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Biochemistry, Molecular Biology, and Biophysics

Solution Structure of the Catalytic Domain of APOBEC3G

According to estimates from the UNAIDS 2008 Report on the global AIDS epidemic, around 30.8 million adults and 2 million children were living with the human immunodeficiency virus (HIV) at the end of 2007. During 2007, some 2.7 million people became infected with HIV, which causes AIDS. The year also saw two million deaths from AIDS *(www.avert.org/worlstatinfo.htm)*.

Needless to say, it is of great importance to fight this disease. Associate Professors Hiroshi Matsuo and Reuben S. Harris, Department of Biochemistry, Molecular Biology, and Biophysics, and their research groups, including postdoctoral associate Dr. Elena Harjes, are investigating the human APOBEC3G (A3G) protein. A3G is capable of altering the HIV genome by deaminating cytosines to uracils. (Cytosine is one of the bases in DNA; uracil is a base in RNA.) DNA deamination can genetically inactivate HIV and recent studies have shown that this activity is as potent as any current anti-

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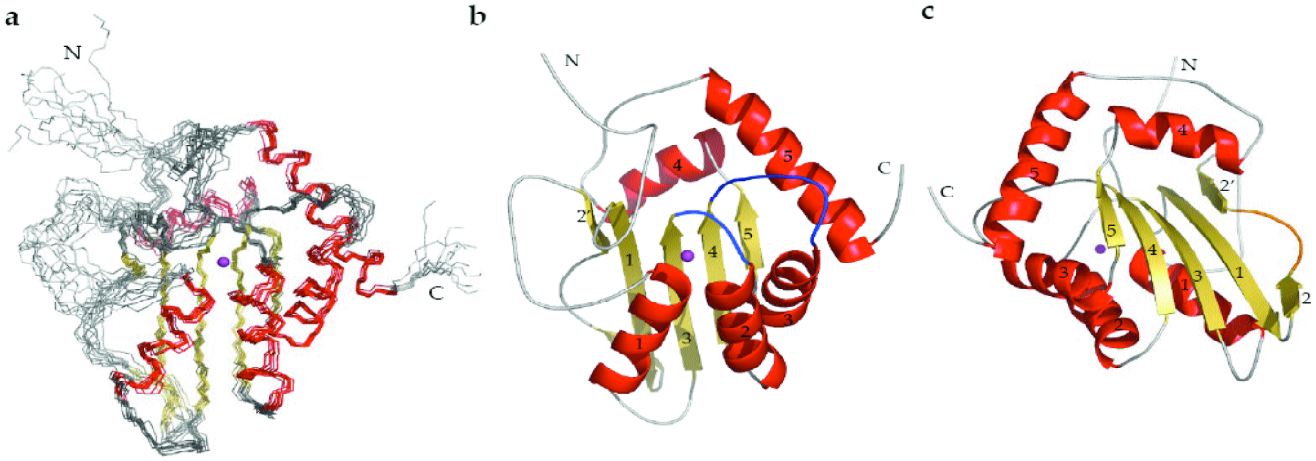


Figure 1a. Superimposition of ten NMR structures showing α-helices in red, β-sheets in yellow and Zn^{2+} in purple.
1b, 1c. Ribbon diagrams of the NMR structure shown in 1a from the same (b) and 180° (c) angles, respectively. The β3-to-β2 and β4-to-α3 loops are colored blue in 1b, and the β2-bulge-β2′ is colored orange in 1c. This figure was generated by modifying Figure 2 in Chen et al., *Nature,* **452**, 116–119 (2008).

