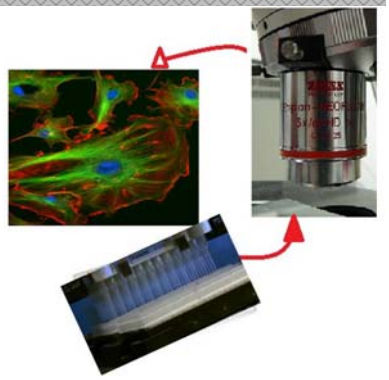


EMGEN Newsletter

Vol. 5, Issue 10

IN THIS ISSUE:

Eastern Mediterranean Health Genomics and Biotechnology Network (EMGEN) was created in 2004 with collaboration of representatives of selected centers of excellence in (health related) molecular biology, biotechnology & genomics in the Eastern Mediterranean region by recommendations and efforts of WHO/EMRO. Sponsored by Iran Biotechnology Development Council.

Address:
Biotechnology building, #69, Pasteur Ave., Pasteur Institute of Iran
Tehran, Iran, 13164
Tel: +98-21-66954324
Fax: +98-21-66465132
E-mail: emhgbn@gmail.com, emgen@pasteur.ac.ir
Websites: www.emgen.net
www.emhgbn.net

Prepared by: Fazeleh Hosseinpour
Page design: Fazeleh Hosseinpour
Assisted by: Mohammad Kargar
Editor: Dr. Soroush Sardari

WHAT IS HIGH CONTENT SCREENING (HCS)?

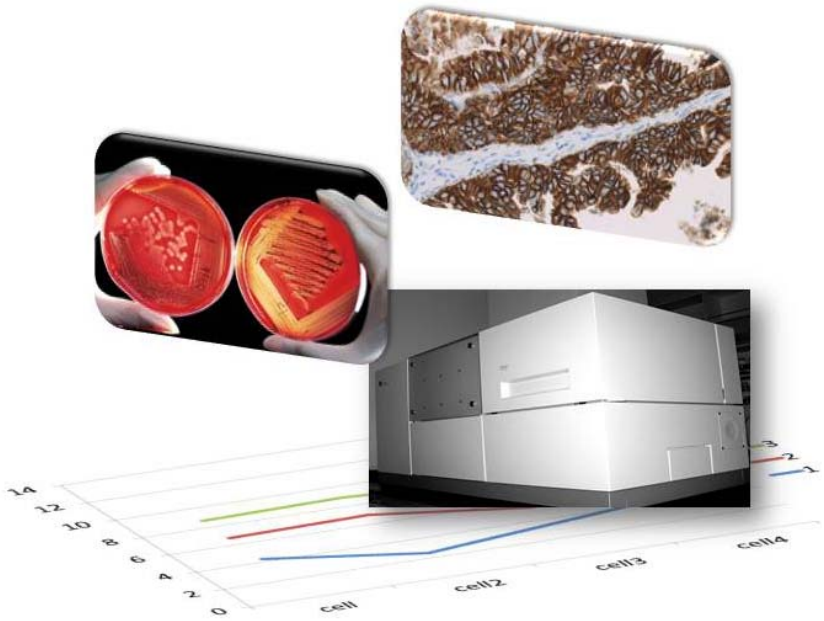


Figure 1. High Content Screening System

High Content Screening (HCS) or programmed microscope-based testing inspects biological processes in single cells or the whole organisms after treatment by thousands of agents, such as compounds or siRNAs, in multi-well plates. multiple features of the cell or organism are usually measured with one or more fluorescent dyes leading to the phrase High Content. Sometimes HCS has been recognized high content analysis (HCA) high content imaging (HCI) or image cytometry (IC). Generally, HCA, HCI and IC hint to small throughput automated microscope based tests, although HCA sometimes hint to the analysis portion of HCS. The term HCS was first used in a 1997 paper by Giuliano et al. It appears to be the next tool to the automation of clinical histology and a continuation of HTS plate reader systems, with early references to the automation of the analysis of microscope images dating back to the advent of the desk top computing.

The recent automated analysis methods found their origins to Metamorph and ImagePro in addition to a 1969 publication by Rosenfeld.

Contrary to traditional HTS, which has a single read out of activity, HCS allows a scientist to measure many

characteristics or features of individual cells or organisms at once. The ability to study many characteristics and multiplex simultaneously is both what gives HCS tremendous power and challenging complication. Like its privious technologies such as standalone low throughput automated image analysis systems and screening instruments including the FMAT, HCS can be very efficiently used to offer improved signal to background or signal to noise. But it can also enable both targeted and phenotypic tests that evaluate movement within a cell or between cells or permit analysis of specific sub-populations of cells in a contradictory mix that would be difficult or inconceivable to perform with other techniques. Most prominently, HCS can be used to assist expect the performance of probable drugs in unique cellular niches when used to physiologically relevant cellular systems.

