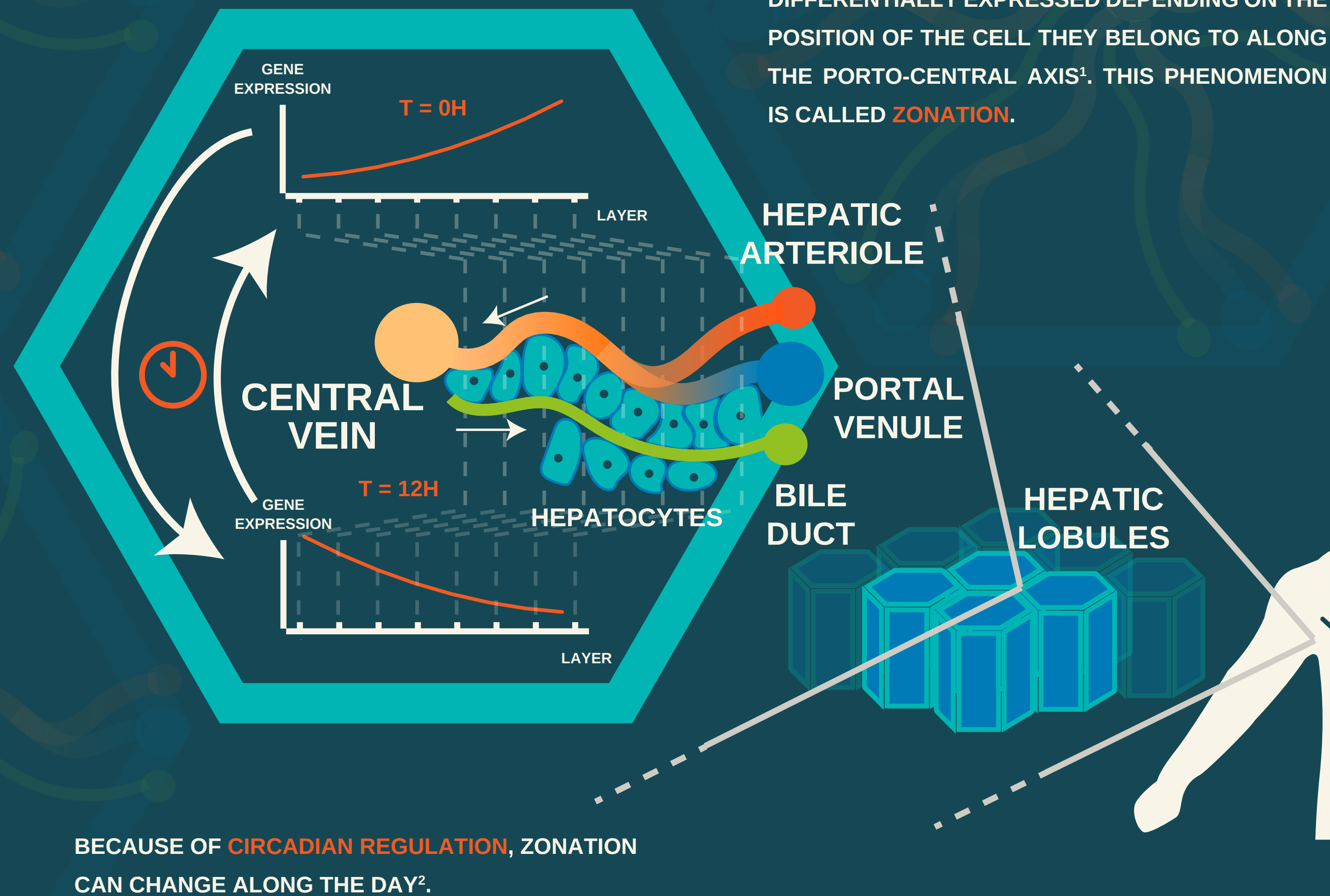


EXPLORING CIRCADIAN LIVER ZONATION

COLAS DROIN, JAKOB EL KHOLTEI, KEREN BAHAR HALPERN, CLEMENCE HURNI, SHALEV ITZKOVITZ, FELIX NAEF

I. WHAT IS CIRCADIAN LIVER ZONATION



III. THE MODEL

WE USE A **MIXED-MODEL** APPROACH THAT ACCOUNTS FOR BOTH THE SPATIAL AND THE TEMPORAL VARIANCE, THROUGH POLYNOMIAL AND SINUSOIDAL REGRESSIONS. THE INTER-ANIMAL VARIABILITY IS ABSORBED INTO THE RANDOM EFFECTS OF THE MODEL (μ_i).

