motion of the system causes transitions to occur between distinct classes of minima. From this perspective, the venerable absolute reaction rate theory (*17*) devised to describe activated chemical reactions in the gas phase would require generalization and modification to accommodate the distributions of minima and of transition states that appear in the present multidimensional description.

Biopolymer conformational problems continue to receive vigorous experimental and computational attention (*18*). The latter typically has involved a search for optimal conformations, that is, the absolute minimum of some postulated potential energy function that incorporates chemical bond lengths and angles, as well as more remote atom-pair nonbonding interactions. Solvation is usually disregarded, or at best incorporated in some simple averaged way. We conclude that the type of complete configuration space analysis outlined above (for biopolymers plus solvent) would be useful. First, it would help to assess the importance of solvent packing fluctuations. Second, consideration of the full distribution of potential minima would demonstrate how special the absolute minimum is geometrically. Third, examination of transition states would be enlightening with respect to annealing kinetics of suboptimal conformations to the absolute potential minimum. Systematic study of a few select cases could provide an important contribution to quantitative understanding of kinetic processes in molecular biology.

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Networking in International Agricultural Research

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International cooperation in agricultural research is rapidly increasing as supplies of funding tighten and the benefits of collaboration are realized. Networking among agricultural scientists is not new, but the current extent of collaboration is unprecedented (*1*). Researchers are forging working partnerships on a regional or a global scale to trim costs, avoid duplication of research efforts, and accelerate transfer of technology to farmers.

Scientists characteristically cultivate informal networks of contacts for exchanging ideas and information. Such networks often develop as an outgrowth of professional meetings and are maintained by correspondence and telephone. Sometimes these informal groups establish a more formal organization, particularly if the research involves technological exchange between countries.

In some formal networks information is exchanged between participants and a central hub. Information outreach networks generally function in this way. Other networks are designed to allow participants to interact with each other as well as with the hub; international nurseries established to screen crop germplasm are generally set up in this way. More complex networks retain this structure, but participants may set up subnetworks to focus on a particular problem. In the latter case the central hub is less dominant because decision-making is delegated more to satellite nodes. Some collaborative programs pass through all three formats.

Agricultural networks can assume various forms, but the cooperative efforts discussed in this article are all concerned with international research, involve a two-way flow of information and materials, and entail a commitment of resources from participants. The Philippines-based International Rice Research Institute (IRRI) and the International Maize and Wheat Improvement Center (CIMMYT; Centro Internacional de Mejoramiento de Maíz y Trigo) in Mexico have relied on extensive networks for more than two decades, so we will focus our attention on the experience of these institutions.

History

During the colonial period the Belgians, British, Dutch, and French established networks of research stations in their territories to increase the flow of export crops. Colonial stations improved the output of several crops, including cotton, groundnuts, and sugarcane, but collaboration with territories outside the individual empires was limited (*2*). Furthermore, many stations ceased operations after independence because they were staffed mainly by expatriates (*3*).

In the United States, networking in agricultural research began with informal groups working together on a local basis. The continental expanse of the nation and its diverse ecosystems, however, created a need to link research at the state, regional, and national levels. A two-tier system was developed to increase agricultural productivity across the country: the U.S. Department of Agriculture at the federal level and a series of state-run agricultural experiment stations. Both systems synchro-

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nized research programs on widely shared problems. Wheat research, for example, greatly benefited from several regional networks coordinated by USDA in the late 1920's (*4*). Networking also provided a springboard for the development of hybrid corn. In 1925, researchers at state agricultural experiment stations in the Midwest coordinated their programs to avoid duplication and to share results. This USDA-coordinated network led to the release of commercial hybrids in the 1930's (*5*).

Before World War II scientists in different countries exchanged a limited amount of plant germplasm, but agricultural networks were largely informal and national in scope. In the early 1950's a serious outbreak of a new race (15B) of wheat stem rust in the United States led to the first formal, multinational network to screen crop germplasm. The International Stem Rust Nursery, established in 1950 and coordinated by USDA, was the first systematic nursery to transcend national borders. Wheat breeders were eager to participate, since they realized that a neighbor's problem today could be theirs tomorrow. Researchers in the United States, Canada, Mexico, Colombia, Ecuador, Peru, Chile, and Argentina benefited by sharing and evaluating wheat materials together. The positive feedback from this pioneer international network attracted more participants; by 1970, 150 scientists in 40 countries in the Americas, Europe, and the Middle East had joined.

