



Cyrus Levinthal

1922–1990

BIOGRAPHICAL

*Memoirs*

*A Biographical Memoir by  
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NATIONAL ACADEMY OF SCIENCES

# CYRUS LEVINTHAL

May 2, 1922–November 4, 1990

Elected to the NAS, 1970

During the 50 years of his outstanding career in science, Cyrus Levinthal made many fundamental contributions impacting different areas of biology. He focused on molecular genetics early in his career, making important discoveries in mechanisms of DNA replication, in the relationship between genes and proteins, and in the nature of messenger RNA. His later work, starting at MIT and continuing at Columbia University until his untimely death in 1990, focused on the application of computers to three-dimensional (3D) imaging of two types of very different biological structures: folded protein molecules, and cell connectivity in the nervous system.

CL was a true pioneer in both of these areas, laying the groundwork for the computer-generated graphical display of protein structure that is commonplace today, and for the renewed interest in computer reconstruction of neural architecture and connectivity that is a key component of the current efforts to map the human brain. He was also deeply involved in social issues. As an active member of the National Academy of Sciences (elected in 1970) and of the Institute of Medicine (elected in 1974), he chaired many committees devoted to national scientific and medical problems and was an NAS representative to the United Nations Educational, Scientific, and Cultural Organization.



A handwritten signature in dark ink, appearing to read "Eduardo Macagno, Barry Honig, and Larry Chasin". The signature is written in a cursive, flowing style.

*By Eduardo Macagno,  
Barry Honig,  
and Larry Chasin*

## Personal life

CL was born in Philadelphia in 1922. He received a B.A. in physics from Swarthmore College in 1943 and a Ph.D. in physics from UC Berkeley in 1951, following a stint in the Armed Services during World War II. He was appointed assistant and then associate professor of physics at the University of Michigan until 1957, when he moved to MIT as professor of biophysics. In 1968 he became professor of biological sciences at Columbia University, where he held the William R. Kenan, Jr., Chair in Biophysics until his death on November 4, 1990. At both MIT and Columbia CL helped build outstanding departments based on the directions and technologies of modern biological research.

CL was married twice. He and his first wife, Geana, had three children, Sarah Shartal (Toronto), David Levinthal (Portland, Oregon) and Adam Levinthal (Marin County, California). His second marriage, to Françoise Chasseigne, a disciple of biologist Jacques Monod, produced two children, Nina Levinthal (Paris) and Lisa Levinthal (New York City), as well as a long-standing and fruitful scientific partnership. Their work together produced important contributions in two areas—the structure of colicin E1 and its capacity to function as an ion channel, and the structure and development of neurons. In particular, their early work on the nervous system of the zebrafish, *Danio rerio*, was a seminal contribution to the rise of this species as an important vertebrate genetic model system.



Cy Levinthal at Columbia University in 1980.

### Early science: the molecular biology revolution

Although CL's doctoral work was in high energy physics, within a year after receiving his Ph.D. he published his first paper in what was then the rapidly emerging field of molecular biology, where he was to make several fundamental contributions. He continued his work in molecular biology into the 1960s, but by 1964 had begun to shift his principal efforts to developing and implementing computer-based molecular graphics for studying biological structures, which remained his central research interest for the remainder of his career. Among his more notable contributions in the field of molecular biology are:

#### **1) Replication and recombination during the growth of bacteria-infecting viruses (also called bacterial viruses or bacteriophages).**

This first period of studies placed CL within a group of physicists and physical-science-oriented biologists who set up bacterial viruses as a model of the simplest living system, in order to get at the fundamental mechanism governing living things, their reproduction. Many of these early experiments were performed while CL was a fellow of the National Foundation for Infantile Paralysis working at L'Institut Pasteur in Paris,



Cy and Françoise Levinthal in the mid-1960's.

where he was associated with the laboratories of A. Lwoff and J. Monod. During this period CL collaborated with other key figures, including S. Luria, C. A. Thomas, and N. Visconti, to describe the processes by which phages replicate their DNA and how they exchange DNA molecules in the process of genetic recombination. In a key experiment published in 1961, CL used an elegant and ingenious new method to establish that the size of the intact DNA molecule that

constituted the genetic material of the virus was much greater than the then-current size estimates, which were based on direct but flawed measurements. This work was one of the first to measure the size of a genome in a living system.

## **2) Collinearity of genes and proteins (early 1960s).**

During this period CL addressed the very basic question of how DNA codes for proteins. His study of the bacterial gene for the enzyme alkaline phosphatase showed that there was a collinear relationship between a gene and the amino acid sequence of the protein it specifies. Mutations mapped to specific locations in the alkaline phosphatase gene showed up as amino acid changes at corresponding sites in the polypeptide structure. This kind of relationship represents one of the underpinnings of the molecular biological view of life that we know today.

## **3) Genetic complementation (mid-1960s).**

CL's work on alkaline phosphatase led to another fundamental finding: that two mutant alleles expressed in the same cell could complement each other's deficiency to produce a normal enzyme. In a series of careful experiments, he clearly and completely documented this process of intragenic complementation for the first time.

## **4) RNA metabolism (mid- and late 1960s).**

The concept of messenger RNA had recently been established. After devising rigorous quantitative measurement methods, CL was the first to show that messenger RNA in bacteria was very unstable. The rapid turnover of this genetic information provided an explanation for the ability of bacteria to respond quickly to environmental changes by modulating the activity of their genes, giving physical supporting evidence to the

key model of Jacob and Monod. In later experiments, he extended this general work, explaining the kinetics of synthesis of the specific messenger RNA of model inducible bacterial genes (the lac operon) and of more stable ribosomal RNAs.

