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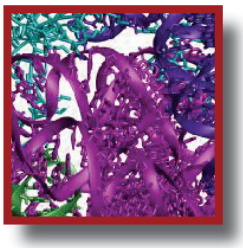
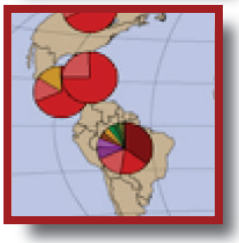
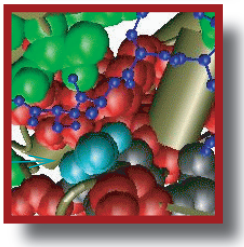
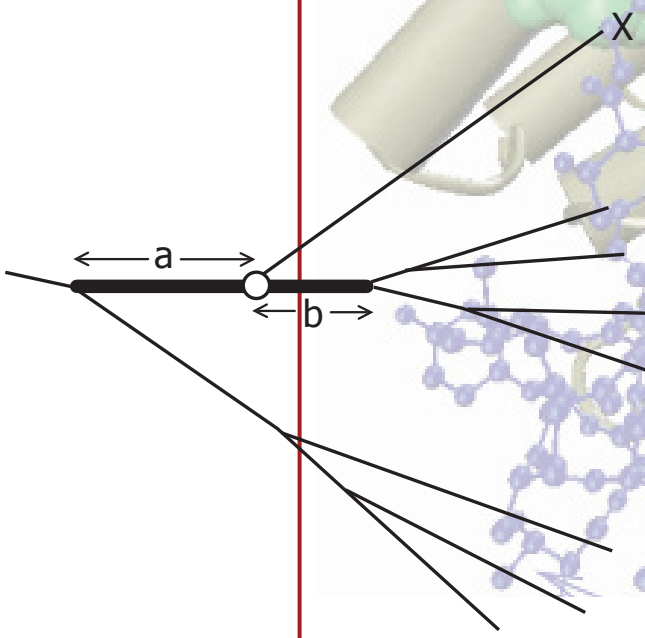
Biosciences in T-Division









- Bone Remodeling
- Cell Signaling
- DNA
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- Hepatitis C Database
- HIV
- Morphogenesis
- Protein Physics
- Structural Biology
- Tumor Growth Modeling
- Virology

Theoretical Division

Introduction

A major strength of T-Division lies in the multiple disciplines practiced by its scientific staff. While discovering new approaches in one field, they often exploit applications in quite different directions. This creative environment enables and encourages a rich interconnectivity that benefits the entire Laboratory. – Alan R. Bishop, Division Leader

Biosciences, one of the many areas of our research, is being performed in several groups in the Theoretical Division in collaboration with other parts of the Laboratory and researchers around the world. Current focuses embrace both global societal challenges such as bioinformatics, HIV vaccine strategies and immunology, and frontiers of biological physics and computational biology.

T-Division groups currently involved:

Theoretical Biology and Biophysics T-10
Mathematical Modeling and Analysis T-7
Elementary Particles and Field Theory T-8
Condensed Matter and Statistical Physics T-11
Theoretical Chemistry and Molecular Physics T-12
Complex Systems T-13
Explosives & Organic Materials T-14

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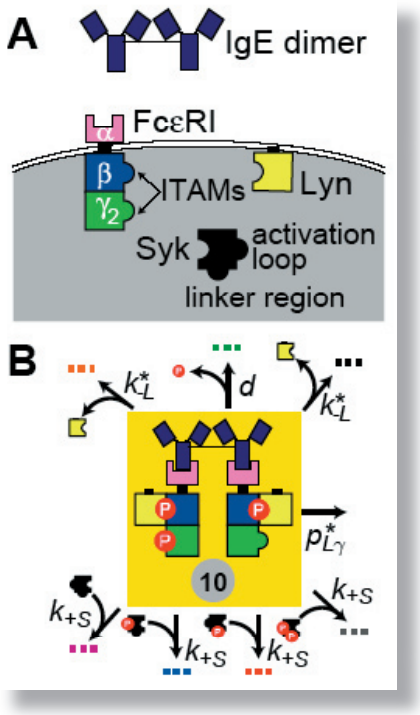
Sampling of Biosciences Work in Theoretical Division



Cell Signaling

Contact: Byron Goldstein, T-10, bxg@lanl.gov

Cells use receptor proteins in their plasma membrane to sense and respond to chemical and physical changes in their environment. For most receptors, the event that initiates signaling is binding to an external molecule, called a ligand, which triggers a complex cascade of biochemical reactions leading to a response. The transfer of information about the ligand-receptor binding event often begins when multiple receptors bind to the same ligand, forming an aggregate on the cell surface. Aggregate formation brings the tails of the receptors that lie inside the cell close together for times that are much longer than can occur with random collisions. The proximity of receptors within the aggregate permits specific amino acid residues in these tails to become modified (typically phosphorylated) by enzymes, and these modification sites become docking sites for other proteins within the cell. This leads to large molecular complexes forming around the cytoplasmic tails of the receptors. With William S. Hlavacek (T-10), James Faeder (T-10), Carla Wofsy (T-10), Michael Blinov (T-10), Dan Coombs (UBC), and Antonio Redondo (T-12).

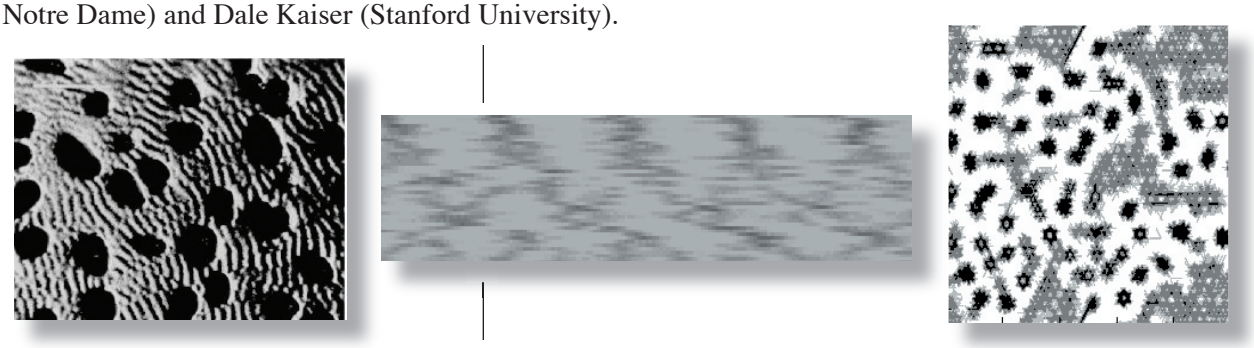
The figure illustrates the complexity that arises in a model of early events in signal transduction through the receptor FcεRI, which plays a critical role in allergic responses. Although only four molecules (A) are considered by the model, a large number of chemical species (354) and chemical reactions (3680) arise when all of the ways in which the components can combine and be modified are considered. A typical complex is shown in (B) along with the eight possible reactions that it may undergo.

