Classification of Prostate Cancer Grades and T-Stages based on Tissue Elasticity Using Medical Image Analysis

Supplementary Document

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1 Continuum Mechanics Basics

In this supplementary document, we introduce some basic concepts in the continuum mechanics for readers, who may not be familiar with some of these terminology and models.

1.1 Stress And Stress Tensor

Stress is defined simply as Force/Area, but some complexity arises, because the relative orientation of the force vector to the surface normal dictates the type of stress [2]. When the force vector is normal to the surface, as shown in Fig. 1, the stress is referred to as "normal stress" and represented by σ [2]. When the force vector is parallel to the

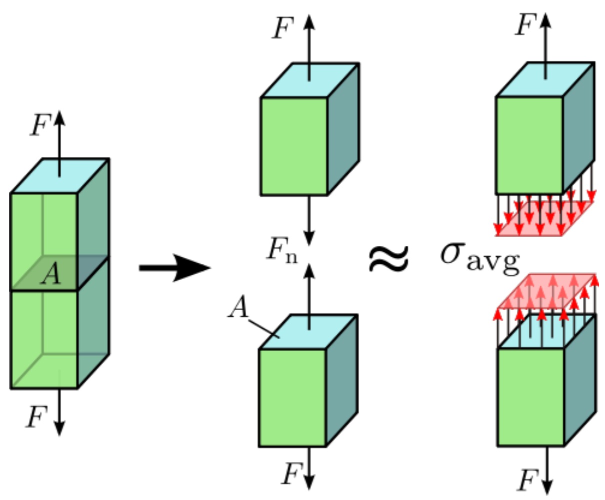


Fig. 1. This figure shows force vector normal to the surface or parallel to the surface. Copyright Wikipedia [9]

surface, the stress is referred to as "shear stress" and represented by τ [2]. When the force vector is somewhere in between, then its normal and parallel components are used as follows [2].

$$\sigma = \frac{F_{normal}}{A}, \tag{1}$$

$$\tau = \frac{F_{parallel}}{A}. \tag{2}$$

Of course, things can get complicated in nonlinear problems with large deformations (and rotations) because the final deformed area may be different from the initial area, among other things [2].

Stress is in fact a tensor [2]. It can be written in any of several forms as follows [2]. (Cauchy stress tensor shown in Fig. 2) In 3-D it can be written as,

$$\sigma = \begin{bmatrix} \sigma_{11} & \sigma_{12} & \sigma_{13} \\ \sigma_{21} & \sigma_{22} & \sigma_{23} \\ \sigma_{31} & \sigma_{32} & \sigma_{33} \end{bmatrix} = \begin{bmatrix} \sigma_{xx} & \sigma_{xy} & \sigma_{xz} \\ \sigma_{yx} & \sigma_{yy} & \sigma_{yz} \\ \sigma_{zx} & \sigma_{zy} & \sigma_{zz} \end{bmatrix} = \begin{bmatrix} \sigma_{xx} & \tau_{xy} & \tau_{xz} \\ \tau_{yx} & \sigma_{yy} & \tau_{yz} \\ \tau_{zx} & \tau_{zy} & \sigma_{zz}, \end{bmatrix} \tag{3}$$

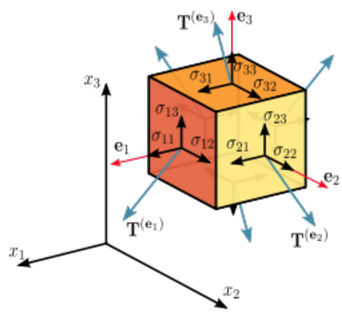


Fig. 2. The figure shows the components of Cauchy stress tensor. Copyright Wikipedia [9]

1.2 Strain And Strain Tensor

Strains, like stress, are classified into "normal strains" and "shear strains" (parallel). Normal in normal strain does not mean common or usual strain [3]. It means a direct length changing stetch (or compression) of an object resulting from a normal stress [3]. As the quantities shown in Fig. 3), it is defined as

$$\epsilon = \frac{\Delta L}{L_o}, \tag{4}$$

This is also known as Engineering Strain [3].

