

In vivo variability of regulatory programs and single cell physiology in central homeostatic control circuits

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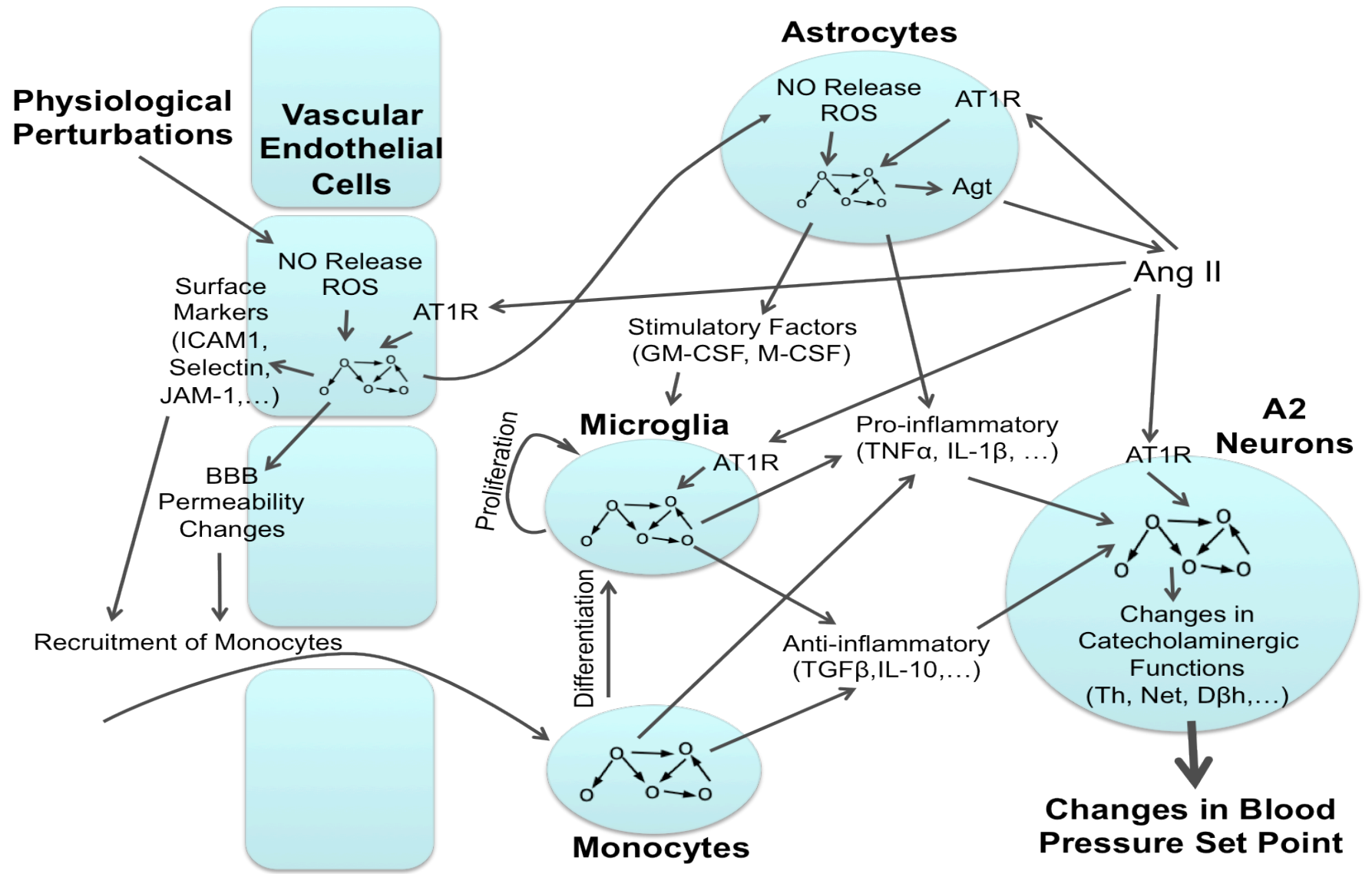