Our models illustrate the enormous complexity of the biochemical events involved in signal transduction.

Morphogenesis

Contact: Yi Jiang, T-7, jiang@lanl.gov

Morphogenesis of myxobacteria: myxobacteria are one of the prime model systems for studying cell-cell interaction and cell organization preceding differentiation. When starved, myxobacteria undergo a complex multistep process of alignment, rippling, streaming, and aggregation that culminates in the differentiation of highly elongated, motile cells into round, nonmotile spores. We use lattice-gas cellular automaton models to simulate different stages in myxobacteria fruiting body formation, e.g., rippling, aggregation. Our models test various hypotheses regarding the mechanisms of fruiting body formation and suggest new experiments. With Mark Alber (University of Notre Dame) and Dale Kaiser (Stanford University).



This work opens the possibility for high-throughput modeling of ribosomal structures from different organisms.

DNA Telomore Dynamics

Contact: Krastan B. Blagoev, T-11, krastan@lanl.gov

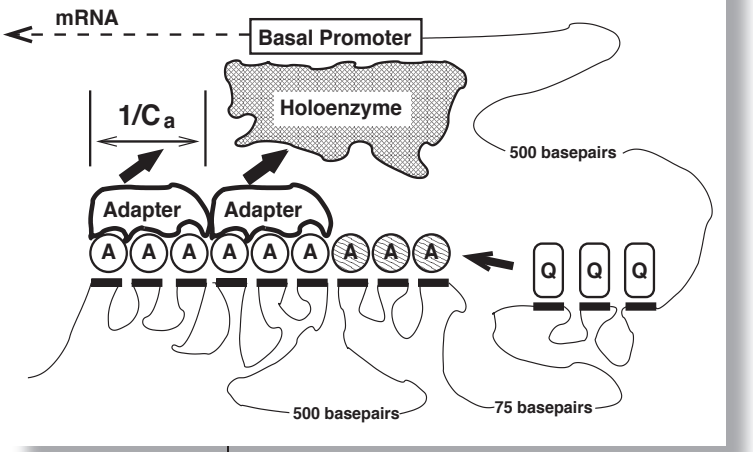
Telomore dynamics and senescence: don't set your watch by the mitotic clock. In recent years, DNA telomere length changes have been found to be far more dynamic than previously thought. Several demonstrated and proposed mechanisms contribute to telomere dynamics including telomere rapid deletion, recombination-mediated telomere extension, and telomeric sister chromatid exchange. How these processes modulate cellular proliferative potential will have to be carefully considered if we are to understand the growth and senescence of telomerase-negative cells in the real world. We are working towards a new quantitative model of cellular proliferation and senescence that incorporates telomere dynamics. We expect the model will cast light on relationships not otherwise easily explained by a deterministic "mitotic clock," such as that between the senescent cell fraction and population doubling time, or oxidative stress and lost proliferative potential. We also hope to shed light on the transition to unlimited growth potential found in telomerase-negative tumor cells having the ALT phenotype. With Edwin H. Goodwin (B-2).

We expect the model will cast light on relationships not otherwise easily explained by a deterministic "mitotic clock" . . .

Genomics

Contact: Shuling Hou, T-13, hou@lanl.gov

The continuing progress of the ongoing revolution in genomics requires an answer to the fundamental question of molecular biology: how does DNA control differential gene expressions? The noncoding region of DNA contains regulatory sequences in which promoters and enhancers are the most important components necessary for controlling where and when a particular gene is transcribed. A gene's promoter contains sites where RNA polymerase binds to the DNA to initiate transcription. In eukaryotic cells, RNA polymerase requires additional protein factors and basal transcription factors in order to bind efficiently to the promoter. This entire complex is called the polymerase holoenzyme. An enhancer is a DNA sequence that can activate a promoter, controlling the efficiency and rate of transcription from that particular promoter. An enhancer contains binding sites for protein transcription factors that may function as activators or repressors. There are evidences that regulatory functions of metazoans are encoded by groups of binding sites (modular) and many adaptor proteins are also involved in gene transcriptions. Based on these facts, we have developed a mathematical model and tested on the eve gene of Drosphila. With David Sharp (T-13), John Reinitz (SUNYSB), and Hilde Janssens (SUNYSB).

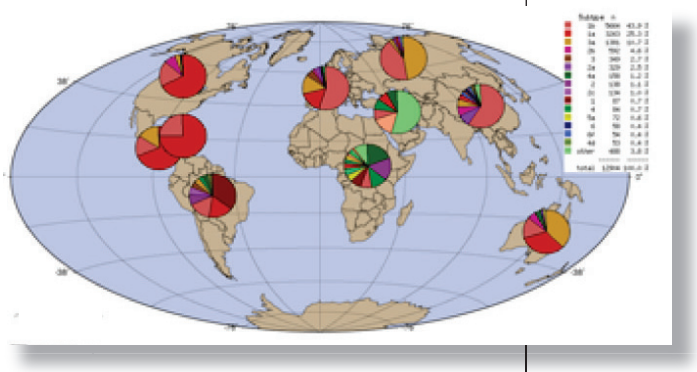


This drawing shows a schematic view of elements of the transcription model. The DNA upstream of the basal promoter is shown by a line, with thick areas to denote binding sites. Activators, shown as circles with the letter A, are bound to nine sites that are spaced at varying intervals along the DNA. The left-most six activators can bind "adaptor" molecules (labeled "adaptor"). The right-hand three activator molecules are quenched (shown by hatching) because there are three quenchers; the rectangles labeled "Q" are bound less than 100 base pairs away.

Based on these facts we have developed a mathematical model and tested on the eve gene of Drosphila.

Hepatitis C Database

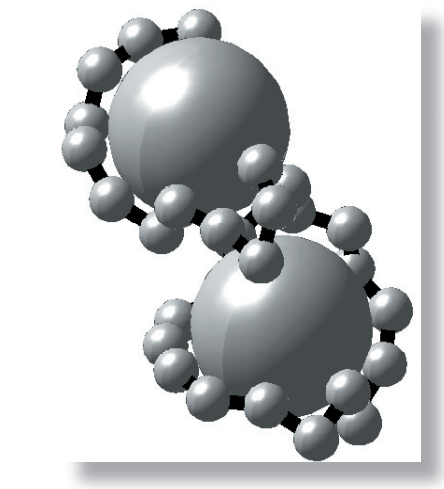
Contact: Carla L. Kuiken, T-10, kuiken@lanl.gov



The geographical distribution of hepatitis C sequences of genotypes 1–6 in the database. The figure was generated using the Geography tool, available on the HCV Website.

