

What is Biological Informatics?

(<http://www.esp.org/rjr/canberra.pdf>)

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Abstract

In the last 25 years, Moore's Law has transformed society, delivering exponentially better computers at exponentially lower prices. Biological informatics is the application of powerful, affordable information technology to the problems of biology. With \$2500 desktop PCs now delivering more raw computing power than the first Cray, bioinformatics is rapidly becoming the critical technology for 21st-century biology.

DNA is legitimately seen as a biological mass-storage device, making bioinformatics a *sine qua non* for genomic research. Other areas of biological investigation are equally information rich — an exhaustive tabulation of the Earth's biodiversity would involve a cross-index of the millions of known species against the approximately 500,000,000,000,000 square meters of the Earth's surface.

Bioinformatics is also becoming a scholarly discipline in its own right, melding information science with computer science, seasoning it with engineering methods, and applying it to the most information rich component of the known universe — the Biosphere.

What is Biological Informatics?

What are the differences among:

- biological informatics
- bioinformatics
- informatics
- computational biology

What is Bioinformatics?

Semantic tuning:

- **X-informatics** is the application of information technology to discipline X, with emphasis on persistent data stores.
- **Computational X** is the application of information technology to discipline X, with emphasis analytical algorithms.

What is Bioinformatics?

Bioinformatics is:

- the use of computers (and persistent data structures) in pursuit of biological research.
- an emerging new discipline, with its own goals, research program, and practitioners.
- the *sine qua non* for 21st-century biology.
- the most *significantly underfunded* component of 21st-century biology.
- all of the above.

Topics

- Biotechnology and information technology will be the “magic” technologies of the 21st Century.
- Moore’s Law constantly transforms IT (and everything else).
- Information Technology (IT) has a special relationship with biology.
- 21st-century biology will be based on bioinformatics.
- Bioinformatics is emerging as an independent discipline.
- A connected, federated information infrastructure for 21st-century biology is needed.
- Current support for public bio-information infrastructure seems inadequate.

Introduction

Magical Technology

Magic

To a person from 1897, much current technology would seem like magic.

What technology of 2097 would seem magical to a person from 1997?

Candidate: Biotechnology so advanced that the distinction between living and non-living is blurred.

Information technology so advanced that access to information is immediate and universal.

Moore's Law

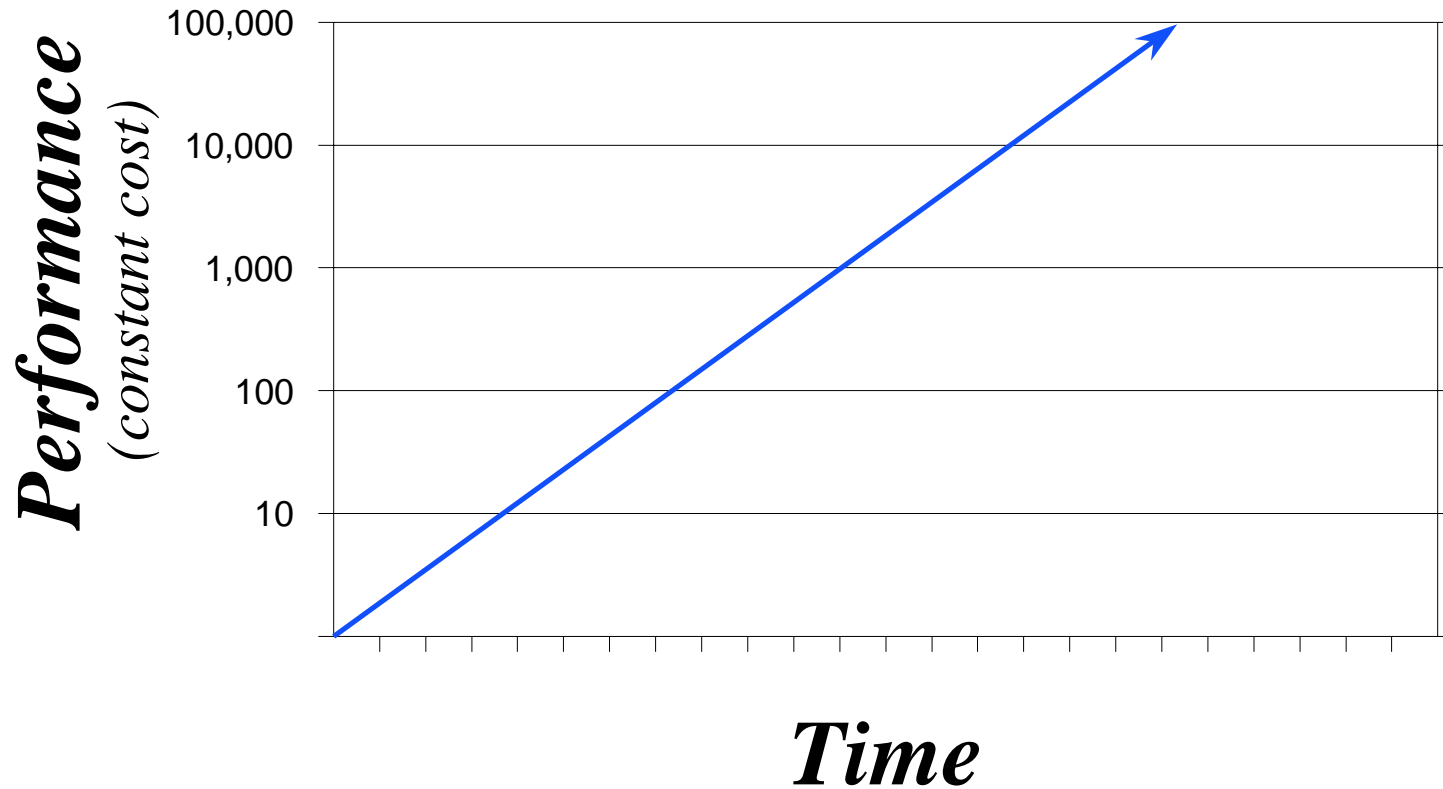
*Transforms InfoTech
(and everything else)*

Moore's Law: *The Statement*

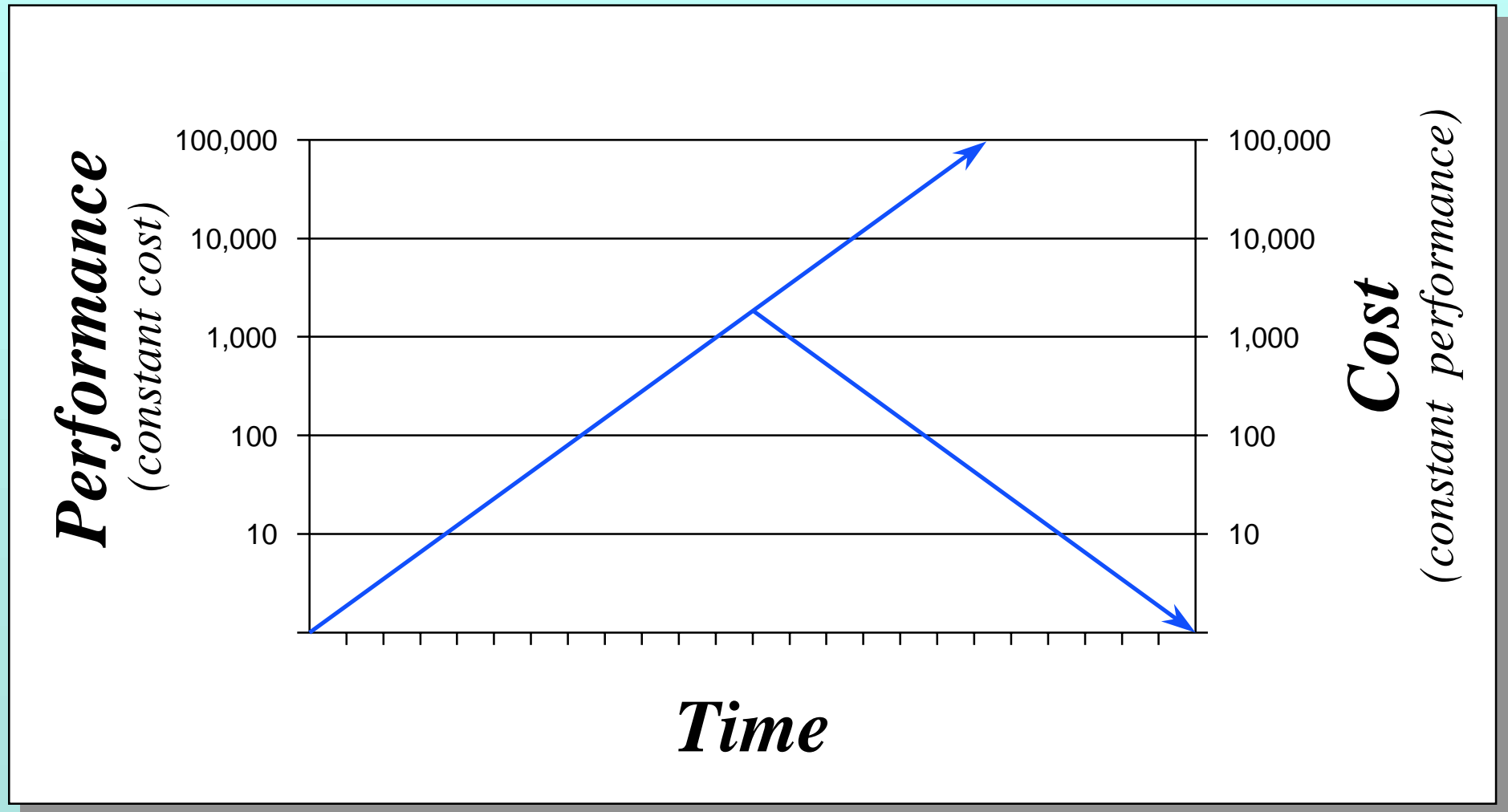
Every eighteen months, the number of transistors that can be placed on a chip doubles.

Gordon Moore, co-founder of Intel...

