

Calvin Ahlbrandt<sup>1</sup> · Gary Benson<sup>2</sup> · William Casey<sup>3</sup>

## Minimal Entropy Probability Paths Between Genome Families

the date of receipt and acceptance should be inserted later

Composed: S A T U R D A Y 2 5 J A N U A R Y 2 0 0 3

**Abstract.** We develop a metric for probability distributions with applications to biological sequence analysis. Our distance metric is obtained by minimizing a functional defined on the class of paths over probability measures on  $N$  categories. The underlying mathematical theory is connected to a constrained problem in the calculus of variations. The solution presented is a numerical solution, which approximates the true solution in a set of cases called *rich paths* where none of the components of the path is zero. The functional to be minimized is motivated by entropy considerations, reflecting the idea that nature might efficiently carry out mutations of genome sequences in such a way that the increase in entropy involved in transformation is as small as possible. We characterize sequences by frequency profiles or probability vectors, in the case of DNA where  $N$  is 4 and the components of the probability vector are the frequency of occurrence of each of the bases A, C, G and T. Given two probability vectors  $\mathbf{a}$  and  $\mathbf{b}$ , we define a distance function based as the infimum of path integrals of the entropy function  $H(p)$  over all admissible paths  $p(t)$ ,  $0 \leq t \leq 1$ , with  $p(t)$  a probability vector such that  $p(0) = \mathbf{a}$  and  $p(1) = \mathbf{b}$ . If the probability paths  $p(t)$  are parameterized as  $y(s)$  in terms of arc length  $s$  and the optimal path is smooth with arc length  $L$ , then smooth and “rich” optimal probability paths may be numerically estimated by a hybrid method of iterating Newton’s method on solutions of a two point boundary value problem, with unknown distance  $L$  between the abscissas, for the Euler–Lagrange equations resulting from a multiplier rule for the constrained optimization problem together with linear regression to improve the arc length estimate  $L$ . Matlab code for these numerical methods is provided which works only for “rich” optimal probability vectors. These methods motivate a definition of an elementary distance function which is easier and faster to calculate, works on non–rich vectors, does not involve variational theory and does not involve differential equations, but is a better approximation of the minimal entropy path distance than the distance  $\|\mathbf{b} - \mathbf{a}\|_2$ . We compute minimal entropy distance matrices for examples of DNA myostatin genes and amino-acid sequences across several species. Output tree dendograms for our minimal entropy metric are compared with dendograms based on BLAST and BLAST identity scores.

---

### 1. Introduction

Sequence alignment and analysis are among the most important and widely used techniques in computational molecular–biology. The realm of problems for which sequence analysis plays a part is extensive, but includes homology searching, gene finding, detection of open reading frames, protein structural/functional prediction, population and species structure inference.

One of the most commonly used techniques for sequence alignment is the Smith–Waterman dynamic programming algorithm for local alignment. Designed to detect highly conserved fragments in two sequences, it is highly

---

Calvin Ahlbrandt: Department of Mathematics, University of Missouri, Columbia, MO 65211–0001, calvin@math.missouri.edu

Gary Benson: Department of Biomathematical Sciences, Mount Sinai School of Medicine, 1 Gustave L. Levy Place, New York, NY 10029, benson@ecology.biomath.mssm.edu

William Casey: Courant Institute, New York University, 251 Mercer St, NYC, NY-10012, wcasey@cims.nyu.edu

**Key words:** ACGT sequences – entropy – probability vectors – probability paths – distance between genome families – constrained variational problems – Euler-Lagrange multiplier rules.

*Mathematics Subject Classification (1991):* 92B05, 92D20

informative but in general it has difficulty identifying two sequences which share a sufficiently long fragment with more than 70% similarity ([3]). This problem has led to innovative ideas including ‘n-mers’ and randomized hashing techniques ([9]). Local Sequence Alignment algorithms employing dynamical programming are similarity measures but not distance metrics. Global Sequence Alignment can use either similarity or distance measures. At the center of a similarity score is the substitution matrix, gap opening penalty, and gap extension penalty. A statistical theory relating the structure of the substitution matrix to identification of similarity in sequences is developed for un-gaped alignment ( gap penalty =  $\infty$  ). (See [8,1].)

In addition to dynamic programming alignment algorithms several similarity scores and metrics, which are independent of the order of characters, are in common use. These scores and distances may depend on frequency profile, size of sequence or a combination of both.

The technique developed in this paper is a distance metric on frequency profiles. This allows us to compare sequences based on their composition as a whole, rather than by sequence alignment.

Alignment between two profiles requires a function for comparing distributions. Such a scoring function  $F$ , given two probability distributions  $d_1$  and  $d_2$ , returns a measure of the similarity or distance between them. Functions  $F$  are called *divergence measures*. Preferred functions will take into account the ‘conserved nature’ of the distributions. A distribution is least conserved when each of the  $t$  possible alphabet characters occurs with frequency  $1/t$  and more conserved when one or two alphabet characters dominate. Two distributions should be judged closer if they share the same conserved characters than otherwise. A simple example of a function which disregards conserved nature is *variational distance*, the sum of differences in frequency for each letter in the distributions.

A variety of *entropy related functions* have been used as divergence measures. Examples are the relative entropy and the symmetric relative entropy [10,12]. These measures are excellent for detecting conserved nature, but are undefined (divide-by-zero) when one distribution has a character that the other lacks. Related functions include the  $K$ ,  $L$  and Jensen-Shannon divergence measures defined by Lin [12] and similar measures defined by Wong et al. [19]. These are relative entropy measures which compute similarity to an *average* or *weighted average* distribution and thereby avoid the divide-by-zero problem. But, these functions are extremely sensitive to the location of the average distribution relative to those being tested and can produce a range of similarity measures which span several orders of magnitude making them unsuitable for use in alignment algorithms.

A function commonly used in multiple alignment algorithms is the *sum-of-pairs*, based on the product of matching and mismatching letter frequencies. Related measures have been used by Cavalli-Sforza [6] and Nei [13]. In the case of DNA, where nucleotide bases are generally scored as either a match or a mismatch, this scheme inappropriately overemphasizes the mismatches and does not give consistent scores when distributions are identical (for example if both distributions are  $(A,C,G,T) = (1.0, 0, 0, 0)$  the sum-of-pairs score is much better than if both distributions are  $(A,C,G,T) = (0.5, 0, 0.5, 0)$ ).

We define a divergence measure  $d(\mathbf{a}, \mathbf{b})$  based on the shortest path between a pair of probability vectors  $\mathbf{a}$  and  $\mathbf{b}$  with the path constrained to lie on the entropy surface. A simplified elementary measure  $d_G(\mathbf{a}, \mathbf{b})$  is also defined. It can be computed in a case free manner whereas, thus far, we are only able to use our numerical package for solving the Euler–Lagrange equation in order to compute  $d(\mathbf{a}, \mathbf{b})$  whose optimal probability paths are smooth and have no zero components in their probability vectors. For probability paths with monotone components, it is shown that the distance function  $d_G$  may be used to find a lower bound for the more intuitive distance function  $d$ . These new distance functions do not base the comparison on an average distribution and give intuitively appealing distances between distributions.

The paper is organized as follows: Section 2, “Entropy distance of a path”, defines the objective functional and argument class as the set of paths in the space of measures on  $N$  categories. It is shown that the functional defines a metric satisfying the triangle inequality. Section 3, “Elementary distance”, explores the relation of the defined distance metric to the  $L^2$  norm. Section 4, “Computing the minimal entropy distance”, gives a formal argument of how the function minimization problem may be reformulated as a dynamical system. The features of this section are the formulation of a Lagrange–Multiplier rule, consistency and norm conditions, definition of the ROPI class of matrices. This section defines how a numerical procedure may commence for *rich* probability vectors. Section 5, “The deflated problem”, discusses how the  $L^1$  norm constraint may reduce the dimensionality of the problem in implementation. A full implementation and numerical method is presented. Section 6, “Myostatin gene and protein

examples”, presents the results of the new divergence method on a family of myostatin genes. Section 7, “Example  $N = 2$ ”, verifies the optimality of a given function is the lowest dimensional case. Section 8, “Software description and links”, gives access to numerical code which was used in the numerical examples.

## 2. Entropy distance of a path.

For  $p$  an  $N \times 1$  vector  $p = (p_i)$  with  $N \geq 2$ , then  $p$  is said to be a *probability vector* if  $p_i \geq 0$  for  $i = 1, \dots, N$  and  $\sum_{i=1}^N p_i = 1$ . The components  $p_i$  will be called the *state variables*. An entropy function  $H(p)$  is defined on the set of probability vectors by

$$H(p) = \sum_{i=1}^N p_i \log_2(1/p_i), \quad (1)$$

where  $p_i \log_2(1/p_i)$  is defined to be 0 if  $p_i = 0$ , since that is its limit as  $p_i \rightarrow 0+$ . This makes  $H$  a nonnegative continuous function of  $p$ . A probability vector  $p$  is *pure* if some  $p_i = 1$ , i.e.,  $p$  is an elementary vector. A probability vector  $p$  will be called *rich* if no  $p_i$  takes on the value of 0, i.e.,  $p$  is a positive probability vector. Since we assumed  $N \geq 2$ , we know that  $H(p)$  is positive if and only if  $p$  is not pure, i.e., only pure vectors have zero entropy. By the Lagrange multiplier rule,  $H(p)$  has maximum on the set of probability vectors  $p$  of  $\log_2(N)$  if and only if  $p$  is the uniform probability distribution of  $p_i := 1/N$ . Thus  $H(p)$  is a measure of disorder from a pure probability vector, where the entropy is 0, to a maximum which occurs only for the uniform probability distribution.

Let  $\mathbf{a}$  and  $\mathbf{b}$  be probability vectors in  $\mathbb{R}^N$ . A *probability path*  $p(t)$  is an  $N \times 1$  probability vector valued function defined for  $t \in [0, 1]$ . A probability path  $p(t)$  is said to be *admissible* if  $p(0) = \mathbf{a}$ ,  $p(1) = \mathbf{b}$ , and  $p(t)$  is *piecewise smooth* on  $[0, 1]$ , i.e.,  $p$  is continuously differentiable or there exist  $t_1, \dots, t_k$  with  $p$  continuous on  $[0, 1]$  and of class  $C^1$  on each  $[t_{i-1}, t_i]$ . Note that some component of  $p$  could have different finite one-sided derivatives at one or more  $t_i$ , i.e., a component of  $p$  could have “corners”.

Let us label the class of admissible probability paths from  $\mathbf{a}$  to  $\mathbf{b}$  as  $\mathcal{P}_{\mathbf{a}\mathbf{b}}$ . Define a functional  $E(p)$  on this admissible class  $\mathcal{P}_{\mathbf{a}\mathbf{b}}$  by

$$E(p) = \int_0^1 H(p(t)) \|p'(t)\|_2 dt. \quad (2)$$

For motivation, see the calculus formulation of line integrals along curves given in [17, Theorem 1, p. 974]. Our formulation entails a cost based not only on the path length but is weighted by the entropy along the path. A similar measure was described in [4]. The *variational principle* which we are formulating is that *the most efficient transition between probability state vectors is the probability path which minimizes the line integral of the entropy function*.

We defined a distance function  $d$  on pairs of probability vectors  $\mathbf{a}$ ,  $\mathbf{b}$  in  $\mathbb{R}^N$  as the infimum of  $E(p)$  on  $\mathcal{P}_{\mathbf{a}\mathbf{b}}$ , i.e.,

$$d(\mathbf{a}, \mathbf{b}) = \inf_{p \in \mathcal{P}_{\mathbf{a}\mathbf{b}}} E(p). \quad (3)$$

In order to establish that  $d$  is a *metric* we define a scalar function  $h(u)$  for  $u$  in  $[0, 1]$  by

$$h(0) = 0, \quad \text{and} \quad h(u) = u \log_2(1/u), \quad 0 < u \leq 1. \quad (4)$$

Then for  $u \in (0, 1]$  we have  $h(u) = -u \log_2(u) = u(-\ln u)/(\ln 2)$ . Replace  $u$  by  $1 - x$  and use the Maclaurin series of  $f(x) := -\ln(1 - x)$ , valid for  $|x| < 1$ , which gives

$$-\ln u = -\ln(1 - x) = \sum_{n=1}^{\infty} x^n/n.$$

Thus we have the series representation

$$h(u) = \frac{1}{\ln 2} \sum_{n=1}^{\infty} \frac{u(1-u)^n}{n}, \quad \text{valid for } 0 \leq u \leq 1. \quad (5)$$

Let  $\mathbb{P}^N$  be the set of  $N \times 1$  probability vectors.

