

MODULE 2

INTRODUCTION TO INTEGRATIVE MODELS OF AGING CORE

2021 SDNSC Workshops



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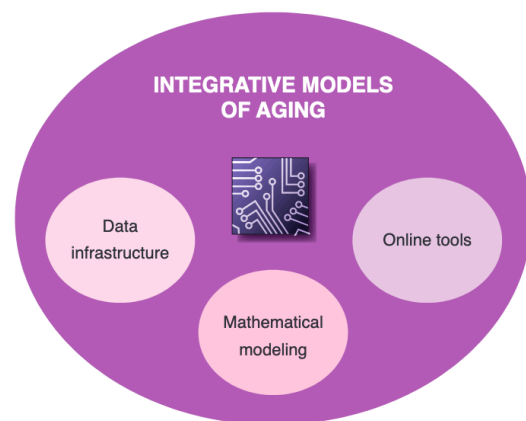
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INTRODUCTION TO INTEGRATIVE MODELS OF AGING CORE

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where curio begins

- **THE CHALLENGE OF STUDYING AGING**
- **TECHNOLOGIES**
- **SERVICES OFFERED**
- **WHO WE ARE**
- **PROJECT EXAMPLE**
- **HIERARCHICAL DATA VISUALIZATION METHODS**
- **CONTACT INFORMATION AND Q&A**



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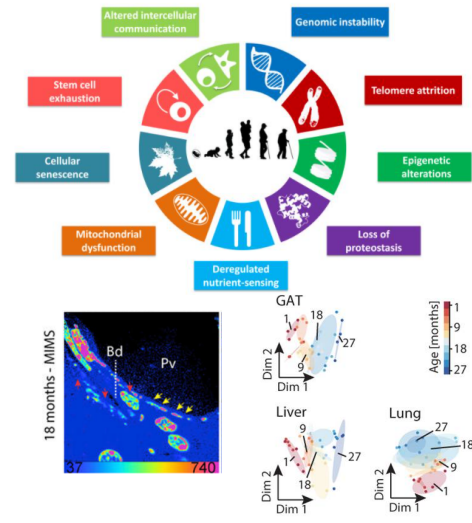
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Aging is a challenging problem

- Dysregulation across virtually all cellular processes
 - 9 hallmarks of aging (López-Otín et al, 2013)
- Heterogeneous
 - Not all cells age at the same rate (Arrojo e Drigo et al., 2019)
- Organ-specific
 - Each organ has its own aging phenotype (Schaum et al, 2020)
 - Interactions between organs (e.g. liver->blood->brain ; Currais et al, 2019; Schaum et al, 2020)
- Varies between individuals in a population.



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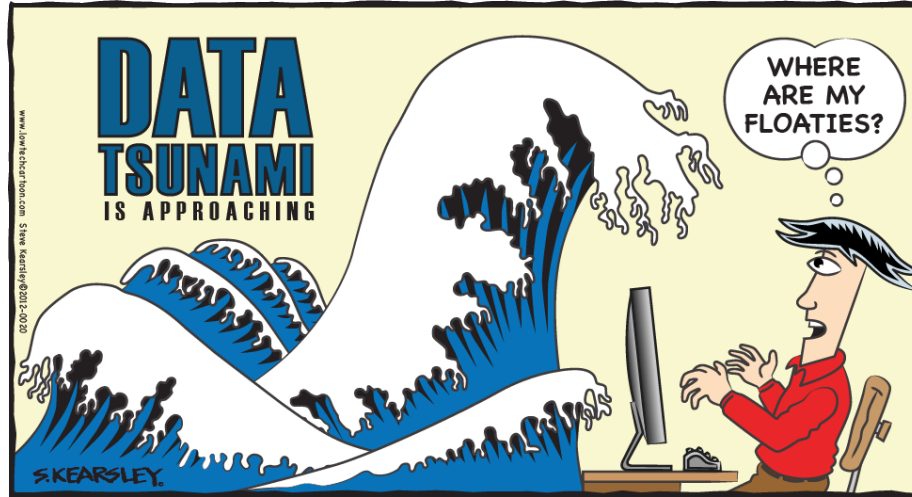
Technologies for addressing these challenges