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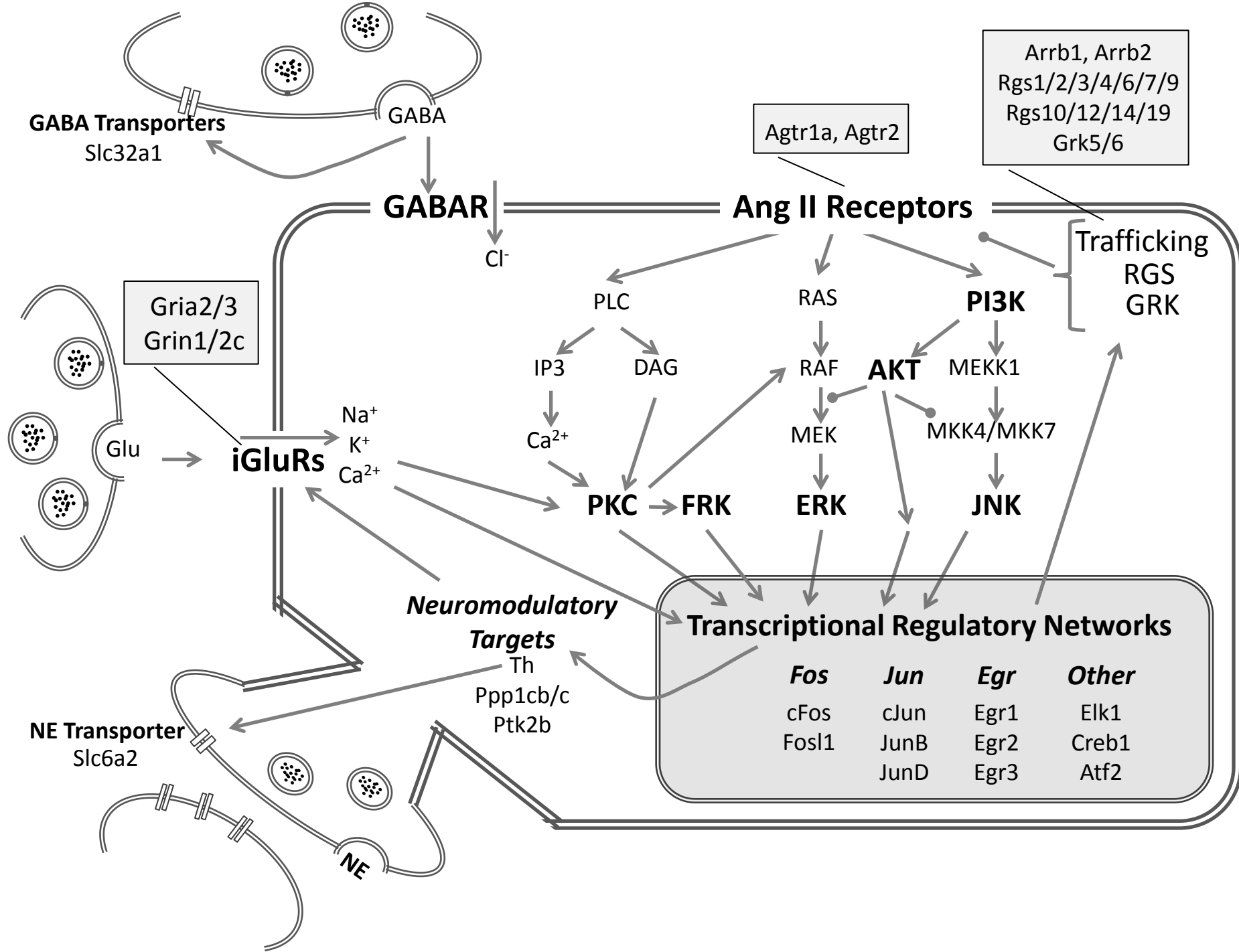
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Neurogenic Hypertension

