

2020-Fast intelligent cell phenotyping for high-throughput optofluidic time-stretch microscopy based on the XGBoost algorithm

Nowadays, imaging cytometry is increasingly considered a solution to the detection of cells or particles without demanding a biomarker. Continuous ultrafast imaging enabled by optical timestretch technology achieves unprecedented imaging speed of millions of frames per second.The high-throughput label-free imaging cytometer based on optofluidic time-stretch technology combines time-wavelength-space mapping using spatial and temporal dispersion with high-speed single-pixel detection.It has facilitated circulating tumor cells detection at single-cell sensitivity from abundant cells by capturing cell images rapidly, which is a proper solution for the highly sensitive detection of rare cells.Researchers have explored extensively to further improve the performance of optofluidic time-stretch microscopy, such as having a higher resolution,a lower system cost, and an application to broader scenarios.However, high-throughput time-stretch imaging cytometry still suffers from the analysis of mass amounts of cell images. A high processing cost would prevent further developments and clinical applications of time-stretch flow cytometry, such as cell sorting. Machine learning is a powerful tool for finding patterns and identifying different cell types from large-scale data, providing a nonmanual method to process biomedical information. Many different machine learning approaches to phenotype cell images obtained by optofluidic time-stretch microscopy have been developed. Nitta et al. proposed a method of cellular deep neural network that classifies cells accurately to sort cells on-chip according to their images. Kobayashi et al. applied the support vector machines (SVM) classification algorithm to distinct drug-treated and untreated cells properly. Jiang et al. chose logistics regression (LR) to identify aggregated platelets in blood. Meanwhile, most of these previous studies have overlooked the processing speed of the algorithms while focusing on classification accuracy. As large amounts of cells are continuously imaged by the cytometer, a cell classification algorithm with accuracy and celerity is highly demanded. However, the LR, SVM, and deep neural network are all missing the standard. LR underfits complicated models due to its linearity; the complexity of SVM models explodes with larger sample sets; and deep neural network with multilayer convolution operation results in high computational complexity. A classification algorithm with low computation cost and sufficient fitting capability is required. Boosting is a tool of massively parallel simple weak classifiers that operates fast and from a complicated model. It appreciates plain features. A mutual characteristic of the images of flowing cells is their regularity containing predictable contents and little impurities or noise, which implies extractable and explicable features.Therefore, boosting may be the solution to the problem. Here, we introduce a recent boosting algorithm for big data processing called XGBoost. It is currently one of the best open-source boosted tree toolkits and has shown outstanding performance in many standard classification tasks. Soon after XGBoost was raised, of the champions of the 2015 Kaggle data challenges used the XGBoost method, which beat neural networks with 11 champions.Moreover, as cell libraries are constructed automatically, the noise in images among them affect learning-based classification models severely. To enhance the trained model’s robustness, we adopt density-based clustering algorithms to detect and remove the noise samples in advance. In this paper, we implement a framework based on XGBoost for the problem of fast phenotyping of cells in high-throughput optofluidic time-stretch microscopy. The phenotyping consists of detection of outlier samples, extraction of fused features, and XGBoost classification. It is tested on a collection of over 20,000 flow cell images obtained by an optofluidic time-stretch microscope

如今，越来越多地将成像细胞计数法视为无需生物标记物即可检测细胞或颗粒的解决方案。借助光学时延技术实现的连续超快速成像，实现了前所未有的每秒数百万帧的成像速度。基于光流时延技术的高通量无标记成像细胞仪结合了时空分布和时空色散特性，并具有快速的单像素检测。它通过快速捕获细胞图像，促进了从丰富细胞中以单细胞敏感性对循环肿瘤细胞的检测，这是对稀有细胞进行高灵敏度检测的合适解决方案。研究人员进行了广泛探索，以进一步提高性能具有高分辨力，较低的系统成本以及在更广泛的场景中的应用等光流时间拉伸显微技术的研究。然而，高通量时间拉伸成像细胞术仍受细胞图像质量分析的困扰。高昂的处理成本将阻止时间延伸流式细胞术（例如细胞分选）的进一步发展和临床应用。