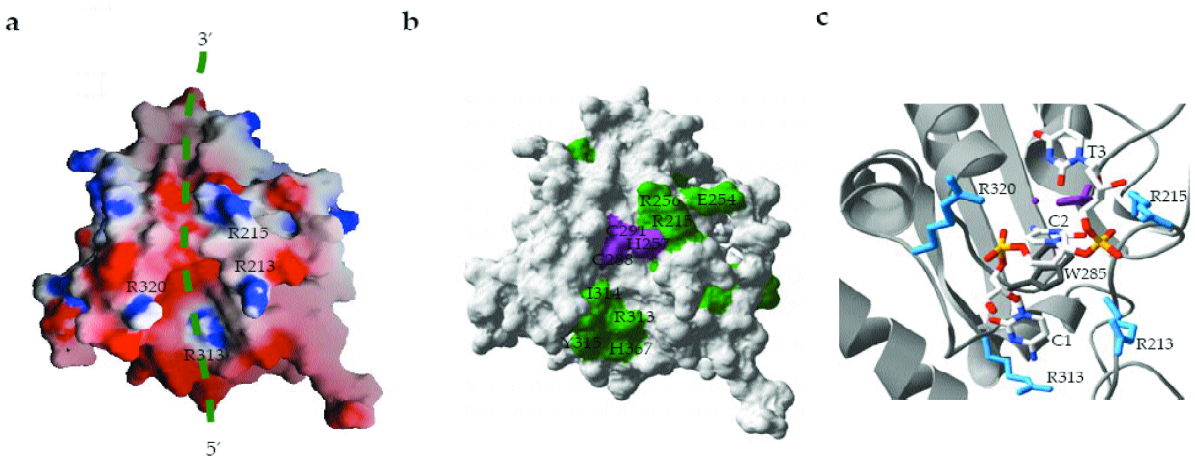


Figure 2a. Surface representation of A3G-CTD, highlighting positions of positive (blue), negative (red), or neutral (white) charge. Arginines that brim the concave active site are labeled. The hypothesized position and polarity of ssDNA is indicated (green dashed line).
2b. NMR ssDNA-titration data summary. Residues with chemical shift perturbations more than 1 s.d. above average are colored green (E259 is perturbed but hidden by H257). H257, C288, and C291 are shaded purple.
2c. Model depicting the interaction between A3G-CTD and ssDNA (5′-C1-C2-T3-3′). H257 (purple) is shown partially stacked with the ring of the flipped-out target cytosine (C_2). W285 (gray) helps to form a hydrophobic catalytic cavity. Arginines forming the positively charged brim of the active site are indicated (see text for discussion). Single-stranded DNA is colored white (carbon), blue (nitrogen), red (oxygen), and yellow (phosphate). This figure was generated by modifying Figure 4 in Chen et al., *Nature*, **452**, 116–119 (2008).

retroviral drug (Haché et al., *Current Biology*, **18**, 819–24 (2008)). However, as a counter-defense, HIV uses an auxiliary protein called Vif (virion infectivity factor) to degrade A3G. Structural information is valuable for understanding protein function including enzymatic activity and interactions with other molecules.

In the case of A3G the interaction with DNA and Vif are of the greatest interest. Understanding the A3G-DNA or A3G-Vif interaction provides fundamental knowledge of the mechanisms by which A3G catalyzes single-strand DNA (ssDNA) cytosine deamination or Vif degrades A3G, respectively.

A3G consists of two domains, containing the N-terminal Vif interacting domain (NTD) and the C-terminal catalytic domain (CTD). The researchers have calculated the structure of the A3G catalytic domain using NMR data and proposed model for DNA binding (Chen et al., *Nature*, **452**, 116–119 (2008)). Five helices are arranged over five strands (Figure 1). The structure of A3G-CTD shares some attributes with previously known structures of cytosine deaminases. The α-β-α Zn^{2+}-binding motif, α1-β3-α2 in A3G-CTD, is the clearest characteristic trait in structures of this deaminase superfamily. The unique β2 strand, which is interrupted with a loop-like bulge of six residues (Figure 1c) is a remarkable feature of A3G-CTD. The only other available APOBEC structure, the crystal structure of APOBEC2, has a continuous 11-residue β2 strand, which mediates dimerization through the β2 strand of another molecule (Prochnow, et al., *Nature*, **445**, 447–451 (2007)). The presence of β2-bulge-β2′ suggests that different contacts will connect N- and C-terminal domains of A3G. It is possible that the β2-bulge-β2′ mediates interactions with RNA and/or other proteins, although the researchers have not yet found any specific sequence or molecules. Since amino acid residues located in the β2-bulge region are not important for the deamination activity, the interactions involving this region may not affect A3G's catalytic activity.

