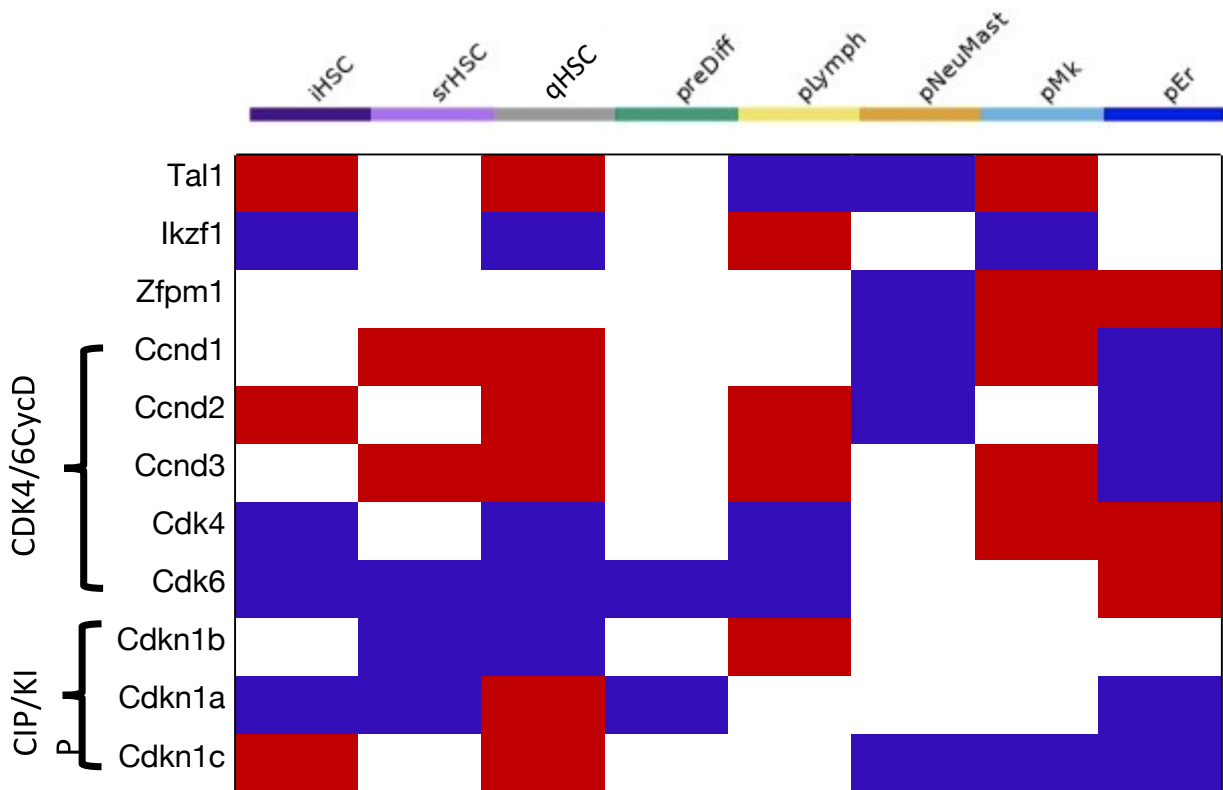
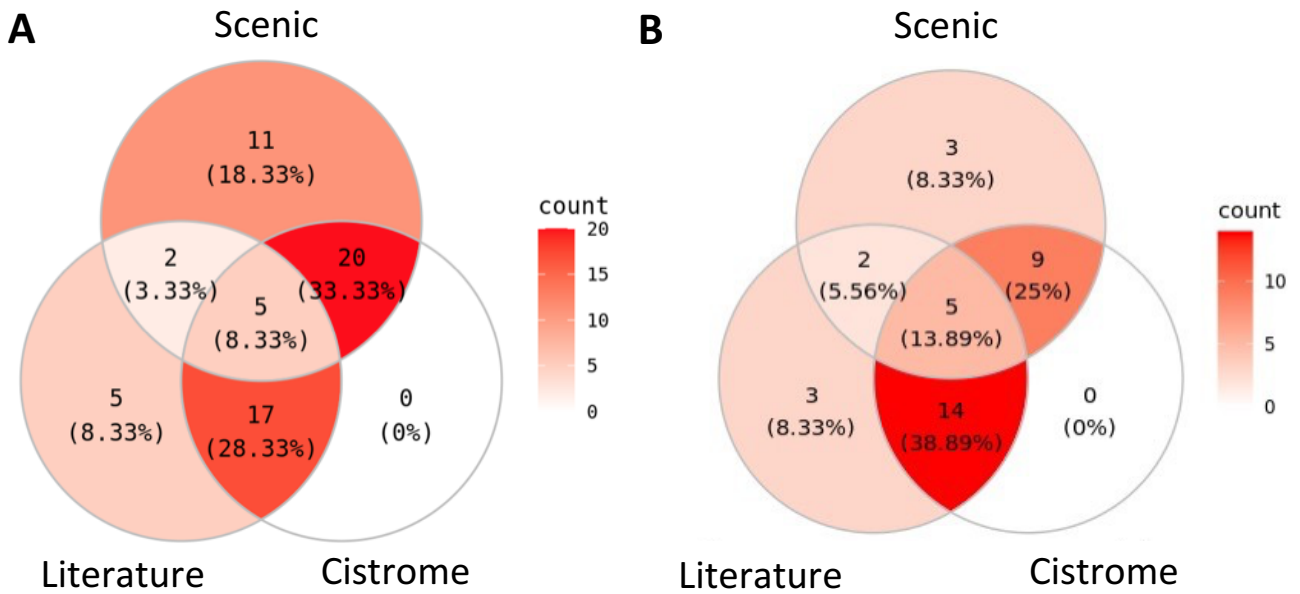