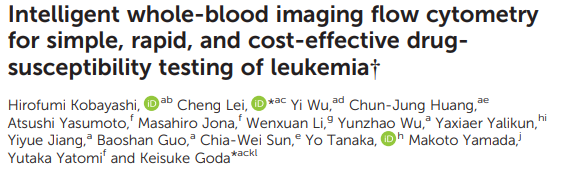
机器学习是一种功能强大的工具，可用于从大规模数据中查找模式并识别不同的细胞类型，从而提供了一种非人工方法来处理生物医学信息。已经开发了许多不同的机器学习方法来通过光流时间拉伸显微镜获得表型细胞图像。

Nitta等。提出了一种细胞深层神经网络的方法，该方法可以对细胞进行精确分类，并根据其图像对芯片进行分类。

小林等。将支持向量机（SVM）分类算法正确地应用于了不同的药物处理和未处理细胞。

江等。选择物流回归（LR）识别血液中聚集的血小板。同时，大多数这些先前的研究在关注分类准确性的同时却忽略了算法的处理速度。由于大量细胞通过流式细胞仪连续成像，因此非常需要具有准确性和快速性的细胞分类算法。

但是，LR，SVM和深度神经网络都缺少该标准。由于其线性，LR不适合复杂的模型。支持向量机模型的复杂性随着样本集的增加而爆炸。多层卷积运算的深度神经网络导致计算复杂性高。需要一种具有低计算成本和足够拟合能力的分类算法。 Boosting是大规模并行的简单弱分类器的一种工具，可从复杂模型快速运行。它欣赏朴素的功能。流动细胞图像的共同特征是其规则性包含可预测的内容，并且杂质或噪声很少，这意味着具有可提取和可解释的特征，因此增强可以解决该问题。在这里，我们介绍一种用于大数据处理的最新提升算法XGBoost。它是目前最好的开源增强树工具包之一，并且在许多标准分类任务中都表现出出色的性能。 XGBoost提出后不久，在2015年Kaggle数据挑战赛的冠军中，使用了XGBoost方法，该方法击败了11位冠军，击败了神经网络。此外，由于细胞库是自动构建的，因此图像中的噪声严重影响了基于学习的分类模型。为了增强训练后模型的鲁棒性，我们采用了基于密度的聚类算法来预先检测和去除噪声样本。在本文中，我们实现了一个基于XGBoost的框架，用于高通量光流时间拉伸显微镜中细胞的快速表型化问题。表型包括检测异常样本，提取融合特征以及XGBoost分类。在通过光流时间拉伸显微镜获得的20,000多个流通池图像的集合上进行了测试



2019-Intelligent whole-blood imaging flow cytometry for simple, rapid, and cost-effective drug-susceptibility testing of leukemic

Leukemia is a malignancy of the body's blood-forming tissues, such as the bone marrow and lymphatic system, which results in large populations of abnormal white blood cells (WBCs). It is often difficult to cure, with a 5 year survival rate of less than 30%.While treatment outcomes for a few types of leukemia including chronic myeloid leukemia and acute promyelocytic leukemia have been remarkably improved by virtue of the advent of molecular targeted therapies such as imatinib and alltrans-retinoic acid (ATRA), treatments for other types of leukemia including acute myeloid leukemia and acute lymphoblastic leukemia (ALL) still rely on intensified use of anticancer drugs for chemotherapy that often causes severe damage to organs. Consequently, treatment-related mortality rates are considerably high and the number of treatment-applicable patients is limited. Meanwhile, precision medicine has become one of the most anticipated approaches to leukemia therapy in recent years for its characteristic of customizing medical treatments and practices to individual patients. Genomic analysis plays a dominant role in precision medicine as it is practically the only reference available to determine the right drugs in clinical applications. However, a recent study has shown that treatments based on genomic analysis are no better in progression-free survival than those based on the physician's best choice. This is because therapy decisions based on genomic data are limited by scant knowledge of the complex dynamics between genotype and phenotype. For this reason, genotype-based prediction of drug resistance or drug susceptibility with high accuracy remains as a major challenge.