International Agricultural Research Centers (IARC's), particularly those under the aegis of the Consultative Group on International Agricultural Research, have acted as catalysts for many of the agricultural research networks in the Third World since the 1960's (*6*). IARC's have been especially active in international nurseries that evaluate the genetic potential of cereals, pulses, root crops, and forage plants. Most of the transnational nurseries are relatively recent because the IARC's are generally less than 12 years old. IRRI, for example, initiated the first international rice nursery in 1963. In 1964 CIMMYT organized the International Spring Wheat Yield Nursery by merging two regional programs in the Middle East and Latin America. All IARC's are teaming up with national programs to further their studies of crops and livestock.

Summary. Informal and structured collaboration is becoming increasingly common in international agricultural research. A network approach to research generally reduces costs, minimizes duplication, and boosts efficiency. Collaborative teams, sometimes involving hundreds of scientists in dozens of countries, have been formed to tackle numerous constraints to boosting food production. Networks have been established to test crop germplasm over a broad range of environments, explore ways of boosting the efficiency of fertilizer use, upgrade disease resistance in livestock, and identify socioeconomic obstacles to improved agricultural output. The benefits of networking are especially valuable to countries with limited funds and scientific manpower.

Principles for Success

Successful networks are grounded on seven main principles. The most important is that the problem be clearly defined and a realistic research agenda drawn up. For example, the Lima-based International Potato Center (CIP; Centro Internacional de la Papa), recognizing that it is difficult for Latin American countries to address all the factors limiting potato production, in 1978 initiated an international collaborative effort, Programa Regional Cooperativa de Papa (*7*). Nine major factors limiting potato yields in the region were identified: and research responsibilities were assumed accordingly: late blight disease, viral diseases, seed production, and socioeconomics (Mexico); tuber moth (Costa Rica); golden nematode (Panama); bacterial diseases (Peru and Costa Rica); early blight (Dominican Republic); and rustic storage practices (Guatemala). CIP has employed this principle of first outlining a problem and then drawing up a practical research plan to initiate four other regional potato networks in Africa, Asia, and Latin America.

A second essential element in a viable collaborative effort is that the problem be widely shared. Only when participants feel that they are likely to gain from the venture will they be motivated to contribute. The third principle then follows that strong self-interest underpins productive networks; effective networking cannot be mandated.

A fourth principle underlying successful networks is that participants be willing to commit resources, such as personnel and facilities. Goodwill and a desire to cooperate are important, but the acid test for a network is whether collaborators are prepared to make staff available and offer the use of land, buildings, and equipment.

Although national programs are usually willing to contribute staff and facilities, restrictions on international travel often hamper the desire to cooperate. A fifth principle, then, is that outside funding be available to facilitate the birth of networks and to keep them functioning for at least the first few years. Because of the scarcity of foreign exchange in most developing countries, Third World nationals often find it difficult to travel abroad to attend meetings and to join monitoring tours. Donors in the industrial nations thus play a key role in starting and sustaining many international networks.

The sixth principle is that participants have sufficient training and expertise to make a contribution. The caliber of participants is just as important as a willingness to contribute. Linking a group of ill-prepared scientists to a collaborative effort could be counterproductive. Not all individuals in a network can have the same scientific training, but they must have sufficient preparation to perform their portion of the research effort effectively. Networks are not a substitute for the long-term task of upgrading national programs. In the Third World, agricultural networks are generally better developed in Asia and Latin America because national programs are stronger in those regions.

Finally, networks need to be guided by strong and efficient leaders who have the confidence of the participants. Cooperation will wane if researchers feel that the leader is coercing them into a methodological straightjacket or if they do not receive recognition for their contributions. Such dissatisfaction is less likely when participants elect the network coordinator for a specified period. If leadership changes hands too frequently, however, research drives can stall and the network's cohesion will suffer. When the research capability of institutes varies markedly, collaboration is best served by leaving the leadership post with the strongest participant.

Network Variety

More than 100 international agricultural networks are currently operating; only a few can be discussed here. International nurseries set up to test advanced breeding material are the most numerous and extensive networks, but collaborative teams have been assembled to investigate such topics as the transferability of agrotechnology within soil families, the use of crop by-products for livestock feed, livestock diseases, agricultural machinery, and farming systems (*8*). The rich assortment of networks reflects the multifaceted nature of agriculture and the need to tap the perspectives of various disciplines in order to improve productivity.

