Biology past and biology present: Where have we been and where are we going?

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Talk outline

1) Some personal history.
2) The central role of protein machines.
3) Textbook writing highlights important new challenges for biological scientists.
4) How to promote innovation?
5) My new life at Science magazine
I was a high school student, when the revolution in biology began with the Watson and Crick structure for DNA in 1953.
The next major breakthrough: the discovery of the enzyme that synthesizes DNA

1) The **DNA polymerase** enzyme was discovered by Arthur Kornberg and earned him a Nobel Prize.

2) This protein will add a new nucleotide to the end of one DNA strand (the “primer strand”) only if that strand is paired to a complementary strand that can serve as the template. This strand (the “template strand”) must be **single stranded**, with its bases exposed.

3) DNA polymerase moves in only **one chemical direction**, growing the 3’ end of a new DNA strand.
In 1960, it was generally assumed that a single enzyme, DNA polymerase, alone replicated DNA, but how?

**Two problems:**

- DNA is double-helical inside the cell, not single-stranded.

- The two DNA strands run in opposite directions (they are anti-parallel), yet the polymerase only goes one-way.
My dismal career as a graduate student, Harvard 1961-1965

• Inspired by the success of Watson & Crick, I had my own theory about how DNA polymerase might be able to start its DNA synthesis on a chromosome (a double-helical DNA molecule).

• I did many experiments trying to see if the theory was right; the many “NO” answers did not surprise anyone and they did not add to the store of scientific knowledge.
A wake-up call
How failing a PhD led to a strategy for a successful scientific career.

Bruce Alberts

One of my most important formative experiences as a scientist was very traumatic at the time. In the spring of 1965, I had finished writing my PhD thesis at Harvard University, in Cambridge, Massachusetts, and had purchased aeroplane tickets to take my wife Betty and our one-year-old daughter with me for a postdoctoral year in Geneva, Switzerland. Only one step remained — a meeting of my thesis committee to approve the granting of my PhD degree in biophysics. No one in recent memory had failed at this late stage. But to my great surprise, the committee failed me, specifying the need for more experiments that eventually required six more months of research.

This was, of course, a great embarrassment and a shock to my ego. There were the practical problems of having to remain at Harvard — our apartment had already been rented to the next tenant and my small family had nowhere to live. But most importantly, I was to spend the next few months struggling to answer two questions that would be critical for my future: What had gone wrong, and did I really have what it takes to be a scientist?

As an undergraduate working with Jacques Fresco in Paul Doty’s laboratory at Harvard, I was handed a research project that proved to be very successful. My undergraduate thesis was quickly converted into two important papers in 1960. This largely under-rated success gave me a false image of how easy it would be to do science. It also enabled me to persuade Paul Doty to allow me to test my own theoretical model for the initiation of chromosome replication as the centrepiece of my PhD research.

Bruce Alberts' 'failure' was a blessing in disguise. A critical step in shaping me as a scientist, because it forced me to recognize the central importance of the strategy that underlies any major scientific quest.

I had witnessed the frustration of scientists who were pursuing obvious experiments that were simultaneously being carried out in other laboratories. These scientists were constantly in a race. It had always seemed to me that, even if they were able to publish their results six months earlier, the months of analysis triggered by the wake-up call of my PhD failure finally produced an answer. I would look for a unique experimental approach, but one that would have a high probability of increasing our knowledge of the natural world, regardless of the experimental results obtained.

After a great deal of soul-searching, I decided that I would begin by developing a new method — one that would allow me to isolate proteins required for DNA replication that had thus far escaped detection. I knew that the enzyme DNA polymerase, which reads out the genetic information in DNA, binds weakly to any DNA sequence — even though this protein’s biologically relevant binding sites are specific DNA sequences. If the proteins that cause DNA to replicate have a similar weak affinity for any DNA molecule, I would be able to isolate them by passing crude cell extracts through a column matrix containing immobilized DNA molecules.

