

Symposium presents "smorgasbord" of theoretical biology

Last Tuesday's symposium in Caspary Auditorium, "Modeling Life Processes," signaled the "arrival of theoretical biology, if not its existence," commented George Church, professor of genetics and director of Lipper Center for Computational Genetics at Harvard Medical School. A collaboration between The Rockefeller University and The Institute for Advanced Studies in Princeton, the historic meeting clearly demonstrated the impact of the fields of mathematics and physics on biology.

"The genomic revolution is rapidly changing the way scientists look at life processes," Rockefeller President Arnold J. Levine said during introductory remarks. "Math and physics are playing important roles in everything from gene sequencing and the combinatorics of expression arrays to the impact of environment and life styles."

RU Professor Joel E. Cohen began the afternoon talks with a discussion on the household transmission of Chagas disease, a parasitic condition, which infects 16 to 18 million people in Latin America and is the fourth cause of morbidity worldwide, according to the World Health Organization in 1993. Spread by bloodsucking household



David D. Ho, left, RU professor and scientific director of the Aaron Diamond AIDS Research Center, stands with Alan S. Perelson, group leader of theoretical biology and biophysics at the Los Alamos National Laboratory, at the Modeling Life Processes Symposium, Tues., Jan. 11. Photo by Linne Ha.

bugs, it can infect humans and dogs. In collaboration with Argentinean scientists, Cohen has been developing a model of the household transmission of the disease based on data from a longitudinal field study of three rural villages, which has been going on for over a decade. Using the tools of statistics and probability, Cohen's model predicted that the human prevalence of Chagas disease would decrease when the number of dogs residing in a home decreased. One of the take-home messages, Cohen said, is that mathematical models can be use-

ful in helping to understand diseases.

Church followed with a talk on functional genomics, which he called a "spin-off" of the various gene sequencing projects, many of which have been completed. By analyzing expression data, he said, scientists can compare predictions and observations or correct DNA sequencing errors.

The discussion shifted to qualitative modeling and Internet collaboration during Peter D. Karp's talk. Karp, director of the Bioinformatics Research Group at SRI International, demonstrated how software his group developed helps researchers from different institutions collaborate on the same project. Results can be posted on the Internet and made available to a great number of researchers. He showed some maps that SRI has done that demonstrate pathways based on the genome of *E. coli*, a project they call EcCyc (*E. coli* Encyclopedia) and showed a "meta map" called MetaCyc that was a metabolic encyclopedia of *E. coli* and non-*E. coli* organisms.

Walter Fontana, a research professor at the Santa Fe Institute and a member of The Institute for Advanced Study, talked about RNA as a model system for under-

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Friday Lecture: "Molecular Analysis of Neural Crest Development"

Marianne Bonner-Fraser, a professor at the California Institute of Technology, will give today's Friday lecture (Jan. 21). The topic will be "Molecular Analysis of Neural Crest Development."

The neural crest is a population of migratory cells that arise from the ectoderm of vertebrate embryos in the early stages of embryonic development. Following neurulation, when the neural tube is formed, the neural crest cells emerge from the neural tube and undergo extensive movements along pathways, usually characteristic of their axial level of origin. After migration, the cells differentiate, forming a variety of cell types, from neurons and glia of the peripheral nervous system to pigment cells and cells of the facial skeleton. Bronner-Fraser's lab analyzes the cellular and molecular events underlying the formation, cell lineage decisions and migration of neural crest cells.



Marianne Bronner-Fraser will present today's Friday lecture (Jan. 21). Photo by Levien Willemse.

Through studies on avian embryos, her lab found that contrary to the classical assumptions, individual precursor cells can form neural tube, neural crest or epidermal derivatives. Further study on what interactions were responsible for the formation of the neural crest found that neural crest cells are generated when epidermis and neural plate are juxtaposed. Current studies in her lab focus on the inductive interactions that lead to formation of the neural crest populations along the rostrocaudal axis.

Neural crest cells are involved in a number of birth defects and cancers, such as neurofibromatosis and melanoma. The findings of Bronner-Fraser's lab on normal neural crest development provide important clues about the mistakes that may lead to abnormal development or loss of the differentiated state.