Shear strain is usually represented by γ and defined as [3],

$$\gamma = \frac{D}{T}. \tag{5}$$

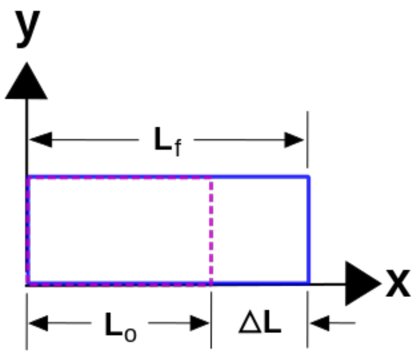


Fig. 3. The figure shows the stetch from a normal stress and the resulted normal strain. Copyright Continuum Mechanics [3]

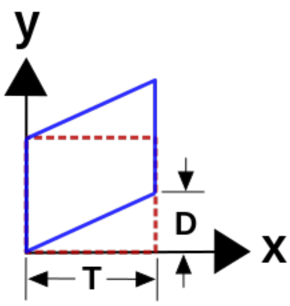


Fig. 4. The figure shows the shear strain definition. Copyright Continuum Mechanics [3]

This is the shear-version of engineering strain [3].

Strain, like stress, is a tensor [3]. And like stress, strain is a tensor simply because it obeys the standard coordinate transformation principles of tensors [3]. It can be written in any of several different forms as follows [3].

$$\epsilon = \begin{bmatrix} \epsilon_{11} & \epsilon_{12} & \epsilon_{13} \\ \epsilon_{21} & \epsilon_{22} & \epsilon_{23} \\ \epsilon_{31} & \epsilon_{32} & \epsilon_{33} \end{bmatrix} = \begin{bmatrix} \epsilon_{xx} & \epsilon_{xy} & \epsilon_{xz} \\ \epsilon_{yx} & \epsilon_{yy} & \epsilon_{yz} \\ \epsilon_{zx} & \epsilon_{zy} & \epsilon_{zz} \end{bmatrix} = \begin{bmatrix} \epsilon_{xx} & \gamma_{xy}/2 & \gamma_{xz}/2 \\ \gamma_{yx}/2 & \epsilon_{yy} & \gamma_{yz}/2 \\ \gamma_{zx}/2 & \gamma_{zy}/2 & \epsilon_{zz}. \end{bmatrix} \tag{6}$$

1.3 Deformation Gradient

Displacement and deformations are the essentials of continuum mechanics. The deformation gradient is used to separate rigid body translations and rotations from deformations, which are the source of stresses [4]. In this tutorial, we will not cover rigid body dynamics. As is the convention in continuum mechanics, the vector $\mathbf{X}$ is used to define the undeformed reference configuration, and $\mathbf{x}$ defines the deformed current configuration [4]. The deformation gradient $\mathbf{F}$ (shown in Fig. 5) is the derivative of each component of the deformed $\mathbf{x}$ vector with respect to each component of the reference $\mathbf{X}$ vector [4], then

$$F_{ij} = x_{i,j} = \frac{\partial x_i}{\partial X_j} = \begin{bmatrix} \frac{\partial x_1}{\partial X_1} & \frac{\partial x_1}{\partial X_2} & \frac{\partial x_1}{\partial X_3} \\ \frac{\partial x_2}{\partial X_1} & \frac{\partial x_2}{\partial X_2} & \frac{\partial x_2}{\partial X_3} \\ \frac{\partial x_3}{\partial X_1} & \frac{\partial x_3}{\partial X_2} & \frac{\partial x_3}{\partial X_3} \end{bmatrix} \tag{7}$$

The displacement $\mathbf{u}$ can be defined as,

$$\mathbf{u} = \mathbf{x} - \mathbf{X} \tag{8}$$

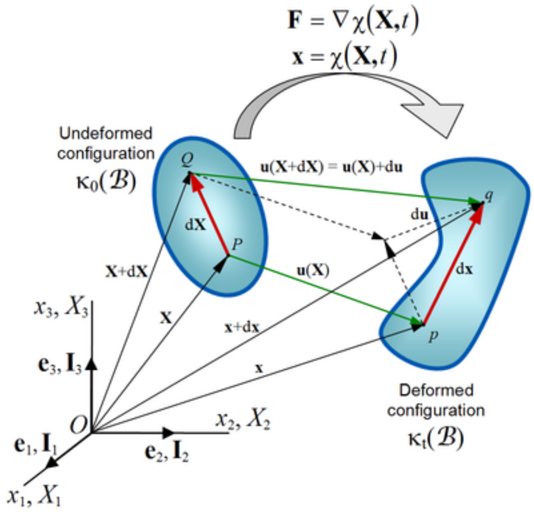


Fig. 5. The figure shows the displacement field and the deformation gradient. Copyright Wikipedia [8]

2 Nonlinear Material Models

For many materials, linear elastic models cannot accurately capture the observed material behavior; hyperelastic material models that can capture the nonlinear material behavior are subjected to large strain. For example, animal tissue and some common organic materials are often simulated using hyperelastic material.