Moore's Law: *The Effect*



Moore's Law: *The Effect*

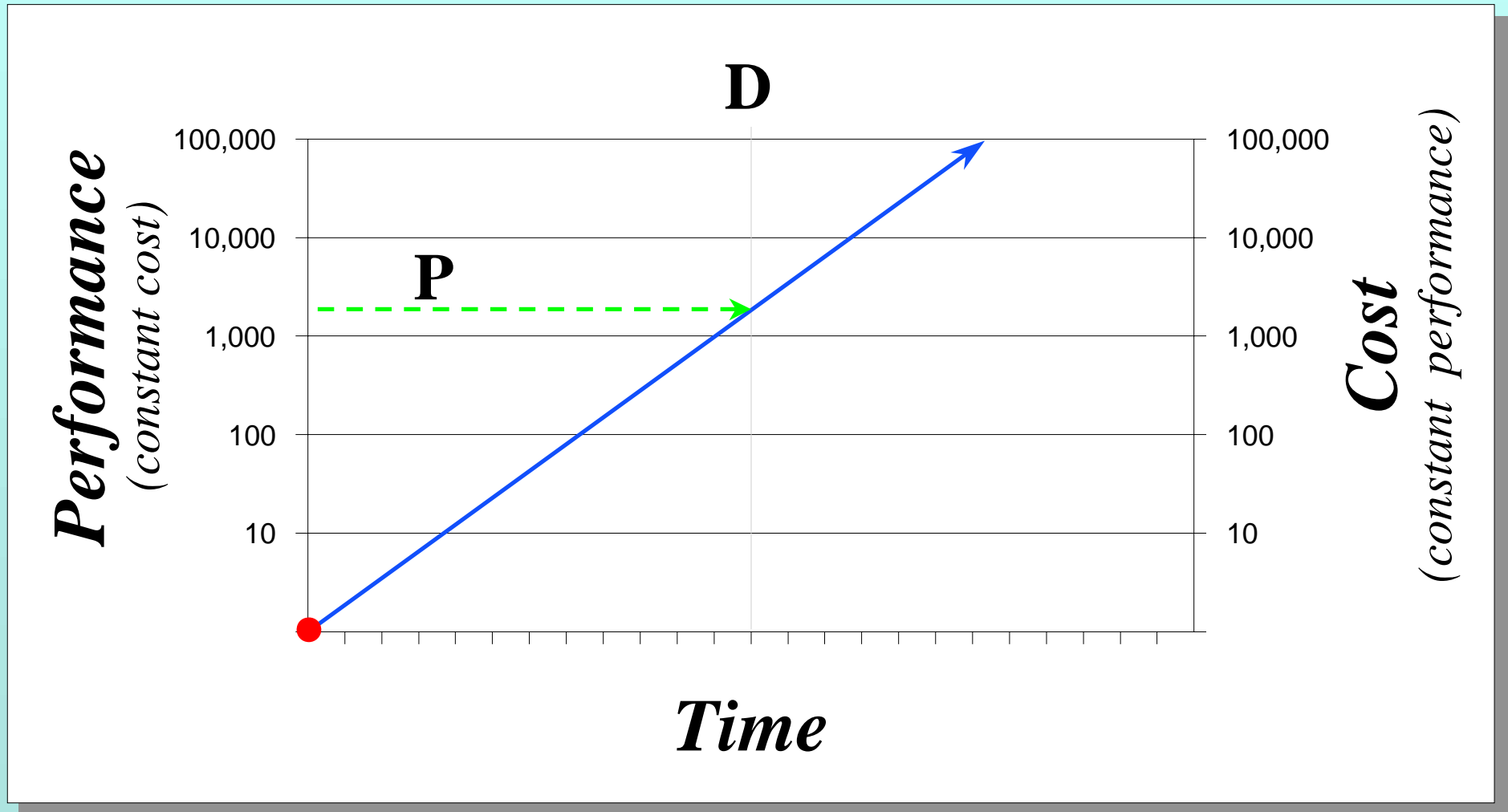


Moore's Law: *The Effect*

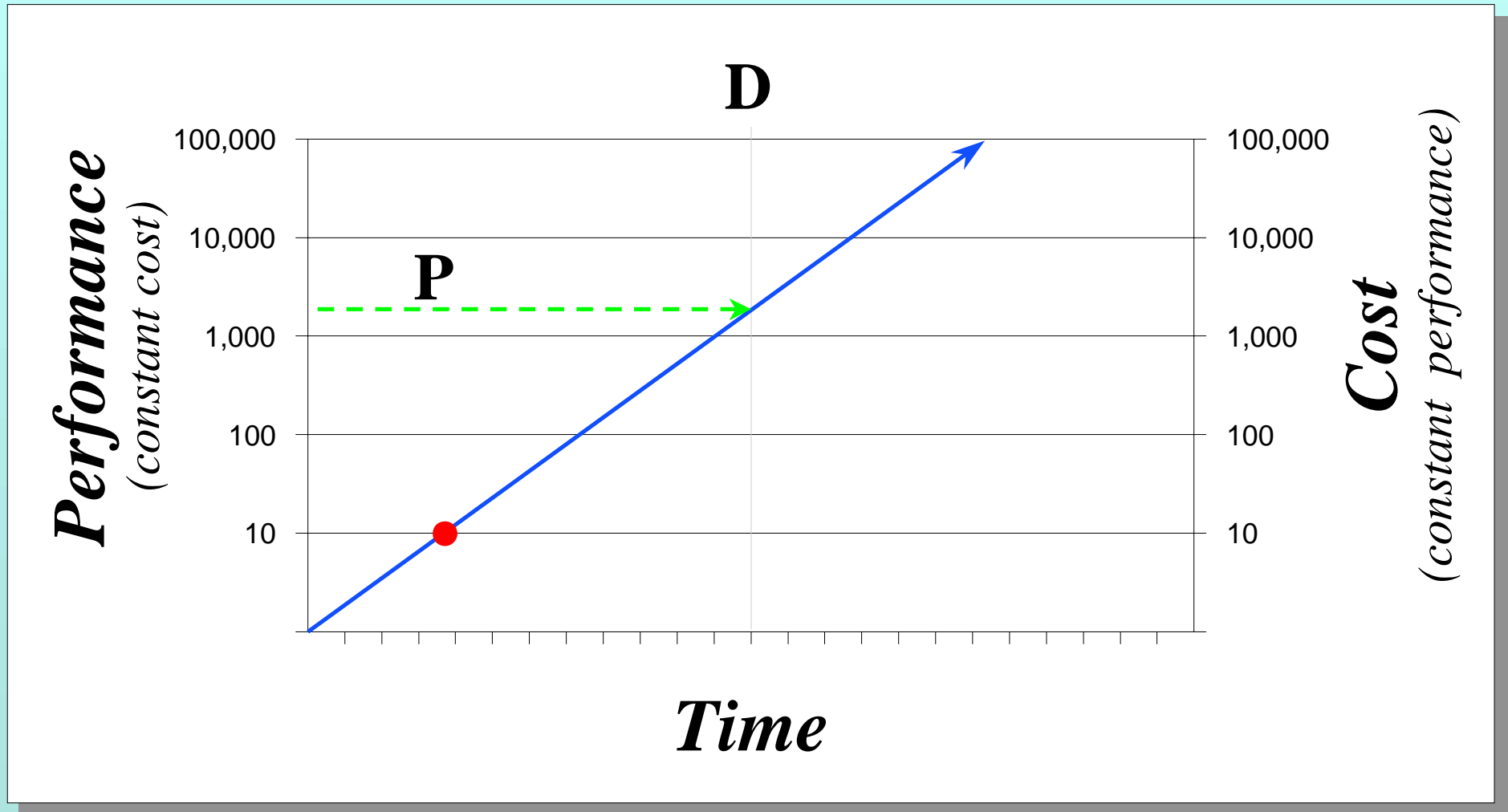
Three Phases of Novel IT Applications

- It's Impossible
- It's Impractical
- It's Overdue

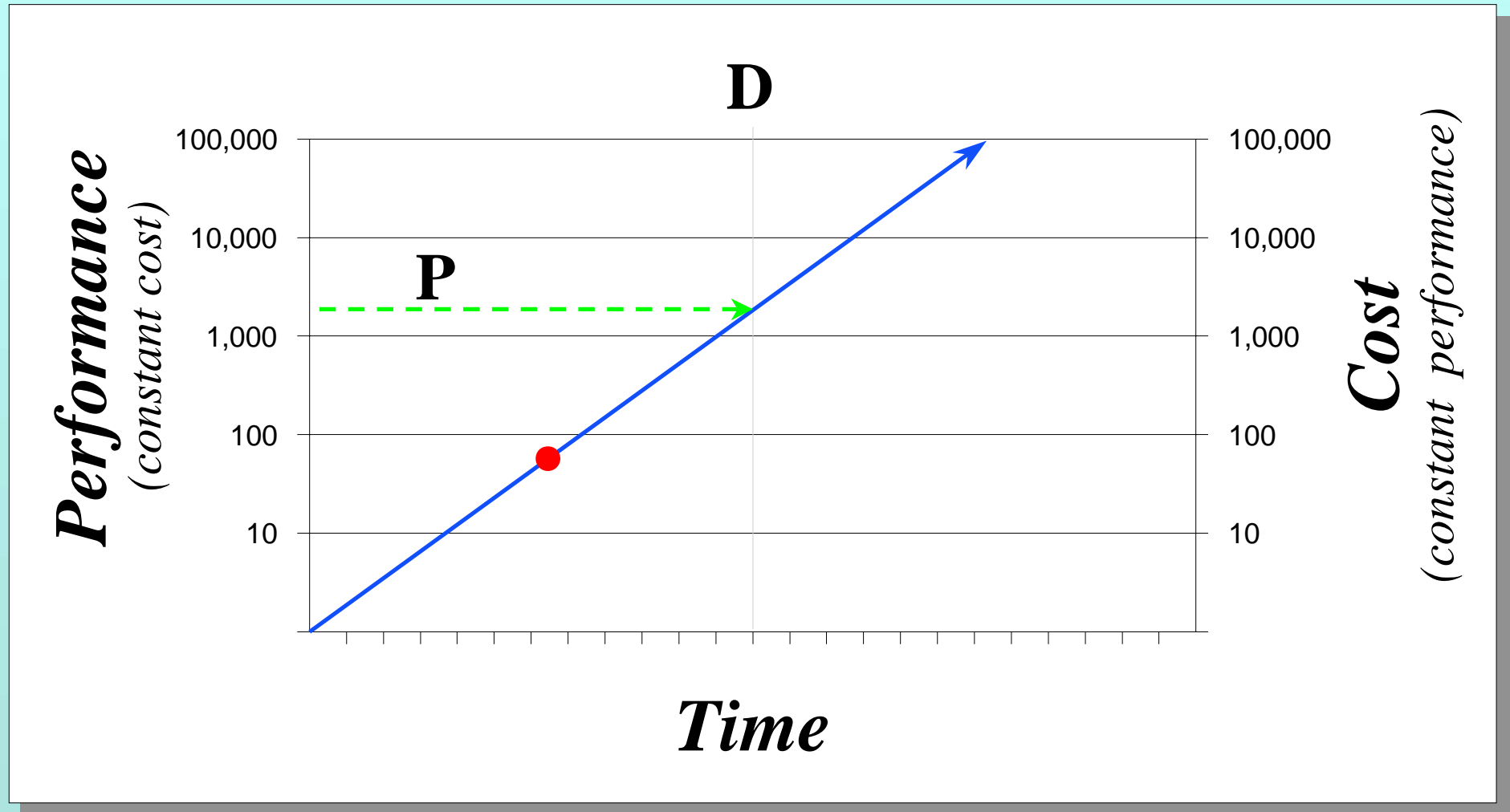
Moore's Law: *The Effect*



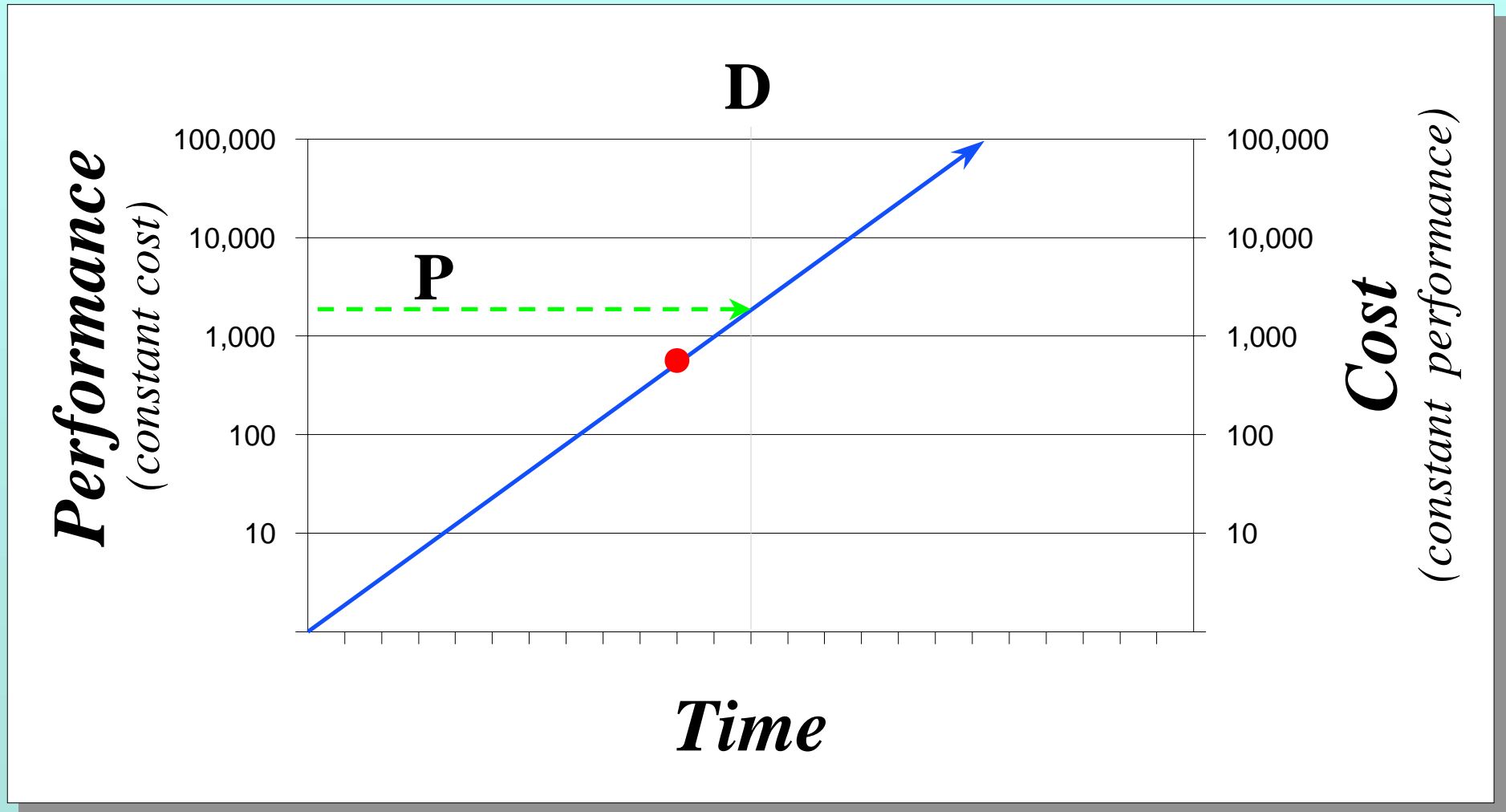
Moore's Law: *The Effect*



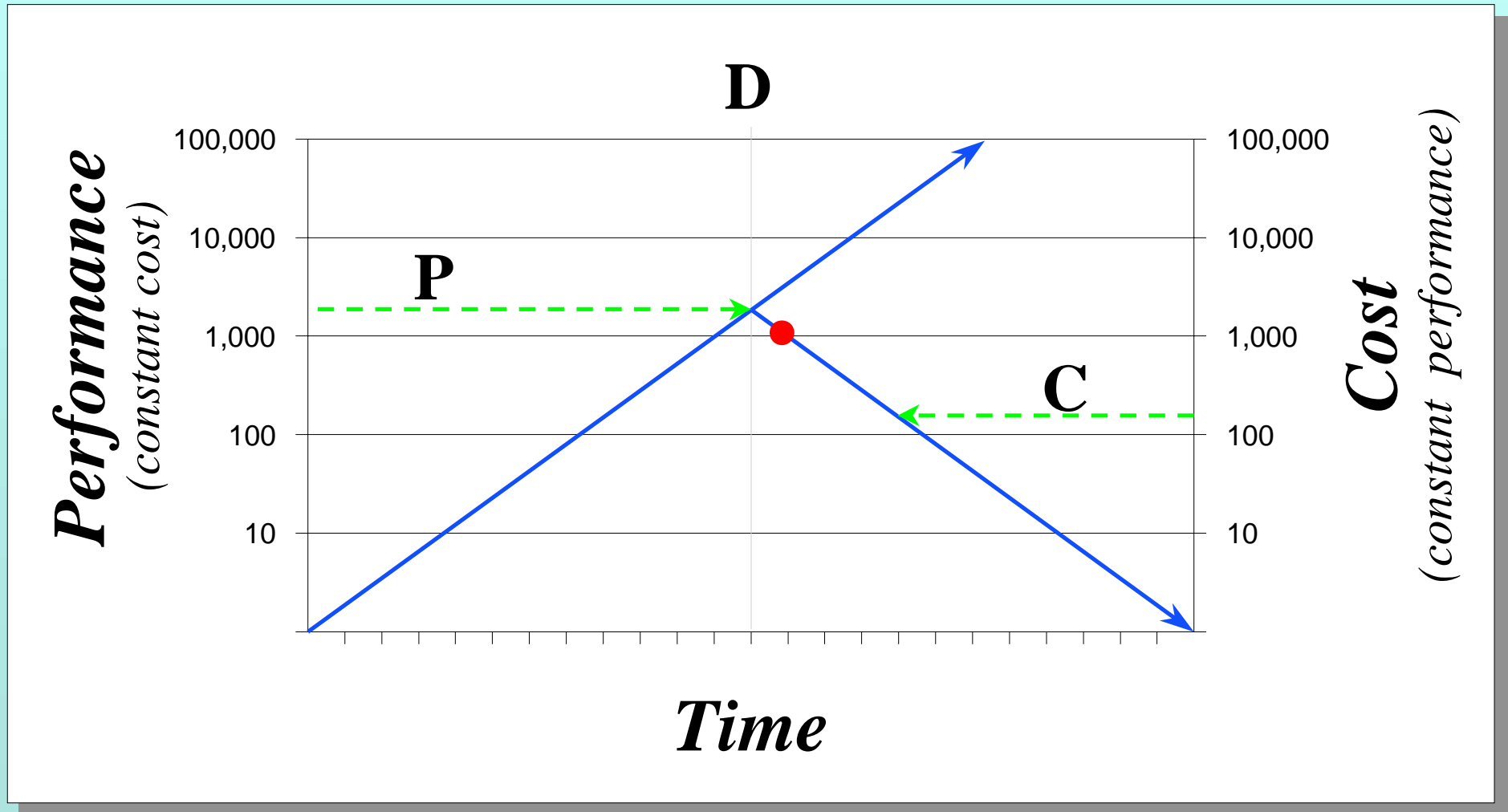
Moore's Law: *The Effect*



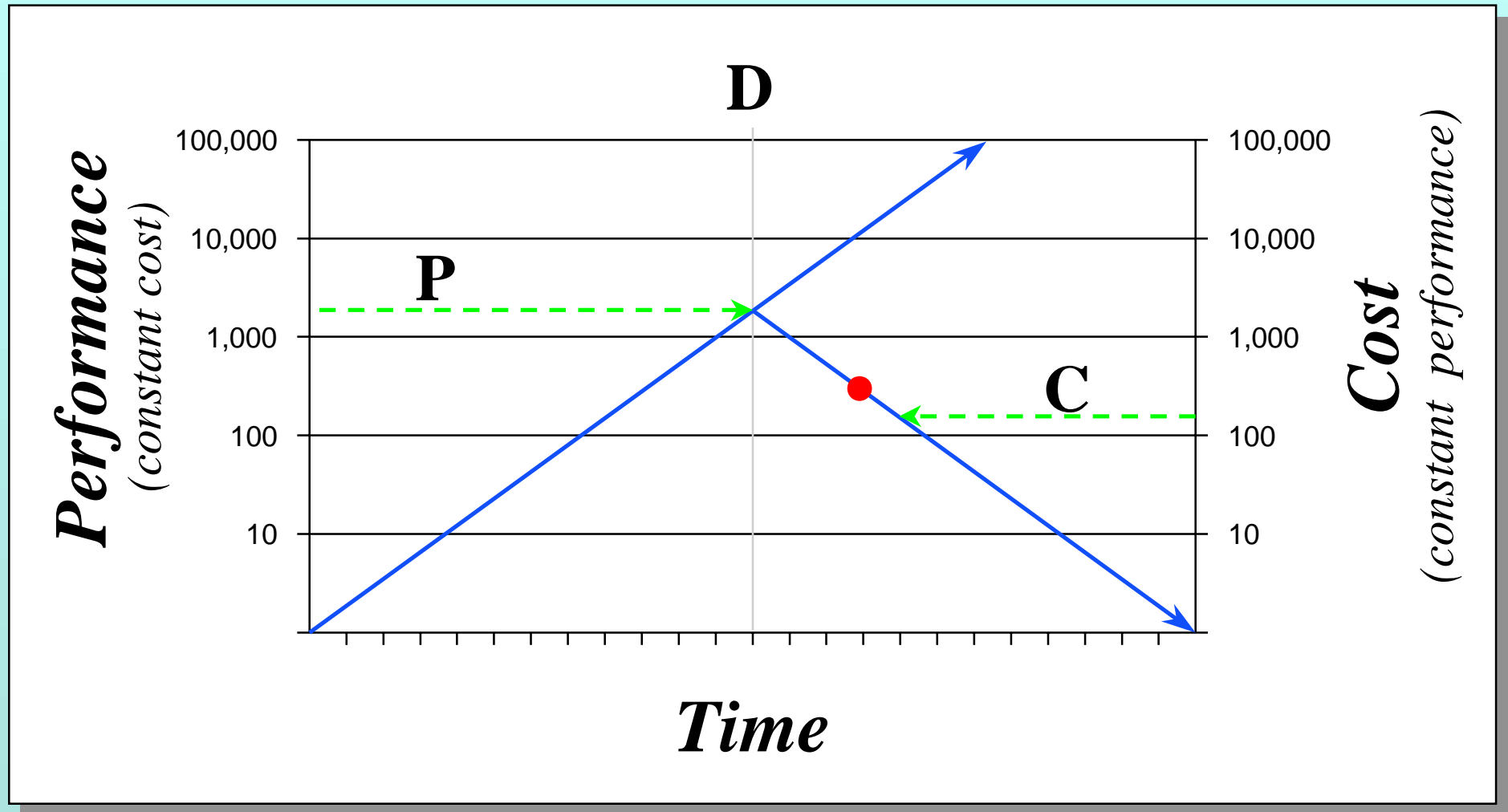
