Entropy in the Cancer Cell

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Introduction

Early efforts in the interpretation of the vast swathes of high throughput data detailing gene expression, copy number state and DNA methylation levels have focused on identifying individual, significantly altered objects in the phenotype of interest. This is often called the "*gene list*" approach, because upon choosing some threshold of significance the eventual output is often a list of significantly altered genes. More recently, combining this information with network data consisting of known and inferred interactions between such objects has led to progress in key problems in cancer research, like classification, prognosis, and the elucidation of systems-level principles underlying the cancer phenotype. The purpose of this research is to study the way in which cancer is associated with disorder at the systems level in a way that extends and enriches these approaches.

Materials and Methods

Following recent insights that differential subnetworks may be key to understanding the functional changes associated with cancer phenotypes [1], we recently proposed a measure to identify hotspots where network rewiring associated with cancer metastasis takes place [2]. Specifically, the measure we proposed reflects either gain or loss of functionality of a protein with its interaction partners. The measure represents a dynamical entropy and is derived from considering a random walk on the interaction network, where probability fluxes are given by the strength of correlations across a given phenotype. In effect, the dynamical flux entropy around a given protein quantifies how disordered the natural interaction patterns are and changes in this disorder can identify rewiring hotspots as demonstrated by us previously [2]. More recently, we have generalised our notion of local flux entropy to a global one [3]. It arises from the same stochastic process defined on the network of protein interactions but is modified to satisfy an approximate heat-diffusion equation.

We have recently applied the "entropy flux" approach to a wide range of different cancers, which has highlighted the disruption of the WNT differentiation pathway and epigenetic gene modules as important cancer hallmarks, potentially constituting novel targets for intervention and therapy (unpublished results).

Disorder in cancer also occurs at the genomic level; for example chromosomal gains and losses and rearrangements have long been associated with certain cancers. Thus, the disorder/entropy associated with genomic instability can be of interest and could provide a better indicator of clinical outcome. To study this, we considered the "*slide*" *approximate entropy* (a measure of sequential disorder) of the degree sequence of a network and studied this for scale free and Poisson networks [4]. Next, we associated to the copy number profiles ordered across the genome a network capturing its spatial correlative structure and found that this network indeed encodes clinical information extractable via approximate entropy.

Results

We found that dynamical flux entropy was consistently increased in cancer across six different tissue types, whilst a non-dynamical measure (*covariance entropy*) was inconsistent [Figure 1].

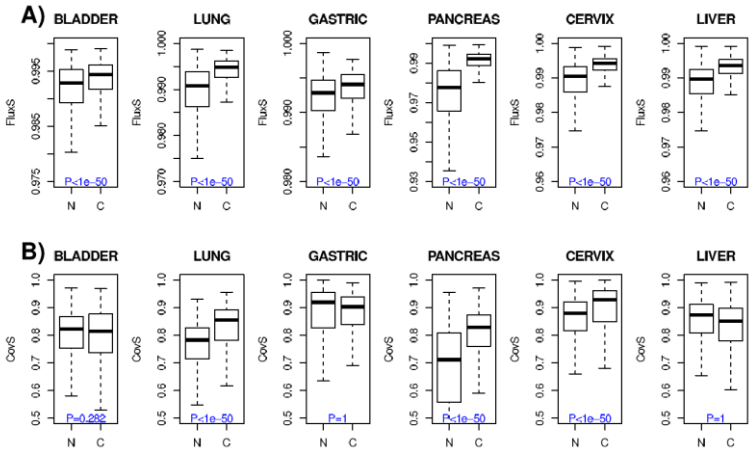

Figure 1: A) Distributions of flux entropy (*FluxS*) between normal (*N*) and cancer (*C*) samples. B) Inconsistency of changes in covariance entropy (*CovS*).

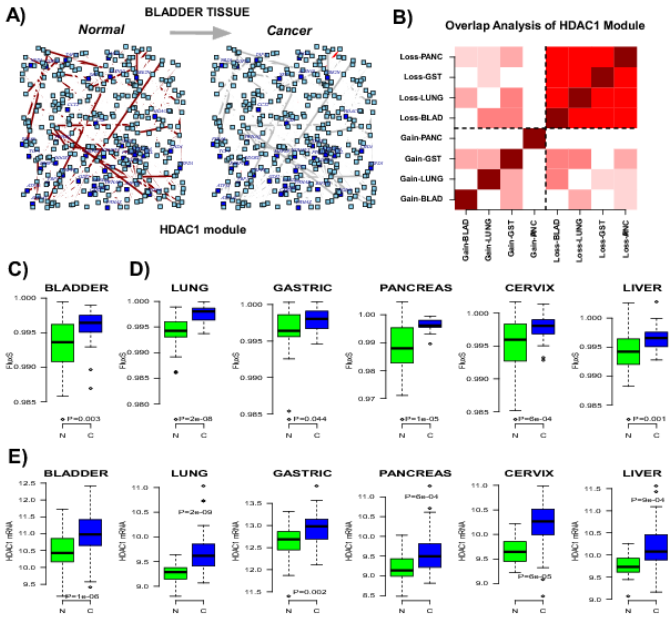

Figure 2: Identification of an HDAC1 module associated with increased dynamical entropy and loss of function in cancer.

Conclusion

Measures of entropy and disorder are useful for elucidating systems-level properties of cancer and for identifying hotspots were network rewiring takes place. Similarly, at the genomic DNA level, measures of entropy associate with important clinical characteristics of cancers and may lead to novel insights and improved molecular classifications.

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References

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