Intelligent Systems and Computational Biology

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Intelligent Systems and Computational Biology

- **Artificial Intelligence for Biology and Medicine**
  - **Biology is data-rich and knowledge-hungry**
  - **AI is well suited to biomedical problems**

- **Examples**
  - Machine learning -- drug discovery
  - Rule-based systems – drug-resistant HIV
  - Heuristic search -- protein structure prediction
  - Constraints – design of large synthetic genes

- **Current Project**
  - Machine learning and p53 cancer rescue mutants

- **Goal of talk: The power of information science to influence molecular science and technology**

Goal of talk: The power of information science to influence molecular science and technology

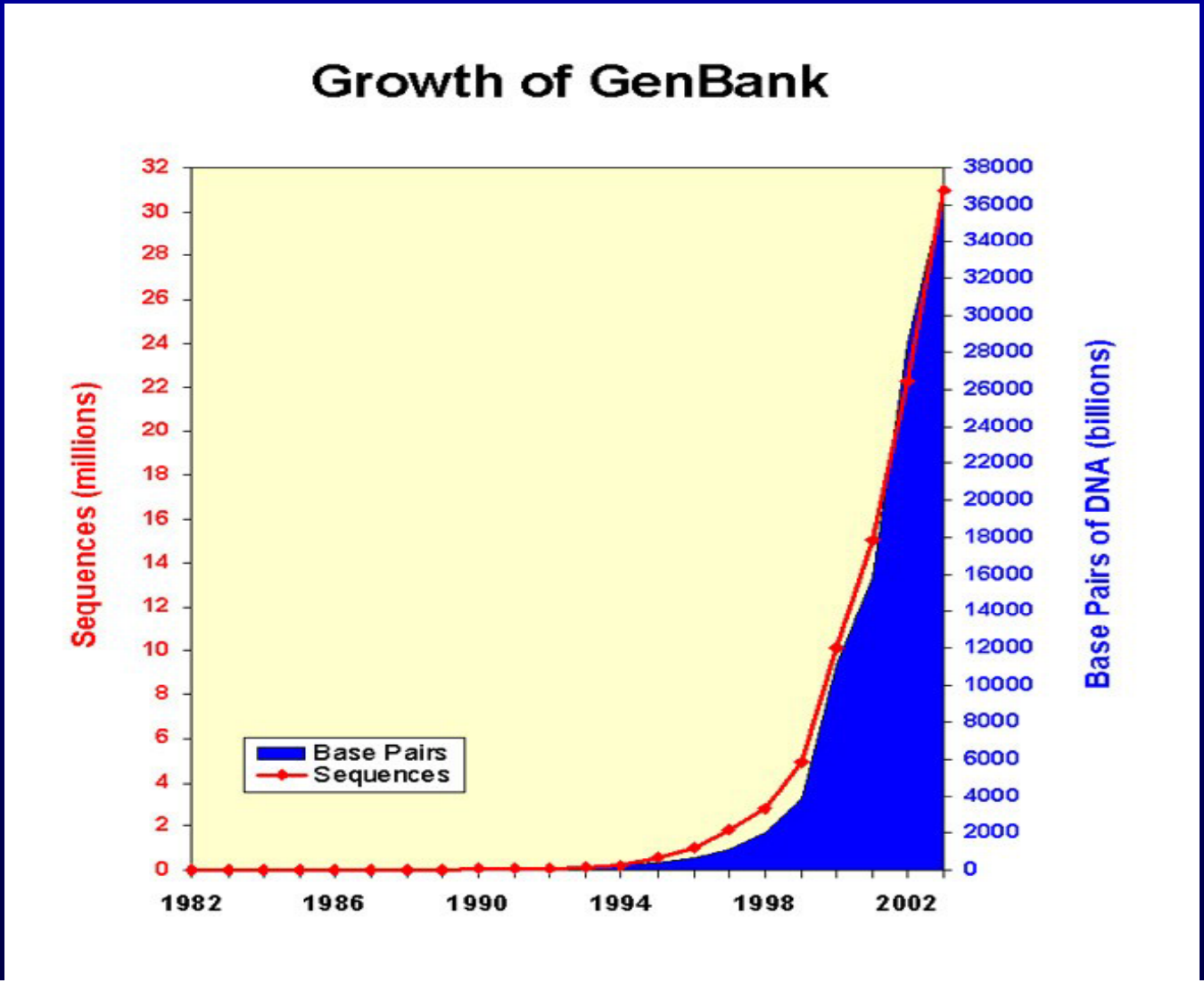
"Computers are to Biology as Mathematics is to Physics."

--- Harold Morowitz
(spiritual father of BioMatrix, and Intelligent Systems for Molecular Biology Conference)

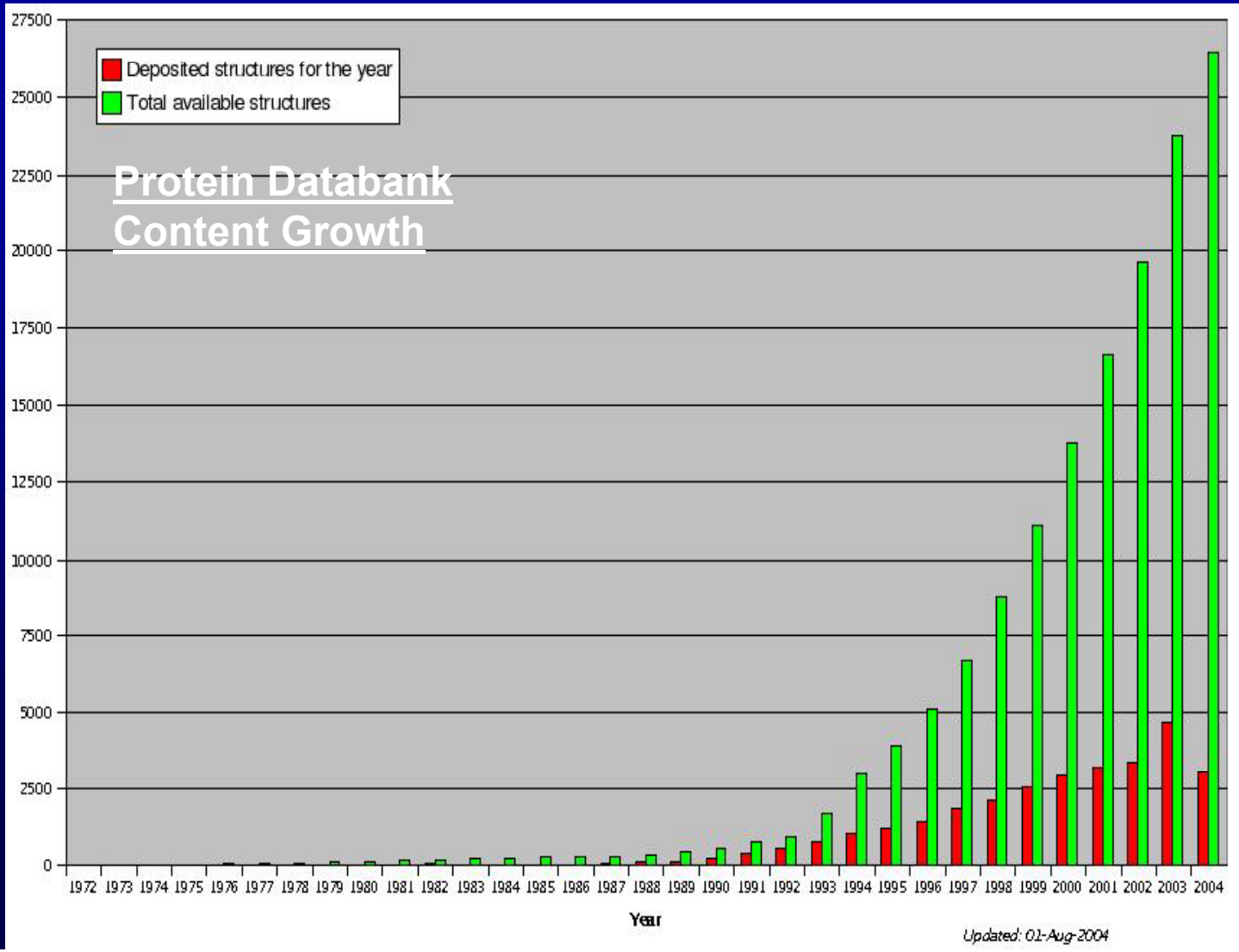
Biology has become Data Rich

- Massively Parallel Data Generation
  - Genome-scale sequencing
  - High-throughput drug screening
  - Micro-array “gene chips”
  - Combinatorial chemical synthesis
  - “Shotgun” mutagenesis
  - Directed protein evolution
  - Two-hybrid protocols for protein interaction
  - Half a million biomedical articles per year

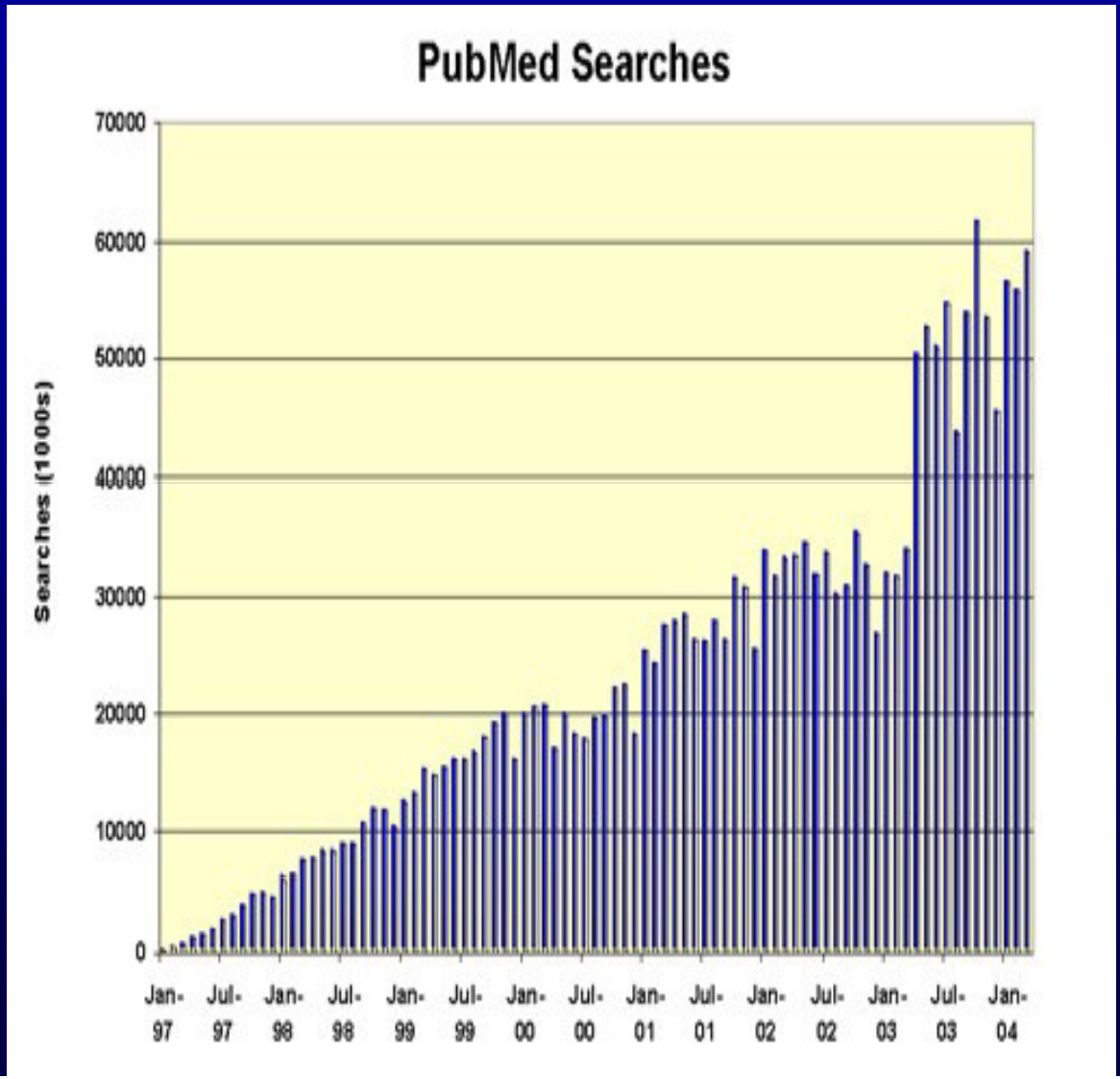
“Data Rich”
Genomic sequence data



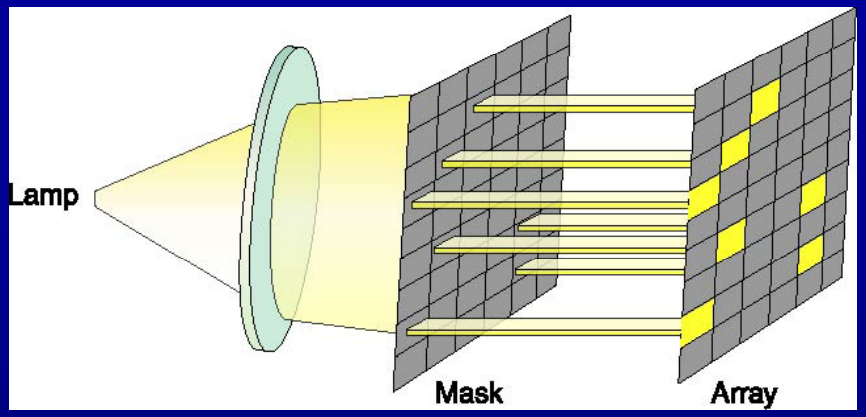
“Data Rich”
Protein 3D structure data

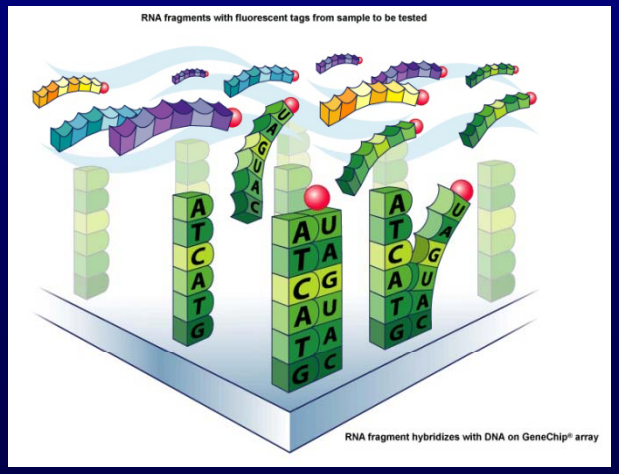


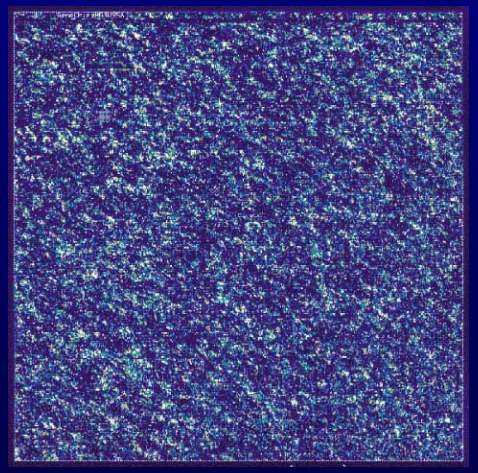
“Data Rich” Biomedical literature



“Data Rich”
10-100K data points per gene chip







Characteristics of Biomedical Data

- Noise!!
  - => need robust analysis methods
- Little or no theory.
  - => need statistics, probability
- Multiple scales, tightly linked.
  - => need cross-scale data integration
- Specialized (“boutique”) databases
  - => need heterogeneous data integration

Intelligent Systems are well suited to biology and medicine

- Robust in the face of inherent complexity
- Extract trends and regularities from data
- Provide models for complex processes
- Cope with uncertainty and ambiguity
- Content-based retrieval from literature
- Ontologies for heterogeneous databases
- Machine learning and data mining

- Intelligent systems handle complexity with grace

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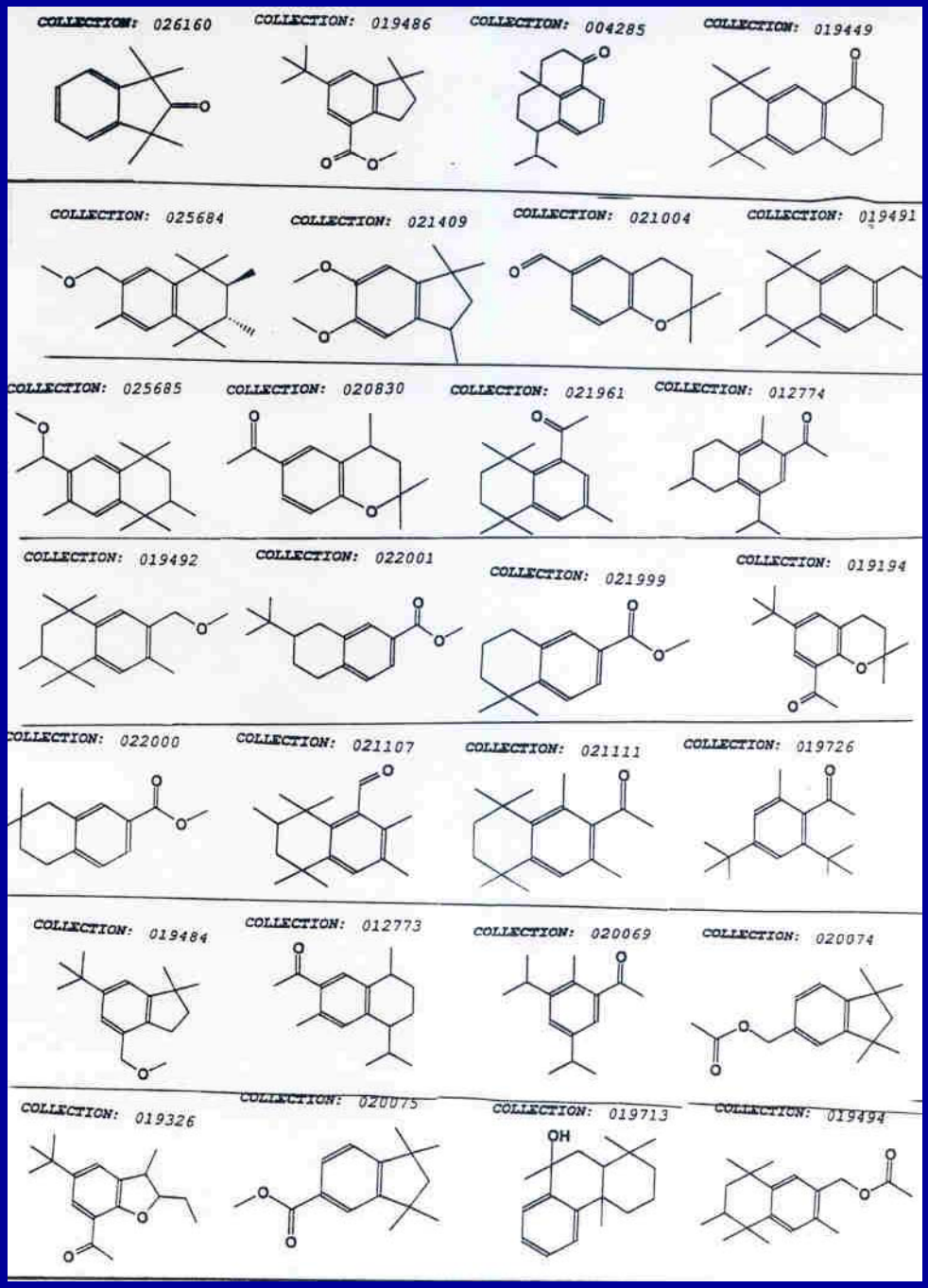
Drug Discovery Background

