VISION AND OVERVIEW OF NIST'S BIOSCIENCE AND HEALTHCARE ACTIVITIES

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Outline

- NIST History
- Early activities ….to meet societal needs
- Expansion of activities in the Biosciences
- Early 1990's Commitment to Bioscience
  - Formation of Biotech Division
- Expansion of Bioscience Activities in the late 1990's early 2000's
- The Way Forward

Early Drivers for Standards and Measurements

THE EVENING STAR, MONDAY, MARCH 11, 1901

CORRECT MEASURES

Function of the New Bureau of Standards.

LABORATORY TO BE ERECTED

Prof. Stratton, the Director, Details Need of Establishment.

A HANDICAP REMOVED

A new bureau of the government, authorized by the last Congress, will be established in this city in the near future and will give employment to a number of persons. It is to be known as the national bureau of standards and is to be under the control of the Treasury Department. A separate building for a laboratory, to cost not to exceed $250,000, is to be erected on a site to be purchased at a cost of $25,000.

Mr. Samuel W. Stratton of Chicago has been appointed by the President to be chief of the bureau at an annual salary of $5,000. Prof. Stratton is to have the following as-

Director Stratton.

National Bureau of Standards established in 1901

Early in its history, develops a reputation of being responsive to societal needs…

1904

Out-of-town fire companies arriving at a Baltimore fire cannot couple their hoses to the hydrants. 1526 buildings razed.

NBS → NIST Mission

NBS Mission: To aid U.S. manufacturing and commerce

NIST Mission 2006:

To promote U.S. **innovation** and industrial **competitiveness** by advancing measurement science, standards and technology in ways that enhance economic security and promote our quality of life

Our original mission and our mission today give us a wide berth to impact new areas related to US commerce as they develop

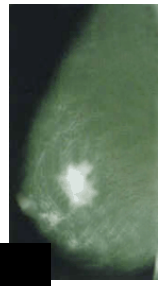
Early Bio at NBS (NIST)- Responding to a Need in Healthcare

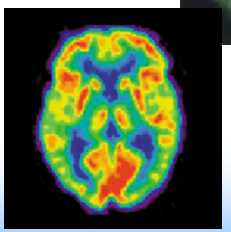
1928 - Today: NIST & the American Dental Association

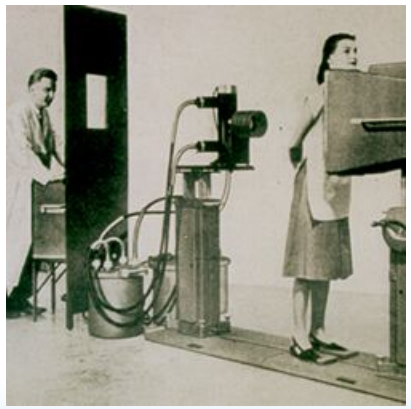
- Led to the development of mercury-free amalgams and the air-driven turbine drill now found in virtually all dentist offices

1920s - Today: NIST & Radiation Physics

- Critical program in dosimetry initially involving X-ray calibration and now standards for mammography and brachytherapy
- Radionuclide standardization for radiopharmaceuticals







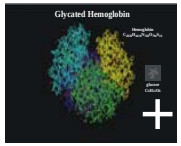
Early Bio at NBS (NIST) - Responding to a Need in Healthcare

1969 -Today: Health Status Markers in Blood/Urine

Characteristics of first markers:

- Relatively small well-defined molecular or elemental species
- Typically, can be determined using methodology well-studied and characterized by NIST for many years

Characteristics of new markers:



- Proteins, peptides or DNA-
- based
- Heterogeneity and instability of analyte form
- Low concentration in blood or urine

Marker	Disease State
Calcium	Cancer, Blood Clotting
Chloride	Kidney Function
Cholesterol	Heart Disease
Creatinine	Kidney Function
Glucose	Diabetes
Lithium	Antipsychotic Treatment
Magnesium	Heart Disease
Potassium	Electrolyte Balance
Urea	Kidney Function

Marker	Disease State
Troponin-I	Myocardial Infarction
C-Reactive Protein	Risk of Heart Attack
DNA Triplet Repeats	Fragile X Syndrome
Glycated Hemoglobin	Diabetes Status
HER2	Breast Cancer
Homocysteine	Risk of Heart Disease
TSH, T3,T4	Thyroid Function
Speciated Iron	Hemochromatosis
PSA	Prostate Cancer

Early Healthcare and Bio at NBS (NIST)

- Early efforts led to high-impact programs as a result of our ability to deliver critical physical and chemical measurement services

- Played to our greatest strength in ‘best in the world’, quantitative measurement science

- However, leading up to the 1990’s there was no organized focus for bio activities at NIST

- And in the 1980’s and 1990’s, biotechnology emerged as a new market sector with predictions that biotech would become a major player in world markets leading to a new opportunity for NIST

In the Early 1990s…

- At the request of US Senate, NIST proposed a plan for a national effort to develop measurements and standards to support the emerging biotechnology industry.
- Measurements are required at all stages of product development: research, scale up, production, QC.
- Measurements are CHEMICAL AND PHYSICAL in nature.