### 5) Bacterial virus-host interactions (late 1960s).

CL also looked at the effects of bacterial virus infection on host functions. In particular, he demonstrated the ability of the virus to specifically stop bacterial protein synthesis while maintaining production of its own proteins.

### Computer Graphics and Protein Structure (1960s on)

CL is generally credited with having pioneered the application of 3D computer graphics to the study of proteins. He began this work in 1964 when he heard from the director of MIT's project MAC about the possibility of creating a moving image on a video screen that would give the illusion of a rotating 3D object. Within three weeks he had learned enough programming to generate the first rotating alpha-helix, a protein structure in the conformation of a simple right-handed spiral.

Over the next few years he and his colleagues developed a battery of interactive programs, known then as Chemgraf, that carried out interactive display and structural and energetic analysis of proteins and nucleic acids.

Interactive minimizations were carried out rapidly in torsion space, and the structures generated were displayed in real time on the video screen. A feature that has not been reproduced by other software to this day was the ability to generate structures on the screen by manually manipulating dials and then inputting the coordinates that were generated into a molecular mechanics minimization program. Additional Levinthal innovations upon which many modern algorithms are based included fast side chain and loop minimizations and the first simulations of inter-domain motions in proteins.

The use of programs such as Chemgraf and, later, a more specialized program for proteins called Pakggraf revolutionized the study of protein structure and function. Some



Don Kennedy and Cy Levinthal, circa 1965.

of the programs were adapted for the refinement of x-ray coordinates, while others were precursors of modern protein simulation packages. In the course of visualizing protein structures, CL realized that the problem of finding the global energy minimum of a protein (presumably that seen in the crystal structure) was different from the problem faced by an unfolded protein in finding that minimum. To dramatically illustrate the magnitude of the problem, he pointed out that a random search for the global minimum involving all torsional degrees of freedom, starting from an unfolded protein, would take more time than the lifetime of the universe.

This insight became widely known as the “Levinthal paradox” and numerous papers have been written to explain it. CL’s own explanation was simply that there exist a series of pathways to the native site that are determined by the amino acid sequence—for example, the formation and subsequent coalescence of secondary structure elements such as alpha-helices. The impact of the Levinthal paradox, a seemingly simple, but in fact remarkable, intuitive leap is a testimony to CL’s special brilliance.

### **Computer Graphics and 3D Reconstruction of Nerve Cells (Early 1970s on)**

In the late 1960s CL, along with several other well-known molecular biologists (Sidney Brenner, Seymour Benzer, Gunther Stent), decided that the critical questions in molecular biology had been addressed and that the next exciting frontier in biology was to understand the structure and function of the brain. They switched the main directions of their research efforts accordingly.

An initial question was: which brain? Brenner chose to work with the very small nematode *Caenorhabditis elegans*, which presented a system in which serial-section electron microscopic analysis of the whole organism could yield full detail of all the neurons and synaptic connections in its nervous system. Benzer focused on *Drosophila melanogaster*, because it enabled the power of forward mutational analysis to be used to elucidate mechanisms of learning and memory in its much larger, but still tractable, nervous system. CL wanted to ask to what extent the genes specify the morphology and synaptic connectivity of a simple nervous system, and he chose to study the structure and development of the visual system of the small fresh-water crustacean *Daphnia magna*, which reproduces by parthenogenesis and hence could generate isogenic clones.

Mapping all the branches and synaptic contacts of a neuron requires a resolution of about 0.1 nanometer or less, hence the use of an electron microscope (EM) to image

the tissue. The tissue must be properly fixed, stabilized, sectioned, and stained to reveal membrane boundaries and synaptic contacts. Serial thin sections had to be generated by the hundreds or thousands in order to fully include complete neurons, and these had to be imaged in the EM and printed, and features belonging to each cell identified and traced, usually on transparent acetate sheets that could later be aligned and stacked with proper spacing in order to generate a model of a neuron. This method was very arduous and permitted the reconstruction of only a few cells at a time.

CL reasoned that the computer was ideal for creating a 3D notebook storing all the characteristics of all the cells in the volume of tissue being studied. As designed by CL and his group in the early 1970s, the CARTOS (Computer Aided Reconstruction by Tracing of Serial Sections) system used a digitizing tablet to draw perimeters of selected cell profiles from projected 35 mm film clips of aligned serial electron micrographs. Each profile was identified as belonging to a particular nerve cell and could be displayed either individually or along with all other profiles belonging to an entity. Various representations of the cells could be displayed in 3D (split screen) or in a rotating or oscillating projection that was perceived as 3D, using surface rendering and shadows, etc. CL's group also developed algorithms for automatic cell boundary recognition, but they could not achieve fully automatic reconstruction because of tissue distortions produced by the electron beam.

The early work on *Daphnia* yielded some novel information, such as the observation that an identified neuron in different specimens of an isogenic clone had varying morphology, indicating therefore that morphology was not strictly controlled by the genome but resulted from a partially stochastic process. The researchers also observed that the creation of electrical junctions appeared to precede the formation of chemical synaptic circuits. At this point (1973), however, CL decided that it was important to pursue work on vertebrate systems and shifted his laboratory to work first on the Mauthner cell and spinal motor neurons in the nervous system of the zebrafish *Danio rerio*, which was then being developed as a vertebrate model organism with forward genetics, and later on the mouse, which would become mutationally accessible with the rise of mouse genetics.

Computer reconstruction from serial sections was adopted by other neurobiological laboratories in the 1970s and '80s and was even commercialized. Even so, only recently has it come to be extensively used, thanks to some important technical advances, such as imaging the block face to avoid the problems of alignment and distortion. Moreover, with a renewed interest due to the BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative announced by President Obama in 2014, human

brain mapping and network analysis has come to the forefront. Cy Levinthal's pioneering efforts in this area are widely acknowledged by contemporary neuroscientists.

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