Platform-Independent Genome-Wide Pattern of DNA Copy-Number Alterations Predicting Astrocytoma Survival and Response to Treatment Revealed by the GSVD Formulated as a Comparative Spectral Decomposition

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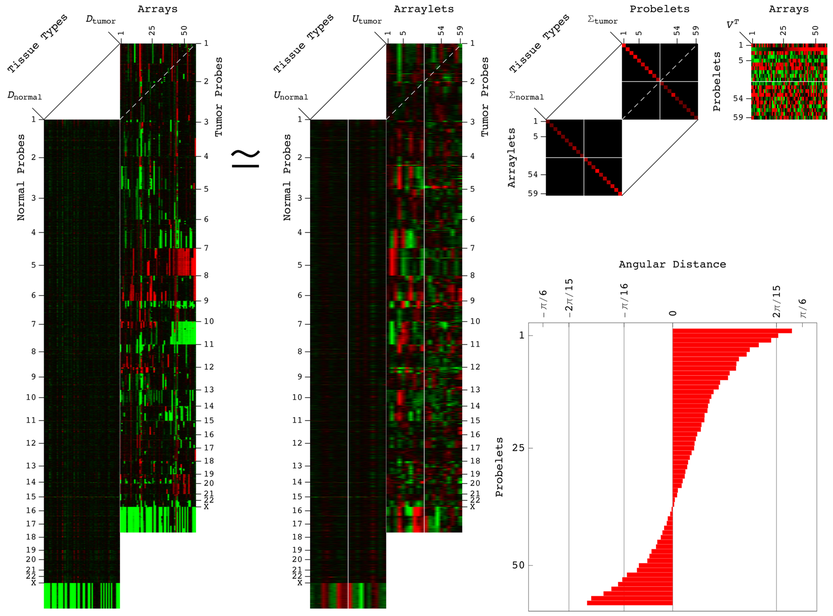
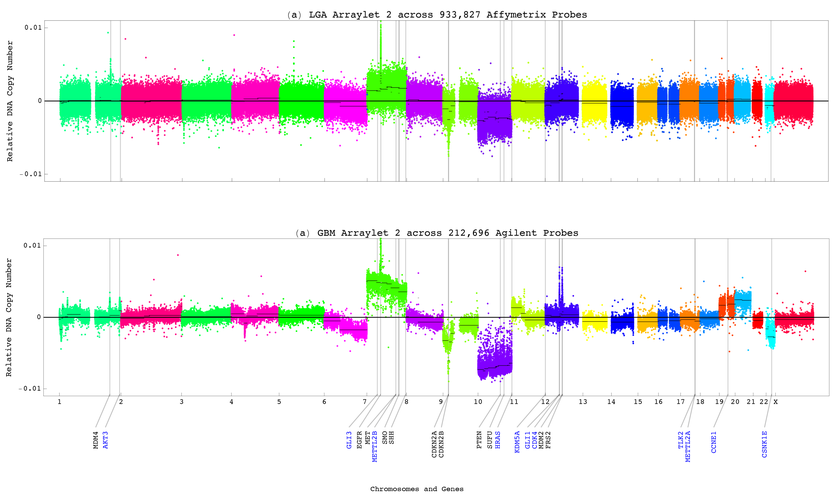
Mathematical Framework: GSVD

We use the generalized singular value decomposition (GSVD), formulated as a comparative spectral decomposition, to model patient-matched grades III and II, i.e., lower-grade astrocytoma (LGA) brain tumor and normal DNA copy-number profiles [1,2].



Biological Results

A genome-wide tumor-exclusive pattern of DNA copy-number alterations (CNAs) is revealed, encompassed in that previously uncovered in glioblastoma (GBM), i.e., grade IV astrocytoma [3], where GBM-specific CNAs encode for enhanced opportunities for transformation and proliferation via developmental and growth signaling pathways in GBM relative to LGA.