Material model describes the behavior of a deformable body by defining the relation between the displacement field and the stress. Through the material model, we can compute the displacement field given the stress and vice versa. In order to define a nonlinear material model, we need to define the following,

1. Displacement-Strain Relation
2. Energy-Strain Relation
3. Strain-Stress Relation

2.1 Displacement-Strain Model

The displacement-strain model describes the relation between the displacement and the strain. In this section we will introduce the Green-Lagrange strain model. Before we introduce the strain model, we first set some notations. We will use small $\mathbf{n}$ as the surface normal for the deformed configuration while the $\mathbf{N}$ for that of the reference configuration. The Green-Lagrange strain model is designed for the measurement of large strain. It is defined through the right Cauchy strain tensor $\mathbf{C}_r = \mathbf{F}^T\mathbf{F}$, where $\mathbf{F}$ is the deformation gradient. The right Cauchy strain tensor measures the square of the changes of local deformation. The Green-Lagrange strain tensor $\mathbf{E}$ removes the rigid body transformation from the right Cauchy strain tensor. It is defined as

$$\mathbf{E} = \frac{1}{2}(\mathbf{C}_r - \mathbf{I}). \tag{9}$$

Specifically each element of the strain tensor matrix $\mathbf{E}$

$$\mathbf{E}_{ij} = \frac{1}{2}(\frac{\partial \mathbf{u}_i}{\partial \mathbf{X}_j} + \frac{\partial \mathbf{u}_j}{\partial \mathbf{X}_i} + \frac{\partial \mathbf{u}_k}{\partial \mathbf{X}_i}\frac{\partial \mathbf{u}_k}{\partial \mathbf{X}_j}) \tag{10}$$

It basically consists two parts, the small strain terms and the quadratic terms as shown in Eqn. 10. When the strain is small the quadratic terms can be ignored, and the Green-Lagrange strain behaves the same as the Engineering strain model which only contains the first part. But when the strain is large the quadratic terms record the strain. The quadratic terms also accounts for the **geometric non-linearity** of the strain-displacement relations.

2.2 Energy-Strain Model

The internal energy of an object consists of thermal energy and elastic strain energy. For the hyperelastic material model, the variation of the thermal energy is neglected. The stress-strain relation for a nonlinear material model is defined through the strain energy. The strain energy is the work done by the stress as is shown in Fig. 6.

The energy density function determines the behavior of the deformable object when subjected to stress. The energy density function is essentially a mapping from the stretches to the energy. For a material model to be isotropic in general, the energy function is expressed as a function of the invariants $\mathbf{I}_1, \mathbf{I}_2, \mathbf{I}_3$ of strain tensor. The invariants are computed from the principal stretches. When we do polar decomposition on the deformation gradient $\mathbf{F}$, we obtain,