Arriving in Geneva in late 1965 with my PhD degree finally in hand, I found that by drying an aqueous solution of DNA onto plain cellulose powder, I could construct a durable and effective ‘DNA cellulose’ matrix. A large number of different proteins in a crude, DNA-depleted extract of the bacterium Escherichia coli bound to a column containing this matrix. Moreover, these DNA-binding proteins could be readily purified by elution with an aqueous salt solution. Using this new biochemical tool and a large library of mutant T4 bacteriophages obtained from Dick Epstein in Geneva, I discovered the T4 gene 32 protein after moving to Princeton a year later as an assistant professor. This proved to be the first...
My failures taught me important lessons

- Theoretical biology is much more difficult than my generation had imagined. It turns out that we had been misled by the striking success of the 1953 Watson-Crick DNA model.

- Having a good strategy in scientific research is the key to success; in addition, always try to do an experiment where any answer you get will advance our scientific knowledge to at least a small extent.
Only when I moved to Geneva Switzerland in 1965, as a post-doctoral fellow with Alfred Tissieres and Richard Epstein, did I discover that DNA replication requires much more than DNA polymerase!
Bacteriophage T4, a large bacterial virus that infects *E. coli*, had about 100 genes discovered by genetics by 1963.
A major **mystery**: why were there at least 7 T4 genes that were absolutely required for replication of the T4 virus?

1) These 7 T4 genes had been given numbers: 32, 41, 43, 44, 45, 61, 62.

2) One of these, the gene 43, had been shown to produce the T4 bacteriophage DNA polymerase.

3) Why are at least 6 additional proteins needed for any replication of the T4 chromosome when the virus infects the *E. coli* bacterium?

4) Clearly, **DNA replication must involve at least 7 proteins** and be much more complicated than anyone had imagined!
My strategy for solving the mystery of so many replication genes:

**Develop a new method** (DNA cellulose chromatography) **to find the mutant proteins**

- Many proteins that function on DNA in the cell will have a site on their surface for binding to DNA.
- By fixing a high concentration of single stranded or double helical DNA on a solid support such as cellulose, one should be able to trap these proteins specifically and purify them.
- Many proteins in a T4 bacteriophage-infected cell bound to a **DNA-cellulose column**. Would one of them be missing if a mutant virus was used for the infection?
Gel electrophoresis of the proteins that elute from a single-stranded DNA cellulose column identifies the T4 gene 32 protein.
My favorite protein (for historical reasons)

Single-strand DNA binding protein (SSB)

One 32 protein molecule per every 10 nucleotides
Circular DNA single strands, with and without 32 protein.

Seeing is believing.
How the gene 32 protein helps DNA polymerase

The human version is Replication Protein A (RPA)

cooperative protein binding straightens region of chain
Now there were only 5 mysterious proteins left

I could not find these other proteins on my DNA column. So we tried a different approach called an “in vitro complementation assay”.

• Here a mutant-infected cell lysate was made, and an extract from a cell infected with a normal virus was added.

• Could we find a stimulation of DNA synthesis in this crude mixture that depended on adding one of the 5 missing proteins?

The answer was yes!
Two-fold stimulation of lousy DNA synthesis (lasting for only 2 min in extract) provides the assay needed to purify each of the 5 remaining “mystery proteins”
Finally, in 1975 we had collected purified preparations of all of the 7 proteins. We discovered that when we mixed them all together we could now replicate a double-helical DNA template!

In contrast, DNA polymerase alone, or a mixture missing any one protein, would only make new DNA when provided with a single-stranded DNA template.

It took another 6 years for us to figure out why each of the proteins was needed in this reaction!
Your own Chung-Cheng Liu was a major contributor as a graduate student with me

Now President and General Director, Biomedical Engineering Research Laboratories Industrial Technology Research Institute


The gene 45 protein turned out to form a 
sliding clamp for the DNA polymerase, 
allowing the polymerase to move for many 
thousands of nucleotides without dissociating.
How we viewed DNA replication in the 1960’s

primer strand

5’ → 3’

DNA polymerase adds one nucleotide and then dissociates

template strand

A second DNA polymerase molecule adds the next nucleotide
A sliding clamp for DNA polymerase makes possible much more rapid DNA synthesis.

First demonstration was by Mike O’Donnell, who also solved these structures collaborating with John Kuriyan.

