Minimum Error Calibration and Normalization for Genomic Copy Number Analysis

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Introduction

In this study, we present a novel method named Minimum Error Calibration and Normalization of Copy Numbers Analysis (Mecan4CNA). In general, Mecan4CNA provides an advanced method for CNA data normalization especially in research involving data of high volume and heterogeneous quality. With its informative output and visualization, it can also facilitate analysis of individual CNA profiles. Mecan4CNA is freely available as a Python package and through Github.

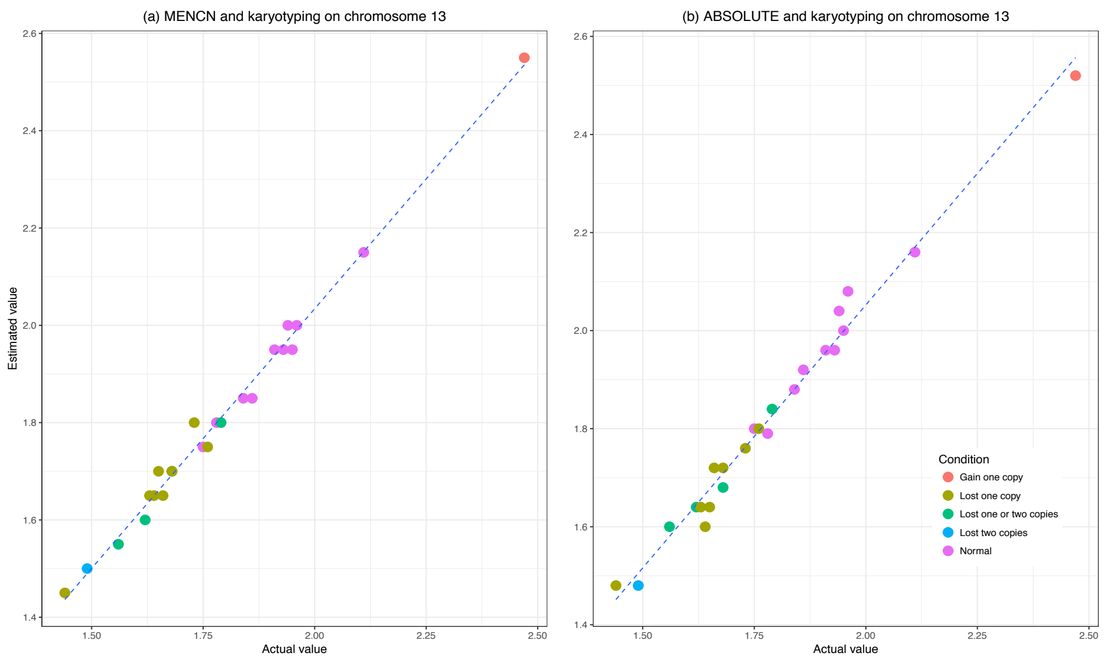
Background

Copy number variations (CNV) are regional deviations from the normal autosomal bi-allelic DNA content. While germline CNVs are a major contributor to genomic syndromes and inherited diseases, the majority of cancers accumulate extensive "somatic" CNV (sCNV or CNA) during the process of oncogenetic transformation and progression. While specific sCNV have closely been associated with tumorigenesis, intriguingly many neoplasias exhibit recurrent sCNV patterns beyond the involvement of a few cancer driver genes. Currently, CNV profiles of tumor samples are generated using genomic micro-arrays or high-throughput DNA sequencing. Regardless of the underlying technology, genomic copy number data is derived from the relative assessment and integration of multiple signals, with the data generation process being prone to contamination from several sources. Estimated copy number values have no absolute and linear correlation to their corresponding DNA levels, and the extent of deviation differs between sample profiles which poses a great challenge for data integration and comparison in large scale genome analysis.

