

Geometry of Correlation Networks for Studying the Biology of Cancer

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Abstract—In this note, we extend the notion of Ollivier-Ricci curvature on weighted graphs with all positive weights to the case in which the weights may also be negative. This is done by employing the Hahn-Jordan decomposition of signed measures, allowing us to extend the Earth Mover’s Distance to an extended class of measures. The resulting curvature will be utilized to study the robustness properties of general networks with particular implications in cancer transcription networks to elucidate fragility (in the sense of a rate function from large deviations theory) with respect to those genes responsible for maintaining cellular homeostasis as it pertains to growth and proliferation.

I. INTRODUCTION

In previous work [26], we demonstrated that a graph-theoretic notion of curvature was positively correlated to robustness defined in terms of a the rate function from large deviations theory. More precisely, we have proposed an integrative framework to identify genetic features related to cancer networks and to distinguish them from the normal tissue networks by geometrical analysis of the networks provided by The Cancer Genome Atlas (TCGA) data. This relationship was exploited to show that curvature could be regarded as a *cancer hallmark*.

The underlying notion of curvature on weighted graph is based on the Wasserstein 1-metric [21] from optimal mass transport theory [30]. This is called *Ollivier-Ricci* curvature. As such, one needs all the correlations to be positive giving well-defined positive measures in order to define this notion of graph curvature. In the present work, based upon the Hahn-Jordan decomposition of a signed measure [18], we extend the definition of Ollivier-Ricci curvature to the more realistic case in which one allows both negative and positive

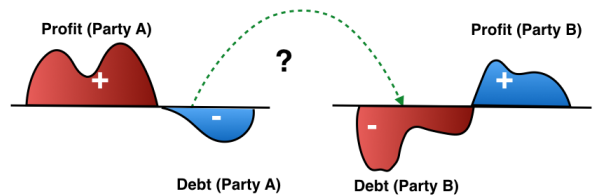


Fig. 1. This paper extends the notion of discrete Ricci curvature on graphs for signed measures. In the sense of resource allocation, this is akin to notions redistributing “profit” and “debt” between two parties in an optimal manner

weights (correlations) in our cancer networks. Figure 1 illustrates this concept in the context of resource allocation.

This will also allow one to formally consider directed graphs in which one allows both negative and positive weights. To illustrate this method, results will be first shown for toy-like networks to motivate intuition. Then, our focus will shift attention towards a short example on Liver Hepatoceular Carcinoma whereby we examine areas of fragility and its relationship to uncontrolled cellular growth. We note that a complete biological understanding and merits of the proposed method will be a subject of future work - our intention here is to introduce the mathematical underpinnings of a much needed extension as it relates to network robustness (curvature).

The remainder of the present note is outlined as follows: In the next section, we revisit background on Ricci curvature and its connection to functional robustness. Section IV introduces a compatible (highly parallelizable) discrete notion of Ricci curvature for the case in which one deals with an undirected graph with positive weights. Following this, Section V provides an extension of Ollivier-

Ricci curvature for the case of positive and negative weights via a Hahn-Jordan decomposition. Proof-of-concept results are then given in Section VI and we conclude with remarks on future research in Section VII.

II. CURVATURE OF NETWORKS

Since the object of interest for a cancer network will be a weighted graph (see Section VI), we will consider notions of curvature that best fit this mathematical model and can lead to interesting new quantitative biological insights. Accordingly, we will first sketch some material on curvature before moving on to the proposed notions for networks modeled as graphs.

A. Background on Ricci curvature

In order to motivate generalized notions of Ricci curvature suitable for complex networks, we will begin with an elementary treatment of curvature following [10], [31], [32]. Let M be an n -dimensional Riemannian manifold, $x \in M$, let $T_x M$ denote the tangent space at x , and $u_1, u_2 \in T_x M$ orthonormal vectors. Then for geodesics $\gamma_i(t) := \exp(tu_i)$, $i = 1, 2$, the *sectional curvature* $K(u_1, u_2)$ measures the deviation of geodesics relative to Euclidean geometry, i.e.,

$$d(\gamma_1(t), \gamma_2(t)) = \sqrt{2}t \left(1 - \frac{K(u_1, u_2)}{12}t^2 + O(t^4)\right). \quad (1)$$

The Ricci curvature is the average sectional curvature. Namely, given a (unit) vector $u \in T_x M$, we complete it to an orthonormal basis, u, u_2, \dots, u_n . Then the *Ricci curvature* is defined by $Ric(u) := \frac{1}{n-1} \sum_{i=2}^n K(u, u_i)$. (There are several different scaling factors used in the literature. We have followed [10]). It may be extended to a quadratic form, giving the so-called *Ricci curvature tensor*.

