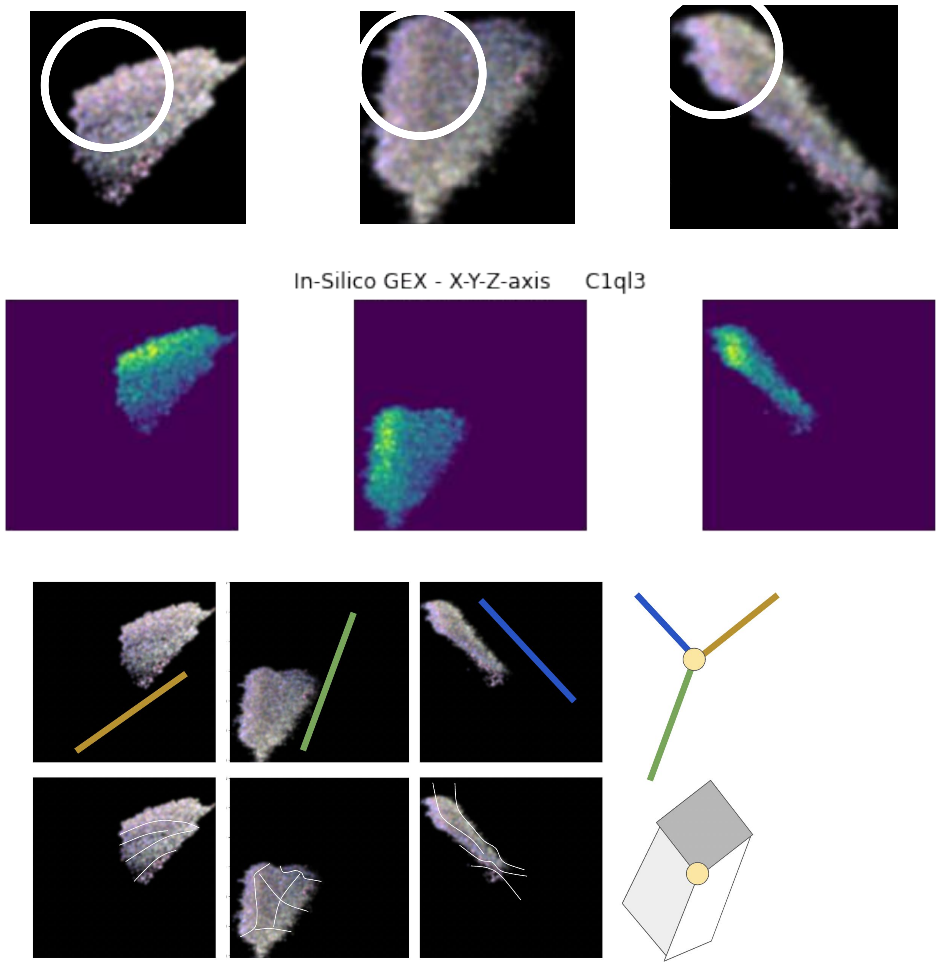


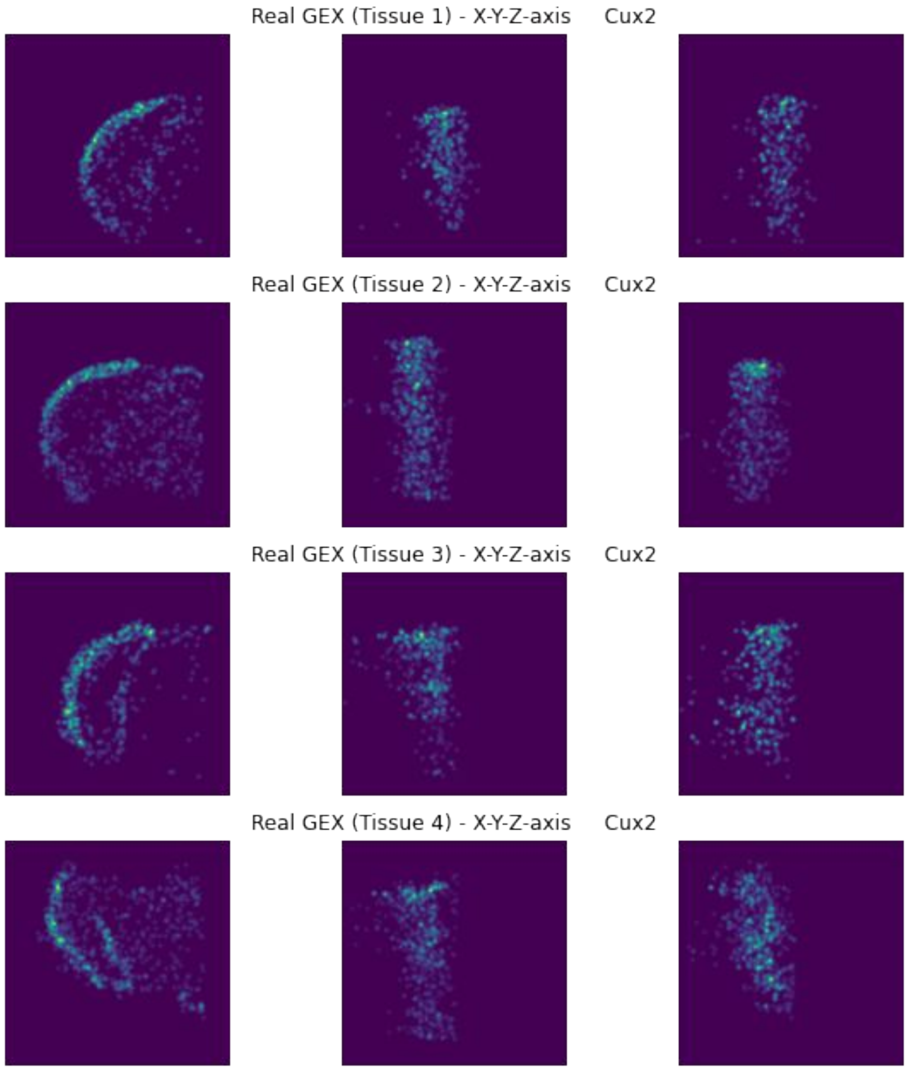


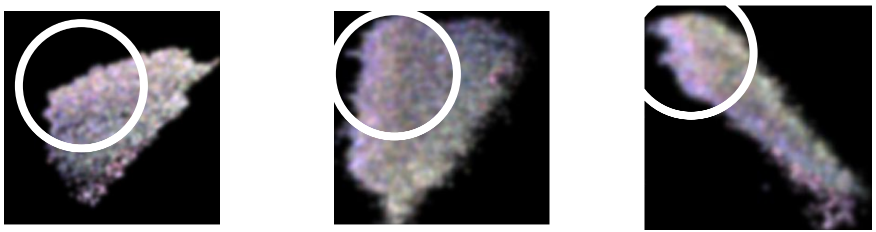
Next set of slides show the trajectory of gene expression based on location for different genes

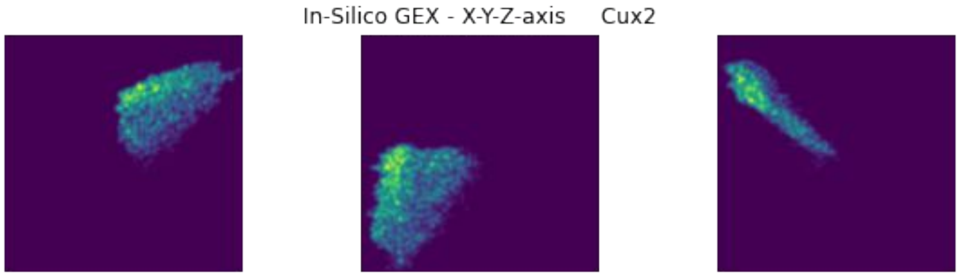


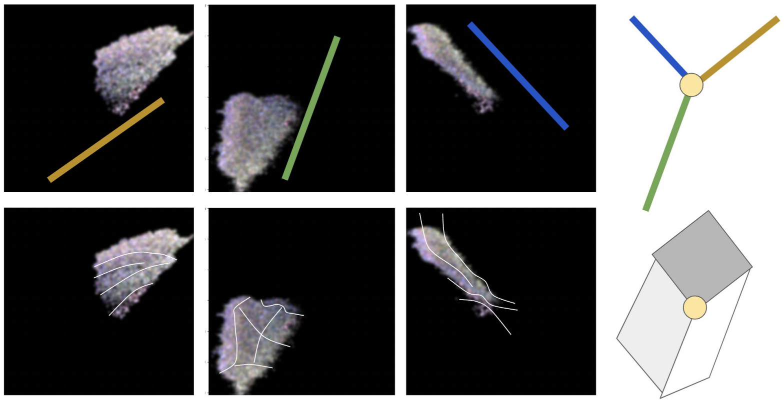

Real GEX (Tissue 1) - X-Y-Z-axis C1ql3
Real GEX (Tissue 2) - X-Y-Z-axis C1ql3
Real GEX (Tissue 3) - X-Y-Z-axis C1ql3
Real GEX (Tissue 4) - X-Y-Z-axis C1ql3

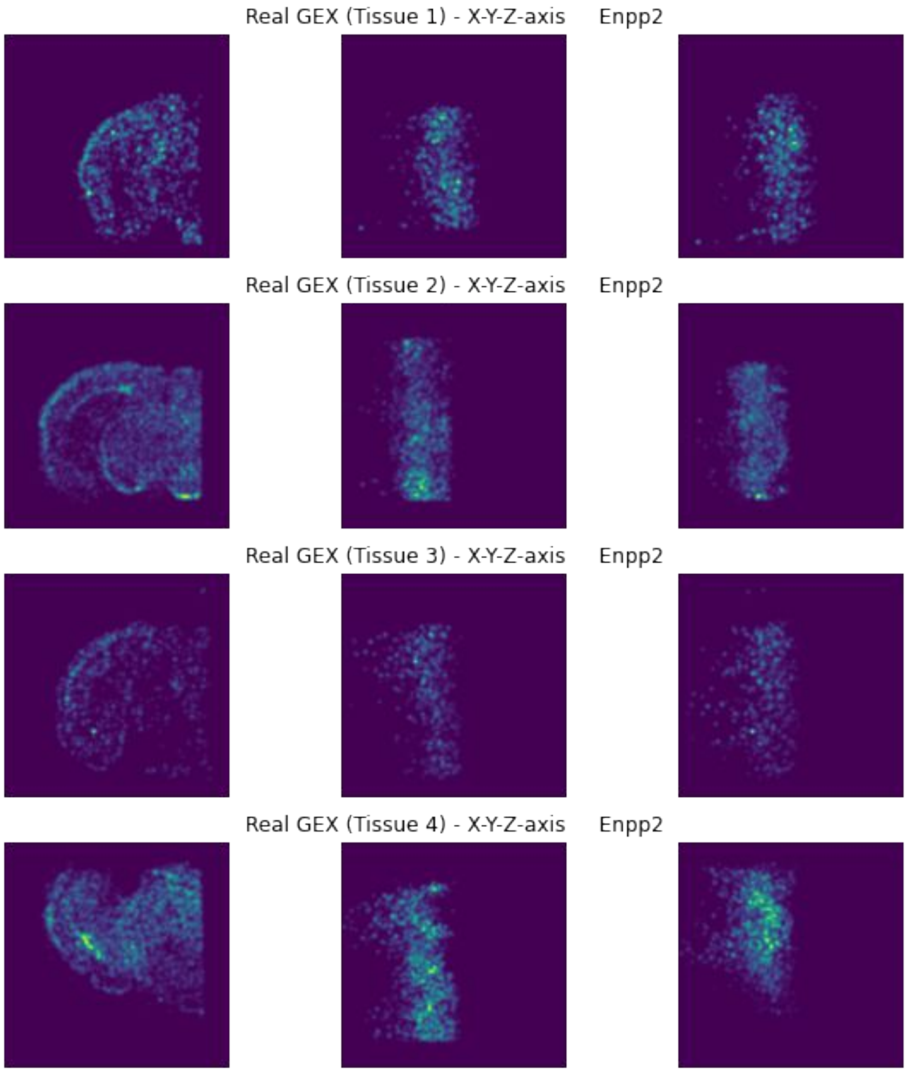

In-Silico GEX - X-Y-Z-axis C1ql3

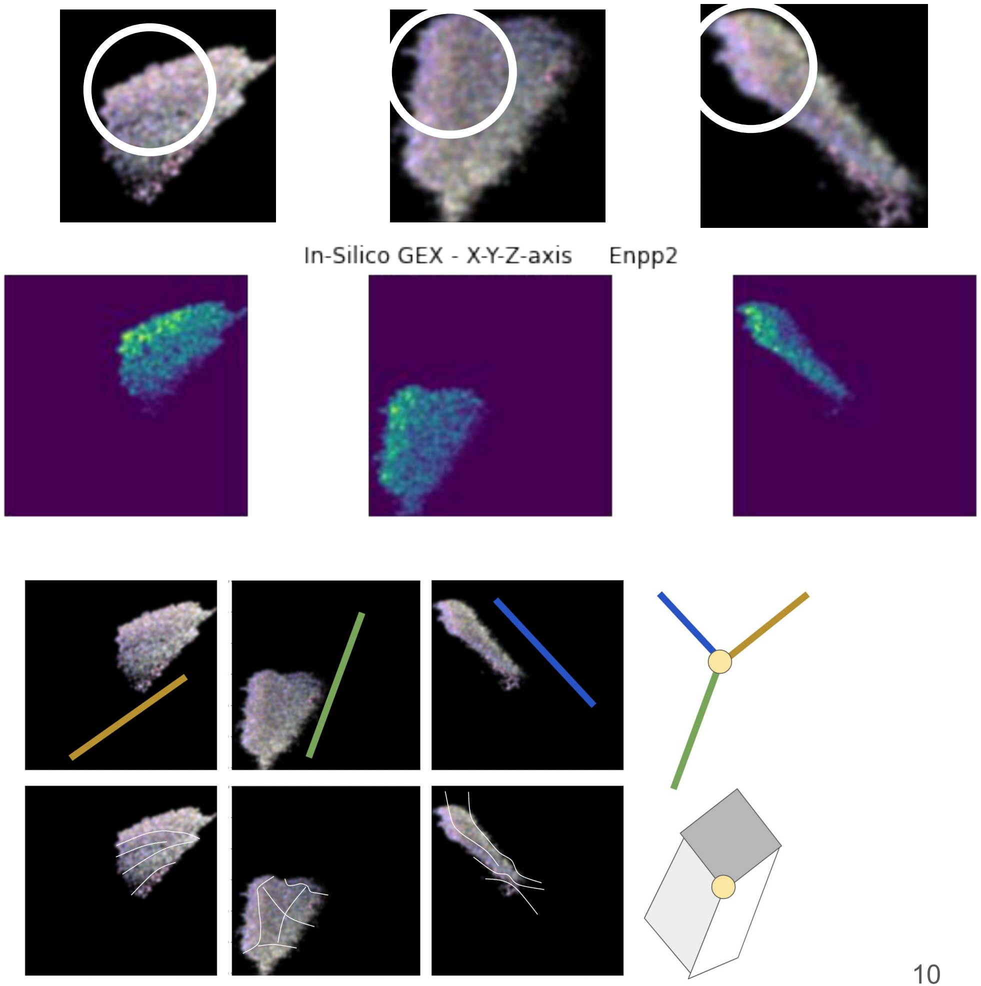

Real GEX (Tissue 1) - X-Y-Z-axis Cux2
Real GEX (Tissue 2) - X-Y-Z-axis Cux2
Real GEX (Tissue 3) - X-Y-Z-axis Cux2
Real GEX (Tissue 4) - X-Y-Z-axis Cux2