↓

Biotechnology Division is established

Early efforts focused on:

- Bioanalytical Separations
- Sensor Technologies
- Biophysical Chemistry
- Structural Biology
- Bioprocess Engineering

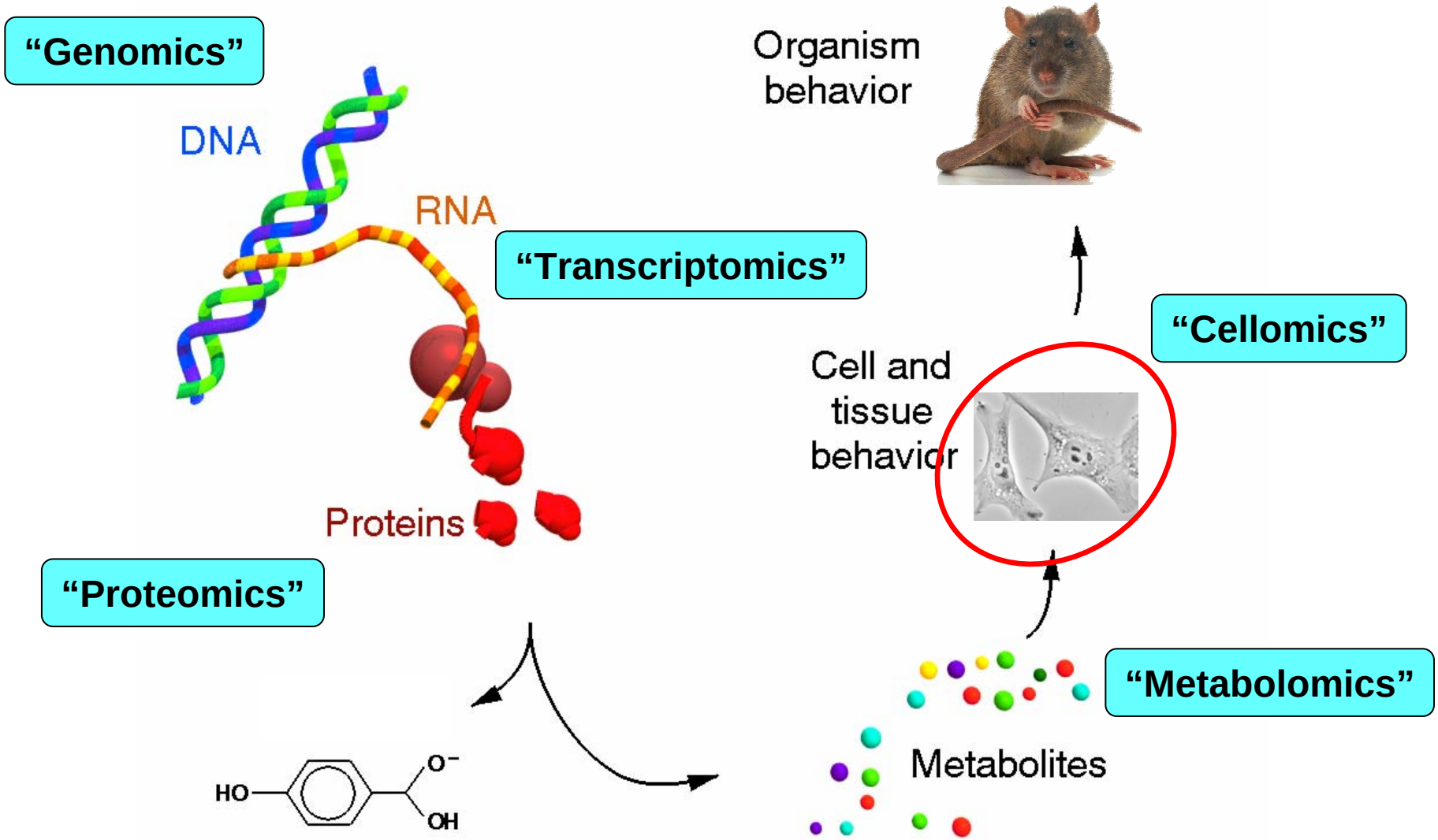
Initial NIST investment in the Biotechnology Division ~$3M (STRS) but doubled in 3 years.

