Metabolomics- and methylomics-based predictors for estimating health and biological aging

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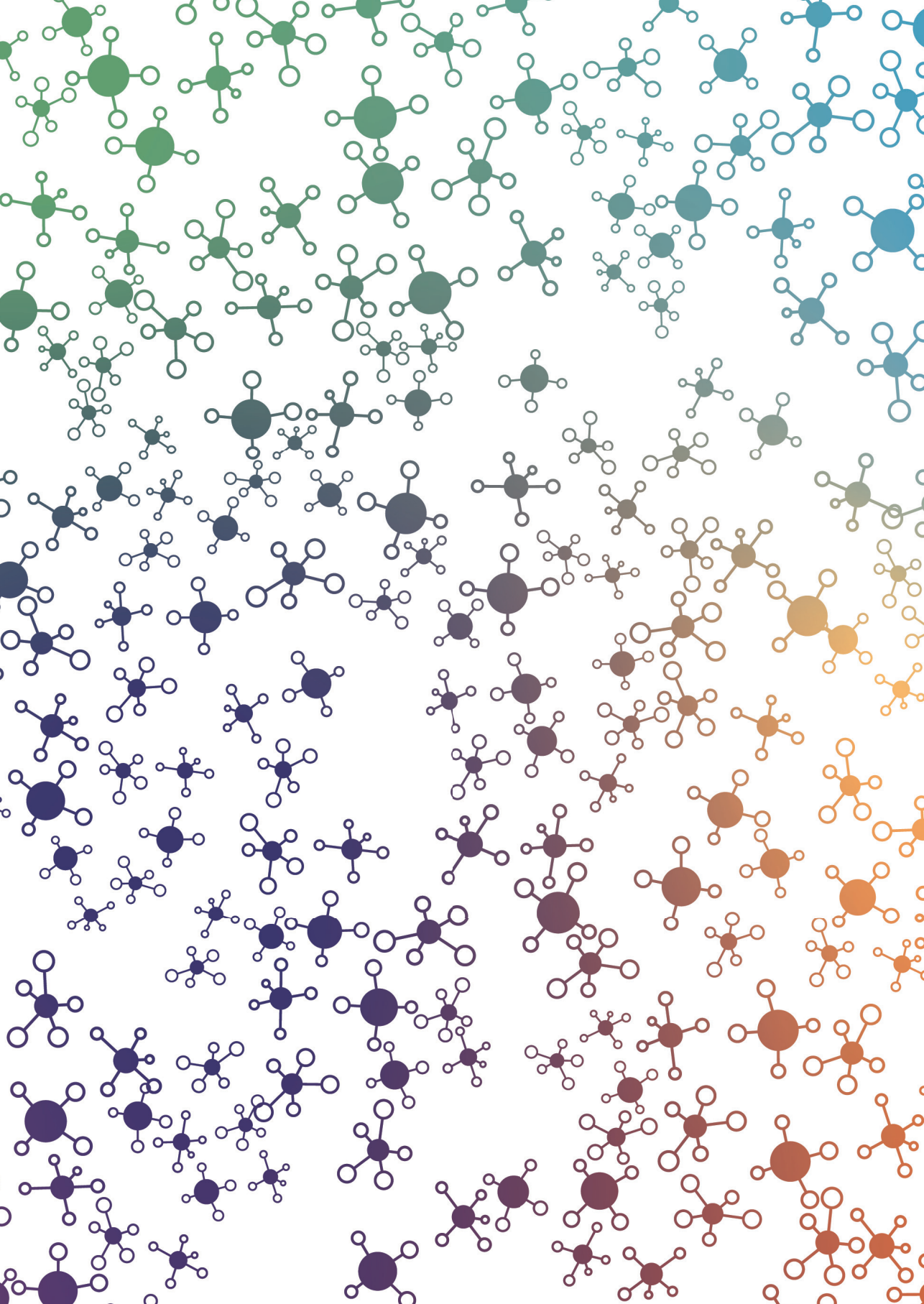

Chapter 9

Appendix

Summary

In the last century, human life expectancy has significantly increased, leading to a larger elderly population and increased burden on healthcare systems. Aging is a multifaceted phenomenon marked by the cumulative occurrence of degenerative processes that collectively contribute to systemic pathologies, functional decline, and ultimately, death. It is a highly heterogeneous process, with individuals of the same chronological age exhibiting varied health and susceptibility to external hazards. Hence, identifying biomarkers that can accurately reflect this variability, so-called markers of biological aging, holds potential to assist strategies to slow ageing and enhance healthspan.

Advances in high-throughput technologies, coupled with machine learning algorithms, enabled condensing of extensive molecular information into digestible multi-biomarker scores. Various data sources have been investigated, with ^{1}H-NMR metabolomics and DNA methylation emerging as two particularly compelling omics-layers for this purpose. On one hand, DNA methylation is frequently acknowledged as the most accurate estimator of chronological age, also enabling prediction of mortality and other risk factors (e.g., smoking). On the other hand, ^{1}H-NMR metabolomics demonstrated a strong value in predicting cardiovascular mortality, achieving accuracies at least comparable to DNA methylation. Additionally, ^{1}H-NMR quantifications metabolomics offers a more affordable quantification, with comprehensible biological basis as compared to the methylation sites. Notably, recent findings highlight that mortality-oriented scores derived from both -omics layers, provide distinct and complementary information, independently contributing to the prediction of both frailty and mortality in older adults.

In this thesis, we developed, evaluated, and deployed omics-based models to predict human health mostly focusing on ^{1}H-NMR metabolomics, but also DNA methylation, capitalizing on the extensive information available in the BBMRI-NL Consortium. This dataset incorporates 28 separate Dutch cohorts comprising individuals of all ages and health conditions.

First, we focus on exploring the potential of ^{1}H-NMR metabolomics by Nightingale Health as a comprehensive assay capable of encoding 20 clinical variables commonly measured in epidemiological studies. We developed 19 accurate metabolomics-based surrogates, systematically evaluating their accuracy and their performance as biomarkers of biological aging. Then, these metabolomics-based surrogates are further evaluated as potential substitutes for incomplete or unreliable phenotypic information within transcriptome-wide association studies.

To investigate the synergy between metabolomics and methylation information on the prediction of biological aging, we trained epigenetic-based prediction models for metabolomic features and mortality score. Through ad-hoc calibration and feature selection techniques, we developed robust models potentially refining the state of the art epigenetic-based clocks.

To facilitate the application and evaluation of the available multivariate models trained on Nightingale Health metabolomics, we introduce MiMIR, a user-friendly application that enables a harmonized projection of the scores, as well as ad-hoc statistical analyses of the Nightingale Health platform. Moreo-

ver, we addressed the technical challenges associated with updates in omics-platform supplier, such as the 2020 quantification updates from Nightingale Health.

Finally, we show to which extent the ^{1}H-NMR metabolomics assay could indicate the elusive adverse effects associated with nightshift working. Although we observed minor association among female participants, we identified informative markers particularly related to low grade inflammation, triglycerides, and VLDL particles.

Collectively, this thesis endeavors to advance the quantification of biological aging, by harnessing the potential of ^{1}H-NMR metabolomics and DNA methylation profiles.