- Cost and time, per drug, start to finish
  - US$500 million to US$1 billion
  - 6 to 12 years
  - High failure rate
- “Blockbuster” drugs
  - Revenues > US$1 billion/year
  - Profits > US$1 million/day
  - Blood pressure, ulcers, ….
- A risky business….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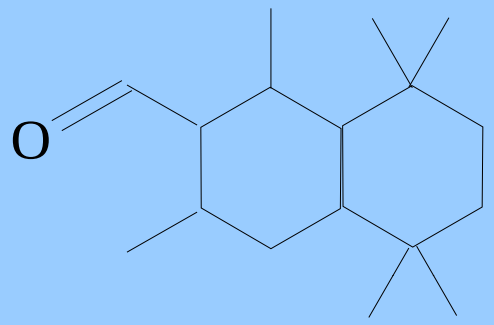
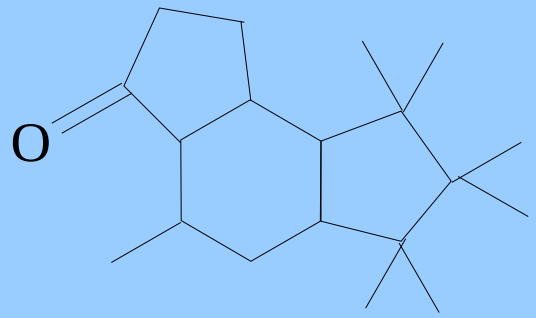
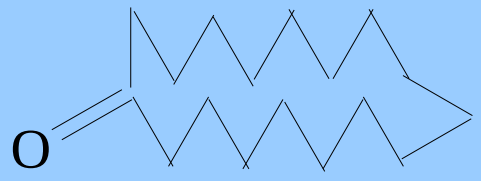
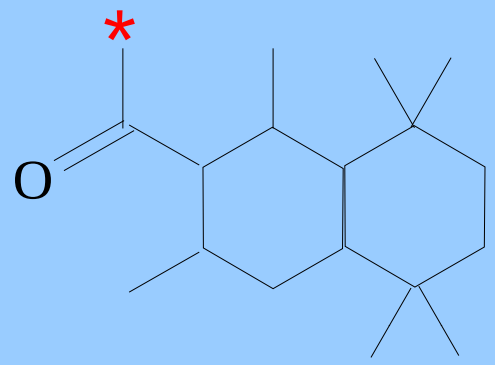
COLLECTION: 019449
COLLECTION: 025684
COLLECTION: 021409
COLLECTION: 021004
COLLECTION: 019491
COLLECTION: 025685
COLLECTION: 020830
COLLECTION: 021961
COLLECTION: 012774
COLLECTION: 019492
COLLECTION: 022001
COLLECTION: 021999
COLLECTION: 019194
COLLECTION: 022000
COLLECTION: 021107
COLLECTION: 021111
COLLECTION: 019726
COLLECTION: 019484
COLLECTION: 012773
COLLECTION: 020069
COLLECTION: 020074
COLLECTION: 019326
COLLECTION: 020075
COLLECTION: 019713
OH
COLLECTION: 019494

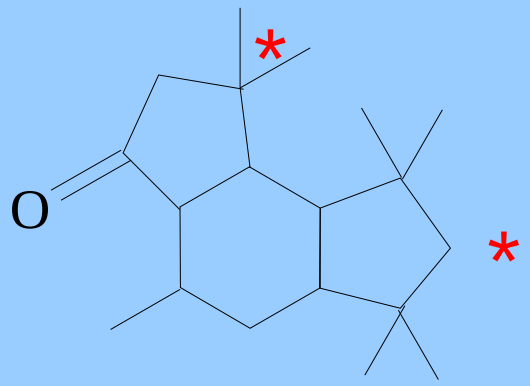
Positive Examples | Negative Examples



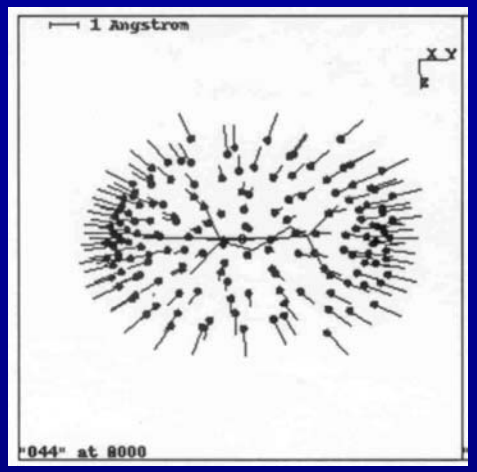


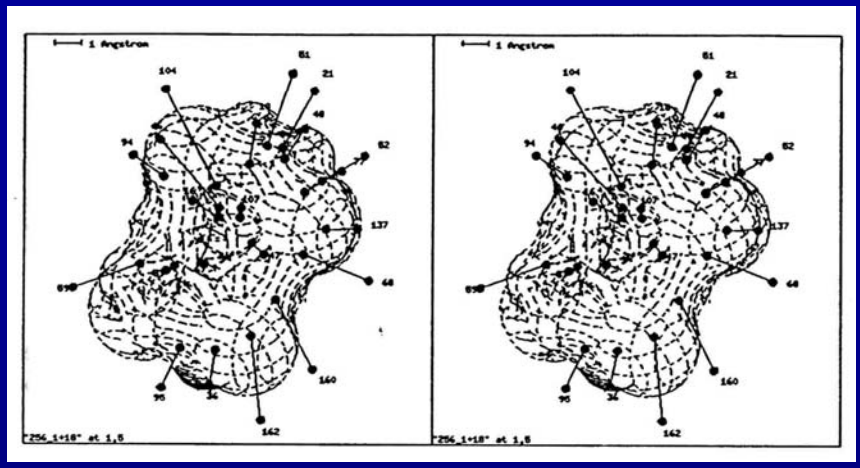


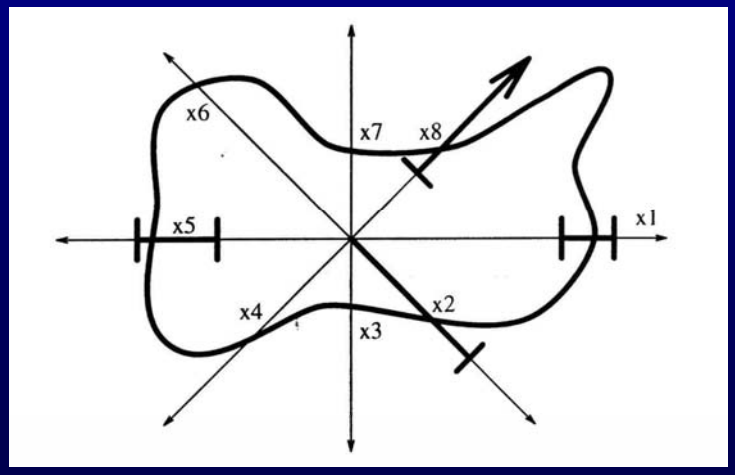


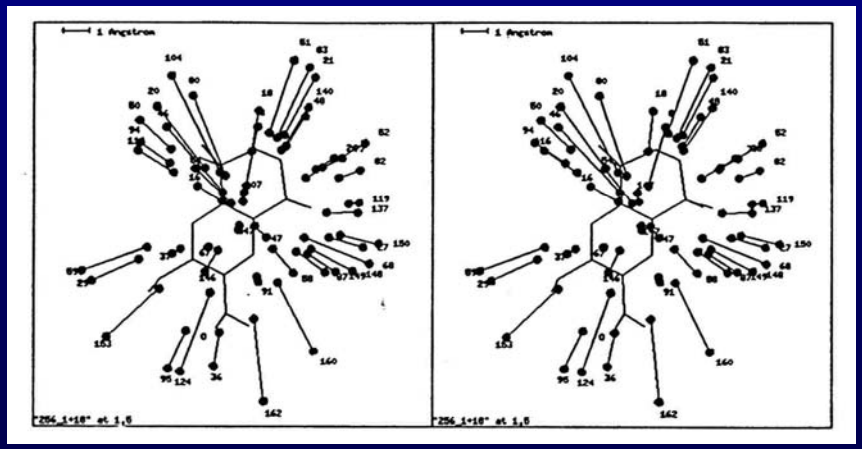


Digital 3D Shape Representation

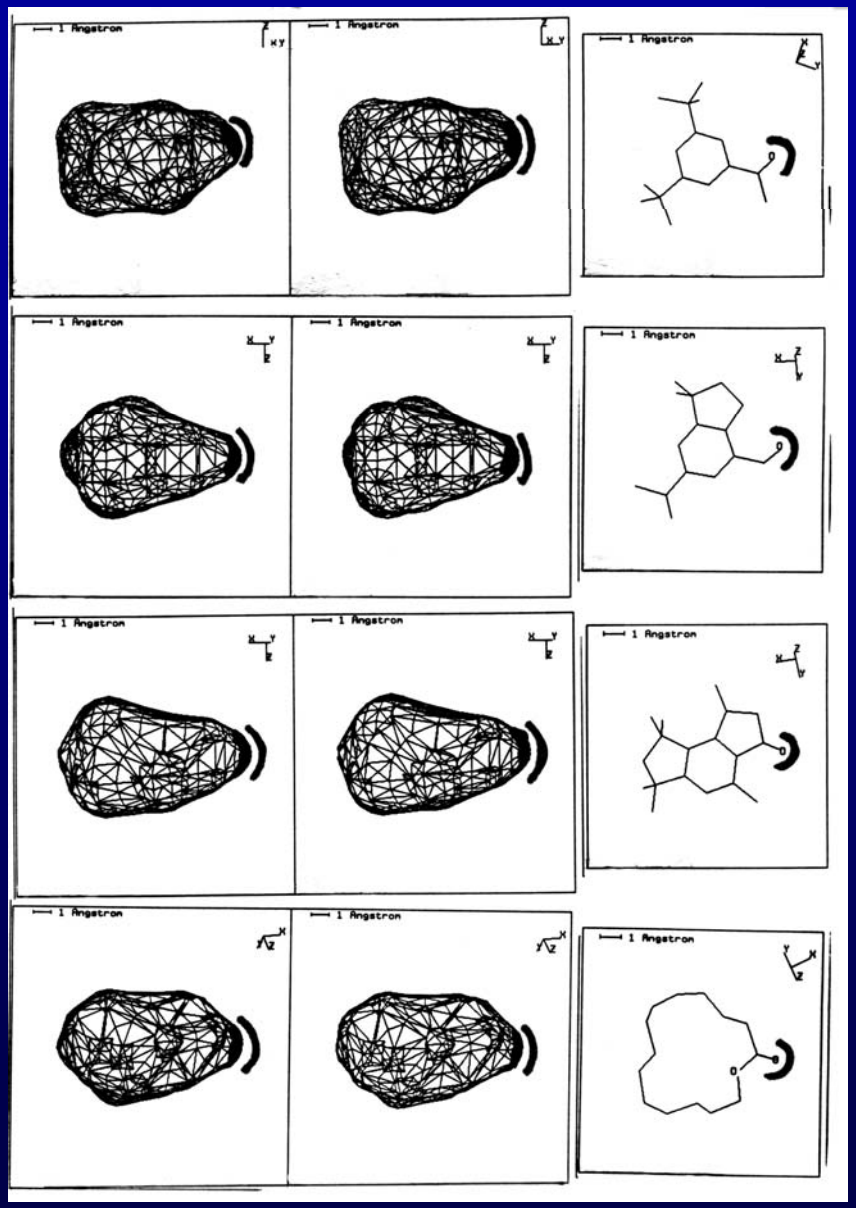




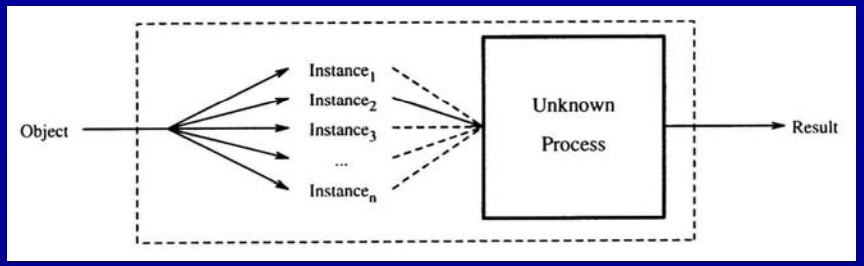


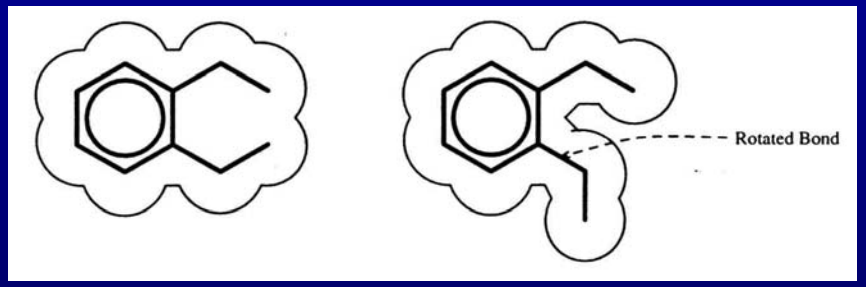


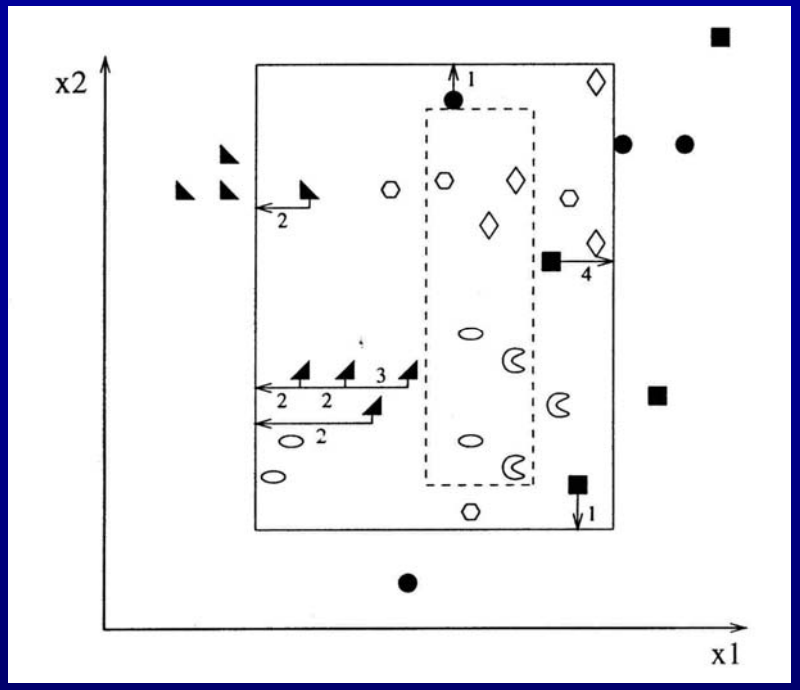
The Power of a Good Representation



Learning the “Multiple Instance” Problem







“Solving the multiple instance problem with axis-parallel rectangles”

Dietterich, Lathrop, Lozano-Perez, Artificial Intelligence 89(1997) 31-71

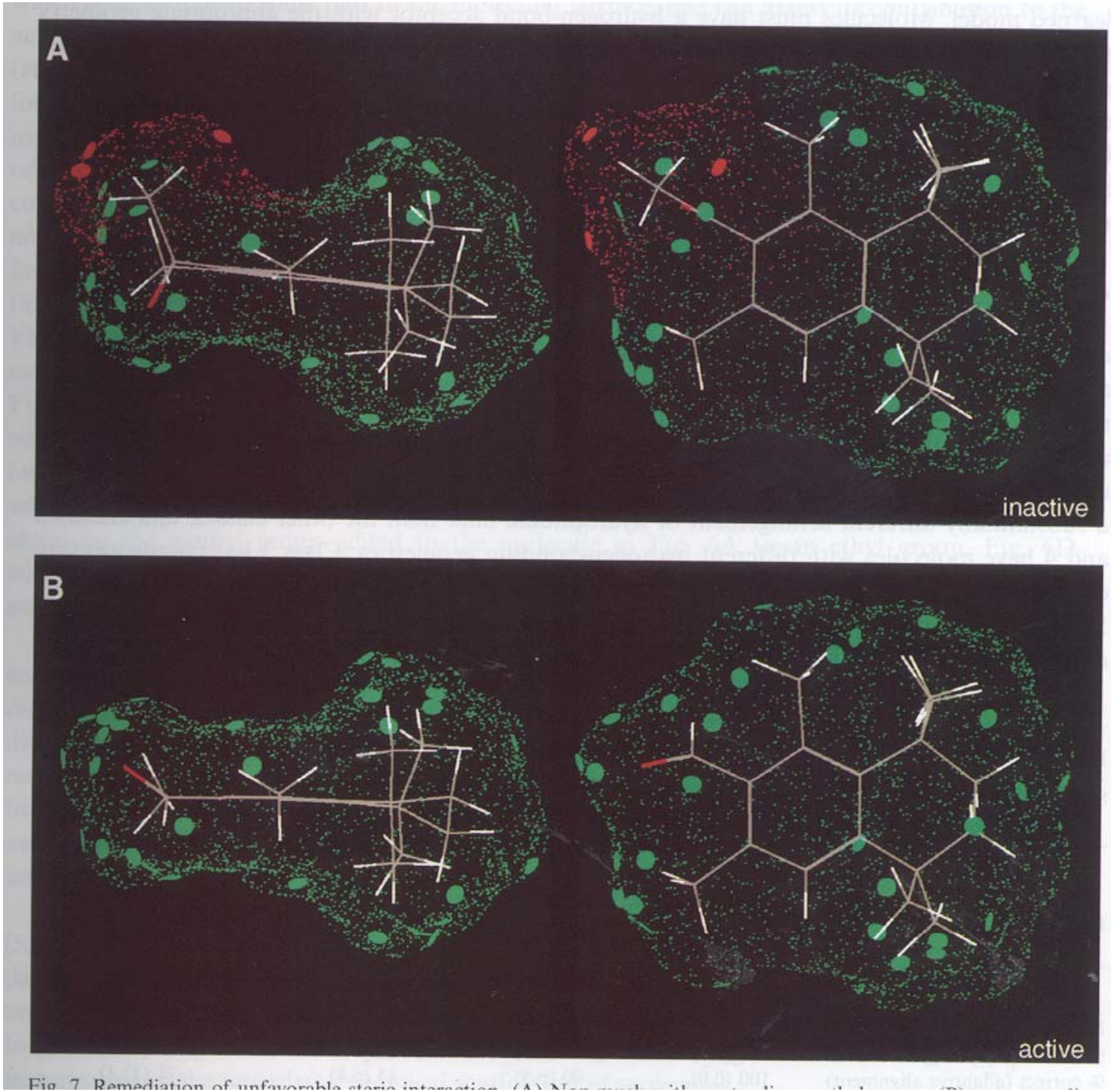


Fig. 7. Remediation of unfavorable steric interaction. (A) Non-[illegible]

"Compass: A shape-based machine learning tool for drug design," Jain, Dietterich, Lathrop, Chapman, Critchlow, Bauer, Webster, Lozano-Perez,

J. Of Computer-Aided Molecular Design, 8(1994) 635-652

New Start-up Company: Arris Pharmaceutical Corp.

