

From all the physical-organic work on phosphate esters, we presumed that enzyme-catalyzed phospho transfers would follow one of three paths: “in-line associative” (where the acceptor attacks phosphorus from the side opposite to the leaving group, not unlike an  $S_N2$  reaction in carbon chemistry), “dissociative” (where monomeric metaphosphate is transiently formed, analogously to an  $S_N1$  reaction), or “adjacent associative” (where the acceptor attacks phosphorus from the same side as the leaving group and—after a pseudorotation of the phosphorus ligands—the leaving group departs).

In the 1970s and 1980s, the use of substrates having chiral [ $^{16}\text{O}$ ,  $^{17}\text{O}$ ,  $^{18}\text{O}$ ]-phospho groups suggested that all single, enzyme-catalyzed phospho-group transfers proceed with stereochemical inversion at phosphorus (4). That conclusion limited the pathways to those having “in-line” geometry, but it left unanswered the question of whether the mechanism is fully dissociative via metaphosphate (with apical P-O distances of  $\geq 3.3$  Å and bond orders of zero),  $S_N2$ -like (with apical P-O distances of 1.91 Å and bond orders of a half), or fully associative via an oxyphosphorane (with apical P-O distances of 1.73 Å and bond orders of 1) (5).

With exquisite clarity, the high-resolution crystal structures of Lahiri *et al.* (1) now provide the answer. The coordination

states of the two phosphorus atoms in the intermediate that is formed from the phospho-enzyme and either glucose 1-phosphate or glucose 6-phosphate are quite different. One, at the sugar’s 6-position, has the normal, four-coordinate tetrahedral arrangement of a phosphate monoester. But the other is a stretched pentacoordinate trigonal bipyramidal oxyphosphorane, with the substrate’s C1 oxygen and the carboxylate of the enzyme’s aspartate-8 as its apical ligands (see the figure). The electron density at phosphorus is not ellipsoidal, which argues against the structure being a time average of those of a phosphorylated aspartate and a 1-phosphorylated sugar. The network of hydrogen bonds (and a bound magnesium cation) shows how precisely the enzyme grips this species, to sequester and preferentially stabilize an otherwise unstable entity.

So what is this species? Apical bond lengths of 2.0 to 2.1 Å correspond to P-O bond orders of a quarter to a third, and the structure is thus close to what we’d expect for the transition state of a partly associative in-line displacement (5). Could this actually be the transition state, seductively consistent with Pauling’s view (6) that enzymes are designed explicitly to bind (and thus to stabilize) the transition states of the reactions they catalyze? But transition states are at free energy maxima and could never be ob-

served directly. In this case, we must conclude that the temperature coefficients of the various enzyme-bound species are such that what is a transition state at physiological temperatures has become the most stable intermediate at the very low temperature of the crystallographic work. Or perhaps the uncatalyzed reaction involves a transient intermediate oxyphosphorane and the enzyme has evolved to stabilize that intermediate, lowering in the process the free energies of the two transition states that flank it. Indeed, we must hope that the authors will explore what happens to their structure as the temperature is raised.

But such questions are less important than the fact that the simple, attractive, and anticipated mechanism for enzyme-catalyzed phospho-group transfer has now been so gratifyingly confirmed.

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## MATHEMATICS AND BIOLOGY

# A Bright Future for Biologists and Mathematicians?

Alan Hastings and Margaret A. Palmer

Why, despite vaccination efforts, is Boulder, Colorado, weathering an outbreak of whooping cough (pertussis)—a potentially fatal illness in young children—this winter? The answer to this biological question comes from the classic mathematical analysis of Kermack and McKendrick, whose threshold theorem calculates the minimum level of vaccination required to prevent an outbreak of an infectious disease (1). This example of how mathematics can help biology was just one of many discussed at a recent series of Quantitative Environmental and Integrative Biology workshops (2) and at a recent NIH-NSF workshop that examined forging

stronger links between mathematicians and biologists (3). A goal of the workshops was to seek answers to the questions: Which biological problems will yield to mathematical analyses, and how should biology and mathematics be integrated to achieve this?

Kermack and McKendrick developed the threshold theorem to determine the conditions under which infectious disease epidemics occur. This theorem has proved crucial for calculating the level of vaccination (less than complete coverage) required to eradicate diseases like polio and smallpox, and for preventing outbreaks of diseases such as pertussis. This theorem relates the occurrence of an epidemic to the number of susceptible individuals, the duration of the infectious period, and the infectivity of the disease. The threshold theorem was initially developed to answer two fundamental biological questions: Why do infectious disease epidemics occur, and

why do they typically die out before all susceptible individuals contract the disease? These questions were answered by using the threshold theorem to develop the SIR (susceptible, infective, removed) model (1), which consists of three differential equations. The SIR model assumes that over the time scale of an epidemic, births and deaths in the host population can be ignored. The model includes the rate of removal (through death or recovery) of infected persons from the group passing on the infection, instead of specifying the more correct but harder to analyze assumption that there is a fixed time period during which an individual can infect others. The threshold theorem was originally illustrated using methods that relied on the graphic display of the number of infective and susceptible individuals during an infectious disease outbreak. The graphic representation of the threshold theorem reveals that the density of susceptible individuals must exceed a certain critical value for an epidemic to occur. This theorem has unquestionable relevance, given heightened concerns about the deliberate introduction of new infectious bioterrorist agents.