The State of Biotechnology in 1991

- Pre-omics era
- Before genome was sequenced
- Biotechnology does not impact markets until late 1990s
- PCR was just starting to have broad impact-*Science* named PCR and polymerase as its first "Molecule of the Year" in 1989. Mullis wins Nobel Prize in 1993.
- Bioprocess engineering, biomedical engineering, biochemical engineering becoming established as scientific disciplines
- Starting to develop tools to support quantitative bio measurements
  - CE, PCR, automated imaging systems

"The Human Genome has been sequenced in large part owing to the invention of capillary electrophoresis." Curr Opin Biotechnol. 2003 Feb;14(1):58-64.

Biotechnology Measurements Today



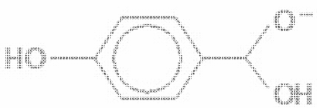
Bio-Related Activities Have Grown Throughout NIST

DNA and RNA Science
Metrology for Gene Expression
Nanobiotechnology

Marine Bioscience and Health
Metrology for Drug Delivery Systems
Standards for Food Safety and Nutrition

Cell and Tissue Measurements
Nanoparticle Imaging in Tissue
Quantitative Cell Biology

Structural Biology
Standards for Clinical Proteomics



Standards for Metabolomics

…and Continue to Grow Throughout NIST

- **Building Systems Impact on Biocontamination:** airborne release of spores; infectious disease transport in buildings **(BFRL)**
- **Bioelectronics and Biomedical Imaging:** interfacing integrated circuit technologies to biological systems; optical coherence tomography, MRI standards **(EEEL)**
- **Biometrics:** automated methods of recognizing a person based on a physiological or behavioral characteristic **(ITL)**
- **Biosurveillance, Bioinformatics, Bio-devices:** applying expertise in information modeling, information interchange and standards developed for manufacturing **(MEL)**
- **Biomaterials:** materials and delivery systems for tissue engineering and related technologies **(MSEL)**
- **Biophysics:** measuring structure, dynamics, and function of biosystems using optical and ionizing radiation and nanoprobes **(PL)**
- **Proteomics, Genomics, Cellomics:** developing standards/methods to support quantitative biological measurements (CSTL)

Why Does NIST Need to Support Bio Measurements in the 21st Century?

- Biology is becoming more and more of a quantitative science with great advances in technology

Bioimaging, biological mass spectrometry, capillary electrophoresis, microfluidics, qPCR, gene arrays, protein arrays

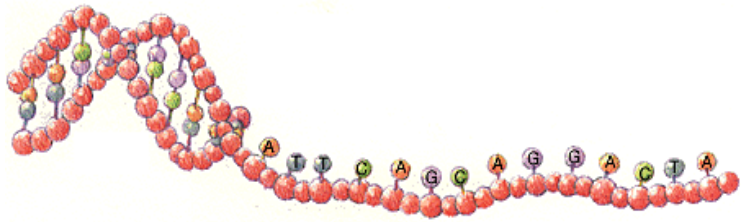
- Rapid implementation of technology has led to major discovery

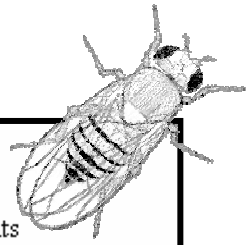
Genome sequenced!
Total serum proteins measured!
Whole cell mRNA measured!

- However, bioanalytical measurements still very difficult and results highly variable

  *example: the dna story

“Fly in the Ointment” – The DNA Story





Fly in the Ointment

When biotech firm Celera was attacked for its cockiness in vowing to sequence the human genome before university and government scientists did, the company had a powerful comeback: hey, we sequenced the fruit fly first,

found “significant discrepancies,” he reports in Nature: 45 percent of the fly genes contained serious errors (like letters in the wrong place). Celera admits its sequence “is still a work in progress.” And the human genome, which the

spring? It, too, may contain substantial errors. Oops.