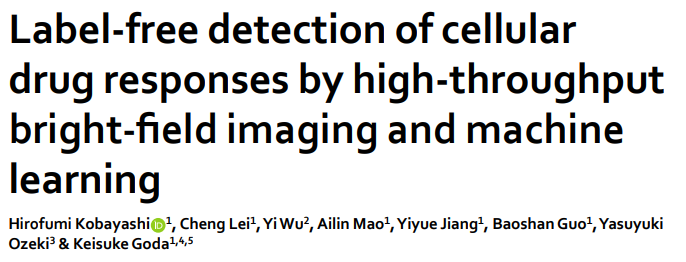
Direct measurement of cellular responses to anticancer drugs, known as functional assays, is an alternative means toward precision medicine for leukemia. Specifically, the combination of automated fluorescence microscopy and a compound library has opened the gateway for high-content screening (HCS), by which cellular responses to drugs can be continuously monitored using fluorescence images. Recently, HCS has been used to investigate the drug-response profiles of clinical samples from patients with leukemia. Although the HCS approach to precision medicine for leukemia is successful as it provides molecular information, its practical utility to clinical settings is hindered by its relatively low throughput, high complexity, and high cost due to the combination of low imaging speed and the need for fluorescent labeling. Furthermore, the precision of the HCS approach is limited as it requires the enrichment of target cells by hemolysis, centrifugation, or fixation, leading to disruption of original cellular responses to drugs.

In this article, we present a highly simple, rapid, and costeffective liquid biopsy for ex vivo drug-susceptibility testing (also called chemosensitivity testing) of leukemia to overcome the above limitations. The method is based on an extreme-throughput (>1 million cells per s), label-free, wholeblood imaging flow cytometer with a deep convolutional autoencoder. Consequently, it enables image-based identification of the drug susceptibility of WBCs in whole blood within hours by simply flowing a drug-treated whole blood sample as little as 500 μL into the imaging flow cytometer without labeling. Specifically, we validated the method with K562 (a human chronic myelogenous leukemia cell line) and K562/ADM (a drug-resistant strain of K562), showing the difference in their drug susceptibility via dose-dependent morphological changes with the same sensitivity as a conventional cell viability assay. Furthermore, we used it to accurately evaluate the drug susceptibility of WBCs from untreated ALL patients. To facilitate the interpretation of drug susceptibility for medical experts, we also demonstrated using the Hilbert–Schmidt independence criterion (HSIC) as an index to represent the degree of drug susceptibility (ESI†). Finally, our method allowed us to quantitatively identify that leukemia cells are more vulnerable to adriamycin (a commonly used anticancer drug) than healthy cells using only the label-free images. Our results may pave the way for creating a drug susceptibility panel of all available anticancer drugs for each patient and thus providing a new diagnostic method to determine which anticancer drug is more suitable for the patient. Selecting more effective anticancer drugs in a simple, rapid, and cost-effective way can eventually improve the survival rate of leukemia patients

白血病是人体血液形成组织（如骨髓和淋巴系统）的恶性肿瘤，会导致大量异常白细胞（WBC）。它通常很难治愈，其5年生存率不到30％。尽管由于分子靶向疗法的出现，包括慢性髓样白血病和急性早幼粒细胞白血病在内的几种类型的白血病的治疗效果已得到显着改善。与伊马替尼和全反式维甲酸（ATRA）一样，对其他类型的白血病（包括急性髓细胞性白血病和急性淋巴细胞性白血病（ALL））的治疗仍然依靠大量使用抗癌药物进行化学疗法，这经常会对器官造成严重损害。因此，与治疗有关的死亡率很高，并且可治疗患者的数量受到限制。同时，精准医学由于其针对个别患者定制医学治疗和实践的特征，已经成为近年来最令人期待的白血病治疗方法之一。基因组分析在精密医学中起着主导作用，因为它实际上是在临床应用中确定正确药物的唯一参考。但是，最近的一项研究表明，基于基因组分析的治疗的无进展生存期并不比基于医生最佳选择的治疗更好。这是因为基于基因组数据的治疗决策受限于对基因型和表型之间复杂的动力学缺乏了解。因此，以基因型为基础的耐药性或药敏性预测仍然是主要挑战。

直接测量细胞对抗癌药物的反应（称为功能测定法）是针对白血病的精准医学的另一种方法。具体来说，自动荧光显微镜和化合物库的结合为高含量筛选（HCS）打开了大门，通过它可以使用荧光图像连续监测对药物的细胞反应。最近，HCS已用于研究白血病患者临床样品的药物反应情况。尽管HCS方法可提供分子信息，因此成功用于白血病的精准医学方面，但由于其相对较低的通量，较高的复杂性和较高的成像速度以及对荧光的需求，因此阻碍了其在临床环境中的实用性标签。此外，HCS方法的精度受到限制，因为它需要通过溶血，离心或固定来富集靶细胞，从而导致对药物的原始细胞反应中断。