**Proposition 1** *The distance function  $d : \mathbb{P}^N \times \mathbb{P}^N \rightarrow \mathbb{R}$  is a metric.*

*Proof:* If  $\mathbf{a}$  and  $\mathbf{b}$  are probability vectors in  $\mathbb{R}^N$ , then  $d(\mathbf{a}, \mathbf{b})$  is nonnegative since  $H$  is a nonnegative function. Also,  $d(\mathbf{a}, \mathbf{a}) = 0$  since  $E(p) = 0$  for  $p(t) := \mathbf{a}$  on  $[0, 1]$ .

Before we establish that  $\mathbf{a} \neq \mathbf{b}$  implies  $d(\mathbf{a}, \mathbf{b}) > 0$ , note that if  $p$  is admissible and joins  $\mathbf{a}$  to  $\mathbf{b}$ , then  $q(t) := p(1-t)$  has  $q(0) = \mathbf{b}$ ,  $q(1) = \mathbf{a}$ ,  $q$  is admissible, and  $E(p) = E(q)$ . Take the infimum over all  $p$  for  $d(\mathbf{a}, \mathbf{b}) = d(\mathbf{b}, \mathbf{a})$ , i.e., the distance is symmetric.

For the triangle inequality, let  $\mathbf{a}$ ,  $\mathbf{b}$ , and  $\mathbf{c}$  be probability vectors in  $\mathbb{R}^N$ . Consider admissible paths  $p \in \mathcal{P}_{\mathbf{a}\mathbf{b}}$  and  $q \in \mathcal{P}_{\mathbf{b}\mathbf{c}}$  and define a path  $r \in \mathcal{P}_{\mathbf{a}\mathbf{c}}$  by

$$r(t) = p(2t) \text{ if } t \in [0, .5] \text{ and } r(t) = q(2(t - .5)) \text{ if } t \in [.5, 1]. \quad (6)$$

Then

$$d(\mathbf{a}, \mathbf{b}) \leq E(r) = \int_0^{.5} H(p(2t)) \|2p'(2t)\|_2 dt + \int_{.5}^1 H(q(2(t - .5))) \|2q'(2(t - .5))\|_2 dt = E(p) + E(q)$$

and we have  $d(\mathbf{a}, \mathbf{b}) \leq E(p) + E(q)$  for all  $p \in \mathcal{P}_{\mathbf{a}\mathbf{b}}$  and all  $q \in \mathcal{P}_{\mathbf{b}\mathbf{c}}$ . Now take infimums over  $\mathcal{P}_{\mathbf{a}\mathbf{b}}$  and  $\mathcal{P}_{\mathbf{b}\mathbf{c}}$  to establish the triangle inequality.

We now complete the proof that  $d$  is a metric by showing that  $d$  satisfies  $d(\mathbf{a}, \mathbf{b}) > 0$  if  $\mathbf{a} \neq \mathbf{b}$ . Suppose  $\mathbf{a}$  and  $\mathbf{b}$  are distinct probability vectors in  $\mathbb{R}^N$ . Then there exists an index  $k$  such that  $a_k \neq b_k$ . Assume without loss of generality (by symmetry of  $d$ ) that  $a_k < b_k$ . Let  $p$  be in  $\mathcal{P}_{\mathbf{a}\mathbf{b}}$ . Then

$$\begin{aligned} E(p) &= \int_0^1 H(p(t)) \|p'(t)\|_2 dt \geq \int_0^1 h(p_k(t)) \|p'(t)\|_2 dt \\ &\geq \int_0^1 h(p_k(t)) |p'_k(t)| dt \geq \int_0^1 h(p_k(t)) p'_k(t) dt = \int_{a_k}^{b_k} h(u) du \end{aligned} \quad (7)$$

Since  $0 \leq a_k < b_k \leq 1$  and equation (5) implies the lower bound  $h(u) \geq u(1-u)/(\ln 2)$ , for  $0 \leq u \leq 1$ , we know that

$$E(p) \geq \frac{1}{\ln 2} \int_{a_k}^{b_k} u(1-u) du > 0.$$

Since  $E(p)$  is bounded away from 0 and that bound depends only upon  $a_k$  and  $b_k$  and is therefore independent of the choice of path  $p$  between  $\mathbf{a}$  and  $\mathbf{b}$ , then the infimum over  $\mathcal{P}_{\mathbf{a}\mathbf{b}}$  is bounded away from 0 and  $d(\mathbf{a}, \mathbf{b}) > 0$ .  $\blacksquare$

### 3. An elementary distance

We use the above calculation to motivate the definition of an elementary distance function. Modify the above argument as follows. Suppose that  $\mathbf{a}$  and  $\mathbf{b}$  are probability vectors in  $\mathbb{R}^N$  and  $p$  is an admissible probability path joining  $\mathbf{a}$  to  $\mathbf{b}$ . Then the norm bound on  $\mathbb{R}^N$  of  $\|x\|_2 \geq N^{-1/2} \|x\|_1$  [16, p. 170] and  $h$  defined by equation (4) imply

$$\begin{aligned} E(p) &= \int_0^1 \sum_{k=1}^N h(p_k(t)) \|p'(t)\|_2 dt \\ &\geq \frac{1}{\sqrt{N}} \int_0^1 \left( \sum_{k=1}^N h(p_k(t)) \right) \left( \sum_{k=1}^N |p'_k(t)| \right) dt \\ &\geq \frac{1}{\sqrt{N}} \int_0^1 \left( \sum_{k=1}^N h(p_k(t)) |p'_k(t)| \right) dt \geq \frac{1}{\sqrt{N}} \sum_{k=1}^N \int_0^1 h(p_k(t)) p'_k(t) dt \\ &= \frac{1}{\sqrt{N}} \sum_{k=1}^N \int_{a_k}^{b_k} h(u) du . \end{aligned} \quad (8)$$

Let  $g(u) := (\ln 2)h(u) = u \ln(1/u) = -u \ln u$  for  $0 < u \leq 1$  and  $g(0) := 0$ . Choose the antiderivative

$$G(u) = u^2((1/2) - \ln u)/2 \quad \text{for } 0 < u \leq 1 \quad \text{and} \quad G(0) = 0. \quad (9)$$

Define a distance  $d_G(\mathbf{a}, \mathbf{b})$  by

$$d_G(\mathbf{a}, \mathbf{b}) := \frac{\sqrt{2}}{\ln 2} \sum_{k=1}^N |G(b_k) - G(a_k)|. \quad (10)$$

The factor of  $\sqrt{2}$  in the numerator was an arbitrary choice made to improve the comparison with  $d(\mathbf{a}, \mathbf{b})$  when  $N$  is 2. Note that as for  $d$ , the above  $d_G$  has the property that if  $M$  additional zeros are appended after the last components of  $\mathbf{a}$  and  $\mathbf{b}$  to produce vectors  $\hat{\mathbf{a}}$  and  $\hat{\mathbf{b}}$  in  $R^{N+M}$ , then  $d_G(\hat{\mathbf{a}}, \hat{\mathbf{b}}) = d_G(\mathbf{a}, \mathbf{b})$ . We now compare  $d_G(\mathbf{a}, \mathbf{b})$  to  $E(p)$  for  $p \in \mathcal{P}_{\mathbf{a}\mathbf{b}}$  with monotone components.

**Proposition 2** *Suppose  $\mathbf{a}$  and  $\mathbf{b}$  are joined by an admissible  $p$  which has monotone components. Then*

$$d_G(\mathbf{a}, \mathbf{b}) \leq (\sqrt{2N})E(p). \quad (11)$$

*Proof:* If  $p_k'(t)$  is of constant sign, then

$$\int_0^1 g(p_k(t))|p_k'(t)| dt = (\pm 1) \int_0^1 g(p_k(t))p_k'(t) dt = (\pm 1) \int_{a_k}^{b_k} g(u) du = |G(b_k) - G(a_k)|. \quad \blacksquare$$

Examples show that minimizing paths need not have monotone components if  $N > 2$ , although they do for  $N = 2$ . Before discussing how we estimate  $d(\mathbf{a}, \mathbf{b})$ , we give an example.

**Example 3** *Suppose that  $N \geq 2$  and  $e_j$ , for  $j = 1, \dots, N$ , is the elementary vector  $[\delta_{i,j}]$  and  $\mathbf{c}^N$  is the centroid of the simplex  $\mathbb{P}^N$ , i.e.,  $\mathbf{c}^N = [1/N \dots 1/N]^T$ . If  $i \neq j$ , then an estimate for  $d(e_i, e_j)$  is 1.0201 and estimates for  $d(\mathbf{c}^N, e_j)$  are 0.51006 for  $N = 2$ ; 0.9125 for  $N = 3$ ; and 1.2020 for  $N = 4$ .*

**Remark 4** *If  $\mathbf{a}$  and  $\mathbf{b}$  are near the centroid  $\mathbf{c}^N$  of  $\mathbb{P}^N$ , then  $d(\mathbf{a}, \mathbf{b})$  is approximated by  $(\log_2 N)\|\mathbf{b} - \mathbf{a}\|_2$  since in a neighborhood of  $\mathbf{c}^N$ , the entropy function has a maximum of  $\log_2 N$  and  $\|\mathbf{b} - \mathbf{a}\|_2$  is an approximation of the arc length of the minimizing curve.*

#### 4. Computing the minimal entropy distance

The variational problem as stated requires the paths  $p(t)$  to satisfy the  $N + 1$  constraints

$$\sum_{i=1}^N p_i(t) = 1 \quad \text{and for each } i = 1, \dots, N, \quad p_i(t) \geq 0 \quad \text{on } [0, 1]. \quad (12)$$

In order to formulate the minimal entropy problem as a constrained variational problem with a single equality constraint, introduce *hidden variables*  $q_i$  which satisfy

$$q_i^2 = p_i, \quad i = 1, \dots, N. \quad (13)$$

Then  $p_i(t) \geq 0$ . Also,  $\sum_{i=1}^N p_i = 1$  if and only if  $\sum_{i=1}^N q_i^2 = 1$ . Suppose that  $\mathbf{c}$  and  $\mathbf{d}$  are vectors in  $\mathbb{R}^N$  with  $c_i^2 = a_i$  and  $d_i^2 = b_i$  for  $i = 1, \dots, N$ . Define a function  $K(q)$  by

$$K(q) := H(p) = \sum_{i=1}^N q_i^2 \log_2(1/q_i^2). \quad (14)$$

Then the *hidden variational problem* is that of minimizing the functional

$$J(q) = \int_0^1 2K(q(t)) \left\{ \sum_{i=1}^N q_i^2(t) [q_i'(t)]^2 \right\}^{1/2} dt \quad (15)$$

on the class  $\mathcal{Q}_{\mathbf{c}\mathbf{d}}$  of admissible piecewise smooth  $q$  defined on  $[0, 1]$  which satisfy

$$q(0) = \mathbf{c}, \quad q(1) = \mathbf{d}, \quad \text{and} \quad \|q(t)\|_2^2 \equiv 1 \quad \text{on} \quad [0, 1]. \quad (16)$$

If  $q \in \mathcal{Q}_{\mathbf{c}\mathbf{d}}$  and  $p$  is defined by  $p_i = q_i^2$  for  $i = 1, \dots, N$ , then  $p \in \mathcal{P}_{\mathbf{a}\mathbf{b}}$ . If, on the other hand,  $q$  is defined for  $p \in \mathcal{P}_{\mathbf{a}\mathbf{b}}$  by  $q_i = \sqrt{p_i}$ , for  $i = 1, \dots, N$ , we ask if  $q$  is in  $\mathcal{Q}_{\mathbf{c}\mathbf{d}}$ ? Since the square root function is continuous on  $[0, \infty)$ , the  $q_i$  are continuous on  $[0, 1]$ . However, the square root function of a real variable is differentiable on  $(0, \infty)$  but does not have a right hand derivative at 0. Thus a  $q_i$  might fail to have one-sided derivatives at zeros of  $q_i$ . For example, the real valued function  $f$  defined on  $[0, 1]$  by  $f(t) = |t - 1/2|$  is piecewise smooth and nonnegative on  $[0, 1]$  but  $g$  defined by  $g(t) = \sqrt{f(t)}$  fails to have one sided derivatives at  $t = 1/2$ .