Networks set up to tackle agronomic problems, develop agricultural machinery, and examine socioeconomic constraints are generally more recent than international nurseries. Some of the younger consortiums, though, such as the Trypanotolerance Network in Africa, are poised to deliver tangible research results that will help boost agricultural productivity. The Trypanotolerance Network is coordinated by the Addis Ababa–based International Livestock Center for Africa and unites the efforts of 20 scientists working at other international centers, such as the International Laboratory for Research on Animal Diseases and the International Center for Insect Physiology and Ecology both headquartered in Nairobi, as well as national programs. The network team is learning about mechanisms for resistance in certain breeds of livestock, especially cattle, to trypanosomiasis, a debilitating and often fatal parasitic disease that plagues some 50 countries in Africa, Asia, and Latin America (*9*).

International Nurseries

International nurseries are among the oldest and most pervasive of the agricultural research networks. The logistics of running an international nursery are enormous. Advanced breeding lines, obtained from IARC's and national programs, are packaged and air-freighted to numerous countries, often on several continents. The IRRI-coordinated International Rice Testing Program, for example, embraces 800 scientists in 75 countries in Asia, Africa, Latin America, Oceania, and Europe (*10; 11*, p. 7). The number of countries participating in international nurseries often fluctuates but is trending upward. In 1974, for example, CIMMYT sent trials of wheat, triticale, and barley to 83 countries; in 1979 and 1981, 134 and 101 countries participated (*12*). Scientists travel to nursery sites to monitor crop performance and use standardized reporting procedures so that data can be transferred to computers for rapid analysis. International nurseries are able to surmount ideological, religious, ethnic, and language differences: more than 130 nations joined networks to test crop breeding material during the 1970's (*13*).

The larger international nurseries typically screen for high yield and wide adaptability. Other, usually smaller, nurseries measure resistance to pests, diseases, or other environmental stresses. Specialized nurseries are chiefly designed to test materials in certain hot spots where insect or disease pressure is particularly severe so that sources of resistance can be identified. IRRI coordinates 11 specialized international nurseries to screen rice for tolerance to diseases, insects, and adverse soils and weather. The Republic of Korea, for example, provides facilities for identifying rice lines tolerant of low temperatures while Thailand participates in a specialized rice nursery by monitoring the performance of rice lines in deep water. CIMMYT has several specialized nurseries for evaluating the performance of wheat lines in the face of disease pressure, particularly from rust pathogens. The Regional Disease and Insect Screening Nursery, for example, involves over 30 countries and emphasizes the early detection and identification of resistance by screening at locations where new and diverse races of pathogens are present or evolving.

A major benefit of international nurseries is that germplasm is evaluated across a wide range of geographical conditions. Breeding for resistance to several pest and disease problems is possible at the scattered testing sites. Also, new pests and diseases are spotted and sources of resistance identified; nurseries thus serve as an early warning system for agriculture. CIMMYT's specialized disease-monitoring nurseries provide national programs with 3 to 5 years of lead time between detection of a new race of a pathogen and its pandemic establishment in an area. The intricate web of international nurseries thus helps to build stability and safety into crop varieties.

The CIMMYT and IRRI have attracted an impressive number of collaborators in their various international nursery programs by successfully providing several key services. First, CIMMYT- and IRRI-instigated networks are flexible and profit from regular feedback from participants. Trials can be easily added or dropped. The advisory committee of the International Rice Testing Program, for example, meets once a year to discuss new directions and priorities. Recently the committee decided to step up the screening of rice lines that benefit from biological nitrogen fixation through the action of various bacteria and blue-green algae. To further this objective, the International Rice Testing Program is forging links with IRRI's biological nitrogen fixation program, which involves 12 laboratories in China, India, the Philippines, Senegal, Sri Lanka, Thailand, and Vietnam. IRRI's international nurseries program also interacts with other networks, such as the Asian Farming Systems Network and the International Network on Soil Fertility and Fertilizer Evaluation for Rice. By tapping into knowledge generated by other networks, the international nursery programs of CIMMYT and IRRI provide material better suited to the diverse and ever-changing environments in which wheat, barley, triticale, maize, and rice are grown. The other main attributes accounting for the success of these nurseries are their emphasis on training and on communication of results. The International Rice Testing Program each year publishes three reports to keep participants informed of the outcome of thousands of entries: an interim report summarizing initial returns, an annual report, and a shorter publication containing highlights of outstanding performers in the various nurseries.