$$Y_{x,t,i} = \mu_i + \mu(x) + a(x)\cos(\omega t) + b(x)\sin(\omega t) + \epsilon_{x,t,i}$$

$$\mu(x) = \mu_0 + \mu_1 P_1(x) + \mu_2 P_2(x)$$

$$b(x) = b_0 + b_1 P_1(x) + b_2 P_2(x)$$

$$a(x) = a_0 + a_1 P_1(x) + a_2 P_2(x)$$

$$M_1 : \{\mu_0\} : \text{FLAT}$$

$$M_2 : \{\mu_0, \mu_1\} : \text{ZONATED}$$

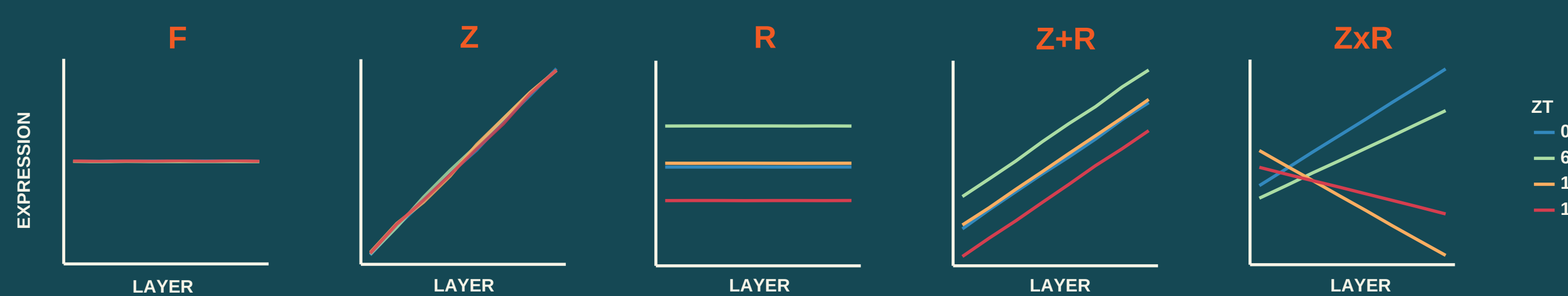
$$M_3 : \{\mu_0, a_0, b_0\} : \text{RHYTHMIC}$$