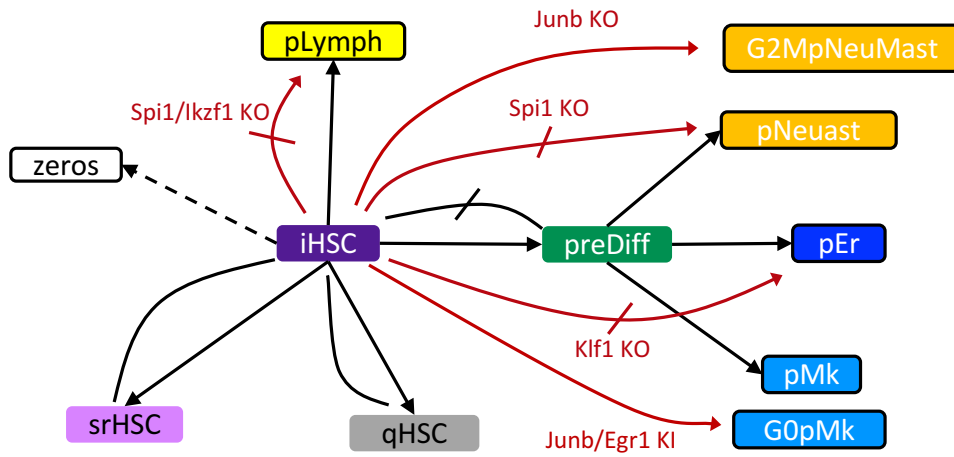
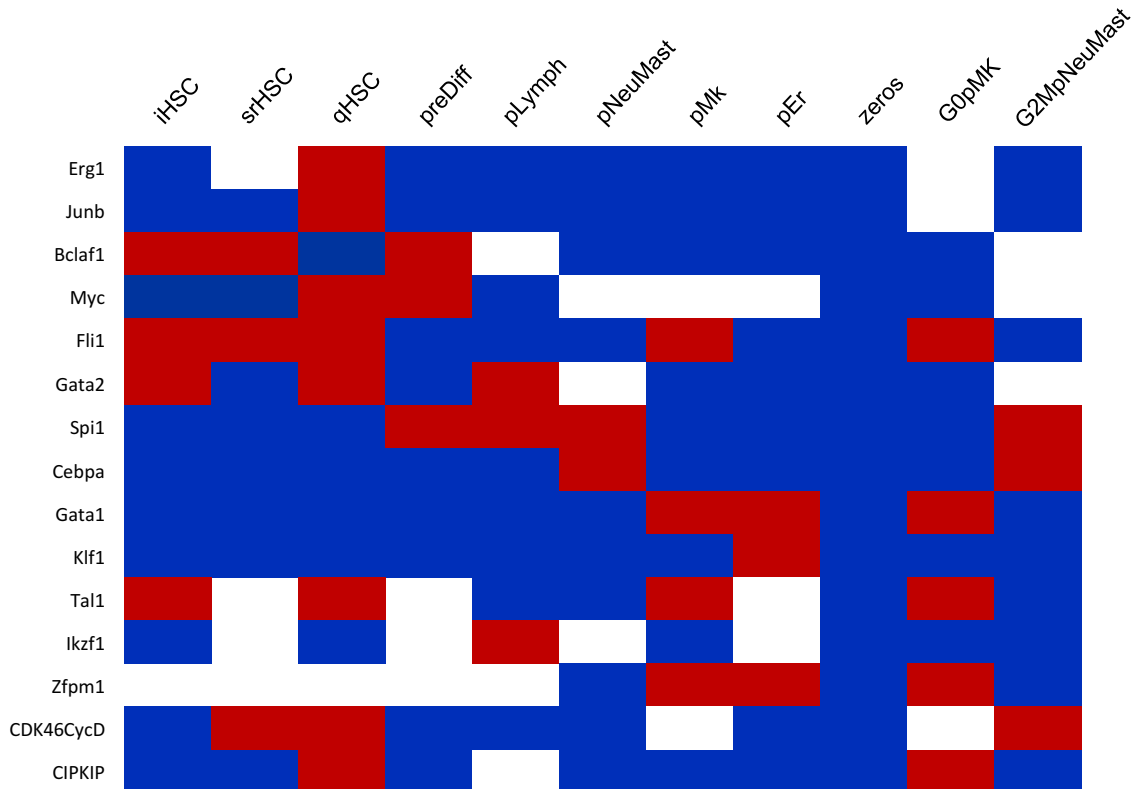
Supplementary Figure 1: Comparison of the HSC state distribution according to the hscScore (left) and Monocle2 pseudotime (right).