Problems

Although the value of networking in agricultural research is widely recognized (*14*), problems occasionally surface. National programs sometimes feel burdened by the enormous quantity of entries to be planted in international nurseries, and the uneven feedback of results partly reflects this irritation. Even IARC's occasionally complain that some entries are of little use to them. Many nurseries would benefit from streamlining; too much poorly evaluated germplasm is fed into international networks. Inflexible experimental designs also stir complaints; scientists periodically withdraw from international nurseries when they are asked to conduct trials tailored to someone else's interests.

Quarantine bottlenecks occasionally impede the work of international nurseries. Valuable seed destined for testing sometimes deteriorates in government warehouses because clearance has not been arranged. Even when the proper paper work has been filled out, quarantine clearance can be slow, endangering the viability of plant material.

Feedback from participants in international nurseries and other networks is often sporadic because of manpower shortages and deficiencies in mail and telecommunication services. Information may be received too late to be incorporated into planning for the next planting cycle. More interim reports could help overcome this problem. Improvements in telecommunications will permit the linking of computers and the speeding up of data processing and dissemination.

Communication with scientists outside networks can also be unsatisfactory. Networks can become closed clubs. Researchers who do not participate in a network may experience difficulty trying to secure reports; a clear policy for dealing with individuals who have not contributed to the cooperative program is usually lacking. Linkages between networks can also be tenuous because of problems in communication or weak relationships between disciplines.

Network leadership can trigger contention, especially when participants differ in experience and research capability. Management of an enterprise by democratic processes whereby all partners have equal responsibility regardless of their expertise is not necessarily cost-effective (*15*). IARC's coordinate most international networks, at least during the early stages, but leadership is gradually shifting to national programs as they strengthen. IARC's no longer play leading roles in many networks; in the International Rice Testing Program, for example, national programs now contribute more than 50 percent of the entries, up from 30 percent in 1975 (*16*).

When networks fail to adhere to the principle that participants should have sufficient expertise to participate fully, progress may stall. If a participant is unable to deliver on his task, the entire work schedule may be interrupted. The International Potato Center has occasionally found it necessary to shift the responsibility for a task in its regional networks from one country to another because of such delays. When a collaborator fails to play his part, the other participants reassess their opportunity costs. Networks are a drain on the time of scientists, and they will continue to collaborate only if sufficient benefits flow from the effort.

Payoffs

Although some problems have surfaced in networks, cooperative projects have also generated numerous benefits. It is difficult to measure the value of networking in monetary terms, but, judging from the proliferation of collaborative programs, the benefits generally outweigh the problems.

The saving of time and money is one of the most important benefits of networking. Large international networks can be expensive; the 5-year budget of the International Rice Testing Program, starting in 1980, was $7.8 million. But well-organized networks are generally cost-effective. International nurseries, for example, trim costs because much of the preliminary breeding work is done by others. In the case of the International Rice Testing Program, the network spares national programs 2 to 5 years of breeding effort.

Networks use existing facilities and staff rather than erecting buildings and acquiring more personnel. Start-up is rapid because networks are not saddled by a large bureaucracy and do not require extensive hiring or the building of infrastructure. Networks are flexible and programs can be easily adjusted or terminated (*17*). IRRI, for example, disbanded its regional rice agroeconomics network after the work was completed. Networks also economize by making better use of current information even as they generate new knowledge. Most networks publish newsletters to speed up dissemination of results and hold regular workshops to resolve methodological difficulties and to chart future research. Adoption of a common methodology permits more effective training as well as dissemination and use of results by user groups. Furthermore, donors generally regard networks favorably, since the problems are likely to be widely shared and a consortium approach provides for the efficient use of funds.

Networking has been especially useful in launching crop germplasm with wide adaptability. Through cooperative arrangements with national programs, CIMMYT-coordinated maize nurseries have led to the development of 24 open-pollinated populations with various degrees of resistance to diseases and with different agronomic and grain qualities. These populations have served as genetic reservoirs for 70 maize varieties that have been released by national programs in 20 developing countries (*18*). Since its inception in 1975, the International Rice Testing Program has launched 60 high-yielding varieties of rice in 32 Asian, African, and Latin American countries (*11, 19*). National programs have contributed varieties that other countries have found useful under their conditions; this illustrates the organizational concept in networking in which members interact with each other as well as with a central hub. The International Bean Yield and Adaptation Nursery, coordinated by the Colombia-based International Center of Tropical Agriculture (CIAT; Centro Internacional de Agricultura Tropical), has delivered 48 varieties that have been distributed to farmers or are being multiplied for release. All bean selections leaving the second stage of the network resist bean common mosaic virus, and the nursery has helped to locate lines that survive all known races of anthracnose (*Colletotrichum lindemuthianum*), a worldwide and highly destructive fungal disease of beans and other important crops.