Moore's Law: *The Effect*



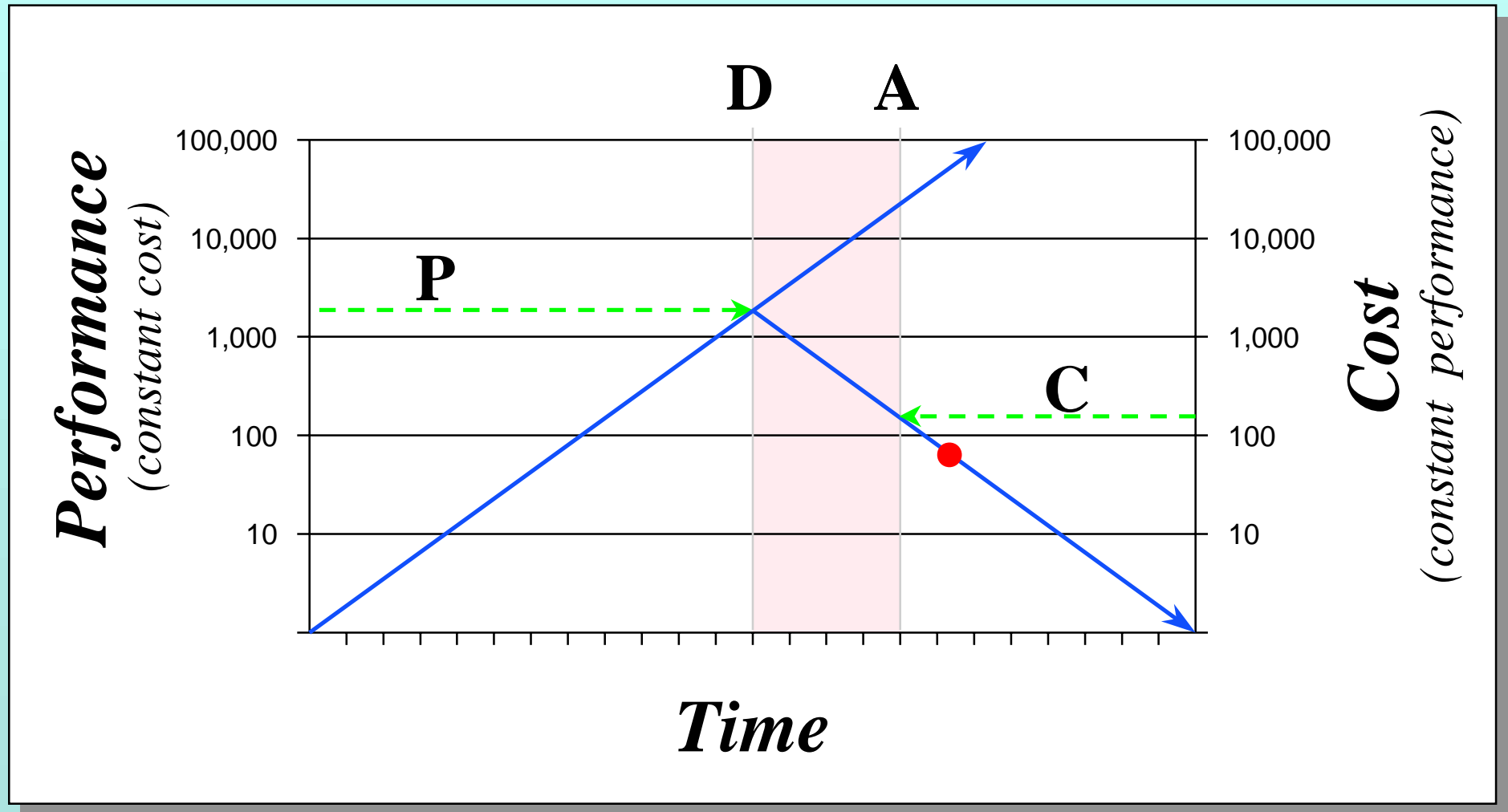
Moore's Law: *The Effect*



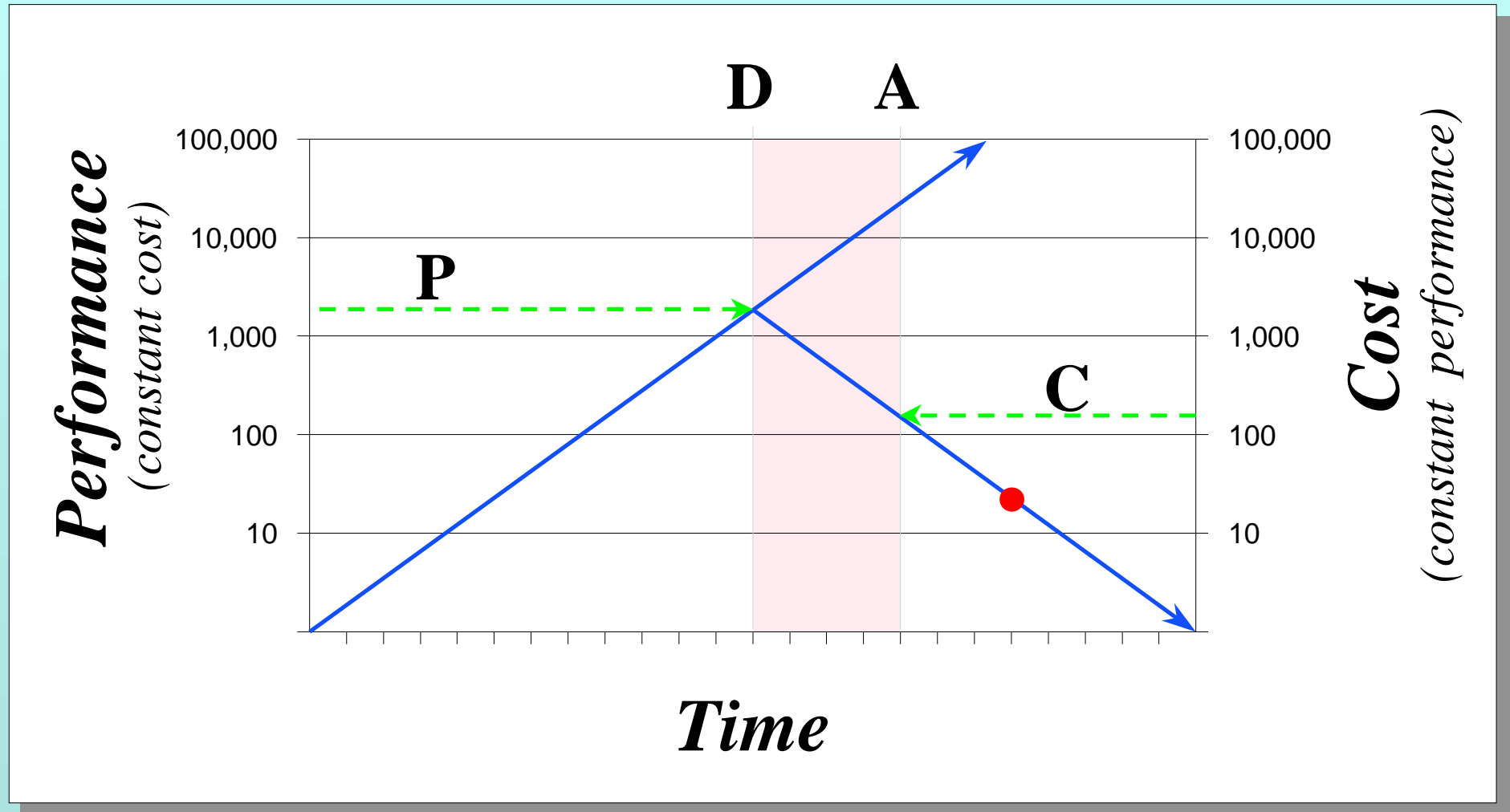
Moore's Law: *The Effect*



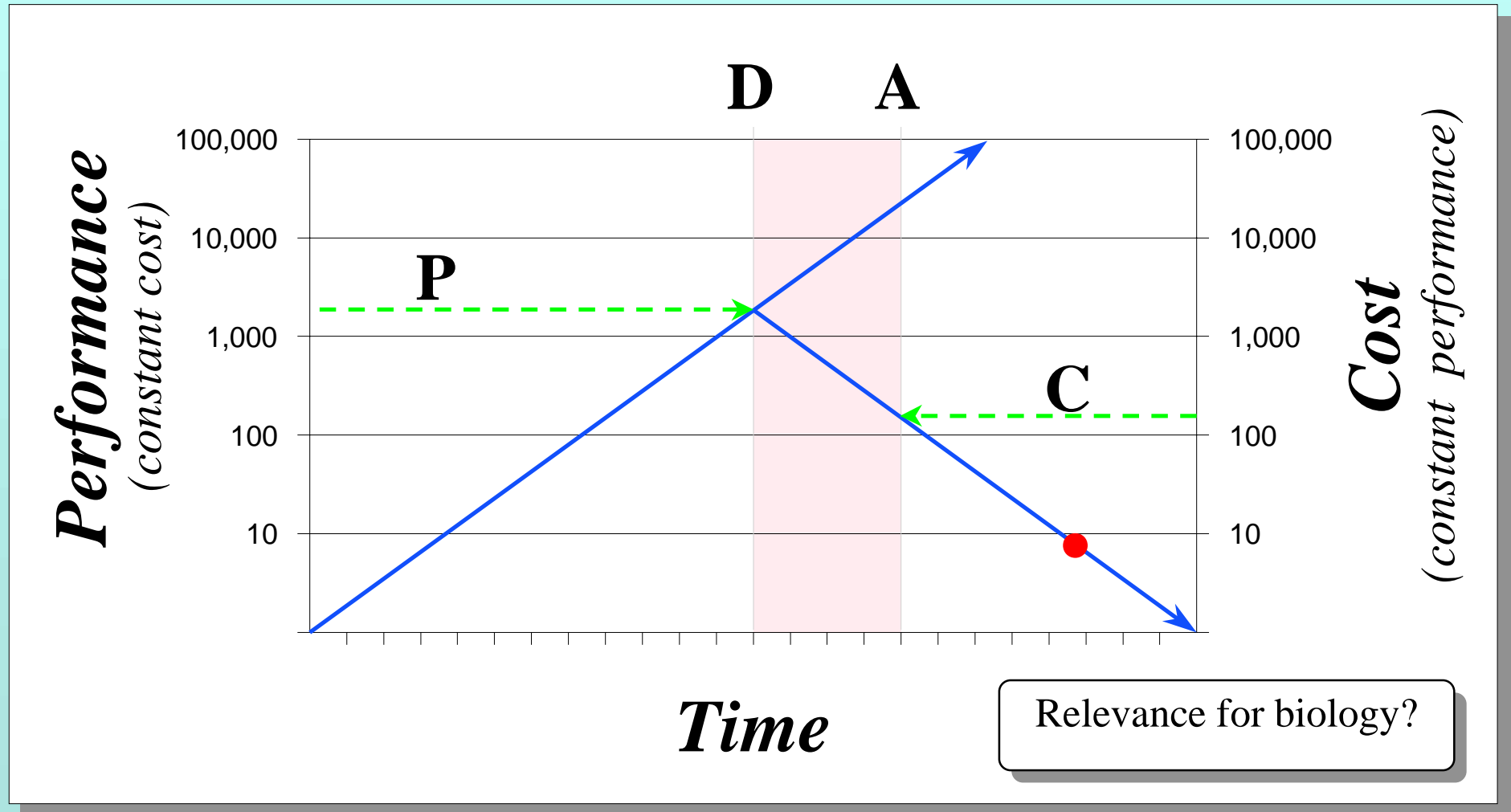
Moore's Law: *The Effect*



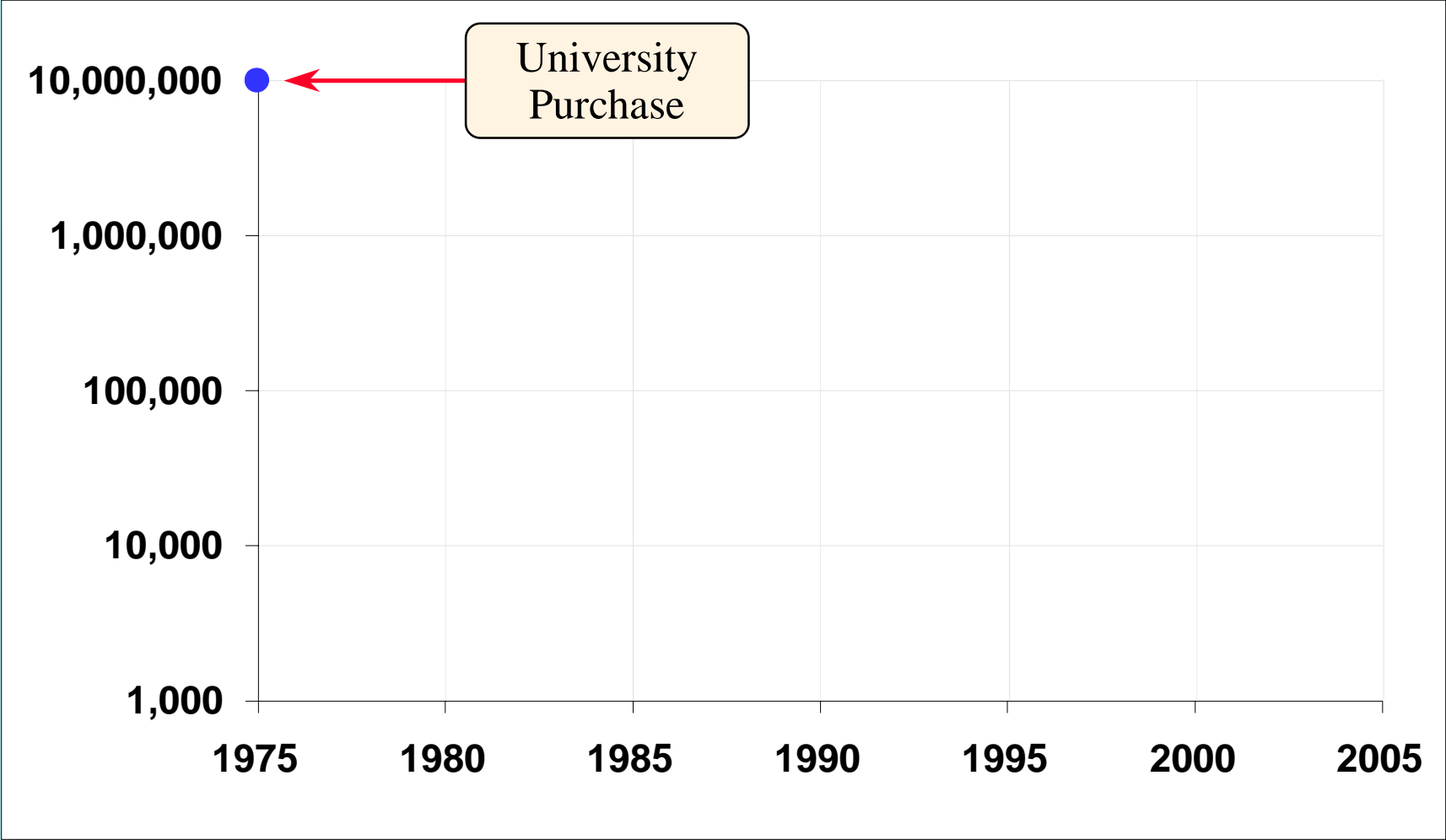
Moore's Law: *The Effect*



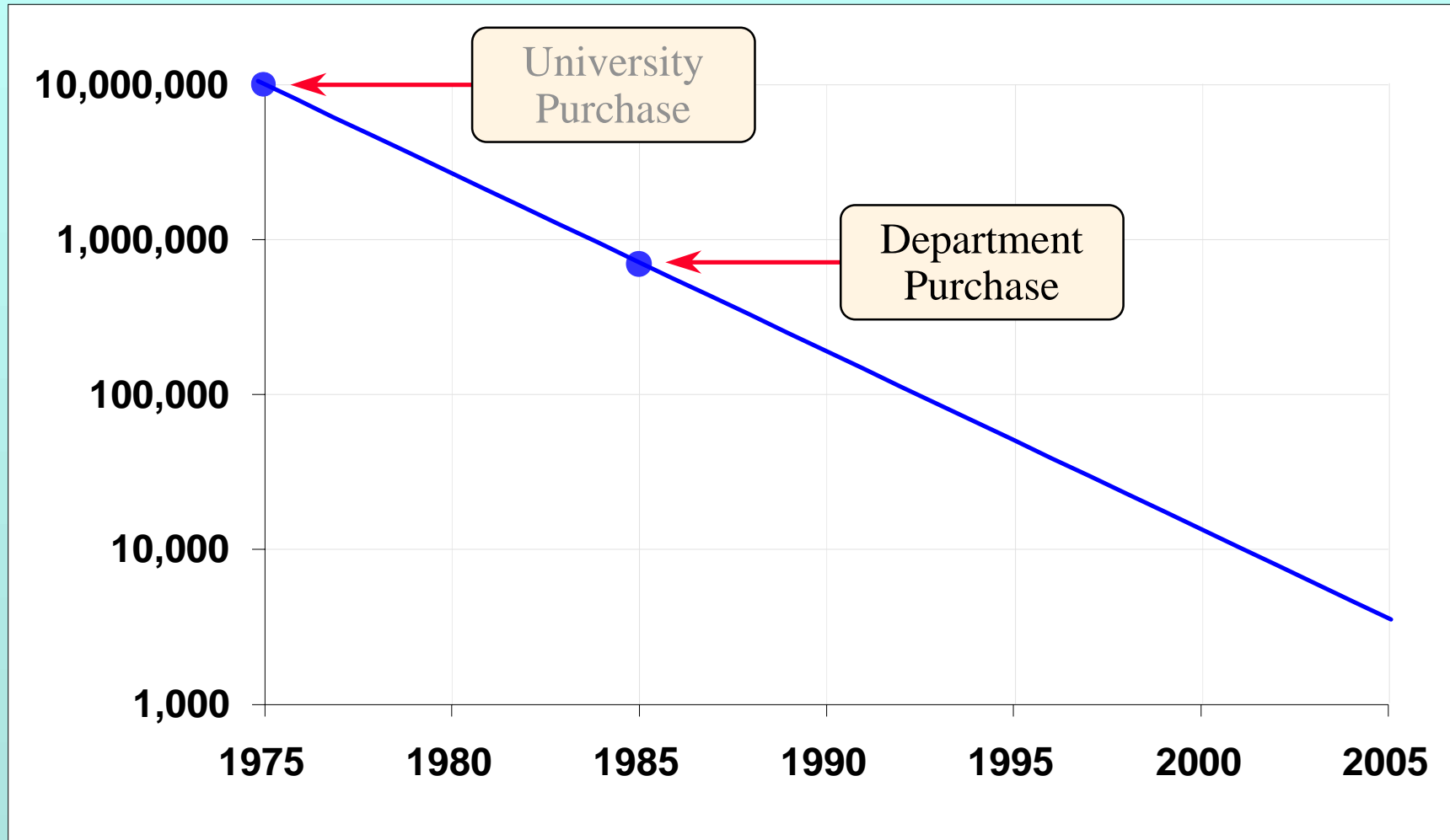
Moore's Law: *The Effect*



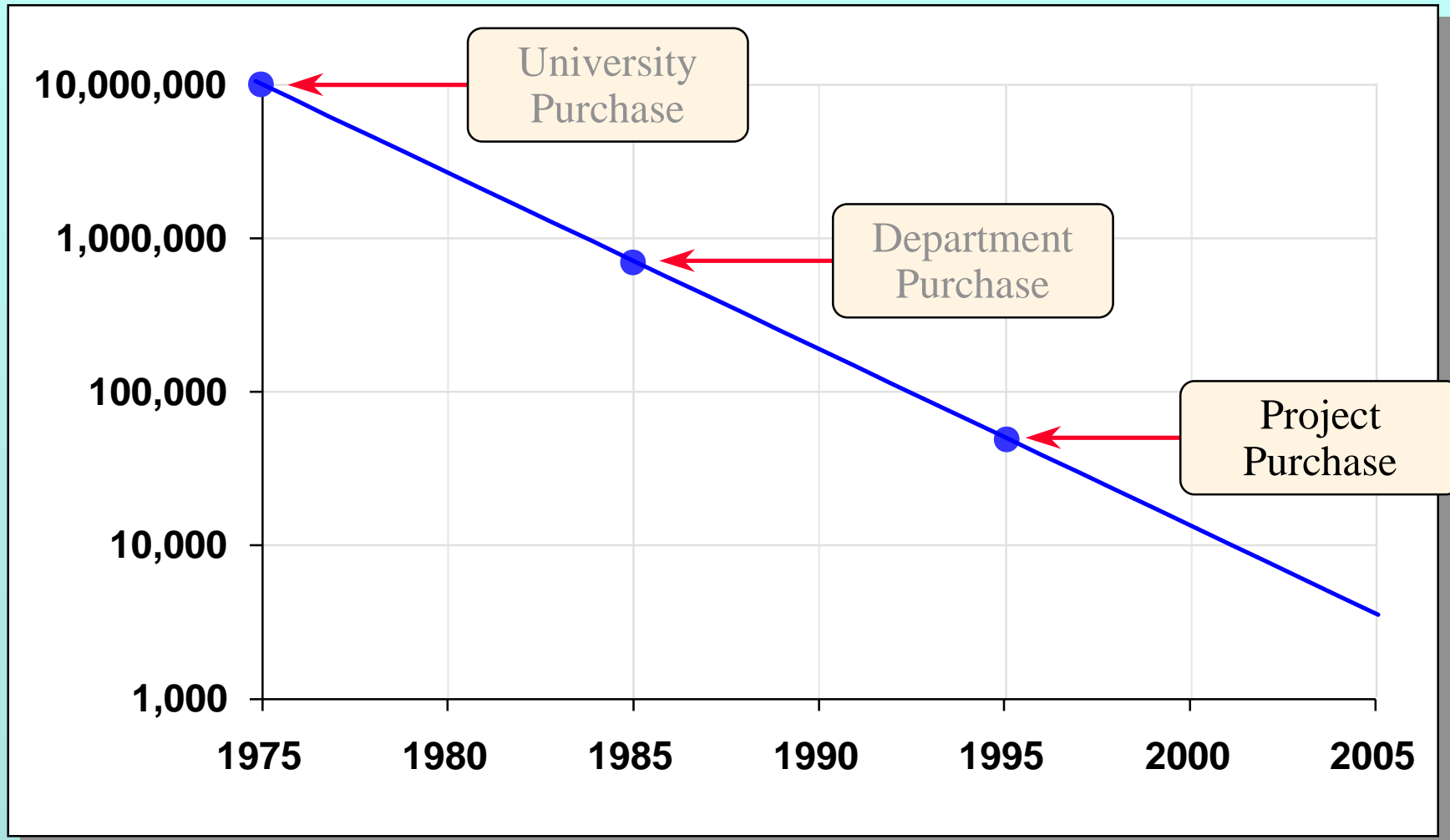
Cost (constant performance)



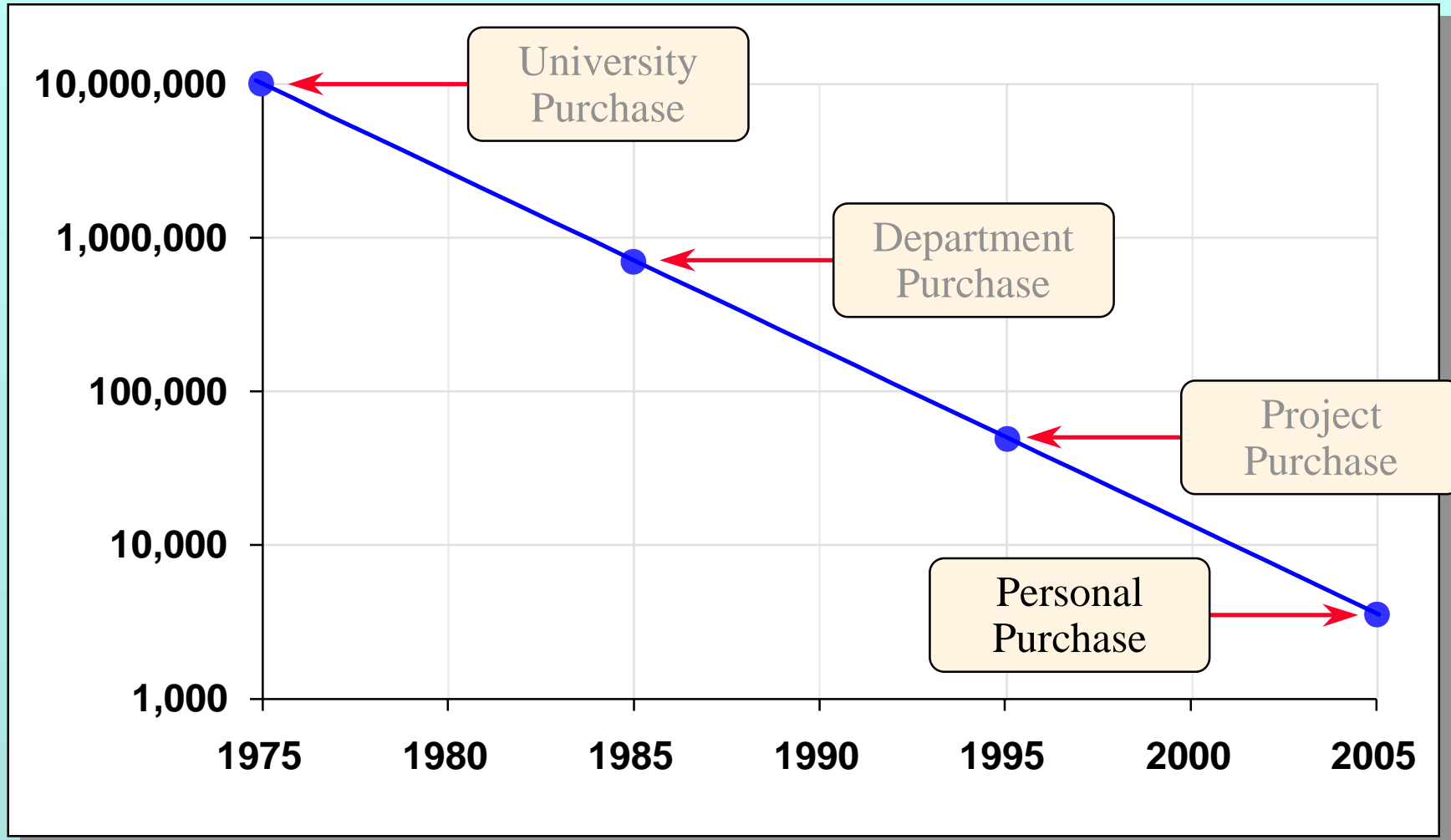
Cost (constant performance)



