Genome-scale morphological mapping of the mechanisms underlying cell invasion

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***Short Abstract* — Understanding and modeling cellular signaling networks and the decision processes they drive is a crucial step towards personalized and targeted treatments of cancers. Here we integrate morphological data from high-throughput cellular imaging, quantitative phosphoproteomics and sequencing data with state-of-the-art dimensionality reduction, feature selection and modeling techniques to unravel global cellular networks driving cell invasion in cancer.**

***Keywords* — High-throughput microscopy, cell morphology, non-linear modeling, biological forecasting.**

I. Purpose

Contemporary life science is characterized by an era where the many components of cellular signaling have been identified by a combination of reductionist approaches and genetic and other types of screens. In addition, the last decade of genome sequencing and mass-spectrometry-based mapping of post-translational modifications has provided detailed catalogs of the global cellular inventory. Future advances in life science depend on the development of technologies that facilitate the exploration of these resources at a systems-level scale [1]. This will boost our ability to understand and model cellular signaling networks and the decision processes they drive for example in cancer progression.

II. Our approach

Importantly, the development of such technology and computational tools to interpret multiplexed genome manipulations and proteomics data must be done in the context of living cells. An Opera (PerkinElmer, MA, USA) high content screening (HCS) confocal microscope is employed to perform a genome-wide RNAi screen of live cells. Morphological features are extracted from the images with the Acapella software (PerkinElmer, MA, USA). This produces a data cube as large as 400,000 cells x 1,400 features x 20,000 genes for a human genome-wide screen.

In order to analyze these cubes, we use advanced non-linear dimensionality reduction based on Locally Linear Embedding [2], neural networks [3] or non-linear Independent component analysis. Markov Random Fields, Bayesian Networks and Artificial Neural Networks finally integrate the morphological features with phospho-proteomics and sequencing data. Because such a large amount of data (several terabytes) cannot be loaded into memory in a typical cluster of many small-sized nodes with limited amount of RAM each, we use a UV Large Shared Memory System from SGI to carry out the analysis.

III. Expected results

As demonstrated by Bakal *et al.* in 2007 [4], it is possible to reconstruct signaling networks by measuring morphological feature of cells in an RNAi screen. By performing a similar assay in a high-throughput, genome-wide RNAi screen on human cells, and integrating the morphological measurements with genomics and phospho-proteomics measurements, we will be able to reconstruct the human phosphorylation network. The construction of this network is a crucial step towards the ability to predict the impact of a given change in the signaling network on cell behavior.

IV. Conclusion

By capturing the intrinsic properties of cancer signaling networks with a combination of high-content cell imaging and morphology measurements, phosphoproteomics and sequencing, we provide deeper understanding of the processes by which perturbed networks lead cancer cells to adopt malignant phenotypes [5], and highlight potential network drug targets [6] through biological forecasting.

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