Supplementary Figure 2: Discretization of gene expressions for the two cycle-related complexes and regulons with less than 10 targets. Results of K-means clustering on averaged RNA levels of the selected HSPC states. Blue: inactivated; white: unknown/free; red: activated.



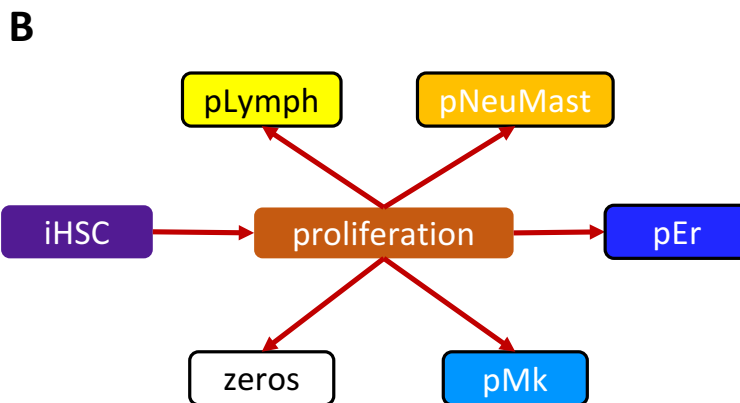
Supplementary Figure 3: Venn diagrams of influence graph interaction sources. **A** The initial influence graph interactions retrieved from SCENIC results and/or literature investigation and supported or not by the Cistrome database analysis (see Supplementary Table 3). **B** Final influence graph interactions after pruning.

