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Bioinformatics up to Date

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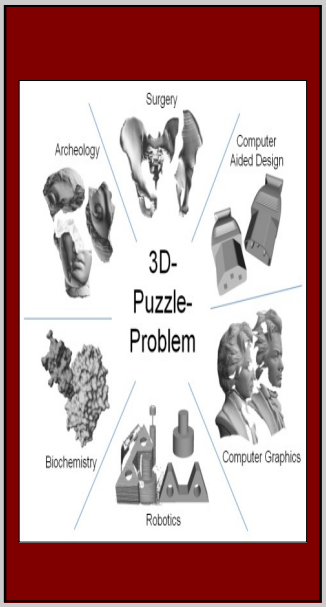
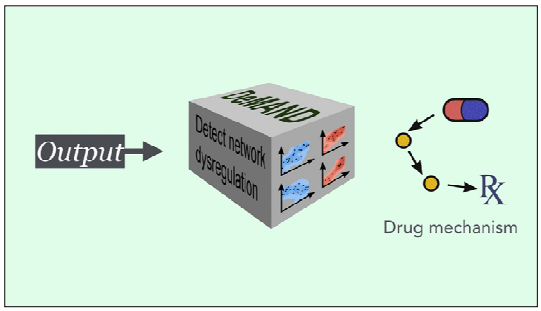


Algorithm that Helps Scientists Decipher How Drugs Work Inside the Body

Researchers at Columbia University Medical Center (CUMC) have developed a computer algorithm that is helping scientists see how drugs produce pharmacological effects inside the body.

The study, published in the journal Cell, could help researchers create drugs that are more efficient and less prone to side effects, suggest ways to regulate a drug's activity, and identify novel therapeutic uses for new and existing compounds.



"For the first time we can perform a genome-wide search to identify the entire set of proteins that play a role in a drug's activity," says study co-author Dr. Andrea Califano, the Clyde and Helen Wu Professor of Chemical Systems Biology and chair of the department of Systems Biology at CUMC.

Members of Dr. Califano's lab have devised a new approach called DeMAND (Detecting Mechanism of Action by Network Dysregulation) to characterize a drug's effects more precisely. The method involves creating a computational model of the network of protein interactions that occur in a diseased cell. Experiments are then performed to track gene expression changes in diseased cells as they are exposed to a drug of interest. The DeMAND algorithm combines data from the model with data from the experiments to identify the complement of proteins most affected by the drug.

DeMAND improves on more labor intensive and less efficient methods, which are only capable of identifying targets to which a compound binds most strongly. This provides a more comprehensive picture, because DeMAND identifies many molecules that are affected in addition to the drug's direct target.

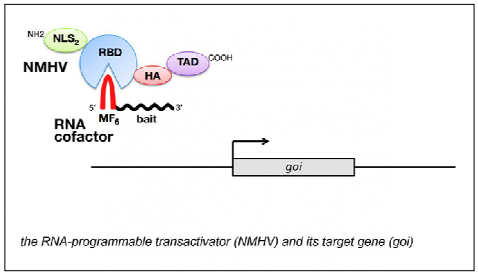
The algorithm makes it possible to identify a variety of compounds that cause similar pharmacological outcomes. Using DeMAND, the researchers showed that a similar subset of proteins is affected by the unrelated drugs sulfasalazine and altretamine. Altretamine is currently used to treat ovarian cancer, but these results suggest that, like sulfasalazine, it could be used for bowel inflammation or rheumatoid arthritis too.

Co-senior author Mukesh Bansal sees great potential in this approach, saying, "DeMAND could accelerate the drug discovery process and reduce the cost of drug development by unraveling how new compounds work in the body. Our findings on altretamine also show that it can determine novel therapeutic applications for existing FDA-approved drugs."

[*Elucidating Compound Mechanism of Action by Network Perturbation Analysis. Woo, Jung Hoon et al. Cell (2015)*]

Scientists Created Enzyme that Activates Genes Selectively

Scientists from the International School for Advanced Studies in Trieste created an enzyme able to distiguish between tissue types and only activate genes when it reached its destination. "We have created an enzyme that is able to 'see' the difference and act only where appropriate," says Prof. Antonello Mallamaci of the International School for Advanced Studies (SISSA) in Trieste, who led the recently-published study which can be found in the journal Nucleic Acids Research.



the RNA-programmable transactivator (NMHV) and its target gene (goi)

Mallamaci and Cristina Fimiani, a student at SISSA and first author of the article, created synthetic hybrid enzymes. "Hybrid" because , unlike classical transcription factors, which are made up almost entirely of proteins, these have a protein component , but they recognize the target gene via a dedicated RNA decoy, " explains Fimiani .

"An artificial RNA-programmable transcription factorwas previously developed in other laboratories by domesticating the bacterial immune system Ours are the first to be fully synthetic, even if their most important feature has nothing to do with this fact," notes Mallamaci. In fact, our enzymes do not stimulate gene transcription dramatically, but in a way comparable to endogenous regulators.

