Characterizing Longevity Therapies' Impacts on Aging-Associated Decay of Transcriptional Order

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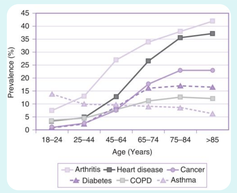
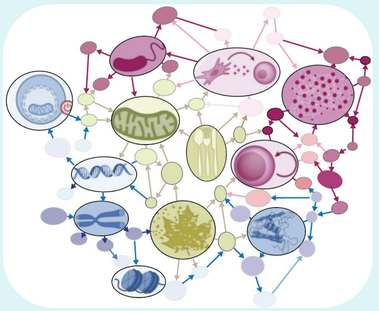
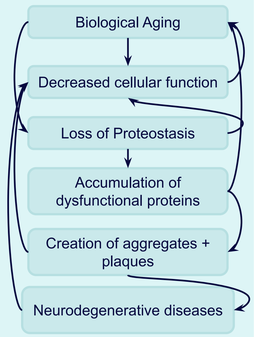
Aging Is Associated with Disease

- Life expectancy continues to increase
- Increased age results in increased risk for disease
- Aging is interconnected – effects are cascading
  - Causes change in transcriptome stoichiometry – proteins interact differently
  - Observed changes in gene expression and transcription initiation levels





Interconnected nature of hallmarks of aging



Example of cascading effect of aging on disease

- **Geroscience hypothesis**: reducing or reversing impacts of aging can attenuate onset of age-associated diseases

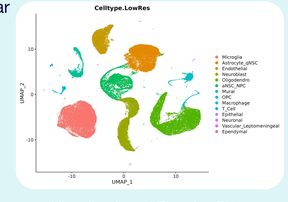
Research Goals + Hypotheses

- Understanding of aging remains fragmented
- Lack of research comparing methods of quantifying biological aging on the same dataset
- Research goal: Implement methods to characterize changes in transcriptome with age
  - Cell type balance, differential expression analysis, transcriptional noise/drift variance

Dataset Characterization

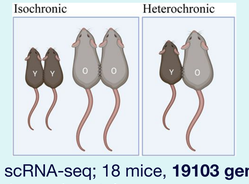
- Datasets collected from the subventricular zone of the brain, provided by Buckley et al.
- Exercise dataset:
  - Provided 5 weeks of access to exercise wheels
  - scRNA-seq dataset collected from 15 mice, 17671 genes
  - 4 experimental groups

	Old	Young
Control	3	4
Exercise	4	4



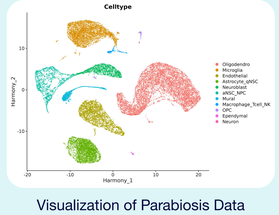
Visualization of Exercise Data

- Parabiosis dataset
  - Parabiosis – surgical connection of circulatory system of two individuals



  - scRNA-seq; 18 mice, **19103 genes**
  - 4 experimental groups

	Old	Young
Isochronic	3	4
Heterochronic	4	4



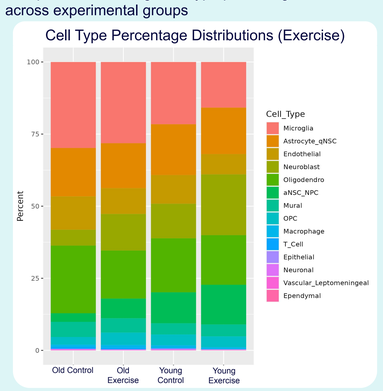
Visualization of Parabiosis Data

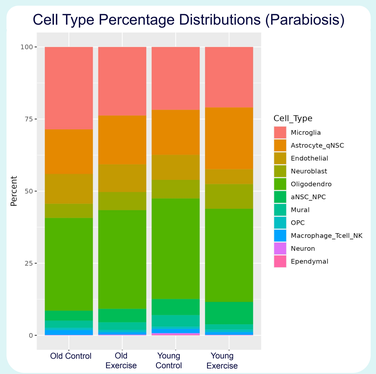
Cell / Gene	1	2	3	4
Rps26	3	1	0	0
Cox7c	0	0	2	1
Atp5k	2	0	5	0