Sharon Begley

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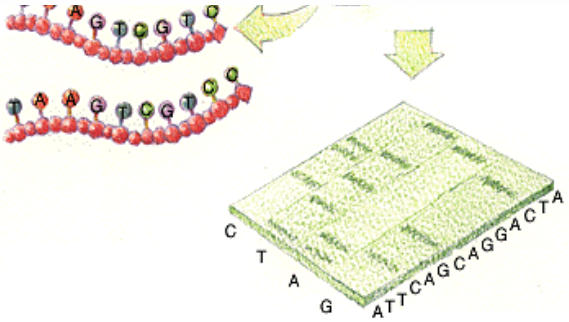
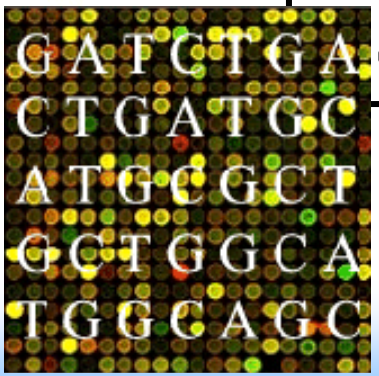
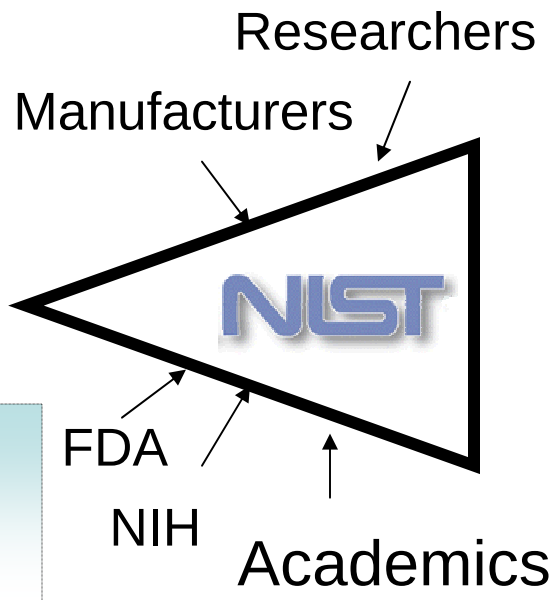




Recognizing NIST's Role as a Federal Partner in the Biosciences

Rapid advances in technology for the biosciences

Rapid use of technology leading to discovery



Federal and private partners have asked NIST to insert itself into the process to help bridge the disconnect between technology and biodiscovery

NIST's Role as a Federal Partner in the Biosciences

Rapid advances in technology for the biosciences

NIST

Rapid use of technology leading to discovery

NIST can play a critical role by building confidence in bio measurements through standards, methods, technologies

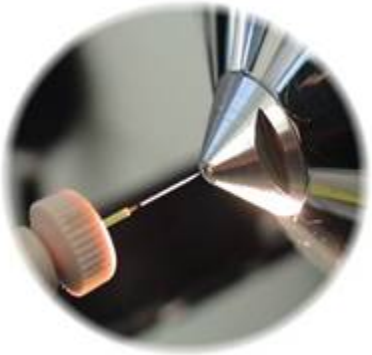
Many NIST programs have sprung out of this need ....

Proteomics

Proteomics – The Goal

*The goal of **proteomics** is to identify and quantify all proteins in the cells, tissues from an organism.*

Proteomics research can lead to development of new drug targets and identification of biomarkers of disease and treatment.



Proteomics – The Problem

"In order for proteomics to be accepted as a valid science in clinical medicine, it is vital that the experimental results be reliable and reproducible within the scientific community. The absence of these standards… is a barrier to innovation… and … delays the discovery and transfer of proteomic technologies into clinical applications."

-- Anna Barker, Deputy Director, NCI

Proteomics – The NIST Solution

- NCI has requested that NIST provide the proteomics community with a suite of proteomic standards to underpin and provide confidence in proteomics measurements

- In response to this need, NIST has initiated a strategic partnership with NCI to develop methods and standards
  - Reference methods and standards for individual proteins and simple mixtures
  - Plasma materials with assigned-values for these proteins
  - Reference mass spectra of peptide products from tryptic digests of proteins

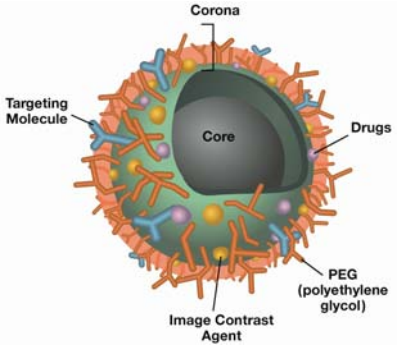
Many NIST programs have sprung out of this need ....

