A200 · A top-down/bottom-up pipeline for the automatic construction of mechanistic mathematical models: reconstructing the regulatory network of tamoxifen resistance in breast cancer

Presenter: Vikas Pandey — The University of Osaka

Authors: Vikas Pandey, Shigeyuki Magi, Mariko Okada, Elisa Domínguez-Hüttinger

Session: Day 2 · Fri Oct 2, 2026 · 2:15–4:15 PM

Tamoxifen resistance develops in approximately 30% of breast cancer patients, limiting the long-term efficacy of endocrine therapy; however, the regulatory logic that drives the transition from a drug-sensitive to a resistant state remains poorly resolved. Herein, we present an automated top-down/bottom-up pipeline that reconstructs a mechanistic, interpretable model of resistance directly from longitudinal transcriptomic data. The top-down stage performs dimensionality reduction, from~20,000 genes down to a core regulatory module of ~20 genes that carries the dynamics of the phenotypic switch. The bottom-up stage then assembles these components into an ordinary-differential-equation network whose edges correspond to explicit biochemical pathways, yielding a compact model in which network topology, kinetic parameters, and phenotype are mechanistically linked. We apply the pipeline to MCF7 cell line over a 12-week course of resistance development, and recover the core network underlying the sensitive-to-resistant transition. To validate the reconstructed model, we use proliferation measurements as a proxy for a drug-holiday ('holiday') experiment and compare model predictions against data withheld from calibration, confirming that the inferred network generalizes beyond its training conditions. The resulting framework reveals how kinetic changes and biochemical conditions partition cells among sensitive, pre-resistant, and resistant states, and enables in silico exploration of induction–maintenance tamoxifen dosing schedules as candidate optimal interventions. The same pipeline has previously reconstructed mechanistic models of osteoarthritis progression and of the cellular response to vitamin D, indicating this pipeline is generalizable strategy for turning high-dimensional omics data into predictive, mechanistically grounded models of disease.