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TITLE: Artificial Intelligence-Based Diffraction Analysis (AIDA) for Point-of-Care Breast Cancer Classification

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CONTRACTING ORGANIZATION: Worcester Polytechnic Institute
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14. ABSTRACT

The overall goal of this project is to advance the next generation imaging cytometer, AIDA (Artificial Intelligence-based Diffraction Analysis), for automated molecular screening on individual cancer cells. AIDA will integrate cutting-edge developments in computational optics and machine learning: digital diffraction imaging and deep neural network. We will implement an AIDA imaging system equipped with multiple light sources with different wavelengths. This setup will allow us to detect different molecular markers through color-based multiplexing. We will implement a deep-learning framework for cellular analyses. Specifically, we will train deep neural networks to i) recognize individual cells directly from diffraction images, ii) extract levels of molecular information, and iii) unravel hidden phenotypes for cell stratification. Then, we will perform a clinical study to test AIDA's clinical utility. Cellular samples will be obtained from breast cancer patients and will be color-stained for triple markers: HER2, ER/PR. We will then apply AIDA to image a large number of individual cells and automatically extract their features; these data will be used to construct the molecular profile of a given sample.

15. SUBJECT TERMS
breast cancer, holography, deep learning, point-of-care

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1. INTRODUCTION

Cellular inspection using microscopy and histology remains integral for diagnosis, prognosis, and treatment decisions. The principal technique, conventional microscopy, has low throughput, requires manual inspection by trained microscopists, and often yields variable, operator-dependent results. Such drawbacks are exacerbated in resource-limited settings where pathology bottlenecks delay cancer diagnoses and potentially lead to over/under-treatment. The problem is relevant not only across low or middle-income countries, but also in the US; nearly a quarter of the US population live in rural areas, but only 10% of physicians practice in those areas8. Developing cost-effective, scalable technologies to feasibly detect (especially at early stages) and classify cancers is thus a key mandate to better manage cancer and improve survivorship. Unfortunately, no such platforms are currently available for translational testing. The ***goal*** of this proposal is to advance a new diagnostic imaging platform for on-site, high-throughput breast cancer cell screening. Termed AIDA (Artificial Intelligence Diffraction Analysis), this platform integrates cutting-edge developments in computational optics and deep learning to facilitate accurate, fast, and automated molecular analyses of breast cancer down to the single cell.

2. KEYWORDS

Breast cancer, Holography, Deep learning, Point-of-care

3. ACCOMPLISHMENTS

What were the major goals of the project?

The major goals of the first-year funding period (2019/07 - 2020/07) were two-fold.

Goal 1: Implement an AIDA platform for large-scale single cell imaging (90% completion, Massachusetts General Hospital).

Goal 2: Develop AIDA deep-learning framework for single cell detection and classification (90% completion, WPI)

What was accomplished under these goals?

We have made significant progresses in developing both the imaging system and deep learning algorithm.

Massachusetts General Hospital (PI, Hakho Lee)

New AIDA system. We have recently implemented a new whole-slide imaging system for real-time breast biopsy validation (**Fig. 1a**). The system incorporates an on-board embedded GPU (NVIDIA Jetson Nano) for on-site holographic reconstruction without the need to communicate with a cloud-based GPU server (**Fig. 1b**). The GPU's128 cores deliver 450 GFLOPS of computing power which compute holographic reconstruction on images acquired by a 10MP CMOS sensor (Imaging Source) with less than 100 ms of processing latency per acquisition. To complement these enhanced optical and computing modules, we designed a high-precision scanning optical assembly that maintains a constant distance to the sample within 25 μm, and has fine-adjustment mechanisms for tilt, angle, and spatial correction to ensure the highest quality data. Further, the system facilitates automated data acquisition and processing of an entire breast pathology sample (~10^7 cells) using a custom motorized stage. Samples are processed in 7 min; an order of magnitude faster than our previously reported system.

