Anomalies in Ox-Phos:
Six of One Theory, a Half-Dozen of Another

Douglas Allchin
University of Minnesota

Abstract. The interpretation and analysis of anomalies is theory-dependent. Hence, even the level of "threat" of anomalies to an existing research lineage itself depends on perspective or (in Kuhnian terms) paradigm. The ambiguous status of anomalies amplifies the Kuhnian incommensurability problem. The asymmetric organization of multiple anomalies is a strong indicator to interparadigm discourse and thus indicates how to orient discourse and frame evidence persuasively. Peter Mitchell's analysis of anomalies in oxidative phosphorylation in 1961 (and contrast it with other views) is a primary case study, while comments also extend to Darwin's synthesis and to racial and sexist bias in biology.

In developing our session's theme today, I want to focus on the challenge presented when the interpretation or analysis of anomalies varies with theoretical context. This potentially amplifies any problem, say, between two conflicting Kuhnian paradigms: an anomaly for one scientist may not be the same anomaly for another—or even seem significantly anomalous at all. Still, such varied interpretations may also offer clues that help profitably reorient discourse and experiment. I will illustrate the challenge through a case from cellular biochemisty. In this instance, six disparate anomalies from one perspective could also be characterized (from another perspective) as unifed: a half dozen anomalies. **In this case, six was not the same as a half-dozen. This asymmetry critical indicates how to resolve the underlying disagreement.** Afterwards, I'll briefly address a few other historical cases to amplify my conclusions.

! ! ! ! Krebs/cycle; Lipmann/ATP; Keilin/ETC; Slater/1957 ox-phos analogy

Let's return to 1961. Hans Krebs has elucidated the reactions of the citric acid cycle, and Fritz Lipmann has described the central role of phosphate bonds, notably in ATP, as an energy carrier in the cell. David Keilin has helped identify the cytochrome chain that transforms energy from the Krebs cycle and for the last decade, research has focused on deciphering the final energy reactions that use oxygen and produce ATP, oxidative phosphorylation, or ox phos.

The Anomalies of Ox Phos

! Mitchell/1961 diagram

In this historical context, Peter Mitchell introduced a remarkably different theory, which would ultimately earn him a Nobel Prize in 1978: what he called the chemiosmotic hypothesis. In his original **1961 paper**, in a deceptively modest four column-inches of text citing twenty articles, Mitchell presented six anomalies: "facts . . . that are generally acknowledged to be difficult to reconcile with this orthodox (chemical) view" (1961c, 144). Given our focus today on anomalies, I want to consider these **six anomalies** more closely. In particular, I want to address how the historical context shaped how other chemists interpreted the very same experimental phenomena — and how this makes a philosophical analysis of anomalies more complex.

! Mitchell (1961b)

Mitchell noted that loss of the ATP product on one side of the mitochondrial membrane led to changes in the equilibrium of the reactions on the other side of the membrane. Mitchell contended that moving hydrogen ions across the membrane was central to the energy reactions — and here he emphasized how his conception could explain this particular effect, bridging the two sides of the membrane. But the chemists would not have seen this fact as threatening their view. They saw ox-phos, like all chemical reactions, as reversible. When one uses the product, **equilbrium shifts**. There was no broken expectation, no inadequate explanation. No anomaly, here, at least.

! high-energy intermediates (Chance)

Second, Mitchell noted, the proposed **high-energy intermediates** of the reaction series were **"elusive to identification"**. In classic scientific understatement, he implied that there were no intermediates at all. Rather, the intermediate energy stage was a build of protons outside the membrane: an electrochemical pH gradient. Those studying ox phos were arguing about whether such intermediates were phosphorylated, or whether there was a second non-phosphorylated intermediate, so Mitchell's claim seemed to betray a fundamental confusion. Moreover, from recent reports, biochemists seemed on the verge of isolating the intermediates. They were likely short-lived and thus hard to isolate experimentally, especially if embedded in the membrane. This was a technical challenge, not a theoretical failure — and certainly not epistemically threatening.