Multi-scale maladaptive control system





Need to reconcile

Physiological consistency
of hypertension

Variability of molecular
and cellular networks

Biological
Variability = Structured
Heterogeneity + Random
Noise



Many aspects are variable

but

Few contribute to functional variation



Model simplification

Our Strategy

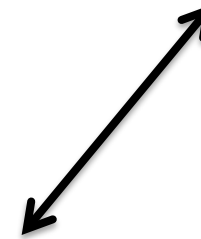
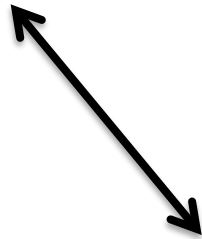
Computational Models

simulations of variability in
parameters, structure



Experimental Monte Carlo

single cell and cell network
regulatory programs



Multivariate Analysis

Global Sensitivity Analysis

Decision Trees

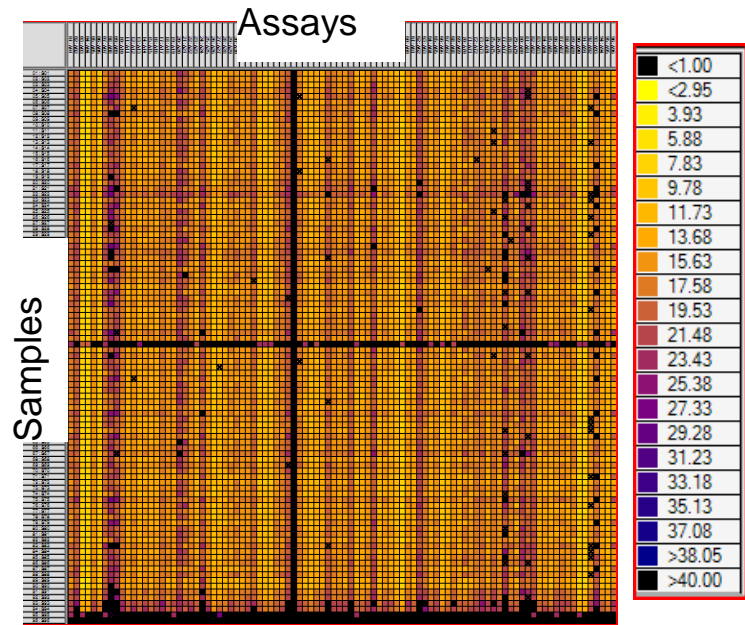
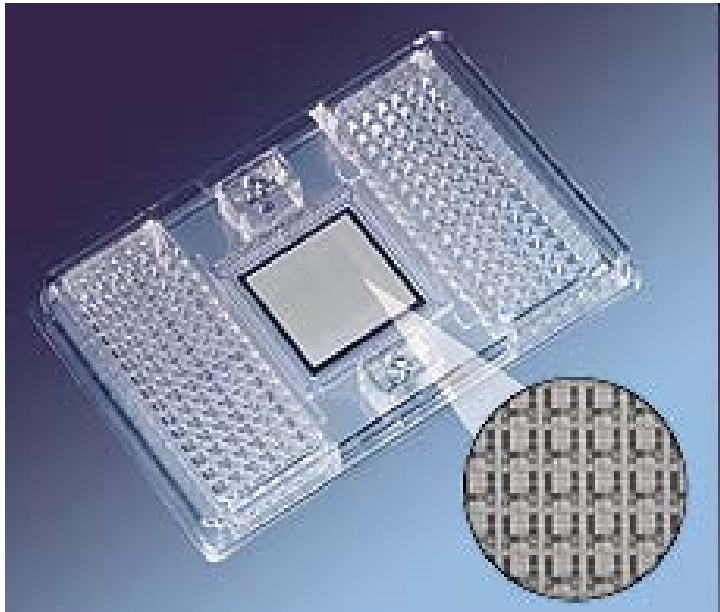
Variability Partitioning