The predictive feature of these systems can often be increased by working with basic cells or differentiated stem cells and in 3-D culture rather than with cell lines in a traditional 2-D culture where many unique aspects of cellular physiology have been missed. Bickmore concentrated on this crucial issue when she noted “the exquisite cell-type specificity of regulatory constituents divulged by the ENCODE studies emphasizes the importance of having appropriate biological material on which to examine hypotheses” in the 2012 publication of the data from the ENCODE project.

Figure 2. HCS and helping Drug Discovery

History

High-content screening technology paves the way for the evaluation of several biochemical and morphological scales in intact biological systems.

The efficiency of mechanized cell biology for cell-based procedures requires an evaluation of how automation and objective measurement can expand the experimentation and the understanding of disease. First, it removes the trace of the investigator in most, but not all, levels of cell biology research and secondly, it makes new approaches totally feasible.

Normal 20th century cell biology utilized cell lines are grown in culture in evaluation where the experiments were conducted using very comparable to that explained here, but there the investigator made the decision on what was measured and how. near the beginning 1990s, the development of CCD cameras (charge coupled device cameras) for research created the chance to measure characteristics in pictures of cells- such as how much protein exist in the nucleus, how much is outside. High level measurements soon led in using new fluorescent molecules, which are used to assess cell traits such as second messenger concentrations or the pH of internal cell sections. The widespread application of the green fluorescent protein, a normal fluorescent protein molecule from jellyfish, then accelerated the process toward cell imaging as a principal technology in cell biology. Regardless of these advances, the choice of which cell to image and which data to present and how to analyze it was yet chosen by the investigator.

By similarity, if one envisions a football field and dinner plates laid across it, instead of looking at all of them, the investigator would choose a group close to the score line and had to neglect the rest. In this analogy the field is a considered a tissue culture dish, the plates the cells breeding on it. While this was a logical and pragmatic approach automation of the entire procedure and the analysis makes probable the analysis of the whole population of living cells, so that the whole football field can be analyzed.

Figure 3. One of the applications of HCS is the discovery of new drug candidates

Applications

This technology permits many tests to be operational, allowing explorative screening. Cell-based systems are chiefly employed in chemical genetics where large, diverese small molecule collections are systematically tested because of their effect on cellular model systems. Novel drugs can be observed by screens of tens of thousands of molecules, and these have good perspective for the future of drug development. Further than drug discovery, chemical genetics is aimed at employing the genome by discovering small molecules that take actions on most of the 21,000 gene products in a cell. High-content know-how will be part of this attempt which could prepare useful tools for learning where and when proteins act with taping them out chemically. This would be most beneficial for gene where killing mice (missing one or several genes) cannot be prepared because the protein is needed for development, growth or otherwise death when it does not exist there. Chemical knock out could address how and where these genes work.

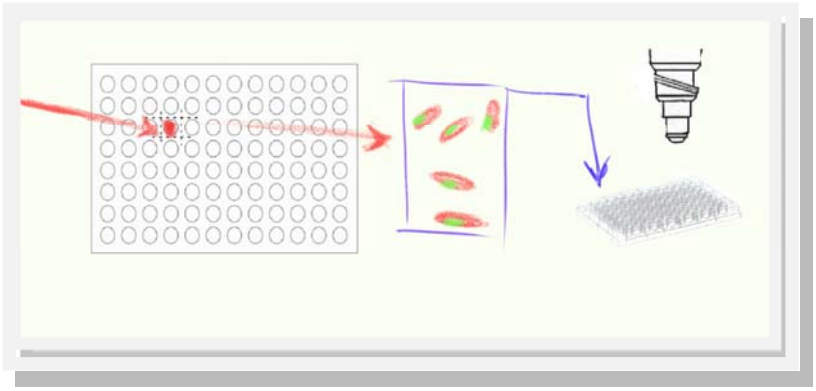


Figure 4. HCS to identify sets of genes involved in specific mechanisms

Moreover, the technology is used along with RNAi to recognize sets of genes involved in specific mechanisms, for instance cell division. Here, libraries of RNAi, covering a whole collection of predicted genes in the target organism's genome can be applied to detect pertinent subsets, facilitating the annotation of genes for which no obvious role has been established earlier. The large datasets created by automated cell biology contain spatially resolved, quantitative data which can be used for constructing for systems level models and simulations of how cells and organisms function. Systems biology models of cell task would provide prediction of why, where and how the cell reacts to external changes, growth and disease.

Summary

HCS has the potential to detect new drug targets or new fundamental compounds, help predict cellular *in vivo* toxicity, suggest molecular targets of orphan compounds, and assess *in vivo* interaction among other yet to be explored uses. HCS can be used to evaluate the effects of compounds and biological molecules such as plasmids carrying cDNAs, or RNA is on subpopulations of cells and some cell types in mixed cultures. It can be used to evaluate movement, be it intracellular, cellular or intercellular. Any phenomenon that can be observed reproducibly in a microscope can finally be assayed with HCS.

