A Bright Future for Biologists and Mathematicians?
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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 [^{18}O]PO-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 ≥ 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 oxynphosphorane (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 lengths of 2.0 to 2.1 Å correspond to P-O bond orders of a half, or fully associative via an oxynphosphorane (with apical P-O distances of 1.73 Å and bond orders of 1) (5).

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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 observed 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.

**References**


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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 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.

References