Integrative network modeling of large multidimensional cancer datasets

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II. **Kling, T.***, Ferrarese, R.*, Ó hAilín, D., Heiland, H. H., Dai, F., Vasilikos, I., Weyerbrock, A., Jörnsten, R., Carro**, M. S., Nelander, S**. *Integrative modeling reveals ANXA2 as a determinant of mesenchymal transformation in glioblastoma.* 2015
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III. **Kling, T.***, Johansson, P.*, Sánchez, J., Marinescu, V. D., Jörnsten, R., Nelander, S. *Efficient exploration of pan-cancer networks by generalized covariance selection and interactive web content.* Nucleic Acids Research, 2015.
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ABSTRACT

Our ability to conduct detailed molecular investigations on tissue samples have, during the past decade, enabled the formation of databases containing measurements from thousands of cancer tumors. To harness the potential of the amassing data sets, we introduce new modeling techniques and generalise existing methods for large-scale integration of cancer data. These methods aim to construct network models that link genetic, epigenetic, transcriptional and phenotypic events, by combining genome-wide measurements of multiple kinds.

In paper I we constructed a modeling framework, EPoC, for creating causal networks between gene copy number levels and mRNA expression, and applied it to data from the brain tumor glioblastoma. Some of the predicted regulators were tested in four glioblastoma-derived cell lines and confirmed that the network model could be used to find unknown regulators of cell growth in glioblastoma.

In paper II we used data integrative network modeling to identify novel genomic, epigenetic and transcriptional regulators of glioblastoma subtypes. In addition to confirming known regulators of gliomagenesis, the model also predicted that Annexin A2 (ANXA2) promoter methylation and mRNA expression were linked to the signature target genes of the clinically aggressive mesenchymal molecular subtype. Our findings were validated by knockdown of ANXA2 in glioblastoma-derived cell cultures.

Paper III presents an extension of sparse inverse covariance selection (SICS), which is adapted and optimized for modeling of genetic, epigenetic, and transcriptional data across multiple cancer types. To evaluate the potential of the method, we applied it to data from eight cancers available in The Cancer Genome Atlas and published the model online at cancerlandscapes.org for anyone to explore. The derived multi-cancer model detected known interactions and contained interesting predictions, including functionally coupled network structures shared between cancers.

In summary, we use network modeling of cancer to identify possible drug targets, drivers of molecular subclasses, and reveal similarities and differences between cancer types. The developed tools for network construction can assist in further investigation of the cancer genome, potentially including other data sources and additional cancer diagnoses.

Keywords: network modeling, data integration, glioblastoma, pan-cancer analysis, The Cancer Genome Atlas

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