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Cellular and Theoretical Chimeras: Piecing Together How Cells Process Energy

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AMONG THE fantastic creatures that Homer described in the *Iliad* is the chimera, a fire-breathing monster with the head of a lion, the body of a goat and the tail of a serpent. Biologically, the chimera is unimaginable—a quintessentially mythical creature. Yet as an improbable hybrid, it also served as a model for naming another, very real product of cellular biochemistry in the 1970s. Using a dramatic new experimental technique, chemists pieced together parts of cell organelles from different species.[1] Though the fragments had been extracted from cells representing three different kingdoms, they functioned together to produce adenosine triphosphate, or ATP, the unit of energy in the cell. The chimeric vesicles were striking—and persuasive, as well. They helped resolve a deep theoretical debate about how cells process energy at the stage of oxidative phosphorylation. The experimentally produced cellular chimeras are thus important landmarks in the history of bioenergetics. They are also relevant to the philosophy of experiment. In this case, they represent a special category of 'capstone experiments'. The chimeras demonstrated that several domains of experiment could be pieced together (though none of the individual elements was itself novel). The notion of a chimera, or a mosaic of divergent components, also describes how the broader controversy itself was resolved. The episode illustrates that, contrary to many models of scientific change, theories or models may be pieced together into 'conceptual chimeras'. The image of chimeras thus offers a common theme for several significant conclusions about the history of bioenergetics, the philosophy of experiment, and the dynamics of conceptual change.

1. Experimental Culs-de-sac and Debate in Ox–Phos

Biochemists have sometimes been caricatured as viewing the cell simplistically as 'a bag of enzymes'. In the 1950s and 1960s, this was largely true. It had also been

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[1]These chimeras are distinct from embryonic chimeras, which combine whole cells of genetically distinct embryos.

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eminently successful. To understand how the cell produced ATP, biochemists traced the series of chemical reactions through which energy flowed. One needed to identify the various intermediate molecules and the enzymes that catalyzed each step in the sequence. The central task, experimentally, was roughly to break the cell open, isolate the essential components—the enzymes, substrates, cofactors, etc.—and then reconstitute the system again from scratch in a test tube. Ironically perhaps, the *in vitro* solution was the standard by which a complete understanding of the *in vivo* reality would be judged (e.g. Racker, 1968, p. 32). The researchers thus exhibited two widely used strategies. First, biochemists worked reductionistically to 'divide and conquer', to try to understand the system through its individual components or sequential stages (e.g. Simon, 1969; Kauffman, 1971; Wimsatt, 1980; Bechtel and Richardson, 1994). Second, they 'intervened', trying to prove their claims by manipulating the experimental object in a wholly man-made reconstruction (Hacking, 1983; Galison, 1992).

The experimental approach had proved successful over several decades as chemists revealed the details of glycolysis, substrate level phosphorylation, the citric acid cycle and various other metabolic pathways (e.g. Holmes, 1991–93; Bechtel, 1986). All these reactions occur in solution, however, and thus were amenable to this type of analysis. Initially, of course, there was nothing to signal that the reactions of oxidative phosphorylation, or 'ox–phos', would be any different. Quite the contrary, substrate-level phosphorylation from succinyl Co-A to ATP offered an explicit model for ox–phos (Slater, 1953).

But beginning in the mid-1950s and continuing through the 1960s, chemists encountered numerous unexpected difficulties in deciphering the reactions that lead to ATP in the mitochondrion. Reagents that interfered with the reactions (uncouplers), for example, generated non-whole-number ratios between reactants and products. How could so basic a rule of chemical equations be violated? Chemists concluded that experimental preparations must somehow be inadequate (Peter Hinkle, personal communication; Rowen, 1986). In addition, the components of the ox–phos system were embedded in the inner membrane of the mitochondrion and researchers were unable to extract them in a still functional state. The membrane was a 'nuisance' (Lehninger, 1964, p. 6). For example, chemists wanted to isolate and identify a set of high-energy intermediate molecules, but found the task unduly difficult. They began to suspect that the compounds might be tightly bound to membrane proteins. That, at least, could account for their persistent failures (e.g. Griffiths, 1965; Chance *et al.*, 1967).