The Los Alamos Hepatitis C Sequence Database collects HCV sequences and associated data. The data are made accessible to HCV scientists worldwide, by providing access to the central database via a web-accessible search interface and supplying a number of analysis tools. Of the roughly 20,000 sequences, 80% are annotated with genotype and 70% with country information. Annotation provided by the database currently includes host data (host species, health status at time of sampling, therapy history and response, sampling date and location, likely infection route, infection date and location), virus data (genotype and subtype, sequenced region), data on transmission clusters and related sequences obtained from the same host, and publication data (including publication links not annotated in Genbank). Future plans include building tools for automatic tree building, optimal tree selection, distance matrix analysis, and automatic alignment of user-base and database sequences. A database of immunological epitopes will be ready for release in the fall of 2004. This database will be accompanied by its own set of search and analysis tools. Database is accessible at http://hcv.lanl.gov or http://hcv-db.org.

Of the roughly 20,000 sequences, 80% are annotated with genotype, and 70% with country information.



Brownian dynamics simulation of polyelectrolyte chain complexation with large counter polyions.

Macromolecules

Contact: Yi Jiang, T-7, jiang@lanl.gov

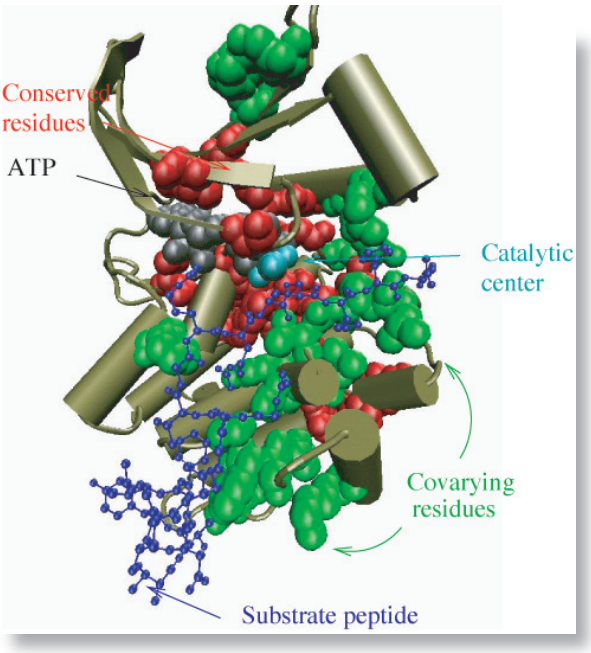
Self-assembly of macromolecules: molecular self-assembly plays a crucial role as a structural and an organizational principle in supramolecular architecture. The key feature of this process, solely determined at the molecular level, is the generation of higher order structures carrying novel functionalities only at the supramolecular aggregates. Self-assembling is the key for understanding and exploiting, for instance, mono and multilayer adsorption of polyelectrolytes and other molecules, allowing easy and quick synthesis of complicated surface structures, showing highly differentiated features. Adequate modeling of molecules or macromolecules self-assembling must span many orders of time and length scales. Parallel to the experimental efforts in B-4, we are developing coarse-grained molecular dynamics models to investigate the self-assembly of polyelectrolytes. With Andy Shreve (B-4) and Gabe Montano (B-4).

. . . we are developing coarse-grained molecular dynamics models to investigate the self-assembly of polyelectrolytes.

Protein Function

Contact: Benjamin H. McMahon, T-10, mcmahon@lanl.gov

Functional pressures are derived from protein kinase sequences: protein kinases comprise 2 percent of the human genome, approximately half of all oncogenes, and are present in most eukaryotic cell-regulation processes. We have decomposed a multiple sequence alignment of 5,913 protein kinase catalytic subunits into a phylogeny of 10 families, 61 sub-families, and 333 groups, as well as functional pressures on the amino acid positions, shown in the figure. Conserved residues (red) make up a contiguous core of the protein, controlling catalysis, binding ATP, and stabilizing the protein structure. Covarying residues (green) line the substrate recognition surfaces and highlight an allosteric region at the top of the protein. The complete analysis is available online at cellsignaling.lanl.gov/structure/kinase, and is being used to guide structure-based models of protein dynamics and quantum chemical reaction pathways. With Paul W. Fenimore (T-10) and Willam J. Bruno (T-10).

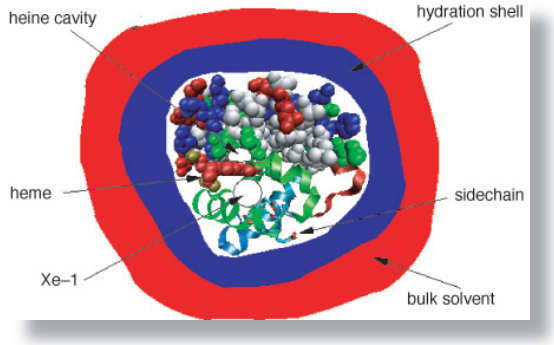


The complete analysis is available online at cellsignaling.lanl.gov/structure/kinase.

Protein Dynamics

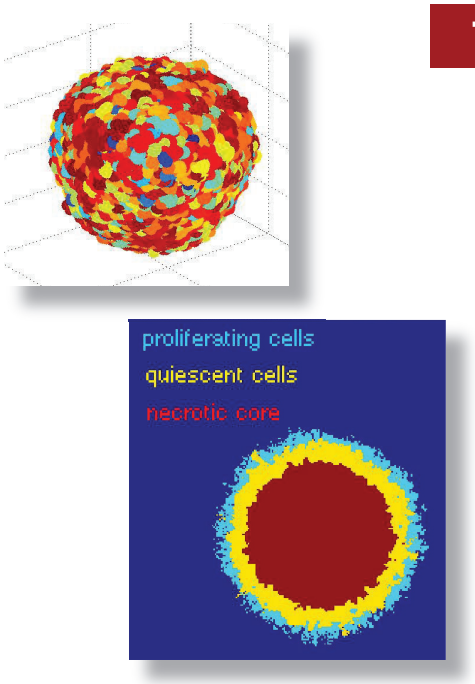
Contact: Paul W. Fenimore, T-10, paulf@lanl.gov

Fluctuations are crucial for protein functions: proteins are the dynamic workhorses of biology; they wiggle and move to perform their functions. Analyzing a range of experiments, particularly neutron scattering and Mössbauer effect, we show that the protein motions fall into three classes, slaved, semislaved, and nonslaved. Slaved motions follow the dielectric fluctuations in the bulk solvent, are absent in a solid environment, and their rate coefficients can be approximated by a Vogel-Tammann-Fulcher relation. They involve large-scale conformational changes and allow, for instance, the entrance and exit of ligands such as dioxygen in myoglobin. Semislaved motions follow fast fluctuations in the protein's hydration shell, occur even if the protein is embedded in a solid, but are absent in dehydrated proteins; their rate coefficient can be approximated by a Ferry relation. They involve side-chains and the hydrogen-bond network and may permit processes such as the passage of ligands inside myoglobin. With Hans Frauenfelder (T-10), Benjamin H. McMahon (T-10), and Robert D. Young (Northern Arizona University).