We want extend this notions to discrete graphs and networks. For discrete spaces corresponding to networks modeled as graphs, ordinary notions such as differentiability needed to define Ricci curvature as in the previous section do not make sense. There is however a very nice argument due to Villani [32] that indicates a possible way to getting around such difficulties via two approaches to convexity.

More precisely, let $f : \mathbb{R}^n \rightarrow \mathbb{R}$. Then if f is C^2 , convexity may be characterized as

$$\nabla^2 f(x) \geq 0$$

for all x . This is called by Villani an *analytic* definition of convexity (as the usual definition of Ricci given above). On the other hand, one can also define convexity in a *synthetic* manner via the property that

$$f((1-t)x + ty) \leq (1-t)f(x) + tf(y),$$

for all $x, y \in \mathbb{R}^n$, and $t \in [0, 1]$. In the latter case, no differentiability is necessary.

Following [17], [20], one may define a synthetic notion of Ricci curvature in terms of so-called *displacement convexity* inherited from the Wasserstein geometry on probability measures. This will be explicated in the next section. the references therein.

B. Curvature and robustness

There have been a number of approaches (see [6], [7], [19], [21] and the references therein) to extending the notion of Ricci curvature to more general metric measure spaces. At this point, the exact relationship of one approach as compared to another is unclear. Roughly, the techniques fall into two categories: the first generalizing the weak k -convexity of the entropy functional on the Wasserstein space of probability measures as in [6], [17], [20], and the second directly working with Markov chains to define the generalization [7], [19], [21] on networks. Finally there is a notion of “hyperbolicity” due to Gromov [13] based on the “thinness” or “fatness” of triangles compared to the Euclidean case. For our purposes, it seems that the work of [17] seems most relevant. We therefore outline this approach.

Let (X, d, m) denote a geodesic space, and set

$$\mathcal{P}(X) := \{\mu \geq 0 : \int_X \mu dm = 1\}, \quad (2)$$

$$\mathcal{P}^*(X) := \{\mu \in \mathcal{P}(X) : \lim_{\epsilon \searrow 0} \int_{\mu \geq \epsilon} \mu \log \mu dm < \infty\} \quad (3)$$

We define

$$H(\mu) := \lim_{\epsilon \searrow 0} \int_{\mu \geq \epsilon} \mu \log \mu dm, \text{ for } \mu \in \mathcal{P}^*(X), \quad (4)$$

which is the negative of the *Boltzmann entropy* $S(\mu) := -H(\mu)$; note that the concavity of S is equivalent to the convexity of H . Then we say that X has *Ricci curvature bounded from below by k* if for every $\mu_0, \mu_1 \in \mathcal{P}(X)$, there exists a constant speed geodesic μ_t with respect to the Wasserstein 2-metric connecting μ_0 and μ_1 such that

$$S(\mu_t) \geq tS(\mu_0) + (1-t)S(\mu_1) + \frac{kt(1-t)}{2} W(\mu_0, \mu_1)^2, \quad (5)$$

for $0 \leq t \leq 1$. This means that changes in entropy and curvature are **positively correlated**. We express this relationship as

$$\Delta S \times \Delta Ric \geq 0. \quad (6)$$

We will describe a specific notion of Ricci curvature and entropy on graphs below. We just note here that changes in *robustness*, i.e., the ability of a system to functionally adapt to changes in the environment (denoted as ΔR) is also positively correlated with entropy via the Fluctuation Theorem [8], [11], and thus with network curvature:

$$\Delta R \times \Delta Ric \geq 0. \quad (7)$$

See Section III below for a discussion of the Fluctuation Theorem. Since the curvature is very easy to compute for a network as we will see in Section IV, this may be used as an alternative way of expressing functional robustness.

III. FLUCTUATION THEOREM

We give now an intuitive discussion of the Fluctuation Theorem [8], [11]. Recall that if $p_\epsilon(t)$ denotes the probability that the mean deviates by more than ϵ from the original (unperturbed) value at time t , then

$$R := \lim_{t \rightarrow \infty, \epsilon \rightarrow 0} \left(-\frac{1}{t} \log p_\epsilon(t) \right).$$

This is the *rate function* from large deviations theory [29].