A fundamental question is how A3G binds ssDNA. To bind DNA, proteins usually need positive charges on their surfaces. The electrostatic potential of the active-site face of A3G-CTD was

largely negative. Only a few positively charged residues were arranged on an apparent brim surrounding the concave catalytic site (Figure 2a). To test directly whether any of these residues interacted with DNA, NMR chemical shift perturbation experiments were conducted by titration of 21-base ssDNA oligonucleotide, which contained an A3G deamination hotspot. Significant chemical shift perturbations occurred predominantly on the active-site face of A3G-CTD (Figure 2b), including catalytically key residue glutamic acid E259. Additional chemical shift perturbations were detected for conserved arginines R215 and R313. Residues adjacent to R313 (located in the β4-to-α3 loop) and to E259 also showed strong chemical shift perturbations. Unfortunately, NMR signals of R213 and R320 could not be detected with this technique.

The NMR titration data and a computational method were used to find the lowest energy A3G-ssDNA binding model (Figures 2b and 2c). This model predicted that the 5′ nucleotide C_1 would interact with the conserved R313, the phosphate of the 3′ nucleotide T3 would contact both R215 and R213, and the C_2 phosphate would interact with R320.

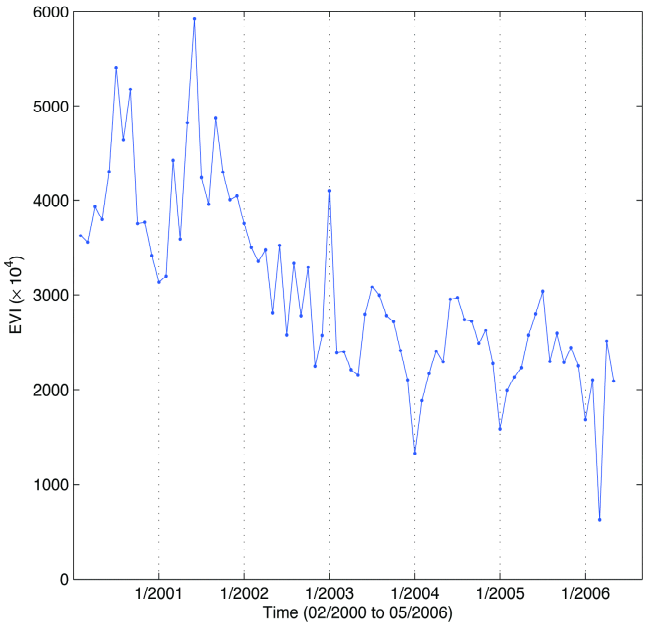
To test this DNA binding model, the researchers tried to determine whether residues, mentioned above, would be important for catalytic activity. The model predicted that R215 and R313 would promote DNA binding and that W285 would help to form the hydrophobic active site. E259 is predicted to be important for exchanging protons during the catalytic reaction. All of these residues proved essential for the catalytic activity using *Escherichia coli*-based activity assay. R213 and R320 were predicted to interact with the phosphate backbone of ssDNA. Therefore, an alanine substitution at these positions might be tolerated, but a negatively charged substitution might kill the catalytic activity by repelling the phosphate backbone. Indeed, R213A and R320A derivatives still retained 20% of wild-type activity, whereas R213E and R320E derivatives were nearly dead.

The catalytic domain of the HIV-1 restriction factor A3G represents the first high-resolution ssDNA cytosine deaminase structure and provides insights into the A3G-DNA interaction. Future research directions include deciphering the catalytic mechanism of full-length A3G, the interaction between A3G and Vif, and small molecules that work by disrupting this axis.

Using Data-Mining Techniques to Assess Changes in Land Cover

Professor Vipin Kumar, Department of Computer Science and Engineering and MSI Fellow, and his team have developed scalable algorithms to detect changes in land cover using data from NASA's Earth Observing System (EOS) satellites, and have shown their effectiveness in detecting changes in forest cover due to fires, logging, and other events. The need to assess the state of the forest ecosystem and how it is changing has become increasingly urgent. In particular, detecting changes in the forest ecosystem and their recovery periods is critical for sustainable management of forest resources, monitoring the impacts of climate change on forests, documenting a nation's compliance with United Nations protocols, and carbon trading. Even though changes in forests account for as much as 20% of the greenhouse gas emissions into the atmosphere (second only to fossil fuel emissions), the lack of technology to reliably determine changes in the global forest cover has prevented forests from becoming part of the carbon trading system.

