卒研配属学生向け

# 研究論文の読み方

理学部 物理学科 固体物理学講座 西沢 グループ



Department of Physics,
School of Science, Kitasato University

# なぜ論文を読むのか

## 最新の研究を行うには、

- 何が求められているのか、何をしりたいのか
- どのようにすれば明らかになるか
- どのように考えればいいのか

が分かる必要がある



- これまでに何がわかっていて、何がわかっていないのか
- 先人はどのようにして明らかにしたか
- 先人はどのように考えたか

ゼロから新たなアイデアは生まれない。 なぜならアイデアとは既存知識の組み合わせであるから。

既存知識にとらわれない新たなアイデアというものは存在しない。たとえあっても同じことを世界の誰かはすでに考え、試した上で失敗している。

アイザック・ニュートン

『私がかなたを見渡せたのだとしたら、それは巨人の肩の上に立っていたからです。』 *If I have seen further it is by standing on the shoulders of Giants*.



# 学部生が論文を読む上での注意



最初から全て理解しようとしない わからないところは放置か教員に聞く

少しでも知識があると理解できるところが増える

基礎物理 とにかく理解のための前提知識を増やす

対象の性質
考え方
知識

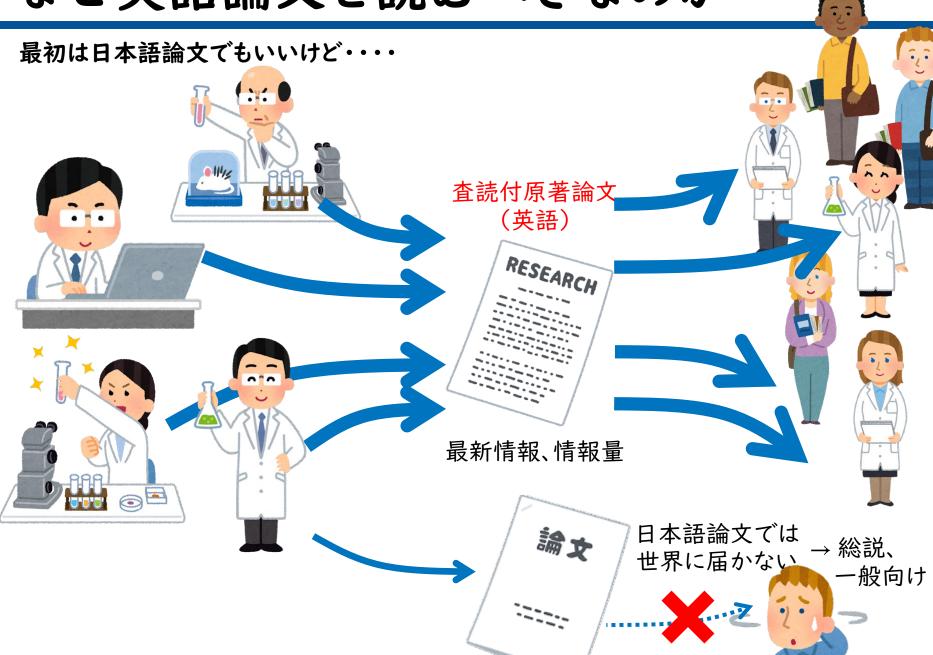
解析方法

得られた知見

論文理解

とにかくこのサイクルを回すことが大切

理解できる部分から分かる範囲のものを蓄積する



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# 配属学生向けの論文読みの進め方

1. 研究テーマに沿った日本語の総説を読む

知らない専門用語などは調べて 研究の流れ、必要な情報をざっくりと理解する

専門用語をざっくり掴むためには学部1~3年の授業が重要だったりするこのときに、キーワードとなる単語は英訳しておくこと



論文

- 日本レーザー医学会誌 2024年45巻 2号
- 「光アライアンス」2022年8月号
- 「光学」2023年5月号 (いずれも所属時に配布)

2. 研究テーマのうちで指標となっている英語原著論文のうちできるだけ最新のものを読む

研究の流れのうちでマイルストーンとなる論文は必ず1.の日本語論文でも参照されているはず。その論文(複数ある場合は最新のもの)を読む。または配属された研究室(教授)が出した最新の論文のうち最新かつ高IFのもの

- Kunnen *et al.*,
  - J. Biophotonics **8**, 317-323 (2015)
- N. Nishizawa et al.,
  - J. Biophotonics 14, 202000380 (2020)
- 3. 2.を読んで理解を深める上で重要と思われる論文を過去に遡って読む もしくは、2.の論文を参照しているそれよりも新しい論文を読む
  - 2.の論文を基点にして1つ<u>過去</u>のマイルストーン論文を読む (1.の総説にも載っているはず) 同時に、2.の論文を基に研究された一つ**未来**の論文を読む



# 読む上でのポイント

- 1. 完璧を求めない 100%理解するなんて無理なので50%でOK、60%で上出来
- 2. 論文選びに迷ったら教員や先輩を頼る 最初は先人に貰うのが手っ取り早い 自分で選んでもこれでよさそうか聞こう
- 3. 最初から最後に向かってまっすぐ読まない 論文は小説ではないので最初から最後に向かって読む必要はない。 8ページ以降に示すような順序で読むと理解は早いと思われる
- 4. 論文の内容を鵜呑みしない 教科書ではないので、必ずしも正しいとは限らない (そもそも大学以上では教科書も100%正しい訳では無いけど)
- 5. 論文の内容を自分の研究と結びつけておく 自分の研究と直接結びつかないと思われる論文であっても、 常に自分の研究との関連を意識しながら読む。 新たなアイデア(研究)になる可能性や自分の研究で予想外の結果が出たときの助けになることも あるが、それ以上に理解したことを記憶に定着させるのに役に立つ。
- 6. 英語翻訳ソールは使ってもいいが頼りすぎないこと
  DeepLやGoogle翻訳などを使うことは悪いことではない。大枠を捉える、読むべきかどうかを判断するなどの場合は積極的に使う。ただし、本文を一度も読まずにコピペではいつまでたっても読めるようにはならない。辞書を使ってじっくり読む時間も作ること。

# 論文の読み方

1. 批判的に読む

常に疑問の姿勢で読む。良い論文の著者はその疑問を解消させるように書いている。 生じた疑問は<u>メモ</u>をとっておき、それについて書いてあるかチェックする

- 図(フローチャート)を書きながら読む 論理展開を→で結びながらフローチャートを書く。 論理の結びつき、対応、並列関係、因果関係を書く。
- 3. 紙に印刷し、色を付けながら読む (私の場合) 4色ボールペンを使う

Important sentence (重要な文章:赤だけ読んでも論文が一貫する文)

Unknown word (専門用語のうち知らない単語 → 後で復習)

Authors thoughts (著者の解釈、推測、結論)

My thoughts (3.の疑問、著者の考えに対する自分の意見)

4. 記録をつける

(私の場合) 白紙の紙を用意して、そこに

フローチャート(4.)とともにImportant sentence (3.の赤)、

著者の意見(3.の青)、自分で生じた疑問や意見(5.の黒)

をまとめて書く。

それを論文の最後に入れてホッチキスでとめてファイリング

# 具体的な論文の読み方。 M. Nishiwawa *et al.*, J. Biophotonics **14**, 202000380 (2020) を手本に

Check for update

Received: 19 September 2020 Revised: 17 November 2020 Accepted: 3 December 2020
DOI: 10.1000/Sio-Verservisor

FULL ARTICLE

JOURNAL OF BIOPHOTONICS

1

### Angular optimization for cancer identification with circularly polarized light

Nozomi Nishizawa<sup>18</sup> | Bassam Al-Qadi<sup>2</sup> | Takahiro Kuchimaru<sup>3</sup>

Research and Technology, Tokyo Institut of Technology, Yokohama, Japan <sup>2</sup>College of Engineering and Technology, Palestine Technical University - Kadoorie <sup>5</sup>Center for Molecular Medicine, Jichi Medical University, Tochigi, Japan

Correspondence Sozoni Nishirawa, Laboratory for Putun

Depolarization of circularly polarized light scattered from biological tissues nuclei, which can provide valuable information for differentiating cancer tissues oncealed in healthy tissues. In this study, we experimentally verified the postering of circularly polarized light. We

scattered from a sliced biological tissue with various optical configurations. A cancerous and healthy tissues is observed, which is sufficient to distinguish a cancerous region. The line-scanning experiments along a region incorporating healthy and cancerous parts indicate step-like behaviors in the degree of circular polarization corresponding to the state of tissues, whether cancerous or normal. An oblique and perpendicular incidence induces different resolutions for identifying concernus tissues, which indicates that the ontical arrangement can be selected according to the priority of resolution.

cancer detection, circularly polarized light, multiple scattering, optical biopsy, tissue sample

### 1 | INTRODUCTION

The multiple scattering phenomenon of polarized light provides valuable information regarding scatterers in a urbid material, based on the polarization state as well as the remnant intensity of the scattered light. When polarized light beams implinge on a biological tissue, they pen-etrate and propagate into the tissue and are scattered multiple times by cell nuclei, which are the main

absorbed inside or discharged outside the tissue. Depolar-ization of the resultant scattered light mainly depends on the size and axial ratio of scatterers, that is, cell nuclei, as well as the frequency of scattering events associated with the density and distribution of cell nuclei.

