

Defining the Phenomic Landscape for Genes, Chemicals, and Diseases

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Achieving understanding of the functions of all human genes, accelerating drug development and evaluation of chemical toxicity are important biomedical goals today. Advances in genetics, physics, engineering and computational sciences have made it possible to collect physiological, behavioral and morphological data at unprecedented resolution. We review the exciting potential uses of such complex data, and how we might obtain it, focusing on the promise of high-throughput synchrotron-based micron-scale tomographic X-ray imaging.

In clinical medicine, combinations of clinical signs and symptoms are associated with specific diseases. Greater accuracy of diagnosis is associated with breadth and precision of measurements of those signs and symptoms. Similarly, combinations of phenotypes, often affecting multiple organ systems, are associated with specific deficiencies in gene function and chemical exposures. The “phenotypic signatures” for all genes, all chemicals, and all diseases comprise genetic, chemical and disease phenomes, respectively. Recent advances in micron-scale tomographic X-ray imaging at 2BM at the Advanced Photon Source at Argonne National Labs have recently allowed us to achieve whole-body imaging of a vertebrate animal from embryonic through juvenile stages. The voxel sizes achieved, 1.43 and 0.743 microns for fields of view of 2.93 and 1.52 mm, respectively, allow recognition of nearly every cell type; modeling of individual cells is possible at the higher resolution. Notably, the length scale of the smallest well-developed vertebrate model, the zebrafish, makes it possible to image the entire animal at these resolutions. From these results, and the results of whole-body imaging of zebrafish mutants using histological analysis, we infer that, sufficient increase in throughput of imaging, image processing, feature extraction and measurement, and web-based accessibility to those data, will make it possible to define the genetic and chemical phenomes for a vertebrate, leading to great advances in understanding of human gene function, toxicological assessment, and disease. Since toxicological assessment is a bottleneck in drug development, such an advance may lead to significant acceleration of drug development. Hundreds of petabytes of phenotypic data from such phenome projects may be anticipated.