

Analysis of the Retinal Nerve Fiber Layer Texture Related to the Thickness Measured by Optical Coherence Tomography

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Abstract The retinal nerve fiber layer (RNFL) is one of the most affected retinal structures due to the glaucoma disease. Progression of this disease results in the RNFL atrophy that can be detected as the decrease of the layer's thickness. Usually, the RNFL thickness can be assessed by optical coherence tomography (OCT). However, an examination using OCT is rather expensive and still not widely available. On the other hand, fundus camera is considered as a common and fundamental diagnostic device utilized at many ophthalmic facilities worldwide. This contribution presents a novel approach to texture analysis enabling assessment of the RNFL thickness in widely used colour fundus photographs. The aim is to propose a regression model based on different texture features effective for description of changes in the RNFL textural appearance related to the variations of RNFL thickness. The performance evaluation uses OCT as a gold standard modality for validation of the proposed approach. The results show high correlation between the models predicted output and RNFL thickness directly measured by OCT.

1 Introduction

Glaucoma is one of the most common causes of permanent blindness worldwide with mean prevalence of 2.4 % for all ages and of 4.7 % for ages above 75 years [1]. One of the glaucoma symptoms is progressive atrophy of the retinal nerve fiber

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layer (RNFL) resulting in decrease of the layer's thickness. Degeneration of the nerve fibers starts many years before any changes in the patient's vision can be registered. Unfortunately, pathological changes in the RNFL cannot be revitalized by current medicine. Only, an immediate treatment can help to stop progression of the disease. Hence, it is extremely desirable to detect the disease as soon as possible. The RNFL thickness can be measured by optical coherence tomography (OCT), which is relatively new approach and it is still not widely available due to the high costs. In comparison, fundus camera is considered as a common diagnostic device currently available at many ophthalmic clinics around the world. Moreover, in contrast with OCT, examination by fundus camera is much faster, reducing workload of specialists, and cheaper. Hence, it brings an idea to use this widely available device for the RNFL assessment, especially for screening purposes.

Since the RNFL atrophy is one of the first signs of glaucoma disease that can be visible in fundus images, many researchers try to assess the visual appearance of RNFL. Historically, an attempt to utilize fundus cameras for glaucoma detection by evaluation of the RNFL appearance has been first introduced by Hoyt et al. [2]. The authors qualitatively revealed that the fundusoscopic signs of the RNFL pattern provide the earliest objective evidence of the RNFL atrophy in the retina. Other authors followed this subjective evaluation of fundus photographs afterwards. Airaksinen et al. [3] investigated the RNFL pattern visually and scored glaucomatous damage in a numerical scale. Peli et al. [4] performed one of the first semi-automatic analysis of the RNFL texture using digitized black-and-white fundus photographs. Yogesana et al. [5] made preliminary analysis of digitized fundus photographs via texture analysis based on gray level run length matrices. In addition, an intensity information about the RNFL texture was utilized again by Dardjat et al. [6] and Lee et al. [7]. Beside these older articles, recent authors have been investigating fundus photographs in more or less similar way. In the case of glaucomatous damage, the RNFL appears darker in fundus images. Therefore, many authors tried to involve intensity criteria for the glaucoma assessment [8–11]. A pilot study to search the RNFL thinning in digital colour fundus images was recently presented by Oliva et al. [10]. The article presents semi-automatic method to texture analysis based on evaluation of the RNFL pattern intensity. Hayashi et al. [8] used an approach with Gabor's filters to enhance certain regions with the RNFL pattern and to cluster these regions towards glaucoma detection. The paper presented preliminary results that were further followed up by the same group in [9]. The authors extended the earlier concept to analysis and performed evaluation using larger dataset. Furthermore, Prageeth et al. [11] published a method for glaucoma detection using intensity criterion as well. Although, the results seemed to be promising, utilization of intensity criteria used alone is probably not a good solution. Intensity changes in the RNFL pattern can be detected only if the RNFL atrophy is so distinctive than the patient has rather large vision loss already. Moreover, image intensity can be influenced by many factors as non-homogenous illumination, reflection of the retina, (in) homogeneity of light power used for image acquisition, etc.

