VBI

e_Connections

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Why we need to work FASTA

On September 7, Professor Bill Pearson from the Department of Biochemistry and Molecular Genetics at the University of Virginia Health System, gave a seminar entitled "From sequences to science: new perspectives on sequences and structures" at the Virginia Bioinformatics Institute Conference Center. Dr. Pearson outlined some of the reasons why he believes protein folding – the way in which a protein molecule adopts its functional shape – is perhaps a lot easier than conventional wisdom might have us believe. The presentation was part of the Genetics, Bioinformatics, and Computational Biology (GBCB) seminar program.

In This Issue

In the 1980s, Dr. Pearson was the driving force behind the development of the FASTA program for sequence comparison. FASTA allows researchers to compare a protein sequence to another protein sequence or to entries in a protein database. It also allows users to compare a DNA sequence with another DNA sequence or a DNA library. Widely used by the scientific community, FASTA has since been superseded by BLAST searches but remains a useful tool for sequence comparison.

Dr. Pearson uses similarity searching to determine when proteins have diverged from a common ancestor. Using state-of-the-art methods, it is already possible to identify novel proteins that are likely to have emerged in the last 500 - 800 million years. If proteins can be identified that emerged in the last 100 - 250 million years, it may be possible to pinpoint the mechanisms by which new proteins are formed. He hopes to push this threshold to well beyond 2 billion years.

Pearson remarked: "The 'big picture' idea that I want to discuss here is that protein folding is much easier than people think. When new genomes are sequenced, they typically encode for around 20% new proteins. Novel sequences will therefore have new structures. Nature frequently reinvents the wheel and convergent evolution has produced similar protein structures at different points in time. Successful protein structures have also been duplicated for use in different settings."

Dr. Bill Pearson

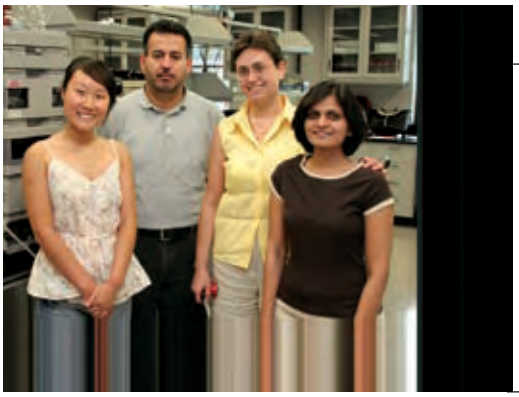
Dr. Pearson added: "Sequence similarity statistics are extremely accurate and have allowed us to gain important insight into the way that nature has generated new protein structures. We can look back at proteins 1.2 billion years ago and identify common ancestors due to the slow rate of change of protein sequences over time and the retention of significant sequence similarity. Glycine decarboxylase in *Escherichia coli* and glycine dehydrogenase in humans, for example, have retained around 50% similarity after 2.5 billion years of evolution."

When compared with sequence comparison methods, the information that can be gained from structural comparisons is not so easy to interpret. There are no optimal alignment algorithms for structural comparisons and tools like Dali, VAST, Compass, and Psi-blast, while useful in some circumstances, do not provide the accuracy and degree of confidence that can be achieved with sequence comparisons.

Dr. Pearson concluded: "The current protein universe samples a small fraction of protein structures. There's a whole collection of proteins out there that we haven't even looked at. We will need to work much faster just to even scratch the surface of the important evolutionary relationships inherent in those proteins sequences."

