Compressive Spectral Imaging Microscopy for Cancer Detection (COSMIC)

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ABSTRACT

We developed a novel spectral microscopy imaging method that opens the path towards automated cancer detection in biopsies. By using the advanced compressive sensing framework, we are able to capture spectral images with unprecedented resolution and speed. We tested the performance of our compressive hyperspectral imaging system for histopathology of cancer cells and have been able to demonstrate unprecedented high detection accuracy. Our method is based on a commercial microscope, it is modular and versatile, and can be used for other applications that require rapid acquisition of high quality spectral images.

Keywords: cancer histopathology; hyperspectral microscopy; compressive sensing

1. INTRODUCTION

Cancer diagnostics still relies nowadays on a pathological interpretation of biopsies using glass-slide microscopy of stained tissues. The number of biopsies is constantly increasing, and it requires highly experienced pathologists. The process is highly laborious, time consuming, it is seldom subjective and often results in a delayed report. There is therefore an unmet need for automated systems that can expedite the diagnostics process. In the last decade, digital pathology has evolved to answer this demand and systems for whole slide imaging (WSI) are available in the market [1]. These systems can scan biopsy slides rapidly, but capture only color information based on three numbers per pixels, red-green-blue (RGB), which provide unaccepted low values for reliable diagnostics. Even the addition of artificial intelligence (AI) still did not result in a successful commercial application, although there is some progress. On the other hand, spectral images, which provide the full spectrum to every pixel, carry valuable information that can be used for object detection in many applications, including cancerous cell detection. However, available systems cannot capture high resolution spectral images at high frame rates because there is a fundamental difficulty to acquire the full 3D spatial-spectral data information with available 2D sensors.

In this project we achieved two main breakthroughs. The first one is the development of a novel hyperspectral (HS) microscopy system and method that takes advantage of the revolutionary theory of compressive sensing (CS) theory [2-4]. Owing to the CS approach we are able to reduce the acquisition time and to increase the sensitivity by more than an order of magnitude. With the developed CS spectroscopic method, we have been able to demonstrate a second breakthrough in the field of cancer detection; that is, accurate detection of cancerous cells in breast cancer biopsies.

Our CS realization is based on a special illumination unit which we developed during this project. This unit is easily plugged in a commercial microscope. With our approach, we demonstrated the acquisition of microscope images having more than 700 spectral bands, within less than 1sec! We have applied our compressive spectral microscopy technique on stained breast cancer biopsies. From the spectral reconstructed data, we have been able to obtain excellent discrimination between cancerous and normal cells.

2. STATE OF THE ART

Cancer histopathology is performed traditionally manually by pathologists. In the last decade, digital pathology (DP) has evolved to answer the growing demand for microscopy-based diagnostics using systems for Whole Slide Imaging (WSI). However, currently, WSI is based solely on measuring RGB measurements and it is used solely for one purpose: to change the way they work, by saving them the work with the microscope and providing them a digital image on the monitor screen. The diagnostics itself, is done only by the pathologist, and there is not commercial use of computer diagnostics. In order to enable initial diagnostics, it is well accepted that spectral imaging (together with AI) is the future of diagnostic aid, what is called decision support [5]. Spectral imaging is an established modality for biomedical imaging [6] and can be implemented by

different optical principles. However, conventional spectral imaging methods are time consuming and typically suffer from low optical efficiency. Consequently, the acquisition time of a spectral image of a histological slide, which may occupy as much as 2 (spatial) Gigapixels, may be in order of hour, which prohibits the application of a commercial use. This time limitation is a fundamental one, therefore it is common to all conventional spectral imaging techniques. In this project we broke this paradigm by realizing a CS method [5].