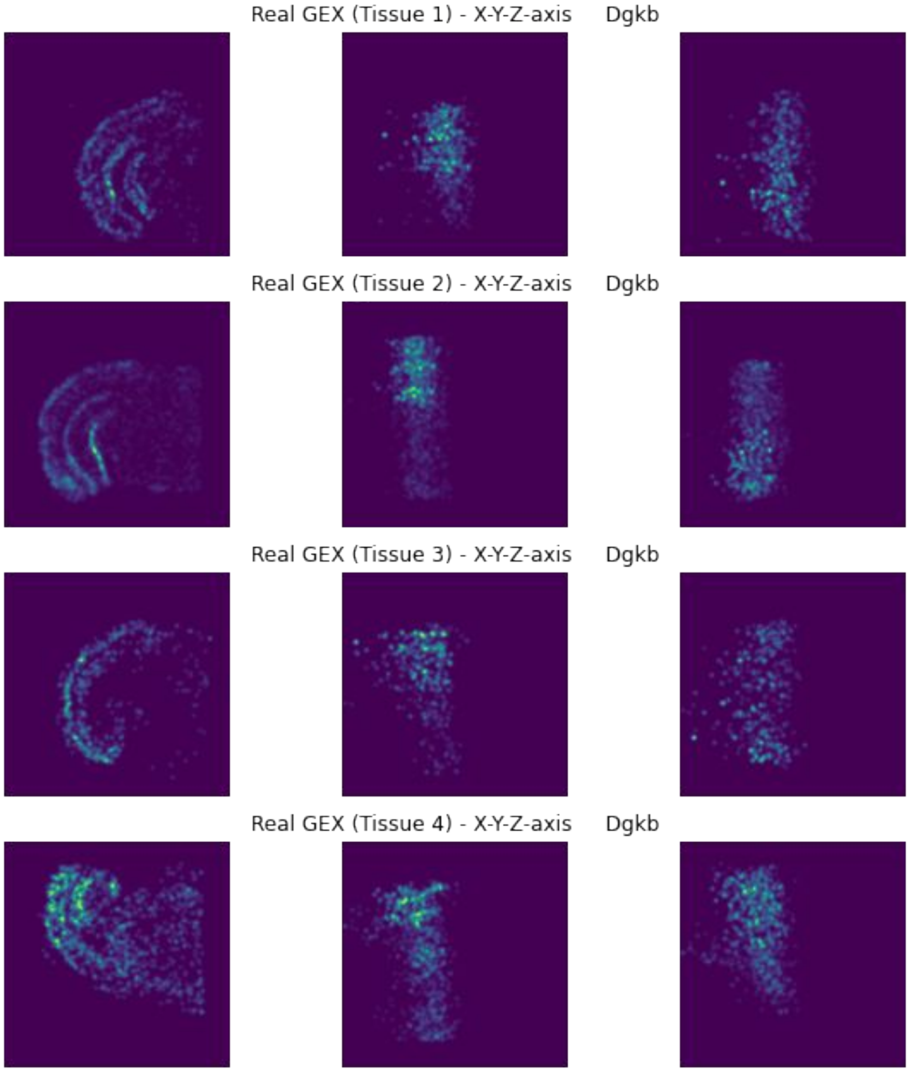


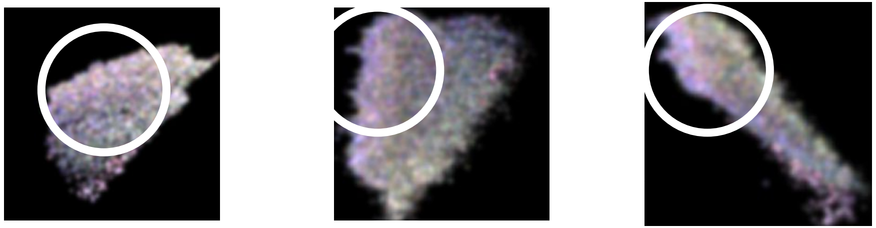

In-Silico GEX - X-Y-Z-axis Cux2

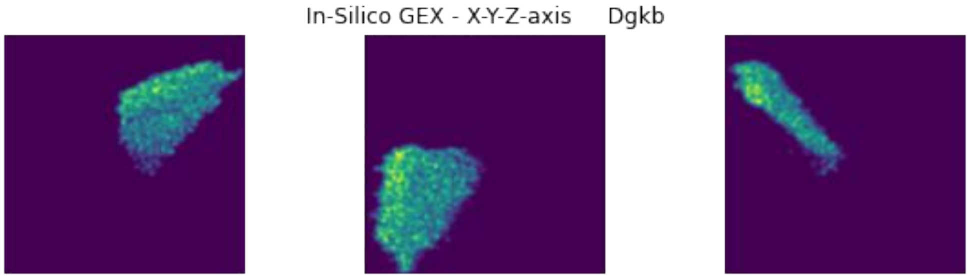


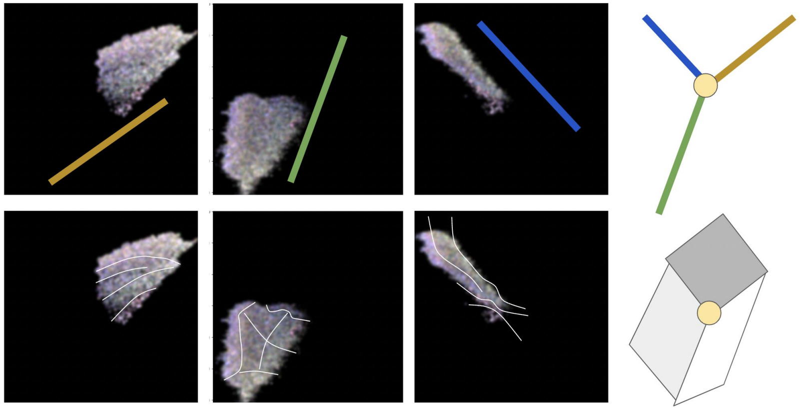

Real GEX (Tissue 1) - X-Y-Z-axis
Enpp2
Real GEX (Tissue 2) - X-Y-Z-axis
Enpp2
Real GEX (Tissue 3) - X-Y-Z-axis
Enpp2
Real GEX (Tissue 4) - X-Y-Z-axis
Enpp2

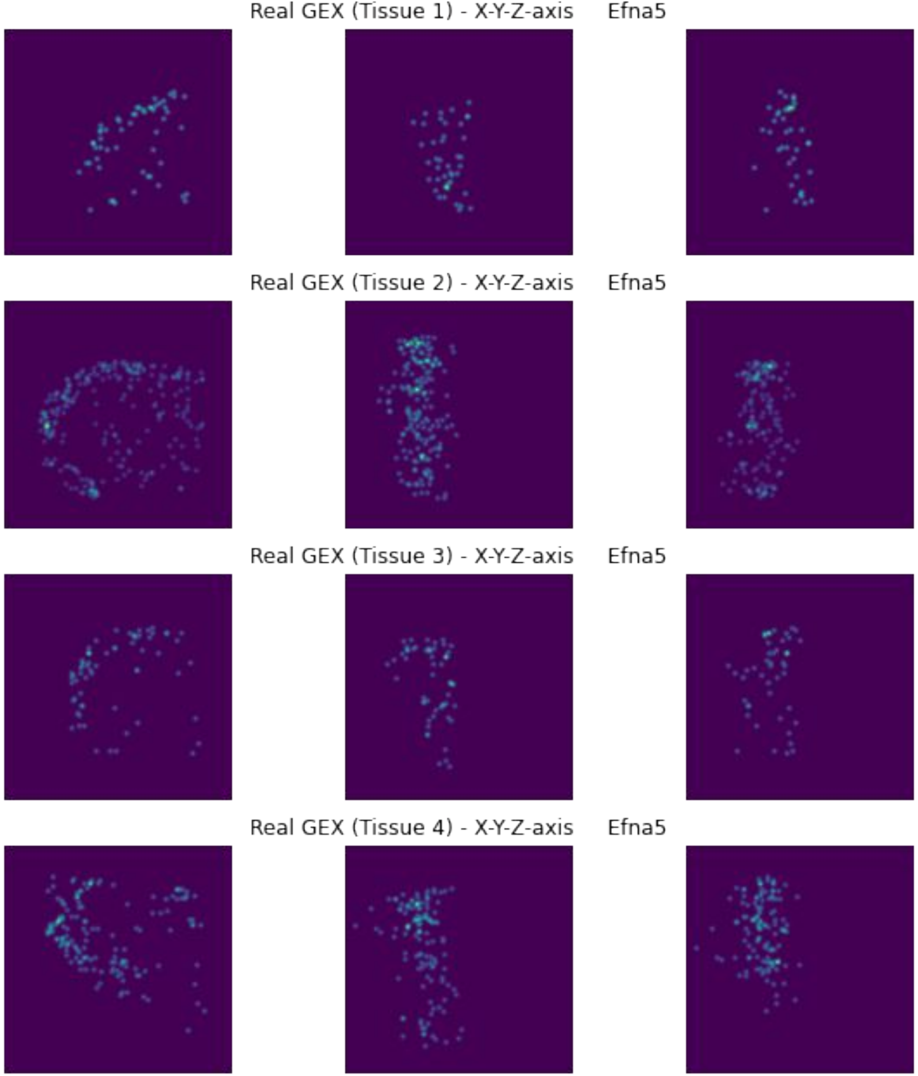

In-Silico GEX - X-Y-Z-axis
Enpp2

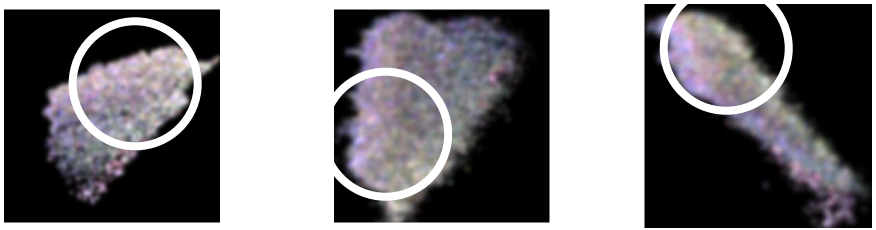

Real GEX (Tissue 1) - X-Y-Z-axis Dgkb
Real GEX (Tissue 2) - X-Y-Z-axis Dgkb
Real GEX (Tissue 3) - X-Y-Z-axis Dgkb
Real GEX (Tissue 4) - X-Y-Z-axis Dgkb

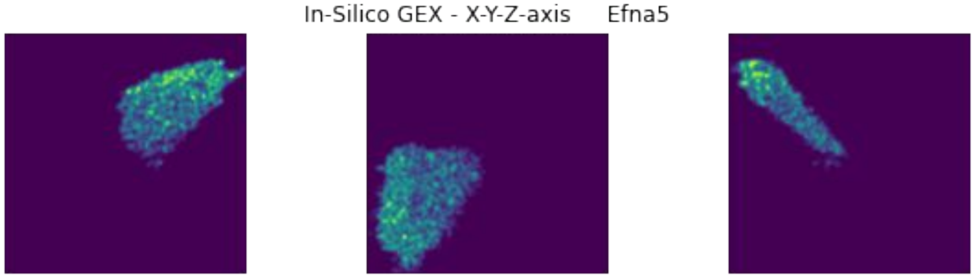


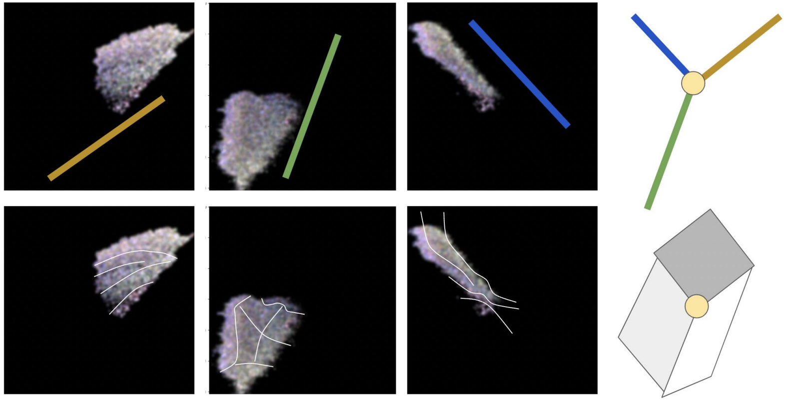

In-Silico GEX - X-Y-Z-axis Dgkb

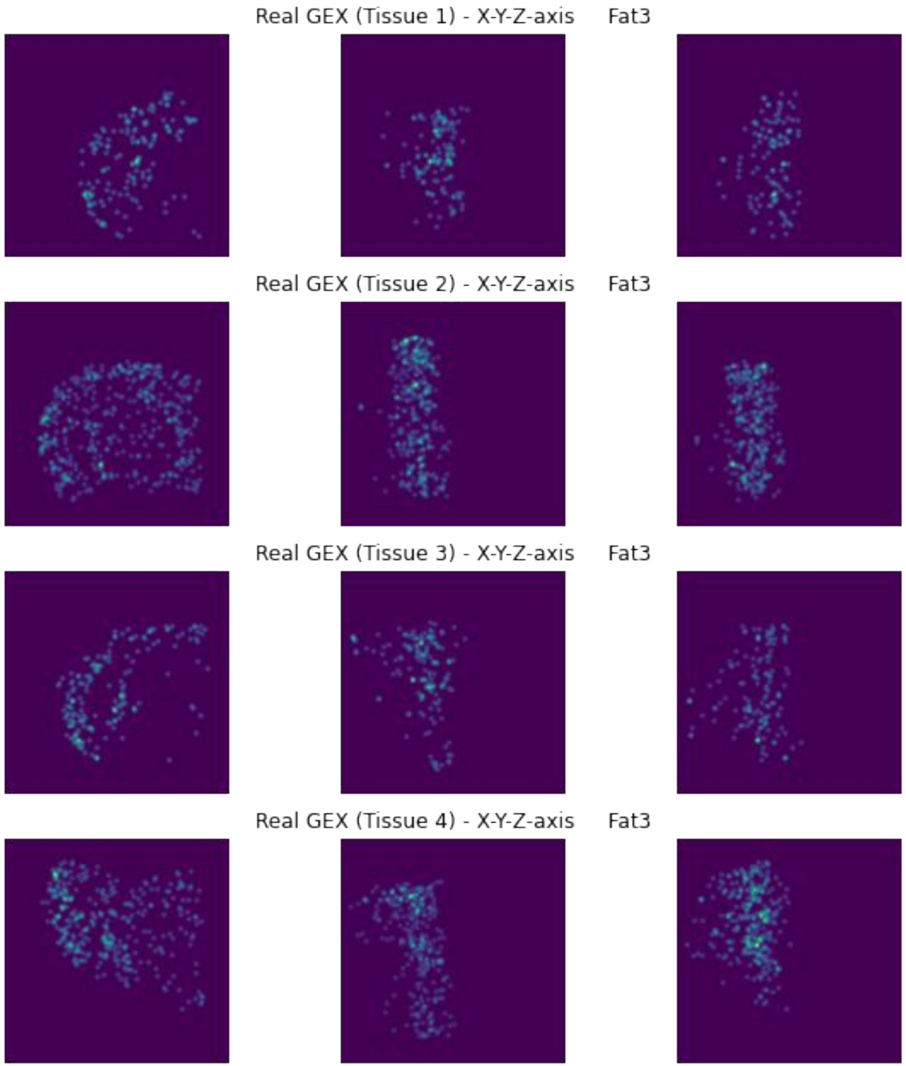


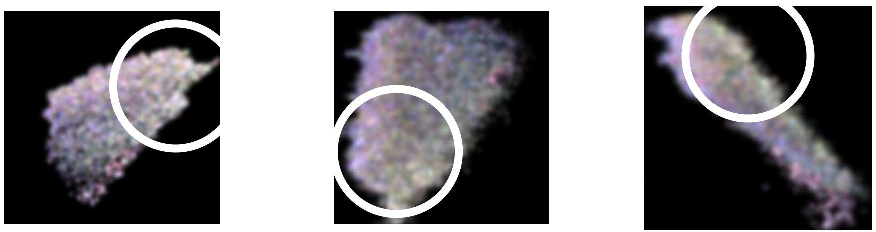

Real GEX (Tissue 1) - X-Y-Z-axis Efna5
Real GEX (Tissue 2) - X-Y-Z-axis Efna5
Real GEX (Tissue 3) - X-Y-Z-axis Efna5
Real GEX (Tissue 4) - X-Y-Z-axis Efna5