- Started a Venture Pharmaceutical Company
  - Apply machine learning to drug discovery
- Became a Publicly Traded Company (1993)
  - Value of $60 Million, 59 Full-time Employees
- Merged with Sequana Pharmaceuticals (1998)
  - Merger result became Axys Pharmaceuticals
- Finally bought by Celera Genomics (2001)
  - Purchase price $188 Million
  - Became Celera Therapeutics

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Knowledge-based avoidance of drug-resistant HIV mutants

- Physician's advisor for drug-resistant HIV
- Rules link HIV mutations & drug resistance
- Rules extracted from literature manually
- Patient's HIV is sequenced
- Rules identify patient-specific resistance
- Rank approved combination treatments

Input/Output Behavior

- INPUT = HIV SEQUENCES FROM PATIENT:
  - 5 HIV clones (clone = RT + PRO)
  - = 5 RT + 5 PRO (RT = 1,299; PRO = 297)
  - = 7,980 letters of HIV genome
- OUTPUT = RECOMMENDED TREATMENTS:
  - 12 = 11 approved drugs + 1 humanitarian use
  - Some drugs should not be used together
  - 407 possible approved treatments

Example Patient Sequence of HIV Reverse Transcriptase (RT)

CCA GTA AAA TTA AAG CCA GGA ATG GAT GGC CCA AAA GTT AAA CAA TGG CCA CCC ATT AGC CCT
ATT GAG ACT GTA TTG ACA GAA GAA AAA ATA AAA GCA TTA GTA GAA ATT TGT ACA GAG ATG GAA
AAG GAA GGG *AA ATT TCA AAA ATT GGG CCT GAA AAT CCA TAC AAT ACT CCA GTA TTT GCC ATA
AAG AAA AAA GAC AGT ACT AAA TGG AGA AAA TTA GTA GAT TTC AGA GAA CTT AAT AAG AGA ACT
CAA GAC TTC TGG GAA GTT CAA TTA GGA ATA CCA CAT CCC GCA GGG TAA AAA AAG AAA AAA TCA
GTA ACA GTA CTG GAT GTG GGT GAT GCA TAT TTT TCA GTT CCC TTA GAT GAA GAC TTC AGG AAG
TAT ACT GCA TTT ACC ATA CCT AGT ATA AAC AAT GAG ACA CCA GGG ATT AGA TAT CAG TAC AAT
GTG CTT CCA [CAG] GGA TGG AAA GGA TCA CCA GCA ATA TTC CAA AGT AGC ATG ACA AAA ATC TTA
GAG CCT TTT AGA AAA CAA AAT CCA GAC ATA GTT ATC TAT CAA TAC ATG GAT GAT TTG TAT GTA
GGA TCT GAC TTA GAA ATA GGG GAG CAT AGA ACA AAA ATA GAG GAG CTG AGA CAA CAT CTG TTG
AGG TGG GGA CTT ACC ACA CCA GAC AAA AAA CAT CAG AAA GAA CCT CCA TTC CTT TGG ATG GGT
TAT GAA CTC CAT CCT GAT AAA TGG ACA GTA CAG CCT ATA GTG CTG CCA GAA AAA GAC AGC TGG
ACT GTC AAT GAC ATA CAG AAG TTA GTG GGG AAA TTG AAT TGG GCA AGT CAG ATT TAC CCA GGG
ATT AAA GTA AGG CAA TTA TGT AAA CTC CTT AGA GGA ACC AAA GCA CTA ACA GAA GTA ATA CCA
CTA ACA GAA GAA GCA GAG CTA GAA CTG GCA GAA AAC AGA GAG ATT CTA TAA GAA CAA GTA CAT
GGA GTG TAT TAT GAC CCA TCA AAA GAC TTA ATA GCA GAA ATA CAG AAG CAG GGG CAA GGC CAA
TGG ACA TAT CAA ATT TAT CAA GAG CCA TTT AAA AAT CTG AAA ACA GGA AAA TAT GCA AGA ATG
AGG GGT GCC CAC ACT AAT GAT GTA AAA CAA ATA ACA GAG GCA GTG CAA AAA ATA ACC ACA GAA
AGC ATA GTA ATA TGG TGA AAG ACT CCT AAA TTT AAA CTG CCC ATA CAA AAG GAA ACA TGG GAA
ACA TGG TGG ACA GAG TAT TGG CAA GCC ACC TGG ATT CCT GAG TGG GAG TTT GTT AAT ACC CCT
CCC ATA GTG AAA TTA TGG TAC CAG TTA GAG AAA GAA CCC

The bracketed codon [CAG] causes strong resistance to AZT.

Rules represent knowledge about HIV drug resistance

IF <antecedent> THEN <consequent>
[weight] (reference).

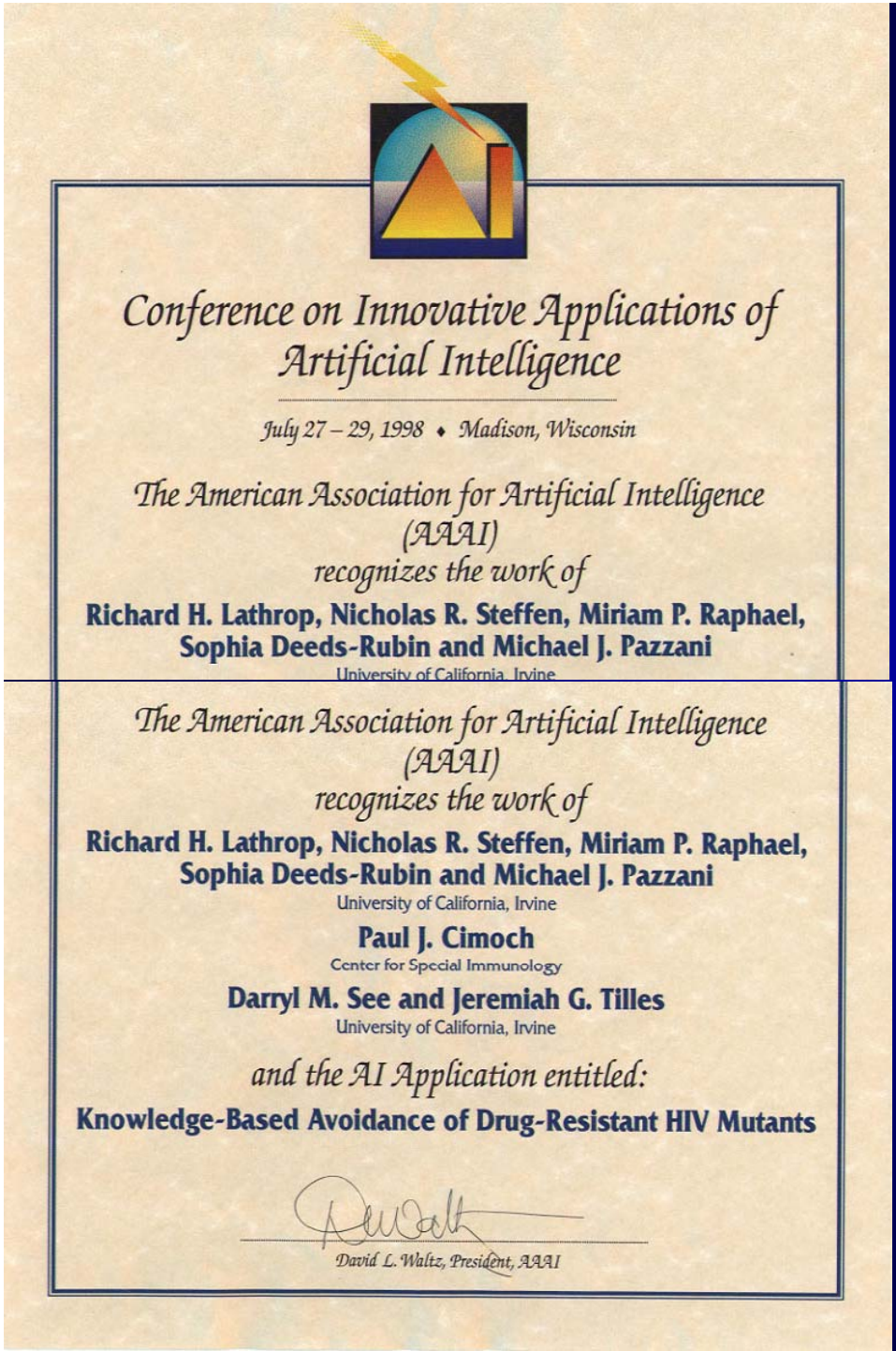
IF RT codon 151 is ATG

THEN do not use AZT, ddI, d4T, or ddc.

[weight=1.0] (Iversen et al. 1996)

The weight is the degree of resistance,

NOT a confidence or probability.



Conference on Innovative Applications of Artificial Intelligence

July 27 – 29, 1998 ♦ Madison, Wisconsin

The American Association for Artificial Intelligence (AAAI) recognizes the work of

Richard H. Lathrop, Nicholas R. Steffen, Miriam P. Raphael, Sophia Deeds-Rubin and Michael J. Pazzani

University of California, Irvine

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Paul J. Cimoch

Center for Special Immunology

Darryl M. See and Jeremiah G. Tilles

University of California, Irvine

and the AI Application entitled:

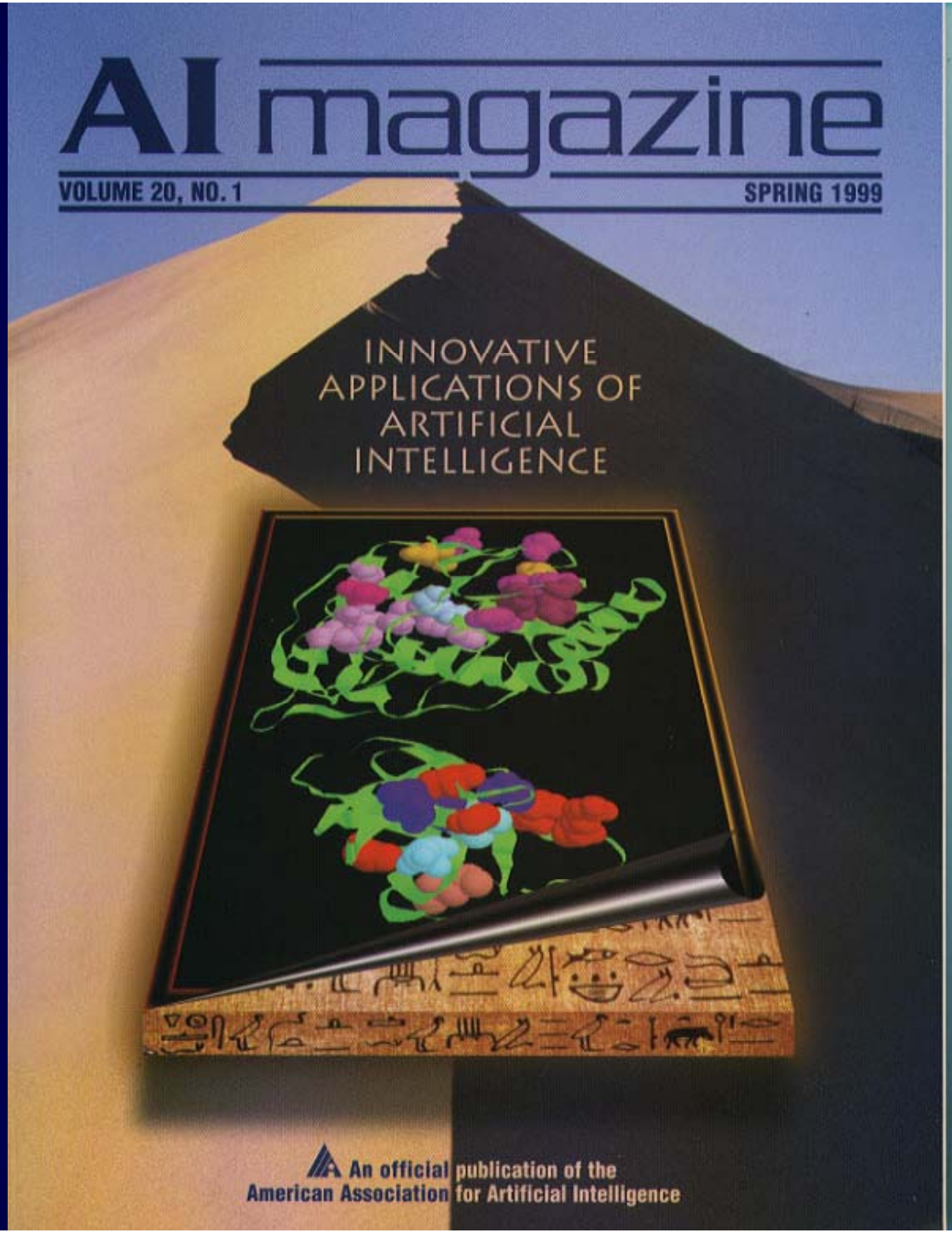
Knowledge-Based Avoidance of Drug-Resistant HIV Mutants

David L. Waltz, President, AAAI

"Knowledge-based avoidance of drug-resistant HIV mutants"

Lathrop, Steffen, Raphael, Deeds-Rubin, Pazzani

Innovative Applications of Artificial Intelligence Conf. Madison, WI, USA, 1998



"Knowledge-based avoidance of drug-resistant HIV mutants"

Lathrop, Steffen, Raphael, Deeds-Rubin, Pazzani, Cimoch, See, Tilles

AI Magazine 20(1999)13-25

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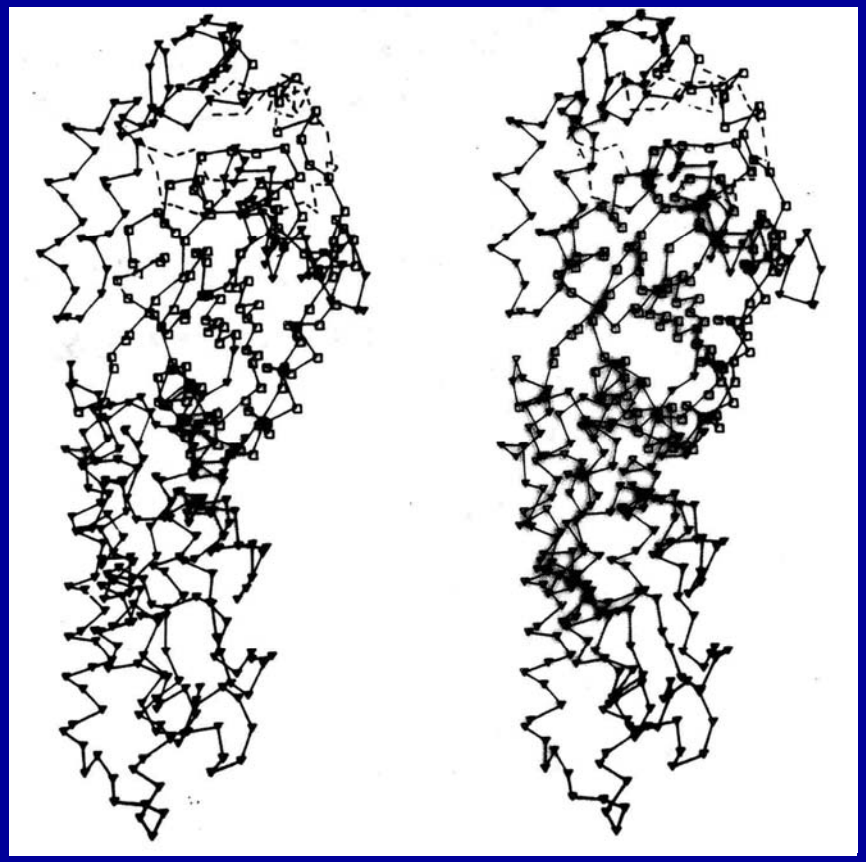
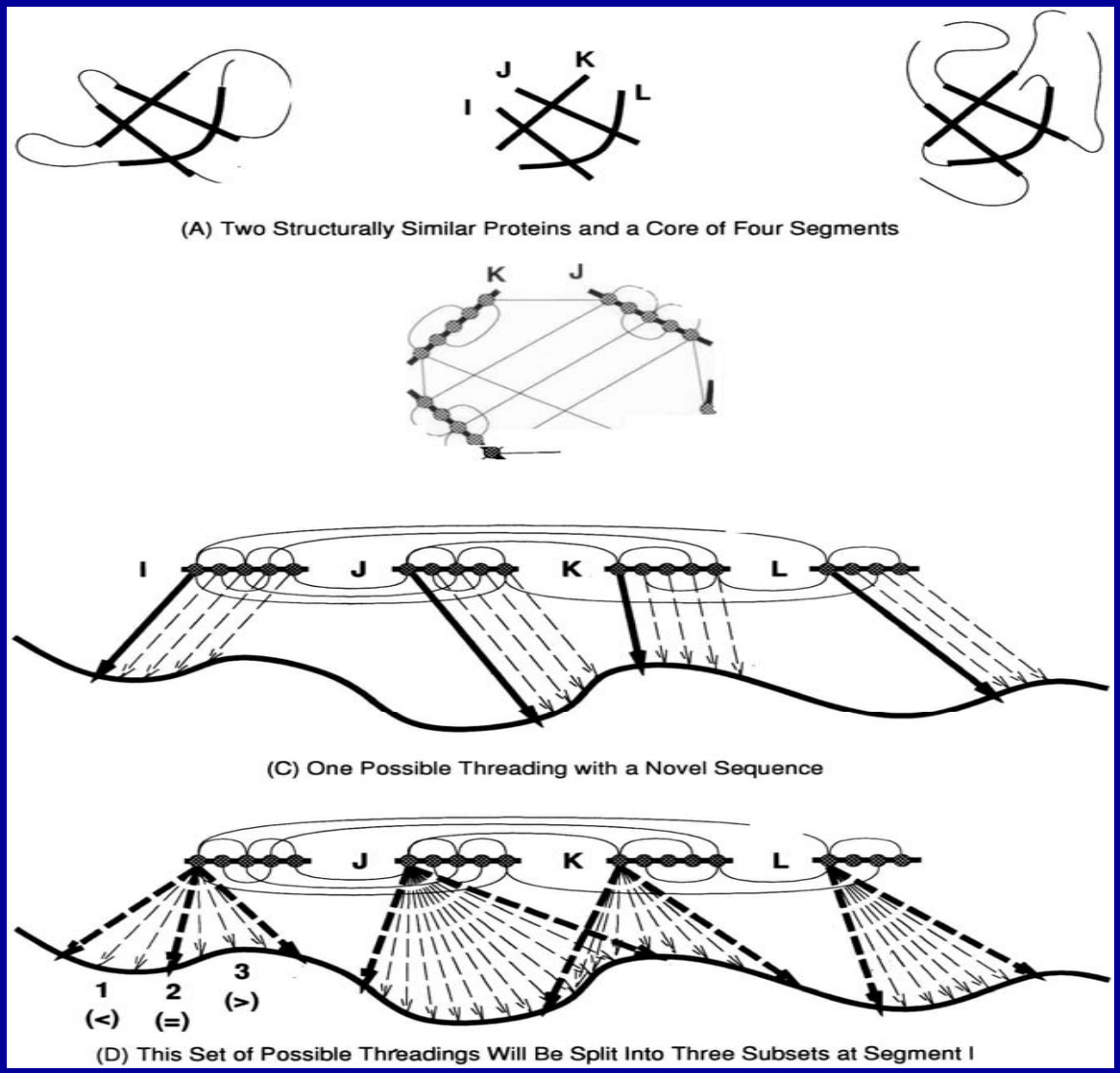
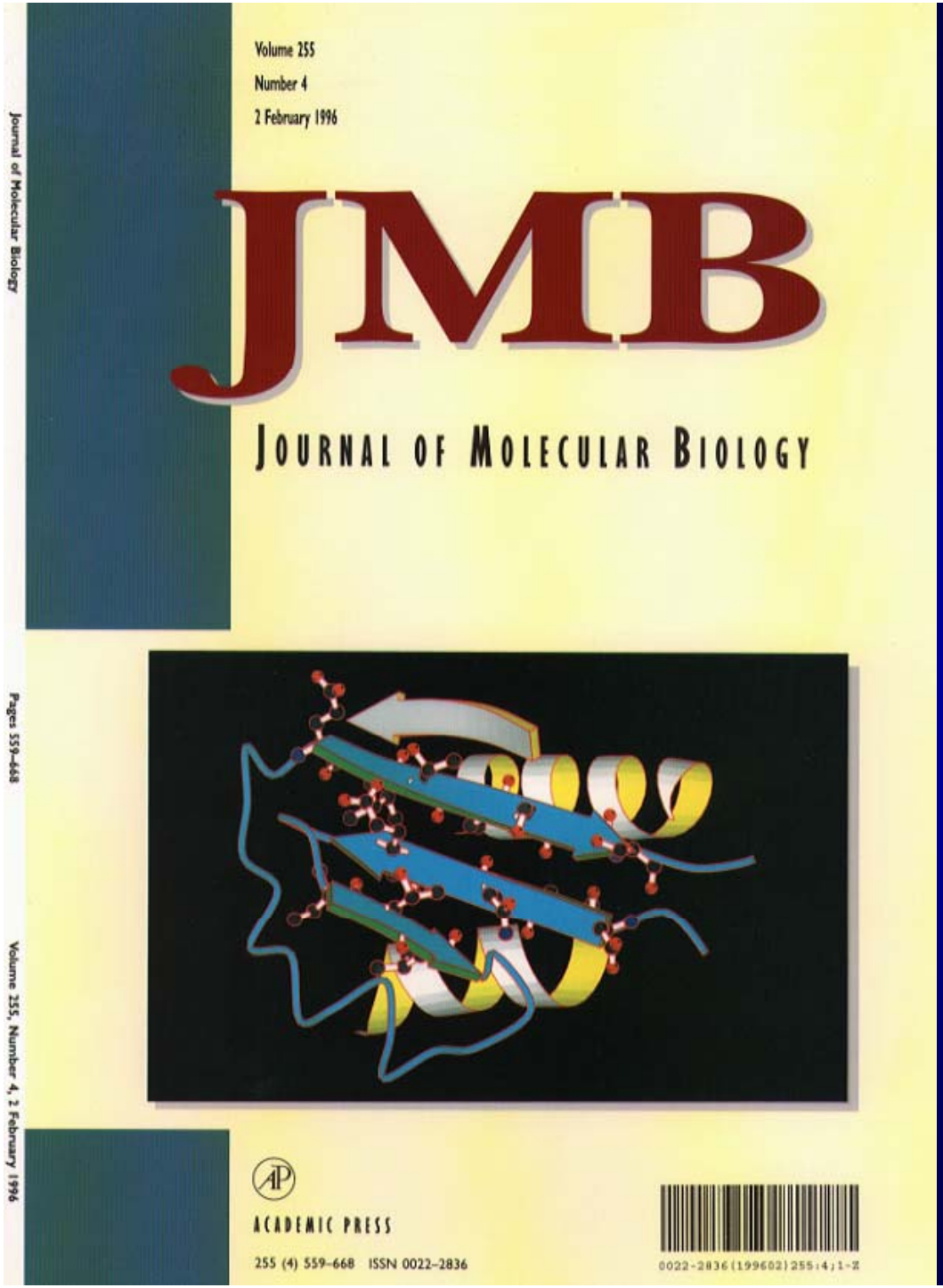
Protein structure prediction