A look into myoglobin. The lower half of the structure shows three alpha helices, part of the protein backbone, with one side chain as an example. The upper half provides a space-filling view. Between the two halves is a heme group, in red. Two cavities, the heme cavity and the Xe1 cavity, are also depicted. The hydration shell (blue) and the bulk solvent (red) envelop the protein.

. . . we show that the protein motions fall into three classes, slaved, semislaved, and nonslaved.



Three-dimensional surface view and cross-sectional view of a 8.5-days-old tumor in simulation.

Tumor Growth

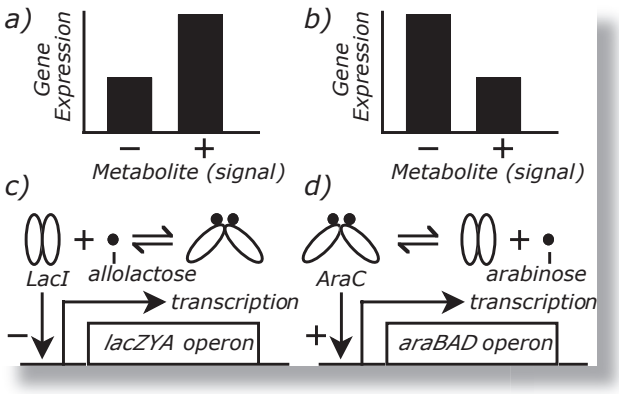
Contact: Yi Jiang, T-7, jiang@lanl.gov

Tumor growth modeling: the microenvironment inside a tumor is extremely complex and adaptive, involving spatial and temporal variations in chemical gradients, cellular physiology and viability, metabolism, and the expression patterns of genes and proteins as well as the malignant progression. The multicellular spheroid system is one example of an *in vitro* experimental model for the tumor microenvironment. We develop a multiscale mathematical model to study tumor growth, cell death, and angiogenesis. At the cellular level, a discrete Monte Carlo model describes cell growth and division, cell death, and intercellular adhesion. At the subcellular level, a simplified protein regulatory network controls cell cycle and cell cycle arrest. On the extracellular level, a set of reaction-diffusion equations describe the dynamics of nutrients, wastes, and growth factors. This multiscale cellular model provides a realistic representation of both structure and dynamics over a large range of time and length scales, and is able to propose and test specific hypotheses about tumor regulatory mechanisms. We have demonstrated the ability to model growth from a single tumor cell to a solid tumor. The results agree well with spheroid experiments. With Jim Freyer (B-3).

We have demonstrated the ability to model growth from a single tumor cell to a solid tumor.

Genetics

Contact: William S. Hlavacek, T-10, wish@lanl.gov



One aspect of elementary gene circuits that has been examined carefully is the response of the regulator gene in gene circuits to signals.

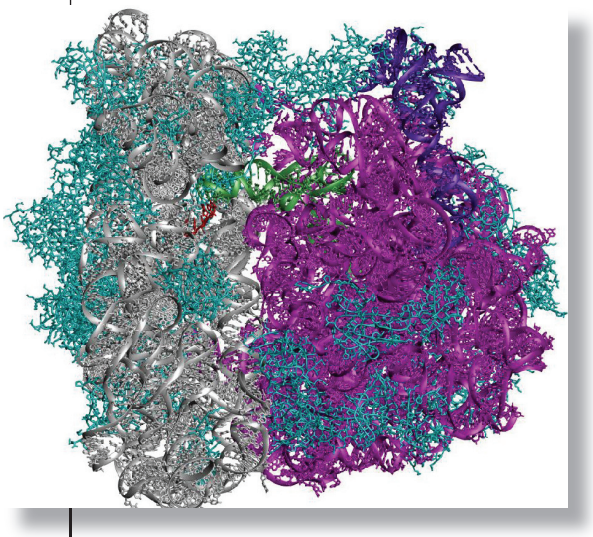
Design principles of genetic regulatory networks: the identification of predictive design principles is recognized as one of the grand challenges of systems biology. We are studying design principles of genetic regulatory circuits in bacteria, i.e., trying to understand how the structure of a system for regulating gene expression affects the system's function. An understanding of gene regulation is important because the cellular circuitry that controls gene expression is largely responsible for the ability of a cell to cope with changes in its environment. Genes must be expressed when needed and, for efficiency, turned off when not in demand. Gene regulation has been the subject of countless studies since the pioneering work of Jacob and Monod. Today, diverse systems, mostly in bacteria, have been characterized, and are beginning to be examined together to identify patterns and rules. With Michael E. Wall (CCS-3).

Genes must be expressed when needed and, for efficiency, turned off when not in demand.

Structural Biology

Contact: Chang-Shung Tung, T-10, ct@lanl.gov

Ribosome structural modeling: the ribosome is a complex and dynamic molecular machine that translates genetic information from nucleic acid and makes proteins accordingly. The proper functioning of ribosome is essential to all living organisms. It is the target for natural as well as synthetic antibiotics. To understand ribosomal functions requires the knowledge of detailed ribosomal structures. To date, the complete structure of the ribosome has not been solved to atomic-resolution experimentally. Using a knowledge-based approach developed here at LANL, we have modeled atomic structures of both the E. coli 30S ribosomal subunit and the T. thermophilus 70S ribosome (the molecular complex shown in the figure). Our work represents the largest asymmetrical biomolecular complex (over 200,000 atoms) in atomic details ever been modeled in silico. This work opens the possibility for high-throughput modeling of ribosomal structures from different organisms. With Kevin Y. Sanbonmatsu (T-10) and Simpson Joseph (UCSD).

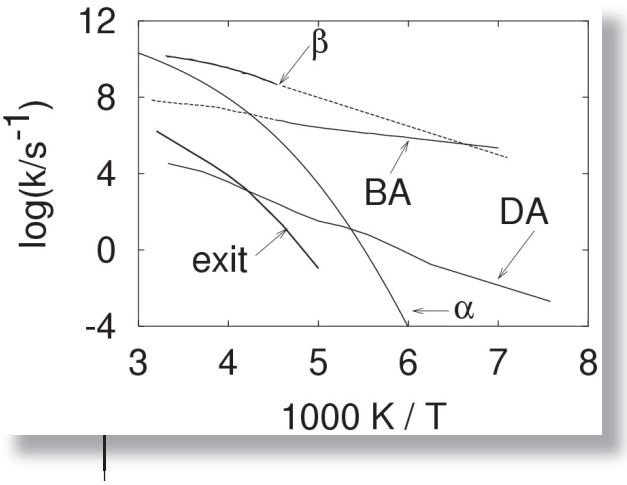


"Using a knowledge-based approach developed here at LANL, we have modeled atomic structure of both the E. coli 30S ribosomal sub-unit and the T. thermophilus 70S ribosome."