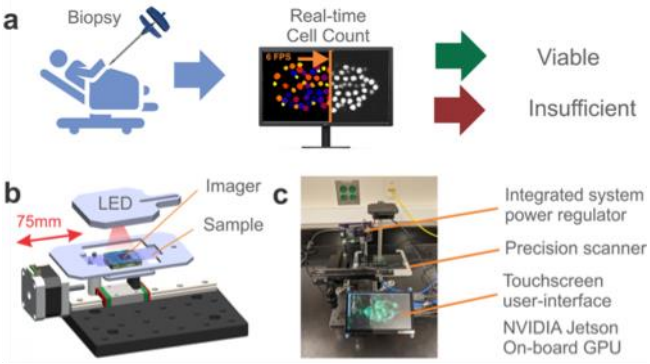


Fig. 1. 2nd generation AIDA system. (a) Updated patient workflow illustrating real-time biopsy validation at the point-of-care **(b)** Precision optical scanning mechanism with 10MP CMOS image sensor **(c)** Photograph of constructed system

Real-time hologram reconstruction. Individual breast cells are holographically reconstructed using a novel deep learning system that is fast and reliable. The system implements fast Fourier transform (FFT)-based two-dimensional image convolutions using the C++ based NVIDIA "CUDA" interface to perform holographic magnitude reconstruction. This pipeline is paired with a custom 5-layer convolutional deep learning

architecture, named HoloNet, in order to accomplish fast and accurate phase recovery. The integrated system can reconstruct holographic image data at a maximum throughput of 15 frames per second on high resolution (2048 × 2048) tiles which are stitched together to yield a field-of-view (FOV) as large as 75 mm × 50 mm: large enough for any pathology application. We are currently implementing graphical, user-friendly software to streamline the system operation using a high definition capacitive touchscreen.

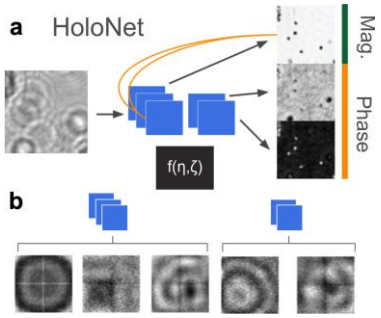
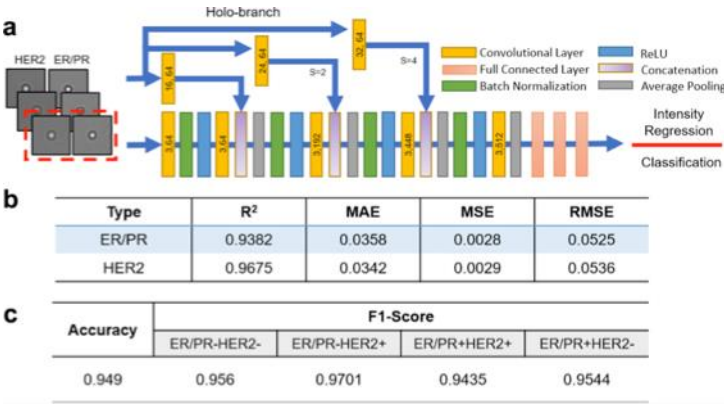


Fig. 2. HoloNet deep learning system. (a) Deep learning pipeline with a sample 192 × 192 input hologram tile. Tile is processed in realtime by five magnitude and phase recovery filters to output a three-channel reconstruction. **(b)** Visualization of the learned filters, demonstrating the machine's ability to learn complex optical transformations.