Bickel et al [1] reported that the polarization state of light scattered differentially from suspended biological scatterers can provide structural information about

biological tissues. They suggested that this technique is side facet and can detect CP light without applying an useful for distinguishing closely related structural biological systems and for identifying subsequent time-dependent structural changes. Most of the earlier studies dependent structural changes though of the cartiers with a sen endoscope, the polarimetry larva were conducted to observe biological structures with the polarization state of the back-scattered light have seen performed using the linear polarized (LP) light [2-8]. In the Mie scattering regime [9], the size of a scat [2-8]. In the Mie scattering regime [9], the size of a scat-terer (cell nucleus) is larger than the wavelength of inci-dent light, and the degree of depolarization for LP light is significantly large such that the scattered light results in complete depolarization by a small number of scattering events [10, 11]. Therefore, these studies using the LP light have successfully provided scientific significance specifi-

cally for surface observations [12-14]. In contrast, the circular polarization of light has more In contrast, the circular polarization of tight rais more persistence against multiple scattering in the Mie regime. The depolarization process is caused by two randomized processes roations of the polarization plane and interfer-ence with the backscattered light. When the size of a scat-terer is almost equivalent or smaller than the wavelength of incident, light (Rayleigh regime), LP light is randomized mostly by the former process, whereas circularly polarized (CP) light is disturbed dominantly by the latter process. orth of the resultant depolarization was almost The strength of the resultant depolarization was almost equivalent. In the Mie regime, in which forward scattering is dominant [9], complete depolarizations of CP light require more scattering events compared with those of LP light towing to the reduction in the backward scattering [10, 11]. Therefore, scattering of CP light can provide more specific information about not only the outermost surface but also the interior of tissues, which suggests the possibility of identifying carcinoma concealed in tissues.

ex vivo using incident CP light ( $\lambda = 639$  nm). They con cluded that the difference in polarization is caused by the enlargement of the nucleus size due to canceration the enlargement of the nucleus size due to canceration. Furthermore, they suggested that this technique would generate noninvasive diagnostic technology for early disease detection. Triggered by these reports, the disease polarimetry technique has been widely studied to develop an optical diagnostic tool that can provide sup-demonstrate. In formation for anti-decision, 172–281. plementary information for pathologists [17-24]. Recently, the polarimetry technique has been applied and demonstrated for grading colon cancer [25] and

side facet and can detect CP light without applying an external magnetic field or a large electrical field [27-30]. If spin-LED devices are integrated at the tip of a biopsy probe apparatus such as an endoscope, the polarimetry technique suggested by Meglinski et al can be developed from ex vivo observation to in vivo observation, which also enables observation in real time while avoiding the risk of administering a fluorescent agent. However, to

risk of administering a fluorescent agent. However, to develop this technique for practical use, more intensive and detailed investigations are required from both theo-retical and experimental approach the scattering Previously, we theoretically investigated the scattering process of CP light against cell nacled in peudo the grocess of CP light against cell nacled in peudo the Mic scat-tering Monte Carlo (MC) methods based on the Mic scat-tering the control of the control of the Mic scat-tering the control of the control of the Mic scat-tering the control of the Mic scat-tering the control of the control of the Mic scat-tering the control of the Mic scat-tering the control of the control of the Mic scat-tering the Mic scat-tering the control of the Mic scat-tering the Mic scat-tering the control of tering mechanism [31]. MC simulations were performed for cancerous and healthy pseudo tissues in aqueou for cancerous and healthy pseudo issues in aqueous medium containing dispersed particles with the typical sizes of cell muclei in healthy and cancerous cells, that is, 6 and 11 µm, respectively. Accordingly, a distinct differ-ence in the resultant polarization values between healthy and cancerous tissues can be obtained over a wide range of detection angles, which suggests that this technique car

degree of circular polarization (DOCP) values degree of circular polarization (DOCP) values. In this study, we experimentally demonstrated the identification of cancer in sliced biological tissue with the scattering of CP light. We measured the DOCP values of scattered light in various optical angular arrangements with incident and detection angles. Line-scanning experiments were performed to demonstrate clear discrimina-tion of the cancerous and healthy parts, which was partially published in ref. [32]. In addition, we assessed Meglinski et al [15] pioneered the application of CP the in-plane dispersion of the detected values according

characterize the size of cell nuclei in biological tissues

The difference is estimated to be approximately 0.2 in the

Figure 1A shows the experimental setup used to measure the DOCP values in this study. The incident and detection angles,  $\theta$  and  $\varphi$ , are defined as angles made by the line angles, 0 and 0, are defined as angles made by the lines connecting from a measurement point on the sample to the light source and the detector with a perpendicular line at the measurement point, respectively. The unpolarized laser beam emitted from a diode-pumped solid-state laser (Sanctity Laser Technology Co., Ld., China) with a wavelength of 914 nm and a power of 100 mW was converted to right-handed CP light with 0.5 mW through an ND filter, a linear polarizer and a quarter-wave (3/4) plate. Subsequently, it is focused by a plane







issues with stained cell nuclei in the specimen. The insets show he magnified images of the region in white boxes +1.0. The light scattered from the sample at an angle of φ± 5.7° is collected by a plano-onnex lens (f = 30 mm) and detected by a polarimeter with a high dynamic range (PAX1000, Therlabs, Inc.), which consists of an optical input aperture (φ 3 mm), a rotating (J4 plate, a fixed lin-ear polarizer and a photodiode. The polarization state of the scattered light is assessed by the DOCP values, which is defined by the equation, DOCP =  $S_1/S_2$ , where  $S_0$  and S, are the Stokes polarization parameters that describe the

row shows the area where line-scanning expe

performed, which is across normal and metastasis part Sucrescence micrographs of, C, healthy liver and, D, meta we confirmed that the changes in circular polarization  $\Delta S_3$  are considerably larger than the variations in the total intensity A.S.: therefore, the obtained DOCP values are intrinsically derived from the circular polarization of light intrinsically derived from the circular potarization of light in all of the experiments in this study. The incident angle dependences were investigated by varying  $\theta$  from 35° to 55° and fixing  $\varphi$  to 0°. Conversely, the detection angle dependences were assessed by changing  $\varphi$  from 35° to 55° and fixing  $\theta$  to 0°.

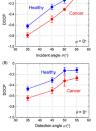
Sliced tissue specimens of liver metastasis were prepared from a murine xenograft model with human pancre atic cancer SUIT2 cells. To establish liver metastasis in mice, human pancreatic cancer SUIT2 cells were intrasplenically injected. After 47 days of injecting cancer intrasplenically injected. After 47 days of injecting cancer cells, the livers were harvested to prepare sliced specimens containing liver metastatic lesions. The livers harvested from the mice were immediately frozen in a frozen tissue matrix. The frozen liver was serially sectioned into specicryostat. One of the serial sections were used to me CP scattering and the other were utilized to observe the stained cell nuclei. Figure 1B shows a micrograph of the stained cell nuclei. Figure II is shows a micrograph of the specimen for measurement of CP scattering with neither staining nor any support. The liver section for the CP scat-tering measurements is laid on a glass plate and then tightly adhered to the glass with its moisture. The speci-men with a glass plate was placed upight in the optical setup. The right illustration of Figure III is a schematic map that indicates the characteristics. The metastasis parts are shown by the light-blue area surrounded by a dotted line. The red dotted arrow denotes the linear area along line. The red dotted arrow denotes the linear area along which the line-scanning measurements were performed. The fluorescence micrographs of healthy liver and metastatic area with stained cell nuclei in the specimen are shown in Figure 1.O.P. respectively. The liver sections were fixed with 4% paraformaldehyde for 10 minutes. After washing with phosphate-buffered saline, the fixed sections were stained with 10 µg/mL Hoechst 33342 for 5 minutes. The stained sections were sealed with cove slips and fluorescently observed with an inverted fluores slips and fluorescently observed with an inverted fluore-cent microscope (BcX800, Keynco). Fluorescent images were acquired with a >40 objective lens under fixed expo-sure time of the CMOS camera. The cell nuclei in the healthy part are comparatively small and dispersed, and the average diameter of the nuclei is approximately 6.4 µm. In the metastasis part, relatively large and aggre gated cell nuclei are observed, which indicates that the enlargement of cell nuclei is observed in metastasis part due to canceration. The average diameter of the cell nuclei s) are the closes posturation plastimeters are understanted to the contract of the contract of the contract of the right CP over the left CP, respectively. The S<sub>8</sub> values can be changed according to the difference in the changed according to the difference in the changed according to the difference in the contract of the product of the contract of

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pproximately  $1 \text{ mm} \times 1 \text{ mm} \times 40 \text{ } \mu\text{m}$ , independent of the angular configurations. The sampling depth at  $(\theta, \varphi) = (1^{\circ}, 30^{\circ})$  is estimated to be 1.65 mm from the MC calculations for the tissue with infinite thickness [31]. Therefore, a significant portion of incident light is tran Therefore, a significant portion of incident tight is trans-parent through the back of the sample or reflected at the interface between the specimen and the glass plate. The remaining portion of light and reflected light at the back undergo multiple exattering events in the entire sample with a thickness of 40 µm and then arrive at the detector. This sampling volume includes approximately 750 nuclei

### 3 | RESULTS AND DISCUSSION

Figure 2A,B shows the dependence of the DOCP value of scattered light on the incident angle  $\theta$  and detection angle  $\phi$ , respectively. The blue and red dots and lines rep resent the DOCP values measured at the point in the



function of, A, incident angles  $\theta$  with  $\phi = 0^{\circ}$  and, B, detection

DOCP value on the incident angle  $\theta$  with  $\omega = 0^{\circ}$ , shown in Figure 2A, indicates that the DOCP values from the in Figure 2A, indicates that the DOCP values from the healthy parts are larger than those from the cancerous parts with an approximately constant difference of 0.20, except for the case with  $\theta=55^\circ$ , while the DOCP value increases with increasing  $\theta$  [33]. The dependence of the DOCP value on the detection angle  $\phi$  with  $\theta=0^\circ$ , shown in Figure 2B, indicates the two characteristics similar to

The DOCP values are the average values measured a

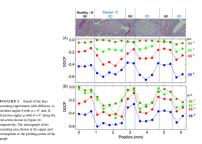
four different points in each part. The dependence of the

those of  $\theta$  dependence: the increase in the DOCP value with increasing  $\theta$  or  $\omega$  and a difference of approximately 0.20 between the DOCP values obtained from both parts the former characteristics are due to the injection efficiency of CP light and irregular reflections at the surface. When the incident angle approaches the Brewster's angle between the air and the sample surface. (approximately 53°, in this study), the p-polarizatio ponent is dominantly penetrated into the sample, but the s-polarization component is mostly reflected because of the difference in reflectance at the surface [9]. Thereof the difference in reflectance at the surface [9]. Therefore, the CP of light penetrating into the tissue is decreased and the scattered light has less information inside the tissue. The result shows that almost zero CP values are observed at  $(\theta, \phi) = (55^\circ, 0^\circ)$ . Moreover, the influence of surface reflection should be considered. Some of the incident CP light penetrate into tissues and considered and the considered considered and the considered considered and the considered provides information about the state of the sample. The remaining part of the incident light is irregularly reflected at the rough surface of the tissues. The sign of reflected at the rough surface of the tissues. The sign of the DOCP of the reflected light is opposite to that of the incident CP light. As the incident direction approaches the detection direction, the component due to the irregu-lar reflection in the total detected light becomes larger, resulting in a decrease (negative increase) in the DOCP value. When the difference between the incident and detection angles becomes less than 30°, most of the detected light is reflected light, which has insufficient information. The latter characteristic of the difference in information. The latter characteristic of the difference in the DOCP value corresponds reasonably well with the simulation results calculated for almost the same optical configurations (Figure 2C in ref. [31]), which implies that the observed difference in the DOCP value is derived from the difference in particle (cell nucleus) size. The magnitude of the detected DOCP value can be influenced by extrinsic factors such as surface reflection, while the difference in the DOCP value is intrinsic and robust in the optical configuration with an angle within the appro-priate range, which provides valuable information about the state of the biological tissue.