Chemists soon recognized that, experimentally, the smallest functional unit for the ox–phos reactions was a small membranous vesicle, produced from mitochondria by either sonication or cholate dialysis. It may be indicative of their perspective, however, that they tended to disregard the structure of the vesicles themselves, referring to them merely as sub-mitochondrial 'particles'. At other times, however, some biochemists acknowledged a role for the fundamental relationship between

structure and function. If the ox–phos components were in a membrane, then perhaps the membrane contributed to how the system worked. Albert Lehninger posed the possibility of a geometric structure that controlled how the components interacted—a theme which also permeated David Green's thinking (e.g. Green and Baum, 1970). Perhaps the membrane regulated protein–protein collisions or the distance between components that exchanged electrons (Lehninger, 1960; Chance, *et al.*, 1967). If the membrane skeleton or its hydrophobic environment were essential, then chemists faced a formidable technical challenge indeed—though one researcher modestly called it only 'rather formidable' (Racker, 1970, p. 137). One set of reviewers, therefore, entertained the possibility that 'classical approaches to reconstruction applied to the highly integrated and structure-dependent respiratory chain and its energy-coupling mechanisms may never succeed' (Lehninger *et al.*, 1958, p. 456).

By contrast, according to the chemiosmotic model introduced by Peter Mitchell in 1961 (and that now dominates our thinking; Cramer and Knaff, 1990), the membrane is perhaps the central feature in ox–phos. The system's components are oriented directionally within the membrane and transport protons across the membrane, thereby generating a pH or electrochemical gradient. This then fuels the phosphorylation of ATP. The integrity of the closed membrane is critical. Little wonder then (by today's standards), that chemists could not reconstitute the system without a fully membraned vesicle(!). Indeed, one may note the irony in chemists trying to eliminate the membrane to get at the 'essential' enzymes, thereby destroying a fundamental feature of the very system they hoped to understand. Further, in the current model, there are no stable high-energy intermediate compounds to be found. Failure to isolate them had nothing to do with experimental technique: they simply were not there to be extracted. Many background variables shifted to the foreground, and vice versa. Relevant domain was redefined. The chemiosmotic hypothesis (Mitchell, 1961) cast the phenomena surrounding ox–phos reactions in a completely different gestalt.

Experimental approaches to ox–phos, then, were coupled to theoretical commitments. The chemiosmotic research framework, for example, called for different measurements and experimental controls. Whereas earlier, rates of reactions, temperatures and radioactive labels were mostly sufficient, now the pH of the solution gained new relevance. Changes in pH or electric potential, and ion movements across the membrane of the submitochondrial vesicles all had to be controlled or monitored. One had to know the membrane's permeability to various ions, especially protons. Variable permeability, for example, could account for non-integer ratios in reactions. All these factors seemed strange to biochemists already at work on ox–phos in the 1960s. E. C. Slater may have expressed the general skepticism of the community when he commented,

> I do not believe that the only or even the primary function of this unbelievably complicated chain of reactions is to produce protons at the right place (Slater, 1967, p. 1).

Controversy emerged on both research methods and theory (Weber, 1991; Gilbert, and Mulkay 1984a). Disagreement became 'tempestuous', according to one researcher, and 'debates on crucial problems ... uncompromising' (Skulachev, 1988, p. v). Most importantly, perhaps, researchers saw the two interpretations and their experimental agendas as incompatible alternatives. They thus framed the controversy in stark 'either–or' terms (see Racker, 1970; Slater, 1971; analysis in Allchin, 1994).

During the 1960s, many investigations in Mitchell's lab and elsewhere brought legitimacy to chemiosmotic notions. Chemists variously measured or documented the effects of factors predicted by chemiosmotic theory. In one series of experiments, following an interventive style, they demonstrated that one could generate ATP in a presumably 'unnatural' state—from an artificially induced pH gradient. Proton gradients were thus causally relevant. These various experiments and demonstrations are richly documented and celebrated in several textbooks (e.g. Nicholls, 1982, pp. 20–22; Harold, 1986; Cramer and Knaff, 1990, pp. 103–115). They pervade folk histories in the field, as well (Gilbert and Mulkay, 1984a, pp. 18–33). For many retrospective accounts, then, these various studies seemed decisive. One researcher has even contended that 'logically', the chemiosmotic hypothesis had been 'experimentally proved' by evidence available in 1970 (Skulachev, 1988, p. 342). Yet while many chemists raised their eyebrows or even reoriented their work to address or include the new chemiosmotic concerns (Robinson, 1984), the suite of experiments did not resolve the controversy. At the close of the 1960s, the oxidative phosphorylation community had not developed a consensus (see e.g. Racker, 1970; Slater, 1971). It was in the context of the substantial residual disagreement that the chimeric vesicles would prove important.