Worcester Polytechnic Institute (PI, Kwonmoo Lee)

Development of a deep neural network (HoloNet) for the hologram analysis. Using the AIDA system, we obtained high-resolution, large FOV diffraction images that lens-based microscopes cannot achieve. The diffraction images, however, are complicated to discern. There is a computational algorithm that converts the diffraction patterns to cell images, but it is inefficient and prone to errors. To resolve this issue, we developed a deep neural network, called HoloNet, which directly analyzes diffraction patterns (**Fig. 3a**). In addition to the standard CNN (Convolutional Neural Network), the HoloNet includes a holo-branch that extracts large features from holograms and integrate them with the small features from the standard CNN. Since low-level cell features can diffract more than high-level features, the large filters in the holo-branch can effectively capture this information. Using HoloNet, we built a regression model to predict the intensity values of ER/PR and HER2 in breast cancer cell lines. The R^2 values of ER/PR and HER2 regression was 0.9382 and 0.9675, respectively (**Fig. 3b**). We also trained the classifier based on the Holo-Net. The accuracy of the classification for four subtypes of breast cancer was 0.949 (**Fig. 3c**).



b

Type	R^2	MAE	MSE	RMSE
ER/PR	0.9382	0.0358	0.0028	0.0525
HER2	0.9675	0.0342	0.0029	0.0536

c

Accuracy	F1-Score			
	ER/PR-HER2-	ER/PR-HER2+	ER/PR+HER2+	ER/PR+HER2-
0.949	0.956	0.9701	0.9435	0.9544

Fig. 3. HoloNet analyzes the holograms of breast cancer cells. (**a)** Structure of HoloNet. **(b)** The performances of the regression from ER/PR and HER2 intensities. **(c)** The performances of the classification of breast cancer cell types.

Identification of sub-clusters of breast cancer cells using hologram features. After we trained the classifier, we used the trained HoloNet as a feature extractor from breast cancer cell holograms. We visualized the feature vectors of individual holograms on the three-dimensional space using UMAP (**Fig. 4a**). This revealed that there exist more detailed subtypes within the previously known four breast cancer cell types (**Figs. 4b-e**). To identify the clinical relevance of these sub-clusters, we confirmed that some of these sub-clusters existed in breast cancer patient samples (from the previous study). We used the trained HoloNet to extract the features from the holograms of two breast cancer patients. In both patients, we found that a substantial amount of the breast cancer cells of Cluster 1, 3, 8, and 9 existed (**Fig. 4f**), suggesting that new clusters may have clinical importance.

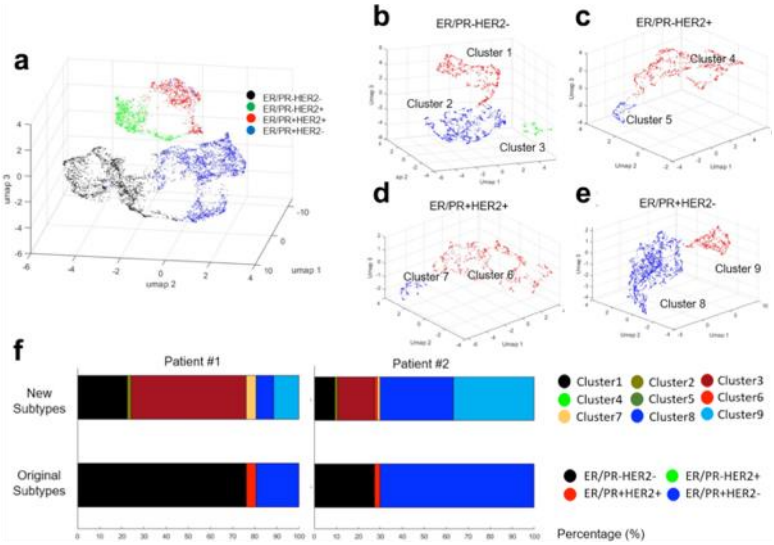
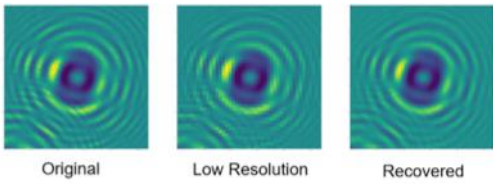


Fig. 4. Sub-clusters of breast cancer cells. (a) Holo-Net-embedded feature distribution of the holograms of breast cancer cells. **(b-e)** Sub-clusters in each breast cancer cell type. **(f)** Distribution of the original molecular phenotypes and new hologram phenotypes from breast cancer patients.