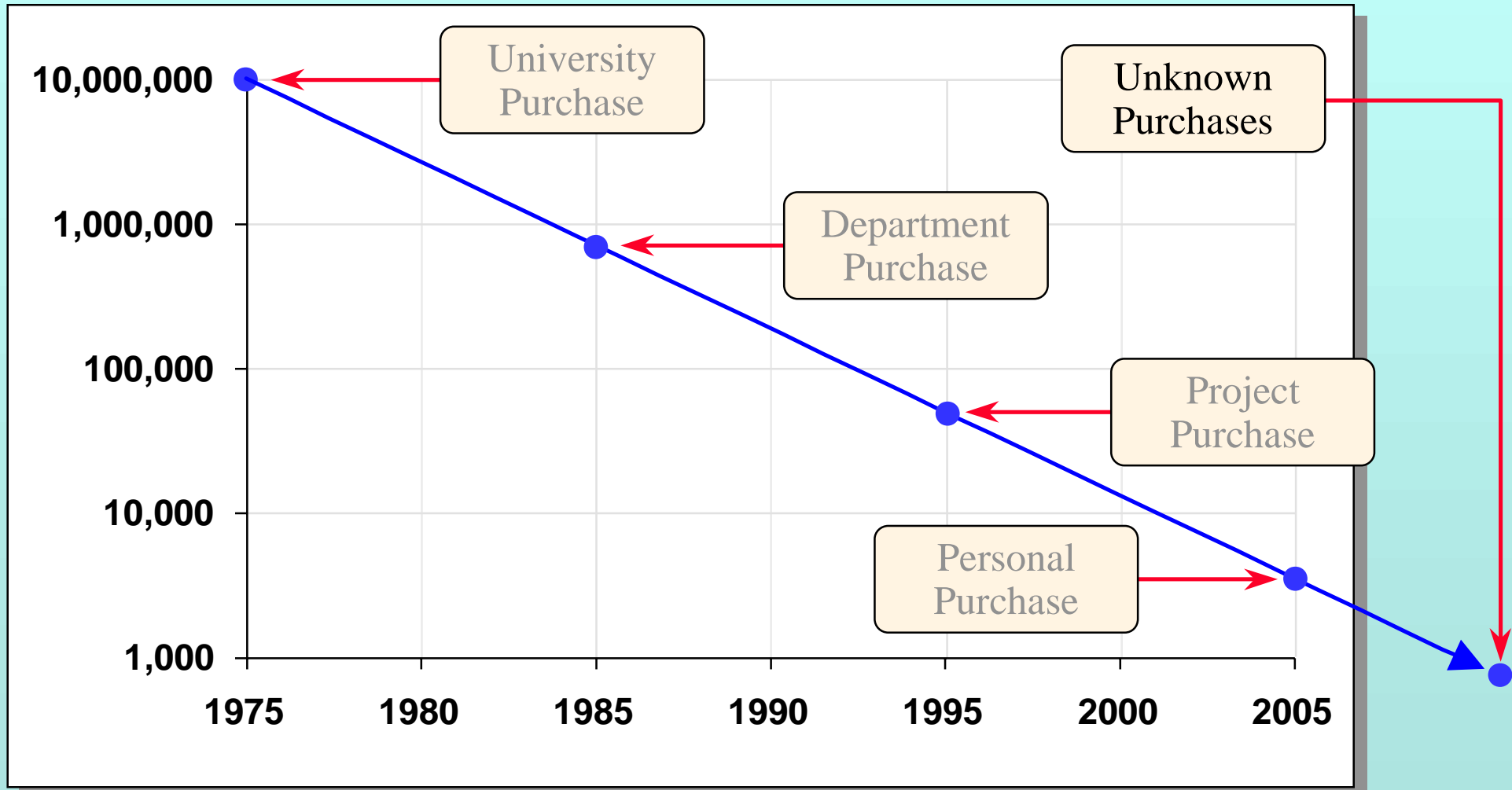
Cost (constant performance)



Cost (constant performance)



Cost (constant performance)



IT-Biology Synergism

IT is Special

Information Technology:

- *affects the performance **and** the management of tasks*
- *allows the manipulation of huge amounts of highly complex data*
- *is incredibly plastic*
(programming and poetry are both exercises in pure thought)
- *improves exponentially* (Moore's Law)

Biology is Special

Life is Characterized by:

- *individuality*
- *historicity*
- *contingency*
- *high (digital) information content*

No law of large numbers, since every living thing is genuinely unique.

IT-Biology Synergism

- *Physics needs calculus, the method for manipulating information about statistically large numbers of vanishingly small, independent, equivalent things.*
- *Biology needs information technology, the method for manipulating information about large numbers of dependent, historically contingent, individual things.*

Biology is Special

For it is in relation to the statistical point of view that the structure of the vital parts of living organisms differs so entirely from that of any piece of matter that we physicists and chemists have ever handled in our laboratories or mentally at our writing desks.

Erwin Schrödinger. 1944. *What is Life*.

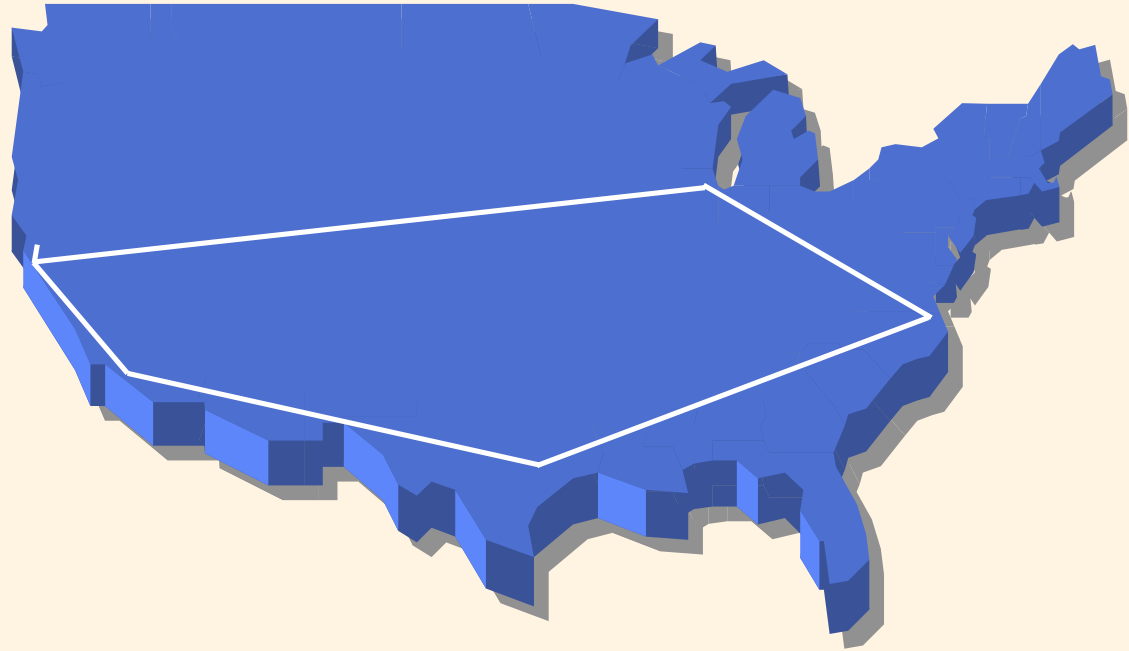
Genetics as Code

[The] chromosomes ... contain in some kind of code-script the entire pattern of the individual's future development and of its functioning in the mature state. ... [By] code-script we mean that the all-penetrating mind, once conceived by Laplace, to which every causal connection lay immediately open, could tell from their structure whether [an egg carrying them] would develop, under suitable conditions, into a black cock or into a speckled hen, into a fly or a maize plant, a rhodo-dendron, a beetle, a mouse, or a woman.

Erwin Schrödinger. 1944. *What is Life*.

One Human Sequence

We now know that Schrödinger's mysterious human "code-script" consists of 3.3 billion base pairs of DNA.



Typed in 10-pitch font, one human sequence would stretch for more than 5,000 miles. Digitally formatted, it could be stored on one CD-ROM. Biologically encoded, it fits easily within a single cell.

One Human Sequence

A variant of this factoid actually made it into *Ripley's Believe It or Not*, but that's another story...



For details on Ripley's interest in DNA, see

[HTTP://LX1.SELU.COM/~rjr/factoids/genlen.html](http://lx1.selu.com/~rjr/factoids/genlen.html)

Bio-digital Information

DNA is a highly efficient digital storage device:

- There is more mass-storage capacity in the DNA of a side of beef than in all the hard drives of all the world's computers.
- Storing all of the (redundant) information in all of the world's DNA on computer hard disks would require that the entire surface of the Earth be covered to a depth of three miles in Conner 1.0 gB drives.

Genomics: An Example

Human Genome Project - Goals

- construction of a high-resolution genetic map of the human genome;
- production of a variety of physical maps of all human chromosomes and of the DNA of selected model organisms;
- determination of the complete sequence of human DNA and of the DNA of selected model organisms;
- development of capabilities for collecting, storing, distributing, and analyzing the data produced;
- creation of appropriate technologies necessary to achieve these objectives.

USDOE. 1990. *Understanding Our Genetic Inheritance. The U.S. Human Genome Project: The First Five Years.*

Infrastructure and the HGP

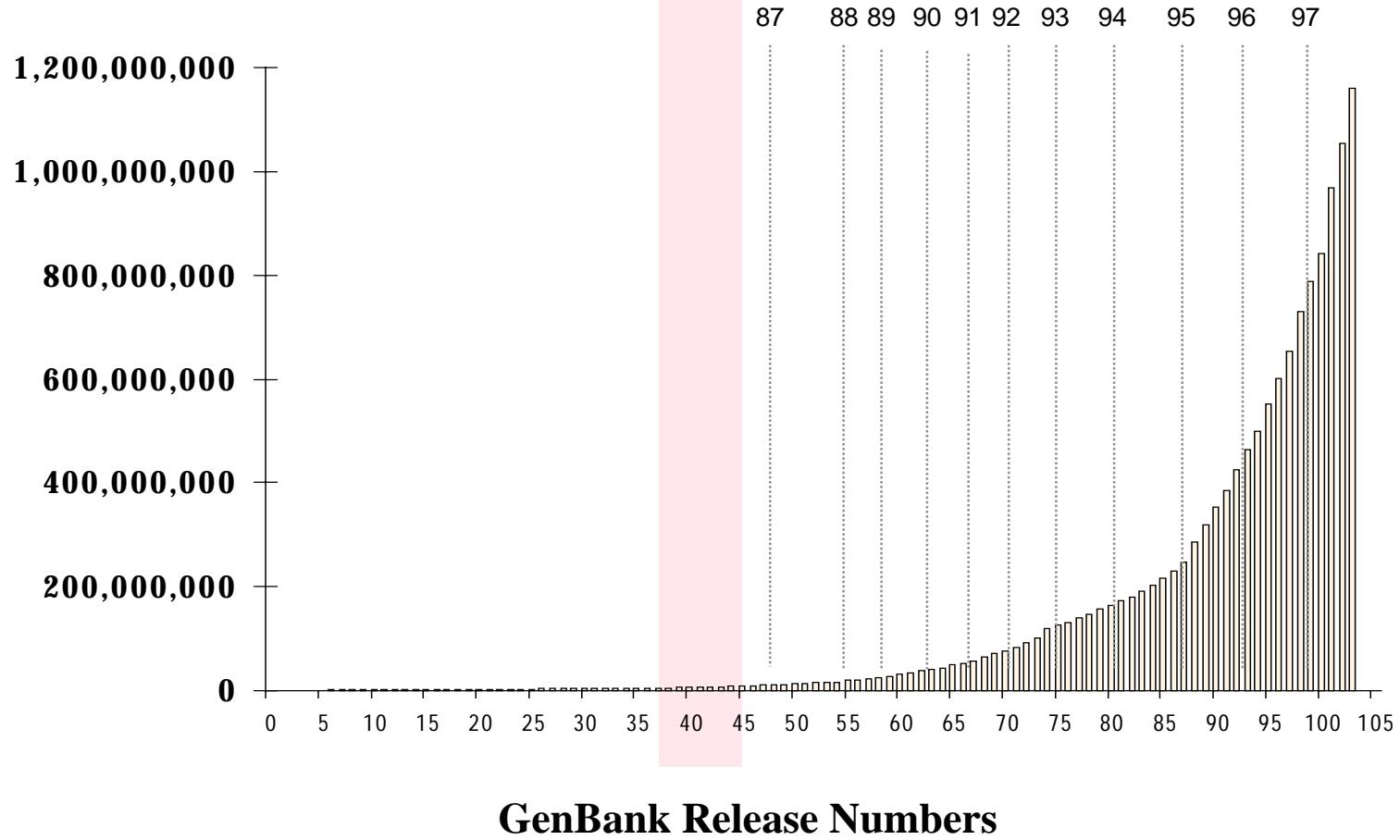
Progress towards all of the [Genome Project] goals will require the establishment of well-funded centralized facilities, including a stock center for the cloned DNA fragments generated in the mapping and sequencing effort and a data center for the computer-based collection and distribution of large amounts of DNA sequence information.

National Research Council. 1988. *Mapping and Sequencing the Human Genome*. Washington, DC: National Academy Press. p. 3

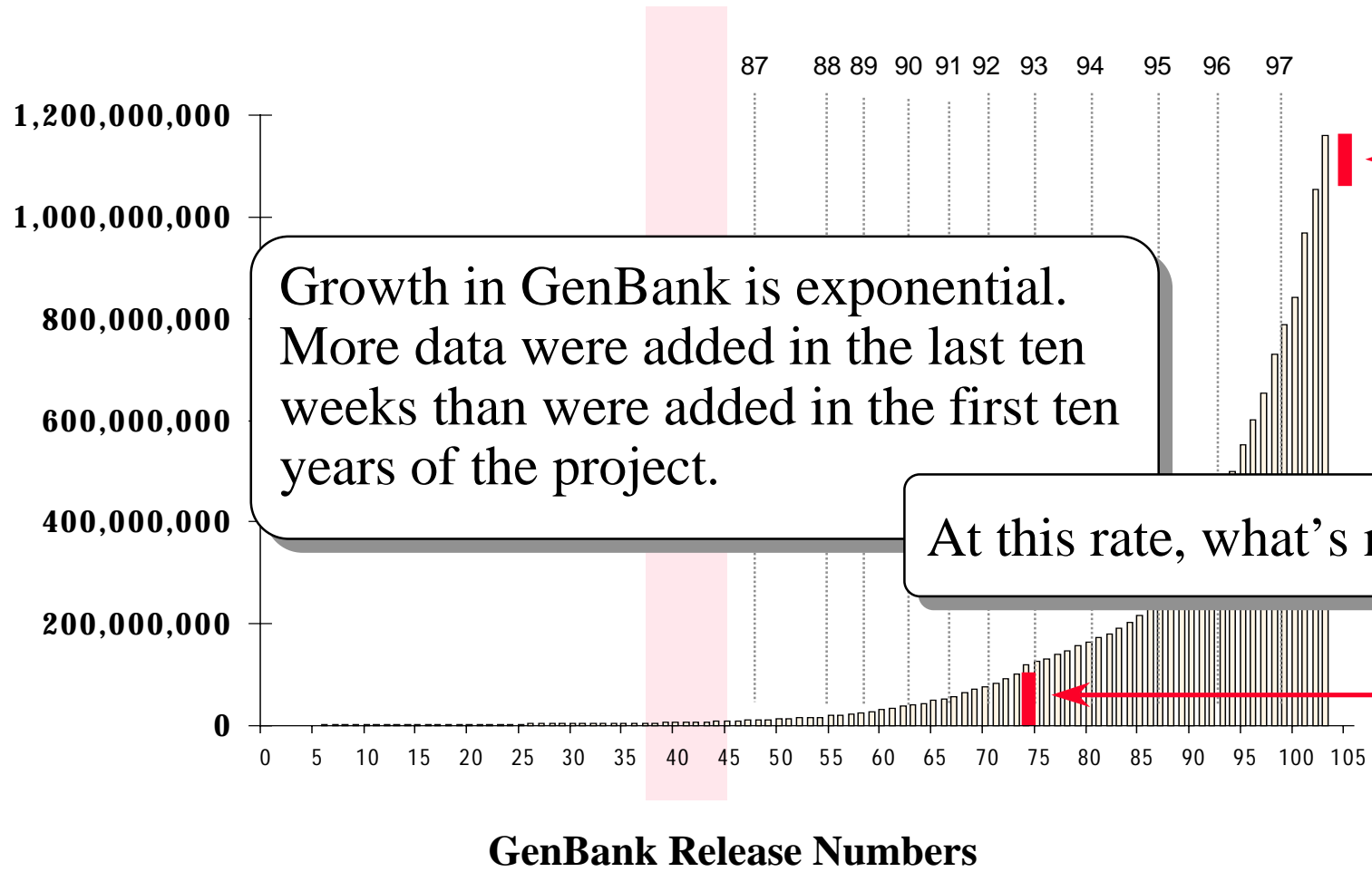
GenBank Totals *(Release 103)*

DIVISION	Entries	Per Cent	Base Pairs	Per Cent
Phage Sequences (PHG)	1,313	0.074%	2,138,810	0.184%
Viral Sequences (VRL)	45,355	2.568%	44,484,848	3.834%
Bacteria (BCT)	38,023	2.153%	88,576,641	7.634%
Plant, Fungal, and Algal Sequences (PLN)	44,553	2.523%	92,259,434	7.951%
Invertebrate Sequences (INV)	29,657	1.679%	105,703,550	9.110%
Rodent Sequences (ROD)	36,967	2.093%	45,437,309	3.916%
Primate Sequences (PRI1-2)	75,587	4.280%	134,944,314	11.630%
Other Mammals (MAM)	12,744	0.722%	12,358,310	1.065%
Other Vertebrate Sequences (VRT)	17,713	1.003%	17,040,159	1.469%
High-Throughput Genome Sequences (HTG)	1,120	0.063%	72,064,395	6.211%
Genome Survey Sequences (GSS)	42,628	2.414%	22,783,326	1.964%
Structural RNA Sequences (RNA)	4,802	0.272%	2,487,397	0.214%
Sequence Tagged Sites Sequences (STS)	52,824	2.991%	18,161,532	1.565%
Patent Sequences (PAT)	87,767	4.970%	27,593,724	2.378%
Synthetic Sequences (SYN)	2,577	0.146%	5,698,945	0.491%
Unannotated Sequences (UNA)	2,480	0.140%	1,933,676	0.167%
EST1-17	1,269,737	71.905%	466,634,317	40.217%
TOTALS	1,765,847	100.000%	1,160,300,687	100.000%