! closed vesicle

Third, Mitchell noted, **structurally intact membranes seemed essential**. For Mitchell, the membrane preserved the pH energy gradient. Here, chemists did consider this problematic — but only experimentally. The conventional research, epitomized in the work of Krebs, Lipmann and others, targeted enzymes in aqueous solutions. The ox-phos components, however, were located in the mitochondrial membrane, a hydrophobic (or oil-like) environment. Researchers could not isolate the components while still functional. For biochemists, the challenge was to discover how to isolate enzymes intact from membrane-like structures.

Later, Albert Lehninger viewed the membrane more positively: "There may be a biological necessity for structural organization of these catalysts in a moderately rigid, geometrically organized constellation in the membrane." The membrane might hold enzymes in close proximity and proper

orientation. The implied remedy, as before, was to search experimentally for ways to prepare such complex membrane-bound structures. The same acknowledged "fact"—the structural integrity of membranes—had two quite different meanings.

! DNP, FCCP,

Fourth, Mitchell noted that **many compounds interfered with ox phos,** but they seemed to share no specific chemical characteristic. Mitchell noted, however, that these compounds were all soluble in the membrane's oil-like environment. They could thus enter the membrane and transport protons (or other charged particles), dissipating the pH gradient. For chemists, the solubility could certainly explain how the compounds entered the membrane. But understanding how they worked required more specific elucidation of their structure. Mitchell seemed to miss the critical features, which might not be known until all the reactions and their enzymes had been studied. Nor did anything dictate one common mechanism for all the chemicals.

! inflated mitchondrion

Fifth on Mitchell's list: **mitochondria would swell and shrink during ox-phos.** According to the chemiosmotic view, the movement of various ions caused the corresponding osmotic movement of water. While such osmotic effects were not uncommon, they were more familiar to the lipid biochemists who studied membranes. Biochemists studying energy-related reactions focused primarily on enzymes and protein chemistry. Osmotic phenomena fell outside their concerns. Swelling might occur incidentally, as a by-product, but hardly seemed relevant to the how the enzymes functioned. Here, Mitchell and the other chemists addressed different potentially relevant variables.

! cytochrome chain & 3 ATP cross reactions

Last among Mitchell's list of anomalies: reactants and products did **not always exhibit integer ratios**. When studying chemistry, we all learned to balance chemical equations. Reactants relate to products in whole numbers. Chemists observed that this "rule" was occasionally broken for mitochondria. For Mitchell, the membrane held a pH gradient, which could "leak" any amount, even if the reactions creating the gradient followed exact ratios. Other chemists acknowledged, for their part, that intermediate products might be used in other reactions, altering *observed* ratios. The uneven ratios, so common, reflected experimental static, or noise, not meaningful signal. Technical mastery would eventually dissolve this artifact. Once again, the chemists isolated Mitchell's "anomaly" to experimental methods, not theoretical concepts.

Interpreting Anomalies

! anomaly list

Well, now we have six anomalies. All could agree in 1961 about the basic "facts." Yet where Mitchell saw many fundamental counterinstances and explanatory flaws, chemists perceived only a handful of familiar technical challenges, complex experimental puzzles and, sometimes, no problem at all. Mitchell's anomalies were only anomalous using the chemiosmotic perspective as an interpretive guide. ***The meaning of the anomalies varied with theoretical context.*** Of course, this should surprise no one. Anomalies, like any observation, may be theory-laden, or interpreted contextually.

! paradigm shift wedge

Let me amplify this problem briefly. According to Kuhn, anomalies lead to crisis. They expose weaknesses in the paradigm that eventually lead to developing a successor. In the ox-phos case, however, the view from the established paradigm seems to eclipse the very revision that Kuhn suggested is inevitable. Indeed, it seems rather to epitomize Kuhnian incommensurability itself. **How then can anomalies lead productively to scientific change?** How can one correct an error if one may be blinded to its "meaning"—that is, if the anomalies are theory-laden?

! Darden's strategies

Now, consider here Darden's **strategies for resolving anomalies**. No single strategy is guaranteed. They are not algorithmic. They are not "methods" in the conventional sense. As exemplified in the ox-phos case, one cannot always immediately isolate an individual anomaly unambiguously. **Nor do the strategies seem to function wholly independently of perspective**. Research may thus appropriately follow multiple trajectories simultaneously (perhaps as exemplified in Kevin's cases?).