2. A Capstone Experiment

The horizon of debate shifted significantly with the discovery in 1973 of a new photosynthetic pigment, bacteriorhodopsin, in the membrane of halobacteria. Bacteriorhodopsin generated energy for the cells by creating a proton membrane gradient in light (Oesterfelt and Stoeckenius, 1973). That in itself was novel and was highly suggestive of chemiosmotic mechanisms. But the more dramatic results came the following year in a collaboration between Stoeckenius and Efraim Racker at Cornell (Racker and Stoeckenius, 1974).

Applying a technique Racker's lab had recently developed, they constructed artificial vesicles from an unlikely combination: they inserted bacteriorhodopsin into a membrane made with molecules from soybeans, along with an ATP enzyme from beef heart. The fragments from the bacterium, plant and animal—that is, from three kingdoms—formed a chimeric vesicle which could do something that none of the individual elements could do on its own: it could generate ATP in light. The bacteriorhodopsin could generate a proton gradient, but it did not have the bacterium's molecules for producing ATP. The ATP enzyme from the mitochondrion, by contrast, had been stripped of the other basic elements of the ox–phos system used to generate

energy. It could not respond to light by itself—but it could use the induced proton gradient to produce ATP. Finally, the membrane from the plant could maintain a gradient, but it could not have been uniquely structured to integrate or organize the functional interaction of the bacterial and bovine elements (as suggested in Lehninger's model, say). The role of the various parts—from evolutionarily divergent groups—complemented each other and worked as a patchwork ensemble, while highlighting the particular role of each element.

In the chimeras, Racker and Stoeckenius had pieced together a surrogate reality, based on expressing Mitchell's chemiosmotic concepts in the laboratory. The chimeras were, as aptly described by Joseph Robinson, 'an experimental tour de force' (Robinson, 1984, p. 378). The signal 1974 paper alone would be cited 363 times in the next decade (excluding self-cites), peaking at 62 cites in 1977. Of these, 99 citations were in review articles and 58 in book volumes, reflecting the widespread attention paid to the experiments. Most importantly, perhaps, the chimeric vesicles helped significantly towards resolving the remaining controversy over ox–phos.

First, the project producing chimeric vesicles effectively upstaged efforts to reconstitute ox–phos as a soluble enzyme system—which chemists were already abandoning in frustration (Allchin, forthcoming). Racker had essentially fulfilled the chemists' (including even his own) original goal of producing oxidative phosphorylation outside the living organism. But he 'solved' the problem by dissolving it. That is, he had redefined or reframed the problem in terms that were wholly inconceivable given earlier experimental themes. Indeed, the new 'solution' emerged from another lineage of thought and practice altogether. At the same time, it was also not merely a positive addition to existing knowledge: the chimeric vesicles implied that the premises of earlier efforts were grossly misconstrued.

Further, Racker's lab had not intervened as originally imagined. Initially efforts had been aimed at reproducing nature as closely as possible, merely isolating the necessary and sufficient conditions. But the chimeric vesicles clearly did not serve as *re*constructions; rather, they were conspicuously original constructions. No one conceived them as replicating any natural system. They were notably shaped by human imagination. The mythical image of the chimera was indeed appropriate in this case. Paradoxically, perhaps, the 'unnatural' hybrid convinced most chemists and biologists about what was 'natural'. They interpreted departure from nature as bringing their understanding closer to nature. Racker's studies on chimeras thus resonate with other experiments in which reality is uniquely gleaned through 'artificial' reality in the laboratory.[2] That is, reality is interpreted foremost through phenomena that would never occur under normal circumstances in nature. The

[2]Galison (1992) and Galison and Assmus (1989) have highlighted examples of the 'creation' of events in particle physics. In the ox–phos case, one may also mention: the man-made phenomena of reversed electron flow (by Chance and Hollunger in 1960 and Ernster in 1963); the production of ATP with artificially induced pH gradients (Jagendorf and Uribe, 1966; Reid, Mitchell and Moyle, 1967); and the measurement of membrane gradients with synthetic ions (Lieberman and Skulachev, 1970).

striking rearrangement of nature in the chimeric vesicles contributed substantially to their persuasive power.