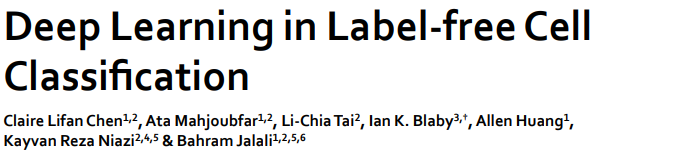
在本文中，我们提出了一种用于白血病的离体药物敏感性测试（也称为化学敏感性测试）的高度简单，快速且经济高效的液体活检，以克服上述限制。该方法基于具有深卷积自动编码器的超高通量（> 1百万个细胞/秒），无标签的全血成像流式细胞仪。因此，通过简单地将少至500μL的经过药物处理的全血样品流入成像流式细胞仪而无需标记，即可在数小时内基于图像识别全血中WBC的药物敏感性。具体来说，我们用K562（人类慢性骨髓性白血病细胞系）和K562 / ADM（K562耐药菌株）验证了该方法，通过剂量依赖性形态变化显示了它们的药敏性差异，其敏感性与常规细胞活力测定。此外，我们使用它来准确评估未经治疗的ALL患者的WBC的药物敏感性。为方便医学专家对药物敏感性的解释，我们还证明了使用希尔伯特-施密特独立性标准（HSIC）作为代表药物敏感性程度（ESI†）的指标。最后，我们的方法允许我们仅使用无标签图像定量鉴定白血病细胞比健康细胞更容易受到阿霉素（一种常用的抗癌药）的侵害。我们的结果可能为创建针对每个患者的所有可用抗癌药的药敏性铺平道路，从而为确定哪种抗癌药更适合患者提供了一种新的诊断方法。以简单，快速和经济有效的方式选择更有效的抗癌药物最终可以提高白血病患者的生存率



2017-Label-free detection of cellular drug responses by high-throughput bright-field imaging and machine learning

In the last decade, high-content screening based on multivariate single-cell imaging has been proven effective in drug discovery to evaluate drug-induced phenotypic variations in gene expression, protein localization, and cytoskeletal structure . A number of studies have shown that cellular responses to drugs or even the mechanism of action for unknown compounds can be correctly predicted with such variations . "e primary advantage of image-based screening over conventional univariate screening is its capability of multivariate profiling with a large number of variables by which leading compounds can be identified with high sensitivity . Moreover, with advances in molecular biology, image-based screening has been coupled with RNA interference or gene-modified cell lines to provide further information on cellular responses to drugs . In a recent study, for instance, a library of fluorescently tagged reporter cell lines has been produced to find an optimal cell line for image-based screening . Unfortunately, conventional multivariate single-cell imaging for high-content screening falls short in addressing the full needs of the drug discovery community as it inherently requires fluorescent labeling which has several drawbacks. First of all, fluorescent probes are not available for all target molecules and may interfere with natural cellular functions . While a wide range of immunofluorescent probes are commonly used in single-cell imaging for multivariate profiling, they are costly and require time-consuming labeling processes, including cell fixation which kills the cells, hindering large-scale assays. Fluorescently tagged cell lines can offer live-cell assays without the labeling process, but the development of such cell lines requires more effort than immunofluorescent labeling . therefore, an alternative for image-based high-content screening without the need for fluorophores is clearly needed for easy manipulation and economical assays. In this paper, to avoid the above limitations, we present a method for evaluating cellular drug responses only by high-throughput bright-field imaging with the aid of machine learning. "is was made possible by acquiring a large number of bright-field images of numerous drug-treated and -untreated cells (N=~240,000) by opto- fluidic time-stretch microscopy with high throughput up to 10,000 cells/s and using the label-free cell images and machine learning to identify their morphological variations which are too subtle for human eyes to detect. Consequently, we successfully identified drug-treated and -untreated cells with a high accuracy of 92% without the need for any labeling techniques. Specifically, we used MCF-7 as a model cell line and paclitaxel, an anti-cancer drug, as a model drug to induce morphological change to the cells. We quantitatively analyzed the morphological change of paclitaxel-treated MCF-7 cells compared with a negative control, or untreated cells. "e degree of the morphological change, inferred from classification accuracy, increased with the drug concentration and treatment time, suggesting that the morphological change observed from bright-field images can be utilized as an indicator for drug discovery. Our work lays the groundwork for label-free drug screening in pharmaceutical science and industry