Hologram resolution enhancement. The resolution of the hologram is limited by the pixel size of the image sensor. We tested the feasibility of enhancing hologram resolution using deep learning. We made the original hologram low resolution by 8 pixel averaging (**Fig. 5a**). Then, we trained EDSR to recover the hologram resolution, resulting in increased pixel signal-to-noise ratio (pSNR) and the structural similarity index (SSIM; **Fig. 5b**). The recovered resolution was shown to increase the performance (R^2) of the intensity prediction in each channel in comparison to low resolution hologram (**Fig. 5c**).

a



b

	Low Resolution	Recovered Resolution
pSNR (dB)	34.3	39.9
SSIM	0.93	0.98

c

Channel	Original	Low	Recovered
ER/PR	0.9169	0.8747	0.8981
HER2	0.8970	0.6981	0.8129

Fig. 5. Resolution enhancement of hologram. **(a)** Examples of holograms. **(b)** Increased pSNR and SSIM by deep learning-based resolution enhancement. **(c)** R^2 for the intensity prediction using the original, low resolution, recovered resolution holograms

What opportunities for training and professional development has the project provided?

Training activities.

Practical skill sets for optics and computation. [MGH] With the guidance of the PI (H. Lee) and other research fellows, the graduate student (Mr. Ismail Degani, MIT) involved in this project has advanced his skills in low-level GPU programming, optical systems assembly, and data acquisition. Mr. Degani is now conducting this project independently. [WPI] With the guidance of the PI (Dr. Kwonmoo Lee), the graduate students (Mengzhi Cao and Pengyi Ye, Master Students at WPI) involved in this project have advanced their skills on deep learning application to image datasets.

Undergraduate senior design project. [WPI] PI (Dr. Kwonmoo Lee) provided a weekly mentorship to senior undergraduate students (Finn Casey, Robert Farrell, Adam Kaminski, Joseph LeBlanc) for the design project of an AI imaging system for holographic live cell imaging. The students continued to work on the project during Covid-19 pandemic and successfully presented their project on a virtual platform (**Fig. 6**).

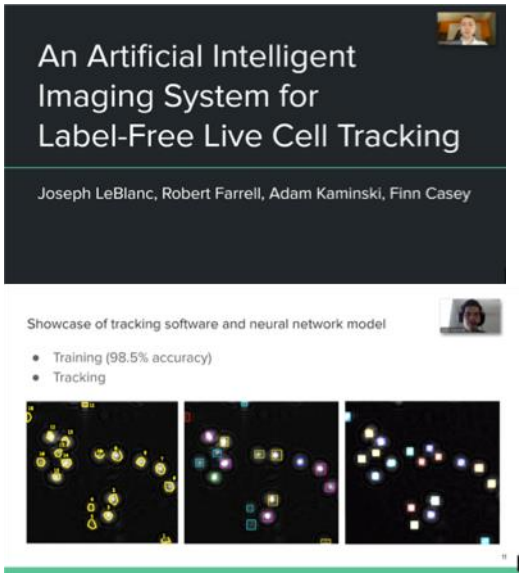


Fig. 6. Virtual presentation of the senior design project during Covid-19 pandemic

Professional development.

Course work. The concepts developed in this project (e.g., hologram, deep learning) has been incorporated into the intramural coursework of *CSB10 – Engineering Biosensors* taught by the PI (H. Lee, MGH), that explores key topics in biosensing.

Conference. Mr. Degani was encouraged to present at extramural meetings and conferences (see **Section 6**).

Seminar. The PI (Dr. Kwonmoo Lee, WPI) presented the progress of the project at Samsung Genome Institute, University at Buffalo, and Boston Children's Hospital.

How were the results disseminated to communities of interest?

Nothing to Report

What do you plan to do during the next reporting period to accomplish the goals?