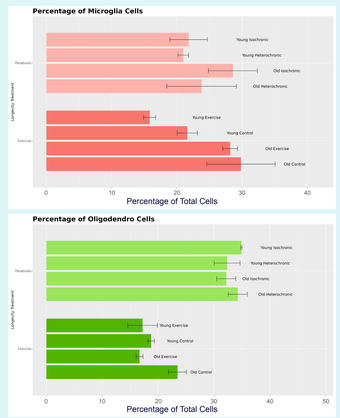
Example of scRNA-seq data

Cell Type Balance Changes with Age and Longevity Treatment

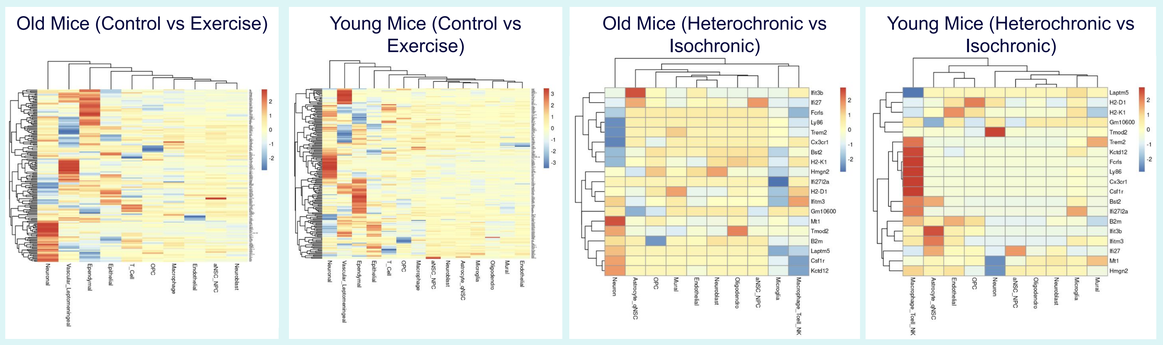
Comparison of average cell type percentage distributions (# of a certain cell type/total number of cells in a mouse) across experimental groups





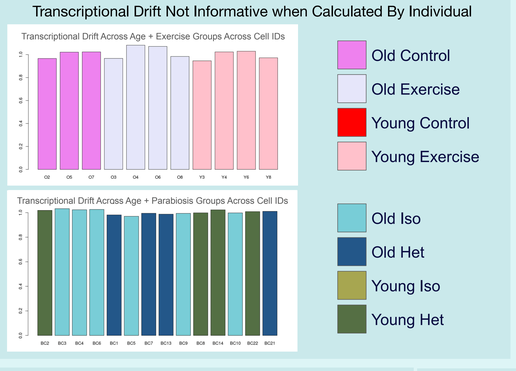


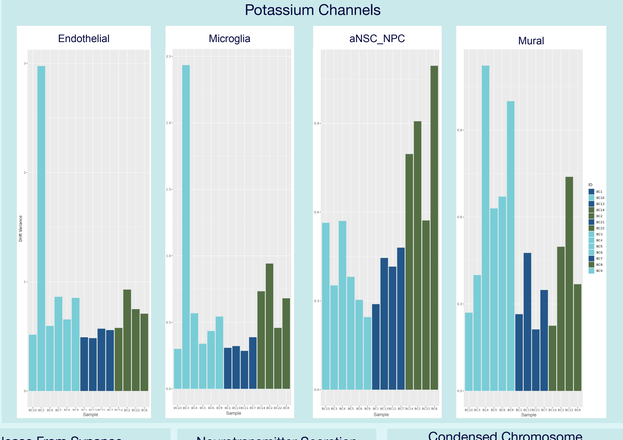
Analysis of Differential Expression in Genes Demonstrates Age-Specific Responses to Longevity Treatment