在过去的十年中，基于多元单细胞成像的高内涵筛选已被证明可有效地用于药物发现，以评估药物诱导的基因表达，基因表达，蛋白质定位和细胞骨架结构的表型变异。大量研究表明，通过这种变化可以正确预测细胞对药物的反应，甚至未知化合物的作用机理。 “基于图像的筛查相对于常规单变量筛查的主要优势在于其具有大量变量的多元谱分析能力，通过这些变量可以以高灵敏度鉴定领先的化合物。此外，随着分子生物学的发展，基于图像的筛查已得到广泛应用。结合RNA干扰或基因修饰的细胞系以提供有关药物对细胞的反应的更多信息，例如，在最近的一项研究中，已经建立了一个荧光标记的报告细胞系文库，以寻找用于基于图像筛选的最佳细胞系不幸的是，传统的用于高内涵筛选的多变量单细胞成像不能满足药物发现界的全部需求，因为它固有地需要荧光标记，这有几个缺点：首先，并不是所有目标分子都可以使用荧光探针并可能干扰自然的细胞功能。 bes通常在单细胞成像中用于多变量分析，它们昂贵且需要耗时的标记过程，包括杀死细胞的细胞固定，阻碍了大规模测定。荧光标记的细胞系无需标记过程即可提供活细胞检测，但与免疫荧光标记相比，此类细胞系的开发需要更多的努力。因此，显然需要一种无需荧光团的基于图像的高含量筛选方法，以便于操作和经济分析。在本文中，为避免上述限制，我们提出了一种仅通过借助机器学习的高通量明场成像评估细胞药物反应的方法。 “通过光流时间拉伸显微镜以高达10,000个细胞/秒的高通量，并通过使用光流时间拉伸显微镜来获取大量药物处理和未处理的细胞（N =〜240,000）的大量明场图像，这才成为可能。无标记的细胞图像和机器学习可以识别出人眼无法察觉的细微形态变化，因此，我们无需使用任何标记技术就可以成功地以92％的准确度鉴定出经过药物处理和未经处理的细胞。具体而言，我们以MCF-7为模型细胞系，以紫杉醇（一种抗癌药）作为模型药物来诱导细胞形态变化，并定量分析了紫杉醇处理的MCF-7细胞的形态学变化。阴性对照或未处理的细胞。“根据分类准确度推断，形态变化的程度随药物浓度和治疗时间的增加而增加，表明从明bright观察到形态变化ld图像可以用作药物发现的指示剂。我们的工作为制药科学和工业中的无标签药物筛选奠定了基础