The human version is PCNA.
The DNA replication fork in two dimensions
But the fork is actually folded, so as to allow the DNA polymerase on the lagging strand to be used over and over
The result of 20 years of research at Princeton, UCSF and in other labs

The folded replication fork

A protein machine

[Diagram of DNA replication fork with labels for lagging and leading strands, DNA polymerase, helix-destabilizing proteins, RNA primase, and DNA helicase]
We now know that the same basic mechanism is used to replicate DNA from large viruses, like T4 bacteriophage, to mammals.

However, as more complex organisms evolved, each function in T4 was carried out by more proteins.

- For example, bacteria use 13 protein molecules instead of 7, and humans seem to use at least 27!
Some personal lessons learned:

1) Go after mysteries!

2) There are remarkable homologies between living things; therefore use model organisms wherever possible.

3) Nearly all cell processes will be based on elegant mechanisms, too hard to predict.
The magic of protein machines is best appreciated by a movie that shows such a machine in action.

The movie was made by Bruce Stillman at the Cold Spring Harbor Laboratory, as part of the 50 year DNA celebration there. It can be found on Cold Spring Harbor DNA Learning Center website in the section that deals with “Copying the code”.
“Protein machines”

Almost every process in the cell is now recognized to be driven by a complex of 10 or more proteins.

These protein machines function very much like the machines in everyday life that are driven by electric energy.

They undergo ordered movements driven by proteins in the set that harness the energy of ATP or GTP hydrolysis.

The protein machines in cells are also assembled only where and when they are needed, in reactions catalyzed by proteins that hydrolyze ATP or GTP.
An Important Challenge for the Next Generation of Cell Biologists:

Obtaining the information needed to accurately describe the mechanism of every type of protein machine in a cell

• This will require the reconstitution of many hundreds of protein machines from their purified components, so that the detailed chemistry of each machine can be deciphered through reactions studied in a test tube.

• Rate constants and affinities will need to be measured, and we can only claim to understand the machine when we can accurately predict the effect of altering each of these parameters.
We will also need to work out the many interactions between different protein machines:

For example, the replication fork constantly collides with RNA polymerase molecules transcribing on the DNA, without creating problems.
When we purified each of the individual T4 replication proteins using serial steps of column chromatography, we observed that some of the proteins lost all of their activity if the magnesium concentration was not kept above a certain level, or if we did not use double-distilled water, high glycerol concentrations, etc.

**CONCLUSION:** Without an activity assay, one can expect some purified proteins to have lost all of their activity, and thus be useless for reconstituting biological reactions.

*Largely forgotten in this age of proteomics: the importance of activity assays!"*
The authors have all learned a great deal from 25 years of writing this very large textbook.
5th edition in Antarctica 2008
The joy of textbook writing

You might like to consider rewriting this section completely to raise the questions.

V. Where are the neural crest cells initially determined by origin or by their actual position.

2. Whether the embryonic

In the normal course of events, the question of embryonic cell migration is usually determined by the time of migration or induced by the target.

81. The pathways of migration are defined by the host connective tissue.

On the other side of the trunk of the embryo, the cells from the neural crest by two main pathways, one just below the ectoderm, and the other...
Two recent surprises for textbook authors (of many)

1) The recognition that positive and negative feedback loops underlie nearly all cell chemistry.

2) The recognition that extensive scaffold networks produce biochemical sub-compartments in the cell, without requiring a membrane.
How nearly all of biology works

There is no way to understand such pathways without mathematics
Example: the actin cytoskeleton

1. **Actin Filament**
   - **Actin Subunits**
   - **Formin**
     - Nucleates assembly and remains associated with the growing plus end.
   - **ARP Complex**
     - Nucleates assembly to form a web and remains associated with the minus end.
   - **Thymosin**
     - Binds subunits, prevents assembly.
   - **Profilin**
     - Binds subunits, speeds elongation.
   - **Cofilin**
     - Binds ADP-actin filaments, accelerates disassembly.
   - **Gelsolin**
     - Severs filaments and binds to plus end.
   - **Capping Protein**
     - Prevents assembly and disassembly at plus end.
   - **Tropomyosin**
     - Stabilizes filament.
We will need mathematical/computational models to decipher such complex systems.

**One example:**

- Modern computers make possible individual-molecule based simulations, in which tens of thousands of molecules are simultaneously allowed to diffuse randomly and “react” in a virtual space.