Bronner-Fraser received her bachelor of science in biophysics from Brown University and her doctorate in biophysics from Johns Hopkins University. She has been a professor of biology at the California Institute of Technology since 1996.

Her talk begins at 3:45 p.m. in Caspary Auditorium and is preceded by a tea in Abby Aldrich Lounge at 3:15 p.m.

Ten Science Outreach students reach semifinals of Intel Science Talent Search

Ten out of the 60 high school students who participated in RU's Science Outreach program have been named semifinalists in the Intel Science Talent Search (formerly the Westinghouse Science Talent Search). This program, now in its 59th year, is one of the most prestigious science awards for high school students in the country. More than 70 percent of the former finalists have gone on to earn Ph.D.s or M.D.s; five have won Nobel Prizes.

"The performance of our students is incredible. Ten semifinalists is a new record for our program. The dedication and hard work of these students and their mentors really shows," says Bonnie Kaiser, director of the Science Outreach Program.

The lab mentors have high praise for their students. Stefan Heller calls his student, Evan Fink, a "math wunderkind." Ethan Marin admires the way his student, Eugene Simuni, wrote what amounts to a mini-Ph.D. dissertation.

Of her experience in the program, Cara Wolfish says, "I have a strong yearning to



Eight of the Science Outreach students who are Intel Science Talent Search semifinalists gathered with Bonnie Kaiser, center, director of the Science Outreach Program. Photo by Ann-Marie Blaber.

be part of the scientific community in the future, and the Science Outreach Program contained much of the needed background for future attainment of these goals." Elizabeth McKenna says, "The writing component of the program helped a great deal in preparing my research paper."

Professor Mary Jeanne Kreek, who was herself a winner of the contest, notes that the contest provides students with a wonderful opportunity to meet other like-minded students and senior scientists. She recounts how she met Detlev Bronk (RU president from 1953 to 1968) when she was a finalist, and Bronk remembered her years later when she came to Rockefeller.

This year's winners from RU's Science Outreach Program are Timothy Kyusik Cha, of Garden City Senior H.S., mentored by Professor Emeritus Robert Schoenfeld; Evan Fink, of Stuyvesant

H.S., mentored by Postdoctoral Associate Stefan Heller in the Hudspeth lab; Adam Kahn, of the Hackley School, mentored by Schoenfeld; Chrisann Kyi, of John Jay H.S., mentored by Associate Professor Jonathan Smith in the Breslow lab; Evan Mandel, of Stuyvesant H.S., mentored by Research Associate Penio Penev in the Feigenbaum lab; Elizabeth McKenna, of Stuyvesant H.S., mentored by Associate Professor Sonoko Ogawa in the Pfaff lab; Raymond Raad, of Stuyvesant H.S., mentored by Associate Professor Marcelo Magnasco; Marianna Shnyderman, of Midwood H.S., mentored by Postdoctoral Associate Hayes Dansky in the Breslow lab; Eugene Simuni, of Midwood H.S., mentored by Biomedical Fellow Ethan Marin in the Sakmar lab; Cara Wolfish, of Hebrew Academy of the Five Towns and Rockaway, mentored by Graduate Fellow Dvora Shmulewitz in the Friedman lab.

Save the date: Mon., Jan. 31
The Zanvil A. Cohn Forum

Horace Freeland Judson will present, "What Do We Talk About When We Talk About the Human Genome Project?"

At 5 p.m. in the Abby Aldrich Dining Room. All are welcome. Admission is free.

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Jonathan Weiner to be RU "writer-in-residence"

On Mon., Jan. 10, Jonathan Weiner, Pulitzer Prize-winning author of *The Beak of the Finch*, was the featured speaker at an informal gathering of graduate fellows, hosted by President Arnold Levine and his wife, Linda Levine, at the President's House. The evening included dinner, a slide show presentation and a group discussion. The gathering was part of the student lecture series, supported by the Alfred P. Sloan Foundation.

