

Towards uncovering phenotype/genotype relationships and systems level modeling of tumor heterogeneity

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Uncovering and interpreting genotype/phenotype relationships are among the most challenging open questions in disease studies. In complex diseases, such as cancer, uncovering of this relationship is complicated by the heterogeneous nature of these diseases. We have recently developed three complementary approaches to address this challenge. First, we utilized interaction network and an information flow approach to model the propagation of the perturbation from genetically altered regions to abnormally expressed genes [1]. This approach helps to elucidate the relationship between genetic perturbations and expression dys-regulation, but does not capture differences between patient groups. To address the second challenge we developed a new approach, called module cover [2]. Module cover allows capturing differences between patients using by identifying dys-regulated modules. Finally, the third approach is based on a probabilistic mixture modeling [3]. Based on phenotypic similarity between the patients and a spectrum of possible disease causes/explanation such as mutations, copy number variation, microRNA levels, etc. the method identifies disease subtypes together with their causes and models the disease of each patient as a mixture of the subtypes. Taken together, these approaches help to fill a significant gap between the general current understanding of cancer and existing approaches to model cancer diversity.

References

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