

## A. INTRODUCTION

In this progress report, we describe our findings related to the proposed research and provide details on the external grant applications that are prepared based on the outcomes of this project.

## B. OBJECTIVES

Prostate cancer is the second leading cause of death in men in the United States, with one in six men expected to be diagnosed with the disease in their lifetime [1, 2]. In addition to the high mortality risk, prostate cancer severely diminishes quality of life, with symptoms including pain, difficulty in urinating, and erectile dysfunction. Furthermore, prostate specific antigen (PSA) screening has resulted in an increase in the number of men suspected of having prostate cancer, and has made it increasingly important to evaluate small tumors and monitor their longitudinal changes.

In spite of the importance of prostate cancer, there is still no reliable, clinically acceptable, method of diagnostic imaging for prostate cancer. Although transrectal ultrasound (TRUS) is used routinely as a guide for biopsy, it cannot be used to visualize cancer foci. In fact, 40% of tumors are isoechoic [3]. Therefore, as many as 23% of cancers are missed on first biopsy, necessitating additional uncomfortable biopsies with more than 12 cores being obtained at each sitting [4].

The current diagnostic strategy is clearly unsatisfactory, and there is a tremendous need for accurate, non-invasive, intraprostatic cancer localization. Magnetic-resonance (MR) imaging has emerged as an extremely promising solution to the problem. Although prostate cancer is not adequately visualized in any individual type of MR image, preliminary studies [5-11] have shown that cancer can be accurately localized by its multispectral signature across multiple MR images.

Our collaborators at the University of Toronto have been performing careful and methodical pathological evaluations on the prostate of patients who have undergone in vivo multispectral MR imaging and prostatectomy. Exvivo images of the histological slides are also acquired so that accurate mapping between the histological slides and the in vivo MR images is possible. This provides us with a superb source of data from which to launch a rigorous development and preliminary validation of multispectral MR prostate imaging as a clinical tool. The ground truth obtained from the histological slides accompanying the multispectral MRI will be used in both efficient and accurate training and providing the ground truth that will be used in evaluating the developed methods.

However, the multispectral MR images that are obtained in different sessions is not perfectly aligned, and obviously the histological slides are needed to be matched to the in vivo MR images so that the ground truth obtained from the pathology can be accurately mapped to in vivo images for training and evaluation.

The goal of the proposed project is to develop automated registration algorithms that will be used to register in vivo MR images to histological slides, as well as register multiple in vivo images that are acquired with various MR techniques in different imaging sessions.

Results of the proposed project will be useful for not only prostate cancer, but other types of cancers where localization is performed based on in vivo images and corresponding histological slides, including breast, cervical, kidney, and possibly other types.

The specific aims of the proposed project will be to:

1. Develop automated registration algorithms based on similarity metrics between the ex-vivo images of the prostate and the in vivo MR images.
2. Develop automated registration algorithms based on landmarks that are derived by our collaborators expert radiologists.
3. Evaluate the automated registration algorithms by observing their affect on cancer localization performance, and develop algorithms that will improve localization performance.
4. Prepare an external grant, to be submitted to NIH that will be used to complete the project.

## C. BACKGROUND AND SIGNIFICANCE

### C. 1. Importance of Prostate Cancer and the Need for Improved Imaging

Curative treatment options for men with prostate cancer are radical prostatectomy or radiation therapy. Both of these carry a significant risk of complications, with a prevalence of sexual, urinary and rectal dysfunction of up to 79%, 16% and 29% respectively [12].

Currently, the diagnosis of cancer is made by TRUS-guided biopsy; however TRUS alone cannot reliably visualize cancer foci, with up to 40% of tumors being isoechoic [3]. Since the needle cannot be reliably directed to a cancer target, a grid-like systematic biopsy of the gland is routinely performed in addition to biopsy of suspicious hypoechoic areas. If imaging could localize cancers more accurately, then the biopsy needle could be directed specifically to the site of cancer, thus reducing the false-negative biopsy rate.

For many patients, the cancer is indolent and not life-threatening; therefore, these patients may be candidates for active surveillance rather than more-aggressive intervention. However, it is not possible at present to determine accurately which patients are good candidates for this approach. This is particularly true for younger men with small-volume organ-confined disease.