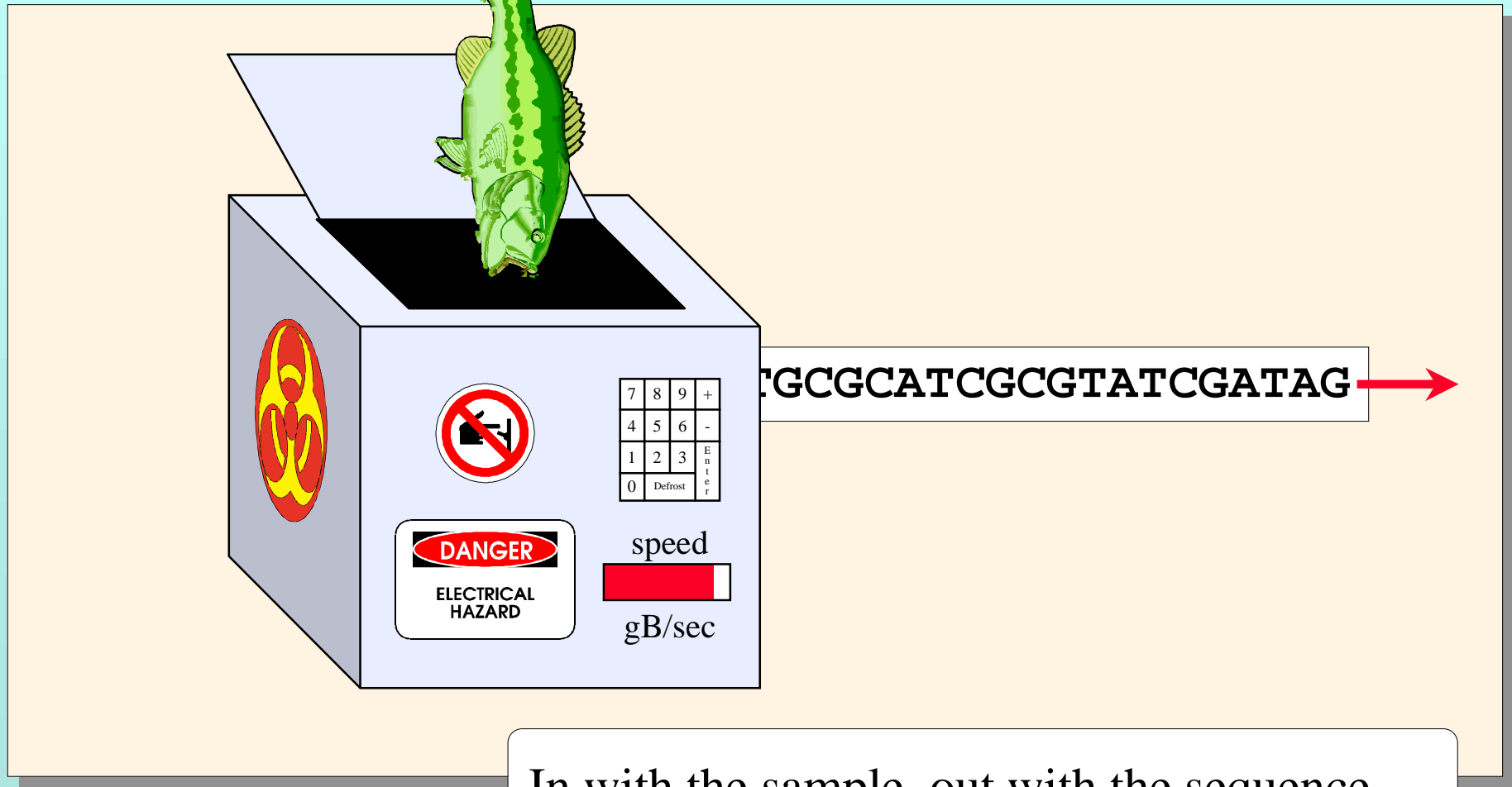
Base Pairs in GenBank



Base Pairs in GenBank



ABI Bass-o-Matic Sequencer



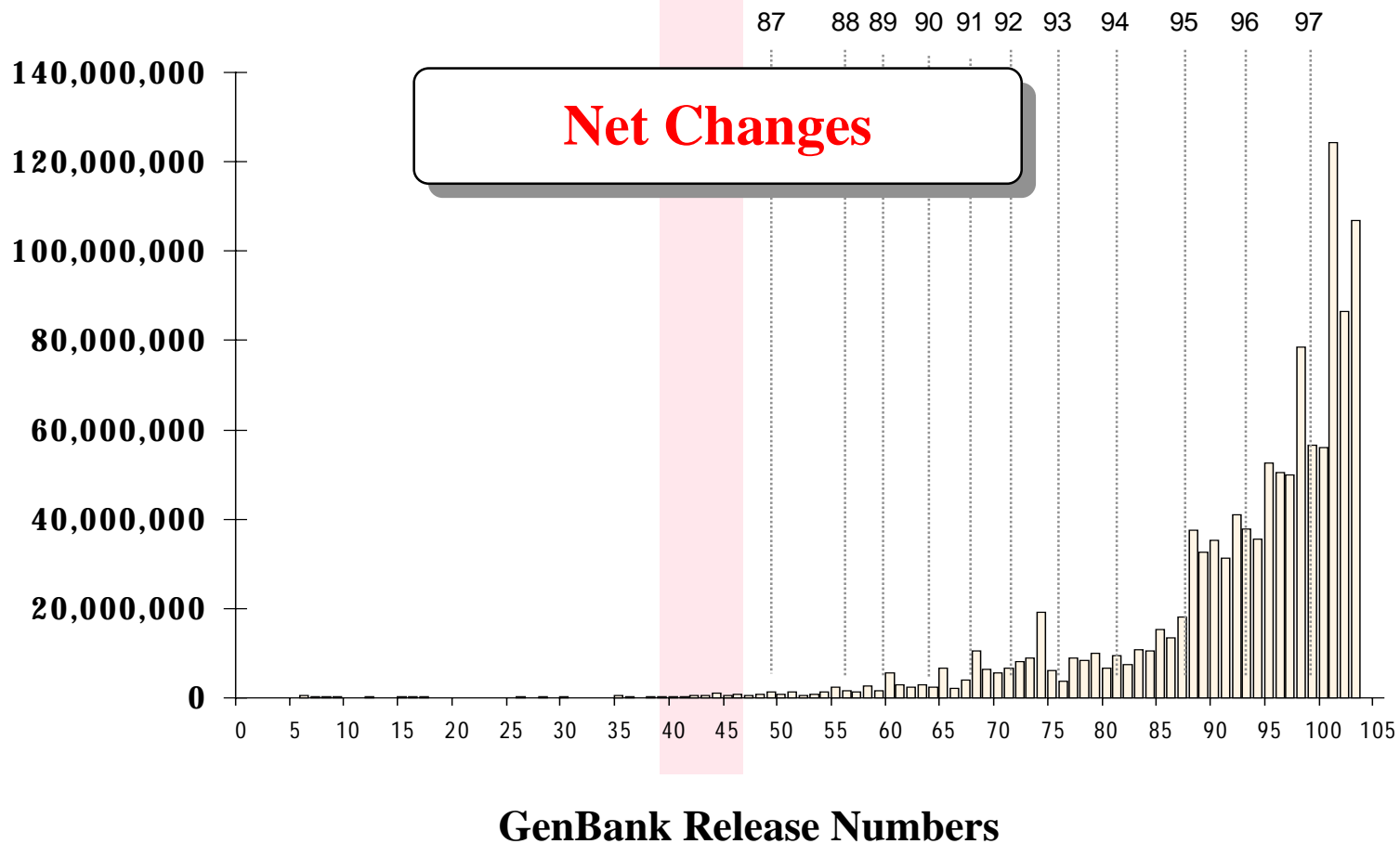
In with the sample, out with the sequence...

What's Really Next

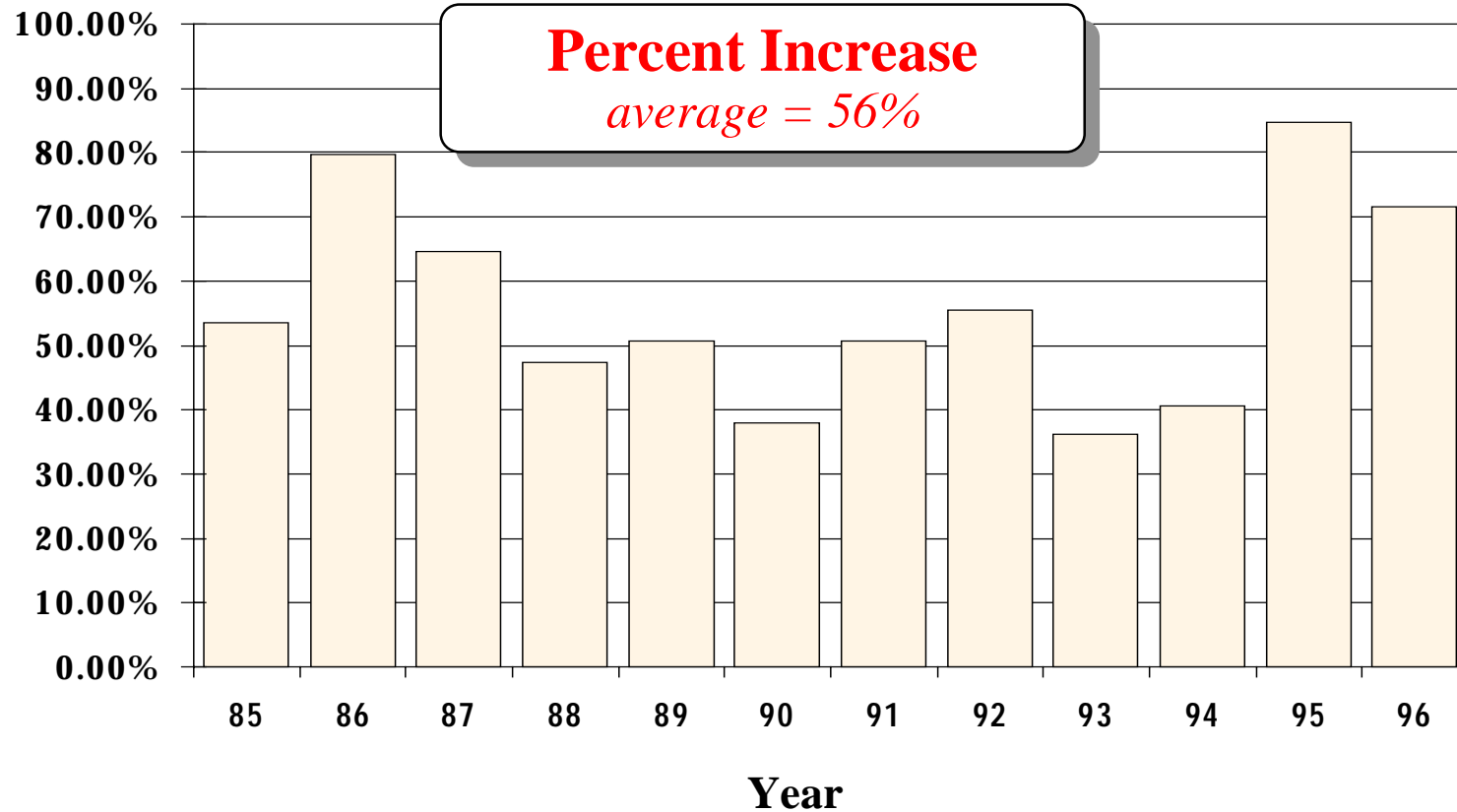
The post-genome era in biological research will take for granted ready access to huge amounts of genomic data.

The challenge will be *understanding* those data and using the understanding to solve real-world problems...

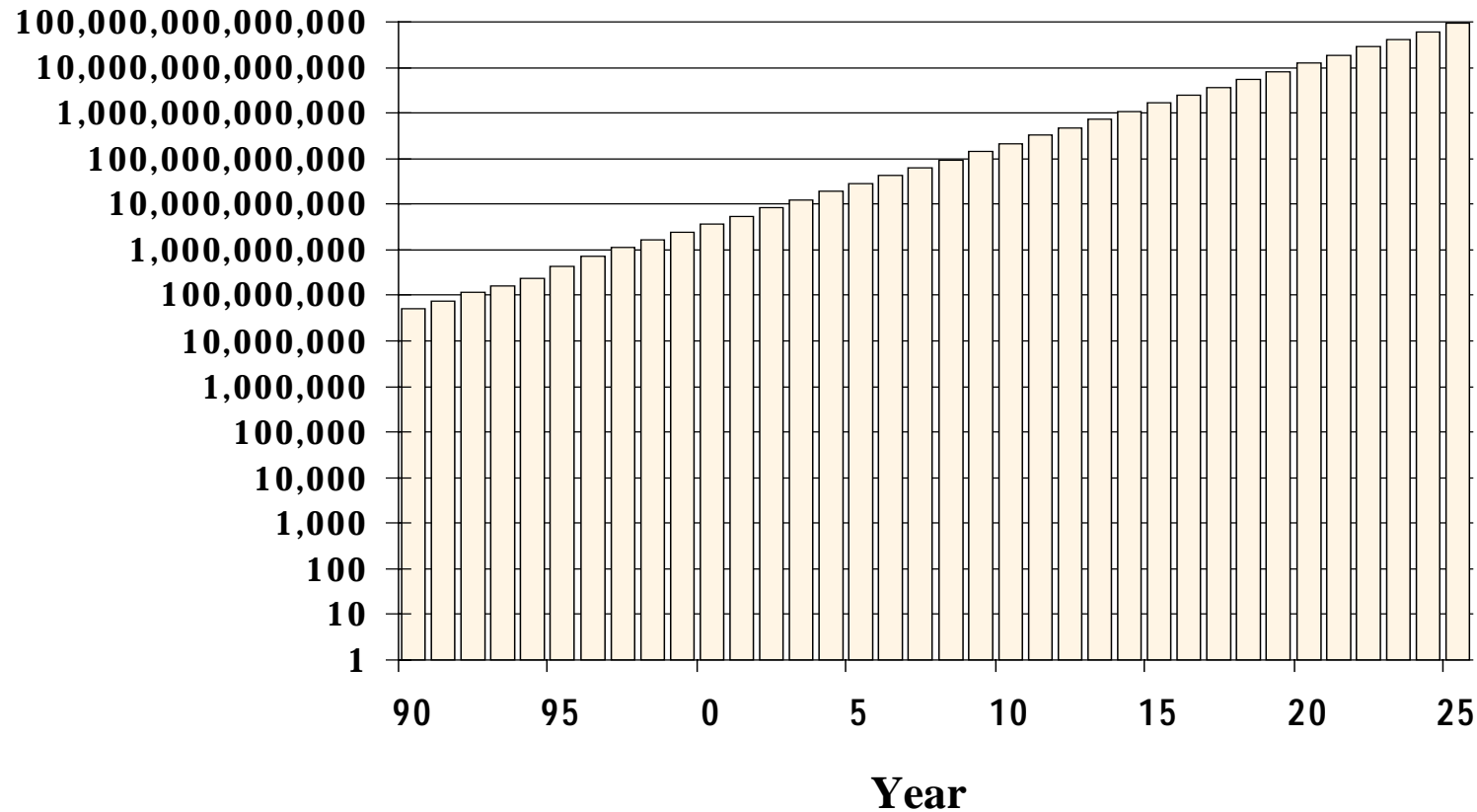
Base Pairs in GenBank



Base Pairs in GenBank (*Percent Increase*)

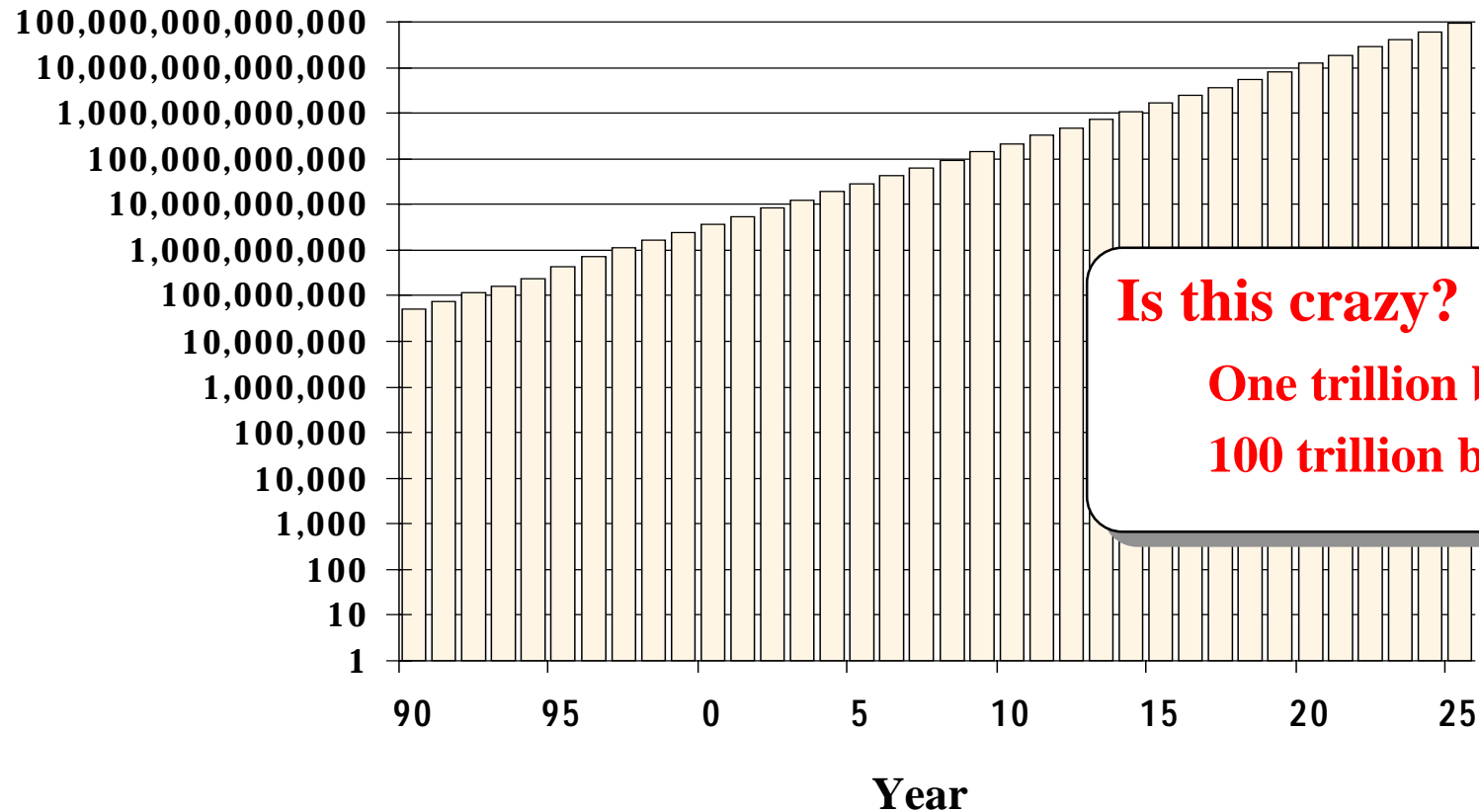


Projected Base Pairs



Assumed annual growth rate: 50%
(less than current rate)