The land cover change detection problem is essentially one of detecting when the land cover at a given location has been converted from one type to another. Examples of this include the conversion of forested land to barren land or farmland (possibly due to logging or a fire) or farmland being converted to land used for housing developments. The general change detection problem has been extensively studied in the fields of statistics, signal processing, and control theory. However, most techniques from these fields are not well-suited for earth science data due to their inability to take advantage of seasonality and spatio-temporal autocorrelation inherent in the data and their inability to



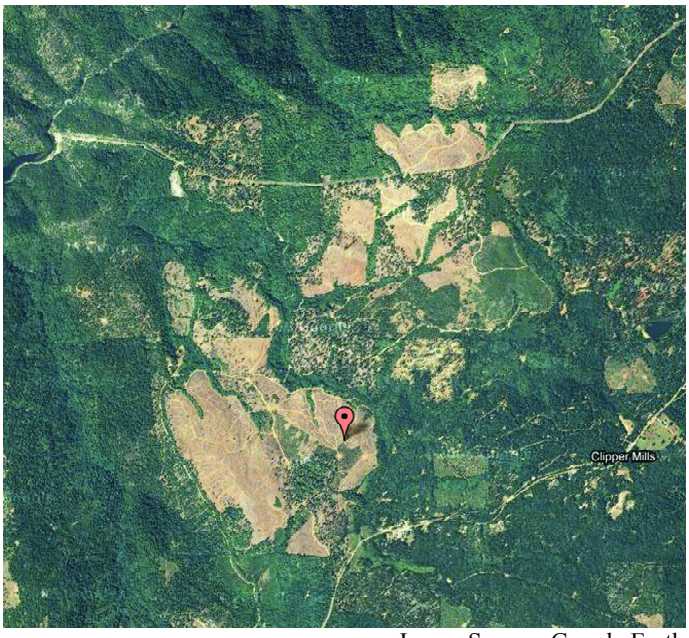


Image Source: Google Earth

Figure 1: Vegetation time series (left) identified by the change detection algorithm shows a sustained decrease in vegetation. The corresponding satellite image from Google Earth (right) shows that logging has indeed occurred in this forested area located in Northern California.