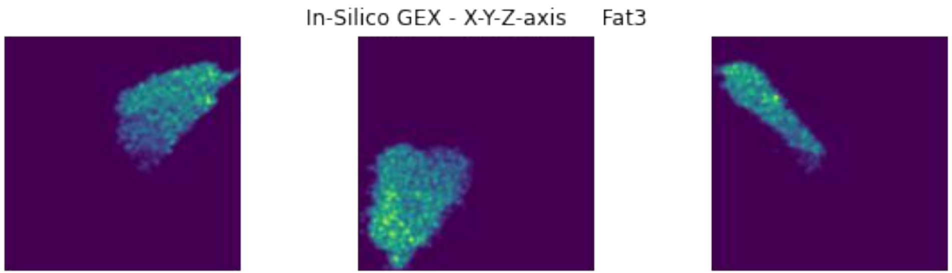


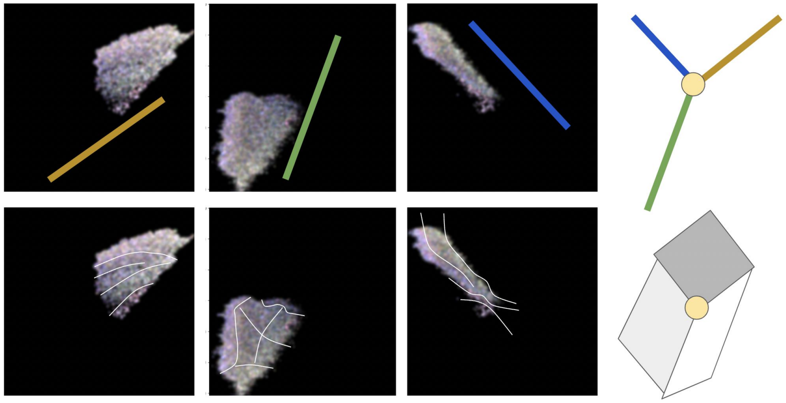

In-Silico GEX - X-Y-Z-axis Efna5

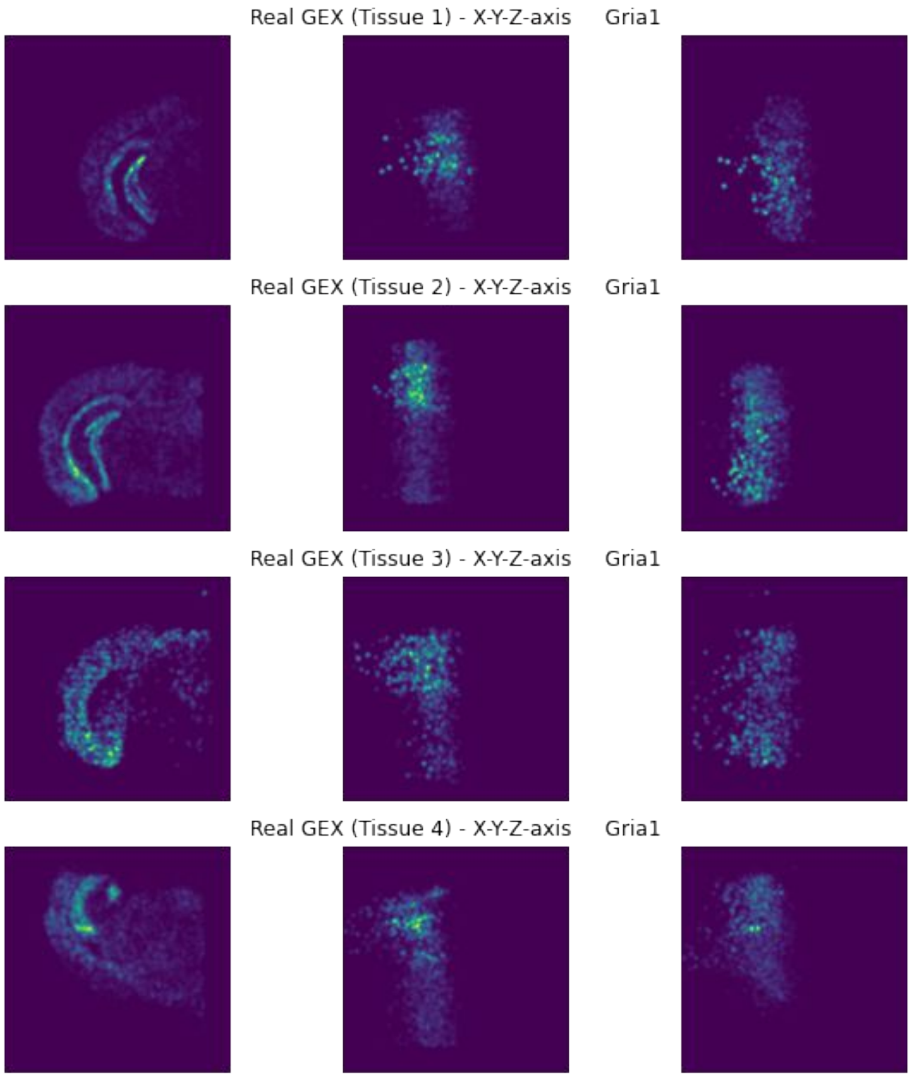


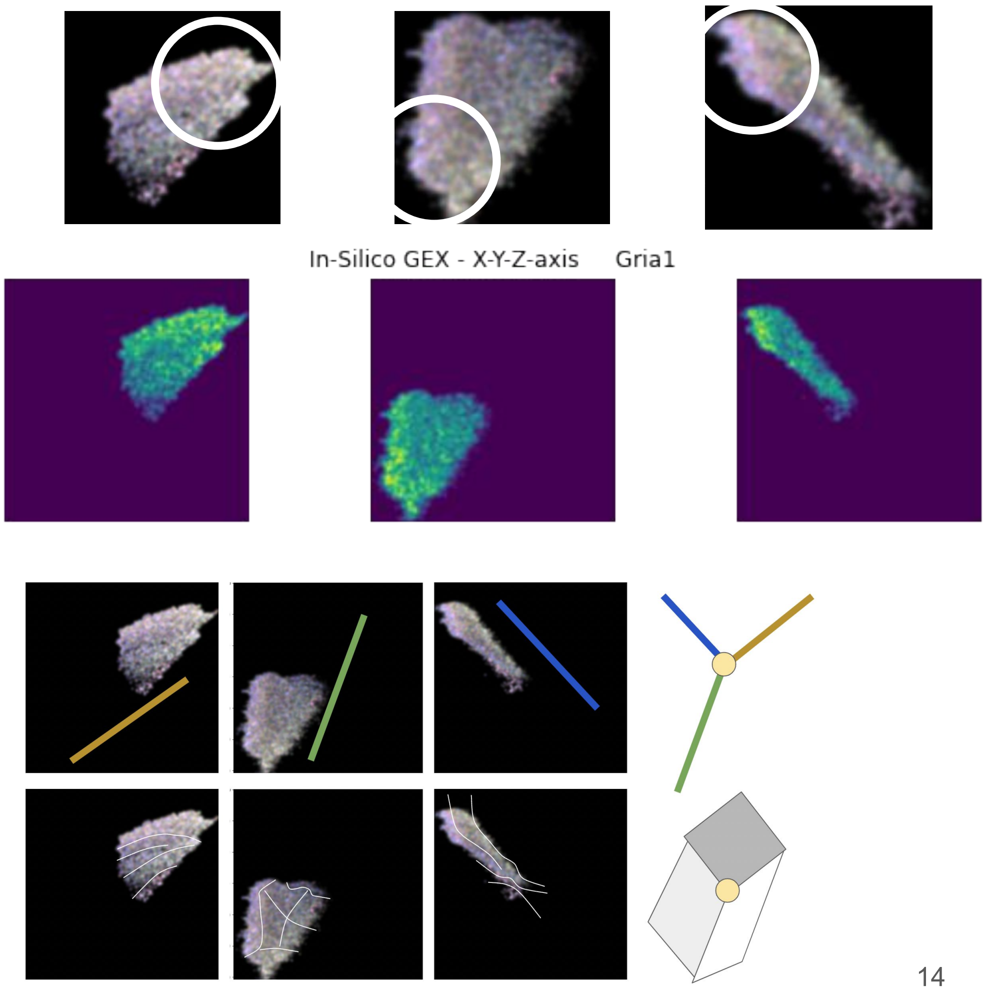

Real GEX (Tissue 1) - X-Y-Z-axis Fat3
Real GEX (Tissue 2) - X-Y-Z-axis Fat3
Real GEX (Tissue 3) - X-Y-Z-axis Fat3
Real GEX (Tissue 4) - X-Y-Z-axis Fat3

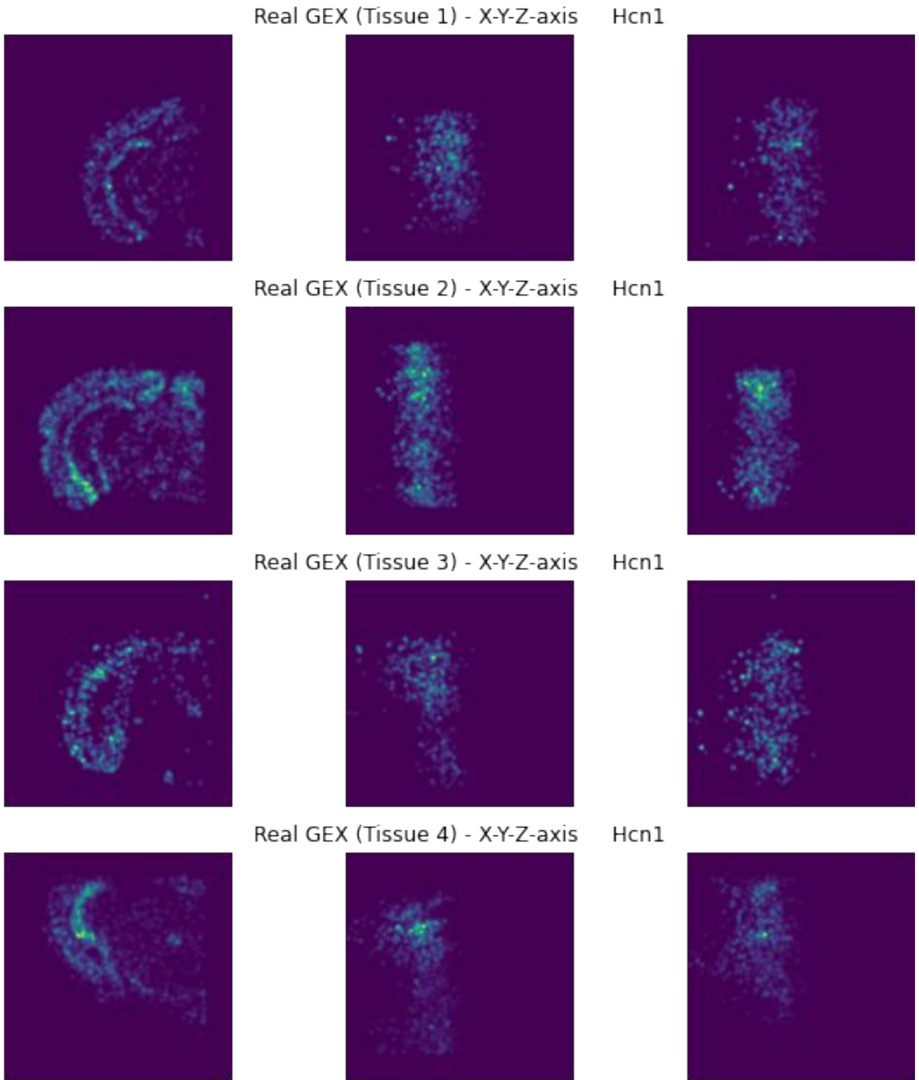


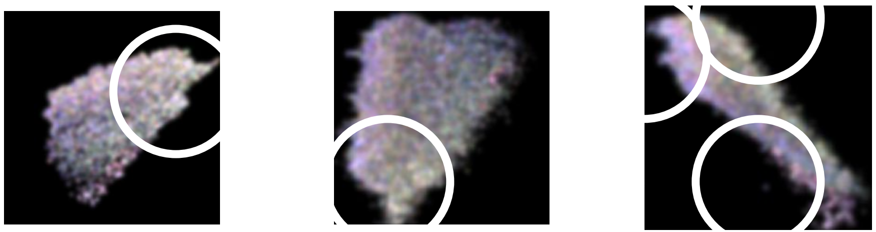

In-Silico GEX - X-Y-Z-axis Fat3

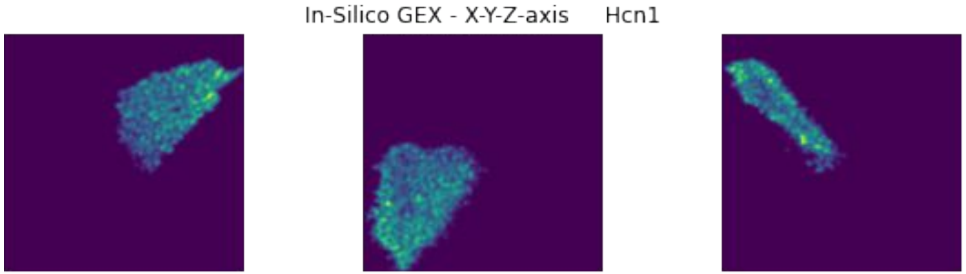


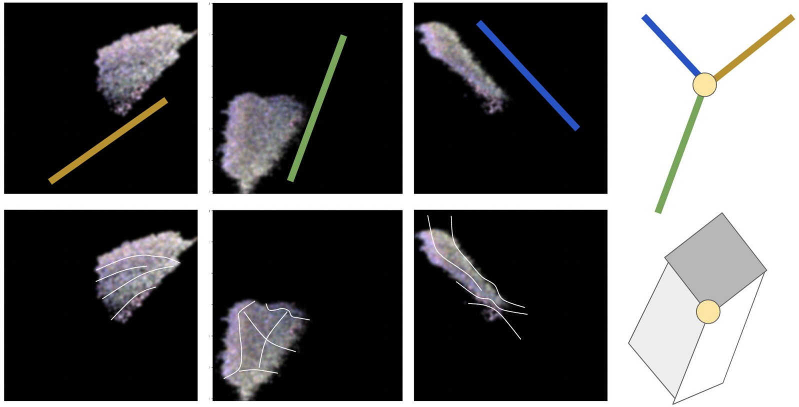

Real GEX (Tissue 1) - X-Y-Z-axis Gria1
Real GEX (Tissue 2) - X-Y-Z-axis Gria1
Real GEX (Tissue 3) - X-Y-Z-axis Gria1
Real GEX (Tissue 4) - X-Y-Z-axis Gria1


In-Silico GEX - X-Y-Z-axis Gria1

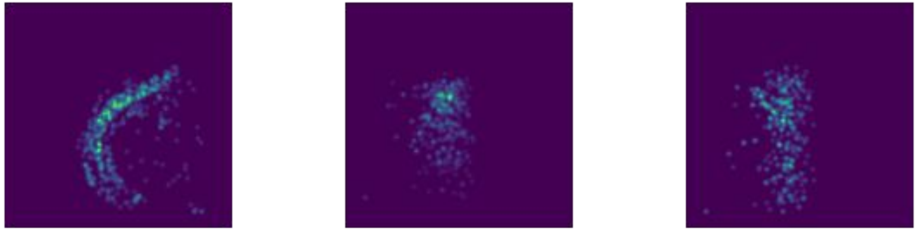

Real GEX (Tissue 1) - X-Y-Z-axis Hcn1
Real GEX (Tissue 2) - X-Y-Z-axis Hcn1
Real GEX (Tissue 3) - X-Y-Z-axis Hcn1
Real GEX (Tissue 4) - X-Y-Z-axis Hcn1



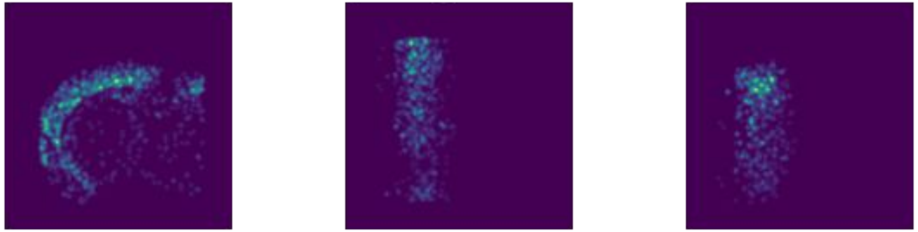

In-Silico GEX - X-Y-Z-axis Hcn1



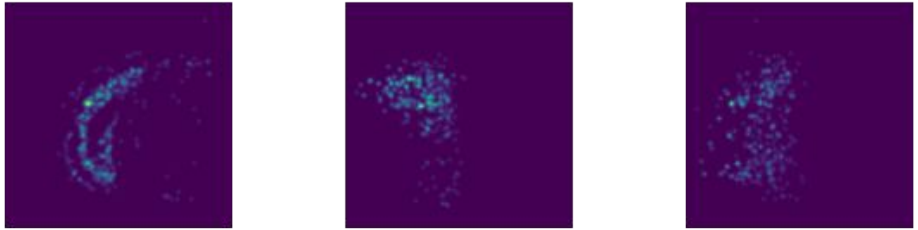
Real GEX (Tissue 1) - X-Y-Z-axis Hs3st2



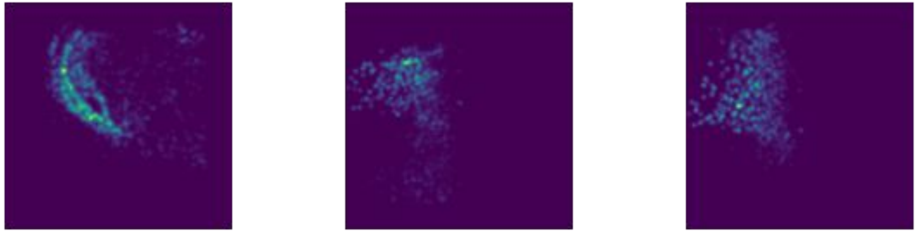
Real GEX (Tissue 2) - X-Y-Z-axis Hs3st2

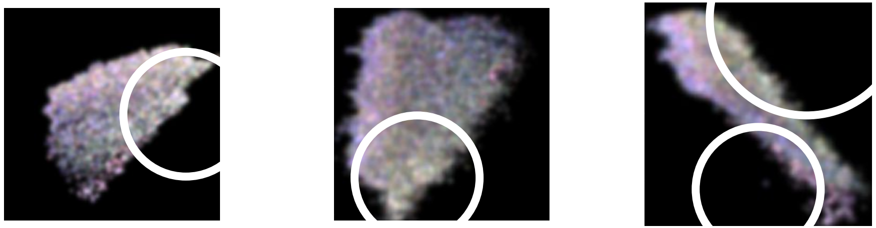


Real GEX (Tissue 3) - X-Y-Z-axis Hs3st2

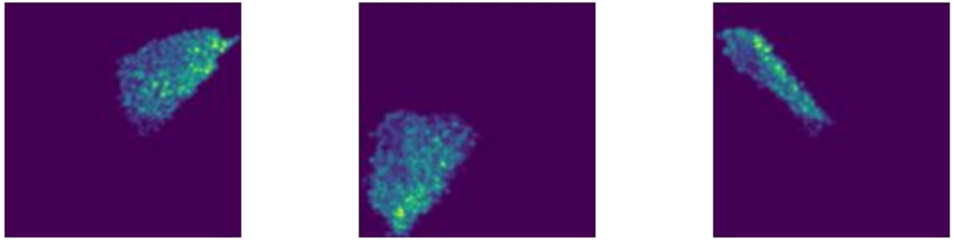


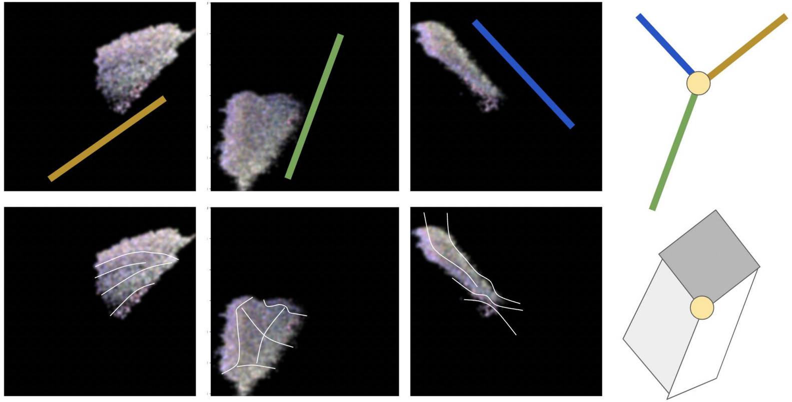
Real GEX (Tissue 4) - X-Y-Z-axis Hs3st2



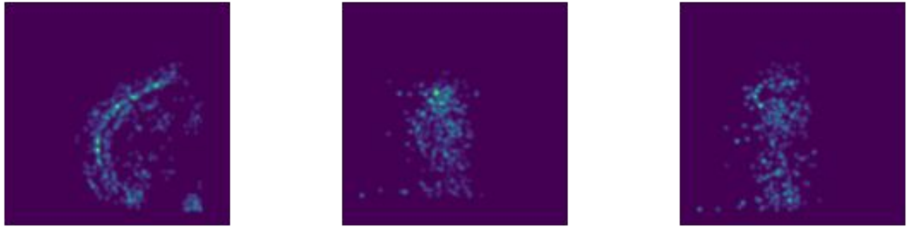


In-Silico GEX - X-Y-Z-axis Hs3st2

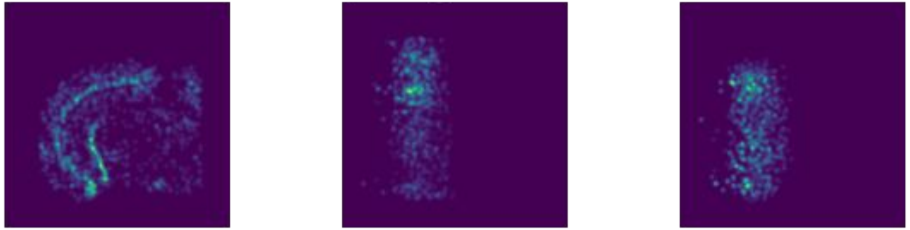




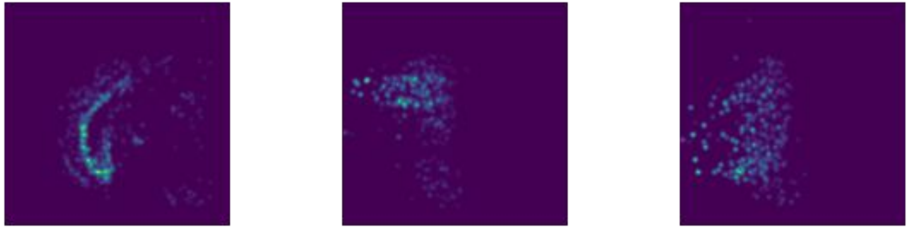
Real GEX (Tissue 1) - X-Y-Z-axis   Hs3st4