is smaller than that from healthy tissues. However, this magnitude relation is opposite to the results shown in ref. [16], which are obtained using the incident CP light with  $\lambda$  = 699 mm. Light scattering is the second radiation from dipoles excited by the first irradiation on the surface of the scatterer. The degree of depolarization varies according to the distribution of dipoles, and strongly depends on the ratio of the wavelength and size of the scatterer. We have ratio of the wavelength and size of the sattlerer. We have calculated the wavelength dependence of the expected DOCP value of light scattered by noncancerous and concross peach-biological tissue in aqueous medium with dispersing scatterers having a diameter of 6.0 and 11.0 µm, respectively, by the same calculation method in ref. [31]. The calculated DOCP values show oscillating behavior derived from spherical harmonics with a variable size parameter,  $x \equiv ka$ . The DOCP values from pseudo cancer-

ments obtained at the optical configurations with  $(\theta,\varphi)\equiv(a)~(\theta,0)$  and (b)  $(0,\varphi)$ . The data plotted in each point. The line-scanning experiments were

performed at 18 points along the red arrow shown in Figure 1B, which crosses the boundary between cancerous and healthy tissues multiple times. A micrograph of the scanning area is shown in the upper part of the graphs in which the area delineated by the blue dotted line is the cancerous parts. Except for (55°, 0°) at which the DOCP values showed almost no change, a differ ence of 0.1 or more in the DOCP value was obence of 0.1 or more in the DOLY value was observed depending on the state of the biological issues, whether healthy or cancerous, which corresponds to the results shown in Figure 2. Distinct differences are observed in each angular configuration; however, at around the boundary between cancerous and healthy parts, steeper changes are observed with the perpen-dicular incidence (Figure 3B) than with the oblique incidence (Figure 3A). The different gradients of the out tissue ( $P_{onton}$ ) are larger than those from pseudo-healthy tissue ( $P_{onton}$ ) at  $\lambda < 680$  nm, whereas  $P_{onton} < P_{antan}$  at  $\lambda < 680$  nm. These calculation results different sampling (scattering) volumes and the subse-DOCP value at the boundary between the oblique and perpendicular incidence could be possibly due to the different sampling (scattering) volumes and the subsequent radiation areas of the scattered light. An abeo-quent radiation areas of the scattered light. An abeo-pendicular to the scattering to



optical configurations with oblique incidence and ver-tical detection have less spatial resolution. From the results of line-scanning experiments, the in-plane res-olution is roughly estimated to be 0.6 and 0.3 mm for the configurations with the oblique and perpendicular

To evaluate the distributions of the DOCP values, scan-To evaluate the distributions of the DOCP values, scan-ning measurements were performed in an area that appeared as uniformly healthy and cancerous parts. The measurements were performed at each point obtained by dividing the scan-ning area into 6 × 11 lattices in length and width, which are schematically drawn on the micrograph of the specimens in Figure 4A. The color-coded spatial distributions of the meaured DOCP values at  $(\theta, \varphi) = (50^\circ, 0^\circ)$  and  $(0^\circ, 50^\circ)$  are shown in Figure 4B,C, respectively. The upper panels show the data in the healthy tissues, while the lower panels show the data in the healthy (assee, while the lower panels show the results in cancernus tissues. Figure ADI, thows thist-gams of the DOCP values corresponding to the data shown in Figure 4RC, respectively, 4.0(#, #) of 20,0° 0, the disper-sion of the DOCP values in the healthy part shows a wide dis-ribution with a pack of 4-0132 and a standard deviation of the pack of 4-0132 and a standard deviation of 4 | CONCLUSION  $\sigma \equiv 5.8$ , whereas the DOCP values in the cancerous part are converged at -0.301 with a standard deviation of  $\sigma \equiv 1.7$ (Figure 4B,D). The almost independent dispersions provide

lurking in healthy tissues. At  $(\theta, \varphi) \equiv (0^{\circ}, 50^{\circ})$ , the DOCP values are distributed with comparatively large dispersions, although the identification of cancerous tissues is possible with comparisons of data from multiple points. The peaks of the dispersions are -0.132 and -0.320, and the deviations are tically, most of the penetrated light tends to progress toward the deeper layer because the forward scattering is dominant in the Mie regime. Therefore, the light experienced a large number of scattering events that were hardly discharged ou ward the sample, and the light scattered by a few times is dominantly detected, resulting in less accuracy for discrimi-

scattered CP light for cancer identification in optical

configurations with various angular relations between the directions of incidence and detection. An incident angle larger than the Brewster's angle for the surface of biological tissues causes a decreased penetration of polar-ized light into the tissue, and the small difference between the angles of incidence and detection increases surface reflection with less information. At the configura surface reflection with less information. At the configura-tion with angles within the appropriate range, that is,  $\theta \leq 53^\circ$  and  $(\theta - \varphi) \geq 30^\circ$ , the significant differences between the DOCP values obtained from the cancerous and healthy parts are observed to be approximately 0.20, which is sufficient to identify the cancer-affected area. Based on the good agreement with our previous calcula-tions [31], here, we concluded that the difference in the DOCP values results from the different sizes of cell nuclei rather than the different reflectance values, which sugrather than the different reflectance values, which sug-gests that this technique could be applied to the identifi-cation of not only carcinomas but also other diseases accompanied by the enlargement of cell radsel, for exam-ple, alcoholic hepatitis and ulcerous colitis. In addition to the cell nuclei, the contribution of cellular walls and other constituents also contributes to polarization scattering. These components, which are strongly associated with the anisotropic cellular shape and birefringence, can greatly contribute to polarization scattering in fibrous tisgreatly contribute to polarization scattering in Birous tis-sue, asymmetric complex tissue, and a tissue in which anisotropic mutation is observed. The samples used in this study consist of uniform, isotropic cell nuclei in both cancerous and healthy parts, in which the centributions of these anisotropic parameters are inconspicuous. Fur-ther research is required to investigate these contrib-tions. In the line-scanning measurements, the obtained DOCP values change in an almost binary manne depending on the state of tissue, whether healthy or canpositional fluctuation. Conversely, the arrangements with perpendicular incident light have higher spatial resoluthe surface of measuring tissues against the fixed optical system. This indicates that this technique is useful even n environments where it is difficult to fix the spatia arrangement between the optics and the target, such as in vivo observations with an endoscope.

epending on the state of assue, whether healthy or can-erous. The optical configurations with oblique incidence rovide larger differences in the DOCP values, which indicates higher accuracy in identifying cancerous parts. Indicates the design of the configuration of the configurat perpetitive in cusers ugpir have inguery spital silve less to describe the control of the contr

ACKNOWLEDGMENTS This work was partially supported by KAKENHI (Nos. 17K14104, 18H03878 and 19H04441) of the Japan Society for Promotion of Science (SPS), the Cooperative Research Project of Research Center for Biomedical Engineering, Futaba Foundation, Spintronics Research Net work of Japan (Spin-RNI) and a Grant-in-Aid fo work of Japan (Spin-RM) and a Grant-in-Add for Challenging Research, Organization of Pandamental Research, Tokyo Institute of Technology, The authors acknowledge schenical support from the Semiconductor and MEMS Processing Division of the Technical Department of Tokyo Institute of Technology, The authors acknowledge Prof. H. Munckata and Prof. J. Voshin for Traifful discussions and technical support at the Tokyo Institute of Technology (TIT). This work was supported by Tokyo Tech World Research work was supported by loxyo leen words research Hub Initiative (WRHI) Program of Institute of Innova tive Research, Tokyo Institute of Technology. W would like to thank Editage (www.editage.com) fo English language editing.

### The data that support the findings of this study are avail able from the corresponding author upon reasonable

### AUTHOR BIOGRAPHIES

Nozomi Nishizawa 10 https://orcid.org/0000-0002-7292-

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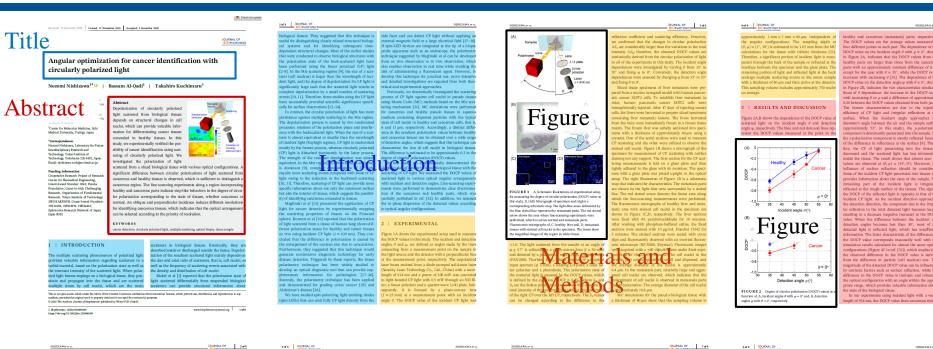
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How to cite this article: Nishizawa N, Al-Qadi B, Biophotonics, 2020;e202000380, https://doi.org/10.