Pathway Impact Analysis

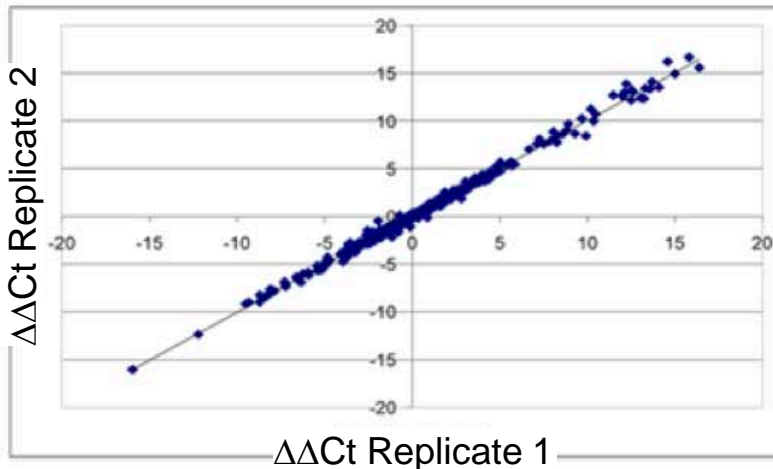
Regulatory Network Identification

High-throughput single-cell quantitative PCR

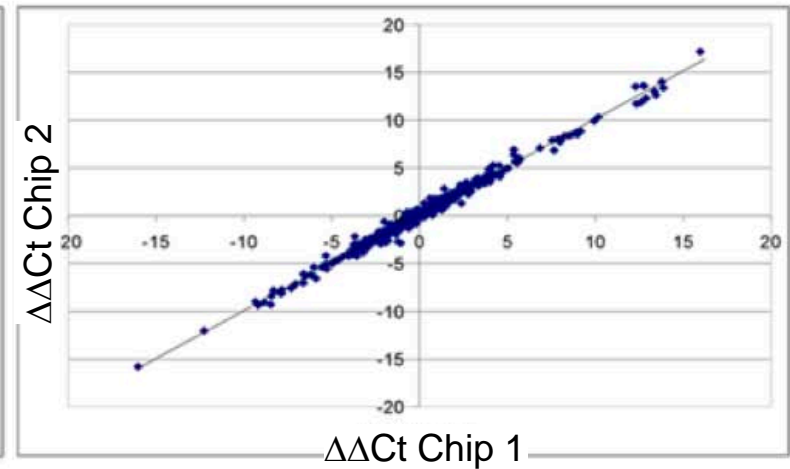
96 Samples * 96 Assays = 9,216 parallel reactions