On the other hand, evolutionary entropy S may be characterized in this setting as

$$S := \lim_{t \rightarrow \infty, \epsilon \rightarrow 0} \left(\frac{1}{t} \log q_\epsilon(t) \right),$$

where $q_\epsilon(t)$ denotes the minimal number of genealogies of length t whose total probability exceeds $1 - \epsilon$. Thus the greater the $q_\epsilon(t)$, the smaller the $p_\epsilon(t)$ and so the larger the decay rate. The Fluctuation Theorem is an expression of this fact for networks, and can be expressed as

$$\Delta S \times \Delta R \geq 0, \quad (8)$$

Considering (5), we conclude that changes in robustness (ΔR) is also positively correlated with the network curvature, as stated in (7). This latter relationship will be a key in studying the robustness of cancer networks. Indeed, according to the work done in [?] and [35], it seems that in many cases the normal protein interaction networks possess a lower entropy than their cancerous analogues; hence from our above discussion they are less robust. This could be justified as the ability of oncoproteins to better respond to the changes in the cellular environment due to their disorganized arrangement which leads to possession of higher degrees of freedom. Since the curvature is positively correlated to the robustness of networks and easier to compute, it can help in quantifying the robustness in terms of the adaptability of networks. In Section VI, curvature will be applied to certain cancer networks to differentiate them from normal tissue networks.

IV. OLLIVIER-RICCI CURVATURE: POSITIVE WEIGHTS

In this section, we will sketch an approach to Ricci curvature due to Ollivier [21], [22] that seems ideal for studying network robustness. The approach was developed as a discrete analogue of a defining property of Ricci curvature in the continuous case. The idea is that for two very close points x and y with respective tangent vectors w and w' , in which w' is obtained by a parallel transport of w , the two geodesics will get closer if the curvature is positive. This is reflected in the fact that the distance between two small (geodesic balls) is less than the distance of their centers. Ricci curvature along direction xy reflects this, averaged on all directions w at x . Similar considerations apply to negative and zero curvature [33].

More formally, we have for (X, d) a metric space equipped with a family of probability measures

$\{\mu_x : x \in X\}$ we define the *Olliver-Ricci curvature* $\kappa(x, y)$ along the geodesic connecting x and y via

$$W_1(\mu_x, \mu_y) = (1 - \kappa(x, y))d(x, y), \quad (9)$$

where W_1 denotes the Earth Mover's Distance (Wasserstein 1-metric), and d the geodesic distance on the graph. For the case of weighted graphs of greatest interest in networks, we put

$$d_x = \sum_y w_{xy}$$

$$\mu_x(y) := \frac{w_{xy}}{d_x},$$

the sum taken over all neighbors of x where w_{xy} denotes the weight of an edge connecting x and y (it is taken as zero if there is no connecting edge between x and y). **All the interaction weights here are positive.** The measure μ_x may be regarded as the distribution of a one-step random walk starting from x . As is argued in [21], this definition is more inspired from an approach such as that given via equation (1). An advantage of this, is that it is readily computable since the Earth Mover's Metric may be computed via linear programming [?], [32].

Moreover, it is interesting to note that if we define the Laplacian operator via

$$\Delta f(x) = f(x) - \sum_y f(y)\mu_x(y), \quad f \text{ real-valued function,}$$

this coincides with the usual normalized graph Laplacian operator [15]. It is also interesting to note in this connection that if $k \leq \kappa(x, y)$ is a lower bound for the Ricci curvature, then the eigenvalues of Δ may be bounded as $k \leq \lambda_2 \leq \dots \leq \lambda_N \leq 2 - k$; see [15] for the exact statement. Note that the first eigenvalue $\lambda_1 = 0$. This relationship is very important since $2 - \lambda_N$ measures the deviation of the graph from being bipartite, i.e., a graph whose vertices can be divided into two disjoint sets U and V such that every edge connects a vertex in U to one in V . Such ideas appear in resource allocation in certain networks.

V. OLLIVIER-RICCI CURVATURE: POSITIVE AND NEGATIVE WEIGHTS

The correlation networks we will be considering have both positive and negative weights, and so one

needs a notion of curvature for this case as well, i.e. for weighted undirected graphs with weights w_{xy} that may be either positive and negative. Accordingly, we need an extension of the Wasserstein distance for signed measures. Following [18], employing the Hahn-Jordan decomposition, one can get a notion of Ollivier-Ricci curvature as follows.

