

# Geometry of Correlation Networks for Studying the Biology of Cancer

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ABSTRACT

## 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 [31]. This 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 weights (correlations) in our cancer networks. This will also allow one to formally consider directed graphs in which one models inhibitions and activations.

Results will be shown for cancer interaction networks derived from TCGA data.

## 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 modelled as graphs.

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### 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], [32], [33]. For  $M$  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.,

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

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 [33] 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  $x$ . Villani calls this 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. In [17], this is done for

measured length spaces, that is, metric measure spaces in which the distance between two points equals the infimum of the lengths of curves joining the points. For discrete spaces (such as those arising in network theory), there are several possibilities that we will compare, especially those from [6], [13], [21]. There have been several other approaches as well to defining Ricci curvature; see [7], [19] and the references therein.

### B. Curvature and robustness

As previously remarked, 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, and more generally a certain four-point criterion. Depending upon the application, each approach seems to be useful, and so we will explicate key aspects and their possible applications to various network problems. In particular, we follow [6], [21] because of connections to notions of metric entropy.

We begin with a characterization given in Lott and Villani [17]. Let  $(X, d, m)$  denote a geodesic space, and set

$$\begin{aligned} \mathcal{P}(X) &:= \{\mu \geq 0 : \int_X \mu dm = 1\}, \\ \mathcal{P}^*(X) &:= \{\mu \in \mathcal{P}(X, d, m) : \lim_{\epsilon \searrow 0} \int_{\mu \geq \epsilon} \mu \log \mu dm < \infty\} \end{aligned}$$

We define

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

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  $\mu_t$  with respect to the Wasserstein 2-metric connecting  $\mu_0$  and  $\mu_1$  such that

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

This means that entropy and curvature are **positively correlated** that we will express as

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

We will describe notions 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  $\Delta R$ ) 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, 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  $\epsilon$  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 [30].

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 ( $\Delta R$ ) is also positively correlated with the network curvature, i.e.,

$$\Delta R \times \Delta Ric \geq 0. \quad (9)$$

According to the work done in [?] and [36], it seems that in many cases the normal protein interaction networks possess a lower entropy than their cancerous analogues; hence 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 the following section, we will apply BER curvature to certain cancer networks to differentiate them from normal tissue networks.

#### IV. OLLIVIER-RICCI CURVATURE: POSITIVE WEIGHTS

We will employ a neat notion of Ricci curvature due to [21], [22]. The approach was inspired from several different directions from properties of Ricci curvature in the continuous case. The idea is that for two very close points  $x$  and  $y$  with 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 [34].

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

$$W_1(\mu_x, \mu_y) = (1 - \kappa(x, y))d(x, y), \quad (10)$$

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  $y$ ). The measure  $\mu_x$  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 [?], [33].

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  $\Delta$  may be bounded as  $k \leq \lambda_2 \leq \dots \lambda_N \leq 2 - k$ ; 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, that is 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 Olliver-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

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

This will be applied to cancer networks in the next section.

## VI. RESULTS

Rome: Can we do an example here?

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