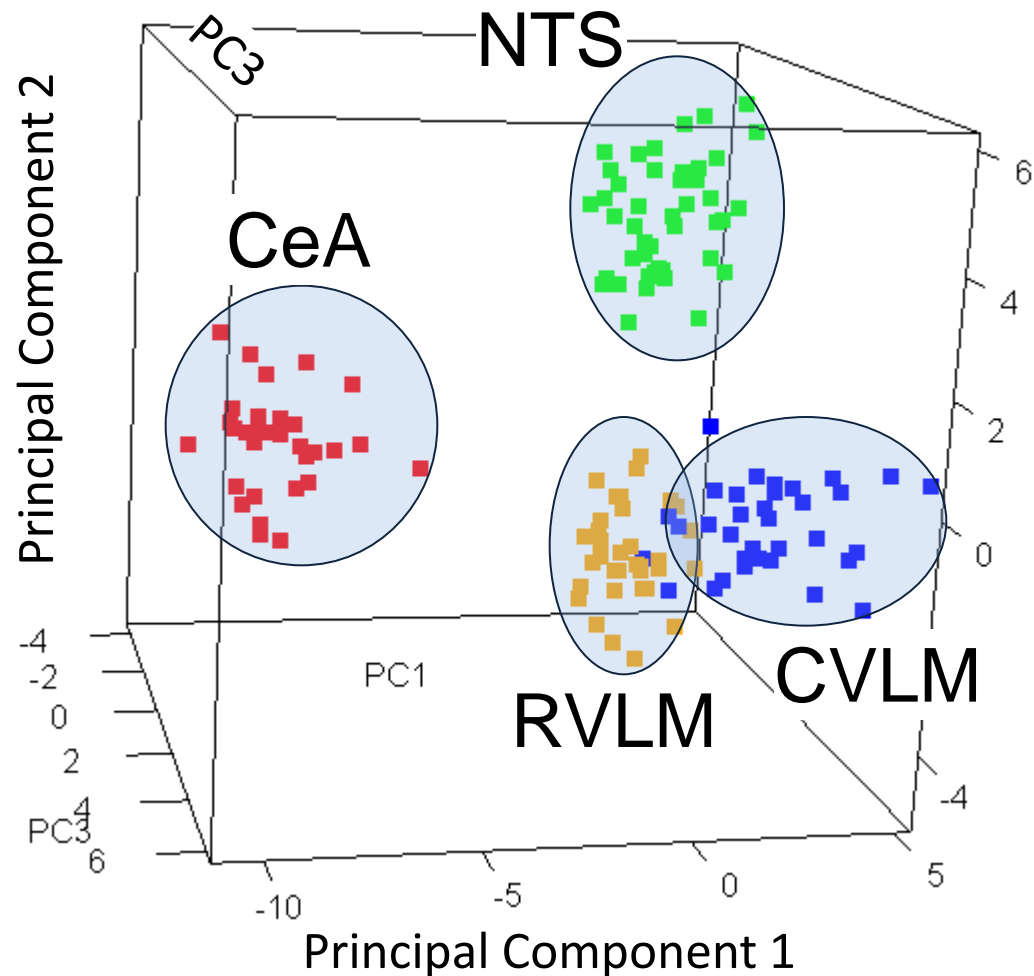
$r=0.997$



$r=0.994$



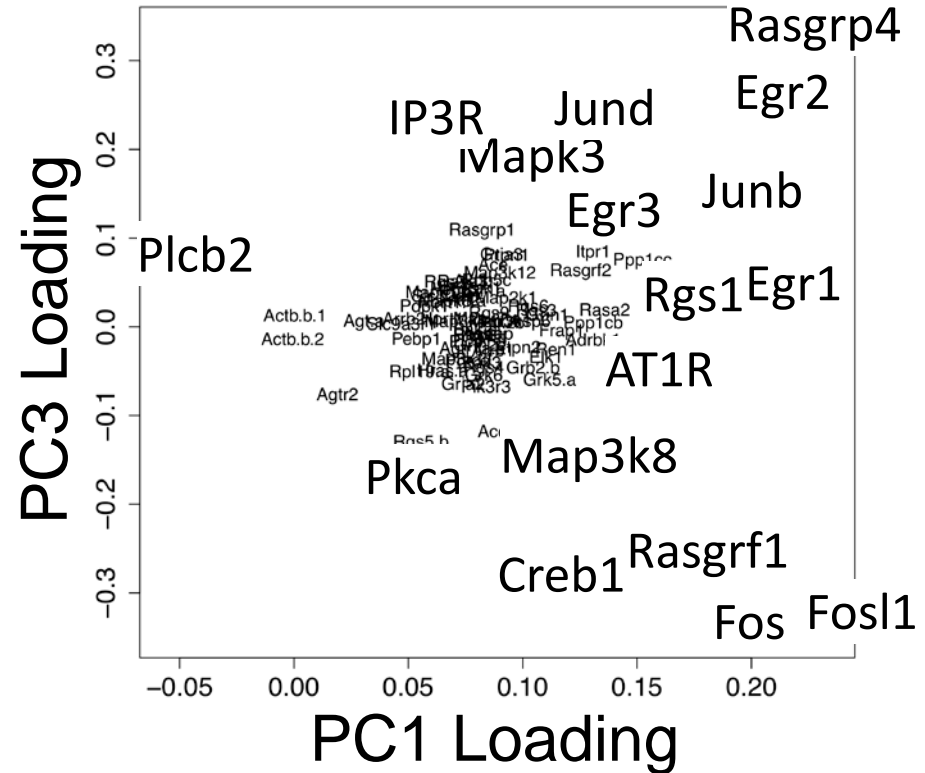