$$\mathbf{F} = \mathbf{RU} = \mathbf{VR}, \tag{11}$$

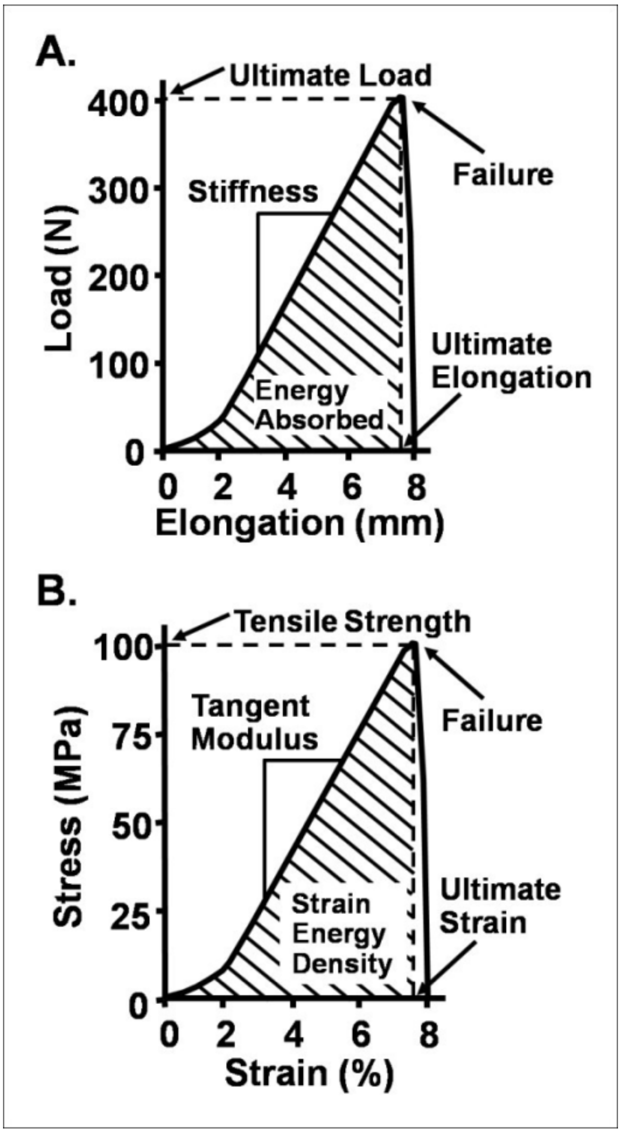


Fig. 6. The figure shows force vector normal to the surface or parallel to the surface. Copyright BioMed Central Ltd [1]

in which the matrix $\mathbf{R}$ is orthogonal. It is the rotation matrix. The matrix $\mathbf{U}$ and the matrix $\mathbf{V}$ have the same eigenvalues. Those eigenvalues are the principal stretches λ.

$$\begin{aligned} \mathbf{I}_1 &= \lambda_1^2 + \lambda_2^2 + \lambda_3^2 \\ \mathbf{I}_2 &= \lambda_1^2\lambda_2^2 + \lambda_2^2\lambda_3^2 + \lambda_1^2\lambda_3^2 \\ \mathbf{I}_3 &= \lambda_1^2\lambda_2^2\lambda_3^2 \end{aligned} \tag{12}$$

If the material is incompressible, the third invariant $\mathbf{I}_3$ is equal to one.

One general energy function of this class of incompressible material proposed by Rivlin [7] is,

$$\boldsymbol{\Psi}_{\mathbf{R}} = \sum_{i,j=0}^{\infty} \mathbf{C}_{ij}(\mathbf{I}_1 - 3)^i(\mathbf{I}_2 - 3)^j, \tag{13}$$

where $\mathbf{C}_{ij}$ are the material parameters. Many classical material models are derived from this equation. One obtains the neo-Hookean model by keeping the first term of the Rivlin expression.

$$\boldsymbol{\Psi}_{\mathbf{NH}} = \mathbf{C}_{10}(\mathbf{I}_1 - 3) \tag{14}$$

The classic Mooney-Rivlin model [5] is,

$$\boldsymbol{\Psi}_{\mathbf{MR}} = \mathbf{C}_{10}(\mathbf{I}_1 - 3) + \mathbf{C}_{01}(\mathbf{I}_2 - 3) \tag{15}$$

By adding the second term, the Mooney-Rivlin model can better describe the uniaxial tension behavior. To better capture the behavior of larger stretches, researchers use higher order of $\mathbf{I}_1$. One such model is the Yeoh model [11],

$$\boldsymbol{\Psi}_{\mathbf{Y}} = \mathbf{C}_{10}(\mathbf{I}_1 - 3) + \mathbf{C}_{20}(\mathbf{I}_1 - 3)^2 + \mathbf{C}_{30}(\mathbf{I}_1 - 3)^3 \tag{16}$$

To account for volume changes, compressible forms of this class of materials are proposed by adding the third principle to the Rivlin expression Eqn. 13.