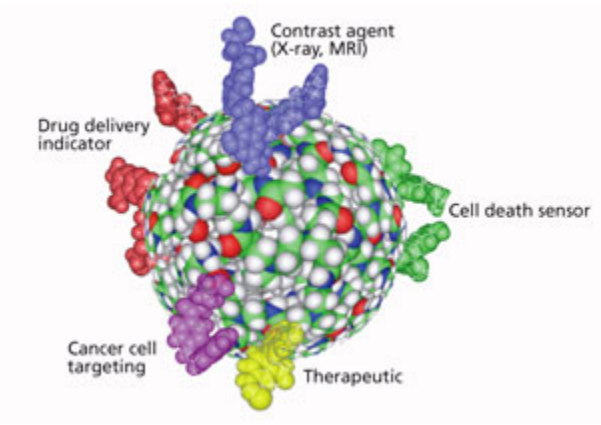
Biomedical Applications of Nanoparticles

NANOTECHNOLOGY CHARACTERIZATION LABORATORY

Biomedical Applications of Nanoparticles - The Goal

- *To transition biomedical nanotechnology research, funded since 1999 by the NCI, into the clinical realm.*
- *To realize the therapeutic benefits of nanoparticles such as improved solubility, multifunctional entities, improved pharmacokinetics, active and passive targeting, and reduced toxicity*





↑ **Solubility** ↑ **Specificity** = ↓ **Toxicity** ↑ **Efficacy**

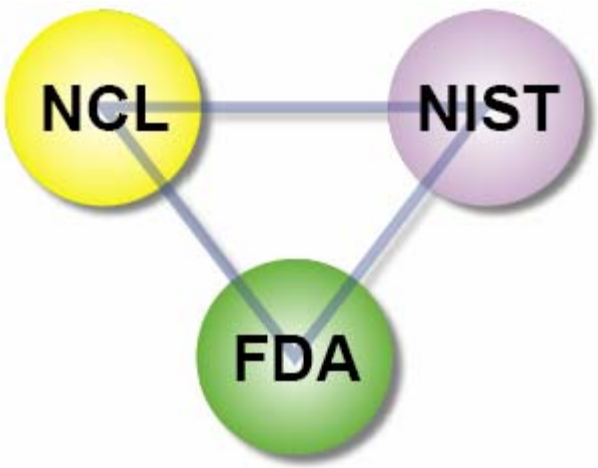
Biomedical Applications of Nanoparticles - The Problem

Before nanoparticles can be used as therapeutics:

- Need to identify and characterize critical parameters related to nanomaterials' biocompatibility; structure-activity relationships.
- Need to establish and standardize an assay cascade for nanomaterial characterization.
- Need to examine the biological characteristics of multi-component/combinatorial platforms.

The Nanotechnology Characterization Laboratory

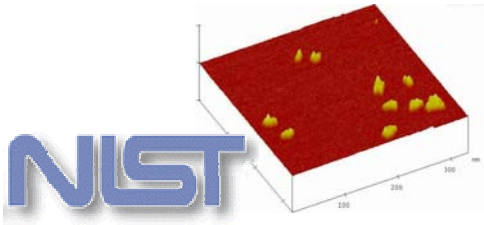
- Collaboration between NCI, NIST, US FDA
- Performs pre-clinical characterization of nanomaterials intended for cancer therapeutics and diagnostics
- Standardization of characterization methods
- Provides critical infrastructure support for Alliance



ASTM – E56 Subcommittee

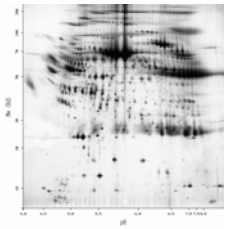
Biomedical Applications of Nanoparticles - The Solution

NCL Assay Cascade



Physico-chemical Characterization:

- Size
- Size distribution
- Topology
- Molecular weight
- Surface characteristics
- Functionality
- Composition
- Purity
- Stability



In vitro:

- Binding
- Pharmacology
- Blood contact properties
- Cellular uptake
- Toxicity

In vivo:

- Absorption
- Pharmacokinetics
- Serum half-life
- Protein binding
- Tissue distribution
- Metabolism
- Excretion

Many NIST programs have sprung out of this need ....

Healthcare IT

Healthcare Information Technology (Health IT): Goals

The President's health IT plan calls for

- *Ensuring that most Americans have electronic records within ten years*
- *Developing an internet-based Nationwide Health Information Network*

- Improve patient safety and quality of care
- Reduce costs
- Increase accessibility

Health IT: The Problem

- Inability of providers to electronically share information
- Inadequate privacy and security controls
- Lack of measurements for evaluating functionality and interoperability

Health IT: The NIST Solution

NIST partners with DHHS to realize President's health IT plan advising on security, privacy & standards

United States Department of Health & Human Services ⟷ NIST

- Collaborate with industry to define Electronic Health Records
- Collaborate with industry to develop clinical information exchange standards
- Provide standards and guidelines to help ensure security and privacy aspects in clinical information exchange