A less tangible but equally important benefit of networking is institution-building in the Third World. Networks help to identify leaders in developing countries and expose scientists to new methodologies and technologies. Workshops and training courses play crucial roles in this effort to upgrade the effectiveness of national programs. The IRRI-coordinated Network on Soil Fertility and Fertilizer Evaluation on Rice, for example, has sponsored five 4-month training courses that have graduated 106 individuals from 14 countries. By 1983, the 5- to 6-month course offered by the Asian Farming Systems Network, another IRRI-instigated research effort, had trained 317 people from 29 countries. Because of growing interest, many networks are planning to add courses. Demand is so strong for the Asian Farming Systems Network that IRRI is considering offering the course twice a year so that as many as 90 students can be served.

Courses offered by IARC's outside their network activities also increase the effectiveness of collaborative programs. Courses for plant breeders from the Third World provide recruiting grounds for future networks. IRRI, for example, has trained 5000 rice specialists who are now employed in national programs (*20*). And CIMMYT instructs over 100 people a year in cereal crop breeding, many of whom subsequently participate in international networks.

Conclusion

Participants have generally found networking to be a straightforward, logical approach to developing effective working relations between countries. Smaller countries with limited capacities to launch broad-based research programs have found networking to be especially useful (*21*). Collaborative programs have clearly buttressed the efforts of developing countries to help themselves.

Although networking is now used in various scientific endeavors, such as medicine, agriculture provided an early seed bed for the concept and most international networks are concerned with crop or livestock production. Breakthroughs in agricultural research have generally come from a combination of cooperation and competition. In food crops, collaboration is widespread, particularly in testing germplasm and devising improved agronomic techniques. In the marketing of finished cultivars, on the other hand, firms often compete for a share of the market; such competition benefits farmers and consumers (*22*).

Whereas most crop networks currently serve only the major cereals and root crops, other collaborative teams are likely to assemble to upgrade the productivity and yield stability of minor crops, such as most millets and tuber cultigens, that are locally important sources of food and cash in the Third World. Networks are also forming to advance research on microorganisms, such as bacteria involved in nitrogen fixation and yeasts important in fermentation processes. The networking concept, then, will continue to permeate virtually all aspects of agricultural research, to the enduring benefit of farmers and consumers.

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RESEARCH ARTICLE

Infectious and Selectable Retrovirus Containing an Inducible Rat Growth Hormone Minigene

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Expression of the growth hormone (GH) gene in animals is restricted to the somatotrophic cells of the anterior pituitary, and is transcriptionally regulated by glucocorticoids, thyroid hormone (T_3), and the hypothalamic peptide growth hormone–releasing factor (GRF) (*1*). To study its hormonal and developmental control we have introduced the cloned GH gene into cultured cells by DNA-mediated gene transfer and into transgenic animals by microinjection into fertilized eggs (*2, 3*). Because the efficiency of introducing this gene into various cells by transfection is low, and since microinjection is technically difficult, we explored the possibility of creating a retroviral vector that would allow the efficient transfer of a functional GH gene into cultured cells, and possibly fertilized mouse eggs, preimplantation blastulas, and somatic tissue.

The structure and mode of propagation of retroviruses makes them ideally suited for gene transfer (*4, 5*). These features include efficient transmission to recipient cells, integration into host chromosomal DNA, plasticity of the viral genome for accommodation of foreign DNA, and the ability to infect a wide variety of cell types from many animal species. Selectable genes expressed by retroviral regulatory elements have been successfully propagated (*5, 6*), but the utility of such vectors would be greatly extended if nonselectable genes expressed from independent promoters could also be transferred. Thus, the many advantages of retroviral gene transfer could be utilized for the study of fundamental aspects of eukaryotic gene expression.

We describe the construction of a selectable retroviral vector containing a rat GH minigene. Recovered high titer retrovirus leads to GH synthesis and secre-

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