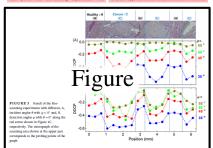
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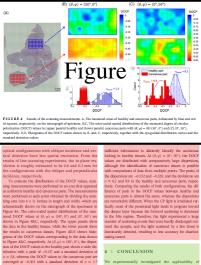
# 典型的な論文の構成

## N. Nishizawa et al., J. Biophotonics 14, 202000380 (2020) を手本に



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### ACKNOWLEDGMENTS

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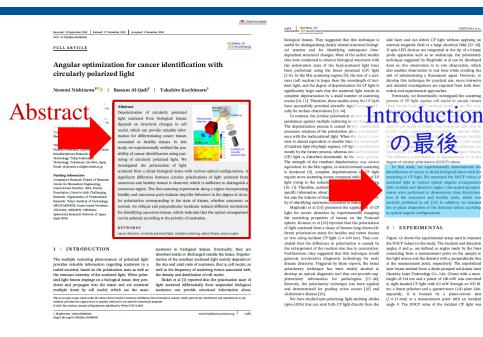
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in the Supporting Information section at the end of this

References

# 最初に読む場所(論文の概要を把握する)<sup>10</sup>



最初に読むのは、 Abstract (要約)、

Introductionの最後 (in this paper 以降)、 Conclusionの前半(Summaryに相当する部分) の3ヶ所

ここにはほぼ同じ内容がほぼ同じ順序で書 かれている。内容の濃さが違うだけ。オ

この3ヶ所を読むと論文の大枠を捉える ことができる。

Introductionの最後にはこの論文で明ら かにしようとした研究目的。

Conclusionには、その目的に対して結果 と考察の要約(明らかになったこと)から 今後の課題(まだ明らかになっていない こと)が書いてあり、

Abstractはそれらを短くまとめている。

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Research, Tokyo Institute of Technolog

ar polarization corresponding to the state of tissues, whether cancerous o

but also the interior of tissues, which suggests the possibility of identifying carcinoma concealed in tissues.

tion of the cancerous and healthy parts, which was partially published in ref. [32]. In addition, we assessed

次に図とConclusionsに短くまとめられていた 結果と考察が結び付けられるかを見てみる

ized light beams impinge on a biological tissue, they penetrate and propagate into the tissue and are scattered multiple times by cell nuclei, which are the main

Bickel et al [1] reported that the polarization state of light scattered differentially from suspended biological scatterers can provide structural information about

artide under the terms of the Creative Commons Attribution NonComm e original work is properly died and is not used for commercial purpose.

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plementary information for pathologists [17-24 Recently, the polarimetry technique has been applie and demonstrated for grading colon cancer [25] an Alzheimer's disease [26].

We have studied spin-polarizing light-emitting diodes

Smetty Laser Technology Co., Ld., China with a way length of 914 nm and a power of 100 mW was convert to right-handed CP light with 0.5 mW through an ND it ter, a linear polarizer and a quarter-wave (\(\lambda\)/4) plate. Su sequently, it is focused by a plano-convex le (f = 25 mm) at a measurement point with an incide Powering Language Lan

FIGURE 1 A, Schematic illustrations of experim for measuring the degree of circular polarization (DOA this study, F. (ddf) Microspids of especimes and (right

the blue dotted line represent the metastasis parts. The red de arrow shows the area where line-scanning experiments were performed, which is across normal and metastasis parts. Fluorescence micrographs of, C, healthy liver and, D, metastatissuess with stained cell nucle in the specimen. The insets sh the magnified images of the region in white boxes

(PAX1000; Thorlabs, Inc.), which consists of an optical input aperture (a) a may a rotating 1/4 plate, a fixed lin ear pdrafree and a photodiod. The polarization state of the scattered light is assessed by the DOCP values, which is defined by the equation, DOCP = \$5/ks, where \$5, as \$5, are the Stokes polarization parameters that describe the total intensity of the scattered light and the perpondemon of the right CP over the left CP, respectively. The \$5\_ks value can be changed according to the difference in the es .

extion coefficient and scattering efficiency. However, confirmed that the changes in circular polarization, are considerably larger than the variations in the total noisy  $\Delta S_c$  therefore, the obtained DOCP values are insically derived from the circular polarization of light III of the experiments in this study. The incident angle endences were investigated by varying  $\theta$  from 35° to and fixing  $\theta$  to 0°. Conversely, the detection angle endences were assessed by changing  $\varphi$  from 35° to 55° Isting  $\theta$  to 0°.

Sliced tissue specimens of liver metastasis were prepared from a murine senograft model with human pancreatic cancer SUTT2 cells. To establish liver metastasis in mice, human pancreasic cancer SUTT2 cells were intrasplenically injected. After 47 days of injecting cancer cells, the livers were harvested to prepare sliced specimens

containing how metastic lesions. The livers harvested from the more was setting sectional ton specimen matrix. The from hiere was setting sectional on specimen matrix. The from hiere was setting sectional on specimen of the sectional section section of the section section of the section section of the section section of the section of

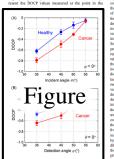
enlargement of cell nuclei is observed in metastasis part due to canceration. The average diameter of the cell nuclei is approximately 10.8 µm.

MC simulations for the populo-biological tissue with 4 of 5 JOURNAL OF

approximately 1 mm × 1 mm × 40 µm, independent of the anglast configuration. The sampling depth at  $(\theta, \phi) \approx (1 \cdot 5, 0^\circ)$  is estimated to be 1.65 mm from the MC calculations for the same with infinite factions [31], and calculations for the same with infinite factions [31] are interested as the same of the same of

### RESULTS AND DISCUSSION

Figure 2A,B shows the dependence of the DOCP value of scattered light on the incident angle  $\theta$  and detection angle  $\phi$ , respectively. The blue and red dots and lines are



by and cancerous (metastatis) parts, respectively, DCC values are the wrange values measured if a DCC value are the wrange values measured in the parts of the parts are larger than these from the cancerose for the parts are larger than these from the cancerose for the parts of the parts of

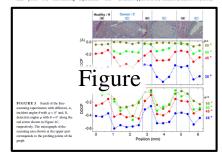
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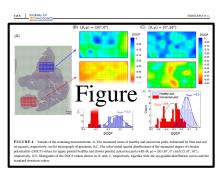
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magnitude relation is appealed not be results shown in 100,00, which are desirated using the incident CP (light with a clear state of large her incident CP (light with a clear state of large her incident configuration of the scattery. The degree of depolarization varies according of excitorer. The degree of depolarization varies according and of the wavelength and size of the satterer. We have calculated the wavelength depolarized configuration of the wavelength and size of the satterer was to a correct product the wavelength depolarized configuration of the wavelength depolarized configuration of the configuration of the wavelength of the configuration of the configurati

can expan note experimental results. Figure 3 shows the results of the line-scanning expments obtained at the optical configurations w  $(\theta, \varphi) = (a) \ (\theta, 0)$  and  $(b) \ (0, \varphi)$ . The data plotted Figure 3 were obtained by acquiring one measurement each point. The line-scanning experiments w preferred at III prints sleng the not arrow decree to Figure 11, which recent be boundary between the figure 11, the hir content of the top the prints of the treatment are in shown in the typer part of the the sansing sens in shown in the typer part of the the sansing sens in shown in the typer part of the Bine in the cancerous parts. Except for 55°, 07° at 80° at 10° whether hashing or accordes, which corresponds to the results shown in Figure 2. Distinct differences as well the results shown in Figure 2. Distinct differences as well the results shown in Figure 2. Distinct differences as well the results shown in Figure 2. Distinct differences as well the results shown in Figure 2. Distinct differences as well the results of the sansing the sansing the sansing the sansing the constant the boundary between the college and the constant and the sansing in the sansing the sansing the sansing the part of the sansing in the sansing the sansing the sansing the part of the sansing in the sansing the sansing the sansing the sansing the part of the sansing in the sansing the





optical configurations with oblique incidence and vertical detection have less spatial resolution. From the results of line-scanning experiments, the in-plane resolution is roughly estimated to be 0.6 and 0.3 mm for the configurations with the oblique and perpendicular

To colusite the distribution of the DOT values, are fragmentations of performed in an inter that appendix representation of the proposal control and appendix representation of the performed in the performance of the perfo

larking in leashly stores,  $N_c(\theta_c) \approx 0.0^{\circ}$ , 50°, the DOL whose are delibrable with emparaturely large depression, although the knothfluiden of carcenvas times in possible with the control of the dependence of the dependence, the difference of peak in the DOC values between bealthy and tenture of the dependence, the difference of peak in the DOC values between bealthy and the dependence of the depend

### 4 | CONCLUSION

We experimentally investigated the applicability of cattered CP light for cancer identification in optical 論理的にしっかりと結びつかなくてもいいので、それぞれの図の論文中での位置づけを 把握しておく。

rather than the different reflectance values, which sugguess that this technique could be applied to the identification of not only carcinomas but also other diseases accompanied by the enlargement of cell madels, for example, alcoholic hepatitis and ulcerous colitis. In addition to the cell nuclei, the contribution of cellular walls and other constituents also contributes to polarization scatter-

the hittaine (WRII) Program of Institute of Innovaive Research, Tokyo Institute of Technology. We would like to thank Editage (www.editage.com) for English language editing.

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Additional supporting information may be four

この論文では、Figure1は試料や実験方法について、Figure2~4が実験結果で、それぞれ一点測定したもの、線上に測定したもの、面内を測定したもの、ぐらいが分かればいい。

e suriace of measuring ussues against the fixed optical idem. This indicates that this technique is useful even environments where it is difficult to fix the spatial angement between the optics and the target, such as

 N. Ghosh, A. Vidin, J. Rossed. Opt. 2011, 16, 110601.
 C. F. Bohren, D. R. Huffman, Absorption and Scattering of Light by Small Particles, Wiley, New York, NY 1983.
 F. C. MacKitzsch, J. X. Zhu, D. J. Pine, D. A. Weitz, Phys. Rev. B 1989, 40 940. があると判断したら、

Introductionから最後に向

tering of circularly polarized light. We

can be selected according to the priority of resolution.

scattered from a sliced biological tissue with various optical configurations.

cancerous and healthy tissues is observed, which is sufficient to distinguish a

cancerous region. The line-scanning experiments along a region incorporating healthy and cancerous parts indicate step-like behaviors in the degree of circu

lar polarization corresponding to the state of tissues, whether cancerous or

for identifying concernus tissues, which indicates that the ontical arrangement

normal. An oblique and perpendicular incidence induces different resolutions

その後、この論文は読む価値

f the back-scattered light have ng regime [9], the size of a scat

that the scattered light results in by a small number of scattering the, these studies using the LP light ions [12-14]. ar polarization of light has more ple scattering in the Mie regime ss is caused by two randomized

h regime), LP light is randomize

(CP) light is disturbed dominantly by the latter process.

eth of the resultant depolarization was almost

estrength of the resultant depolarization was almost uivalent. In the Mie regime, in which forward scattering dominant [9], complete depolarizations of CP light quire more scattering events compared with those of LP ht owing to the reduction in the backward scattering

. Therefore, scattering of CP light can provide mon

cluded that the difference in polarization

ciuded that the difference in polarization in seed by the enlargement of the nucleus sixed due to careche on. Furthermore, they suggested that the technique wit-generate noninvasive diagnostic technology for early disease delection. Triggered by these reports, the dissus-polarimetry technique has been widely studied to develop an optical diagnostic tool that calculated in the control of the control of the control of the Recently, the nolarimetry technique, has been social.