Protein Physics

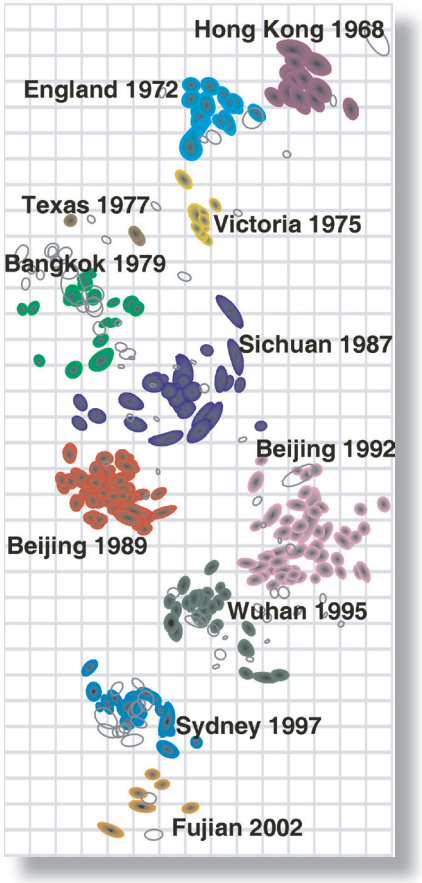
Contact: Hans Frauenfelder, T-10, frauenfelder@lanl.gov

Proteins and glasses have similar short-time relaxation phenomena. We have analyzed many studies that explore protein and glass dynamics using the Mössbauer effect and neutron scattering. Correct analysis shows that proteins and glasses share two major types of fluctuations, α and β. In proteins, these two types of fluctuations have different functional roles. Alpha fluctuations in the bulk solvent control large-scale fluctuations in the protein that are responsible, for instance, for exit and entry of ligands (e.g., oxygen). Beta fluctuations in the hydration shell control motions inside the protein and permit, for example, the migration of ligands through the protein. With Paul Fenimore (T-10) and Benjamin H. McMahon (T-10).



Shown are processes in myoglobin, embedded in glycerol/water solvent. Alpha denotes the dielectric fluctuations in the solvent, β the fluctuations in the hydration shell. "DA" gives the rate of transit through the protein and is parallel to β. "Exit" gives the rate of CO exit from myoglobin and is parallel to α. "BA" gives the rate of covalent binding of CO to the heme iron and is an Arrhenius process, independent of β and α processes.

Correct analysis shows that proteins and glasses exhibit two major types of fluctuations: alpha and beta.



Virology

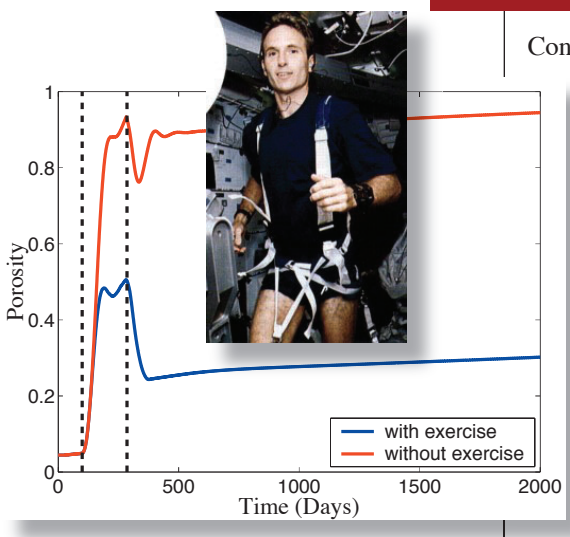
Contact: Alan S. Lapedes, T-13, asl@lanl.gov

Mapping the antigenic and genetic evolution of influenza virus: the antigenic evolution of influenza A (H3N2) virus was quantified and visualized from its introduction into humans in 1968 through to 2003. Remarkable correspondence between antigenic and genetic evolution was observed, but some very significant differences noted as well: antigenic evolution was more punctuated than genetic evolution, and genetic change sometimes had a disproportionately large antigenic effect. This mapping method allows monitoring of antigenic differences among vaccine and circulating strains, and estimation of the effects of vaccination. It also offers a route to predicting the relative success of emerging strains.

Shown is the antigenic map of influenza A(H3N2) virus from 1968 to 2003. The relative positions of strains (colored shapes) and antisera (uncolored open shapes) were adjusted such that the distances between strains and antisera in the map represent the corresponding HI assay measurements with the least error. The shapes represent a confidence area in the placement of the strain or antiserum in the map. Colors identify antigenic clusters of strains; the clusters were named after the first vaccine-strain in the cluster (referenced by city and date of isolation).

The method readily allows monitoring of antigenic differences among vaccine and circulating strains, and offers a route to predicting the relative success of emerging strains.

Bone Remodeling



Contact: Yi Jiang, T-7, jiang@lanl.gov

Modeling bone remodeling: human bones are dynamic tissues that are remodeled constantly through processes that remove existing bone and deposit new bone. We aim to create more informative—and ultimately more medically useful—models of bone dynamics. We developed a mathematical model to study the bone structural change due to remodeling activation under external mechanical stimulus. In particular, we are studying the bone loss due to the microgravity environment (underload). The model predicts the level of bone loss as a function of underload duration and shows how exercise can help reduce bone loss. The model is useful for testing various exercise programs for astronauts. With Antonio Redondo (T-12) and Richard A. LeSar (T-12).

Predicted bone porosity increase (bone loss) under microgravity for half a year (region between dashed lines)—short-term underload causes long-term damage. Exercise can reduce bone loss.

The model predicts the level of bone loss as a function of underload duration and shows how exercise can help reduce bone loss.

HIV-1

Contact: Thomas K. Leitner, T-10, tkl@lanl.gov

In our investigation of novel HIV-1 recombinant forms, we have developed a method, the branching index, for determining if parental DNA sequence representatives are available or are not for recombination analysis. For many reasons, including future vaccine design and monitoring the epidemic, it is important to accurately describe and classify the forms of HIV-1 that are spreading in different geographic regions and among different risk groups.