2016-Deep Learning in Label-free Cell Classification

Deep learning extracts patterns and knowledge from rich multidimenstional datasets. While it is extensively used for image recognition and speech processing, its application to label-free classification of cells has not been exploited. Flow cytometry is a powerful tool for large-scale cell analysis due to its ability to measure anisotropic elastic light scattering of millions of individual cells as well as emission of fluorescent labels conjugated to cells. However, each cell is represented with single values per detection channels (forward scatter, side scatter, and emission bands) and often requires labeling with specific biomarkers for acceptable classification accuracy. Imaging "ow cytometry on the other hand captures images of cells, revealing significantly more information about the cells. For example, it can distinguish clusters and debris that would otherwise result in false positive identification in a conventional "ow cytometer based on light scattering. In addition to classification accuracy, the throughput is another critical specification of a "ow cytometer. Indeed high throughput, typically 100,000 cells per second, is needed to screen a large enough cell population to find rare abnormal cells that are indicative of early stage diseases. However there is a fundamental trade-o$ between throughput and accuracy in any measurement system. For example, imaging "ow cytometers face a throughput limit imposed by the speed of the CCD or the CMOS cameras, a number that is approximately 2000 cells/s for present systems. Higher "ow rates lead to blurred cell images due to the finite camera shutter speed. Many applications of "ow analyzers such as cancer diagnostics, drug discovery, biofuel development, and emulsion characterization require classification of large sample sizes with a high-degree of statistical accuracy. %is has fueled research into alternative optical diagnostic techniques for characterization of cells and particles in "ow. Recently, our group has developed a label-free imaging "ow-cytometry technique based on coherent optical implementation of the photonic time stretch concept11. %is instrument overcomes the trade-o$ between sensitivity and speed by using Amplified Time-stretch Dispersive Fourier Transform. In time stretched imaging16, the object’s spatial information is encoded in the spectrum of laser pulses within a pulse duration of sub-nanoseconds Each pulse representing one frame of the camera is then stretched in time so that it can be digitized in real-time by an electronic analog-to-digital converter (ADC). %e ultra-fast pulse illumination freezes the motion of high-speed cells or particles in "ow to achieve blur-free imaging. Detection sensitivity is challenged by the low number of photons collected during the ultra-short shutter time (optical pulse width) and the drop in the peak optical power resulting from the time stretch. %ese issues are solved in time stretch imaging by implementing a low noise-figure Raman amplifier within the dispersive device that performs time stretching. Moreover, warped stretch transform can be used in time stretch imaging to achieve optical image compression and nonuniform spatial resolution over the field-of-view. In the coherent version of the instrument, the time stretch imaging is combined with spectral interferometry to measure quantitative phase and intensity images in real-time and at high throughput. Integrated with a microfluidic channel, coherent time stretch imaging system in this work measures both quantitative optical phase shift and loss of individual cells as a high-speed imaging "ow cytometer, capturing 36 million images per second in "ow rates as high as 10 meters per second, reaching up to 100,000 cells per second throughput. On another note, surface markers used to label cells, such as EpCAM, are unavailable in some applications; for example, melanoma or pancreatic circulating tumor cells (CTCs) as well as some cancer stem cells are EpCAM-negative and will escape EpCAM-based detection platforms. Furthermore, large-population cell sorting opens the doors to downstream operations, where the negative impacts of labels on cellular behavior and viability are often unacceptable. Cell labels may cause activating/inhibitory signal transduction, altering the behavior of the desired cellular subtypes, potentially leading to errors in downstream analysis, such as DNA sequencing and subpopulation regrowth. In this way, quantitative phase imaging (QPI) methods that categorize unlabeled living cells with high accuracy are needed. Coherent time stretch imaging is a method that enables quantitative phase imaging at ultrahigh throughput for non-invasive label-free screening of large number of cells

In this work, the information of quantitative optical loss and phase images are fused into expert designed features, leading to a record label-free classification accuracy when combined with deep learning. Image mining techniques are applied, for the first time, to time stretch quantitative phase imaging to measure biophysical attributes including protein concentration, optical loss, and morphological features of single cells at an ultrahigh "ow rate and in a label-free fashion. %ese attributes differ widely among cells and their variations reflect important information of genotypes and physiological stimuli. %e multiplexed biophysical features thus lead to information-rich hyper-dimensional representation of the cells for label-free classification with high statistical precision. We further improved the accuracy, repeatability, and the balance between sensitivity and specificity of our label-free cell classification by a novel machine learning pipeline, which harnesses the advantages of multivariate supervised learning, as well as unique training by evolutionary global optimization of receiver operating characteristics (ROC). To demonstrate sensitivity, specificity, and accuracy of multi-feature label-free "ow cytometry using our technique, we classified (1) OT-II hybridoma T-lymphocytes and SW-480 colon cancer epithelial cells, and (2) Chlamydomonas reinhardtii algal cells (herein referred to as Chlamydomonas) based on their lipid content, which is related to the yield in biofuel production. Our preliminary results show that compared to classify- cation by individual biophysical parameters, our label-free hyperdimensional technique improves the detection accuracy from 77.8% to 95.5%, or in other words, reduces the classification inaccuracy by about five times