- High-throughput sequencing
 - RNA-Seq, Cut&Tag/ChIP-Seq, ATAC-Seq, ...
- Single-cell sequencing
 - scRNA-seq, scATAC-seq, Spatial transcriptomics
- Mass spectrometry
 - Proteomics
 - Metabolomics
- Microscopy
 - Measure age-associated features in high-resolution images



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<http://www.lowtechcartoon.com/?p=934>

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Services offered


- Brainstorming / Project Design
 - Assay selection, replicates, controls, timelines
- Data storage and curation
 - Redundant storage, data sharing, submission to online repositories
- Quality control
- Standard and customized analyses
 - Ask us about our pipelines and tools, or we can help implement new ones
- Data integration
 - Mathematical modeling, machine learning, hyperbolic embedding
- Access to analyses through online tools
 - Interactive data visualization and tool development
- Training
 - Workshops, 1-on-1, online materials




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A dedicated team


Prof. Tatyana Sharpee
(Core Lead)


Dr. Max Shokhirev
(Director)


Dr. Ling Huang


Dr. April Williams



Dr. Jingting Yu

Co-authored over 60 publications in the last 4 years on a wide array of topics (including 14 aging papers)


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An example of a recent aging collaboration


Antonio


Ling


Max

Elevating acetyl-CoA levels reduces aspects of brain aging
Antonio Currala*, Ling Huang*, Joshua Goldberg*, Michael Petrascheck*, Ganese Alex*, Antonio Pinto-Duarte*, Maxim N Shokhirev*, David Schubert*, Pamela Maher**
*Cellular Neurobiology Laboratory, The Salk Institute for Biological Studies, La Jolla, United States; **The Razavi Newman Integrative Genomics and Bioinformatics Core, The Salk Institute for Biological Studies, La Jolla, United States; *Department of Molecular Medicine, The Scripps Research Institute, La Jolla, United States; *Computational Neurobiology Laboratory, The Salk Institute for Biological Studies, La Jolla, United States

Biological Questions:

- How does old age affect gene expression and metabolism?
- How do the drug treatments affect expression and metabolism?


Assays:

RNA-Seq
Metabolomics

Conditions:

Middle-Aged vs Old Age
Old Age vs Drug treatments

A)




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A novel multi-omics integration tool

Metabolomics 2020 16:126
<https://doi.org/10.1007/s11306-020-01750-7>




SHORT COMMUNICATION

SUMMER, a shiny utility for metabolomics and multiomics exploratory research

Ling Huang¹ · Antonio Curraiz² · Maxim N. Shokhiev¹

Received: 11 August 2020 / Accepted: 19 November 2020 / Published online: 9 December 2020
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Abstract
Introduction Cellular metabolites are generated by a complex network of biochemical reactions. This makes interpreting changes in metabolites exceptionally challenging.
Objectives To develop a computational tool that integrates multiomics data at the level of reactions.
Methods Changes in metabolic reactions are modeled with input from transcriptomics/proteomics measurements of enzymes and metabolomic measurements of metabolites.
Results We developed SUMMER, which identified more relevant signals, key metabolic reactions, and relevant underlying biological pathways in a real-world case study.
Conclusion SUMMER performs integrative analysis for data interpretation and exploration. SUMMER is freely accessible at <http://summer.salk.edu> and the code is available at <https://bitbucket.org/salkigo/summer>.



LingAntonioMax

Input

Gene Expression (FPKM/Microarray)

Protein Abundance (raw intensity)

Metabolite Abundance (raw intensity)

a

Metabolite log2FC = 0.1

b

Metabolite log2FC = 0.3

c

DE metabolites

d

DE reactions

e

Heatmap

Metabolic pathway diagram showing Acetyl-CoA, Citrate, and other metabolites.