3. BREAKTHROUGH CHARACTER OF THE PROJECT

In this project we have achieved technological breakthroughs which enable unprecedented medical diagnostic performance. From a technological point of view, we demonstrated a CS spectral microscopy method and system which:

1) can capture ultra-spectral images with 710 spectral bands in less than 1 frame-per second,

2) has extremely high sensitivity, which allows fast imaging of dim objects (e.g., samples with low optical transmittance/reflectance),

3) works by employing a special module which is plugged in the illumination arm of a commercial microscope, without altering the well-designed imaging arm. Therefore, the full spatial resolution or image quality of high end microscopes can be preserved. This is in contrast with the vast majority of spectral imaging methods which exhibit spatial resolution degradation,

4) the method is versatile; it can be easily adapted to any microscope,

5) has an optical throughput efficiency which is X50 higher than that of any conventional method. Consequently, it can be applied in extreme conditions, obtaining high signal-to-noise ratio (SNR).

6) The spectral microscope compresses the data optically within the acquisitions process. Thus less storage is necessary, which is a valuable property when large amount of data is captured, such as in histopathology.

7) We have developed a special operation protocol for a Liquid Crystal (LC) device we developed (part of our illumination module) that allows full (compressive) spectral scanning within less than 1 sec.

We have used our CS spectral microscopy method for histopathology testing and obtained the following achievements:

1. Using the spectral information, we were able to distinguish clearly between cancerous and normal cells, which otherwise cannot be distinguished from RGB images captured with a conventional microscope.

2. Preliminary results indicate cancerous cell detection with an accuracy of more than 97% on a cell-by-cell basis, even when an analytical algorithm is used. This merit is better than most of the studies being published, even though they use a complex training and AI algorithms.

3. The acquisition and detection process can be fully automated. This can expedite the diagnostics process, which is done today manually by pathologists.

4. PROJECT RESULTS

We demonstrated our CS spectral imaging method on an Olympus IX81 inverted *commercial* microscope (Fig. 1). The main hardware components of our method consists of our special illumination unit (Fig. 1) and its driver. A laptop computer is used for the acquisition control and image reconstruction. The illumination unit and the microscope camera are controlled by a LabView program code. The reconstruction of the spectral images is performed by a CS algorithm realized in Matlab.
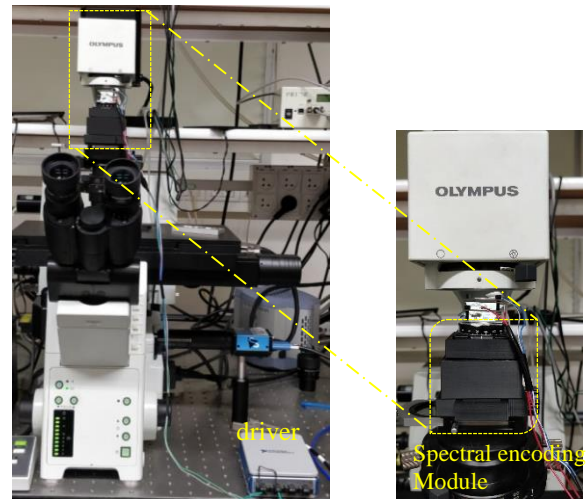

Fig. 1. The spectral imaging system. It is based on a commercial Olympus IX81 microscope (left image) where we plugged in a spectral encoding module in the illumination arm (right image). This module is controlled by the shown driver and a laptop computer (not shown).

Notice that the only hardware change in the Olympus microscope is the extra unit in the illumination arm, therefore we preserve the high spatial imaging capabilities of the commercial microscope.