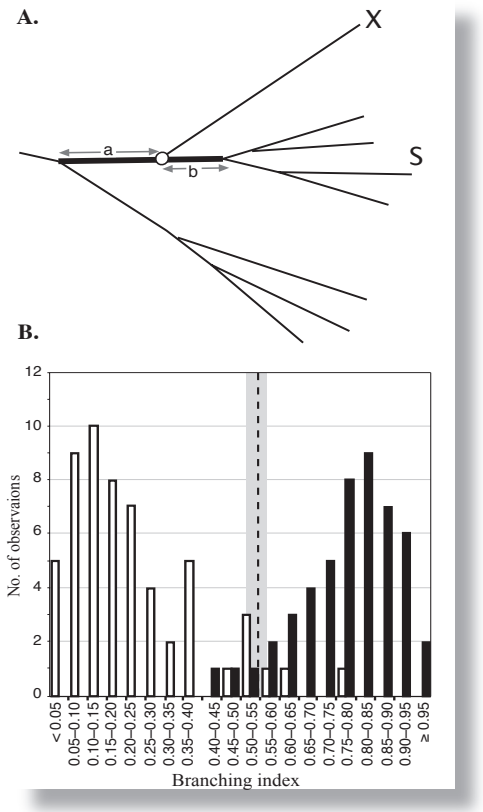


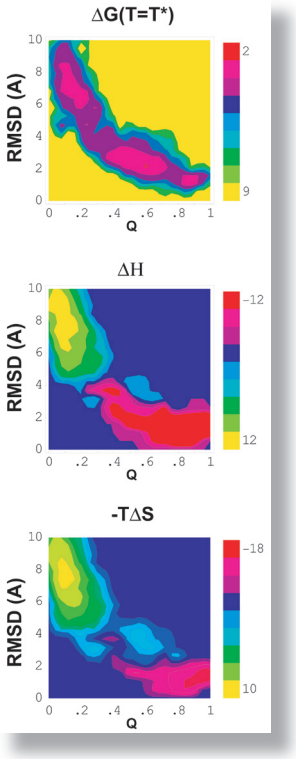
Figure A: schematic picture of the branching index. Here the association of sequence X to the subtype cluster S is investigated. Letters a and b are genetic distances that depend on the position of the node of sequence X (white circle) at the bold branch. The branching index is defined as a/(a+b) and can take values between 0 and 1. Figure B: comparison of branching indexes (BIs) from situations when parental representatives are present or not. White bars show the situation with subtype partners absent, and black bars show the situation with subtype partners present. The BI categories are shown on the x-axis and the number of observations on the y-axis. The vertical dotted line indicates the suggested cut-off value 0.55 for subtype verification, and the gray zone is a zone of uncertainty (< 95% correct classifications).

. . . it is important to accurately describe and classify the forms of HIV-1 that are spreading in different geographic regions and among different risk groups.

Protein Folding

Contact: Angel E. García, T-10, axg@lanl.gov

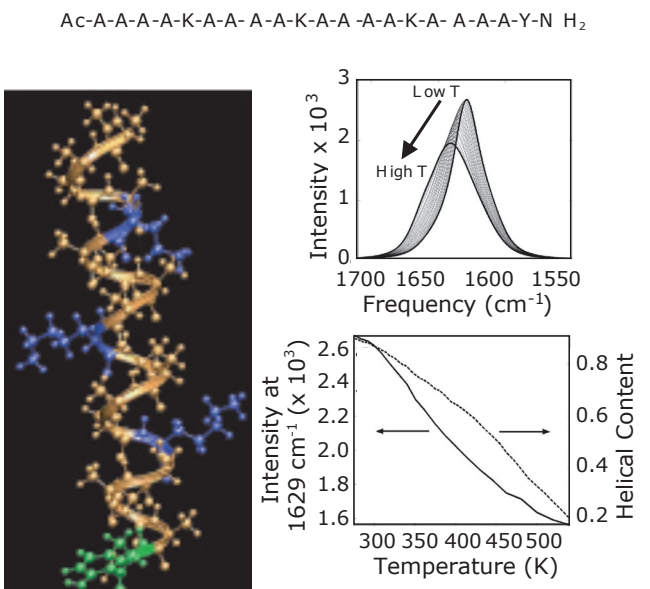
An atomic description of the folding/unfolding of protein A: we studied the folding mechanism of a three-helix bundle protein at atomic resolution, including effects of explicit solvation, and over a broad range of temperatures spanning the folded and unfolded states. Using the replica exchange molecular dynamics (REMD) we performed sufficient sampling to obtain free energy, entropy and enthalpy surfaces as a function of structural reaction coordinates. This is the first all-atom simulation to observe protein folding/unfolding transitions, done with explicit solvent and without any constraints. For the first time, multiple transitions from the unfolded ensemble to the native minimum have been observed in a computer simulation with a fully atomistic description. The highly parallel REMD algorithm allowed us to make numerical investigations that were practically unfeasible about one year ago. With Jose N. Onuchic (UCSD).



For the first time, multiple transitions from the unfolded ensemble to the native minimum have been observed in a computer simulation with a fully atomistic description.

Helix Folding

Contact: S. Gnanakaran, T-10, gnana@lanl.gov



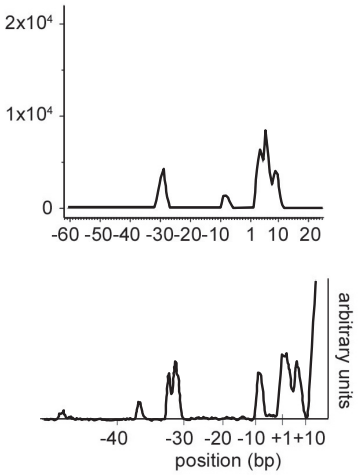
The nature of structural inhomogeneities on folding a helix: the knowledge of unfolded state distributions and how they represent the ensemble of pathways to folded states is a key element in understanding the folding of proteins. We utilize extensive conformational sampling and calculations of vibrational coupling to provide a quantitative basis for the structurally inhomogeneous spectra of the amide unit in aqueous solutions containing folded and unfolded state distributions of helices. Based on the all-atom folding simulations, a microscopic explanation for the well-known behavior of the amide IR band upon thermal denaturation is provided. With Robin M. Hochstrasser (University of Pennsylvania) and Angel E. García (T-10).

Shown is the calculated amide-I spectra showing the behavior upon thermal dentauration.

Interface spectral measurements with theoretical simulations in a manner that will enable the capture of the structural origin and the detailed characterization of the unfolded state distributions.

DNA Transcription

Contact: Kim Ø. Rasmussen, T-11, kor@lanl.gov



Simulated (upper) and experimentally (lower) observed instances of 10 base pair or larger openings versus base pair position in sequence. Transcription start site is at position 1.