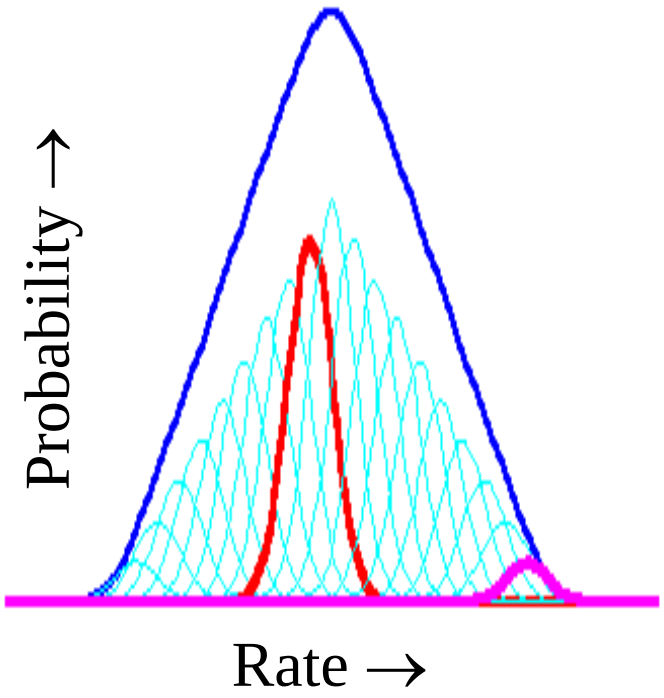
BJ Lide

Many NIST programs have sprung out of this need ....

Single Biomolecule Measurement

Single BioMolecule Measurement - The Goal

- *To perform accurate measurement of kinetics and dynamics without ensemble averaging*
- *To improve new high throughput technologies*
- *To perform rapid and reliable DNA sequencing*



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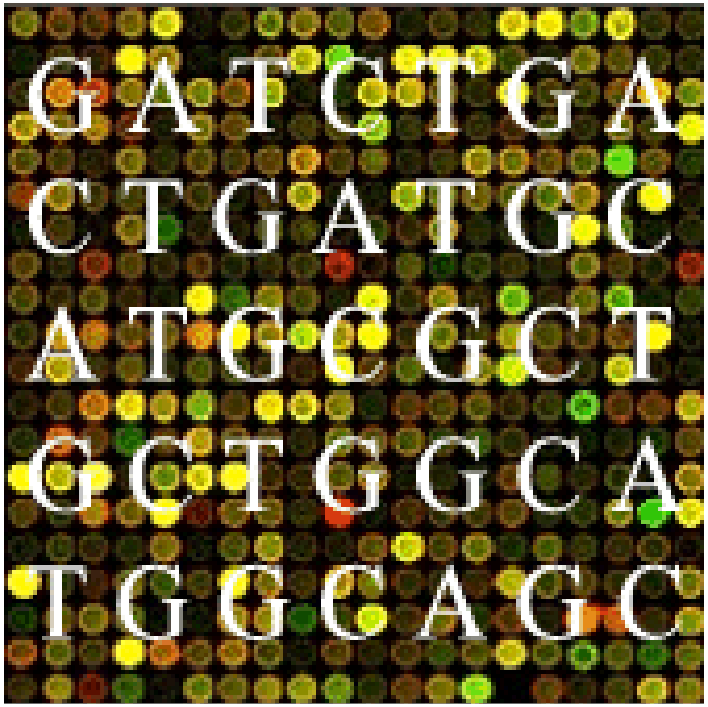

Single BioMolecule Measurement - The Goal

- *To perform accurate measurement of kinetics and dynamics without ensemble averaging*
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YUV420 codec decompressor
are needed to see this picture.

The Theoretical and Computational Biophysics Group, University of Illinois at Urbana-Champagne
http://www.ks.uiuc.edu/Research/nanopore/movies/