$$M_4 : \{\mu_0, \mu_1, a_0, b_0\} : \text{Z+R}$$

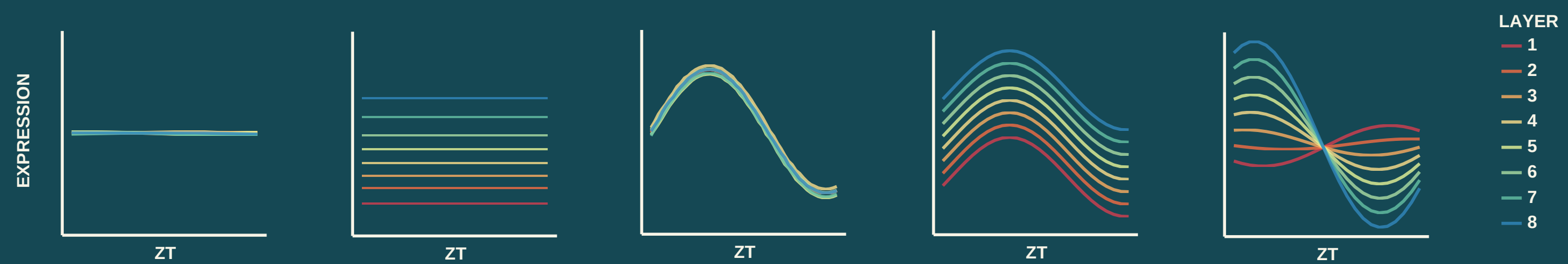
$$\vdots$$

$$M_N : \{\mu_0, \mu_1, \mu_2, a_0, b_0, a_1, b_1, a_2, b_2\} : \text{ZxR}$$

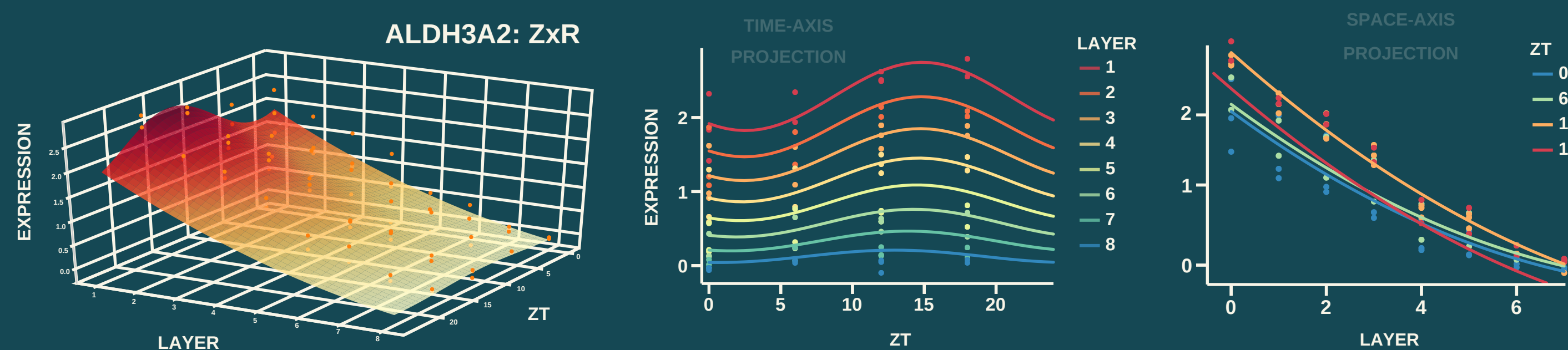
2nd SUB-MODELS M_n CAN BE GENERATED BY REMOVING SOME OF THE PARAMETERS μ_i , a_j AND b_j . WE THEN PERFORM **MODEL SELECTION** ACCORDING TO THE BIC, ENABLING TO SORT GENES ACCORDING INTO DIFFERENT MODEL CATEGORIES:



FOR CHRONOBIOLOGISTS, CATEGORIES EQUIVALENTLY EXPLAIN HOW RHYTHMICITY VARIES WITH THE LAYERS:



WE END UP OBTAINING FITS, WHOSE COMPLEXITY DEPEND ON THE GENE CATEGORY:



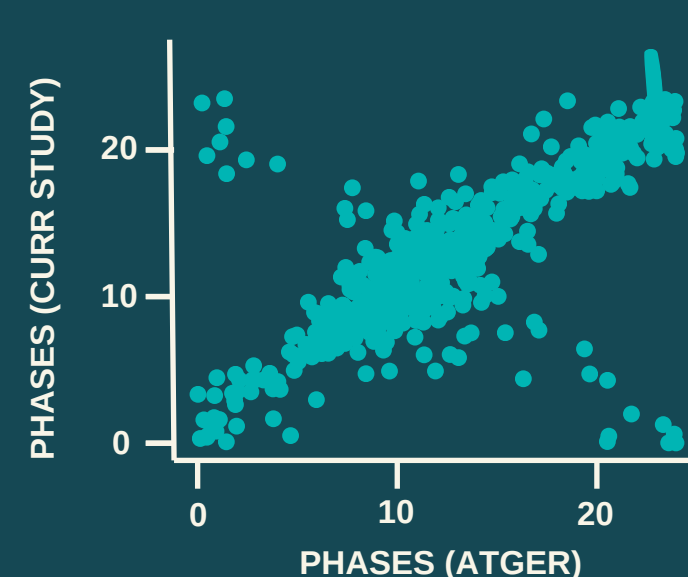
V. VALIDATION

WE VALIDATE OUR CLASSIFICATION **COMPARING** OUR RESULTS WITH THE ONES OBTAINED FROM ATGER. & AL³.