A probability path  $p(t)$  will be called *rich* if no  $p_i(t)$  takes on the value of 0. We will usually suppose that the vectors  $\mathbf{a}$  and  $\mathbf{b}$  are rich. The subset of  $\mathcal{P}_{\mathbf{a}\mathbf{b}}$  consisting of rich probability paths will be denoted by  $\mathcal{P}_{\mathbf{a}\mathbf{b}}^{\text{rich}}$ . The subset of  $\mathcal{Q}_{\mathbf{c}\mathbf{d}}$  consisting of admissible  $q(t)$  which have each  $q_i(t)$  positive on  $[0, 1]$  will be denoted by  $\mathcal{Q}_{\mathbf{c}\mathbf{d}}^{\text{pos}}$ . If  $p \in \mathcal{P}_{\mathbf{a}\mathbf{b}}^{\text{rich}}$  and  $q$  is defined by  $q_i(t) = \sqrt{p_i(t)}$  for each  $i = 1, \dots, N$  and each  $t \in [0, 1]$ , then  $q \in \mathcal{Q}_{\mathbf{c}\mathbf{d}}^{\text{pos}}$ . Conversely, if  $q \in \mathcal{Q}_{\mathbf{c}\mathbf{d}}^{\text{pos}}$  and  $p$  is defined by (13), then  $p \in \mathcal{P}_{\mathbf{a}\mathbf{b}}^{\text{rich}}$ .

**Theorem 5 (Equivalent Minimization Problems)** *Suppose  $\hat{q} \in \mathcal{Q}_{\mathbf{c}\mathbf{d}}^{\text{pos}}$  and  $\hat{p} \in \mathcal{P}_{\mathbf{a}\mathbf{b}}^{\text{rich}}$  are related by  $\hat{q}_i(t) = \sqrt{\hat{p}_i(t)}$  for  $i = 1, \dots, N$ . Then  $E(\hat{p}) = J(\hat{q})$  and  $\hat{p}$  minimizes  $E$  on  $\mathcal{P}_{\mathbf{a}\mathbf{b}}^{\text{rich}}$  if and only if  $\hat{q}$  minimizes  $J$  on  $\mathcal{Q}_{\mathbf{c}\mathbf{d}}^{\text{pos}}$ .*

*Proof:* Suppose  $p \in \mathcal{P}_{\mathbf{a}\mathbf{b}}^{\text{rich}}$  and  $q \in \mathcal{Q}_{\mathbf{c}\mathbf{d}}^{\text{pos}}$  are related on  $[0, 1]$  by  $q_i(t) = \sqrt{p_i(t)}$  for each  $i = 1, \dots, N$ . If  $\hat{p}$  minimizes  $E$  on  $\mathcal{P}_{\mathbf{a}\mathbf{b}}^{\text{rich}}$  then

$$J(\hat{q}) = E(\hat{p}) \leq E(p) = J(q)$$

and  $\hat{q}$  minimizes  $J$  on  $\mathcal{Q}_{\mathbf{c}\mathbf{d}}^{\text{pos}}$ . Conversely, if  $\hat{q}$  minimizes  $J$  on  $\mathcal{Q}_{\mathbf{c}\mathbf{d}}^{\text{pos}}$ , then

$$E(\hat{p}) = J(\hat{q}) \leq J(q) = E(p)$$

and  $\hat{p}$  minimizes  $E$  on  $\mathcal{P}_{\mathbf{a}\mathbf{b}}^{\text{rich}}$ . ■

Note that this theorem does not say that the variational problem of minimizing  $E$  on  $\mathcal{P}_{\mathbf{a}\mathbf{b}}$  is equivalent to the variational problem of minimizing  $J$  on  $\mathcal{Q}_{\mathbf{c}\mathbf{d}}$ . It could be that a minimizer  $p$  for  $E$  on  $\mathcal{P}_{\mathbf{a}\mathbf{b}}$ , while piecewise smooth, would not allow definition of a piecewise smooth  $q$ .

In order to use variational methods, we assume that the hidden problem has the property that  $J$  has a minimum on  $\mathcal{Q}_{\mathbf{c}\mathbf{d}}$  which is assumed by a  $q$  in  $\mathcal{Q}_{\mathbf{c}\mathbf{d}}^{\text{pos}}$ . Then the corresponding  $p$  is a candidate for minimizing  $E$  on  $\mathcal{P}_{\mathbf{a}\mathbf{b}}$  and  $p$  is actually a rich probability path. When the numerics for approximating a function  $q$  in  $\mathcal{Q}_{\mathbf{c}\mathbf{d}}^{\text{pos}}$ , of the boundary value problem arising in the Euler–Lagrange multiplier rule fail, then failure could be caused by flawed code, limitations on the numerical methods, or because the assumption of a rich minimizer for  $E$  on  $\mathcal{P}_{\mathbf{a}\mathbf{b}}$  is invalid, possibly because smaller values of  $E$  can be attained with a probability path having corners.

We seek positive minimizers for  $J$  because the hidden variational problem has a single differentiable side condition and is amenable to the Lagrange multiplier method.

Suppose we succeed in finding a minimizer  $\hat{q}$  for  $J$  on  $\mathcal{Q}_{\mathbf{c}\mathbf{d}}$  which is in  $\mathcal{Q}_{\mathbf{c}\mathbf{d}}^{\text{pos}}$ . Then  $\hat{q}$  is a minimizer for  $J$  on  $\mathcal{Q}_{\mathbf{c}\mathbf{d}}^{\text{pos}}$  and the corresponding  $\hat{p}$  is a minimizer for  $E$  on the subclass  $\mathcal{P}_{\mathbf{a}\mathbf{b}}^{\text{rich}}$ .

Once we have a minimizer  $q$  for  $J$ , it may be possible to numerically check by other methods (such as Dijkstra’s algorithm) that the corresponding  $p$  approximates a minimum for  $E$  on  $\mathcal{P}_{\mathbf{a}\mathbf{b}}$ .

In order to state the multiplier rule, introduce the following terminology and notation. For  $p$  a probability path, let  $v(t) := p'(t)$ , and think of  $v$  as the “velocity vector”. Set  $V(v) := \|v\|_2$ . Then

$$V(p'(t)) = \|p'(t)\|_2 = \left\{ \sum_{i=1}^N [p_i'(t)]^2 \right\}^{1/2} = \left\{ \sum_{i=1}^N [2q_i(t)q_i'(t)]^2 \right\}^{1/2}.$$

Let  $W(q, r) := \{\sum_{i=1}^N [2q_i r_i]^2\}^{1/2}$  and  $M(q, r) := K(q)W(q, r)$ . In this notation we have

$$E(p) = \int_0^1 L(p(t), p'(t)) dt$$

for  $L(p, v) = H(p)V(v)$  and

$$J(q) = \int_0^1 M(q(t), q'(t)) dt = \int_0^1 K(q(t)) W(q(t), q'(t)) dt.$$

We now give the multiplier rule for the problem of minimizing  $J$  on  $\mathcal{Q}_{\mathbf{cd}}$ . Introduce an *auxiliary function*

$$\begin{aligned} F(q, r) &:= \lambda_0 M(q, r) + \lambda_1 g(q), \quad \text{where} \\ g(q) &:= \|q\|_2^2 = \sum_{i=1}^N q_i^2. \end{aligned} \quad (17)$$

From Ewing, [7, Thm 5.2, p. 115], we have the following multiplier rule.

**Theorem 6 (Lagrange Multiplier Rule)** *Suppose that  $\hat{q} \in C^1$  is a minimizer for the hidden variational problem such that each component  $\hat{q}_i(t)$  is never 0 on  $[0, 1]$ . Then there exist multipliers  $\lambda_0$ , a real constant, and a function  $\lambda_1(t)$ , not simultaneously 0 at any point of  $[0, 1]$ , such that the auxiliary function  $F$  satisfies the Euler–Lagrange equation*

$$\frac{d}{dt} F_r(\hat{q}(t), \hat{q}'(t)) = F_q(\hat{q}(t), \hat{q}'(t)) \quad \text{on } [0, 1]. \quad (18)$$

Here  $F_q$  and  $F_r$  denote the  $N \times 1$  column vectors  $[F_{q_i}]$  and  $[F_{r_i}]$ , respectively.

If  $\lambda_0 = 0$ , then it follows that  $\lambda_1(t)q_i(t) \equiv 0$  from which  $q(t)$  would have to be identically the zero vector contrary to  $\|q(t)\|^2 = 1$ . Thus, the problem is “normal” and, without loss of generality, we may choose  $\lambda_0 = 1$ . Denote  $\lambda_1(t)$  by  $\lambda(t)$ . Now  $F(q, r) = M(q, r) + \lambda g(q) = K(q)W(q, r) + \lambda g(q)$  gives

$$\begin{aligned} F_{q_i} &= K_{q_i} W + K W_{q_i} + \lambda g_{q_i} \\ F_{r_i} &= K W_{r_i} \end{aligned} \quad (19)$$

and the Euler–Lagrange multiplier rule is

$$\frac{d}{dt} \{K W_{r_i}\} = K_{q_i} W + K W_{q_i} + \lambda g_{q_i} \quad i = 1, \dots, N, \quad (20)$$

where the functions are evaluated at  $(\hat{q}(t), \hat{q}'(t))$ . These equations become

$$\begin{aligned} \frac{d}{dt} \left\{ K(q) \frac{4q_i^2 q'_i}{\{\sum_{j=1}^N [2q_j q'_j]^2\}^{1/2}} \right\} &= 2\lambda q_i + \\ K(q) \left\{ \frac{4q_i (q'_i)^2}{\{\sum_{j=1}^N [2q_j q'_j]^2\}^{1/2}} \right\} &+ \left[ 2q_i \log_2\left(\frac{1}{q_i^2}\right) - \frac{2q_i}{\ln 2} \right] \left\{ \sum_{j=1}^N [2q_j q'_j]^2 \right\}^{1/2}, \end{aligned}$$

for  $i = 1, \dots, N$ . Multiply the  $i$ th equation by  $q_i$  and use  $p'_i = 2q_i q'_i$  for

$$q_i \frac{d}{dt} \left\{ K(q) \frac{4q_i^2 q'_i}{\|p'\|} \right\} = 2\lambda q_i^2 + K(q) \frac{(p'_i)^2}{\|p'\|} + \left[ 2q_i^2 \log_2\left(\frac{1}{q_i^2}\right) - \frac{2q_i^2}{\ln 2} \right] \|p'\|.$$

Apply  $uv' = (uv)' - u'v$  to the left hand side to obtain

$$\frac{d}{dt} \left\{ K(q) \frac{4q_i^3 q'_i}{\|p'\|} \right\} = 2\lambda q_i^2 + 2K(q) \frac{(p'_i)^2}{\|p'\|} + \left[ 2q_i^2 \log_2\left(\frac{1}{q_i^2}\right) - \frac{2q_i^2}{\ln 2} \right] \|p'\|.$$

Remove a factor of 2 for

$$\frac{d}{dt} \left\{ K(q) \frac{q_i^2 (2q_i q'_i)}{\|p'\|} \right\} = \lambda q_i^2 + K(q) \frac{(p'_i)^2}{\|p'\|} + \left[ q_i^2 \log_2 \left( \frac{1}{q_i^2} \right) - \frac{q_i^2}{\ln 2} \right] \|p'\|$$

which may be expressed in  $p$  variables as

$$\frac{d}{dt} \left\{ H(p) \frac{p_i p'_i}{\|p'\|} \right\} = \lambda p_i + H(p) \left[ \frac{(p'_i)^2}{\|p'\|} \right] + \left[ p_i \log_2 \left( \frac{1}{p_i} \right) - \frac{p_i}{\ln 2} \right] \|p'\|. \quad (21)$$

Change to a dummy index of  $j$ , sum from  $j = 1$  to  $j = N$ , and use the fact that  $p$  is a probability vector to express the multiplier in terms of  $p$  and  $p'$

$$\lambda = \left[ \frac{1}{\ln 2} - 2H(p) \right] \|p'\| + \sum_{j=1}^N \frac{d}{dt} \left\{ H(p) \frac{p_j p'_j}{\|p'\|} \right\}. \quad (22)$$