"It may seem like a disadvantage at first, but it is their strength," says Fimiani. "Their work takes place within the natural physiological interval: they amplify the process in a limited way, and only if the gene is turned on. "In this way additional production of the protein can only occur in tissue where genes are active, even when the enzyme is administered to the entire organism .

"For this reason, our enzymes are excellent candidates for treating gene haploinsufficiencies," says Mallamaci . In the vast majority of cases , a healthy organism possesses two copies of each gene. Individuals with haploinsufficiency , however, are born with only one copy and this results in a production deficit of a given protein. This condition is the basis of some syndromes and neurological diseases."

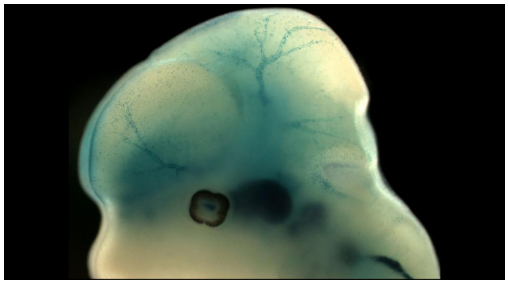
If we can stimulate the remaining gene to work harder, we can reduce the symptoms of the disease in some cases," says Fimiani .

"Hopefully our study will encourage others to repeat our research and confirm the results," says Mallamaci." Meanwhile, we are already working on improving our molecules and developing procedures for testing them in live animals ."

[***Upregulating endogenous genes by an RNA-programmable artificial transactivator.*** *Fimiani, C et al. Nucleic Acid Research July 7, 2015]*

Research Reveals Key Protein May Affect Risk of Stroke

Studies on mice reveal that a special protein in the brain's tiniest blood vessels may affect the risk of stroke. Peter Carlsson, professor in genetics at the University of Gothenburg, and his research team are publishing new research findings in the journal Developmental Cell about how the blood-brain barrier develops and what makes the capillaries in the brain different from small blood vessels in other organs.



The brain's smallest blood vessels differ from those in other organs in that the capillary walls are much more compact. The nerve cells in the brain get the nutrients they need by molecules actively being transported from the blood, instead of passively leaking out from the blood vessels.

This blood-brain barrier is vital, because it enables strict control over the substances with which the brain's nerve cells come into contact. It has a protective function that if it fails, increases the risk of stroke and other complications.

Special cell type essential to development The smallest blood vessels, the capillaries, have a type of cell called pericytes. These are essential to the development of the blood-brain barrier. Pericytes are also found in other organs, and researchers have previously been unable to find out what gives the brain's pericytes this unique ability.

The Gothenburg research team has found that the brain's pericytes contain a protein, FoxF2, which is not present in the pericytes of other organs, and which coordinates the changes that make the blood vessels compact. FoxF2 is needed in order for the blood-brain barrier to form during foetal development.

"Mice that have too little or too much FoxF2 develop various types of defects in the brain's blood vessels," explains Peter Carlsson, professor at the University of Gothenburg's Department of Chemistry and Molecular Biology.

One gene may play a critical role In humans, researchers have noted that major changes in a region of chromosome 6 have been associated with an increased risk of stroke, but it has not been known which of the genes in the area are responsible for this risk.

"The FoxF2 gene is an extremely interesting candidate, as it is located right in the middle of this region, and research is under way now in collaboration with clinical geneticists to investigate the extent to which variations in the FoxF2 gene affect people's risk of suffering a stroke," says Peter Carlsson.

*[**Foxf2 Is Required for Brain Pericyte Differentiation and Development and Maintenance of the Blood-Brain Barrier.** Azadeh Reyahi et al. Developmental Cell (2015)]*

Computer Scientists Develop Web App to Help Researchers Explore Cancer Genetics

Brown University computer scientists have developed a new interactive tool to help researchers and clinicians explore the genetic underpinnings of cancer. The tool dubbed MAGI, for Mutation Annotation and Genome Interpretation -- is an open

-source web application that enables users to search, visualize, and annotate large public cancer genetics datasets, including data from The Cancer Genome Atlas (TCGA) project.

"The main motivation for MAGI has been to reduce the computational burden required for researchers or doctors to explore and annotate cancer genomics data," said Max Leiserson, a Ph.D. student at Brown who led the development of the tool. "MAGI lets users explore these data in a regular web browser and with no computational expertise required."

In addition to viewing TCGA data, the portal also allows users to upload their own data and compare their findings to those in the larger databases. The MAGI project started as a means of looking at the output from algorithms that Raphael's lab develops. Those algorithms comb through large genome datasets, helping to pick out the mutations that are important to cancer development and distinguishing them from benign mutations that are just along for the ride.