- The simulated positions of all of the molecules can be calculated in cycle steps of micro- to milliseconds.

- If after billions of such cycles, the emergent properties observed for the system closely resemble those in the cell, then one can hope to use the model to gain important insights into mechanisms.
These models require a large amount of quantitative data

1. An inventory of the set of interacting molecules and their molecular structures.

2. Identification of all molecular partners in the set, with determination of the rate and equilibrium constants for forming each partner -- as well as quantitative measurements of the effect of partner formation on other molecules.

3. An understanding of the behavior of this set of molecules both in reconstituted in vitro systems with pure proteins and in living cells.
One therefore needs to start with model systems that are simpler than the entire process, choosing those where extensive biochemical work is being done.
The *Listeria* bacterium as a model for the actin-mediated movement of intracellular vesicles
Why use *Listeria* to work out new methods?

- There is an *in vitro* system in which a mixture of 5 purified proteins moves a polystyrene bead mimic of the bacterium (established by Marie-France Carlier and co-workers in France).

- Nearly all of the rate constants and affinities for the proteins in this set have been determined (established by Tom Pollard and co-workers in USA).
A model system for understanding the actin cytoskeleton: actin-mediated movement of a bacterium

Actual bacterium  Computational model
Details from computational model with 5 proteins
(yellow ATP-actin, red ADP-actin)

(Computational model courtesy of Garry Odell & Jonathan Alberts, University of Washington)
Talk available on Web by Garry Odell, presented at the Mathematical Sciences Research Institute

“Why are mindless, individual agent-based computer simulation models less likely to deceive than elegant and thoughtful partial differential equation models of traditional continuum mechanics?”

http://www.msri.org/specials/sbc
Intracellular compartmentation without membranes
A simple example: the whiskers on formin allow actin filaments to grow at rates faster than “diffusion controlled”

(from T. Pollard et al)
Finally, cells are constantly covalently modifying their proteins to move them to specific places in their interior, altering their sub-compartments via “positional codes”

A cell is nothing like a test tube!

(A) A spectrum of covalent modifications produces a regulatory protein code

Cell signals direct addition of covalent modifications:

- and/or
- and/or
- and/or
- and/or

Protein X

The code is read:

- Bind to proteins Y and Z
- Move to nucleus
- Move to proteasome for degradation
- Move to plasma membrane
My conclusion: It will probably take most of this century to gain a true understanding of how cells and organisms work

• Much more biochemistry will be needed (immunoprecipitations are not enough!)

• Also needed: new methods for analyzing and understanding the enormous complexity of life’s chemistry.
How to stimulate innovation?

In attempting to address this question, it is important to recognize how new knowledge arises.
Beyond Discovery™: The Path from Research to Human Benefit is a series of articles that trace the origins of important recent technological and medical advances. Each story reveals the crucial role played by basic science, the applications of which could not have been anticipated at the time the original research was conducted.

**Feature Article: Wavelets: Seeing the Forest and the Trees**

What do oil prospectors, computer animators, and the FBI have in common? They all use tools that rely on wavelets—a mathematical theory that allows researchers to isolate and manipulate certain types of patterns hidden in masses of data. This article describes the history of the research that led to this useful theory.
How do productive ideas in science arise?

A personal example

My field from 1950-1985
THE FUNDAMENTAL REASON FOR THE EXPLOSIVE GROWTH OF SCIENCE

100 units of knowledge can be combined in 100 times more ways than can 10 units of knowledge.
But there is a catch!

As knowledge grows, it becomes increasingly difficult to find the right combinations
The source of creativity in science

To create consists precisely in not making useless combinations and in making those which are useful and which are only a small minority.

Invention is discernment, choice… Among chosen combinations the most fertile will often be those formed of elements drawn from domains which are far apart. …

The true work of the inventor consists in choosing among these combinations so as to eliminate the useless ones.

Henri Poincaré
1908
A problem: the channeling of research topics due to “training inertia”
How then should research be organized to stimulate innovation?