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<https://www.surfer.com/features/surfing-blacks-beach-1998-2016/>

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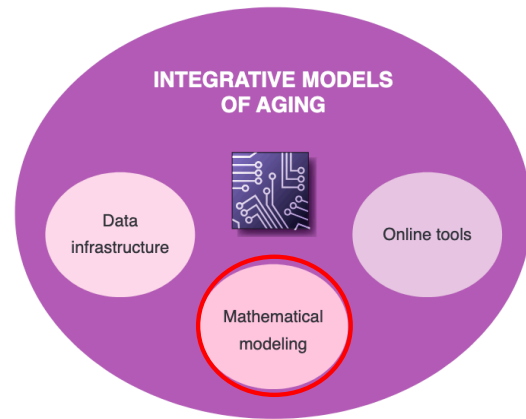
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INTRODUCTION TO INTEGRATIVE MODELS OF AGING CORE: MATHEMATICAL MODELING



- Describing hierarchical data

- Identifying driver nodes & causal interactions in networks
- Visualization methods for hierarchical data
- Custom methods for “batch correction”



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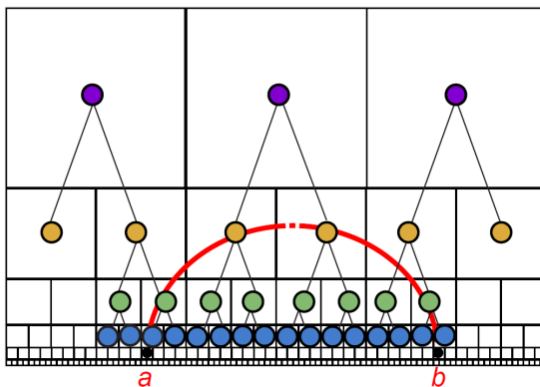
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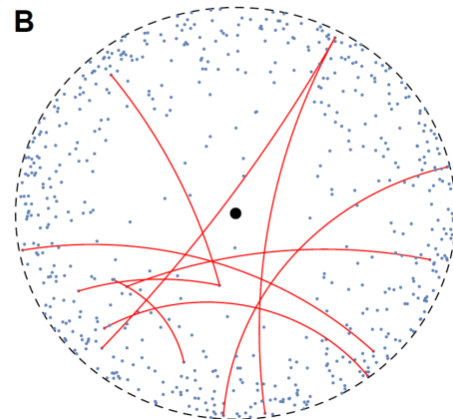


Hierarchical data -> Hyperbolic geometry

A



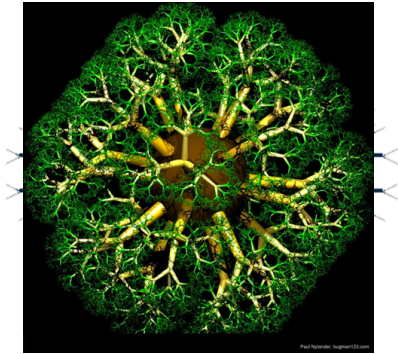
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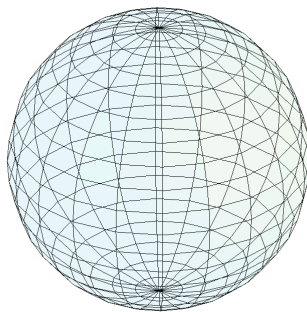
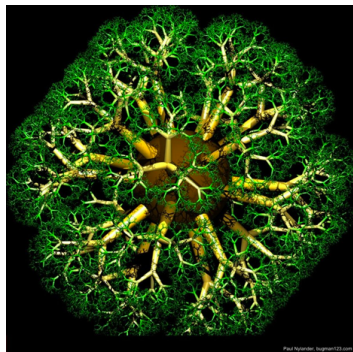
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3D Hyperbolic space