Racker's vesicles were important instrumentally as well as discursively. If the chemists under the conventional paradigm had largely failed in their particular reconstitution efforts, Racker's vesicles showed a way to proceed. Racker's lab had developed a method whereby membrane proteins could be reintroduced selectively into a simple membrane. The method offered a tool for studying at least some elements of the ox–phos system in isolation from one another. Indeed, Racker had already shown how each of the three segments of the electron transport chain could generate a proton gradient, as bacteriorhodopsin had been shown to do. Other researchers pursued the new experimental opportunities offered by the reconstitution technique—and the method has since become indispensable for preparing miniature systems for investigation (see Cramer and Knaff, 1990). The novel method opened a new lineage of experiments within the chemiosmotic paradigm, allowing a new generation of chemists to pursue reductionistic research strategies.

The chimeric systems highlight both the virtues and limitations of reductionism. That is, one must define the boundaries or domain of the system properly in order to reduce or decompose it into its functional parts (Bechtel and Richardson, 1994, pp. 37–62). This is where the chemists' program had stalled and where the chimeras supported chemiosmotic theory. Though 'unnatural', the chimeric vesicles demonstrated precisely how parts could be pieced together—and indirectly, then, what the functionally relevant parts were. When Peter Mitchell (1961) had first introduced the chemiosmotic hypothesis, he had specified the fundamental theoretical elements. Each was represented in the chimeras. The bacteriorhodopsin served as a proton-translocating system situated directionally in the membrane; the membrane formed a topologically closed compartment; and the ATP enzyme was the final, gradient-using protein, also situated directionally in the membrane.[3] As noted above, the parts had already been understood separately in their independent contexts. The noteworthy element of the demonstration was the system as a whole. The functional fit of disparate parts—the distinctive feature of the chimeras—signified that the parts of ox–phos had been identified and assembled appropriately. Research continued in a reductionistic mode because the essential parts—indeed, the boundaries of the whole system—had been redefined. The membrane that was once peripheral, for example, had become central.

The chimeric vesicles were undoubtedly significant historically, but in many ways they were not extraordinarily original experimentally or conceptually. Peter Hinkle contends that the experiment demonstrated nothing that was not already known from previous studies of bacteriorhodopsin and the ATP enzyme, each functioning independently in miniature vesicles (personal communication, June 8, 1993). The dramatic reception by the ox–phos community can only underscore, then, the

[3]Mitchell also mentioned control of subsidiary ion movements across the membrane—a fourth, peripheral element (more important in living cells and other reconstituted systems).

importance of synthesizing the various elements (Gilbert and Mulkay, 1984b; Skulachev, 1988). The chimeric vesicles thus suggest a special category of *'capstone experiments'*. Exemplified by Racker's studies, a capstone experiment need not necessarily introduce novel data. Rather, it incorporates and demonstrates clearly the *relationship* of other findings (see also Darden and Maull, 1977, on 'interfield theories'). It is a material summation device. As such, a capstone experiment would likely serve as the focal point of later reference or procedures and, like the vesicles, be evidenced historically through citation patterns (see also Latour and Woolgar, 1979, ch. 3). Such a capstone experiment could thus hide the very work on which it depends—beginning the process Latour (1987) has dubbed 'black-boxing'. Most fundamentally, though, a capstone experiment would be a synthetic demonstration, a synoptic endpoint to a line of research.

3. Resolution by Redrawing Domains

The chimeric vesicles hold clues to appreciating many features of the broader debate about ox–phos, as well. From one perspective, the chimeric vesicles were a crucial experiment in a revolutionary transition whereby the chemiosmotic paradigm replaced the chemical one. 'That is perhaps the touchstone', one researcher remarked, for example, 'that is the one single experiment that people cite' (Gilbert and Mulkay, 1984a, p. 29). Indeed, one can easily cast this episode as a Kuhnian revolution, especially where one characterizes the gestalt switch in *experimental* terms (Chen, 1994). But a more textured—and more interesting—history lies in the understanding of how some chemists interpreted the import of the chimeric vesicles differently.

Many researchers did not view the chimeric vesicles as 'key' experiments (Gilbert and Mulkay, 1984b, pp. 111–112; Skulachev, 1988, pp. 342–343). For example, some chemists saw the vesicles as 'too artificial' to represent real processes in real cells, or thought the amount of ATP produced was too small. For Gilbert and Mulkay (1984b), the conflicting interpretations lead the historian to a crippling agnosticism about the role of experiments. But they do not consider each researcher's domain of concern and how the various domains relate. These contexts illuminate the meaning and nature of the alternative perspectives and allow one to interpret and appreciate them more fully. For example, one researcher acknowledged, 'You don't reconstitute the same system, but maybe it works and maybe because it works it tells you something.' Another concurred: 'Now this is not to deny that all of that work gives you a sound or a different basis in which to set up experiments on' (p. 111). For these chemists, Racker and Stoeckenius' results did lead to certain valid and useful conclusions. They were simply not relevant to their own central concerns—in this case, focused on the more detailed enzymological processes. Their criticisms were thus based on local (ir)relevance in certain domains.