Although, there is a considerable range of articles focused on analysis of fundus images aimed at glaucoma diagnosis, a complex methodology for the RNFL assessment in colour fundus images is still missing. Many published articles present methods based on evaluation of the RNFL intensity. As discussed above, utilization of intensity as a feature for detection of changes in the RNFL is less robust and unsuitable due to many physical as well as physiological reasons. Moreover, testing of the published methods is based mainly on low-resolution images. Thus, subtle variations in the RNFL thickness cannot be easily handled, since the RNFL texture is not detailed enough due to the low-resolution. The RNFL pattern is much more detailed and easily observed in current high-resolution fundus images. This offers a potential application of advanced texture analysis techniques taking into account not only the intensity criteria, but also various spatial characteristics of adjacent pixels in the texture [12–17].

As presented in this contribution, we have utilized our previous methods [13, 15, 16] to RNFL texture analysis using commonly available high-resolution colour fundus images. We extended the potential of these methods in order to show usability of the proposed texture features and their combination. Our approach utilizes Gaussian Markov random field (GMRF) texture modeling and local binary patterns (LBP) to generate features useful for description of changes in the RNFL texture. Different regression models are tested as the predictors of the RNFL thickness using the proposed features. The models are satisfactorily validated utilizing direct measurement of the RNFL thickness via OCT. The results proved that the model predicted output is closely correlated with the RNFL thickness, thus enabling detection of possible RNFL thinning.

2 Image Database

The database contains a number of 19 fundus image sets of healthy subjects and a number of 8 image sets of glaucomatous subjects with distinctive focal wedge-shaped RNFL loss. Only one eye of each subject was imaged. Each image set contains images acquired by a common non-mydriatic digital fundus camera CANON CR-1 (EOS 40D) with 60-degree field of view (FOV). The images have size of 3504×2336 pixels. Standard CANON raw data format (CR2) was used for storage of the images (Fig. 1).

The database also contains three-dimensional volume data and circular scans, acquired by spectral domain OCT system (Spectralis HRA—OCT, Heidelberg Engineering) for each of the 27 subjects. Infrared reflection images (scanning laser ophthalmoscope—SLO) and OCT B-scan (cross-sectional) images were acquired simultaneously. Acquisition of the OCT image volume (Fig. 2a) was performed within the peripapillary area. Circular scan pattern (Fig. 2b) is usually used for glaucoma diagnosis via OCT. A circle with diameter 3.4 mm is placed in the center of the optic disc (OD) and one B-scan is measured along this circle [18].

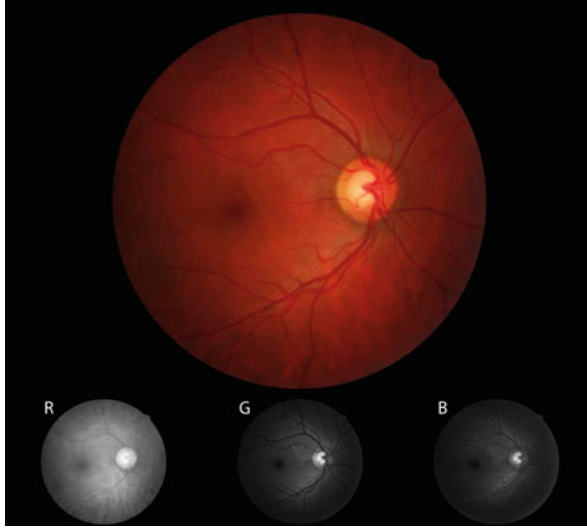


Fig. 1 An example of an original RGB fundus image of the healthy eye and individual colour channels of the image. In standard fundus image, the red (*R*) channel appears oversaturated, while the green (*G*), and the blue (*B*) channels show the blood vessels and retinal nerve fiber layer highly contrasted

3 Methods

An illustrative schematic diagram of the proposed RNFL assessment methodology is depicted in Fig. 3. The texture analysis is carried out within the peripapillary area at the locations without the blood vessels only. Our previously published matched filtering approach [19] is used for the blood vessel segmentation. Various regression models are tested towards prediction of the RNFL thickness using the proposed texture features. The regression models are trained on small square image regions (ROIs) selected from fundus images in the database and known measurement of the RNFL thickness. Circular profiles are extracted from the predicted images provided by the regression models. The resulted profiles are further validated with respect to the real RNFL thickness measured via OCT. The following subsections deal with the description of particular processing steps as well as evaluation of the approach.