Let $d_x = \sum_{y \sim x} w_{xy}$. We assume that $d_x \neq 0$. Let W be the set of all weights. Set

$$W^+ := \{w_{xz} > 0\}, \quad W^- := \{w_{xz} < 0\}.$$

Case 1: $d_x > 0$.

$$\mu_x^+(z) = \frac{w_{xz}}{d_x}, \quad w_{xz} \in W^+,$$

$$= 0, \quad \text{otherwise;}$$

$$\mu_x^-(z) = \frac{-w_{xz}}{d_x}, \quad w_{xz} \in W^-;$$

$$= 0, \quad \text{otherwise.}$$

Case 2: $d_x < 0$.

$$\mu_x^+(z) = \frac{w_{xz}}{d_x}, \quad w_{xz} \in W^-,$$

$$= 0, \quad \text{otherwise;}$$

$$\mu_x^-(z) = \frac{-w_{xz}}{d_x}, \quad w_{xz} \in W^+;$$

$$= 0, \quad \text{otherwise.}$$

Then clearly,

$$\mu_x = \mu_x^+ - \mu_x^-,$$

$$\mu_y = \mu_y^+ - \mu_y^-.$$

We define

$$W_1(\mu_x, \mu_y) := W_1(\mu_x^+ + \mu_y^-, \mu_y^+ + \mu_x^-).$$

This is under the hypothesis that $d_x \neq 0$ and $d_y \neq 0$. If either is 0, we set $W_1(\mu_x, \mu_y) = 0$.

We define the *Ollivier-Ricci curvature* as

$$W_1(\mu_x, \mu_y) = (1 - \kappa(x, y))d(x, y).$$

In the next Section, we use this result to define curvature (and therefore robustness) on varying network structures.

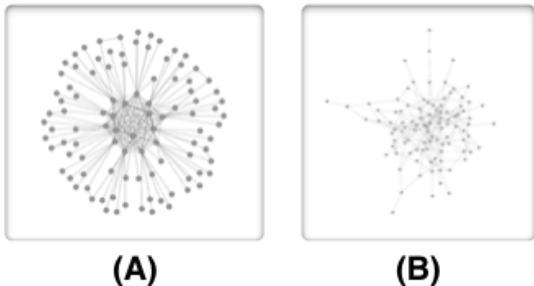


Fig. 2. Two synthetic examples represent classical structures of a “star” network and a corresponding random network.

VI. RESULTS

This section provides preliminary results of the proposed method.

A. Toy Networks

We begin with two classical network structures that exist in literature when examining a notion of robustness, namely a star-like network and a corresponding random network. To ensure a fair comparison, each of the networks as seen in Figure 2 comprise of 200 nodes and 400 edges for which we assigned positive and negative weights in a random fashion. Intuitively, graph robustness as it is measured here very loosely highlights nodes whose random walks are equally likely (i.e., uncertainty is increased if a “hop” from node x is equally likely to adjacent nodes y). Motivated by this basic concept, we chose to assign weights based on several uniform intervals in which the variances increases. Specifically, we measured the average Ricci curvature for these networks *over the adjacency* when edge weights were chosen to be: (a) all ones (b) rand [-.5, 1], (c) rand [0, 1], (d) rand [-.5, 1], and (e) rand [-1 1]. The following results are presented in Figure 2 and as expected, curvature decreases as variances of weights is increased and is unimpeded when values are chosen in the negative regime.

B. Liver Hepatocellular Carcinoma

One of the main attractions in working on signed measures is its implications in biological networks for which correlation network data may be used

in the context of drug targeting [26], [35]. As such, we examined normal and cancerous expression samples of liver cancer (LIHC) derived from the publicly available TCGA database using the Broad Institute Firehose. This particular network is visualized in Figure 3 for which we examine a set of 500 cancer related genes of varying types of cancers as studied in [26]. In particular, this data was used to test our hypothesis that under metastasis, cellular growth remains unchecked and there is a “breakdown” in certain tumor suppressor like genes as opposed to oncogenes. This remark relates to an increase in fragility towards tumor suppressors. To understand such activity of possible indirect and direct interactions, we define a nodal scalar curvature measure: $M(x) := \sum_x \kappa(x, y)$ and utilize this to measure gene activity in our data set.