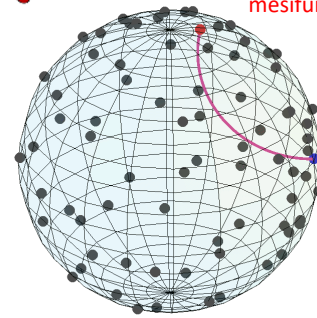
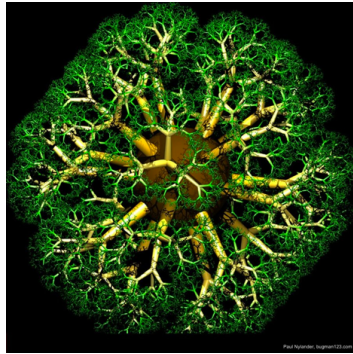
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Representing 3D Hyperbolic Space with Poincare Sphere

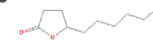


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3D Hyperbolic space

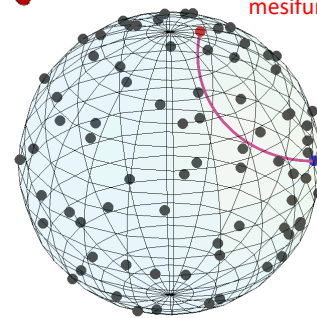
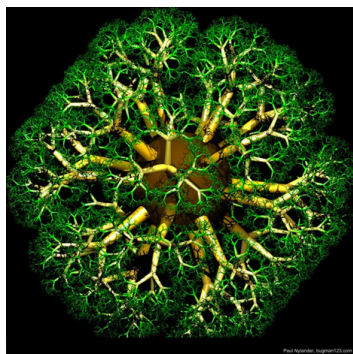


mesifurane

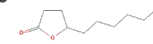
 γ -Decalactone

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3D Hyperbolic space




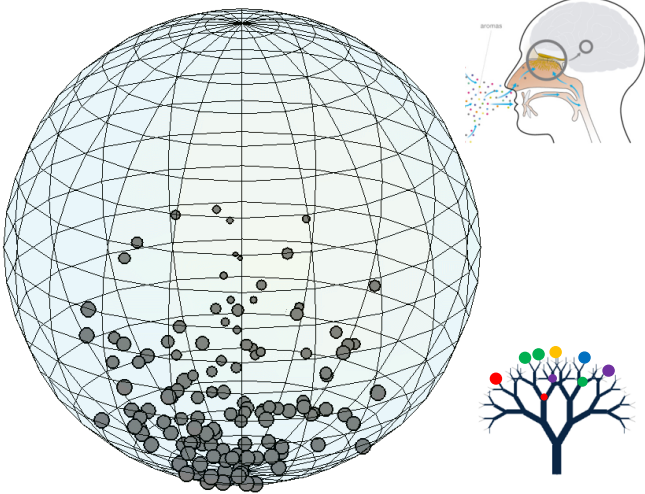
mesifurane

 γ -Decalactone

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C

- Nervous system neoplasm
- Non-neoplastic cell line
- Breast cancer
- Solid tissue neoplasm cell line