3.1 Data Preprocessing

3.1.1 Preprocessing of Fundus Images

The fundus images are preprocessed in several steps. First, standard uncompressed TIFF format is reconstructed from the raw data, whereas a linear gamma transfer function is applied in the reconstruction process. Secondly, non-uniform illumination

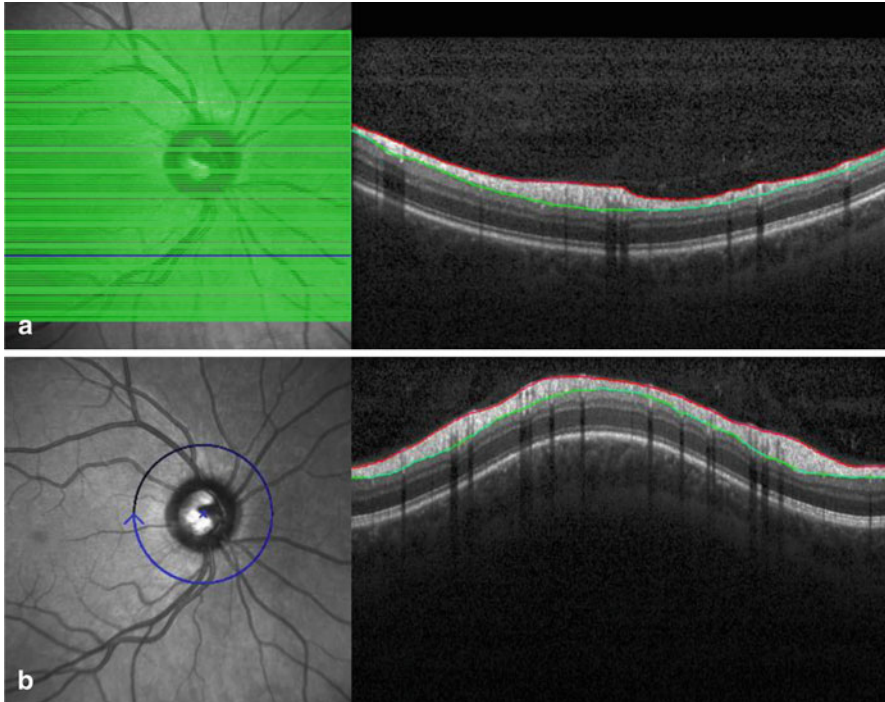


Fig. 2 An example of OCT volume and circular scans. **a** SLO image (*left*) with the volume scan pattern allocated by the *green lines* and one B-scan (*right*) measured at the position depicted by the *blue line* in SLO image; **b** SLO image (*left*) with the circular scan pattern defined by the *blue circle* and the B-scan (*right*) measured along this circle in direction given by the *arrow*. The curves in individual B-scans define segmentation of the RNFL

of fundus images is corrected together with the increase of image contrast using CLAHE (Contrast Limited Adaptive Histogram Equalization) technique [20]. The RNFL texture is the most contrasted in the green (G) and the blue (B) channels of the input RGB image (Fig. 1). Therefore, an average of G and B channel (called GB image) is computed for each fundus image after CLAHE. Further, only the GB images are used for processing.

In the first step, we manually selected small square-shaped image regions of interest (ROIs) with size of 61×61 pixels from all fundus images included in the group of normal subjects. Extraction of ROIs was performed uniformly in the peripapillary area to the maximum distance not exceeding $1.5 \times$ diameter of the OD; whereas only locations without the blood vessels were considered (Fig. 4). In this way, a total number of 354 ROIs was collected. Particular ROIs then represent the typical RNFL pattern depending on the position in the peripapillary area for normal subjects without any signs of glaucoma disease.