References:

1. Giuliano K.A., Haskins J.R. (2010). High Content Screening: A Powerful Approach to Systems Cell Biology and Drug Discovery. *Totowa, NJ: Humana Press*. ISBN 1-61737-746-5.
2. Haney S.A. (2008). High content screening: science, techniques and applications. *New York: Wiley-Interscience*. ISBN 0-470-03999-X.
3. https://en.wikipedia.org/wiki/File:Agarplate_redbloodcells_edit.jpg
4. https://en.wikipedia.org/wiki/File:Automated_confocal_image_reader.jpg
5. https://en.wikipedia.org/wiki/File:Immunohistochemistry_HER2_on_human_xenograft.jpg
6. https://en.wikipedia.org/wiki/File:14LaAc_periodic_table_IIb.jpg
7. https://en.wikipedia.org/wiki/File:Nexium_(esomeprazole_magnesium)_pills.JPG
8. https://en.wikipedia.org/wiki/File:MTT_Plate.jpg
9. https://en.wikipedia.org/wiki/File:Pills_on_uv_box.jpg

HCS MICROSCOPY TRENDS

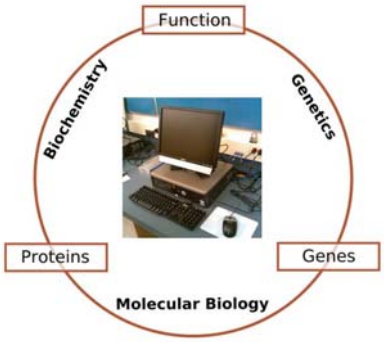


Figure 1. HCS Targets

The main objective of HCS experiments is to employ images of cells to produce multidimensional profiles that identify aberrant phenotypes, such as those caused by the adding a compound or genetic mutation, to make operational predictions. Below, we concentrate on protein imaging and explain five distinct classes of experiment that have been successfully used HCS to respond important biological problems. There is a few instances for each experiment and we try to explain some of the restrictions and advantages of each method.

Detection of Genes and/or Activities needed for a definite Biological procedure

Generally speaking, the identification of genes and/or activities needed for a specific biological procedure involves worrying about many (or all) genes in a standard genetic background transmitting one or a few reporters of the biological process of interest. This kind of method encompasses most of screens in the literature, probably because it is relatively straightforward to set up, calling for only a perturbation collection and a robust phenotypic readout that is amenable to HTP and reproducibly descriptions on a biological compartment or function of interest. In some recent examples of this class of experiment, genes drawn in in cell division and the appropriate morphology of the mitotic spindle were identified in screens of both the fission and budding yeast removal collections using a GFP-tubulin reporter gene. The attainment of multiple time periods allows for a more detailed analysis of the biological consequences of the perturbation, a method that is predominantly beneficial when studying dynamic processes. For example, in another study, automated HTP time-lapse microscopy was used to observe the effect of an RNAi library in a HeLa cell line expressing a GFP-tagged histone: 109 000 time-lapse movies were gathered and the nucleus tracked, leading to the discovery of several novel genes involved in mitosis. In addition, to obtain a more in-depth analysis of an entire process, screens

for perturbations using multiple reporters, as contrasting to single reporter screens, have been productive. For example, 13 RNAi screens of multiple different endocytic interactions and their downstream organelles in HeLa cells recognized genes that set up specific subsets of endocytic uptake routes and organelle profusions. Other examples of this class are screening for genes required for HeLa cells secretion and a screen for regulators of a signal transduction pathway using an immunofluorescence-based information of the human TORC1 effector RPS6 expressed activation in microarrays of *Drosophila* cells that treated with RNAi.

Identification of Genes Required for Differentiation and Proliferation

Tests to discover genes necessary for differentiation and proliferation also use perturbation libraries and a few reporters, but they must be conducted in specific cell types under conditions that induce differentiation, which often makes them strictly tricky. Interesting examples of this type of screen include: a screen for stimulators of cardiomyocyte proliferation engrossing a library of miRNA mimics and markers of cell division; a screen for regulators of human embryonic stem cell identity entailing an RNAi library and a GFP reporter for quantitative analysis of the expression of the key pluripotency gene POU5F1; and a screen for small molecules that regulate cell differentiation in zebrafish embryonic cells expressing lineage-specific GFP reporters. In addition to the technical challenges, screens in specialized systems are subject to the caution that their findings may be unrelated to *in vivo.*

