**Gerstein Lab Experience in Leveraging AI and Biosensors for Personalized Medicine and Predictive Health Analytics**

Drawing on a strong foundation of research, the Gerstein Lab has advanced the fields of personalized medicine and predictive health analytics by integrating artificial intelligence and biosensor technologies to tailor health interventions and predict disease outcomes:

We have established a strong foundation in developing practical tools for genomic analysis, highlighted by our contributions to major consortia such as PsychENCODE. We helped generate a comprehensive online resource for the functional genomics of the human brain, an initiative that has informed subsequent models and tools44. This resource offers a detailed mapping of gene expression and regulatory networks across a large sample size, which aids in the understanding of the genomic basis of psychiatric disorders. We developed LNCTP, an innovative omics-based deep-learning approach designed to predict various psychiatric phenotypes from genotypes and detailed single-cell data. The LNCTP model utilizes a multi-level architecture incorporating a Boltzmann-machine gene expression imputation engine and hierarchical linear predictors (Fig. 2). This tool enabled us to explore the gene expression and chromatin states across a diverse cohort, including individuals diagnosed with various psychiatric disorders. The resulting insights have provided a robust foundation for our real-time analysis capabilities45. Moreover, we have been developing methods for genomic privacy and data anonymization, which are important given the sensitive nature of the data we handle. This work includes developing algorithms that prevent linkage attacks in genomic datasets and proposing novel data formats like the Mapped Read Format (MRF), which anonymizes sequence data while retaining useful information for analysis46,47,48,49.

*Figure 2: LNCTP Architecture. This figure presents the architecture of the LNCTP model, detailing its components and data flow. The diagram visualizes the integration of genotype data with cell-type-specific gene expression to predict psychiatric phenotypes. Key elements include the use of a conditional energy-based model for imputing gene expression and a hierarchical linear model for phenotype prediction.*

We have developed various methods to analyze and integrate large-scale genomic data, including non-coding regions and their coding targets, to prioritize variants and understand their impacts on gene function and regulation50,51,52,53,54. Such genomic mapping efforts have informed the predictive models we are developing, enhancing accuracy and applicability. In our previous work, we successfully incorporated advanced techniques to enhance network inference capabilities in our analytical tools. We have developed various methods for processing datasets, demonstrating our capacity to handle and analyze genomic data from varied sources, as highlighted in our publications55,56,57. We are actively expanding our work to include more complex models of gene regulation and network dynamics, utilizing cutting-edge machine learning techniques to predict and simulate the effects of genetic variations on cellular and organismal phenotypes. These efforts not only improve our understanding of the human genome but also facilitate the translation of these findings into practical applications in medicine and healthcare.

Our previous work has also demonstrated advancements in the analysis and interpretation of multi-omics data, providing a solid foundation for integrating advanced deep learning architectures. In the context of enhancing the interpretability and application of machine learning models in neuroimaging and genomics, we have integrated LLMs and other advanced techniques into biomedical research. For instance, the BIOCODER project showcased the effectiveness of LLMs in managing and interpreting diverse biological data formats58. We developed MolLM, a pre-trained model that captures biomedical text and molecular information, enhancing performance65. Preliminary studies revealed the potential of LLMs and chain-of-thought reasoning to enhance complex reasoning tasks and develop autonomous agents66. Our Multi-disciplinary Collaboration framework significantly improved LLM reasoning in medicine67, and ML-Bench demonstrated LLMs' ability to utilize open-source libraries68. Additionally, our structure-aware fine-tuning improved LLMs' capability to generate complex structured data69, and the BioCoder benchmark illustrated our proficiency in bioinformatics coding and domain-specific challenges70. Finally, we fine-tuned an LLM to predict protein phase transitions, showing superior performance and interpretability, particularly for Alzheimer’s disease-related proteins71. In the EN-TEx study, we developed a predictive multi-omics transformer model for evaluating the impact of genetic variants. The cross-tissue, cross-individual, and cross-assay aggregation strategies enhanced the detection power of allele-specific events, enabling the generation of a sizable catalog of such events that can be used to predict variant impact with high accuracy62. Moreover, we also have experience in developing integrated regulatory networks using high-throughput sequencing data. These networks provide a view of gene regulation by merging data from different omics layers, thus aiding our understanding of the transcriptional and post-transcriptional landscape59. Another area of our expertise is in the application of various sophisticated tools to map intricate relationships in biological systems. These models have proven particularly effective in analyzing microbial communities and their metabolic pathways, demonstrating our team’s capability to correlate environmental factors with biological data, which can help delineate metabolic impacts on brain functions and disorders60. We also have successful experience in using CNNs interpret machine learning and deep learning models. For example, our DECODE framework, which outperforms state-of-the-art methods in enhancer prediction and precise boundary detection, significantly enhances the accuracy and resolution of regulatory element mapping, thus improving downstream analyses and variant enrichments72. ThermoNet, a 3D-convolutional neural network that accurately predicts mutation-induced changes in protein stability (ΔΔG), has demonstrated its utility in clinical and biophysical applications73.

We have a considerable history of conducting simulation and perturbation calculations. For instance, we developed Forest Fire Clustering, a method that efficiently identifies and evaluates cell-type transitions, aiding in robust simulation and perturbation calculations in large-scale single-cell data.74 Additionally, we developed VarSim, a comprehensive framework for simulating and validating genetic variants, which supports the simulation and evaluation of perturbations in next-generation sequencing data75. We also developed Paired-End Mapper, an analysis pipeline for processing genomic structural variants, featuring simulation-based error models that support the evaluation of perturbations in next-generation sequencing data76. In the DREAM3 Challenges, we performed computational reconstruction of *in silico* GRNs, effectively integrating heterogeneous data from deletion strains and perturbation time series to enhance network prediction accuracy77. Furthermore, we introduced SCAN-ATAC-Sim, an efficient and scalable method for simulating scATAC-seq experiments with known cell-type labels, enhancing the benchmarking and evaluation of scATAC-seq analysis techniques78. We also embedded the regulatory network into a deep-learning model, the precursor to LNCTP, to predict psychiatric phenotypes from genotype and expression. The model has improved prediction accuracy over traditional additive models44. It can highlight key genes and pathways associated with disorder prediction, including immunological, synaptic, and metabolic pathways, recapitulating *de novo* results from more targeted analyses.

We have also sufficient experience in developing tools that support interpretation purposes, as well as on a cloud-based platform for real-time processing ability. For instance, we developed "Gene Tracer," an innovative voice-controlled tool designed to enhance the interactive querying and visualization of genomic information. This cloud-based approach not only meets the computational demands of processing large genomic datasets but also guarantees that the system remains responsive and accessible to users from any location61.

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