Research Spending & Results

Award Detail

Awardee:	BROAD INSTITUTE, INC., THE
Doing Business As Name:	Broad Institute, Inc.
PD/PI:	Anne Carpenter (617) 714-7130 anne@broadinstitute.org
Award Date:	03/01/2012
Estimated Total Award Amount:	$ 796,459
Funds Obligated to Date:	$ 850,352 FY 2014=$186,909 FY 2016=$168,845 FY 2013=$154,517 FY 2015=$163,927 FY 2012=$176,154
Start Date:	03/01/2012
End Date:	02/28/2017
Transaction Type:	Grant
Agency:	NSF
Awarding Agency Code:	4900
Funding Agency Code:	4900
CFDA Number:	47.074
Primary Program Source:	040100 NSF RESEARCH & RELATED ACTIVIT
Award Title or Description:	CAREER: Image information extraction from heterogeneous populations of co-cultured cells
Federal Award ID Number:	1148823
DUNS ID:	623544785
Parent DUNS ID:	623544785
Program:	ADVANCES IN BIO INFORMATICS
Program Officer:	Jennifer Weller (703) 292-7121 jweller@nsf.gov

Awardee Location

Street:	415 Main Street
City:	Cambridge
State:	MA
ZIP:	02142-1401
County:	Cambridge
Country:	US
Awardee Cong. District:	07

Primary Place of Performance

Organization Name:	Broad Institute, Inc.
Street:	7 Cambridge Center
City:	Cambridge
State:	MA
ZIP:	02142-1401
County:	Cambridge
Country:	US

Cong. District: 07

Abstract at Time of Award

An award is made to the Broad Institute to identify and validate automated image analysis approaches to extract information from fluorescence microscopy images of co-cultured cell systems, while educating students, scientists, and the public about the theory, practice, and societal impact of biological image analysis. Biologists increasingly use co-culture systems, where two or more cell types are grown together in order to more accurately model their native environment. In order to use these powerful co-culture systems to tackle a wide range of basic biological research questions, the remaining challenge is to accurately extract quantitative measurements from each cell in microscopy images of such co-cultures, given that cell types with diverse morphologies are present. In close collaboration with researchers using co-culture systems, and building on the PI?s successful work in biological image analysis, this CAREER project integrates image analysis research and education.

The project will give the scientific community a validated, open-source software toolbox of image processing and machine learning algorithms readily usable by biologists. The education and outreach efforts of the project will produce validated, engaging educational materials that can be freely implemented by high school teachers around the world. More information about the project can be found at: http://www.broadinstitute.org/~anne/Carpenter_NSF_CAREER.html

Publications Produced as a Result of this Research

Note: *When clicking on a Digital Object Identifier (DOI) number, you will be taken to an external site maintained by the publisher. Some full text articles may not yet be available without a charge during the embargo (administrative interval).*

Some links on this page may take you to non-federal websites. Their policies may differ from this site.

Wawer MJ, Li K, Gustafsdottir SM, Ljosa V, Bodycombe NE, Marton MA, Sokolnicki KL, Bray M-A, Kemp MM, Winchester E, Taylor B, Grant GB, Hon CSY, Duvall JR, Wilson JA, Bittker JA, Dan?ík V, Narayan R, Subramanian A, Winckler W, Golub TR, Carpenter AE, Sham "Toward performance-diverse small-molecule libraries for cell-based phenotypic screening using multiplexed high-dimensional profiling" PNAS, v.111, 2014, p.10911. doi:http://dx.doi.org/10.1073/pnas.1410933111

Rohban MH, Singh S, Wu X, Berthet JB, Bray M-A, Shrestha Y, Varelas X, Boehm JS, Carpenter AE "Systematic morphological profiling of human gene and allele function via Cell Painting" ELIFE, v., 2017, p.. doi:10.7554/eLife.24060

Gustafsdottir SM, Ljosa V, Sokolnicki KL, Wilson JA, Walpita D, Kemp MM, Seiler KP, Carrel HA, Golub TR, Schreiber SL, Clemons PA, Carpenter AE, Shamji AF "Multiplex cytological profiling assay to measure diverse cellular states." PLOS ONE, v., 2013, p..