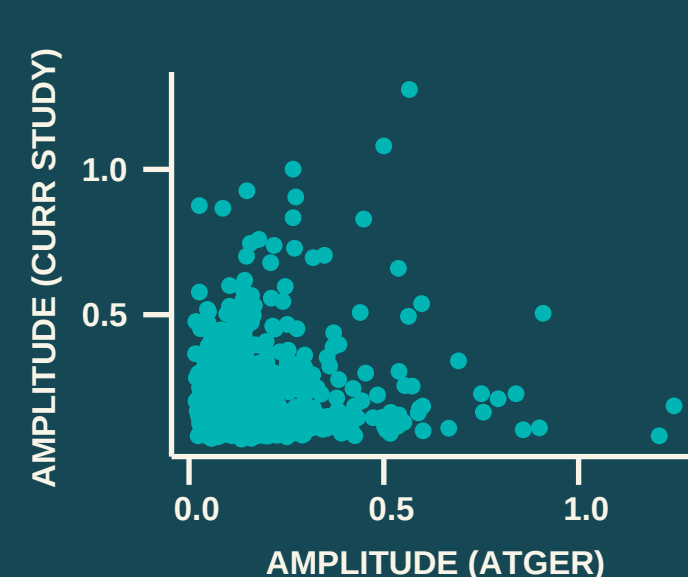
CONFUSION MATRIX

	Atger, F	Atger, R
R	42	4.6e+02
Z+R	36	2.4e+02

PHASE COMPARISON



AMPLITUDE COMPARISON

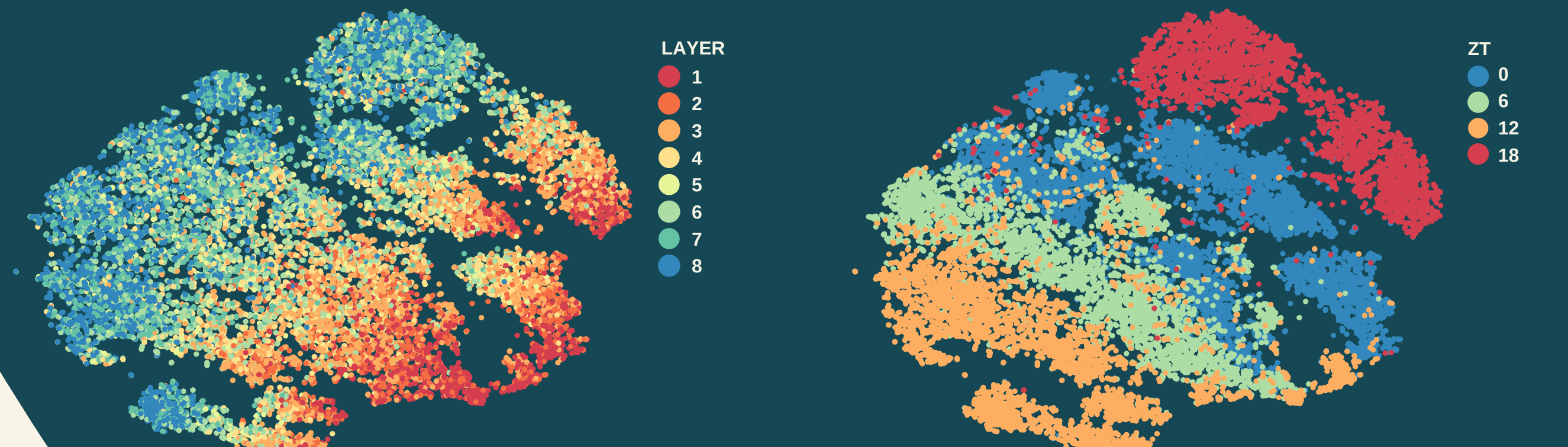


II. THE DATA

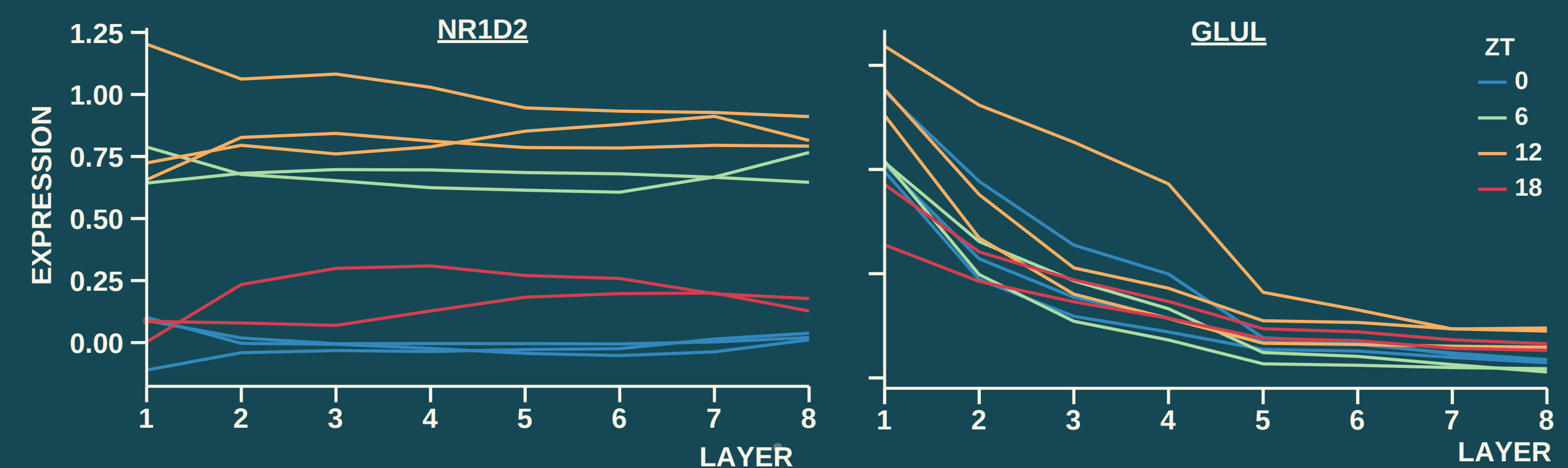
- SINGLE-CELL **RNA-SEQ** FROM **MOUSE LIVER**
- **4 TIMEPOINTS**: ZT0, ZT6, ZT12 AND ZT18