TQVAKKILVTCALPYANGSIHLGHMLEHIQADVWVRYQRMRG
HEVNFICADDAHGTPIMLKAQQLGITPEQMIGEMSQEHQTDF
AGFNISYDNYHSTHSEENRQLSELIYSRLKENGFIKNRTISQLY
DPEKGMFLPDRFVKGTCPKCKSPDQYGDNCEVCGATYSPTEL
IEPKSVVSGATPVMRDSEHFFFDLPSFSEMLQAWTRSGALQEQ
VANKMQEWFESGLQQWDISRDAPYFGFEIPNAPGKYFYVWLD
APIGYMGSFKNLCDKRGDSVSFDEYWKKDSTAELYHFIGKDI
VYFHSLFWPAMLEGSNFRKPSNLFVHGYVTVNGAKMSKSRGT
FIKASTWLNHFDADSLRYYYTAKLSSRIDDIDLNLEDFVQRVN
ADIVNKVVNLASRNAGFINKRFDGVLASELADPQLYKRFTDA
AEVIGEAWESREFGKAVREIMALADLANRYVDEQAPWVVAK
QEGRDADLQAIAQWGINLFRVLMTYLKPVLPKLTERAEAFLN
TELTWDGIQQPLLGHKVNPFKALYNRIDMRQVEALVEASKEE
VKAAAAPVTGPLADDPQDGCGRHDRVVDSGSK



“Protein Threading”





"Global Optimum Protein Threading with Gapped Alignment and Empirical Pair Score Functions"

Lathrop and Smith

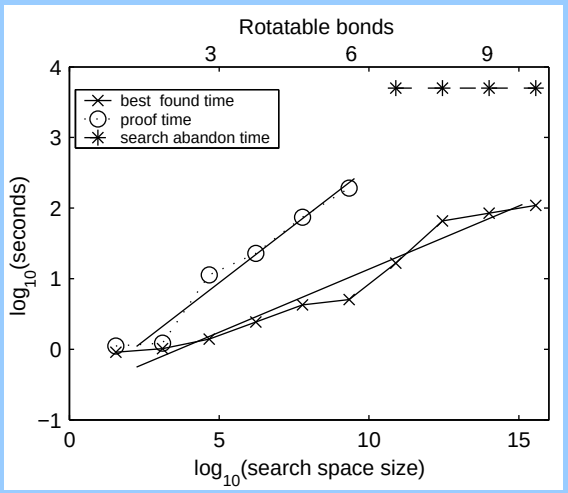
J. Mol. Biol. 255(1996)641-665

Multi-queue Branch-and-Bound

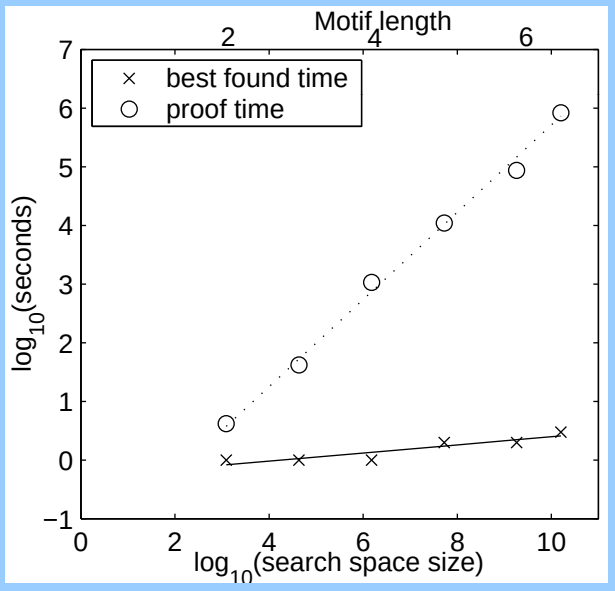
- Originally developed for protein structure prediction by “protein threading”
- Abstracted to a general-purpose method
  - Have also run on SAT, Traveling Salesman
  - Small molecule conformation search, DNA motif discovery, DNA nanotechnology, synthetic gene design and assembly
- Difficult applications inspire new techniques. New techniques enable other applications.

Optimal Exponent < Proof Exponent

Small organic molecule conformation search



Protein-DNA binding motif search



X axis = log10(search space size), Y axis = log10(time in seconds)

“x” = time to best result, “o” = time to optimal, “*“ = search abandoned

The Best Paper Award

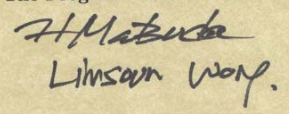
The Twelfth International Conference on Genome Informatics
(GIW 2001)
December 17–19, 2001
Tokyo

◇

Authors: Richard H. Lathrop, Anton Sazhin, Ye Sun, Nick Steffen, and Sandra S. Irani

Title: A Multi-Queue Branch-and-Bound Algorithm for Anytime Optimal Search with Biological Applications

GIW 2001
The Program Committee Co-Chairs



Organized and Sponsored by
Japanese Society for Bioinformatics JSBi
Grant-in-Aid for Scientific Research "Genome Information Science", MEXT of Japan
Bioinformatics Center, Institute for Chemical Research, Kyoto University
Human Genome Center, Institute of Medical Science, University of Tokyo

"A multi-queue branch-and-bound algorithm for anytime optimal search with biological applications"

Lathrop, Sazhin, Sun, Steffen, Irani

Genome Informatics 12(2001)73-82

GIW'2001, Tokyo, Japan

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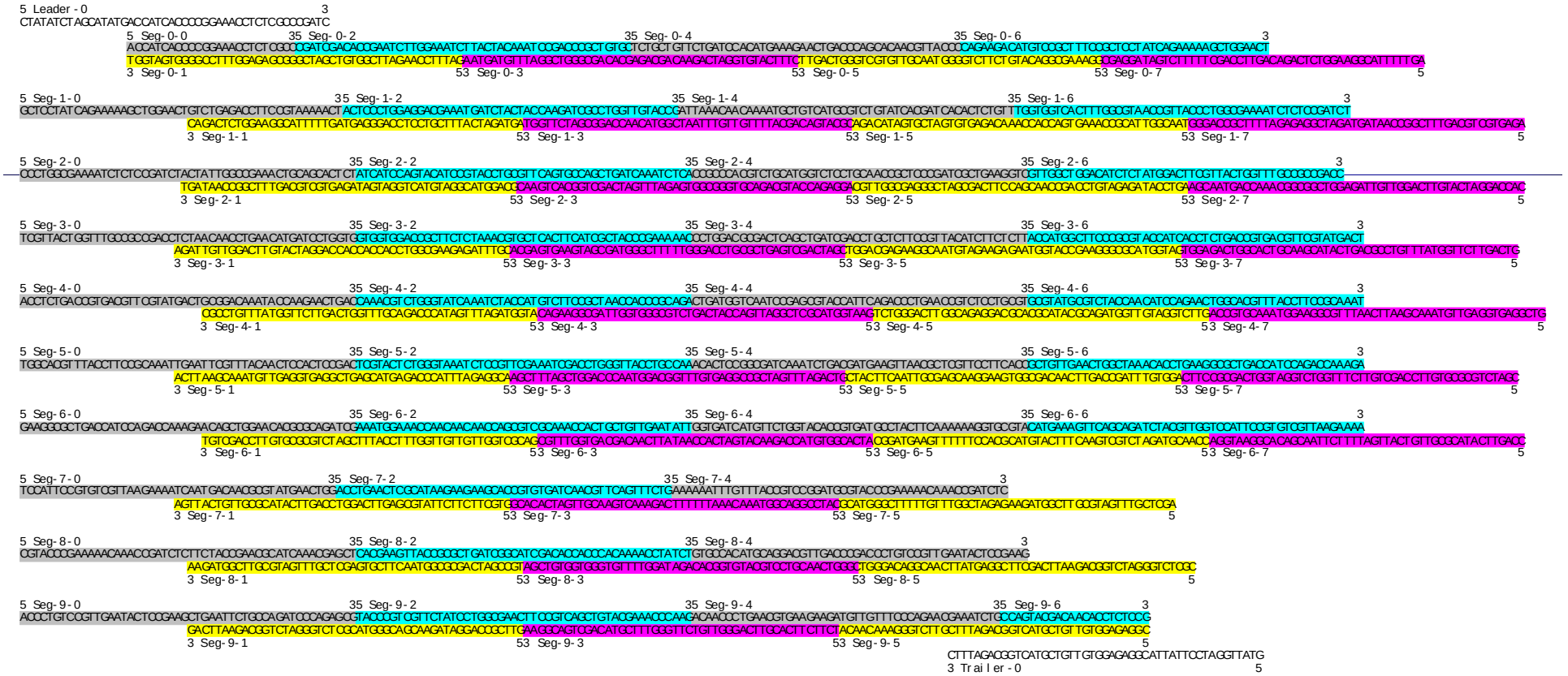
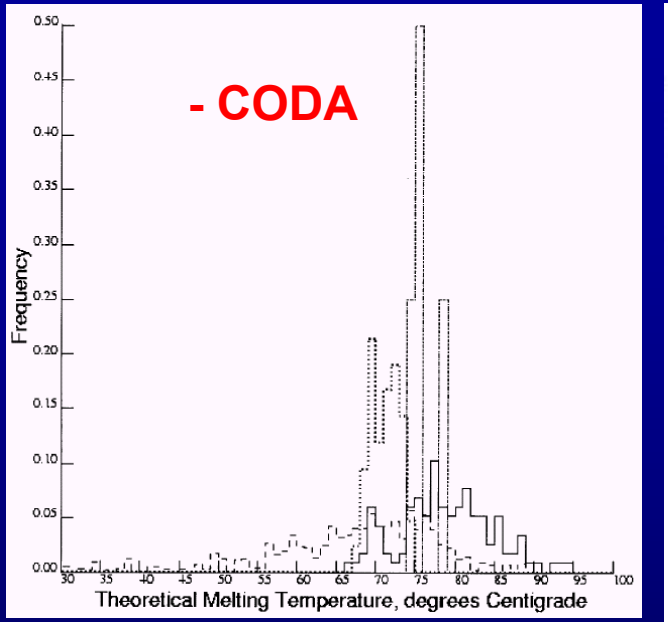
Current Application: Synthetic gene design

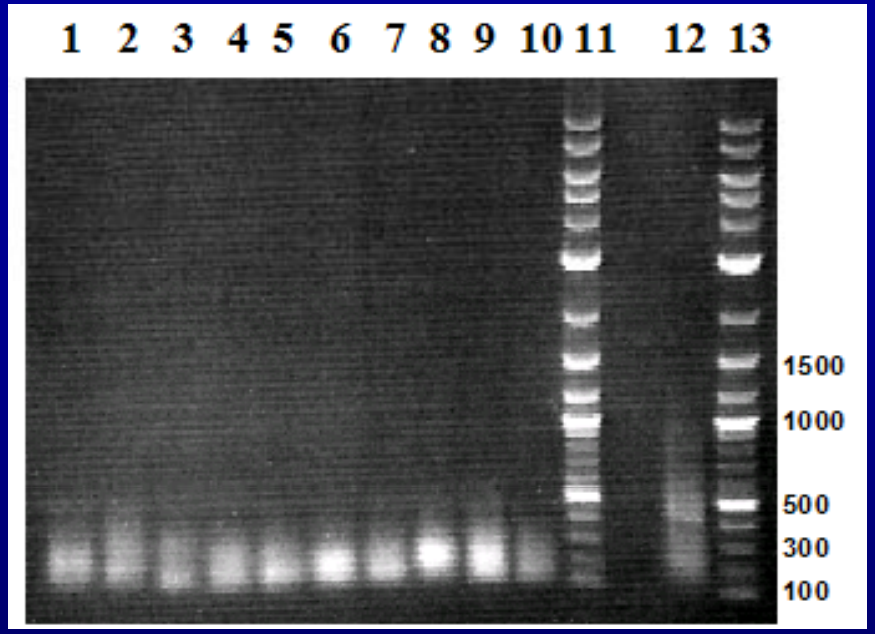
- Constraint-based search through sequence space
- Constraints guarantee correct self-assembly and other desirable properties
- Underlying domain-specific computation done on a 64-node cluster of 3GHz Xeon dual processors

Assembly of Integrase Gene (1640 bp)



Problem: Melting Temperatures of correct and incorrect hybridization assemblies overlap

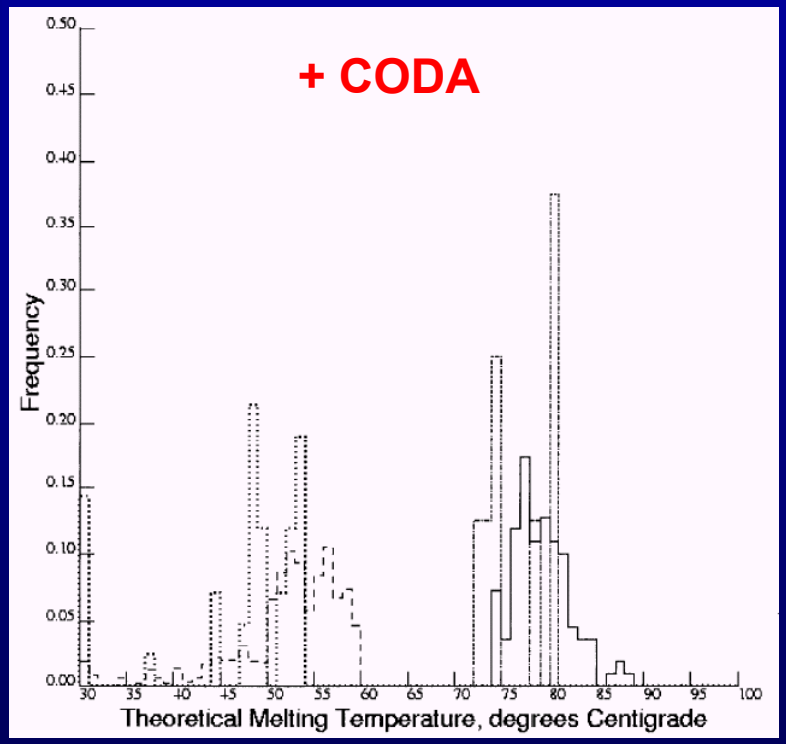


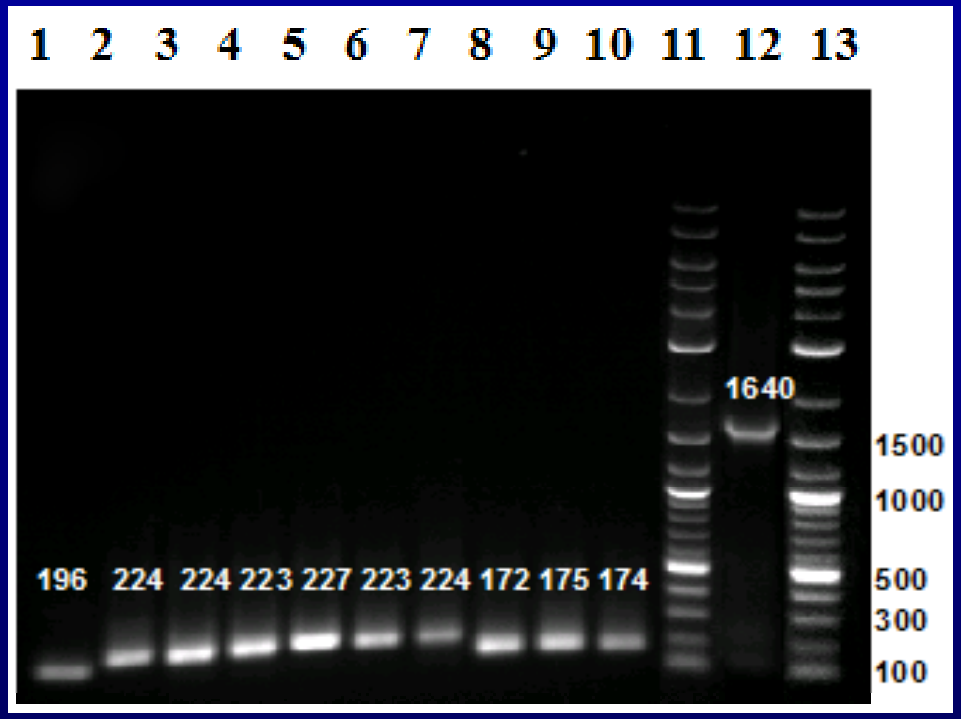


solid: correct overlap of oligos
dashdot: correct overlap of intermediate fragments
dashed: incorrect overlap of small oligos
dotted: incorrect overlap of intermediate fragments

Result: Intermediate assemblies contain multiple fragments and error products (smears above)

Solution: Fragments designed with non-overlapping melting temps

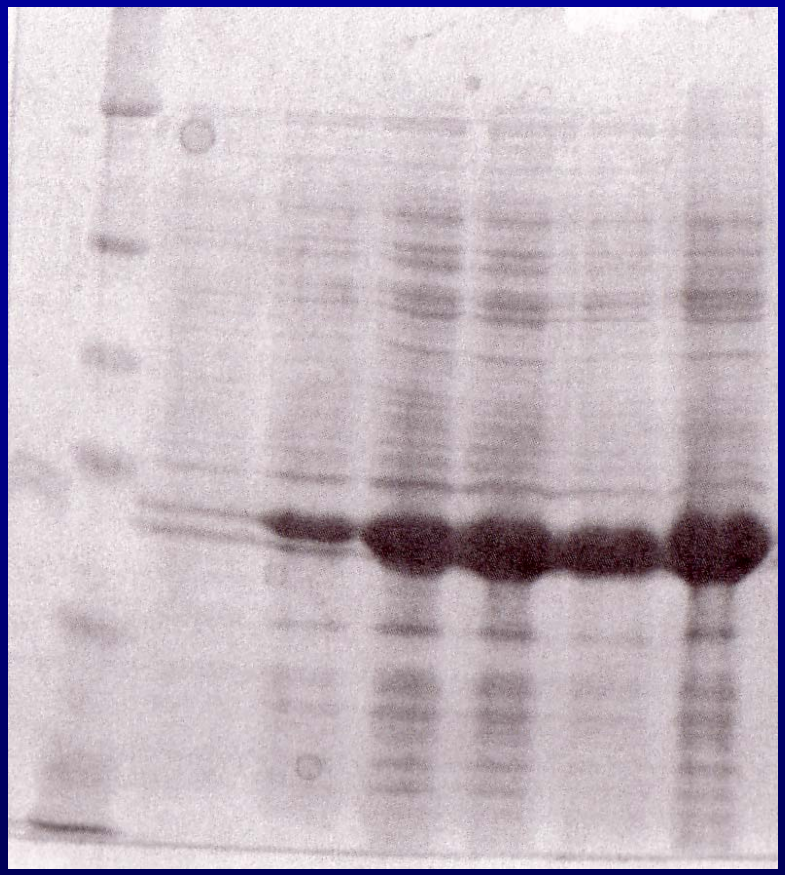




solid: correct overlap of oligos
dashdot: correct overlap of intermediate fragments
dashed: incorrect overlap of small oligos
dotted: incorrect overlap of intermediate fragments

Result: Single products assembled correctly.