In his talk, Weiner described Peter and Rosemary Grant's research on the evolution of finches in the Galapagos Islands, as well as the development of behavioral genetics and the work of Seymour Benzer, which Weiner details in his most recent book, *Time, Love, Memory*.

This event was the first opportunity for members of campus to meet Weiner, who joins the RU community as writer-in-residence through December 2000. While here, Weiner will serve on university committees, including the Lewis Thomas Prize committee and the Committee for Centennial Events; get to know the community by visiting labs; and lead a reading and discussion course for graduate fellows. While the details of the course are not yet finalized, Weiner says it will pair science texts with literary texts, both books sharing similar topics and time periods. Discussion groups will then look at the different pleasures each work gives and how they complement each other.

As a child, Weiner aspired to be either a writer or a biologist. In college, he decided on the former, receiving his bachelor of arts degree in English and American Literature from Harvard University. Unable to avoid the lure of science for long, he began writing and editing for *The Sciences* magazine, and in the process launched a career that ful-



Pulitzer Prize-winning author Jonathan Weiner joins the university this year as writer in residence. Photo © Dickson Sorenson.

filled both of his childhood dreams. His science writing has led to several grants and fellowships, including a science writing fellowship at the Marine Biological Laboratory in Woods Hole, Mass., a visiting fellowship in the Department of Molecular Biology at Princeton University from 1995 to 1997 and a research grant awarded by the Alfred P. Sloan Foundation from 1995 to 1997. Weiner was the McGraw Professor in Writing at Princeton University during 1998. He is the author of four science books, including *Planet Earth*, *The Next One Hundred Years*, *The Beak of the Finch* and *Time, Love, Memory*.

Of Rockefeller, Weiner says he has always held pleasant associations with the university. He first became acquainted with RU during the '80s while an editor at *The Sciences*. He recalls walking onto the campus from York Ave. and instantly experiencing a "combination of peace and concentration." Asked about his expectations at RU, Weiner says, "I am excited to be part of Rockefeller's interdisciplinary tradition."

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standing the evolution of development. Fontana noted that RNA is the smallest component subject to both artificial and natural selection. He showed how a quantitative analysis of mutations in the phenotype of RNA can yield clues about evolution that might apply to more complicated processes.

After a short break, the symposium reconvened for an unconventional discussion of lunar illusion. RU Professor Mitchell Feigenbaum, director of the Center for Studies in Physics and Biology, spoke about why the moon sometimes appears to be much larger than it is. This optical illusion, he explained, results from our eyes' having more than one way to process information. The brain takes angle and distance into account, but sometimes our brain is fooled into using the "wrong" viewing method, and we see optical illusions, such as the overly large moon.

The day concluded with a pair of talks dealing with mathematical modeling of HIV infection. RU Professor David D. Ho, scientific director of the Aaron Diamond AIDS Research Center (ADARC), discussed "viral kinetics" during acute infection by the human immunodeficiency virus (HIV), the simian immunodeficiency virus (SIV) and the chimeric SHIV and the implications it has for developing vaccines. When a person or animal is first infected, the amount of virus in the plasma soars in an initial burst, peaks and then drops to a "setpoint," at which it plateaus. Ho and his colleagues devised a mathematical model to measure the change of concentration of virus in the blood over time, both in newly infected hosts and those who had stopped antiviral therapy.

The precise method of calculating HIV dynamics taught the scientists what they had to achieve to establish longstanding control of viral replication—in essence, how much the virus had to be slowed

down in order for the drugs to be effective. Ho also said that the task of achieving an effective vaccine may not be as daunting as suggested by animal studies because the experimental models using SIV are "artificially difficult." Therefore, an HIV vaccine could offer partial protection and still be effective in blocking transmission.

Following Ho's presentation was a talk by Alan S. Perelson, group leader of theoretical biology and biophysics at Los Alamos National Laboratory, who has collaborated with ADARC researchers in subjecting clinical data to rigorous mathematical analysis. Perelson pointed out that mathematical models of HIV dynamics in the body had to account for the virus subpopulation that settled in the body's follicular dendritic cells (FDCs) and lymphoid tissue. Since it is not in the plasma, this subpopulation of virus can elude measurement at first and not be considered a factor. At a later stage, however, the bits of virus may detach from the dendritic cells and lymphoid tissue and be found (and measured) in plasma. This may explain why the viral load of patients receiving multidrug treatment drops very quickly at first and then at a much slower rate; the second phase reflects the elimination of virus lurking in undetected sites. Because of this, mathematical models guiding drug and vaccine development need to incorporate the factor of virus that may be in these sites.