This is the first step. Now substitute for  $\lambda$  in equation (21) for the resulting Euler–Lagrange system of equations in terms of state and velocity vectors

$$\begin{aligned} \frac{d}{dt} \left\{ H(p) \frac{p_i p'_i}{\|p'\|} \right\} &= -2p_i H(p) \|p'\| + p_i \sum_{j=1}^N \frac{d}{dt} \left\{ H(p) \frac{p_j p'_j}{\|p'\|} \right\} \\ &\quad + H(p) \left[ \frac{(p'_i)^2}{\|p'\|} \right] + \left[ p_i \log_2 \left( \frac{1}{p_i} \right) \right] \|p'\| \end{aligned} \quad (23)$$

for  $i = 1, \dots, N$ . These equations become tractable if one makes the assumption that  $\|p'(t)\|$  is always positive on  $[0,1]$  and then (as in differential geometry) makes a change of independent variable from  $t$  to arc length  $s$ , i.e.,

$$s := \int_0^t \|p'(\tau)\| d\tau.$$

Let  $L = \int_0^1 \|p'(\tau)\| d\tau$ , i.e.,  $L$  is the arc length of the optimal probability path. Then let  $y(s) := p(t)$  and let an overdot be differentiation with respect to  $s$ . Since  $\frac{ds}{dt} = \|p'(t)\|$ , the chain rule applied to any differentiable function  $u(t)$  gives

$$\frac{du}{dt} = \frac{du}{ds} \frac{ds}{dt} = \dot{u}(s) \|p'(t)\|$$

which implies

$$\frac{1}{\|p'(t)\|} \frac{du}{dt} = \dot{u}(s).$$

Thus  $p'_j / \|p'\| = \dot{y}_j$ . Divide system (23) by  $\|p'\|$  and replace  $p(t)$  by  $y(s)$  for the equivalent Euler–Lagrange equation

$$\begin{aligned} \frac{d}{ds} \{ H(y) y_i \dot{y}_i \} &= -2y_i H(y) + y_i \sum_{j=1}^N \frac{d}{ds} \{ H(y) y_j \dot{y}_j \} \\ &\quad + H(y) (\dot{y}_i)^2 + y_i \log_2 \left( \frac{1}{y_i} \right), \end{aligned} \quad (24)$$

for  $i = 1, \dots, N$ . Define  $z$  by

$$z_j(s) := y_j(s) \dot{y}_j(s) H(y(s)) \quad (25)$$

for  $j = 1, \dots, N$ . Equation (24) becomes

$$\dot{z}_i - y_i \sum_{j=1}^N \dot{z}_j = -2y_i H(y) + (\dot{y}_i)^2 H(y) + y_i \log_2(1/y_i), \quad i = 1, \dots, N. \quad (26)$$

Then express  $\dot{y}_i$  in terms of  $H(y)$ ,  $y_i$ , and  $z_i$ . It will be possible to solve for  $\dot{y}_i$  as

$$\dot{y}_i = P_i(y, z) := \frac{z_i}{y_i H(y)}, \quad i = 1, \dots, N, \quad (27)$$

if we use the assumption that the  $q_i$  never vanish. Then our probability path is *rich*, i.e., no  $p_i(t)$  takes on the value of 0 at any  $t \in [0, 1]$ . Rewrite equation (26) as

$$\begin{aligned} \dot{z}_i - y_i \sum_{j=1}^N \dot{z}_j &= R_i(y, z) \\ &:= -2y_i H(y) + \frac{z_i^2}{y_i^2 H(y)} + y_i \log_2(1/y_i), \quad i = 1, \dots, N. \end{aligned} \quad (28)$$

Let

$$A(y) := \begin{bmatrix} 1 - y_1 & -y_1 & -y_1 & \dots & -y_1 \\ -y_2 & 1 - y_2 & -y_2 & \dots & -y_2 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ -y_N & -y_N & -y_N & \dots & 1 - y_N \end{bmatrix} = I_N - yw^T, \quad (29)$$

where  $w^T := [1 \ 1 \ \dots \ 1]$ . Then equation (28) may be written as

$$A(y)\dot{z} = R(y, z) \quad (30)$$

An  $N$ -vector  $y$  will be called *positive* if each  $y_i$  is positive [11, p. 352].

**Theorem 7 (Consistency and Norm Conditions)** *If  $y, z$  is a solution of the system*

$$\dot{y} = P(y, z), \quad A(y)\dot{z} = R(y, z) \quad (31)$$

*on  $[0, L]$  with  $y(s)$  a rich probability vector for every  $s \in [0, L]$ , then  $y, z$  satisfies the “consistency condition”*

$$\sum_{i=1}^N z_i/y_i \equiv 0 \quad \text{on } [0, L] \quad (32)$$

*and the “norm condition”*

$$\frac{1}{(H(y))^2} \sum_{i=1}^N \frac{z_i^2}{y_i^2} \equiv 1 \quad \text{on } [0, L], \quad (33)$$

*i.e.,  $\|\dot{y}(s)\|_2 \equiv 1$  on  $[0, L]$ . Conversely, if  $y, z$  is a solution of (31) with  $y(s)$  a positive vector on  $[0, L]$  such that the consistency condition is satisfied, then  $\sum_{i=1}^N y_i(s)$  is constant on  $[0, L]$ ; if, in addition,  $y(0)$  is a probability vector, then  $y(s)$  is a probability vector for each  $s \in [0, L]$  and  $\|\dot{y}(s)\|_2 \equiv 1$  on  $[0, L]$ .*

*Proof.* If  $y$  is a probability vector, then  $\sum_{i=1}^N \dot{y}_i \equiv \frac{d}{ds} 1 \equiv 0$ . Sum equation (27) on  $i$  for the consistency condition. Summing equation (28) on  $i$  gives

$$0 = -2H(y) + \frac{1}{H(y)} \sum_{i=1}^N \frac{z_i^2}{y_i^2} + H(y) = -H(y) + \frac{1}{H(y)} \sum_{i=1}^N \frac{z_i^2}{y_i^2}.$$

Thus  $1 = (1/H(y))^2 \sum_{i=1}^N z_i^2/y_i^2 = \sum_{i=1}^N (\dot{y}_i)^2 = \|\dot{y}\|^2$ . Conversely, the consistency condition and summing of (27) implies that  $\sum_{i=1}^N \dot{y}_i$  is 0 and  $\sum_{i=1}^N y_i$  is constant.  $\blacksquare$

In order to numerically approximate solutions of (31) by methods for autonomous vector systems, we would like to replace that system with a system

$$\dot{y} = P(y, z) \quad \dot{z} = Q(y, z) \quad (34)$$

**Theorem 8 (Explicit E–L System)** *Assume that  $y$  is a rich probability path on  $[0, L]$  and  $y, z$  is a solution of (31) on  $[0, L]$  with  $P, R,$  and  $A$  defined by (27), (28), and (29), respectively. Then  $y, z$  satisfies the consistency condition (32) on  $[0, L]$ ,  $\|\dot{y}\| \equiv 1$ , and there exists a continuous  $Q(y, z)$  such that  $y, z$  is a solution of the system (34) on  $[0, L]$ .*

Before presenting a construction of  $Q$ , which suggests code for use of a numerical integration package, we need some general comments about matrices of the form of  $A(y)$ . Observe that  $A(y)$  is of a more general form than a Householder matrix, i.e., an elementary reflector,  $H := I - 2uu^T$  where  $u^T u = 1$ , which has the properties  $H^T = H$ ,  $H^2 = I$  and hence  $H^{-1} = H$ . [16, p. 45]. Observe that  $A(y)$  of equation (29) and Householder matrices  $H$  share the property of being *rank one perturbations of  $I$* .

In a wider sense, the concept of rank one perturbations of matrices, or of operators, has been employed previously by Wilkinson [18] in finding a nearest singular matrix to a given nonsingular matrix and in the study of sensitivity of eigenvalues of matrices; also Simon [15] gave a spectral analysis of rank one perturbations of a positive selfadjoint operator on a separable Hilbert space.

The acronym *ROPI* will denote a special class of rank one perturbations of  $I$  defined as follows:

**Definition 9 (ROPI Matrices)** *Let  $\gamma \neq 0$  and consider nonzero  $N \times 1$  vectors of real numbers  $y$  and  $w$ . If  $\delta := w^T y$  is such that  $\gamma\delta \neq -1$ , then the  $N \times N$  matrix  $A$ , called a *ROPI matrix*, is defined by*

$$A = I_N + \gamma y w^T. \quad (35)$$

**Theorem 10 (Inverses of ROPI Matrices)** *If  $A = I_N + \gamma y w^T$  is a *ROPI matrix*, then  $A$  is nonsingular,  $A^{-1}$  is *ROPI*, and*

$$A^{-1} = I_N - \left( \frac{\gamma}{1 + \gamma\delta} \right) y w^T \quad (36)$$

*Proof.* Let  $B = \gamma y w^T$ . Then  $A = I + B$  and

$$B^2 = \gamma y w^T (\gamma y w^T) = \gamma^2 y (w^T y) w^T = \gamma^2 y \delta w^T = \gamma\delta (\gamma y w^T) = \gamma\delta B.$$

Replace  $B$  by  $A - I$  to obtain

$$(A - I)^2 = \gamma\delta(A - I) \quad \text{which implies} \quad A[A - (2 + \gamma\delta)I] = -(1 + \gamma\delta)I.$$

The assumption  $\gamma\delta \neq -1$  implies that  $A$  has an inverse which is given by

$$A^{-1} = - \left( \frac{1}{1 + \gamma\delta} \right) [A - (2 + \gamma\delta)I] = - \left( \frac{1}{1 + \gamma\delta} \right) [I + \gamma y w^T - (2 + \gamma\delta)I]$$

and  $A^{-1} = I - \frac{\gamma}{1 + \gamma\delta} y w^T$  as claimed. ■

Unfortunately, in our application the matrix  $A(y)$  defined by (29) does not have an inverse if  $y$  is a probability vector. In that case, every column of  $A(y)$  sums to 0 and the rows of  $A(y)$  are linearly dependent. Thus  $A(y)$  is singular. Also,  $\gamma = -1$  and  $\delta = w^T y = 1$  imply  $\gamma\delta = -1$ , contrary to our definition of a ROPI matrix. However, since the system of equations  $A(y)\dot{z} = R(y, z)$  is redundant, any one equation, say the  $k$ th equation, may be deleted without loss of information if we carry along the consistency condition. The concept of ROPI matrices then may be applied to the deflated problem.

*Proof of Theorem 8.* Suppose that  $y$  is a rich probability vector and  $k \in \{1, \dots, N\}$ . If  $z$  is an  $N \times 1$  matrix, let  $z^{[k]}$  be the  $(N - 1) \times 1$  matrix, i.e, column vector, obtained by deleting the  $k$ th entry of  $z$ . For the  $N \times N$  matrix  $A$ , let  $A^{[k]}$  be the submatrix obtained from  $A$  by deleting the  $k$ th row and  $k$ th column from  $A$ . Then

$A^{[k]} = I_{N-1} - y^{[k]}(w^{[k]})^T$  has  $\delta = (w^{[k]})^T y^{[k]} = \sum_{j \neq k} y_j = 1 - y_k$ . Since  $\gamma = -1$ , we have  $\gamma\delta = y_k - 1 \neq -1$  and the matrix  $A^{[k]}$  is ROPI with inverse

$$(A^{[k]})^{-1} = I_{N-1} + \frac{1}{y_k} y^{[k]} (w^{[k]})^T. \quad (37)$$

For  $i \neq k$ , equation (28) implies

$$\dot{z}_i - y_i \sum_{j \neq k} \dot{z}_j = R_i(y, z) + y_i \dot{z}_k \quad (38)$$

and we have shown that any solution of system (30) satisfies the system

$$A^{[k]} \dot{z}^{[k]} = R^{[k]} + y^{[k]} \dot{z}_k. \quad (39)$$

Use the above form of the inverse of  $A^{[k]}$  to obtain

$$\dot{z}^{[k]} = S + T \dot{z}_k, \quad \text{for } S := R^{[k]} + \frac{\sum_{j \neq k} R_j}{y_k} y^{[k]} \quad \text{and} \quad T := \frac{1}{y_k} y^{[k]} \quad (40)$$

If we remove dependence upon  $y_k$  by writing  $y_k = 1 - \sum_{j \neq k} y_j$ , we have

$$S = R^{[k]} + \frac{\sum_{j \neq k} R_j}{1 - \sum_{j \neq k} y_j} y^{[k]} \quad \text{and} \quad T := \frac{1}{1 - \sum_{j \neq k} y_j} y^{[k]} \quad (41)$$

