

Ph.D. in Information Technology: Thesis Defense

September 9th, 2020

Conference Room "Emilio Gatti" and online by Zoom – at 9.30

Eirini STAMOULAKATOU – XXXII Cycle

“Impact of mutational processes on regulatory elements in human cancer”

Advisor: Prof. Stefano Ceri

Topics:

- Impact of Mutational Processes on Transcription Factor Binding Sites
- Impact of Mutational Processes on microRNA and their Response Elements
- Somatic Mutations and Alterations in Insulated Neighborhood Boundaries
- Visualization of Mutational Enrichment for Selected Genomic Regions

Abstract:

This thesis answers the general research question about how to predict the impact of mutational processes on specific genomic regions. In addition, it provides a systematic pan-cancer characterization of the associations between constitutive boundaries and genome alterations in cancer. The results reveal the impact of mutational processes in functional genomic regions underlying the development of cancer, with potential implications for the understanding of cancer etiology, prevention, and therapy.

The thesis includes a novel probabilistic model describing the impact of mutational processes operative on specific genomic regions in human cancer and develops a systematic computational framework to identify which mutational processes are more likely to hit and harm binding sites of a given transcription factor. The major research result of this framework is that it identifies which mutational processes are more likely to disrupt transcription factor binding sites, and in which cancer types these disruptions are more likely to occur. This research establishes for each mutational process a catalog of binding motif disruption frequencies, which correspond to an expected background effect of the mutational patterns.

In addition, the thesis investigates the effect of mutational processes on the disruption of microRNA binding sites. Mutations in the seed regions of the microRNA, which is of crucial importance for its target recognition, may disrupt the binding of microRNAs to their target genes. I develop a probabilistic framework for analyzing the alteration of microRNAs and their response elements (MRE) based on cancer-associated mutagenic processes. To the best of my knowledge, this is the

first study that provides a probabilistic framework for microRNA and MRE sequence alteration analysis based on mutational processes and computationally assessing the disruptive impact of mutational signatures on human microRNA-target interactions. Recent evidence shows that the disruption of TADs might lead to tumorigenesis. As a further step in the analysis of the key role of CTCF bindings in cancer after the initial application of the impact of mutational processes on CTCF binding sites, this thesis investigates the enrichment of somatic mutation, abnormal methylation (hyper and hypomethylation), and copy number alteration events in the proximity of CTCF bindings overlapping with TADs boundaries.

Several studies highlight the relevance of somatic mutations in non-coding regions of the genome which exhibit similar function, e.g., promoters or transcription factor binding sites. In the last part of the thesis, I introduce MutViz, a tool for the identification of mutation enrichments on arbitrary sets of user-defined regions; for a variety of cancer types, it contains preloaded mutations from major public datasets, well organized within an effective database organization. MutViz provides a user-friendly interface helping the user in providing sets of regions as input and in obtaining their fast exploration as output, together with statistical testing for enrichment. All the above-visualized results can give a user the general mutational landscape of the genomic sites under investigation. MutViz is an excellent tool for visualizing non-coding mutations, especially for clinicians or researchers without any bioinformatics background, as no programming skills are required.

PhD Committee

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