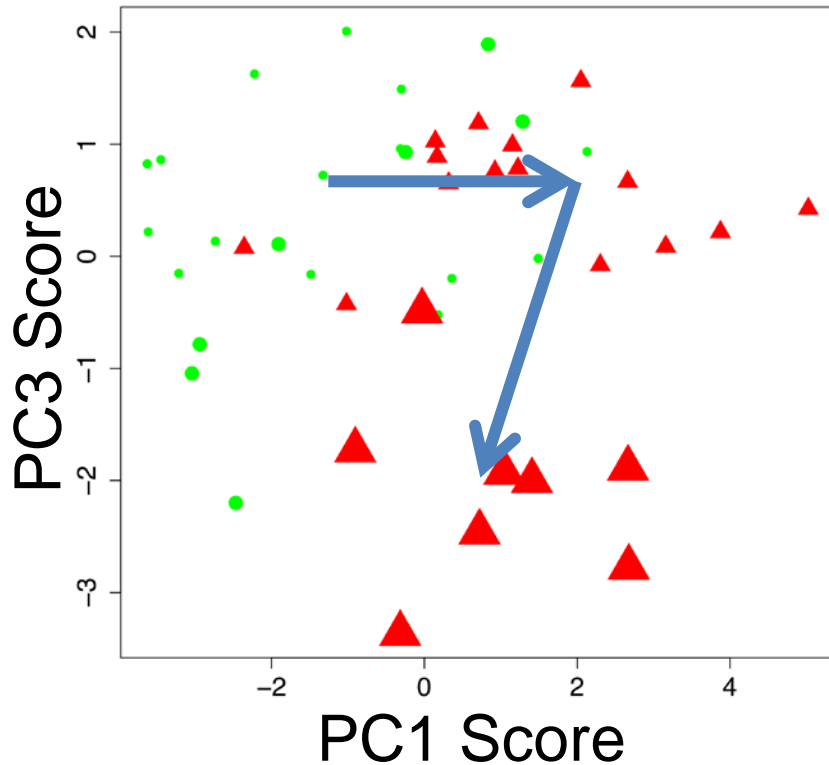
“Anatomy” of variation in transcriptional programs