David J. Logan, Jing Shan, Sangeeta N. Bhatia, Anne E. Carpenter "Quantifying co-cultured cell phenotypes in high-throughput using pixel-based classification" METHODS,v., 2015, p.. doi:10.1016/j.ymeth.2015.12.002

Singh S, Bray M-A, Jones TR, Carpenter AE "Pipeline for illumination correction of images for high-throughput microscopy" JOURNAL OF MICROSCOPY, v.256, 2014, p.231.doi:http://onlinelibrary.wiley.com/doi/10.1111/jmi.12178/full

Meijering E, Carpenter AE, Peng H, Hamprecht F, Olivo-Marin, JC "Imagining the future of bioimage analysis" NATURE BIOTECHNOLOGY, v.34, 2016, p.1250.doi:10.1038/nbt.3722

Shan J, Schwartz RE, Ross NT, Logan DJ, Thomas D, Duncan SA, North TE, Goessling W, Carpenter AE, Bhatia SN "Identification of small molecules for human hepatocyte expansion and iPS differentiation." NATURE CHEMICAL BIOLOGY, v.9, 2013, p.514. doi:http://dx.doi.org/10.1038/nchembio.1270

Caicedo JC, Singh S, Carpenter AE "Applications in image-based profiling of perturbations" CURRENT OPINION IN BIOTECHNOLOGY, v.39, 2016, p.134.doi:10.1016/j.copbio.2016.04.003

Shan J, Logan DJ, Root DE, Carpenter AE, Bhatia SN "High-Throughput Platform for Identifying Molecular Factors Involved in Phenotypic Stabilization of Primary Human Hepatocytes In Vitro" JOURNAL OF BIOMOLECULAR SCREENING, v.21, 2016, p.897. doi:10.1177/1087057116660277

Ljosa V, Caie PD, ter Horst R, Sokolnicki KL, Jenkins EL, Daya S, Roberts ME, Jones TR, Singh S, Genovesio A, Clemons PA, Carragher NO, Carpenter AE "Comparison of Methods for Image-Based Profiling of Cellular Morphological Responses to Small-Molecule Treatment" JOURNAL OF BIOMOLECULAR SCREENING, v.18, 2013, p.1321.doi:http://dx.doi.org/10.1177/1087057113503553

Bray MA, Gustafsdottir SM, Ljosa V, Singh S, Sokolnicki KL, Bittker JA, Bodycombe NE, Dancík V, Hasaka TP, Hon CS, Kemp MM, Li K, Walpita D, Wawer MJ, Golub TR, Schreiber SL, Clemons PA, Shamji AF, Carpenter AE "A dataset of images and morphological profiles of 30,000 small-molecule treatments using the Cell Painting assay"GIGASCIENCE, v., 2017, p.. doi:10.1093/gigascience/giw014

Hartwell KA, Miller PG, Mukherjee S, Kahn AR, Stewart AL, Logan DJ, Negri JM, Duvet M, Järås M, Puram R, Dancik V, Al-Shahrour F, Kindler T, Tothova Z, Chattopadhyay S, Hasaka T, Narayan R, Dai M, Huang C, Shterental S, Chu LP, Haydu JE, Shieh JH, Steensm "Niche-based screening identifies small-molecule inhibitors of leukemia stem cells." NATURE CHEMICAL BIOLOGY, v.9, 2013, p.840. doi:http://dx.doi.org/10.1038/nchembio.1367

Nick Pawlowski, Juan C Caicedo, Shantanu Singh, Anne E Carpenter, Amos Storkey "Automating Morphological Profiling with Generic Deep Convolutional Networks" NIPS WORKSHOP ON MACHINE LEARNING IN COMPUTATIONAL BIOLOGY, v., 2016, p.. doi:https://doi.org/10.1101/085118

Singh S, Wu X, Ljosa V, Bray MA, Piccioni F, Root DE, Doench JG, Boehm JS, Carpenter AE "Morphological profiles of RNAI-induced gene knockdown are highly reproducible but dominated by seed effects" PLOS ONE, v.10, 2015, p.e(0131370. doi:http://dx.doi.org/10.1371/journal.pone.0131370

Shantanu Singh, Anne E. Carpenter, and Auguste Genovesio "Increasing the Content of High-Content Screening: An Overview" JOURNAL OF BIOMOLECULAR SCREENING, v.19, 2014, p.640. doi:10.1177/1087057114528537