Single Molecule Measurement – The Problem

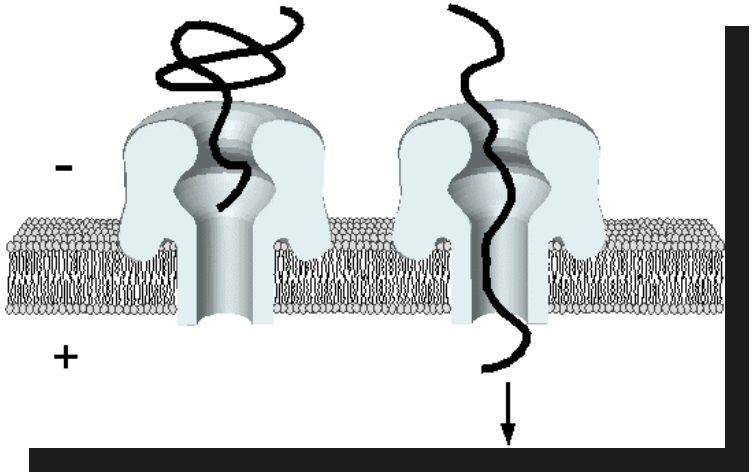
- Technologies and techniques for isolating, handling, and probing single molecules are in their infancy
- Single molecule data is difficult to acquire and interpret - requires the ultimate sensitivity and background reduction
- Need to measure a large numbers of single molecules so quickly becomes a massive data problem needing bioinformatics and biocomputing solutions

Single Molecule Measurement - The NIST Solution

To develop new cutting edge SM measurement techniques

Electronic SM Signatures

Measuring SM translocation through a biological nanopore can provide information on biopolymer size, pore size, some sequence information

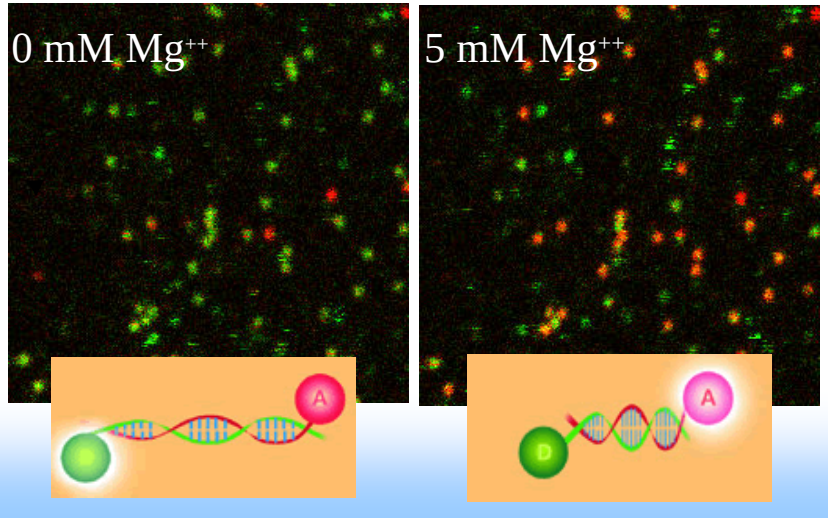


John Kasianowicz, Vince Stanford

Optical SM Signatures

Measuring optical signatures using Fluorescence Resonance Energy Transfer (FRET) can provide information on DNA, RNA, protein folding and unfolding kinetics

David Nesbitt

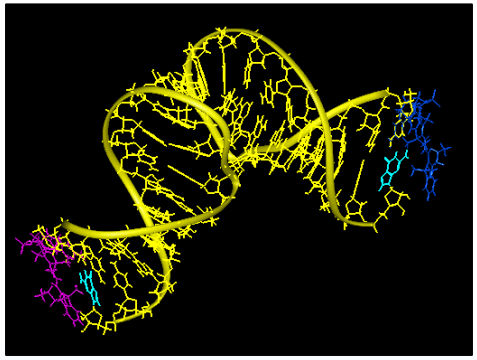


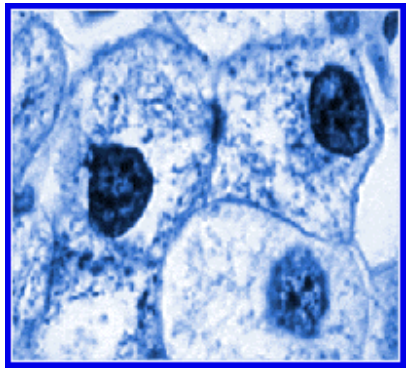
Single Molecule Measurement - The NIST Solution

- Paradigm for this work is different
- Leadership team recognized the need to push our measurement capabilities to the single molecule level to support our reputation as best in the world measurement laboratory
- Developing an expertise to contribute to a future measurement problem and a future industry
- Funded internally

Some Potential Strategic Growth Areas

- Biofuels
- Health & Environmental Effects of Nanoparticles
- Next Generation Clinical Diagnostics & Therapies
  - Bioimaging
  - Cellular Metrology
  - Subcellular Measurements
  - Nanobiosensing
  - Bioinformatics