深度学习从丰富的多维数据集中提取模式和知识。虽然它广泛用于图像识别和语音处理，但尚未用于细胞无标签分类。流式细胞术具有测量数百万个细胞的各向异性弹性光散射以及发射与细胞结合的荧光标记的能力，因此是进行大规模细胞分析的强大工具。但是，每个检测通道的每个检测单元（前向散射，侧向散射和发射带）用单个值表示，并且通常需要使用特定的生物标记来标记才能获得可接受的分类精度。另一方面，“流式细胞术成像”捕获细胞图像，显示有关细胞的更多信息。例如，它可以区分簇和碎片，否则将导致基于光散射的常规“流式细胞仪”中的假阳性识别。除分类准确性外，通量是“低细胞计数仪”的另一个关键指标。确实，需要高通量（通常为每秒100,000个细胞）来筛选足够大的细胞群，以发现指示早期疾病的罕见异常细胞。但是，在任何测量系统中，通量和精度之间都存在根本的权衡。例如，“流式细胞仪成像”面临着由CCD或CMOS相机的速度强加的通量限制，该数目约为2000个细胞/秒对于当前的系统。由于有限的相机快门速度，较高的“流率”会导致细胞图像模糊。“流”分析器的许多应用（例如癌症诊断，药物发现，生物燃料开发和乳化液表征）都需要对大样本量进行分类，并具有高度统计性准确性。 ％is推动了用于表征“ ow”中细胞和粒子的替代光学诊断技术的研究。最近，我们小组基于光子时间拉伸概念的相干光学实现，开发了一种“无标记成像” ow-cytometry技术。该仪器通过使用放大的时间拉伸色散傅里叶变换克服了灵敏度和速度之间的折衷。在时间拉伸成像16中，对象的空间信息在亚纳秒的脉冲持续时间内以激光脉冲的频谱进行编码，然后将代表相机一帧的每个脉冲及时拉伸，以便可以通过数字实时将其数字化。电子模数转换器（ADC）。 ％e超快速脉冲照明可冻结高速细胞或粒子的运动，从而实现无模糊成像。在超短快门时间（光脉冲宽度）内收集到的光子数量较少，挑战了检测灵敏度在时间拉伸成像中，可以通过在执行时间拉伸的色散器件中实现低噪声数字的拉曼放大器来解决这些问题，并且可以使用翘曲拉伸变换来解决这些问题。时间拉伸成像可在视野范围内实现光学图像压缩和非均匀的空间分辨率，在该仪器的相干版本中，时间拉伸成像与光谱干涉仪相结合可实时并在一定程度上测量定量的相位和强度图像高通量，相干时间拉伸成像系统与微流体通道集成在一起，可测量定量的光学相移和ind损失普通细胞作为高速成像“流式细胞仪”，以每秒高达10米的“流率”每秒捕获3600万张图像，每秒吞吐量高达100,000个细胞。另外，在某些应用中无法使用用于标记细胞的表面标记，例如EpCAM。例如，黑色素瘤或胰腺循环肿瘤细胞（CTC）以及某些癌干细胞均为EpCAM阴性，将逃脱基于EpCAM的检测平台。此外，人口众多的细胞分选为下游操作打开了大门，其中标签对细胞行为和生存力的负面影响通常是不可接受的。细胞标记可能会引起激活/抑制性信号转导，从而改变所需细胞亚型的行为，从而可能导致下游分析中的错误，例如DNA测序和亚群再生。以这种方式，需要定量相成像（QPI）方法，该方法可以对未标记活细胞进行高精度分类。相干时间拉伸成像是一种能够以超高通量进行定量相位成像的方法，用于无创无标签筛选大量细胞

在这项工作中，将定量的光损耗和相位图像的信息融合到专家设计的功能中，从而在与深度学习相结合时可达到无记录分类的准确性。图像挖掘技术首次应用于时间拉伸定量相成像，以超高“欠载”率和无标记方式测量生物物理属性，包括蛋白质浓度，光学损失和单个细胞的形态特征。细胞之间的属性差异很大，它们的变异反映了基因型和生理刺激的重要信息，多种生物物理特征从而获得了信息丰富的超维表示，可用于无标记分类的细胞，具有很高的统计精度，从而进一步提高了准确性新型机器学习管道对无标签细胞分类的准确性，可重复性以及敏感性和特异性之间的平衡，该管道利用了多元监督学习的优势以及通过对接收器工作特性（ROC）进行进化式全局优化的独特训练。证明多重敏感性，特异性和准确性使用我们的技术，通过“无特征”“流式细胞术”，我们将（1）OT-II杂交瘤T淋巴细胞和SW-480结肠癌上皮细胞分类，并且（2）基于莱茵衣藻的藻类藻细胞（在本文中称为衣藻）它们的脂质含量，这与生物燃料生产的产量有关。我们的初步结果表明，与按单个生物物理参数进行分类相比，我们的无标记超多维技术将检测准确度从77.8％提高到了95.5％，换句话说，将分类错误减少了大约五倍