Performance evaluation

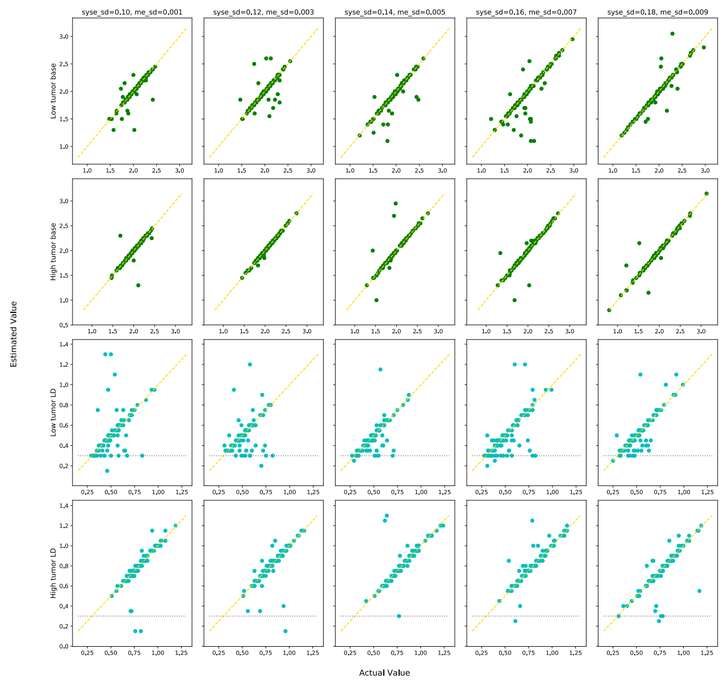
NCI-60 cancer cell line data:

Comparison of baseline and level distance estimation with existing methods and karyotyping data on the NCI-60 tumor cell line produced coherent results.



Simulated data:

Experiments of Mecan4CNA on simulated data showed an overall accuracy of 93% and 91% in determining the baseline and level distance, respectively.

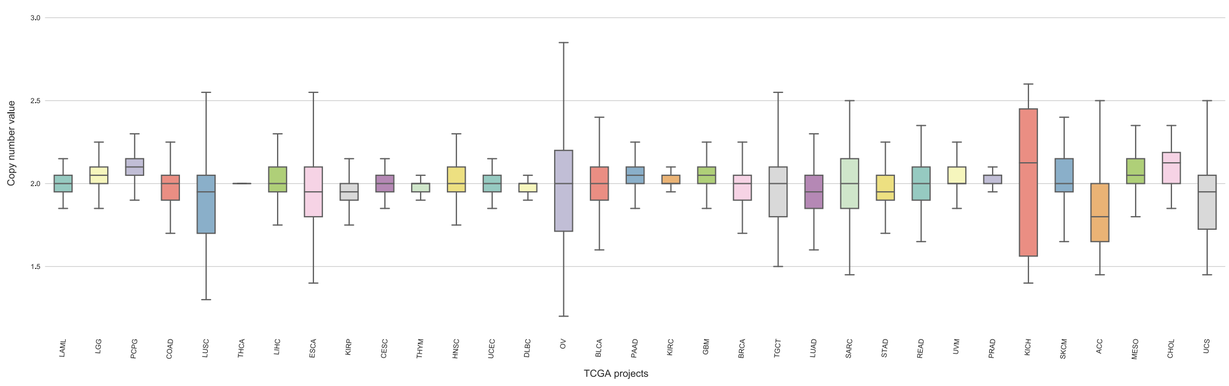


The comparisons of estimated values and actual values on simulated data with different settings.

Applications

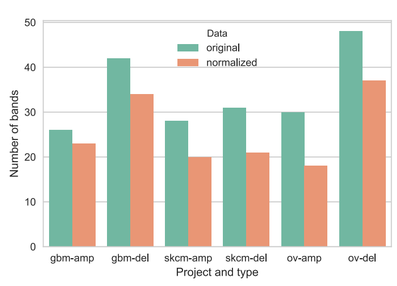
Baseline deviation of TCGA data:

The generally good quality of these datasets allowed us to show that baseline variation is a common and recurring problem among copy number data.