Recently, the polarimetry technique has been applied and demonstrated for grading colon cancer [25] and

ormation about not only the outermost surface

oma concealed in tissues.

rior of tissues, which suggests the possibil-

risk of administering a fluorescent agent. However, to develop this technique for practical use, more interview and detailed investigations are required from both theo-retical and experimental approach the scattering process of CP light against cell nuclei in preudo tissues using Monte Carlo (MC) methods based on the Mis scat-tering methods (11) Mrs dissolation (11) Mrs dissolation (12) Mrs dissolation (13) Mrs dissolation (14) Mrs dissolation (13) Mrs dissolation (13) Mrs dissolation (14) Mrs dissolation (13) Mrs dissolation (14) Mrs dissolation tering mechanism [31]. MC simulations were performed for cancerous and healthy pseudo tissues in aqueou characterize the size of cell nuclei in biological tissues

echnique suggested by Meglinski et al can be developed

from ex vivo observation to in vivo observation, which

also enables observation in real time while avoiding the

risk of administering a fluorescent agent. However, to

degree of circular polarization (DOCP) values er in sliced biological tissue with th identification of cancer in sticed biological tissue with the scattering of CP light. We measured the DOCP values of scattered light in various optical angular arrangements with incident and detection angles. Line-scanning experiments were performed to demonstrate clear discrimina tion of the cancerous and healthy parts, which wa partially published in ref. [32]. In addition, we assessed pioneered the application of CP the in-plane dispersion of the detected values according

the DOCP values in this study. The incident and detection angles,  $\theta$  and  $\varphi$ , are defined as angles made by the line parter-wave (2/4) plate. Sub-

we confirmed that the changes in circular polarization  $\Delta S_3$  are considerably larger than the variations in the total

intensity A.S.; therefore, the obtained DOCP values an

intrinsically derived from the circular polarization of ligh

intrinsically derived from the circular potarization of light in all of the experiments in this study. The incident angle dependences were investigated by varying  $\theta$  from 35° to 55° and fixing  $\varphi$  to 0°. Conversely, the detection angle dependences were assessed by changing  $\varphi$  from 35° to 55° and fixing  $\theta$  to 0°.

Sliced tissue specimens of liver metastasis were pre-

pared from a murine xenograft model with human pancre

atic cancer SUIT2 cells. To establish liver metastasis in

mice, human pancreatic cancer SUIT2 cells were intrasplenically injected. After 47 days of injecting cancer

ryostat. One of the serial sections were used to me

CP scattering and the other were utilized to observe the

stained cell nuclei. Figure 1B shows a micrograph of the stained cell nuclei. Figure 1B shows a micrograph of the specimen for measurement of CP scattering with neither staining nor any support. The liver section for the CP scat-tering measurements is laid on a glass plate and then gightly adhered to the glass with its moisture. The speci-men with a glass plate was placed upright in the optical

setup. The right illustration of Figure 1B is a schemati

nap that indicates the characteristics. The metastasis part

which the line-scanning measurements were performed. The fluorescence micrographs of healthy liver and meta-static area with stained cell nuclei in the specimen are shown in Figure 1CD, respectively. The liver sections were fixed with 4% paraformaldehyde for 10 minutes.

After washing with phosphate-buffered saline, the fixed

sections were stained with 10 µg/mL Hoechst 33342 for

5 minutes. The stained sections were sealed with cove

are shown by the light-blue area surro







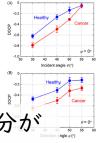
Fluorescence micrographs of, C, healthy liver and, D, meta tissues with stained cell nuclei in the specimen. The insets show the magnified images of the region in white boxes

多少、分からない部分が あっても読み飛ばす (ただし、メモしておく)

ately  $1 \text{ mm} \times 1 \text{ mm} \times 40 \text{ } \mu\text{m}$ , independent of the angular configurations. The sampling depth at  $(\theta, \varphi) \equiv (1^{\circ}, 30^{\circ})$  is estimated to be 1.65 mm from the MC alculations for the tissue with infinite thickness [31]. Therefore, a significant portion of incident light is tran Therefore, a significant portion of incident tight is trans-parent through the back of the sample or reflected at the interface between the specimen and the glass plate. The remaining portion of light and reflected light at the back undergo multiple scattering events in the entire sample with a thickness of 40 µm and then arrive at the detector. This sampling volume includes approximately 750 nuclei

### 3 | RESULTS AND DISCUSSION

angle  $\phi$ , respectively. The blue and red dots and lines rep resent the DOCP values measured at the point in the



in Figure 2A, indicates that the DOCP values from the healthy parts are larger than those from the cancerous parts with an approximately constant difference of 0.20, except for the case with  $\theta = 5\%$ , while the DOCP value increases with increasing  $\theta$  [31]. The dependence of the DOCP value on the detection angle  $\phi$  with  $\theta = 0^\circ$ , shown in Figure 2B, indicates the two characteristics similar to those of  $\theta$  dependence: the increase in the DOCP value with increasing  $\theta$  or  $\omega$  and a difference of approximately 0.20 between the DOCP values obtained from both part (approximately 53°, in this study), the p-polarizatio conent is dominantly penetrated into the sample, but the s-polarization component is mostly reflected because of the difference in reflectance at the surface [9]. Then of the difference in reflectance at the surface [9]. Therefore, the CP of light penetrating into the tissue is decreased and the scattered light has less information inside the tissue. The result shows that almost zero CP values are observed at  $(\theta, \phi) = (55^\circ, 0^\circ)$ . Moreover, the influence of surface reflection should be considered. Some of the incident CP light penetrate into tissues and considered and the considered considered and the considered considered and the considered provides information about the state of the sample. The remaining part of the incident light is irregularly reflected at the rough surface of the tissues. The sign of the DOCP of the reflected light is opposite to that of the incident CP light. As the incident direction approaches the detection direction the commenced due to the incident direction approaches the detection direction the commenced due to the incident direction. he detection direction, the component due to the irrego ar reflection in the total detected light becomes large detection angles becomes less than 30°, most of the detected light is reflected light, which has insufficient information. The latter characteristic of the difference in information. The latter characteristic of the difference in the DOCP value corresponds reasonably well with the simulation results calculated for almost the same optical configurations (Figure 2C in ref. [31]), which implies that the observed difference in the DOCP value is derived from the difference in particle (cell nucleus) size. The magnitude of the detected DOCP value can be influenced by extrinsic factors such as surface reflection, while the difference in the DOCP value is intrinsic and robust in difference in the DOCP value is intrinsic and robust in the optical configuration with an angle within the appro-priate range, which provides valuable information about the state of the biological tissue. In our experiments using indent light with a wave-length of 914 nm, the DOCP value from cancerous tissues

The DOCP values are the average values measured

DOCP value on the incident angle  $\theta$  with  $\omega = 0^{\circ}$ , show

four different points in each part. The dependence of the

in Figure 2A, indicates that the DOCP values from the

absorbed inside or discharged outside the tissue. Depolar-ization of the resultant scattered light mainly depends on

the size and axial ratio of scatterers, that is, cell nuclei, as

well as the frequency of scattering events associated with

Bickel et al [1] reported that the polarization state of light scattered differentially from suspended biological scatterers can provide structural information about

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Punding information Cooperative Research Project of Research Center for Biomedical Engineering, Grant/Award Number: 2043; Putaba

the density and distribution of cell nuclei.





with the anisotropic cellular shape and birefringence, can

greatly contribute to polarization scattering in fibrous tisgreatly contribute to polarization scattering in fibrous tis-sue, asymmetric complex tissue, and a tissue in which anisotropic mutation is observed. The samples used in this study consist of uniform, sortopic cell nucled in both cancerous and healthy parts, in which the contributions of these anisotropic parameters are incompicuous. Fur-ther research is required to investigate these contrib-tions. In the line-canning measurements, the obtained

DOCP values change in an almost binary manne

depending on the state of tissue, whether healthy or can-

perpendicular incident light have higher spatial resoluperpediacular incusers uppl have inguest passial resolu-tion due to a narrow sampling volume but slightly less accuracy due to fewer scattering events. These arrange-ments should be selected according to the objective dis-case, organ, apparatus and environment. Moreover, an almost constant difference in the DOCP values can be obtained at the configuration with angles within the appropriate range, which makes it permissible to incline

the surface of measuring tissues against the fixed optical system. This indicates that this technique is useful even

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magnitude relation is opposite to the results shown in ref. [16], which are obtained using the incident CP light with  $\lambda$  = 639 nm. Light scattering is the second radiation from dipoles excited by the first irradiation on the surface of the scatterer. The degree of depolarization varies according to ratio of the wavelength and size of the scatterer. We have ratio of the wavelength and size of the scatterer. We have calculated the wavelength dependence of the expected DOCP value of light scattered by noncancerous and can-cerous pseudo-biological tissue in aquecus medium with dispersing scatterers having a diameter of 60 and 11.0 µm, respectively, by the same calculation method in ref. [31]. The calculated DOCP values show oscillating behavior

The multiple scattering phenomenon of polarized light

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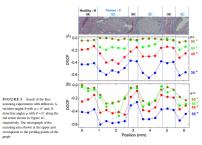
the remnant intensity of the scattered light. When polar-