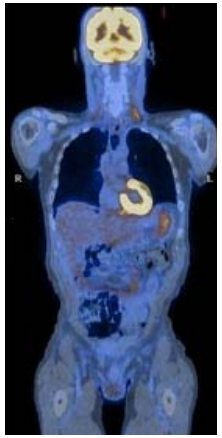




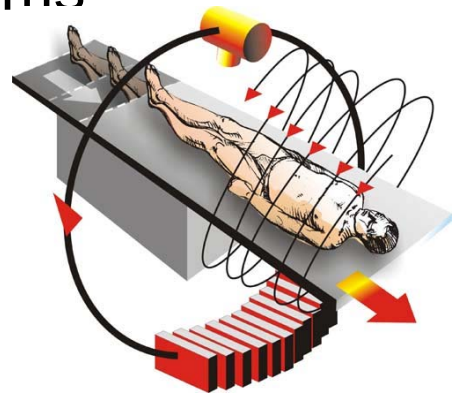
Bioimaging -
An Initiative for 2007 and Beyond

Measurement foundation to enable breakthroughs in medical imaging

Bioimaging
An Initiative for 2007 and Beyond



- Whole body/medical imaging
  - Provide support for new technologies and increase reliability of measurements made on existing; MRI contrast agents, PET radionuclide standards and phantoms; Spiral CT x-ray standards, measurements, phantoms
- Imaging software validation
  - Advances in IT for data fidelity for whole body medical imaging
- Cell and tissue
  - Development of metrology infrastructure to support these critical test systems; advanced imaging methodologies, standards, validated protocols



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NIST & Bio

- NIST programs in bio started small and have grown into large multi-lab, multi-institutional efforts
- Bio efforts around NIST have historically been largely by invitation - *passive and responsive*
- Over the past 5 years, NIST has initiated efforts in strategic growth areas to develop critical expertise to impact future - *forward thinking*
- Engaged in the development of a comprehensive vision for bio at NIST

The New Challenges in Bio

- Biology can be a quantitative science
- But there is a barrier to innovation and discovery if measurement results are not reliable, transferable
- Measurement problems are not trivial
  - Biological structures are complex - modified, heterogeneous, dynamic, unstable
  - Important biological markers may be present at the single copy/single molecule level requiring ultimate sensitivity/specificity

A Biovision for NIST

To leverage our vast expertise in the quantitative physical and informational sciences to provide the measurement infrastructure to underpin innovation in the biosciences

We do this by

- *Strengthening partnerships with the medical, environmental and agricultural communities*
- *Growing our in-house knowledge of interdisciplinary bio-related fields*
- *Teaching our federal and private partners in the biotechnology/healthcare fields about NIST's broad capabilities and strengths*

Joint Institutes at NIST

Center for Advanced Research in Biotechnology

A partnership between NIST and University of Maryland

Research in fundamental problems at the forefront of biotechnology focusing on structural biology, bioinformatics, proteomics, plant and insect transformation

JILA

A partnership between NIST and the University of Colorado

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Center for teaching and research in atomic, chemical, optical, laser, gravitational, and solar physics; semiconductors; precision measurement; astrophysics; astronomy; and now bioscience

Hollings Marine Laboratory

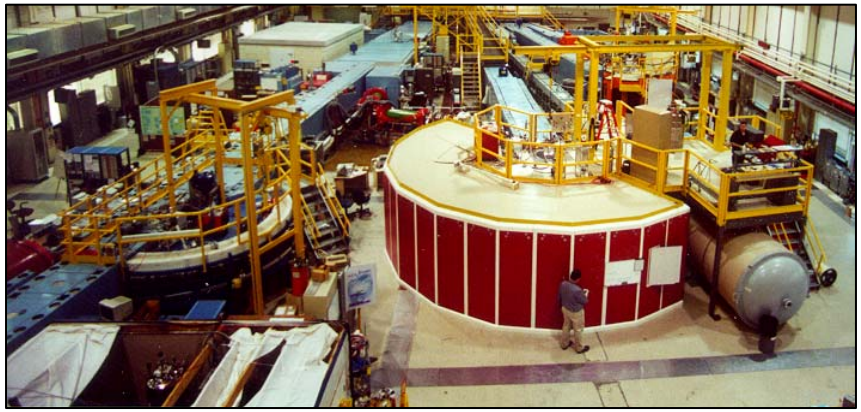
A partnership between NIST, NOAA College of Charleston, Medical University of South Carolina

Research in science and biotechnology to understand linkages between environmental condition and the health of marine organisms and humans

NIST
National Institute of Standards and Technology

Other Unique Resources in Bio

The NIST Center for Neutron Research (NCNR)



The best U.S. capability for studies of biological dynamics because of low background and high sensitivity. Only neutron capability designed as research facility.