• Here I will give you my personal view, based on my 30 years in universities.
The start of my career in science policy
1985

Limits to Growth: In Biology Small Science Is Good Science

These days, many people grow up believing that bigger is better. Giant factories that produce Wonder Bread have replaced thousands of corner bakeries, driven by the increased efficiency of scale. There is an unfortunate tendency to extend this view to the biological research community, and I have on occasion heard a major symposium speaker introduced in glowing terms as the coauthor of more than fifty papers per year. While I can admire the energy and management skills required to maintain a very large laboratory, the best biology is rarely done this way. With a few notable exceptions, the biochemists and molecular biologists I most respect run relatively small laboratories and publish when they have something important to report. As I shall argue here, doing good science is very different from producing bread, and there are compelling reasons why large laboratories are in general less efficient and less interesting than small ones. To reflect this fact, I believe that changes in funding patterns and expectations would be useful in the biological sciences.

to choose priorities carefully, as is required to use one's limited intellectual resources wisely. Moreover, because of the need to maintain the operation at a certain level of activity, it is inevitable that most of the work being done is rarely innovative or outstanding. Some large laboratories tend to jump quickly to exploit the original observations of others, believing that their extensive resources will enable them to compete effectively.

Many large laboratories represent a poor training environment for young scientists. Graduate students and postdoctoral scientists are treated as though workers in a factory, contributing strictly to their own part of the production line. This does not prepare them to function as independent scientists and may even impede their development by preventing the acquisition of habits of independent research at a crucial point in their careers. Even those rare individuals who succeed can become disillusioned and cynical, when they see their own ideas and efforts credited to a group leader who made no scientific contribution to the research that they performed.
Structuring institutions to maximize innovation

• In general, we should encourage our institutions to support a set of laboratories of modest size (9 to 12 people, maximum), each headed by an outstanding, innovative independent investigator.

• These laboratories should be clustered, embedded in a cooperative culture in which techniques and equipment are freely shared.

• Our reward systems must change to strongly encourage risk taking and originality.

• And everything must be done to encourage a random collision of people and ideas.
Another way to stimulate new science:

Focused workshops with 5 experts and 20 leading scientists in other areas

**Workshop on Schizophrenia**

*(mental illness/neurobiology/neurodevelopment/neurogenetics)*

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**ABSTRACT**

On November 29–30, 1995, the National Academy of Sciences and the Institute of Medicine brought together experts in schizophrenia and specialists in other areas of the biological sciences in a workshop aimed at...
My life at Science magazine

Published last October
Ardi, our 4.4 million year old ancestor!

From the inside out. Artist’s reconstructions show how Ardi’s skeleton, muscles, and body looked and how she would have moved on top of branches.
Sequence of Neanderthal genome in last week’s issue of *Science* magazine

Close Encounters Of the Prehistoric Kind

The long-awaited sequence of the Neandertal genome suggests that modern humans and Neandertals interbred tens of thousands of years ago, perhaps in the Middle East.

Kissing cousins. A few Neandertals mated with early modern humans and passed on some of their genes to living humans.

As a result, many people living outside Africa have inherited a small but significant amount of DNA from these extinct humans. “In a sense, the Neandertals are then not altogether extinct,” says lead author Svante Pääbo, a paleogeneticist at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, who was surprised to find he was part Neandertal. “They live on in some of us.”

The team also used the Neandertal DNA like a probe to find the genes that make us modern. Even though the genomes of humans and Neandertals are 99.84% identical, the researchers identified regions that have changed or evolved since our ancestors and Neandertals diverged sometime between 270,000 and 440,000 years ago—their new, slightly younger estimate of the split. So far, the team has detected tantalizing differences in genes involved in metabolism, skin, the skeleton, and the development of cognition, although no one knows yet how these genetic changes affect physiology. “This is a groundbreaking study!” enthuses evolutionary geneticist Hendrik Poinar of McMaster University in Hamilton, Canada. “We can actually discuss an extinct human species—Neandertals—on a genetic level rather than strictly on morphological grounds.”

Mixed marriage

The discovery of interbreeding in the nuclear genome surprised the team mem-
Using science and Science to create more coherence in the field of education

Redefining Science Education

THERE IS A MAJOR MISMATCH BETWEEN OPPORTUNITY AND ACTION IN MOST EDUCATION SYSTEMS today. It involves around what is meant by “science education,” a term that is incorrectly defined in current usage. Rather than learning how to think scientifically, students are generally being told about science and asked to remember facts. This disturbing situation must be corrected if science education is to have any hope of taking its proper place as an essential part of the education of students everywhere.