Because tumor size is a predictor of outcome, an imaging method that could reliably localize cancer foci within the gland would allow for determination of the size and growth rate, guiding therapy of the most significant cancers. The door would open to less morbid subtotal targeted ablative approaches to therapy such as cryotherapy, high-intensity focused ultrasound, brachytherapy, intensity-modulated radiation therapy and photodynamic therapy [13], as well as conformal dose-escalation approaches to radiation therapy. Pre-operative knowledge of tumor size could guide adjuvant therapeutic approaches, since maximum Gleason grade is not always well predicted with biopsy. For example, in centers performing routine radical prostatectomy, the pre-operative knowledge of tumor location may alter the surgical approach to ensure negative margins while minimizing side effects through nerve-sparing techniques.

Owing to the poor performance of grey-scale ultrasound for visualization of prostate cancer, several alternatives have been considered in research studies. Multispectral MRI is one of the most promising novel imaging technology. T2-weighted MRI (T2MRI) has been studied for many years for staging of prostate cancer. As MRI techniques have advanced, MR proton spectroscopy (MRS), diffusion-weighted MRI (DWI) and dynamic contrast-enhanced MRI (DCEMRI) have been applied to the prostate. The DCE MRI parameters that reflect tumor microvasculature such as peak enhancement and permeability-surface area product show promise in distinguishing benign from malignant tissue [14]. Permeability is known to be elevated in tumor microvasculature

and this is a key characteristic of angiogenesis in malignancy. Based on the different microenvironmental mechanisms that lead to altered vascular permeability and water diffusion we might expect these imaging methods to be complimentary in the segmentation of tumor from normal tissue. Prostate cancers have demonstrated low T2 signal on T2MRI, a low apparent diffusion coefficient (ADC) on DWI, a high choline + creatine to citrate ratio on MRS and high permeability on DCE MRI compared to normal prostatic tissue. T2MRI alone can localize cancer larger than 0.5cc in volume with only 65-74% sensitivity and low specificity [15]. MRS has not been shown to add to T2MRI in a multi-institutional study (ACRIN 6659) [16]. This result has prompted a shift in focus to include DWI, and DCE MRI combined with T2MRI. Studies have been published showing localization accuracies of slightly greater than 80% in the detection of cancers by combining these methods entering the realm of clinical utility [17-18].

### C.2. The Need for an Automated Method of Cancer Localization

Given the promising early results of multispectral MRI it is clear that automated techniques for prostate cancer will be extremely important. The studies performed with multispectral MRI to date have been single-intuition studies with expert readers. The precise methods of interpretation are almost always vague and are not based strictly on quantitative thresholds but on a combination of qualitative and quantitative analysis. In addition, for cancer localization, interobserver agreement among experienced readers has only been moderate. In a recent study from a major prostate MRI research center [11], the kappa values for interobserver agreement in combined interpretation of T2 and MRS was only 0.48. Given the high prevalence of prostate cancer and the widespread applicability of MRI, an observer-independent method of data analysis could enable multispectral MRI to be applied consistently and repeatably across sites and across patient examinations (for longitudinal monitoring).

The volume of unprocessed imaging data flooding the clinic has also led to problems in image viewing and interpretation. It is simply not practical in today's health-care environment for practitioners to meticulously scrutinize co-registered parametric DCEMRI, DWI, and MRS prostate images slice-by-slice, especially when looking for very small tumor foci. Because all these images contain quantitative information tied to tumor characteristics, they lend themselves to quantitative analytic methods that will go beyond the abilities of simple visual interpretation of partially processed image sets.

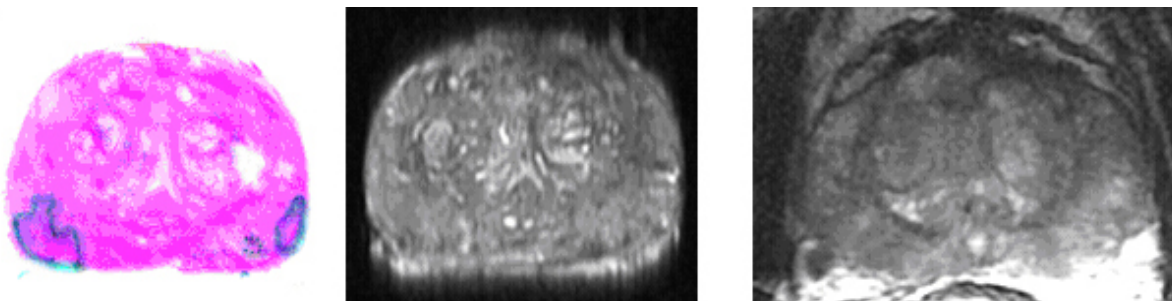
Therefore, there is a need for automated localization algorithms [19,20] for the prostate cancer based on multispectral MRI data. An important problem to be solved before efficient automated localization algorithms can be developed, is the misalignment between histological slides and *in vivo* MR images.