The illumination module generates a set of spectrally encoded patterns. The full set of patterns is generated

within less than 1 sec. Thus, acquisition of the compressed spectral image can be done at 1 spectral frame per second. From the captured data we are able to reconstruct spectral images with 710 spectral bands with full spatial resolution. In our experiments we limited the spectral range to 400-750nm.
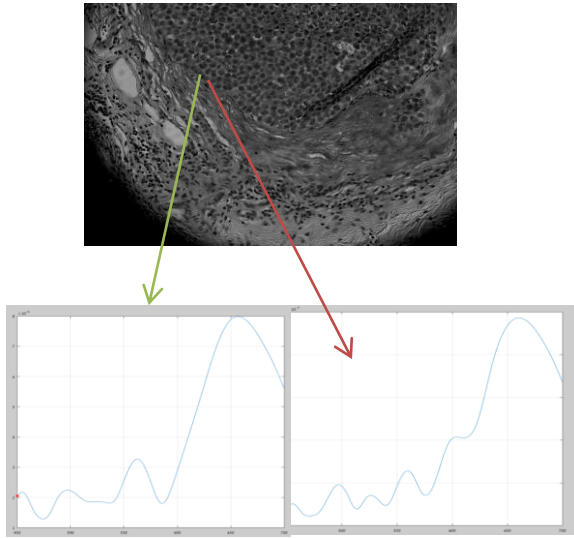

Fig. 2. The spatial distribution of the biopsy sample and the spectra of a pixel in a cancerous cell and in a healthy cell.

We have used our CS spectral microscopy method for histopathology testing. Breast cancer biopsies were prepared, stained with Hematoxylin and Eosin (H&E) and different cell types were identified by a pathologist.

Fig. 2 shows the spatial image of a biopsy sample together with the reconstructed spectra of a cancerous and a normal cell picked up from two cells in the image. Notice that while there is no spatial difference between the spatial distribution of the cells, their spectra are clearly different.

Fig. 3 shows the spectral distribution of an ensemble of cancerous and healthy cells. The average and standard deviation of 20 healthy and cancerous pixels is plotted. The difference is evident and can be easily detected by machine learning algorithms. Preliminary tests show an accuracy larger than 97% in detection of cancerous cells by using a basic machine learning algorithm. We expect

even better results with deep learning algorithms, such as we have applied for remote sensing compressive spectral images [8].

As already mentioned, the acquisition of spectral images such as in Fig. 2 is done within less than 1 second. Another important property of our system is its high sensitivity. Fig. 4 shows that our method has an optical throughput which is about 50 times higher than that of conventional methods. Consequently, there is no need to use long exposure times for the acquisition of dim images.

The advantage of our method over conventional ones is clearly evident in Table 1 which compares the performance of our HS microscope to the commercial ones.
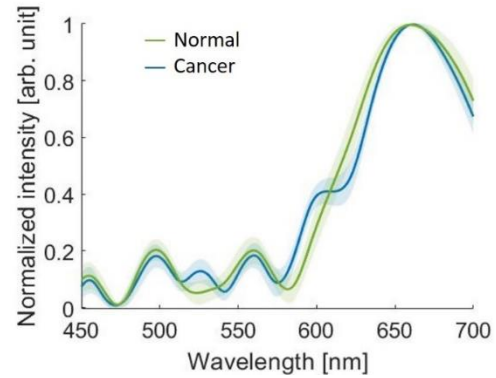

Fig. 3. Difference between the spectral distribution of normal and cancerous cells.
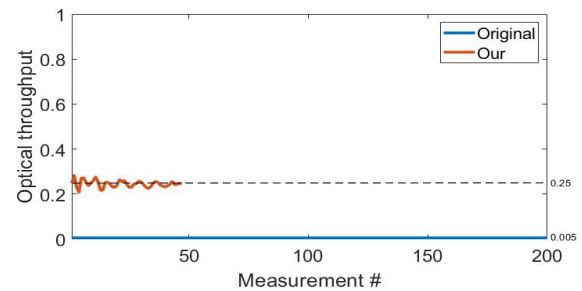

Fig. 4. Optical throughput and number of measurements of our system compared to a conventional one.

Tab. 1. Comparison of our HS system to commercial available ones.