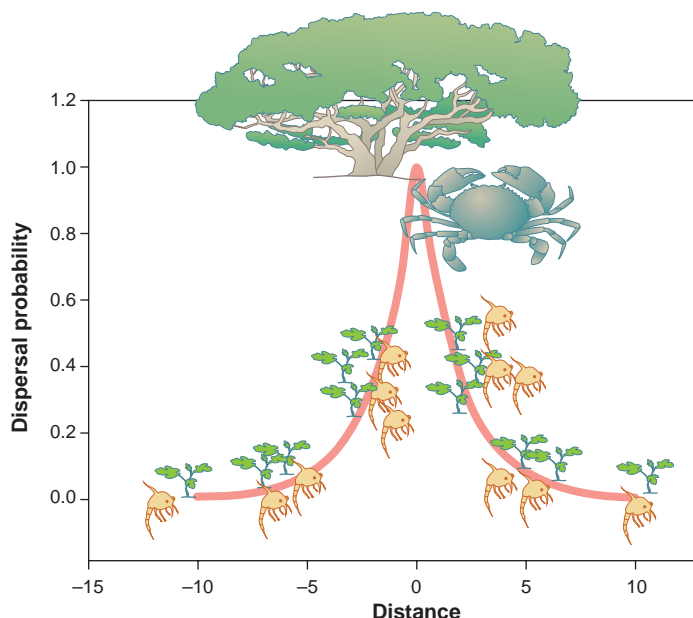
Workshop participants agreed that progress in understanding biological problems will depend on mathematical ad-

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## PERSPECTIVES

vances in spatial dynamics (4); stochastic (nonlinear) dynamics, especially as applied to spatial systems (5); and how models are best fit to the data (6). Spatial stochastic systems in biology, such as the population dynamics of species in forest or grassland ecosystems, are motivating development of new mathematical models. A complete description of spatial dynamics is extremely complex (as it would include the dynamics of means, variances, third moments, and higher order moments), and so approximations are needed. For example, moment-closure methods approximate complete dynamics using only a few moments, thus enabling the tracking of, for example, the spatial dynamics of infection rates. This type of mathematical model is particularly valuable for analyzing the dynamics of infectious diseases because the likelihood of a susceptible individual becoming infected does not depend on the overall level of infected individuals in the population, but rather on the severity of infection among those individuals with whom the susceptible individual is in contact.

Meeting delegates viewed several areas as especially promising candidates for successful application of mathematical and quantitative approaches to solving biological and societal problems. Examples include how natural resources should be managed, forecasting the effects of global climate change, and evaluating the movement of agricultural pests. A good example of how mathematics can benefit biology is the calculation of the size and spatial configuration of marine reserves needed to sustain a fish population that may be overexploited. The basic question is how to calculate the total rate of settlement of new individuals at any point in space, summing up contributions from all other locations. Conditions for the survival and persistence of marine species have been derived from discrete-time and continuous-space models. These models are based on a dispersal kernel model, which gives the probability of offspring from marine organisms being recruited at a given distance along the coast from the point of release from the parent (see the figure) (7). The dispersal kernel model has



**Far away, so close.** The dynamics of spatial systems are often at the interface between biology and mathematics. The spatial distribution of offspring around a parent is one example of a spatial process taking place over a discrete time period and can be represented by the dispersal kernel model. The figure shows the dispersal of crustacean larvae along ocean currents away from the parent and, for comparison, the dispersal of seeds from a mature tree. The fact that more offspring land close to the parent rather than far away is described by the double decaying exponential of the dispersal kernel model. This model is valuable not only for predicting the dispersal of offspring but also for addressing biological problems such as the design of marine reserves, the spread of invasive species, and the potential influence of GMOs on natural populations.

spurred the design of a series of interconnected marine reserves off the California coast. The next step is to make sustainability of marine populations apply to more realistic descriptions of oceanographic processes, to integrate economics more fully into calculations of marine reserve management, and to account for the uncertainty in the growth rates of marine populations.

Quantitative approaches can also be used to calculate how spreading of alleles from genetically modified organisms (GMOs) to natural organism populations might affect those populations. Related mathematical analyses examine the best approach for controlled introduction of GMOs that are resistant to insect pests. GMO technology is threatened by the risk that insect pests will evolve resistance to GMOs, and mathematical modeling suggests ways to reduce this risk (8).

Mathematics continues to be essential for understanding the dynamics of infectious disease outbreaks. One dramatic example is the foot-and-mouth epidemic in the United Kingdom in 2001 (9, 10). Tools such as the dispersal kernel model and explicit spatial models allowed comparison of different strategies for controlling the epidemic. These analyses enabled the design of a control strategy based on local culling

of infected and exposed animals that resulted in halting of the epidemic.

Many of the same mathematical themes emerge in cellular and molecular processes. In the cell, chemical energy in the form of ATP is converted into mechanical work by molecular motors—molecules that govern movement in living systems (11). The dynamics of these movements within the cell depend on stochastic forces that lead to discrete conformations of the motors, enabling them to operate like molecular ratchets (12). Mathematical modeling opens the door to predicting force-velocity relations and other quantitative characteristics of the motors' actions, which can then be compared to actual measurements (13). Computational approaches make it possible to attack problems that are much more complex than the mere mechanics of single motors and to generate "virtual" structures that can be compared to real data from time-lapse microscopy (14).

Workshop participants agreed that a vital next step will be to promote the training of scientists with expertise in both biology and mathematics. A new generation of empiricists with stronger quantitative skills and of theoreticians with an appreciation for the empirical structure of biological processes will facilitate a bright future for the application of mathematics to solving biological problems.

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