Scientists may tend to blame others for the problem, but—strange as it may seem—we have done more than anyone else to create it. Any objective analysis of a typical introductory science course taught today in colleges and universities around the world, whether it be biology, chemistry, physics, or earth sciences, would probably conclude that its purpose is to prepare students to “know, use, and interpret scientific explanations of the natural world” (strongly emphasizing the “know”). This is but one of four goals recommended for science education by the distinguished committee of scientists and science education experts convened by the U.S. National Academies that produced Taking Science to School: Learning and Teaching Science in Grades K-8. And yet college courses set the model for the teaching of science in earlier years.

The three other goals of equal merit and importance are to prepare students to generate and evaluate scientific evidence and explanations, to understand the nature and development of scientific knowledge, and to participate productively in scientific practices and discourse (summarized in the Academies’ Ready, Set, Science!). Scientists would generally agree that all four types of science understanding are critical not only to a good science education but also to the basic education of everyone in the modern world. Why then do most science professors teach only the first one?

As the scientist and educator John A. Moore emphasized in his pro-
April 23, 2010

Special issue:

Connecting science to language and literacy
Arguing for more time for science in schools

Prioritizing Science Education

In this special issue on Education, Science focuses on the connection between learning science in school and the acquisition of language and communication skills, emphasizing the benefits of teaching science and literacy in the same classrooms whenever possible. In the United States, this would be viewed as a radical proposal. Unfortunately, the great majority of Americans are accustomed to science classrooms where students memorize facts about the natural world and, if they are lucky, perform an experiment or two; in language arts classes, students generally read fictional literature and write about it in fossilized formats such as “compare and contrast.”

The exciting news, affirmed in many articles in this issue, is that “science learning entails and benefits from embedded literacy activities [and]…literacy learning entails and benefits from being embedded within science inquiry.”** Here, it is helpful to distinguish between factual (or informational) and fictional (or narrative) text. Science reading and writing is largely of the former type, and it is this factual, informational text that dominates today’s knowledge-everywhere world. Yet, most of the formal teaching in language arts classrooms deals with fictional text. My own failed efforts at storytelling lacked the imagination to do anything more than rewrite Hansel and Gretel in a thinly disguised new context. Without doubt, learning to write and read clear and concise informational text, as in summaries of investigations in science class, is an essential preparation for nearly all of life out of school.

By reconceptualizing science education through closely connecting literacy lessons with active inquiry learning in science class, one can make a strong argument for greatly expanding the time spent on science in primary school, to at least 4 hours a week. This alone would...
Also critical to work to improve the scientific enterprise itself!

Collaborating with the chief editors of *Nature* and the *Proceedings of the National Academy of Sciences*:

1. To establish an “author ID” system” so that each author can be specifically identified in databases like PubMed.

2. To discourage “honorary authorships,” require that the contribution of each author be published with a paper.
Also critical to work to improve the scientific enterprise itself!

Collaborating with the chief editors of *Nature* and the *Proceedings of the National Academy of Sciences*:

3. To **insure data quality**, require that a senior author take responsibility for having seen the original data for each type of method used in a publication.

4. To **encourage mentoring** by senior scientists, establish a separate mentoring search feature in PubMed and other databases.
In summary, where has biology been?

• In the past 50 years, tremendous advances have been made in our understanding of the molecular basis of life, driven largely by the development of powerful new techniques.

• We can see our way to the end of remarkable descriptive phase in cell biology, since all of the molecular structures and pathways can now be deciphered, although this will still require a lot of hard work.
In summary, where is biology going?

• We now know that the chemistry of life is incredibly complex, by far the most sophisticated chemistry known.

• Many of the most interesting attributes of life are due to emergent properties: properties that stem from very complicated networks of chemical interactions, whose consequences can not be deciphered from the details of a few individual parts alone.

• Innovative new methods and approaches will therefore be needed before we can claim to “understand” even the simplest living cells.
There are many wonderfully exciting challenges for young scientists. BE CREATIVE AND INTELLECTUALLY AMBITIOUS!