These other domains were themselves 'key' in the outcome of debate. That is, the chemists' experimental repertoire had been radically transformed but not wholly

replaced by chemiosmotic concerns. Chemists still used spectroscopic data and radioactive labels, for example, to investigate how the individual proteins in ox–phos functioned. In particular, many researchers were still trying to work out the critical mechanism by which phosphate is added to ATP (e.g. Boyer, 1977; Racker, 1977). They had found—through conventional biochemical means—for example, that bond formation and the use of energy occurred unexpectedly in two distinct steps. Further, chemists wanted to determine the details of the number of protons translocated across the membrane in each partial reaction (e.g. Chance, 1977). Though the measurements were now based on chemiosmotic gradients, the task was largely conventional. Experimentally, one had to piece together old familiar methods with strange new ones, thereby straddling different theoretical schemes. In the process, the social relationships defined by researchers sharing results and communicating about common concerns changed, splitting a formerly unified community.

The chimeric vesicles contributed to articulating the new boundaries that separated the domains of investigation and, with them, the professional social networks. Prior to the vesicles, evidence supporting the chemiosmotic framework had accumulated piecemeal. Mitchell, as detailed above, had outlined a prospective scope for chemiosmotic concepts in ox–phos as early as 1961, but no single experiment had effectively bridged the independent findings. As a 'capstone experiment', the chimeras filled that role. At the same time, they helped to define and thereby distinguish an emerging field of bioenergetics, centered on chemiosmotic notions. The chimeric vesicles were not universally persuasive, in the sense of converting all chemists to a new research enterprise. They did not need to be. Instead, they demonstrated more clearly the shifting boundaries of research domains in oxidative phosphorylation. In the wake of the chimera experiments, major participants in the debate thus had to be more careful about defining the particular scope and nature of their claims (Boyer *et al.*, 1977). That was largely how debate was resolved.

In the ox–phos episode, new research agendas were introduced, some were preserved, others altered, and many eliminated. The major loss was the imagined context in which many conventional methods and techniques could be meaningfully applied. For oxidative phosphorylation viewed as a soluble system with many high-energy intermediates, the loss was large, indeed. The scope or domain of application of numerous methods was severely limited. Yet others remained. The chemical research enterprise was thus selectively replaced, or 'displaced'. Distinct chemical and chemiosmotic styles of experiment now complement each other in a sort of inter-paradigm hybrid. The outcome of debate was a chimera, as well: a chimera of experimental research programs (see also Koertge, 1971; Whitt, 1990).

The image of the chimera in this second context offers a model from which one may generalize, and through which one may interpret other controversies or cases of scientific change. Positivist models of growth in science, as well as revolutionary models of wholesale replacement, are each inadequate for capturing the complexities exemplified by the ox–phos case. One needs to be sensitive to the scope or context

(or domain) in which each experimental research enterprise functions. In periods of disagreement or debate, researchers may significantly redraw the divisions between domains. The rearrangement may allow for distinct scientific theories, models or research enterprises to exist simultaneously as mosaic entities, or chimeras. The pattern poses further unanswered questions, of course, about exactly when and how scientists differentiate domains.

4. Conclusion

In the ox–phos episode, the image of piecing together oxidative phosphorylation through chimeras has multiple meanings. Historically, a revolutionary new view of oxidative phosphorylation stabilized due to Racker and Stoeckenius' novel style of experiment involving chimeric vesicles. They dramatically brought together divergent cell fragments and, in so doing, synthesized the piecemeal evidence that had accumulated. As a 'capstone experiment', they demonstrated how elements from different and formerly separate domains could be arranged into a functional unit. They thereby invite historians to reconsider the role of experiments as 'capstones' in other episodes. Finally, though a single experiment can be dramatic in validating a particular research enterprise in inter-paradigm debate, it will not always establish exclusive support for one experimental program. The outcome of debate can be a chimera, of sorts, just like the hybrid vesicles in Racker's lab.

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