### C.3. The Need for Automated Registration of Histology and *in vivo* Multispectral MRI

The unique source data that we have consists of a rich family of multispectral MRI data, and the accompanying histological slides for accurate prostate cancer localization. However, the multispectral MR images that are obtained in different sessions is not perfectly aligned, and obviously the histological slides are needed to be matched to the *in vivo* MR images so that the ground truth obtained from the pathology can be accurately mapped to *in vivo* images for training and evaluation. Figure 1 shows an example of a histological slide, its *ex vivo* MR image, and the corresponding *in vivo* T2 MR image. It is very clear that the prostate is considerably deformed. This deformation is basically due to two main reasons: (i) The *in vivo* MR image is for the prostate inside the body causing to be shaped in a different way than the prostate after surgery, (ii) the

pathology tests deforms the prostate especially during the slicing and HistOmer gel used to hold the prostate.

All automated prostate cancer localization algorithms that our group have been developing depend on fusing information from multispectral images, and the ground truth obtained from the histological slides. Therefore, it is very crucial to obtain an accurate alignment between the images, and an accurate transformation of the ground truth from the histological slides to the *invivo* MR images. This procedure of mapping of the ground truth from the histology to the *invivo* MR images is both vital for efficient training of the algorithms, and also for the evaluation of the developed methods.



**Figure 1.** Left: Histological slides with tumors outlined based on pathology, center: *ex vivo* MR image of the histological slide, left: *invivo* MR image. The deformation of the prostatectomy and pathological processing is very clear motivating for an automated registration.

Current technology of registering the histological slides to the *invivo* MR images is manual. An expert radiologist views the tumor outlines obtained from the pathology, the *ex vivo* MR images of the histological slides, and the *invivo* MR image, and manually outlines the tumor in the *invivo* MR image. Clearly this is a very time consuming and subjective process. Automated registration algorithms will not only improve efficiency but also decrease the subjective evaluation of the human reader.

Recently, there have been isolated attempts to automatically register histological slides to *invivo* MR images [23-25]. However, some of these techniques are two-dimensional and some are based on generic registration software packages, which is not tailored for the specific problem of histological slides and the anatomy of the prostate. We propose to develop fully 3-D and automated registration algorithms that are specifically designed for the prostate.

In addition to the registration of histology to the *invivo* MR images, we need to align the multispectral MR images among themselves since they are acquired in different sessions. There are mainly three types of MR images that produce the family of multispectral MR images (summarized in Table 1) that will be used for prostate cancer localization: (i) T2 MR images, (ii) Diffusion weighted images (DWI), (iii) Dynamic contrast enhanced (DCE) MRI. These three raw MR data are acquired in different sessions, and hence are not perfectly aligned. The deformation between the *invivo* MR images is not as severe as the deformation of the histological slides, and we anticipate this problem to be solved much more easily as explained in Section C.2.