As described by Cohen, the symposium was "like a smorgasbord with more dishes than you can possibly consume; it was a highly stimulating overview. The diversity of views, of approaches taken, of levels of analysis and of biological questions were truly fascinating."

According to Cohen and other presenters, President Levine's belief in the importance of quantitative modeling in modern biology and symposiums such as "Modeling Life Processes" are bringing "theoretical biology" closer to the mainstream.

Potpourri

1999 FSA Participants

If you participated in the Flexible Spending Account benefit in 1999, please be aware that all claims for expenses you incurred in 1999 must be made before Sat., Apr. 15, 2000. Claim forms are available in Human Resources. If you have questions regarding your flexible spending account, call Human Resources, x8300.

Theatre Tickets

Human Resources is pleased to offer discounted tickets for *Wrong Mountain*, a new hit comedy starring Ron Rifkin, for Thurs., Jan. 27, at 8 p.m. Tickets are \$21.00 each and are limited. Call Ron Kurtz, x8303, to reserve them today.

Call to Authors

If you have recently published a book, journal article or other published piece, *News&Notes* would like to know about it. Please send your publication particulars, along with a summary or copy of the piece to Ann-Marie Blaber at Box 68 or fax x7876.

Weather Emergency

RU rarely closes, but in the event of a weather emergency, an announcement will be made on the inclement weather/university emergency phone number, 327-7200. You can also check your personal voice mail for an announcement about a campus closing.

news¬es is published each Friday throughout the academic year by The Rockefeller University, 1230 York Avenue, New York, NY 10021-6399. Phone: 212-327-8967. http://www.rockefeller.edu/pubinfo/news_notes.html

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Ideas and submissions can be sent interoffice (Box 68), by electronic mail (newsno), or by fax (212-327-7876).

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Andrea Lucchesini to perform at the next Peggy Rockefeller Concert



Andrea Lucchesini will perform at the next Peggy Rockefeller Concert, Wed., Jan. 26. Photo © Lelli & Masotti.

The Peggy Rockefeller Concerts will begin the second half of the season on Wed., Jan. 26, at 8 p.m. in Caspary Auditorium with a recital by Andrea Lucchesini, one of Italy's foremost young pianists. In 1994, international critics awarded him the Accademia Chigiana Prize, and in 1995 he received the prestigious Premio Franco Abbiati from the Italian Association of Music Critics.

Born in 1965, Lucchesini studied piano with Maria Tipo. In 1983, he

became the first Italian prizewinner of the Dino Ciani International Piano Competition, which launched his international career. Since then, he has performed with major orchestras such as the Berlin Philharmonic, Munich Philharmonic, Vienna Symphony, London Philharmonic, National Symphony and the Gustav Mahler Youth Orchestra under Semyon Bychkov, Giuseppe Sinopoli, Charles Dutoit, Gianluigi Gelmetti, Daniele Gatti, Dennis Russell Davies, Claudio Abbado and Daniel Harding.

Lucchesini's repertoire ranges from Scarlatti to Luciano Berio. He has performed Berio's *Echoing Curves* Piano Concerto all over the world and recorded it for BMG with the London Symphony under the baton of the composer in 1995. Two years later, he recorded works of Berg and Schönberg with the Dresden Staatskapelle and Giuseppe Sinopoli for the Teldec label.

Deeply committed to chamber music, Lucchesini presents special projects, particularly with the Italian cellist Mario Brunello. They are the artistic directors of Chamber Music Encounters, which takes place in Turin every year.

At The Peggy Rockefeller Concerts on Wed., Jan. 26, Lucchesini will perform Beethoven's *Sonata in E minor, Op. 90*, *Sonata in C Major, Op. 53* and Chopin's *Twenty-Four Preludes, Op. 28*.