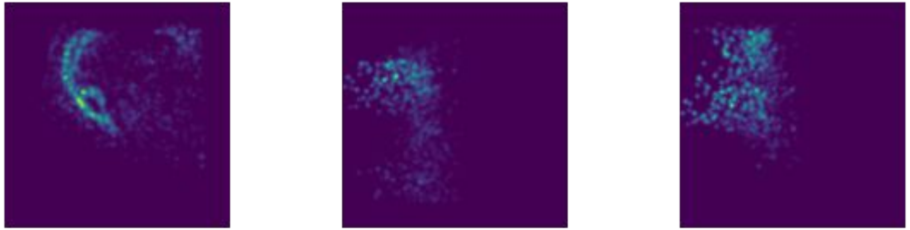
Real GEX (Tissue 2) - X-Y-Z-axis   Hs3st4

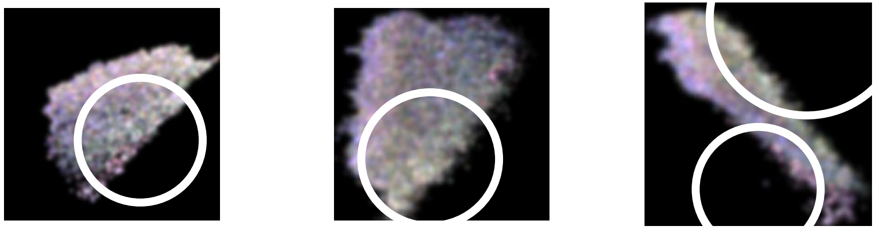


Real GEX (Tissue 3) - X-Y-Z-axis   Hs3st4

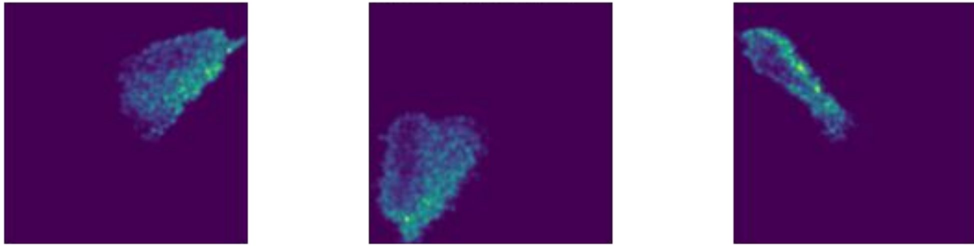


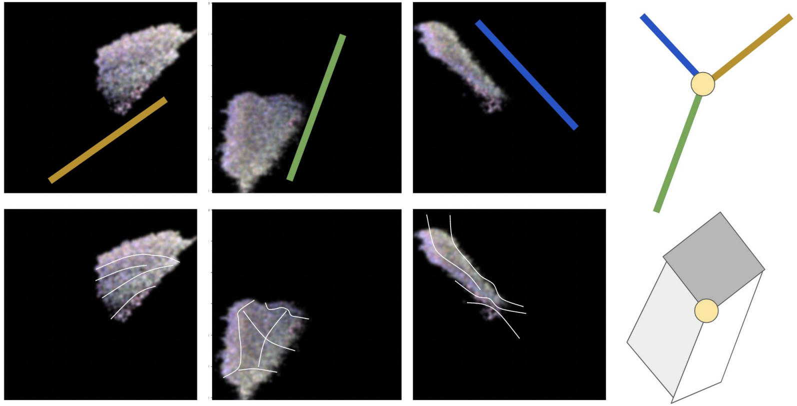
Real GEX (Tissue 4) - X-Y-Z-axis   Hs3st4

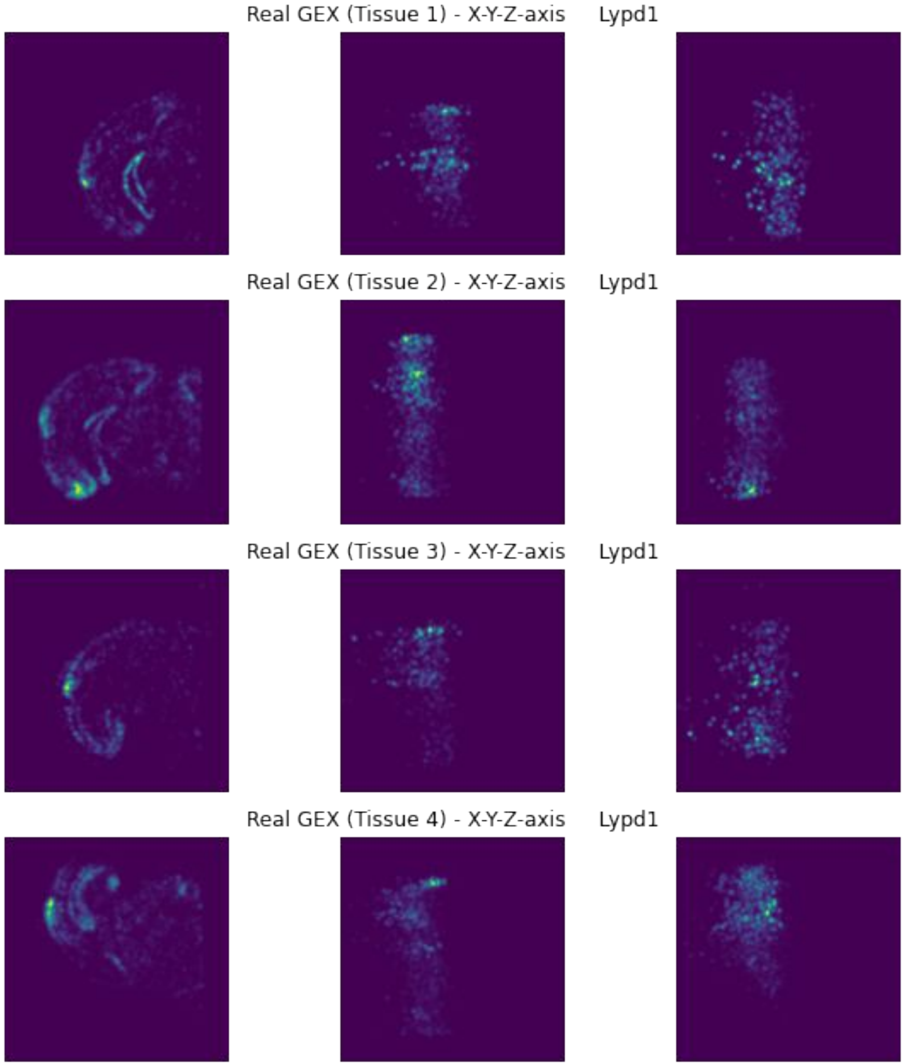


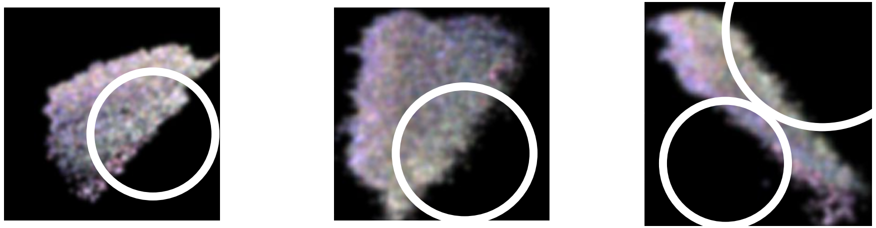


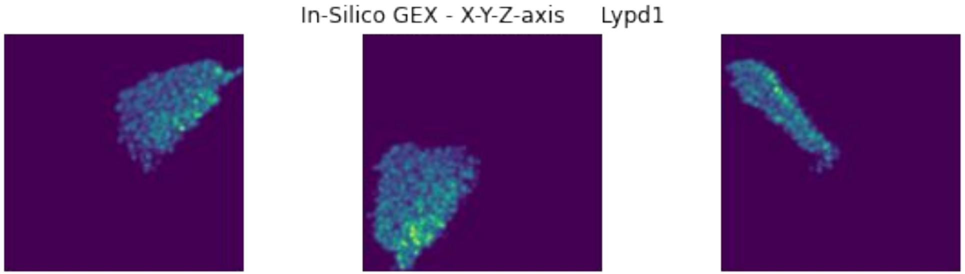
In-Silico GEX - X-Y-Z-axis   Hs3st4

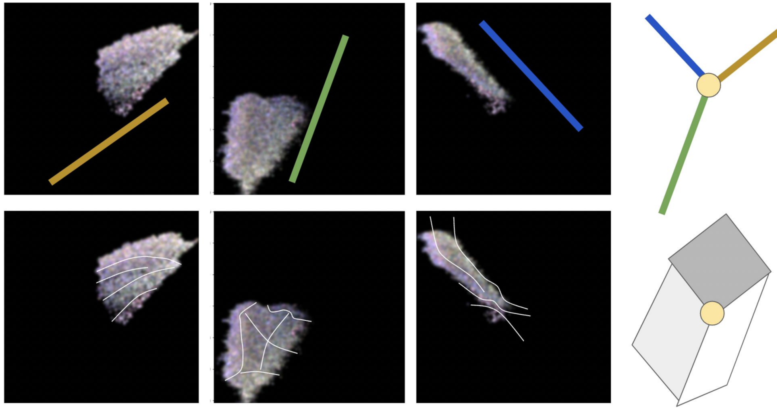


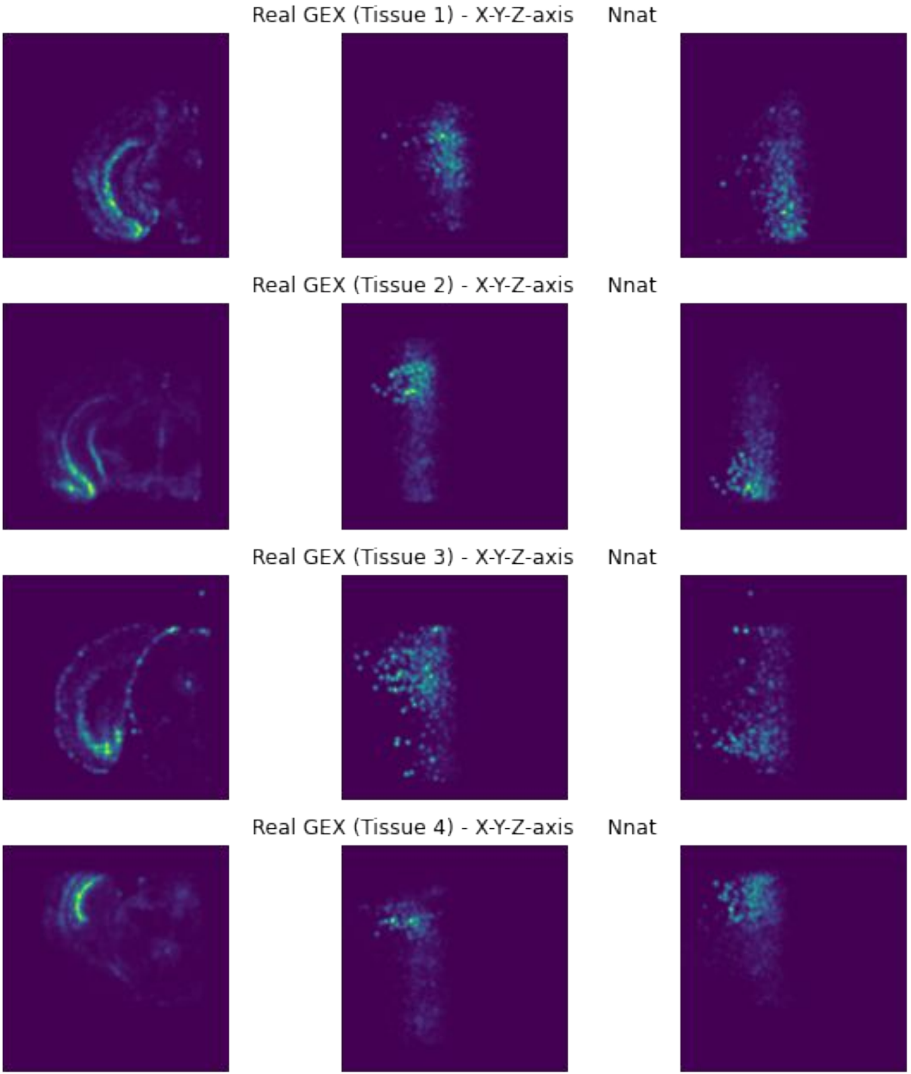


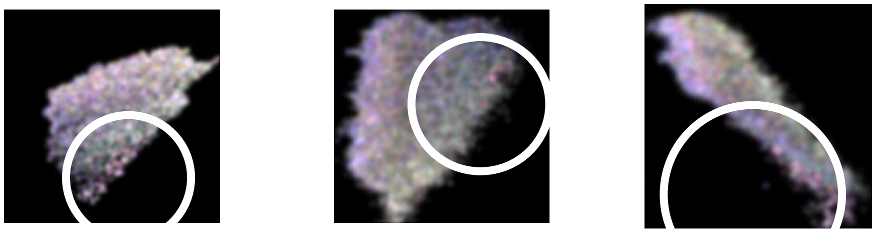

Real GEX (Tissue 1) - X-Y-Z-axis
Lypd1
Real GEX (Tissue 2) - X-Y-Z-axis
Lypd1
Real GEX (Tissue 3) - X-Y-Z-axis
Lypd1
Real GEX (Tissue 4) - X-Y-Z-axis
Lypd1

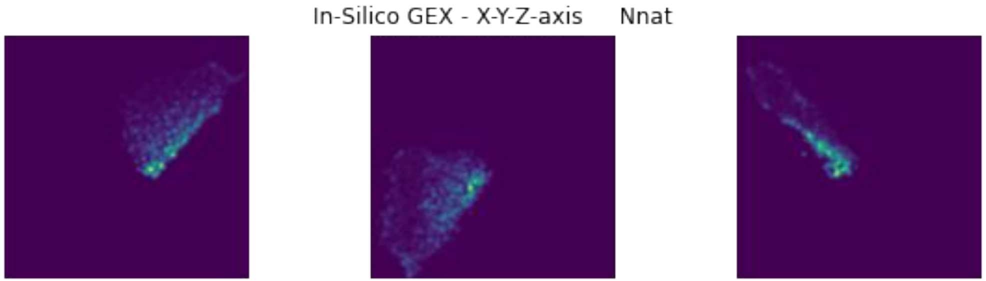


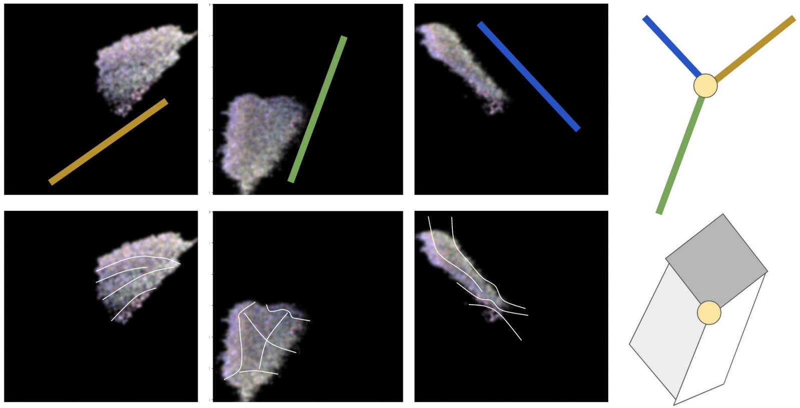

In-Silico GEX - X-Y-Z-axis
Lypd1



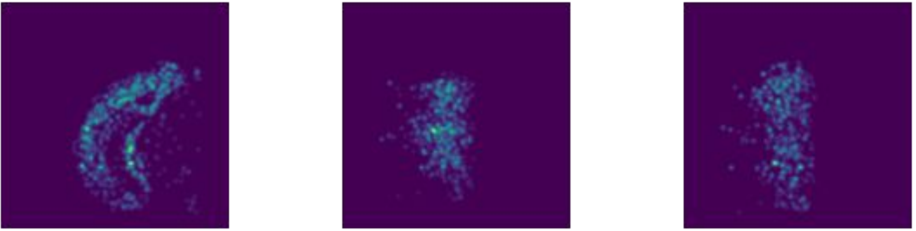

Real GEX (Tissue 1) - X-Y-Z-axis Nnat
Real GEX (Tissue 2) - X-Y-Z-axis Nnat
Real GEX (Tissue 3) - X-Y-Z-axis Nnat
Real GEX (Tissue 4) - X-Y-Z-axis Nnat