## D. RESEARCH DESIGN AND METHODS

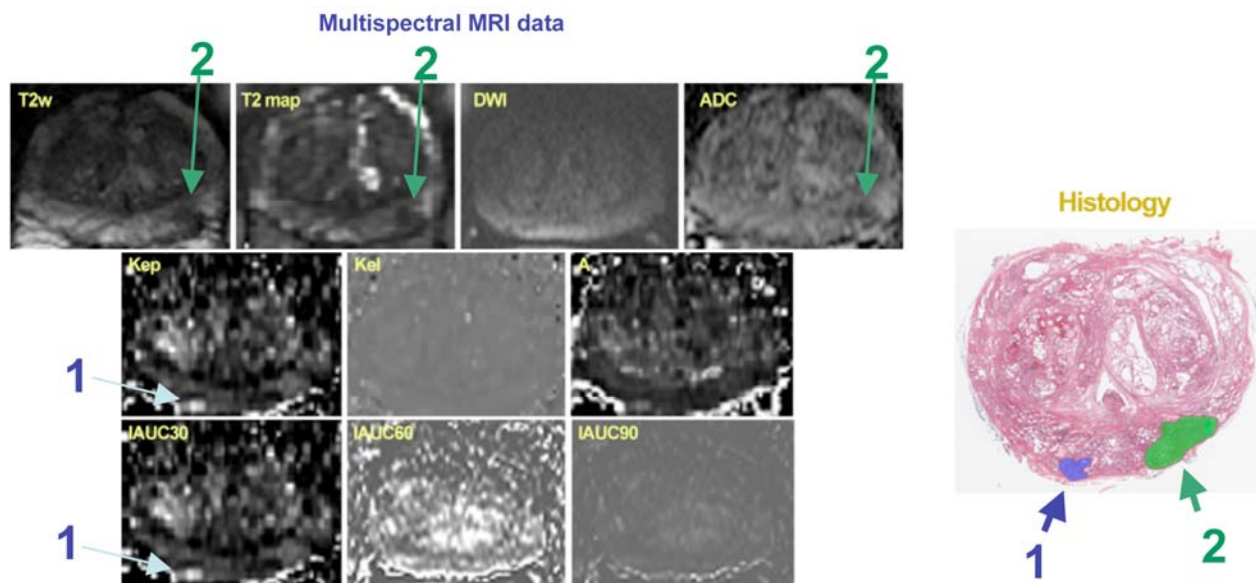
### D.1. Overview of the Research Plan

The overall goal of our project is to develop automated registration algorithms to align histological slides to in vivo multispectral MR images and aligning multiple types of MR images to aid prostate cancer localization. Accurate alignment is a crucial step for both efficiently training segmentation algorithms and also evaluating the developed localization methods. This seed grant will be used to develop basic methods for registration and produce preliminary results so that an external grant can be prepared for submission to NIH. The results that are obtained throughout the course of this project will also be very helpful in boosting the funding chances of an R01 NIH grant on prostate cancer localization we recently submitted.

First six months of the project will be used to develop registration algorithms, next two months will be used to apply the methods to the real data that our collaborators at the University of Toronto will provide us. Last four months will be reserved for the evaluation of the developed methods and the completion of the external grant for NIH.

There are two main registration problems that need to be solved. First one is the registration of in vivo multispectral MR images since they are based on raw MR data that are acquired in different sessions. Second one is the registration of the histological slides to the in vivo MR images. Next, we explain the methodologies that we propose to develop to solve these problems as well as our plans for evaluation of the developed registration algorithms.

#### D.2. Registration of in vivo Multispectral MR Images



**Figure 2.** One slice from a multispectral MRI data set (upper left) and a histology slide (right). Note that cancer focus 1 appears only in certain images, while cancer focus 2 appears only in others motivating for multispectral MRI. The multispectral MR images on the left are not perfectly aligned and registration is needed since they are obtained based on three MR imaging techniques obtained at different sessions.

A sample of the multispectral MR images that we plan to use for prostate cancer localization are given in Figure 2. These 10 different images are obtained based on three MR imaging techniques: (i) T2, (ii) DWI, (iii) DCE MRI. Therefore we need to align

the images obtained from three groups. Since the invivo MR images that need to be registered are all obtained from the same patient around the same time (no anatomical change occurs between scans), the registration problem is relatively easy to solve. Since the images are from different MR techniques, and difference between images is not only due to geometric distortion, we cannot use intensity-based techniques for alignment. Information based registration techniques [26,27] can be used to estimate the deformation between these three groups. Mutual information between two images

$A$  and  $B$  is defined as  $I(A,B) = H(B) - H(B/A)$ , where  $H(B) = -\sum p_i \log(p_i)$  is the Shannon entropy. Then registration based on mutual information can be formulated as

finding an estimate of the distortion parameters  $\theta$  by  $\hat{\theta} = \arg \max_{\theta} H(B) - H(B/C(A,\theta))$ ,

where the image  $C$  the registered version of  $A$ , and therefore a function of both  $A$  and the distortion parameters  $\theta$  to be estimated. There are two main steps in constructing a registration algorithm in this way: (i) selection of a model for deformation that determines the structure of  $\theta$ , (ii) a numerical method that performs the optimization. Since our goal is to register invivo images that are not anatomically different (no change in the prostate or tumor), we can use a rigid deformation with slight non-linear variations. The registration then will be performed in two steps. First, we find the optimum rigid deformation that best matches the pair of images we want to register. As a second step, we will use a non-linear deformation model such as the B-splines to compensate for small elastic deformation due to the different posture of the prostate during different imaging sessions.