It is convenient to label the entries of the  $(N-1) \times 1$  column vectors  $S$  and  $T$  as  $(S_i)$  and  $(T_i)$  for  $i \neq k$ . Then each  $\dot{z}_i$ , for  $i \neq k$ , has the form

$$\dot{z}_i = S_i + T_i \dot{z}_k, \quad \text{for } i \neq k. \quad (42)$$

Another condition is needed in order to determine  $\dot{z}_k$  in terms of  $y$  and  $z$ . Differentiate the consistency condition (32) with respect to  $s$  to obtain

$$\frac{\dot{z}_k}{y_k} + \sum_{i \neq k} \frac{\dot{z}_i}{y_i} = \sum_{i=1}^N \frac{z_i \dot{y}_i}{y_i^2} = \frac{1}{H(y)} \sum_{i=1}^N \frac{z_i^2}{y_i^3}. \quad (43)$$

Replace each  $\dot{z}_i$ , for  $i \neq k$ , on the left by using (42) to obtain the equation in  $\dot{z}_k$  of

$$U \dot{z}_k + V = W, \quad (44)$$

for

$$U := \frac{1}{y_k} + \sum_{i \neq k} \frac{T_i}{y_i} = \frac{N}{y_k}, \quad V := \sum_{i \neq k} \frac{S_i}{y_i}, \quad \text{and} \quad W := \frac{1}{H(y)} \sum_{i=1}^N \frac{z_i^2}{y_i^3}. \quad (45)$$

Thus  $U > 0$  and

$$\dot{z}_k = (W - V)/U = \frac{y_k}{N} (W - V) := X := Q_k(y, z). \quad (46)$$

Replace  $\dot{z}_k$  by this value in each of the equations (42) to obtain

$$\dot{z}_i = S_i + X T_i := Q_i(y, z), \quad \text{for } i \neq k, \quad (47)$$

which provides a construction of  $Q$  of Theorem 8. ■

## 5. The Deflated Problem

Assume that  $\mathbf{a}$  is a rich probability vector. Reorder the entries of  $\mathbf{a}$  so that

$$a_1 \geq a_2 \geq \dots a_N > 0.$$

If  $P$  is a permutation matrix such that  $P\mathbf{a}$  has entries in descending order, then replace  $\mathbf{a}$  by  $P\mathbf{a}$  and  $\mathbf{b}$  by  $P\mathbf{b}$  before trying to find a minimizing probability path  $p \in \mathcal{P}_{\mathbf{a}\mathbf{b}}$ . Matlab's `sort`, which sorts in ascending order may be employed to accomplish this reordering by the commands

$$[aa, I] = \text{sort}(-a), \quad a = a(I), \quad b = b(I). \quad (48)$$

Simultaneous reordering of  $\mathbf{a}$  and  $\mathbf{b}$  by the same permutation matrix  $P$  will not change  $d$ , i.e.,  $d(P\mathbf{a}, P\mathbf{b}) = d(\mathbf{a}, \mathbf{b})$ . With the entries of  $\mathbf{a}$  in descending order, we deflate the problem by choosing  $k$  of the previous section as  $N$  and set  $M := N - 1$ . If  $y, z$  are  $N \times 1$  vectors with  $y$  a probability vector, introduce vectors  $u, v, w$  by

$$u = y^{[N]}, \quad v = z^{[N]}, \quad w = \begin{bmatrix} u \\ v \end{bmatrix}. \quad (49)$$

If  $y$  is a rich probability vector, then  $u$  satisfies  $u_i > 0$ , for  $i = 1, \dots, M$ , and  $\sum_{i=1}^M u_i < 1$ . If  $u$  satisfies these conditions we will call  $u$  a *truncated rich probability vector*.

Conversely, for given  $M \times 1$  vectors  $u$  and  $v$  with  $u$  a truncated rich probability vector,  $N$  vectors  $y$  and  $z$ , for  $N = M + 1$ , may be generated from

$$y_i = u_i, \quad z_i = v_i, \quad i = 1, \dots, M \quad (50)$$

and

$$y_N = 1 - \sum_{i=1}^M u_i, \quad z_N = - \left( 1 - \sum_{i=1}^M u_i \right) \sum_{i=1}^M v_i / u_i \quad i = 1, \dots, M. \quad (51)$$

Then  $y$  is a rich probability vector and the pair  $y, z$  satisfies the consistency condition (32). For  $y$  and  $z$  defined in terms of  $u$  and  $v$  by (50),(51) we define  $2M \times 1$  column vectors  $w$  and  $f$  by  $w = \begin{bmatrix} u \\ v \end{bmatrix}$  and

$$f(w) := \begin{bmatrix} P^{[N]}(y, z) \\ Q^{[N]}(y, z) \end{bmatrix} \quad (52)$$

If  $y, z$  is a solution of system (34) with  $y(s)$  a rich probability vector for every  $s \in [0, L]$ , then  $u, v, w$  defined by (49) defines a solution  $w = \begin{bmatrix} u \\ v \end{bmatrix}$  of

$$\dot{w} = f(w) \quad (53)$$

on  $[0, L]$  with  $u(s)$  a truncated rich probability vector for each on  $s \in [0, L]$ .

In order to implement our code, we need to note that evaluation of the function  $h$  by (4) can cause errors due to floating point restrictions on the base 2 logarithm. For example in either Matlab 5 or Matlab 6, values of  $h$  for  $u$  in the interval  $(0, 2^{(-1074)})$  cannot be produced by (4). We avoid that difficulty by means of the following code.

**Proposition 11 (Code for h)**

```
function h=e02h(u)
if u < 2^(-1074),
h=0;
elseif u >= 1,
h=0;
else
h = - u*log2(u);
end
```

The following pseudo-code gives an explicit representation of  $f$  as a function of  $u$  and  $v$ .

**Proposition 12 (Explicit f)** *Given column vectors  $u, v$  each of length  $M$  with  $u$  a truncated rich probability vector. Set  $N=M+1$ , use the scalar function  $h$  of Proposition 11 and define  $f$  by the following steps:*

1.  $r := 1 - \sum_{j=1}^M u_j$
2.  $z_N := -r \sum_{j=1}^M v_j/u_j$
3.  $K := h(r) + \sum_{j=1}^M h(u_j)$
4. for  $i = 1 : M$ ,  $R_i := -2u_i K + h(u_i) + v_i^2/(u_i^2 K)$ , end
5. for  $i = 1 : M$ ,  $S_i := R_i + (u_i/r) \sum_{j=1}^M R_j$ , end
6. for  $i = 1 : M$ ,  $T_i := u_i/r$ , end
7.  $U := N/r$
8.  $V := \sum_{j=1}^M S_j/u_j$
9.  $W := \left[ z_N^2/(r^3) + \sum_{j=1}^M v_j^2/(u_j^3) \right] / K$
10.  $X := (W - V)/U$
11. for  $i = 1 : M$ ,  $f_i := v_i/(K u_i)$ , end
12. for  $i = 1 : M$ ,  $f_{M+i} := S_i + X T_i$ , end

Our problem now is to find an initial slope, i.e.  $v(0)$ , and an interval length  $L$  such that the solution of the initial value problem (let us now use  $t$  for the independent variable)

$$\dot{w} = f(w), \quad w(0) = \begin{bmatrix} a^{[N]} \\ v(0) \end{bmatrix}, \quad (54)$$

with  $w(t)$  denoted by  $w(t) = \begin{bmatrix} u(t) \\ v(t) \end{bmatrix}$ , satisfies the boundary condition  $u(L) = b^{[N]}$ .

We would like to apply the following discrete Newton's method to this problem.

**Algorithm 13 (M Variable Discrete Newton's Method)** *Suppose  $F$  is a mapping of  $\mathbb{R}^M$  into  $\mathbb{R}^M$  such that  $F(x)$  has continuous partials of the first two orders. For  $\hat{x} \in \mathbb{R}^M$ , let  $B$  be the  $M \times M$  derivative matrix  $F'(\hat{x})$  defined as  $B := [B_1 \dots B_M]$  where  $B_j := \frac{\partial F}{\partial x_j}(\hat{x})$ . The vector Taylor's Theorem states that*

$$F(x) = F(\hat{x}) + B(x - \hat{x}) + R(x, \hat{x}), \quad \text{with } \|R(x, \hat{x})\| = O(\|x - \hat{x}\|^2). \quad (55)$$

Set  $F(x) = d$ , choose  $\varepsilon > 0$ , and redefine  $B_j$  by

$$B_j := [F(\hat{x} + \varepsilon e_j) - F(\hat{x})] / \varepsilon. \quad (56)$$

*One step of a Discrete Newton's Method is to solve for  $w$  in  $Bw = d - F(\hat{x})$  and set  $x = \hat{x} + w$ . Replace  $\hat{x}$  with  $x$  and repeat. If this iteration produces a sequence  $x^{(j)}$  of  $x$  values which converges to a solution  $x^{(0)}$  of  $F(x^{(0)}) = d$ , then the norm of the remainder term  $R(x^{(j)}, \hat{x}^{(0)})$  converges quadratically to 0 as  $j \rightarrow \infty$ .*

*Proof of the vector Taylor's Theorem.* For  $F(x) := [F_k(x)]_{M \times 1}$  apply Taylor's Theorem for a scalar valued function of  $M$  real variables to each  $F_k$  to obtain

$$F_k(x) = F_k(\hat{x}) + \sum_{i=1}^M (x_i - \hat{x}_i) \frac{\partial F_k}{\partial x_i}(\hat{x}) + R_k(x, \hat{x}) \quad (57)$$

where

$$R_k(x, \hat{x}) = \sum_{i=1}^M \sum_{j=1}^M (x_i - \hat{x}_i)(x_j - \hat{x}_j) \frac{\partial^2 F_k}{\partial x_i \partial x_j}$$

with second partials evaluated at  $\hat{x} + \xi_k(x - \hat{x})$ , for some  $\xi_k \in (0, 1)$ . For  $M_k$  this matrix of second order partials, (the Hessian matrix for  $F_k$ ),  $M_k$  is symmetric, and on each  $\delta$  neighborhood  $M_\delta(\hat{x})$ , the largest eigenvalue of  $M_k$  is bounded above by some  $\mu_k$ . Thus

$$R_k(x, \hat{x}) = (x - \hat{x})^T M_k (x - \hat{x}) \leq \mu_k \|x - \hat{x}\|^2$$

and for  $\mu = \{\sum_k \mu_k^2\}^{1/2}$ , we have  $\|R\|_2^2 \leq \mu^2 \|x - \hat{x}\|_2^4$ , i.e.,  $\|R\|_2 \leq \mu \|x - \hat{x}\|_2^2$ , and  $\|R(x, \hat{x})\|_2$  is "big O" of  $\|x - \hat{x}\|_2^2$ . ■

Our first thought is to use  $M = N$ ,  $x$  as the  $N \times 1$  column vector defined by  $x_i = v_i(0)$ , for  $i = 1, \dots, N - 1$  and  $x_N = \sigma$ , and let  $F(x)$  be the value of the solution  $y(t)$  at  $t = \sigma = x_N$ . Then  $F$  is a mapping from  $\mathbb{R}^N$  to  $\mathbb{R}^N$  and it seems that the discrete Newton's method should be applicable. However, if the method were to converge to our desired answer for the nondeflated problem, then  $F(x)$  approximates the probability vector  $b$  and for each  $j$  the partial derivatives  $\frac{\partial}{\partial x_j} F_i(x)$  must add to zero since the entries of  $b$  add to 1 and their derivatives must add to 0. Thus  $B$  becomes singular as the method converges and due to ill-conditioning, Gaussian Elimination provides unreliable output in Newton's method. We avoid this obstacle to convergence by deflating the problem by using  $M = N - 1$  and removing the  $N$ th components of  $y$  and  $z$ . Formulate the deflated problem as follows: Let the symbols  $c$  and  $d$  be defined by  $c := a^{[N]}$  and  $d := b^{[N]}$ . For an estimate  $\sigma$  of  $L$ , such as for example  $\sigma := \theta \|b - a\|_2$  for  $0 < \theta \leq 1$  and  $\zeta := v(0)$ , let  $\Phi(\zeta, \sigma)$  denote the functional value of  $u(t)$  at  $t = \sigma$  for  $u(t)$ ,  $v(t)$  the components of the solution  $w(t)$  of (54) with initial conditions determined by  $u(0) = c$ ,  $v(0) = \zeta$ . (We are assuming that this solution extends to  $[0, \sigma]$ .) Let  $M := N - 1$  and let  $x$  be the  $N \times 1$  column vector defined by  $x_i = \zeta_i$  for  $i = 1, \dots, M$  and  $x_N = \sigma$ . Since  $\sigma > 0$  and for  $\sigma$  sufficiently small, solutions are locally defined, we know that  $\Phi$  maps a subset of  $\mathbb{R}^N$  into  $\mathbb{R}^M$ . Our objective is to find  $x$  such that  $\Phi(x) = d$ . We have one too many independent variables, so for  $x_N$  fixed as  $\sigma$ , the remaining  $M$  entries of  $x$  give us a problem amenable to a discrete Newton's method for  $F(\zeta) := \Phi(\zeta, \sigma)$  with  $F$  a mapping from  $\mathbb{R}^M$  to  $\mathbb{R}^M$ .