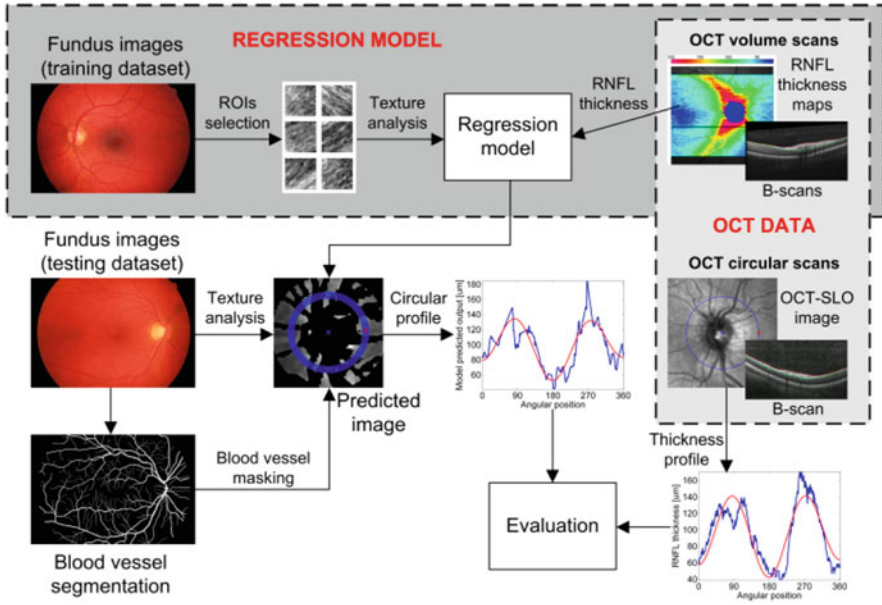


Fig. 3 Schematic diagram of the proposed methodology

3.1.2 Preprocessing of OCT Data

The OCT volume data were preprocessed in order to obtain the RNFL thickness in the peripapillary area of each subject in the database. Hence, the RNFL was segmented and the corresponding RNFL thickness map was created using freely available research software [21]. Segmentation of the RNFL layer was done automatically with very good precision so that only subtle manual corrections had to be performed in some B-scans using this software package (see segmentation of the RNFL in Fig. 2), especially in the area of large blood vessels (shadow artifacts in the B-scans). The final RNFL thickness map can be seen in Fig. 5.

3.1.3 Fundus-OCT Image Registration

Our previously published [22] landmark-based retinal image registration approach with manually selected landmarks and second-order polynomial transformation model was applied for registration of fundus to OCT-SLO image data. This registration step was necessary to be able to compare the proposed texture features with the RNFL thickness at various positions on the retina. However, different registration approaches could be used for this purpose as well, e.g. as in [23].