As such, Figure 3C presents scalar curvature results of the top five genes ranked by increases in fragility for LIHC. Here, it is shown that the gene GPC3 and EXT1 exhibit the greatest increases in fragility and specifically, the gene GPC3 has been noted in controlling cell migration, negatively regulating cell growth and inducing apoptosis with its down-regulation being marked in several cancer types. Thus, from a biological sense, it would appear that such genetic dysfunction would relate to an increase in fragility - a property now seemingly captured by curvature. Moreover, another interesting insight relates to the gene EXT1 (apart of the EXT gene family) that have been recently implicated in the role of liver regeneration. Thus, a marked increase in fragility is again pertinent to liver cancer. A similar argument can be seen with NTRK3 and FANCC gene which again is responsible for protein production that *delays* the onset of apoptosis.

This said, we should note that the above practical results are very limited. Our primary motivation here is to simply introduce the mathematical underpinnings of extending Wasserstein distance towards signed measures on graphs and to ensure that such results are reasonable in the context of networks. One careful aspect that needs further attention relates to a notion of “auto-annihilation” and is discussed in the next section.

Type	All 1's	Rand [.5,1]	Rand[0,1]	Rand[-.5,1]	Rand [-1,1]
Star Network	0.0623	-0.0278	-0.0715	-0.1669	-0.2250
Random Network	-0.6127	-0.6214	-0.6680	-0.6944	-0.7105

TABLE I

AVERAGE RICCI CURVATURE RESULTS FOR SYNTHETIC NETWORKS WHEN WEIGHTS ARE CHOSEN FROM UNIFORMLY.

VII. FUTURE WORK & SUMMARY

This paper extends the notion of the Earth Mover's Distance on networks via the Hahn-Jordan decomposition of signed measures. In doing so, we are able to define curvature-based quantities on signed networks with particular implications in understanding robustness and fragility of biological cancer (correlation) networks. This was followed by preliminary results on synthetic networks as well as understanding localized changes in genes in liver cancer.

Given the importance of directed signed graphs role in biological networks, we note one key area (and possible drawback) of the proposed method. In particular, due to the rearrangement of distribution in the decomposition, there is also an implicit indirect rearrangement of the cost matrix required in the computation of the Wasserstein 1-metric. Akin to an economics perspective, if we alternatively view this rearrangement as distributing "profit" and "debt", it would be logical progression for one to first ensure that debt is resolved through profit before redistributing profit to another party. This is referred to as "auto-annihilation" and is particularly important in graphs in the currently formulated approach, i.e., nodes "far away" in network structures such as a "chain" will appear to be closer, in the Wasserstein sense, resulting in higher curvature (increases in robustness). Therefore, further study with potential constraints on auto-annihilation will be necessary and will be a subject of future work.

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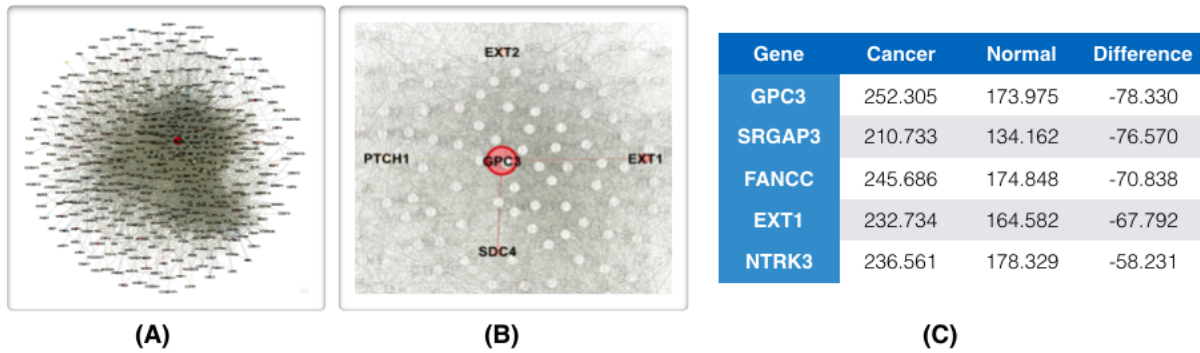


Fig. 3. This figure presents a network visualization of the network under study (a) along with a localized visualization of the direct interactions involved with GPC3 (b). We also present the top five genes (via scalar curvature) whose genes exhibit the greatest increase in fragility.

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