Projected Base Pairs



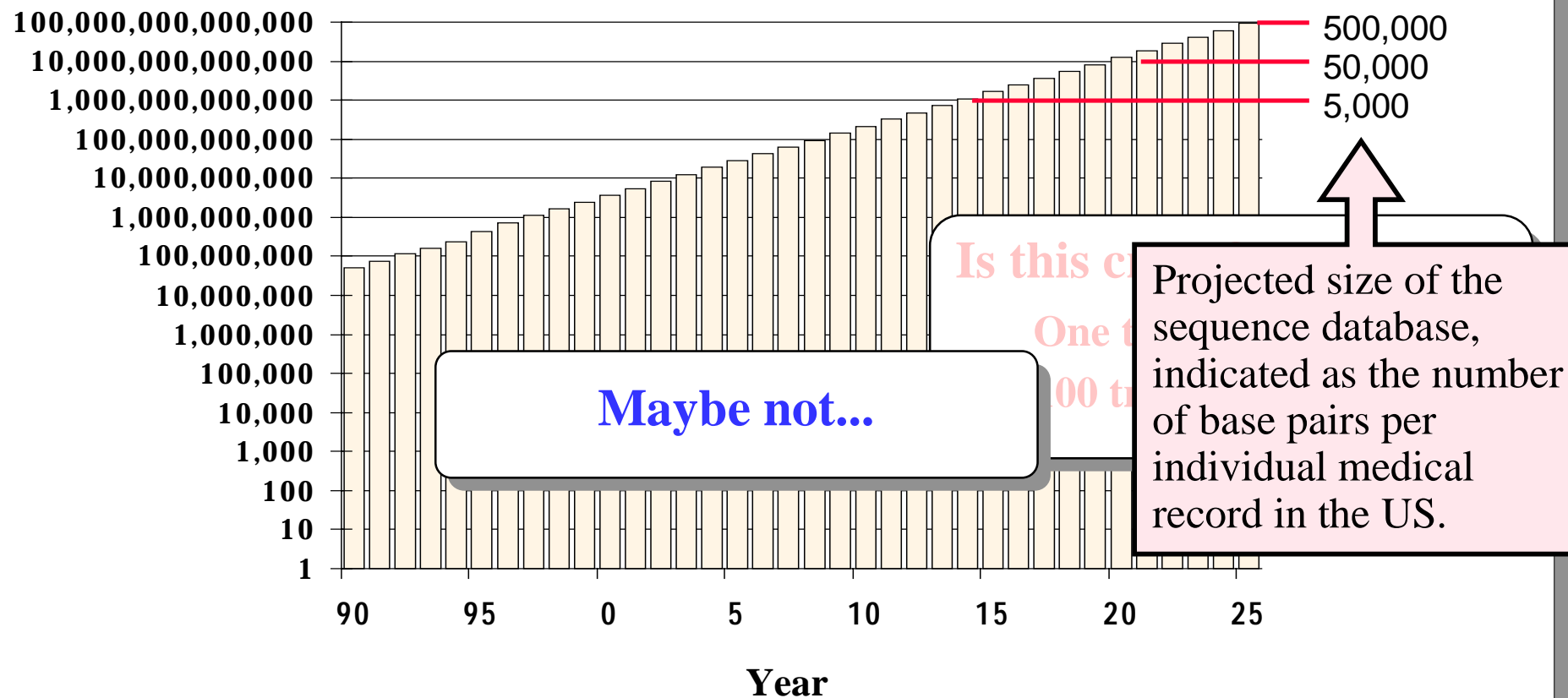
Is this crazy?

One trillion bp by 2015

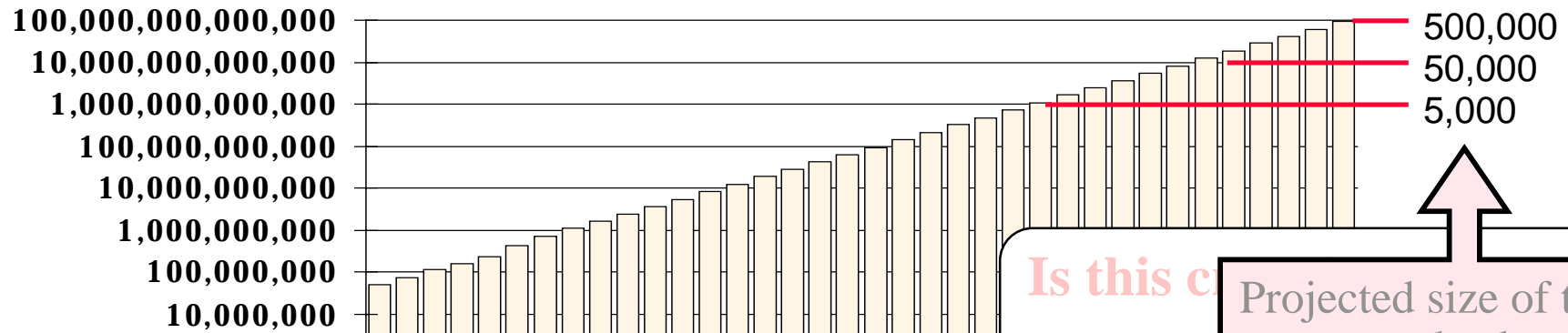
100 trillion by 2025

Assumed annual growth rate: 50%
(less than current rate)

Projected Base Pairs



Projected Base Pairs



Note too:

The amount of digital data necessary to store 10^{14} bases of DNA is only a fraction of the data necessary to describe the world's microbial biodiversity at one square meter resolution...

Is this c

One t
00 t

Projected size of the sequence database, indicated as the number of base pairs per individual medical record in the US.

20

25

21st Century Biology

Post-Genome Era

The Post-Genome Era

Post-genome research involves:

- applying genomic tools and knowledge to more general problems
- asking new questions, tractable only to genomic or post-genomic analysis
- moving beyond the structural genomics of the human genome project and into the functional genomics of the post-genome era

The Post-Genome Era

Suggested definition:

- functional genomics = biology

The Post-Genome Era

An early analysis:

Walter Gilbert. 1991. Towards a paradigm shift in biology. *Nature*, 349:99.

Paradigm Shift in Biology

To use [the] flood of knowledge, which will pour across the computer networks of the world, biologists not only must become computer literate, but also change their approach to the problem of understanding life.

Walter Gilbert. 1991. Towards a paradigm shift in biology. *Nature*, 349:99.

Paradigm Shift in Biology

The new paradigm, now emerging, is that all the 'genes' will be known (in the sense of being resident in databases available electronically), and that the starting point of a biological investigation will be theoretical. An individual scientist will begin with a theoretical conjecture, only then turning to experiment to follow or test that hypothesis.

Walter Gilbert. 1991. Towards a paradigm shift in biology. *Nature*, 349:99.

Paradigm Shift in Biology

Case of Microbiology

< 5,000 known and described bacteria

5,000,000 base pairs per genome

25,000,000,000 TOTAL base pairs

If a full, annotated sequence were available for all known bacteria, the practice of microbiology would match Gilbert's prediction.

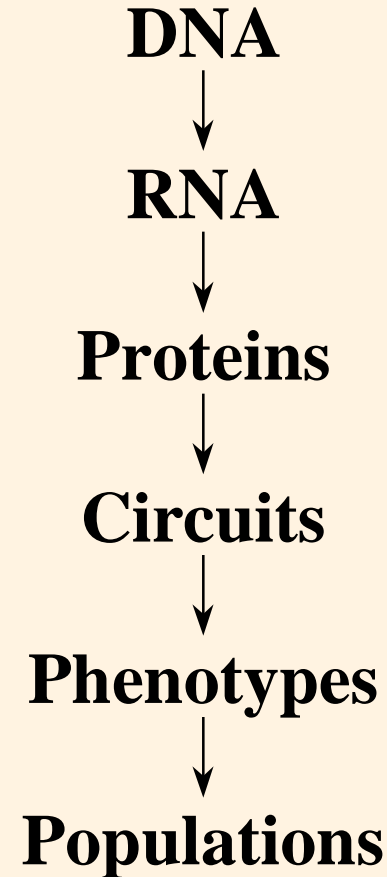
21st Century Biology

The Science

Fundamental Dogma

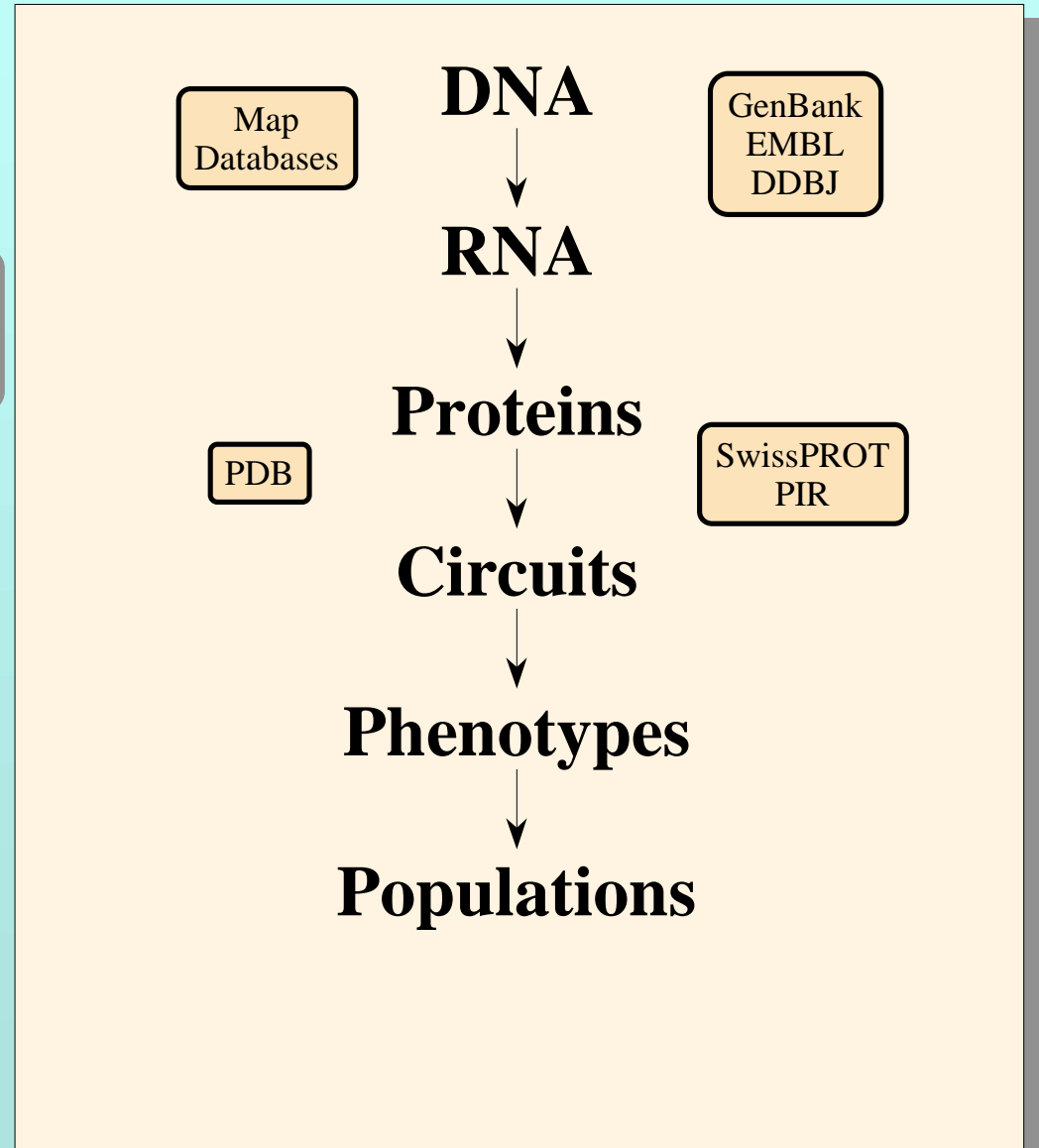
The fundamental dogma of molecular biology is that genes act to create phenotypes through a flow of information from DNA to RNA to proteins, to interactions among proteins (regulatory circuits and metabolic pathways), and ultimately to phenotypes.

Collections of individual phenotypes, of course, constitute a population.



Fundamental Dogma

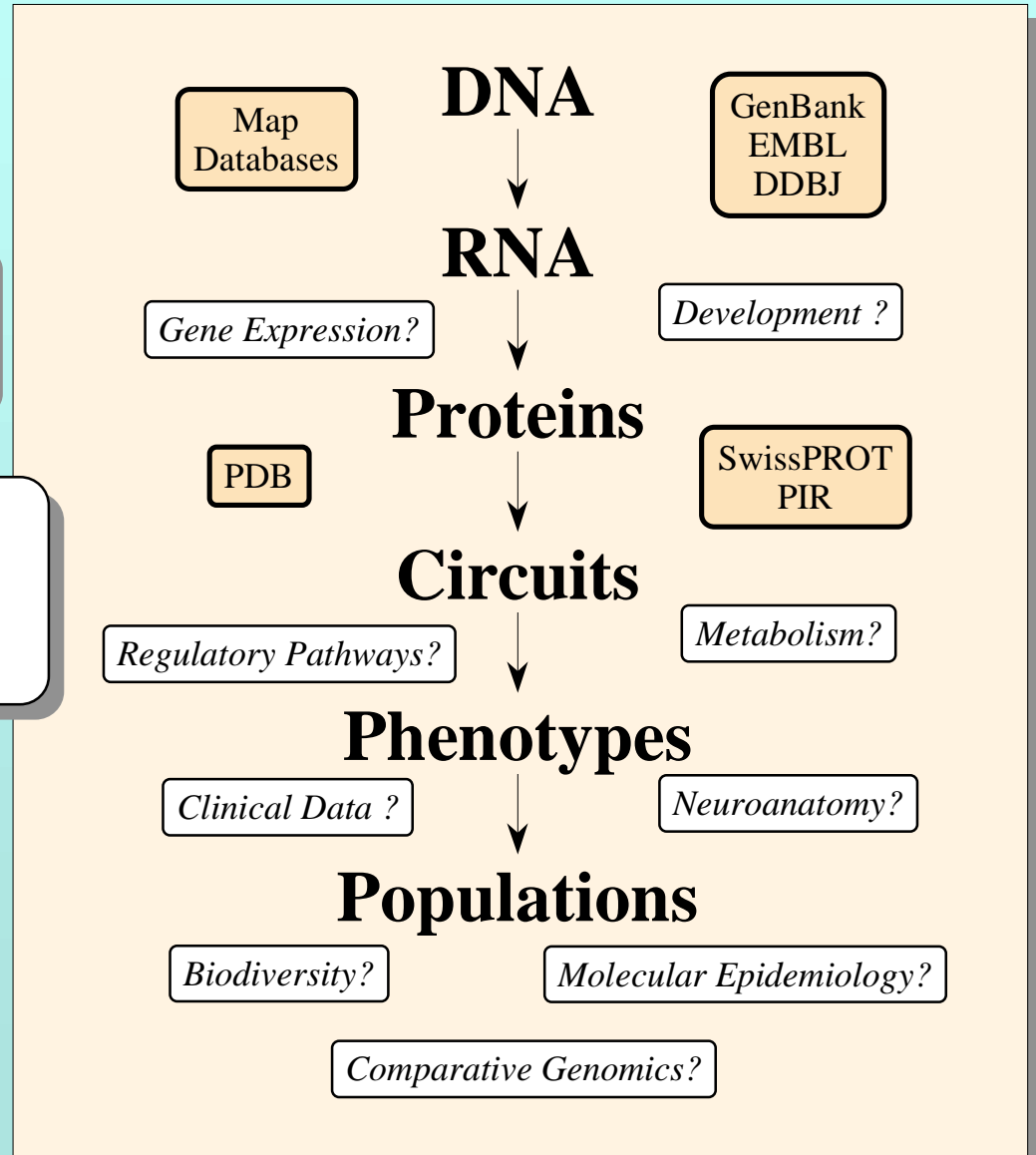
Although a few databases already exist to distribute molecular information,



Fundamental Dogma

Although a few databases already exist to distribute molecular information,

the post-genomic era will need many more to collect, manage, and publish the coming flood of new findings.

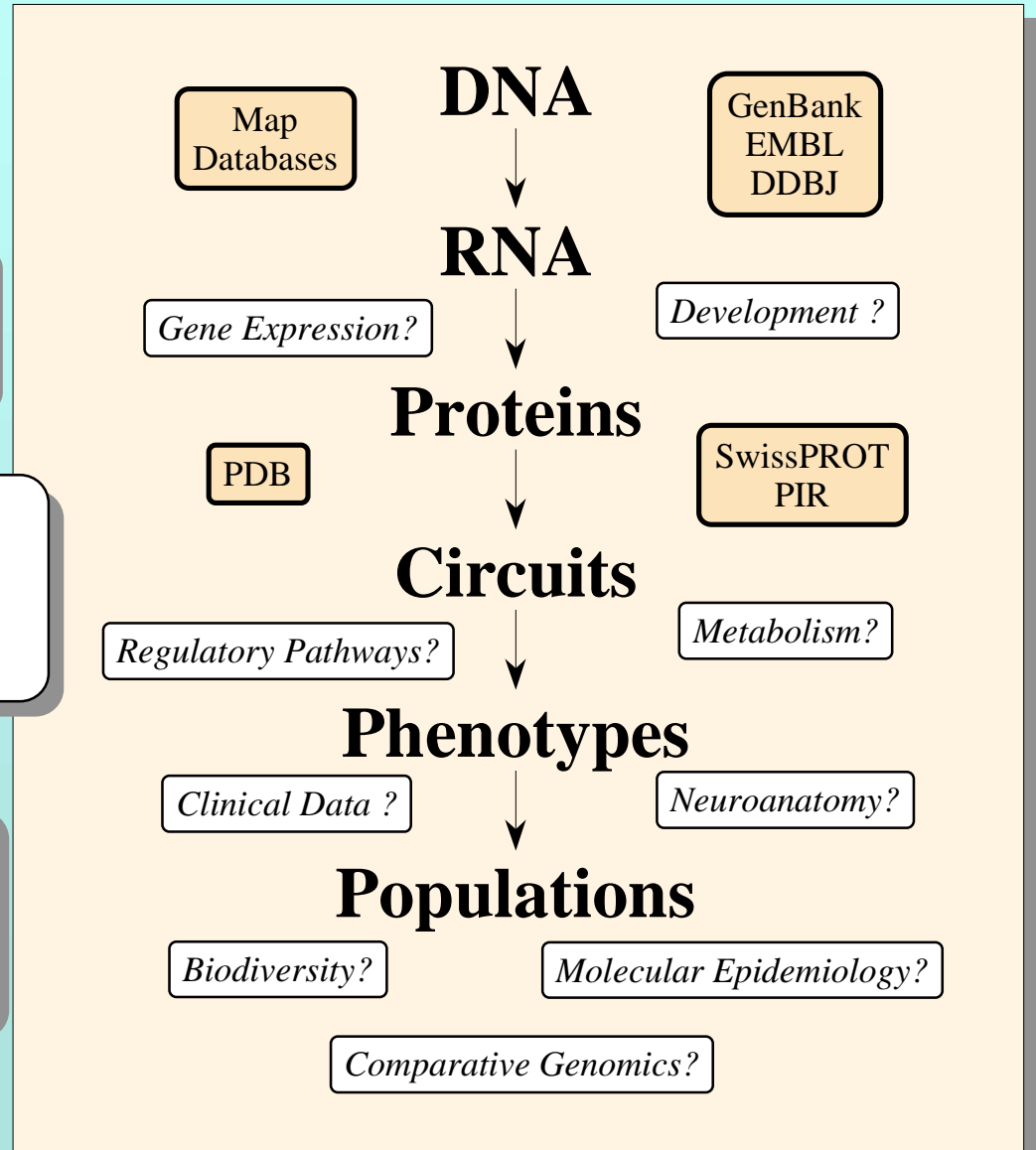


Fundamental Dogma

Although a few databases already exist to distribute molecular information,

the post-genomic era will need many more to collect, manage, and publish the coming flood of new findings.