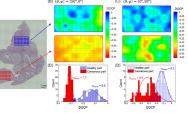
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optical configurations with oblique incidence and ver-tical detection have less spatial resolution. From the results of line-scanning experiments, the in-plane re-olution is roughly estimated to be 0.6 and 0.3 mm for the configurations with the oblique and perpendicular

To evaluate the distributions of the DOCP values, scan To evaluate the distributions of the DOCY values, scan-ning measurements were performed in an area that appeared as uniformly healthy and cancerous parts. The measurements were performed at each point obtained by dividing the scan-ning area into 6 × 11 lattices in length and width, which are schematically drawn on the micrograph of the specimens in Figure 4A. The color-coded spatial distributions of the meaured DOCP values at  $(\theta, \varphi) = (50^\circ, 0^\circ)$  and  $(0^\circ, 50^\circ)$  are shown in Figure 4B,C, respectively. The upper panels show the data in the healthy tissues, while the lower panels show the data in the healthy tissues, while the lower panels show the results in concreous tissues. Figure 4D, E shows listo-grams of the DOCP values corresponding to the data shown in Figure 4R,C, respectively. At  $(\theta_i, \phi) = (30^\circ, 0^\circ)$ , the disper-sion of the DOCP values in the health part shows a wide dis-tribution with a peak of -0.137 and a standard deviation of  $\sigma \equiv 5.8$ , whereas the DOCP values in the cancerous part an converged at -0.301 with a standard deviation of  $\sigma = 1.7$ (Figure 4RD). The almost independent dispersions provide

lurking in healthy tissues. At  $(\theta, \varphi) \equiv (0^{\circ}, 50^{\circ})$ , the DOCP values are distributed with comparatively large dispersions, although the identification of cancerous tissues is possible with comparisons of data from multiple points. The peaks of the dispersions are -0.132 and -0.320, and the deviations ar tically, most of the penetrated light tends to progress toward the deeper layer because the forward scattering is dominant in the Mie regime. Therefore, the light experienced a large number of scattering events that were hardly discharged or ward the sample, and the light scattered by a few times is dominantly detected, resulting in less accuracy for discrimi-

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ACKNOWLEDGMENTS

incidence and detection. An incident the Brewster's angle for the surface of This work was partially supported by KAKENHI (Nos. 17K14104, 18H08878 and 19H04441) of the Japan Society for Promotion of Science (ISPS), the Cooperative Research Project of Research Center for Biomedical Engice and detection increases neering, Futaba Foundation, Spintronics Research Net neering, Futaba Foundation, Spintronies Research Net-work of Japan (Spin-RM) and a Grant-in-Ald for Challenging Research, Organization of Pandamental Research, Tokyo Institute of Technology. The authors acknowledge technical support from the Semiconductor and MEMS Processing Division of the Technical Department of Tokyo Institute of Technology. The authors acknowledge Prof. III, Munckata and Prof. ion. At the configura tion with angles within the approximate range,  $\theta \leq 55^\circ$  and  $(\theta = \phi) \geq 30^\circ$ , the sign part disbetween the DOCP values obtained from the control and healthy parts are observed to be approximately by the cancer-affect of the control of the control of the cancer-affect of the control of the cancer-affect of the cancer-aff Based on the good agreement with our previous calcu-tions [31], here, we concluded that the difference in the oshino for fruitful discussions and technical sup at the Tokyo Institute of Technology (TIT), This DOCP values results from the different sizes of cell nuclei rather than the different reflectance values, which sugsupported by Tokyo Tech World Research rather than the different reflectance values, which suggests that this technique could be applied to the identification of not only carcinomas but also other diseases accompanied by the enlargement of cell radels; for example, alcoholic hepatitis and ulcerous cellitis. In addition to the cell radels, the contribution of cellular walls and other constituents also contributes to polarization scatter-(WRHI) Program of Institute of Innova ing. These components, which are strongly associated The data that support the finding

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結論に対しての位置 づけを意識しながら 読もう

# 2回目以降

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tering of circularly polarized light. We

can be selected according to the priority of resolution.

scattered from a sliced biological tissue with various optical configurations. A

cancerous and healthy tissues is observed, which is sufficient to distinguish a

cancerous region. The line-scanning experiments along a region incorporating healthy and cancerous parts indicate step-like behaviors in the degree of circu-

lar polarization corresponding to the state of tissues, whether cancerous or

for identifying concernus tissues, which indicates that the ontical arrangement

cancer detection, circularly polarized light, multiple scattering, optical biopsy, tissue sample

normal. An oblique and perpendicular incidence induces different resolutions

absorbed inside or discharged outside the tissue. Depolar-ization of the resultant scattered light mainly depends on the size and axial ratio of scatterers, that is, cell nuclei, as

well as the frequency of scattering events associated with the density and distribution of cell nuclei.

Bickel et al [1] reported that the polarization state of light scattered differentially from suspended biological scatterers can provide structural information about

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biological tissues. They suggested that this technique is useful for distinguishing closely related structural biologi-cal systems and for identifying subsequent time-dependent structural changes. Most of the earlier studies that were conducted to observe biological structures with the polarization state of the back-scattered light have seen performed using the linear polarized (LP) light [2-8]. In the Mie scattering regime [9], the size of a scat [2-8]. In the Mie scattering regime [9], the size of a scat-terer (cell nucleus) is larger than the wavelength of inci-dent light, and the degree of depolarization for LP light is significantly large such that the scattered light results in complete depolarization by a small number of scattering events [10, 11]. Therefore, these studies using the LP light

have successfully provided scientific significance specifi cally for surface observations [12-14]. In contrast, the circular polarization of light has more In contrast, the circular polarization of light has more persistence against multiple scattering in the Mile regime. The depolarization process is caused by two randomized processes: rotations of the polarization plane and interfer-ence with the backscattered light. When the size of a scat-terer is almost equivalent or smaller than the wavelength of incident light (Rayleigh regime), LP light is randomized (CP) light is disturbed dominantly by the latter process. orth of the resultant depolarization was almost The strength of the resultant depolarization was almost equivalent. In the Mie regime, in which forward scattering is dominant [9], complete depolarizations of CP light require more scattering events compared with those of LP light owing to the reduction in the backward scattering [10, 11]. Therefore, scattering of CP light can provide more specific information about not only the outermost surface but also the interior of tissues, which suggests the possibil-

ity of identifying carcinoma concealed in tissues. ex vivo using incident CP light ( $\lambda = 639$  nm). They con cluded that the difference in polarization is caused by cluded that the difference in polarization is caused by the enlargement of the nucleus size due to canceration. Furthermore, they suggested that this technique would generate noninvasive diagnostic technology for early disease detection. Triggered by these reports, the fissue polarimetry technique has been widely studied to develop an optical diagnostic tool that can provide sup-plementary information for pathologists [17–34]. Recently, the polarimetry technique has been applied

and demonstrated for grading colon cancer [25] and

6 of 8 JOURNAL O

echnique suggested by Meglinski et al can be developed from ex vivo observation to in vivo observation, which also enables observation in real time while avoiding the risk of administering a fluorescent agent. However, to

risk of administering a fluorescent agent. However, to develop this technique for practical use, more intensive and detailed investigations are required from both theo-retical and experimental approach the scattering Previously, we theoretically investigated the scattering process of CP light against cell nacled in peudo the grocess of CP light against cell nacled in peudo the Mic scat-tering Monte Carlo (MC) methods based on the Mic scat-tering the control of the control of the Mic scat-tering the control of the control of the Mic scat-tering the control of the Mic scat-tering the control of the control of the Mic scat-tering the control of the Mic scat-tering the control of the control of the Mic scat-tering the Mic scat-tering the control of the Mic scat-tering the Mic scat-tering the control of tering mechanism [31]. MC simulations were performed for cancerous and healthy pseudo tissues in aqueou for cancerous and healthy pseudo issues in aqueous medium containing dispersed particles with the typical sizes of cell muclei in healthy and cancerous cells, that is, 6 and 11 µm, respectively. Accordingly, a distinct differ-ence in the resultant polarization values between healthy and cancerous tissues can be obtained over a wide range of detection angles, which suggests that this technique car characterize the size of cell nuclei in biological tissues The difference is estimated to be approximately 0.2 in the degree of circular polarization (DOCP) values

er in sliced biological tissue with th identification of cancer in sticed biological tissue with the scattering of CP light. We measured the DOCP values of scattered light in various optical angular arrangements with incident and detection angles. Line-scanning experiments were performed to demonstrate clear discrimina-tion of the cancerous and healthy parts, which was partially published in ref. [32]. In addition, we assessed Meglinski et al [15] pioneered the application of CP the in-plane dispersion of the detected values according

Figure 1A shows the experimental setup used to measure the DOCP values in this study. The incident and detection angles,  $\theta$  and  $\varphi$ , are defined as angles made by the line angles, 0 and \(\phi\), are defined as angles made by the lines connecting from a measurement point on the sample to the light source and the detector with a perpendicular line at the measurement point, respectively. The unpolarized laser beam emitted from a diode-pumped solid-state laser (Sanctity Laser Technology Co., Ld., China) with a wavelength of 914 nm and a power of 100 mW was converted to right-handed CP light with 0.5 mW through an ND fil ter, a linear polarizer and a quarter-wave (3/4) plate. Subuently, it is focused by a plane







FIGURE 1 A. Schematic illustrations of experi row shows the area where line-scanning expe performed, which is across normal and metastasic parts Sucrescence micrographs of, C, healthy liver and, D, meta tissues with stained cell nuclei in the specimen. The insets show the magnified images of the region in white boxes