We will use ODE45 of the Matlab ODE Suite [14] to generate  $w(t)$  across a tspan of  $[0, s]$ . Then  $\Phi(x)$  will be the value of  $u(t)$  at  $t = s = x_N$ , where  $w$  is the solution of the initial value problem

$$\dot{w} = f(w), \quad w(0) = \begin{bmatrix} c \\ x^{[N]} \end{bmatrix}. \quad (58)$$

The major difficulty in using Newton's Method is choosing starting values  $\hat{x}$  sufficiently close to the desired  $x$ . If we can get close enough to assure convergence, then we expect quadratic convergence. Our problem also has the difficulty that solutions of initial value problems might not extend to the interval  $[0, L]$  if the initial  $v(0)$  is not properly chosen. Thus  $\Phi(x)$  might not be defined for some initial conditions  $v(0) = x^{[N]}$  and interval lengths  $\sigma = x_N$ .

In order to start Newton's method, we must estimate the arc length  $L$  and the initial  $v(0)$ . The arc length  $L$  of the probability path  $y(s)$  must satisfy  $L \geq \|b - a\|_2$ . (For  $N = 2$ , we are moving on a straight line and  $L$  is  $\|b - a\|_2$ .) Then, thinking first of the nondeflated problem,  $\hat{z}(0)$  may be chosen by using forward difference quotients on  $[0, \|b - a\|_2]$  to estimate  $\dot{y}_i(0)$  from (27). If we knew  $L$ , then we would have  $z_i(0) = 2y_i(0)H(y(0))\dot{y}_i(0)$  where  $\dot{y}_i(0) \approx (y_i(L) - y_i(0))/L = (b_i - a_i)/L$ . The choice of initial vector

$$\tilde{z}_i(0) := a_i H(a) (b_i - a_i) / L$$

is unsatisfactory not only because  $L$  is unknown, but because we have not satisfied the norm condition (33). However, this initial condition satisfies the consistency condition (32) because  $\mathbf{a}$  and  $\mathbf{b}$  are probability vectors. Let us denote by  $\nu(y, z)$  the expression

$$\nu(y, z) := \frac{1}{(H(y))^2} \sum_{i=1}^N \frac{z_i^2}{y_i^2}.$$

Then for fixed  $y$  and constant  $\alpha$ , we have  $\nu(y, \alpha z) = \alpha^2 \nu(y, z)$ , i.e.,  $\nu(y, z)$  is homogeneous of degree 2 in  $z$ . Now we want to find  $\alpha$  such that  $\hat{z} := \alpha \tilde{z}$  satisfies the norm condition, i.e.,  $\nu(y, \alpha \tilde{z}) = 1$ . This is resolved by the condition  $\alpha^2 \nu(y, \tilde{z}) = 1$  which has a solution  $\alpha = L / \|\mathbf{b} - \mathbf{a}\|_2$ . Thus the desired initial condition on  $\hat{z}$  is

$$\hat{z}_i(0) := a_i H(a) (b_i - a_i) / \|\mathbf{b} - \mathbf{a}\|_2 \quad (59)$$

and the corresponding initial condition on  $v(0)$  is

$$\hat{v}_i(0) := a_i H(a) (b_i - a_i) / \|\mathbf{b} - \mathbf{a}\|_2 \quad i = 1, \dots, M. \quad (60)$$

Set  $\hat{x} = \begin{bmatrix} \hat{v}(0) \\ \hat{\sigma} \end{bmatrix}$ . With  $\sigma$  fixed as  $\hat{\sigma}$ , let  $F(\zeta) := \Phi(\zeta, \hat{\sigma})$  and use the above discrete Newton's method to iteratively improve  $\zeta$ .

If  $N = 2$ , we have  $L = \sigma = \|\mathbf{b} - \mathbf{a}\|_2$  and Newton's method suffices. We now show how to improve the estimate of  $L$  in the cases of  $N > 2$ .

**Proposition 14** *Suppose  $\zeta$  is fixed and is the result of Newton's iteration for  $\Phi(\zeta, \hat{\sigma}) = d$ . Suppose that for  $k = 1, \dots, 4$ ,  $s_k$  is an increasing sequence of positive numbers with  $s_4 = \hat{\sigma}$ ,  $A$  is the  $4 \times 2$  matrix with first column consisting of 1's and second column  $s_k$ , for  $k = 1, \dots, 4$ , and  $\Gamma_k$  is defined by  $\Gamma_k = \|\Phi(\zeta, s_k) - d\|_2$ . Let  $v = A \setminus \Gamma$  and  $s = -v_1/v_2$  for an improved estimate of  $L$ .*

Then Newton's method with this new estimate of  $L$  can be used again, followed by linear regression to update.

If a few of these loops of Newton's method and linear regression give satisfactory convergence to a vector  $x$ , then we find the optimal distance  $d$  by augmenting the differential system with a final equation of  $\dot{E} = K(u)$ , where  $K(u)$  is  $H(y)$  for the probability vector  $y$  associated with  $u$ . This can be done by adding one line to our code for  $f$  in Proposition 12, namely,

$$13. f_{N+1} = K.$$

Then the integral of  $E$  from 0 to  $L := x(N, 1)$  is the final value of  $w_{N+1}$  which estimates the desired distance  $d$ . This is achieved by using ODE45 of Matlab 5 or Matlab 6 on the augmented system. Then  $d$  is the last row, last column entry of the output vector matrix. The use of this ode solver on the augmented system in  $2N - 1$  dependent variables produces superior numerics to using quadrature methods on  $H(y)$ , for  $y$  the vector of numerical output values, in order to find  $d$ .

## 6. Examples: the myostatin gene and proteins in various species

First we illustrate how our new divergence measure with  $N = 4$  may be used for DNA sequences by an example of 14 myostatin genes among several species. Then we examine a group of amino-acid sequences where  $N = 20$  corresponds to the number of bases in these amino acids chains.

Any distance metric or similarity score on sequences will produce a set of pairwise distances. We compare the results of the new entropy path minimizing function to that of known distances and similarity scores. In order to visualize how these functions relate we use dendrograms constructed by a general weighted neighbor joining algorithm implmented in Weighbor ([5]). The output tree is the best organization of the data satisfying the hypothesized stucture of evolution formalized as an 'Ultrametric Condition.' We refer the interested reader to ([5]) for further details and note that the dendrograms provide a convenient method of visualizing the relation of pairwise distance data. The full data is available on our website for download at <http://www.math.missouri.edu/~calvin/entropyfiles/index.html>

In addition we give a table of how the  $L_1, L_2, L_{\text{inf}}, H, H$ -linear differ in terms of Frobenius norm applied to the pairwise distance data they produce, here  $H$  and  $H$ -linear are our new divergence metrics.

## 6.1. DNA sequences

The web page <http://cytokine.medic.kumamoto-u.ac.jp/CFC/TGF/GDF/GDF8cDNA.html> includes the myostatin gene sequences and base counts summaries which we use as an illustrative example. If each base count is divided by the total number of base pairs, then the following 14 examples give test examples for our code.

**Table 1. Myostatin gene BASE COUNTS by Species**

Identification code	Species	base pairs	BASE COUNT	Vector Label $g_i$
AF019627 [gi:2623581]	Homo sapiens	1128 bp	373 a 220 c 238 g 297 t	$g_1$
AF104922 [gi:4028595]	Homo sapiens	2823 bp	978 a 457 c 497 g 891 t	$g_2$
AF019619	baboon	1128 bp	372 a 224 c 237 g 295 t	$g_3$
AF019620	bovine	1128 bp	352 a 241 c 249 g 286 t	$g_4$
AF019621	chicken	1128 bp	357 a 246 c 255 g 270 t	$g_5$
AF019622	sheep	1128 bp	366 a 235 c 241 g 286 t	$g_6$
AF019623	pig	1128 bp	371 a 234 c 238 g 285 t	$g_7$
AF019624	Norway rat	1131 bp	348 a 249 c 267 g 267 t	$g_8$
AF019625	common turkey	1128 bp	367 a 243 c 244 g 274 t	$g_9$
AF019626	zebrafish	1125 bp	310 a 285 c 294 g 236 t	$g_{10}$
AF019761	bovine	1128 bp	351 a 246 c 250 g 281 t	$g_{11}$
AF033855	pig	210 bp	557 a 313 c 319 g 464 t	$g_{12}$
AF151692	duck	partial cds 288 bp	88 a 74 c 59 g 67 t	$g_{13}$
NM_010834	mouse	2676 bp	881 a 506 c 508 g 781 t	$g_{14}$

The function  $d_{\text{linear}}(\mathbf{a}, \mathbf{b}, M)$ , which depends upon  $\mathbf{a}$ ,  $\mathbf{b}$  and an integer  $M \geq 3$  is the result of a generalized Simpson's rule quadrature of the entropy function evaluated at  $M$  points along the straight line from  $\mathbf{a}$  to  $\mathbf{b}$ . This function was used to estimate  $d(\mathbf{c}^N, e_j)$  in Example 3. For each  $i = 1, \dots, 14$ , let  $\mathbf{a}_i$  be the probability vector associated with the above  $g_i$ . In this case, we are able to compute  $d(\mathbf{a}_i, \mathbf{a}_j)$  by our code and it agrees with the distance  $d_{\text{linear}}(\mathbf{a}_i, \mathbf{a}_j, 100)$  within .0001 throughout the table.

**Table 2. Distance matrix  $d(\mathbf{a}_i, \mathbf{a}_j)$  for myostatin genes of Table 1**

0	0.1419	0.0082	0.0587	0.0774	0.0351	0.0324	0.0995	0.0588	0.2161	0.0692	0.0519	0.1460	0.0708
0.1419	0	0.1472	0.1929	0.2179	0.1736	0.1698	0.2389	0.1976	0.3522	0.2045	0.0940	0.2663	0.0821
0.0082	0.1472	0	0.0530	0.0714	0.0279	0.0248	0.0944	0.0518	0.2106	0.0630	0.0554	0.1379	0.0740
0.0587	0.1929	0.0530	0	0.0325	0.0302	0.0405	0.0487	0.0350	0.1602	0.0127	0.1028	0.1013	0.1136
0.0774	0.2179	0.0714	0.0325	0	0.0449	0.0513	0.0276	0.0275	0.1413	0.0237	0.1254	0.0915	0.1404
0.0351	0.1736	0.0279	0.0302	0.0449	0	0.0105	0.0695	0.0259	0.1845	0.0373	0.0806	0.1127	0.0969
0.0324	0.1698	0.0248	0.0405	0.0513	0.0105	0	0.0771	0.0279	0.1919	0.0466	0.0762	0.1161	0.0947
0.0995	0.2389	0.0944	0.0487	0.0276	0.0695	0.0771	0	0.0551	0.1172	0.0395	0.1485	0.0962	0.1614
0.0588	0.1976	0.0518	0.0350	0.0275	0.0259	0.0279	0.0551	0	0.1669	0.0329	0.1039	0.0961	0.1214
0.2161	0.3522	0.2106	0.1602	0.1413	0.1845	0.1919	0.1172	0.1669	0	0.1495	0.2628	0.1354	0.2724
0.0692	0.2045	0.0630	0.0127	0.0237	0.0373	0.0466	0.0395	0.0329	0.1495	0	0.1134	0.0909	0.1248
0.0519	0.0940	0.0554	0.1028	0.1254	0.0806	0.0762	0.1485	0.1039	0.2628	0.1134	0	0.1766	0.0273
0.1460	0.2663	0.1379	0.1013	0.0915	0.1127	0.1161	0.0962	0.0961	0.1354	0.0909	0.1766	0	0.1862
0.0708	0.0821	0.0740	0.1136	0.1404	0.0969	0.0947	0.1614	0.1214	0.2724	0.1248	0.0273	0.1862	0