- **8 LAYERS** CONSIDERED
- ABOUT **15.000 GENES**
- **2 TO 3 REPLICATES** PER TIME CONDITION



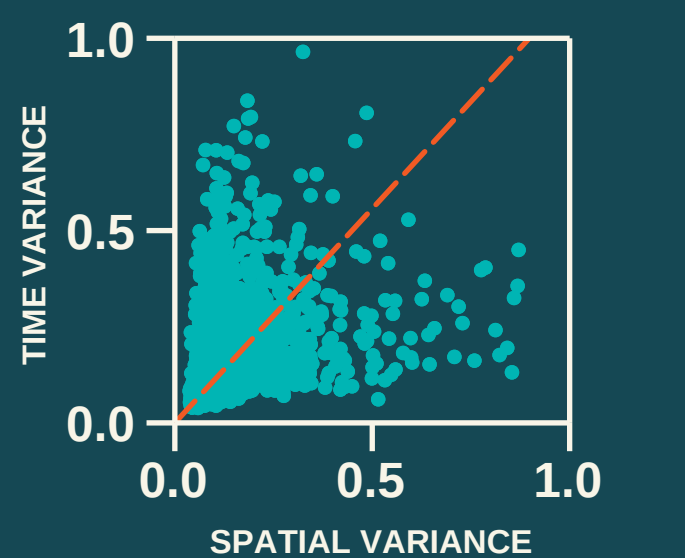
EXPLORING THE VARIANCE OF THE DATASET WITH **T-SNE** REVEALS THAT THE CELLS CLUSTER ACCORDING TO THEIR **POSITION** AND **TIME** LABELS:



FOR EACH GENE, WE GET A TIME-DEPENDENT ZONATION PROFILE:



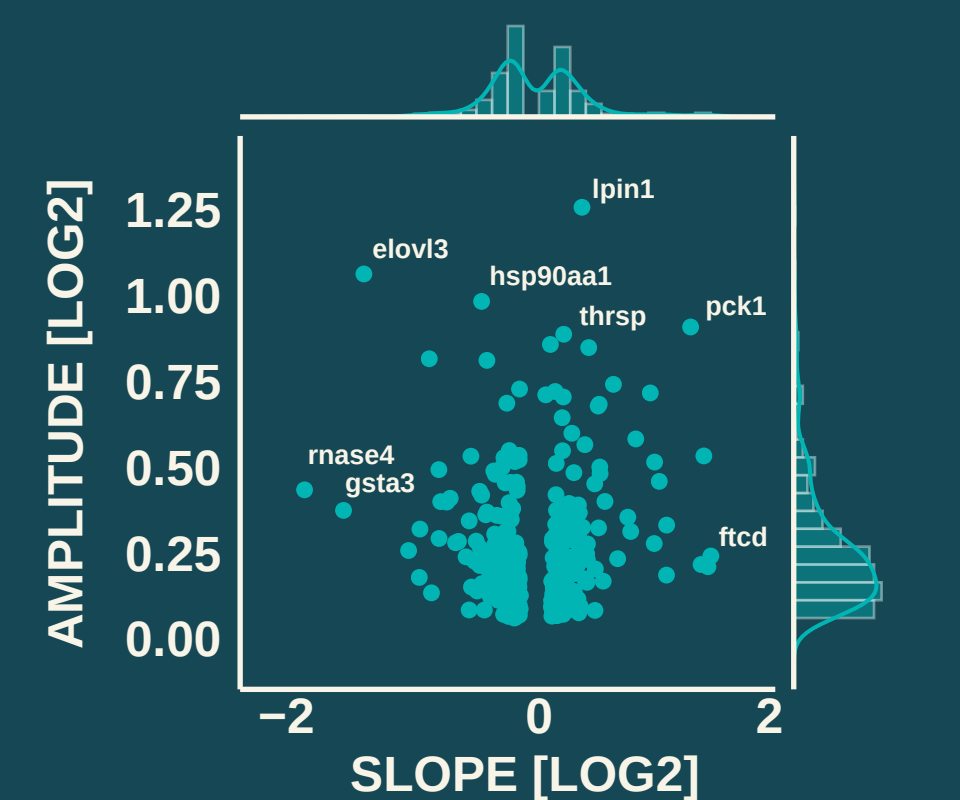
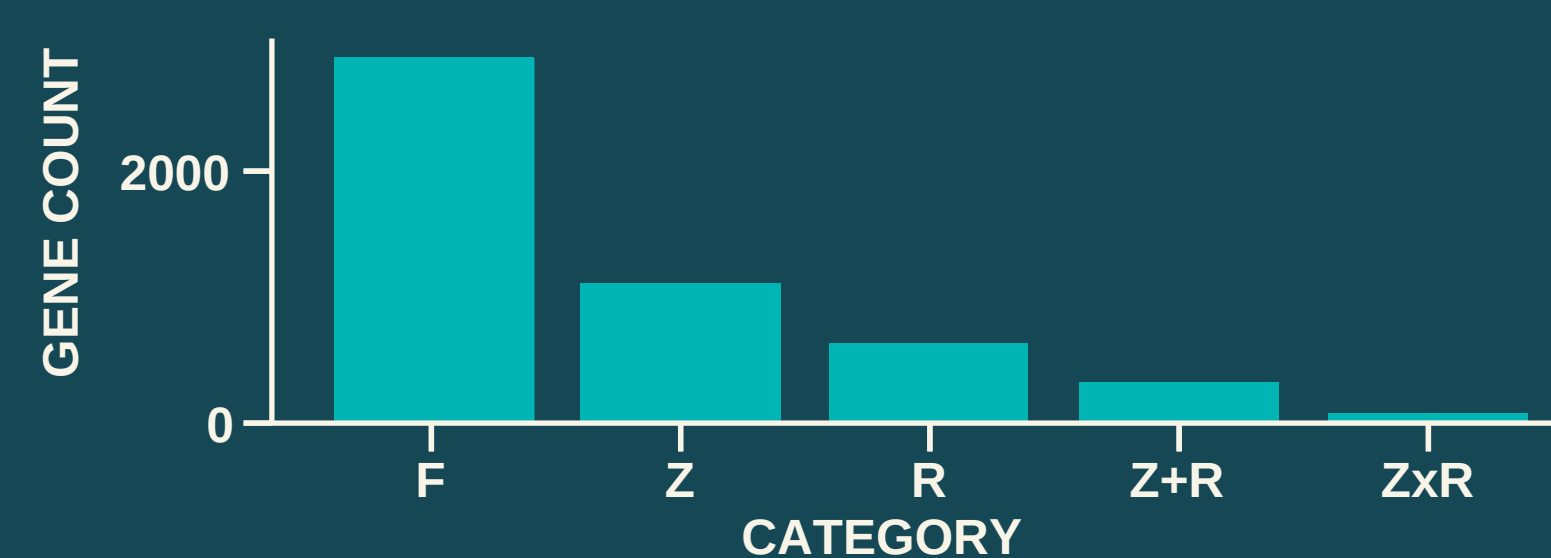
LOOKING AT THE **SPATIAL** AND **TEMPORAL** VARIANCES OF THE GENES IN THE WHOLE DATASET CONFIRMS THAT THERE ARE **LARGE DIFFERENCES** IN TERMS OF RHYTHMICITY AND ZONATION AMONG GENES.