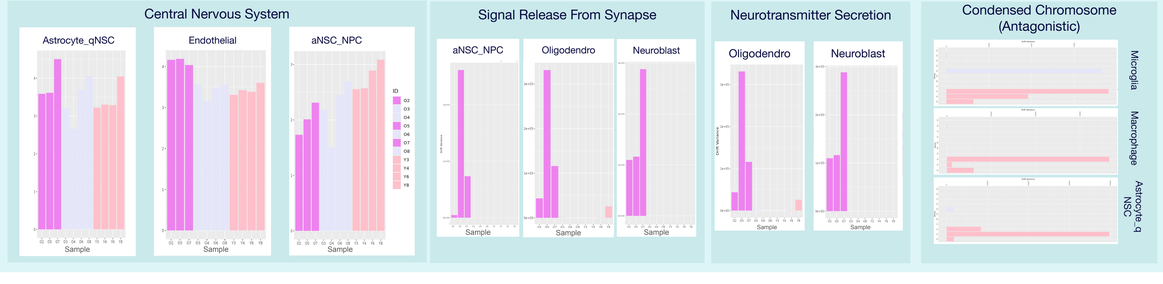


Transcriptional Drift Reveals Patterns of Gene Set Dysregulation with Age

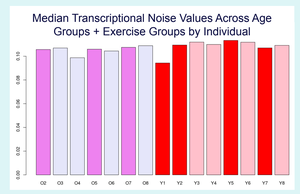
$$td_{gene\ x} = \left(\frac{\text{cpm}_{\text{age[t]}}}{\text{cpm}_{\text{young reference}}}\right) \qquad drift\ variance = \frac{1}{n-1}\sum_{i=1}^{n}\left(\text{td}_i - \overline{\text{td}}\right)^2$$

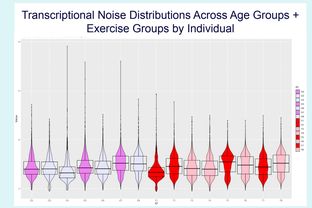


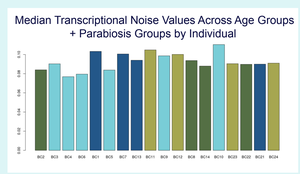


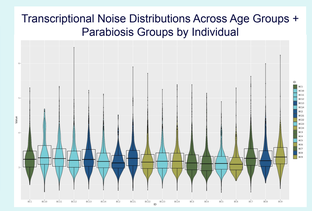


Transcriptional Noise Lacks Significant Differences Across Age and Treatment Groups









Conclusions, Discussion, and Future Work

- Conducted unified analysis of different ways to quantify changes in the transcriptome with age and longevity treatments to understand which metrics are most effective
- Transcriptional noise doesn't appear to be effective
  - No strong evidence transcriptional noise changes with age/longevity treatment
  - 2 possible interpretations of this:
    - Not effective for quantifying changes in transcriptome
    - No correlation between age/longevity treatment & transcriptional noise
      - Assumes method of quantifying transcriptional noise is adequate
  - Possible that other methods of quantification may work
- Diff. expression analysis shows longevity treatments impact genes differently
- Exercise and parabiosis impact cell type percentages differently
  - Oligodendrocyte cells decrease with exercise but increase in more 'youthful' parabiosis induced transcriptomes (old heterochronic)
- Parabiosis + exercise have unique differential effects on transcriptome
- Transcriptional drift reveals increased dysregulation with age in nervous system related gene sets in particular
  - Signal release from synapse
  - Neurotransmitter secretion
  - Central nervous system
  - Condensed chromosome associated genes have antagonistic behavior, higher transcriptional drift in younger animals
- Future work:
  - Further analysis of differential expression
  - Calculate transcriptional noise through alternative methods (Scallop, GCL – Global Coordination Level)
  - Calculate transcriptional drift by gene set for parabiosis experimental groups
- Limitations:
  - Small sample size
    - Exercise: 3 mice (old control), 4 mice (old + young exercise/young control)
    - Parabiosis: 6 mice (old isochronic), 4 mice (old/young heterochronic, young isochronic)
  - Transcriptional noise meant for cell type identity; analysis figures not included in poster but results remain similar to above
  - Diversity in expression is not necessarily a universal negative
    - Increased drift/noise may be positive in some cases
  - Manually picked out gene sets for transcriptional drift; leaves room for bias
  - Trends observed visually rather than through statistics

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