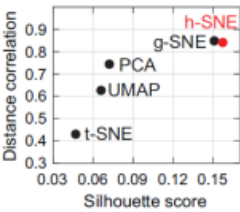
g-SNE

h-SNE

PCA

UMAP

Hyperbolic geometry in gene expression data

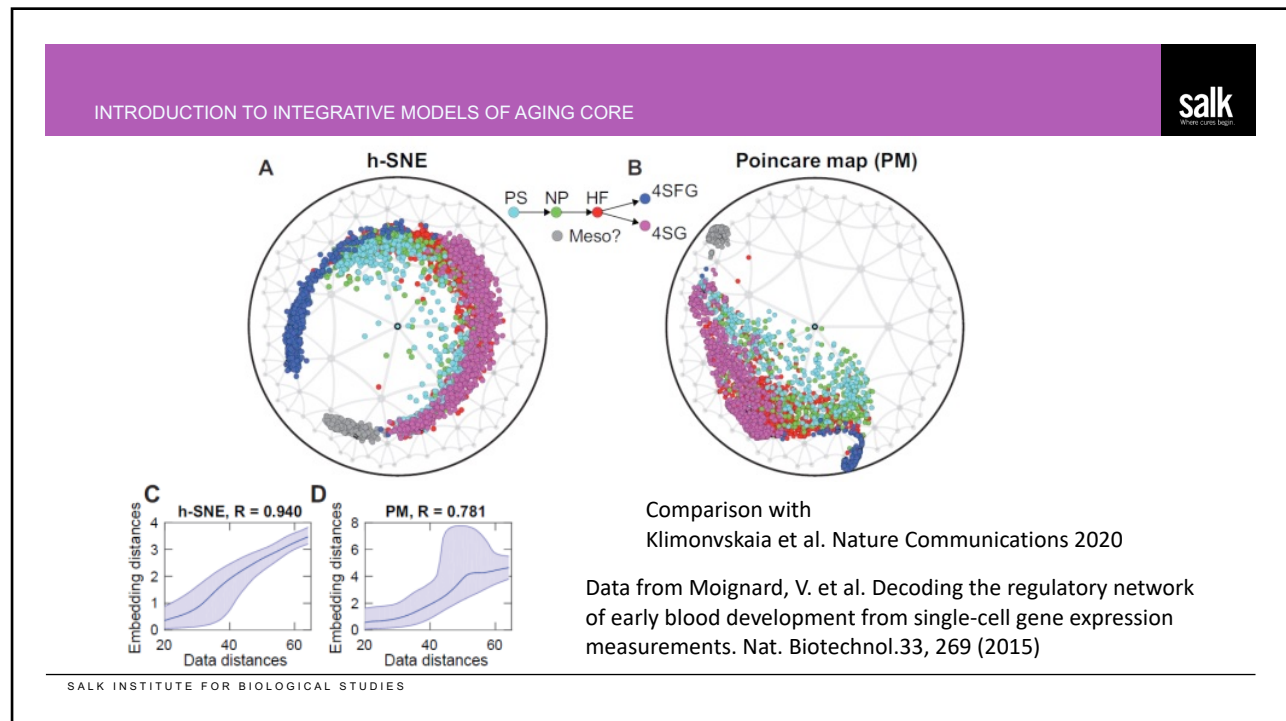


Method	Silhouette score	Distance correlation
t-SNE	0.03	0.45
PCA	0.06	0.75
UMAP	0.08	0.65
h-SNE	0.15	0.85

Zhou & Sharpee, *iScience* 2021

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Summary of current methods for analyzing hierarchical data

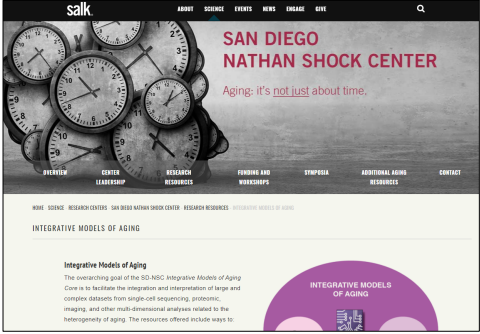
- Visualization methods (t-SNE, UMAP, PCA, **hyperbolic SNE, hyperbolic MDS**).
- Methods for geometry detection, dimensionality reductions
- Methods for identifying driver nodes

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Contact information



<https://www.salk.edu/science/research-centers/san-diego-nathan-shock-center/research-resources/integrative-models-of-aging/>



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Q&A

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Please type your questions in the chat

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