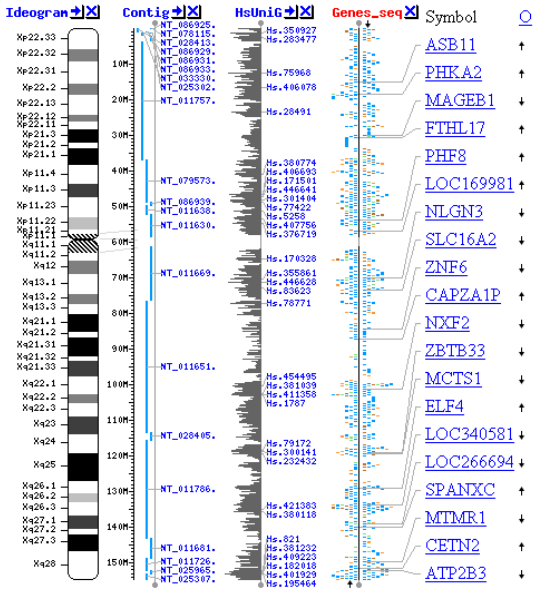


Figure 2. Identification of Genes Required

Models of Disease

HCS screens are aimed to search disease mechanisms typically require the use of cells expressing mutant alleles that is caused disease in relevant cell types coupled with reporters or assays specially designed to ask questions about aspects of disease biology. For instance, factors that may affect the pathology of Huntington disease were identified by screening *Drosophila* primary neurons expressing an RFP-tagged type of the pathogenic Huntingtin protein for small molecule and genetic perturbations that is revert aberrant neuronal morphology. Applying an analogous strategy, potential modifiers of the cystic fibrosis phenotype were found by combining RNAi and HCS to measure the activity of the epithelial sodium channel ENaC in human alveolar epithelial cells. As with other cell type-specific models, it is important to confirm any discoveries *in vivo*; researchers in the cystic fibrosis study were achieved to validate one of their results as a probable drug target using cells from the lungs of patients with cystic fibrosis.

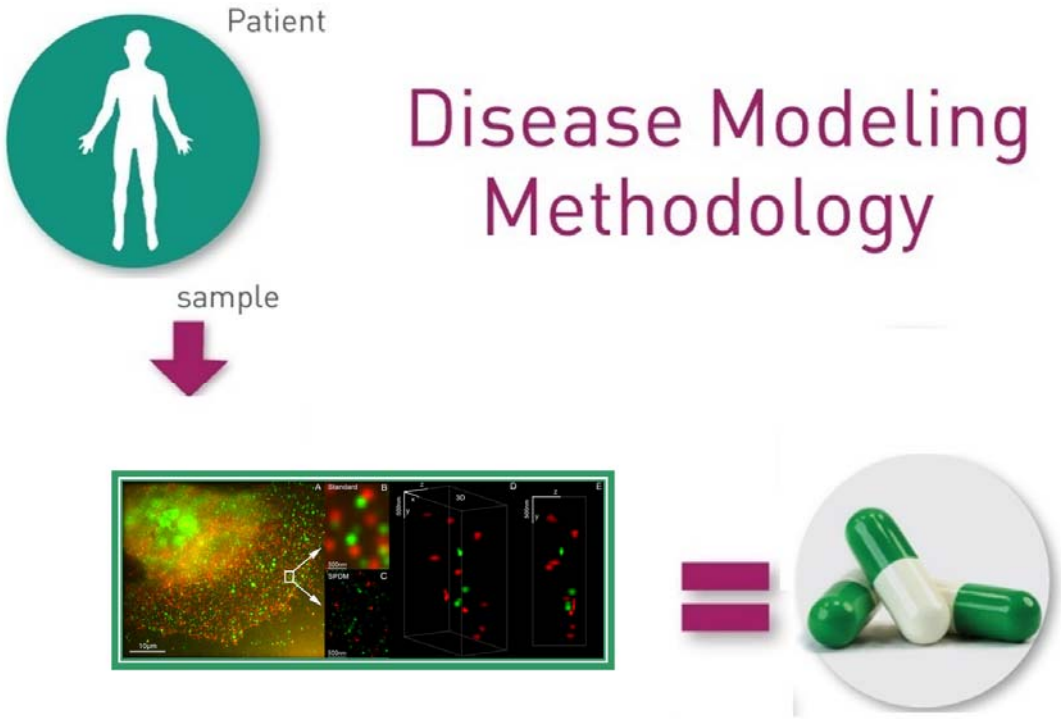


Figure 3. HSC and Disease Modeling

Identification of Proteome-Wide Changes in Response to Chemical or Genetic Perturbation

The recognition of protein-wide changes need a strains collection where each protein is separately tagged. Currently, an open reading frame (ORF)-GFP collection has been constructed only for *Saccharomyces cerevisiae*. The properties of that ORF-GFP collection is each strain to have a unique fusion gene that generates an ORF-GFP fusion protein directed by the endogenous promoter. Automated yeast genetics, which are combined with HCS of the ORF-GFP collection, was measured in the richness and localization of the yeast proteome regarding both genetic and chemical perturbation, with a time series recorded measurements. The challenge with this type of screen lies in finding multiple different proteins that localize to a given section, but that may not look same; therefore, some type of machine learning is essential. On the other hand, this type of approach is suggested the advantage of being able to request the whole proteome in an impartial method.