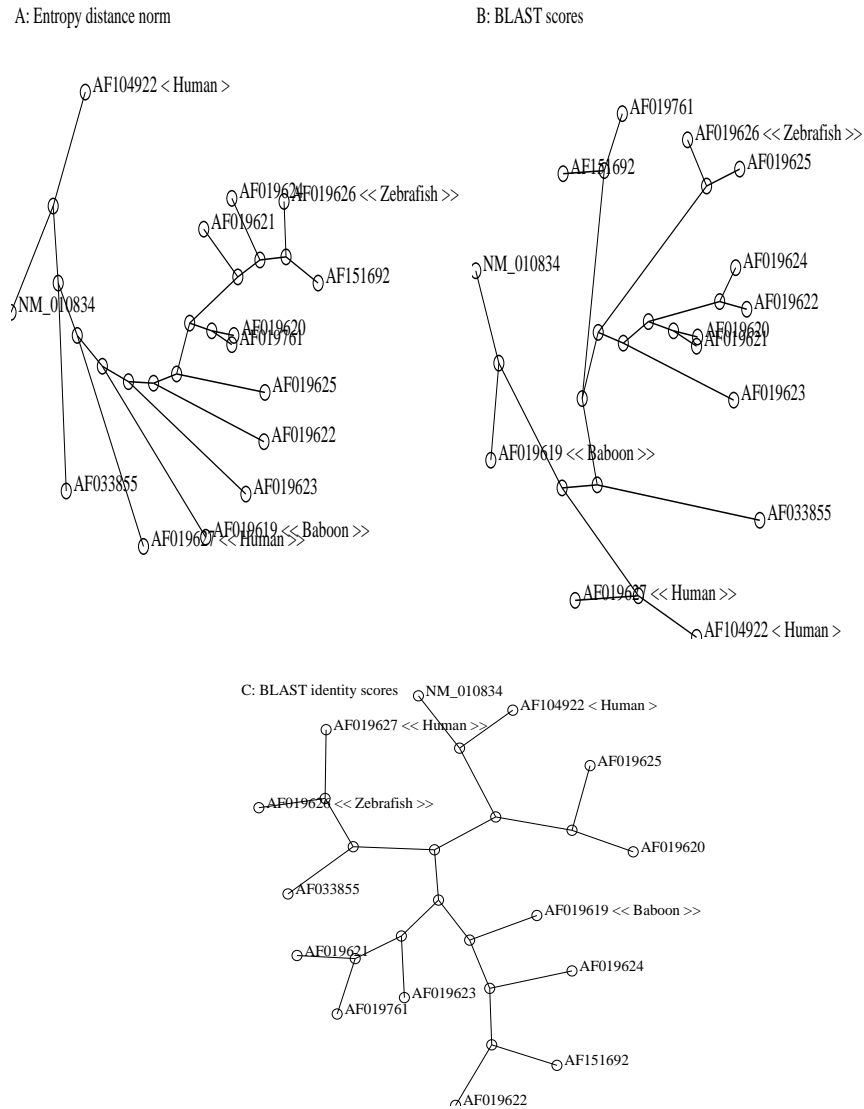
Observe that the minimal distance between any two distinct myostatin genes in this list is exhibited by the distance  $d(\mathbf{a}_1, \mathbf{a}_3) = 0.0082$  between the human gene AF019627 [gi:2623581], labeled here as  $g_1$ , and the baboon gene AF019619, labeled here as  $g_3$ . In the following table we use  $N = 100$  in the evaluation of H-linear.

**Table 3. Frobenius norm between pairwise distance matrices for vectors  $a_i, i \in [1, \dots, 14]$** 

	$L_1$	$L_2$	$L_{\text{inf}}$	H	H-linear
$L_1$	0	0.7794	1.0865	0.1135	0.1135
$L_2$	0.7794	0	0.3099	0.8381	0.8382
$L_{\text{inf}}$	1.0865	0.3099	0	1.1404	1.1404
H	0.1135	0.8381	1.1404	0	0.0000
H-linear	0.1135	0.8382	1.1404	0.0000	0

Next we display dendrograms showing cluster relations for DNA sequence data:

The output tree is the best organization of the data satisfying the hypothesized structure of evolution. As a consequence we obtain a tree resulting from our minimal entropy metric which contrasts with those generated by



**Fig. 1.** DNA Dendrogram: A: Entropy Distance ( Same tree topology for  $L_1, L_2, L_\infty$  ), B: BLAST Score, C: BLAST Identity Score.

BLAST scores with default parameters and BLAST identity scores for the myostatin example across species. In particular, note the rearrangements of the two human, the baboon and the zebrafish myostatin genes in the three trees.

In general the entropy metric shows a close relation to the other distance metrics  $L_1, L_2, L_\infty$  for the input data taken from biological data. The entropy metric shows a closer relation to the BLAST score than to the BLAST Identity score.

## 6.2. Amino Acid sequences

**Table 4. Myostatin protein and information**

Accession Number	Further Information	size	label
AAK53545	myostatin [Sparus aurata]	385	$g_1$
AAK53544	myostatin [Sparus aurata]	385	$g_2$
NP_005802	differentiation factor 11; bone morphogenetic protein 11 [Homo sapiens]	407	$g_3$
NP_005250	differentiation factor 8; myostatin [Homo sapiens]	375	$g_4$
NP_034964	differentiation factor 8; myostatin [Mus musculus]	376	$g_5$
O14793	factor 8 precursor (GDF-8) (Myostatin)	375	$g_6$
NP_571094	differentiation factor 8; myostatin [Danio rerio]	374	$g_7$
NP_062024	differentiation factor 8; myostatin [Rattus norvegicus]	376	$g_8$

For each  $i = 1, \dots, 8$ , let  $\mathbf{a}_i$  be the probability vector associated with the above  $g_i$ . In this case, we are able to compute  $d(\mathbf{a}_i, \mathbf{a}_j)$  by our code and it agrees with the distance along a linear path within  $1.0e - 04$  throughout the table.

**Table 5. Distance matrix  $d(\mathbf{a}_i, \mathbf{a}_j)$  for myostatin proteins of Table 4**

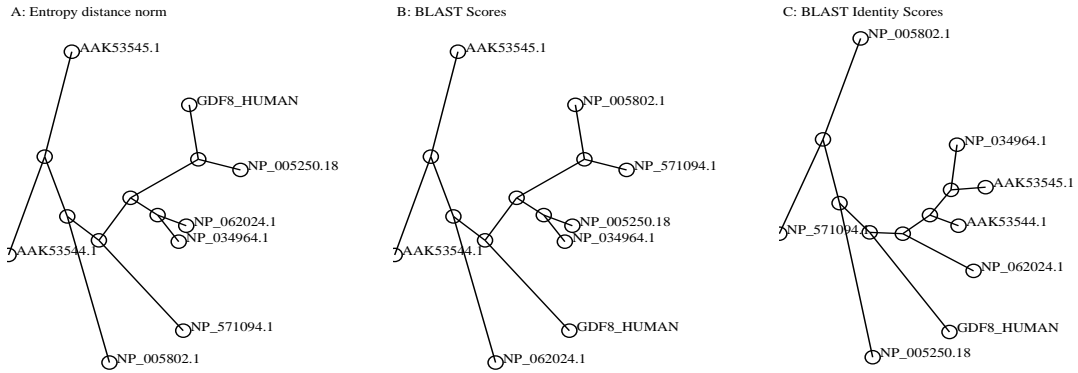
0	0	0.3416	0.2546	0.2564	0.2546	0.2046	0.2570
0	0	0.3416	0.2546	0.2564	0.2546	0.2046	0.2570
0.3416	0.3416	0	0.3624	0.3192	0.3624	0.2942	0.3202
0.2546	0.2546	0.3624	0	0.0835	0	0.1480	0.0947
0.2564	0.2564	0.3192	0.0835	0	0.0835	0.1323	0.0420
0.2546	0.2546	0.3624	0	0.0835	0	0.1480	0.0947
0.2046	0.2046	0.2942	0.1480	0.1323	0.1480	0	0.1263
0.2570	0.2570	0.3202	0.0947	0.0420	0.0947	0.1263	0

In the following table, we use  $M = 500$  in the evaluation of H-linear.

**Table 6. Frobenius norm between pairwise distance matrices for vectors  $a_i, i \in [1, \dots, 8]$** 

	$L_1$	$L_2$	$L_{\text{inf}}$	H	H-linear
$L_1$	0	0.9936	1.1677	0.3394	0.3397
$L_2$	0.9936	0	0.1753	1.3224	1.3227
$L_{\text{inf}}$	1.1677	0.1753	0	1.4952	1.4956
H	0.3394	1.3224	1.4952	0	0.0003
H-linear	0.3397	1.3227	1.4956	0.0003	0

Next we display dendrograms showing cluster relations:



**Fig. 2.** Protein Dendrogram: A: Entropy Distance ( Same tree topology for  $L_1, L_2, L_\infty$  ), B: Blast Score, and C: Blast Identity Score

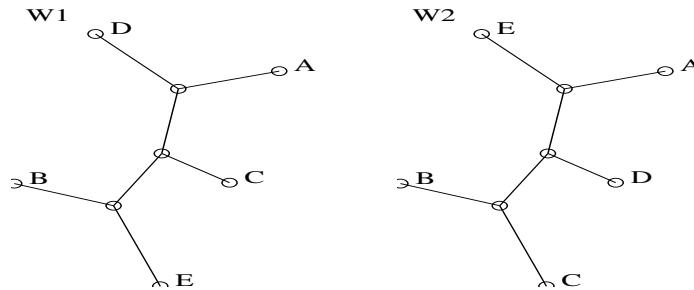
6.3. Mathematical divergence of measures

Although the dendrograms for the above Myostatin data suggest that the all of the distance metrics produce a related tree topology we give an example for which this is not the case. Consider the dendrograms of Fig. 3.

These dendrograms are produced from the five points in  $\mathbb{P}^4$ , chosen as  $A = [1, 0, 0, 0]$ ,  $B = [1/4, 1/4, 1/4, 1/4]$ ,  $C = [1/3, 1/3, 1/3, 0]$ ,  $D = [1/2, 1/2, 0, 0]$  and  $E = [0, 0, 0, 1]$ . The following matrix  $W_1$  is the pairwise distance matrix evaluated with the  $L_2$  distance norm for these points amd the matrix  $W_2$  is the pairwise distance matrix evaluated with the  $H$ -linear function for  $M = 100$ .

$$W_1 = \begin{bmatrix} 0 & 0.8660 & 0.8165 & 0.7071 & 1.4141 \\ 0.8660 & 0 & 0.2887 & 0.5000 & 0.8660 \\ 0.8165 & 0.2887 & 0 & 0.4082 & 1.1547 \\ 0.7071 & 0.5000 & 0.4082 & 0 & 1.2247 \\ 1.4141 & 0.8660 & 1.1547 & 1.2247 & 0 \end{bmatrix}, \quad W_2 = \begin{bmatrix} 0 & 1.2020 & 0.9125 & 0.5101 & 1.0201 \\ 1.2020 & 0 & 0.5460 & 0.8607 & 1.2020 \\ 0.9125 & 0.5460 & 0 & 0.5833 & 1.7480 \\ 0.5101 & 0.8607 & 0.5833 & 0 & 1.4958 \\ 1.0201 & 1.2020 & 1.7480 & 1.4958 & 0 \end{bmatrix}$$

The dendrograms for this choice of points shows that the nonlinearity of the entropy based distance function produce different geometric structures on these pairs of points. This difference was illustrated by using the Neighbor Joining algorithm for dimension 4. It would be reasonable to suggest that the structural differences increase with



**Fig. 3.** Example for which  $L_2$  and  $H$  differ.

dimension. This shows that our entropy based distance functions can give a different topology to dendograms than other measures. This is not to suggest that our methods are “better” than any another; indeed, they are just different.