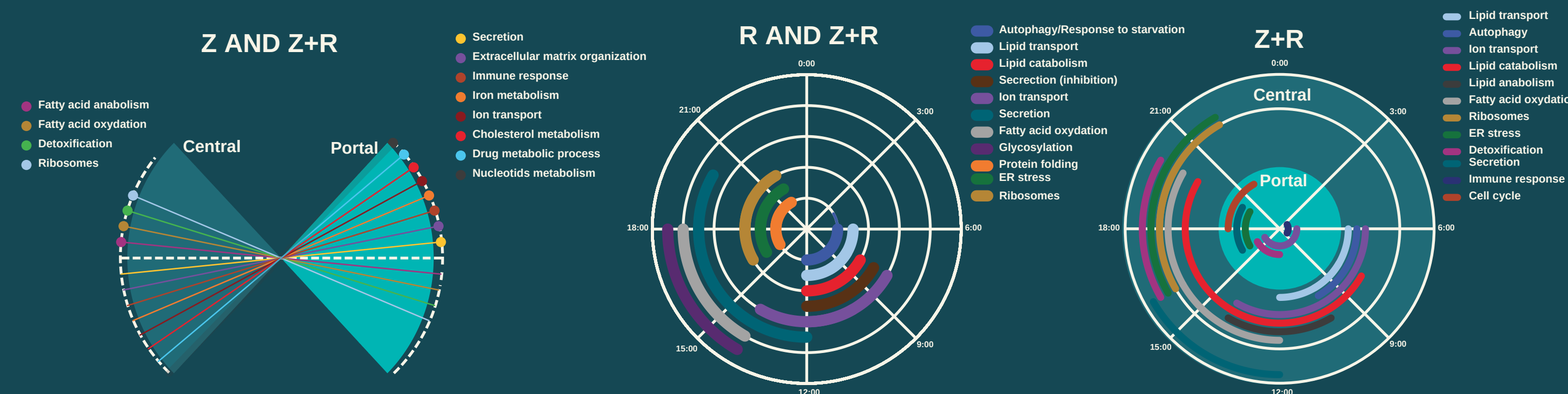
IV. RESULTS

THE **FINAL CLASSIFICATION** REVEALS THAT FEW GENES EXHIBIT WAVE-LIKE BEHAVIORS (ZxR), BUT A SIGNIFICANT PART OF THEM ARE INDEPENDENTLY ZONATED AND RHYTHMIC (Z+R).