Product	Spatial Resolution	Spectral range	Spectral resolution	Acquisition rate [HS frame /sec]	Normalized spectral image acquisition time *
CytoViva	2048 x 2048	400-1000 nm 900-1700 nm	1.5nm 5 nm	0.1	800 (estimated)
HinaLea 4200M	1920X1200	400-1000 nm	4 nm	NA	144 (estimated)
COSMIC (our)	2048x1088 6144X3264 (opt)	400-1000 nm 1000-1700 nm(opt)	~1 nm	1	1

5. FUTURE PROJECT VISION

As we showed, the technology that we have developed has outstanding advantages for objective cancer detection and the development of new drugs. Accordingly, we are planning to start a company that will commercialize the system and develop its application to these markets. We strongly believe that:

1. The potential market is huge and the company can evolve into a world-wide company.

2. The technology can improve healthcare and help pathologists by providing them a decision support to their hard and responsible time-consuming work.

3. The same technology can expedite the process of drugs development, where a lot of cancer tissues are used and the cancer have to be identified. The system can also identify biomarkers that are aimed to predict treatment prognosis.

5.1. Technology Scaling

In order to move to TRL 5-7, a few steps have to be taken. Our core technology is ready (2 working prototypes built) and can become an industrial system in 12 months (with the right investment). Once built, it can be part of every pathology department and cancer research center. To create an Industrial System, two main components need to be added/completed:

1. Automatic Slide-loader (commercially available) – enabling automating multi-sample detection process

2. Software - algorithms & data management providing AI based 'decision support' to pathologists based on our systems unique data (digital image and spectral data).

We have a pretty good description of the demo-system minimal viable product (MVP) description and it can be ready in a rather short time. Constructing the system will require optical engineering design.

5.2. Project Synergies and Outreach

As mentioned, in order to get to TRL 5-7, we will have to team with a hospital and maybe also pathology departments in medical schools. We already have excellent contact and collaboration with Sheba Medical Center in Israel, that has a very high reputation world-wide, and the biggest pathology department.

For public dissemination, we plan to develop a website that will include relevant information to the public. Moreover, we will present the technology and system in relevant conferences (once it returns.), take part in relevant public fairs in order to educate about the technology, spectrum and imaging.

Furthermore, we will look for other partners in Europe, both strategic partners, as well as partners that can be synergic to our project in fields such as: optical and medical devices, artificial intelligence and big data.

5.3. Technology application and demonstration cases

The demo cases we plan for are:

1. Select a rather common cancer type, such as breast or colon cancer that the pathologists can easily identify, and test the performance of the system with respect to the pathologists "gold standard" diagnostics. We will also run 'blind tests' on few cases.

2. We will identify with the pathologists a difficult type of cancer for them to diagnose and try to develop a method for classifying this case and examine the accuracy of the method.

5.4. Technology commercialization

Commercialization of such a high-end product for hospitals can only be predicted at this time. Through our collaboration, we will make contacts with pathology organization make more contacts, develop presentations, demo cases and white papers, and start the process of marketing and sales. We will publish, take part in international conferences of the relevant fields, expand our contact list, and continue from there.

We already had contacts with few venture capital companies and unofficially presented our technology and idea. The feedback is excellent.

5.5. Envisioned risks

The main core risks that we see are not in the technological part, but rather in the application field:

1. It may be difficult to penetrate to hospitals and recommend a different way of working relative to what they do now. We will therefore work with leading medical centers, as well as leading pathologists in medical schools.

2. We will require to go over regulations approvals. We will build a team (including consultants) and start with simple claims, such as just providing high quality images on the screen, followed by 'decision support' strategy of objective parameters, leaving the decision for the pathologists. These can be, for example, the amount of chromatin in the nucleus, which is indicative to aneuploidy.

5.6. Liaison with Student Teams and Socio-Economic Study

We strongly believe that this can be done in Israeli and European universities. We will start with excellent contacts we have with relevant departments in Israel, and continue from there. We will team with the deans of the relevant universities and enter to an agreement for having student working on the project for their MSc. We will define few relevant projects in optics, biopsies labeling scheme, algorithm development, artificial intelligence and big-data.

6.   ACKNOWLEDGEMENT

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