For more information about the GBCB program, please visit www.grads.vt.edu/academics/programs/gbcb

Lab-on-a-chip technology development at VBI

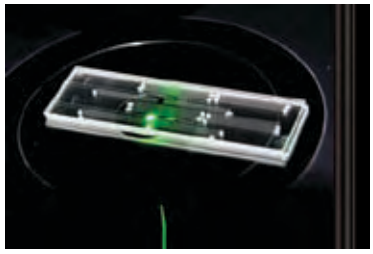


The Lazar research group
Left to right: Yang Xu, Abdulilah Dawoud, Iuliana Lazar, and Nileshwari Vaghela

A research group at VBI is working on the development of fully integrated, stand-alone microfluidic devices that integrate mass spectrometric detection for high-throughput proteomic investigations. Iuliana Lazar, assistant professor at VBI and of biology at Virginia Tech, and her group, which consists of microfluidics and mass spectrometry specialist Abdulilah Dawoud and graduate research assistants Nileshwari Vaghela and Yang Xu, are creating such a platform for high-throughput screening and discovery of biomarkers in cancer cells and tissues.

Disposable microchip

The group's efforts have resulted in the development of a disposable microchip that replaces space-consuming instrumentation with fast, cost-effective, lab-on-a-chip technology. This work should open the door for large-scale screening of disease-related protein biomarkers, which are useful as "molecular indicators" for a wide range of diseases. The lab-on-a-chip integrates a pump, valve, separation column, and detection interface onto a 3-by-1-inch glass microchip and delivers a performance to match benchtop instrumentation typically occupying a few square feet of lab space.



Disposable microchip replaces space-consuming instrumentation

VBI e_Connections

VBI e_Connections is a quarterly publication of the Virginia Bioinformatics Institute produced by the Public Relations & Education and Outreach team. The newsletter includes feature articles, technology updates as well as interviews that may be of interest to VBI's audiences. Contributions are welcomed.
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Under the research umbrella

"Lab-on-a-chip is still new technology and mostly under the research umbrella," research group member Dawoud explains. "It has the advantage of low-cost and high-speed analysis. We are trying to take it to another level by demonstrating that it can be used in real applications, such as disease-screening, where conventional systems have been used."

According to Lazar, sample injection, separation, labeling and detection of important biomolecules can be performed with this new technology in only a few minutes, but adds that short analysis times isn't the only advantage to using the microchip. Lazar explains that, "Increased specificity and sensitivity are paving the way for high-throughput testing that will, in time, permit screening at the population level for prognostic or diagnostic markers for a whole range of diseases."

Conventional benchtop instrumentation to identify disease-related proteins occupies a few square feet of lab space

Microfluidic device

The system designed by Lazar and her team combines liquid chromatographic separation of proteins driven by hundreds of parallel micro- and nanochannels. These channels, which have dimensions in the micrometer domain, serve to generate an electroosmotic flow. This flow of liquid helps to separate the proteins which are then identified by state-of-the-art mass spectrometric detection instruments. To date, researchers in Lazar's laboratory used the microchip to detect more than 2,000 cancer biomarkers in cellular extracts generated from the MCF7 breast cancer cell line. Seventy-seven proteins were identified with confidence, five of which are known to be cancer-specific biomarkers. The fully integrated microfluidic liquid chromatography system has been shown to be suitable for the detection of multiple disease-specific biomarkers.

Microchips consist of hundreds of parallel microchannels that help to generate a flow of liquids under the influence of a small current.

Lazar IM, Trisiripisal P, Sarvaiya HA (2006) Microfluidic liquid chromatography system for proteomic applications and biomarker screening, *Analytical Chemistry*, vol. 78, no. 15: 5513-5524.

VBI Teams With Brazilian Institute to Develop Infectious Disease Products

Paulo Buss, President of the Oswaldo Cruz Foundation, and Bruno Sobral, Executive and Scientific Director of VBI, sign agreement at FIOCRUZ, Rio de Janeiro, Brazil. (photo: Analucia Limp, FIOCRUZ)

NEW YORK, May 3 (GenomeWeb News) - The Virginia Bioinformatics Institute and a Brazilian health institute yesterday said they plan to develop a wide range of medical products and technologies.

The initial three-year alliance calls for the VBI and the Oswaldo Cruz Foundation to "facilitate the development of" drugs, vaccines, diagnostics, and "other technologies" for infectious diseases, including dengue fever, hepatitis C, HIV/AIDS, influenza, malaria, and pneumonia.