In vivo Expression of Gag protein in *E. coli*



Confirmed by Western blot and sequencing

Intelligent Systems and Computational Biology

- **Artificial Intelligence for Biology and Medicine**
  - **Biology is data-rich and knowledge-hungry**
  - **AI is well suited to biomedical problems**

- **Examples**
  - Machine learning -- drug discovery
  - Rule-based systems – drug-resistant HIV
  - Heuristic search -- protein structure prediction
  - Constraints – design of large synthetic genes

- **Current Project**
  - **Machine learning and p53 cancer rescue mutants**

- **Goal of talk: The power of information science to influence molecular science and technology**

p53 and Human Cancers

- p53 is a central tumor suppressor protein

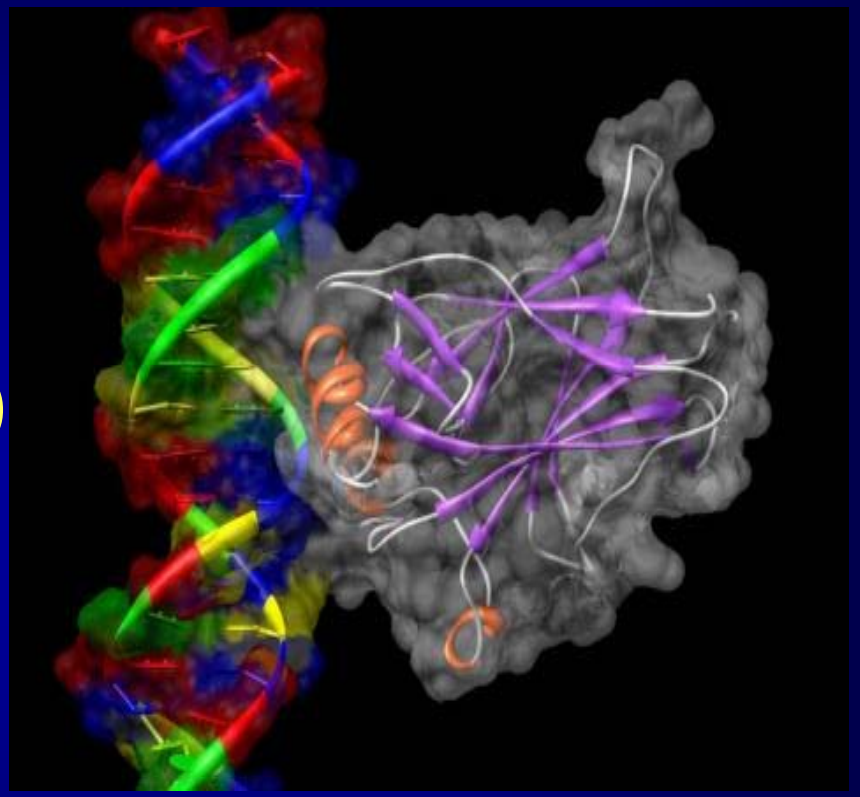
  "The guardian of the genome"

- Controls apoptosis (programmed cell death) and cell cycle arrest

  Monitors cellular distress

- **The most-mutated gene in human cancers**

  All cancers must disable the p53 apoptosis pathway.



p53 core domain bound to DNA

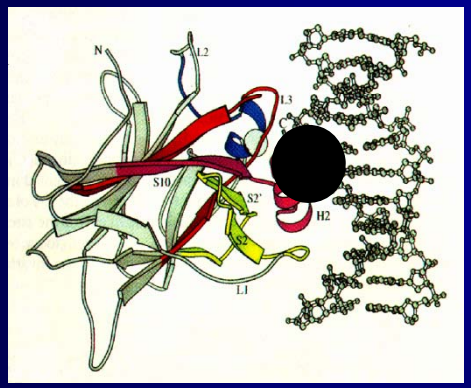
Image generated with UCSF Chimera

Cho, Y., **Gorina, S.**, **Jeffrey, P.D.**, **Pavletich, N.P.**
Crystal structure of a p53 tumor suppressor-DNA complex: understanding tumorigenic mutations.
Science v265 pp.346-355, 1994

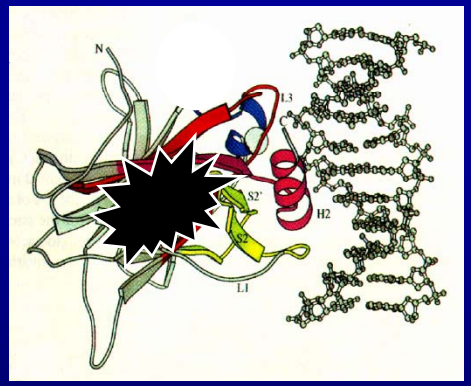
Consequences of *p53* mutations

~250,000 US deaths/year

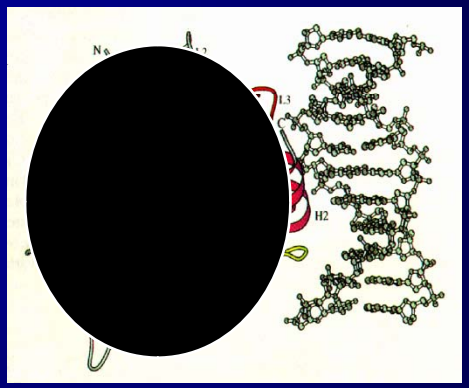
Loss of DNA contact



Disruption of local structure



Denaturation of entire core domain

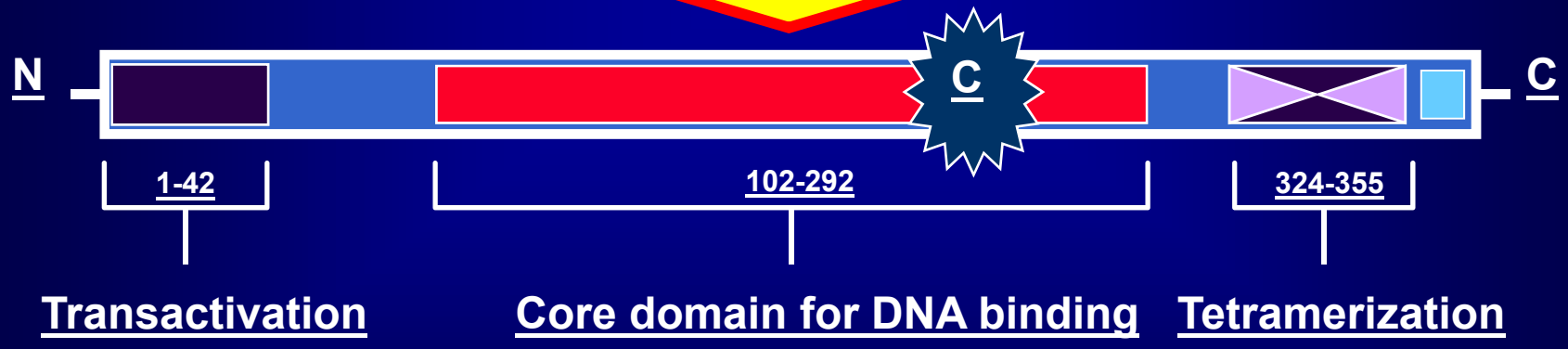


Over 1/3 of all human cancers express full-length p53 with only one a.a. change

Cho et al., Science *265*, 346-355 (1994)

A Long-held Goal of Anti-cancer Therapy

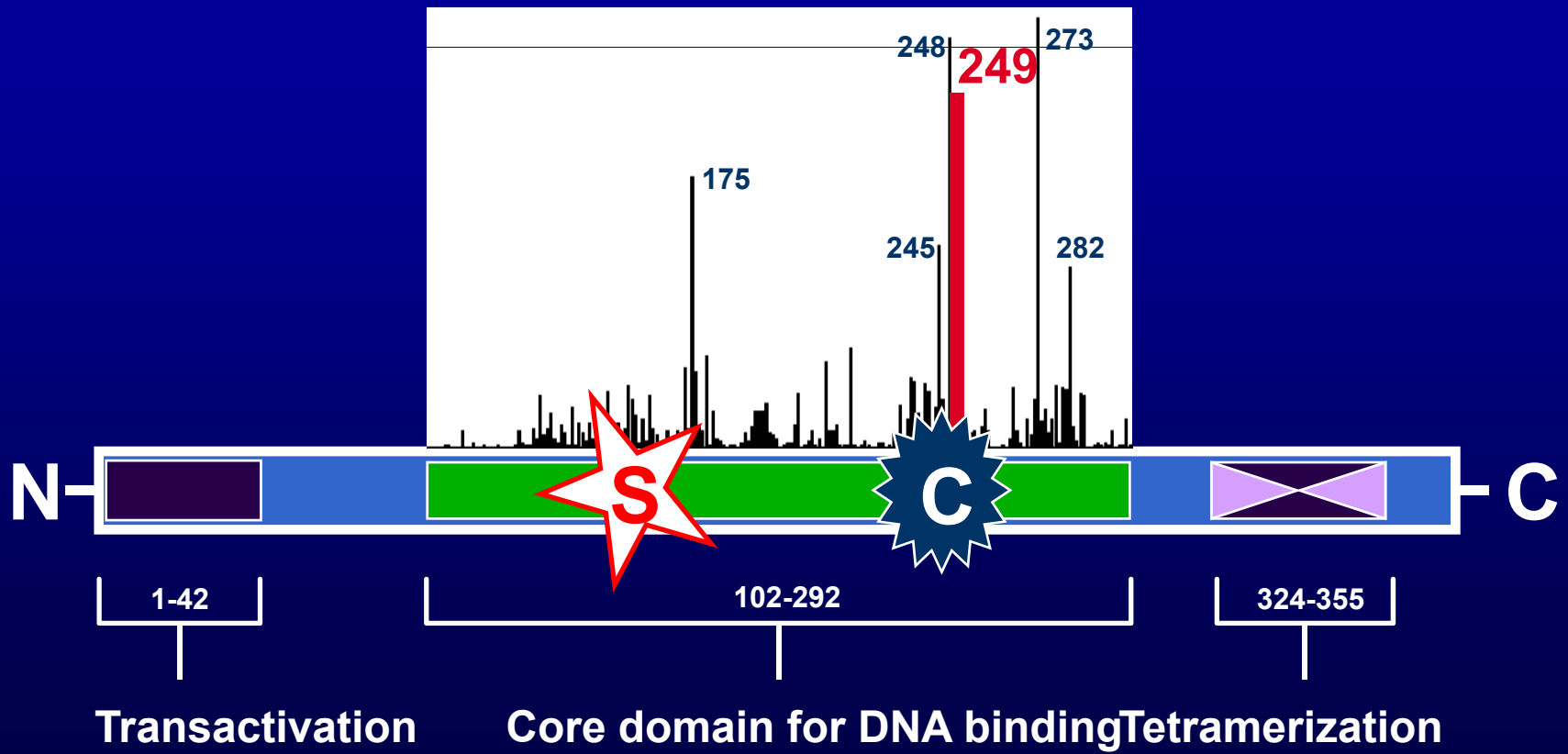
Restore integrity of p53 core domain



Restore apoptosis (cell death) in tumor cells

Suppressor Mutations

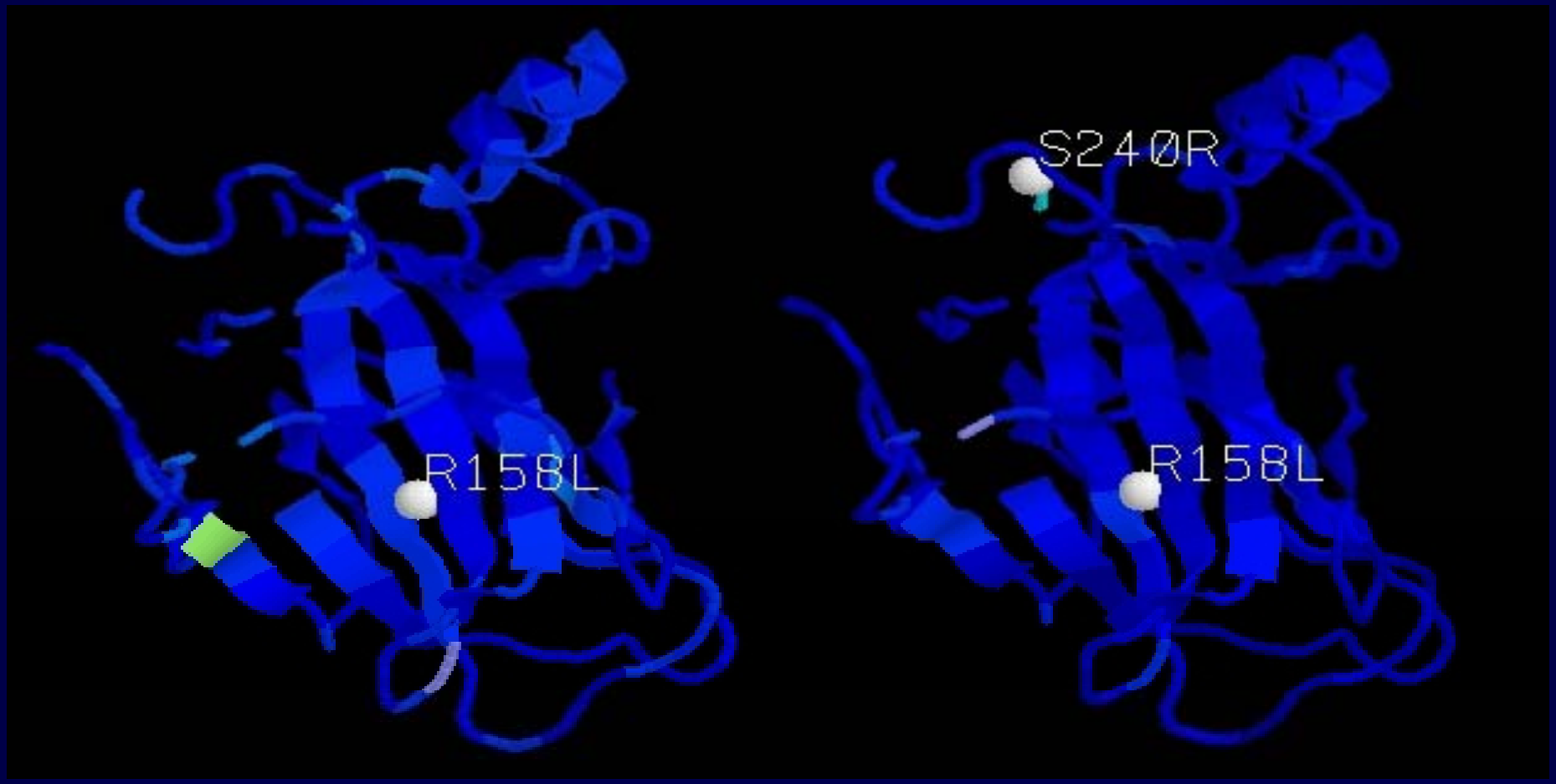
Several second-site mutations restore functionality to some p53 cancer mutants *in vivo.*



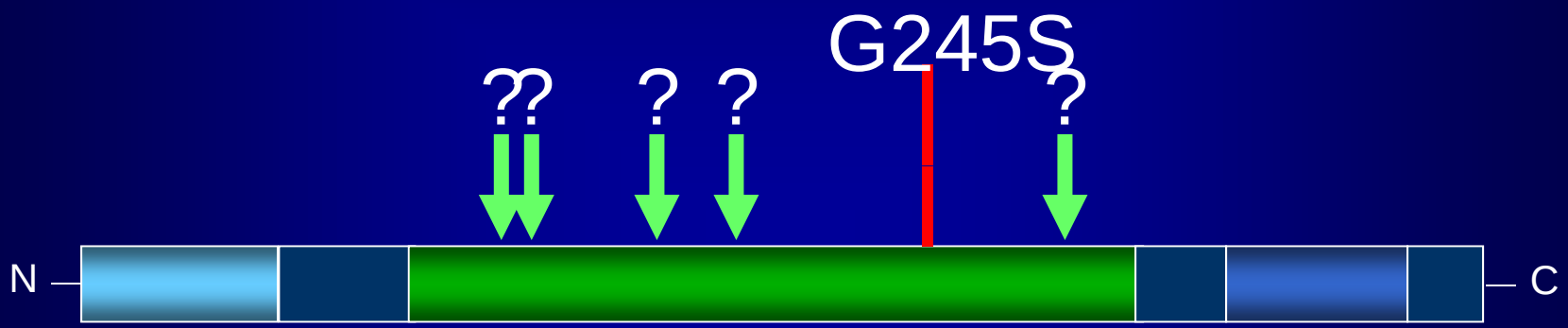
PREDICT

Cancer Mutant

Rescued Cancer Mutant



Machine Learning:
Predict phenotype from genotype



A functional census of p53
“cancer rescue” mutants

=> Catalog *all* Actives

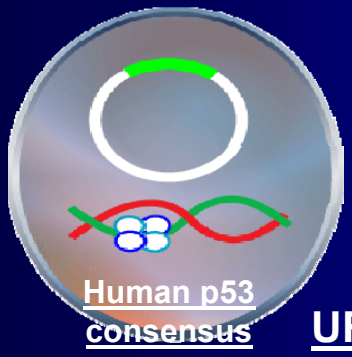
Class Labels: Active/+ or Inactive/-

p53 Transcription Assay

Initial: Yeast Growth Selection, Sequencing

ACTIVE (+)

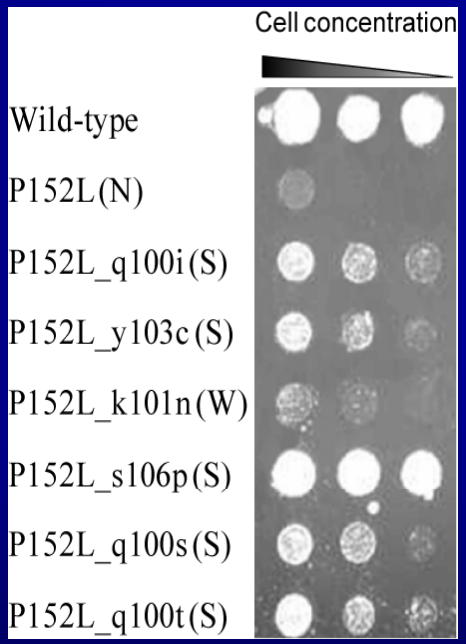
Will grow.



URA−

Will not grow.