A**B**

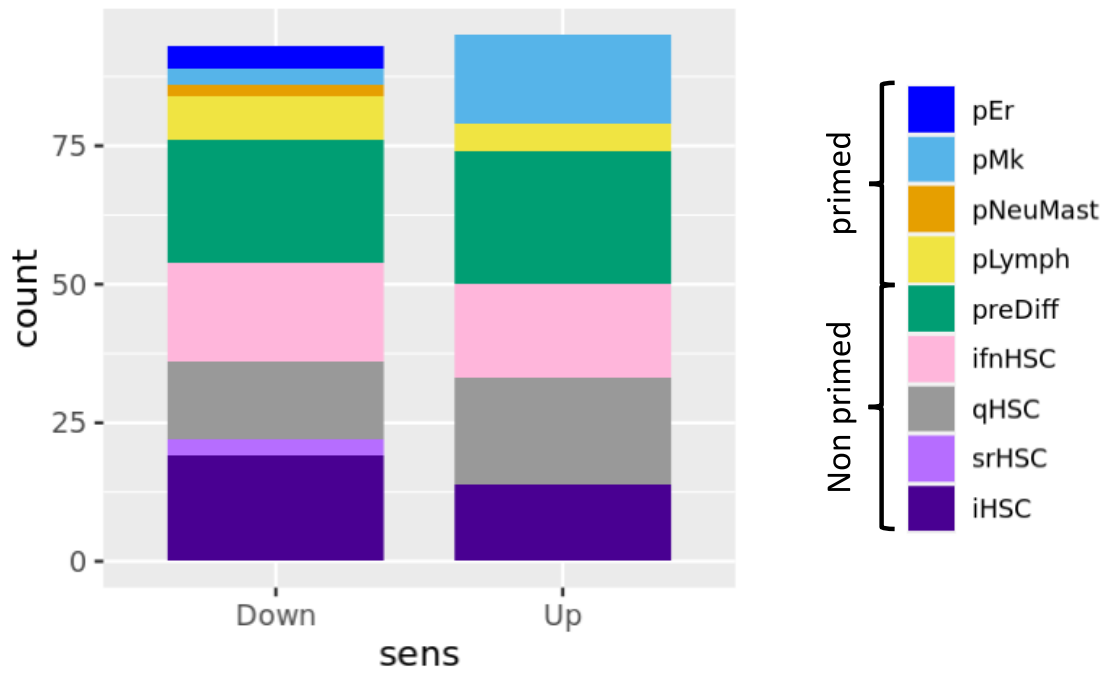
Supplementary Figure 4: Constraints and discretization used for the influence graph pruning and the final rule inference. **A** Dynamical constraint used for the update of the influence graph and the final rule inference. Black arrows (resp. crossed out arrows) indicate reachability (resp. unreachability) between source and target configuration. Framed configurations are constrained as fixed points. Dashed line highlights the allowed reachability of a fixed point with all node activities at 0 from iHSC. Red (crossed out) arrow highlight the additional (non)reachable constraints of mutant behaviors: loss of pLymph reachability with *Ikzf1* or *Spi1* KO, loss of pNeuMast reachability with *Spi1* KO; loss of pEr reachability with *Klf1* KO; additional pNeuMast cycling fixed point (G2MpNeuMast) with *Junb* KO; a unique pMk quiescent fixed point with *Junb/Egr1* KI (G0pMk). **B** Discretization of component activities in the configurations used for the pruning of the influence graph and the final rule inference. Blue: inactivated (0); white: free (*); red: activated (1). G0pMk and G2MpNeuMast configurations were defined according to the first solution space exploration.