If this extension covers functional genomics, then “functional genomics” is equivalent to biology.



21st Century Biology

The Literature

Electronic Data Publishing

GenBank -- Beta Hemoglobin

DEFINITION [DEF]
 [HUMHBB] Human beta globin region

LOCUS [LOC]
 HUMHBB

ACCESSION NO. [ACC]
 J00179 J00093 J00094 J00096
 J00158 J00159 J00160 J00161

KEYWORDS [KEY]
 Alu repetitive element; HPFH;
 KpnI repetitive sequence; RNA
 polymerase III; allelic
 variation; alternate cap site;

SEQUENCE
 gaattctaatctccctctcactactgtctagt
 atccctcaaggagtgggtggctcatgtcttgag
 ctcaagagtttgatataaaaaaaaaattagcca
 ggcaaatgggaggatcccttgagcgcactcca

O M I M -- Beta Hemoglobin

LOBIN--BETA LOCUS
 CELL ANEMIA,
 A-THALASSEMIA,
 Z BODY ANEMIAS,
 TYPE, ...]

beta loci determine the
 types of polypeptide
 hemoglobin, Hb A. By
 using heavy-labeled
 specific messenger RNA,
 found
 and a g
 cluded
 the bet
 s on a
 ce the zone of labeling
 at chromosome than on
 which by this reasoning

G D B -- Beta Hemoglobin

il View **

n, beta

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Enzyme

=====

RsaI
 AvaI
 BamHI

PIR -- Beta Hemoglobin

obin beta chain
 nzee, pygmy
 d gorilla

ght 15867

42

K S A V T A L W G
G G E A L G R L L
R F F E S F G D L
G N P K V K A H G
S D G L A H I D N
K L
V C

Many findings will be published
 in structured databases...

Electronic Scholarly Publishing

Scientific papers will also be published in electronic format, perhaps even including some important papers originally published only in print format.

HTTP://WWW.ESP.ORG

For example, the ESP site is dedicated to the electronic publishing of scientific and other scholarly materials. Of particular interest are the history of science, genetics, computational biology, and genome research.

The screenshot shows a web browser window with the address bar containing <http://www.esp.org/>. The browser's toolbar includes buttons for Back, Forward, Stop, Refresh, Home, Search, Favorites, Print, Font, and Mail. The website content features the ESP logo in a small box on the left and a larger 'ESP' logo at the top center. Below the logo is the text 'ELECTRONIC SCHOLARLY PUBLISHING' and 'Publication Collections'. Two entries are listed: 'Classical Genetics' (reprints of key papers from the early history of genetics, TEXT ONLY version) and 'Classical Genetics' (reprints of key papers from the early history of genetics, HIGH GRAPHICS version). A mouse cursor is positioned over the second 'Classical Genetics' entry. At the bottom of the page, a 'Reprints' entry is partially visible, describing publications, slide presentations, instructional materials, and data. The browser's status bar at the bottom shows 'Shortcut to browse1.htm'.

Electronic Scholarly Publishing

The *Classical Genetics: Foundations* series provides ready access to typeset-quality, electronic editions of important publications that can otherwise be very difficult to find.

Back Forward Stop Refresh Home Search Favorit... Print Font Mail


Address <http://www.esp.org/graphics/browse1.htm> Links

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ELECTRONIC
SCHOLARLY
PUBLISHING

Classical Genetics: Foundations *Early Mendelism*

(395,699 bytes; 41 pages, no figures) PDF

▶ Mendel, Gregor. 1865. Experiments in plant hybridization. *Verhandlungen des naturforschenden Vereines in Brünn, Bd. IV für das Jahr 1865, Abhandlungen*, 3-47.



Gregor Mendel, 1862

In February and March of 1865, the Brünn Natural History Society in Brünn, Czechoslovakia, heard Gregor Mendel present the results of his investigations into the mechanisms governing inheritance in pea plants. The next year, the work was published as Mendel, Gregor. 1866. "Versuche über Pflanzen Hybriden." *Verhandlungen des naturforschenden Vereines in Brünn*, 4:3-47.

In this remarkable work, Mendel established the foundation for what later became the science of genetics. However, his work was largely ignored when it appeared and Mendel moved on to other things. He died in 1884, never knowing that his experiments in plant hybridization were of any consequence.

His work was rediscovered at the turn of the century and its significance immediately recognized. Genetics, as a formal scientific discipline, exploded into activity in 1900.

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Electronic Scholarly Publishing

For example, “Hardy” (of Hardy-Weinberg) is a name well known to most students of biology, but few have access to his original publications dealing with the basic principles of population genetics.

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Address <http://www.esp.org/graphics/browse1.htm> Links

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Classical Genetics: Foundations *Early Mendelism*

(19,473 bytes; 1 page, no figures)  [▶ Hardy, G. H. 1908. Mendelian Proportions in a Mixed Population. *Science*, NS. XXVIII: 49-50](#)

Every geneticist has heard of the Hardy-Weinberg Law and of Hardy-Weinberg Equilibrium, and nearly all basic biology texts teach that G. H. Hardy played a seminal role in founding population genetics. But, what most biologists don't realize is that Hardy's **total** contribution to biology consisted of a **single** letter to the editor in *Science*. The letter began,

I am reluctant to intrude in a discussion concerning matters of which I have no expert knowledge, and I should have expected the very simple point which I wish to make to have been familiar to biologists. However, some remarks of Mr. Udny Yule, to which Mr. R. C. Punnett has called my attention, suggest that it may still be worth making.

With that, Hardy offered his "simple point" and then washed his hands of biology. His autobiography, *A Mathematician's Apology*, makes no mention of population genetics.

Electronic Scholarly Publishing

And when they do have access, they may be surprised to find that **all** of Hardy's biological writings consist of a single, one-page letter to the editor of *Science*.

The screenshot shows a web browser window with the address bar containing <http://www.esp.org/history/hardy.pdf>. The browser interface includes standard navigation buttons (Back, Forward, Stop, Refresh, Home, Search, Favorit..., Print, Font, Mail) and a toolbar with various document manipulation icons. The main content area displays a page from the journal *SCIENCE*, dated JULY 10, 1908, Volume XXVIII:49-50. The page title is "DISCUSSION AND CORRESPONDENCE" and the specific article is "Mendelian Proportions in a Mixed Population". The text is a letter to the editor, starting with "To The Editor of Science: I am reluctant to intrude in a discussion concerning matters of which I have no expert knowledge..." and discussing Mendelian genetics and the concept of a "stable" distribution. The page number at the bottom is "Page 1 of 1".

21st Century Biology

The People

Human Resources Issues

- Reduction in need for non-IT staff
- Increase in need for IT staff, especially “information engineers”

In modern biology, a general trend is to convert expert work into staff work and finally into computation. New expertise is required to design, carry out, and interpret continuing work.

Human Resources Issues

Elbert Branscomb: “You must recognize that some day you may need as many computer scientists as biologists in your labs.”

Craig Venter: “At TIGR, we already have twice as many computer scientists on our staff.”

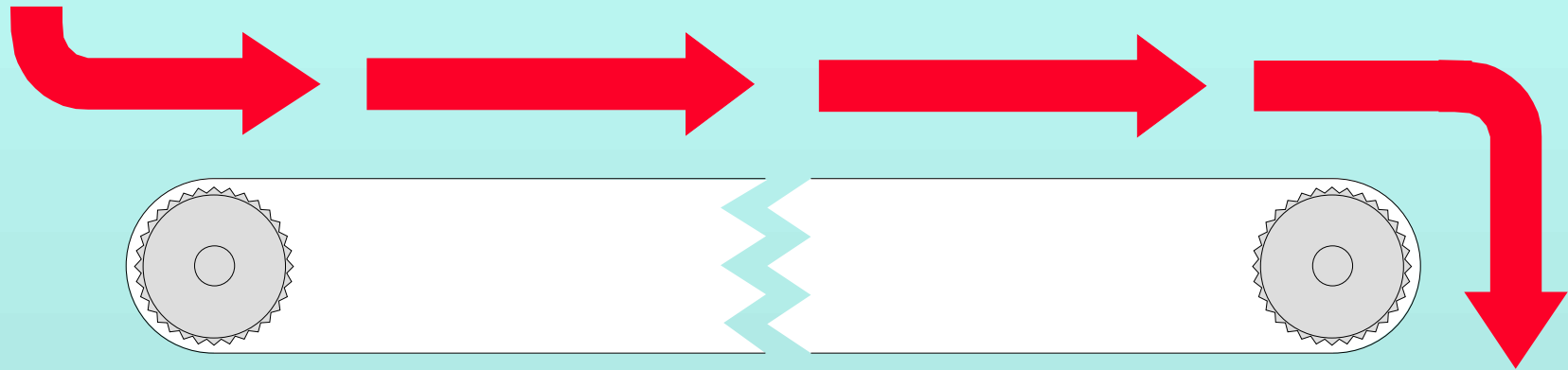
Exchange at DOE workshop on high-throughput sequencing.

New Discipline of Informatics

What is Informatics?

Computer
Science
Research

----- Informatics -----



Informatics is a conveyor belt that carries the fruits of basic computer science research to the biological community, transforming them along the way from theory to practical applications.

Biological
Application
Programs

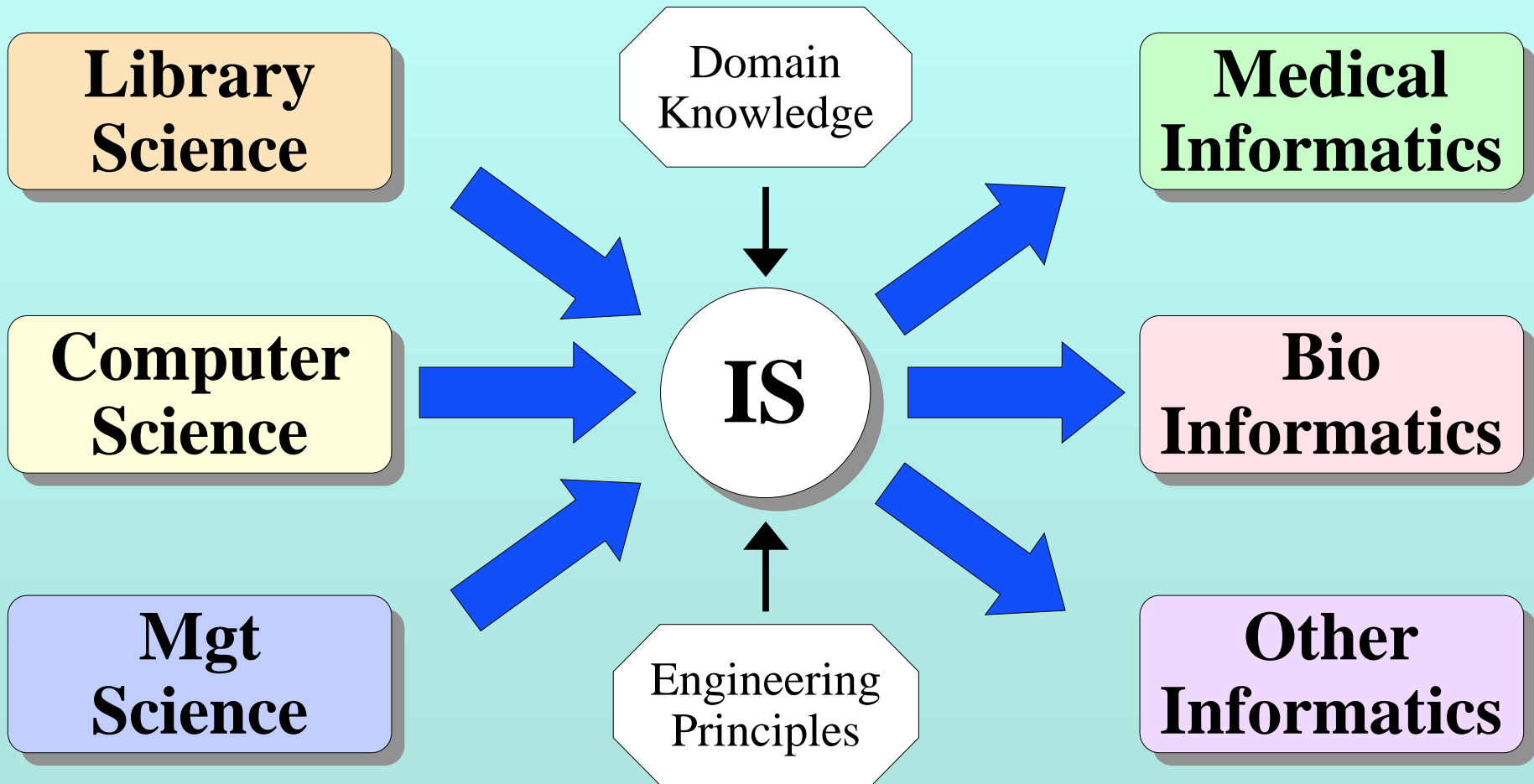
What is Informatics?

Informatics combines expertise from:

- *domain science (e.g., biology)*
- *computer science*
- *library science*
- *management science*

All tempered with an engineering mindset...

What is Informatics?



Engineering Mindset

Engineering is often defined as the use of scientific knowledge and principles for practical purposes. While the original usage restricted the word to the building of roads, bridges, and objects of military use, today's usage is more general and includes chemical, electronic, and even mathematical engineering.

Parnas, David Lorge. 1990. *Computer*, 23(1):17-22.

... or even information engineering.

Engineering Mindset

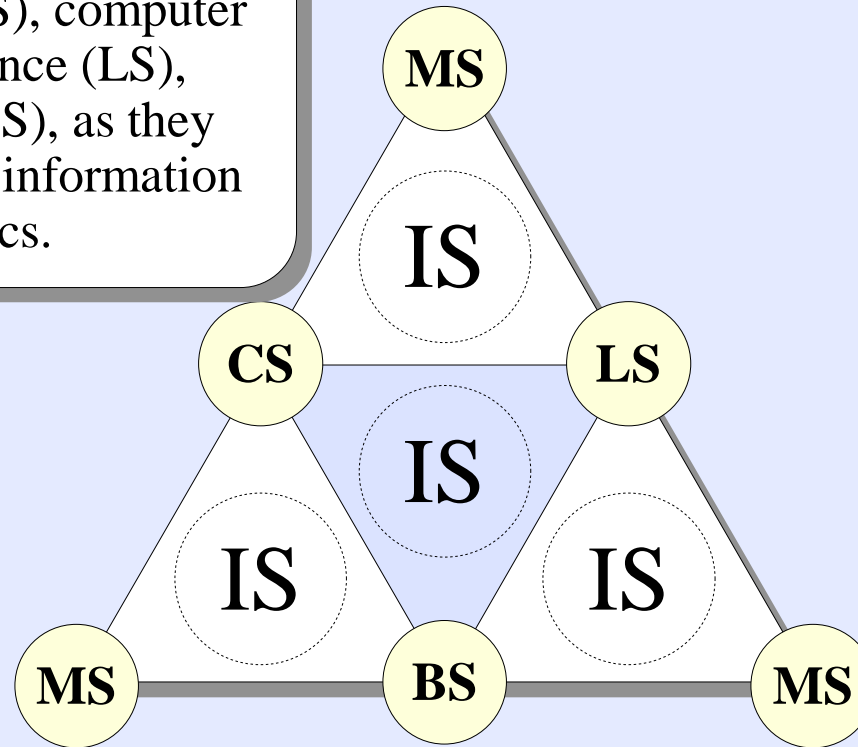
Engineering education ... stresses finding good, as contrasted with workable, designs. Where a scientist may be happy with a device that validates his theory, an engineer is taught to make sure that the device is efficient, reliable, safe, easy to use, and robust.

Parnas, David Lorge. 1990. *Computer*, 23(1):17-22.

The assembly of working, robust systems, on time and on budget, is the key requirement for a federated information infrastructure for biology.

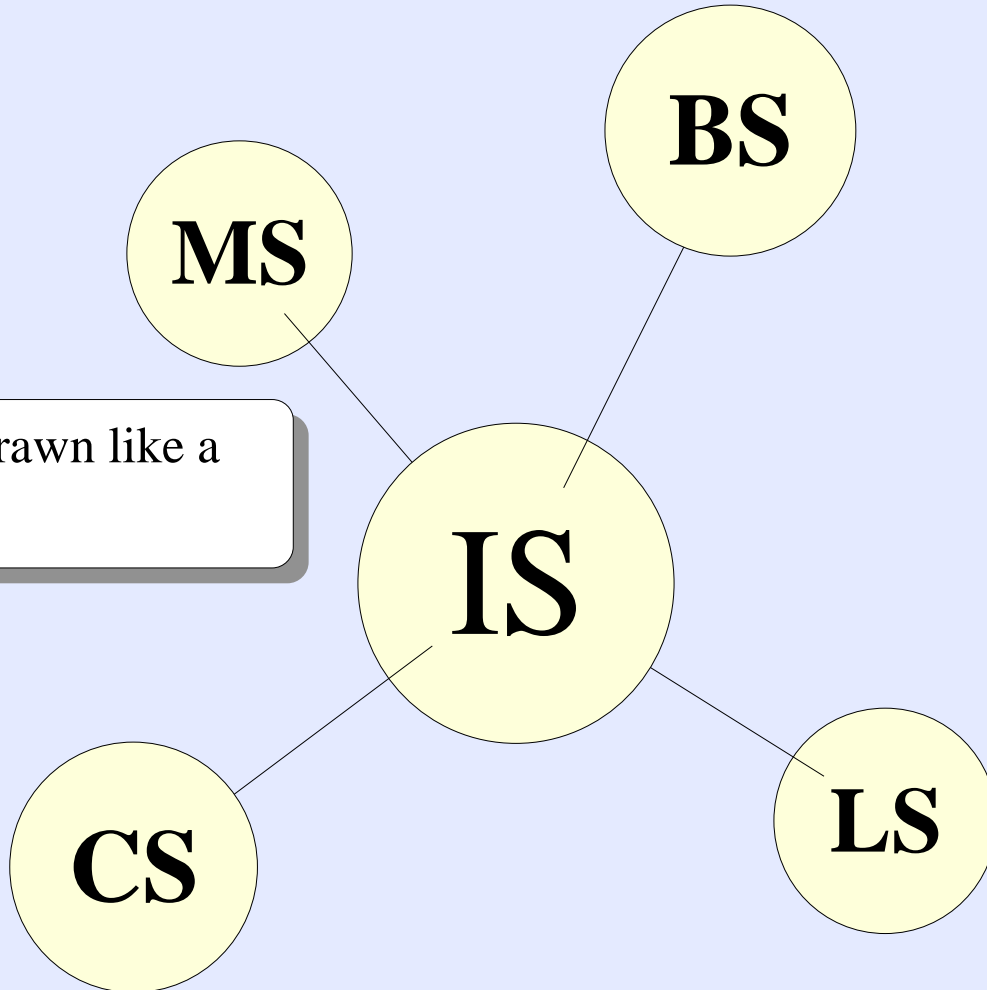
Informatics Triangle

An unfolded tetrahedron can represent the relationships among management science (MS), computer science (CS), library science (LS), and biological science (BS), as they connect around a core of information science (IS), or informatics.