Chemical and Genetic Profiling

The other application of general phenotypic profiling can be analysis generation of the cellular response profiles to various insults by providing a pattern for explanation of the effects of unidentified compounds or genetic injuries. For example, amounts of cell and nuclear shape and texture were used to produce profiles characteristic of the response of about 30 well-characterized drugs in HeLa and rat kidney cells over time and by dose. The comparison of profiles directed to the recognition of several natural products as tubulin inhibitors. With this type of experiment, the probability of similarity to an unidentified compound is limited by the number of profiles in a set. In a second example, in budding yeast, staining of the cell wall, actin, and DNA and studying 501 cell morphology parameters, directed to drugs discovering that restrict cell wall synthesis which is concluded by comparison with profiles of mutant strains recognized to be involved in this process.

Furthermore, experiments that request a specific process, cell state, or chemical, imaging screens have also been utilized to query more fundamental biological questions. For example, HCS has been one of the methods to recognize genetic interactions that affect morphology rather than viability.

1. ATG CAA TGG GGA AAT GTT ACC AGG TCC GAA CTT ATT GAG GTA AGA CAG ATT TAA
2. A TGC AAT GGG GAA ATG TTA CCA GGT CCG AAC TTA TTG AGG TAA GAC AGA TTT AA
3. AT GCA ATG GGG AAA TGT TAC CAG GTC CGA ACT TAT TGA GGT AAG ACA GAT TTA A

Figure 4. Sample of ORF

Concluding Remarks

In recent years the HCS literature search is increased which is showed developing and execution of these types of enormously multiplexed assays is becoming more available to academic laboratories. However, while there have been many recent improvements in the progress of useful reagent sets, HTP imaging techniques, and multi-parametric data mining of high content microscopy data, many sides of HCS are still in their beginning and several questions remain.

A main change in assay design that is needed to understand the full complexity and dynamics of cellular processes is guided more use of HTP live cell and time lapse microscopy. Although live cell imaging is usually performed in HCS screens with uni-cellular organisms or small multicellular organisms, fixed cells are still the standard when working with mammalian cell cultures. With a few omissions, generating and analyzing single frame and single time point images is the modus operandi of most reported studies. Detailed kinetic information can be achieved by high-dimensional images collections, including multiple time points or using 3D resolved time-lapse microscopy (4D imaging).

Microscopy has always been the option for cell biologists. With recent developments in automated microscopy stages and computational image-analysis methods, the data resulting from microscopy images on a large scale can now be accurately considered to find even subtle phenotypic changes after genetic, chemical, or other disorders. The challenges associated with HTP microscopy, we can imagine this technique to be helpful in answering diverse biological questions.

References:

1. Mattiazzi U.M., Styles E.B, Verster A.V., Friesen H., Boone C. and Andrews B.J. (2016). High-Content Screening for Quantitative Cell Biology. *Trends in Cell Biology*, DOI: 10.1016/j.tcb.2016.03.008
2. https://en.wikipedia.org/wiki/File:Desktop_personal_computer.jpg
3. https://en.wikipedia.org/wiki/File:Genome_viewer_screenshot_small.png
4. https://en.wikipedia.org/wiki/File:3D_Dual_Color_Super_Resolution_Microscopy_Cremer_2010.png
5. https://en.wikipedia.org/wiki/File:Sampleorf.png

NEW OPEN SOURCE SOFTWARE FOR HIGH RESOLUTION MICROSCOPY

With their particular microscopes, investigational physicists can previously see single molecules. Nevertheless, unlike traditional light microscopes, the raw image records from some ultra-high resolution tools have firstly to be processed for an image to come into view. For the ultra-high resolution fluorescence microscopy that is also used in biophysical study at Bielefeld University, members of the Biomolecular Photonics Group have made a new open source software solution that can process such raw data rapidly and resourcefully. The Bielefeld physicist Dr. Marcel Müller explained about this new open source software in the newest issue of *Nature Communications* published on 21 March.

Traditional light microscopy can reach only a definite lower resolution limit that is limited by light diffraction to approximately 1/4 of a micrometre. High resolution fluorescence microscopy provides condition to obtain images with a resolution noticeably below these physical boundaries. The physicists Stefan Hell, Eric Betzig, and William Moerner were honored the Nobel Prize in 2014 for evolving this significant key technology for biomedical studies. At present, one of the manners in which scientists in this domain are struggling to get a better resolution is by using prearranged illumination. At present, this is one of the most general processes for representing and presenting dynamic processes in living cells. This approach realizes a resolution of 100 nanometres with a high frame rate while concurrently not harming the specimens during assessment. Such high resolution fluorescence microscopy is also being used and further progressed in the Biomolecular Photonics Group at Bielefeld's Faculty of Physics. For instance, it is being exercised to survey the application of the liver or the means in which the HI virus spreads.