+1.0. The light scattered from the sample at an angle of φ± 5.7° is collected by a plano-onnex lens (f = 30 mm) and detected by a polarimeter with a high dynamic range (PAX1000, Therlabs, Inc.), which consists of an optical input aperture (φ 3 mm), a rotating (J4 plate, a fixed lin-ear polarizer and a photodiode. The polarization state of the scattered light is assessed by the DOCP values, which is defined by the equation, DOCP =  $S_1/S_2$ , where  $S_0$  and S, are the Stokes polarization parameters that describe the of the restrict postal and the preponderance of the right CP over the left CP, respectively. The  $S_0$  values can be changed according to the difference in the

reflection coefficient and scattering efficiency. Howe we confirmed that the changes in circular polarization  $\Delta S_3$  are considerably larger than the variations in the total intensity A.S.; therefore, the obtained DOCP values an intrinsically derived from the circular polarization of ligh intrinsically derived from the circular potarization of light in all of the experiments in this study. The incident angle dependences were investigated by varying  $\theta$  from 35° to 55° and fixing  $\varphi$  to 0°. Conversely, the detection angle dependences were assessed by changing  $\varphi$  from 35° to 55° and fixing  $\theta$  to 0°. Sliced tissue specimens of liver metastasis were pre-

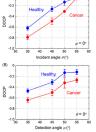
pared from a murine xenograft model with human pancre atic cancer SUIT2 cells. To establish liver metastasis in mice, human pancreatic cancer SUIT2 cells were intrasplenically injected. After 47 days of injecting cancer intrasplenically injected. After 47 days of injecting cancer cells, the livers were harvested to prepare sliced specimens containing liver metastatic lesions. The livers harvested from the mice were immediately frozen in a frozen tissue matrix. The frozen liver was serially sectioned into speciryostat. One of the serial sections were used to me CP scattering and the other were utilized to observe the stained cell nuclei. Figure 1B shows a micrograph of the stained cell nuclei. Figure 18 shows a micrograph of the specimen for measurement of CP stattering with notiber staining nor any support. The liver section for the CP scat-tering measurements is laid on a glass plate and then tightly adhered to the glass with its moisture. The speci-men with a glass plate was placed upright in the optical setup. The right illustration of Figure 1B is a schematic nap that indicates the characteristics. The metastasis part are shown by the light-blue area surro line. The red dotted arrow denotes the linear area alon line. The red dotted arrow denotes the linear area along which the line-scanning measurements were performed. The fluorescence micrographs of healthy liver and metastatic area with stained cell nuclei in the specimen are shown in Figure 1CD, respectively. The liver sections were fixed with 4% paraformaldehyde for 10 minutes. After washing with phosphate-buffered saline, the fixed sections were stained with 10 µg/mL Hoechst 33342 for 5 minutes. The stained sections were sealed with cove slips and fluorescently observed with an inverted fluores slips and fluorescently observed with an inverted fluore-cent microscope (BCX900, Keynec). Fluorescent images were acquired with a ×40 objective lens under fixed expo-sure time of the CMOS camera. The cell nuclei in the healthy part are comparatively small and dispersed, and the average diameter of the nuclei is approximately 6.4 µm. In the metastasis part, relatively large and aggre gated cell nuclei are observed, which indicates that the enlargement of cell nuclei is observed in metastasis nar due to canceration. The average diameter of the cell nucle

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ately  $1 \text{ mm} \times 1 \text{ mm} \times 40 \text{ } \mu\text{m}$ , independent of the angular configurations. The sampling depth at  $(\theta, \varphi) = (1^{\circ}, 30^{\circ})$  is estimated to be 1.65 mm from the MC alculations for the tissue with infinite thickness [31]. Therefore, a significant portion of incident light is tran Therefore, a significant portion of incident tight is trans-parent through the back of the sample or reflected at the interface between the specimen and the glass plate. The remaining portion of light and reflected light at the back undergo multiple scattering events in the entire sample with a thickness of 40 µm and then arrive at the detector. This sampling volume includes approximately 750 nuclei

### 3 | RESULTS AND DISCUSSION

scattered light on the incident angle  $\theta$  and detection angle  $\phi$ , respectively. The blue and red dots and lines rep resent the DOCP values measured at the point in the



function of, A, incident angles  $\theta$  with  $\varphi = 0^\circ$  and, B, detection

four different points in each part. The dependence of the DOCP value on the incident angle  $\theta$  with  $\omega = 0^\circ$ , shown in Figure 2A, indicates that the DOCP values from the in Figure 2A, indicates that the DOCP values from the healthy parts are larger than those from the cancerous parts with an approximately constant difference of 0.20, except for the case with  $\theta$  = 5%; while the DOCP value increases with increasing  $\theta$  [3]. The dependence of the DOCP value on the detection angle  $\phi$  with  $\theta$  = 0%, shown in Figure 2B, indicates the two characteristics similar to those of  $\theta$  dependence: the increase in the DOCP value with increasing  $\theta$  or  $\omega$  and a difference of approximately 0.20 between the DOCP values obtained from both part The former characteristics are due to the injection efficiency of CP light and irregular reflections at the surface. When the incident angle approaches the ponent is dominantly penetrated into the sample, but the s-polarization component is mostly reflected becaus of the difference in reflectance at the surface [9]. Then of the difference in reflectance at the surface [9]. Therefore, the CP of light penetrating into the tissue is decreased and the scattered light has less information inside the tissue. The result shows that almost zero CP values are observed at  $(\theta, \phi) = (55^\circ, 0^\circ)$ . Moreover, the influence of surface reflection should be considered. Some of the incident CP light penetrate into tissues and considered and the considered considered and the considered considered and the considered provides information about the state of the sample. The remaining part of the incident light is irregularly reflected at the rough surface of the tissues. The sign of reflected at the rough surface of the tissues. The sign of the DOCP of the reflected light is opposite to that of the incident CP light. As the incident direction approaches the detection direction, the component due to the irregu-lar reflection in the total detected light becomes larger resulting in a decrease (negative increase) in the DOC value. When the difference between the incident and detection angles becomes less than 30°, most of the detected light is reflected light, which has insufficient information. The latter characteristic of the difference in

The DOCP values are the average values measured

Punding information Cooperative Research Project of Resea Center for Biomedical Engineering, Grant/Award Number: 2043; Putaba

1 | INTRODUCTION

The multiple scattering phenomenon of polarized light provides valuable information regarding scatterers in a urbid material, based on the polarization state as well as

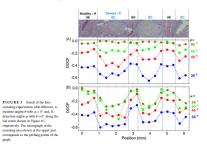
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is smaller than that from healthy tissues. However, this magnitude relation is opposite to the results shown in ref. [16], which are obtained using the incident CP light with  $\lambda = 639$  nm. Light scattering is the second radiation from dipoles excited by the first irradiation on the surface of the scatterer. The degree of depolarization varies according to the distribution of dipoles, and strongly depends on the ratio of the wavelength and size of the scatterer. We have ratio of the wavelength and size of the scatterer. We have calculated the wavelength dependence of the expected DOCP value of light scattered by noncancerous and can-cerous pseudo-biological tissue in aquecus medium with dispersing scatterers having a diameter of 60 and 11.0 µm, respectively, by the same calculation method in ref. [31]. The calculated DOCP values show oscillating behavior derived from spherical harmonics with a variable size parameter,  $x \equiv ka$ . The DOCP values from pseudo cancer ous tissue ( $P_{\rm cancer}$ ) are larger than those from pseudo-healthy tissue ( $P_{\rm beakh}$ ) at  $\lambda < 680$  nm, whereas  $P_{\rm cancer} < P_{\rm health}$  at  $\lambda > 680$  nm. These calculation results

ments obtained at the optical configurations with  $(\theta,\varphi)\equiv(a)~(\theta,0)$  and (b)  $(0,\varphi)$ . The data plotted in

Figure 1B, which crosses the boundary between cancer-ous and healthy tissues multiple times. A micrograph of the scanning area is shown in the upper part of the graphs in which the area delineated by the blue dotted the DOCP values showed almost no change, a differ ence of 0.1 or more in the DOCP value was of ence of 0.1 or more in the DOCP value was observed depending on the state of the biological tissues, whether healthy or cancerous, which corresponds to the reaults shown in Figure 2.1 Suttient differences are observed in each angular configuration; however, at around the boundary between cancerous and healthy parts, steeper changes are observed with the perpen-dicular incidence (Figure 38) than with the oblique DOCP value at the boundary between the oblique and DOCP value at the boundary between the oblique and perpendicular incidence could be possibly due to the different sampling (scattering) volumes and the subsequent radiation areas of the scattered light. An elongated elliptic spot due to the oblique incident beams induces the expansion of the scattering volume toward the in-plane direction inside the dissue. Accordingly,



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scattered CP light for cancer identification in optical

configurations with various angular relations between the directions of incidence and detection. An incident angle larger than the Brewster's angle for the surface of biological dissues causes a decreased penetration of polar-ized light into the tissue, and the small difference

between the angles of incidence and detection increases surface reflection with less information. At the configura surface reflection with less information. At the configura-tion with angles within the appropriate range, that is,  $\theta \leq 53^\circ$  and  $(\theta - \varphi) \geq 30^\circ$ , the significant differences between the DCCP values obtained from the cancerous and healthy parts are observed to be approximately 0.20, which is sufficient to identify the cancer-affected area. Based on the good agreement with our previous calcula-tions [31], here, we concluded that the difference in the DOCP values results from the different sizes of cell nuclei rather than the different reflectance values, which sugrather than the different reflectance values, which sug-gests that this technique could be applied to the identi-cation of not only carcinomas but also other diseases accompanied by the enlargement of cell radsel, for exam-ple, alcoholic hepatitis and ulcerous colitis. In addition to the cell nuclei, the contribution of cellular walls and other constituents also contributes to polarization scattering. These components, which are strongly associated with the anisotropic cellular shape and birefringence, can greatly contribute to polarization scattering in fibrous tisgreatly contribute to polarization scattering in Birous tis-sue, asymmetric complex tissue, and a tissue in which anisotropic mutation is observed. The samples used in this study consist of uniform, isotropic cell nuclei in both cancerous and healthy parts, in which the centributions of these anisotropic parameters are inconspicuous. Fur-ther research is required to investigate these contrib-tions. In the line-scanning measurements, the obtained DOCP values change in an almost binary manne depending on the state of tissue, whether healthy or candepending on the state of ususe, whether neatiny or can-crous. The optical configurations with oblique incidence provide larger differences in the DOCP values, which indicates higher accuracy in identifying cancerous parties. However, the elongated elliptic spot due to oblique inci-dence reduces the spatial resolution and enhances the positional fluctuation. Conversely, the arrangements with perpendicular incident light have higher spatial resoluperpediacular incusers uppl have inguest passial resolu-tion due to a narrow sampling volume but slightly less accuracy due to fewer scattering events. These arrange-ments should be selected according to the objective dis-case, organ, apparatus and environment. Moreover, an almost constant difference in the DOCP values can be obtained at the configuration with angles within the appropriate range, which makes it permissible to incline the surface of measuring tissues against the fixed optical system. This indicates that this technique is useful even n environments where it is difficult to fix the spatia arrangement between the optics and the target, such as in vivo observations with an endoscope.