$$\boldsymbol{\Psi} = \boldsymbol{\Psi}_{\mathbf{R}} + \boldsymbol{\Psi}(\mathbf{J}), \tag{17}$$

where $\mathbf{J}$ is the volume ratio $\mathbf{J} = \sqrt{\mathbf{I}_3}$. In this paper, we use this form of energy function of Mooney-Rivlin material [10,6]:

$$\boldsymbol{\Psi} = \frac{1}{2}w_1((\mathbf{I}_1^2 - \mathbf{I}_2)/\mathbf{I}_3^{\frac{2}{3}} - 6) + w_2(\mathbf{I}_1/\mathbf{I}_3^{\frac{1}{3}} - 3) + v_1(\mathbf{I}_3^{\frac{1}{2}} - 1)^2. \tag{18}$$

where w_1, w_2 and v_1 are the material parameters. The first two elasticity parameters, w_1 and w_2, are related to distortional response (i.e., together they describe the response of the material when subject to shear stress, uniaxial stress and equibiaxial stress), while the last parameter, v_1, is related to volumetric response (i.e. it describes the material response to bulk stress). $\mathbf{I}_1$, $\mathbf{I}_2$ and $\mathbf{I}_3$ are the three invariants. The invariants are computed from the principal stretches, which are the corresponding singular values of the deformation gradient $\mathbf{F}$.

2.3 Strain-Stress Model

We will be using the second Piola-Kirchhoff stress tensor with the Green-Lagrange strain tensor. The second Piola-Kirchhoff stress $\boldsymbol{\sigma}^{\mathrm{PK2}}$ tensor for hyperelastic material is defined through the energy function and the Green-Lagrange strain tensor $\mathbf{E}$. Thus the Green-Lagrange strain and the second Piola-Kirchhoff stress relation is defined as,

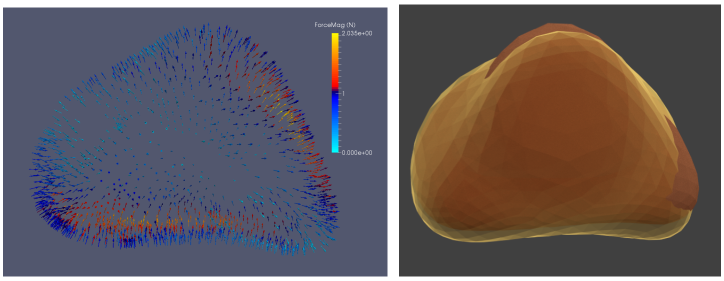
$$\boldsymbol{\sigma}^{\mathrm{PK2}} = \frac{\partial \boldsymbol{\Psi}}{\partial \mathbf{E}}. \tag{19}$$

Again, the energy density $\boldsymbol{\Psi}$ for hyperelastic material contains only the elastic energy. We can now give the deformation energy computed from the Green-Lagrange strain tensor $\mathbf{E}$ and the second Piola-Kirchhoff stress tensor $\boldsymbol{\sigma}^{\mathrm{PK2}}$ of the deformable body Ω,

$$\int_{\Omega} \boldsymbol{\sigma}^{\mathrm{PK2}} : \mathbf{E} \, \mathrm{d}\Omega \tag{20}$$

2.4 Boundary Condition

To solve the linear system defined in Eqn (1) in the paper, we need to set boundary conditions. We use the tractions on the boundary of the deformable body as the boundary condition. To illustrate this, the boundary condition we applied is the traction forces as shown in Fig. 7a and computed based on the displacement of the surrounding tissue (overlapping surfaces shown in Fig. 7b).



(a) (b)

Fig. 7. External Force Field and the Overlay of Initial/Target Surfaces. (a) shows the external force field we recovered. (b) shows the diferences between the initial organ surface (solid dark red) and the target surface (transparent yellow).

3 Correlate Elasticity Parameter with Cancer Aggression/Stages Study

We study the correlation between the recovered relative elasticity parameters and the prostate cancer T-Stage and Gleason score. A tabulated summary of the patient data is given in Table 3. The correlation results between the recovered elasticity parameter with the prostate cancer T-Stage are shown in Fig. 8a, with Gleason score are shown in Fig. 8b. To illustrate the cancer prognosis of these patients, we also plot their Gleason score distribution against cancer T-Stage in Fig. 8c. Our study suggests that the recovered relative elasticity parameters correlate better with the cancer T-Stage than with the Gleason score.