FIOCRUZ, based in Rio de Janeiro, has expertise in biology, medicine, and the epidemiology of infectious diseases, while VBI is known for its genomics, proteomics, and bioinformatics tools and data.

Source: GenomeWeb News

COPASI: Bleeding-Edge Simulation in a Friendly Package

On the public sector side, the first official release of COPASI is the culmination of six years of co-development by Pedro Mendes at VBI and Ursula Kummer at EML Research. COPASI is the successor to Mendes' Gepasi simulation program, but includes new capabilities such as stochastic simulation and support for Windows, Linux, Mac OS X, and Solaris. Like SimBiology, COPASI supports SBML and enables biologists to construct their own biochemical models.

"The main interest is really to target the wider biological community," Mendes told *BioInform*. "Having said that, we're trying to add a number of quite advanced packages. So there is a little bit of a challenge there, because in order to make a program powerful you normally have an interface that is not so easy to use, and we've been really trying to stay on the edge there of making it easy enough for the average biologist to use, but then also to have the most advanced and powerful numerical algorithms."

Source: Bioinform newsletter

Calendar of VBI Sponsored Events

- October 28-31: 9th Annual Computational Genomics Conference, Baltimore, Maryland
- October 26-29: SACNAS Annual Conference, Tampa, Florida

See calendar of events at: www.vbi.vt.edu

VBI scientific publications

Mitochondrial AZT metabolism

IUBMB Life. 2006 Jul: 58(7): 403-408.

Samuels DC

Zidovudine (azidothymidine or AZT) is used successfully as part of Highly Active Anti-Retroviral Therapy (HAART) to control the level of the human immunodeficiency virus in HIV-infected individuals. However, long-term use of AZT may lead to side-effects in some patients. David Samuels and coworkers are interested in finding out whether the toxic side effects of AZT can eventually be minimized or even eliminated. For this purpose, they have been developing a detailed computational model that allows scientists to simulate the biochemical reactions that take place when AZT is metabolized in cells, including their mitochondria, under different metabolic conditions. A review article describing some of this work was recently published in the journal *IUBMB Life*.

Microfluidic liquid chromatography system for proteomic applications and biomarker screening

Anal Chem. 2006 Aug: 78(15): 5513-5524.

Lazar IM, Trisiripisal P, Sarvaiya HA

Researchers at the Virginia Bioinformatics Institute (VBI) at Virginia Tech have developed a disposable microchip that replaces space-consuming instrumentation with fast, cost-effective, lab-on-a-chip technology. The microfluidic device is suitable for large-scale screening of disease-related biomarkers. Protein biomarkers are useful as "molecular indicators" for a wide range of diseases including breast cancer. The lab-on-a-chip integrates a pump, valve, separation column, and detection interface onto a 3- by 1-inch glass microchip and delivers a performance to match benchtop instrumentation typically occupying a few square feet of lab space.

Education initiative in cyberinfrastructure

Cynthia Barnes, a computer science major at Bluefield State College, is participating this semester in an introductory cyberinfrastructure course, which was created as a direct result of a National Science Foundation-funded program designed to support an education initiative in cyberinfrastructure.

"I had intended on going into network administration/network security after graduation, but I must say this class is opening up my eyes to new things. I would like to continue my education and work on my Master's degree at Virginia Tech, and I am now very interested in obtaining a student internship at VBI."

Last year, VBI, Bluefield State College in Bluefield, WV, and the Galileo Magnet High School in Danville, VA received a $250,000 grant from the National Science Foundation (NSF) to support an education initiative in cyberinfrastructure. The goal of the project is to introduce high school and undergraduate students to the science of bioinformatics and, in particular, the concept and practice of cyberinfrastructure. The program is specifically designed for students who might not normally have the chance to receive formal training in bioinformatics.