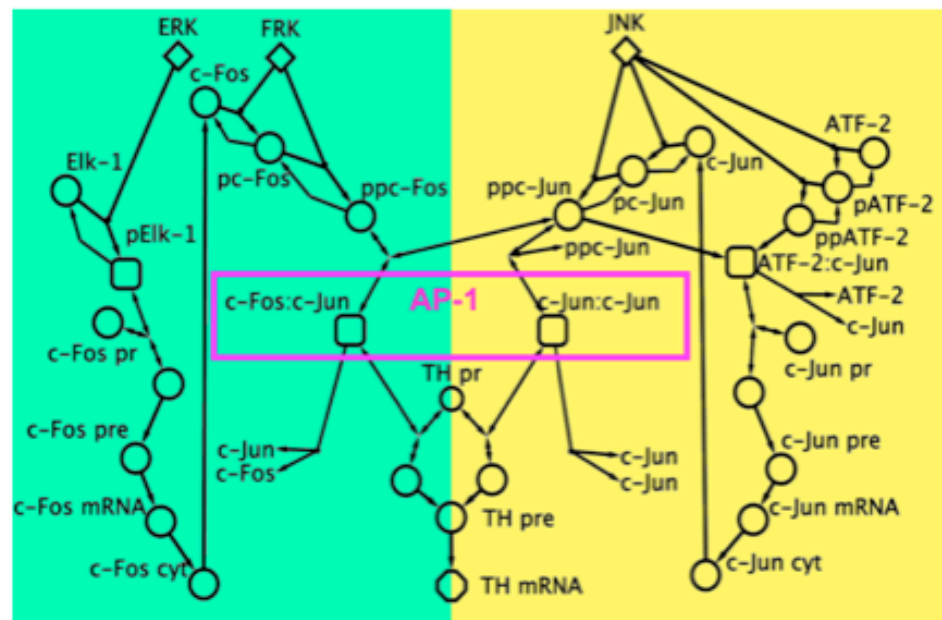


Hypertension-responsive Gene Expression Dynamics

1h 4h
● ● Control
▲ ▲ Hypertension

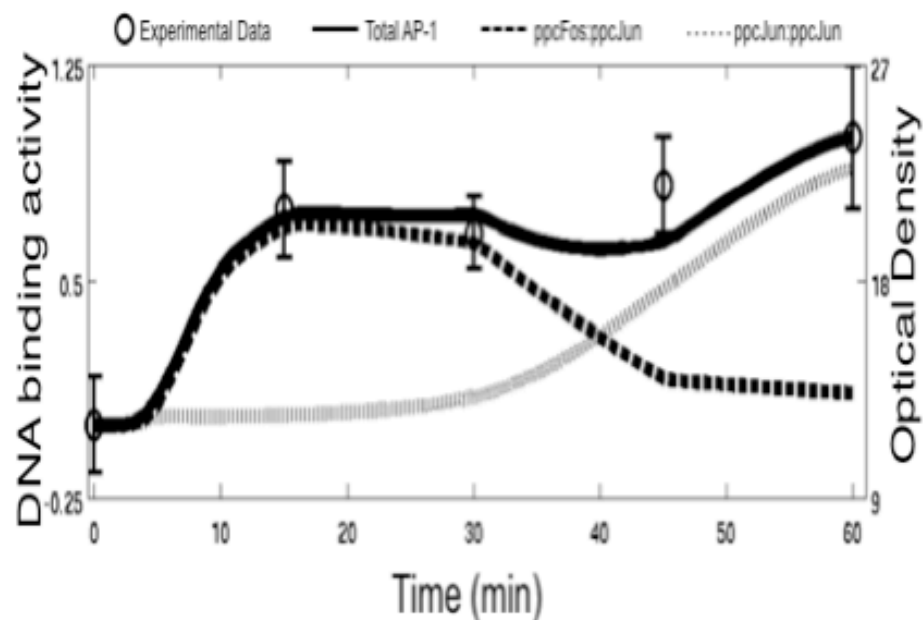
NTS



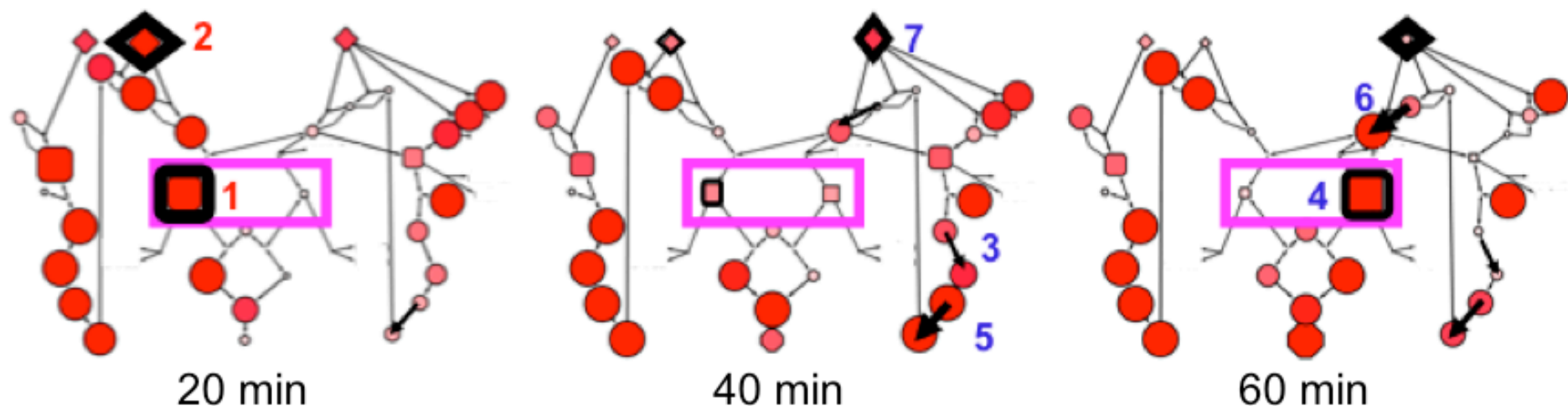


Fos:Jun

Jun:Jun



Sensitivity of AP-1 activation to network parameters



20 min

40 min

60 min

Edge thickness: Sensitivity of AP-1 to corresponding parameter