INACTIVE (-)



(S) = Strong
(W) = Weak
(N) = Negative

Confirm: Human 1299 Cell-based Luciferase

First measurement
Firefly luciferase
p53 dependent

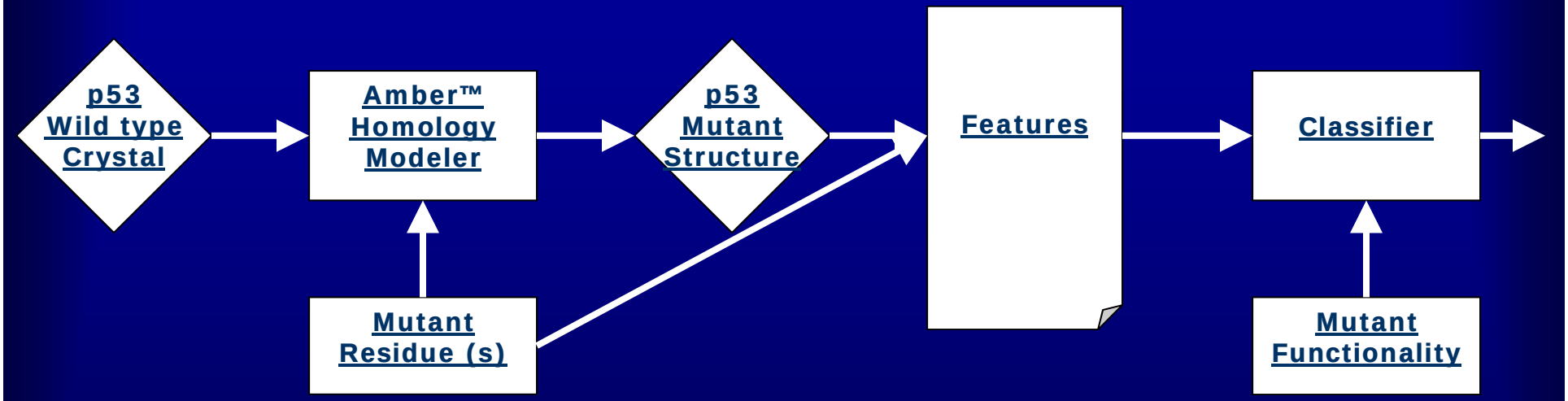
Second measurement
Renilla luciferase
p53 independent

Baroni, T.E., et al., 2004

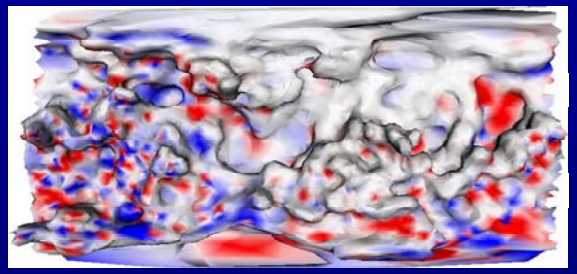
Danziger, S.D., et al., 2009

Baronio, R., et al., 2010

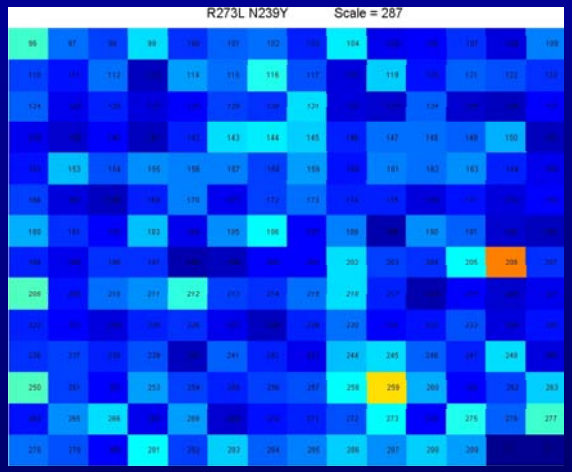
Classifier & Feature Overview



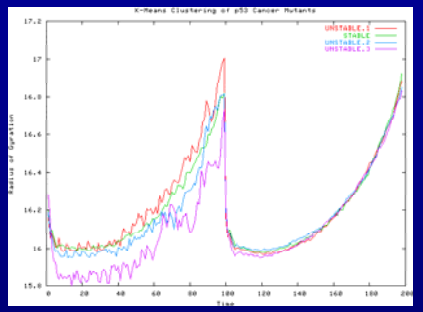
Multi-dimensional Features



2D Surface Map



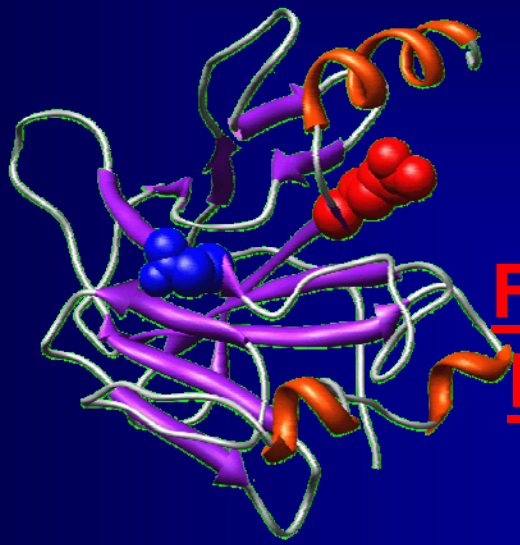
3D Structural Changes



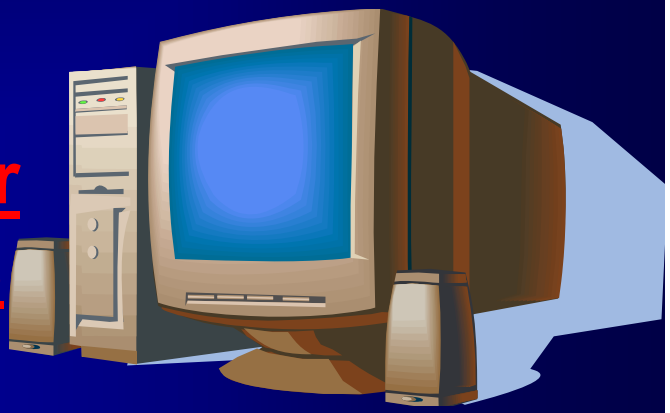
4D Unfolding Trajectory

Danziger et al., Functional Census of Mutation Sequence Spaces, IEEE/ACM Trans Comput Biol Bioinform (2006)

Active Machine Learning for Biological Discovery

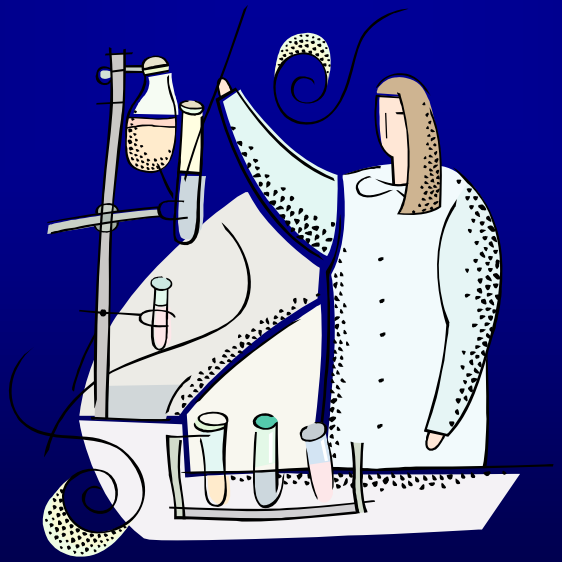


Find New Cancer
Rescue Mutants



Knowledge

Theory



Experiment

How Big is The Problem?

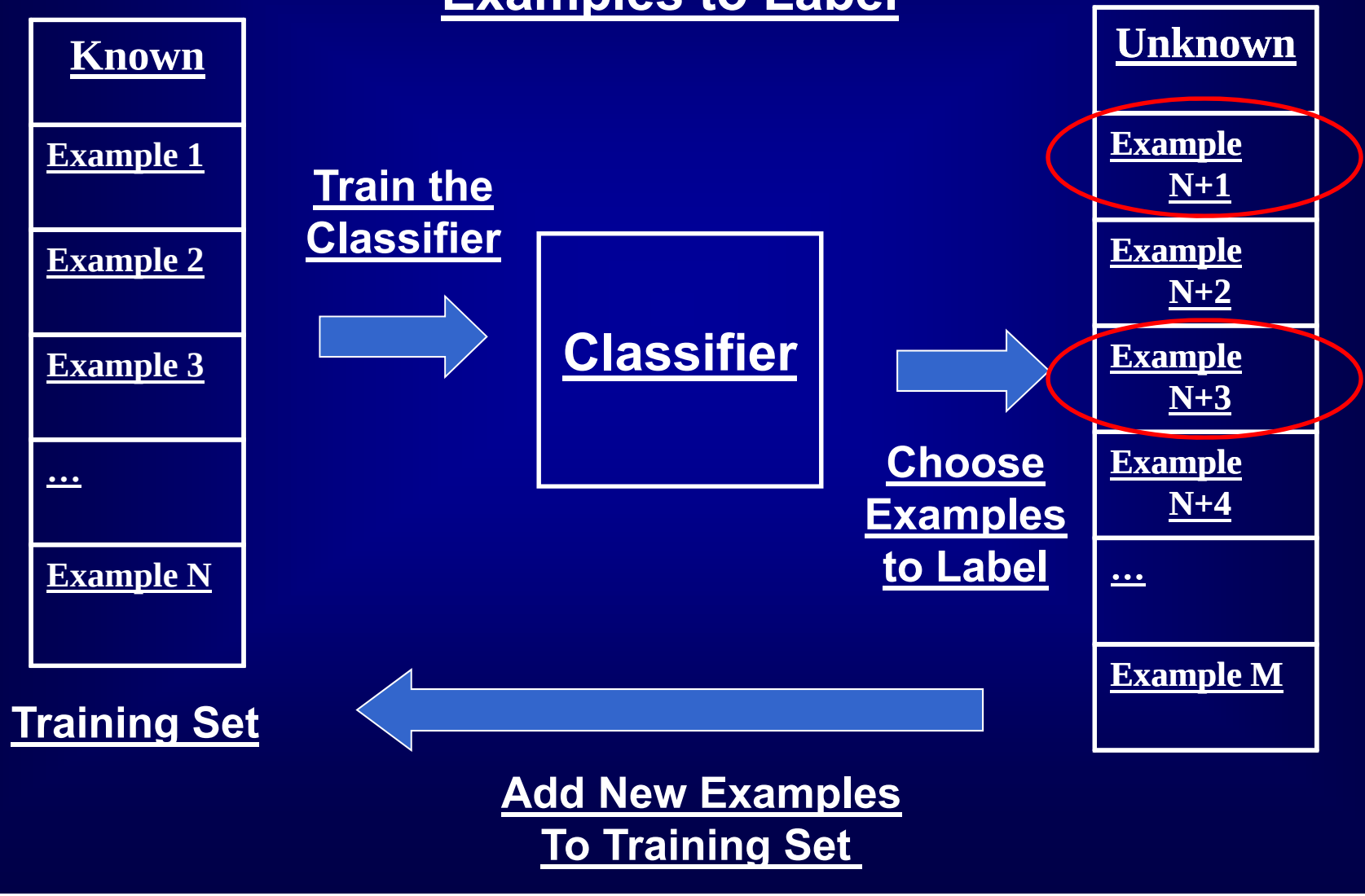
Known Mutants: 16,722
Known Actives: 143

Assuming up to 5 mutations in 200 residues
How Many Mutants are There?: ~10^11

Spiral Galaxy M101
http://hubblesite.org/
~10^9 stars.

Computational Active Learning

Pick the Best (= Most Informative) Unknown Examples to Label



Example of Active Learning: Minimum Marginal Hyperplane

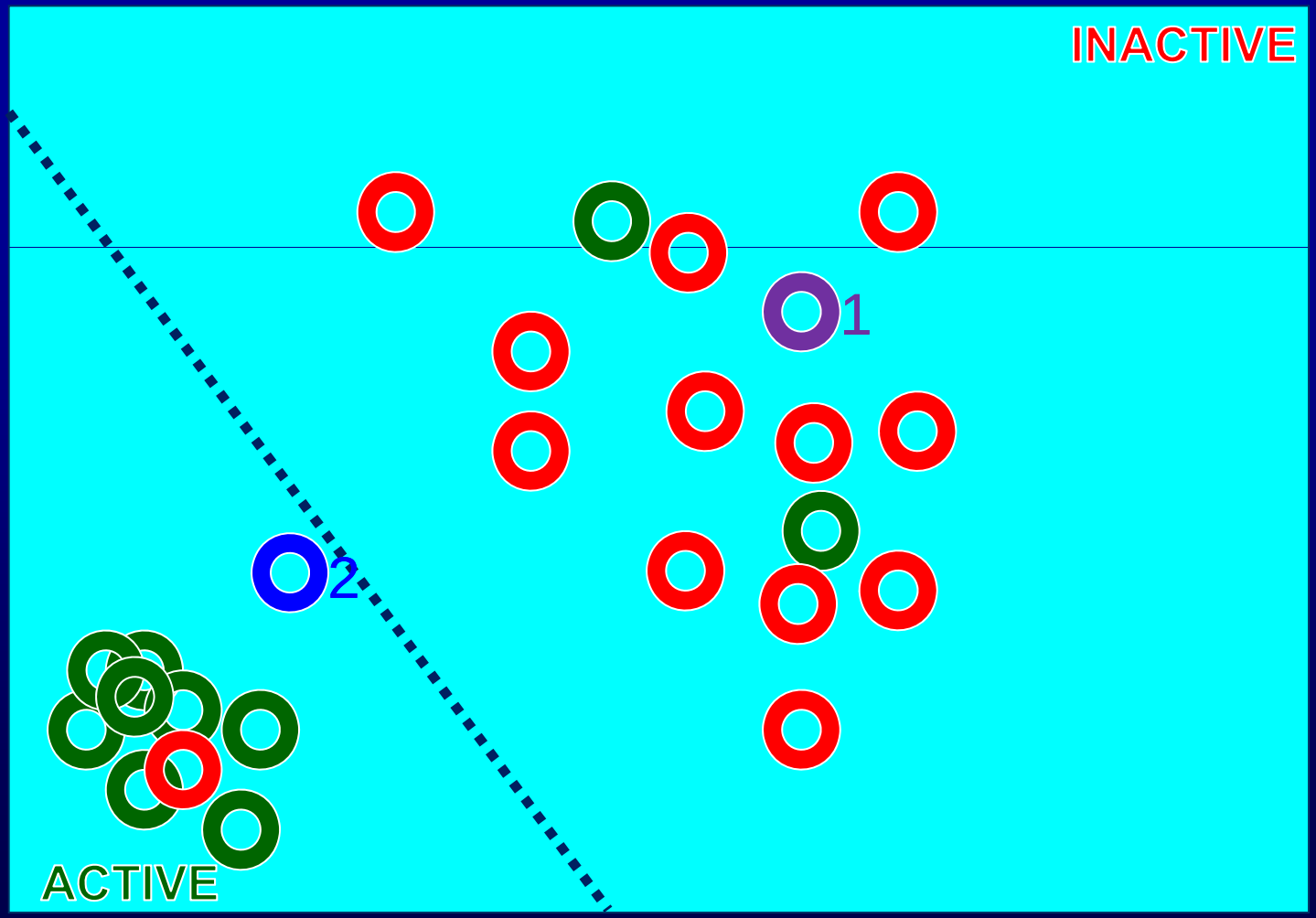
Should unknown **Mutant 1** or **Mutant 2** be added to the training set?

Known Inactive

Known Active

1 Unknown **Mutant 1**

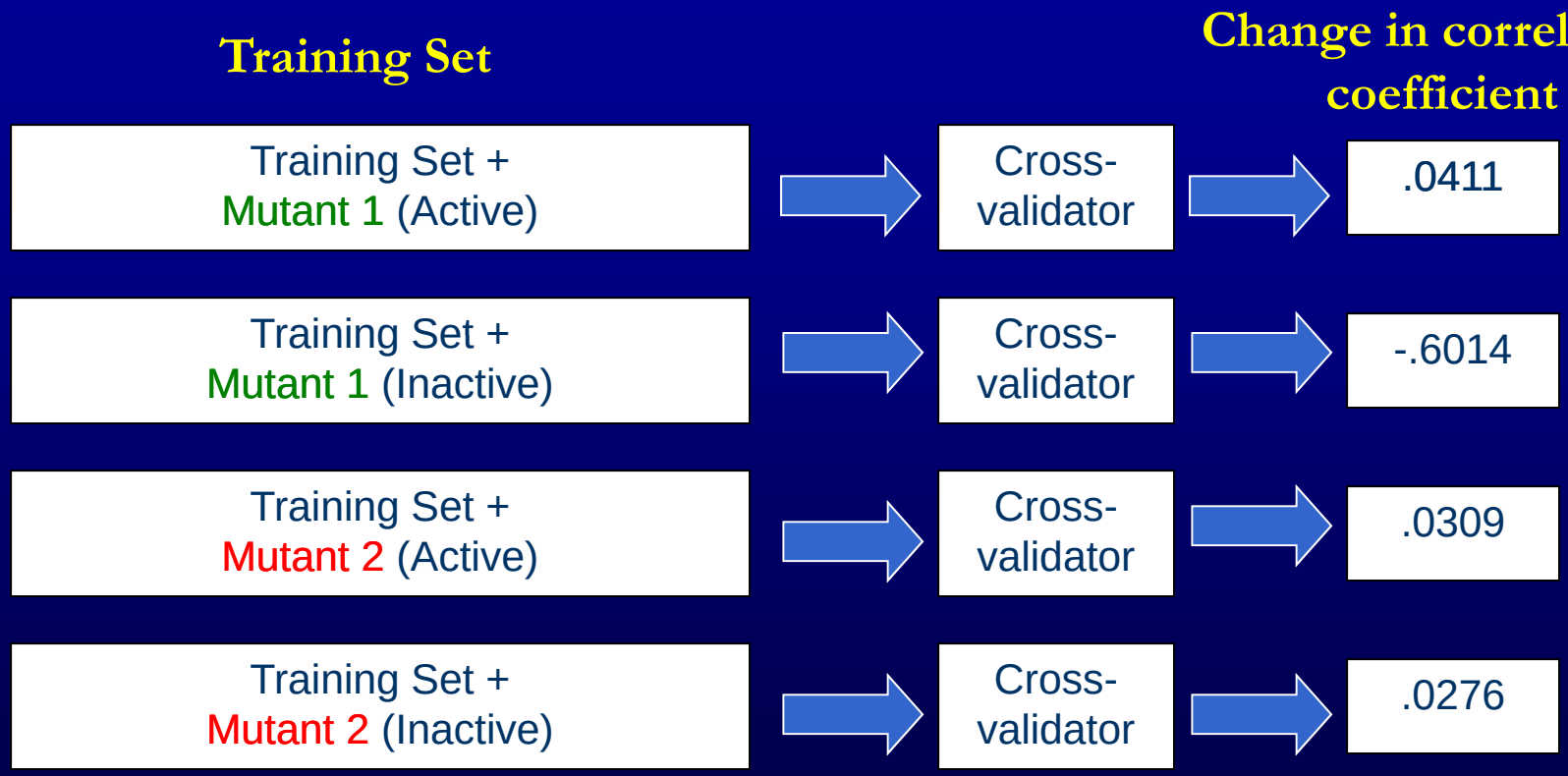
2 Unknown **Mutant 2**



Select **Mutant 2**

Example of Active Learning: Maximum Curiosity

Should Mutant 1 or Mutant 2 be added to the training set?



Select Mutant 1

Which is the Best Active Learning Method?

TYPE I: Select mutants that most improve the classifier if correctly predicted.

- **Maximum Curiosity**
- **Composite Classifier**
- **Improved Composite Classifier**

TYPE II: Select mutants that most improve the classifier.

- **Additive Curiosity**
- **Additive Bayesian Surprise**

TYPE III: Common methods taken from the literature.

- **Minimum Marginal Hyperplane**
- **Maximum Entropy**

TYPE IV: Variations on methods from the literature.