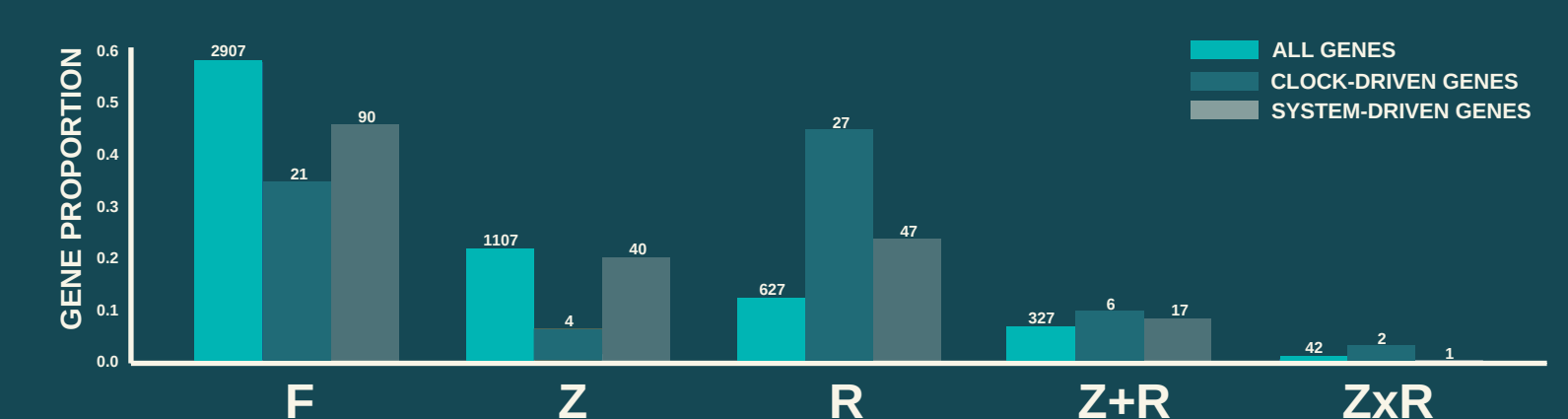
COMPARING **AMPLITUDE** AND **SLOPE** IN THE Z+R GENES SHOW **INDEPENDENT** EFFECTS:



ENRICHMENT ANALYSIS OF THE **GO PATHWAYS** REVEAL THAT SOME BIOLOGICAL PROCESSES ARE REGULATED IN BOTH SPACE AND TIME:



ENRICHMENT ANALYSIS ALSO REVEALS THAT THE **CLOCK-DRIVEN GENES** ARE MAINLY NOT ZONATED WHILE THE **SYSTEM-DRIVEN RHYTHMIC GENES** ARE:

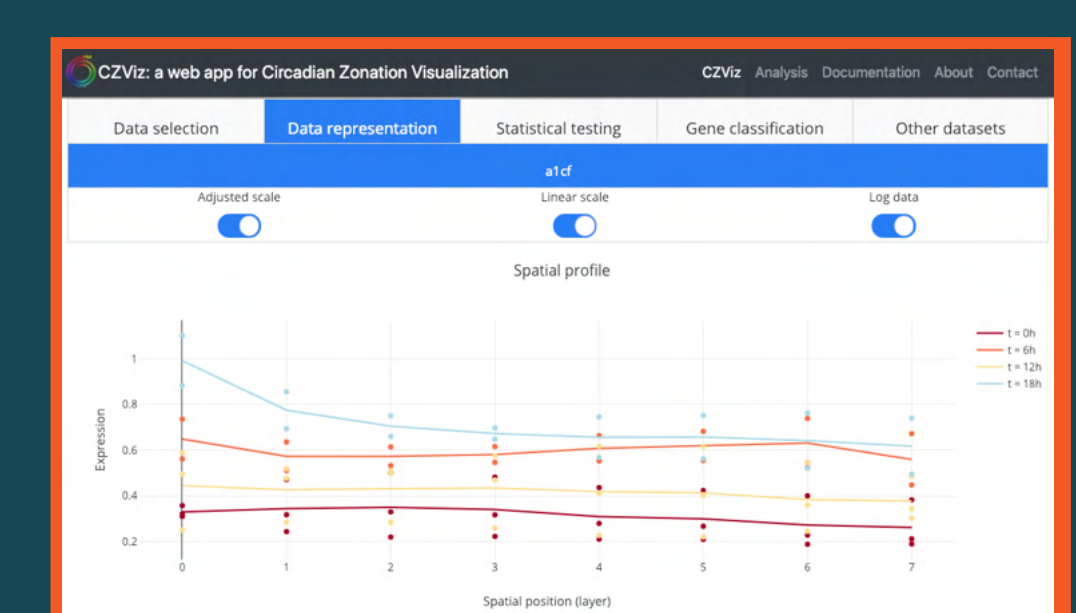


VI. WEB-APP

A WEB-APP, BUILT USING THE FRAMEWORK DASH BY PLOTLY, ENABLES TO EXPLORE THE WHOLE DATASET AND THE RESULTS OF THE ANALYSIS. IT IS AVAILABLE AND FULLY DOCUMENTED ON THE WEBSITE:

[C2VIZ.EPFL.CH](https://c2viz.epfl.ch)

FEEDBACKS WELCOME!



SCAN ME!