What is Informatics?

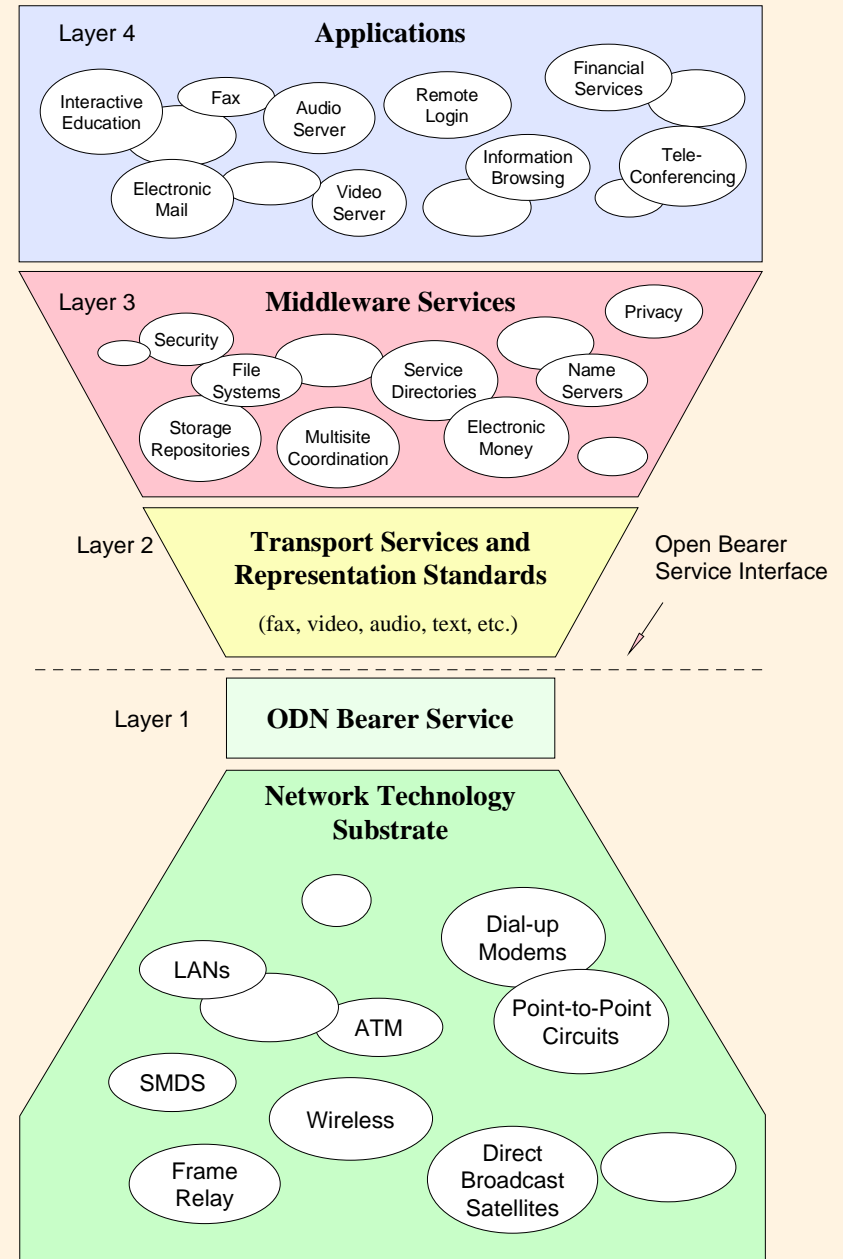
This might also be drawn like a methane molecule...




Federated Information Infrastructure

ODN Model

Several years ago, a report, *Realizing the Information Future*, laid out a vision of an Open Data Network, in which any information appliance could be operated over generic networking protocols...




National Information Infrastructure

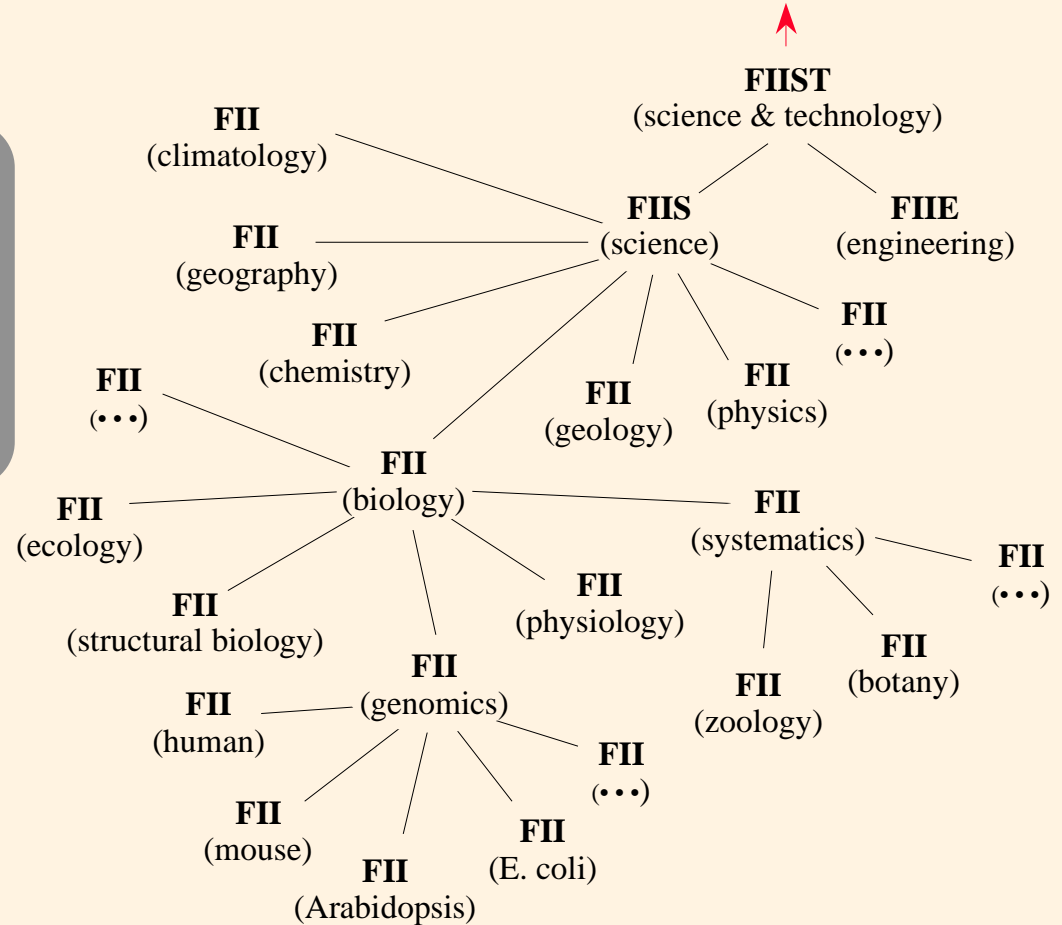
	commercial uses		non-commercial uses		
	ETC	other	Edu	Lib	Res
analog					
digital					

A national information infrastructure can be partitioned according to technology (analog vs digital) and usage (commercial vs non-commercial). Scientific use of the internet involves the non-commercial, digital component. Entertainment, telephony, and communication now primarily falls in the commercial, analog realm.

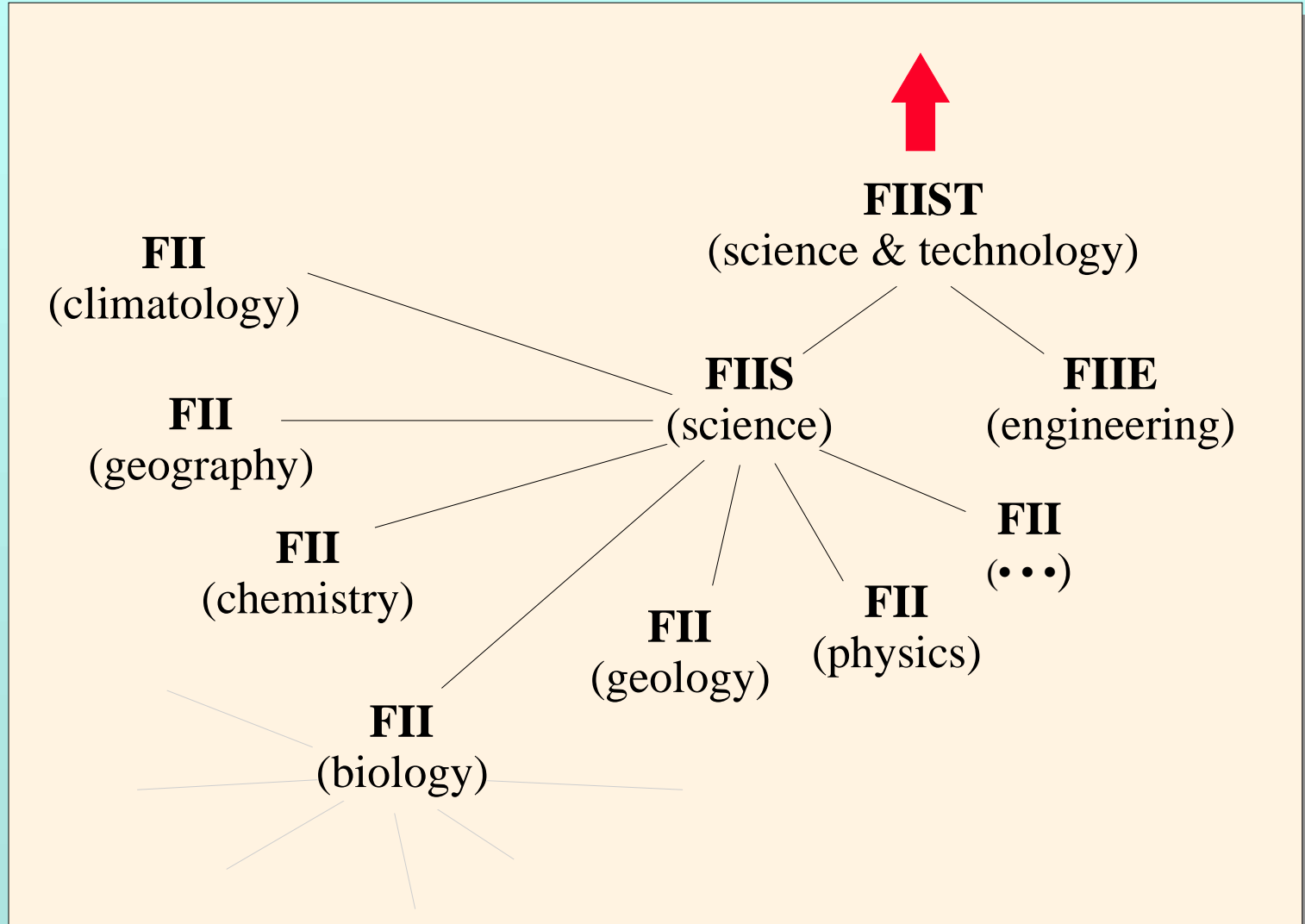
FIIST & NII

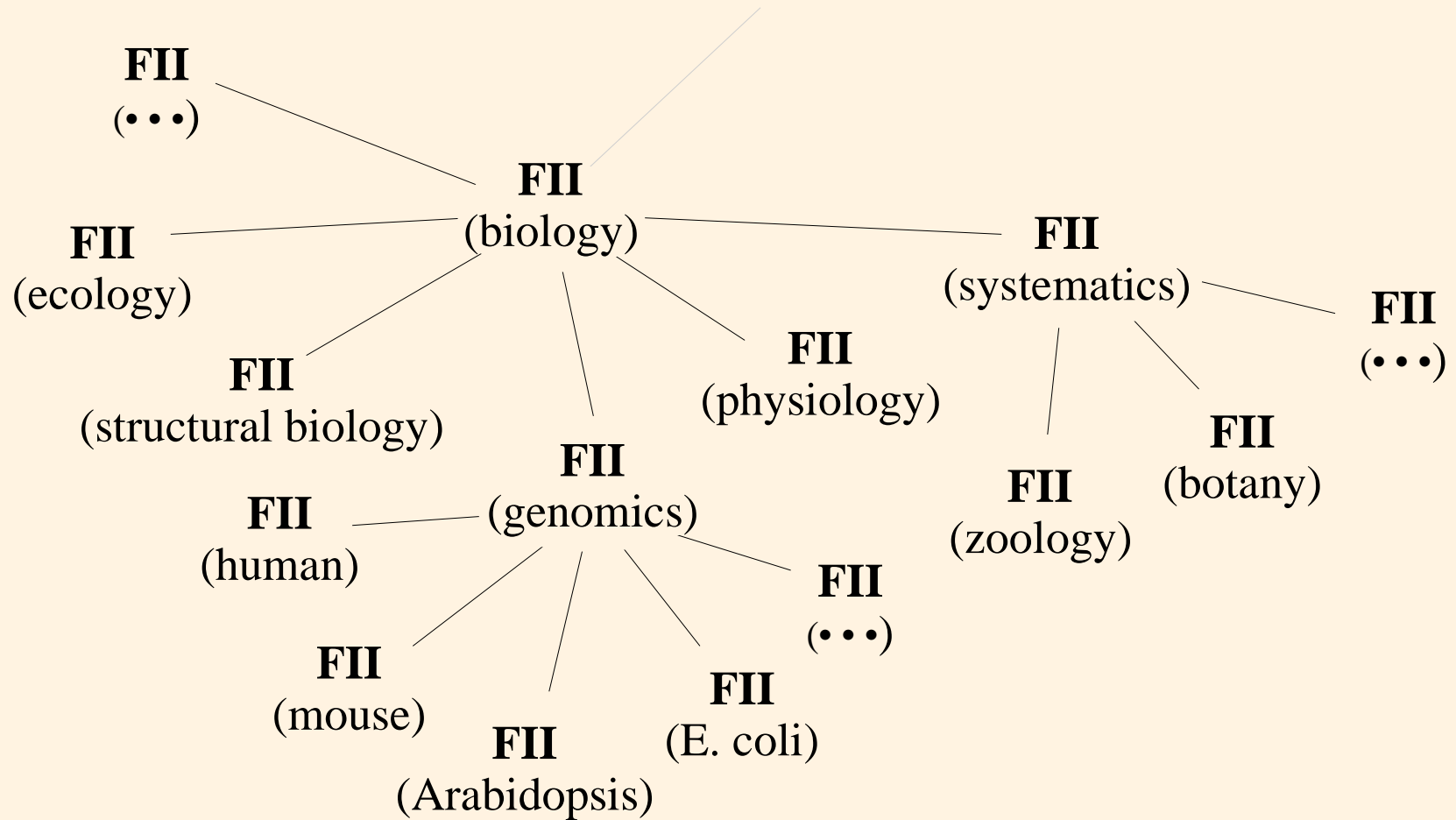
The research component of the NII contains a Federated Information Infrastructure for Science and Technology..

	commercial uses		non-commercial uses		
	ETC	other	Edu	Lib	Res
analog					
digital					



FIIST





Funding for Bio-Information Infrastructure

Call for Change

Among the many new tools that are or will be needed (for 21st-century biology), some of those having the highest priority are:

- bioinformatics
- computational biology
- functional imaging tools using biosensors and biomarkers
- transformation and transient expression technologies
- nanotechnologies

Impact of Emerging Technologies on the Biological Sciences: Report of a Workshop. NSF-supported workshop, held 26-27 June 1995, Washington, DC.

The Problem

- IT moves at “Internet Speed” and responds rapidly to market forces.
- IT will play a central role in 21st Century biology.
- Current levels of support for public bio-information infrastructure are too low.
- Reallocation of federal funding is difficult, and subject to political pressures.
- Federal-funding decision processes are ponderously slow and inefficient.

Public Funding of Bio-Databases

The challenges:

- providing adequate funding levels
- making timely, efficient decisions

IT Budgets

A Reality Check

Rhetorical Question

Which is likely to be more complex:

- identifying, documenting, and tracking the whereabouts of **all parcels** in transit in the US at one time
- identifying, documenting, and analyzing the structure and function of **all individual genes in all economically significant organisms**; then analyzing **all significant gene-gene and gene-environment interactions** in those organisms and their environments

Business Factoids

United Parcel Service:

- uses two redundant 3 Terabyte (yes, 3000 GB) databases to track all packages in transit.
- has 4,000 full-time employees dedicated to IT
- spends one billion dollars per year on IT
- has an income of 1.1 billion dollars, against revenues of 22.4 billion dollars

Business Comparisons

Company	Revenues	IT Budget	Pct
Chase-Manhattan	16,431,000,000	1,800,000,000	10.95 %
AMR Corporation	17,753,000,000	1,368,000,000	7.71 %
Nation's Bank	17,509,000,000	1,130,000,000	6.45 %
Sprint	14,235,000,000	873,000,000	6.13 %
IBM	75,947,000,000	4,400,000,000	5.79 %
MCI	18,500,000,000	1,000,000,000	5.41 %
Microsoft	11,360,000,000	510,000,000	4.49 %
United Parcel	22,400,000,000	1,000,000,000	4.46 %
Bristol-Myers Squibb	15,065,000,000	440,000,000	2.92 %
Pfizer	11,306,000,000	300,000,000	2.65 %
Pacific Gas & Electric	10,000,000,000	250,000,000	2.50 %
Wal-Mart	104,859,000,000	550,000,000	0.52 %
K-Mart	31,437,000,000	130,000,000	0.41 %

Federal Funding of Biomedical-IT

Appropriate funding level:

- approx. 5-10% of research funding
- *i.e.*, 1 - 2 **billion** dollars per year

Source of estimate:

- Experience of IT-transformed industries.
- Current support for IT-rich biological research.

Conference on Biological Informatics

Conference Sessions

- Overview of Biological Informatics
- Biodiversity Informatics
- Environmental Informatics
- Molecular Informatics
- Medical / Neuroinformatics
- Teaching and Training in Informatics

Slides:

<http://www.esp.org/rjr/canberra.pdf>