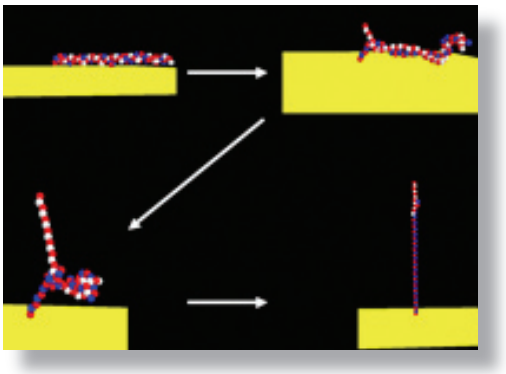
Understanding and predicting the initiation of DNA transcription: genetic information is stored in the sequence of DNA bases, which are protectively embedded in the hydrophobic center of the distinctive double helix. In order to read this code, the bases must be physically exposed by locally separating the strands at the transcriptional start sites. The mechanisms behind the initiation of this essential process are presently unclear. Based on a deceptively simple model that explicitly incorporates sequence and entropy effects, we have predicted the existence of sequence depended thermally induced local separations of the double stranded molecule. These local openings are observed to extend over 10 base pairs or more at physiological temperatures, which is similar in size to transcriptional openings. More importantly, we have, with the help of our experimental colleagues at Harvard Medical School, confirmed that such openings predominantly occur at the transcriptional start sites [1]. Our work therefore suggests that DNA carries information that helps direct its own transcription through thermal effects. With Alan R. Bishop (T-DO).

Our work therefore suggests that DNA carries information that helps direct its own transcription through thermal effects.

Cleaving DNA

Contact: Shirish M. Chitanvis, T-14, shirish@lanl.gov

Cleavage of double-stranded DNA (dsDNA) is one of the basic processes of life. Without cleavage, DNA transcription cannot occur. On the other hand, unnatural cleavage caused by cancerous proteins can be life-threatening. We are in the process of laying the basis of understanding this issue by contemplating a system of two coupled elastica, acted upon by an external force. We consider the double-stranded DNA as being characterized by finite-ranged correlations among the base pairs along the spine. We apply a cleaving force along varying lengths of the dsDNA. With this formalism based on functional path integrals, we can predict the minimum force required to disrupt a helical configuration. Our approach allows us to conclude that there is a correlation between the amount of supercoiling of a helical dsDNA and the minimum disruptive force. With Paul M. Welch (T-14).



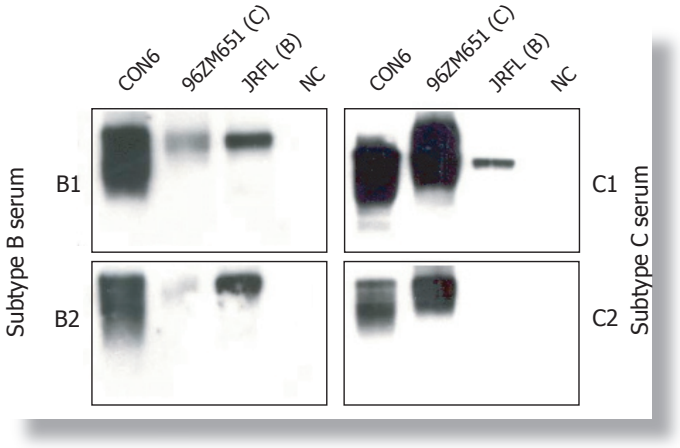
Numerical experiment pulling apart a model double-stranded polymer attached to a surface (yellow), indicating a schematic of the theory discussed in the text.

On the other hand, unnatural cleavage caused by cancerous proteins can be life-threatening.

HIV Research

Contact: Tanmoy Bhattacharya, T-8, tanmoy@lanl.gov

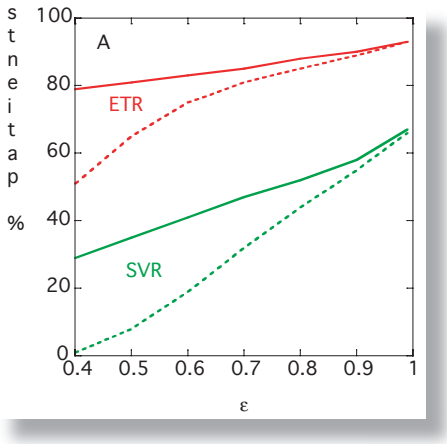
Rational vaccine design: much of the research on new vaccines is heuristic and empirical—all candidate HIV vaccines currently in clinical development are derived from natural isolates, and the strain used is often selected based on availability, with the hope that they will be sufficiently cross-reactive to protect against circulating viruses. This may be overly optimistic, however, given that HIV-1 envelope proteins can differ in more than 30% of their amino acids. Attempts at rationally designing an artificial "central" strain with increased similarity to circulating viral strains show promise in studies *in vitro*. A consensus M group gp120 protein bind to soluble CD4 as well as to neutralizing (b12 and 2G12) and conformation sensitive (17b and A32) monoclonal antibodies, and exhibit enhanced interclade antigenic cross-reactivity. Further research is in progress to modify the structure of the protein to increase the neutralizing antibody response essential for a succesful vaccine development. With colleagues listed on page 15.



Broad cross-clade reactivity of the M group consensus gp120 with patient sera of different clades in a Western blot assay. The central (CON6) construct shows activity comparable to subtype B (JRFL) and C (96ZM651) isolates against sera of the same subtype, and markedly more than that against sera of the dissimilar subtype.

Attempts at rationally designing an artificial "central" strain with increased similarity to circulating viral strains show promise in studies in vitro.

Viral Infection



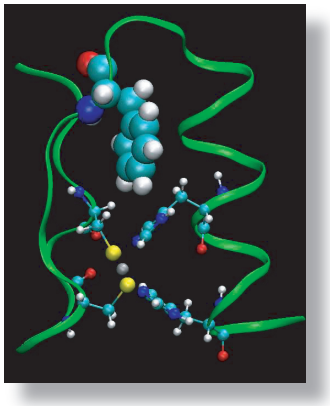
Model predictions of the fractions of patients treated for 24 weeks that would exhibit end-of-treatment, ETR (red), or sustained virological responses, SVR (green), with interferon monotherapy (dotted lines) or combination therapy (solid lines) as functions of interferon effectiveness, ε. The model predictions agree surprisingly well with clinical trial data.