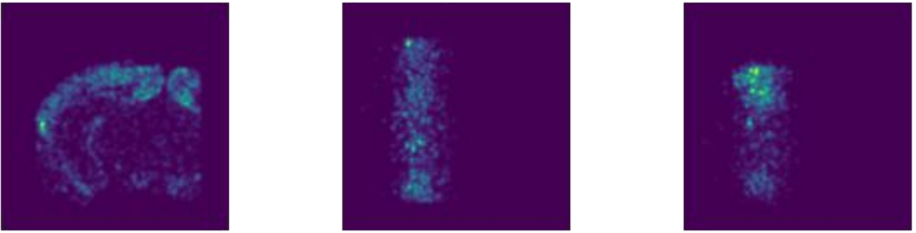

In-Silico GEX - X-Y-Z-axis Nnat



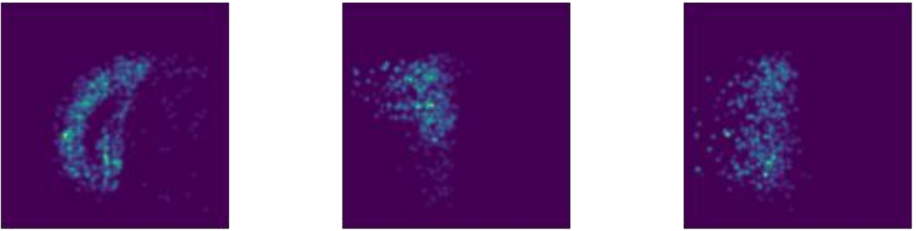
Real GEX (Tissue 1) - X-Y-Z-axis Satb1



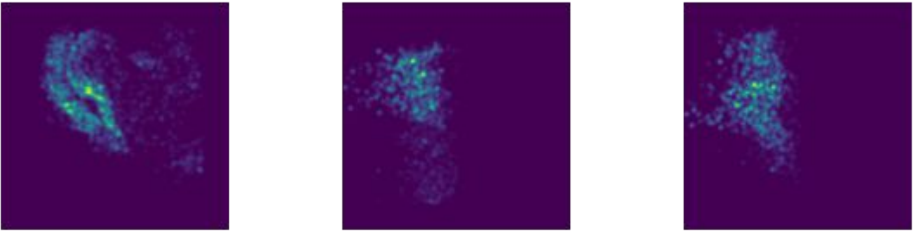
Real GEX (Tissue 2) - X-Y-Z-axis Satb1

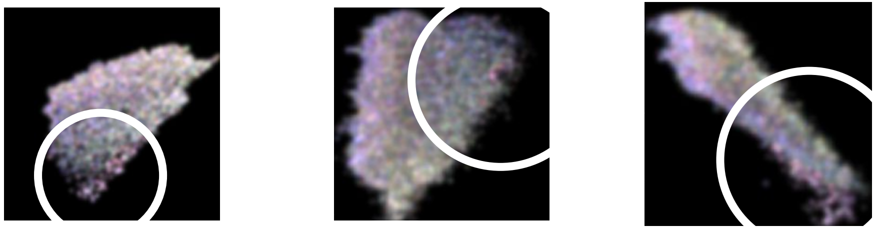


Real GEX (Tissue 3) - X-Y-Z-axis Satb1

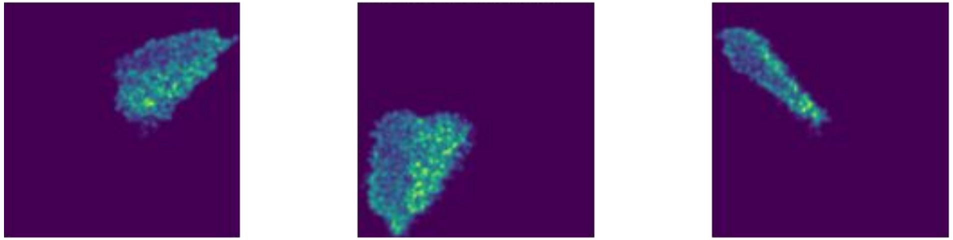


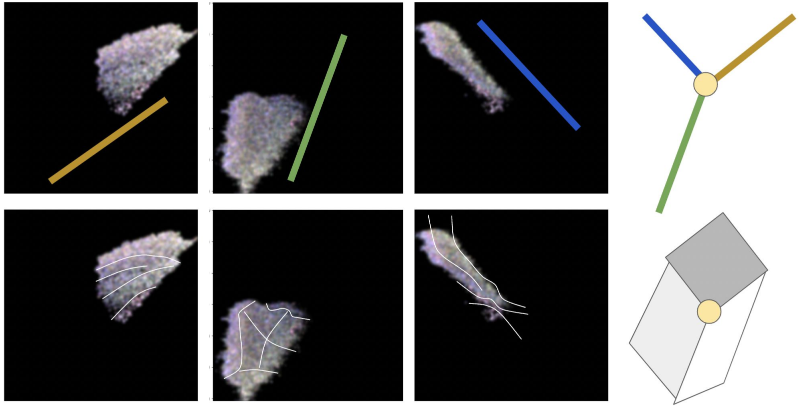
Real GEX (Tissue 4) - X-Y-Z-axis Satb1





In-Silico GEX - X-Y-Z-axis Satb1





Model primer

$$\arg\min \left(\left\{ \left\{ A + B + C + D + E + F \right\}^2 \right\}^{\frac{1}{2}} \right)$$

A: How accurate are cell distributions compared to training?

B: Whether the parameters for the new cell locations are actual signals?

C: Whether gene to pixel transformations are learned correctly?

D: Whether pixel image prediction is aligned with reality on a local predicted imaging spot level?

E: Whether pixel image prediction is aligned with reality on a global predicted imaging tissue level?

F: Whether the movement of cells around fits well with the idea of Waddington's marble analogy?

Actual model layers …

```
# beta is to learn gene expression
# spatial signals from scRNAseq only
self.summary_beta = nn.Linear(10,window_size*2*window_size*2*106,bias=False)

# gex and pix are to learn transformation parameters that
# assign based on image similarity to real histology
self.summary_gex = nn.Linear(len(genes),100,bias=False)
self.summary_pix = nn.Linear(32*32*3,100,bias=False)
```

… and that's it!

A fully interpretable linear neural network

beta : maps KNN gene convolutions to **predict coordinates**

gex : maps gene to **shared space** with images

pix : maps images to **shared space** with genes

How are coordinates predicted?

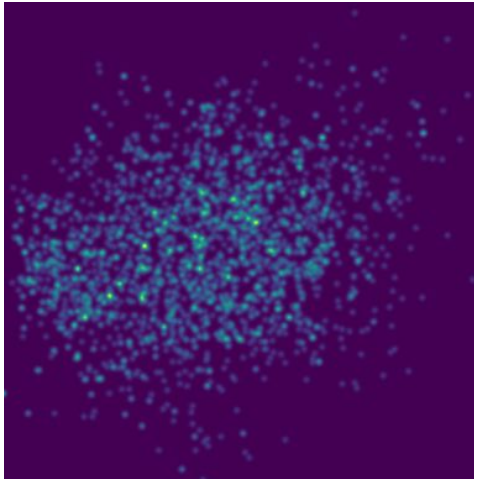
1
Cells are randomly distributed onto a grid (e.g. 1000 x 1000 x G) with G gene channels and a spatial kernel applied to diffuse genes

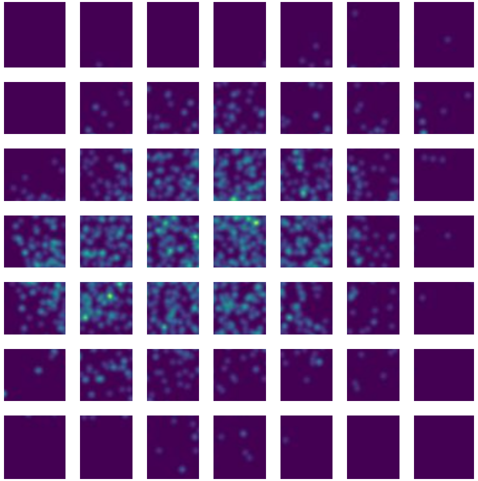
2
Convolutions around each cell are taken, giving a small window of about 5 x 5 x G, where G are the gene channels

3
Convolutions of cells are put through a Neural Network to predict where the cell is next likely to occur

4
This is a repeated process to continuously update a walking process of the cell to the next likely location based on gene expression around the grid …

… like Waddington's marble analogy!





What is a shared space?

$$\boldsymbol{Y}$$

$$y = f(x)$$

$$f^{-1}(y) = x$$

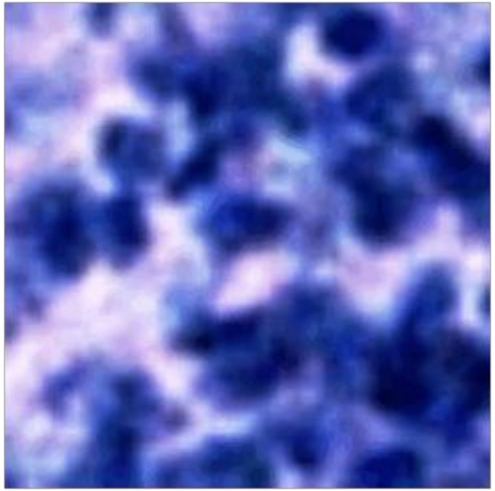
$$\boldsymbol{X}$$

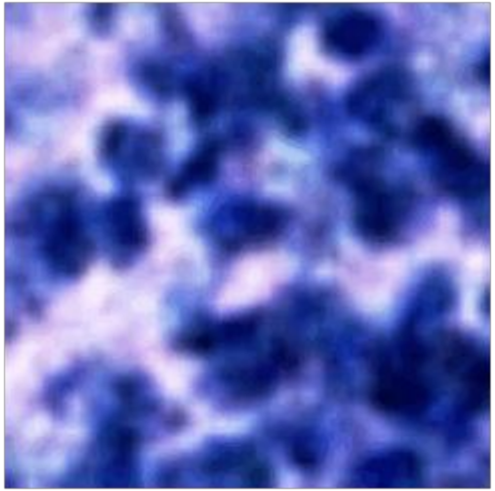
Spatial Histology to Spatial Transcripts

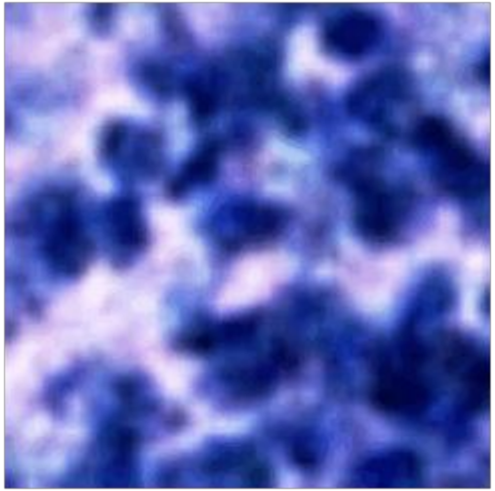
Methylation to Chromatin Accessibility to Chromatin Conformation to Chromatin Profiles

Genomics to Epigenomics to Transcriptomics to Proteomics

What can a shared space do?







https://github.com/AskExplain/scRNA_maps/

Acknowledgements for inspiration

Fei Yang	University of Queensland
Dr Alan Huang	University of Queensland
Professor Geoffrey McLachlan	University of Queensland
Professor Cinzia Viroli	University of Bologna
Dr Quan Nguyen	University of Queensland
Dr Jessica Mar	University of Queensland
Dr Ruth Pidsley	Garvan Institute of Medical Research

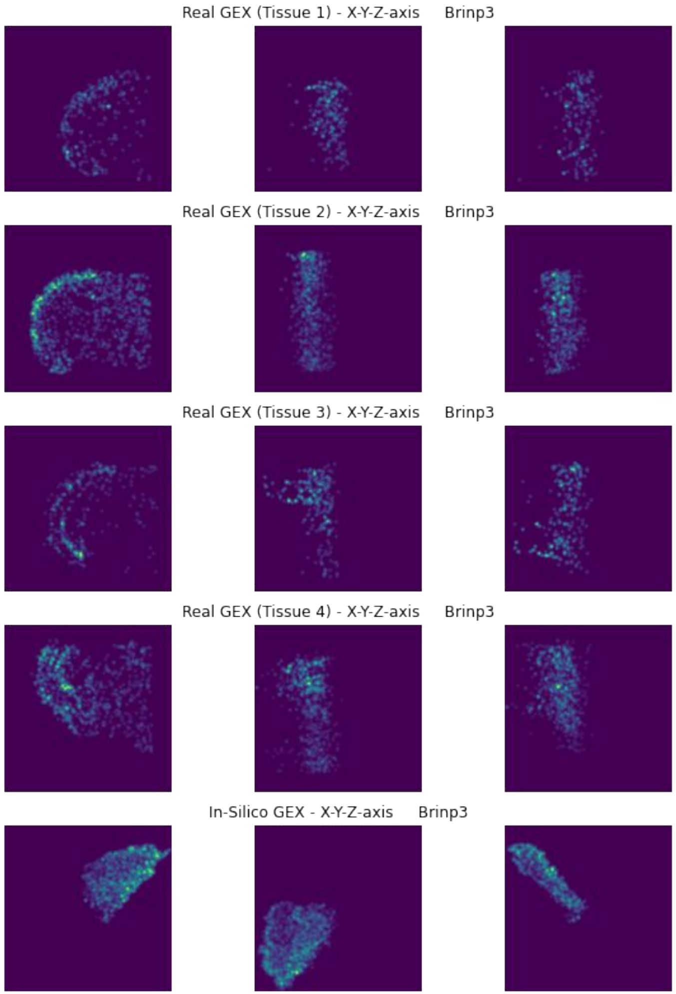
Our vision is to create great collaborations from science to industry

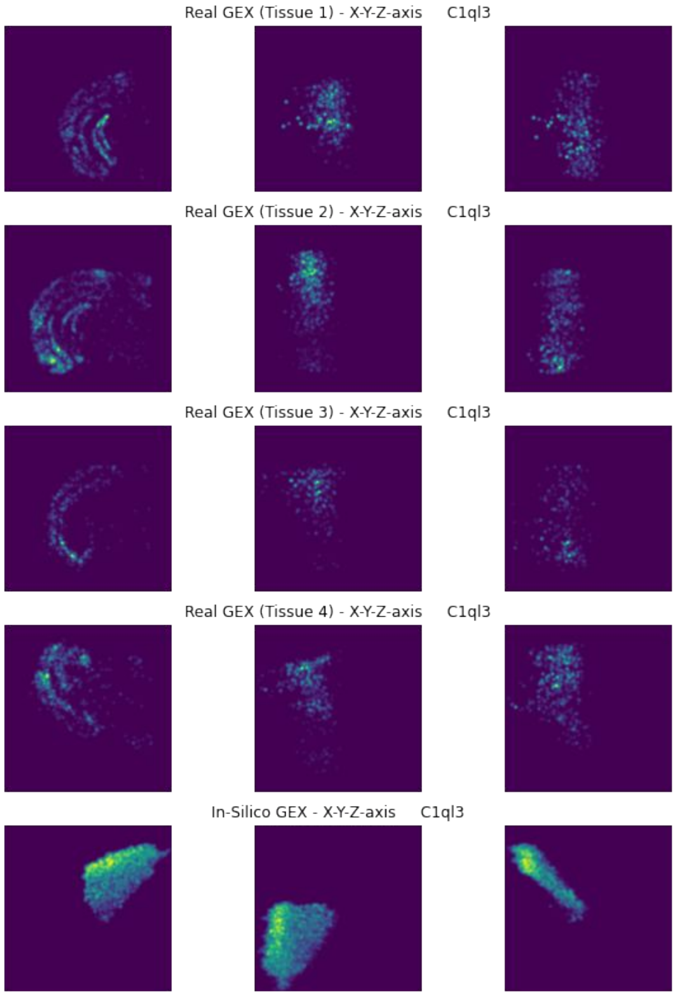
Through an interest and passion for science to progress, our commitment is to work on, communicate around, and support collaborations

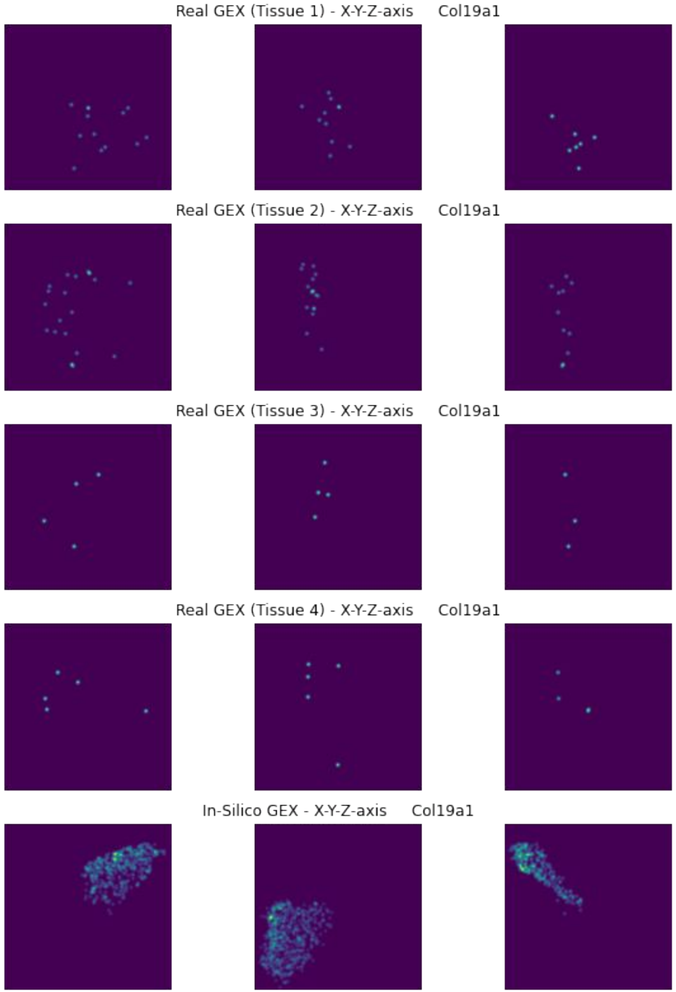
AskExplain
david.b@askexplain.com

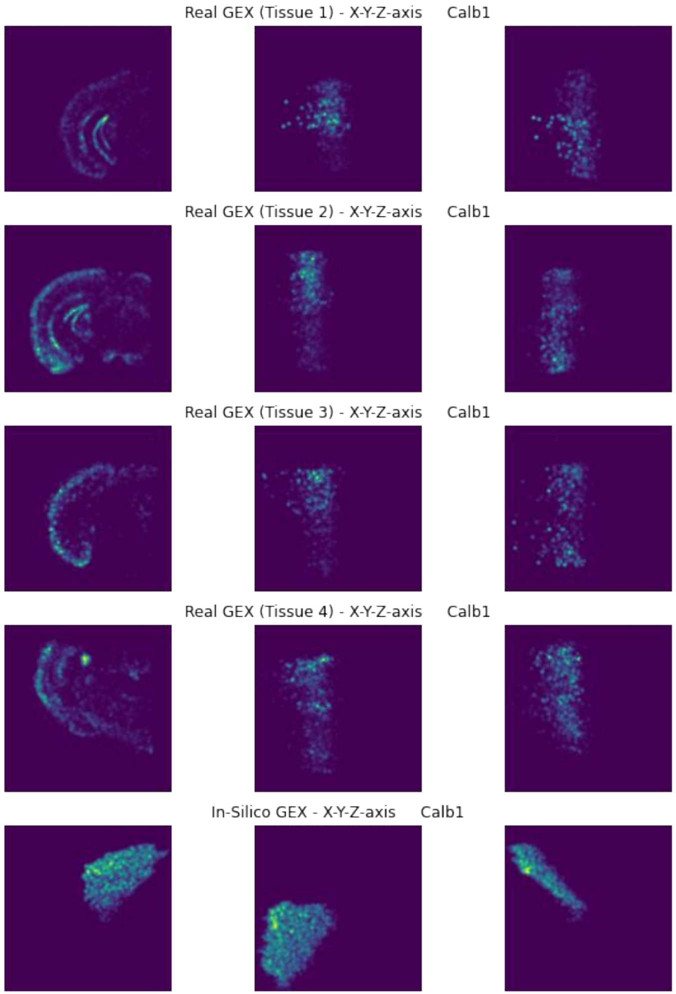
How about some interesting genes?