A

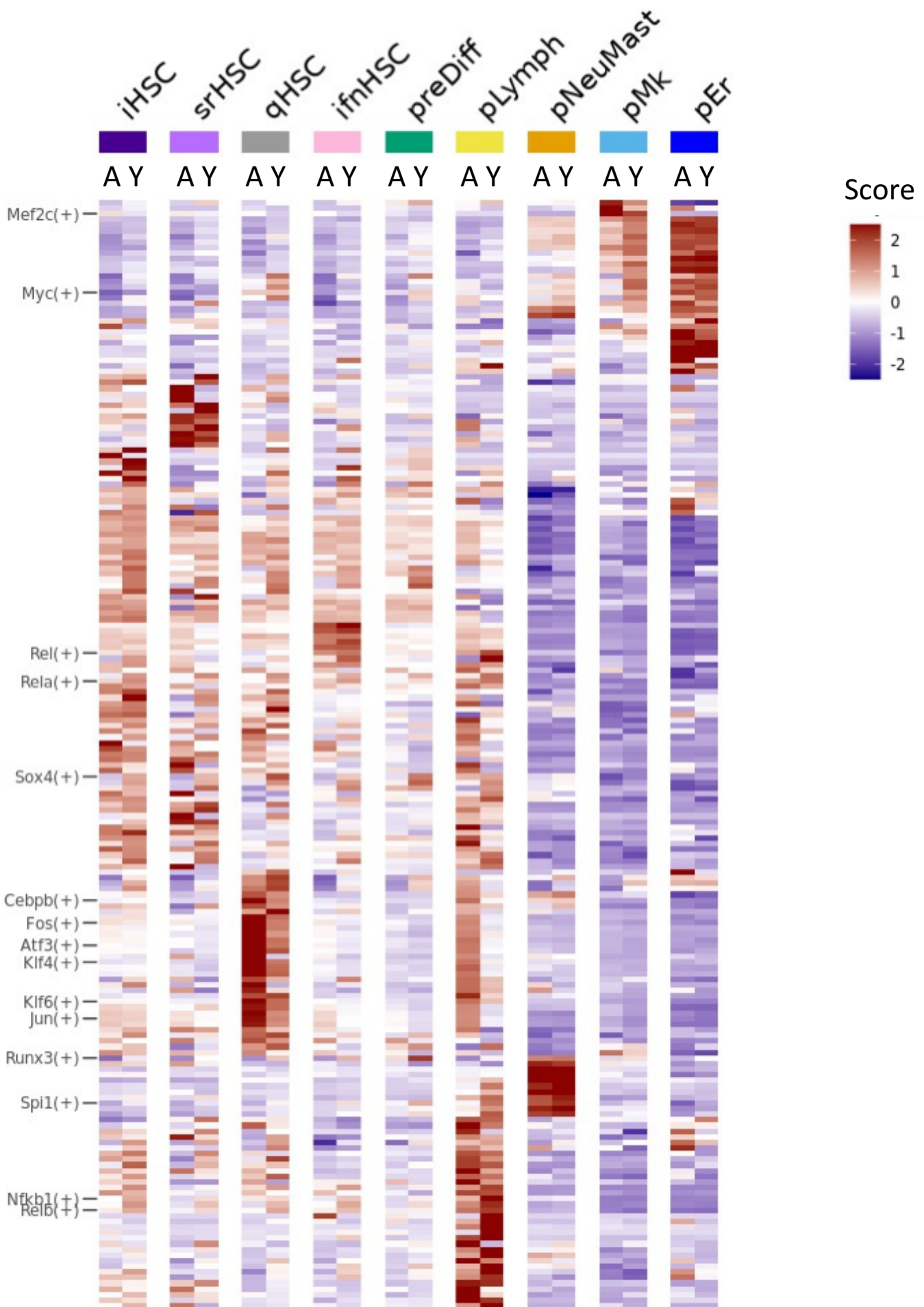
	iHSC	proliferation	Fixed points				
			zeros	pLymph	pNeuMast	pMk	pEr
Egr1	0	*	0	0	0	0	0
Junb	0	*	0	0	0	0	0
Bclaf1	1	*	0	0	0	0	0
Myc	0	*	0	0	0	0	0
Fli1	1	*	0	0	0	1	0
Gata2	1	*	0	1	0	0	0
Spi1	0	*	0	1	1	0	0
Cebpa	0	*	0	0	1	0	0
Gata1	0	*	0	0	0	1	1
Klf1	0	*	0	0	0	0	1
Tal1	1	*	0	0	0	1	1
Ikzf1	0	*	0	1	0	0	0
Zfp1	*	*	0	0	0	1	1
CDK46CycD	0	1	0	0	0	0	0
CIPKIP	0	0	0	0	0	0	0