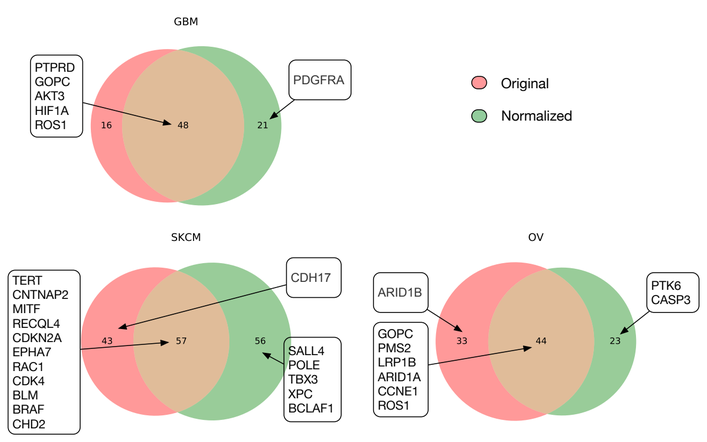


Normalized data as GISTIC input:

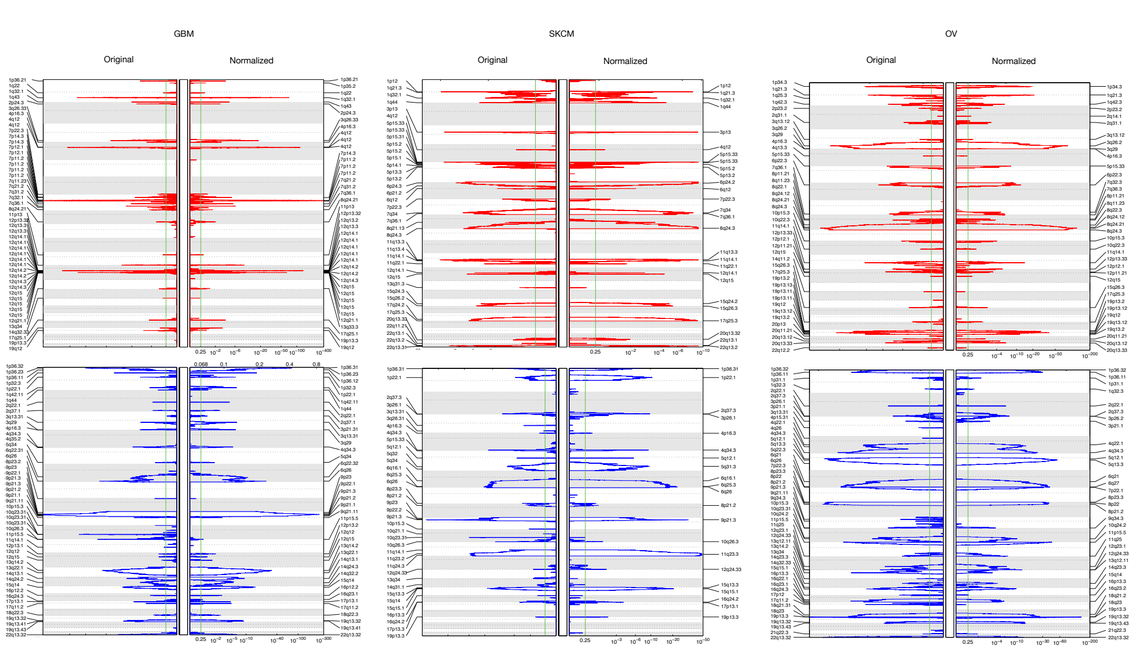
To estimate the method's impact on downstream analyses we performed GISTIC analyses on original and normalized (using Mecan4CNA) data from the Cancer Genome Atlas (TCGA). The normalized data showed prominent improvements of both sensitivity and specificity in detecting focal regions.



The number of significant bands detected by GISTIC using different datasets.



Detected cancer census genes using the original and normalized data in GBM, SKCM and OV datasets of TCGA. Numbers in circles represents the total of detected census genes. Gene symbols in boxes show the known drivers for the disease.



Comparisons of GISTIC calling results using the original and normalized copy number data from 3 TCGA projects. Normalized data shows both regions with reduced noise level and regions with improved significance. Overall, normalized data shows improvement in both sensitivity and specificity.

Availability

1. Python installation: `pip install mecan4cna`
2. github: https://github.com/baudisgroup/mecan4cna
3. Software license: MIT
4. Contact: bo.gao@imls.uzh.ch