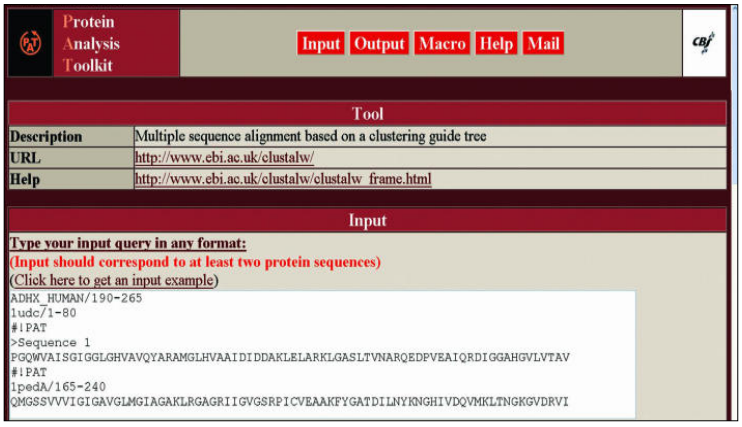
The lab is making MAGI available for free, with the hope that many in the cancer genomics community will take advantage of it.

"We think this could be a really useful piece of software," Raphael said. "There's great value in just being able to look at these data. We hope MAGI will lead to some new discoveries."

*[**MAGI: visualization and collaborative annotation of genomic aberrations.** Mark D M Leiserson et al. Nature Methods (2015)]*

PAT: a protein analysis toolkit for integrated biocomputing

PAT, for Protein Analysis Toolkit, is an integrated biocomputing server. The main goal of its design was to facilitate the combination of different processing tools for complex protein analyses and to simplify the automation of repetitive tasks. The PAT



server provides a standardized web interface to a wide range of protein analysis tools. It is designed as a streamlined analysis environment that implements many features which strongly simplify studies dealing with protein sequences and structures and improve productivity. PAT is able to read and write data in many bioinformatics formats and to create any desired pipeline by seamlessly sending the output of a tool to the input of another tool. PAT can retrieve protein entries from identifier-based queries by using pre-computed database indexes. Users can easily formulate complex queries combining different analysis tools with few mouse clicks, or via a dedicated macro language, and a web session manager provides direct access to any temporary file generated during the user session. PAT is freely accessible on the Internet at http://pat.cbs.cnrs.fr.

[Nucleic Acids Res. 2005 Jul 1; 33(Web Server issue): W65–W71.]

Bioinfo. Animation

Patent News

Bioinformatics system

US 8296116 B2

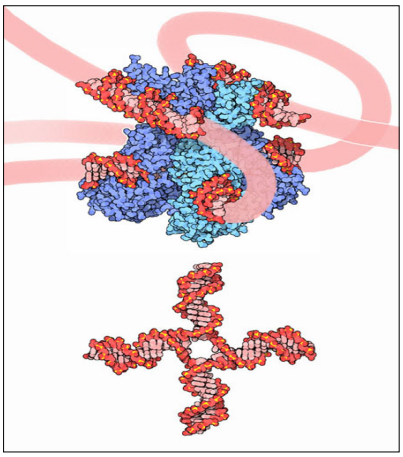
Inventors : Neal Solomon

ABSTRACT

The invention develops models of functional proteomics. Simulation scenarios of protein pathway vectors and protein-protein interactions are modeled from limited information in protein databases. The system focuses on three integrated subsystems, including (1) a system to model protein-protein interactions using an evolvable Global Proteomic Model (GPM) of functional proteomics to ascertain healthy pathway operations, (2) a system to identify haplotypes customized for specific pathology using dysfunctional protein pathway simulations of the function of combinations of single nucleotide polymorphisms (SNPs) so as to ascertain pathology mutation sources and (3) a pharmacoproteomic modeling system to develop, test and refine proposed drug solutions based on the molecular structure and topology of mutant protein(s) in order to manage individual pathologies. The system focuses on simulating the degenerative genetic disease categories of cancer, neurodegenerative diseases, immunodegenerative diseases and aging. The system reveals approaches to reverse engineer and test personalized medicines based upon dysfunctional proteomic pathology simulations.

Transposes

In the 1940's, Barbara McClintock discovered that the genome is a dynamic, changing place. She was studying maize, and she found that the beautiful mosaic colors of the kernels did not follow typical laws of inheritance. When she looked inside



the cells, she found that the chromosomes changed shape, swapping pieces from one chromosome to the next. From this work, she found that the color changes were caused by the removal of a particular piece of DNA from the general area of the gene that caused the color, allowing the gene to be expressed and create pigments. She called this process transposition, where a piece of DNA is cut out of one place and pasted into another location

In the simplest cases, transposition needs only two things: a transposon (the DNA that moves), and a transposase (the enzyme that cuts out the DNA and moves it to a different place). Transposases use many different mechanisms for cutting and pasting DNA. This one, the lambda integrase from a bacteriophage (PDB entry `1z1g`), uses a more complex mechanism than the Tn5 transposase. This structure again catches the enzyme in the middle of its reaction, which involves an elaborate looping of DNA in and around the enzyme. In the process, an X-shaped Holliday junction is formed inside the enzyme, as shown in the lower illustration. .

Upcoming Events

"4 Days Workshop on Protein Modeling & Simulation"

20th to 23rd August 2015.

Shivaji Nagar, Pune

Kindly send us your feedback to

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