Nevertheless, researchers cannot use the raw images achieved with this procedure straight away. 'The data acquired by the microscopy method need a very difficult mathematical image reconstruction. Only then do the raw data recorded with the microscope lead to a high-resolution image,' adds Professor Dr. Thomas Huser, head of the Biomolecular Photonics Group. Because this phase needs a complex mathematical process that has been available for just a few scientists up to now, there was formerly no open source software solution that was simply accessible for all scientists. Huser considers this as a main barrier to the application and progress of the technology. The software designed in Bielefeld is now filling this gap.

Dr. Marcel Müller from the Biomolecular Photonics Group has attempted to generate such generally implementable software. Scientists all over the world are struggling on building new, quicker, and more responsive microscopes for structured illumination, principally for the two-dimensional illustration of living cells. For the essential post-processing, they no longer require developing their own complex solutions but can utilize our software unswervingly, and, due to its open source accessibility, they can regulate it to fit their issues,' Müller clarifies. The software is freely accessible to the worldwide academic community as an open source solution, and as soon as its accessibility was publicized, numerous scientists, mainly in Europe and Asia, demanded and installed it. 'We have previously obtained a lot of positive comment,' says Marcel Müller. 'That also echoes how indispensable this new development has been.'

Reference:

https://www.sciencedaily.com/releases/2016/03/160324133032.htm

NEW MICROSCOPY TECHNOLOGY AUGMENTS SURGEON'S VIEW FOR GREATER ACCURACY

Researchers at the University of Arizona (UA) have created a prototype of a new microscope skill that could assist surgeons work with a better level of precision. The new technology, named augmented microscopy, overlays images showing diagnostic data such as blood flow and cancerous tissue over real images of blood vessels and other tissues and structures being observed in the microscope.

A statement on the research by Jeffrey Watson and co-authors from the UA departments of Biomedical Engineering and Surgery was printed in the *Journal of Biomedical Optics*, published by SPIE, the international society for optics and photonics.

Surgical microscopes are very dedicated stereomicroscopes mounted on articulated mounts and offer a long working distance and functional improvements, and are extensively used in certain subtle operations, particularly neurosurgery.

In the last decade, surgical microscopes have been mixed with near-infrared (NIR) fluorescence imaging, wherein contrast agents are injected into tissue and their fluorescence identified in NIR scans. The scans may disclose models of blood flow, or distinguish cancerous from usual tissue.

But there are restrictions. For instance, some microscopes utilized in complex vascular surgeries change between two different views: the fully optical bright-field (real) view and the computer-processed projection of NIR fluorescence. The NIR image is two-dimensional, and on its own lacks the spatial cues that would help out the surgeon discover anatomical points of reference. Consequently, the surgeon has to imagine how the fluorescence in the NIR image arrays with the relevant anatomical structures illustrated in the bright-field view.

The UA researchers' article, "Augmented microscopy: Real-time overlay of bright-field and near-infrared fluorescence images" explains their prototype of an enhanced stereomicroscope that provides a concurrent view of actual objects in the surgical field and computer-processed images superimposed in real time.

"Surgeons would like to observe the molecular signals visually, with the intention that they can feel convinced about what is there," said journal associate editor Brian Pogue of Dartmouth College. "Too frequently, what

they observe is a report of the signals illustrated in false color on a monitor. By exhibiting information through the surgical scope itself, the surgeon subsequently perceives the information with his or her own eyes."

Pogue believed he perceives the work being significant in advancing the transformation of research into clinical application. "There are extremely few papers on this proposal of augmenting the surgical field of view that the surgeon sees, yet this is a interesting subject," he said. "This article offers a very practical notion and pioneering accomplishment which is well done technologically."

The prototype provide advantages over previous versions of augmented microscopes. By utilizing the optical path of the stereomicroscope, it maintains full three-dimensional stereoscopic view, which is lost in fully digital display systems.

It also makes the imaging setting recognizable to surgeons, including significant characteristics of surgical microscopes such as real-time enlargement and focus adjustments, camera mounting, and multiuser access.

One potential function for this microscope is laser surgery. In the past, surgeons were not able to observe the laser beam through the standard stereomicroscope, nor anatomical aspects in the NIR images.

The researchers also recommend that this technology can be helpful in the surgical treatment of brain tumors. Surgeons belligerently removing a tumor run the danger of harming normal brain tissue and damaging the patient's brain functions; alternatively, imperfect removal of a tumor brings forth instant relapse in 90% of patients. Being able to concurrently witness the surgical field and the contrast agent exploring cancerous tissue within the augmented microscope may permit surgeons to eradicate these challenging tumors more precisely.