This initiative is perfectly suited for Bluefield State College student Cynthia Barnes. Barnes, a computer science major at the college, is participating this semester in an introductory cyberinfrastructure course, which was created as a direct result of the NSF-funded program. The course helps students from a diverse array of academic backgrounds, including mathematics, biology, computer science, and engineering, learn more about bioinformatics while retaining their own unique perspectives. While this new class isn't a requirement for computer science majors at Bluefield State College, Barnes was attracted to the uniqueness of the class and wanted to be a part of something that was "a first" for the college.

"Since the course is interdisciplinary, we have four instructors and that is definitely something I've never experienced before," Barnes explained. "We have a biology professor, computer science professor, project management professor, and a physics professor all working together to teach us about cyberinfrastructure as it pertains to bioinformatics specifically. Also, all of the students in the class are involved in different fields, which brings an interesting perspective to the class."

Students enrolled in the course are exploring the relevant literature through discussions and forum postings, helping to emphasize interdisciplinary teamwork in both face-to-face and online environments. Each week, the students are given a topic related to cyberinfrastructure and bioinformatics to discuss in an online forum. Each student posts his or her opinion to spark a discussion on the topic. The first topic assigned to the class involved a report from NSF's Blue-Ribbon Advisory Panel on Cyberinfrastructure authored by Daniel Atkins and colleagues, which is also referred to as the Atkins Report.[1] The accompanying box shows Barnes' contribution to the Atkins Report discussion. Her thoughts, she explained, originated from thinking about the Advanced Cyberinfrastructure Program discussed in the report.

Barnes says she hopes the class will help her to be successful and efficient working in a team environment. She seems confident that the class will have a positive impact on her future.

"I had intended on going into network administration/network security after graduation, but I must say this class is opening up my eyes to new things," Barnes said. "I would like to continue my education and work on my Master's degree at Virginia Tech, and I am now very interested in obtaining a student internship at VBI."

Atkins Report Class Discussion, by Cynthia Barnes

Cyberinfrastructure was a brand new term to me when this class started and though I could speculate as to its meaning I was looking for a good definition while reading the Atkins Report.[1] I picked up the meaning but didn't really find what I wanted. I did, however, find a definition in a report called "Our Cultural Commonwealth." They state that, "cyberinfrastructure is meant to denote the layer of information, expertise, standards, policies, tools, and services that are shared broadly across communities of inquiry but developed for specific scholarly purposes."[2] So it's something more specific than a network but more general than a tool. The base technologies of cyberinfrastructure are computation, storage, and communication. Without these integrated electro-optical components, cyberinfrastructure wouldn't be. The whole point, as I understand it and as is stated in the Atkins Report, is to revolutionize what people can do, how they do it, and who participates by enabling them to share and collaborate over time and over geographic, organizational, and disciplinary distance. Without the base technologies there wouldn't be much progress, time and money would be wasted. I think achieving the vision of the Advanced Cyberinfrastructure Program will be so beneficial to all fields of study that's it's worth the extra $1 billion annual budget. Like we discussed in class, when it comes to bioinformatics, the collaboration of cyberinfrastructure is needed to find out what is really going on in a living organism. This fact was backed up in *Science* in an article called "Cyberinfrastructure: Empowering a "Third Way" in Biomedical Research", where it said, "Biomedicine is at the precipice of unlocking the very essence of biologic life and enabling a new generation of medicine. Development and deployment of cyberinfrastructure may prove to be on the critical path to obtaining these goals". [3]

References:

1. Atkins D, Droegemeier K, Feldman SI, Garcia-Molina H, Klein ML, Messerschmitt DG, Messina P, Ostriker JP, Wright MH (2003) Revolutionizing science and engineering through cyberinfrastructure: Report of the National Science Foundation Blue-Ribbon Advisory Panel on Cyberinfrastructure, National Science Foundation.
2. Our cultural commonwealth: The Report of the ACLS Commission on Cyberinfrastructure for the Humanities and Social Sciences, July 18, 2006
3. Buetow, K (2005) Cyberinfrastructure: empowering a "third way" in biomedical research. *Science* **308**(5723): 821-824.