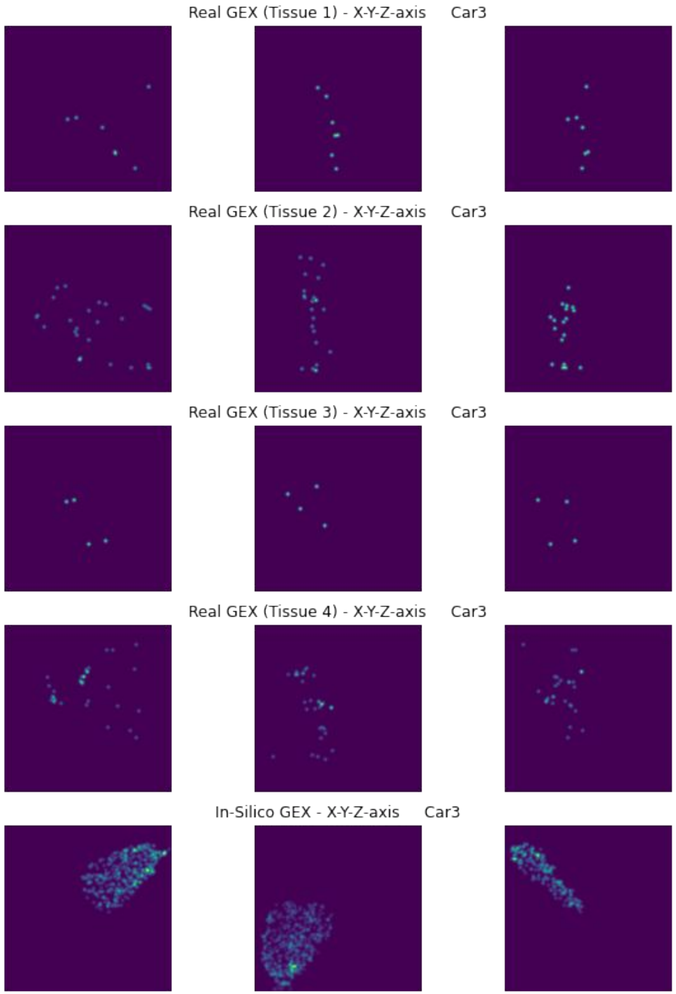
pg#	Gene	pg#	Gene	pg#	Gene	pg#	Gene	pg#	Gene
23	Brinp3	28	Cbln2	33	Efna5	34	Kcnip1	39	Scnn1a
24	C1ql3	29	Cdh3	34	Gnb4	35	Lypd1	40	Nrg1
25	Col19a	30	Cpne4	35	Hgf	36	Otof	41	Zfpm2
26	Calb1	31	Cux2	36	Hs6st3	37	Oprk1	42	Zfp804b
27	Car3	32	Dcc	37	Htr2a	38	Sgcd	43	Zfp804a

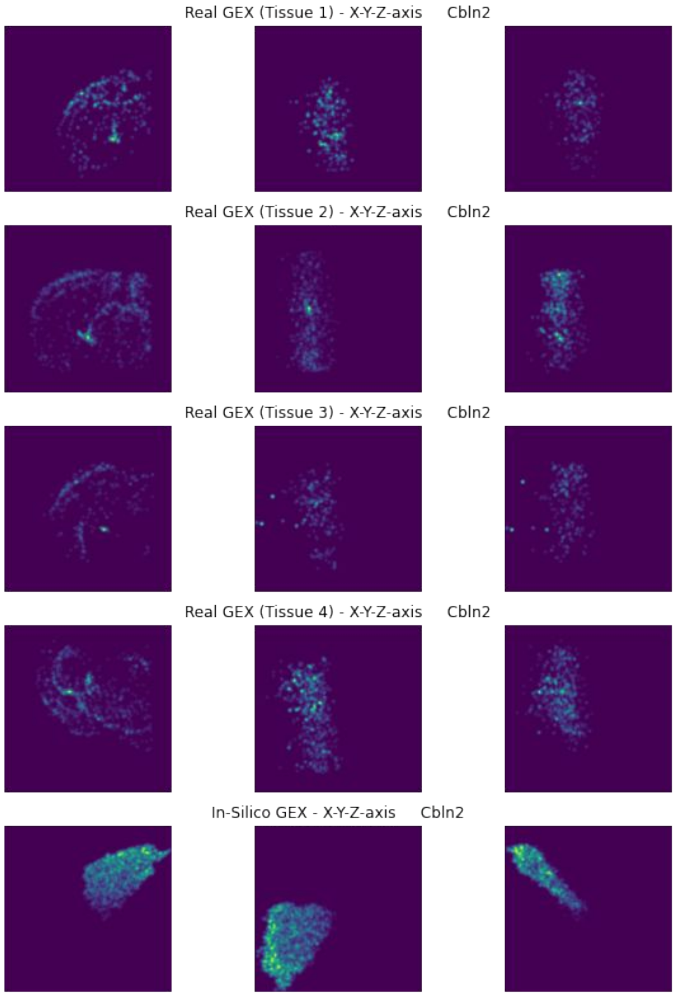

Real GEX (Tissue 1) - X-Y-Z-axis Brinp3
Real GEX (Tissue 2) - X-Y-Z-axis Brinp3
Real GEX (Tissue 3) - X-Y-Z-axis Brinp3
Real GEX (Tissue 4) - X-Y-Z-axis Brinp3
In-Silico GEX - X-Y-Z-axis Brinp3

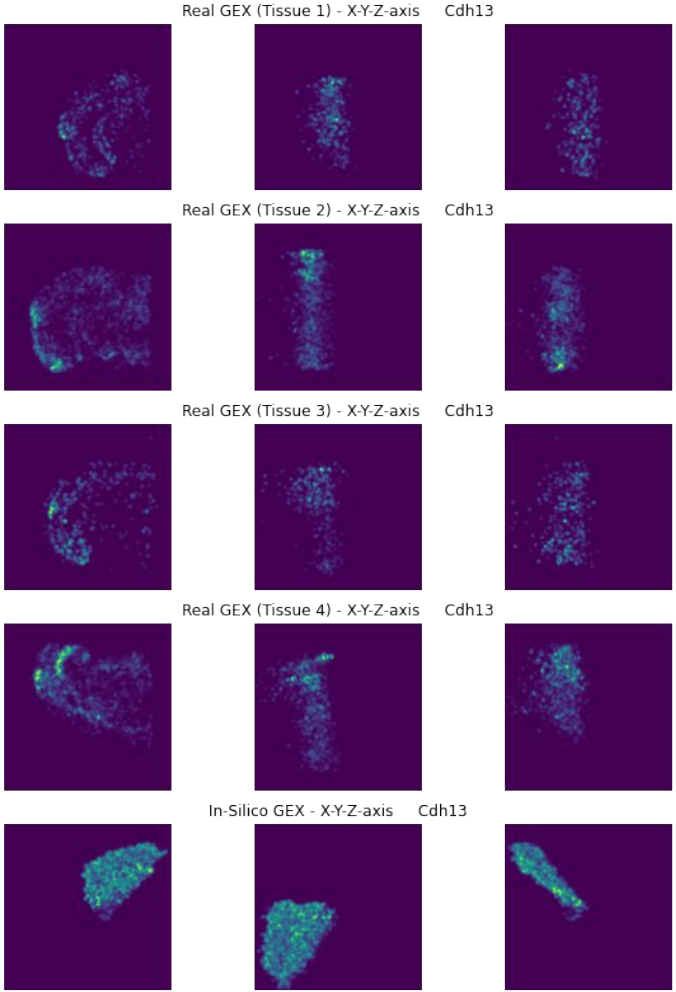

Real GEX (Tissue 1) - X-Y-Z-axis C1ql3
Real GEX (Tissue 2) - X-Y-Z-axis C1ql3
Real GEX (Tissue 3) - X-Y-Z-axis C1ql3
Real GEX (Tissue 4) - X-Y-Z-axis C1ql3
In-Silico GEX - X-Y-Z-axis C1ql3

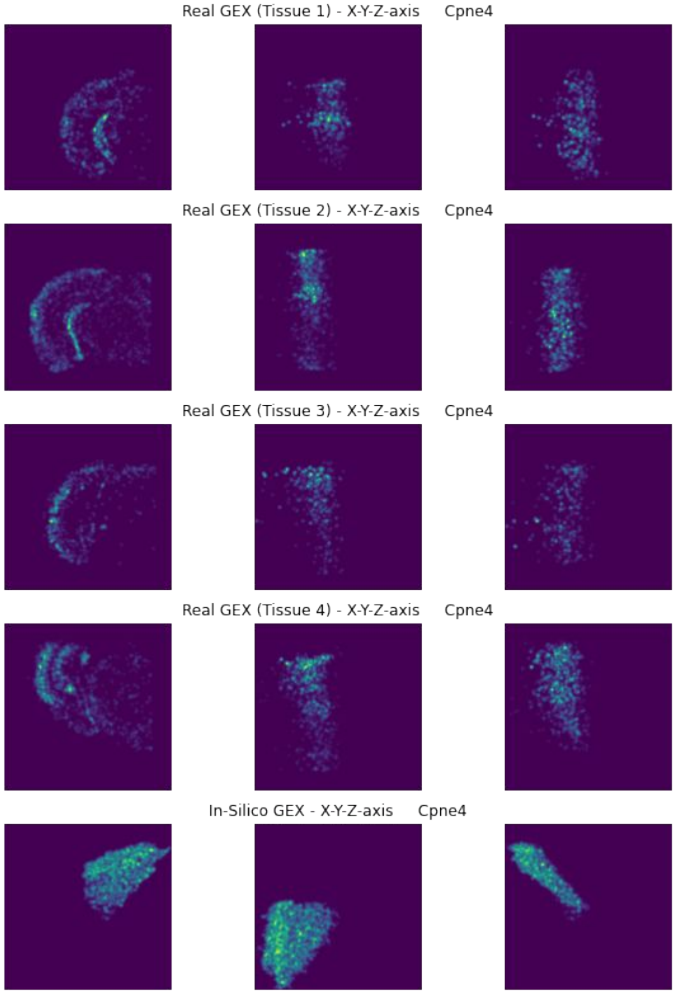

Real GEX (Tissue 1) - X-Y-Z-axis Col19a1
Real GEX (Tissue 2) - X-Y-Z-axis Col19a1
Real GEX (Tissue 3) - X-Y-Z-axis Col19a1
Real GEX (Tissue 4) - X-Y-Z-axis Col19a1
In-Silico GEX - X-Y-Z-axis Col19a1

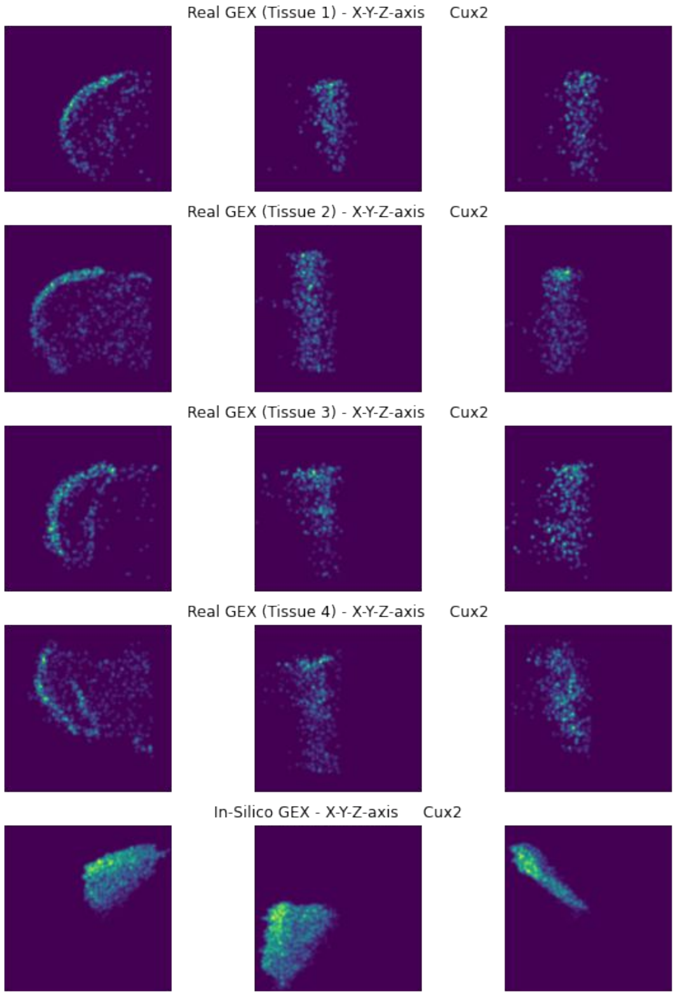

Real GEX (Tissue 1) - X-Y-Z-axis Calb1
Real GEX (Tissue 2) - X-Y-Z-axis Calb1
Real GEX (Tissue 3) - X-Y-Z-axis Calb1
Real GEX (Tissue 4) - X-Y-Z-axis Calb1
In-Silico GEX - X-Y-Z-axis Calb1

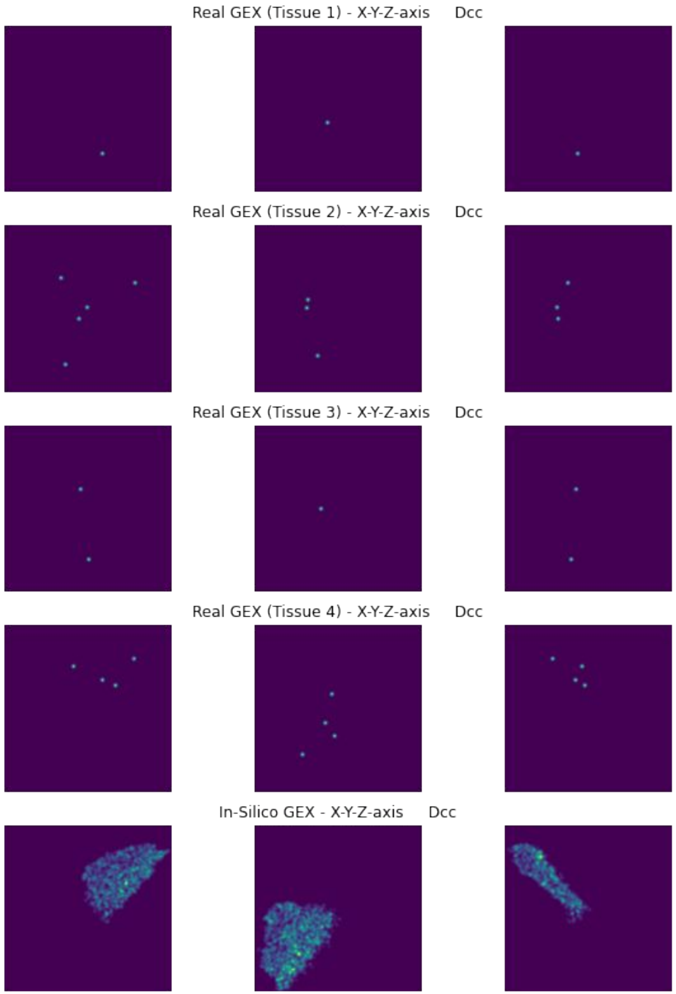

Real GEX (Tissue 1) - X-Y-Z-axis Car3
Real GEX (Tissue 2) - X-Y-Z-axis Car3
Real GEX (Tissue 3) - X-Y-Z-axis Car3
Real GEX (Tissue 4) - X-Y-Z-axis Car3
In-Silico GEX - X-Y-Z-axis Car3

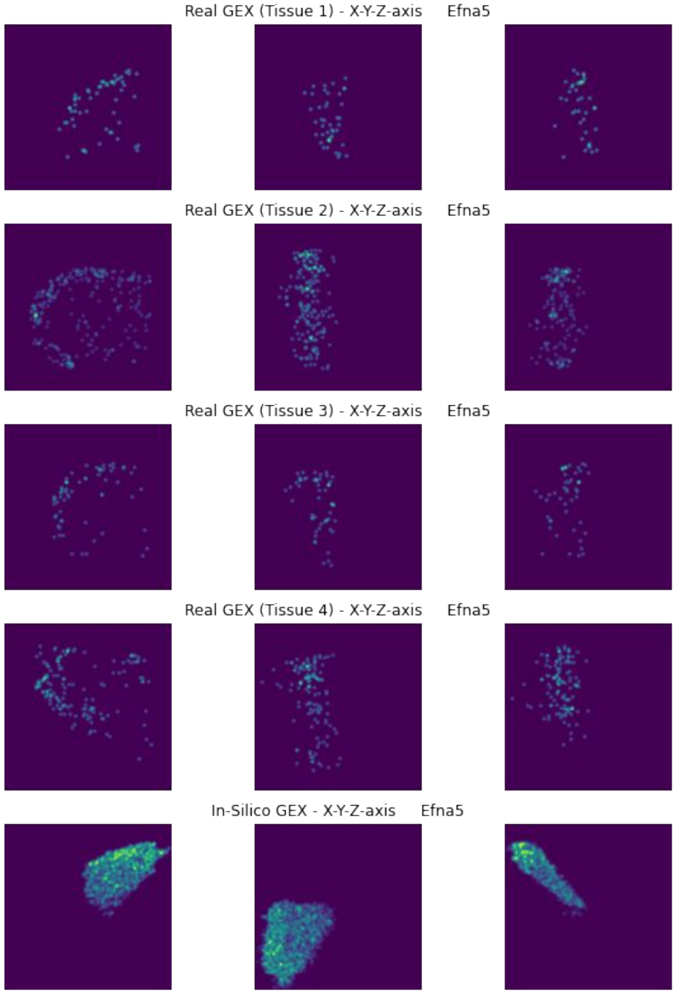

Real GEX (Tissue 1) - X-Y-Z-axis Cbln2
Real GEX (Tissue 2) - X-Y-Z-axis Cbln2
Real GEX (Tissue 3) - X-Y-Z-axis Cbln2
Real GEX (Tissue 4) - X-Y-Z-axis Cbln2
In-Silico GEX - X-Y-Z-axis Cbln2