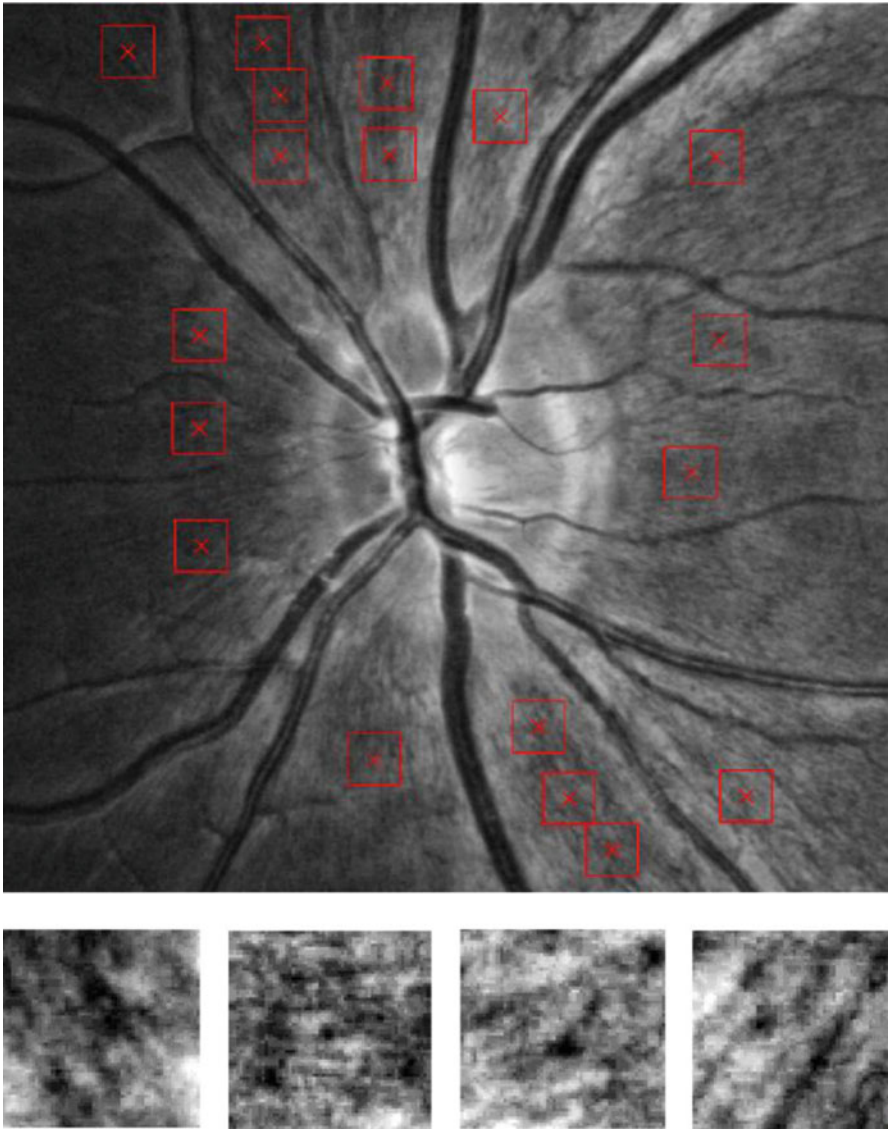
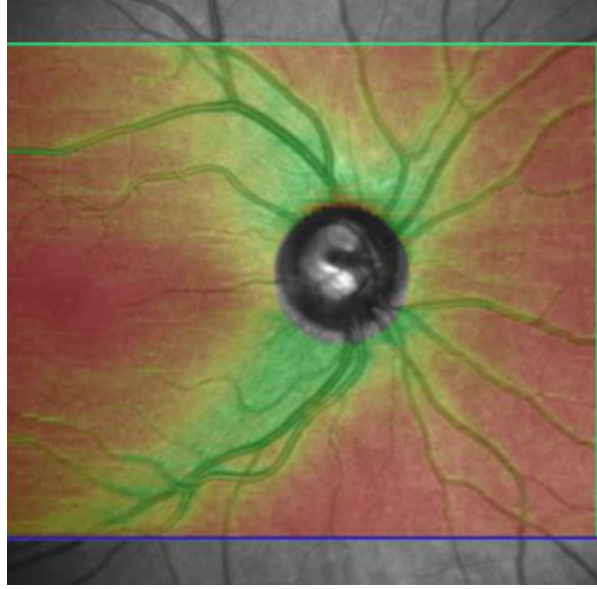


Fig. 4 At the top: section of the GB image after CLAHE processing with depiction of ROI positions; at the bottom: few examples of magnified ROIs with the RNFL texture taken in different positions in the peripapillary area (around the OD)

Fig. 5 The RNFL thickness map mapped on the SLO image of a normal subject. The colour spectral scale represents the changes of RNFL thickness approx. from $20\text{ }\mu\text{m}$ (red) to $180\text{ }\mu\text{m}$ (green)



3.2 Feature Extraction

The advance texture analysis methods, namely Gaussian Markov random field (GMRF) [24] and local binary patterns (LBP) [25] were used for the description of RNFL texture. These approaches were selected due to their rotation- and illumination-invariant properties as well as noise robustness.

3.2.1 Gaussian Markov Random Fields

First set of features is given by GMRF non/causal two/dimensional autoregressive model [24]. The model assumes the image texture is represented by a set of zero mean observations $y(s)$ [24]:

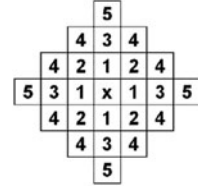
$$y(s), s \in \Omega, \Omega = \{s = (i, j) : 0 \leq i, j \leq M - 1\} \quad (1)$$

for a rectangular $M \times M$ image lattice Ω . An individual observation is then represented by the following difference Eq. [24]:

$$y(s) = \sum_{r \in N_s} \phi_r y(s + r) + e(s) \quad (2)$$

where N_s is a neighborhood set centered at pixel s , ϕ_r is the model parameter of a particular neighbor r , and $e(s)$ is a stationary Gaussian noise process with zero mean and unknown variance σ . A neighborhood structure depends directly on the

Fig. 6 A fifth-order symmetric rotation-invariant neighborhood structure



order and type of the model. We assume a fifth-order symmetric rotation-invariant neighborhood structure as shown in Fig. 6. The structure considers five parameters expressed by particular numbers. These five parameters describe the relationship between central pixel and its neighbors. Gaussian variance σ is the sixth parameter of the model. Then, these 6 parameters represent features, which are used for the RNFL texture description.