## 7. Example of $N = 2$

If the original probability path  $p(t) \in R^2$ , for  $0 \leq t \leq 1$ , were interpreted as lying on the closed line segment in the plane of  $p_1 + p_2 = 1$ ,  $p_1 \in [0, 1]$ , then a minimizer for  $E$  could not retrace any portion of its path, because that would give a larger value of  $E$  than if one proceeded monotonically from  $a$  to  $b$ . Thus the length  $L$  of the path from  $a$  to  $b$  is  $L = \|b - a\|_2$  and if  $L > 0$  and one uses arc length  $s$  as parameter, then variables  $y_1$  and  $y_2$  are uniquely given by  $y_1(s) = a_1 + \frac{s}{L}(b_1 - a_1)$  and  $y_2(s) = a_2 + \frac{s}{L}(b_2 - a_2)$ . For  $y$  the vector probability path with these components, the minimum value of the entropy is then

$$E = \int_0^L H(y(s)) ds.$$

In particular, for  $a = [1 \ 0]^T$  and  $b = [0 \ 1]^T$ ,  $E$  attains the largest possible value for any  $a$  and  $b$  in  $R^2$  of about 1.020139, which is obtained by linearly parameterizing a discrete path of  $M$  points from  $(1, 0)$  to  $(0, 1)$  and using Simpson’s rule to estimate the entropy integral along this path. Let us verify that these functions  $y_1$  and  $y_2$  satisfy the Euler–Lagrange system (24) on  $[0, L]$ . For  $h$  defined by (4) we have  $H(y) = h(y_1) + h(y_2)$ . Introduce notation  $A_i$  and  $\Gamma_i$  for the left and right sides of equation (24), i.e.,  $A_i = \frac{d}{ds} \{H(y)y_i\dot{y}_i\}$  and

$$\Gamma_i = y_i \sum_{j=1}^2 \frac{d}{ds} \{H(y)y_j\dot{y}_j\} - 2y_i H(y) + H(y)(\dot{y}_i)^2 + h(y_i).$$

We wish to show that the above functions make  $A_i = \Gamma_i$ , for  $i = 1, 2$ . Note that  $y_i$  has second derivative with respect to  $s$  of 0. For  $i = 1$  we have

$$A_1 = \frac{d}{ds} \{H(y)y_1\dot{y}_1\} = \left[ \frac{d}{ds} H(y) \right] y_1\dot{y}_1 + H(y)(\dot{y}_1)^2$$

and

$$\Gamma_1 = y_1 \frac{d}{ds} \{H(y)y_1\dot{y}_1 + H(y)y_2\dot{y}_2\} - 2y_1 H(y) + H(y)(\dot{y}_1)^2 + h(y_1).$$

However,

$$y_1 \frac{d}{ds} \{H(y)y_1\dot{y}_1 + H(y)y_2\dot{y}_2\} = y_1 \left[ \frac{d}{ds} H(y) \right] (y_1\dot{y}_1 + y_2\dot{y}_2) + y_1 H(y)[(\dot{y}_1)^2 + (\dot{y}_2)^2],$$

where  $[(\dot{y}_1)^2 + (\dot{y}_2)^2] \equiv 1$ . Thus

$$\Gamma_1 = y_1 \left[ \frac{d}{ds} H(y) \right] (y_1\dot{y}_1 + y_2\dot{y}_2) + h(y_1) - y_1 H(y) + H(y)(\dot{y}_1)^2.$$

and we are left to show that the quantity  $\Omega_1$ , defined by  $\Omega_1 := \Gamma_1 - A_1$ , is 0. Grouping terms in

$$\Omega_1 = y_1 \left[ \frac{d}{ds} H(y) \right] (y_1\dot{y}_1 + y_2\dot{y}_2) + h(y_1) - y_1 H(y) - \left[ \frac{d}{ds} H(y) \right] y_1\dot{y}_1$$

gives

$$\Omega_1 = \left[ \frac{d}{ds} H(y) \right] (y_1^2\dot{y}_1 + y_1y_2\dot{y}_2 - y_1\dot{y}_1) + h(y_1) - y_1 H(y)$$

But  $y_1^2 \dot{y}_1 + y_1 y_2 \dot{y}_2 - y_1 \dot{y}_1 = y_1(y_1 - 1)\dot{y}_1 + y_1 y_2 \dot{y}_2 = y_1 y_2 \dot{y}_2 - y_1 y_2 \dot{y}_1$  and  $\frac{d}{ds} H(y) = h'(y_1)\dot{y}_1 + h'(y_2)\dot{y}_2$ , where  $h'(u) = -\log_2 u - 1/\ln 2$ . Thus

$$\Omega_1 = -[(\log_2 y_1 + 1/\ln 2)\dot{y}_1 + (\log_2 y_2 + 1/\ln 2)\dot{y}_2](y_1 y_2 \dot{y}_2 - y_1 y_2 \dot{y}_1) + (1 - y_1)h(y_1) - y_1 h(y_2)$$

Since  $y_1 + y_2 = 1$ , we have  $\dot{y}_2 = -\dot{y}_1$  and

$$\Omega_1 = -[(\log_2 y_1)\dot{y}_1 + (\log_2 y_2)\dot{y}_2](y_1 y_2 \dot{y}_2 - y_1 y_2 \dot{y}_1) - y_2 y_1 \log_2 y_1 + y_1 y_2 \log_2 y_2,$$

i.e.,

$$\Omega_1 = y_1 y_2 [(\log_2 y_1)\dot{y}_1 - (\log_2 y_2)\dot{y}_1](\dot{y}_1 - \dot{y}_2) - y_1 y_2 \log_2 y_1 + y_1 y_2 \log_2 y_2,$$

and we conclude that

$$\Omega_1 = y_1 y_2 [(\dot{y}_1)^2 + (\dot{y}_2)^2 - 1][\log_2 y_1 - \log_2 y_2] = 0.$$

Note that interchanging the subscripts 1 and 2 gives  $\Omega_2 = -\Omega_1 = 0$  and we have verified that our given path  $y(s)$  satisfies the Euler–Lagrange system (24). While this calculation is not enlightening, it does give a gross–error check, and we did find that our first calculations were in error by doing this example. Furthermore, it illustrates the futility of attempting to “closed form solve” the Euler–Lagrange system, since we did not find our solution by “solving” the differential equation. For values of  $N$  larger than 2, we would not expect to solve the Euler–Lagrange system and wouldn’t expect to be able to guess a solution except possibly when we consider points  $\mathbf{a}$  and  $\mathbf{b}$  which lie on the same edge of the set of probability vectors  $\mathbb{P}^N$ .

Now consider the Euler–Lagrange system (34) for this case of  $N = 2$ . If in addition to the initial condition of  $y(0) = a$ , one applies the initial condition (59) to this case we have  $z_i(0) = a_i H(a)(b_i - a_i)/L$  and the initial condition on  $\dot{y}(s)$  from (25) is  $z_i(0) = y_i(0)\dot{y}_i(0)H(a)$ . For any  $s$  in  $[0, L]$ , one step of Euler’s method of numerically solving the system (34) on  $[0, s]$  with these initial conditions gives the exact solution at  $s$  of the prescribed boundary value problem for the differential system.

## 8. Software Description and Links

The link <http://www.math.missouri.edu/~calvin/entropyfiles/index.html> contains Matlab program files for three methods of estimating the minimal entropy distance  $d(a, b)$ .

The minimal entropy distance  $d(a, b)$ , assuming a rich probability path minimizing arc, is computed by the Matlab program `e02daug.m` via `e02daug(a,b)` which calls functions `e02faug`, `e02fdyn`, `e02h`, `e02HN`, `e02Hofh`, `e02init`, `e02Jacsq`, `e02phi` and `e02regr`. The function `e02init` initializes variables “hatsig” and “hatz” for use of the differential system determined by `e02fdyn` which implements Proposition 12 for  $f$ . The functions `e02Hofh` and `e02HN` use `e02h` (which is the code given in Proposition 11) to evaluate the entropy function of a vector. The program `e02phi` gives the result of following the solution of the initial value problem across the  $s$  interval. Newton’s method uses `e02Jacsq`, the numerical Jacobian matrix. Linear regression to improve the arc length estimate is accomplished via `e02regr`. Finally, the differential system is augmented by `e02faug` which adds step 13 of Section 5 in order that  $d$  can be computed without quadrature methods by solving the augmented system.

The program `e02dlinear` uses an input argument  $N$ , an integer of at least 100, to estimate the value of the entropy integral over the linear path containing  $N$  equally spaced points on the closed linear path joining  $a$  to  $b$ . It calls `e02Hofh` and `e02h` to generate the functional values followed by `e02quad` which calls `e02regr` to carry out a composite Simpson’s rule. Note that  $N$  can be any integer as opposed to the usual Simpson’s rule which requires and even number of subintervals, which would have made  $N$  odd.

The elementary metric  $d_G(a, b)$  is computed by `e02d_G(a,b)` which calls the function `e02G`.

Programs `e02dlinear` and `e02d_G` will run on any pair of probability vectors  $a$  and  $b$  of the same length  $N$ .

For C programs implementing “weighbor” to generate the dendronic trees from distance matrix arrays for  $k$  vertices see the URL <http://void.cat.nyu.edu/will/Work/Code/> or the link to Will’s Code on the web page <http://www.math.missouri.edu/~calvin/entropyfiles/code.html>

## References

1. S. Altschul, Amino acid substitution matrices from an information theoretic perspective, *J. Mol. Evol.*, 219:555–565, 1991.
2. S. Altschul, W. Gish, W. Miller, E. Myers, and D. Lipman, Basic local alignment search tool, *J. Mol. Biol.*, 215:403–410, 1990.
3. A. Arslan, O. Egecioglu, and P. Pevzner, A new approach to sequence comparison: normalized sequence alignment, *Bioinformatics*, 17:327–337, 2002.
4. G. Benson, A new distance measure for comparing sequence profiles based on paths along an entropy surface, Proceedings of the European Conference on Computational Biology (ECCB 2002), October 6-9, 2002, Saarbrücken, Germany, Bioinformatics, 18 (Supplement 2):S44-S53, 2002, Oxford University Press.
5. W. Bruno, N. Succi, and A. Halpern, Weighted Neighbor Joining: A Fast Approximation to Maximum-Likelihood Phylogeny Reconstruction, *Molecular Biology and Evolution*, 17(1): 189-197, (2000).
6. A.W.F. Edwards and C.C. Cavalli-Sforza, Reconstruction of evolutionary trees, In V.H. Heywood and J. McNeill, editors, *Phenetic and Phylogenetic Classification*, London, UK: Systematics Association, 1964.
7. G.M. Ewing, *Calculus of Variations with Applications*, W. W. Norton, New York, 1969.
8. D. Feng, M. Johnson, and R. Doolittle, Aligning amino acid sequences: comparison of commonly used methods, *J. Mol. Evol.*, 2:434–447, 1985.
9. R. Karp and M. Rabin, Efficient randomized pattern-matching algorithms, *IBM J. Res. Dev.*, 31(2):249-260
10. S. Kullback, *Information Theory and Statistics*, Dover Publications, 1968.
11. S.J. Leon, *Linear Algebra with Applications*, Fourth Edition, Prentice-Hall, Upper Saddle River, New Jersey, 1994.
12. J. Lin, Divergence measures based on the Shannon entropy, *IEEE Trans. Inf. Theor.*, 37:145–151, 1991.
13. M. Nei, F. Tajima, and Y. Tateno, Accuracy of estimated phylogenetic trees from molecular data: II. gene frequency data, *J. Molec. Ecol.*, 19:153–170, 1983.
14. L.F. Shampine and M.W. Reichelt, The MATLAB ODE Suite, *SIAM Journal on Scientific Computing*, 18:1-22, 1997.
15. B. Simon, Spectral analysis of rank one perturbations and applications, *Mathematical Quantum Theory, II. Schrödinger Operators* (Vancouver, BC, 1993), 109-149, CRM Proc. Lecture Notes, 8, Amer. Math. Soc., Providence, RI. 1995. MR 97c:47008
16. G.W. Stewart, *Introduction to Matrix Computations*, Academic Press, New York, 1973.
17. G.B. Thomas and R.L. Finney, *Calculus and Analytic Geometry*, 8th edition, Addison-Wesley Publishing Co., New York, 1992.
18. J.H. Wilkinson, Sensitivity of eigenvalues, *Utilitas Math.* 25 1984, pp 5–76, and part II, *ibid*, 30 1986, pp. 243–286.
19. A.K.C. Wong, S.C. Chan, and D.K.Y. Ch, A multiple sequence comparison method. *Bull. Math. Biol.*, 55:465–486, 1993.