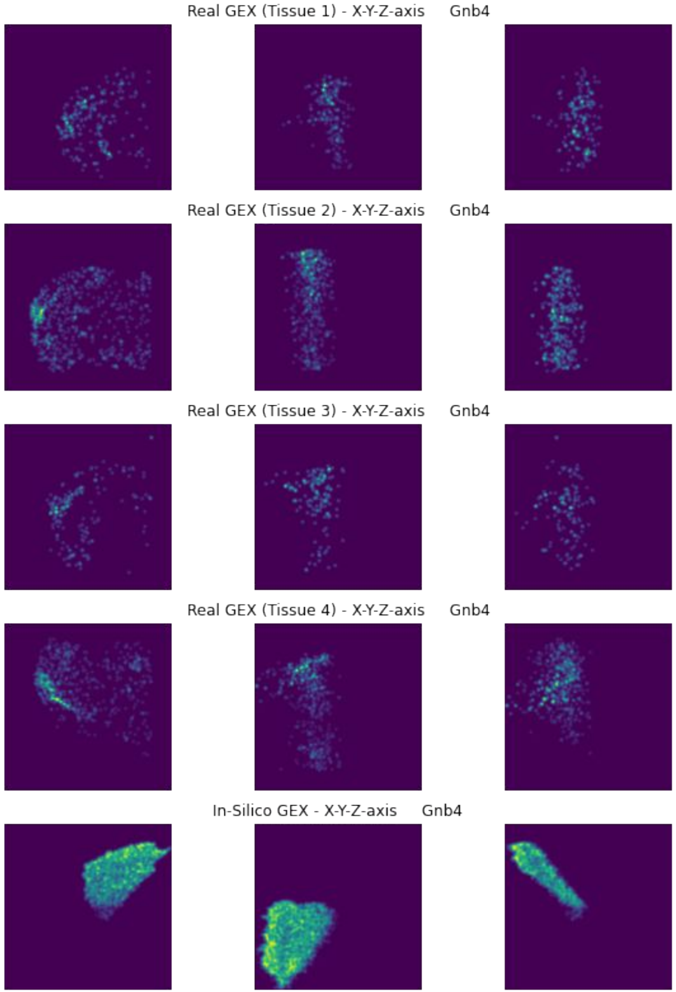

Real GEX (Tissue 1) - X-Y-Z-axis Cdh13
Real GEX (Tissue 2) - X-Y-Z-axis Cdh13
Real GEX (Tissue 3) - X-Y-Z-axis Cdh13
Real GEX (Tissue 4) - X-Y-Z-axis Cdh13
In-Silico GEX - X-Y-Z-axis Cdh13

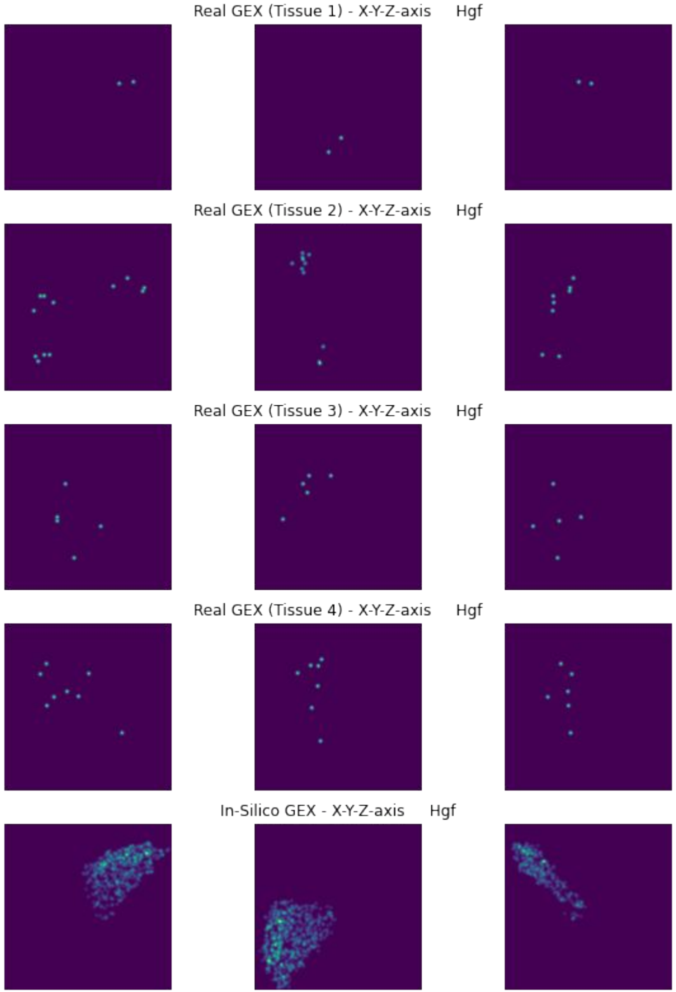

Real GEX (Tissue 1) - X-Y-Z-axis Cpne4
Real GEX (Tissue 2) - X-Y-Z-axis Cpne4
Real GEX (Tissue 3) - X-Y-Z-axis Cpne4
Real GEX (Tissue 4) - X-Y-Z-axis Cpne4
In-Silico GEX - X-Y-Z-axis Cpne4

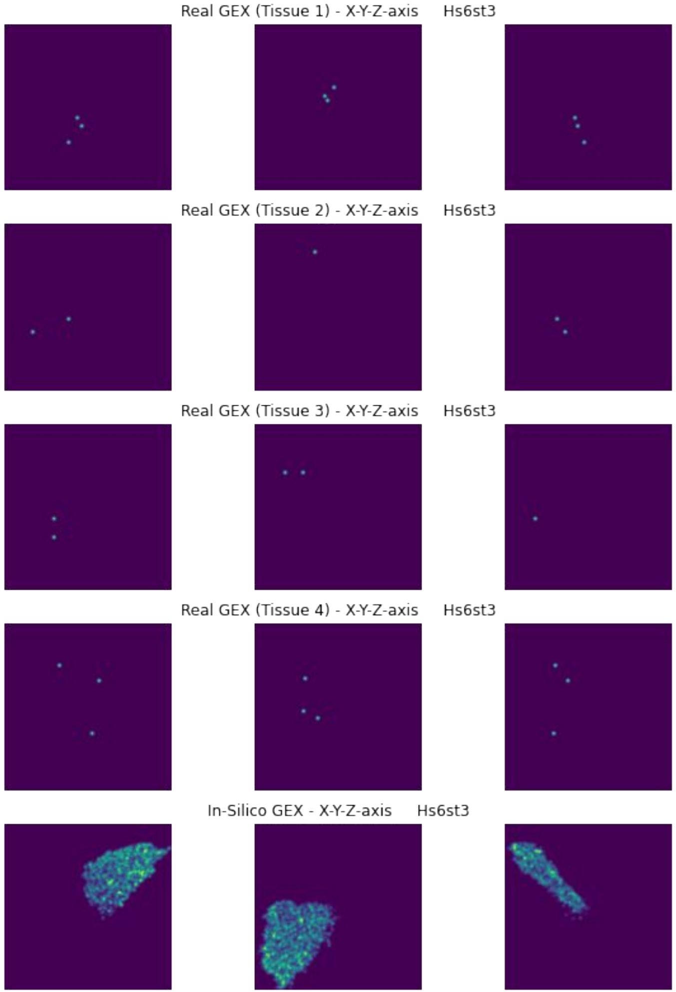

Real GEX (Tissue 1) - X-Y-Z-axis Cux2
Real GEX (Tissue 2) - X-Y-Z-axis Cux2
Real GEX (Tissue 3) - X-Y-Z-axis Cux2
Real GEX (Tissue 4) - X-Y-Z-axis Cux2
In-Silico GEX - X-Y-Z-axis Cux2

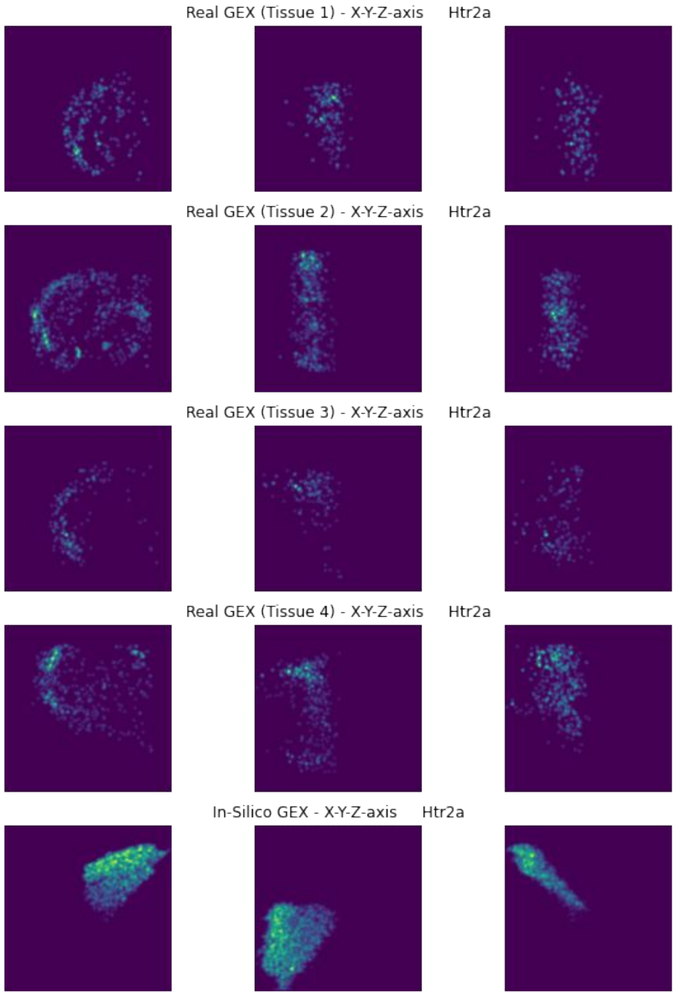

Real GEX (Tissue 1) - X-Y-Z-axis Dcc
Real GEX (Tissue 2) - X-Y-Z-axis Dcc
Real GEX (Tissue 3) - X-Y-Z-axis Dcc
Real GEX (Tissue 4) - X-Y-Z-axis Dcc
In-Silico GEX - X-Y-Z-axis Dcc

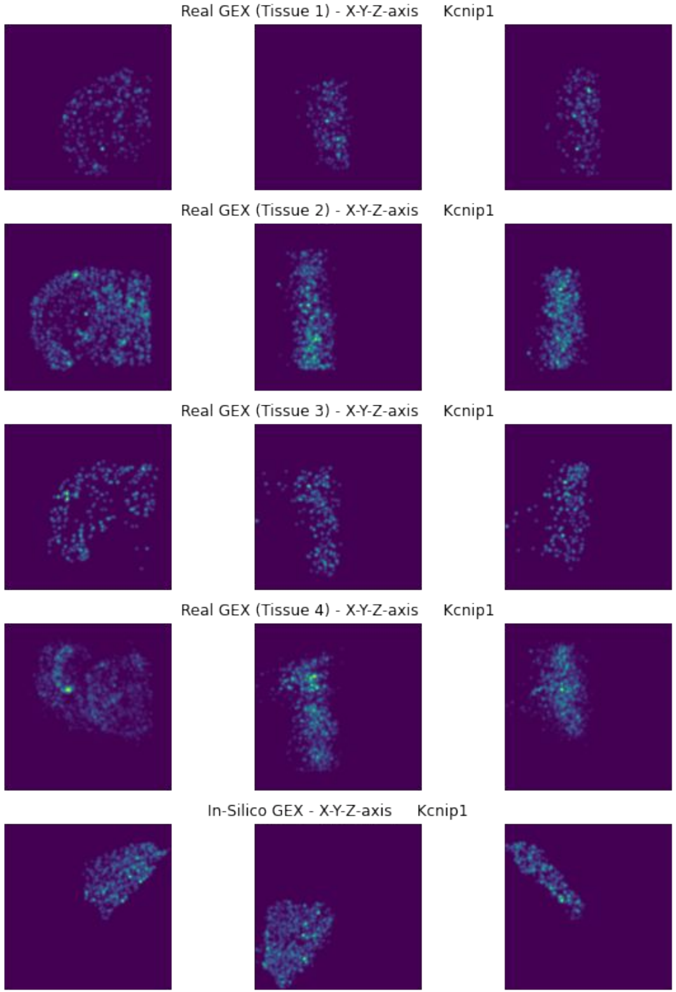

Real GEX (Tissue 1) - X-Y-Z-axis Efna5
Real GEX (Tissue 2) - X-Y-Z-axis Efna5
Real GEX (Tissue 3) - X-Y-Z-axis Efna5
Real GEX (Tissue 4) - X-Y-Z-axis Efna5
In-Silico GEX - X-Y-Z-axis Efna5

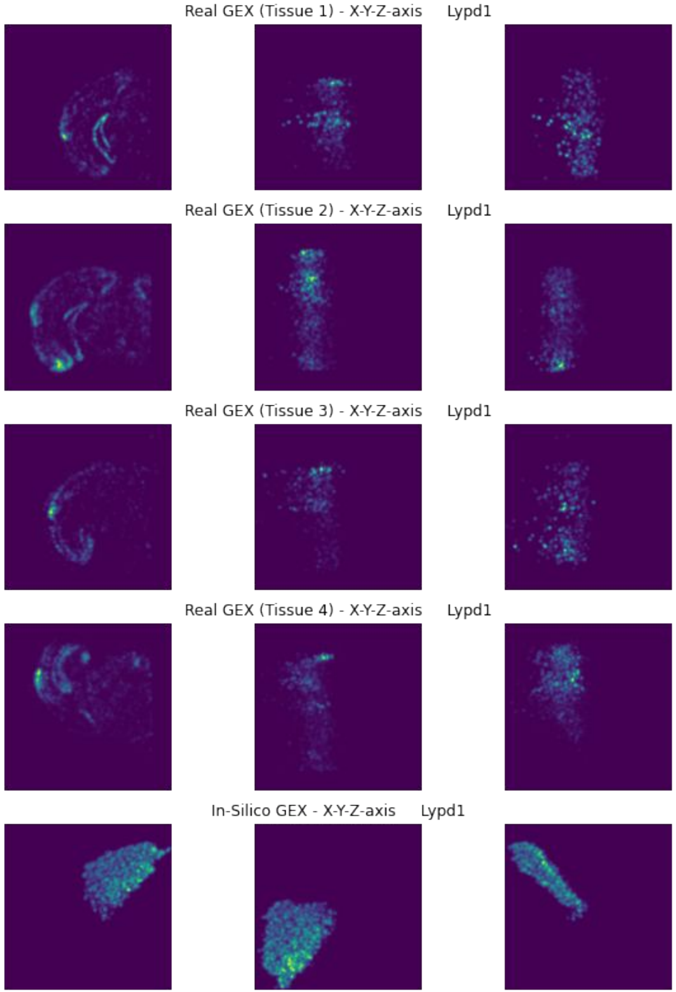

Real GEX (Tissue 1) - X-Y-Z-axis Gnb4
Real GEX (Tissue 2) - X-Y-Z-axis Gnb4
Real GEX (Tissue 3) - X-Y-Z-axis Gnb4
Real GEX (Tissue 4) - X-Y-Z-axis Gnb4
In-Silico GEX - X-Y-Z-axis Gnb4

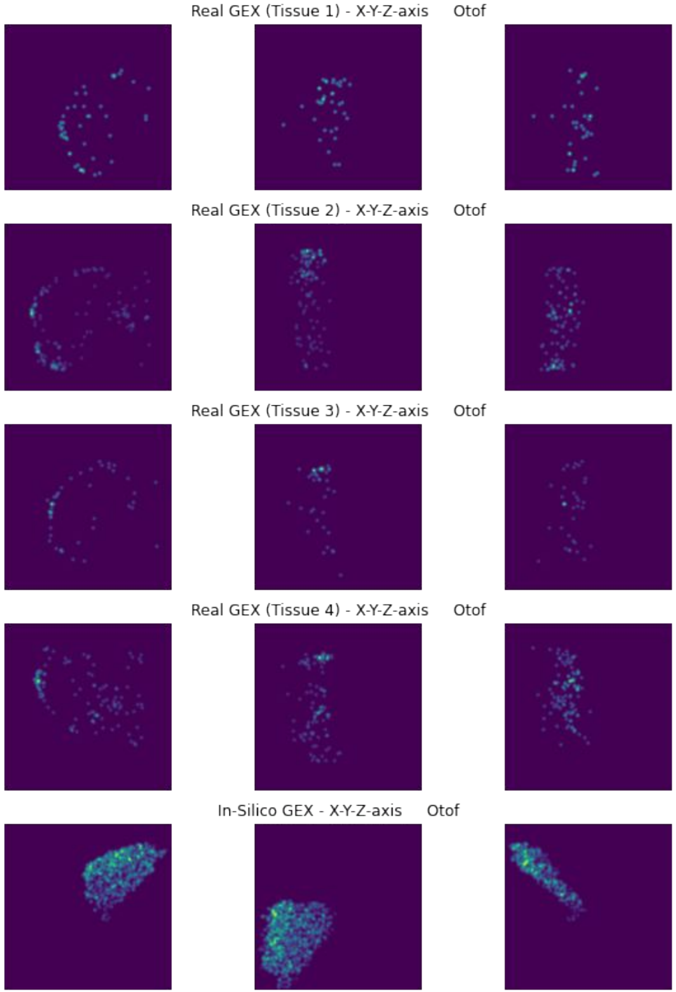

Real GEX (Tissue 1) - X-Y-Z-axis Hgf
Real GEX (Tissue 2) - X-Y-Z-axis Hgf
Real GEX (Tissue 3) - X-Y-Z-axis Hgf
Real GEX (Tissue 4) - X-Y-Z-axis Hgf
In-Silico GEX - X-Y-Z-axis Hgf