We observe that the T2 images and DWI images are sufficiently noise-free so that the slight misalignment between these two groups can be estimated relatively easily. However, the parametric images obtained from DCE MRI are quite noisy; therefore we anticipate that the performance of the information based registration algorithms may suffer. To overcome this problem, instead of using the derived parametric images, we propose to use the DCE MRI images directly (possibly the mean of the time series MRI). Although the mean image does not have the physiological information that the parametric images (such as  $k_{el}$ ,  $k_{ep}$  and  $A$ ) have, it is certainly less noisy and a good candidate to be used in the registration algorithms.

### D.3. Registration of the histological slides and the invivo multispectral MR images

Registration of the multispectral MR images and the histological slides is a more difficult problem since the deformation is much more nonlinear and strong because of the surgery, slicing, and the pathological processing. Therefore, we will consider alternative strategies for this problem.

#### D.3.1. Registration based on mutual information

Since, we have the exvivo MR images of the histological slides, these can be used to match with the invivo multispectral MR images based on the mutual information as explained in Section C.2. However, we anticipate that the two-step approach (rigid registration followed by a minor elastic registration) will not work in this case, since the non-linear deformation might be significant. Then, we will have to use non-linear deformation models that can handle large elastic deformations. However, there is a possibility that this type of approach to estimate large elastic deformations directly based on mutual information might not function well because of the convergence

problems. In such a case we will consider an alternative strategy where landmarks are utilized.

#### D.3.2. Registration based on landmarks

Registration based on landmarks is a relatively simple procedure, since the corresponding points or structures are known a priori. Then a simple cost function that penalizes the position error can be used to find the optimum deformation parameters  $\theta$ . The drawback in this case is the additional procedure of deriving the landmarks.

We will initially use landmarks that are manually extracted by a radiologist. An expert will determine the landmarks on the ex vivo MR image of the histological slides, and corresponding landmarks on the in vivo MR images. Then, the deformation parameters that best match the location of the landmarks will be selected as the optimum deformation parameters. The deformation function based on these estimated parameters will then be used to transfer the boundary of the tumor from the histological slides to the in vivo MR images.

During the course of the project, we will also test methods that utilize automatically extracted landmarks. As a part of another project, our group is developing methods to automatically extract the whole prostate and different zones (such as the peripheral and transition zones). Then these outlines can be used as automatically determined landmarks, and potentially yield sufficiently accurate elastic registration.

#### D.4. Three-dimensional registration

The histological slides consist of slices that do not necessarily correspond to a particular slice of the in vivo MR image. Therefore a fully 3-D registration strategy is necessary for accurate alignment. We will construct 3-D blocks of the prostate based on the ex vivo MR images of the histological slides. Since, the slice thickness will be different for the in vivo MR images and the ex vivo images of the histological slides, we will use an interpolation algorithm to be able to perform a fully 3-D registration. Complexity of the interpolation scheme will be determined during the course of the project. We will start with simple linear interpolation and consider more complicated schemes as necessary.

#### D.5. Evaluation

It is usually a very complicated task to evaluate registration algorithms that are developed for real-world images since the ground truth is not known. We will consider three methodologies to evaluate registration methods.

First one is based on the assumption that, when perfect registration is achieved (that is the exact tumor location is known in the in vivo MR images) the separation of cancerous and normal regions based on the multispectral will be more apparent. Then, within class variance will be minimum, and interclass variance will be maximum when the classes are based on correct outlining of the tumor. For each of the registration algorithm to be evaluated the corresponding within class variance of the pixels can be used as a metric for evaluation.

Second evaluation method will be based on the assumption that the landmarks derived on two images to be registered are the ground truth. Then different registration algorithms can be evaluated by their capability of matching these landmarks.