! error types

As I've noted on other occasions, one needs to consider a spectrum of error types (Allchin 2001). For my focus today, I want to underscore the **additional layer of epistemic process** not explicit in Darden's discussions: **how researchers communicate effectively when interpretations diverge and how they frame their evidence persuasively**.

! six/half-dozen

I want to highlight important clues in **the pattern of the anomalies** themselves, apart from how each is interpreted. So: reconsider the anomalies, not individually, but as an ensemble. From the chemiosmotic perspective, they formed a *unified syndrome.* They all implicated the membrane in energy transfer. The flaws were thus *systematic*. They functioned together as a *half-dozen* anomalies. From the earlier perspective in ox-phos, on the other hand, these were still *six separate* anomalies. There was a distinctive asymmetry, expressed in my title: **six anomalies of one theory, a half-dozen of another**.

! six/half-dozen on a balance

As a researcher, what dos thie mean? Applying a standard of conceptual economy — simplicity, or consilience — you just choose the chemiosmotic perspective as a clear winner. Indeed, many researchers were impressed by the coherence of the chemiosmotic gestalt and began to entertain it seriously or reorient their research trajectories. Here, one may note a strategy to prospectively add to Darden's catalog: **a meta-analysis using multiple anomalies**, as suggested also by Glymour (1975). Just as independent observations or lines of reasoning from multiple sources may provide robust support for a particular conclusion, so too they may indicate a robust weakness, vulnerability or error. Thus: **"Search for an intersection of prospective error types among many anomalies."** In this view, a half-dozen anomalies would be inherently more informative than six — and perhaps decisive.

But here I also want to underscore the **historian's caveat**: namely, philosophical analysis perhaps biased by retrospect cannot trump the **situatedness of the researchers**. The evidence is not yet in. (For example: Lindley's case of the central dogma shows how a set of anomalies each came to be resolved separately.) Searching for a common root error is merely another strategy, not a final

evaluative judgment. Again, response to anomalies need not be universal or univocal. Philosophical analysis must thereby focus instead on the discursive dimension: how pluralistic explorations from different perspectives are resovled. Researchers need to know how to present and use each others' findings effectively.

! six/half-dozen [reprise]

Without resolving all the anomalies, Mitchell's alternatives did, nonetheless, dramatically change the investigative landscape. He had shown how the anomalies could be related. The chemiosmotic investigator resolved all the anomalies at once, by adopting a new theory (or paradigm). The conventional chemist who resolved one anomaly, still had five others to resolve. For example, showing that the membrane functioned as scaffolding would not thereby solve the anomaly of the missing intermediates, and vice versa. Piecemeal solutions for each anomaly no longer sufficed. **The six/half-dozen asymmetry here thus indicated a critical shift: from *intra*paradigm to *inter*paradigm discourse.** In showing a plausibel role for the membrane in all cases, Mitchell essentially destabilized the background assumptions that had guided experimental reasoning and interpretation. Those assumptions could no longer be regarded as justified unproblematically. The asymmetric stacking of anomalies reflected this altered epistemic environment.

! scales3 [reprise]

How does this shift affect the researcher? Generally, when two alternatives present themselves, an investigator hopes to test them against each other under controlled conditions, isolating the variable in question against a stable background. In the context of anomaly asymmetry, such narrowly parallel comparisons are no longer possible. Mitchell could not appeal to experimental evidence that supported his view while simultaneously excluding the chemists' interpretations as "wrong." Indeed, his criticisms fell relatively flat because chemists felt no need to abandon their own interpretations. How could he present evidence, then, for the integrated nature of the six anomalies? As I've profiled on other occasions (Allchin 1992), Mitchell and others had to show, or *demonstrate*, that the chemiosmotic perspective had merit, was cogent and fruitful and solved relevant problems. Typically, this strategy does not effectively resolve anomalies, because it is "uncontrolled"; it does not address alternatives. Here, however, **in an interparadigm context, the appropriate strategy was demonstration**. **The asymmetric stacking of anomalies—six of one, a half-dozen of another— was primarily a diagnostic signal of** (rather than a solution to) **this significant shift in argumentative and experimental strategy**.