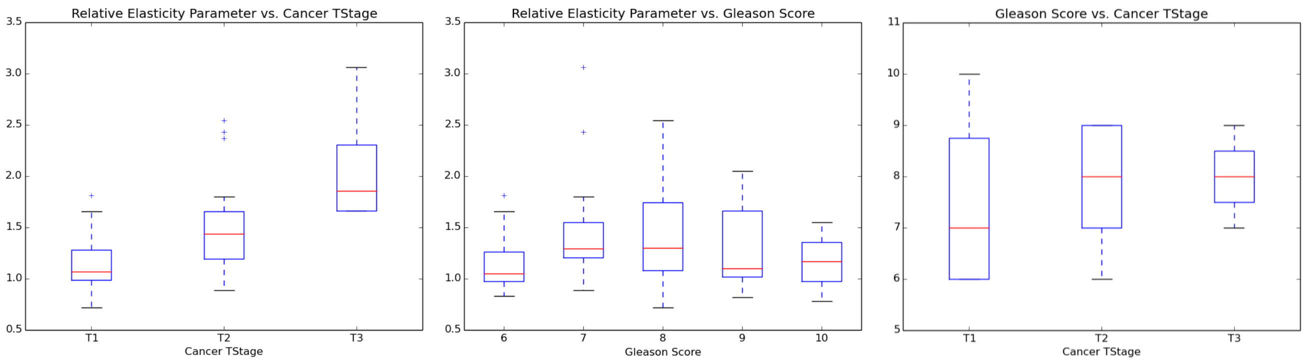
4 Classification Methods

For classification of cancer prognostic scores, we develop a classifier to predict patient cancer T-Stage and Gleason score based on the relative elasticity parameters recovered

Table 1. Patients' Cancer T-Stage, Gleason Score and Age.

Patient	Cancer T Stage	Gleason Score	Age	Patient	Cancer T Stage	Gleason Score	Age
1	T1c	7	56	15	T1c	9	68
2	T1c	6	59	16	T2	8	59
3	T1c	7	74	17	T3a	7	54
4	T2a	8	73	18	T1c	8	83
5	T3	9	66	19	T1c	10	74
6	T1c	6	65	20	T2	9	58
7	T1c	8	73	21	T1c	10	58
8	T2a	7	66	22	T1c	8	72
9	T2a	7	75	23	T1c	9	65
10	T1c	6	69	24	T2b	9	74
11	T1c	7	59	25	T2c	7	66
12	T2a	6	52	26	T1c	6	74
13	T1c	6	58	27	T2c	9	73
14	T1c	6	67	28	T1c	6	59
				29	T1c	9	60

Table 1. Patient Data. Patients' Cancer T Stage, Gleason Score, and Age.



(a) (b) (c)

Fig. 8. Correlation between Recovered Relative Elasticity Parameter and Cancer T-Stage & Gleason Score, as well as Gleason Score distribution vs. Cancer T-Stage.(a) shows the correlation between the recovered relative elasticity parameter and the prostate cancer T-Stage. (b) shows the correlation between the recovered relative elasticity parameter and the Gleason score.

from CT images. For oridinal logistic regression, we choose the cumulative logit model. It is also known as the "proportional-odds model". We use Y as the ordinal response variable, $\mathbf{x}$ as the vector of covariates and $\boldsymbol{\beta} = (\beta_1, \beta_2, \ldots, \beta_k)'$ as the unknown regression coefficients. The categories are represented by $1, 2, \ldots, k$ and the kernel function is denoted as $K()$.

$$Pr(Y \leq j|\mathbf{x}) = \frac{\exp(f(x))}{1 + \exp(f(x))}, j = 1, 2, \ldots, k \tag{21}$$

where $f(x) = \sum_{i=1}^{N} \alpha_i K(\mathbf{x}, \mathbf{x}_i)$. In logit form, it represented with $\Pi_j = Pr(Y \leq j)$, which is the cumulative probability as

$$\begin{aligned} \text{logit}(\Pi_j) = \log \left[\frac{\Pi_j}{1 - \Pi_j} \right] \\ \log \left[\frac{Pr(Y \leq j|\mathbf{x})}{Pr(Y > j|\mathbf{x})} \right] = f(x), j = 1, 2, \ldots, k \end{aligned} \tag{22}$$

where α_j is the known intercept parameters. For multinomial or polytomous logistic regression, we use the softmax loss function.

We compare this method with the Random Forests. Both the multinomal and ordinal regression method outperform the Random Forests method.

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