The least square error (LSE) estimation method is used for estimation of the GMRF model's parameters according to the following equations [24]:

$$\phi = \left[\sum_{\Omega} q(s)q^T(s) \right]^{-1} \left(\sum_{\Omega} q(s)y(s) \right), \quad (3)$$

$$\sigma = \frac{1}{M^2} \sum_{\Omega} (y(s) - \phi^T q(s))^2, \quad (4)$$

where

$$q(s) = \text{col} \left[\sum_{r \in N_i} y(s+r); i = 1, \dots, I \right], \quad (5)$$

for an i -th-order neighborhood structure.

3.2.2 Local Binary Patterns

The second applied method—LBP is based on conversion of the local image texture into the binary code using rotation-invariant and uniform LBP operator [25]. The local image texture around the central pixel (x_c, y_c) can be characterized by the LBP code, which is derived via the Eq. [25]:

$$LBP_{P,R}^{riu2}(x_c, y_c) = \begin{cases} \sum_{p=0}^{P-1} s(g_p - g_c) & U(G_P) \leq 2, \\ P + 1 & \text{otherwise} \end{cases} \quad (6)$$

where $U(G_p)$ means:

$$U(G_p) = |s(g_{P-1} - g_c) - s(g_0 - g_c)| + \sum_{p=1}^{P-1} |s(g_p - g_c) - s(g_{p-1} - g_c)| \quad (7)$$

In Eqs. 6 and 7, g_c corresponds to the grey value of the central pixel (x_c, y_c) of a local neighborhood and g_p ($p=0, \dots, P-1$) corresponds to the grey values of P equally spaced pixels on a circle of radius R ($R > 0$) that form a circularly symmetric neighborhood structure. The LPB operator expressed by Eq. 6 assumes uniform patterns. The “uniformity” of a pattern is ensured by the term $U(G_p)$. Patterns with U value of less than or equal to two are considered as “uniform” [25]. It means these patterns have at most two 0–1 or 1–0 transitions in the circular binary code.

Two variants of LBP were utilized in the proposed approach. Both variants are based on the rotation-invariant and uniform $LBP_{16,2}$ operator (i.e. $P=16, R=2$). One variant uses only LBP distribution computed from an input GB image. Then, the grey-level histogram of such parametric image is computed and extraction of 6 statistical features follows [25]: mean value, standard deviation, skewness, kurtosis, total energy and entropy. In the second variant, standard LBP distribution is supplemented with computation of local contrast $C_{P,R}$:

$$C_{P,R} = \frac{1}{P} \sum_{p=0}^{P-1} (g_p - \mu)^2, \text{ where } \mu = \frac{1}{P} \sum_{p=0}^{P-1} g_p \quad (8)$$

Then, in turn, a joint histogram of $LBP_{P,R}^{riu2}$ and $C_{P,R}$ (LBP/C) is computed. A feature vector is then obtained from LBP/C joint histogram by extraction of 14 texture features proposed by Haralick et al. [26] and Othmen et al. [27] (energy, contrast, homogeneity, entropy, correlation, sum average, sum variance, sum entropy, difference variance, difference entropy, two information measures of correlation, cluster shade, and cluster prominence).

3.2.3 Pyramidal Decomposition

Finally, a 26-dimensional feature vector assembled via connection of particular texture analysis approaches (GMRF, LPB, and LBP/C) is obtained. In addition, the features are computed for an original image resolution and even for each of the two levels of Gaussian pyramid decomposed images. Let the original image be denoted as $G_0(i,j)$, which is zero level of the Gaussian pyramid. Then, the l -th level of the pyramid is defined as follows:

$$G_l(i, j) = \sum_m \sum_n w(m, n) G_{l-1}(2i + m, 2j + n), \quad (9)$$

where $w(m,n)$ is a two-dimensional weighting function, usually called as “generating kernel”. According to, [28] recommended symmetric 5×5 kernel, written in

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