Ultimately, then, one can accommodate the interpretive flexibility, or theory-ladenness, of anomalies at the social or discursive level (through variation and selection). When anomalies are asymmetrically stacked, as in the ox phos case of six for one theory and a half-dozen for another, evidence must be styled accordingly. This distinctive pattern of multiple anomalies is itself a clue to focus on experimental demonstrations, without undo concern for discounting alternatives. Resolving an anomaly, then, may depend on considering whether other anomalies are related.

Beyond Ox-Phos

! Darwin / eye

Let me extend the focus, now, to cases beyond ox phos, to sketch the generality and import of my comments. Consider, first, Darwin's theory of evolution by natural selection as an alternative to natural theology. How is one to decide between them? The design of an eye, for example, was an anomaly for Darwin, not for natural theologians. Darwin addressed numerous "Difficulties on Theory" in Chapter 6 of the *Origin*. At the same time, he showed how one could recognize and resolve other anomalies about biogeography, embryology, rudimentary organs, classification and the "species problem" itself, all by postulating common descent. Here, asymmetry appears again when one considers *multiple* anomalies. Darwinism, of course, represented a major paradigm shift.

Darwin's grand synthesis, linking all these anomalies, might possibly further illustrate the strategy, "Search for intersecting anomalies." —Most historians and philosophers of biology would agree, I think, that conceptual synthesis was central to Darwinism's persuasiveness (Janssen 2001). One may wonder, then, why Darwin's arguments seem ineffective for many creationists today. While one can surely cite cases of improper understanding of the evidence, trust of ill-informed authorities, etc., I want to highlight the nature of the public debate. Creationists perpetually appeal to "anomalies" in evolutionary theory as though each such anomaly should be decisive in rejecting evolutionary theory. At the same time, educators frequently rehearse the canonical list of evidence and appeal to each anomaly explained. My analysis suggests why both arguments may be ineffective. Anomalies themselves depend on perspective. In this case, opponents are each using intraparadigm-styled arguments in interparadigm discourse, with little success.

! craniology

Let me close with one final case: the history of craniology and intelligence. Here, by contrast, asymmetric stacking of anomalies (and interparadigm dispute) was not evident. Rather, the case further illustrates the "interpretive flexibility" of anomalies and what strategies may —or may not— resolve them. In retrospect, craniology was shaped by racist and sexist politics. The error was not just poor evidence; it was the entire framework of questions and the assumptions behind them. The field was plagued by a cascade of anomalies (Fee 1979). The first criterion for intelligence was brain size. But the large brains of elephants, or even whales, were judged anomalies. So anthropologists found another metric: the ratio of brain size to body size. This revised solution fell afoul of, in many cases, women (with their smaller bodies). Again, researchers retreated in the face of anomalies. Without recognizing the prejudices that guided their work, they looked for yet other measures. Cuvier proposed the relative proportion of the cranial bones to the bones of the face, since it would "measure" the dominance of the brain over other senses. Here, however, birds, anteaters and bear-rats ranked above humans. Enter cranial height, indicative of expanded brains. Alas, John Cleland noted, since Kaffirs, Negroes and Australians had large cranial heights, it could not be a genuine index of intelligence. And so on (Gould 1977). The case of craniology is important to the student of anomalies because it shows the power of perspective in interpreting anomalies. The pursuit of craniological measures of intelligence persisted for decades, anthropologists neatly finessing each successive anomaly.

Why did it finally collapse? Two women, mentored by Karl Pearson, focused anomalies at

deeper levels. They were sensitive to and exposed the gender bias, enlisting a new statistical rigor to support their claims. Although the craniologists had responded to anomalies, they had never identified what we now regard as the central error: cultural prejudice. Like Mitchell's analysis of ox phos, someone from a different perspective was needed to assign the anomaly to common assumptions. The two cases illustrate how anomaly resolution may rely in part on the interaction of perspectives at the social level of science (Longino 1990, Harding 1991, Solomon 2001).

If one assumes that every anomaly exposes a prospective "error" to be remedied, then a catalog of error types (from the material and experimental to the discursive-social) may be a healthy tool for anomaly resolution. Still, the process of anomaly resolution may also rely on interpreting anomalies in multiple ways and framing the evidence appropriately in discourse.

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