[MGH site] As planned in our original Aim 2, we will apply the developed AIDA system to molecularly profile breast cancer cells. We will optimize our staining protocol for ER/PR and HER2. The planned activities will involve a set of controlled titration experiments. Obtained images will be sent to Partnering PI's lab to develop neural networks for image analyses. To ascertain the AIDA's accuracy, the profiling results will be compared with those by gold standard methods (e.g., flow cytometry). In anticipation of the pilot clinical test, we will secure IRB approval at MGH (pending now) and apply for HRPO approval.

[WPI site] *Pixel super-resolution.* To restore subpixel spatial information, we will apply an EDSR deep neural network for super-resolution restoration. We will acquire the training set 1× and 4× magnified diffraction patterns from the same cells. The network will use these matching image pairs to learn spatial details. The

trained network will improve the pixel density of the original diffraction patterns by 16-fold without reducing the field of view. *Generative modeling of cellular details for the fine-grained deconvolution.* To learn the fine-grained features from holograms, we will apply Generative Adversarial Networks (GANs), whose strength is its capacity to learn the cost function, recapitulating fine details in imaging data. The generator of GANs will synthesize reconstructed images of stained cells for given input of diffraction images. The embedded feature vectors of the generator will be used to identify fine-grained clusters, and the molecular markers will be quantified. *AI porting to a microcomputer.* Once algorithm development is complete on a workstation, we will transfer deep neural networks to a local controller for the POC (Point-Of-Care) operation by pruning deep neural network to reduce the model complexity and size for efficient execution. We will use an NVIDIA Jetson TX2 module, which provides deep learning computation in a small form-factor device and offers low power consumption.

4. IMPACT

What was the impact on the development of the principal discipline(s) of the project?

[MGH site] The developed system introduces *a new concept in biosensor design* by combining the advantages of GPU computing advances and lensless holographic imaging. In this improved system, internet connectivity speed and reliability is no longer a limiting factor in the throughput of the system. Rather, the system's self-contained design allows for exceedingly fast and reliable biopsy validation. ***Real-time biopsy validation:*** Our real-time strategy significantly improves the patient workflow by assessing the viability of a biopsy at the point-of-care. This eliminates the possibility of a non-diagnostic sample (having insufficient cell counts) forcing a patient to return for a second biopsy, which in many low-resource settings can be a significant burden. This innovation therefore offers not only higher efficiency but also significantly reduces patient harm. ***Increased spatial and temporal resolution.*** Utilizing the latest semiconductor technology, the imaging sensors can acquire theoretical spatial pixel resolution of 1.1um. This allows the system to resolve very fine details of each cell in the sample biopsy, greatly increasing the accuracy of cell segmentation and classification tasks. ***Novel whole-slide scanning architecture.*** In previous iterations, the system could only image a field-of-view (FOV) of 24mm^2, corresponding to the area of the image sensor. Our new scanning system has increased this *by a factor of 150* to 3750mm$^{2.}$ This FOV allows imaging of much larger samples which improves the overall versatility of the system. ***Guided optical Calibration.*** Motorized optical systems often need to be extensively calibrated by trained professionals in order to function optimally. Our system by contrast interprets the information-rich holographic image data to readily calculate the system's tilt/axial misalignment. An operator can then easily be guided by the system through the calibration sequences, minimizing the need for labor-intensive, potentially error-prone manual procedures. ***Robustness and user-friendly interface.*** One of the significant merits of the hybrid system is its durability and reproducibility. The system presents simple interfaces for accomplishing all aspects of biopsy validation; users can enjoy the same level of intuitive interfaces which are now standard in consumer electronics.