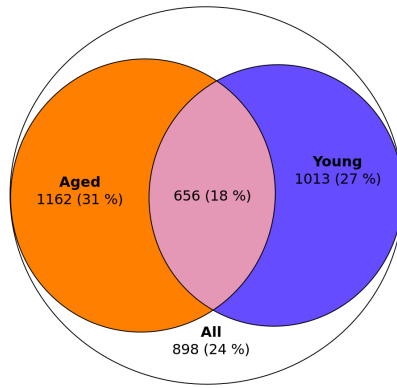
Supplementary Figure 5: A Table describing configurations of the model matching the HSPC states dynamically linked to a proliferation configuration (column: HSPC states, lines: components of the model). Colors represent the activation levels of the nodes (blue: inactive; red: active, white: free). The five last columns are the fixed points of the model. The proliferation configuration (2nd column) results from the analysis of the model. **B** Graph representation of the reachabilities toward/from proliferation configuration. The framed configurations represent fixed points, a red arrow indicate a reachability from a source to a target configuration.



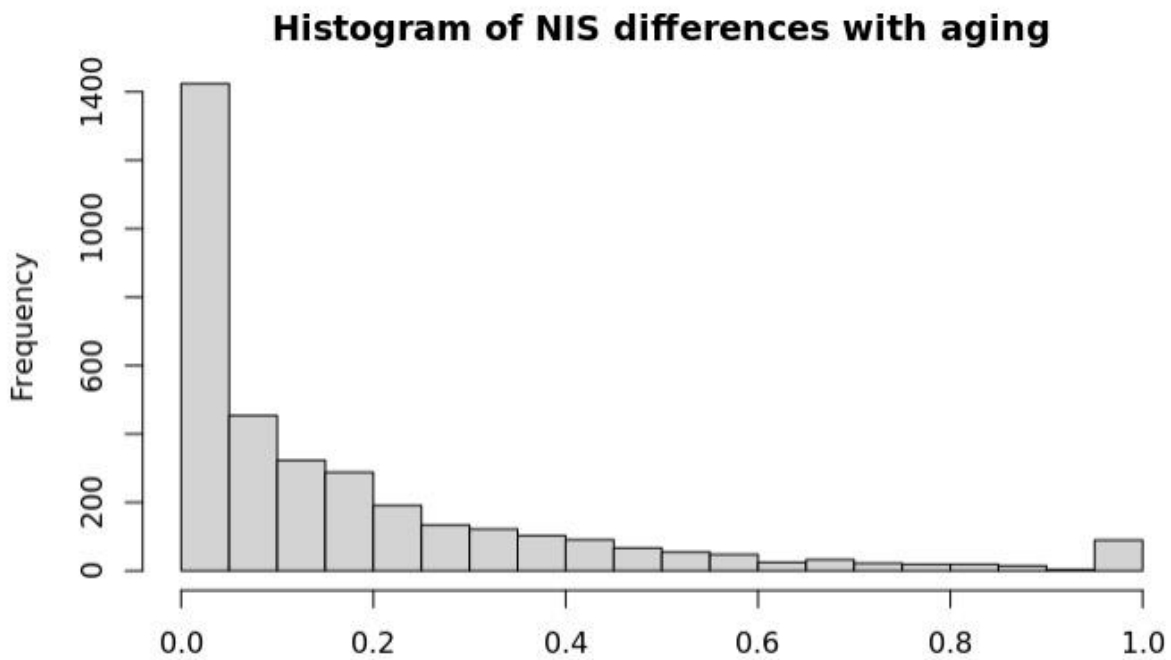
Supplementary Figure 6: Quantification of regulon activity changes upon aging per state. Up (Down) marks significant increases (decreases) in activity upon aging (average differences > 0.001, p-value < 10^{-3}). An alteration of a regulon activity can be recovered in several HSPC states. States are indicated on the right



Supplementary Figure 7: Heatmap of AUCell scores of regulon activity averaged by group of cells from the HSPC states in young and aged cells. Scores are standardized on aged (A) and young (Y) cells of the different states. Rows are ordered as in Figure 1.



Supplementary Figure 8: Repartition of the SCENIC interactions retrieved from the analysis of all cells in aged or/and young cells only analysis.



Supplementary Figure 9: Histogram of normalized interaction score (NIS) differences with aging. Interactions found only in all cells analysis with SCENIC have a null difference.