### ACKNOWLEDGMENTS

This work was partially supported by KAKENHI (Nos. 17K14104, 18H08878 and 19H04441) of the Japan Society for Promotion of Science (ISPS), the Cooperative Research Project of Research Center for Biomedical Engineering, Futaba Foundation, Spintronics Research Net anrk of Janan (Snin-RNI) and a Grant-in-Aid fo work of Japan (Spin-RN) and a Grant-in-Add for Challenging Research, Organization of Fundamental Research, Tokyo Institute of Technology. The authors acknowledge technical support from the Semiconductor and MEMS Processing Division of the Technical Department of Tokyo Institute of Technology. The authors acknowledge Prof. II. Munekata and Prof. J. Yoshino for Traitful discussions and technical support at the Tokyo Institute of Technology (TIT). This work was supported by Tokyo Tech World Research Hub Initiative (WRHI) Program of Institute of Innova tive Research, Tokyo Institute of Technology. W would like to thank Editage (www.editage.com) fo English language editing.

The data that support the findings of this study are avail able from the corresponding author upon reasonable

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Foromi Nishizawa https://orcid.org/0000-0002-7292

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in the Supporting Information section at the end of this

How to cite this article: Nishizawa N, Al-Qadi B,

Biophotonics, 2020;e202000380, https://doi.org/10. 1002/jbio.202000380

## 重要だと思ったら 何度も読む

(approximately 53°, in this study), the p-polarizatio information. The latter characteristic of the difference in the DOCP value corresponds reasonably well with the simulation results calculated for almost the same optical configurations (Figure 2C in ref. [31]), which implies that the observed difference in the DOCP value is derived from the difference in particle (cell nucleus) size. The magnitude of the detected DOCP value can be influenced by extrinsic factors such as surface reflection, while the difference in the DOCP value is intrinsic and robust in

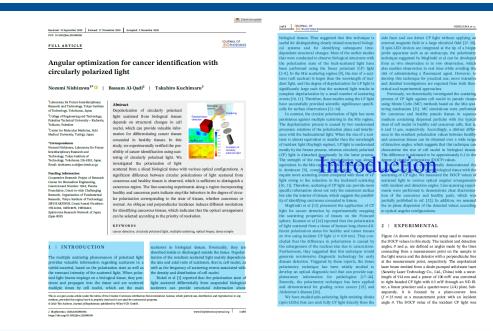
the optical configuration with an angle within the appro-priate range, which provides valuable information about the state of the biological tissue.

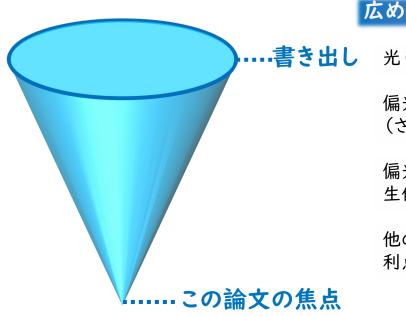
s of s JOURNAL OF BIOPHOTONICS

# 各部の読み方 Introduction

Introductionは一般に広いところから 狭いところへ、そしてこの論文の焦点 のところまで話の焦点を絞っていくよ うに書かれている

研究の歴史や既存技術や対抗技術・手法・材料の研究動向や利点・問題点などを整理してくれている場合もあるので研究全体の流れを捉えるのに便利。この部分の参考文献は把握しておくべき





光(偏光)とは 編光の利用 (されてない) 偏光を使った 生体観察が報告 他の技術を凌 他の技術を凌 利点は? がん診断は大切

がん検出の 現状と課題

偏光を使うと 解決できるかも 偏光の多重散乱は有用

狭め

がんを観察できる可能性

他のがん観察技術

偏光が他技術を凌ぐ点

偏光の研究動向と課題

偏光を利用した生体評価

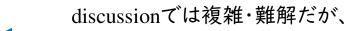
# 各部の読み方 Conclusion

Conclusion部は

SummaryとConclusion(Message)からなる

Summaryは これまでの内容のまとめ (この部分に初見の内容は書かれない)

- 研究目的
- 研究手法と内容、結果
- それぞれの結果に対する考察

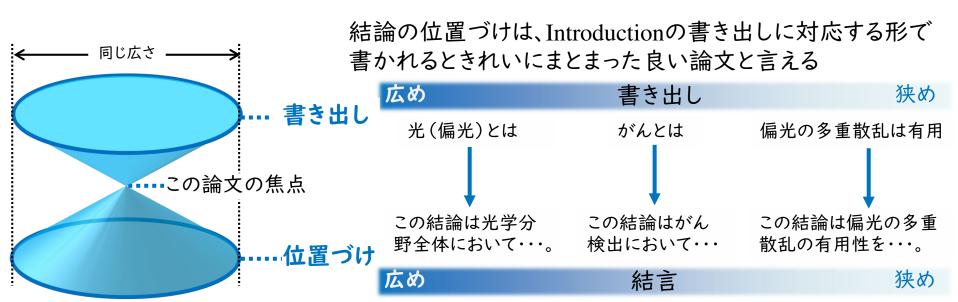


ここでは簡素に書かれるので 読みやすくなっている

Conclusionは著者が読者に向けたMessageに相当する

- 考察を集約して導き出された結論
- この結論の研究全体における位置づけ(結言)

configurations with various angular relations between the direction of incidence and detection, An incident in the contract is an incident in the contract in a factories. An incident in the contract is a factories of the contract in the



# 各部の読み方 Materials and methods

Materials and methods部は実際に行った実験や解析の手法が書かれている。

## Materials部は

- 対象となる材料、検体、素子の特性
- 準備方法
- 加工方法等

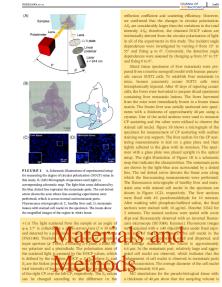
## Methods部は

## [実験]

- 実験手法や条件、
- 使用した装置(市販品か自作か)
- 振ったパラメーターとその根拠
- データ解析の手法

## [Simulationや計算]

- 計算手法、条件
- 振ったパラメーターとその根拠
- 得られたデータの正当性(予め示せる 場合のみ)



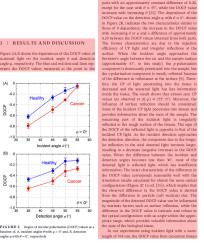
appendiculably 1 mm s. 1 mm s. 62 pm; polyometer of the singular configuration. The simpling depth is  $\theta_{\rm c}(s) \approx 1.0^{\circ}$ ,  $\theta_{\rm c}(s) \approx 0.0^{\circ}$ ,  $\theta_{\rm c}(s) \approx 0.00$ , so defining to let  $\theta_{\rm c}(s) \approx 0.00$ . Therefore, a significant portion of facilities flight is minimized by the simplificant portion of facilities flight is in the size of the si

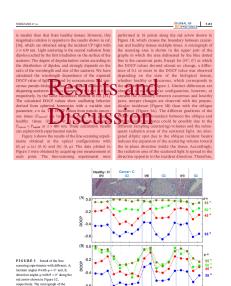
細かい記述で理解が大変ではあるが、次の結果を理解する上では重要な部分。 また、結論が正しいのかどうかを判定する、 同じ(様な)実験をする等の場合には一字 一句よく読み込む必要がある

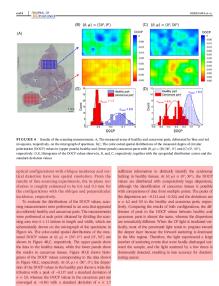
Nature系などは論文の最後の方にまとめられていたり、補足資料 (Supplementary materials) に入れられている論文誌もある

# 各部の読み方 Results and Discussion

Results and Discussion部は 文字通り結果と考察について 書かれている







(Result → Discussion) ×n または Results → Discussion 見出して分けられている という構成のどちらかが多い

## Results部は

得られた結果を示した図、グラフ、画像に対しての説明を中心にかかれているため、 比較的理解しやすい

## Discussion部は

得られた結果の解釈、著者の考察が書かれている論文でいちばん重要な部分

結果の位置づけや解釈の他、今後の展望 や今回はできなかった部分なども書かれ ることがあるので、読者にとっては有益な こともある

根拠となる参考文献のうち重要と考えられるものをリスト化しておく

# 各部の読み方 References

## References (引用文献)

本文中で引用、または参考にした論文の リスト(すべてを読む必要はないが重要な ものは目を通す必要がある)

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      SUPPORTING INFORMATION

How to cite this article: Nishizawa N, Al-Qadi B, Kuchimaru T. Angular optimization for cancer identification with circularly polarized light. J. Biophotonics, 2002;e200008. https://doi.org/10.

## Introductionに紐づけされた引用文献

その研究に至った歴史の部分においてはマイルストーンとなる論文を順に挙げていることが多いので、次に読む論文を探す場合などはここまた、焦点の絞り具合によって、より広い領域の重要論文などが挙げられており、必要とする段階に応じて目を通す必要がある

Materials and Methodsに紐づけされた引用文献 同様の試料や手法を使った実験、手法そのものについての論文などもある

Results and Discussionに紐づけされた引用文献 考察の根拠などに関しての引用の場合、詳細が書かれている場合もある

Conclusionsに紐づけされた引用文献 今後の展望の部分では次の研究の指標になる論文が挙げられている場合もある

※ 本論文と著者が同じなのか違うのかによって意味合いが変わることがあるので注意

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英語で検索すること 専門用語で検索すること

 $\triangle$  stomach cancer

O gastric cancer

キーワードをできれば複数 動詞を入れる、出版年代を限定する 限定検索にするなどで絞れることがある また、検索結果をサイト検索でスクリーニ ングするのも手である

その論文の引用文献から探る方が早い 引用文献は代表となる論文を挙げてい るので選択しなくても重要であることが わかる

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