[WPI site] Conventional imaging analysis for lensless holographic imaging is based on the reconstructed images from the phase retrieval algorithm, which is prone to errors and still requires human curation. Our deep learning model enables us to directly analyze the holograms without the reconstruction process, which significantly reduces the time needed for manual supervision and correction. ***Deep learning for holograms:*** The trained neural network, HoloNet, which contains the branch of large filters, is specifically designed for hologram images. This facilitates automated hologram analyses such as regression and classification. ***Sub-clusters of breast cancer cells:*** Using the features learned by HoloNet, we were able to identify previously unknown sub-clusters of breast cancer cells. This suggests that it is possible to identify minor but clinically relevant sub-populations of cancer cells using deep learning and a lensless holographic system. This will enables us to build a more accurate breast cancer diagnosis system that considers the full heterogeneity of samples. ***Hologram resolution enhancement:*** We demonstrated that the high-resolution information lost by the pixelation of image sensors could be restored by the deep learning-based super-resolution method. This will enable a more accurate analysis of holograms and breast cancer diagnosis.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?
Nothing to report.

5. CHANGES/PROBLEMS

Nothing to report.

6. PRODUCTS

Publications, conference papers, and presentations

Journal publications.

[MGH site]

1. Weissleder, R., and Lee, H. (2020) Automated molecular-image cytometry and analysis in modern oncology. ***Nature Reviews Materials***, 5, 409–422. Acknowledgement of federal support (yes).

Presentations

(All of the following presentations acknowledged the federal support.)

[MGH site]

High-throughput protein profiling for cancer diagnostics & prognostic
ISEV-MRS Joint Meeting on EVs in Cancer
Hakho Lee,
Nashville, TN; 02-Aug-2019

Liquid biopsies - overview
SWOG Fall 2019 Group meeting
Hakho Lee
Chicago, IL, 01-Oct-2019

Sample preparation for clinical diagnostics/ Seminar
Korean Institute of Machinery and Materials (KIMM)
Hakho Lee
Seoul, Korea; 10-Oct-2019

Promise of liquid biopsy for cancer management
Applied Pharmaceutical Nanotechnology
Hakho Lee
Cambridge, MA; 25-Oct-2019

[WPI site]

Unravelling Cellular and Subcellular Heterogeneity Using Deep Learning
Samsung Genome Institute
Kwomoo Lee
Seoul, Korea; 10-Jan-2020

Unravelling Cellular and Subcellular Heterogeneity Using Deep Learning
University at Buffalo
Kwomoo Lee
Buffalo, NY; 12-Mar-2020

Unravelling Cellular and Subcellular Heterogeneity Using Deep Learning
Boston Children’s Hospital
Kwomoo Lee
Boston,MA; 12-Mar-2020

Technologies or techniques.
The research has produced a library of procedures to make optical systems, fluidic devices, and bioconjugtation (antibodies). We also advanced new neural network algorithms to rapidly analyze holograms. All data will be electronically stored and archived, and will be made available through publications in peer

reviewed journals. As in the past, all of these resources will be shared freely with scientific community upon execution of a proper MTA through the Office of Corporate Licensing (MGH or WPI).

Other products
Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	*Hakho Lee (MGH)*
Project Role:	*Principal Investigator*
Researcher Identifier	*orcid.org/0000-0002-0087-0909*
Nearest person month worked:	*2*
Contribution to Project:	*Dr. Lee supervised the overall research, interacting with investigators and research fellows, and discussing all experimental designs and data.*
Funding Support:	

Name:	*Cesar M. Castro (MGH)*
Project Role:	*Co-Investigator*
Researcher Identifier	*N/A*
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Castro guided the biological research, identifying biomarkers for breast cancer detection, and validating the selection through in-vitro assays.*
Funding Support:	

Name:	*Michelle Specht (MGH)*
Project Role:	*Co-Investigator*
Researcher Identifier	*N/A*
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Specht provided translational guidance for the development of proposed imaging technology. She will help procure breast cancer specimens for diagnostic testing.*
Funding Support:	

Name:	*Ismail Degani (MGH)*
Project Role:	*Graduate student*
Researcher Identifier	*N/A*
Nearest person month worked:	*6*
Contribution to Project:	*Mr. Degani designed the holographic imaging system, constructed the deep learning framework for cell classification/segmentation, and validated the entire system.*
Funding Support:	