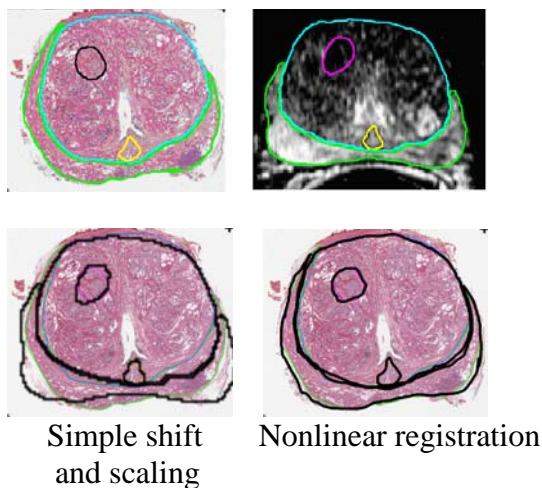
As a third method of evaluation, we will use the transitivity concept. Assuming that we want to register images  $A$  and  $B$ . We will find the deformation  $\theta_1$  of  $A$  that best matches  $B$ , and the deformation  $\theta_2$  of  $B$  that best matches  $A$ . Then for an ideal registration algorithm,  $\theta_1 \theta_2^{-1}$  should be the identity operation. For each of the

registration algorithm to be evaluation,  $\theta_1 \theta_2^{-1}$  can be calculated, and its distance to the identity operation can be used as metric for evaluation.

### E. PRELIMINARY REGISTRATION RESULTS

We have found that registration with mutual information does not yield satisfactory results. However, the future MRI images that will be used as will be acquired with 3.T instead of 1.5 T. This will provide us images with improved SNR and resolution. Hence, the methods we have developed based on mutual information will be applied on these images to observe a potential change.

Based on this preliminary findings, we have focused more on the landmark based registration. Our collaborators from University of Health Network/University of Toronto have provided us with histological slides and *in vivo* MR images with landmarks determined by an expert. Then, we have used these landmarks for alignment as explained in Section D.



**Figure 3:** Nonlinear registration. Top-left: landmarks on histological slide, top-right: landmarks on an example *in vivo* image. Bottom-right: overlap between landmarks after a simple shift and scaling, bottom-left: overlap between landmarks after non-linear registration.

As explained before there is a considerable nonlinear deformation between the *in vivo* MR images, and the histological slides due to histological processing. The landmarks, such as the prostate boundary, peripheral zone boundary, and nodules on the prostate, were marked on both *in vivo* images and the histological slides as shown in Figure 3. Then, these were used for nonlinear registration based on B-splines. Figure 3 shows that the automated registration method we applied can successfully align the histological slide and the *in vivo* MR image; see the overlap between the landmarks before (Fig. 3, lower left) and after (Fig. 3, lower right) nonlinear registration.

We have followed a multistep alignment procedure as follows: (i) use the prostate boundary to align for scaling and shift, (ii) use nodules and peripheral zone for rotation, (ii) use prostate boundary, the

peripheral zone boundary, and nodules on the prostate to align for nonlinear distortions due to prostate motion and histological processing. Validation of the registration method will be performed by comparing the overlap between landmarks before and after registration using the location and shape of the landmarks as well as the dice measure. Difference between shapes will be quantified using measures such as mean and maximum boundary difference. More details are provided in Section D.

## F. EXTERNAL FUNDING

The preliminary registration results that are obtained in this grant was used to significantly enhance and support the following four external grant applications:

1. NIH R01 grant titled "Automated Prostate Cancer Localization with Multispectral MRI", role: PI, duration 4 years, Amount \$1,775,450.", submitted June 2009.
2. NIH R21 grant titled "Visualization of Prostate Cancer Using Multispectral MRI", role: PI, duration 2 years, Amount: \$380,048.", submitted April 2009.
3. DOD new investigator grant titled "Image Fusion Methods for Prostate Cancer Localization with Multispectral MRI", role: PI, duration 2 years, Agency: DOD, Amount: \$262,595, submitted May 2009.
4. DOD Population based idea development grant titled "Automated Prostate Cancer Localization with Multispectral MRI", role: PI, duration 3 years, Amount \$742,624, submitted May 2009.

This seed grant will also be used to prepare an NIH AREA grant application that will be submitted on October 5, 2009.

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