Bray MA, Singh S, Han H, Davis CT, Borgeson B, Hartland C, Kost-Alimova M, Gustafsdottir SM, Gibson CC, Carpenter AE "Cell Painting, a high-content image-based assay for morphological profiling using multiplexed fluorescent dyes" NATURE PROTOCOLS, v.11, 2016, p.1757. doi:10.1038/nprot.2016.105

Project Outcomes Report

Disclaimer

Microscopy images are a rich source of information to the biologist's eye, revealing the appearance and physiological state of cells or organisms. In this project, we made several leaps forward in our ability to make images "computable", that is, making images a source of useful biological data to identify the underlying causes and potential cures for disease.

Biologists want to test genetic and chemical treatments in environments that more closely mimic the human body, to increase the likelihood that their experiments will uncover causes and cures for human disease. Increasingly, they are able to create complex cell systems in a dish, mixing two or more cell types such as liver cells and their supporting fibroblasts. These systems are proven to more accurately reflect tissues from the human body, but it has been challenging to measure key features of cells in images of cell mixtures.

In our work, we created open-source software, freely available to everyone, which can recognize and measure individual cells of different types. Working closely with liver disorder researchers, we tested this software in experiments that uncovered the genetic pathways involved in liver functions. We also found chemicals that can cause liver cells to grow, which could be developed into therapeutics or used in the laboratory to generate renewable sources of functional human liver cells, potentially for transplants. With cancer researchers, we discovered chemical compounds that inhibit the growth of leukemia cells without damaging normal blood-making cells, including a class of drugs called statins that are already safely used for patients with high cholesterol.

In these experiments, biologists aimed to measure one particular cellular response relevant to their goals. But microscopy experiments can measure hundreds of biologically valuable features from each cell and capture rich mechanistic information about cell state; this information is rarely mined to its full potential. Some of this information is, in fact, not even noticeable to the human eye, yet we hypothesized that accurate measurements of individual cells can reveal highly reproducible and relevant differences between two treatment conditions. If this is true, it could speed up several steps along the drug discovery pipeline.

After years of struggle and several dead ends, our team worked out computational algorithms that allowed us to identify the function of an unknown chemical by grouping it with known chemicals, an important step in a compound becoming a drug approved for human therapy. To do this, we extract 1,400+ features from each cell's image, then compare the resulting "fingerprint" of the cell's appearance with fingerprints from other treatments. We also experimented with deep learning networks "taught" using natural images (of cars, animals, people, etc.). Their accuracy currently matches that of classical methods (that explicitly locate and measure cells), but we expect future improvements to beat prior approaches.

Encouraged by this, we used our new methods to create an initial morphological map of gene function where 110 genetic treatments were grouped based on their similarity in morphological "fingerprints". This revealed many known-to-be-related genes grouping nearby each other. It also uncovered in human cells a new connection between two cancer signaling pathways, both of which critically regulate tumor initiation and progression. This provides evidence that a full map of all human genes would be useful to uncover other novel gene functions and connections between genes. We can now imagine a personalized medicine future, wherein a patient's cancer is sequenced and their mutation is tested to reveal similarities with other patients' mutations, thus guiding personalized treatments suited to the particular abnormality of their cells.

Our work has served as the foundation for discoveries in other stages of drug development. For example, we contributed to devising a method to produce better drug libraries for screening experiments, enabling researchers to test a smaller set of drugs while capturing most of those relevant to treating a particular disease. This method relies on choosing drugs based on their diverse image-based fingerprints. Our methods also enable chemists who are creating novel chemical structures to rapidly get feedback about the cellular impact induced by their compounds, using image-based fingerprints. This field of image-based profiling is now blossoming and the methods, software, and algorithms developed by our laboratory have provided an important foundation for discovering new disease mechanisms and medicines.

The education and outreach efforts of the project focused on educating students, scientists, and the public about the theory, practice, and societal impact of biological image analysis. In particular, we produced validated, engaging educational materials that can be freely implemented by high school teachers around the world. Throughout the project, we produced open-source software, online tutorials, online protocols, and review articles to help guide others in this field to use and build upon our work.

Last Modified: 04/07/2017
Modified by: Anne Carpenter