Name:	*Kwonmoo Lee (WPI)*
Project Role:	*Principal Investigator*
Researcher Identifier	*orcid.org/0000-0001-6838-7094*
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Lee supervised the overall research, interacting with investigators and research fellows, and discussing all computational analysis results.*
Funding Support:	

Name:	*Tzu-Hsi Song (WPI)*
Project Role:	*Postdoctoral fellow*
Researcher Identifier	*N/A*
Nearest person month worked:	*4*
Contribution to Project:	*Dr.Song designed the holographic deep learning structure (Holo-Net), and perform the unsupervised learning using holograms.*
Funding Support:	

Name:	*Pengyi Ye (WPI)*
Project Role:	*Graduate student*
Researcher Identifier	*N/A*
Nearest person month worked:	*4*
Contribution to Project:	*Mr. Ye performed deep learning-based super-resolution restoration of holograms*
Funding Support:	

Name:	*Mengzhi Cao (WPI)*
Project Role:	*Graduate student*
Researcher Identifier	*N/A*
Nearest person month worked:	*4*
Contribution to Project:	*Mr. Cao performed deep learning-based regression analysis to predict the molecular marker intensities*
Funding Support:	

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

New support (Kwonmoo Lee, WPI)

Title:	Unraveling subcellular heterogeneity of molecular coordination by machine learning
Goals:	The major goal of this project is to develop a novel machine learning framework for large-scale analyses of subcellular heterogeneity of cell protrusion.
Specific Aims:	1) Deconvolution of subcellular heterogeneity of protrusion and molecular coordination in live cells 2) Deep learning based high-throughput fluorescence live cell imaging 3) Mechanosensitivity of subcellular bioenergetic status in cell protrusion
Start Date:	15-Sep-2019
End Date:	31-Aug-2024
Level of Effort:	2 Summer Months, 16.67%
Level of Funding:	$1,738,826.00
Funding Agency:	National Institutes of Health/NIGMS
Contracting/Grants Officer:	Dr. Paul Sammak, sammakpj@nigms.nih.gov, 301-594-8494
Role on Project:	Principal Investigator

Overlap:	None. This project is focused on developing a machine learning method applied to fluorescence live cell images to characterize actin regulator dynamics in cell migration. The machine learning method proposed here is focused on noisy fluorescence movies and time series data, which are substantially different from those in the DoD project. The application area is basic cell biology which is also different from breast cancer diagnosis in the DoD project. This project overlaps with the above pending NIH R01 project, but not with the DoD project.

Expired support (Kwonmoo Lee, WPI)

Title:	Wearable Devices for In-Home Monitoring of Patients at Risk for Heart Failure
Goals:	The major goal of this project is to develop a novel device for in-home monitoring of heart failure patients who are at risk of developing acute decompensated heart failure.
Specific Aims:	1) Develop reuseable carbon-black and polydimethylsiloxane (CB/PDMS) electrodes that capture bioimpedance and electrocardiogram data 2) Develop hardware and algorithms for acute decompensated heart failure detection, resulting in a wearable monitor with embedded CB/PDMS electrodes 3) Develop hardware and algorithms for atrial fibrillation detection using a smart watch 4) evaluate the performance and usability of both detection systems in a prospectively recruited cohort study.
Start Date:	01-Oct-2015
End Date:	30-Sep-2019
Level of Effort:	0 Calendar month, 0.0%
Level of Funding:	$32,593.00
Funding Agency:	National Science Foundation
Contracting/Grants Officer:	Dr. Wendy Nilsen, wnilsen@nsf.gov, (703) 292-2568
Role on Project:	Co-Principal Investigator
Overlap:	None

What other organizations were involved as partners?
Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

Not applicable.

9. APPENDICES

The following papers are attached.

Weissleder, R., and Lee, H. (2020) Automated molecular-image cytometry and analysis in modern oncology. ***Nature Reviews Materials***, 5, 409–422. Acknowledgement of federal support (yes).