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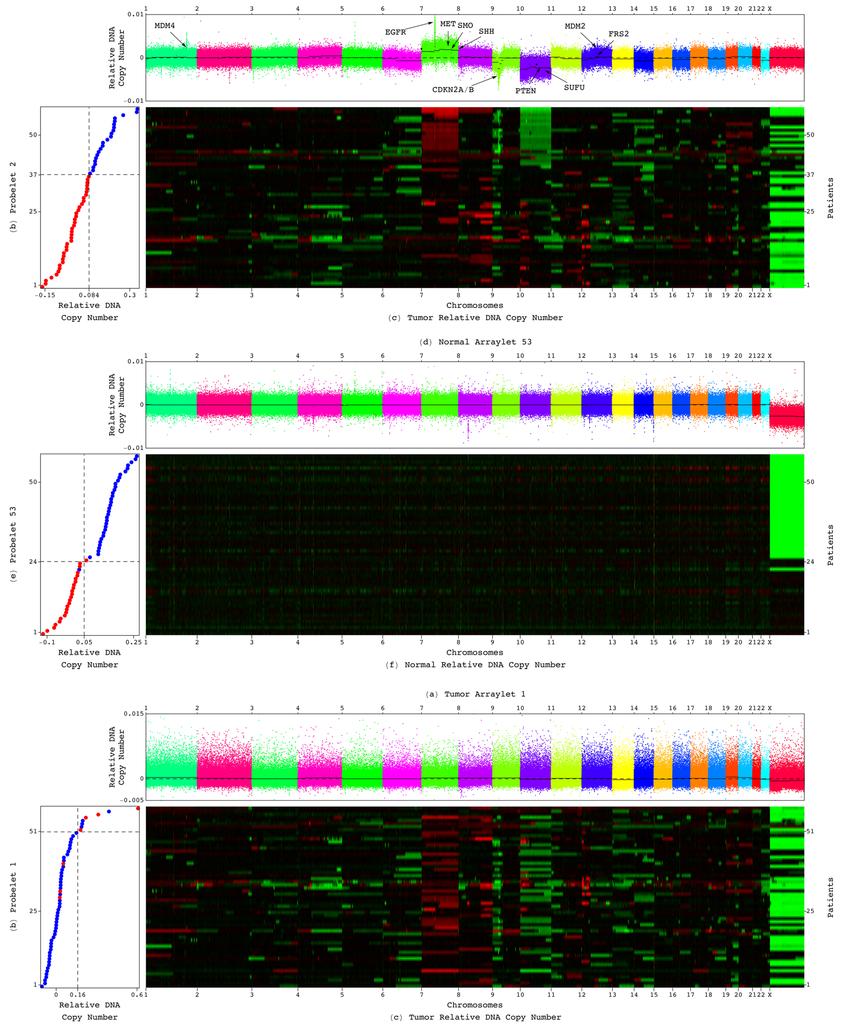
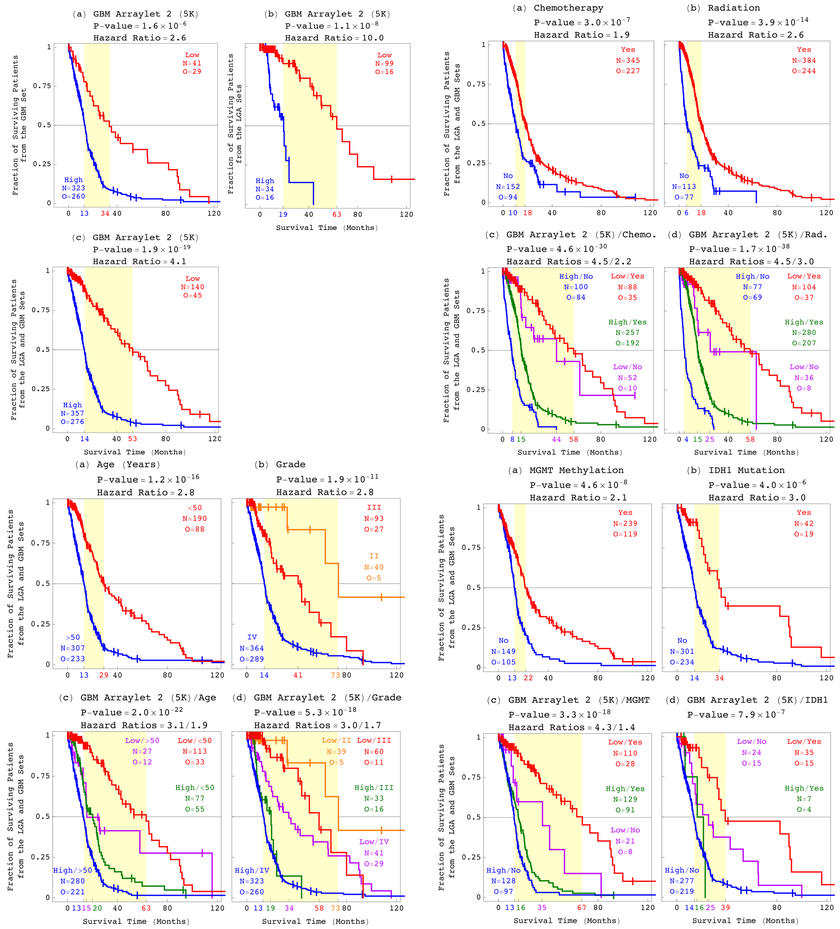
The GSVD separates the LGA pattern from other sources of biological and experimental variation, common to both, or exclusive to one of the tumor and normal datasets.



We find, first, and computationally validate, that the LGA pattern is correlated with a patient's survival and response to treatment. Second, the GBM pattern identifies among the LGA patients a subtype, statistically indistinguishable from that among the GBM patients, where the CNA genotype is correlated with an approximately one-year survival phenotype. Third, cross-platform classification of the Affymetrix-measured LGA and GBM profiles by using the Agilent-derived GBM pattern shows that the GBM pattern is a platform-independent predictor of astrocytoma outcome.

Statistically, the pattern is a better predictor (corresponding to greater median survival time difference, proportional hazard ratio, and concordance index) than the patient's age and the tumor's grade, which are the best indicators of astrocytoma currently in clinical use, and laboratory tests. The pattern is also statistically independent of these indicators, and, combined with either one, is an even better predictor of astrocytoma outcome.



Discussion

Recurring DNA CNAs have been observed in astrocytoma tumors' genomes for decades, however, copy-number subtypes that are predictive of patients' outcomes were not identified before. This is despite the growing number of datasets recording different aspects of the disease, and due to an existing fundamental need for mathematical frameworks that can simultaneously find similarities and dissimilarities across the datasets [4—6]. This illustrates the ability of comparative spectral decompositions to find what other methods miss.

References

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Acknowledgments

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