Contact: Alan S. Perelson, T-10, asp@lanl.gov

Modeling viral infection and treatment: nearly 200 million individuals worldwide are currently infected with hepatitis C virus (HCV). Combination therapy with interferon and ribavirin, the state-of-the-art treatment for HCV infection, elicits long-term responses in only ~ 50% of the patients treated. No alternative treatments exist for nonresponders. Rational therapy optimization is precluded by the poor understanding of the mechanism(s) of ribavirin action against HCV. Ribavirin alone induces marginal or no reduction in HCV viral load but dramatically improves long-term response rates in combination with interferon. We have developed a model of HCV dynamics in which, based on growing evidence, we assume that ribavirin decreases the infectivity of HCV possibly by inducing mutagenesis. The model quantitatively predicts long-term response rates to interferon monotherapy and combination therapy, fits observed patterns of HCV RNA decline in patients undergoing therapy, reconciles conflicting observations of the influence of ribavirin on HCV RNA decline, elucidates the mechanism of ribavirin action against HCV, and establishes a framework for rational therapy optimization. With Narendra M. Dixt (T-10).

The model quantitatively predicts long-term response rates to interferon monotherapy and combination therapy . . .

Metalloproteins



A minimalist zinc-finger polypeptide showing the Zn-binding pocket (ball-and-sticks), and the hydrophobic phenyl-alanine (top) necessary for stability of these polypeptides. This is an optimized configuration of the dry 345-atom system obtained with MondoSCF.

Contact: Lawrence R. Pratt, T-12, lrp@lanl.gov

Metalloproteins comprise a large fraction, an estimated 1/3rd, of cellular proteins, and participate in tasks as diverse as gene-regulation, metal homeostasis, respiration, and metabolism. Their aberrant functioning has been linked to numerous physiological disease states. The diversity of the chemical roles played by metal ions in proteins largely renders metalloproteins outside the scope of current molecular modeling tools. T-12 is home to two break-through efforts on metal ions in biomolecules: one the modern theory of molecular solutions—quasi-chemical theory—and the other a linear scaling quantum chemistry suite—MondoSCF—aimed at investigating systems containing hundreds to thousands of atoms. We are currently directing these efforts toward a coordinated advancement of (a) the application of the theory to practical cases and (b) the further development of the computational tools, to build a framework for the study of metalloproteins and metals as therapeutics.

T-12 is home to two break-through efforts on metal ions in biomolecules . . .

Notes

Page 4, top, Byron Goldstein:
Faeder et al., *J. Immunol*. **96**, 3769–3781 (2003).

Page 10, top, Alan Lapedes:
"Mapping the Antigenic and Genetic Evolution of Influenza Virus," Derek J. Smith, Alan S. Lapedes, Jan C. de Jong, Theo M. Bestebroer, Guus F. Rimmelzwaan, Albert D. M. E. Osterhaus, and Ron A. M. Fouchier, *Science* **305**, 371–376 (2004).

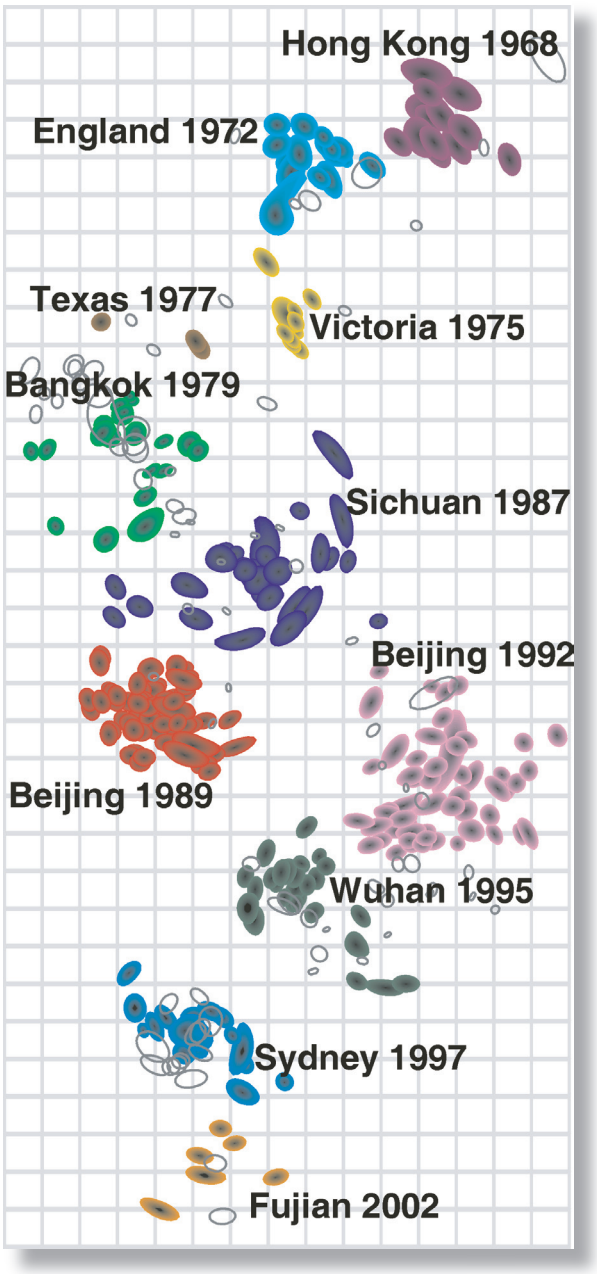
Page 12, bottom, Kim Rasmussen:
[1] C. H. Choi, G. Kalosakas. K. Ø. Rasmussen, M. Hiromura, A. R. Bishop, and A. Usheva, *Nucleic Acids Research* **32**, 1584 (2004).

Page 13, bottom, Tanmoy Bhattacharya:
With F. Gao (Duke Univ.), Brian K. Gaschen (T-10), Jesse E. Taylor (T-10), J. P. Moore (Cornell Univ.), V. Novitsky (Harvard Univ.), Karina Yusim (T-10), Dorothy M. Lang (T-10), Brian T. Foley (T-10), S. Beddows (Cornell Univ.), M. Alam (Duke Univ.), B. Haynes (Duke Univ.), B. H. Hahn (Univ. of Alabama at Birmingham), and Bette T. Korber (T-10 and Santa Fe Inst.).

Page 13, bottom, Tanmoy Bhattacharya:
Science **299,** 1517–1518, (2003). doi:10.1126/science.299.5612.1515c.

Biosciences in Theoretical Division

Theoretical Division



Shown is the antigenic map of influenza A(H3N2) virus from 1968 to 2003. The relative positions of strains (colored shapes) and antisera (uncolored open shapes) were adjusted such that the distances between strains and antisera in the map represent the corresponding HI assay measurements with the least error. The shapes represent a confidence area in the placement of the strain or antiserum in the map. Colors identify antigenic clusters of strains; the clusters were named after the first vaccine-strain in the cluster (referenced by city and date of isolation).

See page 10, top, Alan Lapedes. Figure: copyright *Science*, created by R. Fouchier.

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