Understanding *Drive*: Rockefeller researchers uncover the biological basis of sexual motivation

by Lisa Stillman

For most people, sex is a complicated topic. A new book by RU Professor Donald Pfaff, however, is based on the idea that the primitive, biological side of sex is explainable—at least from a scientific point of view. Pfaff's lab researches the neurobiological and molecular aspects of sexual motivation. In *Drive* (MIT Press), he shows that the biological basis for sex drive—one of the most primitive human instincts—is largely explained by mechanisms uncovered in animal brains that have not changed in millions of years of evolution.

“For the first time,” says Pfaff, “we are able to reason all the way from molecular genetics and cellular detail to an explanation of how hormones and environmental stimuli interact to control behavior.”

“For the first time,” says Pfaff, “we are able to reason all the way from molecular genetics and cellular detail to an explanation of how hormones and environmental stimuli interact to control behavior.” (He carefully makes the distinction that he is not studying the culturally induced phenomenon of love; his lab looks at physiology and behavior, “not why you feel a certain way when you hear songs from when you were in high school.”)

Pfaff's motivation for initiating this field of work came from wanting to understand more fully how the brain works. Because the brain is so complicated, he decided to concentrate on what he calls a single “analyzable” behavior. Looking at libido from a biologist's perspective also made sense because sex drive is an “aspect of mental life closest to being dominated by biological determinants,” he says.

It's also a good candidate for rigorous scientific analysis because it is present in other animals. (You can't study music composition in lab rats, Pfaff observes.)

All animals have basic drives that contribute to the survival of the individual and the species: The first, and most basic, is answering biological needs for the survival of the individual; second comes the biological drive to reproduce. Humans are no exception. *Drive* cites psychologist Abraham Maslow, who observed that people can turn their attention to the “higher motives” of love, altruism and intellectual pursuits only after their basic drives are met.

But where do these primal drives come from? A tremendous amount of genetic and neurobiological evidence forces the conclusion that in the evolutionary process, animals do not create

whole new systems from scratch, but instead reuse the same materials inherited from common ancestors. *Drive* documents a large number of libido-related neurobiological, endocrine, physiological and molecular mechanisms that humans share with a variety of other animals. These similarities strongly suggest that the primitive aspects of libido in humans derive from what happens in other mammals. The burden of proof, Pfaff says, is on those who would claim that humans are unique. (Again, he cautions that his lab is looking only at the biological side of sexual desire, not the cultural factors that influence it.)

Classic research on motivational behavior shows that every drive has two components: one to arouse the brain and another to direct behavior. Some of these drives are controlled by hormones—chemicals produced in the body that circulate in the bloodstream and affect other organs. (In one study, increased levels of estrogen drove female rats to

cross over an electrified grid to get to a male—not that different, Pfaff notes, from the “ridiculous” things college students will do to get next to each other on a weekend.) “Given that we can explain hormonal, neuronal and molecular bases of certain forms of animal reproductive behavior in considerable detail, we can infer that these investigations have a lot to do with the human mind and behavior,” he says.

The techniques of modern molecular biology allow researchers to move from the “big picture” of behavior to the microscopic view of genes, neurons and chemical reactions inside the body. One thing Pfaff's lab looks at, for example, is the set of genes turned on in certain nerve cells when certain hormones make their way to the brain.

The relationship of genes and hormones is intertwined. We are programmed to produce hormones at particular times, and conversely, sex hormones can turn on specific genes in particular neurons—a process important for producing normal reproductive behavior. The researchers in Pfaff's lab knew that to understand the biological basis of libido, they had to take an interdisciplinary approach (see article below). By looking with morphological and electrophysiological methods, as well as at behavior, they made the first discovery of a complete neural circuit for a vertebrate animal's behavior (see “Completing the Circuit” at right). What was surprising—even to Pfaff, who was mentally prepared for the findings—was how exquisitely the molecular, physiological, behavioral and zoological results fit together. Pfaff figures that “this is the kind of multilevel approach you can do more successfully at Rockefeller than at other places.”