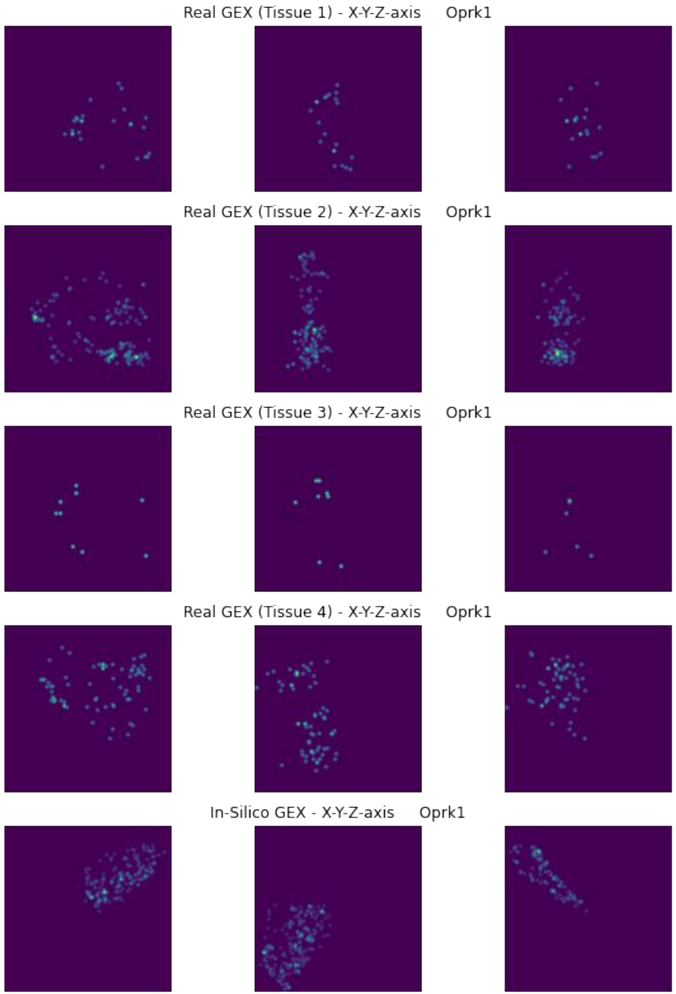

Real GEX (Tissue 1) - X-Y-Z-axis Hs6st3
Real GEX (Tissue 2) - X-Y-Z-axis Hs6st3
Real GEX (Tissue 3) - X-Y-Z-axis Hs6st3
Real GEX (Tissue 4) - X-Y-Z-axis Hs6st3
In-Silico GEX - X-Y-Z-axis Hs6st3

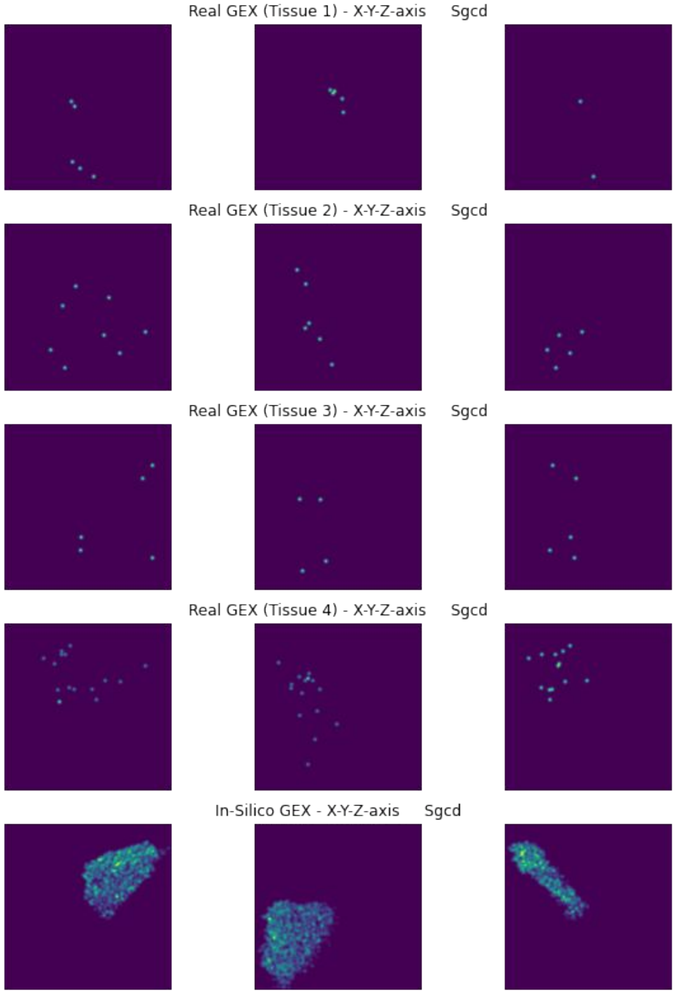

Real GEX (Tissue 1) - X-Y-Z-axis Htr2a
Real GEX (Tissue 2) - X-Y-Z-axis Htr2a
Real GEX (Tissue 3) - X-Y-Z-axis Htr2a
Real GEX (Tissue 4) - X-Y-Z-axis Htr2a
In-Silico GEX - X-Y-Z-axis Htr2a

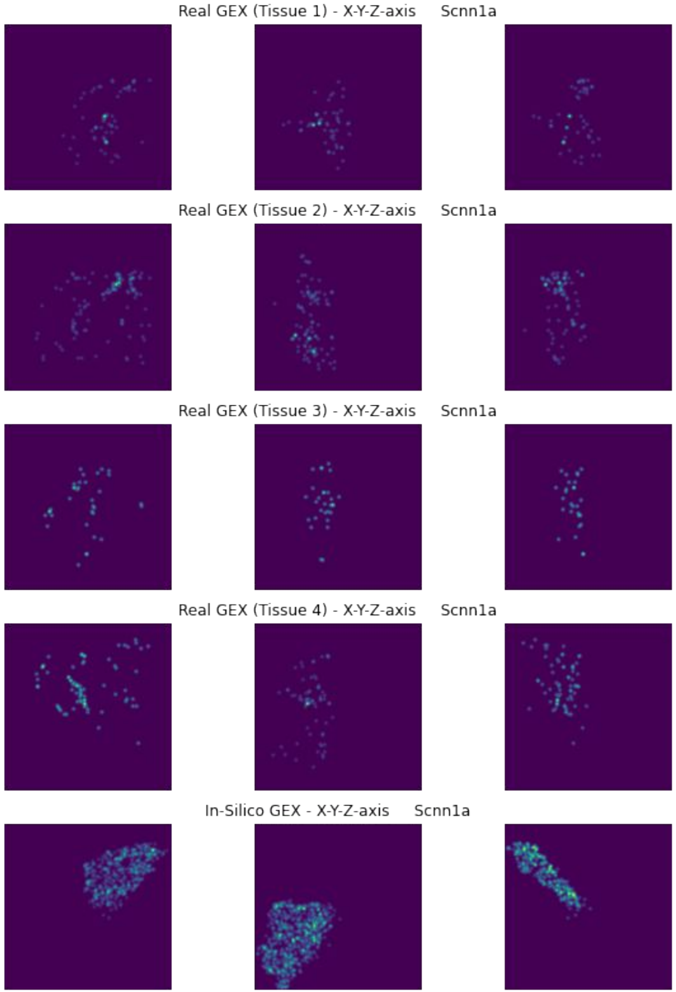

Real GEX (Tissue 1) - X-Y-Z-axis Kcnip1
Real GEX (Tissue 2) - X-Y-Z-axis Kcnip1
Real GEX (Tissue 3) - X-Y-Z-axis Kcnip1
Real GEX (Tissue 4) - X-Y-Z-axis Kcnip1
In-Silico GEX - X-Y-Z-axis Kcnip1

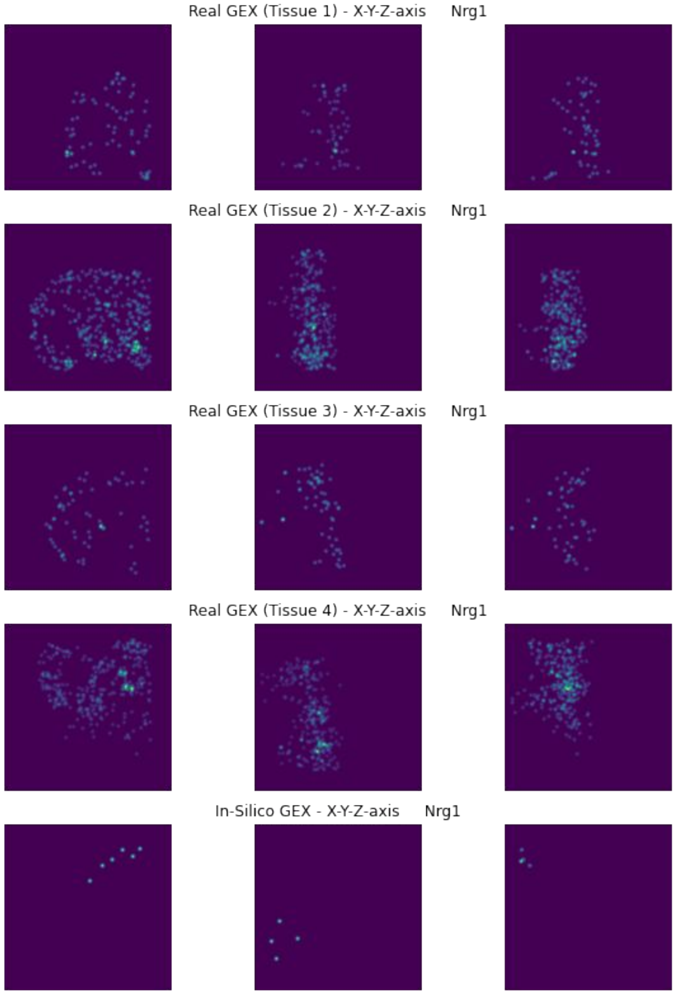

Real GEX (Tissue 1) - X-Y-Z-axis Lypd1
Real GEX (Tissue 2) - X-Y-Z-axis Lypd1
Real GEX (Tissue 3) - X-Y-Z-axis Lypd1
Real GEX (Tissue 4) - X-Y-Z-axis Lypd1
In-Silico GEX - X-Y-Z-axis Lypd1

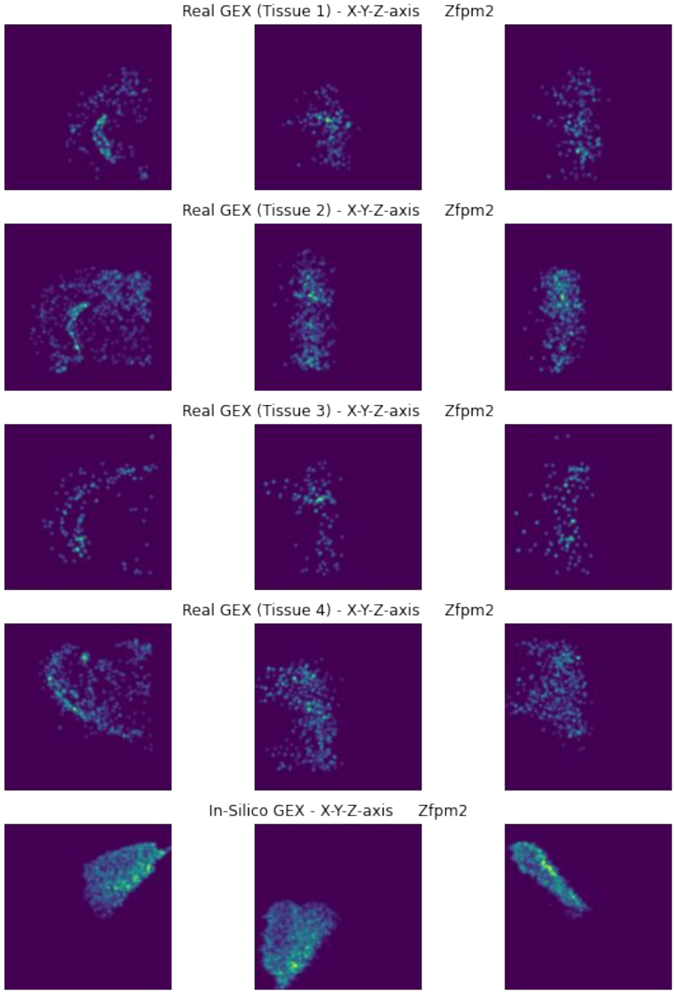

Real GEX (Tissue 1) - X-Y-Z-axis Otof
Real GEX (Tissue 2) - X-Y-Z-axis Otof
Real GEX (Tissue 3) - X-Y-Z-axis Otof
Real GEX (Tissue 4) - X-Y-Z-axis Otof
In-Silico GEX - X-Y-Z-axis Otof

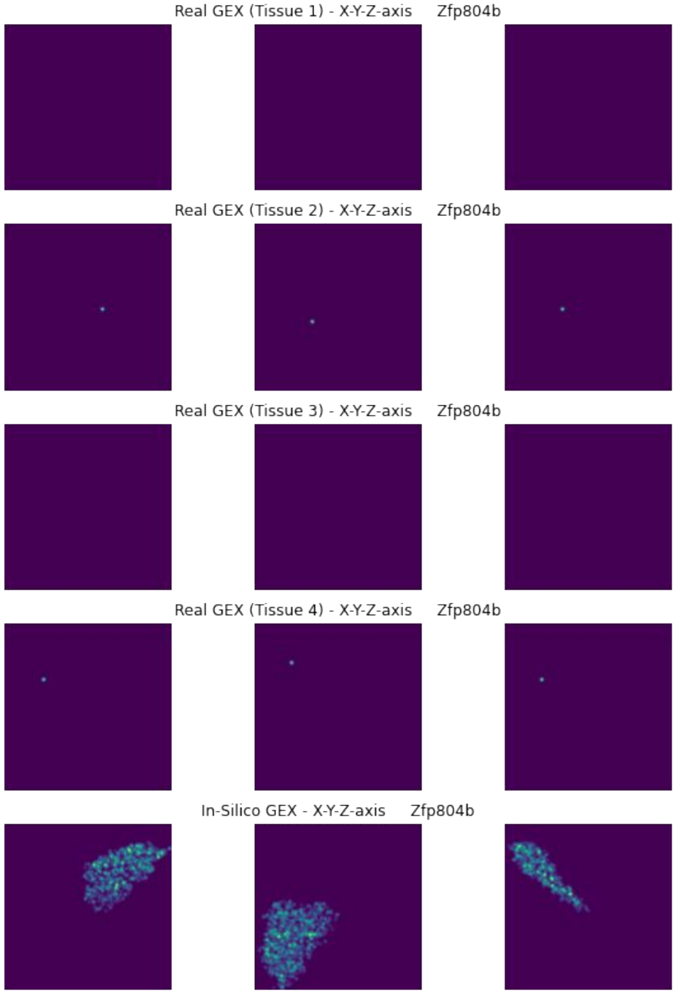

Real GEX (Tissue 1) - X-Y-Z-axis Oprk1
Real GEX (Tissue 2) - X-Y-Z-axis Oprk1
Real GEX (Tissue 3) - X-Y-Z-axis Oprk1
Real GEX (Tissue 4) - X-Y-Z-axis Oprk1
In-Silico GEX - X-Y-Z-axis Oprk1

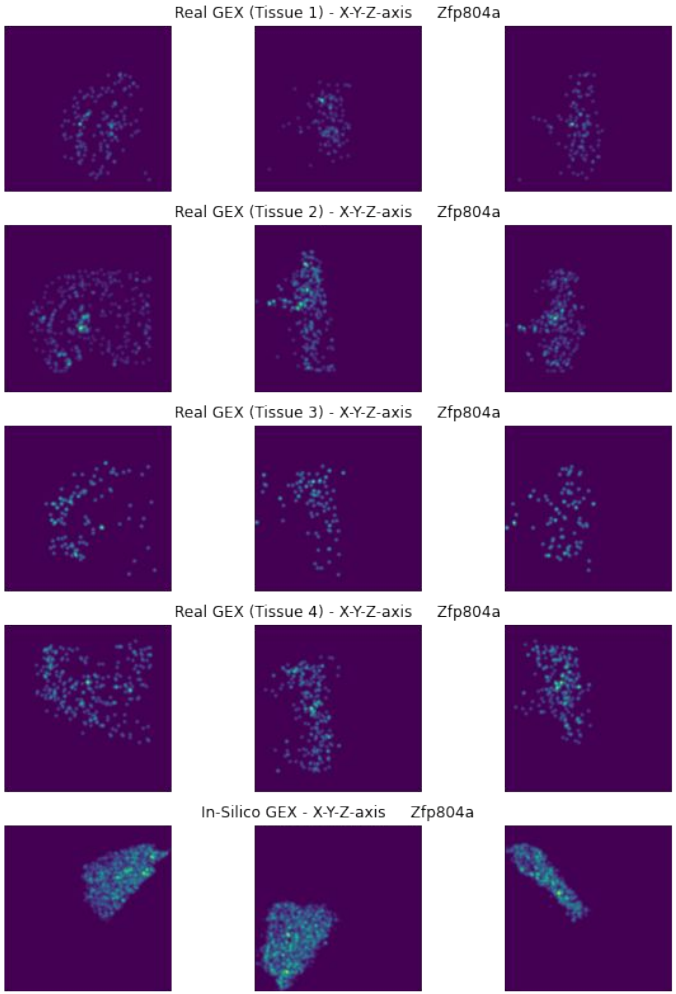

Real GEX (Tissue 1) - X-Y-Z-axis Sgcd
Real GEX (Tissue 2) - X-Y-Z-axis Sgcd
Real GEX (Tissue 3) - X-Y-Z-axis Sgcd
Real GEX (Tissue 4) - X-Y-Z-axis Sgcd
In-Silico GEX - X-Y-Z-axis Sgcd


Real GEX (Tissue 1) - X-Y-Z-axis Scnn1a
Real GEX (Tissue 2) - X-Y-Z-axis Scnn1a
Real GEX (Tissue 3) - X-Y-Z-axis Scnn1a
Real GEX (Tissue 4) - X-Y-Z-axis Scnn1a
In-Silico GEX - X-Y-Z-axis Scnn1a


Real GEX (Tissue 1) - X-Y-Z-axis Nrg1
Real GEX (Tissue 2) - X-Y-Z-axis Nrg1
Real GEX (Tissue 3) - X-Y-Z-axis Nrg1
Real GEX (Tissue 4) - X-Y-Z-axis Nrg1
In-Silico GEX - X-Y-Z-axis Nrg1


Real GEX (Tissue 1) - X-Y-Z-axis Zfpm2
Real GEX (Tissue 2) - X-Y-Z-axis Zfpm2
Real GEX (Tissue 3) - X-Y-Z-axis Zfpm2
Real GEX (Tissue 4) - X-Y-Z-axis Zfpm2
In-Silico GEX - X-Y-Z-axis Zfpm2


Real GEX (Tissue 1) - X-Y-Z-axis Zfp804b
Real GEX (Tissue 2) - X-Y-Z-axis Zfp804b
Real GEX (Tissue 3) - X-Y-Z-axis Zfp804b
Real GEX (Tissue 4) - X-Y-Z-axis Zfp804b
In-Silico GEX - X-Y-Z-axis Zfp804b


Real GEX (Tissue 1) - X-Y-Z-axis Zfp804a
Real GEX (Tissue 2) - X-Y-Z-axis Zfp804a
Real GEX (Tissue 3) - X-Y-Z-axis Zfp804a
Real GEX (Tissue 4) - X-Y-Z-axis Zfp804a
In-Silico GEX - X-Y-Z-axis Zfp804a