Reference:

https://www.sciencedaily.com/releases/2015/10/151007111007.htm

EMGEN REPORT

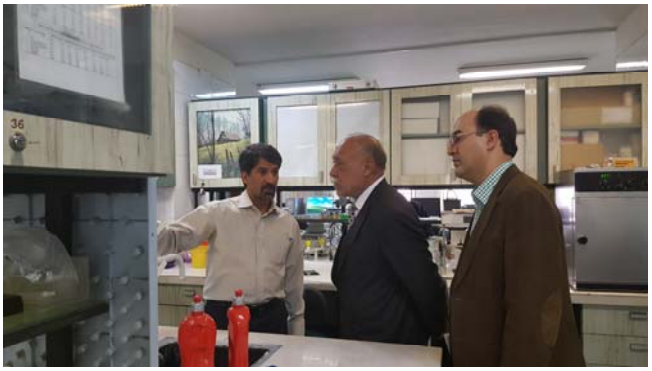
Founder of Cheragh Medical Institute and Hospital oF Afganistan Dr. CheraghAlli Cheragh and Mr. Shahir Sadr and Dr Hasan Mirzahoseini, head of Medical Biotechnology Department of Pasteur Institute of Iran, in a meeting with Dr. Soroush Sardari Director of EMGEN, underlined the importance of research centers and expansion of relations between institutes.

“Investigation is an unavoidable part of each institute and based on the enrichment of pharmatheutical plant source of Afghanistan we could found a research center in Afghanistan and by years of experience of Iran we could encourage students, therefore we could save human resource” Dr. Cheragh said during the meeting that was held in Tehran Pasteur Institute.

Dr. Sardari, for his part, pointed to the need of proficient education to result a good research and said “EMGEN do their best to consolidate educational and experimental parts between institutes”.

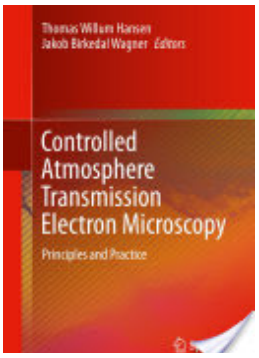
During the meeting on 4 May, 2016, they underscored the necessity for expansion of student exchange and trade relations between countries.

After that they visit different parts of bioinformatics and drug design group of Pasteur Institute.



Book Alert

CONTROLLED ATMOSPHERE TRANSMISSION ELECTRON MICROSCOPY: PRINCIPLES AND PRACTICE

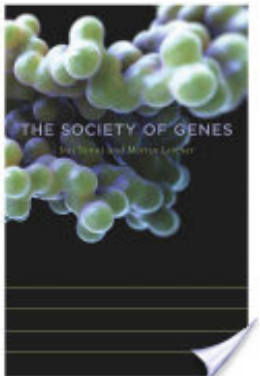


Editors: Thomas Willum Hansen, Jakob Birkedal Wagner

Publisher: Springer, 2015

ISBN: 3319229885, 9783319229881

THE SOCIETY OF GENES

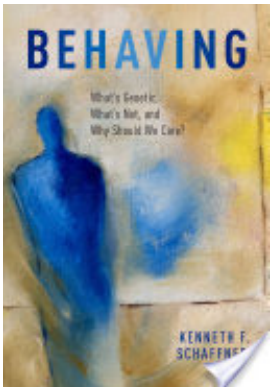


Authors: Itai Yanai, Lercher Martin

Publisher: Harvard University Press, 2016

ISBN: 0674425022, 9780674425026

BEHAVING: WHAT'S GENETIC, WHAT'S NOT, AND WHY SHOULD WE CARE?