The phenomenon of sex drive, produced through the combination of endocrine, neuronal and molecular mechanisms, has clearly been geared toward survival and reproduction. In a way, feelings of lust make good evolutionary sense. “After all,” Pfaff notes, “if sex were not enjoyable, we might fail to do it.”

Completing the circuit

Sigmund Freud's theory of libido “straddled the border between biological and psychological thought,” says Pfaff—but scientific techniques invented since Freud enable us to answer some of the simpler aspects of the mind/body divide with neural and genetic methodology.

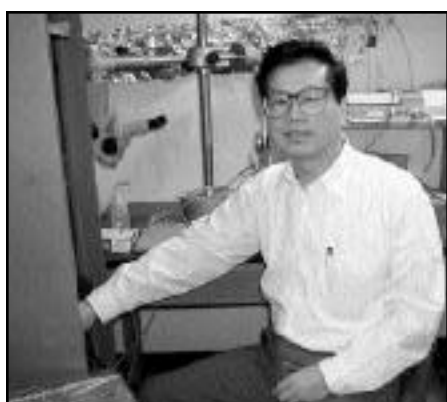
Successful reproduction depends on more than merely hormones and a mate. A virtual suite of senses are involved in determining whether an animal will be sexually receptive. Extreme temperatures or stress or lack of food, for example, bode ill for reproductive success, and can thus diminish or preempt an animal's sex drive. Conversely, certain smells (from pheromones in animals to the modern-day perfume industry) can have a positive effect on libido. How does the brain process all the information required for successful reproduction—evaluating everything from environmental conditions to the body's readiness to the choice of a mate?

Pfaff's idea of how to study the brain has been to start as simply as possible and work his way up. Because the mouse's and rat's elementary reproductive behavior is so hormone-dependent and so simple, he and Senior Research Associate Lee-Ming Kow were able to discover its neural circuit—the first for any vertebrate animal behavior. The researchers were then able to use this circuit knowledge as a “launching pad” to discover how hormones turn on genes that, in turn, trigger mating behavior.

The experiments, which are explained in detail in *Drive*, show step-by-step how specific hormonal inputs and sensory signals interact in a neural circuit and allow for integrated reproductive behavior. At the same time, Pfaff notes, the animals' instinctive behavior sequences have a “feed forward” quality, in which the very performance of early behaviors in a response chain exquisitely prepares the neural circuitry for later responses.

The drive continues Ongoing research in the Pfaff lab

The research chronicled in *Drive* continues today in the Pfaff lab. Current projects include using DNA microarray technology to discover new patterns of genes turned on or repressed by a hormone as a function of



Senior Research Associate Lee-Ming Kow at work in the lab.
Photo by Linne Ha.

time after hormone administration. Assistant Professor Sonoko Ogawa is also using gene knockouts, coupled with manipulations in the adult brains of mice, to analyze exactly how individual genes contribute to sexual behavior. Overall, Pfaff hopes to broaden the behavioral question, from studying hormone effects to explicating the fundamental neural processes underlying brain arousal.

As for the molecular and genetic part of this effort, Postdoctoral Fellow Nandini Vasudevan is currently looking at the transcriptional interference of estrogen action by thyroid hormones, a phenomenon recently reported by the lab in *The Proceedings of the National Academy of Sciences*. One current puzzle is that the *in vivo* knockout data for genes for the thyroid receptor (TR alpha) are the opposite for those for TR beta and cannot be understood as a simple result of the lab's transcriptional data.

Senior Research Associate Lee-Ming Kow, whose work was instrumental in the discovery of the new neural circuit, has been in the Pfaff lab for more than 20 years. He is a biophysicist and neuropharmacologist who studies electrophysiological responses by individual neurons in genetically altered mice. Kow has always been interested in how the brain formulates and regulates behavior and says that the neurogenetic studies in mice are exciting because their steroid hormone-driven system is simple enough to allow researchers to make sense of how indi-



Postdoctoral Fellow Nandini Vasudevan concentrates on her work.
Photo by Linne Ha.

vidual neurons behave. For him, the animals' behavior itself “is just a convenient end point” as a target for neurochemical explanation. —L.S.