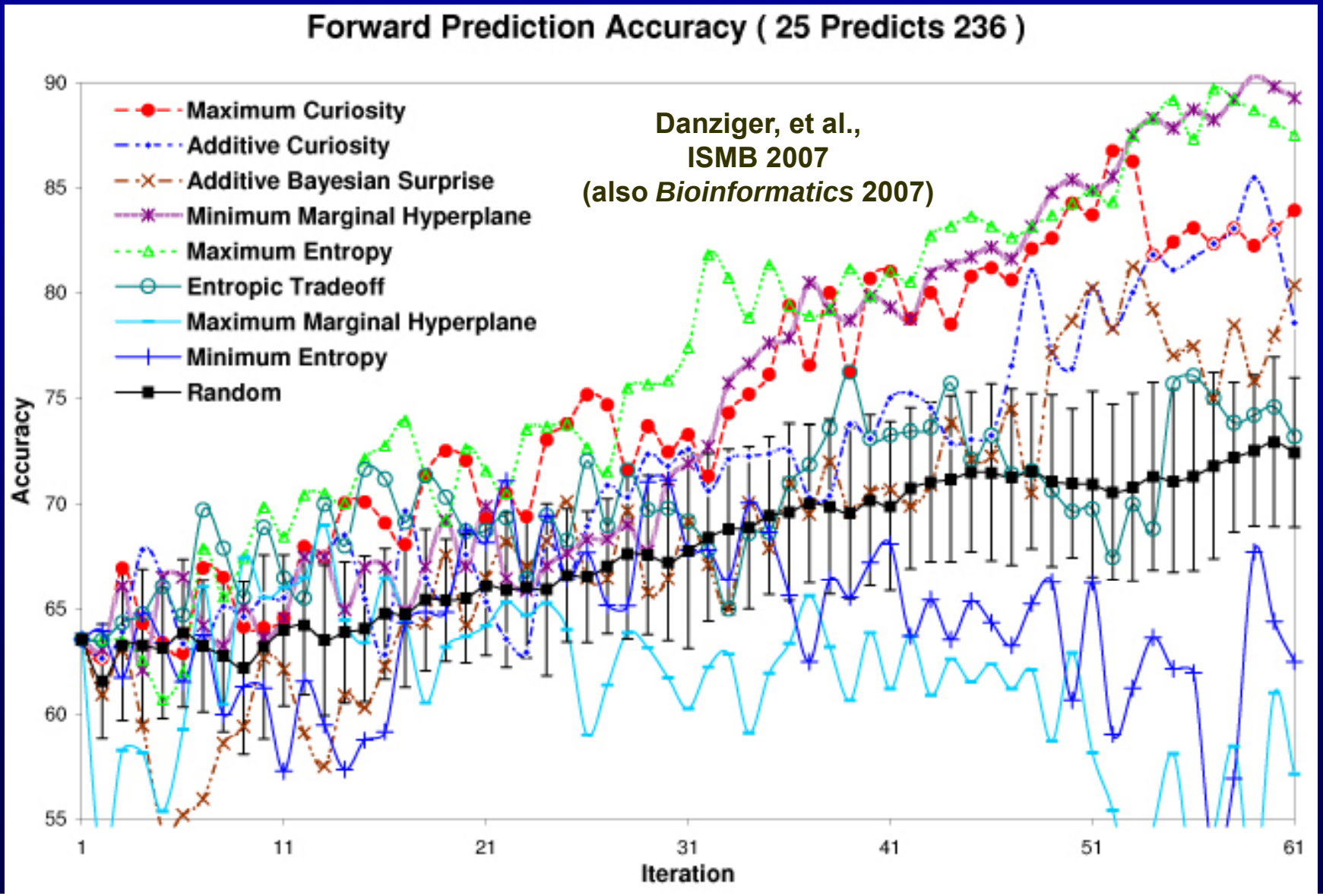
- **Maximum Marginal Hyperplane (negative control)**
- **Minimum Entropy (negative control)**
- **Entropic Tradeoff**

TYPE C: Controls

- **Non-iterated Prediction**
- **Predict All Inactive**
- **Random (30 trials)**

The Active Learning Tradeoff:

How Fast Does It Learn?



Blind *in vivo* Trial of MIP On Three p53 Regions

- MIP Positive Region:
  - Predicted to be Informative & Many Positive Mutants
- MIP Negative Region:
  - Predicted to be Informative & Few Positive Mutants
- Expert Region:
  - Selected by a Human Cancer Biologist
- **No previous single-a.a. rescue mutants in any region**

Danziger, et al. (2009)

Visualization of Selected Regions

- **Positive Region:**

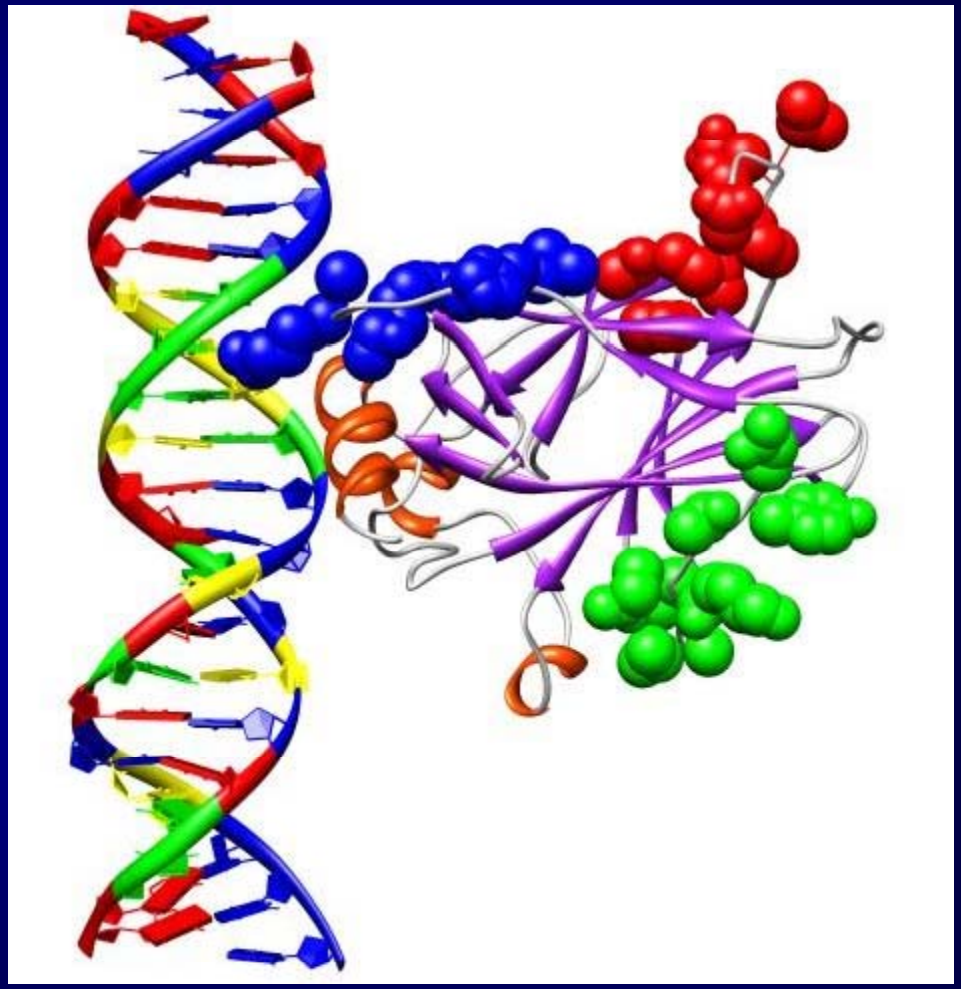
  Predicted Active
  96-105 (Green)

- **Negative Region:**

  Predicted Inactive
  223-232 (Red)

- **Expert Region:**

  Predicted Active
  114-123 (Blue)



Danziger, et al.
(2009)

Novel Single-a.a. Cancer Rescue Mutants

	MIP Positive (96-105)	MIP Negative (223-232)	Expert (114-123)
# Strong Rescue	8	0 ($p < 0.008$)	6 (not significant)
# Weak Rescue	3	2 (not significant)	7 (not significant)
Total # Rescue	11	2 ($p < 0.022$)	13 (not significant)

p-Values are two-tailed, comparing Positive to Negative and Expert regions. Danziger, et al. (2009)

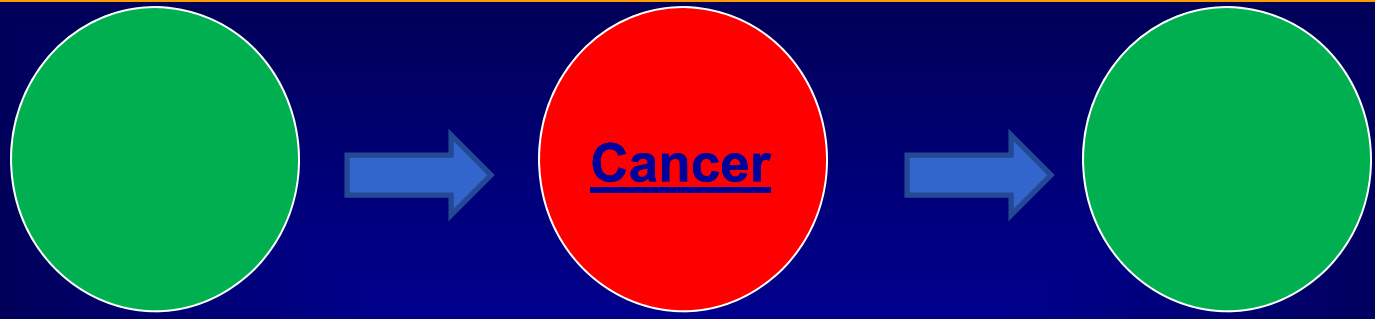
No significant differences between the MIP Positive and Expert regions.

Both were statistically significantly better than the MIP Negative region.

The Positive region rescued for the first time the cancer mutant P152L.

No previous single-a.a. rescue mutants in any region.

Mutations Rescue Cancerous p53



Wild Type

Active p53

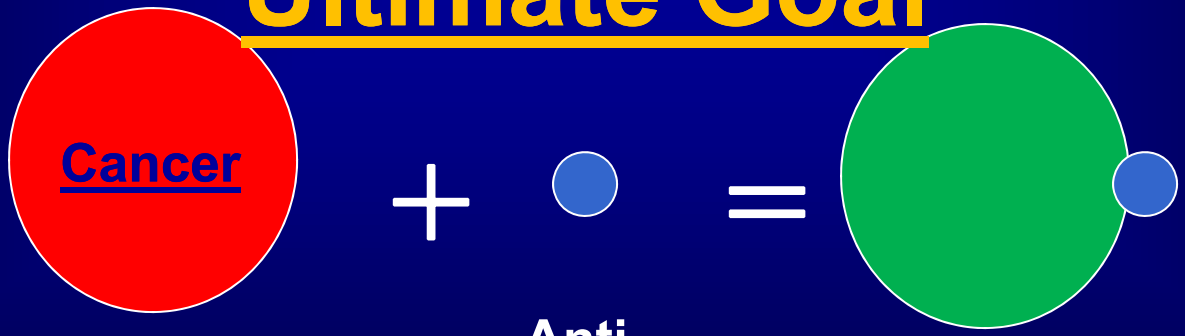
Cancer Mutation

Inactive p53

Cancer+Rescue Mutations

Active p53

Ultimate Goal



Cancer Mutation

Inactive p53

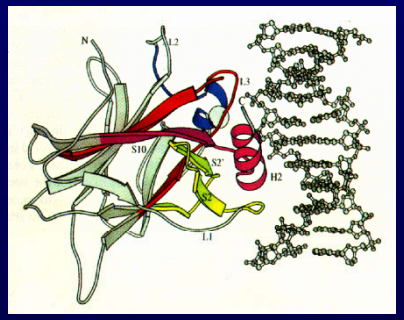
Anti-Cancer Drug

Active p53

The long road to a future anti-cancer drug

Peter Kaiser
Rommie Amaro
Dick Chamberlin
Melanie Cocco
Hudel Luecke
Wes Hatfield
Chris Wassman
Roberta Baronio
Ozlem Demir
Faezeh Salehi
Edwin Vargas
Da-Wei Lin

drug



Intelligent Systems and Computational Biology

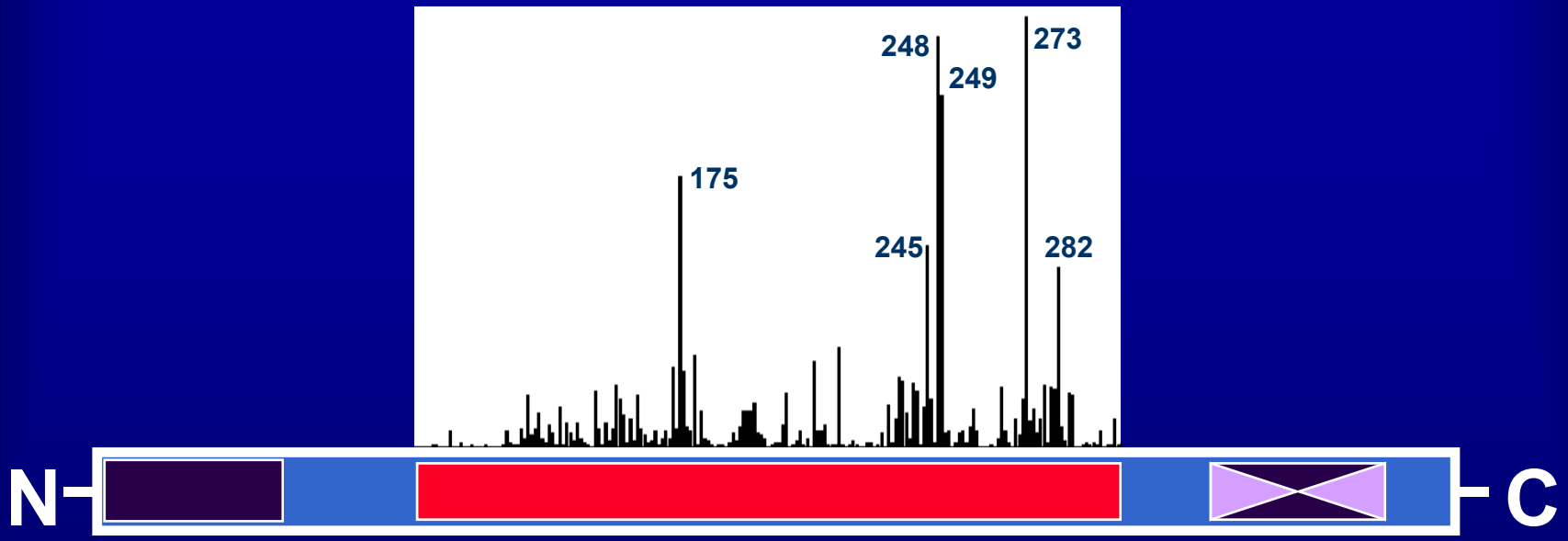
- **Artificial Intelligence for Biology and Medicine**
  - **Biology is data-rich and knowledge-hungry**
  - **AI is well suited to biomedical problems**

- **Examples**
  - Machine learning -- drug discovery
  - Rule-based systems – drug-resistant HIV
  - Heuristic search -- protein structure prediction
  - Constraints – design of large synthetic genes
  - DNA nanotechnology and space-filling DNA tetrahedra

- **Current Project**
  - Machine learning and p53 cancer rescue mutants

- **Goal of talk: The power of information science to influence molecular science and technology**

The spectrum of *p53* mutations

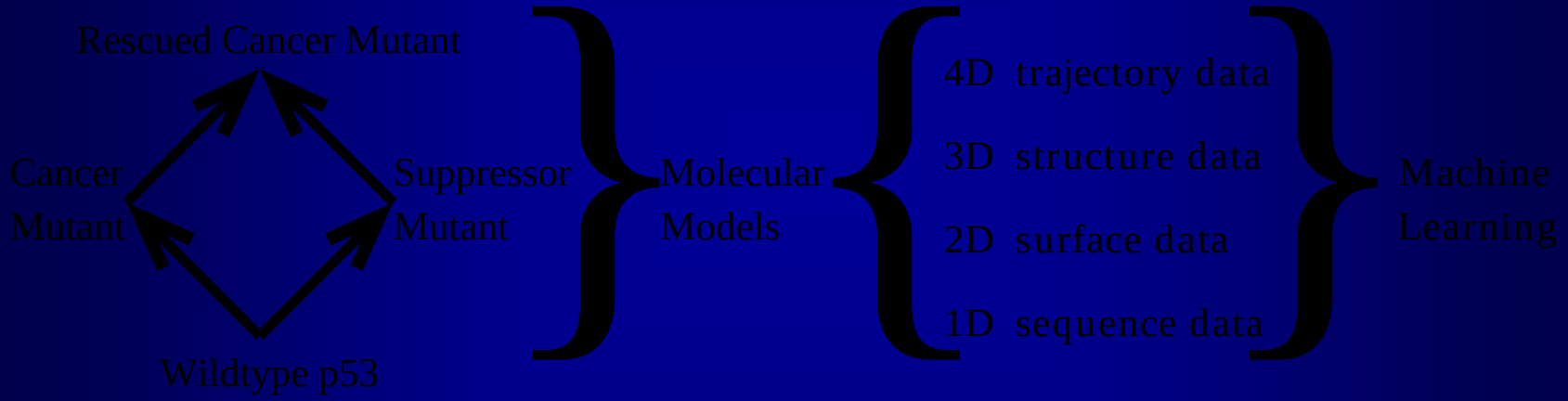


IARC *TP53* Mutation Database (R7, Sep. 2002):

17,689 somatic mutations

12,631 (71%) missense mutations affecting codons 100-300

974 different amino acid changes in core domain


Rescued Cancer Mutant
Cancer Mutant
Suppressor Mutant
Wildtype p53
Molecular Models
4D trajectory data
3D structure data
2D surface data
1D sequence data
Machine Learning

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3D DNA Nanostructures

Christopher D. Wassman

UC Irvine

Dept. of Computer Science

Why DNA Nanotechnology

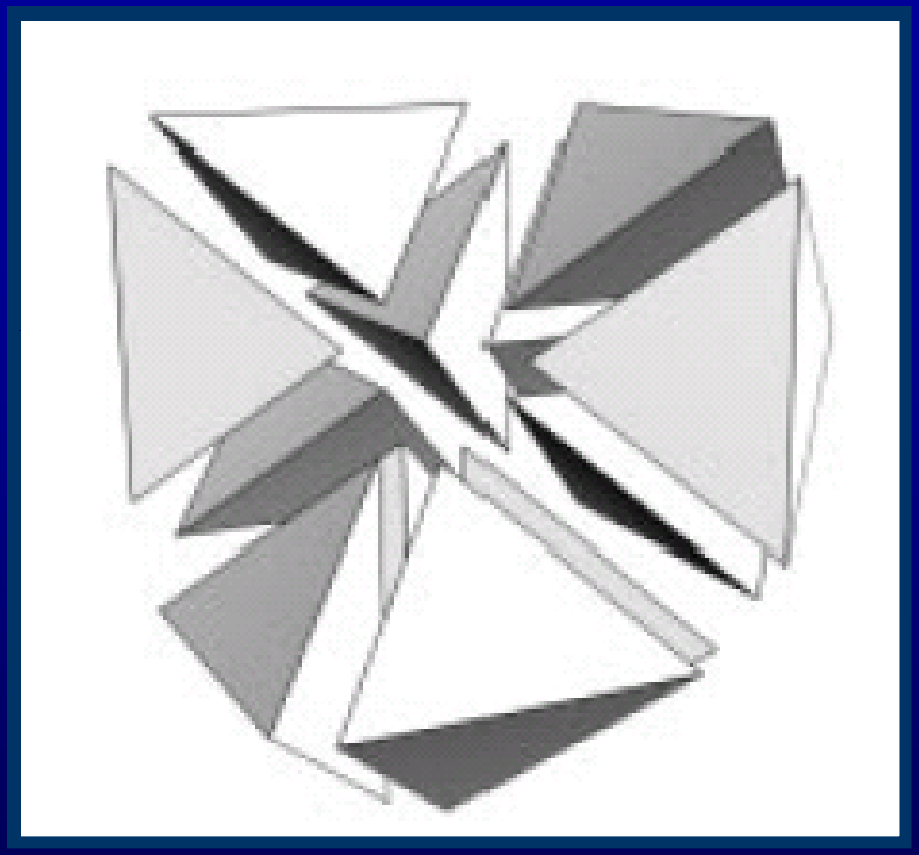
- DNA has an well understood 3D structure
- DNA is easily synthesized and manipulated
- DNA Feature Sizes:
  - 3.6 nm per helical rise,
  - 2 nm helical width
- Intel Feature Sizes:
  - Current chips, 45nm feature size
  - Research chips, 32nm feature size (Sept, 2008)
- Bio-Nanotechnology is a emerging field
  - Lots to do, and lots of fun to be had!