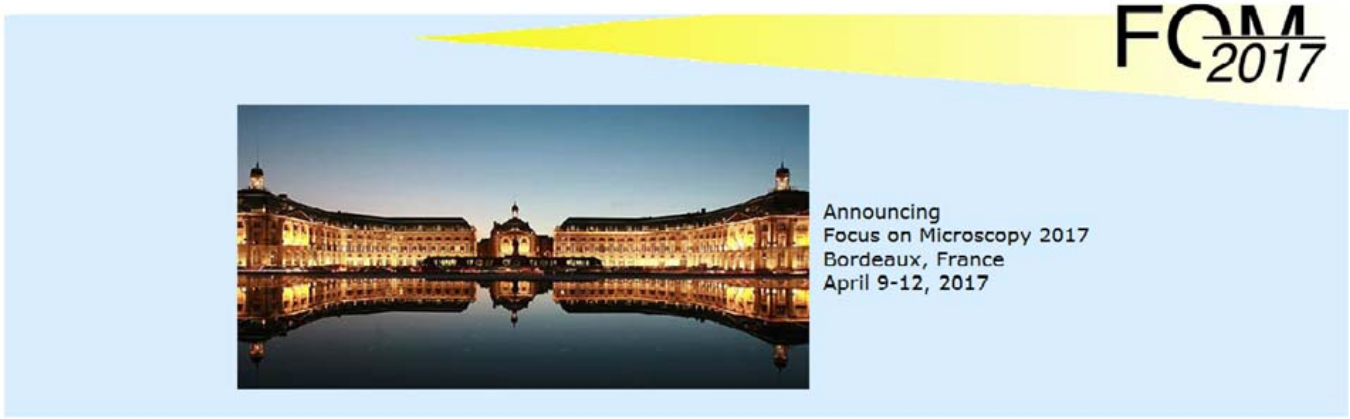


Author: Kenneth F. Schaffner

Publisher: Oxford University Press, 2016

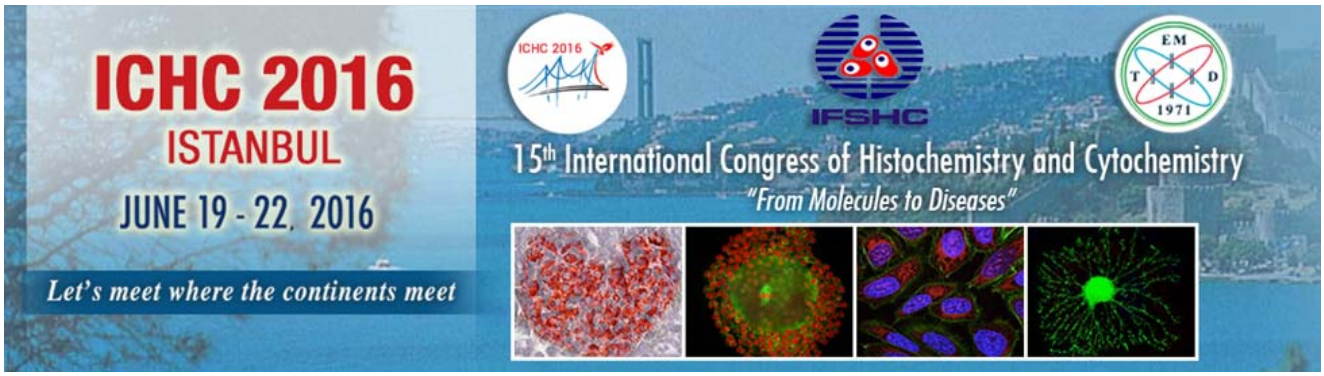
ISBN: 0195171403, 9780195171402

Announcements



http://www.focusonmicroscopy.org/

http://www.xrm2016.com/



http://www.ichc2016.com/

Announcements

http://www.singlecellasia-congress.com/download-agenda-marketing/

http://www.icg-11.org/

http://emc2016.fr/en/

ANTHER OF THALE CRESS (ARABIDOPSIS THALIANA)

Confocal laser scanning fluorescence micrograph of thale cress anther (part of stamen). The picture shows among other things a nice red flowing collar-like structure (just below the anther) that makes it somehow similar to jellyfish. However, an intact thale cress stamen does not have such collar, this is a fixation artifact: the stamen has been cut below the picture frame, and epidermis (upper layer of cells) of stamen stalk has peeled off, forming a non-characteristic structure.

Reference:

https://en.wikipedia.org/wiki/File:Anther_of_thale_cress_%28Arabidopsis_thaliana%29,_an_artefact.jpg

AN AUTOMATED CONFOCAL MICROSCOPE

Confocal microscopy, most frequently confocal laser scanning microscopy (CLSM), is an optical imaging technique for increasing optical resolution and contrast of a micrograph by means of adding a spatial pinhole placed at the confocal plane of the lens to eliminate out-of-focus light. It allows the reconstruction of three-dimensional structures from the obtained images by collecting sets of images at different depths within a thick object. This technique has gained popularity in the scientific and industrial communities and typical applications are in life sciences, semiconductor inspection and materials science.

Reference:

https://en.wikipedia.org/wiki/File:Automated_confocal_image_reader.jpg

HIGH CONTENT SCREENING PROCESS

In the previous decade, high-content screening has become a very developed method to gain richly expressive quantitative phenotypic data by automated microscopy. Since early use in drug screening, the technique has developed to embrace a varied series of applications in both educational and industrial areas and is now broadly known as providing a useful and valuable method to large-scale programs examining cell biology in situ and in context.

References:

1. https://en.wikipedia.org/wiki/File:FluorescentCells.jpg
2. https://en.wikipedia.org/wiki/File:Loupe-binoculaire-p1030891.jpg
3. https://en.wikipedia.org/wiki/File:BioMek_FX_P200_96_liquid_handling_robot.jpg