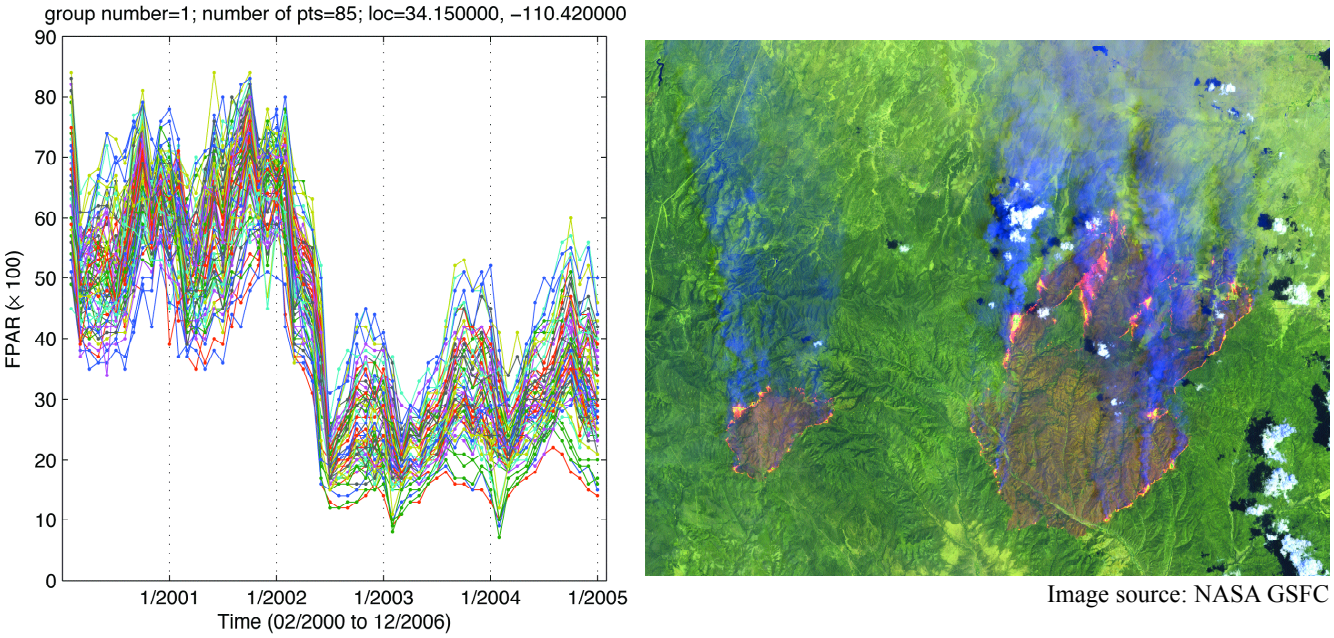


Figure 2: The collection of time series (left) identified by the change detection algorithm show a dramatic drop in the vegetation index (FPAR) around the summer of 2002. Satellite imagery (right) for this location (a forested area near Phoenix) from June 2002 shows a large-scale forest fire in progress–the well-documented Rodeo Fire.

handle massive global datasets.

Professor Kumar's work addresses these challenges with new change-detection techniques that are based on novel data-mining approaches. Specifically, these techniques take advantage of some of the inherent characteristics of spatio-temporal data and are scalable so that they can be applied to increasingly high-resolution earth science datasets.

Application of the new algorithm to EOS data (specifically MODIS (moderate-resolution imaging spectroradiometer) EVI (enhanced vegetation index) and FPAR (fraction of photosynthetically active radiation) products) has detected a number of interesting land cover changes in California, including logging (Figure 1), conversion from desert to farmland, and large-scale forest fires worldwide (Figure 2). This work is unique because it is among the first time series-based schemes for land cover change detection and because of the high quality of the changes detected. The ability to reliably detect forest cover changes across the globe in a timely fashion will have a significant impact on conservation efforts and carbon-trading markets. The collaborators on this project (funded by NSF and NASA) are graduate student Shyam Boriah, Dr. Michael Steinbach and Professor Joe Knight of the University of Minnesota, Dr. Chris Potter of NASA Ames Research Center, Steve Klooster of California State University, and Professor Pang-Ning Tan of Michigan State University.

More details about this project can be found in "Land Cover Change Detection: A Case Study" (S. Boriah, V. Kumar, M. Steinbach, C. Potter, and S. Klooster, in *KDD '08: Proceedings of the 14th ACM SIGKDD International Conference on Knowledge Discovery and Data Mining*, 857–865, 2008).

Summer 2009
Undergraduate Internship Program

The Supercomputing Institute is pleased to announce its Undergraduate Internship Program for Summer 2009. Appointments are for full-time, 10-week internships, and will run from June 1 through August 9, 2009. A student interested in becoming an intern must still be an undergraduate in August 2009 and must be a citizen or permanent resident of the United States or its possessions. Interns will be paid a stipend of $5,000 and are responsible for their own travel and housing costs.

All applications are evaluated competitively based on the qualifications of the applicant and the availability of a suitable project. Prospective applicants should review the research projects list and indicate projects in which they are interested, although they may be offered other projects due to availability.

Complete application information, application forms, and project lists are available on the Supercomputing Institute Web site at:

www.msi.umn.edu/programs/undergraduateinternship.html

Application forms and project lists are also available from:

Undergraduate Internship Coordinator
University of Minnesota
Supercomputing Institute
599 Walter
117 Pleasant Street SE
Minneapolis, MN 55455

Phone: (612) 624-2330
Email: uip@msi.umn.edu

All applications and letters of recommendation must be received by March 2, 2009.

MSI Open House 2009

The April 2009 Open House previously announced on this page will be combined with an event honoring MSI's 25th anniversary. This event is tentatively scheduled for Fall 2009. Information will be posted on our Web site as it becomes available:

www.msi.umn.edu/programs/

Bioinformatics: Building Bridges 2009

The bioinformatics programs at the University of Minnesota will be sponsoring another Bioinformatics: Building Bridges conference at the Digital Technology Center on the University's East Bank campus in Minneapolis. The conference will be held on April 16–17, 2009 and is sponsored in part by the Supercomputing Institute. As in past years, the conference will include speakers, a poster session, and tutorials presented by Supercomputing Institute User Support staff members. Some events will be available as Webcasts.

The previous Building Bridges conference was held in April 2007 (see *Research Bulletin* Volume 23, Number 1, Spring 2007 and *www.binf.umn.edu/bisymp07*).

Information about the 2009 conference can be found on the conference Web site:

www.binf.umn.edu/bisymp09/

The conference organizer is MSI Principal Investigator Professor Lynda Ellis, Department of Laboratory Medicine and Pathology.

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