Tiling 3-Space

- A familiar concept
  - Building blocks
  - Cubes fill space
  - Cylinders do not

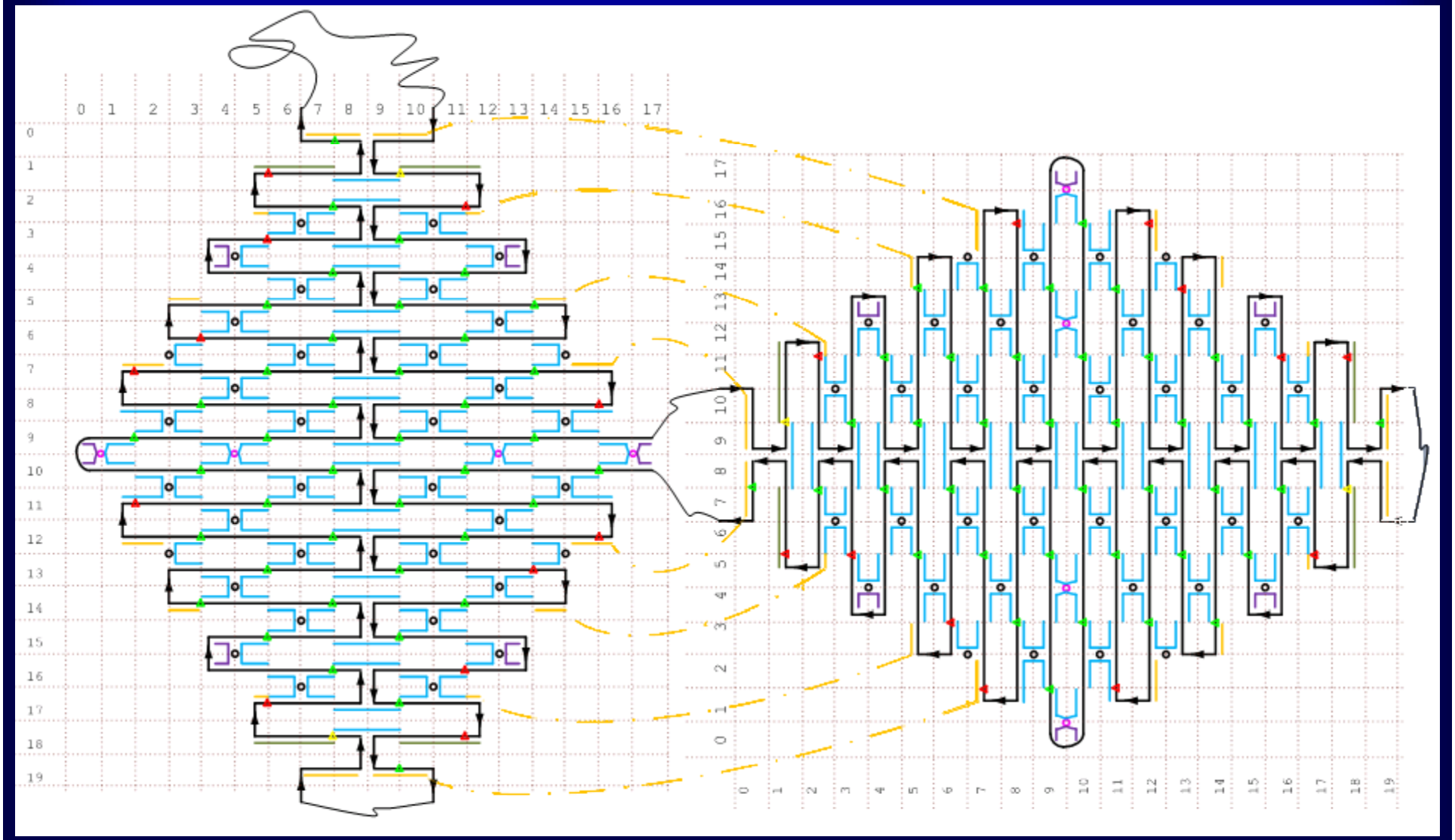
- Other building blocks are possible
  - We will focus on tetrahedral building blocks, constructed by “folding DNA”

Irregular Tetrahedra…

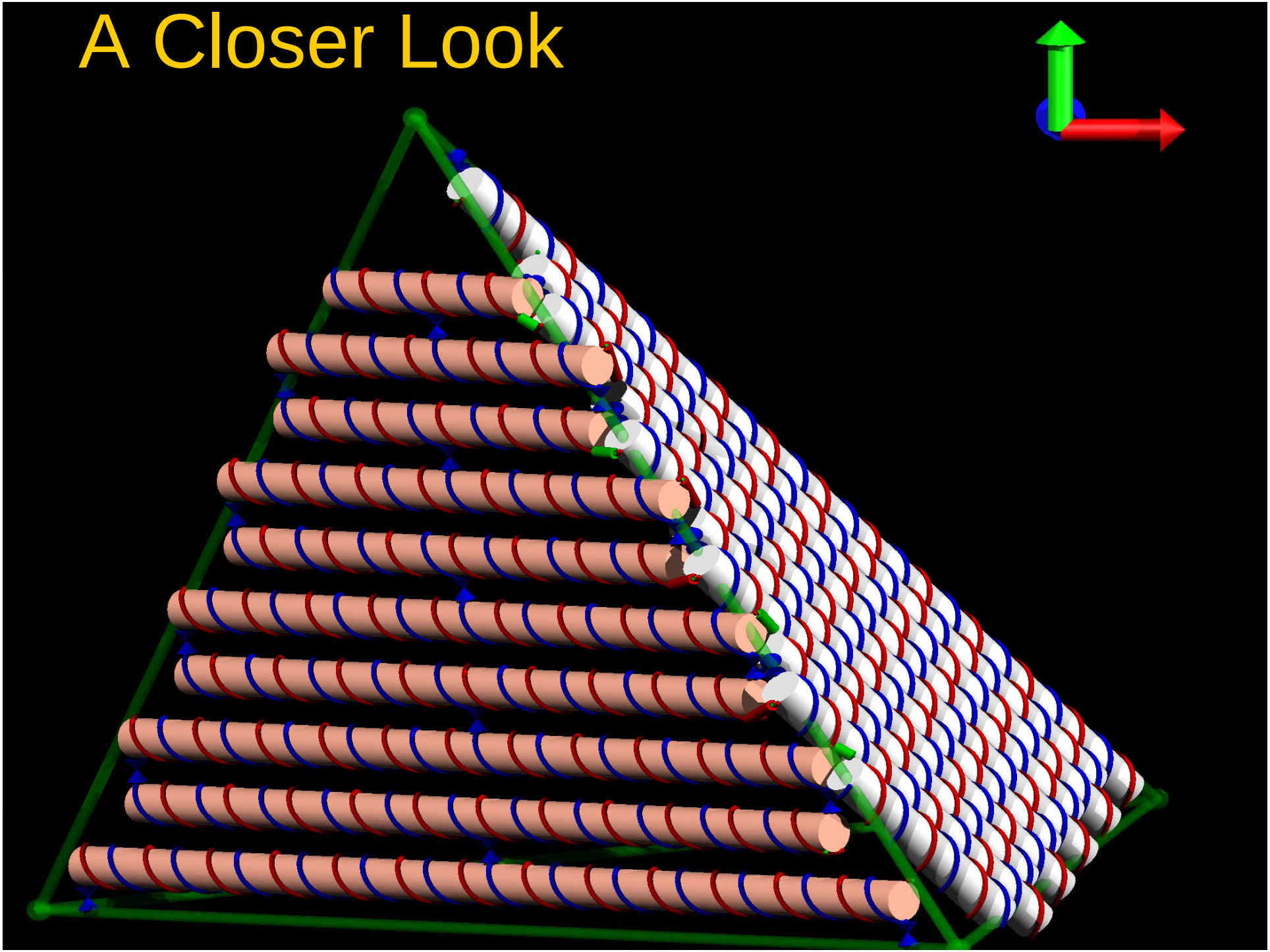


Can Tile 3-Space Completely!

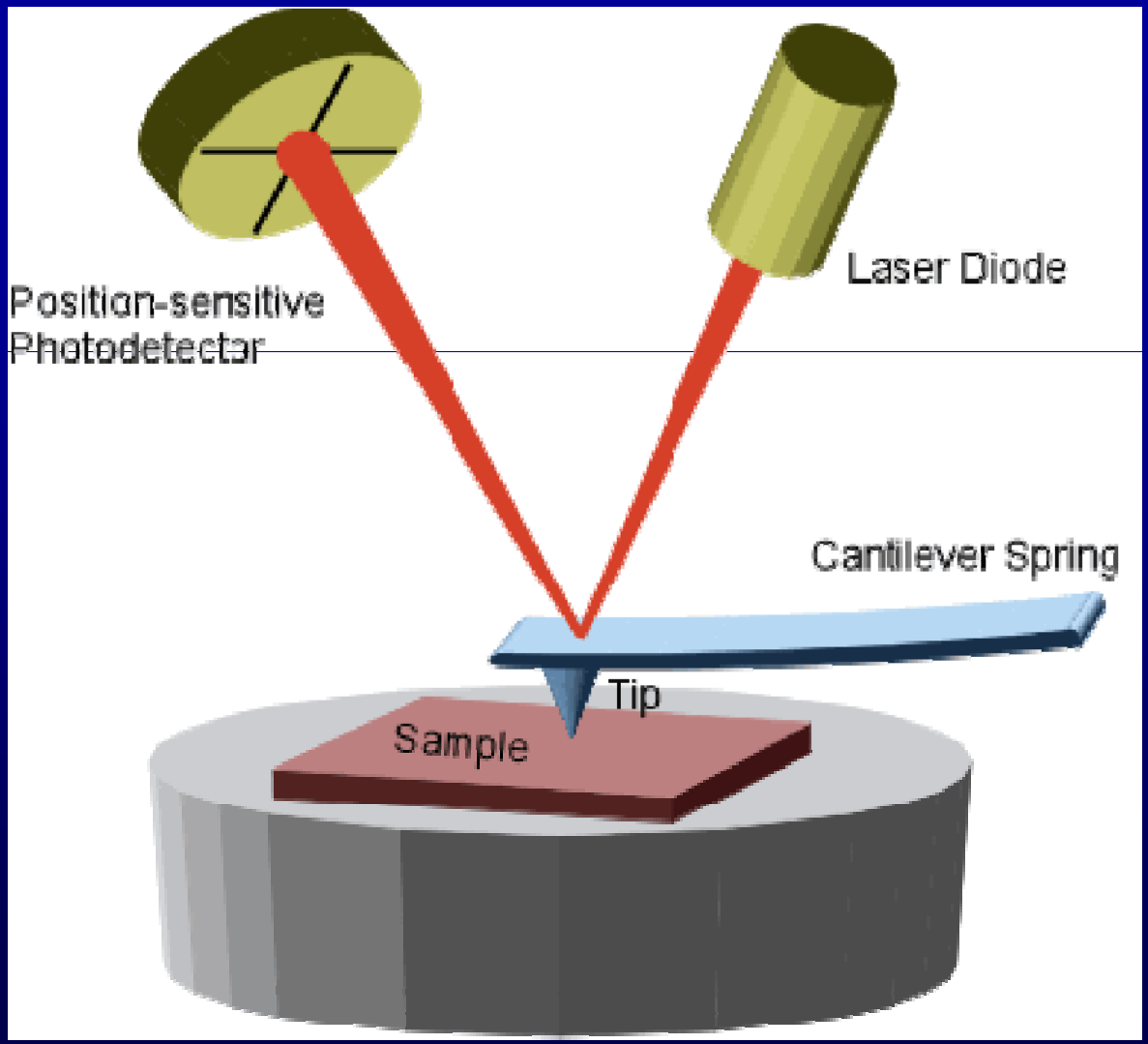
Full Tetrahedron



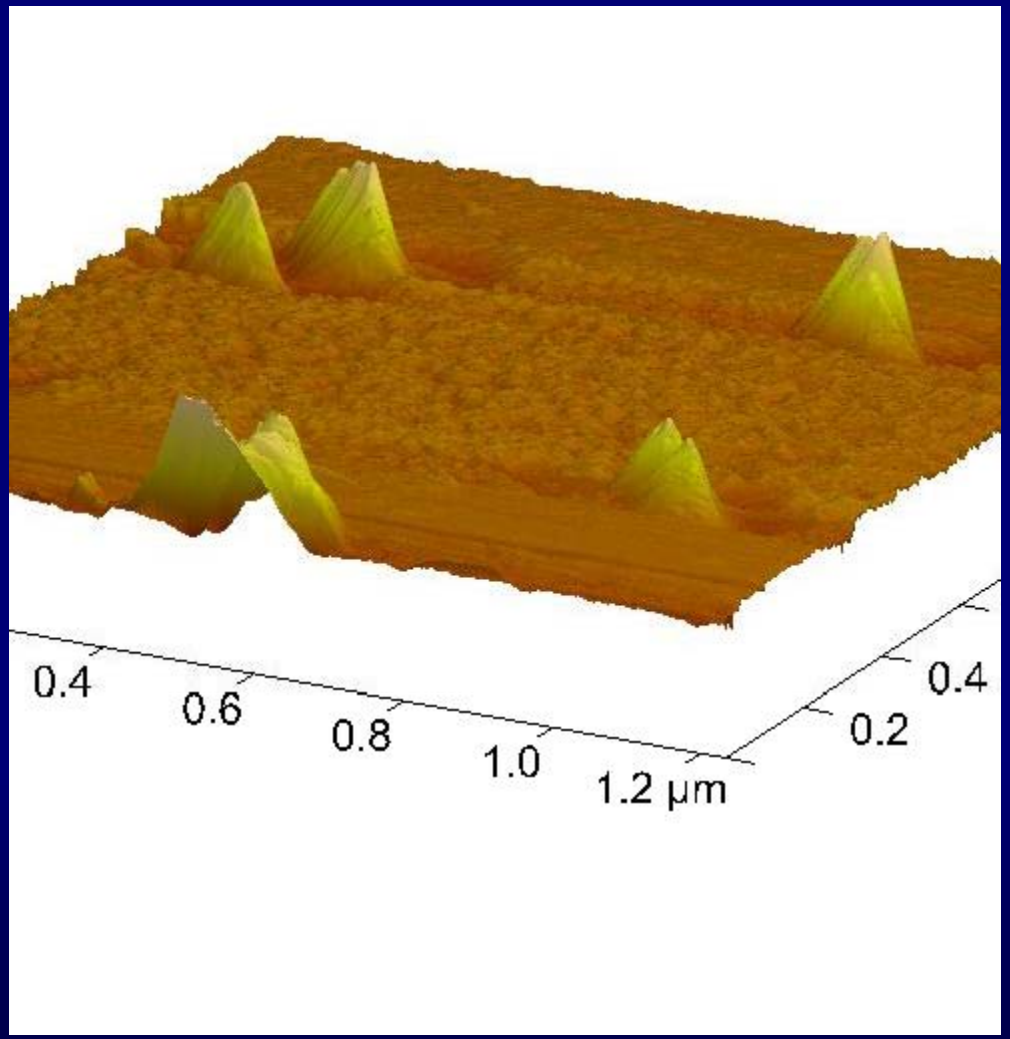
A Closer Look



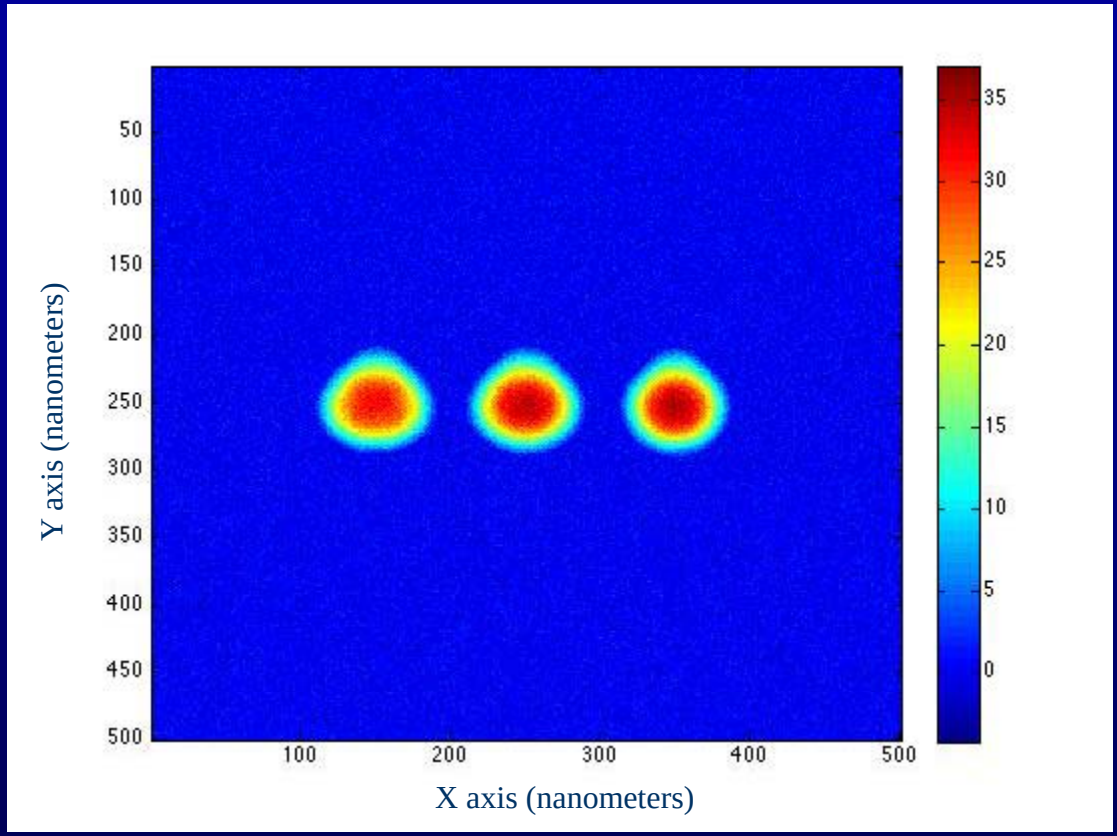
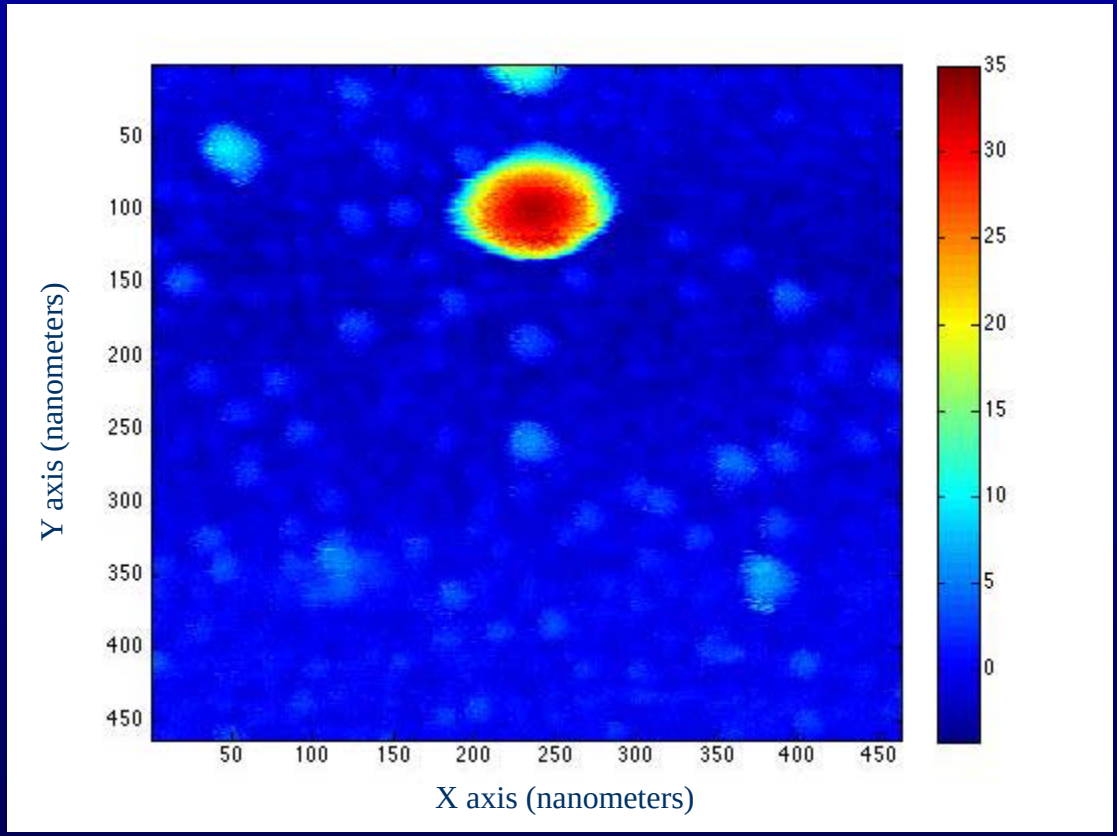
Atomic Force Microscopy (AFM)



Experimental AFM Image



Simulated AFM Image



Experimental AFM Image